TARGETS IN HETEROCYCLIC SYSTEMS

Chemistry and Properties

Volume 6 (2002)

Reviews and Accounts on Heterocyclic Chemistry

http://www.sci.uniba.it

Editors

Prof. Orazio A. Attanasi
Institute of Organic Chemistry, University of Urbino
Urbino, Italy

and

Prof. Domenico Spinelli
Department of Organic Chemistry, University of Bologna
Bologna, Italy

Italian Society of Chemistry
Division of Organic Chemistry
Division of Medicinal Chemistry
Division of Mass Spectrometry

Publisheb by:

Società Chimica Italiana

Viale Liegi, 48

00198 Roma

Italy

Volume 1 (1997)	First edition 1997	ISBN 88-86208-24-3
	Second edition 1999	ISBN 88-86208-24-3
Volume 2 (1998)	First edition 1999	ISBN 88-86208-11-1
Volume 3 (1999)	First edition 2000	ISBN 88-86208-13-8
Volume 4 (2000)	First edition 2001	ISBN 88-86208-16-2
Volume 5 (2001)	First edition 2002	ISBN 88-86208-19-7
Volume 6 (2002)	First edition 2003	ISBN 88-86208-23-5

Printed and bound in Italy by:
Arti Grafiche Editoriali s.r.l.
Via S. Donato, 148/C
61029 Urbino (PU)
Italy
July 2003

Indexed/Abstracted in: Chemical Abstracts; Current Contents; ISI/ISTP&B online database; Index to Scientific Book Contents; Chemistry Citation Index; Current Book Contents; Physical, Chemical & Earth Sciences; Methods in Organic Synthesis; The Journal of Organic Chemistry; La Chimica e l'Industria; Synthesis.

Dear Reader,

The Volume 6 (2002) keeps the international standard of THS series and contains fourteen Chapters, covering the synthesis and reactivity, as well as some medicinal properties of different heterorings. In various way, Austria, Egypt, France, Hungary, Italy, Portugal, and Spain are present in this book.

Comprehensive Reviews reporting the overall state of the art on wide fields as well as personal Accounts highlighting significative advances by research groups dealing with their specific themes have been solicited from leading Authors. The submission of articles having the above-mentioned aims and concerning highly specialistic topics is strongly urged. The publication of Chapters in THS is free of charge. Firstly a brief layout of the contribution proposed, and then the subsequent manuscript, may be forwarded either to a Member of the Editorial Board or to one of the Editors.

The Authors, who contributed most competently to the realization of this Volume, and the Referees, who cooperated unselfishly (often with great patience) spending valuable attention and time in the review of the manuscripts, are gratefully acknowledged.

Orazio A. Attanasi and Domenico Spinelli
Editors

Table of Contents

(for the contents of Volumes 1-5 please visit: http://www.sci.uniba.it)

ENANTIOSELECTIVE RING EXPANSION VIA AZIRIDINIUM INTERMEDIATES. SYNTHESIS OF SUBSTITUTED PIPERIDINES FROM SUBSTITUTED PYRROLIDINES. SYNTHETIC APPLICATIONS

Janine Cossy* and Domingo Gomez Pardo

Laboratoire de Chimie Organique, associé au CNRS, Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI), 10 rue Vauquelin, 75231 Paris Cedex 05, France

(e-mail: janine.cossy@espci.fr)

Abstract. *Enantioselective ring expansion of 2-(halomethyl)pyrrolidines and 2-(hydroxymethyl)pyrrolidines to 3-substituted piperidines via aziridinium intermediates implies a two step process: displacement of a leaving group by the nitrogen of the pyrrolidine via an internal backside nucleophile substitution (S_Nib) mechanism and an attack of a nucleophile on the formed aziridinium by a S_N2-type of displacement. This rearrangement is used to synthetize a great variety of biologically active compounds in a very efficient way.*

Contents

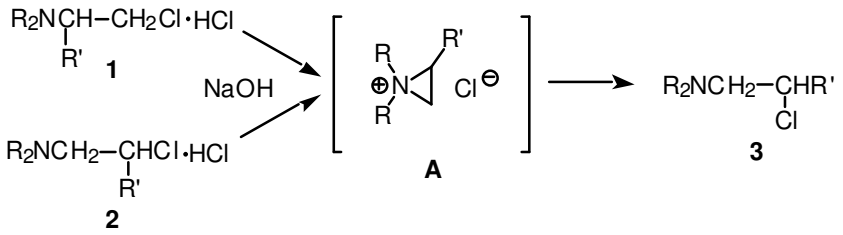
1. Introduction

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks of natural and synthetic compounds with important biological activities. Therefore, a huge amount of synthetic effort has been spent on the preparation of these systems.[1] With respect to biologically active target molecules there is an increasing interest in the diastereo- and enantioselective synthesis of piperidines. The most important process for obtaining substituted piperidines from pyrrolidines is probably a ring expansion *via* aziridinium intermediates.

2. Mechanism

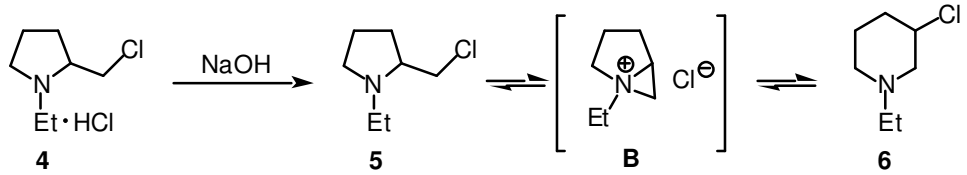
In 1947, it was noticed that β-chloroamine hydrochlorides undergo a rearrangement under basic conditions.[2,3] The products from hydrochlorides **1** and **2**, are identical and possess structure **3**.[3] This rearrangement is believed to occur through the cyclic aziridinium intermediate **A** (Scheme 1).[2-4]

This behaviour of β-chloroamines suggested the interesting possibility that 2-chloromethyl heterocyclic amine compounds might undergo a similar rearrangement to produce ring expanded products.[5] This hypothesis was verified when 1-ethyl-2-(chloromethyl)pyrrolidine hydrochloride **4** was treated with sodium hydroxide.



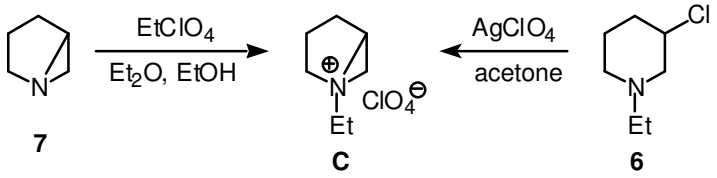
Scheme 1

The free base obtained was not the pyrrolidine derivative **5** but the isomeric 1-ethyl-3-chloropiperidine **6**.[5a] This rearrangement proceeds through intermediate **B** which is attacked at the more substituted carbon by the nucleophile (Scheme 2).



Scheme 2

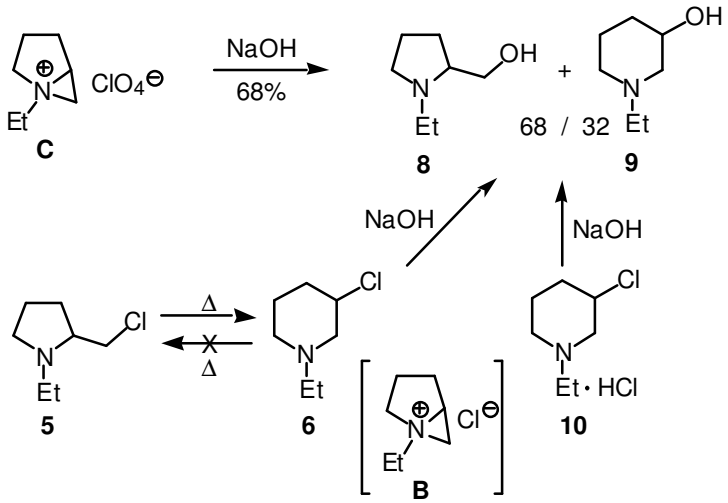
It was only in 1966 that the isolation of the aziridinium intermediate **C** as the perchlorate salt, as well as its independent synthesis were reported.[6] The reaction of 1-azabicyclo[3.1.0]hexane **7** in dry ether with ethyl perchlorate in absolute ethanol produced a semi-solid, which gave a ^{1}H NMR spectrum similar to the ^{1}H NMR spectrum of the oil obtained from the reaction of *N*-ethyl-3-chloropiperidine **6** with silver perchlorate in dry acetone consistent with the aziridinium perchlorate salt **C** (Scheme 3).



Scheme 3

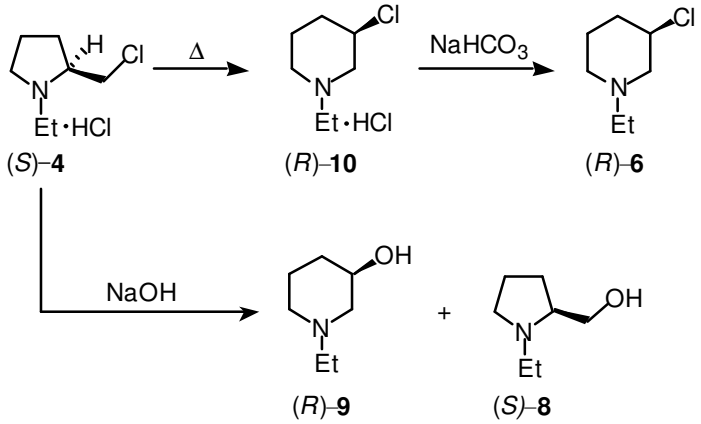
To verify that aziridinium **C** was the intermediate in the rearrangement of C(2)-substituted pyrrolidines to C(3)-substituted piperidines, the aziridinium intermediate **C** was heated in the presence of NaOH. Under these conditions, the 2-(hydroxymethyl)pyrrolidine **8** and the 3-hydroxypiperidine **9** were formed in a ratio 68/32 in 68% yield. Furthermore, treatment of the *N*-ethyl-3-chloropiperidine hydrochloride **10** with NaOH led to a mixture of **8** and **9** in a similar ratio of 68/32. It should be pointed out that *N*-ethyl-2-(chloromethyl)pyrrolidine **5** cannot be isolated pure as it rearranged easily into **6**. But, in contrast, the 3-chloropiperidine **6** did not rearrange to **5**.[6] It is worth noting that this rearrangement takes place under thermodynamic control (Scheme 4).

Synthetic, kinetic and stereochemical evidence has confirmed that **5** reacts with nucleophiles *via* a two steps neighbouring group participation mechanism involving the intervention of the bicyclic aziridinium ion intermediate **B** (Scheme 4), formed by the initial rate-determining displacement of chloride by nitrogen *via* an "internal" backside nucleophilic substitution ($S_N$ib) mechanism.



Scheme 4

The second step involves the attack of a nucleophile on **B** by a S_N2-type of displacement to give 5- and 6-membered ring products. It is worth noting that the entire process is stereospecific since complete retention of configuration is observed when (*S*)-**4** was converted to (*R*)-**10** by simple heating or to (*R*)-**9** when treated with NaOH, thereby ruling out a dissociated carbocation intermediate (Scheme 5).[7]

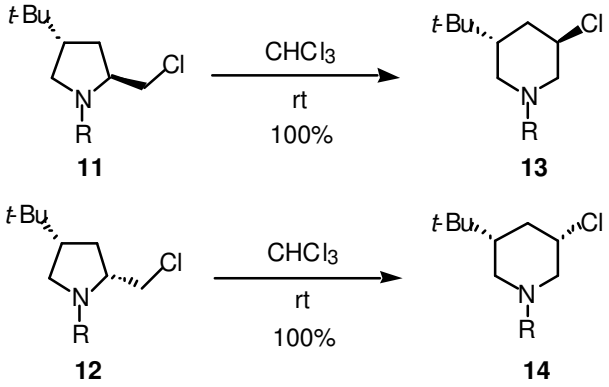


Scheme 5

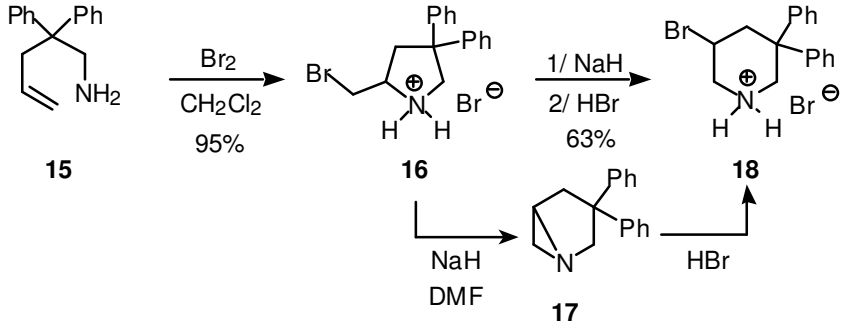
3. Synthesis of 3-halogenopiperidines

2-, 4-, 5- or 6-Alkyl substituted 3-halogenopiperidines can be obtained stereoselectively from the corresponding unstable alkyl *N*-alkyl-2-(halogenomethyl)pyrrolidines.[8] Pyrrolidines **11** and **12** rearranged readily when dissolved in chlorinated solvents to form the corresponding thermodynamically stable piperidines **13** and **14** in quantitative yield (Scheme 6).[8f]

5,5-Disubstituted-3-chloropiperidines can be obtained from 2,2-disubstituted-4-pentenylamines. It has been found that the addition of bromine at room temperature to a dichloromethane solution of 2,2-diphenyl-4-pentenylamine **15** gave fair to excellent yields of a bromohydrobromide salt to which the five-membered structure **16** was assigned. Treatment of this salt with two equivalents of sodium hydride in DMF gave the aziridine **17** which subjected to the action of dry hydrogen bromide led to the six-membered structure **18** in 63% yield (Scheme 7).[9]

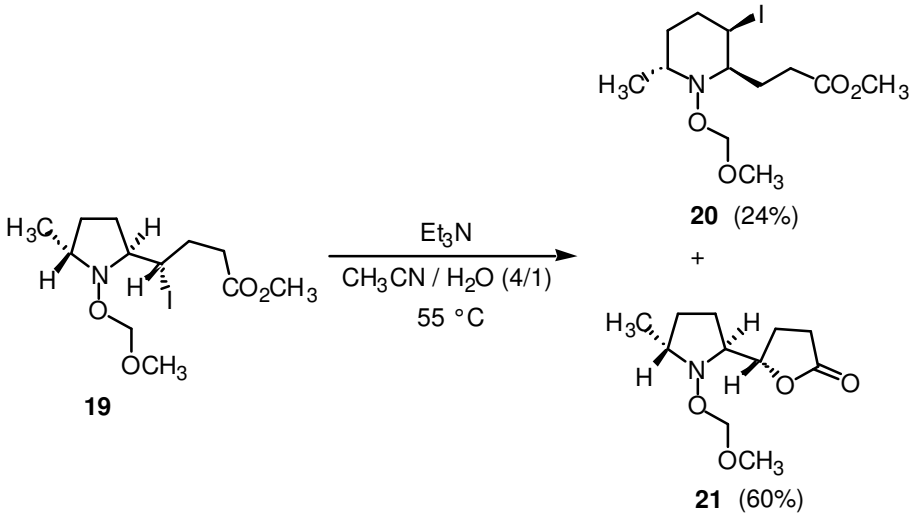


Scheme 6

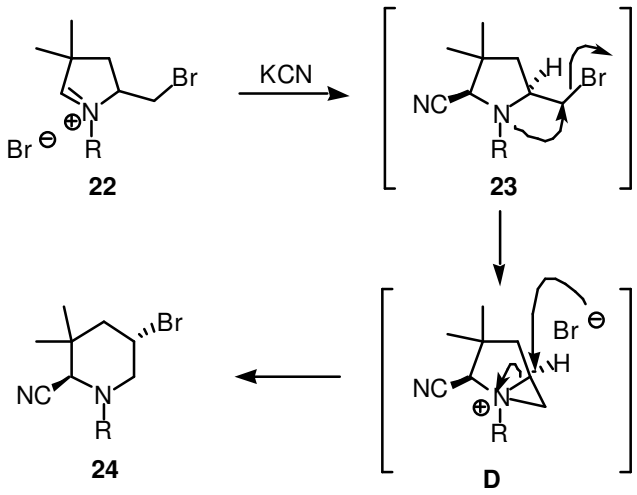


Scheme 7

A stereospecific nucleophilic substitution *via* anchimeric assistance by the nitrogen of 2-(α-iodoalkyl)-*N*-methoxymethylene oxypyrrolidine **19** was observed during its thermolysis at 55 °C as the dialkylsubstituted 3-iodopiperidine **20** was isolated in 24% yield along with butyrolactone **21** in 60% yield (Scheme 8).[10] This stereoselective rearrangement was also used to prepared trisubstituted 3-bromopiperidines.[11] When pyrrolidinium salt **22** was treated with KCN in a biphasic system (THF/H_2O:1/1), the 2-cyano-5-bromopiperidine **24** was obtained in good yield *via* pyrrolidine **23** and aziridinium intermediate **D** (Scheme 9).[11b]

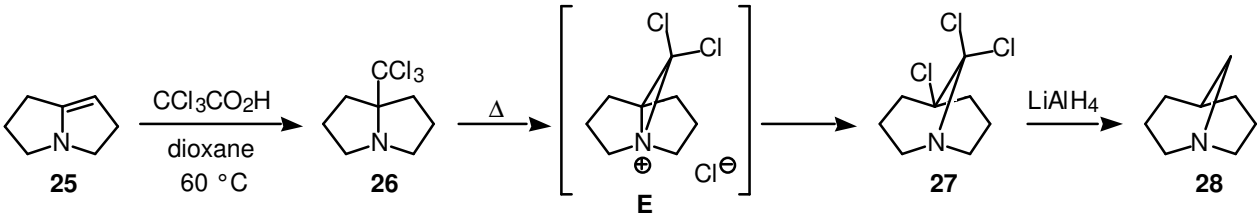


Scheme 8

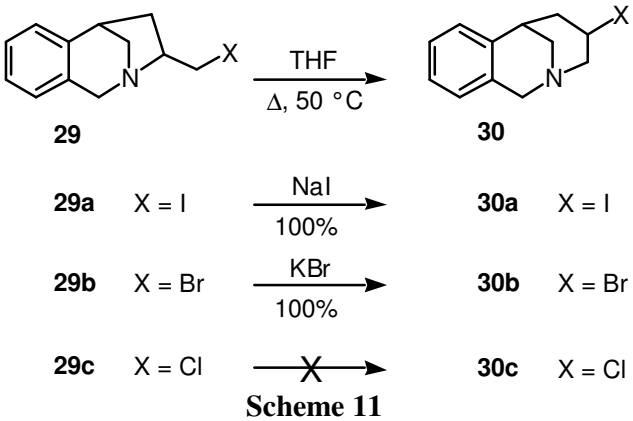


Scheme 9

Bicyclic compounds such as the substituted 1-azabicyclo[3.3.1]nonane **27** were obtained from the thermal rearrangement of 7*a*-trichloromethyl-2,3,5,6,7,7*a*-hexahydro-1H-pyrrolizidine **26** which was synthesized from **25**. Taking into account of the difficulties involved in the synthesis of 1-azabicyclo[3.3.1]nonanes **28**[12a] and analogues,[12b] the readily availability of compound **25** and related heterocyclic enamines, the ring expansion rearrangement provides an easy access to compounds of type **28** after reduction of the rearranged product by $LiAlH_4$ (Scheme 10).



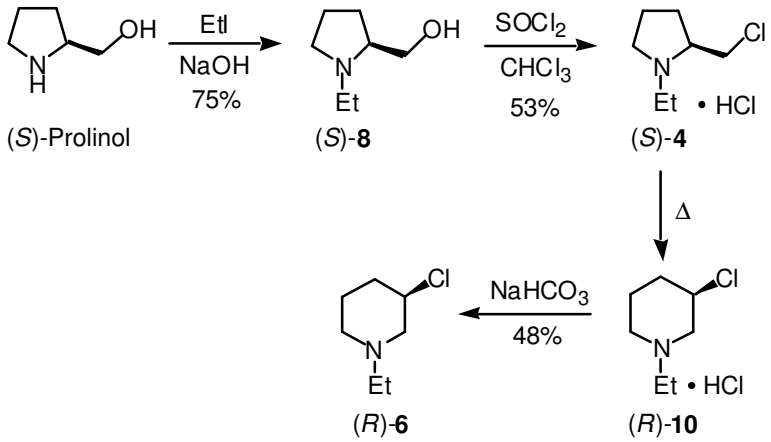
Scheme 10



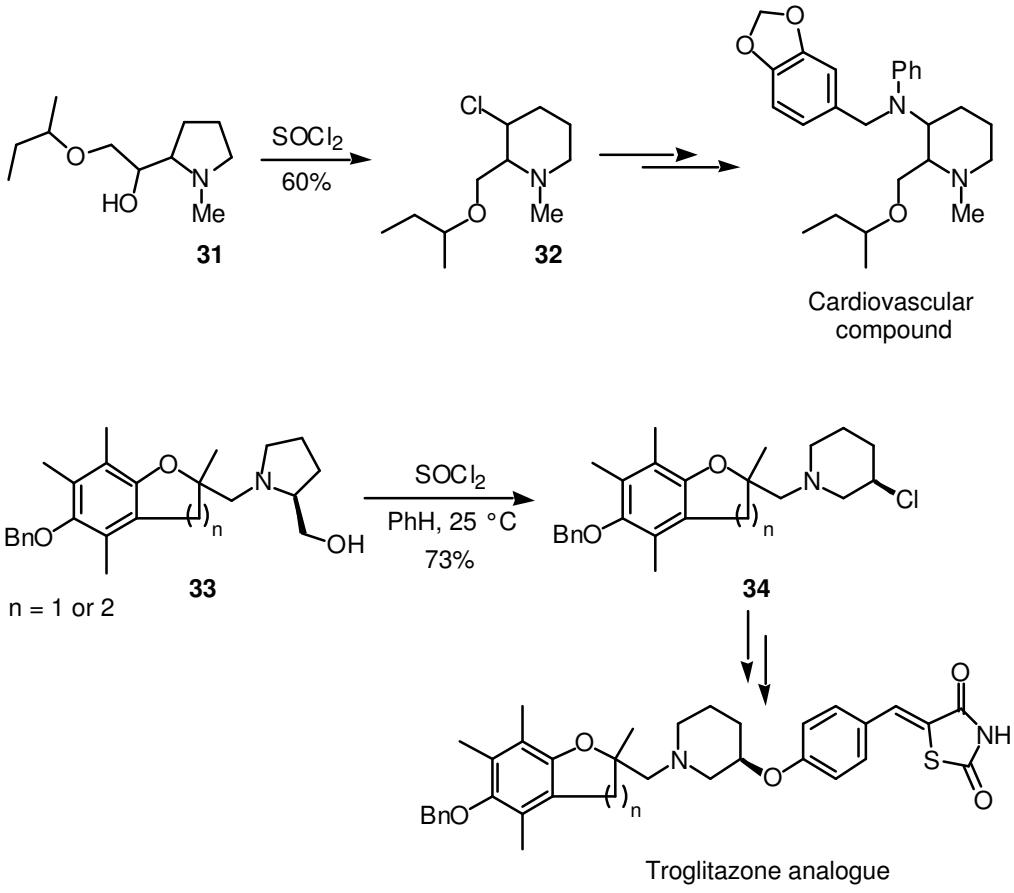
Scheme 11

The rearrangement of *N*-ethyl-2-(chloromethyl)pyrrolidines to 3-chloropiperidines has been used to synthesize compounds **30a-b**, precursors of *N*-methyl-D-aspartic acid (NMDA) non-competitive antagonists. Haloamines **29a** and **29b** were thermally rearranged to the thermodynamically favored azabicyclo[3.1.1]octane **30a** and **30b**. This process was more efficient in the presence of NaI or KBr in acetone. It is worth noting that the chloride **29c** failed to rearrange under these conditions (Scheme 11).[13]

As the ring expansion of C(2)-substituted pyrrolidines is highly stereoselective, enantiopure 3-halopiperidines could be prepared from (*S*)-prolinol. For example, alkylation of (*S*)-prolinol with ethyl iodide gave (*S*)-**8**, which was treated with thionyl chloride in chloroform to give (*S*)-**4**, which rearranged to (*R*)-**10** upon heating. The free base (*R*)-**6** was isolated from the hydrochloride salt after treatment with $NaHCO_3$ (Scheme 12).[7a]



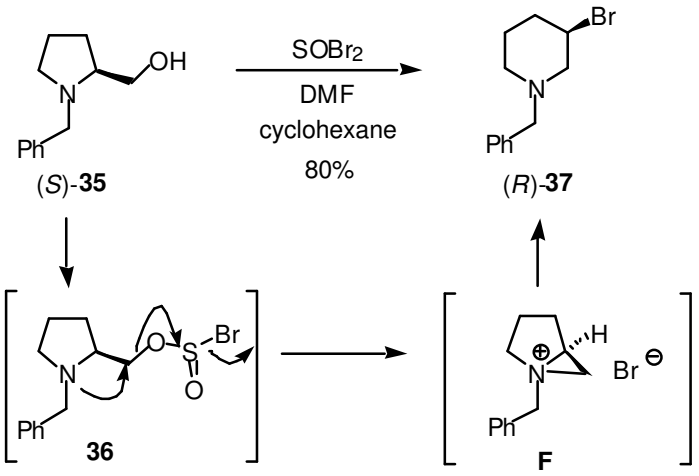
Scheme 12



Scheme 13

This procedure was used to synthesize 3-halogenopiperidines **32** and **34** which are respectively the precursors of cardiovascular compounds[14] and troglitazone analogues[15] (Scheme 13).

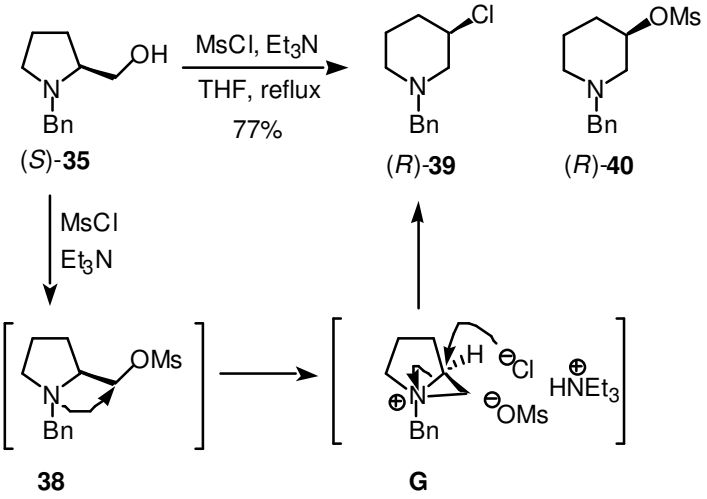
A similar reaction was observed with *N*-benzyl prolinol *(S)*-**35**, which was smoothly converted to 3-bromopiperidine (*R*)-**37** by using thionyl bromide in the presence of DMF. The addition of DMF as a catalyst was found to accelerate significantly the reaction through a Vilsmeier-Haack type $SOBr_2$-DMF complex. Cyclohexane was the solvent of choice to achieve this reaction. On the contrary, polar solvents such as dichloromethane were avoided because undesired side reactions were observed. As usual, the neighbouring amino group facilitates the reaction rate and intermediate **36** was transformed to aziridinium salt **F** to produce (*R*)-**37** (Scheme 14).[16]



Scheme 14

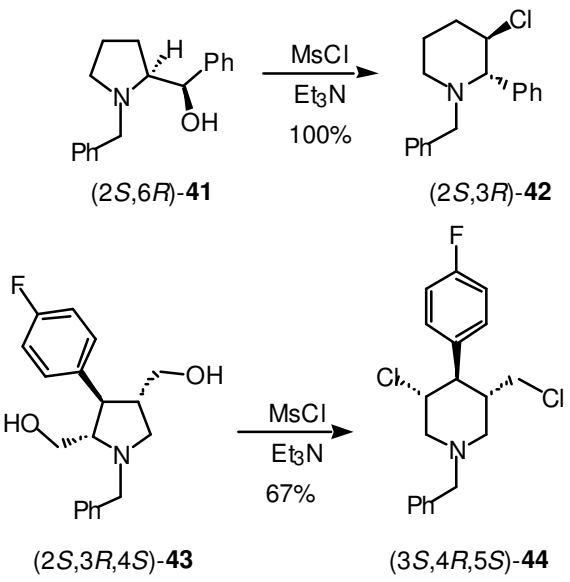
Another reagent that allowed the formation of 3-chloropiperidines from *N*-alkyl prolinols is mesyl chloride in the presence of triethylamine in THF.[17,18]

Thus, treatment of *N*-benzyl prolinol (*S*)-**35** with mesyl chloride in the presence of triethylamine in THF, led to 3-chloropiperidine (*R*)-**39** in 77% yield. Under these conditions, no trace of 3-mesyloxypiperidine (*R*)-**40** was detected. It is postulated that mesylate **38** is formed and that internal assistance of the nitrogen produces the aziridinium salt **G** which was attacked by the more nucleophilic anion present in the reaction medium *e.g.* the chloride anion (*versus* mesylate anion) (Scheme 15).[17]

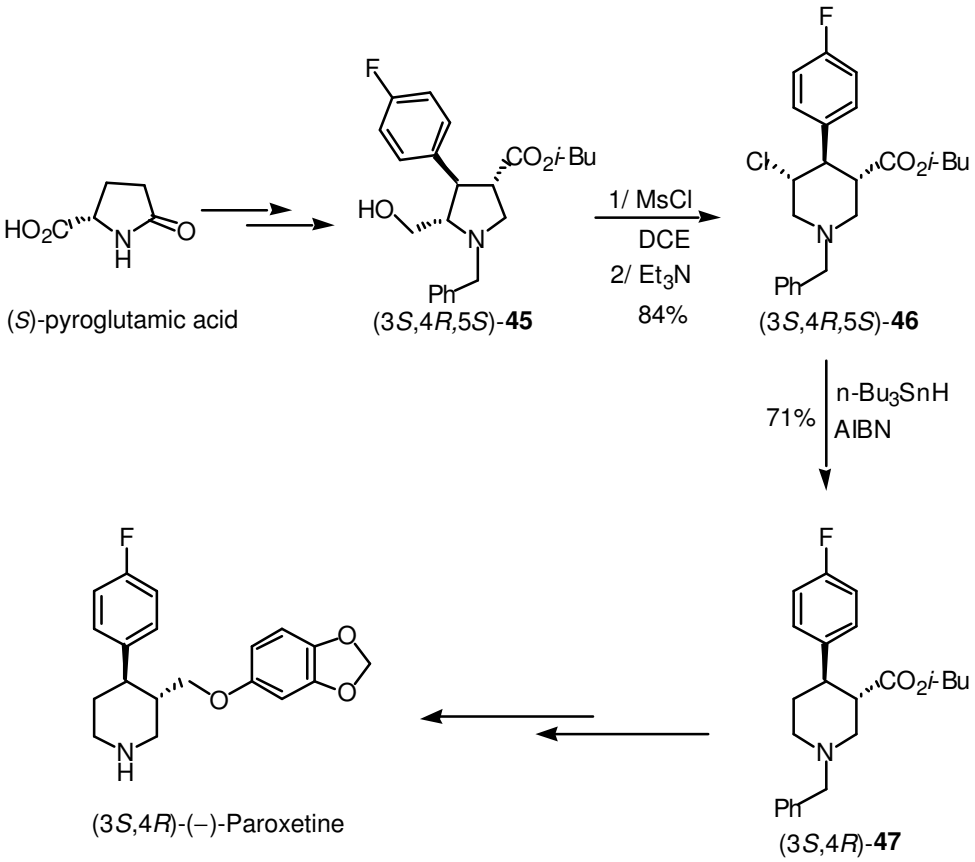


Scheme 15

By using this latter procedure, the enantioselective synthesis of the 2,3-disubstituted piperidine (2*S*,3*R*)-**42** was achieved from prolinol (2*S*,6*R*)-**41** in quantitative yield[18] and the 3,4,5-trisubstituted piperidine **44** was obtained from prolinol **43** in 67% yield[19] (Scheme 16).



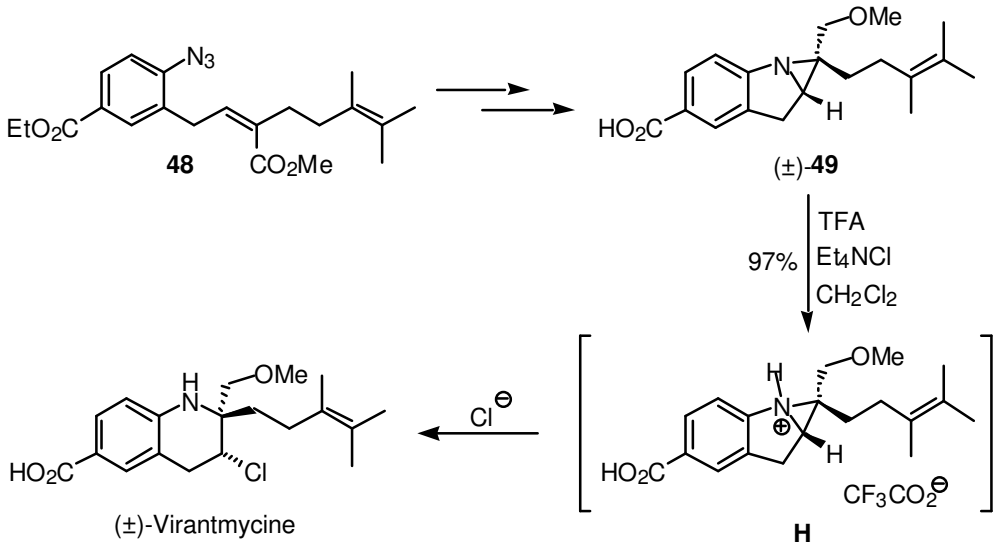
Scheme 16



Scheme 17

This procedure was used to synthesize (–)-paroxetine which is a selective serotonin reuptake inhibitor (SSRI). This drug (Paxil®, Deroxat®) is used in the treatment of depression, obsessive compulsive disorder and panic disorder. The precursor of (–)-paroxetine, 3-chloropiperidine **46** was obtained from prolinol **45** which was synthesized from L-pyroglutamic acid. When the prolinol derivative **45** was treated with MsCl in 1,2-dichloroethane and then refluxed in the presence of Et_3N, 3-chloropiperidine **46** was obtained in 84% yield. After selective reduction of the chloride by Bu_3SnH in the presence of AIBN, the disubstituted piperidine **47** was isolated and transformed to (–)-paroxetine (Scheme 17).[20]

When aziridinium intermediates were treated with tetraalkylammonium halides, they were transformed to 3-halogenopiperidines. The ring opening of 1-aziridinium[3.1.0]hexane intermediate **H** by chloride ion is the key step in the synthesis of (±)-virantmycine, an antibiotic agent. This intermediate was prepared from azide **48** *via* the aziridino carboxylic acid **49**. The racemic aziridine **49** was treated with trifluoroacetic acid in the presence of tetraethylammonium chloride to produce (±)-virantmycine (Scheme 18).[21]

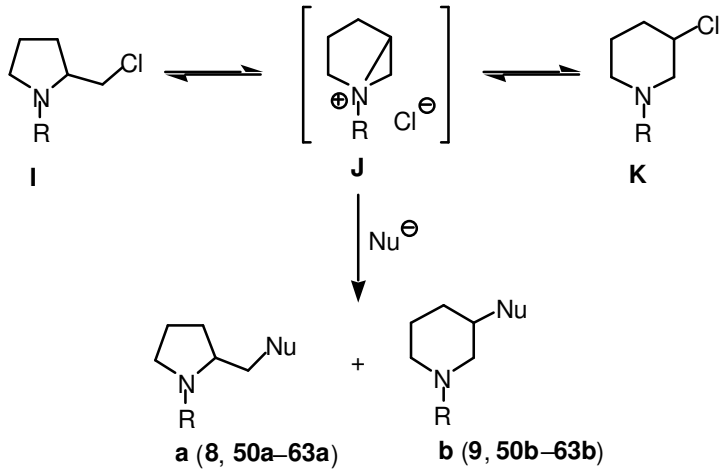


Scheme 18

4. Synthesis of 3-oxygenated and 3-amino-piperidines derivatives

3-Hydroxypiperidine derivatives as well as 3-amino piperidine derivatives are present in a great number of natural products and/or biologically active compounds.[22] The reaction of *N*-alkyl-2-(halogenomethyl)pyrrolidines with amine- or oxygen-nucleophiles should led to 3-aminopiperidine and 3-hydroxypiperidine derivatives *via* an aziridinium intermediates of type **J**. *N*-alkyl-2-(chloromethyl)pyrrolidine of type **I** rearranged so easily to 3-chloropiperidine of type **K** that they could not be isolated and, as previously observed, treatment of **5** or **6** in refluxing aqueous sodium hydroxide gave a mixture of **8** and **9** with a similar ratio of 68/32. These two latter isomers could be distilled without rearrangement and the products were stable under the reaction conditions. Furthermore, the 68/32 ratio of **8/9** is essentially the same as the one obtained from the treatment of aziridinium **B** with NaOH (Scheme 4 and Scheme 19, Table 1, entry 1). As the displacement of the halide by nucleophiles produced the same ratio of pyrrolidine and piperidine by starting either from compound of type **I** or **K**, the studies were conducted on 3-chloropiperidines of type **K**.

The reaction of these 3-chloropiperidines with an excess of amines gave exclusively the corresponding pyrrolidines of type **a** in yields between 35% and 80% (Table 1, entries 2–8). When these 3-chloropiperidines were treated with oxygenated nucleophiles such as alcoholates and carboxylates, a mixture of pyrrolidines of type **a** and piperidines of type **b** were obtained. The ratio of **a** and **b** depends on the reaction conditions (Table 1, entries 9–17). For example, when **6** was treated with potassium acetate in acetic anhydride at 139 °C for 6 h, a mixture of acetates **57a/57b** was obtained in a ratio 17/83. When the reaction was repeated at 90 °C for 8 h, the ratio of **57a/57b** was 75/25 (Table 1, entries 9 and 10). Heating the latter mixture at 106 °C for one day left the ratio unchanged. However elevating the temperature to 126 °C for 6 days resulted in a slow rearrangement of **57a** to **57b**. The preponderance of **57b** in the reaction run at 139 °C is apparently due to the rearrangement of the predominant initial product **57a**.[7a] Compound **8** reacts with refluxing acetic anhydride to give the same product ratio of **57a** and **57b** as found from the reaction of **6** with sodium acetate in refluxing acetic anhydride. No rearrangement was encountered in synthetizing **57b** by refluxing **9** in acetic anhydride.[23] From the above results,[24] it is evident that strong nucleophiles (amines) give mainly 5-membered ring products of type **a**, whereas, weaker nucleophiles ($^{-}$OH and $^{-}$OAc) give a mixture of 5-membered ring products of type **a** and 6-membered ring products of type **b** except when sodium benzylate or sodium phenate were used. In this case, pyrrolidine **59a** (R= Me, Nu= OBn) and piperidine **60b** (R= Me, Nu= OPh) respectively were the only obtained product (Table 1, entries 13 and 14).

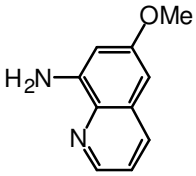
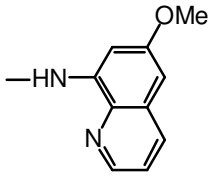
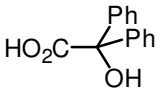
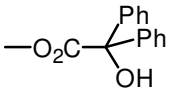
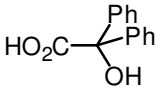
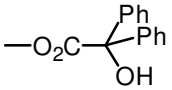
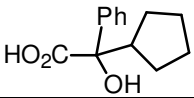
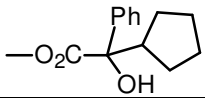


Scheme 19

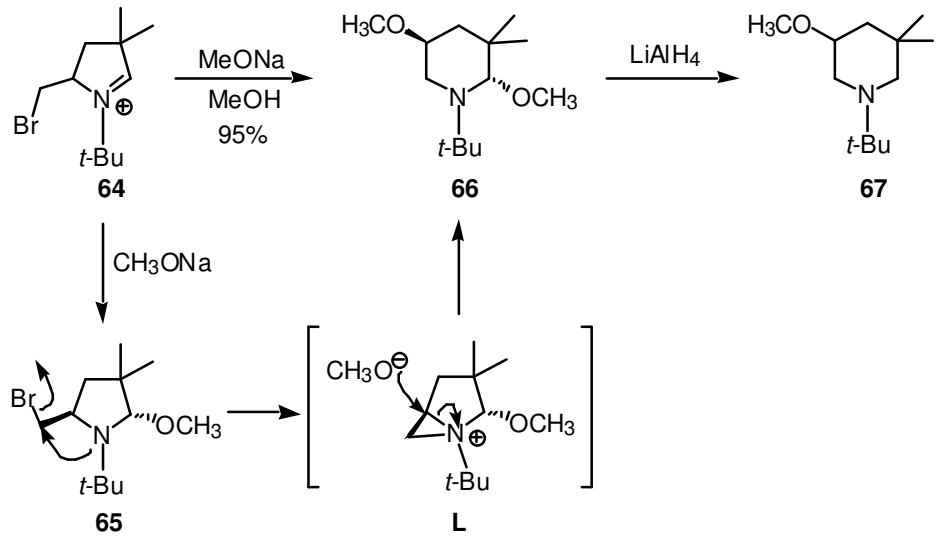
It is worth noting that substituted *N*-alkyl-2-(halogenomethyl)pyrrolidines can be prepared from 5-(halogenomethyl)-1-pyrrolidinium salts and transformed to 3-oxygenated piperidines. When 5-(bromomethyl)-1-pyrrolidinium salt **64** was treated with an excess of sodium methoxide in methanol under reflux, the *N*-*tert*-butyl-2-(bromomethyl)pyrrolidine **65** intermediate rearranged cleanly to one major isomer, presumably the *trans*-dimethoxypiperidine **66** (>95%) *via* the aziridinium salt **L**. After reduction of **66** with $LiAlH_4$, the 3-methoxypiperidine **67** was isolated in good yield (Scheme 20).[32]

The transformation of 2-(halogenomethyl)pyrrolidines to 3-hydroxypiperidines was used to synthesized 14-α-hydroxyvincadifformine and (±)-pseudoconhydrine.

Table 1.

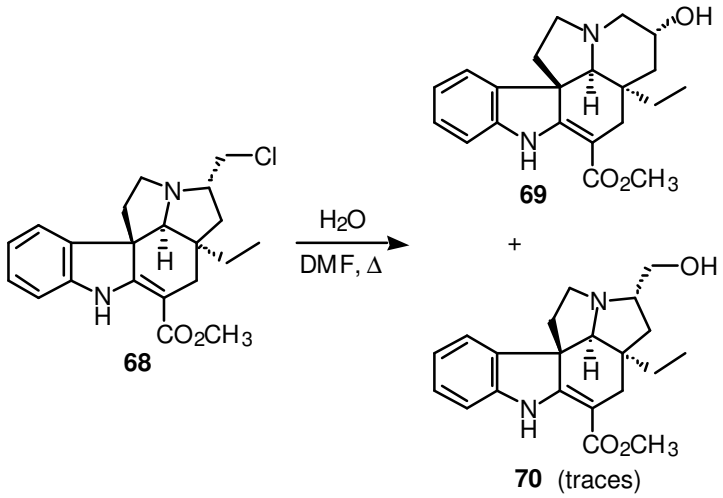
entry	**K** (R=)	Compounds **a / b** (yield, ratio)	Nucleophile	Subst (—Nu)	References
1	Et	**8 / 9** (65%, 68/32)	NaOH	—OH	7a
2	Et	**50a / 50b** (56%, 100/0)	NH_3	—NH_2	25
3	Et	**51a / 51b** (80%, 100/0)	$PhCH_2NH_2$	—$NHCH_2Ph$	7a
4	Me	**52a / 52b** (43%, 100/0)	$PhCH_2NH_2$	—$NHCH_2Ph$	26
5	Et	**53a / 53b** (43%, 100/0)	$(PhCH_2)_2NH$	—$NH(CH_2Ph)_2$	7a
6	Me	**54a / 54b** (68%, 100/0)	NH_2NH_2	—$NHNH_2$	27
7	Me	**55a / 55b** (69%, 100/0)	$NH_2(CH_2)_3N(CH_3)_2$	—$NH(CH_2)_3N(CH_3)_2$	27
8	Et	**56a / 56b** (37%, 100/0)			26
9	Et	**57a / 57b** (66%, 17/83)[a]	KOAc	—OAc	23
10	Et	**57a / 57b** (75/25)[b]	NaOAc	—OAc	7a
11	Me	**57a / 57b** (84%, 75/25)[c]	NaOAc	—OAc	5b
12	Et	**58a / 58b** (67%, 30/70)	NaOEt	—OEt	23
13	Me	**59a / 59b** (53%, 100/0)	NaOBn	—OBn	5b
14	Me	**60a / 60b** (83%, 0/100)	NaOPh	—OPh	28
15	Et	**61a / 61b** (89%, 60/40)			29,30
16	Me	**62a / 62b** (70/30)			5b,31
17	Et	**63a / 63b** (61%, 70/30)			29

[a] The reaction with acetate gave different product ratios, depending on the reaction conditions. Refluxing in acetic anhydride at 139 °C for 6 hr. [b] Heating in acetic anhydride at 90 °C for 8 hr. [c] Refluxing in 2-propanol at 83 °C for 6 hr.



Scheme 20

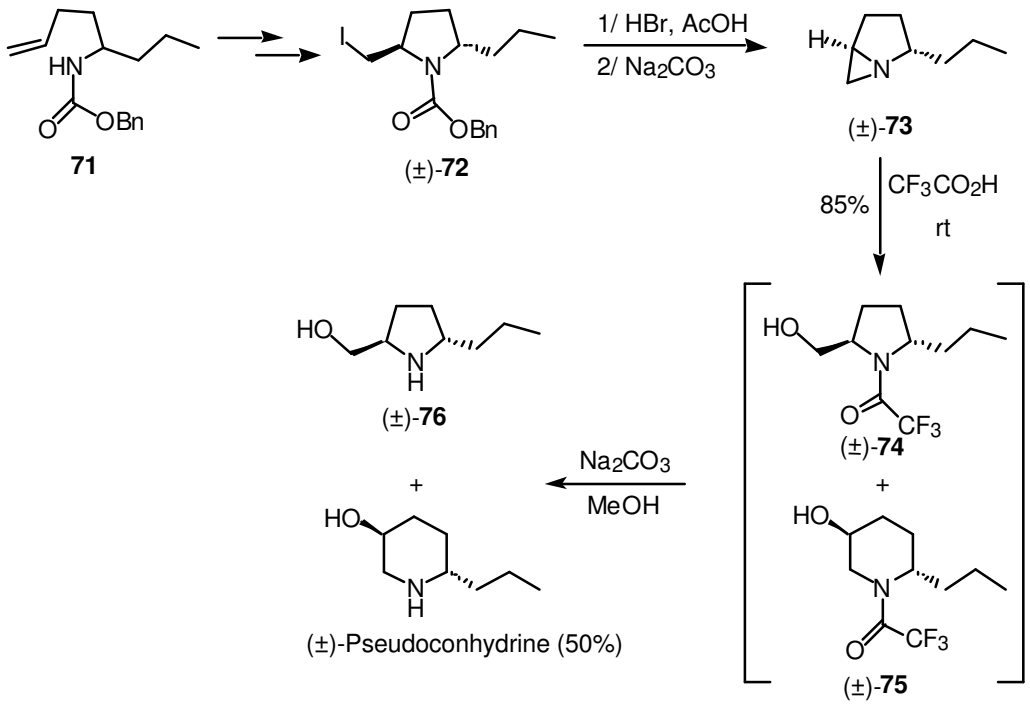
The former was prepared by ring expansion of (chloromethyl)-D-norvincadifformine **68**. When this latter compound was heated in aqueous DMF, 14-α-hydroxyvincadifformine **69** was generated as the major isomer accompanied by traces of **70** (Scheme 21).[33]



Scheme 21

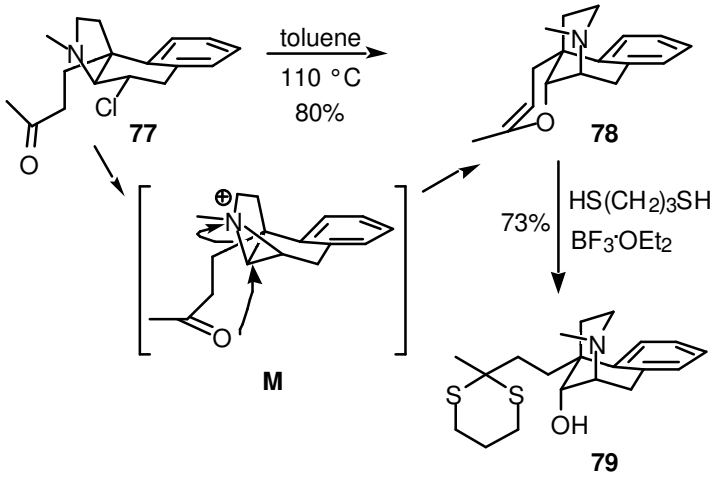
(±)-Pseudoconhydrine was obtained from 2-(iodomethyl)pyrrolidine **72** which was obtained by aminomercuration of the unsaturated carbamate **71**. After treatment of **72** with HBr in acetic acid and then with Na_2CO_3, the bicyclic aziridine **73** was formed and transformed to a mixture of 2-(hydroxymethyl)-pyrroline **74** and 3-hydroxypiperidine **75** by slow addition of trifluoroacetic acid. The major compound, 3-hydroxypiperidine **75** was obtained in 85% yield and, after hydrolysis of the trifluoroacetyl group with Na_2CO_3 in methanol, (±)-pseudoconhydrine was isolated in 50% yield (Scheme 22).[34]

Intramolecular attacks of aziridinium salts by a carbonyl oxygen lone pair have been observed to produce exclusively 3-oxygenated piperidine derivatives. In tuning up new routes to the morphinan ring system, compound **78** has been isolated after thermolysis of **77**.



Scheme 22

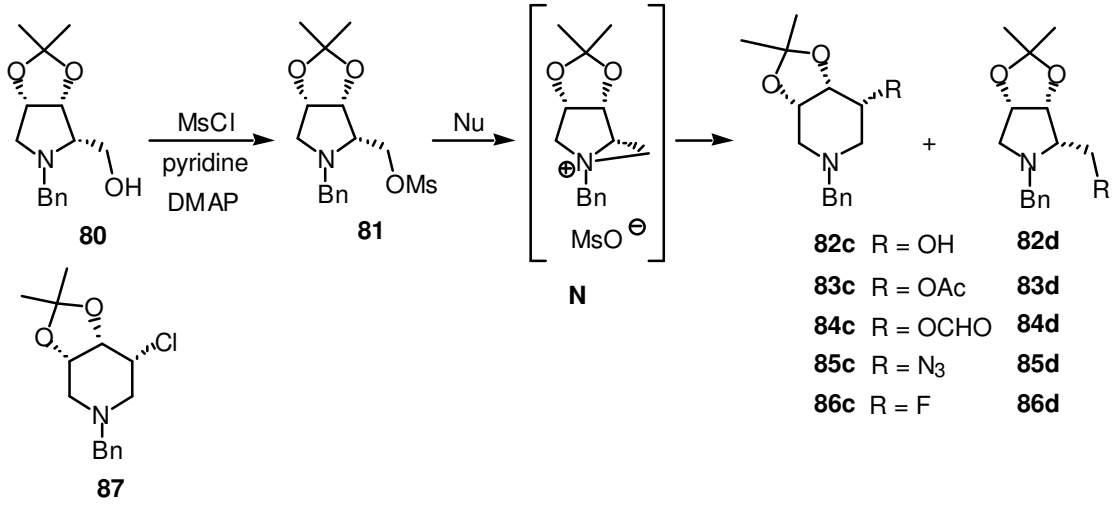
The formation of **78** can be explained by the generation of an aziridinium cation **M** which is then attacked intramolecularly by the oxygen lone pair of the ketone. After treatment of **78** by 1,3-propanethiol in the presence of $BF_3.OEt_2$, tricyclic compound **79** was isolated in 73% yield (Scheme 23).[35]



Scheme 23

2-(Hydroxymethyl)pyrrolidines can also be transformed to 3-hydroxypiperidines and 3-aminopiperidines *via* *N*-alkyl-2-(methanesulfonylmethyl)pyrrolidines. *N*-Alkyl-2-(methanesulfonyl-methyl)pyrrolidines can be prepared under specific conditions and can be used to prepare 3-oxygenated and 3-aminopiperidines. Thus, when substituted (*S*)-prolinol **80** was treated with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine at room temperature for two hours, the mesylate **81** was isolated in 98% yield (Scheme 24). We have to point out that under these conditions, the corresponding 3-chloropiperidine **87** was not detected. The reactivity of the mesylate **81** with

NaOH (3 equiv) in water/dioxane and with AcONa (2 equiv) in DMF, respectively afforded diastereomerically pure substituted piperidines **82c** and **83c** in 52-54% yield along with the pyrrolidine isomers **82d** and **83d** in 26-34% yield. It is worth noting that DMF itself could serve as a nucleophile in this reaction. When mesylate **81** was treated in DMF at 100 °C for five hours, diastereomerically pure products **84c** (38%) and **84d** (50%) were obtained after standard work-up. The formation of **84c** and **84d** further indicates that this reaction must proceed *via* a highly reactive aziridinium intermediate **N** since DMF is much less nucleophilic compared with other nucleophiles. Similar reactions of mesylate **81** with NaN_3 in *N*,*N*-dimethylformamide was observed. When **81** was heated at 100 °C in the presence of NaN_3 for one hour, the diastereomerically pure piperidine **85c** was obtained in 63% yield along with pyrrolidine **85d** in 28% yield. Neither the replacement of NaN_3 with LiN_3 or changes of reaction temperature and reaction time had any effect on the total yield and on the product selectivity (Table 2, entries 4–7). The azide **85c** could be transformed to the corresponding 3-aminopiperidine. Furthermore, treatment of **81** with TBAF in refluxing THF led to **86c** as the major product (54% yield) accompanied by **86d** (26% yield).[36,37]

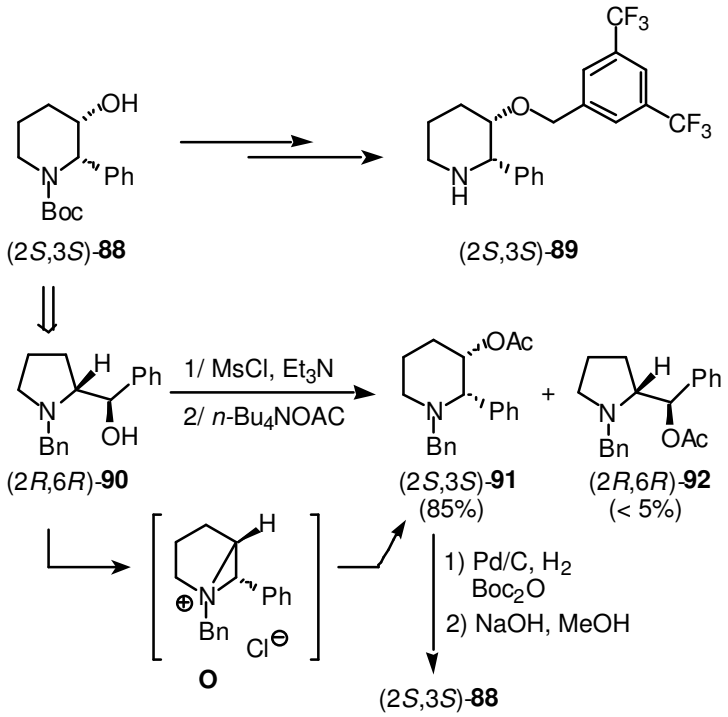


Scheme 24

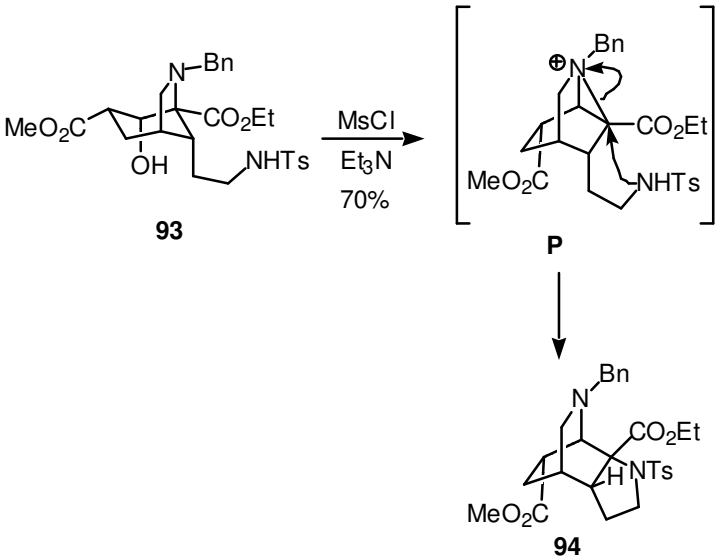
Table 2.

Entry	R	Nucleophile (mol equiv.)	Solvent	Temp. (°C)	Time (h)	Products **c/d** (% yield)
1	OH	NaOH (3.0)	H_2O–1,4-dioxane	reflux	0.5	**82c** (54)/ **82d** (26)
2	OAc	NaOAc (2.0)	DMF	100	5	**83c** (52)/ **83d** (34)
3	OCHO	DMF	DMF	100	0,5	**84c** (38)/ **84d** (50)
4	N_3	NaN_3 (1.1)	DMF	100	1	**85c** (63)/ **85d** (28)
5	N_3	LiN_3 (1.1)	DMF	100	1	**85c** (61)/ **85d** (29)
6	N_3	NaN_3 (1.1)	DMF	60	15	**85c** (64)/ **85d** (24)
7	N_3	LiN_3 (1.1)	DMF	60	15	**85c** (65)/ **85d** (25)
8	F	TBAF (3.0)	THF	reflux	5	**86c** (54)/ **86d** (26)

The precursor of the neuropeptide substance-P (neurokinin-1) receptor antagonist **89** has been prepared *via* the piperidine intermediate (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **88**. Piperidine **88** was obtained easily from prolinol **90** by treatment with MsCl in the presence of Et_3N, to produce the aziridinium intermediate **O** which was subsequently treated with tetra-*n*-butylammonium acetate (4.5 equiv) to afford the desired acetoxypiperidine **91** in 85% yield and 99% ee.



Scheme 25



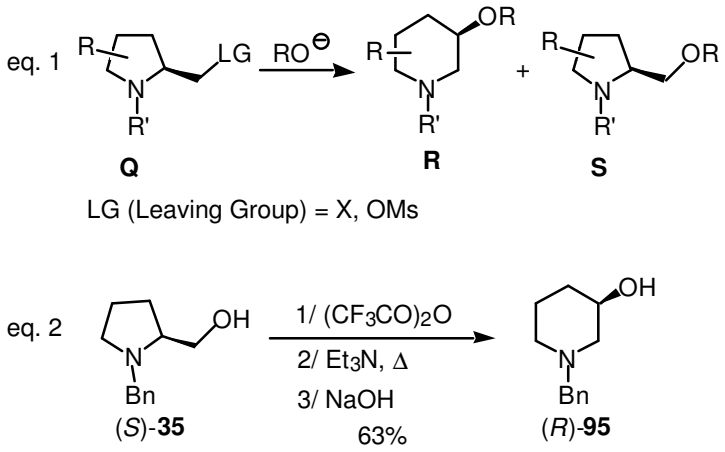
Scheme 26

Interestingly, only a small amount of the isomeric pyrrolidinyl acetate **92** (~ 5%) was detected in the crude reaction mixture. For obtaining **88**, the next step involved a selective *N*-debenzylation/Boc protection

using Pd/C, H_2 in the presence of Boc_2O followed by the hydrolysis of the acetyl group using NaOH in methanol (Scheme 25).[38]

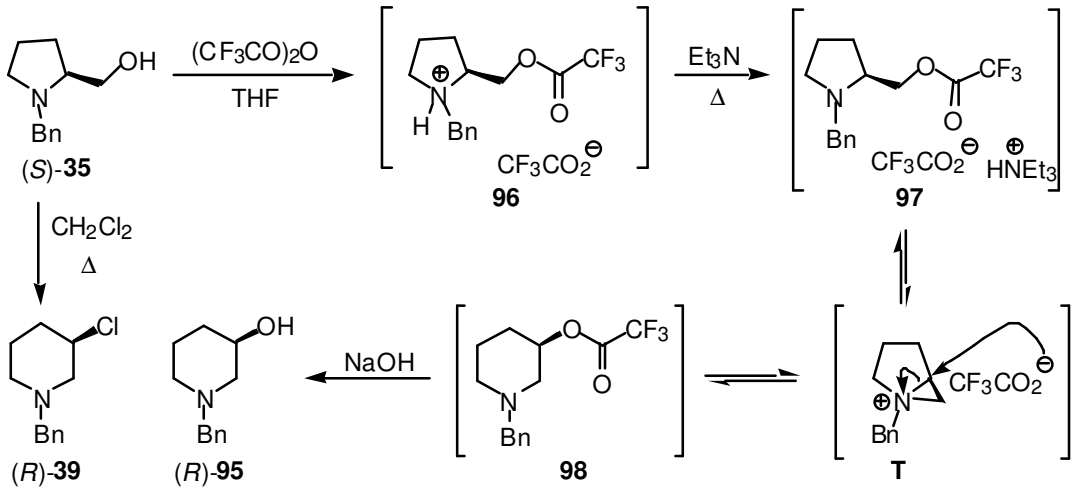
An intramolecular trapping of the aziridinium salt by an amino group can lead to the total conversion of a 2-(hydroxymethyl)pyrrolidine to a 3-aminopiperidine. When the bicyclo[3.2.1]octane **93** was treated with $MsCl/Et_3N$, aziridinium salt **P** was formed and was attacked intramolecularly by the sulfonamido group to produce the bicyclo[2.2.1]octane compound **94** (Scheme 26).[39]

As it was noticed previously, intermolecular attack of pyrrolidines of type **Q** by oxygenated nucleophiles ($^-$OH, $^-$OAc, $^-$OR) produced a mixture of 3-oxygenated piperidines of type **R** and pyrrolidines of type **S** (Scheme 27, eq. 1). In contrast, when prolinol (*S*)-**35** was treated with trifluoroacetic anhydride (TFAA), then with triethylamine in THF, followed by NaOH the corresponding 3-hydroxypiperidine (*R*)-**95** was the only isolated product (Scheme 27, eq. 2).[40]



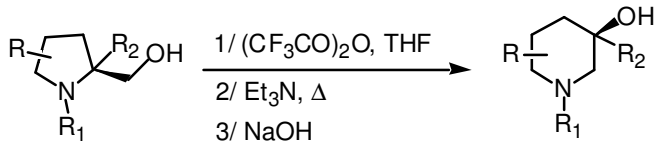
Scheme 27

The enantiomeric excess of (*R*)-**95** was determined to be superior to 95%. The ring expansion of (*S*)-**35** did not proceed in solvents such as toluene or hexane. In CH_2Cl_2 at reflux, the only product formed was the 3-chloropiperidine (*R*)-**39**.



Scheme 28

The first step in the formation of 3-hydroxypiperidine (*R*)-**95** from 2-(hydroxymethyl)pyrrolidine (*S*)-**35** involves esterification of the hydroxy group by trifluoroacetic anhydride and formation of the corresponding quaternary ammonium salt **96**. In the absence of triethylamine, no rearrangement was observed. The addition of Et_3N produced the aminoester **97** which underwent a S_Ni process to give a tight ion-pair **T** that reacted to generate the stable ester **98**. Finally saponification of ester **98** by NaOH (2.5 M) afforded the 3-hydroxypiperidine (*R*)-**95** (Scheme 28).[17,40]



Scheme 29

Table 3. Formation of 3-hydroxypiperidine from pyrrolidine-methanol derivatives

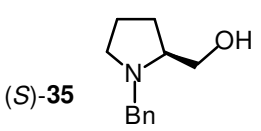
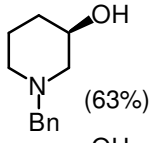
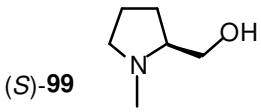
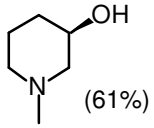
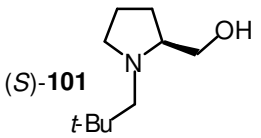
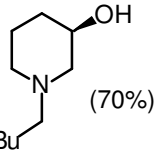
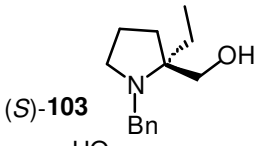
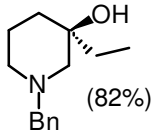
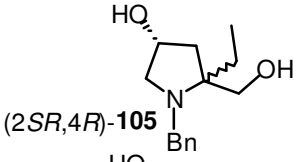
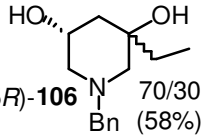
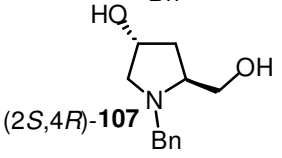
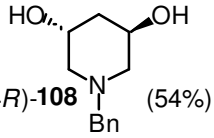
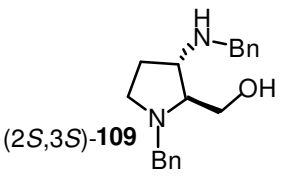
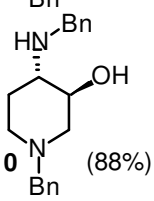
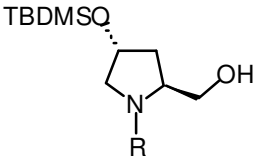
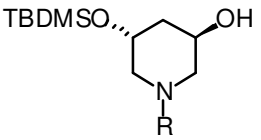
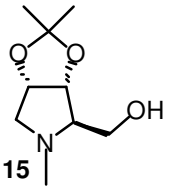
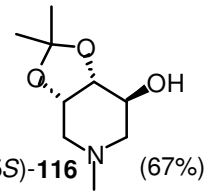
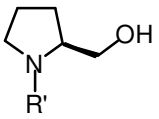
starting material	product (yield)	ref.
 (*S*)-**35**	 (*R*)-**95** (63%)	17,40
 (*S*)-**99**	 (*R*)-**100** (61%)	17
 (*S*)-**101**	 (*R*)-**102** (70%)	17,40
 (*S*)-**103**	 (*R*)-**104** (82%)	40
 (2*SR*,4*R*)-**105**	 (3*SR*,5*R*)-**106** 70/30 (58%)	17
 (2*S*,4*R*)-**107**	 (3*R*,4*R*)-**108** (54%)	17
 (2*S*,3*S*)-**109**	 (3*S*,4*S*)-**110** (88%)	41

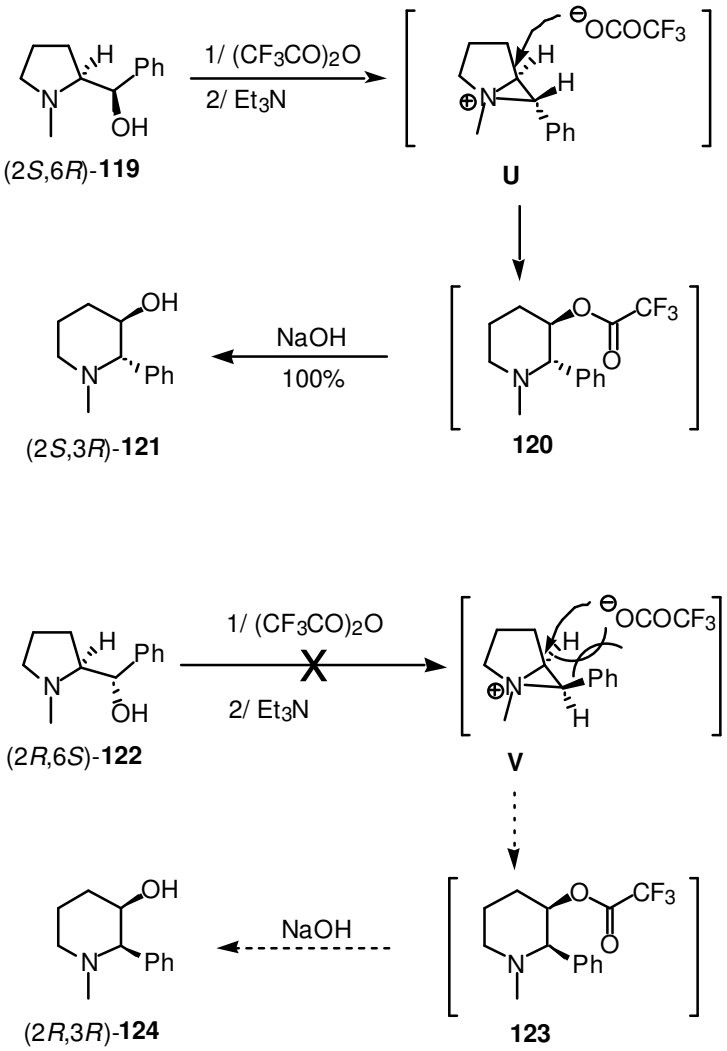
Table 3 (continuation). Formation of 3-hydroxypiperidine from pyrrolidine-methanol derivatives

starting material	product (yield)	ref.
		
(2*S*,4*R*)-**111** R = Bn	(3*R*,5*R*)-**112** R = Bn (65%)	17
(2*S*,4*R*)-**113** R = PMB	(3*R*,5*R*)-**114** R = PMB (100%)	42
 (2*R*,3*R*,4*S*)-**115**	 (3*S*,4*R*,5*S*)-**116** (67%)	17
 (*S*)-**117** R' = H	—	17
(*S*)-**118** R' = p-NO_2Ph	—	17

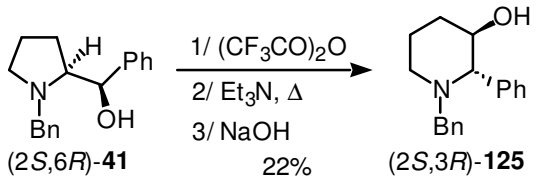
The ring expansion of *N*-alkylated prolinols appears to be general (Scheme 29) and highly stereoselective as shown in Table 3, except for (*S*)-prolinol **117** and for the *N*-(4-nitrophenyl) derivatives (*S*)-**118**. In these two cases, the ring expansion products were not detected. The nucleophilicity of the amino moiety of the prolinol derivative has to be high enough for the rearrangement to occur. We note that acid sensitive hydroxy protecting groups (compounds **111**, **113**, **115**) were tolerated under these conditions. The (4*R*)-hydroxyprolinol derivative **107** was isomerized smoothly into a single diastereomeric diol **108** with a yield of 54%. The $[\alpha]_D^{20}$ value [$(\alpha)_D$= + 151] of this compound is consistent with the (3*R*,5*R*) configuration in **108** and strongly supports the mechanism of Scheme 26, (2 eq.) (inversion of configuration during the nucleophilic attack at C(2) of aziridinium intermediate **T**).

2-(Hydroxymethyl)pyrrolidine derivatives with secondary alcohols were also submitted to this rearrangement. 2-(Hydroxymethyl)pyrrolidine **119** was transformed to substituted piperidinol **121** in 100% yield, with an enantiomeric excess of 95%. In contrast, the diastereomer **122** was not reactive under the same conditions (Scheme 30). The non-reactivity of **122** can be attributed to a gauche effect (steric interactions) between the phenyl and the C(2)-C(3) bond in the aziridinium ion intermediate **V**. In contrast, 2-(hydroxymethyl)pyrrolidine **119** was transformed to piperidinol **121**, as no serious steric repulsions were developed during the formation of the aziridinium intermediate **U**, the phenyl group and the C(2)-C(3) bond being antiperiplanar (Scheme 30). This interpretation implies that the amino moiety participates (anchimeric effect) in the heterolysis of the trifluoroacetate intermediate generated by esterification of the benzyl alcohol **119** (Scheme 30).[17]

The *N*-benzyl-2-(hydroxymethyl)pyrrolidine **41** was also studied in the aim of synthesizing the neuropeptide substance-P (neurokinin-1) receptor antagonist **88** (Scheme 25). However, the yield in the ring expansion **125** is not as high as for the transformation of **90** to **91** (Scheme 31 and Scheme 25).[18]



Scheme 30

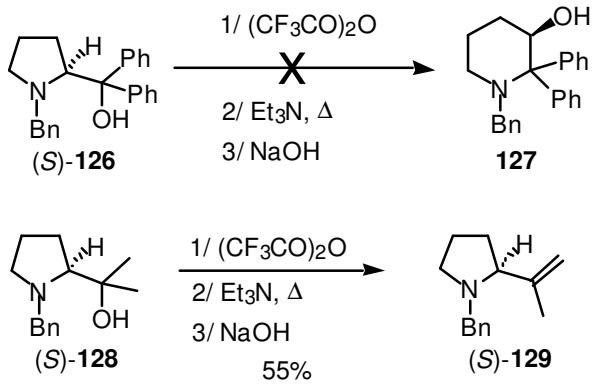


Scheme 31

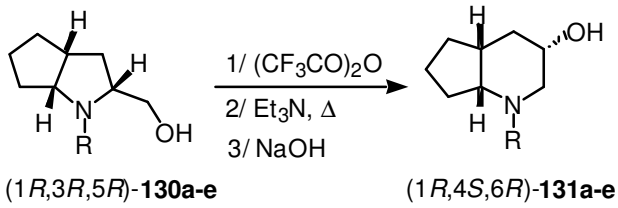
Treatment of 2-(hydroxymethyl)pyrrolidine derivatives **126** and **128**, did not lead to the ring expansion products under the TFAA conditions as **126** was recovered, whereas **128** underwent dehydration to produce alkene **129** (55% yield) (Scheme 32).[17] These results are consistent with the fact that **126** and **128** can generate ion-pairs without the participation of the amino moiety, giving stable tertiary carbocation intermediates.

A ring expansion of pyrrolidine to piperidine was used for the diastereoselective synthesis of azabicyclo[4.3.0]nonane systems. Treatment of the bicyclic 2-(hydroxymethyl)pyrrolidine derivative **130** with trifluoroacetic anhydride in THF followed by addition of Et_3N led, after hydrolytic work-up with NaOH, to the formation of **131** which corresponds to the ring expanded product with a diastereomeric ratio

>95/5. The formation of bicyclic 3-hydroxypiperidines **131a-e** from 2-(hydroxymethyl)pyrrolidine derivatives **130a-e** is general and does not depend on the *N*-alkyl group (Scheme 33, Table 4).[43]



Scheme 32



Scheme 33

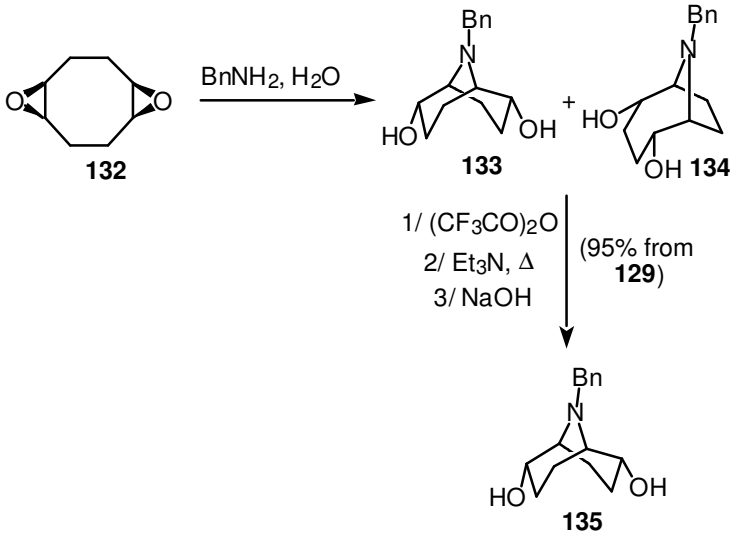
Table 4.

Entry	Product	R	Yield (%)
1	**131a**	$CH_2C_6H_5$	41
2	**131b**	CH_3	41
3	**131c**	CH_2CH_3	43
4	**131d**	$CH_2(CH_3)_3$	66
5	**131e**	$CH_2CH_2C_6H_5$	36

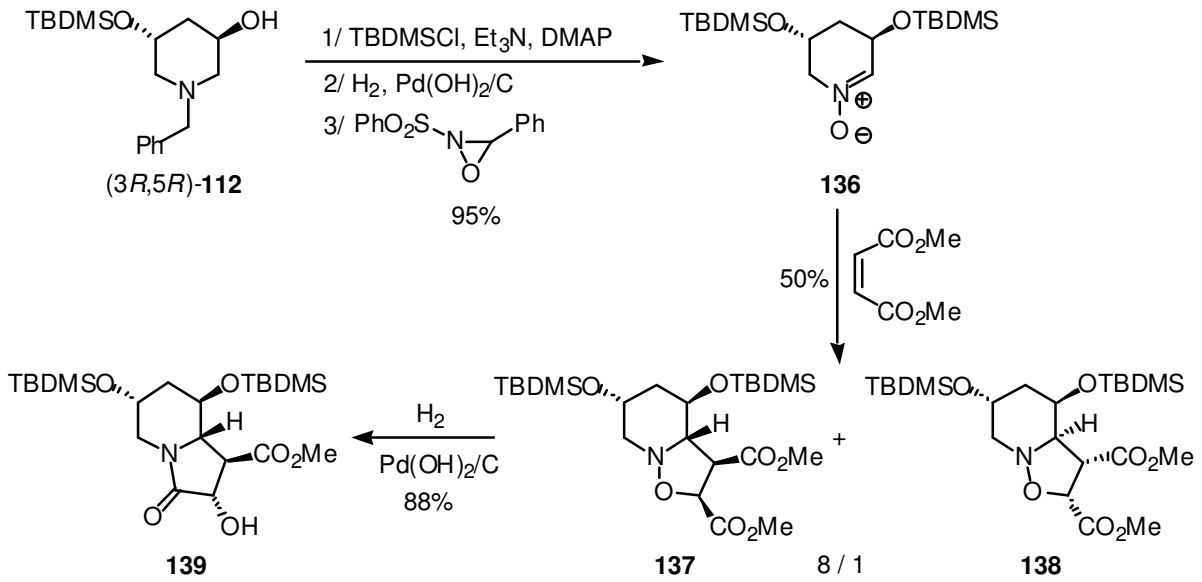
The TFAA/Et_3N/NaOH procedure was also applied to the synthesis of 2,6-dihydroxy-9-azabicyclo[3.3.1]nonane **135** (Scheme 34).[44]

The ring expansion of prolinols induced by TFAA allowed the synthesis of polyhydroxyindolizidinones. For example, 3,5-dihydroxypiperidine (3*R*,5*R*)-**112**, obtained from prolinol (3*S*,4*R*)-**111** was transformed to nitrone **136** which, after treatment with dimethyl maleate, led to two diastereomeric adducts **137** and **138** in a ratio 8/1. Reductive cleavage of the N–O bond afforded polyhydroxyindolizidinone **139** in 88% yield (Scheme 35).[45]

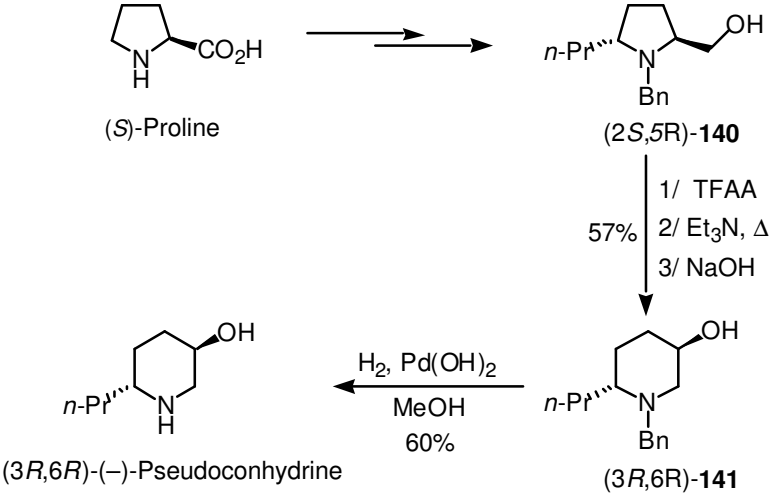
Substituted 3-hydroxypiperidines which are present in natural products and/or biologically active compounds such as (–)-pseudoconhydrine, (–)-velbanamine or (+)-zamifenacin can be prepared from ring expansion of optically active prolinols.



Scheme 34

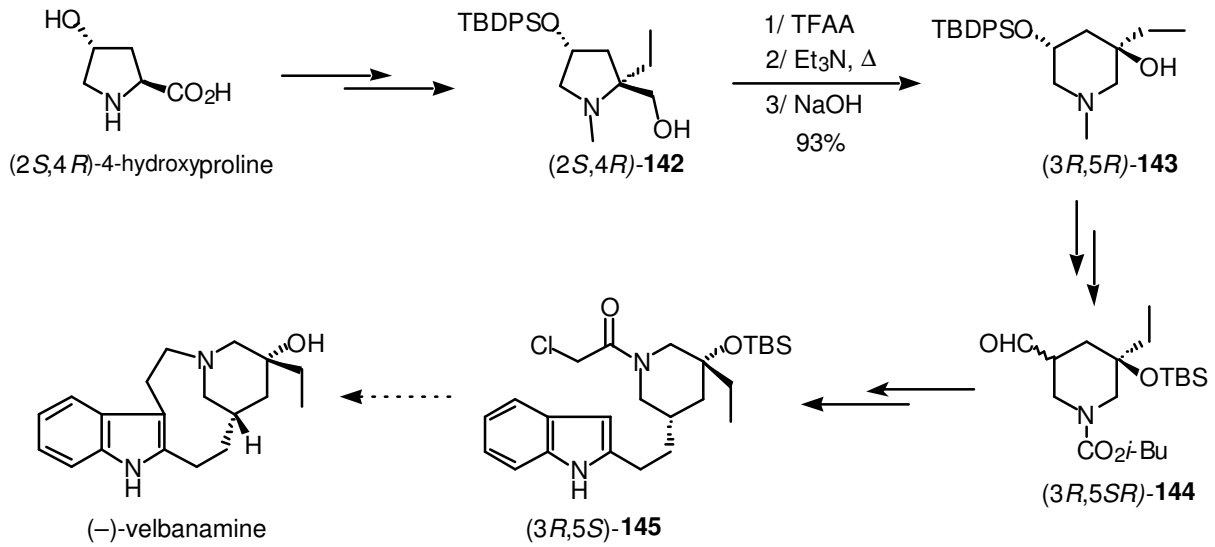


Scheme 35

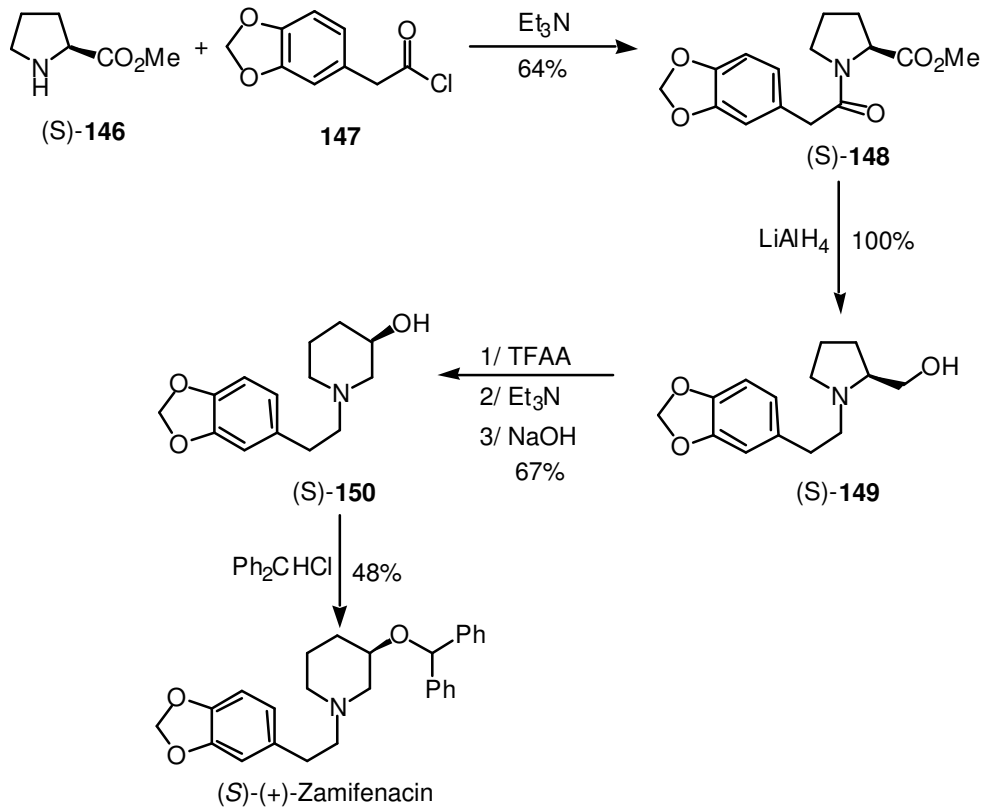


Scheme 36

(L)-Proline was transformed in 6 steps to 2,5-disubstituted prolinol **140**. After treatment of **140** with TFAA, with Et_3N and then with NaOH, 3-hydroxypiperidine **141** was obtained and transformed to (–)-pseudoconhydrine after hydrogenation (Scheme 36).[46]



Scheme 37



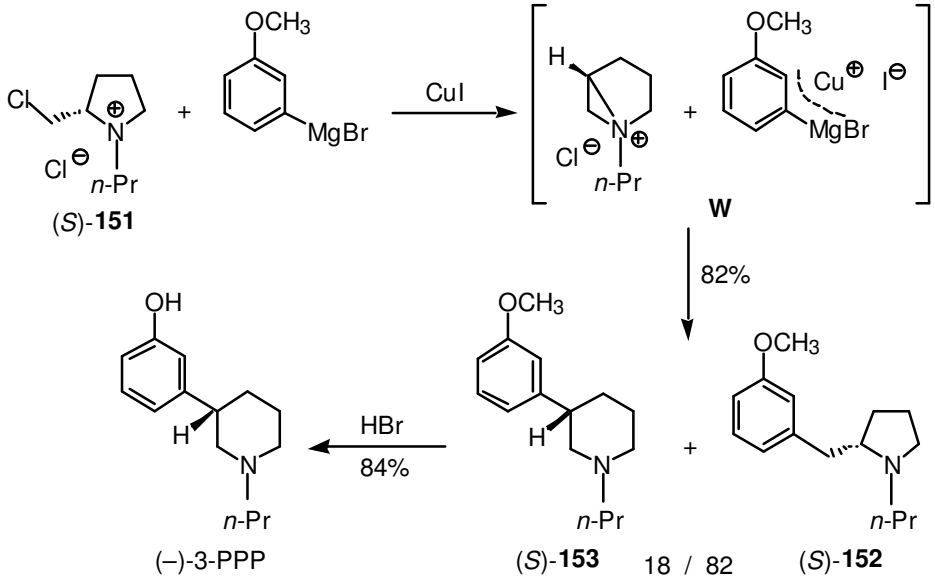
Scheme 38

Ring expansion of the trisubstituted prolinol **142** by the TFAA/Et_3N/NaOH procedure, led to the trisubstituted piperidin-3-ol **143** in 93% yield. This intermediate was transformed to the indole compound **145** than can be used to achieve the synthesis of (–)-velbanamine (Scheme 37).[47]

The selective muscarinic M_3 antagonist, (+)-zamifenacin has been obtained with high enantiomeric excess by ring enlargement of prolinol **149** by the TFAA/Et_3N/NaOH ring expansion method. By this method, (+)-zamifenacin was synthetized in four steps from the (L)-proline methyl ester **146** (Scheme 38).[48]

5. Synthesis of C(3)-alkylated piperidine derivatives

Aziridinium ions can be opened by cuprates. For example, aziridinium intermediate **W** was formed from the hydrochloride **151** by using one mole of 3-methoxyphenylmagnesium bromide as a base. Addition of another mole of Grignard reagent gave no coupling products. However, by adding a catalytic amount of cuprous cyanide or cuprous iodide to the reaction mixture, the nucleophilic attack on the aziridinium intermediate was successfully initiated and the pyrrolidine derivative **152** as well as the piperidine compound **153** were obtained in a ratio 82/12 respectively (82% yield). Demethylation of **153** by using HBr gave **(–)-3-PPP** in 84% yield. This compound is a selective dopamine (DA) autoreceptor agonist devoid of any appreciable postsynaptic DA-mimetic activity (Scheme 39).[49]

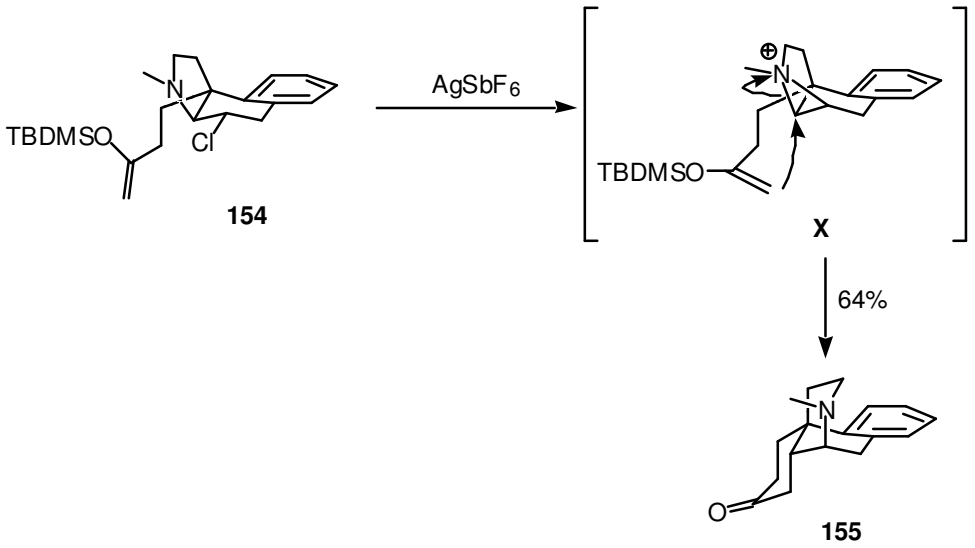


Scheme 39

In contrast, the intramolecular attack on an aziridinium cation, which comes from a 2-(chloromethyl)pyrrolidine, by an internal carbon nucleophile allowed the formation of C(3) alkylated piperidines. In an approach to the morphinan ring system, compound **154** was transformed to **155** by treatment with $AgSbF_6$. This product arises through intramolecular attack by the silyl enol ether on the aziridinium intermediate **X** (Scheme 40).[35]

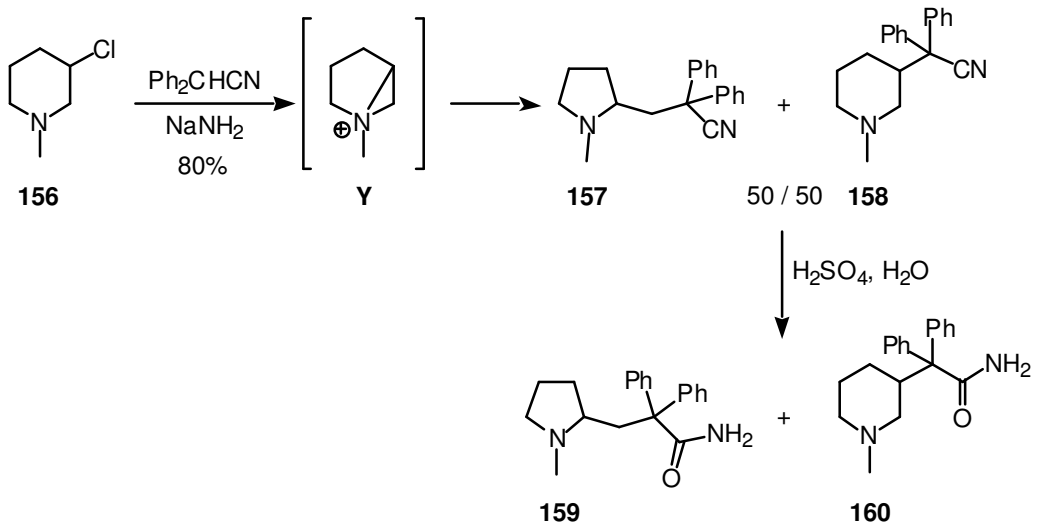
Alkylation at the C3 position of the piperidine ring was achieved from a 3-chloropiperidine. When diphenylacetonitrile was allowed to react with *N*-methyl-3-chloropiperidine **156** in the presence of sodium amide and toluene, compounds **157** and **158** were obtained, *via* aziridinium **Y**, in 80% yield in a ratio 1 to 1. After hydrolysis with 90% sulphuric acid, the corresponding diphenylacetamides **159** and **160** were separated (Scheme 41).[50]

It should be pointed out that upon treatment of *N*-ethyl-3-chloropiperidine with NaCN, the only isolated product was the 2-(cyanomethyl)pyrrolidine.[7a]



154 X 155

Scheme 40



156 Y 157 50 / 50 158 159 160

Scheme 41

6. Conclusions

In summary, ring expansion reactions (RER) of 2-(halomethyl)pyrrolidines and 2-(hydroxymethyl)pyrrolidines to form substituted piperidines are highly stereo- and enantioselective and can be used to synthetize a great diversity of substrates for obtaining biologically active compounds in a very efficient way. In the future, it will be of great interest to further extend ring expansions of 2-(halomethyl)- and 2-(hydroxymethyl)pyrrolidine by using carbanions as nucleophiles.

Acknowledgements

We sincerely acknowledge Ph. D. students, C. Dumas, O. Mirguet, P. Michel, and B. Burger for their fruitful efforts in this area. Financial support for our research program by the Ville de Paris, the CNRS, and Rhodia is gratefully acknowledged. We thank also the MRET for a grant to O. M.

References

1. (a) Harrison, T. *Contemp. Org. Synth.* **1996**, *3*, 259; (b) Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Proced. Int.* **1996**, *28*, 501; (c) Enders, D.; Bettray, W. *Pure Appl. Chem.* **1996**, *68*, 569; (d) Wanner, M. J.; Koomen, G. J. *Pure Appl. Chem.* **1996**, *68*, 2051; (e) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023; (f) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637; (g) De Raadt, A.; Ekhart. C. W.; Ebner, M.; Stutz, A. E. *Top. Curr. Chem.* **1997**, *187*, 157; (h) Holmes, A. B.; Bourdin, B.; Collins, I.; Davison, E. C.; Rudge, A. J.; Stork, T. C.; Warner, J. A. *Pure Appl. Chem.* **1997**, *69*, 531; (i) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 287; (j) Gawley, R. E. *Curr. Org. Chem.* **1997**, *1*, 71; (k) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633; (l) Kazmaier, U. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 351; (m) Depezay, J.-C. *Carbohydr. Mimics* **1998**, 307; (n) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (o) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493; (p) Schneider, C.; Börner, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1999**, 3353; (q) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435; (r) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862; (s) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.
2. (a) Schultz, E. M.; Robb, C. M.; Sprague, J. M. *J. Am. Chem. Soc.* **1947**, *69*, 188; (b) Schultz, E. M.; Robb, C. M.; Sprague, J. M. *J. Am. Chem. Soc.* **1947**, *69*, 2454; (c) Ross, S. D. *J. Am. Chem. Soc.* **1947**, *69*, 2982.
3. (a) Brode, W. R.; Hill, M. W. *J. Am. Chem. Soc.* **1947**, *69*, 724; (b) Kerwin, J. F.; Ullyot, G. E.; Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1947**, *69*, 2961; (c) Schultz, E. M.; Sprague, J. M. *J. Am. Chem. Soc.* **1948**, *70*, 48.
4. (a) Golumbic, C.; Fruton, J. S.; Bergmann, M. *J. Org. Chem.* **1946**, *11*, 518; (b) Golumbic, C.; Bergmann, M. *J. Org. Chem.* **1946**, *11*, 536; (c) Fruton, J. S.; Bergmann, M. *J. Org. Chem.* **1946**, *11*, 543; (d) Golumbic, C.; Stahmann, M. A.; Bergmann, M. *J. Org. Chem.* **1946**, *11*, 550; (e) Bartlett, P. D.; Ross, S. D.; Swain, C. G. *J. Am. Chem. Soc.* **1947**, *69*, 2971; (f) Bartlett, P. D.; Davis, J. W.; Ross, S. D.; Swain, C. G. *J. Am. Chem. Soc.* **1947**, *69*, 2977; (g) Cohen, B.; Van Artsdalen, E. R.; Harris, J. *J. Am. Chem. Soc.* **1948**, *70*, 281.
5. (a) Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1948**, *70*, 2760; (b) Brain, E. G.; Doyle, F. P.; Mehta, M. D. *J. Chem. Soc.* **1961**, 633.
6. Hammer, C. F.; Heller, S. R. *J. Chem. Soc., Chem. Commun.* **1966**, 919.
7. (a) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239; (b) Hammer, C. F.; McCarthy Ali, M.; Weber, J. D. *Tetrahedron* **1973**, *29*, 1767; (c) Hammer, C. F.; Weber, J. D. *Tetrahedron* **1981**, *37*, 2173.
8. (a) Surzur, J.-M.; Stella, L.; Tordo, P. *Bull. Chem. Soc. Chim. Fr.* **1970**, 115; (b) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337; (c) Hemmerling, M.; Sjöholm, Å.; Somfai, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4091; (d) Göttlich, R. *Synthesis* **2000**, 1561; (e) Göttlich, R.; Noack, M. *Tetrahedron Lett.* **2001**, *42*, 7771; (f) Sjöholm, Å.; Hemmerling, M.; Pradeille, N.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 891; (g) Heuger, G.; Kalsow, S.; Göttlich, R. *Eur. J. Org. Chem.* **2002**, 1848; (h) Helaja, J.; Göttlich, R. *J. Chem. Soc., Chem. Commun.* **2002**, 720; (i) Noack, M.; Göttlich, R. *Eur. J. Org. Chem.* **2002**, 3171.
9. Horning, D. E.; Muchowski, J. M. *Can. J. Chem.* **1974**, *52*, 1321.
10. Williams, D. R.; Osterhout, M. H.; McGill, J. M. *Tetrahedron Lett.* **1989**, *30*, 1331.
11. (a) Abbaspour Tehrani, K.; Van Syngel, K.; Boelens, M.; Contreras, J.; De Kimpe, N.; Knight, D. W. *Tetrahedron Lett.* **2000**, *41*, 2507; (b) Rosas Alonso, E.; Abbaspour Tehrani, K.; Boelens, M.; Knight, D. W.; Valentina, Y.; De Kimpe, N. *Tetrahedron Lett.* **2001**, *42*, 3921.
12. (a) Miyano, S.; Mibu, N.; Irie, M.; Fujii, S.; Fujisaki, F.; Abe, N.; Sumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 313; (b) Miyano, S.; Irie, M.; Mibu, N.; Miyamoto, Y.; Nagata, K.; Sumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1057.
13. Blough, B. E.; Mascarella, S. W.; Rothman, R. B.; Carroll, F. I. *J. Chem. Soc., Chem. Commun.* **1993**, 758.
14. Carlier, P.; Simon, J. A. L.; Monteil, A. J.-C. FR 2608602 A1, 1988; *Chem. Abstr.* **1989**, *110*, 57525.
15. (a) Anji Reddy K.; Lohray, B. B.; Bhushan, V.; Bajji, A. C.; Vivekananda Reddy, K.; Rajamohan Reddy, P.; Hari Krishna, T.; Nageswara Rao, I.; Kumar Japoo, H.; Mamidi Rao, N. V. S.; Chakrabarti, R.; Dileepkumar, T.; Rajagopalan, R. *J. Med. Chem.* **1999**, *42*, 1927; (b) Anji Reddy K.; Lohray, B. B.;

Bhushan, V.; Sekar Reddy, A.; Rao Mamidi, N. V. S.; Papi Reddy, P.; Saibaba, V.; Jaipal Reddy, N.; Suryaprakash, A.; Misra, P.; Vikramadithyan, R. K.; Rajagopalan, R. *J. Med. Chem.* **1999**, *42*, 3265.
16. Nagle, A. S.; Salvatore, R. N.; Chong, B.-D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011.
17. Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693.
18. Calvez, O.; Chiaroni, A.; Langlois, N. *Tetrahedron Lett.* **1998**, *39*, 9447.
19. Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *Eur. J. Org. Chem.* **2002**, 3543.
20. Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, *42*, 5705.
21. (a) Morimoto, Y.; Matsuda, F.; Shirahama, H. *Tetrahedron* **1996**, *52*, 10609; (b) Morimoto, Y.; Shirahama, H. *Tetrahedron* **1996**, *52*, 10631.
22. (a) Rubiralta, M.; Giralt, E.; Diez, A., in *Piperidines. Structure, Preparation, Reactivity, and Synthetic applications of Piperidines and its Derivatives*; Elsevier Ed.; Amsterdam, 1991; (b) Watson, P.S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
23. Paul, R.; Tchelitcheff, S. *Bull. Chem. Soc. Chim. Fr.* **1958**, 736.
24. For related ring expansion from other substrates see: Moragues, J.; Prieto, J.; Spickett, R. G. W.; Vega, A., *J. Chem. Soc., Perkin Trans. 1* **1976**, 938.
25. Shen, T. Y.; Rogers, E. F.; Sarett, L. H. US 3031452, 1962; *Chem. Abstr.* **1962**, *57*, 49261.
26. Reitsema, R. H. *J. Am. Chem. Soc.* **1949**, *71*, 2041.
27. Biel, J. H.; Hoya, W. K.; Leiser, H. A. *J. Am. Chem. Soc.* **1959**, *81*, 2527.
28. Biel, J. H. US 2831862, 1958; *Chem. Abstr.* **1958**, *52*, 98039.
29. Biel, J. H.; Abood, L. G.; Hoya, W. K.; Leiser, H. A.; Nuhfer, P. A.; Kluchesky, E. F. *J. Org. Chem.* **1961**, *26*, 4096.
30. Biel, J. H.; Friedman, H. L.; Leiser, H. A.; Sprengeler, E. P. *J. Am. Chem. Soc.* **1952**, *74*, 1485.
31. Blicke, F. F.; Lu, C.-J. *J. Am. Chem. Soc.* **1955**, *77*, 29.
32. De Kimpe, N.; Boelens, M.; Contreras, J. *Tetrahedron Lett.* **1996**, *37*, 3171.
33. (a) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335; (b) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924.
34. Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1984**, *49*, 40.
35. Broka, C. A.; Gerlits, J. F. *J. Org. Chem.* **1988**, *53*, 2144.
36. Kim, D.-K.; Kim, G.; Kim, Y.-W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 803.
37. For related ring expansion from other substrates see: (a) Setoi, H.; Takeno, H.; Hashimoto, M. *Heterocycles* **1986**, *24*, 1261; (b) Zhi-cai, S.; Chun-min, Z.; Guo-Quiang, L. *Heterocycles* **1995**, *41*, 277; (c) Knaack, M.; Fleischhauer, I.; Charpentier, P.; Emig, P.; Kutscher, B.; Müller, A. *Liebigs Ann.* **1996**, 1477.
38. Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. *Tetrahedron Lett.* **2001**, 42, 6223.
39. Griffith, D. A.; Heathcock, C. H. *Tetrahedron Lett.* **1995**, *36*, 2381.
40. Cossy, J.; Dumas, C.; Michel, P.; Gomez Pardo, D. *Tetrahedron Lett.* **1995**, *36*, 549.
41. Langlois, N.; Calvez, O. *Synth. Commun.* **1998**, *28*, 4471.
42. Davis, P. W.; Osgood, S. A.; Hébert, N.; Sprankle, K. G.; Swayze, E. E. *Biotechnol. Bioeng.* **1999**, *61*, 143.
43. Wilken, J.; Kossenjans, M;, Saak, W.; Haase, D.; Pohl, S.; Martens, J. *Liebigs Ann.* **1997**, 573.
44. Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 2572.
45. Brandi, A.; Cicchi, S.; Paschetta, V.; Gomez Pardo, D.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357.
46. Cossy, J.; Dumas, C.; Gomez Pardo, D. *Synlett* **1997**, 905.
47. (a) Cossy, J.; Mirguet, O.; Gomez Pardo, D. *Synlett* **2001**, 1575; (b) Mirguet, O. Ph. D. Dissertation, Université P. et M. Curie (Paris 6), **2001**.
48. Cossy, J.; Dumas, C.; Gomez Pardo, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1343.
49. Thorberg, S.-O.; Gawell, L.; Csöregh, I.; Nilsson, J. L. G. *Tetrahedron* **1985**, *41*, 129.
50. Biel, J. H.; Sprengeler, E. P.; Leiser, H. A.; Horner, J.; Drukker, A.; Friedman, H. L. *J. Am. Chem. Soc.* **1955**, *77*, 2250.

THE FORMATION OF THE CARBON-CARBON BOND CATALYSED BY METALLOPORPHYRINS

Pietro Tagliatesta

Dipartimento di Scienze e Tecnologie Chimiche, Universita' di Roma-Tor Vergata, Via della Ricerca Scientifica, 00133 Roma, Italy (e-mail: pietro.tagliatesta@uniroma2.it)

Abstract. *In this review, the results reported in the literature during the last twenty years for the metalloporphyrins-catalysed formation of the carbon-carbon bond are described. Cyclopropanation reactions, Diels-Alder additions, olefination of aldehydes and cyclotrimerization of alkynes are important processes in organic chemistry and all of them are catalysed by metalloporphyrins. Such catalysts afford interesting results in terms of chemical yields and stereospecificity, due to the differences in the electron densities of the substituted macrocycles and the possibility to have the access to flat or saddle-shaped conformations of the tetrapyrrolic rings, depending on the substituents located on their skeleton.*

Contents

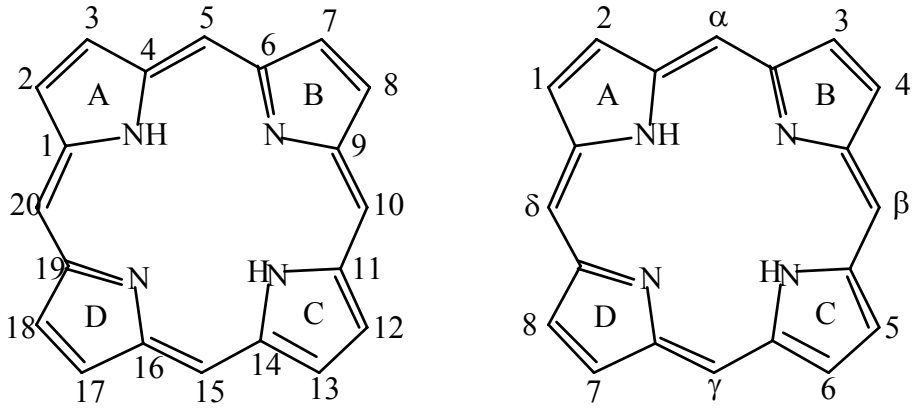
1. Introduction

The formation of the carbon-carbon bond is a step of great importance in organic synthesis and several industrial processes for the production of valuable chemicals are based on reactions that involve the formation of new C-C bonds.[1-3] Many procedures involve carbanions, obtained from organometallic compounds or activated methyl or methylene groups.[4-6] The Grignard reaction, the Claisen condensation, the Diels-Alder reaction and many other processes have been discovered in the last century but even if the catalytic formation of this bond has been well studied, many general and efficient methods for affecting this

reaction still remaining to be found or optimized. From many points of view, catalysis by metal complexes is an important and powerful tool in organic chemistry and within this field of research, the metalloporphyrin catalysts have achieved important results. In this review, the formation of carbon-carbon bond catalysed by synthetic metalloporphyrins and their application in organic chemistry is reported.

1.1. Catalysis by metalloporphyrins: general remarks

The investigations on the natural and synthetic porphyrins and their metallo-derivatives are a fundamental field of research to better understand how some classes of natural enzymes work and their structural relation with the substrates. Natural enzymes like cytochrome P450 are able to perform the epoxidation of olefins and the hydroxylation of alkanes with great efficiency and stereospecificity. Such systems, all of them containing the *heme* group, are ubiquitous in the living organisms and their main task is the intracellular transformation of non-polar organics into polar compounds, making the excretion easier and eliminating by way the most likely toxic and mutagenic substances.[7] The structure of the porphyrins skeleton is reported in Figure 1.



The skeleton of porphyrins encloding the IUPAC(left) and the classical Fischer (right) numeration of the substituents.

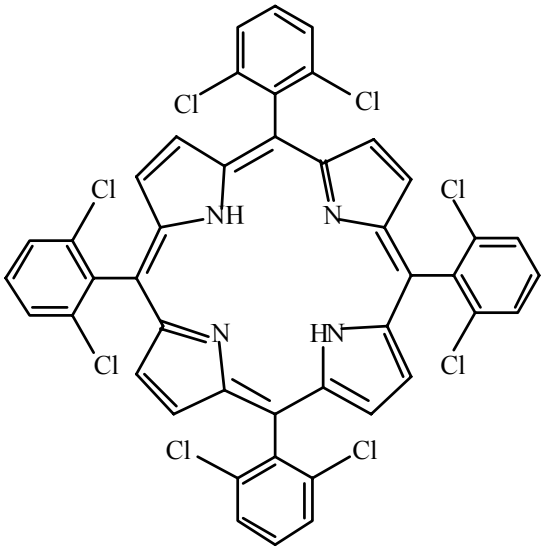
Figure 1

For our convenience, the methine bridges (α, β, γ, δ) will be also called *meso* positions.

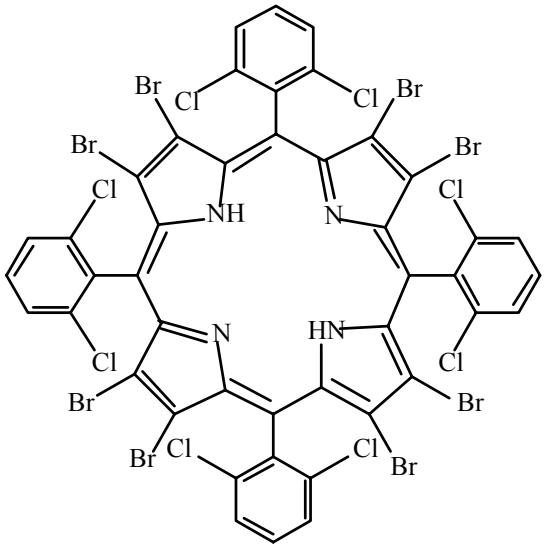
The use of synthetic metalloporphyrins as model catalysts in oxidation reactions, like epoxidation of olefins and hydroxylation of saturated hydrocarbons, has been largely documented during the last decade.[8,9] Among the metalloporphyrins tested for such reactions, much attention has been devoted to the *meso*-tetraphenyl substituted ones, which show the most interesting properties. The first report on the catalytic activity of the iron (III) *meso*-tetraphenylporphyrin in the oxidation reactions came from Groves and co-workers, who used iodosilbenzene as oxygen donor.[10] This class of macrocycles is known as the "first generation" of porphyrin catalysts. Following this pioneering work, other authors showed that manganese(III) and iron(III) *meso*-tetraphenylporphyrins bearing suitable substituents (Cl, OCH_3, Br, F, CH_3, etc.) on the 2', 6' positions of all the phenyl groups, are able to catalyse the oxygen transfer, showing a

high resistance to the oxidative conditions.[11-15] These sterically hindered groups prevent the formation of the μ-oxo dimeric complexes, which are not catalytically active.[11,14]

This class of compounds is actually known as the "second generation" of porphyrin catalysts. The "third generation" of porphyrin catalysts is formed by the aforementioned second class bearing further electron-withdrawing groups, like halogens, nitro or cyano, in some or all the *beta* positions.[16-17] Examples of porphyrins of the second and third generation are reported in Figure 2.



5,10,15,20-tetrakis-(2',6'-dichlorophenyl)porphyrin



2,3,7,8,12,13,17,18-octabromo-5,10,15,20-tetrakis-(2',6'-dichlorophenyl)porphyrin

Figure 2

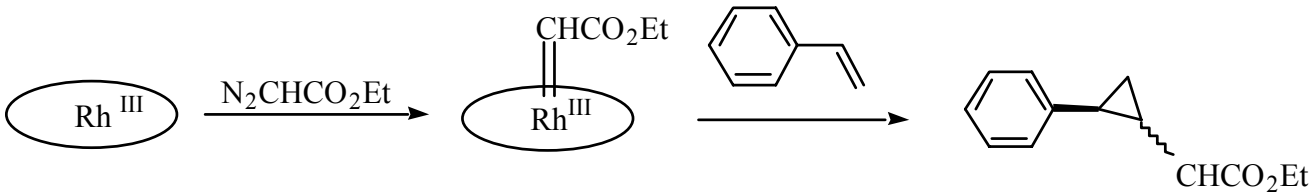
Such catalysts are able to perform the hydroxylation of aromatic compounds giving phenols or quinones as the final products.[18-19] Furthermore, the iron porphyrins of the third class are also able to catalyse the hydroxylation of simple and short hydrocarbons, like propane or isobutane using the molecular oxygen in the suprabiotic catalytic systems.[20-21]

2. Cyclopropanation reactions

The cyclopropyl ring formation is an important reaction in organic synthesis, due to the presence of such structure in a number of interesting natural products. Many methods have been developed in the past for obtaining such reaction and several copper, rhodium and osmium complexes have been reported to be efficient catalysts for the synthesis of cyclopropanes from diazocompounds.[22]

Synthetic iron, rhodium, osmium and ruthenium porphyrins have also been reported as catalysts for the cyclopropanation reaction of simple olefins by ethyldiazoacetate (EDA).[23-29] In comparison with the copper catalysts, like CuCl, which do not afford synthetic useful *cis/trans* ratios of the final products, the porphyrin catalysts give larger selectivities, depending on the nature of the metal. The reaction mechanism of the metalloporphyrins catalysed cyclopropanation reaction is not completely elucidated, because of the lability of the bond between the central metal and the acetate residue.

The intermediate of the reaction, showed in Scheme 1, proposed, in the case of rhodium, by Callot *et al.* [23] was later studied by Kodadek, who used the NMR spectroscopy for detecting the tentatively suggested carbene species, **A**.[26,30]



A *cis+trans*

Scheme 1

2.1. Rhodium porphyrin catalysts

Almost twenty years ago, Callot and co-workers reported the first study on the rhodium(III) porphyrins catalysed cyclopropanation reaction of olefins.[23] They used the easily obtainable rhodium(III) *meso*-tetraphenylporphyrin iodide, Rh(TPP)I as catalyst for the decomposition of EDA in the presence of different olefins, obtaining the cyclopropanation products with remarkable *cis* selectivities.

In Table 1, the total yields of the reactions and the *cis/trans* ratios for all the substrates are reported and compared with the results obtained using different catalysts, such as rhodium pivalate or copper chloride.

From the reported data, it is clear that the structure of the catalysts influence the stereochemical results, giving larger *cis* selectivity and this fact was used for planning the synthesis of more hindered porphyrins, able to give higher selectivities. In fact, in the presence of rhodium 2',6' phenyl substituted porphyrins, the *cis* selectivities changes and using rhodium meso-tetra-(2', 4', 6'-trimethylphenyl)porphyrin, Rh(TMPP)I instead of Rh(TPP)I in the case of cyclohexene, the *cis/trans* ratio increases from 0.84 to 1.17 and for norbornene from 1.85 to 2.14.[24]

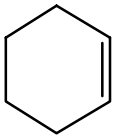
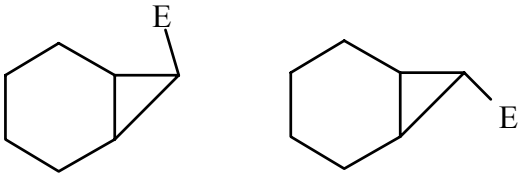
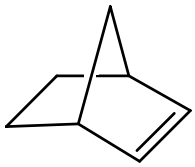
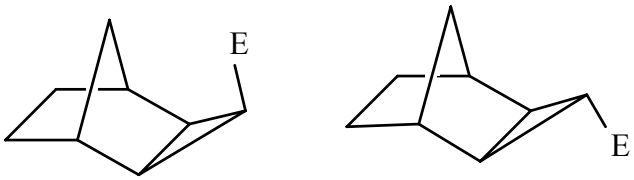
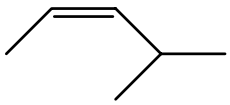
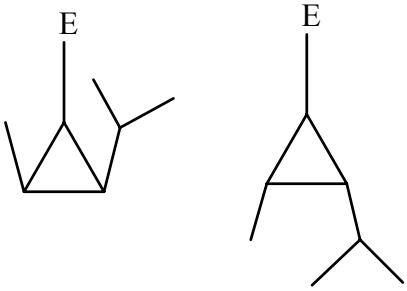
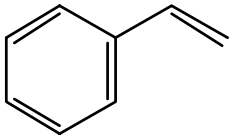
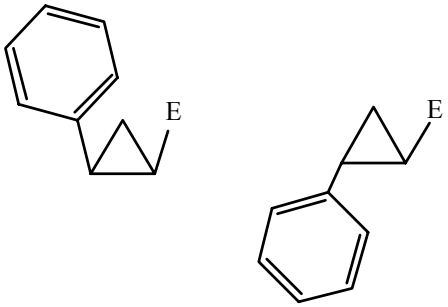
These first studies prompted other groups in the searching of more sterically hindered porphyrins and for such reason Kodadek and co-workers synthesised the so-called rhodium "chiral wall", Rh(TBNP)I and "chiral fortress" Rh (TPBNP)I porphyrins.[25,31,32] The non-metalated macrocycles were synthesised by inserting, in all the *meso*-positions, the optically active binaphtyl or 1'-pyrenyl-1-naphtalene groups. In scheme 2 is reported the synthetic pathway for obtaining one of them. The rhodium derivatives of such porphyrins were used for the EDA cyclopropanation of simple olefins and the enantiomeric excesses were determined on both the *cis* and *trans* isomers. In this way, two sterically hindered and optically active catalysts have been made available and the *cis* selectivities of the cyclopropanation reactions of standard olefins by EDA were the best ever reported in the literature for this reaction.

Furthermore, such intrinsically chiral catalysts afforded diastereoselectivities in moderate or good excess but the difficult to prepare large quantities of such porphyrins made them not useful for large scale preparations. Some results of the use of these chiral catalysts are collected in Table 2.

As to the mechanism of the reaction for the rhodium porphyrins catalysis, Kodadek [33,34] proposed that the olefin could approach the metallocarbene intermediate in a perpendicular orientation relative to the

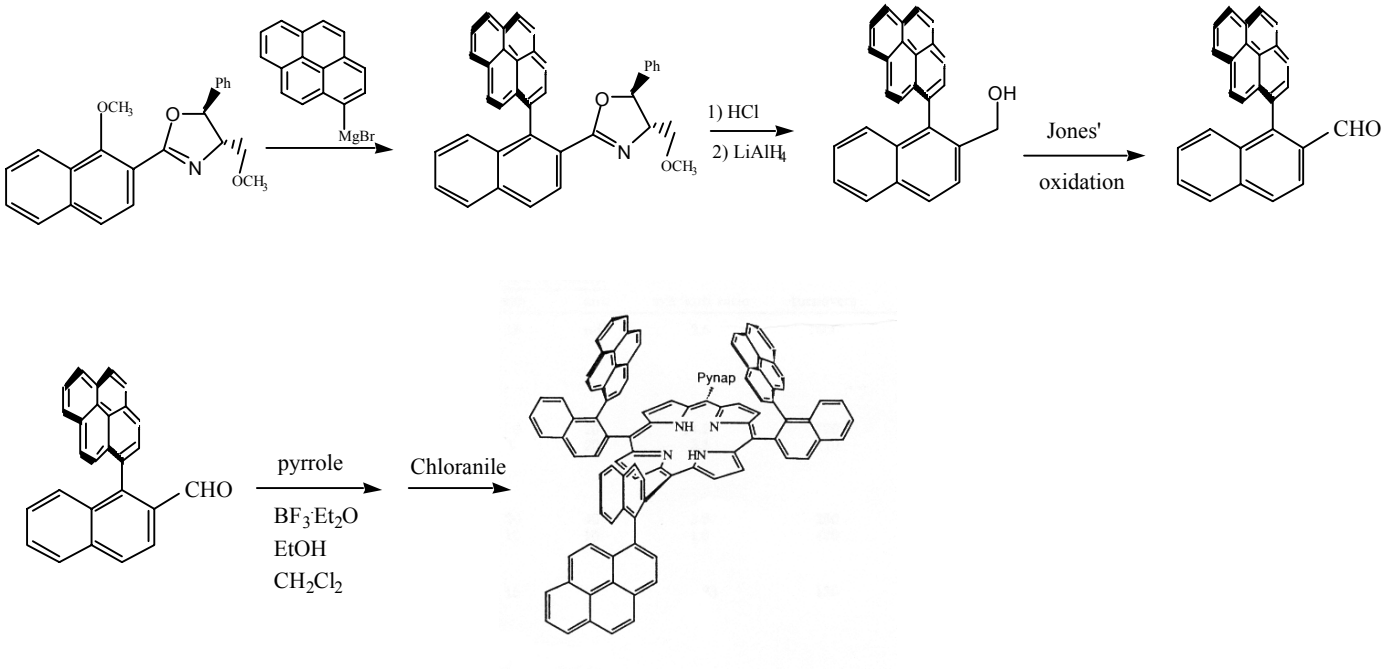
metal-carbon bond axis, giving after a rotation the arrangement found in the final *cis* or *trans* product. In Scheme 3, a simplified representation of the transition state is reported.

Table 1. The total yields and the *cis/trans* ratios obtained using Rh(TPP)I, compared with the results obtained using other catalysts, such as rhodium pivalate or copper chloride. (According to ref. 23. Reprinted from *Tetrahedron Lett.* **1980**, *21*, 3489-3492, Callot, H. J. and Piechocki, C.: Cyclopropanation using rhodium(III) porphyrins: large *cis vs trans* selectivity. Copyright 1980, with permission from Elsevier Science).

olefin	*cis* and *trans* products E=CO_2Et	catalyst	*cis/trans* ratio	Total yield(%)
		RhTPPI Rhpiv CuCl	0.84 0.32 0.12	62
		RhTPPI Rhpiv CuCl	1.85 0.44 0.02	71
		RhTPPI Rhpiv CuCl	4.9 2.2 0.56	60
		RhTPPI Rhpiv CuCl	1.13 0.67 -	71

In this early suggestion, the transfer of the acetate residue to an unsimmetrical alkene, bearing a smaller, R_S and a larger, R_L, substituent, is obtained mantaining the large substituent far from the ester group while the olefin, rotating clockwise or counterclockwise around an axis orthogonal to the metal-carbon bond, can reach the transition state in a concerted fashion. This fact is also supported by the absence of a secondary isotope effect, determined in a competitive experiment with styrene and d_8-styrene, which gave the value of 1.0±0.07. For bulky porphyrins, like the 2', 6' phenyl substituted ones, the interaction between ligand and

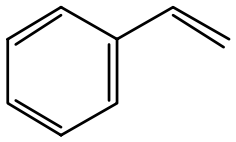
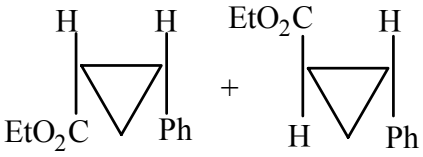
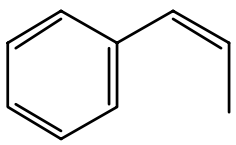
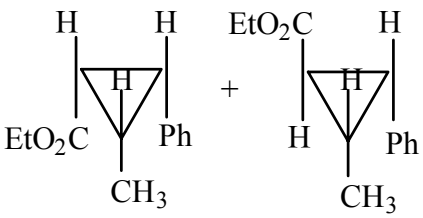
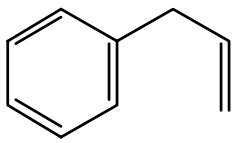
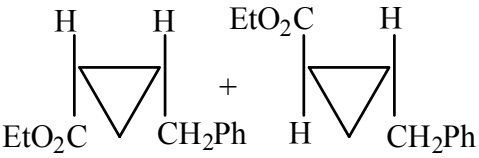
substrate dominates, giving a clockwise rotation and the final *cis* product. If the interaction ester-substrate is stronger, the rotation will be counterclockwise leading to the *trans* product.

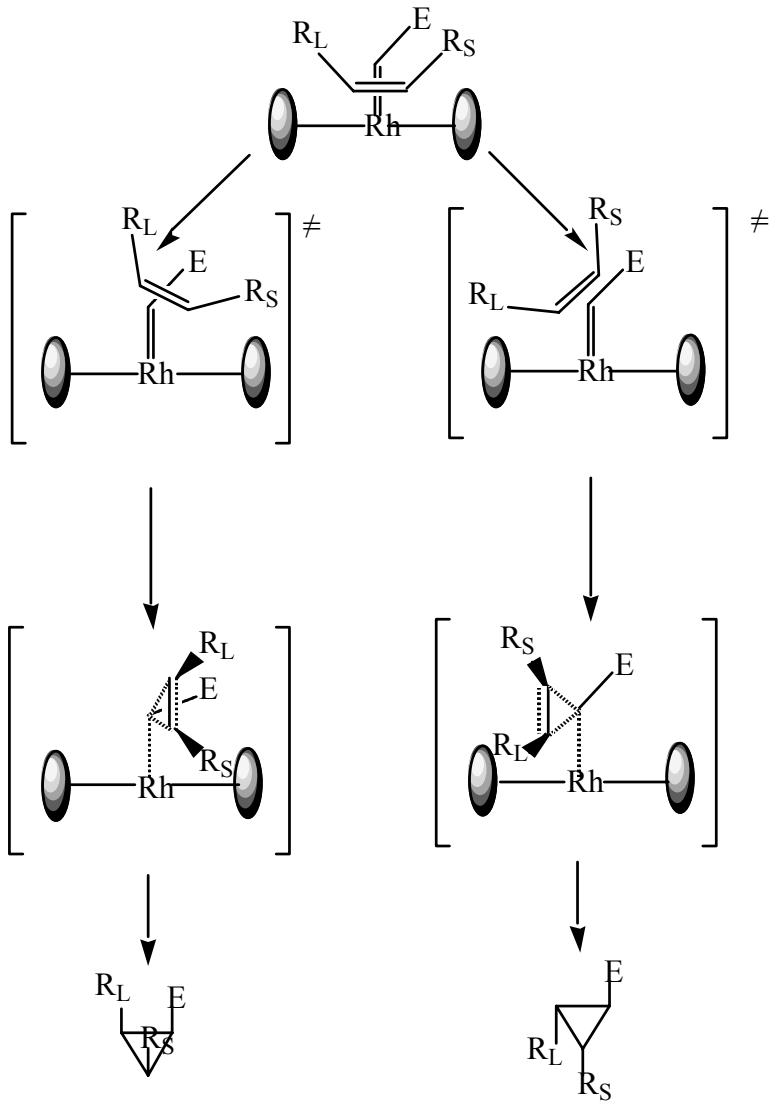


(Reprinted from *Organometallics* **1992**, *11*, 2299. Copyright 1992 American Chemical Society)

Scheme 2

Table 2. Selected yields and enantiomeric excesses for the cyclopropanation reactions catalysed by Rh (TPBNP)I. (According to ref. 31. Reprinted from *Organometallics* **1992**, *11*, 2299. Copyright 1992 American Chemical Society).

substrate	Products	ee % (± 5%) *cis*	ee % (± 5%) *trans*	*cis/trans* ratio
		15	nd	2.5
		25	20	5.1
		10	10	0.83



(Reprinted from *J. Am. Chem. Soc.* **1992**, *114*, 8337. Copyright 1992 American Chemical Society)

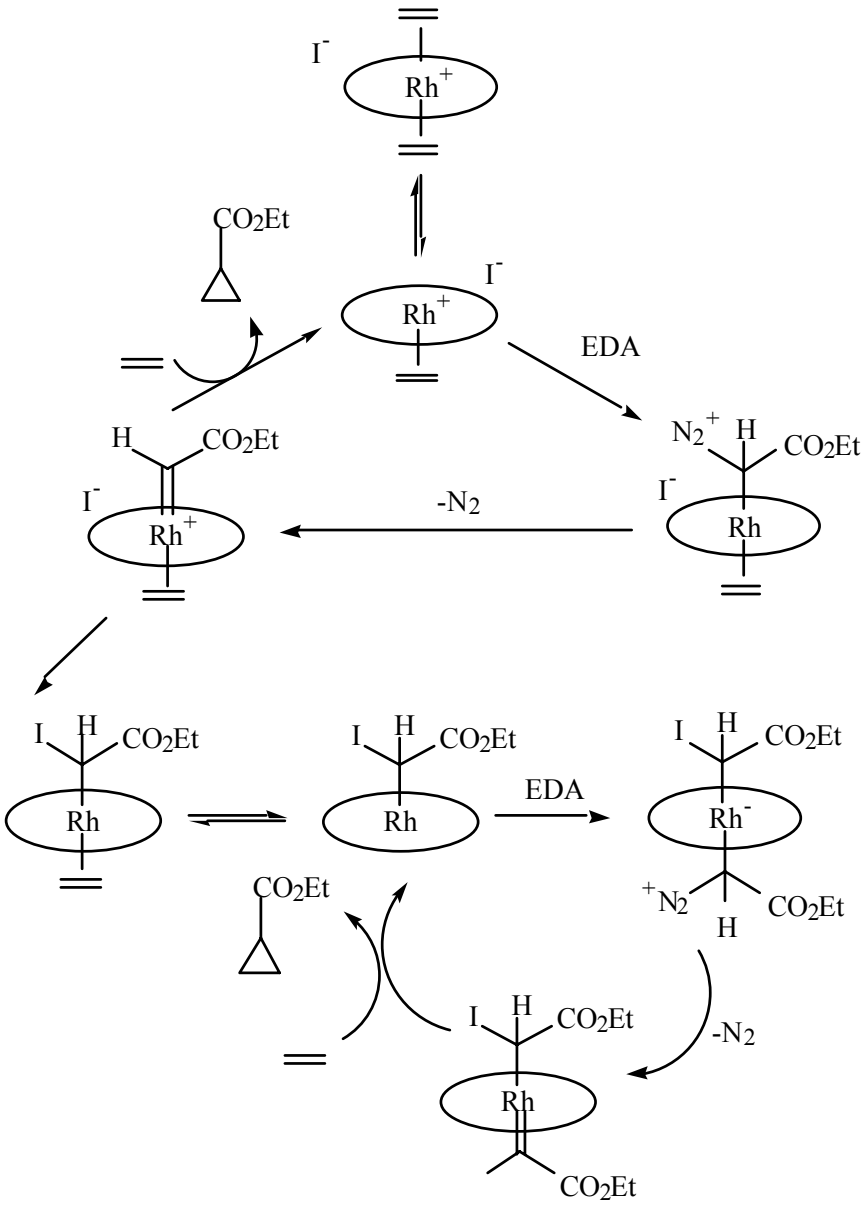
Scheme 3

This model was successively refined by using the ^{1}H NMR spectroscopic observation of another reactive intermediate, the iodoalkyl rhodium derivative, **B** which has been proved to be the possible active catalyst.[30] The proposed modified mechanism for the cyclopropanation of olefins catalysed by rhodium porphyrins is reported in Scheme 4.

The possibility to vary the electronic properties and steric hindrance of the *meso*-tetraphenylporphyrins, introducing different groups on the β-positions and/or on the phenyl rings, prompted us to investigate which parameters govern the stereochemical results obtained in the cyclopropanation reactions using their rhodium derivatives as catalysts.[35] It is well known from previous studies[36,37] that $(PorBr_X)M$, where $PorBr_X$ is the dianion of different β-halogenated 5, 10, 15, 20-tetraphenylporphyrins, M is Fe, Co, Zn or H_2 and $x \geq 3$ or 4, show saddle-shaped distortion of the macrocycles.

This fact suggested the possibility to direct the cyclopropanation reaction to give the most hindered isomer in excess without building complicated porphyrinic structures.[31,32] For this purpose we decided to use the rhodium derivatives of 5, 10, 15, 20-tetra(2', 6'-dimethoxyphenyl)porphyrin , Rh(TDMPP)Cl and 5, 10, 15, 20-tetra(2', 6'-dichlorophenyl)porphyrin, Rh(TDCPP)Cl which both show good steric hindrance on both

sides of the macrocycle due to the presence of bulky groups. The starting free bases of such metal derivatives are now available in grams quantity by new synthetic methods, much cheaper than those previously reported in the literature and comparable with those for obtaining the simple 5, 10, 15, 20-tetraphenylporphyrin.[38] Furthermore, we examined the possibility to quantify the influence of the β-bromine groups on the stereoselectivity of the reaction and we report all the new data obtained for styrene, comparing with CuCl and Rh(TPP)Cl catalysts in Table 3.



B

(Reprinted from *J. Am. Chem. Soc.* **1993**, *115*, 1656. Copyright 1993 American Chemical Society)

Scheme 4

It is clear that there is a small but evident influence of the β-bromination on the stereoselectivity of the reaction and, plotting the logarithm of the *cis/trans* ratio against the sum of the Hammett's σ_p of the β-bromine groups, a good linear correlation (r^2=0.98, ρ=-0.132) is evident (see Figure 3). The selectivity changes on increasing the number of the halogens and this fact, in our opinion, is due to different factors; the

electrophilic character of the metal is clearly enhanced by the electron-withdrawing effects of the βsubstituents and this is in agreement with the mechanism proposed by Kodadek but we also believe that, during the catalytic process, styrene can approach the core of the macrocycle through a π–πinteraction with the higher halogenated pyrrole rings stabilising the transition state which leads to the *trans* product.

Table 3. *cis/trans* Molar ratios and yields in parentheses for the cyclopropanation reaction of styrene with EDA catalysed by rhodium porphyrins (According to ref. 35. Reprinted from *J. Mol. Cat. A: Chemical* **2002**, *185*, 127-133, Tagliatesta, P. and Pastorini, A.: Electronic and steric effects on the stereoselectivity of cyclopropanation reactions catalysed by rhodium meso-tetraphenylporphyrins. Copyright 2002, with permission from Elsevier Science.)

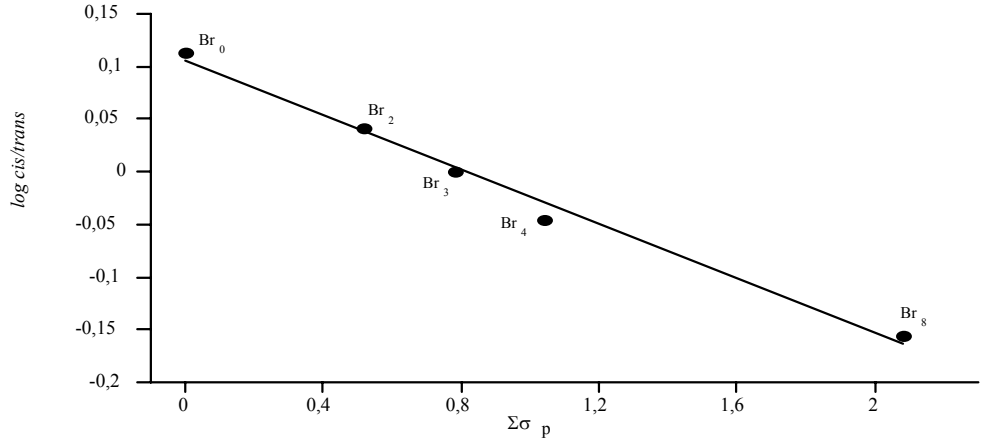
Entry[a]	Catalyst	Molar ratios
1	CuCl	0.6(79.3)
2	RhTPPCl	1.3(70.4)
3	Rh(Br2)TPPCl	1.1(95.0)
4	Rh(Br3)TPP]Cl	1.0(90.1)
5	Rh(Br4)TPPCl	0.9(91.2)
6	Rh(Br8)TPPCl	0.7(26.5)
7	RhTDMPPCl	0.4(88.8)
8	RhTDCPPCl	1.7(43.7) [b]

[a] Reactions were carried out at 60 ˚C with a molar ratio substrate/EDA/catalyst=2500:1000:1;
[b]Room temperature

The situation is different for cyclohexene and norbornene, which show different behaviours with the β-brominated porphyrins. For cyclohexene, the most conformationally flexible substrate among those examined, we obtained almost the same *cis/trans* ratio for all the above mentioned catalysts (0.5÷0.8). This is not surprisingly and such effect can be attributed to the possibility for cyclohexene to have the access to different conformations.

On the contrary, norbornene, a more rigid substrate, shows a non linear decrease in the stereochemical ratio on increasing the number of the halogen atoms on the β-positions. Rh(TDCPP)Cl shows the most interesting results when compared with the data obtained by Callot and co-workers,[24] who used the rhodium derivatives of porphyrins bearing other bulky substituents as catalysts for the reaction of EDA with the same substrates. This catalyst is able to give good improvement of the stereochemical results with all the substrates reported above. For styrene, we obtained a *cis/trans* ratio of 1.7 *vs* 0.98, for cyclohexene 1.5 *vs* 1.17 and for norbornene 3.5 *vs* 2.14, at room temperature. These last results are quite remarkable for several reasons, first of all because of the low cost of the starting free base.

Furthermore, the result for norbornene, to the best of our knowledge, is the higher so far reported in the literature and also the other ratios obtained for styrene and cyclohexene are interesting when compared with the values obtained by Kodadek who used more complicated and expensive porphyrin catalyst.[31,32]



(According to ref. 35. Reprinted from *J. Mol. Cat. A: Chemical* **2002**, *185*, 127-133, Tagliatesta, P. and Pastorini, A.: Electronic and steric effects on the stereoselectivity of cyclopropanation reactions catalysed by rhodium meso-tetraphenylporphyrins. Copyright 2002, with permission from Elsevier Science.)

Figure 3

Table 4. Catalytic Cyclopropanation of Olefins with EDA Using Iron Porphyrin Complexes as Catalysts(According to ref. 38. Reprinted from *J. Am. Chem. Soc.* **1995**, *117*, 9194. Copyright 1995 American Chemical Society).

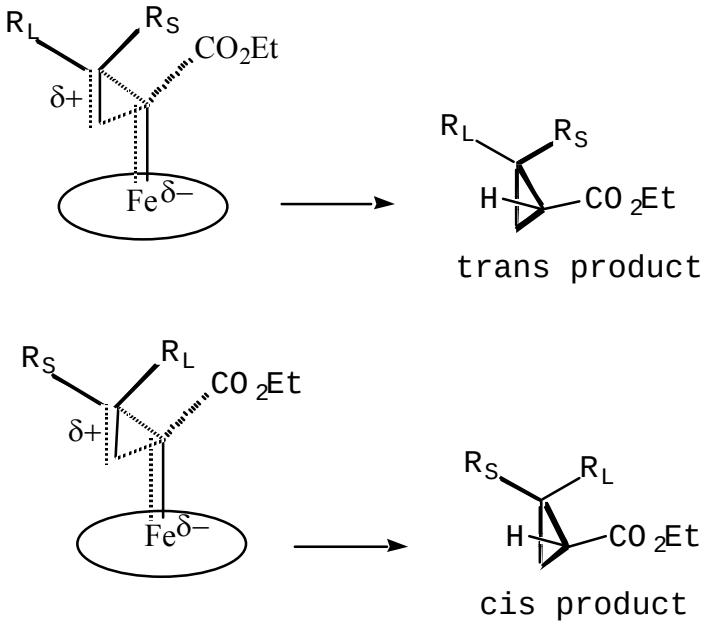
olefin	Catalyst[a]	ratio of *trans/cis* products	ratio of cyclopropane/ diethyl maleate products
styrene	Fe(PFP)Cl	6.0	75:25
	Fe(TPP)Cl/40ºC	5.5	76:24
	Fe(TPP)Cl/$CoCp_2$	8.7	80:20
	Fe(TTP)	8.8	b
	Fe(TPP-*p*-OMe)Cl/$CoCp_2$	9.0	b
	Fe(TMP)Cl/$CoCp_2$	13	b
	Fe(OEP)Cl/$CoCp_2$	10	b
α-methylstyrene	Fe(PFP)Cl	1.1	67:33
	Fe(TPP)Cl/40º C	3.4	70:30
	Fe(TMP)Cl/$CoCp_2$	3.0	97:3
	Fe(OEP)Cl/$CoCp_2$	3.7	85:15
	Fe(TTP)	4.2	b
p-methoxystyrene	Fe(PFP)Cl	5.8	b
	Fe(TPP)Cl/40º C	5.5	b
	Fe(TMP)Cl/$CoCp_2$	11	b
ethyl vinyl ether	Fe(PFP)Cl	3.3	67:33
	Fe(TMP)Cl/$CoCp_2$	4.1	82:18
	Fe(OEP)Cl/$CoCp_2$	4.5	34:66
2-ethyl-1-butene	Fe(PFP)Cl		30:70

[a]0.02-0.05% catlyst. [b]Trace diethyl maleate observed. PFP=*meso*-tetra(2', 3', 4', 5', 6'-pentafluorophenyl)-porphyrin; TMP=*meso*-tetra(2', 4', 6'-trimethylphenyl)porphyrin; TTP=*meso*-tetra(4'-methylphenyl)-porphyrin; OEP= 2, 3, 7, 8, 12, 13, 17, 18 octaethylporphyrin

2.2. Iron porphyrin catalysts

The first report on the catalytic activity of the iron(II) porphyrins in the cyclopropanation reactions was published in 1995 and came from Kodadek's laboratory.[39] Although the iron(II) porphyrins are isoelectronic with the rhodium(III) ones, their stereoselectivity is completely opposite. In fact the iron(II) *meso*-tetraphenylporphyrin was found to be quite active in catalysing for example the reaction between styrene and EDA but a ratio of 8.8 to 1 of *trans* to *cis* isomers was produced. In Table 4 we report some results obtained by Kodadek using different catalytic systems on five standard olefins.

The active intermediate of the reaction was attributed to an iron(II) carbene species which can be formed from a starting iron(III) porphyrin by the chemical reduction with cobaltocene ($CoCp_2$) and subsequent complexation or generated *in situ* by the direct reaction with EDA. The same observation was reported by Kodadek, who observed the EDA direct reduction of the iron(III) *meso*-tetra(2', 3', 4', 5' 6'-pentafluorophenyl)porphyrin chloride and it was attributed to the presence of the electron-withdrawing groups on the phenyl rings which make easier the reduction of the iron by EDA. The secondary kinetic isotope effect was determined using styrene and d8-styrene in a competitive experiment and gave the value of 0.87±0.07, suggesting a rehybridization of the olefin in the transition state. This proposal implied the presence of a carbocation or radical species which is formed in a non-concerted insertion of the acetate residue into the olefin. A simple scheme of this mechanism is reported in Figure 4.



(Reprinted from *J. Am. Chem. Soc.* **1995**, *117*, 9194. Copyright 1995 American Chemical Society)

Figure 4

Moreover, the iron(II) porphyrins catalyse the carbene transfer with a great preference for the aromatic olefins or those bearing π-heteroatoms. At variance with the rhodium catalysed reactions, the aliphatic olefins are poor substrates and almost no reaction was observed for cyclohexene, indene and 1-methyl-cyclohexene. For the cyclopropanation of such substrates, only diethyl fumarate and/or maleate were detected as reaction by-products. In our opinion this fact could be due to the presence of two separate mechanisms involved in the cyclopropanation of the aromatic olefins. For iron catalysts, an asynchronous

transfer can be present and, in this case, the intermediate after rotation along the carbon-carbon bond, can give a mixture of the *cis* and *trans* isomers.

This mechanism is reminiscent of that reported for the epoxidation of *cis*-stilbene catalysed by manganese porphyrins[40] which involves two different routes, depending on the electron withdrawing substituents on the macrocycle ring.

In our opinion, for the iron catalysis, the rotation can depend on the steric hindrance of the substituents on the porphyrin ring and also on the relative stability of the radical intermediates. Another observation which supports our interpretation, derives from the fact that only rhodium porphyrins give the carbene transfer for both aromatic and aliphatic substrates. In the case of iron, only styrenes undergo to the formation of cyclopropanes because the radical intermediate can be stabilised by the resonance effect. The effect of the DMSO seems to be related to the coupling interaction of the unpaired electron of the radical with the lone pair of the sulfoxide, stabilizing the radical intermediate.

Table 5. Catalytic cyclopropanation of olefins with EDA using Fe(TDCPP)Cl as catalyst (According to ref. 41).

Entries	Olefin	Catalyst[a]	Reaction time(h)[b]	Ratio of *trans/cis* products(reaction yield)[c]	Ratio of cyclopropane/ diethyl maleate products
1	styrene	Fe(TDCPP)Cl	2	20(80)	82:12
2		Fe(TDCPP)Cl/$CoCp_2$	1.5	30(97)	98:2
3	*p*-chlorostyrene	Fe(TDCPP)Cl	0.5	13(80)	80:20
4		Fe(TDCPP)Cl/$CoCp_2$	0.5	78(94)	94:6
5	*p*-methoxystyrene	Fe(TDCPP)Cl	6	8.3(85)	d
6		Fe(TDCPP)Cl/$CoCp_2$	2	50(95)	d
7	α-methylstyrene	Fe(TDCPP)Cl	8	1.6(80)	d
8		Fe(TDCPP)Cl/$CoCp_2$	3	2.0(95)	d
9	β-methylstyrene	Fe(TDCPP)Cl	18	-	e
10		Fe(TDCPP)Cl/$CoCp_2$	16	-	e

[a]0.03-0.07% catalyst. [b]Room temperature. [c]Determined by GC analysis. [d]Trace diethyl maleate observed. [e]Only diethyl maleate observed

This coupling could be depressed by the methoxy substituent in *p*-methoxystyrene which destabilises the radical intermediate. This is also in agreement with other observations on the reaction performed on styrene. By using Rh(TDCPP)Cl as catalyst, in neat $CHCl_3$, we have been able to obtain an *trans/cis* ratio of 0.58 while with 0.5% of DMSO the result increases to 3.0. This last result is also in agreement with value of 2.8 obtained adding 1% of 3-carbamoyl tempo, a free radical, in the reaction media instead of DMSO and strongly support our interpretation of the obtained data.

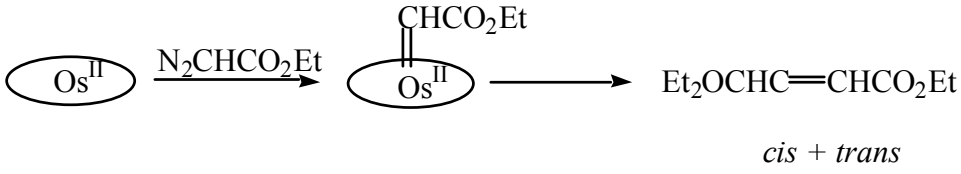
Interesting results were recently obtained in our laboratory using the Fe(TDCPP)Cl, a sterically hinderd and electron-poor metalloporphyrin.[41] In the reactions catalysed by such macrocycle, we obtained,

for some aromatic olefins, the highest *trans/cis* ratios ever obtained, going from a value of 30 for styrene to 78 for *p*-chlorostyrene. The total yields were also very interesting and the number of turnovers reached the value of $3 \cdot 10^3$.

Interesting results have been recently obtained by Woo and co-workers who used aromatic diazocompounds as carbene source.[42] They were able to obtain a *trans/cis* ratio of 14 for the reaction of styrene with *p*-tolyldiazomethane, catalysed by $Fe^{II}TPP$. Furthermore, they reported the reaction of EDA with styrene catalysed by $Fe^{II}TDMPP$ which gives a remarkable ratio of 21 and the ^1H NMR spectroscopic identification of a carbene iron(II) porphyrin derivative from the stoichiometric addition of mesityl diazomethane to $Fe^{II}TPP$.

2.3. Osmium porphyrin catalysts

Woo and co-workers reported in 1992 the first use of an osmium porphyrin in the synthesis of olefins from diazocompounds.[43] This method afforded the *cis* isomers in great excesses and with remarkable yields. An example of this reaction is given in scheme 5 for the EDA conversion to diethyl fumarate or maleate.



Scheme 5

Table 6. Catalytic cyclopropanation of olefins with EDA using osmium porphyrins as catalysts (According to ref. 44. Reprinted from *J. Am. Chem. Soc.* **1993**, *115*, 2511. Copyright 1995 American Chemical Society).

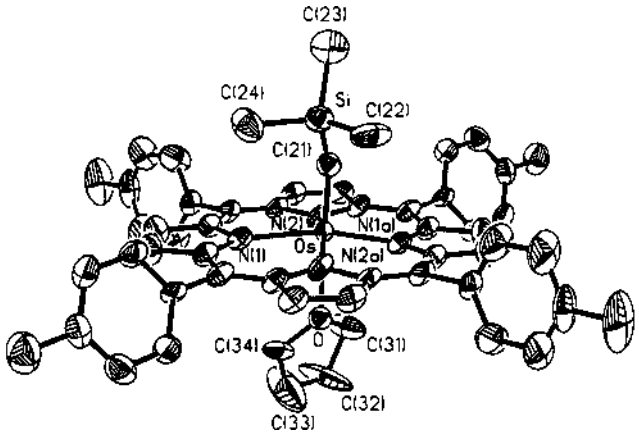
Catalyst	Substrate	Olefin[a]		Cyclopropane	
		Yield	(z/e)	Yield	a/s
(TPP)Os(CO)(Py)	styrene	11(2)	b	54(1)	9.0(1)
(TPP)Os(CO)(Py)	styrene	12(1)	b	65(3)	9.5(2)
(TPP)Os(CO)(Py)	styrene	26(1)	b	44(1)	9.0(3)
$[Os(TPP]_2$	styrene	trace	b	79(2)	10.2(1)
$(TPP)Os{=}CHCO_2Et$	styrene	trace	b	63(2)	8.9(6)
(TPP)Os(CO)(Py)	PhC≡CH	41(1)	b	11(1)[c]	d
$[Os(TPP]_2$	PhC≡CH	20(1)	b	46(2)[c,e]	d
(TPP)Os(CO)(Py)	1-decene	31(1)	b	32(1)	4.3 (1)
(TPP)Os(CO)(Py)	α-methylstyrene	29(1)	b	39(1)	2.8(1)
(TPP)Os(CO)(Py)	(E)-β-methylstyrene	43(2)	23	13(2)	f
$(TPP)Os{=}CHCO_2Et$	styrene			73(5)	11.5(4)

[a]Diethyl maleate/diethyl fumarate products. [b](Z)-isomer is the only one detected. [c]Bicyclobutanes are the only cyclopropane products detected. No cyclopropene has been observed. [d]Only one isomer observed. [e]Ten-hour addition. [f]Ethyl-*trans*-2-phenyl-*cis*-3-methylcyclopropane-(r)-carboxylic acid ester was the only isomer

After this first report on the catalytic activity of the osmium porphyrins, another paper appeared in the literature on the cyclopropanation of olefins by EDA.[44] In that contribution, several catalysts have been tested using styrene, α-methylstyrene, β-methylstyrene or 1-decene as substrates. Furthermore, such catalysts were also used for the cyclopropanation of phenylacetylene, giving the bicyclobutanes as the final

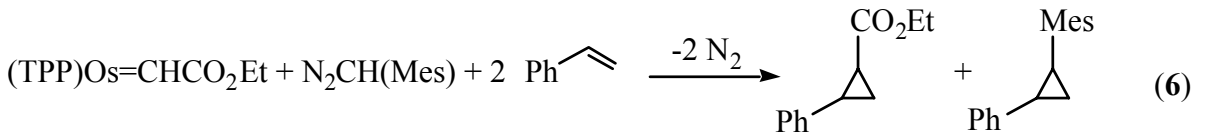
products. All results are reported in Table 6. Two osmium porphyrin carbene complexes have been later isolated and fully characterised.[45]

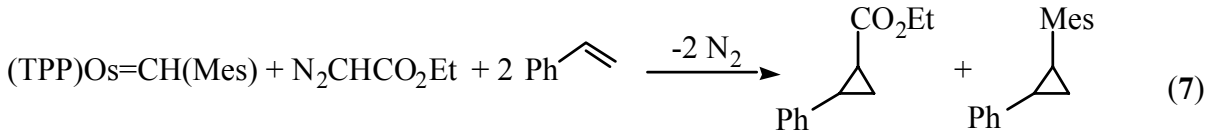
The x-ray analysis of the *trans*-(TPP)Os=CHSi$(CH_3)_3$•THF and *trans*-(TPP)Os=C$(C_6H_4$-p-$CH_3)_2$•THF shows distorted geometries due to the steric interactions of the metal ligand with the macrocycle. The molecular structures provide new information about the intermediate of the reaction and in Figure 5 we report the ORTEP drawing of the *trans*-(TPP)Os=CHSi$(CH_3)_3$•THF.

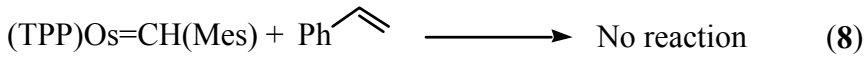


(Reprinted from *Organometallics* **1994**, *13*, 3020. Copyright 1994 American Chemical Society)

Figure 5







(Reprinted from *Organometallics* **2001**, *20*, 5189. Copyright 2001 American Chemical Society)

Scheme 6

The reaction mechanism has been recently studied in detail by Woo and co-workers.[46] They used the isolated (TPP)Os=CH(Mes) carbene complex for a key experiment using it stoichiometrically with styrene at room temperature. No reaction was observed, whilst this was not the case when the reaction was performed in the presence of EDA and a mixture of two cyclopropanated products was obtained. This last result was also obtained generating (TPP)Os=$CHCO_2$Et directly in solution by stoichiometric amount of EDA on the

osmium porphyrin and reacting the obtained carbene compound with $N_2CH(Mes)$ and styrene. For clarity, in scheme 6 we report the simple equations of these experiments.

All the above cited experiments demonstrate that the active species in the reaction is probably a bis(carbene) complex and this conclusion is also supported by the evidence that (TPP)Os=$CHCO_2Et$, generated in *situ* by the stoichiometric addition of EDA to (TPP)Os, in the presence of styrene, gives the cyclopropanated product after many hours. The authors concluded that the attack of the olefin to the second carbene ligand is favoured by the electron-withdrawing effect of the first one.

2.4. Ruthenium porphyrin catalysts

Few reports appeared in the literature for the cyclopropanation reactions of olefins catalysed by ruthenium porphyrins. The first paper was published in 1997 as a short communication and reported on the cyclopropanation of styrene derivatives performed with different ruthenium *meso*-tetraphenylporphyrins, one of which bearing chiral residues.[47] The results for the non-chiral catalysts are reported in Table 7.

Table 7. Cyclopropanation of styrene derivatives by EDA using ruthenium porphyrin complexes as catalysts (According to ref. 47. Reproduced from *J. Chem. Soc., Chem. Commun.* **1997**, 927 by permission of The Royal Society of Chemistry).

Substrate	Catalyst	Ratio of *trans:cis* products[a]	Alkene yield[b]
Styrene	Ru(TPP)CO	13.1	7
Styrene	Ru(TMP)CO	7.9	<5
Styrene	$Ru(TMP)(O)_2$	7.1	<5
α-methylstyrene	Ru(TPP)CO	3.1	7
α-methylstyrene	Ru(TMP)CO	1.6	<5
α-methylstyrene	$Ru(TMP)(O)_2$	1.5	<5
p-chlorostyrene	Ru(TPP)CO	14.0	8
p-chlorostyrene	Ru(TMP)CO	8.2	<5

[a]Determined by GC. [b]Diethyl maleate and fumarate

The *trans* selectivities are very similar to those reported for iron and osmium porphyrin catalysts and only a low increase in the diastereoselectivity is observed using Ru(TPP)CO instead of the more crowded Ru(TMP)CO. The enantioselectivity was tested on the styrene using the dioxoruthenium(VI) picket-fence complex bearing optically active α-methoxy-α-(trifluoromethyl)phenyl acetyl residues on both sides of the porphyrin plane(α, β, α, β isomer) and the enantiomeric excesses obtained for the *trans* and *cis* products were 14 and 34% respectively. The formation of an active carbene ruthenium derivative was demonstrated by ^1H NMR spectroscopy when Ru(TMP)CO was used as the catalysts. The α-carbon proton of the coordinated carbene appeared at δ 13.23 due to the deshielding effect of the porphyrin ring.

In the same year, two other communications from different groups appeared in the literature, reporting interesting results in the asymmetric catalytic cyclopropanation of styrene, both based on the same

ruthenium catalyst.[48,49] This enantiomerically pure catalyst was the metal derivative of the D_4 porphyrin (H_2P^*), which was reported, for the first time, by Halterman and Jan and is shown in Figure 6.

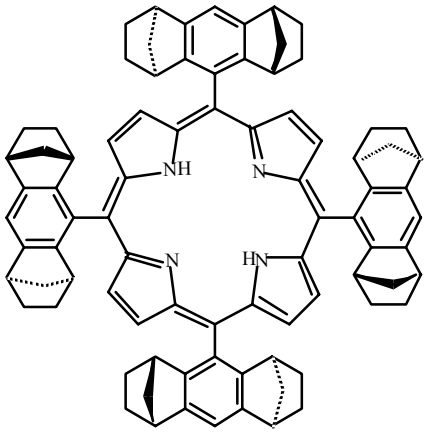


Figure 6

In the first paper, the results obtained using other ruthenium porphyrins were also reported. However the most interesting results were the enantiomeric excesses obtained for the *trans* isomer which were reported in both the papers between 80 and 91%. For the *cis* isomer the results were less interesting and for this reason two further studies were later performed by other research groups.[50,51] They used the approach developed by Gross for the synthesis of chiral porphyrins, consisting in the alkylation of the *meso*-tetra(2', 6'-dihydroxyphenyl)porphyrin with chiral residues. The molecular structure of such catalysys are reported in Figure 7.

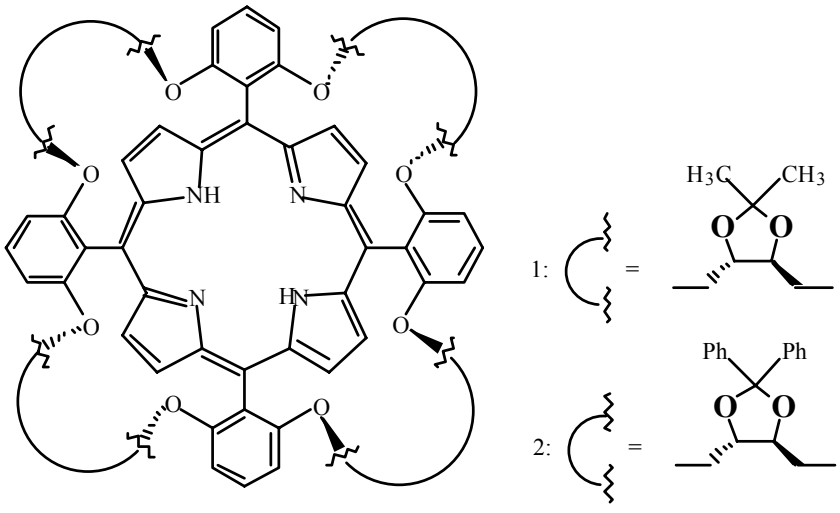


Figure 7

The Gross' group was able to obtain 23% of enantiomeric excess for the *cis* isomer obtained by the reaction of EDA on styrene catalysed by ruthenium derivatives of the above cited chiral porphyrins.[50] More recently, the structure of a ruthenium porphyrin carbene has been reported by Simonneaux and co-workers.[52] Such complex was obtained by reacting Ru(TPP) with diethyl diazomalonate and it is stable at room temperature. The isolated carbene was kept to react with styrene and gave a *trans/cis* ratio of 14, similar to the value of 13.8 obtained for the one-pot reaction.

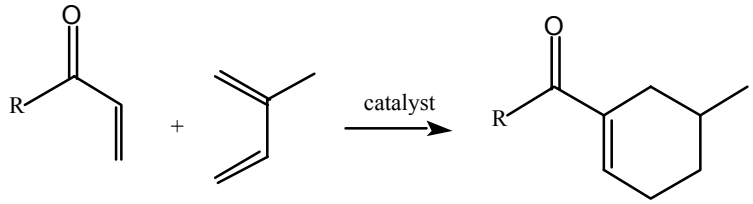
Some interesting developments have been recently obtained by Che and co-workers.[53,54] In a first paper they reported the immobilization of the catalysts on a soluble polymer and the use of such system for the epoxidation, aziridation and cyclopropanation of several alkenes. In particular they reported the cyclopropYl ring formation from EDA and *para* substituted styrenes. The yields of these reactions are quite good and the *trans/cis* ratio are all around 10. The second paper reports on the use of the ruthenium porphyrins as catalysts in the reactions of diazo ketones with π-unsaturated compounds with the formation of interesting cycloadducts.

3. Diels-Alder reaction

The Diels-Alder reaction is one of the most important synthetic process in organic chemistry and belongs to the general class of the cycloaddition reactions.[55-57] In this reaction a 1, 3-diene reacts with an olefinic or acetylenic compound, the dienophile, to give a six-membered adduct. Two σ-bonds are formed from two π-bonds of the diene. Sometimes, with unreactive starting products, vigorous reaction conditions are necessary and catalysts can be useful for accelerating the process.[58-60]

3.1. Catalysis by aluminium and rhodium porphyrins

It is well known from the literature that the Lewis acids are efficient catalysts for promoting the addition of the α,β-unsaturated compounds to a diene and compounds like diethyl aluminium chloride (DEAC) catalyses this reaction affording good yields in cycloadducts.[61-63] The simple reaction equation is reported in Scheme 7.



Scheme 7

Table 8. Isolated yields of cycloadducts (According to ref. 64. Reprinted from *Tetrahedron Lett.* **1990**, *44*, 6303-6306, Bartley, D. W. and Kodadek, T., Catalysis of Diels-Alder reactions by metalloporphyrins. Copyright 1990, with permission from Elsevier Science.).

	Cyclopentadiene			Isoprene		
	None	DEAC	AlTPPCl	None	DEAC	AlTPPCl
R=H	7.5%	67.4%	74.0%	0.0%	48.3%	47.8%
R=CH_3	15.7%	64.9%	73.3%	0.0%	48.2%	3.8%
R=CH_2CH_3	10.8%	70.8%	67.6%	0.0%	45.4%	5.9%
R=OCH_3	0.0%	77.0%	0.0%	0.0%	51.6%	0.0%

The mechanism of this reaction is based on the complexation of carbonyl oxygen of the α, β unsatured compounds by the metal which acts as a Lewis acid making the double bond more electrophilic. This fact suggested the possibility to use a metalloporphyrin as catalyst for the cycloaddition of carbonyl

compounds to simple dienes and in Table 8 are reported the results obtained by Kodadek using Al(TPP)Cl as catalysts.[64] It is interesting to note that the reaction is selective toward the substrates and only ketones and aldehydes are enough reactive to give the final compounds, while the esters are completely unreactive.

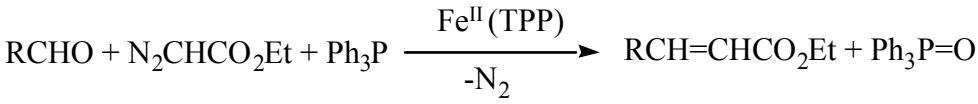
This selectivity can give the possibility to discriminate between different groups within the same starting compounds.

4. **Olefination of aldehydes**

The formation of the carbon-carbon double bond is an interesting and important reaction because it can be found in the synthesis of natural products and polymers.[65,66] There are several methods in the literature for the conversion of different organic groups into the double bond and many are based on the catalysis by the organometallic compounds and the iron systems are particularly efficient and not expensive.

4.1. Catalysis by iron porphyrins

Recently, in the literature appeared a new application of the porphyrins catalysis based on the reaction of an iron porphyrin carbene, formed from EDA and Fe^{II}(TPP), with aldehydes.[67] Such new method involves the formation of an olefinic compound as described in Scheme 8.



R= Ph-, *p*-$CH_3C_6H_4$-, *p*-ClC_6H_4-, *p*-$NO_2C_6H_4$-, $PhCH_2$-, Ph_2CH-

1 **2** **3** **4** **5** **6**

Scheme 8

Such reaction gives excellent yields of final compounds at room temperature in toluene, with good *trans* selectivities. In the reaction pathway is present the triphenylphosphine which acts as oxygen scavenger forming the phospine oxide which must be separated from the other products. The yields, the selectivities and other important parameters of the above cited reaction for different substrates are reported in Table 9.

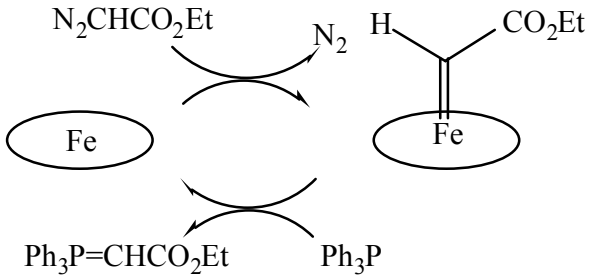
Table 9. Olefination of aldehydes with EDA/PH_3P/Fe^{II}(TPP) (According to ref. 67. Reprinted from *J. Am. Chem. Soc.* **2002**, *124*, 176. Copyright 2002 American Chemical Society).

alde-hyde	reaction time(h)	yield (%)	turnover no.	*trans/cis* selectivity	alde-hyde	reaction time(h)	yield (%)	turnover no.	*trans/cis* selectivity
1	6	94	128	24:1	**4**	2	90	80	24:1
2	12	99	119	24:1	**5**	23	85	95	10:1
3	3	95	98	13:1	**6**	12	93	64	49:1

The proposed mechanism of the reaction involves the formation of a phosphorane intermediate which is actually the active species. In fact, when a phosphorane is isolated from the reaction of the carbene with

the phospine, it produces the olefin and the phosphine oxide when reacting with the aldehyde. The formation of the phosphorane, with the final step of the reaction is reported in Scheme 9.

The reaction rates and the *tran/cis* selectivities seems to be affected by the nature of the aldeheyde, the most reactive being those bearing electron-withdrawing groups, *i.e.* chlorine or nitro.



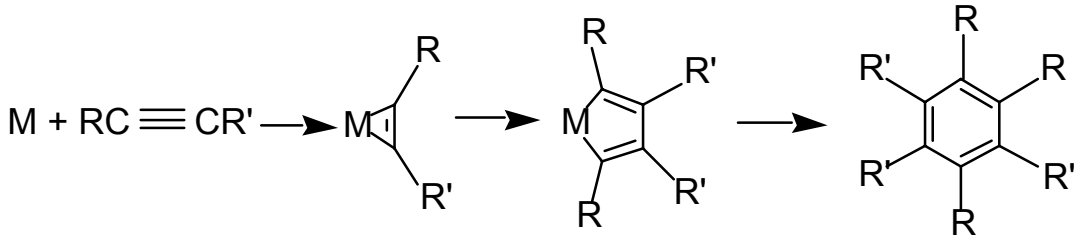
$$Ph_3P{=}CHCO_2Et + RCH{=}O \longrightarrow RCH{=}CHCO_2Et + Ph_3P{=}O$$

(Reprinted from *J. Am. Chem. Soc.* **2002**, *124*, 176. Copyright 2002 American Chemical Society**)**

Scheme 9

5. Cyclotrimerization of acetylene derivatives

The activation of the triple bond, namely the Reppe's reaction, to give aromatic compounds is a well known process[68-70] and several catalysts have been used to promote it. Such reaction, starting from mono or disubstituted acetylenes, usually gives a mixture of symmetrical (1,3,5) and unsymmetrical(1,2,4) substituted benzenes.[71,72]



Scheme 10

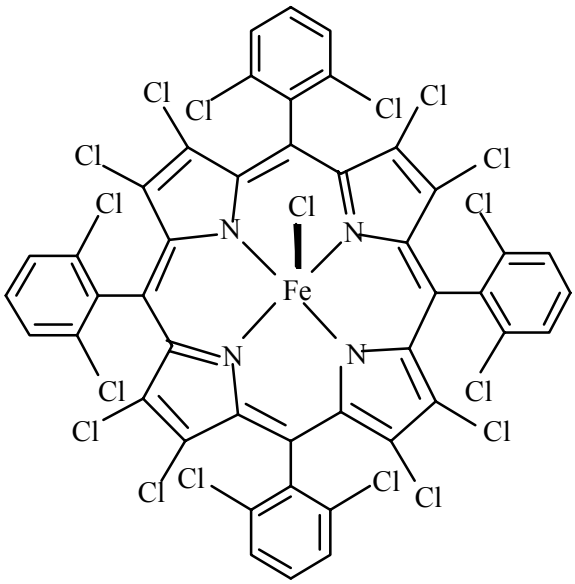
The mechanism of the formation of the 1,2,4 substituted isomer was established to involve the consecutive presence of metallocyclopropene and metallocyclobutadiene compounds formed from the consecutive addition of three molecules of acetylene to the metal residue, as shown in Scheme 10.[69]

However, a simple trend in the formation of the products was tentatively proposed on the basis of the different metals and the steric interaction between the catalysts and the intermediates. Cobalt, rhodium, nickel, aluminum and other metal complexes were used as catalysts for such reaction, which can give also the cycloctatetraene (COT) derivatives as by-products.

5.1. Substituted benzenes from acetylenes: catalysis by iron porphyrins

In this review we want to report our recent results on the investigation of the remarkable properties, in catalysing the formation of benzene derivatives from substituted acetylenes, of $Fe^{II}(Cl_8)TDCPP$, where

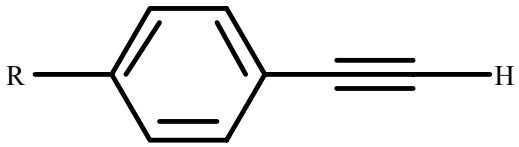
(Cl_8)TDCPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis-(2',6'-dichlorophenyl) porphyrin.[73] The reactions were performed, when possible, without solvents at 120 °C or in boiling dry chloroform and under strictly anaerobic conditions. The catalyst was generated *in situ* by the cobaltocene stoichiometric chemical reduction of the iron(III) porphyrin chloride precursor. This porphyrin catalyst precursor was synthesised by literature method and its structure is reported in Figure 8.[74]



iron (III) 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis-(2',6'-dichlorophenyl)porphyrin chloride

Figure 8

An interesting observation derived from the fact that, in our experiments, only iron(II) catalyst , bearing eight chlorine atoms on the beta positions of the macrocycle, is able to catalyse the reaction while other iron(II) porphyrins, like FeTPP or FeTDCPP systematically fail. This fact, in our opinion, is related to the stabilization in the +2 oxidation state of the iron[75] due to the presence of *beta* halogen atoms on the porphyrins skeleton. Furthermore, running the experiments in the presence of oxygen, which maintains the iron to +3 oxidation state, the reaction does not occur. In addition, it should be also considered the difficulties of the acetylenic compounds to be coordinated on an electron-rich iron(II). We report the molecular structures of the phenylacetylene derivatives used for the experiments in Figure 9.

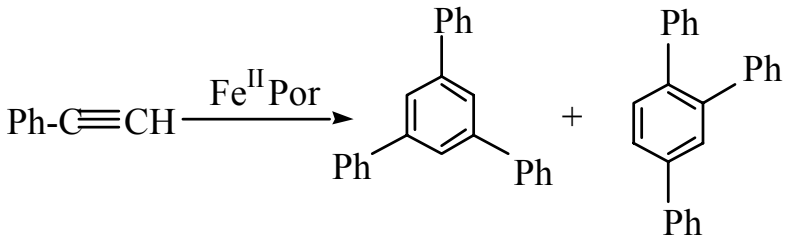


1. R=H
2. R=Cl
3. R=Br
4. R=OCH_3

Figure 9

The reaction performed on the substrates using our catalyst always give a mixture of the 1,2,4 and 1,3,5 triphenyl substituted benzenes as reported in Scheme 11 for the case of phenylacetylene. We report the

reaction yields and the selectivities for several phenyl acetylene derivatives in Table 10. The final conversions were always between 72 and 90% depending on the nature of the substituents.



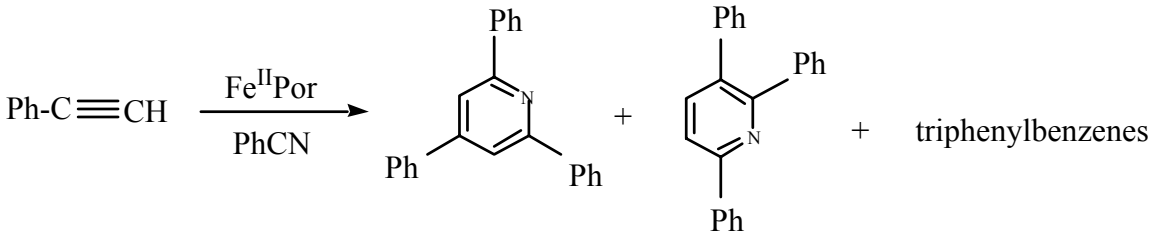
Scheme 11

Table 10. Catalytic cyclotrimerization of substituted phenylacetylenes using $Fe^{II}(Cl_8)$TDCPP as Catalyst (According to ref. 73).

Entry	R	R'	Conditions	Conversion	Yield(%)	ratio of of 1, 2, 4 /1, 3, 5 products
1	H	H	120° C, 18h	90	86	1.8
2	Cl	H	120° C, 18h	72	70	3.0
3	Br	H	120° C, 36h	72	70	1.6
4	OCH_3	H	120° C, 24h	85	78	1.7

[a]Reaction performed in $CHCl_3$

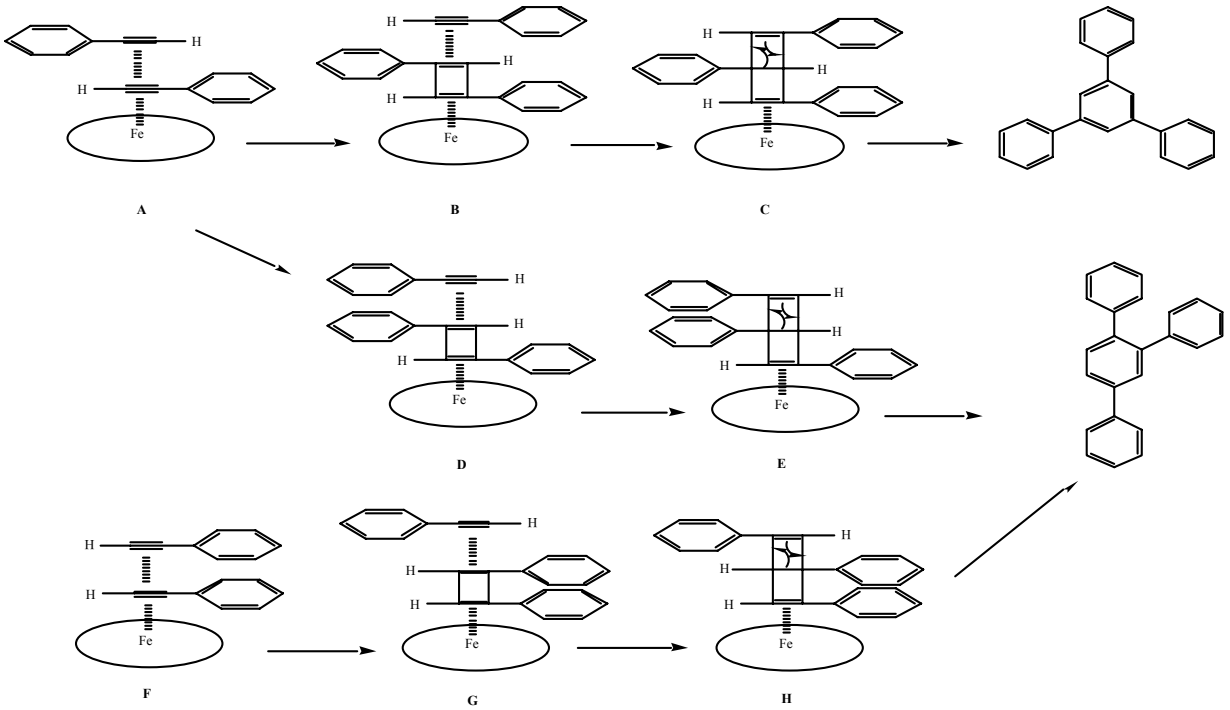
Another interesting reaction has been found running the experiments with phenylacetylene in the presence of benzonitrile, a reagent with a triple bond between carbon and nitrogen.[76] We found that such triple bond acts like a carbon-carbon triple bond, giving a mixture of substituted piridine in 60% of yield, based on benzonitrile. This reaction affords a mixture of two regio-isomers with an isomeric ratio of 26 as reported in Scheme 12.



26 1

Scheme 12

It is also important to remark that, in our opinion, a complicated reaction mechanism is involved in the porphyrin catalysed reactions but first of all we believe to exclude the formation of the metallocycle intermediates. Such intermediates should involve the formation of two σ metal-carbon bonds on the same face of the macrocycle and this possibility can be ruled out for the iron which does not have the suitable orbitals for binding. We propose a tentative mechanism to explain the stereochemistry found for the products and we have reported our interpretation of the obtained results, in the case of phenylacetylene in Scheme 13.



Scheme 13

In such a scheme, the iron porphyrin coordinates the first molecule of the alkyne through a π orbitals-metal interaction, activating the triple bond for the attack of a second molecule as in **A** or **F,** where are reported the two statistical isomers. The subsequent reaction gives unstable cyclobutadiene intermediates, as shown in **B** or **G**, still coordinated on the metal. Such adduct undergoes the attack of the third molecule of phenylacetylene, again in a statistical way, giving the intemediates **C**, **E** and **H,** which easily rearranges to the final benzene derivatives. The intermediate **G** might undergo to the attack of the third molecule of alkyne from the same side giving the 1,2,3 substituted isomer, but this possibility can be ruled out, because of the steric hindrance between the phenyls and the porphyrin.

5.2. Substituted benzenes from acetylenes: catalysis by rhodium porphyrins

As reported in the case of the cyclopropanation of the olefins by EDA, the iron(II) porphyrins are isoelectronic with Rh(III) ones and for this reason we tried to make the ciclotrimerization of alkynes in the presence of different rhodium porphyrins.[77] The reactions were performed as reported above for the iron porphyrins but the deaereation was not necessary because the stability of the Rh(III) porphyrins is high and we did not observe any decomposition of the catalysts, even in the presence of molecular oxygen.

The results of the reactions with phenylacetylene are reported in Table 11. The yields of the reactions are lower if compared with those for the iron catalysts, but the selectivities are higher, giving in many cases, the 1,2,4 substitued isomer as the main product.

It is interesting to note that the electron-withdrawing substituents on the macrocycle seems to have an influence on the selectivities, giving higher quantities of the 1,2,4 isomer. The most intriguing observation on this catalytic system derived from the GC-mass data obtained from all the reactions performed in the presence of rhodium porphyrins.We found a chromatographic peak at a retention time shorter than those for the triphenylbenzenes, giving an m/z=204. This value corresponds to that calculated for diphenyciclobutadiene but this compound could not be isolated from the reaction media due to its high

reactivity. However it can be concluded that the diphenylciclobutadiene can be a good candidate as a reaction intermediate in the cyclotrimerization of alkynes catalysed by rhodium porphyrins.

Table 11. Catalytic cyclotrimerization of phenylacetylene using rhodium porphyrins as catalysts (According to ref. 75).

Catalyst	Yield(%) (conversion)	ratio of of 1, 2, 4 /1, 3, 5 substitued products	ratio of 1, 2, 4 /diphenylcyclobutadiene products
Rh(TPP)Cl	40(48)	3	2
Rh(TDCPP)Cl	50(70)	9	29
Rh(TDMPP)Cl	40(50)	2.5	0.8
Rh(Cl_{16}TDMPP)Cl	40(45)	8.6	80

6. Conclusions

We have reported on the catalytic formation of the carbon-carbon bond by metalloporphyrins and the extreme promising potentiality of such catalysts in the organic synthesis. The selectivities of these systems depend on the steric hindrance experimented by the substrates when approaching the core of the macrocycles and on the electronic situation of the metal. More work is necessary to have the access to new sets of reactions that can be catalysed by the metalloporphyrins and this field of research, in our opinion, can be considered a stimulating challenge for all the scientists involved in the porphyrins chemistry.

Acknowledgements

The author wish to thank all the students cited in the references who worked in his laboratory on the cyclopropanation and cyclotrimerization projects and Prof. Barbara Floris and Dr. Pierluca Galloni for their scientific contribution. He likes also to thank Giuseppe D'Arcangelo and Alessandro Leoni for their valuable technical support in recording mass spectra and GC analysis.

References

1. Masters, C. *Homogeneous Transition-Metal Catalysis*, Chapman Hall, 1981.
2. Parshal, G. W. *Homogeneous Catalysis*, Wiley-Interscience, New York, 1980.
3. James, B. R. *Adv. Organomet. Chem.* **1979**, *17*, 319.
4. Karasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, New York, 1954.
5. Jones, R. G.; Gilman, H. *Org. React.* **1951**, *6*, 339.
6. Fleming, I.; Paterson, I. *Synthesis* **1979**, 446.
7. Ortiz de Montellano, P. R. ed., *Cytochrome P450, Structure, Mechanism and Biochemistry,* Plenum Press, New York, 1986.
8. Meunier, B. *Chem. Rev*. **1992**, *92*, 1411.
9. Mansuy, D. *Coord. Chem. Rev*. **1993** *125*, 129.
10. Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101,* 1032.
11. Traylor, T. S.; Dolphin, D.; Traylor, T. G. *J. Chem. Soc., Chem. Commun.* **1984**, 279.
12. De Poorter, B.; Meunier, B. *Tetrahedron Lett.* **1984**, 1895.
13. Traylor, T. G.; Marsters, J. C.; Nakano, T.; Dunlap, B. E. *J. Am. Chem. Soc.* **1985**, *107,* 5537.
14. Renaud, J. P.; Battioni, P.; Bartoli, J. F.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1985**, 888.

15. Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110,* 8462.
16. Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26,* 1338.
17. Wijesekera, T.; Matsumoto, A.; Dolphin, D.; Lexa, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1028.
18. Artaud, I.; Ben Aziza, K.; Mansuy, D. *J. Org. Chem.* **1993**, *58,* 3373.
19. Artaud, I.; Ben Aziza, K.; Chopard, C.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1991**, 31.
20. Ellis, P. E.; Lyons, J. E. *Cat. Lett*. **1989**, *3*, 389.
21. Lyons, J. E.; Ellis, P. E. *Cat. Lett*. **1991**, *8,* 45.
22. Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.
23. Callot, H. J.; Piechocki, C. *Tetrahedron Lett.* **1980**, *21*, 3489.
24. Callot, H. J.; Metz, E.; Piechocki, C. *Tetrahedron* **1982**, *38*, 2365.
25. O'Malley, S.; Kodadek, T. *Tetrahedron Lett.* **1991**, *32*, 2445.
26. Maxwell, J. A.; Kodadek, T. *Organometallics* **1991**, *10*, 4.
27. Hamaker, C. G.; Djukic, J-P.; Smith, D. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5189.
28. Hamaker, C. G.; Mirafzall, G. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5171.
29. Che, C-M.; Huang, J-S. *Coord. Chem. Rev.* **2002**, *231*, 151.
30. Bartley, D. W.; Kodadek, T. *J. Am. Chem. Soc.* **1993**, *115*, 1656.
31. O'Malley, S.; Kodadek, T. *Organometallics*, **1992**, *11*, 2299.
32. Maxwell, J. A.; O'Malley, S.; Brown, K. C.; Kodadek, T. *Organometallics* **1992**, *11*, 645.
33. Maxwell, J. A.; Brown, K. C.; Bartley, D. W.; Kodadek, T. *Science* **1992**, *2561*, 1544.
34. Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.
35. Tagliatesta, P.; Pastorini, A. *J. Mol. Catal. A : Chemical* **2002**, *185*, 127.
36. Mandon, D.; Ochsenbein, P.; Fischer, J.; Weiss, R.; Jayaraj, K.; Austin, R.N.; Gold, A.; White, P. S.; Brigaud, O.; Battioni, P.; Mansuy, D. *Inorg. Chem*. **1992**, *31*, 2044.
37. Ochsenbein, P.; Ayougou, K.; Mandon, D.; Fischer, J.; Weiss, R.; Austin, R. N.; Jayaraj, K.; Gold, A.; Terner, J.; Fajer, J. *Angew. Chem*. *Int. Ed. Engl.* **1994**, *33*, 348.
38. Rocha-Gonçalves, A. M. A.; Varejao, J. M. T. B.; Pereira, M. M. *Heterocyclic Chem.* **1991**, *28*, 635.
39. Robbins Wolf, J.; Hamaker, C. G.; Djukic, J-P.; Kodadek, T.; Woo, L. K *J. Am. Chem. Soc.* **1995**, *117*, 9194.
40. Baciocchi, E.; Cassioli, L.; Galli, G.; Jaquinod, L.; Lapi, A.; Paolesse, R.; Smith, K. M.; Tagliatesta, P. *Eur. J. Org. Chem*. **1999**, 3281.
41. Tagliatesta, P.; Pastorini, A. *J. Mol. Catal. A : Chemical*, in press.
42. Hamaker, C. G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5171.
43. Woo, L. K.; Smith, D. A. *Organometallics* **1992**, *11*, 2344.
44. Smith, D. A.; Reynolds, D. N.; Woo, L. K. *J. Am. Chem. Soc.* **1993**, *115*, 2511.
45. Djukic, J-P.; Smith, D. A.; Young, V. G. Jr.; Woo, L. K. *Organometallics* **1994**, *13*, 3020.
46. Hamaker, C. G.; Djukic, J-P.; Smith, D. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5189.
47. Galardon, E.; Le Maux, P.; Simonneaux, G. *J. Chem. Soc., Chem. Commun.* **1997**, 927.
48. Lo, W-C.; Che, C-H.; Cheng, K-F.; Mak, T. C. W. *J. Chem. Soc., Chem. Commun.* **1997**, 1205.
49. Frauenkron, M.; Berkessel, A. *Tetrahedron Lett.* **1997**, *41*, 7175.
50. Gross, Z.; Galili, N.; Simkhovich, L. *Tetrahedron Lett.* **1999**, *40*, 1571.
51. Galardon, E.; Roue', S.; Le Maux, P.; Simonneaux, G. *Tetrahedron Lett.* **1998**, *39*, 2333.
52. Galardon, E.; Le Maux, P.; Toupet, L.; Simonneaux, G. *Organometallics* **1998**, *17*, 565.
53. Zang, J-L.; Che, C-M. *Org. Lett.* **2002**, *4*, 1911.
54. Zhou, C-Y.; Yu, W-Y.; Che, C-M. *Org. Lett.* **2002**, *4*, 1911.
55. Huisgen, R.; Grashey, R.; Sauer, J. in *The Chemistry of Alkenes*; Patai S., Ed; Interscience, London, 1964.
56. Huisgen, R. *Angew. Chem*. *Int. Ed. Engl.* **1968**, *7*, 321.
57. Schmidt, R. R. *Angew. Chem*. *Int. Ed. Engl.* **1973**, *12*, 212.
58. Onischenko, A. S. in *Diene Synthesis*, Davey, New York, 1964.
59. Sauer, J. *Angew. Chem*. *Int. Ed. Engl.* **1966**, *5*, 211.
60. Sauer, J. *Angew. Chem*. *Int. Ed. Engl.*, **1967**, *6*, 16.
61. Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789.

62. Corey, E. J.; Iminkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.
63. Kreiser, W.; Haumesser, W.; Thomas, A. F. *Helv. Chim. Acta* **1974**, *57*, 164.
64. Bartley, D. W.; Kodadek, T. *Tetrahedron Lett.* **1990**, *44*, 6303.
65. Katz, T. J. *Adv. Organomet. Chem.* **1977**, *16*, 283.
66. Chien, J. C. W. *Coordination Polymerization*, Academic Press, New York, 1975.
67. Mirafzall, G. A.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 176.
68. Reppe, W.; Kutepow, N.; Magin, A. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 727.
69. Yur'eva, L. P. *Russ. Chem. Rev.* **1974**, *43*, 48.
70. Vollhardt, K. P. C. *Acc. Chem. Res.* **1976**, *10*, 1.
71. Reikhsfel, V. O.; Makovetskii, K. L. *Russ. Chem. Rev.* **1966**, *35*, 510.
72. Maitlis, P. M. *J. Organometal. Chem.* **1980**, *200*, 161.
73. Tagliatesta, P.; Leoni, A.; Galloni, P.; D' Arcangelo, G. to be submitted.
74. Rocha Gonsalves, A. M. A.; Johnstone, R. A. W.; Pereira, M. M.; Shaw, J.; Sobral, A. J. F. N. *Tetrahedron Lett.* **1991**, *32*, 1355.
75. Autret, M.; Ou, Z.; Antonini, A.; Boschi, T.; Tagliatesta, P.; Kadish, K. M. *J. Chem. Soc., Dalton Trans.* **1996**, 2793.
76. Tagliatesta, P, to be submitted.
77. Tagliatesta, P; Galloni, P. to be submitted.

PYRAZOLES AS DRUGS: FACTS AND FANTASIES

José Elguero,*[a] Pilar Goya,[a] Nadine Jagerovic[a] and Artur M. S. Silva[b]

[a]*Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain (e-mail: iqmbe17@iqm.csic.es)*

[b]*Departamento de Química, Universidade de Aveiro, Campus Universitário de Santiago, P-3800-193 Aveiro, Portugal (e-mail: arturs@dq.ua.pt)*

Abstract. *This review examines the past and the present of pyrazole derivatives in medicinal chemistry. From an important past, exemplified in the analgesic and anti-inflammatory pyrazolones and pyrazolindiones, not devoid of severe complications, to a glorious present with some of the most important drugs of recent times (sildenafil, celecoxib) being pyrazole derivatives. The progress of the last twenty years will be emphasized although some older references will be reported when significant.*

Contents

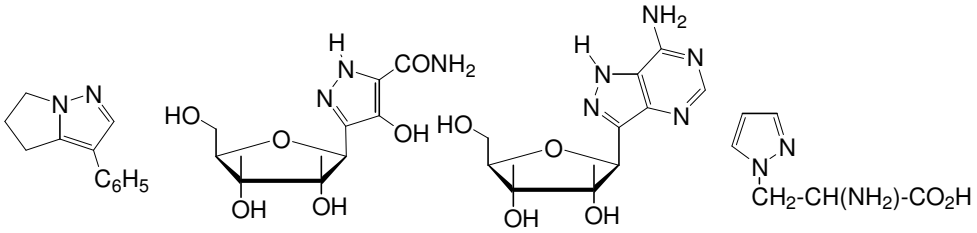
1. Introduction

This review deals with the medical applications of pyrazoles and their derivatives (pyrazoles, pyrazolines, pyrazolidines, pyrazolones, pyrazolidinones, indazoles…), herbicidal and other agrochemical compounds being excluded. In general, references are from 1980 onwards but some earlier important papers are quoted; only journals have been considered, thus patents have been excluded.

In the pharmaceutical industry, pyrazoles and their derivatives are not so well considered as other azoles, such as imidazole. This is probably related to the problems associated with the large class of analgesics and anti-inflammatory agents having a pyrazole skeleton (see Sections **2.2.2.** and **4.1.**). These compounds, known from old, have shown a variety of serious haematological side effects, like agranulocitosis, aplastic and hemolytic anemias and thrombocytopenia.

It is true that compared with imidazoles, natural pyrazoles are rare compounds. In three ouvrages,[1-3] four pyrazoles found in nature are reported: whitasomnine **1** (an alkaloid isolated from the roots of an Indian medicinal plant, *Withania somnifera*), pyrazofurin or pyrazomycin **2** (an antibiotic isolated from the fermentation broth of *Streptomyces candidus*), formycin **3** (a naturally occurring isomer of adenosine) and L-β-pyrazolylalanine **4** (found in the seeds of many species of *Cucurbitaceae*).

Classification by chemical structure is important in medicinal chemistry. This allows direct considerations of structure-activity relationships. Without discarding this concern, a classification[4] taking into account the mode of action of the drugs and the nature of the disease was adopted for this review. Four major classes are distinguished: agents acting on the central nervous system, pharmacodynamic and chemotherapeutic agents and agents acting on metabolic diseases and on endocrine functions.

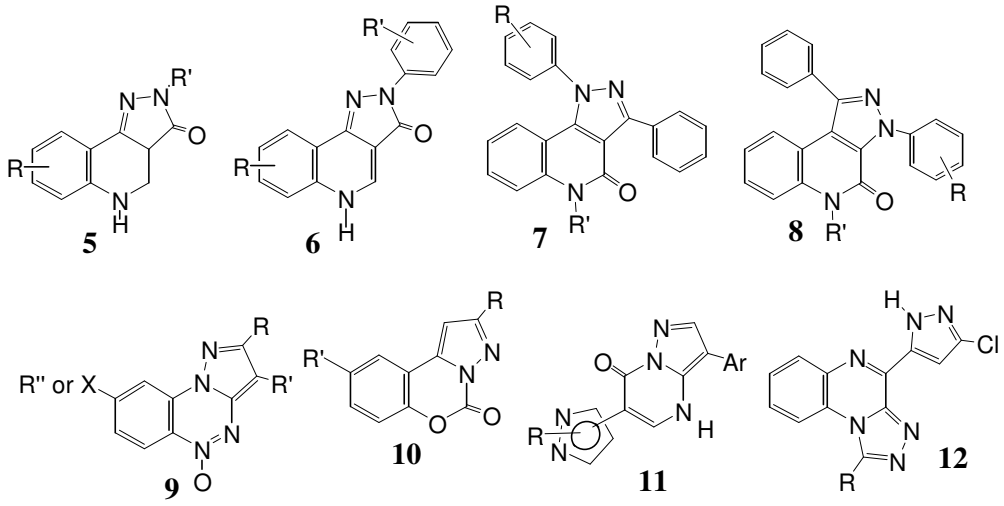


Withasomnine **1** Pyrazofurin **2** Formycin **3** L-β-Pyrazolylalanine **4**

Although in this review no attempt has been made to classify the reported compounds with a chemistry criterion, we will occasionally consider that the pyrazole nucleus is part of the central core of the drug or that it is a substituent of the pharmacophore. When the compounds have been reported in the *Merck Index* (13th Edition, 2001, hereafter MI) the corresponding number will be quoted in bold.

2. Agents acting on the central nervous system

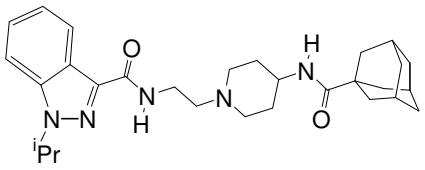
Most of the novel central BDZ receptor ligands, not related to benzodiazepine, contain a pyrazole ring and thus, pyrazoloquinolines **5**,[5] pyrazoloquinolones **6-8**,[6,7] pyrazolobenzotriazines **9**,[8,9] pyrazolo-benzoxazines **10**,[10] pyrazolopyrimidines **11**[11] or chloropyrazolyl-triazoloquinoxalines **12** have been reported in the literature.[12] There are marked differences in the biological profiles of these ligands.[13] Full agonist ligands exhibit anticonvulsant, sedative and muscle relaxant effects together with anxiolytic properties. In contrast, partial agonists provide anxiolytic activity without the undesired side effects and inverse agonists cause the opposite behavioural effects such as anxiogenesis and proconvulsant action. Since small modifications in the structure of pyrazole containing ligands can cause a shift from agonistic to antagonistic activities, common structural features responsible for specific intrinsic activity have been studied. Recently, several pharmacophore models have been proposed although they have not achieved yet the ability to correctly predict the intrinsic activity.[11,12,14] The pyrazoles that display a specific medical application will be reported in the corresponding sections.



2.1. Antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics

The extraordinary variety of subtypes, increasing importance and manifold CNS activities of serotonine receptors,[15-18] decided us to describe here some pyrazoles acting on 5-HT_{1A} (depression, section

2.1.1., references 19-21; anxiety, section **2.1.3.**, reference 22), 5-HT_3 (emesis, section **3.2.2.**, references 23,24) and 5-HT_4 receptors. Close to serotonine is the *N*-methyl-*d*-aspartate receptor (NMDA)[18,25] related to depression (section **2.1.1.**, reference 26). They will be discussed in the corresponding sections, save a publication dealing with the 5-HT_4 receptor, whose proposed therapeutic applications include the treatment of irritable bowel syndrome, atrial arrhythmias, urinary incontinence, and various diseases of the central nervous system.[27] The authors have identified LY353433 (1-(1-methylethyl)-*N*-[2-[4-[(tricyclo [3.3.1.1^{3,7}]dec-1-yl-carbonyl)amino]-1-piperidinyl]ethyl]-1*H*-indazole-3-carboxamide) (**13**) as a potent and selective 5-HT_4 receptor antagonist with clinical suitable pharmacodynamics.[27]



13

2.1.1. Antidepressants

In the search of drugs with antidepressant activities and reduced adverse effects, pyrazoles, as part of a tricyclic structure or not, were found to be interesting compounds. Among a series of indazoles studied in the late seventies, **14** (FS-32) presented antidepressant properties with a pharmacological profile different from conventional benzodiazepine derivatives.[28] In this context, ten years later, the corresponding pyrazole, fezolamine, *N*,*N*-dimethyl-(3,4-diphenyl-1*H*-pyrazole)-1-propanamine (**15**), was identified by Sterling-Winthrop Research as a potential antidepressant with significant reduced side effects.[29]

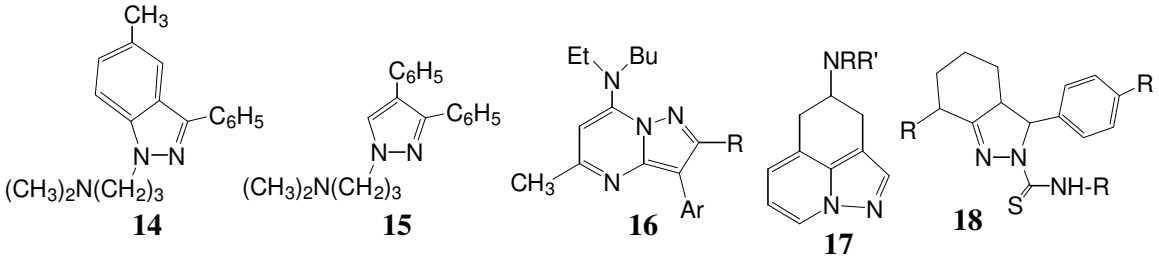
Tricyclic structures **9** containing a pyrazole moiety[8] and pyrazoloquinolin-3-ones[30] have been synthesised to evaluate their $GABA_A$-benzodiazepine receptor affinities. 3-Chloropyrazole as substituent of tricyclic heterocycles, triazoloquinoxalines **12**, has shown to be efficient for binding to the $GABA_A$-benzodiazepine and A_1/A_{2A}-adenosine receptors.[12] It is worthy to note that most of the adenosine receptor antagonists, which are of interest for the treatment of depression, dementias or morbus Parkinson, are pyrazolopyrimidines or pyrazolopyridines and some of them are currently under clinical development.[31] Pyrazolopyrimidine structures **16**[32] have been also studied for their antagonistic properties for the corticotropin releasing factor CFR-1 receptor whose activation is related to depression and anxiety. In search of new class of neuroleptic drugs, pyrazolo[1,5-*a*]pyridine structures **17**[33] have been evaluated for presynaptic dopamine autoreceptor agonist activity.

An attempt to substitute the terminal carboxylic group of (*S*)-α-aminoadipic acid, an excitatory amino acid (EAA) by a 3-pyrazolone failed because the compound did not show significant effects on EAA receptors.[26]

2-Pyrazolines bearing a thiocarbamoyl group **18** have been reported as good leads for BSAO-bovine serum amine oxide inhibitors.[34] These enzymes, which seem to display biochemical behaviour similar to that of MAOB, are useful models in the search of antidepressant, antiparkinson and anticholinergic agents.

It is assumed that 5-HT_{1A} receptors are implicated in major depressive disorders. Ligands (buspirone, ipsapirone) reported so far are partial agonists and present limited clinical efficacy and long duration of onset. As a consequence, these last years, efforts have been dedicated to design ligands with high intrinsic

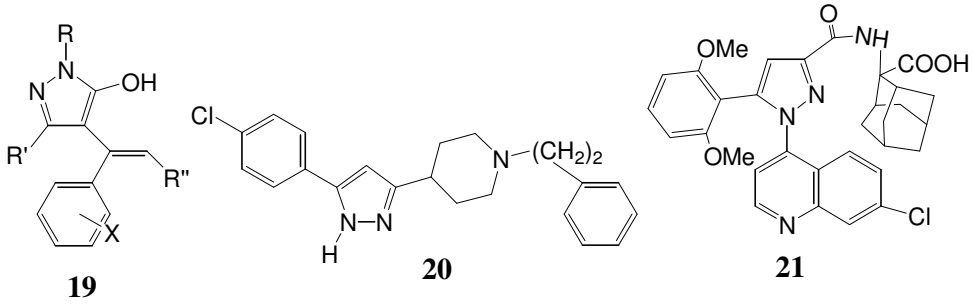
activity. Among these studies, pyrazole,[19,20] as a π-electron-releasing substituent of 6-substituted-2-pyridinylmethylamine, has shown to increase recognition and activation of 5-HT_{1A} receptors.



2.1.2. Antipsychotics

Due to the interest in improving antipsychotic efficacy and neurological side effects of antipsychotic agents such as chlopromazine, a series of 1,3-dialkyl-4-(iminoarylmethyl)-1*H*-pyrazol-5-ols **19** has been described.[35] Since they do not act *via* the brain dopamine receptors like classical antipsychotics do, they do not present neurological side effects such as the extrapyramidal syndrome or dyskinesia; structural modifications were examined to further reduce their toxicity.[36]

Recent advances in molecular biology have identified five cloned human subtypes of dopamine receptors. The human D_4 subtype receptors have been reported to be involved with antipsychotic activity. Pyrazolopiperidine **20** and a series of structural analogs have been identified as novel highly and selective human D_4 receptor antagonists.[37,38] Structural modifications include incorporation of piperazine in place of piperidine and conformational restriction to give 4,5-dihydro-1*H*-benzo[*g*]indazoles. A recently reported CoMFA study describes the correlation of biological activity with structural parameters of twenty-five dopamine D_4 antagonists; the lead compound was 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine, FAUC113.[39]



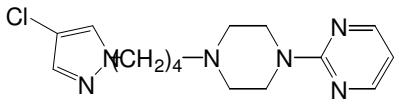
Modulation of the dopaminergic system by neurotensin (NT) receptor antagonists offers the possibility of a new treatment for psychotic disorders. The first non-peptide antagonist of the NT receptor, pyrazole **21**, was reported by Quéré *et al.*[40,41] providing a pharmacophoric model of neurotensin non-peptide antagonists and new information about NT receptor subtypes.

2.1.3. Anxiolytics

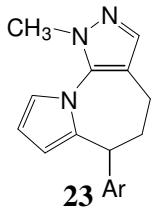
Lesopitron **22** (E-4424), a pyridinylpiperazine substituted by 1-butyl-4-chloropyrazole, was introduced in 1994 as a new non-benzodiazepine anxiolytic acting on 5-HT_{1A} receptors, showing greater

anxiolytic potency, lack of sedative effects, sustained activity even on long-term treatments and lack of withdrawal problems.[12] Lesopitron, currently in advanced clinical trials (phase III), has been shown to be efficient and safe in patients with generalised anxiety disorder.[42]

Behavioural effects in mice of pyrazolopyrrolodiazepines **23** have been studied and some of these compounds have shown anxiolytic activity similar to that of diazepam with weak anticonvulsant and sedative actions.[43]



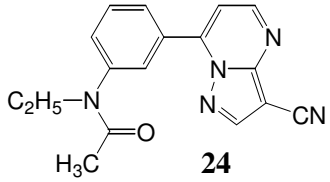
22



23

2.1.4. Sedatives and hypnotics

Recent studies of non-benzodiazepine compounds acting at benzodiazepine recognition sites, which form part of the $GABA_A$ receptor complex, suggested that sedative effects of agonists are mediated by the BZ_1-benzodiazepine receptor subtype.[13] Of particular interest is zaleplon, *N*-[3-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl]-*N*-ethylacetamide **24**, a BZ_1-receptor selective ligand.[44-49] Zaleplon (Sonata, Wyeth-Pharma, MI **10165**) is a non-benzodiazepine sedative hypnotic which has been recently introduced for clinical use, indicated for short-term treatment of insomnia and showing weak anxiolytic activity and reduced risk of tolerance.

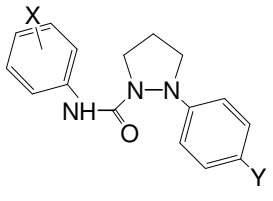


24

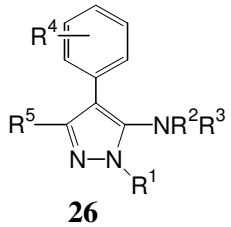
2.2. Anticonvulsants, analgesics, anti-Parkinson and anti-Alzheimer drugs

2.2.1. Anticonvulsants

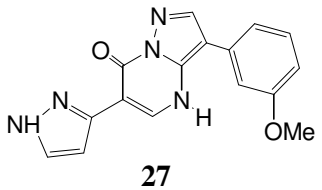
In 1979, Kornet *et al.*[50] reported pyrazolidines **25** as potential anticonvulsant agents, showing moderate anticonvulsant activity in the maximal electroshock seizure and pentylenetetrazole seizure assays.



25



26



27

Recent investigations on 3-amino-4-arylpyrazoles **26** revealed a strong anticonvulsant activity *in vivo*.[51] These pyrazole structures have been proposed to fulfil requirements of a suggested pharmacophore for sodium channel blocking compounds. In particular, a derivative of this series, 4-chlorophenyl-3-

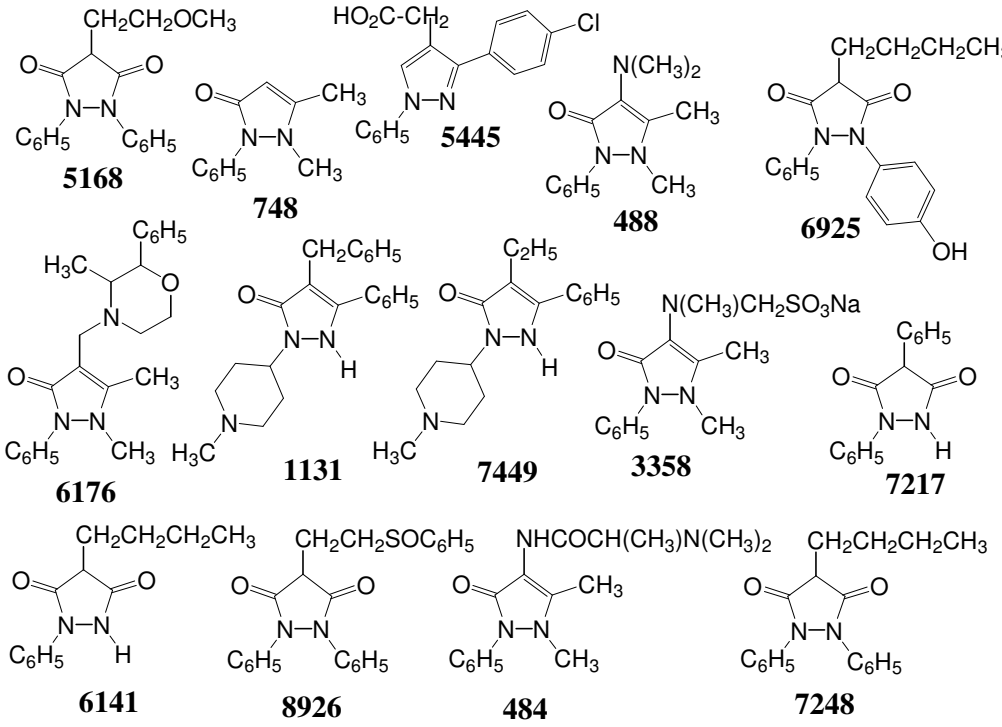
(morpholin-4-yl)-1*H*-pyrazole, blocked sodium channels and was strongly effective in the maximal electroshock seizure test.

Pyrazolopyrimidin-7-ones, *e.g.* **27**, benzodiazepine receptor ligands, have been tested *in vitro* to determine their agonism/antagonism profiles and *in vivo* for anticonvulsant activity.[11]

2.2.2. Analgesics

Although classified in different sections, we should note the close relationship existing between analgesics (this section) and anti-inflammatory drugs (section **4.1.**). This was, by far, the main area of biological activity of pyrazoles often associated with antipyretic activity. In reference 3 are reported several analgesics which are part of the Merck Index (11th Edition).

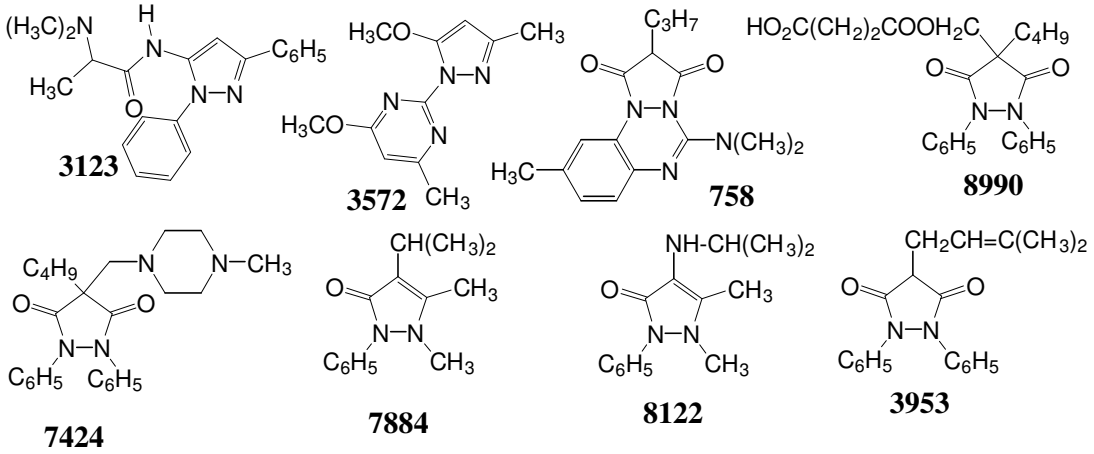
They belong to three main classes: pyrazolin-5-ones (piperylone, **7449**; benzpiperylon, **1131**; antipyrine, **748**; pyramidon, **488**; metamizol or dipyrone, **3358**; aminopropylon, **484**; morazone, **6176**), pyrazolin-3,5-diones (phenylbutazone, **7248**; kebuzone, **5168**; sulfinpyrazone, **8926**; mofebutazone, **6141**; phenopyrazone, **7217**; oxyphenylbutazone, **6925**) and one pyrazole (actually, an acetic acid, lonazolac, **5445**). Other compounds described in the same book are: difenamizole (**3123**), epirizole (**3572**), apazone (**758**), feprazone (**3953**), pipebuzone (**7424**), propyphenazone (**7884**), ramifenazone (**8122**), suxibuzone (**8990**) and thiazolinobutazone **(9236)** (a salt of phenylbutazone with 2-aminothiazoline) (Schemes 1 and 2). Some of them (piperylone, phenopyrazone, oxyphenylbutazone) have dissapeared in the 13th Edition of MI.



Scheme 1

Structural modifications and pharmacological studies of these pyrazoles have been extensively studied in the late 70's and in the 80's. For example, lipophilic derivatives of the analgesic

oxyphenylbutazone **6925** have been designed seeking for locally applicable nonsteroidal anti-inflammatory activity.[52]



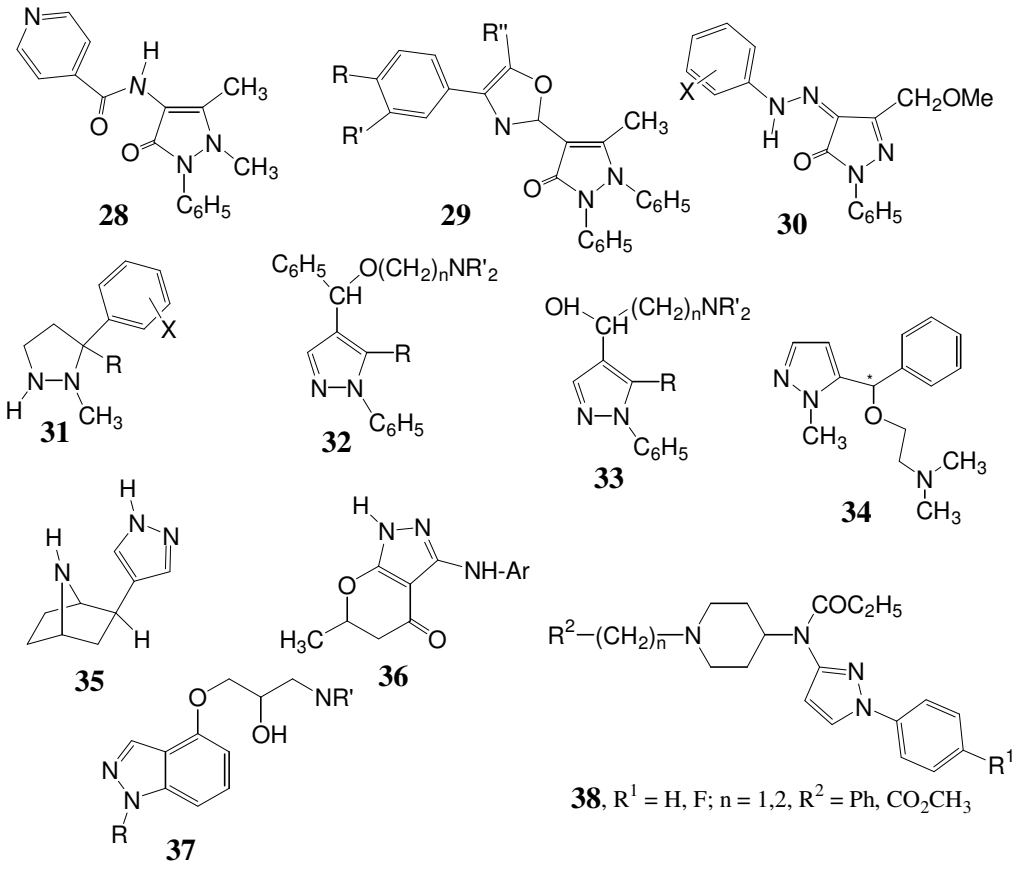
Scheme 2

Another example is the study in 1985 by Beyer *et al.*[53] of the metabolites of nifenazon **28**, an analgesic that belongs to the pyrazolin-5-ones class used, as already commented, in the management of pain and inflammation. Research focused on this class of analgesics is still very active. New 3-pyrazolin-5-ones **29**[54] and new 2-pyrazolin-5-ones **30**[55] have recently shown *in vivo*, antinociceptive properties superior to those of antipyrine and acetylsalicylic acid in mice. A review by Mehlisch compared analgesic efficacy of pyrazolinones (dipyrone) with salicylates and acetaminophen:[56] in comparable amounts, dipyrone seemed to be less effective in reducing mean pain relief, however, it produced greater relief in postepisiotomy pain.

Besides the main families already described, various pyrazole structures display antinociceptive activity. Recently, it has been shown that pyrazolo[3,4-*c*]pyridazines and related systems are of interest as analgesics and anti-inflammatories.[57] Analgesic properties of 1-methyl-3-alkyl-3-arylpyrazolidines **31** have been assessed in mice using the hot-plate test. Some of the pyrazolidines were about one half to one-third as active as phenacetin.[58] Indazole revealed to be an interesting nucleus in this field. Structural modifications of the anti-inflammatory agent bendazac **85** (section **4.1.**), an indazole derivative, have provided compounds showing analgesic effects along with anti-inflammatory properties.[59,60] Pyrazolopyridine hydrazones have been prepared and their antinociceptive activity was evaluated by the classical acetic acid test in mice.[61] The authors concluded that this series could represent a pharmacophoric tool for the development of more efficacious analgesics. Some *N*-substituted 1-(2- or 3-aminopropyl)-3,5-diphenylpyrazoles have shown weak analgesic, antipyretic, anti-arrhythmic and hypotensive activities and marked anti-inflammatory effect in mice and rats.[62] These pharmacological properties have also been observed in 1-aryl-1*H*-pyrazoles[63] such as 1-phenyl-1*H*-pyrazoles **32**[64] and **33**[65] and pyrazoles condensed with a thiophene moiety.[66] Cizolirtine,[67] **34** (E-3710; citrate salt: E-4018) is a new analgesic currently undergoing advanced clinical trials. The presence of a chiral centre in this molecule prompted academic and pharmaceutical industry researchers to obtain each enantiomer separately in order to compare their biological activities with that of the racemic. Therefore, the optical resolution of (±)-cizolirtine has been realised by the classic procedure of recrystallising diastereoisomeric salts[68] and by an efficient enantioselective synthesis;[69,70] the use of cyclodextrins as NMR chiral resolving agents has also been reported.[71] With regard to analgesic activity,[72] no significant difference

was observed between the pure enantiomers and the racemic compound. Epibatidine, a natural alkaloid, isolated from the skin of an equatorial frog is a novel, highly potent, non opioid analgesic agent and a specific agonist of central nicotinic acetylcholine receptors. Replacement of the chloropyridyl ring of the epibatidine structure by 4-pyrazole has been reported.[73] The moderate binding potency of the 4-pyrazole analog **35** was somewhat disappointing when compared with the high binding potency of the isoxazole analog. The authors suggested that the presence of the N-H functionality in **35** hinders efficient hydrogen bond formation with the acetylcholine receptor.

There have been several reports in the literature dealing with pyrazole derivatives which beside analgesic properties show other biological activities, one concerned pyrano[4,3-*c*]pyrazoles **36** which showed analgesic effects together with antipyretic, anti-arrhythmic and hypotensive activity in rats or mice, as well as weak anti-inflammatory, local anesthetic and *in vitro* platelet antiaggregating activity.[74] Another one dealt with indazoles **37** whose pharmacological evaluation *in vivo* showed a predominant significance as analgesic, antiarrhythmic (section **3.1.1.**) and local anaesthetic agents.[75] Finally, long-acting fentanyl analogs having a *N*-(1-phenylpyrazolyl)-*N*-(1-phenylalkyl -4-piperidyl) propanamide structure **38** have been recently described.[76]

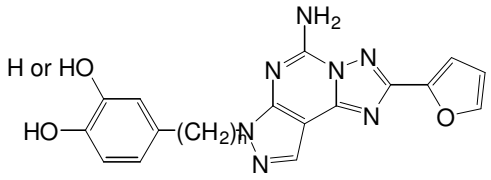


2.2.3. Anti-Parkinson drugs

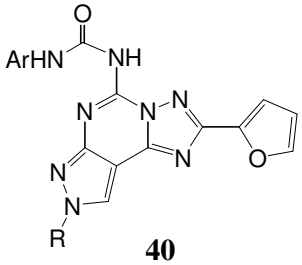
In the late nineties, Baraldi *et al.*[77,78] presented an emerging class of new selective A_{2A} adenosine receptor antagonists, pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **39**. The development of A_{2A} antagonists will contribute to a better understanding of the role of A_{2A} receptors in physiological and pathological states and will provide potential drugs for the treatment of cerebral ischemia or

neurodegenerative disorders, such as Parkinson's disease.[31] Other pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **40** have been reported by the same author[79] to be highly potent and selective human A_3 adenosine receptor antagonists.

As already reported in section **2.1.1.** related to antidepressants, thiocarbamoyl pyrazolines **18** represent a new class of BSAO inhibitors.[34] According to their evaluation of experimental parkinsonism *in vivo*, these pyrazolines can be considered leads for anti-parkinson agents. Since neuroleptic drugs may be useful for depression and Parkinson's disease, pyrazolo[1,5-*a*]pyridines **17**, dopamine autoreceptor agonists already described in section **2.1.1.**, might be targets for treatment of neuropsychiatric disorders.[33]



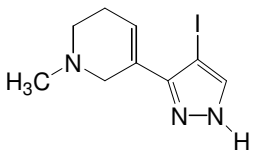
39



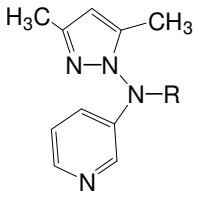
40

2.2.4. Anti-Alzheimer drugs

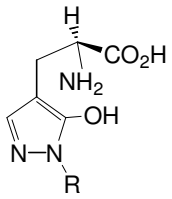
In current strategies to treat the cognitive symptoms of Alzheimer's disease, the loss of cholinergic transmission is improved either by increasing the availability of acetylcholine *via* cholinesterase inhibitors or by direct stimulation with a cholinergic agonist. Although the search for cholinergic agonists has focussed on ligands selective for muscarinic M_1 cholinergic receptor subtype, Plate *et al.*[80] have observed that ligands for M_3 receptors might present therapeutic benefit. Thus, from a series of 3-(pyrazolyl)-1,2,5,6-tetrahydropyridine derivatives designed to measure M_3 functional activity, compound **41** has shown some positive mnemonic properties in rats.



41



42



43

Drugs that combine cholinergic and adrenergic properties are part of the strategies to attenuate symptoms of Alzheimer's disease, a recent example being that of 3,5-dimethylpyrazoles **42** which have shown moderate activities in both muscarinic and adrenergic receptor binding tests.[81]

Pyrazoles **43**, synthesized as heterocyclic analogs of glutamic acid, have shown biological activity at central glutamate receptors.[82] Several diseases such as Alzheimer's disease, septic shock, inflammatory arthritis, schizophrenia, impotence and susceptibility to infection involve disfunction of the three nitric oxide synthase (NOS) isoforms (neuronal, endothelial or inducible macrophage) which regulate NO production. Recently, 1*H*-pyrazole-1-carboxamidines have been shown to be competitive inhibitors of all three isoforms:

the most selective compound, 1*H*-pyrazole-*N*-(3-aminomethylanilino)-1-carboxamidine, was 100-fold selective for neuronal NOS over endothelial NOS.[83]

In neuroprotection studies, concerning inhibition of NOS by indazole agents, it was confirmed that 5-nitro-, 6-nitro-, and 7-nitroindazoles exert their action by hindering oxygen to bind. 7-Nitroindazole, as selective inhibitor of neuronal nitric oxide synthase, has been studied for neuroprotective activity and was used to investigate the role of nitric oxide.

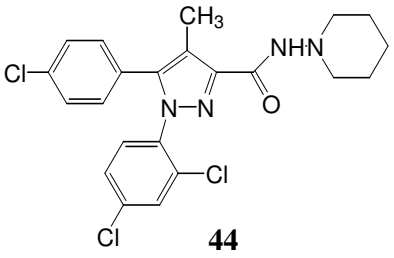
2.3. Pyrazoles acting on the cannabinoid receptors

Pyrazoles play a major role in cannabinoid chemistry. Two subtypes of cannabinoid receptors are currently recognised, CB_1, found in brain and neuronal cells, and CB_2, found mainly in spleen and immune cells.

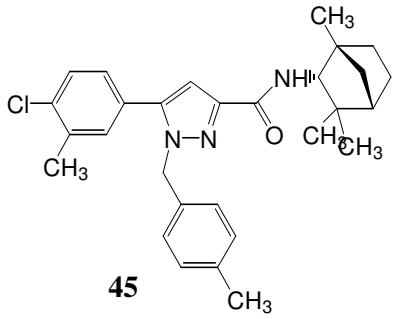
In 1994, Sanofi[85] reported pyrazole SR141716A (Rimonabant), **44**, as the first cannabinoid antagonist possessing nanomolar affinity. This selective and orally active CB_1 antagonist has become an experimental tool for studying CB_1 subtype recognition and activation and for clinical applications such as treatment of psychosis, eating disorders or memory deficits.[86]

The availability in 1997 of a highly specific antagonist SR144528 (**45**),[88] for the CB_2 receptor has allowed to investigate the architecture of ligand binding sites, whose approach was difficult due to the structural disparity of cannabinoid agonists, and to investigate also the respective contribution of cannabinoid receptor subtypes in functional cannabinoid effects *in vivo*. Its potential therapeutic applications include immune disorders such as rheumatoid arthritis, multiple sclerosis, psoriasis, infections and asthma.

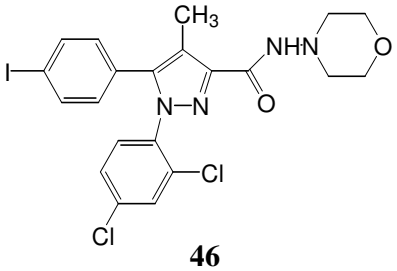
Various derivatives of SR141716A have been synthesized[89,90] and Makriyannis *et al.*[91] have reported a SAR study of pyrazole derivatives as cannabinoid receptor antagonists and have proposed structural requirements for CB_1 antagonistic activity: they suggested that the structural properties of 1- and 5-substituents are primarily responsible for the antagonist activity.



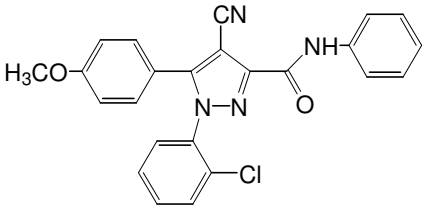
44



45



46



47

An iodophenyl derivative of SR141716A, pyrazole **46** [^{123}I]AM281, showed to be suitable for *in vivo* imaging of human brain CB_1 receptors using positron emission tomography (PET) or single photon emission computed tomography (SPECT), two techniques already used to study the pharmacokinetics and pharmacodynamics of abuse drugs in the human brain.[92] Recently, the syntheses of two [^{18}F]-labeled analogs of **44** and **46**, both by incorporation of the label into a fluoromethyl group have been reported.[93]

3-Azido- and isothiocyanato-substituted aryl pyrazoles have been suggested to be useful tools for the investigation of tolerance and receptor down-regulation both *in vitro* and *in vivo* studies.[94] Recently, it has been proposed that inverse cannabimimetic effects produced by pyrazoles (CB_1 or CB_2 antagonists) are due to inverse agonistic rather than pure antagonistic properties.[86] It has also been recently demonstrated,[95] that aryl pyrazole SR141716 and the new synthesized pyrazole CP272871 (**47**), behave as antagonists and as inverse agonists in G-protein-mediated signal transduction in endogeneous expressed CB_1 receptors.

3. Pharmacodynamic agents

3.1. Antiarrthythmics, antianginals, vasodilators, antihypertensives, diuretics, antithrombotics and anti-allergics

3.1.1. Antiarrthythmics, antianginals, vasodilators, antihypertensives

In the search of antihypertensive agents, the angiotensin II (AII) levels, involved in the regulation of blood pressure can be reduced either by inhibiting the angiotensin converting enzyme (ACE) or by antagonising the AII receptors directly.

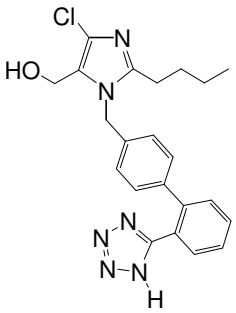
Since the discovery of losartan (DuP753) (**48**), the first orally active nonpeptide AII receptor antagonist several structurally related compounds have been synthesized. For example, researchers at Yamanouchi have replaced the imidazole ring of DuP753 by a bicyclic ring providing a series of azopyrazolo[5,1-a]imidazoles (**49**) from which compound **49a** was the most interesting.[96] A three-fold improvement in potency was achieved by the introduction at position 6 of the pyrazolotriazoles of a *C*-linked oxygen functional group which resulted in compound **49b**, the most interesting of this series.[97]

Based also on the biaryltetrazole structure of losartan, *C*-linked pyrazole biaryl tetrazoles have been prepared by Glaxo.[98,99] Derivatives of general formula **50** are potent orally active AII antagonists selective for the AT_1 receptor. Their oral activity seems to be very sensitive to the nature of the nitrogen substituent and thus the cyclopropylmethyl derivative **50a** is very effective at lowering blood pressure in hypertensive rats, whereas the closely related cyclobutyl analog **50b** is ineffective despite having superior activity *in vitro*.

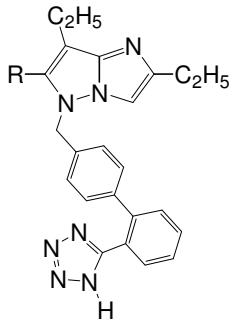
Carpibem have also prepared two series of *C*-linked pyrazole derivatives, 5-oxysubstituted pyrazoles and 5-*C*-substituted pyrazoles.[100] The biphenyl tetrazole derivatives 5-*C*-substituted turned out to be the most active and compound **50c**, UP 221-78, was claimed to be equipotent to losartan in oral antihypertensive activity in rats.

Independently, researchers at Merck have also reported 3-alkyl-1-phenyl-pyrazole-5-carboxylic acids incorporating also the biaryltetrazole substituent as AII receptor antagonists which can also be represented by the general formula **50**.[101] A more recent publication has dealt with 5-(biphenyl-4-ylmethyl) pyrazoles in which the disposition of the ring nitrogen atoms was altered. Compound **51**, UR-7280, showed high potency *in vitro* and *in vivo* and has been selected for clinical evaluation as an antihypertensive agent.[102]

Computer graphics have been used to design hexahydropyrazolo[1,2-*a*]pyridazine diones as bicyclic mimetics of the angiotensin converting enzyme (ACE).[103]

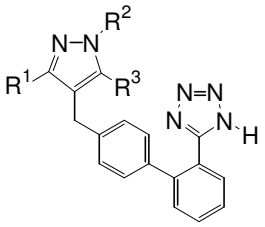


48



49a R= CO_2H

49b R=$CO_2CH(Me)OCO_2Et$



50a, R^1=Bu, R^2=CPM, R^3=CO_2H

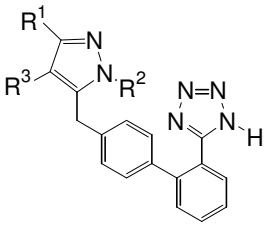
50b, R^1=Bu, R^2=cyclo Bu, R^3=CO_2H

50c, R^1=Pr, R^2=CH_2CF_3, R^3=CH_2OH

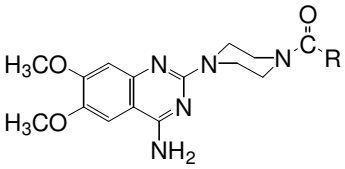
50d, R^1=alkyl, R^2=aryl, R^3=COR

A different kind of antihypertensive agents are the α1-adrenoceptor antagonists of which prazosin (**52a**, MI **7803**) is the reference compound. Pyrazole analogs have been synthesised (**52b**) but all of the compounds displayed lower affinity for the α1 receptor than prazosin.[104]

Within this context, a series of new 3-aryl-tetrahydropyrazolo[4,3-*c*]pyridines (**53**) was synthesised and screened for *in vitro* [^{3}H] prazosin displacement activity. Compound **53a** (L 16052), was selected for further pharmacological evaluations.[105]

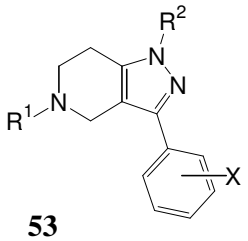


51, R^1 = ^{t}Bu, R^2 = Pr, R^3 = CO_2H



52a , R =

52b, R =



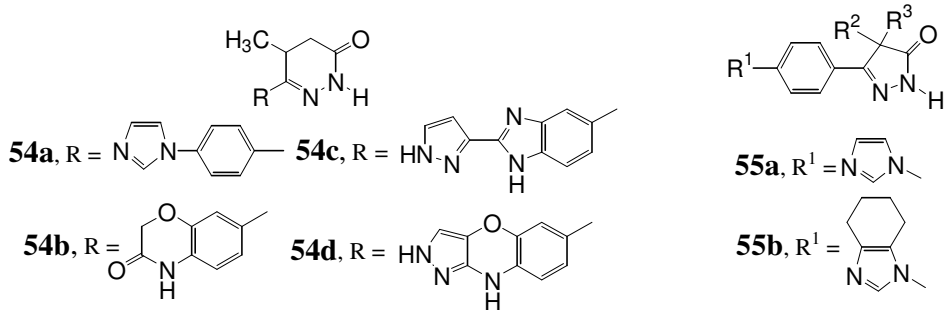
53

53a, R^1 = H, R^2 = CH_2Ph, X = 4-F

In what concerns cardiotonic agents, a prototype of them that has both inotropic and vasodilator activities are 6-aryl-tetrahydropyridazin-3-ones. Imazodan (**54a**) and bemoradan (**54b**) are two representatives of this family which are supposed to exert their actions by selective inhibition of phosphodiesterase type 3 enzymes (PDE3). Many different structural variations have been performed in this series and related to pyrazoles, two compounds are worth mentioning. One is meribendan (**54c**), which was the most interesting compound from a series of benzimidazolyl-pyridazinones. Meribendan inhibited myocardial PDE3, showed an interesting calcium sensitising effect and was selected for development as a positive inotrope.[106] The other interesting compound is the pyrazolo[4,3-*b*][1,4]benzoxazine **54d** derivative, a pyrazole fused analog of bemoradan (**54b**) which had displayed potent positive inotropic actions *in vivo* and had more than twice the peak of activity of the parent compound **54b**.[107]

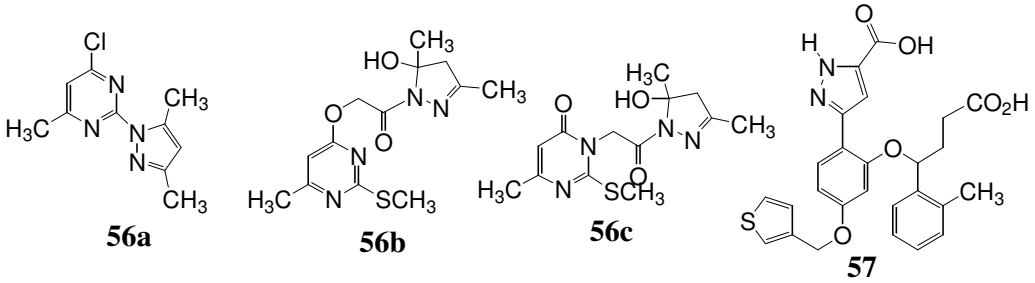
In a conceptually different approach, the pyridazinedione ring of these structures has been replaced by a pyrazolone. Since it is well known that a key element for inotropic activity in this series is an acidic hydrogen adjacent to a polar group, a number of 4,4'-disubstituted pyrazolones, in which the tautomeric keto form is blocked, were synthesised and their inotropic activity studied.[108] Among these ring contracted

analogs of imazodan, compounds **55a** and **55b** were the most interesting. The PDE III inhibitory activity of the five-membered pyrazolone **55a** was similar to that of its six-membered analog imazodan (**54a**). The tetrahydrobenzimidazole derivative **55b** was the most potent compound of this series.



Pyrazolylpyrimidines, such as **56a-c**, showed positive inotropic effects similar to milrinone, a potent nonglycosidic cardiotonic agent belonging to the 5-arylpyridinone family.[109]

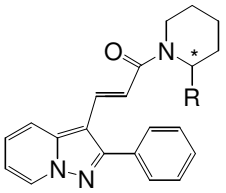
Selective endothelin A (ET_A) receptor antagonists can be used for the treatment of diseases in which a pathophysiological role for endothelin has been implicated such as hypertension, ischemic diseases and artherosclerosis. In an extensive report dealing with the SAR of 4-phenoxybutanoic acids as ET_A receptor antagonists, a promising derivative was the pyrazole diacid **57** which was designed to fit the requirements of the cation binding model proposed. The compound did show interesting binding properties but it had negligible oral bioavailability in the rat.[110] Another series of pyrazole-5-carboxylic acids as endothelin antagonists has been described; these compounds have potent ET_A selective, mixed ET_A/ET_B, or moderately ET_B selective antagonist activities.[111]



Endothelin converting enzyme (ECE) inhibitors are expected to produce therapeutic benefits similar to those proposed for ET receptor antagonists. In the reported approach, SM-19712 {4-chloro-*N*-[[(4-cyano-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)amino]carbonyl] benzenesulfonamide, monosodium salt} proved to be a structurally novel, potent and selective inhibitor of ECE, and represents a new tool for elucidating the pathophysiological role of ECE.[112]

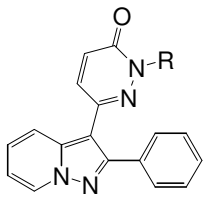
3.1.2. Diuretics

Interesting diuretic activity has been reported for phenylpyrazolo[1,5-*a*]pyridines **58**. The most interesting compound **58a**, of which only the (*R*)-enantiomer was active, turned to be a potent and selective adenosine antagonist.[113]



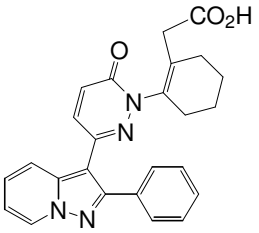
58

58a, R=CH_2CH_2OH



59

59a, R=$(CH_2)_3CO_2H$



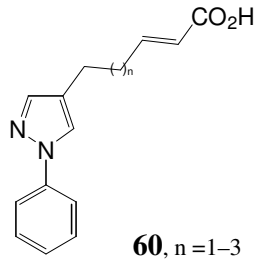
59b

Although **58a**, FK 453, was a potent diuretic in several species it had low bioavailabity, poor solubility in water and, in solution, was isomerized to the less active isomer. To overcome these problems, the researchers from Fujisawa used SAR studies and the X-ray crystal structure of FK 453 to improve the pyrazolo[1,5-*a*]pyridine diuretics by introducing heteroaryl groups at position 3 of the ring.[114] Among these A1 receptor antagonists exemplified by formulae **59**, compound **59a**, FK 838, incorporating a butanoic moiety, is undergoing clinical trials. A newer, water-soluble derivative within this series is **59b**, FR 166124, of which an improved synthesis through a novel Horner-Emmons isomerization has been published.[115]

3.1.3. Antithrombotics

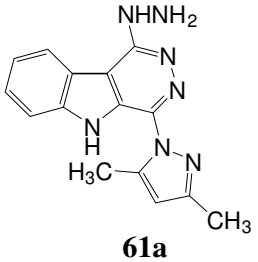
Antithrombotic drugs can act on several steps of the coagulation cascade being of significant importance the control of platelet aggregation. One effective approach is the control of the prostacyclin (PGI2) thromboxane A2 (TXA2) system. A large variety of heterocyclic compounds have been described as TXA2 synthetase inhibitors including a series of ω-carboalkenyl pyrazoles represented by **60**, of which **60a** was the most interesting.[116]

Monge *et al.* have reported pyridazino[4,5-*b*]indole derivatives which have additional inotropic properties. Compound **61a** was the first compound described to have both activities as inhibitor of PDE-4 and selective inhibitor of TXA2 synthetase.[117] A further modification of the structure including a triazole moiety **61b** which had a good profile as an inodilator with anti-aggregating activity due to the inhibition of phosphodiesterase.[118]

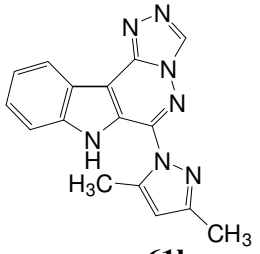


60, n =1–3

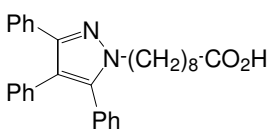
60a, n = 1



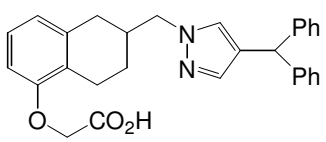
61a



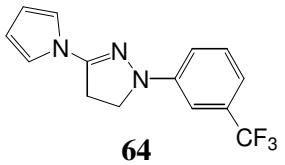
61b



62



63



64

Another approach is to develop analogs of prostacyclin (PGI2), the most powerful endogenous stimulator of blood platelet adenylate cyclase which inhibits platelet activation. Triphenyl-1*H*-pyrazole-1-nonanoic acid (**62**) is a non-prostanoid prostacyclin mimetic which inhibited ADP induced human platelet aggregation.[119] Other pyrazole containing PGI2 agonists without the PG skeleton are the di- or tetrahydronaphthalene 5-oxyacetic derivatives with a 4-benzhydryl pyrazole group such as **63**.[12]

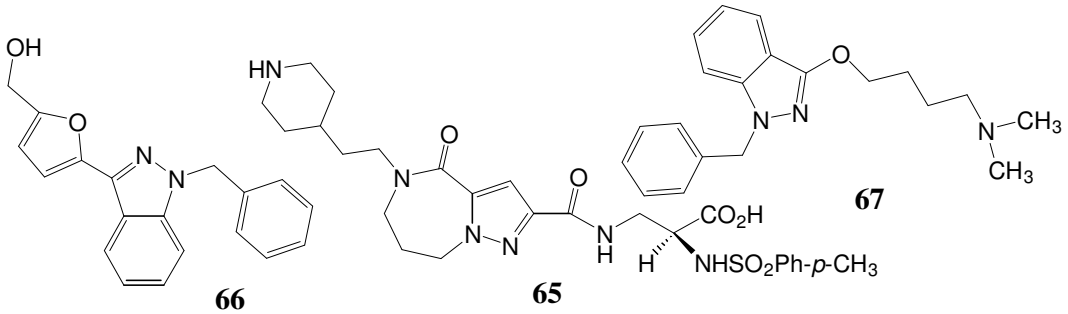
The synthesis and inhibitory effects on cyclooxygenase, lipoxygenase and thromboxane synthetase of 3-amino-4,5-dihydro-1*H*-pyrazoles and related compounds have been reported, the trifluorophenyl methyl derivative **64** being the most interesting.[121]

A series of papers by Mosti and others, have dealt with pyrazole derivatives that beside anti-aggregating properties have also analgesic, anti-inflammatory and antipyretic activities such as 4-carboxy-1-phenyl-1*H*-pyrazole-5-propanamides[63] and thieno[3,4-*c*]pyrazoles.[66]

Since the final step in platelet aggregation is the binding of fibrinogen to activated glycoprotein IIb/IIIa, inhibitors of this protein are another possibility to obtain anti-aggregating agents. In this context, the design and synthesis of orally active, long-acting non-peptide fibrinogen receptor antagonists have been reported.[122] Compound L-738,167 (**65**) inhibited the aggregation of human gel-filtered platelets, probably due to its high-affinity binding to GPIIb/IIIa on circulating platelets.

Very recently, direct inhibition of factor Xa, a trypsin-like serine protease holding the central position that links the intrinsic and extrinsic mechanisms in the blood coagulation cascade, has emerged as an attractive strategy for the discovery of novel antithrombotic agents. A SAR study of a series of pyrazoles culminated in the discovery of DPC423, 1-[3-(aminomethyl)phenyl]-*N*-[3-fluoro-2'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl]-3-(trifluoro-methyl)-1*H*-pyrazole-5-carboxamide, a highly potent, selective, and orally active factor Xa inhibitor which was chosen for clinical development.[123]

In 1991 was identified the protease-activated receptor-1, PAR-1, a thrombin receptor which represents an attractive drug discovery target for the possible treatment of various disorders such as thrombosis, restenosis, atherosclerosis, inflammation, cancer metastasis, and stroke. So far, the only PAR-1 antagonists were synthetic peptides containing the recognition sequence SFLLRN. Ten years later, through a *de novo* design approach, was generated a novel series of indole-based PAR-1 antagonists. Optimization of this series, through *in vivo* studies, led to an indazole-based SFLLR peptide mimetic (RWJ-58259). This potent and selective PAR-1 antagonist served as a pharmacological tool for assessing the therapeutical potential of these ligands in different disorders.[124]



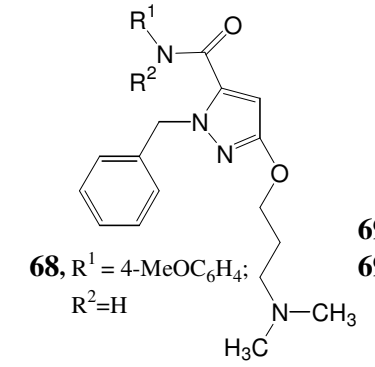
66 **65** **67**

Several recent papers have dealt with the synthesis and biological evaluation of pyrazoles and indazoles as activators of the nitric oxide receptor soluble guanylate cyclase (sGC).[125-128] sGC catalyses the

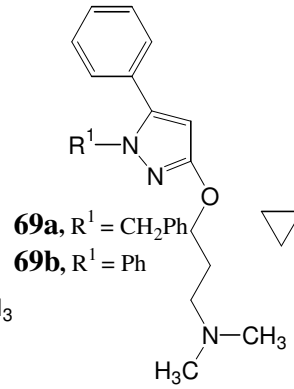
conversion of GTP to cGMP and is the only known receptor for the signalling molecule nitric oxide, NO. The NO-cGMP signalling pathway is important in many physiological processes including vasodilatation, neurotransmission and platelet aggregation. Using the structure of **66** (YC1, a known activator of sGC) the authors generated 2D substructural queries in commercially available compound databases and found that benzydamine **67** (see also section **4.1.**) a known anti-inflammatory and analgesic agent, of unknown mechanism, was a more potent activator of sGC than YC-1.

SAR studies indicated that the indazole ring of **67** could be replaced by appropriately substituted pyrazoles and thus, compounds **68**, **69a** and **69b** showed potent activation of sGC and potent inhibition of platelet aggregation,[126] showing no significant inhibition of phosphodiesterases or NO synthases.

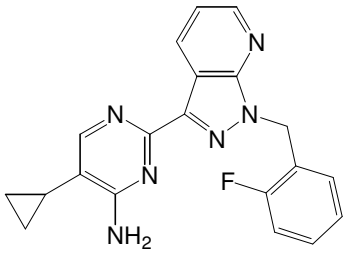
Researches from Bayer have also reported NO-independent stimulators of guanylate cyclase mainly derivatives of pyrazolopyridinylpyrimidine,[127] BAY 41-2272 (**70**) being selected for further studies.[128]



68, R^1 = 4-$MeOC_6H_4$; R^2=H

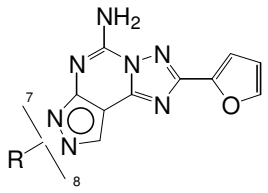


69a, R^1 = CH_2Ph
69b, R^1 = Ph



70

Finally, a paper dealing with pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives as potent inhibitors of A_{2A} adenosine antagonists will be discussed in this section because the functional studies reported were platelet aggregation inhibition which is one of the biological responses mediated by the A_{2A} receptor subtype (see also section **2.2.3.**). Adenosine which has already been mentioned along this review modulates a wide range of physiological functions by interacting with specific cell surface receptors (A_1, A_{2A}, A_{2B} and A_3), and the efforts made by the medicinal chemists have focused on obtaining selective agonists and antagonists. Baraldi *et al*. have reported the design and synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives bearing alkyl and arylalkyl chains on positions 7 and 8, as represented by general formula **71**.[78] Some compounds were potent and selective A_2 antagonists and their potential for treating CNS disorders such as Parkinson's disease should be further studied.

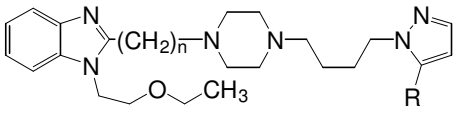


71

3.1.4. Anti-allergics

Researchers at Dr. Esteve Laboratories have reported the synthesis and SAR studies of a new series of benzimidazoles (**72**) as H1 antihistaminic agents.[129] The best antihistaminic activity required the

simultaneous presence of a homopiperazinyl benzimidazole system/or a methylene link between the benzimidazole and the piperazine ring and an unsubstituted pyrazole ring.



72

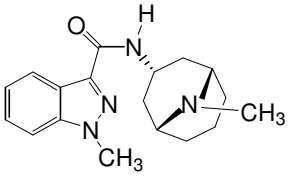
3.2. Drugs acting on gastrointestinal, respiratory and urogenital systems

3.2.1. Antihistaminics

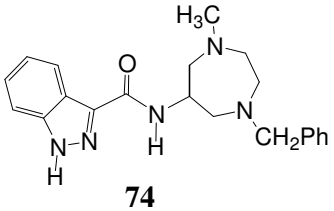
A pyrazole derivative, [5-(3-*N'*-2,2,2-trifluoroethyl)guanidino]pyrazol-1-yl (ICI 162,846) has been reported as a histamine H2-receptor antagonist.[130]

3.2.2. Antiemetics

Antagonists of the serotonin $5HT_3$ receptor are now used clinically for the treatment of emesis. An example is granisetron (**73**, MI **4551**) in the market since 1991 for the treatment of chemotherapy induced nausea.



73



74

One of the first $5HT_3$ antagonists reported was tropisetron (MI **9853**), a tropanyl ester of indole-3-carboxylic acid which was used for performing bioisosteric replacement of the indole moiety by an indazole.[131,132] Pyrazolo[1,5-*a*]pyridines and pyrazolo[1,5-*b*]pyridazines have also been reported as indole isosteres of selective $5HT_3$ antagonists.[133]

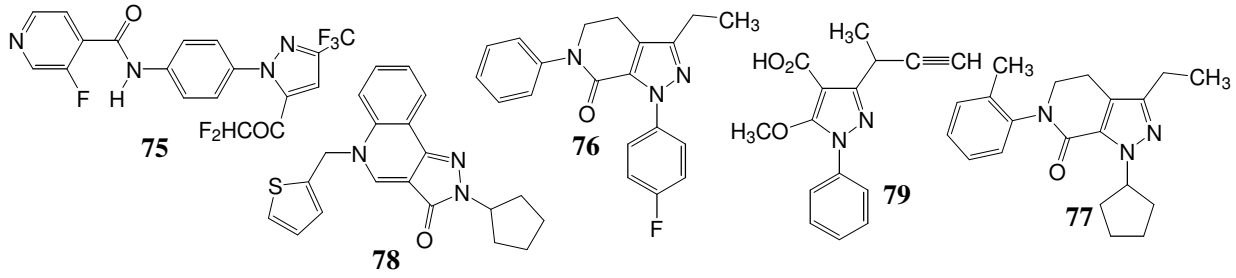
In an extensive SAR study on *N*-benzyl-1,4-diazepin-carboxamides, compound **74** was identified to be equipotent to ondansetron (MI **6916**) and granisetron (**73**).[23] The resolution of this compound by preferential crystallization has also been reported (see also section **2.1.**).[24]

3.2.3. Respiratory system

Using solution phase parallel synthesis and SAR studies for the optimization, a series of 3,5-bis(trifluoromethyl)pyrazoles have been reported as a novel class of NFAT transcription factor regulator. The compounds are novel inhibitors of cytokine production and even inhibit IL-2 production with a 10-fold enhancement over the immunosuppressive drug, cyclosporine. The difluoromethoxy ether **75** showed remarkable efficacy in an Ascans-induced nonhuman primate model of asthma.[134]

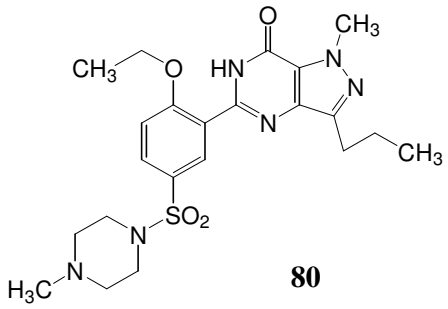
In Pfizer laboratories, high-throughput file screening against inhibition of human lung phosphodiesterase 4 (PDE4) led to the discovery of 3-ethyl-1-(4-fluorophenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine (**76**) as a novel PDE4 inhibitor. Subsequent SAR development, using

an eosinophil PDE assay, led to analogs which were up to 50-fold more potent than **76**, one interesting example being CP-220,629 (**77**).[135] Almirall-Prodesfarma investigations led to the synthesis and biological evaluation of 2,5-dihydropyrazolo[4,3-*c*]quinolin-3-ones, a novel series of PDE4 inhibitors, such as **78**, with low emetic potential and antiasthmatic properties.[136]



3.2.4. Urogenital system

On 27 March 1998, the US Food and Drug Administration approved sildenafil citrate (Viagra) (**80**, MI **8563**) for treating male erectile dysfunction (MED). The drug works by inhibiting cyclic guanosine monophosphate (cGMP) phosphodiesterase Type 5 (PDE5). Further structural manipulations have included α-thiagra, the thiophene bioisoster,[138] and monagra, a chiral 5-(2-methyl-2,3-dihydro-7-benzofuryl)-pyrazolo pyrimidone analog.[139]



In Bristol-Myers Squibb recent PDE5 screening of a series of pyrazolopyridines identified a lead compound with modest potency. Based on this template and using parallel synthesis, merged a new pyrazolopyridine showing comparable *in vitro* functional PDE5 inhibition as sildenafil and improved PDE isozyme selectivity. Thus, due to its pharmacokinetic profile, it is expected to have fewer PDE-related side effects than sildenafil.[140]

The synthesis of a series of halogenated 1-benzylindazole-3-carboxylic acids with anti-spermatogenic properties have been described.[141]

3.3. Drugs acting on skin diseases

3.3.1. Psoriasis

Tyrosine kinases are attractive targets for the design of therapeutic agents because deregulated tyrosine kinase activity has been observed in many proliferative diseases such as cancer, psoriasis, etc. A pharmacophore model of the ATP-binding site of the epidermal growth factor receptor (EGFR) kinase has

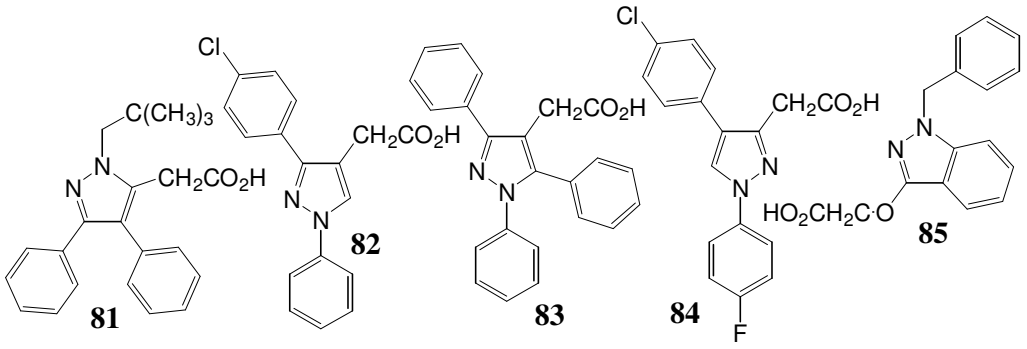
been built and used successfully to design selective kinase inhibitors such as phenylamino-pyrazolo[4,3-d]pyrimidines.[142]

4. Agents acting on metabolic diseases and on endocrine functions

4.1. Anti-inflammatory drugs and antiarthritics

The coexistence in the same molecule of analgesic (section **2.2.2.**) and anti-inflammatory activities is common, and so, in the present section, these compounds previously commented will no longer be discussed. Many compounds are also described as antipyretics.

This field has many subsections related to the different ways to attack inflammatory processes. One is the arylacetic acids,[3] related to fenclofenac and sulindac, for instance bufezolac **81**, lonazolac **82** (MI **55587**) and trifezolac **83**[143] or Schering' s pirazolac **84** (MI **7571**).[144-146] Somewhat related to them are benzadac **85** and benzydamine **67** (MI **1124**). Egyptian authors have studied pyrazol-4-yl-propenoic acids and found some compounds more potent than ketoprofen.[147]



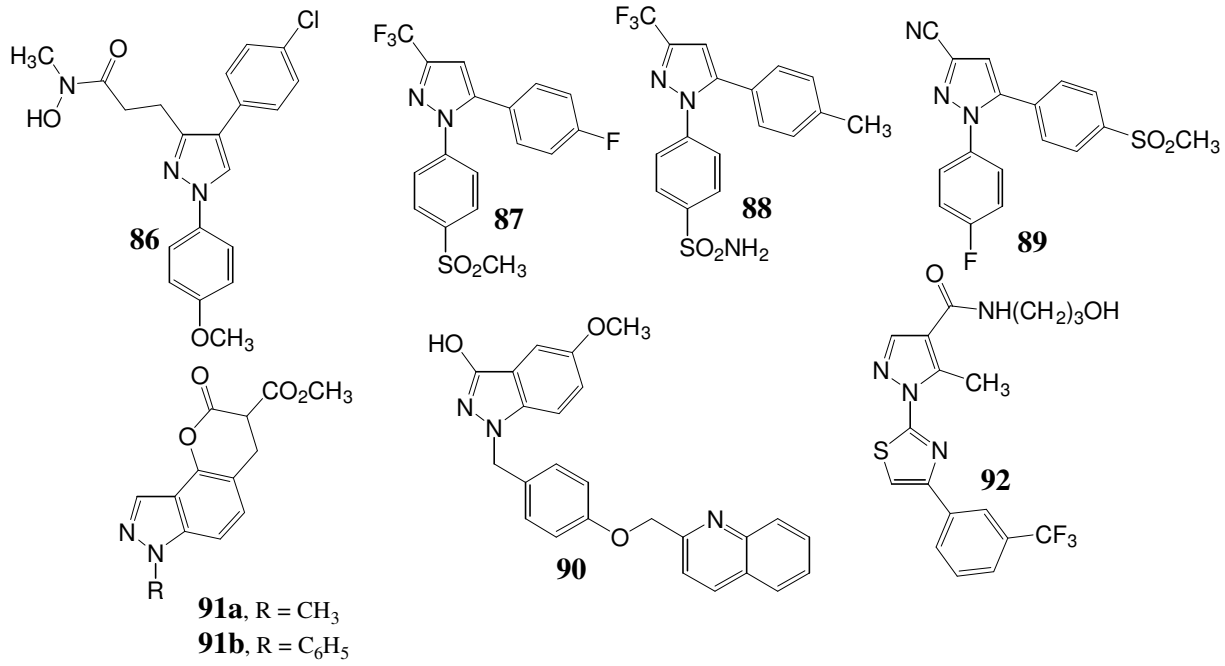
Progress in the understanding of the inflammatory processes led to the search of inhibitors of both the cyclooxygenase (COX) and lipoxygenase (LOX) pathways of the arachidonic acid cascade. In this way tepoxalin **86** was prepared and found to be a potent anti-inflammatory agent.[148,149]

The discovery of a second, inducible form of cyclooxygenase (COX-2) that exists along with the constitutive form (COX-1) led to the hypothesis that selective inhibitors of COX-2 would be anti-inflammatory without causing the side effects associated with inhibition of COX-1 in the gastrointestinal tract and kidney. This is for the moment most promising approach, which ultimately led Searle to SC-58125 **87** and then to celecoxib SC-58635 **88** (**MI** 1968) useful for the treatment of rheumatoid arthritis and osteoarthritis.[150,151] Fujisawa has developed **89**[152] and Uriach presented a series of pyrazolo[1,5-*a*]pyrimidines as potent and selective COX-2 inhibitors.[153]

Other groups, like ASTA, have approached the problem by inhibiting the enzyme 5-LOX. By analogy with zileuton, one of the first launched 5-LOX inhibitors for the treatment of asthma (see section **3.2.3.**), they prepared a series of 1,5-disubstituted indazol-3-ols, the most potent being **90**.[154] Mosti *et al.* also reported indazoles related to angelicin, like compound **91a**, which shows good anti-inflammatory and antipyretic properties, while **91b** shows significant local anaesthetic activity.[155]

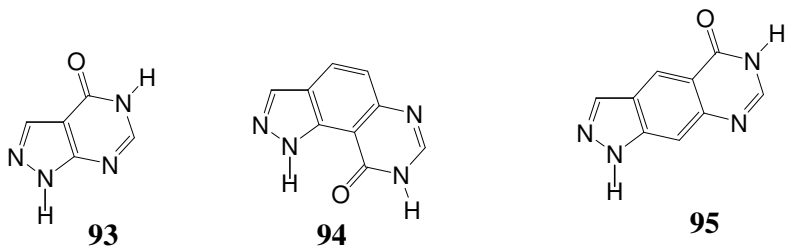
A completely different approach was used by Sanfilippo *et al.* who defined as target the cell adhesion molecules (CAMs).[156] These molecules are important in the regulation of the immune response and inflammation. An agent that inhibits leukocyte adhesion and transmigration represents a novel mechanism of

action as an immunosuppresive (section **5.2.**) and/or anti-inflammatory drug. In this way, these authors identified RWJ-50271 **92** a potent anti-inflammatory.



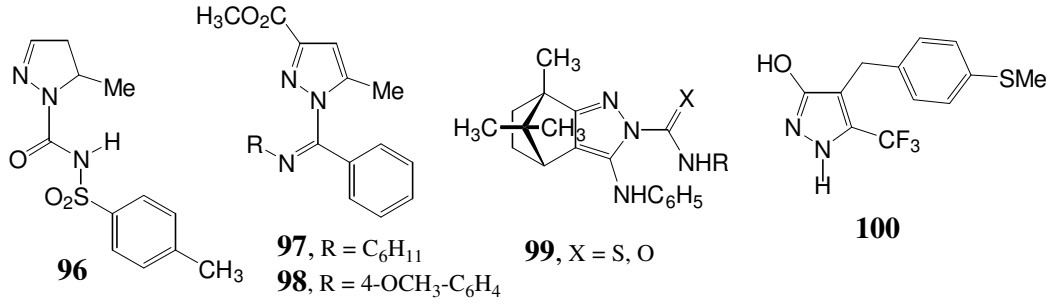
For the treatment of hyperuricemia and chronic gout, the antiurolitic agent allopurinol **93** (MI **276**) an inhibitor of xanthine oxidase is still in much use as the numerous publications about it testify. Leonard has prepared *prox*-benzoisoallopurinols **94** and **95** that inhibit xanthine oxidase only in concentrations comparable to their K_m' s.[157]

Recently, looking for novel anti-allergic agents, indazole-3-ols and indazole-2-ones were synthesized and exhibited a high anti-inflammatory activity both i.p. and orally; one of the pyrazoles is expected to be useful in the treatment of a variety of eosinophilia-mediated disorders, including bronchial asthma.[158]



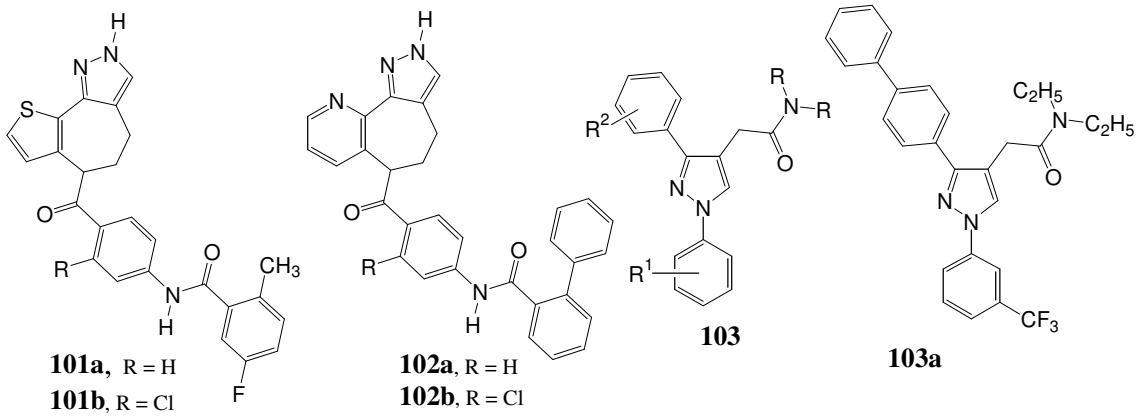
4.2. Hypoglycemic, hypolipidemic and antiobesity agents

For the treatment of diabetes, a series of hypoglycemic agents derived from pyrazoles have been prepared and tested. Thus, the metabolism of sulfonylurea SPC-703 **96** was reported by Polish authors.[159] Shroff *et al.*[160] have described the synthesis of thirty-eight benzimidoyl-pyrazoles, the two more interesting compounds **97** and **98**, combine in one molecule some of the biological activities of the β-cytotrophic sulfonylureas and some of the activities of the biguanides.



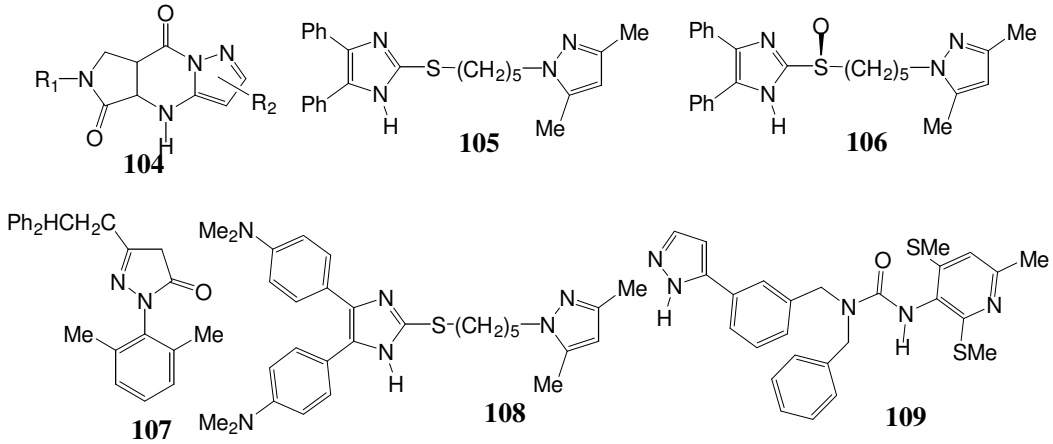
96 **97**, R = C_6H_{11} **98**, R = 4-OCH_3-C_6H_4 **99**, X = S, O **100**

Derivatives of 4,5,6,7-tetrahydro-7,8,8-trimethyl-3-phenylamino-4,7-methano-2*H*-indazoles **99** with hypotensive and hypoglycemic activities have been described by Italian authors.[161] But the most interesting antidiabetic in this field is WAY-123783 (**100**), obtained after extensive SAR studies; it acts by blocking SGTL (sodium-glucose cotransporter) in the kidney.[162]



101a, R = H **101b**, R = Cl **102a**, R = H **102b**, R = Cl **103** **103a**

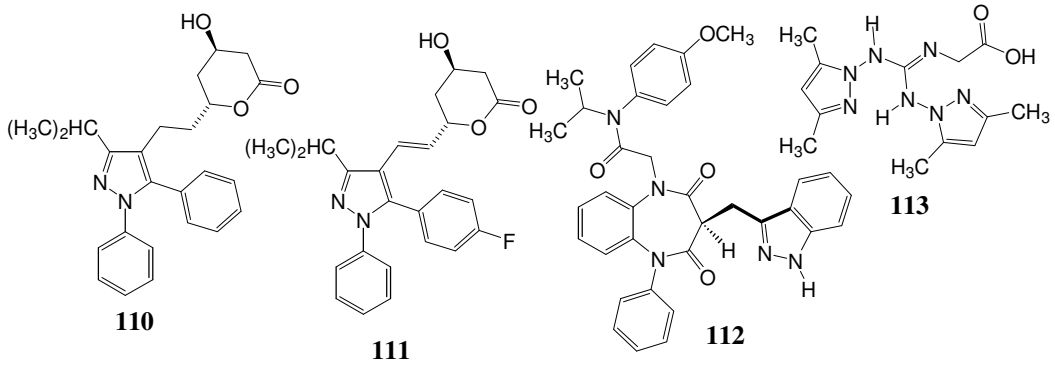
The approach to the treatment of diabetes by means of arginin-vasopressin (AVP) receptor antagonists has lead Wyeth-Ayerst to *N*-[4-[(4,5-dihydropyrazolo[3,4-*d*]thieno[3,2-*b*]azepin- 6(2*H*)-yl)carbonyl]phenyl]benzamides **101**-**102**, potent and orally active.[163] Novartis has studied the effect of 1,3-diaryl-(1*H*)-pyrazole-4-acetamides **103** on glucose-utilization in ob/ob mice:[164] compounds such as **103a** represent a potentially new class of agents for the treatment of diabetes.



104 **105** **106** **107** **108** **109**

In the field of hypolipidemic (also known as hypocholesterolemic and antihyperlipo-proteinemic) agents, most publications deal with ACAT (acylCoA: cholesterol *O*-acyltransferase, EC 2.3.1.26) inhibitors. For instance, a number of 6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*d*] pyrimidine-5,8-diones **104**, developed by Upjohn, were found to be potent modulators of serum lipoprotein levels in cholesterol-fed rats.[165] Several other pharmaceutical companies, have explored ACAT inhibitors: Rhone-Poulenc Rorer **105** (RP 70676) and **106 (**RP 73163**),**[166,167] Parke Davis **107**,[168] DuPont Merck **108 (**the presence of the dimethylamino groups caused a significant drop-off in potency compared with RP 70676)[169] and Fujisawa **109** (FR 186054).[170]

A more recent approach is that of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) inhibitors of the class of "statins". Researchers at Parke Davis prepared and evaluated a series of 1,3,5-trisubstituted pyrazolo mevalonolactones, concluding that **110** is almost equipotent to compactin lactone.[171] The same company has described **111**, claimed to be as much more efficacious than lovastatin.[172]



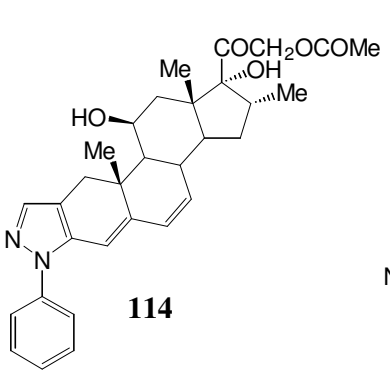
110 **111** **112** **113**

For the treatment of obesity, Henke from Glaxo Wellcome, has optimised a series of 3-(1*H*-indazol-3-ylmethyl)-1,5-benzodiazepines, potent and orally active CCK-A agonists derived from **112**.[173] Amongst a series of aminoguanidines and diaminoguanidines analogs of the antidiabetic/antiobesity agent 3-guanidopropionic acid, compound **113** is devoid of activity.[174] Rimonabant, **44**, is in clinical trials as an antiobesity drug.

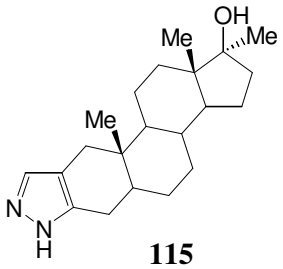
4.3. Peptide and steroidal hormones

Steroidal pyrazoles have been known for a long time. Kirsche (ref. 3, p. 405) reported several of these compounds like cortivazol **114** (MI **2565**, X-ray structure)[175] and stanozolol **115** (MI **8873**), both important and commonly used drugs. Cortivazol **114** is an anti-inflammatory glucocorticoid while stanozolol **115** is an anabolic steroid used as androgen. Nivazol **116** also belongs to the glucocorticoid class.[176] As will be discussed in section **5.1.**, some steroidal pyrazoles have been proposed for the treatment of prostate cancer through inhibition of human cytochrome 17α-hydrolase-$C_{17,20}$-lyase ($P450_{17\alpha}$).[177]

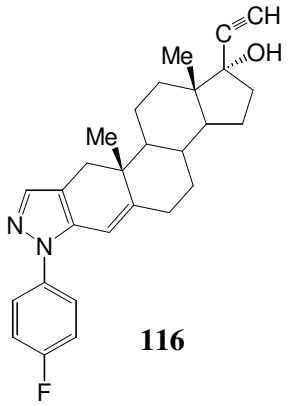
Postmenopausal osteoporosis is caused by increased bone resorption following the loss of endogenous estrogens. Hormone replacement therapy with steroidal estrogens has been shown to prevent the onset of osteoporosis, however the observed increase in uterine cancer has limited its utility. The major inorganic component of bone is hydroxyapatite (HA), a hydrated form of calcium phosphate. In order to identify compounds for use as "bone targeting" agents, Wilson *et al.* decided to identify small molecules with HA affinity.[178]



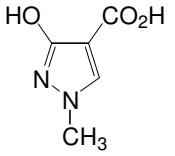
114



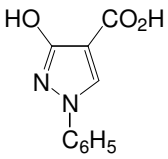
115



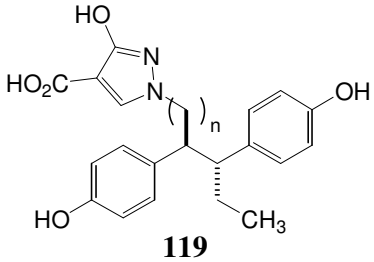
116



117



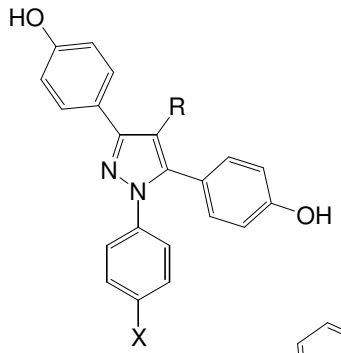
118



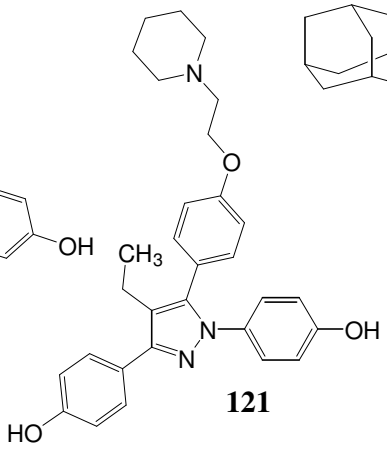
119

Amongst these compounds, 4-carboxy-3-hydroxypyrazoles **117** and **118**, demonstrated good HA affinity which it is unaffected by the nature of the *N*-1 substituent. In a subsequent paper,[179] they combined the bone targeting affinity of these pyrazoles with the non-steroidal estrogen hexestrol preparing compounds **119** (n = 1 or 4) which retained weak estrogenic activity *in vitro*.

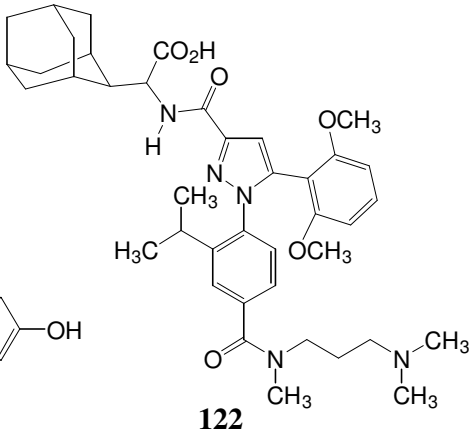
In a series of papers, Katzenellenbogen *et al.*[180-183] developed a series of 1,3,5-triaryl-4-alkylpyrazoles selective agonists for the estrogen α-receptor (ERα). The optimised core for high-affinity ER binding and agonist potency is represented by **120** (X = H, OH, R = alkyl). The most potent is R = Pr, X = OH with an affinity ca. 50% that of estradiol. These compounds were the subject of considerable structural variation, changing the 1,3,5-triaryl-4-alkyl by the 1,3,4-triaryl-5-alkyl series with a decrease in affinity and, using basic side chains, developed a series of ER antagonists like **121**.



120



121



122

Related to neurotensin [an endogenous tridecapeptide neurotransmitter (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Try-Ile-Leu-OH) that has been called the peptide for the next millennium,[184] is SR 142948A 2-{[5-(2,6-dimethoxyphenyl)-1-(4-(*N*-(3-dimethylaminopropyl)-*N*-methylcarbamoyl)-2-isopropyl-phenyl)-1*H*-pyrazole-3-carbonyl]amino}adamantane-2-carboxylic acid, hydrochloride (**122**), a new and extremely potent neurotensin (NT) receptor antagonist.[185]

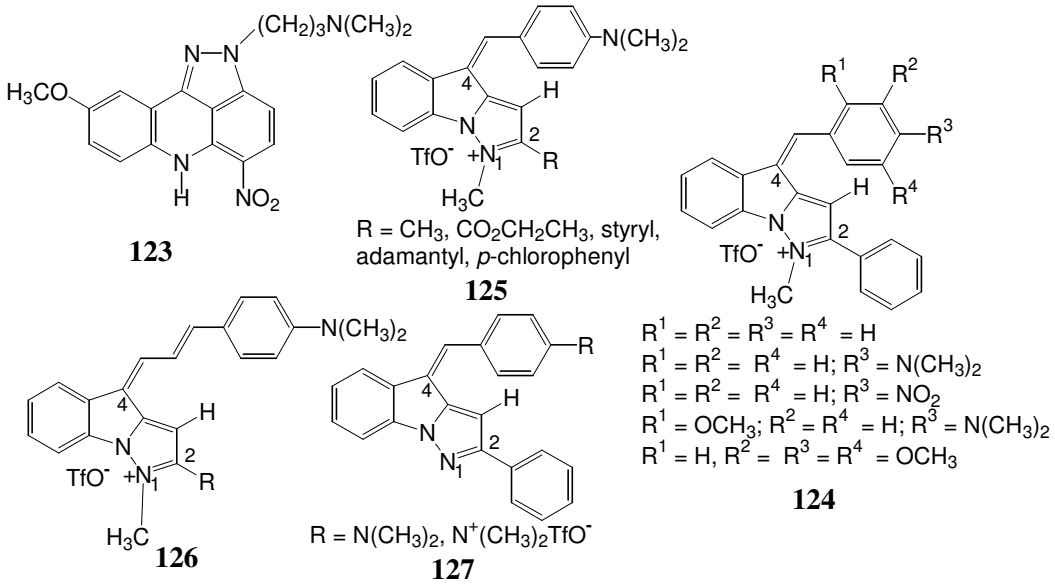
4.4. Liver alcohol dehydrogenase inhibitors

Liver alcohol dehydrogenase (EC 1.1.1.1) catalyses the first step in alcohol metabolism and is a rational target for inhibiting alcohol metabolism. Prevention of poisoning by methanol and damaging effects of ethanol metabolism are potential applications of inhibitors of alcohol dehydrogenase. From the pioneering work of Theorell[186] it is known that pyrazole and some of its 4-substituted derivatives (methyl, iodo and bromo) are potent inhibitors of ethanol metabolism *in vivo*. Pyrazoles have been proposed as therapeutic agents for treatment of alcohol intoxication. Unfortunately, pyrazole is itself toxic and may not be useful for long-term treatment of humans.

Although some interesting efforts have been made, including X-ray studies and molecular modelling,[187-190] 4-methylpyrazole (fomepizol) continues to be the most efficient and less toxic of all the liver alcohol dehydrogenase inhibitors and inactivators. Note also, that pyrazole itself, an alcohol dehydrogenase inhibitor, has dual effects on *N*-methyl-D-aspartate (NMDA) receptors of hippocampal pyramidal cells, agonist and noncompetitive antagonist (see Section **2.1.**).[191]

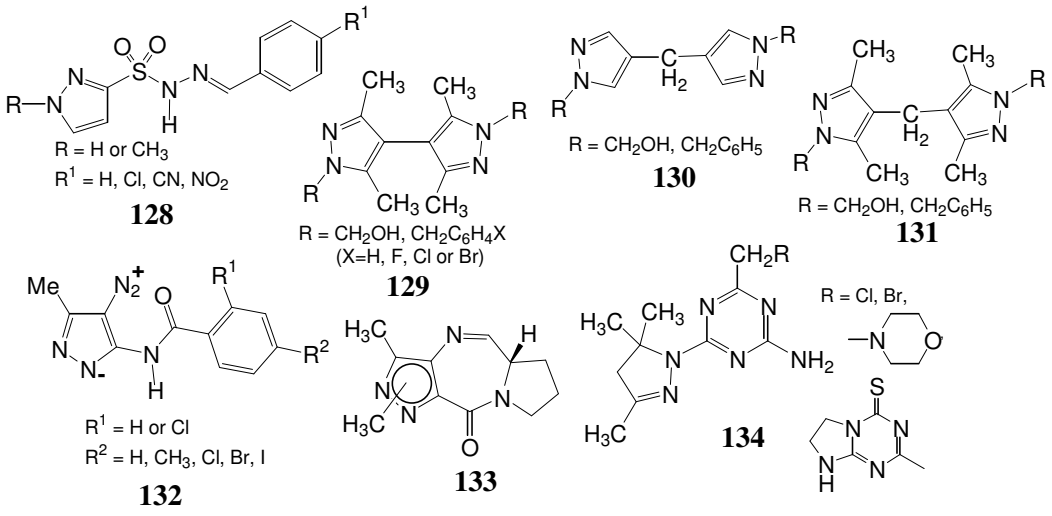
5. Chemotherapeutic agents

5.1. Anticancer drugs



Pyrazoloacridine, PZA, **123**, 9-methoxy-*N,N*-dimethyl-5-nitro-pyrazolo[3,4,5-*kl*]acridine-2(6*H*)-propanamine (NSC 366140) is the first of a new class of rationally synthesised acridine derivatives to undergo clinical testing as an anticancer agent. Recent studies suggest that PZA might be a dual inhibitor of

DNA topoisomerases I and II and exerts its effects by diminishing the formation of topoisomerase-DNA adducts. PZA exhibits broad-spectrum antitumor activity in pre-clinical models *in vivo* and displays several remarkable properties including solid tumour selectivity, activity against hypoxic cells, and cytotoxicity in noncycling cells. PZA has been studied in phase I trials in adults and children, and is currently undergoing broad phase II trials. No significant antitumour activity has been seen in gastrointestinal malignancies and prostate cancer. Due to its unique properties, combination studies with other antineoplastic agents are in progress.[192,193]

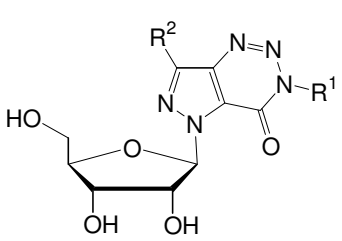


Katayama *et al.*[194,195] have demonstrated that some quaternary salts of pyrazolo[1,5-*a*]indole derivatives **124-126** possess strong anticancer activities against cancer cells both *in vitro* and *in vivo* tests. These studies have also shown that quaternarization on the nitrogen of position 1 (pyrazolium salts) is essential for anticancer activity, since the free bases **127** lost most of their activity. Besides, the size and lipophilicity of the substituent at position 2 seem to be crucial for the *in vitro* activity, since in the case of small 2-alkyl substituents the anticancer activity is lower. These compounds also showed strong inhibitory activities against both DNA topoisomerase I and II, which could be the main course of their anticancer activity.

The alkylating agents represent one of the most efficient therapies in use for the treatment of several types of human tumours. These agents have in common the property of becoming strong electrophiles through the formation of carbonium ion intermediates or of transition complexes with the target molecules. These reactions result in the formation of irreversible covalent bonds with biomolecules (nucleic acids, enzymes, structural proteins, lipids or amino acids), by alkylating several of their nucleophilic moieties. Pyrazolylsulfonylhydrazones **128** bearing electron-withdrawing substituents in the phenyl ring presented cytostatic activity against HeLa cells, being the *p*-nitro derivatives the most effective ones.[196] A quantitative structure-activity study of several binuclear pyrazoles **129-131** demonstrated that only those derived from the 4,4'-bispyrazole ring **129** have shown interesting activity against HeLa cells, being 1,1'-dibenzyl-3,3' ,5,5tetramethyl-4,4'-bispyrazole a powerful cytotoxic agent.[197] 5-Benzamido-4-diazopyrazoles **132** have also shown moderate activity against a panel of human leukaemia, lymphoma and solid tumour cell lines,[198] while pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepinones **133** revealed appreciable *in vitro* antitumor

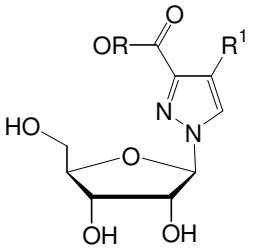
activity on a L 1210 tumour cell line.[199] Recently, some 2-pyrazoline-1,3,5-triazine derivatives **134** possessing strong inhibition on various tumour panel cell lines derived from nine cancer types (leukaemia, lung, colon, brain, melanoma, ovarian, prostate, renal and breast) have been described.[200]

The broad spectrum of biological properties of formycin **3** [1-C-(7-amino-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)-1,4-anhydro-(1*S*)-D-ribitol, now called formycin A to differentiate it from its related derivative formycin B [1,4-dihydro-3-β-D-ribofuranosyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one] are related to its ability to replace an adenosine unit in a number of enzymatic reactions at the nucleotide level.[201] The great importance of formycins A and B has led to the design and synthesis of new nucleoside analogues with modifications either in the carbohydrate or/and in the base. From a series of some substituted pyrazoles and pyrazolo[4,3-*d*]-1,2,3-triazin-4-one nucleosides and pyrazolo[3,4-*d*]oxazoles, Manfredini *et al.*[202-204] found that **135** presented moderate cytostatic activity against T-cells while **136** and **137** were potent and selective cytotoxic agents against T-lymphocytes. Certain pyrazole *C*-nucleosides **138** and 1**39** showed moderate cytotoxic effects against mouse neuroblastoma tumour cell lines, while the former showed also moderate activity against baby hamster kidney tumour cell lines.[205] However, a study of structure-activity relationship of pyrazoles related to nucleosides, involving modifications of the glycosylic portion, showed that *N*-substituted pyrazoles **140** and **141** displayed no interesting cytotoxicity and antiproliferative activity on several leukaemia/lymphoma and solid tumour cell lines.[206]



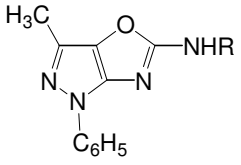
a) $R^1 = CH_2C_6H_5$, $R^2 = CH_3$
b) $R^1 = C_6H_{11}$, $R^2 = CH_3$

135



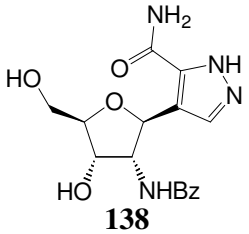
a) R = OCH_3, $R^1 = NO_2$
b) R = OCH_3, R^1 = Br
c) R = OCH_3 or O^{t}Bu, R^1 = I

136

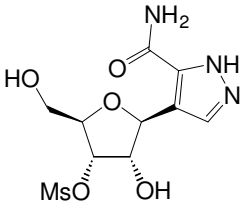


(Me, Et, tBu, $CH_2C_6H_5$, CH_2CO_2Et)

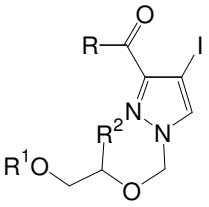
137



138

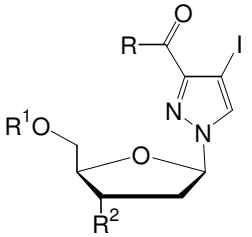


139



R = OCH_3 or NH_2;
$R^1 = R^2$ = H, CH_2OH

140



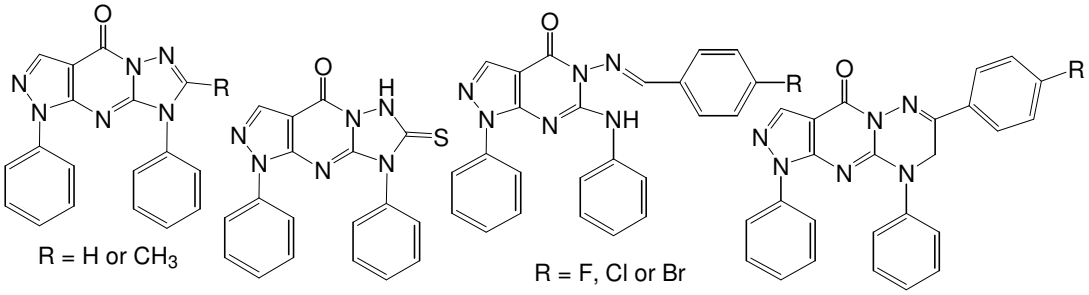
R = OCH_3 or NH_2;
$R^1 = R^2$ = H, CH_2OH

141

Certain pyrazolo[3,4-*d*][1,2,4]triazolo[2,3-*a*]pyrimidines **142** and **143** have shown high binding affinity for DNA. The presence of the 1,2,4-triazole nucleus seems to be crucial for this antitumor activity since the other pyrazolo[3,4-*d*]pyrimidines **144** and **145** presented lower affinity for DNA.[207]

The binding affinity and specificity of pyrazoles to DNA was also demonstrated when they were incorporated in eight-ring hairpin polyamides, which specifically recognise predetermined sequences as

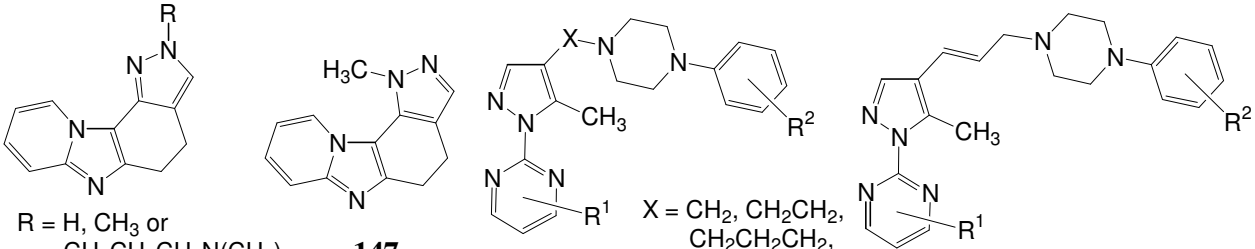
side-by-side pairs in the minor groove of DNA. When they were incorporated at the *N*-terminus of the synthetic polyamides, the pair 3-pyrazole/pyrrole mimics the imidazole/pyrrole pair but with enhanced binding affinity and sequence specificity for guanidine-cytosine base pairs.[208] The *N*-methylpyrazole/*N*-methylpyrrole pair, incorporated at the middle of these polyamides, specifies the adenine-thymine/thymine-adenine base pairs.[209]



142 **143** **144** **145**

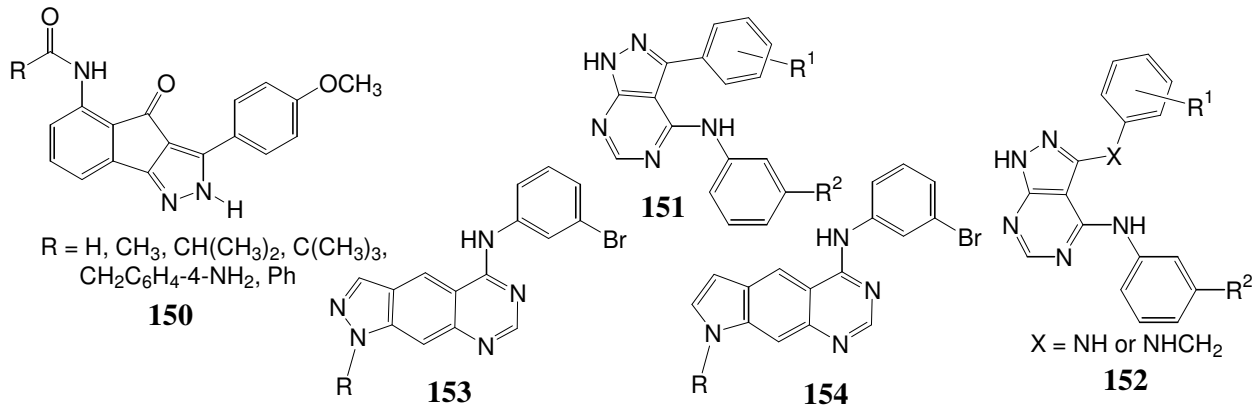
Anticancer drugs still have limited efficacy against numerous tumour types because cancer cells can develop mechanisms of resistance allowing them to evade chemotherapy. One type of multidrug resistance has been shown to be mediated by an energy dependent P-glycoprotein (PGP) which possesses low substrate specificity. A large number of actual used drugs are eliminated through PGP mediated efflux. In this context, the search for new drugs active towards such cells is of crucial interest for future cancer treatments. Pyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazoles **146** and **147** exhibited significant *in vitro* cytotoxic activities against human leukaemia K562S and HL60S sensitive cell lines, but lower than the commercial drug doxorubicin. In the case of resistant cell lines (multidrug resistance +; K562R and HL60R) compounds **146**, **147** and doxorubicin showed the same activity. These results indicate no resistance phenomena against these leukaemia cells.[210]

In the search of new pharmacophores as antitumor agents, Ejima *et al.*[211] discovered that the pyrazole hydrochloride derivatives **148** and **149** showed *in vitro* cytotoxic activity against P388 leukaemia cells and PC-6 human lung carcinoma cells. The most potent derivatives were those having a halogen atom at the *o*- and *m*-positions of the phenyl ring, which exhibited potent cytotoxic activity against some tumour cell lines including multidrug resistance cell lines due to the overexpression of P-glycoprotein. Among these compounds, the *m*-chloro derivative (R^1 = H, R^2 = *m*-Cl) was one of the most interesting.



146 **147** **148** **149**

Protein dependent kinases (PDK) play a key role in regulating the cell cycle machinery. An increasing body of evidence has shown a link between tumour development and PDK-related malfunctions and this has led to an intense search for small molecules of the PDK family as an approach to cancer chemotherapy. To date, only two compounds (flavopyridol and UCN-01) have entered into clinical trials as cancer chemotherapeutics based on cyclin dependent kinase (CDK) inhibition mechanism. Indenopyrazoles **150** were disclosed as a new structural class of cyclin dependent kinase inhibitors. These compounds are selective for the CDK related serine/threonine kinase family and are active in cell culture against a transformed human colon carcinoma cell line (HCT116). In addition, these compounds demonstrate *in vivo* activity by reducing tumour growth in a human xenograft mouse model in a dose dependent manner.[212]

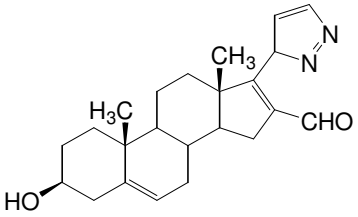


The epidermal growth factor receptor (EGF-R) is known to be overexpressed in a large percentage of clinical cancers of various types and to be associated with poor diagnosis. Inhibitors of the EGF-R PTK are therefore expected to have great therapeutic potential in the treatment of malignant and non-malignant epithelial diseases. Using a pharmacophore model for ATP-competitive inhibitors interacting with the active site of the EGF-R PTK, Traxler *et al.*[213] developed a series of 4-(phenylamino)-1*H*-pyrazolo[3,4-*d*]pyrimidines **151** and **152** as highly potent inhibitors of the EGF-R tyrosine kinase, which also showed high selectivity toward a panel of nonreceptor PKCα and CDK1. Additionally, two of these compounds **152** (R^1 = *m*-Cl, R^2 = Cl or CH_3, X = NH) showed satisfactory oral bioavailability in mice after oral administration and exhibited good *in vivo* efficacy in a nude mouse tumour model using xenografts of the EGF-R overexpressing A431 cell line. Denny *et al.*[214] prepared a series of 5-[(3-bromophenyl)amino] pyrazolo[3,2-*g*]quinazolines and pyrrolo[3,2-*g*]quinazolines, **153** and **154**, which also showed high potency for the inhibition of tyrosine kinase activity of the isolated EGF-R and of its autophosphorylation in EGF-stimulated A431 cells.

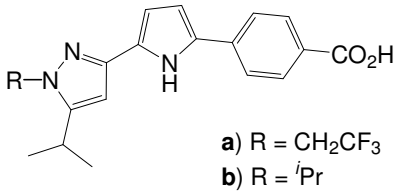
17-(1*H*-Pyrazol-1-yl)androstadiene **155** may be an alternative for the treatment of androgen-dependent diseases, namely prostate cancer, which is the second leading cause-related mortality in men in the USA and Europe. This compound is a moderate inhibitor of the human steroidal enzyme 17α-hydroxylase-$C_{17,20}$-lyase ($P450_{17\alpha}$) a cytochrome P450 monooxygenase complex that catalyses the formation of androgens; its inhibition is an actual strategy in the treatment of patients with prostatic cancer. However, the actual drugs are not very potent inhibitors of $P450_{17\alpha}$ and cause significant side effects, while 17-azolyl steroids, including **155**, are specific inhibitors of this enzyme.[177]

Although retinoids are thought to have great therapeutic potential, their toxic effects have so far limited their clinical use mainly to dermatological diseases and also some cancers, for which retinoids may have both therapeutic and chemopreventive applications. Recent research has focused on the synthesis and development of subtype-selective retinoids in order to reduce their toxicity. Nagai *et al.*[215] synthesised a series of pyrazoles **156** as candidate retinoid acid receptor (RAR) agonists. These compounds have strong transactivation activities, but one of them, 4-[5-(1,5-diisopropyl)-1*H*-3-pyrazolyl)-1*H*-2-pyrrolyl]benzoic acid **156b**, showed selective transactivation activity for the RARα receptor and had highly potent cell-differentiating activity on HL-60 cells.

Adenosine deaminase (ADA) is present in all mammalian cells and plays a central role in the differentiation and maturation of lymphoid system cells. Deficiency and abnormalities of this enzyme are reported in some leukaemia and immunodeficiency (including AIDS) diseases. It has been suggested that modulating ADA activity may be a target for chemotherapy. Among azole derivatives, pyrazoles were those presenting the lowest inhibitory activity on ADA.[216]



155



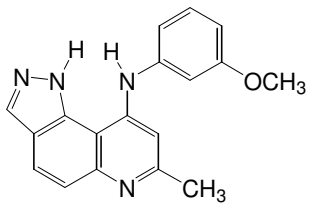
156

a) R = CH_2CF_3
b) R = ^{i}Pr
c) R = ^{t}Bu
d) R = 2,5-$(CH_3)_2$Ph

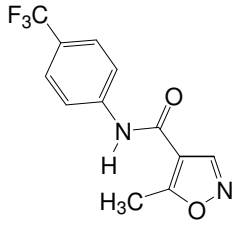
In the 80s some authors studied the effects of pyrazole on animals treated with carcinogenic and mutagenic agents.[217,218] Moriya *et al*. demonstrated that unsubstituted pyrazole is an effective inhibitor of the carcinogenicities of two large-bowel carcinogens, 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM), in rats when taken orally. They showed that this activity of pyrazole is due to its ability to inhibit at least two steps in the metabolism of DMH and AOM, preventing the formation of carcinogenic species.[217,218]

5.2. Immunosuppressants and immunostimulants

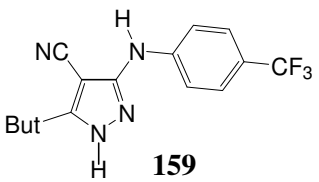
Moyer *et al*. working at Pfizer discovered that pyrazolo[3,4-*f*]quinoline derivatives such as **157** are potent immunostimulants *in vivo*.[219,220] Scientists from Novartis, reported pyrazole bioisosters of leflunomide **158** (MI **5451**) as B-cell immunosuppressants for xenotransplantation and chronic rejection with only compound **159** being equipotent with leflunomide.[221]



157



158



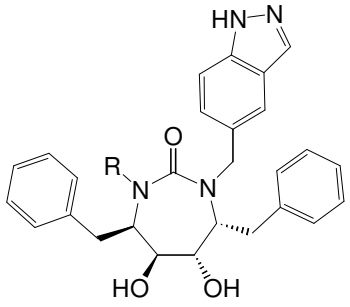
159

5.3. Antiviral, antibacterial, antiparasitic, antiprotozoa and fungicides

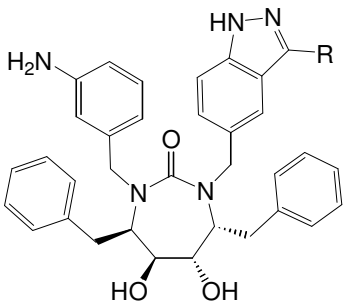
5.3.1. Antiviral

The identification of HIV as the causative agent of AIDS has prompted an intense international research effort to find effective therapies for this disease. One of the prime targets of research has been the effort to find inhibitors of the essential aspartic protease (PR) of HIV. Several HIVPR (saquinavir, ritonavir, indinavir and nelfinavir) have been approved by the FDA and are being used in AIDS therapy in combination with reverse transcriptase (RT) inhibitors. However, the ability of the virus to generate resistant mutants suggests that there is an ongoing need for new, structurally diverse HIVPR inhibitors. Using the structural information gathered from the X-ray structures of various cyclic urea/HIVPR complexes, researchers from Dupont Merck Pharmaceutical company designed and synthesised many nonsymmetrical P2/P2'-substituted cyclic urea analogues **160**. Their efforts have been concentrated on using an indazole as one of the P2 substituents since this group imparted enzyme potency as well as translation into excellent antiviral potency. The second P2 substituent was used to adjust the physical and chemical properties in order to maximise oral bioavailability. Using this approach several very potent and orally bioavailable compounds were discovered, **161** (R = H or 3-pyrazolyl) being the lead structures.[222-225]

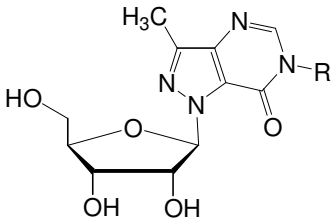
Some pyrazole nucleosides **136** and **162** inhibited the HIV-1 multiplication in acutely infected C8166 and Vero cells, and **136c** showed a selective, although not potent, activity against the coxsackie virus,[202,226] whereas compounds **132**, **137**, **140**, **141** and **163** displayed no interesting antiviral activity, including HIV-1.[198,203,206] The *C*-nucleoside antibiotics formycin A **3** and formycin B have also shown antiviral properties.[201]



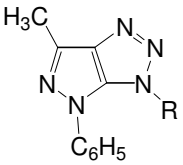
160



161



162



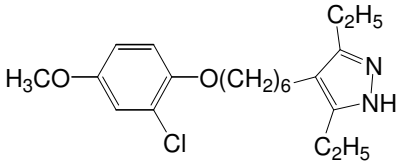
163

Win 41258-3 **164** {4-[6-(2-chloro-4-methoxyphenoxy)hexyl]-3,5-diethyl-1*H*-pyrazole}, a water-soluble pyrazole, showed *in vitro* and *in vivo* activity against herpes simplex virus types 1 and 2 (HSV-1 and -2). *In vivo* it was effective against HSV-1 and -2 in mouse genital infection, after intravaginal administration, and also against guinea pig skin infection, produced by HSV-1, by topical application.[227] Some pyrazolo[3,4-*d*]pyrimidines **143** and **144** also showed *in vitro* activity against several types of virus, including the HSV-1.[207,228]

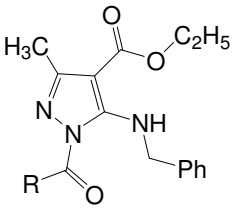
Preliminary bioassays showed that some of the 3-methyl-1*H*-pyrazole-4-carboxylic ester derivatives **165**-**167** presented antiviral activity against TM Virus.[229]

The capacity of an organism to produce interferon in response to infection by viruses of certain protozoan parasites in thought to be an important non-specific defence mechanism. The interferon system is the earliest component of the host defence to become operative following virus infection and may also play a role in the later stages of recovery. It is now well established that, once evoked, interferon will inhibit the

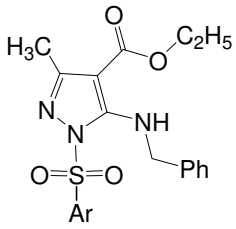
replication of a wide variety of both RNA- and DNA-containing cytopathic and oncogenic viruses. An agent which stimulates release and/or *in vivo* synthesis of interferon has thus implications for the development of clinically useful broad-spectrum antiviral drugs. In a structure-activity study Crenshaw *et al.*[230] found that pyrazolo[3,4-*b*]quinoline derivatives **168** are a new class of low-molecular-weight inducers of interferon.



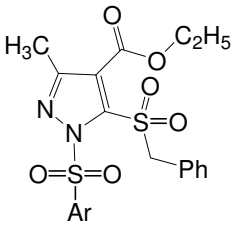
Win 41258
164



165

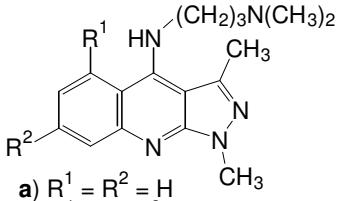


166



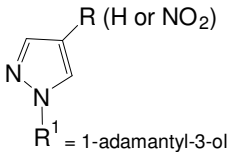
167

On the basis of the antiviral activity of 1-adamantaneamine (amantadine) and in order to assess the possible pharmacodynamic effect of the adamantyl group, a highly lipophilic hydrocarbon moiety associated with the compact symmetrical architecture of the adamantane molecule, a series of *N*-adamantyl azoles and benzazoles have been tested against Semliki Forest Virus (SFV). Pyrazoles **169** protected cells from cytopathic effect at lower concentrations than amantadine, whereas they had equal or lower toxicity.[231]



a) $R^1 = R^2 = H$
b) $R^1 = H$, $R^2 = CH_3$
c) $R^1 = R^2 = OCH_3$

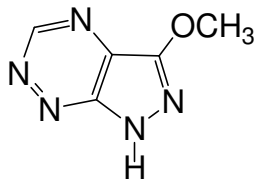
168



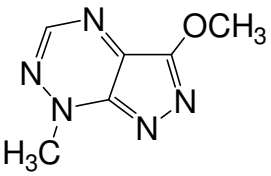
169

5.3.2. Antibacterial

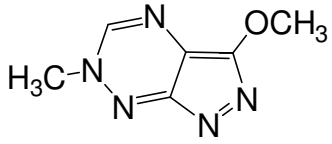
There are some natural antibiotics that contain a pyrazole ring, such as pyrazofurin or pyrazomycin **2** (an antibiotic isolated from the fermentation broth of *Streptomyces candidus*) and formycin **3** (section **1.**). Formycin has antiviral (section **5.3.1.**) and antitumor properties (section **5.1.**) and its total synthesis has been reported several times.[201] Recently, Russian authors[232] have described fifteen fluorescent pseudomonas, isolated from the rhizosphere of agricultural plants, which were similar in both their phenotypic properties and the chemical nature of produced pigments, to the previously described *Pseudomonas fluorescens* var. *pseudoiodinum.* DNA-DNA hybridization data showed their genetic similarity (but not identity) to different varieties of *P. fluorescens*. A family of antibiotics-*fluviols*, belonging to pyrazolo[4,3-*e*]*as*-triazine derivatives, was isolated from studied strains; isolation, properties, antimicrobial and antitumor activity of *fluviols* A **170**, B, C **171**, D **172**, and E **173** are described. Two other antibiotics APHE-1 and APHE-2 **174** have been isolated from the culture filtrate and mycelia of *Streptoverticillium griseocarneum* NCIMB 40447 and their structure has been established as pyrazolo-isoquinolinone derivatives.[233]



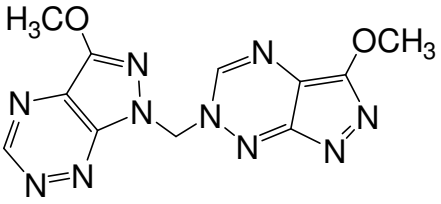
170



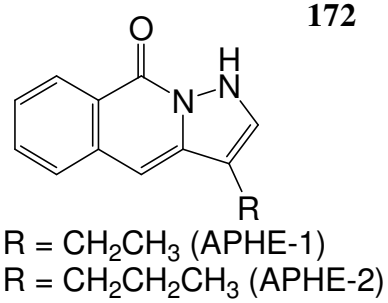
171



172

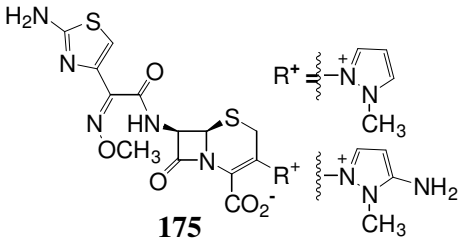


173

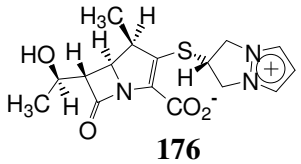


174

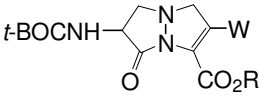
In the 80s a number of new parenteral cephalosporins with a broad spectrum of antibacterial activity and high stability against various β-lactamases have been marketed. They showed excellent activity against Gram-negative bacteria except *Pseudomonas aeruginosa* and moderate activity against Gram-positive bacteria, especially *Staphylococcus aureus*. Kawabata *et al.*[234] prepared 3'-quaternary ammonium cephalosporins **175** which possess antibacterial activity superior to the marketed cephalosporins. For instance, 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methylpyrazolium) methyl-3-cephem-4-carboxylate showed extremely potent broad-spectrum activity against both Gram-positive bacteria, including *S. aureus*, and Gram-negative bacteria, including *P. aeruginosa*. Following the discovery of a non-natural 1β-methylcarbapenem antibiotic by a Merck Sharp & Dohme research group, Nagao *et al.*[235] prepared a new derivative **176** bearing a σ-symmetric bicyclopyrazoliumthio group as a pendant moiety which exhibited excellent antibacterial activities against several strains.



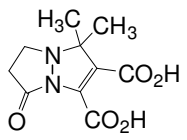
175



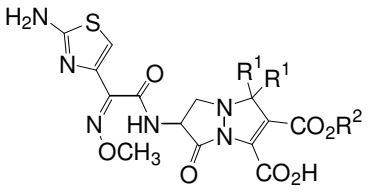
176



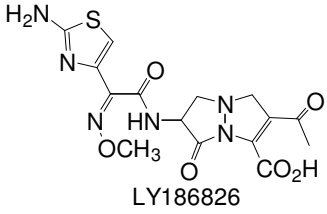
177



178



179

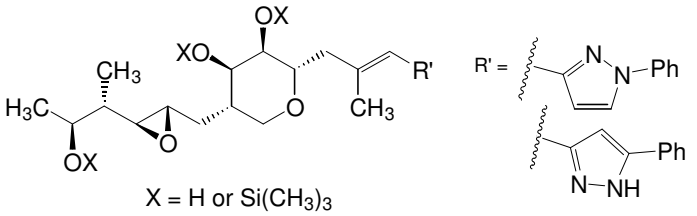


180

β-Lactams exert their activity by acylation of several specific enzymes, the penicillin binding proteins (PBP's), involved in bacterial cell wall biosynthesis. Jungheim *et al.*[236-239] have prepared several

bicyclic pyrazolidinones **177-180** as γ-lactam analogues of the β-lactam antibiotics, assuming that these compounds might possess sufficient reactivity to react with the referred enzymes. Several of the synthesised compounds exhibited broad spectrum *in vitro* antibacterial activity against a variety of Gram-positive and Gram-negative bacteria and one of the lead compounds **180** (LY186826) is indeed a bacterial cell wall synthesis inhibitor which acts on β-lactam target enzymes.

Mupirocin is the compound utilised by SmithKline Beecham for Bactroban ointment, which is a highly effective topical antibiotic for the treatment of skin infections and for the prevention of nasal carriage of multiple resistant *S. aureus* in the hospital environment. The replacement of the metabolically sensitive alkoxycarbonyl moiety by a variety of heterocycles, yielded antibacterially active compounds in the case of oxazoles, while pyrazole analogues **181** were poorly active.[240]



181

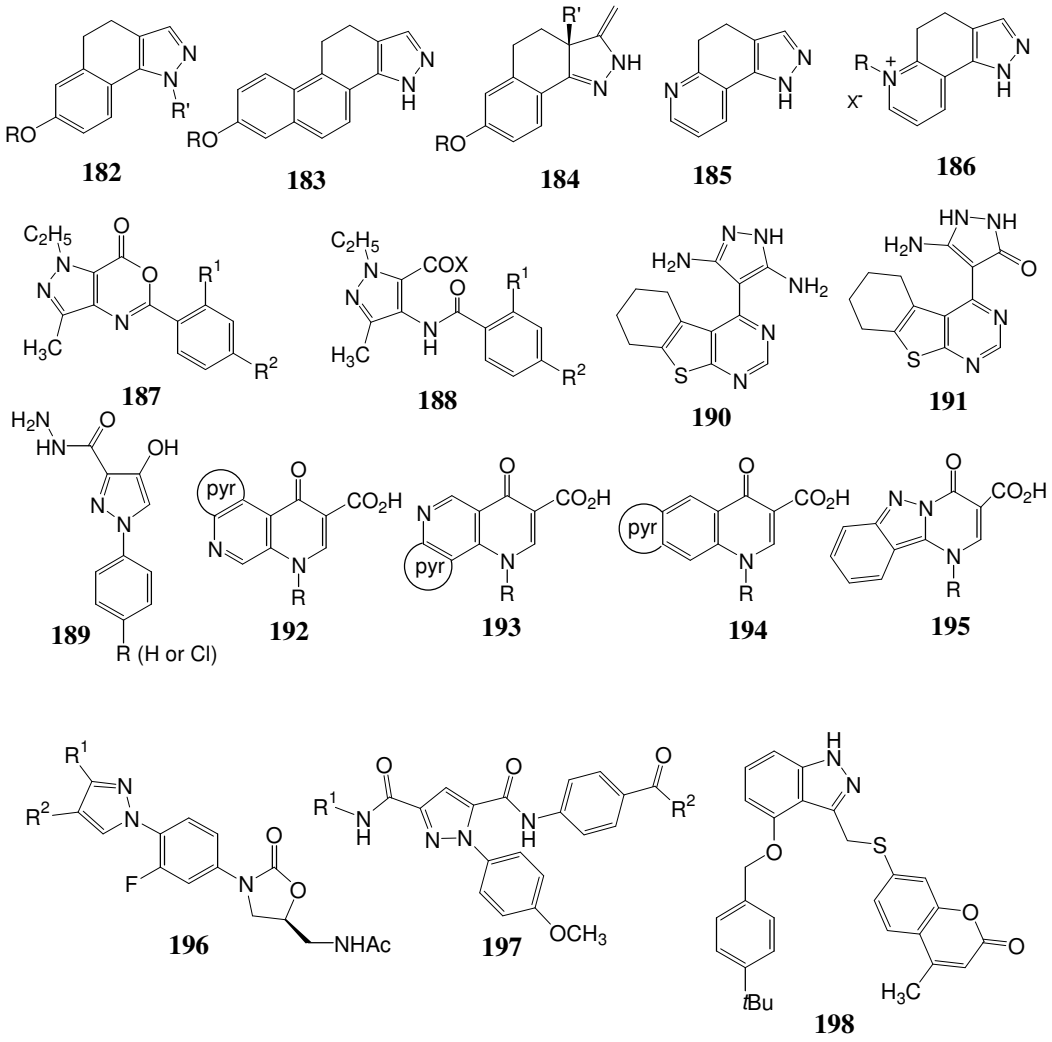
A structure-activity relationship study on the bacteriocidal and bacteriostatic ability of azasteroids **182-186** showed that they possess moderate *in vitro* inhibitory activity against *Bacillus subtilis* and *Pseudomonas fluorescens*.[241] Pyrazoles **187-189** were ineffective against standard strains of several bacteria[242] while others like **189** showed inhibitory effect on the growth of *S. aureus*.[147] Some pyrazolo[1,5-*a*]pyrimidines (*e.g.* **190** and **191**) showed *in vitro* moderate antibacterial activity against some Gram-positive and Gram-negative bacteria[243,244] and various pyrazolo-azaquinoline carboxylic acids **192** and **193** showed interesting activity against some Gram-positive bacteria but were ineffective against some Gram-negative bacteria.[245] Some pyrazoloquinolines **194** and pyrimidoindazoles **195** showed potent antibacterial activity against *S. aureus* and *Streptococcus foecalis* and moderate activity against Gram-negative bacteria.[246] 5-Benzamido-4-diazopyrazoles **132** have shown *in vitro* inhibitory activity against Gram-positive bacteria, some of them being active at concentrations equal to that of spreptomycin.[198]

Apart from classical barbiturates, the pyrimidine ring is present in several pharmaceuticals, such as antimicrobial and antitumour agents. In the search of new, non-benzodiazepine anxiolytic drugs, Spanish researchers evaluated the action of bacteria *Agrobacterium* sp. DSM 6136 and *Rhodococcus erythropolis* DSM 6138 on a series of unexplored pyrazolylpyrimidines, including the anxiolytic lesopitron **22**. They found that all their substrates were regioselectively oxidised, when free, at the C-2 and/or C-4 positions of the pyrimidine moiety, up to a maximum of two oxidations.[247]

Multi-drug-resistant Gram-positive bacterial pathogens have become a serious problem in hospitals and the community being particularly alarming the emergence of staphylococcal strains with reduced susceptibility to vancomycin. More recently, a multinational team reported high rates of resistance among aerobic Gram-negative bacilli in European care units. Thus, the search for novel potent broad-spectrum antibacterial agents is being fervently pursued by pharmaceutical houses world-wide. A series of new nitrogen-carbon-linked (azolylphenyl)oxazolidinone antibacterial agents has been prepared in order to

expand the spectrum of activity of this class of antibiotics to include Gram-negative organisms. Some of these azolyl derivatives **196** presented good antibacterial activity *in vitro* and *in vivo* against the fastidious Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis*.[248]

Helicobacter pylori is a causative agent of gastritis and gastric ulcers in humans and has also been associated with some types of gastric cancers. The widespread use of a battery of antibacterials for treatment of general infections has generated resistant strains of *H. pylori* in patient populations. Recently, it was reported a class of pyrazole-based compounds **197** which are the first examples of *H. pylori*-specific antibacterial agents; in culture these compounds inhibit the growth of *H. pylori* selectively, showing no effect on other Gram-negative and Gram-positive bacteria or humans.[249]



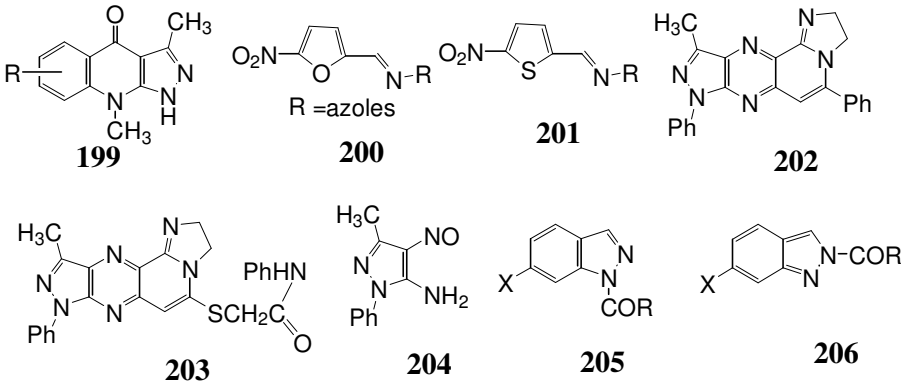
DNA gyrase (E.C. 5.99.1.3) is a well-established antibacterial target. It is an essential prokaryotic type II topoisomerase with no direct mammalian counterpart. It is involved in the vital processes of DNA replication, transcription and recombination. DNA gyrase catalyses the ATP-dependent introduction of negative supercoils into bacterial DNA as well as the decatenation and unknotting of DNA. In the search of novel inhibitors of DNA gyrase, Hoffmann-La Roche researchers developed a promising alternative approach to random screening which is based on the detailed 3D structural information of the targeted ATP

binding site. The 3D guided optimisation provided highly potent DNA gyrase inhibitors, *e.g.* indazole **198** is a tenfold more potent DNA gyrase inhibitor than the marketed drug novobiocin.[250]

5.3.3. Antiparasitic and antiprotozoa

Malaria remains one of the most important infectious diseases in the world. A significant and increasing problem in malaria control is the resistance of malaria parasites to available chemotherapeutic agents. There is a pressing need to identify new antimalarial drugs. Charris *et al.*[251,252] reported the synthesis of 3-amino-9-phenylpyrazolo[3,4-*b*]-4-quinolones and 2,4-diamino-10-phenyl-pyrimido[4,5-*b*]-5-quinolones, which showed to be an interesting family of antimalarial agents *in vitro*. More recently this group showed that 3-amino-9-methyl-1*H*-pyrazolo[3,4-*b*]-4-quinolone **199** derivatives possess high antimalarial activity *in vitro* against a chloroquine-resistant strain of *Plasmodium falciparum*.[253]

Nifurtimox (nfx) is the most important drug for the treatment of trypanosomiasis. However its use is limited due to its mutagenicity, side effects and non-curative action in certain cases. In these circumstances the development of new compounds alternative to the currently used nfx is a research area of great importance. In the search of new and more potent drugs against *Trypanosoma cruzi*, the aethiological agent of Chaga's disease or American trypanosomiasis, some of us demonstrated that azole derivatives **200** and **201**, structurally related to nfx, inhibited *in vitro* the growth of this protozoal.[254,255] Some of these compounds showed trypanocidal activity similar to that of nfx. However the *in vivo* assays indicated that they were not able to completely eradicate the infection in treated mice.



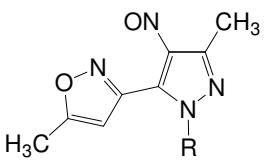
As pyrazolo[3,4-*b*]pyrazines have demonstrated important biological properties, recently El-Kashef *et al.*[256] synthesised several new derivatives and evaluated their antiparasitic activity against *Trichomonas vaginalis* and promastigotes of two *Leishmania* strains. Compound **202** displayed good *in vitro* activity against both parasites while compound **203** showed greater trichomonacidal than leishmanicidal activity; they also reported that pyrazole **204** has the same behaviour.

Benzimidazoles are the anthelmintic agents against the intestinal nematodes of sheep with the broadest known spectra of activity, but 1- and 2-carbamoylbenzotriazoles are also reported to have similar activity. However 1- and 2-acyl, alkoxycarbonyl- and carbamoylindazoles **205** and **206** showed some activity against *Trichinella spiralis* in mice but none of them demonstrated activity against sheep nematodes.[257]

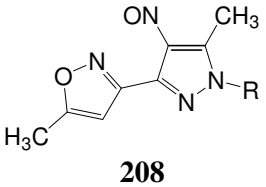
5.3.4. Fungicides

The field of antifungal azoles has been reviewed comprehensively by Zirngibl in 1998.[258] It is apparent that the chemical basis of these drugs is dominated by imidazole and 1,2,4-triazole derivatives, other azoles, like pyrazole, playing a minor role. Although in our introduction we have pointed out that herbicidal and other agrochemical compounds will be excluded from this review, this is a difficult aspect in the present section because most fungus used in preliminary tests have no relevance in human medicine.

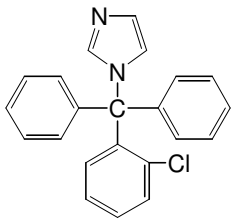
Aiello *et al.*[259] demonstrated that nitrosopyrazoles **207** and **208** displayed antifungal activity at non-cytotoxic concentrations. They showed that the lead compound (**208**, R = CH_3CH_2) was 9 times more potent *in vitro* than miconazole and 20 times more selective against *Cryptococcus neoformans*, a pathogen for immunocompromised patients, and also 8- and 125-fold more potent than amphotericin and fluconazole, respectively. Activities higher than that of chlotrimazol **209** were found for some *N*,*N*'-bis-azolylarylmethanes including pyrazole and indazole derivatives **210**.[260] A related approach was used by Menozzi *et al*. but with another imidazole derivative, bifonazole **211**, the resulting [α-(1,5-disubstituted 1*H*-pyrazol-4-yl)benzyl]azoles **212** were tested *in vitro* against *Candida albicans* and other fungus with no significant results.[261]



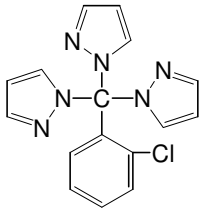
207



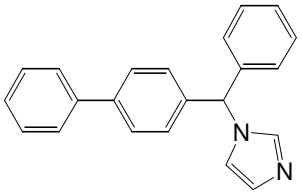
208



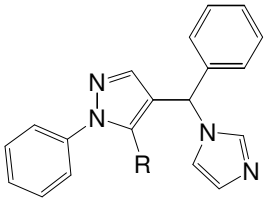
209



210



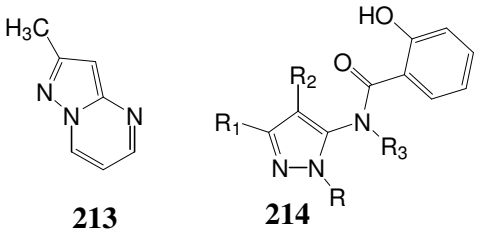
211



212

A series of pyrazolo[1,5-*a*]pyrimidines were synthesised and tested as systemic fungicides, the parent compound **213** was quite a potent inhibitor of mycelial growth.[262] The pyrazolo[3,4-*b*]pyrazines **202** and **203** and several other derivatives described in the paper of El-Kashef *et al.*[256] have also antifungal properties against *Penicillium chrysogenum*, *Fusarium latertium* and *Rhizopus stolonifer* but were inactive against *Aspergillus flavus*. Pyrazoles **187** and **188** (R^1 = NO_2) showed moderate activity against *Candida Albicans*,[242] while preliminary assays showed that some of the 3-methyl-1*H*-pyrazole-4-carboxylic ester derivatives **165-167** presented fungicidal activity against wheat rust and phoma asparagi.[229] A number of *N*-pyrazolylsalicylamides, such as **214**, show moderate antifungal activity.[263] Garuti *et al*. reported the lack of *in vitro* activity of a series of 3-methoxypyrazole derivatives.[264]

There are other reports showing that 5-benzamido-4-diazopyrazoles **132,**[198] pyrazoles related nucleosides **140** and **141**[206] and some pyrazolo[3,4-*d*]oxazoles **137**[204] displayed no antifungal activity while other 5-alkylaminopyrazolo[3,4-*d*]oxazoles[265] possess only weak to moderate antifungal activity.



213 **214**

6. Conclusions: structure-biological activity relationships and modelling

On different occasions in the previous sections, different techniques to improve the properties of a drug have been reported. In this last section, we will summarise and classify these publications according to the methodologies used.

SAR (pharmacophore), QSAR and CoMFA: Qualitiative structure-activity relationships (SAR), often related to establishing the topology of a receptor or/and the minimum structural characteristics of the pharmacophore, quantitative structure-activity relationships (QSAR) associated to Hansch,[266] and the more recent comparative molecular field analysis (CoMFA)[267] have been used to improve pyrazole-derived drugs. Leaving aside publications dealing with bioisosterism (for instance N/CH),[215] most publications, including very recent ones, correspond to qualitative SAR discussions.[10,12,14,19,20,27,91,154,160,162,173, 195,220,241] In some cases, although the discussion remains qualitative, log *P* y pK_a values are reported.[129] In the case of triphenyl-1*H*-pyrazole-1-nonanoic acid (**62**), based on a SAR approach, the authors have proposed a topological descriptor of a portion of the PGI_2 receptor occupied by pyrazole derivatives.[119] QSAR studies are scarce and decreasing in interest: the multidrug resistance (MDR)-modulating activity of a series of 4-acylpyrazolones was studied using as descriptors the lipophilicity (calculated log *P*) and hydrogen bond acceptor strengths.[268] The affinity for the benzodiazepine receptor of pyrazolo[4,3-*c*]quinolin-3-ones **6** was optimized using Hansch approach[6] while an example of application of the CoMFA to the field of dopamine D4 receptor antagonists can be found in ref. 39.

Computational (molecular mechanics) and theoretical chemistry (semi-empirical and ab initio): The size of the molecules described in this review is small enough to be calculated by high-level *ab initio* methods. A limitation occurs for molecules with many degrees of freedom (rotation about single bonds) because, then, the different minima may have very close energies and, consequently, be of little information value. In any case, these calculations correspond to isolated molecules (assumedly in the gas phase) that may have little resemblance to the real situation. A step further would be the inclusion of water molecules, but still far away to the interaction with the receptor. Using a combination of AM1 calculations to study the conformational properties of compound **21** and of model compounds, the authors were able to propose a model of the bioactive conformation adopted by neurotensin receptor antagonists.[40] A similar approach has been used in the case of compounds **74** and **52**.[23,104] Other authors have used, for similar purposes, molecular modelling with different force fields (amongst other, compounds **40**, **57**, **120**, **153** and **154**).[79,103,110,123,180,182,214] One of the rare cases of *ab initio* 6-31G* calculations is reported in ref. 39.

Acknowledgements

Thanks are given to the Ministry of Science and Technology of Spain (SAF-00-114-C02-01), to the University of Aveiro and "Fundação para a Ciência e a Tecnologia" of Portugal for financial support. We gratefully acknowledge "Patro" for her help in searching bibliography.

References

1. Elguero, J. *Comp. Heterocycl. Chem.* **1984**, *5*, 167.
2. Elguero, J. *Comp. Heterocycl. Chem. II*, **1996**, *3*, 1.
3. Kirsche, K. in *Methoden der Organische Chemie* (Houben-Weyl), **1994**, *Hetarene III*, 399 and 764.
4. Wermuth, C. G. in *The Practice of Medicinal Chemistry*. Wermuth, C. G. (ed), Academic Press, London: 1996.
5. Savini, L.; Massarelli, P.; Pellerano, C.; Fiorini, I.; Bruni, G.; Romeo, M. F. *Farmaco* **1993**, *48*, 65.
6. Savini, L.; Massarelli, P.; Nencini, C.; Pellerano, C.; Biggio, G.; Maciocco, A.; Tuligi, G.; Carrieri, A.; Cinone, N.; Carotti, A. *Bioorg. Med. Chem.* **1998**, *6*, 389.
7. Palazzino, G.; Cecchi, L.; Melani, F.; Colotta, V.; Filacchioni, G.; Martini, C.; Lucacchini, A. *J. Med. Chem.* **1987**, *30*, 1737.
8. Guerrini, G.; Costanzo, A.; Bruni, F.; Ciciani, G.; Selleri, S.; Gratteri, P.; Costa, B.; Martini, C.; Lucacchini, A. *Farmaco* **1999**, *54*, 375.
9. Costanzo, A.; Guerrini, G.; Ciciani, G.; Bruni, F.; Selleri, S.; Costa, B.; Martini, C.; Lucacchini, A.; Aiello, P. M.; Ipponi, A. *J. Med. Chem.* **1999**, *42*, 2218.
10. Varano, F.; Catarzi, D.; Colotta, V.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C. *Arch. Pharm.* **1996**, *329*, 529.
11. Selleri, S.; Bruni, F.; Costanzo, A.; Guerrini, G.; Casilli, M. L.; Costagli, C.; Giusti, L.; Lucacchini, A.; Martini, C.; Aiello, P. M.; Lamberti, C. *Eur. J. Med. Chem.* **1997**, *32*, 941.
12. Matuszczak, B.; Pekala, E.; Müller, C. E. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 163.
13. Sanger, D. J.; Griebel, G.; Perrault, G.; Claustre, Y.; Schoemaker, H. *Pharmacol., Biochem. Behav*. **1999**, *64*, 269.
14. Colotta, V.; Catarzi, D.; Varano, F.; Melani, F.; Filacchioni, G.; Cecchi, L.; Galli, A.; Costagli, C. *Farmaco* **1996**, *51*, 223.
15. Cohen, Z.; Bouchelet, I.; Olivier, A.; Villemure, J.-G.; Ball, R.; Stanimirovic, D. B.; Hamel, E. J. *Cereb. Blood Flow Metab*. **1999**, *19*, 908.
16. Bardin, L.; Lavarenne, J.; Eschalier, A. *Pain* **2000**, 86, 11.
17. Bourdon, D. M.; Camden, J. M.; Landon, L. A.; Levy, F. O.; Turner, J. T. *Br. J. Pharmacol*. **2000**, *130*, 104.
18. Aghajanian, G. K.; Marek, G. J. *Brain Res. Rev*. **2000**, *31*, 302.
19. Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assié, M-B.; Cosi, C.; Kleven, M. *J. Med. Chem.* **1998**, *41*, 5070.
20. Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assié, M-B.; Cosi, C.; Kleven, M. *J. Med. Chem.* **1999**, *42*, 1648.
21. Pawlowski, M.; Katlabi, J.; Drabczynska, A.; Duszynska, B.; Charakchieva-Minol, S.; Deren-Wesolek, A.; Tatarczynska, E.; Chojnacka-Wojcik, E.; Mokrosz, M. J.; Bojarski, A. J. *Eur. J. Med. Chem.* **1999**, *34*, 167.
22. Farré, A.; Frigola, J. *Drugs Future* **1994**, *19*, 651.
23. Harada, H.; Morie, T.; Hirokawa, Y.; Terauchi, H.; Fujiwara, I.; Yoshida, N.; Kato, S. *Chem. Pharm. Bull*. **1995**, *43*, 1912.
24. Harada, H.; Morie, T.; Hirokawa, Y.; Kato, S. *Tetrahedron Asymm*. **1997**, *8*, 2367-2374.
25. Petrie, R. X. A.; Reid, I. C.; Stewart, C. A. *Pharmacol. Ther*. **2000**, *87*, 11.
26. Zimmermann, D.; Janin, Y. L.; Brehm, L.; Bräuner-Osborne, H.; Ebert, B.; Johansen, T. N.; Madsen, U.; Krogsgaard-Larsen, P. *Eur. J. Med. Chem*. **1999**, *34*, 967.
27. Schaus, J. M.; Thompson, D. C.; Bloomquist, W. E.; Susemichel, A. D.; Calligaro, D. O.; Cohen, M. L. *J. Med. Chem.* **1998**, *41*, 1943.
28. Ikeda, Y.; Takano, N.; Matsushita, H.; Shiraki, Y.; Koide, Nagashima, R.; Fujimura, Y.; Shindo, M.; Suzuki, Iwasaki, T. *Arzneim. Forsch. Drug Res.* **1979**, 511.
29. Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; DeFelice, A. F.; Feigenson, M. E. *J. Med. Chem.* **1985**, *28,* 256.
30. Yu, S.; He, X.; Ma, C.; McKernan, R.; Cook, J. M. *Med. Chem. Res*. **1999**, *9*, 186.
31. Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Borioni, A.; Viziano, M.; Dionisotti, S.; Ongini, E. *Current Med. Chem.* **1995**, *2*, 707.

32. Wustrow, D. J.; Capiris, T.; Rubin, R.; Knobelsdorf, J. A.; Akunne, H.; Davis, M. D.; MacKenzie, R.; Pugsley, T. A.; Zoski, K. T.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2067.
33. Gmeiner, P.; Sommer, J.; Mierau, J.; Höfner, G. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1477.
34. Yesilada, A.; Gökhan, N.; Özer, I.; Vural, K.; Erol, K. *Farmaco* **1996**, *51*, 775.
35. Wise, L. D.; Butler, D. E.; DeWald, H. A.; Lustgarten, D.; Pattison, I. C.; Schweiss, D. N.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. *J. Med. Chem.* **1987**, *30*, 1807.
36. Wise, L. D.; Butler, D. E.; DeWald, H. A.; Lustgarten, D.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. *J. Med. Chem.* **1986**, *29*, 1628.
37. Bourrain, S; Collins, I.; Neduvelil, J. G.; Rowley, M.; Leeson, P. D.; Patel, S.; Emms, F.; Marwood, R.; Chapman, K. L.; Fletcher, A. E.; Showell, G. A. *Bioog. Med. Chem.* **1998**, *6*, 1731.
38. Collins, I.; Rowley, M.; Davey, W. B.; Emms, F.; Marwood, R.; Patel, S.; Fletcher, A.; Ragan, I. C.; Leeson, P. D.; Scott, A. L.; Broten, T. *Bioorg. Med. Chem.* **1998**, *6*, 743.
39. Lanig, H.; Utz, W.; Gmeiner, P. *J. Med. Chem*. **2001**, *44*, 1151.
40. Quéré, L.; Boigegrain, R.; Jeanjean, F.; Gully, D.; Evrard, G.; Durant, F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2639.
41. Quéré, L.; Longfils, G.; Boigegrain, R.; Labeeuw, B.; Gully, D.; Durant, F. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 653.
42. Fresquet, A.; Sust, M.; Loret, A.; Murphy, M. F.; Carter, F. J.; Campbell, G. M.; Giedra, M.; Marion-Landais, G. *Ann. Pharmacother.* **2000**, *34*, 147.
43. Vega, S.; Gil, M. S.; Darias, V.; Sánchez-Mateo, C. C.; Expósito, M. A.; Oset-Gasque, M. J.; Parramón, M.; González, M. P. *Eur. J. Med. Chem*. **1994**, *29*, 233.
44. Mealy, N.; Castañer, J. *Drugs Future* **1996**, *21*, 37.
45. Sanger, D. J.; Morel, E.; Perrault, G. *Eur. J. Pharmacol*. **1996**, *313*, 35.
46. Hurst, M.; Noble, S. *CNS Drugs* **1999**, *11*, 387.
47. Brunner, U.; Gensthaler, B. *Pharm. Ztg*. **1999**, *144*, 2122.
48. Heydorn, W. E. *Expert. Opin. Invest. Drugs* **2000**, *9*, 841.
49. Drover, D.; Lemmens, H.; Naidu, S.; Cevallos, W.; Darwish, M.; Stanski, D. *Clin. Ther.* **2000**, *22*, 1443.
50. Kornet, M. J.; Garrett, R. J. *J. Pharm. Sci.* **1979**, *68*, 377.
51. Lankau, H.-J.; Menzer, M.; Rostock, A.; Arnold, T.; Rundfeldt, Unverferth, K. *Arch. Pharm*. **1999**, *332*, 219.
52. Rahtz, D.; Böttcher, I. *Eur. J. Med. Chem*. **1982**, *17*, 429.
53. Beyer, K.-H.; Friese, J. *Arch. Pharm.* **1985**, *318*, 855.
54. Gürsoy, A.; Demirayak, S.; Capan, G.; Erol, G.; Vural, K. *Eur. J. Med. Chem*. **2000**, *35*, 359.
55. Ergenc, N.; Çapan, G.; Demirdamar, R. *Arzneim. Forsch*. **2001**, *51*, 118.
56. Mehlisch, D. R. *Amer. J. Med.* **1983**, 47.
57. Tewari, A. K.; Mishra, A. *Bioorg. Med. Chem*. **2001**, *9*, 715.
58. Omar, N. M.; Mrongovius, R. I.; Schulte, K. E. *Eur. J. Med. Chem.* **1979**, *14*, 23.
59. Mosti, L.; Menozzi, G.; Fossa, P.; Schenone, P. *Farmaco* **1992**, *47*, 567.
60. Mosti, L.; Menozzi, G.; Schenone, P.; Molinario, L.; Conte, F.; Montanario, C.; , Marmo, E. *Farmaco* **1988**, *43*, 763.
61. Gaston, M. A.; Dias, L. R. S.; Freitas, A. C. C.; Miranda, A. L. P.; Barreiro, E. J. *Pharm. Acta Helv*. **1996**, *71*, 213.
62. Bruno, O.; Ranise, A.; Bondavalli, F.; Schenone, P. *Farmaco* **1992**, *47*, 1235.
63. Menozzi, G.; Mosti, L.; Schenone, P.; D' Amico, M.; Falzarano, C.; Rossi, F*Farmaco* **1993**, *48*, 539.
64. Menozzi, G.; Mosti, L.; Merello, L.; Piana, A.; Armani, U.; Ghia, M.; Angiola, M.; Mattioli, F. *Farmaco* **2000**, *55*, 219.
65. Menozzi, G.; Mosti, L.; Fossa, P.; Mattioli, F.; Ghia, M. *J. Heterocycl. Chem*. **1997**, *34*, 963.
66. Menozzi, G.; Mosti, L.; Schenone, P.; D' Amico, M.; Filippelli, A.; Rossi, F*Farmaco* **1992**, *47*, 1495.
67. Alvarez, I.; Andreu, F.; Buxens, J.; Colombo, M.; Dordal, A.; Fort, M.; Gutiérrez, B.; Farré, A. J. *Methods Find. Exp. Clin. Pharmacol.* **2000**, *22*, 211.
68. Torrens, A.; Castrillo, J. A.; Frigola, J.; Salgado, L.; Redondo, J. *Chirality*, **1999**, *11*, 63.

69. Hueso-Rodríguez. J. A.; Berrocal, J.; Gutiérrez, B.; Farré, A. J.; Frigola, J. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 269.
70. Torrens, A.; Castrillo, J. A.; Claparols, A.; Redondo, J. *Synlett* **1999**, *6*, 765.
71. Redondo, J.; Blázquez, M. A.; Torrens, A. *Chirality* **1999**, *11*, 694.
72. Monck, N. *Curr. Opin. Investig. Drugs* **2001**, *2*, 1269.
73. Seerden, J.-P. G.; Tulp, M. T. M.; Scheeren, H. W.; Kruse, C. G. *Bioorg. Med. Chem.* **1998**, *6*, 2103.
74. Bruno, O.; Ranise, A.; Schenone, P.; D' Amico, M.; Falzarano, C.; Rossi, F*Farmaco* **1993**, *48*, 1697.
75. Mosti, L.; Menozzi, G.; Fossa, P.; Filipelli, W.; Gessi, S.; Rinaldi, B.; Falcone, G. *Arzneim-Forsch. Drug Res*. **2000**, *50*, 963.
76. Jagerovic, N.; Cano, C.; Elguero, J.; Goya, P.; Callado, L. F.; Meana, J. J.; Girón, R.; Abalo, R.; Ruiz, D.; Goicoechea, C.; Martín, M. I. *Bioorg. Med. Chem*. **2001**, in press.
77. Baraldi, P. G.; Cacciari, B.; Spallulto, G.; Bergonzoni, M.; Dionisotti, S.; Ongini, E.; Varani, K.; Borea, P. A. *J. Med. Chem*. **1998**, *41*, 2126.
78. Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Villatoro, M. J. P. I.; Zocchi, C.; Dionisotti, S.; Ongini, E. *J. Med. Chem.* **1996**, *39*, 1164.
79. Baraldi, P. G.; Cacciari, R.; Romagnoli, R.; Spalluto, G.; Moro, S.; Klotz, K. N.; Leung, E.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2000**, *43*, 4768.
80. Plate, R.; Plaum, M. J. M.; de Boer, T.; Andrews, J. S.; Rae, D. R.; Gibson, S. *Bioorg. Med. Chem*. **1996**, *4*, 227.
81. Rodríguez-Franco, M. I.; Dorronsoro, I. Martínez, A.; Pérez, C.; Badía, A.; Baños, J. E. *Arch. Pharm*. **2000**, *333*, 118.
82. Bowler, A. N.; Dinsmore, A.; Doyle, P. M.; Young, D. W. *J. Chem. Soc., Perkin Trans 1* **1997**, 1297.
83. Lee, Y.; Martasek, P.; Roman, L. J.; Silverman, R. B. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2771.
84. Wolff, D. J.; Gribin, B. J. *Biochem. Biophys*. **1994**, *311*, 300.
85. Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G. *FEBS Lett.* **1994**, *350*, 240.
86. Pertwee, R. G. *Exp. Opin. Invest. Drugs* **2000**, *9*, 1.
87. Wiley, J. L.; Jefferson, R. G.; Grier, M. C.; Mahadevan, A.; Razdan, R. K.; Martin, B. R. *J. Pharmacol. Exp. Ther*. **2001**, *296*, 1013.
88. Rinaldi-Carmona, M.; Barth, F.; Millan, J.; Derocq, J.-M.; Casellas, P.; Congy, C.; Oustric, D.; Sarran, M.; Bouaboula, M.; Calandra, B.; Portier, M.; Shire, D.; Breliere, J.-C.; Le Fur, G. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 644.
89. Barth, F. *Exp. Opin. Ther. Pat*. **1998**, *8*, 301.
90. Goya, P.; Jagerovic, N. *Exp. Opin. Ther. Pat.* **2000**, *10*, 1529.
91. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, *J. Med. Chem.* **1999**, *42*, 769.
92. Gatley, S. J.; Lan, R.; Volkow, N. D.; Pappas, N.; King, P.; Wong, C. T.; Gifford, A. N.; Pyatt, B.; Dewey, S. L.; Makriyannis, A. *J. Neurochem.* **1998**, *70*, 417.
93. Mathews, W. B.; Scheffel, U.; Finley, P.; Ravert, H. T.; Frank, R. A.; Rinaldi, C. M.; Barth, F.; Dannals, R. F. *Nucl. Med. Biol*. **2000**, *27*, 757.
94. Howlett, A. C.; Wilken, G. H.; Pigg, J. J.; Houston, D. B.; Lan, R.; Liu, Q.; Makriyannis, A. *J. Neurochem.* **2000**, *74*, 2174.
95. Meschler, J. P.; Kraichely, D. M.; Wilken, G. H.; Howlett, A. C. *Biochem. Pharmacol*. **2000**, *60*, 1315.
96. Okazaki, T.; Suga, A.; Watanabe, T.; Kikuchi, K.; Kurihara, H.; Shibasaki, M.; Fujimori, A.; Inagaki, O.; Yanagisawa, I. *Chem. Pharm. Bull*. **1998**, *46*, 69.
97. Okazaki, T.; Suga, A.; Watanabe, T.; Kikuchi, K.; Kurihara, H.; Shibasaki, M.; Fujimori, A.; Inagaki, O.; Yanagisawa, I. *Chem. Pharm. Bull*. **1998**, *46*, 287.
98. Watson, S. P.; Middlemiss, D.; Pass, M.; Hubbard, T.; Panchal, T. A.; Heron, N. M.; Paton, J. M. S.; Butt, A.; Dean, A. W.; Donnelly, M.; Bayliss, M. K. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 151.
99. Middlemiss, D.; Ross, B. C.; Eldred, C.; Montana, J. G.; Shah, P.; Hirst, G. C.; Watson, S. P.; Panchal, T. A.; Paton, J. M. S.; Hubbard, T.; Drew, G. M.; Robertson, M. J.; Hilditch, A.; Clark, K. L. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 1243.

100. Nicolaï, E.; Curé, G.; Goyard, J.; Kirchner, M.; Teulon, J.-M.; Versigny, A.; Cazes, M.; Virone-Oddos, A.; Caussade, F.; Cloarec, A. *Chem. Pharm. Bull*. **1994**, *42*, 1617.
101. Ashton, W. T.; Hutchins, S. M.; Greenlee, W. J.; Doss, G. A.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem*. **1993**, *36*, 3595.
102. Almansa, C.; Gómez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; García-Rafanell, J.; Forn, J. *J. Med. Chem*. **1997**, *40*, 547.
103. Hassall, C. H.; Kröhn, A.; Moody, C. J.; Thomas, W. A. *J. Chem. Soc., Perkin Trans 1* **1984**, 155.
104. Ermondi, G.; Boschi, D.; Di Stilo, A.; Tironi, C.; Gasco, A. *Farmaco* **1998**, *53*, 519.
105. Winters, G.; Sala, A.; Barone, D.; Baldoli, E. *J. Med. Chem*. **1985**, *28*, 934.
106. Jonas, R.; Klockow, M.; Lues, I.; Prücher, H.; Schliep, H. J.; Wurziger, H. *Eur. J. Med. Chem.* **1993**, *28*, 129.
107. Combs, D. W. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1663.
108. Sircar, I.; Morrison, G. C.; Burke, S. E.; Skeean, R.; Weishaar, R. E. *J. Med. Chem.* **1987**, *30*, 1724.
109. Sedereviciute, V.; Garaliene, V.; Vainilavicius, P.; Hetzheim, A. *Pharmazie* **1998**, *53*, 233.
110. Astles, P. C.; Brealey, C.; Brown, T. J.; Facchini, V.; Handscombe, C.; Harris, N. V.; McCarthy, C.; McLay, I. M.; Porter, B.; Roach, A. G.; Sargent, C.; Smith, C.; Walssh, R. J. A. *J. Med. Chem*. **1998**, *41*, 2732.
111. Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrancois, D.; Uridat, E.; Vevert, J. P. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2575.
112. Umekawa, K.; Hasegawa, H.; Tsutsumi, Y.; Sato, K.; Matsumura, Y.; Ohashi, N. *Jpn. J. Pharmacol*. **2000**, *84*, 7.
113. Akahane, A.; Katayama, H.; Mitsunaga, T.; Kita, Y.; Kusunoki, T.; Terai, T.; Yoshida, K.; Shiokawa, Y. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2059.
114. Akahane, A.; Katayama, H.; Mitsunaga, T.; Kato, T.; Kinoshita, T.; Kita, Y.; Kusunoki, T.; Terai, T.; Yoshida, K.; Shiokawa, Y. *J. Med. Chem.* **1999**, *42*, 779.
115. Kuroda, S.; Akahane, A.; Itani, H.; Nishimura, S.; Durkin, K.; Kinoshita, T.; Nakanishi, I.; Sakane, K. *Tetrahedron* **1999**, *55*, 10351. Kuroda, S.; Takamura, F.; Tenda, Y.; Itani, H.; Tomishima, Y.; Akahane, A.; Sakane, K. *Chem. Pharm. Bull*. **2001**, *49*, 988.
116. Barreiro, E. J.; Freitas, A. C. C. *J. Heterocycl. Chem*. **1992**, *29*, 407.
117. Monge, A.; Aldana, I.; Alvarez, T.; Font, M.; Santiago, E.; Latre, J. A.; Bermejillo, M. J.; López-Unzu, M. J. *J. Med. Chem*. **1991**, *34*, 3023.
118. Monge, A.; Aldana, I.; Losa, M. J.; Font, M.; Castiella, E.; Frechilla, D.; Cenarruzabeitia, E.; Martínez de Irujo, J. J.; López-Unzu, J.; Alberdi, E.; Santiago, E. *J. Pharm. Sci*. **1993**, *82*, 526.
119. Meanwell, N. A.; Rosenfeld, M. J.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Seiler, S. M. *J. Med. Chem.* **1992**, *35*, 389.
120. Hamanaka, N.; Takahashi, K.; Nagao, Y.; Toritsu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett*. **1995**, *5* 1083.
121. Frigola, J.; Colombo, A.; Parés, J.; Martínez, L.; Sagarra, R.; Roser, R. *Eur. J. Med. Chem*. **1989**, *24*, 435.
122. Askew, B. C.; Bednar, R. A.; Bednar, B.; Claremon, D. A.; Cook, J. J.; McIntyre, C. J.; Hunt, C. A.; Gould, R. J.; Lynch, R. J.; Lynch, J. J. Jr.; Gaul, S. L.; Stranieri, M. T.; Sitko, G. R.; Holahan, M. A.; Glass, J. D.; Hamill, T.; Gorham, L. M.; Prueksaritanont, T.; Baldwin, J. J.; Hartman, G. D. *J. Med. Chem.* **1997**, *40*, 1779.
123. Pinto, D. J. P.; Orwat, M. J.; Wang, S.; Fevig, J. M.; Quan, M. L.; Amparo, E.; Cacciola, J.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. M.; Luettgen, J. M.; Liang, L.; Aungst, B. J.; Wright, M. R.; Knabb, R. M.; Wong, P. C.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem*. **2001**, 44, 566.
124. Zhang, H.-C.; Derian, C. K.; Andrade-Gordon, P.; Hoekstra, W. J.; McComsey, D. F.; White, K. B.; Poulter, B. L.; Addo, M. F.; Cheung, W.-M.; Damiano, B. P.; Oksenberg, D.; Reynolds, E. E.; Pandey, A.; Scarborough, R. M.; Maryanoff, B. E. *J. Med. Chem.* **2001**, *44*, 1021.
125. Fernandez, P. A.; Bellamy, T.; Kling, M.; Madge, D. J.; Selwood, D. L. *Heterocycles* **2001**, *55*, 1813.
126. Selwood, D. L.; Brummell, D. G.; Glen, R. C.; Goggin, M. C.; Reynolds, K.; Tatlock, M. A.; Wishart, G. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1089. Selwood, D. L.; Brummell, D. G.; Budworth, J.; Burtin, G. E.; Campbell, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.;

Hobbs, A. J.; Kling, M. R.; Liu, Q.; Madge, D. J.; Meillerais, S.; Powell, K. L.; Reynolds, K.; Spacey, G. D.; Stables, J. N.; Tatlock, M. A.; Wheeler, K. A.; Wishart, G.; Woo, C. K. *J. Med. Chem*. **2001**, *44*, 78.
127. Straub, A.; Stasch, J.-P.; Alonso-Alija, C.; Benet-Buchholz, J.; Ducke, B.; Feurer, A.; Furstner, C. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 781.
128. Stasch, J.-P.; Becker, E. M.; Alonso-Alija, C.; Apeler, H.; Dembowsky, K.; Feurer, A.; Gerzer, R.; Minuth, T.; Perzborn, E.; Pleiss, U.; Schroder, H.; Schroeder, W.; Stahl, E.; Steinke, W.; Straub, A.; Schramm, M. *Nature* **2001**, *410*, 212.
129. Cuberes, M. R.; Contijoch, M.; Calvet, C.; Alegre, J.; Quintana, J. R.; Frigola, J. *Chem. Pharm. Bull*. **1997**, *45*, 1287.
130. Wilson, J. A.; Johnston, D. A.; Penston, J.; Wormsley, K. G. *Br. J. Clin. Pharmacol.* **1986**, *21*, 685.
131. Fludzinski, P.; Evrard, D. A.; Bloomquist, W. E.; Lacefield, W. B.; Pfeifer, W.; Jones, N. D.; Deeter, J. B.; Cohen, M. L. *J. Med. Chem*. **1987**, *30*, 1535.
132. Kaumann, A. J.; King, F. D.; Young, R. C. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 419.
133. Hansen, J. B.; Weis, J.; Suzdak, P. D.; Eskesen, K. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 695.
134. Djuric, S. W.; BaMaung, N. Y.; Basha, A.; Liu, H.; Luly, J. R.; Madar, D. J.; Sciotti, R. J.; Tu, N. P.; Wagenaar, F. L.; Wideman, P. E.; Zhou, X.; Ballaron, S.; Bauch, J.; Chen, Y.-W.; Chiou, X. G.; Fey, T.; Gauvin, D.; Gubbins, E.; Hsieh, G. C.; Marsch, K. C.; Mollison, K. W.; Pong, M.; Shaughnessy, T. K.; Sheets, M. P.; Smith, M.; Trevillyan, J. M.; Warrior, U.; Wegner, C. D.; Carter, G. W. *J. Med. Chem.* **2000**, *43*, 2975.
135. Duplantier, A. J.; Andresen, C. J.; Cheng, J. B.; Cohan, V. L.; Decker, C.; DiCapua, F. M.; Kraus, K. G.; Johnson, K. L.; Turner, C. R.; UmLand, J. P.; Watson, J. W.; Wester, R. T.; Williams, A. S.; Williams, J. A. *J. Med. Chem.* **1998**, 41, 2268.
136. Crespo, M. I.; Gracia, J.; Puig, C.; Vega, A.; Bou, J.; Beleta, J.; Domenech, T.; Ryder, H.; Segarra, V.; Palacios, J. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2661.
137. Galietta, L. J.; Springsteel, M. F.; Eda, M.; Niedzinski, E. J.; By, K.; Haddadin, M. J.; Kurth, M. J.; Nantz, M. H.; Verkman, A. S. *J. Biol. Chem*. **2001**, *276*, 19723.
138. El-Abadelah, M. M.; Sabri, S. S.; Khanfar, M. A.; Voelter, W.; Abdel-Jalil, R. J.; Maichle-Mössmer, C.; Al-Abed, Y. *Heterocycles* **2000**, *53*, 2643.
139. Al-bojuk, N. R.; Eñ-Abadelah, M. M.; Sabri, S. S.; Michel, A.; Voelter, W.; M.-Mössmer, C.; Al-abed, Y. *Heterocycles* **2001**, *55*, 1789.
140. Yu, G.; Mason, H. J.; Wu, X.; Wang, J.; Chong, S.; Dorough, G.; Henwood, A.; Pongrac, R.; Seliger, L.; He, B.; Normandin, D.; Adam, L.; Krupinski, J.; Macor, J. E. *J. Med. Chem*. **2001**, *44*, 1025.
141. Corsi, G.; Palazzo, G.; Germani, C.; Barcellona, P. S.; Silvestrini, B. *J. Med. Chem.* **1976**, *19*, 778.
142. Traxler, P.; Furet, P. *Pharmacol. Ther*. **1999**, *82*, 195.
143. Rainer, G.; Krüger, U.; Klemm, K. *Arzneim. Forsch*. **1981**, *31*, 649.
144. Biere, H.; Schöder, E.; Ahrens, H.; Kapp, J.-F.; Böttcher, I. *Eur. J. Med. Chem*. **1982**, *17*, 27.
145. Biere, H.; Böttcher, I.; Kapp, J.-F. *Arch. Pharm*. **1983**, *316*, 588.
146. Biere, H.; Böttcher, I.; Kapp, J.-F. *Arch. Pharm*. **1983**, *316*, 608.
147. Farghaly, A. M.; Soliman, F. S. G.; El Semary, M. M. A.; Rostom, S. A. F. *Pharmazie* **2001**, *56*, 28.
148. Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18.
149. Murray, W. V. *Tetrahedron Lett.* **1993**, *34*, 1863.
150. Penning, T. D.; Kramer, S. W.; Lee, L. F.; Collins, P. W.; Koboldt, C. M.; Seibert, K.; Veenhuizen, A. M.; Zhang, Y. Y.; Isakson, P. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2121. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
151. Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem*. **2001**, *44*, 3039.
152. Tsuji, K.; Nakamura, K.; Konishi, N.; Tojo, T.; Ochi, T.; Senoh, H.; Matsuo, M. *Chem. Pharm, Bull.* **1997**, *45*, 987.
153. Almansa, C.; de Arriba, A. F.; Cavalcanti, F. L.; Gómez, L. A.; Miralles, A.; Merlos, M.; García-Rafanell, J.; Forn, J. *J. Med. Chem*. **2001**, *44*, 350.

154. Schindler, R.; Fleischhauer, I.; Höfgen, N.; Sauer, W.; Egerland, U.; Poppe, H.; Heer, S.; Szelenyi, I.; Kutscher, B.; Engel, J. *Arch. Pharm*. **1998**, *331*, 13.
155. Mosti, L.; Lo Presti, E.; Menozzi, G.; Marzano, C.; Baccichetti, G.; Falcone, G.; Filipelli, W.; Piucci, B. *Farmaco* **1998**, *53*, 602.
156. Sanfilippo, P. J.; Jetter, M. C.; Cordova, R.; Noe, R. A.; Choumouzis, E.; Lau, C. Y.; Wang, E. *J. Med. Chem*. **1995**, *38*, 1057.
157. Foster, R. H.; Leonard, N. J. *J. Org. Chem.* **1980**, *45*, 3072.
158. Schindler, R.; Hoefgen, N.; Heinecke, K.; Poppe, H.; Szelenyi, I. *Pharmazie* **2000**, *55*, 857.
159. Jakubowski, Z.; Angielski, S. *Pol. J. Pharmacol. Pharm.* **1980**, *32*, 37.
160. Shroff, J. R.; Bandurco, V.; Desai, R.; Kobrin, S.; Cervoni, P. *J. Med. Chem*. **1981**, *24*, 1521.
161. Ranise, A.; Bondavalli, F.; Schenone, P.; Lampa, E.; Greco, R.; Scafuro, M.; Marmo, E. *Farmaco* **1983**, *39*, 200.
162. Kees, K. L.; Fitzgerald, J. J. Jr.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. *J. Med. Chem*. **1996**, *39*, 3920.
163. Albright, J. D.; De los Santos, E. G.; Dusza, J. P.; Chan, P. S.; Coupet, J.; Ru, X.; Mazandarani, H. *Bioorg. Med. Chem.* **2000**, *10*, 695.
164. Bebernitz, G. R.; Argentieri, G.; Battle, B.; Brennan, C.; Balkan, B.; Burkey, B. F.; Eckhardt. M.; Gao, J. P.; Kapa, P.; Strohschein, R. J.; Schuster, H. F.; Wilson, M.; Xu, D. D. *J. Med. Chem.* **2001**, *44*, 2601.
165. Larsen, S. D.; Spilman, C. H.; Bell, F. P.; Dinh, D. M.; Martinborough, E.; Wilson, G. J. *J. Med. Chem.* **1991**, *34*, 1721.
166. Ashton, M. J.; Bridge, A. W.; Bush, R. C.; Dron, D. I.; Harris, N. V.; Jones, G. D.; Lythgoe, D. J.; Ridell, D.; Smith, C. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 375
167. Smith, C.; Ashton, M. J.; Bush, R. C.; Facchini, V.; Harris, N. V.; Hart, T. W.; Jordan, R.; MacKenzie, R.; Riddell, D. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 47.
168. Augelli-Szafran, C.; Roth, B. D.; Essenburg, A.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1095.
169. Wilde, R. G.; Klaczkiewicz, J. D.; Billheimer, J. T.; Wexler, R. R.; Gillies, P. J. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 177.
170. Tanaka, A.; Teresawa, T.; Hagihara, H.; Kinoshita, T.; Sakuma, Y.; Ishibe, N.; Sawada, M.; Takasugi, H.; Tanaka, H. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 81. Tanaka, A., Teresawa, T.; Hagihara, H.; Sakuma, Y.; Ishibe, N.; Sawada, M.; Takasugi, H.; Tanaka, H. *J. Med. Chem*. **1998**, *41*, 2390. Tanaka, A., Teresawa, T.; Hagihara, H.; Ishibe, N.; Sawada, M.; Sakuma, Y.; Hashimoto, M.; Takasugi, H.; Tanaka, H. *J. Med. Chem*. **1998**, *41*, 4408.
171. Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem*. **1990**, *33*, 31.
172. Sliskovic, D. R.; Blankley, C. J.; Krause, B. R.; Newton, R. S.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Sekerle, C.; Shaw, M. K.; Stanfield, R. L. *J. Med. Chem.* **1992**, *35*, 2095.
173. Henke, B. R.; Aquino, C. J.; Birkemo, L. S.; Croom, D. K.; Dougherty, R. W.; Ervin, G. N.; Grizzle, M. K.; Hirst, G. C.; James, M. K.; Johnson, M. F.; Queen, K. L.; Sherrill, R. G.; Sugg, E. E.; Suh, E. M.; Swewczyk, J. W.; Unwalla, R. J.; Yingling, J.; Willson, T. M. *J. Med. Chem*. **1997**, *40*, 2706.
174. Vaillancourt, V. A.; Larsen, S. D.; Tanis, S. P.; Burr, J. E.; Connell, M. A.; Cudahy, M. M.; Evans, B. R.; Fisher, P. V.; May, P. D.; Meglasson, M. D.; Robinson, D. D.; Stevens, F. C.; Tucker, J. A.; Vidmar, T. J.; Yu, J. H. *J. Med. Chem*. **2001**, *44*, 1231.
175. Czerwinski, E. W. *Acta Crystallogr., Sect. C* **1991**, *47*, 2598.
176. Spence, C. D.; Coghlan, J. P.; Denton, D. A.; Mills, E. H.; Whitworth, J. A.; Scoggins, B. A. *J. Steroid Biochem*. **1986**, *25*, 411.
177. Njar, V. C. O.; Kato, K.; Nnane, I. P.; Grigoryev, D. N.; Long, B. J.; Brodie, A. M. H. *J. Med. Chem*. **1998**, *41*, 902.
178. Willson, T. M.; Charifson, P. S.; Baxter, A. D.; Geddie, N. G. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1043.
179. Wilson, T. M.; Henke, B. R.; Momtahen, T. M.; Garrison, D. T.; Moore, L. B.; Geddie, N. G.; Baer, P. G. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1047.

180. Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934.
181. Stauffer, S. R.; Katzenellenbogen, J. A. *J. Comb. Chem*. **2000**, *2*, 318.
182. Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A. *Bioorg. Med. Chem*. **2001**, *9*, 141.
183. Stauffer, S. R.; Huang, Y. R.; Aron, Z. D.; Coletta, C. J.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 151.
184. Tyler-McMahon, B. M.; Boules, M.; Richelson, E. *Regul. Pept*. **2000**, *93*, 125.
185. Gully, D.; Labeeuw, B.; Biogegrain, R.; Oury-Donat, F.; Bachy, A.; Poncelet, M.; Steinberg, R.; Suaud-Chagny, M.-F.; Santucci, V.; Vita, N.; Pecceu, F.; Labbe-Jullie, C.; Kitabgi, P.; Soubrie, P.; Le Fur, G.; Maffrand, J.-P. *J. Pharmacol. Exp. Ther*. **1997**, *280*, 802.
186. Theorell, H.; Yonetani, T.; Sjöberg, B. *Acta Chem. Scand*. **1969**, *23*, 255.
187. Fries, R. W.; Bohlken, D. P.; Plapp, B. V. *J. Med. Chem*. **1979**, *22*, 356.
188. Horjales, E.; Eklund, H.; Braenden, C. I. *J. Mol. Biol*. **1987**, 197, 685.
189. Rozas, I.; Arteca, G. A.; Mezey, P. G. *Int. J. Quantum Chem., Quantum Biol. Symp*. **1991**, *18*, 269.
190. Echevarria, A.; Martin, M.; Pérez, C.; Rozas, I. *Arch. Pharm*. **1994**, *327*, 303.
191. Pereira, E. F. R.; Aracava, Y.; Aronstam, R. S.; Barreiro, E. J.; Albuquerque, E. X. *J. Pharmacol. Exp. Ther*. **1992**, *261*, 331.
192. Adjei, A. A. *Investig. New Drugs* **1999**, *17*, 43.
193. Horwitz, J. P.; Massova, I.; Wiese, T. E.; Wozniak, A. J.; Corbett, T. H.; Sebolt-Leopold, J. S.; Capps, D. B.; Leopold, W. R. *J. Med. Chem*. **1993**, *36*, 3511.
194. Katayama, H.; Kawada, H.; Kaneko, K.; Oshiyama, T.; Takatsu, N. *Chem. Pharm. Bull.* **1999**, *47*, 48.
195. Katayama, H.; Kiryu, Y.; Kaneko, K.; Ohshima, R. *Chem. Pharm. Bull.* **2000**, *48*, 1628.
196. Vega, S.; Diaz, J. A. *Pharmazie* **1992**, *47*, 765.
197. Cuadro, A. M.; Elguero, J.; Navarro, P. *Chem. Pharm. Bull.* **1985**, *33*, 2535.
198. Daidone, G.; Maggio, B.; Plescia, S.; Raffa, D.; Musiu, C.; Milia, C.; Perra, G.; Marongiu, M. E. *Eur. J. Med. Chem.* **1998**, *33*, 375.
199. Baraldi, P. G.; Leoni, A.; Cacciari, B.; Manfredini, S.; Simoni, D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2511.
200. Brzozowski, Z.; Saczewski, F.; Gdaniec, M. *Eur. J. Med. Chem.* **2000**, *35*, 1053.
201. Buchanan, J. G.; Edgar, A. R.; Hutchinson, R. J.; Strobie, A.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1980**, 237.
202. Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Simoni, D.; Marongiu, M. E.; Pani, A.; Tramontano, E.; La Colla, P. *J. Med. Chem.* **1992**, *35*, 917.
203. Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Simoni, D.; Vertuani, S.; Pani, A.; Pinna, E.; Scintu, F.; Lichino, D.; La Colla, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1279.
204. Vicentini, C. B.; Manfredini, S.; Manfrini, M.; Bazzanini, R.; Musiu, C.; Potzolu, M.; Perra, G.; Marongiu, M. E. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 269.
205. Popsavin, M.; Torovic, L.; Spaic, S.; Stankov, S.; Popsavin, V. *Tetrahedron Lett.* **2000**, *41*, 5737.
206. Manfredini, S.; Baraldi, P. G.; Bazzanini, R.; Durini, E.; Vertuani, S.; Pani, A.; Marceddu, T.; Demontis, F.; Vargiu, L.; La Colla, P. *Nucleos. Nucleot. Nucleic Acids* **2000**, *19*, 705.
207. El-Bendary, E. R.; Badria, F. A. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 99.
208. Zhan, Z.-Y. J; Dervan, P. B. *Bioorg. Med. Chem.* **2000**, *8*, 2467.
209. Nguyen, D. H.; Szewczyk, J. W.; Baird, E. E.; Dervan, P. B. *Bioorg. Med. Chem.* **2001**, *9*, 7.
210. Dupuy, M.; Pinguet, F.; Blache, Y.; Chavignon, O.; Teulade, J.-C.; Chapat, J.-P. *Chem. Pharm. Bull.* **1998**, *46*, 1820.
211. Naito, H.; Sugimori, M.; Mitsui, I.; Nakamura, Y.; Iwahana, M.; Ishii, M.; Hirotani, K.; Kamazawa, E.; Ejima, A. *Chem. Pharm. Bull.* **1999**, *47*, 1679.
212. Nugiel, D. A.; Etzkorn, A.-M.; Vidwans, A.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Cox, S.; Czerniak, P. M.; Doleniak, D.; Seitz, S. P. *J. Med. Chem.* **2001**, *44*, 1334.
213. Traxler, P.; Bold, G.; Frei, J.; Lang, M.; Lydon, N.; Mett, H.; Buchdunger, E.; Meyer, T.; Mueller, M.; Furet, P. *J. Med. Chem.* **1997**, *40*, 3601.

214. Palmer, B. D.; Trumpp-Kallmeyer, S.; Fry, D. W.; Nelson, J. M.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 1519.
215. Cristalli, G.; Eleuteri, A.; Volpini, R.; Vittori, S.; Camaioni, E.; Lupidi, G. *J. Med. Chem.* **1994**, *37*, 201.
216. Kikuchi, K.; Hibi, S.; Yoshimura, H.; Tai, K.; Hida, T.; Tokuhara, N.; Yamauchi, T.; Nagai, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 619.
217. Moriya, M.; Harada, T.; Shirasu, Y. *Cancer Lett.* **1982**, *17*, 147.
218. Evarts, R. P.; Raab, M. M.; Haliday, E.; Brown, C. *Cancer Res.* **1983**, *43*, 496.
219. Moyer, M. P.; Weber, F. H.; Gross, J. L. *J. Med. Chem*. **1992**, *35*, 4595.
220. Moyer, M. P.; Weber, F. H.; Canning, P. C.; Gross, J. L.; Saint Fort, R. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1663.
221. Papageorgiou, C.; Albert, R.; Floersheim, P.; Lemaire, M.; Bitch, F.; Weber, H.-P.; Andersen, E.; Hungerford, V.; Schreier, M. H. *J. Med. Chem*. **1998**, *41*, 3530.
222. De Luca, G. V.; Kim, U. T.; Liang, J.; Cordova, B.; Klabe, R. M.; Garber, S.; Bacheler, L. T.; Lam, G. N.; Wright, M. R.; Logue, K. A.; Erickson-Viitanen, S.; Ko, S. S.; Trainor, G. L. *J. Med. Chem.* **1998**, *41*, 2411.
223. Han, Q.; Chang, C.-H.; Li, R.; Ru, Y.; Jadhav, P. K.; Lam, P. Y. S. *J. Med. Chem.* **1998**, *41*, 2019.
224. Rodgers, J. D.; Lam, P. Y. S.; Johnson, B. L.; Wang, H.; Ko, S. S.; Seitz, S. P.; Trainor, G. L.; Anderson, P. S.; Klabe, R. M.; Bacheler, L. T.; Cordova, B.; Garber, S.; Reid, C.; Wright, M. R.; Chang, C.-H.; Erickson-Viitanen, S. *Chem. Biol.* **1998**, *5*, 597.
225. Patel, M.; Rodgers, J. D.; McHugh Jr. R. J.; Johnson, B. L.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Ko, S. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3217.
226. Baraldi, P. G.; Simoni, D.; Periotto, V.; Manfredini, S.; Guarneri, M.; Manservigi, R.; Cassai, E.; Bertolasi, V. *J. Med. Chem.* **1984**, *27*, 986.
227. Pancic, F.; Steinberg, B. A.; Diana, G. D.; Carabateas, P. M.; Gorman, W. G.; Came, P. E. *Antimicrob. Agents Chemother.* **1981**, *19*, 470.
228. Saladino, R.; Stasi, L.; Nicoletti, R.; Crestini, C.; Botta, M. *Eur. J. Org. Chem.* **1999**, 2751.
229. Zhao, W. G.; Yuan, P. W.; Wang, W. Y. *Chin. J. Chem.* **2001**, *19*, 184.
230 Crenshaw, R. R.; Luke, G. M.; Siminoff, P. *J. Med. Chem.* **1976**, *19*, 262.
231. Gonzalez, M. E.; Alarcon, B.; Cabildo, P.; Claramunt, R. M.; Sanz, D.; Elguero, J. *Eur. J. Med. Chem. – Chim. Ther.* **1985**, *20*, 359.
232. Smirnov, V. V.; Kiprianova, E. A.; Garagulya, A. D.; Esipov, S. E.; Dovjenko, S. A. *FEMS Microbiol. Lett*., **1997**, *153*, 357.
233. Fidalgo, M. L.; Arias, M. S.; Soliveri, J.; Arias, M. E. *J. Antibiotics* **1992**, *45*, 1759.
234. Ohki, H.; Kawabata, K.; Okuda, S.; Kmimura, T.; Sakane, K. *J. Antibiotics* **1995**, *48*, 1049.
235. Nagao, Y.; Tamai, S.; Tanigawa, N.; Sano, S.; Kumagai, T.; Kishi, I. *Heterocycles* **1998**, *48*, 617.
236. Jungheim, L. N.; Sigmund, S. K.; Fisher, J. W. *Tetrahedron Lett.* **1987**, *28*, 285.
237. Jungheim, L. N.; Sigmund, S. K.; Jones, N. D.; Swartzendruber, J. K. *Tetrahedron Lett.* **1987**, *28*, 289.
238. Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007.
239. Jungheim, L. N.; Barnett, C. J.; Gray, J. E.; Horcher, L. H.; Shepherd, T. A.; Sigmund, S. K. *Tetrahedron* **1988**, *44*, 3119.
240. Forrest, A. K.; O'Hanlon, P. J.; Walker, G. *J. Chem. Soc., Perkin Trans 1* **1994**, 2657.
241. Ramalingam, K.; Wong, L. F.; Berlin, K. D.; Brown, R. A.; Fischer, R.; Blunk, J.; Durham, N. N. *J. Med. Chem.* **1977**, *20*, 664.
242. Migliara, O.; Daidone, G.; Plescia, S.; Schillaci D. *Pharmazie* **1998**, *53*, 346.
243. Elgaby, M. S. A.; Atalla, A. A.; Gaber, A. M.; Abdalwahab K. A. *Farmaco* **2000**, *55*, 596.
244. Ghorab, M. M. *Phosphorous Sulfur & Silicon* **2000**, *165*, 221.
245. Dong, P. Le H.; Coquelet, C.; Bastide, J.-M.; Lebecq, J.-C. *Eur. J. Med. – Chim. Ther.* **1981**, *15*, 119.
246. Dong, P. Le H.; Coquelet, C.; Bastide, J.-M.; Lebecq, J.-C. *Eur. J. Med. – Chim. Ther.* **1981**, *16*, 39.
247. Gotor, V.; Quirós, M.; Liz, R.; Frigola, J.; Fernández, R. *Tetrahedron*, **1997**, *53*, 6421.
248. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.

249. Copeland, R. A.; Marcinkeviciene, J.; Haque, T. S.; Kopcho, L. M.; Jiang, W.; Wang, K.; Ecret, L. D.; Sizemore, C.; Amsler, K. A.; Foster, L.; Tadesse, S.; Combs, A. P.; Stern, A. M.; Trainor, G. L.; Slee, A.; Rogers, M. J.; Hobbs, F. *J. Biol. Chem.* **2000**, *275*, 33373.
250. Boehm, H.-J.; Boehringer, M.; Bur, D.; Gmuender, H.; Huber, H.; Klaus, W.; Kostrewa, D.; Kuehne, H.; Luebbers, T.; Meunier-Keller, N.; Mueller, F. *J. Med. Chem.* **2000**, *43*, 2664.
251. Domínguez, J. N.; Basante, W.; Charris, J. E.; Riggione, F. *Farmaco* **1996**, *51*, 407.
252. Domínguez, J. N.; Charris, J. E.; Basante, W.; Méndez, B. *Magn. Reson. Chem.* **1998**, *36*, 454.
253. Charris, J. E.; Domínguez, J. N.; Lobo, G.; Cordero, M. I.; López, S. E.; Méndez, B.; Pekerar, S.; Riggione, F. *Magn. Reson. Chem.* **2000**, *38*, 1039.
254. Mester, B.; Elguero, J.; Claramunt, R. M.; Castanys, S.; Mascaró, M. L.; Osuna, A.; Vilaplana, M. J.; Molina, P. *Arch. Pharm. (Weinheim)* **1987**, *320*, 115.
255. Mester, B.; Claramunt, R. M.; Elguero, J.; Atienza, J.; Barrio, A. G.; Escario, J. A. *Chem. Pharm. Bull*. **1991**, *39*, 1990.
256. El-Kashef, H. S.; El-Emary, T. I.; Gasquet, M.; Timon-David, P.; Maldonado, J.; Vanelle, P. *Parmazie* **2000**, *55*, 572.
257. Kingsbury, W. D.; Gyurik, R. J.; Theodorides, V. J.; Parish, R. C.; Gallagher Jr, G. *J. Med. Chem.* **1976**, *19*, 839.
258. Zirngibl, L. *Antifungal Azoles*, Wiley-VCH, Weinheim (1998).
259. Aiello, E.; Aiello, S.; Mingoia, F.; Bacchi, A.; Pelizzi, G.; Musiu, C.; Setzu, M. G.; Pani, A.; La Colla, P.; Marongiu, M. E. *Bioorg. Med. Chem.* **2000**, *8*, 2719.
260. Ballesteros, P.; Claramunt, R. M.; López, C.; Elguero, J.; Gómez-Alarcón, G. *Chem. Pharm. Bull*. **1988**, *36*, 2036.
261. Menozzi, G.; Mosti, L.; Bruno, O.; Lo Presti, E.; Musiu, C.; Longu, S.; La Colla, P.; Filippelli, W.; Falcone, G.; Piucci, B. *Farmaco* **1999**, *54*, 416.
262. Huppatz, J. L. *Aust. J. Chem*. **1985**, *38*, 221.
263. Daidone, G.; Plescia, S.; Raffa, D.; Bajardi, M. L.; Milici, M. *Farmaco* **1985**, *40*, 683.
264. Garuti, L.; Roberti, M.; Rossi, M.; Giovanninetti, G. *Farmaco* **1995**, *50*, 815.
265. Vicentini, C. B.; Brandolini, V.; Guarneri, M.; Giori, P. *Farmaco* **1992**, *47*, 1021.
266. Hansch. C.; Leo, A. *Exploring QSAR*, ACS: Washington, DC, 1995, Vol. 1.
267. Cramer, R. D.; Patterson, D. E.; Bruce, J. D. *J. Am. Chem. Soc*. **1988**, *110*, 5959.
268. Chiba, P.; Holzer, W.; Landau, M.; Bechmann, G.; Lorenz, K.; Plagens, B.; Hitzler, M.; Richter, E.; Ecker, G. *J. Med. Chem*. **1998**, *41*, 4001.

PYRAZOLES AS DRUGS: FACTS AND FANTASIES

RECENT ADVANCES IN THE SYNTHESIS OF SATURATED NITROGEN HETEROCYCLES USING *N*-ACYLIMINIUM ION INTERMEDIATES

Marino Petrini

Dipartimento di Scienze Chimiche,Università di Camerino, via S.Agostino 1, I-62032 Camerino, Italy

(e-mail: marino.petrini@unicam.it)

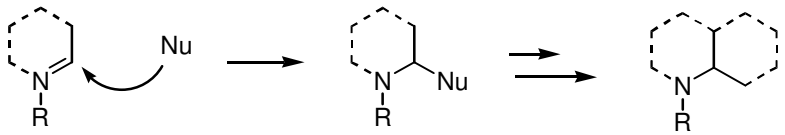
Abstract. *The reaction of N-acyliminium ions with carbon nucleophiles represents a powerful synthetic tool for the preparation of several nitrogen derivatives. This review reports some recent developments in the synthesis of saturated nitrogen heterocycles using N-acyliminium ions as reactive electrophilic intermediates.*

Contents

1. Introduction

Saturated nitrogen heterocycles are of paramount importance among the whole body of structurally defined substances endowed of biological and industrial interest.[1] It is really difficult to browse whatever organic chemistry journal without to meet at least one article dealing with the synthesis and/or synthetic application of these heterocyclic derivatives. Beside simple ring systems containing few functional groups, many complex polycyclic structures are unceasingly discovered and this obviously represents a formidable challenge for every synthetic organic chemist. Furthermore, an increasing number of these compunds are needed in enantiopure form thus requiring the accomplishment of enantioselective processes.[2,3] In this context, the availability of nitrogen containing chiral pools greatly facilitate the synthetic approach to these

heterocyclic systems.[4-6] The addition of nucleophilc reagents to carbon-nitrogen double bonds is a common practice toward the synthesis of amino derivatives (Scheme 1).[7-9]



Scheme 1

Imines are usually poor electrophilic substrates for this purpose and therefore, strong nucleophilic reagents are required to carry out an efficient addition reaction. These carbanionic reagents in the presence of enolizable imines, frequently give deprotonation rather than addition products. Alternatively, the electrophilic character of the imino derivative can be suitably tuned by the appropriate choice of the nitrogen substituent. Nitrones are readily available starting materials for this purpose; they react with nucleophiles but can also be used as 1,3-dipoles in cycloaddition reactions.[10-12] An enhanced reactivity toward nucleophiles is displayed by *N*-acylimines.[13,14] These substrates can be prepared directly from aromatic or non-enolizable aldehydes, but must be generated *in situ* from a suitable precursor when tautomerization to the more stable enamide is possible.[15-18] A remarkable increase in the electrophilc character of carbon-nitrogen unsaturated substrates can be obtained moving to iminium ions that are able to react even with weak nucleophiles. The classical Mannich reaction, also referred as the aminoalkylation process of enols and enolates, is one of the most important carbon-carbon bond-forming reactions in organic synthesis.[19,20] The vinylogous version of this process represents an important method for the preparation of several nitrogen heterocycles, including alkaloids, and has been recently reviewed.[21,22] Among these electrophilic substrates *N*-acyliminium ions have deserved a special interest because of their availability and superior reactivity in comparison with *N*-alkyliminium ions toward nucleophilic systems.[23-26]

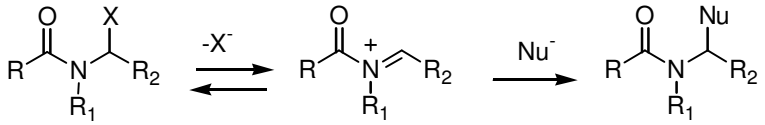
This review reports some recent applications of these reactive intermediates towards the synthesis of saturated nitrogen heterocycles appeared in the literature during the period January 2000-August 2002. Emphasis is given to innovative synthetic approaches using *N*-acyliminium ion intermediates as well as significative extensions of previously known methods. The term "saturated" concerning the heterocycles examined in this review refers to the core structure of the molecule containing the nitrogen atom. Therefore, polycylic structures containing unsaturations and aromatics in remote parts of the molecule are included.

2. *N*-Acyliminium ions

2.1. General aspects

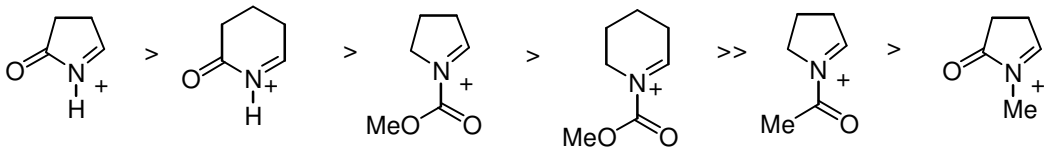
N-Acyliminium ions are also referred as α-amidoalkylating cations and can be prepared according to Scheme 2.

The equilibrium in which the *N*-acyliminium ion is involved is usually favored by acidic catalysts; the subsequent reaction with the nucleophile is an irreversible process and leads to the addition product. The nature of the acyl group greatly affects the ease of formation of the corresponding iminium ion. Recent studies of Eberlin and coworkers on the gas-phase electrophilic reactivity of cyclic *N*-acyliminium ions with allyltrimethylsilane has allowed to establish the following order of intrinsic reactivity (Scheme 3).[27,28]



1 **2** **3**

Scheme 2



4 **5** **6** **7** **8** **9**

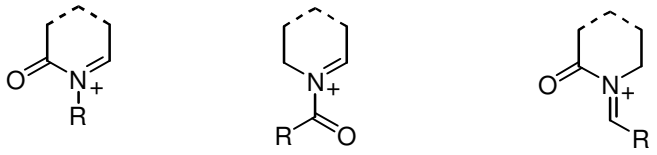
Scheme 3

It is worth noting that five-membered endocyclic iminium ions **4**,**6** are more reactive than their six-membered homologues **5**,**7**, furthermore *N*-alkyl substitution (**9**) lowers the electrophilicity of the iminium group making it less reactive than protonated ions **4** and **5**. Another interesting observation concerns the higher reactivity displayed by exocyclic *N*-acyl groups (**6**,**7**,**8**) compared with endocyclic system **9**. This behavior could be ascribed to a better resonance effect involving the nitrogen lone pair in exocyclic derivatives. Finally, carbamate derivatives **6**,**7**, are more reactive than amide **8**, probably because a carbamate nitrogen lone pair is more effective in cation stabilization than an amide nitrogen.

A judicious choice of the leaving group X is also essential for the success of the procedure. In principle every group that can be easily removed through an elimination process is suitable for this purpose but, for practical reasons, only a limited number of them are used in synthesis.

2.2. Precursors of cyclic *N*-acyliminium ions

Different kind of cyclic *N*-acyliminium ions used for synthetic purposes are portrayed in Scheme 4.

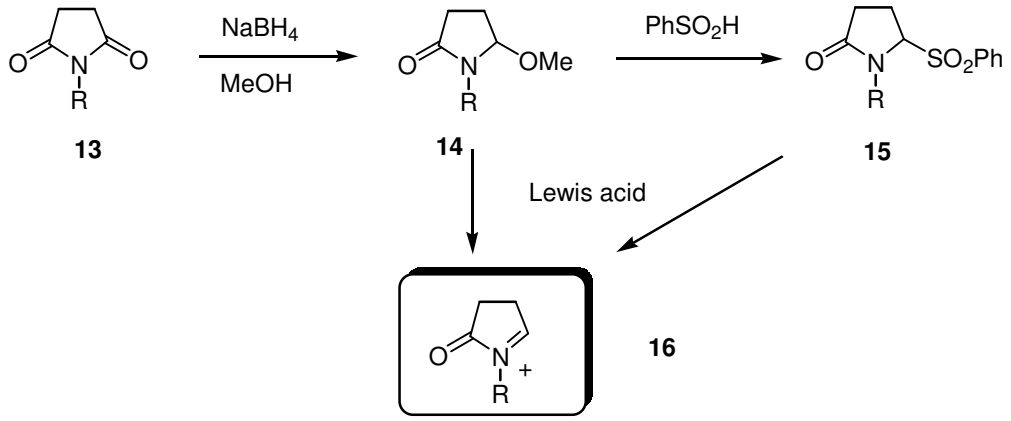


10 **11** **12**

Scheme 4

Iminium derivatives **10** and **11** can be readily obtained by elimination from the corresponding α-hydroxy- or α-alkoxyamides/carbamates **14** that in turn can be prepared by selective reduction of cyclic imides **13** or lactams.[20] Sometime, these α-oxygenated derivatives are more profitably converted into other α-substituted systems, as phenylsulfonyl derivative **15**, in order to obtain different substrates that can be easily purified or are more reactive than their precursors (Scheme 5).[29,30]

For ordinary ring systems (five or six) $NaBH_4$ is the reagent of choice, however, only DIBALH is able to reduce a wide range of medium and large ring lactams without any ring opening to the corresponding amino aldehydes.[31]



Scheme 5

Exocyclic iminium ions **12** are much less exploited mainly because their precursors are difficult to prepare using direct methods.[32,33]

2.3. Acidic catalysts and nucleophiles

Lewis acids are commonly used as catalysts to obtain *N*-acyliminium ions from their precursors. A proper choice of the acid used is mandatory for the success of the synthetic protocol, since different activators can often lead to different results both in terms of efficiency and stereocontrol of the process. Of general use are Lewis acids as $TiCl_4$, $SnCl_4$, BF_3 Et_2O and TMSOTf that is expecially useful with α-hydroxylated precursors. A wide range of nucleophiles are compatible with the use of these activators namely allylsilanes, enol ethers, (hetero)aromatics and even some organometallic reagents as organocuprates. For obvious reasons protic acids as TFA or formic acid find only a narrow application as promoters and their utilization is practically restricted to intramolecular processes in which simple alkenes or aromatic groups are involved as nucleophiles.[23]

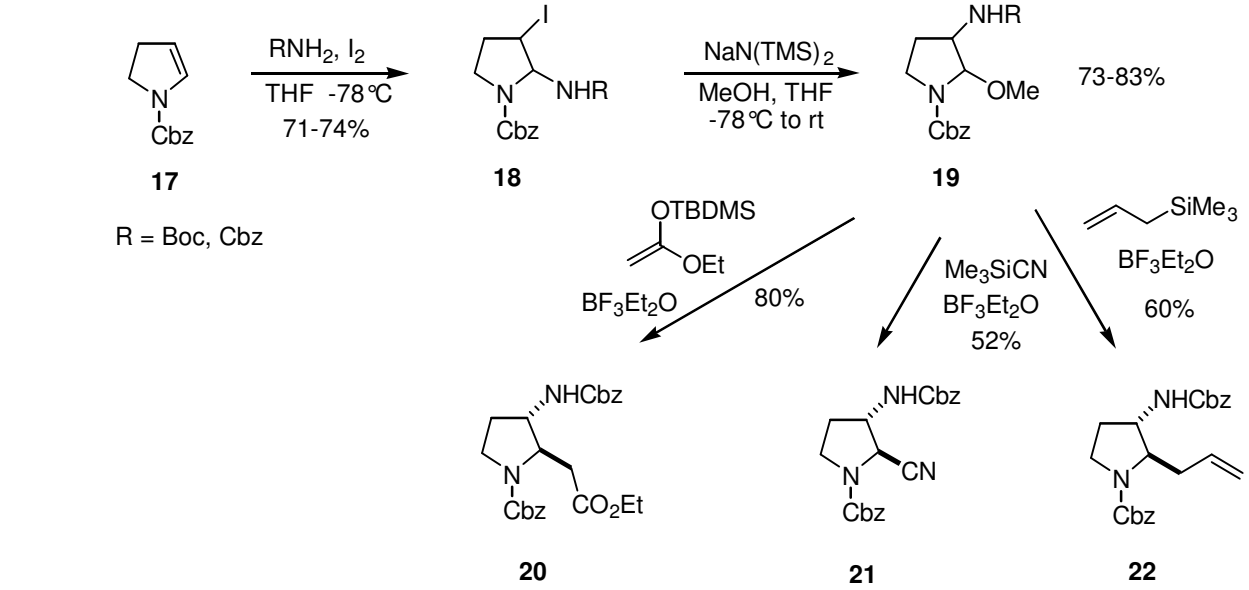
3. Synthesis of saturated nitrogen heterocycles

3.1. Pyrrolidines

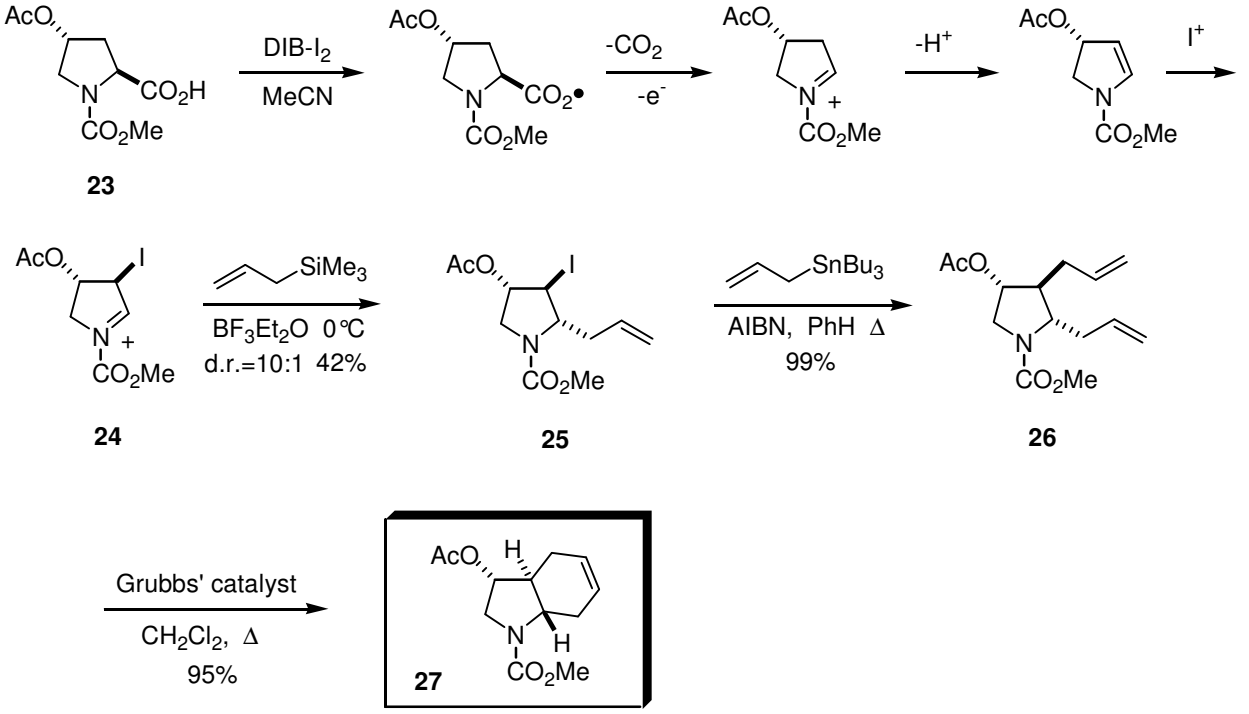
The synthesis of substituted pyrrolidines can be accomplished by a suitable ring closure starting from open chain frameworks or by functionalization of commercially available pyrrolidinones, pyrrolines and other derivatives.[34] Cyclic enecarbamates **17** can be functionalized at the double bond to afford 2-amido-3-iodo pyrrolidines **18**. Aziridination-methanolysis of the obtained adducts leads to the corresponding 2-methoxy-3-amido pyrrrolidines **19** that *via* *N*-acyliminium ion intermediates are transformed into 2,3-disubstituted pyrrolidines **20-22** with a preference for *trans* diastereomer (Scheme 6).[35] The *trans* diastereo-selectivity can be substantially increased in the formation of ester derivatives **20** using titanium enolates of thiopyridyl esters as nucleophiles.[36]

α-Amino acid carbamates **23** react with (diacethoxyiodo)benzene (DIB) and iodine under irradiation with visible light giving a carboxyl radical that by loss of CO_2 and further oxidation gives the corresponding *N*-acyliminium ion **24** (Scheme 7).[37,38]

Iminium ion can be trapped with allyltrimethylsilane producing the allylated derivative **25** with high diastereoselectivity (10:1). Further radical allylation using allyltributiltin gives diallyl derivative **26** that by ring closing metathesis is transformed into the hexahydroindole **27**. This procedure can be also extended to other carbon nucleophiles as silyl enol ethers and trimethylsilyloxyfuran.[39,40]



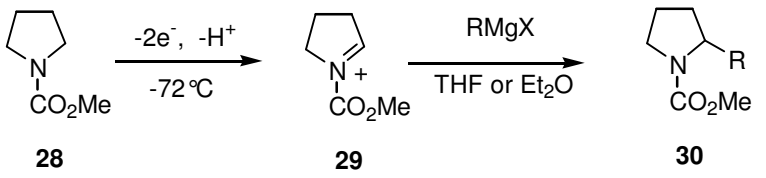
Scheme 6



Scheme 7

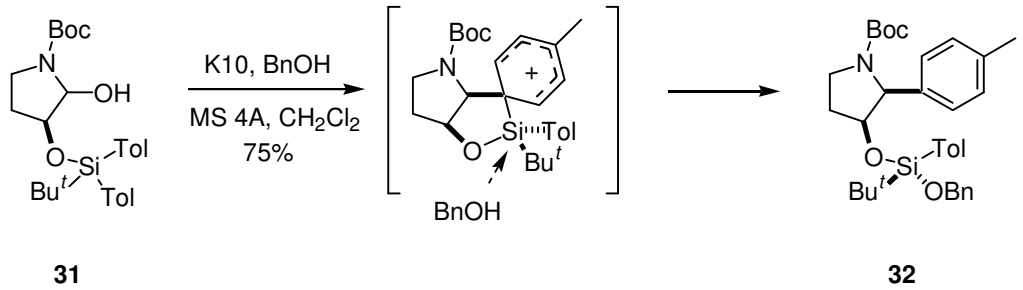
Conventional electrochemical oxidation of *N*-protected pyrrolidines usually affords the corresponding α-alkoxy derivatives that can be isolated and converted into *N*-acyliminium ions by Lewis acid catalysts.[41] This two-step method can be avoided exploiting a low temperature electrolysis of carbamate **28** that directly affords the *N*-acyliminium ion **29**.[42] By this way there is no need to use an acidic catalysis to generate the iminium ion and thus several organometallic reagents can be used as nucleophiles in this process (Scheme 8).

A silicon to carbon migration of aromatic rings is observed on optically active cyclic hemiaminals **31**. Formation of the *N*-acyliminium ion is induced by a clay (montmorillonite K10) and release of the aromatic group is highly *syn* diastereoselective (Scheme 9).[43]

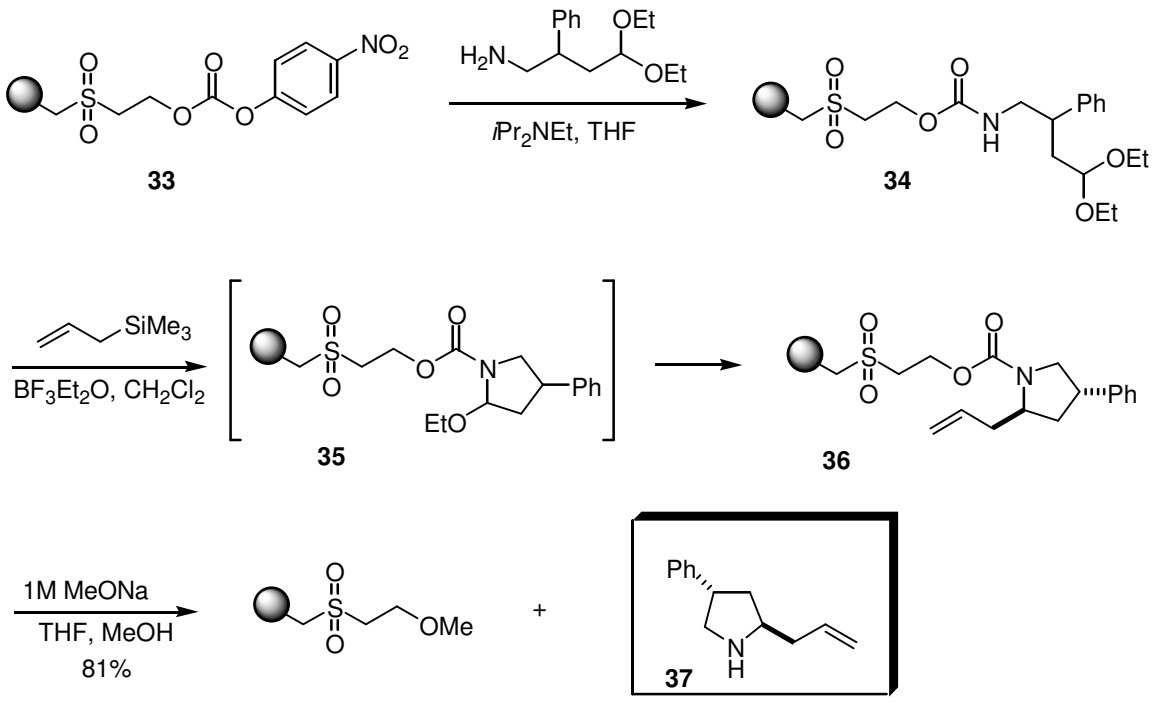


R	Et	*i*Pr			Ph—	F—
yield %	65	57	45	68	58	66

Scheme 8



Scheme 9

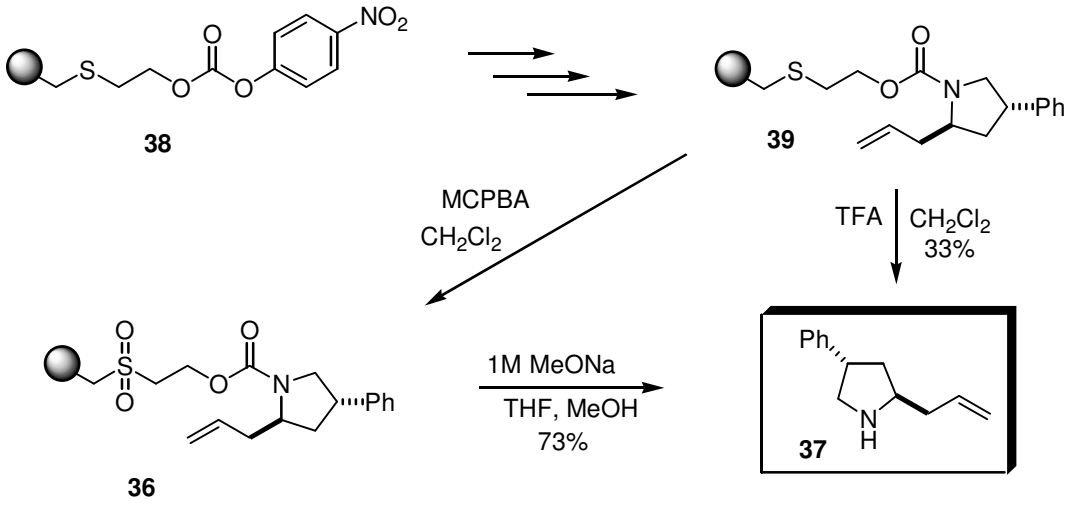


Scheme 10

The main problem associated with the application of solid phase synthesis to the chemistry of *N*-acyliminium ions concerns the stability of the linker under cationic reaction conditions and its efficient cleavage after the process has been completed. Hiemstra and coworkers have developed two interesting systems for this purpose, namely the 2-sulfonylethyl (SEC) and 2-thioethyl (TEC) carbamate linkers.[44] A general strategy for the synthesis of 2,5-disubstituted pyrrolidines is portrayed in Scheme 10: carbonate **33** is

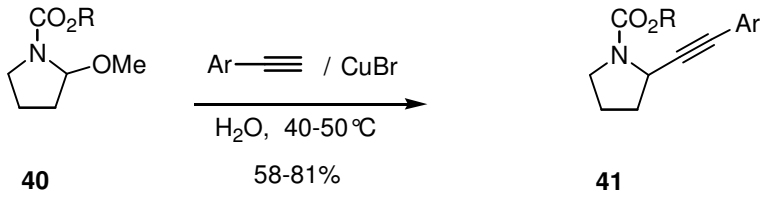
condensed with a suitable amine giving the corresponding carbamate **34**. This acetal is treated with allyltrimethylsilane in the presence of BF_3 Et_2O giving the allylated product **36** in a tandem process involving α-ethoxypyrrolidine **35** as intermediate. Cleavage of the linker is realized under basic conditions using MeONa to afford *trans*-**37** as main product.

The utilization of TEC as linker follows a similar synthetic pathway, but cleavage of the produced carbamate can be obtained directly under strong acidic conditions or oxidizing the sulfide moiety to a sufonyl group and then using MeONa (Scheme 11).



Scheme 11

Generation and reaction of *N*-acyliminium ions are generally realized in anhydrous conditions, expecially when strong Lewis acid are used as catalysts. Copper(I) bromide is able to promote the formation of *N*-acyliminium ion from α-methoxypyrrolidine **40** and to effect a coupling reaction with arylacetylene derivatives in water to afford the corresponding 2-propargyl pyrrolidines **41** (Scheme 12).[45]

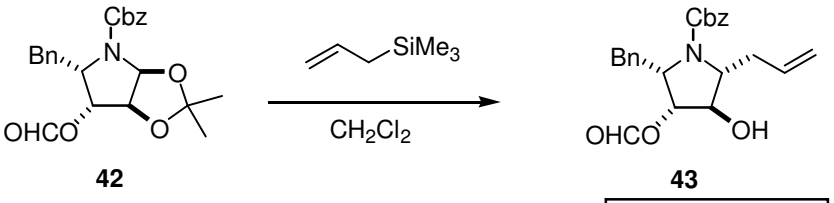


40 **41**

Scheme 12

Allylation of substituted α-alkoxy pyrrolidines usually occurs with moderate levels of diastereoselection. However, 2,3-*O*-isopropylidenepyrrolidine **42** reacts with allyltrimethylsilane in the presence of BF_3 Et_2O with exclusive formation of the 2,3-*trans* diastereomer **43** (Scheme 13).[46]

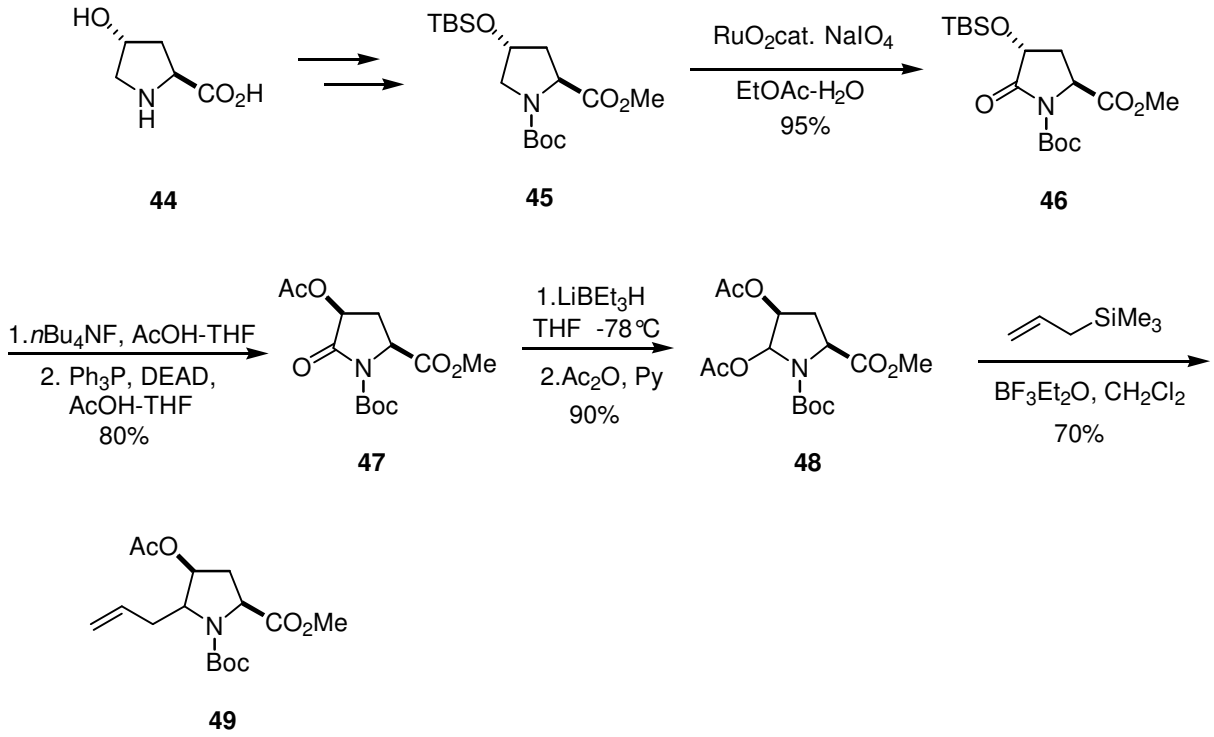
The attack of the silane always occurs from the *exo* face of the bicyclic molecule and the stereochemical outcome is not affected by the relative position of other substituents. This probably means that no iminium ions are involved as reactive intermediates in this process. A consistent decrease in stereoselectivity is observed using a combination of BF_3 Et_2O and TMSOTf thus indicating that in these conditions the formation of *N*-acyliminium ions is more probable.



42 **43**

	α:β	yield
$BF_3•Et_2O$	100:0	62%
$BF_3•Et_2O$/TMSOTf	70:30	92%

Scheme 13



44 **45** **46** **47** **48** **49**

Scheme 14

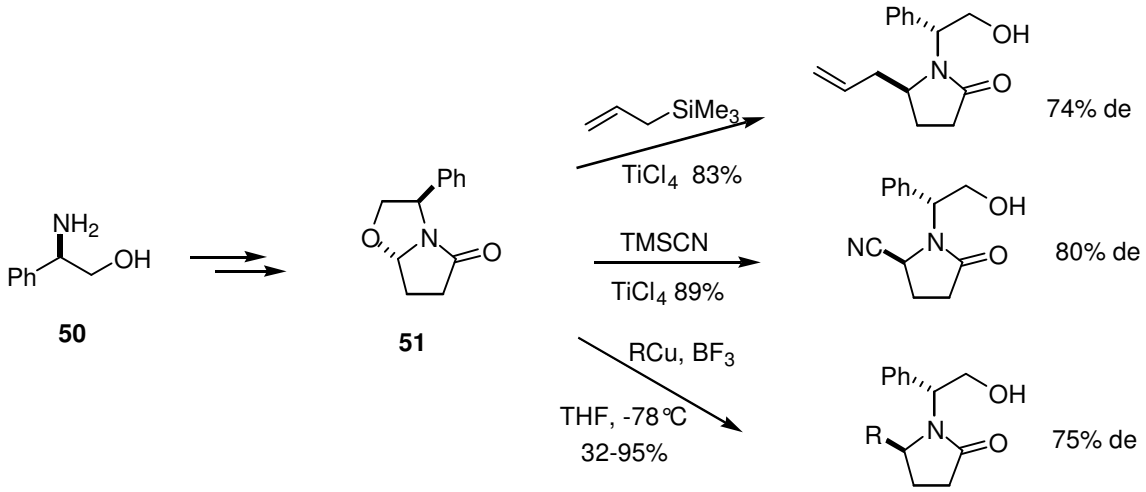
Functionalized 4-hydroxypyroglutamates are important building blocks for the synthesis of many interesting biologically active heterocycles.[47] (4*R*)-Hydroxyproline **44** is a cheap, commercially available compound that represents an ideal starting material for many syntheses leading to pyroglutamate derivatives. Fully protected proline **45** can be oxidized by $RuO_2/NaIO_4$ in nearly quantitative yield to the corresponding pyrrolidinone **46**. After Mitsunobu inversion in C-3, acetoxy derivative **47** is selectively reduced using $LiBEt_3H$ and then allylated or cyanated using the corresponding silyl reagents to compound **49** (Scheme 14).[48]

3.2. Pyrrolidinones

These heterocyclic systems are strictly related to pyrrolidines since the easy reduction of the carbonyl group represents an alternative method for their preparation. However, the importance of these lactam derivatives is not restricted to this synthetic opportunity since ring cleavage of pyrrolidinones provides a rapid and efficient entry to open chain derivatives. Functionalization of pyrrolidinones takes advantage from

their rigid structure that may allows the introduction of several functional groups in a stereoselective fashion.

Chiral pyrrolidinone **51** first introduced by Meyers *et al.*[49] can be prepared starting from (*R*)-(-)-phenylglycinol **50**[50] and used as precursor for *N*-acyliminium ions (Scheme 15).[51]

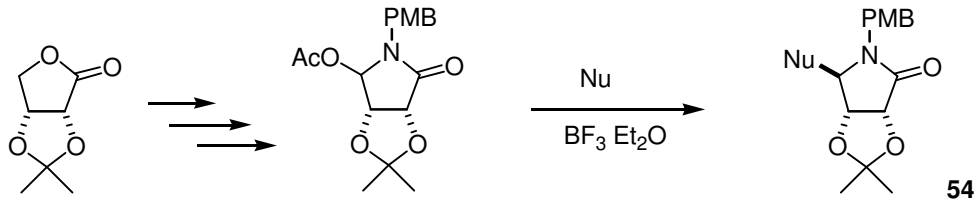


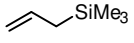
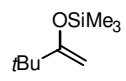
Scheme 15

$TiCl_4$ is used as promoter for allylations and cyanations while BF_3 Et_2O is recommended for addition of low order cuprates. The diastereomeric excess never exceeds 80%.

Among the usual Lewis acid activators $InCl_3$ represents a new option to convert α-alkoxylactams into *N*-acyliminium ions.[52] Only 0.6 equivalents of this acid are needed to promote the reaction.

A stereocontrolled addition of different nucleophiles to lactam **53** prepared from chiral lactone **52** has been studied by Smith III en route to the total synthesis of phosphatase inhibitors Calyculin A and B. Outstanding diastereoselection is observed using allyltrimethylsilane as well as silyl enol ethers, while TMSCN gives only modest results (Scheme 16).[53]

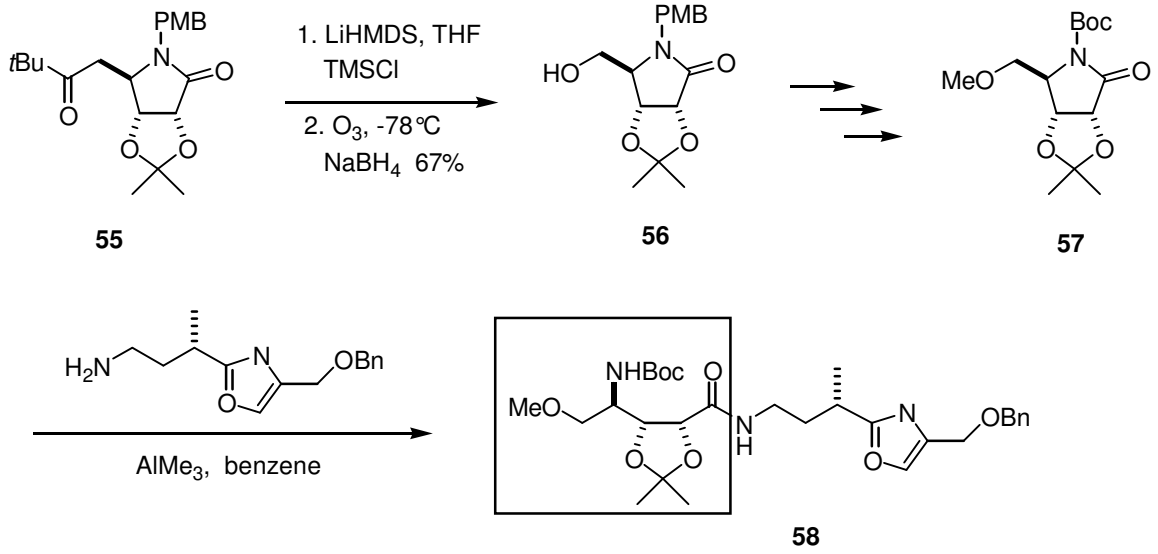


reagent	α:β	yield
	0:100	86%
TMSCN	15:85	91%
	0:100	81%

Scheme 16

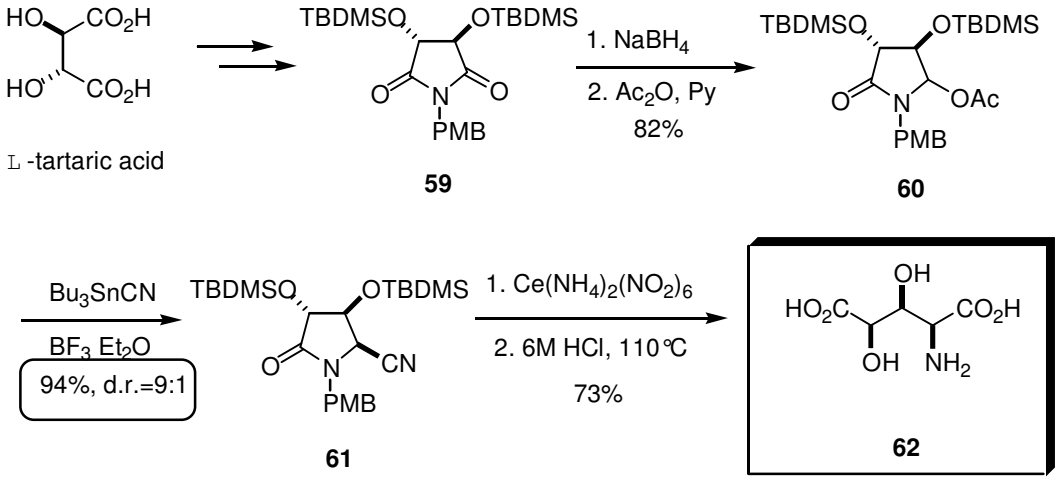
The addition product **55** obtained by reaction of **53** with enol ether of *t*-butylmethyl ketone is converted to alcohol **56** by ozonolysis of the corresponding silyl enol ether followed by reduction. A suitable

manipulation of the protecting groups leads to the synthesis of pyrrolidinone **57** that is cleaved to compound **58** a key intermediate to the synthesis of Calyculin A (Scheme 17).



Scheme 17

Hydroxylated glutamic acids are potent ligands for glutamate receptors as NMDA, AMPA and KA. These open-chain derivatives can be conveniently prepared starting form L-tartaric acid that is converted into *N*-protected imide **59** and then to α-acetoxypyrrolidinone **60** by a selective reduction-acetylation procedure (Scheme 18).[54] Pyrrolidinone **60** upon reaction with Bu_3SnCN gives the corresponding cyano derivative **61** with satisfactory 4,5-*cis*-diastereoselectivity. Utilization of acetoxy derivative **60** is mandatory for the success of this procedure since neither hydroxylactam itself nor the corresponding methoxylactam are active toward the subsequent cyanation reaction. Cleavage of PMB-protecting group and acid hydrolysis of the cyano group completes the synthesis of 3,4-dihydroxyglutamic acid **62**.



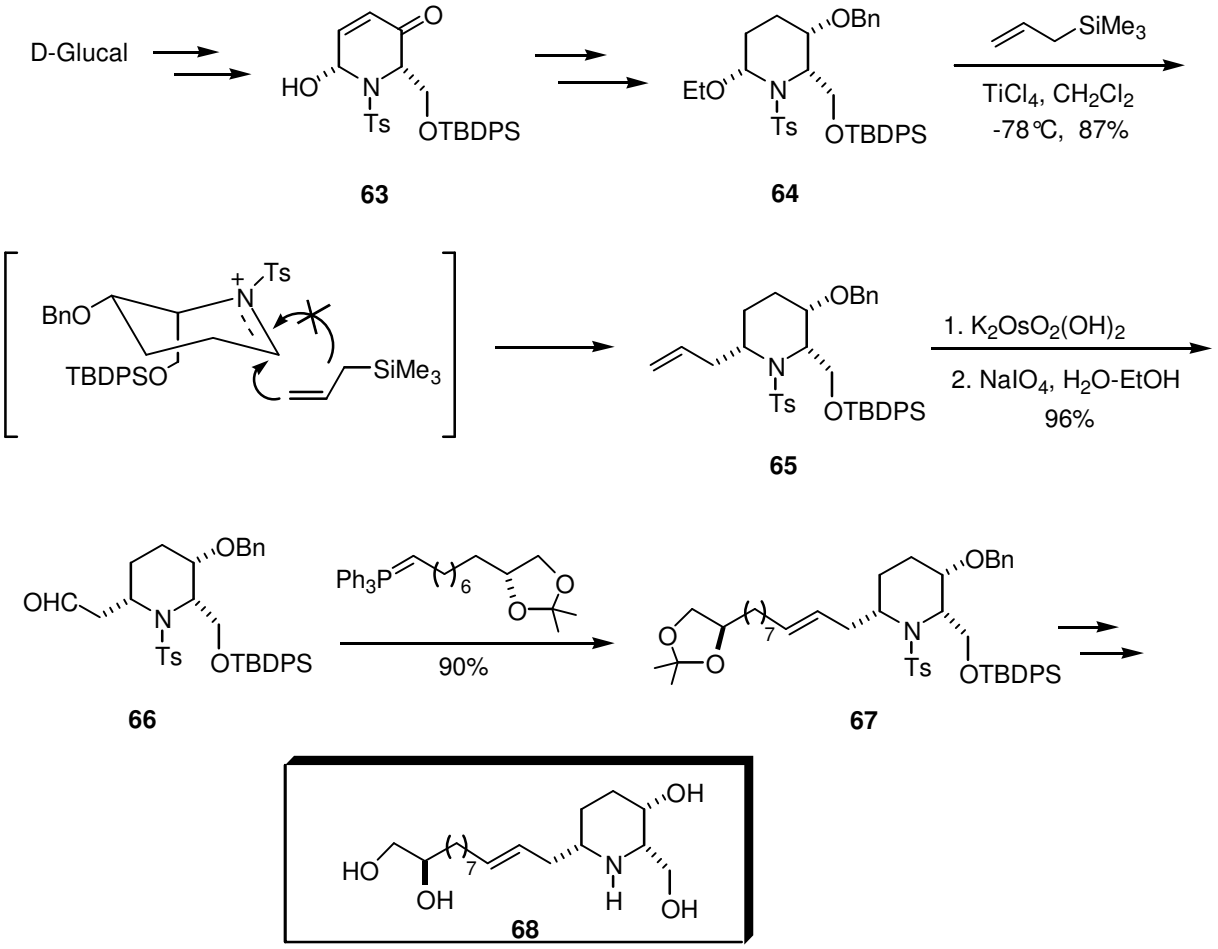
Scheme 18

Other nucleophiles as electron rich aromatics and propargylsilanes add to cyclic *N*-acyliminium ions and this constitute a synthetic route to enantiopure amidines,[55] tetrahydroisoquinolines[56] and other heterocycles.[57]

3.3. Piperidines

The importance and synthetic applications of functionalized piperidines parallels that of their five membered homologs and several method for their stereoselective synthesis have been recently reviewed.[58]

Leptophylline A is a bioactive extract of the Brazilian legume *Cassia leptophylla* and with other compounds of similar structure represents the first example of an alkaloid lipid that shows interesting anticancer activity. A structurally related analogue of this alkaloid can be prepared starting from commercially available D-glucal that is transformed into trisubstituted piperidine **64** (Scheme 19).[59] This α-ethoxy derivative is converted into *N*-tosyliminium ion using $TiCl_4$ and is allylated stereoselectively from the less hindered α side to give **65** as the only diastereomer. Oxidative cleavage of the double bond affords the corresponding aldehyde **66** that undergoes a Wittig reaction leading to chain elongated derivative **67**. Removal of all protecting groups in **67** completes the synthesis of alkaloid **68** in 15% overall yield from D-glucal.

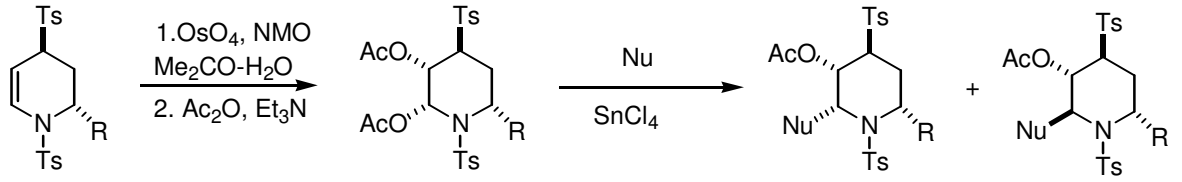


Scheme 19

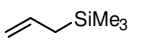
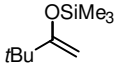
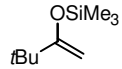
Functionalization of six-membered ring enecarbamates represents a proper method to prepare suitable precursors of *N*-acyliminium ions. Dihydroxylation of chiral 1,4-ditosyltetrahydropyridines **69** realized using OsO_4 produces, after acetylation, α-acetoxy piperidines **70**.

A range of various nucleophiles was tested in order to evaluate the effect of different groups present in the structure on the stereochemical outcome of the addition product (Scheme 20).[60]

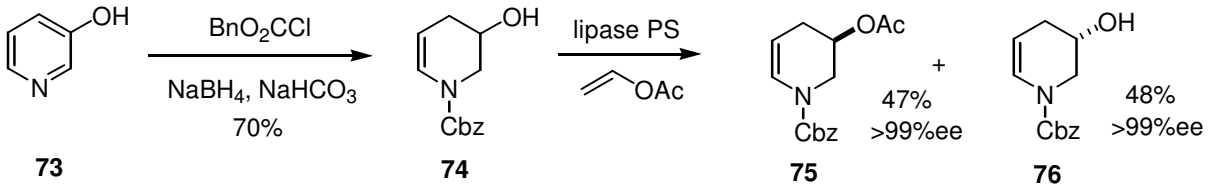
Allylation shows no diastereoselection while reaction with silyl enol ethers gives opposite diastereofacial preference depending on the nature of R group.



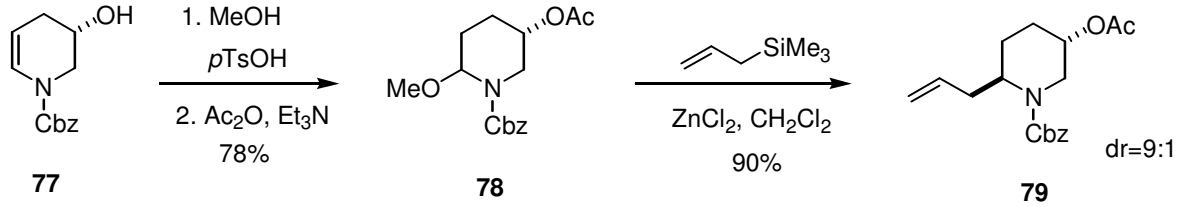
69 **70**

reagent	yield	R	**71**	**72**
	88%	*i-Pr*	50	50
	90%	*i-Pr*	15	85
	92%	*i*-Bu	85	15

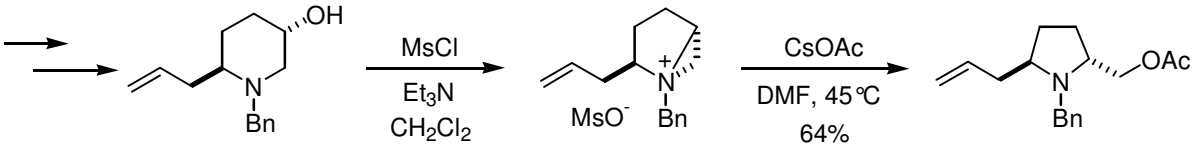
Scheme 20



73 **74** **75** **76**



77 **78** **79**



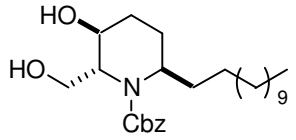
80 **81** **82**

Scheme 21

The success of synthetic procedures that employ chiral carbamates as precursors of *N*-acyliminium ions is often related to the availability of these unsaturated derivatives. Reduction of 3-hydroxypyridine **73** in the presence of benzyl chloroformate affords the corresponding enecarbamate **74** in racemic form (Scheme 21).[61] This derivative can be resolved by a lipase-mediated kinetic resolution and (S)-3-hydroxycarbamate **76** is transformed into α-methoxycarbamate **78** and then allylated in satisfactory yield and diastereoselectivity.

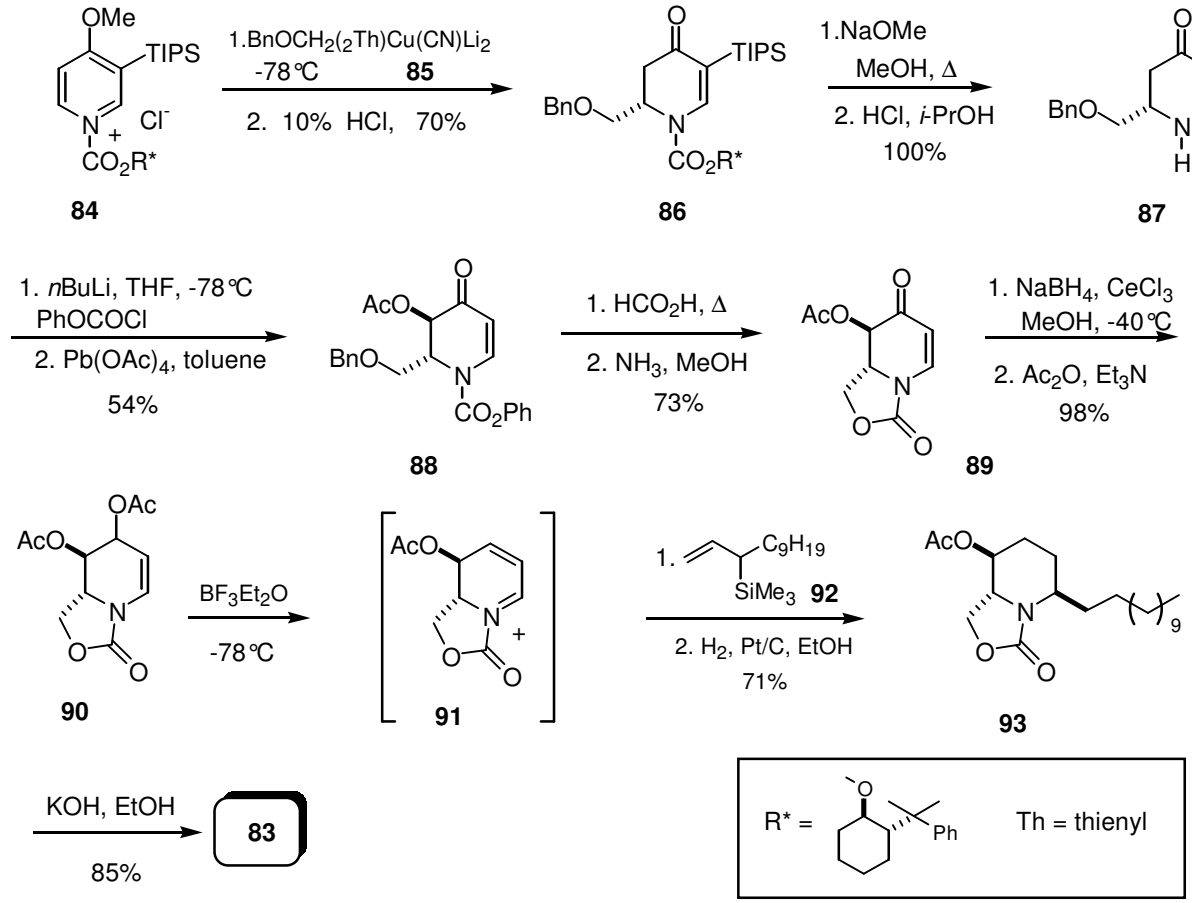
An intreresting process concerns 3-oxy derivative **79** that can be converted through simple protecting groups manipulation into 3-hydroxypiperidine **80**. Upon mesylation, an intramolecular nucleophilic substitution leading to aziridinium salt **81** occurs, and by action of CsOAc in DMF this salt furnishes the ring-contracted product *trans*-5-allylprolinol acetate **82**.

N-acylpyridinium salts have been used as precursors of a consistent number of piperidine alkaloids.[62,63] Deoxoprosopinine **83** and other analogues have been isolated from the leaves of *Prosopis africana* and are endowed with antibiotic and anesthetic properties.



83

The strategy adopted by Comins *et al.* for the synthesis of these piperidine alkaloids utilizes chiral *N*-acylpyridinium salt **84** that reacts with high order cyanocuprate **85** to afford the corresponding addition product **86** in a regioselective fashion by the presence of triisopropylsilyl (TIPS) group (Scheme 22).[64]

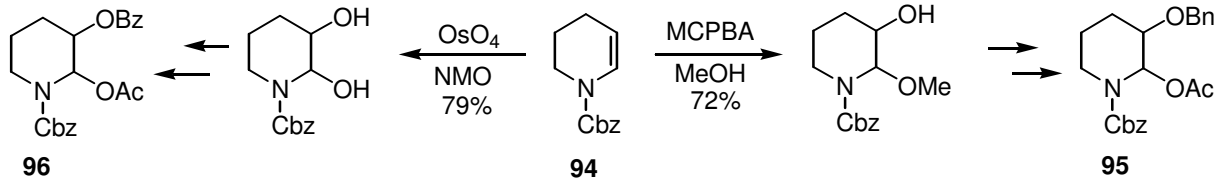


Scheme 22

Removal of the TIPS group produces **87** that is protected at nitrogen and then acylated using $Pb(OAc)_4$. Enone **88** needs to be converted into bicyclic derivative **89** that presents a more rigid structure

and ensures a better diastereoselectivity in the next synthetic steps. After selective 1,2-reduction and acetylation, diacetate derivative **90** is converted into conjugate *N*-acyliminium ion **91** that is attacked regio- and stereoselectively by allylsilane **92** to give the addition product **93** that is converted into (+)-deoxoprosopinine **83** by basic ethanolysis.

A detailed study on nucleophilic additions to *N*-acyliminium ions derived from 2-acyloxy-3-alkoxy piperidines has been recently carried out by Kobayashi and coworkers.[65,66] Synthesis of 2,3-dioxy piperidines can be realized starting from enecarbamate **94** by oxidation with MCPBA or microencapsulated OsO_4 (Scheme 23).

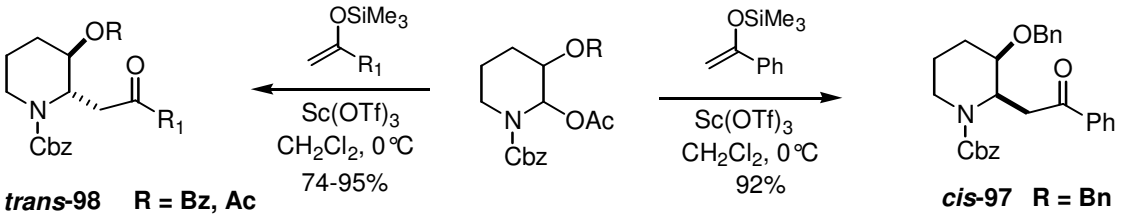


96 **94** **95**

Scheme 23

Catalytic amounts of metal triflates are able to activate these dioxygenated derivatives **95, 96** towards the reaction with silyl enol ethers and silyl ketene acetals; in particular, $Sc(OTf)_3$ in dichloromethane is the most effective catalyst for this reaction.

The stereochemical outcome displayed by the process is affected by the nature of the substituent at C-3. Compound **95** usually affords the corresponding addition product **97** with *cis*-selectivity, while 3-acyloxypiperidines of type **96** provide the formation of the *trans* stereoisomers **98** as main products (Scheme 24).

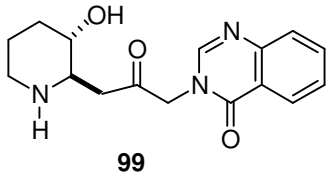


***trans*-98 R = Bz, Ac** ***cis*-97 R = Bn**

Scheme 24

Several factors as anomeric effects, neighboring groups participation and steric bulkiness of the nucleophile play a crucial role in the stereoselectivity of the addition process on *N*-acyliminium ions.

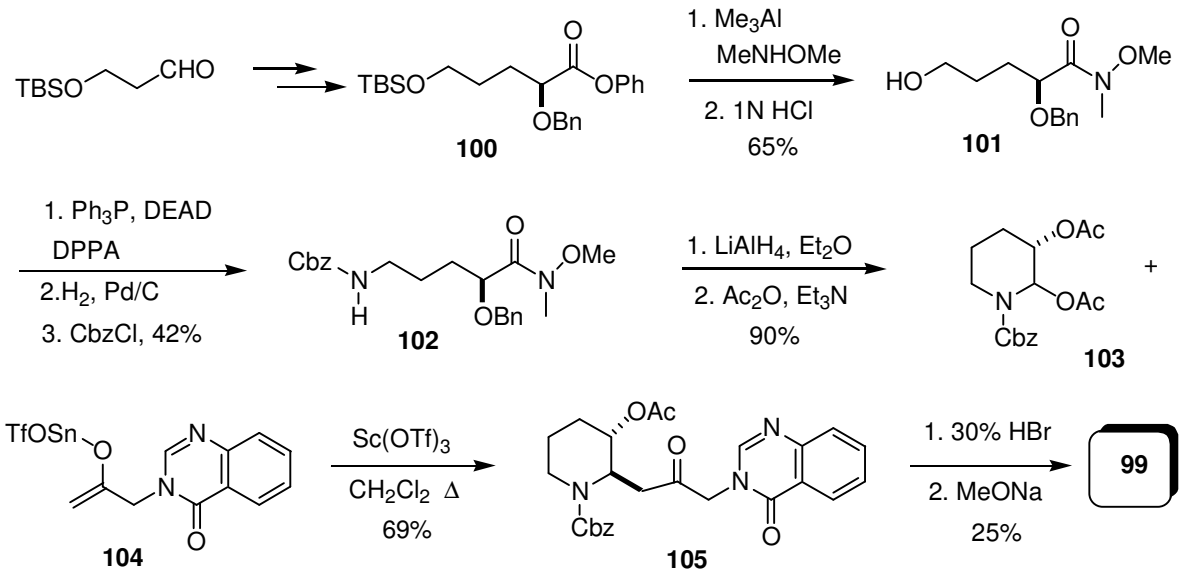
All these effects have been studied during the work aimed to the enantioselective synthesis of febrifugine **99** an alkaloid found in *Dichroa febrifuga*, a chinese plant known for its antimalarial properties.



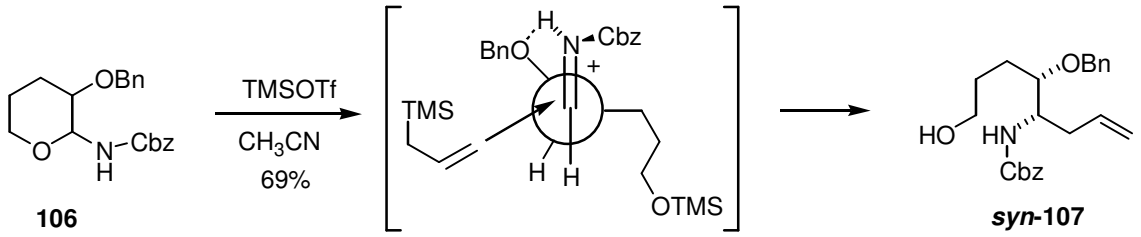
99

Construction of the piperidine ring with a proper sterocenter at C-3 can be made starting from ester **100** that is converted into Weinreb amide **101** and then aminated following a modified Mitsunobu procedure using diphenylphosphoric azide (DPPA) (Scheme 25).

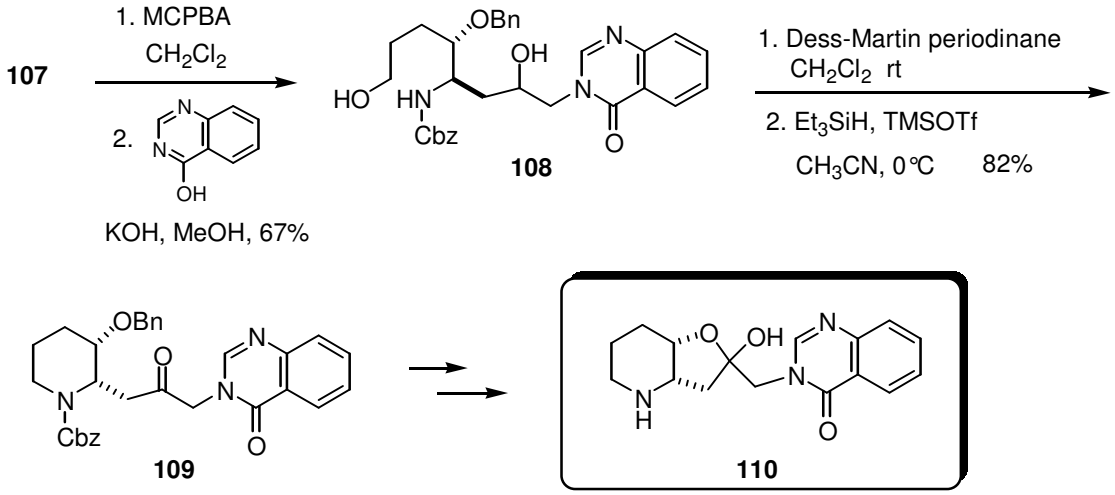
Reduction of the amide **102** follows a spontaneouos cyclization to a lactol that is successively transformed to diacetoxy derivative **103**. This diacetate reacts with tin enolate **104** in the presence of $Sc(OTf)_3$ to afford addition product **105** in a *trans/cis* ratio of 80:20. Removal of Cbz and acetate protecting groups gives febrifugine **99**.



Scheme 25



Scheme 26



Scheme 27

A complementary strategy for the preparation of functionalized piperidines consists in the ring-opening allylation of *N,O*-acetals **106** catalyzed by Lewis acids. In this case, an open-chain compound **107**

with *syn* stereoselectivity is obtained at first from the reaction as results of an acyclic *N*-acyliminium ion intermediate (Scheme 26).[67]

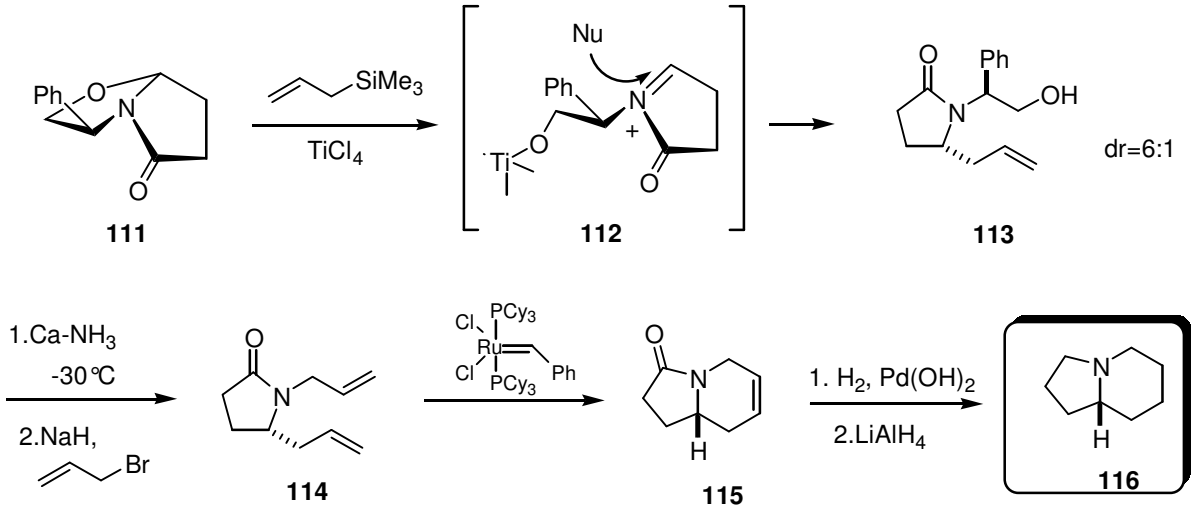
After suitable double bond functionalization to compound **108**, the piperidine ring in **109** can be builded as illustrated in Scheme 27 for the synthesis of isofebrifugine **110**.

A solid-phase synthesis of substituted piperidines has been realized by Hiemstra and coworkers as a logical extension of a previous procedure portrayed in Schemes 10 and 11. However, in this case the *N*-acyliminium ion precursor is isolated as 2-benzotriazolyl derivative and then made to react with allylsilanes in the presence of $BF_3 \cdot Et_2O$.[68]

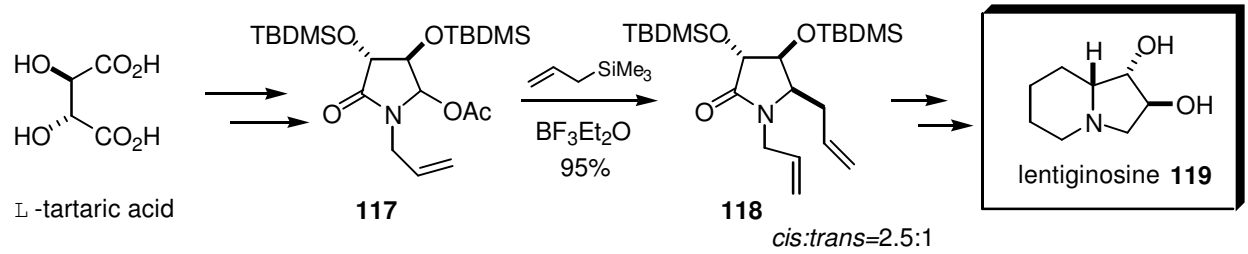
3.4. Indolizidines

A consistent number of biologically active compounds endowed of indolizidine structure have recently emerged as potent glycosidase inhibitors (slaframine, lentiginosine, castanospermine etc.);[69] other compounds as pumiliotoxin B are poisonous frog-alkaloids with interesting pharmacological activity.[70,71]

(-)-Coniceine **116** represents the simplest structure belonging to this class of derivatives and for its preparation Meyers and Groaning[72] start from chiral bicyclic lactam **111** which is converted into the corresponding *N*-acyliminium ion **112** and then stereoselectively allylated to afford pyrrolidinone **113** (Scheme 28).



Scheme 28



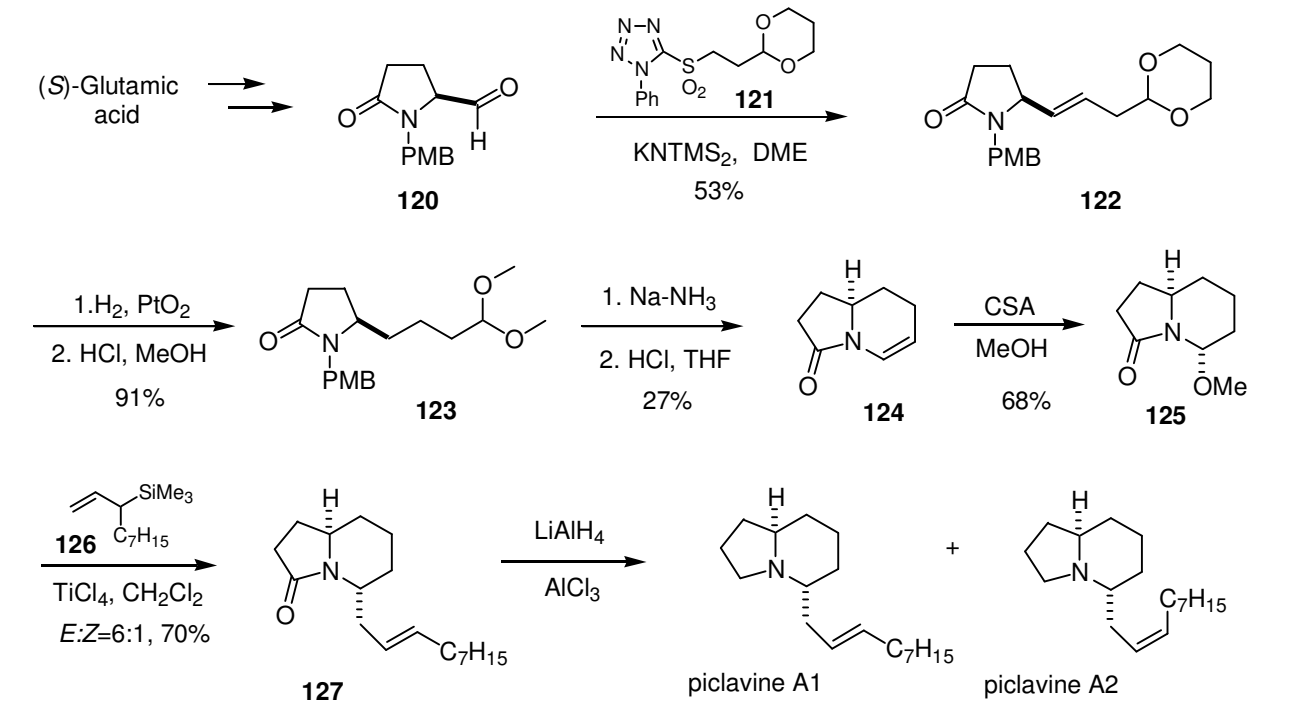
Scheme 29

Removal of the *N*-benzyl framework and *N*-allylation gives diallyl pyrrolidinone **114** that is treated with Grubbs' catalyst for a metathesis process leading to bicyclic derivative **115.** Full reduction of this unsaturated compound affords (-)-coniceine **116** in good overall yield.

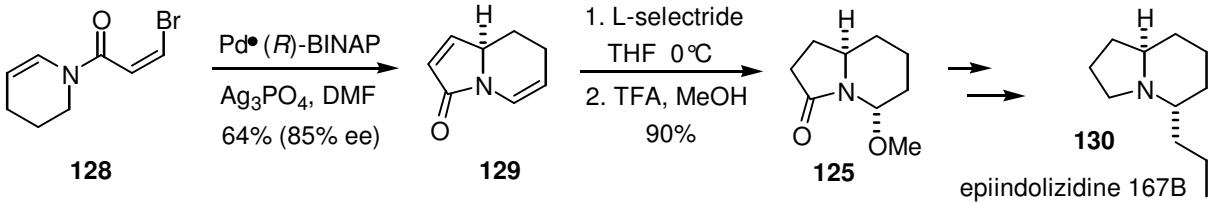
Ring closing metathesis of diallylated pyrrolidines **118** has been also used for the synthesis of hydroxylated indolizidines starting from natural tartaric acid (Scheme 29).[73,74] By this way a number of hydroxy derivatives including lentiginosine **119** can be prepared.

Piclavines have been found in the organic extract of the Bermudan tunicate *Clavelina picta* and are some of the few known indolizidines of marine origin. These compounds are antimicrobial and cytotoxic agents and the synthetic approach that leads to their preparation is depicted in Scheme 30.[75,76]

Aldehyde **120** prepared from (*S*)-glutamic acid is made to react with sulfone **121** leading to pyrrolidinone **122** according with the method of Kocienski. Double bond reduction and transacetalization affords derivative **123** that by removal of the *N*-protection followed by cyclization gives enecarbamate **124**. Methoxylation of **124** in the presence of camphorsulfonic acid (CSA) produces substrate **125** for the subsequent addition *via N*-acyliminium ion of silane **126** that occurs with high diastereofacial selectivity but with modest *E/Z* stereoselectivity to adduct **127**. Reduction of the mixture of stereosomers provides piclavine A1 and A2.



Scheme 30



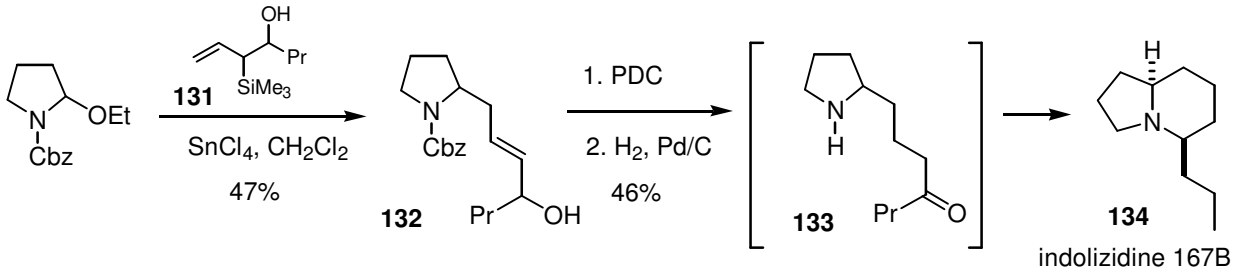
Scheme 31

Since bicyclic derivative **125** has been recognized as a central intermediate for the synthesis of indolizidine systems, a different preparation of this indolizidinone has been reported using an asymmetric intramolecular Heck cyclization (Scheme 31).[77] Vinyl bromide **128** reacts in the presence of a chiral

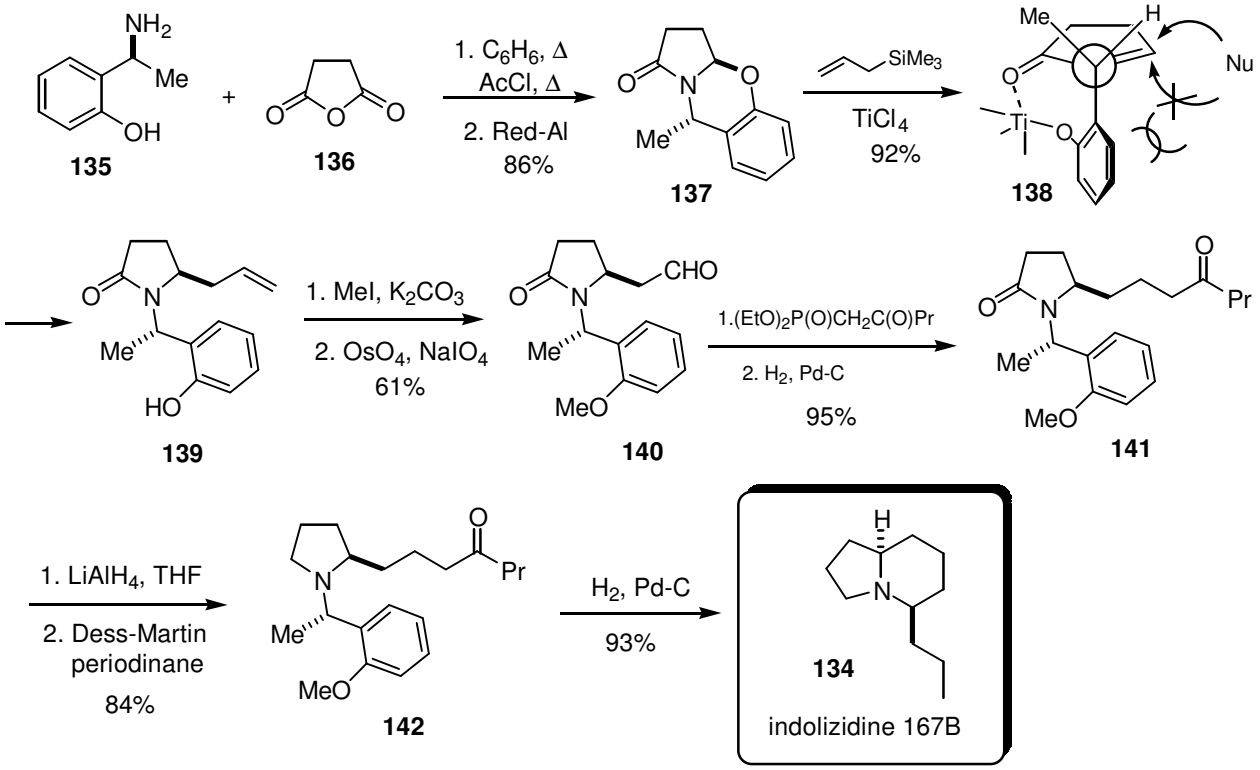
palladium complex giving indolizidinone **129** that suffers a chemoselective reduction of the conjugate double bond and a successive methoxylation of the enecarbamate system. By a similar procedure described in Scheme 30 product **125** can be converted into epiindolizidine 167B **130**.

Functionalization of *N*-acyliminium ion derived from **125** invariably leads to epiindolizidines, however, addition reactions on monocylic iminium ions followed by ring closure can afford indolizidine rings.

When silane **131** is made to react with α-alkoxypyrrolidines the corresponding allylic alcohol **132** is obtained (Scheme 32).[78] Oxidation of the hydroxy group and double bond reduction leads to ketone **133** that is not isolated but spontaneously cyclizes to the iminium ion and upon reduction of the C=N bond gives racemic indolizidine 167B **134** in satisfactory overall yield.



Scheme 32

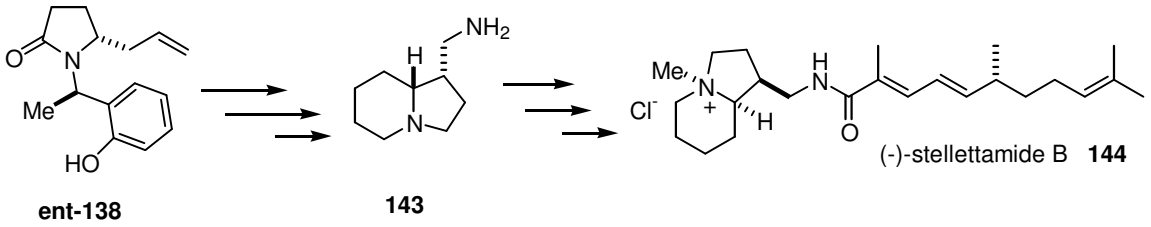


Scheme 33

A chiral tricyclic *N*-acyl-*N,O*-acetal incorporating (*S*)-2-(1-aminoethyl)phenol **137** has been introduced by Kibayashi *et. al.* as rigid system in order to obtain elevated diastereoselections in the addition of the corresponding *N*-acyliminium ion (Scheme 33).[79] The origin of the diastereoselectivity in the

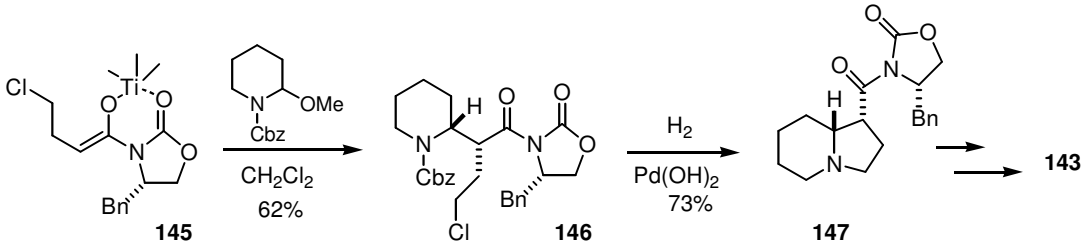
formation of **139** can be found in the chelation between titanium, carbonyl and phenolic oxygens that hinders one face of the iminium ion intermediate **138**. Protection of the hydroxyl group and oxidative cleavage of the double bond affords aldehyde **140** that is converted into ketone **141** by a Horner-Wittig reaction followed by a reduction of the conjugate double bond. Pyrrolidinone **141** is then reduced to pyrrolidine **142** and finally catalytic hydrogenation leads to indolizidine 167B **134**.

A similar strategy has been applied by the same group for the synthesis of (-)-adaline[80] and (-)-stelletamide B **144**, a cytotoxic metabolite isolated from marine sponges of the genus *Stelletta* (Scheme 34).[81] In this case the enantiomer of adduct **138** has been used and the synthesis of key intermediate indolizidine **143** was achieved.



Scheme 34

An efficient synthesis of 1-aminomethyl indolizidine **143** has been accomplished exploiting the reaction of a chiral titanium enolate **145** with *N*-carbobenzoxy-α-methoxypyrrolidine (Scheme 35).[82] Removal of the Cbz group from adduct **146** occurs with a tandem cyclization to indolizidine **147** that is converted into desired amino derivative **143** by simple functional groups manipulation.

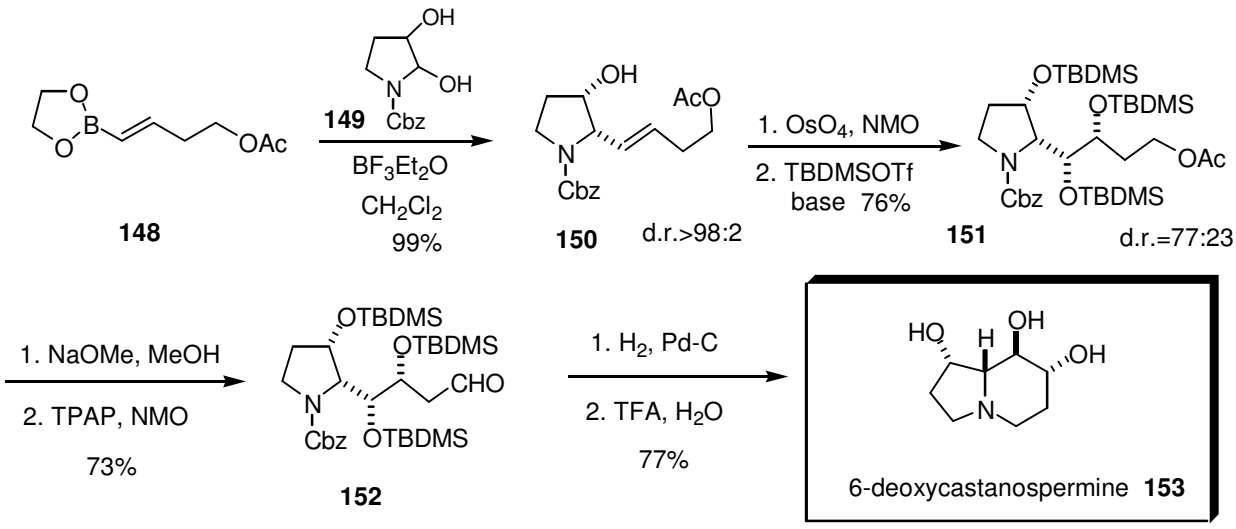


Scheme 35

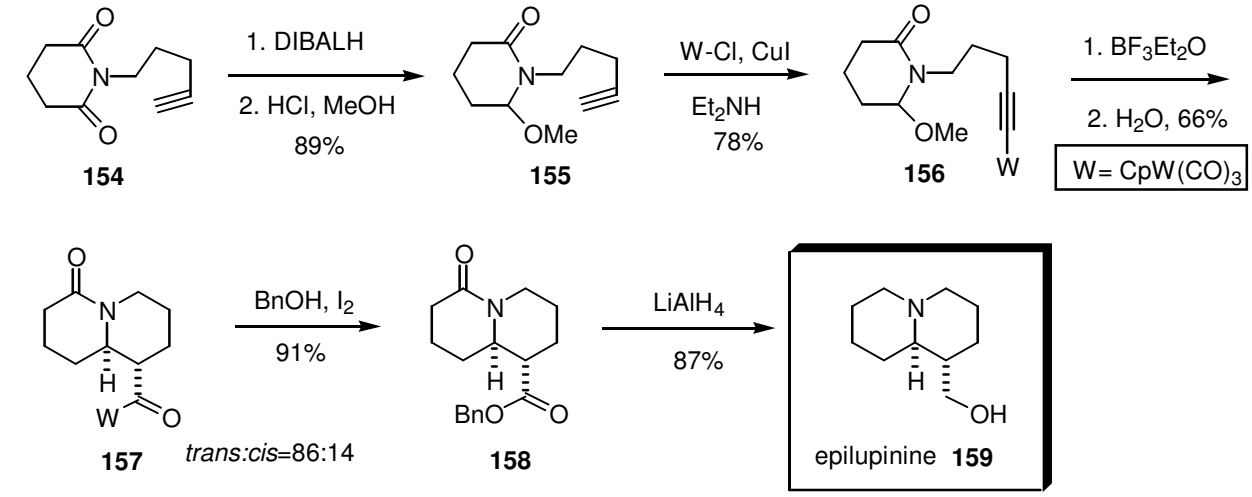
The number of nucleophilic systems that can react with reactive iminium ions has been continuosly increasing over recent years. Alkenylboronates are able to introduce an alkenyl fragment in the reaction with *N*-acyliminium ions that is amenable of further functionalization. This strategy has been applied to the stereoselective synthesis of 6-deoxycastanospermine **153** as illustrated in Scheme 36.[83] Organoboronate **148** reacts with dihydroxypyrrolidine **149** to give in high yield and diastereoselectivity alkenyl derivative **150** that is dihydroxylated and then protected at the OH groups to compound **151**. Hydrolysis of the acetate and oxidation with tetrapropylamonium perruthenate (TPAP) leads to aldehyde **152** that is converted into 6-deoxycastanospermine by usual procedures.

3.5. Quinolizidines

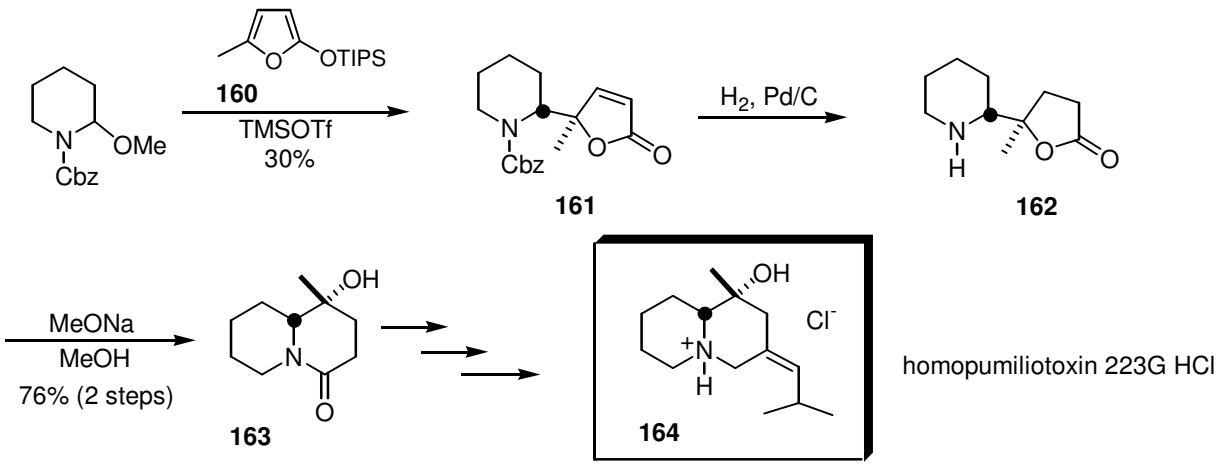
Intramolecular cyclization of alkynyltungsten complexes with *N*-acyliminium ions derived from α-alkoxy piperidines is able to produce a quinolizidine skeleton. In this context the organometallic complex acts as an ester enolate equivalent (Scheme 37).[84]



Scheme 36



Scheme 37



Scheme 38

The alkynyltungsten specie is generated by reaction of a terminal alkyne **155** with $CpW(CO)_3Cl$ and complex **156** is made to react with a Lewis acid following an aqueous work-up to afford in a

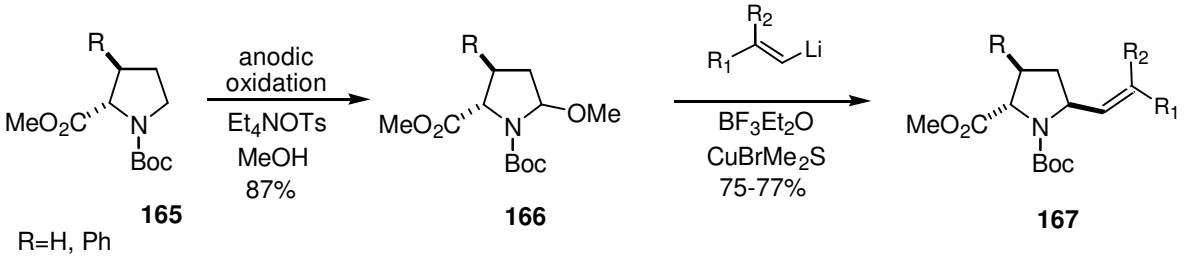
diastereoselective fashion quinolizidinone **157**. Tungsten can be easily replaced by a benzyloxy group in **158** and by reduction of the carbonyl functions epilupinine **159** can be finally obtained.

Reaction of silyloxyfurans **160** with cyclic *N*-acyliminium ions gives butenolide systems in a vinylogous nucleophilic addition (Scheme 38).[85] Compounds of type **161** can be reduced to lactones **162** and then converted into a quinolizidinone structure **163** that can be used to prepare several alkaloids as for instance homopumiliotoxin 223G **164**.

Using a related strategy is also possible to prepare 5-hydroxy indolizidinones and quinolizidinones that are useful precursors of more complex heterocyclic systems.[86,87]

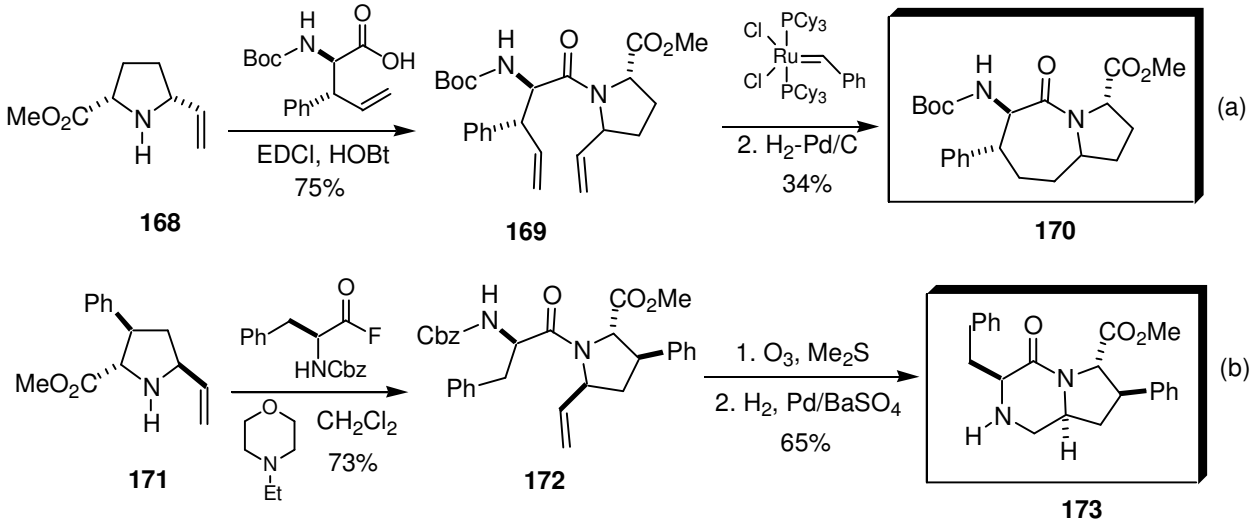
3.6. Other bicyclic systems

Several bicyclic systems containing saturated nitrogen heterocycles act as constrained peptidomimetics, a class of substances particularly useful for probing the biological relevance of a proposed peptide conformation.[88] 2-Alkenyl pyrrolidines have been recognized as pivotal intermediates for the synthesis of different peptidomimetics and an efficient method for their preparation has reported by Moeller *et al.* (Scheme 39).[89-92] Anodic oxidation of pyrrolidine derivatives **165** is a very regioselective process that allows the preparation of suitable α-alkoxypyrrolidines **166**. Reaction of these compounds with lithium alkenyl cuprates in the presence of BF_3Et_2O affords alkenylpyrrolidines **167** with high diastereoselectivity.



165 R=H, Ph **166** **167**

Scheme 39



168 **169** **170**

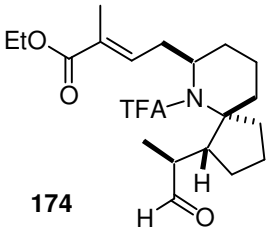
171 **172** **173**

Scheme 40

With derivatives **168**,**171** in hand, different kind of peptidomimetics summarized in Scheme 40 can be prepared. For the synthesis of compound **170** a ring closing metathesis of diallyl derivative **169** using

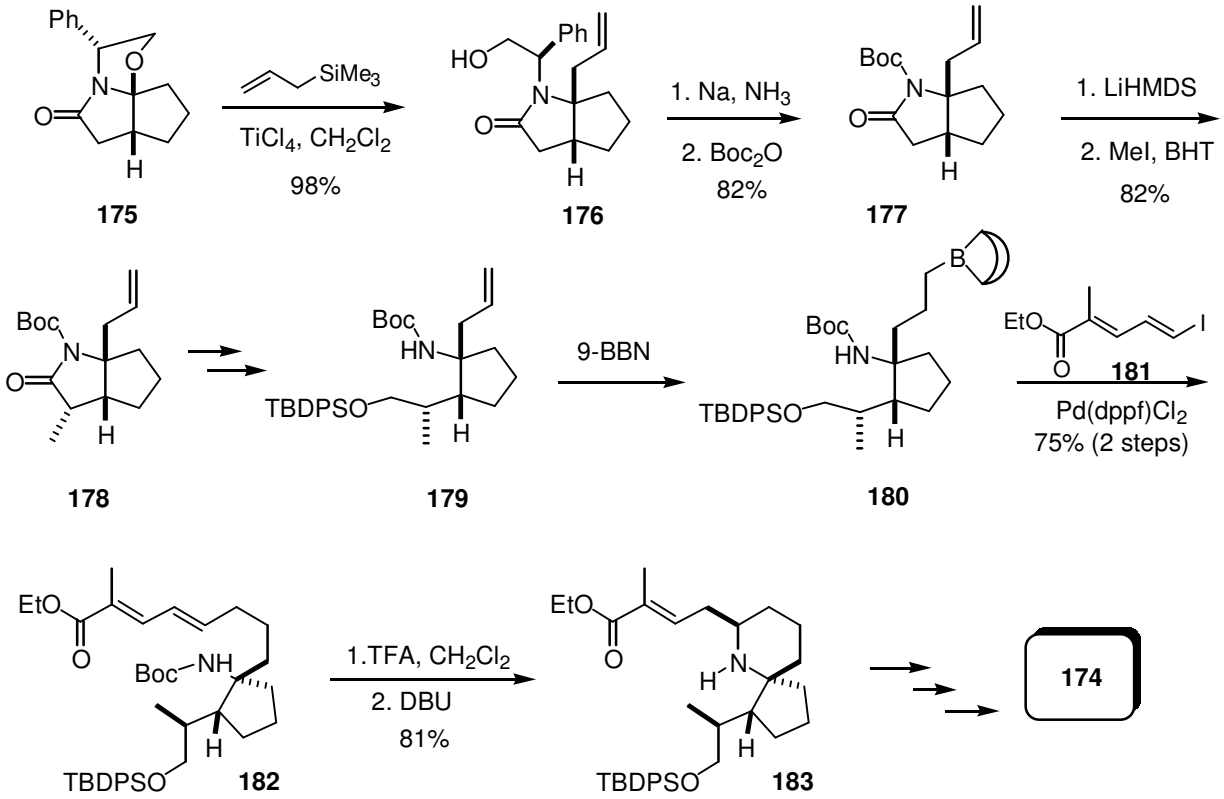
Grubbs' catalyst is the crucial step (eq. a),[89] while compound **173** is prepared using a classical ozonolysis of the vinyl group in **172**, followed by reduction of the spontaneously formed six-membered ring hemiaminal (eq. b).[92]

Azaspirocycles constitute the core of many substances of practical interest. Azaspirocycle **174** is an important intermediate toward the synthesis of pinnaic acid, a marine metabolite that shows anti-inflammatory properties.



174

Danishefsky *et al*. have developed an interesting synthesis of this precursor starting from Meyers' tricyclic lactam **175** that is allylated using standard conditions affording derivative **176** (Scheme 41).[93]



178 **179** **180** **182** **183**

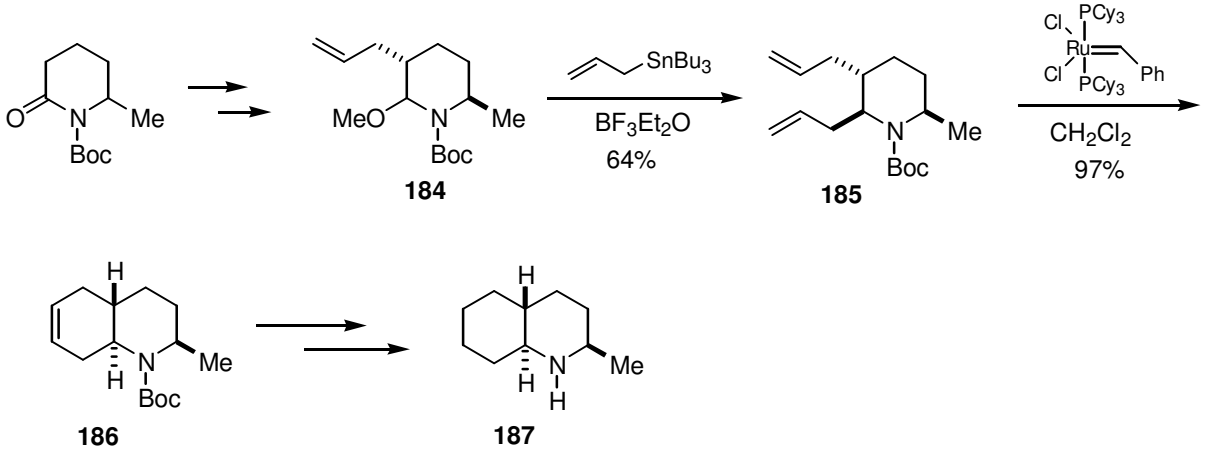
Scheme 41

Successively, Boc protecting group is inserted and stereoselective methylation of the lactam **177** gives bicyclic derivative **178**. Using a known chemistry compound **178** is cleaved to furnish cyclopentane **179** that is hydroborated at the double bond and then coupled with iododiene **181** in the presence of palladium catalyst. After removal of the Boc protection from derivative **182**, the azaspiro system is

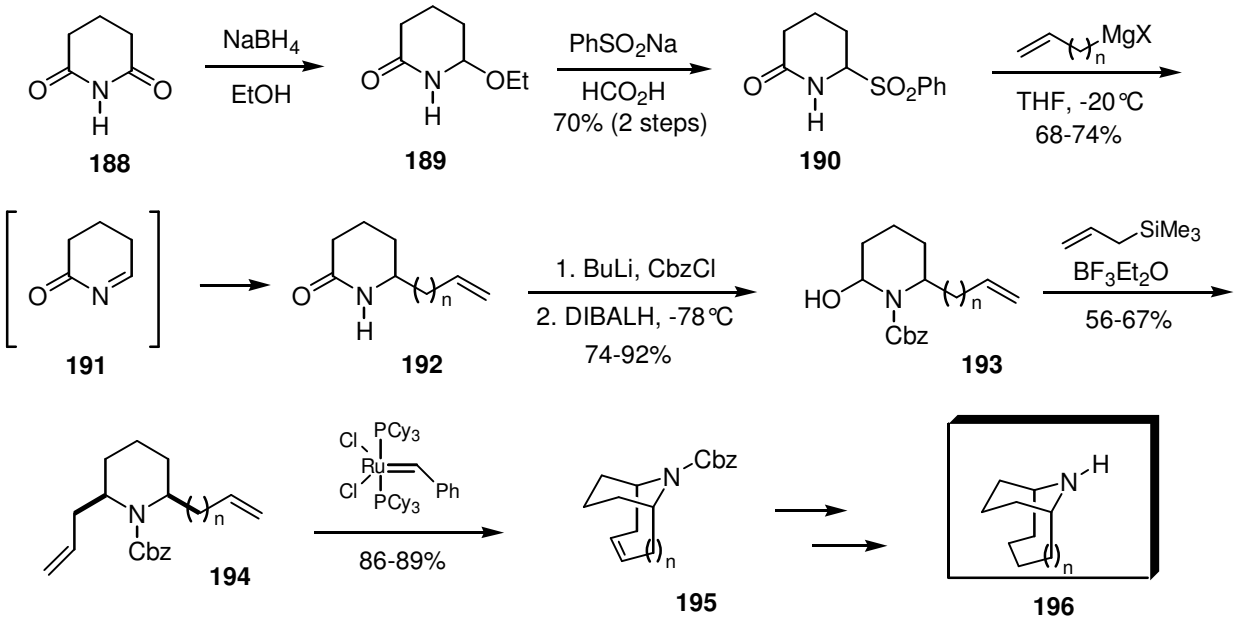
generated by intramolecular Michael addition of the nitrogen atom to dienyl ester appendage affording compound **183** that is transformed into desired intermediate **174** in few steps.

1-Azaspirocycles can be also prepared starting from cyclic *N*-acyl-*N,O*-acetals exploiting an intramolecular olefin-iminium cyclization.[94]

Ring closing metathesis has found a large application in the synthesis of cyclic derivatives and its utilization will probably increase even more in the future. Decahydroquinolines and other bicyclic derivatives can be prepared following the strategy depicted in Scheme 42.[95] Allyl derivative **184** is further allylated using allyltributyltin to give the 2,3-*trans*-**185** that undergoes a ring closure using Grubbs' catalyst to bicyclic derivative **186**. Reduction of the double bond and deprotection of the nitrogen give decahydroquinoline **187**.



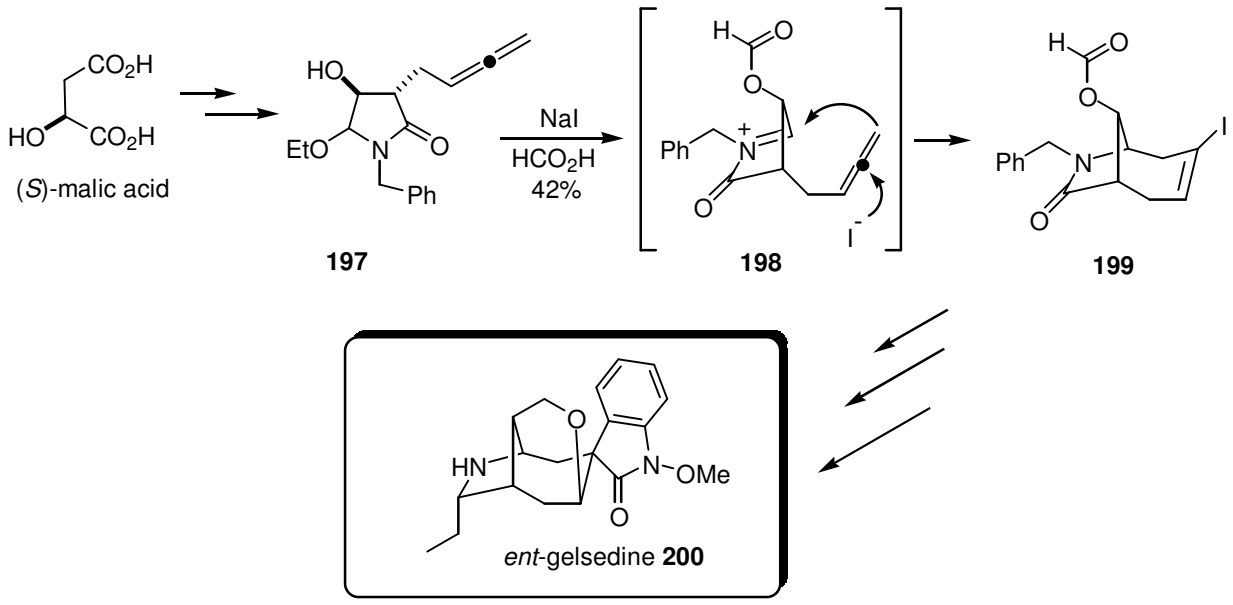
Scheme 42



Scheme 43

A related procedure using both ring closing metathesis or intramolecular Heck reaction allows the preparation of different bicyclic derivatives,[96] and bridged azabicyclic structures. Glutarimide **188** is reduced to give α-ethoxylactam **189** but every attempts to introduce the alkenyl side chain using organometallic reagents fails (Scheme 43).[97] Converting **189** into the corresponding 2-phenylsulfonyl derivative **190** make the reaction with Grignard reagents successful to give alkenyl derivative **192**. It is worth noting that this reaction occurs through a neutral *N*-acylimine derivative **191** that is formed by elimination of benzenesulfinic acid caused by the excess of Grignard reagent.[98] Protection of the nitrogen atom and reduction of the carbonyl group gives piperidine **193** that is allylated to give predominantly the *cis*-stereoisomer **194**. Ring closing metathesis affords bridged azabicycles **195** and after reduction, saturated compounds **196**.

The *Gelsemium* alkaloids possess as a common feature a bridged polycylic structure that can be assembled starting from a bridged azabicyclic building block. Ethoxylactam **197** is conveniently prepared from (*S*)-malic acid and upon reaction with formic acid in the presence of sodium iodide it is transformed into the corresponding *N*-acyliminium ion **198** that undergoes an intramolecular ring closure to azabicycle **199** (Scheme 44).[99] This derivative is then converted into *ent*-gelsedine **200** by further synthetic transformations.

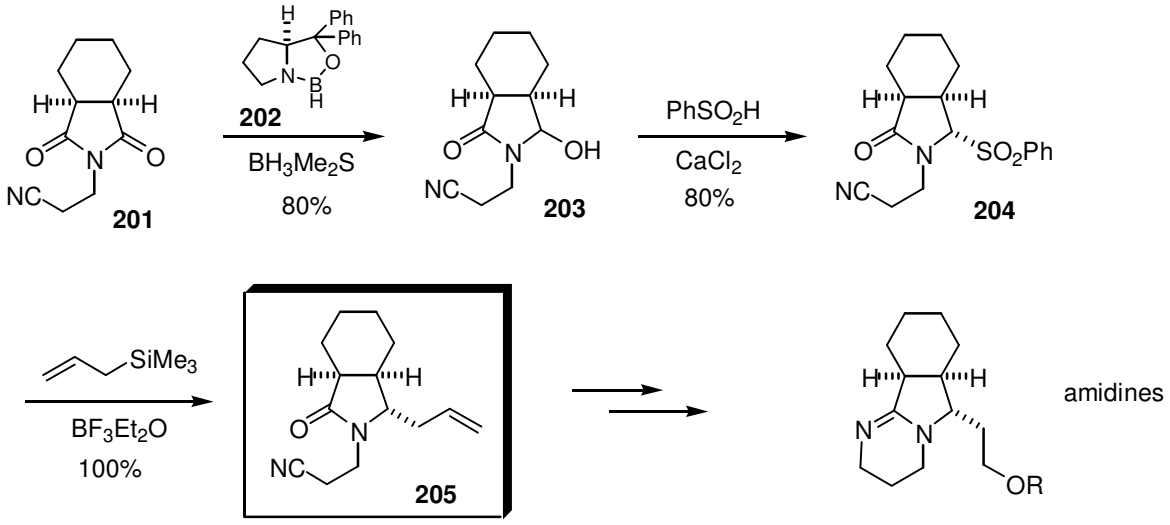


Scheme 44

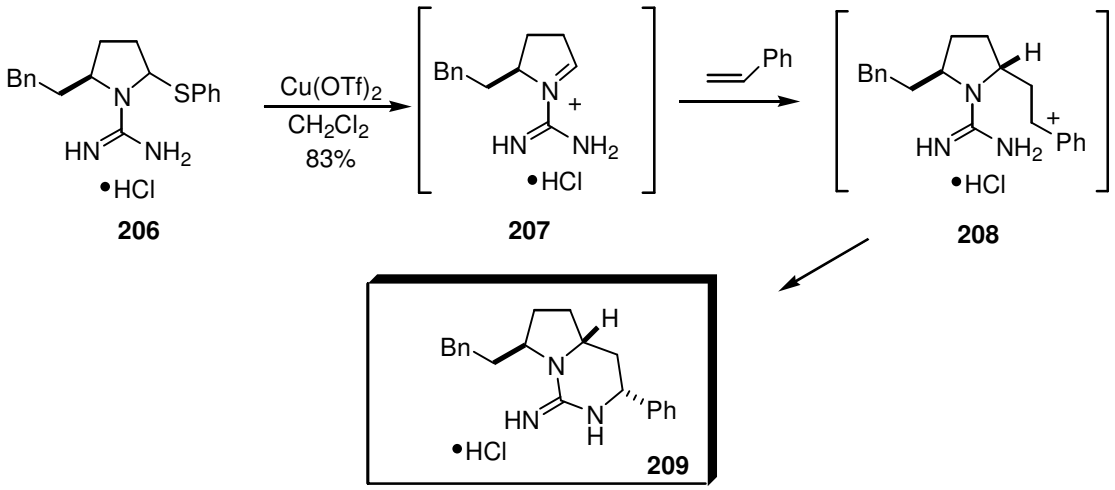
Cyclic α-sulfonyl lactams present the advantage over common α-alkoxy derivatives to be crystalline compounds easy to purify by crystallization. Therefore Hiemstra *et al.* decided to transform bicyclic α-hydroxylactam **203**, obtained by reductive desymmetrization of *meso*-imide **201** using chiral catalyst **202**, into α-sulfonyl lactam **204** (Scheme 45).[100] This lactam can be obtained in 99% ee after repeated crystallizations and upon allylation gives product **205** that can be converted into chiral amidines.

Cyclic *N*-amidinyliminium ions present an interesting reactivity toward unsaturated derivatives as styrenes and 1,3-dienes. These reactive iminium ions **207** are prepared from thioaminal **206** by reaction with $Cu(OTf)_2$ (Scheme 46).[101] Reaction of **207** with styrene occurs regio- and stereoselectively affording a

benzyl carbocation intermediate **208** that gives a cyclocondensed product **209** with d.r. 5:1. Reaction of **206** with β-dicarbonyl compounds affords unsaturated bicyclo derivatives arising from a Biginelli process.[102]



Scheme 45



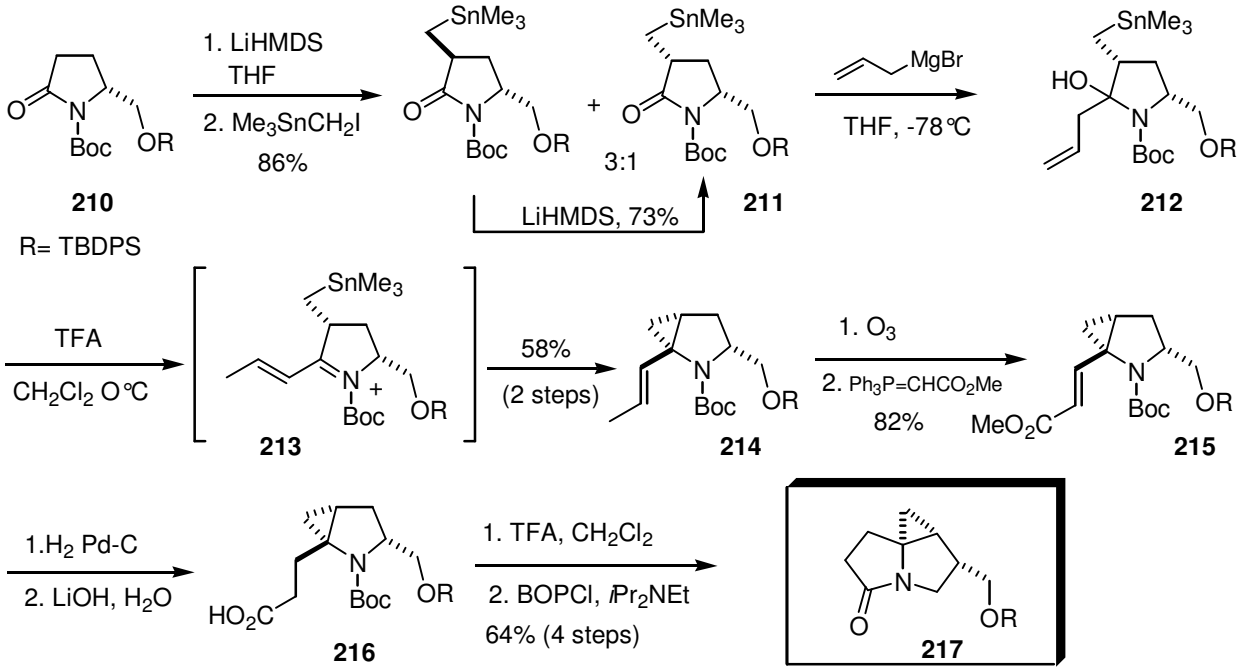
Scheme 46

3.7. Tricyclic systems

Tricyclic pyrrolizidinone carboxylic acids harboring an angular methano group are mimics of carbapenems and carbapenams. Hanessian *et al.* have devised an interesting approach to these heterocyclic derivatives starting from lactam **210** that is alkylated using Me_3SnCH_2I giving a diastereomeric mixture of *cis* and *trans* adducts **211** (Scheme 47).[103]

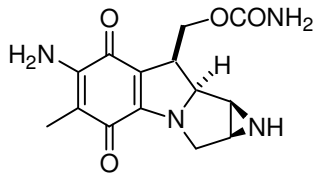
The major *trans* stereoisomer can be isomerized to the more stable *cis* isomer in basic conditions and is then made to react with allylmagnesium bromide to give the hemiaminal **212**. Reaction with trifluoroacetic acid presumably forms the corresponding *N*-acyliminium ion **213** that favors a cyclopropyl ring closure to bicyclic derivative **214**. Ozonization and Wittig olefination leads to compound **215** that is

reduced at the double bond and hydrolyzed to acid **216**. Boc protecting group is finally removed and ring closure to lactam **217** completes this interesting synthetic procedure.



Scheme 47

Mitomycins belong to a family of antitumor agents as mitomycin C **218** which preparation has been the focus of many synthetic efforts.

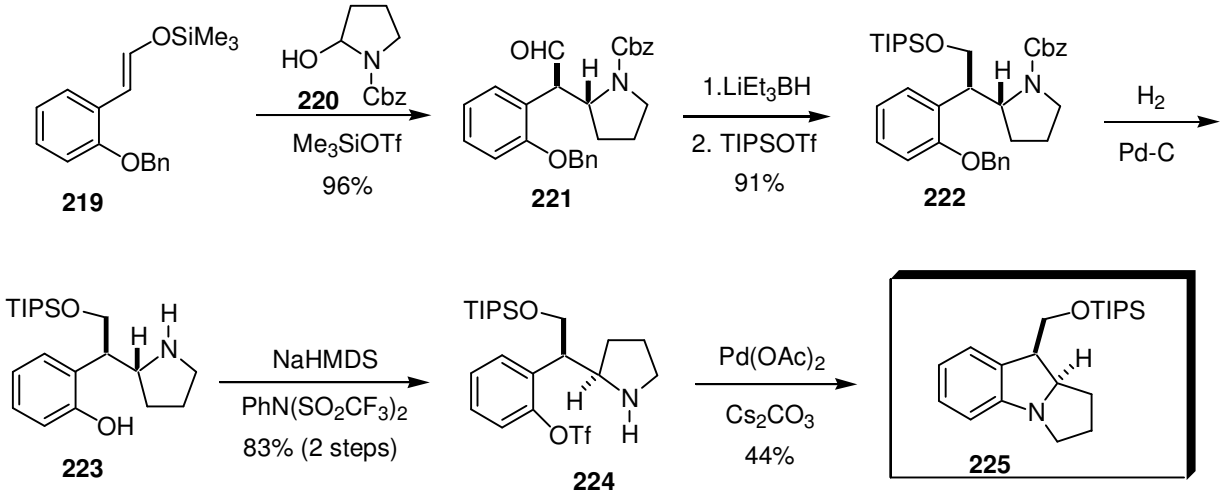


mitomycin C **218**

A general approach to the mitomycin ring system developed by Coleman and Chen involves as crucial step the addition of silyl enol ether **219** with *N*-acyliminium ion derived from α-hydroxy pyrrolidine **220** (Scheme 48).[104] Aldehyde **221** is formed in high yield as a sole stereoisomer and after reduction, the resulting alcoholic function is protected as triisopropylsilyl (TIPS) ether **222**. Catalytic hydrogenation provides removal of the benzyl based protections and the phenolic hydroxyl group in **223** is converted into triflate ester **224**. An intramolecular palladium-catalyzed coupling affords the tricyclic core of the mitomycin system **225** that can be further manipulated to obtain the desired derivatives of this important family of substances.

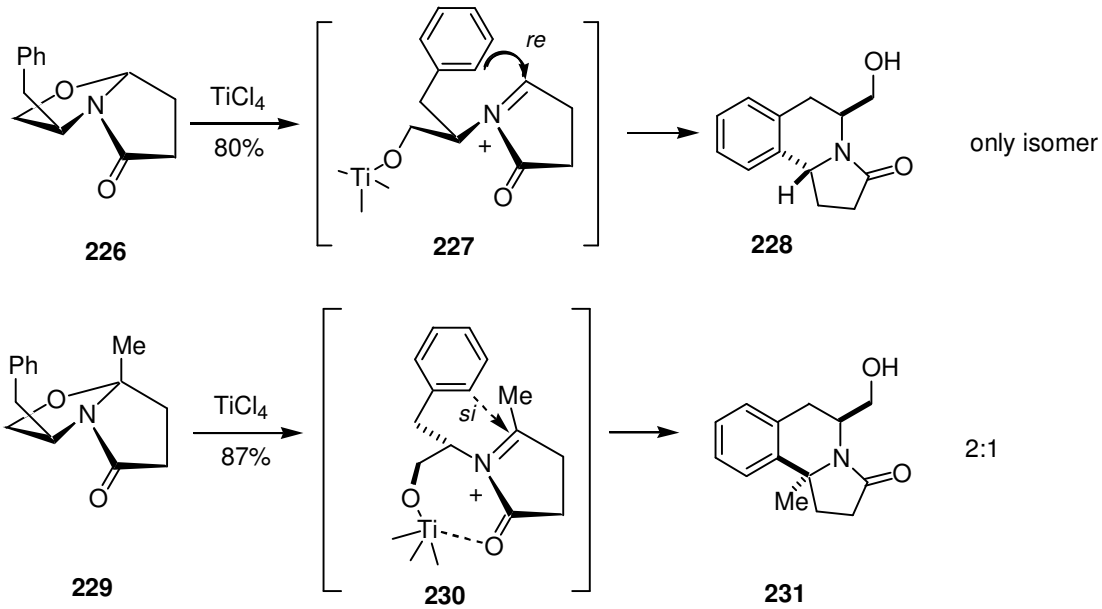
The pyrroloisoquinoline ring system is present in several molecules of the *Erytrina* alkaloids and the interest in this structural unit is witnessed by many synthetic approaches presented over recent years.[105]

Bicyclic lactams are ideal substrates for the preparation of these tricyclic derivatives exploiting an intramolecular attack of the aromatic ring to the *N*-acyliminium ion intermediate (Scheme 49).[106-108]



Scheme 48

When unsubstituted lactam **226** is used the attack of the aromatic ring comes from the top *re* side of the iminium ion **227** thus giving tricyclic derivative **228** as the exclusive stereoisomer. However the presence of a methyl group in **229** probably slowers the reactivity of the intermediate iminium ion thus making possible a chelation by titanium as in **230**. This offers an alternative pathway for the attack of the aromatic group from the *si* side leading to **231** with modest diastereoselectivity. Similar results have been recently reported by Katritzky *et al.* for the reaction of benzotriazolyl precursors of *N*-acyliminium ions in the same process,[109] and by Sotomayor *et al.* for related stuctures containing a sulfur atom in the tricylic ring.[110-111]

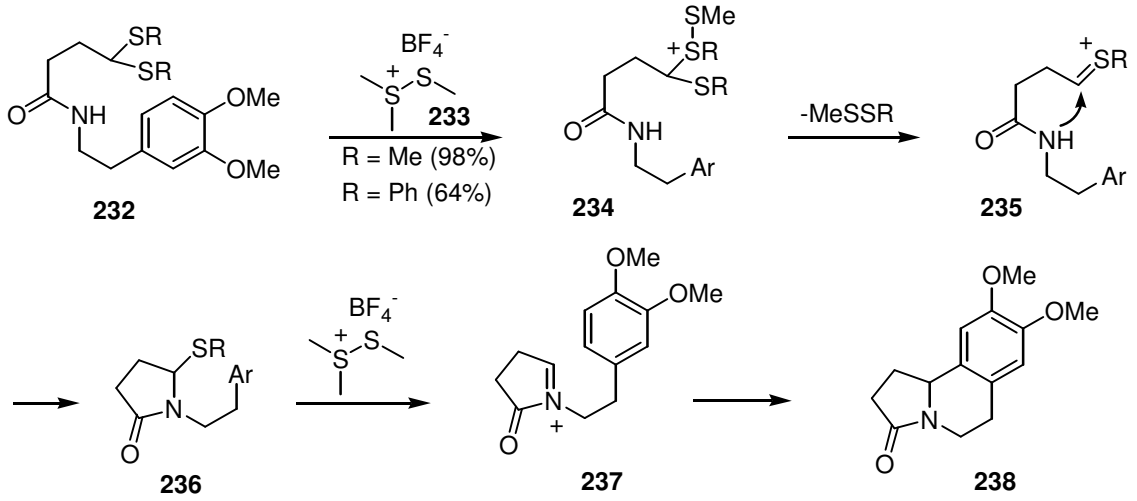


Scheme 49

Gathering several synthetic transformations in a sequential process is one of the major goals of the modern organic synthesis. The utilization of a domino sequence allows the preparation of complex structures in a single step with a considerable reduction in costs and environmental impact.

Recently Padwa and Waterson have developed a consecutive thionium/*N*-acyliminium ion cyclization sequence using dimethyl (methyltio)sulfonium tetrafluoroborate (DMTSF) **233** as promoter (Scheme 50).[112]

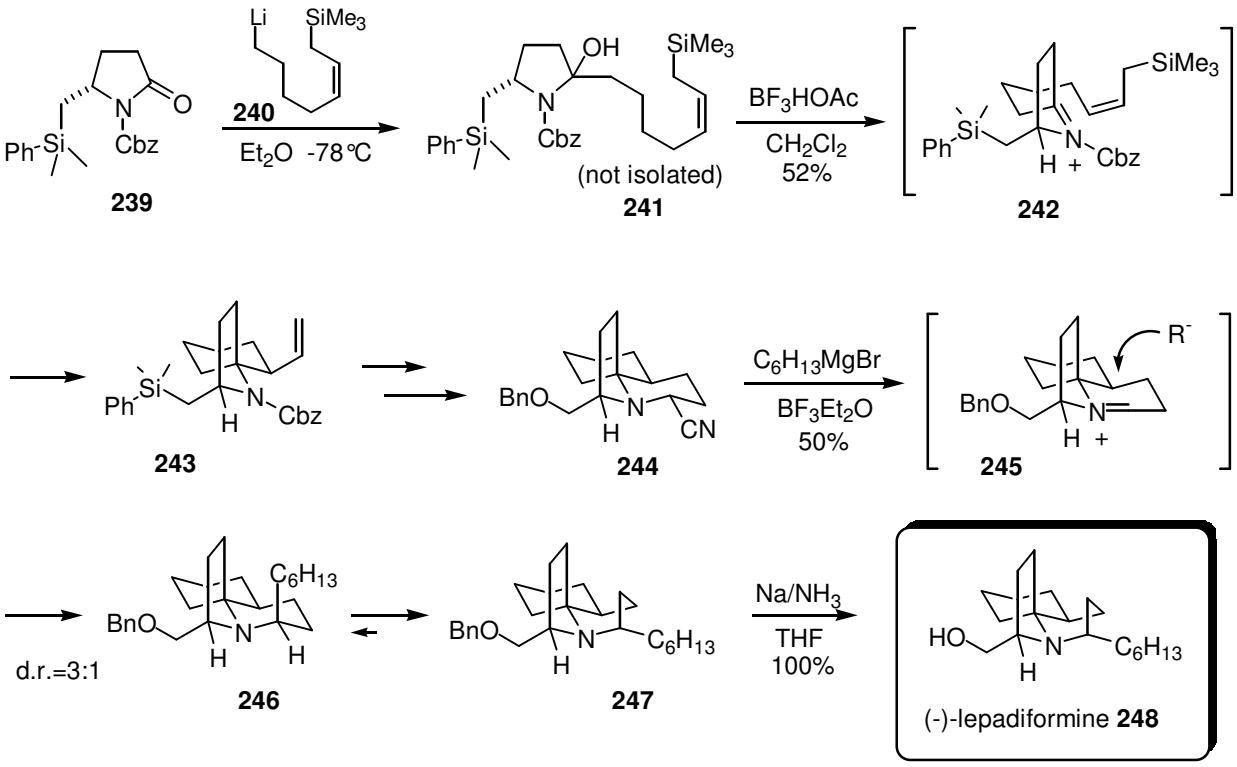
DMTSF first acts as methylthiolating agent converting thioacetal **232** into alkylthiosulfonium salt **234** that by losses of methylalkyl sulfide is converted into thionium ion **235**. Attack of nitrogen atom onto the cationic center gives α-phenyltiolactam **236** that reacting with excess of DMTSF affords *N*-acyliminium ion **237**. This iminium ion cyclizes in the usual way to afford tricyclic derivative **238**. Thionium salts can be also obtained starting from phenyl sulfoxides by reaction with silyl ketene acetals in the presence of ZnI_2.[113] It is worth to note that this strategy although illustrated for the synthesis of tricyclic compound **238** is suitable for the preparation of many polycyclic derivatives.



Scheme 50

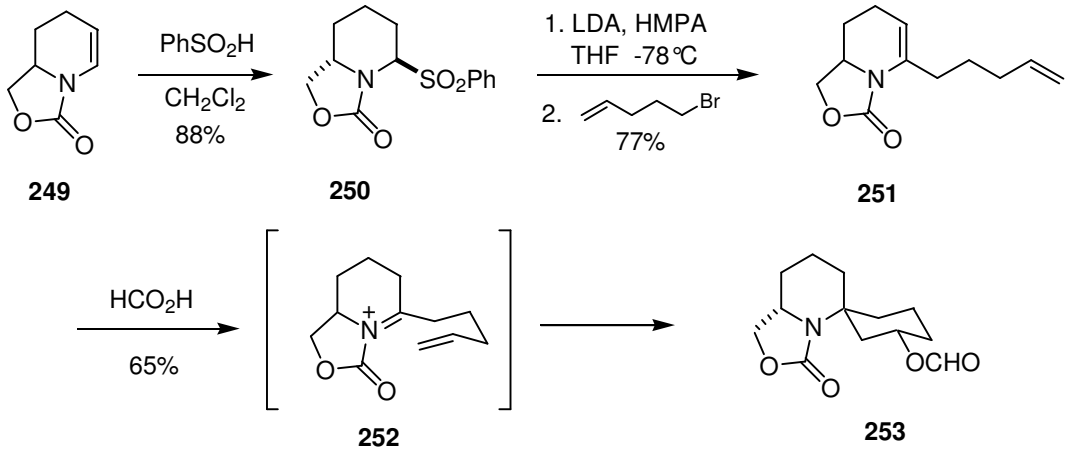
Lepadiformine is a tricyclic alkaloid of marine origin (*Clavelina lepadiformis*) featured by a spirocyclo structure with moderate cytotoxic activity. Weinreb *et al.* have realized a very elegant total synthesis of the natural enantiomer of lepadiformine using iminium ion intermediates in two crucial steps of the synthesis (Scheme 51).[114-115]

Reaction of organolithium **240** with chiral pyrrolidinone **239** gives addition product **241** that without isolation is transformed into *N*-acyliminium ion **242** using boron trifluoride-acetic acid complex. Attack of the allylsilane onto the less hindered side of the iminium ion **242** leads to spirocyclo derivative **243** in 52% overall yield. Compound **243** is then transformed into tricyclo derivative **244** and made to react with hexylmagnesium bromide in the presence of BF_3Et_2O assuming the formation of an iminium ion intermediate **245**. Although the diastereoselectivity of this addition is not particularly high, derivative **246** which is in equilibrium with its conformer **247**, after removal of the benzyl protecting group affords (-)-lepadiformine **248** in enantiopure form. A related approach has been used by Kibayashi *et al.* for the same synthesis exploiting a vinylogous intramolecular addition on a cyclic *N*-acyliminium ion.[116]



Scheme 51

Phenylsulfonyl group can act as good leaving group in the formation of *N*-acyliminium ions, but it is also able to promote the formation of carbanions α to the sulfone moiety.[117] This feature has been used by Lhommet *et al.* to prepare some azaspirocyclic derivatives as illustrated in Scheme 52.[118] Enecarbamate **249** is transformed into sulfone **250** by addition of benzenesulfinic acid and then converted into the corresponding carbanion using LDA. Alkylation of this anion occurs with concomitant elimination of benzenesulfinic acid to afford substituted enecarbamate **251**. This enecarbamate upon treatment with formic acid gives the *N*-acyliminium ion **252** that cylizes to spiro derivative **253**.

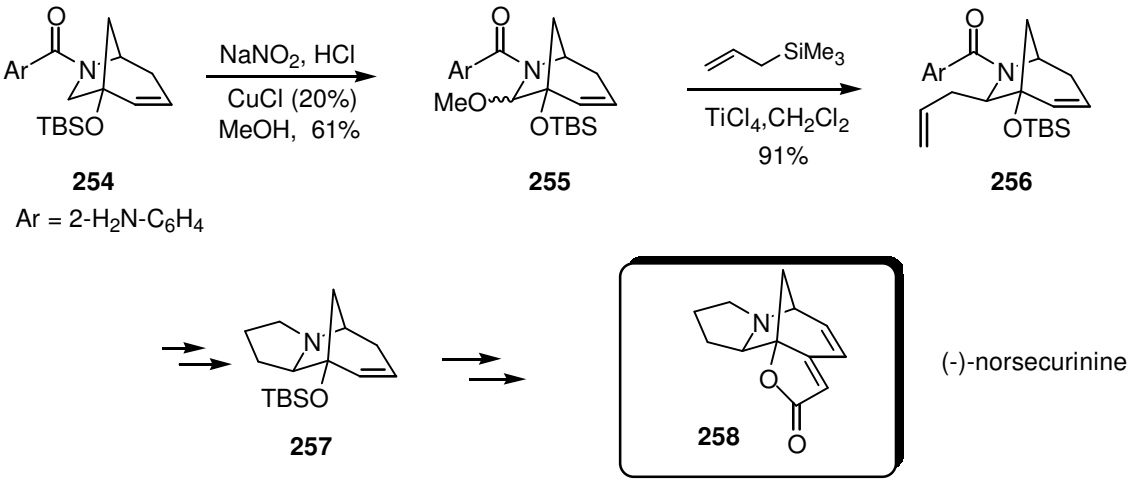


Scheme 52

As discussed previously, synthesis of α-alkoxyamido derivatives starting from simple amides or carbamates often entails anodic oxidation of these nitrogen compounds. However, the apparatus required to

carry out such procedure is not always available in every laboratory. In this context diazotization of amides affords the same result using non-electrochemical conditions as illustrated in Scheme 53 for the synthesis of norsecurinine alkaloids.[119-120]

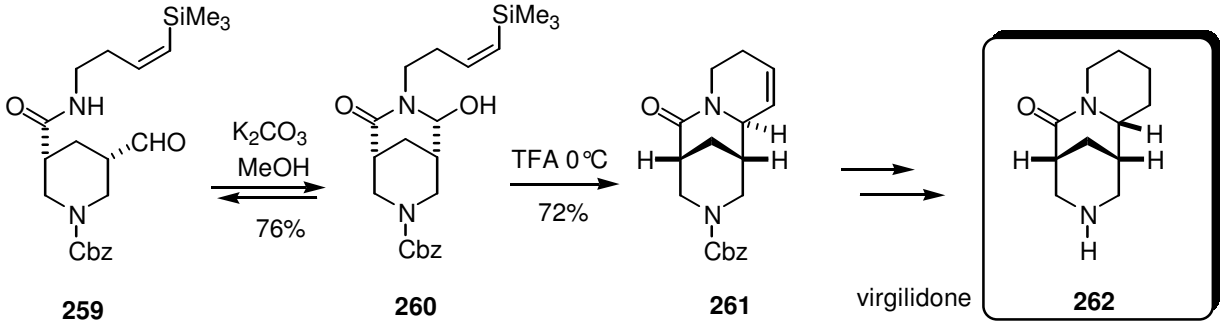
Bicyclic derivative **254** is treated with nitrous acid in the presence of CuCl to give α-methoxy derivative **255** that is allylated in the usual way to compound **256**. Tricyclic system **257** is obtained after few steps while further synthetic manipulations leads to (-)-norsecurinine **258.**



Scheme 53

Some related strategies have been used in a stereocontrolled synthesis of the BCD ring of sparteine analogues,[121] and in the preparation of azamide immunosuppressive drugs.[122]

Vinylsilanes of *Z* configurations and terminal alkynes tethered to a bicyclic structure are able to attack *N*-acyliminium ions giving a 6-*endo* ring closure. This approach allowed the preparation of quinolizidine alkaloid virgilidone (Scheme 54).[123] Aldehyde **259** is converted into α-hydroxylactam **260** and then cyclization occurs in trifluoroacetic acid (TFA) to give **261** as single diastereomer. Product **261** is then reduced to virgilidone **262** in 65% yield.

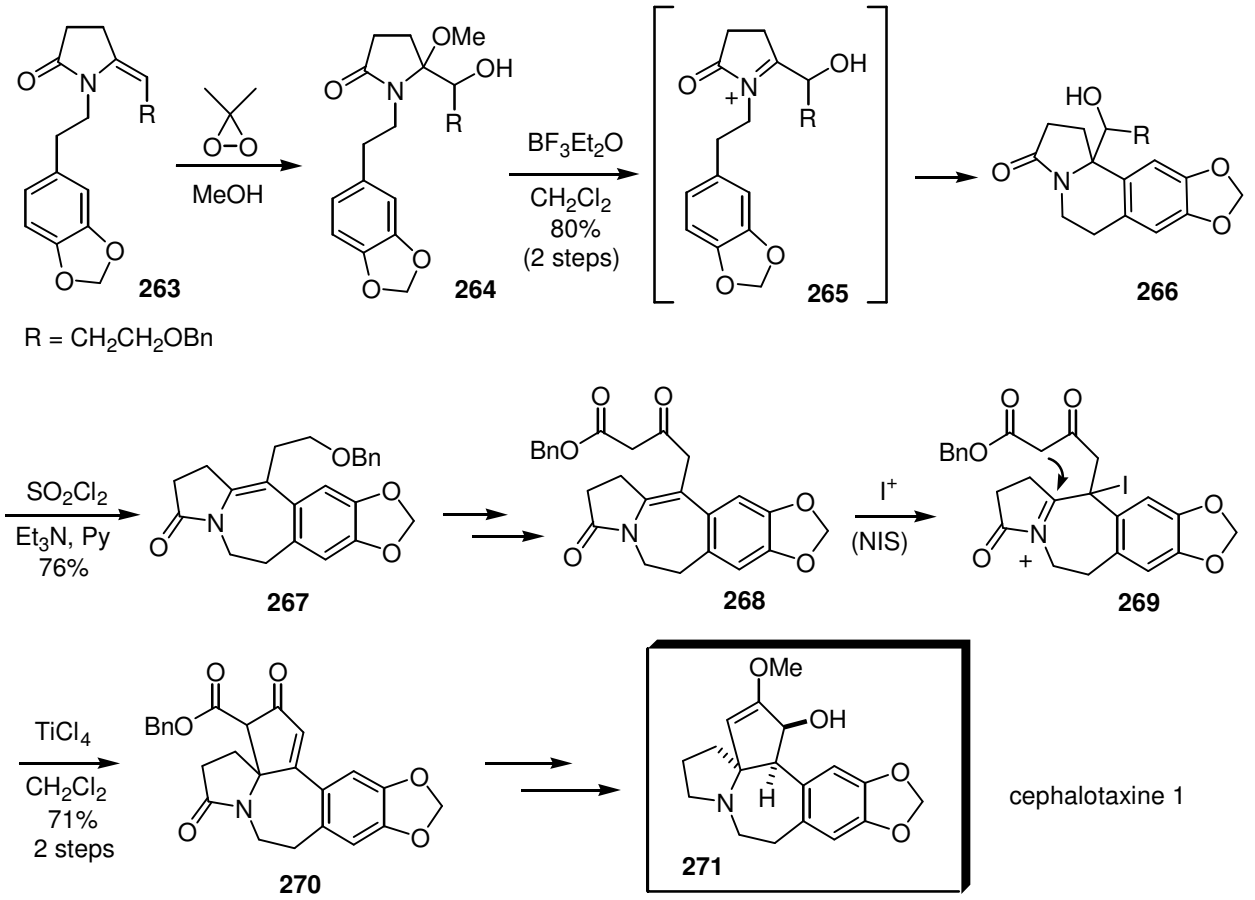


Scheme 54

3.8. Polycyclic systems

The chemistry of *N*-acyliminium ions has been often instrumental for the success of many synthetic procedures for the preparation of complex polycyclic molecules, expecially when an elevated degree of diastereoselection is needed.

Since the synthesis of polycyclic derivatives usually requires a consistent number of steps to go to completion it is possible that these iminium ions intermediates are generated sequentially during the whole process as in the case of the synthesis of Cephalotaxine, an antileukemic alkaloid from *Cephalotaxus* specie (Scheme 55).[124] Double bond hydroxylation of **263** with dimethyldioxirane gives methoxylated derivative **264** that is converted into tetrasubstituted *N*-acyliminium ion **265** using BF_3 Et_2O. Reactive iminium ion undergoes an intramolecular ring closure to give tetracyclic compound **266** and a subsequent ring expansion mediated by sulfuryl chloride affords compound **267**. After simple synthetic manipulations, β-keto ester **268** thus obtained is reacted with *N*-iodosuccinimide that provides an electrophilic source of iodine generating a second *N*-acyliminium ion **269**. This ion is attacked intramolecularly by the β-keto ester function allowing the assembling of the fifth ring of the pentacyclic structure **270**. This intermediate is then converted into cephalotoxin 1 **271** by means of few other synthetic steps.

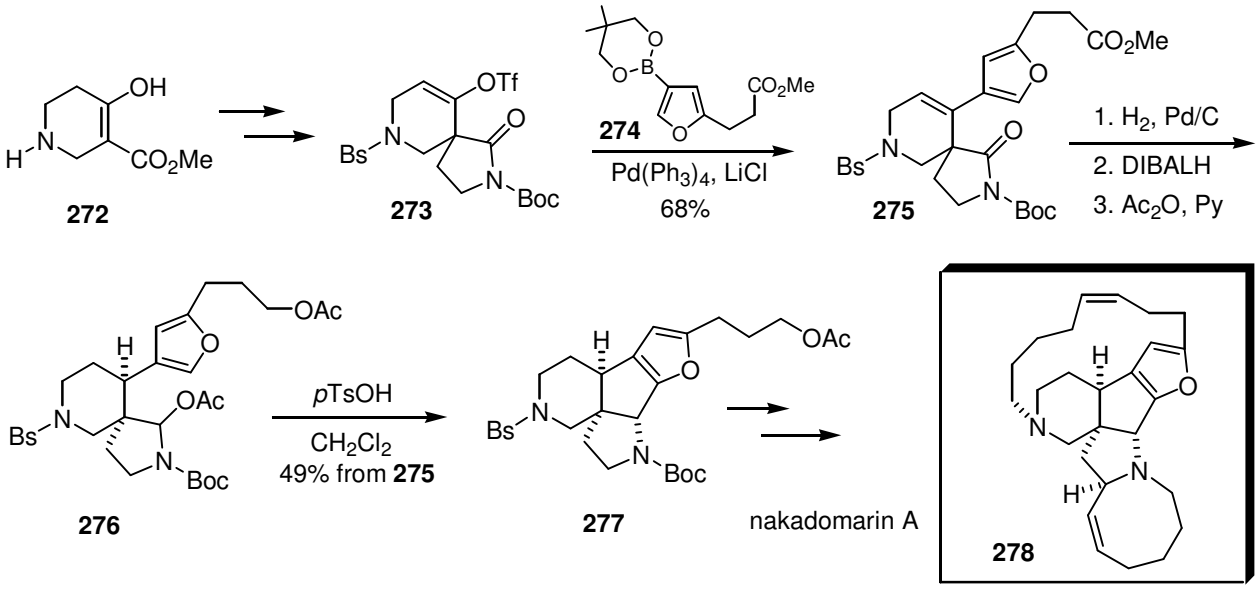


Scheme 55

A related procedure has been used for the synthesis of some tetracyclic structures that includes aromatic and heteroaromatic rings in the terminal part of the molecular framework.[125,126]

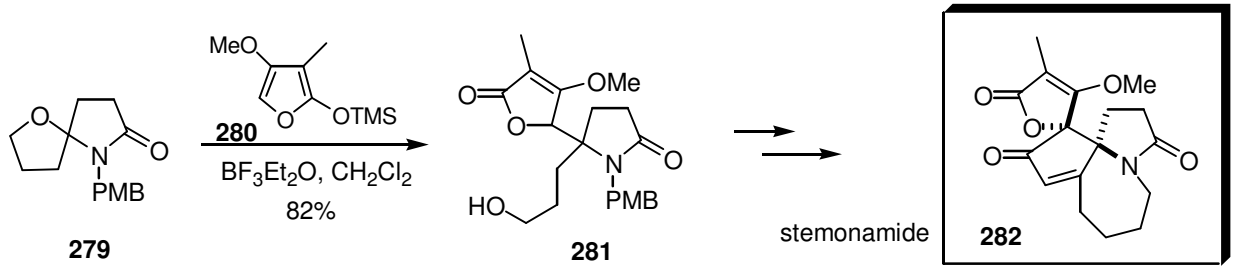
The high reactivity of the furan ring toward electrophilic substitutions makes this heterocyclic ring a good candidate for the reaction with *N*-acyliminium ions as illustrated for the synthesis of the central tetracyclic core of nakadomarin A. Spirocycle **273**, prepared from commercially available tetrahydropyridine **272** is coupled with boronic ester **274** in the presence of palladium complex (Scheme 56).[127]

After reduction of the double bond of compound **275** the lactam and the ester groups are reduced with DIBALH and acetylated to give derivative **276**. Simple treatment of **276** with *p*-TsOH in dichloromethane allows the intramolecular ring closure to give tetracyclic derivative **277**. This last intermediate can be converted into nakadomarin A **278** after several synthetic steps.



Scheme 56

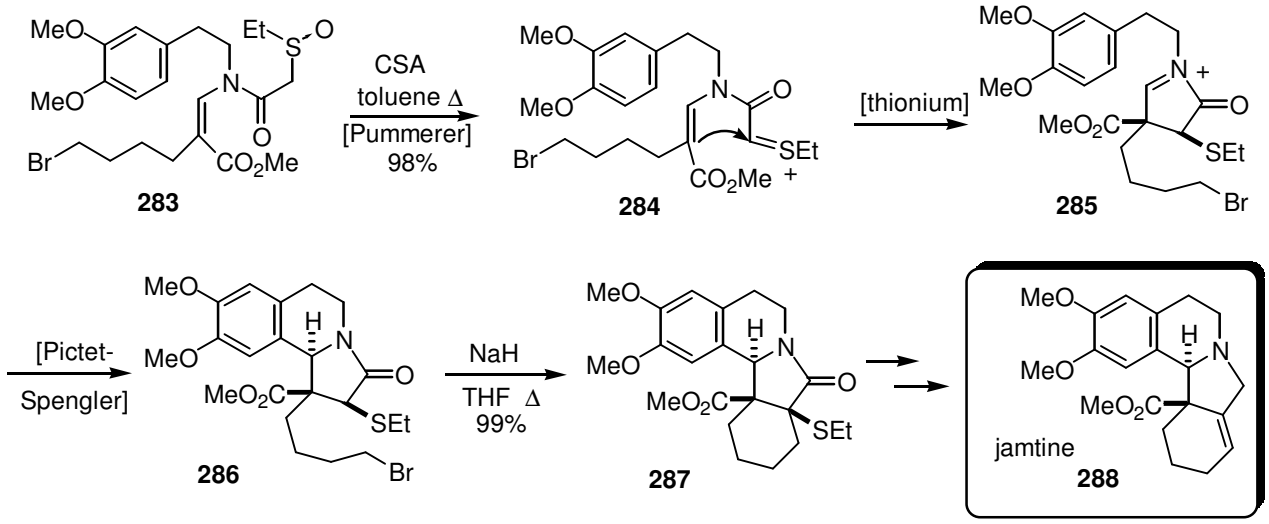
As previously described, 2-silyloxyfuran derivatives are syntetic equivalents of butenolide moieties in the reaction with electrophilic substrates. For the first total synthesis of stemonamide **282**, a tetracyclic alkaloid, Kende *et al.* have used as crucial step for the assembling of the first two units, the addition of silyloxy derivative **280** to lactam **279** (Scheme 57).[128] By this way it is possible to introduce in the molecular framework a densely functionalized structural entity.



Scheme 57

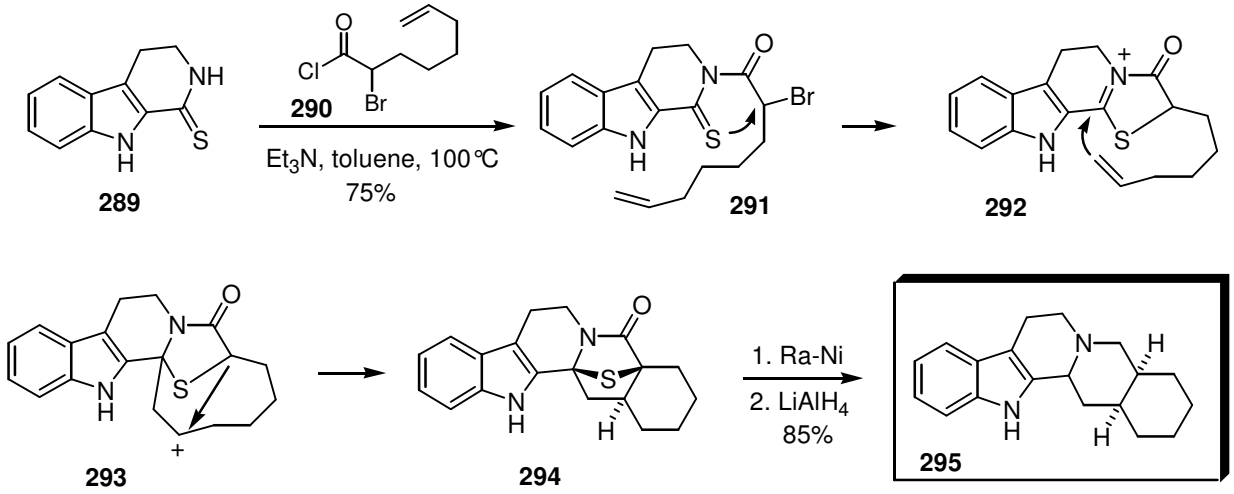
More than a single cationic intermediate can be involved in cascade processes that permit the assembling of complex structural systems with high diastereoselectivity.[129] For the total synthesis of jamtine **288**, Padwa and Danca have exploited a Pummerer/thionium/*N*-acyliminium ion (Pictet-Spengler) cascade process that leads to the preparation of a tricyclic intermediate in a single step (Scheme 58).[130] Heating sulfoxide **283** in the presence of camphorsulfonic acid (CSA) leads to thionium ion **284** *via* Pummerer

rearrangement followed by a ring closure that generated *N*-acyliminium ion **285**. This reactive intermediate gives tricyclic derivative **286** by means of a Pictet-Spengler process[131] and the fourth cycle is then introduced by a nucleophilic substution of an enolate anion to afford product **287**.



Scheme 58

A Pictet-Spengler reaction also constitutes the key step in the synthesis of azapolycyclic derivatives starting from thioamides. Reaction of thioamide **289** with acid chloride **290** produces the corresponding thioimide **291** that undergoes an intramolecular nucleophilic substitution of bromide by the sulfur atom thus creating the *N*-acyliminium ion **292** (Scheme 59).[132] Terminal double bond in **292** attacks the iminium ion and the resulting intermediate carbocation further cyclizes to polycyclic compound **294**. Sulfur bridge and carbonyl group can be removed by reductive methods affording pentacyclic derivative **295**.



Scheme 59

4. Conclusions

An increasing number of synthetic procedures directed toward the preparation of saturated nitrogen heterocycles make use of *N*-acyliminium ions as reactive intermediates. The success of *N*-acyliminium ions in synthesis is mainly due to the ease of their preparation coupled with the high reactivity displayed in the reaction with a large variety of nucleophiles including alkenes and enol derivatives. Intermolecular formation of carbon-carbon bonds is an efficient process that occurs in good yields and with variable diastereoselectivity, depending on the nature of the stereodirecting group and by the nucleophile employed. Intramolecular processes usually display a better diastereoselectivity and are often used for the assembling of architecturally complex polycyclic molecules.

Acknowledgments

Financial support from University of Camerino and MIUR (National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni") is gratefully acknowledged.

References

1. Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892.
2. Crosby, J. *Tetrahedron* **1991**, *47*, 4789–4846.
3. Crossley, R. *Tetrahedron* **1992**, *48*, 8155–8178.
4. Blaser, H.-U. *Chem Rev*. **1992**, *92*, 935–952.
5. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem Rev*. **1995**, *95*, 1677–1716.
6. Franklin, A. S.; Overman L. E. *Chem Rev.* **1996**, *96*, 505–522.
7. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
8. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
9. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946.
10. Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759–774.
11. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442–454.
12. Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; pp. 83–168.
13. Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131–184.
14. Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525–1534.
15. Zaugg, H. A. *Synthesis* **1984**, 85–110 and 181–212.
16. Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530–4535 and references cited therein.
17. Kise, N.; Ueda, N. *J. Org. Chem.* **1999**, *64*, 7511–7514.
18. Mecozzi, T.; Petrini, M. *Synlett* **2000**, 73–74.
19. Volkmann, R. A. In *Comprehensive Organic Synthesis ,* Schreiber, S. L. Ed. Pergamon: Oxford. Vol. 1, 1991, p. 355-396.
20. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.
21. Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221–3242.
22. Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904.
23. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817-3856.
24. De Koning, H.; Speckamp, W. N. *Stereoselective Synthesis (Houben-Weyl)*, Helmchen, G.; Hoffman, R. W.; Mulzer, J.; Shaumann, E.; Eds. Georg Thieme Verlag: Stuttgart, Vol. E21, 1995, p. 1953-2009.
25. Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis,* Heathcock, C. H. Ed. Pergamon: Oxford. Vol. 2, 1991, p. 1047-1082.
26. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367-4416.
27. D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854–3864.
28. Tomazela, D. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N.; D'Oca, M. G. M. *J. Org. Chem.* **2002**, *67*, 4652–4658.
29. Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311-1328.

30. Ostendorf, M.; Romagnoli, R.; Cabeza Pereiro, I.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773-1789.
31. Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165–3167.
32. Giardinà, A.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2000**, *65*, 8277–8282.
33. Marcantoni, E.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2002**, *67*, 2989–2994.
34. Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964.
35. Norton Matos, M. R. P.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron Lett.* **2001**, *42*, 7007–7010.
36. Cooke, J. W. B.; Berry, M. B.; Caine, D. M.; Cardwell, K. S.; Cook, J. S.; Hodgson, A. *J. Org. Chem.* **2001**, *66*, 334–336.
37. Boto, A.; Hernández, R.; de León, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796–7803.
38. Boto, A.; Hernández, R.; Suarez, E. *Tetrahedron Lett.* **2000**, *41*, 2495–2498.
39. Boto, A.; Hernández, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930–4937.
40. da Conceição, M.; de Oliveira, F.; Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995–6997.
41. Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176.
42. Suga, S.; Okajima, M.; Yoshida, J. *Tetrahedron Lett.* **2001**, *42*, 2173–2176.
43. Tomoka, K.; Nakazaki, A.; Nakai, T. *J. Am. Chem. Soc.* **2000**, *122*, 408–409.
44. van Maarseveen, J. H.; Meester, W. J. N.; Veerman, J. J. N.; Kruse, C. G.; Hermkens, P. H. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 994–1001.
45. Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731–5733.
46. de Armas, P.; Garcia-Tellado, F.; Marrero-Tellado, J. *J. Org. Lett.* **2000**, *2*, 3513–3515.
47. Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
48. Zhang, X.; Schmitt, A. C.; Jang, W. *Tetrahedron Lett.* **2001**, *42*, 5335–5338.
49. Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1–8.
50. Baussanne, I.; Chiaroni, A.; Husson, H.-P.; Riche, C.; Royer J. *Tetrahedron Lett.* **1994**, *35*, 3931–3934.
51. Baussanne, I.; Chiaroni, A.; Royer, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1219–1224.
52. Russowsky, D.; Petersen, R. Z.; Godoi, M. N.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 9939–9942.
53. Smith, III, A. B.; Friestad, G.; Barbosa, J.; Bertounesque, E.; Duan, J. J.-W.; Hull, K. G. Iwashima, M. M.; Qiu, Y.; Spoors, P. G.; Salvatore B. A. *J. Am. Chem. Soc.* **1999**, *121*, 10478–10486.
54. Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron Lett.* **2001**, *42*, 5901–5902.
55. Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115–124.
56. Bianchi, D. A.; Kaufman, T. S. *Synlett* **2000**, 801–804.
57. Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron.* **2000**, *57*, 5123–5130.
58. Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813.
59. Koulocheri, S. D.; Pitsinos, E. N.; Haroutounian, S. A. *Synthesis* **2002**, 111–115.
60. Adelbrecht, J.-C.; Craig, D.; Dymock, B. W.; Thorimbert, S. *Synlett* **2000**, 467–470.
61. Sakagami, H.; Ogasawara, K. *Synlett* **2001**, 45–48.
62. Comins, D. L.; Green, G. M. *Tetrahedron Lett.* **1999**, *40*, 217–218.
63. Comins, D. L.; Joseph, S. P.; Gohering, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728.
64. Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829–6832.
65. Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989–990.
66. Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823.
67. Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *Synlett* **2001**, 1225–1228.
68. Veerman, J. J. N.; Klein, J.; Aben, R. W. M.; Schereen, H. W.; Kruse, C. G.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2002**, 3133–3139.
69. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
70. Kibayashi, C.; Aoyagi, S. in *Studies in Natural Product Chemistry*, Atta-ur-Rahman Ed.; Elsevier Science B. V. 1997, vol. 19, pp. 3–88.
71. Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505–522.
72. Meyers, A. I.; Groaning, M. D. *J. Chem. Soc., Chem. Commun.* **2000**, 1027–1028.
73. Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 753–764.
74. Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605–5608.
75. Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 275–278.
76. McAlonan, H.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 5411–5414.

77. Kiewel, K.; Tallant, M.; Sulikowski, G. A. *Tetrahedron Lett.* **2001**, *42*, 6621–6623.
78. Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron Lett.* **2001**, *42*, 4617–4619
79. Yamazaki, N.; Itoh, T.; Kibayashi, C. *Org. Lett.* **2000***, 2*, 465–467.
80. Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469–2472.
81. Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193–196.
82. Pilli, R.; Zanotto, P.; Böckelmann, M. A. *Tetrahedron Lett.* **2001**, *42*, 7003–7005.
83. Batey, R. A.; MacKay, D. B. *Tetrahedron Lett.* **2000**, *41*, 9935–9938.
84. Huang, H.-L.; Sung, W.-H.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 6193–6196.
85. Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999–7001.
86. D'Oca, M. G. M.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709–9712.
87. Reichelt A.; Bur, S. K.; Martin, S. F. *Tetrahedron* **2002**, *58*, 6323–6328.
88. Zhang, X.; Jang, W.; Schmitt, A. C. *Tetrahedron Lett.* **2001**, *42*, 4943–4945.
89. Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113–10125.
90. Duan, S.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 6407–6415.
91. Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547–1550.
92. Tong, Y.; Fobian, Y. M; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484–2493.
93. Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4450–4452.
94. Ito, T.; Yamazaki, N.; Kibayashi, C. *Synlett* **2001**, 1506–1510.
95. Maldaner, A. O.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 7843–7846.
96. Lennartz, M.; Steckhan, E. *Synlett* **2000**, 319–322.
97. Neipp, C. E.; Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779–1782.
98. Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972.
99. Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T. Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317–8325.
100. Ostendorf, M.; van der Neut, S.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 105–113.
101. Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2001**, *66*, 3167–3175.
102. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6993.
103. Hanessian, S.; Buckle, R.; Bayrakdarian, M. *J. Org. Chem.* **2002**, *67*, 3387–3397.
104. Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, *3*, 1141–1144.
105. Tanaka, H.; Tanaka, T.; Etoh, H.; Goto, S.; Terada, Y. *Heterocycles* **1999**, *51*, 2759–2764.
106. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1715–1721.
107. Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D.; Elsegood, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3029–3036.
108. Garcia, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2001**, *42*, 1511–1513
109. Katritzky, A. R.; Metha, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148–152.
110. Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Synlett* **2000**, 101–103.
111. Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2001**, 1267–1277.
112. Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235–244.
113. Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159–10173.
114. Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507–3510.
115. Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.***2002**, *67*, 4337–4345.
116. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3017–3020.
117. Simpkins, N. S. *Sulphones in Organic Synthesis*, Pergamon Press: Oxford, 1993.
118. David. M.; Dhimane, H.; Vanucci-Baqué, C.; Lhommet, G. *Heterocycles* **2001**, *55*, 941–949.
119. Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 237–240.
120. Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.***2000**, *65*, 6293–6306.
121. Harrison, J. R.; O'Brien, P. *Tetrahedron Lett.* **2000**, *41*, 6167–6170.
122. Guo, C.; Reich, S.; Showalter, R.; Villafranca, E.; Dong, L. N. *Tetrahedron Lett.* **2000**, *41*, 5307–5311.

123. Consonni, A.; Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Silvani, A. *Eur. J. Org. Chem.* **2001**, 1371–1383.
124. Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885–888.
125. Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1446–1451.
126. Lee, J. Y.; Baek, N. J.; Lee, S. J.; Park, H.; Lee, Y. S. *Heterocycles* **2001**, *55*, 1519–1526.
127. Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett,* **2001**, *42*, 8345–8349.
128. Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505–2508.
129. Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S.; Wang, Q. *J. Org. Chem.* **2002**, *67*, 2684–2695.
130. Padwa, A.; Danca, M, D. *Org. Lett.* **2002**, *4*, 715–717.
131. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
132. Padwa, A.; Beall, L.S.; Heidelbaugh, T. M.; Liu, B.;Sheehan, S.M. *J. Org. Chem.* **2000**, *65*, 2684–2695.

REDUCTIVE OPENING OF HETEROCYCLES WITH LITHIUM METAL AS A SOURCE OF FUNCTIONALISED ORGANOLITHIUM COMPOUNDS: SYNTHETIC APPLICATIONS

Miguel Yus* and Francisco Foubelo*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain (e-mail: yus@ua.es)

Abstract. *Different heterocycles (strained heterocycles and heterocycles with allylic and benzylic carbon-heteroatom bonds) can be opened reductively by treatment with lithium metal itself or in the presence of a stoichiometric or catalytic amount of an arene to give functionalised organolithium compounds which, by reaction with electrophiles lead to the formation of polyfunctionalised molecules in a direct manner.*

Contents

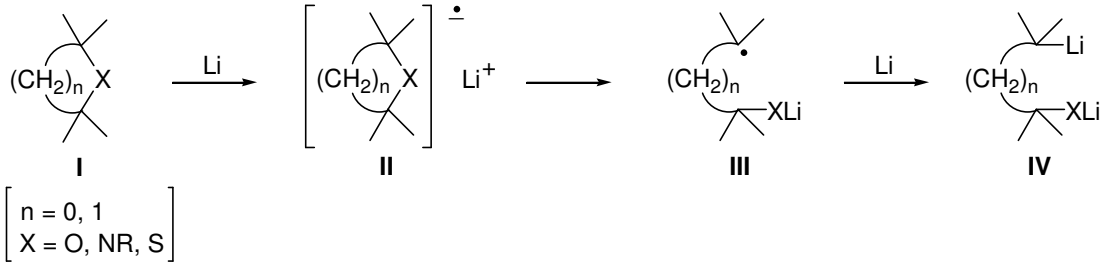
1. Introduction

Functionalised organolithium compounds[1] are of interest in synthetic organic chemistry because polyfunctionalised molecules are obtained in only one step by reaction with electrophilic reagents.[2] Due to the high reactivity of the organolithium compounds, these processes can be carried out under very mild reaction conditions. Functionalised organolithium compounds can be prepared by halogen-lithium exchange, metal-lithium exchange, direct deprotonation, addition of organolithium compounds to unsaturated systems,[1,3] and probably one of the most elegant and direct strategies consists in the reductive opening of different appropriate oxygen-, nitrogen- and sulfur-containing heterocycles.[4] Since most functionalised organolithium compounds are very unstable molecules, they have to be prepared at low temperature in order to avoid their decomposition.[5] For that purpose, in the last few years a methodology consisting in the use of

an excess of lithium in the presence of a catalytic amount of an arene has been developed as lithiating agent,[6] naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most commonly used.[7] More recently, polymer supported naphthalene, biphenyl[8] and also polyphenylene[9] have been used as electron transfer reagents in these processes.[10] Some requirements should be accomplished in order to get the reductive opening of a heterocycle: (a) Small heterocycles (three and four membered-rings) due to a release of strain energy[4] and (b) heterocycles with activated bonds that can be reductively broken by means of the lithiating reagent, as in the case of compounds with allylic[11] and benzylic[12] carbon-heteroatom bonds as well as cyclic aryl ethers[13] and thioethers.[14] In this review, which updates our previous review,[4] we will consider the reductive opening of different heterocycles and the synthetic application of the resulting functionalised organolithium compounds.

2. Reductive opening of strained heterocycles

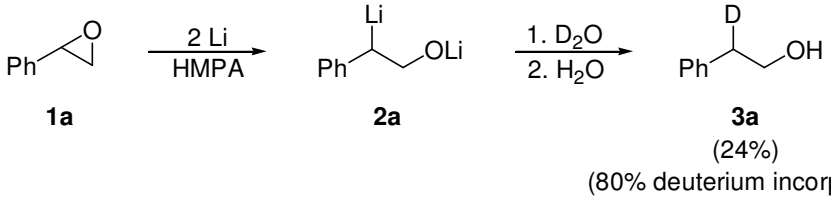
The mechanism of strained heterocycles reductive opening with lithium metal, or other alkali metals, by stepwise electron transfer is less well understood than that of nucloephilic ring opening by means of a hydride ion.[15] In the proposed mechanism an initial single-electron transfer (SET) from the metal to the hetorocycle **I** takes place. The radical anion formed **II** suffers carbon-heteroatom bond scission to generate a new radical anion **III**. The late radical anion, which is very unstable, among other process can be further reduced to a dianion **IV** (Scheme 1). In the case of non symmetrically substituted heterocycles, two possible reductive opening products could be obtained, in most cases being one of them predominant, playing an important role the nature of the alkali metal and the solvent.[16]



Scheme 1

2.1. Reductive opening of epoxides

Kaiser *et al.* reported in 1971 that the treatment of aromatic epoxides with alkali metals in liquid ammonia led to isomerically pure less substituted alcohols.[17] However, in the case of aliphatic epoxides, the most substituted alcohols were obtained by treatment with lithium in ethylenediamine.[18]

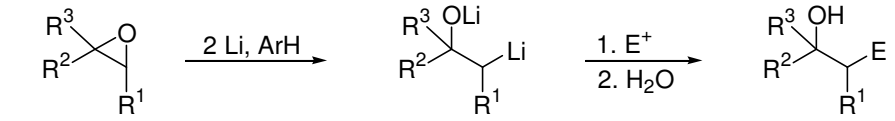


Scheme 2

In both cases, the reductive opening of epoxides takes place through the most stable of the two possible carbanions. In the case of styrene oxide (**1a**), reductive opening by treatment with two equivalents

of lithium in HMPA-diethyl ether followed by addition of deuterium oxide afforded 2-deuterio-2-phenylethanol (**3a**) (Scheme 2).[17] This result is a proof of that β–functionalised organolithium compounds of type **2** are involved as reaction intermediates. These dianionic intermediates have also been prepared by deprotonation of β–hydroxymercurials followed by mercury-lithium transmetallation[19] and by deprotonation of β–chlorohydrins followed by lithiation with lithium naphthalenide.[20] In the case of using a chiral chlorohydrin, non-racemic β–functionalised organolithium compounds can be obtained.[21]

In 1986 Bartmann developed a methodology which allowed the preparation and characterisation of dianions **2** in reasonable yields by reductive opening of epoxides, using lithium metal and a stoichiometric amount of an arene (biphenyl and naphthalene), and their reaction with electrophiles to explore the synthetic application of intermediates **2**.[22] The process did not take place with lithium itself at low temperature (around –90 ºC) and it should be performed in the presence of an arene which acts as an electron carrier. Low temperature is necessary in order to prevent decomposition. Regarding the regioselectivity of the ring opening process for monosubstituted epoxides, in all cases only one regioisomer was detected after reaction with electrophiles. The most substituted carbanion is obtained when a phenyl or ester group is the substituent, but for alkyl substituents, the cleavage of the carbon-oxygen bond leading to the primary alkyl anion, which is more stable than a secondary one, takes place. These results can be explained either by assuming a stabilizing effect of the substituents during the formation of the carbanion or by considering the stability of the two possible radical anions initially formed after the ring opening.[23] In all cases better yields were obtained by addition of lithium bromide (Scheme 3).



1a; R^1 = Ph, R^2 = R^3 = H
1b; R^1 = R^2 = H, R^3 = Me
1c; R^1 = R^2 = H, R^3 = Et
1d; R^1 = H, R^2 = R^3 = Me
1e; R^1-R^2 = $(CH_2)_4$, R^3 = H
1f; R^1=R^2 = Et, R^3 = H
1g; R^1 = CO_2Et, R^2 = R^3 = H

2

3
(31-70%)

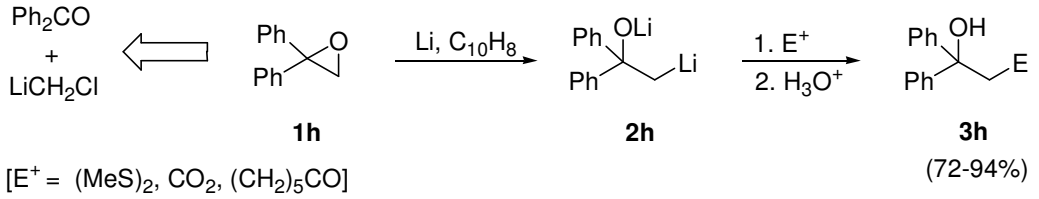
[ArH = $C_{10}H_8$, Ph_2
E^+ = H_2O, D_2O, $(MeS)_2$, $(PhS)_2$, MeI]

Scheme 3

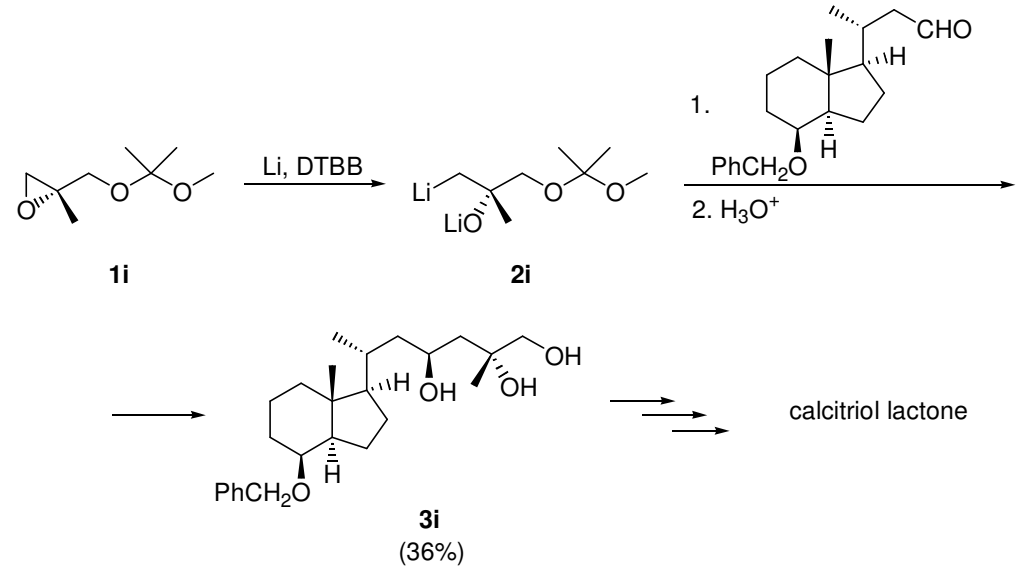
Starting epoxides can be prepared following different methodologies. The reaction of a carbonyl compound with *in situ* generated chloromethyllithium at –78 ºC to room temperature yields after cyclisation the corresponding epoxides,[24] which by reaction with lithium naphthalenide at –78 ºC undergoes reductive opening. Reaction with different electrophiles followed by final acidic hydrolysis leads to functionalised alcohols **3h** (Scheme 4).[25]

Reductive opening of enantiomerically pure epoxides, which can be easily prepared from natural occurring hydroxy acids or by epoxidation of allylic alcohols,[26] yields chiral dianions of type **IV** (X = O, n =

0, Scheme 1). The latter strategy has been employed in one of the steps of the synthesis of calcitriol lactone,[27] lithium di-*tert*-butylbiphenylide being used as lithiating reagent of chiral epoxide **1i** (Scheme 5).

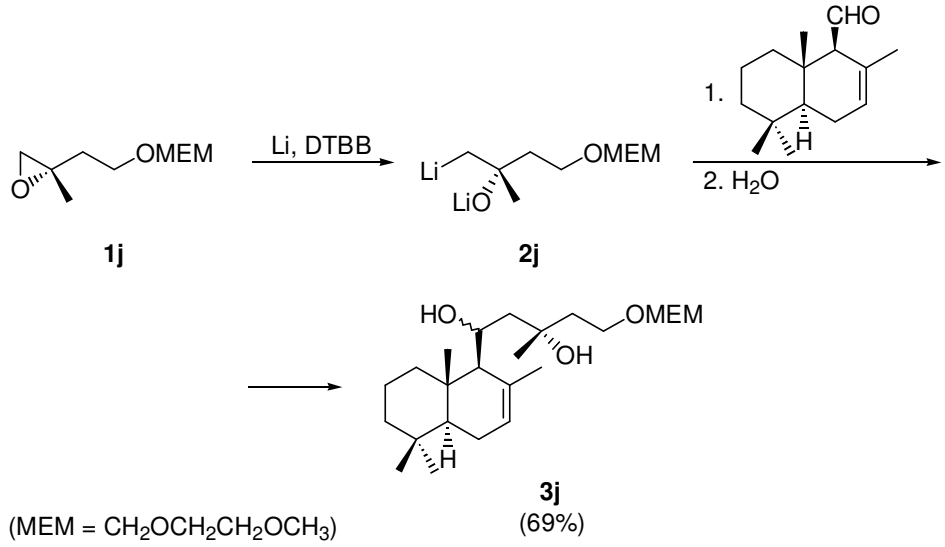


Scheme 4



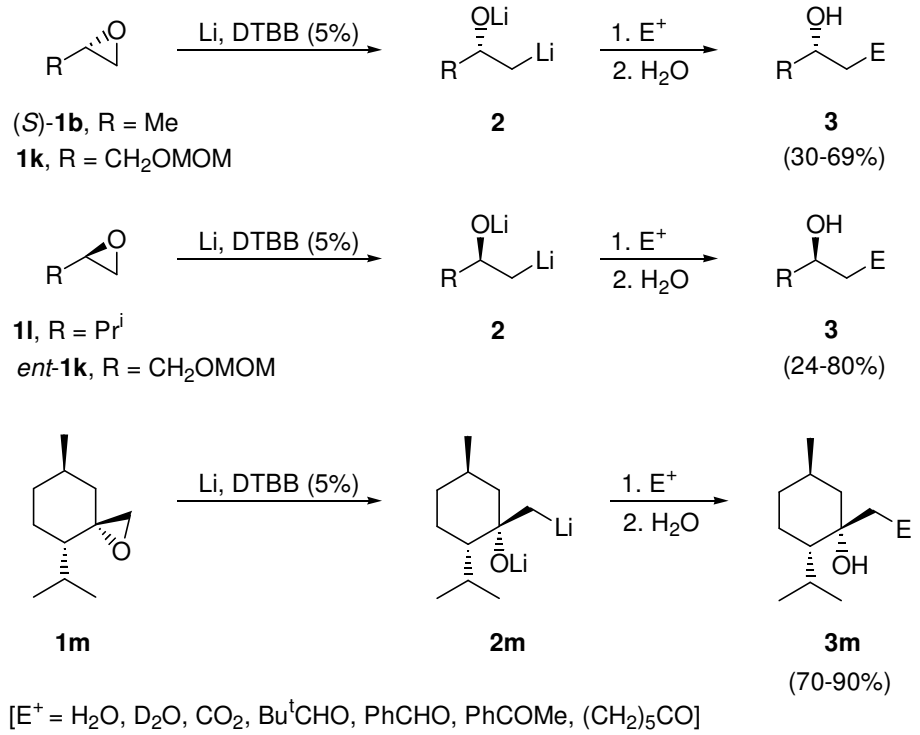
Scheme 5

Same reaction conditions have been applied to the synthesis of an advanced forskolin intermediate **3j**. Reductive opening at –78 °C of an optically active epoxide **1j** to give dianionic intermediate **2j** and reaction with drimenal gives compound **3j** after hydrolysis (Scheme 6).[28]



Scheme 6

The use of carbonyl compounds and carbon dioxide as electrophiles reacting with these chiral intermediates are of great interest because, 1,3-diols and β-hydroxy acids can be prepared in enantiomerically pure form. The reductive opening of commercially available (*S*)-**1b** or easily available chiral epoxides [**1k**, *ent*-**1k**, **1l**, **1m**] with an excess of lithium and a catalytic amount of DTBB at –78 °C gives the corresponding dianionic intermediates **2**, which by reaction with several electrophiles followed by hydrolysis with water afford products **3** (Scheme 7).[29] In the case of using prostereogenic carbonyl compounds as electrophiles, an almost 1:1 mixture of diasteromers is obtained, which could be easily separated by flash chromatography.

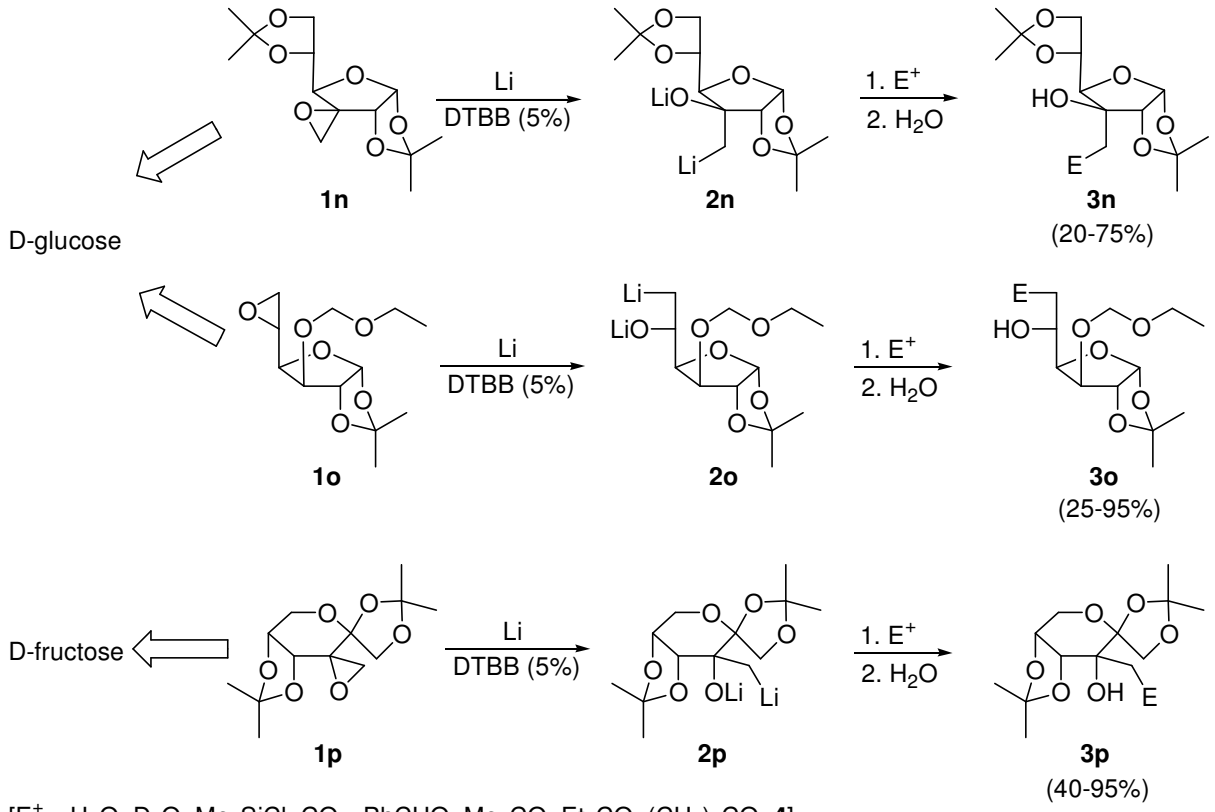


Scheme 7

The above mentioned methodology has been applied to the synthesis of branched-chain modified carbohydrates, which are glycosidic components of many antibiotics.[30] Thus, DTBB-catalysed lithiation of epoxide **1n**, easily prepared from D-glucose, yields intermediate **2n**, which reacts with different electrophiles to give, after hydrolysis, compounds **3n**. These compounds are 3-*C*-substituted D-allose derivatives (Scheme 8).[31] Another epoxide **1o** was also easily prepared from D-glucose and submitted to the same reaction conditions as for compound **1n**, thus the expected products **3o**, 6-*C*-substituted-3-deoxy-D-glucose derivatives, are isolated through the intermediate **2o** (Scheme 8).[32] For the D-fructose derivative **1p**, a DTBB-catalysed lithiation followed by reaction with electrophiles and final hydrolysis yields 3-*C*-substituted-D-psicose derivatives **3p** (Scheme 8). The reaction of intermediate **2p** with ketone **4** (derived from D-fructose) affords C_2-symmetrical disaccharide **3pa** in low yield (Figure 1).[32]

Methodologies to modify selectively the structure of steroids are also of interest and welcome because minor changes in their structure cause extensive changes in their biological activity. Reductive opening of epoxides derived from steroids, such as estrone derivative **1q** and cholestanone derivative **1r**, by a DTBB-catalysed lithiation followed by reaction with electrophiles and final hydrolysis gives 17α-

substituted-17β-estradiol derivatives **3q** and 3β-substituted-3α-cholestanol derivatives **3r**, respectively, through organolithium compounds **2q** and **2r** (Scheme 9).[33,34]



Scheme 8

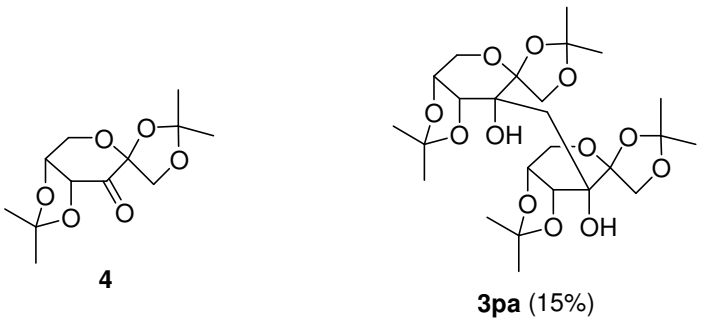
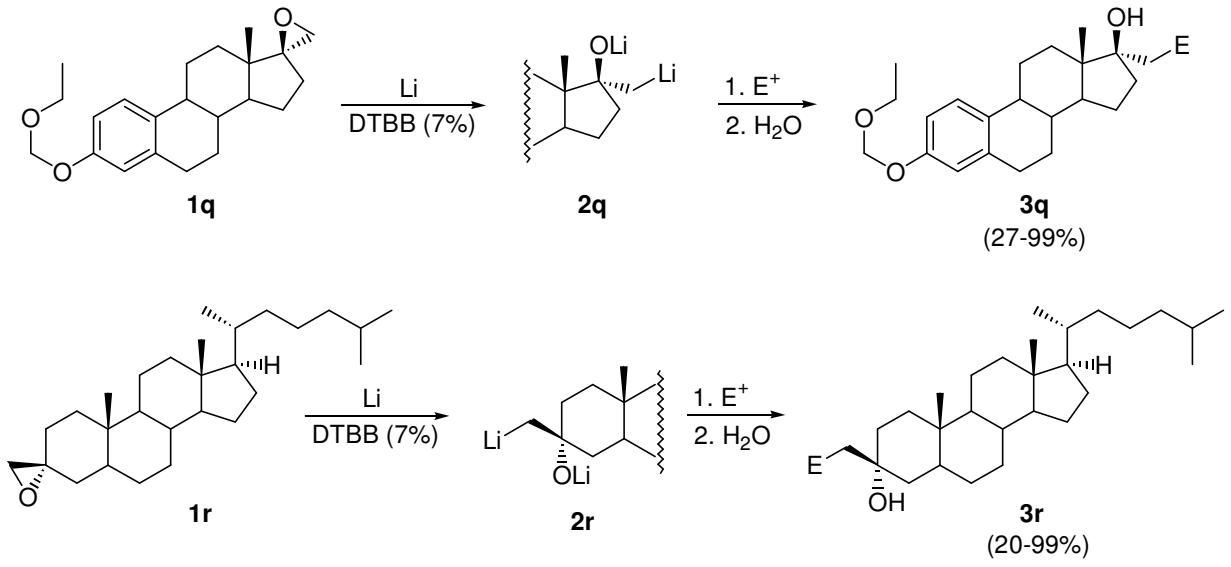


Figure 1

When keto sugars **4** (Figure 1) and **5** (D-glucose derivative, Figure 2) are used as electrophiles, in the case of the estrone derivative **1q**, mixed products **3qa**,**b**, having both a steroid and a sugar fragment, are obtained (Figure 2).[34] Finally, the reaction of intermediate **2q** with *O*-protected estrone **6** gave, after hydrolysis the expected C_2-symmetrical steroid dimer **3qc** (Figure 2).[34]

2.2. Reductive opening of aziridines

Triphenyl aziridine **7a** undergoes reductive opening by treatment with sodium in liquid ammonia to give *N*-(1,2-diphenylethyl)aniline (**9a**). However, a dianionic specie of type **IV** (Y = NPh, n = 0, Scheme 1), which is supposed to be the reaction intermediate, could neither be isolated nor used synthetically (Scheme 10).[17]



[$E^+ = H_2O$, D_2O, CO_2, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, **4**, **5**, **6**]

Scheme 9

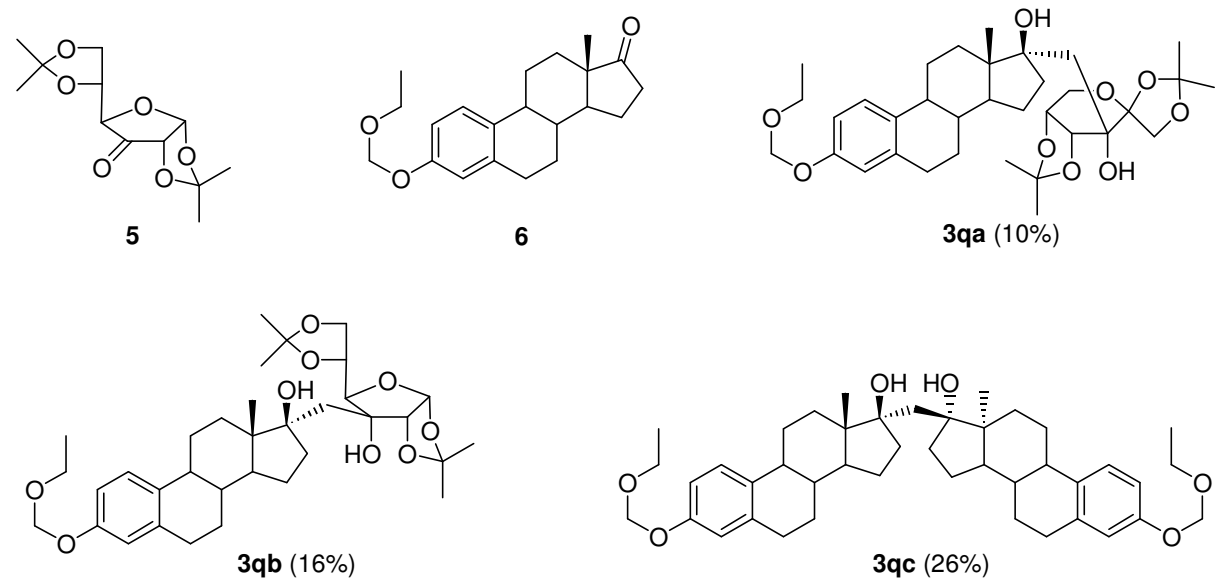
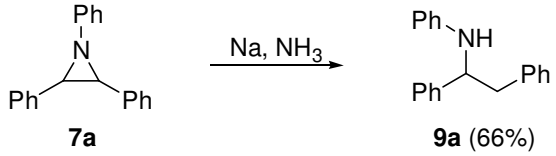


Figure 2

Stamm and co-workers studied also the reductive opening of the so-called activated aziridines (*N*-carbonyl or *N*-sulphonyl derivatives), using anthracene hydride or the xanthenyl anion as reducing reagents. After a single electron transfer (SET) from the reducing reagent, a ketyl intermediate is formed, which undergoes ring cleavage (carbon-nitrogen bond) to generate a new radical anion.

The latter radical anion decomposes mainly by both homo or cross combination leading to a mixture of reaction products. The metal accompanying the reducing reagents and the subtituents in the aziridine rings plays an important role in the structure of the reaction products.[35] Aziridine-2-carboxylate can be also reductively opened by means of a palladium catalyst. The process can be performed in a regioselective manner, thus the catalytic hydrogenation by Pd/EtOH leads to carbon(2)-nitrogen cleavage[36] and the catalytic transfer hydrogenation with $Pd/HCO_2H/EtOH$ leads to carbon(3)-nitrogen cleavage.[37] More recently, Pak *et al.* reported the regioselective reductive cleavage of aziridines substituted with an electron

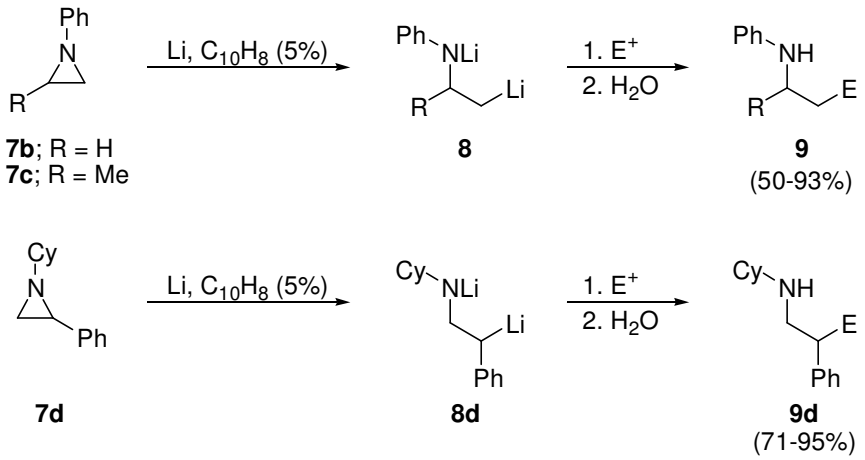
acceptor group with magnesium in methanol, ketyls being the reaction intermediates, which undergo the cleavage.[38] Functionalised organolithium intermediates, which are the targets of this review, are not involved as reaction intermediates in all these processes.



7a **9a** (66%)

Scheme 10

Lithioarenes are not reactive enough to open reductively aziridines at low temperatures under the reaction conditions necessary to prevent decomposition of the dianionic resulting intermediates **8**. However, the use of an excess of lithium in the presence of a catalytic amount of an arene is an effective lithiation mixture for these aziridines. Treatment of aziridines **7b**-**d** under these reactions conditions at –78 °C gave intermediates **8**, which reacted with different electrophiles and after final hydrolysis led to functionalised amines **9** (Scheme 11).[39,40]



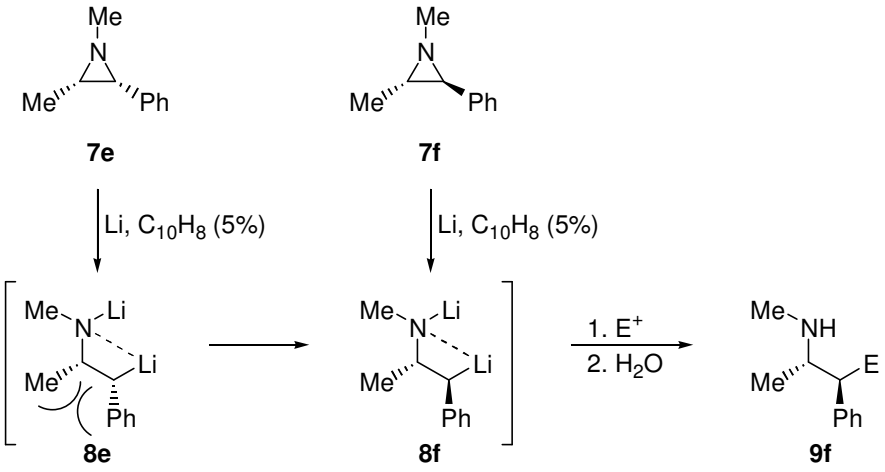
[$E^+ = H_2O$, D_2O, $(MeS)_2$, MeI, $CH_2{=}CHCH_2Br$, Bu^tCHO, PhCHO, $CH_2{=}CHCO_2Et$, $(EtO)_2CO$, $PhCON(CH_2)_4$, PhCH=NPh]

Scheme 11

Concerning the regiochemistry of the process for non symmetrically substituted aziridines (**7c** and **7d**), the ring opening leads in general to the formation of the most stable β-nitrogenofunctionalised organolithium compound, such as primary carbanionic derivative **8c** or benzylic dilithioderivative **8d** (Scheme 11). In the case of *N*-phenyl-2-methylaziridine (**7c**), *N*-propylaniline was always a side-reaction product with less than 15% yield. This indicates that the other possible reductive opening process, leading to the less stable secondary dilithium derivative that abstracts a proton from the reaction medium took also place to a small extent.

Starting from chiral aziridines and applying the above mentioned procedure it is possible to prepare enantiomerically pure functionalised amines. Thus, when aziridines **7e** and **7f** are submitted to a naphthalene-catalysed lithiation followed by reaction with electrophiles and final hydrolysis with water, only one reaction product **9f** is isolated, independently of the starting aziridine.[39] These results can be rationalised

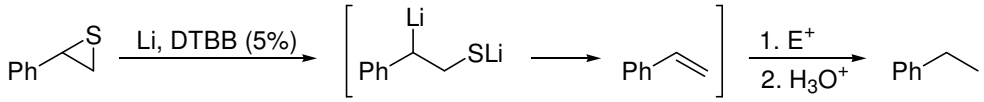
assuming that initially formed benzylic dianionic species **8e** from **7e**, undergoes epimerization to the less-hindered intermediate **8f**, which is the same that results for reductive opening of **7f** (Scheme 12). The starting aziridines **7e** and **7f** were easily prepared from (-)-ephedrine by tandem chlorination-intramolecular cyclisation and using a Mitsunobu-type reaction, respectively.



[E^+ = H_2O, D_2O, CH_2=$CHCH_2Br$, Me_2CO, (c-C_3H_5)$_2CO$]

Scheme 12

Following with this systematic study on the reductive ring opening of three-membered heterocycles, reductive opening of thiiranes could not be applied to the preparation of β–thiofunctionalised organolithium compounds. Thiiranes are easily available from epoxides upon treatment with thiourea in chloroform.[41]



[E^+ = H_2O, Bu^tCHO, PhCHO]

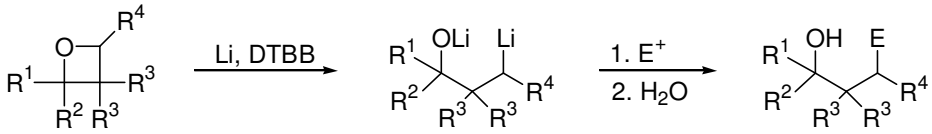
Scheme 13

In the case of phenylthiirane (**10**), a DTBB-catalysed lithiation followed by reaction with electrophiles and final hydrolysis with water at –78 °C, leads to ethyl benzene **13** as the major reaction product (Scheme 13). The lithiation can be performed also under Barbier-type conditions (lithiation in the presence of the electrophile) but the expected functionalised thiol has never been isolated.[42] An explanation for these results is that the initially formed highly reactive dianionic derivative **11** undergoes β-elimination leading to styrene **12**, even at –78 °C and, after hydrolysis in the reductive medium, the conjugate double bond is hydrogenated to ethylbenzene **13**.

2.3. Reductive opening of oxetanes

Cohen *et al.* reported for the first time in 1989 on the reductive opening of oxetanes.[43] Thus, treatment of oxetanes **14** with lithium and a stoichiometric amount of DTBB in THF at 0 °C gave dianionic species **15**, which by reaction with electrophiles and final hydrolysis yielded functionalised alcohols **16** (Scheme 14). The main difference compared to oxiranes is the reaction temperature, because β–oxidofunctionalised organolithium compounds **2** should be prepared at –78 °C in order to avoid

decomposition, meanwhile the corresponding γ-functionalised ones **15** are stable even at room temperature. These species have also been prepared from γ-chlorohydrines through a chlorine-lithium exchange previous deprotonation.[21] Regarding the regiochemistry of the process for unsymmetrical substituted oxetanes, reductive opening takes place always to give the most stable organolithium compound **15**, which are the less substituted (such as **15c**) or the benzyl substituted (**15d**) (Scheme 14).



14a; $R^1 = R^2 = R^3 = R^4 = H$
14b; $R^1 = R^2 = R^4 = H$, $R^3 = Me$
14c; R^1-$R^2 = (CH_2)_5$, $R^3 = R^4 = H$
14d; $R^1 = R^2 = R^3 = H$, $R^4 = Ph$

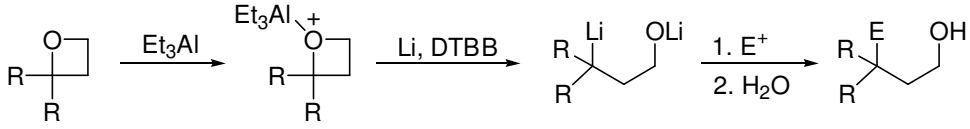
15

16
(45-87%)

[$E^+ = CO_2$, CH_2=CHCHO, (*E*)-PhSCH=CHCHO, *p*-$MeOC_6H_4CHO$, $(CH_2)_5CO$]

Scheme 14

When reductive opening of unsymmetrical oxetanes takes place in the presence of a Lewis acid such as $AlEt_3$, the regiochemistry of the ring cleavage is the opposite as that commented above. In this case lithiation should be performed in the presence of a stoichiometric amount of DTBB in THF at –78 °C, this strategy being complementary to the former one (Scheme 15).[44]



14c; R-R = $(CH_2)_5$
14e; R = Me

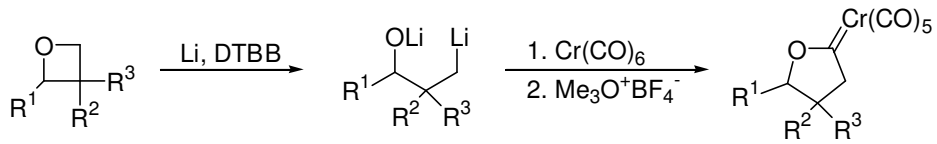
15

16
(38-68%)

[E^+ = Pr^iCHO, Bu^tCHO, (*E*)-MeCH=CHCHO, PhCHO, $(CH_2)_5CO$]

Scheme 15

The above shown methodology has found wide application in organic synthesis. For instance, the reaction of carbonyl compounds with intermediates **15** gives 1,4-diols which under acidic conditions undergo cyclisation leading to tetrahydrofurans.



14a; $R^1 = R^2 = R^3 = H$
14b; $R^1 = H$, $R^2 = R^3 = Me$
14f; $R^1 = Me$, $R^2 = R^3 = H$
14g; $R^1 = H$, $R^2 = CH_2OH$, $R^3 = Me$
14h; $R^1 = H$, $R^2 = Pr^n$, $R^3 = Me$
14i; $R^1 = H$, $R^2 = Bu^n$, $R^3 = Me$

15

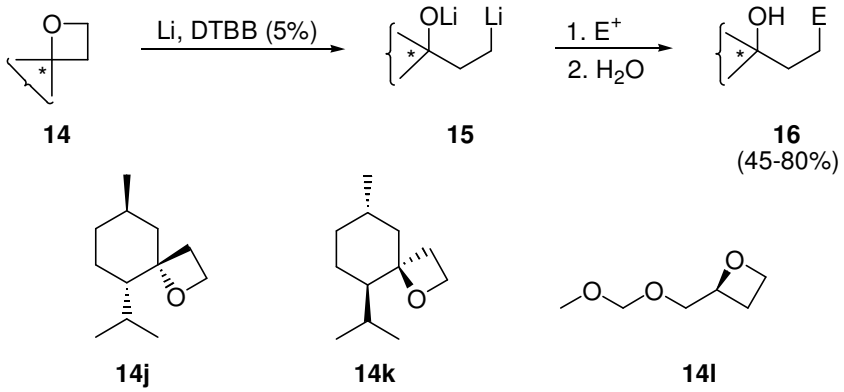
17
(14-53%)

Scheme 16

In the case of using lactones as electrophiles in the presence of cerium trichloride, spiroketals are obtained after acidic work-up.[45] Also cyclic Fischer-type chromium carbene complexes **17** have been prepared when hexacarbonyl chromium was added first, followed by treatment with trimethyloxonium tetrafluoroborate (Scheme 16).[46]

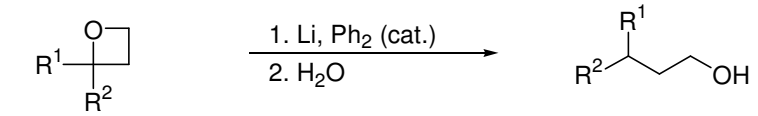
Enantiomerically pure functionalised alcohols **16** are obtained from chiral oxetanes **14j**-**l** when the reductive opening is performed with lithium and a substoichiometric amount of DTBB in THF at 0 °C, followed by reaction with electrophiles and final hydrolysis with water (Scheme 17).[47]

The reaction with prostereogenic carbonyl compounds as electrophiles gives an almost 1:1 mixture of diastereoisomers, which are easily separated by column chromatography, so enantiomerically pure diastereoisomers are obtained. Starting chiral oxetanes can be prepared from double methylenation of ketones or by methylenation of epoxides with trimethylsulfonium ylide.[48] Oxetanes **14j** and **14k** were prepared from (-)- and (+)-menthone, respectively, and oxetane **14l** was prepared from commercially available (-)-glycidol.



Scheme 17

Recently Rama and Pasha found that lithium in the presence of biphenyl (catalytic amount) under refluxing THF is capable of inducing the oxetanes **14** to undergo regiospecific ring opening leading exclusively to the formation of terminal alcohols **16**, under aprotic conditions, in almost quantitative yield (Scheme 18).[49] On the contrary internal alcohols are obtained when metallic hydrides are used as nucleophiles. In this process dianionic species of type **IV** (X = O, n = 1, Scheme 1) have been neither characterised nor proposed as reaction intermediates.

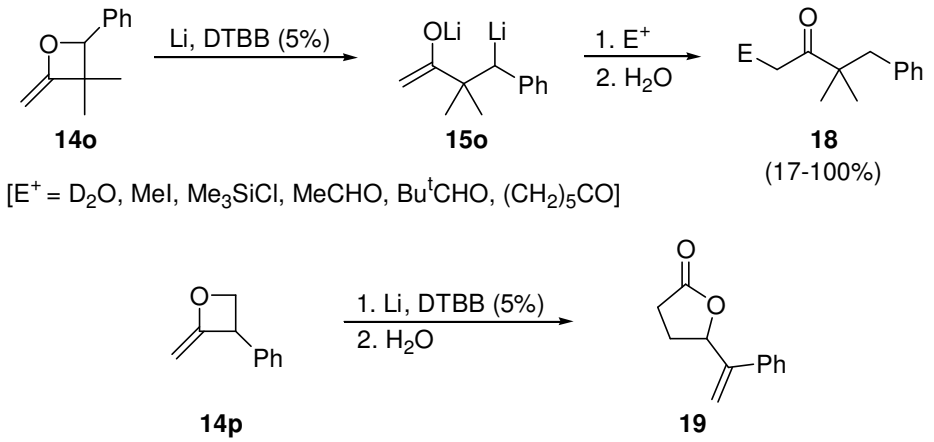


14c; R^1-R^2 = $(CH_2)_5$
14d; R^1 = Ph, R^2 = H
14m; R^1 = Me, R^2 = Ph
14n; R^1 = R^2 = Ph

Scheme 18

The reductive cleavage of 2-methyleneoxetanes has been study by Howell and Hashemzadeh. In the case of 3,3-dimethyl-2-methylene-4-phenyloxetane **14o**, it undergoes reductive opening with lithium and a catalytic amount of DTBB at temperatures ranging from –78 to 0 °C to give the dianionic intermediate **15o**, which reacts regioselectively with aldehydes and ketones to give aldol adducts **18** in variable yields (Scheme 19).[50]

However, under the same reaction conditions, 2-methylene-3-phenyloxetane **14p** gave unexpected lactone **19** with 84% yield (Scheme 19).[51] It is postulate that **19** arises from a coupling of a radical enolate derived from **14p** and the enolate of acetaldehyde, a product of THF decomposition under the reaction conditions.

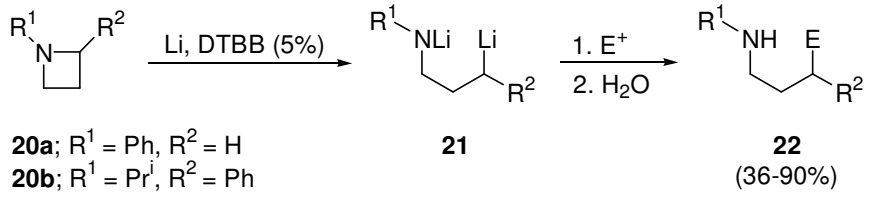


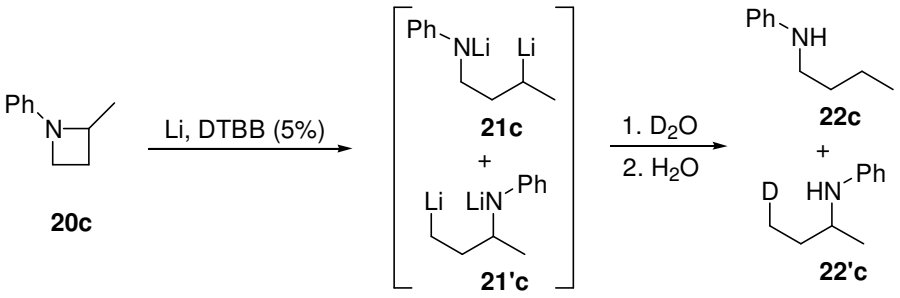
Scheme 19

2.4. Reductive opening of azetidines

Azetidines **20** are less reactive than aziridines **7** toward the reductive opening with excess of lithium and a catalytic amount of DTBB, mainly due to the decrease in ring strain. For that reason, the process should be performed at higher temperatures, that is –15 °C, compared to –78 °C for aziridines (see above). Dianionic intermediates **21** are obtained in the lithiation of azetidines which upon reaction with electrophiles and hydrolysis with water lead to regioselectively functionalised amines **22** (Scheme 20).[52] A phenyl substituent (aryl, in general) is necessary at 1- or 2-position for the reductive opening to take place. For instance, *N*-cyclohexylazetidine does not undergo reductive cleavage with the mentioned lithiating mixture even at room temperature. Concerning the regiochemistry of the process for unsymmetrically substituted azetidines, in the case of 2-phenylsubstituted heterocycle **20b**, the most stable benzylic organolithium derivative **21b** is formed instead of the primary one. However, for 2-methyl-1-phenylazetidine (**20c**), after reductive opening and reaction with deuterium oxide as electrophile, a 2:1 mixture of compounds **22c** and **22'c** is surprisingly obtained. Compound **22c** comes from the less stable secondary organolithium derivative **21c**, which decomposes by proton abstraction prior to react with deuterium oxide, whereas deuterated compound **22'c** results from the more stable dianion **21'c**, which remains stable under the reaction conditions until the addition of deuterium oxide (Scheme 20).

Alternatives to the reductive opening of azetidines for the synthesis of γ-aminofunctionalised organolithium compounds **21** are deprotonation of amines,[53] chlorine-lithium exchange in *N*-benzoyl-γ-chloramines[54] and addition of alkyllithium reagents to allylic amines.[55]

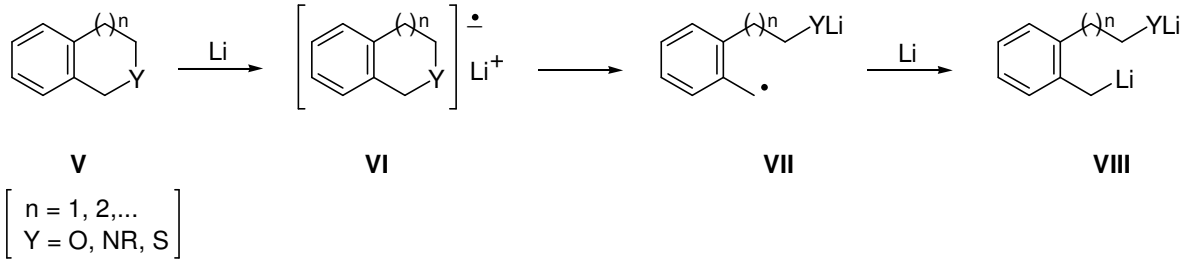




Scheme 20

3. Reductive opening of cyclic allyl and benzyl ethers, amines and thioethers

Allylic and benzylic carbon-heteroatom bonds can be reductively cleaved by means of alkali metals through a SET process in the same way as for strained heterocycles (see above). In the case of cyclic allylic and benzylic systems, a reductive ring opening takes place, leading to functionalised dianionic compounds.



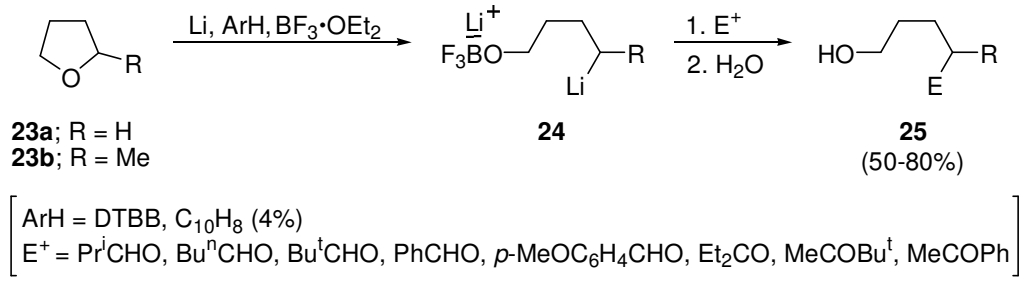
Scheme 21

In the proposed mechanism, a radical anion **VI** is initially formed after electron transfer from the metal to the heterocyclic substrate **V**. This highly unstable radical anion undergoes cleavage of the activated allylic or benzylic carbon-heteroatom bond to generate a new and more stable radical anion **VII** where the negative charge is placed on the heteroatom, which is newly reduced to the dianionic intermediate **VIII** (Scheme 21).

3.1. Reductive opening of cyclic allyl ethers, amines and related thioethers

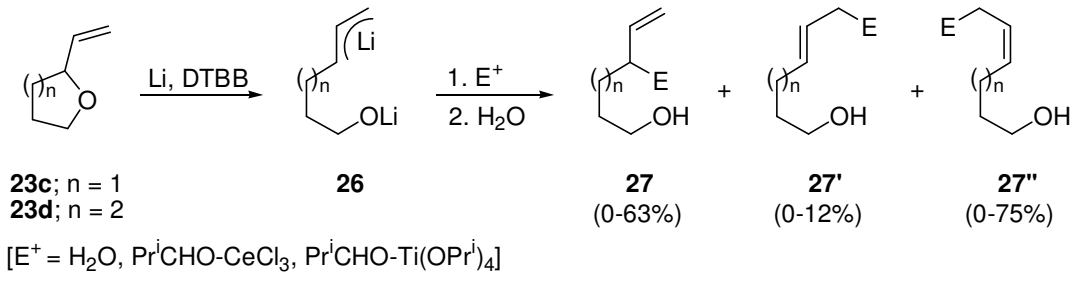
In sharp contrast to the behaviour of epoxides and oxetanes, tetrahydrofuran (**23a**) as well as tetrahydropyran do not undergo reductive opening by means of lithium metal itself and in the presence of arenes as electron carriers at low temperatures.[56] An explanation for that could be the difference in ring strain among these heterocycles. However tetrahydrofuran (**23a**) can undergo reductive opening when treated with lithium biphenylide at 66 °C, but the resulting dianion decomposes under these conditions before reacting with electrophiles. It is possible also to carry out this process at low temperature but

necessarily in the presence of boron trifluoride etherate. Thus, treatment of the complex resulting from **23a** and the Lewis acid with lithium and DTBB in a stoichiometric ratio at –78 °C leads to δ-oxygenofunctionalised organolithium compound **24a** which after reaction with electrophiles and final hydrolysis gives functionalised alcohols **25a** (Scheme 22).[57] The same process can be performed using an excess of lithium and a catalytic amount of naphthalene as lithiating mixture (Scheme 22).[58] In the case of 2-methyltetrahydrofuran (**23b**), reductive ring opening leads to the formation of the more substituted organolithium derivative **24b** in a similar way as for oxetanes (see above) (Scheme 22).[57]



Scheme 22

However, tetrahydrofuran and tetrahydropyran derivatives with a vinyl (alkenyl, in general) substituent at the 2-position **23c**,**d** are easily opened reductively with lithium in the presence of DTBB at 0 °C (Scheme 23).[57] In this case it is not necessary the presence of a Lewis acid for carbon-oxygen bond activation due probably to the stability of the resulting allylic dianions **26**. The reaction of these dilithium derivatives with electrophiles leads to a mixture of regio- and stereoisomers **27**-**27''** (Scheme 23).

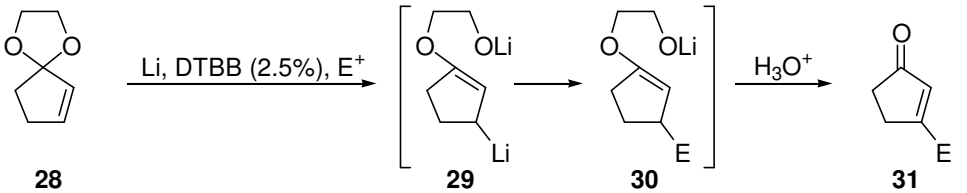


Scheme 23

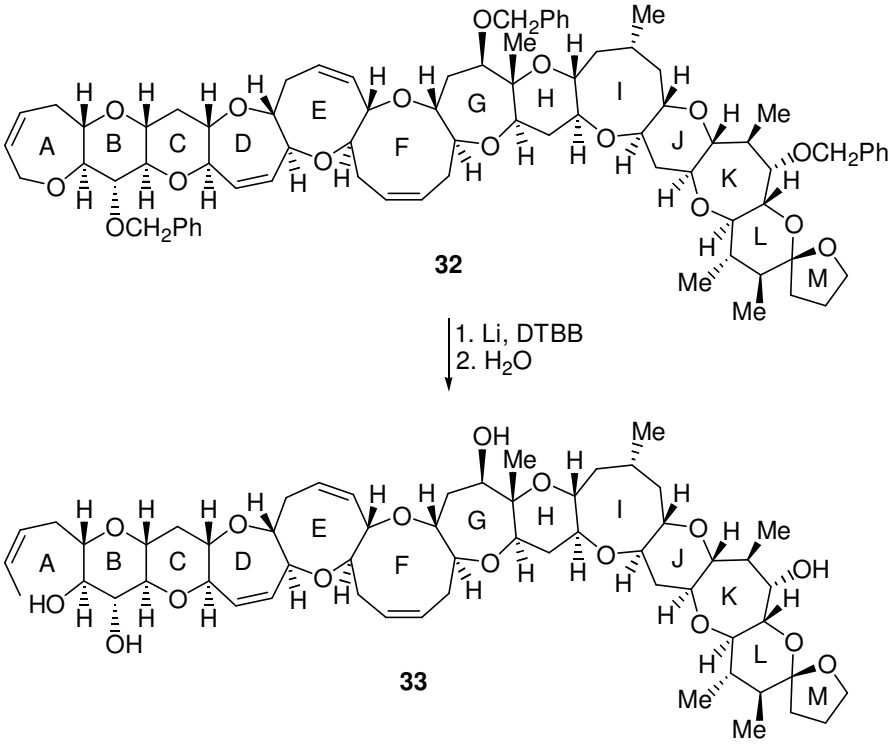
Ketalysation of α,β-unsaturated carbonyl compounds with 1,2-ethanodiol leads to a special kind of allyl ethers, which are able to undergo reductive opening. In the case of the 2-cyclopentenone derivative **28**, lithiation under Barbier-type conditions (lithiation in the presence of the electrophile) with lithium and a catalytic amount of DTBB leads first to the formation of dianion **29**. This intermediate can be considered a masked homoenolate[59] and reacts with the electrophile which is present in the reaction medium to give **30**. Final acidic hydrolysis leads to 3-substituted cyclopentenone **31** (Scheme 24).[60] The whole process represents the conjugate addition of an electrophile to an α,β-unsaturated carbonyl compound and is analogous to an umpoled Michael reaction.

The reductive opening of a 3,4-dihydro-2*H*-oxepine ring has been reported by Hirama *et al.* as a undesired side reaction in the last step of the convergent synthesis of ciguatoxin CTX3C,[61] which along with brevetoxins are structurally classified as ladderlike polyethers. The lithium DTBB-mediated reduction of *O*-

tribenzyl ciguatoxin CTX3C derivative **32** at –78 °C is accompanied by reductive cleavage of the A ring allylic ether to give **33** (Scheme 25). This problem has been overcome by using sodium in a mixture of ammonium, ethanol and THF as solvents at –90 °C.[62]



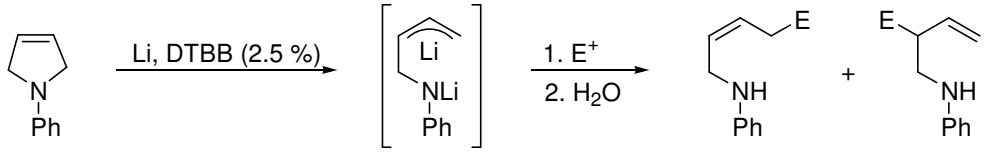
Scheme 24



Scheme 25

It is known that strained nitrogenated heterocycles such as *N*-phenylaziridines and *N*-phenylazetidines undergo reductive opening upon treatment with lithium in the presence of an arene but, *N*-phenylpyrrolidine remains unchanged under the same reaction conditions even after three days at room temperature because of the lack of ring strain and of instability of the resulting dianionic species.[63] However, *N*-phenylpyrroline **34** gives a stable allylic dianion **35** when treated with an excess of lithium in the presence of a catalytic amount of DTBB at 20 °C. The reaction of **35** with different electrophiles followed by hydrolysis gives a mixture of regioisomeric functionalised amines **36a**,**b** (Scheme 26). The ratio of isomeric amines **36** depends strongly on the electrophiles. Thus, in the case of using H_2O or D_2O as electrophiles, **36a** was obtained exclusively, and for carbonyl compounds and CO_2, mixtures of **36a** and **36b** were obtained, the latter being always more abundant (Scheme 26).[63]

Gleason and Manthorpe have reported on the reductive opening of bicyclic thioglycolate lactams **37**, by using lithium DTBB as reducing reagent at –78 °C. The mentioned process takes place by formation of a relatively stable dianion enolate derivative **38** through a carbon-sulfur bond cleavage at the α-position with respect to the carbonyl group.

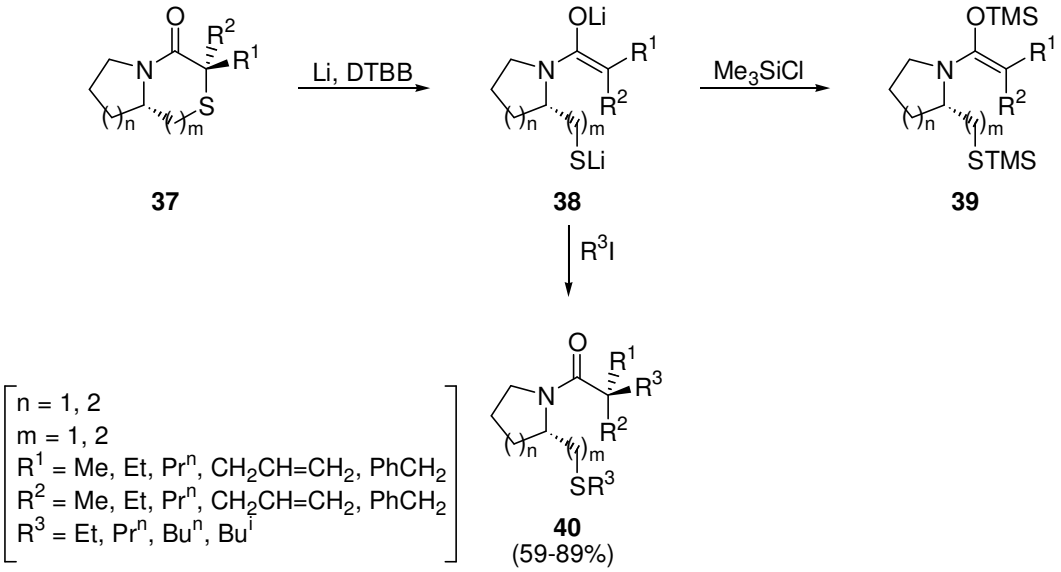


34 **35** **36a** (9-85%) **36b** (0-50%)

[E^+ = H_2O, D_2O, CO_2, Bu^tCHO, Me_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$]

Scheme 26

These dianion enolates **38** are trapped by addition of trimethylsilyl chloride to give silyl ketene aminals **39**.[64] In the case of α,α-disubstituted amide enolates, the reaction with unactivated alkyl iodides leads to a stereoselective formation of quaternary carbon centres in compounds **40** (Scheme 27).[65]



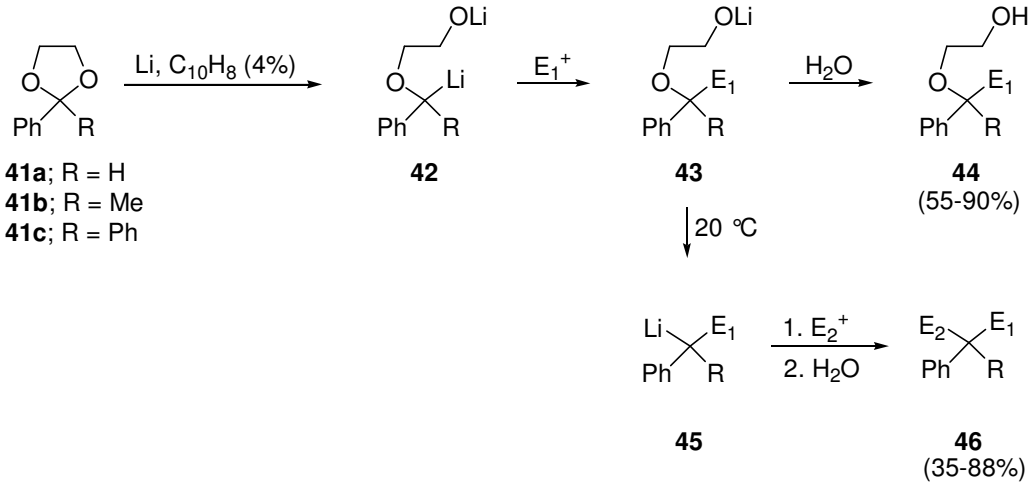
37 **38** **39** **40** (59-89%)

Scheme 27

3.2. Reductive opening of cyclic benzyl ethers

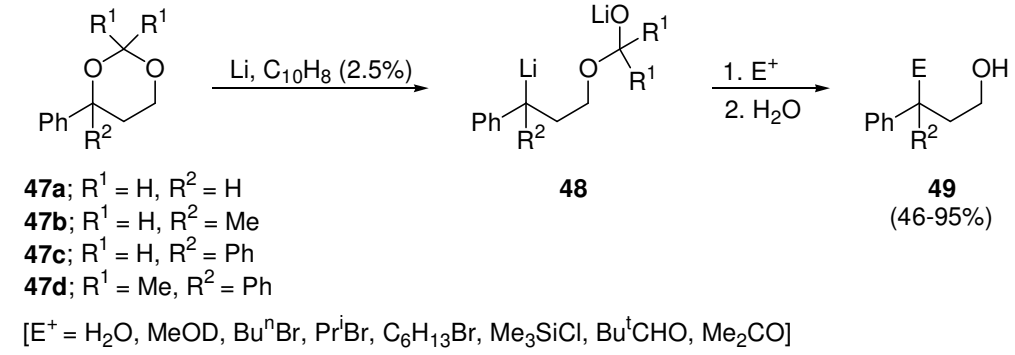
As previously commented, benzylic carbon-oxygen bonds are susceptible of suffering reductive cleavage by means of lithium metal to generate benzylic organolithium compounds. In the case of cyclic benzyl ethers, oxygenofunctionalised organolithium compounds are the reaction intermediates. The treatment of 2-phenyl-1,3-dioxolanes **41** (easily available by ketalysation of the corresponding carbonyl compounds) with an excess of lithium and a catalytic amount of naphthalene at –40 °C affords dianions **42**. The reaction of these intermediates with different electrophiles leads to compounds **43** and after hydrolysis to polyfunctionalised compounds **44** (Scheme 28).[66] When after addition of the first electrophile, the reaction mixture is allowed to reach room temperature, a second benzylic carbon-oxygen bond reductive cleavage

takes place to give intermediate **45**, which after reaction with a second electrophile and final hydrolysis gives compounds **46** (Scheme 28).[66]



Scheme 28

The same process described in Scheme 28 has been applied to substituted 4-aryl-1,3-dioxanes **47**. The reaction of intermediates **48**, resulting from the reductive opening of starting dioxanes **47**, with electrophiles, followed by hydrolysis, gives 3-substituted-3-phenylpropan-1-ols **49** in good yields. The reaction works well in the case of methylene derivatives **47a**-**c**, the process being synthetically no useful for acetone derivatives **47d** (Scheme 29).[67]

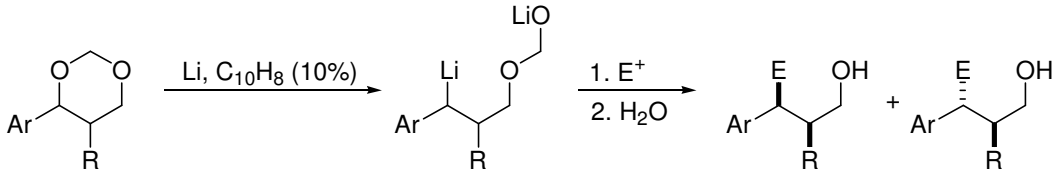


Scheme 29

The reductive lithiation of diastereomeric mixtures of 4-aryl-5-alkyl-1,3-dioxanes **47e**-**g** with lithium in the presence of a catalytic amount of naphthalene at –78 °C occurs with epimerisation at the benzylic centre to give intermediates **48**, which by reaction with alkyl halides or carbon dioxide affords 2-alkyl-3-substituted-3-arylpropan-1-ols **49**, or the corresponding lactones with satisfactory to high diastereoselectivities (Scheme 30).[68]

1,3-Oxazolidines **50** are the mononitrogenated derivatives related to 1,3-dioxolanes **41** and they can also undergo reductive cleavage by means of lithium metal in the presence of a catalytic amount of

naphthalene at –20 °C to generate α-*N*,*N*-dialkylaminosubstituted benzyllithium derivatives **51**, which are of great interest in synthetic organic chemistry because by reaction with electrophiles, functionalised aminoalcohols **52** are obtained in satisfactory yields (Scheme 31).[69] Starting oxazolidines are readily available by reaction of the corresponding aromatic aldehydes with 2-(*N*-methyl)aminoethanol.



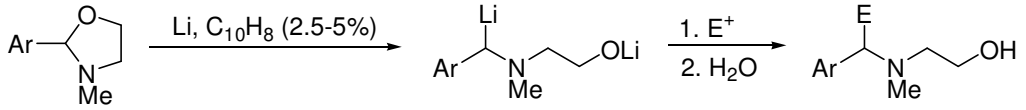
47e; Ar = Ph, R = Me
47f; Ar = 4-(MeO)C_6H_4, R = Me
47g; Ar = Ph, R = Bu^n

48

49
(50->95%)
(51:49-93:7)

[E^+ = H_2O, D_2O, CO_2, Pr^iBr, $C_6H_{13}Br$, $PhCH_2Cl$]

Scheme 30



50a; Ar = Ph
50b; Ar = 2,3-$(MeO)_2C_6H_3$
50c; Ar = 4-$(Me_2N)C_6H_4$

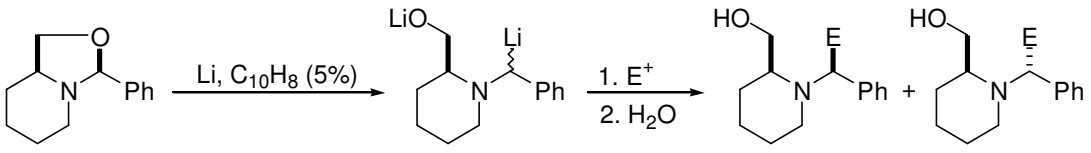
51

52
(38-95%)

[E^+ = H_2O, D_2O, EtBr, Bu^nBr, $C_6H_{13}Br$, MeI, Bu^tCHO, Me_2CO, $(CH_2)_5CO$]

Scheme 31

This process has been studied for diastereomeric bicyclic 2-phenyloxazolidine **53**, derived from 2-hydroxymethylpiperidine and benzaldehyde upon acid-catalysed cyclisation. In this case a 92:8 mixture of racemic diastereoisomers is obtained and the stereochemistry of the major stereoisomer is shown on Scheme 32. Reductive metallation of **53** with lithium in the presence of a substoichiometric amount of naphthalene at –20 °C occurs with epimerisation at the benzylic carbon atom. Reaction of dianionic intermediates **54** with alkyl halides affords substituted amino alcohols **55** in a highly *syn*-selective fashion. Observed diastereoselectivities are rationalised in terms of rapid equilibration of epimeric intermediate organolithiums **54**, one of which reacts preferentially under appropriate reaction conditions. Deuteration of the same intermediates usually leads to deuterated amino alcohols with low diastereoselectivities, unless the resulting mixture is allowed to equilibrate before deuteration (Scheme 32).[70,71]



53

54

syn-**55**

anti-**55**

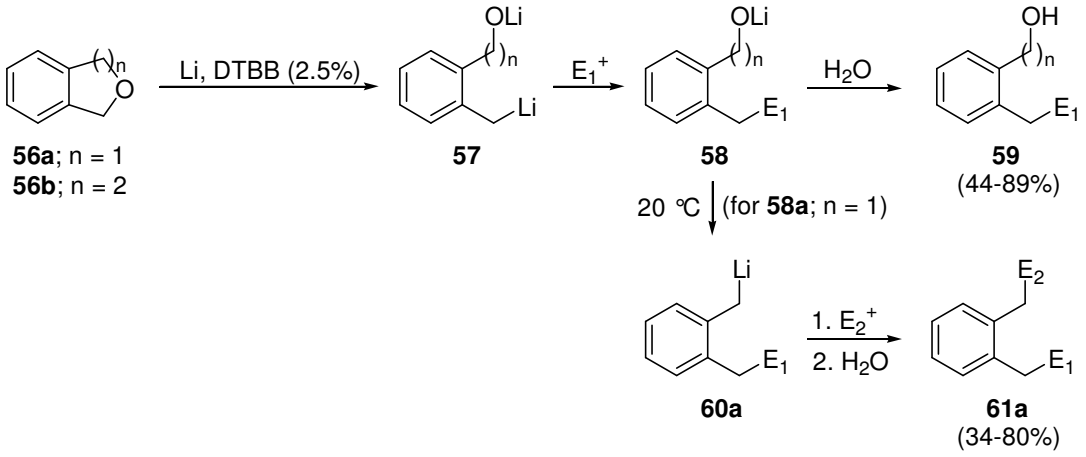
(52:48->95:<5)
(5-95%)

[E^+ = H_2O, D_2O, Bu^tOD, ArOD, Bu^nCl, $PhCH_2Cl$, Bu^nBr, $C_6H_{13}Br$]

Scheme 32

Phthalan (**56a**) and isochroman (**56b**) are a special kind of cyclic benzyl ethers. In this case, **56a** and **56b** are benzocondensed cyclic ethers and there is not a phenyl group as substituent. These heterocycles are opened reductively with lithium and a catalytic amount of DTBB at 0 °C to afford dianions **57** which have shown a wide use in organic synthesis, giving by reaction with electrophiles at –78 °C and final hydrolysis products **59** (Scheme 33).[72,73]

In addition, the lithiation of **56a** can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. After addition of the first electrophile, the resulting alcoholate **58a** is stirred in the presence of the excess of lithiating mixture at room temperature for four additional hours to give a new organolithium intermediate **60a**, which finally reacts with a second electrophile to yield difunctionalised products **61a** (Scheme 33).[72]



E_1^+ = H_2O, D_2O, CO_2, EtCHO, Pr^iCHO, Bu^iCHO, Bu^tCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, MeCOPh, $Me_3SiN{=}CHR$

E_2^+ = H_2O, D_2O, CO_2, EtCHO, Bu^tCHO, PhCHO, $(CH_2)_5CO$

Scheme 33

Diols **59a** and **59b**, derived from the reaction of intermediates **57** with carbonyl compounds (E_1^+=R^1R^2CO), are easily cyclised under acidic contidions to give the corresponding six- and seven-membered benzocondensed cyclic ethers **62** (Figure 3).[72,73] Using *N*-silylaldimines as electrophiles, aminoalcohols **59'** are obtained as reaction products, which after chlorination followed by cyclisation under basic conditions lead to the formation of tetrahydroisoquinolines and benzoazepines **62'**, interesting units in many naturally occurring compounds (Figure 3).[74] When ketones derived from D-fructose **4** (Figure 1) and D-glucose **5** (Figure 2), as well as *O*-ethoxymethylsubstituted estrone **6** (Figure 2) and cholestanone [precursor of the epoxides **1r** (Scheme 9)] are used as electrophiles, diols **59aa**-**ad** and **59ba**-**bd**[32,34] are obtained as reaction products. Cholestanone derivatives **59ad**,**bd** are obtained as an almost 1:1 diastereomeric mixture due to the lack of diastereoselectivity in the nucleophilic addition to the carbonyl group. The transformation of these compounds into the expected heterocyclic products **62aa**-**ac** and **62ba**-**bc** is easily achieved under typical Mitsunobu reaction conditions (Figure 3).[31,33]

Dianionic intermediates **57** behave as typical organolithium compounds, so they react with common electrophiles. However, reactions like acylation, dimerisation or specially conjugate addition to electrophilic

olefins are problematic because the high reactivity of the intermediates leads to many side-reactions. Exchanging lithium by another metal it is possible to modulate the mentioned reactivity.

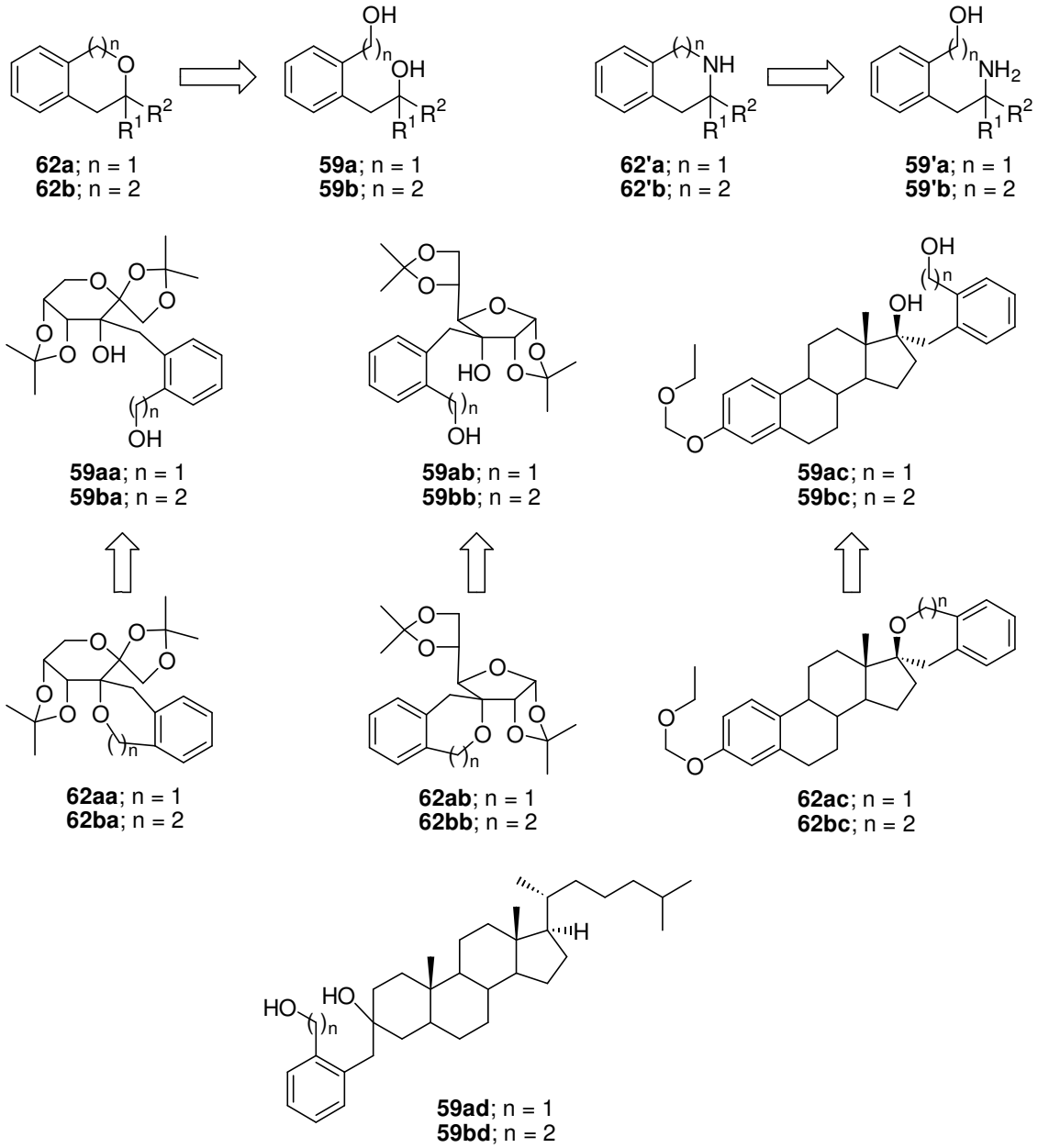
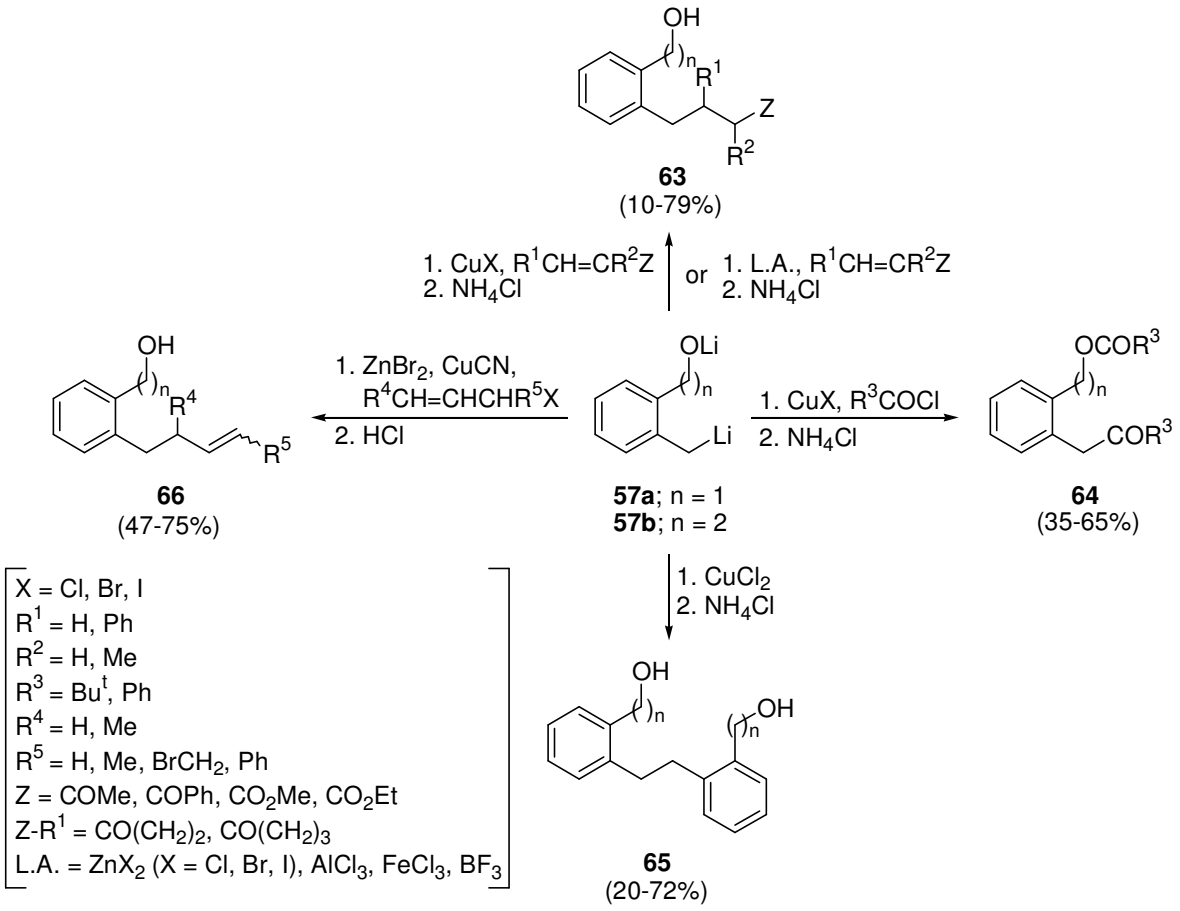


Figure 3

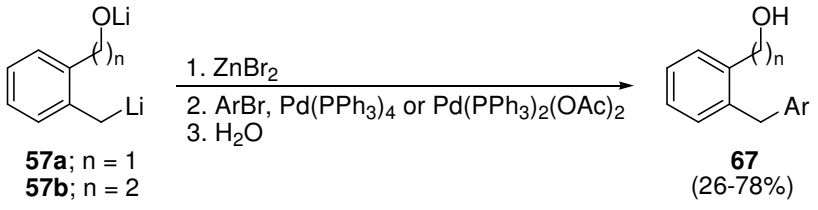
Thus, the reaction of organolithium intermediates **57** with electrophilic olefins in the presence of copper(I) salts and HMPA in THF at –78 °C leads, after hydrolysis with a saturated solution of ammonium chloride, to products **63**, resulting from a conjugate addition (Scheme 34).[75,76] The same process but using an acyl chloride instead of electrophilic olefins affords the expected ketones **64** from an acylation process (Scheme 34). Compounds **63** are also obtained when the reaction between **57** and olefins was carried out in the presence of Lewis acids [ZnX_2 (X=Cl, Br, I), $AlCl_3$, $FeCl_3$, BF_3] instead of CuI (Scheme 34).[77] By contrast, intermediates **57** undergo dimerisation in the presence of copper(II) chloride to yield dimers **65** (Scheme 34).[75,76] Working in the presence of triisopropoxytitanium chloride, functionalised organolithium compounds **57** could discriminate between aldehydes and ketones, the process being selective for aldehydes

at room temperature.[78] Another synthetically useful finding is that the reaction of intermediates **57** with an equimolecular amount of zinc bromide and copper cyanide, followed by treatment with different allylic chlorides or bromides, leads, after hydrolysis, almost exclusively to the corresponding alcohols **66** resulting from a S_N2' displacement, the process being highly regioselective (Scheme 34).[79]



Scheme 34

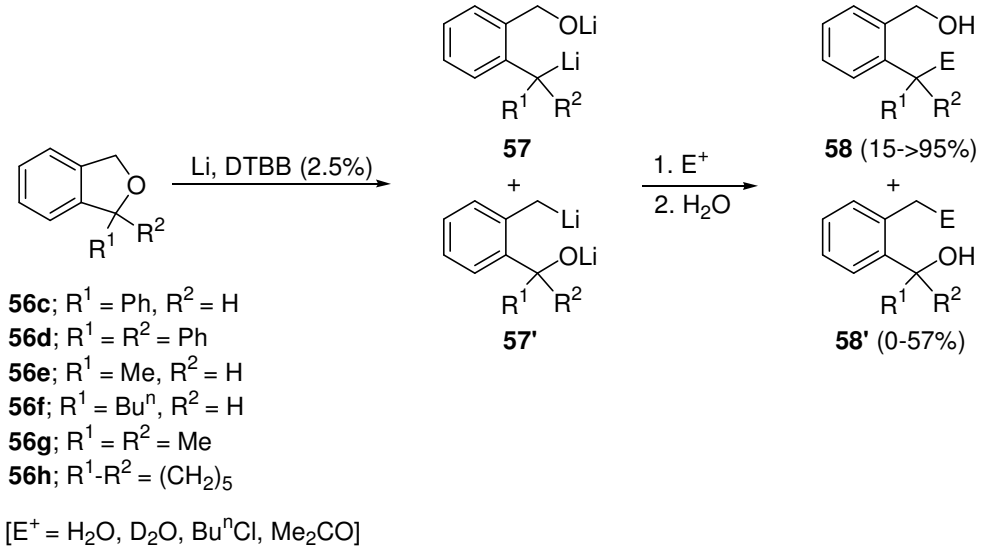
The palladium-catalysed Negishi cross-coupling reaction can be applied also to *in situ* generated functionalised organozinc reagents, which are easily prepared from functionalised organolithium compounds **57** by a lithium-zinc transmetallation process with zinc bromide. This reaction is not possible without the help of both the zinc and palladium components. The process works well for arylic and vinylic bromides, as well as with iodides, compounds **67** being generally obtained in good yields (Scheme 35).[80,81]



Ar = Ph, 4-ButC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-$MeCOC_6H_4$, 4-NCC_6H_4, 4-$EtO_2CC_6H_4$, 1-naphthyl, 4-pyridyl, 2-thiophenyl, 3-furyl

Scheme 35

Azzena *et al*. studied also the DTBB-catalysed reductive opening lithiation of several substituted phthalans **56c**-**h**. The regiochemistry of the reductive opening process always takes place to lead to the most stable of the two possible dilithium intermediates **57**,**57'** after arylmethyl carbon-oxygen bond cleavage, and it depends on the substituents. So aryl substituents stabilise anionic species and by contrast alkyl substituents do the opposite (Scheme 36).[82]



Scheme 36

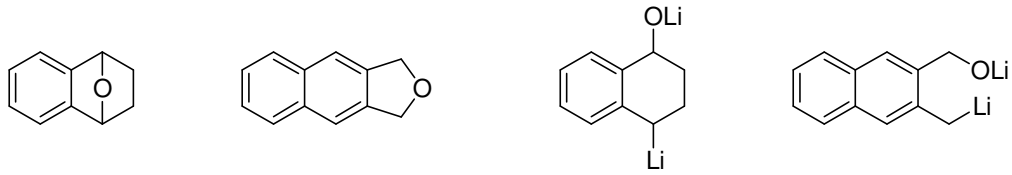


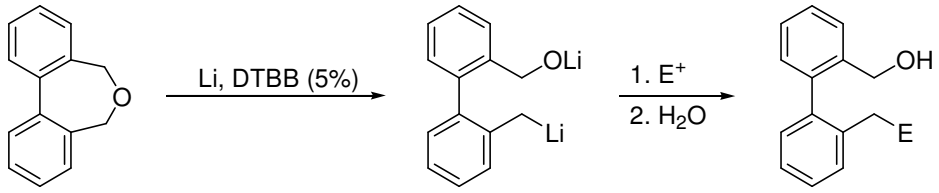
Figure 4

Heterocyclic compounds such as the polycyclic ether **56i** and the naphthalene derivative **56j** undergo also reductive ring opening to give the corresponding dilithiated intermediates **57i** and **57j** under the same reaction conditions (Figure 4). In the first case after reaction with D_2O a quantitative yield was obtained. However, in the case of **56j** the reaction products resulting for one or two reductive carbon-oxygen bond cleavage were obtained depending mainly on the relative amount of lithium used for the lithiation.[82b]

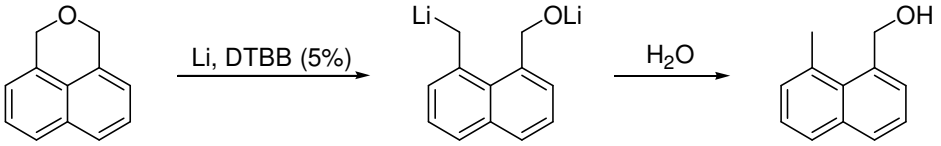
Biphenyl derivative **68** and naphthalene derivative **71** are symmetrical cyclic diarylmethyl ethers and after treatment with lithium and a catalytic amount of naphthalene give intermediates **69** and **72** respectively. The reaction of these dianionic species with electrophiles followed by hydrolysis with water allows the access to unsymmetrically 2,2'-disubstituted-1,1'-biphenyl and 1,8-disubstituted naphthalene derivatives **70** and **73**, respectively (Scheme 37).[83]

Treatment of benzo[*c*]-1,3-dioxane and 1,3-oxathiane derivatives **74**, with excess of lithium and a catalytic amount of DTBB at 20 °C (for dioxanes **74a**-**g**) or at –78 °C (for oxathianes **74h**-**n**) followed by hydrolysis, leads to the formation of 2-substituted homobenzylic alcohols **75**.

Cyclisation of these alcohols either under acidic conditions in refluxing toluene or under Mitsunobu-type reaction conditions gives 2,3-dihydro-2-substituted benzofurans or thiophenes **76**.



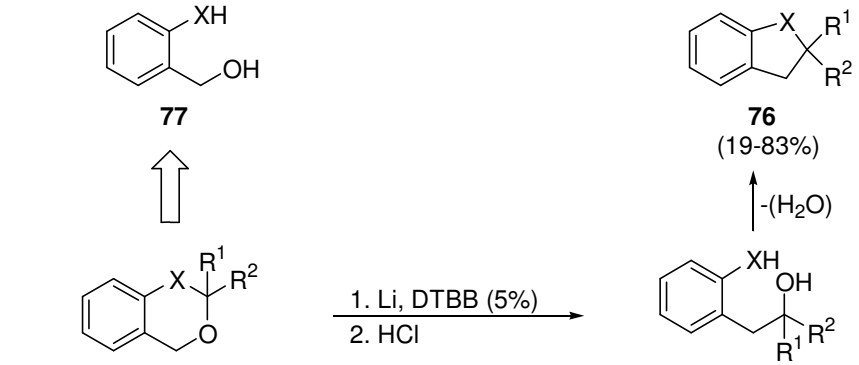
68 **69** **70** (56->95%)



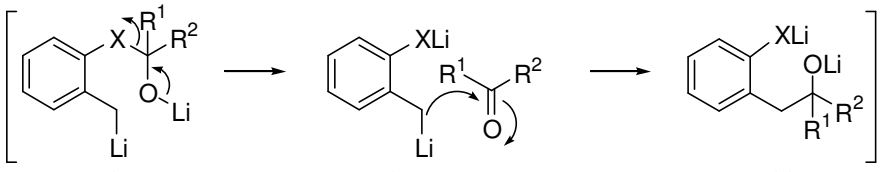
71 **72** **73** (55%)

[$E^+ = H_2O, D_2O, Pr^iBr, Bu^nBr, Me_3SiCl, Me_2CO$]

Scheme 37



74a; X = O, R^1 = H, R^2 = Me
74b; X = O, R^1 = R^2 = Me
74c; X = O, R^1 = H, R^2 = Pr^i
74d; X = O, R^1 = H, R^2 = Bu^i
74e; X = O, R^1 = H, R^2 = Bu^t
74f; X = O, R^1-R^2 = $(CH_2)_5$
74g; X = O, R^1 = H, R^2 = $Ph(CH_2)_2$
74h; X = S, R^1 = H, R^2 = Me
74i; X = S, R^1 = R^2 = Me
74j; X = S, R^1 = H, R^2 = Pr^i
74k; X = S, R^1 = H, R^2 = Bu^i
74l; X = S, R^1 = H, R^2 = Bu^t
74m; X = S, R^1 = R^2 = $(CH_2)_5$
74n; X = S, R^1 = H, R^2 = $Ph(CH_2)_5$



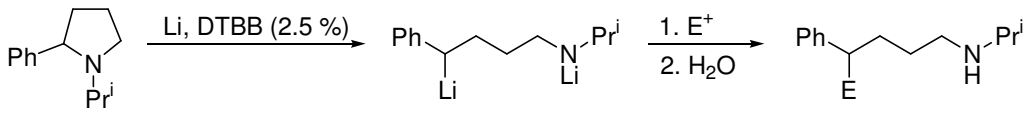
78 **79** **80**

Scheme 38

Starting heterocycles **74** are easily prepared by ketalysation of carbonyl compounds with *o*-(hydroxymethyl)phenol or *o*-(hydroxymethyl)thiophenol **77** (Scheme 38). In this process, a benzylic carbon-oxygen bond cleavage takes place first leading to dianionic alcoholates **78**, which undergo β-elimination giving benzylic dianions **79** together with the carbonyl compound used for the preparation of the starting heterocycles **74**. These species react immediately to give **80**, which after hydrolysis with hydrochloric acid, lead to final compounds **75** (Scheme 38).[84]

3.3. Reductive opening of cyclic benzyl amines

As commented above, strained *N*-phenylsubstituted nitrogenated heterocycles undergo reductive opening by an arene-catalysed lithiation, *N*-phenylpyrrolidine remaining unchanged under the same reaction conditions. However, *N*-isopropyl-2-phenylpyrrolidine (**81**) gives the dianion **82** when treated with an excess of lithium in the presence of a catalytic amount of DTBB at 20 °C for 30 min. In this case reductive opening takes place due to the stability of resulting benzylic intermediate **82**, which after reaction with different electrophiles and final hydrolysis with water, gives functionalised amines **83** (Scheme 39).[63]



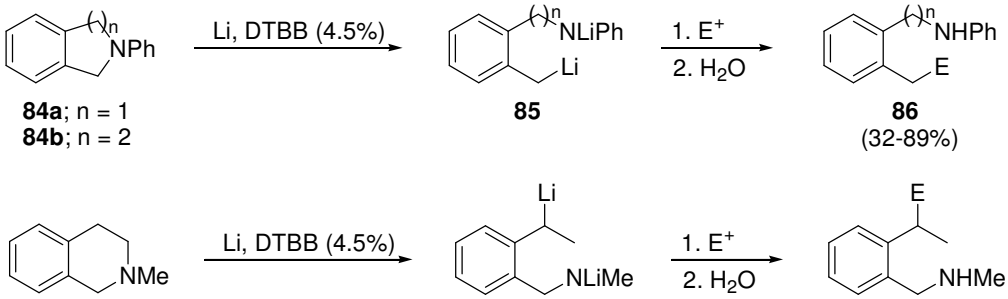
81 **82** **83** (28-85%)

[E^+ = H_2O, D_2O, MeI, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, CO_2]

Scheme 39

Other types of cyclic benzyl amines are isoindoline and tetrahydroisoquinoline derivatives **84**, which are the analogous nitrogenated compounds of oxygen-containing heterocycles phthalan (**56a**) and isochroman (**56b**). Treatment of *N*-phenylisoindoline (**84a**) or *N*-phenyltetrahydroisoquinoline (**84b**) with an excess of lithium and a catalytic amount of DTBB at 20 °C followed by addition of an electrophile at low temperature and final hydrolysis with water gives functionalised amines **86**, benzylic dianionic intermediates **85** resulting from the reductive ring opening being involved in the process (Scheme 40).[63]

N-Isopropylisoindoline does not undergo reductive opening under the same reaction conditions. *N*-Methyltetrahydroisoquinoline (**84c**) leads to the formation of functionalised amines **88c** instead of the expected **86** through dianion **87c** (Scheme 40).[63]



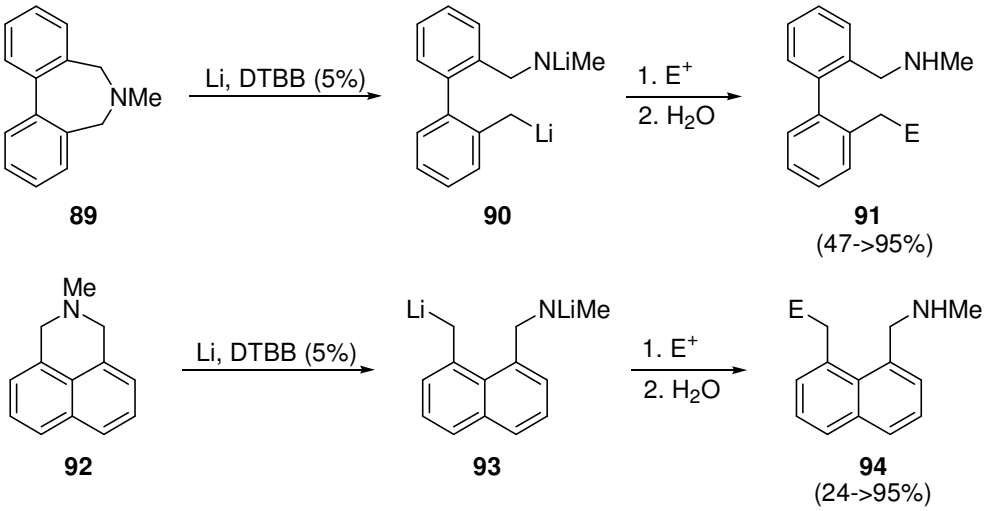
84a; n = 1
84b; n = 2 **85** **86** (32-89%)

84c **87c** **88c** (39-76%)

[E^+ = H_2O, D_2O, CH_2=$CHCH_2Br$, CO_2, Pr^iCHO, Bu^tCHO, PhCHO, Me_2CO, Pr^nCOMe, $(CH_2)_4CO$, PhCOMe]

Scheme 40

In the same way as for symmetrical cyclic diarylmethyl ethers **68** and **71** (Scheme 37), the corresponding *N*-methylamino biphenyl derivative **89** and the naphthalene derivative **92** give under the same reaction conditions the unsymmetrically 2,2'-disubstituted-1,1'-biphenyl and 1,8-disubstituted naphthalene derivatives **91** and **94**, respectively, benzylic dianions **90** and **93** being in this case the reaction intermediates, respectively (Scheme 41).[83]

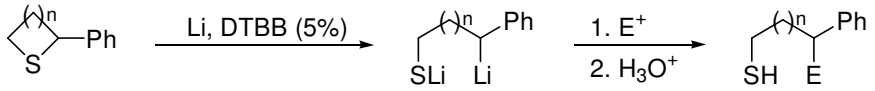


[E^+ = H_2O, D_2O, Pr^iBr, Bu^nBr, Me_3SiCl, Me_2CO]

Scheme 41

3.4. Reductive opening of cyclic benzyl thioethers

Oxetanes **14** and azetidines **20** (see above) undergo reductive opening by means of alkali metals in the presence of an arene, but thietane itself or alkyl substituted thietanes are stable compounds towards the same reductive reagents because they are less strained heterocycles due to the longer carbon-heteroatom bond distances. However, 2-phenylthietane (**95a**) can be reductively opened with lithium in the presence of a catalytic amount of DTBB at low temperature. In this case a phenyl group at 2-position is necessary for the reductive opening to take place in order to stabilise the γ-thiofunctionalised organolithium compound **96a**, intermediate which has also been prepared through a halogen-lithium exchange[85] as well as the corresponding functionalised radicals from iodinated procursors.[86]



95a; n = 1
95b; n = 2
95c; n = 3

96

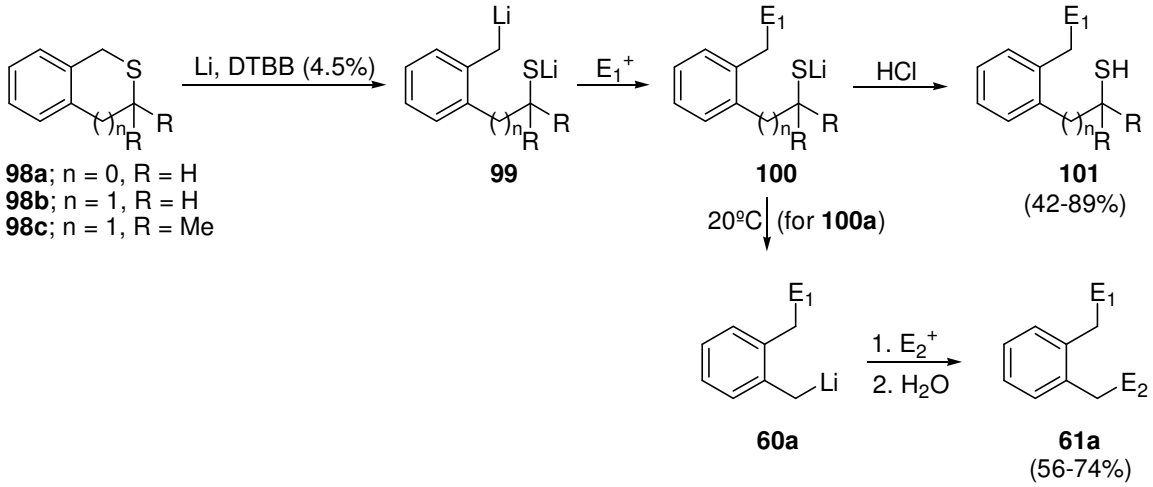
97
(50-89%)

[E^+ = H_2O, D_2O, CO_2, Me_3SiCl, Bu^tCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$]

Scheme 42

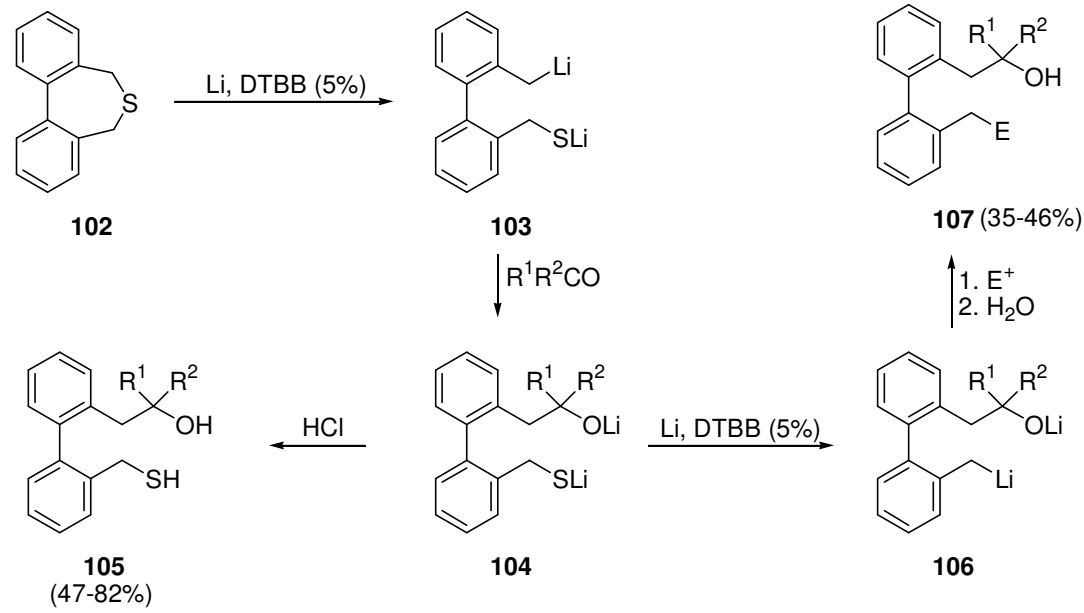
The same methodology has also been applied to the reductive opening of 2-phenyltetrahydrothiophene (**95b**) and 2-phenylthiane (**95c**). The reaction of the resulting dianionic intermediates **96** with electrophiles, followed by hydrolysis with hydrochloric acid, leads to the formation of regioselective functionalised thiols **97** (Scheme 42).[87]

As it could be expected by considering the reactivity of phthalan (**56a**) and isochroman (**56b**), thiophthalan (**98a**) and thioisochromans **98b**,**c** are reductively opened with lithium and a catalytic amount of DTBB at –78 °C (instead of 0 °C for**56**) in order to avoid undesired side reactions.



[E_1^+ = H_2O, D_2O, CO_2, Pr^iCHO, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_4CO$, MeCOPh
E_2^+ = H_2O, D_2O]

Scheme 43



[R^1R^2CO = Bu^tCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, $[Me(CH_2)_4]_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (-)-menthone
E^+ = Me_2CO, Et_2CO, $(CH_2)_5CO$, $ClCO_2Et$]

Scheme 44

The reaction of the resulting dianionic intermediates **99** with different electrophiles leads to compounds **101**, after acidic hydrolysis (Scheme 43).[88] In a similar manner to phthalan (**56a**) (see Scheme 33), in the case of thiophthalan (**98a**), two electrophilic fragments can be introduced at both benzylic positions if after reductive opening and reaction with the first electrophile, the resulting intermediate **100a** is

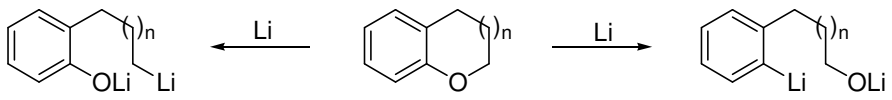
allowed to react at room temperature, leading to organolithium compounds **60a**, which after reaction with a second electrophile and hydrolysis with water yields *o*-xylene derivatives **61a** (Scheme 43).

Applying the same strategy as for phthalan (**56a**) and thiophthalan (**98a**), the lithiation of 2,7-dihydrodibenzothiepin (**102**) can be directed either to the formation of sulfanyl alcohols **105** or to the introduction of two different electrophiles at both benzylic positions in a sequential manner, to yield difunctionalised biphenyls **107**. Thus, the treatment of compound **102** with an excess of lithium and a catalytic amount of DTBB at –78 °C leads to intermediate **103**, which reacts with carbonyl compounds to give alkoxides **104**, and after acidic hydrolysis to the afore mentioned sulfanyl alcohols **105**. However, when alkoxides **104** are stirred at room temperature in the presence of the excess of the lithiating mixture, the remaining benzylic carbon-sulfur bond is cleaved leading to new intermediates **106**, which after reaction with a second electrophile and final hydrolysis with water lead to polyfunctionalised compounds **107** (Scheme 44).[89]

4. Reductive opening of cyclic aryl ethers and thioethers

4.1. Reductive opening of cyclic aryl ethers

Alkyl aryl ethers, in general, and the corresponding cyclic alkyl aryl ethers **IX**, in particular, have not been used extensively for the generation of organolithium compounds by means of lithium metal itself or in the presence of an arene, because of the competition of two different bond cleavages:[13a] alkyl-oxygen bond cleavage leading to alkyllithium phenolates **X** (dealkylation process) and aryl-oxygen bond cleavage leading to aryllithium alcoholates **XI** (dearylation process) (Scheme 45). There are many factors which control this reductive cleavage, among them (a) the electronic effect of the metallic cation resulting after the electron transfer to the substrate when using alkali metals as reducing reagents,[13b] (b) the presence of other contraions,[13c] (c) the conformation of the substrate[13b] and (d) the polarity of the solvent.[13d,e]

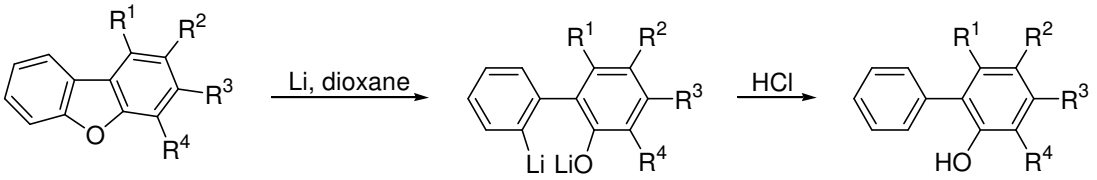


X **IX** **XI**

Scheme 45

The reductive ring opening of dibenzofuran (**108a**) was initially investigated by Gilman and Esmay,[90] further developments of the reaction with the aim of synthetic applications having been made by Keumi and collaborators.[91] They found that 2-hydroxybiphenyls **110** are obtained in high yields in the reaction of three equivalents of lithium in dioxane with cyclic diaryl ethers **108** under reflux and after final acidic hydrolysis. For alkyl substituted dibenzofurans **108b-g**, non-substituted aryl-oxygen bond is cleaved selectively to give dianionic intermediates **109** (Scheme 46).

The synthesis of 2'-phosphanyl-1,1'-biphenyl- and 2'-phosphanyl-1,1'-binaphthyl-2-ols and their silyl ethers **110a** and **113**, respectively, has been developed by a DTBB-catalysed lithiation of dibenzofuran (**108a**) and dinaphthofuran (**111**) in THF at room temperature to give intermediates **109a** and **112**, respectively, after subsequent reaction with chlorophosphanes (and work-up with acetic acid) or trimethylchlorosilane. When the reaction is performed in ether, in the absence of arene and with sonication at ether reflux, reaction times are considerably longer (Scheme 47).[92]

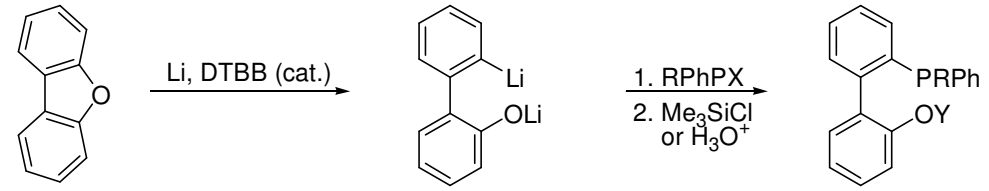


108a; $R^1 = R^2 = R^3 = R^4 = H$
108b; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
108c; $R^1 = R^2 = R^3 = H$, $R^4 = Me$
108d; $R^1 = R^3 = Me$, $R^2 = R^4 = H$
108e; $R^1 = R^4 = Me$, $R^2 = R^3 = H$
108f; $R^1 = R^3 = H$, $R^2 = R^4 = Me$
108g; $R^1 = R^2 = R^3 = R^4 = Me$

109

110
(70-99%)

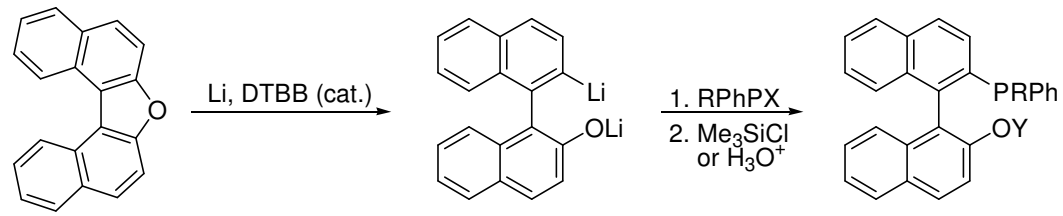
Scheme 46



108a

109a

110a
(30-60%)



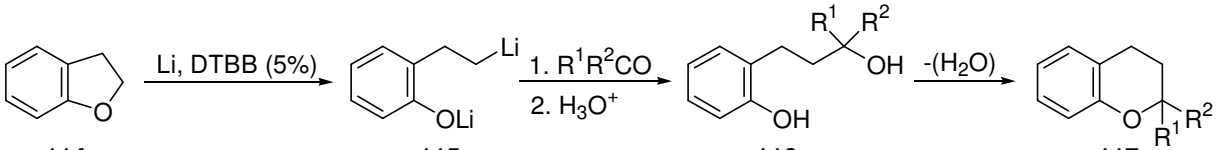
111

[R = Me, Pr^i, Bu^t, Ph
X = Cl, OBu^t
Y = H, Me_3Si]

112

113
(32-68%)

Scheme 47



114

115

116
(33-78%)

117
(68-95%)

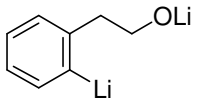
[R^1R^2CO = Bu^tCHO, PhCHO, $PhCH_2CHO$, $Ph(CH_2)_2CHO$, furfural, Me_2CO, Et_2CO, $(CH_2)_5CO$, $(CH_2)_7CO$, (-)-menthone]

Scheme 48

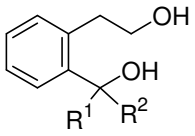
It has recently been reported the preparation of alkyllithiums from alkyl phenyl ethers through an arene catalysed lithiation,[93] so in the case of cyclic alkyl aryl ethers functionalised organolithium compounds could be generated after a carbon-oxygen bond cleavage. Thus, the treatment of 2,3-dihydrobenzofuran (**114**) with an excess of lithium in the presence of a catalytic amount of DTBB in THF at 0 °C gives the

dianion **115**, which after reaction with different carbonyl compounds and final hydrolysis with water leads to compounds **116** (Scheme 48).[93,94]

Dehydration under acidic conditions of diols **116** leads to chromans **117**, homologous heterocycles of starting 2,3-dihydrobenzofuran (**114**). In some cases diols **119** are also isolated as side reaction products in less than 18% yield (Figure 5). An explanation for this result is that dealkylation leading to intermediate **115** is the predominant process and dearylation to **118** (Figure 5) occurs in a minor extension.



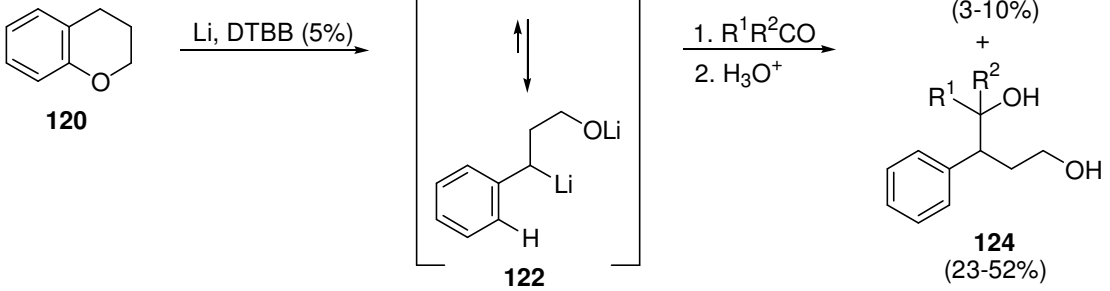
118



119
(0-18%)

Figure 5

Chroman (**120**) [homologous heterocycle of 2,3-dihydrobenzofuran (**114**)] undergoes DTBB-catalysed lithiation, but reaction conditions are different than for compound **114**. In this case, the process should be performed at room temperature instead of 0 °C and for a longer reaction time (3 h instead of 1.5 h). After addition of different carbonyl compounds as electrophiles, followed by acidic hydrolysis, a mixture of regioisomeric alcohols **123** and **124** is surprisingly obtained, indicating that dianions **121** and **122** are involved as reaction intermediates. These results can be explained assuming that dearylation leading to intermediate **121** is in this case the only process, but under the reaction conditions used (room temperature and long reaction time), the initially formed dianion **121** is in equilibrium with the apparently more stable benzylic dianion **122** through an inter- or intra-molecular deprotonation process (Scheme 49).[94]



120

121

122

123
(3-10%)
+

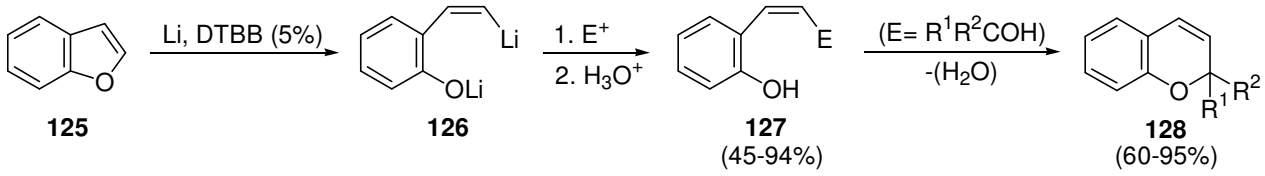
124
(23-52%)

[R^1R^2CO = Bu^tCHO, PhCHO, Me_2CO, $[Me(CH_2)_4]_2CO$, PhCHO, $(CH_2)_4CO$, $(CH_2)_5CO$, (-)-menthone]

Scheme 49

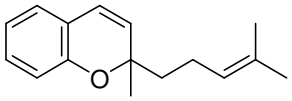
In the case of 2,3-benzofuran (**125**), a stereoselective ring opening lithiation takes place under the same reaction conditions as for 2,3-dihydrobenzofuran (**114**) shown on Scheme 48, yielding the (*Z*)-organolithium intermediate **126** which, by reaction with different electrophiles and final acidic hydrolysis,

gives the expected (*Z*)-products **127**. Cyclisation of the products obtained by reaction with carbonyl compounds, under acidic conditions, affords the expected substituted 2*H*-chromenes **128** (Scheme 50), including deoxycordiachromene **128h** (Figure 6).[95]



[E^+ = H_2O, D_2O, Bu^tCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, $MeCOPr^n$, $MeCO(CH_2)_2CH=CMe_2$, MeCOPh, $(CH_2)_4CO$]

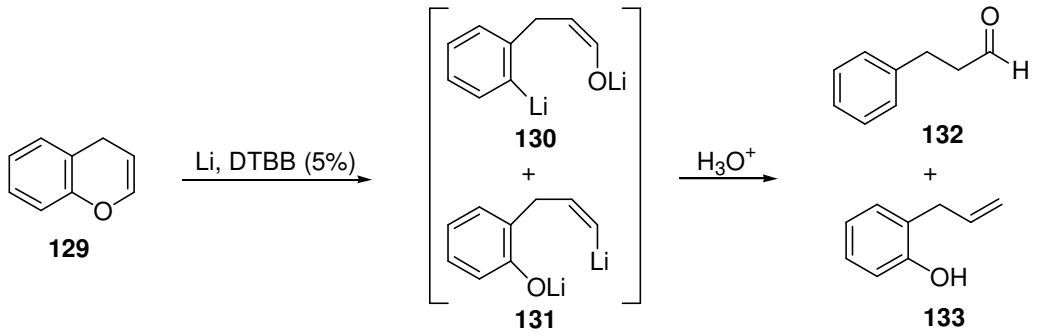
Scheme 50



128h

Figure 6

Finally, when 4*H*-chromene (**129**) is submitted to the same lithiation mixture as above, at 20 °C, followed by acidic hydrolysis, a mixture of 3-phenylpropanal (**132**) and 2-allylphenol (**133**) in a 2:1 ratio, is respectively obtained in 95% overall yield, intermediates **130** (through dearylation) and **131** (through dealkylation) being probably involved in the process. In this case dearylation is predominant over dealkylation, the use of carbonyl compounds as electrophiles leading to a complex mixture of reaction products (Scheme 51).[94]

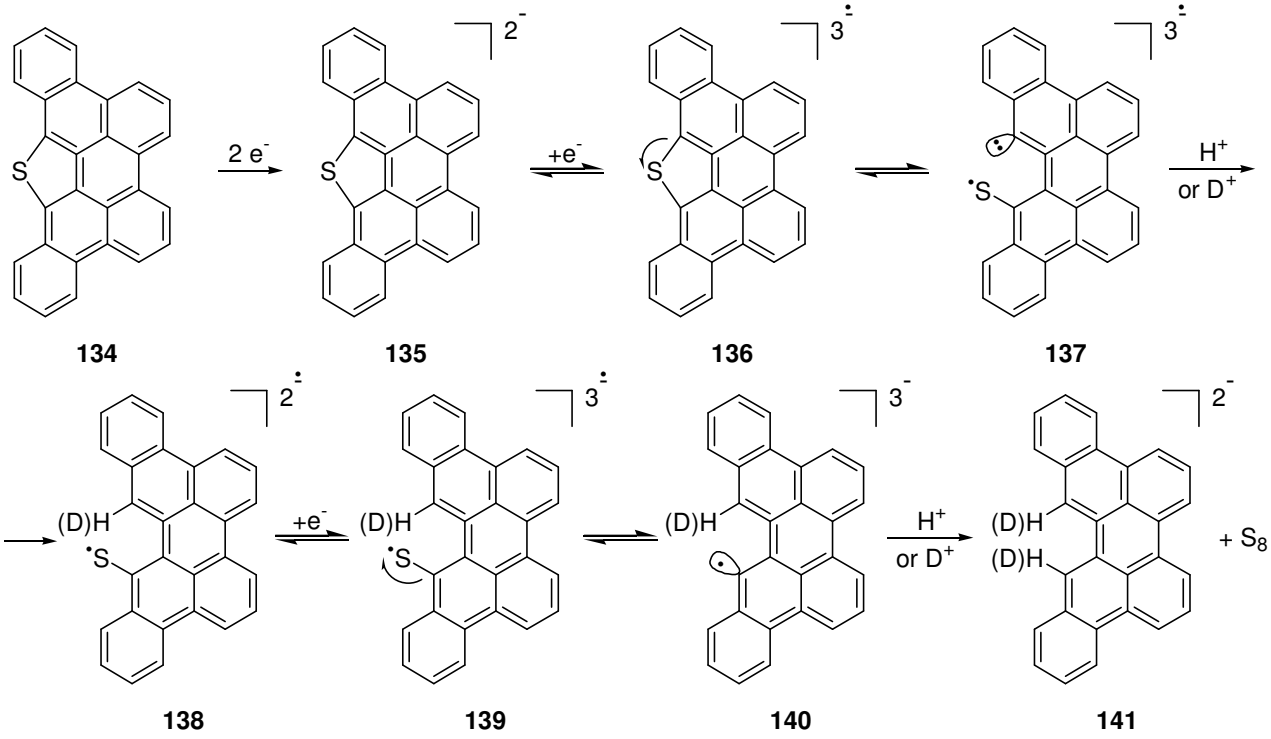


Scheme 51

4.2. Reductive opening of cyclic aryl thioethers

In the case of the polyaromatic sulfur-containing heterocycle flavophen **134**, a reduction with potassium metal yields a stable dianion **135**, whereas under identical reaction conditions with lithium or sodium the reduction does not proceed beyond the radical anion.

Sulfur extrusion from this dianion proceeds upon further contact with the reducing metal: the extrusion begins with the introduction of a third electron in the polycyclic ring system **135** to give a radical trianion **136**, weakening one the carbon-sulfur bonds giving after scission the carbanion sulfur radical **137**. Proton (or deuterium) abstraction by **137** results in the radical dianion **138**. Transfer of another electron yields radical trianion **139** and the second carbon-sulfur bond is cleaved giving atomic sulfur and carbanion **140**, which abstracts another proton (or deuterium) to give compound **141** (Scheme 52).[96]

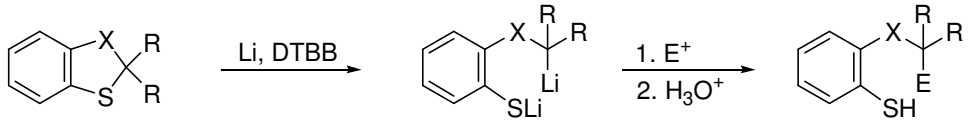


134 **135** **136** **137**

138 **139** **140** **141**

Scheme 52

Screttas and Micha-Screttas[14a,b] developed a methodology for the preparation of organolithium compounds starting from phenylthioethers, being an alternative to the use of chlorinated materials as precursors of this intermediates. Since then, the cleavage of the carbon-sulfur bond in phenylthioethers using either the stoichiometric[14c] or the catalytic version of the arene-mediated lithiation[97] has been extensively used to generate organolithium compounds by sulfur-lithium exchange. Applying this methodology, sulfur-containing heterocycles, such as dihydrobenzothiophene (**142a**)[98] 3,4-dihydro-2*H*-benzothiane (**142b**)[98] and trimethylbenzo-1,3-thiazolidine (**142c**)[98b,99] in which the sulfur atom is attached to a fused aromatic ring, have been reductively opened by the mixture lithium-DTBB at 0 °C to give dianions **143**. The reaction of these dianionic intermediates with electrophiles followed by acidic hydrolysis gives functionalised thiophenols **144** (Scheme 53).



142a; X = CH_2, R = H
142b; X = $(CH_2)_2$, R = H
142c; X = NMe, R = Me

143

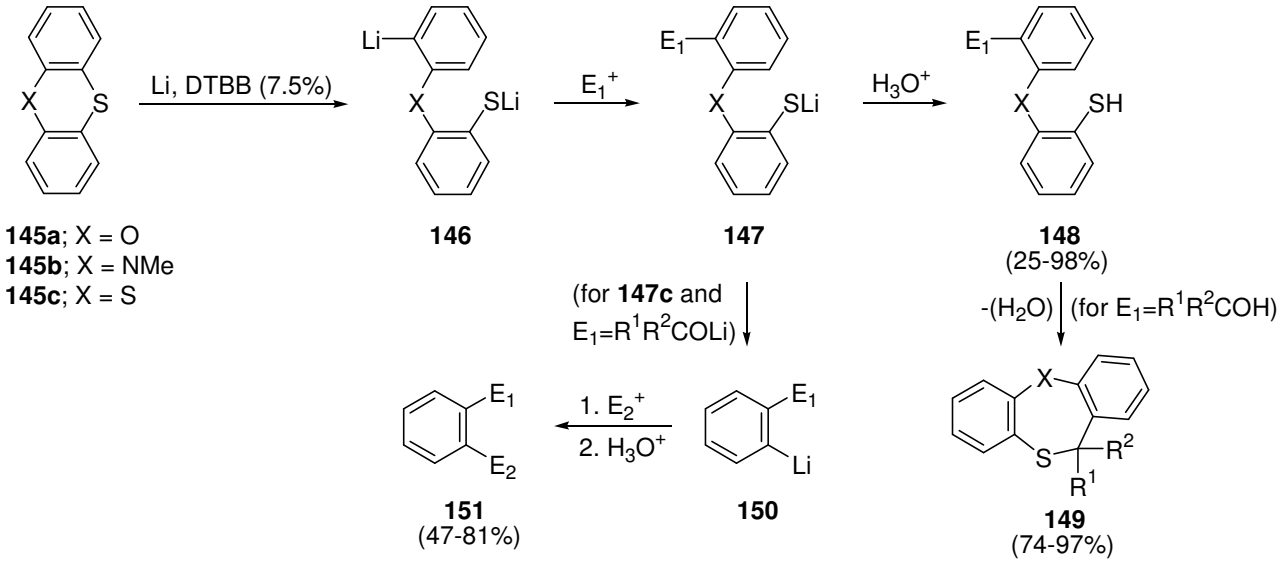
144
(35-86%)

[E^+ = MeOD, $(CH_2O)_n$, Pr^iCHO, PhCHO, 4-MeC_6H_4CHO, 4-$MeOC_6H_4CHO$, 4-ClC_6H_4CHO, (*E*)-PhCH=CHCHO, $(CH_2)_5CO$]

Scheme 53

The DTBB-catalyzed lithiation of 4-hetero-substituted dibenzothiins **145** [phenoxathiin (**145a**), phenothiazine (**145b**), and thianthrene (**145c**)] at low temperature gives the corresponding functionalised

organolithium intermediates **146**, which by reaction with different electrophiles afford the expected functionalised thiols **148**, after hydrolysis.



[E_1^+ =H_2O, D_2O, R^1R^2CO [Bu^tCHO, PHCHO, $Ph(CH_2)_2CHO$, Me_2CO, Et_2CO, $(CH_2)_5CO$
E_2^+ = CO_2, Bu^tCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, Et_2CO, $(CH_2)_5CO$]

Scheme 54

The cyclization of some carbonyl compound derivatives under acidic conditions gives the corresponding homologous seven-membered dibenzo heterocycles **149** (Scheme 54).[100] From a synthetic point of view, the whole process **145 • 149** represents a homologation of the starting materials **145**. In the case of thianthrene (**145c**), all the reactions should be performed at –90 °C in order to avoid undesired side processes. However, when after the addition of a carbonyl compound as the first electrophile, the resulting intermediate **147c** is allowed to react with the excess of the litihiation mixture present in the reaction medium, a new intermediate **150** is formed. The addition of a second electrophile, and final hydrolysis with water, yields 1,2-difunctionalised benzene derivatives **151** (Scheme 54).[101]

Acidic cyclization of diols **151**, resulting from the use of two carbonyl compounds as electrophiles, gives substituted phthalans **152** practically in quantitative yields (Figure 7). Specially interesting is the use of carbon dioxide as the second electrophile because after acidic work-up, substituted ftalides **153** are obtained (Figure 7). Through this methodology, thianthrene **145c** acts as a dianionic synthon of type **XII** (Figure 7) but making possible to discriminate between both carbanionic centers, so two different (or equal) electrophiles can be used.[101]

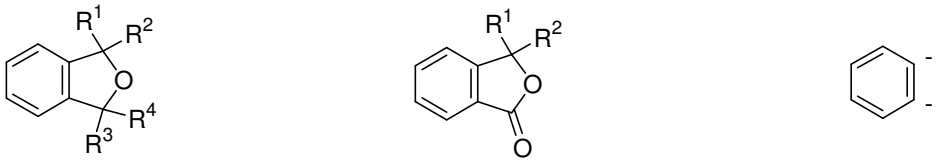


Figure 7

5. Conclusions

The reductive opening of heterocycles with lithium metal itself or in the presence of a stoichiometric or catalytic amount of an arene has proved to be a direct and easy way to achieve the preparation of functionalised organolithium compounds in only one single step starting, in general, from readily available materials. The reaction of these intermediates with electrophiles gives polyfunctionalised reaction products in only one step. In the case of using carbonyl compounds as electrophiles, the resulting functionalised acohols can undergo dehydration to give a new heterocyclic systems, representing the whole process a homologation of the starting heterocycles. Finally, enantiomerically pure reaction products can be obtained when starting from chiral heterocycles.

References

1. For reviews, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155. (b) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67.
2. Wakefield, B. *Organolithium Methods*, Academic Press, London, **1988**.
3. For a review on the generation of organolithium reagents from non-halogenated materials, see: Guijarro, D.; Yus, M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 713.
4. For a review, see: Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73.
5. Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Org. Chem.* **1981**, *46*, 2721 and references cited therein.
6. For the first account on this reaction, see: Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398.
7. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, 155. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225. (c) Yus, M. *Synlett* **2001**, 1197.
8. (a) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397. (b) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017.
9. Yus, M.; Gómez, C.; Candela, P. *Tetrahedron* **2002**, *58*, 6207.
10. For studies on the mechanism of this reaction, see: (a) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455. (b) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574.
11. (a) Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2534. (b) Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 3303. (c) Lorenzo, E.; Alonso, F.; Yus, M. *Tetrahedron* **2000**, *56*, 1745. (d) Lorenzo, E.; Alonso, F.; Yus, M. *Tetrahedron Lett.* **2000**, *41*, 1661.
12. (a) Azzena, U.; Demartis, S.; Fiori, M. G.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 5641. (b) For a review, see: Azzena, U. *Trends Org. Chem.* **1997**, *6*, 55. (c) Azzena, U.; Carta, S.; Melloni, G.; Sechi, A. *Tetrahedron* **1997**, *53*, 16205.
13. (a) Maercker, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 972. (b) Lazana, M. C. R. L. R.; Franco, M. L. T. M. B.; Herold, B. J. *J. Am. Chem. Soc.* **1989**, *111*, 8640. (c) Casado, F.; Pisano, L.; Farriol, M.; Gallardo, I.; Marquet, J.; Melloni, G. *J. Org. Chem.* **2000**, *65*, 322. (d) Azzena, U.; Denurra, T.; Melloni, G.; Piroddi, A. M. *J. Org. Chem.* **1990**, *55*, 5386. (e) Azzena, U.; Denurra, T.; Melloni, G.; Fenude, E.; Rassu, G. *J. Org. Chem.* **1992**, *57*, 1444.
14. (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713. (c) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.
15. For a review, see: Smith, J. G. *Synthesis* **1984**, 629.
16. Franco, M. L. T. M. B.; Herold, B. J.; Maercker, A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 119.
17. Kaiser, E. M.; Edmonds, C. G.; Grubb, S. D.; Smith, J. W.; Tramp, D. *J. Org. Chem.* **1971**, *36*, 330.
18. (a) Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243. (b) Brown, H. C.; Kawakami, J. H.; Ikegami, S. *J. Am. Chem. Soc.* **1970**, *92*, 6914. (c) Benkeser, R. A.; Rappa, A.; Wolsieffer, L. A. *J. Org. Chem.* **1986**, *51*, 3391.
19. Barluenga, J.; Fañanás, F. J.; Villamaña, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2685 and references cited therein.

20. Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1153.
21. Nájera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289.
22. Bartmann, E. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 653.
23. Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976.
24. (a) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villeras, J. *Tetrahedron Lett.* **1984**, 835. (b) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, 795.
25. (a) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 915. (b) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3339.
26. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
27. Conrow, R. E. *Tetrahedron Lett.* **1993**, *34*, 5553.
28. Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Müller, D.; Thormann, M.; Hofmann, H.-J. *Tetrahedron* **2000**, *56*, 1081.
29. (a) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1907. (b) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2997.
30. See, for instance: Sato, K.; Suzuki, K.; Ueda, M.; Katayama, M.; Kajihara, Y. *Chem. Lett.* **1991**, 1469.
31. Soler, T.; Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3939.
32. Soler, T.; Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 493.
33. Falvello, L. R.; Foubelo, F.; Soler, T.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2063.
34. Yus, M.; Soler, T.; Foubelo, F. *Tetrahedron: Asymmetry* **2001**, *12*, 801.
35. (a) Stamm, H.; Sommer, A.; Woderer, A.; Wiesert, W.; Mall, T.; Assithianakis, P. *J. Org. Chem.* **1985**, *50*, 4946. (b) Stamm, H.; Mall, T.; Falkenstein, R.; Werry, J.; Speth, D. *J. Org. Chem.* **1989**, *54*, 1603. (c) Falkenstein, R.; Mall, T.; Speth, D.; Stamm, H. *J. Org. Chem.* **1993**, *58*, 7377.
36. (a) Ambrosi, H.-D.; Duczek, W.; Ramm, M.; Jähnisch, K. *Tetrahedron Lett.* **1994**, *35*, 7613. (b) Lim, Y.; Lee, W. K. *Tetrahedron Lett.* **1995**, *36*, 8431.
37. (a) Bouayad, Z.; Chanet-Ray, J.; Ducher, S.; Vessiere, R. *J. Heterocycl. Chem.* **1991**, *28*, 1757. (b) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (c) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. (d) Eastwood, F. W.; Perlmutter, P.; Yang, Q. *Tetrahedron Lett.* **1994**, *35*, 2039. (e) Davoli, P.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1995**, *6*, 2011. (f) Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2073. (g) Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* **1996**, *37*, 6893.
38. (a) Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523. (b) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006.
39. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 1649.
40. Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210.
41. Bordwell, F. G.; Andersen, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 4959.
42. Almena, J.: Ph. D. Dissertation, Universidad de Alicante, **1996**.
43. Mudryk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657.
44. Mudryk, B.; Cohen, T. *J. Org. Chem.* **1991**, *56*, 5760.
45. Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.
46. Licandro, E.; Maiorana, S.; Papagni, A.; Zanotti-Gerosa, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1623.
47. Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2633.
48. Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133.
49. Rama, K.; Pasha, M. A. *Tetrahedron Lett.* **2000**, *41*, 1073.
50. Hashemzadeh, M.; Howell, A. R. *Tetrahedron Lett.* **2000**, *41*, 1855.
51. Hashemzadeh, M.; Howell, A. R. *Tetrahedron Lett.* **2000**, *41*, 1859.
52. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5775.
53. (a) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 1135. (b) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1988**, *29*, 4859.
54. (a) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *Tetrahedron* **1989**, *45*, 2183. (b) Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 10103.

55. Hänssgen, D.; Odenhausen, E. *Chem. Ber.* **1979**, *112*, 2389.
56. Ramón, D. J.; Yus, M., unpublished results.
57. Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866.
58. Ramón, D. J.; Yus, M. *Tetrahedron* **1992**, *48*, 3585.
59. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
60. Gil, J. F.; Ramón, D. J. ; Yus, M. *Tetrahedron* **1994**, *50*, 3437.
61. Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975.
62. Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.
63. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1996**, *52*, 8545.
64. Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091.
65. Manthorpe, J. M.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 2338.
66. (a) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 9535. (b) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 7307.
67. Azzena, U.; Pilo, L. *Synthesis* **1999**, 664.
68. Arrica, M. A.; Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron Lett.* **2002**, *43*, 5137.
69. Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron* **2000**, *56*, 3775.
70. Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron Lett.* **2001**, *42*, 129.
71. Azzena, U. *J. Chem. Soc., Perkin Trans. 1* **2002**, 360.
72. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3351.
73. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3365.
74. Foubelo, F.; Gómez, C.; Gutiérrez, A.; Yus, M. *J. Heterocycl. Chem.* **2000**, *37*, 1061.
75. Pastor, I. M.; Yus, M. *Tetrahedron Lett.* **2000**, *41*, 1589.
76. Pastor, I. M.; Yus, M. *Tetrahedron* **2001**, *57*, 2371.
77. Yus, M.; Pastor, I. M.; Gomis, J. *Tetrahedron* **2001**, *57*, 5799.
78. Pastor, I. M.; Yus, M. *Tetrahedron* **2001**, *57*, 2365.
79. Yus, M.; Gomis, J., unpublished results.
80. Yus, M.; Gomis, J. *Tetrahedron Lett.* **2001**, *42*, 5721.
81. Yus, M. ; Gomis, J. *Eur. J. Org. Chem.* **2002**, 1989.
82. (a) Azzena, U.; Demartis, S.; Fiori, M. G.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 8123. (b) Azzena, U.; Demartis, S.; Melloni, G. *J. Org. Chem.* **1996**, *61*, 4913.
83. Azzena, U.; Demartis, S.; Pilo, L.; Piras, E. *Tetrahedron* **2000**, *56*, 8375.
84. Choudhury, P. K.; Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 17373.
85. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 11883.
86. Foubelo, F.; Gutiérrez, A. M.; Yus, M. *An. Quim. Int. Ed.* **1996**, *92*, 280.
87. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 5563.
88. Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1996**, *61*, 1859.
89. Foubelo, F.Yus, M.; Foubelo, F. *Tetrahedron Lett.* **2001**, *42*, 2469.
90. Gilman, H.; Esmay, D. L. *J. Am. Chem. Soc.* **1953**, *75*, 2947.
91. Keumi, T.; Murata, C.; Sasaki, Y.; Kitajima, H. *Synthesis* **1980**, 634.
92. Kadyrov, R.; Heinicke, J.; Kindermann, M. K.; Heller, D.; Fischer, C.; Selke, R.; Fischer, A. K.; Jones, P. G. *Chem. Ber.* **1997**, *130*, 1663.
93. Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 7759.
94. Yus, M.; Foubelo, F.; Ferrández, J. V.; Bachki, A. *Tetrahedron* **2002**, *58*, 4907.
95. Yus, M.; Foubelo, F.; Ferrández, J. V. *Eur. J. Org. Chem.* **2001**, 2809
96. Benshafrut, R.; Rabinovitz, M.; Hoffman, R. E.; Ben-Mergui, N.; Müllen, K.; Iyer, V. S. *Eur. J. Org. Chem.* **1999**, 37.
97. (a) Foubelo, F.; Gutiérrez, A.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 4837. (b) Foubelo, F.; Gutiérrez, A.; Yus, M. *Synthesis* **1999**, 503. (c) Foubelo, F.; Gutiérrez, A.; Yus, M. *Tetrahedron Lett.* **1999**, *40*, 8173. (d) Foubelo, F.; Gutiérrez, A.; Yus, M. *Tetrahedron Lett.* **1999**, *40*, 8177. (e) Yus, M.; Gutiérrez, A.; Foubelo, F. *Tetrahedron* **2001**, *57*, 4411.
98. (a) Cohen, T.; Chen, F.; Kulinski, T.; Florio, S.; Capriati, V. *Tetrahedron Lett.* **1995**, *36*, 4459. (b) Florio, S.; Capriati, V.; Gallo, A.; Cohen, T.; Chen, F.; Kulinski, T. *Gazz. Chim. Ital.* **1996**, *126*, 351.

99. Florio, S.; Capriati, V.; Gallo, A.; Cohen, T. *Tetrahedron Lett.* **1995**, *36*, 4463.
100. Yus, M.; Foubelo, F.; Ferrández, J. V. *Chem. Lett.* **2002**, 726.
101. Yus, M.; Foubelo, F.; Ferrández, J. V. *Tetrahedron Lett.* **2002**, *43*, 7205.

FURAN-2,3-DIONES: CONVENIENT SYNTHONS IN HETEROCYCLIC CHEMISTRY

Gert Kollenz* **and Sabine Leber**

Institute of Chemistry, Organic and Bioorganic Division, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria (e-mail: kollenz@kfunigraz.ac.at)

Abstract. *The chemistry of 4,5-mono- and/or di-substituted monocyclic furan-2,3-diones is surveyed covering a ten-years period from 1991–2001. Besides methods of preparation particular emphasis is directed towards thermolysis reactions which afford highly reactive α-oxoketenes, either as neat compounds or " in situ", and their behaviour in cycloaddition reactions ([4+2] versus[2+2] processes) as well as reactions with nucleophiles. Furan-2,3-diones themselves undergo thermally as well as photochemically initiated cycloaddition reactions, in particular 4-acyl derivatives serve as oxa-1,3-diene systems in hetero-Diels-Alder reactions, mostly accompanied by unexpected novel rearrangements, which were investigated with aid of isotopic labelling. Applying several mono-or bis-nucleophiles as reagents various novel heterocyclic systems including some deeply coloured dyes were obtained too.*

Contents

1. Introduction

This review on the chemistry of functionalized furan-2,3-diones covers the literature of a 10-years period starting from 1991. It should be regarded as a continuation of a preceding report on a similar topic[1] covering the literature up to 1991. Furthermore, some results dating back before 1991 are also enclosed, since they have now become accessible.

In order to get a concise and convenient view on that kind of compounds some general restrictions have to be made first:

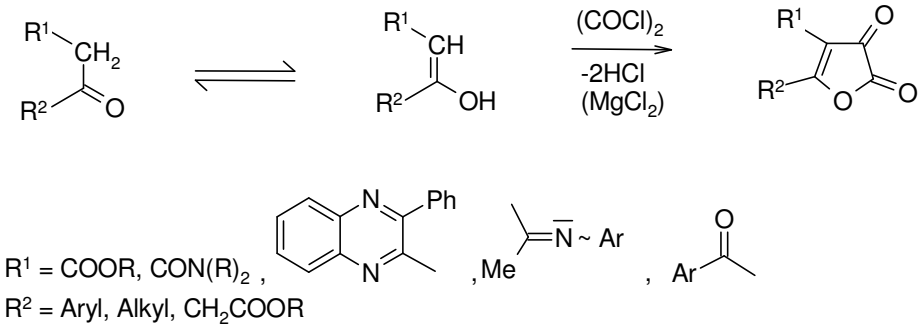
a) Monocyclic 2,3-dihydro-furandiones (4,5-unsaturated) are under discussion exclusively, fully saturated or fused systems are *a priori* excluded (Chart 1).

b) The furandiones are further subdivided into separate sections depending on the substitution pattern on C-4,5. In particular, derivatives having carbonyl functionalities at C-4 offer specific reactivities towards nucleophiles as well as cycloaddition processes.

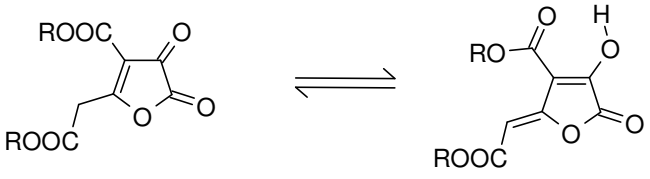
Chart 1

2. Synthesis and preparation

Cyclocondensation reactions of 1,3-H-active substrates with oxalyl chloride still looks to be the most convenient and widely used procedure to generally prepare 4,5-substituted furan-2,3-diones (Scheme 1).[2-10] In particular, applying $MgCl_2$ as catalyst, established by Saalfrank *et al.*,[4,5] the scope of that methodology has been significantly expanded:



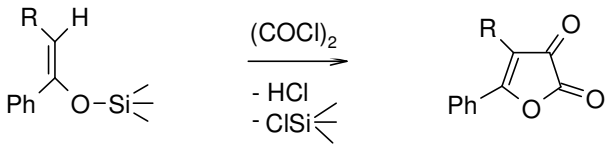
Scheme 1



Scheme 2

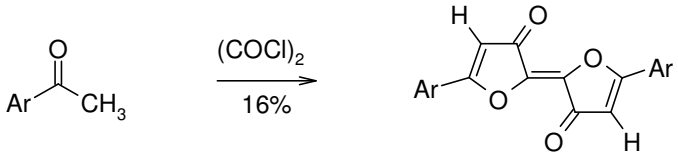
It is interesting to note, that the product obtained from acetone dicarboxylic ester (R_2=CH_2COOR) in solution predominantly is found in its tautomeric form exhibiting an exocyclic C=C-bond (Scheme 2).[5]

In a suitable variation of that general methodology the enolic form of the substrate before reacting with oxalyl chloride may first be converted into a silyl ether derivative (Scheme 3).[2,6]



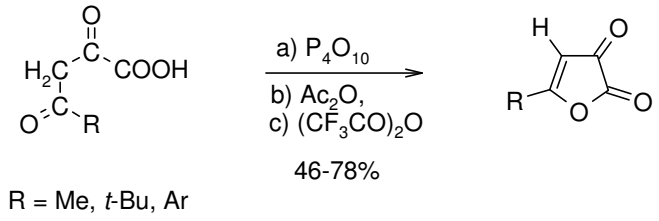
Scheme 3

Surprisingly, from reaction of acetophenone and oxalyl chloride instead of the expected furan-2,3-dione a bis-furanone derivative is obtained in very low yield (16%), obviously the result of an unusual dimerization process (Scheme 4).[11]



Scheme 4

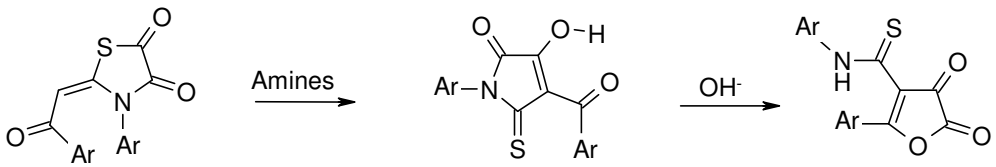
A totally different approach makes use of intramolecular cyclocondensation of acylpyruvic acid derivatives in the presence of polyphosphoric acid or better trifluoroacetic anhydride/KOH affording the corresponding furandiones in good yields (60–70%) (Scheme 5).[12,13] For preparing 5–alkylfuran-2,3-diones this clean and efficient method seems far superior to the previously reported cyclocondensation reactions of silyl enol ethers with oxalyl chloride.[2,6]



R = Me, *t*-Bu, Ar

Scheme 5

In a very specific case, starting from thiazolidinediones and alkylamines pyrrolinethiones were obtained, which in alkaline medium rearrange into the corresponding functionalised furan-2,3-diones (Scheme 6).[14]

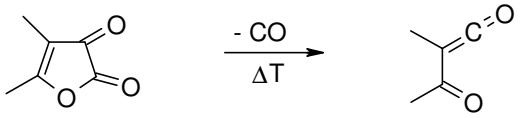


Scheme 6

3. Thermolysis

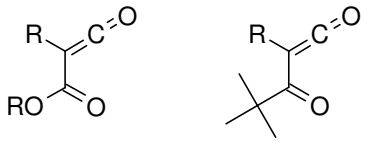
3.1. Formation of neat α-oxoketenes

Furan-2,3-diones in general are suitable precursors for the formation of highly reactive α-oxoketenes, which, depending on their specific substitution pattern, may be trapped as reactive intermediates only or generated and characterized as stable species (Scheme 7).[15]



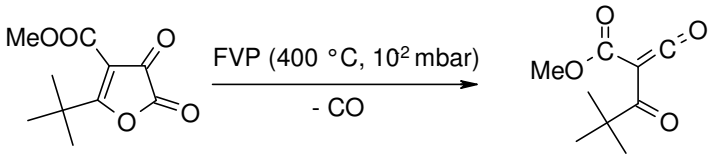
Scheme 7

Stabilization may be achieved either electronically[16] or sterically,[17] *e.g.* ketene carboxylic esters are well known as rather stable molecules since the nineteen twenties,[16a] and the bulky *t*-butyl group also dramatically enhances the stability of the α-oxoketene moiety (Scheme 8).[17]



Scheme 8

Very recently, methoxycarbonyl-pivaloylketene[8] has been prepared as neat compound from flash vacuum pyrolysis (FVP) of 5-*t*-butyl-4-methoxycarbonyl-2,3-dihydrofuran-2,3-dione in 80% yield (Scheme 9). This α-oxoketene combines both stabilizing effects within the molecule, represented by the ester as well as the *t*-butyl group.



Scheme 9

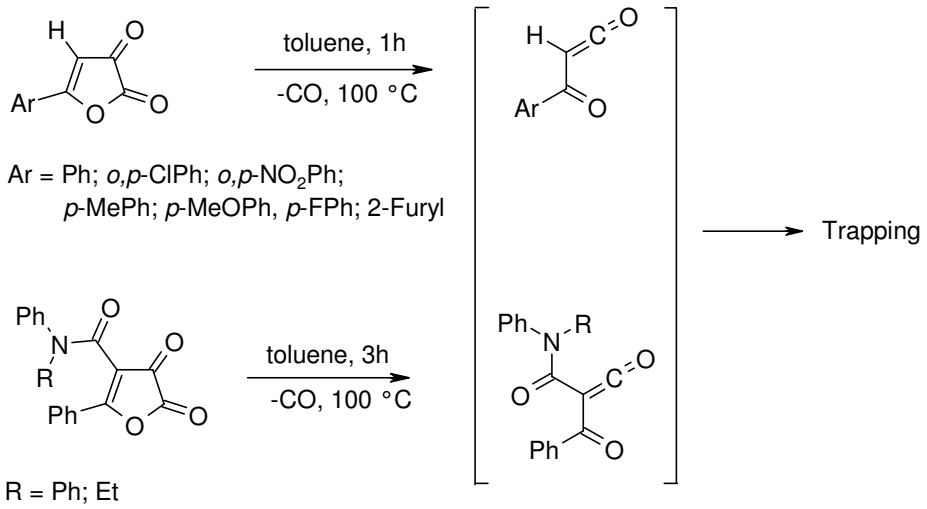
3.2. *In situ*-generation of α-oxoketenes

Several 5-aryl substituted furan-2,3-diones eliminate carbon monoxide upon refluxing in toluene to generate the corresponding α-oxoketene as reactive intermediate.[18-21] This also stands for 4-*N*-phenylcarbamoyl-5-phenylfuran-2,3-diones (Scheme 10).[3] Evidence for the *in situ* formation of the oxoketene was taken from various trapping reactions only (see **3.3.** and **3.4.**) since direct observation was not possible.

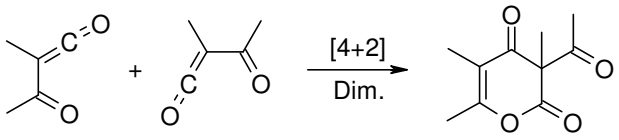
3. 3. α-Oxoketenes–Chemical reactions

3.3.1. Dimerization

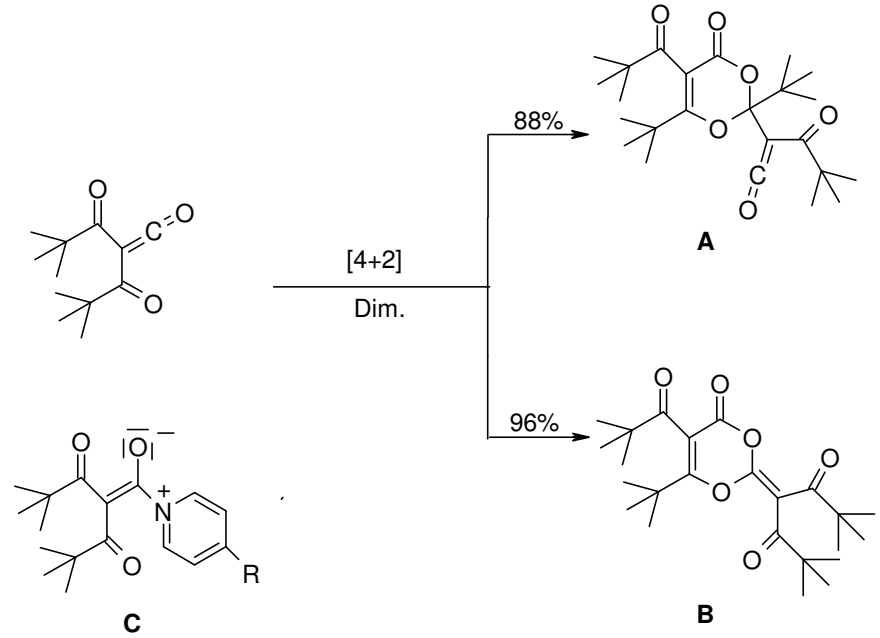
It is well known that in the absence of any other reactant α-oxoketenes generated *in situ* have a strong tendency to undergo [4+2] cyclodimerization usually affording α-pyrone derivatives (Scheme 11).[15] Thus, one molecule represents the oxa-1,3-diene system while the C=C of the second ketene acts as dienophile.



Scheme 10



Scheme 11

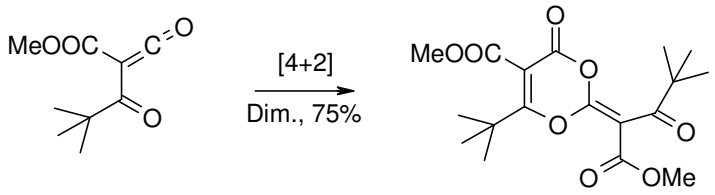


Scheme 12

However, while ketene carboxylic esters are highly reluctant to form any dimerization products,[15] sterically stabilized neat α-oxoketenes follow different routes. Obviously due to severe steric hinderance coming from the bulky *t*-butyl groups dimerization of neat dipivaloylketene at room temperature takes place involving a ketene C=O as dienophile and leads to different 1,3-dioxinones (A and B, Scheme 12) depending on the specific reaction conditions,[17a,b] *e.g.* the presence of pyridines causes exclusive formation of dimer B.[17b] The reason for that behaviour was seen in the formation of a zwitterionic intermediate generated by nucleophilic attack of the pyridine nitrogen at the central ketene carbon. The existence of such highly reactive zwitterions (C, Scheme 12) could recently be verified applying 4-dimethylamino- pyridine (Steglich base) as pyridine derivative.[22]

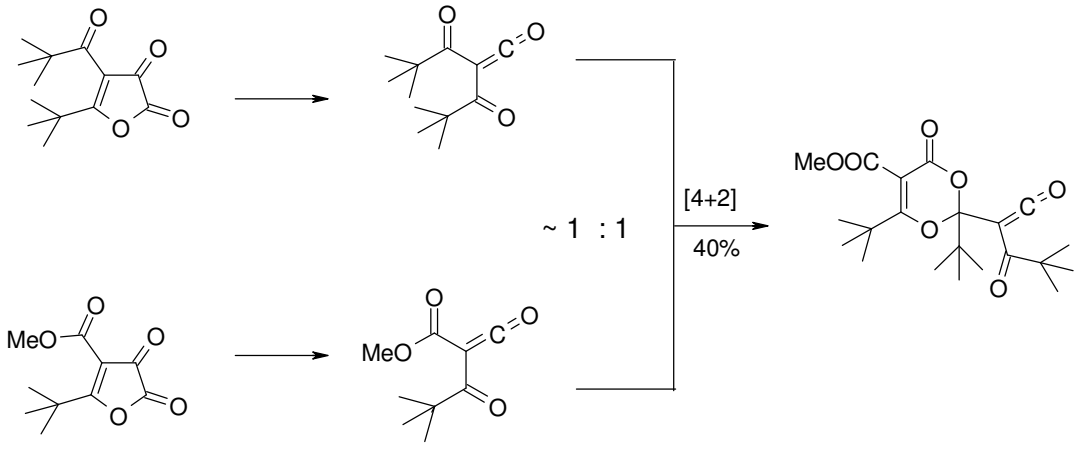
Similarly, methoxycarbonyl-pivaloylketene (see Scheme 9) exclusively undergoes dimerization across the ketene C=O irrespective of any reaction conditions applied (Scheme 13).[8]

The exact structural approval of the dimer regarding *E/Z* isomerism was achieved with aid of extensive ^{13}C NMR experiments.[8]



Scheme 13

When dipivaloylketene and methoxycarbonyl-pivaloylketene are generated simultaneously by FVP of an equimolar mixture of both precursors, namely the corresponding furan-2,3-diones, after warm-up of the cold finger besides small amounts of homo-dimers a mixed dimer is obtained as the main reaction product (Scheme 14).[23] Its exact structural approval is based on a single crystal X-ray analysis indicating that dipivaloylketene has served as the dienophile.[23]



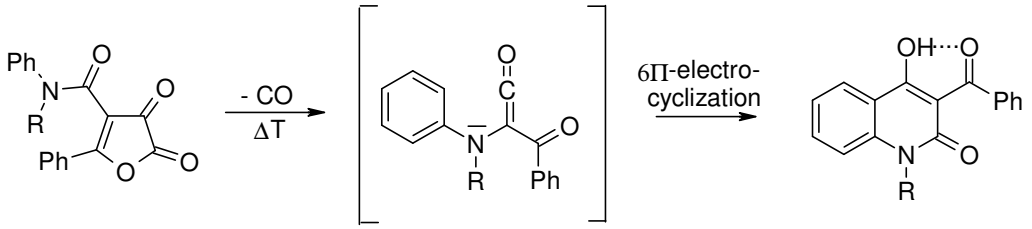
Scheme 14

This overall experimental findings on the different dimerization behaviour of monomeric α-oxoketenes depending on their specific substitution pattern has also be confirmed with aid of semiempirical (AM1) calculations on the substituent effect in such dimerization reactions comparing dibenzoylketene and dipivaloylketene, respectively.

In good agreement with the experimental results it clearly came out, that in case of the latter dimerization across both the carbonyl groups (A and B, Scheme 12) should be favoured because of its lower activation energy.[24]

3.3.2. Electrocyclization

Furan-2,3-diones bearing a *N*-phenylcarbamoyl side-chain at C-4 on heating in toluene afford a 3-benzoyl-4-hydroxy-2-quinolone ring system as a result of a 6π-electrocyclization of the corresponding α-oxoketene intermediate (Scheme 15).[3]

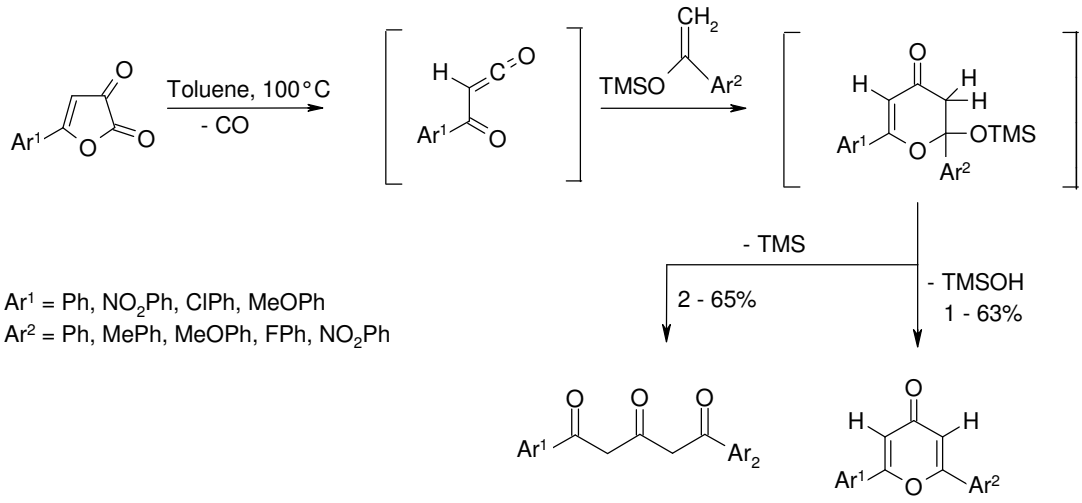


Scheme 15

3.3.3. Cycloadditions

As observed with the dimerization reactions (see **3.3.1.**) cycloadditions of α-oxoketenes, irrespective whether generated *in situ* or as neat compounds, usually proceed regioselectively as [4+2] processes[15] mainly of the inverse- or hetero-Diels-Alder type, where the oxoketene represents the electron-deficient oxa-1,3-diene reactant.[8,18,19]

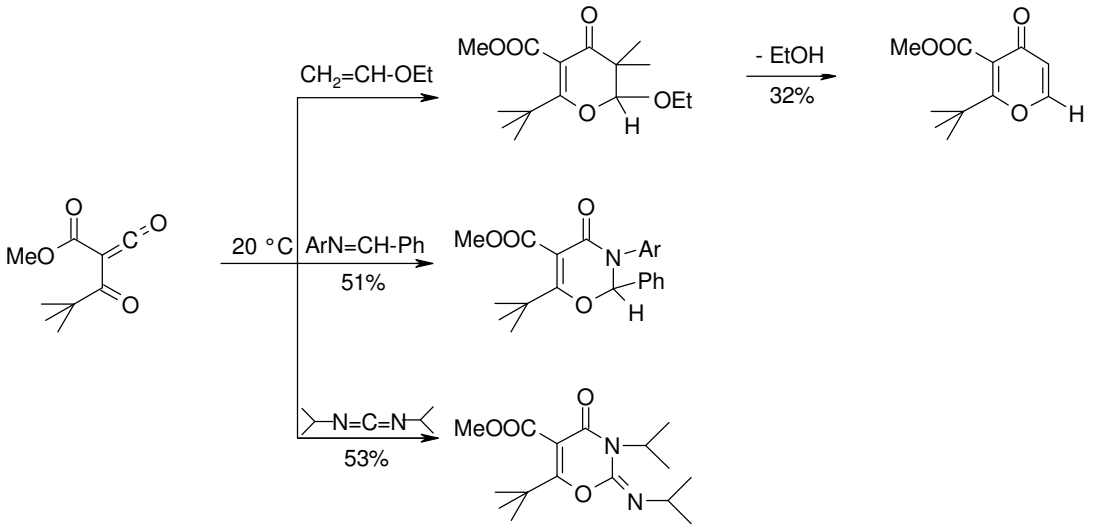
Therefore, electron withdrawing substituents in the aroyl group facilitate these cycloaddition reactions.[19] Examples are given in Scheme 16.



Scheme 16

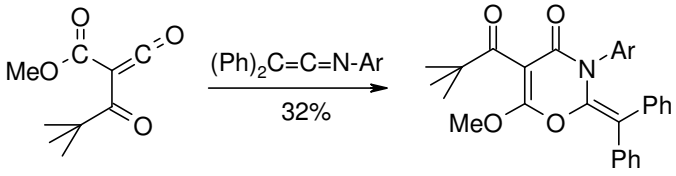
Depending on the substitution pattern of the aryl groups in diene and dienophile, the primarily formed cycloadduct stabilizes predominantly either affording a 4-pyrone derivative or an open-chain 1,3,5-triketone.[19]

In a similar way neat methoxycarbonyl-pivaloylketene, generated *in situ* by thermolysis of the corresponding furan-2,3-dione, serves as electron deficient oxa-1,3-diene adding different kinds of dienophiles, *e.g.* carbodiimides, Schiff bases, alkenes (Scheme 17).[40]



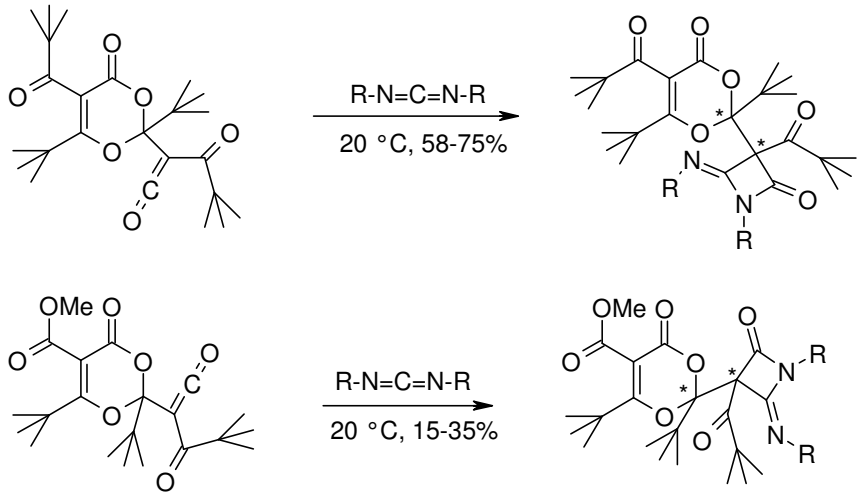
Scheme 17

Surprisingly, in case of the reaction of methoxycarbonyl-pivaloylketene with diphenylketen-*N*-arylimine, instead of the pivaloyl-carbonyl the less active ester carbonyl group is involved in the cycloaddition process (Scheme 18).[8] The reason for that unexpected behaviour can be seen in the strong steric hinderance of the bulky *t*-butyl group in the s-*Z* conformation required and the diphenylmethylidene unit of the keteneimine during the approach of the reactants forming the transition state. But, if the ester C=O participates in the oxadiene system the steric interaction is minimized.



Scheme 18

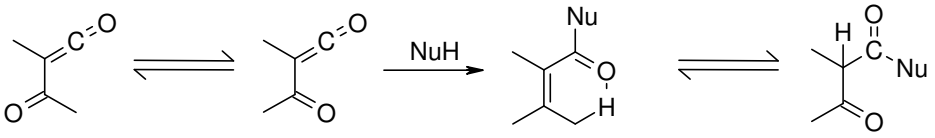
Quite different results are obtained applying remarkably stable dimeric α-oxoketenes described in Schemes 12 and 14, respectively, in cycloaddition reactions. Both molecules are rather reluctant to undergo reactions with different types of dienophiles. In case of dialkylcarbodiimides only reaction products were isolated in low to moderate yields, but, as evidenced by X-ray structure analyses, instead of [4+2] adducts obviously [2+2] cycloaddition reactions across the ketene moiety leading to spiro-ß-lactams must have occurred (Scheme 19).[17b, 23] This behaviour is well known from simple ketenes,[15b,16] but has never been observed with α-oxoketenes so far. With aid of *ab initio* as well as semiempirical (AM1, PM3) calculations on α-oxoketenes in general it came clear, that sterically crowded derivatives, as the two dimeric oxoketenes presented in Schemes 12, 14 and 19, are found to exist solely as s-*E* conformers. The rotational barrier to adopt the s-*Z* conformation essential for generating [4+2] adducts would be approximately 15 Kcal/mol.[25]



Scheme 19

3.3.4. Reactions with nucleophiles

One of the most common reactions of α-oxoketenes - as with ketenes in general - is the addition of nucleophiles which leads to ß-ketoacid derivatives following a reaction pathway outlined in Scheme 20. Preparative,[21] structural and stereochemical,[27,28] mechanistic[27,29] and theoretical[30] aspects have been thoroughly investigated.[15,26]

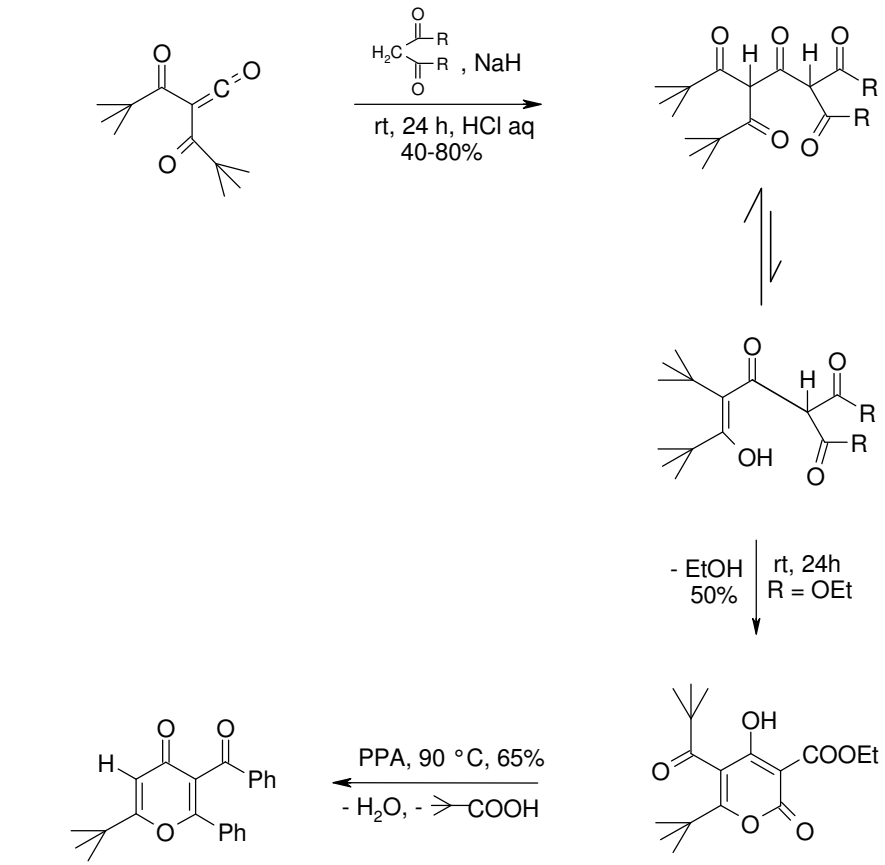


Scheme 20

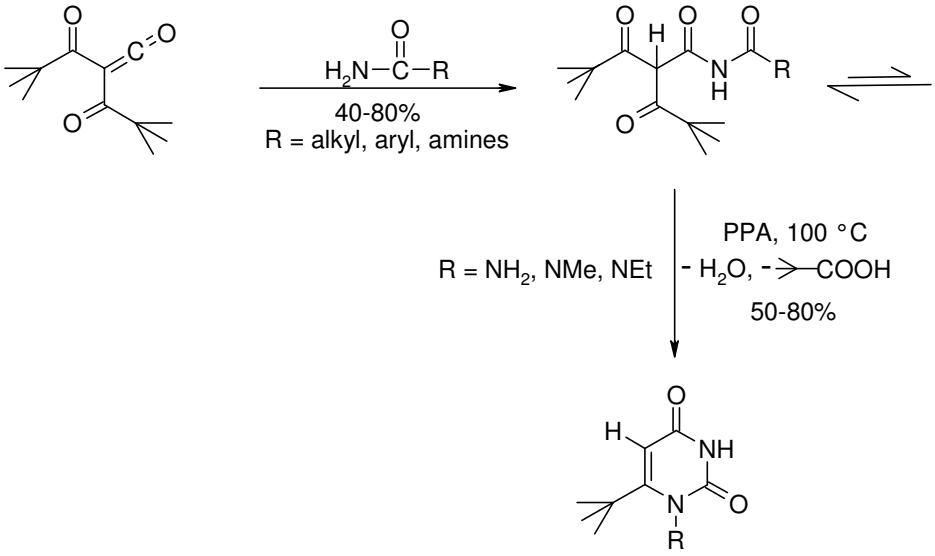
Some more recent examples are presented in Schemes 21 and 22: dipivaloylketene adds C-nucleophiles with subsequent ring closure to pyrono-compounds,[31] while functionalised NH_2-nucleophiles afford dipivaloyl acetic acid amide derivatives, which in some case may be cyclized to pyrimidines.[32]

In a similar way, methoxycarbonyl-pivaloylketene adds primary amines to afford pivaloyl-malonic ester amide derivatives (Scheme 23),[8] which by no means could be cyclized as successfully done with dipivaloyl acetic acid derivatives (Schemes 21 and 22). Furthermore, it is interesting to note, that all primary adducts depicted in Schemes 21–23 unequivocally prefer the non-enolized tautomeric conformation in solution, evidenced by the presence of the corresponding C-H signals in ^{1}H as well ^{13}C nmr spectra, although the enolic species should considerably be stabilized by hydrogen bridges. These rather surprising experimental findings were supported by semiempirical calculations on the keto-enol tautomerism of diacylacetic acid derivatives in general.[33]

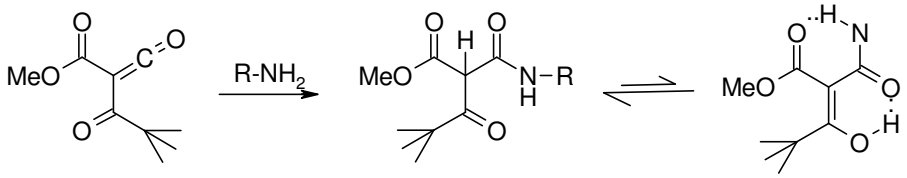
More exciting results were obtained from reactions of neat dimeric α-oxoketenes and *e.g.* electron rich aromatic primary amines.[34,35] The dioxinonyl-oxoketene ring is transformed into a mono-functionalized bridged bisdioxine derivative, exhibiting axial chirality. This rather rare heterocyclic system is further converted into the 2,4,6,8-tetraoxaadamantane skeleton by simple acidic hydrolysis (Scheme 24).[36]



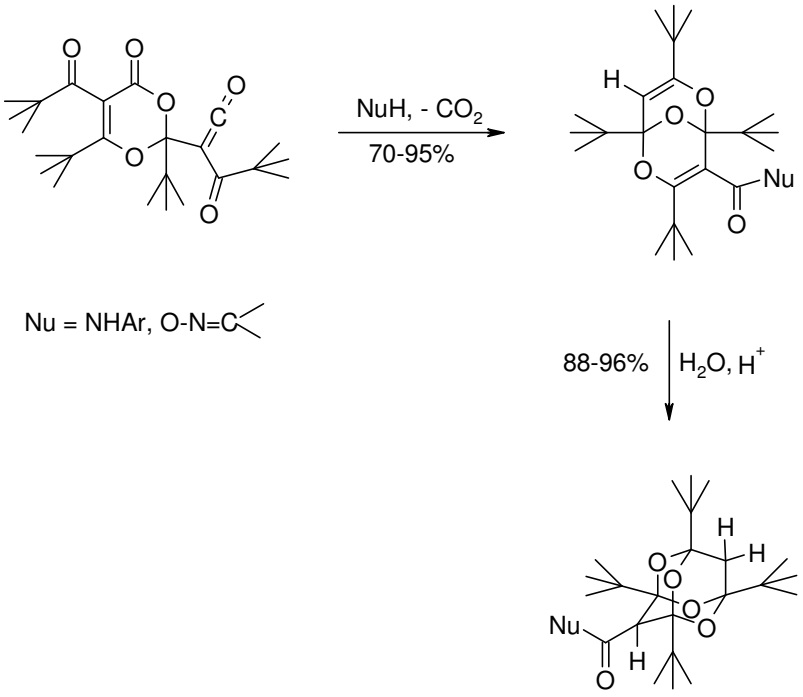
Scheme 21



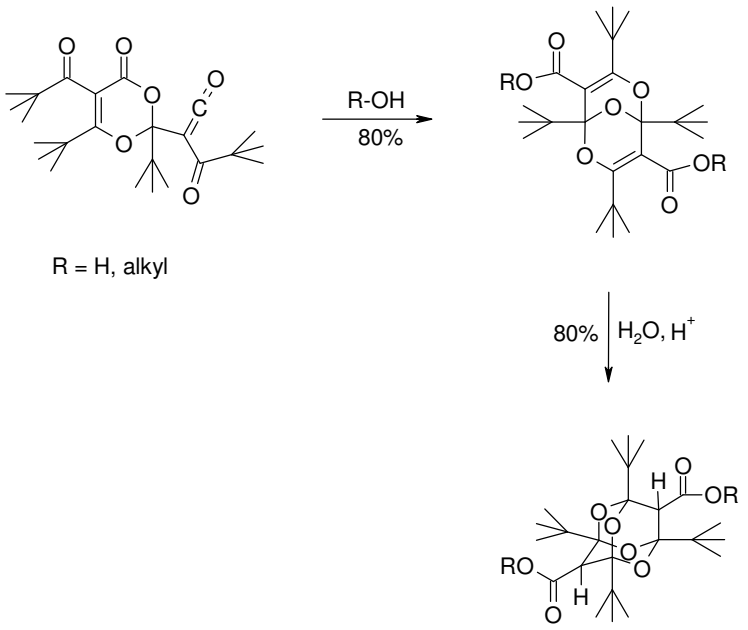
Scheme 22



Scheme 23



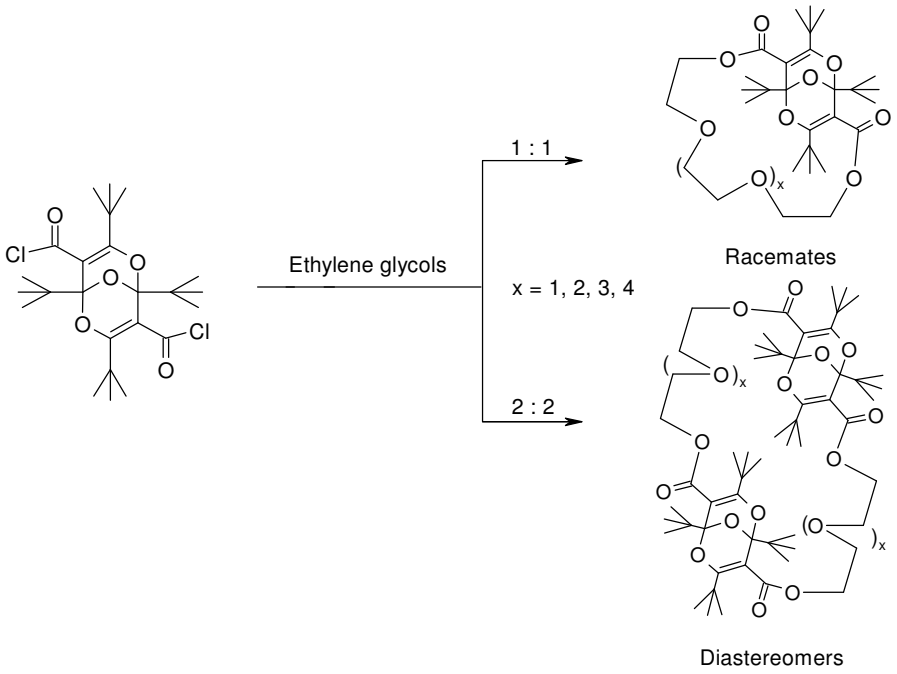
Scheme 24



Scheme 25

This reaction sequence could be extended to oximes and mono-substituted hydrazines[37] and furthermore, from reaction with OH-nucleophiles bis acid-functionalized bisdioxine molecules are obtained (Scheme 25).[35]

Due to their specific geometry the bifunctionalized derivatives, in particular the bisacid chloride, are suitable to serve as novel chiral spacer units in macrocyclic systems of different sizes, which are currently tested as new host-systems in several host-guest interactions (Scheme 26).[38,39]



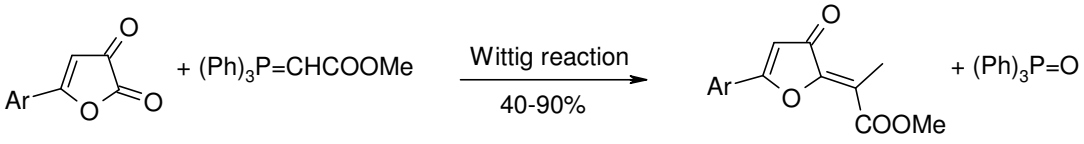
Scheme 26

4. Cycloaddition Reactions

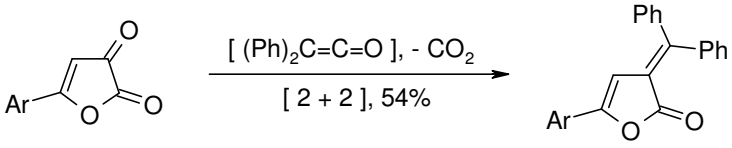
Due to their different chemical behaviour in cycloaddition reactions in general, the furan-2,3-diones have to be devided into two groups: a) furan-2,3-diones without any functionality at C-4 (**4. 1.**); b) 4-acyl-furan-2,3-diones (**4. 2.**).

4.1. 5-Aryl-furan-2,3-diones

5-Aryl-furan-2,3-diones have been reported to undergo Wittig reactions[41] with acylmethylene-triphenylphosphoranes affording regioselectively 2-acylmethylene-5-aryl-3(2*H*)-furanones in good yields (40–90%).[42] These reactions in general might be regarded as 2+2 cycloaddition processes[43] to give oxaphosphetanes as intermediates,[44] followed by the corresponding 2+2 cycloreversions (Scheme 27).



Scheme 27

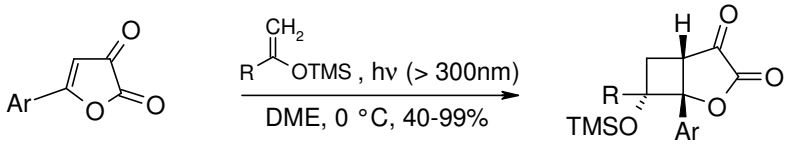


Scheme 28

On the other hand, when 5-aryl-furan-2,3-diones were treated with diphenylketene, generated *in situ* by thermolysis of benzoyl-phenyldiazomethane, 2+2 cycloaddition of the ketene with subsequent

cycloreversion occurred across the carbonyl at C-3, thus ending up with 2(3*H*)furanone derivatives (Scheme 28).[42,45] A quite similar behaviour was also observed reacting 4-acylfuran-2,3-diones with diphenylketene (see also **4. 2.**).[49]

The [2+2] photocycloaddition reaction of 5-arylfuran-2,3-diones to trimethylsilyloxyethylenes proceeds with excellent stereoselectivity to form *cis*-fused cyclobutano-4,5-dihydrofuran-2,3-diones in moderate to high yields (Scheme 29).[4]

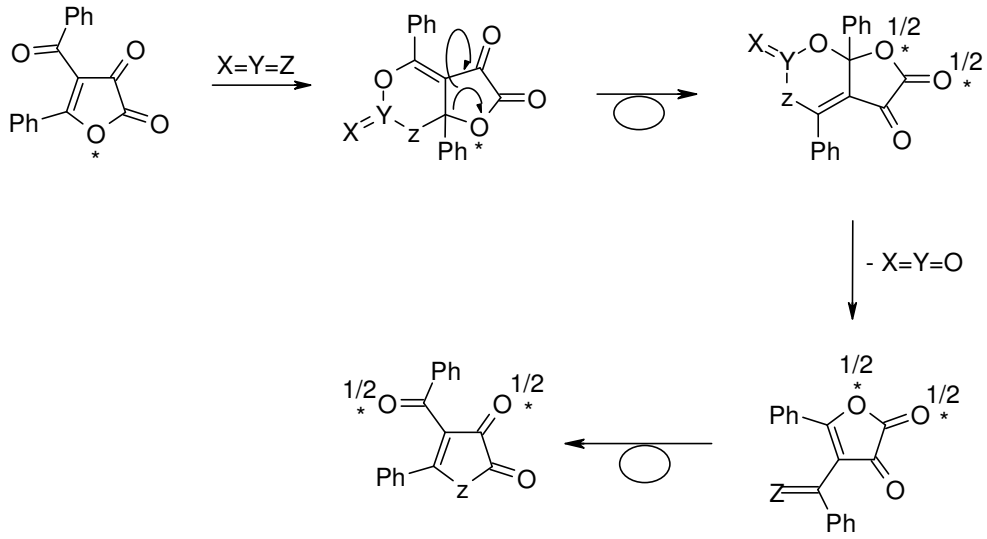


Scheme 29

4.2. 4-Acyl-furan-2,3-diones

4.2.1. Thermal cycloaddition reactions

The oxa-1,3-diene moiety in those furan-2,3-diones, formed from the carbonyl group at C-4 and the endocyclic C=C-bond, is capable to add several dienophiles *via* 4+2 (or 4+1, with isocyanides) cycloaddition processes, in most cases accompanied by surprising novel molecular rearrangements (Scheme 30).

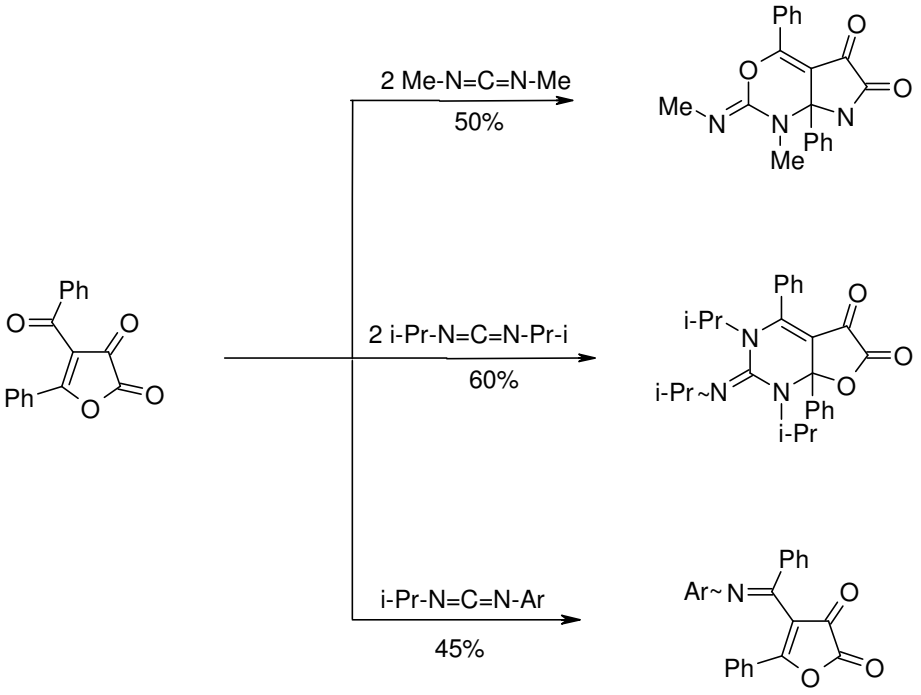


Scheme 30

The basic experimental findings with 4-benzoyl-5-phenylfuran-2,3-dione as suitable educt, outlined in Scheme 30, describing reactions of isocyanates,[47] carbodiimides,[48] ketenes,[49] ketenimines,[50] isocyanides[51] and imines,[52] as well as the mechanistic investigation of the molecular rearrangements with aid of ^{17}O-labelling,[53] have already been reported in a previous review.[1]

A closer look to the outcome of the reaction of 4-benzoyl-5-phenylfuran-2,3-dione with carbodiimides made obvious, that, depending on the specific substitution pattern of the carbodiimide, different heterocyclic systems were obtained (Scheme 31).[54] With aid of ^{17}O-labeling studies, by comparison of the distribution of the label within starting materials and various products applying ^{17}O-NMR spectroscopy, again an unusual furandione-furandione rearrangement was disclosed (Scheme 30). This

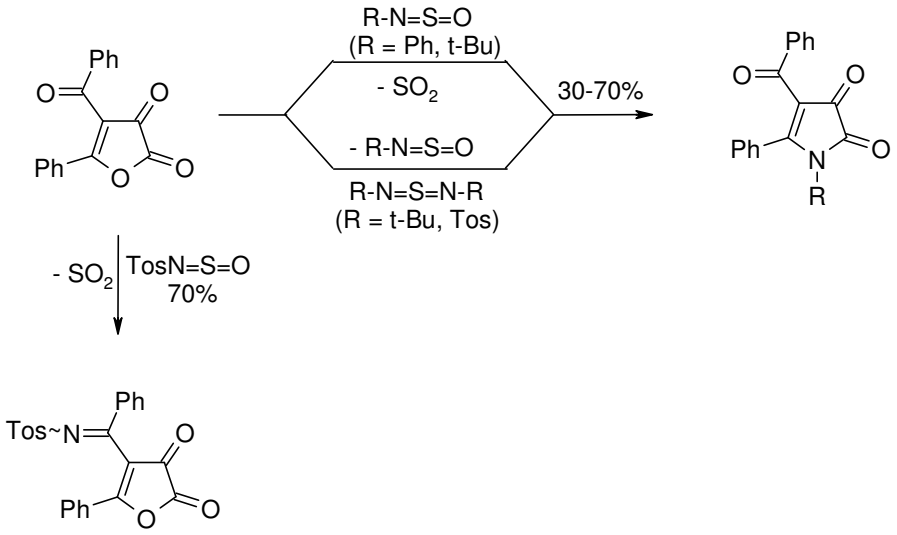
rearrangement can be regarded as a peculiar variation of the well known nucleophilic substitution at a vinylic carbon.[55]



Scheme 31

On the first view, the experimental results of reactions of 4-benzoyl-5-phenylfuran-2,3-dione with S-heterocumulenes (*N*-sulfinylamines, sulfur diimides) looked rather simple since either the corresponding pyrrol-2,3-diones or iminobenzyl-furan-2,3-diones were obtained (Scheme 32).[56]

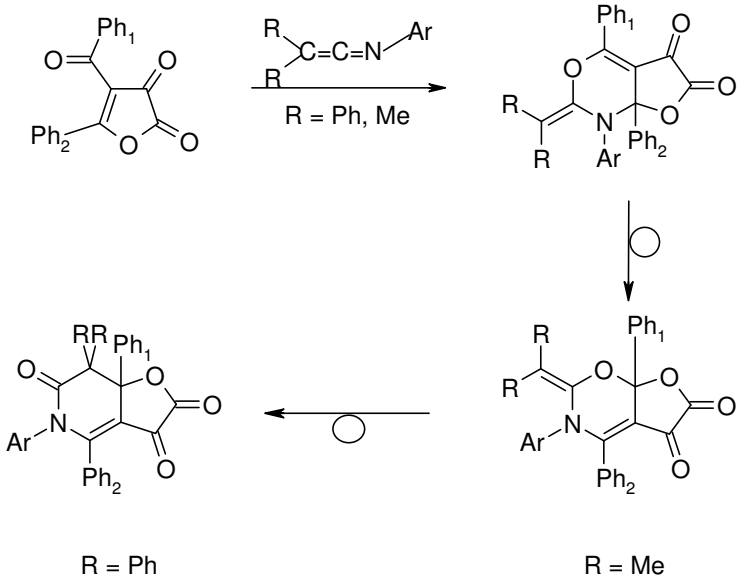
But, based upon ^{17}O-labeling experiments, again evidence was found for all reactions to proceed *via* several molecular rearrangements of the furandione-furandione type accompanied also by *long-range* Dimroth rearrangements.[56,57]



Scheme 32

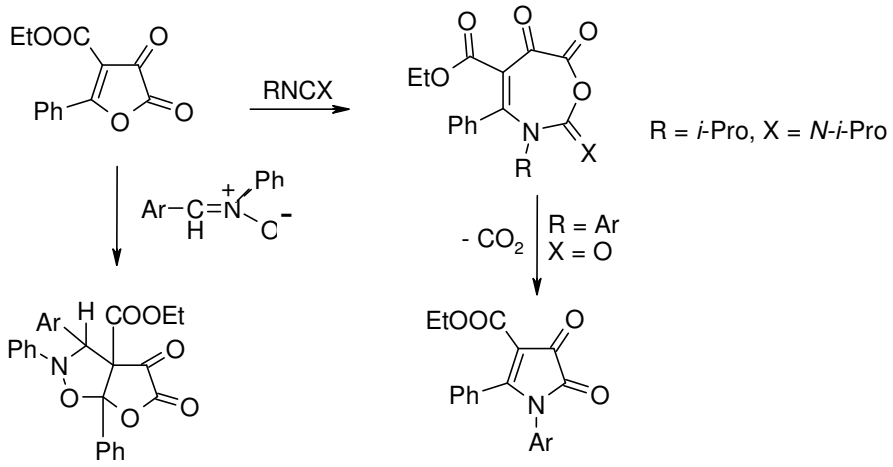
In addition, in order to get some more insight into these rather complex reaction sequences several semiempirical as well as density functional calculations were performed. In particular, this was successfully done with the reaction of 4-benzoyl-5-phenylfuran-2,3-dione and ketenimines, where, depending on the substituents of the ketenimine, either furo[3,2-e]1,3-oxazines or furo[3,2-c]pyridines were obtained (Scheme 33).[59,60]

The overall outcome of these calculations was in nice accordance with all sometimes divergent experimental findings and brought about a final confirmation for these novel rearrangements.[58,59, 60]



Scheme 33

Exchange of the aroyl- against an ester group at C-4 of the furandione obviously changes the chemical reactivity significantly. The ester carbonyl is not sufficiently active to serve as part of the heterodiene unit essential for hetero Diels-Alder reactions. Alternatively, the heterocumulene is inserted into the furandione ring forming a seven-membered ring system, which is stable in case of the carbodiimide, while decarboxylates in case of the isocyanate (Scheme 34).[61]

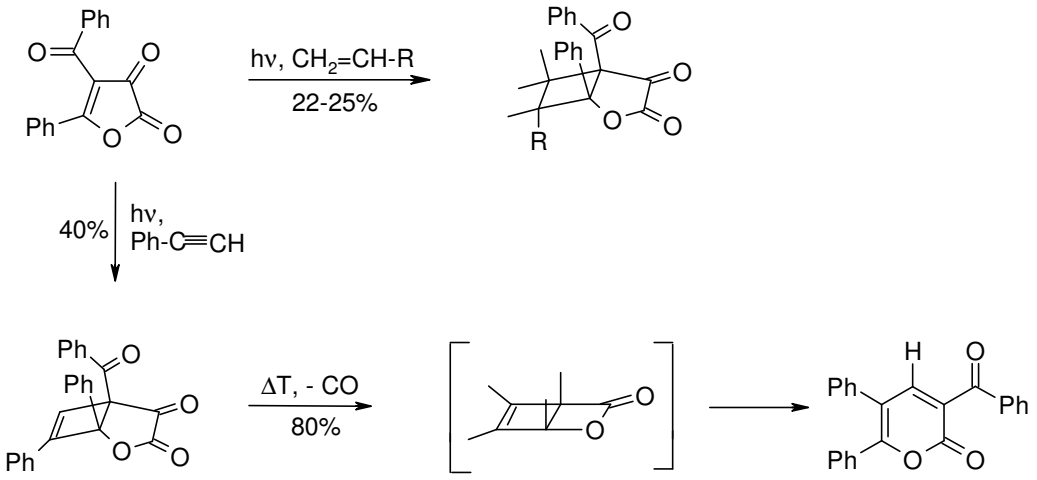


Scheme 34

It was further reported[62] that nitrons undergo a 1,3-dipolar cycloaddition regioselectively across the C=C bond of the furandione (Scheme 34).

4.2.2. Photocycloaddition reactions

Photocyclization of 4-benzoyl-5-phenylfuran-2,3-dione with electron rich alkenes and phenylethyne afford regio- and stereoselectively the corresponding [2+2] adducts in low to moderate yields. On heating the phenylethyne adduct after decarbonylation may form a cyclobuta[b]oxetanone intermediate which undergoes electrocyclic ring opening to afford a α-pyrono derivative (Scheme 35).[63]



Scheme 35

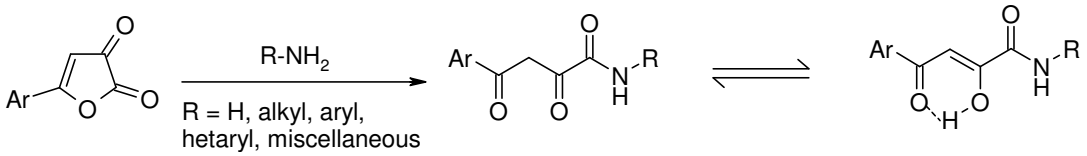
5. Reactions with nucleophiles

5.1. 5-Aryl-furan-2,3-diones

Due to their specific structural feature the 5-aryl-furan-2,3-diones offer several positions to be attacked by nucleophiles: a lactone moiety at C-2, a carbonyl group at C-3 and an endocyclic enol ester carbon at C-5. However, all experimental results reported indicate an attack of the corresponding nucleophile at the lactone carbonyl with subsequent ring opening (see the following paragraphs).

5.1.1. NH-Nucleophiles

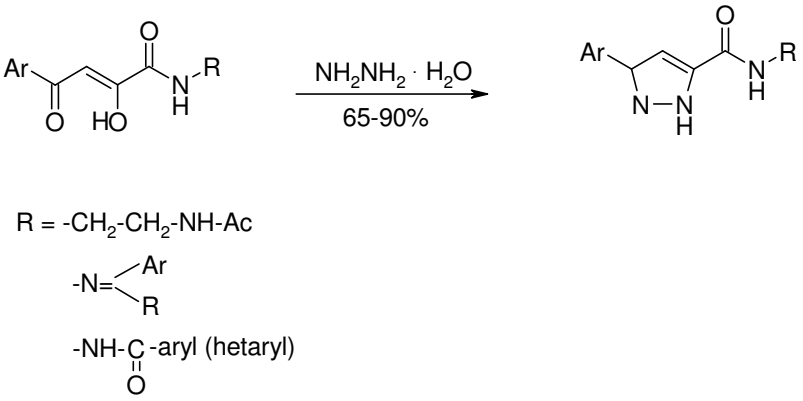
Primary amines bearing a great variety of substituents (*e.g.* R=H, alkyl, aryl, hetaryl) and 5-arylfuran-2,3-diones react in a general mode with ring opening to afford open-chain multi-carbonyl compounds (Scheme 36).[64]



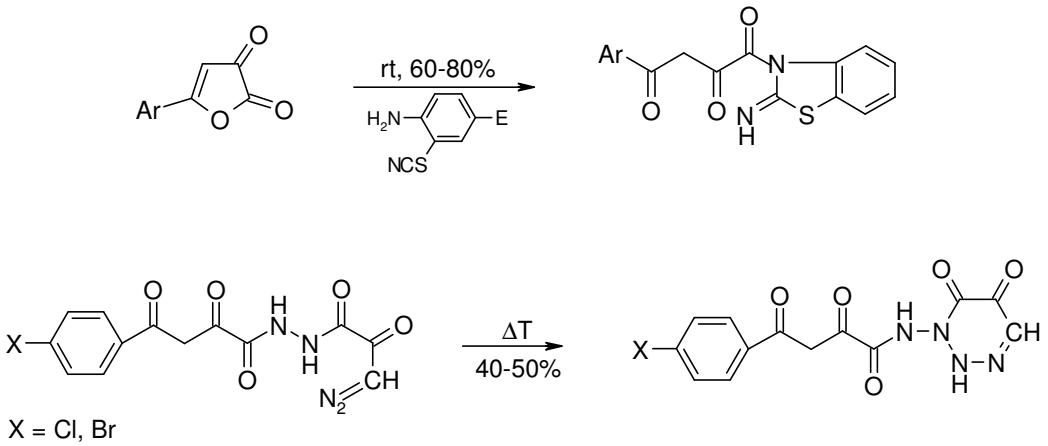
Scheme 36

In addition, the so formed 1,3-dicarbonyl units in many cases were then cyclized to 1,2-diazoles by reaction with hydrazine hydrate[65] and/or, depending on the specific functionalization of the amine originally

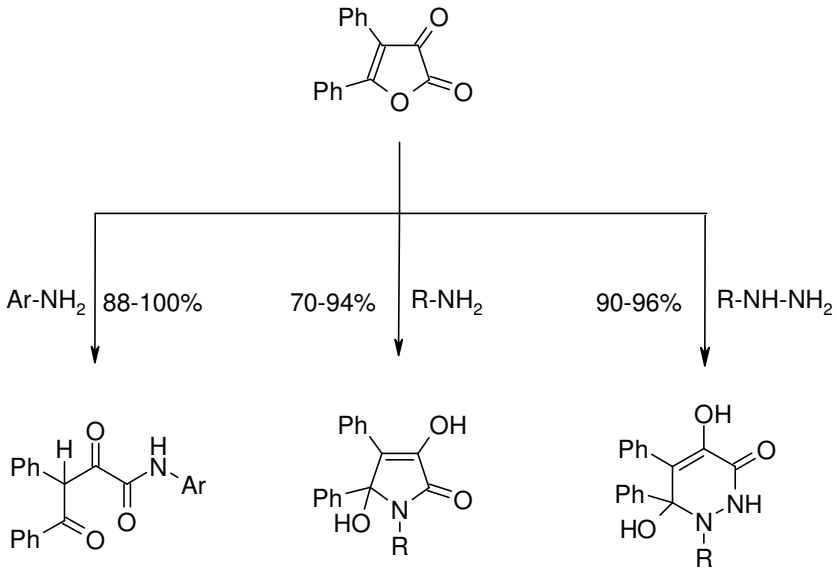
applied, further heterocyclization was achieved.[66,67] Some selected examples are presented in Schemes 37 and 38.



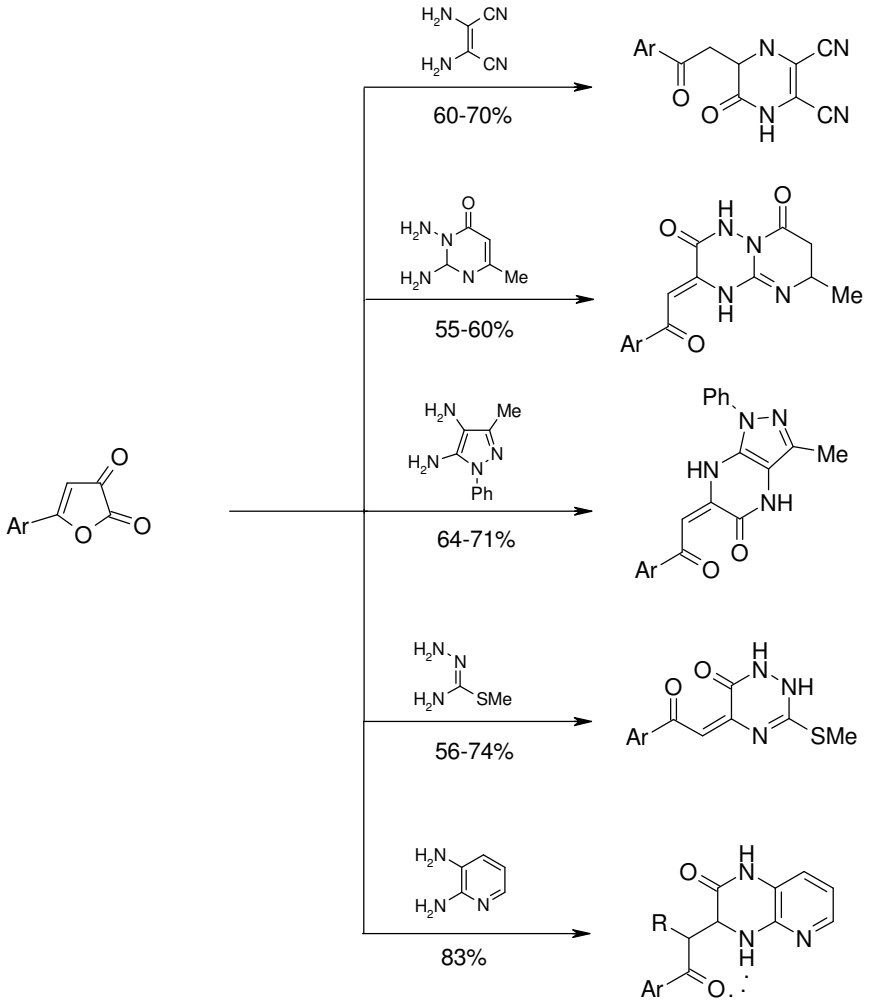
Scheme 37



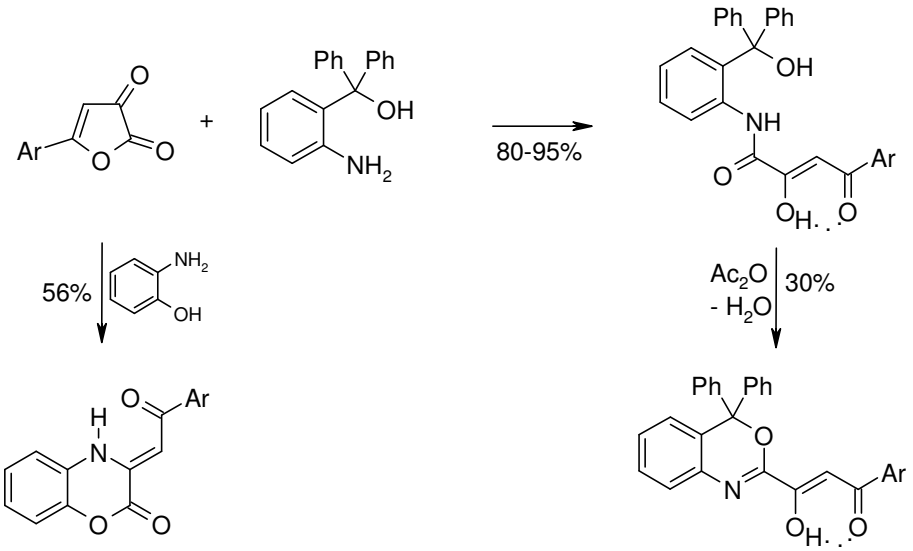
Scheme 38



Scheme 39



Scheme 40



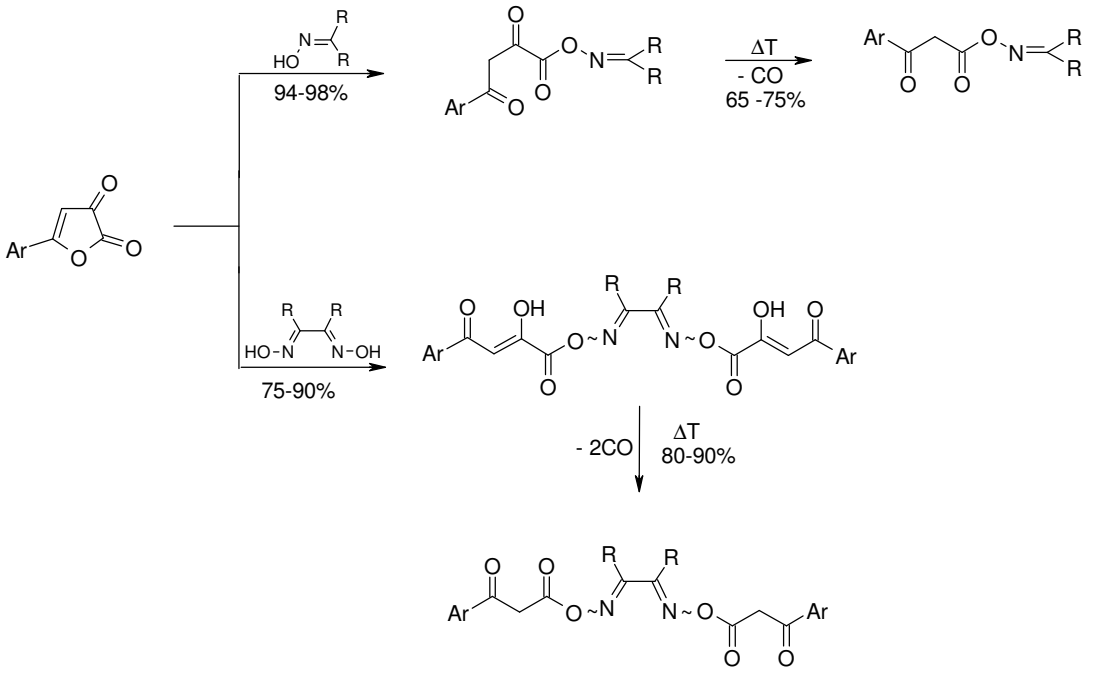
Scheme 41

4,5-Diphenylfuran-2,3-dione and arylamines gave the aroylpyruvic acid amides as expected, with alkylamines, obviously due to their stronger basicity, recyclization to pyrrolone derivatives occurs. A similar behaviour is also observed applying alkylhydrazines which afford 1,2-diazinones (Scheme 39).[68]

When bis-amines[69] or hydroxy-amines[70] were applied, the primary ring-opened product immediately underwent cyclocondensation to the corresponding heterocyclic system as the final reaction product (Schemes 40 and 41).

5.1.2. OH–Nucleophiles

Several oximes and bis-oximes have been reacted at 25–60 °C with 5-arylfurandiones providing *O*-aroylpyruvoyloximes in nearly quantitative yields. In boiling toluene (110 °C) O-aroylacetyloximes were formed due to decarbonylation reactions (Scheme 42). Most of these compounds exhibit marked bacteriostatic and anti-inflammatory effects.[71]



Scheme 42

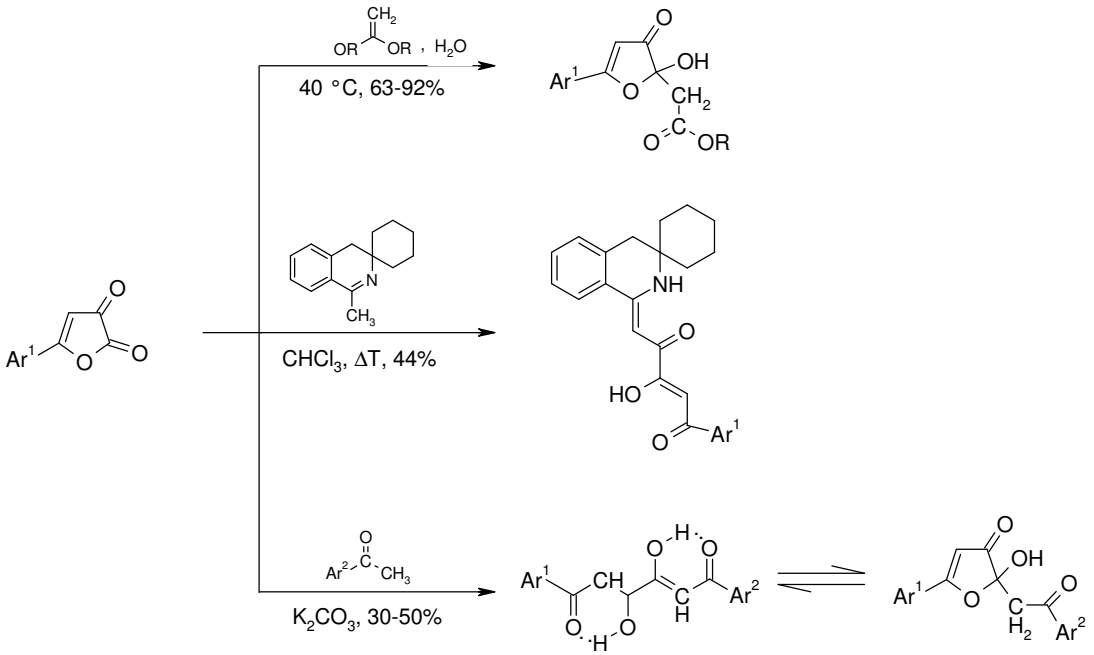
In a similar way, with bis-oximes the corresponding bis(*O,O*'-aroylpyruvoyl-) and bis(*O,O'*-aroylacetyl)-1,2-dioximes were obtained in high yields. These compounds possess moderate to high analgesic activities.[72]

5.1.3. C-Nucleophiles

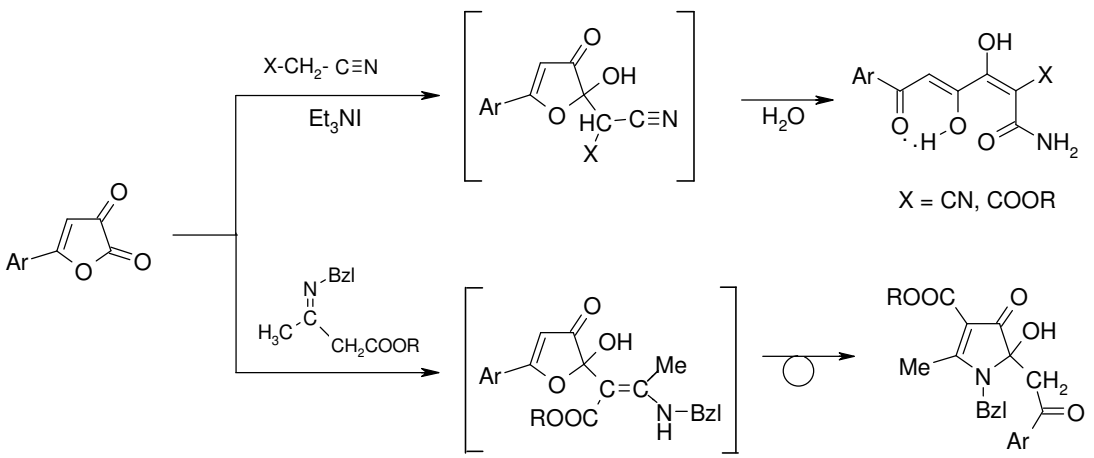
CH-acidic compounds are also capable to add to the lactone carbonyl in furan-2,3-diones either with, in order to generate a carbanion intermediate,[73] or without[74] basic catalysis, thus affording 2-hydroxy-furan-2-ones or open-chain tetracarbonyl compounds, occasionally in oxo-cyclo tautomerism with their cyclized forms (Schemes 43 and 44).[75]

The course in the reaction of furan-2,3-diones with diazoalkanes is shown to strongly depend on the nature of the diazo compound employed. Whilst with diazomethane a 2-spirocyclopropane-3-oxofuran is obtained, the reaction with diphenyldiazomethane takes place at C-3 to afford a 3-oxiranyl-furan-2-one.

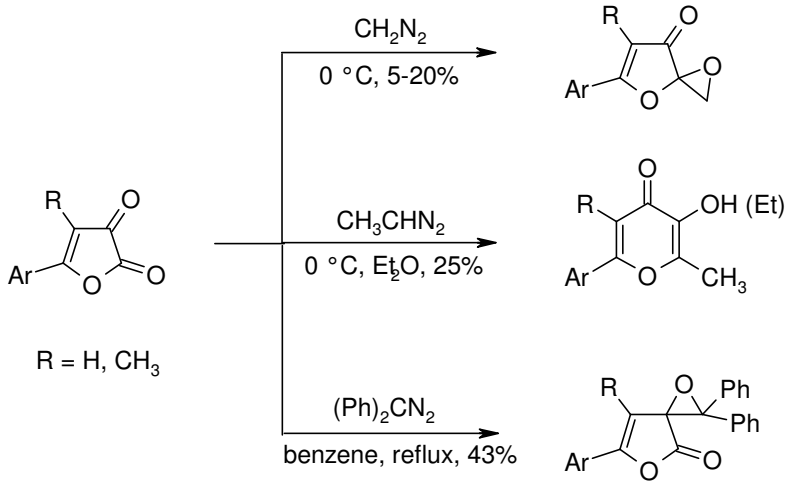
The diazoethane also attacks C-2 but obviously induces a ring enlargement reaction inserting the CH thus forming a 4-pyran-4-one system (Scheme 45).[76]



Scheme 43



Scheme 44

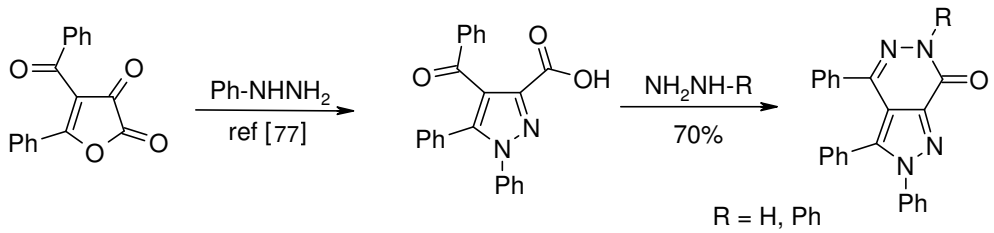


Scheme 45

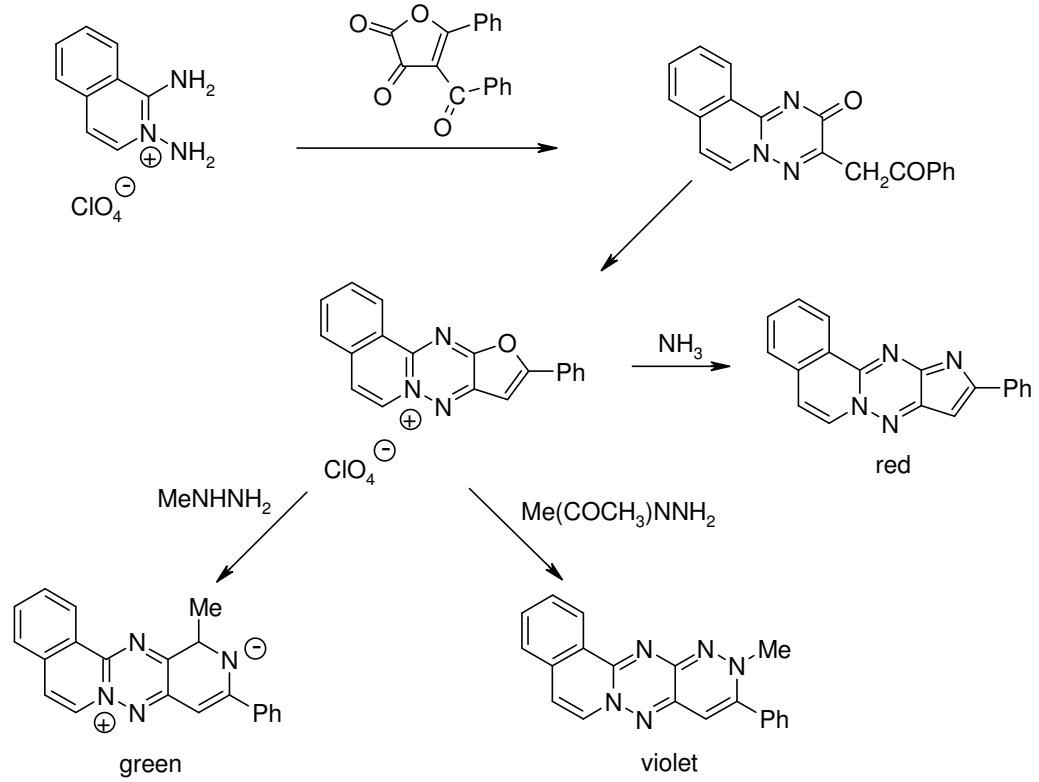
5.2. 5-Acyl-furan-2,3-diones

5.2.1. NH_2-Nucleophiles

In continuation of previous investigations on reactions of 4-benzoyl-5-phenyl-furan-2,3-dione with hydrazines[77] which afforded the corresponding pyrazole-3-carboxylic acid, a further cyclization to a pyrazolo[3,4-d]pyridazine system was achieved by cyclocondensation with phenylhydrazine or hydrazine, respectively (Scheme 46).[78]



Scheme 46



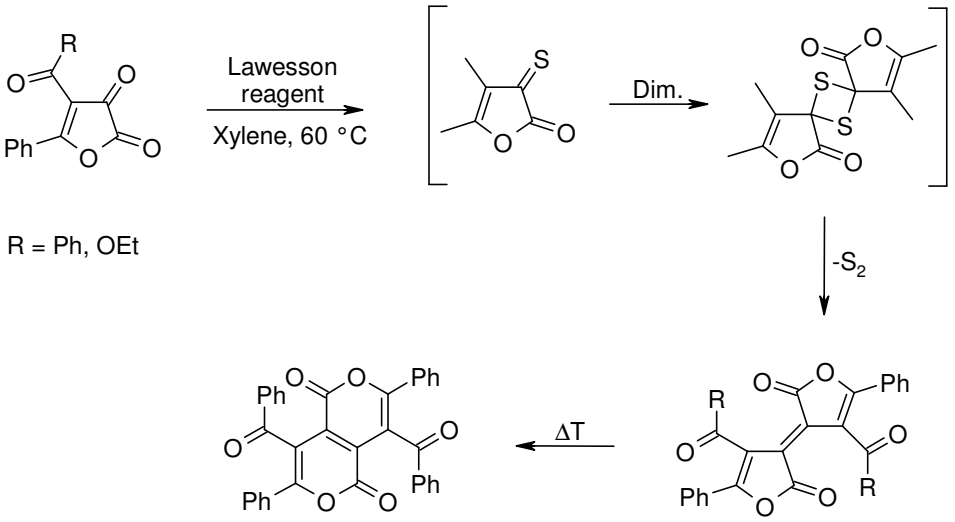
Scheme 47

Several deeply coloured compounds representing poly-fused tetraaza heterocyclic skeletons as chromophores were obtained from cyclocondensation reactions of 4-benzoyl-5-phenylfuran-2,3-dione with 1,2-diaminoquinolinium, or 1,2-diaminoisoquinolinium perchlorates and subsequent treatment of the so formed furo[2,3-e]quinolino(isoquinolino)[1,2-b]-*as*-triazinium perchlorate with ammonia or hydrazines (*e.g.* Scheme 47).[79]

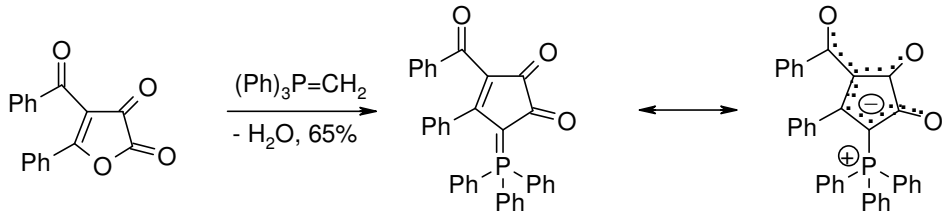
5.2.2. Miscellaneous

A novel isoindigoide dye[80] has been prepared from reaction of 4-benzoyl-5-phenylfuran-2,3-dione with Lawesson reagent[81] *via* sulfurization of the carbonyl at C-3, dimerization across the C=S bond and

extrusion of sulfur (Scheme 48). This dye can thermally be isomerised into a pyrano[4,3-c]pyrane, accompanied by a significant hypsochromic shift.



Scheme 48



Scheme 49

Deeply violet crystals, obtained from reaction of 4-benzoyl-5-phenylfuran-2,3-dione with methylenetriphenylphosphorane according to a known procedure,[82] were disclosed as a resonance stabilized cyclic acylidenetriphenylphosphorane as the result of a *transylidation* process[83] (Scheme 49). In a similar reaction, 5-aryl-furan-2,3-dione and triphenylphosphoranylidenepyruvate afforded a deeply coloured cyclic oxalyl ylide.[84]

References

1. Kollenz, G.; Heilmayer, W. in *Trends in Heterocyclic Chemistry*, Research Trends, ed. **1993**, *3*, 379.
2. Hnach, M.; Ayard, J. P.; Zineddine, H. *Bull. Soc. Chim. Fr*. **1991**, 393.
3. Borowiec, H.; Grochowski, J.; Serda, P. *J. Chem. Res. (S)* **1996**, 248.
4. Saalfrank, R. W.; Hoerner, B.; Reck, S.; Nachtrab, J.; Peters, E. M.; Peters, K.; von Schnering, H. P. *Z. Naturforschg. B* **1996**, *51*, 1084.
5. Saalfrank, R. W.; Nachtrab, J.; Reck, S.; Hampel, F. *Z. Naturforschg. B* **1999**, *54*, 179.
6. Maslivets, A. N.; Tarasova, O. P.; Andreichikov, Y. S. *Russ. J. Org . Chem*. (Engl. Transl) **1992**, 1011.
7. Saripinar, E.; Guzel, Y.; Onal, Z.; Ilhan, I. O.; Akcamur, Y. *J. Chem. Soc. Pak*. **2000**, *22*, 308.
8. Stadler, A.; Zangger, K.; Belaj, F.; Kollenz, G. *Tetrahedron* **2001**, *57*, 6757.
9. Maslivets, A. N.; Lisovenko, N. Y.; Golovnina, O. V.; Vostrov, E. S.; Tarasova, O. P. *Chem. Heterocycl. Compd*. (Engl. Transl.) **2000**, 483.

10. Zankowska-Jasinska, W.; Burgiel, M.; Golus, J.; Kolasa, A.; Walocha, K.; Zaleska, B. Chojnacka-Wojcik, E.; Wiczynska, B.; Tatrczynska, E. *Pol. J. Pharmacol. Pharm.* **1982**, *34*, 391.
11. Koz'minykh, E. N.; Trapeznikova, N. N.; Chupilova, E. A.; Igidov, N. M.; Koz'minykh, V. O. *Russ. J. Org. Chem.* (Engl. Transl.) **2000**, *37*, 116.
12. Kappe, C. O.; Kollenz, G.; Wentrup, C. *Heterocycles* **1994**, *38,* 779.
13. Koz'minykh, V. O.; Igidov, N. M.; Koz'minykh, E. N.; Aliev, Z. G. *Pharmazie* **1993**, *43*, 99.
14. Zaleska, B.; *Monatsh. Chem*. **1986**, *117*, 671.
15. Recent Reviews: a) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219; b) Tidwell, T. T., Ed., *Ketenes* , J. Wiley & Sons, Inc., **1995**, p. 1.
16. a) Staudinger, H.; Hirzel, H. *Ber. dtsch. chem. Ges*. **1916**, 2522. b) Newman, S. M.; Zuech, E. A. *J. Org. Chem*. **1962**, *27*, 1436. c) Leung-Toung, R.; Wentrup, C. *Tetrahedron* **1992**, *48*, 7641.
17. a) Kappe, C. O.; Evans, R.; Kennard, C. H. L.; Wentrup, C. *J. Am. Chem. Soc*. **1991**, *113*, 4234. b) Kappe, C. O.; Faerber, G.; Wentrup, C.; Kollenz, G. *J. Org. Chem.* **1992**, *57*, 7078. c) Nikolaev, V. A.; Frenkh, Y.; Korobytsina, I. K. *Russ. J. Org. Chem*. **1978**, *14*, 1338. d) Zhdankin, V. V.; Stang, P. J. *Tetrahedron Lett*. **1993**, *34,* 1461.
18. Saitoh, T.; Oyama, T.; Horiguchi, Y.; Toda, J.; Sano,T. *Chem. Pharm. Bull*. **1996**, *44*, 1298.
19. Saitoh, T.; Oyama, T.; Sakurai, K.; Niimura, Y.; Hinata, M.; Horiguchi, Y.; Toda, J.; Sano, T. *Chem. Pharm. Bull*. **1996**, *44*, 956.
20. Toda, J.; Saitoh, T.; Oyama, T.; Horiguchi, Y.; Sano, T. *Heterocycles* **1996**, *43*, 2457.
21. Sano, T.; Saitoh, T.; Toda, J. *Heterocycles* **1993**, *36*, 2139.
22. Kollenz, G.; Holzer, S.; Kappe, C. O.; Dalvi, T. S.; Fabian, W. M. F.; Sterk, H.; Wong, M. W.; Wentrup, C. *Eur. J. Org. Chem.* **2001**, 1315.
23. Wallfisch, B. C.; Belaj, F.; Wentrup, C.; Kappe, C. O.; Kollenz, G. *J. Chem. Soc., Perkin Trans 1* **2002**, 599.
24. Fabian, W. M. F.; Kollenz, G. *J. Mol. Struct. (Theochem)* **1994** , *313*, 219.
25. Janoschek, R.; Fabian, W. M. F.; Kollenz, G.; Kappe, C. O. *J. Comput. Chem*. **1994**, *15*, 132.
26. Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587.
27. Freiermuth, B.; Wentrup, C. *J. Org. Chem*. **1991**, *56*, 2286.
28. Sakaki, J.; Sugita, Y.; Sato, M.; Kaneko, C. *Tetrahedron* **1991**, *47*, 6197.
29. Nikolaev, V. A.; Popik, V. V. *Tetrahedron Lett*. **1992**, 33, 4483.
30. Allen, A. D.; McAllister, M. A.; Tidwell, T. T. *Tetrahedron Lett*. **1993**, *34,*1095.
31. Kollenz, G.; Dalvi, T. S.; Kappe, C. O.; Wentrup, C. *Arkivoc* **2000**, *1*, 84.
32. Kollenz, G.; Kappe, C. O.; Dalvi, T. S.; Wentrup, C. *Arkivoc* **2001**, *2*, 30.
33. Fabian, W. M. F.; Kollenz, G.; Akcamur, Y.; Kök, T. R.; Teczan, M.; Akkurt, M.; Hiller, W. *Monatsh. Chem*. **1992**, *123*, 265.
34. Kappe, C. O.; Faerber, G.; Wentrup, C.; Kollenz, G. *Tetrahedron Lett.* **1992**, *33,* 4553.
35. Kappe, C. O.; Kollenz, G.; Fabian, W. M. F.; Wentrup, C.; Faerber, G. *J. Org. Chem.* **1993**, *58*, 3361.
36. Heilmayer, W.; Dalvi, T. S.; Kappe, C. O.; Wentrup, C.; Gruber, K.; Sterk, H.; Kollenz, G. *J. Chem. Soc., Chem. Commun*. **1995,** 797.
37. Dalvi, T. S.; Kappe, C. O.; Wentrup, C.; Kollenz, G. *Heterocycles* **1998**, *48*, 1841.
38. Kollenz, G.; Heilmayer, W.; Kappe, C. O.; Wallfisch, B.; Wentrup, C. *Croat. Chem. Acta* **2001**, *74*, 815.
39. Wallfisch, B. C.; Egger, T.; Heilmayer, W.; Kappe, C. O.; Wentrup, C.; Belaj, F.; Klintschar, G.; Kollenz, G. *Supramolecular Chem*. **2002**, *14*, 383.
40. Abd El-Nabi, H. A.; Kollenz, G. *Monatsh. Chem.* **1997**, *128*, 381.
41. Review : Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 836.
42. Kozminykh, V. O.; Igidov, N. M.; Kozminykh, E. N.; Aliev, Z. G. *Pharmazie* **1993**, *48*, 99.
43. Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc*. **1990**, *112*, 3905.
44. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R. Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc*. **1986**, *108*, 7684.
45. Igidov, N. M.; Kozminykh, E. N.; Shavkunova, G. A.; Kozmynikh, V. O.; Berezina, E. S. *Russ. Chem. Bull*. **1995**, *44*, 322 (engl.).

46. Sano, T.; Koseki, N.; Saitoh, T.; Horiguchi, Y.; Toda, J.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull*. **1997**, *45*, 608.
47. Kollenz, G.; Penn, G.; Dolenz, G.; Akcamur, Y.; Peters, K.; Peters, E. M.; von Schnering, H. *Chem. Ber*. **1984**, *117*, 1299.
48. Kollenz, G.; Penn, G.; Ott, W.; Peters, K.; Peters, E. M.; von Schnering, H. G. *Chem. Ber*. **1984**, *117,* 1310.
49. Terpetschnig, E.; Penn, G.; Kollenz, G.; Peters, K.; Peters, E. M.; von Schnering, H. G. *Tetrahedron* **1991**, *47*, 3045.
50. Kollenz, G.; Penn, G.; Ott, W.; Peters, K.; Peters, E. M.; von Schnering, H. G. *Heterocycles* **1987**, *26*, 625.
51. Kollenz, G.; Ott, W.; Ziegler, E.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Formacek, V.; Quast, H. *Liebigs Ann. Chem*. **1984**, 1137.
52. Ott, W.; Terpetschnig, E.; Sterk, H.; Kollenz, G. *Synthesis* **1987**, 176.
53. Kollenz, G.; Sterk, H.; Hutter, G. *J. Org. Chem*. **1991**, *56,* 235.
54. Heilmayer, W.; Sterk, H.; Kollenz, G. *Tetrahedron* **1998**, *54*, 8025.
55. Review: Modena, G. *Acc. Chem. Res*. **1971**, 73.
56. Heilmayer, W.; Kappe, C. O.; Sterk, H.; Kollenz, G.; Peters, K.; Peters, E. M.; von Schnering, H. G.; Walz, L. *Chem. Ber*. **1993**, *126*, 2061.
57. Review on Dimroth-rearrangements: Wahren, M. *Z. Chem*. **1969**, *9*, 241.
58. Fabian, W. M. F.; Kollenz, G. *Croat. Chem. Acta* **1992**, *65*, 55.
59. Fabian, W. M. F.; Kollenz, G. *J. Chem. Soc., Perkin Trans. 2* **1995**, 515.
60. Fabian, W. M. F.; Kollenz, G. *J. Org. Chem*. **1997**, *62,* 8497.
61. AbdElNabi, H. A.; Kollenz, G. *Monatsh. Chem*. **1997**, *128*, 381.
62. Abd ElNabi, H. A. *J .Chem. Res. (S)* **1996**, *10*, 466.
63. Kollenz, G.; Terpetschnig, E.; Sterk, H.; Peters, K.; Peters, E.M. *Tetrahedron* **1999**, *55*, 2973.
64. Some selected papers: *a)* Kozlov, A. P.; Sychev, D. I.; Andreichikov, Y. S. *Zh. Khim. Org.* **1988***,* 24, 416; b) Milyutin, A. V.; Amirova, L. R.; Krylova, I. V.; Nazmedinov, F. Y.; Novolelova, G. N.; Andreichikov, Y. S.; Kolla, V. E. *Khim. Farm. Zh*. **1997**, *31*, 32; c) Milyutin, A. V.; Amirova, L. R.; Nazmetdinov, F. Y.; Makhmudov, R. R.; Golovanenko, A. I.; Andreichikov, Yu.S.; Kolla, V. E. *Kh.im. Farm. Zh*. **1996**, *30*, 47; d) Nekrasov, D. D.; Kolt'sova, S. V.; Andreichikov, Y. S. *Khim. Geterotsikl. Soedin*. **1994**, 173; e) Koz'minykh, V. O.; Safonova, N. V.; Milyutin, A. V.; Armaginova, V. G.; Kolla, V. E.; Shelenkova, S. A.; Yakovlev, I. V.; Novoselova, G. N.; Andreichikov, Y. S.; Il'enko, V. I. *Khim. Farm. Zh*. **1994**, *28*, 42.
65. a) Koz'minykh, V. O.; Igidov, N. M.; Il'enko, V. I.; Milyutin, V. A.; Kolla, V. E.; Semenova, Z. N.; Andreichikov, Y. S. *Khim. Farm. Zh*. **1992**, *26*, 28; b) Milyutin, A. V. Safonova, N. V.; Chesnokov, V. P.; Nazmetdinov, F. Y.; Voronina, E. V.; Krylova, V. I.; Andreichikov, Y. S.; Kolla, V. E.; Kozhevnikov, Y. V. *Khim. Farm. Zh*. **1996**, *30*, 26. c) Milyutin, A. V.; Amirova, L. R.; Kolla, V. E.; Nazmetdinov, F. Y.; Drovosekova, L. P.; Andreichikov, Y. S. *Khim. Farm. Zh*. **1998**, *32*, 24; d) Igidov, N. M.; Koz'minykh, E. N.; Kolotova, N. V.; Koz'minykh, V. O. *Russ. Chem. Bull*. **1999**, *48*, 1383.
66. Nekrasov, D. D.; Kol'tsova, S. V.; Andreichikov, Y. S.; Tul'bovich, G. A. *Zh. Org. Khim*. **1995,** *31*, 907.
67. Vyaznikova, N. G.; Zalesov, V. V.; Andreichikov, Y. S. *Zh. Org. Khim*. **1995**, *31*, 1218.
68. Maslivets, A. N.; Tarasova, O. P.; Andreichikov, Y. S. *Zh. Org. Khim*. 1992, *28*, 1287.
69. a) Sofyina, O. A.; Igidov, N. M.; Koz'minykh, E. N.; Trapeznikova, N. N.; Kasatkina, Y. S.; Koz'minykh, V. O. *Zh. Org. Khim*. **2001**, *37*, 1067; b) Andreichikov, Y. S.; Koltsova, S. V.; Zhikina, I. A.; Nekrasov, D. D. *Russ. J. Org. Chem.* **1999**, *35*, 1538; c) Nekrasov, D. D.; Koltsova, S. V.; Andreichikov, Y. S. *Zh. Org. Khim*. **1995**, *31*, 591; d) Nekrasov, D. D.; Shurov, S. N.; Ivanenko, O. I.; Andreichikov, Y. S. *Zh. Org. Khim*. **1994**, *30*, 126; e) Yanborisov, T. N.; Zhikina, I. A.; Yanborisova, O. A.; Shurov, S. N.; Andreichikov, Y. S. *Zh. Org. Khim*. **1992**, *28*, 2554.
70. a) Koz'minykh, E. N.; Igidov, N. M.; Sh avkunova, G. A.; Koz'minykh, V. O. *Russ. Chem. Bull*. **1997**, *46*, 1285; b) Kolotova, N. V.; Koz'minykh, V. O.; Dolbilkina, E. V.; Koz'minykh, E. N. *Russ. Chem. Bull*. **1998**, *47*, 2246.
71. Nekrasov, D. D.; Chizh, V. G.; Andreichikov, Y. S. Mkhmudov, R. R. *Khim. Farm. Zh*. **1994**, *28,* 30.

72. Nekrasov, D. D.; Chizh, V. G.; Andreichikov, Y. S.; Tul'bovich, G. A.; Aleksandrova, G. A. *Khim. Farm.*;
73. Koz'minykh, V.O.; Konshina, L. O.; Igidov, N. M. *J. Prakt. Chem*. **1993**, *335*, 714.
74. a) Shklyaev, Y. V.; Maslivets, A. N. *Zh. Org. Khim*. **1996**, *32*, 319; b) Shurov, S. N.; Pavlova, E. Y.; Livantsova, L. I.; Zaitseva, G. S.; Andreichikov, Y. S. *Zh. Org. Khim*. **1993**, *29*, 2275.
75. Koz'minykh, E. N.; Armaginova, V. G.; Shavkunova, G. A.; Igidov, N. M.; Berezina, E. S.; Koz'minykh, V. O. *Zh. Org. Khim*. **1997**, *33*, 256.
76. Zalesov, V.V.; Kataev, S.S.; Pimenova, E.V.; Nekrasov, D.D. *Zh. Org. Khim.* **1998**, *34*, 112.
77. Akcamur, Y.; Penn, G.; Ziegler, E.; Sterk, H.; Kollenz, G.; Peters, K.; Peters, E. M.; von Schnering, H. G. *Monatsh. Chem*. **1986**, *117*, 231.
78. Akcamur, Y.; Sener, A.; Ipekoglu, A. M.; Kollenz, G. *J. Heterocycl. Chem*. **1997**, *34*, 221.
79. Riedl, Z.; Hajos, G.; Kollenz, G.; Sterk, H.; Messmer, A. *Monatsh. Chem*. **1992**, *123*, 1181.
80. Kollenz, G.; Penn, G.; Theuer, R.; Fabian, W. M. F.; AbdElNabi, H. A.; Zhang, X.; Peters, K.; Peters, E. M.; von Schnering, H. G. *Tetrahedron* **1996**, *52*, 5427.
81. Scheibye, S.; Shabana, R.; Lawesson, S. O.; Romming, C. *Tetrahedron* **1982**, *38,* 993.
82. Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc*. **1975**, *97*, 4327.
83. Bestmann, H. J. *Angew. Chem. Int. Ed. Engl*. **1965**, *4,* 645.
84. Koz'minykh, V. O.; Igidov, N. M.; Koz'minykh, E. N.; Berezina, E. S. *Phosph. Sulf. Silicon* **1993,** *8*1, 191.

METAL-CATALYZED CYCLOCARBONYLATION REACTIONS FOR THE SYNTHESIS OF LACTONES AND LACTAMS

Giuseppe Vasapollo and Giuseppe Mele

Dipartimento di Ingegneria dell'Innovazione, Università di Lecce, Via Arnesano, 73100 Lecce, Italy

(e-mail: giuseppe.vasapollo@unile.it)

Abstract. *The preparation of a variety of heterocyclic compounds such as lactones, lactams, pyrrolidinones, and others can be achieved by cyclocarbonylation reactions catalysed by various metal complexes. Palladium salts with the combination of phosphine ligands have resulted effective catalyst systems for the cyclization reactions. New synthetic strategies and novel approaches devoted to the preparation of such compounds having different ring size still remain a stimulating area of academic and industrial research.*

Contents

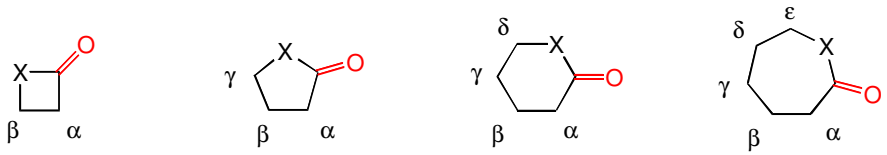
1. Introduction

This review is mainly focused on the catalytic preparation of different heterocyclic compounds in particular lactones and lactams having 4, 5, 6 or 7-membered (indicated also as $\beta, \gamma, \delta, \varepsilon$ lactones and lactams) (Figure 1), and in larger rings by pursuing innovative routes that consist mainly in the incorporation of carbonyl moiety (C=O) into an organic molecule and subsequent formation of carbonyl compounds.[1]

The studies of Falbe and Korte, pioneers of the carbonylation chemistry, have opened the way to this metal catalyzed chemistry for the preparation of a variety of cyclic compounds (lactams, succinimide derivatives, etc.).[2] Today, there are different new methods available for cyclocarbonylation reactions.

The methods reported in the literature are mainly identified with different names and among the most important cited are *carbonylative ring formation (that is* carbon monoxide insertion reactions into suitable functional groups) and *ring expansion reactions (that is* insertion of carbon monoxide into a previously formed heterocycles).

These processes have been usually accomplished by metal catalysed carbonylation and palladium based catalysts were among the most efficient for the preparation of a variety of mono-, bis-lactones and lactams.



X = O, -NH, -NR

Figure 1

This review is mainly focused to describe recent results on the preparation of those heterocycles containing both saturated and unsaturated five, and larger rings through metal catalysed cyclocarbonylation reactions. It is important to note that there is a great interest to develop new selective processes for the synthesis of these compounds because of their use in building up biologically active compounds[3] with pharmacologically activity (fungicidal, antitumoral and anti-inflammatory)[4] and undergo easily ring opening for the synthesis of polyesters.[5]

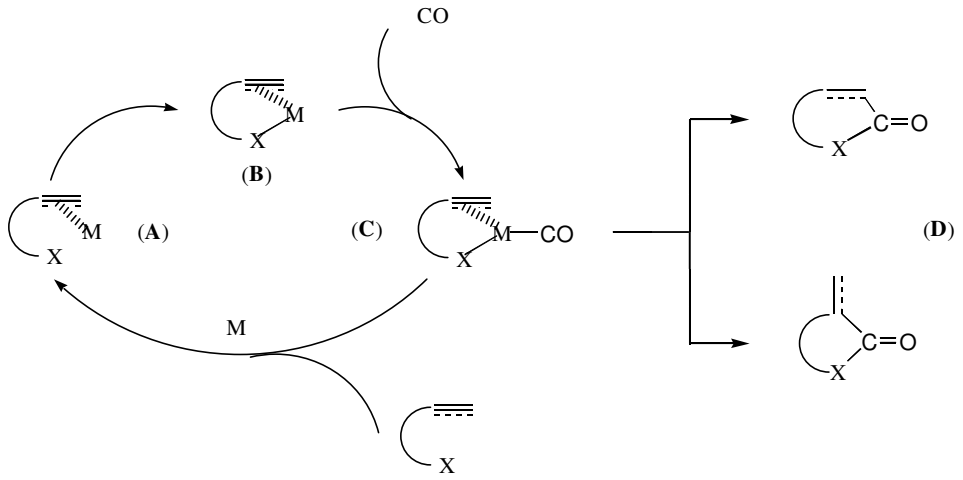
2. Cyclocarbonylation reactions

2.1. General features on cyclocarbonylation reactions

Different synthetic approaches for the construction of targeted heterocyclic compounds have been reported. Also, various mechanisms have been proposed based on the reactivity of different functional groups present in the substrate (double bond, triple bond, amine group etc.). For example, the accepted mechanism of the carbonylation reaction of alkenes or alkynes catalysed by transition-metal complex is shown in the Scheme 1.

Double or triple bond of unsaturated substrates, bearing an adjacent functional group X (such as hydroxyl, amino, formyl, and ester), could be initially coordinates to the metal to give the intermediate **A**. Then, there is an intramolecular interactions of the metal with the functional groups X and formation of metallocycle intermediate **B**. Successive step is the coordination of carbon monoxide leading to the

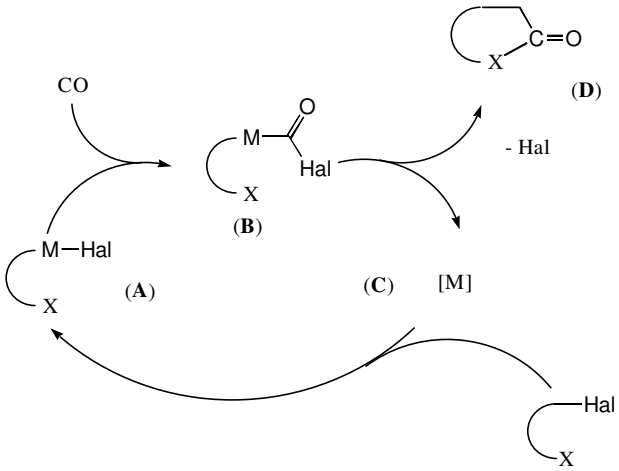
formation of the intermediate **C**. Elimination of the metal followed by ring closure affords cyclic carbonyl compounds **D**.



X= -OH, -NH_2, -CHO, -COOR

Scheme 1

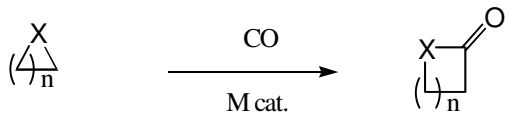
In the case of halo-alcohol or halo–amine compounds, a different pathway is proposed (Scheme 2).



Hal = Cl, Br, I

X= -OH, -NH_2

Scheme 2



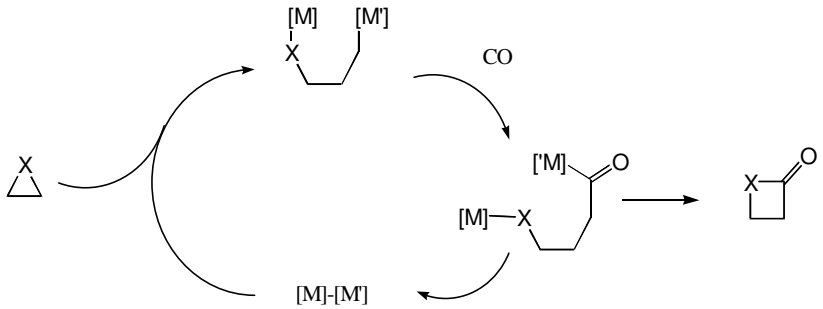
X=O, -NH, -NR

Scheme 3

The insertion of the metal M into the C-Hal bond (oxidative addition) would give the intermediate **A** which contains the functional group X such as -OH or -NH_2 adjacent to the C-halide bond. The successive coordination and insertion of carbon monoxide forms the intermediate **B**. The subsequent elimination of the metal produces the carbonyl compound **D**.

A different mechanism is proposed for the ring expansion. This can be explained through insertion of CO in the ring (Scheme 3) in which the driving force of the process is the strain small cycle (oxirane, aziridine, etc.) which usually favours the formation of a larger cycle.

Recent papers reported another possible alternative mechanism (Scheme 4) in which a bi-metal catalyst is the intermediate key of the process.



Scheme 4

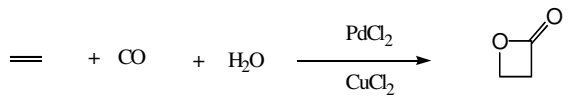
Although these mechanisms are not exhaustive because they depend on the metals and ligands involved, however, they resume possible pathways through which it is possible to describe the formation of the cyclic compounds.

2.2. Synthesis of lactones

2.2.1. Synthesis of four-membered lactones (β-lactones)

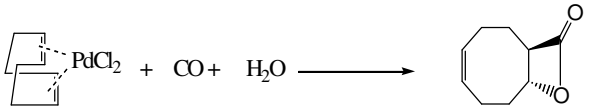
β-Lactones represent an important class of naturally occurring compounds. Cyclocarbonylation reaction catalysed by transition metal is a useful methodology for their synthesis. However, only a limited number of papers have been reported in the literature for their synthesis. *β*-Lactones were usually obtained by cyclisation of *β*-halo derivatives or *β*-hydroxy acid derivatives or by addition of ketene to carbonyl compounds.

Palladium-catalysed reactions provided an important route for clean preparation of such compounds. For example, the oxidative carbonylation of alkenes **1**, **3** in the presence of water (Schemes 5 and 6) is a direct way for the preparation of *β*-lactones **2**, **4**.[6]



1 **2** (72%)

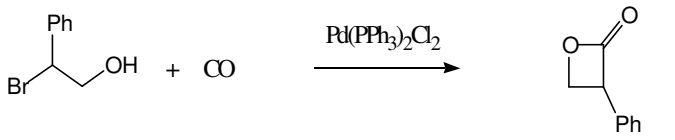
Scheme 5



3 **4** (79%)

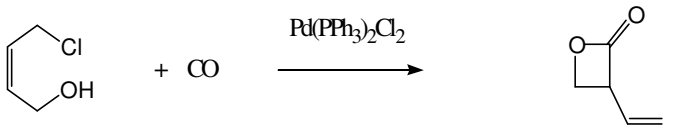
Scheme 6

The carbonylation of the saturated and unsaturated the halogen-alcohols **5** and **7** has been also used to synthesize the four membered ring compounds **6** and **8** (Schemes 7 and 8).[7]



5 **6** (63%)

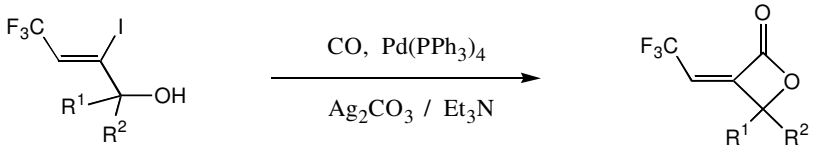
Scheme 7



7 **8** (52%)

Scheme 8

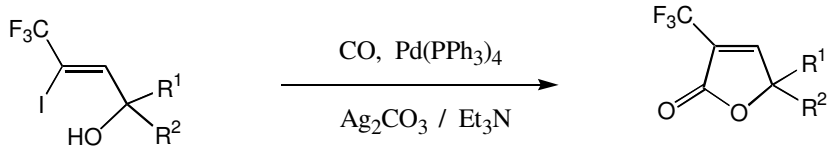
Recently, Qing and co-workers have reported a successful synthesis of 3-(2,2,2- trifluoroethylidene)-2-oxetanones (β-lactones) in the presence of palladium (0) complex as a catalyst (Scheme 9).[8]



R^1, R^2= alkyl (4 examples) 62-86%

Scheme 9

On the contrary, the cyclocarbonylation reaction of *Z*-3-iodo-3-trifluoromethyl allylic alcohols, in the presence of a catalytic amount of $Pd(PPh_3)_4$ produced five member ring lactones such as 3-trifluoromethyl-2-(5*H*)-furanones (Scheme 10).[9]



R^1, R^2= alkyl or aryl (5 examples) 58-82%

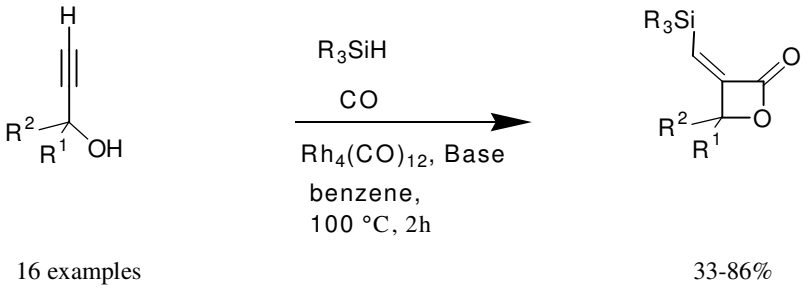
Scheme 10

Some of these products were also obtained by cyclocarbonylation reaction of trifluoromethyl propargylic alcohols in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3.[10]

Recently, Matsuda and co-workers have reported a new method for the preparation of novel four membered ring compounds by cyclocarbonylation reaction of alkynes bearing a trialkyl silyl group, catalysed by rhodium complexes. (Scheme 11).[11]

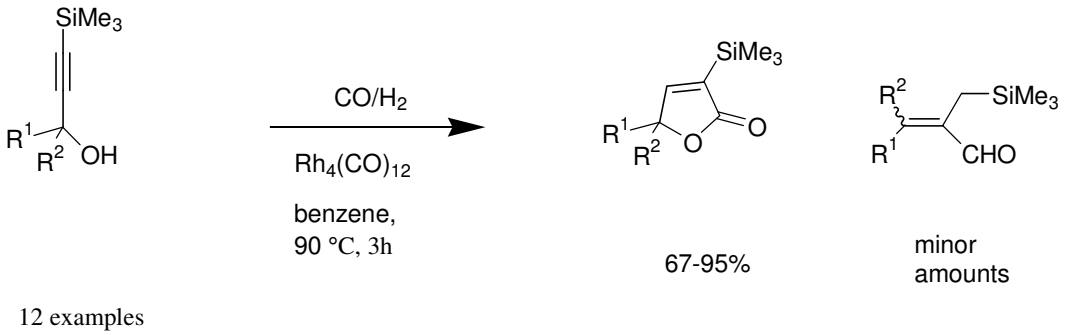
These examples represent a particular cases of rhodium-catalysed reactions in which the alkynes, bearing a trialkyl silyl group on the *sp*-carbon, smoothly incorporate carbon monoxide to form the four

membered ring lactone. The propensity to form β-lactone depends on both steric and electronic factors. The authors have reported that a better selectivity for β-lactone was obtained in the case of bulkier silyl group, such as Bu^tMe_2Si and by using a stronger base such as DBU (DBU=1,8-diazabicyclo [5.4.0] undec-7-ene). The method was also valid for the preparation of spiro type β-lactones.



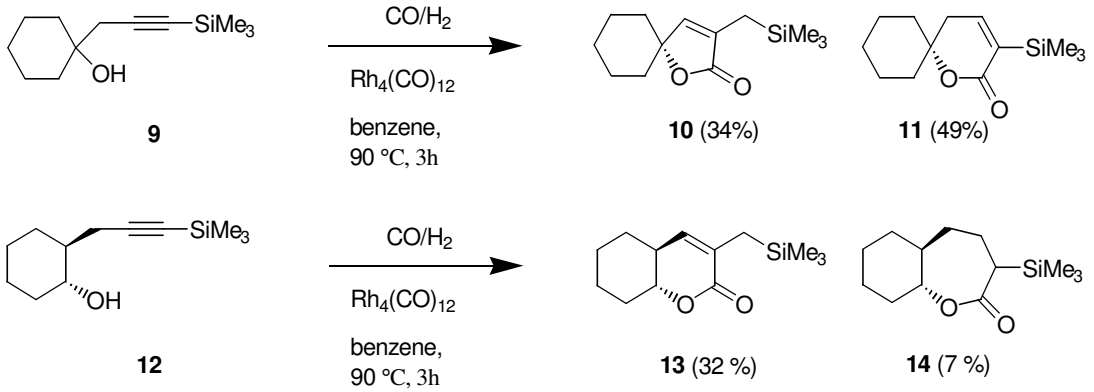
Scheme 11

Matsuda and co-workers reported successively, one–pot synthesis of silyl-3-2-(5*H*)-furanones by reacting 1-substituted-3-silylpropyn-1-ols CO and H_2 in the presence of a catalytic amount of $Rh_4(CO)_{12}$ (Scheme 12).[12] Hydroformylation compounds were also obtained as by-product.



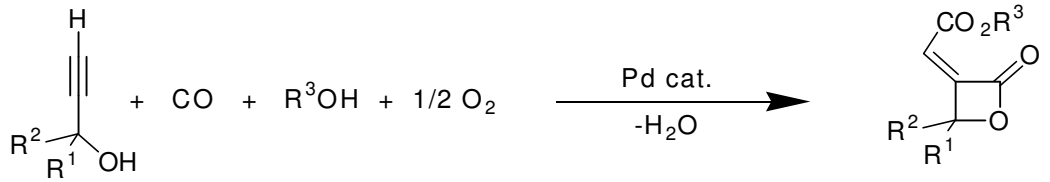
Scheme 12

The authors have also reported that lower selectivity was obtained in the case of other molecules where a mixture of five, six and seven membered ring heterocycles was produced (Scheme 13).



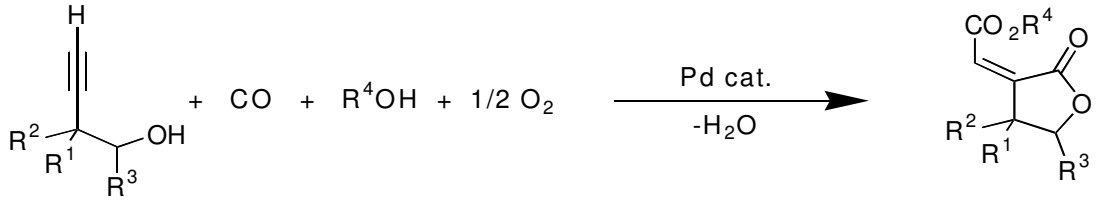
Scheme 13

(*Z*)-α-(Alkoxycarbonyl)methylene-β- and γ-lactones were also obtained in good yields by PdI_2/KI catalysed carbonylation reactions of propynyl alcohols and but-3yn-1ols respectively (Schemes 14 and 15).[13]



5 examples 31-80 %

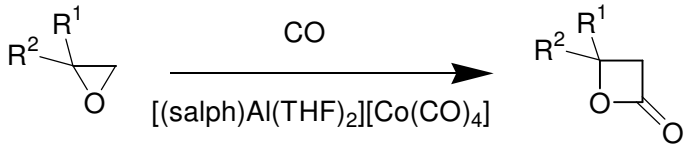
Scheme 14



5 examples 28-94%

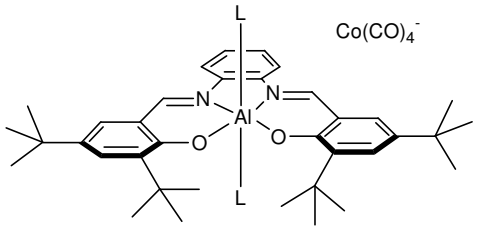
Scheme 15

The insertion of carbon monoxide in an epoxide and aziridine rings represents an alternative way to β-lactones and lactams,[14,15,16] precursors for the synthesis of polymers[17] and polypeptides.[18] However, various transition metal complexes have been used to catalyze the CO insertion in these small rings,[19,20] and very few catalysts were able to promote such transformation selectively and with high yields.[21]



5 examples 73-99%

Scheme 16



L = THF

15

Structure of [(salph)Al(THF)$_2$][Co(CO)$_4$] (**15**)

Figure 2

Dicobalt octacarbonyl in the presence of hydroxy-substituted pyridines has been used for the carbonylation reactions of a variety of epoxides (such as ethylene and propylene oxide). A mixture of lactones and polyester oligomers were obtained and their ratio was dependent on reaction condition.[20d,21a,22] Yield and selectivity in such reactions were typically low.[23]

Recently Coates and co-workers have reported a novel catalytic synthesis of β-lactones (Scheme 16) catalyzed by the complex $[(salph)Al(THF)_2][Co(CO)_4]$ **15** (Figure 2).[24]

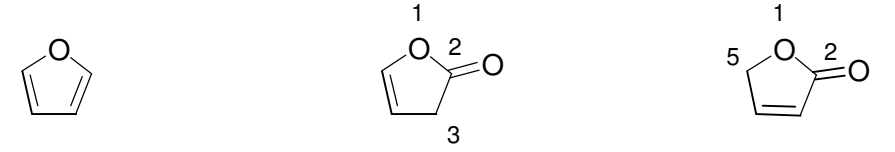
Catalyst **15** was able to carbonylate selectively a variety of epoxides; such as propylene oxide and epichloridrin and the conversion was 95% and 73% respectively. In the case of carbonylation of isobutylene oxide the corresponding lactone was obtained, as a mixture of the two possible regioisomers, with conversion of about 90% after 1h.

The authors elucidated the mechanisms of the formation of the lactones according to two different hypothesised pathways: the first one is related to a nucleophilic attack by the anionic $Co(CO)_4^-$ to the epoxide related to give the substituted lactone; the second is an electrophilic attack to the epoxide ring by Lewis-acidic complex $[(salph)Al]^+$ successively trapped by $Co(CO)_4^-$ leading to the corresponding lactone. Relatively high yields and good selectivity were also obtained using $[Cp_2Ti(thf)_2][Co(CO)_4]$ as catalyst.[21b]

2.2.2. Synthesis of five-membered lactones

2.2.2.1. Synthesis of five-membered unsaturated lactones (furanones)

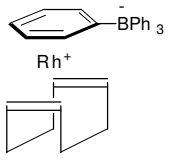
Furanones are unsaturated lactones and represent an important class of heterocyclic compounds due to their biological activity (Figure 3).



Furane 2-, 2(3*H*)- furanon 2-, 2(5*H*)-furanone

Figure 3

The synthesis of these compounds was achieved catalytically and more easily than β-lactones. Mixture of furanones 2-, 2(3*H*)-, and 2(5*H*)-furanones, for example, were catalytically obtained in 61-93% yields by reacting α-keto alkynes with CO and H_2 in the presence of a catalytic amount of the zwitterionic rhodium complex $(\eta^6\text{–}C_6H_5BPh_3)^-Rh^+$(1,5-COD) **16**, (Figure 4) and triphenyl phosphite as a ligand (Scheme 17).[25]

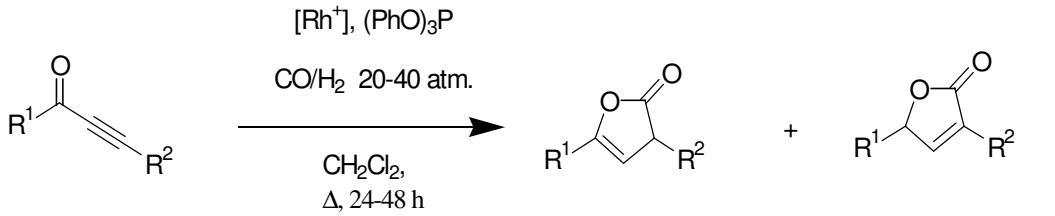


16

Figure 4

The complex **16** was reported to be a very active catalyst for the cyclohydrocarbonylation reaction of a variety of substrates containing different alkyl, aryl, vinyl, and alkoxy groups attached to the acetylenic moiety. The steric and electronic properties present in the molecules influence the chemo- and regioselectivity of the reaction. For example, when the substituent R_2 is an alkyl chain, 2(3*H*)-furanones were selectively obtained in high yields; and when R_2 is an aromatic group, 2(5*H*)-furanones were instead

formed. 3(2*H*)-Furanones were obtained by reacting alkynols, carbon monoxide and halogens in the presence of transition metals complexes.[25]



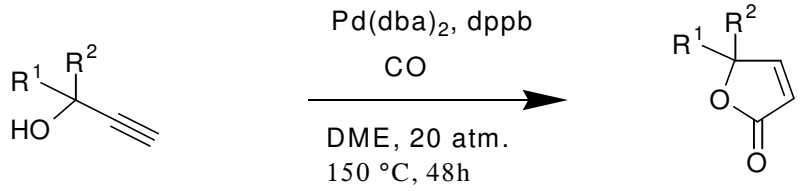
23 examples

Total yields 61-93 %

Scheme 17

The synthesis of 3(2*H*)-furanones was explained by the authors considering a possible mechanism in which there is catalytic intermolecular cyclocarbonylation of iodoarenes with alkynes or alkynols, or considering that there is intramolecular cyclocarbonylation of alkynols.

Palladium bis(dibenzylideneacetone) [$Pd(dba)_2$] in the presence of 1,4-bis(diphenylphosphino)butane (dppb) in 1,2-dimethoxyethane (DME) was able to promote intramolecular carbonylative cyclisation of alkynols affording to the corresponding 2(5*H*)–furanones (Scheme 18).[26]



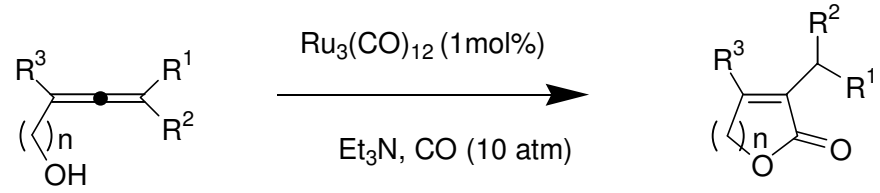
8 examples

62-80%

Scheme 18

The ruthenium complex $Ru_3(CO)_{12}$ in the presence of Et_3N was also an effective catalyst for the cyclocarbonylation of different allenyl alcohols producing a mixture of γ- and δ-lactones.

Similarly, the cyclocarbonylation of 3,4-pentadien-1-ol and 2-methyl-4,5-hexadien-2-ol, in the presence of $Ru_3(CO)_{12}/Et_3N$ as a catalytic system, produced *δ*-lactones, 5,6-dihydro-3-methyl-2*H*-pyran-2-one, and 5,6-dihydro-6,6-dimethyl-3-methyl-2*H*-pyran-2-one, respectively, in quantitative yield (Scheme 19).[27]



n = 1 or 2

11 examples

91-99%

Scheme 19

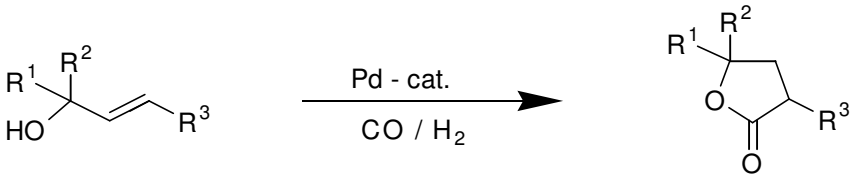
It was observed that the presence of a heteroatom in the molecule may influence the rate and the chemoselectivity of the reaction.

Gabriele and co-workers reported the synthesis of 3-alkyl or 3-aryl substituted 2(5*H*)-furanones by reductive carbonylation of alk-1-ynes in the presence of KI and water and catalytic amounts of palladium iodide.[28]

2.2.2.2. Synthesis of five- and six-membered saturated lactones

The preparation of five-membered ring saturated lactones have been achieved by homogeneous catalyst *via* the direct insertion of carbon monoxide into four-membered cyclic or, in phase transfer catalysis, by lactonisation of various allylic alcohols.

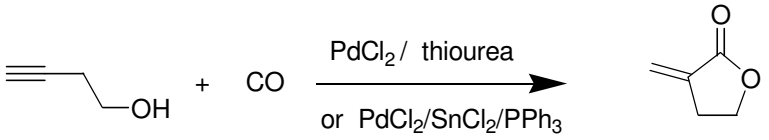
For example, primary allylic alcohols with CO in the presence of the catalytic system $PdCl_2$-$CuCl_2$, hydrochloric acid and oxygen, gave the corresponding five membered lactones in good yields.[29] Differently substituted five-membered ring saturated lactones were also obtained reacting secondary and tertiary allylic alcohols with CO/H_2 mixture in the presence of palladium based catalysts (Scheme 20).[26]



12 examples 45-92%

Scheme 20

Palladium complexes were also used as catalysts for the cyclocarbonylation of 3-butyn-1-ol **17** to give α-methylene lactone **18** in good yield (Scheme 21).[30]

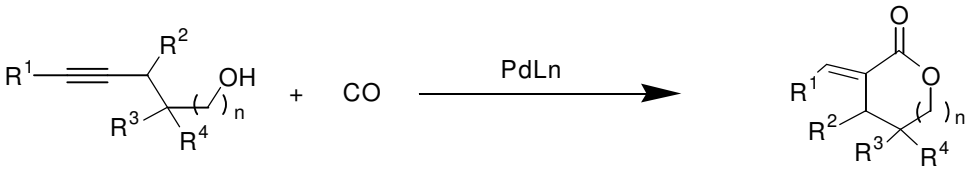


17 **18**

4 examples (in different reaction conditions) 31-100%

Scheme 21

Inoue and co-workers reported the cyclocarbonylation of 3-butyn-1-ols catalysed by cationic palladium-phosphine complexes affording selectively six- or five-membered ring lactones (Scheme 22).[31]



n = 0 or 1

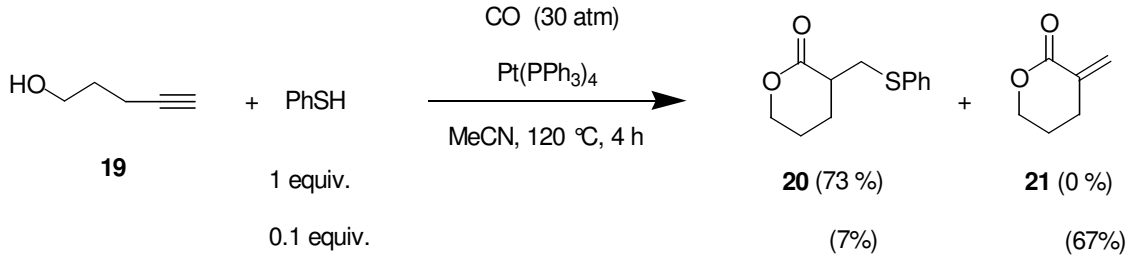
9 examples 24-77%

Scheme 22

Other additional methods for the preparation of five membered γ-lactones have been reported.

Differently, very few examples on the carbonylative route to six-membered δ-lactone rings are reported.

For example, 5-hydroxy-1-pentyne **19** in the presence of 1 equivalent of benzenethiol and 1 mol % of platinum (0) catalyst was carbonylated to α-[(phenylthio)methyl]-δ-lactone **20** with high selectively and good yield. The same reaction was performed with 0.1 equiv. of benzenethiol, led to α-methylene γ-lactone **21** as a major product (Scheme 23).[32]

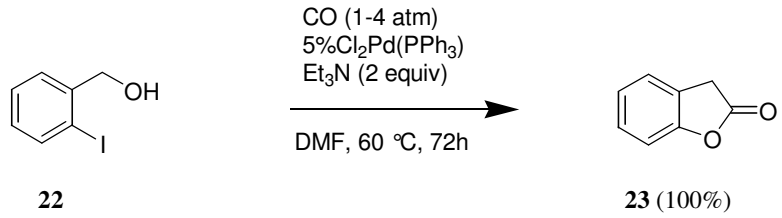


Scheme 23

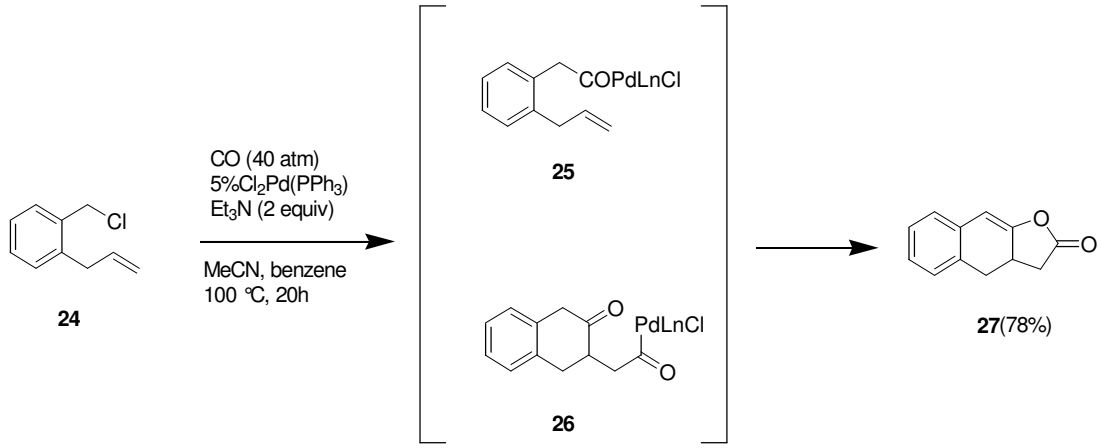
2.2.3. Synthesis of five-, six- and seven-membered fused to aromatic rings lactones and bis-lactones

Another important class of lactones is the five-, six-, and seven-membered fused to aromatic ring lactones.

As a general method, palladium-catalysts promoted carbonylation reactions of a variety of substrates for the preparation of fused aromatic ring lactones. For an example, the benzylic alcohol **22** bearing an halogeno (or halogenomethyl) substituent in *orto*-position was cyclocarbonylated easily to five-membered ring lactone **23** using a catalytic amount of $Pd(PPh_3)_2Cl_2$ and tertiary amine (Scheme 24).[7]



Scheme 24

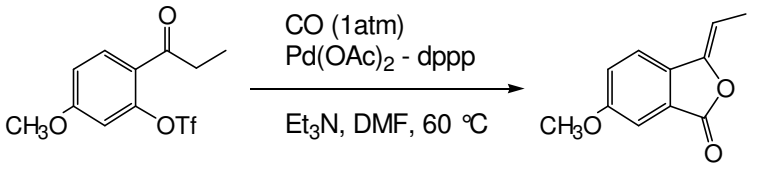


Scheme 25

Cyclocarbonylation of *o*-allylbenzyl chloride **24** in the presence of a palladium catalyst and triethylamine provided an efficient route to benzoannulated enol lactone **27** in high yield (Scheme 25).

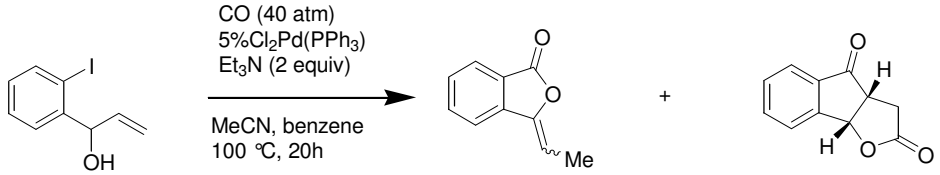
Product **27** is considered a useful intermediate for the synthesis of antiulcer agent **U-68,215**.[33,34] The authors reported **25** and **26** as intermediates in the reaction.

Cyclocarbonylation of the trifluoro-methanesulfonic acid 5-methoxy-2-propionyl-phenyl ester **28** in the presence of $Pd(OAc)_2$, dppp [1,3-bis(diphenylphpsphino)propane] and triethylamine afforded five-membered ring lactone **29** in good yield (Scheme 26).[35]



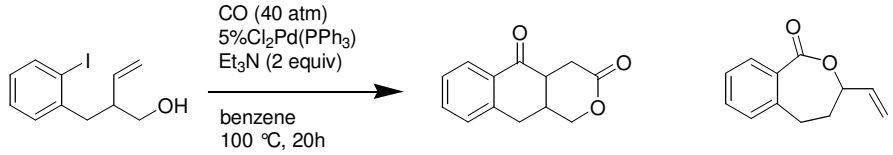
28 **29** (85%)

Scheme 26



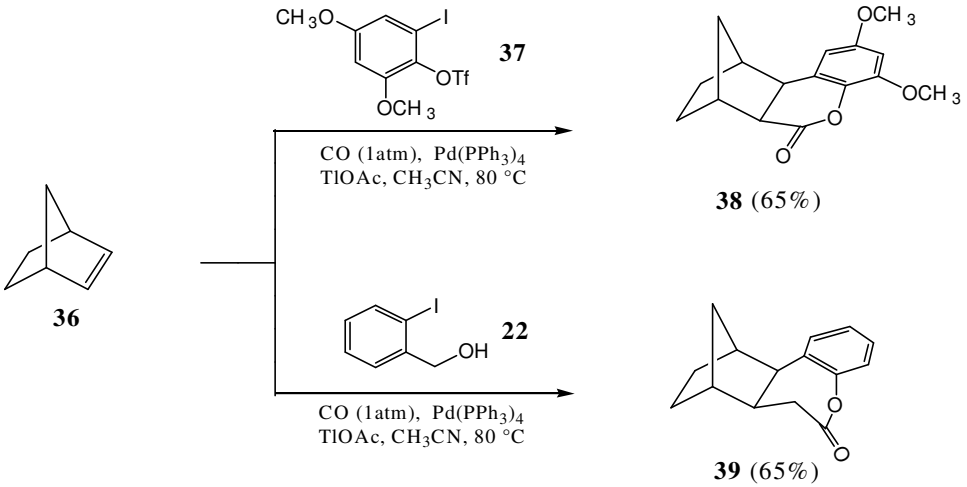
30 **31** (90 % Z/E=92/8) **32** (3 %)

Scheme 27



33 **34** (36% *trans*/*cis*=82/18) **35** (31%)

Scheme 28



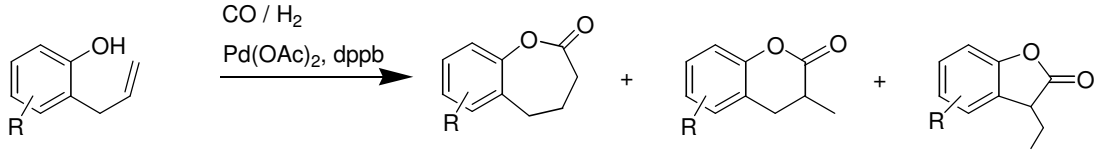
Scheme 29

Palladium-catalyzed carbonylation reaction of **30** produced **31** in 90 % yields (*Z* /*E* isomers were in the ratio 92:8) and trace amount of **32** (Scheme 27). Carbonylation of **33** in benzene produced also a mixture of lactones **34** (*trans*/*cis* = 82/18) and **35** in 36 and 31% yields respectively (Scheme 28).[36]

Cyclocarbonylation of norbornene **36** in the presence of palladium catalysts and aryl iodide compounds, such as **37** or **22**, produced six- and seven-membered ring lactones **38** and **39** (Scheme 29).[37]

With few exceptions, these palladium catalyzed carbonylation reaction exhibits preference for five- or six-membered rings.

Recently, the cyclocarbonylation of 2-allyl phenol derivatives, using $Pd(OAc)_2$ and dppb system affording a mixture of five-, six- and seven-membered rings lactones has been reported (Scheme 30).[38]

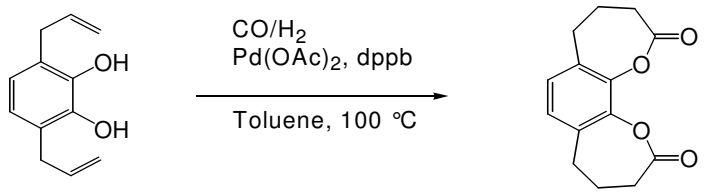


Scheme 30

It was observed that, when the reaction was carried out using toluene as a solvent and CO/H_2 in the molar ratio 1/1, the seven-membered ring lactone was produced as the major product; and, when the reaction was conducted in dichloromethane and using CO/H_2 in the molar ratio 1/5, the five-membered ring lactone was the major product.

The homogeneous catalytic system $Pd(OAc)_2$ - dppb was demonstrated to be active catalyst also for double cyclocarbonylation reactions of bis-allyl phenols to the corresponding of bis-lactones.

For example, 3,6-bis allylcatechol **40** reacted with CO and H_2 in the presence of a catalytic amount of $Pd(OAc)_2$ and dppb in toluene to give selectively in one-pot synthesis, 7-membered ring bis-lactone **41** in 79% isolated yield (Scheme 31).



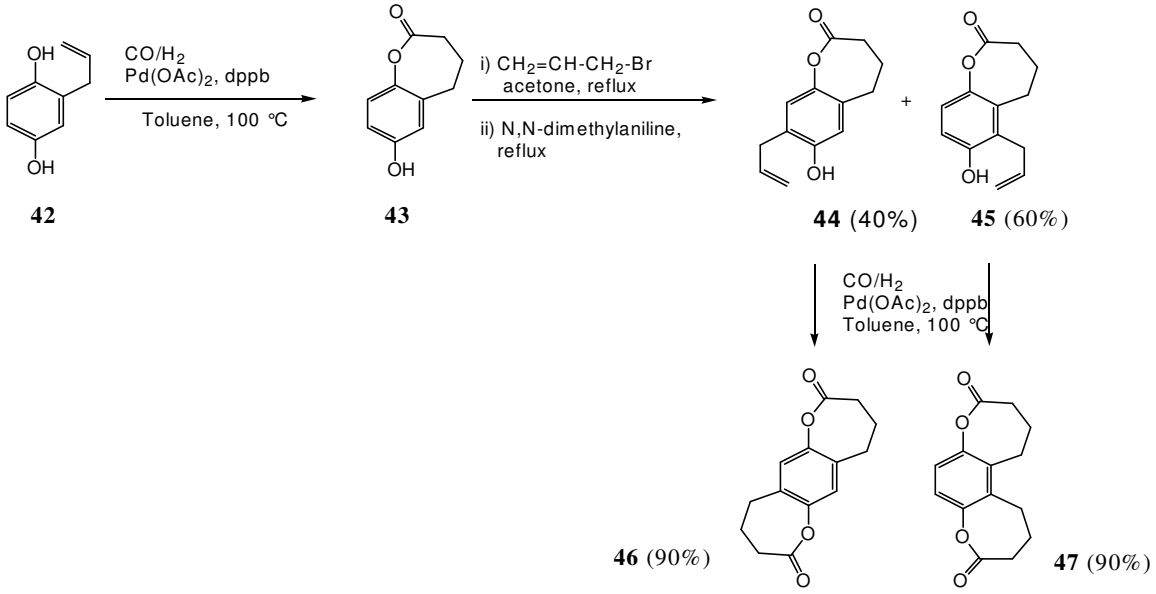
40 **41** (79%)

Scheme 31

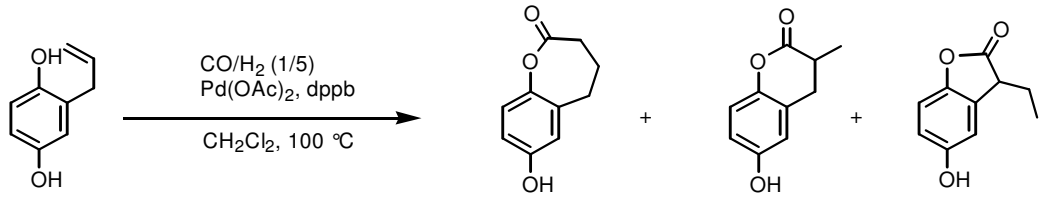
The synthesis of bis-lactones can be achieved in two steps reaction. For example, the mono allyl hydroquinone **42** was first cyclocarbonylated in toluene to give **43** in 92% yield. This latter, after further allylation and Claisen rearrangement, was converted into the isomers **44** and **45** which were successively cyclocarbonylated to be transformed into the corresponding bis-lactones **46** and **47** (Scheme 32).

Using different reaction conditions, it was possible to obtain bis-lactones having two different ring sizes (7-6, 7-5, 6-6). For example, **42** can be carbonylated in CH_2Cl_2 to give a mixture of 5-, 6-, 7-membered ring mono-lactones **43**, **48**, **49** (Scheme 33).

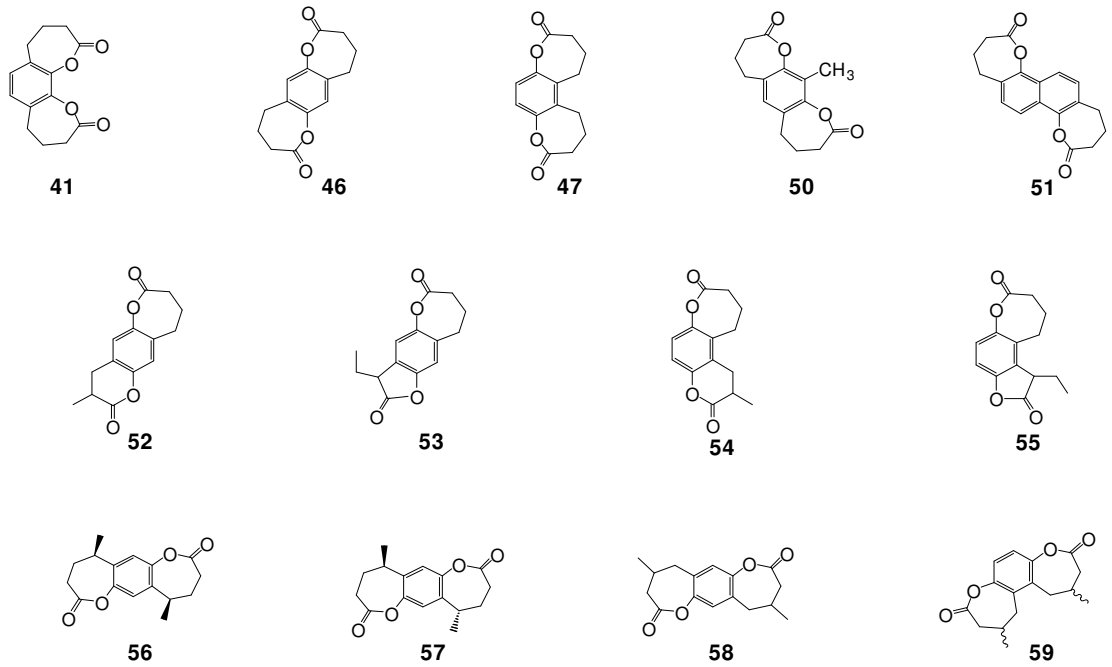
Compounds **43**, **48**, **49,** after allylation and Claisen rearrangement, were successively cyclocarbonylated to bis-lactones containing 7-5, 7-6, 7-7 or 6-7, 6-6, 6-5 or 5-7, 5-6, 5-5 rings.[39] Other bis-lactones, **50**-**59**, were also prepared (Figure 5).[39,40]



Scheme 32



Scheme 33



Bis-lactones synthesized by cyclocarbonylation reactions

Figure 5

2.3. Synthesis of lactams and pyrrolidinones

Heterocyclic compounds containing amido group in the ring are counted among many important natural products, such as vitamins, hormones, antibiotics, as well as pharmaceuticals and herbicides.

Carbon monoxide insertion and/or addition to allylic precursors may lead to the formation of both linear and cyclic carbonyl compounds. In these transformation, rhodium, platinum, palladium and nickel based catalysts have represented the most active catalysts for the synthesis of γ-butyrolactam and *N*-alkyl-pyrrolidinones.

2.3.1. Synthesis of four-membered lactams (β-lactams)

The preparation of four-membered ring lactams (*β*-lactams) was achieved by ring expansion of aziridines usually obtained by inserting catalytically carbon monoxide molecule in the aziridine ring.[19b, 20a-j]

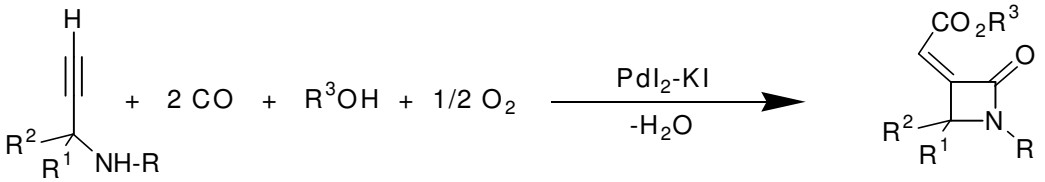
For instance, *N*-alkyl phenylaziridines undergo CO insertion in the presence of $[Rh(CO)_2Cl]_2$ as a catalysts to give in quantitative yields the corresponding *β*-lactams with regiospecific insertion of the CO into the most substituted ring carbon-nitrogen bond.[20h]

However, this method was limited to aziridines bearing an activating group such as a phenyl or vinyl in the 2-position of the aziridine ring.

Interestingly, in the presence of excess of $Ni(CO)_4$ as a catalyst the CO insertion occurred into the less substituted C-N bond of the ring with the retention of configuration.[19b]

In the case of *N*-alkylaziridines by using $Co_2(CO)_8$ as a catalyst very high yields were obtained.[20a] According to the authors, the CO insertion occurred into the less substituted carbon-nitrogen bond by a S_N2 like mechanism with the inversion of configuration. It was observed that $Co_2(CO)_8$ was the active catalyst also for the preparation of various *β*-lactams bearing different functionalities (2-alkoxycarbonyl, silyl, 2-hydroxymethyl) and for the preparation of optically active *β*-lactams.[41]

Very few examples of synthesis of *β*-lactams obtained by direct cyclocarbonylation have been reported in literature. Salerno and co-workers reported one of these peculiar cases as an extension of the synthesis for the analogous *β*-lactones systems (Scheme 34).[42,13a,13b]



5 examples

78-95%

Scheme 34

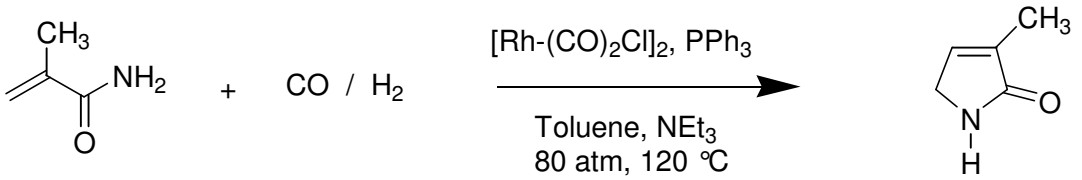
2.3.2. Synthesis of five-membered unsaturated and saturated lactams

2.3.2.1. Synthesis of five-membered unsaturated lactams

The cyclocarbonylation of methylacrylamide **60** catalyzed by rhodium-phosphine complex gave the unsaturated five membered ring lactam **61** in good yields (Scheme 35).

As reported by Negishi and co-workers, the method was used as a general route to prepare unsaturated 5-membered ring lactams.[43,44]

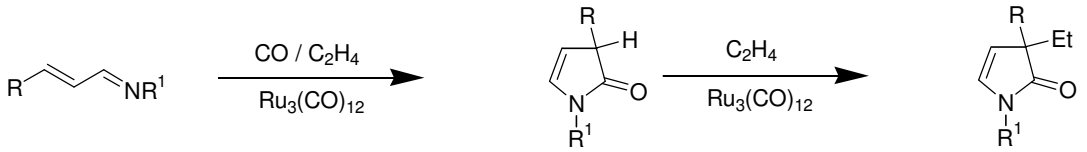
Recently, another group has reported the carbonylation of imines in the presence of $Ru_3(CO)_{12}$ elucidating the role of the ruthenium catalyst, $Ru_3(CO)_{12}$ (Scheme 36).[44]



60 **61** (45

Scheme 35

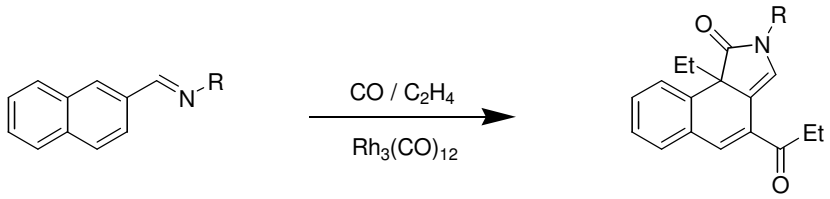
The catalyst induces firstly the catalytic C-C coupling of α,β-unsaturated imines with CO to yield an imine-aldehyde in β position with respect to the C-N double bond; the intramolecular cyclization reaction takes place *via* the nucleophilic attack of the nitrogen towards the carbonyl carbon atom forming a pyrrolidinone system. A second ruthenium complex catalysed C-C coupling reaction leads to the formal insertion of one molecule of ethylene into a C-H bond of the pyrrol-2-one in *ortho* position with respect to the keto group. By this selective reaction 1,3-dihydro-pyrrol-2-one derivatives can be easily prepared.



6 examples (15-95%)

Scheme 36

Analogously, the carbonylation of β-naphthylaldimines produced ethyl-4-propionyl-2,9b-dihydro-benzo[*e*]isoindol-1-one derivatives (Scheme 37).[45]



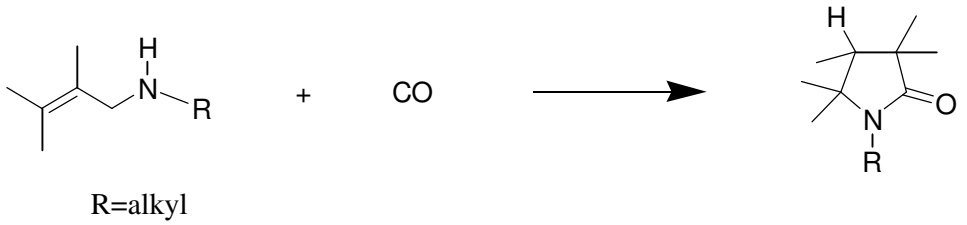
2 examples (70%)

Scheme 37

2.3.2.2. Synthesis of five-membered saturated lactams (pyrrolidinones)

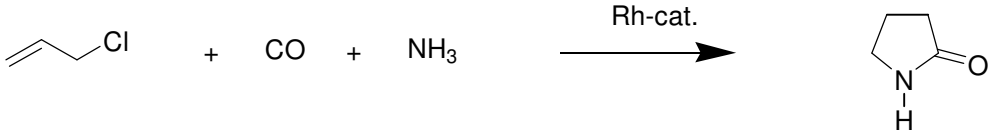
N-Alkyl-2-pyrrolidinones, mainly obtained *via* the carbonylation of *N*-alkylamines, are important compounds widely used as extractants in the petrochemical industry and as monomers for the production of synthetic fibres. Cobalt complexes were the most employed catalysts for the preparation of saturated five-membered ring lactams or their homologous (Scheme 38); but, these processes required drastic reaction conditions and exhibited poor selectivity (*e.g.* temperature high than 280 °C) favouring also competing allylic isomerization and polymerisation.[46,47]

Rhodium based catalysts showed much better catalytic activity. For example, in the presence of carbon monoxide and ammonia, rhodium catalysts promoted the cyclocarbonylation reaction of allylic chloride **62** affording the corresponding γ-butyrolactam **63** with good yield and high selectivity (Scheme 39).[48]



R=alkyl

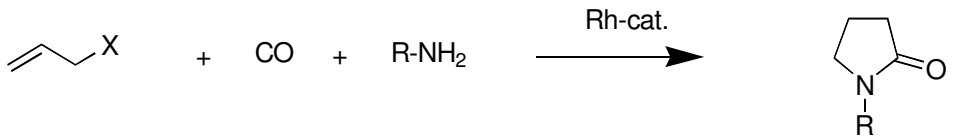
Scheme 38



62 **63**

Scheme 39

In a similar manner, the carbonylation of allylic halides in the presence of primary alkylamines catalysed by rhodium complexes led to *N*-alkyl substituted-2-pyrrolidinones (Scheme 40).[48]



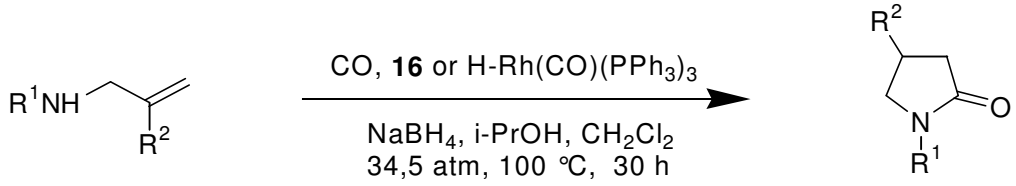
X=Cl, I

Scheme 40

These reactions were catalyzed by different rhodium complexes such as $Rh(acac)_3$ and $RhCl(PPh)_3$, producing the *N*-alkyl-2 pyrrolidones in high yields and good selectivity. Cobalt catalysts were totally ineffective for these transformations.

In 1997 Jegorov and co-workers have reported cyclocarbonylation reactions of a variety of substrates using different Rh-phosphine complexes and confirmed that the mixture of CO/H_2 in the molar ratio 1:1 promoted better than pure carbon monoxide under milder conditions. They observed also a minor selectivity in the case of monodentate phosphine ligands and hypothesized the formation of Rh (0) clusters in the catalytic process.[49]

The Zwitterionic complex η^6–$C_6H_6BPh_3^-Rh(COD)^+$, in the presence of sodium borohydride showed to be an active catalyst for the carbonylation reactions of *N*-allylic arylamines (Scheme 41) but with relatively lower yield when $R^1=C_6H_{11}$ and $R^2=H$.

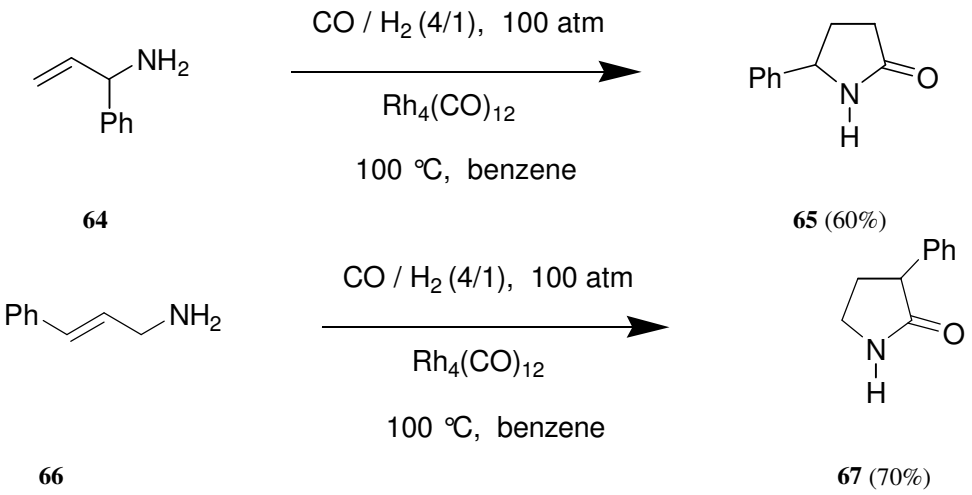


9 examples 20-78%

Scheme 41

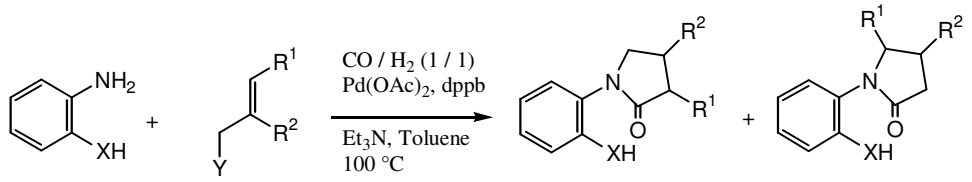
The addition of dichlorotricarbonylruthenium as a co-catalyst in the reaction increased the yields to 59%. $Ru(CO)_3Cl_2$, dppb in the presence of syn-gas was also active catalyst in these transformations.[50]

$Rh_4(CO)_{12}$ in the presence of syn-gas (CO/H_2) promoted also the carbonylation of 1-phenyl allylamine **64** and 3-phenyl allylamine **66** to 5-phenyl -2-pyrrolidinone **65** and 3-phenyl-2-pyrrolidinone **67** respectively in relative good yield (Scheme 42).[51]



Scheme 42

Interestingly, 2-pyrrolidinones were obtained also *via* Wacker–type reaction by the conversion of *N*-carbamoyl or acetyl-4-trimethylsilyl-3-alkyn-1-amines.[52] This catalysis has been extended to the carbonylation of certain vinylic (and propargyl) congeners.



68-69 **70-72** 35-72%

68 (X=O) **70** (R^1=CH_3, R^2=H, Y=Br)

69 (X=S) **71** (R^1=H, R^2=CH_3, Y=Cl)

72 (R^1=Ph, R^2=H, Y=Cl)

7 examples

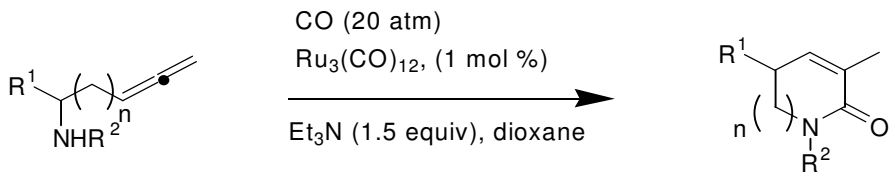
Scheme 43

In spite of various methodologies for the synthesis of *N*-allyl or *N*-benzyl 2-pyrrolidinones, very few examples of other *N*-aryl**-**2-pyrrolidinones have been reported. These interesting compounds have been prepared recently by the carbonylation of 2-aminophenol **68** or 2-aminothiophenol **69** in the presence of a stoichiometric amount of allyl halides derivatives **70-72** and catalyzed by $Pd(OAc)_2$ and dppb (Scheme 43).[53]

2.3.3. Synthesis of six-membered unsaturated lactams

Few examples on the synthesis of six-membered ring unsaturated lactams are reported in the literature. They have been usually prepared by cyclocarbonylation reactions catalyzed by metal-complexes.

The cyclocarbonylation of α-or β-allenic sulfonamides, for example, in the presence of $Ru_3(CO)_{12}$ and Et_3N under CO atmosphere in dioxane produced heterocyclic γ- and δ-unsaturated lactams in good yields (Scheme 44).[54]



n= 0,1

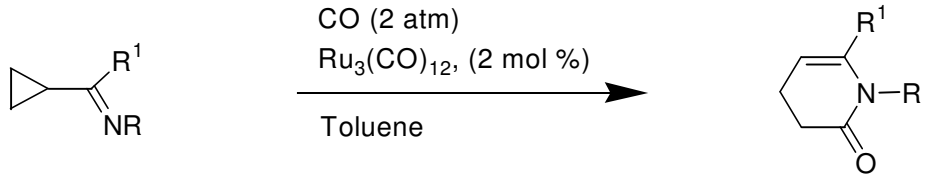
R^1= alkyl, aryl

R^2= Ts, Mts, Bn

54-95%

Scheme 44

A cycloaddition [5+1] involving the ring-opening of cyclopropane has represented a great potential way for the construction of six-membered carbonyl compounds. Wender and co-workers have reported the catalytic cycloaddition reactions which involve the opening of a cyclopropane ring. Murai and coworkers reported another example in which cyclopropyl imines behaved as an assembling unit. Some other examples include $Ru_3(CO)_{12}$-catalyzed carbonylative [5+1] mode of cycloaddition reactions of cyclopropyl imines leading to six-membered unsaturated lactams (Scheme 45) have been reported.[55]

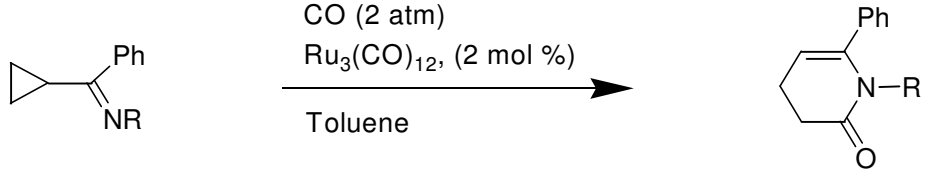


11 examples

10-76%

Scheme 45

The reaction of the cyclopropyl imine **73** (anti/syn = 3.3/1, 1 mmol) in toluene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ under CO atmosphere at 160 °C gave 3,4-dihydro-1-(1,1-dimethylethyl)-6-phenyl-2(1*H*)-pyridinone **74** in good yield. When the reaction was carried out at 140 or 180 °C, only trace amount of **74** was formed. This reaction was substituent dependent. In fact, the use of $PhCH_2$, *p*-$MeOC_6H_4$, or OMe as R substituent on the imine nitrogen gave no product of the reaction. The use of a cyclohexyl group as the *N*-substituent, such as in **75**, gave a comparable yield (61%) of the corresponding γ–lactam **76** (Scheme 46).



73 (R=*t*-Bu)

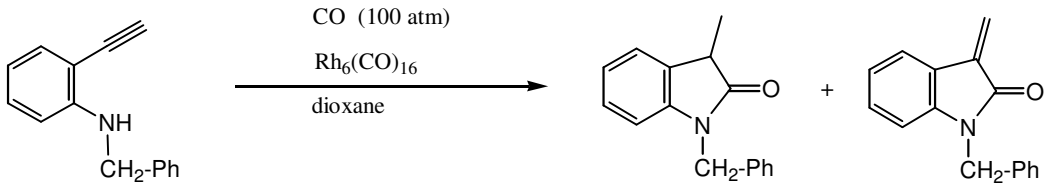
75 (R=Cy)

74-76 (75-61%)

Scheme 46

2.3.4. Synthesis of five- and six-membered fused to aromatic rings lactams

In 1995, Takahashi and co-workers have described the rhodium-catalysed cyclocarbonylation of 2-alkylaniline **77** to five membered ring lactam; once again it was possible to control the selectivity of **78** or **79** acting on the reaction condition (Scheme 47).[56]

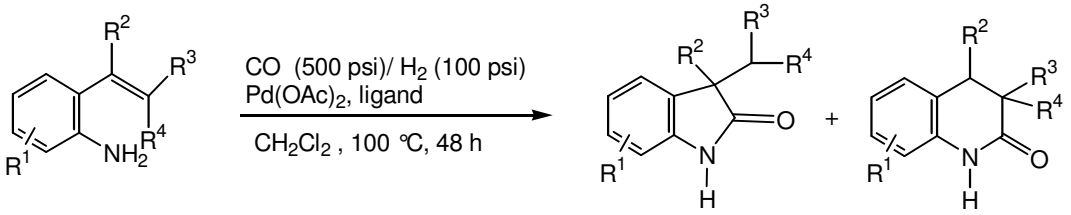


77 **78** (86-2%) **79** (0-85%)

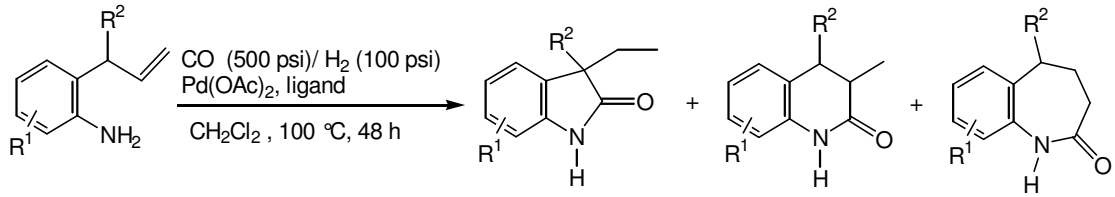
Scheme 47

More recently, Gabriele and co-workers reported the palladium oxidative carbonylation reactions of 2-ethynylaniline derivatives in methanol and PdI_2/KI as the catalytic system under a 4:1 CO/air mixture at 25 °C for the synthesis of (*E*)-3-(methoxycabonyl)methylene-1,3-dihydroindol-2-ones.[57]

Controlling the reaction conditions it is possible to have good selectivity in the palladium acetate-phosphine cyclocarbonylation reaction of 2-aminostyrenes to five- and six–membered lactams (Scheme 48) and 2-allylanilines to five, six and seven membered lactams (Scheme 49).[38]



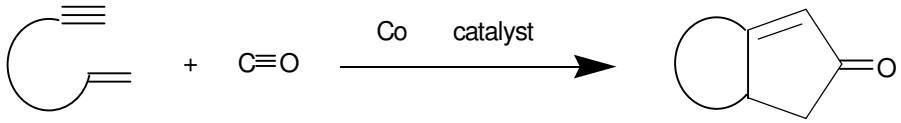
Scheme 48



Scheme 49

2.2. The Pauson-Khand reaction

Pauson-Khand reaction is one of the most important carbon skeleton-forming reactions by transition metal where a carbonylative coupling of alkene-alkyne or alkyne-alkyne occurs.

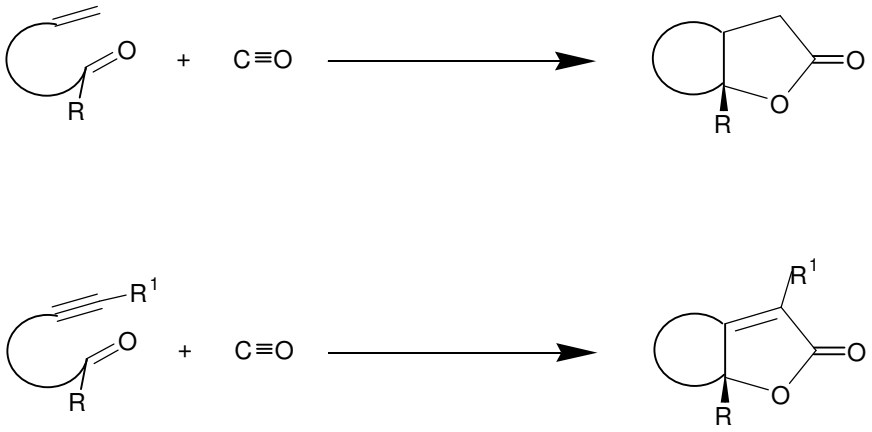


Scheme 50

These transformations take place in the presence of $Co_2(CO)_8$ where alkyne and alkene functionalities present in the same molecule react with carbon monoxide in a formal [2+2+1] cycloaddition to form cyclopentenones (Scheme 50).[58]

The interest for this class of reactions is due to the capability of transition metals to assemble simple molecules and carbon monoxide in a convergent manner. However, the limit of this reaction is represented by the requirement of stoichiometric amount of transition complex. Only recently the reactions were performed catalytically in concomitance with the development of the titanocene and oxa-titanocene chemistry.[59]

The intramolecular Pauson-Khand reaction mediated by $Cp_2Ti(PMe_3)_2$ has been also reported for molecules in which one of the alkyne or the alkene group is replaced by a carbonyl group and in this case γ-butyrolactones or fused butenolides are the products of the reaction (Scheme 51). The process, in this case, is known as "Hetero Pauson-Khand" reaction.

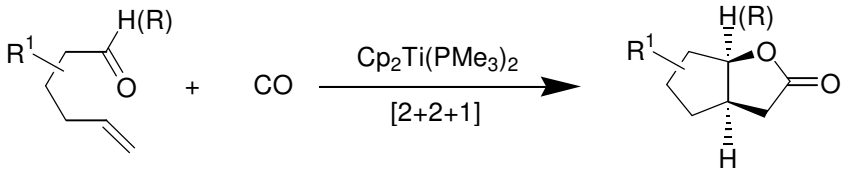


Scheme 51

A similar approach has been successfully employed for the construction of five-membered ring carbocycles, but not for heterocycle synthesis.

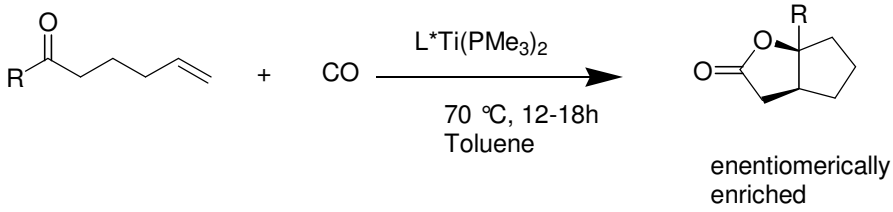
In 1996, Crowe and Vu reported a titanium-mediated synthesis of γ–butyrolactones which proceeds, under mild conditions, through coupling-carbonylation-reductive elimination. The procedure has been successfully applied to molecules containing aldehyde or ketone groups and a terminal olefinic group forming bicyclic γ–butyrolactone (Scheme 52).[60]

Buchwald and co-workers have reported the carbonylation reaction of *o*-allyl aryl ketones into γ–butyrolactones catalysed by $Cp_2Ti(PMe_3)_2$ or $Cp_2Ti(CO)_2$. The reaction proceeded *via* the carbonylation of an oxatitanacycle followed by thermally-induced reductive elimination and formation of the γ–butyrolactone.[61] The authors have suggested that the key step in the catalytic cycle is the formation of a charge transfer complex or the reversible electron transfer between the catalyst and the substrate.



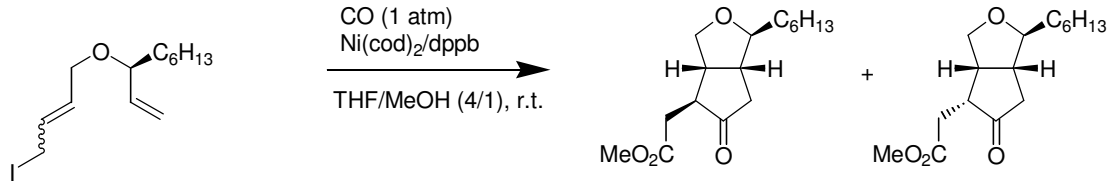
Scheme 52

Interestingly, a general catalytic procedure for the asymmetric intramolecular Hetero-Pauson-Khand cyclization of various substrates catalyzed by a chiral titanocene complex was successively developed (Scheme 53).[62]



Scheme 53

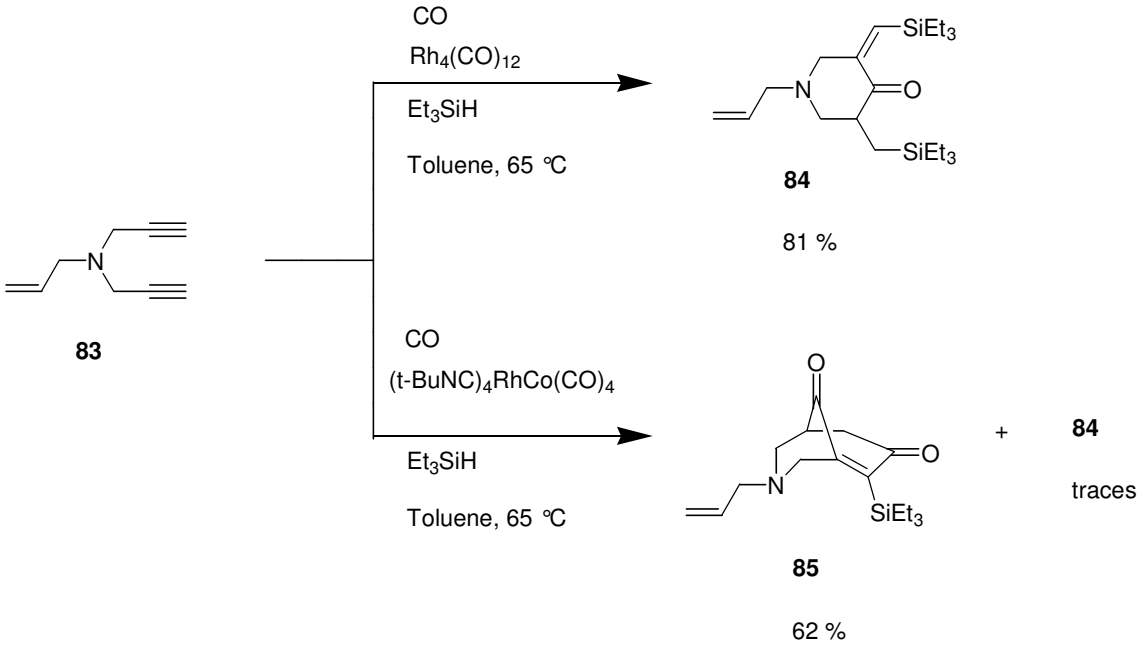
Several nickel-complexes were able to promote such carbocyclization reactions but only in stoichiometric way.[63] Dienes and enynes bearing allylic acetate or an allylic halide moiety; such as for example the compound **80**, undergo nickel-catalyzed reactions affording monocyclization or bicyclization products **81, 82** and the conversion was 68%. The authors reported that the reaction proceeds *via* olefin insertion into an initially formed allylnickel complex, followed by hydride elimination (Scheme 54).[1i]



80 **81** (89%) **82** (11%)

Scheme 54

Allyldipropargylamine **83** reacted with a triethylsilane under CO atmosphere in the presence of rhodium complexes via silylcarbocyclization reaction involving only 1,6-diyne moiety to give exo-methylene-4-piperidinone **84** in high yield (Scheme 55).[64] The same reaction catalyzed by $(t\text{-BuNC})_4RhCo(CO)_4$ in toluene produced **85** as the predominant product together to a small amount of **84**.



Scheme 55

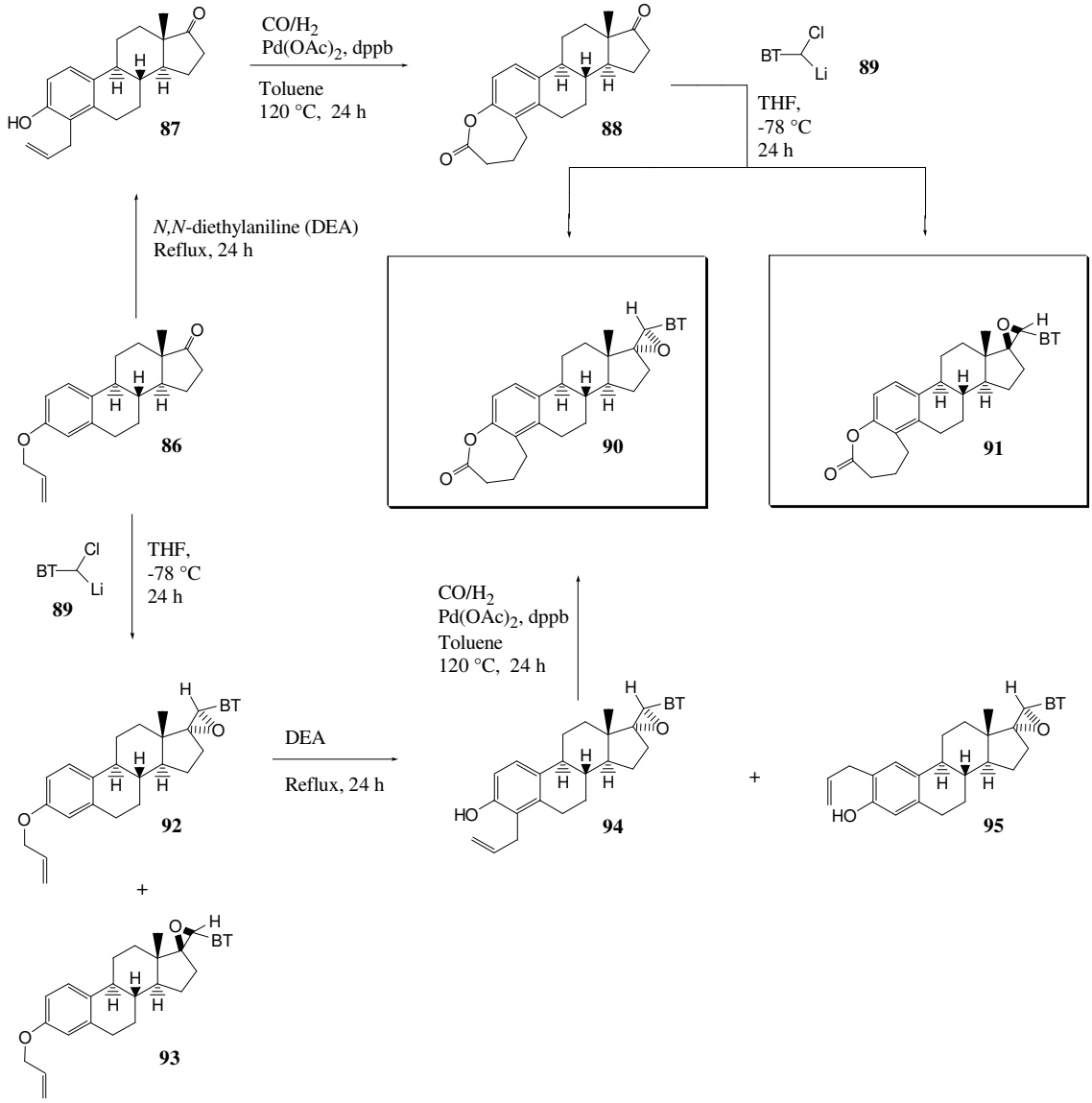
3. Trends in cyclocarbonylation reactions

3.1. Cyclocarbonylation of steroids and other natural substrates

Steroids are a biologically important class of compounds because of the large range of applications in the pharmaceutical industry. Steroids bearing different functionalities can represent an important new class of compounds. For example, new estrone derivatives having contemporary lactone and epoxide functionality can improve their biological activity.

Recently, it has been reported that palladium acetate and dppb catalyze the regioselective lactonization of allyl steroids forming exclusively 7-membered ring lactones with excellent isolated yields (98%).[65]

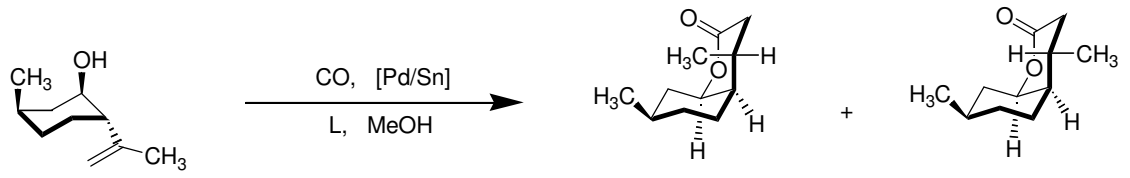
Very interestingly, the addition of one epoxide function in the seven-membered ring lactone steroid was obtained by coupling of the carbonyl group of the cyclopentanone ring with 2-benzothiazoliychloromethyllitium survive to the transformation (Scheme 56).[65]



Scheme 56

Lenoble and co-workers reported that the cyclocarbonylation of (*1R, 2S, 5R*) isopulegol **96** using $PdCl_2(PPh_3)_2$-$SnCl_2$, the catalytic system produced two compounds **97** and **98** with a diasteroisomeric excess up to 60 % (Scheme 57).

Interestingly, the enantiodifferentiation took place also by using non-chiral conventional ligand and could be attributed to the chiral starting material itself.[66]



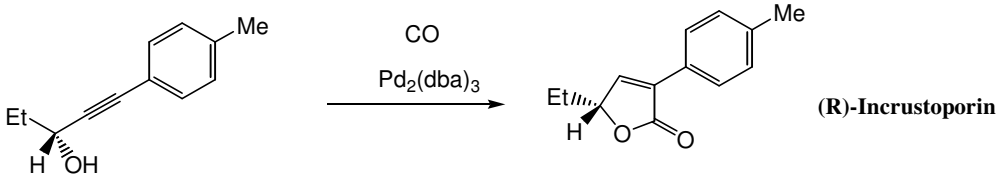
96 **97** **98**

97:*(1 R, 5R, 6S,9R)*-5,9-dimethyl-2-oxabicyclo [4.4.0] decan-3-one

98: *(1R, 5S, 6S,9R)*-5,9-dimethyl-2-oxabicyclo [4.4.0] decan-3-one

Scheme 57

$Pd_2(dba)_3$ catalized cyclocarbonylation reaction of the highly enantiomerically enriched (R)-1-p-tolyl 1-pentyn-3-ol **99** producing (R)-incrustoporin (R)-**100** (Scheme 58), an important antibiotic isolated from *Incrustoporia Carneola,*with retention of configuration.[67]

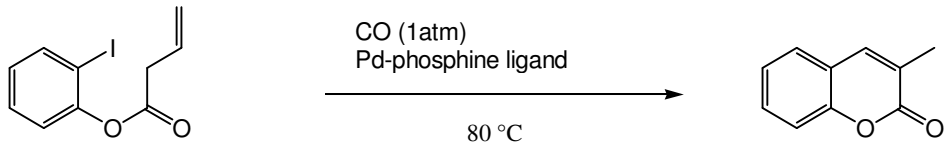


99 (R)-**100** (68%)

Scheme 58

Some coumarin derivatives have been obtained by palladium catalyzed reaction (Scheme 59).[68,69]

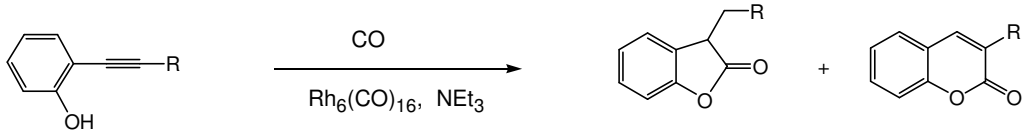
The authors explained that the role of carbon monoxide in this case was important just to form the catalyst.



101 **102** (44-85%)

Scheme 59

Rhodium-catalysed carbonylation of 2-alkynylphenol derivatives under water-gas shift reaction conditions gives benzofuranone derivatives and coumarin derivatives in high yield (up to 96%, 2:3 = 65:35), in which the hydroxy group adjacent to the carbon-carbon triple bond participates in the cyclic carbonylation (Scheme 60).[70]



6 examples 11-52% 20-47%

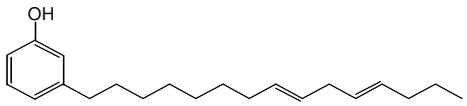
Scheme 60

A variety of substituted coumarins has been prepared in good yields by palladium-catalyzed coupling of *o*-iodophenols with alkynes and 1 atm of carbon monoxide.[71]

Recently **"**Cardanol**"** derivatives have been transformed into the corresponding lactones through cyclocarbonylation reactions.

Cardanol, which can be considered a renewable organic source, is simply obtained by vacuum distillation of "Cashew Nut Shell Liquid" (CNSL), the international name of the alkylphenolic oil contained in the spongy mesocarp of the cashew nut shell and derived as by-product of cashew industry.[72] Its production in the world (Africa, Asia, and South America are the main producer countries) is estimate to be about 500,000 tons *per* year and for that could represent a very interesting renewable organic source.[73]

Cardanol is considered a mixture of 3-*n*-pentadecylphenol and its unsaturated derivatives having respectively one, two or three conjugated double bonds on the alkyl chain with an average value of two double bonds *per* molecule (Figure 6), together with minor amount of cardol (3-*n*-pentadecylresorcinol) and methyl cardol (2-methyl-5-*n*-pentadecylresorcinol).

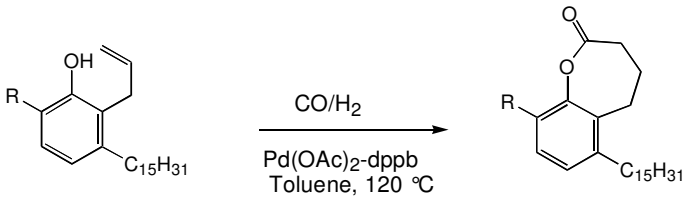


103

One of the unsaturated component of cardanol

Figure 6

Hydrogenation of the double bonds in the side-chain of distilled cardanol leads to 3-*n*-pentadecylphenol. This was used to prepare allyl derivatives **104-106** and cyclocarbonylated in the presence of palladium acetate and dppb in toluene to give selectively 7-membered ring lactones **107-109** in relative good yields (Scheme 61).[74]



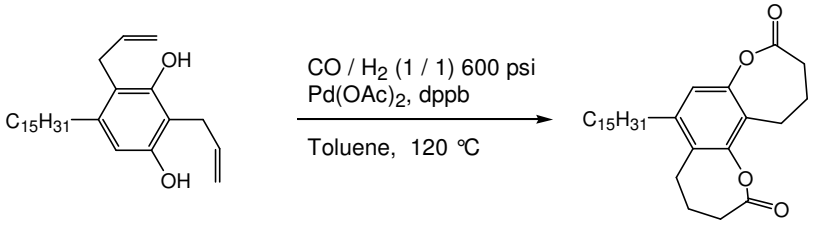
104-106 **107-109** (90-95%)

104 (R=H)

105 (R= *t*-Bu)

106 (R= *t*-Amyl)

Scheme 61



110 **111** (90%)

Scheme 62

The bis-allyl 3-*n*-pentadecyl resorcinol derivative **110**, under the same reaction conditions gave 7-membered ring bis-lactones **111** (Scheme 62).

3.2. More hetero atoms in the cyclic system

Palladium(0) catalysts are able to catalyse carbonylation of both isolable 1,2-diaza-1,3-butadienes and those generated *in situ* by extrusion of SO_2 and CO_2. The reaction have been demonstrated proceed easily at room temperature and under CO atmosphere affording 2,3-pyrazol-1(5H*)*-ones in good yields.[75]

Costa and co-workers reported the synthesis of β- and γ-lactams obtained by oxidative carbonylation of acetylenic amines catalysed by PdI_2-KI and evidenced in same case the formation different oxazolidin-2-one derivatives.[76]

3.3. 8,9-Membered and larger rings compounds

One more exciting field is the synthesis of more larger rings and only recently it has been reported a chemoselective and regioselective catalytic way to novel nine-membered lactones. In particular, cyclocarbonylation of dihydromyrcenol into the corresponding lactone has been selectively performed in the presence of $PdCl_2(PPh_3)_2/SnCl_2{\cdot}2H_2O$ and molecular sieves.[77]

In this context Yoneda and co-workers reported the synthesis of eight-membered lactones by carbonylation of 7-hydroxyhepta-1,2-dienes as an extension of analogous reactions performed on 6-hydroxyhexa-1,2-dienes transformed into the corresponding seven-membered lactones using $Ru_3(CO)_{12}$ as the catalyst and triethylamine as the solvent.[78]

3.4. Heterogeneous catalyzed cyclocarbonylations

Very few examples of carbonylation reactions in heterogeneous phase have been reported in the literature. Recently, in view of possible future development of environmental sustainable processes, it has been reported an heterogeneous catalytic systems for cyclocarbonylation reactions.[79] In particular, it was observed that palladium on commercial activated carbon or on carbon obtained from vegetable wastes, in the presence of dppb as ligand promoted cyclocarbonylation reactions of various allylphenol derivatives into the corresponding lactones. The authors showed that the regioselectivity in this case resulted different compared to the homogeneous one and dependent on the reaction conditions (CO/H_2 ratio, solvent, temperature). Palladium-montmorillonite clay, as reported by Alper and co-workers, was also effective catalyst for cyclocarbonylation reactions of 2-allylphenols affording seven membered ring lactones as the principal products.[80]

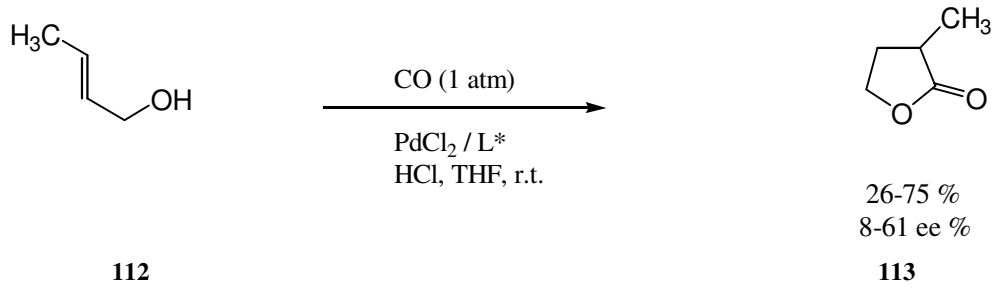
3.5. Enantioselective cyclocarbonylatyon reactions

The synthesis of optically active lactones and lactams has polarized a great interest in the last years. In fact, heterocyclic structures are presents in large variety of natural or synthetic products having biologic or pharmacologic activity.

Despite the great potential for asymmetric carbonylation reactions and the extensive effort devoted to this reaction, only moderate success (<90% ee) has been achieved, and the development of efficient asymmetric carbonylations is still viewed as one of the most challenging problems in asymmetric catalysis.

Alper and co-workers have extensively studied palladium-catalyzed cyclocarbonylation of allylic alcohols and developed the first enantioselective variant of this reaction using commercially available chiral bisphosphine ligands obtaining reasonable ee's.

Treatment of but-2-en-1-ol **112** with carbon monoxide, oxygen copper(II) salts and hydrochloridric acid in tetrahydrofuran containing palladium chloride and polyleucine affords (R)–α-methy-γ-butyrolactone **113** in 61% enantiomeric excess; (L)-diethyl tartrate and (R)-and (S)-'bis(diphenylphosphino)-1, 1' binaphthyl (BINAP) can also produce the optically active lactone, but in lower optical purity (Scheme 63).[81]



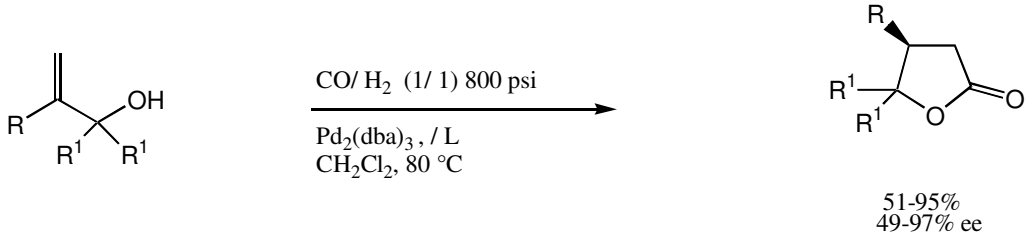
112 **113**

Scheme 63

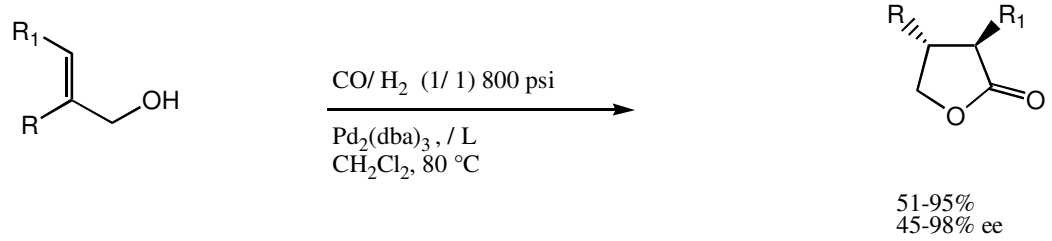
Various chiral agents (L*) were used (D-menthol, (R).1,1-bi-2naphthol, L-DET, D-DET, (-)-DMBT (S,S)CHIRAPHOS, (S)-BINAP, (R)-BINAP,Poly-L-leucine. Poly-D-alanine.

In the paper it was evidenced that the use of diethyltartrate or poly-L-leucine as chiral ligand resulted in the synthesis of optically active lactones in good enantiomeric excess. Furthermore this is the first example of the use of poly-a-aminoacids as added chiral ligands in homogeneous catalysis.

However, the asymmetric reaction is restricted to *β*-substituted allylic alcohols with dialkyl substitution at the α position (geminal dialkyl effect) (Scheme 64). Cyclocarbonylation reaction of allylic alcohols catalyzed by palladium complexes with BICP (see Figure 7) and related ligands produced good enantiomeric excess.



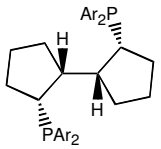
Scheme 64



Scheme 65

Another major advance in this study was the development of the first highly enantioselective cyclocarbonylation of *β*, *γ*–substituted allylic alcohols bearing geminal dialkyl substituents in α–position

(Scheme 65), which significantly increases the scope and synthetic utility of the asymmetric carbonylation reaction.[82]

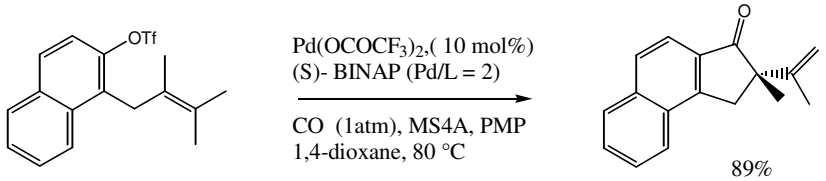


L1: BICP Ar=Ph

L2: Xyl-BICP Ar3,5-dimethyl phenyl

Figure 7

β,γ-Substituted allylic alcohols react with CO in the presence of catalytic quantities of palladium acetate and 1,4-bis(diphenylphosphino)butane affording α,β-substituted-γ-butyrolactones in 42-85% isolated yields. The complete stereoselectivity observed in some cases is a significant feature of the lactonization reaction.

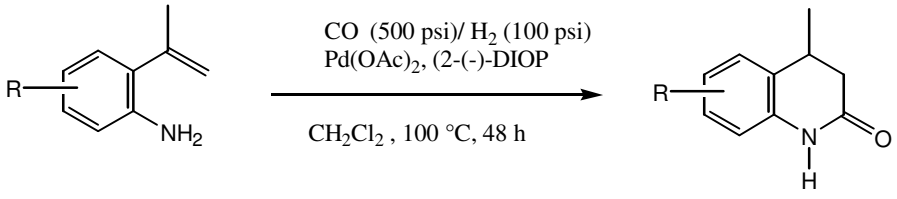


114 **115**

Scheme 66

Depending on the structure of the allylic alcohol the formation of the corresponding alkene or the *β,γ*-unsaturated carboxylic acid was also observed as a side or the principal reaction.[83] This represented the first stereoselective palladium-catalyzed cyclocarbonylation of *β,γ*-substituted allylic alcohols $Pd(OCOCF_3)_2$/(*S*)-binap has been used to effect asymmetric carbonylative cyclization of prochiral *o*-allylaryl triflates and 2-allylalkenyl triflates to produce high yields of enantiomerically enriched cyclopentenones up to 96% ee (Scheme 66).[84]

The asymmetric cyclocarbonylation of 2-vinylaniline derivatives catalyzed by palladium acetate 2(-)-DIOP produced 3,4-dihydro-4-methyl-2(1H)-quinolin-2-ones in up to 54 enantiomeric excess (Scheme 67).[85]



9 examples

48-99 %

0-54% ee

Scheme 67

Iridium salts in the presence of chiral diphosphine were able also to catalyze highly enantioselective intra and intermolecular Pauson-Khand type reactions producing various chiral cyclic enones in high enantiomeric excesses.[86]

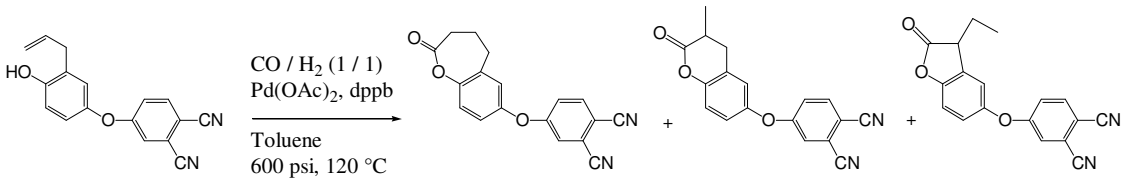
3.6. Cyclocarbonylated products as building blocks for new materials

Cyclocarbonylation reactions have been recently applied to transform particular substrates containing different functionalities (cyano, formyl, fullerene groups etc.), for the preparation of new compounds which can be used as building blocks for new compounds.

Macrocyclic molecules such as phthalocyanines (*Pcs*) or metal phthalocyanines (*MPcs*) or their analogous structural derivatives have been receiving an increasing interest due to their various applications in the area of new materials such as active layers for gas sensors, homogeneous and/or heterogeneous catalysts, modified electrodes and so on.[87]

It is well known also that the presence of alkyl or aryl groups in such molecules is important not only because can increase the solubility in the most common organic solvents, but can also change the aggregation state in solution as well as the physical and photo-physical properties.[88]

Pcs containing lactone moiety in their structure represent a very stimulating area for the preparation of novel classes of "functional" *Pcs*.



116 **117** (90%) **118** (3%) **119** (7%)

Scheme 68

It is noteworthy that some of the most used methodologies for the synthesis of a variety of phthalocyanines consist into the tetramerization reaction of phthalonitrile derivatives.

For this reason a particular significance was associated to the synthesis of the dicyano lactone derivative **117** which was easily prepared by cyclocarbonylation reaction of **116** (Scheme 68) in terms of precursor of novel phthalocyanines.

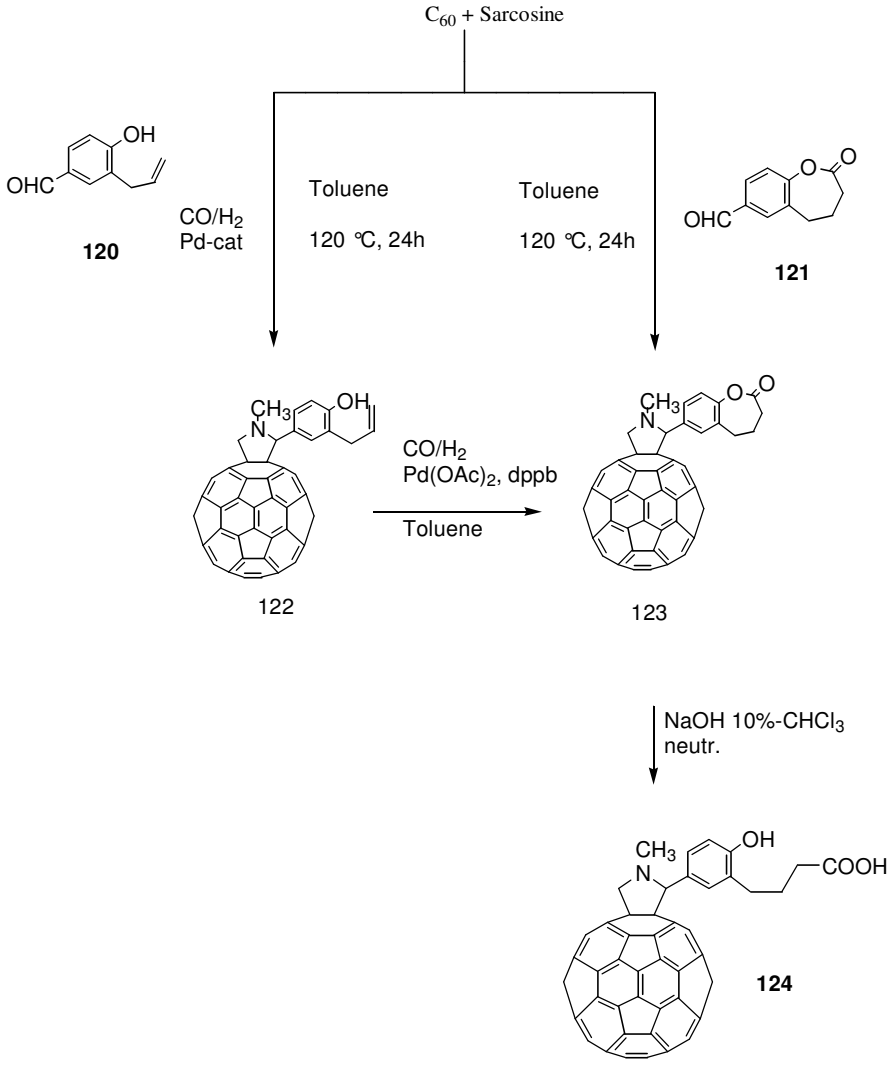
In particular, lactone **117** was prepared in high yield by cyclocarbonylation reaction of **116** in toluene and syn-gas condition in a process catalyzed by Pd $(OAc)_2$ and dppb.

Another stimulating area in new material science involve the fullerene [C_{60}] chemistry. Many fundamental properties of fullerene derivatives have been discovered and reported[89] and their metal complexes evidence attractive characteristics, such as superconductivity[90,91,92] or charge-transfer behaviour.[93,94,95] It is well known also that the ball-like structure of C_{60} molecules is very rigid, hydrophobic, and exhibit peculiar properties totally different from those of rod-like self-assembling amphiphilic molecules.

Further, the use of highly organized fullerene derivatives in the form of supramolecular array (thin films, nanotubes etc.) could represent new technological potentialities and one of the most common approaches to control the architecture of organized thin films containing the fullerene moiety[96,97] is the functionalisation of C_{60}.

Cyclocarbonylation reaction catalyzed by palladium acetate dppb were used to synthesize novel functionalized fulleropyrrolidines C_{60}-based molecules having polar groups suitable to study their behaviour at the air water interface and their transfer onto solid surfaces.

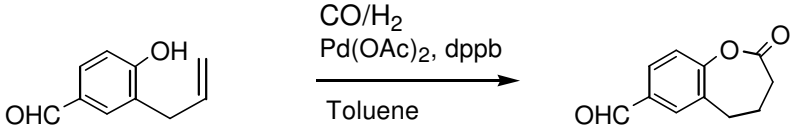
Compounds **120** and **121** were used as aldehydic precursors in the reaction in the presence of sarcosine and C_{60} giving the corresponding fulleropyrrolidine **122** and **123** respectively in 45 and 50% yields (Scheme 69).[98] Two different synthetic strategies have been pursued for the preparation of new molecules that contain both the fullerene moiety and the lactone group.



Scheme 69

Fulleropyrrolidines **123** was successively hydrolysed treating a their chloroform solution with a 10 % solution of NaOH for 2-7 h at 70 °C. The compound **124** was recovered after neutralisation and chloroform extraction of the mixture of reaction.

In particular, compound **121** was synthesised by cyclocarbonylation reaction of 3-allyl-4-hydroxybenzaldheyde **120** in presence of CO and H_2 using $Pd(OAc)_2$ and 1,4-bis(diphenylphosphino) butane (dppb) as catalytic system (Scheme 70).[3]



120 **121** (90%)

Scheme 70

4. Conclusion

A variety of heterocyclic compounds such as lactones, lactams, pyrrolidinones, and others can be achieved by cyclocarbonylation reactions catalysed by various transition metals and their complexes. The cyclocarbonylation reaction methodology is useful for the preparation of cyclic compounds containing five-, six-, seven- and other membered ring lactones and lactams. Another important area of application is the catalytic asymmetric cyclocarbonylation and the preparation of cyclocarbonylated products as building block for new materials.

References

1. a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. b) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct synthesis of carbonyl compounds*. Plenum Press : New York **1991**. c) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis* Eds. Pergamon Press: New York, **1991**. d) Alper, H. *Aldrichimica. Acta* **1991**, *24*, 3. e) Hosakawa, T.; Murahshi, S. I. *Heterocycles*, **1992**, *33*, 1079. f) Parshall, G. W.; Ittel, S. D. *"Homogeneous Catalysis"*, Wiley , New York **1993**. g) Masters, C. *"Homogeneous Transition Metal Catalysis",* Wiley , New York **1993**. h) Negishi, E.; Copèret, C.; Ma, S.; Lion, S.Y.; Liu, F. *Chem. Rev*. **1996**, *96*, 365. i) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev*. **1996**, *96*, 635. j) Ungvary, F. *Coord. Chem. Rev.* **1998**, *170*, 245. k) El Ali, B.; Alper, H. *Synlett* **2000**, 161.
2. a) Falbe, J.; Korte, F. *Chem. Ber.* **1962**, *95*, 2680. b) Falbe, J.; Huppes, N.; Korte, F. *Chem. Ber.* **1964**, *97*, 863. c) Falbe, J.; Korte, F. *Chem. Ber.* **1965**, *98*, 886.
3. a) Nakanishi, K.; Goto, T.; Ito, S. *Natural Product Chemistry*; Kodansya: Tokyo, **1974**; vols. 1-3. b) *Dictionary of Natural Products*, 1st ed.; Buckingam, J., Ed. Chapman & Hall: New York. **1994**. c) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 5. d) Barton, D.; Nakanishi, K.; Meth-Cohn, O. In *Comprehensive Natural Products Chemistry*; Elsevier Science Ltd.: Oxford, 1999; Vol. 8, pp 378-385. e) Rao, G. V.; Cain, R. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2111. f) Handa, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1281. g) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287.
4. a) Raphael, R. A.; Ravenscroft, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, *7*, 1823. b) Dueholm, K. L.; Pederson, L. B. *Synthesis* **1992**, 1. c) Robertson, D. W.; Krushinski, J. H.; Utterback, B. G.; Kauffman, R. F. *J. Med. Chem.* **1989**, *32*, 1476. d) Bjeldanes, L. F.; Kim, I. S. *J. Org. Chem.* **1977**, *42*, 2333. e) Weidner-Wells M. A.; Decamp, A.; Mazzocchi, P. H. *J. Org. Chem.* **1989**, *54*, 5746.
5. a) Al-Alzemi, T. F.; Kondaveti, L. ; Bisht, K. S. *Macromolecules* **2002**, *35*, 3380. b) Trollasas, M.; Hedrick, J. L.; Mecerreyes, D.; Dubois, P.; Jerome, R.; Ihre, H.; Hult, A. *Macromolecules* **1998**, *312*756.
6. a) Stille, J. K.; Divakarumi, R. *J. Am. Chem. Soc.* **1975**, *97*, 674. b) Stille J. K.; Divakarumi, R. *J. Am. Chem. Soc.* **1978**, *100*, 1303.
7. Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.
8. Qing, F. L.; Jiang, Z. X. *J. Fluorine Chem.* **2002**, *114*, 177.
9. Qing, F. L.; Jiang, Z. X. *Tetrahedron Lett.* **2001**, *42*, 5933.
10. Jiang, Z. X.;. Qing, F. L. *Tetrahedron Lett.* **2001**, *42*, 9051.
11. Matsuda, I.; Ogiso, A.; Sato, S. *J. Am. Chem. Soc.,* **1990**, *112*, 6120.
12. Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **2001**, *42*, 1301.
13. a) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa M.; Chiusoli G. P. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 147. b) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun*. **1994**, 1429.
14. a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, *2nd ed*., University Science Books, Sausalito, **1987**. b) Heck, R. F. *Organic Synthesis via Metal Carbonyls, Vol. 1* (Eds.: I. Wender, P. Pino), Interscience Publishers, New York, **1968**, pp. 373-404. c) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules,* University Science Books, Mill Valley, **1994**.
15. Yang, H. W.; Romo, D. *Tetrahedron*, **1999**, *55*, 6403.
16. a) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414. b) Magriotis, P. A. *Angew. Chem.* **2001**, *113*, 4507; Magriotis, P. A. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 4377.

17. Müller, H. M.; Seebach, D. *Angew. Chem.* **1993**, *105*, 483; Müller, H. M.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 477.
18. a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. b) Cheng, R. P.; Gellman, S. H.; De Grado, W. F. *Chem. Rev.* **2001**, *101*, 3219. c) Cheng, J. J.; Deming, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 9457. d) Jia, L.; Ding, E.; Anderson, W. R. *J. Chem. Soc., Chem. Commun.* **2001**, 1436. e) Allmendinger, M.; Eberhardt, R.; Luinstra, G.; Rieger, B. *J. Am. Chem. Soc.* **2002**, *124*, 5646.
19. a) Chamchaang, W.; Pinhas, A. R. *J. Chem. Soc., Chem. Commun.* **1988**, 710. b) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943. c) Ley, S. V.; Middleton, B. *J. Chem. Soc., Chem. Commun.* **1998**, 1995.
20. For Co-catalyzed aziridine carbonylations, see: a) Piotti, M. E.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 111. b) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. c) Davoli, P.; Prati, F. *Heterocycles* **2000**, *53*, 2379. d) Lee, J. T.; Thomas, P. J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 5424. e) Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801. For Rh-catalyzed aziridine carbonylations, see: f) Alper, H.; Urso, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737. g) Roberto, D.; Alper, H. *Organometallics* **1984**, *3*, 1767. h) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931. For Pd-catalyzed aziridine carbonylations, see: i) Alper, H.; Hamel, N. *Tetrahedron Lett.* **1987**, *28*, 3237. j) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91. k) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415.
21. (a) Drent, E.; Kragtwijk E. Shell Internationale Research B. V. Maatschappij, Neth., EP 577206, 1994 [*Chem. Abstr.* **1994**, 120, 19 1517c]. b) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2781.
22. For the use of $Co_2(CO)_8$ to carbonylate ethylene oxide to oligomeric polyesters, see: Hattori, N.; Nishida, H. (Tokuyama Soda Co.). Jpn. Pat. 09169753; *Chem. Abstr*. **1997**, *127*, 95188.
23. a) Kamiya, Y.; Kawato, K.; Ohta, H. *Chem. Lett*. **1980**, 1549. b) Bates, R. W.; Fernandez-Moro, R.; Ley, S. V. *Tetrahedron* **1991**, *47*, 9929. c) Shimizu, I.; Maruyama, T.; Makuta, T.; Yamamoto, Y. *Tetrahedron Lett*. **1993**, *34*, 2135.
24. Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174.
25. Van den Hoven, B. G.; El Ali, B.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4131.
26. El Ali, B.; Alper, H. *J. Org. Chem.* **1991**, *56*, 5357.
27. Yoneda, E.; Kaneko, T.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441.
28. Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1999**, *40*, 989.
29. a) Alper, H.; Leonard, D. *J. Chem. Soc., Chem. Commun.* **1985**, 511. b) Alper, H.; Leonard, D. *Tetrahedron Lett.* **1985**, *26*, 5639.
30. a) Norton, J. R.; Shenton, K. E.; Schwartz, J. *Tetrahedron Lett.* **1975**, *16*, 51. b) Murray, T. F.; Samsel, E. G.; Varma, V.; Norton, J. R. *J. Am. Chem. Soc*. **1981**, *103*, 7520.
31. Tezuka, K. Y.; Ishizaki, Y.; Inoue, Y. *J. Mol. Catal.* **1998**, *129*, 199.
32. Ogawa, A.; Kawabe, K.; Kawakami, J.; Mihara, M.; Hirao, T.; Sonoda, N. *Organometallics* **1998**, *17*, 3111.
33. Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.
34. Wu, G. Z.; Shimoyama, I.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 6506.
35. Ciattini, P. G.; Mastropietro, G.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1993**, *34*, 3763.
36. Negishi, E.; Copéret, C.; Ma, S.; Mita, T.; Sugihara, T.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5904.
37. Grigg, R.; Khlil, H.; Levett, P.; Virica, J.; Sridharan, V. *Tetrahedron Lett*. **1994**, *35*, 3197.
38. El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc*. **1996**, *118***,** 4264.
39. Vasapollo, G.; Scarpa, A.; Mele, G.; Ronzini, L.; El Ali, B. *Appl. Organomet. Chem.*, **2000**, *14*, 739.
40. Vasapollo, G.; Mele, G.; El Ali, B. *J. Mol. Cat. A*. **2002**, 0000.
41. a) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994** , *33*, 599. b) Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 3041.
42. Bonardi, A.; Costa, M.; Gabriele, B.; Salerno, G.; Chiusoli, G. P. *Tetrahedron Lett.* **1995**, *36*, 7495.
43. Copéret, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.* **1995**, *40*, 1771.
44. Copéret, C.; Shengming, M.; Sugihara, T.; Negishi, E. *Tetrahedron* **2000**, *56*, 11529.
45. Berger, D.; Imhof, W. *Tetrahedron* **2000**, *56*, 2015.

46. Matsuda, A. *Bull. Chem. Soc. Jap.* **1968**, *41*, 1876.
47. Falbe, J.; Korte, F. *Chem. Ber.* **1965**, *28*, 1928.
48. Knifton, J. F. *J. Organomet. Chem.* **1980**, *188*, 223.
49. Jergorov, A.; Trnka, T.; Turecek, F.; Hanus, V. *J. Mol. Cat.* **1990**, *63*, 335.
50. Zhou, J. Q.; Alper, H. *J. Org. Chem*. **1992**, *57*, 3328.
51. Bertozzi, S.; Salvatori, P. *Synth. Commun.* **1996**, *26*, 2959.
52. Dong Doan, H.; Gore, J.; Vatèle, J. M. *Tetrahedron Lett.* **1999**, *40*, 6765.
53. Longo, L.; Mele, G.; Ciccarella, G.; Sgobba, V.; El Ali, B.; Vasapollo, G. *Appl. Organomet. Chem.* **2002**, *16*, 537.
54. Kang, S. K.; Kim, K. J.; Yu, C. M.; Hwang, J. W.; Do, Y. K. *Org. Lett.,* **2001**, *3*, 2851.
55. Kamitani, A.; Chatani, N.; Morimoto ,T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 9230.
56. Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* **1995**, *36*, 6243.
57. Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607.
58. a) Schore, N. E. *In Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Kidlington, 1995; Vol. 12, p 703 and references within. b) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. c) Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793. d) Pagenkopf, B. L.; Livinghouse, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 2285.
59. a) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 394. b) Binger, P.; Müller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krüger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035. c) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun*. **1990**, 1684. d) Mashima, K.; Haraguchi, H.; Oyoshi, A.; Sakai, N.; Takaya, H. *Organometallics* **1991**, *10*, 2731. e) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. f) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785.
60. Crowe, W. E.; Vu , A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557.
61. Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.*, **1997**, *119*, 4424.
62. Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.,* **2001**, *123*, 6457.
63. Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818.
64. Ojima, I.; Donovan, R. J.; Shay, W. R. *J. Am. Chem. Soc.* **1992**, *114*, 6580.
65. Troisi, L.; Vasapollo, G.; El Ali, B.; Mele, G.; Florio, S.; Capriati, V. *Tetrahedron Lett*. **1999**, *40*, 1771.
66. Lenoble, G.; Naigre, R.; Chenal, T.; Urrutigoity, M.; Daran, J. C.; Klack, P. *Tetrahedron Asymmetry* **1999**, *10*, 929.
67. Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Asymmetry* **1999**, *10*, 1163.
68. Castellani, M.; Chiusoli, G. P.; Fagnola, M. F.; Salari, G. *Tetrahedron Lett*. **1994**, *35*, 5923.
69. Castellani, M.; Chiusoli, G. P.; Marzolini, G.; Rossi, E. *J. Organomet. Chem.* **1996**, 65, 525.
70. Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S. W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477.
71. Kadnikov D. V.; Larock, R. C. *Org. Lett*. **2000**, *2*, 3643.
72. Cashew Nut tree is a plant species (its botanical name is *Anacardium Occidentale* Linn) founds in many parts of the world Asia (eastern coast of India), Africa (Bay of Bengal), South America (Brazil).
73. Attanasi, O. A.; Buratti, S.; Filippone, P. *Chim. Ind.* (Milan), **1996**, *78*, 693.
74. Amorati, R.; Attanasi, O. A.; El Ali, B.; Filippone, P.; Mele, G.; Spadavecchia, J.; Vasapollo, G. *Synthesis* **2002**, 2749.
75. Boeckman, R. K., Jr.; Reed, J. E.; Ge, P. *Org. Lett.,* **2001**, *3*, 3651.
76. a) Bacchi, A. ; Chiusoli, G. P.; Costa, M.; Gabriele, B.; Righi, C.; Salerno, G. *J. Chem. Soc., Chem. Commun*. **1997**, 1209. b) Chiusoli, G. P.; Costa, M.; Gabriele, B.; Salerno, G. *J. Mol. Catal*. A **1999**, *143*, 297.
77. Lenoble, G.; Urrutigoity, M.; Kalck, P. *Tetrahedron Lett.* **2001**, *42*, 3697.
78. Yoneda, E.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett*. **2001**, *42*, 5459.
79. Maffei, A.; Mele, G.; Ciccarella, G.; Vasapollo, G.; Crisafulli, C.; Scirè, S.; La Mantia, F. *Appl. Organomet. Chem.* **2002**, *16*, 543.
80. Orejon, A.; Alper, H. *J. Mol. Catal*. A **1999**, *143*, 137.
81. Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun.* **1990**, 135.

82. Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708.
83. Brunner, M.; Alper, H. *J. Org. Chem.* **1997**, *62*, 7565.
84. Hayashi, T.; Tang, J.; Kato, K. *Org. Lett.* **1999**, *1*, 1487.
85. Okuro, K.; Kai, H.; Alper, H. *Tetrahedron Asymm.* **1997**, *8*, 2307.
86. Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852.
87. a) Clòaessens, C. G.; Blau, W. J.; Cook, M.; Hanack, M.; Nolte, R. J. M.; Torres, T.; Wöhrle, D. *Monatsh. Chem.* **2001**, *132*, 3 and references therein. b) Leznoff, C. C.; Lever, A. B. P. *Phthalocyanines: Properties and Applications*, Vols 1-4. VCH: Weinheim, 1989-1996.
88. a) McKeown, N. B. *Phthalocyanines Materials Synthesis Structure and Function*; Cambridge University Press: Cambridge, 1998. b) Gürek, A. G.; Bekeroglu, O. *J. Porphyrins Phthalocyanines* **1977**, *1*, 67. c) Gürek, A.G.; Bekeroglu, O. *J. Porphyrins Phthalocyanines* **1977**, *1*, 227. d) Polley R, Heckmann H, Hanack M. In Houben-Weyl; 4th ed. Vol E9; Thieme, Stuttgart, 1997; 718.
89. Hirsch, A. *The Chemistry of the Fullerenes*; Georg Thieme Verlag: Stuttgart, 1994.
90. Hebard, A. F.; Rosseinsky, M. J.; Haddon, R. C.; Murphy, D. W.; Glarum, S. H.; Palstra, T. T. M.; Ramirez, A. P.; Kortan, A. R. *Nature* **1991**, *350*, 600.
91. Wang, P.; Metzger R. M.; Bandow, S.; Maruyama, Y. *J. Phys. Chem.* **1993**, *97*, 2926.
92. Wang, P.; Maruyama, Y.; Metzger, R. M. *Langmuir* **1996**, *12*, 3932.
93. Thomas, K. G.; Biju, V.; Guldi, D. M.; Kamat, P. V.; George, M. V. *J. Phys. Chem. A* **1999**, *103*, 10755.
94. Da-Ros, T.; Prato, M.; Guldi, D. M; Alessio, E.; Ruzzi, M.; Pasimeni, L. *J. Chem. Soc., Chem. Commun.* **1999**, 635.
95. D' SouzaF.; Deviprasad, G. R.; El-Khouly, M. E.; Fujitsuka, M.; Ito, O. *J. Am. Chem. Soc.* **2001**, *123*, 5277.
96. Wang, P.; Metzger, R. M.; Chen, B. *Thin Solids Flims* **1998**, *327-329*, 96.
97. Shi, X.; Caldwell, W. B.; Chen, K.; Mirkin C. A. *J. Am. Chem. Soc.* **1994**, *116*, 11598.
98. Maggini, M.; Scorrano, G.; Prato, M. *J. Am. Chem. Soc*. **1993**, *115*, 9798.

PREPARATION AND SYNTHETIC APPLICATIONS OF (*S*)- AND (*R*)-*N*-BOC-*N*,*O*-ISOPROPYLIDENE-α-METHYLSERINALS

Alberto Avenoza,[a*] Jesús H. Busto,[a] Carlos Cativiela,[b] Francisco Corzana,[a] Jesús M. Peregrina,[a] David Sucunza[a] and María M. Zurbano[a*]

[a]*Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, U.A.-C.S.I.C., 26006 Logroño, Spain (e-mail: mariadelmar.zurbano@dq.unirioja.es)*

[b]*Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain*

Abstract. *This report describes the behaviour of* (*S*)- *and* (*R*)-*N-Boc-N,O-isopropylidene-α-methylserinals, two new versatile chiral building blocks in organic synthesis. The preparation of both compounds on a multigram scale is reported. Likewise, we explored the applications of these compounds in asymmetric synthesis. Several products of considerable importance have been synthesised including α-methyl-α-amino acids and carbohydrates of glycopeptide antibiotics.*

Contents

1. Introduction

The synthesis of optically active organic compounds is one of the most important challenges in contemporary chemistry.[1] Stereochemical control is an essential feature of the synthesis of these organic molecules. There are several methods for achieving enantiopure compounds and the field of asymmetric (enantioselective and diastereoselective) synthesis has certainly contributed greatly to progress in the highly controlled formation of new stereogenic centres.[2] In diastereoselective synthesis with chiral reagents, it is important that starting materials are readily available. Natural products (monosaccharides, amino acids, and their derivatives) constitute an attractive source of chirality for asymmetric synthesis. This is due in part to the commercial availability of these substances or to the small number of steps required for their synthesis from available starting materials.

In the last decade there has been sustained interest in the development of chiral *N*-protected α-amino aldehydes[3] –compounds that are derived from natural products. These compounds are of great interest due either to their intrinsic properties or for use as powerful synthetic intermediates. In particular, (*S*)-*N*-Boc-*N*,*O*-isopropylideneserinal **1**, known as Garner's aldehyde, and its *R*-enantiomer **2** (Figure 1) are widely used as chiral building blocks in organic synthesis.[4] The presence of the formyl group and the suitably protected amino and hydroxyl groups in the oxazolidine ring has been used in several synthetic strategies that involve stereochemical control, transformation and/or deprotection reactions to form part of an essential backbone in biologically active compounds.

Since Garner published the synthesis of **1** in 1987,[5] the versatility of **1** and its enantiomer **2** in stereocontrolled organic chemistry has been reported in more than 300 articles.[4] Furthermore, the syntheses of these compounds from readily available chiral sources, (*S*)- and (*R*)-serine, have been optimised[6] to provide a simple and practical gram-scale procedure – a situation that is crucial in their extensive applications in synthesis. Nevertheless, α-amino aldehydes are often susceptible to racemization and, as such, special attention must be paid to the reaction conditions employed. Several authors have observed partial racemization during reactions with Garner's aldehyde (*e.g.* Wittig olefination,[6a,7] Swern oxidation[8]).

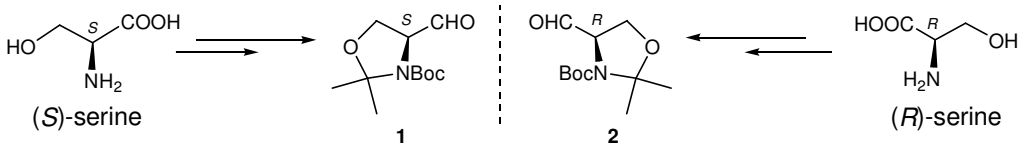


Figure 1

In this context, and as a part of our research project on asymmetric synthesis, we focused our attention on a number of biologically active natural products that contain quaternary carbon atom(s) (amino acids, amino alcohols, antibiotics, carbohydrates, terpenes, alkaloids). Interest in the synthesis of molecules with quaternary stereocentres is reflected in the increase in the number of articles that have been published in this area in the last decade.[9]

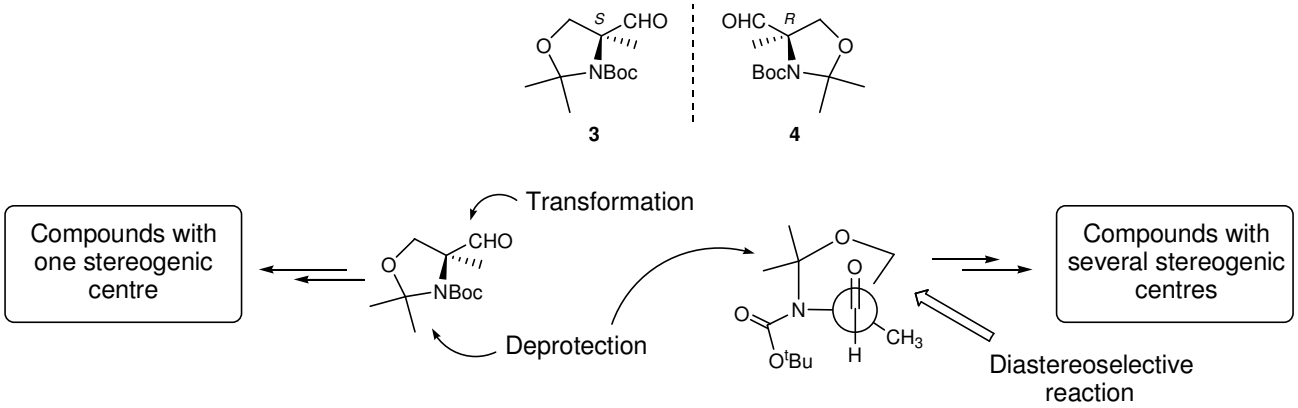


Figure 2

Bearing in mind that the stereocontrolled chemistry of the 4-formyl-1,3-oxazolidine group in Garner's aldehyde has been widely studied, we fixed our interest on the synthesis of the α-methyl homologues of

serinals **1** and **2**, the (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals **3** and **4** (Figure 2). These new chiral building blocks are convenient precursors of methyl quaternary compounds:

- the formyl group can be transformed to obtain several compounds with a quaternary carbon atom;
- the oxazolidine ring can be used as a chiral inductor in diastereoselective reactions with the generation of new stereogenic centres;
- the problem of racemization is not an issue.

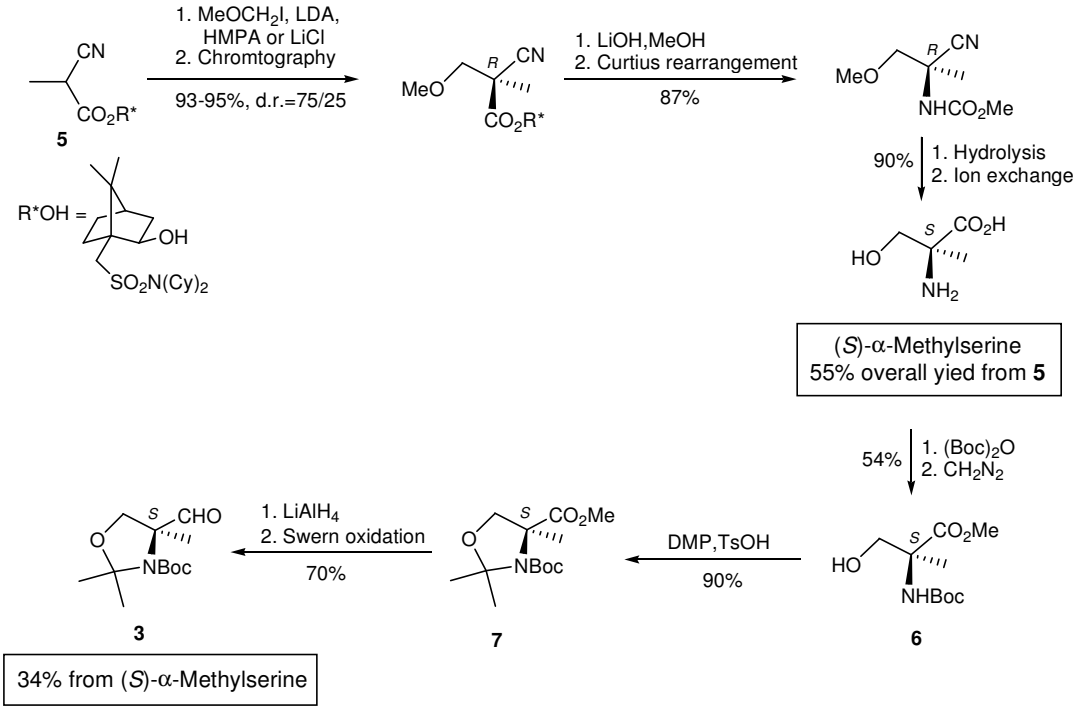
The development of a convenient large-scale procedure for the preparation of compounds **3** and **4** is important for the use of these chirons in asymmetric synthesis.

The present review covers the synthesis of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals **3** and **4**, as well as their versatility in stereocontrolled organic synthesis as methyl quaternary chiral building blocks.

2. Synthesis of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals

In the same way as (*S*)- and (*R*)-serine were used as starting materials in the preparation of chiral aldehydes **1** and **2**, Cativiela *et al.* described[10] the first synthesis of serinal derivative **3**, on a milligram scale, starting from (*S*)-α-methylserine.

This amino acid was synthesized using the methodology developed by them for the asymmetric synthesis of α,α-dialkyl-α-amino acids. Indeed, α-methylserine was obtained by a diastereoselective alkylation reaction between chiral 2-cyanopropanoate **5** and methoxymethyl iodide (LDA as base and HMPA or LiCl as external lithium complexing agent) and appropriate transformations: carboxylic ester group to amino group (Curtius-type rearrangement) and cyano group to carboxylic acid group (acid hydrolysis).



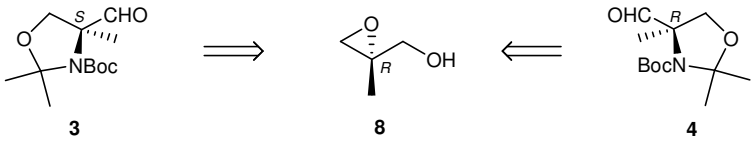
Scheme 1

Serinal derivative **3** was later obtained by a similar procedure to that described for Garner's aldehyde. Treatment of the free amino acid with di-*tert*-butyldicarbonate (Boc_2O) using conditions reported by Johnson[11] (NMe_4OH, CH_3CN) and subsequent esterification of the carboxylic acid group (diazomethane) afforded compound **6**.

Formation of the oxazolidine ring was achieved with 2,2-dimethoxypropane (DMP) and a catalytic amount of *p*-toluenesulfonic acid (TsOH) to give compound **7**. Finally, *N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3** was obtained by a convenient route, which involved a reduction-oxidation sequence ($LiAlH_4$ and Swern oxidation), in 34% overall yield starting from (*S*)-α-methylserine (19% starting from 2-cyano ester **5**) (Scheme 1).

The ready access to both chiral building blocks through a simple and economically viable gram-scale procedure is crucial to the extensive applications of these materials in synthesis. However, this procedure cannot translate to larger scale due to the expense involved in the synthesis of enantiomerically pure α-methylserine (either by this method or by any other asymmetric synthesis reported to date).

In 1999, we reported a new and more convenient synthetic procedure for (*S*)- and (*R*)-α-methylserinals (**3** and **4**) on a multigram scale.[12] Starting from the commercially available (*R*)-2-methylglycidol **8**, and employing a stereodivergent synthetic route, we carried out a short and easy procedure for the preparation of both enantiomers (Figure 3).



3 **8** **4**

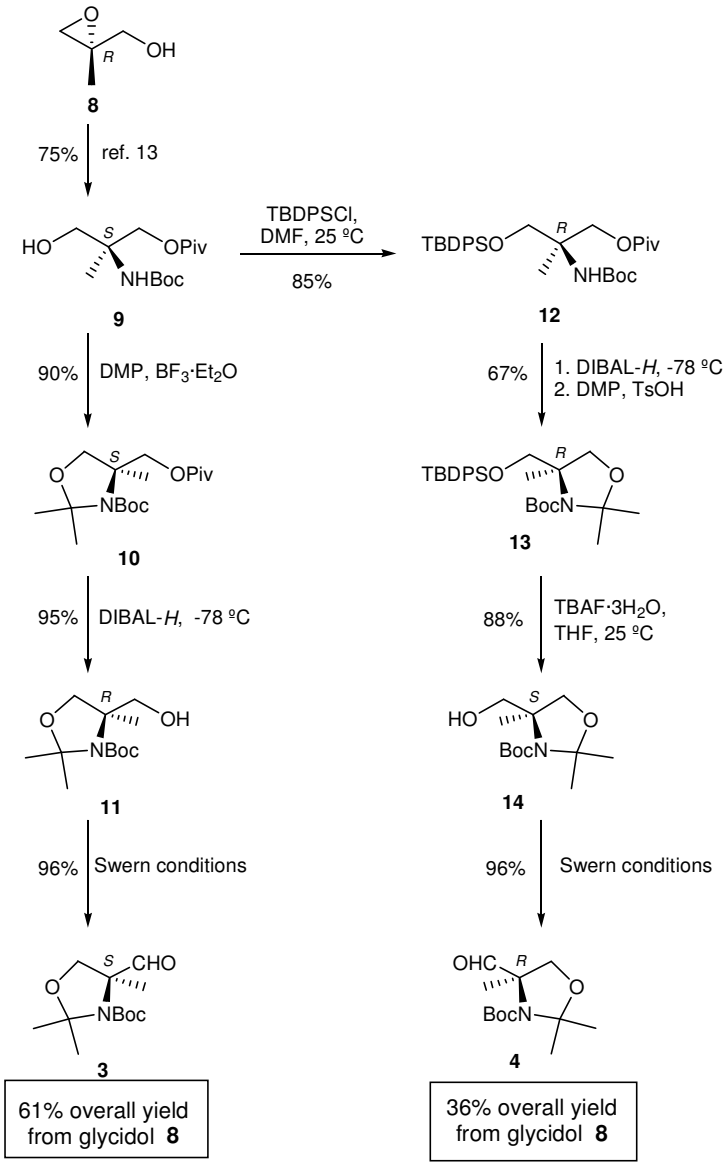
Figure 3

As shown in Scheme 2, (*R*)-2-methylglycidol **8** (94% ee) was transformed according to the procedure described by Hatekeyama,[13] which involves as a key step the regioselective Et_2AlCl-catalysed intramolecular cyclization of the trichloroacetimidate derivative of glycidol **8**. Subsequent acylation with PivCl followed by hydrolysis of the oxazoline ring and *N*-Boc protection gave alcohol **9** with an overall yield of 75% from **8**. A stereodivergent route with selective protection and deprotection reactions of compound **9** afforded the two serinal acetonides **3** and **4**.

In the first strategy (Scheme 2),[12] alcohol **9** was converted into oxazolidine **10** using DMP with boron trifluoride etherate as catalyst. Cleavage of the pivaloate ester was achieved by reduction with DIBAL-*H*. Alcohol **11** was therefore oxidised under Swern conditions to obtain the required (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3** (82% overall yield from alcohol **9** and 61% overall yield from commercially available glycidol **8**).

In the second route (Scheme 2),[12] the hydroxyl group of compound **9** was protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) to give orthogonally protected compound **12**. In this case, cleavage of the pivaloate ester (DIBAL-*H*) and acetonide formation using DMP with TsOH as catalyst afforded compound **13**. This compound was desilylated by treatment with tetrabutylammonium fluoride (TBAF $3H_2O$) to give alcohol **14**. Finally, oxidation of alcohol **14** under Swern conditions was completed to give the required (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **4** in high yield (48% overall yield from alcohol **9** and 36% overall yield from commercially available glycidol **8**).

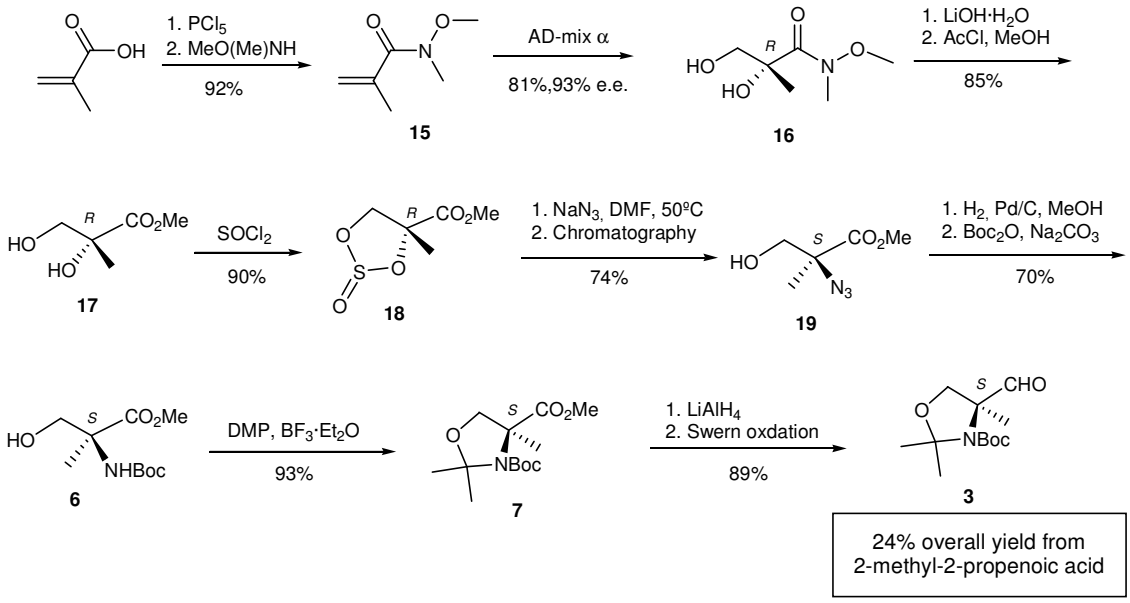
Unfortunately, glycidol **8** is no longer commercially available and, because of this, we had to develop an alternative synthetic route[14] to obtain serinal derivatives **3** and **4** on a multigram scale. In order to achieve this goal, we envisaged Sharpless asymmetric aminohydroxylation (AA) of 2-methyl-2-propenoic acid derivatives to be the quickest method to obtain the convenient precursors for serinal acetonides **3** and **4**, but all attempts gave the opposite regioisomer.[15] Nevertheless, the correct regioisomer was synthesised by a sequence reaction that involves two key steps: Sharpless asymmetric dihydroxylation (AD)[16] and regioselective nucleophilic substitution of a cyclic sulfite derivative.[17]



Scheme 2

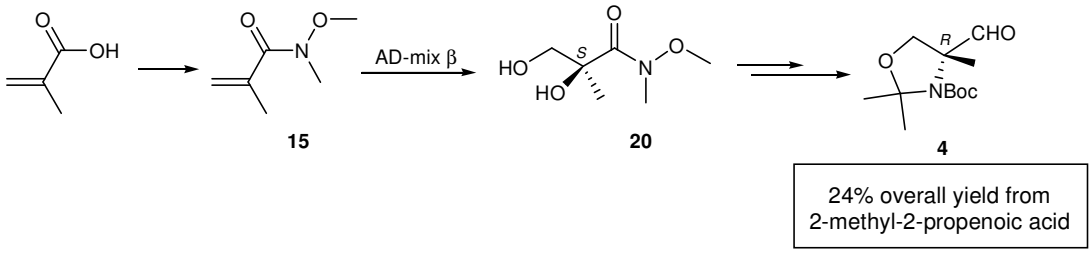
Thus, commercially available 2-methyl-2-propenoic acid was transformed into the corresponding Weinreb amide **15**. The AD reaction of **15** in the presence of AD-mix α [$(DHQ)_2PHAL$] proceeded efficiently to yield the diol **16** with excellent enantiomeric excess.[14] The amide group of the diol was converted into the corresponding methyl ester to give diol **17** in two steps: basic hydrolysis and esterification with AcCl in MeOH. This diol was transformed into its 2,3-cyclic sulfite **18** by treatment with thionyl chloride (Scheme 3).

The second key step is the reaction of sulfite **18** with NaN_3 in the presence of DMF as a solvent. Nucleophilic substitution occurred with high yield and a regioselectivity of 4:1 in favour of the α-azido ester **19**. Once separated, α-azido ester **19** was readily hydrogenated in MeOH in the presence of palladium to give the corresponding α-amino ester, which was subsequently treated with Boc_2O in a basic medium to give compound **6**. This compound was converted into the required building block by the same reaction sequence described above: formation of the oxazolidine ring and reduction-oxidation sequence. (*S*)-α-Methylserinal **3** was obtained on a multigram scale from commercially available 2-methyl-2-propenoic acid with an overall yield of 24%.[14]



Scheme 3

The other enantiomer, (*R*)-α-methylserinal **4**, was also obtained from the Weinreb amide of 2-methyl-2-propenoic acid using the same strategy, but changing the chiral catalytic ligand to AD-mix β in the AD reaction to give compound **20** (Scheme 4).[14]



Scheme 4

3. Synthetic applications

3.1. α-Methyl-α-amino acids

The conformational flexibility of peptides is one of the limitations of their use as drug leads. In recent years, several conformationally restricted analogues of bioactive peptides (pseudopeptides and/or peptidomimetics) have therefore been developed in order to establish a three-dimensional structure-

bioactivity relationship and to design new pharmacological agents with more selective properties than the original peptides.[18] α-Alkyl-α-amino acids have been shown to impart well-defined conformational constraints to a peptide backbone and thereby change their biological activity and stability.[19] For this reason, α-alkyl-α-amino acids have attracted a great deal of research interest and a number of interesting approaches have been developed.[9c, 20]

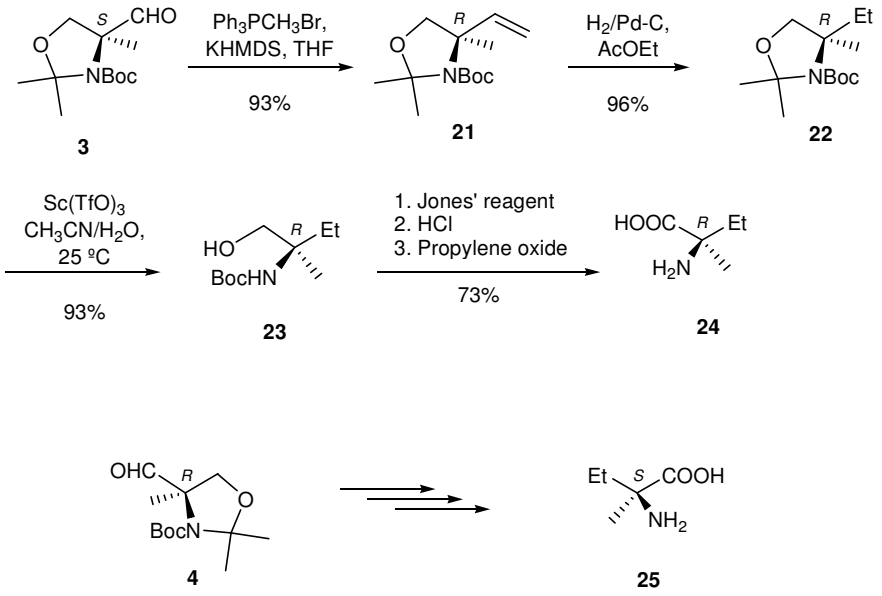
In this sense, (*S*)- and (*R*)-*N*-Boc-α-methylserinal acetonides **3** and **4** have recently been reported[12,21] as excellent chiral building blocks in the preparation of enantiomerically pure α-substituted alanines by transformation of the aldehyde group. In this methodology, the serinal derivatives **3** and **4** contribute the stereogenic centres and the amino acid moiety is protected as an oxazolidine ring. Transformation reactions on the aldehyde group afforded the different alanine derivatives.

Moreover, the oxazolidine ring can be used as a chiral inductor in diastereoselective reactions with the generation of new stereogenic centres (Figure 2). The diastereomeric excess obtained in the asymmetric Grignard addition reaction to aldehydes **3** and **4** proved that these compounds are better chiral inductors than Garner's aldehyde and its enantiomer. As an example, the four enantiomerically pure α-methyl-β-phenylserines have been synthesised using this methodology.

3.1.1. Enantiomerically pure α-substituted alanines

3.1.1.1. (*R*)- and (*S*)-Isovaline

(*R*)- and (*S*)-2-Amino-2-methylbutanoic acids (**24** and **25**) (Iva) are important chiral α-alkyl-α-amino acids that play a special role in the design of peptides with antimicrobial activity (peptaibols) by stabilisation of specific conformations.[22] Both enantiomers of isovaline (Iva) **24** and **25** have been obtained starting from (*S*)- and (*R*)-α-methylserinals **3** and **4** with an overall yield of 61%.[12]



Scheme 5

The initial step involved Wittig methylenation of (*S*)-methylserinal **3**, a reaction that was carried out under salt-free Wittig conditions using methyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDS) as base. Olefin **21** was then hydrogenated using Pd-C to give

oxazolidine **22**. Cleavage of the acetonide moiety of **22** was achieved using $Sc(OTf)_3$ (10 mol%) to yield alcohol **23**, which was oxidised by treatment with Jones' reagent to give the corresponding protected amino acid. Acid hydrolysis and liberation of the amino acid from its hydrochloride salt with propylene oxide gave (*R*)-isovaline **24** in high yield (Scheme 5).

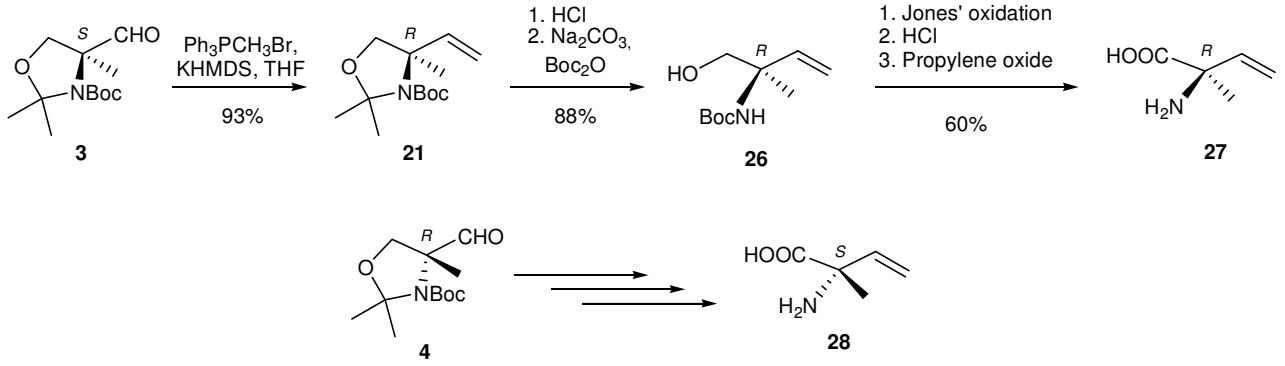
(*S*)-Iva **25** was obtained using the same strategy but starting from (*R*)-α-methylserinal **4** (Scheme 5).[12]

3.1.1.2. Unsaturated α-substituted alanines: vinylalanines and ethynylalanines

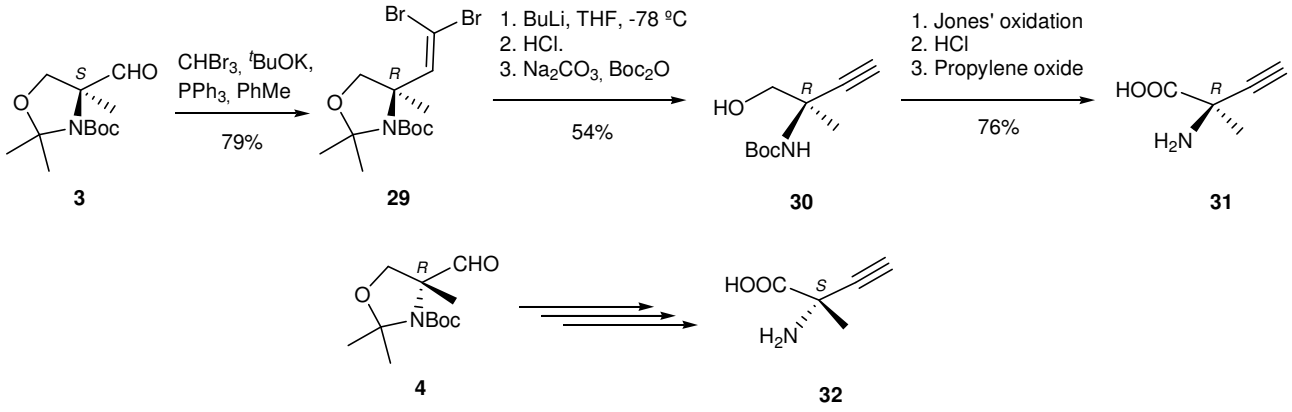
β,γ-Unsaturated amino acid derivatives have received special attention since they are important enzyme inhibitors.[23,24] Serinal derivatives **3** and **4** have been used as chiral starting materials in a straightforward route for the synthesis of β,γ-unsaturated α-methyl-α-amino acids: enantiomerically pure vinylalanines and ethynylalanines.[21]

Starting from olefin **21**, the *N*,*O*-deprotection was carried out by acid hydrolysis (HCl). The corresponding amino alcohol hydrochloride was then protected with Boc_2O to give **26**. The transformation of this compound into the quaternary amino acid (*R*)-α-vinylalanine **27** was achieved according to the protocol described above (Jones' oxidation, acid hydrolysis and liberation of the hydrochloride salt) (Scheme 6).[21]

The (*S*)-vinylalanine **28** was obtained using the same strategy but starting from (*R*)-α-methylserinal **4**. Both enantiomers of α-vinylalanine were obtained with an excellent overall yield (49%)[21] starting from *N*,*O*-protected α-methylserinals **3** and **4** (Scheme 6).



Scheme 6



Scheme 7

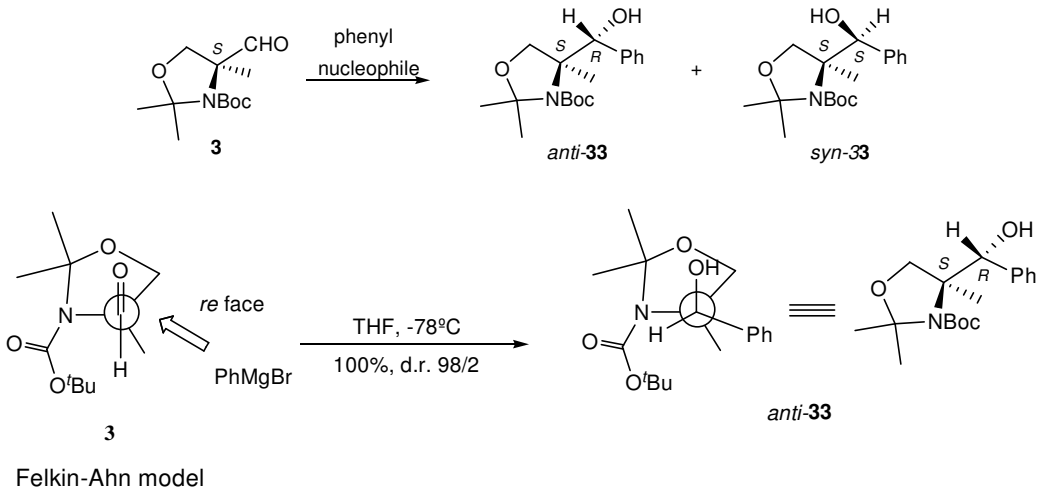
Finally, (*R*)- and (*S*)-ethynylalanines **31** and **32** were also obtained from *N*,*O*-protected α-methylserinals **3** and **4** with an overall yield of 32% (Scheme 7).[21]

The aldehyde-to-acetylene conversion was undertaken in two steps using a dibromovinyl intermediate (the Corey–Fuchs strategy). The chiral building block **3** was converted into the corresponding alkyne **30** using the vinyl intermediate **29**. The conversion of alkyne derivative **30** into (*R*)-ethynylalanine **31** was achieved in the same way as described above for the preparation of amino acid **24** from alcohol **23** (Scheme 7). The enantiomer of **31**, (*S*)-ethynylalanine **32**, was obtained by the same strategy but employing α-methylserinal **4** as the chiral starting material (Scheme 7).

3.1.2. α-Methyl α-amino acids with two stereogenic centres

In this methodology the oxazolidine ring can be exploited as the precursor of the amino acid moiety and, at the same time, as an inductor auxiliary to create a new stereogenic centre. The first diastereoselective reaction to be explored was the addition of phenyl nucleophiles to aldehydes **3** and **4**,[25] which behaved as excellent chiral building blocks in asymmetric synthesis.

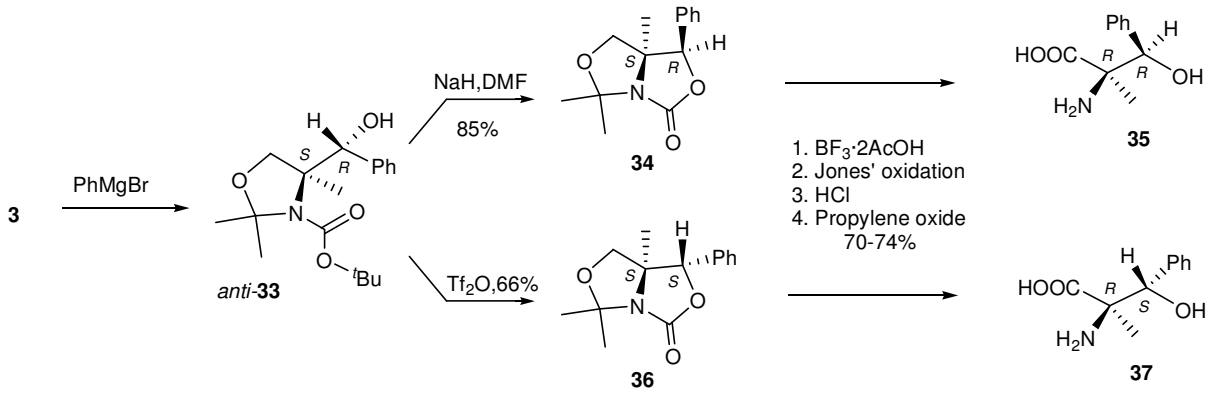
The addition of phenylmagnesium bromide and phenyllithium to aldehyde **3** was carried out under several sets of conditions.[25] In general, the results obtained indicate that the model proposed to explain the diastereoselectivity observed in the nucleophilic additions is similar to that described for Garner aldehyde **1**.[3a,4,6b] The sole difference observed is a significant increase in the diastereoselectivity in favour of the *anti* diastereoisomer product when serinals **3** and **4** were used. Nucleophilic addition of phenylmagnesium bromide to aldehyde **3** occurs as a non-chelation-controlled Felkin–Ahn attack on the least hindered face to give the *anti*-**33** isomer as the major adduct. The diastereoselectivity is affected by temperature, solvent and additives.[6b,26] The best conditions involve THF as solvent, –78 ºC and without chelation control to obtain *anti*-**33** (d.r. 98/2) (Scheme 8).



Scheme 8

Starting from enantiomerically pure *anti*-**33**, (2*R*,3*R*)- and (2*R*,3*S*)-α-methyl-β-phenylserines **35** and **37** have been synthesised using two different characteristics of compound **33** in the intramolecular cyclization (Scheme 9).[25]

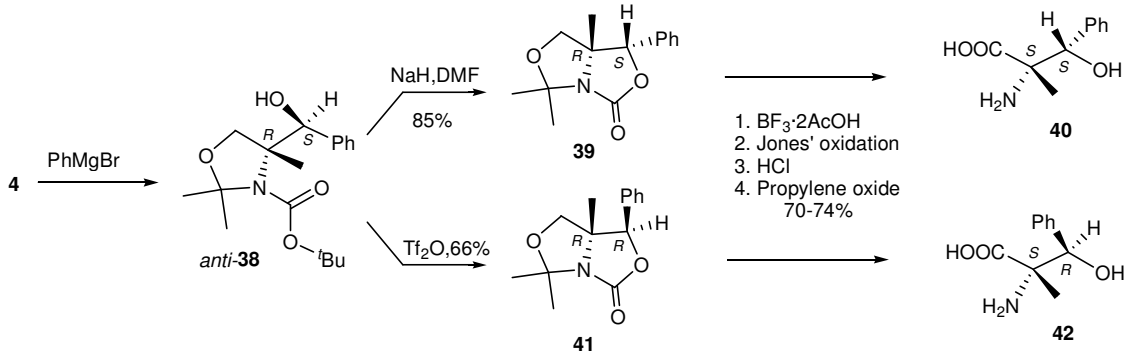
The first intramolecular cyclization was promoted by attack of the alkoxide ion on the carbonylic carbon of the Boc group to give the bicyclic compound **34**. Selective deprotection of the acetonide moiety of **34** by the action of $BF_3 \cdot 2AcOH$ gave the corresponding oxazolidinone, which was oxidised with Jones' reagent. Acid hydrolysis and liberation of the amino acid from its hydrochloride salt afforded the (2*R*,3*R*)-α-methyl-β-phenylserine **35** with an overall yield of 54% from *anti*-**33** (53% from α-methylserinal **3**).[25]



Scheme 9

The second intramolecular cyclization used triflic anhydride. The oxygen of carbonyl of Boc group, that is described as a good nucleophile in basic conditions,[6b,27] attack to activated benzylic carbon with inversion of configuration, to give the bicyclic compound **36** (Scheme 9). The strategy described above was then used and amino acid **37** was obtained from compound **36** with an overall yield of 43% from *anti*-**33** (42% from α-methylserinal **3**).[25]

The enantiomers (2*S*,3*S*)- and (2*S*,3*R*)-α-methyl-β-phenylserines **40** and **42** were also obtained using the strategy represented in Scheme 9, but starting from (*R*)-α-methylserinal **4** (Scheme 10).[25]



Scheme 10

3.2. Carbohydrates of glycopeptide antibiotics

During the last decade, the glycopeptide antibiotics have been intensively investigated[28] and two new antibiotics are in clinical use; vancomycin (Figure 4) and teicoplanin, which are considered to be the last line of defence for many bacterial infections.[29]

However, resistance to vancomycin is unfortunately now on the increase.[30] Although the structure-activity relationship (SAR) of the glycopeptide antibiotics has been extensively studied, the modifications

necessary to improve the resistance situation remain unclear. Because of this, many investigations aimed at enhancing the activity of the vancomycin group of glycopeptide antibiotics are in progress.[31]

In this sense, different vancomycin derivatives are currently under investigation; for example A82846B (vancomycin plus one additional carbohydrate substituent: 4-*epi*-vancosamine) and LY333328 (a vancomycin derivative that features both the chlorobiphenyl side chain and the additional sugar substituent of A82846B) are highly efficient against vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) and are now undergoing clinical trials.[32] The structures of vancomycin and the aforementioned derivatives are shown in Figure 4.

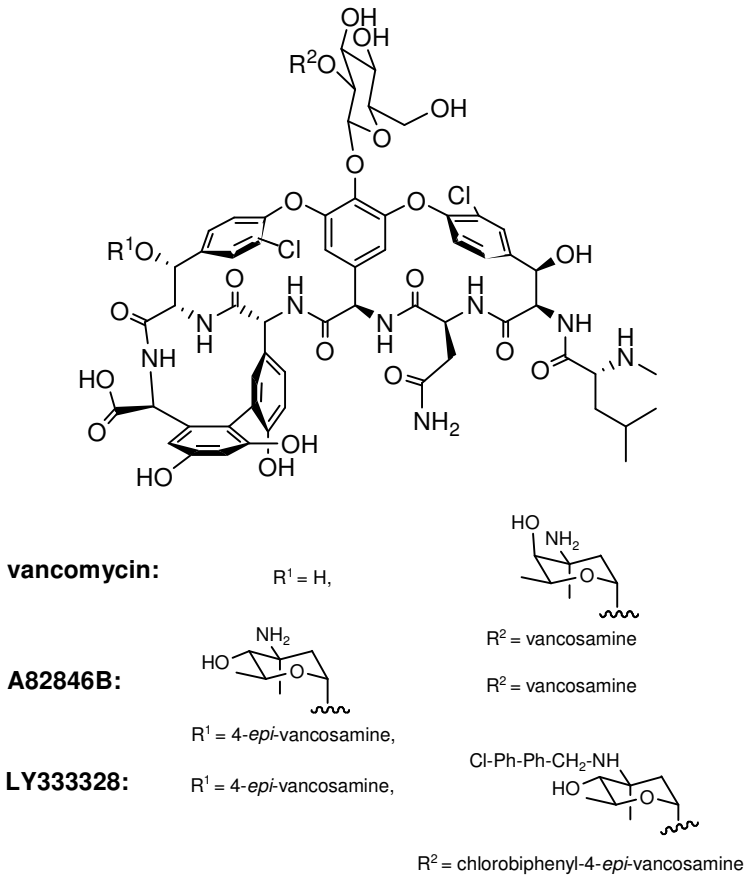
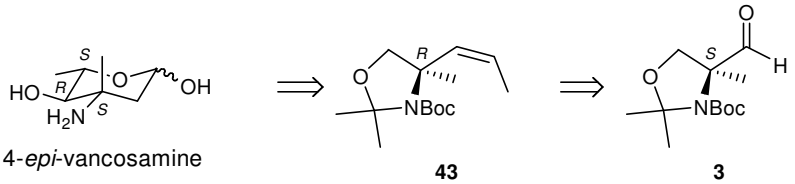


Figure 4

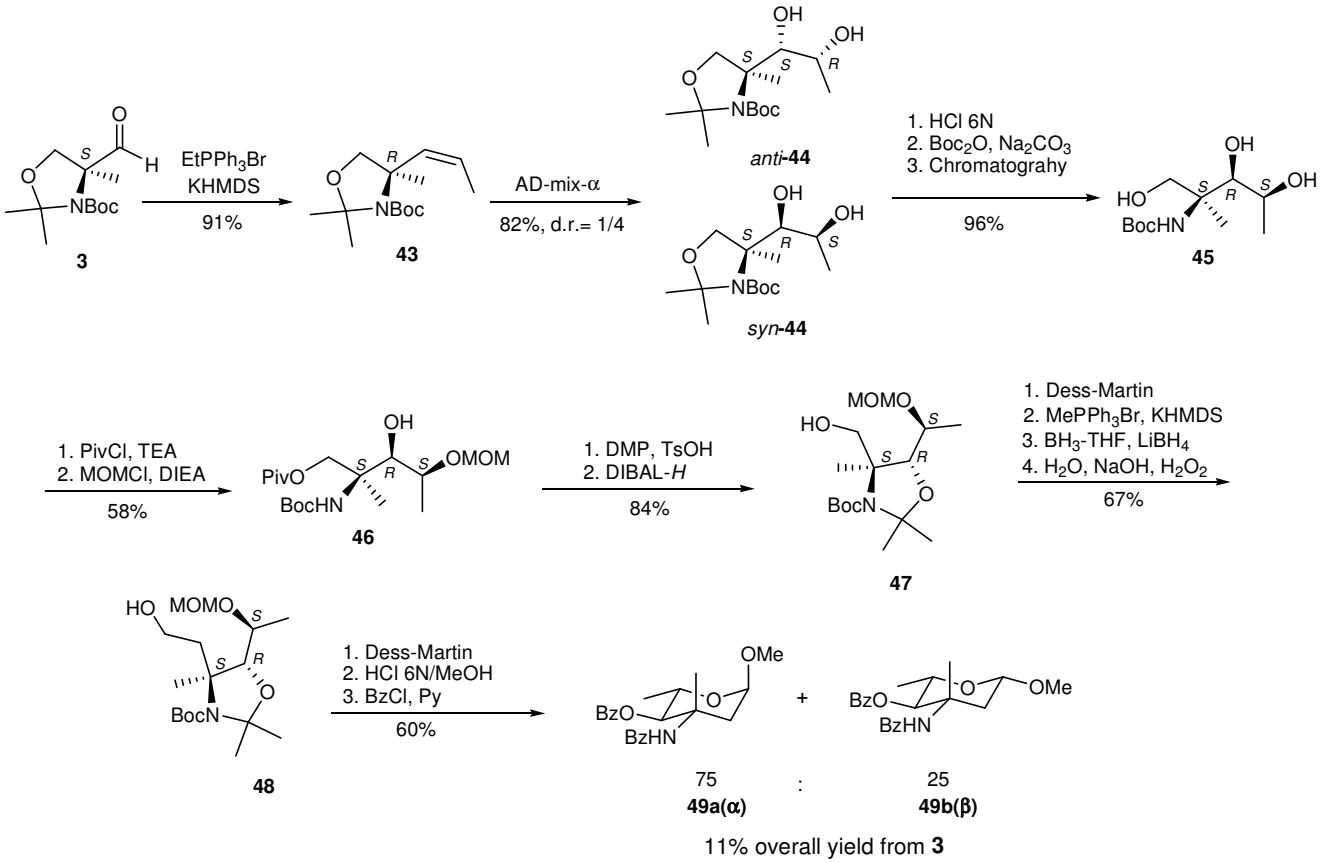
Taking into account the importance of glycopeptide antibiotics, and in order to construct combinatorial libraries of vancomycin analogs for biological screening, the synthesis of vancosamine donors has been the focus of many researchers. To this end, several stereoselective syntheses of protected vancosamines have been described.[33] Nevertheless, the synthesis of 4-*epi*-vancosamine derivatives has received little attention.[34]



Scheme 11

In this context, the asymmetric synthesis of a suitably protected 4-*epi*-vancosamine has been receiving our attention.[35] Our synthesis involves, as the key step, the asymmetric *cis*-dihydroxylation of the *Z*-olefin **43**, which is derived from the chiral building block (*S*)-*N*,*O*-protected-α-methylserinal **3** (Scheme 11).

The synthesis started with the Wittig olefination of *N*-protected α-amino aldehyde **3**, using ethyltriphenylphosphonium bromide and KHMDS as base, to give the expected *Z*-olefin **43** in high yield. The diol derivative was obtained by double asymmetric induction by Sharpless asymmetric dihydroxylation (AD) using AD-mix α as the catalyst. Good stereoselection was obtained in favour of the *syn* diol **44** (*anti/syn* = 20/80), which has the three stereocentres required for the final product – the protected 4-*epi*-vancosamine. The *anti*- and *syn*-diol mixture was transformed by acid hydrolysis and subsequent treatment with Boc_2O. Both compounds were easily separated by column chromatography to give enantiomerically pure **45**. The absolute configuration of their stereogenic centres was determined by X-ray analysis, showing that the stereochemistry of the major compound **44** is 1*S*,2*R*,3*S* (Scheme 12).[35]



Scheme 12

The three hydroxyl groups of the major compound **45** were orthogonally protected.[35] First, the primary alcohol was protected with a pivaloyl group and then one secondary alcohol with a MOM group; the structure was again established by X-ray analysis. Finally, the NH and OH groups of compound **46** were protected at the same time by addition of DMP and TsOH, generating the corresponding oxazolidine ring. The primary alcohol was then deprotected (DIBAL-*H*) to afford compound **47**. In order to synthesize the *arabino*-hexosa skeleton of 4-*epi*-vancosamine, it was necessary to increase the chain length by one additional carbon. This transformation was achieved by the following reaction sequence: oxidation of the alcohol to the aldehyde, Wittig methylenation of this aldehyde, regioselective hydroboration-oxidation of the

terminal olefin to give the primary alcohol **48** and oxidation of the primary alcohol to the aldehyde using Dess–Martin periodinone. Finally, the compound was suitably protected to obtain the enantiomerically pure *N*,*O*-dibenzoyl-4-*epi*-vancosamine as a mixture of two anomers **49a**(α) and **49b**(β) in a 75/25 ratio with an overall yield of 11% from α-methylserinal **3** (Scheme 12).[35]

4. Conclusions

In this report, we have described the synthesis of the enantiomers (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals **3** and **4**, respectively. In a very short time these compounds have proved to be extremely useful as chiral building blocks in organic chemistry. The simplicity and, at the same time, the key groups present in the structure of methylserinals (amino and hydroxyl groups – protected as the oxazolidine ring – and the aldehyde group) make these compounds valuable chiral starting materials in the synthesis of different quaternary methyl products. A simple transformation of the aldehyde group afforded α-methyl-α-amino acids in which one stereogenic carbon was provided by the oxazolidine ring. Moreover, this ring gives rise to excellent diastereoselectivity as a chiral inductor in asymmetric reactions. The use of this strategy has allowed the synthesis of several stereogenic multicentre compounds of biological interest (quaternary amino acids and carbohydrates of antibiotics).

Acknowledgements

We are indebted to the *Ministerio de Ciencia y Tecnología* (project PPQ2001-1305), to the *Gobierno de La Rioja* (project ANGI-2001/30, grant of D. Sucunza) and to the *Universidad de La Rioja* (project API-02/03) for their generous support.

References

1. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44.
2. (a) Lin, G.-Q.; Li, Y.-M.; Chan, A. S.-C.; *Principles and Applications of Asymmetric Synthesis*, Wiley-Interscience, 2001. (b) Procter, G.; *Asymmetric Synthesis*, Oxford University Press, 1997. (c) Stephenson, G. R.; Routledge, C., Eds.; *Advanced Asymmetric Synthesis*, Chapman & Hall, 1996. (d) Ager, D. J.; East, M. B.; *Asymmetric Synthetic Methodology*, CRC Press, 1996. (e) Gawley, R. E.; Aube, J.; *Principles of Asymmetric Synthesis*, Pergamon Press, 1996. (f) Koskinen, A. M. P.; *Asymmetric Synthesis of Natural Products*, Wiley&Sons, 1993.
3. (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121.
4. Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2136 and references cited therein.
5. (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18.
6. (a) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31. (b) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673. (c) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Synthesis* **1997**, 1146. (d) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.
7. Moriwake, T.; Hamano, S-I.; Saito, S.; Torri, S. *Chem. Lett.* **1987**, 2085.
8. (a) Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798. (b) Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527. (c) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051.
9. (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asimmetry* **1998**, *9*, 3517.
10. Alías, M.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapeña, Y. *Tetrahedron* **1998**, *54*, 14963.

11. Khalin, E. M.; Subasinghe, N. L.; Johnson, R. L. *Tetrahedron Lett.* **1996**, *37*, 3441.
12. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220.
13. Hatekeyama, S.; Matsumoto, H.; Fukuyama, H.; Makugi, Y.; Irie, H. *J. Org. Chem.* **1997**, *62*, 2275.
14. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949.
15. (a) Sharpless, K. B.; Bruncko, M.; Schlingloff, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483. (b) Sharpless, K. B.; Li, G.; Chang, H.-T. *Catalytic Asymmetric Aminohydroxylation of Olefins with Sulfonamides.* PCT Int. Appl. (1997), p 77.
16. For reviews on AD reactions, see: (a) Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059. (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; 2nd edition, Ojima, I., Ed.; VCH Publishers: New York, 2000.
17. (a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
18. (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *3*2, 1244. (b) Abell, A. *Advances in Amino Acid Mimetics and Peptidomimetics*, vol. I, Jai Press Inc: Greenwich, 1997.
19. Mossel, E.; Formaggio, F.; Toniolo, C.; Crisma, M.; Boesten, W. H. J.; Broxterman, Q. B.; Kamphuis, J.; Quaedflieg, P. J.; Temussi, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1305 and references cited therein.
20. (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.
21. Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653.
22. (a) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1445. (b) Jaun, B.; Tanaka, M.; Seiller, P.; Kühnle, F. N. M.; Braun, C.; Seebach, D. *Liebigs Ann. Chem.* **1997**, 1697. (c) Jung, G.; Brückner, H.; Schmitt, H.; *Structure and Activity of Natural Peptides.* Eds.: Voelter, W.; Weitzel de Gruyter, G. Berlin, 1981, p. 75.
23. (a) Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800 and references cited therein. (b) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966. (c) Aurell, M. J.; Gil, S.; Martínez, P. V.; Parra, M.; Tortajada, A.; Mestres, R. *Synth. Commun.* **1991**, *21*, 1833.
24. (a) Hegedus, L. S.; Colson, P. J. *J. Org. Chem.* **1993**, *58*, 5981. (b) Groth, U.; Schöllkopf, U.; Chiang, Y.-C. *Synthesis* **1982**, 864.
25. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195.
26. (a) Koskinen, A. M. P.; Hassila, H.; Myllymäki, V. T.; Rissanen, K. *Tetrahedron Lett.* **1995**, *36*, 5619. (b) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1679.
27. Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701.
28. (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1173. (b) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1576.
29. Nagarajan, R. *J. Antibiot.* **1993**, *46*, 1181.
30. (a) Walsh, C. T.; Fisher, S. L.; Park, I. S.; Prahalad, M.; Wu, Z. *Chem. Biol.* **1996**, *3*, 21. (b) Courvalin, P. *Antimicrob. Agents Chemother.* **1990**, *38*, 1675.
31. Ritter, T. K.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3508.
32. (a) Biavasco, F.; Vignaroli, C.; Lupidi, R.; Manso, E.; Facinelli, B.; Varaldo, P. E. *Antimicrob. Agents Chemother.* **1997**, *41*, 2165. (b) Rodriguez, M. J.; Snyder, N. J.; Zweifel, M. J.; Wilkie, S. C.; Stack, D. R.; Cooper, R. D. G.; Nicas, T. I.; Mullen, D. L.; Butler, T. F.; Thompson, R. C. *J. Antibiot.* **1998**, *51*, 560.
33. (a) Nicolaou, K. C.; Baran, P. S.; Zhong,Y.-L.; Vega, J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2525. (b) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749 and references cited therein.
34. Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35 and references cited therein.
35. Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry*, in press.

SYNTHESIS AND REACTIVITY OF 1-(2,4,6-TRIALKYLPHENYL)PHOSPHOLES WITH A FLATTENED P-PYRAMID

György Keglevich

Department of Organic Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary (e-mail: keglevich@oct.bme.hu)

Abstract. *Due to their flattened P-pyramid, the title phospholes are of aromatic character and hence they undergo aromatic electrophilic substitution, such as Friedel-Crafts acylations. The arylphospholes were functionalized via the site-selective reaction with phosphorustribromide to provide substituted phospholes that are appropriate ligands in rhodium complexes used in hydroformylations. Despite their aromaticity, the arylphospholes take part in Diels-Alder reaction with dienophiles to result in the formation of phosphanorbornene derivatives useful in fragmentation related phosphorylations. At 150 °C, the 1H-phospholes were converted to the 2H-derivatives by a sigmatropic rearrangement to give, after trapping, 1-phosphanorbornadienes. The complexation and the oxidation reactions of the arylphospholes also revealed special features due to the presence of the trialkylphenyl substituent.*

Contents

1. Introduction

1.1. General considerations

The phosphacyclopentadienes with phosphine function called 1H-phospholes form perhaps the most important part of contemporary P-heterocyclic chemistry. The field under discussion has undergone an

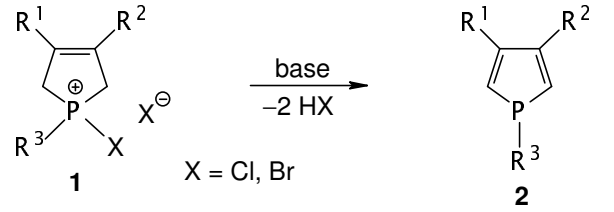
enormous development. This is well demonstrated by the fact that while in the first edition of Comprehensive Heterocyclic Chemistry (1984) only four pages were devoted to phospholes,[1] the second edition (1996) discusses the field in a lengthy chapter.[2] Moreover, exhaustive monographs have been published in P-heterocyclic chemistry incorporating also the new developments of phosphole chemistry.[3,4] The first review in the subject was written by *Mathey*.[5]

Beside the problem of aromaticity and syntheses there are a number of fascinating reactions, such as substitutions, (cyclo)additions, modification of the phosphorus atom, rearrangements, conversion to metallic derivatives and to coordination complexes etc. showing how rich the chemistry of phospholes is.

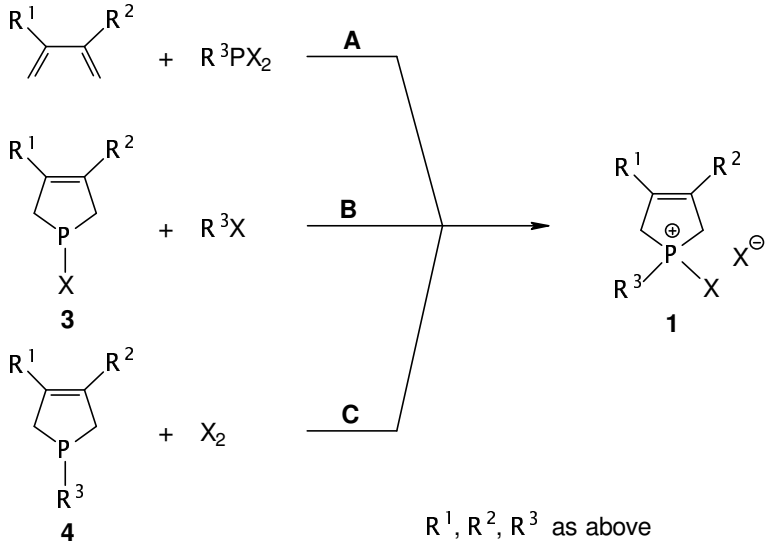
At the Department of Organic Chemical Technology, Budapest University of Technology and Economics, we have been dealing with the synthesis and utilization of P-heterocycles for more than 1.5 decades. In this paper the synthesis and properties of phospholes with sterically demanding substituent on the phosphorus atom are described.

1.2. Synthesis of phospholes

The most practical synthesis of phospholes (**2**) was suggested by *Mathey*. The method involves the double dehydrohalogenation of phospholium salts (**1**) by *e.g.* α-picoline (Scheme 1).[6,7]



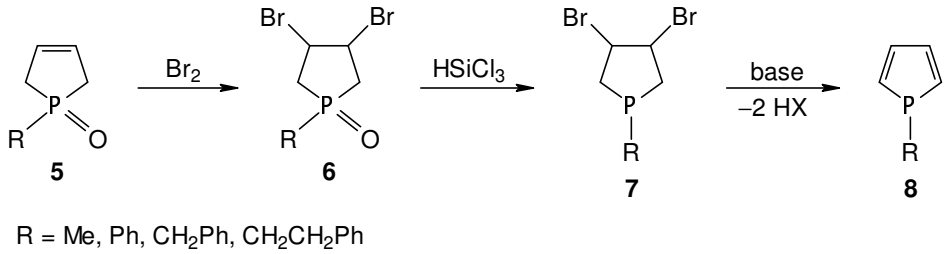
Scheme 1



Scheme 2

The phospholium salts (**1**) are available by the McCormack cycloaddition of butadiene derivatives with phosphonous dihalogenides (route A/Scheme 2),[8-10] by the quaternerisation of chlorophospholenes (**3**) with alkylhalogenides (route B/Scheme 2)[11] or by the reaction of alkylphospholenes (**4**) with bromine or chlorine (route C/Scheme 2).[11]

A "historical" method for the preparation of phospholes involves the bromination of phospholene oxides (**5**), the deoxygenation of the dibromophospholane oxides (**6**) so obtained and finally the dehydrobromination of dibromophospholanes **7** (Scheme 3).[12,13]

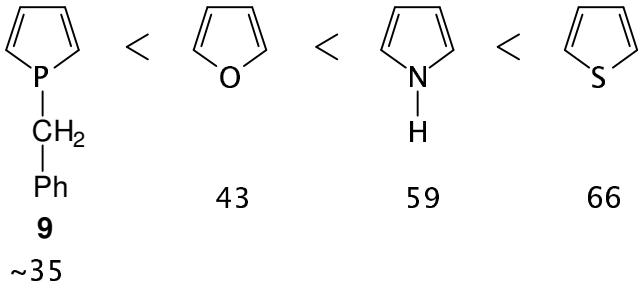


5 **6** **7** **8**

Scheme 3

1.3. Aromaticity of phospholes

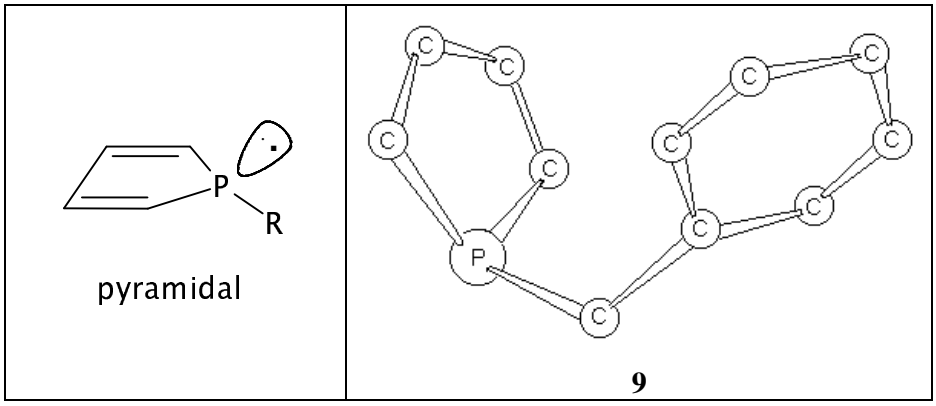
One may consider the phospholes to be close relatives of the family of pyrrole, furan and thiophene. A significant difference is, however, that the phospholes described in the literature are not aromatic at all, or they display only a slight extent of aromaticity.



9

~35

Figure 1. The aromaticity of five-membered heterocycles characterised by the Bird-Index



9

Figure 2. Stereostructure of the phospholes

This is well demonstrated by the comparison of the Bird-indexes[14] of benzylphosphole,[15] furan, pyrrole and thiophene (Figure 1). The Bird-index is an indicator of aromaticity based on the bond-equalizaton. It is the maximum (100) for benzene.

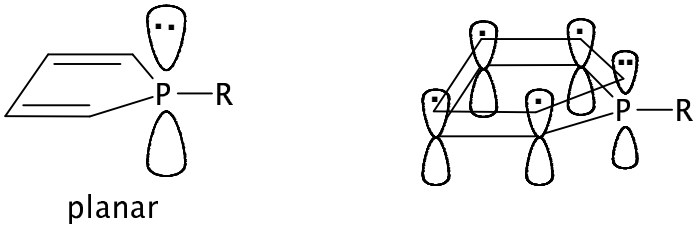
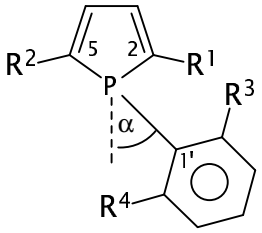


Figure 3. Stereostructure and electron-delocalisation in hypothetical phospholes

Table 1. The effect of *ortho* alkyl substituents on the flattening of the phosphorus atom in substituted arylphospholes (**10**)



10

R^1	R^2	R^3	R^4	α [deg]	
				MNDO	HF/6-31G*
H	H	H	H	62.0	68.3
H	H	Me	Me	55.5	59.5
H	H	i-Pr	i-Pr	52.6	
H	H	Me	t-Bu	53.7	
H	H	t-Bu	t-Bu	49.1	49.0
t-Bu	t-Bu	t-Bu	t-Bu	41.0	
$SiMe_3$	$SiMe_3$	t-Bu	t-Bu	40.8	

Beside the bigger atomic size of phosphorus atom, as compared to that of the nitrogen, the lack of aromaticity is due to the pyramidal geometry around the phosphorus atom: the criterion of coplanarity is not fulfilled and hence the lone electron pair of the phosphorus cannot overlap with the p_z orbitals of the sp^2 carbon atoms (Figure 2, the stereostructure of benzylphosphole **9** is also shown[15]). While in the case of

pyrrole, the aromatic stabilization covers the energy requirement of the planarization, with phospholes there is a bigger barrier for the inversion.

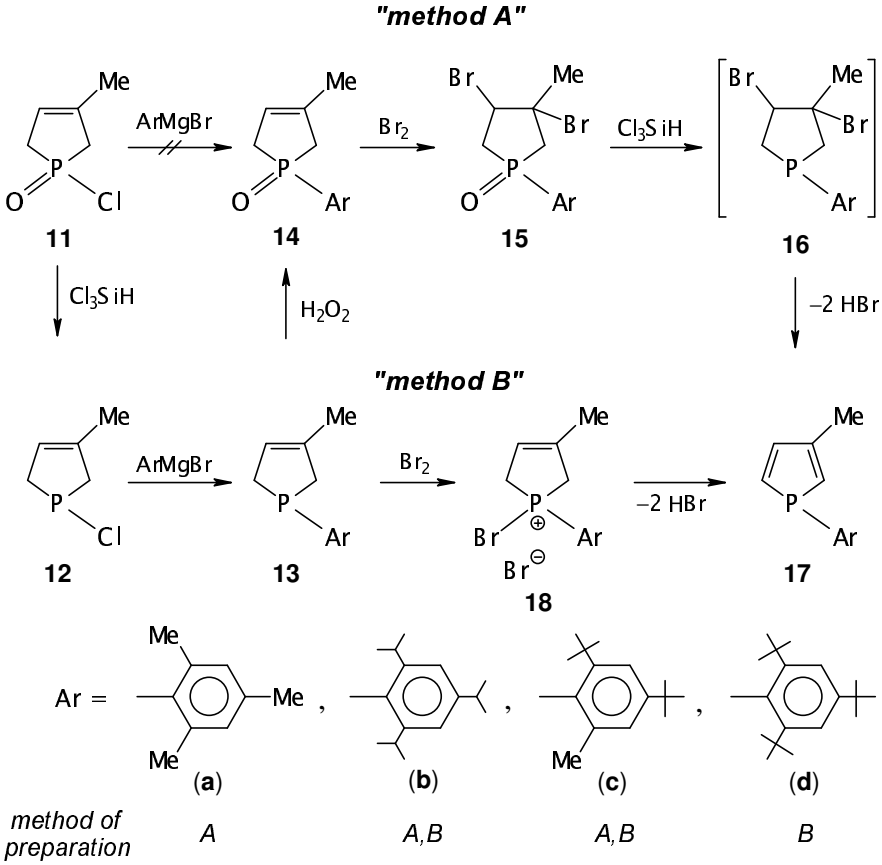
The electron-delocalisation in the hypothetical planar phospoles is shown in Figure 3.

An excellent review has been published recently on the aromaticity of phospholes and on the possibilities to create aromatic phospholes.[16]

We thought that the phosphole molecule (**10**) might perhaps be planarized by the introduction of a bulky P-substituent and hence the aromaticity may be increased. Semiempirical and, in some cases, *ab initio* calculations were carried out to evaluate the effect of the ortho alkyl substituent of the aryl ring on the geometry of the phosphole molecule. The calculations suggested that with the increase in the size of the alkyl groups, the extent of the planarization was also increased. The planarization was measured by the "Out of Plane" angle that means the angle connecting the P–$C_{1'}$ bond to the C_2–P–C_5 plane. Already two methyl groups have some planarizing effect, but the presence of two *tert*-butyl groups is much more efficient. The most promising molecules contained bigger substituents also in positions 2 and 5 of the hetero ring (Table 1).[17]

2. Synthesis of 1-(2,4,6-trialkylphenyl)phospholes

We have elaborated the synthesis of phospholes (**17**) with 2,4,6-trialkylphenyl substituent on the phosphorus atom. The chlorine atom of the chlorophospholene oxide (**11a-c**) could not be substituted due to the considerable steric hindrance.



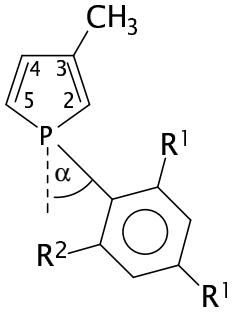
Scheme 4

After deoxygenation of the phosphinic chloride **11a-c**, the aryl group could, however, be easily introduced by the reaction of phosphinous chloride **12a-c** with arylmagnesium bromide. Following the oxidation of arylphospholene **13a-c**, bromine was added onto the double-bond of phospholene oxide **14a-c** and the oxygen atom was again removed. The elimination of two molecules of hydrogen bromide from intermediate **16a-c** took place spontaneously to afford the expected phospholes (**17a-c**), (*method A*, Scheme 4).[17-20] In the case of supermesityl substituent, the steric hindrance was so considerable that it prevented the deoxygenation of the dibromophospholane oxide (**15d**). We were lucky to experience that the phosphorus atom of the arylphospholene (**13d**) reacted with one equivalent of bromine in a selective manner leaving the double-bond completely intact. The phospholium salt (**18d**) so obtained could be easily dehydrohalogenated to give the corresponding phosphole (**17d**), (*method B*, Scheme 4).[21] *Method B* was also efficient in the preparation of arylphospholes **17b,c**.

3. Aromaticity of 1-(2,4,6-trialkylphenyl)phospholes

The new arylphospholes were examined by means of photoelectron spectroscopy and, in two cases, by X-ray crystallography. The ionization energy of 7.5 eV obtained for the supermesityl phosphole (**17d**) is the smallest value that have ever been recorded for phospholes.[22]

Table 2. Experimental evidences on the flattening of the phosphorus atom in arylphospholes



R^1	R^2		IE	α	bond distances					BI
			[eV]	[deg]	P–C_2	C_3–C_4 [Å]	C_5–P	C_2–C_3	C_4–C_5	
H	H	(**19**)	8.5	68	~1.783*	1.438*	1.783*	1.343*	1.343*	35.5*
Me	Me	(**17a**)	8.1	60						
i-Pr	i-Pr	(**17b**)	7.9	56	1.782	1.436	1.778	1.340	1.366	40.4
t-Bu	Me	(**17c**)	7.9	56						
t-Bu	t-Bu	(**17d**)	7.5	45	1.750	1.390	1.763	1.347	1.352	54.9
*for phosphole **9**[14,15]										

The OOP angles calculated from the ionization energies were in good agreement with the angles predicted by the semiempirical calculations.[17] With increasing planarization, the P–C and the C_3–C_4 bonds were significantly shortened, at the same time the double-bonds somewhat elongated. This equalization in the bond lengths refers to a considerable aromatic stabilization (Table 2).[18,21] The Bird-index of 55 obtained for the supermesitylphosphole (**17d**) sets a new record and suggests an aromaticity that is comparable with that of pyrrole and thiophene. Hence, the supermesitylphosphole (**17d**) indeed belongs to the family of heteroaromatic compounds with five-membered ring.

The X-ray structure of the triisopropylphenyl- and the tri-*tert*-butylphenylphospholes (**17b** and **17d**, respectively) are shown in Figure 4. In the latter case, the OOP angle is 11 degrees smaller, than in the other instance.

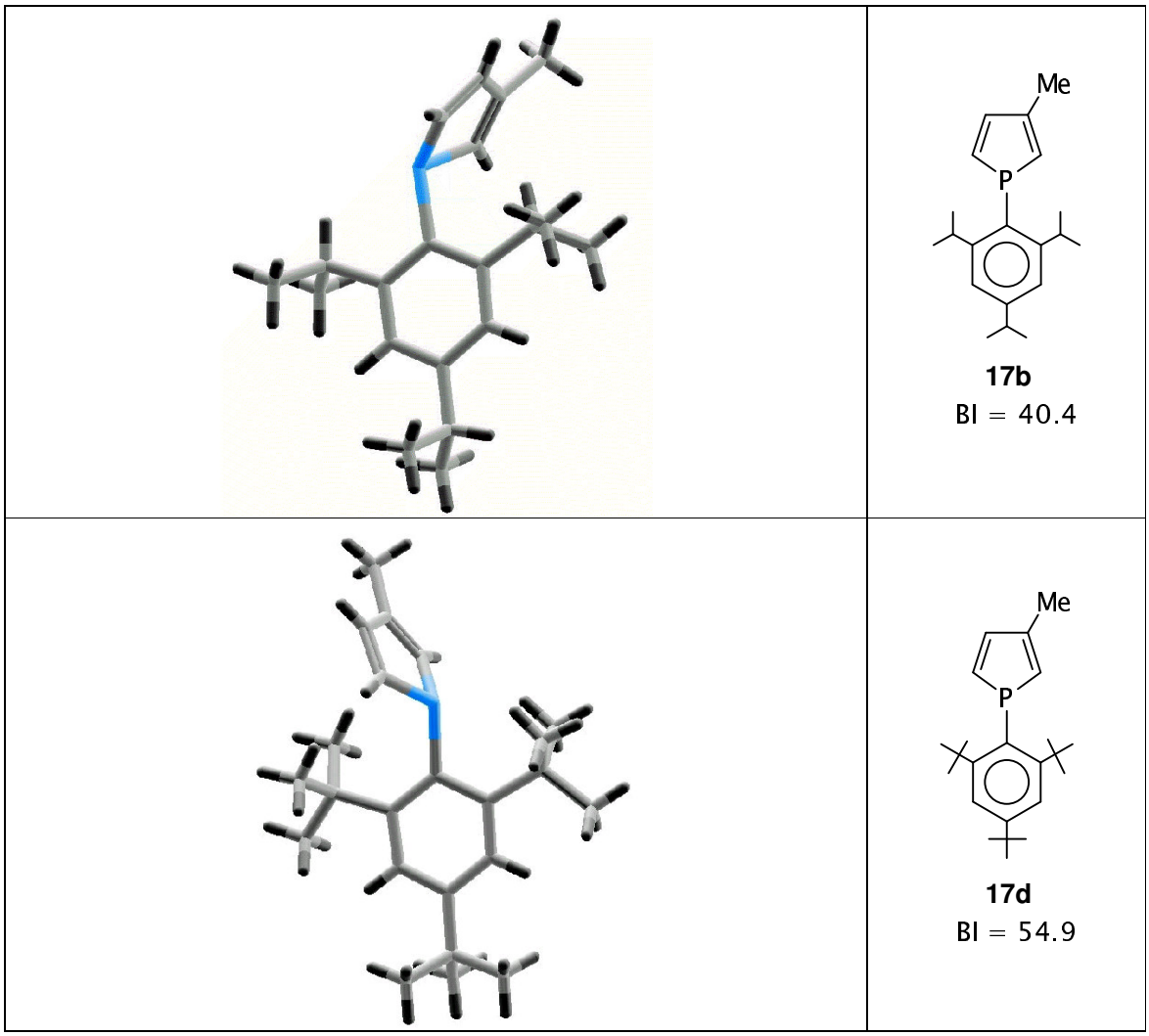


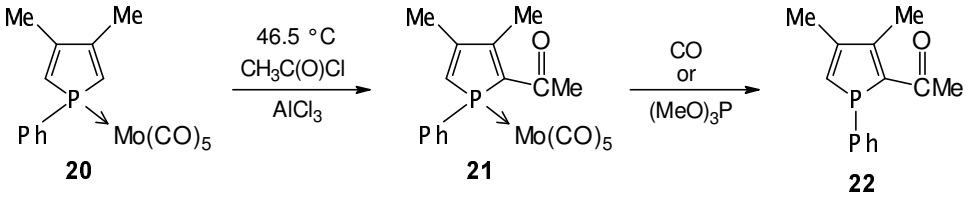
Figure 4. X-ray structure of selected trialkylphenylphospholes

4. Reactivity of 1-(2,4,6-trialkylphenyl)phospholes

4.1. Aromatic electrophilic substitutions

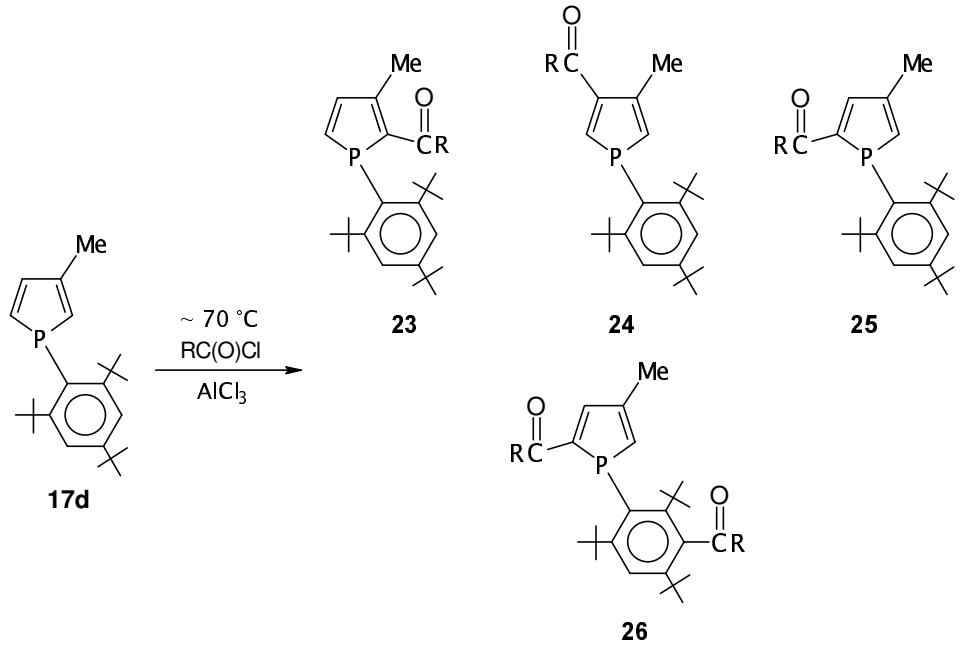
The 3,4-dimethyl-1-phenylphosphole entered into Friedel-Crafts reaction with acetyl chloride only through the molybdenum complex (**20**). Elimination of the metallic group from complex **21** furnished 2-

acylphosphole **22** (Scheme 5).[23] Aromatic electrophilic acylations were described only in the coordination sphere of the phospholide anion involving phosphacymantrenes[24,25] or phosphaferrocenes.[26]



Scheme 5

Aromaticity of the supermesitylphosphole (**17d**) was also manifested in chemical reactions: the phosphole under discussion underwent aromatic electrophilic substitution. In Friedel-Crafts reaction with acetyl chloride, the mixture of 2-, 4- and 5-acetyl phospholes (**23a**, **24a** and **25a**, respectively), as well as a diacetyl derivative (**26a**) was formed. Interestingly, the most crowded 2-acetyl derivative (**23a**) was the main component. A similar situation was observed for 3-methylpyrrol (Scheme 6).[21]



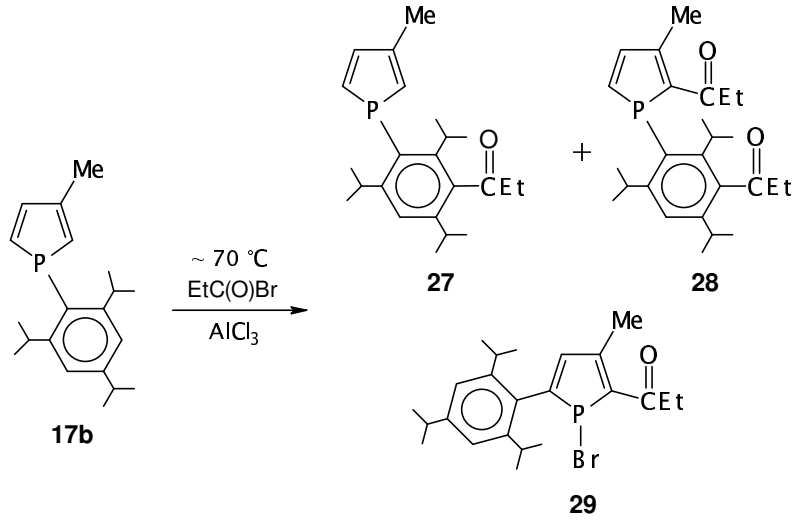
R		Product composition [%]				Yield [%]
		23	**24**	**25**	**26**	
Me	(**a**)	31	16	9	44	~21%
Et	(**b**)	~60	*	*	~40	~50%
n-Pr	(**c**)	~60	*	*	~40	~45%

*not relevant

Scheme 6

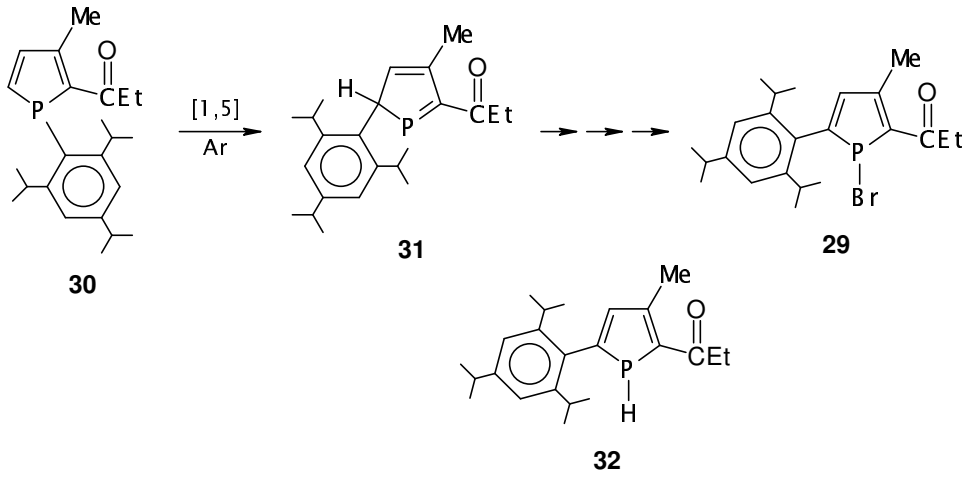
The use of other carboxylic acid chlorides, such as propionyl chloride and butyril chloride led to similar results: the corresponding monoacyl- and diacyl-phospholes (**23b,c** and **26b,c**, respectively) were found to form. In these cases, the 2-acylphosphole (**23b,c**) was practically the only monoacylderivative formed (Scheme 6).[27]

We wished to check the reactivity of triisopropylphenylphosphole (**17b**), exhibiting a somewhat smaller Bird-index, than the tri*tert*-butyl derivative (**17d**). We learned that the acylation of the hetero ring took place only to a small extent. Acylation of the trialkylphenyl ring was a concurrent reaction path, but the major product was 2-acyl-5-aryl-bromophosphole (**29**) shown in Scheme 7.[27]



Scheme 7

According to our explanation, a 2H-phosphole (**31**) formed by a sigmatropic rearrangement from the starting acylphosphole (**30**), might be the key-intermediate for the unexpected by-product. It is not clear, however, how the 2H-phosphole (**31**) is converted to the 1H-derivative (**29**). One possibility is that a prototropic rearrangement of the 2H-phosphole (**31**) to another 1H-derivative (**32**) is involved, driven by the energy gain of aromatization (Scheme 8).[27]



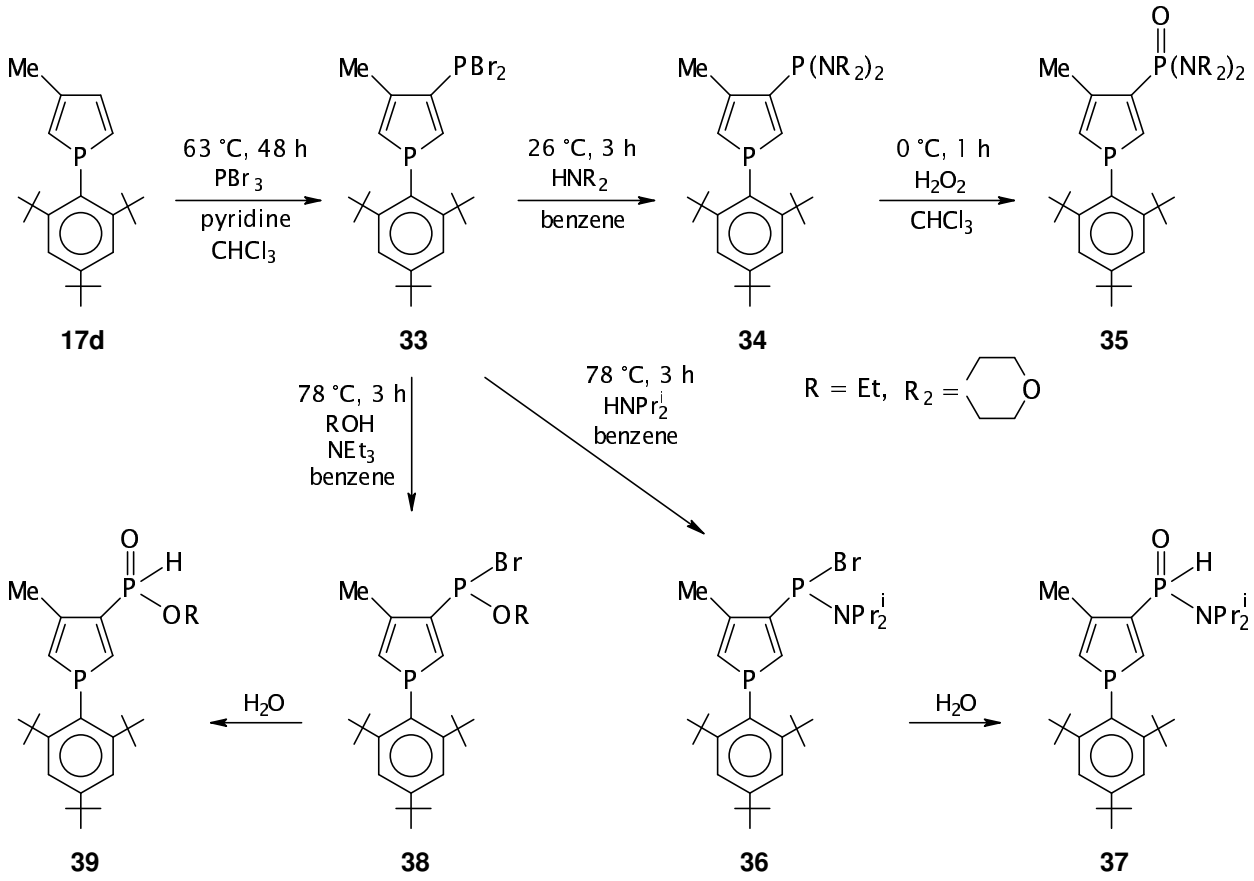
Scheme 8

4.2. Reactions with phosphorus tribromide

We observed that the supermesitylphosphole (**17d**) entered into reaction with phosphorus tribromide to afford the 3-dibromophosphoniophosphole (**33**), after reaction with secondary amines the phosphonous diamides (**34**), and finally after oxidation the phosphonic diamides (**35**) (Scheme 9).[28,29] It is noteworthy that the phosphorus atom of the phosphole ring resisted oxidation. Spectral parameters including stereospecific J_{PP} and J_{PC} couplings confirmed position 3 of the P-function introduced.

By reaction of intermediate **33** with diisopropylamine, only one of the bromine atoms could be replaced, to give a H-phosphinic amide (**37**) after hydrolysis (Scheme 9).[29]

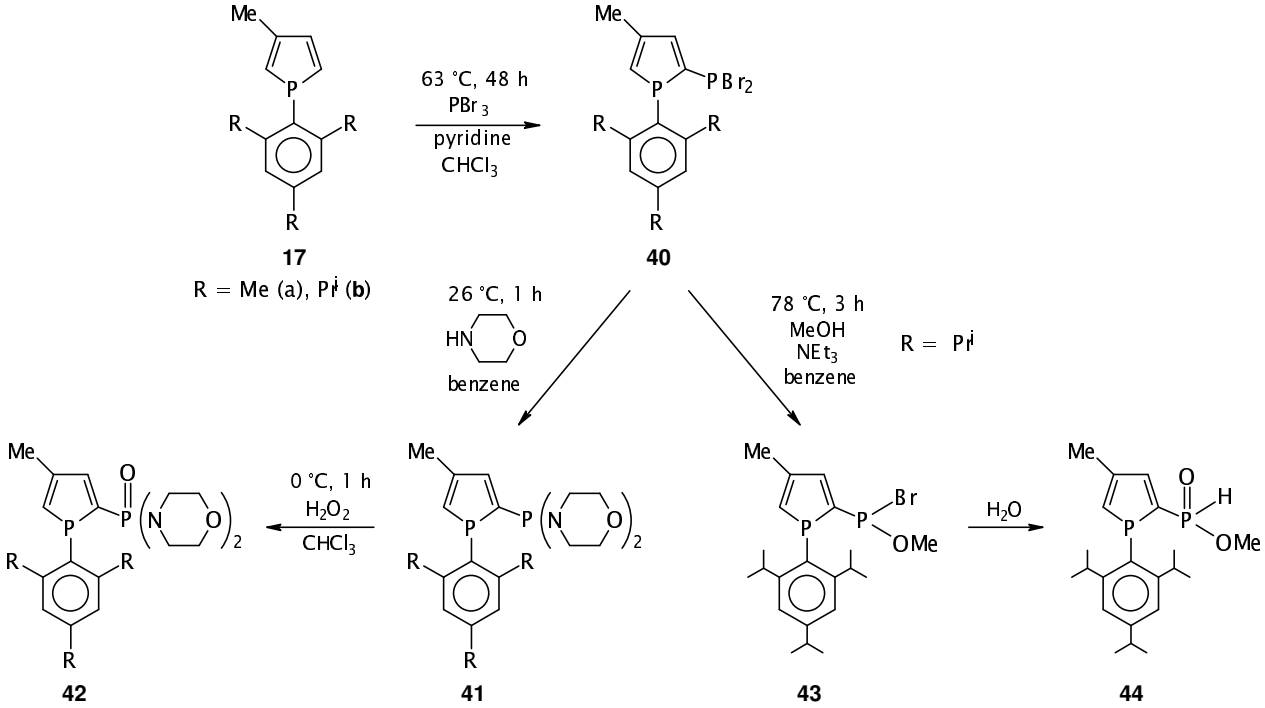
Also monosubstitution was the result of the reaction of the dibromophosphine (**33**) with alcohol to furnish a H-phosphinate (**39**) after hydrolysis (Scheme 9).[29]



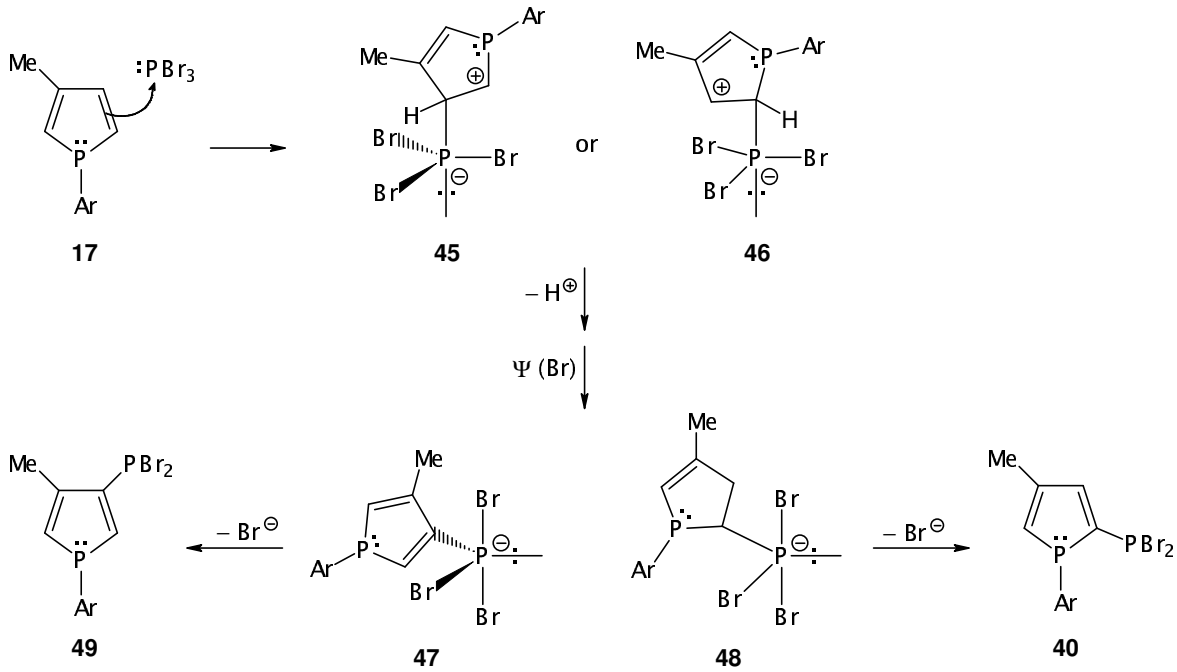
Scheme 9

A similar series of reactions of the triisopropylphenylphosphole or with the mesitylphosphole (**17b** and **17a**, respectively) with phosphorus tribromide led to the corresponding 2-substituted products. The reaction of dibromophosphine **40** with nucleophiles followed by oxidation or by hydrolysis gave phosphonic or H-phosphinic derivatives (**42** or **44**, respectively) (Scheme 10).[28,29] The regioselectivity is obviously the consequence of the presence or the lack of the steric hindrance; with ortho *tert*-butyl groups, only position 3 is available, while with the smaller triisopropyl substituent, position 2 is the appropriate reaction site.

The mechanism may involve a nucleophilic attack of the double-bond of the phosphole (**17**) on the phosphorus atom of phosphorustribromide to yield two kinds of intermediates (**45** or **46**) that are stabilized by the loss of proton, pseudorotation and finally by the departure of a bromide anion (Scheme 11).[28,29]



Scheme 10

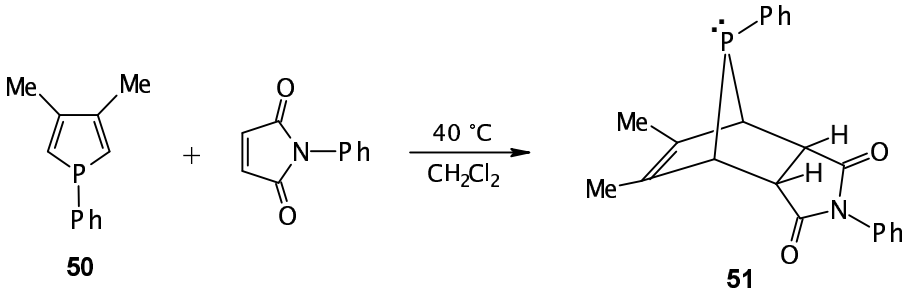


Scheme 11

According to our recent studies, phospholes without any aromaticity could also be involved in reaction with phosphorustribormide, although these reactions were not so efficient. This means that the above substitution protocol does not have too much to do with the heteroaromaticity.

4.3. Diels-Alder cycloadditions

The Diels-Alder reaction of phospholes was not studied in details previously. It is known, however, that the cycloaddition of the *Mathey* phosphole (**50**) with *N*-phenylmaleimide afforded phosphanorbornene **51** (Scheme 12).[30] Similar reactions with fumaronitrile or with another unit of phosphole led to products with the same configuration of the bridging P-moiety.[31,32]



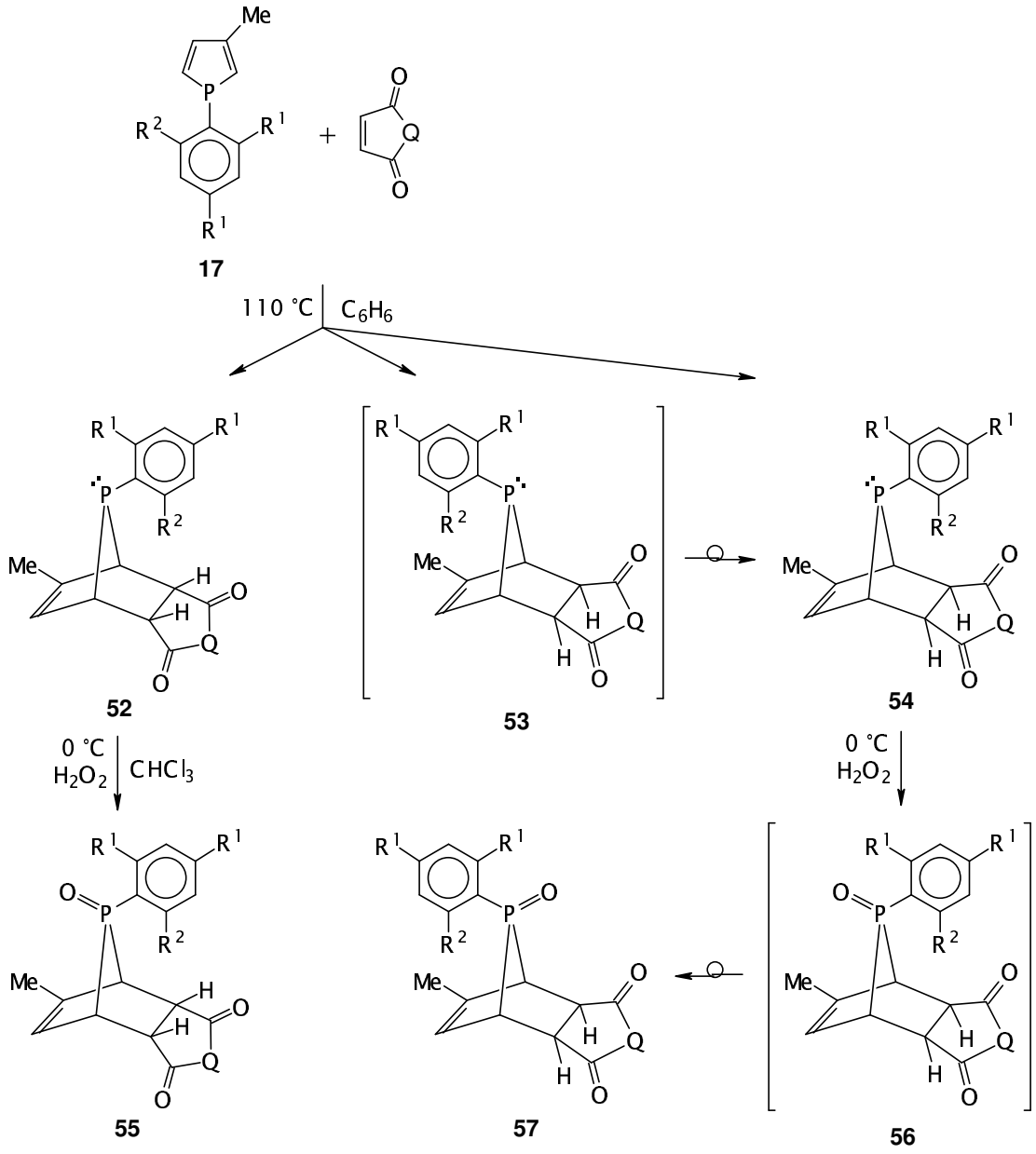
Scheme 12

Despite their heteroaromaticity, the aryl phospholes (**17**) could also be involved in Diels-Alder reaction. In cycloaddition with *N*-phenylmaleimide, mostly the endo ring-fused phosphanorbornene containing the aryl group *anti* to the double-bond (**52**) was formed. In certain cases, the other isomer with similar P-configuration, but with exo ring fusion (**54**) was also formed. Stereostructure of the phosphanorbornenes (**52** and **54**) was confirmed by stereospecific $^{2}J_{PC}$ couplings obtained from the ^{13}C NMR spectra. We think that initially, under kinetic control, the *syn* isomer (**53**) is formed that is inverted at phosphorus to give the thermodynamically more stable *anti* product (**54**) (Scheme 13).[33-35] It was experienced that the Diels-Alder cycloaddition became reluctant with the increase of the aromaticity and the steric hindrance. To obtain stable products, the phosphines (**52** and **54**) were oxidized to phosphine oxides (**55** and **56**, respectively). In this case, another inversion at the phosphorus atom of species **56** was observed to take place (Scheme 13).[33-35]

The analogue (**60**) of isomer (**57**) was prepared by a structure proving synthesis (Scheme 14). It was proved that the *syn* isomer (**61**) obtained after deoxygenation is transformed spontaneously to the *anti* form (**62**). The phosphine (**62**) was stabilized as the phosphone oxide (**63**) (Scheme 15).[35]

4.4. Sigmatropic rearrangements

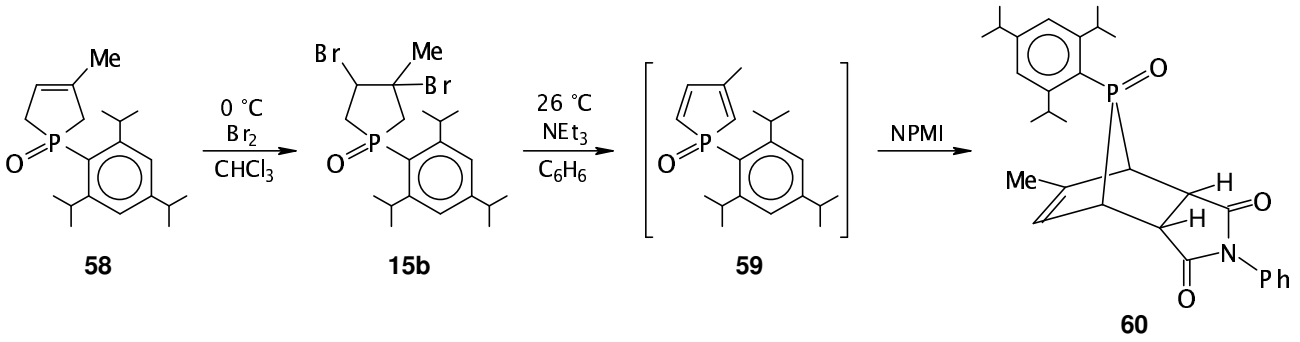
It was found that the P-phenyl substituent of phospholes underwent migration to carbon forming the corresponding 2H-phosphole intermediate.[36,37] The reaction is illustrated on the double rearrangement of biphosphole **64** to give intermediate **65** that was trapped by two equivalents of diphenylacetylene. The optically active form of product **66** is known as BIPNOR that is a useful bidental ligand (Scheme 16).[38]



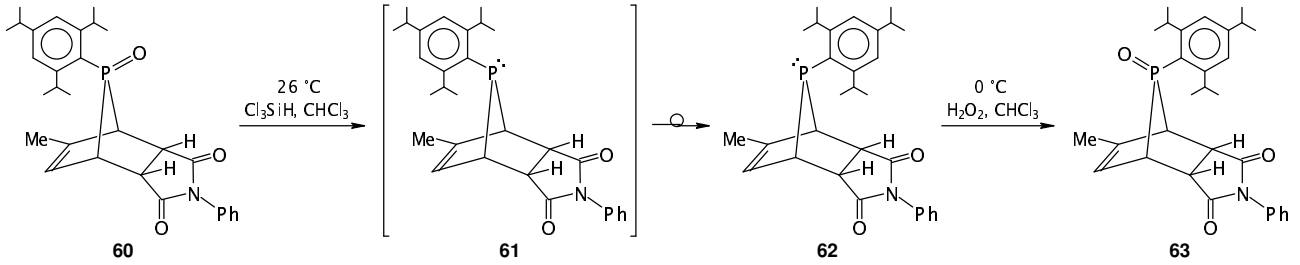
R^1	R^2	Q	**52**	**54**	**55**	**57**	Yield*
			[%]		[%]		[%]
			(before oxidation)		(after oxidation)		
Me	Me	N–Ph	100	–	100	–	52
i-Pr	i-Pr	N–Ph	90	10	88	12	68
t-Bu	Me	N–Ph	42	58	46	54	61
t-Bu	t-Bu	N–Ph	100	–	100	–	43
i-Pr	i-Pr	N–Me	100	–	100	–	53
i-Pr	i-Pr	O	100	–	100	–	33

*based on phosphine oxide(s)

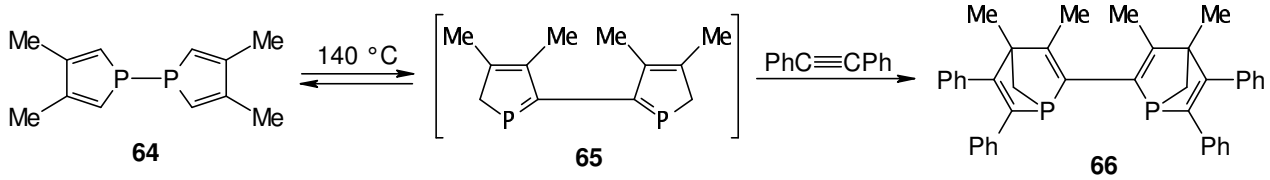
Scheme 13



Scheme 14

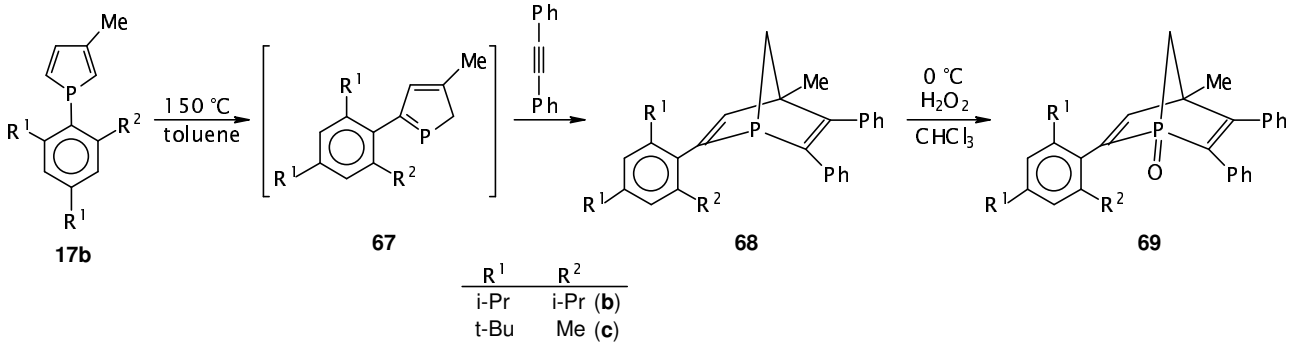


Scheme 15



Scheme 16

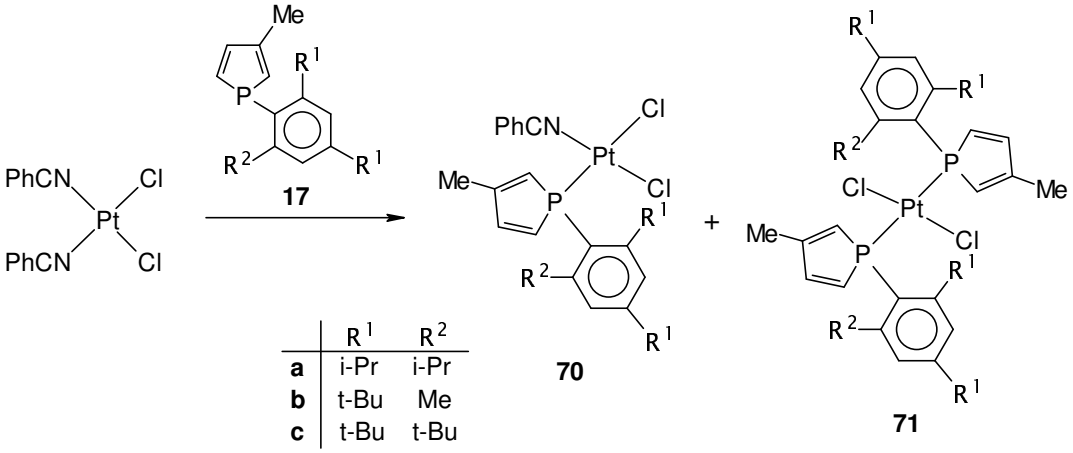
The trialkylphenylphospholes (**17b** and **17c**) were found to have been isomerised at 150 °C to the corresponding 2H-phospholes (**67b** and **67c**, respectively) by a sigmatropic rearrangement. The intermediates (**67b** and **67c**) were trapped by tolane to give the corresponding cycloadducts (**68b** and **68c**, respectively). The phosphines (**68b,c**) were oxidized to phosphine oxides (**69b,c**) (Scheme 17).[39]



Scheme 17

4.5. Complexation reactions

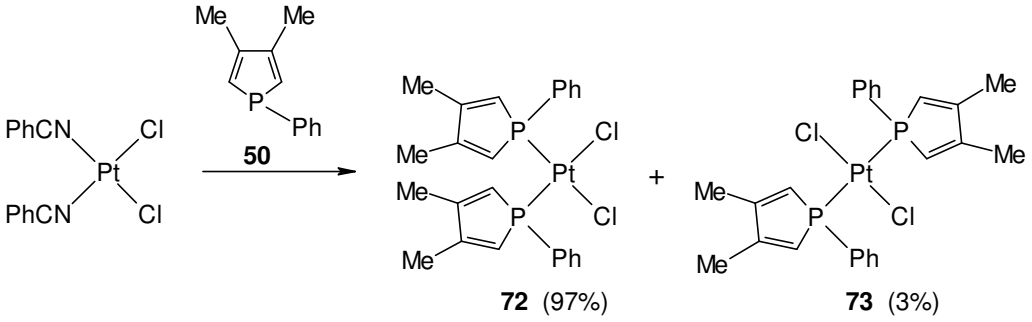
The phospholes are important ligands in transient metal complex catalysts. The complexing ability of trialkylphenylphospholes (**17**) differs significantly from that "of common or garden variety" phospholes. In reaction with dichlorodibenzonitril platinum, the complexes containing one or two phosphole ligands **70** and **71** were found to form as shown in Scheme 18.[40,41] Stereostructure of the complexes (**70** and **71**) was evaluated utilizing the stereospecific Pt–P NMR couplings.



	R^1	R^2
a	i-Pr	i-Pr
b	t-Bu	Me
c	t-Bu	t-Bu

Scheme 18

It can be seen that the outcome of the complex forming reaction of the *Mathey* phosphole (**50**) is quite different (Scheme 19).[42]

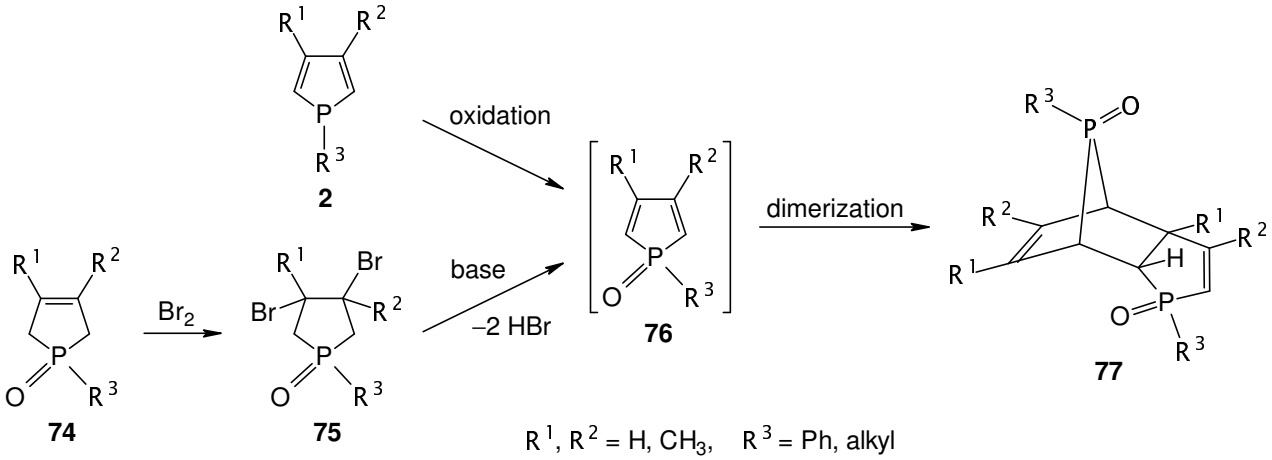


Scheme 19

With increasing steric hindrance, the rate of the reaction of the trialkylphenylphospholes (**17a-c**) with dichlorodibenzonitril platinum decreased, but due to the electron-releasing ability of the trialkylphenyl ring, the complexation took place in all cases on the P-center.

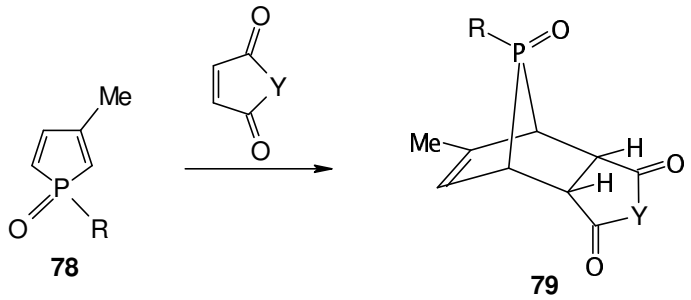
4.6. Oxidation reactions

It is known that the phosphole oxides (**76**), obtained either by the oxidation of phospholes (**2**) or by the dehydrobromination of dibromophospholane oxides (**75**) undergo dimerization to furnish cycloadducts **77** (Scheme 20)[4,43]

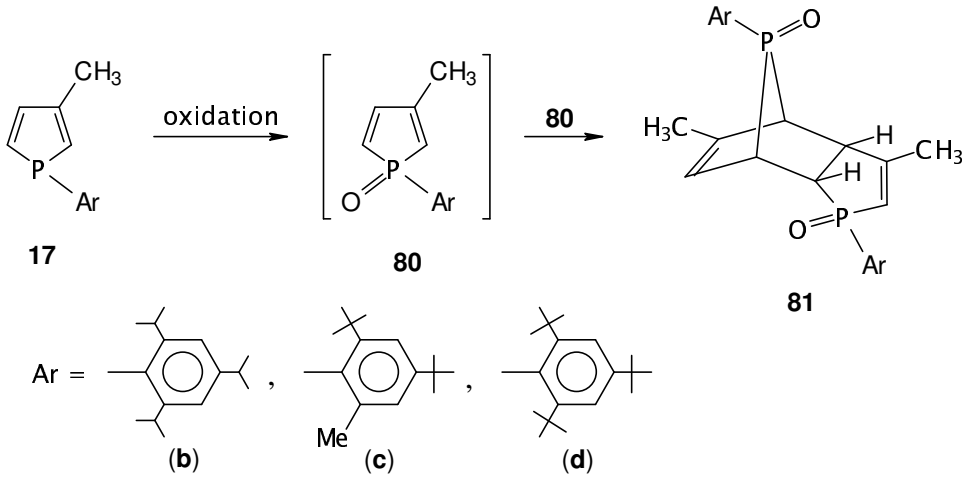


Scheme 20

Generating the phosphole oxides (**78**) in the presence of trapping agents, such as maleic acid derivatives, phosphanorbornenes of type **79** were obtained (Scheme 21).[4,43]



Scheme 21



Scheme 22

Oxidation of the arylphospholes (**17**) by peroxides led to phosphole oxides (**80**) that dimerized instantly to the corresponding phosphanorbornene derivatives (**81**) (Scheme 22).[18,20,44] As in earlier cases, the cyclodimerization took place in a regio- and stereospecific manner. The interesting observation was that, due to the bulky P-substituent, the oxidation got slower and the phosphole oxides (**80**) became relatively stable; hence, they could be characterized by NMR. The diagram included in Figure 5 shows the concentration of the P-species (**17**, **80** and **81**) involved in the oxidation – cyclodimerization consecutive series of reactions.[44] X-Ray structure of the dimer with supermesityl substituent on the phosphorus atoms (**81d**) indicated a considerable steric compression around the heteroatoms (Figure 6).[44]

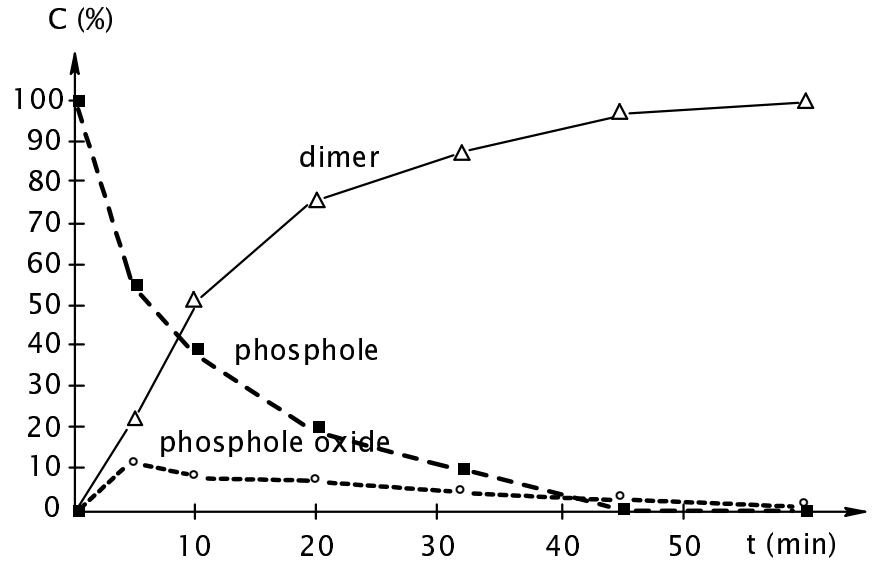
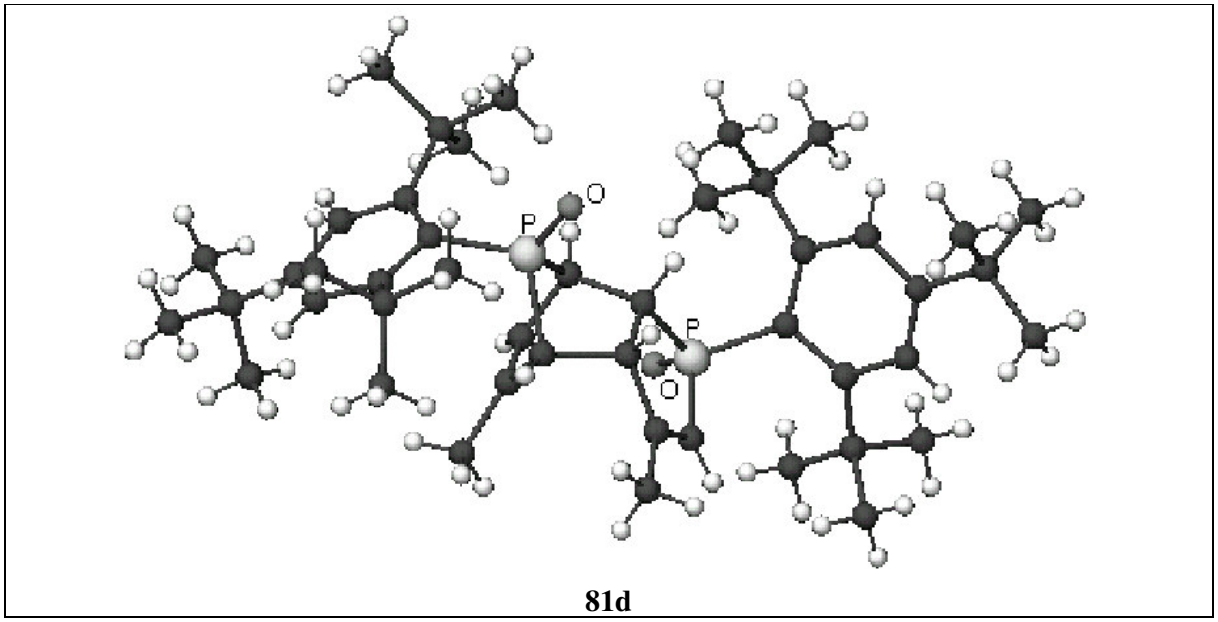


Figure 5. Regio- and stereospecific dimerization of phosphole oxide **80d**

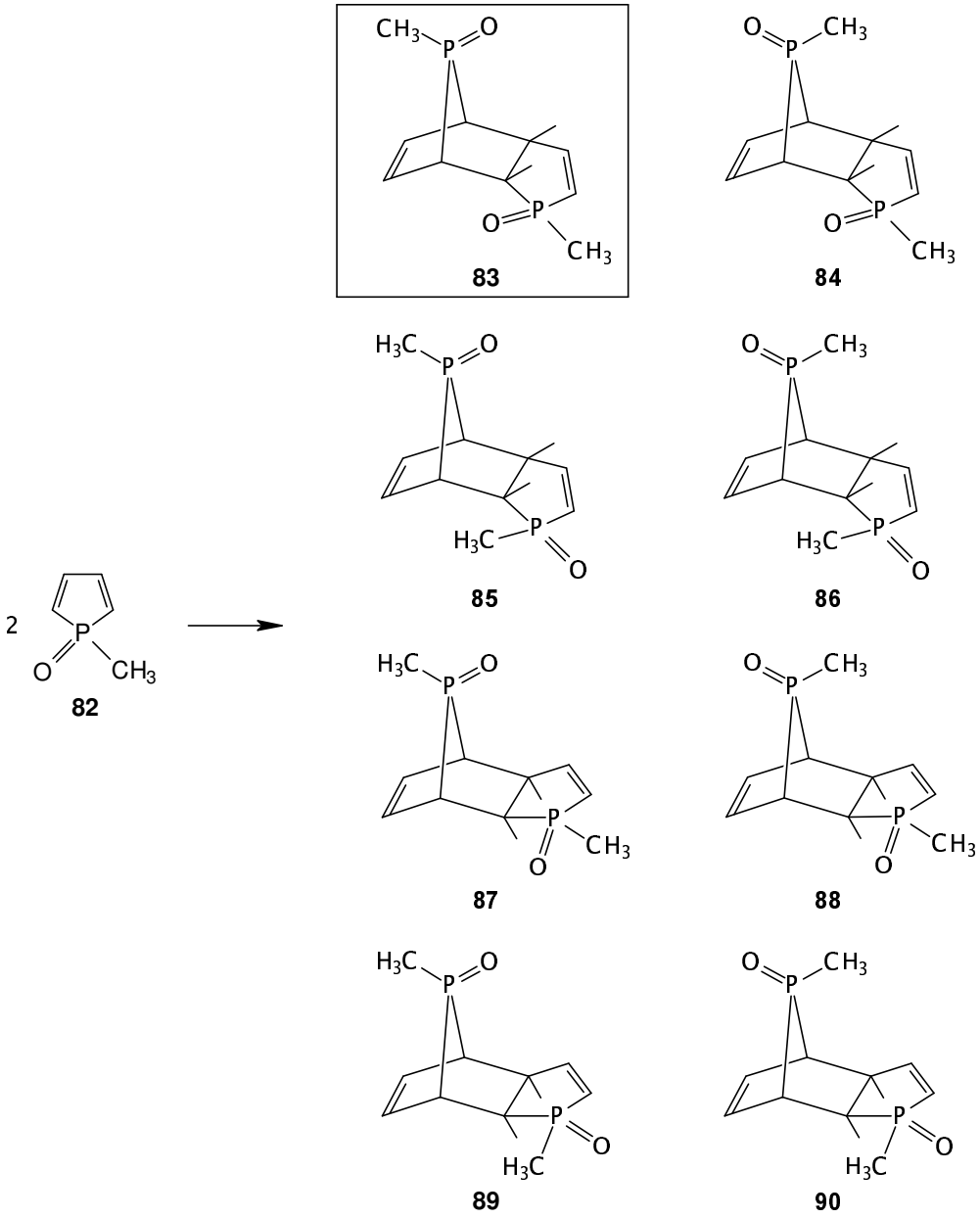


81d

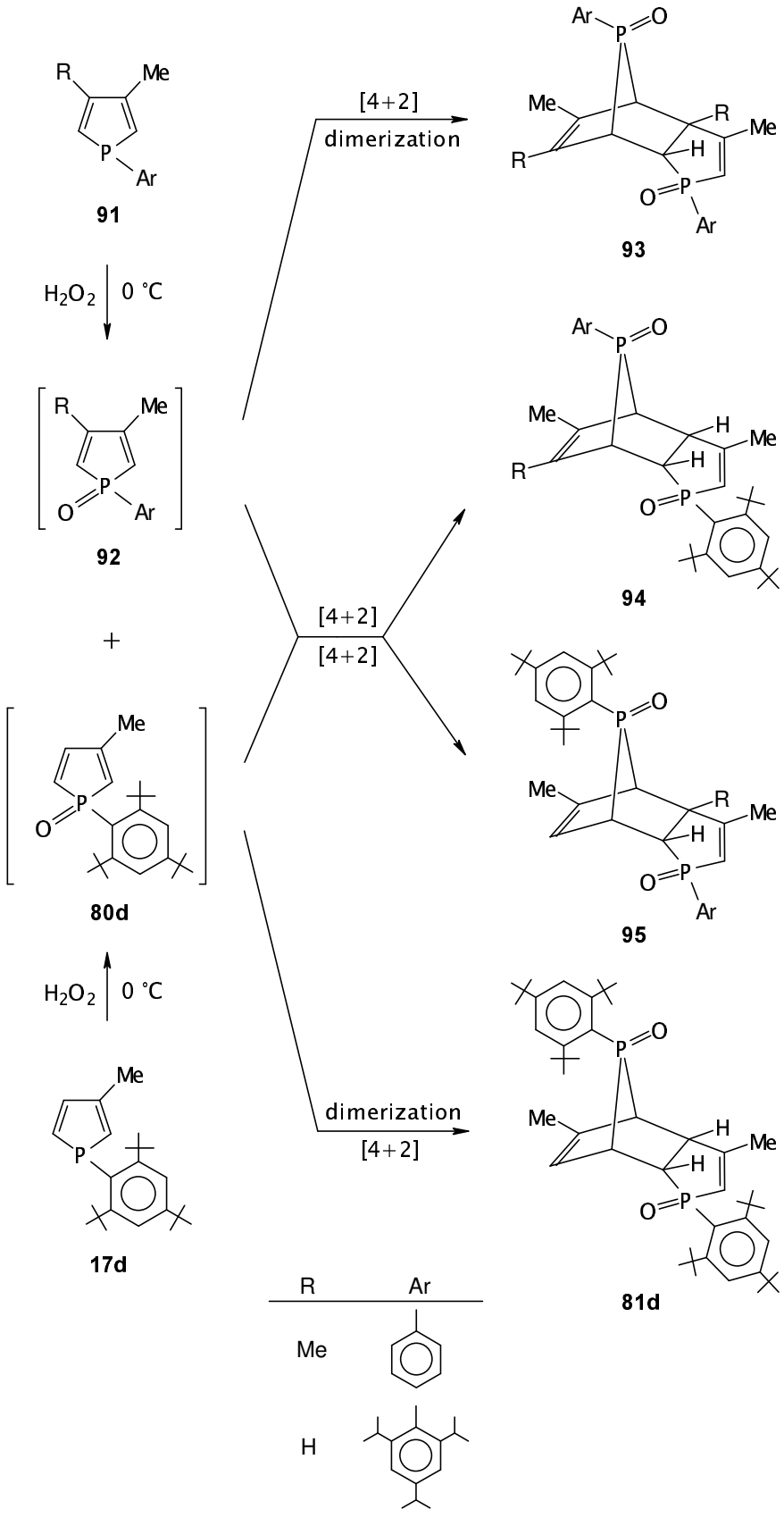
Figure 6. X-ray structure of phosphole oxide dimer **81d**

Considering the cyclodimerization of the phosphole oxides, it is recalled that although a number of isomers could be envisaged, only a single isomer is formed in all cases. If there is a methyl group in position 3, all together 64 isomers can be imagined; if there is no methyl group, the number of the possible isomers is 8 (see Scheme 23). The favoured isomer is where the phosphole rings are connected in the endo fusion and where the oxygen atoms of the phosphoryl groups are directed towards the center of the molecule (*e.g.* as in isomer **83**).

Semiempirical and *ab initio* calculations were performed on the cyclodimerization of 1-methylphosphole oxide (**82**). The relative order of the values of the heat of formation for the transient states leading to the possible isomers (**83**-**90**) confirmed that the formation of the single isomer having in hand (**83**) is indeed favored to a high extent (Scheme 23).[45] The selectivity can be explained by steric reasons and by kinetic factors.



Scheme 23


R
Me
P
Ar
91
H2O2
0 °C
92
+
80d
17d
[4+2]
dimerization
[4+2]
[4+2]
dimerization
[4+2]
93
94
95
81d
R
Ar
Me
H

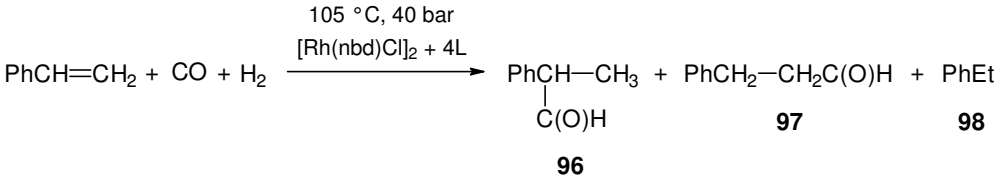
Scheme 24

Mixed phosphole oxide dimers (**94** and **85**) were prepared by the possible combinations of two different phosphole oxides (**92** and **80d**) generated simultaneously in the same flask. In the reaction shown homo dimers **93** and **81d** were also formed (Scheme 24).[46]

5. Phosphole ligands in rhodium complexes

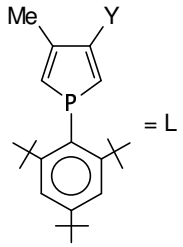
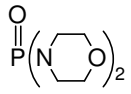
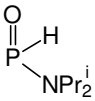
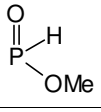
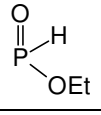
The phospholes are widely used ligands in transient metal complexes used as catalysts.

It was evaluated how the phosphorylation of the arylphosphole ligands (**17b,d**) affects the activity of the *in situ* rhodium complex in the hydroformylation of styrene (Scheme 25).



Scheme 25

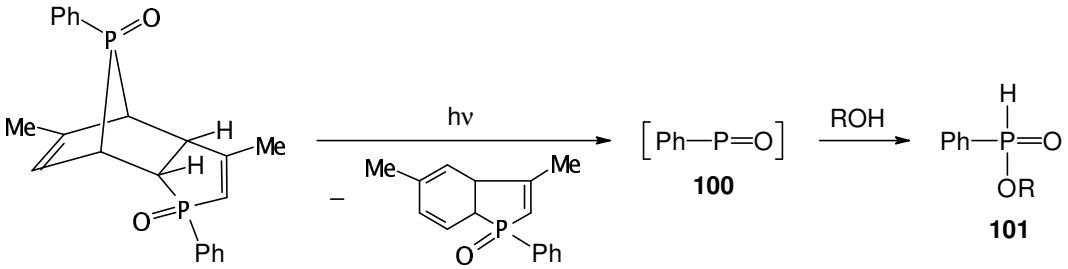
Table 3. Hydroformylation of styrene in the presence of $[Rh(nbd)Cl]_2$ + 4L phosphole ligands at 100 °C, 40 bar

			
Y	Reaction time	Conversion	R_b
H	6	99	66
	6	98	57
	6	99	62
	6	90	72
	2	98	75
	2	99	80

The chemoselectivity ($R_c = \frac{\text{mol}\,\mathbf{96} + \text{mol}\,\mathbf{97}}{\text{mol}\,\mathbf{96} + \text{mol}\,\mathbf{97} + \text{mol}\,\mathbf{98}} \times 100$) was found to be excellent (≥98%) in all cases, while the regioselectivity ($R = \frac{\text{mol}\,\mathbf{96}}{\text{mol}\,\mathbf{96} + \text{mol}\,\mathbf{97}} \times 100$) was improved in the case of certain substituents (Table 3).[29,47]

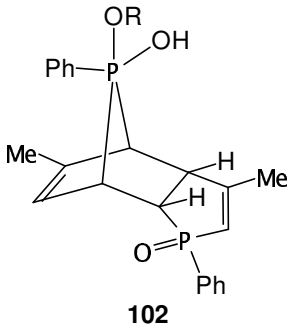
6. Fragmentation of phosphole-based phosphanorbornenes

The photolysis of phosphanorbornenes (e.g. **99**) was suggested to provide phosphinidenes (e.g. **100**) that reacted with the alcohol to give H-phosphinates (*e.g.* **101**) (Scheme 26).[48-50]



Scheme 26

Later on, an intermediate with a pentavalent pentacoordinated phosphorus atom (**102**) was suggested on the basis of kinetic examinations.[51]



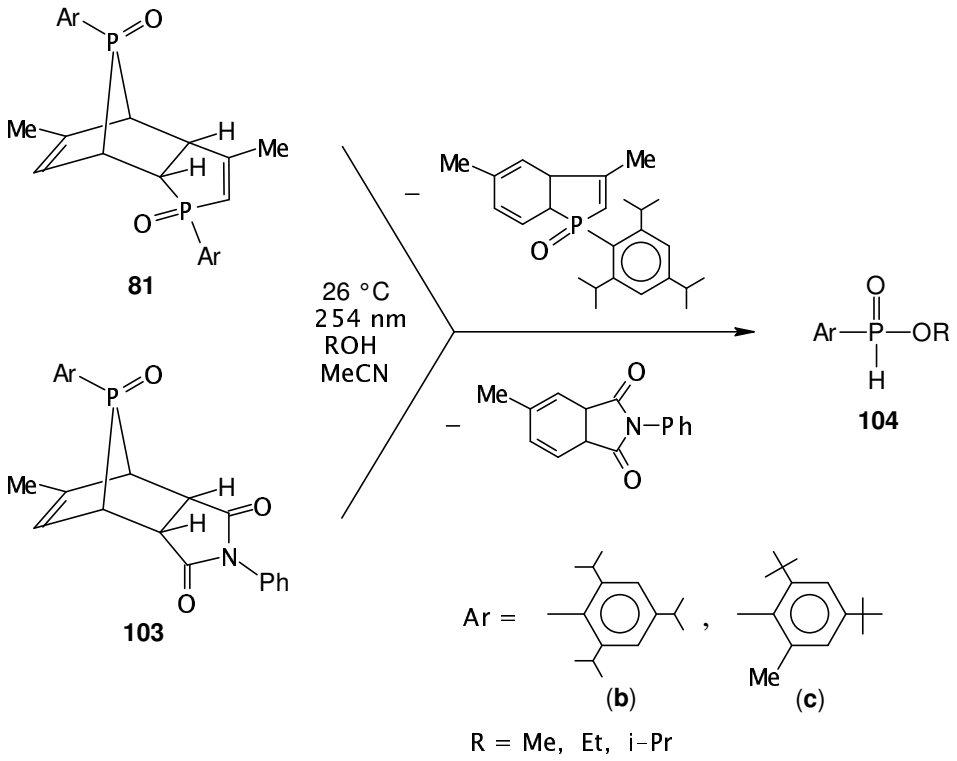
The P-aryl phosphanorbornenes (**81** and **103**) prepared by us served as excellent model compounds in photoinduced fragmentation-related phosphorylations. On one hand, new H-phosphinates (**104**) were prepared (Scheme 27), while on the other hand, our experiments showing a high sensitivity towards the steric effects confirmed the AE mechanism involving a pentacoordinated intermediate (**105**) (Scheme 28).[52,53]

Concurrent reactions applying either equimolar mixtures of methanol and isopropylalcohol or equimolar mixtures of two different precursors (**109** and **60**) (Schemes 29 and 30, respectively) again underlined the importance of the steric factors.

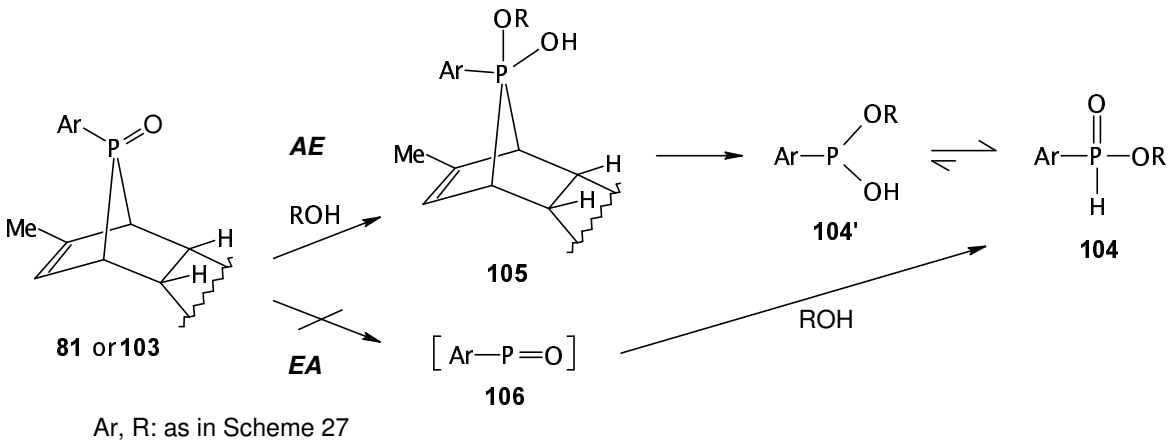
7. Conclusions

The new class of phospholes with 2,4,6-trialkylphenyl substituent on the phosphorus atom display, in many respects, a special reactivity. Due to the flattening of the P-pyramid, the arylphospholes are of

aromaticity and hence they entered into aromatic electrophilic Friedel-Crafts acylations. The site-selective functionalization through reaction with phosphorustribromide furnished a variety of phospholes with an exocyclic P-moiety that were useful ligands in rhodium complexes used as catalysts in hydroformylations. The phosphole platinum complexes prepared are also of novelty.



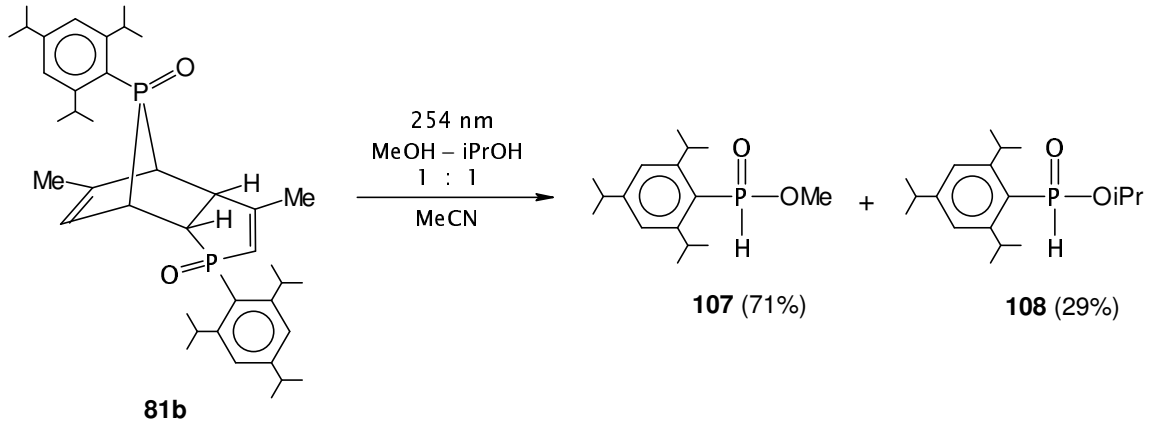
Scheme 27



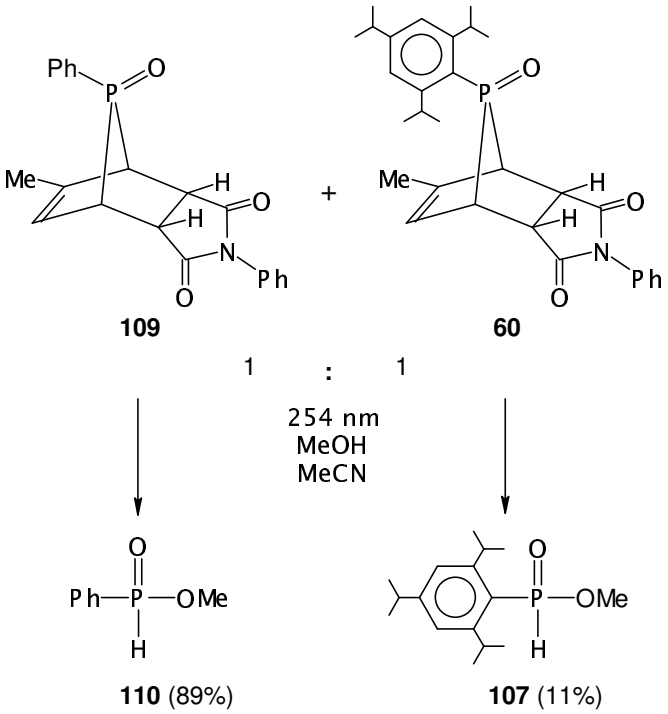
Scheme 28

Despite the planarization of the P-pyramid, the arylphospholes could also be involved in Diels-Alder reactions to give new type of phosphanorbornenes. These products together with the phosphanorbornenes obtained by the region- and stereospecific dimerization of arylphosphole oxides were useful model compounds in the UV light mediated fragmentation-related phsophorylation of alcohols. A novel mechanism

was substantiated. The sigmatropic rearrangement of 1H-phospholes to the 2H derivatives gives a new entry to novel 1-phosphanorbornadienes after trapping with diphenylacetylene.



Scheme 29



Scheme 30

Acknowledgment

Gy. K. thanks the Hungarian National Science Foundation (OTKA, Grant No. T 029039 and T 042479) for the financial support and is indebted to the co-authors whose names appear in the references.

References

1. Dimroth, K. In *Comprehensive Heterocyclic Chemistry*, Vol. 1; Katritzky, A. R.; Rees, C. V.; Met-Cohn, O., Eds.; Pergamon: Oxford, 1984; Ch. 1.17, p. 518.
2. Quin, L. D. 'Phospholes' In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R.; Rees, C. V.; Scriven, E. F. V., Eds.; Bird, C. W.; Vol. ed.; Pergamon: Oxford, 1996; Ch. 15.

3. Dillon, K. B.; Mathey, F.; Nixon, J. F. In *Phosphorus: the Carbon Copy, from Organophosphorus to Phospha-Organic Chemistry*; Wiley: Chichester, 1998; Ch. 8, p. 203.
4. Quin, L. D. 'Phospholes' In *Phosphorus-Carbon Heterocyclic Chemistry: the Rise of a New-Domain*; Mathey, F., Ed.; Pergamon: Amsterdam, 2001; Ch. 4.2.1, Ch. 4.2.2.
5. Mathey, F. *Chem. Rev.* **1988**, *88*, 429.
6. Breque, A.; Mathey, F.; Savignac, P. *Synthesis* **1981**, 983.
7. Mathey, F.; Mankowski-Favelier, R. *Org. Magn. Resonance* **1972**, *4*, 171.
8. McCormack, W. B. *US Pat.* 2 663 737 (1953) (Chem. Abstr. **1955**, *49*, 7602).
9. McCormack, W. B. *US Pat.* 2 663 738 (1953) (Chem. Abstr. **1955**, *49*, 7602).
10. Quin, L. D.; Gratz, J. P.; Barket, T. P. *J. Org. Chem.* **1968**, *33*, 1034.
11. Quin, L. D.; Borleske, S. G.; Engel, J. F. *J. Org. Chem.* **1973**, *38*, 1858.
12. Quin, L. D.; Bryson, J. G. *J. Am. Chem. Soc.* **1967**, *89*, 5984.
13. Quin, L. D.; Bryson, J. G.; Moreland, C. G. *J. Am. Chem. Soc.* **1969**, *91*, 3308.
14. Bird, C. W. *Tetrahedron* **1985**, *41*, 1409.
15. Coggon, P.; McPhail, A. T. *J. Chem. Soc., Dalton Trans* **1973**, 1888.
16. Nyulászi, L. *Chem. Rev.* **2001**, *11*, 1229.
17. Nyulászai, L.; Soós, L.; Keglevich, Gy. *J. Organomet. Chem.* **1998**, *566*, 29.
18. Keglevich, Gy.; Quin, L. D.; Böcskei, Gy.; Keserü, Gy. M.; Kalgutkar, R.; Lahti, P. M. *J. Organomet. Chem.* **1997**, *532*, 109.
19. Quin, L. D.; Ionkin, A. S.; Kalgutkar, R.; Keglevich, Gy. *Phosphorus, Sulfur, Silicon* **1996**, *109-110*, 433.
20. Quin, L. D.; Keglevich, Gy.; Ionkin, A. S.; Kalgutkar, R.; Szalontai, G. *J. Org. Chem.* **1996**, *61*, 7801.
21. Keglevich, Gy.; Böcskei, Gy.; Keserü, Gy. M.; Újszászy, K.; Quin, L. D. *J. Am. Chem. Soc.* **1997**, *119*, 5095.
22. Nyulászai, L.; Keglevich, Gy.; Quin, L. D. *J. Org. Chem.* **1996**, *61*, 7808.
23. Santini, C. C.; Mathey, F. *J. Org. Chem.* **1985**, *50*, 467.
24. Mathey, F. *Tetrahedron Lett.* **1976**, 4155.
25. Mathey, F.; Mitschler, A.; Weiss, R. *J. Am. Chem. Soc.* **1978**, *100*, 5748.
26. Roberts, R. M. G.; Wells, A. S. *Inorg. Chim. Acta* **1987**, *130*, 93.
27. Keglevich, Gy.; Chuluunbaatar, T.; Dajka, B.; Dobó, A.; Szöllösy, Á.; Töke, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2895.
28. Keglevich, Gy.; Chuluunbaatar, T.; Dobó, A.; Töke, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1495.
29. Keglevich, Gy.; Chuluunbaatar, T.; Dajka, B.; Ludányi, K.; Parlagh, Gy.; Kégl, T; Kollár, L.; Töke, *J. Organomet. Chem.* **2002**, *643-644*, 29.
30. Mathey, F.; Mercier, F. *Tetrahedron Lett.* **1981**, *22*, 319.
31. Isaacs, N. S.; El-Din, G. N. *Tetrahedron* **1989**, *45*, 7083.
32. Caster, K. C.; Quin, L. D. *Phosphorus, Sulfur* **1985**, *25*, 117.
33. Keglevich, Gy.; Trecska, M.; Dajka, B.; Pete, B.; Dobó, A.; Töke, L. *Heteroatom Chem.* **2000**, *11*, 271
34. Keglevich, Gy.; Chuluunbaatar, T.; Dajka, B.; Bat-Amgalan, N.; Fekete, M.; Kollár, L.; Töke, L. *Phosphorus, Sulfur, Silicon* **2002**, *177*, 1991.
35. Keglevich, Gy.; Nyulászi, L.; Chuluunbaatar, T.; Bat-Amgalan, N.; Ludányi, K.; Imre, T.; Töke, L. *Tetrahedron* **2002**, *58*, 9801.
36. Mathey, F.; Mercier, F.; Charrier, C.; Fischer, J.; Mitschler, A. *J. Am. Chem. Soc.* **1981**, *103*, 4595.
37. Mathey, F. Mercier, F. *Compt. Rend. Acad. Sci. Paris*, Ser. II. B, **1997**, *324*, 701.
38. Mathey, F.; Mercier, F.; Robin, F.; Ricard, L. *J. Organomet. Chem.* **1998**, *557*, 117.
39. Keglevich, Gy.; Farkas, R. *Heteroatom Chemistry*, **2003**, in press.
40. Csók, Zs.; Keglevich, Gy.; Petöcz, Gy.; Kollár, L. *J. Organomet. Chem.* **1999**, *586*, 79.
41. Csók, Zs.; Keglevich, Gy.; Petöcz, Gy.; Kollár, L. *Inorg. Chem.* **1999**, *38*, 831.
42. Holt, M. S.; MacDougall, J. J.; Mathey, F.; Nelson, J. H. *Inorg. Chem.* **1984**, *23*, 449.
43. Quin, L. D. Rev. *Heteroatom Chem.* **1990**, *3*, 39.
44. Keglevich, Gy.; Böcskei, Zs.; Harmat, V.; Töke, L. *Heteroatom Chem.* **1997**, 8, 527.
45. Keserü, Gy. M.; Keglevich, Gy. *J. Organomet. Chem.* **1999**, *586*, 166.

46. Keglevich, Gy.; Chuluunbaatar, T.; Dajka, B.; Bat-Amgalan, N.; Ludányi, K.; Töke, L., *Heteroatom Chem.* **2001**, *12*, 633.
47. Keglevich, Gy.; Kégl, T.; Chuluunbaatar, T.; Dajka, B.; Mátyus, P.; Balogh, B.; Kollár, L. *J. Mol. Cat*. **2003**, in press.
48. Quin, L. D.; Szewczyk, J. In *Multiple Bonds and Low Coordination in Phosphorus Chemistry*; Regitz, M.; Scherer, O. J., Eds.; Thieme: Stuttgart, 1990; Ch. D11, P. 355.
49. Tomioka, H.; Hirano, Y.; Izawa, Y. *Tetrahedron Lett.* **1974**, 4477.
50. Tomioka, H.; Miura, S.; Izawa, Y. *Tetrahedron Lett.* **1983**, *24*, 3353.
51. Quin, L. D.; Jankowski, S.; Rudzinski, J.; Sommese, A. G.; Wu, X.-P. *J. Org. Chem.* **1993**, *58*, 6212.
52. Keglevich, Gy.; Ludányi, K.; Quin, L. D. *Heteroatom Chem.* **1997**, *8*, 135.
53. Keglevich, Gy.; Trecska, M.; Nagy, Z.; Töke, L. *Heteroatom Chem.* **2001**, *12*, 6.

CHIRAL β-AMINOALCOHOLS AND DERIVATIVES IN THE ASYMMETRIC SYNTHESIS OF TETRAHYDROISOQUINOLINES

Eneritz Anakabe, Dolores Badía, Luisa Carrillo, Efraim Reyes and Jose L. Vicario

Departamento de Química Orgánica II, Universidad del País Vasco/Euskal Herriko Unibertsitatea, P.O. Box 644, 48080 Bilbao, Spain (e-mail: qopbaurm@lg.ehu.es)

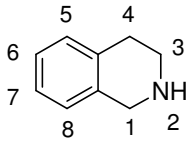
Abstract. *We describe herein different synthetic procedures for the stereocontrolled synthesis of 1,2,3,4-tetrahydroisoquinolines and derived alkaloids, which are of crucial interest because of the interesting biological activities displayed by this group of products. Our strategy relies on the use of chiral β-aminoalcohols as chirality source. In this context, (S)-phenylglycinol has been used as chiral building block, which is afterwards completely or partially incorporated into the structure of the final heterocycles. Alternatively, we have used (S,S)-pseudoephedrine as chiral auxiliary which is recovered after the creation of the desired stereogenic centre. The described methodologies have allowed us to prepare a wide range of differently substituted tetrahydroisoquinolines and, in some cases, other more elaborated alkaloids like isopavines, protoberberines or benzo[c]phenanthridines have also been prepared.*

Contents

1. Introduction

The isoquinoline core is a structural feature common to a large and diverse family of natural products with a widespread occurrence in nature and which play a very important role in the secondary metabolism of

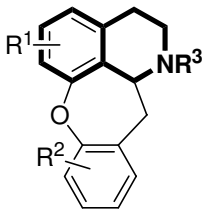
numerous vegetal families.[1] Among the members of this family, those in which the nitrogen-containing ring is partially hydrogenated, that is, the 1,2,3,4-tetrahydroisoquinolines, constitute the major group into this class of interesting alkaloids (Figure 1).



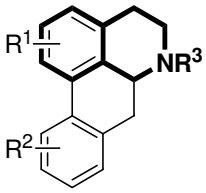
The 1,2,3,4-tetrahydroisoquinoline nucleus with the adopted numbering scheme.

Figure 1

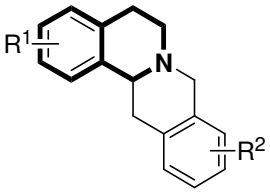
There are a wide number of different groups of alkaloids containing the tetrahydroisoquinoline core in their structure (Figure 2).[2] When analysing the constitution of these alkaloids, it can be found that several stereogenic centres are present in their carbon skeleton. As it is very often found in these cases, one enantiomer is normally the responsible of the biological activity of the product while the other results to be inactive or toxic.[3] Consequently, the design of synthetic routes for their obtention in an enantiopure form becomes a field of increasing interest for the organic chemists.[4]



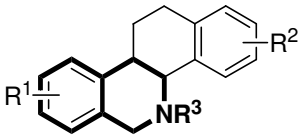
Cularines



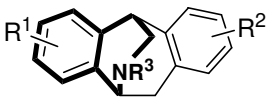
Aporphines



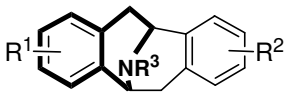
Protoberberines



Benzo[*c*]phenanthridines



Isopavines



Pavines

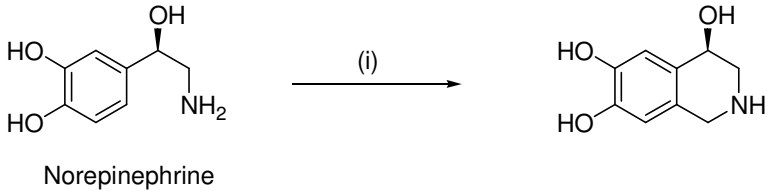
Figure 2

In this review, the quest for new procedures for the stereocontrolled synthesis of differently substituted tetrahydroisoquinolines in which our research group has been engaged during the last years will be presented. In some cases, the obtained heterocycles have also been used as key synthetic intermediates for the preparation of other naturally occurring isoquinoline alkaloids. The common feature to the methodologies developed by us relies upon the use of the β-aminoalcohols (*S*)-phenylglycinol or (*S,S*)-pseudoephedrine as chirality sources, which can act either as building blocks or auxiliaries in the course of the designed synthetic scheme. Prior to the presentation of the most outstanding results obtained by us, a revision of related works by other research groups worldwide will be performed.

1.1. β-Aminoalcohols and derivatives as chiral building blocks

The first reported attempts in this area belong to the use of chiral 2-arylethylamines as starting materials in which any of the typical heterocyclization procedures, *i.e.* Pictet-Spengler,[5] Bischler-Napieralsky[6] or Pommeranz-Fritsch[7] and related procedures, allowed the access to the final heterocycles.

In this context, Bates has employed epinephrine and norepinefrine as starting materials, which, after a Pictet-Spengler reaction with formaldehyde in slightly acidic medium afforded the corresponding heterocycles in good yields (Scheme 1).[8] The use of acetaldehyde was examined as well, but no 1,4-asymmetric induction was found to occur in this case and a 1:1 mixture of epimers was obtained.

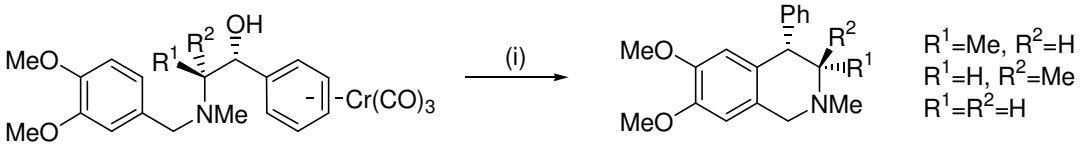


Norepinephrine

Reagents and conditions: (i) HCHO, HCl, pH=6.5, rt.

Scheme 1

Analogously, Davies has used *N*-benzylephedrine as chiral precursor for the synthesis of 4-phenyl-3-methyl-6,7-dimethoxytetrahydroisoquinoline, using in this case an asymmetric variant of the classical Pomeranz-Fritsch heterocyclization. Acid promoted cyclization of these derivatives occurred with complete diastereoselection to give exclusively the 3,4-*trans* derivatives, although previous aryl complexation with $Cr(CO)_3$ was necessary in order to stabilize the intermediate carbocation (Scheme 2).[9] The same procedure was applied using (-)-pseudoephedrine[9] and (+)-2-amino-1-phenylethanol[10] with excellent results.



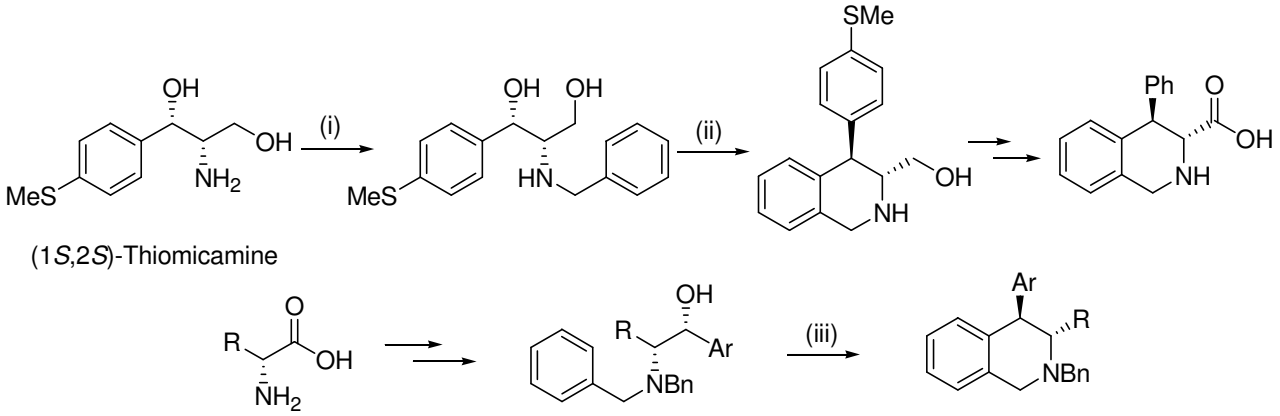
Reagents and conditions: (i) 1. TFA/H_2SO_4 refl. or HBF_4, CH_2Cl_2, -20 ºC. 2. Air oxidation

Scheme 2

Rozwadwoska has followed a similar approach and has succeeded in the synthesis of 3,4-disubstituted tetrahydroisoquinolines starting from the chiral aminoalcohol (1*S*,2*S*)-thiomicamine.[11] In this case, the acid-catalyzed cyclization was achieved in refluxing 40% HBr. More recently, similar derivatives have been prepared by Friedel-Crafts cyclization of chiral *N*,*N*-dibenzylaminoethanols,[12] which were prepared *via* diastereoselective addition of ArMgCl to the corresponding *N,N*-dibenzyl-α-aminoaldehydes derived from the corresponding aminoacids (Scheme 3).[13]

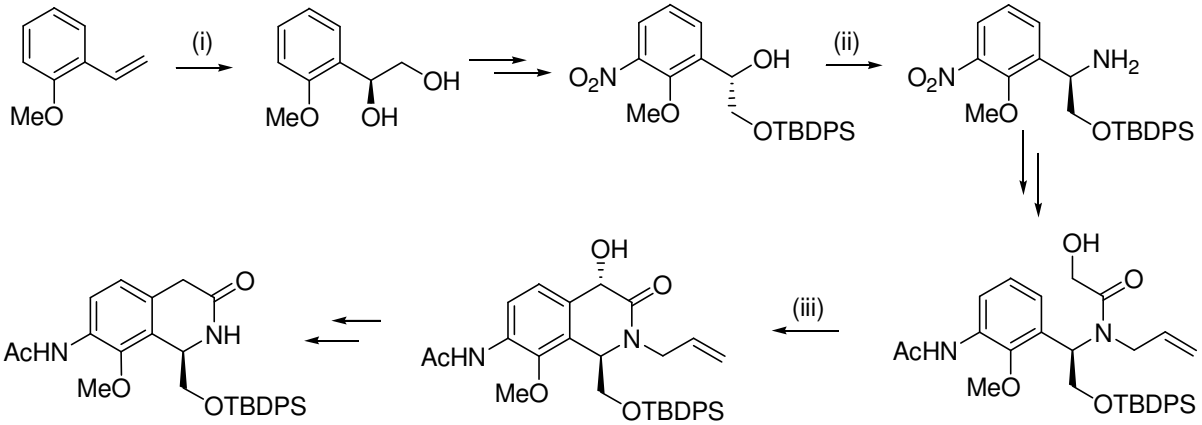
Another chiral modification of the Pomeranz-Fritsch cyclization has been applied by Wipf for the stereocontrolled synthesis of the AB-ring system of *tetrazomine*,[14] an alkaloid belonging to the naphthyridinomycin/bioxalomycin class of antitumour antibiotics.[15] In this way, the first stereocentre was introduced by means of an asymmetric dihydroxylation/Mitsunobu reaction sequence. Further transformations led to a 2-aryl-2-aminoethanol with the convenient substitution pattern at the aromatic

moiety, which was converted into the corresponding *N*-(2-hydroxyacetyl) derivative. Subsequent Swern oxidation and acid-catalyzed cyclization afforded the target chiral nonracemic 1-substituted 4-hydroxytetrahydroisoquinolin-3-one. Further elaboration led to the synthesis of the final heterocyclic system (Scheme 4).



Reagents and conditions: (i) 1. PhCHO, MeOH, $CuSO_4$; 2. $NaBH_4$, MeOH (ii) 40% HBr, refl. (iii) $AlCl_3$, CH_2Cl_2, rt.

Scheme 3

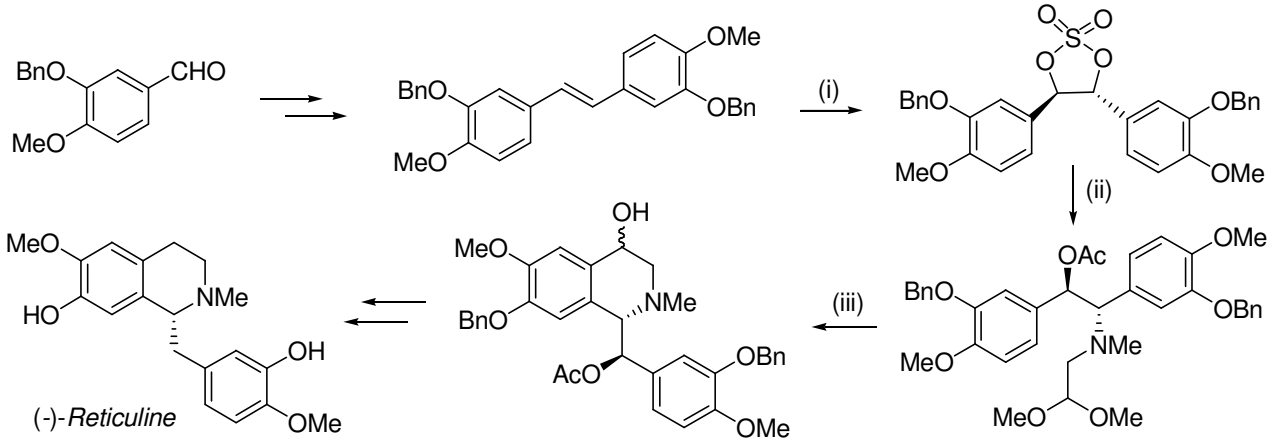


Reagents and conditions: (i) AD-Mix-α, *t*-BuOH/H_2O, 0 ºC (ii) 1. Phtalimide, Ph_3P, DEAD, THF; 2. H_2NNH_2, H_2O, refl. (iii) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; 2. *p*-TsOH, dioxane, refl.

Scheme 4

In the same context, a report by Hirsenkorn can be found in which an asymmetric Pomeranz-Fritsch cyclization is employed for the building up of the isoquinoline skeleton.[16] The required starting chiral material is a 2-amino-1,2-diarylethanol, which was obtained in an enantioenriched form by asymmetric Sharpless dihydroxylation of an styrene derivative, followed by formation of a cyclic sulfate and subsequent nucleophilic ring-opening reaction with methylaminoacetaldehyde dimethylacetal (MADMA). Once the chiral aminoalcohol was obtained, the cyclization was achieved under carefully controlled conditions in order to avoid formation of pavine and isopavine side products.[17] Final removal of the protecting groups together with dehydroxylation of the benzylic alcohol moieties afforded the 1-benzyltetrahydroisoquinoline

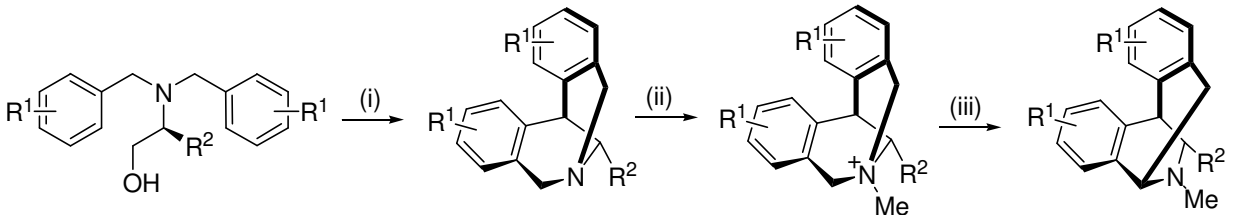
(-)-*reticuline*. Alternatively, 1,2-dihydroisoquinolines are obtained if modified conditions are employed at the cyclization step (Scheme 5).[18]



Reagents and conditions: (i) 1. $OsCl_3$, dihydroquinidine 4-chlorobenzoate, NMO, acetone/H_2O, rt. 2. $SOCl_2$, Et_3N, Et_2O, 0 ºC to rt; 3. $RuCl_3$, NaOCl, CH_3CN. (ii) 1. MADMA, 130 ºC. 2. Ac_2O, NaOAc, xylene, refl. (iii) HCl/acetone, 0 ºC.

Scheme 5

Very recently, Hanessian has succeeded in preparing functionalized isopavines starting from chiral nonracemic 13-substituted dihydromethanodiazocines *via* [1,2]-Stevens rearrangemens.[19] These tetracyclic key synthetic intermediates were easily prepared from *N*,*N*-dibenzyl substituted enantioenriched β-aminoalcohols by Swern oxidation followed by a Lewis acid-catalyzed double cyclization process. The subsequently performed Stevens rearrangements[20] proceeded with high selectivity and the final isopavines were obtained as single diastereoisomers (Scheme 6).

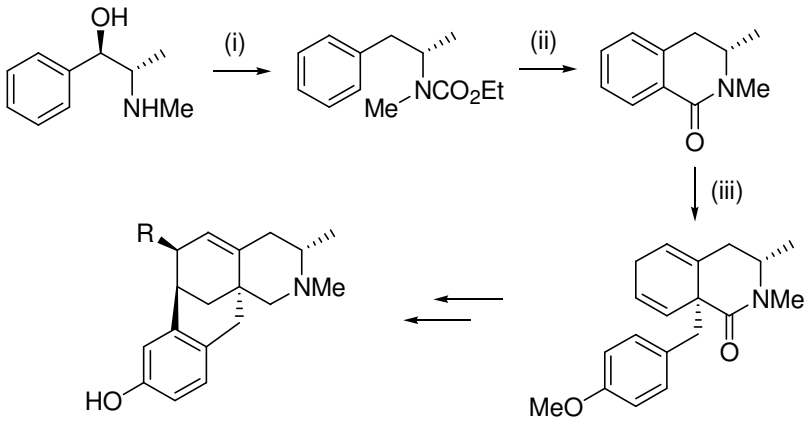


Reagents and conditions: (i) 1. Swern oxidation; 2. $AlCl_3$, CH_2Cl_2, 0 ºC. (ii) MeI, acetone, refl. (iii) *t*-BuOK, 1,4-dioxane, 80 ºC.

Scheme 6

The aminoalcohol (1*R*,2*S*)-ephedrine has also been used by Schultz as chiral building block for the stereocontrolled synthesis of 3-methyl-1,2,3,4-tetrahydroisoquinolin-1-ones.[21] In this case, the cyclization procedure for the construction of the heterocyclic ring involved the formation of an intermediate uretane which was subsequently cyclized with methanesulfonic acid/P_2O_5 under a previously reported procedure.[22] Prior to the cyclization, the OH group from ephedrine was removed *via* Raney Nickel hydrogenolysis. The obtained heterocycle was used afterwards for the preparation of different analogues of the potent analgesic

agent *levorphanol*. The key step in this transformation consisted on a Birch reduction procedure followed by diastereoselective trapping of the intermediate enolate with a benzylic bromide (Scheme 7).

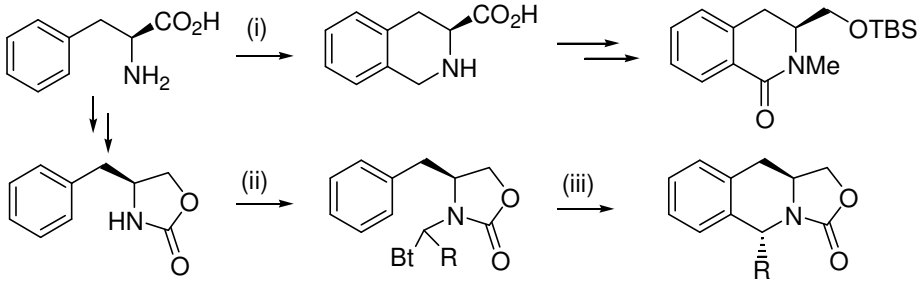


(R=H, OH) *Levorphanol* analogues

Reagents and conditions: (i) 1. $ClCO_2Et$, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C; 2. Raney Ni, H_2, EtOH, refl. (ii) $MeSO_3H$, P_2O_5, 120 °C (iii) Li, NH_3/THF, *t*-BuOH, $ArCH_2Br$, -78 °C.

Scheme 7

In a different approach, chiral nonracemic tetrahydroisoquinoline 3-carboxylate derivatives are also readily available *via* Pictet-Spengler cyclization using phenylalanine as precursor.[23] Schultz himself used this approach for the synthesis of 3-substituted tetrahydroisoquinolin-1-ones,[21] Burger has prepared tetrahydroisoquinoline-1,3-dicarboxylates in a similar way[24] and very recently, tricyclic tetrahydroisoquinolines incorporating the BCD subunit of the protoberberine skeleton have been prepared by cyclization of a phenylalaninol-derived bicyclic lactam *via* a *N*-acyliminium intermediate.[25] In addition, Katritzky has applied his benzotriazole chemistry for the synthesis of different analogues of the natural product *podophyllotoxin*.[26] In the later case, the oxazolidin-2-one derived from phenylalaninol was treated with benzotriazole/RCHO and the obtained adducts were subjected to cyclization under Friedel-Crafts conditions, affording 5-substituted oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones as pure diastereoisomers.[27] In a recent paper, the asymmetric synthesis of tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones applying the same concept has been reported (Scheme 8).[28]

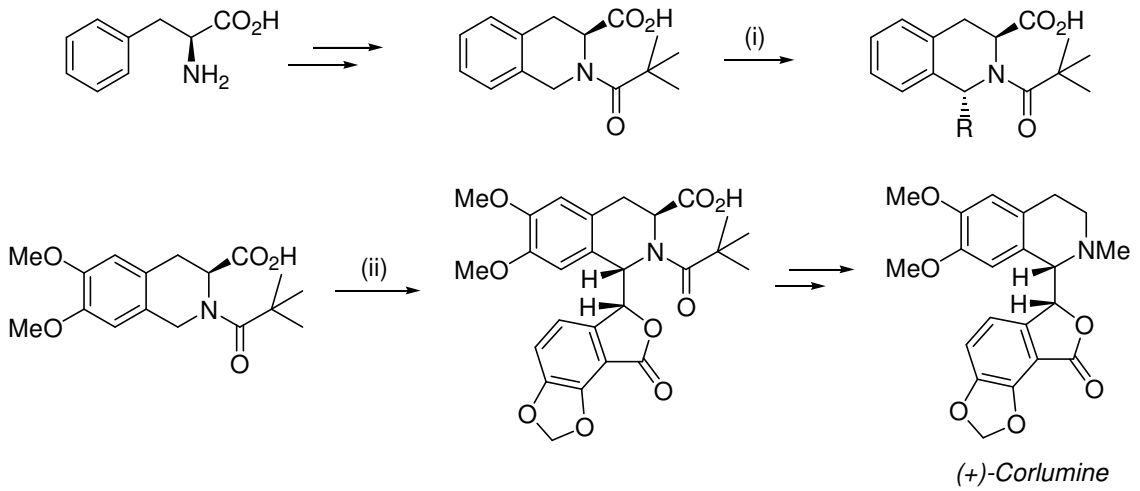


Reagents and conditions: (i) HCHO, HCl, 85 °C (ii) BtH, RCHO, toluene, or CH_2Cl_2, *p*-TsOH (cat), Dean-Stark. (iii) $TiCl_4$, CH_3CN or CH_2Cl_2, 60 °C.

Scheme 8

Another useful and versatile approach to 1,3-disubstituted tetrahydroisoquinolines starting from phenylalanine relies on the diastereoselective heteroatom-directed metallation/alkylation sequence which has

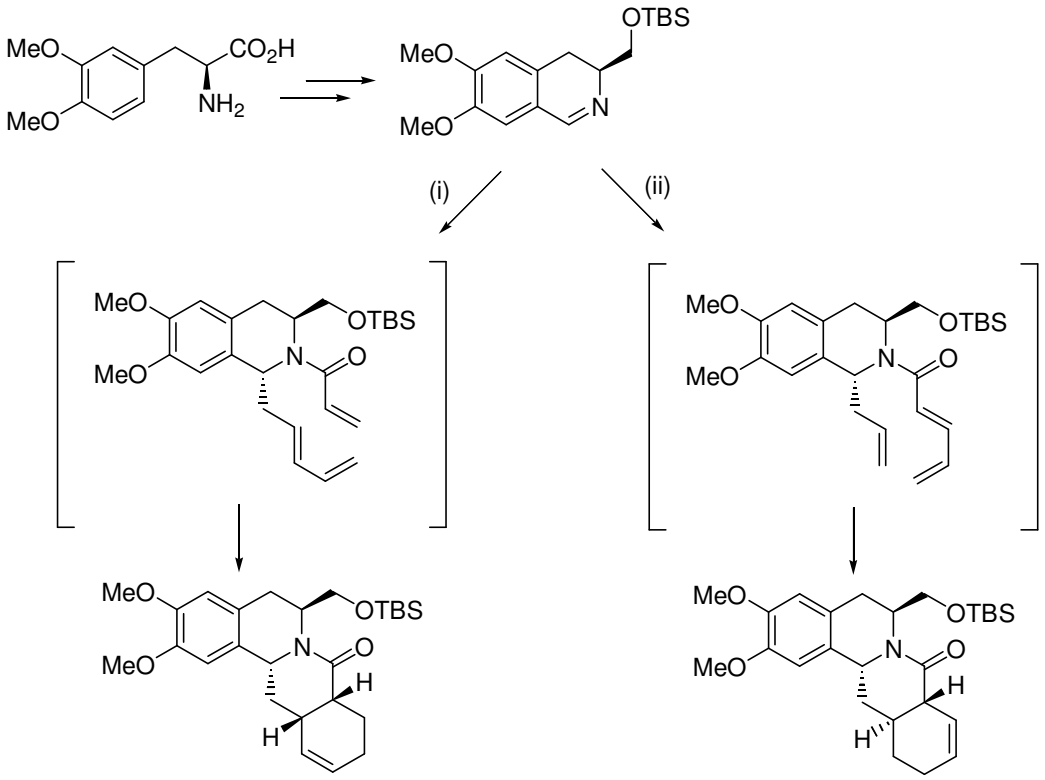
been set up by Seebach[29] and subsequently applied for the asymmetric synthesis of the phtalide alkaloid *(+)-corlumine*.[30] *N*-Pivaloyltetrahydroisoquinoline-3-carboxylic acid was prepared by Pictet-Spengler cyclization of phenylalanine followed by esterification/*N*-pivaloylation/hydrolysis. This compound was metallated with 2 eq. of *t*-BuLi and the obtained carbanion reacted with several carbon electrophiles, affording the corresponding 1,3-disubstituted heterocycles in good yields and diastereoselectivities. It has to be pointed out that, in some cases, transmetallation with $MgBr_2$ was necessary prior to the reaction with the electrophile in order to reach to high diastereoselection. For the synthesis of *(+)-curlumine* a 3,4-dimethoxylated derivative of (*S*)-phenylalanine[31] had to be used as starting material and a highly functionalized aromatic aldehyde as the required electrophile. A similar approach for the alkylation of 3-substituted tetrahydroisoquinolines has been employed by Laschat, but in this case the *O*-TBS protected derivative of phenylalaninol was used as chiral starting material (Scheme 9).[32]



Reagents and conditions: (i) 1. *t*-BuLi, THF, -78 °C; 2. RX or RCHO. (ii) *t*-BuLi, THF, -78 °C; 2. $MgBr_2.OEt_2$; 3. ArCHO

Scheme 9

Analogously, Yamaguchi has proven that efficient 1,3-asymmetric induction can be achieved in the diastereoselective 1,2-addition of organometallic reagents to chiral 3,4-dihydroisoquinolines derived from phenylalaninol.[33] In this context, the asymmetric synthesis of 7,8-dimethoxyberbane systems was achieved through a tin mediated three component coupling.[34] The already mentioned chiral starting material, a 3,4-dimethoxyphenylalaninol derived dihydroisoquinoline, was prepared starting from (*S*)-DOPA *via* first Pictet-Spengler heterocyclization followed by reduction/*O*-silylation[35] and final oxidation of the obtained tetrahydroisoquinoline, thus building up the C=N moiety into the heterocyclic ring. When 1,2-dihydroisoquinoline was made to react with 2,4-pentadienyltributyltin, in the presence of acryloyl chloride, a diastereoselective addition of the organometallic reagent across the C=N double bond occurred together with *N*-acylation, and the obtained adduct underwent a subsequent intramolecular Diels-Alder cyclization to afford, in a single step, the berbane system with very high diastereoselectivity. Inverting the nature of reagents, that is, using allyltributyl tin and 2,4-pentadienoyl chloride, the addition/acylation/Diels-Alder reaction also took place smoothly to afford the corresponding isomer with comparable degree of diastereoselection (Scheme 10).



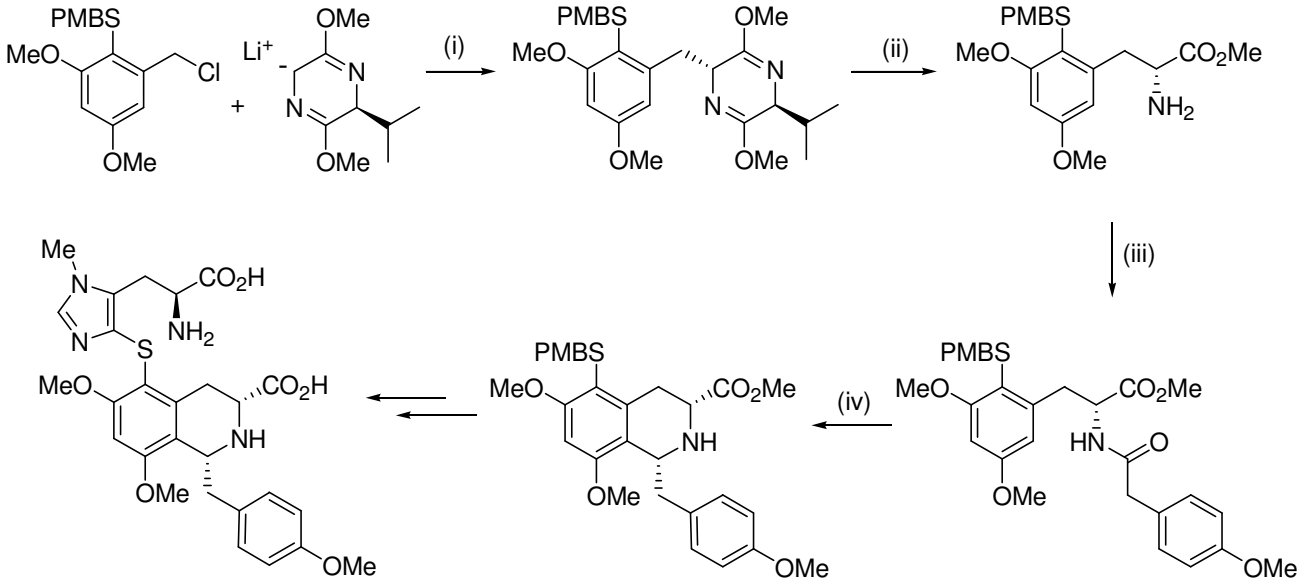
Reagents and conditions: (i) CH_2=CHCH=CHCH$_2$SnBu$_3$, CH_2=CHCOCl, CH_2Cl_2, rt.
(ii) CH_2=CHCH$_2$SnBu$_3$, CH_2=CHCH=CHCOCl, CH_2Cl_2, refl.

Scheme 10

When other different tetrahydroisoquinoline-3-carboxylates are needed, particularly in the case of special substitution patterns at the aromatic ring, the natural aminoacid phenylalanine is not a suitable starting material. In this context, Ohba has prepared an *O*-trimethyl analogue of the natural product *imbricatine*, a 1-benzyltetrahydroisoquinoline-3-carboxylate, starting from an arylalanine analogue.[36] This modified aminoacid was prepared in an enantioenriched form by electrophilic addition of an appropriately substituted benzyl chloride with the organolithium reagent that results from the lithiation of (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine,[37] a valine-based heterocycle. Base hydrolysis of the addition product afforded the desired arylalanine methyl ester which was converted into the corresponding *N*-(*p*-methoxyphenyl)acetyl derivative under standard reaction conditions. Next, Bischler-Napieralsky cyclization procedure followed by diastereoselective reduction was performed, leaving to the 1,3-disubstituted heterocycle in the right 1,3-*cis* relationship. Further elaboration on this synthetic intermediate led to the target *O*-trimethylated derivative of the already mentioned natural product (Scheme 11).

The nucleophilic addition to 3,4-dihydroisoquinolines has also been applied to the synthesis of simple chiral nonracemic 1-alkyltetrahydroisoquinolines, incorporating the chiral information at the nitrogen. In this sense, Yamato has prepared several 1-alkyl substituted derivatives in high optical purity using (*R*)-phenylglycinol as chirality source.[38] Bromination of isochromanones in the presence of sunlight afforded differently substituted 2-(2-bromoethyl)benzaldehydes and afterwards they reacted with the chiral aminoalcohol to yield the corresponding 1,2-dihydroisoquinolinium salt, that, upon base-induced

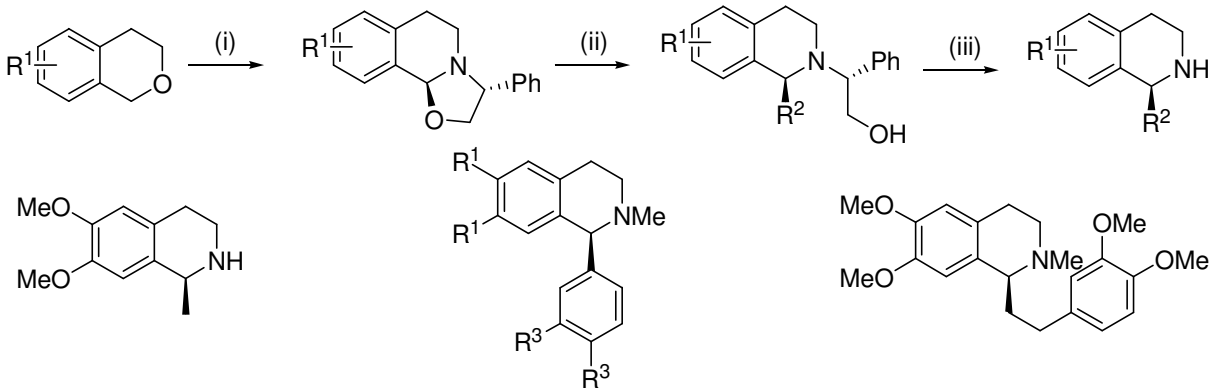
cyclization, afforded the oxazolo[2,3-*a*]isoquinolines, in which a masked C=N bond is present at the oxazolidine ring junction in the form of a *N*,*O*-acetal.[39]



Tri-O-methylimbricatine

Reagents and conditions: (i) THF, -50 °C. (ii) HCl, MeOH, rt. (iii) (*p*-$MeOC_6H_4$)CH_2COCl, Na_2CO_3, H_2O/C_6H_6. (iv) 1. trimethylsilylpolyphosphate, $CHCl_3$, refl. 2. $NaBH_4$, MeOH, -78 °C.

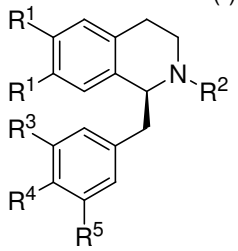
Scheme 11



(-)-*Salsolidine*

(-)-*Cryptostyline I*: R^1=OMe; R^3=OCH_2O
(-)-*Cryptostyline II*: R^1=R^3=OMe

(-)-*Homolaudanosine*



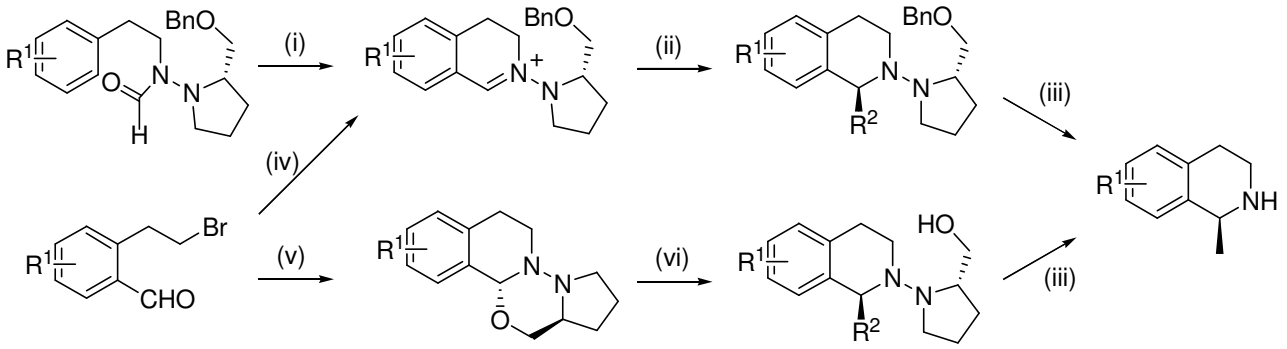
(-)-*Laudanosine*: R^1=R^3=R^4=OMe; R^2=Me; R^5=H
(-)-Norarmepavine: R^1=R^4=OMe; R^2=R^3=R^5=H
(-)-*Trimetoquinol*: R^1=OH; R^2=H; R^3=R^4=R^5=OMe

Reagents and conditions: (i) 1. Br_2, light; 2. (*R*)-Phenylglycinol, EtOH, rt.; 3. Et_3N, -78 °C. (ii) R^2MgX or $ArCH_2Ti(O^iPr)_3$, Et_2O, -78 °C. (iii) H_2, Pd/C.

Scheme 12

These tricyclic derivatives were subjected to nucleophilic addition with different Grignard reagents to afford, after removal of the chiral appendage by a simple hydrogenolysis procedure, the target 1-alkyltetrahydroisoquinolines in good to excellent enantiomeric excesses. This methodology allowed the authors to synthesize the biologically active products (-)-*salsolidine*,[38c] (+)-*cryptostyline II*,[38c] and (-)-*homolaudanosine*.[38c] In the same way, the use of benzyltitanium reagents as nucleophiles allowed the preparation of (-)-*laudanosine*, (-)-*norarmepavine* and (-)-*trimetoquinol*.[40] Alternatively, Roussi has applied the same strategy for the asymmetric synthesis of (+)-*cryptostyline I,* although the employed synthetic pathway to the key oxazoloisoquinolines was slightly different (Scheme 12).[41]

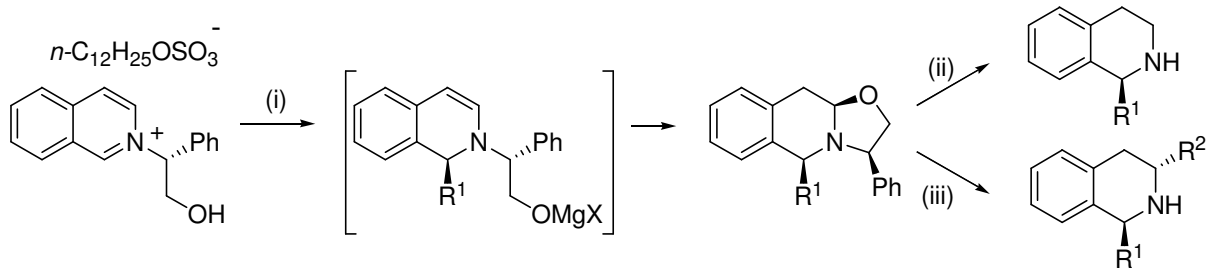
Similarly, Kibayashi has applied this methodology to the addition of Grignard reagents to chiral hydrazonium ions derived from *O*-protected prolinol, which were prepared starting from the corresponding *N*-formyl hydrazine *via* Bischler-Napieralsky cyclization.[42] The nucleophilic addition of the corresponding organometallic reagent led to the obtention of enantioenriched 1-alkyltetrahydroisoquinolines after removal of the chiral appendage by means of reductive N-N bond cleavage. Alternatively, the same compounds were obtained by Lewis acid promoted nucleophilic addition of Grignard reagents to [6,3a,4]oxadiazaindano[5,4-*a*]isoquinolines, which were prepared starting from the corresponding 2-(2-bromoethyl)benzaldehydes and (*S*)-*N*-aminoprolinol.[43] The synthetic potential of this method was demonstrated with the total synthesis of (-)-*salsolidine* (Scheme 13).



Reagents and conditions: (i) $POCl_3$, benzene, refl. (ii) R^2MgX, THF, -50 °C. (iii) BH_3, THF, refl. (iv) (*S*)-*N*-amino-*O*-benzylprolinol, toluene, refl. (v) 1. (*S*)-*N*-aminoprolinol, AcOH, EtOH; 2. Et_3N. (vi) R^2MgX, Et_2AlCl, THF, -80 °C.

Scheme 13

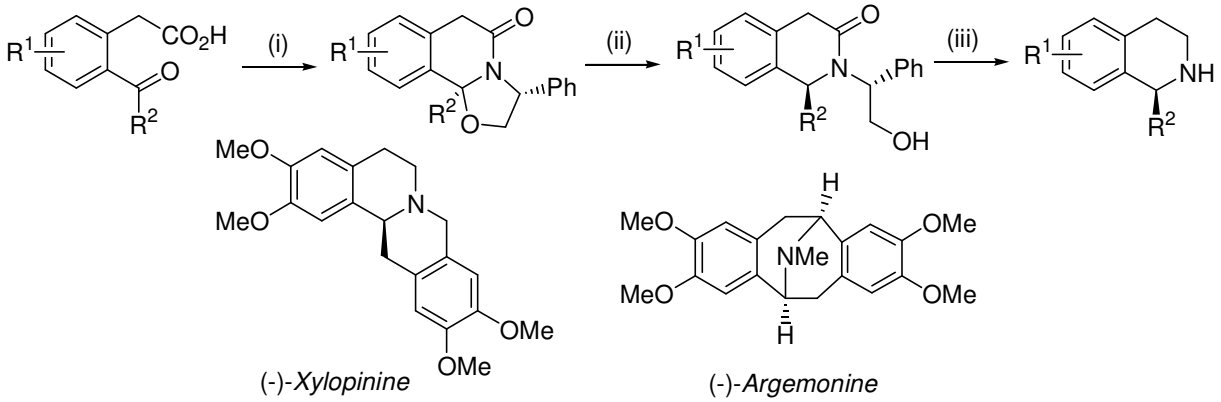
In the same way, isoquinolinium salts derived from (*R*)-phenylglycinol have been employed as suitable chiral starting materials which are prone to undergo nucleophilic addition with carbon nucleophiles,[44] thus allowing the preparation of 1,2-dihydroisoquinolines, which yield the final 1-substituted heterocycles in high enantiomeric excess after C=C bond reduction.[45] Besides, these 1,2-dihydro derivatives are also appropriate compounds to undergo a second base cyclization procedure, in order to afford an oxazolo[2,3-*b*]isoquinoline that can undergo alkylation with a second Grignard reagent, yielding 1,3-disubstituted tetrahydroisoquinolines. This procedure has also been applied to the asymmetric synthesis of (-)-*salsolidine*. More recently, other authors have reached to chiral nonracemic 1-benzyltetrahydroisoquinolines, which have been prepared by diastereoselective reduction of 1-benzyl substituted 1,2-dihydroisoquinolinium salts derived from phenylglycinol (Scheme 14).[46]



Reagents and conditions: (i) R^1MgX, THF, 0 °C (ii) 1. $NaBH_4$, AcOH, THF; 2. H_2, Pd/C. (iii) 1. R^2MgX, toluene, 0 °C; 2. H_2, Pd/C.

Scheme 14

In a similar context, Meyers has also successfully employed his bicyclic lactam methodology[47] to the asymmetric synthesis of 1-substituted tetrahydroisoquinolines.[48] According to this procedure, a properly substituted δ-ketoacid reacted with (*S*)-phenylglycinol affording the key chiral nonracemic bicyclic lactam which, upon diastereoselective reduction with a hydride reagent, yielded the corresponding 1-substituted tetrahydroisoquinolin-3-one as a single diastereoisomer. Further reduction of the amide moiety and removal of the *N*-substituent furnished the final compounds. This methodology has been applied to the asymmetric synthesis of the natural tetrahydroisoquinolines (-)-*salsolidine*,[48] (+)-*cryptostyline II*,[48] the protoberberine (-)-*xylopinine*[49] and the pavine (-)-*argemonine* (Scheme 15).[49]

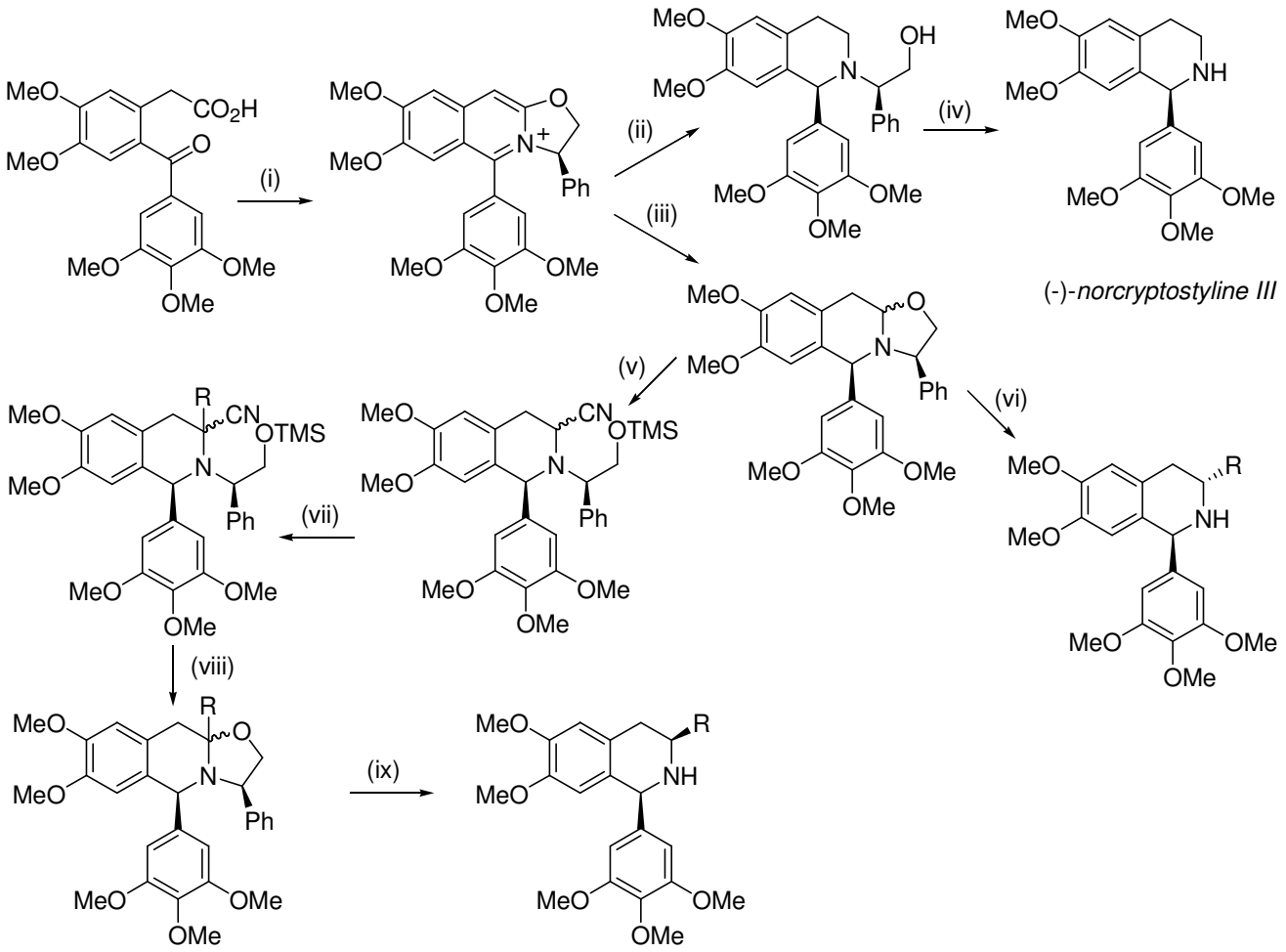


Reagents and conditions: (i) (*S*)-Phenylglycinol, toluene, refl. (ii) Red-Al, THF, -30 °C. (iii) 1. $LiAlH_4$, THF, rt.; 2. H_2, Pd/C.

Scheme 15

Chiral nonracemic 1,3-disubstituted tetrahydroisoquinolines have also been prepared in an similar way by Husson using his CN(*R,S*) method.[50] The condensation of the properly substituted δ-ketoacid with (*S*)-phenylglycinol led to the corresponding amide, which was cyclized to the corresponding isoquinolinium salt by treatment with TFA. Diastereoselective reduction of this synthetic intermediate afforded, depending upon the conditions employed, fully reduced 1-substituted tetrahydroisoquinoline (-)-*norcryptostyline III* or an oxazolo[2,3-*b*]isoquinoline as a result of a single reduction step.[51] In the same way as previously indicated, the later is a suitable substrate to undergo nucleophilic addition with carbon nucleophiles, thus leaving to 1,3-trans disubstituted tetrahydroisoquinolines. Now, application of the CN(*R,S*) method allowed the synthesis of the 1,3-*trans* diastereoisomers starting from the same chiral synthetic intermediate.[52] The

authors applied the same methodology for the asymmetric synthesis of hydroxylated analogues of *podophyllotoxin*,[53] an antitumour benzoquinolizidine alkaloid (Scheme 16).



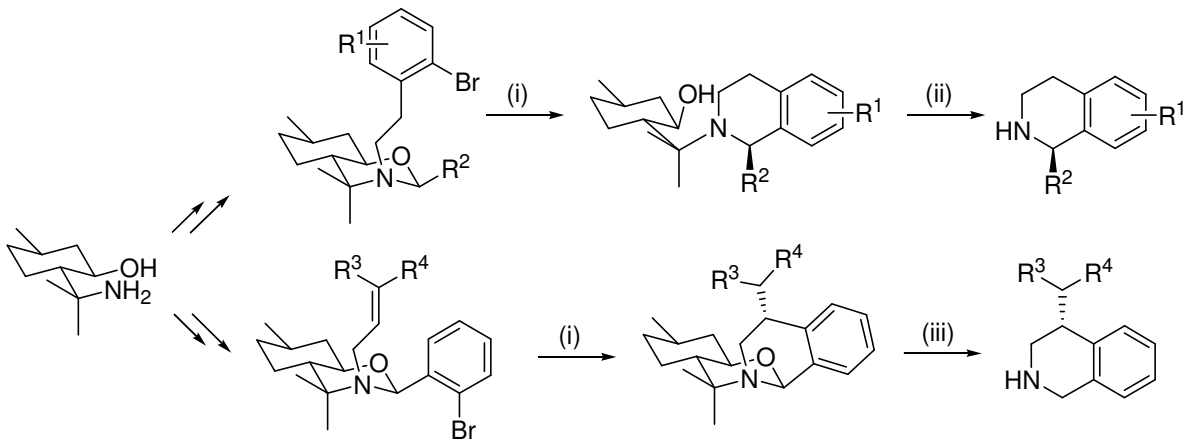
Reagents and conditions: (i) 1. (*R*)-phenylglycinol, DCC, C_6F_5OH rt; 2. TFA, toluene, refl. (ii) $NaBH_4$ (8 eq.), MeOH, rt. (iii) $NaBH_4$ (4 eq.), MeOH, -10 °C. (iv) H_2, Pd/C. (v) TMSCN, toluene, $AlCl_3$, rt. (vi) 1. RMgX, toluene, $AlCl_3$, rt; 2. H_2, Pd/C. (vii) LDA, RX, THF, -78 °C. (viii) HF, CH_3CN, rt. (ix) 1. $NaBH_4$, TFA, THF, 0 °C; 2. H_2, Pd/C.

Scheme 16

The nucleophilic ring-opening reaction of aminoalcohol-derived cyclic *N*,*O*-acetals has also been brightly employed by Pedrosa for the synthesis of 1-alkyltetrahydroisoquinolines using a conceptually different approach.[54] In this report, aryllithium reagents undergo intramolecular addition to a conveniently located N,O-acetal derived from (-)-8-aminomenthol. The final compounds were obtained after removal of the chiral appendage by oxidation/hydrolysis. Analogously, 4-substituted derivatives have been prepared by intramolecular carbolithiation with a double bond moiety linked to the nitrogen substituent (Scheme 17).[55]

(*R*)- and (*S*)-Phenylglycinol have also been extensively used as chirality sources in the synthesis of piperidines and piperazines in an optically active form by diastereoselective alkylation of lactams based on the already mentioned aminoalcohols.[56] This methodology has found further application in the asymmetric synthesis of 4-substituted tetrahydroisoquinolines. In this case, the commonly used methodology involves

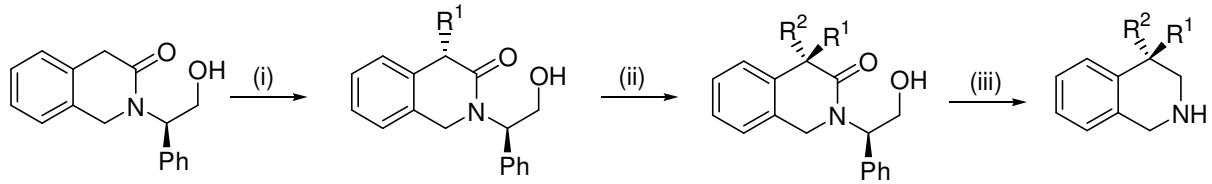
the use of the corresponding 1,2,3,4-tetrahydroisoquinolin-3-ones derived from (*S*)- or (*R*)-phenylglycinol which can be deprotonaded and alkylated with a variety of carbon electrophiles to afford the corresponding alkylation products.



Reagents and conditions: (i) 1. *t*-BuLi, Et_2O, -90 °C; 2. Et_2AlCl, -90 °C to rt. (ii) 1. PCC, NaOAc buffer, mol. sieves, CH_2Cl_2; 2. KOH, MeOH/THF. (iii) 1. $LiAlH_4$, $AlCl_3$, THF, -20 °C; 2. PCC, NaOAc buffer, mol. sieves, CH_2Cl_2; 3. KOH, MeOH/THF.

Scheme 17

Subsequent reduction of the amide function and removal of the chiral appendage by hydrogenolysis leaves to the target heterocycles. In this way simple 4-alkyl[57] or 4,4-dialkyl[58] substituted tetrahydroisoquinolines have been prepared in moderate to good optical purities. Conceptually similar is a later work, in which 4-aryl substituted tetrahydroisoquinolines, which are not susceptible to be prepared by alkylation of the aforementioned lactams, were prepared by deprotonation/diastereoselective protonation of the corresponding 4-aryl substituted analogues (Scheme 18).[59]



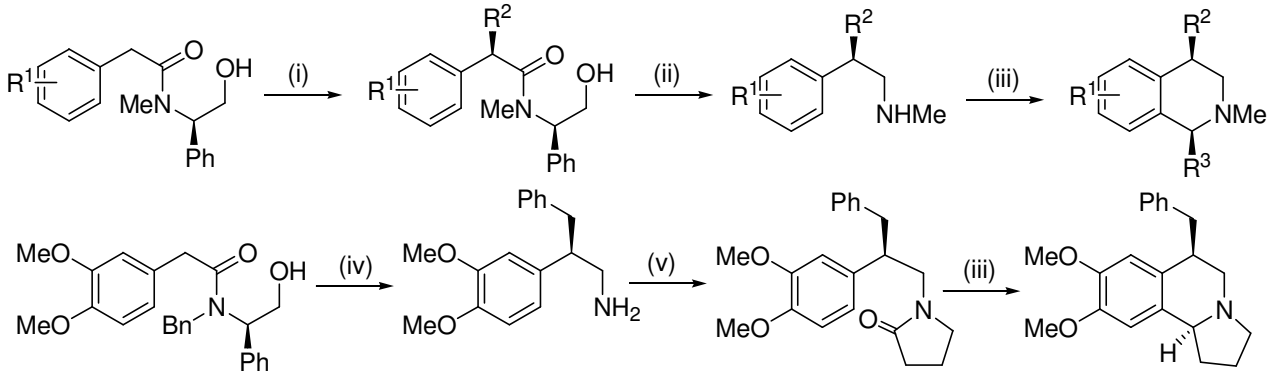
Reagents and conditions: (i) 1. LDA or LHMDS, THF, -78 °C; 2. R^1X. (ii) *n*-BuLi, HMPA, THF, -78 °C; 2. R^2X. (iii) 1. LAH, THF, refl.; 2. H_2, Pd/C.

Scheme 18

Applying this methodology to open-chain amides, the same authors succeeded in preparing enantioenriched 2-alkylphenethylamines,[60] which acted as versatile building blocks for the asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines. A Bischler-Napieralsky cyclization procedure was used for the building up of the heterocyclic core followed by diastereoselective reduction. This procedure was also applied to the asymmetric synthesis of a benzyl-substituted pyrroloisoquinoline (Scheme 19).[61]

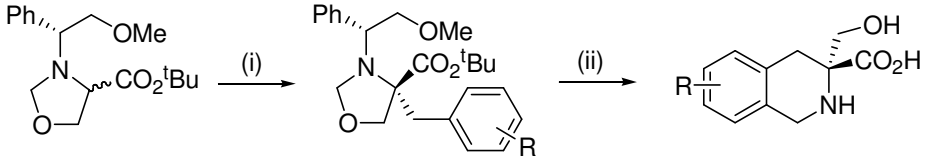
The *O*-methylated analogue of (*R*)-phenylglycinol has also been used as chirality source in the stereocontrolled synthesis of quaternary tetrahydroisoquinoline-3-carboxylic acid derivatives. In this

example, starting form the 3-*tert*-butoxycarbonyloxazolidine prepared from this aminoether, a diastereoselective alkylation with differently substituted benzyl iodides was performed as key step of the proposed synthesis. Next, a Lewis acid catalysed cyclization followed by removal of the chiral appendage by hydrogenolysis furnished the final heterocycles (Scheme 20).[62]



Reagents and conditions: (i) 1. *s*-BuLi, DMPU, THF, -78 °C 2. R^2X. (ii) 1. $LiALH_4$, THF, refl.; 2. H_2, Pd/C. (iii) 1. *N*-acylation; 2. $POCl_3$, toluene, refl.; 3. $NaBH_4$, MeOH, 0 °C. (iv) 1. *s*-BuLi, DMPU, THF, -78 °C; 2. BnCl.; 3. $LiALH_4$, THF, refl.; 4. H_2, Pd/C. (v) $Br(CH_2)_3CO_2Et$, DBU, EtOH, refl. (vi) 1. $POCl_3$, toluene, refl.; 2. $NaBH_4$, MeOH, 0 ºC.

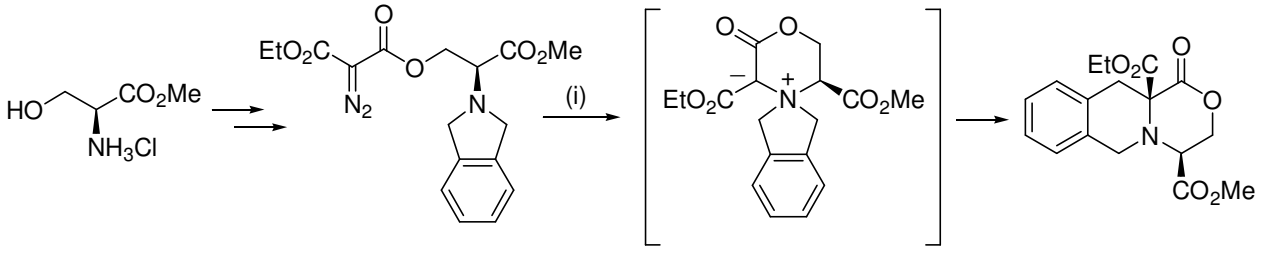
Scheme 19



Reagents and conditions: (i) 1. KHMDS, THF, -78 °C; 2. $ArCH_2I$. (ii) 1. $TiCl_4$, Et_3N, CH_2Cl_2, rt.; 2. H_2, Pd/C, $EtOH/H_2O$.

Scheme 20

The aminoacid L-serine has also been employed as chirality source for the asymmetric synthesis of isoquinoline alkaloids. Zaragoza has obtained enantiopure tetrahydroisoquinoline 3,3-dicarboxylates by [1,2]-Stevens rearrangement of spiroammonium ylides derived from dihydroisoindoles,[63] which were accessible by *N*-alkylation of *N*-alkyldihydroisoindoles with electrophilic rhodium carbenoids (Scheme 21).[64]

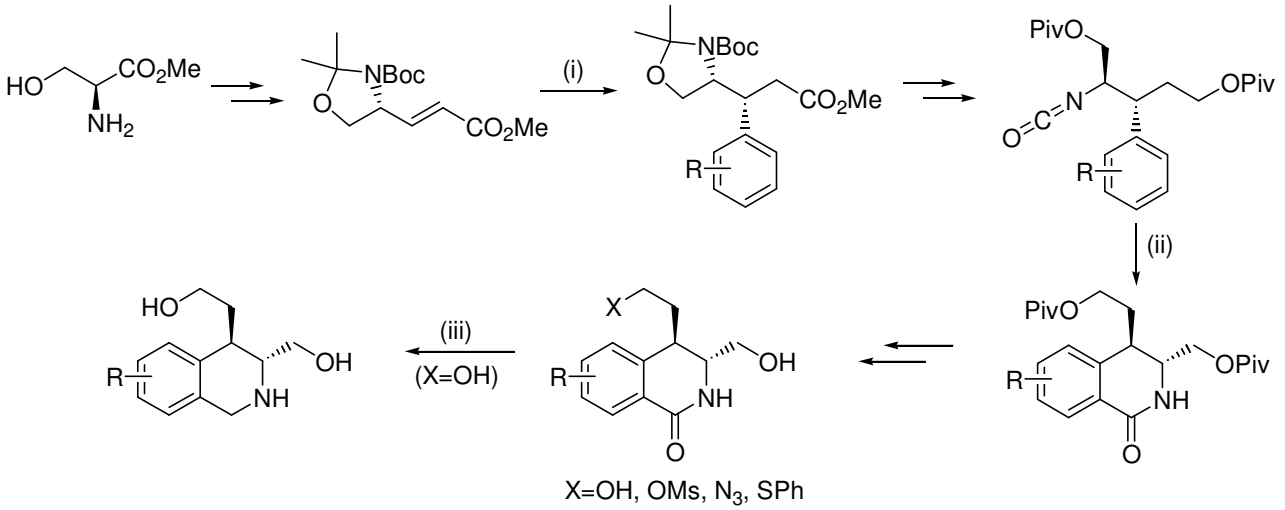


Reagents and conditions: (i) $Rh_2(OAc)_4$, CH_2Cl_2, refl.

Scheme 21

Hanessian has obtained highly functionalized chiral nonracemic 3,4-disubstituted tetrahydroisoquinolines started from the same aminoacid.[65] Key steps in this approach rely on a

stereocontrolled conjugate addition of diarylmagnesiocuprates to a chiral α,β-unsaturated ester derived from the starting material,[66] subsequent transformation of the amino group into the corresponding isocyanate and final Friedel-Crafts intramolecular cyclization to provide the key chiral nonracemic tetrahydroisoquinolin-1-ones. Further elaboration on these synthetic intermediates furnished the target heterocycles (Scheme 22).

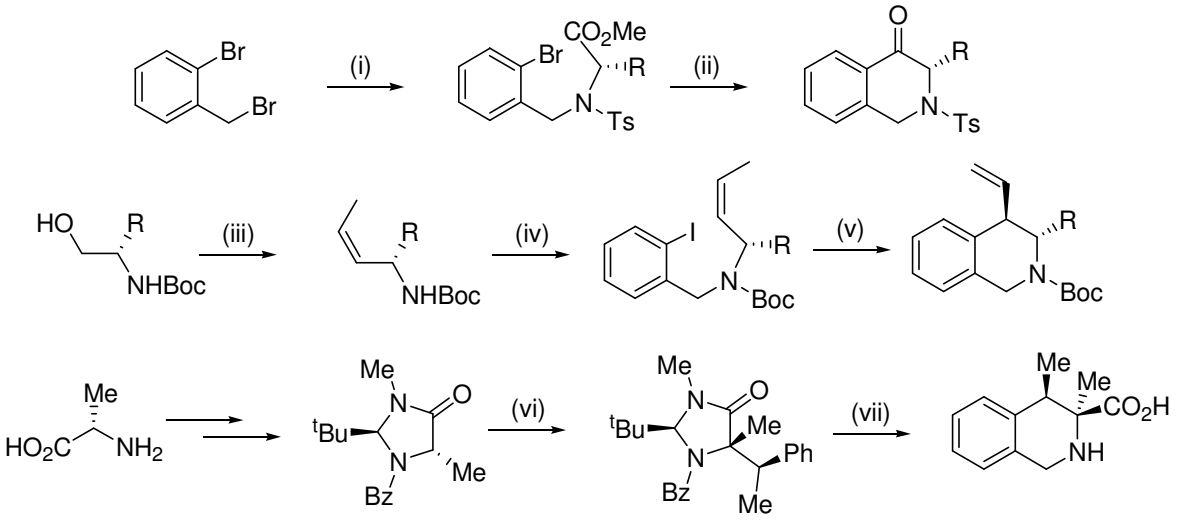


Reagents and conditions: (i) $Ar_2CuMgCl$, TMSCl, THF, -78 °C. (ii) $AlCl_3$, CH_2Cl_2, rt. (iii) $LiAlH_4$.

Scheme 22

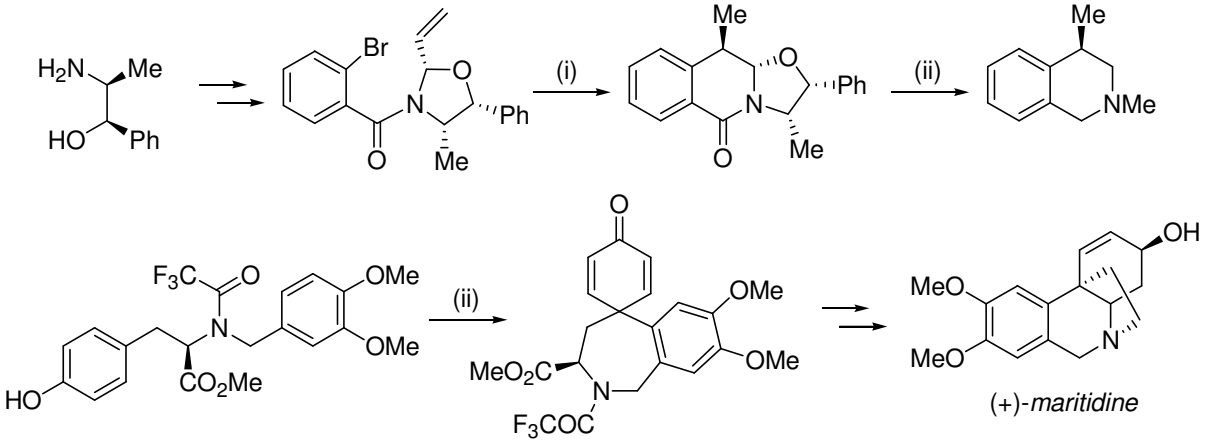
α-Aminoacids and their alcohol counterparts have also been incorporated as a part of the tetrahydroisoquinoline skeleton in the particular case of 3-substituted derivatives, in the sense that the substituent at the stereogenic centre at the 3 position results to be the aminoacid alkyl chain. This approach has been used by Liebscher, *via* intramolecular acylation of aryllithium reagents derived from *N*-(*o*-bromobenzyl)aminoesters.[67] Tietze has applied an intramolecular Heck reaction of N-(*o*-iodobenzyl)-*N*-allylamines, also prepared from chiral β-aminoalcohols, in order to reach to 3-alkyl-4-vinyl-1,2,3,4-tetrahydroisoquinolines in highly enantioenriched form[68] and in a different approach, Hruby has prepared 3,4-disubstituted tetrahydroisoquinolines starting from the corresponding chiral nonracemic 1,2-diarylethylamines *via* Pictet-Spengler reaction.[69] These key amines were prepared by alkylation of an alanine-based imidazolin-4-one enolate with racemic (1-bromo)ethylbenzene, which occurred together with a kinetic resolution process. In a more recent work, α-aminoacids have been incorporated into diketopiperazine-fused tetrahydroisoquinoline derivatives in which the heterocyclic core was built up by means of *N*-acyliminium chemistry (Scheme 23).[70]

Radical cyclizations have also been applied to the synthesis of isoquinoline heterocycles. Gennari and Scolastico have reported the asymmetric synthesis of 4-substituted derivatives *via* diastereoselective 6-*exo-trig* radical cyclization of a norephedrine-derived *o*-bromobenzamide.[71] This key reaction leaves to the corresponding tricyclic δ-lactam which, upon reduction/removal of the chiral appendage, afforded the enantiomerically enriched target compounds. In a different work, Kita and Zenk have described an easy and straightforward procedure for the stereocontrolled synthesis of (+)-*maritidine*, an amarillidaceae isoquinoline alkaloid, by oxidative phenolic coupling of a *N*-benzyl substituted *L*-tyrosine methyl ester derivative, using the hypervalent iodine(III) reagent PIFA as key step (Scheme 24).[72]



Reagents and conditions: (i) (*S*)-RCH(NHTs)CO_2Me, K_2CO_3, MeCN. (ii) *t*-BuLi, THF, -78 °C. (iii) 1. $(COCl)_2$, DMSO, NMM, CH_2Cl_2, -65 °C; 2. $NaNH_2$, $Br^-PPh_3P^+Et$, THF, -78 °C. (iv) 2-iodobenzyl iodide, KH, THF, 0 °C. (v) $Pd(OAc)_2$, PPh_3, KOAc, TPAB, DMF, 80 °C. (vi) 1. LDA, THF, -78 °C; 2. PhCH(Br)Me. (vii) 1. 6M HCl, refl.; 2. HCHO, concd. HCl, refl.

Scheme 23



Reagents and conditions: (i) Bu_3SnH, AIBN, benzene, refl. (ii) 1. $LiAlH_4$, $AlCl_3$, THF, -78 °C; 2. MeI, MeOH; 3. NaH, dioxane, refl. (iii) PIFA, CF_3CH_2OH, -40 °C.

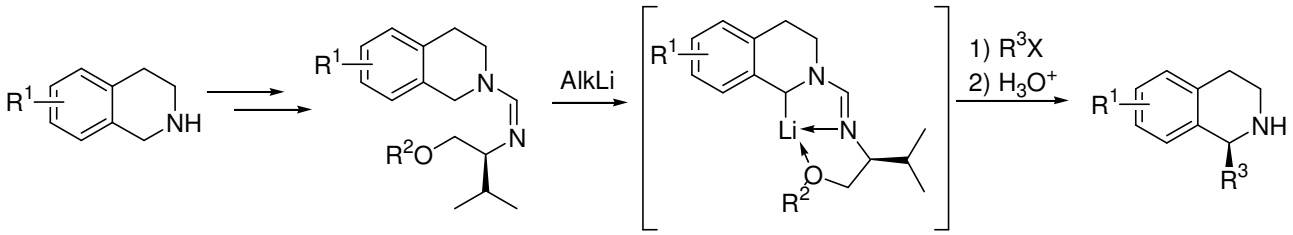
Scheme 24

1.2. β-Aminoalcohols and derivatives as chiral auxiliaries

Aminoalcohols can as well be employed as chiral auxiliaries, that is, as compounds that act as the source of chiral information during the creation of one or more stereogenic centres and which are subsequently removed and recovered, ready to be used again for further reactions. In this way, chiral β-aminoalcohols derived from natural α-aminoacids are promising candidates for these purposes because they are normally cheap reagents and are usually available in both enantiomeric forms.[73]

The most important contribution made in this field is the Meyers work related to the use of formamidines as chiral auxiliaries.[74] This methodology has proved to be extremely useful and versatile for the preparation of enantioenriched 1-substituted tetrahydroisoquinolines, which have also been employed as extremely useful synthetic intermediates for the preparation of a large variety of other isoquinoline alkaloids.

The designed strategy involves C-metallation/alkylation of a tetrahydroisoquinoline derivative which bears the chiral information linked to the nitrogen heterocycle in the form of a formamidine moiety, which derives from a chiral β-aminoalcohol, typically valinol *tert*-butyl or methyl ether. The presence of the formamidine moiety not only contributes to stabilize the formed carbanion but also provides a chiral environment *via* coordination of the ether moiety of the aminoalcohol chain to the metal center, therefore allowing stereochemical control on the incoming of the carbon electrophile (Scheme 25).[75]



Scheme 25

This methodology has successfully been applied by the authors to the synthesis of natural and unnatural products in high enantiomeric excess. Among them, the asymmetric synthesis of several isoquinoline alkaloids has been reported: 1-alkyltetrahydroisoquinolines like (-)-*salsolidine*, (+)-*homolaudanosine*[76] or (+)-*reticuline*,[77] protoberberines like (-)-*xylopinine*[74b] or (-)-*tetrahydropalmatine*,[78] aporphines like (+)-*ocoteine*,[79] (+)-*glaucine*[80] or (+)-*homoglaucine*,[80] isopavines like (-)-*O-methylthalisopavine* or (-)-*reframoline*[76] and the bis-isoquinoline alkaloid (-)-*emetine* (Figure 3).[81]

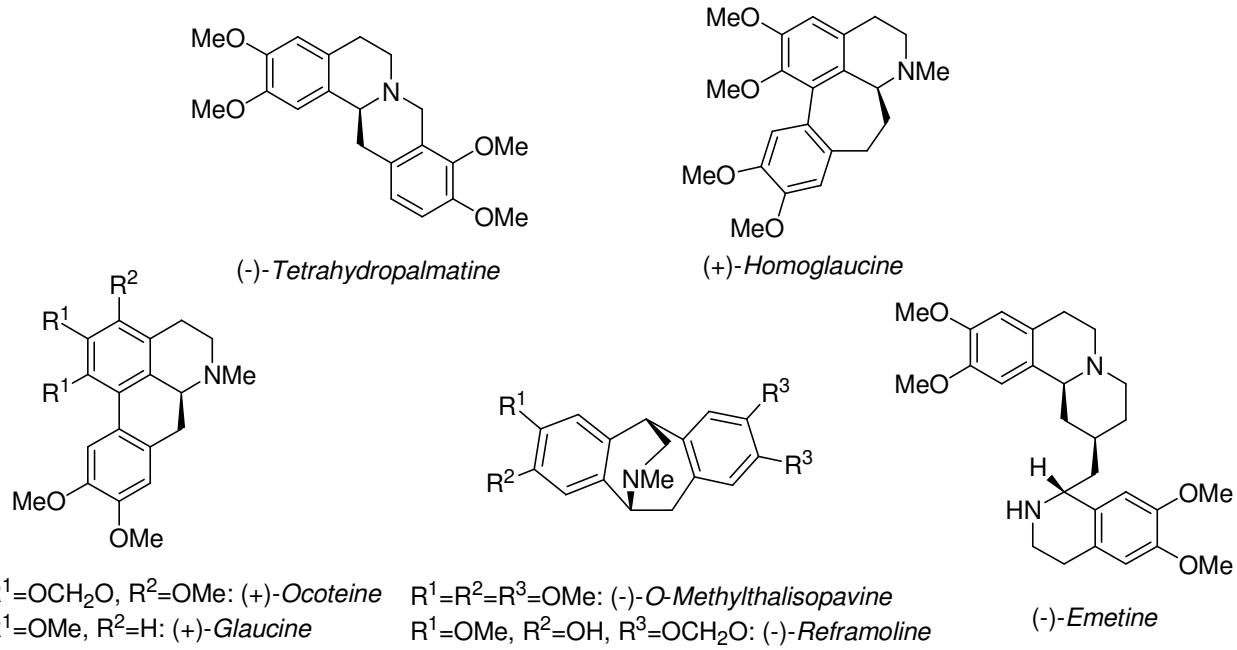
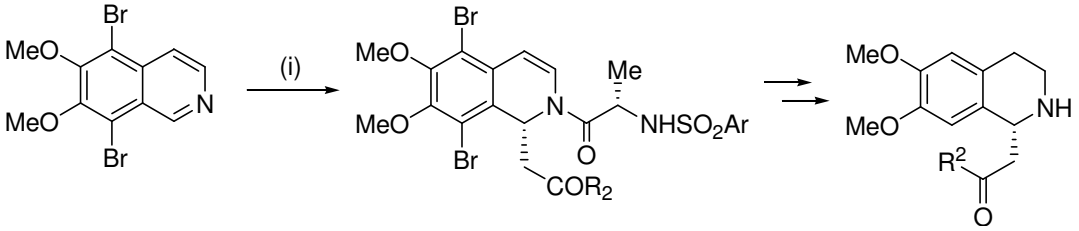


Figure 3

The other example of chiral auxiliary mediated asymmetric synthesis of tetrahydroisoquinolines found in the literature consists on the stereocontrolled addition of silyl enol ethers to isoquinolines in the presence of α-aminoacid-derived chiral acyl chlorides.[82] The procedure consisted on the activation of the

isoquinoline ring by *N*-acylation and the formed *N*-acyliminium ion subsequently underwent nucleophilic addition with several silyl enol ethers, thus furnishing 1-alkyl-1,2-dihydroisoquinolines with an excellent degree of diastereoselection. Next, hydrogenation of the intramoleculatr C=C bond was performed, followed by removal of the chiral auxiliary, leaving to simple 1-alkylated tetrahydroisoquinolines. This methodology was successfully applied to the total synthesis of (-)-*homolaudanosine* (Scheme 26).[83]



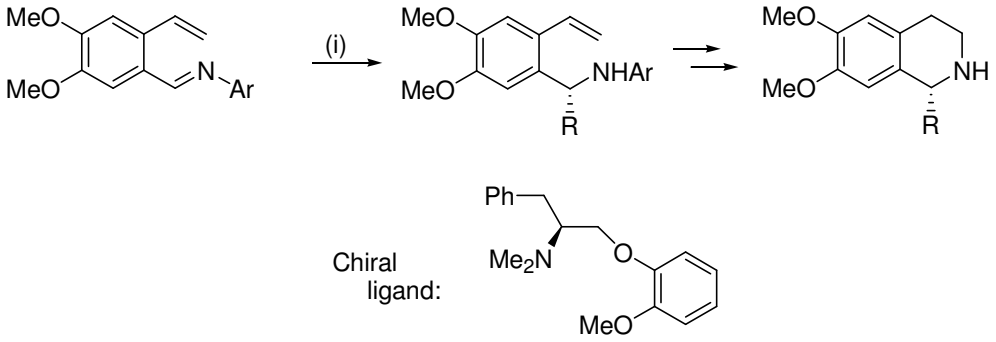
Reagents and conditions: (i) Silyl enol ether, (*S*)-*N*-(*p*-nitrophenylsulphonyl)alanyl chloride, CH_2Cl_2, -78 °C.

Scheme 26

1.3. β-Aminoalcohols and derivatives as chiral ligands

β-Aminoalcohols have also been employed as chiral ligands in the asymmetric synthesis of tetrahydroisoquinoline alkaloids. The efforts in this field belong mainly to the preparation of 1-substituted derivatives using chiral benzylamines as precursors. The preparation of these key chiral amines in an enantioenriched form involves an enantioselective 1,2-addition reaction of an organometallic species across the C=N bond of an aromatic imine or related species in the presence of the already mentioned chiral β-aminoalcohol or derivatives as ligands.

In this context, Tomioka has exploited the use of a phenylalaninol-based chiral ligand in the asymmetric addition of organolithium reagents to an adequately substituted *N*-aryl-*N*-benzylidenamine.[84] The addition proceeded with moderate to good enantioselectivity and the final 1-alkyl substituted tetrahydrosisoquinolines were obtained after hydroboration, followed by an oxidation/cyclization step and final removal of the *N*-aryl group.[85] This approach has been successfully applied to the asymmetric synthesis of (+)-*salsolidine* (Scheme 27).[86]

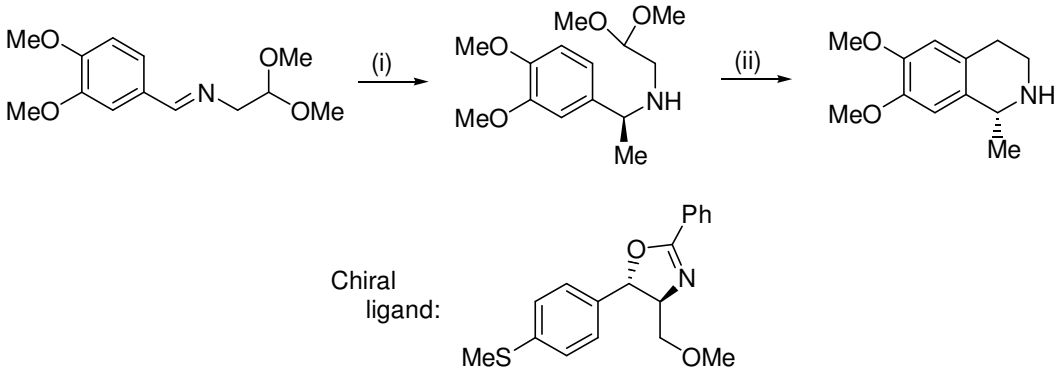


Reagents and conditions: (i) RLi, chiral ligand, toluene, -95 °C.

Scheme 27

In a similar approach, Rozwadowska has exploited the enantioselective addition of methyllithium to an imine derived from veratraldehyde and aminoacetaldehyde dimethylacetal (AADA). In this way, the obtained amine was susceptible to undergo Pommeranz-Fritsch cyclization to afford directly the desired 1-

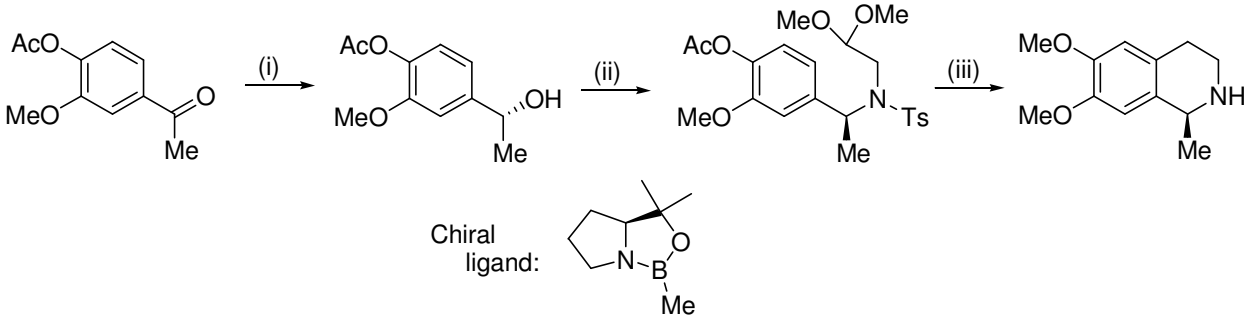
methyl-1,2,3,4-tetrahydroisoquinoline. The asymmetric addition reaction was carried out in the presence of different enantiopure oxazolidine derived from the aminoalcohol (+)-thiomicamine as chiral ligand (Scheme 28).[87] However, the enantioselectivity of the reaction was moderate and the obtained amines did not exceed 50% ee.



Reagents and conditions: (i) MeLi, chiral ligand, toluene, -65 °C. (ii) 1. 6M HCl, rt; 2. H_2, Pd/C.

Scheme 28

Finally, Kaufman has optimized a conceptually different design for the asymmetric synthesis of (-)-*salsolidine*. In this case, the key chiral starting material is a benzyl alcohol, which was prepared in an enantioselective way by oxazaborolidine-catalyzed asymmetric reduction of the corresponding aryl methyl ketone. The synthesis of the target heterocycle was completed by introduction of an aminoacetaldehyde moiety by Mitsunobu reaction, followed by Pomeranz-Fritsch cyclization (Scheme 29).[88]



Reagents and conditions: (i) $BH_3.SMe_2$, chiral ligand, THF, -20 °C. (ii) $TsNHCH_2CH(OMe)_2$, PPh_3, DEAD, THF, rt. (iii) 1. CH_2N_2, $EtOH/Et_2O$, pyridine, rt.; 2. 6M HCl, dioxane, refl.; 3. H_2, Pd/C; 4. Na/NH_3; 5. NH_4Cl.

Scheme 29

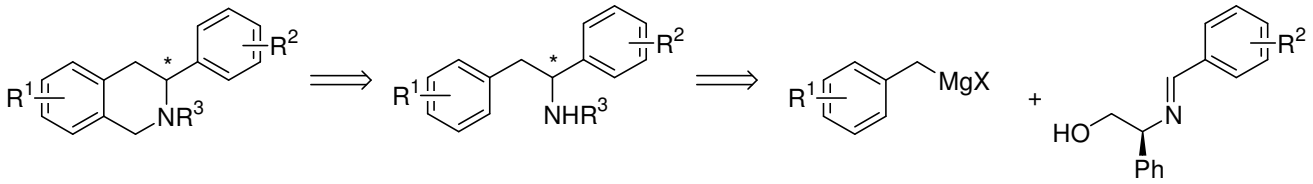
With all this efforts in mind, in the last years our research group has been engaged in a major effort directed towards the design of new general routes to the asymmetric synthesis of isoquinoline alkaloids using two β-aminoalcohols as chirality source: (*S*)-phenylglycinol and (*S,S*)-pseudoephedrine, both readily available from cheap commercial sources. The most important results obtained in the last years will be presented in the following pages.

2. (*S*)-Phenylglycinol as chirality source

2.1. Asymmetric synthesis of 3-aryltetrahydroisoquinolines

As it can be seen from the introduction, although chiral non racemic 3-aryltetrahydroisoquinolines are of considerable interest, both as a pharmacologically active compounds[89] as well as versatile building blocks for the preparation of other alkaloids like protoberberines, or benzo[*c*]phenanthridines,[90] the research towards their stereoselective synthesis is not as extended as in the case of the parent 1-substituted analogues. It is clear that some papers have appeared for the asymmetric synthesis of these derivatives when the substituent at C-3 bears an alkyl chain,[91] but only few reports can be found when at this specific position aryl moiety is located.[92]

As shown before, one of the most widely employed methods for the construction of the isoquinoline core involves a heterocyclization procedure using either Pictet-Spengler or Bischler-Napieralsky cyclizations and therefore, starting from chiral nonracemic 1,2-diarylethylamines, the already mentioned 3-aryl-1,2,3,4-tetrahydroisoquinolines should be accessible in an enantiopure form (Scheme 30). For that reason, the asymmetric 1,2-addition of a benzyl-type Grignard reagent across a C=N bond of an aromatic imine using (*S*)-phenylglycinol as chirality source should be a good approach for the obtention of these key 1,2-diarylethylamines in an enantioenriched form.

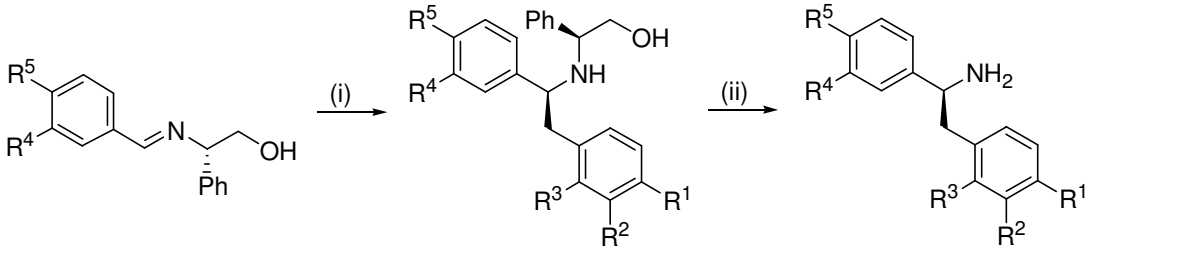


Scheme 30

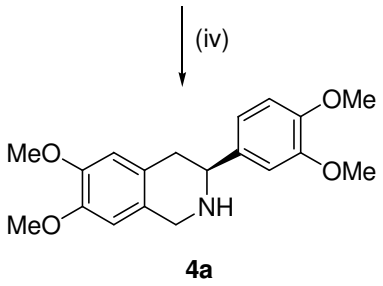
The synthesis of the 1,2-diarylethylamines **2a-d** (Scheme 31) started with the reaction between freshly prepared Grignard benzylic reagents and imines **1a-b**. These imines were synthesized, in turn, in good yields by condensation of the corresponding β-amino-alcohol (readily prepared by reduction of (*S*)-phenylglycine)[93] with aryl aldehydes in refluxing benzene. The so-obtained condensation derivatives were stable and proved to consist of the typical imine-oxazolidine tautomeric mixture.[94] The aldimines **1a-b** were assumed to be in the *E* configuration based upon the report by Hine[95] and ^{13}C-NMR studies which showed only a single resonance for the amino carbon (163 ppm). At this point, imines **1a-b** were submitted to addition reactions with various Grignard reagents, prepared *in situ*, exhibiting good to excellent levels of diasteroselection. The transformations were carried out with 5 equivalents of the organometallic reagent at -10 ^{o}C; then, the crude was later heated at 45-50 ^{o}C for 5 hours, quenched with ammonium chloride and worked up in the usual manner. Next, the chiral appendage was cleanly removed from (1*S*,1'*S*)-**2a-d** by hydrogenolysis, thus providing the corresponding primary (*S*)-amines **3a-d** in high yields without racemization. The optical purity in all the cases studied was shown to be greater than 94% by HPLC. Finally, the enantioselective preparation of the target (3*S*)-3-aryl-tetrahydroisoquinolines **4a-d** was accomplished by reaction of amines **3a-d**, with formaldehyde in acidic medium, thus, affording the target heterocycles in high yield (80%) and without racemization.

We presume that the remarkable stereocontrol observed in the alkylation reactions of imines **1a-b** can be attributed to the formation of an internal chelate between the magnesium atom of the Grignard reagent

with the hydroxy group and the lone pair electrons of the nitrogen atom. Thus, the *re* and *si* faces are differentiated towards the attack of the nucleophile because of the bulkiness of the group at the α position of the imines. Consequently, the attack of the nucleophile occurs from the less hindered *si-si* face of the C=N bond (Figure 4) leading to the (1*S*, 1'*S*) isomer formation.[96]



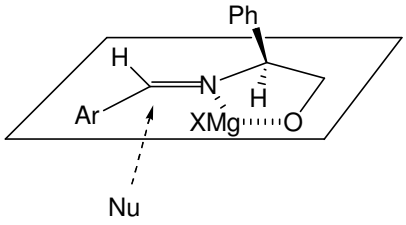
	R^1	R^2	R^3	R^4	R^5
3a	OMe	OMe	H	OMe	OMe
3b	H	OMe	OMe	OMe	OMe
3c	H	OMe	H	OMe	OMe
3d	OMe	OMe	H	OCH_2O	



4a

Reagents and conditions: (i) $ArCH_2MgCl$, THF, 40 °C. (ii) H_2, Pd/C, EtOH. (iii) HCHO, 1M HCl, 60 °C.

Scheme 31

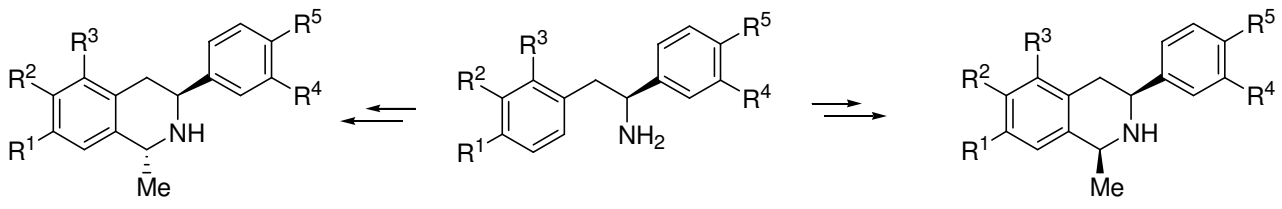


attack from *si-si* face

Figure 4

2.2. Diastereodivergent synthesis of 1,3-disubstituted tetrahydroisoquinolines

As already shown in the introduction,[97] some examples on the enantioselective syntheses of 1,3-disubstituted tetrahydroisoquinolines are known but, in all cases reported, alkyl but not aryl substituents were placed at C-3.

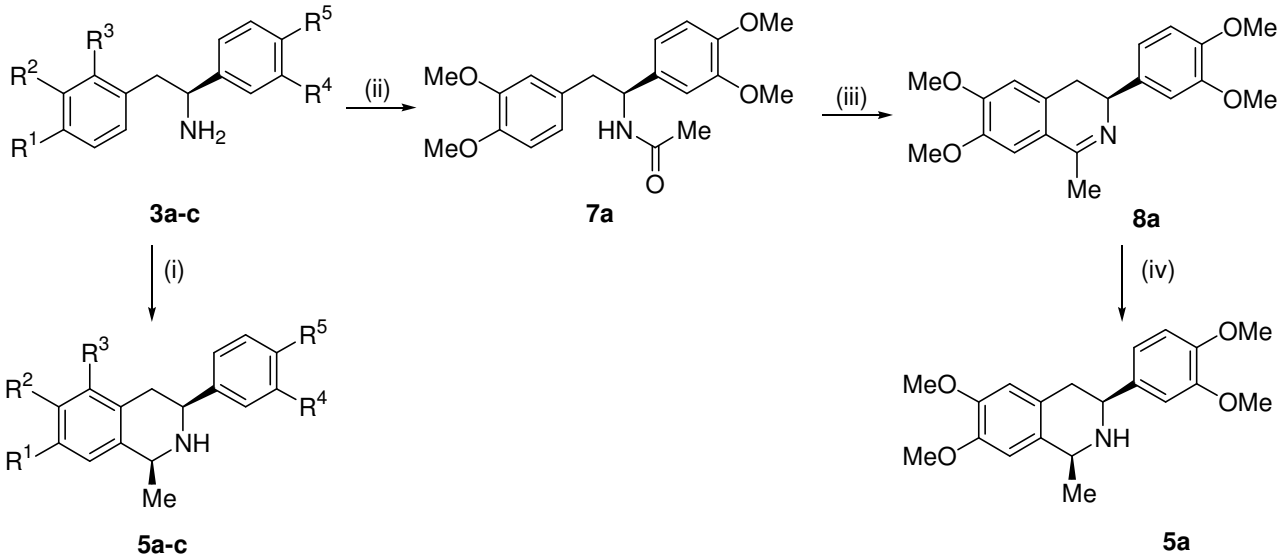


6 **3** **5**

Scheme 32

In this context, the chiral nonracemic 1,2-diarylethylamines **3** can be suitable starting materials for the stereocontrolled synthesis of C-1 substituted 3-aryl-1,2,3,4-tetrahydroisoquinolines and, by choosing the adequate reaction conditions for the formation of the isoquinoline ring, both epimers at the 1 position **5** or **6** can be obtained (Scheme 32).[98]

When 1,2-diarylethylamines **3a-c** were subjected to Pictet-Spengler cyclization under similar conditions as employed before (*vide supra*), but using acetaldehyde instead of formaldehyde, a series of (1*S*,3*S*)-1-methyl-3-aryl-tetrahydroisoquinolines **5a-c** were respectively obtained, in good yields (70-82%) and as a single enantiomer in each case. NMR studies (nOe experiments) proved the 1,3-*cis* relationship between the substituents at both stereogenic centres. This result can be explained by assuming that in the transition state the intermediate iminium salt is stabilized in a chair-like conformation with the aryl substituent in an equatorial position, and where the C=N bond adopts (*E*) configuration, as it has been previously rationalized for the cyclization of related compounds.[99] In this preferred conformation, the attack of the aryl ring leads to the observed stereochemistry in isoquinolines **5a-c**. Moreover, since the unique stereoisomer obtained is the less sterically hindered one, the corresponding heterocyclization reaction seems to be a thermodynamically controlled process.[97]

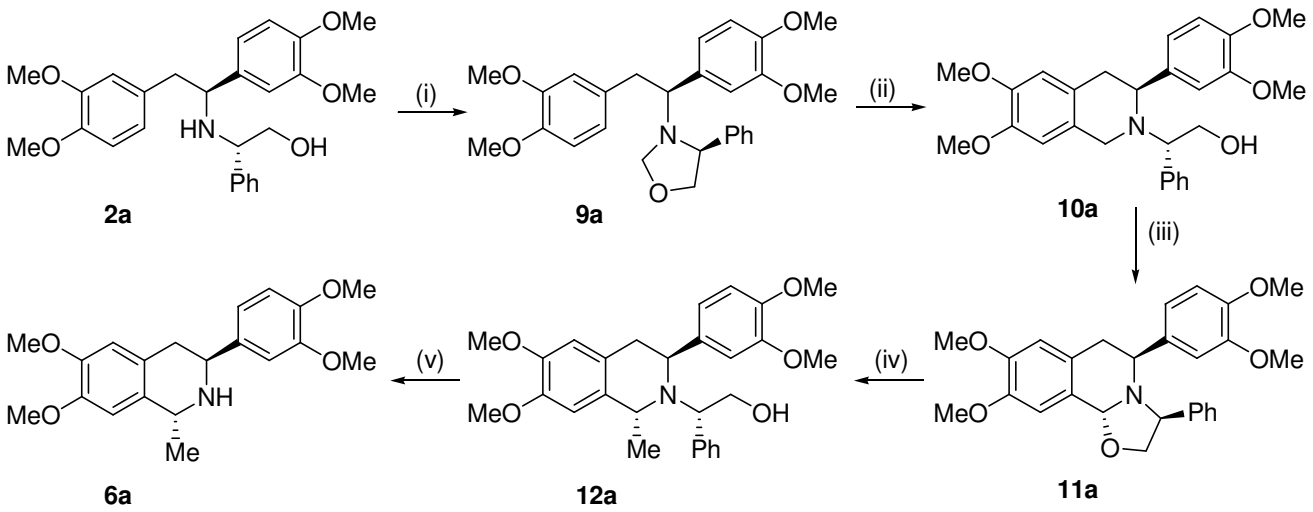


Reagents and conditions: (i) MeCHO, H_2SO_4. (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt.. (iii) PCl_5, MeCN. (iv) H_2, Pd/C or $NaBH(OAc)_3$, CH_2Cl_2, refl.

Scheme 33

Once the stereocontrolled synthesis of 1,3-*cis* disubstituted tetrahydroisoquinolines **5a-c** has been optimized, a second synthetic alternative was evaluated and optimized for the obtention of the corresponding 1,3-*trans* derivatives (Scheme 33). For that purpose, we first evaluated the Bischler-Napieralsky/reduction protocol and dihydroisoquinoline **8a** was prepared using amine **3a** as precursor *via* heterocyclization of the acetamide intermediate **7a**. The subsequent reduction of the azomethine function in dihydroisoquinoline **8a** was studied under different conditions. Disappointingly, the major diastereoisomer obtained in all cases was the 1,3-*cis* isomer **5a**, regardless the nature of the reducing agent (nucleophilic hydride source or catalytic hydrogenation).

In order to circumvent the difficulties found during the preparation of the target 1,3-*trans* disubstituted heterocycles **6**, a modified synthetic route was evaluated (Scheme 34). Oxazolidine **9a**, quantitatively prepared from the aminoalcohol precursor **2a** by reaction with aqueous formaldehyde, was heated in 1N HCl to attempt heterocyclization, yielding the expected tetrahydroisoquinoline **10a**. Thus, after oxidation and subsequent treatment with a base, the 5,10b-*trans*-oxazolotetrahydroisoquinoline **11a** (no nOe was observed between the protons at C-10b and C-5 or C-3) was obtained as a single diastereoisomer. To conclude the projected synthesis, the diastereoselective methylation of **11a** was performed by nucleophilic ring-opening reaction of the *N,O*-acetal moiety with MeMgBr, affording the target 1,3-disubstituted derivative **12a** which, after removal of the chiral appendage with H_2 (Pd-C), yielded the 1,3-*trans* tetrahydroisoquinoline **6a** (de >95% by ^{1}H-NMR). The observed stereocontrol at C-1 during the formation of tetrahydroisoquinoline **12a** can be attributed to the nucleophilic attack to the less hindered face of the developing iminium intermediate formed with simultaneous opening of the oxazolidine ring.[100] This stereochemical proposal was confirmed *a posteriori* by nOe experiments carried out on the final heterocycle **6a**.



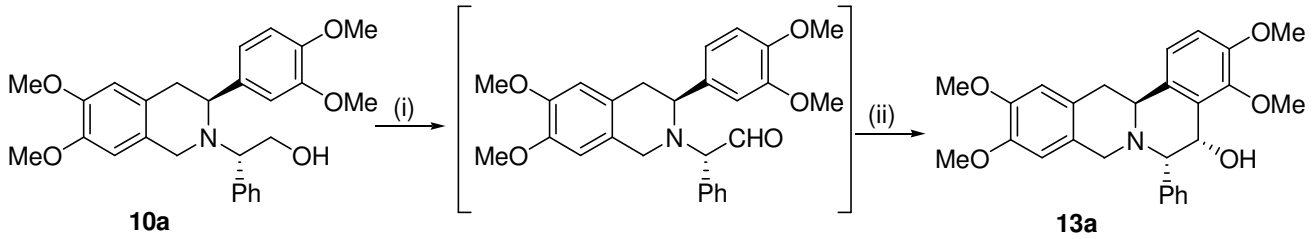
Reagents and conditions: (i) HCHO, CH_2Cl_2, rt. (ii) 1M HCl, 60 °C. (iii) 1. I_2, NaOAc, EtOH; 2. Et_3N, CH_2Cl_2. (iv) MeMgI, THF, 0 °C. (v) H_2, Pd/C.

Scheme 34

2.3. Asymmetric synthesis of protoberberines

Once the feasibility of the proposed strategies for the preparation of different non-racemic 1,3-disubstituted tetrahydroisoquinoline derivatives had been demonstrated, we moved to our next synthetic goal, which was the stereoselective synthesis of protoberberine derivatives of type **13** (Scheme 35). This protocol illustrates the possible diastereoselection that the presence of the adjacent asymmetric carbon would induce in the generation of the new stereogenic centre.

Thereby, the already available isoquinoline **10a** was oxidized under Swern conditions to give the corresponding labile α-aminoaldehyde.[101] When treating this compound with an acetone solution of aqueous HCl it was transformed into (5*S*,6*S*,14*S*)-5-hydroxy-6-phenyl-2,3,10,11-tetramethoxyprotoberberine **13a** with complete diastereoselection, as a result of a very effective 1,2-induction exerted by the presence of an adjacent stereogenic centre (de >95% by ^{1}H-NMR). The relative configuration at the newly created stereogenic centre accounts for the observation of an intense nOe between H-5 and H-6.

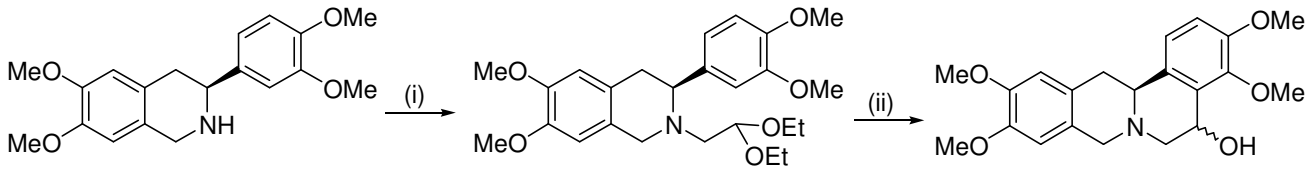


10a **13a**

Reagents and conditions: (i) DMSO, $(COCl)_2$, DIPEA, CH_2Cl_2, -40 °C (ii) 1M HCl/acetone, 0 °C.

Scheme 35

In order to confirm that the presence of a substituent (*i.e.* phenyl) adjacent to the new stereogenic centre was required to obtain diastereoselection in the above-mentioned synthesis of protoberberine **13a**, the following experiment was designed (Scheme 36). Acetal **14a**, prepared from tetrahydroisoquinoline **4a** by *N*-alkylation with bromoacetaldehyde diethylacetal (BADA), was submitted to the same cyclization conditions as mentioned above. In this case, the acidic treatment[102] of acetal **14a** yielded protoberberine **15a** as a separable 1:1 diastereomeric mixture of protoberberines **(*S,R*)-15a** and **(*S,S*)-15a** respectively, which resulted to be hydroxylated analogs of the naturally occurring protoberberine (-)-*xylopinine*. For both diastereoisomers, the ee (95%) was determined by chiral HPLC analysis under conditions optimized for racemic standard of each of them.



4a **14a** **(*S,R*)-15a** and **(*S,S*)-15a**

Reagents and conditions: (i) BADA, KOH, DMSO, rt. (ii) 1M HCl/acetone, 0 °C.

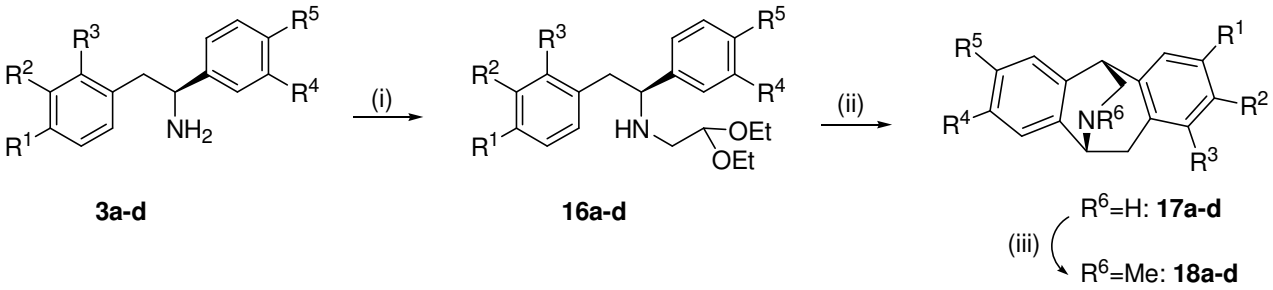
Scheme 36

2.4. Asymmetric synthesis of isopavines

Isopavines are a small group of natural products which have shown to display important pharmacological properties for the treatment of the nerve system disorders: Alzheimer's disease, Hungtington's chorea, amyotrophic lateral sclerosis and Parkinson's and Down's syndromes.[103,2] Few examples of syntheses of these compounds have been reported up to date.[104] Moreover, the enantioselective synthesis of isopavines has not been deeply developed yet, although their interest for future pharmacological studies should be emphasized. As far as we know, there is only one example in the literature where the synthesis of an enantiomerically enriched naturally occuring isopavine does not involve a resolution step of any of the intermediates[76] and furthermore, in all the cases reported, the final cyclization step takes place in moderate yields requiring rather long reaction times.

The projected synthesis is shown in Scheme 37 and starts from the chiral nonracemic 1,2-diarylethylamines **3a-d**.[105] These substrates were alkylated with bromoacetaldehyde diethyl acetal (BADA) to afford the corresponding acetals **16a-d** and, at this stage, isopavines **17a-d** were successfully obtained in one step by acid-catalyzed double cyclization. The observed behavior can be explained by assuming that the synthetic route involves two sequential electrophilic cyclizations probably through a 1-

benzyltetrahydroisoquinoline intermediate.[106] It is noteworthy to point out that, when compared with other previously reported synthesis of isopavines, the method employed by our group, which uses H_2SO_4/HOAc as cyclizing agent at room temperature, allows the preparation, in a short reaction time, of the isopavine framework in almost quantitative yield. Besides, racemization processes are not observed under the reaction conditions chosen. These conditions gave better results than other methods previously reported for this kind of double cyclization. Finally, in order to accomplish the final products, a *N*-methylation reaction was carried out, thus affording a series of *N*-methylated isopavines **18a-d** with optical purities greater than 94%. Noteworthy, two of these final compounds resulted to be the natural alkaloids (-)-*O-methylthalisopavine* (**18a**: R^1=R^2=R^4=R^5=OMe, R^3=H) and (-)-*amurensinine* (**18d**: R^1=R^2= OMe, R^3=H, R^4=R^5=OCH_2O).

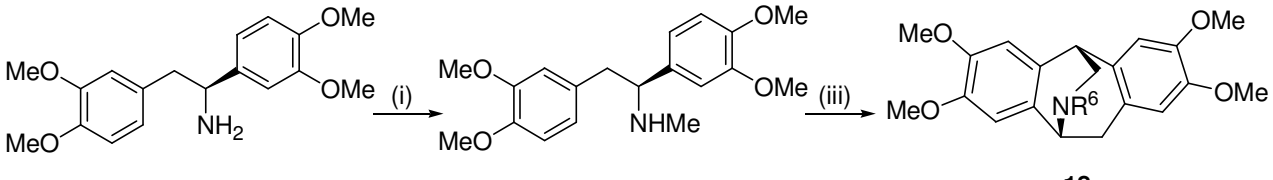


3a-d **16a-d**

Reagents and conditions: (i) BADA, Na_2CO_3, MeCN, refl. (ii) H_2SO_4/AcOH, rt.
(iii) $HCHO_{aq}$, $NaBH_3CN$, CH_3CN, rt.

Scheme 37

It should also be pointed out that an alternative sequence of steps in the route towards the synthesis of *N*-methylisopavines **18a-d** was also studied. In this case (Scheme 38), when the methylation step was carried out *prior* to the final cyclization process, a partial racemization was detected in the final product. This low optical purity was also observed in dialkylated amine **19a** and was calculated to be 88% ca. by HPLC.



3a **19a** **18a**

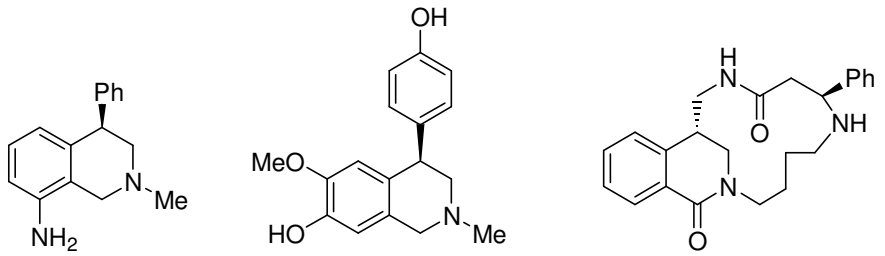
Reagents and conditions: (i) 1. $HCONMe_2$, 140 °C; 2. $LiAlH_4$, THF, refl.
(ii) 1. BADA, Na_2CO_3, MeCN, refl. 2. H_2SO_4/AcOH, rt.

Scheme 38

2.5. Asymmetric synthesis of 4-alkyl tetrahydroisoquinolines

Although 4-substituted tetrahydroisoquinoline derivatives are of considerable interest due to their biological activity and as naturally occuring alkaloids,[107] the research towards their stereoselective synthesis is not as extended as in the case of the 1-substituted tetrahydroisoquinolines. As seen in the introduction, some papers have appeared for the asymmetric synthesis of tetrahydroisoquinoline derivatives when the substituent at C-4 bears a hydroxy function but only few reports can be found when the substitution at this

position is not an heteroarom,[108] which occurs in nature quite often *e.g.* in *nomifemsine*, *cherylline* and the spermidine alkaloids *cyclocelabencine* and *isocyclocelabencine* (Figure 5).

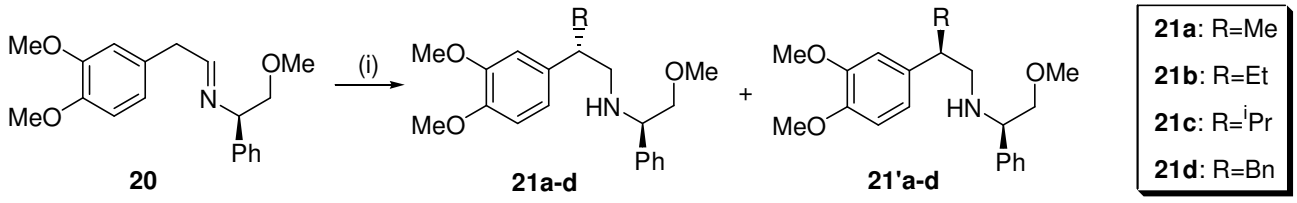


nomifemsine *cherylline* *cyclocelabencine*

Figure 4

In this context, we have developed a suitable and general enantioselective synthetic method to obtain simple 4-alkyl-1,2,3,4-tetrahydroisoquinolines starting from chiral arylethylamine precursors,[109] which were prepared employing an asymmetric metalloenamine alkylation protocol starting from an imine derived from homoveratraldehyde and (*R*)-(+)-phenylglycinol methyl ether.[110] The developed protocol is interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at the 4-position of the isoquinoline core. This can lead to the synthesis of a wide range of naturally and unnaturally occurring isoquinoline derivatives.

The starting imine **20** was subjected to deprotonation with LDA at –78 °C followed by alkylation with several alkyl halides at the same temperature and the crude reaction mixture was reduced *in situ* with $NaBH_4$ yielding the aminoethers **21a-d** in good yields and moderate to good diastereoselectivities (Scheme 39). Concerning to this topic, it was observed that when increasing the steric bulk of the incoming electrophile, the **21/21'** ratio became notably improved varying from 67/33 when R=Me to 93/7 when R=Bn. In all cases, it was possible to isolate and fully characterize each of the obtained diastereomers by flash column chromatography purification of the reaction crude. The stereochemistry of the newly created chiral centre in the major isomers **21a-d** was provisionally assigned as (*S*) attending to the mechanism proposed by Meyers for a similar case.[110h]



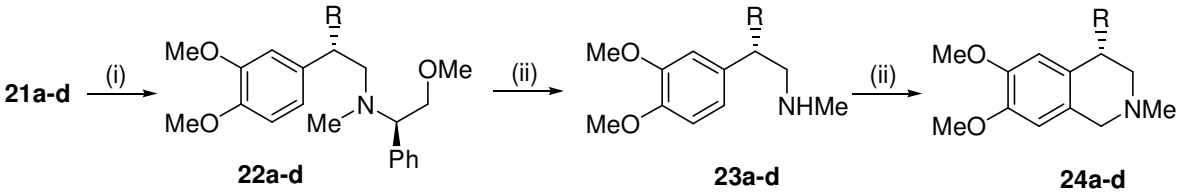
20 **21a-d** **21'a-d**

Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2. RX, THF, -78 °C; 3. $NaBH_4$, MeOH, -20 °C.

Scheme 39

Proceeding with the planned synthesis, the aminoethers **21a-d** were *N*-methylated under standard conditions and the obtained products **22a-d** were subjected to a hydrogenolysis procedure to remove the benzylic part of the chiral appendix, yielding the corresponding 2-substituted 2-arylethylamines **23a-d** in good yields (Scheme 40). Their analysis by chiral HPLC showed that they were obtained as only one detectable enantiomer, indicating that both processes, *N*-methylation and hydrogenolysis, proceeded without racemization in the previously formed chiral centre. The fact that amine **23a** is a known product[61] allowed us

to unambiguously establish the absolute configuration of its chiral centre by comparison of the obtained $[\alpha]_D^{20}$ value ($[\alpha]_D^{20}$=-16.3, *c*=1.75, $CHCl_3$) with the reported in the literature ($[\alpha]_D^{20}$=+13.0, *c*=1.75, $CHCl_3$ for the *R* enantiomer), thus confirming the previously assigned *S* configuration for **23a** and, by extension, to the rest of amines **23b-d** and all the obtained aminoethers **21a-d**, and **22a-d**. Finally, in order to complete the synthesis, the amines **23a-d** were converted into the target heterocycles by Pictet-Spengler heterocyclization reaction and the isoquinolines **24a-d** were obtained in excellent yields and again as only one detectable enantiomer as chiral HPLC analysis indicated.



Reagents and conditions: (i) $HCHO_{aq}$, $NaBH_3CN$, CH_3CN, rt. (ii) H_2, Pd/C. (iii) HCHO, 1M HCl, 60 °C.

Scheme 40

3. (*S*)-Arylglycinols as chiral templates

3.1. Synthesis of 3-aryl-4-hydroxytetrahydroisoquinolines

Tetrahydroisoquinoline-4-ol derivatives are of considerable interest due to their biological activity and as naturally occuring alkaloids[111] and, as shown before, some papers have appeared for the asymmetric synthesis of these kind of derivatives.[112] However, only few reports can be found when additionally the substitution at the 3-position is an aryl moiety,[113] which is found in nature quite often *e.g.* in the protoberberine alkaloids ophiocarpine or papaverberine among others (Figure 6).

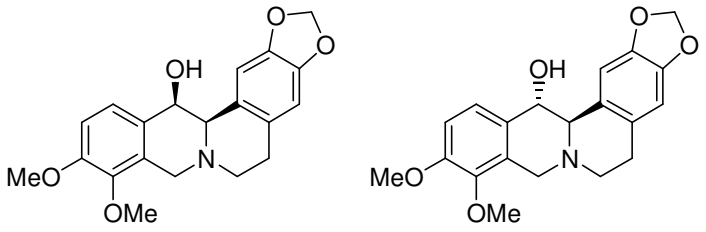


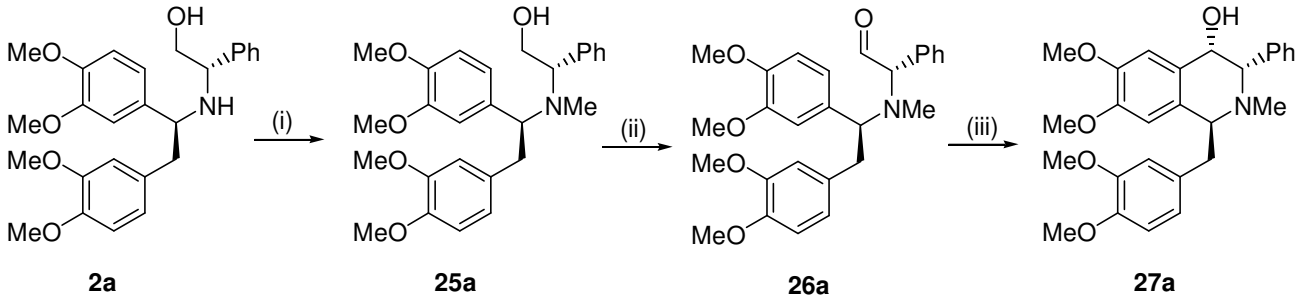
Figure 6

As previously demonstrated in the asymmetric synthesis of 3-aryltetrahydroisoquinolines, a suitable method, and one of the most widely employed one for the construction of the isoquinoline core involves an heterocyclization procedure using either Pictet-Spengler or Bischler-Napieralsky cyclizations. Therefore, starting from chiral nonracemic 1,2-diarylaminoethanols, the already mentioned 3-aryl-1,2,3,4-tetrahydroisoquinoline-4-ols should be obtained in an enantiopure form.[113b] However, the use of these cyclization procedures as key steps in the construction of the heterocyclic system has a very strong limitation, which is that the substitution pattern at the aromatic ring of the isoquinoline skeleton becomes imposed by the electronic requirements of the cyclization step. This, for example, makes these already mentioned procedures unviable for the synthesis of derivatives with any desired substitution pattern, and

becomes a very important problem when 7,8-disubstituted heterocycles have to be prepared,[114] which is the most common substitution pattern found in many of the isolated natural products belonging to this family. (see Figure 6).

A straightforward solution to this problem could be the use of an alternative heterocyclization procedure for the construction of the heterocyclic system and, in this context, the Pomeranz-Fritsch cyclization can be considered as a very promising tactic. In fact, the presence of the aminoalcohol moiety in aminoalcohols **2a-d** should allow us to use these compounds as suitable starting materials because hypothetical oxidation of the hydroxylic function should provide the α-aminoaldehyde moiety required for the Pomeranz-Fritsch cyclization.

This hypothesis was positively confirmed (Scheme 41) when aminoalcohol **2a** was *N*-methylated and oxidized under Swern reaction conditions to α-aminoaldehyde **26a**. Due to its lability, it was immediately made to react with an acetone solution of conc. HCl, yielding the corresponding tetrahydroisoquinolin-4-ol **27a** as the major 3,4-*cis* diastereoisomer (d.e.=80%), assigning the relative configuration of the major stereoisomer on the basis of nOe experiments. Thus, a 3,4-*cis* relationship between the substituents at C-3 and C-4 accounts for the observation of that effect between H-3 and H-4, as well as H-3 and the NMe group, which is in good agreement with the absence of nOe in the corresponding minor C-4 epimer.

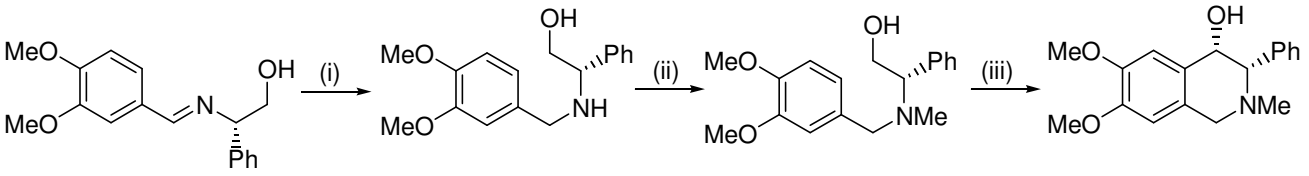


Reagents and conditions: (i) $HCHO_{aq}$, $NaBH_3CN$, CH_3CN, rt. (ii) DMSO, $(COCl)_2$, DIPEA, CH_2Cl_2, -40 °C. (iii) HCl/acetone, 0 °C.

Scheme 41

This approach was also applied to the asymmetric synthesis of 3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol,[115] the parent compound without substitution at the 1-position. For this purpose, (*S*)-phenylglycinol-based imine **1a** was used as starting material, which, upon reduction of the C=N bond furnished the corresponding amine **28a**. Next, *N*-methylation, Swern oxidation and acid-catalyzed cyclization afforded the isoquinolin-4-ol in good yield and as a single 3,4-*cis* diastereoisomer (Scheme 42).

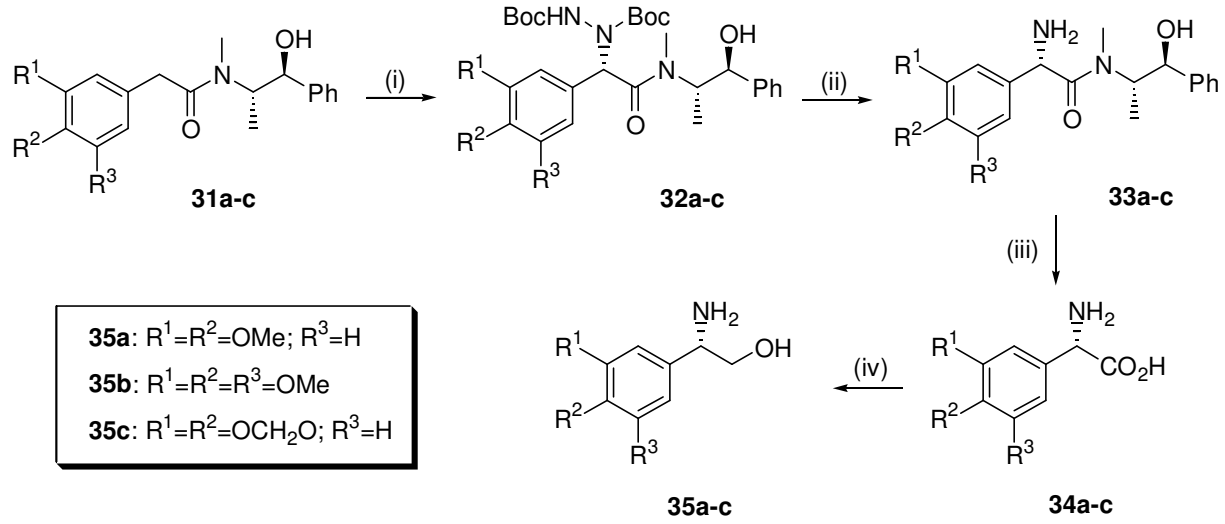
This strategy, in principle, would provide us an easy and straightforward access to tetrahydroisoquinolin-4-ols with any desired substitution pattern at the isoquinoline aromatic ring. However, the wanted 3-aryl substituent would be limited just to the phenyl ring due to the fact that phenylglycine (from which phenylglycinol is prepared) is the only commercially available arylglycine. Therefore, the development of a general procedure for the stereocontrolled synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols with any substitution pattern implies to have an easy and straightforward method for synthesizing arylglycines in an enantiopure form.[116]



Reagents and conditions: (i) $NaBH_4$, MeOH, rt. (ii) $HCHO_{aq}$, $NaBH_3CN$, CH_3CN, rt.
(iii) 1. DMSO, $(COCl)_2$, DIPEA, CH_2Cl_2, -40 °C; 2. HCl/acetone, 0 °C.

Scheme 42

In this context, and taking into account that many of the methods reported for the stereocontrolled synthesis of arylglycines,[117] although quite effective, they often require multistep syntheses, the use of highly toxic reagents, laborious separation of diastereoisomers, harsh reaction conditions or they lack of the required high chemo- and diastereoselectivity for subsequent synthetic purposes, we have recently developed a suitable, easy to perform and high-yielding procedure for the stereocontrolled synthesis of this particular kind of racemization-prone aminoacids (Scheme 43).[118] The access to these derivatives was achieved by means of a stereocontrolled amination reaction[119] of arylacetamide enolates using (*S,S*)-(+)-pseudoephedrine as chiral auxiliary as key reaction. Then, the *N-N* bond cleavage followed by hydrolysis of the obtained adducts would afford the wanted α-aminoacids which upon reduction under the usual conditions furnished the target arylglycinols **35a-c** in a highly enantioenriched form.

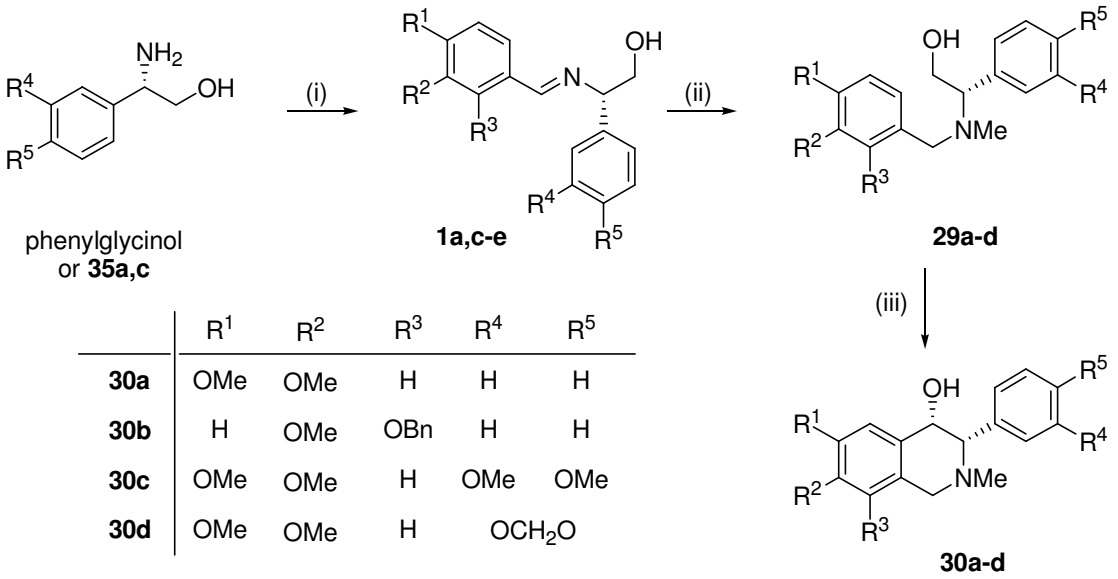


Reagents and conditions: (i) 1.LDA, THF, -78 °C; 2. BocN=NBoc, -105 °C. (ii) H_2, Ni/Raney.
(iii) 9M H_2SO_4, dioxane, refl. (i) $LiBH_4$, TMSCl, THF, 0 °C.

Scheme 43

Focussing now in the stereocontrolled synthesis of the target 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols, arylglycinols **35a,c** and the simple phenylglycinol were easily transformed into the corresponding *N*-benzyl derivatives **29a-d** by previous formation of an imine intermediate **1a,c-e** with a conveniently substituted aromatic aldehyde, followed by reduction with $NaBH_4$ and *N*-methylation (Scheme 44). Then, proceeding in the same way as previously indicated, Swern oxidation and final acid-catalyzed cyclization furnished the target 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols in good yields and high optical purity.

Remarkably, we were able to introduce an extended variety of different kind of substitutions at both the isoquinoline and the 3-aryl aromatic rings, including the valuable 7,8-disubstitution pattern (**30b**).



	R^1	R^2	R^3	R^4	R^5
30a	OMe	OMe	H	H	H
30b	H	OMe	OBn	H	H
30c	OMe	OMe	H	OMe	OMe
30d	OMe	OMe	H	OCH_2O	

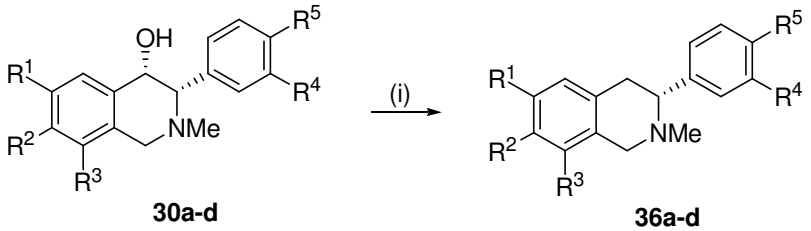
Reagents and conditions: (i) ArCHO, C_6H_6, refl. (ii) 1. $NaBH_4$, MeOH, rt. 2. $HCHO_{aq}$, $NaBH_3CN$, CH_3CN, rt. (iii) 1. DMSO, $(COCl)_2$, DIPEA, CH_2Cl_2, -40 °C; 2. HCl/acetone, 0 °C.

Scheme 44

3.2. General procedure for the asymmetric synthesis of 3-aryl tetrahydroisoquinolines

The 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols **30a-d** could constitute extremely useful starting materials for the synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines, provided that a procedure is found for removing the OH moiety present at C-4. This transformation was successfully achieved with the help of an ionic hydrogenation procedure, which has shown to be a very effective method to convert alcohols into alkanes, especially in the particular case of benzylic alcohols as it is our case.[120]

Therefore, isoquinolin-4-ols **30a-d** were treated with $NaBH_4$ in trifluoroacetic acid as solvent,[121] thus affording the desired reduced heterocycles **36a-d** in excellent yields and, which is more important, with no loss of optical purity which concerns to the stereogenic centre still present at C-3 in the final compounds **36a-d** (Scheme 45).



Reagents and conditions: (i) $NaBH_4$, TFA, CH_2Cl_2, 0 °C.

Scheme 45

This procedure results to be a complementary method for the stereocontrolled synthesis of 3-aryltetrahydrosioquinolines to the already employed (Section 2.1.), which proceeds *via* Pictet-Spengler

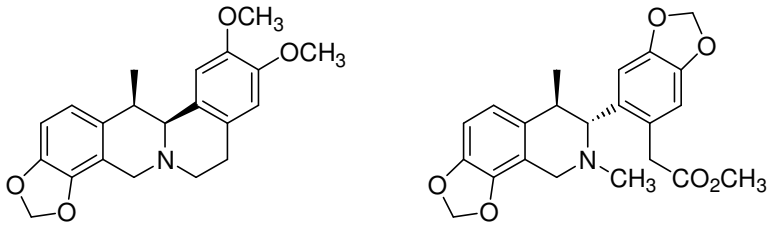
cyclization of 1,2-diarylethylamines **3a-d**. However, in former case, although more synthetic steps are required compared to the later, any desired substitution pattern can be introduced at the 3-aryl substituent and at the aromatic ring of the tetrahydroisoquinoline core.

4. (*S*,*S*)-(+)-Pseudoephedrine as chiral auxiliary

Pseudoephedrine, which is a cheap and commercially available reagent in both enantiomeric forms, has been recently used as chiral auxiliary in asymmetric enolate-addition reactions with excellent results.[122] In this context, we decided to engage in the task of applying the chemistry developed around this aminoalcohol as chiral auxiliary in enolate alkylation reactions to the asymmetric synthesis of tetrahydroisoquinoline alkaloids.

4.1. Asymmetric synthesis of 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines

As we have already showed, some papers have appeared for the asymmetric synthesis of tetrahydroisoquinoline derivatives when the substituent at C-4 bears an hydroxy function but only few reports can be found when the substitution at this position is an alkyl chain and none can be found in which additionally the substitution at the 3 position is an aryl moiety, which is also found in nature quite often e.g. in the protoberberine alkaloids *thalictrifoline* and *corydalin methyl ester* (Figure 7).



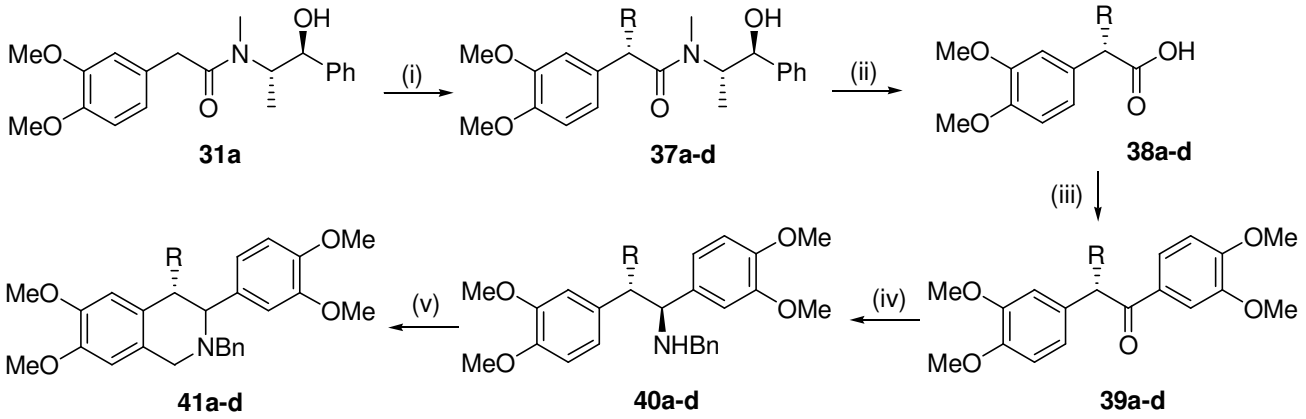
Thalictrifoline *Corydaline methyl ester*

Figure 7

In this context, we have developed a suitable and general stereoselective synthetic method to obtain 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines in which the key step concerning to the stereochemical control of the stereocentres present in the final compounds relies on the asymmetric alkylation of arylacetamide enolates using (*S,S*)-(+)-pseudoephedrine as chiral auxiliary.[123] The developed protocol is interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at the 4 position of the isoquinoline core and the high degree of stereoselectivity in which all the chiral centres in the molecule are generated.

The projected synthesis started with the already mentioned asymmetric alkylation of (*S,S*)-(+)-pseudoephedrine derived arylacetamide **31a** by kinetic deprotonation with LDA/LiCl in THF at -78 °C and followed by electrophilic attack of the corresponding alkyl halide to the formed dianion (Scheme 46). The diastereselectivity of this reaction was determined by ^{1}H-NMR spectroscopy and was found to be >95% in all cases. The relative stereochemistry of the final product resulted to be 1,4-*syn*, which was *a posteriori* confirmed on the arylacetic acids **38a-d** by chemical correlation.[124] The chiral inductor was cleanly removed by hydrolysis thus providing, after typical acid-base work-up, the α-alkylated arylacetic acids **38a-d** in

excellent yields. Additionally, from the extracts obtained from the aqueous basic layer it was possible to recover the chiral auxiliary (*S,S*)-(+)-pseudoephedrine in 88% yield after crystallization (hexanes/ethyl acetate 1:1) and without any racemization as the measurements of the $[\alpha]_D^{20}$ value indicated. Finally, the so obtained α-alkylated arylacetic acids were converted into the corresponding acid chloride derivatives and subjected to Friedel-Crafts acylation with 1,2-dimethoxybenzene (veratrole) using $AlCl_3$ as Lewis acid, yielding the corresponding ketones **39a-d** in good yields and with no loss of enantiomeric purity compared with the starting amides **37a-d**, as chiral HPLC analysis showed.



Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2. RI. (ii) 9M H_2SO_4, dioxane refl. (iii) 1. $SOCl_2$, CH_2Cl_2, refl.; 2. veratrole, $AlCl_3$, CH_2Cl_2, -20 °C. (iv) 1. $BnNH_2$, $TiCl_4$, Et_3N, CH_2Cl_2, -20 °C; 2. $NaBH_4$, MeOH, -20 °C. (v) HCHO, 1M HCl, 60 °C.

Scheme 46

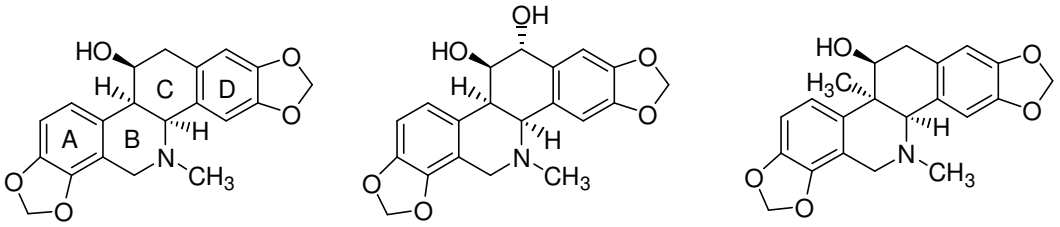
Proceeding with the synthesis, the ketones **39a-d** were converted into *N*-benzylketimine intermediates[125] which were reduced *in situ* with several reducing agents yielding the wanted 1,2-diarylethylamines **40a-d** as *N*-benzyl derivatives in good yields and with a variable diastereomeric ratio (*anti/syn* ratio ranging from 78:22 to 94:6). Among all the hydride reagents employed, the most efficient one was proved to be $NaBH_4$. Bulkier metal hydride reagents like sodium triacetoxyborohydride or lithium triethylborohydride were not able to react with the intermediate ketimines. The two obtained diastereoisomers were separated by flash column chromatography and it could be determined that the major product showed the relative stereochemistry of the two stereogenic centres to be *anti* from the value of the coupling constant $J_{(H\text{-}H)}$ between the two benzylic protons of the 1,2-diarylethylamine moiety. This could also be proved *a posteriori* in the stereochemistry of the final tetrahydroisoquinoline derivatives employing nOe difference experiments. As the absolute configuration of the remaining stereogenic centre at C-2 was already known and it remains unchanged, it can also be proposed a (*1S,2S*) absolute configuration for the *anti* 1,2-diarylethylamines **40a-d**. The choice of temperature when forming the intermediate imine was found to have a critical effect in the ee of the final product. At high temperatures the imine-enamine tautomerism takes place at a fast enough rate to allow notable racemization in the molecule but when lowering the temperature to -20 °C no racemization occurred and the wanted 1,2-diarylethylamines were obtained with no loss of enantiomeric purity compared to the starting ketones.

Finally, in order to complete the synthesis, the amines **40a-d** were subjected to the standard Pictet-Spengler cyclization procedure (Scheme 46), yielding the wanted 4-alkyl-3-aryl-1,2,3,4-

tetrahydroisoquinolines **41a-d** in excellent yield and with no racemization as the optical purity in all cases was shown to be higher than 99% by HPLC.

4.2. Asymmetric synthesis of B/C-hexahydrobenzo[*c*]phenanthridines

The B/C-hexahydrobenzo[*c*]phenanthridines are a group of isoquinoline alkaloids that naturally occur in papaveraceous and rutaceous plants[126] and are characterized by the basic skeleton shown in the examples of in Figure 8. Most of the members of this family have shown interesting antitumor[127] and antileukemic[128] properties as well as inhibiting HIV 1 and 2 reverse transcriptases.[129] However, toxicity problems have precluded their medical application.[130] As a result of that there is a growing interest in determining structure-activity relationships and in developing structural analogues of these compounds with improved pharmacological properties. Most of the synthetic studies on benzo[*c*]phenanthridines have been mainly focussed towards fully aromatised derivatives and only limited efforts towards the synthesis of B/C hexahydrobenzo[*c*]phenanthridines have been previously reported.[131] Additionally, just a few of them have been directed towards stereocontrolled procedures.[132]

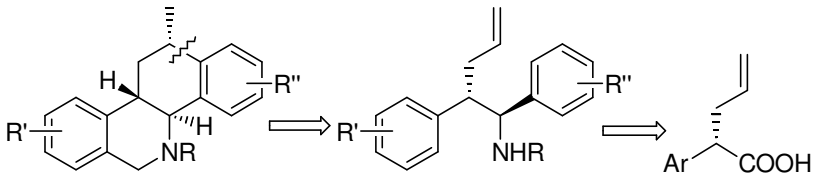


(+)-Chelidonine *(+)-Chelamine* *(+)-Corynoline*

Figure 8

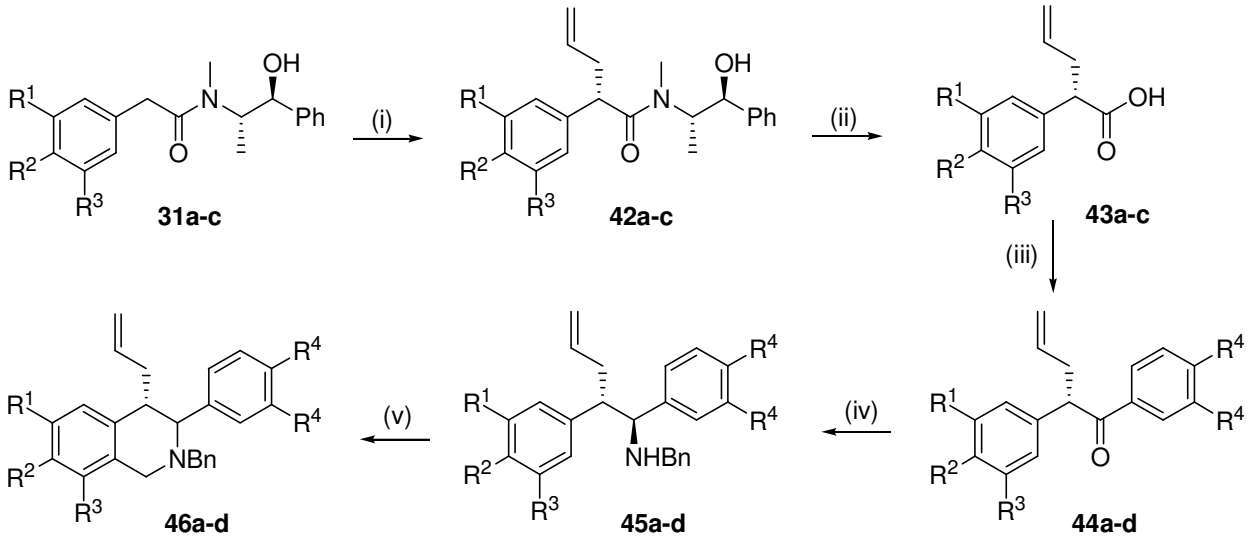
The basic benzo[*c*]phenanthridine skeleton should be accesible from a 3-aryl-1,2,3,4-tetrahydroisoquinoline, with an appropriately functionalized substituent at the 4-possition, which should be easily obtained in a stereocontrolled way by the methodology shown in section 4.1. Therefore, the designed synthetic pathway (Scheme 47) involves the introduction of an allyl group as the functionalized substituent in the 2-position of the starting (*S*,*S*)-(+)-pseudoephedrine arylacetamide. Subsequent hydrolysis and acylation followed by reductive amination of the resulting ketone would lead to the key 2-allyl-1,2-diarylethylamine precursor in which the configuration of the newly created stereogenic centre should be controlled by the other stereogenic centre present in the starting amide. Next, the B ring closure should leave to a 4-allyl functionalized 3-aryl-1,2,3,4-tetrahydroisoquinoline which on the last C ring formation step should give raise to the target heterocycles in which again a new stereogenic centre has been created during the cyclization having a well defined stereochemistry which has been controlled by the other stereogenic centres present in the molecule.[133]

Therefore, the starting arylacetic acid based pseudoephedrine amides **31a-c** were diastereoselectively alkylated with allyl bromide affording the corresponding alkylated amides **42a-c** in excellent yields and diastereoselectivities as could be seen by ^{1}H-NMR spectroscopy (Scheme 48). The stereochemistry of the newly created stereogenic centre was assigned as *S* as previously found for the alkylation of the same kind of substrates with similar carbon electrophiles.



Scheme 47

The resulting amides **42a-c** were hydrolized to yield the corresponding enantiomerically enriched 2-aryl-4-pentenoic acids **43a-c** after standard acid-base work-up procedure from which the basic aqueous layers it could be recovered pure (*S,S*)-(+)-pseudoephedrine in ca 83% yield and with no racemization which allows its recyclation for further uses. The acids **43a-c** were subjected to Friedel-Crafts acylation either with 1,2-dimethoxybenzene (veratrole) or 1,2-methylenedioxybenzene yielding the corresponding aryl benzyl ketones **44a-d** in excellent optical purities (ee >99%) as chiral HPLC analysis demonstrated. When methylenedioxy bridges were present either at the starting arylacetic acid (**44c**) or at the alkoxybenzene moiety (**44d**) the Friedel-Crafts acylation reaction had to be performed using $SnCl_4$ as the activating Lewis acid, because the use of $AlCl_3$ yielded mixtures of products in which the mentioned methylenedioxy bridge was broken.[134]

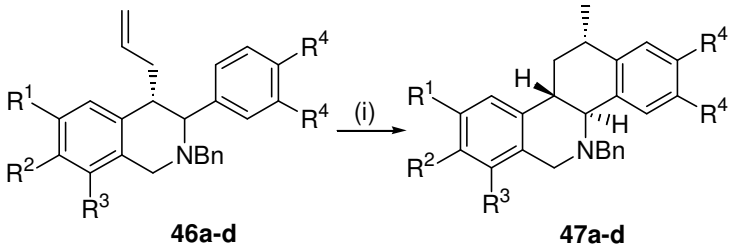


Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2. allyl bromide. (ii) 9M H_2SO_4, dioxane refl. (iii) 1. $SOCl_2$, CH_2Cl_2, refl.; 2. Arene, $AlCl_3$ or $SnCl_4$, CH_2Cl_2, -20 °C. (iv) 1. $BnNH_2$, $TiCl_4$, Et_3N, CH_2Cl_2, -20 °C; 2. $NaBH_4$, MeOH, -20 °C. (v) HCHO, 1M HCl, 60 °C.

Scheme 48

Continuing with the synthesis, the ketones **44a-d** were subjected to the next stereocontrolled reductive amination reaction (Scheme 48) yielding the wanted 1,2-diarylethylamines **45a-d** with an excellent degree of diastereoselectivity (*anti/sin* ratio 98:2) and again in excellent optical purities. The tetrahydroisoquinolines **46a-d** were then obtained by the subsequent standard Pictet-Spengler cyclization procedure (84-91% yield). The final cyclization step in order to obtain the desired benzo[*c*]phenanthridines was performed using acidic reaction conditions that lead to the formation of a carbocation at the alkene moiety followed by electrophilic aromatic substitution leading to the ring closure. In this way, treatment of

the isoquinolines **46a-d** with poliphosphoric acid (PPA) at 60 °C for 24h led to the obtention of the desired final heterocycles **47a-d** in excellent yields and optical purities, indicating that both Pictet-Spengler and PPA-catalyzed cyclizations proceed without racemization in any of the stereogenic centres present in the molecule. The last cyclization step showed to be highly diastereoselective as only one of the two possible epimers could be observed by ^{1}H-NMR. The stereochemistry of this newly created stereogenic centre was assigned to be (*S*) as nOe difference experiments indicated.



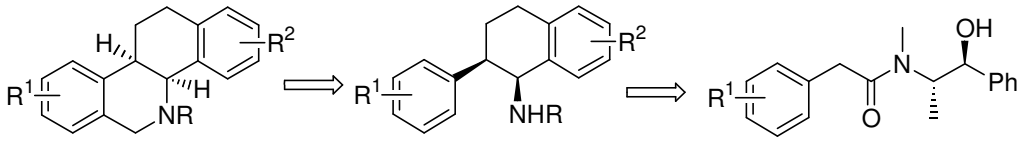
46a-d **47a-d**

	R^1	R^2	R^3	R^4	R^5
47a	OMe	OMe	H	OMe	OMe
47b	OMe	OMe	OMe	OMe	OMe
47c	OCH_2O		H	OMe	OMe
47d	OMe	OMe	H	OCH_2O	

Reagents and conditions: (i) PPA, 60 °C.

Scheme 49

Another approach to the benzo[*c*]phenanthridine skeleton could be the one envisaged in Scheme 50. As it can be seen in this scheme, the heterocyclic skeleton would be built up from a 2-aryl-1-naphtylamine which could be prepared by reductive amination of a chiral 2-tetralone. This ketone should be available in an enantiopure form by using our methodology of diastereoselective alkylation of (*S*,*S*)-(+)-pseudoephedrine based arylacetamides.



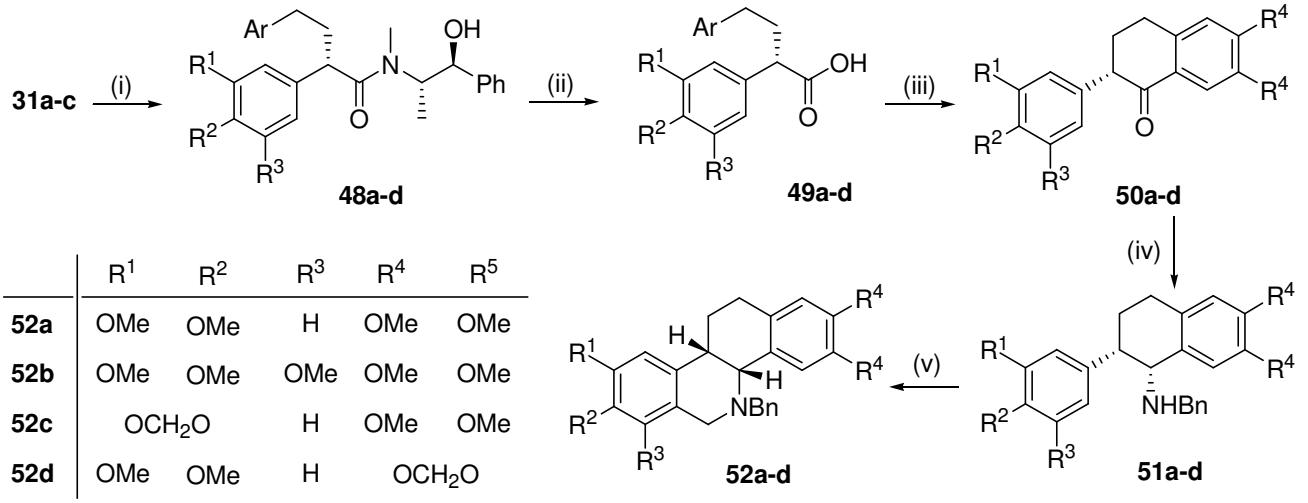
Scheme 50

The synthesis starts with the alkylation of the arylacetic based (*S,S*)-(+)-pseudoephedrine amides **31a-c** with 2-aryl-1-iodoethane derivatives yielding the final products in good yields and excellent stereoselectivities (Scheme 51). The amides **48a-d** were hydrolized to the corresponding acids **49a-d** and subjected to intramolecular Friedel-Crafts acylation reaction, yielding the wanted 2-aryl tetralones **50a-d** in more than 99% enantiomeric excesses, as chiral HPLC analysis showed. Again, the selected Lewis acid employed to activate the acyl chloride in the acylation reaction was critical and in the cases where methylenedioxy bridges were present in the substrates, the commonly used $AlCl_3$ had to be changed for the milder $SnCl_4$ Lewis acid.

Proceeding with the synthesis, the tetralones **50a-d** were subjected to the subsequent stereocontrolled reductive amination procedure and the wanted amines **51a-d** were obtained as the only detectable *syn* diastereoisomer from the two possible ones, concerning to the newly created stereogenic centre. Again, careful temperature control was necesary during all this procedure as when reaching temperatures over -20 °C epimerization was observed on the stereogenic centre of the starting tetralone.

The so obtained 2-aryl-1,2,3,4-tetrahydro-1-naphtylamines **51a-d** were subjected to a standard Pictet-Spengler cyclization procedure yielding the target heterocycles **52a-d** in high yields. The relative stereochemistry of the newly created stereogenic centre during the reductive amination step was determined

as *cis* by nOe difference spectroscopy experiments which also makes the stereochemistry of the B/C ring junction in the final benzo[*c*]phenanthridines to be *cis* and therefore the absolute stereochemistry of the stereogenic centres in the final heterocycles **52a-d** could be assigned as (4b*R*, 10b*S*).



	R^1	R^2	R^3	R^4	R^5
52a	OMe	OMe	H	OMe	OMe
52b	OMe	OMe	OMe	OMe	OMe
52c	OCH_2O		H	OMe	OMe
52d	OMe	OMe	H	OCH_2O	

Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2. $ArCH_2CH_2I$. (ii) 9M H_2SO_4, dioxane refl. (iii) 1. $SOCl_2$, CH_2Cl_2, refl.; 2. $AlCl_3$ or $SnCl_4$, CH_2Cl_2, -20 °C. (iv) 1. $BnNH_2$, $TiCl_4$, Et_3N, CH_2Cl_2, -20 °C; 2. $NaBH_4$, MeOH, -20 °C. (v) HCHO, 1M HCl, 60 °C.

Scheme 51

The determination of enantiomeric purities by chiral HPLC analysis showed that all the products were >99% ee, which also indicates that all the synthetic steps proceed without any racemization especially, concerning to the very racemization prone benzylic carbon atom in the tetralones **49a-d.**

5. Concluding remarks

The β-aminoalcohols (*S*)-phenylglycinol and (*S,S*)-pseudoephedrine have shown to be excellent chiral starting materials for the asymmetric synthesis of differently substituted 1,2,3,4-tetrahydroisoquinolines. In most cases, the synthesis involves a common 2-arylethylamine precursor which, upon Pictet-Spengler cyclization furnishes the final isoquinolines. Therefore, depending upon the nature of this key synthetic intermediates 3-aryl, and 1,3-*cis* or 1,3-*trans* 1-methyl-3-aryl tetrahydroisoquinolines can be prepared from amines **3**, 4-alkyltetrahydroisoquinolines from amines **23** and 4-alkyl-3-aryl substituted derivatives from amines **40**. Besides, additional synthetic procedures have been found for the conversion of some of these precursors into naturally occurring alkaloids like isopavines, protoberberines and benzo[*c*]phenanthridines.

On the other hand, a general and straightforward procedure has been settled up for the synthesis of 3-aryltetrahydroisoquinolines with any desired substitution pattern at any of the aromatic rings present in their structure by means of a chiral version of the Pommeranz-Fritsch cyclization and using arylglycinols **35** (also prepared with the help of (*S,S*)-pseudoephedrine as chiral auxiliary) as very versatile chiral building blocks.

Acknowledgments

Financial support for our research program by the University of the Basque Country (Subvención General a Grupos de Investigación, projects UPV 170.310-EA167/95 and UPV37/98 and a fellowship to E.

R.), by the Basque Government (fellowships to J. L. V. and E. A. and projects GV PI 96/53 and GV00170.30-7307/19) and by the Spanish Ministerio de Ciencia y Tecnología (Project BQU2002-00488) is gratefully acknowledged.

References

1. (a) *The Isoquinoline Alkaloids, Chemistry and Pharmacology;* Shamma, M. Ed.; Academic Press: New York, 1972. (b) *The Chemistry and Biology of Isoquinoline Alkaloids;* Philipson, J. D.; Roberts, M. F.; Zenk, M. H. Eds.; Springer-Verlag: New York, 1985.
2. For a review: Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148 and refs. therein.
3. Crosby, J. *Tetrahedron* **1991**, *47*, 4789.
4. For previous reviews see (a) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
5. For a review on Pictet-Spengler cyclization see Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
6. See for example (a) Larsen R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034. (b) Venkov, A. P.; Ivanov, I. I. *Tetrahedron* **1996**, *52*, 12299.
7. See for example (a) Gensler, W. J. *Org. React.* **1951**, *6*, 191. (b) Bobbit, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *J. Org. Chem.* **1967**, *32*, 2225. (c) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1990**, *31*, 3125.
8. (a) Bates, H. A. *J. Org. Chem.* **1981**, *46*, 4931. (b) Bates, H. A. *J. Org. Chem.* **1983**, *48*, 1932.
9. Coote, S. J.; Davies, S. G. *J. Chem. Soc., Chem. Commun.* **1988**, 648.
10. Coote, S. J.; Davies, S. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2223.
11. Bròzda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017.
12. Chandrasekhar, S.; Reddy, N. R.; Reddy, M. V.; Jagannadh, B.; Nagaraju, A.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2002**, *43*, 1885.
13. (a) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *30*, 2198. (b) Reetz, M. T.; Dreves, M. W. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141. (c) Laib, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709.
14. Wipf, P.; Hopkins, C. R. *J. Org. Chem.* **2001**, *66*, 3133.
15. (a) Sato, T.; Hirayama, F.; Saito, T. *J. Antibiot.* **1991**, *44*, 1367. (b) Suzuki, K.; Sato, T.; Morioka, M.; Nagai, K., Abe, K., Yamaguchi, H., Saito, T.; Ohmi, Y.; Susaki, K. *J. Antibiot.* **1991**, *44*, 479. (c) Williams, R. M., Flanagan, M. E.; Tippie, T. N. *Biochemistry* **1994**, *33*, 4086.
16. Hirsenkorn, R. *Tetrahedron Lett.* **1990**, *31*, 7591.
17. (a) Dyke, S. F. *Tetrahedron* **1971**, *27*, 3803. (b) Elliott, R.; Hewgill, F.; McDonald, E.; McKenna, P. *Tetrahedron Lett.* **1980**, *21*, 4633.
18. Hirsenkorn, R. *Tetrahedron Lett.* **1991**, *32*, 1775.
19. Hanessian, S.; Mauduit, M. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3810.
20. For a review on Stevens rearrangements see Markó, I. E. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Pattenden I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p. 913.
21. Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakkar, K.; Bidlack, J. M. *J. Org. Chem.* **1998**, *63*, 7795.
22. Eaton, P.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.
23. Hayashi, K.; Ozaki, Y.; Nunami, K.–I.; Yoneda, N. *Chem. Pharm. Bull.* **1983**, *31*, 312.
24. Spengler, J.; Schedel, H.; Sieler, J.; Quaedflieg, P. J. L. M.; Broxterman, Q. B.; Duchateau, A. L. L.; Burger, K. *Synthesis* **2001**, 1513.
25. Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661.
26. Katritzky, A. R.; Cobo-Domingo, J.; Yang, B.; Steel, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 255.
27. Katritzky, A. R.; He, H.-Y.; Jiang, R.; Long, Q. *Tetrahedron: Asymmetry* **2001**, *12*, 2427.
28. Katritzky, A. R.; Suzuki, K.; He, H.-Y. *J. Org. Chem.* **2002**, *67*, 8224.
29. Huber, I. M. P.; Seebach, D.; Syfrig, M. A. *Helv. Chim. Acta* **1987**, *70*, 1357.
30. Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944.

31. This derivative was prepared from (*S*)-DOPA, according to a patent: Hoefle, M. L.; Klutchko, S. to *Warner-Lambert Company*. U.S. Patent 4,344,949, 1982.
32. Monsees, A.; Laschat, S.; Dix, I. *J. Org. Chem.* **1998,** *63*, 10018.
33. Yamaguchi, R.; Hamasaki, T.; Ohta, T.; Utimoto, K.; Kozima, S.; Takaya, H. *J. Org. Chem.* **1993**, *58*, 1136.
34. Haraguchi, Y.; Kozima, S.; Yamaguchi, R. *Tetrahedron: Asymmetry* **1996**, *7*, 443.
35. O´Reilly, N. J.; Derwin, W. S.; Lin, H. C. *Synthesis* **1990**, 550.
36. Ohba, M.; Nishimura, Y.; Kato, M.; Fujii, T. *Tetrahedron* **1999**, *55*, 4999.
37. (a) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65. (b) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799.
38. (a) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949. (b) Hashigaki, K.; Ishikawa, S.; Wan, W.; Yamato, M. *Synthesis* **1988**, 1001. (c) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909.
39. Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa C.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343 and refs. therein.
40. Hashigaki, K.; Kan, K.; Qais, N.; Takeuchi, Y.; Yamato, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1126.
41. Carbonnelle, A.-C.; Gott, V.; Roussi, G. *Heterocycles* **1993**, *36*, 1763.
42. Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995***, 36*, 6709.
43. Yamazaki, N.; Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 6161.
44. (a) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596. (b) Comins, D. L.; Badawi, M. M. *Heterocycles* **1991**, *32*, 1869.
45. Barbier, D.; Marazano, C.; Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1998**, *63*, 1767.
46. Cabedo, N.; Andreu, I.; Ramírez de Arellano, M. C.; Chagraoui, A.; Serrano, A.; Bermejo, A.; Portáis, P.; Cortes, D. *J. Med. Chem.* **2001**, *44*, 1794.
47. For a recent review see Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.
48. Munchoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086.
49. Munchoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607.
50. For general references on the CN(*R,S*) method see (a) Husson, H. -P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383. (b) Royer, J.; Husson, H. -P. *Janssen Chim. Acta* **1993**, *36*, 468.
51. Gosmann, G.; Guillaume, D.; Husson, H. -P. *Tetrahedron Lett.* **1996**, *37*, 4396.
52. Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475.
53. Lienard, P.; Quirion, J.-C.; Husson, H. -P. *Tetrahedron* **1993**, *49*, 3995.
54. Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243.
55. Pedrosa, R.; Andres, C.; Iglesias, J. M.; Pérez-Encabo, A. *J. Am. Chem. Soc.* **2001**, *123*, 1817.
56. (a) Micouin, L.; Varea, T.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P- *Tetrahedron Lett.* **1994**, *35*, 2529. (b) Shanen, V.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2533. (c) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977.
57. Philippe, N.; Levacher, V.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1996**, *7*, 417.
58. Roussi, F.; Quirion, J.-C.; Tomas, A.; Husson, H.-P. *Tetrahedron* **1998**, *54*, 10363.
59. Philippe, N.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Org. Lett.* **2000**, *2*, 2185.
60. Jullian, V.; Quirion, J.-C.; Husson, H.-P. *Synthesis* **1997**, 1091.
61. Jullian, V.; Quirion, J.-C.; Husson, H.-P. *Eur. J. Org. Chem.* **2000**, 1319.
62. Alezra, V.; Bonin, M.; Micouin, L.; Husson, H. -P. *Tetrahedron Lett.* **2001**, *42*, 2111.
63. Zaragoza, F. *Synlett* **1995**, 237.
64. (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420. (b) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051.
65. Hanessian, S.; Demont, E.; van Otterlo, W. A. L. *Tetrahedron Lett.* **2000,** *41*, 4999.
66. (a) Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1990**, *31*, 1011. (b) Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083. (c) Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, 37, 7477.
67. Falz, H.; Radspieler, A.; Liebscher, J. *Synlett* **1997**, 1071.

68. (a) Tietze, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331. (b) Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann.* **1997**, 1407.
69. (a) Kazmiersky, W. M.; Hruby, V. J. *Tetrahedron Lett.* **1991**, *32*, 5769. (b) Kazmiersky, W. M.; Urbanczyk-Lipkowska, Z.; Hruby, V. J. *J. Org. Chem.* **1994**, *59*, 1789.
70. Zawadzka, A.; Leniewski, A.; Maurin, J. K.; Wijtasiewicz, K.; Czarnocki, Z. *Org. Lett.* **2001**, *3*, 997.
71. Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B. *Tetrahedron: Asymmetry* **1993**, *4*, 273.
72. Kita, Y.; Takada, T.; Gyoten, M.; Toma, H.; Zenk, M. H.; Eichorn, J. *J. Org. Chem.* **1996**, *61*, 5857.
73. (a) Seyden-Penne, J. *Chiral auxiliaries and ligands in asymmetric synthesis;* Wiley & sons: New York, 1995. (b) Studer, A. *Synthesis* **1996**, 793. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
74. (a) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. (b) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 458. (c) Meyers, A. I.; Miller, D.; White, F. *J. Am. Chem. Soc.* **1988**, *110*, 4778. (d) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.
75. (a) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3925. (b) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263. (c) Castonguay, L. A.; Guiles, J. W.; Rappé, A. K.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 3819. (d) Meyers, A. I.; Warmus, J. S.; Gonzalez, M: A.; Guiles, J.; Akahane, A. *Tetrahedron Lett.* **1991**, *32*, 5509.
76. Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095.
77. Meyers, A. I.; Guiles, J. *Heterocycles* **1989**, *28*, 295.
78. Matulenko, M. A. Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573.
79. Dickman, D. A.; Meyers, A. I. *Tetrahedron Lett.* **1986**, *27*, 1465.
80. Gottlieb, L.; Meyers, A. I. *J. Org. Chem.* **1990**, *55*, 5659.
81. Guiles, J. W.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 6873.
82. Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154.
83. Itoh, T.; Nagata, K.; Miyazaki, M.; Kameoka, K.; Ohsawa, A. *Tetrahedron* **2001***, 57*, 8827.
84. For some reviews on the asymmetric addition of organometallic reagents to imines see (a) Denmark, S. E.; Nicaise, O. J. C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
85. Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 221.
86. Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron. Lett.* **2000**, *41*, 5533.
87. Gluszynska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2359.
88. Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, *36*, 9105.
89. (a) Kametani, T.; Hirata, S.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1466. (b) Ito, K.; Furukawa, H.; Iida, Y.; Lee, K. H.; Soine, T. O. *J. Chem. Soc., Chem. Commun.* **1974**, 1037. (c) Shamma, M.; Tomlinson, H. H. *J. Org. Chem.* **1978**, *43*, 2852. (d) Cushman, M.; Choong, T. C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067. (e) Valenta, V.; Holubek, J.; Svatek, E.; Dlabac, A.; Bartosova, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1983**, *48*, 1447. (f) Clark, R. D.; Jahangir, J. *J. Org. Chem.* **1989**, *54*, 1174.
90. (a) Dyke, S. F.; Kinsman, R. G. Kametami, T. G.; Fukumato, K.; McDonald, E. "Isoquinolines", *Heterocyclic Compounds.* Guenther Grethe Ed. Wiley, New York, **1981**, *38*, 1.
91. For other asymmetric syntheses of 3-substituted tetrahydroisoquinolines see (a) Khaldi, M.; Chretien, F.; Champleur, Y. *Tetrahedron Lett.* **1995**, *36*, 3003. (b) Corey, E. J.; Gin, D. Y. *Tetrahedron Lett.* **1996**, *37*, 7163. (c) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901.
92. See also Derdau, V.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 1992.
93. Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766-770.
94. When the ^{1}H-NMR spectra were carried out in $CDCl_3$, equilibrium mixtures of the imines **2** and the corresponding tautomeric oxazolidines were observed, whereas the ^{1}H-NMR in CD_3OD showed resonances for only the open chain structures. For studies in imine-oxazolidine tautomerism see: (a). Lambert, J. B.; Majchrzak, M. W. *J. Am. Chem. Soc*. **1980**, *102*, 3588. (b) Lázár, L.; Lakatos, A. G.; Fülöp, F.; Bernáth, G.; Riddell, F. G. *Tetrahedron*. **1997**, *53*, 1081 and references therein.
95. Hine, J.; Yeh, C. H. *J. Am. Chem. Soc*. **1967**, *89*, 2669.

96. (a) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull*. **1983**, *31*, 31. (b) Takahashi, H.; Suzuki, Y.; Hori, T. *Chem. Pharm. Bull*. **1983**, *31*, 2183. (c) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340.
97. See also Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.
98. Carrillo, L.; Badía, D.; Domínguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem.* **1999**, *64*, 1115.
99. (a) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164. (b) Domínguez, E.; Lete, E.; Badía, D.; Villa, M. J.; Castedo, L.; Domínguez, D. *Tetrahedron* **1987**, *43*, 1943.
100. Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083.
101. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
102. Tellitu, I.; Badía, D.; Domínguez, E.; Carrillo, L. *Heterocycles* **1996**, *43*, 2099.
103. For pharmacological activities see: (a) Weber, E.; Keana, J.; Barmettler, P. PCT Int. Appl. WO 12575, **1990**; *Chem. Abstr.* **1991**, *115*, 106019w. (b) Childers, W. E., Jr.; Abou-Gharbia, M. A., U. S. US, 4940789, **1990**; *Chem. Abstr.* **1990**, *113,* 191190w.
104. For syntheses of natural and non natural isopavines see, for example: (a). Gözler, B. In *The Alkaloids*; Academic Press: New York, 1987; vol. 31, pp. 342. (b) Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.; Shima, K. *Heterocycles* **1992**, *34*, 965. (c) Kametani, T.; Higashiyama, K.; Honda, T. *Chem. Pharm. Bull.* **1984**, *32,* 1614. (d) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc*. **1981**, *103,* 1984-1992. (e) Dyke, S. F.; Kinsman, R. G.; Warren, P.; White, A. W.C. *Tetrahedron* **1978**, *34*, 241. (f) Dyke, S. F.; A.; Ellis, A. C.; Kinsman, R. G.; White, A. W.C. *Tetrahedron* **1974**, *30,* 1193. (g) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601. See also refs. **Errore. Il segnalibro non è definito.** and 80.
105. Carrillo, L.; Badia, D.; Domínguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716.
106. Dyke, S. F.; Ellis, A.C.; Kinsman, R. G.; White, A. W .C. *Tetrahedron* **1974**, *30,* 1193.
107. (a) Aboul-Enein, H. Y.; Islam, M. R.; Baker, S. A. *J. Liq. Chromatog.* **1988**, *11*, 1485. (b) Kihara, M.; Kashimoto, M.; Kobayashi, S. Ishida, Y.; Moritoki, H.; Taira, Z. *J. Med. Chem.* **1990**, *33*, 2283. (c) Rinehart, K. L.; Holt, T. G.; Frege, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512. (d) Wright, A. E.; Forleo, P. A.; Gumahandana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConell, O. *J. Org. Chem.* **1990**, *55*, 4508. (e) Kobayashi, J.; Kondo, J.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *J. Org. Chem.* **1992**, *57*, 6680. (f) Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721. (g) Mondeshka, D. M.; Stensland, B.; Angelova, I.; Ivanov, C. B.; Atanasova, R. *Acta Chem. Scand.* **1994**, *48*, 689.
108. See also: (a) Coote, S. J.; Davies, S. G.; Sutton, K. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1481. (b) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourgignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509.
109. Vicario, J. L.; Badia, D.; Domínguez, E.; Carrillo, L. *Tetrahedron: Asymmetry* **2000**, *11*, 3779.
110. For previous examples of asymmetric metalloenamine alkylations see (a) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253. (b) Méa-Jacheet, D.; Horeau, A. *Bull. Soc. Chim. Fr.* **1968**, 4571. (c) Kitamoto, M.; Hirai, K.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 459. (d) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032. (e) Whitesell, J. K.; Whitesell, M. A. *J. Org. Chem.* **1977**, *42*, 377. (f) Hashimoto, S.; Koga, K. *Tetrahedron Lett.* **1978**, *19*, 573. (g) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892. (h) Meyers, A. I.; Williams, D. R. *J. Org. Chem.* **1978**, *43*, 3245.
111. (a) Kihara, M.; Kashimoto, M.; Kobayashi, S.; Ishida, Y.; Moritoki, H.; Taira, Z. *J. Med. Chem.* **1990**, *33*, 2283. (b) Ohta, S.; Tachikawa, O.; Makino, Y.; Tasaki, Y.; Hirobe, M. *Life Sciences* **1990**, *46*, 599. (c) Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543.
112. For other stereocontrolled syntheses of tetrahydroisoquinolin-4-ols see (a) Kametani, T.; Sugi, H.; Yagi, H.; Fukumoto, K.; Shibuya, S. *J. Chem. Soc. (C).* **1970**, 2213. (b) Blagg, J.; Coote, S. J.; Davies, S. G.; Mobbs, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2257.
113. (a) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627. (b) Tellitu, I.; Badía, D.; Domínguez, E.; García, F. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1567.

114. (a) Badía, D.; Domínguez, E.; Iriondo, C. *Bull. Soc. Chim. Belg.* **1986**, *95*, 207. (b) Schlosser, M.; Simig, G.; Geneste, H. *Tetrahedron* **1998**, *54*, 9023.
115. Carrillo, L.; Badía, D.; Domínguez, E.; Ortega, F.; Tellitu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 151.
116. Anakabe, E.; Vicario, J. L.; Badia, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343.
117. For a review see (a) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. See also (b) Zhu, J.; Bouillo, J.-P.; Singh, G. P.; Chastanet, J.; Beugelmans, R. *Tetrahedron Lett.* **1995**, *36*, 7081. (c) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179. (d) Hegedus, L. *Acc. Chem. Res.* **1995**, *28*, 299. (e) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (f) Decicco, C. P.; Grover, P. *Synlett* **1997**, 529. (g) Harwood, L. M.; Tyler, S. N. G.; Anslow, A. S.; MacGilp, I. D.; Drew, M. G. B. *Tetrahedron: Asymmetry* **1997**, *8*, 4007. (h) Badorrey, R.; Cativiela, C.; Díaz de Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1997**, *53*, 1411. (i) Medina, E.; Vidal-Ferrán, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1581. (j) Park, Y.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (k) Davis, F. A.; Fanelli, D. L. *J. Org. Chem.* **1998**, *63*, 1981. (l) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207. (m) Tabcheh, M.; Guibourdenche, C.; Pappalardo, L.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1493. (n) Dave, R. H.; Hosangadi, B. D. *Tetrahedron* **1999**, *55*, 11295. (o) Moody, C. J.; Gallagher, P. T.; Lightfoot, A. P.; Slavin, A. M. Z. *J. Org. Chem.* **1999**, *56*, 4419. (p) Bravo, P.; Capelli, S.; Crucianelli, M.; Guidetti, M.; Markovski, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M. *Tetrahedron* **1999**, *55*, 3025. (q) Barberis, C.; Voyer, N. *Synlett* **1999**, 1106. (r) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (s) Tunge, J. A.; Gately, D. A.; Norton, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 4520. (t) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. (u) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1279. (v) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (w) Saaby, S.; Fang, X.; Gathergood, N.; Jorgensen, K.A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 4114. (x) Basso, A.; Braiuca, P.; DeMartin, L.; Ebert, C.; Gardossi, L.; Linda, P. *Tetrahedron: Asymmetry* **2000**, *11*, 1789. (y) Kaptein, B.; Elsenberg, H.; Grimbergen, F. F. P.; Broxterman, Q. B.; Hulshof, L. A.; Pouwer, K. L.; Vries, T. R. *Tetrahedron: Asymmetry* **2000**, *11*, 1343.
118. Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L.; Anakabe, E. *Tetrahedron Lett.* **1999**, *40*, 7123.
119. For a review on electrophilic amination reagents see Greck, C.; Genêt, J. P. *Synlett* **1997**, 741. For some examples on enolate aminations see (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395. (c) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397. (d) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991. (e) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189. (f) Pearson, A. J.; Shin, H. *Tetrahedron* **1992**, *48*, 7527. (g) Pearson, A. J.; Chelliah, M. V.; Bignan, G. C. *Synthesis* **1997**, 536. (h) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (i) Vergne, C.; Bouillon, J.-P.; Chastanet, J.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Asymmetry* **1998**, *9*, 3095. (j) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (k) Page, P. C. B.; McKenzie, M. J.; Allin, S. M.; Buckle, D. R. *Tetrahedron* **2000**, *56*, 9683.
120. (a) Kursanov, D. N.; Parnes, Z. N.; Kalinkin, M. I.; Loim, N. M. *Ionic Hydrogenation and Related Reactions,* Harwood Academic Publishers: New York, **1985**. (b) Gribble, G. W. *Reductions in Organic Synthesis*, Ed.: Ahmed F. Abdel-Magid. ACS Symposium Series 641. Washington **1996**, pp. 167-200. (c) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis* Wiley-VCH, New York, **1997**.
121. See for example: (a) Nordlander, E.; Payne, M.J.; Njoroge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikes, G. D.; Balk, M. A. *J. Org. Chem.* **1985**, *50*, 3619. (b) Olah, G. A.; Arvanaghi, M.; Hannesian, L. *Synthesis* **1986**, 770. (c) McComsey, D. F.; Reitz, A. B.; Maryanoff, C. A.; Maryanoff, B. E. *Synth. Commun.* **1986**, *16*, 1535. (d) Lomas, J. S.; Bru-Capdeville, V. *J. Chem. Soc., Perkin Trans 2* **1997**, 2589. (e) Yato, M.; Homma, K.; Ishida, A. *Heterocycles* **1998**, 233. (f) Li, C.; Rehman, A.; Dalley, N. K.; Savage, P. B *Tetrahedron Lett.* **1999**, *40*, 1861.
122. For the use of (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary, see (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A.

G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754. (d) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *Tetrahedron Lett.* **2000**, *41*, 8297. (e) Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2001**,. *3*, 773. (f) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030 (g) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801 (h) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207. (i) Vicario, J. L.; Badía, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2002**, *13*, 745.

123. Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610.
124. Arylacetic acids were converted by oxidation of the aryl ring into *N*-Boc α-aminoacids: Fodor, G.; Csepreghy, G. *J. Chem. Soc.* **1961**, 3222.
125. Sotomayor, N.; Vicente, T.; Domínguez, E.; Lete, E.; Villa, M.-J. *Tetrahedron*, **1994**, *50*, 2207.
126. Krane, B. D.; Fagbule, M. O.; Shamma, M.; Gözler, B. *J. Nat. Prod.* **1984**, *47*, 1.
127. a) Cushman, M.; Mohan, P.; Smith, E. C. R. *J. Med. Chem.* **1984**, *27*, 544. (b) Hanaoka, M.; Motegi, A.; Yokumoto, Y. A.; Takahashi, K. Jpn. Kokai Tokkyo Koho JP 02243629 (*Chem. Abstr.* **1991**, *115*, 780). (c) Hanaoka, M.; Ekimoto, H.; Kobayashi, F.; Irie, Y.; Takahashi, K. Eur. Pat. Appl. EP 432630 (*Chem. Abstr.* **1992**, *116*, 718). (d) Janin, Y. L.; Croisy, A.; Riou, J.-F.; Bisagni, E. *J. Med. Chem.* **1993**, *36*, 3686.
128. (a) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067. (b) Cheng, R. K. Y.; Cheng, C. C. *J. Med. Chem.* **1978**, *21*, 199. (c) Cordell, G. A.; Farnsworth, N. R. *Heterocycles*, **1976**, *4*, 393.
129. Tan, G. T.; Miller, J. F.; Kinghorn, A. D.; Hughes, S. H.; Pezzuto, J. M. *Biochem. Biophys. Res. Comm.* **1992**, *185*, 370.
130. Cushman, M.; Moham, P. *J. Med. Chem.* **1985**, 28*,* 1031.
131. (a) Shamma, M.; Tomlinson, H. H. *J. Org. Chem.* **1978**, *43*, 2852. (b) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *Tetrahedron Lett.* **1980**, *21*, 3845. (c) Oppolzer, W. *Heterocycles,* **1980**, *14*, 1615. (d) Iida, H.; Endo, I.; Narimiya, M.; Kikuchi, T. *Heterocycles,* **1980**, *14*, 1325. (e) Ninomiya, I.; Yamamoto, O.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2165. (f) Cushman, M.; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc.* **1983**, *105*, 2873.
132. a) Harigaya, Y.; Takamatsu, S.; Yamaguchi, H.; Onda, M. *Chem. Pharm. Bull.* **1982**, *30*, 1244. (b) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 2315.
133. Vicario; J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1947.
134. Dyke, S. F.; Ellis, A.C. *Tetrahedron* **1971**, *27*, 3802.
135. Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *Tetrahedron: Asymmetry* **2000**, *11*, 1227.

STEREOSELECTIVE SYNTHESIS OF NITROGEN HETEROCYCLES OF ENANTIOPURE 3-HYDROXY ESTERS THROUGH ELECTROPHILIC AMINATION

Christine Greck[a] and Olivia Poupardin[b]

[a]*Laboratoire SIRCOB (UMR 8086); Université de Versailles Saint-Quentin-en-Yvelines; 45, Avenue des Etats Unis; 78035 Versailles Cédex; France (e-mail: greck@chimie.uvsq.fr)*

[b]*Laboratoire de Synthèse Organique Sélective (UMR 7573); E.N.S.C.P.; 11, rue Pierre et Marie Curie; 75231 Paris Cédex 05; France*

Abstract. *The electrophilic amination of enantiopure 3-hydroxy esters with azocarboxylates leads to anti 2-hydrazino 3-hydroxy esters which are versatile building-blocks for the stereoselective synthesis of nitrogen heterocycles.*

Contents

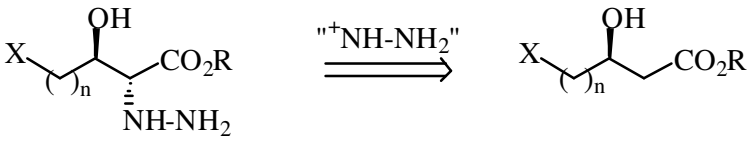
1. Introduction

The electrophilic amination of carbanions allows the preparation of a wide range of amines through unconventional C-N bond-forming reactions. Carbon-nitrogen bonds are usually formed by attack of a nucleophilic nitrogen atom at an electrophilic carbon bearing a leaving group *via* S_N2 type reaction. A major limitation is the difficult access to electrophilic precursors, particularly for multifunctional derivatives.

The reverse process, electrophilic amination, constitutes an example of «Umpolung» methodology for the direct introduction of an amino group into organometallic compounds.[1] It is now an important synthetic process to create C-N bonds, and stereoselective C-N bond forming reactions have been developed based on the addition of chiral carbon nucleophiles to «neutral» aminating agents.

Azodicarboxylates are efficient sources of positive nitrogen as synthetic equivalent of an $[NH\text{-}NH_2]^+$ synthon. They were used in the stereoselective synthesis of α-hydrazino and α-amino acids starting from chiral enolates.[2] Di-*t*-butyl[3] and dibenzyl[4] azodicarboxylates are the most commonly used reagents for diastereoselective electrophilic amination. Both compounds are commercially available.

The following account discusses recent advances in the area of electrophilic amination of enantiopure 3-hydroxy esters and related compounds such as 1,3-dioxan-4-ones. *Anti* 2-hydrazino-3-hydroxyesters are obtained with high diastereoselectivity by this method (Scheme 1).



Scheme 1

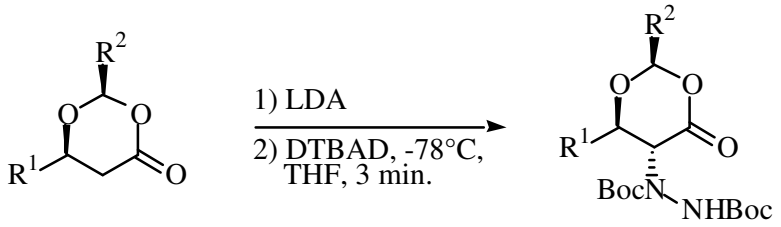
These compounds could be functionalized on the side chain (X: CH=CHR, $CH(OMe)_2$, CH_2OR) and are synthetic precursors of nitrogen heterocycles.

2. Diastereoselective synthesis of *anti* 2-hydrazino 3-hydroxy esters

2.1. Electrophilic amination of 1,3-dioxan-4-ones

1,3-Dioxan-4-ones are well known substrates for diastereoselective alkylation reactions developed by Frater[5] and Seebach.[6] These chiral compounds have been also aminated at the α-carbon with high stereoselectivity.

Thus, 1,3-dioxan-4-ones **1** were deprotonated and the resulting enolates were exposed to di-*t*-butylazodicarboxylate (DTBAD) at –78 °C. The ensuing electrophilic amination afforded the corresponding *trans* adducts **2** in good yields and high diastereomeric excesses >95% (Scheme 2).



	1		**2**
Entry	R^1	R^2	Yield (%)
a	CH_3	CH_2CH_2Ph	95
b	CF_3	*t*-Bu	57
c	CH_3	H	90
d	C_5H_{11}	H	66

b: *t*-BuLi as base; de>98%

Scheme 2

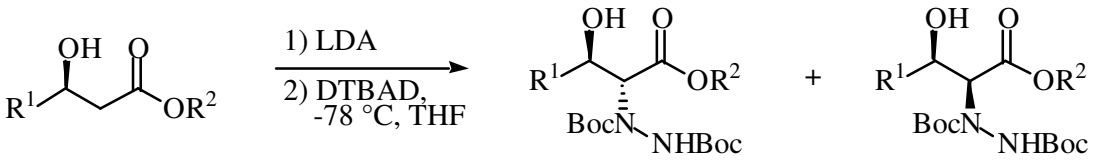
The *trans* 2-hydrazino-1,3-dioxan-4-ones **2** are precursors to *anti* 2-amino-3-hydroxy acids: optically pure *D*-allothreonine was obtained from **2a** after acidic deprotection and hydrogenolysis[7] and *L*-trifluoro allothreonine methyl ester has been synthetized from **2b** using a related approach.[8]

An additional bulky group on the dioxanone moiety was not required for stereoinduction and excellent diastereomeric excesses were also obtained starting from 1,3-dioxan-4-ones derived from paraformaldehyde (R = H) **1c** and **1d**.[9]

2.2. Electrophilic amination of 3-hydroxy esters

The electrophilic amination of enantiopure 3-hydroxy esters occurred with *anti* selectivity.

3-Hydroxy esters **3** were deprotonated with excess LDA and the resulting β-oxidoenolates reacted rapidly with DTBAD at low temperature to give an easily separable mixture of *syn* and *anti* adducts **4** in which the *anti* diastereomer was the major compound (Scheme 3).[7,10] The adducts are very useful intermediates since compounds with *anti* stereochemistry are not easily accessible by other established methods for α-amino β-hydroxy acids synthesis.



3 *anti* **4** *syn* **4**

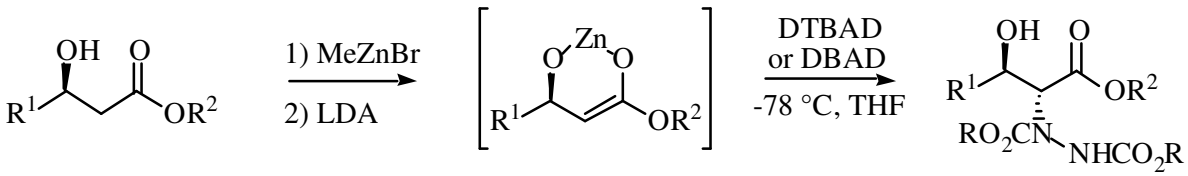
Entry	R^1	R^2	Yield (%)	*anti/syn*
a	CH_3	CH_3	58	82 / 18
b	CH_3	C_2H_5	75	84 / 16
c	CF_3	C_2H_5	62	87 / 13
d	C_5H_{11}	C_2H_5	74	90 / 10
e	C_6H_{13}	C_2H_5	81	85 / 15
f	CH_2OSiPh_2t-Bu	CH_3	62	67 / 33
g	CH_2OCPh_3	CH_3	50	96 / 4

g: 1) LDA; 2) DTBAD, -20 °C to 0 °C

Scheme 3

The moderate diastereoselectivities observed in the electrophilic amination of 3-hydroxy esters with DTBAD may be due to the weakly chelated nature of the intervening dianion. Improved diastereoselectivities may be obtained by stabilizing the chelated form of the dianion with suitable organometallic species.[9] Thus, deprotonation of **3** with LDA in the presence of MeZnBr gave exclusively the *anti* aminated product **4** (d.e.>98%) in chemical yields up to 70%, using DTBAD or dibenzylazodicarboxylate (DBAD) as aminating agents (Scheme 4).

Functionalized 3-hydroxy esters **3e-h** were obtained quantitatively with excellent enantiomeric excesses (>98%) by hydrogenation of β-ketoesters in the presence of chiral ruthenium catalysts. This convenient methodology gives either optical antipodes with equal ease, depending on whether the (*R*) or (*S*) atropoisomer of the ligand is used in the metal complex.[11]

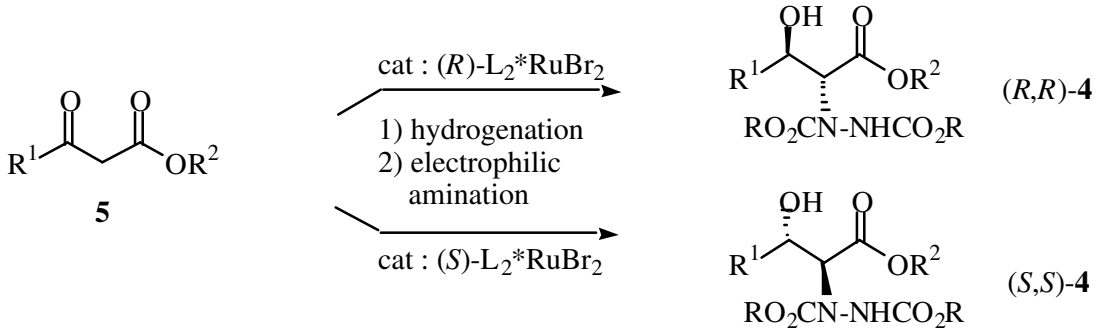


3 *anti* **4**

Entry	R^1	R^2	R	Yield (%)
a	CH_3	C_2H_5	*t*-Bu	63
b	C_2H_5	CH_3	*t*-Bu	58
c	C_5H_{11}	C_2H_5	*t*-Bu	66
d	Ph	CH_3	*t*-Bu	70
e	EtCH=CH	CH_3	*t*-Bu	53
f	Me_2C=CH-CH_2	CH_3	*t*-Bu	55
g	$(MeO)_2$CH-CH_2	CH_3	$PhCH_2$	66
h	$(MeO)_2$CH	CH_3	$PhCH_2$	66

Scheme 4

By coupling the two sequential reactions, catalytic hydrogenation and electrophilic amination, a general and practical method for the preparation of both enantiomers of *anti*-2-hydrazino-3-hydroxy esters (*R*,*R*)-**4** and (*S*,*S*)-**4** from the corresponding β-ketoesters **6** has been proposed (Scheme 5).[9,12]



Scheme 5

These 2-hydrazino-3-hydroxy esters **4** were used as chiral building blocks for the synthesis of functionalized nitrogen heterocycles.

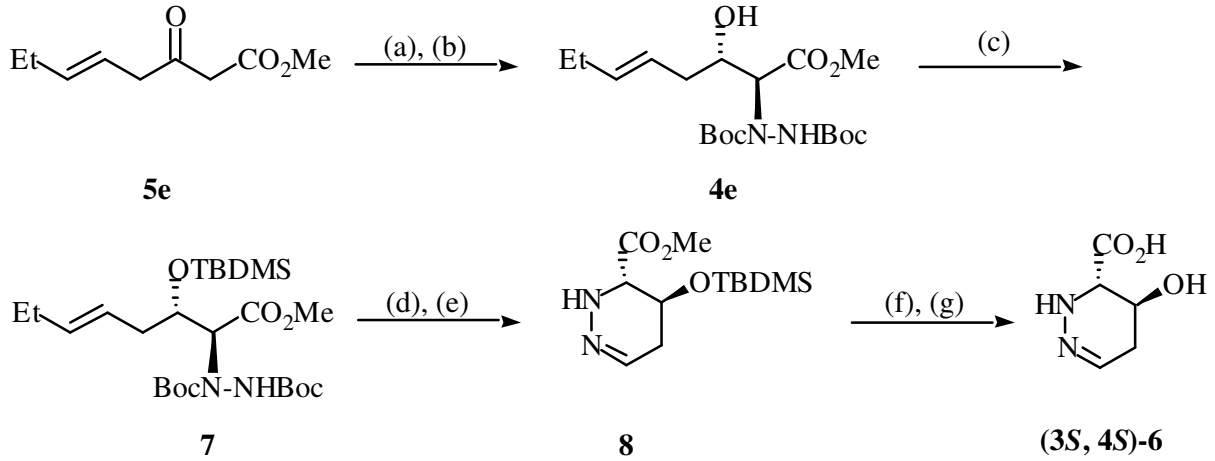
3. Syntheses of nitrogen heterocycles

3.1. Six-membered rings

3.1.1. (3*S*, 4*S*)-4-Hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid

(3*S*, 4*S*)-4-Hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid **6** is an unusual amino acid constituent of Luzopeptin A. Luzopeptin A was isolated from *Actinomadura luzonensis* and is a dimeric cyclic depsipeptide constituted by six amino acids.[13] It is an antibiotic antitumor agent and a bis-intercalator of DNA. The first synthesis of **6** has been reported starting from malonaldehyde dimethylacetal *via*

Sharpless epoxidation and subsequent C-2 ring opening of the epoxyacid with hydrazine.[14] More recently, the synthesis, chemistry and conformational properties of piperazic acids have been reviewed.[15]



(a) H_2, 0.3% (*S*)-Biphemp Ru Br_2, MeOH, 6 bars, 80 °C, 30 min. (100%, ee>99%); (b) i. MeZnBr, ii. LDA, iii. DTBAD, -78 °C (53%, de>98%); (c) TBDMSOTf, 2,6-lutidine (85%); (d) i. O_3, ii. Me_2S; (e) TFA, CH_2Cl_2 then H_2O, MeOH (50% from **7**); (f) nBu_4NF; (g) K_2CO_3, MeOH, H_2O (90% from **8**)

Scheme 6

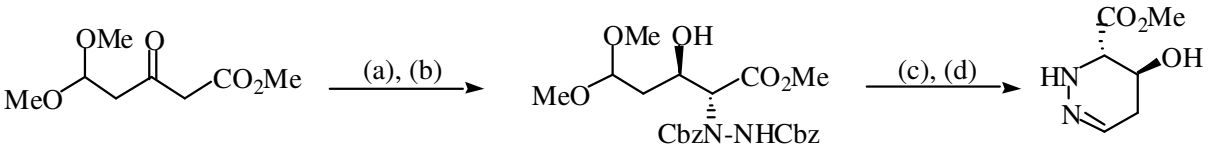
An efficient synthesis of **6** has been developed starting from (*E*)-methyl-3-oxooct-5enoate **5e** (Scheme 6) and using the sequential reactions: enantio and chemoselective hydrogenation catalyzed by (*S*)-Biphemp Ru Br_2 at low pressure and diastereoselective electrophilic amination with DTBAD.[16]

The 2-hydrazino-3-hydroxy ester **4e** presented a double bond at C-5 as a masked aldehyde necessary for the hydrazone formation. The *N,N,O*-protected compound **7** was converted to 2,3,4,5-tetrahydropyridazine **8** without purification of the intermediates. The ozonolysis was conducted under reductive conditions to give the corresponding aldehyde and the acidic treatment produced in one pot the cyclic product **8**. To achieved the synthesis of (3*S*, 4*S*)-**6**, the silyl ether was deprotected and the ester saponified.

More recently, a shorter formal synthesis of (3*R*, 4*R*)-**6** was published starting from methyl 5,5-dimethoxy-3-oxopentanoate **5g** (Scheme 7).[17] This C-5 acetal functionalized β-ketoester presented two symmetrical oxygens in γ positions to the carbonyl group: this could modify the chelation of the ruthenium complex and influence the enantioselectivity of the hydrogenation.

The hydrogenation was performed at room temperature and atmospheric pressure using 2 mol % of (*R*)-Binap Ru Br_2 generated *in situ*.[18] Methanol was used at solvent to avoid secondary reactions such as transacetalisation and transesterification. Under these mild conditions, the corresponding 3-hydroxy ester **3g** was obtained with excellent enantiomeric excess (>95%). The diastereoselective amination was carried out with DBAD as electrophilic agent because the conditions of deprotection of a benzyl carbamate are compatible with the presence of an acetal function.

The (3*R*, 4*R*)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic methyl ester **9**, which is the direct precursor of (3*R*, 4*R*)-**6**, was obtained quantitavely after hydrogenolysis of the carbamates and treatment of the crude deprotected product with aqueous trifluoroacetic acid.



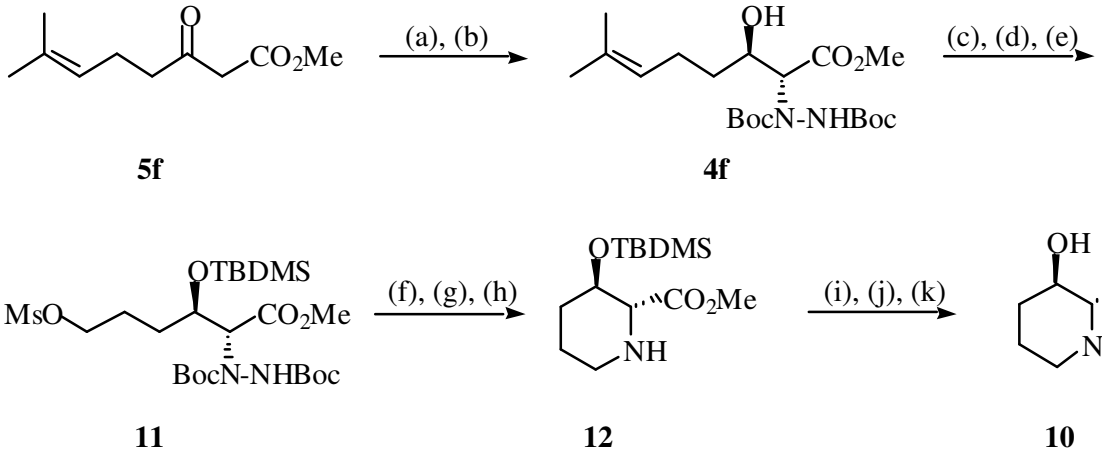
5g **4g** **(3*R*, 4*R*)-9**

(a) H_2, 2% (*R*)-Binap Ru Br_2, MeOH, 1 atm., r.t., 18h. (86%, ee>95%); (b) i. MeZnBr, ii. LDA, iii. DBAD, -78 °C (66%, de>98%); (c) H_2, Pd/C, MeOH, r.t., 0.5 h.; (d) TFA, H_2O (quant)

Scheme 7

3.1.2. *Trans* 3-hydroxypipecolic acid and application to (-)-swainsonine

Syntheses of polyhydroxypipecolic acids have been previously reported and these compounds have been screened as potential inhibitors of HIV replication.[19] Surprisingly, the synthesis of 3-hydroxypipecolic acid is less well documented, although enantioselective preparations of the *cis* diastereomer have been reported.[20] The first enantioselective synthesis of the *trans* diastereomer **10** was described starting from methyl 7-methyl-3-oxooct-6-enoate **5f** *via* the 2-hydrazino-3-hydroxy ester **4f** as key intermediate (Scheme 8).[21] Later, others synthetic routes were described for the *trans* 3-hydroxypipecolic acid.[22]



5f **4f**

11 **12** **10**

(a) H_2, 2% (*R*)-Binap Ru Br_2, MeOH, 1 atm., 50 °C, 2 h. (98%, ee=97%); (b) i. MeZnBr, ii. LDA, iii. DBAD, -78 °C (55%, de>98%); (c) TBDMSOTf, 2,6-lutidine; (d) i. O_3, ii. BH_3-Me_2S; (e) MsCl, py (65% from **11**); (f) TFA, CH_2Cl_2; (g) H_2, Raney-Ni, ultrasounds; (h) Et_3N, CH_2Cl_2 (75% from **11**); (i) HF, CH_3CN; (j) K_2CO_3, MeOH, H_2O; (k) Amberlite CG 50 (80% from **12**)

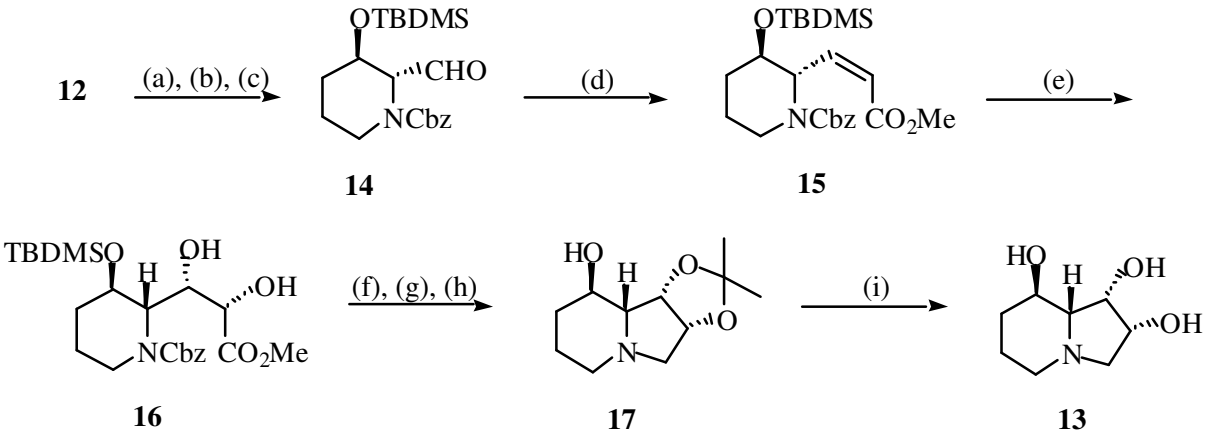
Scheme 8

The β-ketoester **5f** was hydrogenated under mild conditions in presence of (*R*)-Binap Ru Br_2 catalyst. This reaction at atmospheric pressure was highly enantioselective and completely chemoselective: the reduction of the carbonyl group was only observed without any hydrogenation of the double bond at C-6. After electrophilic amination of the resulting 3-hydroxy ester with DTBAD, the 2-hydrazino-3-hydroxy ester **4f** was obtained with excellent enantio and diastereomeric excesses. After protection of the hydroxy group as a silyl ether, the double bond was easily transformed into a primary alcohol, which was mesylated without further purification to give compound **11** in 65% overall yield. The introduction of a primary amino group at C-2 was achieved by acidic hydrolysis of the *t*-butyl carbamates and hydrogenolysis of the hydrazine in

presence of Raney-Ni under ultrasounds.[23] Under these conditions, partial cyclisation was observed and completion of the ring closure occurred in presence of triethylamine. The (2*R*, 3*R*)-3-hydroxy pipecolic acid **5f** was obtained after deprotection of the silyl ether and saponification of the methyl ester.

The compound **12** has the same *trans* relationship than the piperidine ring of (-)-swainsonine **13** and was used as precursor for its total synthesis.[24] Since its initial isolation from the *fungus Rhizoctonia leguminicola*, **13** has aroused considerable interest due to its potent and highly specific α-D-mannosidase inhibitory activity, immunoregulative properties and antimetastatic activity.[25] Most of the previously reported methodologies utilized the chiral pool as starting material.[26] Other approaches employed the Sharpless asymmetric epoxydation and the Masamune/Sharpless iterative methodology or kinetic resolution and the Sharpless asymmetric dihydroxylation.[27]

Starting from the compound **12**, the synthetic goals were achieved through homologation of the ester function and dihydroxylation of the resulting double bond (Scheme 9).



(a) CbzCl, DMAP, CH_3CN (74%); (b) $Ca(BH_4)_2$ (91%); (c) i. $(COCl)_2$, DMSO, CH_2Cl_2, ii. Et_3N then H_2O (100%); (d) $(CF_3CH_2O)_2P(O)CH^-CO_2Me$, K^+, 18-crown-6 (83%, *Z/E* = 19 :1); (e) OsO_4, Me_3NO, ultrasounds (71%); (f) H_2, Pd/C, MeOH (90%); (g) $CH_3CH(OMe)_2CH_3$, Dowex H^+ (97%); (h) BH_3-Me_2S (81%); (i) HCl, 1M then Dowex OH^- (96%)

Scheme 9

The piperidine **12** was first protected as a benzyl carbamate, the ester was reduced with $Ca(BH_4)_2$ and the corresponding alcohol was then oxidized to the aldehyde **14** under classical Swern conditions. The formation of the double bond was run under kinetic control using Still's reagent to afford the *Z*-alkene **15** as the major stereomer (*Z/E* = 19:1). The *Z/E* mixture was not separable and the dihydroxylation proceeded smoothly under ultrasounds with catalytic osmium tetroxide and trimethylamine *N*-oxide as cooxidant. The desired optically pure diastereomer **16** was separated from the mixture by flash chromatography and isolated in 71% yield. The stereochemistry of **16** was correlated with those of the known compounds **17**[26f] and 13:[26a] cleavage of the benzyl carbamates provided the bicyclic lactam, protection of the 1,2-diol into acetonide by treatment with 2,2-dimethoxypropane in presence of an acidic ion exchange resin, cleaved simultaneously the silyl ether and reduction of the lactam with BH_3-Me_2S, gave the known product **17**. The (1*S*, 2*R*) configuration was confirmed at this stage. Finally deprotection of the acetonide produced (-)-swainsonine **13**.

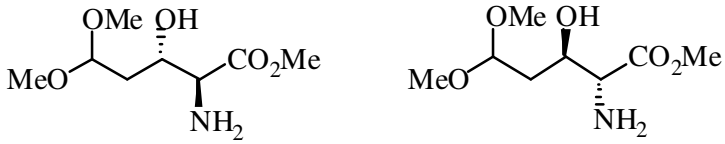
3.2. Five-membered rings

3.2.1. *Trans* 3-hydroxy-*D*-proline

Trans 3-hydroxy-*L*-proline is a constituent of naturally occurring peptides[28] and has been isolated from mediterranean sponge and collagen hydrolysates.[29] Several synthesis of *trans* 3-hydroxyproline and of its reduced form: *trans* 3-hydroxyprolinol have been developed in the literature starting from chiral sources.[30]

The stereocontrolled synthesis of the unnatural *trans* 3-hydroxy-*D*-proline **18** has been described in six steps with 33% overall yield from the prochiral β-ketoester **5g**.[17] The key intermediate is the richly functionalized (2*R*, 3*R*) methyl 2-amino-5,5-dimethoxy-3-hydroxypentanoate **19** which presented three oxygenated groups at different oxydation degrees: an alcohol, an acetal and an ester. Its enantiomer, the (2*S*, 3*S*)-**19** has been also synthetized from **5g** through catalytic hydrogenation and electrophilic amination (Scheme 10). These two *anti* diastereomers are chiral building blocks which should be useful for the synthesis of various 2-amino-3-hydroxy acids of either *L* or *D* configurations.

Recently, the synthesis of *N,O*-diprotected **19** has been reported via aza-Achmatowicz reaction.[31]



(2*S*, 3*S*)-19 **(2*R*, 3*R*)-19**

Scheme 10

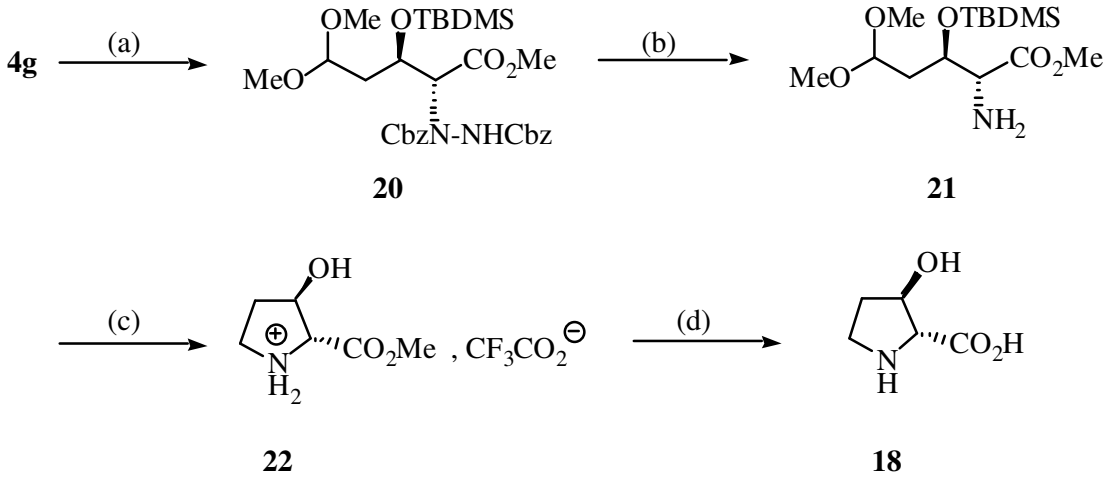
The synthesis of the *trans* 3-hydroxy-*D*-proline **18** was developed from the 2-hydrazino-3-hydroxyester **4g** (Scheme 11) obtained from the β-ketoester **5g** as shown in 3.1.1. The principal step was the cleavage of the hydrazine bond.

The hydroxyl function was first protected as *t*-butyldimethylsilyl ether. After hydrogenolysis of the benzyl carbamates, classical conditions as H_2, PtO_2[32] or H_2, Raney Ni under ultrasounds[23] were used to generate the amine, but degradation of the substrate was observed and no product could be isolated. Deprotection and cleavage of the hydrazine were run simultaneously: **20** was exposed to H_2 in presence of $PtO_2.H_2O$ in methanol and 45% of the 2-aminoester **21** was recovered. Using a 1/1 mixture of methanol-water as solvent for these reactions, the yield increased to 71% of purified compound **21**. This one pot deprotection-cleavage of the N-N bond of a diprotected hydrazine derivative is very efficient. The cyclisation to the proline ring was performed using aqueous trifluoroacetic acid and the silyl ether was cleaved under these conditions. The resulting iminium was reduced *in situ* by H_2 in presence of $PtO_2.H_2O$. The trifluoroacetic salt of methyl *trans*-hydroxy-*D*-prolinate **22** was obtained as a crude product and the methyl ester was saponified without further purification. After elution through an ion exchange resin column, the (2*R*, 3*R*)-*trans*-3-hydroxyproline **18** was isolated as a white solid.

3.2.2. (4*S*, 5*R*)-5-Carbomethoxy-4-hydroxy-Δ^2-pyrazoline

A large number of Δ^2-pyrazolines has been described in the literature[33] due to their synthetic accessibility and important applications. Δ^2-pyrazolines are also known for their biological activity as antinflammatory compounds.[34] Procedures to obtain these systems in enantiomerically pure form are of great interest. Thus, Δ^2-pyrazolines could be used as chiral precursors in the preparation of several heterocyclic

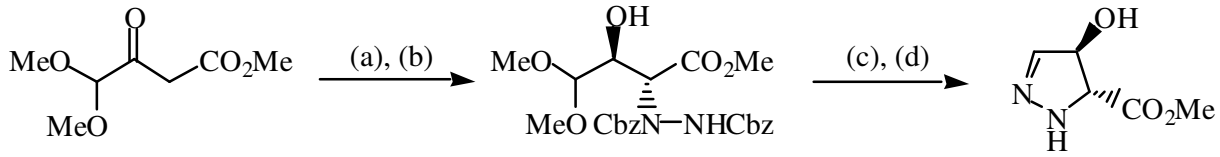
derivatives and as building blocks for the asymmetric synthesis of functionalized chiral acyclic synthons.[35] Recently, two routes to enantiomerically pure Δ^2-pyrazolines were reported: a diastereoselective dipolar cycloaddition reaction of Me_3SiCHN_2 to optically active enoates[36] and a reaction of diazo compounds with alkenyl Fischer carbenes derived from chiral alcohols.[37]



(a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, (96%); (b) H_2, PtO_2. H_2O, MeOH-H_2O (1/1), r.t. (71%); (c) i. TFA, H_2O, ii. H_2; $PtO_2.H_2O$; (d) i. KOH, MeOH-H_2O,ii. Dowex 50x4 (84% from **27**)

Scheme 11

A concise and stereoselective synthesis of the chiral functionalized (4*S*, 5*R*)-5-carbomethoxy-4-hydroxy-Δ^2-pyrazoline **23** was reported recently[38] (Scheme 12). **23** was obtained in four steps from the β-ketoester **5h** in 38% overall yield.



5h **4h** **23**

(a) H_2, 1 mol% [(R)-Binap Ru $Cl_2]_2$-Et_3N, 1 atm., MeOH, 65 °C, 18h. (83%, ee=90%); (b) i. MeZnBr, ii. LDA, iii. DBAD (66% , de>95%) ; (c) H_2, Pd/C, MeOH (quant.); (d) TFA (70%).

Scheme 12

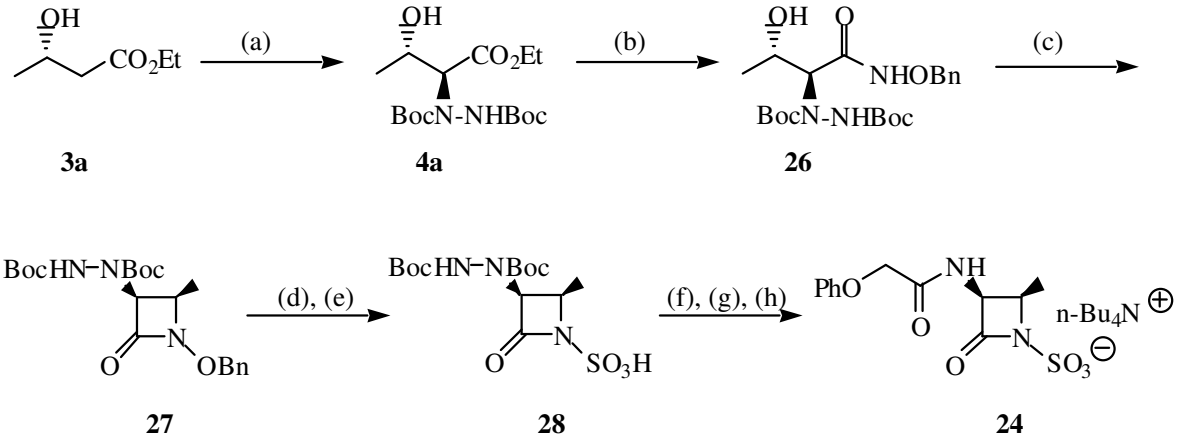
The β-ketoester **5h** was prepared by a two carbon homologation of methyl 2,2-dimethoxyethanoate using the Masamune procedure.[39] The highly functionalized chiral C-4 synthon **4h** was produced by hydrogenation at atmospheric pressure of **5h** in presence of 1 molecular % of [(*R*)-Binap Ru Cl_2]-Et_3N[40] and electrophilic amination of the resulting 3-hydroxy ester with DBAD. The use of (*R*)-Binap Ru Br_2 for the asymmetric hydrogenation step was not successful and secondary reactions were observed giving methyl-3,4-dihydroxybutanoate and hydroxy-δ-lactone as side products. The cyclisation was performed after hydrogenolysis of the benzyl carbamates, by treatment of the crude product with trifluoroacetic acid at room temperature.

3.3. Four-membered rings

An efficient entry into *cis* monobactams has been reported.[41] This synthetic approach is based on the diastereoselective electrophilic amination of 3-hydroxy esters and on Miller's biomimetic synthesis of the β-lactam nucleus.[42] Since 4-substituted monobactams are not accessible through microbiological methods, their preparation requires the development of total syntheses of the corresponding 3-amino monobactamic acids (3-AMA). The monobactams units: *cis* 4-methyl-3-AMA **24** and *cis* 4-carbamoyloxymethyl-3-AMA **25** of pharmacologically important *cis* azatreonam and carumonal, were prepared by this route.

3.3.1. *Cis* 4-methyl-3-AMA

The synthesis of *cis* 4-methyl-3-AMA **24** requires the quite expensive anti α-amino β-hydroxy acid: *L*-allothreonine as starting material (Scheme 13). The electrophilic amination of (*S*) ethyl 3-hydroxybutanoate **3a** with DTBAD furnished the *anti* compound **4a** which is a very useful building block for the synthesis of **24**.



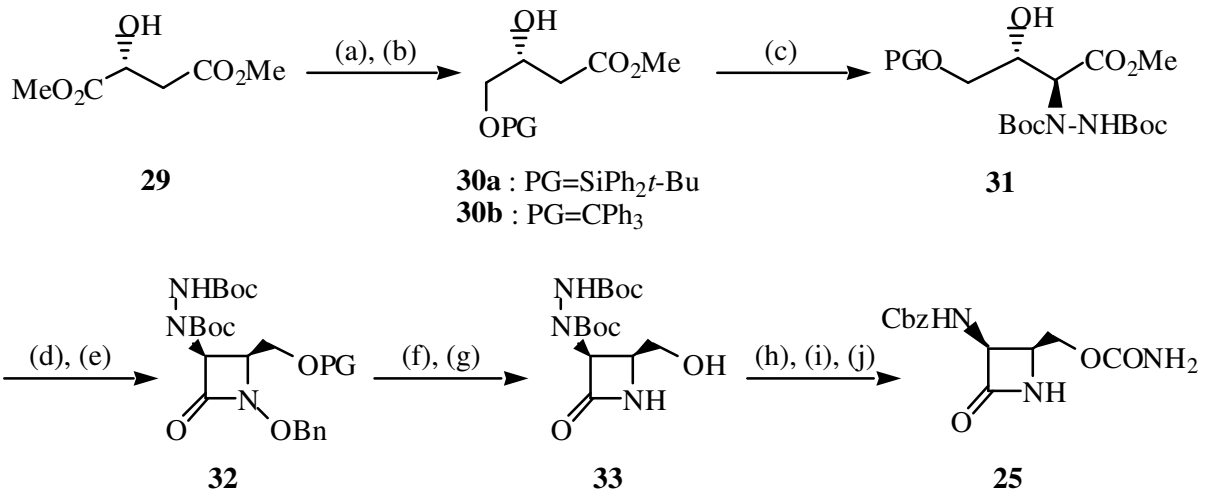
(a) i. LDA, ii. DTBAD (75%, de=68%); (b) i. LiOH, ii. $BnONH_2.HCl$ (80%); (c) DEAD, PPh_3 (90%); (d) i. H_2, Pd/C, EtOH, ii. $TiCl_3$, H_2O-MeOH (69%); (e) i. SO_3.py, py. ii. n-Bu_4NHSO_4, iii. silica gel chromatography (96%); (f) TFA, CH_2Cl_2; (g) H_2, PtO_2, EtOH; (h) $PhOCH_2COCl$, Et_3N, DMF (52% from **28**)

Scheme 13

The ester **4a** was converted into the O-benzylhydroxamate **26** by saponification and coupling with O-benzylhydroxylamine. Cyclisation to the β-lactam **27** proceeded under Mitsonobu conditions. After removal of the benzyl protecting group, reductive cleavage of the N-OH bond was performed using $TiCl_3$. The resulting azetidinone was sulfonated with pyridine-SO_3 complex to give the azetidine sulfonic acid **28**. Finally the hydrazine was deprotected with trifluoroacetic acid and hydrogenated over PtO_2. *Cis* 4-methyl-3-AMA **24** was obtained in 17% overall yield which is comparable with that obtained in the previous synthesis starting from *L*-allothreonine.[42]

3.3.2. *Cis* 4-carbamoyloxymethyl-3-AMA

In order to obtain intermediates useful for the synthesis of carumonam, it is necessary to start from (*R*) methyl 3,4-dihydroxybutanoate selectively protected at the primary alcohol which can be prepared from commercially available (*R*) dimethyl malate **29**, *via* regioselective reduction of the C-1 carboxylic methylester (Scheme 14).[44]



(a) BH_3, cat. $NaBH_4$ (88%); (b) for **30a**: *t*-$BuPh_2SiCl$, imidazole, DMF (71%); for **30b**: Ph_3CCl, py, CH_2Cl_2 (79%); (c) i. LDA, ii. DTBAD (for **31a**: 62%, de=34%; for **31b**: 50%, de=92%); (d) for **31a**: $BnONH_2$.HCl, Me_3Al, THF (85%); for **31b**: i. LiOH, THF-H_2O, ii. $BnONH_2$.HCl (60%); (e) DEAD, PPh_3 (for **32a**: 88% ; for **32b**: 95%); (f) for **32a**: *n*-$Bu_4NF.3H_2O$, THF (73%); for **32b**: p-TSA, MeOH (68%); (g) i. H_2, Pd/C, ii. $TiCl_3$, H_2O-MeOH (62%); (h) i. TFA, CH_2Cl_2, ii. H_2, PtO_2; (i) CbzCl, $NaHCO_3$, H_2O (40% from **33**); (j) i. $ClCH_2CONCO$, CH_2Cl_2, DMF, ii. $MeNHCS_2Na$ (75%)

Scheme 14

If the primary alcohol was protected as a silyl ether **30a**, the electrophilic amination step occurred with only moderate diastereoselectivity. An alternative route was developed using a trityl ether as protecting group. Furthermore, the stability of compound **30b** under basic conditions allowed the use of higher reaction temperatures in the dianion formation, as well as in the condensation with DTBAD. In this case the diastereoselectivity was excellent. The β-lactam **32** was obtained by intramolecular Mitsonobu reaction after conversion of the ester into O-benzylhydroxamate. The primary alcohol was then selectively deprotected, the benzyl group hydrogenolysed and the N-OH bond reduced to afford **33**. The removal of the *t*-butoxycarbonyl groups was carried out with trifluoroacetic acid and the resulting hydrazine salt directly hydrogenolysed. After *in situ* protection of the free amine, the hydroxyl group was converted into the corresponding carbamate **25**.

This synthetic route constitutes a formal synthesis of carumonam which has been obtained from **25** by a three steps sequence.[45]

4. Conclusion

2-Hydrazino 3-hydroxy esters are usefull intermediates for the elaboration of nitrogen heterocycles. Electrophilic aminations were run on functionalized 3-hydroxy esters with side chains bearing a double bond, an acetal function or a silyl ether and the *anti* adducts were obtained with high diastereomeric excesses. They were used as building-blocks for the synthesis of six, five and four membered rings as 2,3,4,5-tetrahydropyridazines, piperidines, Δ^2-pyrazoline, pyrrolidine and β-lactams.

References

1. Reviews and references cited therein: a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947-1980. b) Mulzer, J. *Organic Synthesis Highlights*, VCH, Weinheim, **1991**, pp. 45-53. c) Boche, G. *Stereoselective synthesis* (Houben-Weyl), **1995**, Vol. E21, pp. 5133-5157. d) Genet, J. P.; Greck, C.; Lavergne, D.

Modern Amination Methods, Ed. A. Ricci, WILEY-VCH; **2000**, pp. 65-102. e) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281-1286.
2. a) Gennari, C.; Colombo L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394-6395. b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397. c) L. A. Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399.
3. Klinge, M.; Vederas, J. C. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Chichester, **1995**, pp. 1586-1591.
4. Leblanc, Y. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Chichester, **1995**, pp. 1532-1533.
5. Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825-2828.
6. Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1988**, 1143-1155.
7. Genet, J. P.; Jugé, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765-6768.
8. Gautschi, M.; Seebach, D. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 1083-1085.
9. Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genet, J. P. *Synlett* **1993**, 475-477.
10. a) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553-5562. b) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett*. **1989**, *30*, 5507-5510.
11. Reviews and references cited therein: a) Genêt J.P. *Reductions in Organic Synthesis*, A. C. S. Symposium Series 641, Ed. A. F. Abdel Magid, **1996**, chap. 2, 31-51. b) Ratovelomanana-Vidal V.; Genêt J. P. *J. Organomet. Chem*. **1998**, *567*, 163-171. c) Ohkuma T.; Kitamura M.; Noyori R. *Catalytic Asymmetric Synthesis* Ed. I. Ojima, WILEY - VCH; **2000**, pp. 1-110.
12. Greck, C.; Genet, J. P. *Synlett* **1997**, 741-747.
13. a) Komishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc.* **1981**, *103*, 1241-1243. b) Arnold, E.; Clardy, J. *ibid* **1981**, *103*, 1243-1244.
14. Hughes, P.; Clardy, J. *J. Org. Chem*. **1989**, *54*, 3260-3264.
15. a) For reviews, see: Ciufolini, M.; Xi, N. *Chem. Soc. Rev.* **1998**, *27*, 437-445 and Hale, K. J., *The Chemical synthesis of Natural Products*; Hale, K. J.,Ed.; CRC Press: Boca Raton, FL, **2000**, pp.349ff. b) For recent papers, see: Boger, D. L.; Lederboer, M. W.; Kume, M.; Searcey, M.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 11375-11383. Boger, D. L.; Ichikawa, S.; Tse, W. C.; Hendrick, M. P.; Jin, Q. *J. Am. Chem. Soc*. **2001**, *123*, 561-568. Ciufolini, M. A.; Valognes, D.; Xi, N. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 2493-2495. Valognes, D.; Belmont, P.; Xi, N.; Ciufolini, M. A. *Tetrahedron Lett*. **2001**, *42*, 1907-1909.
16. Greck, C.; Bischoff, L.; Genêt, J. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1989-1994.
17. Poupardin, O.; Greck, C.; Genêt, J. P. *Synlett* **1998**, 1279-1281.
18. Genêt, J. P.; Ratovelomanana-Vidal, V.; Cano de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett*. **1995**, *36*, 4801-4804.
19. Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*; 119-136.
20. a) Roemmele, R. C.; Rapopport, H. *J. Org. Chem*. **1989**, *54*, 1866-1875. b) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Org. Chem*. **1993**, *4*, 625-628.
21. Greck, C.; Ferreira, F.; Genêt, J. P. *Tetrahedron Lett*. **1996**, *37*, 2031-2034.
22. Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett*. **1996**, *37*, 4001-4004.
23 - Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625-626.
24. Ferreira, F.; Greck, C.; Genêt, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615-621.
25. a) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Biochem*. **1980**, *191*, 648. b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. c) Kaushal, G. P.; Elbein, A. D. *Methods Enzymol*. **1994**, *230*, 316. d) Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M. *J. Antibiot*. **1985**, *38*, 936. e) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res*. **1988**, *48*, 1410. f) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Cancer Res*. **1995**, 1, 935.
26. a) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29. b) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc*. **1990**, *112*, 8100. c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem*. **1996**, *61*, 7217. d) Ikata, N.; Hanaki, A. *Chem. Pharm. Bull*. **1990**, *38*, 22712. e) Blanco, M. J.; Sardina, F. J. *J. Org. Chem*. **1996**, *61*, 4748. f) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem*. **1994**, *59*, 1358.

27. a) Adams, C. E.; Walker, F. J.; Sharpless, K .B. *J. Org. Chem*. **1985**, *50*, 422. b) Zhou, W. S.; Xie, W. G.; Lu, Z. H.; Pan, X. F. *J. Chem. Soc., Perkin Trans I* **1995**, 2599.
28. a) Hirschmann, R. *Angew. Chem. Int. Ed. Eng*. **1991**, *103*, 1305-1330. b) Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed. Eng*. **1993**, *105*, 1303-1326. c) Tschesche, R.; Samuel, T. D.; Uhlendorf, J.; Fehlaber, H. W. *Chem. Ber.* **1972**, *105*, 3106-3114. c) Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc*. **1968**, *90*, 462-470.
29. a) Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc*. **1963**, *85*, 2824-2831. b) Wolff, J. S.; Ogle, J. D.; Logan, M. A. *J. Biol. Chem*. **1966**, *241*, 1300-1308.
30. a) Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett*. **1994**, *35*, 119-122. b) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 119-128. c) Dell'Uomo, N.; Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Tetrahedron: Asymmetry* **1996**, *7*, 181-188. d) Mulzer, M. A.; Meier, A.; Bushmann, J.; Luger, P. *J. Org. Chem*. **1996**, *61*, 566-572. e) Durand, J. O.; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1998**, *39*, 5743-5746.
31. a) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105-114. b) Ciufolini, M. A.; Shimizu, T.; Swaminathan, S.; Xi, N. *Tetrahedron Lett.* **1997**, *38*, 4947-4950.
32. Claremon, D. A.; Lumma, P. K.; Phillips, P. *J. Am. Chem. Soc*. **1986**, *108*, 8265-8266.
33. Review : Elguero J. *Comprehensive Heterocyclic Chemistry*, Vol. 5, Pergamon Oxford, **1984**, p. 167.
34. Frigola, J.; Colombo, A.; Pares, J.; Martinez, L.; Sagarra, R.; Roser, R. *Eur. J. Med. Chem*. **1989**, *24*, 435-445.
35. a) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem*. **1997**, *62*, 7916-7917. b) Sasaki, H.; Carreira, E. M. *Synthesis* **2000**, 135-138.
36. Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc*. **1997**, *119*, 8379-8380.
37. a) Barluenga, J.; Fernandez-Mari, F.; Aguilar, E.; Viado, A.L.; Olano, B. *Tetrahedron Lett*. **1998**, *39*, 4887-4890. b) Barluenga, J.; Fernandez-Mari, F.; Aguilar, E.; Viado, A. L.; Olano, B.; Garcia-Granda, S.; Moya-Rubiera, C. *Chem. Eur. J.* **1999**, *5*, 883-896.
38. Poupardin, O.; Greck, C.; Genêt, J. P. *Tetrahedron Lett*. **2000**, *41*, 8795-8797.
39. Brooks, D. W.; Masamune, S. *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 72-74.
40. a) Kawano, H.; Ikariya, T.; Ichii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, J. *J. Chem. Soc., Perkin Trans. I* **1989**, 1571-1575. b) For recent structure elucidation of this catalyst, see: Ohta, T.; Tonomura, Y.; Nozaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *15*, 1521-1523.
41. Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Narisano, E.; Riva, R. *Tetrahedron* **1994**, *50*, 11967-11982.
42. Miller, M. J. *Acc. Chem. Res*. **1986**, *19*, 49-56.
43 Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem*. **1982**, *47*, 5160-5167.
44. Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Morikawe, T. *Tetrahedron* **1992**, *48*, 4067-4086.
45. Sendai, M.; Hashiguchi, S.; Tomimoto, M.; Kishimoto, S.; Matsuo, T.; Kondo, M.; Ochiai, M. *J. Antibiot*. **1985**, *38*, 346-371.

RECENT TRENDS IN SYNTHESIS OF HETEROCYCLES USING KETENE DITHIOACETALS WITH ELECTRON ATTRACTING GROUPS

Galal H. Elgemeie[a]* and Ghada W. Abd-Elaziz[b]

[a]*Department of Chemistry, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt*
(e-mail: elgemeie@hotmail.com)

[b]*Department of Chemistry, Faculty of Science, Cairo University (Beni-Suef Branch), Beni-Suef, Egypt*

Abstract. *New approaches for synthesis of different mono and polyheterocyclic derivatives utilising ketene dithioacetals are surveyed. The scope and limitation of the most important of these approaches are demonstrated.*

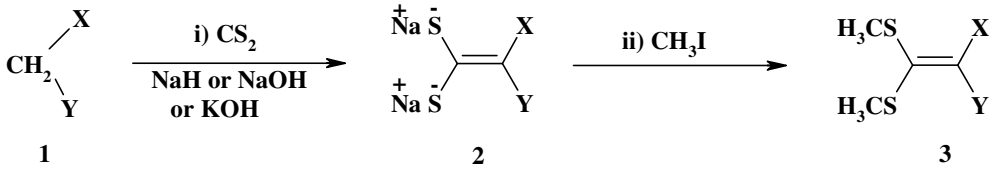
Contents

1. Introduction

Interests in the field of ketene dithioacetals in heterocyclic synthesis are very high. It has been found that ketene dithioacetals are versatile reagents, which have been extensively utilized in the synthesis of many analogues of purine base, nucleosides and pyrimidines.[1-81] Moreover the biological aspects of such class of compounds have been also the subject of a large number of publications as antimalarial activity and for the destruction of harmful organisms.[5,48]

2. Synthesis

Ketene dithioacetals **3a-u** were obtained by the reaction of the corresponding active methylene compounds **1a-u** with carbon disulfide in the presence of a base to give sodium salt of ketene dithioacetals **2a-u** followed by alkylation (Scheme 1).[82-126]



1 2 3

1-3	X	Y	1-3	X	Y	1-3	X	Y
a	CN	CN	h	$COCH_3$	CO_2CH_3	o	H	4-BrC_6H_4CO
b	CN	CO_2CH_3	i	$COCH_3$	$CO_2C_2H_5$	p	H	4-$CH_3C_6H_4CO$
c	CN	$CO_2C_2H_5$	j	$COCH_3$	COC_6H_5	q	CN	$CONHC_6H_5$
d	CN	$CONH_2$	k	COC_6H_5	COC_6H_5	r	CN	4-$ClCONHC_6H_4$
e	CN	COC_6H_5	l	H	NO_2	s	CN	4-$CH_3CONHC_6H_4$
f	CN	$SO_2C_6H_5$	m	H	COC_6H_5	t	CN	4-$OCH_3CONHC_6H_4$
g	$COCH_3$	$COCH_3$	n	H	4-ClC_6H_4CO	u	CN	$CSNH_2$

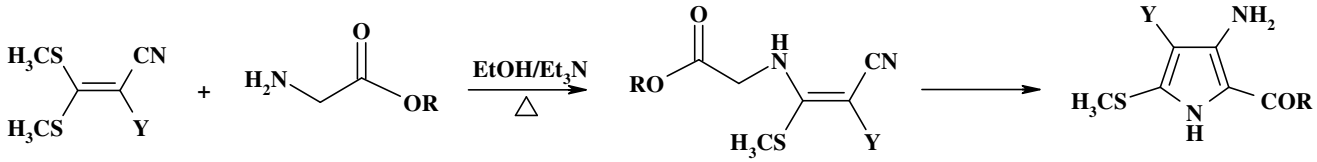
Scheme 1

3. Utility in heterocyclic synthesis

3.1. Five-membered rings

3.1.1. Five-membered rings with one hetero-atom

The reaction of ketene dithioacetals **3a,c** with α-aminoesters **4** in ethanol triethylamine mixture afforded compounds **5**, which were cyclized to yield the 5-(methylthio)-3-aminopyrrole-2-carboxylates **6** (Scheme 2).[127,128]

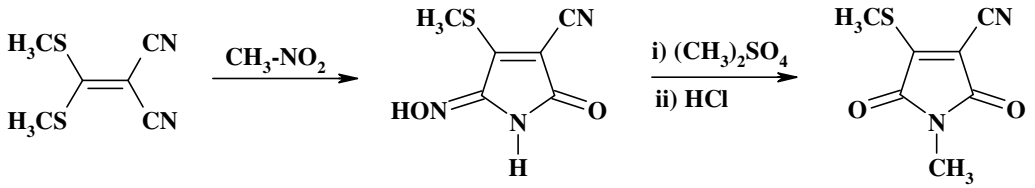


3
a Y=CN
c Y=$CO_2C_2H_5$

4 5

6	R	Y
a	CH_3	CN
b	CH_3	$CO_2C_2H_5$
c	C_2H_5	CN
d	C_2H_5	$CO_2C_2H_5$

Scheme 2



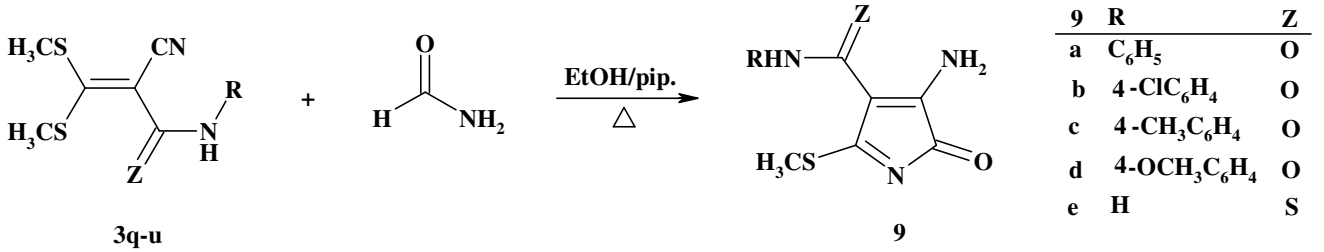
3a 7 8

Scheme 3

It has been reported that the reaction of **3a** with nitromethane gave the 2,5-dihydro-5-hydroxyimino-2-oxo-4-(methylthio)pyrrole-3-carbonitrile **7**, which was readily converted to the corresponding 2,5-dihydro-

2,5-dioxo-4-(methylthio)pyrrole-3-carbonitrile **8**, by methylation with dimethylsulfate followed by hydrolysis with hydrochloric acid (Scheme 3).[129-131]

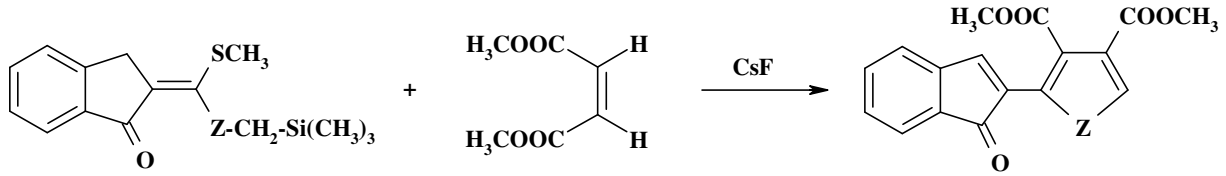
Recently, Elgemeie *et al.* have reported that the ketene dithioacetals **3q-u** were treated with formamide in refluxing ethanol containing catalytic amount of piperidine to afford the 3-amino-5-(methylthio)pyrrole-2-ones **9** (Scheme 4).[123]



9	R	Z
a	C_6H_5	O
b	4-ClC_6H_4	O
c	4-$CH_3C_6H_4$	O
d	4-$OCH_3C_6H_4$	O
e	H	S

Scheme 4

Cycloketene *S,S*- and *N,S*-acetals **10** reacted with dimethylfumarate **11** in the presence of cesium floride to yield the thiophene and pyrrole derivative **12**, respectively (Scheme 5).[132]



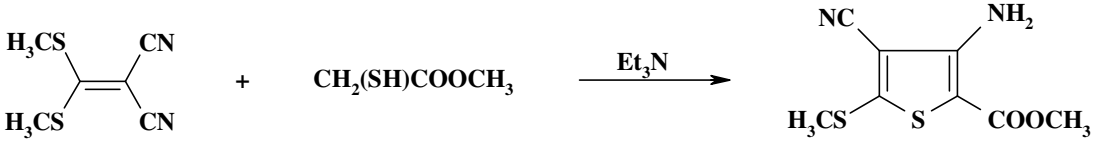
10
a Z=NR
b Z=S

11

12

Scheme 5

The reaction of compound **3a** with methylthioglycolate **13** gave the thiophene derivative **14** (Scheme 6).[92,133]



3a

13

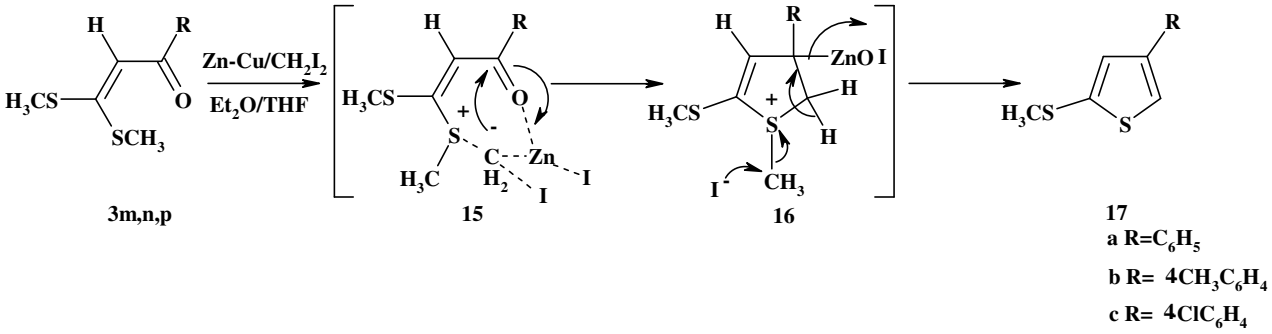
14

Scheme 6

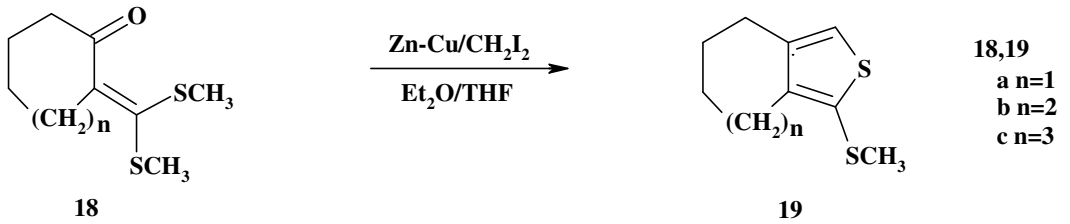
The 2-methylthio-4-arylthiophenes **17**, were prepared from α-oxoketene dithioacetals **3m,n,p** under Simmons-Smith reaction conditions through the intermediates **15, 16** (Scheme 7).[134]

Bhat *et al.* have shown the synthesis of 3,4-anellated thiophenes **19**, through Simmons-Smith reaction from cycloalkanone dithioacetals **18** (Scheme 8). [134]

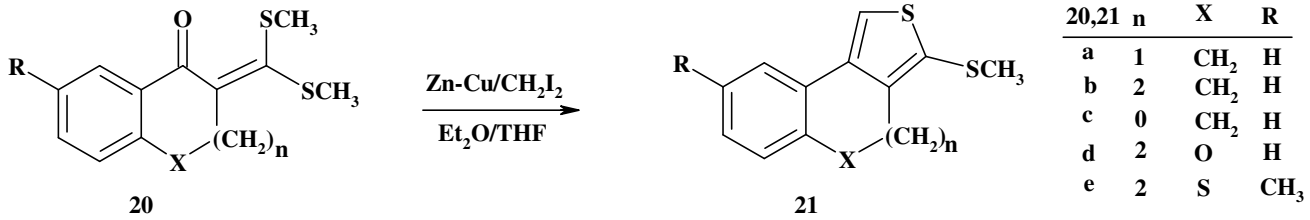
Also, the tricyclic thiophene derivatives **21** have been developed through Simmons-Smith reaction on benzocycloalkanone dithioacetals **20** (Scheme 9).[134]



Scheme 7



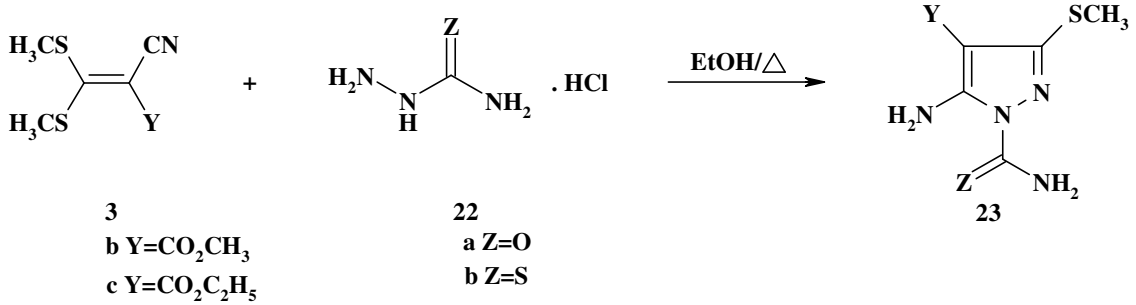
Scheme 8



Scheme 9

3.1.2. Five-membered rings with two hetero-atoms

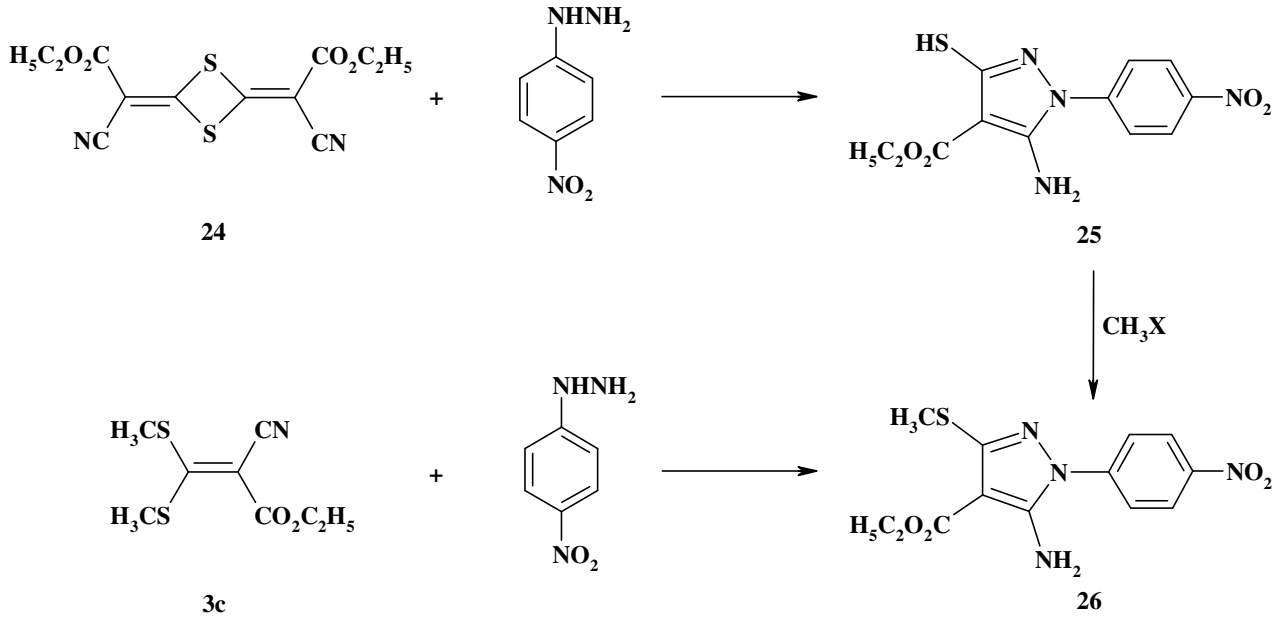
Peseke has reported that the cycloaddition of ketene dithioacetals **3b,c** with semicarbazide or thiosemicarbazide hydrochloride **22a,b** in refluxing ethanol yielded the corresponding 5-aminopyrazole derivatives **23** (Scheme 10).[135,136]



Scheme 10

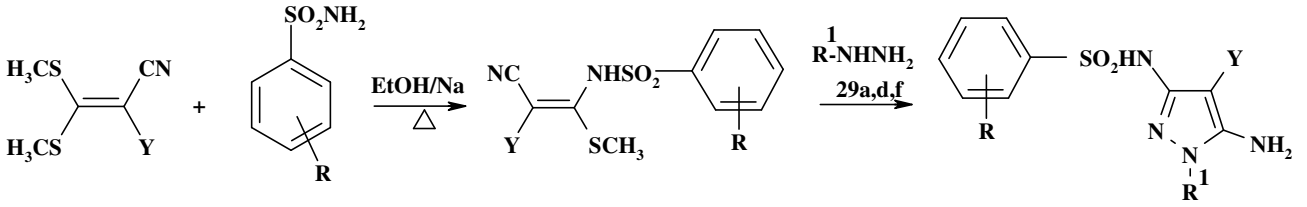
He has also found that the reaction of dithietane derivative **24** with 4-nitrophenylhydrazine gave the substituted pyrazole **25**, which was alkylated in the presence of methyl halide to yield the 5-amino-3-

methylthiopyrazoles **26**. The latter compound **26** has been synthesized by the reaction of **3c** with 4-nitrophenylhydrazine (Scheme 11).[137]



Scheme 11

Treatment of compounds **3b,c** with sulphonamide derivatives **27** in ethoxide gave ketene *N,S*-acetals **28**. Compounds **28** were refluxed with hydrazine derivatives **29a,d,f** to give the substituted 5-amino-3-arylsulfonylaminopyrazoles **30** (Scheme 12).[138]



3
b Y=CO_2CH_3
c Y=$CO_2C_2H_5$

27

28

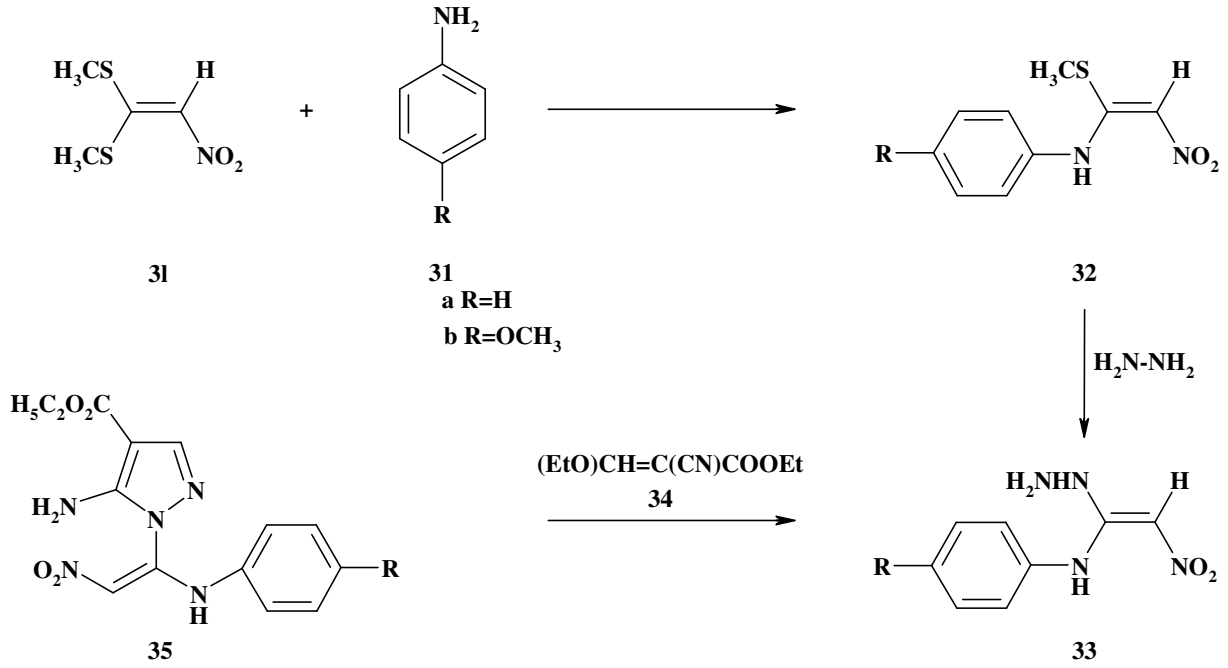
30	Y	R	R^1
a	CO_2CH_3	4-CH_3	H
b	$CO_2C_2H_5$	3-NO_2	4-$NO_2C_6H_4$
c	CO_2CH_3	4-Br	CH_2CH_2OH

Scheme 12

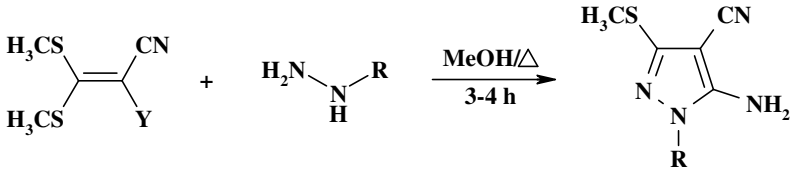
Ketene-*S*,*S*-acetal **3l** reacted with aniline derivatives **31** to give ketene-*N*,*S*-acetals **32**, which were treated with hydrazine to yield compounds **33**. The latters were cyclized with ethyl cyano(ethoxymethylene)acetate **34** to afford the corresponding 1-(2-nitrovinyl)pyrazole derivatives **35** (Scheme 13).[139]

It has been found that the 5-amino-3-(methylthio)pyrazoles **36** were synthesized through the reaction of ketene dithioacetals **3a,d** with hydrazine derivatives **29a-d** in refluxing methanol (Scheme 14).[140-144]

The furfurylaminopyrazole carboxylic acid ester **39** was prepared by treating **3c** with furfurylmethylamine **37** to give compound **38**, which cyclocondensed with hydrazine (Scheme 15).[145]



Scheme 13



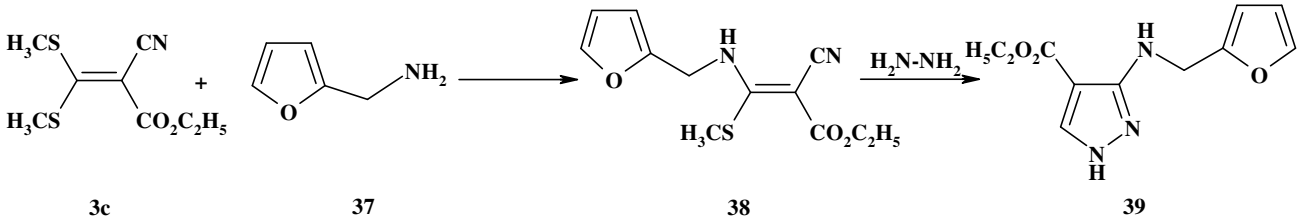
36	R	Y	36	R	Y
a	H	CN	e	H	$CONH_2$
b	C_6H_5	CN	f	C_6H_5	$CONH_2$
c	4-ClC_6H_4	CN	g	4-ClC_6H_4	$CONH_2$
d	4-$NO_2C_6H_4$	CN	h	4-$NO_2C_6H_4$	$CONH_2$

3
a Y=CN
d Y=$CONH_2$

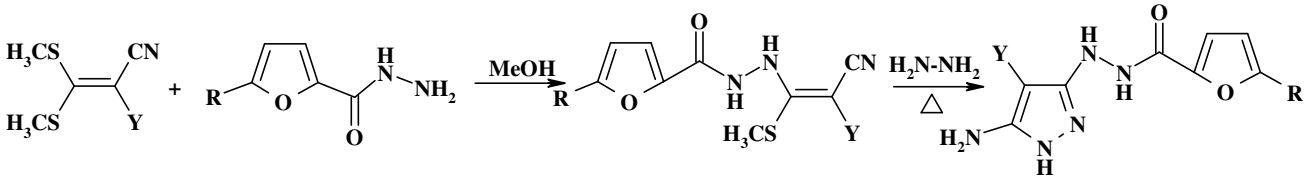
29a-d

36

Scheme 14



Scheme 15



3
b Y=CO_2CH_3
c Y=$CO_2C_2H_5$

40

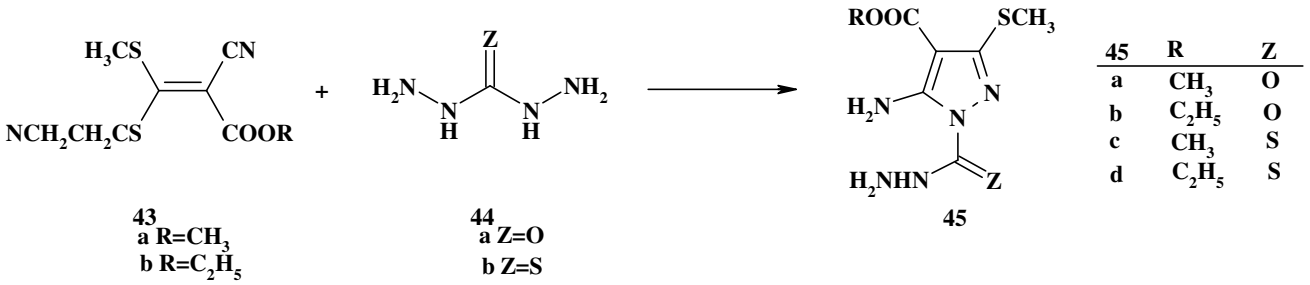
41

42	Y	R
a	CO_2CH_3	H
b	CO_2CH_3	NO_2
c	$CO_2C_2H_5$	H
d	$CO_2C_2H_5$	NO_2

Scheme 16

Treatment of ketene dithioacetals **3b,c** with furancarbohydrazides **40** formed compounds **41**, which were cyclized with hydrazine to yield the corresponding pyrazole derivatives **42** (Scheme 16).[146]

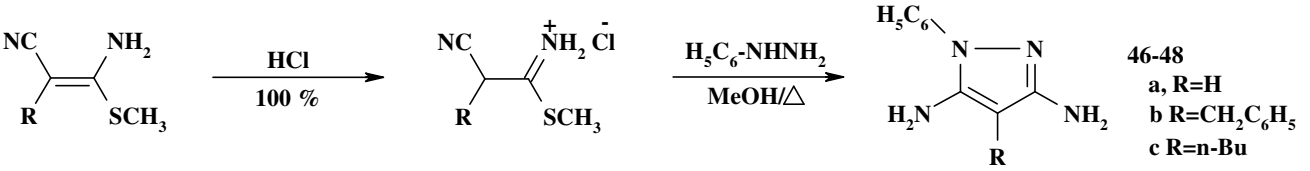
The alkylhydrazinocarbonyl(thiocarbonyl)pyrazolecarboxylates **45** were prepared by the reaction of 2-cyano-3-(2-cyanoethylthio)-3-methylthioacrylic acid esters **43** with either carbonohydrazides or thiocarbonohydrazides **44** (Scheme 17).[147]



43 a R=CH_3, b R=C_2H_5 **44** a Z=O, b Z=S **45**

Scheme 17

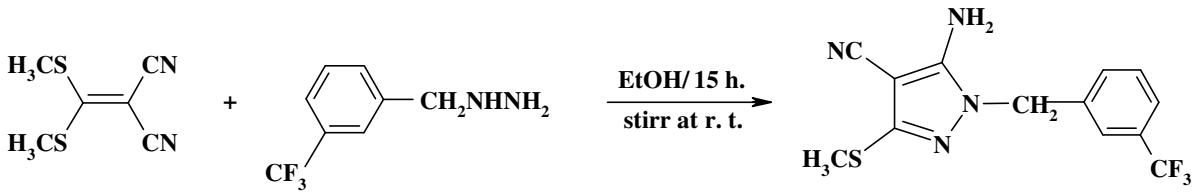
The 2-substituted 3-amino-3-(methylthio)acrylonitriles cyanoketene **46** were converted into its imino esters hydrochloride salts **47** when treated with dry etheral hydrogen chloride, then compounds **47** reacted with phenylhydrazine to yield the 4-substituted 3,5-diaminopyrazoles **48** (Scheme 18).[148]



46 **47** **48**

Scheme 18

When compound **3a** was stirred in ethanol with trifluoromethylbenzylhydrazine **49** the pyrazole derivative **50** was produced (Scheme 19).[149]



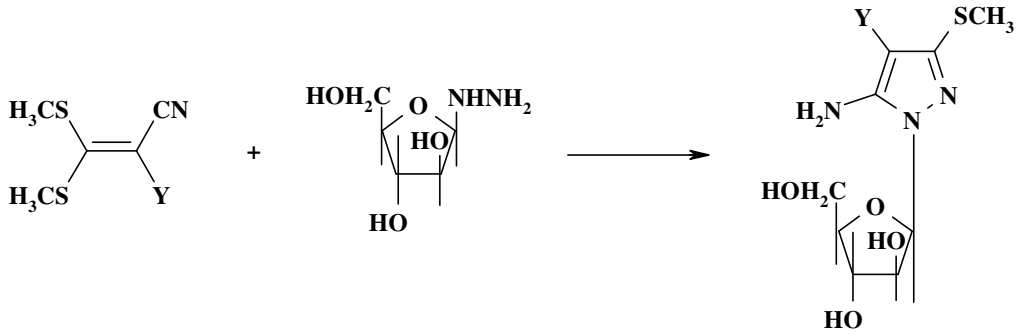
3a **49** **50**

Scheme 19

It has been reported that ketene-*S,S*-acetals **3a,d** reacted with 1-ribofuranosylhydrazine **51** to give the interesting pyrazole nucleosides **52** (Scheme 20).[150-152]

The reaction of ketene dithioacetals **3b,c** with coumarins **53** has been extensively utilized for the synthesis of the pyrazolecarboxylate derivatives **54** (Scheme 21).[153,154]

The 3-arylsulfonylaminopyrazoles **56** were synthesized from the reaction of 3-arylsulfonylamino-3-methylthiocyanoacrylates **55** with hydrazine derivatives **29b,e** (Scheme 22).[155]

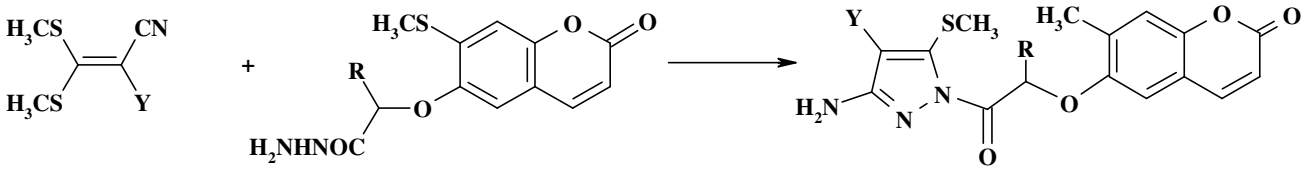


3
a, Y=CN
d, Y=CONH$_2$

51

52

Scheme 20

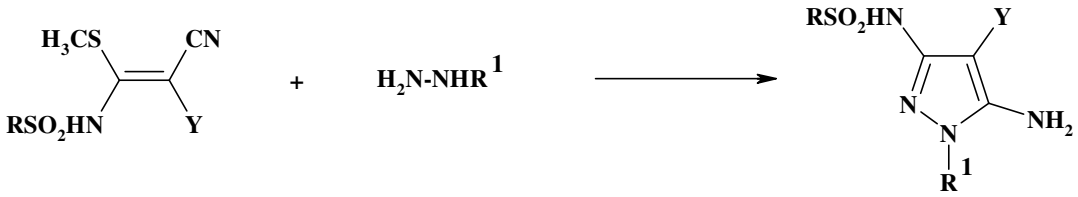


3
b Y=CO$_2$CH$_3$
c Y=CO$_2$C$_2$H$_5$

53

54	**Y**	**R**
a	**CO$_2$CH$_3$**	**H**
b	**CO$_2$CH$_3$**	**CH$_3$**
c	**CO$_2$C$_2$H$_5$**	**H**
d	**CO$_2$C$_2$H$_5$**	**CH$_3$**

Scheme 21



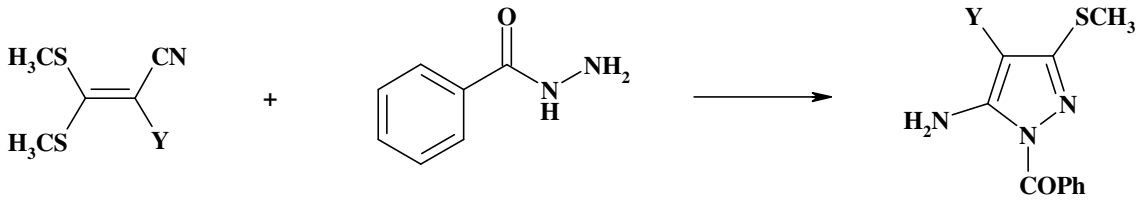
55

29b,e

56

Scheme 22

The 5-amino-1-benzoyl-3-(methylthio)pyrazole derivatives **58** were obtained by the reaction of ketene-*S,S*-acetals **3c,d** with hydrazides **57** (Scheme 23).[156,157]



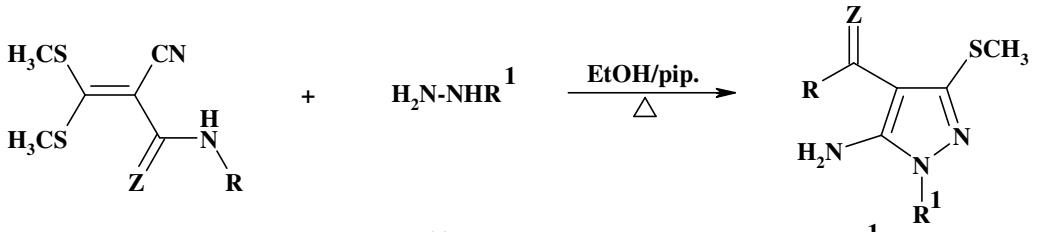
3
c Y=CO$_2$C$_2$H$_5$
d Y=CONH$_2$

57

58

Scheme 23

Recently, it has been reported that when compounds **3q-u** were subjected to react with hydrazine derivatives **29a,b** in refluxing ethanol containing catalytic amount of piperidine, the 5-amino-3-(methylthio)pyrazoles **59** were produced (Scheme 24).[123]

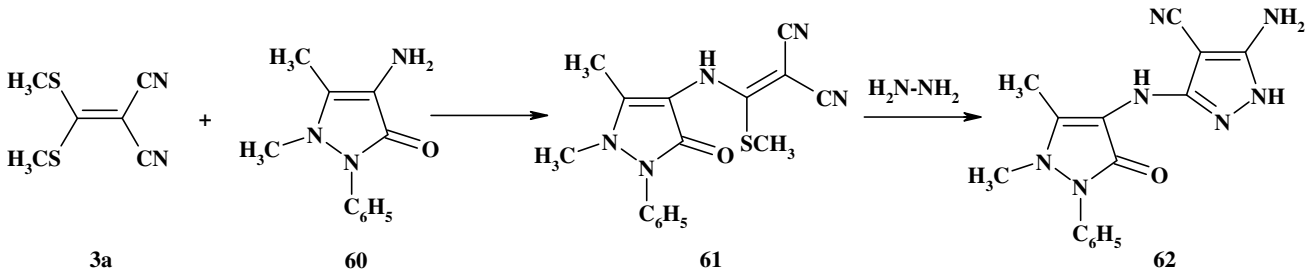


3q-u **29a,b**

59	R	R^1	Z	59	R	R^1	Z
a	C_6H_5	H	O	f	C_6H_5	C_6H_5	O
b	4-ClC_6H_4	H	O	g	4-ClC_6H_4	C_6H_5	O
c	4-$CH_3C_6H_4$	H	O	h	4-$CH_3C_6H_4$	C_6H_5	O
d	4-$OCH_3C_6H_4$	H	O	i	4-$OCH_3C_6H_4$	C_6H_5	O
e	H	H	S	j	H	C_6H_5	S

Scheme 24

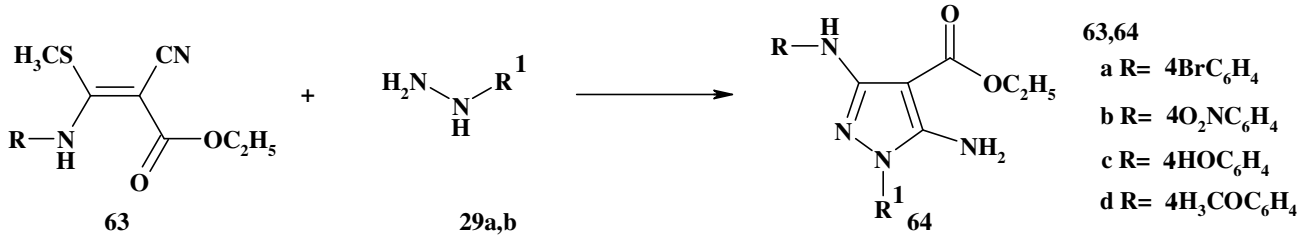
Compound **3a** reacted with 4-aminoantipyrine **60** to give antipyrine derivative **61**; when the latter compound was treated with hydrazine, the 5-amino-3-(*p*-antipyrylamino)pyrazole-4-carbonitrile **62** was afforded (Scheme 25).[158]



3a **60** **61** **62**

Scheme 25

Recently, it has been shown that the substituted pyrazoles **64** were synthesized by the reaction of ketene-*N*,*S*-acetals **63** with hydrazine derivatives **29a,b** (Scheme 26).[159]

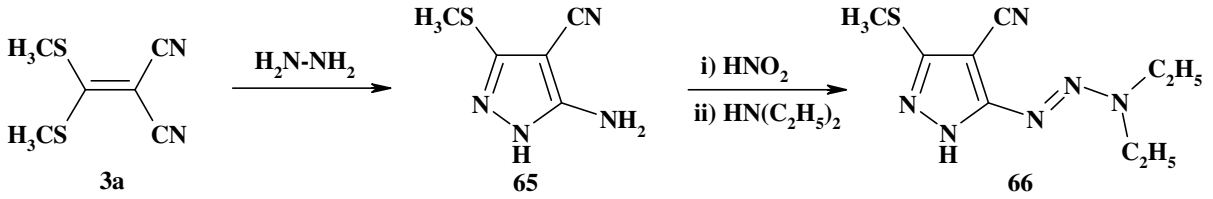


63 **29a,b**

63,64
- **a** R= 4-BrC_6H_4
- **b** R= 4-$O_2NC_6H_4$
- **c** R= 4-HOC_6H_4
- **d** R= 4-$H_3COC_6H_4$

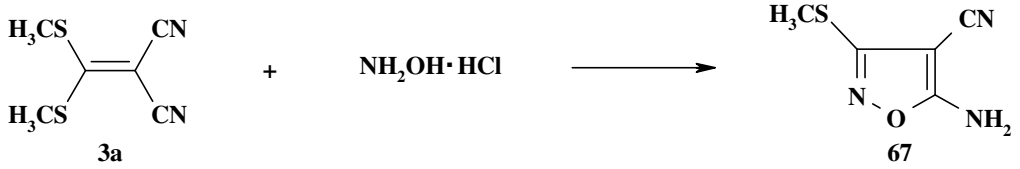
Scheme 26

The condensation of **3a** with hydrazine hydrate yielded the 5-amino-3-(methylthio)pyrazole-4-carbonitrile **65**. Treatment of compound **65** with nitrous acid and then coupling with diethylamine yielded the 5-(3,3-diethyl-1-triazeno)pyrazole-4-carbonitriles **66** (Scheme 27).[160]



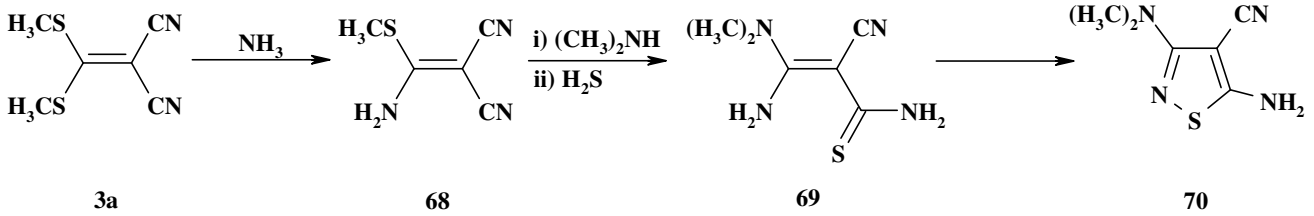
Scheme 27

The isoxazole derivative **67** was produced by the reaction of compound **3a** with hydroxylamine hydrochloride (Scheme 28).[161]



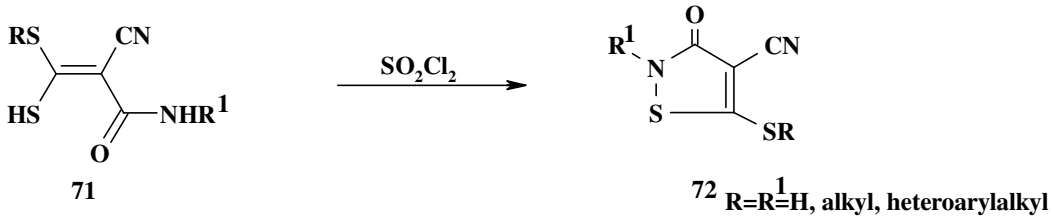
Scheme 28

Treatment of **3a** with ammonia afforded 2-amino-2-(methylthio)methylene malononitrile **68**. The latter reacted with *N,N*-dimethylamine and hydrogen sulfide to give compound **69**, which was cyclized oxidativly to give the 5-amino-3-dimethylaminoisothiazole-4-carbonitrile **70** (Scheme 29).[99]

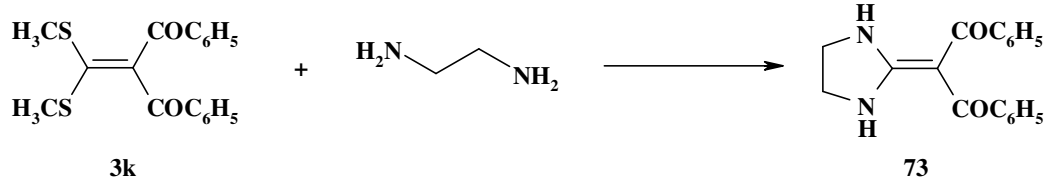


Scheme 29

The cyclization of 3-alkylthio-3-mercapto-2-cyanoacrylamides **71**, by using sulphonyl chloride yielded the corresponding 5-alkylthio-3-oxoisothiazole-4-carbonitriles **72** (Scheme 30).[162]



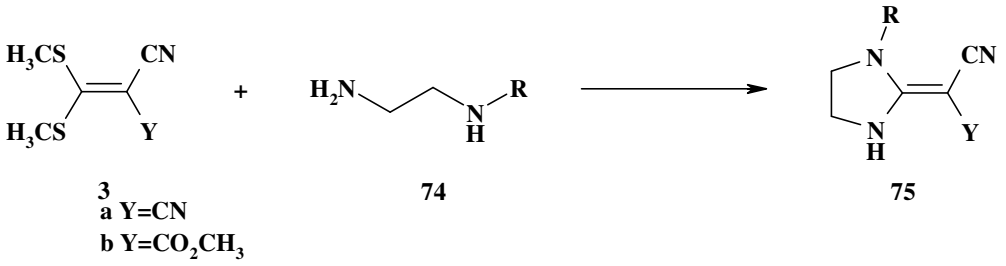
Scheme 30



Scheme 31

It has been reported that ketene dithioacetal **3k** reacted with diamine to give the cyclic heteroacetales **73** (Scheme 31).[163]

The cyano-substituted heterocyclic ketene aminals **75** were synthesized by the reaction of cyano-substituted ketene mercaptals **3a,b** with diamines **74** (Scheme 32).[164]



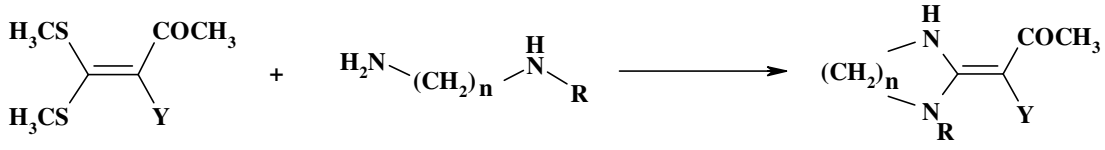
3
a Y=CN
b Y=CO_2CH_3

74

75

Scheme 32

The reaction of ketene dithioacetals **3g-i** with aliphatic diamine compounds **76** afforded the acetyl-substituted heterocyclic ketene aminals **77** (Scheme 33).[165]



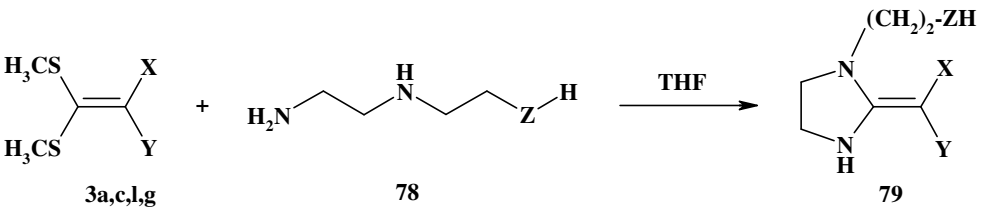
3g-i

76
a, n=2
b, n=3

77	Y	R	77	Y	R
a	$COCH_3$	H	d	$COCH_3$	CH_3
b	CO_2CH_3	H	e	CO_2CH_3	CH_3
c	$CO_2C_2H_5$	H	f	$CO_2C_2H_5$	CH_3

Scheme 33

The imidazolidine derivatives **79** were prepared by the reaction of ketene-*S,S*-acetals **3a,c,l,g** with diethylene triamine or 2-(2-aminoethylamino)ethanol **78** in tetrahydrofuran (Scheme 34).[166,167]



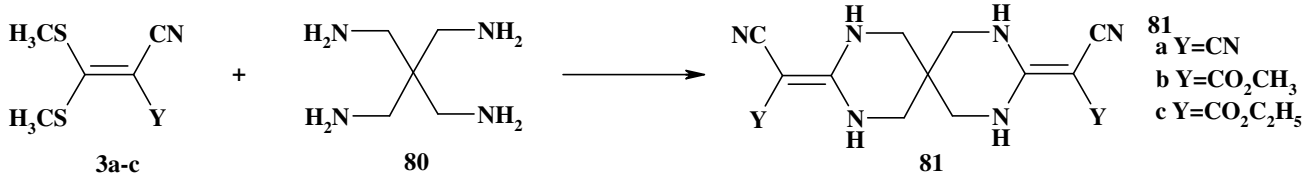
3a,c,l,g

78

79

79	X	Y	Z
a	CN	CN	NH
b	CN	CN	O
c	CN	$CO_2C_2H_5$	O
d	H	NO_2	O
e	$COCH_3$	$COCH_3$	O

Scheme 34



3a-c

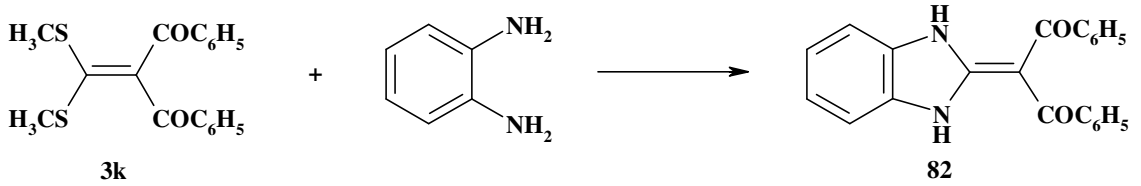
80

81
a Y=CN
b Y=CO_2CH_3
c Y=$CO_2C_2H_5$

Scheme 35

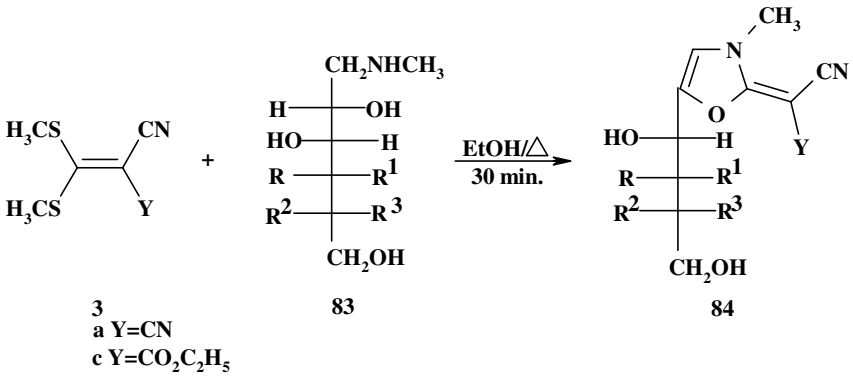
The synthesis of the previously unknown spiro heterocyclic ketene aminals, 3,9-bis(substituted-methylene)-2,4,8,10-tetraazaspiro[5.5]undecane **81** by the cyclocondensation reaction of ketene dithioacetals **3a-c** with tetrakis(aminomethyl)methane **80** was carried out (Scheme 35).[168]

The cyclic heteroacetale derivative **82** was prepared by the reaction of compound **3k** with *o*-phenylenediamine (Scheme 36).[163]



Scheme 36

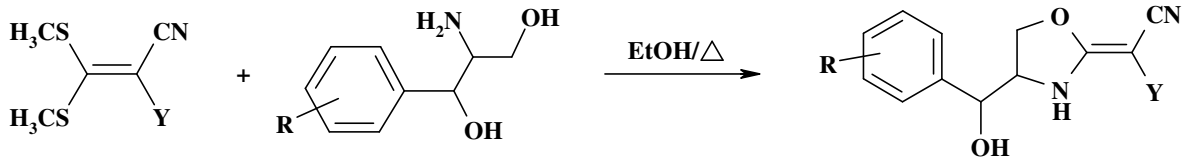
The synthesis of acyclic *C*-nucleosides **84** were obtained through the reaction of ketene dithioacetals **3a,c** with 1-deoxy-1-(methylamino)-*D*-hexitols **83** (Scheme 37).[169]



84	Y	R	R^1	R^2	R^3
a	CN	H	OH	H	OH
b	CN	OH	H	H	OH
c	CN	OH	H	OH	H
d	$CO_2C_2H_5$	H	OH	H	OH
e	$CO_2C_2H_5$	OH	H	H	OH
f	$CO_2C_2H_5$	OH	H	OH	H

Scheme 37

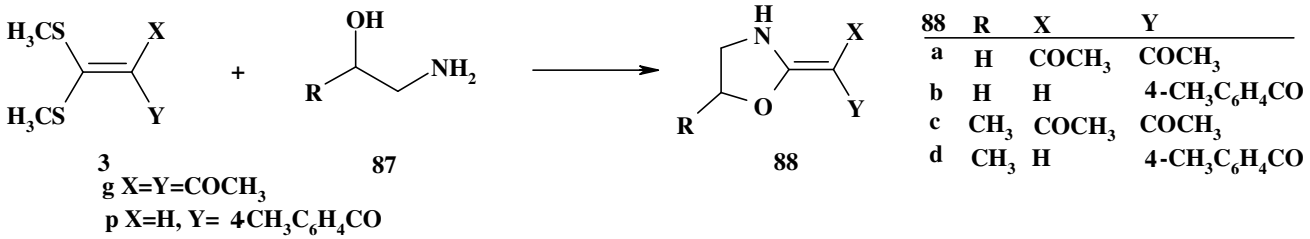
It has been reported that the reaction of compounds **3a,c,d** with 2-amino-1-aryl-propane-1,3-diols **85** afforded the 1,3-oxazolidines **86** (Scheme 38).[170,171]



86	Y	R	86	Y	R
a	CN	H	d	CN	NO_2
b	$CO_2C_2H_5$	H	e	$CO_2C_2H_5$	NO_2
c	$CONH_2$	H	f	$CONH_2$	NO_2

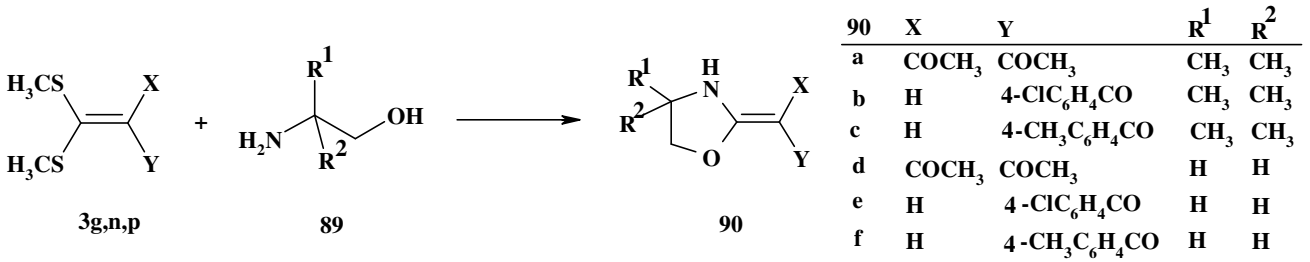
Scheme 38

Huang and Zhang have found that ketene dithioacetals **3g,p** reacted with 2-aminoethanol or 1-amino-2-propanol **87** to yield the substituted 2-methyleneoxazolidines **88** (Scheme 39).[172]

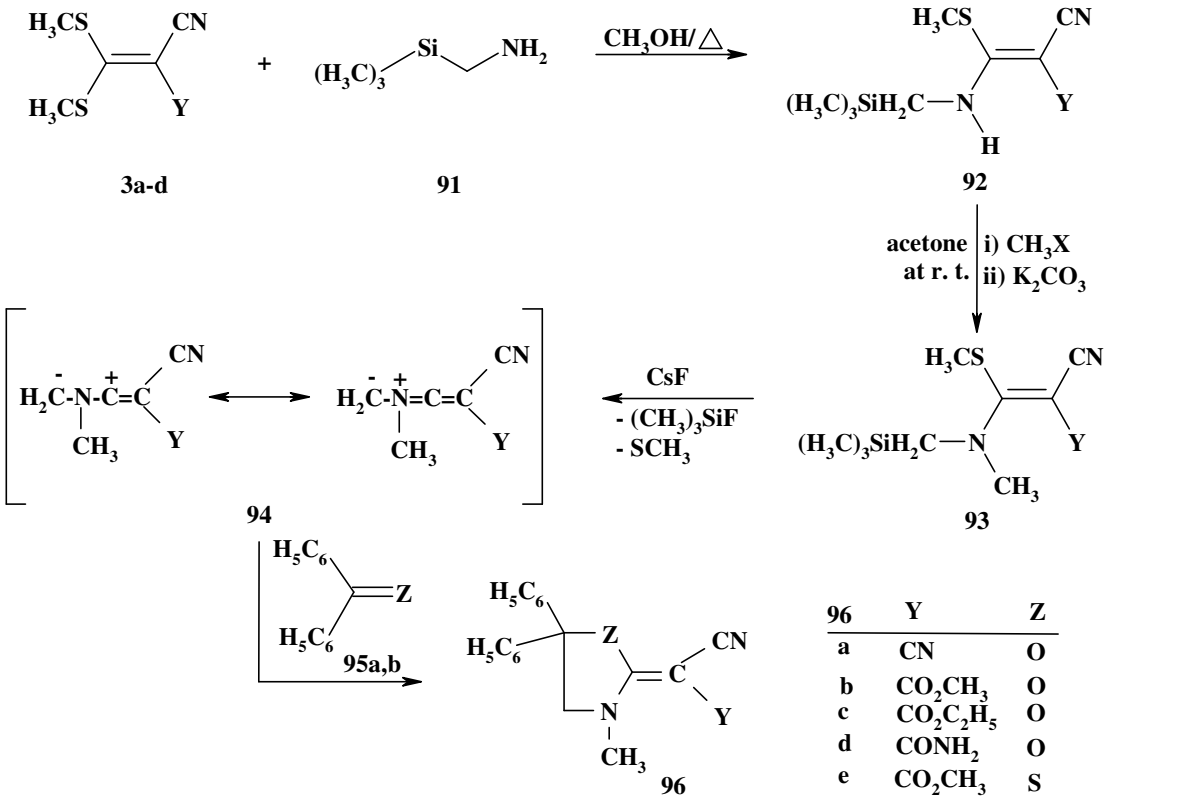


Scheme 39

They have also reported that the reaction of ketene dithioacetals **3g,n,p** with aminohydroxy compounds **89** gave the corresponding substituted oxazolidine derivatives **90** (Scheme 40).[117,173]



Scheme 40

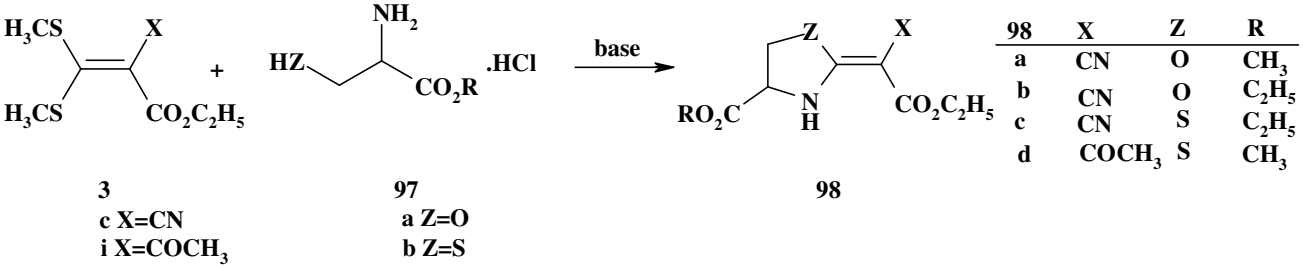


Scheme 41

The reaction of ketene dithioacetals **3a-d** with trimethylsilylmethylamine **91** in methanol yielded the corresponding *N,S*-acetals **92**. *N*-Alkylation of compounds **92** with alkyl halides in the presence of potassium carbonate in acetone at room temperature, gave the *N*-alkylated derivatives **93**. The latters reacted with

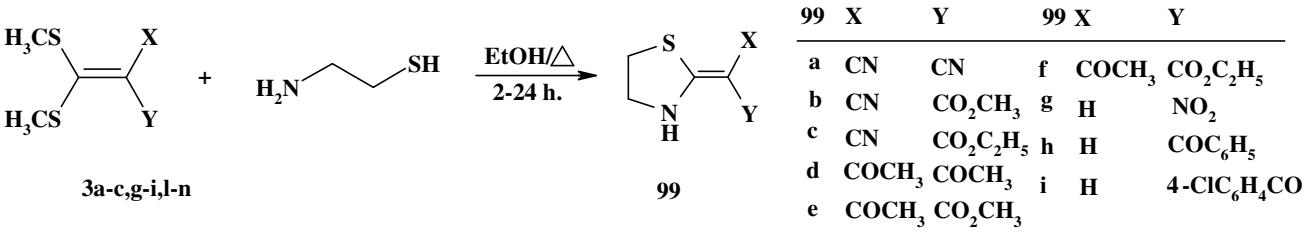
carbonyl compounds or thioketones **95a,b** in the presence of cesium fluoride to afford the corresponding oxazolidines and thiazolidines **96**, respectively (Scheme 41).[174]

The heterocyclic ketene *N*,*O*- and *N*,*S*-acetals with an ester substituent in heterocyclic ring **98** were synthesized by the reaction of ketene *S*,*S*-acetals **3c,i** with serine or cysteine esters hydrochloride **97** in the presence of a base (Scheme 42).[175]



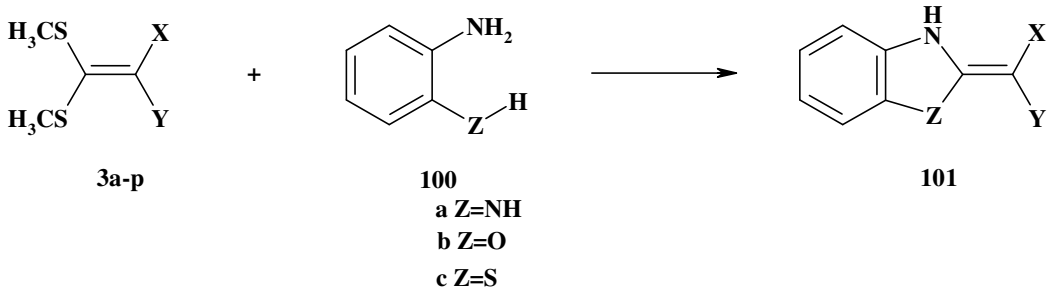
Scheme 42

Ketene dithioacetals **3a-c,g-i,l-n** reacted with 2-amino-1-ethanethiol in boiling ethanol to give the substituted 2-methylenethiazolidine derivatives **99** (Scheme 43).[176]

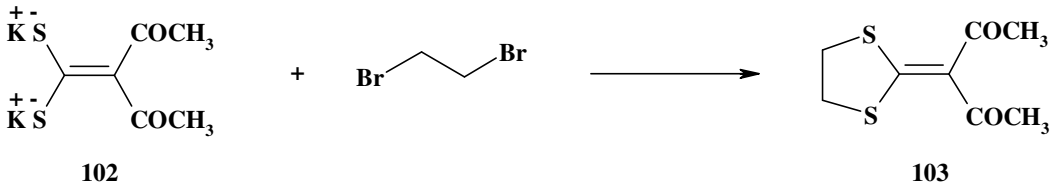


Scheme 43

The reaction of ketene *S*,*S*-acetals **3a-p** with *o*-substituted anilines **100a-c** produced the corresponding benzazole derivatives **101** (Scheme 44).[117,177-180]



Scheme 44

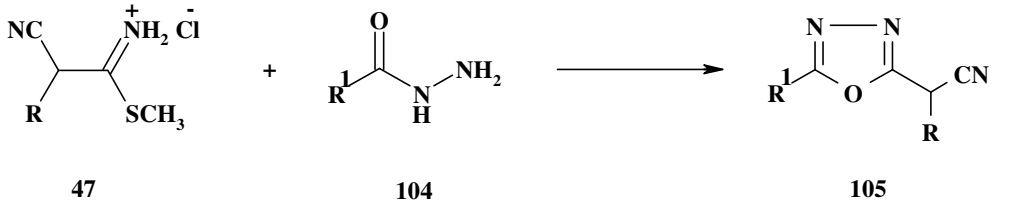


Scheme 45

The salt of 2,2-dioxoketene-*S*,*S*-acetal **102** was cyclized with 1,2-dibromoethane to give the dithiolanes **103** (Scheme 45).[118]

3.1.3. Five-membered rings with three hetero-atoms

Treatment of compounds **47** with carboxylic acid hydrazides **104** in boiling ethanol formed the 2,5-disubstituted 1,3,4-oxadiazole derivatives **105** (Scheme 46).[148]



47 104 105

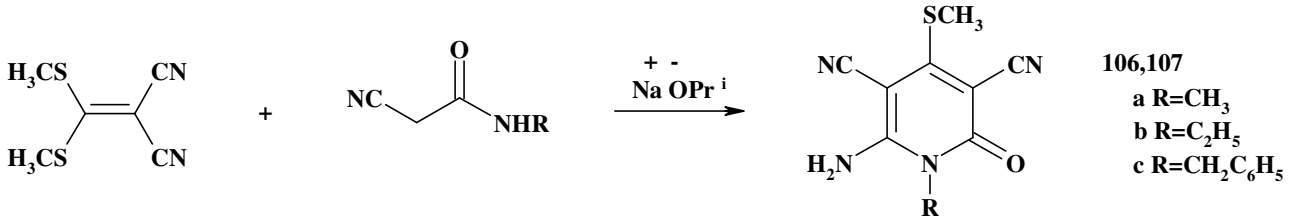
105	R	R1
a	H	C_6H_5
b	H	n-$C_{11}H_{23}$
c	n-Bu	C_6H_5
d	$C_6H_5CH_2$	C_6H_5

Scheme 46

3.2. Six-membered rings

3.2.1. Six-membered rings with one hetero-atom

The pyridine-2(1*H*)-one derivatives **107** were synthesized by the reaction of compound **3a** with *N*-alkylcyanoacetamides **106a-c** in the presence of sodium isopropoxide (Scheme 47).[97,181-183]

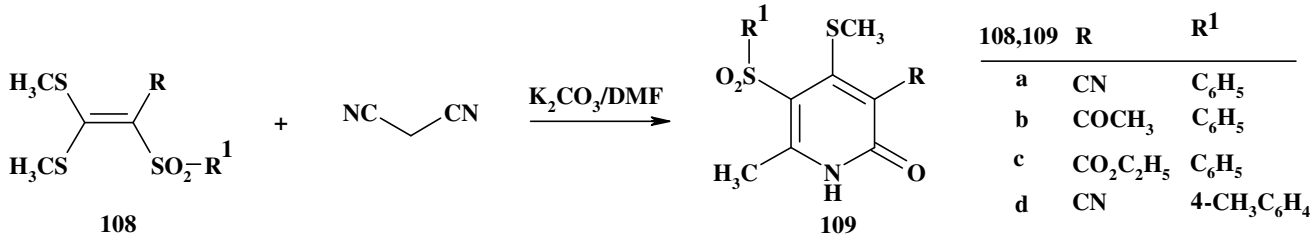


3a 106 107

106,107
a R=CH_3
b R=C_2H_5
c R=$CH_2C_6H_5$

Scheme 47

The sulphonylketene dithioacetals **108** were condensed with malononitrile to give the 3-cyano-6-methyl-4-(methylthio)-5-phenylsulphonyl-2-pyridones **109** (Scheme 48).[184]



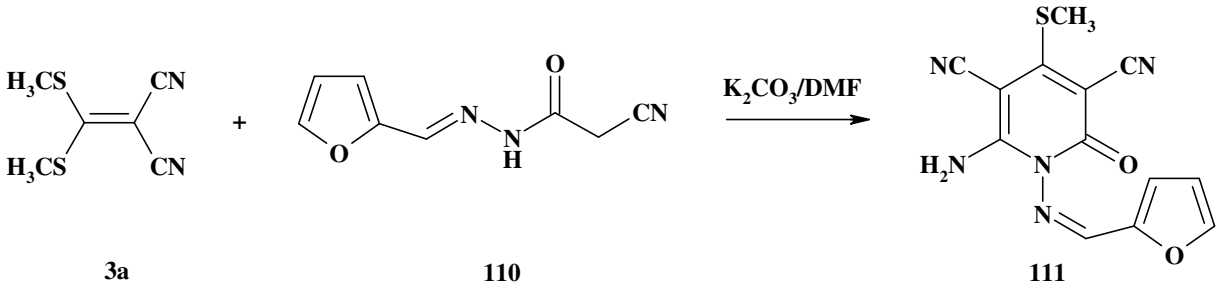
108 109

108,109	R	R1
a	CN	C_6H_5
b	$COCH_3$	C_6H_5
c	$CO_2C_2H_5$	C_6H_5
d	CN	4-$CH_3C_6H_4$

Scheme 48

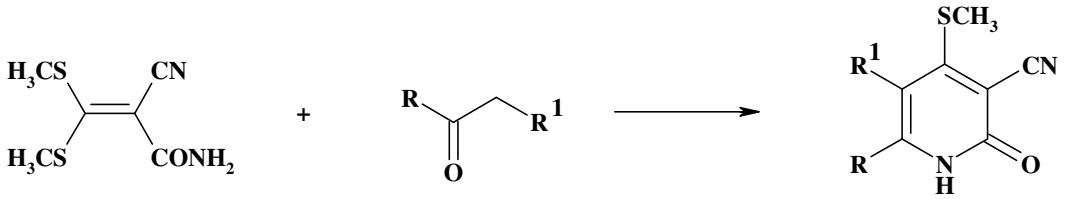
It has been reported that the substituted 6-amino-1-(fur-2-ylmethyleneamino)-1,2-dihydro-4-(methylthio)-2-oxopyridine-3,5-dicarbonitrile **111** was prepared by cyclization of **3a** with furan derivative **110** (Scheme 49).[185]

The reaction of **3d** with substituted ketones **112** afforded the corresponding 3-cyano-4-(methylthio)-2-oxopyridine-3-carbonitriles **113** (Scheme 50).[186]



3a **110** **111**

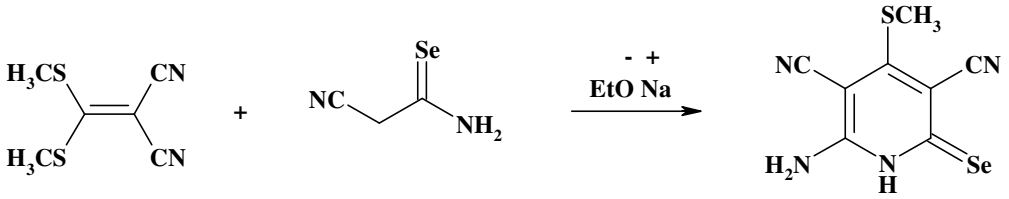
Scheme 49



3d **112** **113**

Scheme 50

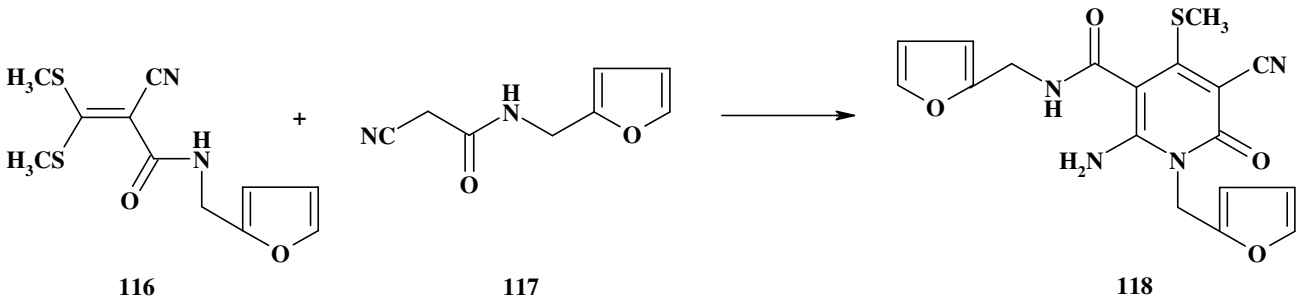
The cyclocondensation of compound **3a** with cyanoselenoacetamide **114** has been utilized for the synthesis of the 6-amino-3,5-dicyano-4-(methylthio)-2(1*H*)-pyridineselenone **115** (Scheme 51).[187]



3a **114** **115**

Scheme 51

Peseke *et al.* have shown that the reaction of ketene dithioacetal **116** with *N*-furfurylcyanoacetamide **117** gave the pyridonecarboxamide derivative **118** (Scheme 52).[188-191]



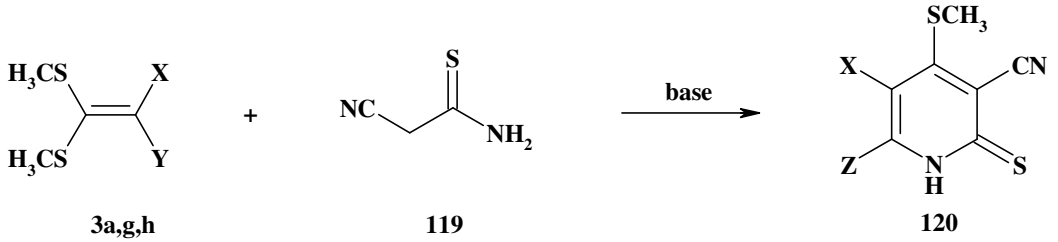
116 **117** **118**

Scheme 52

Ketene *SS*-acetales **3a,g,h** reacted with 2-cyanothioacetamide **119** in basic condition to form the corresponding pyridinethiones **120** (Scheme 53).[192,193]

Elgemeie *et al.* have found that **3a,c** reacted with 1-cyanoacetyl-4-substituted thiosemicarbazides **121** at r.t. in the presence of potassium hydroxide in dioxan to give the corresponding *N*-(4-methylthio-2-oxo-1-

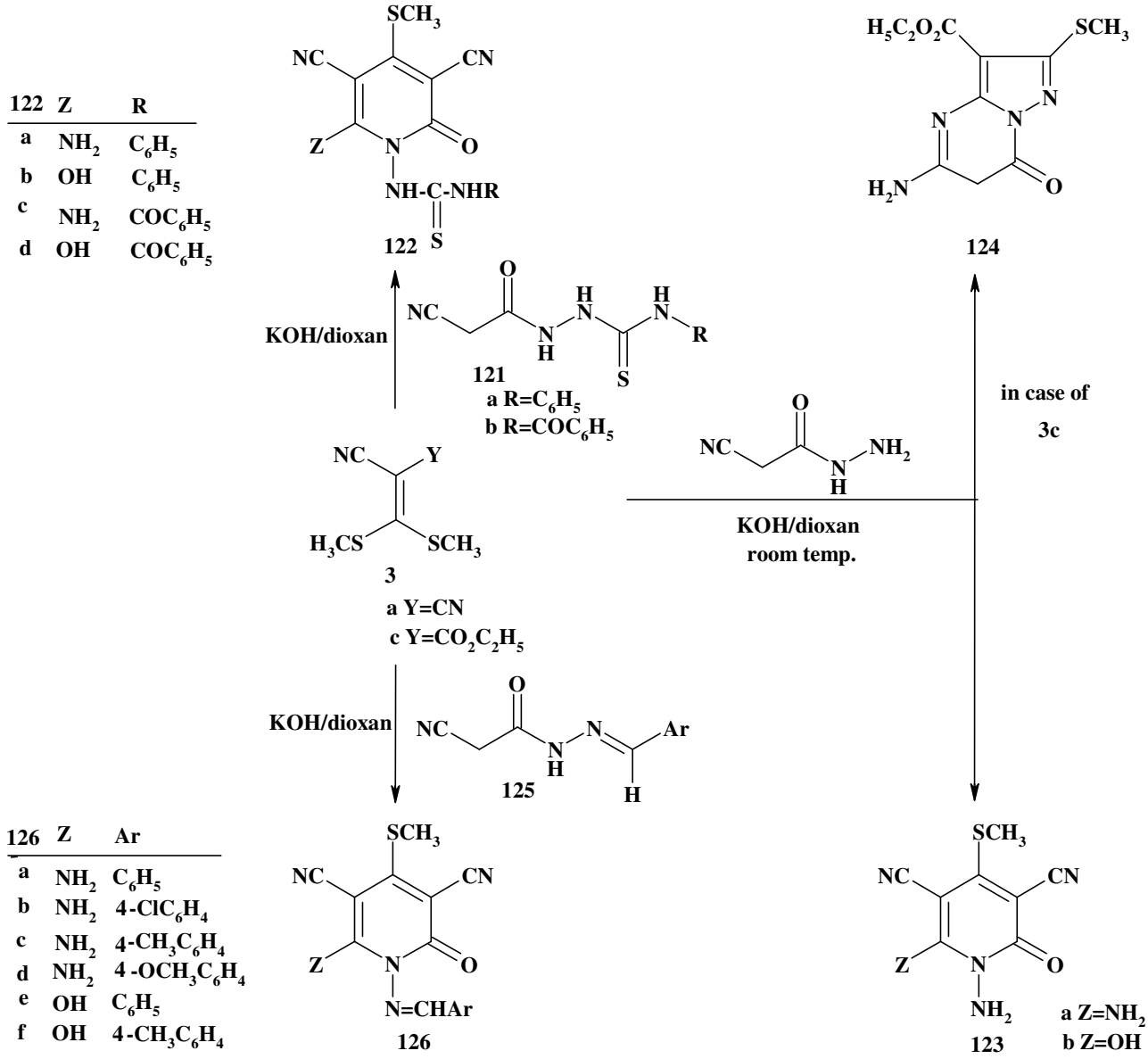
pyridyl)thiourea derivatives **122**. In a typical experiment, when **3a,c** reacted with cyanoacetohydrazide at r. t. in the presence of potassium hydroxide in dioxane, the *N*-amino-4-methylthio-2-pyridones **123** were produced. In related work Peseke *et al.*[194] have reported the synthesis of compound **124** by the reaction of **3c** with cyanoacetohydrazide in ethanol under reflux. Reaction of ketene dithioacetals **3a,c** with Schiff bases was also examined. Thus, when **3a,c** were reacted with 1-cyanoacetyl-4-arylidenesemicarbazides **125** in the presence of potassium hydroxide in dioxane, the Schiff bases **126** were obtained (Scheme 54).[195]



3a,g,h **119** **120**

Scheme 53

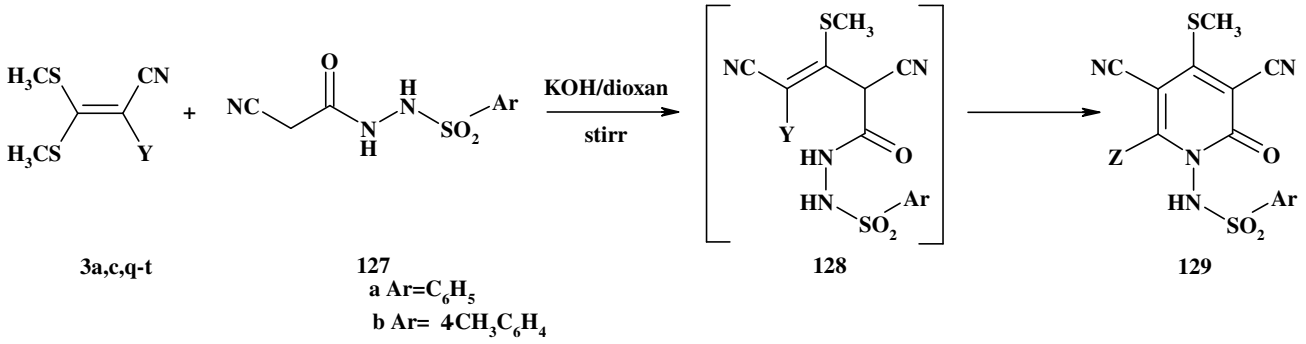
122	Z	R
a	NH_2	C_6H_5
b	OH	C_6H_5
c	NH_2	COC_6H_5
d	OH	COC_6H_5



126	Z	Ar
a	NH_2	C_6H_5
b	NH_2	$4\text{-}ClC_6H_4$
c	NH_2	$4\text{-}CH_3C_6H_4$
d	NH_2	$4\text{-}OCH_3C_6H_4$
e	OH	C_6H_5
f	OH	$4\text{-}CH_3C_6H_4$

Scheme 54

They have also reported that ketene-*S,S*-acetals **3a,c,q-t** reacted with *N*-cyanoarylsulphonylhydrazides **127** in dioxane containing a catalytic amount of potassium hydroxide to yield the corresponding 4-(methylthio)-*N*-arylsulphonylamino-2-pyridone derivatives **129** (Scheme 55).[196]

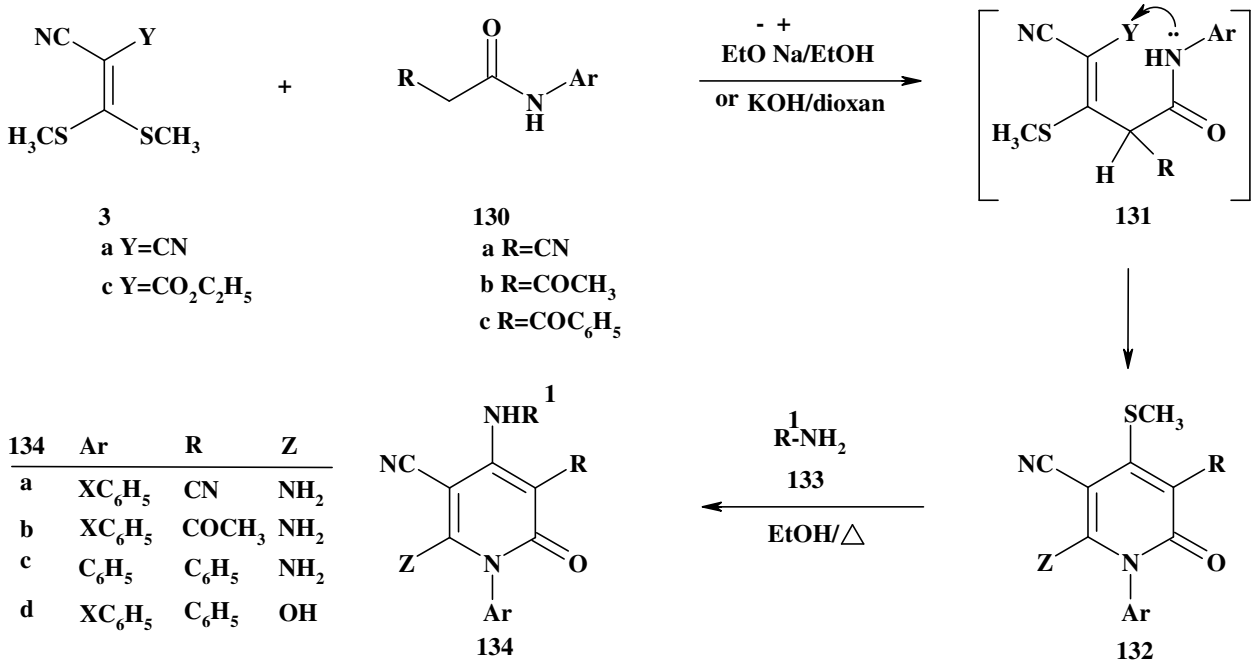


3a,c,q-t **127** **128** **129**

a Ar=C_6H_5
b Ar= 4$CH_3C_6H_4$

Scheme 55

Recently, they have been shown that both **3a** and **3c** reacted with substituted acetanilides **130** in a solution of sodium ethoxide or potassium hydroxide in dioxane to give the corresponding *N*-aryl-4-(methylthio)-2-pyridones **132**. Compounds **132** reacted with aromatic amines **133** in fusion to afford the corresponding 4-amino-2-pyridone derivatives **134** (Scheme 56).[197]



3
a Y=CN
c Y=$CO_2C_2H_5$

130
a R=CN
b R=$COCH_3$
c R=COC_6H_5

131

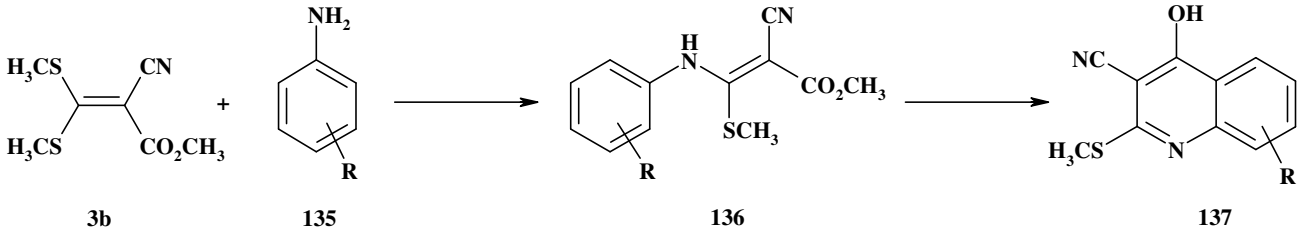
134	Ar	R	Z
a	XC_6H_5	CN	NH_2
b	XC_6H_5	$COCH_3$	NH_2
c	C_6H_5	C_6H_5	NH_2
d	XC_6H_5	C_6H_5	OH

134 **132**

Scheme 56

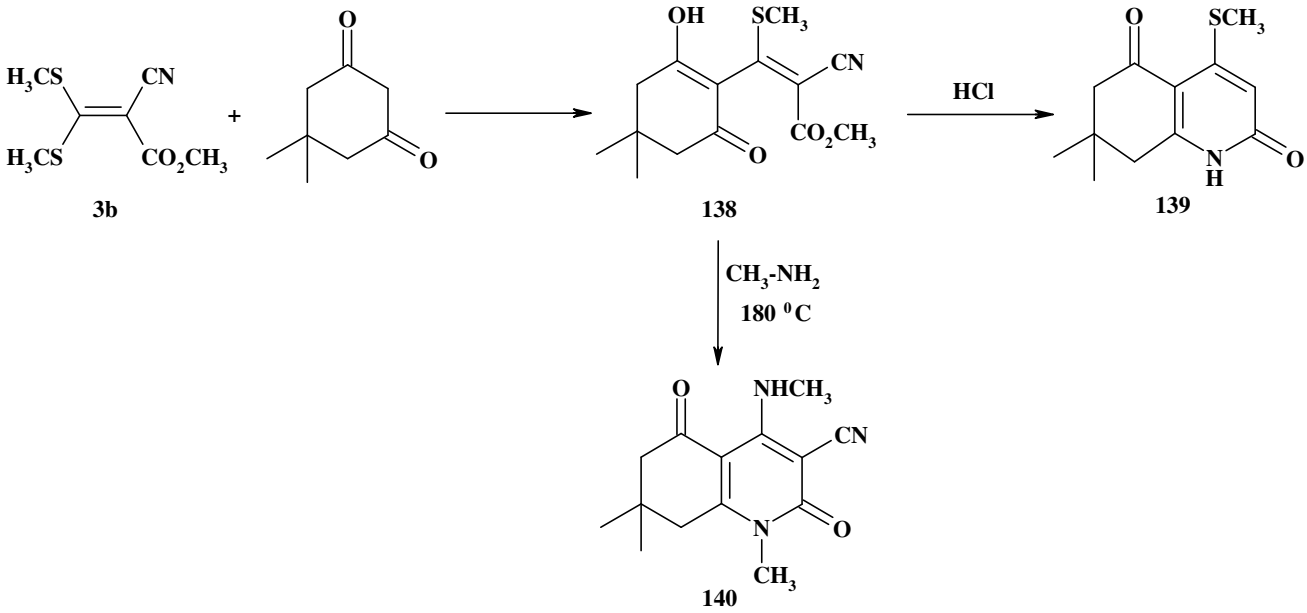
The reaction of ketene-*S,S*-acetal **3b** with aromatic amines **135** gave ketene-*N,S*-acetals **136**, which were cyclized to yield the quinoline derivatives **137** (Scheme 57).[198]

When compound **3b** reacted with dimedone, coumarin derivative **138** was formed. The latter compound **138** was cyclized with hydrochloric acid or methylamine to give the corresponding quinolone derivative **139** or **140**, respectively (Scheme 58).[199]



3b 135 136 137

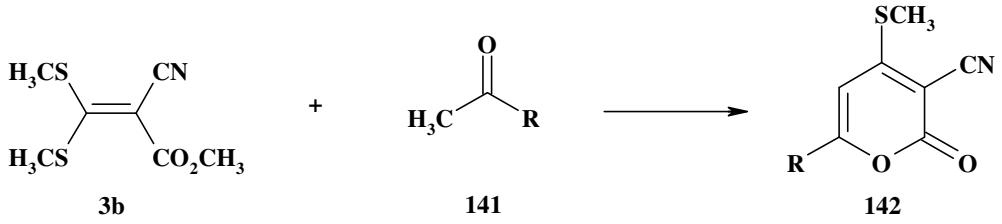
Scheme 57



3b 138 139 140

Scheme 58

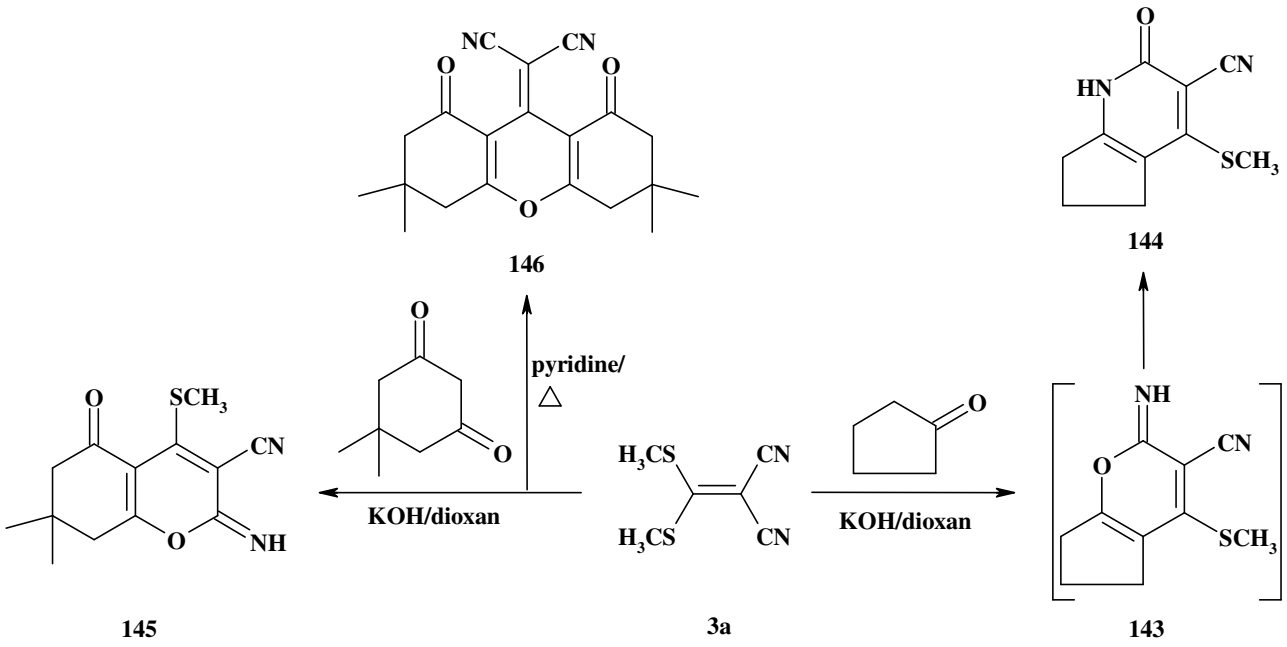
It has been found that the pyran-2-one derivatives **142** were synthesized through the reaction of **3b** with substituted ketones **141** (Scheme 59).[200-204]



3b 141 142

Scheme 59

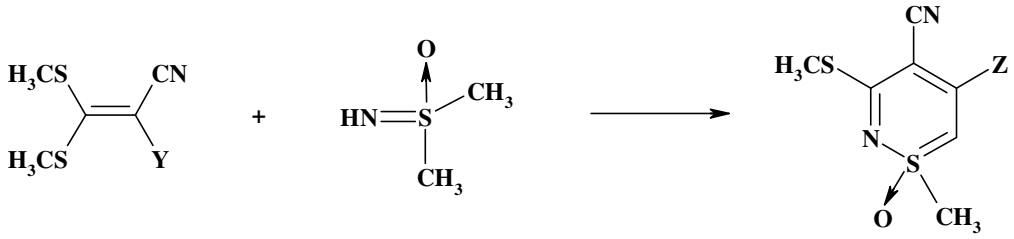
Ketene dithioacetal **3a** reacted with cyclopentanone when the reaction was conducted in the presence of potassium hydroxide in dioxane: the expected cycloalkane ring fused 4-methylsulfanyl-2(1*H*)-pyridone **144** was obtained. In contrast to the behavior of **3a** toward cyclopentanone in potassium hydroxide in dioxane, ketene dithioacetal **3a** reacted with dimedone under the same condition to give the cyclocondensed 2-pyran derivative **145** and not the expected 2(1*H*)-pyridone derivative. On the other hand, the dimedone anhydride derivative **146** was obtained by the reaction of **3a** with dimedone in refluxing pyridine (Scheme 60).[205]



Scheme 60

3.2.2. Six-membered rings with two hetero-atoms

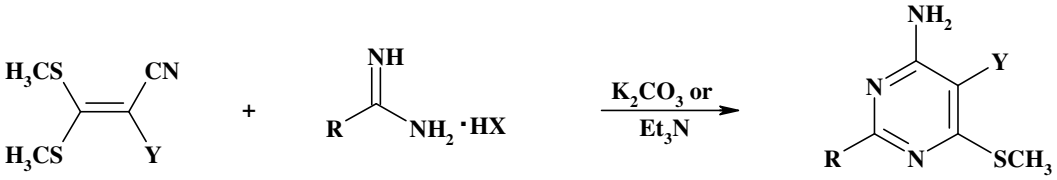
It has been reported that ketene dithioacetals **3a-c** reacted with compound **147** to produce the 1-methyl-2-azathiabenzene-1-oxide derivatives **148** (Scheme 61).[206-208]



3a-c **147** **148**

Scheme 61

The syntheses of the pyrimidines **150** were generally attained by the condensation reaction of ketene dithioacetals **3a,b,f** with amidine derivatives **149a-d** in the presence of an appropriate base (Scheme 62).[209-213]



3a,b,f

149

a R=CH_3 · HCl

b R=SCH_3 · H_2SO_4

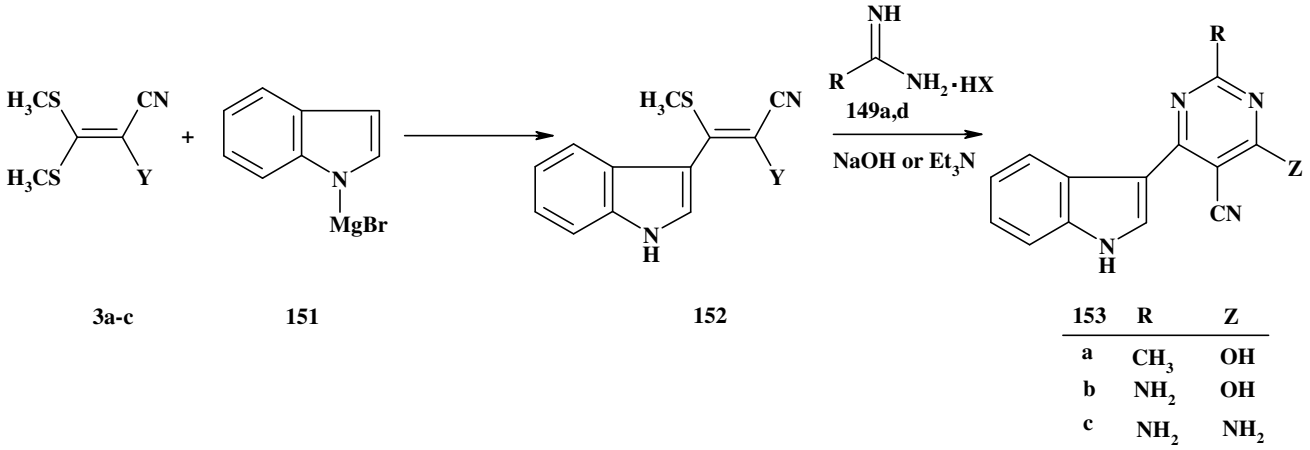
c R=C_6H_5 · HCl

d R=NH_2 · H_2SO_4

150	R	Y
a	SCH_3	CN
b	C_6H_5	CN
c	NH_2	CN
d	CH_3	CO_2CH_3
e	CH_3	$SO_2C_6H_5$

Scheme 62

The 4-(3-indolyl)pyrimidine derivatives **153** were obtained by the reaction of ketene dithioacetals **3a-c** with indolylmagnesium bromide **151** to give 3-indoleacrylate derivatives **152**. The latters smoothly condensed with amidines **149a,d** in the presence of a base (Scheme 63).[214]

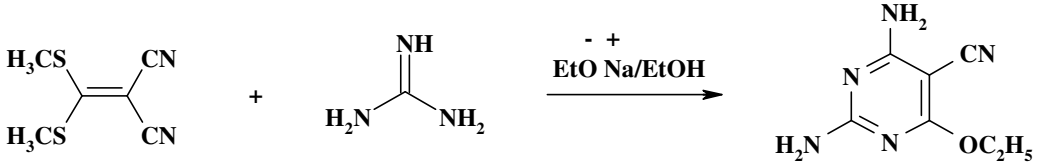


3a-c 151 152

153	R	Z
a	CH_3	OH
b	NH_2	OH
c	NH_2	NH_2

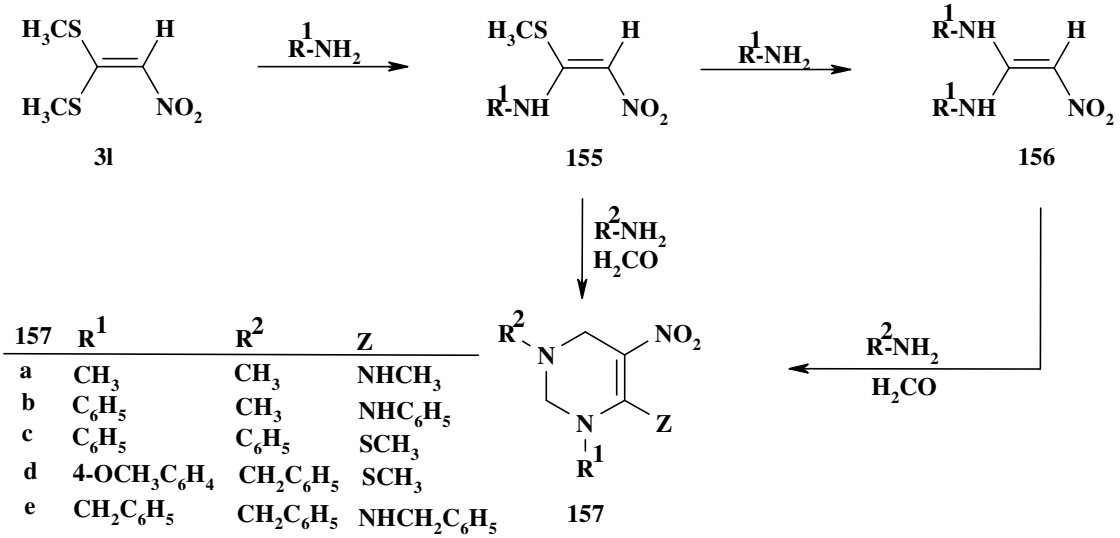
Scheme 63

The reaction of **3a** with guanidine **149d** in the presence of ethanol containing ethoxide gave the 2,4-diamine-6-ethoxypyrimidine-5-carbonitrile **154** (Scheme 64).[210]



3a 149d 154

Scheme 64



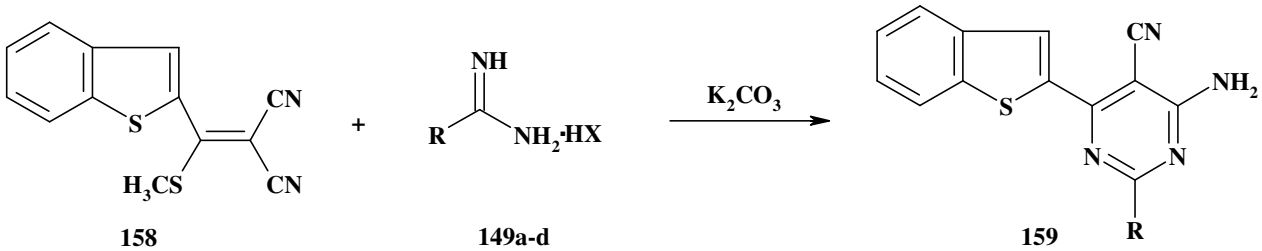
3l 155 156 157

157	R^1	R^2	Z
a	CH_3	CH_3	$NHCH_3$
b	C_6H_5	CH_3	NHC_6H_5
c	C_6H_5	C_6H_5	SCH_3
d	4-$OCH_3C_6H_4$	$CH_2C_6H_5$	SCH_3
e	$CH_2C_6H_5$	$CH_2C_6H_5$	$NHCH_2C_6H_5$

Scheme 65

Compound **3l** reacted with amines to yield nitroamine derivatives **155, 156**; each of them was reacted with formaldehyde and primary amine to give the 1,2,3,6-tetrahydropyrimidine derivatives **157** (Scheme 65).[215]

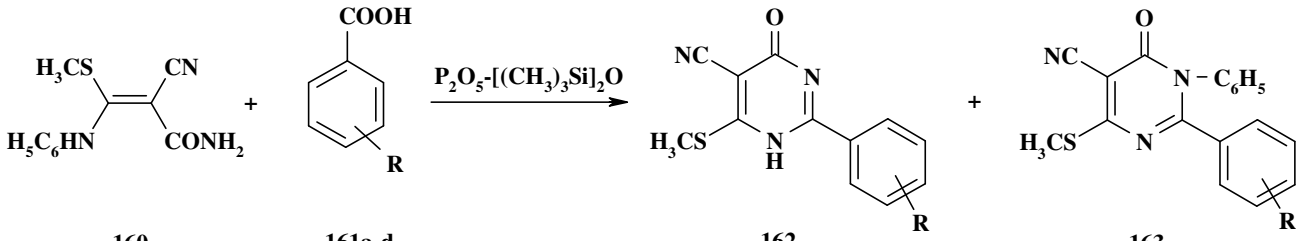
Compound **158** also reacted with amidine derivatives **149a-d** in the presence of potassium carbonate to give the corresponding pyrimidine derivatives **159** (Scheme 66).[216]



158 **149a-d** **159**

Scheme 66

The cyclocondensation of ketene-*N,S*-acetal **160** with carboxylic acid derivatives **161a-d** gave the 1,4-dihydro-4-oxo-6-(methylthio)pyrimidine-5-carbonitriles **162, 163** (Scheme 67).[217]

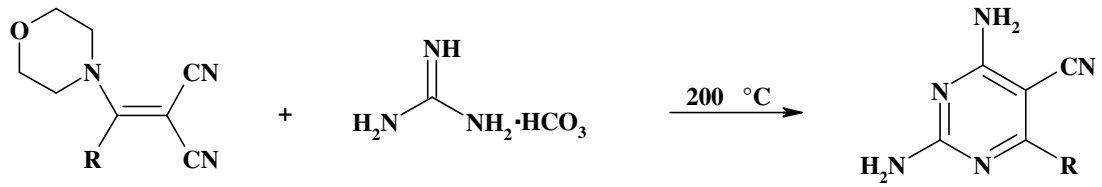


160 **161a-d** **162** **163**

161-163
a R=H
b R= 4Cl
c R= 4CH_3
d R= 4NO_2

Scheme 67

Tominaga *et al.* have found that the polarized ethylenes **164** were smoothly reacted with guanidine carbonate **149d** to yield the corresponding 2,4-diaminopyrimidine-5-carbonitrile derivatives **165** (Scheme 68).[218]

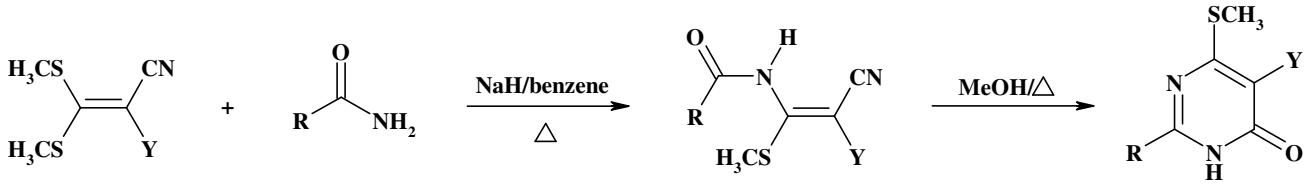


164 **149d** **165**

164,165
a R=C_6H_5
b R= 4ClC_6H_4
c R= 4$OCH_3C_6H_4$
d R= 2thienyl

Scheme 68

The reaction of ketene dithioacetals **3a,b** with carboxamides **166** in sodium hydride/benzene mixture yielded compounds **167**. The latters were cyclized in refluxing methanol to give the pyrimidine derivatives **168** (Scheme 69).[211]



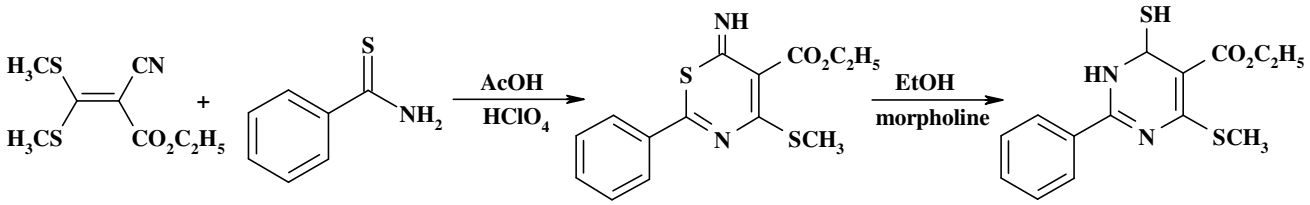
3
a Y=CN
b Y= CO_2CH_3

166

167,168	R	Y	167,168	R	Y
a	C_6H_5	CN	e	C_6H_5	CO_2CH_3
b	4-$NO_2C_6H_4$	CN	f	4-$NO_2C_6H_4$	CO_2CH_3
c	4-$CH_3C_6H_4$	CN	g	4-$CH_3C_6H_4$	CO_2CH_3
d	4-$OCH_3C_6H_4$	CN	h	4-$OCH_3C_6H_4$	CO_2CH_3

Scheme 69

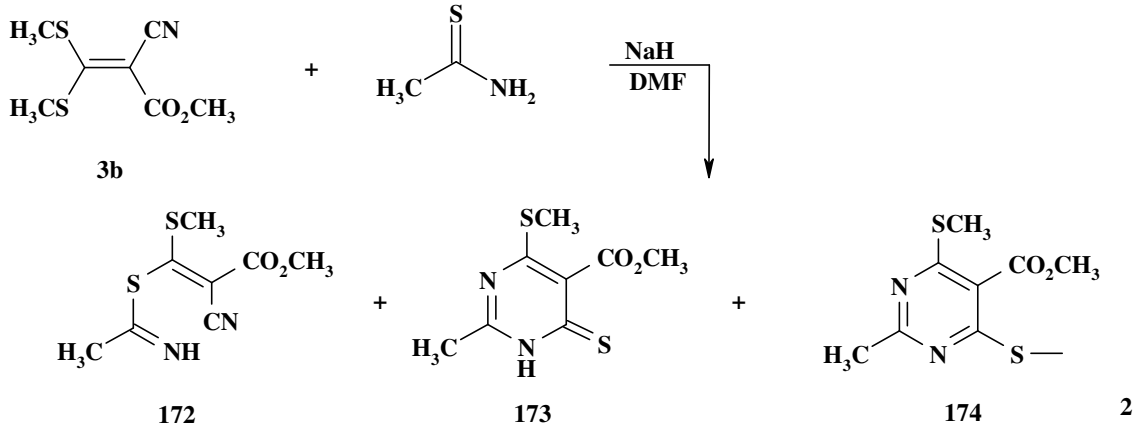
Ketene dithioacetal **3c** reacted with thiobenzamide **169** in AcOH/$HClO_4$ to afford the thiazine derivative **170**. The resulting compound **170** was refluxed in ethanol with morpholine to produce the 6-(methylthio)-2-phenyl-4-thioxopyrimidine-5-carboxylate **171** (Scheme 70).[219]



3c **169** **170** **171**

Scheme 70

The reaction of **3b** with thioacetamide formed the methyl 2-cyano-3-(methylthio)-3-[[(1-methylthio)ethylidene]amino]propenoate **172**, 5-(methoxycarbonyl)-2-methyl-6-(methylthio)-4-thioxo-3,4-dihydropyrimidine **173** and bis[5-(methoxycarbonyl)-2-methyl-6-(methylthio)-4-pyrimidinyl]disulfide **174** (Scheme 71).[211,220]

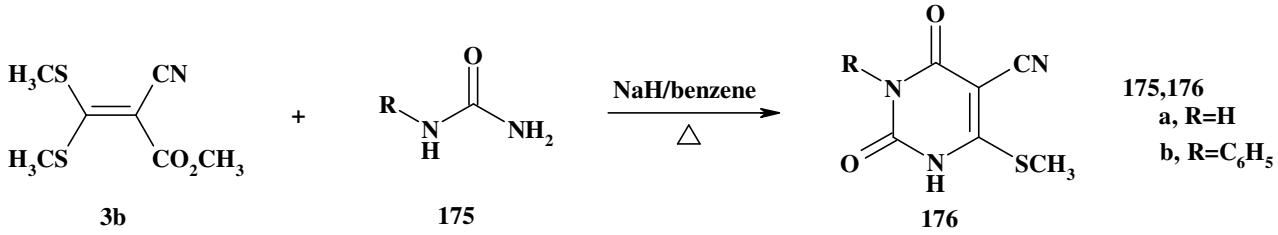


3b

172 **173** **174**

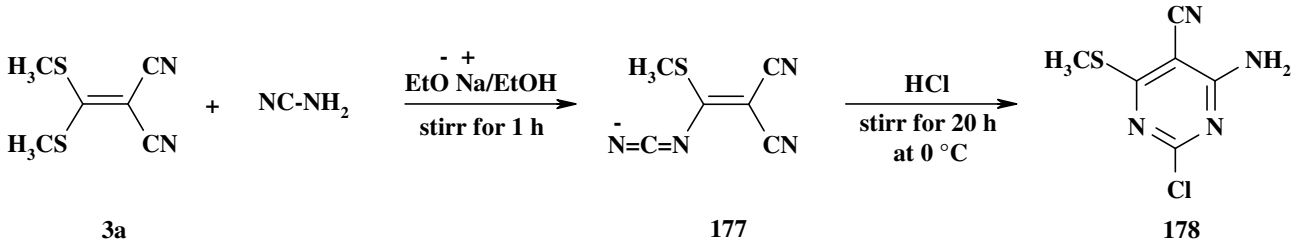
Scheme 71

Compound **3b** also reacted with urea derivatives **175a,b** in sodium hydride/benzene mixture to afford the corresponding 6-methylthiouracil-5-carbonitriles **176a,b** (Scheme 72).[211]



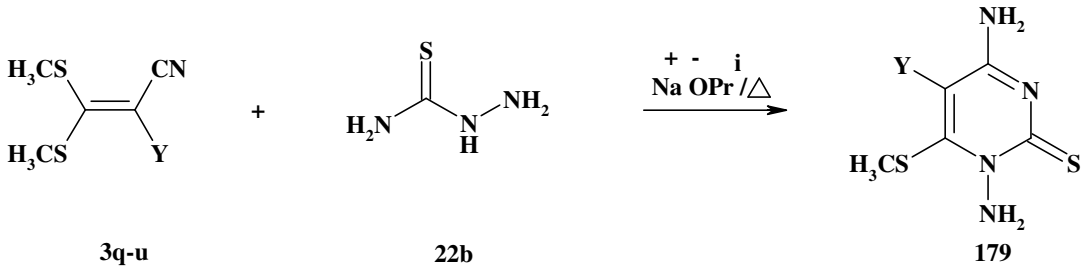
Scheme 72

The condensation of compound **3a** with cyanamide in ethoxide yielded compound **177**, which was cyclized in the presence of hydrochloric acid to give the 4-amino-2-chloro-6-(methylthio)pyrimidine-5-carbonitrile **178** (Scheme 73).[221]

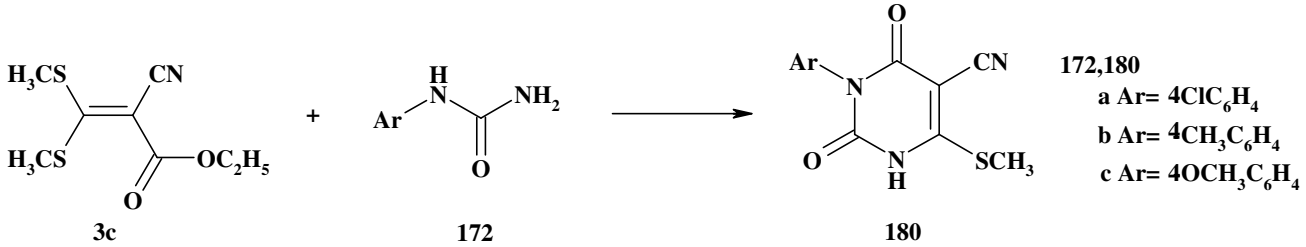


Scheme 73

Recently, it has been found that ketene dithioacetals **3q-u** reacted with thiosemicarbazide **22b** in sodium isopropoxide, to form the corresponding 6-(methylthio)-*N*-amino-2-pyrimidinethione derivatives **179** (Scheme 74).[123]



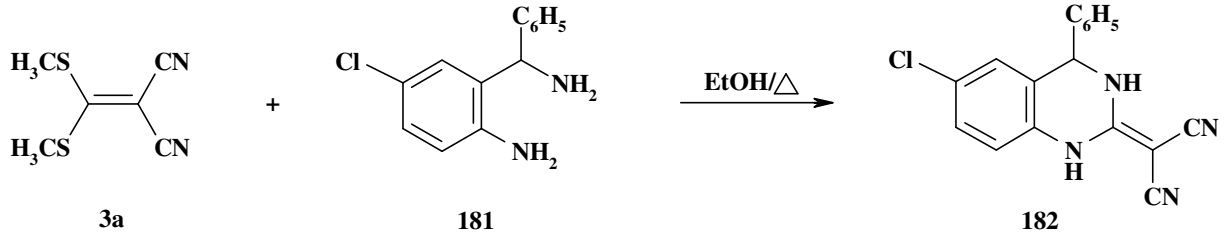
Scheme 74



Scheme 75

The 3-aryl-2,4-dioxo-6-(methylthio)pyrimidine-5-carbonitriles **180** were prepared by the reaction of compound **3c** with arylureas **172a-c** (Scheme 75).[222,223]

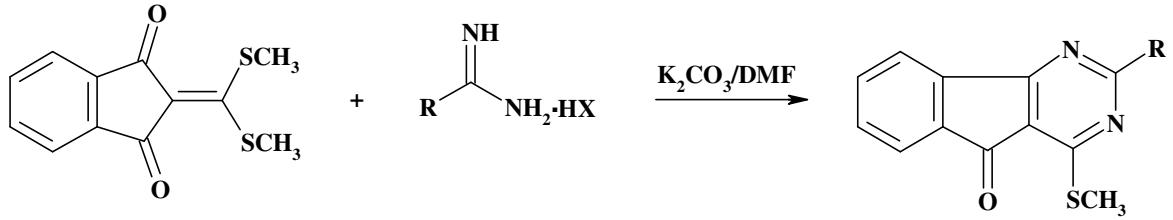
The benzopyrimidine derivative **182** was synthesized by the reaction of **3a** with aminophenylbenzylamines **181** in refluxing ethanol (Scheme 76).[224,225]



3a **181** **182**

Scheme 76

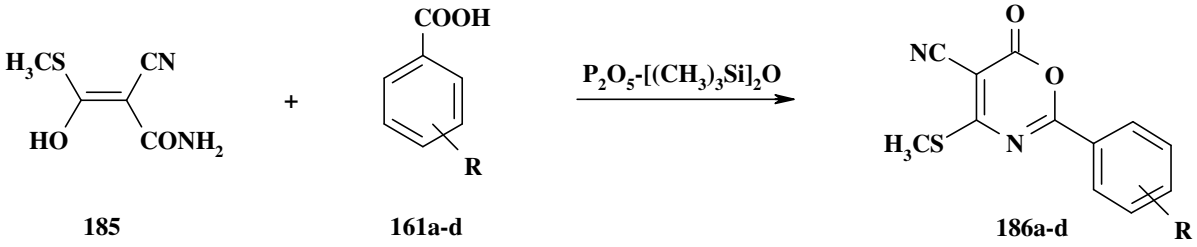
It has been found that 2-[bis(methylthio)methylene]indane-1,3-dione **183** reacted with amidine derivatives **149a-d** in the presence of potassium carbonate in dimethylformamide to give the 2-substituted-4-methylthioindeno[1,2-*d*]pyrimidine-5-ones **184** (Scheme 77).[102,226]



183 **149a-d** **184**

Scheme 77

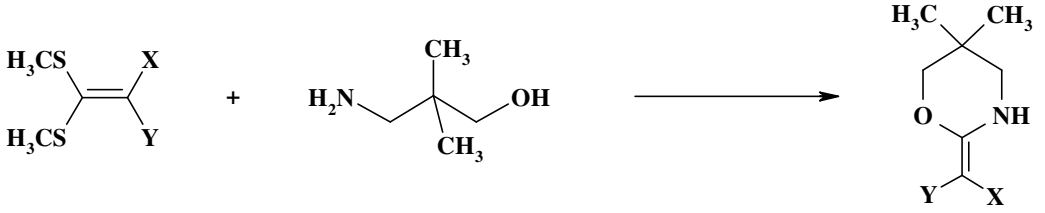
When ketene *O,S*-acetal **185** reacted with carboxylic acid derivatives **161a-d** the corresponding oxazinones **186** were produced (Scheme 78).[220]



185 **161a-d** **186a-d**

Scheme 78

The alkylideneoxazine derivatives **188** were synthesized by cyclization of ketene *S,S*-acetals **3b,e,j** with 3-aminoneopentanol **187** (Scheme 79).[173]

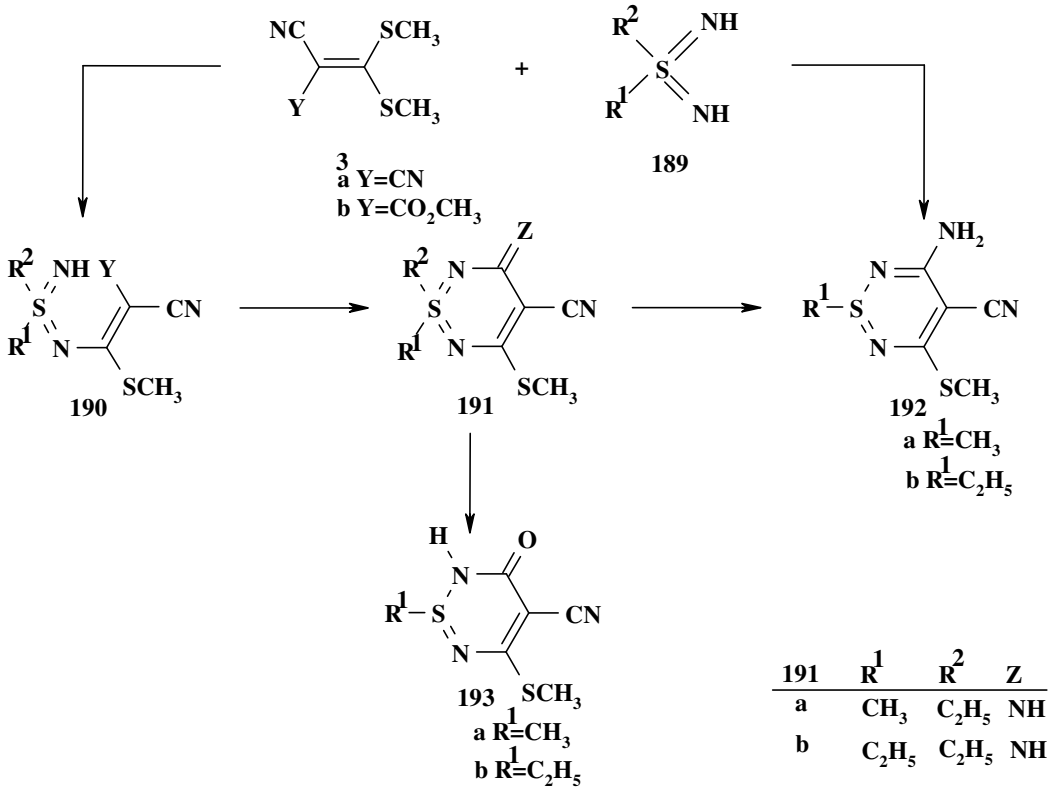


3b,e,j **187** **188**

Scheme 79

3.2.3. Six-membered rings with three hetero-atoms

The reaction of ketene dithioacetals **3a,b** with dialkylsulfurdiimides **189** afforded the corresponding 2,6-thiadiazine derivatives **190-193** (Scheme 80).[227,228]

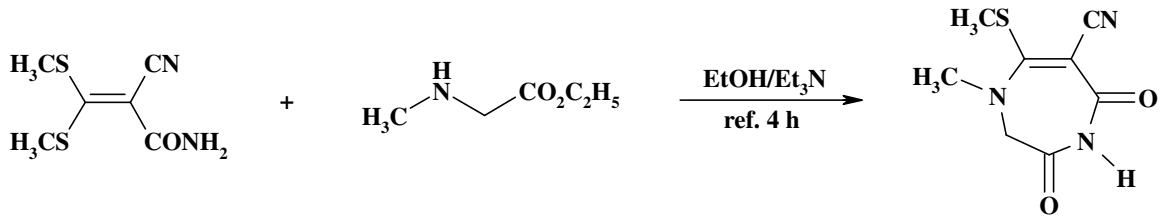


191	R^1	R^2	Z
a	CH_3	C_2H_5	NH
b	C_2H_5	C_2H_5	NH

Scheme 80

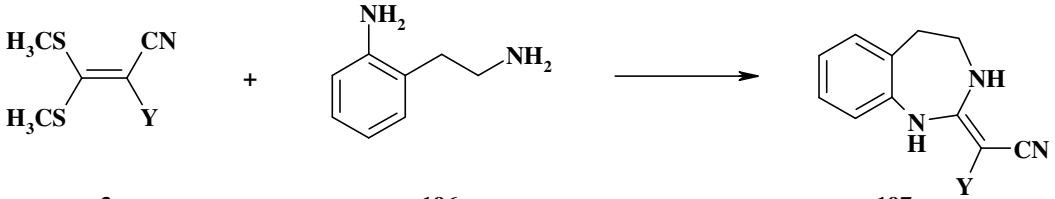
3.3. Seven-membered rings

Treatment of compound **3d** with α-amino acid derivative **194** in ethanol containing triethylamine formed the tetrahydro-1,4-diazepine-2,7-diones **195** (Scheme 81).[127]



3d 194 195

Scheme 81



3
a Y=CN
c Y=$CO_2C_2H_5$

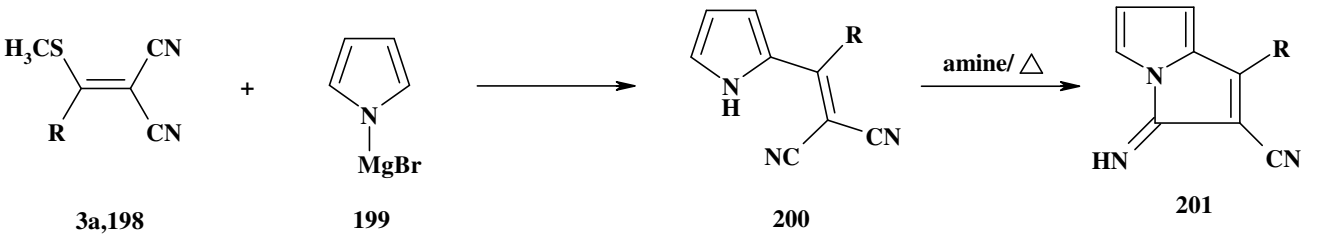
196 197

Scheme 82

Ketene dithioacetals **3a,c** reacted with 1-(2-aminophenyl)-2-aminoethane **196** to afford the 2-substituted hydrogenated 1,3-benzodiazepines **197** (Scheme 82).[229]

3.4. Fused heterocyclic compounds

The reaction of compounds **3a** or **198** with *N*-pyrrolylmagnesium bromide **199** in nonpolar solvent yielded dinitriles **200**, which were cyclized in the presence of amine as a catalyst to give the pyrrolizine derivatives **201** (Scheme 83).[230,231]

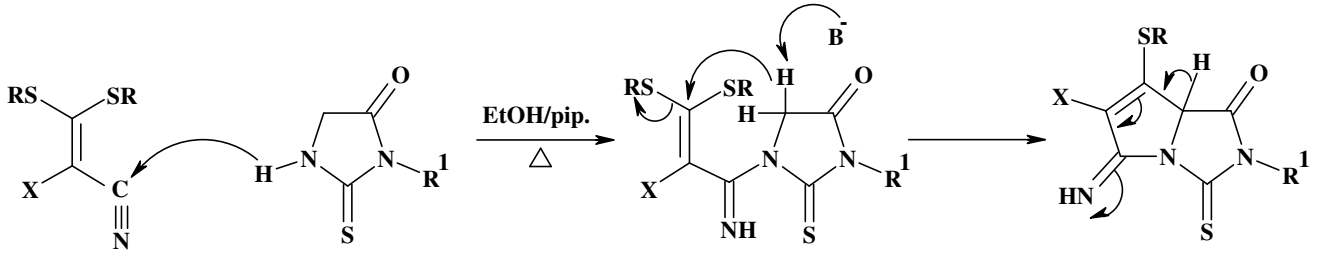


3a,198 **199** **200** **201**

a R=piperidino
b R=morpholino

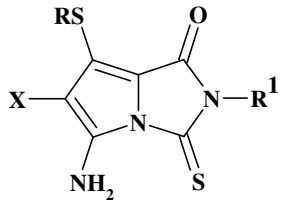
Scheme 83

It has been found that ketene dithioacetals **3a,c** and **202** reacted with 2-thiohydantoin derivatives **203** in refluxing ethanol containing catalytic amounts of piperidine to give the corresponding 4-alkylsulfanylpyrrolo[1,2-*c*]imidazoles **206** (Scheme 84).[232]



3a,c,202 **203** **204** **205**

204-206	R	R^1	X	204-206	R	R^1	X
a	CH_3	H	CN	e	C_2H_5	H	CN
b	CH_3	C_6H_5	CN	f	C_2H_5	C_6H_5	CN
c	CH_3	H	$CO_2C_2H_5$	g	C_2H_5	H	$CO_2C_2H_5$
d	CH_3	C_6H_5	$CO_2C_2H_5$	h	C_2H_5	C_6H_5	$CO_2C_2H_5$

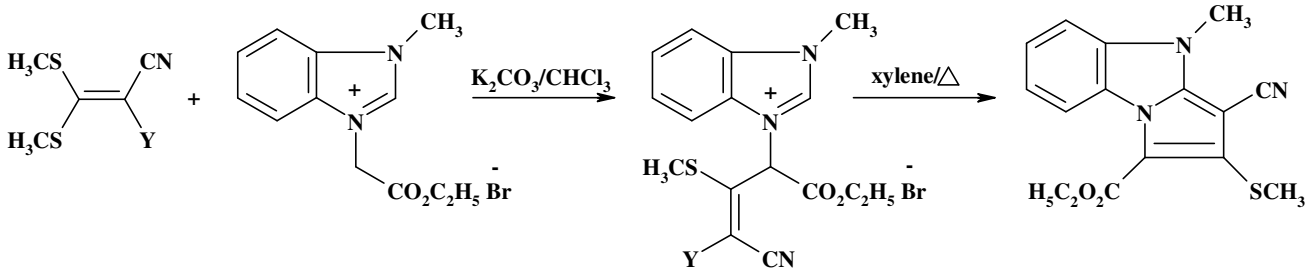


206

Scheme 84

Ketene dithioacetals **3a,b,f** reacted with benzimidazolium salt **207** to give the benzimidazolium *N*-allylides **208**. The latters in refluxing xylene formed the 1,5-dipolar cyclization products the benzopyrroloimidazoles **209** (Scheme 85).[233]

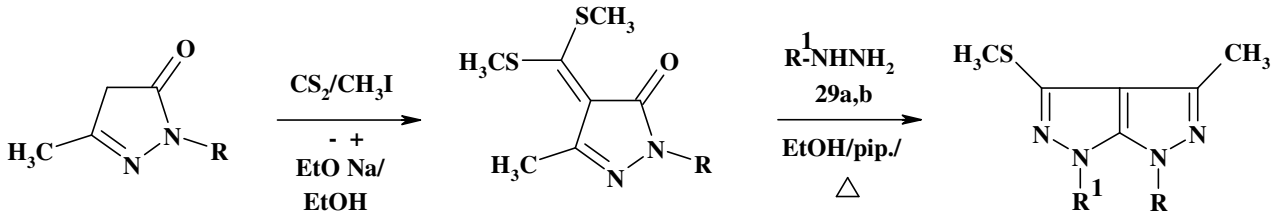
The heterocyclic ketene dithioacetals **211a,b** were chosen as the key intermediate and were prepared by the reaction of pyrazolin-5-ones **210a,b** with sodium ethoxide and carbon disulphide followed by methyl iodide treatment in a one-pot reaction.



3a,b,f 207 208 209

Scheme 85

Compounds **211a,b** reacted with hydrazine derivatives **29a,b** in refluxing ethanol containing catalytic amount of piperidine to give the corresponding 4-methylthiopyrazolo[3,4-*c*]pyrazoles **212** (Scheme 86).[234]

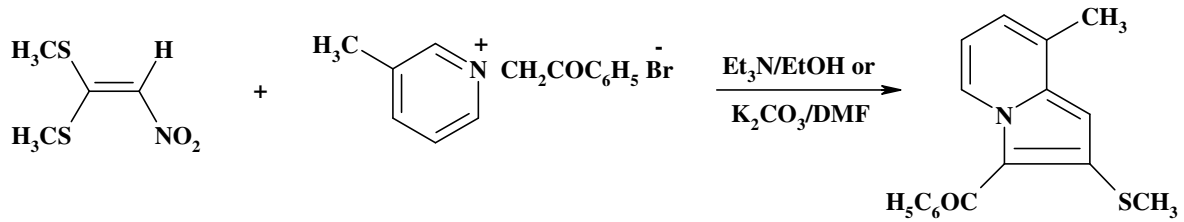


210a,b 211a,b 212

210,211
a R=H
b R=C_6H_5

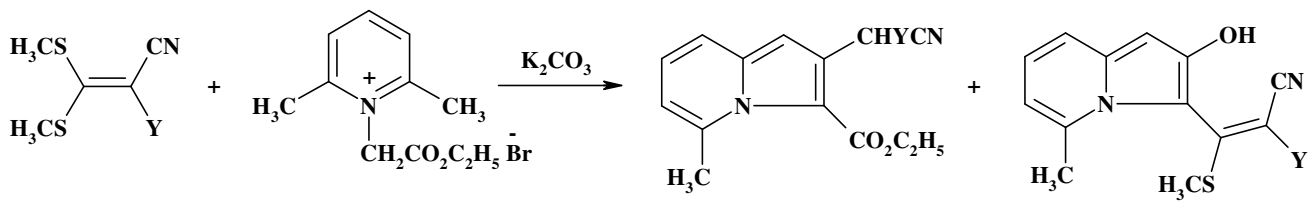
Scheme 86

It has been reported that **3l** reacted with pyridinium *N*-allylides **213** in the presence of a base to produce the indolizine derivative **214** (Scheme 87).[235,236]



3l 213 214

Scheme 87



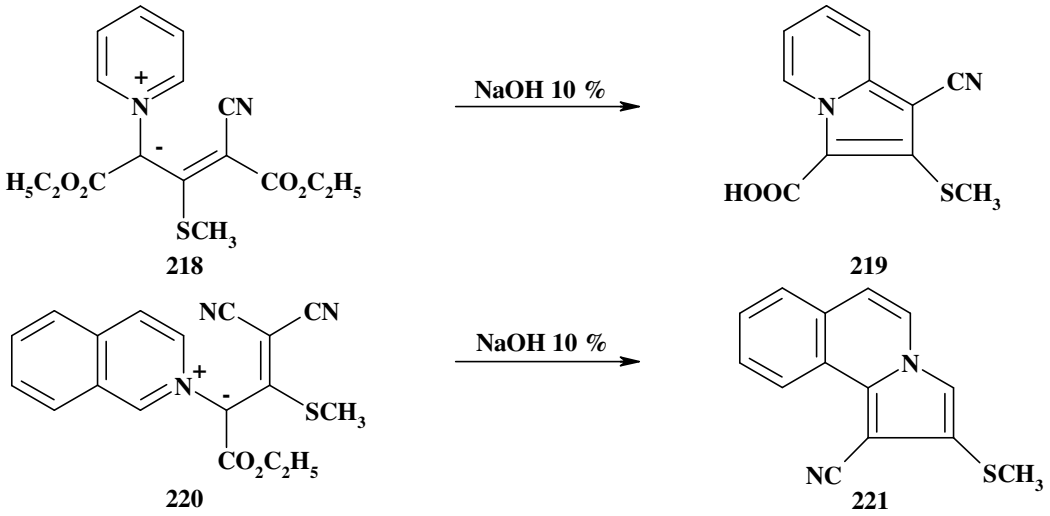
3
a Y=CN
c Y=$CO_2C_2H_5$

215 216 217

Scheme 88

The reaction of ketene dithioacetals **3a,c** with 2,6-dimethyl-1-ethoxycarbonylmethylpyridinium bromide **215** in the presence of potassium carbonate gave the corresponding 3-ethoxycarbonylindolizines **216** and 3-vinylindolizines **217** (Scheme 88).[237]

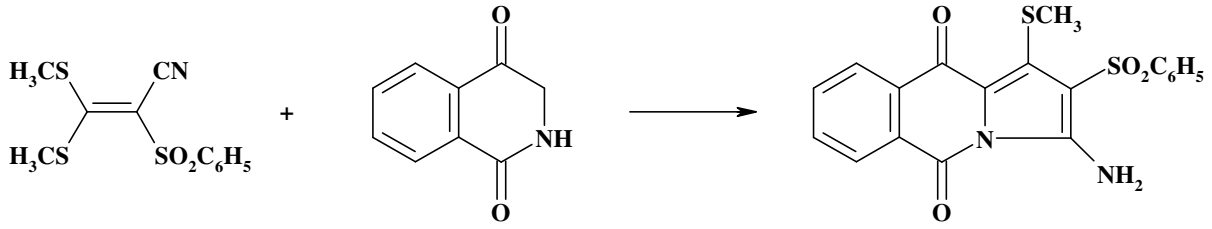
Both pyridinium-3-cyano-2-(methylthio)allyides **218** and isoquinolinium-3-cyano-2-(methylthio)allyides **220** were treated with sodium hydroxide 10 % to give the indolizines **219** and the pyrrolo[2,1-*a*]isoquinolines **221**, respectively (Scheme 89).[238-240]



218 **219** **220** **221**

Scheme 89

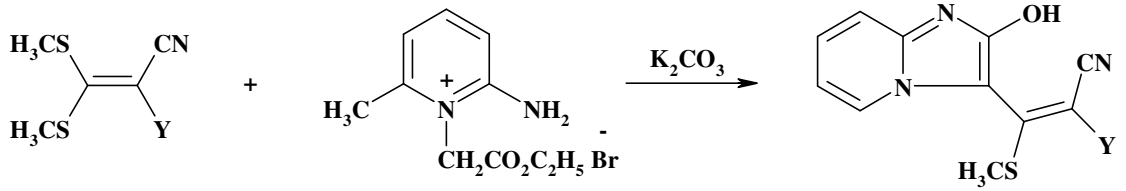
The reaction of compound **108a** with 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline **222** yielded the pyrroloisoquinolines **223** (Scheme 90).[184]



108a **222** **223**

Scheme 90

When **3a,c** were treated with 2-amino-6-methyl-1-ethoxycarbonylmethylpyridinium bromide **224** in the presence of potassium carbonate the 3-vinylimidazo[1,2-*a*]pyridines **225**, were produced (Scheme 91).[237]

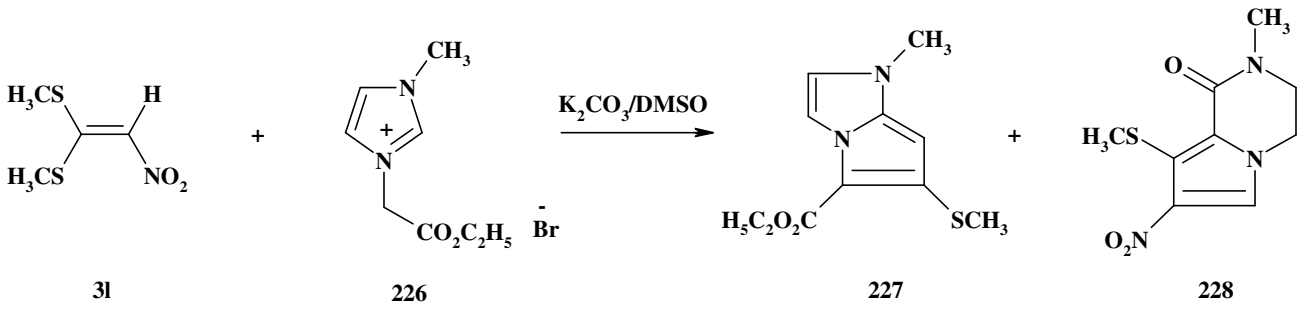


3
a Y=CN
c Y=$CO_2C_2H_5$

224 **225**

Scheme 91

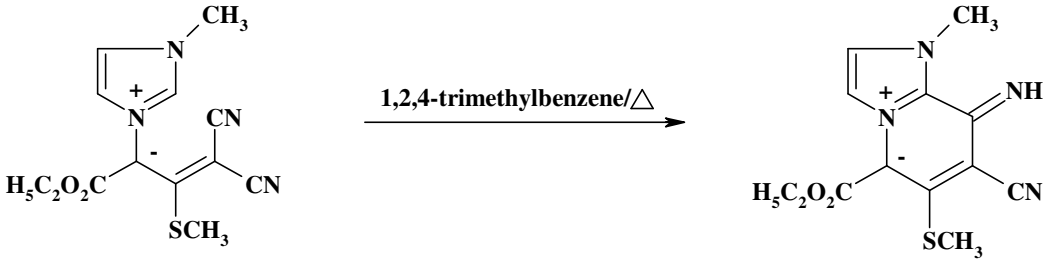
The reaction of nitroketene dithioacetal **3l** with imidazolium salt **226** in the presence of potassium carbonate in dimethylsulfoxide resulted in 1,5-dipolar cyclization to produce the pyrrolo[1,2-*a*]imidazoles **227** and pyrrolo[1,2-*a*]pyrazines **228** (Scheme 92).[241]



3l **226** **227** **228**

Scheme 92

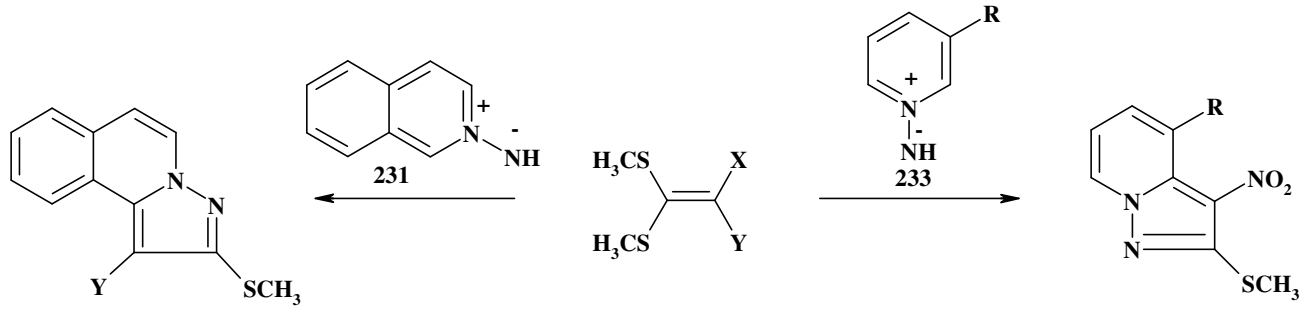
Treatment of imidazolium *N*-allylides **229** in refluxing 1,2,4-trimethylbenzene resulted in 1,6-cyclization to give the mesomeric betaine, 7-iminoimidazo[1,2-α]pyridiniumide derivative **230** (Scheme 93).[241]



229 **230**

Scheme 93

The reaction of ketene dithioacetals **3a,l** with isoquinolinium imine **231** yielded the corresponding pyrazoloisoquinolines **232**. Similarly, **3l** reacted with pyridinium imines **233** to yield the pyrazolopyridines **234** (Scheme 94).[239,242-244]



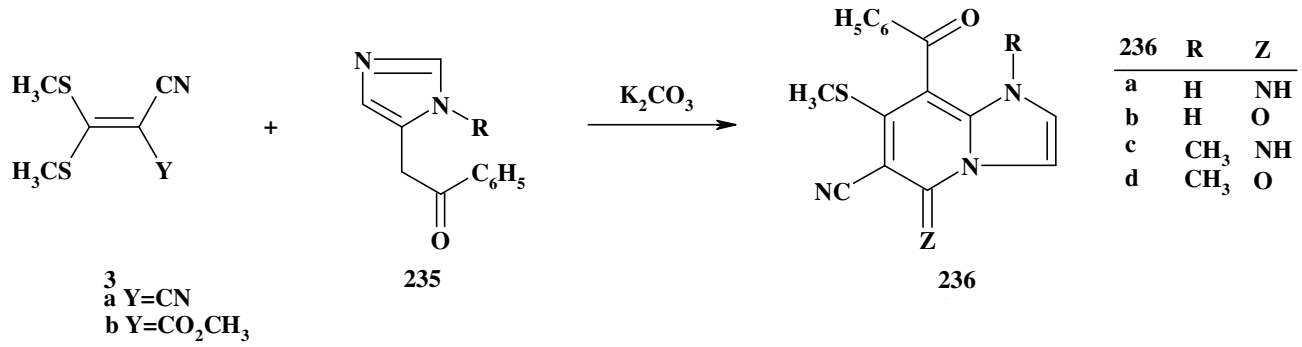
232
a Y=CN
b Y=NO_2

3
a X=Y=CN
l X=H, Y=NO_2

234
a R=H
b R=CH_3

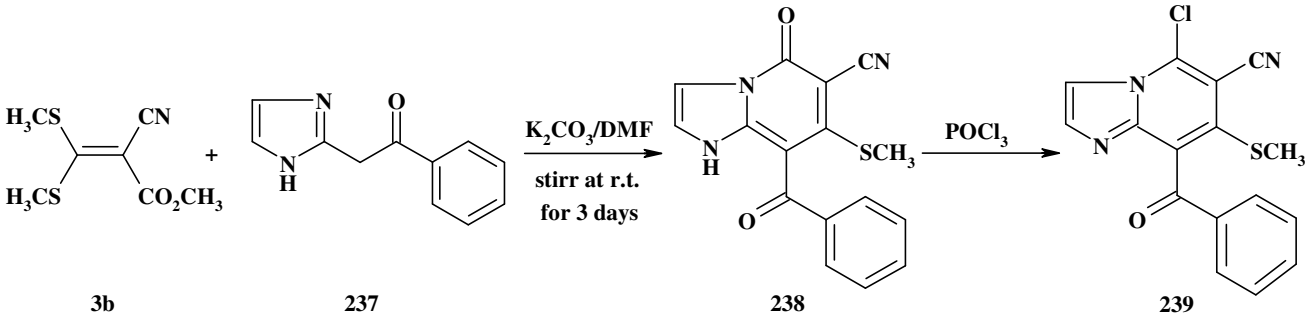
Scheme 94

Ketene-*S*,*S*-acetals **3a,b** reacted with 2-benzoylmethylimidazoles **235** to form the corresponding imidazolo[1,2-*a*]pyridine derivatives **236** (Scheme 95).[245]



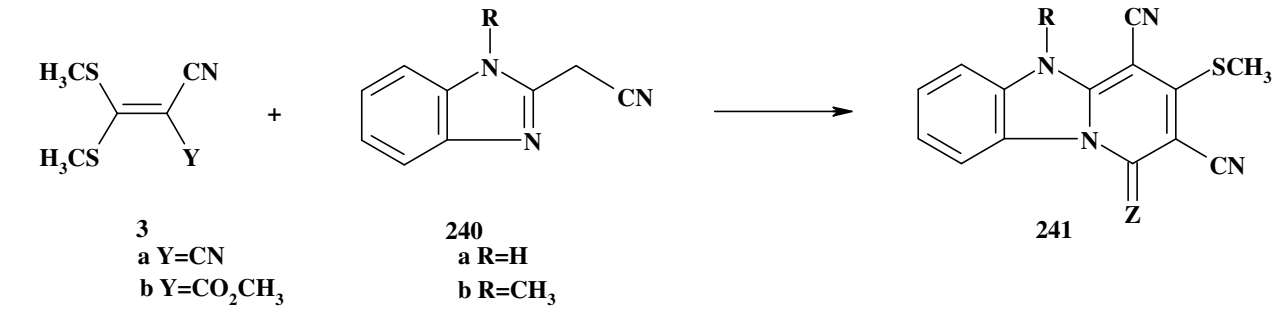
Scheme 95

The cyclocondensation of **3b** with 2-benzoylmethylimidazole **237** in the presence of potassium carbonate in dimethylformamide produced the 8-benzoyl-7-(methylthio)-5-oxo-5*H*-imidazo[1,2-*a*]pyridine-6-carbonitrile **238**, which was refluxed with $POCl_3$ to give the imidazo[1,2-*a*]pyridine derivative **239** (Scheme 96).[246]



Scheme 96

The reaction of compounds **3a,b** with benzimidazole derivatives **240** gave the corresponding benzo[4,5]imidazo[1,2-a]pyridines **241** (Scheme 97).[247]

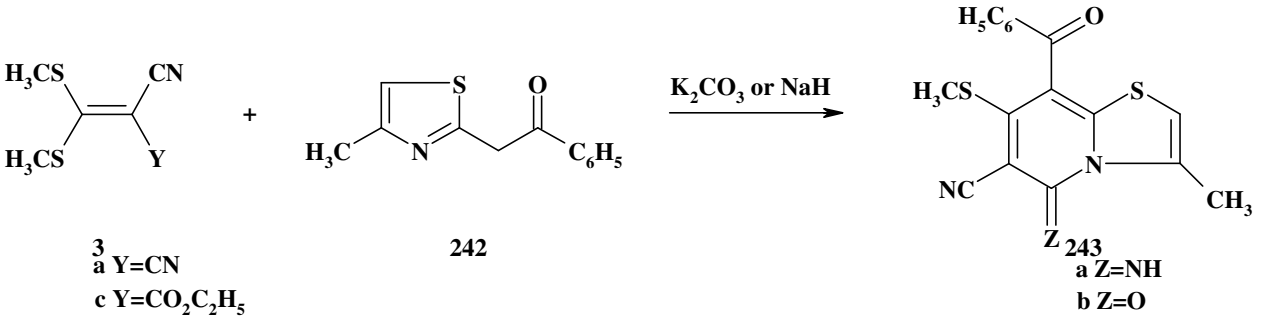


Scheme 97

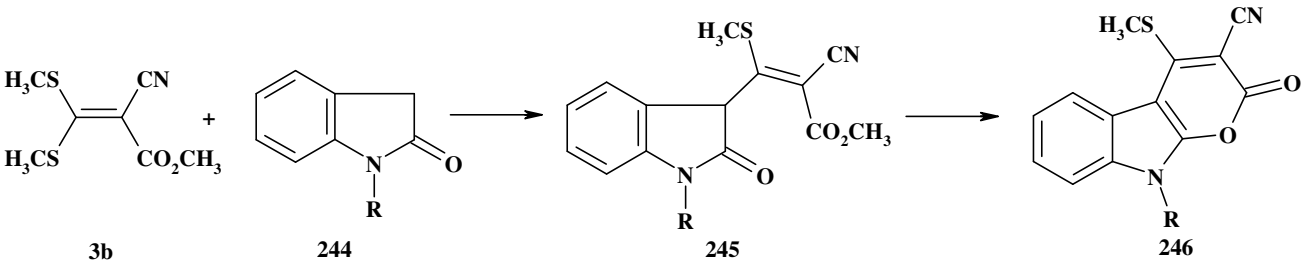
Matsuda *et al.* have reported that the reaction of ketene-*S*,*S*-acetals **3a,c** with 4-methylthiazole derivative **242** yielded the corresponding thiazolo[3,2-*a*]pyridines **243** (Scheme 98).[248,249]

The reaction of compound **3b** with substituted indoles **244** afforded compounds **245**, which were cyclized to form the pyrano[2,3-*b*]indole derivatives **246** (Scheme 99).[250-252]

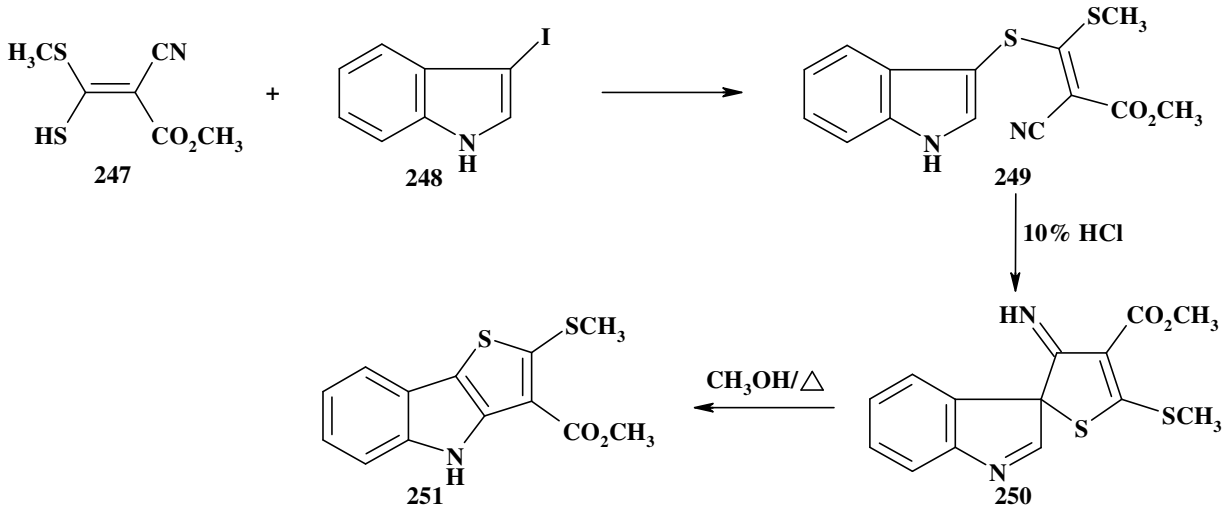
Ketene dithioacetal **247** reacted with 3-iodoindole **248** to give the intermediate **249**, which was cyclized in the presence of hydrochloric acid 10 % to yield the indole derivative **250**. The latter was rearranged in refluxing methanol to give the thieno[3,2-*b*]indoles **251** (Scheme 100).[241,253-255]



Scheme 98

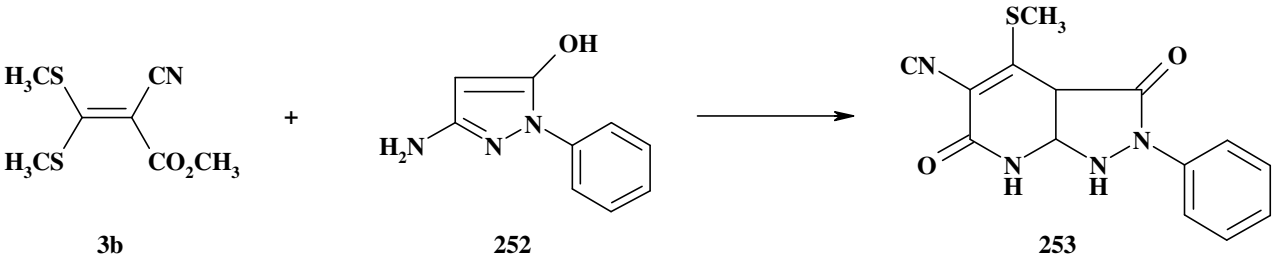


Scheme 99



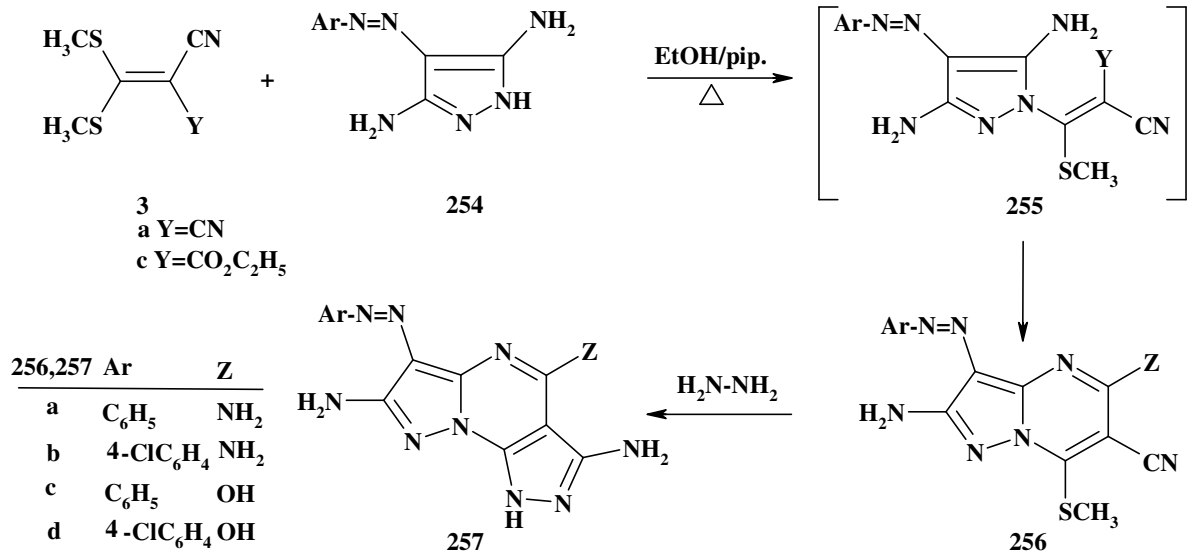
Scheme 100

It has been reported that the pyrazolo[3,4-*b*]pyridones **253** was produced through the reaction of compound **3b** with 3-aminopyrazoles **252** (Scheme 101).[256]



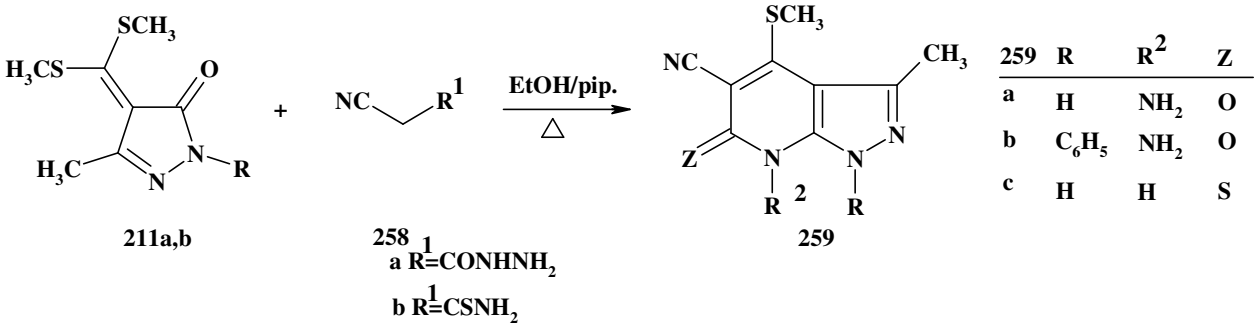
Scheme 101

Elgemeie *et al.* have reported that the reaction of **3a,c** with 5-aminopyrazoles **254** afforded the 7-methylthiopyrazolo[1,5-*a*]pyrimidines **256**. The latters reacted with hydrazine to give the 1*H*-dipyrazolo[1,5-*a*-4',3'-*e*] pyrimidines **257** (Scheme 102).[54,257]



Scheme 102

They have also shown that the heterocyclic ketene dithioacetals **211a,b** reacted with cyanoacetohydrazide or cyanothioacetamide **258** in refluxing ethanol containing catalytic amount of piperidine to obtain the corresponding 4-methylthiopyrazolo[3,4-*b*]pyridines **259** (Scheme 103).[234]

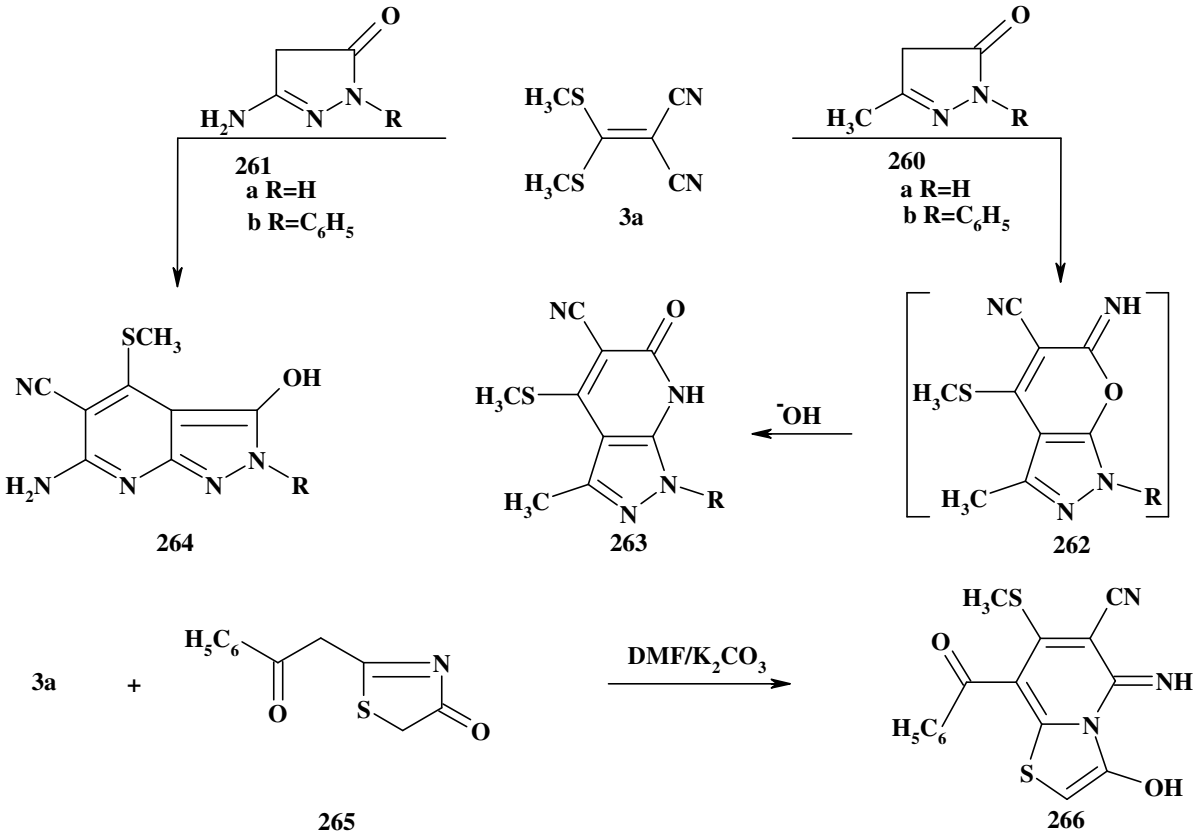


Scheme 103

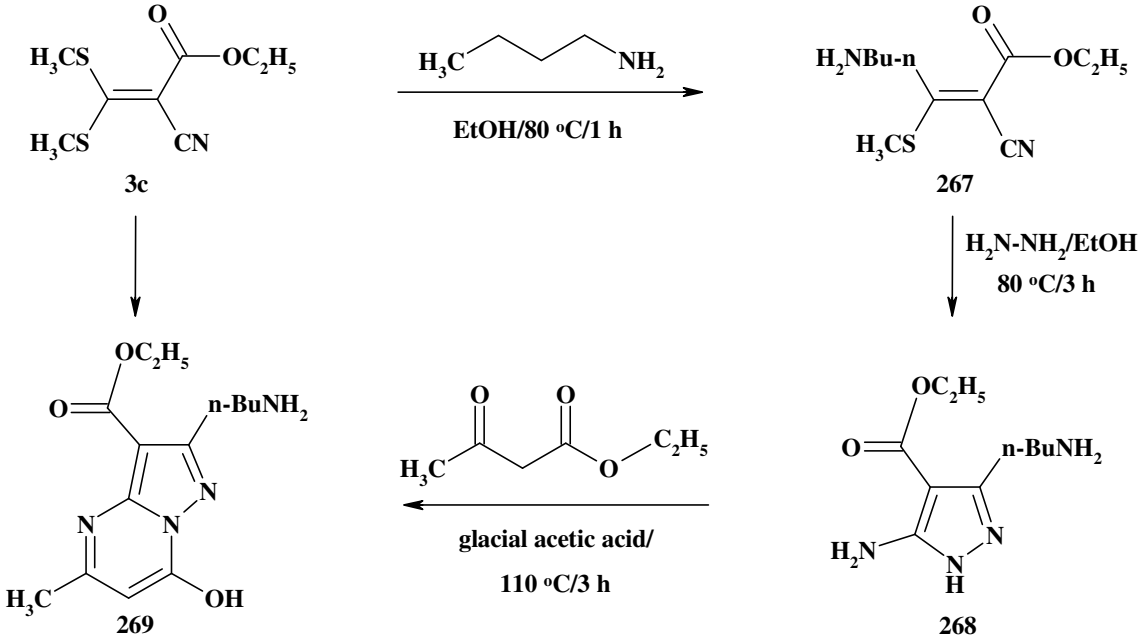
Compound **3a** reacted with 3-methyl-2-pyrazolin-5-ones **260** in dioxane containing an equivalent amount of potassium hydroxide to give the corresponding 4-methylthiopyrazolo[3,4-*b*]pyridines **263** through the intermediates **262**. Also, **3a** reacted with 3-amino-2-pyrazolin-5-ones **261** to yield the corresponding 6-methylthiopyrazolo[3,4-*c*]pyridines **264**.

The behavior of ketene dithioacetal **3a** towards other active methylene heterocycles has been also investigated. Thus, compound **3a** reacted with 5-thiazoline-4-one derivative **265** in refluxing dimethylformamide containing an equivalent amount of potassium carbonate to yield the 7-methylthiothiazolo[3,2-*a*] pyridines **266** (Scheme 104).[205]

Ketene-*S,S*-acetal **3c** reacted with *n*-butylamine to form ketene-*N,S*-acetal **267**, which was cyclocondensed with hydrazine to afford 3-*n*-butylamino-1*H*-pyrazole-4-carboxlate derivative **268**. The latter reacted with ethyl acetoacetate in glacial acetic acid to yield the ethyl 2-(*n*-butylamino)-7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxlate **269** (Scheme 105).[258]

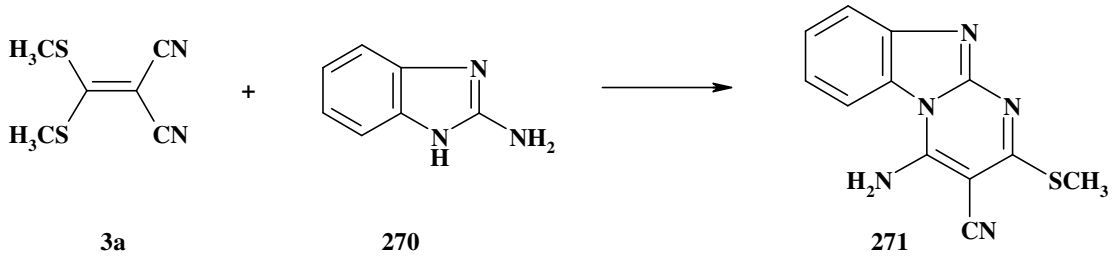


Scheme 104



Scheme 105

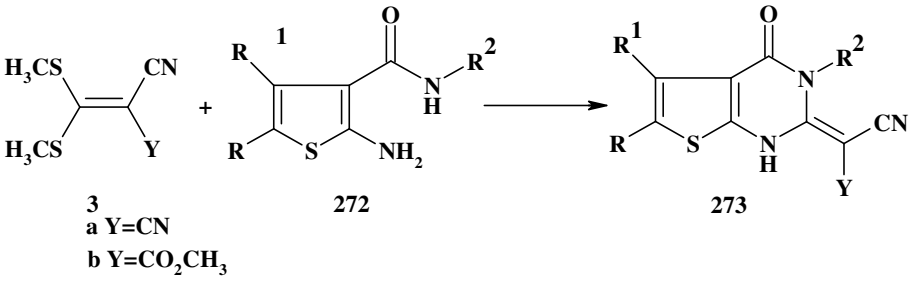
The cyclocondensation of compound **3a** with 2-aminobenzoimidazole **270** yielded the benzoimidazopyrimidine derivative **271** (Scheme 106).[259]



3a **270** **271**

Scheme 106

The thienopyrimidinone derivatives **273** were prepared from the reaction of ketene dithioacetals **3a,b** with 2-aminothiophene-3-carboxylic acid derivatives **272** (Scheme 107).[260]



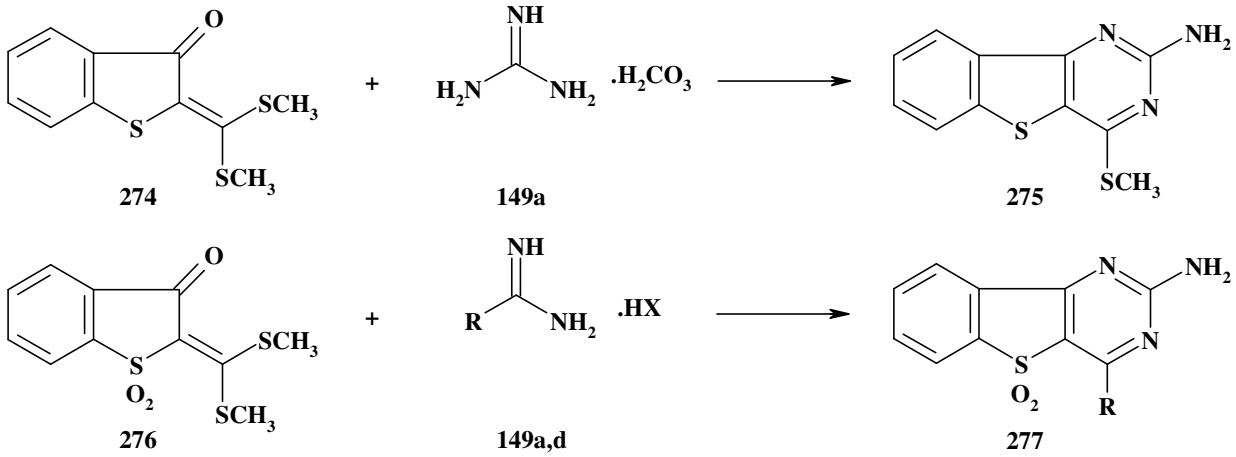
3
a Y=CN
b Y=CO_2CH_3

272 **273**

273	Y	R	R^1	R^2
a	CN	CH_3	CH_3	H
b	CN	C_6H_5	$CO_2C_2H_5$	C_6H_5
c	CO_2CH_3	CH_3	CH_3	H
d	CO_2CH_3	C_6H_5	$CO_2C_2H_5$	C_6H_5

Scheme 107

The reaction of [bis(methylthio)methylene]substituted heterocyclic compounds **274**, **276** with amidine derivatives **149a,d** has been extensively utilized for the synthesis of benzo[4,5]thieno[3,2-*d*]pyrimidines **275** and benzo[4,5]thieno[3,2-*d*]pyrimidine-5,5-dioxides **277**, respectively (Scheme 108).[184,261-263]

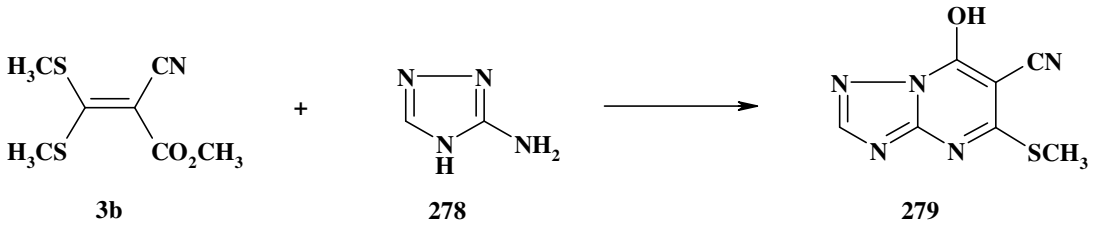


274 **149a** **275**

276 **149a,d** **277**

Scheme 108

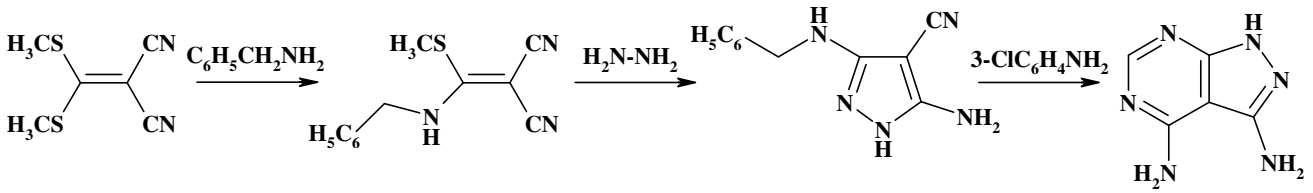
It has been reported that the cyclocondensation reaction of **3b** with triazolamine **278** yielded the triazolopyrimidine derivative **279** (Scheme 109).[264]



3b **278** **279**

Scheme 109

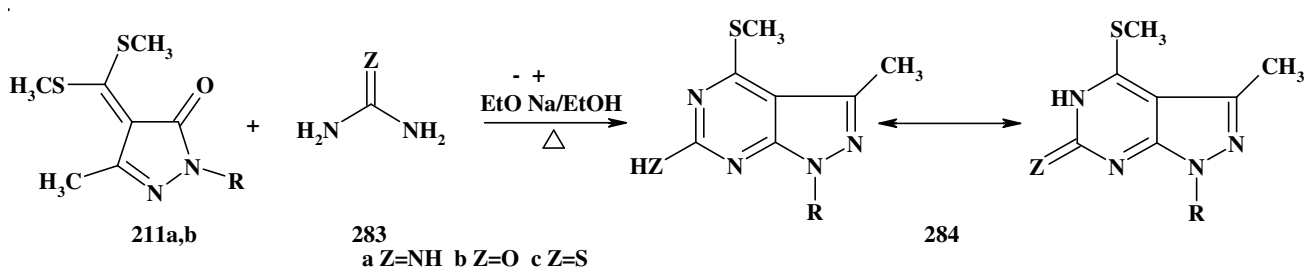
The amination of ketene *S,S*-acetal **3a** with benzylamine afforded ketene *N,S*-acetal **280**, which was cyclocondensed with hydrazine to give the 5-amino-3-benzylamino-1*H*-pyrazole-4-carbonitrile **281**. The latter was cyclized with 3-chloroaniline to prepare the pyrazolo[3,4-*d*]pyrimidines **282** (Scheme 110).[265]



3a **280** **281** **282**

Scheme 110

It has been found that the corresponding 4-methylthio[3,4-d]pyrimidine derivatives **284** were synthesized by the reaction of compounds **211a,b** with guanidine, urea and thiourea **283** (Scheme 111).[234]

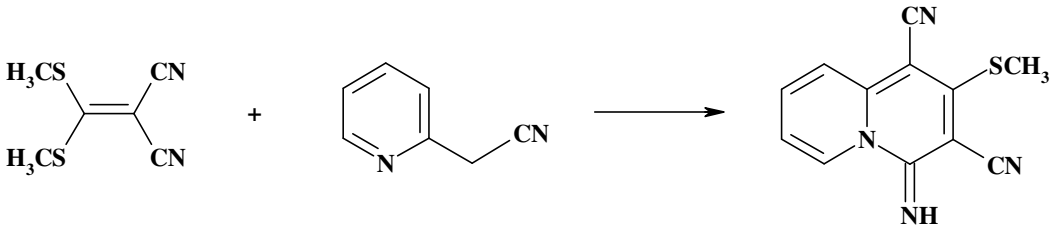


211a,b **283** **284**

a Z=NH b Z=O c Z=S

Scheme 111

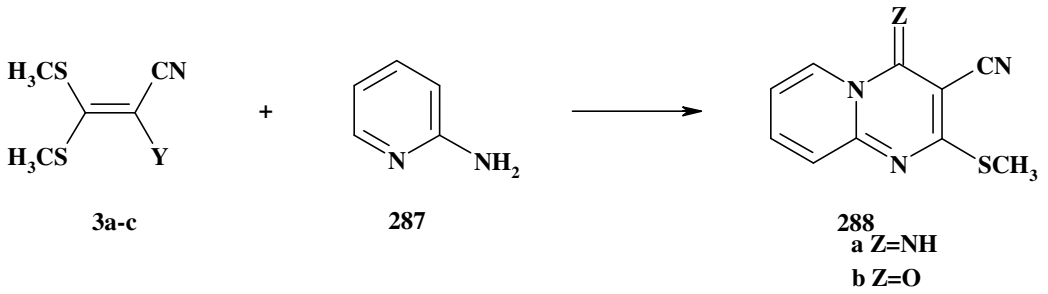
The reaction of **3a** with 2-pyridineacetonitrile **285** afforded the 1,3-dicyano-4-imino-2-methylthio-4*H*-quinolizine **286** (Scheme 112).[266]



3a **285** **286**

Scheme 112

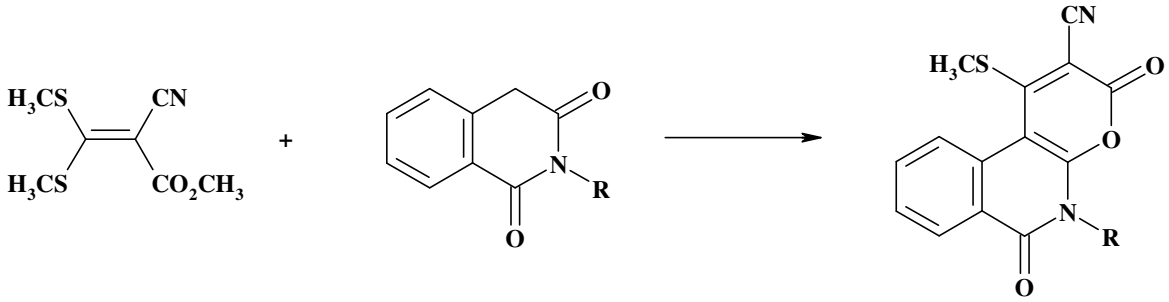
The cyclocondensation of compounds **3a-c** with 2-aminopyridine **287** gave the corresponding 2-methylthiopyrido[1,2-*a*]pyrimidine derivatives **288** (Scheme 113).[267,268]



3a-c **287** **288** **a Z=NH** **b Z=O**

Scheme 113

The 2-*N*-substituted pyranoisoquinolines **290** were synthesized by the reaction of **3b** with 1,3-dioxoisoquinoline derivatives **289** (Scheme 114).[269]



3b **289** **290**

Scheme 114

References

1. Tenor, E.; Ludwig, R. *Pharmazie* **1971**, *26*, 534.
2. Lepage, G. A.; Loo, T. L. *Cancer Medicine (Purine Antagonists*), Holland, J.; Frei, E. Lea & Febiger eds, Philadelphia **1973**.
3. Kristinsson, H. *J. Chem. Soc., Chem. Commun.* **1974**, 350.
4. Kobayashi, G.; Matsuda, Y.; Natsuki, R.; Tominaga, Y.; Maseda, C. *Yakugaku Zasshi* **1974**, *94*, 44; Chem. Abst. **1974**, *80*, 108477b.
5. Foye, O. W.; Lanzillo, J. J.; Lowe, H. Y.; Kauffman, J. M. *J. Pharm. Sci.* **1975**, *64*, 211.
6. Wittenbrook, L. S. *J. Heterocycl. Chem.* **1975**, *12*, 37.
7. Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1975***, 95*, 378; Chem. Abst. **1975**, *83*, 58053z.
8. Peseke, K. *Ger. (East) 108,288 (Cl. C 07c);* Chem. Abst. **1975**, *83*, 9220t.
9. Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1911.
10. Rudorf, W.-D.; Augustin, M. *J. Prakt. Chem*. **1978**, *320*, 576.
11. Robins, R. K.; Srivastava, P. C.; Revankar, G. R. *"Novel Nitrogen Heterocycles as Potential Medicinal Agents in "Lectures in Heterocyclic Chemistry VI",* Castle, R. N. ed, HeteroCorporation, Tampa **1982**, p. 93.
12. Barzen, R.; Schunack, W. *Arch. Pharm*. **1982**, *315*, 680.
13. Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1981**, *101*, 991; Chem. Abst. **1982**, *96*, 104144y.
14. Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 3055.
15. Hermecz, I.; Meszaros, Z. *"Chemistry of Pyrido[1,2-a]Pyrimidines", "Advances in Heterocyclic Chemistry* ", Katritzky, A. R. ed., Academic Press, New York **1983**, *33*, 241.
16. Potts, K. P.; Cipullo, M. J.; Ralli, P.; Theodorids, G. *J. Org. Chem.* **1983**, *48*, 4841.
17. Chamberlin, A. R.; Dezube, M.; Dussault, P.; Mc Mills, M. *J. Am. Chem. Soc.* **1983**, *105*, 5819.

18. Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 858.
19. Yokoyama, M.; Tsuji, K.; Imamoto, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2954.
20. Peseke, K.; Rodriguez, P. R. *Ger. (East)* DD 206,554 (Cl. C07D307/46); Chem Abst. **1984**, *101*, 90752c.
21. Vishwakarma, J. N.; Apparao, S.; Ila, H.; Junjappa, H. *Ind. J. Chem. Sect. B*. **1985**, *24B*, 466.
22. Tominaga, Y.; Matsuda, Y. *J. Synth. Org. Chem. (Japan)* **1985**, *43*, 669.
23. Tominaga, Y.; Matsuda, Y. *J. Heterocycl. Chem.* **1985**, *22*, 937.
24. Martin, D.; Gilbin, M. *Ger. Pat., 227435* (1985); Chem. Abst. **1986**, *104*, 168488e.
25. Reiter, J.; Pongs, L.; Somorai, T.; Dvortsak, P. *J. Heterocycl. Chem.* **1986**, *23*, 401.
26. Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029.
27. Peseke, K.; Quincoces Suarez, J. *Rev. Cubana Quim.* **1985**, *1*, 21; Chem. Abst. **1986**, *105*, 190802v.
28. Chamberlin, A. R.; Nguyen, H. *J. Org. Chem.* **1986**, *51*, 940.
29. Tominaga, Y.; Motokawa, S.; Shiroshita, Y.; Hosomi, A. *J. Heterocycl. Chem.* **1987**, *24*, 1365.
30. Bagli, J.; Bogri, T.; Palameta, B.; Rakhit, S.; Peseckis, S.; Mc Quillan, J.; Lee, D. K. *J. Med. Chem.* **1988**, *31*, 814.
31. Zayas, O.; Quincoces Suarez, J.; Peseke, K. *Ger. (East) DD 255,342 (Cl. C07D307/54)*; Chem. Abst. **1989**, *110*, 38869t.
32. Munns, T. W.; Freeman, S. K. *Bio. Chemistry* **1989**, *28*, 10048.
33. Tominaga, Y. *J. Heterocycl. Chem.* **1989**, *26*, 1167.
34. Tominaga, Y. *J. Heterocycl. Chem.* **1989**, *26*, 477.
35. Tominaga, Y. *J. Synth. Org. Chem. (Japan)* **1989**, *47*, 413.
36. Tominaga, Y.; Kohra, S.; Honkawa, H.; Hosomi, A. *Heterocycles* **1989**, *29*, 1409.
37. Kdb, M. *Synthesis* **1989**, 171.
38. Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990**, *55*, 410.
39. Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423.
40. Tominaga, Y.; Menon, J. ed. *Council Of Scientific Research Integration, Research Trends* **1991**, *2*, 43.
41. Peseke, K.; Heide, G. *Ger. (East) DD 279,243 (Cl. C07C149/42);* Chem. Abst. **1991**, *114*, 185053h.
42. Peseke, K.; Castanedo Cancio, N.; Lozada Gomez, J. A. *Ger. (East) DD 283,137 (Cl. C07D277/34);* Chem. Abst. **1991**, *115*, 29308k.
43. Beslin, P.; Perrio, S. *Tetrahedron* **1991**, *47*, 6275.
44. Lorente, A.; Balcazer, J. L.; Florencio, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3377.
45. Beslin, P.; Marion, P. *Tetrahedron Lett.* **1992**, *33*, 935.
46. Beslin, P.; Perrio, S. *Tetrahedron* **1992**, *48*, 4135.
47. Beslin, P.; Perrio, S. *Tetrahedron* **1993**, *32*, 3131.
48. Pech, R.; Boehm, R. *Pharmazie*, **1993**, *48*, 257.
49. Sasho, S.; Harakawa, H.; Obase, H.; Ichikawa, S.; Kitazawa, T.; Ishii, A. *Jpn. Kokai Tokkyo Koho JP 04/279,581 [92,279,581] (Cl. C07D405/14)*; Chem. Abst. **1993**, *119*, 95522j.
50. Sasho, S.; Obase, H.; Ichikawa, S.; Kitazawa, T.; Yoshizaki, R.; Ishii, A. *Jpn. Kokai Tokkyo Koho JP 05/17,471[43 17,471] (Cl. C07D405/12)*; Chem. Abst. **1993**, *119*, 139063s.
51. Umegaki, S.; Nogami, T.; Mizoguchi, A.; Uemya, T.; Oogaki, Y.; Kuhata, M. *Jpn. Kokai Tokkyo Koho JP 05,158,090 [93,158,090] (Cl. G02F1/35)*; Chem. Abst. **1993**, *119*, 213730a.
52. Ram, V. J.; Haque, N.; Nath, M. *Indian J. Chem., Sect. B*, **1993**, *32*, 754.
53. Canan Koch, S.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725.
54. Elgemeie, G. H.; El Ezbawy, S. E.; Ali, H. A.; Mansour, A. K. *Bull. Chem. Soc. Jpn* **1994**, *67*, 738.
55. Sasho, S.; Obase, H.; Harakawa, H.; Ichikawa, S.; Kitazawa, T.; Kishibayashi, N.; Yokoyama, T.; Nonaka, H.; Yoshizaki, R.; *Bioorg. Med. Chem.* **1994**, *2*, 1107.
56. Ram, V. J.; Nath, M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1995**, *34*, 416.
57. Ram, V. J.; Nath, M.; Patnaik, G. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 695.
58. Ram, V. J.; Haque, N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1995**, *34*, 521.
59. Tominaga, Y. *Wakojunyaku Jihou* **1995**, *63*, 10.

60. Singh, S. K.; Kumar, N.; Kumar, S.; Bisht, K. S.; Parmarand, V. S.; Errington, W. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1995**, *C51*, 1630.
61. Sasho, S.; Obase, H.; Ichikawa, S.; Kitazawa, T.; Nonaka, H.; Yoshizaki, R.; Ishii, A.; Shuto, K. *Bioog. Med. Chem.* **1995**, *3*, 279.
62. Nargund, L. V. G.; Jose, R.; Reddy, Y. S. R. *Arzneim.-Forsch.* **1994**, *44*, 156; Chem. Abst. **1995**, *122*, 10003e.
63. Horton, D.; Norris, P.; Berrang, B. *Carbohydrate. Res.* **1996**, *283*, 3783.
64. Norris, P.; Horton, D.; Giridhar, D. E. *Tetrahedron Lett.* **1996**, *37*, 3925.
65. Rao, M. V. B.; Suresh, J. R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Indian Chem. Soc.* **1997**, *74*, 955.
66. Malhotra, S.; Parmar, V. S.; Errington, W. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1997**, *C53*, 1442.
67. Singh, O. M.; Junjappa, H.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3561.
68. Foulard, G.; Brigaud, T.; Portella, C. *J. Org. Chem.* **1997**, *62*, 9107.
69. Mellor, J. M.; Scholfield, S. R.; Korn, S. R. *Tetrahedron* **1997**, *53*, 17151.
70. Mellor, J. M.; Scholfield, S. R.; Korn, S. R. *Tetrahedron* **1997**, *53*, 17163.
71. Yang, H.; Lu, R.; Zhang, D. *Hecheng Huaxue* **1997**, *5*, 185; Chem. Abst., **1998**, *128*, 294651m.
72. Bold, G.; Frei, J.; Lang, M.; Traxler, P.; Furet, P. *PCT Int. Appl. WO 98 14,452 (Cl. C07D487/04)*; Chem. Abst. **1998**, *128*, 257442y.
73. Liu, H.; Lu, R.; Yang, H. *Synth. Commun.* **1998**, *28*, 3965.
74. Kumar, R.; Parmar, V. S.; Errington, W. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *C55*, 561.
75. Liu, H.-Y.; Lu, R.-J.; Chen, K.; Tan, H.-F.; Yang, H.-Z. *Gaodeng Xuexiao Huexue Xuebao* **1999**, *20*, 411; Chem. Abst. **1999**, *131*, 18816d.
76. Mtynarski, J.; Banaszek, A. *Polish J. Chem.* **1999**, *73*, 973.
77. Yayoicho, I.-K. *J. Carbohydrate Chem.* **1999**, *18*, 333.
78. Ho, Y.-W. *J. Chin. Chem. Soc.* **1999**, *46*, 947.
79. Henin, B.; Huot, J.-F.; Portella, C. *J. Fluorine Chem.* **2001**, *107*, 281.
80. Suresh, J. R.; Barun, O.; Ila, H.; Junjappa, H. *Tetrahedron* **2000**, *56*, 8153.
81. Wang, M.-X.; Liu, Y.; Huang, T. *Tetrahedron Lett.* **2001**, *42*, 2553.
82. Sandstroem, J.; Wennerbeck, I. *Acta Chem. Scand*. **1970**, *24*, 1191.
83. Yates, P.; Lynch, T. R.; Moore, D. R. *Can. J. Chem*. **1971**, *49*, 1467.
84. Larsson, F. C. V.; Lawesson, S. O. *Tetrahedron* **1972**, *28*, 5341.
85. Shahak, I.; Sasson, V. *Tetrahedron Lett.* **1973**, 420.
86. Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, 3817.
87. Kobayashi, G.; Matsuda, Y.; Natsuki, R. *Chem. Pharm. Bull.* **1973**, *21*, 921.
88. Dalgaard, L.; Kolind-Andersen, H.; Lawesson, S. O. *Ibid* **1973**, *29*, 2077.
89. Dalgaard, L.; Jensen, L.; Lawessn, S. O. *Tetrahedron* **1973**, *29*, 2077.
90. Nilsson, N. H. *Tetrahedron* **1974**, *30*, 3181.
91. Ueno, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1974**, *22*, 2624.
92. Dalagaard, L.; Jensen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *30*, 93.
93. Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett*. **1975**, 925.
94. Seebach, D.; Burstighaus, R. *Synthesis* **1975**, 461.
95. Augustin, M.; Schmidt, R.; Rudorf, W.-D. *Z. Chem.* **1977**, *17*, 289.
96. Tominaga, Y.; Fujito, H.; Mizuyama, K.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1977**, *25*, 1519.
97. Rastogi, R. R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 549.
98. Kakehi, A.; Ito, S.; Maeda, T.; Takeda, R.; Nishimura, M.; Tamashima, M.; Yamaguchi, T. *J. Org. Chem.* **1978**, *43*, 4837.
99. Gibbons, L. K. *U. S. 4,075,001 (Cl. 71-90;C07D275/02)*; Chem. Abst. **1978**, *88*, 170135g.
100. Kashima, K.; Hidaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G.; Sakemi, K. *Yakugaku Zasshi* **1978**, *99*, 38; Chem. Abst. **1979**, *90*, 186863v.
101. Augustin, M.; Groth, C. *J. Prakt. Chem.* **1979**, *321*, 215.
102. Augustin, M.; Groth, C. *J. Prakt. Chem.* **1979**, *321*, 205.

103. Rehn, D.; Nolte, H.; Zerling, W.; Rehn, H. *Arch. Pharm*. **1981**, *314*, 817.
104. Carve, L. C.; Van Tamelen, E. E. *J. Am. Chem. Soc*. **1982**, *104*, 867.
105. Myrboth, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, *48*, 5327.
106. Dieter, R. K.; Lin, Y. J.; Dieter, J. W. *J. Org. Chem*. **1984**, *49*, 3183.
107. Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1984**, *49*, 3819.
108. Tominaga, Y.; Matsuda, Y. *Yuki Gousei Kagaku Kyoukaishi J. Org. Synth. Jpn.* **1985**, *43*, 669.
109. Tominaga, Y.; Matsuda, Y. *J. Heterocycl. Chem.* **1985**, *22*, 937.
110. Potts, K. T.; Winslow, D. A. *J. Org. Chem.* **1985**, *50*, 5405.
111. Dieter, R. K. *Tetrahedron Lett.* **1985**, *26*, 39.
112. Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029.
113. Tomisawa, K.; Kameo, K.; Matsunaga, T.; Saito, S.; Hosoda, H; Asami, Y.; Sota, K. *Chem. Pharm. Bull.* **1986**, *34*, 701.
114. Tominaga, Y.; Shiroshita, Y.; Hosomi, A. *Heterocycles* **1988**, *27*, 2251.
115. Tominaga, Y.; Hosomi, A. *J. Heterocycl. Chem*. **1988**, *25*, 1449.
116. Peseke, K.; Quincoces Suarez, J.; Zayas, O. *Ger. (East) DD 255,341 (Cl. C07D307/54)*; Chem. Abst. **1989**, *110*, 38870m.
117. Huang, Z.; Shi, X. *Chem. Ber.* **1990**, *123*, 541.
118. Villemin, D.; Ben-Allaum, A. *Synthesis* **1991**, 301.
119. Beslin, P.; Marion, P. *Tetrahedron Lett.* **1992**, *33*, 5339.
120. Seshadri, S.; Sanghav, N. M.; Naik, R. V.; Tawate, S. R.; Trivedi, M. N.; Fruitwala, M. A. *Indian J. Chem. Sect. B* **1993**, *32B*, 688.
121. Henriksen, L. *Acta Chem. Scand*. **1996**, *50*, 432.
122. Portella, C.; Shermolovich, J. *Tetrahedron Lett.* **1997**, *38*, 4063.
123. Elgemeie, G. H.; Elghandour, A. H.; Elzanate, A. M.; Ahmed, S. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3285.
124. Mtynarski, J.; Banaszek, A. *Tetrahedron Lett.* **1998**, *39*, 5425.
125. Tcherchian, S.; Vallee, Y. *Tetrahedron* **1998**, *54*, 7777.
126. Mashraqui, S. H.; Hariharasubrahmanian, H. *J. Chem. Res. (S)* **1999**, 492.
127. Erdmann, B.; Knoll, A.; Liebscher, J. *J. Prakt. Chem.* **1988**, *330*, 1015.
128. Briel, D.; Maschke, T.; Wagner, G. *Pharmazie* **1992**, *47*, 577.
129. Sone, M.; Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull*. **1973**, *21*, 1667.
130. Sone, M.; Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1973**, *93*, 1008.
131. Sone, M.; Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1973**, *22*, 617.
132. Tominaga, Y.; Takada, S.; Kohra, S. *Tetrahedron Lett*. **1984**, *35*, 3555; Tominaga, Y.; Takada, S.; Kohra, S. *Heterocycles* **1995**, *40*, 105; Tominaga, Y.; Takada, S.; Kohra, S. *Chem. Pharm. Bull*. **1996**, *44*, 653.
133. Tominaga, Y.; Luo, J.-K.; Castle, R. N. *J. Heterocycl. Chem*. **1994**, *31*, 771.
134. Bhat, L.; Thomas, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1992**, *48*, 10377.
135. Peseke, K. *Pharmazie* **1975**, *30*, 258.
136. Peseke, K. *Ger. (East) DD 203,546* **1983**; Chem. Abst. **1984**, *100*, 156642e.
137. Peseke, K. *Pharmazie* **1975**, *30*, 802.
138. Peseke, K. *Pharmazie* **1976**, *31*, 607.
139. French, J.; Peseke, K.; Kristen, H.; Braeuniger, H. *Pharmazie* **1976**, *31*, 851.
140. Taylor, E. C.; Purdum, W. R. *Heterocycles* **1977**, *6*, 1865.
141. Morimoto, K.; Sato, T.; Yamamoto, S. *Jpn. Kokai Tokkyo Koho JP 6204,274 [87,04,274] (Cl. C07D231/52)*; Chem. Abst. **1987**, *107*, 176026e.
142. Ried, W.; Aboul-Fetouh, S. *Tetrahedron* **1988**, *44*, 7155.
143. Okajima, N.; Aoki, I.; Yoshiyuki, Y.; Kuragane, T. *Jpn. Kokai Koho JP 62,242,668* **1987**; Chem. Abst. **1988**, *108*, 167463p.
144. Tominaga, Y.; Honkawa, Y.; Hara, M.; Hosomi, A. *J. Heterocycl. Chem*. **1990**, *27*, 775.

145. Peseke, K.; Rodriguez, P. R.; Bohn, I. *Ger. (East) DD 207,717 (Cl. C07D407/12)*; Chem. Abst. **1984**, *101*, 191895g.
146. Peseke, K.; Rodriguez, P. R.; *Ger. (East) DD 205,163 (Cl. C07D405/12)*; Chem. Abst. **1984**, *101*, 72595z.
147. Braeuniger, H.; Ohm, G.; Peseke, K. *Wiss. Z. Wilhelm-Pieck-Univ. Rostock, Naturwiss. Reihe* **1984**, *33*, 67; Chem. Abst. **1987**, *106*, 61342s.
148. Yokoyama, M.; Sato, K. *Synthesis* **1988**, 813.
149. Lindig, M.; Backer, B. *Ger. Offen*, *DE3, 712 (Cl. C07D231/48)*; Chem. Abst. **1989**, *110*, 135234q.
150. Yokyama, M.; Kumata, K.; Yamada, N.; Noro, H.; Sudo, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2309.
151. Yokoyama, M.; Kumata, K.; Noro, N.; Kogo, A. *Synthesis* **1988**, 553.
152. Yokiyama, M.; Ikuma, T.; Sugasawa, S.; Togo, H. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2306.
153. Spindler, K. *Chem.-Ztg.* **1991**, *115*, 221; Chem. Abst. **1991**, *115*, 255952x.
154. Vogt, K.; Kempter, G.; Peseke, K. *Ger. (East) DD 294,717 (Cl. C07D405/12)*; Chem. Abst. **1993**, *117*, 48546u.
155. Mc Fadden, H. G.; Huppatz, J. L.; Halladay, P. K. *Aust. J. Chem.* **1993**, *46*, 873 Chem. Abst. **1997**, *126*,.
156. Jochheim, M.; Krug, H. G.; Neidlein, R.; Krieger, C. *Heterocycles* **1995**, *41*, 1235.
157. Gadad, A. K.; Kittur, B. S.; Kapsi, S. G.; Mahajanshetti, C. S.; Rajur S. B.; Arzneim-*Forsch.* **1996**, *46*, 1082; Chem. Abst. **1997**, *126*, 84098u.
158. Fathalla, O. A.; Zaki, M. E. A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1998**, *37*, 484.
159. Reddy, Y. S. R.; Mani, T. S.; Sarma, G. V. R.; Suresh, B. *Indian J. Pharm.* **1999**, *61*, 25.
160. Larsen, J. S.; Zahran, M. A.; Pedersen, E. B.; Nielsen, C. *Monatsh. Chem.* **1999**, *130*, 1167; Chem. Abst. **1999**, *131*, 351613p.
161. Rudorf, W.-D.; Augustin, M. *J. Prakt. Chem*. **1978**, *320*, 585.
162. Ikeda, K.; Akita, T. *Jpn. Kokai Tokkyo koho JP 06,0192,245 [94,192,245];* Chem. Abst. **1994**, *121*, 280633a.
163. Augustin, M.; Bielka, S. *Z. Chem.* **1980**, *20*, 96.
164. Wang, X.; Huang, Z. *Huaxue. Xuebao* **1989**, *47*, 890; Chem. Abst. **1990**, *112*, 198216x.
165. Wang, H.; Wang, X.; Huang, Z. *Chem. Ber.* **1990**, *123*, 2141.
166. Matsuoka, T.; Sasho, S.; Mizutaki, S.; Kasai, M.; Tomioka, S. *Jpn. Kokai Tokkyo Koho JP 06,271,546 [94,271,546] (Cl. C07D233/04);* Chem. Abst. **1995**, *122*, 81368p.
167. Wang, L. B.; Huang, Z.-T. *Synth. Commun.* **1996**, *26*, 459.
168. Yu, C.-Y.; Wang, L. B.; Huang, Z.-T. *Synth. Commun.* **1996**, *26*, 2297.
169. Boerner, A.; Kristen, H.; Peseke, K.; Michalik, M. *J. Prakt. Chem*. **1986**, *328*, 21.
170. Evers, R.; Faix, G.; Peseke, K.; Bohn, I.; Warnat, G. *Ger. (East) DD 272,462 (Cl. C07D263/14)*; Chem. Abst. **1990**, *112*, 235288v.
171. Evers, R.; Michalik, M. *J. Prakt. Chem.* **1990**, *333*, 699.
172. Huang, Z.; Zhang, P. *Chem. Ber.* **1989**, *122*, 2011.
173. Huang, Z.; Zhang, P. *Synth. Commun.* **1990**, *20*, 1399.
174. Hosomi, A.; Miyashiro, Y.; Yoshida, R.; Tominaga, Y.; Yanagi, T.; Hojo, M. *J. Org. Chem.* **1990**, *55*, 5308.
175. Huang, Z.; Wang, M. *Synth. Commun.* **1991**, *21*, 1177.
176. Huang, Z.; Shi, X. *Synthesis* **1990**, 162.
177. Bocion, P.; De Silva, W.; Winternitz, P. *Ger. Offen., 2,512,564(Cl. C07D, A01N)*; Chem. Abst. **1976**, *84*, 59434g.
178. Huang, Z.; Zhang, P. *Chin. Chem. Lett.* **1990**, *1*, 167; Chem. Abst. **1991**, *115*, 135980h.
179. El-Shafei, A. K.; Elsaghier, A. M. M.; Ahmed, E. A. *Synthesis* **1994**, 152.
180. El-Shafei, A. K.; Soliman, A. M.; Sultan, A. A.-R.; Elsaghier, A. M. M. *Gazz. Chim. Ital.* **1995**, *125*, 115.
181. Poetsch, E. *Ger. Offen., 1,809,467* **1970**; Chem. Abst. **1970**, *72*, 66443k.
182. Peseke, K.; Schoenhusen, U. *Ger*. (East) *DD150, 894*; Chem. Abst., **1982**, *97*, 162831b.

183. Bartroli, R.; Diaz, M.; Quincoces Suarez, J.; Peseke, K. *Sobre Deriv. Cana Azucar* **1988**, *22*, 44; Chem. Abst. **1990**, *112*, 118601f.
184. Hidaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G.; Sakemi, K. *Yakugaku Zasshi* **1979**, *99*, 1234; Chem. Abst. **1980**, *92*, 198238z.
185. Peseke, K.; Quincoces Suarez, J. *Ger. (East) 142, 549 (Cl. C07D405/12)*; Chem. Abst. **1981**, *94*, 192160n.
186. Tominaga, Y.; Kawabe, K.; Hosomi, A. *J. Heterocycl. Chem*. **1987**, *24*, 1325.
187. Sharanin, Yu. A.; Dyachenko, V. D.; Turov, A. V. *Zh. Obshch. Khim.* **1990**, *60*, 2750; Chem. Abst. **1991**, *115*, 49335v.
188. Peseke, K.; Quincoces Suarez, J.; Bartroli Rivas, R. M. *Ger. (East) DD 267,045*; Chem. Abst. **1990**, *112*, 7385u.
189. Peseke, K.; Quincoces Suarez, J.; Napoles Frias, B. M. *Ger. (East) DD272, 840* **1988**; Chem. Abst. **1990**, *112*, 235191h.
190. Peseke, K.; Quincoces Suarez, J.; Bartroli Rivas, R. M. *Ger. (East) DD272, 850,* **1989**; Chem. Abst. **1990**, *113*, 6169k.
191. Peseke, K.; Bartoli Rivas, R. M.; Quincoces Suarez, J. *Wiss.Z. Wilhelm-Pieck Univ. Rostoch, Naturwiss. Reihe* **1988**, *37*, 46; Chem. Abst. **1991**, *114*, 23860s.
192. Briel, D.; Dumke, S.; Wagner, G.; Olk, B. *J. Chem. Res., (S)* **1991**, *7*, 178; Chem. Abst. **1991**, *115*, 114384 b.
193. Abu-Shanab, F. A.; Elnagdi, M. H.; Ali, F. M.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1994**,1449.
194. Peseke, K.; Quincoces Suarez, J.; Napoles Frias, B. M. *Ger. (East) DD 294,943 (Cl. C07D 487/04);* Chem. Abst. **1992**, *116*, 128960u.
195. Elgemeie, G. H.; Elghandour, A. H.; Elzanate, A. M.; Masoud, W. A. *J. Chem. Res. (S)* **1998**, 164.
196. Elgemeie, G. H.; Elghandour, A. H.; Ali, H. A.; Abd Elaziz, H. M. *J. Chem. Res. (S)* **1999**, 6.
197. Elgemeie, G. H.; Ali, H. A.; Elghandour, A. H.; Abd Elaziz, G. W. *Phosphorus, Sulfur and Silicon* **2000**, *164*, 189.
198. Tominaga, Y.; Michioka, T.; Moriyama, K.; Hosomi, A. *J. Heterocyclic Chem*. **1990**, *27*, 1217.
199. Hatada, T.; Sone, M.; Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1975**, *95*, 623; Chem. Abst. **1975**, *83*, 206076b.
200. Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Heterocycles* **1977**, *4*, 1493.
201. Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull*. **1984**, *32*, 3384.
202. Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 1665.
203. Tominaga, Y.; Ushirogochi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557.
204. Hung, X.; Wu, G. *Youji Huaxue* **1989**, *9*, 460; Chem. Abst. **1990**, *113*, 6090c.
205. Elgemeie, G. H.; Elghandour, A. H.; Ali, H. A.; Hussain, A. M. *J. Chem. Res. (S)* **1997**, 256.
206. Watanabe, M.; Minohara, M.; Matsuda, K.; Kinoshita, T.; Furukawa, S. *Heterocycles* **1979**, *4*, 1875.
207. Watanabe, M.; Matsuda, K.; Kinoshita, T.; Furukawa, S. *Heterocycles* **1977**, *6*, 1781.
208. Ried, W.; Saynovite, M. *Chem. Ber.* **1988**, *121*, 1005.
209. Kisaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1974**, *22*, 2246.
210. Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779.
211. Evers, R. *Z. Chem.* **1979**, *19*, 250; Chem. Abst. **1980**, *92*, 58713a.
212. Kohra, S.; Tominaga, Y.; Hosomi, A. *J. Heterocycl. Chem.* **1988**, *25*, 959.
213. Ram, V. J.; Haque, N.; Shoeb, A. *J. Prakt.Chem. / Chem.-Ztg.* **1992**, *334*, 190.
214. Kobayashi, G.; Matsuda, Y.; Natsuki, R.; Tominaga, Y. *Yakugaku Zasshi* **1972**, *92*, 1468.
215. Sone, M.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1977**, *97*, 262; Chem. Abst. **1977**, *87*, 53195v.
216. Fukuda, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Heterocycles* **1983**, *20*, 1793.
217. Yokoyama, M.; Hatanaka, H.; Sasaki, A.; Shiraishi, T.; Kumata, K.; Sakamoto, K.; Ogata, K. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 1187.
218. Tominaga, Y.; Matsuoka, Y.; Kohra, S.; Hosomi, A. *Heterocycles* **1987**, *26*, 613.
219. Briel, D.; Wagner, G. *Ger. (East) DD 242,226 (Cl. C07D239/58);* Chem. Abst. **1987**, *107*, 39855k.

220. Lorente, A.; Garcia, M. L.; Fernandez, M.; Soto, J. L. *Heterocycles* **1992**, *34*, 1573.
221. Ryan, G.; Mettler, H. P.; Previdoli, F. *Eur. Pat. Appl. EP 508,353 (Cl. C07D239/46);* Chem. Abst. **1993**, *118*, 38943c.
222. Liu, H.-Y.; Yang, G.; Tan, H.-F.; Yang, H.-Z.; Lai, L.-H. *Gaodeng Xuexiao Huaxue Xuebao* **1998**, *19*, 1946; Chem. Abst. **1999**, *130*, 168326n.
223. Liu, H.-Y.; Yang, G.; Yang, H.-Z. *Chin. Chem. Lett.* **1999**, *10*, 191; Chem. Abst. **1999**, *131*, 199670v.
224. Spindler, J.; Peseke, K.; Kempter, G. *Ger. (East) DD 261,1783,* **1988**; Chem. Abst. **1990**, *111*, 97269r.
225. Spindler, J.; Peseke, K.; Kempter, G.; Klepel, M. *Ger. (East) DD 266,101 (Cl. C07D239/74);* Chem. Abst. **1990**, *112*, 35885a.
226. Norisue, H.; MS thesis *(Nagasaki University)* **1981**.
227. Ried, W.; Jacobi, M. A. *Chem. Ber*. **1986**, *119*, 1745.
228. Ried, W.; Jacobi, M. A. *Chem. Ber*. **1987**, *120*, 1455.
229. Spindler, J.; Kempter, G.; Peseke, K.; Kleinpeter, E. *Ger. (East) DD 294,714 (Cl. C07D243/04);* Chem. Abst. **1992**, *117*, 48620p.
230. Hartke, K.; Radau, S. *Liebigs Ann. Chem*. **1974**, 2110.
231. Sobenina, L. N.; Mikkaleva, A. J.; Trafimov, B. A. *Khim. Geteroskil Soedin* **1995**, 41819; Chem. Abst. **1995**, *123*, 256466m.
232. Elgemeie, G. H.; Ali, H. A.; Elzanate, A. M. *J. Chem. Res. (S)* **1996**, 340.
233. Matsuda, Y.; Yamashita, M.; Takahashi, K.; Ide, S.; Torisu, K.; Furuno, K. *Heterocycles* **1992**, *33*, 295.
234. Elgemeie, G. H.; Elghandour, A. H.; Elzanate, A. M.; Ahmed, S. A. *J. Chem. Res. (S)* **1998**, 162.
235. Tominaga, Y.; Miyake, Y.; Fujito, H.; Kurata, K.; Awaya, H.; Matsuda, Y.; Kobayaski, G. *Chem. Pharm. Bull.* **1977**, *25*, 1528.
236. Tominaga, Y.; Shiroshita, Y.; Hosomi, A. *J. Heterocycl. Chem*. **1988**, *25*, 1745.
237. Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1980**, *101*, 980; Chem. Abst. **1982**, *96*, 217667q.
238. Fujito, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1977**, *97*, 1316; Chem. Abst. **1978**, *88*, 152384h.
239. Fujito, H.; Tominaga, Y.; Awaya, H.; Kurata, K.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1978**, *98*, 1412; Chem. Abst. **1979**, *90*, 72024s.
240. Tominaga, Y.; Hidaki, S.; Matsuda, Y.; Kobayashi, G.; Sakemi, K. *Yakugaku Zasshi* **1979**, *99*, 540.
241. Matsuda, Y.; Gotou, H.; Katou, K.; Matsumoto, H.; Yamashita, M.; Takahashi, K.; Ide, S.; Furuno, K.; Torisu, K. *Heterocycles* **1991**, *32*, 2217.
242. Tominaga, Y.; Hidaki, S.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1984**, *104*, 440; Chem. Abst. **1985**, *102*, 6281p.
243. Fuijito, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Heterocycles* **1977**, *6*, 379.
244. Tominaga, Y.; Hosomi, A. *J. Heterocycl. Chem*. **1988**, *25*, 1449.
245. Ide, S.; Katou, K.; Itou, T.; Motokawa, C.; Chiyomaru, Y.; Matsuda, Y. *Yakugaku Zasshi* **1993**, *113*, 861; Chem. Abst. **1994**, *121*, 108618p.
246. Isobe, Y.; Goto, J.; Chiba, S.; Matsuda, Y. *Jpn. Kokai Tokko Koho JP 08,157,363 [96,157,363] (Cl. A61K31/435)* **1996**; Chem. Abst. **1996**, *125*, 195649y.
247. Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Bunseki Kiki* **1977**, *15*, 413; Chem. Abst. **1978**, *88*, 121047w.
248. Yokoyama, M.; Tohnishi, M.; Kurihara, A.; Imamoto, T. *Chem. Lett.* **1982**, 1936.
249. Matsuda, Y.; Matsumoto, H.; Ide, S.; Furuno, K.; Torisu, K.; Itou, T.; Motokawa, C. *Yakugaku Zasshi* **1993**, *113*, 32; Chem. Abst. **1993**, *118*, 233938g.
250. Kobayashi, G.; Matsuda, Y.; Natsuki, R.; Tominaga, Y. *Yakugku Zasshi* **1973**, *93*, 836.
251. Kobayashi, G.; Matsuda, Y.; Natsuki, R.; Nakamura, A. *Yakugaku Zasshi* **1973**, *93*, 964.
252. Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull*. **1975**, *21*, 1658.
253. Kobayashi, G.; Tominaga, Y.; Kisaki, S.; Sone, M.; Ueno, S. *Chem. Pharm. Bull.* **1973**, *21*, 2344.
254. Kisaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1974**, *22*, 2246.

255. Tominaga, Y.; Hidaki, S.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 519.
256. Kumar, A.; Ila, H.; Junjappa, H. *Synthesis* **1976**, 324.
257. Elgemeie, G. H.; Ali, H. A.; Mansour, A. K. *Phosphorus, Sulfur and Silicon* **1994**, *90*, 143.
258. Kovacs, L.; Forgo, P. *Molecules* **2000**, *M143*, 5.
259. El-Desoky, E.-S. I.; Aboul-Fetouh, S.; Metwally, M. A. *J. Chem. Technol. Biotechnol.* **1996**, *67*, 153.
260. Pech, R.; Boehn, R. *Pharmazie* **1993**, *48*, 347.
261. Tominaga, Y.; Morita, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1975**, *23*, 2390.
262. Tominaga, Y.; Sone, M.; Mizuyama, K.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1976**, *24*, 1671.
263. Tominaga, Y.; Kurata, K.; Awaya, H.; Matsuda, Y.; Kobayashi, G. *Heterocycles* **1978**, *9*, 399.
264. Tominaga, Y.; Sakai, S.; Kohra, S.; Tsuka, J.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull*. **1985**, *33*, 962.
265. Bold, G.; Frei, J.; Lang, M.; Traxler, P. *PCT Int. Appl. WO 98 14,450 (Cl. C07D487/04);* Chem. Abst. **1998**, *128*, 270610w.
266. Kobayashi, G.; Matsuda, Y.; Natsuki, R.; Tominaga, Y.; Maseda, C.; Awaya, H. *Yakugaku Zasshi* **1974**, *94*, 50; Chem. Abst. **1974**, *80*, 108339h.
267. Awaya, H.; Maseda, C.; Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1975**, *95*, 13; Chem. Abst. **1975**, *83*, 9966r.
268. Nargund, L. V. G.; Reddy, Y. S. R.; Jose, R. *Indian Drugs* **1991**, *29*, 45.
269. Ueno, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1974**, *22*, 2624.

RECENT DEVELOPMENT IN THE CHEMISTRY OF 4,5-DIHALO-3(2H)-PYRIDAZINONES

Pál Tapolcsányi and Péter Mátyus*

Department of Organic Chemistry, Semmelweis University, Budapest, Högyes u. 7, 1092 Hungary

(e-mail: matypet@szerves.sote.hu)

Abstract. *4,5-Dihalo-3(2H)-pyridazinones have gained increasing importance in the synthetic chemistry of pyridazines over the last decade. In particular, new examples of nucleophilic displacement of halogens, novel types of N-protection leading to a more efficient functionalization, and the introduction of C-C coupling reactions by palladium catalysts illustrate the significant development in the field. All these aspects are covered by this review.*

Contents

1. Introduction

1. 4,5-Dihalo-3(2*H*)-pyridazinones attracted much attention over the last three decades due to their easy availability, and efficient functionalization with electrophiles at the lactam moiety and/or 6-position, and with nucleophiles at the 4- and/or 5-position(s). These properties make them particularly attractive starting materials for the synthesis of 4- and/or 5-substituted monocyclic and 4,5-annelated polycyclic pyridazine derivatives. In the last decade too, considerable advance has been made in the synthetic chemistry of this class compounds. In this review, the most significant progresses from 1993, the date of publication of our first comprehensive review on the field will be covered.[1]

2.

2. Substitution at the lactam moiety

The most convenient source of 4,5-dichloro- and dibromo-3(2*H*)-pyridazinones is the condensation reaction of the respective mucohalic acid (2,3-dichloromalealdehydic acid) with hydrazine hydrate. The *N*-substituted compounds could be obtained either by application of the properly substituted hydrazine for the condensation or, to avoid the highly toxic substituted hydrazines, by functionalization of the parent 4,5-

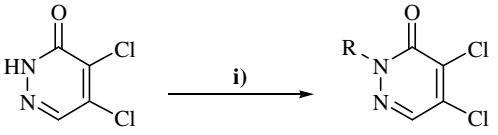
dihalo compounds. Alkylation, sulfonylation and acylation have been thoroughly studied over the last years, particularly a Korean group headed by Yoon has significantly contributed to this field.

Although, in these reactions either *N*- or *O*-substituted derivatives may *a priori* be formed, in the most cases, *N*-substitution has been found to occur, whereas formation of the *O*-substituted derivatives has only been detected under special conditions.

2.1. Alkylated derivatives

Pyridazine nucleosides with potential biological activity are of continous interest.

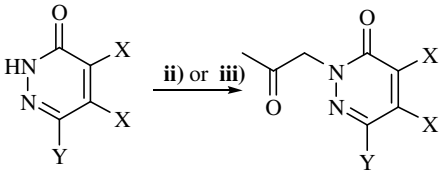
Pyridazinones **2** and **3** containing a 4-oxybutyl moiety, as analogues of nucleosides, were prepared *via* alkylation of 4,5-dichloro-3(2*H*)-pyridazinone (**1a**) with 4-iodobutyl acetate and 4-iodobutyl benzoate in dimethyl sulfoxide in the presence of sodium hydride.[2] Synthesis of 2-(2-oxopropyl)pyridazinones without or with a nitro group, compounds **5** and **6**, respectively, was carried out by using either 4-bromoacetoacetic acid or chloroacetone (Scheme 1). With the latter procedure higher yields were achieved.[3]



1a

2 R= $MeCOO(CH_2)_4$-
3 R= $PhCOO(CH_2)_4$-

i) NaH; DMSO; 2h, rt; RI; (83%, 82%)



1a X=Cl, Y=H
1b X=Br, Y=H
4a X=Cl, Y=NO_2
4b X=Br, Y=NO_2

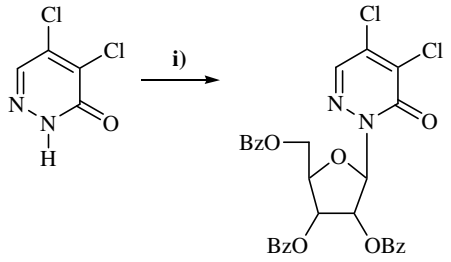
5a: X=Cl, Y=H
5b: X=Br, Y=H
6a: X=Cl, Y=NO_2
6b: X=Br, Y=NO_2

ii) $BrCH_2COCH_2COOH$; TEA; THF; rt; (63-83%)
iii) $ClCH_2COCH_3$; K_2CO_3; DMF; 50-60 °C; (86-93%)

Scheme 1

Pyridazine *N*-nucleosides such as **7** were also prepared. Compound **7** could be conveniently obtained by ribosylation of **1a** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl β-*D*-ribofuranose in the presence of ammonium sulfate, hexamethyldisilazane and stannic chloride (Scheme 2).[4]

The *N*-substituent of the pyridazinone may also serve as a protecting group needed for or facilitating further transformations. As protecting groups at the 2-position, benzyloxymethyl and benzyl are amongst the most popular ones.[5] Improved methods for *N*-benzylation have more recently been reported. Treatment of **1a** or **1b** with benzyl bromide in the presence of potassium carbonate and tetrabutylammonium bromide in acetonitrile,[6] or in the presence of 8N potassium hydroxide as a base in dimethyl sulfoxide,[7] respectively, afforded 2-benzyl derivatives **8** in good yields.

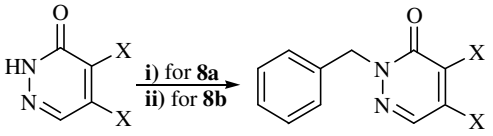


1a **7**

i) 1. $(NH_4)_2SO_2$; hexamethyldisilazane
R^1OAc; $SnCl_4$; 1,2-dichloroethane
2. $NaHCO_3$; EtOH

Scheme 2

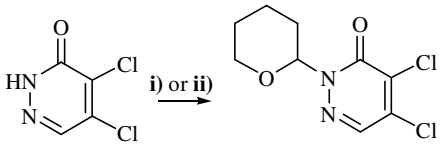
The tetrahydropyranyl group could also be attached to the lactam nitrogen. Synthesis of *N*-tetrahydropyranyl derivative **9** was accomplished from **1a** with an excess of dihydropyran and *p*-toluenesulfonic acid (or pyridinium tosylate) in refluxing tetrahydrofuran (Scheme 3).[8]



1a X=Cl
1b X=Br

8a X=Cl
8b X=Br

i) $PhCH_2Br$; K_2CO_3; Bu_4NBr; MeCN; reflux; 1 h; (81%)
ii) $PhCH_2Br$; 8N KOH; DMF; 50 °C; 0.5 h



1a **9**

i) Dihydropyran; TsOH; THF; reflux; 29 h;
ii) Dihydropyran; pyridinium tosylate; THF; reflux; 25 h

Scheme 3

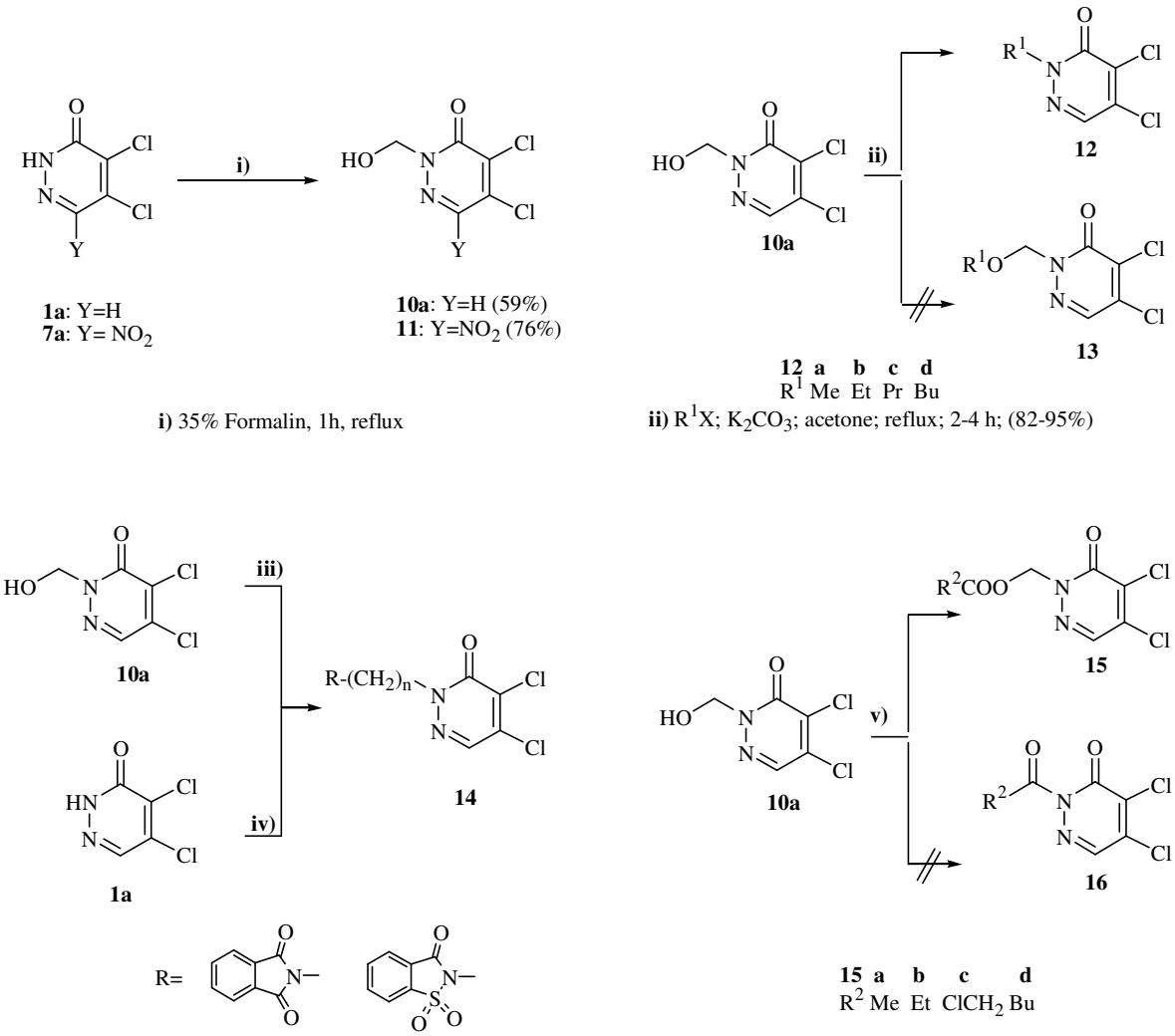
Sometimes , alkylation reactions of the parent dihalopyridazinones could be sluggish due to the low solubility of these compounds. Apparently, this problem could be solved by introduction of a labile functionality to the 2-position. It has been recently reported that 4,5-dichloro-2-hydroxymethyl-3(2*H*)-pyridazinone (**10a**), which itself was prepared from **1a** in hot 35% formalin, can be *N*-alkylated, and with this compound reasonable reaction rates as well as good yields can be achieved. The method is highly versatile, and the conditions are mild. The following examples are provided for illustration.

Treatment of **10a** with various alkyl halides in the presence of potassium carbonate in acetone (or in acetonitrile) at reflux temperature gave the corresponding 2-alkyl derivatives **12** with no formation of 2-alkoxymethyl derivatives **13**. Higher yields of **12** were generally obtained when the synthesis started from compound **10a**.[9]

Synthesis of 4,5-dichloro-2-(ω-phtalimido)- and (ω–saccharin-2'-yl)-3(2*H*)-pyridazinones (**14**) was also studied starting from both **1a** and **10a**. In these cases too, rate of the alkylation reaction of **10a** was higher than that of **1a**.[10]

A plausible mechanism of these transformations involves two steps. In the first step, compound **10a** may undergo a retro-ene type fragmentation with a C-N bond cleavage (it may be facilitated a hydrogen-bonding formed between OH and the pyridazine-carbonyl) to liberate formaldehyde as a leaving enophile; then, in the subsequent step formation of the new C-N bond occurs.

It is noteworthy that acylation of the hydroxymethyl derivative **10a**, takes a different pathway from the route shown for alkylation. Treatment of **10a** with acyl chlorides in the presence of potassium carbonate in refluxing acetone or acetonitrile led smoothly to the formation of the corresponding esters **15**, *i.e. O*-acylation of the hydroxymethyl group took place. Formation of 2-acylpyridazinone derivatives **16** could not be observed (Scheme 4).



i) 35% Formalin, 1h, reflux

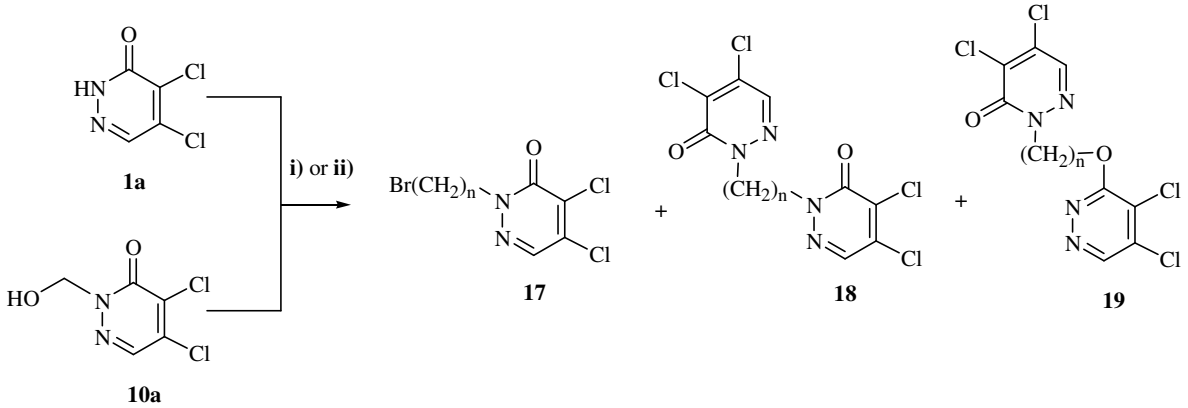
ii) R^1X; K_2CO_3; acetone; reflux; 2-4 h; (82-95%)

iii) $R\text{-}(CH_2)_nX$; K_2CO_3; MeCN; reflux; 0.5-2.5 h; (83-97%)
iv) $R\text{-}(CH_2)_nX$; K_2CO_3; MeCN; reflux; 1-4 h; (86-94%)
n=1-6
X= Br, Cl

v) R^2COCl; K_2CO_3; acetone or MeCN; rt or reflux; 6-10 h; (73-88%); X= I, Br, Cl

Scheme 4

A further application of **10a** for alkylation was provided by reactions with dibromoalkanes. Again, for comparison, the same reactions were also carried with **1a**. The reaction of **1a** with α,ω–dibromoalkanes gave different types of products; seemingly, the chain length (n) of the alkylating agent and the reaction conditions directed the reaction.[11] When **1a** was reacted with dibromomethane (n=1), a *N*,*N*-methylene bridged *bis*(pyridazinyl) derivative **18** was obtained as the only product using either potassium carbonate in acetonitrile at 82 °C (*Method A*, Table 1) or potassium hydroxide and tetrabutylammonium bromide in benzene at 56 °C (*Method B*).



i) 1.8 equiv. Br-$(CH_2)_n$-Br; 1.8 equiv. K_2CO_3; MeCN; 82 °C; (Method A)
ii) 1.8 equiv. Br-$(CH_2)_n$-Br; 1.8 equiv. Bu_4NBr; 1.8 equ. KOH; Benzene; 56 °C; (Method B)
n= 1-6

Scheme 5

Table 1. Alkylation of **1a** with dibromoalkenes

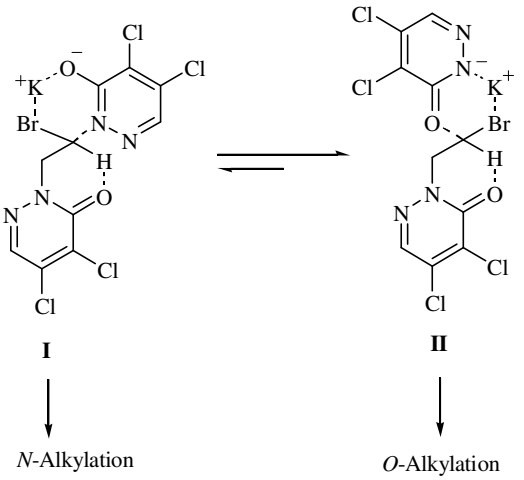
n	Method	Starting from 1a			Starting from 10a		
		Isolated yields			Isolated yields		
		17	**18**	**19**	**17**	**18**	**19**
1	A	-	96	-	-	90	-
1	B	-	97	-	-	91	-
2	A	30	*	59	-	23	72
2	B	90	*	-	91	*	-
3	A	76	16	-	96	*	-
3	B	96	*	-	94	*	-
4	A	95	*	-	93	*	-
4	B	92	*	-	90	*	-
6	A	94	*	-	94	*	-
6	B	61	31	-	60	29	-

*Product was detected by gas chromatography but not isolated

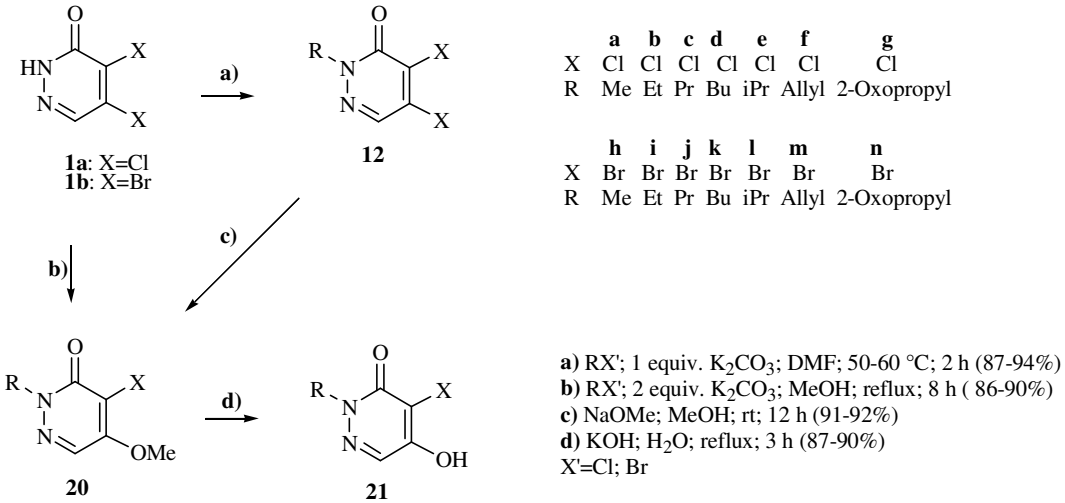
Reactions of **1a** with 1,3-dibromopropane, 1,4-dibromobutane and 1,6-dibromohexane afforded the corresponding *N*-(ω-bromoalkyl) derivative **17** as the major product, and **18** as the minor product. The reaction with 1,2-dibromoethane under the conditions of *Method A*, afforded as major product, a third type

of products, the *O*,*N*-ethylene bridged *bis*(pyridazinyl) compound **19** (Table 1). All these alkylation reactions were also carried out starting from the hydroxymethylpyridazinone **10a**.[12] The product ratio obtained with 1,2-dibromoethane was slightly different from the above results. In this case, compound **19** was again the major product, but **18** was also obtained, as the minor product (Scheme 5).

For the mechanism of *N*- and *O*-alkylation reactions of **1a** with 1,2-dibromoethane, transition states of I and II, respectively, were considered. Being the structure II more favorable in the presence of potassium carbonate, *O*-alkylation may occur predominantly. On the other hand, alkylation in the presence of tetrabutylammonium bromide and potassium hydroxide affords selectively the *N*-alkylated product since formation of II is unfavorable due to the steric hindrance exhibited by the tetrabutylammonium ion (Scheme 6).



Scheme 6



Scheme 7

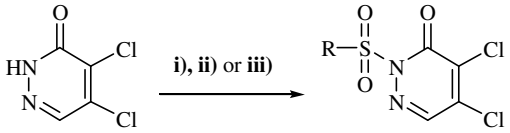
The final example of alkylations relates to a convenient one-pot procedure for the preparation of *N*-alkyl-4-halo-5-methoxypyridazinones **20**.[13] In this process, compounds **1** were treated with various alkyl halides and 2 equivalents of potassium carbonate in refluxing methanol to obtain compounds **20**. However, using potassium carbonate in a different molar ratio in refluxing methanol, a side product was also detected:

either 4,5-dimethoxy-3(2*H*)-pyridazinone (in the presence of more than 2 equivalents of potassium carbonate) or 2-alkyl-4,5-dihalo-3(2*H*)-pyridazinone (**12**) (in the presence of less than 2 equivalents of potassium carbonate) was formed. For comparison, compounds **20** were also synthesized in two steps: i) alkylations of pyridazinones **1** with alkyl halides using potassium carbonate in dimethyl formamide, and ii) nucleophilic substitution with sodium methoxide in methanol.

For preparation of 5-hydroxy derivatives **21**, the 5-methoxy derivatives **20** were *O*-demethylated by hydrolysis in aqueous potassium hydroxide (Scheme 7).

2.2. Sulfonylation

Sulfonylation reactions of **1a** with various sulfonyl chlorides have been studied.[14] In all cases, 2-*N*-sulfonylpyridazinones **22** were obtained (Scheme 8). Effect of the base on the rate and yield of the reaction of **1a** with 4-nitrobenzenesulfonyl chloride was investigated in tetrahydrofuran (Table 2). High rate and excellent yield were obtained by using 4-(*N,N*-dimethylamino)pyridine at room temperature.



1a **22**

i) 4-NO_2-Ph-SO_2Cl; THF; Base
ii) R-SO_2Cl;THF; K_2CO_3; reflux; 1-30 h (51-98%)
iii) R-SO_2Cl;THF; DMAP; rt; 0.08-6 h (81-95%)
R=Me, Ph, 2-CN-Ph, 2-NO_2-Ph, 2-Br-Ph,
3-NO_2-Ph, 4-Me-Ph, 4-Cl-Ph, 4-F-Ph, 4-NO_2-Ph,
2,5-Cl_2-Ph, 2,4-$(NO_2)_2$-Ph, 2,4,6-Me_3-Ph

Scheme 8

Table 2. Reaction of **1a** with 4-nitrobenzenesulfonyl chloride

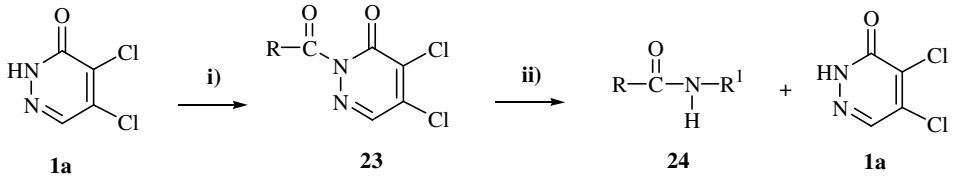
Base	Time (h)	Temp.	Yield %
K_2CO_3	4	Reflux	77
Cs_2CO_3	5	R.t.	75
NaH	50	R.t.	65
Et_3N	2	R.t.	92
DMAP*	0.17	R.t.	92
Pyridine	59	Reflux	63
BuLi	0.33	0 °C	82

*4-(*N,N*-dimethylamino)pyridine

2.3. Acylation

Acylation of pyridazinone **1a** with various acyl chlorides also afforded *N*-acyl derivatives: compounds **23** were obtained in good yields in the presence of triethylamine in dichloromethane. The synthetic utility of these compounds for *N*-acyl transfer reactions has been investigated.[15] Treatment of various *primary* amines including aminoacids or aminoalcohols with 1 equivalent of **23** in tetrahydrofuran

under the conditions listed in Table 3 afforded the corresponding amides (**24**) chemoselectively, and in excellent yields (Scheme 9).



1a **23** **24** **1a**

i) RCOCl; TEA; CH_2Cl_2; -22-+25°C; 5-10 min; (80-99%)
ii) R^1NH_2; CH_2Cl_2 or THF;
R=Me, Et, Pe, Ph, 4-MeO-Ph, 4-Me-Ph, 4-Cl-Ph, cHex
R^1=4-$MeC_6H_4CH_2$; Ph; 4-$HO(CH_2)_2C_6H_4$;
CH_2COOH; 2-$HOOCC_6H_4$; 4-HOC_6H_4

Scheme 9

Table 3. Acylation of amines with acylpyridazinones

R	**R^1**	**Conditions**	**Yield of 24 (%)**
Me	Ph	0.5 h; reflux	95
Me	4-$HO(CH_2)_2C_6H_4$	0.2 h; 17 °C	94
Me	$HOOCCH_2$	4 h; reflux	84
Me	2-$HOOCC_6H_4$	14 h; reflux	94
Me	4-HOC_6H_4	0.2 h; 17 °C	95
Ph	Ph	4 h; reflux	98
Ph	4-$HO(CH_2)_2C_6H_4$	18 h; 18 °C	97
Ph	$HOOCCH_2$	24 h; reflux	98
Ph	2-$HOOCC_6H_4$	34 h; reflux	84
Ph	4-HOC_6H_4	12 h; 18 °C	94
4-$MeOC_6H_4$	Ph	3 h; reflux	99
4-$MeOC_6H_4$	4-$HO(CH_2)_2C_6H_4$	7 h; 18 °C	93
4-$MeOC_6H_4$	$HOOCCH_2$	42 h; reflux	72
4-$MeOC_6H_4$	2-$HOOCC_6H_4$	14 h; reflux	87
4-$MeOC_6H_4$	4-HOC_6H_4	5 h; 18 °C	99

Table 4. Study of steric influences on acyl-transfer reactions of acylpyridazinone

Mixture of starting amines	**Amide product (R=4-$MeOC_6H_4$)**
$EtNH_2$ + Et_2NH	EtNHCOR (85%)+Et_2NCOR (14%)
$C_6H_{11}NH_2$ + $(C_6H_{11})_2NH$	$C_6H_{11}NHCOR$ (97%)
$PhCH_2NH_2$ + $PhCH_2NHMe$	$PhCH_2NHCOR$ (99%)
$PhCH_2NH_2$ + PhCH(Me)NH_2	$PhCH_2NHCOR$ (75%)+ PhCH(Me)NHCOR (21%)
PhCH(Me)NH_2 + $PhCH_2NHMe$	PhCH(Me)NHCOR (9%)+$PhCH_2N$(Me)COR (89%)
$PhCH_2NHMe$ + $PhCH_2NH$(i-Pr)	$PhCH_2N$(Me)COR (98%)

Sensitivity of the acyl transfer to steric effect was studied by the reaction of 4,5-dichloro-2-(4-methoxybenzoyl)-3(2*H*)-pyridazinone with a 1:1 mixture of two sterically different amines (Table 4). The results suggest that *primary* amines (vs. *secondary*) react preferably, and α-branching is still tolerated for reaction.

3. Halogen exchange reactions

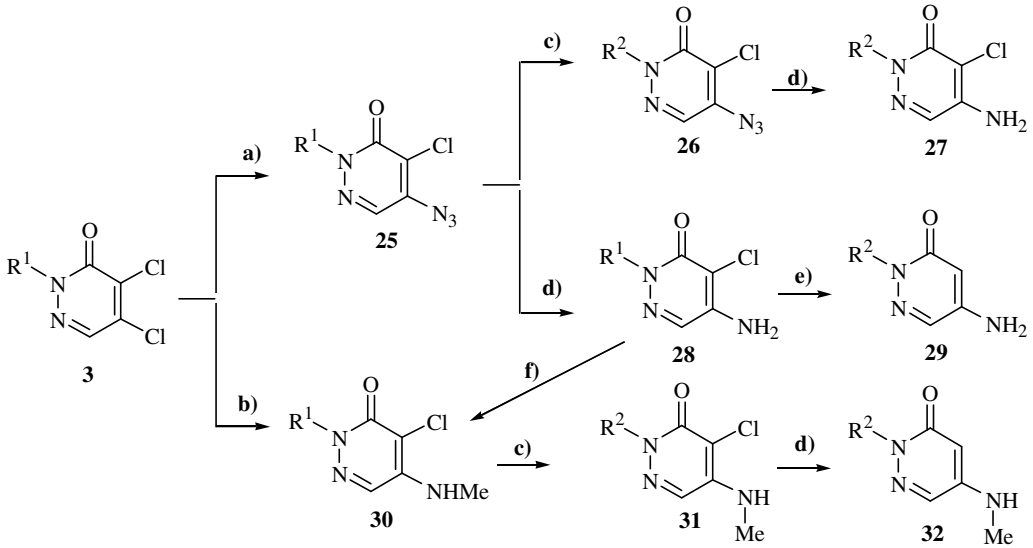
The most characteristic and important reactions of 4,5-dihalo-3(2*H*)-pyridazinones are nucleophilic displacement reactions of halogens. These reactions allow the introduction of a wide variety of nucleophiles, including *N*-, *O*- and *C*-nucleophiles, onto the pyridazine ring, and provide simple synthetic routes to many polycyclic ring systems, too. One of the key issues of these transformations is the regiochemistry of the substitution. A considerable body of experimental evidence and theoretical studies indicate that the reaction follows an addition-elimination pathway, and the regiochemistry might be significantly influenced by the reaction conditions; polar solvent is generally favorable for the 5-substitution. The regiochemistry is more complicated in the presence of 6-nitro group.[16]

The other type of efficient halogen-displacement reactions is represented by C-C coupling reactions catalysed by palladium. These methodologies have currently been explored for pyridazine chemistry.

3.1. Nucleophilic substitution reactions

Pyridazine nucleoside analogues **3** were funtionalized at the 5-position with a variety of nucleophiles.

For preparation of amino derivatives, the nucleophilic displacement of 5-chloro was carried out with sodium azide to obtain **25**.

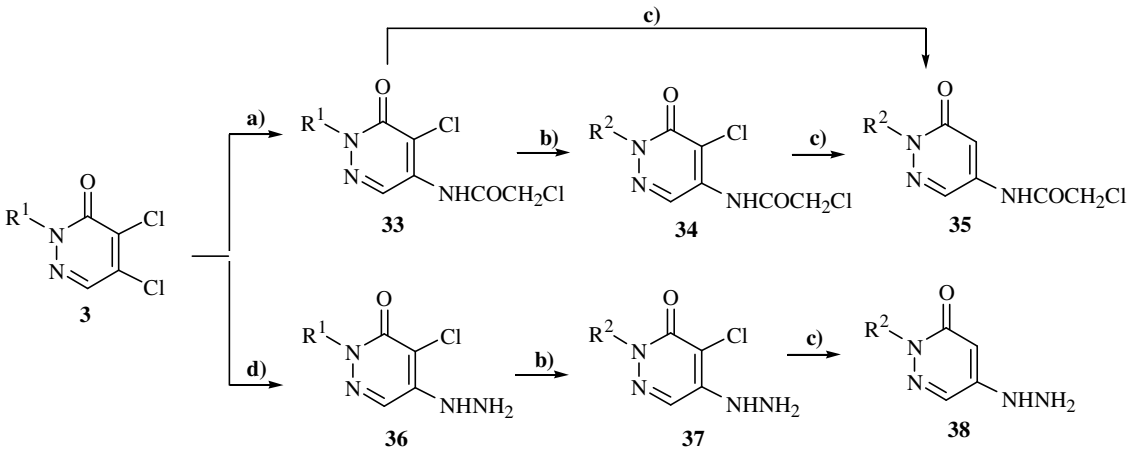


a) NaN_3; DMSO;reflux; 6h; (56%)
b) $MeNH_2$ HCl; MeOH; TEA; reflux; 8h; (91%)
c) 1. NaOMe; MeOH; rt; 13h;
2. Amberlite IRC-50H; rt; 15 h; (**26**: 80%; **31**: 89%)
d) Pd/C; H_2; MeOH; rt; 24 h; (**27**: 86%, **28**: 93%, **32**: 95%)
e) Pd/C; H_2; MeOH; 30% aq NaOH; rt; 24 h; (86%)
f) MeI; K_2CO_3; MeOH; reflux; 18 h; (54%)

Scheme 10

Debenzoylation and subsequent reduction of the 5-azido function to amino group led to the target compound **27**. Nucleophilic substitution reaction of **3** with methylamine resulted in the 5-methylamine derivative **30** which was used to prepare the 5-*N*-methylamino analogues of **27**, **29** *i.e*. compounds **31**, **32** (Scheme 10).[2]

Chloroacetamide proved to be a suitable nucleophile for the preparation of 5-chloroacetamido derivatives **33**, which was then transformed into **35** in two steps *via* debenzoylated compound **34**.[2] Compound **35** also could be obtained directly from **33** by hydrogenolysis under basic conditions. Hydrazine hydrate is a fairly reactive nucleophile towards dihalopyridazinones. Treatment of **3** with hydrazine hydrate in dimethyl sulfoxide in the presence of potassium carbonate led smoothly to 4-chloro-5-hydrazino derivative **36**. Debenzoylation and subsequent dehalogenation resulted in the formation of **38** (Scheme 11).[2]



a) $ClCH_2CONH_2$; TEA; MeOH; reflux; 11 h; (87%)
b) 1. NaOMe; MeOH; rt; 12h;
2. Amberlite IRC-50H; rt; 11 h; (**34**: 85%; **37**: 78%)
c) Pd/C; H_2; MeOH; 30% aq NaOH; rt; 8 h;
(**35** from **34**: 88%, from **33**: 83%; **38**: 36%)
d) $NH_2NH_2.H_2O$; K_2CO_3; DMSO; reflux; 1 h; (66%)

R^1= $PhCOO(CH_2)_4$-
R^2= $HO(CH_2)_4$-

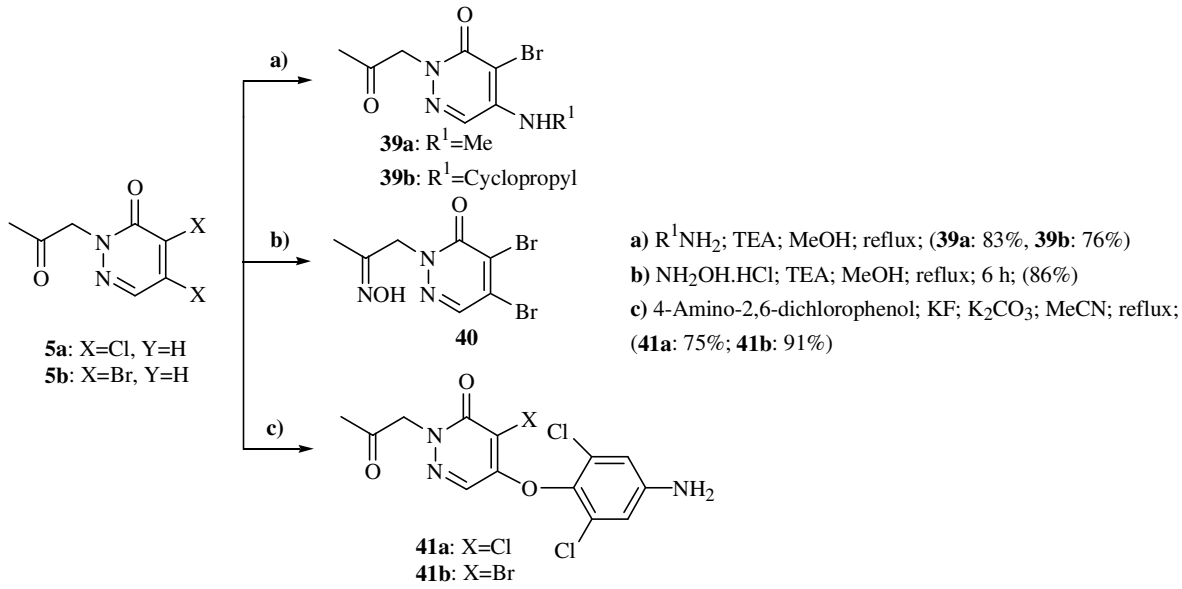
Scheme 11

The relatively easy replacement of halogens with amines is illustrated by the reactions of 4,5-dihalo-3(2*H*)-pyridazinones containing a reactive oxo group in the *N*-substituent.[3] Reaction of **5b** with methylamine or cyclopropylamine in the presence of triethylamine in methanol gave regioselectively the corresponding 5-alkylamino derivatives **39**, without concomitant formation of the 2-(2-alkyliminopropyl) derivatives. Hydroxylamine hydrochloride was the only exception. Its reaction with **5b** afforded 4,5-dibromo-2-(2-hydroxyiminopropyl)-3(2*H*)-pyridazinone **40** as a mixture of the *syn* and *anti* forms of the oxime.

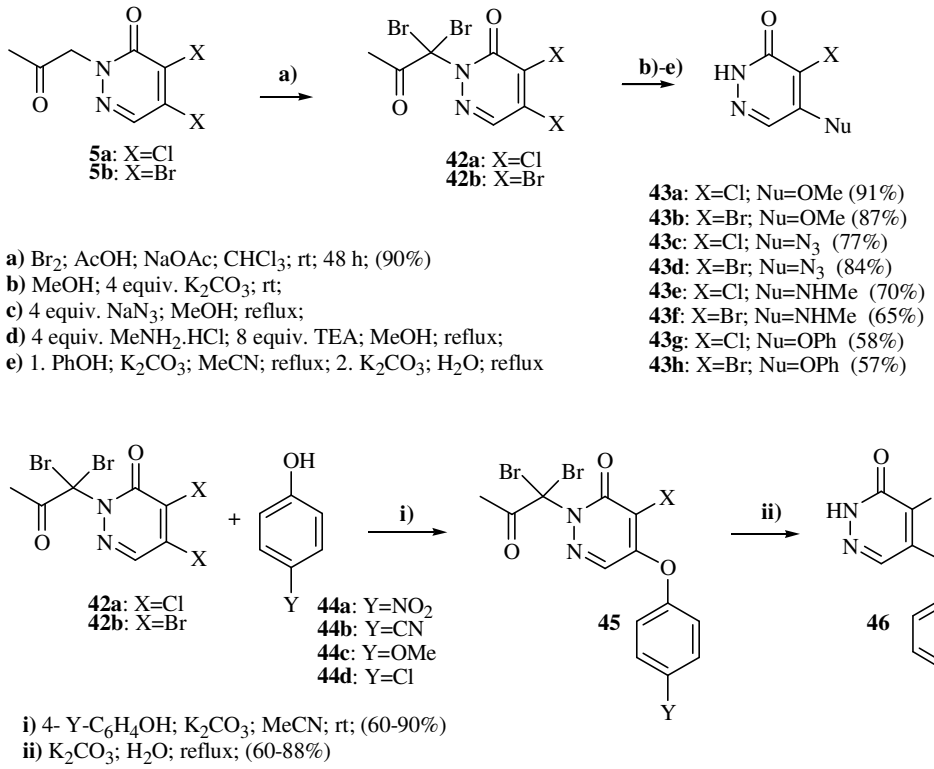
Reaction of **5** with phenols has also been investigated. Dichloro and dibromo compounds **5a** and **5b** with 4-amino-2,6-dichlorophenol in the presence of potassium fluoride and potassium carbonate in acetonitrile gave compounds **41a**,**b**, respectively, regio- and chemoselectively. However, when **5** was treated with 4-amino-2,6-dichlorophenol in the presence of potassium fluoride or potassium carbonate, two products, the phenoxy derivative **41** and the respective anilino compound, 5-(3,5-dichloro-4-hydroxyphenylamino)-4-halo-2-(2-oxopropyl)-3(2*H*)-pyridazinone (not shown) were obtained (Scheme 12).

The influences of *N*-protecting groups on the nucleophilic displacement reactions have been studied systematically. A comparison with unprotected derivatives was also made. In the first type of protecting

groups dibromooxopropyl, acyloxymethyl, and hydroxymethyl are included, all of which, under the conditions of nucleophilic substitution, undergo easily a retro-ene type C-N bond fission, whereas in the second type, the moderately stable sulfonyl, and the more stable tetrahydropyranyl and benzyl are typical examples.

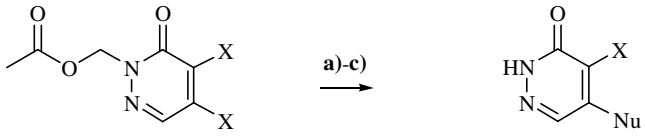


Scheme 12



Scheme 13

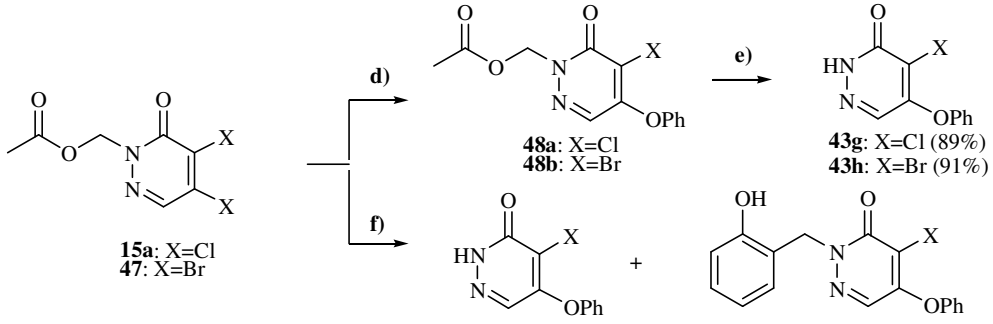
Introduction and removal of the 1,1-dibromo-2-oxopropyl protecting group could be carried out easily, under mild conditions.[17] 4,5-Dihalo compounds **42** were prepared by bromination of **5** at the side chain in the presence of sodium acetate in a mixture of acetic acid and chloroform. The subsequent nucleophilic substitution and deprotection were carried out in a one-pot reaction. Thus, treatment of **42a** or **42b** in methanol with potassium carbonate, with sodium azide or with methylamine hydrochloride in the presence of triethylamine resulted in the formation of 5-substituted-4-halo-3(2*H*)-pyridazinones **43a-f**, respectively (Scheme 13).



15a: X=Cl
47: X=Br

a) MeOH; 4 equiv. K_2CO_3; rt;
b) 2 equiv. NaN_3; MeOH; reflux;
c) 4 equiv. $EtNH_2.HCl$; 4 equiv. K_2CO_3; MeCN; reflux;

43a: X=Cl; Nu=OMe (90%)
43b: X=Br; Nu=OMe (89%)
43c: X=Cl; Nu=N_3 (81%)
43d: X=Br; Nu=N_3 (81%)
43i: X=Cl; Nu=NHEt (77%)
43j: X=Br; Nu=NHEt (78%)



15a: X=Cl
47: X=Br

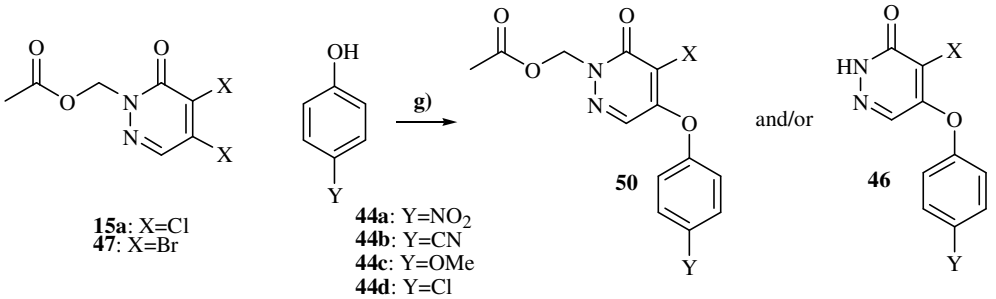
48a: X=Cl
48b: X=Br

43g: X=Cl (89%)
43h: X=Br (91%)

43g: X=Cl (43%)
43h: X=Br (37%)

49a: X=Cl (20%)
49b: X=Br (23%)

d) 1 equiv. PhOH; 1 equiv. K_2CO_3; MeCN; reflux
e) K_2CO_3; H_2O; reflux
f) 2 equiv. PhOH; 2 equiv. K_2CO_3; MeCN; reflux



15a: X=Cl
47: X=Br

44a: Y=NO_2
44b: Y=CN
44c: Y=OMe
44d: Y=Cl

50

and/or

46

g) 2 equiv. substituted phenol; 2 equiv. K_2CO_3; MeCN; reflux

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**
X	Cl	Br	Cl	Br	Cl	Br	Cl	Br
Y	NO_2	NO_2	CN	CN	OMe	OMe	Cl	Cl
50	84%	78%	96%	33%	-	-	-	-
46	-	-	-	37%	60%	72%	45%	71%

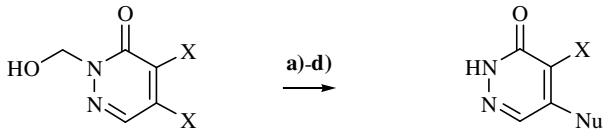
Scheme 14

The reaction took also place with phenol: the *N*-protected-5-substituted derivatives were formed first, which could be deprotected with potassium carbonate in water to yield **43g** or **43h**. Reactions of compounds **42** with *para*-substituted phenols **44** afforded the 2-unsubstituted-5-phenoxypyridazinones **46** in two steps (Scheme 13). In the case of 2-acetoxymethyl group (pyridazinones **15a**, **47)**, the methoxylation, azidation or amination took also place.[18] The nucleophilic substitution at *C*-5 and deprotection at *N*-2 by a retro-ene type mechanism were again carried out in a one-pot reaction (Scheme 14).

Reaction of **15a** or **47** with 1 equivalent of phenol in the presence of 1 equivalent of potassium carbonate gave the respective acetoxymethyl derivative **48a**, **48b**, which could be deprotected to **43g** and **43h**, respectively. Interestingly, reaction of the same starting compounds **15a** and **47** with 2 equivalents of reagents led to a mixture of compounds **43** and a 2-phenoxymethyl derivative **49**. Formation of the latter type was explained by a nucleophilic substitution at *C*-5 followed by Mannich condensation with phenol.

To complete the studies with phenols, **15a** or **47** was treated with 2 equivalents of substituted phenols **44** in the presence of 2 equivalents of potassium carbonate to afford **50** and/or **46** 5-phenoxypyridazinones with or without 2-acetoxy substituent (Scheme 14). Electron-withdrawing substituents on the phenol ring favored the formation of 5-substituted-2-acetoxymethyl derivatives, whereas electron-releasing substituents were preferable for the formation of 5-substituted-2-deprotected products. This observation reveals that the electron-releasing group enhances the rate of retro-ene fragmentation.

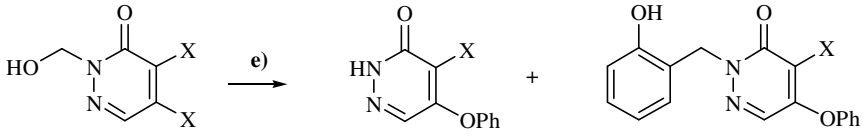
Another type of nucleophilic substitution, consisting of functionalization and retro-ene type deprotection, is represented by transformations of 4,5-dihalo-2-hydroxymethyl-3(2*H*)-pyridazinones (**10**) as starting compounds.[19] Treatment of **10** with various nucleophilic reagents resulted in the correspondingly 5-substituted, at the lactam moiety unprotected **43**. However, when using 2 equivalents of phenol and potassium carbonate instead of one equivalent, a mixture of the **43g** or **43h** and the Mannich product **49a** or **49b** was obtained, respectively (Scheme 15).



10a: X=Cl
10b: X=Br

a) MeOH; 1.2 equiv. K_2CO_3; reflux;
b) 1.2 equiv. NaN_3; MeOH; reflux;
c) 4 equiv. $EtNH_2.HCl$; 4 equiv. K_2CO_3; MeCN; reflux;
d) 1 equiv. PhOH; 1 equiv. K_2CO_3; MeCN; reflux

43a: X=Cl; Nu=OMe (82%)
43b: X=Br; Nu=OMe (94%)
43c: X=Cl; Nu=N_3 (89%)
43d: X=Br; Nu=N_3 (90%)
43i: X=Cl; Nu=NHEt (46%)
43j: X=Br; Nu=NHEt (40%)
43g: X=Cl; Nu=OPh (53%)
43h: X=Br; Nu=OPh (57%)



10a: X=Cl
10b: X=Br

43g: X=Cl (36%)
43h: X=Br (36%)

49a: X=Cl (6%)
49b: X=Br (20%)

e) 2 equiv. PhOH; 2 equiv. K_2CO_3; MeCN; reflux

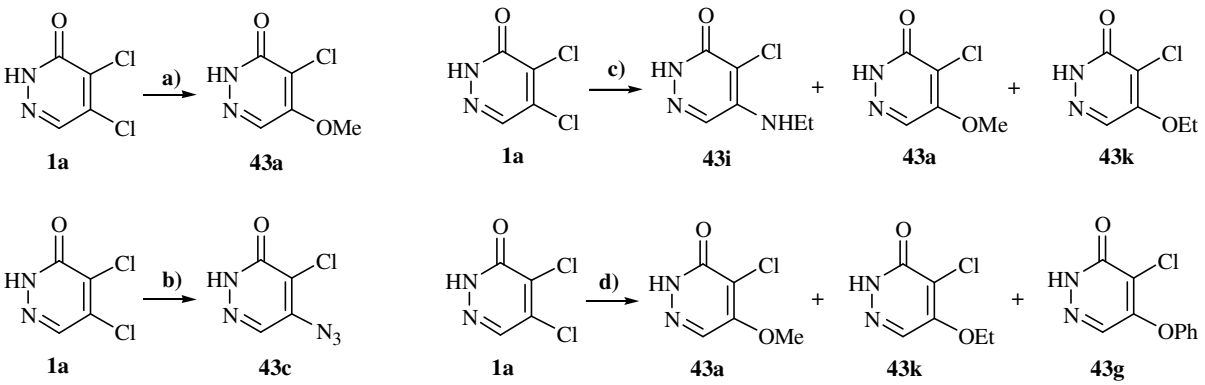
Scheme 15

It seems to be interesting to compare the results of nucleophilic displacement reactions of the parent compound, 4,5-dichloro-3(2*H*)-pyridazinone (**1a**) with those obtained with the *N*-protected derivatives. Four nucleophiles, methoxide, ethylamine, phenols and azide, in different solvents (Table 5) were investigated.[20] Methoxylation of **1a** gave **43a** in moderate to high yield in a mixture of tetrahydrofuran-water, methanol or water, whereas no reaction proceeded in the other four solvent systems.

On the contrary, reaction of **1a** with azide anion in each solvent system afforded the azido derivative **43c** in good yield.

Reaction of **1a** with ethylamine afforded the 5-ethylamino derivative **43i** in moderate yields, except for reactions in methanol or ethanol. In this cases, a mixture of the 5-ethylamino derivative **43i** and the corresponding 5-alkoxy compound **43a** or **43k** were obtained.

Reaction of **1a** with 2 equivalents of phenol in THF-water, acetonitrile-water or water solvents gave the 5-phenoxy derivative **43g**, whereas a mixture of **43k** and **43g** was formed in ethanol. Fairly unexpectedly, performing the reaction in methanol, the 5-methoxy derivative **43a** could only be obtained (Scheme 16).



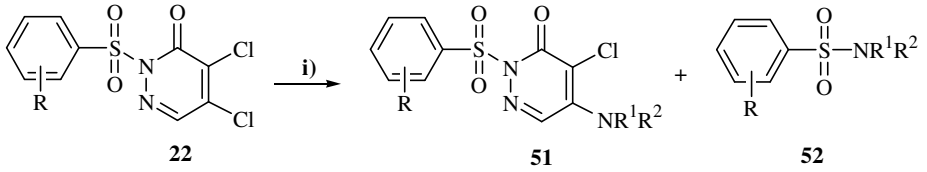
a) MeOH; 2 equiv. K_2CO_3; solvent; reflux;
b) NaN_3;solvent; reflux;
c) $EtNH_2.HCl$; K_2CO_3; solvent; reflux;
d) 2 equiv. PhOH; 2 equiv. K_2CO_3; solvent; reflux

Scheme 16

Table 5. Product distribution in the reaction of **1a** with nucleophiles in various solvents (s. Scheme 16)

Conditions	Product	THF	THF/H_2O	MeOH	EtOH	MeCN	MeCN/H_2O	H_2O
a)	**43a (%)**	0	62	91	0	0	0	90
b)	**43c (%)**	71	92	64	70	69	82	75
c)	**43i (%)**	56	58	19	46	52	76	48
	43a (%)	0	0	52	0	0	0	0
	43k (%)	0	0	0	23	0	0	0
d)	**43a (%)**	0	0	98	0	0	0	0
	43k (%)	0	0	0	14	0	0	0
	43g (%)	0	90	0	52	0	87	82

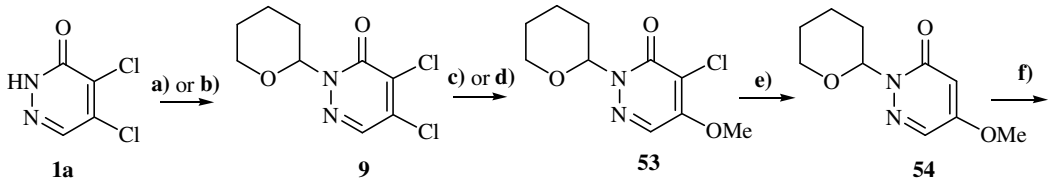
The second type of protecting groups exhibited also a facilitating effect on the nucleophilic substitution. The 2-(arylsulfonyl)-4,5-dichloro-3(2*H*)-pyridazinones (**22**) with or without *ortho* substituent at the arylsulfonyl moiety, in a reaction with amines such as ethylamine, diethylamine, cyclohexylamine and piperidine, gave a mixture of 5-alkylamino-2-arylsulfonyl derivatives **51** and *N*-alkylsulfonamides **52** as the major products (Scheme 17).[13] On the contrary, compounds **51** were obtained as main products in good yields from arylsulfonyl compounds containing an ortho-substituent.

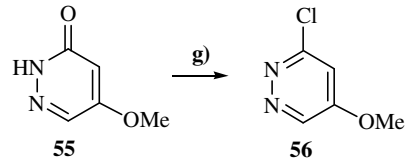


i) 2 equiv.R_1R_2NH; THF; rt
R= H; 2-CN; 2-NO_2; 2-Br; 4-Me; 4-Cl; 4-NO_2; 2,4,6-Me_3
R_1R_2NH= $EtNH_2$; Et_2NH; $cHexNH_2$; Piperidine;

Scheme 17

The tetrahydropyranyl protecting group was completely intact during the nucleophilic displacement reaction. It was applied for the large scale synthesis of 3-chloro-5-methoxypyridazine (**56**) which is an important intermediate for synthesis of pyridazine herbicides.[8] Reaction of **9** with sodium-methoxide in methanol afforded **53** in good yield. Two subsequent transformations, reductive dehalogenation and deprotection, gave **55** which was then treated with phosphorous oxychloride to afford the target compound **56** (Scheme 18).





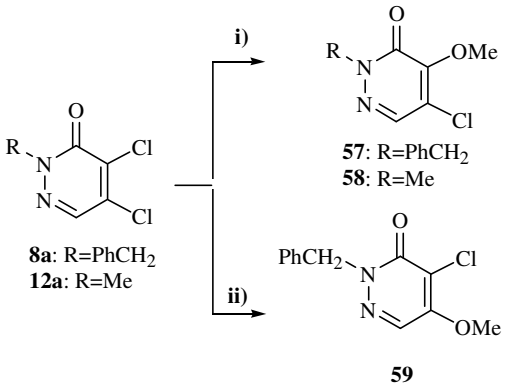
a) Dihydropyran; TsOH; THF; reflux; 29 h;(Method A)
b) Dihydropyran; pyridinium tosylate; THF; reflux; 25 h (Method B)
c) KOH; MeOH; 0-40 °C; 3 h; (**a** and **c** step: 77%)
d) NaOMe; MeOH; 5-20 °C; 30 min; (**b** and **d** step: 73%)
e) Pd/C; H_2; TEA; EtOH; 40 °C; 24 h;
f) 6N HCl; MeOH; reflux; 2h; (65%)
g) $POCl_3$; 75 °C; 30 min; (78%)

Scheme 18

Behavior of the 2-benzyl group was similar to that of the methyl group. Regioselective reactions of 2-benzyl- and 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone could be performed with sodium methoxide: in anhydrous dioxane 5-chloro-4-methoxy derivatives (**57**[4]; **58**[21]) were obtained, whereas in methanol the 4-chloro-5-methoxy isomer **59** was formed (Scheme 19).[4]

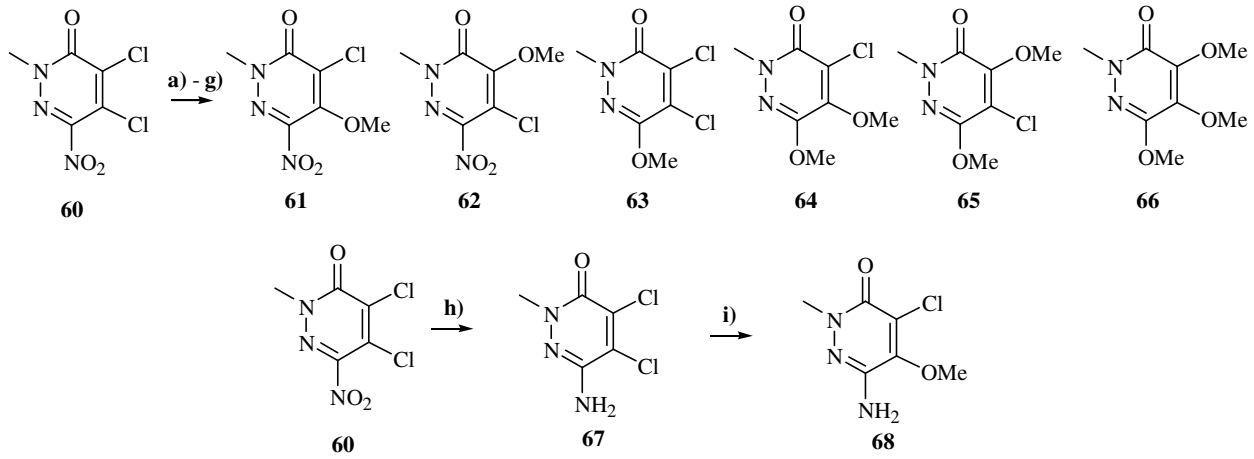
The regiochemical outcome and solvent dependence are less predictable in the case of 4,5-dichloro-2-methyl-6-nitro-3(2*H*)-pyridazinone (**60**). For instance, with potassium carbonate in methanol, different product ratios of 4- and 5-substituted derivatives have been obtained depending on the temperature and the stochiometry of potassium carbonate to the substrate.[22] A lower base/substrate ratio and lower temperature were favorable for formations of both the 4- and 5-monomethoxy products **61**, **62**, whereas a higher base/substrate ratio and higher temperature were preferable for the formations of di- and trisubstituted products **64**-**66**; the 6-methoxy derivative **63** was only a minor product (Table 6).

The 6-amino derivative **67** obtained by the reduction of 6-nitro derivative **60** behaved however differently. Its methoxylation took place regioselectively to afford the 5-methoxy derivative **68** in good yield (Scheme 20).



i) NaOMe; dioxane; 1 h; rt; (**57**: 74%; **58**: 70-80%)
ii) NaOMe; MeOH; 1 h; rt; (85%)

Scheme 19



a)-g): K_2CO_3; MeOH
h) Fe; NH_4Cl; H_2O; $CHCl_3$; rt; 21 h
i) 1.3 equiv. K_2CO_3; MeOH; reflux; 2 h

Scheme 20

The synthesis and selective α_1-adrenoceptor activity of (4-chloro-5-methoxyphenylethyl)-piperazinylpyridazinones were recently reported. These compounds were also obtained by nucleophilic displacement reaction of 4,5-dichloropyridazinones; alkylene-bridged *bis*(pyridazinyl) derivatives were also prepared.[23]

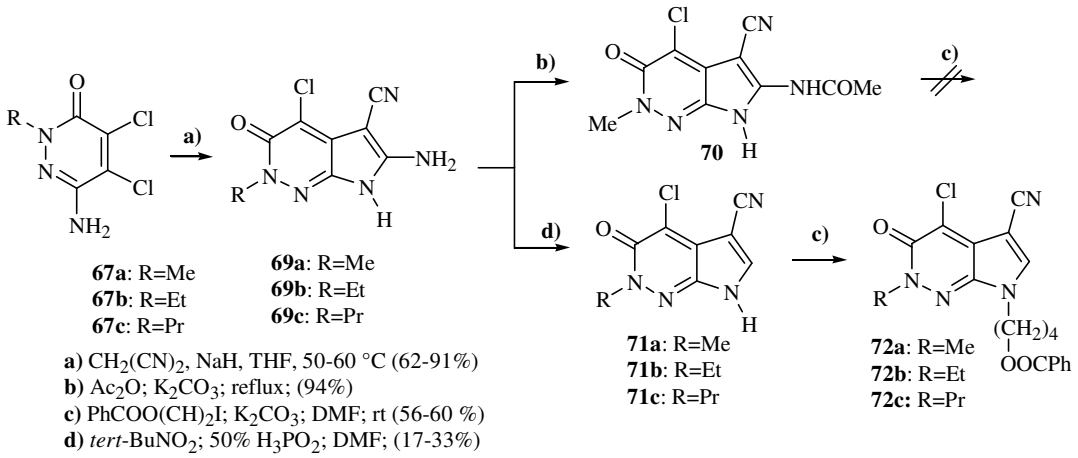
Table 6. Conversion of the 6-nitro derivative **60** into methoxy-substituted derivatives

Method	**60 : K_2CO_3 ratio**	**Temp. (°C)**	**Time (h)**	**Product distribution (yield %)**					
				61	**62**	**63**	**64**	**65**	**66**
A	1:0.5	Reflux	1	28	62	-	-	-	-
B	1:1	Reflux	1.5	-	-	4	22	39	-
C	1:1	35	2	-	52	-	-	4	-
D	1:1.3	Reflux	1	-	-	-	18	52	-
E	1:2	35	4	-	-	-	30	62	-
F	1:2	Reflux	0.5	-	-	-	32	66	-
G	1:3.4	Reflux	24	-	-	-	-	-	92

Reactions of 4,5-dihalopyridazinones with bifunctional nucleophiles can be utilized for the preparations of fused pyridazines.

Malonitrile possessing two proper functionalities for consecutive inter- and intramolecular nucleophilic reactions was employed for the synthesis of pyrrolo[2,3-*c*]pyridazines. This reagent also illustrates the high reactivity of a *C*-nucleophile towards the 5-position of 4,5-dichloropyridazinones.

Pyrrolo[2,3-*c*]pyridazines with hydroxyalkyl substituent as analogues of acyclonucleosides having antiproliferative and/or antiviral activity were prepared from the *N*-alkylated-6-amino-4,5-dichloropyridazinones **67**.[24] On reacting these compounds with the anion of malonitrile, obtained by *in situ* deprotonation, bicyclic compounds **69** were formed regioselectively. Subsequently, further functionalization of the fused system was accomplished in two steps.



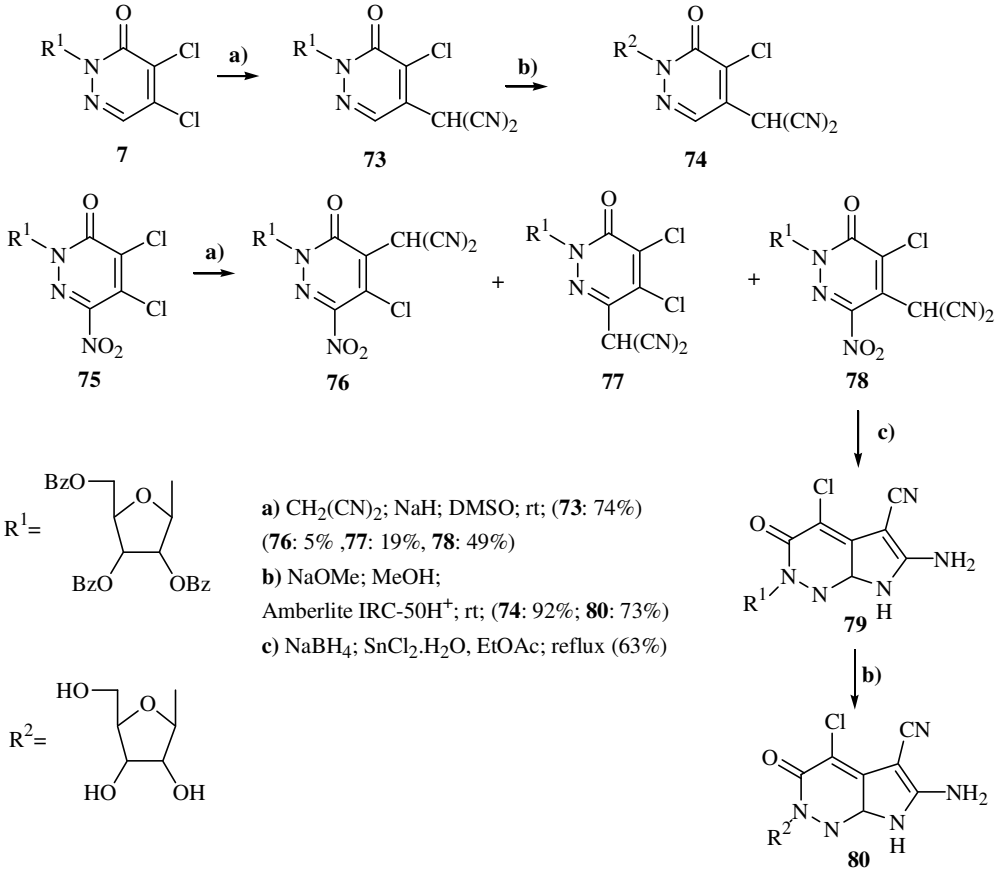
Scheme 21

The methyl derivative **69a** was acetylated with acetic anhydride in the presence of potassium carbonate to give the 2-acetylamino bicyclic derivative **70**; alkylation of which, interestingly, with 4-

iodobutyl benzoate in the presence of potassium carbonate in dimethyl formamide failed to yield the desired *N*-benzoyloxybutyl derivative. *N*-Alkylation could be however performed smoothly with 2-unsubstituted compounds **71**, and compounds **72a-c** were obtained (Scheme 21).

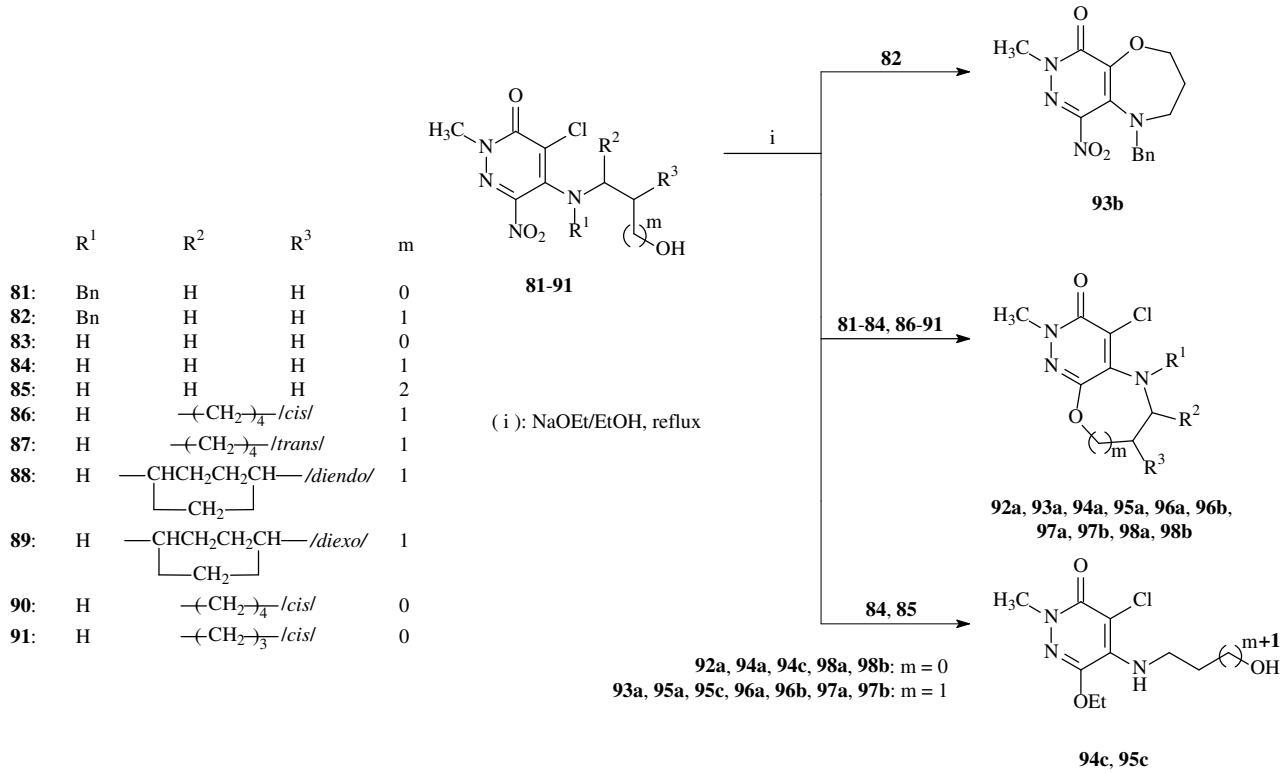
Malonitrile was also reacted with 4,5-dichloro- and 4,5-dichloro-6-nitropyridazinones.

Pyridazine-nucleosides containing a monocyclic pyridazine ring with a malonitrile moiety were prepared from dichloropyridazinone nucleoside **7** with malonitrile in the presence of sodium hydride in dimethyl sulfoxide. Thus, the 5-pyridazinylmalonitrile **73** obtained in this way was then debenzoylated to the desired compound **74**. Pyrrolo[2,3-*c*]pyridazine nucleoside **80** was prepared from 4,5-dichloro-6-nitropyridazinone nucleoside **75**.[7] In the first step, on treatment with malonitrile, each of the possible monosubstituted three regioisomers **76**, **77**, **78** were isolated. Of them, **78** formed as the main product in the previous step, was transformed to the pyrrolopyridazine **79** with sodium borohydride in the presence of stannous chloride dihydrate. Subsequent debenzoylation afforded the nucleoside **80** (Scheme 22).



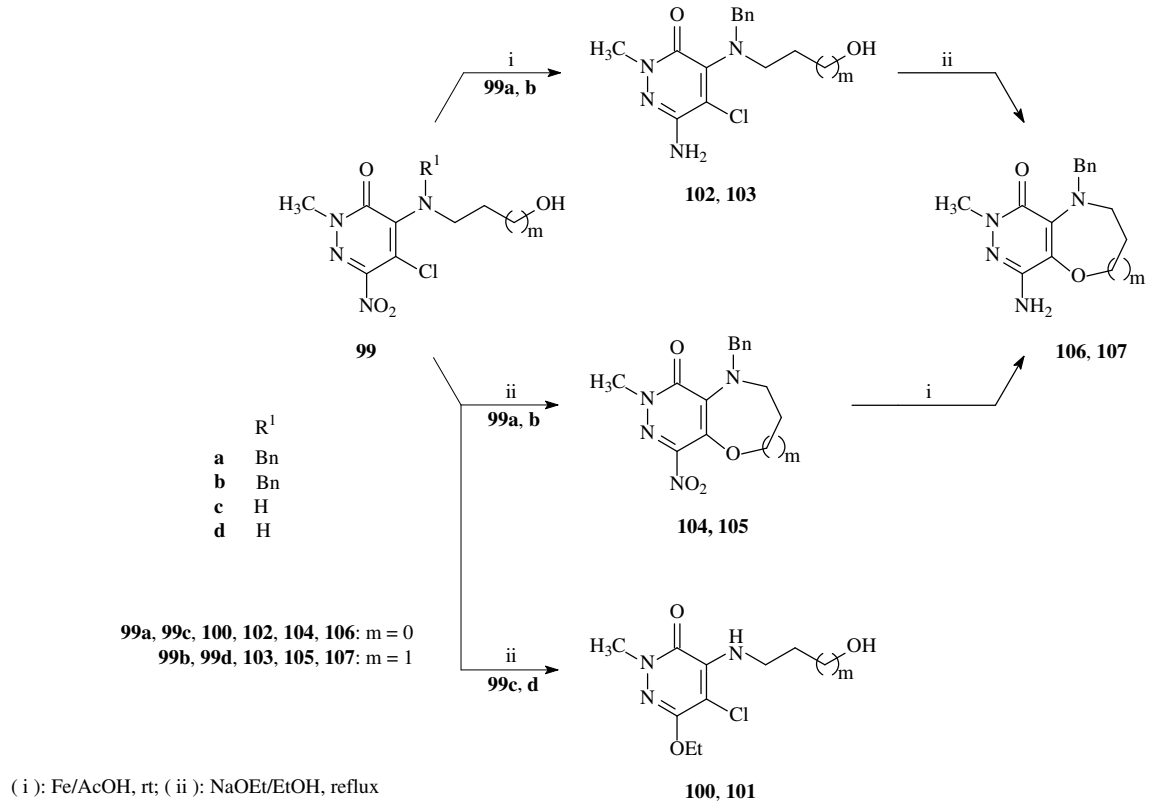
Scheme 22

Aminoethanols and aminopropanols were already successfully reacted with 4,5-dichloropyridazinones to obtain pyridazinooxazines, pyridazinooxazepines, and their thiazine and thiazepine analogues.[16,25] The extension of these reactions to the 4,5-dichloro-2-methyl-6-nitro-3(2*H*)-pyridazinone (Schemes 23-25), has recently been studied experimentally and theoretically as well.[26] Reactions with aminoethanols, aminopropanols and aminobutanol in refluxing ethanol or butanol afforded separable mixtures of 4- and 5-hydroxyalkylaminopyridazinones, the latter being generally the main products.



	R^1	R^2	R^3	m
81:	Bn	H	H	0
82:	Bn	H	H	1
83:	H	H	H	0
84:	H	H	H	1
85:	H	H	H	2
86:	H	$-(CH_2)_4-$ */cis/*		1
87:	H	$-(CH_2)_4-$ */trans/*		1
88:	H	—CHCH$_2$CH$_2$CH— */diendo/* (CH$_2$ bridge)		1
89:	H	—CHCH$_2$CH$_2$CH— */diexo/* (CH$_2$ bridge)		1
90:	H	$-(CH_2)_4-$ */cis/*		0
91:	H	$-(CH_2)_3-$ */cis/*		0

Scheme 23



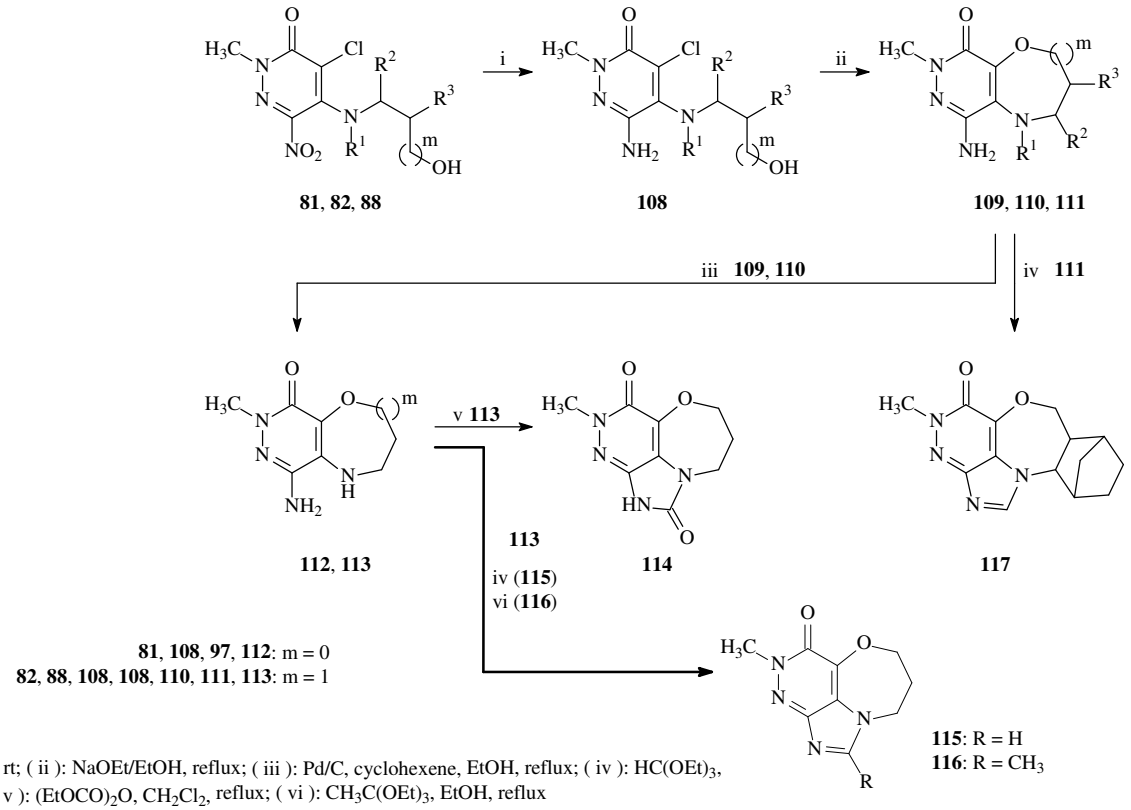
Scheme 24

The ring closure reactions of the 5-isomers **81**-**91** with sodium ethoxide took place with the involvement of C-6 to afford 3,4-annelated products **92**-**98**, and, in a few cases only, a 4,5-annelated system and/or monocyclic compounds formed by intermolecular nucleophilic substitution (**93b**; **94c**, **95c**) (Scheme 23).

Ring closure of the 4-isomers with an *N*-benzyl substituent **99a**, **b** led to the formation of bicyclic products, whereas 4-isomers with no substituent at the nitrogen, compounds **99c**, **d** gave the 6-ethoxy monocyclic derivatives **100**, **101**. A further support for the constitution of the fused system was provided by chemical transformations too. The 6-amino bicyclic **106** and **107** were prepared in two independent ways: either by ring closure of **102**, and **103** or by reduction of the nitro of **104** and **105** (Scheme 24).

The regioisomerically annelated system of **106**, **107**, *i.e.* compounds **109**-**111**, were transformed *via* **112** and **113** into novel *ortho*- and *peri*-fused ring systems **114**-**117** (Scheme 25).

The preparative results were consistent with theoretical considerations based on the FMO theory.



Scheme 25

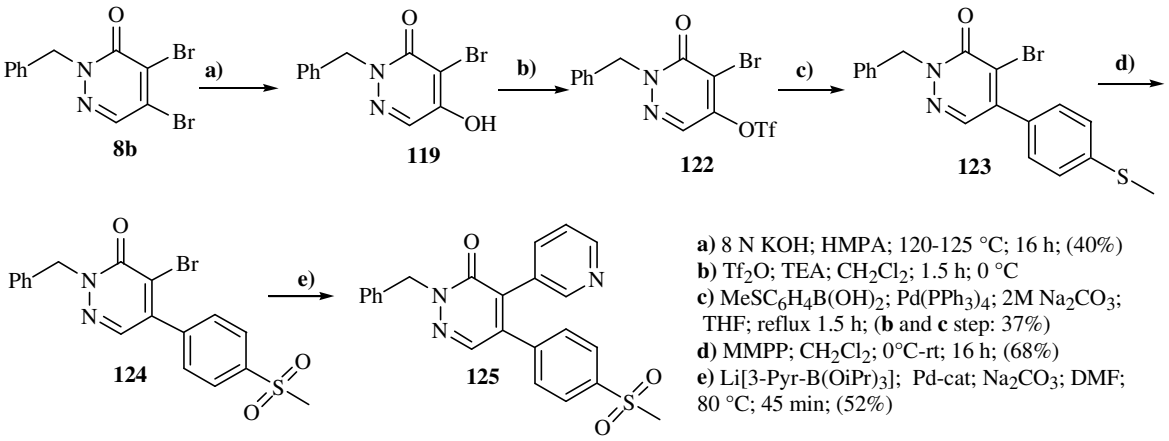
3.2. Palladium catalysed C-C coupling reactions

Carboaromatic as well as heterocyclic compounds, with trifluorosulfonyloxy-, iodo- and bromo-substituents are generally excellent substrates for C-C coupling reactions. The earliest examples of Pd-catalysed C-C coupling reactions of pyridazines were also carried out with such substituents[27,28,29] The reactivity of a chloro-substituent of carboaromatic compounds, is usually very low in Pd-catalysed reactions. Unlike these compounds, however, chloro substituents of pyridazines may be expected to be sufficiently reactive for Pd-catalysed coupling reactions, due to the electrondeficient nature of the heterocyclic

skeleton;[30] although, in many cases, better yields could be obtained with bromo-, iodo- or triflate-substituents.

4,5-Dibromo and dichloro-3(2*H*)-pyridazinones and their derivatives have more recently been utilized for Suzuki arylation and Sonogashira coupling reactions. Scope and limitation of these methodologies, and their possible applications for the synthesis of polycyclic ring systems have been much investigated by Belgian and Hungarian groups headed by Lemière, Maes, Hajós and Mátyus. In these reactions too, selective displacement of halogens is of much concern, and it represents an important issue of further synthetic application, too.

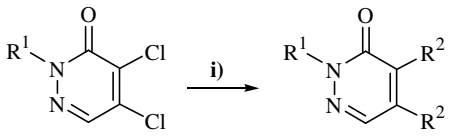
The synthesis of 4,5-diaryl-3(2*H*)-pyridazinones with different aryl groups could be achieved *via* consecutive Suzuki cross-coupling reactions of pyridazines possessing different leaving groups.[7] In this approach, selectivity could be obtained. Thus, 4,5-dibromo-2-benzyl-3(2*H*)-pyridazinone (**8b**) was hydrolyzed with potassium hydroxide to afford the 5-hydroxy derivative **119**, which was next treated with trifluoromethansulfonic anhydride to obtain the corresponding triflate **122**. The Suzuki reaction of **122** was carried out with 4-methyltiophenylboronic acid in the presence of *tetrakis*(triphenylphosphine)palladium(0) as the catalyst in a mixture of 2M aqueous sodium carbonate and tetrahydrofuran. As expected, trifluoromethansulfonyloxy group proved to be much more reactive, than the bromo, and as a result, 4-bromo-5-methyltiophenylpyridazinone **123** was obtained in acceptable overall yield for the last two steps. Oxidation of compound **123** with magnesium monoperoxiphtalate led to the methylsulfonyl derivative **124**. It was subjected to the next Suzuki coupling reaction with lithium tri(2-propoxy)-3-pyridylboronate in dimethylformamide using [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium(II) as catalyst to obtain diaryl substituted pyridazinone **125** exhibiting cyclooxygenese-2 inhibitory properties (Scheme 26).



Scheme 26

Attempts have also been made to perform selective arylations of *N*-substituted 4,5-dichloro-3(2*H*)-pyridazinones **126**. The reaction however failed with 1 equivalent of boronic acid (Table 7).[21] When using 3 equivalents of boronic acid in the presence of palladium-*tetrakis*(triphenylphosphine) and 2M aqueous sodium carbonate in toluene at reflux temperature, in turn, the 4,5-diaryl derivatives (**127-132**) were obtained in excellent yields. Another catalyst, an air-stable oxime derivative in the presence of potassium

carbonate and tetrabutylammonium bromide in refluxing water was also effective for the diarylation to prepare 2-methyl-4,5-diphenyl-3(2*H*)-pyridazinone (**132**) (Scheme 27).[31]



12a: R^1=Me
126: R^1=Ph

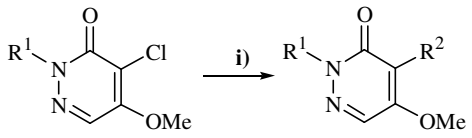
127-132

i) 3 equ. $R^2B(OH)_2$; 3 mol% $Pd(PPh_3)_4$; 2M Na_2CO_3; toluene; reflux

Scheme 27

Table 7. Pyridazinones disubstituted with the same aryl groups

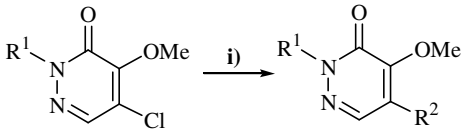
	R^1	R^2	Yield (%)
127	Me	Ph	98
128	Me	4-$MeOC_6H_4$	97
129	Me	4-FC_6H_4	100
130	Ph	Ph	97
131	Ph	4-$MeOC_6H_4$	87
132	Ph	4-FC_6H_4	100



133a: R^1=Me
133b: R^1=Ph

134-143

i) 1.5 equiv. $R^2B(OH)_2$; 3 mol% $Pd(PPh_3)_4$; 2M Na_2CO_3; toluene; reflux



58a: R^1=Me
144b: R^1=Ph

155-162

i) 1.5 equiv. $R^2B(OH)_2$; 3 mol% $Pd(PPh_3)_4$; 2M Na_2CO_3; toluene; reflux

Scheme 28

It could therefore be concluded that reactivity difference of 4- and 5-positions of dichloropyridazinones is not high enough to obtain selective arylations in Suzuki coupling reactions. For efficient utilization of dichloropyridazinones for the preparation of non-identically diarylated pyridazinones

like compound **125**, required a series of steps: i) the temporary blocking of one of the 4- and 5-positions ii) a coupling reaction, iii) re-functionalization of the blocked position for the second Suzuki-reaction, and then iv) the second arylation. A successful realization of this strategy was based on the application of 4-chloro-5-methoxypyridazinones **133** and their 5-chloro-4-methoxy regioisomers **144**, both of these methoxy derivatives were easily and in high yields available by selective nucleophilic displacement reactions of 4,5-dichloropyridazinones. Therefore, the ways were open to both regioisomeric products too.[21] The monoaryl-monomethoxypyridazinone intermediates offered a further application to obtain polycyclic pyridazines in a straightforward way. The key event of this approach is the ring closure with the involvement of the methoxy substituent and a substituent of the aryl group. Both these pathways have been investigated and are next illustrated.

Treatment of **133**, and **144** with boronic acids resulted smoothly in the monoarylated products **134-143** and **155-162**, respectively (Scheme 28).[21]

Table 8. 4-Aryl-5-methoxy-3(2H)-pyridazinones

	R^1	R^2	Yield (%)
134	Me	Ph	100
135	Me	4-$MeOC_6H_4$	100
136	Me	4-$MeSC_6H_4$	100
137	Me	4-FC_6H_4	100
138	Me	3-$CF_3C_6H_4$	97
139	Me	3-$MeOC_6H_4$	100
140	Me	2-MeC_6H_4	100
141	Me	2,4-$Cl_2C_6H_4$*	90
142	Ph	Ph	100
143	Ph	4-$CH_3OC_6H_4$	94

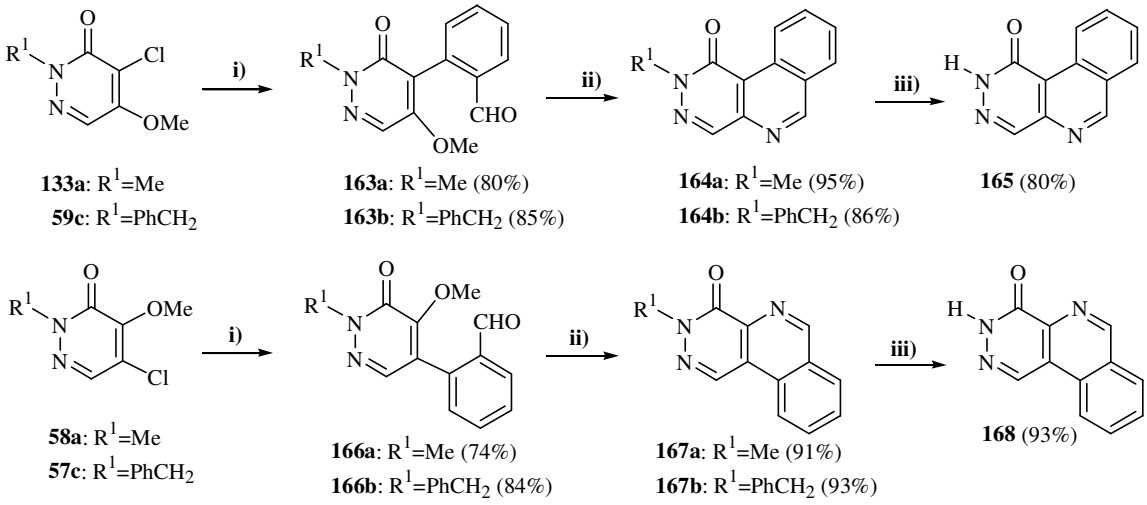
*2.5 equivalents of boronic acid were used

Table 9. 5-Aryl-4-methoxy-3(2H)-pyridazinones

	R^1	R^2	Yield (%)
155	Me	Ph	100
156	Me	4-$CH_3OC_6H_4$	100
157	Me	4-FC_6H_4	100
158	Me	3-$CF_3C_6H_4$	100
159	Me	3-thienyl	85
160	Ph	Ph	100
161	Ph	4-$CH_3OC_6H_4$	100
162	Ph	3-thienyl	100

Suzuki reaction of 4-chloro-5-methoxy-3(2*H*)-pyridazinones **133** with *ortho*-formylphenylboronic acid, an arylboronic acid containing the *ortho*-functionality for further transformations, was used for

preparation of 4-(2-formylphenyl)-5-methoxy derivatives **163**.[6] However, this reaction was particularly sensitive for reaction conditions, presumably due to a steric hindrance exhibited by two *ortho*-substituents of the substrate and reagent as well as to the enhanced hydrolytic deboronation of boronic acid by the presence of the electron-withdrawing formyl group. Yet, the reaction could be completed successfully by using a large excess of boronic acid. The synthesis of the other regioisomers **166** required a smaller excess of boronic acid. Both regioisomers could be transformed to two different tricyclic fused systems.



133a: R^1=Me
59c: R^1=$PhCH_2$

163a: R^1=Me (80%)
163b: R^1=$PhCH_2$ (85%)

164a: R^1=Me (95%)
164b: R^1=$PhCH_2$ (86%)

165 (80%)

58a: R^1=Me
57c: R^1=$PhCH_2$

166a: R^1=Me (74%)
166b: R^1=$PhCH_2$ (84%)

167a: R^1=Me (91%)
167b: R^1=$PhCH_2$ (93%)

168 (93%)

i) 2-CHO-$C_6H_4B(OH)_2$; $Pd(PPh_3)_4$; 2M Na_2CO_3; DME; reflux; 24 h
ii) NH_4OH; MeOH; 60 °C; 0.5 h
iii) $AlCl_3$; 70 °C; 1h

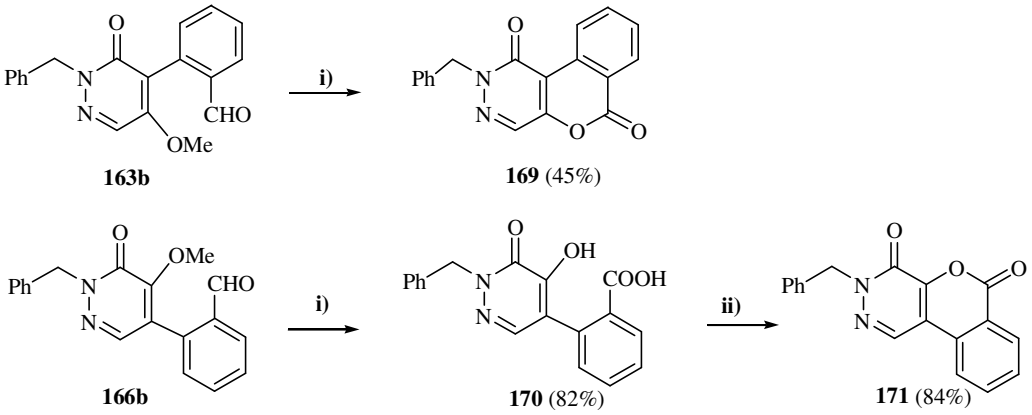
Scheme 29

In the first route, the ring closure was accomplished by the formation of a bond between carbon and nitrogen atoms. Upon treatment of compounds **163** or **166** with aqueous ammonia in methanol, ring closure reaction occurred surprisingly smoothly to give the respective isomers of pyridazino[4,5-*c*]isoquinolinone system (**164**, **167**). The *N*-unsubstituted compounds **165** and **168**, respectively, could also be obtained from **164b**, and **167b**, respectively, by removal of the benzyl group with aluminium trichloride in toluene (Scheme 29).

In the second route, transformation of **163b**, **166b** into another tricyclic ring system was achieved by formation of a carbon-oxygen bond *via* lactonization.[32] The first step was the *O*-demethylation by refluxing the methoxy derivatives in aqueous potassium carbonate solution. The subsequent oxidation of the formyl group with potassium permanganate, then acidification of the reaction mixture led directly to the 2-benzyl-1*H*-isochromeno[3,4-*d*]pyridazine-1,6(2*H*)-dione (**169**) in a one-pot reaction. In the case of the regioisomeric **166b**, the intermediate benzoic acid derivative **170** was cyclized with a catalytic amount of sulfuric acid in dimethoxyethane to obtain 3-benzyl-3*H*-isochromeno[3,4-*d*]pyridazine-4,6-dione (**171**) (Scheme 30).

Utilization of 4(5)-aryl-5(4)-methoxypyridazinones for the synthesis of 4,5-diaryl-3(2*H*)-pyridazinones with different aryl groups involved the hydrolytic demethylation of the 4-aryl-5-methoxy- (**134-143**, **172**) as well as 5-aryl-4-methoxy-3(2*H*)-pyridazinones (**155-162**).

The hydroxy compounds could be converted into triflates using trifluoromethanesulfonic anhydride and triethylamine. Subsequent Suzuki reaction indeed yielded **186-190** diaryl derivatives with different aryl rests (Scheme 31, Tables 10, 11).[32]

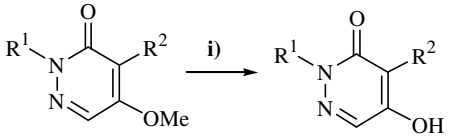


163b **169** (45%)

166b **170** (82%) **171** (84%)

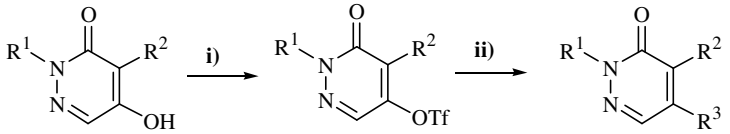
i) 1) KOH; H_2O; reflux; 24 h; 2) $KMnO_4$; rt; 7 h;
3) H_2SO_4; rt; overnight
ii) H_2SO_4; DME; 60 °C; 48 h

Scheme 30



134-136, 138, 140, 141, 143, 172 **173-180**

i) KOH; H_2O; reflux



173, 176, 180 **181-185** **186-190**

i) Tf_2O; TEA; CH_2Cl_2; -5 °C
ii) 2 equiv. $R^3B(OH)_2$; $Pd(PPh_3)_4$; 2M Na_2CO_3; toluene; reflux

Scheme 31

For introduction of alkynyl substituents, the Sonogashira reaction has been widely applied.

Sonogashira cross-coupling reactions of 4,5-dichloro-3(2*H*)-pyridazinones resulted in the formations of disubstituted or a mixture of mono- and disubstituted derivatives.[33] Thus, treatment of **126** with 3 equivalents of phenylacetylene or trimethylsilylacetylene in the presence of $PdCl_2(PPh_3)_2$, CuI and triethylamine in refluxing tetrahydrofuran yielded the corresponding dialkynyl derivatives (**191-194**) in good yields, whereas reaction of **126a** with pent-1-yne resulted in the mixture of disubstituted and monosubstituted products **195**, and **196**, respectively (Scheme 32, Table 12).

Table 10. 4-Aryl-5-hydroxy-3(2*H*)-pyridazinones

			Hydrolysis		
St. comp	R^1	R^2	Product	Time (h)	Yield (%)
140	Me	2-MeC_6H_4	**173**	24	63[a]
134	Me	Ph	**174**	8	84[a]
135	Me	4-$CH_3OC_6H_4$	**175**	7	89[a]
136	Me	4-$CH_3SC_6H_4$	**176**	12	99[a]
138	Me	3-$CF_3C_6H_4$	**177**	4	99[b]
141	Me	2,4-$Cl_2C_6H_4$	**178**	7.5	99[b]
143	Ph	4-$CH_3OC_6H_4$	**179**	24	93[c]
172	$PhCH_2$	4-$CH_3SC_6H_4$	**180**	29	79[d]

[a] 1 mmol of pyridazinone; 35 ml of 0.57 M KOH solution

[b] 1 mmol of pyridazinone; 85 ml of 0.57 M KOH solution

[c] 1 mmol of pyridazinone; 206 ml of 0.57 M KOH solution

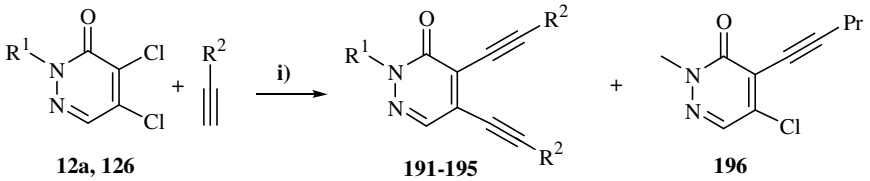
[d] 1 mmol of pyridazinone; 175 ml of 0.57 M KOH solution

Table 11. 4,5-Diaryl-3(2*H*)-pyridazinones

				Suzuki reaction		
St. Comp	R^1	R^2	R^3	Product	Time (h)	Yield (%)
173	Me	2-MeC_6H_4	4-FC_6H_4	**186**	8	72*
176	Me	4-$CH_3SC_6H_4$	4-FC_6H_4	**187**	4	73
176	Me	4-$CH_3SC_6H_4$	Ph	**188**	2	72
180	$PhCH_2$	4-$CH_3SC_6H_4$	4-FC_6H_4	**189**	3	72
180	$PhCH_2$	4-$CH_3SC_6H_4$	4-$CF_3C_6H_4$	**190**	3	54

*3 equivalents of boronic acid were used

Attempts to perform selective Sonogashira reaction of 4,5-dichloro-3(2*H*)-pyridazinones failed. On the other hand, 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**133a**) could be transformed easily to the corresponding triflate **198** by hydrolysis and subsequent triflation reaction. In the next step, selective Sonogashira reaction was achieved by the treatment of the triflate **198** with alkynes at room temperature.



12a, 126 **191-195** **196**

i) 3 equiv. alkyne; 3 mol% $PdCl_2(PPh_3)_2$; 3 mol% CuI; TEA; THF; 80 °C

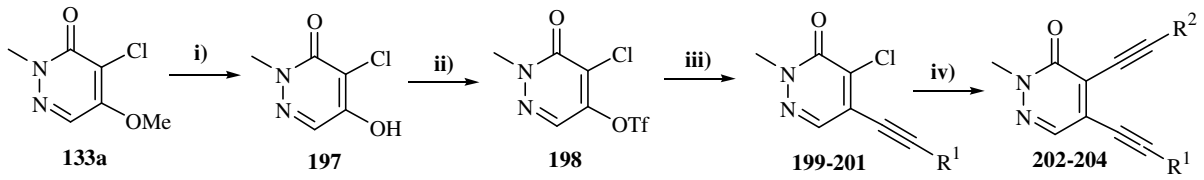
Scheme 32

The monoalkynyl compounds obtained **199-201** were subjected to a further Sonogashira reaction with another terminal alkyne to give the 4,5-dialkynyl-3(2*H*)-pyridazinones (Scheme 33, Table 13). In a

similar way, the regioisomeric products were also prepared starting from 5-chloro-4-methoxy-2-methyl-3(2*H*)-pyridazinone.

Table 12. Mono- and dialkynyl-3(2*H*)-pyridazinones

Pdz	Alkyne	Time (h)	Yield (%)	
R^1	R^2		**191-195**	**196**
Me	Ph	30	82	
Ph	Ph	16	75	
Me	Me_3Si	50	70	
Ph	Me_3Si	30	80	
Me	Pr	72	34	36



i) KOH; H_2O; reflux
ii) Tf_2O; TEA; CH_2Cl_2; -5 °C
iii) 1.01 equiv. alkyne; 3 mol% $PdCl_2(PPh_3)_2$; 30 mol% CuI; 3 equiv. Bu_4NI; TEA; THF; rt
iv) 1.3 equiv. alkyne; 3 mol% $PdCl_2(PPh_3)_2$; 5 mol% CuI; TEA; THF; 80 °C

Scheme 33

Table 13. Dialkynyl-3(2*H*)-pyridazinones

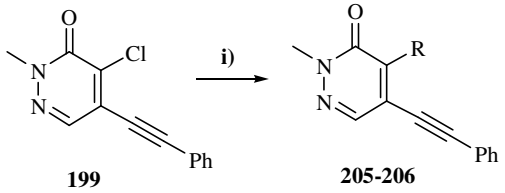
199-201			**202-204**			
R^1	Time (h)	Yield (%)	R^1	R^2	Time (h)	Yield (%)
Ph	2	83	Ph	Me_3Si	24	50
Me_3Si	2	72	Me_3Si	Ph	7	79
Pr	24	60	Pr	Ph	45	51

Suzuki reaction of the 5-alkynyl-4-chloro compound **199** with phenylboronic acid and also with 3-trifluoromethylphenylboronic acid was also successfully carried out to afford the corresponding aryl-alkynyl derivatives **205**, **206** (Scheme 34, Table 14). The 4-alkynyl-5-chloro derivatives also underwent the same transformations.

Although, 5-iodo-2-methyl-3(2*H*)-pyridazinone (**207**), as being a 5-monosubstituted pyridazinone, is not within the scope of this article, its origin from 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone and high synthetic value[34] prompted us to provide one example of its possible application of for the synthesis of tricyclic pyridazinones.

The Suzuki arylation reactions of **207** with phenyl- and 2-pivaloylaminophenyl boronic acids afforded **208** or **209**, respectively.[35] After deprotection, the amines **210** were diazotated to the corresponding diazonium salts, which were subjected *in situ* to an azidation reaction to give the azides **211**. Heating of the

latter compounds resulted in the formation of the 3-methylpyridazino[4,5-*b*]indol-4(3*H*)-one and its chloro derivative (**212**); the reaction takes place most probably through a nitrene intermediate (Scheme 35).

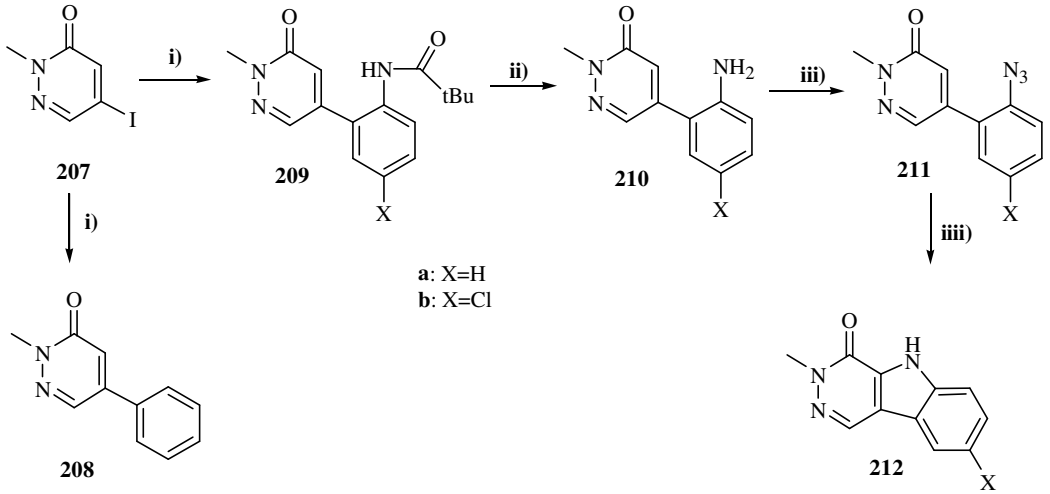


i) 1.5 equiv. $RB(OH)_2$; $Pd(PPh_3)_4$; 2M Na_2CO_3; toluene; reflux

Scheme 34

Table 14. 5-Aryl-4-alkynylpyridazinones

Comp.	R	Time (h)	Yield (%)
205	Ph	15	86
206	3-$CF_3C_6H_4$	16	78



i) $RB(OH)_2$; $Pd(PPh_3)_4$; 2M Na_2CO_3; DME; reflux; (**208**: 81%); **209a**: 64%; **209b**: 79%)
ii) 20% H_2SO_4; reflux; 3h; (**210a**: 69%; **210b**: 79%)
iii) 1) $NaNO_2$; HCl; 0-5 °C; 1.5 h 2) NaN_3; NaOAc; 0-5 °C; 1 h (**211a**: 47%; **211b**: 90%)
iiii) 1,2-dichlorobenzene; reflux; 1 h; (**212a**: 73%; **212b**: 87%)

Scheme 35

4. Concluding remarks

4,5-Dihalo-3(2*H*)-pyridazinones represent an important class of pyridazines from both synthetic and theoretical points of view. Recent results illustrate their usefulness in the preparation of novel types of mono- and polycyclic pyridazines with possible practical applications. We hope that this review, demonstrating many aspects of the progress, will stimulate further interest in this field.

Acknowledgements

We are grateful to our colleagues, B. Dajka-Halász, O. Éliás, L. Károlyházy, G. Krajsovszky, B. Podányi, A. Schwartz, K. Szabó at the Department of Organic Chemistry, Semmelweis University, for their enthusiasm and valuable contribution as well as to our excellent friends Gy. Hajós, Zs. Riedl, G. Lemière, B. Maes, N. Haider for the fruitful and stimulating collaboration.

Financial supports by Hungarian Funds, OTKA (T-31910), and ETT (187/2000) are also acknowledged.

References

3. Mátyus, P.; Czakó, K. *Trends Heterocycl. Chem*. **1993**, *3*, 249-264 (ed. Pandalai, G. S.; Council of Scientific Information Publishing, Triandrum, 1993).
4. Cho, S. D.; Chung, J. W.; Choi, W. Y.; Kim, S. K.; Yoon, Y. J. *J. Heterocycl. Chem.* **1994**, *31*, 1199-1208.
5. Choi, W. Y.; Cho, S. D.; Kim, S. K.; Yoon, Y. J. *J. Heterocycl. Chem.* **1997**, *34*, 1307-1313.
6. Lee, S. G.; Kweon, D. H.; Yoon, Y. J. *J. Heterocycl. Chem.* **2001**, *38*, 1179-1183.
7. Zára-Kaczián, E.; Mátyus, P.; *Heterocycles* **1993**, *36*, 519-528.
8. Riedl, Z.; Maes, B. U. W.; Monsieurs, K.; Lemière, G. L. F.; Mátyus, P.; Hajós, G. *Tetrahedron* **2002**, *58*, 5645-5650.
9. Lee, C. S.; Gauthier, J. Y.; Lau, C. K.; Therien, M. *US Patent,* **1999,** US 6,004,960.
10. Bryant, R. D.; Kunng, F. A.; South, M. S. *J. Heterocycl. Chem.* **1995**, *32*, 1473-1476.
11. Kim, S. K.; Cho, S. D.; Kweon, D. H.; Lee, S. G.; Chung, J. W.; Shin, S. C.; Yoon, Y. J. *J. Heterocycl. Chem.* **1996**, *33*, 245-248.
12. Kim, S. K.; Cho, S. D.; Moon, J. K.; Yoon, Y. J. *J. Heterocycl. Chem.* **1996**, *33*, 615-618.
13. Kim, S. K.; Cho, S. D.; Kweon, D. H.; Yoon, Y. J. *J. Heterocycl. Chem.* **1997**, *34*, 209-214.
14. Kim, S. K.; Cho, S. D.; Yoon, Y. J. *J. Heterocycl. Chem.* **1997**, *34*, 1135-1137.
15. Cho, S. D.; Choi, W. Y.; Yoon, Y. J. *J. Heterocycl. Chem.* **1996**, *33*, 1579-1582.
16. Kweon, D. H.; Kim, H. K.; Kim, J. J.; Chung, H. A.; Lee, W. S.; Kim, S. K.; Yoon, Y. J. *J. Heterocycl. Chem.* **2002**, *39*, 203-211.
17. Kang, Y. J.; Chung, H. A.; Kim, J. J.; Yoon, Y. J. *Synthesis* **2002**, *6*, 733-738.
18. Mátyus, P.; Czakó, K.; Behr, Á.; Varga, I.; Podányi, B.; von Arnim, M.; Várkonyi, P. *Heterocycles* **1993**, *36*, 785-798.
19. Kang, Y. J.; Chung, H. A.; Kweon, D. H.; Cho, S. D.; Lee, S. G.; Kim, S. K.; Yoon, Y. J. *J. Heterocycl. Chem.* **1998**, *35*, 595-605.
20. Chung, H. A.; Kang, Y. J.; Kweon, D. H.; Yoon, Y. J. *J. Heterocycl. Chem.* **1999**, *36*, 413-421.
21. Chung, H. A.; Kang, Y. J.; Chung, J. W.; Cho, S. D.; Yoon, Y. J. *J. Heterocycl. Chem.* **1999**, *36*, 277-281.
22. Chung, H. A.; Kweon, D. H.; Kang, Y. J.; Park, J. W.; Yoon, Y. J. *J. Heterocycl. Chem.* **1999**, *36*, 905-910.
23. Maes, B. U. W.; R' Kyek, O.; Košmrlj, J.; Lemière, G. L. F.; Esmans, E.; Rozenski, J.; Domisse, R. A.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323-1330.
24. Park, J. W.; Kim, J. J.; Kim, H. K.; Kang, Y. J.; Lee, W. S.; Yoon, Y. J. *J. Heterocyclic Chem.* **2000**, *37*, 1603-1606.
25. Strappaghetti, G.; Barbaro, R.; Marucci, G. *Eur. J. Med. Chem*. **2000**, *35*, 773-779.
26. Park, J. W.; Kweon, D. H.; Kang, Y. J.; Lee, W. S.; Cho, S. D.; Yoon, Y. J. *J. Heterocycl. Chem.* **2000**, *37*, 5-10.
27. Mátyus, P.; Zára-Kaczián, E.; Boros, S. *J. Heterocycl. Chem*. **1996**, *33*, 583-590.
28. Éliás, O.; Károlyházy, L.; Stájer, G., Fülöp, F.; Czakó, K.; Harmath, V.; Barabás, O.; Kesergû, K.; Mátyus, P. *J. Mol. Stuct*. (Theochem) **2001**, *545*, 75-96.
29. Trécourt, F.; Turck, A.; Plé, N.; Paris, A.; Quéguiner, G. *J. Heterocycl. Chem*. **1995**, *32*, 1057-1062.
30. Toussaint, D.; Suffert, J.; Wermuth, C. G. *Heterocycles* **1994**, *38*, 1273-1286.
31. Estevez, I.; Coelho, A.; Raviña, E. *Synthesis* **1999**, 1666-1670.
32. Ohsawa, A.; Abe, Y.; Igeta, H. *Chem. Lett*. **1979**, 241-243.

33. Botella, L.; Nájera, C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 179-181.
34. Maes, B. U. W.; Monsieurs, K.; Loones, K.; Lemière, G. L. F.; Dommisse, R.; Mátyus, P.; Riedl, Z.; Hajós, G. *Tetrahedron* **2002**, *58*, 9713-9721.
35. R' Kyek, O.; Maes, B. U. W.; Jonckers, T. H. M.; Lemière, G. L. F.; Domisse, R. A*Tetrahedron* **2001**, *57*, 10009-10016.
36. Mátyus, P.; Fuji, K.; Tanaka, K. *Heterocycles* **1993**, *36*, 1975-1978.
37. Krajsovszky, G.; Mátyus, P.; Riedl, Z.; Csányi, D.; Hajós, G. *Heterocyles* **2001**, *55*, 1105-1111.

SYNTHESIS OF HETEROCYCLES FROM ALLENES BY INTRAMOLECULAR RING CLOSURE

Jacques Hatem

Laboratoire "Chimie, Biologie et Radicaux Libres" UMR 6517, Université de Provence, Avenue Escadrille Normandie-Niemen, 13397 Marseille cedex 20, France (e-mail: hatem@srepir1.univ-mrs.fr)

Abstrac*t. This review is devoted to the synthesis of heterocycles by intramolecular ring closure starting from allenic compounds.*

Contents

1. Introduction

The allene chemistry is of great interest in organic synthesis. Many books or accounts published on this subject attest that.[1-5] Starting from allenes a lot of heterocycles has been synthesised.

In this paper our purpose is to review, for about the ten past years and size by size, the synthesis of heterocycles by intramolecular reactions involving the allenes. So, reactions like epoxidation[6] or other examples of reactions in which at least the allene participation is intermolecular[7-9] are ruled out.

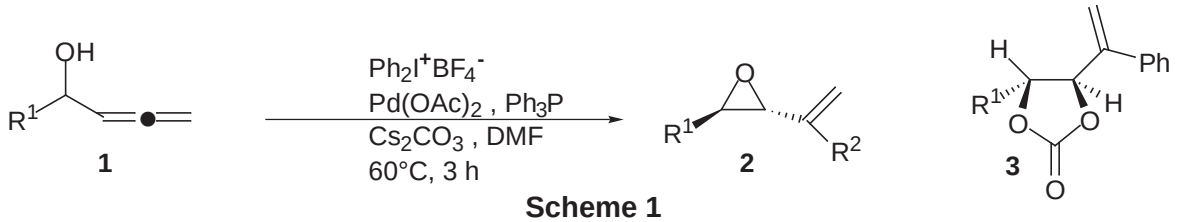
Five-membered rings are the most important kind of cyclic compounds obtained from allenes. In a less extent, six and other-membered rings have been gotten also. In 1999, Banert[10] published a report on the "synthesis of five-membered heterocycles from novel functionalized allenes". So the papers we quote here in the field of the synthesis of five-membered heterocycles from intramolecular ring closure of allenic compounds are essentially additional papers compared with those quoted by Banert.

About the heteroatoms, the most widely used are oxygen and nitrogen but sulphur, phosphorus and others are sometime used.

2. Heterocycles with three-membered rings

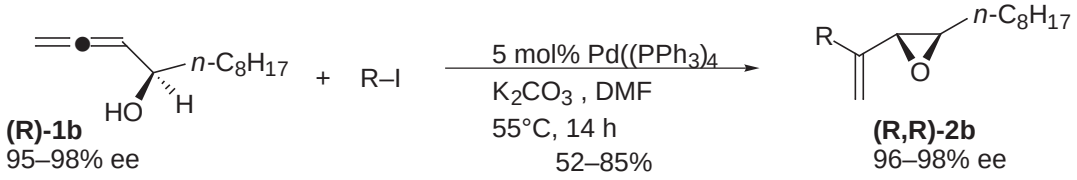
2.1. Epoxydation

Epoxydes may be gotten from α-allenic alcohols in two manners using palladium catalysis. With iodonium salts and palladium acetate, the α-allenic alcohol **1** led to the *trans*- epoxide **2** (R^2 = Ph) when Cs_2CO_3 was used as base (Scheme 1).[11] Nevertheless, in the same conditions, but with K_2CO_3 this reaction led to the formation of the *syn*-diol cyclic carbonate **3**.



Scheme 1

With $Pd(PPh_3)_4$ as catalyst the same kind of alcohol gave a mixture of *trans* and *cis* epoxides with a high diastereoselectivity for the *trans* isomer.[12] Depending on the reaction conditions the *trans/cis* ratio was varying from 14:1 to 30:1 when R^1 was a *n*-C_4H_9 group and R^2 a phenyl. Starting from the chiral allene **1b** the trans epoxyde **2b** is obtained with high enantiomeric excess (Scheme 2).



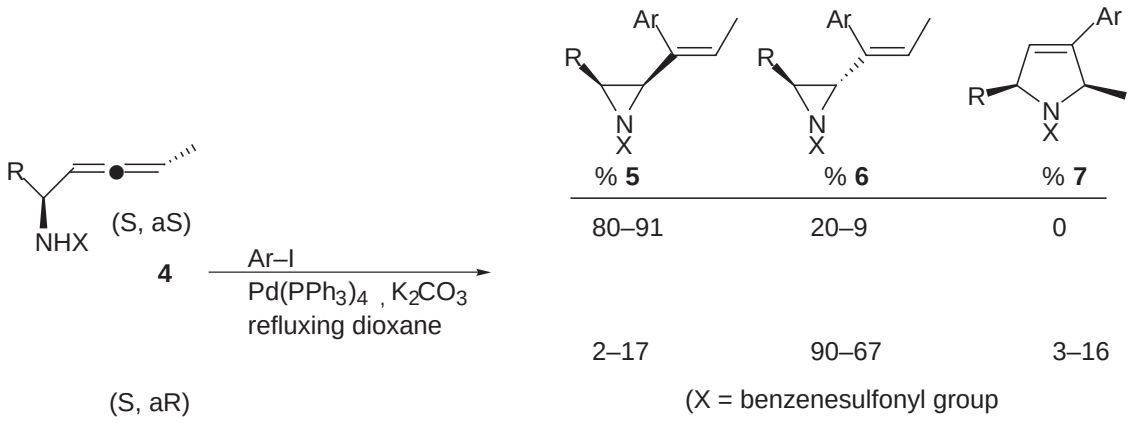
Scheme 2

2.2. Aziridination

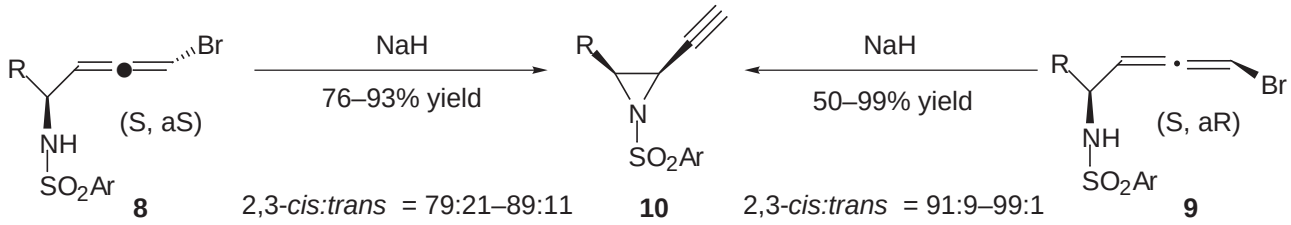
Similar results have been gotten with α-amino allenes **4** (Scheme 3).[13] Dioxane was found to be the best solvent for this reaction.

The reaction was highly stereoselective. Starting from a (S, aS) amino allene, the major product was a 2,3-*cis*-2-alkenylaziridine **5** while from the (S, aR) isomer, the major product was the 2,3-*trans*-2-alkenylaziridine **6**. In this case a few amount of the 3-pyrroline **7** was observed as by-product.

The base-mediated intramolecular amination of bromoallenes led to a chiral 2,3-*cis*-ethynylaziridines.[14] Starting from the (S, aS) or the (S, aR) isomer, the *cis*-aziridine was the major product (Scheme 4). However, the best stereoselectivity was obtained from the (S, aR) isomer.



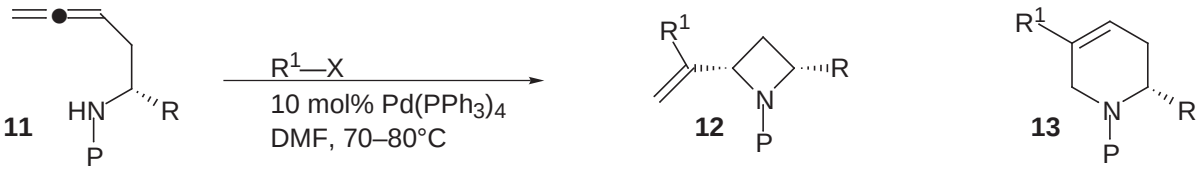
Scheme 3



Scheme 4

3. Heterocycles with four-membered rings

The palladium-catalysed heteroannulation of allene-tethered amines **11** was reported. The reaction provided azacyclobutane **12** or/and tetrahydropyridine **13** (Scheme 5). Starting from **11c** only **12c** was obtained in enantiomerically pure form.[15]



(a) R = H ; (b) R = CO_2Me ; (c) R = alkyl, benzyl
R^1 = aryl, alkenyl ; P = protecting group

Scheme 5

Starting from **11a,b** the ratio **12:13** depends on the substituents R and P but also on the reaction times and R^1–X.[16] With R = CO_2Me (**11b**) both **12b** and **13b** were obtained in enantiomerically pure form. To favour the formation of **12** the best is to use short reaction times and vinylic triflates as R^1–X.

4. Heterocycles with five-membered rings

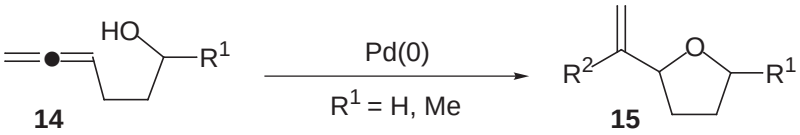
4.1. Oxygen heterocycles

In this heading we found furanic compounds and furanones or butenolides. The first ones are generally produced from allenylalcohols or ketones while the others are usually coming from allene-tethered carboxylic acids.

4.1.1. Saturated oxygen heterocycles (tetrahydrofurans)

Palladium catalysis allows to add a coupling reaction to the ring closure. Starting from γ-allenyl alcohols **14**, the reaction led to 2-vinyl tetrahydrofurans **15** (Scheme 6).

The R^2 group may be brought by an aryl or vinyl halide[17] or by hypervalent iodonium salts.[18] Acylation-cyclisation (R^2=RC=O) is possible using acyltetracarbonylcobalt complexes.[19]

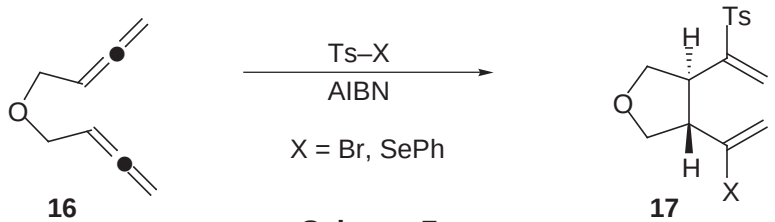


14 **15**

Scheme 6

Also compound **15** (R^2=Ts) may be simply obtained from **14** by radical addition of *p*-toluenesulfonyl bromine or iodide.[20] Actually, in this case, the ring closure occurs in an intramolecular nucleophilic substitution second step.

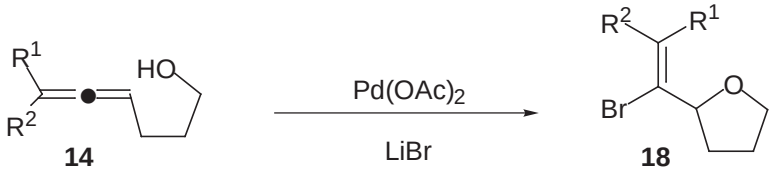
Starting from the bis(allene) **16**, similar reaction using the radical addition of TsBr or TsSePh afforded the tetrahydrofuran **17** bearing a vinyl sulfone and a *trans* vinyl bromide or selenide (Scheme 7).[21]



16 **17**

Scheme 7

Tetrahydrofurans bearing a vinyl bromide may be gotten from γ-allenyl alcohols **14** by Pd (II) catalysis in the presence of LiBr (Scheme 8).[22]



14 **18**

Scheme 8

4.1.2. Unsaturated oxygen heterocycles

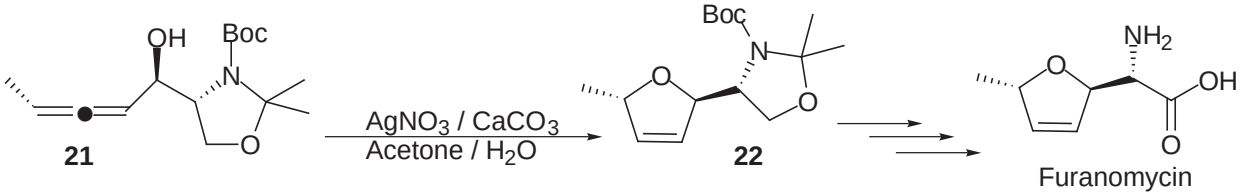
4.1.2.1. Dihydrofurans

19 **20**

Scheme 9

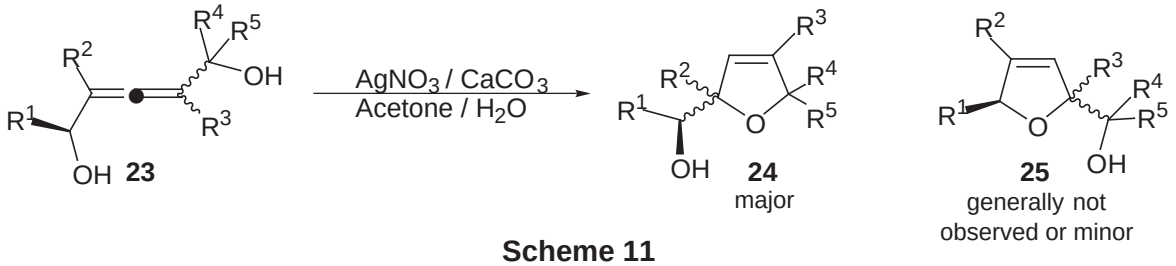
The older way to get dihydrofurans from allenes is probably the silver (I) mediated ring closure of α-allenylalcohols.[23] However HCl gas in chloroform[24] (R^5=COOEt) or $AuCl_3$[25] in CH_2Cl_2 gave similar results (Scheme 9). In all cases the reaction proceeded with complete axis to centre chirality transfer.

Furanomycin, a Streptomyces metabolite, was synthesised in a few steps using the Ag(I) promoted ring closure of the allenic compound **21** as key step (Scheme 10).[26]



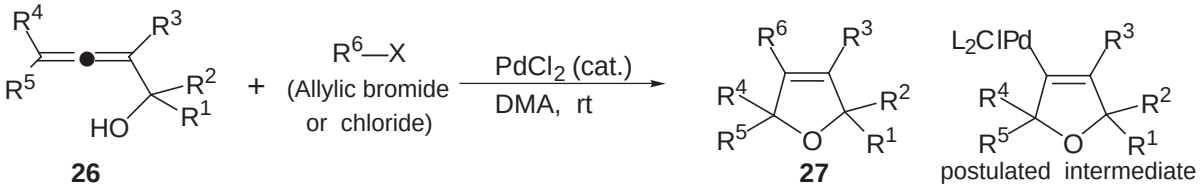
Scheme 10

The Ag (I)-promoted ring closure of 2,3-pentadiene-1,5-diols has been investigated.[27] Generally the cyclisation occurs through the more hindered hydroxyl group (Scheme 11).

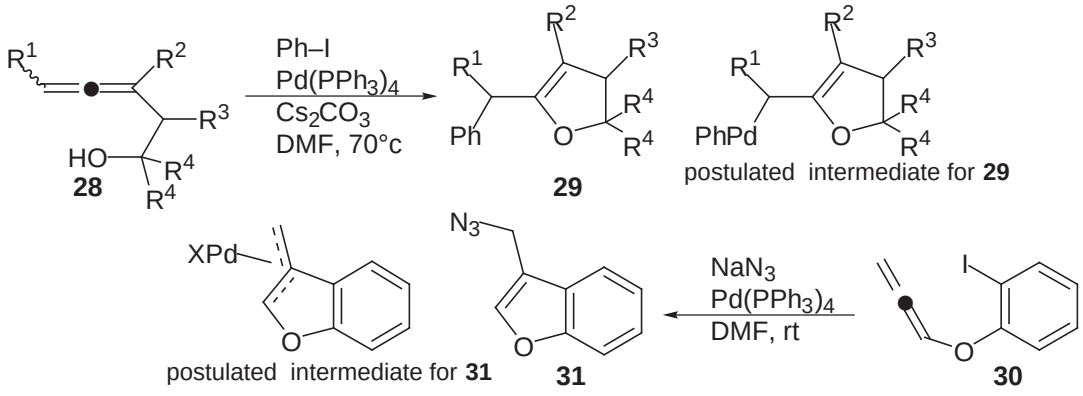


Scheme 11

Cyclisation affording 2,5-dihydrofurans has been also done with coupling using catalytic $PdCl_2$ (Scheme 12).[28,120]



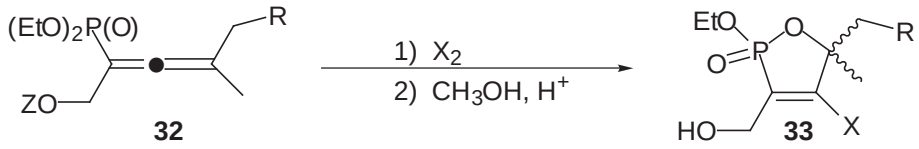
Scheme 12



Scheme 13

2,3-Dihydrofurans have been synthesised by Pd(0) promoted ring closure involving a coupling reaction (Scheme 13). It is possible to start the cyclisation from a β-allenyl alcohol[29] (phenyl, or more generally, aryl iodide was then used) or a 1-allenyloxy-2-iodobenzene[30] with sodium azide. In the latter case, the organic azides so formed were then trapped with dimethylacetylenedicarboxylate to afford the corresponding triazoles.

Although oxaphospholes are not only oxygen heterocycles, one can classify here the formation of 2,5-dihydro oxaphospholes from phosphorylated allenes because it is the oxygen atom which acts as a nucleophile in the ring closure (Scheme 14).[31]

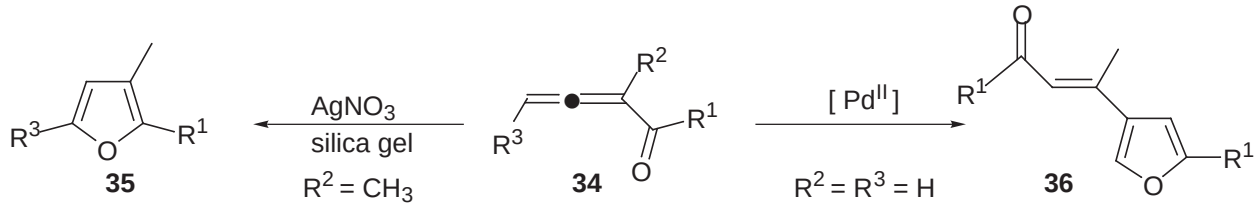


32 **33**

Scheme 14

4.1.2.2. Furans

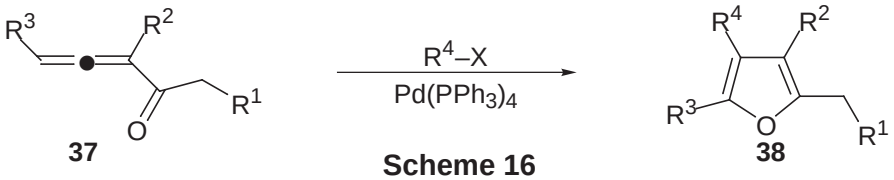
These compounds may be prepared from α-allenyl ketones by silver catalysis[32] as well as Pd(II) catalysis[33] (Scheme 15). In the latter case the ring closure provided mainly the dimer **36**.



35 **34** **36**

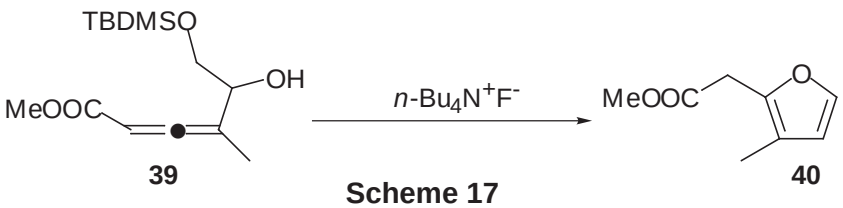
Scheme 15

With palladium(0) catalysis the ring closure of the α-allenyl ketone can be associated with a coupling reaction introducing in this way a substituent at the 3- or 4- position of the corresponding unsubstituted furan (Scheme 16).[34,35]



37 **38**

Scheme 16



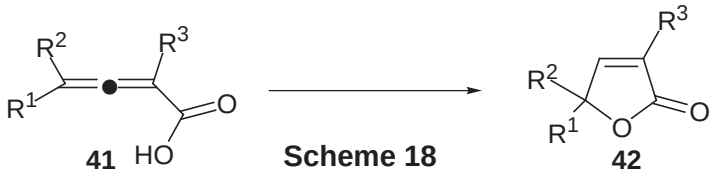
39 **40**

Scheme 17

Deprotection of the β-allenyl silyl ether **39** afforded the furan derivative **40** in good yield (Scheme 17).[36] Actually, the expected diol underwent a 5-*exo*-dig ring closure; deshydratation of the so-formed dihydrofuranol derivative led to **40**.

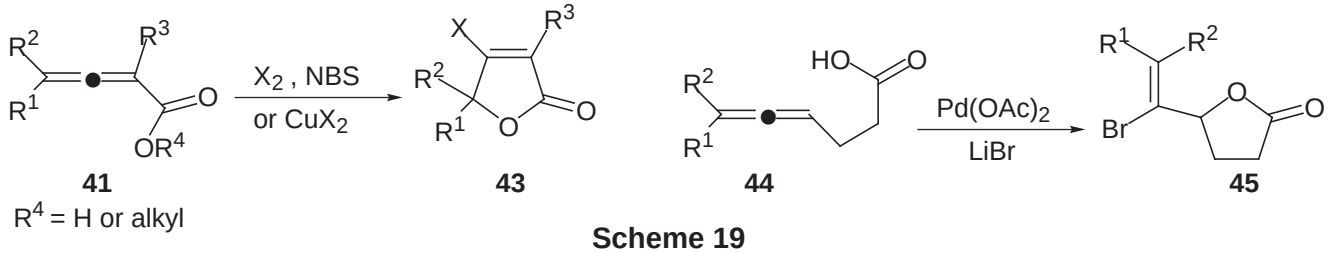
4.1.2.3. Furanones

The most general way to get furanones involves the use of allene-tethered carboxylic acids as starting material. Direct cycloisomerisation of an α-allenylacid directed by metal salts acting as Lewis acids like $CuCl$[37] or $AgNO_3$[38,39] afforded β-unsubstituted butenolides (Scheme 18). The β-halobutenolides **43** were prepared by the ring closure of the α-allenylacids[40-43] **41** (R^4=H) using halogens, NBS or CuX_2 (Scheme 19).



41 **Scheme 18** **42**

The Pd(II)/LiBr-mediated cyclisation of the γ-allenylacids **44** afforded the 5-(1-bromoalkenyl) dihydrofuran-2-one **45** (Scheme 19).[22,44] Moreover, starting from the α-allenoates **41** (R^4=alkyl), the compounds **43** were also produced using halogens[45] or CuX_2 in aqueous ethanol.[46]

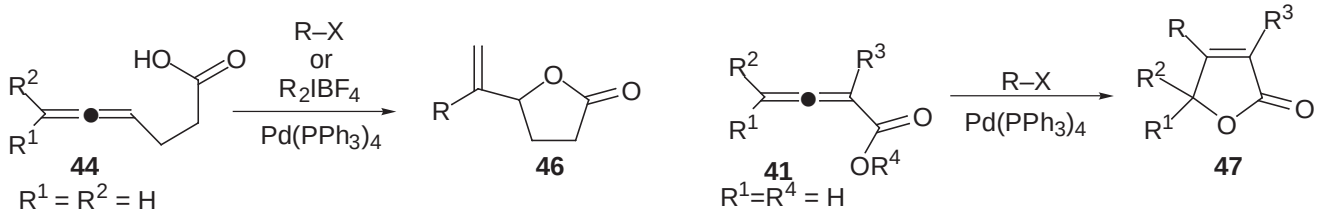


41 **43** **44** **45**

R^4 = H or alkyl

Scheme 19

Palladium(0) catalyses the coupling cyclisation of γ-allenylacids[17,18] to lead 5-vinyl-dihydro furan-2-ones **46** as well as α-allenylacids[47,48] to afford 4-substituted-5*H*-furanones **47** (Scheme 20).



44 **46** **41** **47**

$R^1 = R^2 = H$ $R^1 = R^4 = H$

Scheme 20

Compounds **47** have been obtained with medium to high enantiomeric excess using a chiral ligand in the Pd(0) catalysed coupling cyclisation[49] of **41** or by chirality transfer from 1:1 salts of optically active α-allenylacid–base.[50]

If the allene-tethered carboxylic acids or esters are the main sources of cyclisation to furanones, other methods have been used. For example, several methylene-3-oxabicyclo[3.1.0]hexan-2-ones were obtained by Cu^{2+} induced intramolecular carbene addition from diazoacetates derived from α-allenyl alcohols.[51]

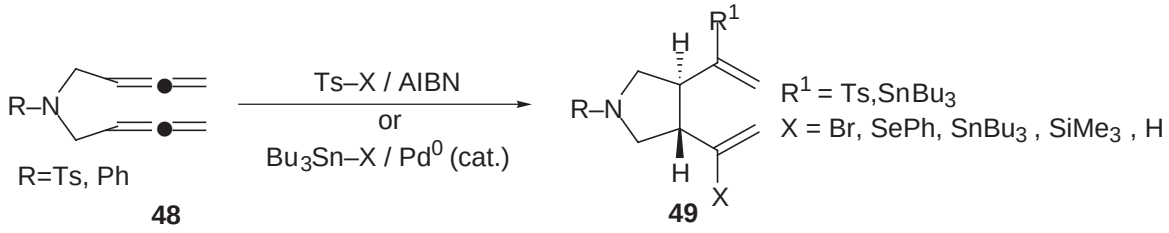
Radical cyclisation of allene-tethered bromoacetal has also been used.[52] This method has nicely been applied as key step to the synthesis of Botryodiplodin.[53] Lithiation and carbonylation of 1-alkyl-1-methoxyallene provided 5-alkyl-5-methoxy-5*H*-furan-2-ones.[54] The ruthenium-catalysed cyclic carbonylation of α-allenylalcohol afforded also substituted 5*H*-furan-2-ones.[55]

4.2. Nitrogen heterocycles

Many papers talking about five-membered nitrogen heterocycles from allenes talk also about oxygen heterocycles.[18–22] Moreover, the "nucleophilic transition metal based cyclisation of allenes" was recently reviewed.[56]

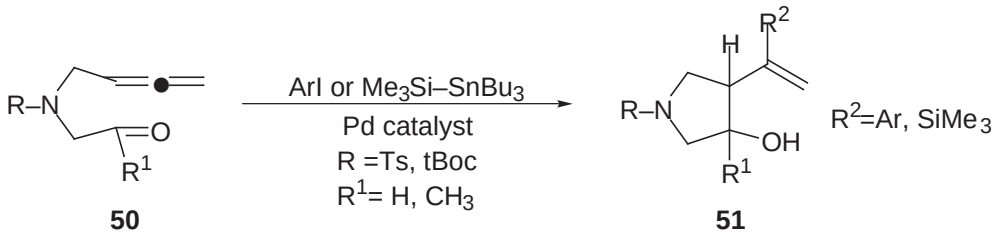
4.2.1. Saturated nitrogen heterocycles

The toluene-*p*-sulfonyl-mediated radical cyclisation of bis(allenes) linked together with an heteroatom was early mentioned in the 4.1.1. section about the tetrahydrofurans.[21] Similar results were obtained for the synthesis of nitrogen heterocycles **49** starting from **48**. Compounds **48** were also carbocyclised using palladium catalysis (Scheme 21).[57]



Scheme 21

Palladium-catalysed carbocyclisation was also performed starting from δ-allenylaldehydes or ketones (Scheme 22).[58,59]



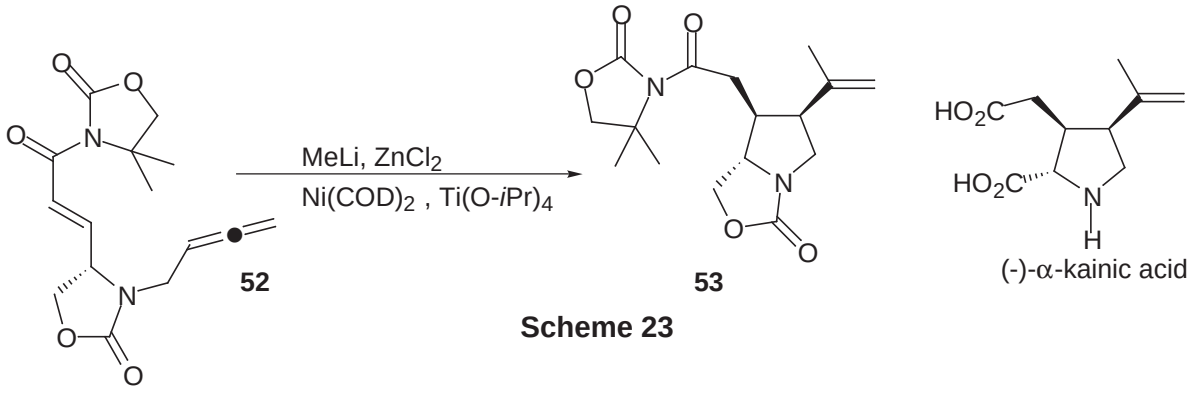
Scheme 22

Very similar results were also obtained using the palladium–indium-mediated arylative ring closure of the same starting material (Scheme 23).[60]

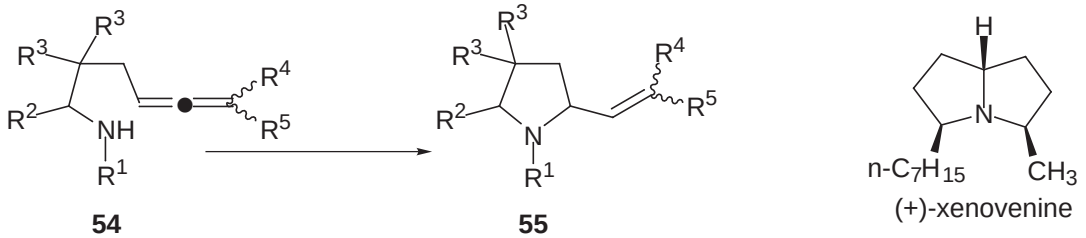
A very nice carbocyclisation was used to build the pyrrolidine unit of (-)-α-kainic acid.[61]

The cyclo-isomerisation of γ-aminoallenes is another efficient way to access to 2-vinyl-pyrrolidines (Scheme 24). The hydroamination ring closure was carried out as well by silver catalysis,[62] palladium catalysis[63] or organolanthanide catalysis.[64] The last-mentioned method was nicely used as key step in the synthesis of the pyrrolizidine alkaloid (+)-xenovenine.[65]

The pyrrolidines **56** were obtained from γ-aminoallenes **54** in several manners (Scheme 25). As we have early seen for oxygen heterocycles, the radical addition of *p*-tosyl bromide or iodide to **54** followed by an intramolecular nucleophilic substitution led to the compound **56** with a *p*-toluenesulfonyl group as X.[20]



Scheme 23



Scheme 24

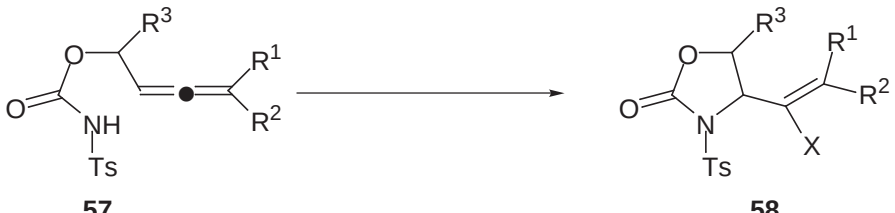
Scheme 25

The palladium catalysis allowed to introduce several others substituents like bromine,[22] aryl,[18,66] alkenyl[66] or, by a carbonylation–coupling cyclisation with aryl iodides and carbon monoxide, benzoyl.[19,67] Similar compounds [X = RC(O)] were also nicely gotten using the cobalt-mediated acylation-cyclisation method.[19,68]

4.2.2. Unsaturated nitrogen heterocycles

Pyrrolidinones were prepared from α-allenylsulfonamides by oxidative cyclisation using dimethyloxirane.[69]

The Scheme 26 shows a palladium-catalysed ring closure providing the oxazolidinones **58** from the allenyl *N*-tosylcarbamates **57**.



Scheme 26

Depending on the reaction conditions, the X group introduced on the 1-alkenyl position in **58** was a bromine atom[22] when the reaction was performed in the presence of LiBr with palladium acetate as the catalyst or a CH_2CH_2CHO group by a conjugate addition with acrolein.[70] It was also an allylic group;[71] an aromatic one[72] with hypervalent iodonium salts or a methoxycarbonyl group.[73]

The reaction of α-allenyl hydrazines with *n*-BuLi in THF was investigated.[74] In this way, 3-pyrrolines were obtained in good yields and high enantiomeric purity when SAMP-hydrazines were used.

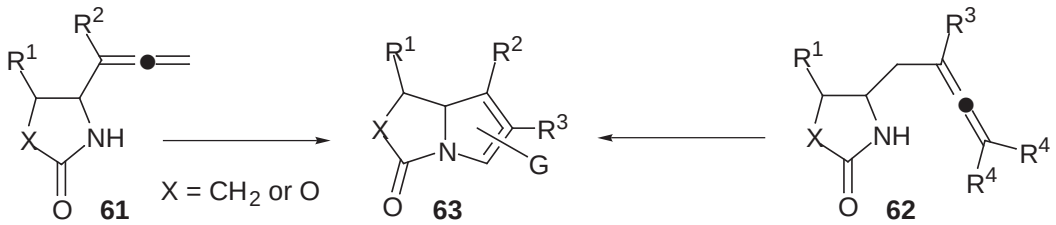
Starting from allene-tethered dithiosemicarbazides, a tin hydride-mediated cyclisation led to both 3*H*-pyrroles and alkylidene pyrrolines.[75] Thermal isomerisation of the former to the latter occurred in some cases.

Silver-mediated ring closure of β-allenylamines afforded 3,4-dihydro-2*H*-pyrroles.[76-78] While, starting from α–allenylamines **59**, the 2,5-dihydro-1*H*-pyrroles **60** have been gotten in two ways (Scheme 27).

Scheme 27

Firstly, the silver-mediated ring closure afforded a compound resulting in just a cycloisomerisation of the starting material (X=H).[79-81] Very recently, compounds like **60** (X=H) were also obtained by the Ru-catalysed ring closure of allene-tethered alkenes.[121] Secondly, the palladium-catalysed ring closure permitted to introduce a carbon-containing group as X. Aryl groups were easily introduced using $Pd(PPh_3)_4$ with an aromatic halide at room temperature;[80] increasing the temperature resulted in the formation of the corresponding pyrrole. A carbonylative cyclisation under CO provided the compound **60** with a benzoyl group as X.[67]

Similarly bicyclic heterocyles have been gotten starting from allenyl or homoallenyl pyrrolidin or oxazolidin-2-ones (Sheme 28).

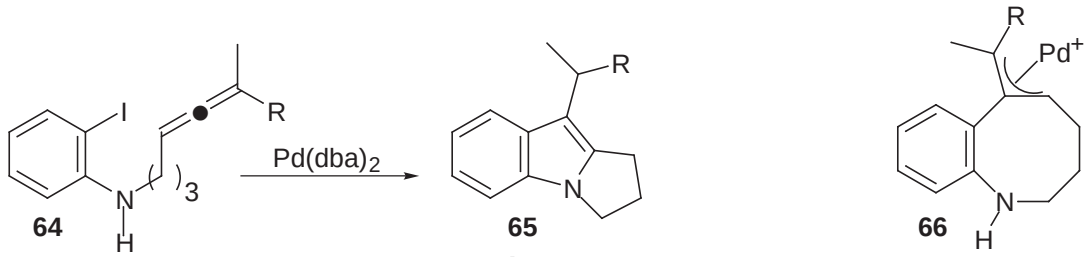


Scheme 28

The 4-allenyl oxazolidinones **61** (X = O) were cycloisomerised to the compound **63** (R^3 = G = H) using silver catalysis involving a 5-*endo*-trig ring closure.[82] On the other hand, the palladium-mediated coupling-cyclisation reaction of the same kind of starting materials afforded the oxazolidinones **63** and their corresponding pyrrolidinones (G = allylic group).[83] The compounds **63** (R^2 =H, G = benzylic group) were also mainly obtained from the homoallenyl oxazolidinones or pyrrolidinones **62** by a palladium-catalysed cyclisation-coupling reaction involving now a 5-*exo*-dig ring closure.[84,85]

In the field of the bicycloheterocycles, it had been reported the synthesis of *N*-alkyl-2-vinylindoles from *N*-alkyl-*N*-homoallenylanilines by a tandem process involving an oxydation at the nitrogen and then a set of three rearrangements.[86]

The compound **65** with an indole skeleton was directly constructed by intramolecular carbopalladation of the allene **64**.[87] The reaction was proposed to proceed *via* the intermediate **66** (Scheme 29).



Scheme 29

Dihydropyrrolones and alkylidenedihydropyrrolones were gotten respectively from α-allenylamines through carbonylative cyclisation by ruthenium catalysis,[88] from α-allenylamides[89] with CuX_2 and from α-allenylimines through carbonylative ring closure by iron catalysis.[90]

Sometimes the same starting material is able to lead to a nitrogen heterocycle or to an oxygen one. To illustrate this purpose and before going to the next point, let us consider a very interesting recent work (Figure 1) showing that the Pd(0)-catalysed coupling-cyclisation of 2,3-allenamides may lead to γ-hydroxy-γ-lactams or iminolactones depending on some steric hindrance factors.[122]

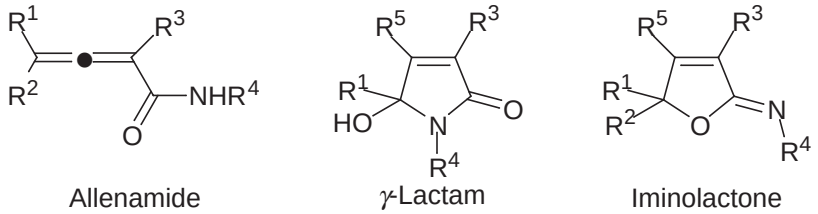


Figure 1

4.3. Other heterocycles

As it is pointed out above, in the overwhelming majority of cases the heterocycles coming from allenes are oxygen or nitrogen heterocycles. However, in some scarce cases other heterocycles were synthesised. It is perhaps useful to recall here the case of the oxaphospholes mentioned above at the paragraph 4.1.2.1.[31]

Very recently a silicon-tethered allenic intramolecular Pauson-Khand reaction was reported.[91] This reaction led to five or six-membered silicon heterocycles.

5. Heterocycles with six-membered rings

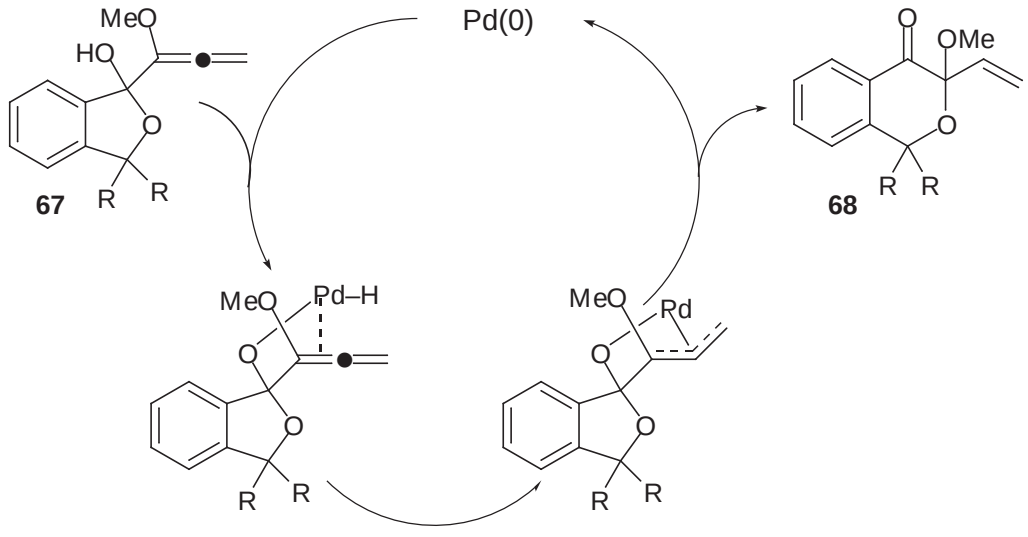
5.1. Oxygen heterocycles

As we have already seen in the case of the five-membered heterocycles, the ring closure may be generated by the formation of a C–C bond inside an allenic ether or ester. In this field, cyclic ethers were obtained using the palladium-mediated intramolecular hydrocarbonation of alkoxyallenes[92] or *o*-iodo-benzoyloxyallenes.[30,93,94] The palladium-catalysed cyclisation-coupling reaction of buta-2,3-dienyloxy-aldehydes or ketones has already been reported about the formation of five-membered rings[58-60] as well as the intramolecular cyclopropanation of allenic diazoacetates.[51]

Of course, six-membered cyclic ethers or esters were also prepared by the intramolecular formation of a C–O bond starting from an allene-tethered alcohol or acid. The radical addition of *p*-toluenesulfonyl bromide or iodide to allene-tethered alcohols has been reported above.[20] Substituted tetrahydropyrans were obtained in this way when TsI was used. It is to be noticed that, with the same starting material, eight-membered ether was the product of the reaction when TsBr was used. The Pd(II)-catalysed oxybromination of allenic alcohols[22] and allenic acids[22] as well as the ruthenium-catalysed cyclic-carbonylation of allenic alcohols[55] were also reported above. Substituted tetrahydropyrans and δ-lactones were obtained in this way.

The *p*-toluenesulfonic acid-mediated cyclisation of benzenesulfinic β-allenylalcohols afforded benzenesulfinyl-dihydro-2*H*-pyrans.[95] While the $PdCl_2$-mediated methoxycarbonylation of a conveniently allene-tethered alcohol was used as the key step in the synthesis of (±) rhopaloic acid A.[96]

At last, it should be noted that hydroxy-methoxyallenylphthalans **67** (Scheme 30) were isomerised to isochromanes **68** with palladium(0) catalysis.



Scheme 30

The reaction took place through a Pd(0)-catalysed ring expansion of the α-allenyl cyclic hemiketal.[97] A mechanism involving a cascade hydropalladation-ring expansion has been suggested.

5.2. Nitrogen heterocycles

Piperidines have been prepared from allenic compounds by carbocyclisation[58–60] or by amino cyclisation using silver catalysis,[62] palladium catalysis[63] or lanthanide catalysis.[64] The silver-mediated ring closure of δ-allenylamines has been used as the key step in the synthesis of the clavepictine A and B.[98,99]

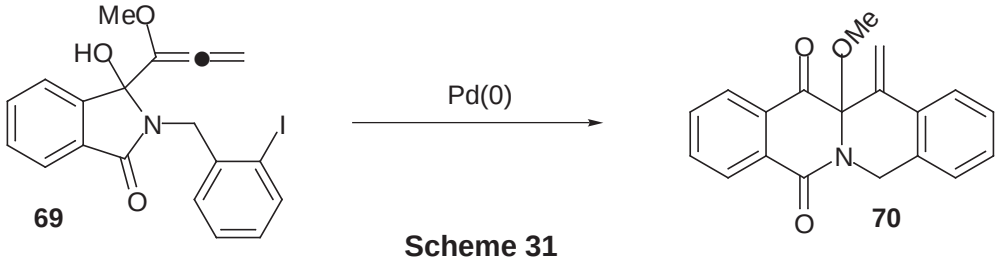
Compounds like 3-hydroxypiperidin-4-ones were obtained from β-allenylsulfonamides by oxidative cyclisation with dimethyldioxirane.[69]

The Pd(II)-catalysed oxydative aminocarbonylation[73] and the Pd(0)-catalysed coupling reaction with hypervalent iodonium salts[72] of allene-tethered *N*-tosylcarbamates provided 4-alkenyl-*N*-tosyl-[1,3]oxazinan-2-ones.

The free-radical addition of the tosylbromide on δ-allenylsulfonamides led to 2-alkenyl-*N*-tosylpiperidines while, starting from β-allenylsulfonamides, the same reaction led to 1,5-ditosyl-1,2,3,6-tetrahydropyridines.[20] Other 1,2,3,6-tetrahydropyridines have also been obtained from silver-mediated 6-*endo*-trig ring closure of β-allenylamines.[76] On the other hand, 2,3,4,5-tetrahydropyridines were gotten by titanium-mediated cyclisation of β-allenylamines.[100] Starting from *gem*-difluoroallenic propargylamines, a novel Mo-catalysed [2+2] cycloaddition afforded *gem*-difluoro-3-azabicyclo[4.2.0.]octa-1[8],5-dienes including a 1,2,3,6-tetrahydropyridine unit.[101]

The tandem hydropalladation-ring expansion reaction early seen about the formation of six-membered oxygen heterocycles allowed also to get 2,3-dihydro-isoquinoline-1,4-dione.[97]

Similarly, the tandem intramolecular carbopalladation-heterocyclic ring expansion reaction permitted the access to the tetracyclic quinolitidine derivatives **70** (Scheme 31).[102]

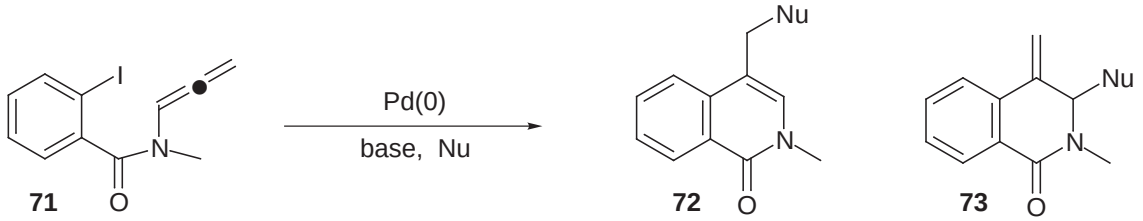


69 **70**

Scheme 31

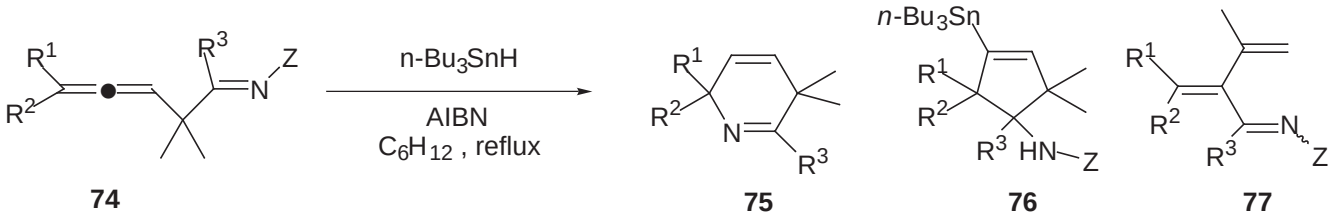
The Ru-mediated cyclocarbonylation of β-allenyl sulfonamides under CO pressure afforded some derivatives of the 5,6-dihydro-1*H*-piperidin-2-one.[88]

The cascade palladium-catalysed cyclisation-anion capture furnished a good access to 2*H*-isoquinolin-1-ones **72**.[30,103,104] Depending on the reaction conditions, the *exo*-methylene isomer **73** was sometimes produced (Scheme 32).



71 **72** **73**

Scheme 32



74 **75** **76** **77**

Scheme 33

Depending on the substitution pattern, the silver-mediated cyclisation of phosphonylated *β*-allenylamines may lead to 2,5-dihydropyridines.[77] These compounds, substituted at the 3-postion by a tributylstannanyl group, have also been obtained by the tin-mediated free radical cyclisation of *β*-allenyl benzoyloximes, oxime ethers or hydrazones. Actually, the main product of the addition of the tin radical on the allenyl moiety results generally in a five membered carbocycle **76** coming from a 5-*exo*-dig ring closure process (Scheme 33). But, depending mainly on the size and the polarity of the R^3 substituent, and, in a lesser extent, on the nature of the Z substituent, a rearranged compound **77** or a dihydropyridine **75** coming from a six-*endo*-trig ring closure on the nitrogen have been obtained.

With a bulky and electron-withdrawing R^3 group the dihydropyridin **75** was the main or the sole product of the reaction.[105,106]

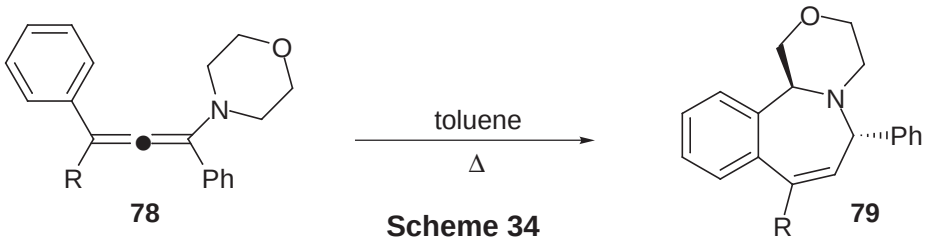
To finish, let us consider the tandem cyclisation-oxidation reaction of allene-tethered hydrazones leading to pyridazinones derivatives.[107]

6. Heterocycles with larger rings

Contrary to the case of five or six-membered heterocycles, there is only a few papers related to the formation of seven and larger-membered heterocycles coming from intramolecular ring closure of allenic compounds.

Concerning the formation of seven-membered rings, let us mention the synthesis of dihydro[*c*] benzazepin-3-ones from allene-tethered nitrones precursors,[108] the synthesis of 2-vinyloxepanes by Pd(II)-catalysed intramolecular hydrocarbonation of alkoxyallenes[92] and the formation of seven-membered lactones by ruthenium-catalysed cyclocarbonylation of allenylalcohols.[109] In this latter case, eight-membered lactones were also prepared in the same way.

The thermal isomerisation of 1-morpholino-3-phenylallenes **78** had also been reported.[110]



78 **79**

Scheme 34

The formation of the seven-membered nitrogen heterocycle in the oxazinobenzazepine derivative **79** was explained in three steps: firstly, a 1,4-shift of a proton affording an unsaturated azomethine ylide; secondly, a conrotatory 1,7-electrocyclisation and thirdly, a rearomatisation by a 1,5-suprafacial hydrogen shift.

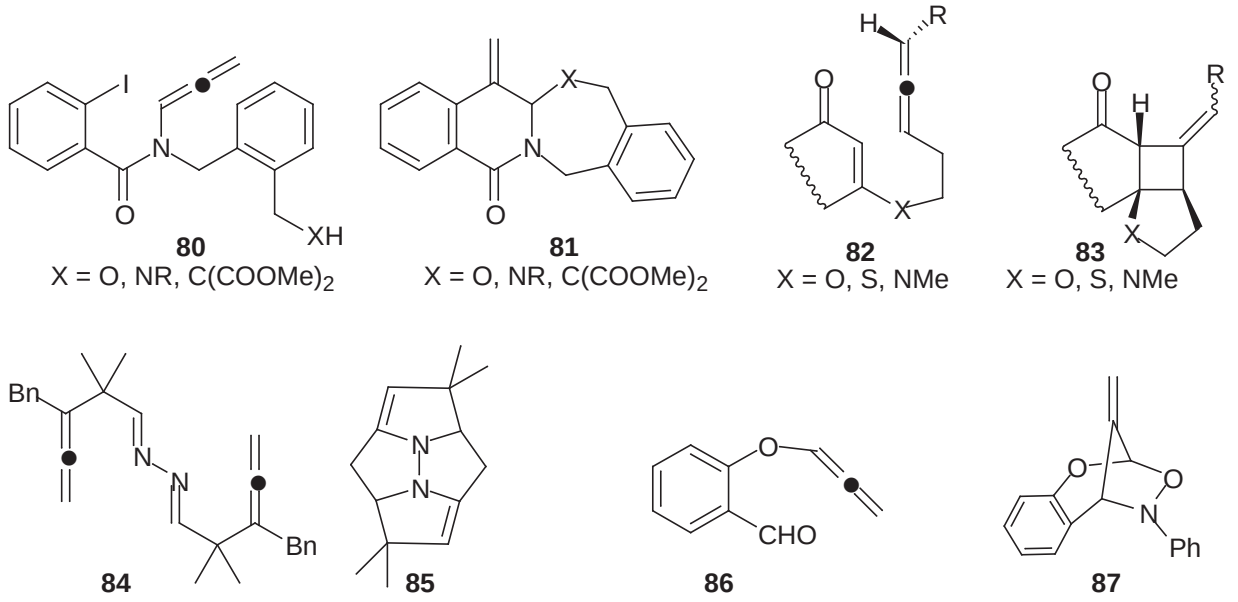
About the eight-membered rings, it should be noticed that 2*H*-oxocines have been gotten from allenylalcohols by the tosylbromide radical addition.[20] The Pd(II)-catalysed cyclisation of *ω*–haloallenes have permitted the access to benzo[*c*]oxepine, benzo[*c*]oxocine derivatives and similar nine-membered heterocycles *via* a cyclic carbopalladation.[111] The formation of medium (7–11) ring azacycles by a tandem iodination-cyclisation process starting from allene-tethered sulfonamides has been investigated.[112,113]

As shown in the case of five-membered heterocycles, the Pd(0)-catalysed coupling of allene-tethered *N*-tosylcarbamates with hypervalent iodonium salts is a good way to provide cyclic carbamates. In this way, oxazonin-2-one and oxazecin-2-one derivatives were synthesised in moderate yields.[72]

7. Miscellaneous

Under this heading we shall consider either reactions involving the formation of more that one cycle (one by one or at the same time) or the formation of bridged polycyclic compounds or else the formation of other heterocycles: sulphur heterocycles for instance. As expected, unlike the case of five and six-membered heterocycles, we only found a few papers talking about that.

In the synthesis of **81** (Figure 2) from **80**, two fused heterocycles were formed by Pd(0) cascade carbo and heteroannulation of allenic compounds.[114] In the enantioselective allene-enone photocycloaddition (**82** → **83**) the cyclobutane ring and the five-membered one were closed at the same time.[115] As for it, the tetracyclic compound **85** was arising from **84** by an intramolecular azide "criss-cross" addition.[116] The reaction of *o*-(1,2-propadienyloxy)benzaldehyde **86** with phenylhydroxylamine led to the dioxa azabicyclo[3.2.1]octene **87**.[117] The nitrone formed in a first step underwent an intramolecular dipolar cycloaddition reaction with the allenic moiety to give **87**.



80 X = O, NR, $C(COOMe)_2$ **81** X = O, NR, $C(COOMe)_2$ **82** X = O, S, NMe **83** X = O, S, NMe

84 **85** **86** **87**

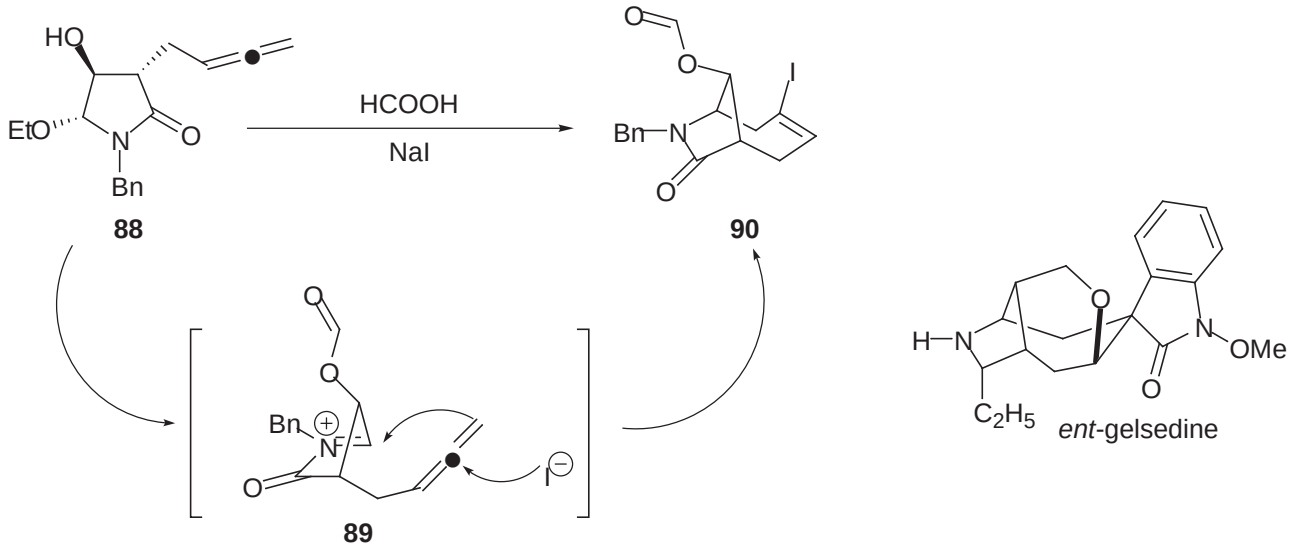
Figure 2

In the total synthesis of *ent*-gelsedine the key step was the formation of the bridged bicyclic compound **90** from the allenylpyrrolidinone **88** coming itself from (*S*)-malic acid.[118] The ring closure was generated by a very nice iodide-promoted allene *N*-acyliminium ion cyclisation (Scheme 35).[119]

8. Conclusion

This short survey shows that the intramolecular ring closure of allenic compounds may be a powerful method for the synthesis of various heterocycles. Most of the papers are talking about the formation of five-membered heterocycles; then, is coming the formation of six-membered heterocycles and, in a less extent the seven and medium-membered rings. The synthesis of three and four-membered heterocycles by intramolecular cyclisation of allenic compounds has not much been investigated.

The heteroatoms used in these syntheses are mainly oxygen and nitrogen but sulphur, phosphorus and silicium also have been used. Two methods were used to make the heterocycle: either bind together two carbons in a compound with a heteroatom in a convenient position inside the molecule, or directly make a link between the heteroatom and one of the allenic carbons.



Scheme 35

A great variety of chemical reactions were used to make the cyclisation. Among these tools, the most widely used are probably the Lewis acid-promoted ring closure and the palladium-catalysed cyclisation; but other methods have been used. The free radical ring closure or the cyclisation promoted by a nucleophilic addition on the allenic moiety as well as the use of other transition metals than palladium as catalyst are some good examples of that.

References

1. *The Chemistry of the allenes* (Ed.: Landor, S. R.), Academic Press, London **1982**.
2. Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805–2827.
3. Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125.
4. Marshall, J. A. *Chem. Rev.* **2000**, *100,* 3163–3185.
5. Back, T. G. *Tetrahedron* **2001**, *57*, 5263–5301.
6. Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem.* **2002**, *67*, 1339–1345.
7. Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031–5041.
8. Grigg, R.; Khamnaen, T.; Rajviroongit, S.; Shridharan, V. *Tetrahedron Lett.* **2002**, *43*, 2601–2603.
9. Ishar, M. P. S.; Kumar, K.; Kaur, S.; Kumar, Girdhar, N. K.; Sachar, S.; Marwaha, A.; Kapoor, A. *Org. Lett.* **2001**, *3*, 2133–2136.
10. Banert, K. *Targets in Heterocyclic Systems* **1999**, *3*, 1–32.
11. Kang, S-K.; Yamaguchi, T.; Pyun, S-J.; Lee, Y-T.; Baik, T-G. *Tetrahedron Lett.* **1998**, *39*, 2127–2130.
12. Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943–7944.
13. Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992–2993.
14. Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett.* **2001**, *3*, 2269–2271.
15. Anzai, M.; Toda, A.; Ohno, H.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett*. **1999**, *40*, 7393–7397.

16. Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717–720.
17. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88–90.
18. Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Kulak, A. N. *Synlett* **1999**, 324–326.
19. Bates, R. W.; Devi, T. R. *Tetrahedron Lett.* **1995**, *36*, 509–512.
20. Kang, S.-K.; Ko, B.-S.; Ha, Y.-H. *J. Org. Chem.* **2001**, *66*, 3630–3633.
21. Kang, S.-K.; Ha, Y.-H.; Kim, D.-H.; Lim, Y.; Jung, J. *J. Chem. Soc., Chem. Commun.* **2001**, 1306–1307.
22. Jonasson, C.; Horváth, A.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600–9609.
23. Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550–5555.
24. Krause, N.; Laux, M.; Hoffmann-Röder, A. *Tetrahedron Lett.* **2000**, *41*, 9613–9616.
25. Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537–2538.
26. VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705–708.
27. Aurrecœchea, J. M.; Solay, M. *Tetrahedron Lett.* **1998**, *54*, 3851–3856.
28. Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933–8936.
29. Ma, S.; Gao, W. *Synlett* **2002**, 65–68.
30. Gardiner,M.; Grigg, R.; Sridharan, V.; Vicker, N. *Tetrahedron Lett.* **1998**, *39*, 435–438.
31. Brel, V. K. *Synthesis* **1998**, 710–712.
32. Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966–5968.
33. Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295–7304.
34. Ma, S.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **2000**, 117–118.
35. Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941–944.
36. Piotti, M. E.; Alper, H. *J. Org. Chem.* **1997**, *62*, 8484–8489.
37. Ma, S.; Yu, Z.; Wu, S. *Tetrahedron* **2001**, *57*, 1585–1588.
38. Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796–797.
39. Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367–371.
40. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393–2396.
41. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137–12148.
42. Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314–9317.
43. Ma, S.; Wu, S. *J. Chem. Soc., Chem. Commun.* **2001**, 441–442.
44. Jonasson, C.; Bäckvall, J.-E. *Tetrahedron Lett.* **1998**, *39*, 3601–3604.
45. Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3228–3239.
46. Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075–4077.
47. Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387–6389.
48. Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419–1422.
49. Ma, S.; Shi, Z.; Wu, S. *Tetrahedron : Asymmetry* **2001**, *12*, 193–195.
50. Ma, S.; Shi, Z. *J. Chem. Soc., Chem. Commun.* **2002**, 540–541.
51. Lautens, M.; Meyer, C.; van Oeveren, A. *Tetrahedron Lett.* **1997**, *38*, 3833–3836.
52. Villar, F.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 8655–8658.
53. Villar, F.; Andrey, O.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3375–3378.
54. Fall, Y.; Gomez, G.; Fernandez, C. *Tetrahedron Lett.* **1999**, *40*, 8307–8308.
55. Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takashashi, S. *Org. Lett.* **2000**, *2*, 441–443.
56. Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12–21.
57. Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc.* **2000**, *122*, 11529–11530.
58. Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143–1146.
59. Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 343–345.
60. Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376–4379.
61. Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139–11143.
62. Shaw, R. W.; Lathbury, D.; Gaallagher, T. *Synlett* **1993**, 710–712.
63. Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421–5424.
64. Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871–4872.
65. Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am . Chem. Soc.* **1999**, *121*, 3633–3639.

66. Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85–87.
67. Kang, S.-K.; Kim, K.-J. *Org. Lett.* **2001**, *3*, 511–514.
68. Bates, R. W.; Satcharœn, V. *Synlett* **2001**, 532–534.
69. Crandall, J. K.; Reix, T. *Tetrahedron Lett.* **1994**, *35*, 2513–2516.
70. Liu, G.; Lu, X. *Org. Lett.* **2001**, *3*, 3879–3882.
71. Kimura, M.; Tanaka, S.; Tamaru, Y. *J. Org. Chem*. **1995**, *60*, 3764–3772.
72. Kang, S.-K.; Baik, T.-G.; Hur, Y. *Tetrahedron Lett.* **1999**, *55*, 6863–6870.
73. Kimura, M.; Saeki, N.; Uchida, S.; Harayama, H.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7611–7614.
74. Breuil-Desvergnes, V.; Goré, J. *Tetrahedron* **2001**, *57*, 1939–1950 (and ref. 11, 19, 20 therein).
75. Depature, M.; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2001**, 941–946.
76. Grimaldi, J.; Hatem, J.; Henriet-Bernard, C.; Maurin, R. *J. Chem. Research (S)*, **1994**, 36–37.
77. Amedjkouh, M.; Faure, R.; Hatem, J.; Tordo, P.; Grimaldi, J. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *126*, 53–64.
78. Amedjkouh, M.; Grimaldi, J. *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 391–398.
79. Amombo, M. O.; Hausherr, A.; Reissing, H.-U. *Synlett* **1999**, 1871–1874.
80. Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855–3858.
81. Billet, M.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2002**, *43*, 1453–1456.
82. Schierle, K.; Vahle, R.; Steckhan, E. *Eur. J. Org. Chem.* **1998**, 509–514.
83. Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron* **2001**, *57*, 5123–5130.
84. Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275–6278.
85. Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Hiemstra, H. *Synlett* **1998**, 1126–1128.
86. Balasubramanian, T.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1994**, 1237–1238.
87. Hiroi, K.; Hiratsuka, Y.; Watanabe, K.; Abe, I.; Kato, F.; Hiroi, M. *Synlett* **2001**, 263–265.
88. Kang, S.-K.; Kim, K.-J.; Yu, C.; Hwang, J.-W.; Do, Y.-K. *Org. Lett.* **2001**, *3*, 2851–2853.
89. Ma, S.; Xie, H. *Org. Lett.* **2000**, *2*, 3801–3803.
90. Sigman, M. S.; Eaton, B. E. *J. Org. Chem.* **1994**, *59*, 7488-7491.
91. Brummond, K. M.; Sill, P. C.; Rickards, B.; Geib, S. J. *Tetrahedron Lett.* **2002**, *43*, 3735–3738.
92. Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1747–1750.
93. Anwar, U.; Grigg, R.; Rasparini, M.; Savic, V.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **2000**, 645–646.
94. Chang, H.-M.; Cheng, C.-H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3799–3807.
95. Edwards, N.; Macritchie, J. A.; Parsons, P. J.; Drew, M. G. B.; Jahans, A. W. *Tetrahedron* **1997**, *33*, 12651–12660.
96. Snider, B. B.; He, F. *Tetrahedron Lett.* **1997**, *38*, 5453–5454.
97. Nagao, Y.; Ueki, A.; Asano, K.; Tanaka, S.; Sano, S.; Shiro, M. *Org. Lett.* **2002**, *4*, 455–457.
98. Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550–4551.
99. Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020.
100. Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475–1478.
101. Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.*, **2002**, *124*, 6534–6535.
102. Nagao, Y.; Tanaka, S.; Ueki, A.; Jeong, I.-Y.; Sano, S.; Shiro, M. *Synlett* **2002**, 480–482.
103. Grigg, R.; Sridharan, V.; Xu, L.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1903–1904.
104. Fretwell, P.; Grigg, R.; Sansano, J. M.; Shridharan, V.; Sukirrthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525–7539.
105. Depature, M.; Diewok, J.; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2000**, 275–280.
106. Depature, M.; Hatem, J. *C. R. Acad. Sci. Paris, Chemistry* **2001**, 523–529.
107. Marek, R.; Potácek, M.; Marek, J. *Tetrahedron Lett.* **1994**, *35*, 6909–6912.
108. Knobloch, K.; Eberbach, W. *Org. Lett.* **2000**, *2*, 1117–1120.
109. Yoneda, E.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459–5461.
110. Mayer, T.; Maas, G. *Tetrahedron Lett.* **1992**, *33*, 205–208.
111. Ma, S.; Negishi, E.-I. *J. Am. Chem. Soc.* **1995**, *117*, 6345–6357.
112. Shaw, R. W.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1994**, 3549–3555.
113. Davies, I. W.; Shaw, R. W.; Wisedale, R.; Gallagher, T. *J. Chem. Soc., Perkin Trans.* **1994**, 3557–3561.

114. Grigg, R.; Köppen, I.; Rasparini, M.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **2001**, 964–965.
115. Shepard, M.; Carreira, E. M. *Tetrahedron* **1997**, *55*, 16253–16276.
116. Potácek, M.; Marek, R.; Zák, Z.; Trottier, J.; Janousek, Z.; Viehe, H. G. *Tetrahedron Lett.* **1993**, *34*, 8341–8344.
117. Padwa, A.; Meske, M.; Ni, Z. *Tetrahedron* **1995**, *51*, 89–106.
118. Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F; P. J. T.; Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317–8325.
119. Beyersbergen van Henegouwen, W. G.; Hiemstra, H. *J. Org. Chem.* **1997**, *62*, 8862–8867.
120. Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104–6112.
121. Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* **2002**, *43*, 6693–6696.
122. Ma, S. ; Xie, H. *J. Org. Chem.* **2002**, *67*, 6575–6578.