Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 4, pp. 927-964, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00091-2

TETRAHEDRON: ASYMMETRY REPORT NUMBER 22

Synthesis of 2,5-Disubstituted Pyrrolidines

Marianne Pichon, Bruno Figadère*

Laboratoire de Pharmacognosie, associé au CNRS (BIOCIS), Université Paris-Sud, Faculté de Pharmacie, rue J.-B. Clément, 92296 Châtenay-Malabry, France.

Contents

Introduction

Pyrrolidines, the 5 membered aza-heterocycles, substituted at the 2 and 5 positions, are very often encountered in the living organisms. Since the 1970's where the first pyrrolidinic alkaloïds were found in the *Solenopsis* ants venom, numerous chemists became involved in the study of these new natural products. Since then these compounds have been extracted from plants, animals and microorganisms, but only in very minute quantities. Because of the low availability of these naturally occuring products, very few studies on their biological activity and mechanism of action have been performed. Nevertheless, for instance, a few 2,5-dialkylated pyrrolidines extracted from venemous ants and frogs (e.g. monomorines I-V)[1] have shown some insecticide[2,3], hemolytic and anticholinergic[4] activities.

From several plants of the Campanulaceae and Fabaceae families, polyhydroxypyrrolidines structurally related to monosaccharides and named "azasugars", have shown very potent activity as enzymes inhibitors (e.g. codonopsine, codonopsinine)[5]. From microorganisms (fungus and bacteria) it has been shown that the bulgecinines A-C[6], when associated to β-lactams, induced the formation of "tumors" on Gram-negative bacteria and therefore are potent antibiotic and antifungus agents[7].

It is worthy of note that besides the potential use of these compounds as chemotherapeutic agents, the 2,5-disubstituted pyrrolidines possessing a C_2 symmetry axis may be used as very powerful catalysts in numerous asymmetric reactions. It is for all these reasons that synthetic chemists have chosen these as target molecules and hence an increasing number of reports appear in the literature. This presentation will focus on the stereoselective syntheses of 2,5-disubstituted pyrrolidines and will be subdivided in two main sections : (1) where the 5 membered ring is formed by a stereospecific method and (2) where the already formed ring is functionalized at the 2 and 5 positions.

1 Syntheses with formation of the pyrrolidine ring

1.1. Cyclizations of bis-homoallylic amines

1.1.a - Radical Cyclization

Numerous syntheses of substituted pyrrolidines by intramolecular cyclisation of δ- alkenyl amines *via* the aminyl radical have been reported in the literature : photolysis[8], thermolysis of N-chloroamines[9] and anodic oxidation of lithium amides and hydroxylamines[10,11] are among the most encountered methods. Two major procedures have been elaborated : the anodic oxidation of γ,δ-unsaturated lithium amides leading stereospecifically to *cis* 2,5-disubstituted pyrrolidines[10], and the intramolecular cyclization of N-chloroalkenylamine in the presence of tributyltin hydride and azoisobutyronitrile (*n*-Bu3SnH-AIBN) giving rise almost exclusively to *trans* -2,5-disubstituted pyrrolidines[11] (Figure 1).

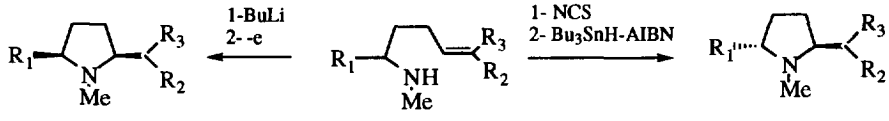


Figure 1

Tokuda *et al* have studied these reactions and the results obtained are summarized in Table 1:

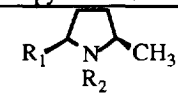
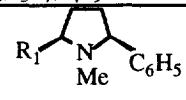
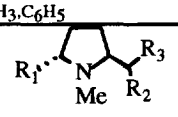
react. cond.	yield	d.e	pyrrolidines	ref.
BuLi/ -e	2 to 52 %	100 % - *cis*	 R1=H,CH3,C2H5,C6H5,p-CH3C6H4,p-CH3OC6H4 R2=CH3,C3H7,C4H9	10
BuLi/ -e	66 to 85 %	100 % - *cis*	 R1= H,CH3,C6H5	10
NCS/Bu3SnH-AIBN	19 to 63 %	100 % - *trans*	 R1= H,CH3,C6H5 R2= H,CH3,C6H5 R3= H,CH3	11

Table 1

1.1.b - Electrophilic cyclization

A - Intramolecular cyclization

A. 1- Iodocyclization

Takano[12] in 1989 developed a strategy related to the oxygenated cases (for the preparation of THF) : namely, treatment of (*S*)-1-benzyloxy-2-benzoylamine-hex-5-ene **1** by iodide in aqueous acetonitrile, led to the stereoselective formation of the *trans* pyrrolidine, (2*S*,5*S*)-5-benzoylmethyl-2-benzyloxymethylpyrrolidine **2** (Figure 2).

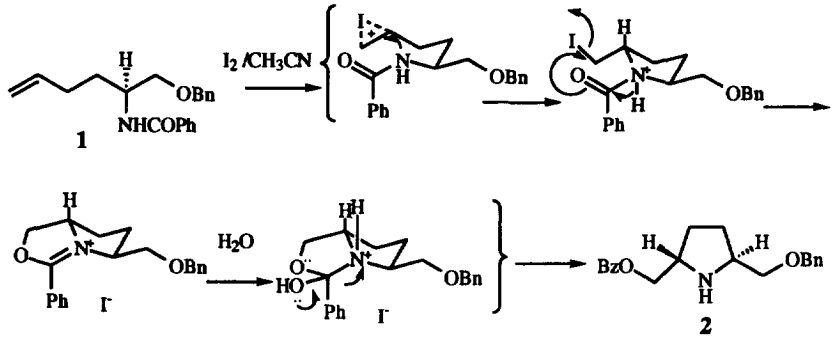


Figure 2

A. 2- Amino- and amidomercuration

Intramolecular aminomercuration (with $HgCl_2$) of δ-alkenylamines have been studied by Perie[13] in 1972, but a mixture of 2,5-disubstituted pyrrolidines and piperidines was then obtained (Figure 3). In 1981 Harding[14] noticed that the regio- and stereoselectivities are better for the amidomercuration than for the aminomercuration and that the *trans* isomer is always the major one formed (*trans*:*cis*/98:2) (Figure 3):

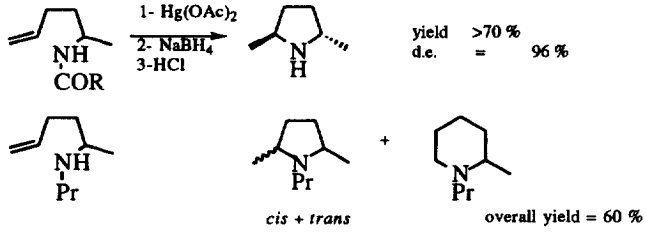
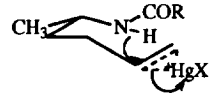


Figure 3

The stereochemistry of the cyclization may be explained by the preferred chair transition state with the equatorial methyl group.



In 1984, Harding showed that ω-alkenylamines, when treated by $Hg(OAc)_2$ in CH_3CN, led to 2,6-disubstituted piperidines, and observed an equilibrium between the *trans* and *cis* products[15]. Takahata[16] used this strategy for the synthesis of *trans* 2,5-dialkylpyrrolidines (with d.e. *trans*:*cis* = 25:1 and e.e. = 98 %) from L-norleucine (Figure 4).

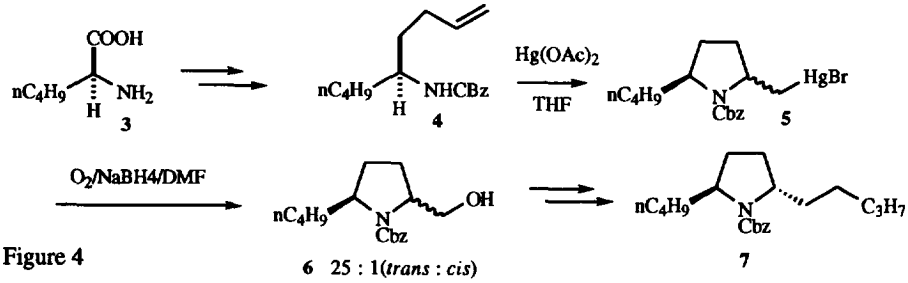


Figure 4

Since then, following this strategy numerous syntheses of 2,5-disubstituted pyrrolidines were performed such as (+) and (-) *trans* 2,5-dimethylpyrrolidines from D or L-alanine, respectively[17,18] (Figure 5).

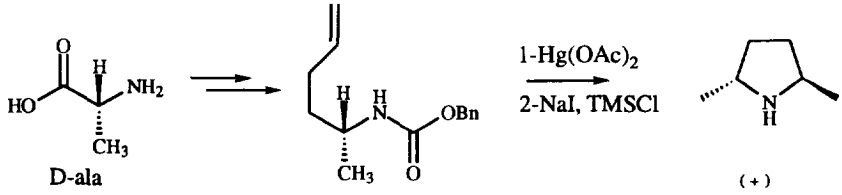


Figure 5

A. 3 - Selenocyclization

Even though this method has been largely used for the synthesis of 2,5-disubstituted THF_S[19] it has only been cited once in the literature for the preparation of pyrrolidines only substituted at C-2[20].

A. 4 - Cyclization of lithium amides

Tokuda[21] reported in 1992 the stereoselective synthesis of 2,5-disubstituted *cis* N-methyl-pyrrolidines (d.e. = 100%) by treating δ-alkenyl amines with a catalytic amount of *n*-BuLi (Figure 6).

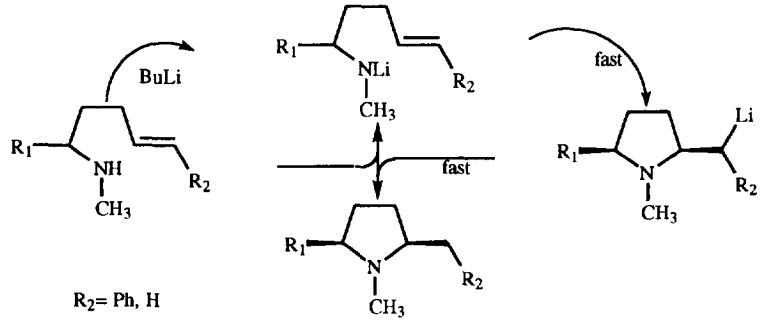


Figure 6

B-Intermolecular cyclization of chiral allylsilanes with imines

Panek[22] treated chiral allylsilanes with N-acylimines generated *in situ* from arylacetals or aldehydes and observed that at temperatures between -78°C and -20°C, N-acylhomoallylic amines are obtained whereas at temperatures between -100°C and -78°C N-acylpyrrolidines are formed (Figure 7).

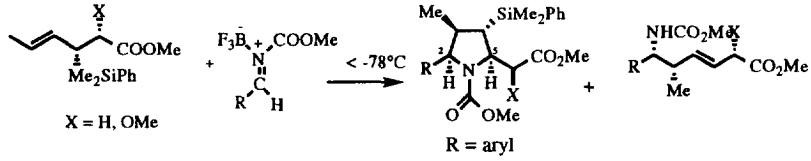
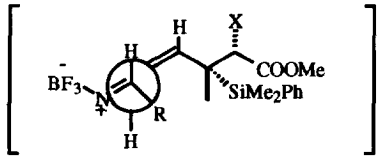


Figure 7

Therefore when (3*R*)-(*E*)-crotylsilane reacted, in the presence of BF3-Et2O at -100°C, with the imine obtained from dimethylacetalbenzaldehyde and methylcarbamate, a mixture of homoallylic amines and pyrrolidines is obtained (ratio=1:12), in which the major pyrrolidines are *cis*, with inversion of the absolute configuration at C-5 and yields ranging from 47% to 72% depending on the nature of R and X. It is worth noting that arylamines are more reactive and give higher yields of pyrrolidines than acetals and that aliphatic aldehydes do not give rise

to the corresponding pyrrolidines. The formation of the major *cis* isomer may be explained by the transition state in which the C-C bond is formed by an *anti* S_E' addition.



1.2. 1,3-Dipolar cycloadditions

The 1,3-dipolar [4πs+2πs] cycloadditions are among the most efficient methods for the preparation of pyrrolidines and pyrrolines[23], and have been reviewed recently[24]. Compounds with 4π electrons, named 1,3-dipole, is formed by 3 atoms with at least one heteroatom, and can be drawn as a zwitterion where the positive charge is localized on the central atom and the negative charge distributed on the two terminal atoms. Compound with 2π electrons is generally an alkene and is named the dipolarophile (Figure 8):

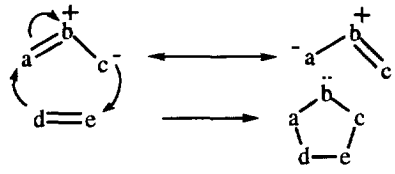


Figure 8

These cycloadditions are concerted and usually regioselective and highly stereoselective. Two types of allylic dipoles are used in order to prepare polysubstituted pyrrolidines : (i) azomethine ylides, and (ii) nitrones

1.2.a. Azomethine ylides

Imines of α-aminoesters are known for reacting with electron deficient alkenes in the presence of Lewis acids to give polysubstituted pyrrolidines (Table 2).

The metallodipole is presumably formed by coordination between the metallic ion and the nitrogen atom and the carboxylic group of the imine, followed by deprotonation. Addition of a tertiary amine would favor the formation of the metallodipole (Figure 9).

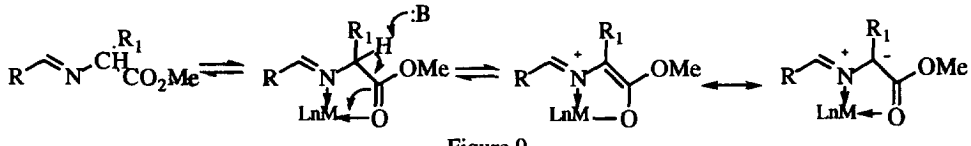
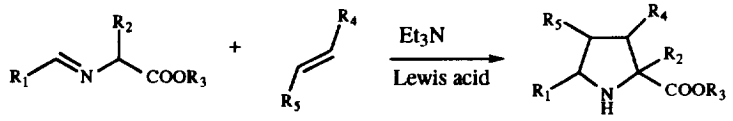


Figure 9

After the study realized in 1988[25] it seems that AgOAc is the most efficient catalyst and acetonitrile the solvant of choice, for the stereospecific preparation of 2,5-disubstituted pyrrolidines. However, it has been shown that the use of LiBr reversed the *exo-endo* selectivity of the reaction compared to AgOTf[26]. Recently asymmetric 1,3-dipolar cycloadditions of azomethine ylides[24] appeared in the literature following 3 main strategies : (i) use of chiral dipolarophiles, (ii) use of chiral azomethine ylides, (iii) use of chiral catalysts.



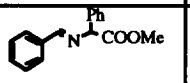
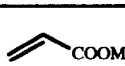
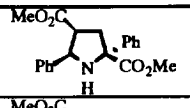
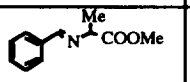
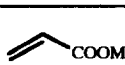
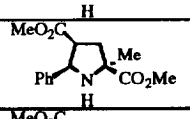
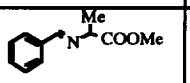
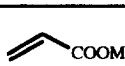
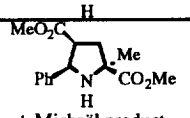
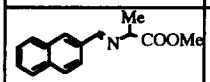
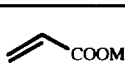
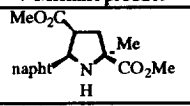
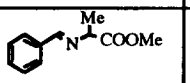
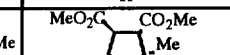
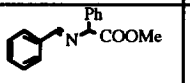
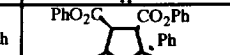
imine	Lewis acid	dipolarophile	product	solvent	yield%
	LiBr			CH_3CN	100
	AgOTs			THF	81
	LiBr		 + Michaël product	CH_3CN	90 (1.2:1)
	AgOAc			CH_3CN	100
	AgOAc			THF	90
	LiBr			THF	85

Table 2

a. - Chiral dipolarophile

Kanemasa[27] in 1991, reported the synthesis of 2,5-*cis* polysubstituted pyrrolidines by cycloaddition of azomethine ylides with α,β-unsaturated esters bearing a chiral imidazoline (Figure 10).

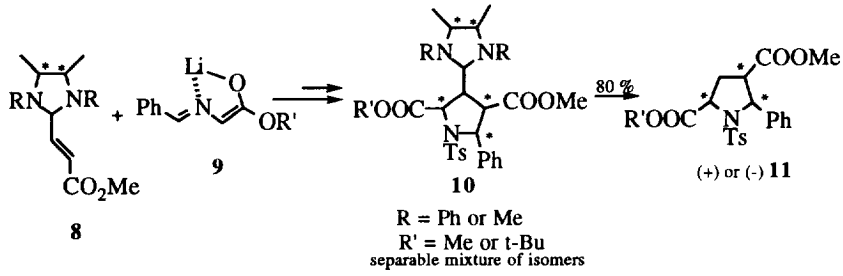


Figure 10

Pyrrolidines **11** are enantiomerically pure, but Kanesama noted a large difference of selectivity for the formation of compounds **10**, depending on the nature of R and R' substituents (d.e. ranging from 10 to 100%).

In 1993 and in 1995, Pätzel[28,29] used chiral α,β-unsaturated enones bearing an alkoxy or an amino group at the γ position such as **12** which reacted with azomethine ylides **13** in the presence of DBU/AgOAc or LiBr, giving rise to enantiomerically pure pyrrolidines **14** with 2,5-*cis* configuration in 60 to 98 % yields, depending on the nature of the substituents at C-5 (phenyl or pyridine) and at C-3 (Figure 11).

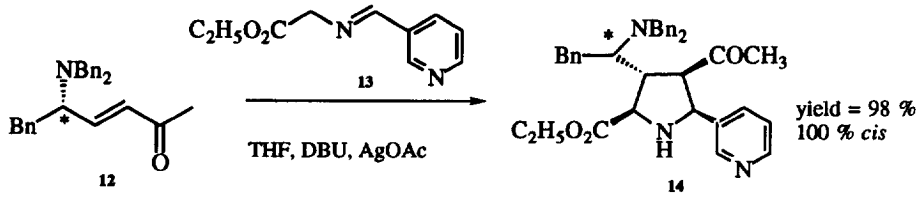


Figure 11

Recently an australian team[30] reported the synthesis of pyrrolidines **19** *via* a 1,3-dipolar cycloaddition of azomethine ylides **16** and chiral oxazolidinones **15** with excellent regioselectivity and an *exo*-diastereoselectivity (Figure 12).

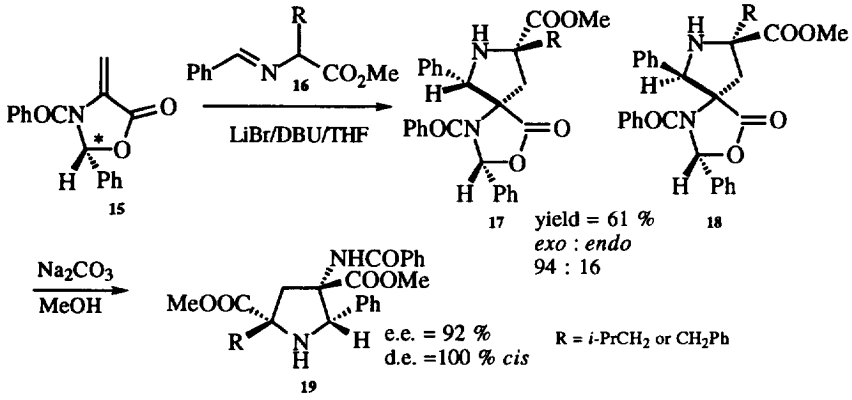


Figure 12

The preference for the exo cycloaddition may be due to the chelation between lithium, N-benzoylcarbonyl group and azomethine ylide (Figure 13).

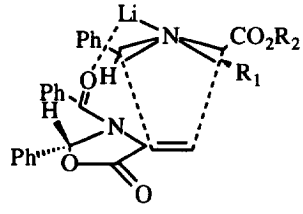


Figure 13

b. - Chiral azomethine ylide

Williams[31] described in 1992 the asymmetric 1,3-dipolar cycloadditions of azomethine ylides derived from (5*S*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one **20**, with several aldehydes and dimethyl maleate. The reactions are *endo*-selective and allow the formation of three contiguous stereogenic centres out of the four centres of the pyrrolidine so formed, with excellent stereochemical control (Figure 14).

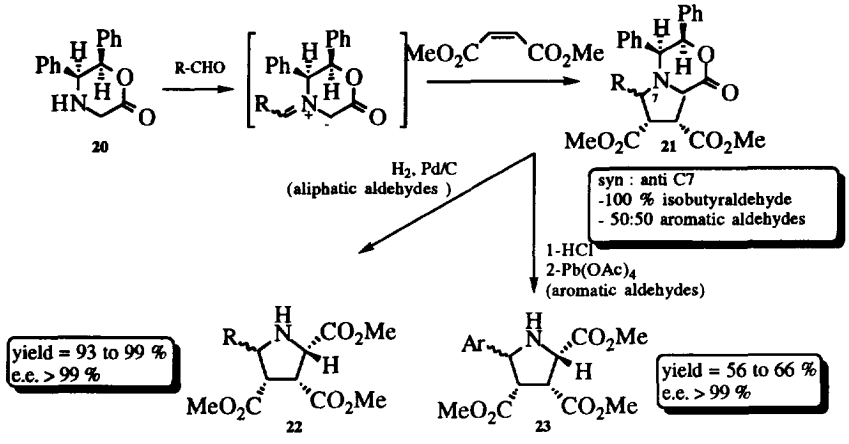


Figure 14

Williams noted the lack of stereoselectivity at C-7 (C-5 of the pyrrolidine) in all cases except with isobutyraldehyde which afforded a single diastereoisomer. Harwood[32] in 1991 described cycloadditions of chiral azomethine ylides (from 4-phenyloxazolidine-(-)8-phenylmenthyl ester), with excellent facial and *endo/exo* stereoselectivities (Figure 15):

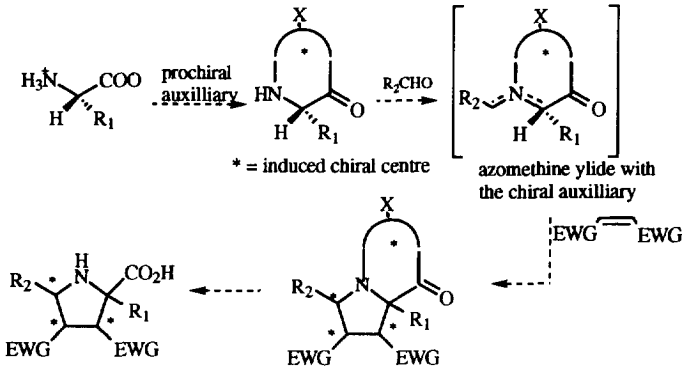


Figure 15

The use of 5-(*S*)-phenylmorpholinone **24** as the chiral auxiliary, allowed the preparation of enantiomerically pure 2,5-disubstituted pyrrolidines[33] **26** (Figure 16):

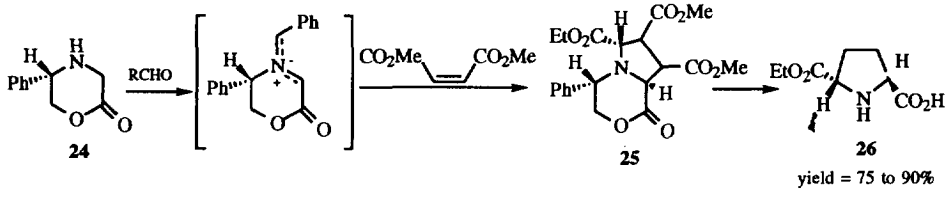


Figure 16

Garner[34] in 1994 used the sultams **27** for the 1,3-dipolar cycloadditions of their derivatized azomethine ylides **28** leading to the *cis endo* pyrrolidine adducts (Figure 17).

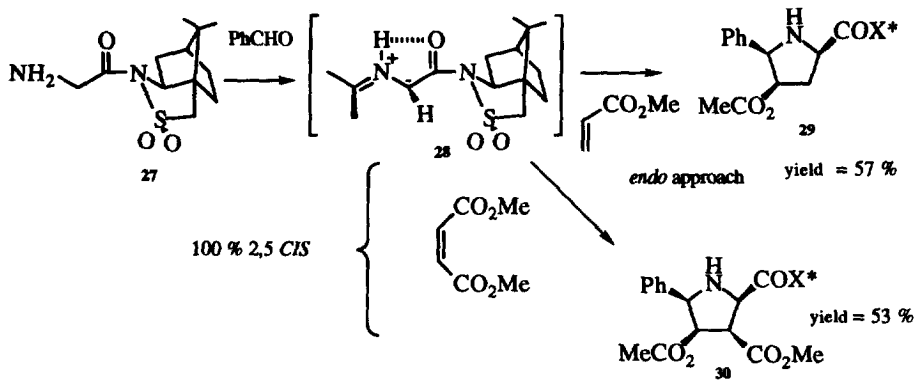
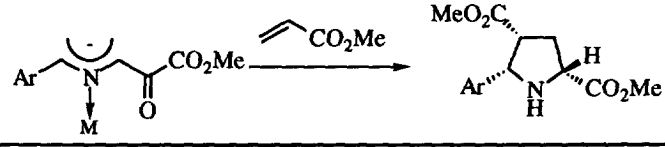


Figure 17

c- Use of chiral catalysts (e.g. ephedrine)

Grigg[35] in 1991 performed the addition of methyl acrylate with imines, obtained from glycine methyl ester, in the presence of Lewis Acids and ephedrine; a few examples are reported in the following table (Table 3):



imine	cat : ephedrine*	rdt %	e.e. %
Ar = 2-naphtyl	$MnBr_2$ (1:4)	64	60
Ar = 2-naphtyl	$CoCl_2$ (1:2)	84	96
Ar = 4 Br-C_6H_4	$CoCl_2$ (1:2)	67	95

Table 3: ephedrine* = (1*R*,2*S*)-N-butyl-ephedrine

It is note worthy that the best result is obtained with $CoCl_2$ in the presence of 2 moles of N-butyl-ephedrine in methyl acrylate (96 %e.e.). Bonnet-Delpon[36] described the synthesis of 2,4,5-trisubstituted-3-trifluoromethyl-2,4-dicarboxylates pyrrolidines *via* a 1,3 dipolar cycloaddition with a good regio- and stereoselectivity (Figure 18).

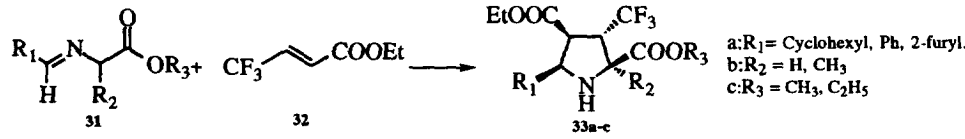


Figure 18

Ethyl (*E*)-4,4,4 trifluorobut-2-enoate **32** reacted with metallo-azomethine ylides **31a-c** obtained from amines derived from glycine (or alanine) esters, in the presence of AgOAc, giving rise to *cis* trifluoromethylated pyrrolidines **33a-c** with 60 to 83 % yields.

1.2.b. Nitrones

In this section, we discuss 1,3-dipolar cyclizations of cyclic nitrones, even though this section could appear in the second part in which the methods for the preparation of 2,5-disubstituted pyrrolidines from already formed 5 membered rings are treated . Tufariello[37] noted in 1986 that cycloadducts **35**, obtained by addition of 1-oxyde-1-pyrroline **34** on monosubstituted alkenes in the presence of a carboxylic peracid, allowed the regiospecific access to aldonitrone **36** (Figure 19) :

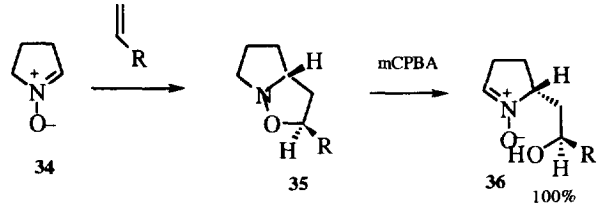


Figure 19

A second cycloaddition will stereoselectively lead to *trans* 2,5-dialkyl-pyrrolidines, generally with good d.e. Asrof Ali[38] in 1993, described the synthesis of *cis* 2,5-disubstituted pyrrolidines and showed that *trans* cycloadducts may be converted to the *cis* pyrrolidines. Nitrone **38** obtained by oxidation with metachloroperbenzoïc acid (*m*-CPBA) of cycloadduct **37**, may be submitted to a cycloaddition with 1-hexene, to afford the *trans*-**39** (70%) through an *exo* attack on the less bulky face of the nitrone. Pyrrolidine **40** is then obtained by treatment of **39** by zinc (0) and acetic acid. When **39** is submitted to a treatment with *m*-CPBA in ethanol, followed by hydrogenation in ethanol-acetic acid, pyrrolidine **42**, with a *cis* configuration is formed (in 92 % yield and e.e. = 100%). This approach, from the nitrones, presents the strong advantage to allow the stereospecific preparation of either the *trans* or *cis* 2,5-dialkylpyrrolidines (Figure 20).

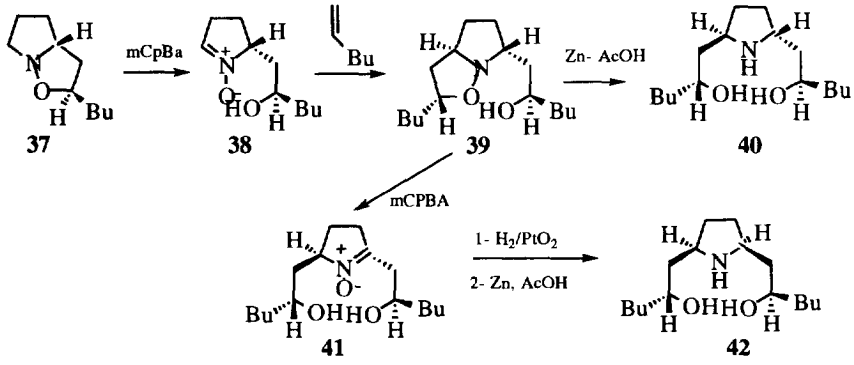


Figure 20

1.2.c. Cycloaddition of azapentadienyl anions

In 1994 Pearson[39] reported the synthesis of 2-alkenylpyrrolidines **45** by anionic cycloaddition of 2-azapentadienyl anion **44** with electron rich alkenes. It is note worthy that this reaction is complementary to those performed by cycloaddition of azomethine ylides which required electron deficient alkenes. 2-azapentadienyl anions are generated by a transmetallation reaction of α,β-unsaturated imines **43** bearing a N-[1-(tri-*n*-butylstannyl)]alkyl group, by action of butyllithium, and added on alkenes to give 2-alkenylpyrrolidines through anionic cycloaddition (4πs+2πs) followed by treatment with an electrophile (Figure 21). Yields are ranging from

43 to 93 %, depending on the nature of the alkene and the electrophile used. In any case, the 2,5 *cis* pyrrolidines **45** are formed, due to the "W" shape (*trans*) of the anion, but a mixture of regio- and stereomers at the positions C-3 and C-4 is observed.

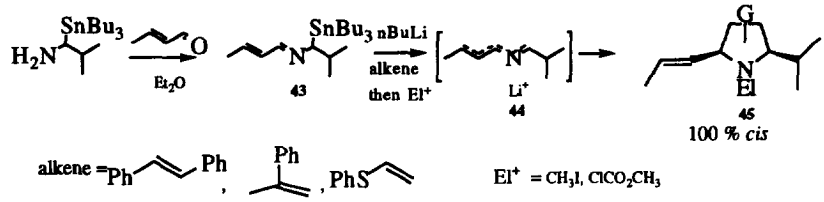


Figure 21

1.3. Reduction-cyclization of γ-azaderivative ketones

1.3.a. Reductive cyclization of γ-aminoketones

In this chapter the reductive amination of γ-aminoketones in the presence of hydrogen and a metal such as Pt or Pd will be presented (Figure 22).

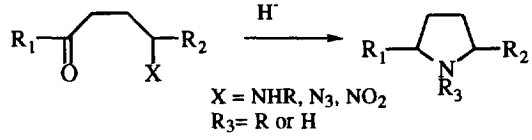


Figure 22

A- Hydrogenation of nitrones

Yoshikoshi[40] reported in 1990 the synthesis of 2,5-dialkylpyrrolidines **49** by hydrogenation of acetyl-nitronates **48** prepared from enolates **46** and nitroalkenes **47** (Figure 23). Unfortunately, the diastereoselectivity is low : 64 to 72 % in favor of the *cis* isomer.

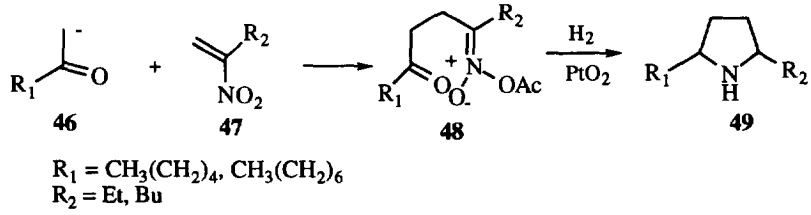


Figure 23

Oppolzer[41] in 1994 described the synthesis of 2,5-dialkylated pyrrolidines **56** *via* a cyclic and chiral nitrone **52** obtained by electrophilic α-hydroxyamination of a chiral sultam **50** (Figure 24). Nitrone **52** obtained from compound **50** is diastereoselectively reduced by NaBH3CN leading to N-hydroxy-pyrrolidine **53**. The chiral auxilliary is then removed by thermolysis through a decarboxylation of the intermediate oxazetidin-4-one **54**, affording the cyclic imines **55**. Addition of an organometallic reagent (e.g. *n*-Buli/CeCl3, 3-butenylMgBr/CeCl3) on the non isolated intermediate **55** led to the 2,5-disubstituted pyrrolidines **56**. Pyrrolidines **56** are thus obtained enantiomerically pure with overall yields ranging from 48 to 60 % from **53**, depending on the nature of R_1 and R_2 and with d.e. = 87 to 99 % in favor of the *trans* isomers.

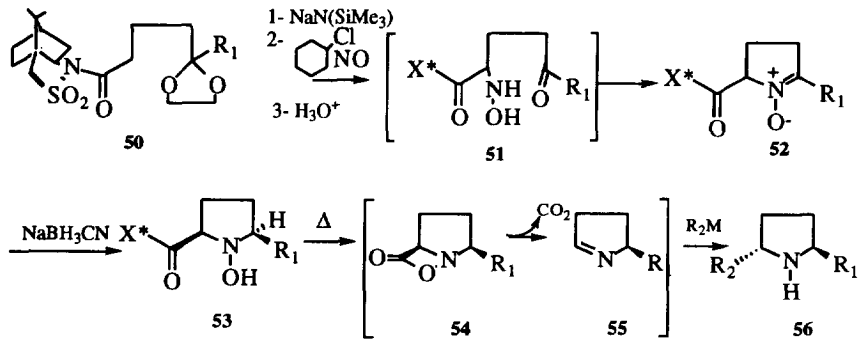


Figure 24

B- Hydrogenation of nitroketones

Hydrogenation of nitroketones is very often used for the synthesis of aza-heterocycles (indolizidine, pyrrolidine or piperidine). Kloetzel[42] in 1947 described the first synthesis of polysubstituted pyrrolidines through the hydrogenation of γ-nitroketones. For instance the *cis* 2,5-disubstituted pyrrolidine **58** was prepared by Stevens[43] in 1982, from γ-nitroketones **57** (Figure 25).The *syn*-addition of hydrogen on the intermediate pyrroline, allows the formation of the thermodynamic *cis* product, monomorine I. This procedure has been used since then by several authors : e.g. Hesse, who described in 1989[44] and 1991[45] the synthesis of *cis* 2,5-disubstituted pyrrolidines.

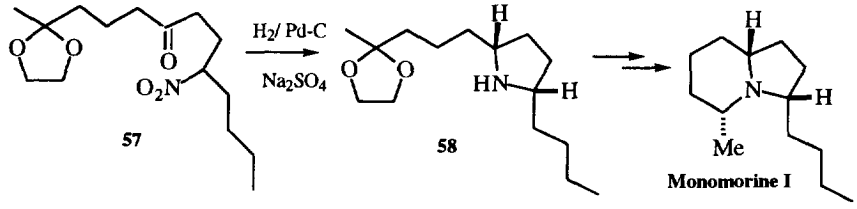


Figure 25

C- Reductive amination of azidoketones.

Most of the syntheses of 2,3,4,5-tetrasubstituted pyrrolidines are built on *via* an azidoketone, as described by Paulsen[46] in 1967 (Figure 26):

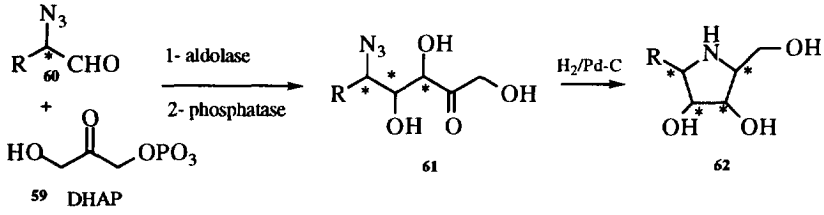


Figure 26

Chiral α-azidoaldehydes **60** are first condensed with DHAP (dihydroxyacetone phosphate) **59**, through an aldolase catalyzed reaction. Then the azidoketone **61**, after removal of the phosphate group, is hydrogenated on palladium to give the expected azasugars **62**. Fischer[47] in 1990 used this sequence. Since then numerous studies were reported in the literature and are summarized in the following table (Table 4):

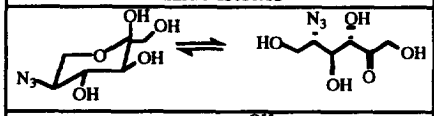
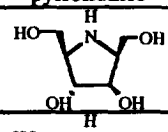
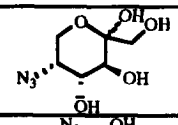
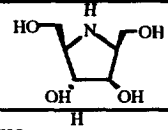
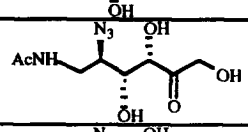
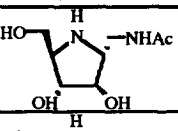
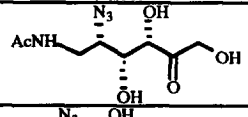
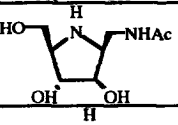
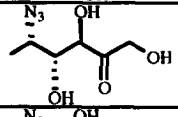
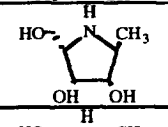
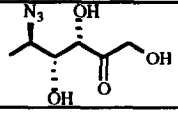
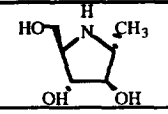
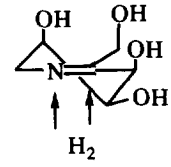
azidoketones	yield%	d.e.%	pyrrolidines	ref.
	97	100		48
	100	100		49
	80	100		50
	80	100		50
	76	100		51
	76	100		51

Table 4

All pyrrolidines described in this table are enantiomerically pure. The diastereoselectivity observed for these reductive aminations was explained by Wong[48] in 1991 in the cases of 2-desoxysugars : hydrogen is added on the imine intermediate, possessing the "twist-chair" configuration, on the opposite face related to the hydroxyles as shown on the following example. The pyrrolidines so obtained will adopt the chair conformation as determined by ^1H NMR spectroscopy.



D- Hydrogenation of aminoketones

Aminoketones **63** can be hydrogenated in the same way than nitroketones and azidoketones. Jegham[52] described in 1989 the synthesis of *cis* and *trans* 2,5-disubstituted pyrrolidines **64** using this strategy. Two different procedures for the hydrogenation step were studied (Figure 27): (i) hydrogenation of aminoketones in the presence of 10 % of palladium on charcoal in methanol allowed the cleavage of the protecting groups of the amino function as well as the reduction of the ketone and the cyclization leading to 2,5-disubstituted pyrrolidines of exclusively *cis* configuration; (ii) treatment of aminoketones with ammonium formate in the presence of 10 % of palladium on charcoal in methanol under reflux, giving a mixture (3:2) of *cis* and *trans* 2,5-disubstituted pyrrolidines.

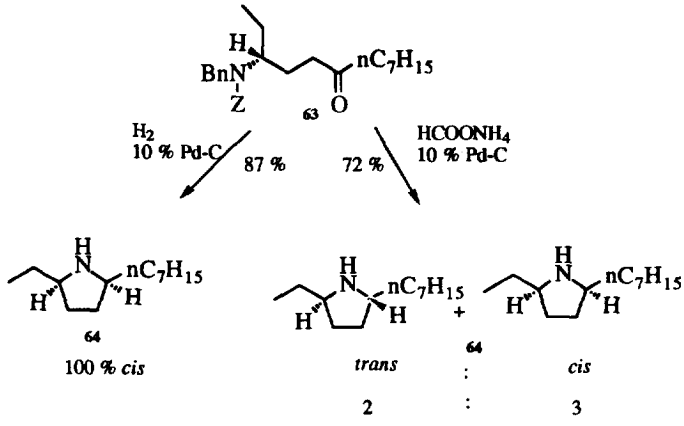


Figure 27

1.3.b. Reductive amination of 1,4-diketones

The reductive amination of 1,4-diketones is one of the oldest method for the preparation of 2,5-disubstituted pyrrolidines (Figure 28).

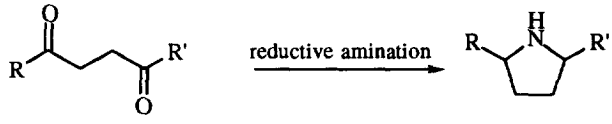


Figure 28

Therefore in 1980, Jones[53] used this strategy for the preparation of natural non symmetrical 2,5-dialkyl-pyrrolidines, and since then a few other authors have used this synthetic pathway, as shown in the following table (Table 5):

It is noteworthy that this method is not stereoselective, since a 1:1 mixture of *cis* and *trans* isomers was obtained. Jones[54] optimized this method and showed that a treatment of 1,4-diketones **65** by an excess of ammonium carbonate allows the formation of the non isolated pyrrole intermediates **66** which are hydrogenated to give the *trans* isomers as the major compounds (d.e. = 85: 15). Alkaloïds **67a-c** were synthesized through this methodology and the *trans* isomer was always the major one (Figure 29).

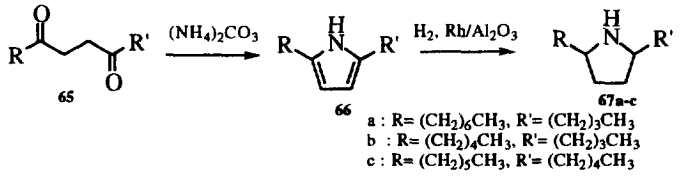


Figure 29

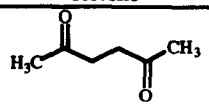
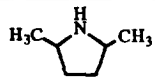
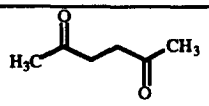
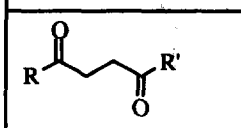
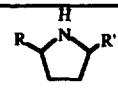
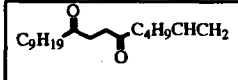
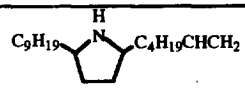
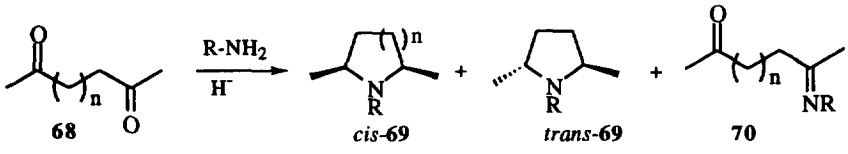
Ketone	reagent	yield%	pyrrolidines (*cis/trans*)
	NH_4OAc KOH $NaCNBH_3$	62	
	NH_4Cl KOH $NaCNBH_3$	0	–
 R,R'=nC_5H_{11},nC_6H_{15}, C_2H_5, nC_5H_{11},$C_4H_9CHCH_2$	NH_4OAc KOH $NaCNBH_3$ then $NaBH_4$	50 to 90 (+pyrrolines)	 50 : 50
	NH_4OAc KOH $NaCNBH_3$ then $NaBH_4$	70 (+pyrroles)	 50 : 50

Table 5

Boga[55] reported in 1994 that several factors may influence the *cis:trans* diastereomeric ratio such as the size of the ring so formed (pyrrolidine or piperidine), the nature of the substituent on the nitrogen, and the nature of the reductive reagent (Table 6).



a : R=H e : R= Me_2N i : R=2,6-Me_2Ph
c : R= $PhCH_2$ f : R= Ph
d : R= Ph(Me)CH g : R=4-MeOPh

Entry	amine R-NH_2	Hydride	Products (yield %)	*cis/trans*
1	NH_4OAc	$NaBH_3CN$	**69a**(62)	50:50
2	Ph(Me)CH-NH_2	$NaBH_3CN$	**69c**(50)	80:20
3	Ph(Me)CH-NH_2	$NaBH(OAc)_3$	**69c**(76),**70c**(22)	76:24
4	Ph_2CH-NH_2	$NaBH_3CN$	**69d**(72),**70d**(4)	75:25
5	Me_2-NH_2	$NaBH_3CN$	**69e**(65)	80:20
6	Ph-NH_2	$NaBH_3CN$	**69f**(99)	30:70
7	4-MeOPh-NH_2	$NaBH_3CN$	**69g**(83), **70g**(4)	40:60
8	2,6-Me_2Ph-NH_2	$NaBH_3CN$	**69i**(35)	64:36

Table 6

Pyrrolidine **69a** is obtained as a 1:1 mixture of *cis:trans* compounds by using ammonium acetate and benzylamine (entry 1), but the *cis*-pyrrolidines are favored when less hindered amines, such as 1-phenylethylamine (entries 2 and 3), benzydrylamine (entry 4) and 1,1-dimethylamine (entry 5) are used. The *cis-trans* ratio of the N-aryl pyrrolidines is affected by the presence of substituents at the *ortho* position (entries 7 and 8). This synthetic pathway was used for the synthesis of polyhydroxylated pyrrolidines, by Reitz[56] in 1994 (Figure 30): The corresponding azasugars **72-74** were obtained with chemical yields ranging from 15 to 68 %, and selectivities from (60: 30:10) to (92:8:0).

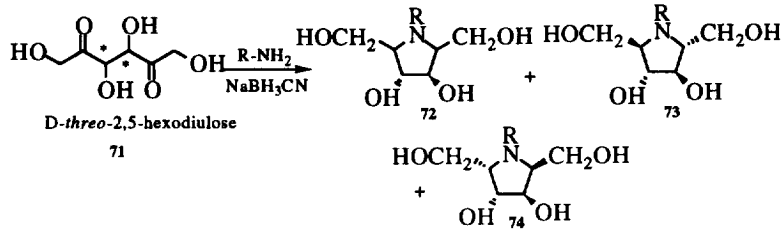


Figure 30

1.4. Cyclizations by S_N2 nucleophilic substitution

1.4.a. - Intramolecular cyclizations

A- Aminoalcohol derivatives

Many examples of syntheses of functionnalized pyrrolidines **76** by intramolecular S_N2 nucleophilic substitution from aminoalcohol derivatives such as **75** are described in the literature. The cyclization is usually stereospecific and a very little epimerisation occurs during the process (Figure 31):

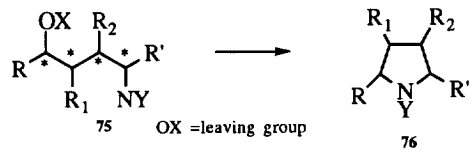


Figure 31

Several examples of cyclization of γ-mesylated amines are given in the following table (Table 7): It is noteworthy that the non isolated aminoalcohol derivative may be obtained through a diastereoselective addition of ammonia to α,β-unsaturated esters **77**, as described by Wightman[64] (Figure 32):

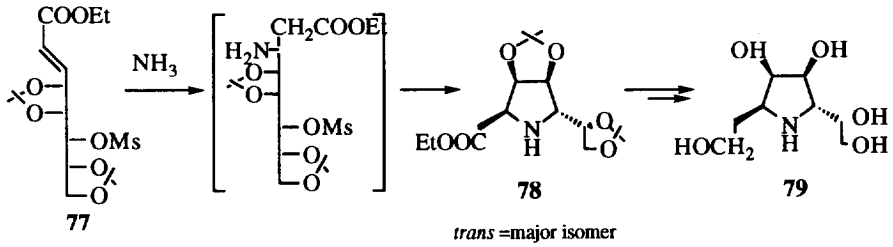


Figure 32

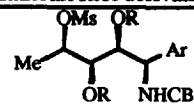
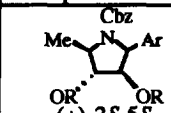
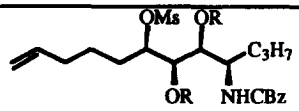
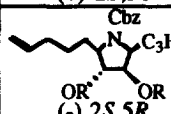
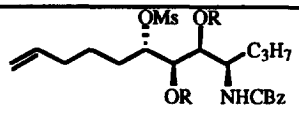
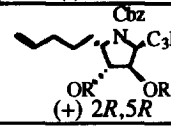
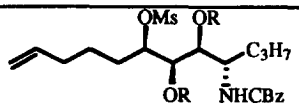
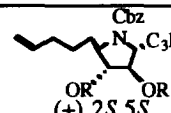
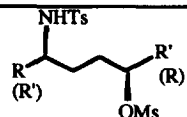
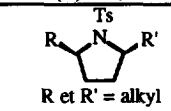
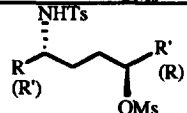
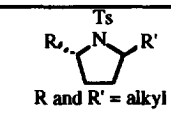
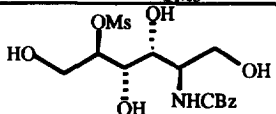
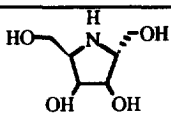
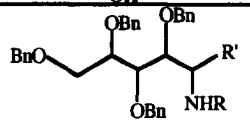
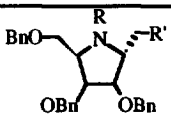
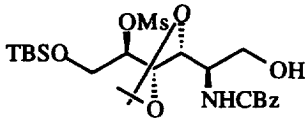
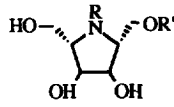
aminoalcohol derivatives	reagent	products	yield%	d.e.%	e.e. %	ref.
	H_2 Pd-C	 (+) 2*S*,5*S*	75	100 *cis*	100	57
	*t*BuOK	 (-) 2*S*,5*R*	83	100 *cis*	100	58
	*t*BuOK	 (+) 2*R*,5*R*	72	100 *trans*	100	59
	*t*BuOK	 (+) 2*S*,5*S*	71	100 *trans*	100	59
	K_2CO_3	 R et R' = alkyl	89 to 90	>98 *cis*	-	60
	K_2CO_3	 R and R' = alkyl	89 to 97	>95 *trans*	-	60
	AcONa Pd/C		78	100 *trans*	100	61
	Tf_2O Pyr	 R: CH_2Ph or alkyl R': $OCH{=}CH_2$ or alkyl	71to 73	100 *trans*	100	62
	Tf_2O Pyr	 R: CH_2Ph or alkyl R': $OCH{=}CH_2$ or alkyl	62	100 *cis*	100	63

Table 7

MacGavrey[65] and Wightman reported that addition of ammonia was dependent both on the stereochemical relationship of the alkene and the bulkyness of the acetal[66]. The major isomer formed was the *trans* pyrrolidine **78** (d.e.=9:1), as shown by the transition state depicted on Figure 33.

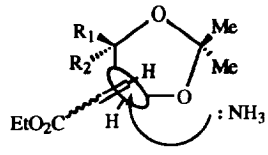


Figure 33

In 1993 Wightman[67] synthesized the hindered pyrrolidines **82** through the same sequence (Figure 34):

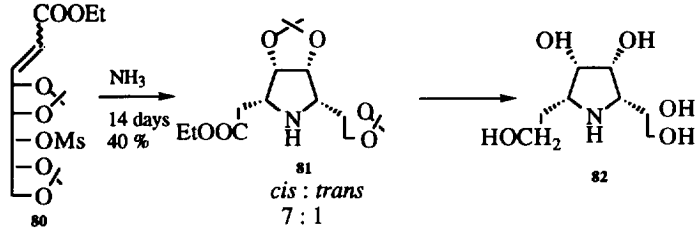


Figure 34

Kibayashi[68] stereospecifically synthesized in high yields (+)- and (-)-2-butyl-5-pentyl-pyrrolidines **85** from azidoalcohols **84** obtained from homochiral diepoxides **83** (Figure 35).

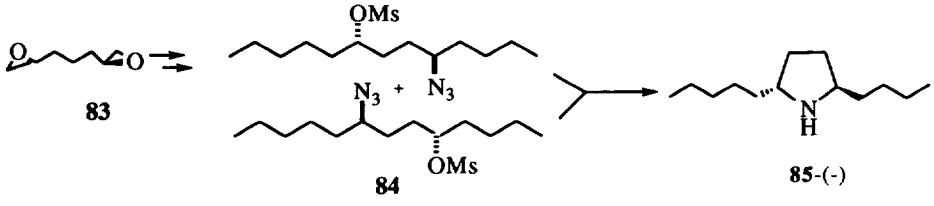


Figure 35

Kibayashi applied this strategy to the synthesis of (+)-(2*S*,5*S*)- and (-)-(2*R*,5*R*)-2-[4(benzoyloxybutyl]-5-pyrrolidines with excellent yields and total stereospecificity[69].

B- Nucleophilic opening of aziridines

Depezay[70] described the nucleophilic opening of bis-aziridines **86** by phenylthiolates ions or azides, followed by cyclization into pyrrolidines. A mixture of polysubstituted pyrrolidines **88b** and piperidines **88a** was thus obtained (Figure 36). Usually, pyrrolidines **88b** are the major compounds so formed (along with 7 % of piperidines **88a**) with chemical yields ranging from 51 to 84 % .

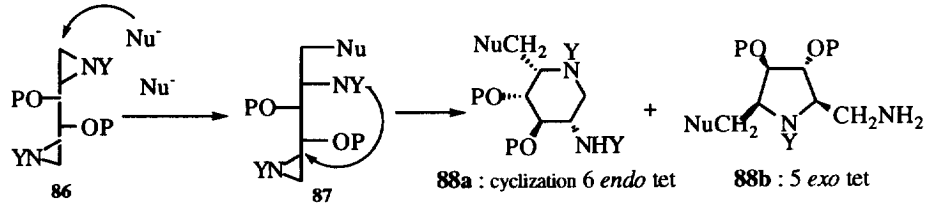
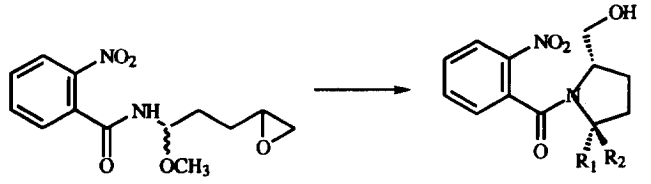


Figure 36

C- Aminoepoxides

Intramolecular cyclization of γ-aminoepoxides is a very attractive method for the preparation of 2,5-disubsituted pyrrolidines. Langlois[71] in 1986 used this strategy for the synthesis of neothramycines (Figure 37).



89 **90** a : $R^1 = OCH_3$, $R^2 = H$; b : $R^1 = H$, $R^2 = OCH_3$

Figure 37

Starting with a mixture of products **89**, 2 diastereomers **90a** and **90b** were obtained with 24 and 46% yield respectively (d.e. = 22 %). In 1992 Baldwin[72] synthesized a 1:1 mixture of *cis* and *trans* 2,5-dicarboxylic acid pyrrolidines through an identical method. Biellmann[73] in 1992 proposed a modification of this strategy : in a stepwise manner, first the C-4-C-5 bond is created with the control of the configurations and then the N-C-2 bond by nucleophilic substitution of the aminoepoxide. The dianion of propynylamine **91** (Figure 38) is obtained by treatment with LDA, and reacted with the bromide **92** leading to an unseparable mixture (30:70) of aminoepoxides **93** with 60% chemical yield. The mixture of **93** is then either treated by silica gel at 65°C giving a mixture of products **94** (*cis*:*trans*/1:9), or by trifluoroacetic acid at 0°C leading to pyrrolidines **94** with a 15:85/*cis*:*trans* ratio.

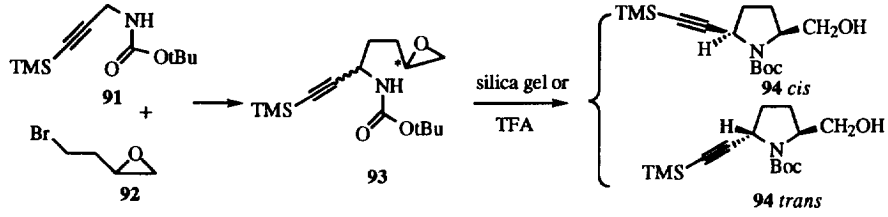


Figure 38

Sasaki[74,75] described the syntheses of 4 isomers of 2,5-disubstituted pyrrolidines, using this strategy (Figure 39). α-Sulfonyl carbanion **96** regioselectively reacted with glycydic triflate **95** to give epoxide **97** which cyclized to lead to 2,3,5-trisubstituted pyrrolidines **98** *via* a 5-*exo* opening of the epoxide.

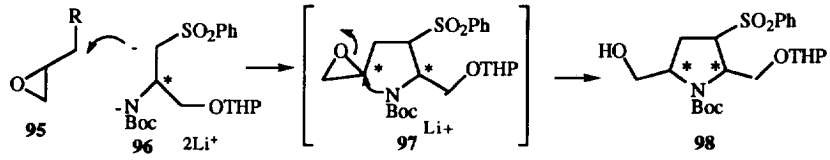


Figure 39

By using either *R* or *S* enantiomer of **95** and **96**, Sasaki prepared all enantiomerically pure stereomers of **98** with excellent chemical yields (90 %) and e.e.s ranging from 84 to 92%. It is note worthy that the best chemical

yields and e.e. are obtained with the triflates rather than with the corresponding tosylates. The "one pot" reduction-cyclization of the γ-azido-epoxides follows the same process, as shown by Fleet[76] (Figure 40) : Hydrogenation in the presence of palladium on charcoal of the azido compound led to the corresponding amine which spontaneously cyclized into the pyrrolidine with 82 % yield and total stereospecificity.

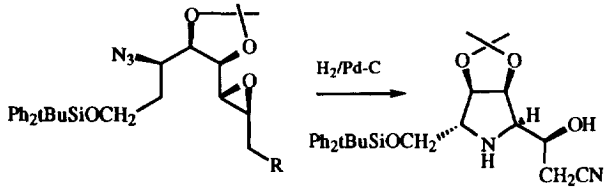


Figure 40

D- Intramolecular cyclization of ω-azidoalkyl boronic esters

Carboni[77] *et al* showed in 1989 that ω-azidoalkyl boronic esters **100**, after reduction, cyclized *in situ* to give the corresponding heterocycles **101** (Figure 41). From diastereoisomerically and enantiomerically pure boronic esters (prepared by asymmetric hydroboration), the corresponding pyrrolidines **102** are obtained with a total control of the configurations and with excellent yields (80 to 89 %, depending on the nature of R_1, R_2 and R_3).

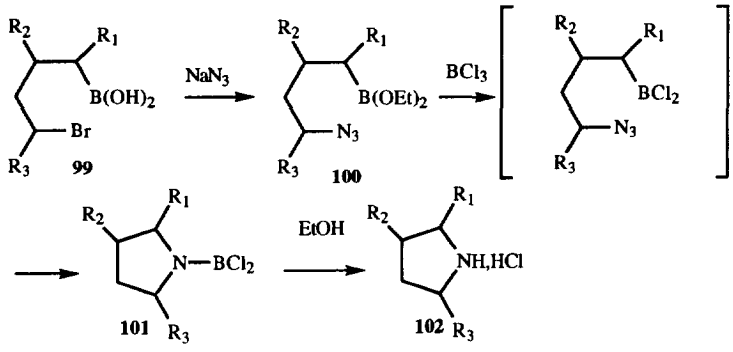


Figure 41

1.4.b. -Intermolecular cyclizations

A- Aminocyclization of 2,5-dibromoadipic acid esters

The preparation of symmetric 2,5-disubstituted pyrrolidines from 2,5-dibromoadipic acid esters **103** and **104** is a very well known method. In the 1960's, Gignarella[78] described this strategy which will be used very often later on[79,80] (Figure 42):

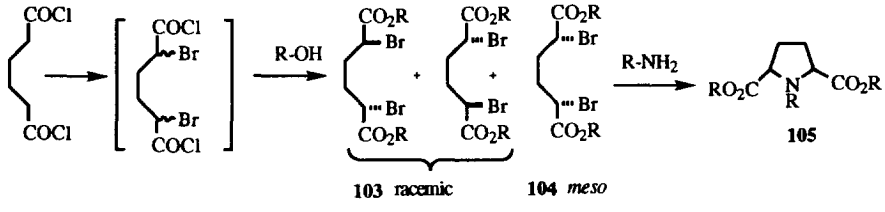


Figure 42

Indeed the *meso* isomer **104** gives the *cis* 2,5-disubstituted pyrrolidine **105** (due to the S_N2 nature of the reaction), whereas the racemic mixture of compounds **103** leads to the *trans* racemic pyrrolidines **105**. Ridley[81] in 1973 and O'Neill[82] in 1990 noticed that the *meso* compound **104** epimerizes into the dl mixture **103** by KBr treatment in dimethylformamide. Seeman[83] in 1923 found that when benzylamine was used, a mixture of stereomers was obtained. In 1992, Yamamoto[84] replaced benzylamine by (-)(*S*-)phenylethylamine and obtained the two diastereomeric *trans* pyrrolidines **106** and the *meso cis* compound **106** which could be easily separated by crystallisation. Then after removal of the chiral group the enantiomerically pure *trans* pyrrolidines **105** were obtained in 24 % for isomer (*S,S*) and 25 % for (*R,R*) isomer and e.e. > 99 % (Figure 43).

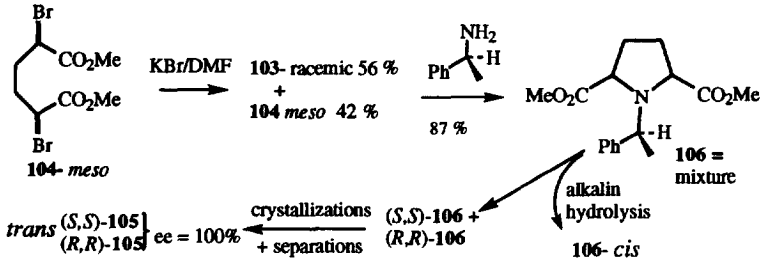


Figure 43

The *trans:cis* stereoselectivity can be improved by using other chiral auxiliaries. For instance Koh[85] in 1994 used (*R*)-pantolactone with benzylamine for the cyclization : both 2,5-dicarboxylic diacid pyrrolidines are obtained with 70:30 *trans:cis* ratios and the two *trans* (*S,S*: and *R,R*) compounds with a 80:10 ratio.

B- Transamination of 1,4-dihydroxy derivatives

Cyclization by nucleophilic attack of 1,4-dihydroxy derivatives by a primary amine to form *trans* 2,5-disubstituted pyrrolidines is a well known reaction directly derived from the studies on the aminocyclizations of 2,5-dibromoadipic acid esters (Figure 44).

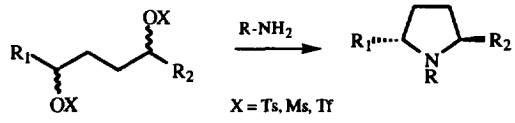


Figure 44

Numerous amines were used : e.g. ammonia, benzylamine, hydrazine, hydroxylamine, allylamine. Several leaving groups were also employed such as tosylates, triflates and mesylates. Usually the stereoselectivity, and the stereospecificity are excellent. In the non racemic cases, the chirality may be introduced by : (i) the diols may be enantiomerically pure and because the cyclization occurs through a S_N2 type reaction, inversions of both stereogenic centres are observed; (ii) a chiral auxiliary such as the amine allows the stereoselective formation of enantiomerically pure pyrrolidines from a racemic mixture of 1,4-dihydroxy derivatives. A few examples are reported in the following table (Table 8):

	R-NH_2	yield%	d.e.%	e.e. %	ref.
diols $\xrightarrow{RNH_2}$	allylamine NH_3 hydrazine benzylamine	33 to 93	100	100	86,87,88, 89,90,91, 92
diol $\xrightarrow{RNH_2^*}$	(*S*) or (*R*) methylbenzyl-amine	68	54	97	93

Table 8

Even though in the case of the reaction of racemic 1,4-dihydroxy derivatives with a chiral amine the diastereomeric excess is not excellent, the synthesis remains interesting since both enantiomers of methylbenzylamine are commercially available, and allows to prepare in a pure form the *trans RR* and *SS* pyrrolidines. Whereas, for the access to enantimerically pure *RR* and *SS* enantiomers, the alternative strategy requires the enantiospecific synthesis of both enantiomers of the chiral starting material.

2. Syntheses from aza-heterocycles

2.1. Syntheses from proline

L-proline is a commercially available α-amino acid possessing a carboxy function at C-2. Functionalization at C-5 will give rise to the 2,5-disubstituted pyrrolidines in a single step.

2. 1. a.- Anodic oxidation followed by a nucleophilic substitution through acyliminiums ions

Shono[94,95] in the 80's, prepared by electrochemical process the α-methoxylated methyl ester of proline with 87 % yield but without diastereomeric excess (Figure 45) :

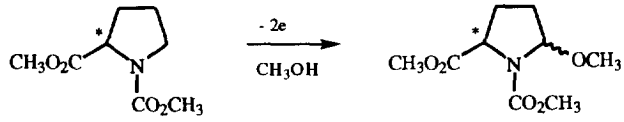


Figure 45

Wistrand[96] in 1986, studied the influence of the hydroxyl group at C-4 (4-hydroxyproline). He observed the formation of a mixture of compounds in a 58:26:16 ratio (*cis:trans* α,α'-disubstituted products) and found that the *cis* isomer can be epimerized into the *trans* product by treatment with BF_3-Et_2O as depicted on Figure 46.

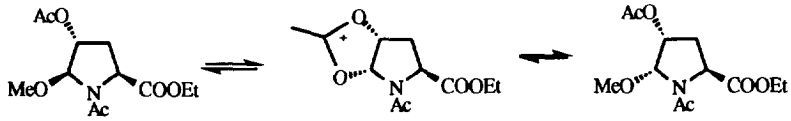


Figure 46

Then starting with these 2-methoxy-5-carbetoxy-proline derivatives, it is possible to perform nucleophilic substitutions at the pseudo-anomeric position. Because of this kind of intermediate is also accessible from pyroglutamic derivatives, this type of reactions will be discussed in the chapter entitled "syntheses from L-glutamic acid".

2. 1. b. -Anodic oxidation followed by radical reaction

Barrett[97] examined the radical cross coupling reaction between a phenylseleno derivative with a vinyltrialkyltin compound (Figure 47): Irradiation of the phenylseleno derivative **108** with hexabutylstannane and either (*E*) or (*Z*) 2-tributylstannylacrylate led to the product **109** as a single *trans* isomer with 67 % yield. The stereospecificity of the reaction is probably due to the steric control of the substituent at C-4. When the 4-desoxy derivatives were treated in the same reaction conditions, a mixture of *cis* and *trans* compounds was thus obtained with a 1:3 ratio.

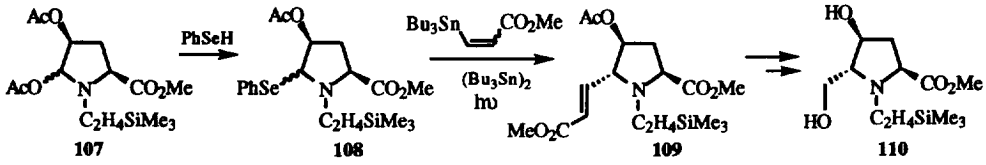


Figure 47

2. 2. Syntheses from glutamic acid

Glutamic acid, possesses 3 advantages which make this natural α-amino acid a very versatile starting material : (i) it is a very inexpensive compound, (ii) commercially available under its (*R*) or (*S*) form, (iii) which can be quantitatively and stereospecifically converted into pyroglutamic acid, a cyclic analogue with a pyrrolidinone ring possessing a stereogenic centre. Syntheses using pyroglutamic acid as starting material can be divided into 4 sections : (i) reductions of the lactam followed by a nucleophilic substitution of the acyliminiums ions, (ii) syntheses through a β-enaminoester intermediate, (iii) or from a thiolactam, (iv) and reactions through an acyclic intermediate obtained by nucleophilic substitution.

2. 2. a. -Reduction followed by nucleophilic substitution of acyliminiums ions

The 2-hydroxy-5-carboxy-pyrrolidine can be obtained from pyroglutamic acid either by a partial reduction of the lactam function or by complete reduction followed by oxidation and cyclization.

A- Partial reduction

The pyroglutamic acid obtained by pyrolysis of the corresponding glutamic acid is partially reduced into the hemiaminal. Then, functionalization of the free hydroxyl followed by nucleophilic substitution allows the access to 2,5-disubstituted pyrrolidines (Figure 48).

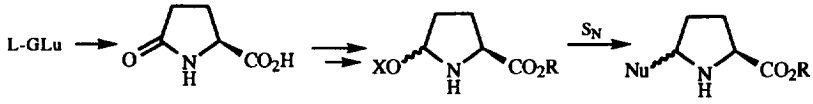


Figure 48

The partial reduction can be performed under several reaction conditions in high yields (Table 9):

reductive reagent/Cn*	yield (%)	ref.
DIBAL-H/2-hydroxymethyl	98	98,100, 101
NaBH4/2-hydroxyalkyl	95	102
LiEt3BH/2-carboxy-4-nitrile	90	99

Table 9 : *Cn = substituent at the C-n position of the lactam

B- Complete reduction

Related hemiaminals can be obtained in a two steps sequence by a first reduction leading to the γ-hydroxylamine which after an oxidation step gives the desired hemiaminal. For instance, Holmes[103] in 1991 used a Swern oxidation for the last step (Figure 49):

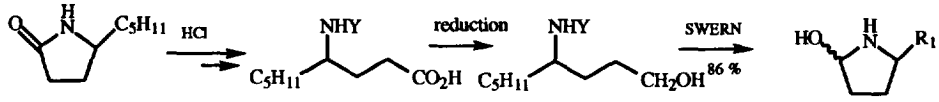


Figure 49

Altman[102] for the synthesis of thymidine analogues used an oxidation with a mixture of tetra-*n*-propylammonium perruthenate and N-methylmorpholine-N-oxyde (Figure 50):

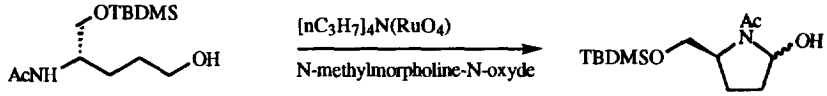


Figure 50

C- Nucleophilic substitution of N-acyliminium ions obtained from L-proline or L-glutamic acid

N-acyliminium ions obtained from the 2-OAc or -OMe pyrrolidinic precursors, are very convenient intermediates for nucleophilic additions. The influence on the stereoselectivity of the reaction of several factors has been studied : e.g. Lewis acid used, nature of the nucleophile and some results are summarized in the following table (Table 10). For the addition of TMSCN on N-carbomethoxy 2-methoxy-5-hydroxymethyl pyrrolidine in the presence of tin tetrachloride ($SnCl_4$) (entries 5 and 6), Langlois[101] explained the reverse selectivity observed by the interaction between the oxygen atom of the hydroxymethyl group with the carbon atom of the N-methoxycarbonyl iminium ion (favoring the attack by CN^- on the opposite face) (Figure 51).

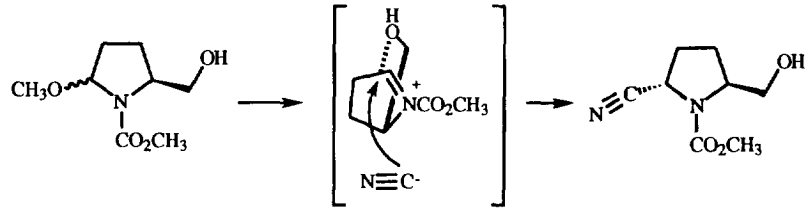
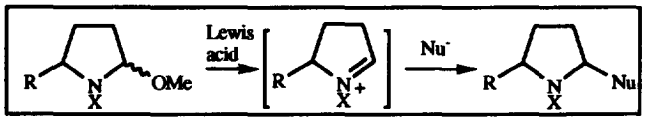


Figure 51

It is worth noting the difference of selectivity of the reaction when either a carbomethoxy group is at position C-5 or a trialkylsilyloxy function (entries 1 and 6). Wistrand observed that the presence of a substituent at C-4 has an influence on the selectivity of the reaction, and that the stereochemistry at this position is also crucial since the selectivity is lower with the 4*S* isomer compared to the 4*R* isomer (entries 8 and 9)[104]. In 1991 Barrett found the same effect when synthesizing bulgecinine (entry 10)[107]. In 1991, Wistrand[104] showed that when cuprates are added to 2-methoxy-5-carbomethoxy pyrrolidines, a complex might be formed as shown on the following scheme (Figure 52), and could rationalize the selectivity observed (entry 12). He then confirmed this hypothesis by studying the reaction of 2-methoxy-5-alkyl pyrrolidine with $BuCu/BF_3$ under the same reaction conditions, and observed the formation of a mixture of the 2,5-dialkylated products in a 1:3 *cis:trans* ratio and in 57 % yield (entry 14).



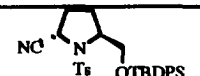
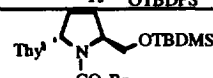
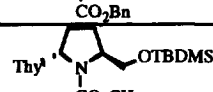
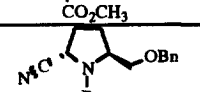
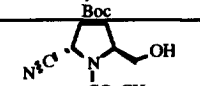
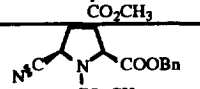
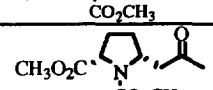
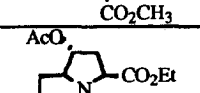
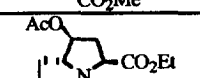
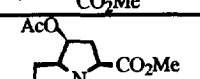
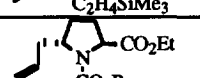
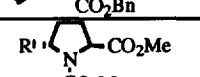
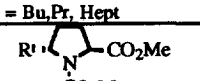
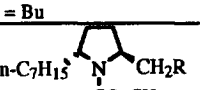
entry	L.A. / Nu	yield%	d.e. %	pyrrolidine	ref.
1	$SnCl_4$ / TMSCN	91	80 *trans*		98
2	$SnCl_4$ / (TMS)2-thymine	64	6 *trans*		102
3	$SnCl_4$ / (TMS)2-thymine	55	50 *trans*		102
4	BF_3-Et_2O / TMSCN	95	38 *trans*		100
5	$SnCl_4$ / TMSCN	89	30 *trans*		101
6	$SnCl_4$ / TMSCN	86	40 *cis*		101
7	 $TiCl_4$	85	40 *cis*		104
8	 BF_3-Et_2O	71	64 *cis*		104
9	 BF_3/Et_2O	70	8 *trans*		104
10	 Me_3SiOTf	84	50 *cis*		97
11	 $TiCl_4$	40	54 *trans*		96
12	RCu BF_3-Et_2O	73 to 84	92 to 94 *trans*	 R = Bu,Pr, Hept	96
13	BuCuCNLi BF_3-Et_2O	15	10 *trans*	 R = Bu	96
14	BuCu/BF_3 BF_3-Et_2O	57	50 *trans*	 R = n-C_3H_7	96

Table 10

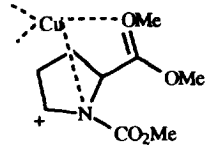


Figure 52

2. 2. b. - Syntheses *via* the β-enaminoesters

The β-enaminoesters **113** are obtained by reaction of the corresponding lactams **111** with dimethylsulfate followed by condensation with either the Meldrum acid[106,108,109] or with 2-acetylbutyrolactone[107] (Figure 53). The β-enaminoesters **113** are decarboxylated (H_3BO_3/Δ or HCl 3N) leading to the corresponding 2,5-disubstituted pyrrolines **114** with chemical yields from 37 to 90% depending on the nature of R_1 and R_2.

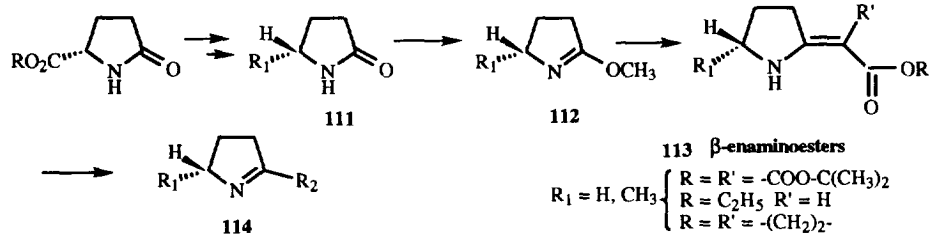


Figure 53

Then, Lhommet[110] studied the reduction of the pyrrolines **114** to obtain the pyrrolidines **115** (Table 11):

reduction cond.	pyrrolidines	*cis* : *trans*	ref.
$AlLiH_4$-Me_3Al	$R_1 = CH_3$ $R_2 = (CH_2)_{10}CH_3$	5 : 95	110
$AlLiH_4$-Ni(acac)$_2$	$R_1 = CH_3$ $R_2 = (CH_2)_{14}CH_3$	70 : 30	110
DIBAL-H	$R_1 = CH_3$ $R2 = (CH_2)_8CH_3$	100 : 0	110
$NaBH_3CN$	$R_1 = CH_3$ $R_2 = (CH_2)_9CHCH_2$	65 : 35	110
$NaBH_4$	$R_1 = CH_3$ $R_2 = (CH_2)_{14}CH_3$	30 : 70	110
H_2-Pd/C HCl 10%	$R_1 = CH_3$ $R_2 = (CH_2)_9CH_3$	100 : 0	107
H_2-Pd/$BaSO_4$	$R_1 = CH_3$ $R_2 = (CH_2)_3OH$	50 : 50	107

Table 11

DIBAL-H seems to be the best reagent in order to get the *cis* pyrrolidines , whereas AlLiH4-AlMe3 allows the access to the *trans* isomers.

2. 2. c - Syntheses *via* the thiolactams

In 1985, Shiosaki and Rapoport[111] described the diastereo- and enantioselective synthesis of *trans* and *cis* 5-butyl-2-heptylpyrrolidines from either D or L-glutamic acid *via* a thiolactam as intermediate. Their strategy is versatile since either the *trans* desired product is obtained (e.d.>99%, e.e.=94%), or the *cis* compound (e.d.>99%, e.e.=94%), from the same intermediate *via* an Eschenmoser reaction (Figure 54).

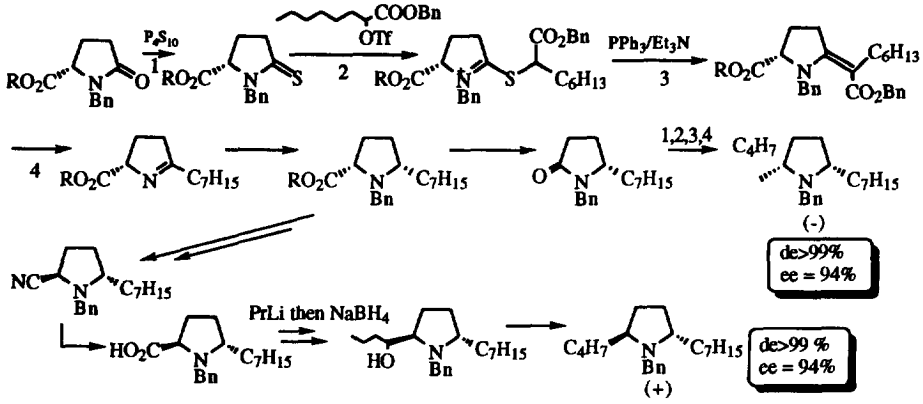


Figure 54

Brossi[112] in 1987 synthesized some (±) *trans* 2,5-dialkylpyrrolidines *via* a thiolactam which was obtained from the *Lukes-Sorm* dilactams **116** (Figure 55).

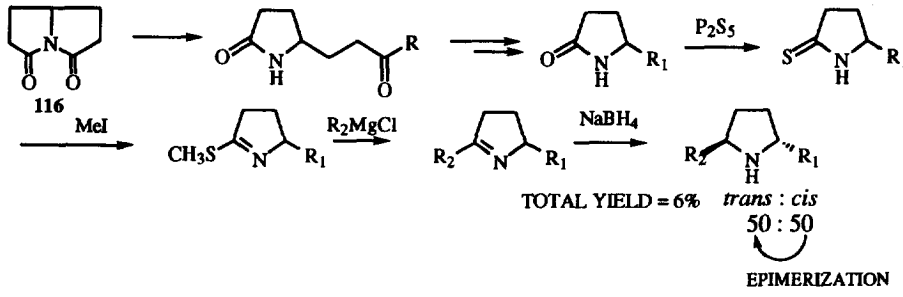


Figure 55

2. 2. d. - Syntheses *via* nucleophilic opening of the pyroglutamic ring

Ezquerra in 1993[113] synthesized the *cis* and *trans* 2,5-dicarboxylic acid pyrrolidines, through the acyclic compound **118** (Figure 56) obtained by opening of N-Boc ethyl pyroglutamate with methyl *p*-tosylsulfinyl lithium anion. Then treatment of **118** by trifluoroacetic acid led to the thioesters **119** which after hydrolysis gave the 2,5-dicarboxylic acid pyrrolidines. Unfortunately the diastereoselectivity of the reaction is low and the chemical yields are ranging from 68 to 70%.

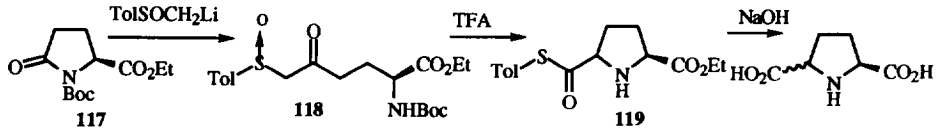
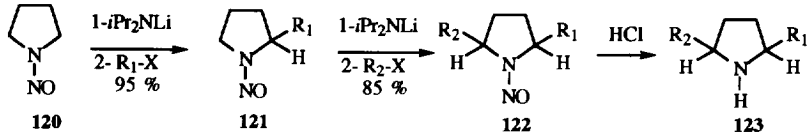


Figure 56

2. 3. Syntheses from commercialy available pyrrolidines and pyrrolines

2. 3. a.- Electrophilic substitutions

In 1976, Fraser[114] synthesized 2,5-dialkylated pyrrolidines *via* alkylation of metallated nitrosamines (Figure 57).



$R_1 = R_2 = CH_2Ph$: total yield= 66 %
$R_1 = C_2H_5$, $R_2 = CH_2Ph$: yield = 33 %

Figure 57

Compound **120** is alkylated twice at the α and α' positions with an excellent regioselectivity and a good stereoselectivity since the *cis:trans* ratios are in favor of the *trans* compounds (d.e. : 85:15 to 62:38), depending on the nature of both the lithium amide and the alkylating reagent. In 1980, Mac Donald[115] described the same type of reaction but starting with a pyrroline derivative and found that the regio-(>97% at α,α'-positions) and diastereoselectivity were excellent (*trans*>95%) (Figure 58) :

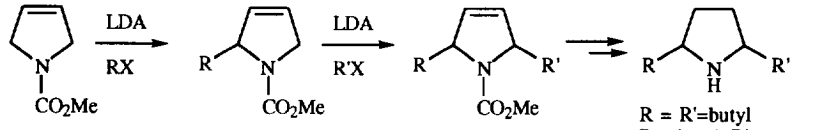


Figure 58

Meyers in 1985, studied the electrophilic substitutions of derivatives of formamidine anions for the preparation of 2,5-dialkylated pyrrolidines (e.g. from enamidine **124**, obtained par lithiation-selenation-elimination of N-*tert*-butylforamidine (TBF) heptylpyrrolidine[116]), (Figure 59).

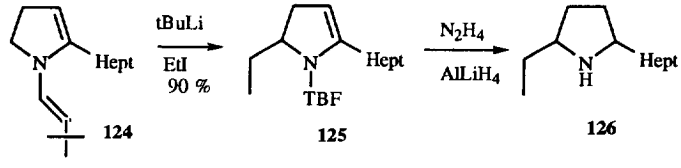


Figure 59

Unfortunately, no selectivity was observed and a 50:50 mixture of *cis* and *trans* isomers was obtained. In 1995, Meyers reported the synthesis of 1,3-dialkylated isoindolines from chiral foramidines[117] (Figure 60) : The desired isoindolines were obtained with 61 to 68% yields and e.e. ranging from 94 to >99%.

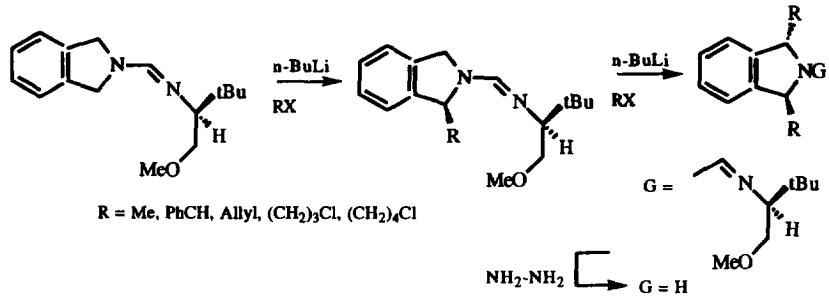


Figure 60

Pandey[118] in 1993, prepared (m.2.1)x-azabicyclo alkanes, using as a key intermediate 2,5-trimethylsilyated pyrrolidines, obtained by treatment of pyrrolidines with *n*-BuLi and TMSCl at -78°C. Beak[119] in 1994 studied the asymmetric deprotonations of pyrrolidines, followed by stereoselective alkylation. The corresponding 2,5-disubstituted pyrrolidines were obtained with excellent d.e and e.e.. For instance, the *trans* -(2*S*,5S) N-Boc-2,5-dimethylpyrrolidine **128** was formed in 3 steps from N-Boc pyrrolidine **127** with 80 % yield, and d.e. = 80% , e.e. >99%, by using *s*-BuLi in the presence of (-)spartein (Figure 61).

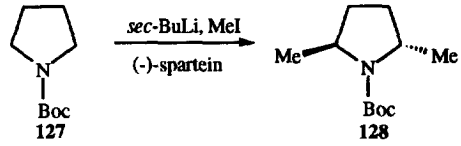


Figure 61

2. 3. b.- Nucleophilic substitutions

Moore[120] noticed that nitrones lead to N-hydroxynitriles in high yields after reaction with KCN (Figure 62).

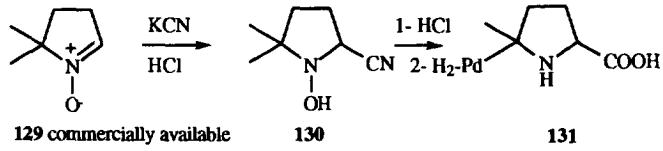


Figure 62

However **131** is not stable enough and is directly protected as its N-Boc derivative with an overall yield of 38%. Magnus[121] in 1994 described the synthesis of 2,5-diazides pyrrolidines **134** by treatment of N-acylated pyrrolidines **132** with the mixture of PhIO/$TMSN_3$ at -25°C (Figure 63). Magnus found that pyrrolidines are more reactive than piperidines, and that α-azidonation increases with the electrondonating power of X. α and α' disubstitution is favored with the N-Boc and N-C_6H_2(-3,4,5-OMe) derivatives leading to the major *trans* compounds.

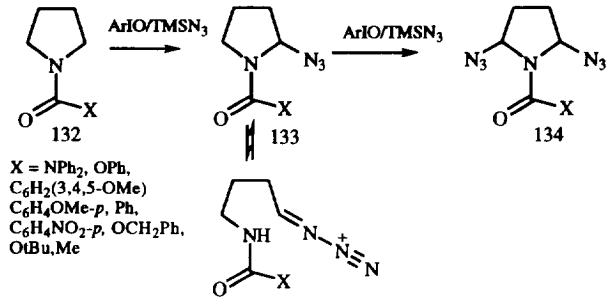


Figure 63

2. 4. Syntheses from pyrrole derivatives

Casiraghi[122] developped the use of N-Boc-2-*tert*-butyldimethylsilyloxypyrrole **135** for the synthesis of natural products. He shown that N-Boc-2-tertbutyldimethylsilyloxypyrrole (TBSOP) **135** adds regio- and stereoselectively on several synthons **136** (Figure 64) leading to α,β-unsaturated-γ-lactams **137**, which can be further reduced and substituted as L-proline or glutamic derivatives **138**.

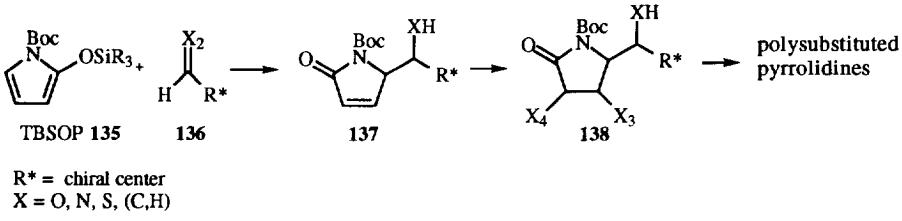


Figure 64

This strategy has been used mainly for the synthesis of azasugars : e.g. N-Boc-4'-azauridine[123] **142** (Figure 65) was prepared from **135** with an overall yield of 64 % and a 92/8 β/α ratio.

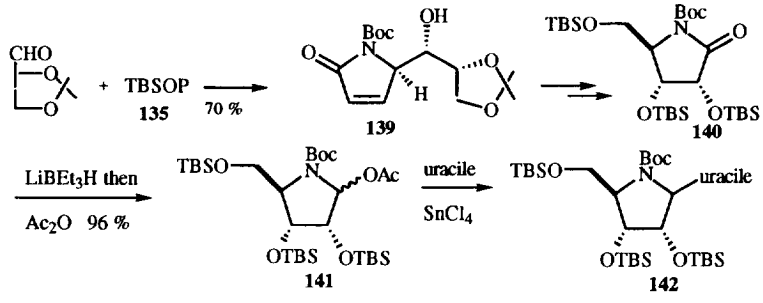


Figure 65

2. 5. Syntheses from bicyclic amino derivatives

This chapter will focus on the preparations of pyrrolidines from bicyclic amino derivatives such as oxazolidones, oxazinones, and oxazolopyrrolidines.

2. 5. a. - Oxazolidinones

A- radical reactions

Shibuya[124] in 1994 proposed the synthesis of 2,5-disubstituted pyrrolidines *via* stereospecific radical cyclization of $\Delta^{4,5}$oxazolidin-2-one **143** (Figure 66). The same year, Shibuya synthesized (+)bulgecinine[125], using the

identical strategy but with the 7-hydroxy compound **144** : the radical cyclization is performed with complete faciale selectivity but with the lack of diastereoselectivity at C-7. Shibuya then oxidized the hydroxyl and reduced the ketone so obtained to give the desired *trans* C-5-C-7 stereochemical relationship.

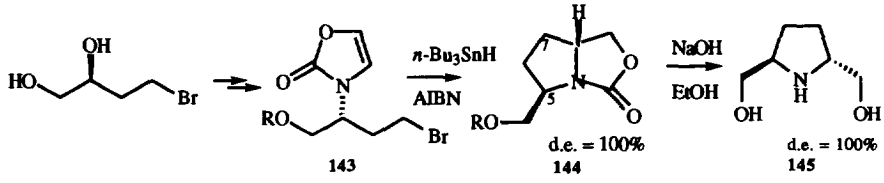
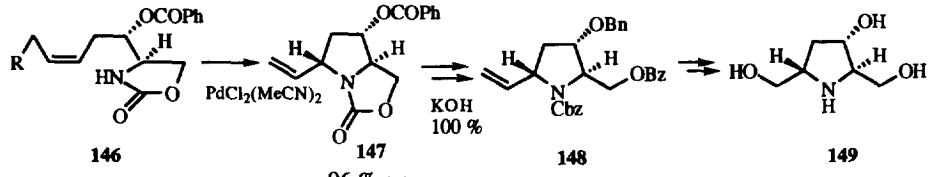


Figure 66

B- S_N2' nucleophilic substitutions

(-) Bulgecinine was synthesized in 1992 by Momose[126] through the intermediate **147** (Figure 67), obtained by palladium catalyzed N⟶π cyclization of a γ-unsaturated oxazolidin-2-one **146**.



96 % e.e.
100 % d.e.

Figure 67

2. 5. b.- Oxazinones

Lhommet[127] described in 1995, the synthesis of pyrrolidines by a zinc catalyzed ring contraction of 1,3-oxazin-2-one intermediates **150** (Figure 68).

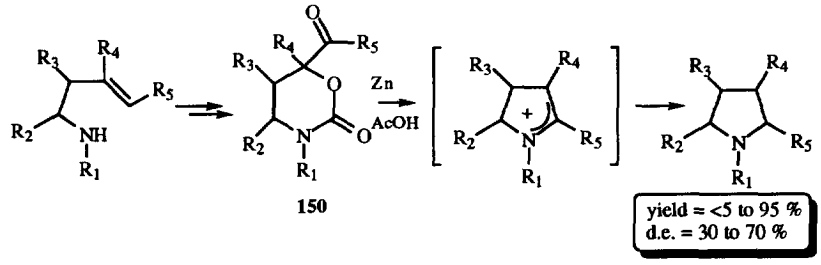


Figure 68

2. 5. c. - [2.2.1] bicyclic amines

In 1987, Fleet[128] reported the synthesis of 2,5-dideoxy-2,5-imino-D-mannitol **153** (Figure 69) *via* the bicyclic [2.2.1] amine intermediate **152** obtained by hydrogenation of azide **151**.

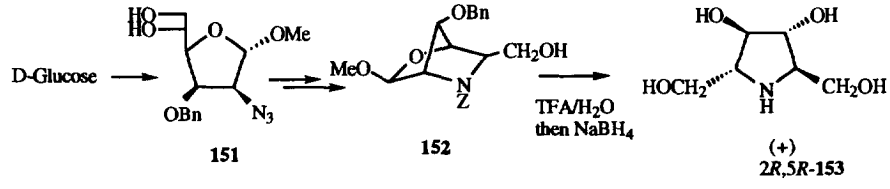


Figure 69

2. 5. d. - Oxazolopyrrolidines

Husson *et al* reported the synthesis of *trans* 2,5-disubstituted pyrrolidines, *via* an oxazolopyrrolidine[129] **156** obtained by condensation between aminonitrile **154** and 3-bromo-propionaldehyde **155**. This synthon **156** allows chemioselective reactions at the C-2-aminonitrile site (electrophilic substitutions) and at the C-5-aminoether position (nucleophilic substitutions) (Figure 70).

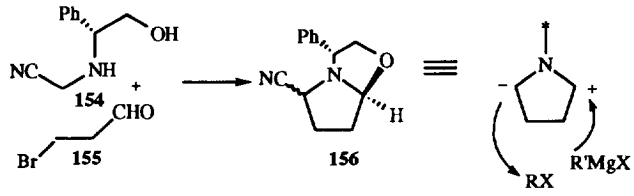


Figure 70

A stereospecific decyanation of the alkylated aminonitrile **157** leads to the formation of a single diastereomer **158**[130]. The control of the configuration at C-5 is performed by a nucleophilic substitution through an iminium intermediate with an opening of the oxazolidine **158** and a selective addition of the nucleophile on the less hindered face of the molecule. Both *cis* and *trans* isomers are obtained in >95 % yields and with d.e. = 50% (Figure 71).

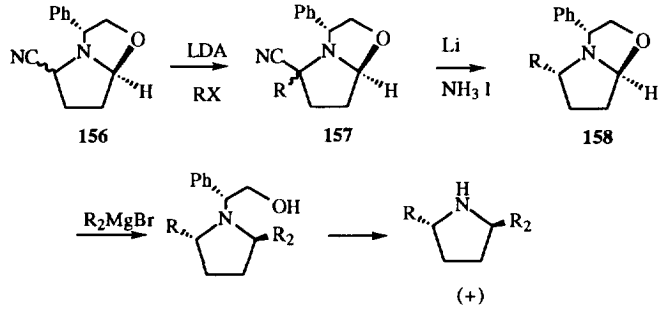


Figure 71

The stereoselectivity of the reaction leading to **158** from **157** may be explained by the formation of the carbanion **159** (Figure 72) which is tetrahedrical and adopts an *anti* position related to the free pair of electron beared by the nitrogen atom[130].

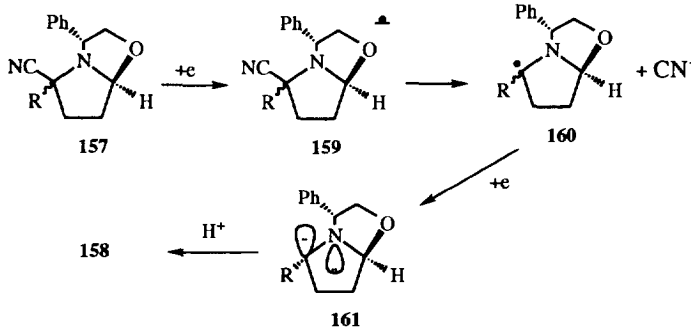


Figure 72

2. 6. Resolution of racemic mixtures of pyrrolidines

Resolution of racemic mixtures of pyrrolidines is still a very efficient method for the preparation of enantiomerically pure compounds. In 1985, Ohno[131] used the enzymatic desymmetrization of *meso* pyrrolidines for the preparation of carbapenem antibiotics (Figure 73).

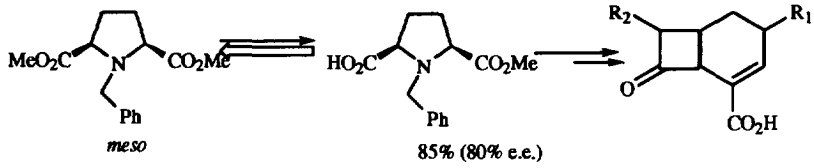


Figure 73

Achiwa[132] reported that the Pig Liver Esterase (PLE) gave different e.e. and chemical yields depending on the substituent on the nitrogen atom (for N-benzylpyrrolidines yield = 54%, e.e.= 23% for *SS* isomer and for N-H compounds, yield = 71%, e.e. = 10% for the *RR* isomer). Boutelje[133] studied the influence of the cosolvant on the enantiomeric purity of the *cis* N-benzyl monoester obtained in this reaction : without dimethylsulfoxyde e.e. = 17%, whereas in the presence of 25% of DMSO the e.e. = 100% . Sibi[134] in 1994 converted the racemic *trans* 2,5-dihydroxymethyl-N-benzylpyrrolidine into the corresponding enantiomerically pure mono or diacetate compound by treatment with the PS enzyme (Figure 74):

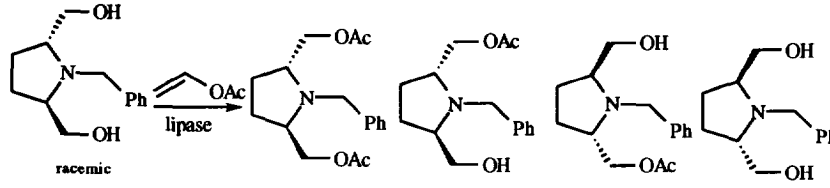


Figure 74

Chemical resolutions were also very often used for the preparation of enantiomerically pure pyrrolidines. Kemp[135] in 1988 reported the base catalyzed epimerization of 2,5-dicarbalkoxy pyrrolidines allowing the modification of the *trans:cis* ratios (55:45 to 52:48) depending on the nature of the base used (e.g. NaOEt-EtOH or DBU-toluene) and the substituent on the nitrogen atom (e.g. CH_2Ph, H, CO_2tBu or CN). Yamamoto[84] in 1992 showed that the *cis* isomers could be separated from the *trans* compounds by alkaline hydrolysis, and that the two *trans* enantiomers could be obtained by fractionnated crystallizations.

Conclusion

2,5-disubstituted pyrrolidines have attracted many synthetic chemists, because of the challenge in synthesizing in an enantiospecific way such products, and because of the biological potential of these bioactive compounds. Furthermore, 2,5-disubstituted pyrrolidines possessing a C_2 symmetry axis are very interesting chiral auxiliaries for numerous asymmetric reactions[136].

The discovery in the next future of new natural 2,5-disubstituted pyrrolidines is probably to come, and efficient syntheses of these products will be still needed for their access in large quantities for biological studies.

Acknowledgments

We thank Pr. André Cavé for his interest for this study.

References

1- Creighton, W.S.; *Bull. Mus. Comp. Zool.*, **1950**, *1*, 104.
2- Bacos, D.; Basselier, J.J.; Célérier, J-P.; Lange, C.; Marx, E.; Lhommet, G.; Escoubas, P.; Lemaire, M.; Clément, J.-P.; *Tetrahedron Lett.*, **1988**, *29*, 3061-3064.
3- Clément, J.-L.; Lemaire, M.; Lange, C.; Lhommet, G.; Celerier, J.-P.; Basselier, J.-J.; Cassier, P.; Fr. Appl. 84/,6980.
4- Ronzani, N.; Lajat, M.; *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 1131-1132.
5- Massiot, G.; Delaude, C.; "The Alkaloïds", Brossi, A.; Ed. , Academic Press, New-York, **1986**, vol. 27, pp 269-322.
6- Shinagawa, S.; Maki, M.; Kintaka, K.; Imada, A.; Asai, M.; *J. Antibiotics*, **1984**, *38*, 17-23.
7- Imada, A.; Kintaka, K.; Nakao, M.; Shingawa, S.; *J. Antibiotics*, **1982**, *35*, 1400-1403.
8- Karady, S.; Corley, E.G.; Abramson, N.L.; Weinstock, L.M.; *Tetrahedron Lett.*, **1989**, *30*, 2191-2194.
9- Stella, L.; *Angew. Chem. Int. Ed. Engl.*, **1983**, *22*, 337-422.
10- Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H; *Tetrahedron*, **1991**, *47*, 747-756.
11- Tokuda, M.; Fujita, H.; Suginome, H.; *J. Chem. Soc. Perkin. Trans.I*, **1994**, 777-778.
12- Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K.; *Tetrahedron Lett.*, **1989**, *30*, 3805-3806.
13- Perie, J.J.; Laval, J.-P.; Roussel, J.; Lattes, A; *Tetrahedron*, **1972**, *28*, 675-716.
14- Harding, K.E.; Burks, S.R.; *J. Org. Chem*, **1981**, *46*, 3920-3922.
15- Harding, K.E.; Marman, T.H.; *J. Org Chem.*, **1984**, *49*, 2838-2840.
16- Takahata, H.; Takehara, H.; Ohkubo, N.; Momose, T.; *Tetrahedron : Asymmetry*, **1990**, *1*, 561-566.
17- Takahata, H.; Bandoh, H.; Momose, T.; *J. Org. Chem.*, **1992**, *57*, 4401-4404.
18- Takahata, H.; Bandoh, H.; Momose, T.; *Heterocycles*, **1993**, *36*, 2777-2782.
19- Harmange, J.-C.; Figadère, B.; *Tetrahedron:Asymmetry*, **1993**, *4*, 174-152.
20- Clive, D.L.J.; Farina, V.; Singh, A.; Wong, C.K.; Kiel, W.A.; Menchen, S.M.; *J. Org. Chem.*, **1980**, *45*, 2120-2126.
21- Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H.; *Tetrahedron Lett.*, **1992**, *33*, 6359-6362.
22- Paneck, J.S.; Nareshkumar, F.J.; *J. Org. Chem.*, **1994**, *59*, 2674-2675.
23- Carruthers, W.; Cycloaddition Reactions in Organic Synthesis, Tetrahedron Organic Chemistry Series, vol. 8, Pergamon Press, **1990**, pp. 269-314.
24- Grigg, R.; *Tetrahedron:Asymmetry*, **1995**, *6*, 2475-2486.
25- Barr, D.A.; Grigg, R.; Gunaratne, H.Q.N.; Kemp, J.; Mc Meekin, P.; Sridharan, V.; *Tetrahedron*, **1988**, *44*, 557-570.
26- Nyerges, M.; Rudas, M.; Toth, G.; Herenyi, B.; Kdas, I.; Bitter, I.; Toki, L.; *Tetrahedron*, **1995**, *51*, 13321-13330.
27- Kanemasa, S.; Hayashi, T.; Tanaka, J.; Yamamoto, H.; Sakurai, T.; *J. Org. Chem.*, **1991**, *56*, 4473-4481.
28- Pätzel, M.; Galley, G.; Jones, P.G.; Chrapkowsky, A.;*Tetrahedron Lett.*, **1993**, *34*, 5707-5710.
29- Galley, G.; Liebscher, J.; Pätzel, M.; *J. Org. Chem.*, **1995**, *60*, 5005-5010.

30- Pyne, S.G.; Safaei-G., J.; Koller, F.; *Tetrahedron Lett.*, **1995**, *36*, 2511-2514.
31- Williams, R.M.; Zhai, W.; Aldous, D.J.; *J. Org. Chem.*, **1992**, *57*, 6527-6532.
32- Anslow, A.S.; Harwood, L.M.; Phillips, H.; Watkin, D.; Wong, L.F.; *Tetrahedron:Asymmetry*, **1991**, *2*, 1343-1358.
33- Harwood, L.M.; Lilley, I.A.; *Tetrahedron : Asymmetry*, **1995**, *6*, 1557-1560.
34- Garner, P.,; Dogan, O.; *J. Org. Chem.*, **1994**, *59*, 4-6.
35- Allway, P.; Grigg, R.; *Tetrahedron Lett.*, **1991**, *32*, 5817-5820.
36- Bonnet-Delpon, D.; Chennoufi, A.; Rock, M.-H.; *Bull. Soc. Chim. Fr*, **1995**, *132*, 402-405.
37- Tufariello, J.J.; Puglis, J.M.; *Tetrahedron Lett.*, **1986**, *27*, 1489-1492.
38- Asrof, A.S.; Wazeer, M.I.M.; *Tetrahedron Lett.*, **1993**, *34*, 137-140.
39- Pearson, W.H.; Jacobs, V.A.; *Tetrahedron Lett.*, **1994**, *35*, 7001-7004.
40- Miyashita, M.; Awen, B.Z.E.; Yoshikoshi, A.; *Chem. Lett.*, **1990**, 239-242.
41- Oppolzer, W.; Bochet, C.G.; Merifield, E.; *Tetrahedron Lett.*, **1994**, *35*, 7015-7018.
42- Kloetzel, M.C.; *J. Am. Chem. Soc.*, **1947**, *69*, 2271-2274.
43- Stevens, R.V.; Lee, A.W.M.; *J. Chem. Soc., Chem. Commun.*, **1982**, 102-103.
44- Chem, W.; Meng, Q.; Piantini, U.; Hesse, M.; *J. Nat. Prod.*, **1989**, *52*, 581-587.
45- Janowitz, A.; Vavrecka, M.; Hesse, M.; *Helv. Chim. Acta*, **1991**, *74*, 1352-1361.
46- Paulsen, M.; Sangster, I.; Heyns, K.; *Chem. Ber.*, **1967**, *100*, 802.
47- Straub, A.; Effenberger, F.; Fischer, P.; *J. Org. Chem.*, **1990**, *55*, 3926-3932.
48- Liu, K.K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H.; *J. Org. Chem.*, **1991**, *56*, 6280-6289.
49 Card, P.J.; Hitz, W.D.; *J. Org. Chem.*, **1985**, *50*, 891-893.
50- Takaoka, Y.; Kajimoto, T.; Wong, C.-H.; *J. Org. Chem.*, **1993**, *58*, 4809-4812.
51- Wang, Y.-F.; Dumas, D.P.; Wong, C.-H.; *Tetrahedron Lett.*, **1993**, *34*, 403-406.
52- Jegham, S.; Das, B.C.; *Tetrahedron Lett.*, **1989**, *30*, 2801-2804.
53- Jones, T.H.; Franko, J.B.; Blum, M.S.; *Tetrahedron Lett.*, **1980**, *21*, 789-792.
54- Blum, M.S.; Jones, T.H.; *Naturwissenschaften*, **1980**, *67*, 144-145.
55- Boga, C.; Manescalchi, F.; Savoia, D.; *Tetrahedron*, **1994**, *50*, 4709-4722.
56- Baxter, E.W.; Reitz, A.B.; *J. Org. Chem.*, **1994**, *59*, 3175-3185.
57- Iida, H.; Yamazaki, N.; Kibayashi, C.; *Tetrahedron Lett.*, **1985**, *26*, 3255-3258.
58- Yamazaki, N.; Kibayashi, C.; *Tetrahedron Lett.*, **1988**, *29*, 5767-5768.
59 Yamazaki, N.; Kibayashi, C.; *J. Am. Chem. Soc.*, **1989**, *111*, 1396-1408.
60- Bäckvall, J.-E.; Schink, H.E.; Renko, Z.D.; *J. Org Chem.*, **1990**, *55*, 826-836.
61- Park, K.H.; Yoon, Y.J.; Lee, S.G.; *Tetrahedron Lett.*, **1994**, *35*, 9737-9740.
62- Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L.; *Tetrahedron Lett.*, **1993**, *34*, 4555-4558.
63- Park, K.H.; *Heterocycles*, **1995**, *41*, 1715-1719.
64- Robina, I.; Gearing, R.P.; Buchanan J.G.; Wightman, R.H.; *J. Chem. Soc. Perkin Trans.I*, **1990**, 2622-2624.
65- Mc Garvey, G.M.; Kimura, M.; Oh, T.; Williams, J.M.; *J. Carbohydr. Chem.*, **1984**, *3*, 125.
66- Matsunga, H.; Sakamaki, T.; Nagoka, H.; Yamada, Y.; *Tetrahedron Lett.*, **1983**, *24*, 3009-3012.
67- Thompson, D. K.; Hubert, C.N.; Wightman, R.H.; *Tetrahedron* , **1993**, *49*, 3827-3840.
68- Machinaga, N.; Kibayashi, C.; *J. Org. Chem.*, **1991**, *56*, 1386-1393.

69- Machinaga, N.; Kibayashi, C.; *J. Org. Chem.*, **1992**, *57*, 5178-5189.

70- Fitremann, J.; Duréault, A.; Depezay, J.-C.; *Tetrahedron Lett.*, **1994**, *35*, 1201-1204.

71- Langlois, N.; Bourrel, P.; Andriamialisoa, Z.Z.; *Heterocycles*, **1986**, *24*, 777-783.

72- Baldwin, J.E.; Hulme, C.; Schofield, C.J.; *J. Chem. Resarch(S)*, **1992**, 173.

73- Manfré, F.; Kern, J.-M.; Biellman, J.-F.; *J. Org. Chem.*, **1992**, *57*, 2060-2065.

74- Sasaki, N.A.; Sagnard, I.; *Tetrahedron*, **1994**, *50*, 7093-7108.

75- Dockner, M.; Sasaki, N.A.; Potier, P.; *Heterocycles*, **1996**, *2*, 529-532.

76- Choi, S.; Bruce, I.; Fairbanks, A.J.; Fleet, G.W.J.; Jones, A.H.; Nash, R.J.; Fellows, L.E.; *Tetrahedron Lett.*, **1991**, *32*, 5517-5520.

77- Jego, J.-M.; Carboni, B.; Vaultier, M.; Carrié, R.; *J. Chem. Soc, Chem. Commun.*, **1989**, 142-143.

78- Cignarella, G.; Nathansohn, G.; *J. Org. Chem.*, **1961**, *26*, 1500-1504.

79- Blackman, S.W.; Baltzly, R.; *J. Org. Chem.*, **1961**, *26*, 2750-2755.

80- Sturm, P.A.; Henry, D.W.; Thompson, P.E.; Zeigler, J.B.; Mc Call, J.W.; *J. Med. Chem.*, **1974**, *17*, 481-487.

81- Lowe, G.; Ridley, D.D.; *J. Chem. Soc., Perkin Trans. I*, **1973**, 2024-2029.

82- Watson, H.A.; O'Neill, B.T.; *J. Org. Chem.*, **1990**, *55*, 2950-2952.

83- Braun, J.V.; Seeman, J.; *Chem. Ber.*, **1923**, *56B*, 1840.

84- Yamamoto, Y.; Hoshina, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S.; *Synthesis*, **1992**, 298-302.

85- Koh, K.; Ben, R.N.; Durst, T.; *Tetrahedron Lett.*, **1994**, *35*, 375-378.

86- Marzi, M.; Minetti, P.; Misiti, D.; *Tetrahedron*, **1992**, *48*, 10127-10132.

87- Shing, T.K.M.; *J. Chem. Soc., Chem. Commun.*, **1987**, 262-263.

88- Marzi, M.; Misiti, D.; *Tetrahedron Lett.*, **1989**, *30*, 6075-6076.

89- Short, R. P.; Kennedy, R.M ; Masamune, S.; *J. Org. Chem.*, **1989**, *54*, 1755-1756.

90- Bloch, R.; Brillet-Fernandez, C.; Kühn, P.; Mandville, G.; *Heterocycles*, **1994**, *38*, 1589-1594.

91- Bloch, R.; Brillet-Fernandez, C.; Mandville, G.; *Tetrahedron:Asymmetry*, **1994**, *5*, 745-750.

92- Chong, J.M.; Clarke, I.S.; Koch, I.; Olbach, P.C.; Taylor, N.J.; *Tetrahedron:Asymmetry*, **1995**, *6*, 409-418.

93- Zwaagstra, M.E.; Meetsma, A.; Feringa, B.L.; *Tetrahedron:Asymmetry*, **1993**, *4*, 2163-2172.

94- Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; *J. Org. Chem.*, **1986**, *51*, 2590-2592.

95- Shono, T; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S-I.; Kanazawa, T.; Aoki, T.; *J. Am.Chem. Soc.*, **1982**, *104*, 6697-6703.

96- Thaning, M.; Wistrand, L-G.; *Helv. Chim. Acta*, **1986**, *69*, 1711-1717.

97- Barrett, A.G.M.; Pilipauskas, D.; *J. Org. Chem.*, **1991**, *56*, 2787-2800.

98- Ahman, J.; Somfai, P.; *Tetrahedron*, **1992**, *48*, 9537-9544.

99- Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M.C.; Ruano, J.L.G; *Tetrahedron Lett.*, **1994**, *35*, 2053-2056.

100- Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S.; *Tetrahedron Lett.*, **1993**, *34*, 5743-5746.

101- Langlois, N.; Rojas, A.; *Tetrahedron* , **1993**, *49*, 77-82

102- Altmann, K-H; *Tetrahedron Lett.*, **1993**, *34*, 7721-7724.

103- Holmes, A.B.; Smith, A.L.; Williams, S.F.; Hughes, L.R.; Lidert, Z.; Swithenbank, C.; *J. Org. Chem.*, **1991**, *56*, 1393-1397.

104- Skrinjar, M.; Wistrand, L-G.; *Tetrahedron Lett.*, **1990**, *31*, 1775-1778.
105- Wistrand, L-G.; Skrinjar, M.; *Tetrahedron* , **1991**, *47*, 573-582.
106- Bacos, D.; Célérier, J-P.; Marx, E.; Rosset, S.; Lhommet, G.; *J. Heterocyclic Chem.*, **1990**, *27*, 1387-1392.
107- Provot, O.; Célérier, J.-P.; Petit, H.; Lhommet, G.; *J. Org. Chem.*, **1992**, *57*, 2163-2166.
108- Fleurant, A.; Grandjean, C.; Provot, O.; Rosset, S.; Célérier, J.-P.; Lhommet G.; *Heterocycles* , **1993**, *36*, 929-932.
109- Saliou, C.; Fleurant, A.; Célérier, J.-P.; Lhommet, G.; *Tetrahedron Lett.*, **1991**, *32*, 3365-3368.
110- Bacos, D.; Célérier, J.-P.; Marx, E.; Saliou, C.; Lhommet, G.; *Tetrahedron Lett.*, **1989**, *30*, 1081-1082.
111- Shiosaki, K.; Rapoport, H.; *J. Org. Chem.*, **1985**, *50*, 1229-1239.
112- Gessner, W.; Takahashi, K., Brossi, A.; *Helv. Chim. Acta*, **1987**, *70*, 2003-2010.
113- Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J.H.; Ruano, J.L.G.; *Tetrahedron Lett.*, **1993**, *34*, 4989-4992.
114- Fraser, R.R.; Passannanti, S.; *Synthesis*, **1976**, 540-541.
115- Mac Donald, T.L.; *J. Org. Chem.*, **1980**, *45*, 193-194.
116- Meyers, A.I.; Edwards, P.D.; Bailey, T.R.; Jagdmann, G.E.; *J. Org. Chem.*, **1985**, *50*, 1019-1026.
117- Meyers, A.I.; Santiago, B.; *Tetrahedron Lett.*, **1995**, *36*, 5877-5880.
118- Pandey, G.; Lakshmaiah, G.; Ghatak, A.; *Tetrahedron Lett.*, **1993**, *34*, 7301-7304.
119- Beak, P.; Kerrich, S.T.; Wu, S.; Chu, J.; *J. Am. Chem. Soc.*, **1994**, *116*, 3231-3239.
120- Magaard, V.W.; Sanchez, R.M.; Bean, J.W.; Moore, M.L.; *Tetrahedron Lett.*, **1993**, *34*, 381-384.
121- Magnus, P.; Hulme, C.; Weber, W.; *J. Am. Chem. Soc.*, **1994**, *116*, 4501-4502.
122- Casiraghi, G.; Rassu, G.; *Synthesis* , **1995**, 607-626.
123- Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G.; *Tetrahedron Lett.*, **1994**, *35*, 4019-4022.
124- Yuasa, Y.; Ando, J.; Shibuya, S.; *J. Chem. Soc., Chem. Commun.*, **1994**, 455-456.
125- Yuasa, Y.; Ando, J.; Shibuya, S.; *J. Chem. Soc., Chem. Commun.*, **1994**, 1383-1384.
126- Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T.; *Tetrahedron Lett.*, **1992**, *33*, 7893-7894.
127- Vanucci, C.; Brusson, X.; Verdel, V.; Zana, F.; Dhimane, H.; Lhommet, G.; *Tetrahedron Lett.*, **1995**, *36*, 2971-2974.
128- Fleet, G.W.J.; Smith, P.W.; *Tetrahedron* , **1987**, *43*, 971-978.
129- Huang, P.Q.; Arseniyadis, S.; Husson, H.-P.; *Tetrahedron Lett.*, **1987**, *28*, 547-550.
130- Arseniyadis, S.; Huang, P.Q.; Piveteau, D.; Husson H.-P.; *Tetrahedron* , **1988**, *44*, 2457-2470.
131- Kurihara, M.-A.; Kamiyama, K.; Kobayashi, S.; Ohno, M.; *Tetrahedron Lett.*, **1985**, *26*, 5831-5834.
132- Morimoto, Y.; Terao, Y.; Achiwa, K.; *Chem. Pharm. Bull.*, **1987**, *35*, 2266-2271.
133- Björkling, F.; Boutelje, J.; Hjalmarsson, M.; Hult, K.; Norin, T.; *J. Chem. Soc. Chem. Commun.*, **1987**, 1041-1042.
134- Sibi, M.P.; Lu, J.L.; *Tetrahedron Lett.*, **1994**, *35*, 4915-4918.
135- Kemp, D.S.; Curran, T.P.; *J. Org. Chem.* , **1988**, *53*, 5729-5731.
136 Shi, M.; Satoh, Y.; Makihara, Y.; Masaki, Y.; *Tetrahedron:Asymmetry*, **1995**, *6*, 2109-2112.

(*Received in UK* 26 *February* 1996)