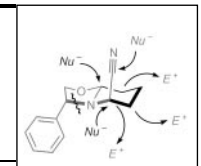
# Chiral non-racemic *N*-cyanomethyloxazolidines: the pivotal system of the CN(*R*,*S*) method



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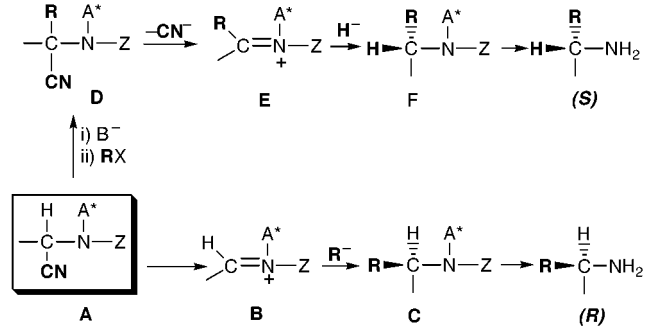
**The α-cyanomethyloxazolidine ring system has been integrated into piperidine and pyrrolidine structures providing chiral non-racemic building blocks. Reaction conditions have been determined for regio- and stereoselective substitution of the ring atoms. This review highlights the applications of the methodology for the diastereoselective synthesis of both natural and unnatural derivatives containing either the piperidine or the pyrrolidine ring as a substructure.**

## Introduction

The piperidine and pyrrolidine rings are an integral feature in the structure of a large number of alkaloids and synthetic products of biological interest. In the past ten years there has been an intense interest in the enantioselective synthesis of such heterocyclic compounds. Most of the synthetic efforts have involved a plethora of approaches specific for each target molecule whereas the development of general methodologies, in which preformed chiral non-racemic building blocks are used for the construction of a wide diversity of simple or complex structures, remained a challenging task.

Fifteen years ago, we felt that for the design of a new and general strategy one should be able to substitute each position of the heterocyclic rings. Simple and conjugated iminium and corresponding enamine systems might be potentially valuable for this purpose. The idea was to take advantage of the reactivity of α-aminonitriles of type **A** bearing a chiral appendage, which was supposed to induce the formation of new chiral centers (Scheme 1). Departure of $CN^-$ gives rise to the prochiral



**Scheme 1**

iminium ion **B** which on axial addition of a nucleophile $R^-$ under stereoelectronic control leads in a stereospecific manner to **C**. Deprotonation of **A** affords the corresponding anion which can trap an electrophile reagent to give **D**. Departure of $CN^-$ from **D** affords the prochiral iminium **E** which reacts with $H^-$ as a nucleophile according to the same control as for its analogue **B**. Thus, according to their mode of formation compounds **F** and

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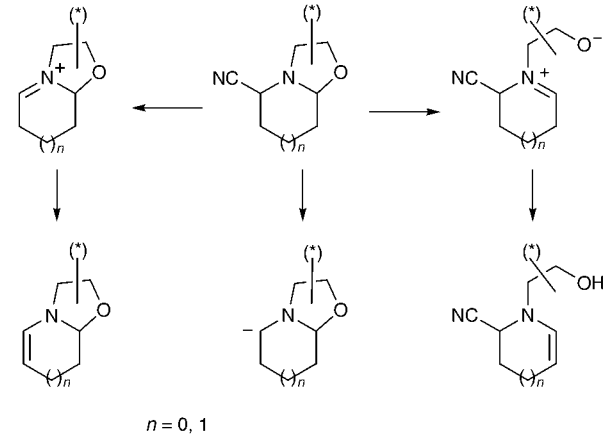
**Jacques Royer**

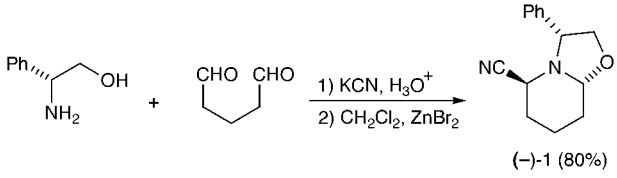
**C** are diastereomers since the newly created stereogenic centers have the opposite absolute configuration. Elimination of the chiral appendage would give enantiomeric amines.

As far as pyrrolidine and piperidine rings are concerned it was necessary to obtain a multifunctional system allowing the substitution at the α,α′ and β,β′ positions of the nitrogen atom. For this purpose we designed the *N*-cyanomethyloxazolidine system, where the nitrogen atom is an integral part of both α-aminonitrile and α-aminoether functions, which represents a synthetic equivalent of various synthons as illustrated in Scheme 2. The opening of the oxazolidine ring can generate




**Scheme 2**

another iminium and regiospecific substitutions could therefore be envisaged. Condensation of a dialdehyde and a β-aminoalcohol in the presence of KCN furnished the *N*-cyanomethyloxazolidine system. The latter was first integrated into a piperidine structure to produce stable synthetic equivalents of piperidine synthons. Thus, (−)-5-cyano-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine **1** was easily prepared on the kilogram scale by treating glutaraldehyde with (*R*)-(−)-phenylglycinol and KCN (Scheme 3).[1,2]




**Scheme 3**

The choice of the chiral β-aminoalcohol was crucial since it is not a recoverable chiral auxiliary but a source of nitrogen and chirality. Thus the chiral moiety must be easily cleavable as a nitrogen protective group. Phenylglycinol, commercially available in both enantiomeric pure forms, proved suitable because of the benzylic position of the amino group allowing facile hydrogenolysis. For this reason phenylglycinol was definitely more interesting than the norephedrines which were previously very popular in asymmetric synthesis.

The simple structure of coniine, the poisonous hemlock alkaloid, was an attractive target for checking the validity and efficiency of our strategy and hence the absolute configuration of the first stereogenic center formed at the C-2 position of the piperidine ring.

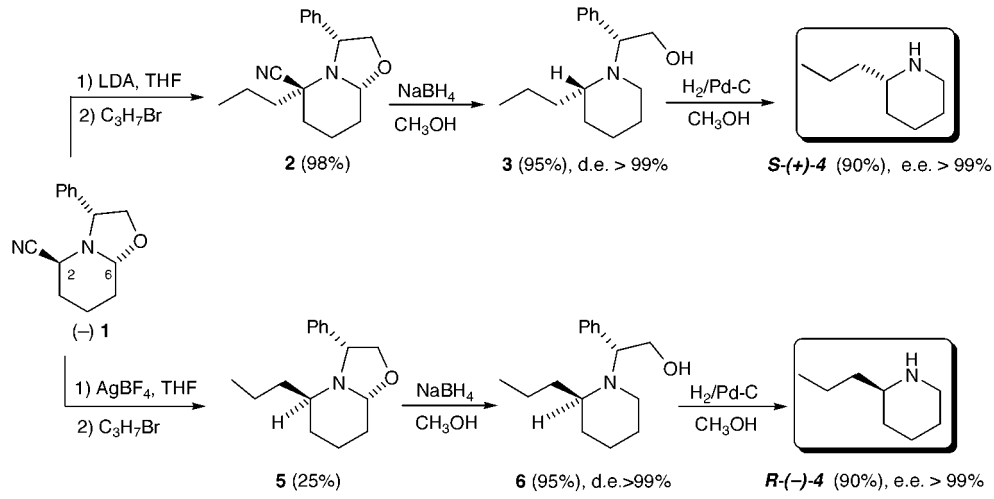
The synthetic scheme for the preparation of (*S*)-(+)-coniine (**4**) involved alkylation of 5-cyano-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine **1** through LDA deprotonation followed by treatment with propyl bromide to give **2** in very high yield (Scheme 4). Reductive decyanation of **2** using $NaBH_4$ in $CH_3OH$ furnished amino alcohol **3** with entire diastereoselectivity. Finally debenzylation allowed to obtain natural (*S*)-(+)-coniine (**4**).[1]

Conversely the propyl chain could be introduced at the C-2 position of **1** in the opposite (*R*) configuration with PrMgBr after prior complexation of the cyano group with silver salts. Compound **5** was obtained in low yield (25%) but with complete C-2 stereoselectivity. It will be shown below that this reaction occurred in much better yields (see Section 2.1.3) with several more complex structures. Reductive opening of the oxazolidine ring ($NaBH_4$, $CH_3OH$) afforded **6** which is in diastereomeric relationship with **3**. Debenzylation of **6** led to enantiomeric (*R*)-(−)-coniine (**4**).[1]

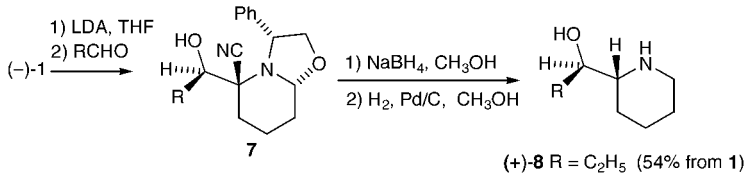
The high diastereoselectivity observed for the reduction or alkylation of the iminium salt generated from the aminonitrile function could be explained by an axial attack onto the preferred conformer of the iminium. This iminium intermediate formed upon addition of a nucleophile $Nu^-$ ($H^-$ or $R^-$) could exist as the two conformers $I_1$ or $I_2$ (Fig. 1). The $I_1$ conformer would be preferred since the bicyclic structure is much less constrained despite the $A^{1,2}$ allylic strain present in such a conformer. Addition of the nucleophile reagent should occur from the axial direction (upper face) to give a chair transition state under the stereoelectronic control.

The enantiodivergent synthesis of *(R)*- or (*S*)-coniine illustrates the mainspring of the CN(*R*,*S*) method which allows, by CN elimination, remarkable stereocontrol for the formation of the new *R* or *S* chiral centers. This result led us to name this method in recognition of the "**C**entre **N**ational de la **R**echerche **S**cientifique" which supported this work.

With respect to the noteworthy stereoselectivity of the formation of the first chiral center at the C-2 position of the




**Scheme 4**




**Scheme 5**

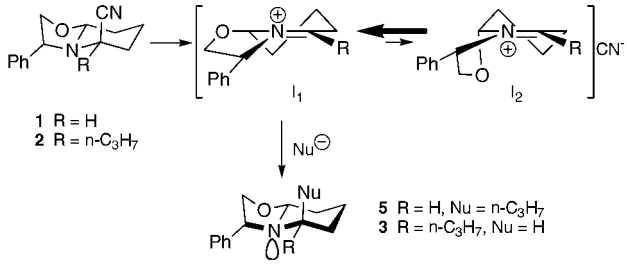



**Fig. 1**

piperidine ring, it appeared promising to envisage further stereocontrolled functionalization. Indeed, successive substitutions of three other carbon centers, *i.e*. C-3, C-5 and C-6, proved possible if taking advantage of the capacity of the *N*-cyanomethyloxazolidine system to react as masked or potential iminium salts (or their corresponding enamines). Elimination of the chiral appendage permitted the generation of a secondary amine which could be incorporated into a new heterocycle. Finally, the cyano group could be reduced, hydrolyzed or involved in a spirocylization reaction.

A similar synthetic strategy could be conducted for the pyrrolidine series using 5-cyano-3-phenylhexahydropyrrolo[2,1-*b*][1,3]oxazole **40** (see Section 2.2.1). However, in this case the exploitation of the enamine reactivity was not possible due to the facile aromatization to a pyrrole.

## 2 Potential and masked iminium reactivity

The use of potential and masked iminium salt reactivity of **1** was proved to be valuable in the synthesis of both enantiomers of coniine **4** (Scheme 4). A clear indication of this dual behaviour has been shown in various and more complex examples.

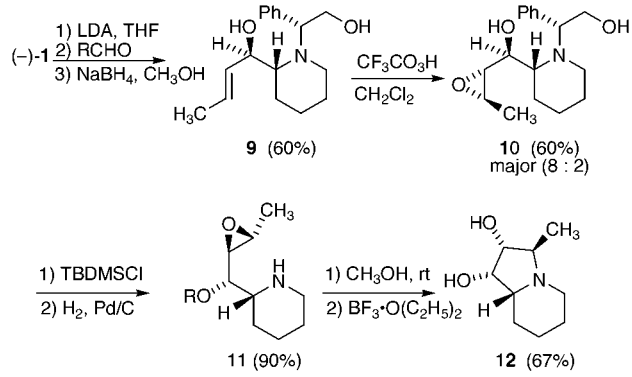
### 2.1 α-Substituted pyrrolidines and piperidines included in complex ring systems

The access to indolizidines, quinolizidines, benzoquinolizidines and the unprecedented skeleton of tetraponerine alkaloids was possible using the reactivity of the α-aminonitrile and the nucleophilicity of the nitrogen atom after elimination of the chiral appendage.

**2.1.1 Indolizidine[3] and quinolizidine.[4]** The preparation of hydroxylated indolizidines was imagined following a scheme where the cyclization step is an intramolecular opening of an epoxide by the piperidine nitrogen.

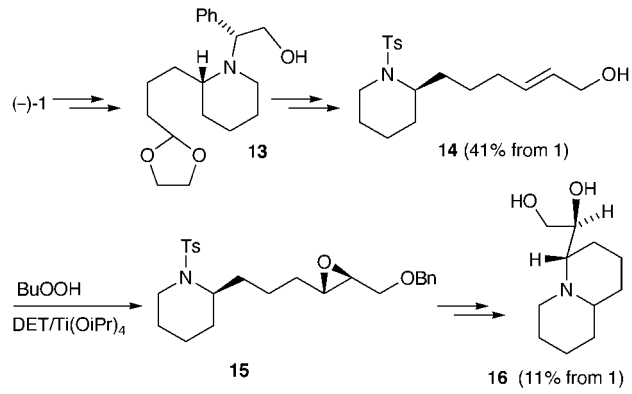
It was first shown that when the anion of **1** was reacted with an aldehyde, a β-amino alcohol could be obtained in a diastereoselective manner. The synthesis of β-conhydrine **8**[5] is an example of the usefulness of this reaction (Scheme 5).

In a similar manner, treatment of the anion of **1** with crotonaldehyde followed by $NaBH_4$ reduction gave **9** (Scheme 6) as the major *threo* derivative. The latter was submitted to stereoselective epoxidation of the double bound. The major epoxide **10**, after *N*-debenzylation was cyclized to the indolizidine skeleton and furnished **12**[3] after *O*-deprotection.




**Scheme 6**

An efficient synthesis of unnatural dihydroxyquinolizidine **16** from **1** was reported by McIntosh.[4] Alkylation of the anion of **1** with iodobutanal ethylene ketal (Scheme 7) permitted the

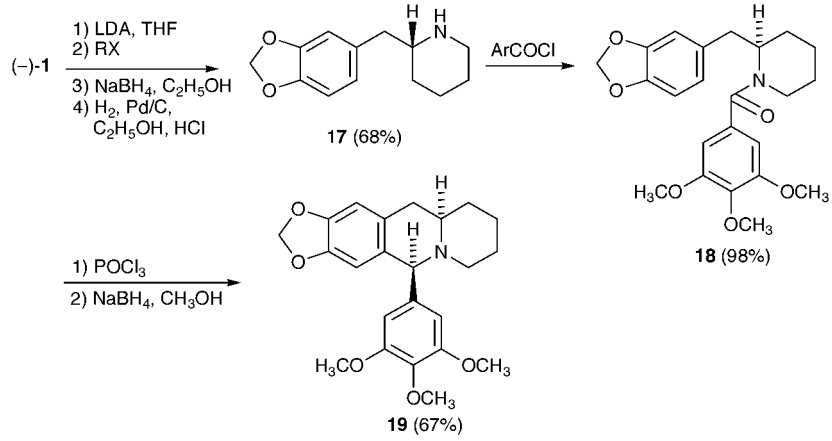



**Scheme 7**

preparation of enantiomerically pure (2*S*)-piperidine derivative **13**, which was transformed to allylic alcohol **14** by classical reactions. Sharpless epoxidation of **14** in the presence of (+)-diethyl tartrate (DET) led to epoxide **15** which was cyclized to **16** upon treatment with sodium naphthalenide.

**2.1.2 Benzoquinolizidine.[6]†** A great deal of interest in aza-analogues of podophyllotoxin has developed on account of the antitumor activity of semi-synthetic derivatives of natural products. Building block **1** was the precursor for two syntheses of benzoquinolizidine analogues of podophyllotoxin. One of them will be described in detail (Scheme 8). Piperidine **17** was obtained from alkylation of the anion of **1** with piperonyl bromide followed by reduction and debenzylation. Upon treatment with 3,4,5-trimethoxybenzoyl chloride, amide **18** could be obtained in good yield. Subsequent cyclization *via* a Bischler–Napieralski reaction and reduction of the iminium gave predominantly (10:1) the *cis* isomer **19**. Once again, the major isomer resulted from a stereoelectronically controlled reduction.

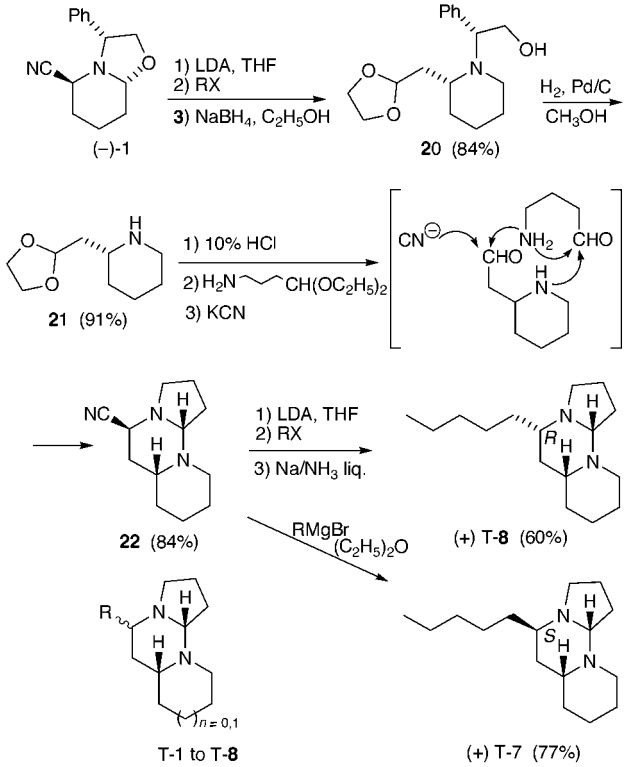
† Benzoquinolizidine is 1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine.




**Scheme 8**

**2.1.3 Tetraponerines.**[7] The concept of the preparation of the α-cyanomethyloxazolidine and the rationale of the CN(*R,S*) method were both used in the asymmetric synthesis of the unprecedented skeleton of tetraponerines derived from either a piperidine or a pyrrolidine ring. Eight alkaloids **T-1** to **T-8** have been extracted from the defensive secretion of *Tetraponera* sp., a New-Guinea ant. All of them were prepared *via* the CN(*R,S*) method from the piperidine **1** or pyrrolidine **40** building blocks allowing the determination of the absolute configuration of the natural enantiomers. As an example the synthesis of epimeric alkaloids **T-7** and **T-8** will be described herein.

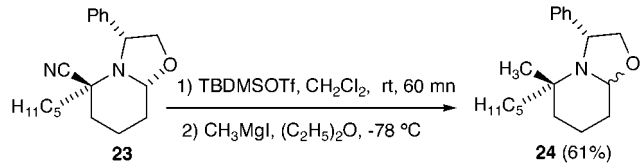
The cyano aminal **22** appeared to be a suitable intermediate in their synthesis (Scheme 9). This key intermediate was thought to be formed by a cross-condensation of two aminoaldehyde equivalents: **21** and aminobutyraldehyde acetal.




**Scheme 9**

According to the established procedure, the ketal **21** was prepared in 3 steps from **1**, with complete stereocontrol. Acidic hydrolysis of **21**, followed by condensation with commercially available aminobutyraldehyde acetal in the presence of KCN at slightly acidic pH gave the cyanoaminal **22** in high yield and as a sole isomer. This condensation parallels the preparation of **1** where a bis-aldehyde was condensed with an amino alcohol in the presence of $CN^-$. As expected the cyanoaminal **22** had the configuration depicted in Scheme 9 which is in accordance with a thermodynamically controlled process. Introduction of the pentyl side chain onto cyanoaminal **22**, could be controlled according to the CN(*R,S*) strategy. Axial addition of the Grignard reagent gave tetraponerine **T-7** with (*S*) configuration in 97% de. On the other hand, electrophilic substitution *via* LDA deprotonation followed by hydride axial attack furnished tetraponerine **T-8** with (*R*) configuration and complete diastereoselectivity.

**2.1.4 Formation of a quaternary center.** Alkylated aminonitriles such as **23** still possess two sites of potential iminium salt reactivity allowing the addition of nucleophiles. It was found that *tert*-butyldimethylsilyltrifluoromethane sulfonate promoted a clean elimination of $CN^-$ despite possible competitive complexation of the silyl reagent with the oxazolidine oxygen atom. The probably more stable substituted iminium is formed since only the cyano group is antiperiplanar to the nitrogen lone pair. Thus, sequential treatment of **23** with TBDMSOTf followed by a Grignard reagent, led to the formation of oxazolidine **24** bearing a quaternary center at C-2 in highly diastereoselective fashion[8] (Scheme 10). The diastereoselectivity could be explained by the mechanism discussed above for the asymmetric synthesis of (+)- and (−)-coniine (Fig. 1). The diastereoselective formation of a quaternary center α to the nitrogen appeared as a valuable synthetic pathway, it will be used in the synthesis of euphococcinine which will be described further below (see Section 2.2.2.3).




**Scheme 10**

## 2.2 α,α′-Disubstituted pyrrolidines and piperidines

**2.2.1 Simple derivatives.** Simple α,α′-disubstituted pyrrolidines and piperidines can currently be synthesized by numerous routes of which some allow the control of optical activity. However, the main problem is the control of the *cis* or *trans* relative relationship of the substituents. The first stereogenic center being created as *R* or *S* as desired at the C-2 position of

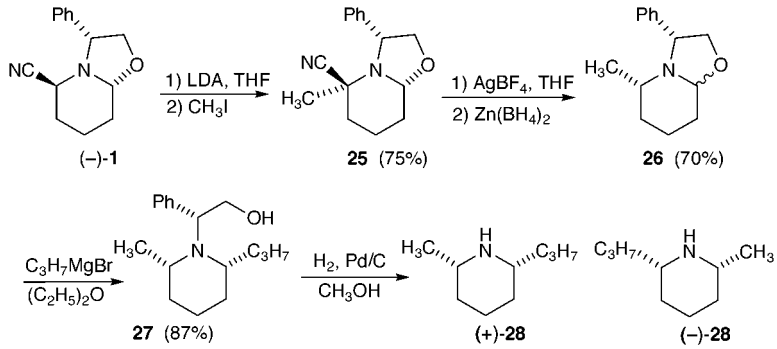
the piperidine ring, the diastereoselective formation of *cis* or *trans* 2,6-disubstituted derivatives could be envisaged. This was illustrated in the syntheses of *cis* and *trans* piperidine alkaloids.

Conditions were found to selectively remove the cyano group of alkylated aminonitriles without opening of the oxazolidine ring. Treatment of **25** (Scheme 11) with $AgBF_4$, followed by reduction with $Zn(BH_4)_2$ at −78 °C, led to compound **26**. The reduction was totally stereoselective and a *2S* configuration was obtained. Addition of propyl Grignard reagent to the oxazolidine ring of **26** gave *cis*-dialkylpiperidine **27** (after separation of the 8:2 *cis/trans* mixture) from which (*2S,6R*)-(+)-dihydropinidine (**28**) was obtained after simple hydrogenolysis. By reversing the order of alkyl substitution, *i.e.* propyl and then methyl, optically pure (−)-dihydropinidine was easily prepared in a similar fashion.[1] Once again, it was possible to prepare both enantiomers starting from a common intermediate.

The major formation of the *cis* isomer is explained by an axial attack (stereoelectronic control) onto the iminium $I_4$. This conformer is preferred to $I_3$ which exhibits a strong $A^{1,2}$ strain (Fig. 2).

Solenopsin-A, a fire ant venom, was an interesting target since it belongs to the *trans*-2,6-dialkylated piperidine series, generally more difficult to synthesize. In order to obtain such derivatives we took advantage of the mechanism of formation of the *cis* compound in the previous synthesis (Fig. 2). Indeed, a cyano group was introduced at the C-6 position of oxazolidine **26** by treatement with TMSCN which gave aminonitrile **29** in good yield (Scheme 12). Then, alkylation of **29** led to a C-6 alkylated derivative which furnished the oxazolidine **30** by $CN^-$ elimination and alcohol deprotection. Reductive ($NaBH_4$) opening of the oxazolidine gave the *trans* derivative (*trans/cis* 70:30). During the reduction step, the hydride ion enters on the same face of the iminium $\mathbf{I_6}$ (Fig. 2) as the Grignard reagent did in the previous synthesis, now giving rise to the *trans* dialkylated product. After debenzylation, pure (2*S*,6*S*)-(+)-solenopsin-A (**31**)[9] could be easily isolated.

A wide range of 2,6-disubstituted piperidines was obtained through the established reactivity of Grignard reagents with the hexahydro-5*H*[1,3]oxazolo[3,2-*a*]pyridine system. Interestingly some new results have been obtained concerning the diastereoselectivity of this reaction. Recently Higashiyama *et al.*[10] described the reaction of C-2 substituted hexahydro-5*H*[1,3]oxazolo[3,2-*a*]pyridine **26** and **34**. The 2-methyl derivative **26** (Scheme 13), previously prepared by the CN(*R,S*) method, afforded on reaction with vinyl or ethynyl magnesium bromide, a majority of *trans* isomers **33**. This behaviour is in contrast with the reactivity of simple alkyl Grignards that gave poor selectivity. The C-2 diastereomer **34**, on the contrary, gave exclusively 2,6 *cis* products. In this manner a totally diastereoselective synthesis of (−)-pinidine **36** has been achieved. The stereochemical outcome of the latter reaction has been explained by a strong $A^{1,2}$ allylic strain as depicted in Fig. 2 for iminium $\mathbf{I_3}$. However, the mechanism of the reaction affording only the *trans* isomer remains uncertain.




**Scheme 11**

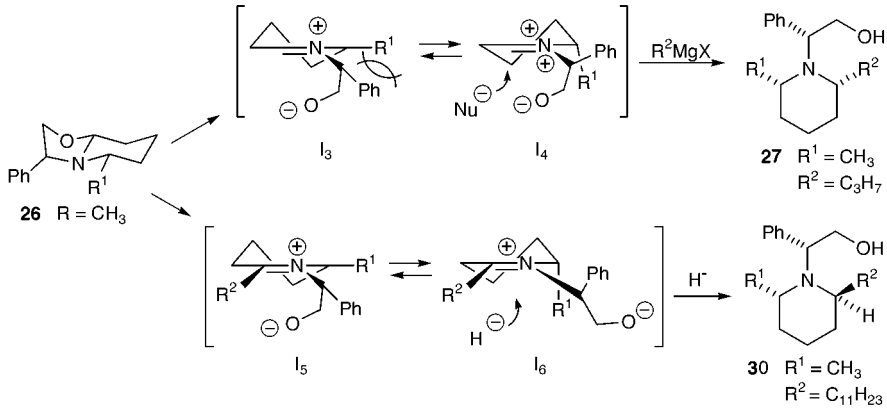
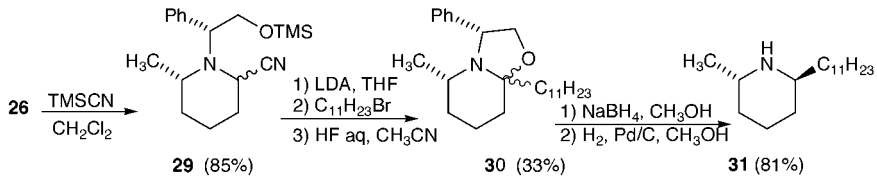
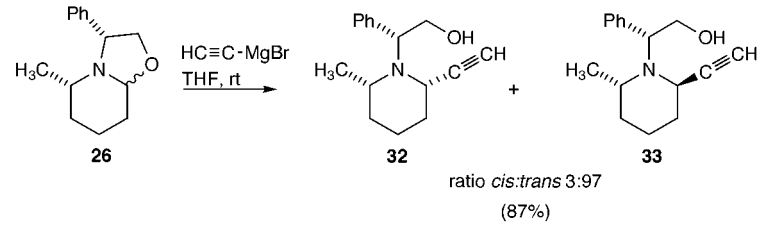



**Fig. 2**



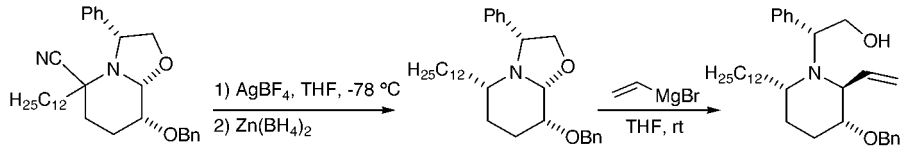

**Scheme 12**




**26** **32** **33**

**34** (63%) **35** (96%) (–)-**36** (70%)

**Scheme 13**

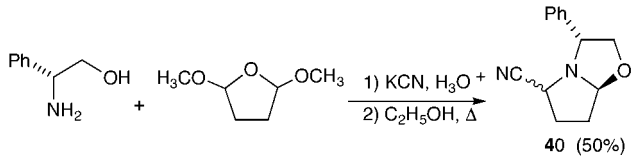



**37** **38** (78%) **39** (86%)

**Scheme 14**

Simple 1,3-oxazolidines derived from phenylglycinol have served as starting materials for the construction of phenyloxazolipiperidines which underwent well established regio- and stereospecific chemistry. For their synthesis of (−)-desoxoprosopinine, Agami *et al.*[11] have elaborated a diastereoselective preparation, through *N*-Boc oxazolidine derivatives, of the 5-cyano-3-phenylhexahydro-5*H*-[1,3]oxazolo-[3,2-*a*]pyridine **37**. The latter was submitted to CN(*R*,*S*) manipulations to create the last two stereogenic centers with excellent selectivity (Scheme 14).

A similar synthetic strategy could be conducted for the pyrrolidine series using 5-cyano-3-phenylhexahydropyrrolo[2,1-*b*][1,3]oxaxole **40** which is analogous to **1**. The preparation of **40**[12] (Scheme 15) parallels the preparation of **1**,

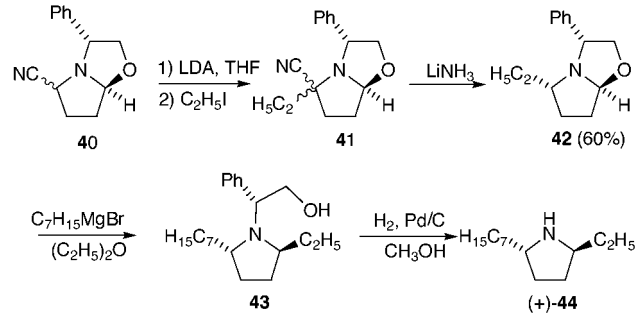



**40** (50%)

**Scheme 15**

using dimethoxytetrahydrofuran as a stable equivalent of succinaldehyde. Compound **40** was isolated as a mixture of two epimers at C-2, which did not influence the diastereoselectivity of the alkylation reactions at all as will be shown below.

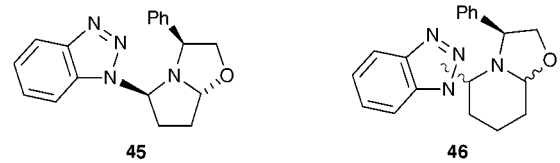
The anion of 5-cyano-3-phenylhexahydropyrrolo[2,1-*b*][1,3]oxazole **40** was alkylated to give aminonitrile **41** as a 1:1 mixture of diastereomers (Scheme 16). Nevertheless, the reductive decyanation, produced oxazolidine **42** in 60% yield as a unique compound. The decyanation was achieved by an alternative method using Li in liquid ammonia. Subsequent reaction with a Grignard reagent in ether led to the *trans* dialkyl derivative **43** being obtained as the major isomer (*trans*/*cis* 7:3). In the pyrrolidine series the *trans* stereoselectivity could be explained by the addition of the Grignard reagent on the less hindered face of the iminium salt formed by the opening of the oxazolidine ring. The asymmetric synthesis of (2*S*,5*S*)-(+)-*trans*-2-ethyl-5-heptylpyrrolidine **44**, a component of the ant *Solenopsis punctaticeps* has been achieved following this strategy (Scheme 16).[13]




**40** **41** **42** (60%) **43** (+)-**44**

**Scheme 16**

By just replacing KCN with benzotriazole in the condensation of (S)-(+)-phenyglycinol with dialdehydes, Katritsky[14] obtained compounds **45** and **46** which are very similar to the aminonitrile series (Scheme 17). Interestingly, in the contrast to

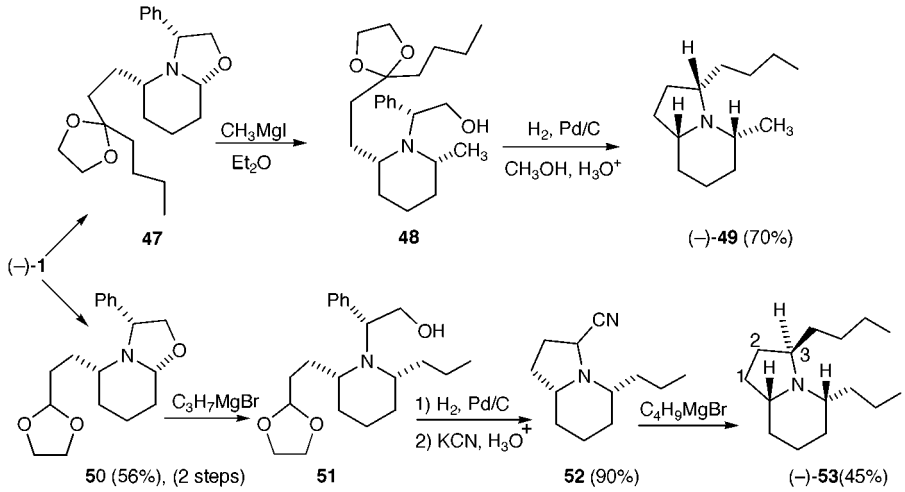


**45** **46**

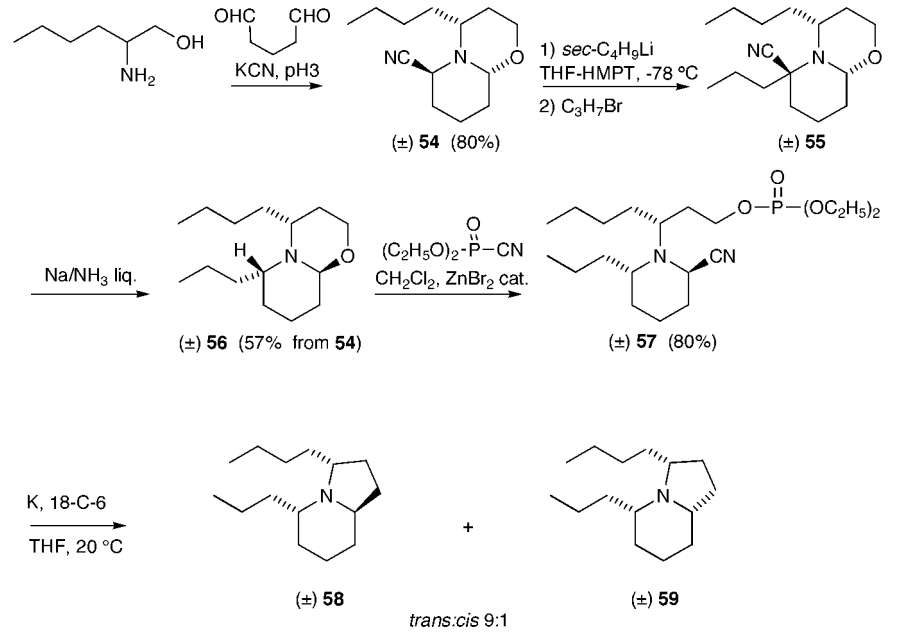
**Scheme 17**

the latter series, the piperidine derivative **46** was obtained as a mixture of diastereomers while the pyrrolidine homologue **45** was isolated as a single more stable *trans* isomer. The benzotriazole moiety was easily substituted by different nucleophiles in a highly diastereoselective manner for both the piperidine and the pyrrolidine series. This approach is limited to this type of reaction since compounds **45** and **46** only acted as iminium equivalents. Nevertheless, monoalkyl and *cis*-dialkyl substituted piperidines and pyrrolidines were obtained using the same methodology as for the aminonitrile series.

**2.2.2 Bicyclic systems.** The synthesis of α,α′-disubstituted pyrrolidines and piperidines was extended to bicyclic systems




**Scheme 18**




**Scheme 19**

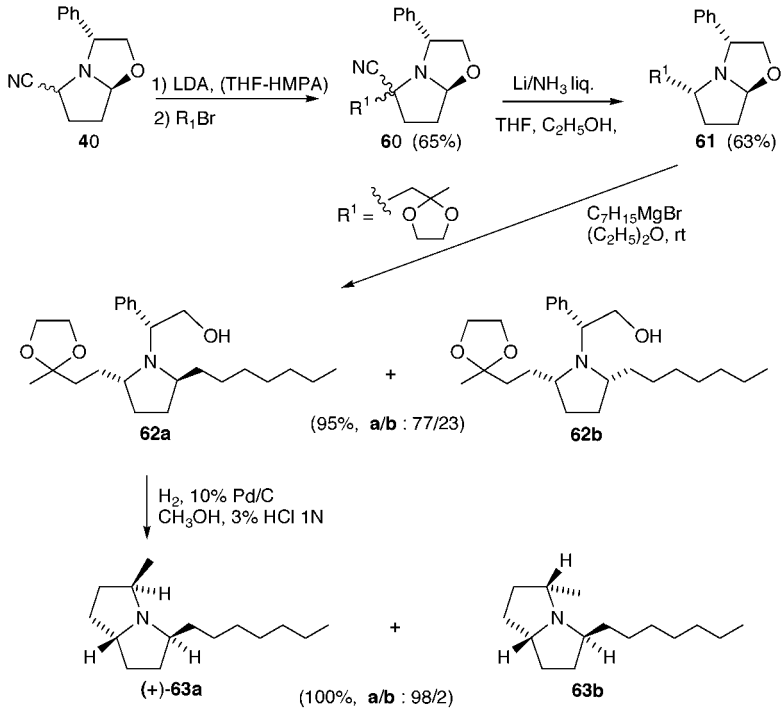
following the possibility of cyclization of the α-side chain onto the nitrogen atom (octahydroindolizines, octahydro-2*H*-quinolizines, *etc*.) or at the α′ position (tropane and related structures).

*2.2.2.1 Indolizidines.*‡ This family of alkaloids is very large and it has been shown with tens of isolated products that some of its members occur as trace amounts in natural sources. In some cases, their structures have been determined only by racemic syntheses. Thus, chiral approaches are needed for the determination of the absolute configuration.

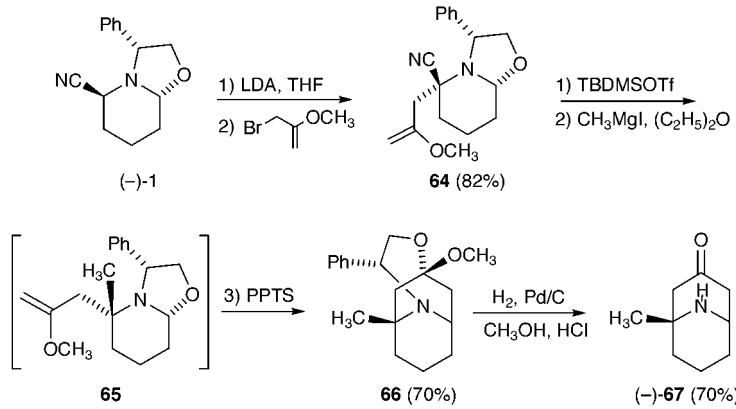
(−)-Monomorine-I (**49**) is an ant trail pheromone from *Monomorium pharaonis*. Only the relative configuration of this indolizidine alkaloid was known until the first asymmetric synthesis[15] of the levorotatory enantiomer was achieved in only four steps starting from (−)-**1**. Introduction of an alkyl chain bearing a protected ketone onto aminonitrile **1** gave oxazolidine **47** (Scheme 18). Treatment of **47** with a methyl Grignard reagent in ether led to the major *cis* derivative **48** which was easily separated from the diastereomeric mixture (*cis/trans* 4:1) by means of chromatography and subjected to hydrogenation in an acidic medium. These one-pot conditions allowed the cleavage of the ketal, hydrogenolysis of the chiral appendage and reduction of the cyclized iminium with the expected *cis* stereochemistry. (3*S*,5*R*,8a*R*)-(−)-Monomorine **49** was obtained after chromatographic separation from the epimeric material. This synthesis permitted determination of the absolute configuration of natural (+)-monomorine-I as 3*R*,5*S*,8a*S*. Obviously, the use of (+)-**1** (available from (*S*)-(+)-phenylglycinol) as starting material or reversal of the order of introduction of substituents would have led to the natural enantiomer.

(−)-Gephyrotoxin-223AB, extracted from the skin of neotropical frogs, exhibits an indolizidine structure **53** analogous to that of monomorine but with the opposite configuration at C-3. It was anticipated to introduce the butyl side chain at this position *via* an α-aminonitrile function. The preparation of **51** with a *cis* configuration (Scheme 18) was performed through the same sequence as for the previous synthesis. This compound was sequentially debenzylated in neutral conditions and treated with KCN in the acidic medium to give the aminonitrile **52** in excellent yield. Alkylation of **52** with butylmagnesium bromide in ether at low temperature gave (3*R*,5*R*,8a*R*)-(−)-gephyrotoxin-223AB (**53**)[16] as the major isomer. Once again, the addition of the Grignard reagent onto the iminium intermediate took place on the same face as the addition of hydrogen in the synthesis of monomorine-I giving rise to the expected *R* configuration at C-3.

‡ Indolizidines are octahydroindolizines.




**Scheme 20**




**Scheme 21**

Using a derived strategy, Grierson[17] reported an interesting preparation of indolizidine alkaloids (Scheme 19). Aminonitrile **54** was prepared through the CN(*R*,*S*) strategy in good yield and transformed to **56** which was obtained as a unique isomer. An elegant and original ring contraction was elaborated to furnish the indolizidine skeleton.

Compound **56** underwent a crucial ring opening with diethylcyanophosphonate to give **57**. Finally, the anion generated α to the nitrogen atom of **57** by decyanation under dissolving metal conditions led to an unprecedented ring cyclization giving diastereomeric indolizidines **58** and **59**.

This approach has been carried out only in the racemic series and deserves to be more widely exploited.

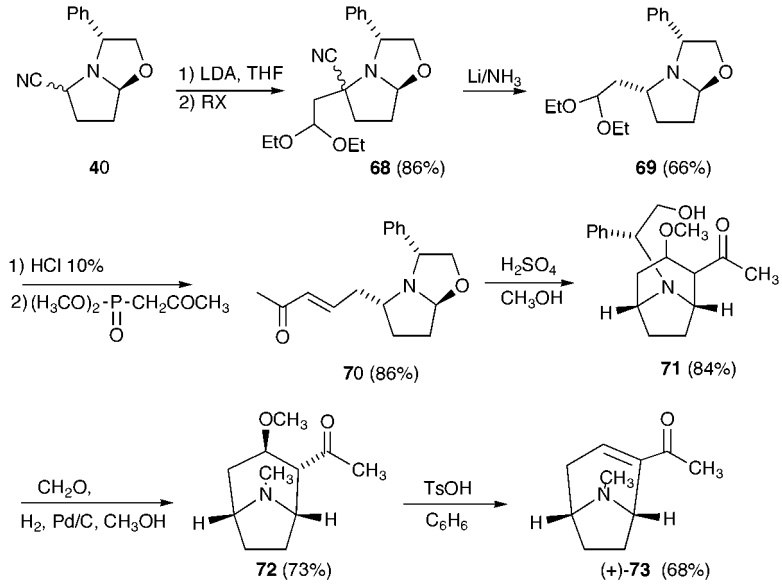
*2.2.2.2 Pyrrolizidine.*§ The synthesis of simple alkyl pyrrolizidines is quite similar to those of monomorine-I or gephyrotoxin-223AB. The preparation of the ant venom (+)-xenovenine **63a**[18] was achieved using the same pathway (Scheme 20). After alkylation and complete diastereoselective decyanation, oxazolidine **61** was alkylated with a Grignard reagent to give the *trans* pyrrolidine **62a** (*trans*/*cis* 77:23). Reductive cyclization gave **63a** in high yield. The absolute configuration of synthetic **63a** was deduced from the synthetic scheme but was in disagreement with data reported in the literature. This discrepancy was eventually lifted by another research group, which confirmed our results.

*2.2.2.3 Tropanes and homotropanes.* To achieve the formation of indolizidine, pyrrolizidine and related skeletons, an α-side chain was cyclized onto the nitrogen atom of the piperidine or pyrrolidine ring. It was anticipated that this cyclization could also occur onto the potential iminium salt of the oxazolidine function to furnish bicylic derivatives of the tropane and homotropane series.

Euphococcinine **67** which possesses a homotropane skeleton, has been extracted from the plant *Euphorbia atoto* as well as from the defense secretion of the ladybugs *Cryptolaenus montrouzieri* and *Epilachna varisvetis*.

The synthesis of the bicyclic system was planned through the intramolecular Mannich reaction of **65**, which could be obtained by nucleophilic alkylation of aminonitrile **64** (Scheme 21). The anion of **1** was treated with 3-bromo-2-methoxyprop-1-ene, to give **64**. The alkylated compound was then reacted with TBDMSOTf to promote the elimination of the nitrile, followed by a methyl Grignard addition and PPTS treatment to give the bicyclic product **66**. The final steps consisted of hydrolysis of the ketal function and hydrogenolysis of the chiral appendage which were achieved in a one-pot reaction to give (−)-euphococcinine **67**.[19] The elaboration and control of the *R* absolute configuration at the C-2 quaternary center was obtained by the

§ Pyrrolizidine is hexahydro-1*H*-pyrrolizine.




**Scheme 22**

entirely diastereoselective addition of the Grignard reagent onto the iminium derived from aminonitrile **64**.

The tropane alkaloid ferruginine **72** was isolated from the arboreal species *Darlingiana ferruginea* and *D. darlingiana*. Interesting nicotinic agonist activity was reported for this type of compound.

It was anticipated that starting from **40**, a Mannich reaction according to a 6-*endo-trig* cyclization would lead to the bicyclic system of ferruginine. In the published syntheses of this alkaloid, introduction of the double bond in the latter steps appeared as a tedious task. This problem was overcome by performing an intramolecular Mannich reaction using an α,β-unsaturated ketone.

Thus, after alkylation of the anion of **40** with bromoacetaldehyde diethyl ketal and decyanation using Li in liquid ammonia, a Wittig reaction permitted the preparation of α,β-unsaturated aldehyde **70** (Scheme 22). This latter product was easily cyclized with $H_2SO_4$ in methanol to give methoxylated bicyclic derivative **71**. This compound was debenzylated and methylated in a one-pot reaction to **72** using $H_2$ with Pd/C in the presence of an aqueous formaldehyde solution. Acidic treatment of **72** in benzene achieved this short (6 steps) and efficient (20% overall yield) synthesis of (+)-ferruginine **73**. This strategy, starting from commercially available materials, compares favorably to previously described synthetic routes.[20]

## 3 Enamine reactivity

Simple α,β-unsaturated piperidines are notoriously unstable and the presence of electron-withdrawing groups at the C-3 position is often a requirement for their synthetic exploitation. It will be shown that building blocks **1** and **40** have proved to be stable and reactive forms of the parent enamine.

### 3.1 Electrophilic substitution

The potential enamine reactivity of **1** was used in an intramolecular cyclization to form the perhydroquinoline skeleton of pumiliotoxin-C,[21] an alkaloid present in the skin secretion of the neotropical frogs, the *Dendrobatidae*. It would appear that the synthesis of the natural enantiomer needs to start with enantiomeric (+)-**1** obtained from (*S*)-(+)-phenylglycinol. The anion of (+)-**1** was easily alkylated to give compound **74** bearing a pentanone side chain (Scheme 23). Ketone **74** gave the cyclized compound **75** upon simple treatment with alumina. In this transformation, the departure of $CN^-$, assisted on alumina, induced the formation of the iminium salt and then the corresponding enamine which reacted with the ketone to give an α,β-unsaturated iminium salt on which 1,4-addition of cyanide afforded **75**. The oxazolidine function of **75** allowed the addition of the propyl side chain. The last two steps consisted of reductive removal of the cyano group ($Na/NH_3$) and hydrogenolysis ($H_2$, Pd/C). A 7:3 mixture of (+)-*2R,5R-trans*-decahydroquinoline **78a** and (−)-pumiliotoxine-C **78b** was then obtained in a 95% combined yield. Among the numerous syntheses of this alkaloid, this scheme represents the second successful synthesis of the natural enantiomer.

### 3.2 Electrochemical halogenation[22]

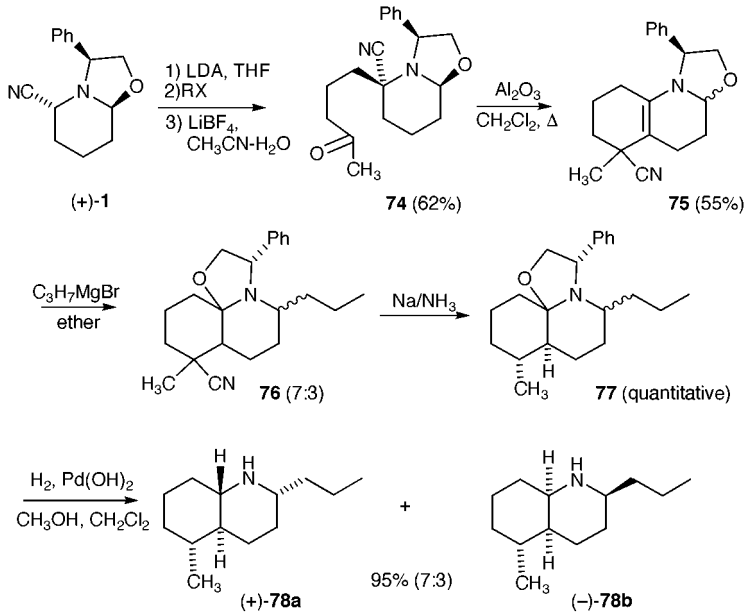
In order to further develop the enamine reactivity, we planned to oxidize one of the potential enamine functions of **1** and **40** by electrochemical means. It was found that anodic oxidation of **1** and **40** in the presence of $Cl^-$, and $Br^-$ as an oxidative mediator, gave respectively the chlorinated derivatives **79** and **80** in high yields (Scheme 24). It is noteworthy that oxidation exclusively occurred at the C-5 position of piperidine and C-4 of pyrrolidine. Moreover, in both series the configuration of the *N*-cyanomethyloxazolidine system remained unchanged. Nevertheless, it has also been shown that it was a specific reaction of the latter system since under these conditions oxazolidine **82** did not afford the corresponding di-halo substitution.

If the $Cl^-$ source was omitted, the reaction occurred with formation of dibromo compound **81** in dry $CH_3CN$ or of lactam **83** in the presence of water.

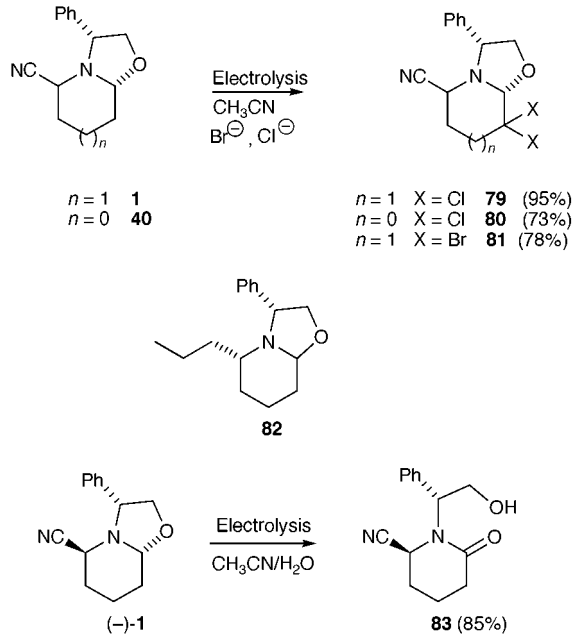
These two latter compounds are useful starting materials for the synthesis of polyfunctionalized piperidines and are currently under investigation.[23]

## 4 Cyano group reactivity

As mentioned above, the α-aminonitrile function of 5-cyano-3-phenylhexahydro-5*H*[1,3]oxazolo[3,2-*a*]pyridine **1** and its derivatives can be used as an iminium equivalent by addition of a nucleophilic reagent: a Grignard or a hydride. In specific cases additions can occur onto the CN group depending upon the experimental conditions.




**Scheme 23**




**Scheme 24**

### 4.1 Nucleophilic addition[24]

When **1** was reacted with BuLi in ether, bicyclic imine **85** was obtained as a rearranged product from imine **84** (Scheme 25). The $NaBH_4$ reduction of **85** followed by hydrogenolysis gave the diamine **86** as a single diastereomer.

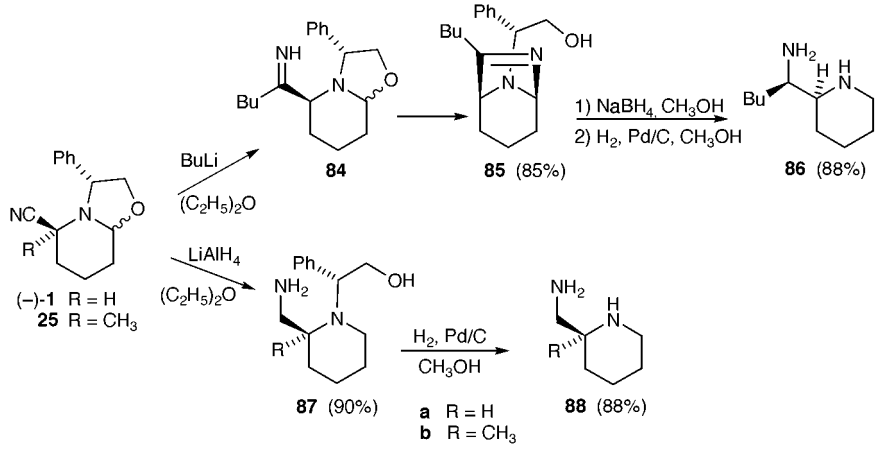
### 4.2 Reduction[24]

The $LiAlH_4$ treatment of **1** in ether led to the reduction of the cyano group as well as the reductive opening of the oxazolidine to furnish the amino alcohol **87a** in high yield (Scheme 25). 1,2-Diamine **88a** was easily obtained after hydrogenolysis. The same strategy applied to the C-2 alkylated compound **25** afforded ((2*S*)-2-methylpiperidin-2-yl)methanamine **88b** difficult to obtain otherwise.

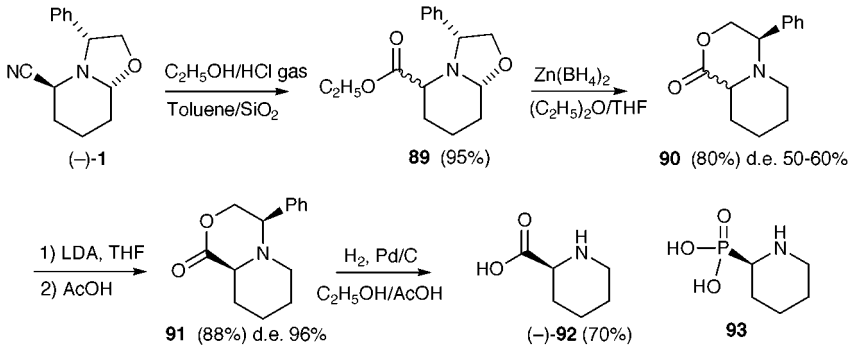
### 4.3 Solvolysis

Compound **1** appeared as a good precursor of (−)-pipecolic acid **92**, an important natural but non-proteinogenic amino acid for the preparation of which only few asymmetric methods are known.

However the solvolysis of **1** was not straightforward; indeed adsorption of a toluene solution of **1** on silica gel was necessary



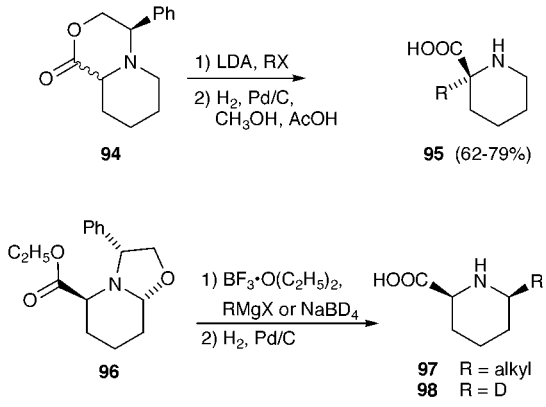

**Scheme 25**




**Scheme 26**

prior to a dry HCl treatment in ethanol. These conditions allowed ester **89** to be isolated in excellent yield (95%) but with some epimerization at C-2 (Scheme 26). Bicyclic lactone **90**, obtained upon reduction of the oxazolidine ring of ester **89**, was expected to allow a controlled epimerization at C-2 through a deprotonation–reprotonation sequence. Treatment of **90** (de 50–60%) by LDA in THF at −78 °C, followed by quenching the enolate with AcOH gave **91** in 96% de, raised to 100% after a single recrystallisation. Pure (*S*)-(−)-pipecolic acid (**92**)[25] was obtained by hydrogenolysis of **91** in the presence of AcOH. The phosphonic analogue **93** of pipecolic acid was also obtained starting from **1** by using an Arbusov reaction as the key step.[26]

The abovementioned intermediates in the pipecolic acid synthesis also enabled access to 2- and 6-substituted pipecolic acids according to previously established chemistry (Scheme 27). Recently, 3-substituted derivatives were also obtained from




**Scheme 27**

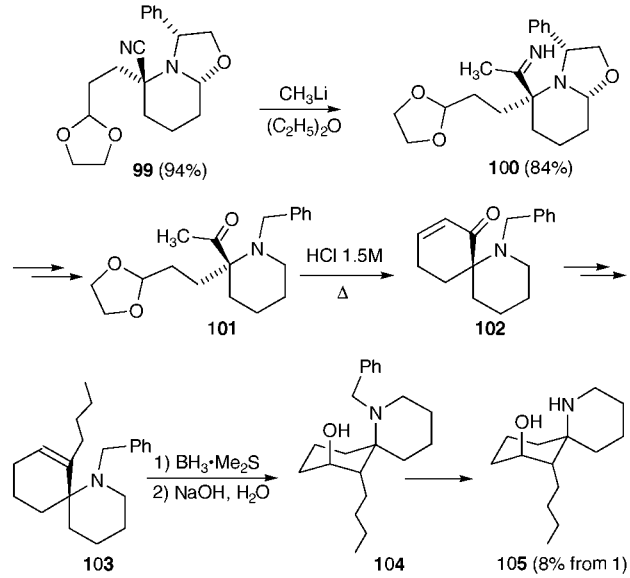
α,β-unsaturated pipecolic intermediates.[27]

The anion of lactone **94** quenched with an alkyl halide gave rise to 2-alkylated amino acids **95** in both high yield and diastereomeric excess. On the other hand the oxazolidine function of ester **96**, after activation with $BF_3{\cdot}O(C_2H_5)_2$, could be alkylated with a Grignard reagent. The 6-alkylated lactones **97** were then obtained in excellent yield. The diastereoselectivity was not as good as for the 2-alkylated products, since the starting material consisted of epimeric mixtures. However, if purified (2*S*)-ester **96** was used, *cis* 6-alkylated compounds **97** were formed with de ranging from 70 to 98%.[25]

This synthetic strategy was recently exploited by Zabriskie *et al*.[28] for the diastereoselective preparation of pipecolic acid derivatives deuterated at C-6, necessary for the study of the stereochemical course of their enzymatic oxidation in mammalians. For instance, **96** was sequentially treated with $BF_3{\cdot}O(C_2H_5)_2$ and $NaBD_4$ to furnish the deuterated lactone precursor of stereoselectively deuterated pipecolic acid **98** (Scheme 27).

### 4.4 Formation of a spiro center[29]

Natural histrionicotoxin, extracted from skins of the Columbian poison frog *Dendrobates histrionicus*, and its analogues are active in neuromuscular transmission. The synthesis of a depentyl analogue of this alkaloid afforded an example for the formation of a spiro carbon center α to the nitrogen of the piperidine ring. The novelty of this synthesis is the use of the cyano group as an integral feature of the target molecule. Introduction of the propanal chain, protected as a ketal, was conducted as usual, and followed by addition of a methyl Grignard in ether to furnish imine **100** in high yield (Scheme 28). Several chemical transformations led to **101**, precursor of




**Scheme 28**

spiro derivative **102** through an aldol reaction. The α,β-unsaturated system permitted the introduction of the butyl chain and the hydroxy group in the required configuration.

## 5 Conclusion

Among the great number of synthetic routes for pyrrolidines and piperidines only two strategies allow a large variety of substitution patterns and enantioselectivity: the substitution of chiral bicyclic lactams developed by Meyers;[30] and the CN(*R*,*S*) method based on the reactivity of the *N*-cyanomethyloxazolidine system.

It should be mentionned that Comins[31] has extended his method of functionalization of 1-acylpyridinium salts to the corresponding chiral series allowing the efficient synthesis of a large variety of piperidine alkaloids. This method is based on

the use of a series of chiral auxiliaries whereas a β-amino alcohol derived from the chiral pool is the source of both nitrogen and chirality in the two others.

A good way to compare the respective advantages of each strategy in the piperidine series is to examine their potential as synthetic equivalent, *i.e*. cationic or anionic synthons (Fig. 3).

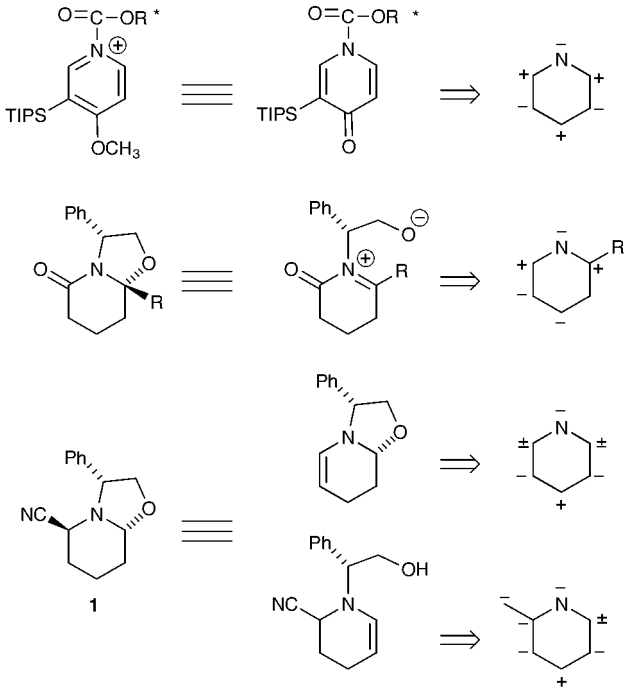



**Fig. 3**

An interesting characteristic of the pyridinium salt is a facile functionalization at C-4 after the first nucleophilic attack at C-2 generating a ketone.

The chiral bicyclic piperidine and pyrrolidine lactams have been successfully employed for the asymmetric construction of quaternary centers in carbocyclic series. They have more recently received applications for the synthesis of alkaloids although their potential has not been extensively exploited. It should be noted that the C-4 position of the piperidine ring can also be substituted by alkylation of α-cyano enamines derived from bicyclic lactams.[32]

As far as the CN(*R*,*S*) method is concerned the presence of a cyano group offers additional synthetic possibilities. Indeed the α-aminonitrile function includes both potential and masked iminium reactivities. Furthermore, the cyano group itself is a precursor for carbonyl and methylamino functions. The challenge of functionalization of the C-4 position of piperidines could be possible by bromination at C-5 followed by elimination providing a potential conjugated iminium system. Thus substitution of any or all of the ring atoms becomes possible. Interestingly, one might consider that most of the syntheses of alkaloids achieved according to the CN(*R*,*S*) method probably follow part of a biomimetic route, that is to say reproduce a key step of what is occurring in nature. The efficiency and the shortness of some syntheses carried out might confirm the likelihood of this hypothesis.

In many examples it has been shown that complicated things can be simple according to this strategy.

## 6 Acknowledgements

The authors are pleased to thank all their colleagues, collaborators and students whose names are listed along the references. Their intellectual and practical participation was outstanding for the development of the CN(*R*,*S*) method.

## 7 References

1 L. Guerrier, J. Royer, D. S. Grierson and H.-P. Husson, *J. Am. Chem. Soc*., 1983, **105**, 7754.
2 M. Bonin, D. S. Grierson, J. Royer and H.-P. Husson, *Org. Synth.*, 1992, **70**, 54.
3 V. Ratovelomanana, L. Vidal, J. Royer and H.-P. Husson, *Heterocycles*, 1991, **32**, 879.
4 J. M. McIntosh and L. C. Matassa, *J. Org. Chem*., 1988, **53**, 4452.
5 V. Ratovelomanana, J. Royer and H.-P. Husson, *Tetrahedron Lett*., 1985, **26**, 3803.
6 P. Lienard, J. Royer, J.-C. Quirion and H.-P. Husson, *Tetrahedron Lett*., 1991, **32**, 2489.
7 C. Yue, I. Gauthier, J. Royer and H.-P. Husson, *J. Org. Chem*., 1996, **61**, 4949.
8 C. Yue, J. Royer and H.-P. Husson, unpublished results.
9 D. S. Grierson, J. Royer, L. Guerrier and H.-P. Husson, *J. Org. Chem*., 1986, **51**, 4475.
10 H. Poerwono, K. Higashiyama, T. Yamauchi, H. Kubo, S. Ohmiya and H. Takahashi, *Tetrahedron*, 1998, **54**, 13955.
11 C. Agami, F. Couty and H. Mathieu, *Tetrahedron Lett*., 1998, **39**, 3505.
12 J. Royer and H.-P. Husson, *Tetrahedron Lett.*, 1987, **28**, 6175.
13 S. Arseniyadis, P. Q. Huang and H.-P. Husson, *Tetrahedron*, 1988, **44**, 2457.
14 A. R. Katrizky, G. Qiu, B. Yang and P. J. Steel, *J. Org. Chem*., 1998, **63**, 6699; A. R. Katrizky, X.-L. Cui, B. Yang and P. J. Steel, *J. Org. Chem*., 1999, **64**, 1979.
15 J. Royer and H.-P. Husson, *J. Org.Chem*., 1985, **50**, 670.
16 J. Royer and H.-P. Husson, *Tetrahedron Lett*., 1985, **26**, 1515.
17 E. Zeller and D. S. Grierson, *Heterocycles*, 1988, **27**, 1575.
18 S. Arseniyadis, P. Q. Huang and H.-P. Husson, *Tetrahedron Lett*., 1988, **29**, 1391.
19 C. Yue, J. Royer and H.-P. Husson, *J. Org. Chem*., 1992, **57**, 4211.
20 I. Gauthier, J. Royer and H.-P. Husson, *J. Org. Chem*., 1997, **62**, 6704.
21 M. Bonin, J. Royer, D. S. Grierson and H.-P. Husson, *Tetrahedron Lett*., 1986, **27**, 1569.
22 F. Billon-Souquet, T. Martens and J. Royer, *Tetrahedron*, 1996, **52**, 15127.
23 F. Billon-Souquet, T. Martens and J. Royer, *Tetrahedron Lett.*, 1999, **40**, 3731.
24 O. Froelich, P. Desos, M. Bonin, J.-C. Quirion and H.-P. Husson, *J. Org. Chem*., 1996, **61**, 6700.
25 J.-F. Berrien, J. Royer and H.-P. Husson, *J. Org. Chem*., 1994, **59**, 3769.
26 C. Maury, Q. Wang, T. Gharbaoui, M. Chiadmi, A. Tomas, J. Royer and H.-P. Husson, *Tetrahedron*, 1997, **53**, 3627.
27 A. Zaparucha, M. Danjoux, A. Chiaroni, J. Royer and H.-P. Husson, *Tetrahedron Lett.*, 1999, **40**, 3699.
28 T. M. Zabriskie, W. L. Kelly and Xi Liang, *J. Am. Chem. Soc*., 1997, **119**, 6446.
29 J. Zhu, J. Royer, J.-C. Quirion and H.-P. Husson, *Tetrahedron Lett*., 1991, **32**, 2485.
30 A. I. Meyers and G. P. Brengel, *Chem. Commun*., 1997, 1.
31 D. L. Comins and S. P. Joseph, in *Advances in Nitrogen Heterocycles*, ed. C. J. Moody, vol. 2, pp. 251–294, JAI Press Inc., 1996.
32 J. B. Schwarz and A. I. Meyers, *J. Org. Chem*. 1998, **63**, 1619.

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