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A NEW APPROACH TO THE ASYMMETRIC SYNTHESIS OF ALKALOIDS[1]

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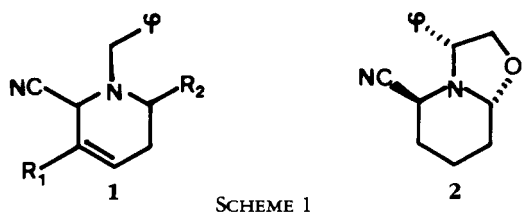
ABSTRACT.—The condensation of glutaraldehyde with (−)-phenylglycinol in the presence of KCN led to the formation of a single chiral 2-cyano-6-oxazolopiperidine synthon equivalent of 1,4-dihydropyridine. Reaction conditions were established that differentiated the reactivity of the aminonitrile and aminoether moieties of the synthon enabling the control of relative and absolute configurations over the 2- and 6-positions. Applications of this versatile synthon to the asymmetric synthesis of simple or complex piperidine alkaloids have been developed. The following alkaloids were obtained in optically pure form: (+) and (−) coniine, (+) and (−) dihydropinidine, (+) solenopsin-A, (−) monomorine, (−) gephyrotoxin-223 AB, (+) and (−) pumiliotoxin-C, (+) nitramine, and (−) isonitramine.

The alkaloids constitute a large group of plant and animal substances that display a wide diversity in structure. Despite this apparent multiformity of structural types, the piperidine ring is an integral feature in the structure of a large number of these natural compounds (simple piperidines, spiropiperidines, decahydroquinolines, azabicyclic systems, monoterpenoid indole alkaloids, etc.).

The development of synthetic methodologies in which preformed piperidine building units are used as synthons for the construction of more complex alkaloid structures is, thus, a challenging problem. Over the past twenty years, several synthetic approaches for the preparation of alkaloids involving the use of dihydro- or tetrahydropyridines in this regard have been proposed (1-7). However, these latter intermediates prepared through existing techniques are notoriously unstable and react efficiently with only a limited number of reagents. Moreover, no attempt has been paid to envisage a general route to an asymmetric synthesis of synthons, which could serve as a chiral template for the synthesis of various alkaloids. Our interest in the biological activities of many piperidine alkaloids led us to seek a general expeditious route to these naturally occurring derivatives from a simple starting material.

We have developed the chemistry of two piperidine synthons that represent stable equivalent forms of the dihydropyridine system. The first involved the facile regiospecific preparation of racemic 2-cyano adducts (**1**) of 5,6-dihydropyridinium salts (8) while the second is based on the utilization of the readily available 2-cyano-6-oxazolopiperidine (**2**), a chiral 1,4-dihydropyridine equivalent (Scheme 1).

At first I shall discuss the chemistry of **1** in connection with the reactivity of α-aminonitriles as potential and masked iminium salts. However, the principal topic of this lecture concerns the piperidine synthon **2**, in which the α-aminonitrile and α-



1 **2**

SCHEME 1

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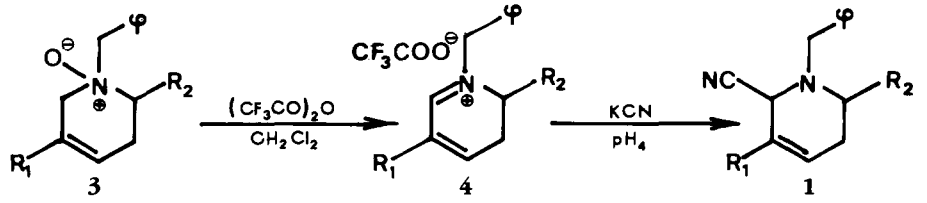
aminoether moities provide control over the substitution of four carbon centers. Inasmuch as **2** was obtained in optically pure form, its utilization for the enantiospecific syntheses of alkaloids became possible.

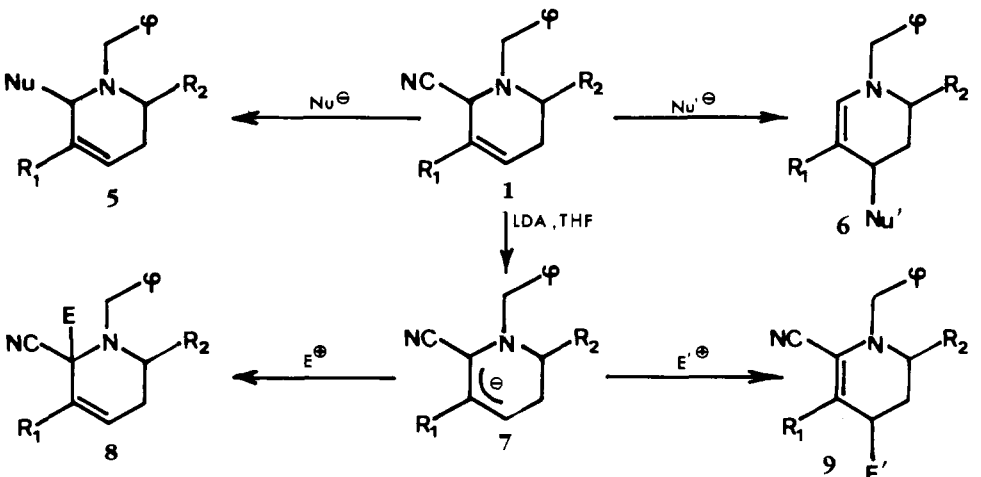
SYNTHESIS AND CHEMISTRY OF 2-CYANO Δ^3 PIPERIDEINES (9).—It was felt that the simplest way to prepare dihydropyridine equivalents would be the formation of adducts with nucleophiles, which could subsequently act as good leaving groups. The introduction of CN^- into iminium salt has been demonstrated to give α-aminonitriles, and it has been shown that this reaction could provide a means for the preparation protected 1,2-dihydropyridines. The reaction of *N*-alkyl-Δ^3-piperideine *N*-oxides (**3**) with $(CF_3CO)_2O$ (modified Polonovski reaction) led to the regiospecific formation of the corresponding 5,6-dihydropyridinium salts (**4**). The C-2 cyano adduct **1** was the only observed regioisomer obtained on treatment of **4** with KCN (Scheme 2). The reactivity of **1** as a "potential" 5,6 dihydropyridinium salt was demonstrated by its regio-



SCHEME 2

specific reaction at C-2 with Grignard reagents and at C-4 with cuprate reagents and β-dicarbonyl anions. Alternatively, aminonitrile **1** was metalated with LDA to give the ambident anion **7**, thus providing an "umpolung" of the normal electrophilicity at C-2 and C-4. Anion **7** reacted regioselectively with a series of alkyl and acyl halides and esters under kinetically controlled conditions to give either the C-2 or C-4 substituted products. Reaction of **7** with aldehydes and lactones occurred under equilibrating conditions (Scheme 3).

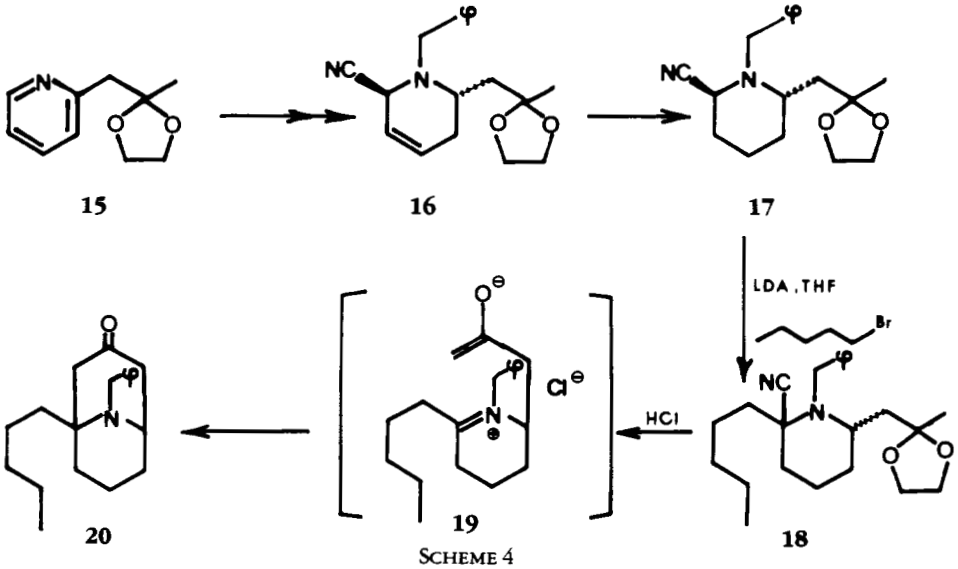
Synthesis of the Ladybug Alkaloid (±) Adaline (**11**).—To illustrate how 2-cyano-Δ^3-piperideines have been used as synthons for a general approach to the construction of various alkaloids (10-19), I shall discuss the synthesis of adaline (**11** (20). The ladybug alkaloids adaline (**11**) and coccinelline (**12**) possess structural similarities suggesting that they are derived from a common biosynthetic precursor, Δ^2 piperideine (**10** (Figure 1). Similarly, it has been proposed that the poison-dart frog toxins pumiliotoxin-C



SCHEME 3.

(**13**) and histrionicotoxin (depicted as its perhydroderivative) (**14**) are also derived from a Δ^2 piperideine of type **10**. Thus, despite the diverse origins of these groups of compound, a common element, a 2,6-disubstituted piperideine, is involved in their biogenesis. It is this element which, in turn, suggests a common biomimetic approach to their syntheses.

The key step in our synthetic route is the regiospecific preparation of a 2,6- disubstituted piperidine wherein an α-aminonitrile group at C-2 allows alkylation with the convenient functionalized chain and retains a potential iminium or enamine function. An intramolecular Mannich reaction of the intermediate iminium-enol **19** derived from the aminonitrile **18** led to the formation of *N*-benzyladaline (**20**) in 90% yield (Scheme 4). Final hydrogenolytic cleavage of the *N*-benzyl group (Pd/C, H_2) then gave adaline (**11**) (Figure 1).



SCHEME 4

In connection with our interest in a general method for the synthesis of optically active alkaloids, we were prompted to consider a new strategy based upon the 1,4-dihydropyridine system. Indeed, 1,4-dihydropyridine considered as a bis-enamine has the synthetic potential of the above-mentioned biogenetic intermediate **10** (Figure 1).

SYNTHESIS AND CHEMISTRY OF 2-CYANO-6-OXAZOLOPIPERIDINE (8).—It was evident that a synthon equivalent of 1,4-dihydropyridine should (a) be readily available; (b) show nonequivalent reactivities at the C-2 and C-6 positions (providing control over four carbon centers); and (c) be chiral. The Robinson-Schopf type condensation of glutaraldehyde with aminoalcohols in the presence of KCN appeared as a particularly attractive route to the type of synthon we were seeking (21). Thus, the condensation of (−) phenylglycinol (**21**) with glutaraldehyde and KCN led in a "one-pot reaction" to the formation of a single chiral crystalline 2-cyano-6-oxazolopiperidine **2** in 50% yield (Scheme 5). Among the desirable structural features of this new synthon is the facile deprotection of the benzylic amine function. Since biological activity of natural products is generally associated with only one enantiomer, it was important to be able to prepare the desired isomer from the single starting material **2**.

As we have previously observed that the nucleophilic substitution of 2-cyanopiperidines occurred under stereoelectronic control, (19) it was thought that the intermediate iminium would be specifically attacked by nucleophiles leading to only one

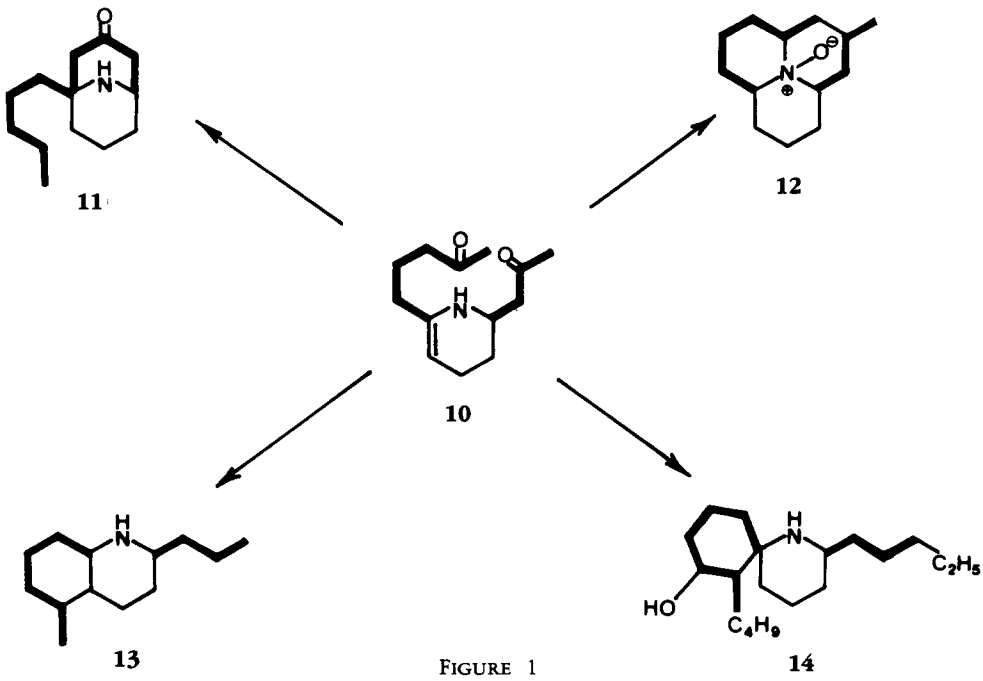
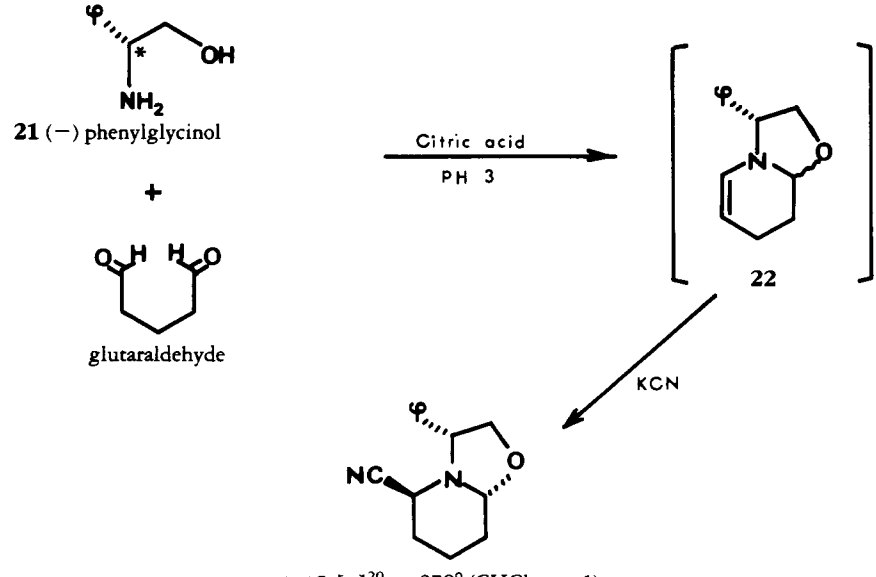


FIGURE 1

diastereomer (Figure 2). In this event, replacement of a nucleophile by an hydride would give the opposite configuration at the same carbon center. This is illustrated by the enantiospecific synthesis of both (+) and (−) enantiomers of 2-propylpiperidine (coniine) and of 2,6-*cis*- or *trans*-dialkylpiperidines (dihydropinidine and solenopsin).

Alkylation of the anion of **2** (Scheme 6) with propyl bromide produced compound **23** in nearly quantitative yields. Reaction of this product with $NaBH_4$ in EtOH then gave alcohol **24** (9:1 mixture of 2*S*:2*R* diastereomers). Under hydrogenolysis conditions, the chiral auxiliary attached to the nitrogen atom was cleaved, giving (2*S*)-(+)-coniine (**25**). The high stereoselectivity observed in the formation of **24** implied a



(−)**2** $[\alpha]^{20}D-278°$ ($CHCl_3$, c=1)
Yield: 50% after crystallization

SCHEME 5

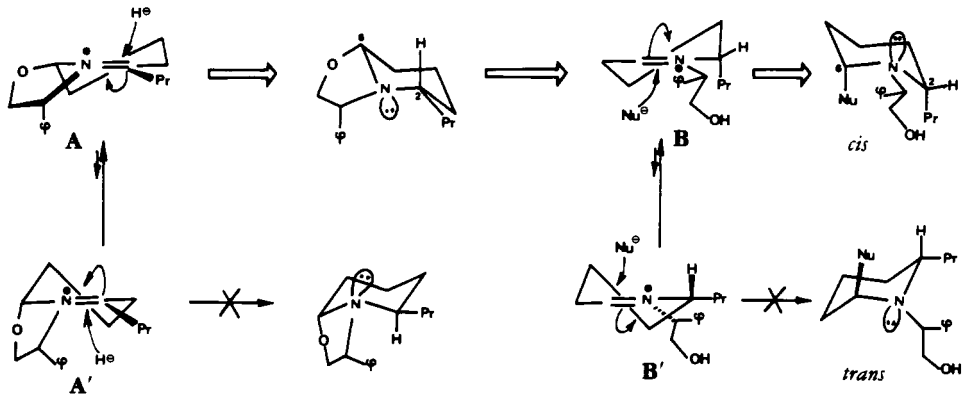


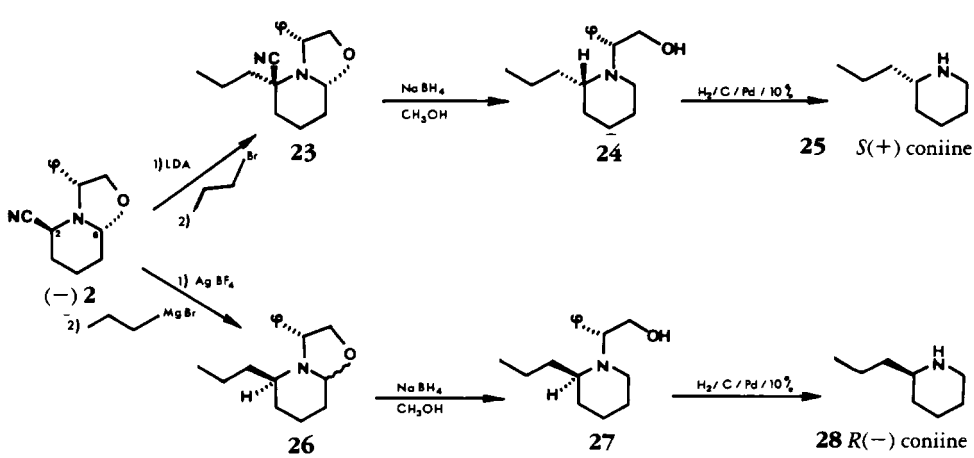
FIGURE. 2. Stereoelectronic control of additions at centers C-2 and C-6.

mechanism wherein the hydride ion approached the intermediate iminium from the axial direction (upper face) generating the 2*S* absolute configuration.

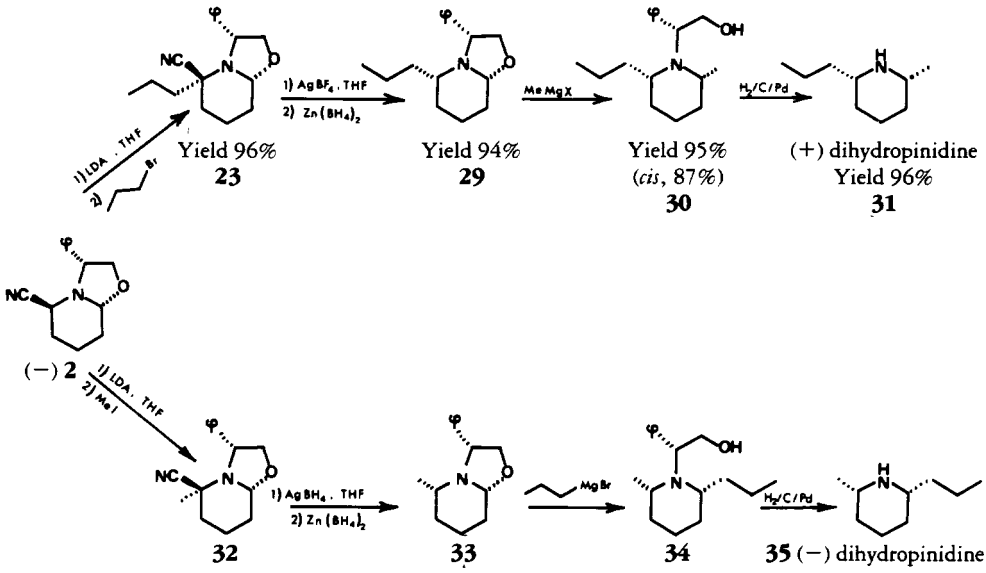
By the same mechanism, a propyl chain was introduced at C-2 of **2** in the opposite *R* configuration on reaction with PrMgBr. For this transformation, prior complexation of the cyano group with $AgBF_4$ was necessary to ensure reaction of the amino nitrile moiety only. (−) Coniine (**28**) was then obtained from **26** by $NaBH_4$ reduction followed by hydrogenolysis.

The functionality at C-6 was lost in the reductive decyanation of **23** and **26**, which was undesirable for the synthesis of 2,6-disubstituted alkaloids. To circumvent this problem, it was necessary to use reaction conditions selective for the removal of the cyano group. This was accomplished by complexation of the cyano group with $AgBF_4$ followed by reaction with $Zn(BH_4)_2$ at low temperature. Thus, compound **23** (Scheme 7) was stereospecifically and regiospecifically reduced to **29**, which was then reacted with MeMgI giving the 2,6-*cis*-dialkylpiperidine (**30**) (*cis-trans*, 87:13). Hydrogenolysis of **30** led to the formation of optically pure (2*S*, 6*R*)-(+)-dihydropinidine (**31**) having the natural configuration. In a similar fashion, (−)-dihydropinidine (**35**) was obtained by reversal of the introduction of the substituents (i.e., at first methyl and then propyl groups).

Concerning the mechanism of stereoselective substitution at C-6, it is felt that allylic $A^{1,2}$ strain interaction between the N-1 and the C-2 substituents is sufficient to confer a preference for the C-2 alkyl pseudo-axial conformation in the transition state



SCHEME 6. Enantiospecific synthesis of (+) and (−) coniine from a single synthon.

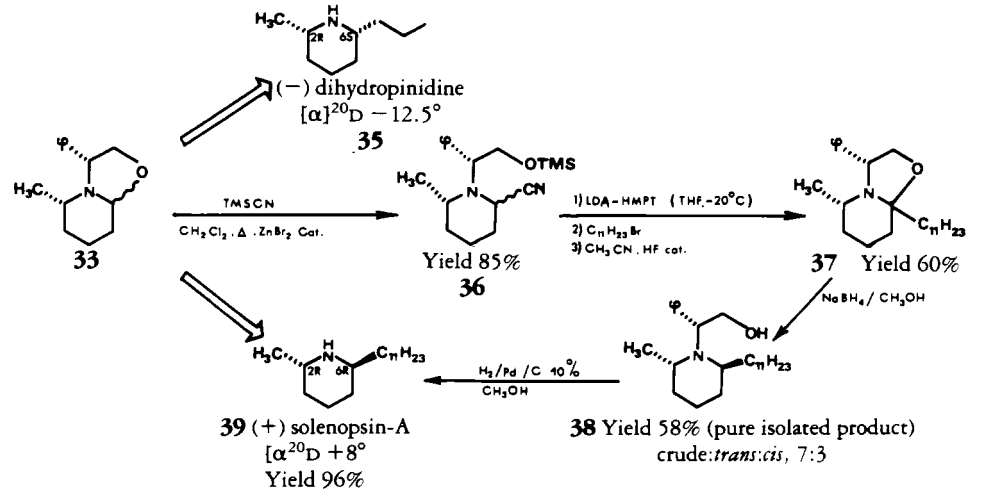


SCHEME 7

(Figure 2). If one considers the most favored chair-like intermediate, the conformer **B′** suffers from unfavorable interactions, and thus the stereoelectronically controlled approach of the nucleophile from the axial direction leads to the 2,6-*cis*-diaxial stereochemistry. Final ring inversion gives the more stable *cis*-diequatorial alkaloids **31** and **35**.

Synthesis of (+) Solenopsin-A (**39**) (22).—Knowing the factors controlling the relative stereochemistry at C-2 and C-6, it became possible to imagine a strategy to synthesize the 2,6-*trans*-derivatives, which are more difficult to obtain than their *cis*-analogs. The key step in this strategy is the efficient opening of the oxazolidine ring to a 6-cyano piperidine, which can be alkylated and stereoselectively reduced. To illustrate this approach, we have synthesized the *trans*-alkaloid (+)-solenopsin-A (**39**), a constituent of the fire-ant venom.

It was found that reaction of the oxazolidine **33** with $(Me)_3SiCN$ in CH_2Cl_2 in the presence of a catalytic amount of $ZnBr_2$ led to the formation of the α-aminonitrile **36** (Scheme 8). Alkylation of **36** under the usual conditions followed by deprotection of



SCHEME 8. Control of relative stereochemistry at C-2 and C-6. Enantiospecific synthesis of (+) solenopsin-A.

the primary alcohol (CH_3CN, HF cat.) resulted in recyclization of the oxazolidine ring (**37**). Finally, $NaBH_4$ reduction of **37** led to predominant formation of the *trans*-isomer **38** (7:3 mixture with the *cis*-isomer; 58% yield of pure isolated *trans*-product). As expected, the hydride attack on the intermediate iminium occurred from the α-face. Compound **38** was then debenzylated to (+)-solenopsin-A, which has 2*R*,6*R* absolute configuration (the rotation of the natural product is unknown).

*Synthesis of (−)-Monomorine-I (**40**) (23) and (−)-Gephyrotoxin-223 AB (**41**) (24).*— As chemio- and stereo-selective reaction can be achieved at either the C-2 or C-6 centers of the chiral synthon **2**, and as hydrogenolysis produces a secondary nitrogen center capable of undergoing an intramolecular ring closure, this synthon represents an ideal starting point for the chiral synthesis of indolizidine alkaloids. Since the ant trail pheromone monomorine-I (**40**) and the neurotoxic frog gephyrotoxin-223 AB (**41**) essentially differ in the stereochemistry at C-3, we were prompted to take advantage of an intermediate $>\overset{+}{N}=$C-3 pyrrolidinium ion for their synthesis. Indeed, as additions should selectively occur at the less hindered β-face of the molecule, there is a possibility for the control of the stereochemistry at C-3 (Figure 3).

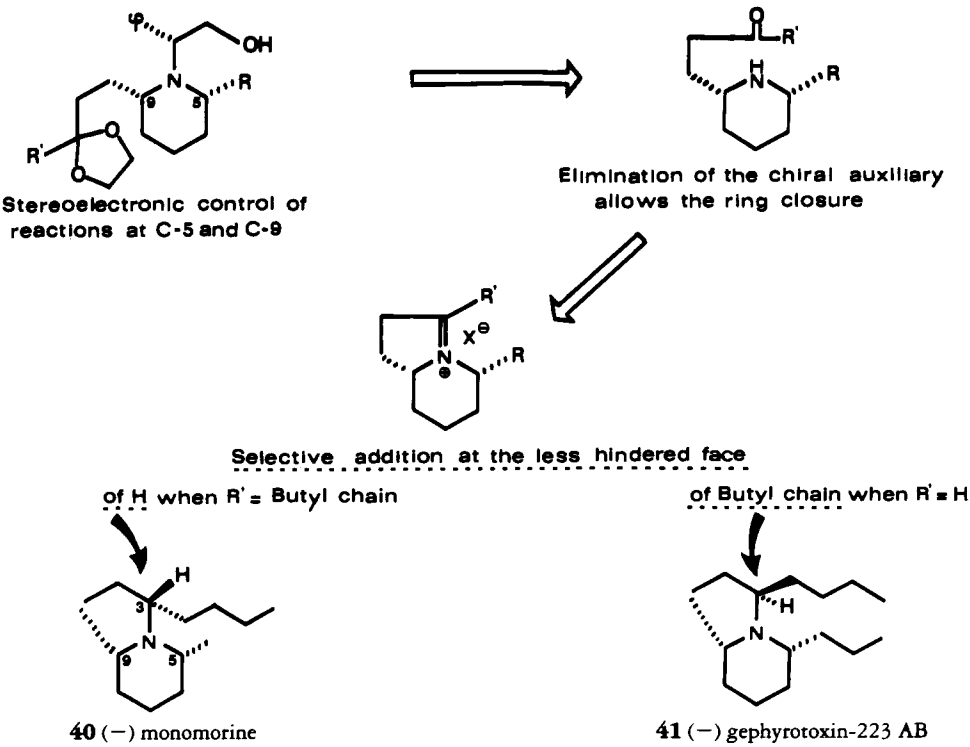
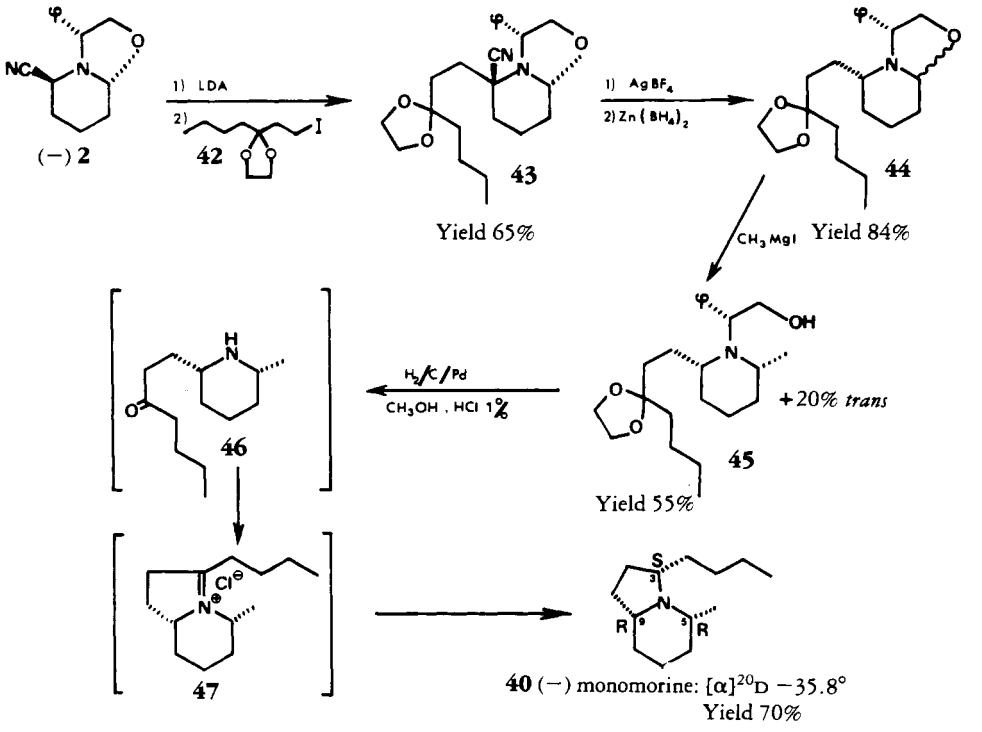


FIGURE 3. Control of stereochemistry in the synthesis of indolizidine alkaloids.

Alkylation of **2** with iodo ketal (**42**) led to the formation of a single product **43** (Scheme 9). The amino nitrile moiety of **43** was then selectively reduced by prior complexation of the cyano group with $AgBF_4$ followed by reaction with $Zn(BH_4)_2$, as described above, to give **44**. Compound **44** was obtained in 84% yield as a 3:2 mixture of C-6 epimeric oxazolidines having the 2*S* configuration. A likely reversible opening of the oxazolidine ring during both the reaction work-up and subsequent chromatographic purification accounts for the observed epimerization at C-6.

The reaction of **44** with CH_3MgI afforded a 4:1 mixture of the desired *cis*-alcohol **45** and its *trans*-isomer. Compound **45** was then treated under catalytic hydrogenation



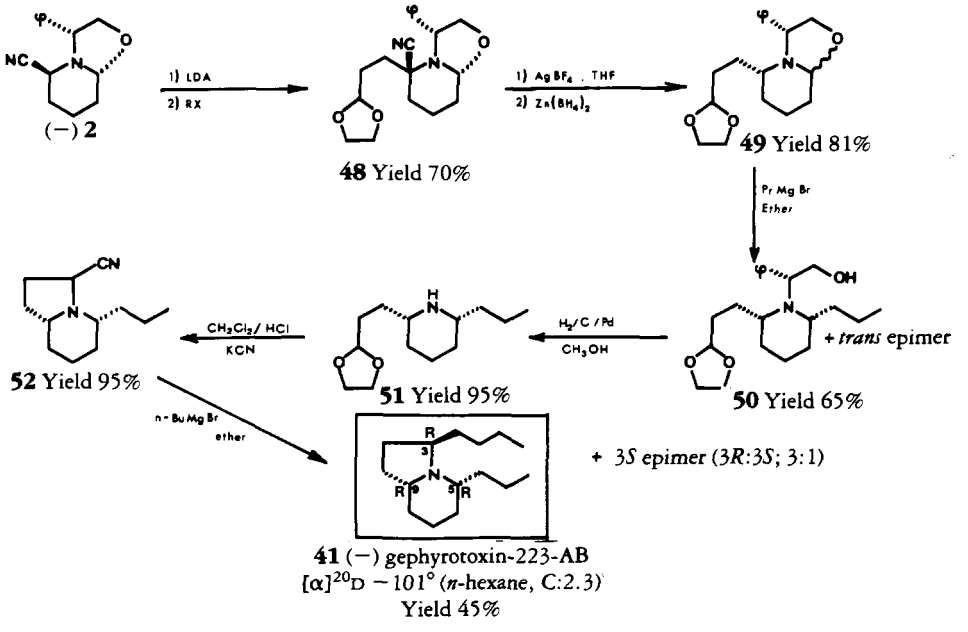
SCHEME 9. Synthesis of (−) Monomorine-I.

conditions in acidic medium, which led to hydrogenolysis of the chiral auxiliary and liberation of the ketone function. Intramolecular formation of the iminium intermediate **47** followed by reduction under the same conditions give (−)-monomorine I (**40**) in a "one-pot" reaction.

As the absolute configuration at the C-5 and C-9 centers of **40** were known on the basis of our previous results, we concluded that the absolute configuration of (−)-monomorine-I is 3*S*, 5*R*, 9*R*. The natural alkaloid being dextrorotatory, it therefore has the 3*R*, 5*S*, 9*S* absolute configuration.

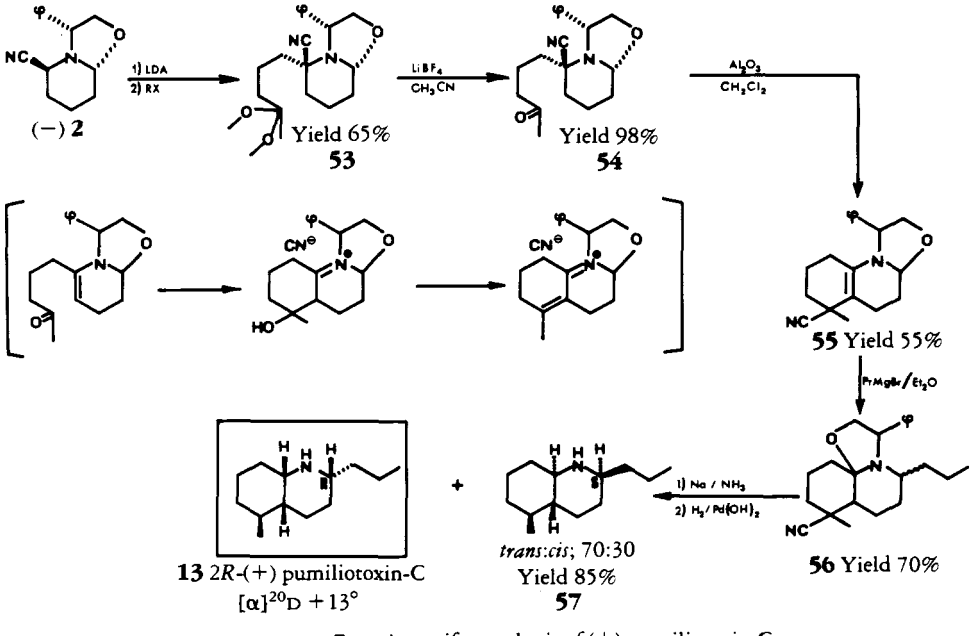
The structure and relative configuration of gephyrotoxin-223 AB (**41**), a neurotoxic alkaloid extracted from the skin of tropical frogs, have been well established, but the absolute configuration of this molecule remained unknown. We thus arbitrarily chose to prepare the 3*R*, 5*R*, 9*R* enantiomer of **41** following a variation of the scheme that was used for (−)-monomorine-I. The crucial step of this synthesis was the stereoselective introduction of the butyl chain at C-3 of **52** via the intermediate iminium ion (Scheme 10). As our synthetic material exhibited the same sign of optical rotation as the natural product, we then deduced that the absolute configuration of the natural (−)-gephyrotoxin-223 AB is 3*R*, 5*R*, 9*R*.

Synthesis of (+) *and* (−) *Pumiliotoxin-C* (**13**) (25).—The alkylated α-aminonitrile **53** can be considered as a potential form of the proposed biogenetic intermediate **10** (Figure 1). To complete the synthesis of the poison-dart frog toxin pumiliotoxin-C from **53**, it was necessary to (a) cyclize it to the quinoline system, (b) control the introduction of the propyl chain at C-2, and, finally, (c) reduce the $\Delta^{9,10}$ enamine double bond. An efficient method for the cyclization of **53** was discovered when the crude product from the ketal hydrolysis **54** was column chromatographed on alumina (Scheme 11). On contact with alumina (Merck, Art. 1097), elimination of CN^-, cyclization, dehydration, and, finally, 1,4-reintroduction of CN^- into the resultant conju-



SCHEME 10. Synthesis of (−) gephyrotoxin-223 AB.

gated *iminium* occurred successively, giving the cyano enamine **55**. The reaction of epimeric **55** with PrMgBr gave **56**, which was transformed to a mixture of pumiliotoxin-C (**13**) and its *trans*-epimer **57** (*trans:cis*:70:30), by decyanation with NH_3/Na liquid followed by hydrogenolytic cleavage of the *N*-benzyl group.

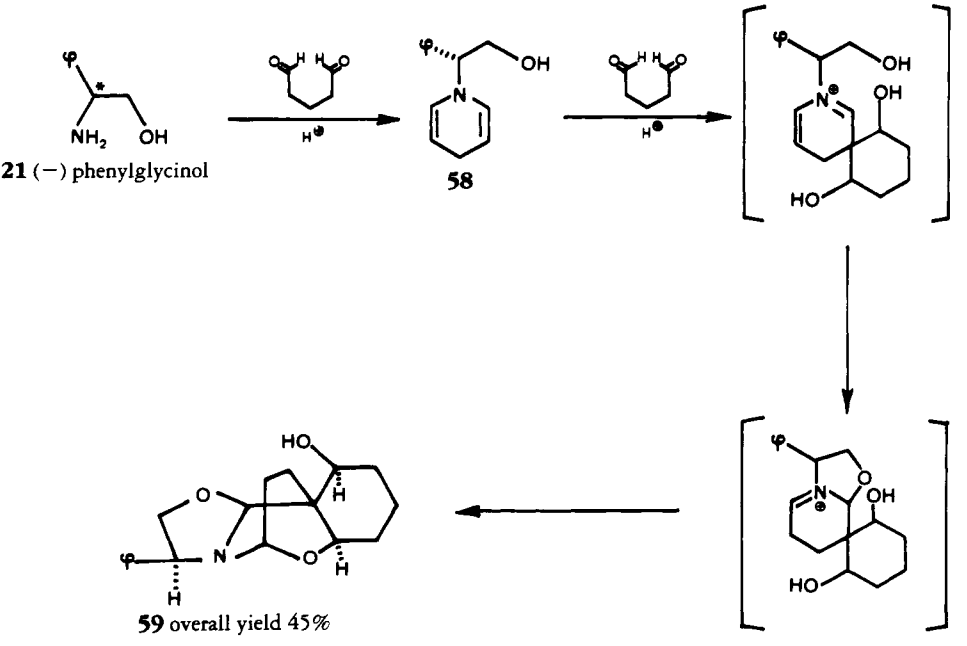


SCHEME 11. Enantiospecific synthesis of (+)-pumiliotoxin-C.

Starting from the usual (−)-synthon **2** the 2*R*-(+)-pumiliotoxin-C was obtained. The natural 2*S*-(−)alkaloid was synthesized in the same way from the enantiomeric (+)-synthon prepared from (+)-phenylglycinol.

Synthesis of (−) and (+) *Isonitramine* (**63**) *and* (**66**) *and of* (+) *Nitramine* (**67**)

(26).—The alkaloids (−) isonitramine (**63**) and (+) nitramine (**67**) were isolated from two species of the genus *Nitraria* by Russian chemists. Their structures have been determined by X-ray analysis (27), and the first synthesis of racemic nitramine has been recently achieved (28). These new alkaloids belong to the unusual spiropiperidine class of alkaloids. A great deal of interest has been shown in the preparation of piperidines containing a spiro cyclohexane substituent, this system occurring in the potent frog toxin histrionicotoxin (**14**) (Figure 1). Although the origin of the nitramine series differs from that of the frog toxins as depicted in Figure 1, it became possible to envisage their synthesis from a dihydropyridine synthon. Indeed, our observation that the condensation of (−)-phenylglycinol with glutaraldehyde in the absence of KCN did not lead to the synthon **2** but to the interesting compound **59** (Scheme 12) prompted us to con-



SCHEME 12

sider the asymmetric synthesis of the nitramine-type alkaloids from **59**. An interesting structural feature of **59** is the presence of symmetrically located functions on the cyclohexane ring at the α and α′ positions of the spiro carbon atom. One can thus imagine that removal of one or the other of these hydroxyls would give both enantiomers of nitramine or isonitramine (Figure 4). As the absolute configuration of the latter alkaloids and of their precursor (**59**) is unknown, it is not at present possible to predict which isomer would be formed.

Synthesis of the desired *O*-mesyl derivative **60** proceeded smoothly. $LiAlH_4$ reduction of the mesylate prepared from **59** under carefully controlled conditions led preferentially to the spiropiperidine **60** (Scheme 13). Examination of a variety of reaction conditions for elimination of the mesylate gave complex mixtures mainly due to Grob-type fragmentations. It thus became necessary to protect the hydroxyl functions by reaction with benzoyl chloride. The resulting benzoate **61** was heated in DMSO in the presence of DBU to give **62** (after removal of the ester function with $LiAlH_4$). Final concomitant hydrogenation of the double bond and hydrogenolysis of the chiral moiety afforded (−)-isonitramine (**63**).

Our second objective was to demonstrate that elimination of the other secondary hydroxyl group could lead to the enantiomeric (+) isonitramine (**66**) (Scheme 14). At

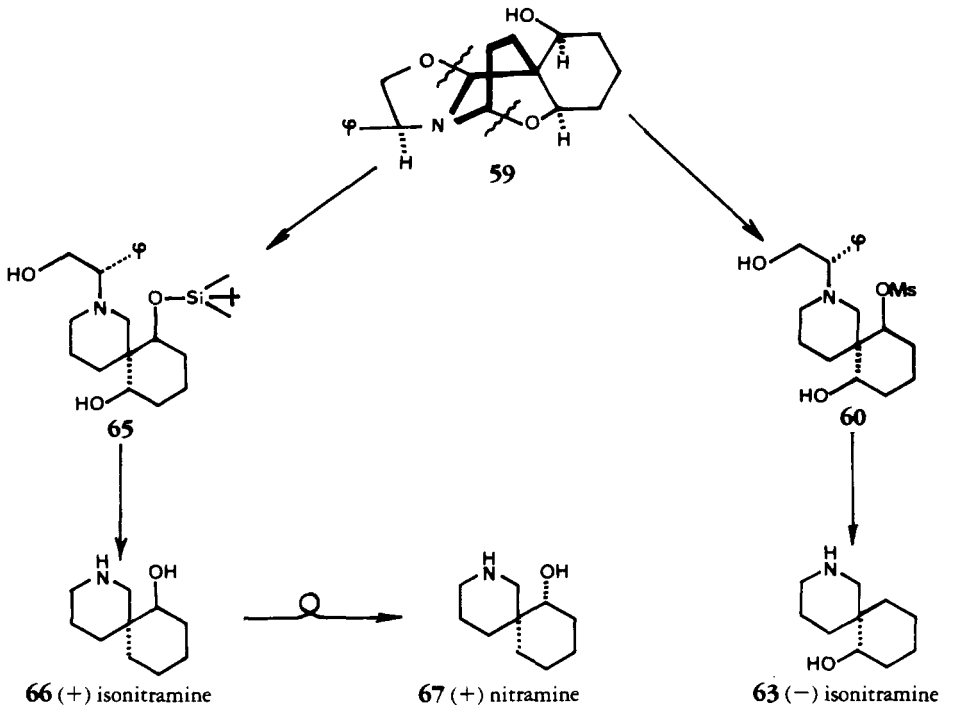
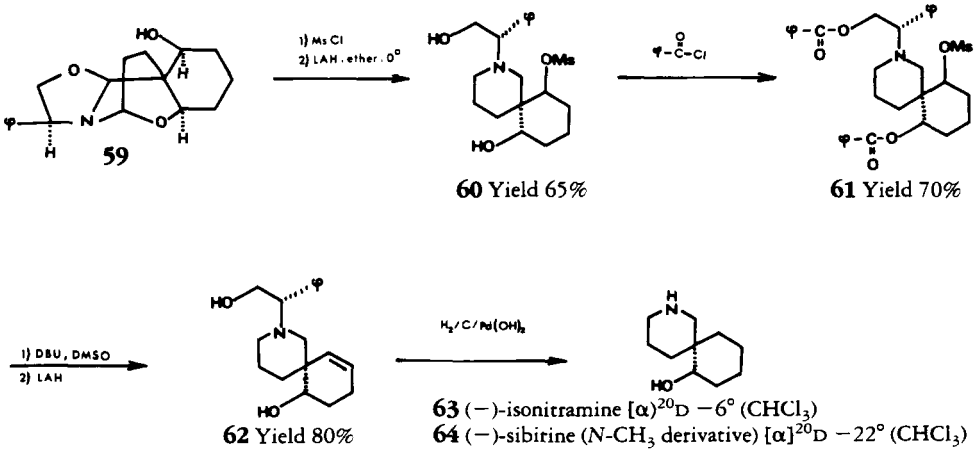


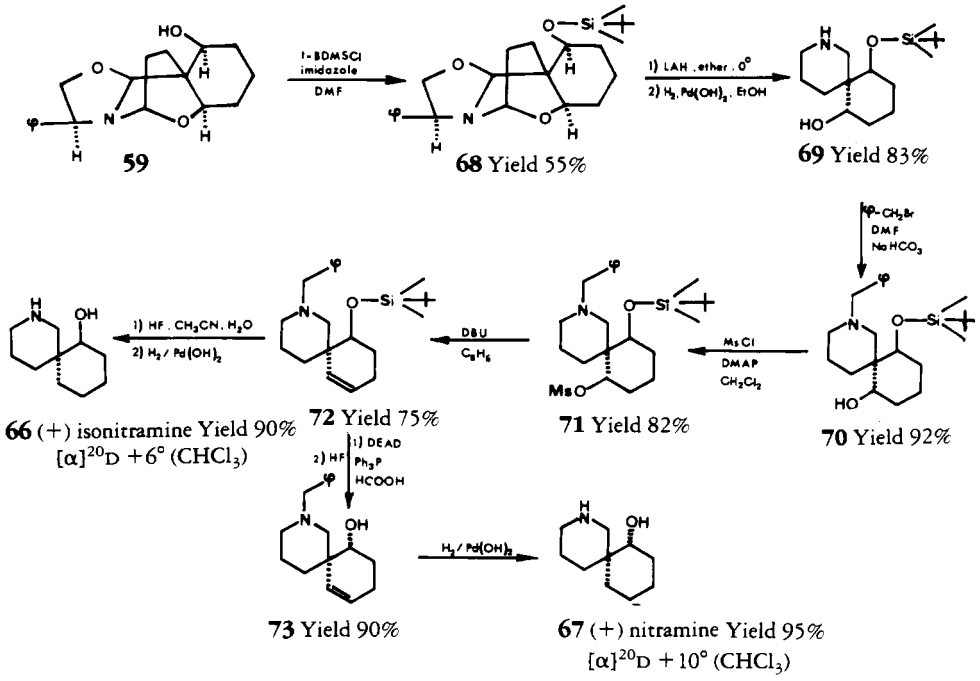
FIGURE 4.

first, the free hydroxyl group of **59**, which will be maintained, was protected as its *t*-butyldimethylsilyl ether. $LiAlH_4$ reduction of the aminoether function of **68** followed by hydrogenation of the α-hydroxymethyl benzyl moiety led to the aminoalcohol **69**. Reprotection of the secondary amine of **69** was made with benzyl bromide. This change of protecting group was necessary due to formation of complex reaction products of the β-aminoalcohol function in the next steps. Finally, elimination of the secondary hydroxyl group of **70** was performed in the same manner as previously to give (+) isonitramine (**66**) after elimination of the N and O protective groups.

The diastereomer of (+) isonitramine (**66**), (+) nitramine (**67**), has been easily synthesized from **72** (Scheme 14) by Mitsunobu inversion in a one-pot, three-step reaction (diethylazodicarboxylate, triphenylphosphine, and HCOOH). These studies demon-



SCHEME 13. Enantiospecific synthesis of (−)-isonitramine.



SCHEME 14. Enantiospecific synthesis of (+) isonitramine and (+) nitramine.

strate the versatility of the key polycyclic intermediate **59** for the enantiospecific synthesis of isomeric alkaloids of the nitramine series.

In conclusion, I hope I have convinced you that we have now in hand a valuable strategy for the asymmetric synthesis of a large variety of alkaloids. Further applications of this versatile synthon are currently in progress in our laboratories.

ACKNOWLEDGMENTS

I gratefully acknowledge all the intellectual and practical contributions of my collaborators whose names are given in the references.

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