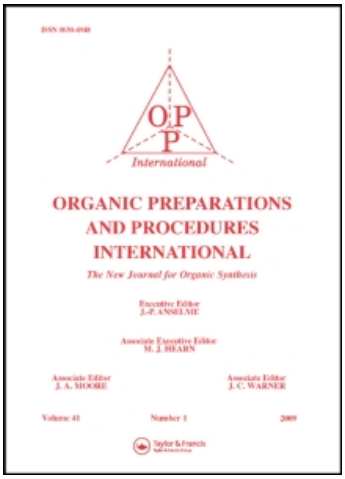

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SYNTHESIS OF THE FIRE ANT ALKALOIDS, SOLENOPSINS. A REVIEW

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INTRODUCTION

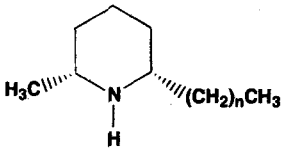
It is a widely held opinion that the prosperity of ants results to a large extent from their use of ecomones to communicate biologically meaningful information among colony members and to defend themselves towards potential predators and competitors. The majority of ants are able to sting. The venom apparatus of the stinging ants, that can be utilized in both offensive and defensive contexts, is composed of a stinger and two exocrine glands: the venom or poison gland and the Dufour gland.[1-3] The secretion of the Dufour gland is thought to function as a sting lubricant. In general it consists of a mixture of linear hydrocarbons.[3] Defense is by far the major function of the secretion of the venom gland. Its constituents have been the subject of many investigations whose results have been reviewed several times.[1-8] The venom of sting bearing ants which have been studied can be classified broadly as proteinaceous and non-proteinaceous.

Among the non-proteinaceous venoms, those of ants of the genus *Solenopsis* (Myrmicinae) have been extensively studied.[9] The *Solenopsis*, named fire ants after the pain elicited by their sting, are New World species that occur primarily in tropical and subtropical areas. In the early part of this century, some species were accidentally introduced to North America through the port of Mobile, Alabama.[10]

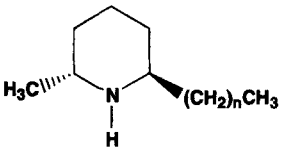
Since then, they have emerged as significant pests in many parts of the Southern U.S. The fire ant venom has an extremely low protein content (0.1% by weight). These proteins are responsible for the allergic reactions in man by their sting.[11] The most severe of these reactions, anaphylaxis, continues to be a public health problem in the Southeastern U.S. The remaining portion of the fire ant venom consists of a complex mixture of 2-methyl-6-alkylpiperidines accompanied in some cases by N-methylated, Δ^1 or side chain unsaturated derivatives. They have no role in allergic response but do have cytotoxic, hemolytic, necrotic, antibacterial, insecticidal and antifungal activities. They are also responsible for the pain associated with the sting.[9a]

These piperidine alkaloids have been assigned the trivial name solenopsins and differ from each other by the relative configuration of their substituents, the length and unsaturation of the alkyl chain.[9] Their structures are represented in Figure 1 and their distribution in the different species of *Solenopsis* investigated until now (about 20) has been published recently.[4] The absolute configuration of *trans*-solenopsin A, B and C has been assigned to be (2R, 6R) and that of the corresponding *cis* derivatives (2R, 6S).[12] Their relative proportions in the venom may differ between castes within a species, as well as between individuals of a particular caste.[13] However, the venom composition of pooled samples from populations of the same species from separated areas are uniform. These pooled

Major alkaloids of *Solenopsis* venoms:

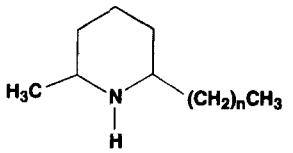


(2R,6S)-**1**: n = 10 *cis*-solenopsin A
(2R,6S)-**2**: n = 12 *cis*-solenopsin B
(2R,6S)-**3**: n = 14 *cis*-solenopsin C

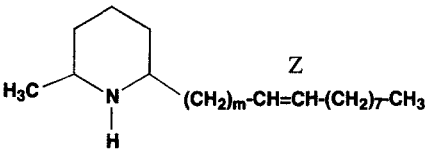


(2R,6R)-**4**: n = 10 *trans*-solenopsin A
(2R,6R)-**5**: n = 12 *trans*-solenopsin B
(2R,6R)-**6**: n = 14 *trans*-solenopsin C

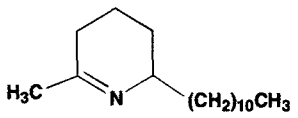
Minor alkaloids of *Solenopsis* venoms:



7: n = 8, *cis*
8: n = 8, *trans*



9: m = 3, *cis*
10: m = 3, *trans*
11: m = 5, *cis*
12: m = 5, *trans*



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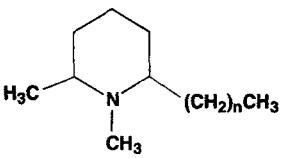

14: n = 8, *cis*
15: n = 8, *trans*
16: n = 10

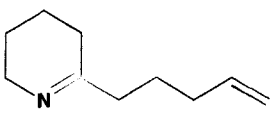

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FIG. 1

samples show considerable interspecific variations.[14] Tracer experiments performed by feeding ants with aqueous solutions of sodium [1-^{14}C] and [2-^{14}C] acetate demonstrated that the solenopsins are acetate-derived.[15] Several synthe[illegible] of both racemic and optically active solenopsins have been published and already partially revie[illegible].[4,5] It is the aim of this paper to review comprehensively the syntheses of these interesting bioactive alkaloids.

II. SYNTHESES OF RACEMIC SOLENOPSINS

Several synthetic routes to *cis*- and *trans*-(±)-solenopsins A, B or C have been reported. The methods used have included one of the following procedures:

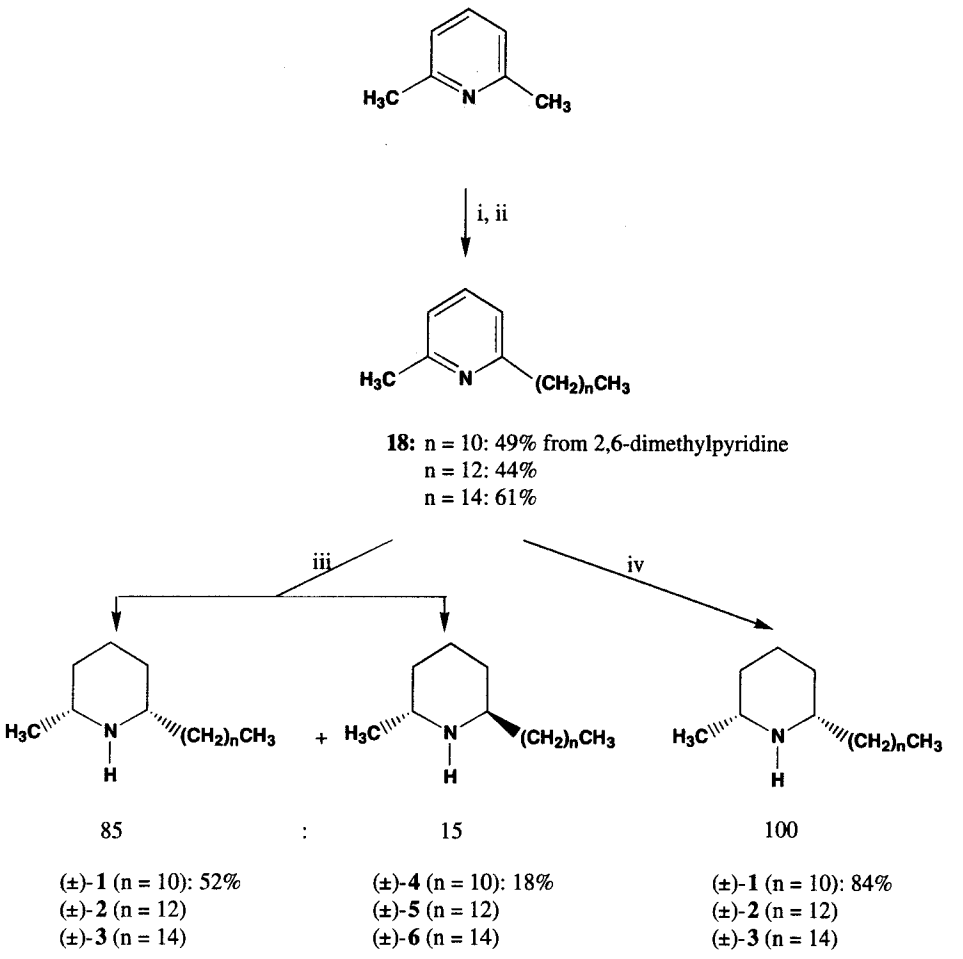
- catalytic or chemical reduction of the corresponding pyridine derivatives,
- intramolecular cyclization of olefins or aminoketones,
- alkylation of pyridinium salts or piperidinic derivatives,
- Beckmann rearrangement of oxime sulfonates,
- cycloaddition.

Cyclization procedures and the reduction of pyridine derivatives are the two most widely applied methods of preparing the parent 2,6-disubstituted piperidine ring structure. Several clever adaptations have been applied to the synthesis of fire ant alkaloids.

1 Reduction of 2,6-Dialkylpyridines

The first but still the most convenient synthesis of racemic solenopsins, has been published by MacConnell *et al.*. It was achieved by the reduction of 2,6-disubstituted pyridine **18** (Fig. 2).[9b] The pure *cis*-(±)-solenopsins A, B and C were prepared by the hydrogenation of the corresponding 2,6-dialkylated pyridine catalysed by 5% rhodium on charcoal. The 2-alkyl-6-methylpyridine, in turn, was obtained by the alkylation of the lithium salt of 2,6-dimethylpyridine with the appropriate bromoalkane. A 85/15 mixture of the *cis* and *trans* isomers was produced by the reduction of **18** with sodium in absolute ethanol. The two isomers were readily separable by column chromatography over alumina; the *cis* isomer elutes first, presumably because of steric hindrance of the nitrogen by the 2,6-diequatorial alkyl substituents. Although the mass spectra of the *cis* and *trans* isomers are indistinguishable, GC retention times and the infrared spectra allow easy differentiation. The pure *cis* isomer absorbs quite strongly near 1320 cm^{-1} compared to the *trans* isomer which exhibits only weak absorption in this region.

A longer synthesis has been published by Fuji *et al.* to obtain a large supply of *trans*-(±)-solenopsin A (**4**) for biological testing (Fig. 3).[16] This synthetic scheme is based on the introduction of the alkyl chain by a Wittig reaction. The reaction of 2,6-*bis*(chloromethyl)pyridine **19** with triphenylphosphine in refluxing benzene afforded the monophosphonium salt **20** in 88% yield. It should be mentioned that the diphosphonium salt was obtained from the same reaction in refluxing dimethylformamide. The Wittig reagent prepared from **20** with sodium hydride in dichloromethane was allowed to react with decanal to give a E/Z mixture of **21** in 80% yield. Catalytic reduction of **21** over Raney Ni and Pd/C under high pressure gave *cis*-(±)-solenopsin A. The authors have developed a method to convert the *cis* into the corresponding *trans* isomer. Based on Fraser's observation[17] that the *trans*-*N*-nitroso derivative **24** is 0.8 kcal more stable than its *cis*-isomer **23** (Fig. 4), the *N*-nitroso diaxial derivative **22** was treated with potassium *t*-butoxide in dimethylsulfoxide and then subjected to hydrogenolysis over Raney Ni to give an oil in 94% yield. Analysis by gas chromatography showed



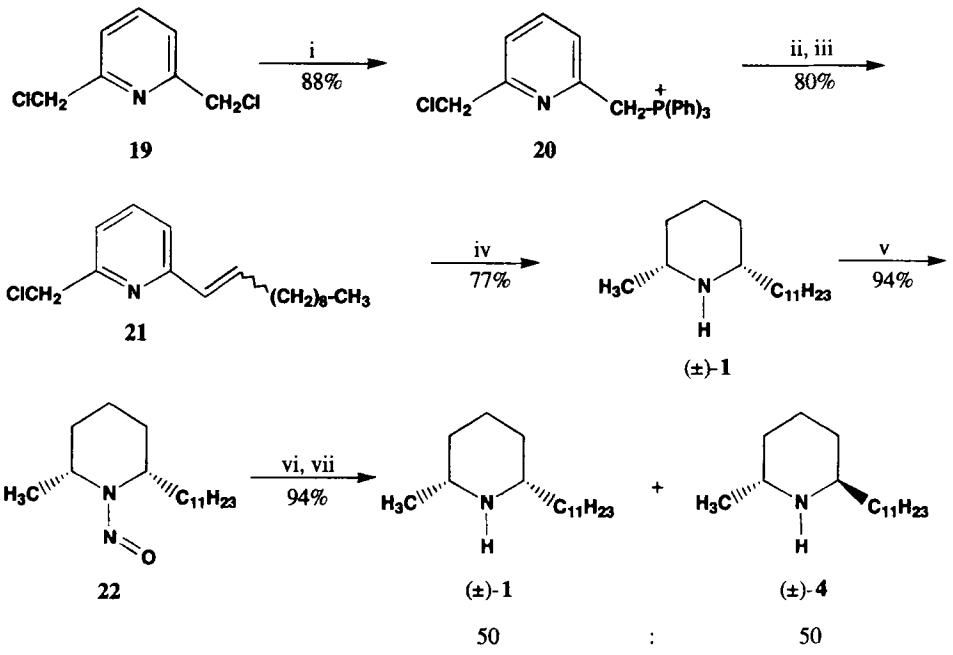
Reaction conditions: i) PhLi, ether, r.t. (15 min) + reflux (15 min); ii) $CH_3(CH_2)_{n-1}Br$, ether, reflux, 1 hr 30; iii) Na, EtOH, reflux, 3 hrs15; iv) H_2, 5% Rh/C, EtOH, 36 hrs

FIG. 2

an almost 50:50 mixture of *cis*- and *trans*-(±)-solenopsin A. The overall yield of (±)-solenopsin A for the 6 steps was 48%. Repetition of the process (nitrosation, equilibration and denitrosation) permits, in principle, the full conversion of the *cis* into *trans*-(±)-solenopsin A.

2. Intramolecular Cyclization

A second approach to synthesize 2,6-dialkylpiperidines is based on the formation of the piperidinic cycle by an intramolecular cyclization.



Reaction conditions: i) PPh_3, C_6H_6, reflux, 6hrs ; ii) NaH, CH_2Cl_2, r.t., 30 min; iii) $CH_3(CH_2)_8CHO$, reflux, 3 hrs; iv) H_2 (50 atm), Raney Ni, Pd/C, MeOH, 60°, overnight; v) isoamyl nitrite, CH_2Cl_2, 2 hrs; vi) *t*-BuOK, DMSO, 90°-100°, 60 hrs; vii) H_2 (30 atm), Raney Ni, MeOH, 60°, overnight.

FIG. 3

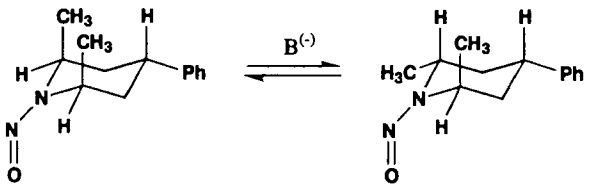
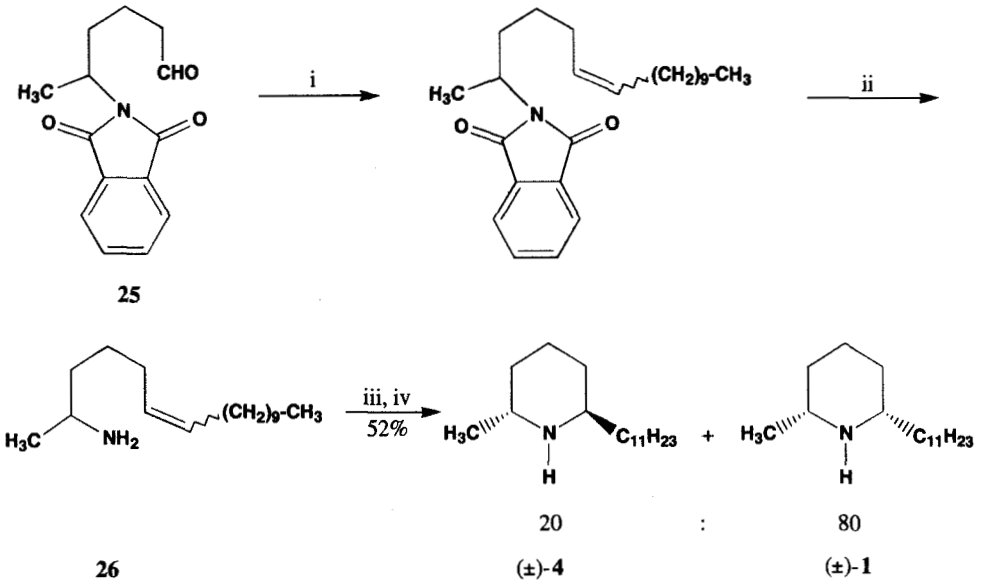


FIG. 4

Moriyama *et al.* reported a synthesis of *cis*- and *trans*-(±)-solenopsin A by intramolecular aminomercuration of the ε-ethylenic amine **26** (Fig. 5), which was derived from the aldehyde **25** prepared in 3 steps from 6-hydroxy-2-hexanone.[18] Wittig reaction of **25** with undecylidenephosphorane and deprotection by hydrazine treatment afforded the ε-ethylenic amine **26**. The organomercurial intermediate, obtained by reaction of **26** with mercuric acetate as double bond activator, was reduced by sodium borohydride to yield a mixture of *cis*-(±)-solenopsin A (41%), *trans*-(±)-solenopsin A (11%) and unchanged ε-ethylenic amine **26** (31%).

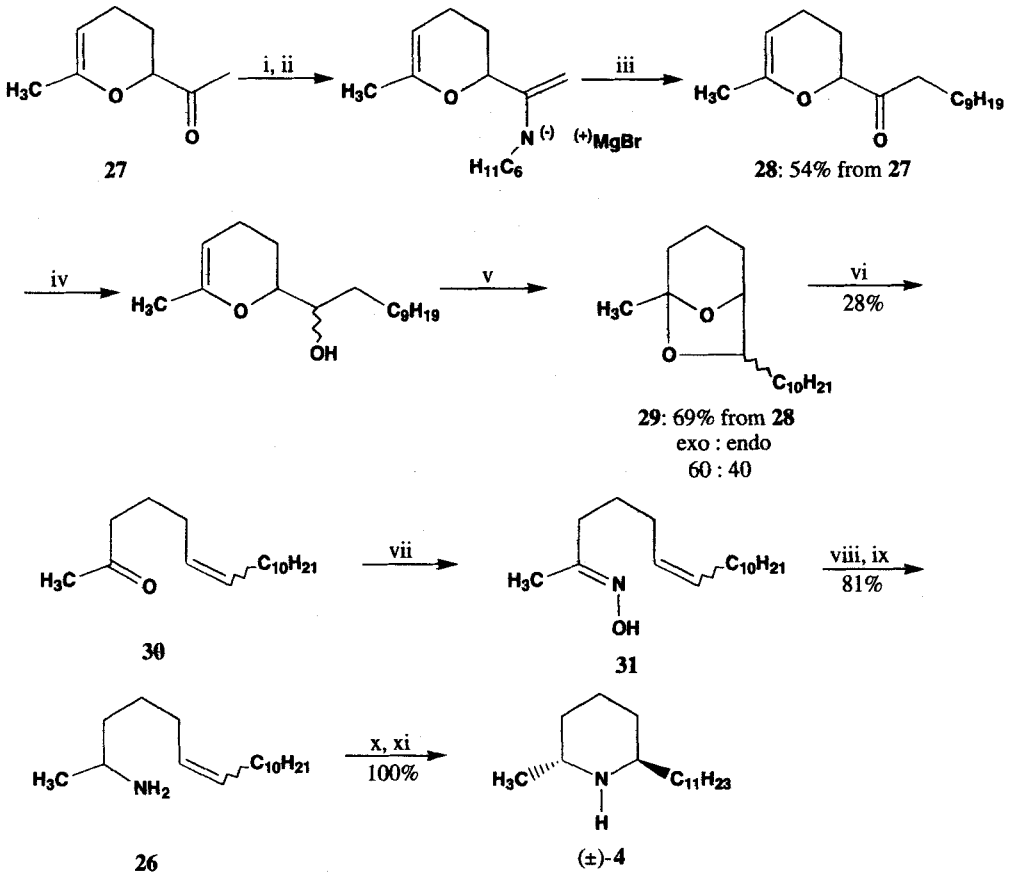


Reaction conditions: i) CH_3-$(CH_2)_9$-CH=PPh_3; ii) NH_2-NH_2; iii) $Hg(OAc)_2$, MeOH; iv) $NaBH_4$

FIG. 5

In the approach of Mundy and Bjorklund[19] (Fig. 6), the ε-ethylenic amine **26** was synthesized from the dimer of methyl vinyl ketone **27** in 7 steps. Using the imine-alkylation procedure developed by Stork[20], **27** was converted to **28** in 54% overall yield. Borohydride reduction of the ketone, followed by acid-catalysed cyclization yielded an exo/endo mixture of **29**. Conversion of **29** to δ,ε-unsaturated ketone **30** involved a novel ketal fragmentation protocol. This fragmentation gave predominantly the *trans* double bond isomer of **30** in a low yield of 28%. Mundy and Bjorklund suggested that bulky C-7 substituents could result in kinetic differences in the fragmentations. Treatment of **30** with hydroxylamine hydrochloride and sodium acetate gave **31** which was then treated with MoO_3 and $NaBH_4$, as described in the procedure of Ipaktschi[21], to afford 81% of ε-ethylenic amine **26**. Mundy and Bjorklund claimed that they were able to "quantitatively convert **26** to *trans*-(±)-solenopsin A by treatment with mercuric acetate followed by basic $NaBH_4$". This result conflicts with that of Moriyama *et al.*[18], although surprisingly Mundy and Bjorklund alleged the results are the same.

Danishefsky *et al.*[22] have reported that heterocyclization can also be performed by intramolecular amidomercuration of N-protected unsaturated amines. Carruthers and co-workers have explored the possibility of employing this reaction to prepare 2,6-dialkylpiperidines including *cis*- and *trans*-(±)-solenopsin A[23] (Fig. 7). In this context, reaction of the urethane **32** with mercuric acetate, according to Harding and Burks[24], gave a crude organomercurial **33**, reductive coupling of which with decen-3-one in the usual way led to the *cis* and *trans* isomers **34** in poor yield. The ratio of isomers



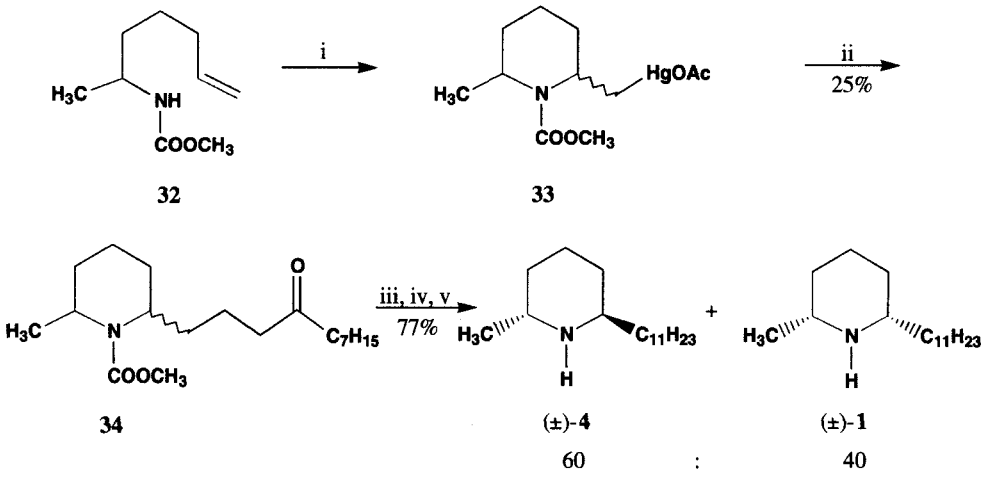
Reaction conditions: i) $C_6H_{11}NH_2$; ii) C_2H_5MgBr; iii) $C_9H_{19}Br$; iv) $NaBH_4$; v) TsOH; vi) AcI; vii) $NH_2OH.HCl$ / AcONa; viii) MoO_3; ix) $NaBH_4$; x) $Hg(OAc)_2$; xi) $NaBH_4$

FIG. 6

formed was about 40:60, but the authors could not say which is which because of their inability to separate them. Reduction of the carbonyl group on the mixture by hydrogenolysis of the derived thioacetals with Raney nickel, and cleavage of the methoxycarbonyl group with ethanolic hydrogen chloride gave 77% of *cis*- and *trans*-(±)-solenopsin A in a 40:60 ratio.

The overall yields of the three syntheses described above cannot be calculated since some yields were not quoted in the original papers.

Along these lines, Clive *et al.*[25] have reported the synthesis of *cis*-(±)-solenopsin A from ethyl urethanes **35** and **36** prepared from the corresponding amine by the standard Schotten-Baumann method in 38% and 73% yield respectively (Fig. 8). The proposed strategy involves making a nitrogen-bond to generate the heterocycle by treatment of urethanes with arylselenenyl halides, instead of mercuric ion as described above. Benzeneselenenyl chloride is known to effect a number of cyclizations and the authors have named the process cyclofunctionalization. Under these conditions, the urethanes **35** and **36** cyclized stereoselectively (see Fig. 8) to the *cis* isomers **37** (84%) and **38** (35%)

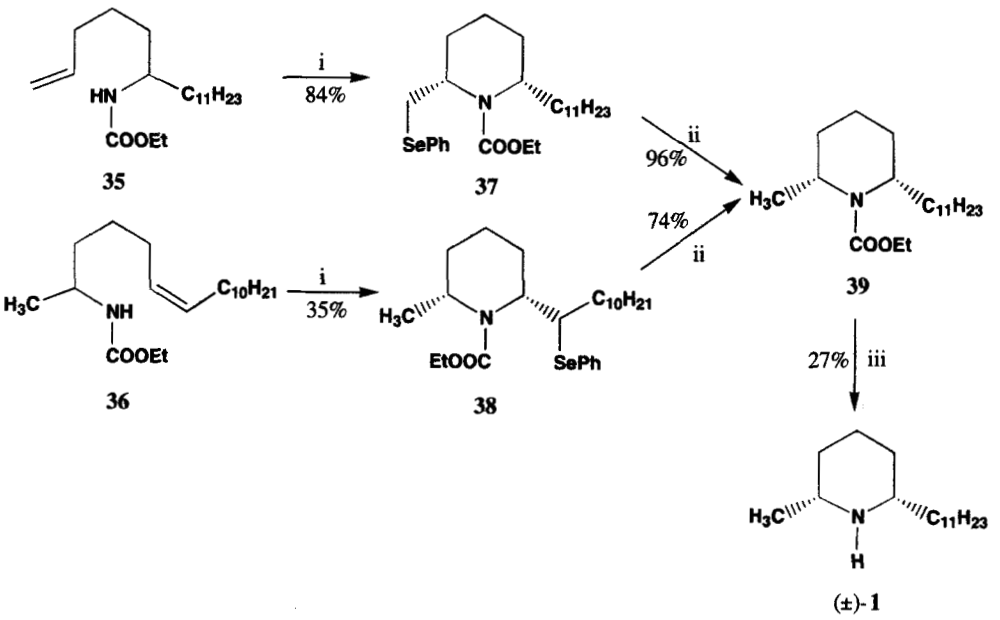


Reaction conditions: i) $Hg(OAc)_2$, THF; ii) CH_2=$CHCOC_7H_{15}$, $NaBH_4$, MeOH; iii) HS-CH_2-CH_2-SH; iv) H_2 / Raney Ni; v) EtOH, HCl.

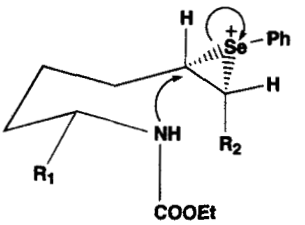
FIG. 7

respectively. The two phenylseleno derivatives were reduced with triphenyltin hydride to furnish the *cis*-(±)-*N*-carbethoxy-2-methyl-6-undecylpiperidine **39** without isomerisation. Hydrolysis of **39** gave a mixture of *cis*-(±)-solenopsin A (27%) and unchanged **39** (72%). It has to be mentioned that the procedure using **35** as starting material provides a 22% overall yield in comparison with its regioisomer **36** which, under the same reaction conditions, yielded only 7% of *cis*-(±)-solenopsin A.

The latest synthesis is based on intramolecular cyclization and has been reported by Wasserman and Rusiecki (Fig. 9).[26] The δ,ε-epoxy imine **41**, obtained from 6-hepten-2-one **40** by treatment with MPBCA and benzylamine, underwent stereospecific intramolecular epoxide ring opening with the formation of the substituted oxatropane **42** in 87% yield from **40**. Quantitative reduction of the bicyclic derivative with sodium borohydride in methanol gave a mixture of *cis*- and *trans*-2,6-disubstituted piperidine **43** and **44** with the *trans* product predominating (10:90). This *cis:trans* ratio varied in the range of 33:67 to 1:99 depending on the conditions of reduction ($NaBH_4$, $LiAlH_4$, $NaBH_3CN$ or DIBALH). This high degree of stereochemical control in the reduction of **42** parallels the findings of Yamamoto in an earlier synthesis of solenopsin A which will be discussed in the next paragraph. The two isomers **43** and **44** could be separated by conversion to the acetates followed by flash chromatography. After deprotection, the pure *trans* alcohol **44** was oxidized under Swern conditions and the aldehyde thus formed was coupled with decylidenetriphenylphosphorane to yield the olefin **45** as a mixture of *cis* and *trans* isomers. Reduction of the double bond and debenzylation afforded *trans*-(±)-solenopsin A. Overall yield was 36% from 6-hepten-2-one **40**.



Reaction conditions: i) PhSeCl, SiO_2, CH_2Cl_2, -78° (30 min) to r.t. (75 min); ii) Ph_3SnH, toluene, 120°, 27 hrs; iii) EtOH, HCl, reflux, 88 hrs



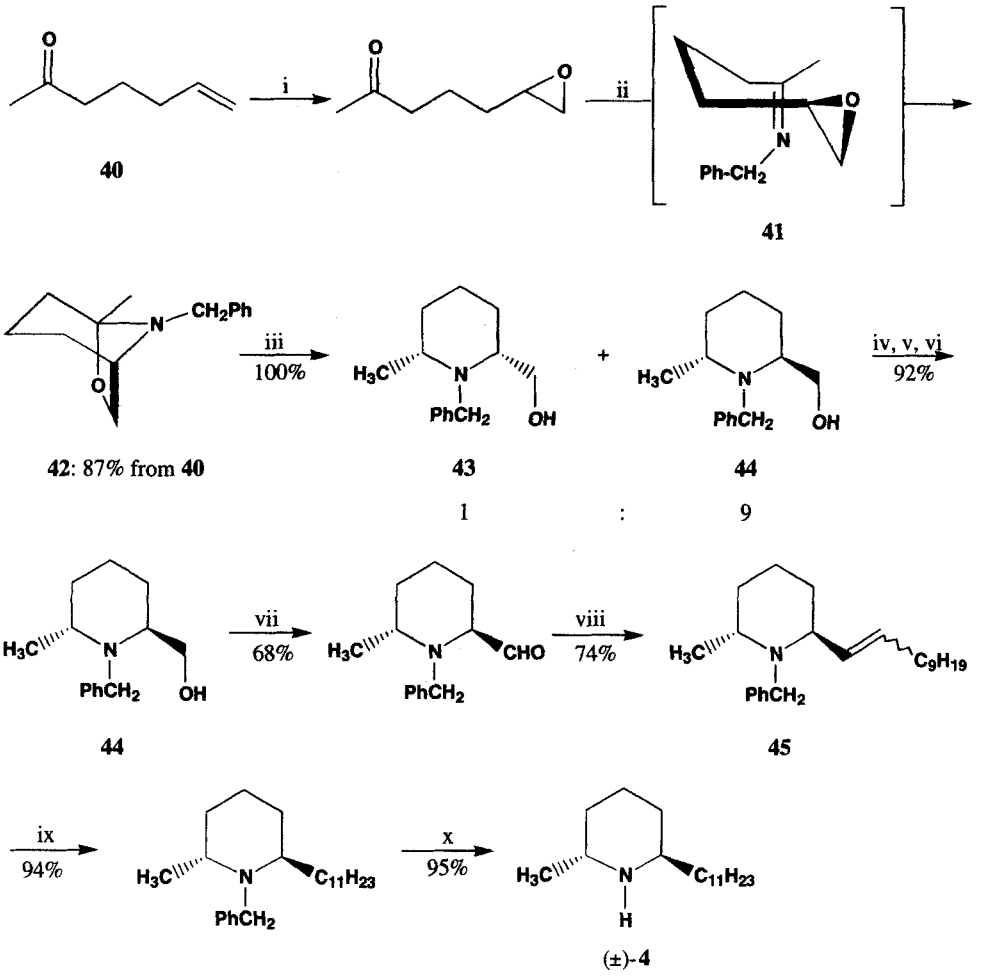
$R_1 = CH_3$, $R_2 = C_{10}H_{21}$

$R_1 = C_{11}H_{23}$, $R_2 = H$

FIG. 8

3. Organoaluminum-promoted Beckmann Rearrangement of Oximesulfonates

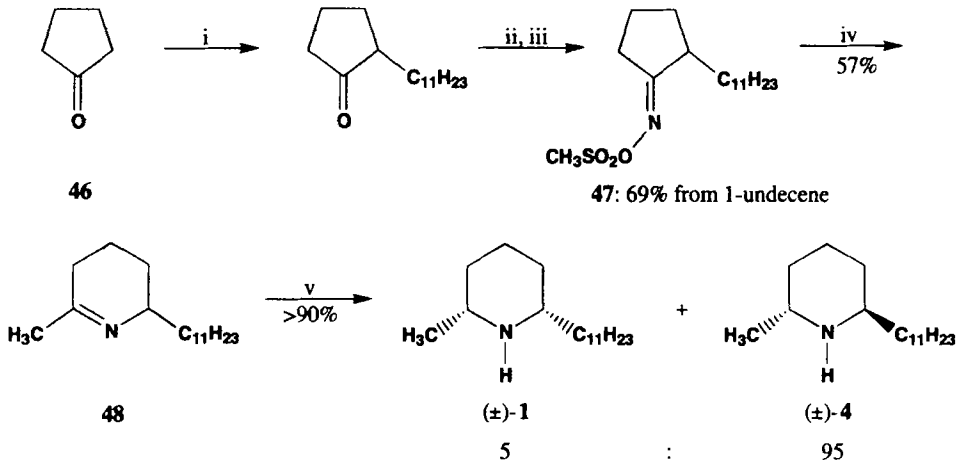
A third approach to the synthesis of racemic solenopsins has been described by Yamamoto and co-workers.[27] It consists in generating the nitrogen heterocycle by a Beckmann rearrangement-alkylation reaction of an oxime sulfonate promoted by organoaluminum reagents (Fig. 10). As oxime derivatives, oxime sulfonates can be used preferentially because of their ready availability from oximes in almost quantitative yield using methanesulfonyl chloride, and their high enough reactivity to undergo the rearrangement promoted by organoaluminum reagents.



Reaction conditions: i) MCPBA; ii) $PhCH_2NH_2$, PhH, reflux, 5 hrs; iii) $NaBH_4$, MeOH; iv) acetylation; v) flash chromatography; vi) K_2CO_3, MeOH; vii) $(COCl)_2$, DMSO; viii) $Ph_3P{=}CH\text{-}CH_2\text{-}C_8H_{17}$; ix) H_2, PtO_2, AcOH, PhH; x) H_2, 10% Pd/C, AcOH, PhH.

FIG. 9

The starting oxime sulfonate **47** was synthesized from cyclopentanone **46** in three steps and 69% overall yield. Reaction of excess cyclopentanone **46** with 1-undecene in the presence of silver oxide produced 2-undecylcyclopentanone which, without purification, was treated with hydroxylamine hydrochloride and sodium acetate to give the pure oxime in 73% overall yield from 1-undecene. The oxime was converted to the corresponding mesylate **47** in 90-95% yield with methanesulfonyl chloride and triethylamine. Treatment of **47** with trimethylaluminum resulted in formation of imine **48**. Completion of the synthesis required reduction of the C=N double bond. Reduction of **48** using the usual aluminum or borohydride-type reagents in different solvents yielded *cis*- and *trans*-(±)-solenopsin A in the range of 5/95 to 99/1.



Reaction conditions: i) $CH_3(CH_2)_8CH{=}CH_2$, Ag_2O, 130°, 5 hrs; ii) $NH_2OH.HCl$, AcONa, MeOH, 25°, 5 hrs; iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, -20°, 40 min; iv) $Al(CH_3)_3$, CH_2Cl_2, 25°,1 hr; v) $LiAlH_4$, $AlMe_3$, THF, -78° (30 min), -45° (1 hr), -20° (1 hr), 0° (1 hr).

FIG. 10

Excellent stereoselectivity was attained in the formation of the *trans* form (±)-**4** using lithium aluminum hydride in the presence of a trialkylaluminum, and *trans*-(±)-solenopsin A was obtained almost exclusively (5:95) in a 34% overall yield from cyclopentanone. In a similar manner, *trans*-(±)-solenopsin B was prepared with high stereoselectivity (5:95) using procedures which exactly paralleled those described above for the synthesis of *trans*-(±)-solenopsin A.

As suggested by Yamamoto, this observed high degree of stereoselectivity could be tentatively rationalized by the Houk theory[28] as well as the theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group.[29] Both theories would predict the strong preference for an anti-periplanar attack of the hydride ion with respect to the $\sigma_{C\text{-}H}$ bond vicinal to the imino functional group (Fig. 11).

Moreover, in conformation **a**, the alkyl group (R) occupies an axial position where an unfavorable steric interaction with the bulky trialkylaluminum group is minimized. Attack of the hydride ion would take place as shown to yield the *trans*-product. On the other hand, addition of the hydride ion to the iminium ion occupying conformation **b** would yield the *cis*-product at the expense of unfavorable steric crowding of the equatorial alkyl (R) and trialkylaluminum groups.

4. Alkylation of Pyridinium Salts

Nucleophilic addition of organometallic reagents to 1-alkoxycarbonyl-2-alkyl-pyridinium salts has been utilized to prepare 2,6-disubstituted-1,6-dihydropyridines which have proved to be valuable synthetic intermediates for nitrogen cycles. It provides an easy access to (±)-solenopsins.

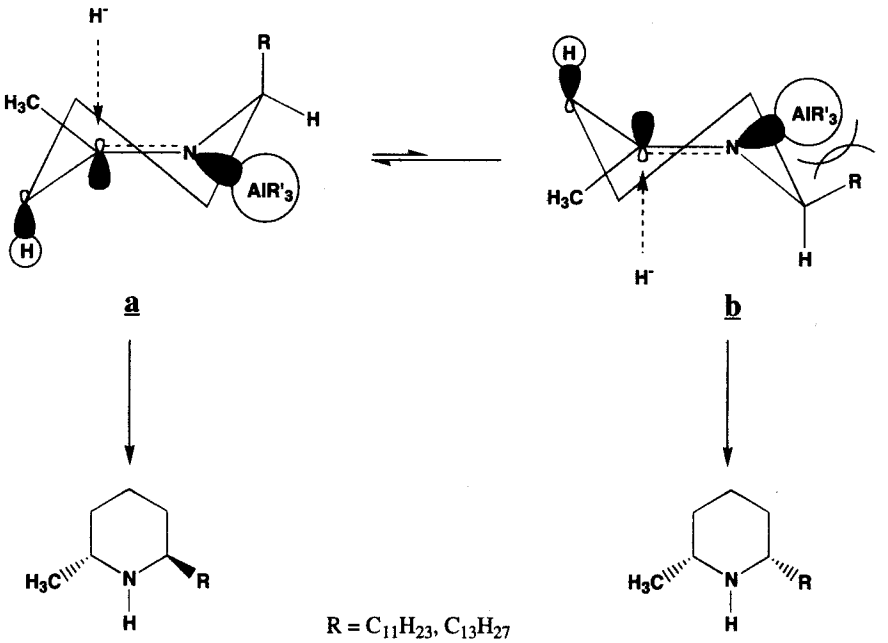
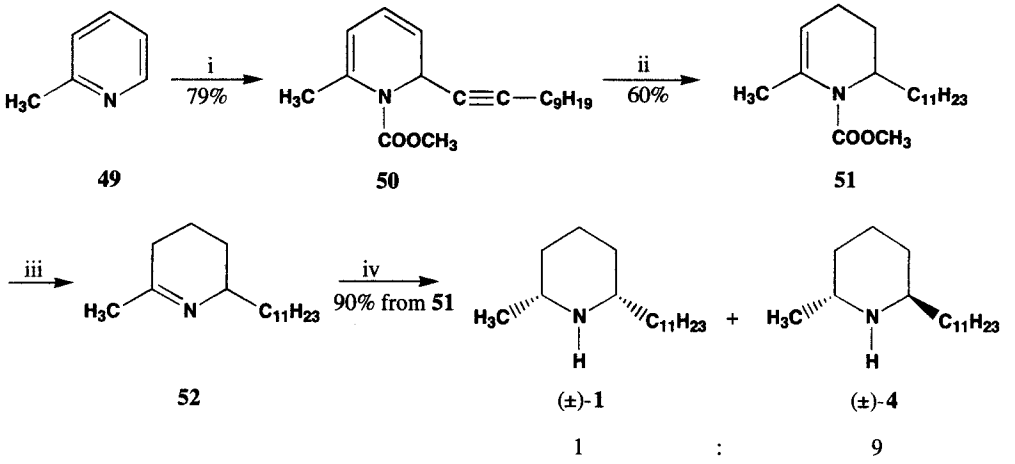


FIG. 11

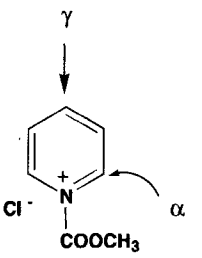
The first synthesis of fire ant alkaloids based on this methodology was published by Yamagushi *et al.* (Fig. 12).[30] Reaction of 2-methylpyridine **49** with undecynylmagnesium bromide in the presence of methyl chloroformate proceeded in a highly regioselective manner to give exclusively the



Reaction conditions: i) undecynyl magnesium bromide, $ClCOOCH_3$, THF, 0°, 30 min; ii) H_2 (1 atm), 5% Pd/C, dry MeOH; iii) Me_3SiI, $CHCl_3$, 50-60°, 1 hr; iv) $LiAlH_4$, $AlMe_3$, THF, -78° to 0°, 2hrs

FIG. 12

2,6-disubstituted derivative **50**, in spite of its steric congestion. In this context, the authors have investigated the reaction of 1-methoxycarbonylpyridinium chloride **53** (Fig. 13) with some alkyl Grignard reagents as well as with other organometallic reagents in more details. The results obtained evidently demonstrate that the regioselectivity is dependent on the character of the metals. This regioselectivity of the attack on the pyridinium cation by nucleophiles may be explained by the HSAB principle.[31,32] The very soft organocopper reagents almost exclusively attack at the γ-position, as was recently suggested by Akiba *et al.*.[33,34] The organozinc reagent, which is slightly harder than an organocopper reagent, reveals a slightly less pronounced γ-selectivity. With harder alkyl Grignard reagents, both α- and γ-attack occur in variable ratios. Accordingly, in order to obtain 2-substituted-1,2-dihydropyridines selectively which may be potential intermediates for alkaloid synthesis, the authors have examined the reaction of **53** with alkynyl as well as alkenyl Grignard reagents, considering that these organic moieties are supposed to be harder than alkyl ones. The α-regioselectivity is far better than expected, with a variety of alkynyl and alkenyl Grignard reagents attacking exclusively the α-position to afford 2-alkynyl- and 2-alkenyl-1,2-dihydropyridines in good to excellent yields (from 71% to 99%). It has been demonstrated that this high α-regioselectivity is completely retained in the reactions of 2-substituted-1-alkoxylcarbonylpyridinium salts.



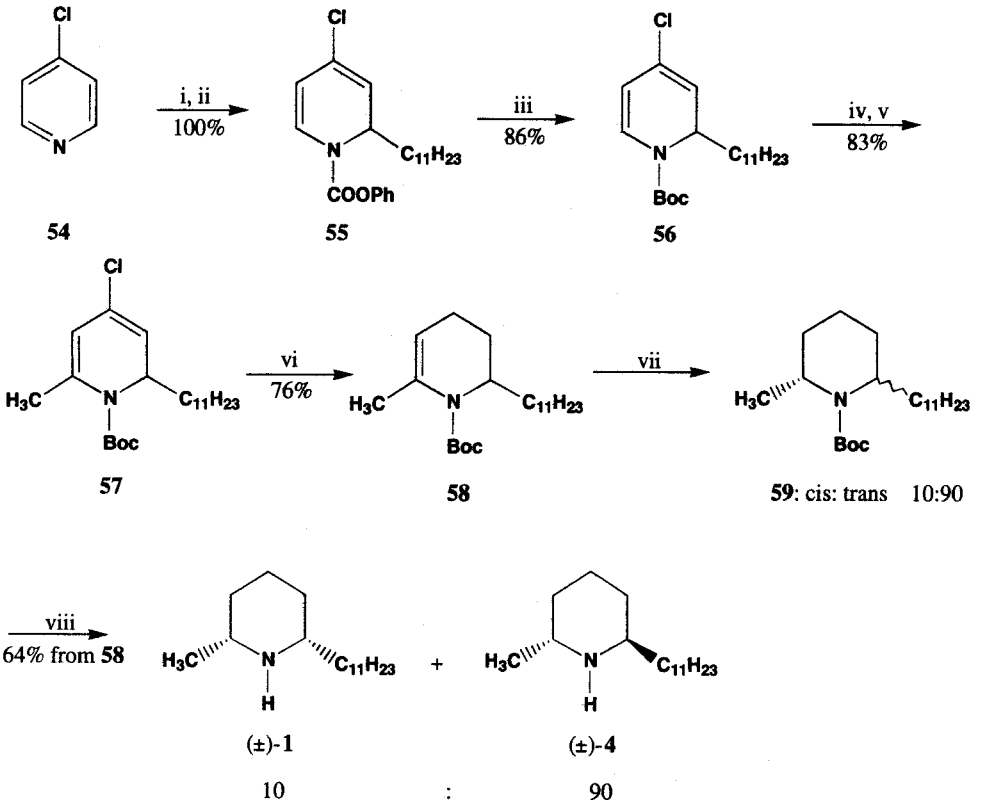
53

FIG. 13

Careful hydrogenation of **50** over 5% Pd/C gave 60% of 1,2,3,4-tetrahydropyridine derivative **51** which was demethoxycarbonylated with iodotrimethylsilane to yield **52**. According to Yamamoto's elegant method for stereoselective reduction of this type of cyclic imine, **52** was reduced with lithium aluminum hydride in the presence of trimethylaluminum to afford *trans*-(±)-solenopsin A, along with a small amount of its cis epimer **(±)-1**. Thus, the present route provides a practical and efficient method for the synthesis of *trans*-(±)-solenopsin A in four steps from 2-methylpyridine (43% overall yield).

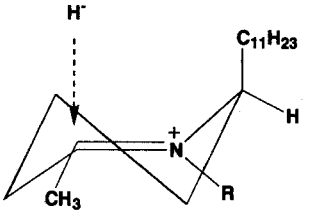
An alternative but longer synthesis of *trans*-(±)-solenopsin A has recently been published by Comins and Weglarz[35] where 4-chloropyridine **54** is utilized as starting material (Fig. 14). **54** was treated with undecylmagnesium bromide and phenylchloroformate to give the 1,2-dihydropyridine **55** which was converted to the *N*-Boc derivative **56** in 86% overall yield from **54**.

A methyl group was introduced at C-6, using directed-lithiation methodology. Indeed, treatment of **56** with *n*-butyllithium and methyl iodide gave a 83% yield of 2,6-dialkylated dihydropyridine **57**. When tetrahydropyridine **58**, obtained from partial reduction of **57**, was submitted to sodium cyanoborohydride/trifluoroacetic acid reduction, a 10:90 mixture of *cis*- and *trans*-products (**59**) resulted. The *trans* stereochemistry comes from stereoelectronically preferred axial attack[36] of hydride on the chair iminium ion **60a** which has the undecyl group in the axial orientation due to $A^{(1,2)}$ strain[37,38] (Fig. 15) (see Yamamoto's explanations).[27] Removal of the *t*-Boc by trifluoroacetic acid afforded *trans*-(±)-solenopsin A with an overall yield of 29% from 4-chloropyridine (6 steps).



Reaction conditions: i) $C_{11}H_{23}MgBr$, Et_2O, -78°, 20 min; ii) PhOCOCl, THF, -78° (30 min) to r.t. (30 min); iii) *t*-BuOK, THF, -42° (1 hr) to r.t. (20 min); iv) *n*-BuLi, THF, -42°, 1 hr; v) CH_3I, -42° (1hr) to r.t. (1 hr); vi) H_2, Pd/C, Li_2CO_3, MeOH, 0°; vii) a) $NaBH_3CN$, CH_2Cl_2, r,t., 15 min; b) TFA, -42°, 4h; viii) TFA, CH_2Cl_2, r.t., 1 hr

FIG. 14



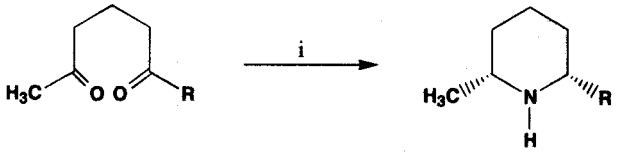
60a: R = Boc
60b: R = Ts

FIG. 15

5. Reductive Aminocyclization

Another approach to the synthesis of 2,6-dialkylpiperidines consists of generating the saturated heterocycle by reductive aminocyclization. Three syntheses have been published along these lines.

Abe *et al.* [39] have demonstrated that sodium cyanoborohydride could be used as reagent in the reductive amination of alkane-2,6-diones (Fig. 16). The methanolic solution of **61** (a-c) was



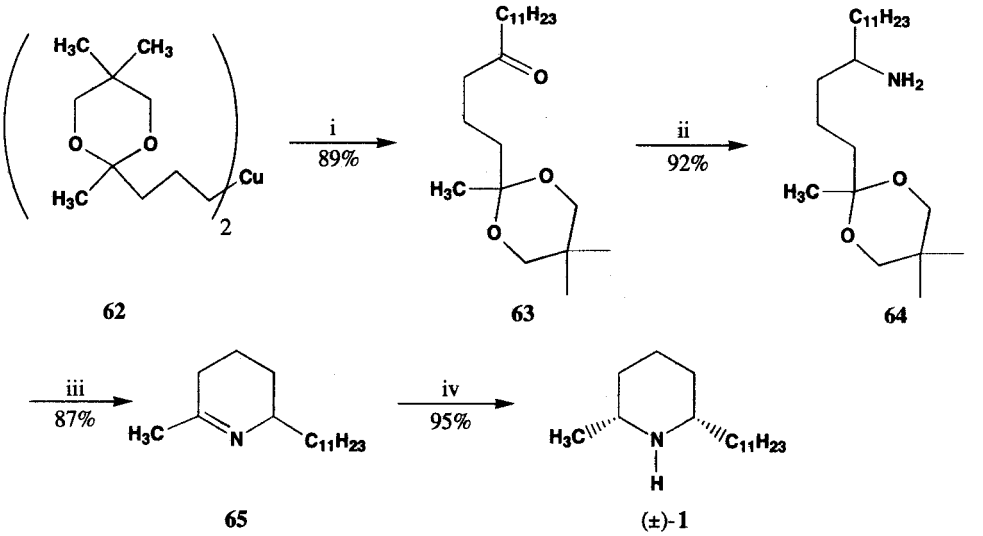
61: **a**: R = n-$C_{11}H_{23}$ (±)-**1**: 75%
b: R = n-$C_{13}H_{27}$ (±)-**2**: 81%
c: R = n-$C_{15}H_{31}$ (±)-**3**: 91%

Reaction conditions: i) $NaBH_3CN$, NH_4Br, MeOH, r.t., 4 days.

FIG. 16

treated with sodium cyanoborohydride and ammonium bromide, at room temperature for 4 days, to afford *cis*-(±)-solenopsins A, B, and C respectively, in 75-91% yields. The overall yield of the synthesis cannot be evaluated since the synthesis of the alkane-2,6-diones **61** (a-c) were not described in the original papers.

The synthesis of *cis*-(±)-solenopsin A described by Ryckman and Stevens is depicted in Figure 17.[40] This procedure provides a means to introduce the long side chains common to the solenopsins in a high yield process. Addition of the dialkylcuprate reagent **62** to lauryl chloride gave



62 **63** **64**

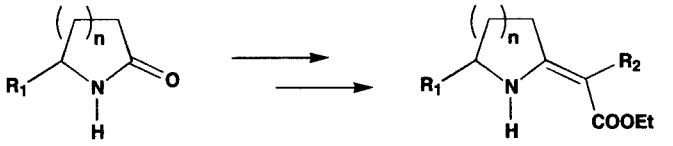
65 (±)-**1**

Reaction conditions: i) lauryl chloride, ether, -78° (15 min) to 0° (45 min); ii) NH_4OAc, $NaBH_3CN$, MeOH, r.t., 4 hrs; iii) HCl, THF, 1 hr; iv) $NaBH_3CN$, THF, citrate-phosphate buffer (pH=5.3), 3 hrs

FIG. 17

the desired protected 1,5-dione **63** in 89% yield. The reaction of a carbonyl-protected organometallic reagent with a carboxylic acid derivative supplies an attractive alternative to the Michael reaction for preparing selectively protected 1,5-dicarbonyl compounds. Reductive amination furnished the desired amine **64** in 92% yield. Hydrolysis of the ketal function and cyclization afforded the ring-closed 2,6-disubstituted imine derivative **65** in 87% yield from **64**. Stereoselective reduction of **65** with sodium cyanoborohydride gave *cis*-(±)-solenopsin A in a 68% overall yield from **62**.

Lhommet *et al.* [41] have recently demonstrated that ω-alkyl cyclic β-enaminoesters **67**, derived from ω-alkyllactam **66**, are good precursors of insect venom alkaloids like solenopsins (Fig. 18). In this context, 6-methyl-2-piperidone **69**, obtained from dimethyl-3-oxoheptanedioate **68** in two



66

67: n = 1, 2
R_1 = H, CH_3
R_2 = alkyl or alkenyl

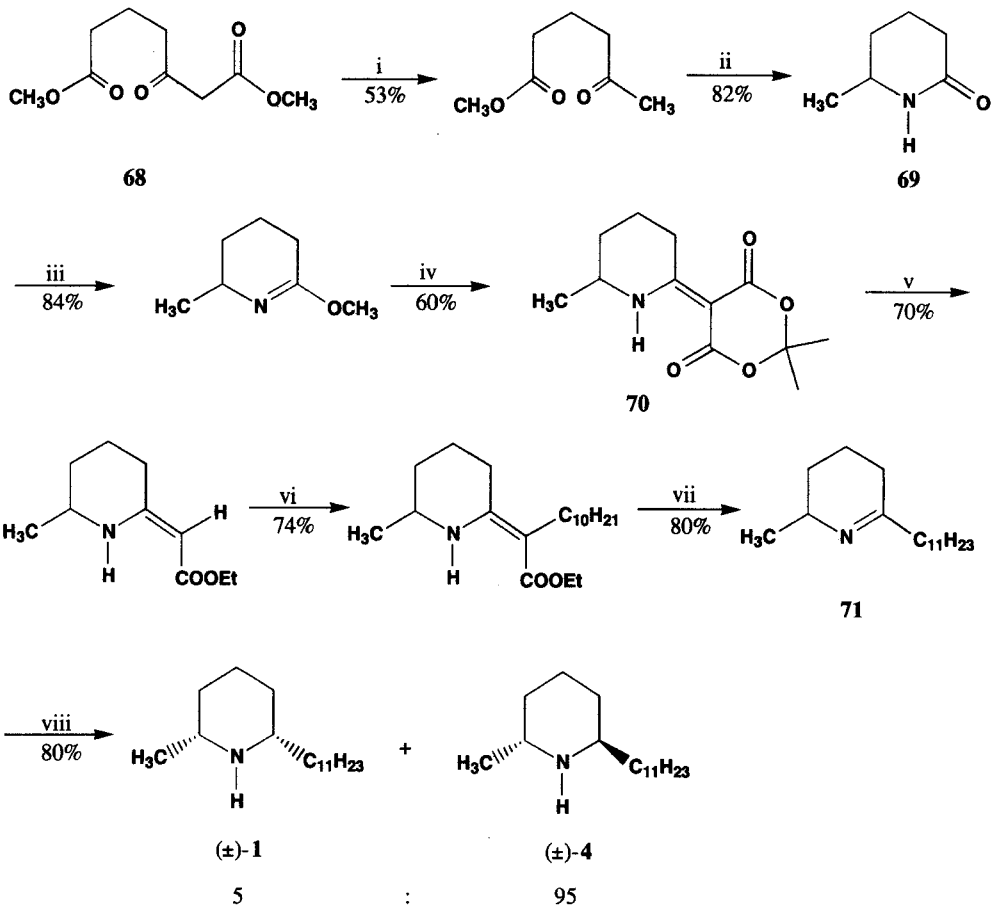
FIG. 18

steps and 43% overall yield, was methylated and then treated with Meldrum's acid to yield β-enaminodiester **70** (Fig. 19). Hydrolysis, alkylation and decarboxylation afforded the cyclic imine **71** in 41% yield from **70**. Stereoselective reduction of **71** with lithium aluminum hydride in the presence of trimethylaluminum led to a mixture of *cis*- and *trans*-(±)-solenopsin A in the expected 5:95 ratio. Overall yield for the eight steps was 7%.

6. Alkylation of Piperidine Derivatives

Alkylation of nitrogen heterocycles, as well as homologated carbonyl compounds, have proven to be useful procedures to synthesize a number of polysubstituted heterocycles. Six syntheses of *cis*- and *trans*-(±)-solenopsin A have been reported using this approach, two of them using piperidone as starting material.

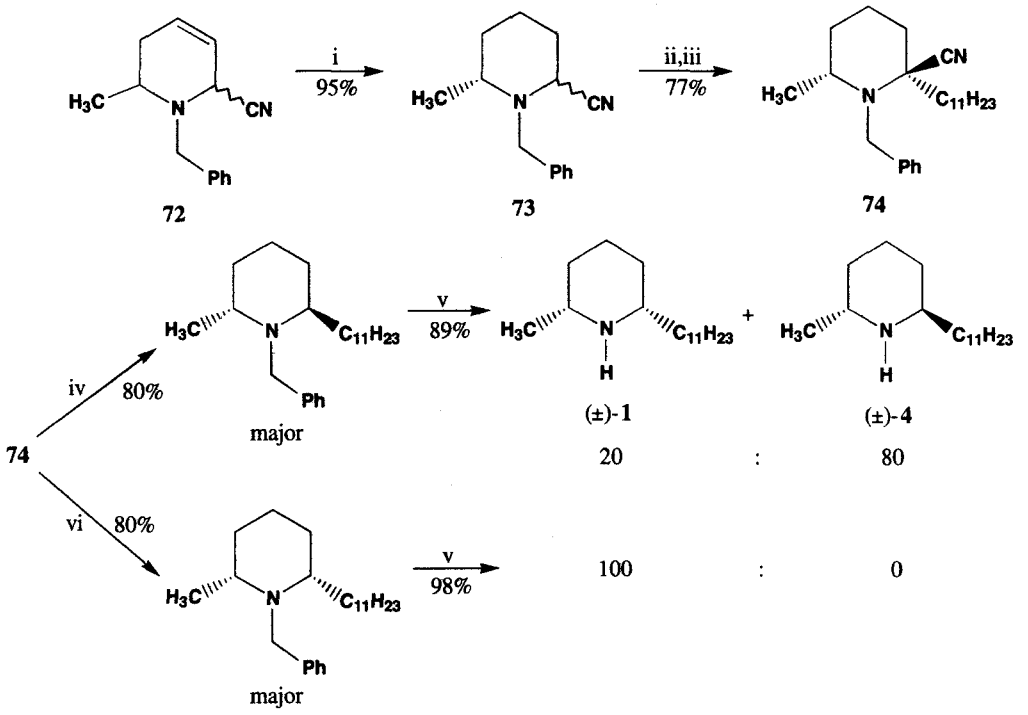
A general alkylating method, described by Husson *et al.*[42], starts from the common synthon 1-benzyl-2-cyano-6-methyl-Δ^3-piperidéine **72** prepared from 2-picoline in 53% overall yield and obtained as an inseparable mixture of epimers (Fig. 20). Chemoselective catalytic reduction of **72** afforded the aminonitrile **73** which was alkylated with undecylbromide yielding 38% of 2,6-disubstituted product **74** from 2-picoline. The key step in this strategy is the efficient reductive decyanation of the intermediate 1-benzyl-2-cyano-2',6-dialkylpiperidine **74** to either *cis* or *trans* alkaloid systems through a proper choice of reaction conditions. Thus, reductive decyanation of **74** with sodium borohydride in methanol and debenzylation led to predominant formation of *trans*-(±)-solenopsin A in 28% overall yield from 2-picoline. In contrast, the *cis* isomer was prepared stereoselectively in 30% overall yield by treatment of **74** with sodium in liquid ammonia and debenzylation.



Reaction conditions: i) H_3BO_3, Δ; ii) NH_3, H_2, MeOH, Raney Ni, 160°, 5 hrs; iii) Me_2SO_4, 12 hrs, 60°; iv) Meldrum's acid, $Ni(acac)_2$, $CHCl_3$, reflux, overnight; v) EtOH, Δ, 0.5 hrs; vi) $C_{10}H_{21}Br$, NaH, toluene, reflux, overnight; vii) H_3BO_3, 180°; viii) $LiAlH_4$, $AlMe_3$, CH_2Cl_2, r.t., 4 hrs

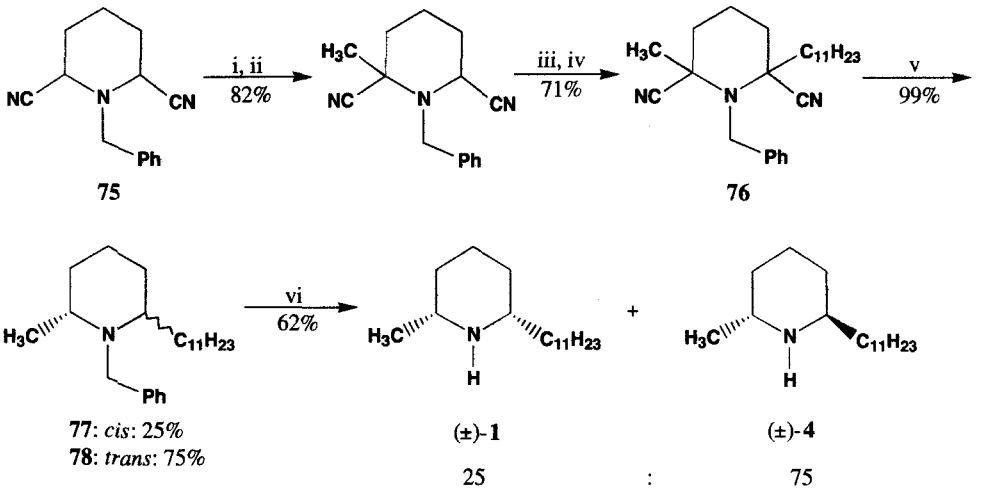
FIG. 19

In a similar manner, Takahashi and co-workers[43] have reported a new synthetic method for preparation of 2,6-disubstituted piperidinic alkaloids using sequential alkylation of 1-benzyl-2,6-dicyanopiperidine **75** (Fig. 21). This starting material **75** was prepared by the Strecker reaction of glutaraldehyde with benzylamine in 65% overall yield (3 steps).[44] The alkylation of N-benzyl derivative **75** selectively gave monoalkylated products, unlike alkylation of 1-phenyl-2,6-dicyanopiperidine which yielded predominantly symmetrical dialkylated products. The selective formation of monoalkylated products was important for the subsequent preparation of unsymmetrical dialkylated product. In this context, solenopsin A was conveniently prepared by sequential alkylation with methyl iodide and undecylbromide to afford **76** in 58% yield from **75**. Almost quantitative decyanation with sodium borohydride in isopropyl alcohol at 70° yielded *cis*- and *trans*-(±)-2,6-dialkyl-1-benzylpiperidines **77**



Reaction conditions: i) H_2, Pd/C, MeOH; ii) LDA; iii) $C_{11}H_{23}Br$; iv) $NaBH_4$, CH_3OH; v) debenzylation; vi) Na, NH_3, THF, -78°

FIG. 20

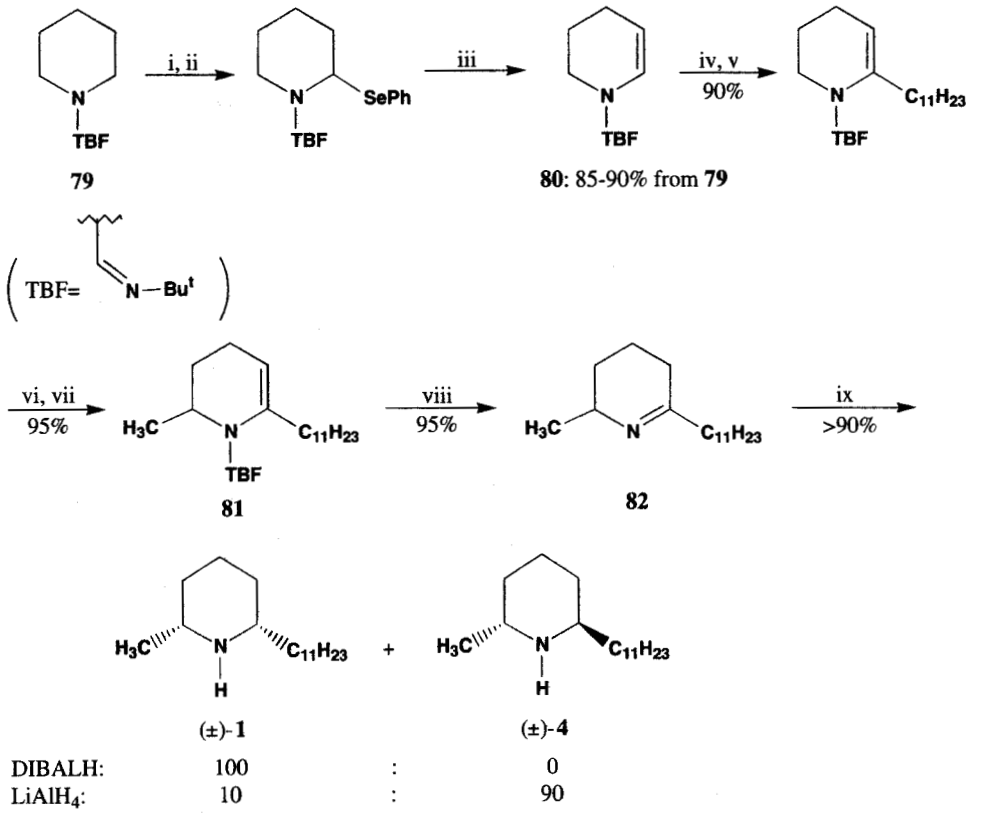


Reaction conditions: i) LDA, THF; ii) CH_3I, -78°, 2 hrs; iii) LDA, THF; iv) $C_{11}H_{23}Br$, -78°, 1 hr; v) $NaBH_4$, isopropyl alcohol, 70°, 9 h; vi) H_2 (1 atm), Pd/C, EtOH, HCl, r.t., 1hr

FIG. 21

and **78** in a 25:75 ratio. The subsequent debenzylation of **77** and **78** by catalytic hydrogenolysis, according to the procedure reported in the literature[45], proceeded smoothly to give *trans*-(±)-solenopsin A as the major isomer. Overall yield of (±)-solenopsin A was 23% from piperidine.

Meyers *et al.* [46] have demonstrated that α-lithio formamidines can undergo selenation and subsequent elimination to provide enamidines which have proven to be useful precursors to a number of polysubstituted heterocycles. In this context, sequential alkylation of enamidine **80** with undecyl halide and methyl bromide gave an excellent yield of 2,6-disubstituted enamidines **81** (Fig. 22). The alkylated enamidine **81** was transformed into its tetrahydropyridine derivative **82** in 95% yield by removal of the formamidine moiety with hydrazine.



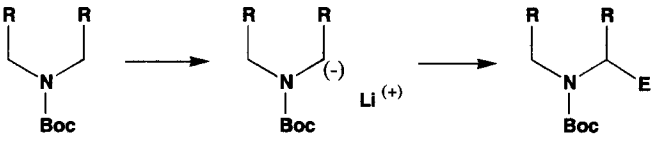
Reaction conditions: i) *t*-BuLi, 80% ether-THF, -20°, 1 hr; ii) $(PhSe)_2$, -78° (1 hr) to r.t.; iii) HCO_3^-; iv) *n*- or *t*-BuLi, 80% ether-THF, -20°, 1 hr; v) $C_{11}H_{23}X$, -20° to 0°; vi) *t*-BuLi, THF, -20°, 1.5 hrs; vii) CH_3Br, TMEDA, THF, -20° to 0°, 4 hrs; viii) N_2H_4, AcOH, EtOH 95%, r.t., <3 hrs; ix) $LiAlH_4$ or DIBALH reduction according to the procedure of Yamamoto.

FIG. 22

The resulting cyclic imine **82** was reduced either with lithium aluminum hydride or diisobutyl aluminum hydride producing *trans*-(±)-solenopsin A **4** in a 90:10 ratio, or the *cis* derivative **1**, respectively. The stereoselectivity compares with that reported by Yamamoto.[27] It should be noted that

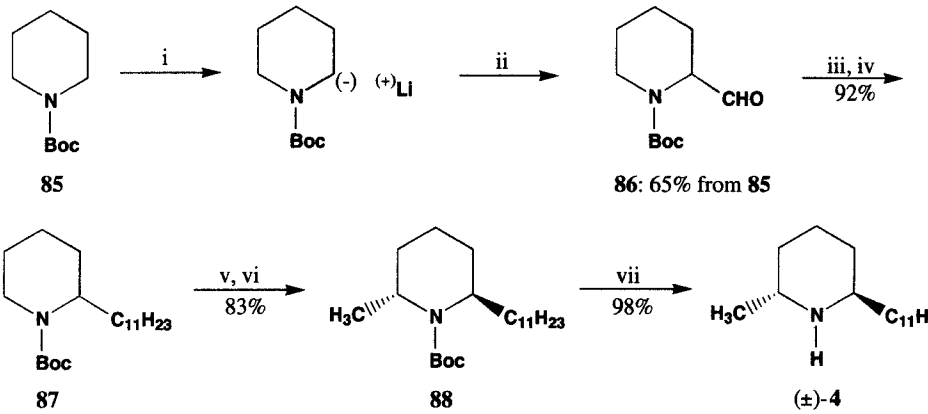
Yamamoto's approach to solenopsin involved reversal of the alkyl groups on the cyclic imine. Overall yield of (±)-solenopsin A was about 73% from *tert*-butylformamidine **79** which was synthesized from piperidine in 93% yield.[47]

Recently, Beak and Lee[48] have reported that the readily available *tert*-butoxycarbonyl (Boc) group, which is convenient to add and remove, can be an effective activator for the elaboration of **83** to **84** by the sequence of α'-lithiation to give a dipole stabilized carbanion, and electrophilic substitution (Fig. 23). This methodology easily provides *trans*-(±)-solenopsin A (Fig. 24).



83 **84**

FIG. 23



85 **86**: 65% from **85**

87 **88** (±)-**4**

Reaction conditions: i) *s*-BuLi, TMEDA, ether, -20°, 10 min; ii) DMF, -78°, 10 min; iii) C_9H_{20}-CH=PPh_3, THF, -78° to r.t.; iv) H_2, EtOH, 24 hrs; v) *s*-BuLi, TMEDA, ether, -20°, 30 min; vi) $(CH_3)_2SO_4$, ether, -78° to r.t.; vii) TFA, CH_2Cl_2, r.t., 2 hrs

FIG. 24

The Boc derivative **85** was prepared from the cyclic secondary amine in 93% yield. Conversion of *N*-Boc-piperidine **85** to *N*-Boc-piperidine-carboxaldehyde **86**, followed by a Wittig reaction with decylidenetriphenylphosphorane and catalytic hydrogenation, provided 60% of *N*-Boc-2-undecylpiperidine **87**. Lithiation of **87** with *s*-BuLi/TMEDA at C-6 and reaction with dimethylsulfate as electrophile yielded 83% of *trans*-*N*-Boc-2-methyl-6-undecylpiperidine **88**. Hydrolysis of the Boc protecting group afforded *trans*-(±)-solenopsin A. This stereoselectivity can be rationalized in terms of removal of an equatorial proton from a chairlike conformation to give the equatorially lithiated species which reacts with an electrophile with retention of configuration[49,50](Fig. 25). Equatorially substituted *N*-acyl-2-piperidines are recognized to be less stable than their axially substituted isomers due to $A^{1,3}$

strain, so that **89** would be expected to undergo conformational equilibration to **90**.[51,52] Subsequent equatorial lithiation and substitution of **90** then would proceed via **91** to provide the equatorially substituted product **92**. Thus, *trans*-(±)-solenopsin A was obtained by this sequence in a 45% yield from piperidine as starting material.

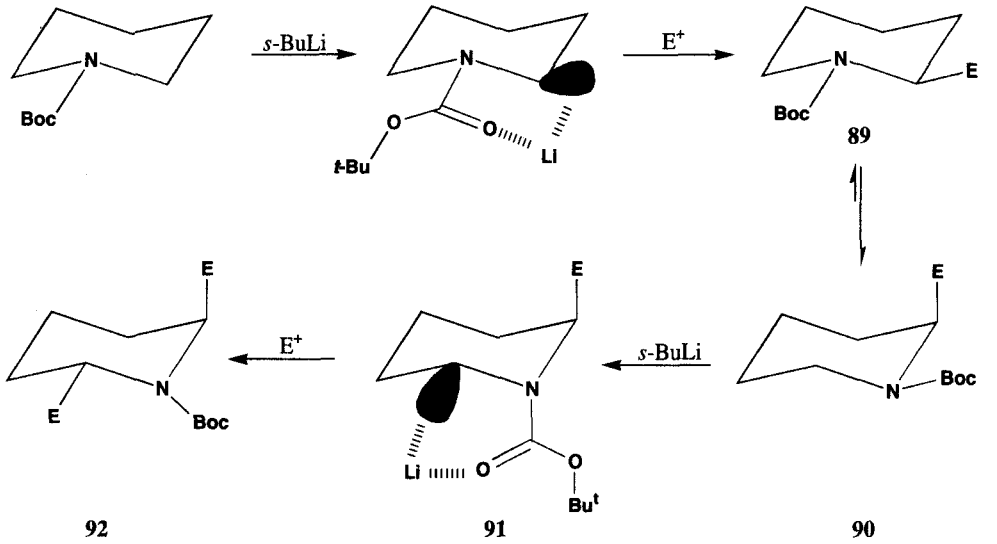
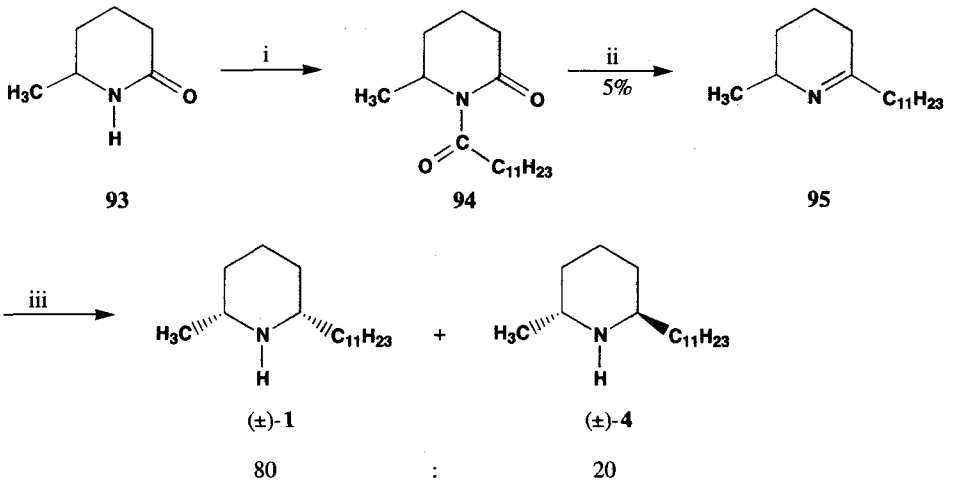


FIG. 25

Two syntheses of (±)-solenopsin A, based on the alkylation of piperidinic derivatives, use 6-methyl-2-piperidone as starting material.

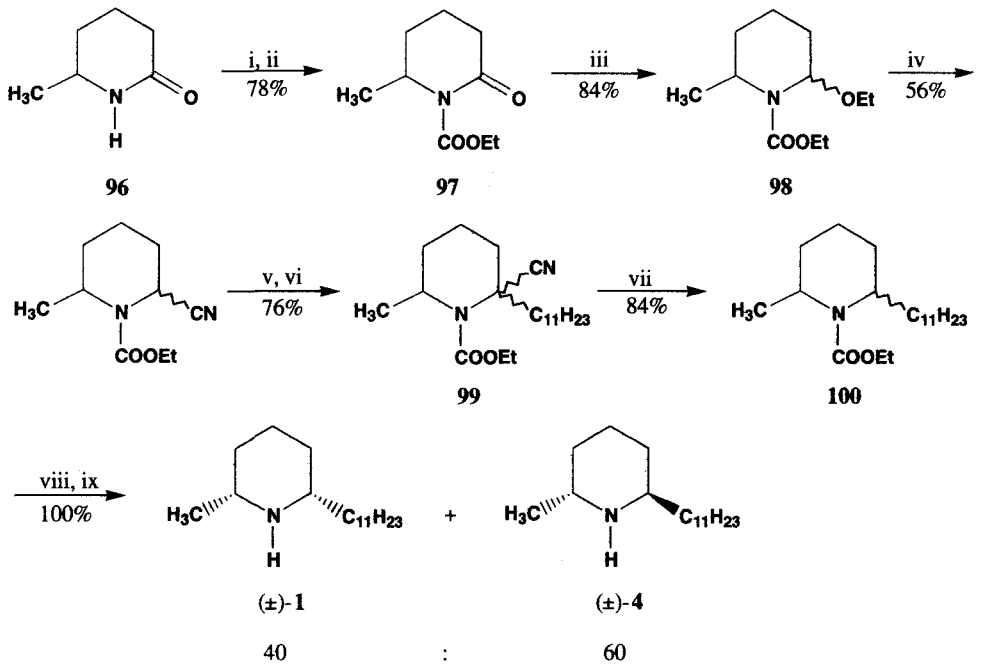
The first one, reported by Hill and Yuri,[53] uses the carbonyl group of the cyclic lactam **93** as a handle for the introduction of alkyl groups (Fig. 26). The racemic lactam **93**, synthesized from 2-methylpiperidine in 12% yield, was converted to imide **94** using lauryl chloride and pyridine at room temperature. The Mundy *N*-acyllactam rearrangement[54] involved the pyrolysis of *N*-lauryl-6-methyl-2-piperidone with calcium oxide to give the cyclic imine **95** in very low yield. Reduction was effected with sodium borohydride to yield a 80:20 mixture of *cis*- and *trans*-(±)-solenopsin A. Though this method works satisfactorily for the pinidine skeleton (2-methyl-6-*n*-propylpiperidine, 15% overall yield), application to the synthesis of solenopsin A is unattractive if we consider the 5% yield of pyrolysis of the *N*-acyllactam **94**.

The second synthesis, described by Nagasaka *et al.*[55], converts the 6-substituted lactam **96** into 2,6-disubstituted cyclic amines in six steps (Fig. 27). This methodology provides *cis*- and *trans*-(±)-solenopsin A without stereoselectivity in a 24% overall yield. The starting cyclic lactam **96** can be prepared by a Schmidt reaction of 2-methylcyclopentanone with hydrazoic acid in 33% yield. Reaction of **96** with ethyl chloroformate in the presence of sodium hydride gave the carbamate **97** which was reduced with sodium borohydride to yield 66% of 2-ethoxycarbamate **98** from **96**. This reduction



Reaction conditions: i) lauryl chloride, pyridine, PhH, r.t., overnight; ii) pyrolysis over CaO, reflux, 1.5 hrs; iii) $NaBH_4$, EtOH.

FIG. 26



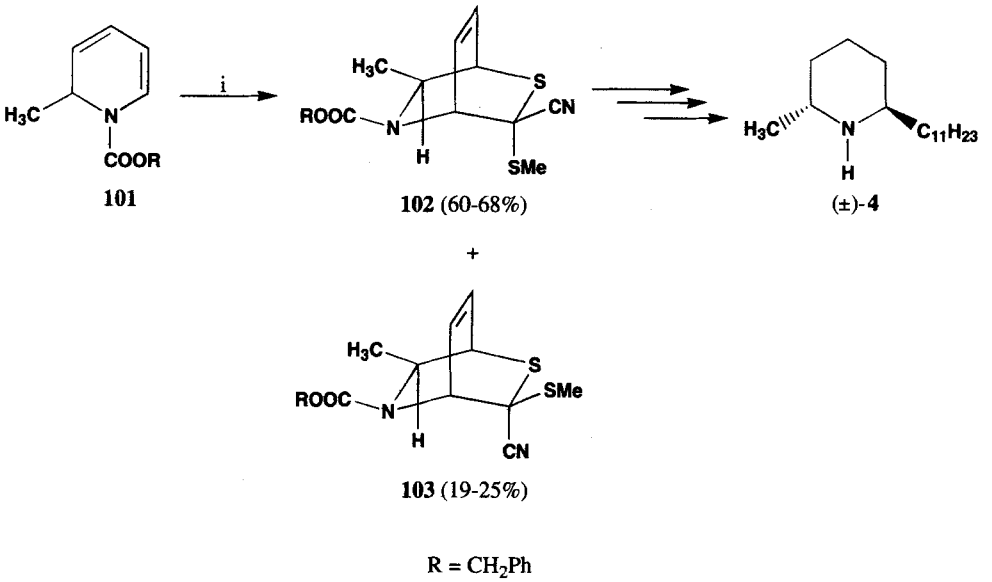
Reaction conditions: i) NaH; ii) ClCOOEt; iii) $NaBH_4$, H^+, EtOH; iv) Me_3SiCN, $ZnCl_2$, CH_2Cl_2, -30° to -40° (5 hrs) to r.t. (overnight); v) LDA, THF, HMPA, -78°, 45 min; vi) $C_{11}H_{23}I$, -78° (1hr) to r.t. (1hr); vii) Na, NH_3, -30 to -40° (1hr) to r.t.; viii) HBr, AcOH; ix) K_2CO_3

FIG. 27

required controlled pH and temperature conditions, since 1-ethoxycarbonyl-6-methyl-1,4,5,6-tetrahydropyridine was produced as a major product in some cases. Treatment of **98** with trimethylsilyl cyanide in the presence of zinc chloride, followed by alkylation with *n*-undecyl iodide afforded 2-cyano-2-*n*-undecylcarbamate **99** which was a mixture of isomers in a 60:40 ratio. Decyanation by Birch reduction with sodium-ammonia gave the two isomers of 2,6-dialkylcarbamate **100** in 84% yield. Without separation, the mixture was treated with a hydrobromic-acetic acid mixture to give, in quantitative yield, *cis*-and *trans*-(±)-solenopsin A in a 60:40 ratio.

7. Cycloadditions

To be complete, we have to mention the synthesis of *trans*-(±)-solenopsin A briefly described by Ogawa and Natsume[56] when they attempted to synthesize 2,6-*trans*-dialkyl-1,2,3,6-tetrahydropyridines. These are important structural units observed in *Sedum* and *Lobelia* alkaloids. Cycloaddition reaction between 1-acyl-2-methyl-1,2-dihydropyridine **101** and methyl cyanodithioformate affords epimers **102** (60-68% yields) and **103** (19-25% yields) (Fig. 28). In order to clarify the regio- and stereochemistry of the cycloadduct **102**, this latter was transformed into *trans*-(±)-solenopsin A in three steps, that were not described by the authors.



Reaction conditions: i) methyl cyanodithioformate

FIG. 28

II. SYNTHESES OF OPTICALLY ACTIVE SOLENOPSINS

To date, ten syntheses of optically active solenopsins have been published. Four of these syntheses used the chiron approach, whereas the other six employed chiral auxiliaries.

1. Syntheses Using Chirons

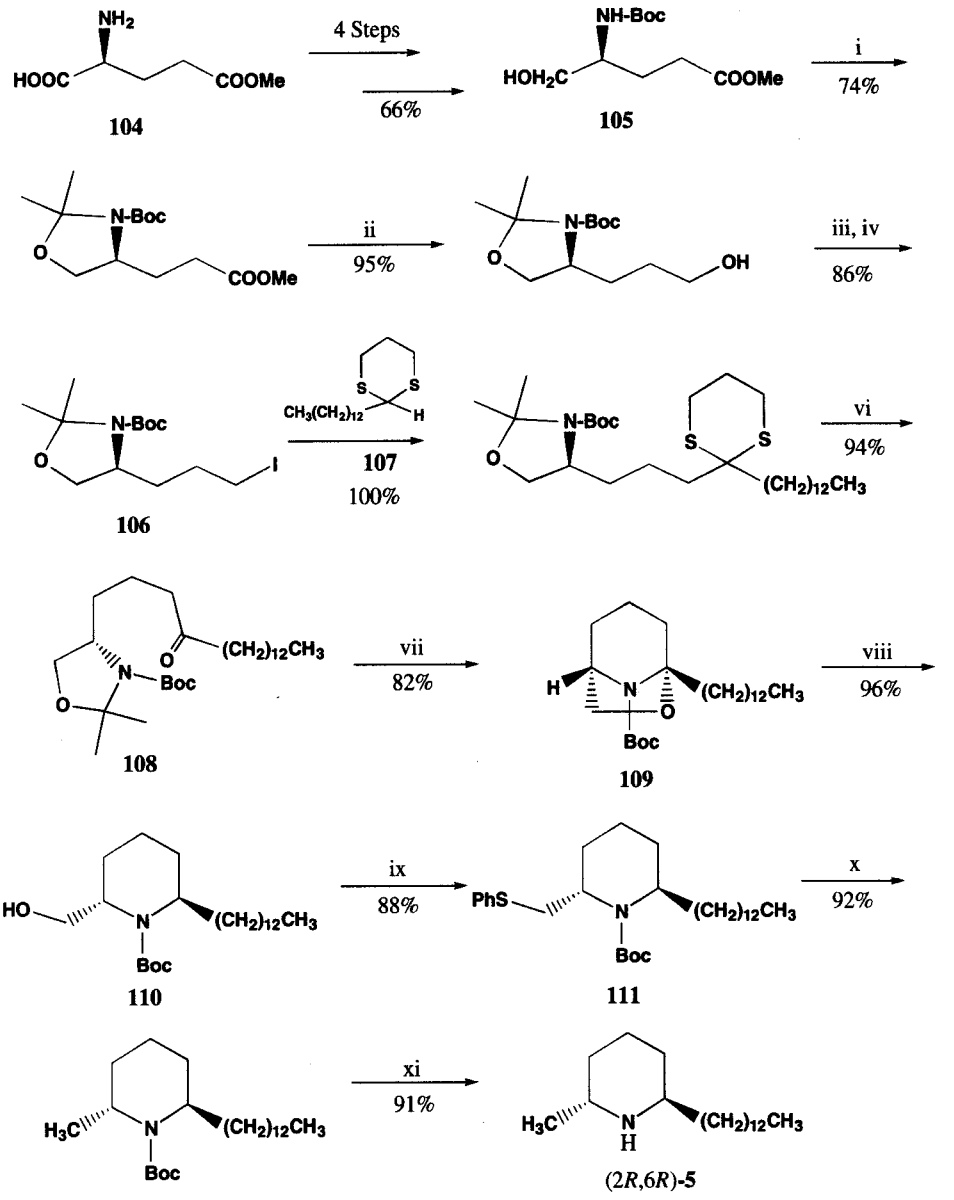
The four solenopsin syntheses based on this approach exploit the innate chirality of readily available α-amino acids. In each case, the strategy requires the transformation of the chosen α-amino acid into a chiron that can undergo both a cyclization and a chain elongation.

a) From L-Glutamic acid

In 1991, Kotsuki *et al.*[57] reported the synthesis of (2*R*,6*R*)-(-)-solenopsin B in 14 steps, starting from L-glutamic acid 5-methyl ester (**104**) (Fig. 29). The key step of this synthesis is the stereoselective reduction of the bicyclic *N,O*-ketal intermediate **109** to afford the *trans*-piperidine **110**. Thus, L-glutamic acid 5-methyl ester (**104**) was converted in a 66% yield into the protected 4-amino-5-hydroxypentanoic acid methyl ester **105**, which was transformed in 3 steps into the iodide **106**, in a 60% yield. Alkylation of **106** with the 1,3-dithiane derivative **107** using a THF/DMPU mixture as solvent, followed by removal of the dithiane group by treatment with $Hg(OAc)_2$ afforded ketone **108**. The transketalization step to the bicyclic *N,O*-ketal **109** proved to be critical and was only achieved in the presence of catalytic amounts of (S)-(+)-camphor-10-sulphonic acid (CSA) in refluxing $CHCl_3$. Reduction of **109** with 4 eq of DIBALH in CH_2Cl_2 at 0° provided the *trans*-alcohol **110** with excellent diastereoselectivity (>99%). The removal of both the OH and *t*-Boc groups of **110** was necessary in order to complete the synthesis. This step proved to be troublesome, as many attempts led to the formation of a carbamate by intramolecular reaction of the OH with the *t*-Boc group. This difficulty was finally circumvented by using Hata's reagent[58] for effecting the elimination of the OH group. Thus, treatment of **110** by Bu_3P and PhSSPh in THF under a 10 kbar pressure afforded the phenylsulfide **111**, which was desulfurized with Raney nickel. Removal of the *t*-Boc by TMSOTf afforded (2*R*,6*R*)-(-)-solenopsin B in 54% yield from the iodide **106**, and 22% from L-glutamic acid 5-methyl ester.

b) From L-Aspartic acid

The synthesis of (2*R*,6*R*)-(-)-solenopsin A of Jefford and Wang[59] is based on their earlier procedure for the synthesis of enantiopure β-amino acids.[60] Thus, L-aspartic acid **112** was first transformed in 4 steps and 65% yield into a key intermediate, the *N*-protected iodohomoserine ester **113** (Fig. 30). Treatment of **113** with lithium didecylcuprate in THF gave the undecyl-β-aminoester **114** in 86% yield. The latter was transformed into the methylketone **117** in 3 steps and 77% yield: i) DIBALH reduction to the aldehyde **115**, ii) Wittig reaction with acetylmethylidene-triphenylphosphorane to the α,β-unsaturated ketone **116**, and iii) hydrogenation over Adams catalyst. Cyclization of **116** into **117** was achieved by catalysis with *p*-TsOH. The resulting dehydropiperidine **118** was then submitted to $NaBH_3CN$ reduction in the presence of trifluoroacetic acid, which afforded the *trans*- and *cis*-tosylpiperidines **119** and **120** in a ratio of 78:22 and 98% yield. After deprotection with sodium naphthalide in DME, the resulting mixture was chromatographed on basic alumina. Pure (2*R*,6*R*)-(-)-*trans*-solenopsin A and (2*S*,6*R*)-(-)-*cis*-solenopsin A were isolated in a 72% and 22%

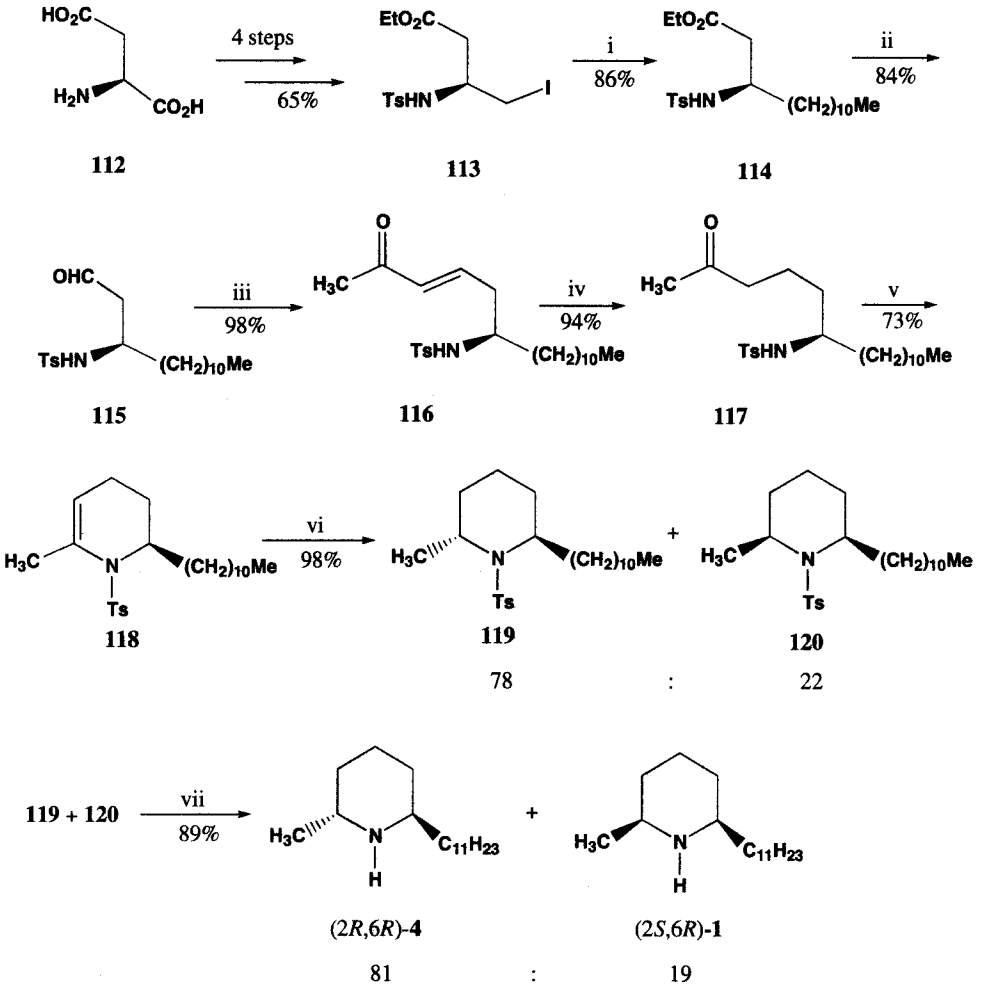


Reaction conditions: i) 2,2-dimethoxypropane, *p*-TsOH; ii) $LiAlH_4$, THF, 0°, 20 min; iii) *p*-TsCl, Et_3N, CH_2Cl_2; iv). KI, K_2CO_3, acetone, Δ; v) *n*-BuLi, THF, DMPU, -78°, 30 min; vi) $Hg(OAc)_2$, aq CH_3CN; vii) cat. CSA, $CHCl_3$, Δ, 6 hrs; viii) DIBALH (4 eq), CH_2Cl_2, 0°, 15 min; ix) PhSSPh, Bu_3P, THF, 10 kbar, 62°, 40 hrs; x) Raney Ni, EtOH, Δ, 1.5 hrs; xi) TMSOTf, CH_2Cl_2, 0 ° 1 hr

FIG. 29

yield, respectively. The overall yield of solenopsin A for the 11 steps was 24%. It is worth pointing out that the diastereoselectivity of the reduction of the dehydropiperidine **118**, even if still satisfactory,

is not as high as that of the corresponding *N*-*t*-Boc (Comins[35]) or *N*-benzyl (Wasserman[27]) derivatives, suggesting that the *N*-tosyl group in the iminium cation **60b** derived from **118** (Fig. 15) is not so susceptible to $A^{1,2}$ strain.



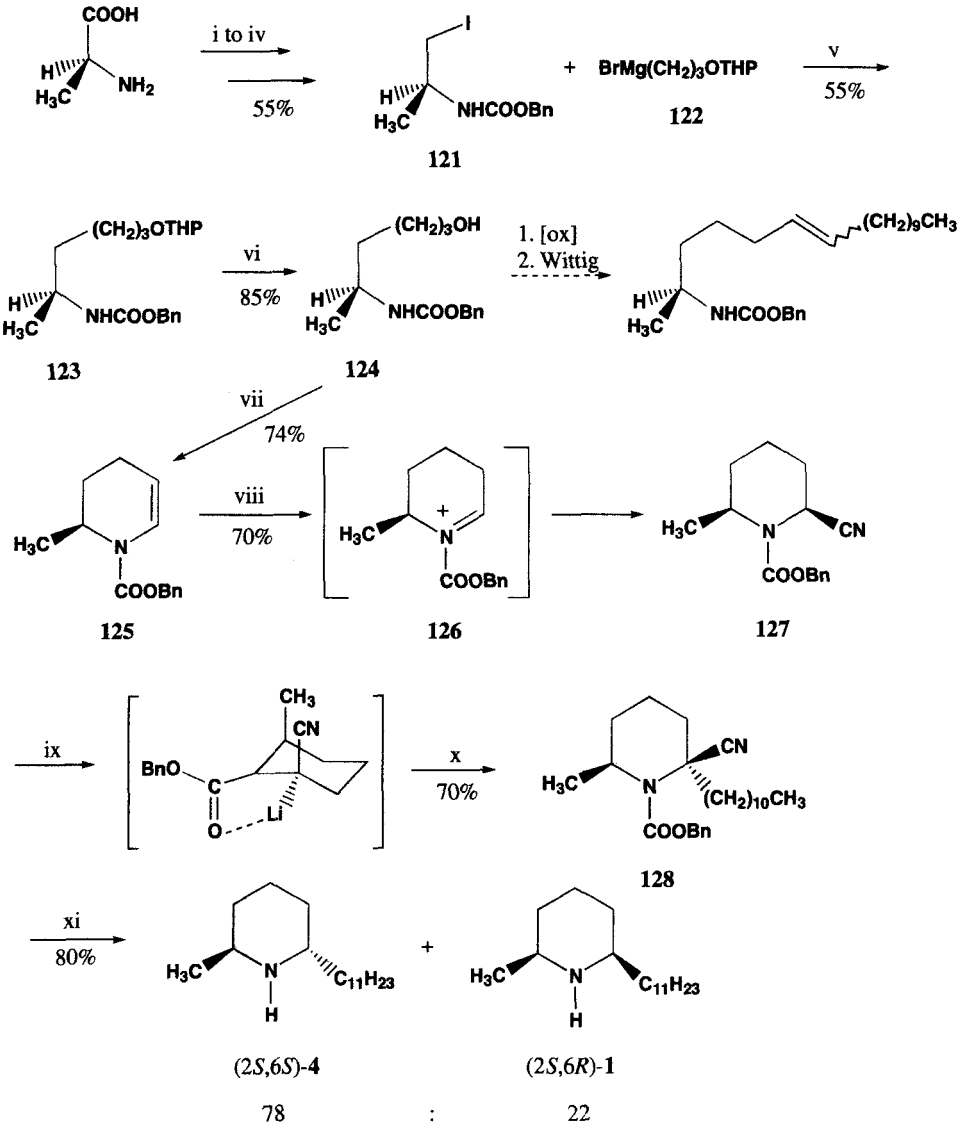
Reaction conditions: i) $(Me(CH_2)_9)_2CuLi$, THF, -18°, 6 hrs; ii) DIBALH, PhMe, -78°, 3 hrs; iii) $MeCOCH{=}PPh_3$, THF, Δ, 12 hrs; iv) H_2, PtO_2, MeOH, 2 h; v) *p*-TsOH, PhMe, reflux, 3 hrs; vi) $NaBH_3CN$, TFA, CH_2Cl_2, -45°, 4 hrs; vii) Na-Naphtalide, DME, -78°, 1 h.r

FIG. 30

c) From L-Alanine

In 1994, Thirionet *et al.*[12] reported the synthesis of (2*S*,6*S*)-(+)-*trans*-solenopsin A and (2*S*,6*R*)-(+)-*cis*-solenopsin A starting from L-alanine (Fig. 31). The latter was first transformed in 4 steps into the protected iodoamine **121** by a procedure already described by Schlesinger and Iwanow-

icz.[61] It has to be noted that the high overall yield (78%) reported for this transformation[61] could not be reproduced (50% to 55%).[12] The coupling of **121** with the protected Grignard reagent **122** in the presence of CuI gave carbamate **123**, the THP group of which was cleaved with 2N HCl in MeOH to afford alcohol **124**. Originally, it had been planned to oxidize **124** into the corresponding aldehyde



Reaction conditions: i) $LiAlH_4$, THF; ii) BnCOOCl, Na_2CO_3; iii) TsCl, pyr.; iv) NaI, acetone, v) THF, r. t.; vi) 2N HCl, MeOH, 20 hrs; vii) PCC on SiO_2, CH_2Cl_2,))), 0.5 h;rs viii) TMSCN, TFA, $TiCl_4$, CH_2Cl_2, -78°, 3 hrs; ix) LDA, diglyme, HMPA, -50°, 20 min; x) *n*-$C_{11}H_{23}Br$, 75 min; xi) Na, NH_3, THF, -78°, 0.5 hr

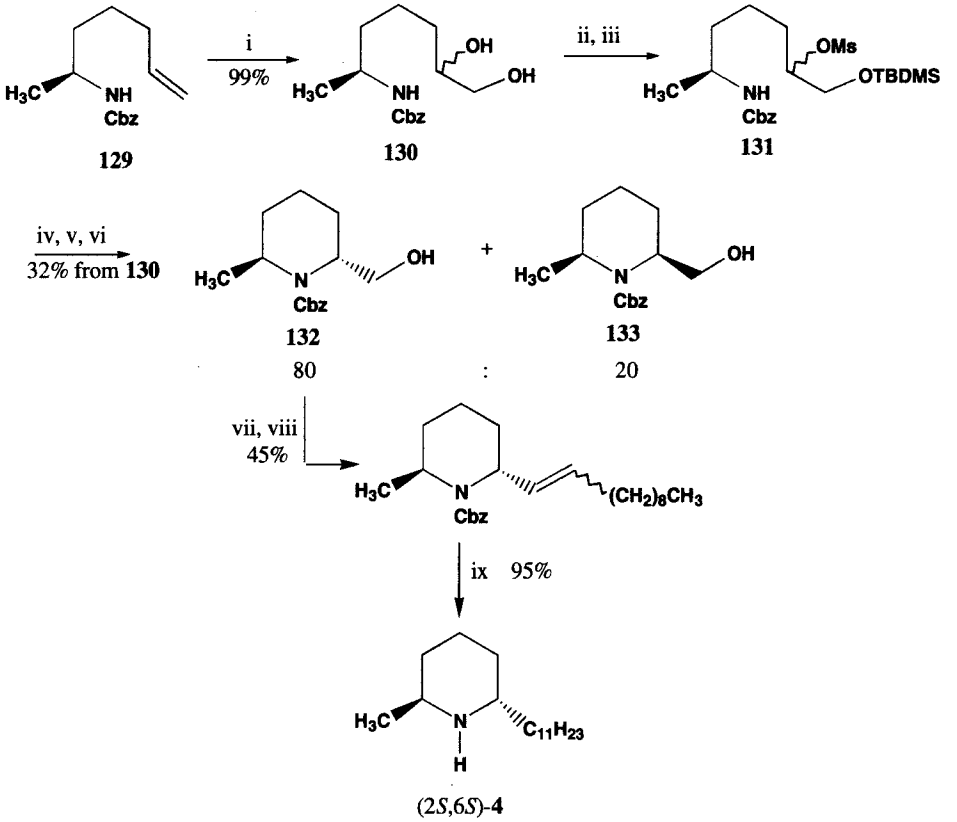
FIG. 31

and to effect a chain elongation through a Wittig reaction. However, oxidation of **124** with PCC did not afford the expected aldehyde but rather the enecarbamate **125** in 75% yield. This was rationalized by assuming that the intermediate aldehyde undergoes an intramolecular nucleophilic attack by the N atom of the carbamate, leading to an unstable α-hydroxycarbamate that might lose water. The fortuitously obtained enecarbamate **125** proved finally to be a pivotal intermediate in the synthesis. Indeed, treatment of **125** first with $TiCl_4$/TFA, to give the iminium **126**, then by TMSCN afforded the α-cyanocarbamate **127**. The addition of cyanide was highly stereoselective, and only the *cis* isomer could be detected by ^1H NMR. Treatment of **127** with LDA, followed by addition of HMPA and 1-bromoundecane afforded the alkylated derivative **128** in 70% yield. Again, the alkylation was stereoselective, affording only one compound which was assigned the stereochemistry shown in **128**, on the basis of the results of Beak and Lee.[48] Simultaneous deprotection of the amino group and decyanation of **128** with sodium in liquid NH_3 provided a mixture of (2*S*,6*S*)-(+)-*trans*-solenopsin A and (2*S*,6*R*)-(+)-*cis*-solenopsin A in a ratio of 78:22. The two compounds were easily separated by chromatography on basic alumina. Overall yield for the 10 steps was 7% from L-alanine or 13% from iodide **121** (6 steps). The availability of samples of solenopsins of known absolute configuration allowed these authors to devise a chromatographic method permitting the assignment of the absolute configuration of natural solenopsins which, in all the samples analyzed, were found to be (2*R*,6*R*) for the *trans* and (2*R*,6*S*) for the *cis* derivative.[12]

The above iodocarbamate **121** from L-alanine (Fig. 31) was also used as an intermediate in the last chiron synthesis published up to now[62] (Fig. 32). The difference with the previous approach lies in the strategy followed for the cyclization step (see hereunder). Iodide **121** was converted in 94% yield to the *N*-alkenylurethane **129** by coupling with homoallylmagnesium bromide in the presence of CuI. **129** was then submitted to an asymmetric dihydroxylation using the AD-mix-β, which afforded a diastereomeric mixture of diols **130** in 99% yield. Selective protection of the primary alcohol of **130** with *tert*-butyldimethylsilyl chloride, followed by mesylation of the secondary alcohol provided the mesylate **131**. The latter was cyclized to a 80:20 mixture of the protected 2,6-*trans*-piperidine **132** and its *cis* isomer **133** by a three steps procedure: i) treatment with H_2 and $Pd(OH)_2$ as catalyst to remove the Cbz group with concomitant cyclization, ii) 1% HCl treatment to remove the TBDMS group and iii) *N*-benzyloxycarbonylation. Overall yield of the mixture of **132** and **133** from diols **130** was 32%. The two stereoisomers were separated at that stage and the *trans* compound was transformed into (2*S*,6*S*)-(+)-solenopsin A by Swern oxidation followed by chain extension through a Wittig reaction with decylidenetriphenylphosphorane and, finally, catalytic hydrogenation. The overall yield from iodide **121** (9 steps) was 13%.

To sum up this section, among the chiron syntheses described above, that of Kotsuki *et al.*[57] has the highest overall yield and the advantage of being totally diastereoselective in favour of the *trans*-solenopsin. However, it suffers from two critical steps: the transketalization (**108** to **109**) and the removal of the primary OH group of **110** which requires a reaction under high pressure (Fig. 29). The three remaining syntheses[12,59,62] afford mixtures of *trans* and *cis* isomers (in an approximately 8:2

ratio) which, however, are easily separated by chromatography on silica gel or on basic alumina so that this lack of stereoselectivity is only a minor drawback.



(2*S*,6*S*)-**4**

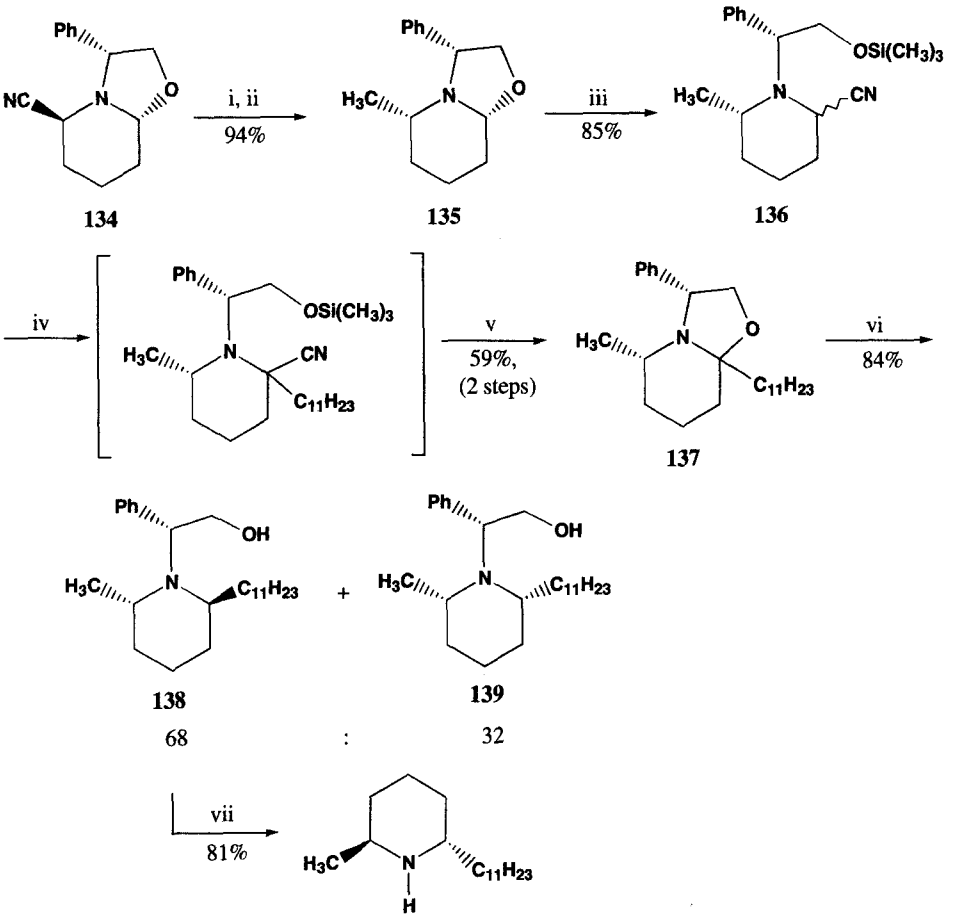
Reaction conditions: i) AD-mix-β; ii) TBDMS/imidazole; iii) MsCl, Et_3N; iv) H_2/$Pd(OH)_2$; v) 1% HCl, EtOH; vi) CbzCl, NaOH; vii) $(COCl)_2$, DMSO, Et_3N; viii) $Ph_3P^+C_{10}H_{21}Br^-$, *n*-BuLi; ix) H_2, $Pd(OH)_2$.

FIG. 32

2. Syntheses Using Chiral Auxiliaries

a) Using the (-)-2-Cyano-6-oxazolopiperidine

Capitalizing on the chemistry developed for the racemic synthesis described in Figure 20, Husson and coworkers reported in 1986 the first enantioselective synthesis of (2*S*,6*S*)-(+)-solenopsin A[63] (Fig. 33). It uses as starting material the (-)-2-cyano-6-oxazolopiperidine **134**, which is a 1,4-dihydropyridine equivalent obtained by a Robinson-Schöpf type condensation between glutaraldehyde and (-)-phenylglycinol, in the presence of KCN. This synthon is amenable to react chemo- and stereoselectively at C-2 and C-6 thus allowing the control of the absolute configuration at these centers. Indeed, the nucleophilic substitution of 2-cyano- and 2-oxazolopiperidines which occurs through the iminium ion is under stereoelectronic control[64] (see Figure 34). Thus, the anion of **134** generated by treatment with LDA was alkylated with CH_3I to afford **135**. This was followed by selective removal



Reaction conditions: i) LDA, CH_3I, THF, -78°, 2.5 hrs; ii) $AgBF_4$, $Zn(BH_4)_2$, THF, -78 ° 1 hr; iii) TMSCN, $ZnBr_2$, CH_2Cl_2, Δ, 15 h;rs iv) LDA, THF/HMPA, $C_{11}H_{23}Br$, -20°, 15 hrs; v) HF aq, CH_3CN; vi) $NaBH_4$, MeOH, -10°, 2 hrs; vii) H_2, Pd/C, MeOH.

FIG. 33

of the cyano group without opening of the oxazolidine ring by complexation of the cyano group of **134** with $AgBF_4$, and $Zn(BH_4)_2$ reduction at -78°, to afford **135**. The introduction of a cyano group at C-6 by opening of the oxazolidine ring was performed by treatment of **135** with TMSCN in the presence of a catalytic amount of $ZnBr_2$, affording nearly quantitatively the TMS-protected cyanoalcohol **136** as a mixture of epimers. The anion at C-6 of **136** could then be generated by treatment with 3 eq of LDA in a THF-HMPA mixture at -20° (THF alone was inefficient). Alkylation of this anion with undecyl bromide followed by deprotection of the alcohol with HF in CH_3CN afforded the recyclized product **137** isolated in 58% yield. Reductive cleavage of the oxazolidine ring of **137** by $NaBH_4$ in

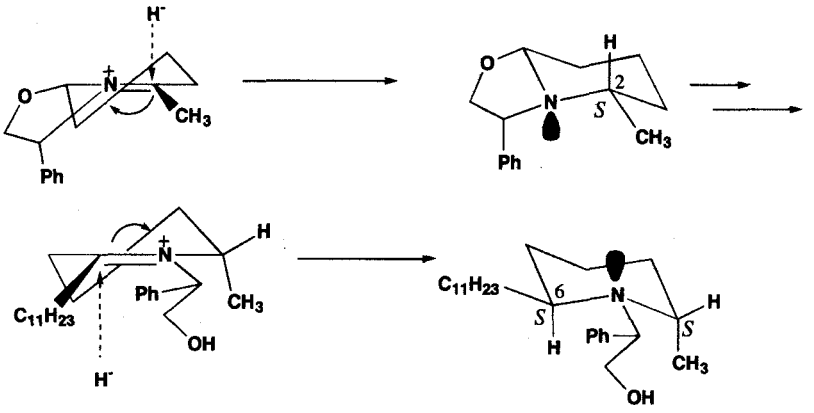
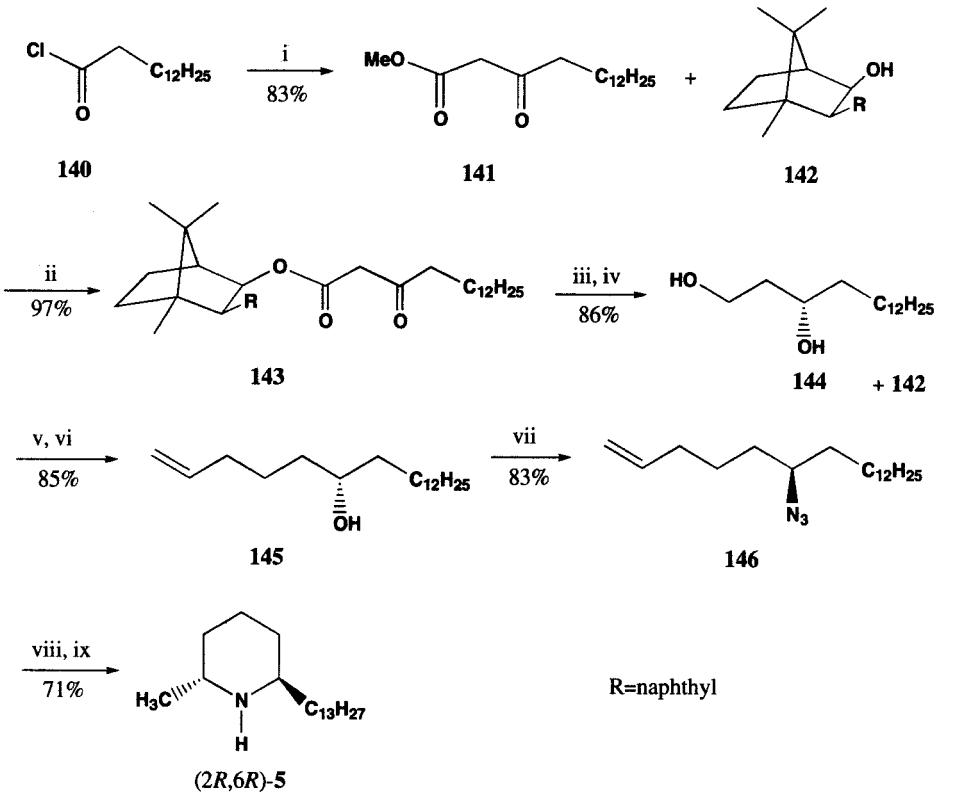


FIG. 34

MeOH yielded a 70:30 mixture of the *trans* and *cis* compounds **138** and **139**. Surprisingly, a complete reversal of stereoselectivity (*trans*/*cis*= 5/95) was observed when **137** was reduced by $Zn(BH_4)_2$ in THF or by $NaBH_4$ in THF containing trifluoroacetic acid. The synthesis was completed by hydrogenolysis of the chiral auxiliary (H_2, Pd/C) to afford (2*S*,6*S*)-(+)-solenopsin A {**4**.HCl: $[\alpha]_D^{20}$ = +7.5 (c 1.3, $CHCl_3$)}. Overall yield for the six steps from synthon **134** was 22%.

b) Using 2-Naphthylborneol

In their retrosynthesic analysis, Taber *et al.*[65] started from the observation[27] that in the racemic series, *trans* solenopsins can stereoselectively be obtained by $LiAlH_4$-$AlMe_3$ reduction of the imine **147** (Fig. 35) which, in turn, can be derived from the alcohol **145** through the intermediacy of the azide **146**. Hence, the key intermediate of the synthesis is the enantiomerically pure alcohol **145**. The latter could be obtained by reduction of the keto group of β-ketoester **141** with the reagent prepared from DIBALH and 2,6-di-*tert*-butyl-4-methylphenol,[66] followed by ester reduction with $LiAlH_4$. The authors explain the high diastereoselectivity of the reduction by activation of the ketone by complexation with a sterically demanding monodentate metal center, thus favoring the anti conformation of the β-keto ester in the transition state. Delivery of the hydride from the face of the carbonyl opposite to the naphtyl group leads to the *S* alcohol. Thus, in order to synthesize solenopsin B, β-ketoester **141** was first prepared through treatment of myristyl chloride with the anion of methyl acetate. Ester exchange with 2-naphthylborneol **142** proceeded to give **143**. Stereocontrolled reduction of **143** as described above and subsequent ester reduction afforded the diol **144** which was converted to the desired secondary alcohol **145** by conversion to a monotosylate which was reacted with an excess of allylmagnesium chloride. Mitsunobu reaction with diphenylphosphorazidate gave the inverted azide **146**. Heating of **146** at 165° for 2.5 hrs, followed by direct hydride reduction of thecrude thermolysis product (proposed mechanism shown in Figure 35), yielded (2*R*,6*R*)-(-)-*trans*-solenopsin B (**5**) with an overall yield of 35% from **140.** Its enantiomeric excess was very high as derivatization with tetraacetyl-β-D-glucopyranosyl isothiocyanate gave only one peak in reversed



Reaction conditions: i) LDA, CH_3COOCH_3, THF, -78° to r. t., 0.5 hr; ii) DMAP, PhMe, reflux, 40 hrs; iii) DIBALH/BHT (0.66/1), PhMe, -65° to 60°, 1.5 hr; iv) $LiAlH_4$ (3 eq), THF, 0°, v) TsCl (1.1 eq), DMAP, CH_2Cl_2, -30° to r. t.; vi) CH_2=CH-CH_2MgCl (5 eq), THF, 0°, 0.5 hr, reflux, 3 hrs; vii) Ph_3P, EtOOCN=NCOOEt, $(PhO)_2P(O)N_3$, THF, r. t., 24 hrs; viii) 165°, 2.5 hrs; ix) $LiAlH_4$ (7 eq), $(CH_3)_3Al$ (7 eq), THF, -78° to 0 °

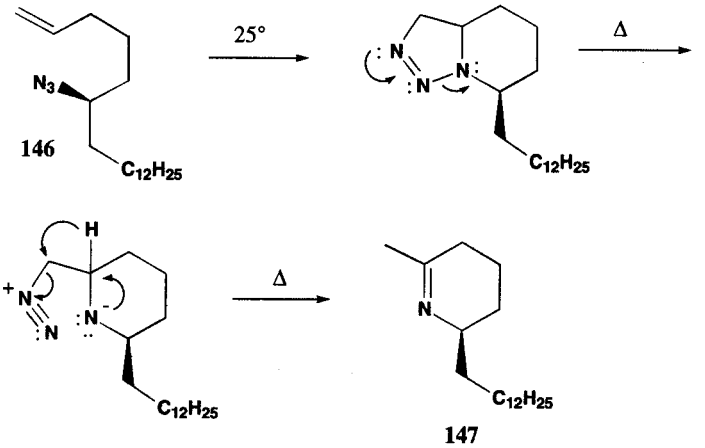
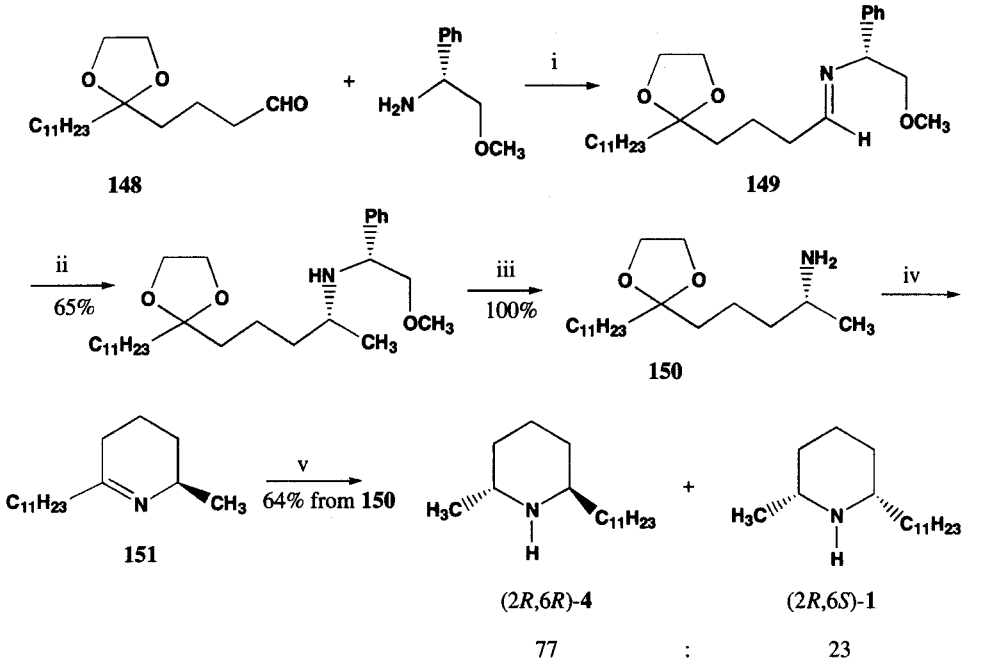


FIG. 35

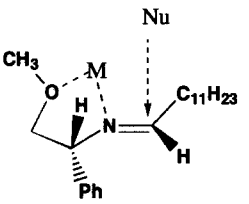
phase HPLC. Comparison of the retention time of this derivative with that of a sample of natural solenopsin B similarly derivatized showed that the latter also has the (2*R*,6*R*) absolute configuration.[65]

c) Using Chiral Imine 149

In their synthesis of (2*R*,6*R*)-(-)-*trans*-solenopsin A (**4**), Fujisawa and coworkers[67] exploited their observation that organometallic reagents can be added with high diastereofacial selectivity to chiral imines derived from (*R*)-2-methoxy-1-phenylethylamine. This selectivity was tentatively explained by a chelation-controlled model which postulates a coordination of the lithium or cerium by both the nitrogen and oxygen atoms of the chiral imine, and concomitant attack of the alkyl group from the less hindered face to give the (*R*,*R*)-isomer (see **152**, Figure 36). Thus, imine **149** was



Reaction conditions: i) 4Å molecular sieves; ii) "$MeCeCl_2$" (4 eq), THF, -65°, 3 hrs; iii) H_2, $Pd(OH)_2/C$; iv) Acetone, cat. *p*-TsOH; v) $LiAlH_4$-$(CH_3)_3Al$.



152

FIG. 36

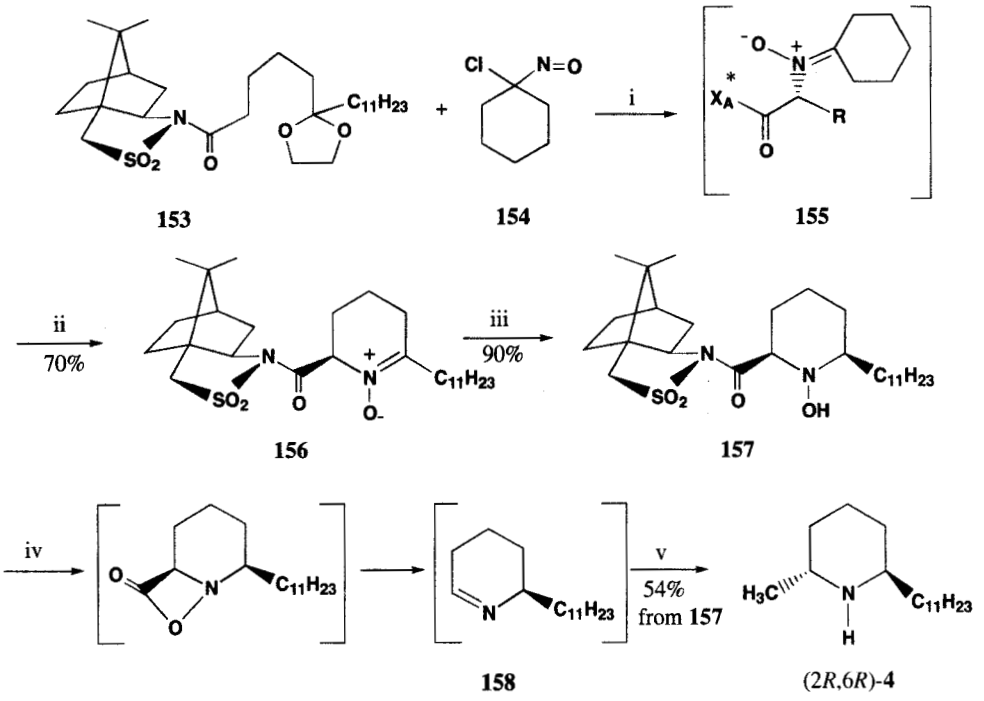
prepared by condensation of the protected 5-oxohexadecanal **148** with (*R*)-2-methoxy-1-phenylethylamine in the presence of 4Å molecular sieves. Addition of either MeLi or $MeCeCl_2$ afforded predominantly the (*R,R*) amine (de: 90:10), from which the chiral auxiliary was removed by catalytic hydrogenolysis. The resulting primary amine **150** was purified by crystallization, its acetal protecting group removed by treatment with a catalytic amount of *p*-TsOH in acetone, and the resulting piperideine **151** reduced by the Yamamoto procedure.[27] This afforded (2*R*,6*R*)-(-)-*trans*-solenopsin A (**4**) in 49% yield from **150** {$[\alpha]_D^{23}$ = -2.2 (c 1.3, $CHCl_3$); **4**.HCl: $[\alpha]_D^{23}$ = -7.6 (c 0.7, $CHCl_3$)}, and the *cis* isomer, (2*R*,6*S*)-**1** in a 15% yield. The overall yield of the synthesis cannot be calculated since the yield of some steps were not quoted in the original paper.[67]

d) Using Camphor-derived sultam 153

The asymmetric synthesis of (2*R*,6*R*)-(-)-*trans*-solenopsin A (**4**) by Oppolzer and coworkers[68] used as key intermediate the nitrone **155**, obtained by the approximately 100% diastereoface-selective C-N bond formation when enolates of *N*-acylsultams (e. g. **153**) are reacted with 1-chloro-1-nitrosocyclohexane (**154**). Acidic hydrolysis of the resulting nitrone-acetals **155** deprotects the ketone group and affords the corresponding cyclized nitrones **156** (Fig. 37). The diastereoface-selectivity was rationalized by assuming transition state A≠ in which a chelated (*Z*)-enolate is attacked by the nitroso electrophile from the C(α)-*Re*-face opposite to the lone electron pair of the sultam nitrogen (Fig. 37). Along these lines, successive treatment of the *N*-(ε-ketoacyl)sultam acetal **153** with NaHMDS, **154**, and finally 1N aqueous HCl provided the expected diastereomerically pure nitrone **156** in a 70% yield. Reduction of the latter with H_2/Pd proceeded from the less hindered side to afford the *cis*-2,6-disubstituted *N*-hydroxypiperidine **157** in a 90% yield. Heating **157** with NaH removed the acylsultam substituent with simultaneous *N,O*-cleavage, leading to the transient imine **158**. Addition of *in situ* prepared "$MeCeCl_2$" (generated by ultrasonication of $CeCl_3$/MeLi in THF at 0°) completed the synthesis of (2*R*,6*R*)-(-)-*trans*-solenopsin A {**4**.HCl: $[\alpha]_D^{20}$ = -8.9 (c 1.3, $CHCl_3$)}, with none of its *cis*-stereoisomer. Overall yield was 54% from **157**.

e) Using (-)-*trans*-2-(α-Cumyl)cyclohexanol [(-)-TCC]

The same year, Comins[69] reported the asymmetric synthesis of (2*R*,6*R*)-(-)-*trans*-solenopsin A (**4**), by employing as key steps i) the addition of an organometallic reagent to the chiral 1-acylpyridinium salt **159**, which proceeds with high diastereoselectivity, and ii) Beak's alkylation[48] of the *t*-Boc-piperidine **164** (Fig. 38). This approach is an extension of the racemic synthesis already presented.[35] Thus, the acylpyridinium salt **159** was prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine and the chloroformate of readily available (-)-TCC. Dropwise addition of undecylmagnesium bromide in THF to **159** in toluene at -78°, followed by acidic workup, provided dihydropyridone **160** in 95% crude yield and 90% de. For achieving this high de, the solvent system used above is critical. Purification by radial PLC furnished pure **160** in 85% yield. A working model that explains the observed stereoselectivity was presented.[70] It assumes that the aryl substituent at C-7 of the chiral



Reaction conditions: i) $Na(N(SiMe)_3)_2$; ii) aq. HCl; iii) H_2, Pd/C; iv) NaH (2 eq), PhMe, reflux, 2 hrs; v) $MeCeCl_2$ (10 eq), THF, -78°, 3 hrs, then, r. t. 16 h.rs

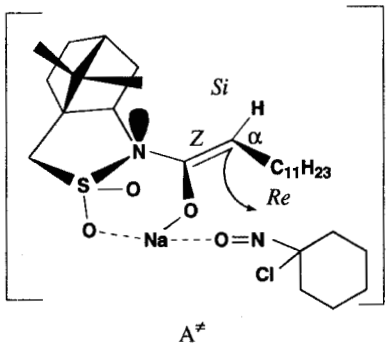
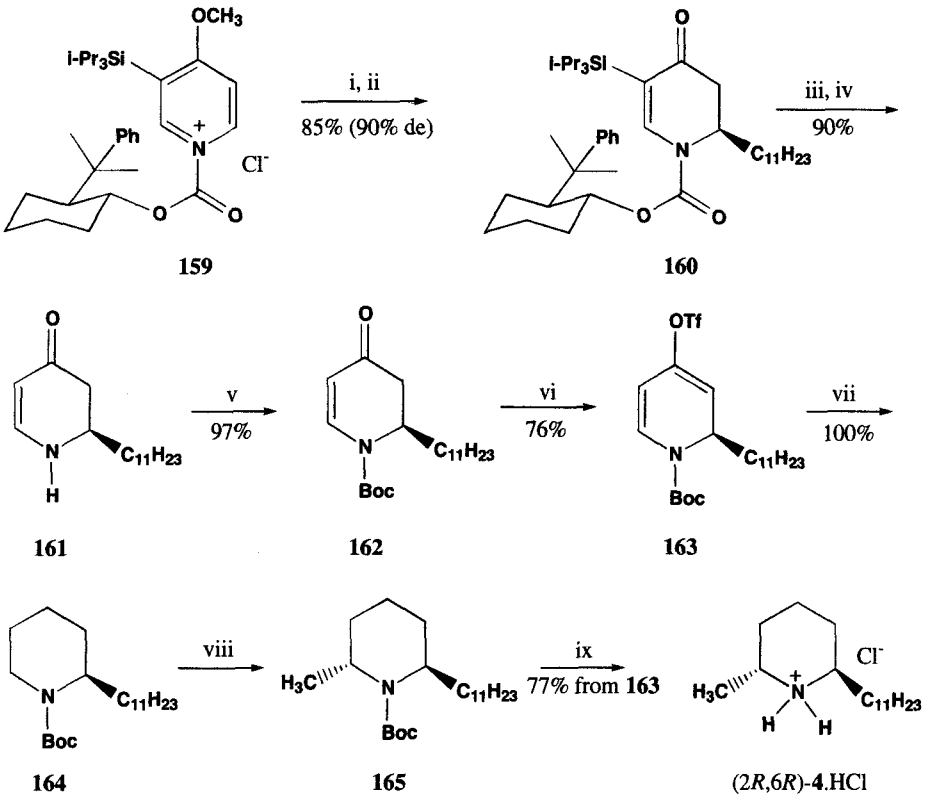


FIG. 37

auxiliary blocks one face of the pyridinium salt, thus favoring the delivery of the alkyl reagent from the opposite face. This explanation however is somewhat complicated by the possibility of free rotation around the carbonyl carbon-nitrogen bond of the carbamate substituent. For a detailed discussion, the reader is referred to ref. 70. Treatment of **160** first with NaOMe/MeOH and then with 10% HCl gave a 90% yield of deprotected dihydropyridone **161** (along with 95% recovered (-)-TCC), which was reprotected as its *t*-Boc derivative **162**. Next, the enone moiety of **162** was totally reduced



Reaction conditions: i) $C_{11}H_{23}MgBr$, -78°, PhMe, 1.5 hrs; ii) H_3O^+; iii) NaOMe, MeOH; iv) 10% HCl; v) $(t\text{-BuO})_2CO$, Et_3N, DMAP, THF, r. t.; vi) NaHMDS, *N*-(5-chloro-2-pyridyl)triflimide; vii) H_2, PtO_2, Li_2CO_3; viii) *sec*-BuLi, TMEDA, THF, -78 °, Me_2SO_4; ix) HCl, Et_2O.

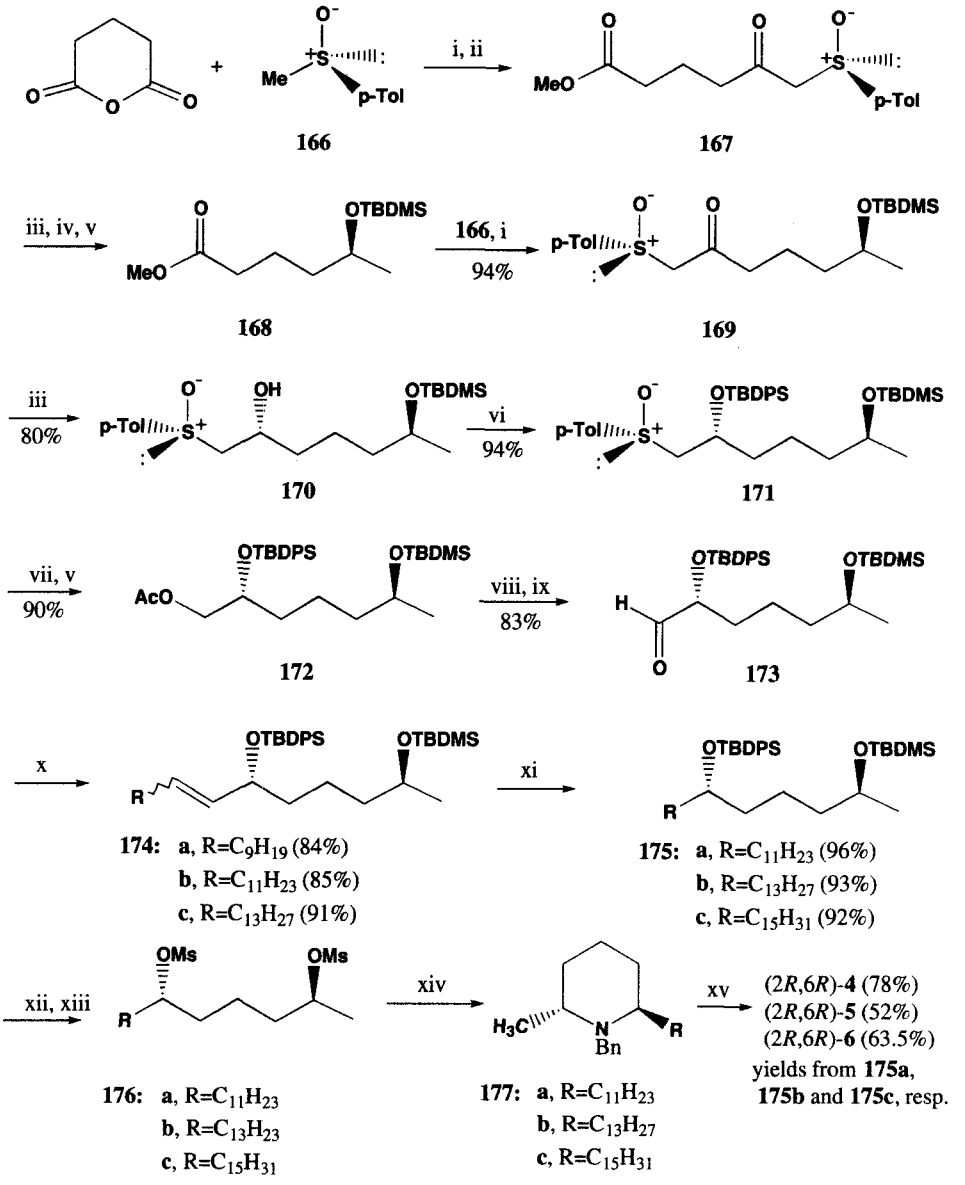
FIG. 38

through the vinyl triflate **163**. Thus, **162** was deprotonated with NaHMDS, and enolate trapping with *N*-(5-chloro-2-pyridyl)triflimide afforded a 76% yield of **163**. Catalytic reduction of **163** gave a quantitative yield of *N*-Boc-piperidine **164**. Finally, lithiation under Beak's conditions (*sec*-BuLi, TMEDA, THF, -78°) and alkylation with Me_2SO_4 gave the 2,6-*trans*-*N*-*t*-Boc-piperidine **165**, which, on treatment with HCl/EtOH at reflux, afforded pure (2*R*,6*R*)-(-)-**4**.HCl $\{[\alpha]_D^{23} = -7.6$ (c 0.7, $CHCl_3)\}$ in 7 steps and 43% overall yield from the acylpyridinium salt **159**.

f) Using Chiral Sulfoxides

Recently, Solladié and Huser[71] published the asymmetric synthesis of (2*R*,6*R*)-(-)-solenopsins A, B and C, by applying the well-known diastereoselective reduction of enantiopure β-keto sulfoxides, which leads to (*R*)- or (*S*)-alcohols depending on the reaction conditions. This strategy requires the preparation of chiral *anti*-1,5 diols which can subsequently be activated and cyclized

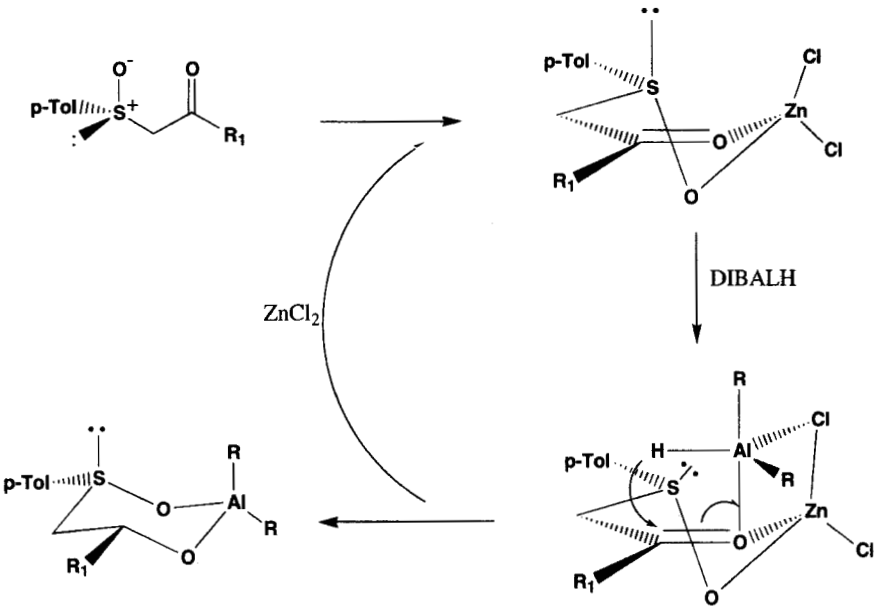
to solenopsins with benzylamine (Fig. 39). The synthesis started from the (*R*)-β-keto sulfoxide **166**, prepared by reaction of glutaric anhydride with (*R*)-(+)-methyl-*p*-tolyl sulfoxide in the presence of



Reaction conditions: i) LDA, THF, -40°; ii) K_2CO_3, Me_2SO_4; iii) $ZnCl_2$, DIBALH, THF, -78°; iv) TBDMSCl, imidaz.; v) Raney Ni, MeOH, 24 hrs, r. t.; vi) TBDPSCl, imidaz., DMF, 72 hrs, r. t.; vii) Ac_2O, AcONa, reflux, 17 hrs; viii) DIBALH, THF, -78°, 0.5 hr, then, 0°, 0.25 hr; ix) DMSO, $(COCl)_2$, Et_3N, -78°; x) R-CH=PPh_3, THF, 0°, 45 min; xi) H_2, Pd/C, EtOH; xii) TBAF (5 eq), THF, 0°, 4 days; xiii) MsCl (2.1 eq), CH_2Cl_2, Et_3N, -20° to r. t., 20 min; xiv) $BnNH_2$, r. t., 16 days; xv) H_2, Pd/C, AcOH, 5 atm..

FIG. 39

base and Me_2SO_4. The highly diastereoselective reduction[72] of (*R*)-**167** with $ZnCl_2$/DIBALH (de > 95%), followed by treatment with TBDMSCl/imidazole and finally desulfurization with Raney nickel, afforded the protected (*S*)-hydroxyester **168**. The (*S*) configuration thus obtained has been explained by hydride transfer from a zinc chelate between the sulfoxide and carbonyl oxygens (Fig. 40a). It should be recalled that reduction of (*R*)-**167** with DIBALH alone leads to the (*R*)-carbinol, presumably by an intramolecular hydride shift from an intermediate having aluminum chelated on the sulfoxide oxygen[72] (Fig. 40b). Reaction of **168** with (*R*)-(+)-methyl-*p*-tolyl sulfoxide and LDA gave **169** which was again stereoselectively reduced to **170** by $ZnCl_2$/DIBALH. The hydroxyl group of **170** was protected by a TBDPS group and the resulting compound **171** was submitted to a Pummerer rearrangement, followed by a desulfurization to afford the acetate **172**. The latter was converted to the



R= *i*-Bu

FIG. 40a

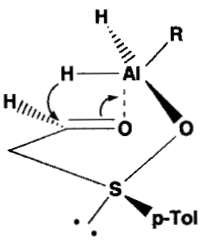


FIG. 40b

aldehyde **173**, which was chain-elongated with the appropriate phosphorus ylide. Subsequent reduction of the E/Z mixture of double bond isomers provided **174a, 174b** and **174c**. After removing the silyl protecting groups with TBAF, the resulting 1,5-*anti* diols were mesylated and allowed to react with benzylamine, affording the benzylated solenopsins **177a**, **177b**, and **177c** after 16 days of reaction. They were finally deprotected with H_2 in the presence of Pd/C to afford (2*R*,6*R*)-(-)-solenopsin A, B and C, respectively, which had a de > 95% and the same rotation {$[\alpha]_D$ -2 (c 1.1, MeOH)}. This synthesis required 16 steps from glutaric anhydride or 12 steps from the protected hydroxyester **168**. Overall yields from the latter were 33%, 22% and 28% for solenopsin A, B and C respectively.

III. CONCLUSIONS

In this paper, we have comprehensively reviewed the synthetic routes to both racemic and optically active *cis*- and *trans*-solenopsins that have been published until now. Since their isolation in 1970 by MacConnel *et al.*[73] from the fire ants, thirty different syntheses of solenopsins have been achieved—20 of the racemic form and 10 of the optically active forms. This relatively large number of syntheses reflects the interest taken by the organic chemists in these natural molecules. This interest can be explained by the fact that the solenopsins because of their *cis/trans* isomerism coupled to a structural simplicity represent an ideal target to test the stereoselectivity of a great variety of reactions (cyclization reactions, reductive procedures, alkylation reactions α to nitrogen atoms, efficiency of chiral auxiliaries, *etc.*). It is nevertheless worth mentioning that despite the multiplicity of the synthetic routes, the most effective and most rapid way to prepare the racemic solenopsins is still that published by MacConnell *et al.*,[9b] that was the first synthesis to be achieved.

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REFERENCES

1. J. O. Schmidt, *"Venoms of the Hymenoptera"*, p. 425, T. Piek (Ed.), Academic Press, London, 1986.

2. M. S. Blum and H. R. Herman, *"Arthropod venoms"*, p. 801, S. Bettini (Ed.), Springer-Verlag, New York, NY, 1978.

3. M. S. Blum, *"Handbook of Natural Toxins"*, Vol. 2, p. 225, A.T. Tu (Ed.), Marcel Dekker, New York, NY, 1984.

4. J. C. Braekman and D. Daloze, *"Studies in Natural Products Chemistry"*, Vol. 6, p. 421, Atta-ur-Rahman (Ed.), Elsevier, 1990.

5. A. Numata and T. Ibuka, *"The Alkaloids"*, Vol 31, p.193, A. Brossi (Ed.), Academic Press, New York, NY, 1987.

6. A. B. Attygalle and E. D. Morgan, *Chem. Soc. Rev.*, **13**, 245 (1984).

7. G. W. K. Cavill and P. L. Robertson, *Science*, **149**, 1337 (1965).

8. T. H. Jones and M. S. Blum, *"Alkaloids: Chemical and Biological Perspectives"*, Vol. 1, p. 33, S.W. Pelletier (Ed.), Wiley, New York, NY, 1983.

9. a) T. H. Jones, M. S. Blum and H. M. Fales, *Tetrahedron*, **38**, 1949 (1982); b) J. G. MacConnell, M. S. Blum and H. M. Fales, *ibid.*, **26**, 1129 (1971).

10. C. S. Lofgren, W. A. Banks and B. M. Glancey, *Ann. Rev. Entomol.*, **20**, 1 (1975).

11. a) D. R. Hoffman, *J. Allergy Clin. Immunol.*, **80**, 300 (1987); b) D. R. Hoffman, D. E. Dove and R. S. Jacobson, *ibid.*, **82**, 818 (1988).

12. S. Leclercq, I. Thirionet, F. Broeders, D. Daloze, R. K. Vander Meer and J. C. Braekman, *Tetrahedron*, **50**, 8465 (1994).

13. J. M. Brand, M. S. Blum and M. R. Barlin, *Toxicon*, **11**, 325 (1973).

14. a) J. M. Brand, M. S. Blum, H. M. Fales and J. G. MacConnell, *ibid.*, **10**, 259 (1972); b) J. G. MacConnell, M. S. Blum, W. F. Buren, R. N. Williams and H. M. Fales, *ibid.*, **14**, 69 (1976).

15. S. Leclercq, J. C. Braekman, D. Daloze, J. M. Pasteels and R. K. Vander Meer, *Naturwissenschaften*, in press.

16. K. Fuji, K. Ichikawa, E. Fujita, *Chem. Pharm. Bull. Jpn*, **27**, 3183 (1979).

17. R. T. Fraser, T. B. Grindley, S. Passannanti, *Can. J. Chem.*, **53**, 2473 (1975).

18. Y. Moriyama, D. Doan-Huynh, C. Monneret and Q. Khuong-Huu, *Tetrahedron Lett.*,**10**, 825 (1977).

19. B. P. Mundy and M. Bjorklund, *ibid.*, **26**, 3899 (1985).

20. G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

21. J. Ipaktschi, *Chem. Ber.*, **117**, 856 (1984).

22. a) S. Danishefsky, E. Taniyama and R. E. Webb, *Tetrahedron Lett.*, **24**, 11 (1983); b) S. Danishefsky, E. Taniyama and R. E. Webb, *ibid.*, **24**, 15 (1983); c) K. E. Harding and S. R. Burks, *J. Org. Chem.*, **49**, 40 (1984).

23. W. Carruthers, M. J. Williams and M. T. Cox, *Chem. Comm.*, 1235 (1984).

24. K. E. Harding and S. R. Burks, *J. Org. Chem.*, **46**, 3920 (1981).

25. D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel and S. M. Menchen, *ibid.*, **45**, 2120 (1980).

26. H. H. Wasserman and V. Rusiecki, *Tetrahedron Lett.*, **29**, 4977 (1988).

27. K. Maruoka, T. M. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 2831 (1983).

28. P. Caramella, N. G. Rondan, M. N. Paddon-Row and K. N. Houk, *ibid.*, **103**, 2438 (1981).

29. A. S. Cieplak, *ibid.*, **103**, 4540 (1981).

30. R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata and M. Kawanisi, *Bull. Chem. Soc. Jpn*, **60**, 215 (1987).

31. R. G. Pearson, *J. Chem. Educ.*, **45**, 581 and 643 (1986).

32. a) R. H. Hudson, *Angew. Chem., Int. Ed. Engl.*, **12**, 36 (1973); b) I. Fleming, *"Frontier Orbitals and Organic Chemical Reactions"*, p. 66, Wiley, New York, NY, 1976; c) T. L. Ho, *"Hard and Soft Bases Principles in Organic Chemistry"*, Academic Press, New York, NY, 1977.

33. K. Akiba, Y. Iseki and M. Wada, *Tetrahedron Lett.*, **23**, 429 (1982).

34. K. Akiba, Y. Iseki and M. Wada, *Bull. Chem. Soc. Jpn*, **57**, 1994 (1984).

35. D. L. Comins and M. A. Weglarz, *J. Org. Chem.*, **56**, 2506 (1991).

36. P. Deslongchamps, *"Stereoelectronic Effects in Organic Chemistry"*, chapter 6, Pergamon Press, New York, NY, 1983.

37. a) R. W. Hoffman, *Chem. Rev.*, **89**, 1841 (1989); b) F. Johnson, *ibid.*, **68**, 375 (1968); c) J. D. Brown, M. A. Foley and D. L. Comins, *J. Am. Chem. Soc.*, **110**, 7445 (1988).

38. a) D. L. Comins and M. A. Foley, *Tetrahedron Lett.*, **29**, 6711 (1988); b) T. Shono, Y. Matsumura, O. Onomura and M. Sato, *J. Org. Chem.*, **53**, 4118 (1988); c) G. J. Hanson and M. A. Russel, *Tetrahedron Lett.*, **30**, 5751 (1989); d) M. Natsume, Y. Sekine, M. Ogawa, H. Soyagimi and Y. Kitagawa, *ibid.*, 3473 (1979); e) A. Brossi, *"The Alkaloids"*, Vol. 32, p. 271, A. Brossi (Ed.), Academic Press, Inc., San Diego, 1988.

39. K. Abe, H. Okumura, T. Tsugoshi and N. Nakamura, *Synthesis*, 597 (1984).

40. D. M. Ryckman and R. V. Stevens, *J. Org. Chem.*, **52**, 4274 (1987).

41. D. Bacos, J. P. Celerier, E. Marx, S. Rosset and G. Lhommet, *J. Heterocyclic Chem.*, **27**, 1387 (1990).

42. M. Bonin, J. R. Romero, D. S. Grierson and H. P. Husson, *Tetrahedron Lett.* **23**, 3369 (1982).

43. K. Takahashi, H. Kurita, K. Ogura and H. Iida, *J. Org. Chem.*, **50**, 4368 (1985).

44. K. Takahashi, H. Kurita, K. Ogura and H. Iida, *ibid.*, **50**, 4372 (1985).

45. M. Konda, T. Shioiri and S. Yamada, *Chem. Pharm. Bull. Jpn*, **23**, 1063 (1975).

46. A. I. Meyers, P. D. Edwards, T. R. Bailey and G. E. Jagdmann, *J. Org. Chem.*, **50**, 1019 (1985).

47. A. I. Meyers, P. D. Edwards, W. F. Reiker and T. R. Bailey, *J. Am. Chem. Soc.*, **106**, 3270 (1984).

48. P. Beak and W. K. Lee, *J. Org. Chem.*, **58**, 1109 (1993).

49. a) R. E. Gawley and K. Rein, *"Comprehensive Organic Synthesis"*, Vol. 1, p. 459, Vol. 3, p. 65, Trost B. and Fleming, I., (Eds.), Pergamon Press, Oxford, England, 1991.

50. a) D. Y. Curtin and W. J. Okehl, *J. Am. Chem. Soc.*, **84**, 1967 (1962); b) M. Witanowski and J. D. Roberts, *ibid.*, **88**, 737 (1966); c) G. Frankel, D. T. Dix and M. Carlson, *Tetrahedron Lett.*, 579 (1968); d) W. G. Still and G. Streekumar, *J. Am. Chem. Soc.*, **102**, 1201 (1980).

51. a) P. Beak and W. J. Zajdel, *ibid.*, **106**, 1010 (1984); b) P. Beak, D. Reitz and A. Tse, *J. Org. Chem.*, **46**, 4316 (1981).

52. a) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); b) R. Hoffman, *ibid.*, **89**, 1841 (1989).

53. R. K. Hill and T. Yuri, *Tetrahedron*, **33**, 1569 (1977).

54. a) B. P. Mundy, K. B. Lipkowitz, M. Lee and B. R. Larsen, *J. Org. Chem.*, **39**, 1963 (1974); b) B. P. Mundy, B. R. Larsen, L. F. McKenzie and G. Branden, *ibid.*, **37**, 1635 (1972); c) B. P. Mundy and B. R. Larsen, *Synth. Commun.*, **2**, 197 (1972).

55. T. Nagasaka, H. Hayashi, M. Kumakawa and M. Sakamoto, *Heterocycles*, **29**, 2157 (1989).

56. M. Ogawa and M. Natsume, *ibid.*, **21**, 769 (1984).

57. H. Kotsuki, T. Kusumi, M. Inoue, Y. Ushio and M. Ochi, *Tetrahedron Lett.*, **32**, 4159 (1991).

58. a) I. Nakagawa and T. Hata, *ibid.*, 1409 (1975); b) I. Nakagawa, K.Aki, T. Hata, *J.Chem. Soc. Perkin Trans. 1*, 1315 (**1983**).

59. C. W. Jefford and J. B. Wang, *Tetrahedron Lett.*, **34**, 2911 (1993).

60. C. W. Jefford and J. B. Wang, *ibid.*, **34**, 1111 (1993).

61. R. H. Schlessinger and E. J. Iwanowicz, *ibid.*, **28**, 2083 (1987).

62. H. Takahata, K. Inose, N. Araya and T.Momose, *Heterocycles*, **38** (1994).

63. D. S. Grierson, J. Royer, L. Guerrier and H. P. Husson, *J. Org. Chem.*, **51**, 4475 (1986).

64. H. P. Husson, *J. Nat. Prod.*, **48**, 894 (1985).

65. D. F. Taber, P. B. Deker and M. D. Gaul, *J. Am. Chem. Soc.*, **109**, 7489 (1987).

66. H. Yamamoto, S. Iguchi, H. Nakai, and M. Hayashi, *J. Org. Chem.*, **44**, 1363 (1979).

67. Y. Ukaji, T. Watai, T. Sumi, T. Fujisawa, *Chemistry Lett.*, 1555 (1991).

68. C. G. Bochet, E. Merifield, W. Oppolzer, *Tetrahedron Lett.*, **35**, 7015 (1994).

69. D. L. Comins and N. R. Benjelloun, *ibid.*; **35**, 829 (1994).

70. D. L. Comins, S. P. Joseph, and R. Goehring, *J. Am. Chem. Soc.*, **116**, 4719 (1994).

71. N. Huser and G. Solladié, *Rec. Trav. Chim. Pays-Bas*, **114**, 153 (1995).

72. J. Suffert, A. Adib, G. Solladié, A. Solladié-Cavallo, *Tetrahedron Lett.*, **31**, 6649 (1990).

73. J. G. MacConnell, M. S. Blum and H. M. Fales, *Science*, **168**, 840 (1970).

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