Synthesis of Enantiomerically Pure Fire Ant Venom Alkaloids: Solenopsins and Isosolenopsins A, B and C

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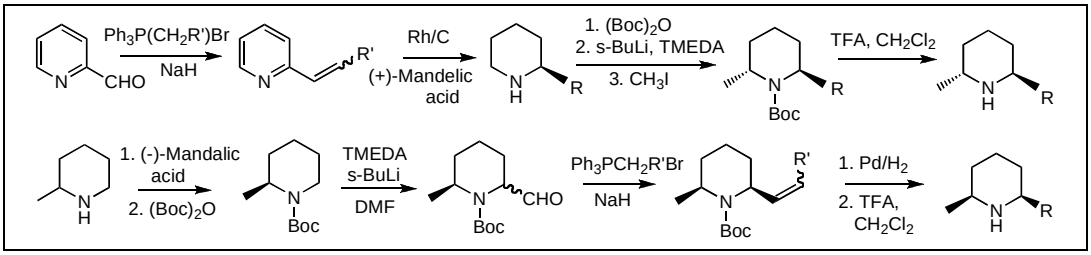

Concise and efficient methods for the synthesis of enantiomers of fire ant venom alkaloids solenopsin and isosolenopsin A, B, and C are described. These syntheses are based on diastereoselective electrophilic substitution of enatiomerically-pure α-lithiated 2-alkylpiperidine.

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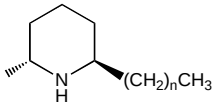
INTRODUCTION

The imported fire ant *Solenopsis invicta*, an aggressive and venomous pest, has had a major impact on agriculture, public safety, and environment in the southern United States [1]. Since their accidental introduction in the 1920's fire ants have spread in both rural and urban areas and pose a threat to young animals or small, confined pets, children, the elderly, and unconscious or injured accident victims [1]. Massive fire ant sting attacks, especially in the case of the elderly and those acutely sensitive to fire ant venom, can lead to severe medical complications, including death [1].

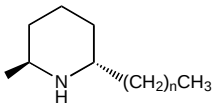
The imported fire ant venom is mainly comprised of three *trans*-2-methyl-6-alkylpiperidines [solenopsin A (**1**), B (**2**), and C (**3**)] and two *trans*-2-methyl-6-alkenylpiperidines [dehydrosolenopsin B (**13**) and C (**14**)] [2]. Varying amounts of three *cis*-2-methyl-6-alkylpiperidines [isosolenopsin A (**7**), B (**8**) and C (**9**)] are also found to be present in the venom of different types of ants [3].

In a previous communication, we reported that racemic isosolenopsin A and solenopsin A possess robust cardiorespiratory depressant activity in rats [4]. In order to investigate individual enantiomers of fire ant venom alkaloids on cardiorespiratory depressant activity, a simple and efficient procedure for their synthesis needed to be developed.

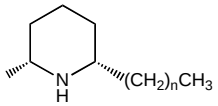
A number of methods have been reported for the stereospecific synthesis of solenopsins and 2,6-dialkylpiperidines [5-9]. Many of these methods involve multistep routes or require expensive starting materials. However, an introduction of the 6-methyl group to enatiomerically-pure α-lithiated 2-alkylpiperidins provides a short and simple procedure to prepare *trans*-2-methyl-6-alkylpiperidine on a medium scale. We chose to explore the application of this synthesis, and experimental details and results are described in this paper.



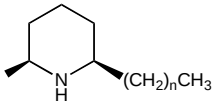
1. n = 10, (2R, 6R)-Solenopsin A
2. n = 12, (2R, 6R) -Solenopsin B
3. n = 14, (2R, 6R) -Solenopsin C



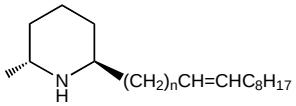
4. n = 10, (2S, 6S)-Solenopsin A
5. n = 12, (2S, 6S)-Solenopsin B
6. n = 14, (2S, 6S)-Solenopsin C



7. n = 10, (2R, 6S)-Isosolenopsin A
8. n = 12, (2R, 6S)-Isosolenopsin B
9. n = 14, (2R, 6S)-Isosolenopsin C



10. n = 10, (2S, 6R)-Isosolenopsin A
11. n = 12, (2S, 6R)-Isosolenopsin B
12. n = 14, (2S, 6R)-Isosolenopsin C



13. n = 3, (2R, 6R)-Dehydrosolenopsin B
14. n = 5, (2R, 6R)-Dehydrosolenopsin C

RESULTS AND DISCUSSION

Formation of α-carbanion and subsequent electrophilic substitution of piperidines with various nitrogen-activating groups has been studied extensively [10-12]. Though this process is known to proceed through the lithiation of the equatorial position followed by electrophilic substitution with retention of the conformation, stereospecificity and yields are highly

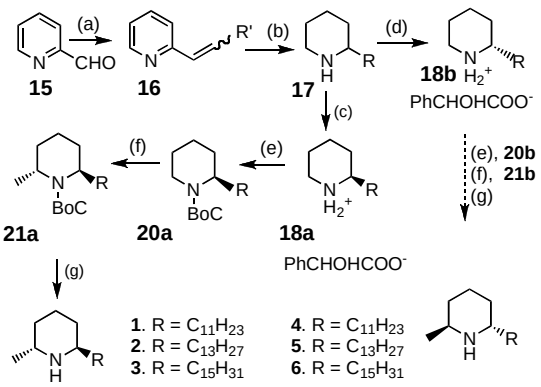
dependent on the nature of the electrophile and the groups present on the piperidine ring [10,11]. Unsubstituted piperidines with *N*-activating groups provide higher yields and stereospecificity with electrophiles that are not readily reducible *via* electron-transfer processes such as with aldehydes and ketones [10-12]. However, alkyl halides that are reducible *via* electron-transfer processes afford poor yields and diastereoselectivity [11,12]. The electron transfer to readily reducible electrophiles appears to be facilitated by free conformational motion of the piperidine ring. The retardation of this process by introduction of bulky substituents at certain positions on the ring can increase the yield and the stereospecificity of the reaction [10,11].

Axially substituted 2-piperidides are known to be more stable than their equatorially substituted isomers due to $A_{1,3}$ strain [10]. Lithiation of 2-piperidides would provide the 6-equatorially lithiated species, which undergo electrophilic substitution with retention of conformation to yield preferentially the *trans* isomer [10]. Hence, lithiation and subsequent alkylation of 2-alkylpiperidines is expected to yield *trans*-2, 6-dialkylpiperidines, the type of major alkaloids present in fire ant venoms [10].

There are three previous reports of the stereospecific synthesis of *trans*-2-methyl-6-alkylpiperidines by employing electrophilic substitution of α-lithiated enantiomerically-pure 2-alkylpiperidine analogs [5,6,13]. In the first method, (+)-*trans*-2,6-dimethylpiperidine and (+)-*trans*-2-methyl-6-propylpiperidine have been prepared by the introduction of methyl and propyl side-chains, respectively, to enantiomerically pure 2-methylalkyl-piperidine [13]. However, our attempt to introduce a long side-chain to lithiated *N*-Boc-2(*S*)-methylpiperidine afforded low yield and diastereoselectivity. In the other two methods [5,6], (-)-solenopsin A was prepared by the introduction of a methyl group to *N*-Boc-2(*R*)-undecylpiperidine. In these cases, it appears that the large alkyl group at C-2 adopts the more stable axial conformation and hinders conformational motion, thereby increasing the yield and stereospecificity of the reaction. A practical method for the preparation of *N*-Boc-2(*R*)-undecylpiperidine would lead to an efficient procedure for the medium-scale synthesis of solenopsin A. Both Comins *et al*. [5] and Beak *et al*. [6] used multi-step procedures to synthesize this intermediate.

To achieve this goal, a method was developed to resolve racemic 2-undecylpiperidine by fractional crystallization as diastereomeric salts. Racemic 2-undecylpiperidine was prepared in high yields by reacting pyridine-2-carboxaldehyde (**15**) with the ylide of *n*-decyltriphenylphosphonium bromide followed by catalytic reduction of the resulting pyridine-2-(undecyl-1-ene) (**16**). Racemic 2-undecylpiperidine (**17**) was resolved by diastereoisomeric fractional crystallization as a salt of (+)-mandelic acid. The first crystallization yielded 2(*R*)-undecylpiperidinemandelate with 85-95% ee, and two subsequent crystallizations afforded an enantiomerically-pure salt of 2(*R*)-undecylpiperidine (**18a**) in 36% yield (ee > 99%). The amine rich in 2(*S*)- enantiomer was regenerated from the combined mother liquor and was crystallized as a salt of (-)-mandelic acid to afford an enantiomerically-pure salt of 2(*S*)-undecylpiperidine (**18b**) (Scheme-1).

Scheme 1

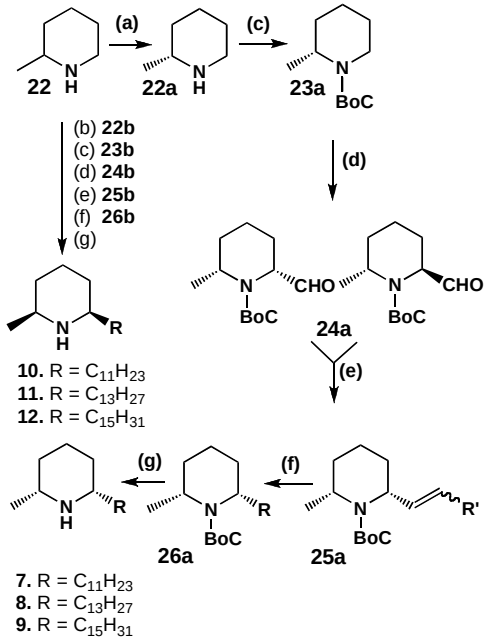


(a). $Ph_3P^+(CH_2R')Br^-$, NaH(60%), CH_2Cl_2 (b). Rh/C, Pd/C, H_2, EtOH
(c). (+)-Mandelic acid, MeOH, Et_2O (d). (-)-Mandalic acid, MeOH, Et_2O
(e). NaOH (10%), (*t*-Boc)$_2$O, THF (f). TMEDA, BuLi, -78 °C, MeI
(g). TFA, CH_2Cl_2, NaOH

Treatment of 2(*S*)-undecylpiperidine and 2(*R*)-undecylpiperidine with di-*tert*-butyldicarbonate [(Boc)$_2$O] gave their respective *N*-Boc amines in high yields. These *N*-Boc-2-undecylpiperidines after lithiation were treated with methyl iodide to yield *N*-Boc-2(*R*)-methyl-6(*R*)-undecylpiperidine and *N*-Boc-2(*S*)-methyl-6(*S*)-undecylpiperidine. Removal of protecting groups of these compounds yielded (+)-solenopsin A and (-)-solenopsin A. In a similar manner, racemic 2-tridecylpiperidine and 2-pentadecylpiperidine were resolved to their enantiomers as diastereomeric salts of mandelic acid and subsequently converted to (+)-solenopsin B, (-)-solenopsin B, (+)-solenopsin C, and (-)-solenopsin C by stereospecific introduction of the 6-methyl group.

Isosolenopsin A, B, and C were synthesized using (*R*)- and (*S*)-2-methylpiperidines as precursors which were obtained by resolving racemic 2-methylpiperidines (**22**) by diastereoisomeric fractional crystallization of their mandelates [13,14]. (*R*)- and (*S*)-2-Methylpiperidines were converted to their *N*-Boc-derivatives by reacting with (Boc)$_2$O. *N*-Boc-2(*R*)-methylpiperidine (**23a**) was lithiated and treated with DMF to afford a mixture of *trans*-*N*-Boc-2(*R*)-methylpiperidine-6(*S*)-carboxaldehyde and *cis*-*N*-Boc-2(*R*)-methylpiperidine-6(*R*)-carboxaldehyde. This mixture was reacted with ylide of decyltriphenylphosphonium bromide in the presence of sodium hydride to yield *cis*-*N*-Boc-2(*R*)-methyl-6(*R*)-(2-undecenyl)piperidine (**25**) as the only product.

Scheme-2



(a). (+)-Mandelic acid (b). (-)-Mandelic acid (c).10% NaOH, BoC
(d).TMEDA, BuLI, DMF, -78° C (e). $Ph_3PCH_2R'Br$, NaH, CH_2Cl_2
(f). Pd/H_2, EtOH (g). TFA, CH_2Cl_2

This indicates that *trans*-*N*-Boc-2(*R*)-methylpiperidine-6(*S*)-carboxaldehyde readily isomerized to its more thermodynamically stable 6(*R*)-epimer before reacting with ylide [10]. Catalytic reduction followed by deprotection of the amine group yielded (2*R*,6*S*)-isosolenopsin A in good overall yield. In a similar manner, other enantiomer of isosolenopsin A and both enantiomers of isosolenopsin B and C were also prepared (Scheme-2).

EXPERIMENTAL

All air and moisture sensitive reactions were carried out under nitrogen in either two or three necked flasks sealed with rubber septa. Reactions at -78° C were performed using dry ice in acetone. Column chromatography was carried out on Merck silica gel 60 (230-400 mesh). Melting points were measured in Uni-melt, Thomas Hoover capillary melting point apparatus and the optical rotations were recorded on Rudolph Research Analytical, Autopol IV polarimeter with path length 0.5 dm. The nmr spectra were recorded on Bruker Avance DRX-400 (400 MHz for ^{1}H nmr and 100 Mz for ^{13}C nmr) spectrometer in deuteriochloroform. The mass spectrometric analysis was performed on an Agilent Series 1100 SL equipped with an ESI source. HPLC analysis were carried out in Hewlett Packard 1100 series instrument with Chiralcel OD column using 0.1% isopropyl alcohol in hexane as mobile phase at the rate of 0.7 ml/min. GC experiments were performed on a Hewlett-Packard 5890 gas chromatograph with FID and autosampler. Cyclodex B capillary column (0.25 mm ID, 30m length, 0.25μm film thickness; J & W Scientific, Folsom, CA) was used. The injector and detector temperatures were set up at 225° C and 250° C respectively and the column temperature was began by holding at 100° C for 5 min, then rising from 100° C to 180° C at 4° C/min, holding at 180° C for 5 min. The enantiomeric purities of compounds **1** – **12** were determined by HPLC analysis after derivartization with (*R*)-(-)-1-(1-napthyl)ethylisocyanate. Derivatization was carried out by treating amines in toluene with equimolar amounts of (*R*)-(-)-1-(1-napthyl)ethylisocyanate in toluene at room temperature. Analyses of the derivartized compounds were performed on an Agilent 1100 series instrument equipped with a photodiode array detector operating at 240 mm and a Chiralcel OD column (250x4.6 mm) with 0.5% isopropyl alcohol in hexane as the mobile phase.

2-(Undecyl-1-ene)-pyridine (16, R' = C_9H_{19}). A solution of *n*-decyltriphenylphosphonium bromide (48.4 g, 0.1 mol) in anhydrous dichloromethane (500 ml) was treated with NaH (60%, 4.0 g, 0.1 mol) at room temperature. The mixture was stirred for 30 min, treated with pyridine-2-carboxaldehyde (**15**) (10.7 g, 0.1 mol) and refluxed for 3 h. The reaction mixture was allowed to cool, filtered, concentrated and chromatographed on short silica gel column to give a mixture of *cis*- and *trans*-2-(undecyl-1-ene) pyridine (17.1 g, 74%).

2-Undecylpiperidine (17, R = $C_{11}H_{23}$). The above mixture of *cis*- and *trans*-2-(undecyl-1-ene)-pyridine (15.0 g, 65 mmol) was dissolved in absolute ethanol (60 ml) and hydrogenated with Pd/C (10% on carbon, 300 mg) and Rh/C (1.5 g) at 30 lbs/in^2 for 12 h. The reaction mixture was filtered through Celite® and evaporated to give a racemic mixture of 2-undecylpiperidine (14.9 g, 96%).

2(*R*)-Undecylpiperidine mandelate (18a, R = $C_{11}H_{23}$). A mixture of racemic 2-undecylpiperidine (10.0 g, 41.8 mmol) and (+)-mandelic acid (6.4 g, 42 mmol) in methanol (40 ml) was diluted with anhydrous ether (300 ml) and left overnight at 0 °C. The resulting fine colorless crystals of 2(*R*)-undecylpiperidine mandelate were separated by filtration and recrystallized twice from methanol/ether to afford the pure enantiomer ee >99% (5.8 g, 36%) yield. The optical purity of the amine was determined as its *N*-Boc derivative by HPLC. mp 103-104 °C; $[\alpha]_D^{24}$ = +53.1 (c 3.0, $CHCl_3$).

2(*R*)-Undecylpiperidine (19a, R = $C_{11}H_{23}$). A solution of 2(*R*)-undecylpiperidine mandelate (100 mg, 0.25 mmol) in water (3 ml) was treated with aqueous NaOH (10%, 2.0 ml) and extracted with ether (3x5.0 ml). The organic solution was dried and evaporated to give 2(*R*)-undecylpiperidine (58 mg). $[\alpha]_D^{24}$ = -2.9 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 3.01 (brd, 1H, J = 12.0 Hz), 2.58 (ddd, 1H, J = 12.0 11.6, 2.8 Hz), 2.35 (m, 1H), 1.72 (brd, 1H J = 11.2 Hz), 1.54 (m, 3H), 1.52 (m, 1H), 1.23(brs, 21H), 0.83 (t, 3H, J = 6.8 Hz). *Anal.* Calcd. for $C_{16}H_{33}N$: C, 80.26; H, 13.89; N, 5.85. Found; C, 80.31; H, 13.84; N, 5.87.

***N*-Boc-2(*R*)-Undecylpiperidine (20a, R = $C_{11}H_{23}$).** A solution of 2(*R*)-undecylpiperidine mandelate (4.0 g, 10.2 mmol) in 10% NaOH (60 ml) was treated with di-*tert*-butyldicarbonate (2.5 g, 11.5 mmol) in THF (40 ml) dropwise. The solution was stirred for 6 h at room temperature, concentrated in vacuum and extracted with diethyl ether (3x100 ml). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel to give *N*-Boc-2(*R*)-undecylpiperidine as colorless oil (3.1 g, 89%). $[\alpha]_D^{24}$ = -19.8 (*c* 4.4, CH_2Cl_2), lit [15] $[\alpha]_D^{24}$ = -21.2 (*c* 4.4, CH_2Cl_2). ^{1}H nmr: δ 4.16 (brs, 1H), 3.93 (m, 1H), 2.70 (brt, J = 12.8 Hz, 1H), 1.62 (m, 2H), 1.52 (m, 4H), 1.42 (s, 9H), 1.23 (brs, 20H), 0.84 (t, J = 6.4 Hz, 3H).

***N*-Boc-2(*R*)-Methyl-6(*R*)-undecylpiperidine (21a, R = $C_{11}H_{23}$).** A solution of *N*-Boc-2(*R*)-undecylpiperidine (3.0 g, 8.8 mmol) in anhydrous ether (75 ml) was cooled to -78 °C and treated with tetramethylethylenediamine (TMEDA) (2.0 ml) and *s*-BuLi (10.5 ml, 13.5 mmol) sequentially. The mixture was slowly warmed to -20 °C, stirred for 30 min and cooled again to -78 °C. MeI (2.0 ml) was added dropwise to the mixture, stirred for 15 min at -78 °C, and allowed to slowly warm to room temperature. The reaction mixture was quenched with water (50 ml) and extracted with ether (3x 100 ml). The ether extract was dried, evaporated and chromatographed on silica gel to give *N*-Boc-2(*R*)-methyl-6(*R*)-undecylpiperidine (2.51 g, 80%). $[\alpha]_D^{24}$ = -28.3 (*c* 4.7, CH_2Cl_2), lit [15] $[\alpha]_D^{24}$ = -26.3 (*c* 4.7, CH_2Cl_2). ^{1}H nmr: δ 3.91 (m, 1H), 3.78 (m, 1H), 1.82 (m, 2H), 1.62(m, 4H), 1.51 (m, 2H), 1.46 (s, 9H), 1.25 (brs, 28H), 1.23(d, 3H, J = 7.8 Hz), 0.88 (t, 3H, J = 6.4 Hz).

2(*R*)-Methyl-6(*R*)-undecylpiperidine [(2*R*, 6*R*)-solenopsin A] (1, R = $C_{11}H_{23}$). A solution of *N*-Boc-2(*R*)-methyl-6(*R*)-undecylpiperidine (2.5 g, 7.0 mmol) in CH_2Cl_2 (50 ml) was treated with TFA (5.0 g) for 6 h at room temperature. The solvent was removed under vacuum and the oil obtained was dissolved in anhydrous ether (30 ml) and neutralized with NaOH powder (2.0 g). The mixture was filtered and evaporated to give *trans*-2(*R*)-methyl-6(*R*)-undecylpiperidine as colorless oil (1.7g, 96%, ee > 99%) $[\alpha]_D^{26}$ = -0.87 (*c* 1.2, $CHCl_3$), lit[15] $[\alpha]_D^{24}$ = -1.2 (*c* 1.2, $CHCl_3$). ^{1}H nmr: δ 3.06 (m, 1H), 2.87 (m, 1H), 1.63 (m, 2H), 1.54(m, 1H), 1.43 (m, 1H), 1.25 (brs, 22H), 1.07 (d, 3H, J = 6.4 Hz), 0.87 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{17}H_{35}N$: C, 80.56; H, 13.92; N, 5.53. Found; C, 80.53; H, 13.89; N, 5.57.

(2*R*,6*R*)-Solenopsin A. HCl. A solution of (2*R*, 6*R*)-solenopsin A (1.0 g) in ethanol (5.0 ml), was treated with HCl (0.5 ml) and diluted with diethyl ether (20 ml) to give colorless crystals of solenopsin A.HCl. (0.97 g, 85%). mp 142-143 °C, lit [5] mp 141-142 °C, $[\alpha]_D^{24}$ = -7.6 (*c* 1.5, $CHCl_3$), lit [5] $[\alpha]_D^{24}$ = -7.6 (c 0.5, $CHCl_3$). ^{1}H nmr: δ 3.47 (brs, 1H), 3.21 (brs, 1H), 1.91 (m, 4H), 1.58 (m, 6H), 1.41 (d, 3H, J = 6.8), 1.18 (br.s, 16H), 0.81 (t, 3H, J = 6.8 Hz).

2(*S*)-Undecylpiperidine mandelate (18b, R = $C_{11}H_{23}$). The combined mother liquors from **4.2.3.** was evaporated to dryness, treated with aqueous NaOH (10%, 50 ml) and extracted with ether (3x 100 ml). The ether layer was evaporated to give an amine rich in 2(*S*)-undecylpiperidine (6.25 g, 26 mmol). This amine was treated with (-)-mandelic acid (4.2 g, 27.5 mmol) in methanol (25 ml), diluted with ether (150 ml) and kept at 0° C overnight. The resulting fine colorless crystals were separated by filtration and recrystallized two more times with methanol/ether to afford pure 2(*S*)-undecylpiperidine mandelate (4.6 g, 45.5%). mp 103 – 104° C, $[\alpha]_D^{26}$ = -52.7 (c 3.0, $CHCl_3$).

2(*S*)-Undecylpiperidine (19b, R = $C_{11}H_{23}$). A solution of (-)-2-undecylpiperidine mandelate (100 mg, 0.25 mmol) in water (3 ml) was treated with aqueous NaOH (10%, 2.0 ml) and extracted with ether (3x5.0 ml). The organic solution was dried and evaporated to give 2(*S*)-undecylpiperidine (56 mg). $[\alpha]_D^{26}$ = +3.0 (c 3.9, $CHCl_3$). ^{1}H nmr: δ 3.00 (brd, 1H, J = 12.0 Hz), 2.54 (ddd, 1H, J = 11.6 11.6, 2.4 Hz), 2.35 (m, 1H), 1.70 (brd, 1H, J = 10.8 Hz), 1.57 (brd, 1H, J = 12.4 Hz), 1.50 (brd, 1H, J = 11.6 Hz), 1.36 (m, 2H), 1.21 (brs, 21H), 0.81 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{16}H_{33}N$: C, 80.26; H, 13.89; N, 5.85. Found; C, 80.29; H, 13.86; N, 5.88.

***N*-Boc-2(*S*)-Undecylpiperidine (20b, R = $C_{11}H_{23}$).** 2(*S*)-Undecylpiperidine mandelate (4.0 g, 10.2 mmol) was treated with di-tert-butyldicarbonate (2.5 g, 11.5 mmol) as described in preparation of (**20a**) to yield *N*-Boc-2(*S*)-undecylpiperidine as colorless oil (2.94 g, 84%). $[\alpha]_D^{26}$ = +19.3 (c 4.7, $CHCl_3$). ^{1}H nmr: δ 4.16 (brs, 1H), 3.92 (m, 1H), 2.71 (brt, 1H, J = 12.4 Hz), 1.62 (m, 2H), 1.52 (m, 4H), 1.42 (s, 9H), 1.23 (brs, 20H), 0.85 (t, 3H, J= 6.4 Hz).

***N*-Boc-2(*S*)-Methyl-6(*S*)-undecylpiperidine (21b, R = $C_{11}H_{23}$).** *N*-Boc-2(*S*)-Undecylpiperidine (2.8 g, 8.2 mmol) reacted with MeI (2.0 ml) as described previously in (**21a**) to give *N*-Boc-2(*S*)-methyl-6(*S*)-undecylpiperidine (2.23 g, 79%). $[\alpha]_D^{26}$ = +29.1 (*c* 3.0, $CHCl_3$). ^{1}H nmr: δ 3.90 (m, 1H), 3.77 (m, 1H), 1.80 (m, 2H), 1.62 (m, 4H), 1.52 (m, 2H), 1.45 (s, 9H), 1.25 (brs, 28H), 1.22 (d, 3H, J = 7.8 Hz), 0.87 (t, 3H, J = 6.4 Hz).

2(*S*)-Methyl-6(*S*)-undecylpiperidine [(2*S*,6*S*)-solenopsin A] (4, R = $C_{11}H_{23}$). *N*-Boc-2(*S*)-Methyl-6(*S*)-undecylpiperidine (2.20 g, 6.2 mmol) was treated with TFA as described earlier preparation of (**1**) to give 2(*S*)-methyl-6(*S*)-undecylpiperidine as colorless oil (1.53 g, 97%, ee > 99%). $[\alpha]_D^{26}$ = +0.88 (c 3.0, $CHCl_3$), lit [3] $[\alpha]_D^{20}$ = +2.5 (c 3.0, $CHCl_3$). ^{1}H nmr: δ 3.07 (m, 1H), 2.88 (m, 1H), 1.66 (m, 2H), 1.56 (m, 1H), 1.43 (m, 1H), 1.26 (brs, 22H), 1.08 (d, 3H, J = 6.4 Hz), 0.89 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{17}H_{35}N$: C, 80.56; H, 13.92; N, 5.53. Found; C, 80.54; H, 13.90; N, 5.56.

(2*S*,6*S*)-Solenopsin A. HCl. (2*S*,6*S*)-Solenopsin A (1.0 g) was treated with HCl, as described earlier in (2*R*,6*R*)-Solenopsin A to give colorless crystals of (2*S*,6*S*)-solenopsin A.HCl (0.95 g, 83%); mp = 144-146 °C, lit [16] mp 146 °C; $[\alpha]_D^{26}$ = +7.7 (c 1.5, $CHCl_3$), lit [3,16] $[\alpha]_D^{20}$ = +7.5 (c, 1.3, $CHCl_3$). ^{1}H nmr: δ 3.49 (brs, 1H), 3.23 (brs, 1H), 1.93 (m, 4H), 1.60 (m, 6H), 1.43 (d, 3H, J = 6.4, 3H), 1.20 (brs, 16H), 0.83 (t, 3H, J = 7.2 Hz).

***cis*- and *trans*-2-(Tridecyl-1-ene)-pyridine (16, R' = $C_{11}H_{23}$).** *n*-Dodecyltriphenylphosphonium bromide (51.2 g, 0.1 mol) and pyridine-2-carboxaldehyde (**22**) (10.7 g, 0.1 mol) were reacted as described earlier (**16**, R' = C_9H_{19}) to give a mixture of *cis*- and *tran*-2-(tridecyl-1-ene)-pyridine (18.7 g, 72%).

2-Tridecylpiperidine (17, R = $C_{13}H_{27}$). The mixture of *cis*- and *trans*-2-(tridecyl-1-ene)pyridine (18.2 g, 70 mmol) was hydrogenated with Pd/C (350 mg) and Rh/C (1.5 g), as described earlier in preparation of (**17**, R = $C_{11}H_{23}$) to yield racemic 2-tridecylpiperidine (17.8 g, 95%).

2(*R*)-Tridecylpiperidine mandelate (18a, R = $C_{13}H_{27}$). The racemic mixture of 2-tridecylpiperidine (15.0 g, 56 mmol) was crystallized with (+)-mandelic acid (8.5 g, 56 mmol) as described in (**18a**, R = $C_{11}H_{23}$) to give (+)-2(*R*)-tridecylpiperidine mandelate (8.6 g, 37%, ee > 99%). mp 106 – 107 °C, $[\alpha]_D^{24}$ = +45.3 (c 3.0, $CHCl_3$).

2(*R*)-Tridecylpiperidine (19a, R = $C_{13}H_{27}$). 2(*R*)-Tridecylpiperidine mandelate (100 mg, 0.24 mmol) was treated with 10% NaOH (2.0 ml) to give 2(*R*)-tridecylpiperidine as a gum (61 mg, 95%). $[\alpha]_D^{24}$ = -3.1 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 3.00 (brd, 1H, J = 12.0 Hz), 2.56 (ddd, 1H, J = 12.0 11.2, 2.8 Hz), 2.36 (m, 1H), 1.71(brd, 1H, J = 10.8 Hz), 1.58 (brd, 1H, J = 12.4 Hz), 1.52 (brd, 1H, J = 11.6 Hz), 1.36 (m, 2H), 1.23 (brs, 25H), 0.82 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{18}H_{37}N$: C, 80.82; H, 13.94; N, 5.24. Found; C, 80.83; H, 13.91; N, 5.27.

***N*-Boc-2(*R*)-Tridecylpiperidine (20a, R = $C_{13}H_{27}$).** 2(*R*)-Tridecylpiperidine mandelate (8.4 g, 20 mmol) was treated with di-*tert*-butyldicarbonate (4.8 g, 22 mmol) to afford *N*-Boc-2(*R*)-tridecylpiperidine (6.2 g, 84%). $[\alpha]_D^{24}$ = -18.3 (c 4.6, $CHCl_3$). ^{1}H nmr: δ 4.17 (brs, 1H), 3.93 (m, 1H), 2.72 (dd, 1H, J = 12.4, 13.2

Hz), 1.63 (m, 2H), 1.53 (m, 4H), 1.43 (s, 9H), 1.24 (brs, 24H), 0.86 (t, 3H, J = 6.4 Hz).

***N*-Boc-2(*R*)-Methyl-6(*R*)-tridecylpiperidin (21a, R = $C_{13}H_{27}$).** *N*-Boc-2(*R*)-Tridecylpiperidine (5.0 g, 13.6 mmol) was reacted with MeI (4.0 ml) as described earlier in preparation of (21a, R = $C_{11}H_{23}$) to give N-Boc-2(*R*)-methyl-6(*R*)-tridecyl-piperidine (3.91 g, 75%). $[\alpha]_D^{26}$ = -27.1 (c 3.0, $CHCl_3$). ^{1}H nmr: δ 3.89 (m, 1H), 3.75 (m, 1H), 1.79 (m, 2H), 1.60 (m, 4H), 1.43 (s, 9H), 1.22 (brs, 24H), 1.20 (d, 3H, J = 6.8 Hz), 0.85 (t, 3H, J = 7.2 Hz).

2(*R*)-Methyl-6(*R*)-tridecylpiperidine [(2*R*,6*R*)-solenopsin B] (2, R = $C_{13}H_{27}$). *N*-Boc-2(*R*)-Methyl-6(*R*)-tridecylpiperidine (3.5 g, 9.2 mmol) was reacted with TFA (6.0g) to give 2(*R*)-methyl-6(*R*)-tridecylpiperidine (2.45 g, 94%, ee > 99%): $[\alpha]_D^{26}$ = -0.63 (*c* 2.0, EtOH), lit [17] $[\alpha]_D^{23}$ = -0.51 (*c* 1.97, EtOH). ^{1}H nmr: δ 3.06 (m, 1H), 2.8 8(m, 1H), 1.63 (m, 2H), 1.55 (m, 1H), 1.43 (m, 1H), 1.25 (brs, 26H), 1.08 (d, 3H, J = 6.4 Hz), 0.88 (t, 3H, J = 6.8 Hz).). *Anal*. Calcd. for $C_{19}H_{39}N$: C, 81.06; H, 13.96; N, 4.98. Found; C, 81.03; H, 13.94; N, 5.03.

(2*R*,6*R*)-Solenopsin B. HCl. (2*R*,6*R*)-Solenopsin B (1.0 g, 3.47 mmol) in ethanol (5 ml) was treated with Conc. HCl (0.5 ml) to give solenopsin B.HCl (0.94 g, 85%); mp 146-147 °C; $[\alpha]_D^{24}$ = -7.3 (c 3.5, $CHCl_3$). ^{1}H nmr: δ 3.50 (brs, 1H), 3.24 (brs, 1H), 1.93 (m, 2H), 1.69 (m, 2H), 1.60(m, 2H), 1.44 (d, 3H, J = 6.8 Hz), 1.21 (brs, 24H), 0.84 (t, 3H, J = 6.8 Hz).

2(*S*)-Tridecylpiperidine mandelate (18b, R = $C_{13}H_{27}$). The combined mother liquors from preparation of (**18a**, R = $C_{13}H_{27}$) was concentrated, basified with 10% NaOH (50 ml) and extracted with diethyl ether (3x100 ml) to yield a base rich in 2(*S*)-tridecylpiperidine (6.72 g). This base was treated with (-)-mandelic acid (4.5 g) in methanol (30 ml), added ether (150 ml) and left overnight at 0 °C to afford 2(*S*)-tridecylpiperidine mandelate **28**, (5.81, 42%, ee > 99). mp 106-107 °C; $[\alpha]_D^{26}$ = -45.0 (c 3.0, $CHCl_3$).

2(*S*)-Tridecylpiperidine (19b, R = $C_{13}H_{27}$). 2(*S*)-Tridecyl-piperidine mandelate (100 mg, 0.24 mmol) was converted to 2(*S*)-tridecylpiperidine (59 mg, 92%) as described in preparation of **19b** (R = $C_{11}H_{23}$). $[\alpha]_D^{26}$ = +3.2 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 2.99 (brd, 1H, J = 11.6 Hz), 2.55 (ddd, 1H, J = 11.6 11.2, 2.4 Hz), 2.34(m, 1H), 1.70 (brd, 1H, J = 10.8 Hz), 1.57 (brd, 1H, J = 12.4 Hz), 1.50 (brd, 1H, J = 11.6 Hz), 1.35 (m, 2H), 1.25 (brs, 25H), 0.81(t, 3H, J = 6.8 Hz).). *Anal*. Calcd. for $C_{18}H_{37}N$: C, 80.82; H, 13.94; N, 5.24. Found; C, 80.86; H, 13.92; N, 5.24.

***N*-Boc-2(*S*)-Tridecylpiperidine (20b, R = $C_{13}H_{27}$).** 2(*S*)-Tridecylpiperidine mandelate (5.0 g, 12 mmol) was treated with di-*tert*-butyldicarbonate (3.0 g, 14 mmol), followed by the similar work up procedure given in **20a** (R = $C_{11}H_{23}$) to give *N*-Boc-2(*S*)-tridecylpiperidine (3.56 g, 81%). $[\alpha]_D^{26}$ =18.5 (c 4.0, $CHCl_3$), ^{1}H nmr: δ 4.15 (brs, 1H), 3.91 (m, 1H), 2.70 (dd, 1H, J = 12.0, 13.2 Hz), 1.61 (m, 2H), 1.51 (m, 4H), 1.41 (s, 9H), 1.22 (brs, 24H), 0.84 (t, 3H, J = 6.4 Hz).

***N*-Boc-2(*S*)-Methyl-6(*S*)-tridecylpiperidine (21b, R = $C_{13}H_{27}$).** *N*-Boc-2(*S*)-Tridecylpiperidine (3.0 g, 8.17 mmol) was reacted with MeI (2 ml) as described in preparation of **21b** (R = $C_{11}H_{23}$) to give *N*-Boc-2(*S*)-Methyl-6(*S*)-tridecylpiperidine (2.21 g, 71%). $[\alpha]_D^{26}$ = +26.9 (c 3.0, $CHCl_3$). ^{1}H nmr: δ 3.89 (m, 1H), 3.76 (m, 1H), 1.79 (m, 2H), 1.60 (m, 4H), 1.43(s, 9H), 1.23 (brs, 24H), 1.20 (d, 3H, J = 6.8 Hz), 0.85 (t, 3H, J = 7.2 Hz).

2(*S*)-Methyl-6(*S*)-tridecylpiperidine [(2*S*, 6*S*)-solenopsin B] (5, R = $C_{13}H_{27}$). *N*-Boc-2(*S*)-Methyl-6(*S*)-tridecylpiperidine (2.0 g, 5.25 mmol) was treated with TFA (4.0 g) followed by the similar work up procedure described in the synthesis of compound **1** to give 2(*S*)-methyl-6(*S*)-tridecylpiperidine (1.26 g, 85%, ee > 99%): $[\alpha]_D^{26}$ = +0.82 (c 4.6, $CHCl_3$). ^{1}H nmr: δ 3.06 (m, 1H), 2.88 (m, 1H), 1.63 (m, 2H), 1.53 (m, 1H), 1.44 (m, 1H), 1.25 (brs, 26H), 1.08 (d, 3H, J = 6.4 Hz), 0.87 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{19}H_{39}N$: C, 81.06; H, 13.96; N, 4.98. Found; C, 81.03; H, 13.98; N, 5.01.

(2*S*, 6*S*) Solenopsin B. HCl. (2*S*, 6*S*)-Solenopsin B (1.0 g, 3.47 mmol) was treated with HCl to give solenopsin B.HCl (0.89 g, 81%). mp 145-146 °C; $[\alpha]_D^{26}$ = +7.4 (c 3.5, $CHCl_3$). ^{1}H nmr: δ 3.48 (brs, 1H), 3,22 (brs, 1H), 1.91 (m, 3H), 1.66 (m, 1H), 1.59 (m, 3H), 1.44 (d, 3H, J = 6.8 Hz), 1.21(brs, 23H), 0.81 (t, 3H, J = 6.8 Hz).

***Cis*- and *trans*-2-(Pentadecyl-1-ene)-pyridine (16, R' = $C_{13}H_{27}$).** *n*-Tetradecyltriphenylphosphonium bromide (64 g, 0.1 mol) reacted with pyridine-2-carboxaldehyde (**22**) (10.7 g, 0.1 mol) as described in the synthesis of **16** to give a mixture of *cis*- and *trans*-2-(pentadecyl-1-ene)pyridine (19.8, 69%).

2-Pentadecylpiperidine (17, R = $C_{15}H_{31}$). The above mixture of *cis*- and *trans*-2-(pentadecyl-1-ene)pyridine (19.0 g, 66 m mol) was reduced with Pd/C (500 mg) and Rh/C (1.5 g) at 30 lbs/in^2 to give (±)-2-pentadecylpiperidine (18.8 g, 96%).

2(*R*)-Pentadecylpiperidine mandelate (18a, R = $C_{15}H_{31}$). 2(*R*)-Pentadecylpiperidine (18.0 g, 61 m mol) was crystallized with (+)-mandelic acid (9.27g, 61 m mol) to afford (+)-2-pentadecyl piperidine mandelate (8.95g, 33%, ee > 99%). mp 108-109 °C; $[\alpha]_D^{24}$ = +42.2 (c 3.5, $CHCl_3$).

2(*R*)-Pentadecylpiperidine (19a, R = $C_{15}H_{31}$). 2(*R*)-Penta-decylpiperidine mandelate (100 mg, 0.22 mmol) was basified with NaOH as described earlier to give 2(R)-pentadecyl-piperidine (54 mg, 83%). $[\alpha]_D^{24}$ = -3.3 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 3.00 (brd, 1H, J = 12.0 Hz), 2.56 (ddd, 1H, J = 11.6, 11.2, 2.4 Hz), 2.36 (m, 1H), 1.72 (brd, 1H, J = 11.2 Hz), 1.56 (m, 3H), 1.34 (m, 3H), 1.23 (brs, 27H), 0.82 (t, 3H, J=6.8 Hz). *Anal*. Calcd. for $C_{20}H_{41}N$: C, 81.28; H, 13.98; N, 4.74. Found; C, 81.30; H, 13.94; N, 4.77.

***N*-Boc-2(*R*)-Pentadecylpiperidine (20a, R = $C_{15}H_{31}$).** 2(*R*)-Pentadecylpiperidine mandelate (8.5 g, 19 mmol) reacted with di-*tert*-butyldicarbonate (4.1 g, 19 mmol) in THF (40 ml) as described in the synthesis of **20a** (R = $C_{11}H_{23}$) to give *N*-Boc-2(*R*)-pentadecylpiperidine (6.42 g, 85%). $[\alpha]_D^{24}$ = -17.1 (c 5.5, $CHCl_3$). ^{1}H nmr: δ 4.17(brs, 1H), 3.93 (m, 1H), 2.72(dd, 1H, J = 12.8, 12.4 Hz), 1.63(m, 2H), 1.54(m, 4H), 1.44(s, 9H), 1.24(brs, 24H), 0.86(t, 3H, J = 6.4 Hz).

***N*-Boc-2(*R*)-Methyl-6(*R*)-pentadecylpiperidine (21a, R = $C_{15}H_{31}$).** *N*-Boc-2(*R*)-pentadecylpiperidine (6.0 g, 15.2 mmol) was reacted with MeI (3 ml) under the similar conditions used in the preparation of 20a (R = $C_{11}H_{23}$), to give *N*-Boc-2(*R*)-methyl-6(*R*)-pentadecyl piperidine (4.21, 67%). $[\alpha]_D^{26}$ = -23.0 (c 2.5, $CHCl_3$). ^{1}H nmr: δ 3.83 (m, 1H), 3.70 (m, 1H), 1.74 (m, 2H), 1.54 (m, 4H), 1.36 (s, 9H), 1.1 6 (brs, 28H), 1.13 (d, 3H, J = 6.6 Hz), 0.78 (t, 3H, J = 6.8 Hz).

2(*R*)-Methyl-6(*R*)-pentadecylpiperidine [(2*R*,6*R*)-solenop-sin C] (3, R = $C_{15}H_{31}$). *N*-Boc-2(*R*)-Methyl-6(*R*)-pentadecyl-piperidine (4.0 g, 9.78 mmol) was reacted with TFA (4.0 g) as described in the final step of the synthesis of compound **1**, to give *trans*-2(*R*)-methyl-6(*R*)-pentadecylpiperidine (2.63 g, 87%, ee > 99%). $[\alpha]_D^{26}$ = -0.63 (c 5.0, $CHCl_3$). ^{1}H nmr: δ 3.05 (m, 1H), 2.87(m, 1H), 1.62(m, 2H), 1.54 (m, 2H), 1.44 (m, 1H), 1.37 (m, 1H), 1.25 (brs, 28H), 1.07(d, 3H, J = 6.8 Hz), 0.87 (t, 3H, J = 6.8

Hz). *Anal*. Calcd. for $C_{21}H_{43}N$: C, 81.48; H, 14.00; N, 4.52. Found; C, 81.50; H, 13.98; N, 4.51.

(2*R*,6*R*)-Solenopsin C. HCl. (2*R*,6*R*)-Solenopsin C (1.0g, 3.23 m mol) was treated with HCl, to give colorless crystals of solenopsin C. HCl (0.91 g, 81%). mp 136-138 °C; $[\alpha]_D^{24}$ **=** -7.1 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 3.49 (brs, 1H), 3,23(br.s, 1H), 1.92 (m, 2H), 1.68 (m, 2H), 1.59 (m, 2H), 1.42 (d, 3H, J = 6.4 Hz), 1.19 (brs, 28H), 0.82 (t, 3H, J = 6.8 Hz).

2(*S*)-Pentadecylpiperidine mandelate (18b, R = $C_{15}H_{31}$). The combined mother liquors after the recrystallization of **18a** (R = $C_{15}H_{31}$) was basified and extracted as described earlier in method (18b, R = $C_{11}H_{23}$) to yield a base rich in 2(*S*)-pentadecylpiperidine. This base was crystallized with (-)-mandelic acid to afford 2(*S*)-pentadecylpiperidine mandelate (7.1g, 46%, ee > 99). mp 108-109 °C; $[\alpha]_D^{24}$ = -42.1 (c 3.0, $CHCl_3$).

2(*S*)-Pentadecylpiperidine (19b, R = $C_{15}H_{31}$). 2(*S*)-Pentadecylpiperidine mandelate (100 mg, 0.22 mmol) was basified with 10% NaOH (2.0 ml) and extracted with ether (3x 5.0 ml) to give 2(*S*)-pentadecylpiperidine (56 mg, 86%). $[\alpha]_D^{24}$ **= +**3.4 (c 5.0, $CHCl_3$). ^{1}H nmr: δ 3.00 (brd, 1H, J = 12.0 Hz), 2.57 (dd, 1H, J = 11.2, 10.4Hz), 2.36 (m, 1H), 1.72 (brd, 1H, J = 11.6 Hz), 1.56(m, 3H), 1.34(m, 3H), 1.20(brs, 27H), 0.83(t, 3H, J = 6.4 Hz). *Anal*. Calcd. for $C_{20}H_{41}N$: C, 81.28; H, 13.98; N, 4.74. Found; C, 81.29; H, 13.99; N, 4.73.

***N*-Boc-2(*S*)-Pentadecylpiperidine (20b, R = $C_{15}H_{31}$).** 2(*S*)-Pentadecylpiperidine mandelate (6.5 g, 14.6 mmol) was derivatized with di-*tert*-butyldicarbonate (3.2 g, 14.6 mmol) followed by the similar procedure used in the synthesis of **20a** (R = $C_{11}H_{23}$), to give *N*-Boc-2(*S*)-pentadecylpiperidine (5.02, 87%). $[\alpha]_D^{24}$ **=** +17.3 (c 4.8, $CHCl_3$). ^{1}H nmr: δ 4.17 (brs, 1H), 3.93(m, 1H), 2.72 (dd, 1H, *J* = 12.8, 12.4 Hz), 1.63 (m, 2H), 1.53 (m, 4H), 1.43 (s, 9H), 1.23 (brs, 24H), 0.86 (t, 3H, J = 6.4 Hz).

***N*-Boc-2(*S*)-Methyl-6(*S*)-pentadecylpiperidine (21b, R = $C_{15}H_{31}$).** *N*-Boc-2(*S*)-Pentadecylpiperidine (4.5 g, 11.4 mmol) was reacted with MeI (2 ml) as described in **21a** (R = $C_{11}H_{23}$), to give *N*-Boc-2(*S*)-methyl-6(*S*)-pentadecylpiperidine (2.98 g, 64%). $[\alpha]_D^{26}$ = +24.1 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 3.84 (m, 1H), 3.71 (m, 1H), 1.74 (m, 2H), 1.55 (m, 4H), 1.38 (s, 9H), 1.18 (brs, 28H), 1.14 (d, 3H, J = 6.6 Hz), 0.80 (t, 3H, J = 6.8 Hz).

2(*S*)-Methyl-6(*S*)-pentadecylpiperidine [(2S,6S)-solenopsin C] (6, R = $C_{15}H_{31}$). *N*-Boc-2(*S*)-Methyl-6(*S*)-pentadecylpiperidine (2.5 g, 6.1 mmol) was treated with TFA (2.5 g) and neutralized with NaOH powder (2.0 g) to give 2(*S*)-methyl-6(*S*)-pentadecylpiperidine (1.62 g, 86%, ee > 99%). $[\alpha]_D^{26}$ = +0.60 (c 5.0, $CHCl_3$). ^{1}H nmr: δ 3.07 (m, 1H), 2.88 (m, 1H), 1.64 (m, 2H), 1.55 (m, 2H), 1.45 (m, 1H), 1.37 (m, 1H), 1.25 (brs, 28H), 1.08 (d, 3H, J = 6.8 Hz), 0.88 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{21}H_{43}N$: C, 81.48; H, 14.00; N, 4.52. Found; C, 81.52; H, 13.97; N, 4.51.

(2*S*,6*S*)-Solenopsin C. HCl. (2*S*,6*S*)-Solenopsin C (1.0 g, 3.23 mmol) in ethanol (5.0 ml) was treated with Conc. HCl (0.5 ml) and recrystalized with ethanol/ether to give colorless needles of (2*S*,6*S*)-solenopsin C. HCl (0.93, 83%). mp 138-140 °C; $[\alpha]_D^{24}$ **=** +7.2 (c 2.0, $CHCl_3$). ^{1}H nmr: δ 3.47 (brs, 1H), 3,21 (brs, 1H), 1.91 (m, 2H), 1.66 (m, 2H), 1.58 (m, 2H), 1.41(d, 3H, J = 6.4 Hz), 1.18 (brs, 28H), 0.80 (t, 3H, J = 6.8 Hz).

2(*R*)-Methylpiperidine mandelate. Racemic 2-methylpiperidine (36.0 g, 36.2 mmol) was dissolved in methanol (125 ml) added equimolar amount of (+) mandelic acid (55 g) and the mixture was cooled to 0 °C, added ether (700 ml) to the mixture and kept at 0 °C overnight. The fine colorless crystals of (+)-2-methylpiperidine mandelate were separated by filtration and recrystallized twice from methanol/ether to afford 2(*R*)-methylpiperidine mandelate ee > 99% (35.6 g, 39%). The enantiomeric purity of compounds was determined by retention time and the peak area of GC chromatogram of the acetylated derivative of each enantiomer.

2(*R*)-methylpiperidine mandelate. mp 119-120 °C; $[\alpha]_D^{24}$ **=** +60.0 (c 2.5, MeOH). Lit [13] $[\alpha]_D^{24}$ **=** +60.0 (c 2.5, MeOH).

***N*-Boc-2(*R*)-Methylpiperidine (22a).** A solution of di-*tert*-butyldicarbonate (21.8, 100 mmol) in THF (100 ml) was added dropwise to a stirred mixture of 2(*R*)-methylpiperidine mandelate (25.1 g, 100 mmol) and 10% aqueous NaOH (100 ml). The reaction mixture was stirred for 6 h at room temperature, concentrated in vacuum and extracted with diethyl ether (3x150 ml). The ether extract was dried over $MgSO_4$, evaporated and chromatographed over silica gel to give *N*-Boc-2(*R*)-methylpiperidine (18.3 g, 92%). $[\alpha]_D^{24}$ **=** -50.7 (c 1.0, $CHCl_3$). Lit [13] $[\alpha]_D$ **=** -51.0 (c 0.83, $CHCl_3$). ^{1}H nmr: δ 4.22 (m, 1H), 3.77 (brd, 1H, J = 13.2 Hz), 2.66 (ddd, 1H, J = 13.2, 12.8, 2.8 Hz), 1.44 (m, 4H), 1.30 (s, 9H), 1.25 (m, 2H), 0.97 (d, 3H, J = 7.2 Hz).

***N*-Boc-2(*R*)-Methylpiperidine-6-carboxaldehyde (24a).** A solution of *N*-Boc-2(*R*)-methylpiperidine (10 g, 50.2 mmol) in anhydrous ether (200 ml) was cooled to -78 °C and treated with TMEDA (8.0 ml) and s-BuLi (20 ml, 1.4 *M*) sequentially. The mixture was slowly warmed to -20 °C, stirred for 30 min, cooled again to -78 °C and treated with DMF (4.4 g, 60 mmol) dropwise. The reaction mixture was stirred for 15 min at -78 °C, and allowed to warm to room temperature. The reaction was quenched with water (100 ml) and extracted with ether. The ether extract was dried, evaporated and chromatographed on silica gel to give the mixture of *cis*- and *trans*-*N*-Boc-2(*R*)-methylpiperidine-6-caboxaldehyde (10.2 g, 89%). *N*-Boc-2(*R*)-Methylpiperidine-6(*S*)-carboxaldehyde (61%). ^{1}H nmr: δ 9.28 (1H, s), 4.26 (m, 1H), 3.61(m, 1H), 1.63 (m, 6H), 1.45 (s, 9H), 1.11 (d, 3H, J = 6.8 Hz).

***N*-Boc-2(*R*)-Methylpiperidine-6(*R*)-carboxaldehyde (26%).** ^{1}H nmr: δ 9.56 (s, 1H), 4.52 (m, 1H), 4.34 (m, 1H), 2.27 (brd, 1H, J = 12.8 Hz), 1.58 (m, 5H), 1.43 (s, 9H), 1.02 (d, 3H, J = 6.8 Hz).

***N*-Boc-2(*R*)-Methylpiperidine-6(*S*)-undecan-1-ene (25a, R'= C_9H_{19}).** A solution of *n*-decyltriphenyl phosphonium bromide (12.8 g) in dichloromethane (100 ml) was treated with equal molar amount of NaH (60%) at room temperature for 30 min. An equal molar amount of *N*-Boc-2(*R*)-methylpiperidine-6(*S*)-caboxaldehyde (6.0 g) was added to the reaction mixture and refluxed for 3 h. The reaction mixture was allowed to cool, filtered through Celite® and chromatographed on silica gel to give *N*-Boc-2(*R*)-methylpiperidine-6-(*S*)-undecan-1-ene (6.8 g, 73%). *N*-Boc-2(*R*)-Methylpiperidine-6(*R*)-caboxaldehyde also yielded *N*-Boc-2(*R*)-methylpiperidine-6(*S*)-undecan-1-ene under identical conditions. ^{1}H nmr: δ 5.61 (dd, 1H, J = 10.8, 9.2 Hz), 5.27 (m, 1H), 4.90 (m, 1H), 4.28 (m, 1H), 2.07 (m, 2H), 1.63 (m, 6H), 1.45 (s, 9H), 1.25 (brs, 14H), 1.18 (d, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 6.8 Hz).

***N*-Boc-2(*R*)-Methyl-6(*S*)-undecylpiperidine (26a, R = $C_{11}H_{23}$).** A solution of *N*-Boc-2(*R*)-methylpiperidine-6(*S*)-undecan-1-ene (6.0 g) in ethanol (50 ml) was hydrogenated with Pd/C (10%) catalyst (0.70 g) to give *N*-Boc-2(*R*)-methyl-6(*S*)-undecylpiperidine (5.7 g, 96%). ^{1}H nmr: δ 3.04 (m, 1H), 2.87(m, 1H), 1.87 (m, 4H), 1.72 (m, 2H), 1.55 (m, 2H), 1.50 (d, 3H, J = 6.0 Hz), 1.18 (brs, 30H), 0.82 (t, 3H, J = 6.8 Hz).

2(*R*)-Methyl-6(*S*)-undecylpiperidine. (7) [(2*R*,6*S*)-isosolenopsin A]. *N*-Boc-2(*R*)-Methyl-6(*S*)-undecyl piperidine (2.5 g, 7.0 mmol)in CH_2Cl_2 (50 ml) was treated with TFA (5.0 g) for 6 h at room temperature and the similar work up procedure was followed up as described in the synthesis of Solenopsin A, B and C to give *trans*-2(*R*)-methyl-6(*S*)-undecylpiperidine as a colorless oil (1.7g. 96%, ee > 99%). $[\alpha]_D^{24}$ = -3.6 (c 2.5, $CHCl_3$), ^{1}H nmr: δ 2.58 (m, 1H), 2.44 (m, 1H), 1.73 (m, 1H), 1.55 (m, 2H), 1.30 (m, 4H), 1.23 (brs, 19H), 1.03 (d, 3H, J = 6.4 Hz), 0.85 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{17}H_{35}N$: C, 80.56; H, 13.92; N, 5.53. Found; C, 80.54; H, 13.96; N, 5.51.

(2*R*,6*S*)-Isosolenopsin A. HCl. (2*R*,6*S*)-Isosolenopsin A (1.0 g) in ethanol (5 ml) was treated with HCl (0.5 ml) as described earlier and crystallized from methanol/ether to yield (2*S*,6*R*)-isosolenopsin A.HCl (0.92 g, 83%) as white needles. mp 150 - 152 °C; Lit [9] mp 152 - 153 °C; $[\alpha]_D^{24}$ = +9.9 (c, 1.5, $CHCl_3$), Lit[9] $[\alpha]_D$ = +10.0 (c 1.1, $CHCl_3$). ^{1}H nmr: δ 2.97 (m, 1H), 2.79(m, 1H), 1.99 (m, 1H), 1.79 (m, 2H), 1.67 (m, 2H), 1.50 (m, 2H), 1.43 (d, 3H, J = 6.4 Hz), 1.25 (m, 2H), 1.11(brs, 17H), 0.74 (t, 3H, J = 6.4 Hz).

2(*S*)-Methylpiperidine mandelate. Racemic 2-methylpiperidine (18.0 g) was recrystallized with equimolar amount of (-) mandelic acid (27.5 g) to give 2(*S*)-methylpiperidine mandelate (17.6 g, 38%). mp 118-119 °C, Lit[13] mp 118-119 °C; $[\alpha]_D^{24}$ = -60.2 (c 3.0, MeOH).

***N*-Boc-2(*S*)-Methylpiperidine (23b).** *N*-Boc-2(*S*)-Methylpiperidine (10.6 g, 94%) was prepared by treatment of 2(*S*)-methylpiperidine mandelate (12.5 g) with di-*tert*-butyl-dicarbonate (11.0 g) as in **22a**. $[\alpha]_D^{24}$ = +50.4 (c 4.3, $CHCl_3$). ^{1}H nmr: δ 4.27 (m, 1H), 3.82 (brd, 1H, J = 13.2 Hz), 2.71 (ddd, 1H, J = 13.2, 12.8, 2.8 Hz), 1.49 (m, 4H), 1.36 (s, 9H), 1.27 (m, 2H), 1.02 (d, 3H, J = 7.2 Hz).

***N*-Boc-2(*S*)-methylpiperidine-6-carboxaldehyde (24b)** *N*-Boc-2(*S*)-Methylpiperidine (10.0 g) was lithiated and treated with DMF (4.4 g) as in **24a** to yield a mixture of *N*-Boc-2(*S*)-methylpiperidine-6(*R*)-carboxaldehyde and *N*-Boc-2(*S*)-methylpiperidine-6(*S*)-carboxaldehyde (9.8 g).

***N*-Boc-2(*S*)-methylpiperidine-6(*R*)-undecan-1-ene (25b, R' = C_9H_{19}).** The above mixture of *N*-Boc-2(*S*)-methylpiperidine-6(*R*)-carboxaldehyde and *N*-Boc-2(*S*)-methylpiperidine-6(*S*)-carboxaldehyde. (3.0 g) was treated with *n*-decyltriphenylphosphonium bromide (6.4 g) in the presence of 60% NaH (0.5 g) similar to that of **25a** to give *N*-Boc-2(*S*)-methylpiperidine-6(*R*)-undecan-1-ene (3.24 g, 70%).

(2*S*, 6*R*)-Isosolenopsin A (10). Catalytic hydrogenation of *N*-Boc-2(*S*)-methylpiperidine-6(*R*)-undecan-1-ene (3.0 g) with Pd/C (10%) (0.4 g) followed by deprotection with TFA as described in solenopsin A (**1**), yielded (2*S*,6*R*)-isosolenopsin A (1.9 g, 87%, ee > 99%). $[\alpha]_D^{24}$ = +3.7 (c 2.0, $CHCl_3$), ^{1}H nmr: δ 2.57 (m, 1H), 2.41 (m, 1H), 1.70 (m, 1H), 1.55 (m, 2H), 1.28 (m, 4H), 1.23 (brs, 19H), 1.01 (d, 3H, J = 6.4 Hz), 0.83 (t, 3H, J = 6.8 Hz). *Anal*. Calcd. for $C_{17}H_{35}N$: C, 80.56; H, 13.92; N, 5.53. Found; C, 80.56; H, 13.93; N, 5.51.

(2*S*,6*R*)-Isosolenopsin A.HCl. (2*S*,6*R*)-Isosolenopsin A (1.0 g) in ethanol (5.0 ml) was treated with HCl (0.5 ml) and recrystallized with ethanol ether to yield colorless crystals of (2*S*,6*R*)-isosolenopsin A.HCl (85%). mp 150 - 151 °C, Lit [9] mp 152 - 153 °C, $[\alpha]_D^{24}$ = -9.8 (c, 2.5, $CHCl_3$), Lit [9] $[\alpha]_D^{24}$ = -10.1 (c 1.0, $CHCl_3$). ^{1}H nmr: δ 3.01 (m, 1H), 2.82 (m, 1H), 2.05 (m, 1H), 1.85 (m, 2H), 1.71 (m, 2H), 1.48 (d, 3H, J = 6.0 Hz), 1.34 (m, 4H), 1.16 (brs, 17H), 0.79 (d, 3H, J = 6.8 Hz).

***N*-Boc-2(*R*)-Methylpiperidine-6(*S*)-tridecan-1-ene (25a, R' = $C_{11}H_{23}$).** A mixture of *cis*- and *trans*-*N*-Boc-2-methylpiperidine-6-carboxaldehyde (3.0 g) (**24a**) was treated with *n*-dodecyltriphenylphosphonium bromide (6.8 g) in the presence of NaH (0.5 g) as described in **25a**, (R' = C_9H_{19}) to yield *N*-Boc-2(*R*)-methylpiperidine-6(*S*)-tridecan-1-ene (3.45 g, 69%). ^{1}H nmr: δ 5.63 (dd, 1H, J = 10.8, 9.2 Hz), 5.32 (m, 1H), 4.92 (m, 1H), 4.31(m, 1H), 2.12 (m, 2H), 1.64 (m, 8H), 1.45 (s, 9H), 1.25 (brs, 16H), 1.20 (d, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 6.8 Hz).

(2*R*,6*S*)-Isosolenopsin B (8). Hydrogenation of *N*-Boc-2(*R*)-methylpiperidine-6(*S*)-tridecan-1-ene (3.2 g) (**25a**) followed by deprotection with TFA (1 ml) yielded trans-2(*R*)-methyl-6(*S*)-tridecylpiperidine as a pale yellow oil (2.06 g, ee > 98%). $[\alpha]_D^{24}$ = -4.6 (c 1.25, $CHCl_3$). ^{1}H nmr: δ 2.73 (m, 1H), 2.58 (m, 1H), 1.81 (m, 1H), 1.69 (m, 2H), 1.55 (m, 2H), 1.41-1.31 (m, 8H), 1.26 (brs, 17H), 1.13 (d, 3H, J = 6.4 Hz), 0.89 (t, 3H, J = 6.8 Hz), *Anal*. Calcd. for $C_{19}H_{39}N$: C, 81.06; H, 13.96; N, 4.98. Found; C, 81.04; H, 13.99; N, 4.96.

(2*R*,6*S*)-Isosolenopsin B. HCl. (2*R*, 6*S*)-Isosolenopsin B (1.0 g) in methanol (5 ml) was treated with HCl (0.5 ml) (**4.2.8**) to yield its hydrochloride (92%). mp 144 - 145 °C; $[\alpha]_D^{24}$ = +10.7 (*c* 1.5, $CHCl_3$). ^{1}H nmr: δ 3.00 (m, 1H), 2.82 (m, 1H), 2.03 (m, 1H), 1.84 (m, 2H), 1.70 (m, 2H), 1.47 (d, J = 6.4 Hz, 3H), 1.34 (m, 3H), 1.16 (brs, 22H), 0.78 (t, J = 6.4 Hz, 3H).

***N*-Boc-2(*S*)-Methylpiperidine-6(*R*)-tridecan-1-ene (25b, R' = $C_{11}H_{23}$).** A mixture of *cis*- and *trans*-*N*-Boc-2-methylpiperidine-6-carboxaldehyde (3.0 g) (**24a**) was treated with n-dodecyltriphenylphosphonium bromide (6.8 g) in the presence of NaH (0.5 g) as described in **25a**, (R' = C_9H_{19}) to yield *N*-Boc-2(*S*)-methylpiperidine-6(*R*)-tridecan-1-ene (3.51 g).

2(*S*)-Methyl-6(*R*)-tridecylpiperidine [(2*S*,6*R*)-isosolenopsin B] (11). Catalytic hydrogenation of (**25b**, R' = $C_{11}H_{23}$) (3.0 g) followed by the deprotection with TFA gave (2*S*, 6*R*)-isosolenopsin B as a pale yellow oil (1.86 g, ee > 99%). $[\alpha]_D^{24}$ = +4.7 (c 1.5, $CHCl_3$). ^{1}H nmr: δ 2.71 (m, 1H), 2.56 (m, 1H), 1.78 (m, 1H), 1.68 - 1.58 (m, 3H), 1.39-1.31 (m, 8H), 1.26 (brs, 17H), 1.11 (d, 3H, *J* = 6.4 Hz), 0.87 (t, 3H, J = 6.8 Hz), *Anal*. Calcd. for $C_{19}H_{39}N$: C, 81.06; H, 13.96; N, 4.98. Found; C, 81.07; H, 13.94; N, 5.01.

(2*S*,6*R*)-Isosolenopsin B. HCl. (2*S*,6*R*)-Isosolenopsin B (1.0 g) in methanol (5 ml) was treated with HCl (0.5 ml) to yield its hydrochloride (89%) mp 146 - 147 °C; $[\alpha]_D^{24}$ = -10.5 (*c* 2.5, $CHCl_3$); ^{1}H nmr: δ 3.06 (m, 1H), 2.87 (m, 1H), 2.13 (m, 1H), 1.91 (m, 2H), 1.78 (m, 2H), 1.55 (d, 3H, J = 6.4 Hz), 1.35 (m, 3H), 1.28 (brs, 22H), 0.85 (t, 3H, J = 6.4 Hz).

***N*-Boc-2(*R*)-Methylpiperidine-6(*S*)-pentadecan-1-ene (25a, R' = $C_{13}H_{27}$).** A mixture of *cis*- and *trans*-*N*-Boc-2-methylpiperidine-6-carboxaldehyde (3.0 g) (**24a**) was treated with n-tetradecyltriphenylphosphonium bromide (7.2 g) as described in **25a**, (R' = C_9H_{19}) to yield *N*-Boc-2(*R*)-methylpiperidine-6(*S*)-pentadecan-1-ene (3.6 g, 67%). ^{1}H nmr: δ 5.64 (dd, 1H, J = 10.8, 9.6 Hz), 5.33 (dt, 1H, J = 9.6, 7.2 Hz), 4.93 (m, 1H), 4.31(m, 1H), 2.11 (m, 2H), 1.64 (m, 8H), 1.44 (s, 9H), 1.25 (brs, 22H), 1.20 (d, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 6.8 Hz).

2(*R*)-Methyl-6(*S*)-pentadecylpiperidine [(2*R*,6*S*)-isosolenopsin C] (9). Catalytic hydrogenation of **25a**, (R' = $C_{13}H_{27}$) (3.0 g) followed by the deprotection as described in gave (2*R*, 6*S*)-isosolenopsin C (1.93 g) as a pale yellow oil. (ee > 99%). $[\alpha]_D^{24}$ = -5.1 (c 2.1, $CHCl_3$), ^{1}H nmr : δ 2.75 (m, 1H), 2.59 (m, 1H), 1.83 (m, 1H), 1.71-1.54 (m, 6H), 1.43-1.30 (m, 8H), 1.26 (brs, 19H), 1.14 (d, 3H, J = 6.4 Hz), 0.88 (t, 3H, J = 6.8 Hz), *Anal.*

Calcd. for $C_{21}H_{43}N$: C, 81.48; H, 14.00; N, 4.52. Found; C, 81.46; H, 13.99; N, 4.56.

(2*R*,6*S*)-Isosolenopsin C. HCl. (2*R*,6*S*)-Isosolenopsin C (1.0 g) in methanol (5 ml) was treated with HCl (0.5 ml) followed by recrystallization to yield its hydrochloride. mp 145 - 146 °C; $[\alpha]_D^{24}$ = +8.3 (c 1.0, $CHCl_3$), ^{1}H nmr: δ 3.03 (m, 1H), 2.84 (m, 1H), 2.08 (m, 1H), 1.87 (m, 2H), 1.73 (m, 2H), 1.51 (d, 3H, J = 6.4 Hz), 1.35 (m, 3H), 1.19 (brs, 26H), 0.82 (t,3H, J = 6.4 Hz).

***N*-Boc-2(*S*)-methylpiperidine-6(*R*)-pentadecan-1-ene (25b, R' = $C_{13}H_{27}$).** A mixture of *cis*- and *trans*-*N*-Boc-2-methylpiperidine-6-carboxaldehyde (3.2 g) (**24a**) was treated with *n*-tetradecyltriphenylphosphonium bromide (7.4 g) in the presence of NaH (0.5 g) by similar procedure used in **25a**, (R' = $C_{13}H_{27}$) to yield *N*-Boc-2(*S*)-methylpiperidine-6(*R*)-pentadecan-1-ene (3.7 g).

2(*S*)-Methyl-6(*R*)-pentadecylpiperidine [(2*S*,6*R*)-isosolenopsin C] (9). Catalytic hydrogenation of **25b** (R' = $C_{13}H_{27}$), (3.0 g) followed by the deprotection with TFA gave (2*S*, 6*R*)-isosolenopsin C as a pale yellow oil (2.01 g, ee > 99%). $[\alpha]_D^{24}$ = +4.9 (c 1.5, MeOH), ^{1}H nmr: δ 2.71 (m, 1H), 2.56 (m, 1H), 1.79 (m, 1H), 1.70 - 1.56 (m, 3H), 1.37-1.29 (m, 10H), 1.25 (brs, 19H), 1.12 (d, 3H, J = 6.4 Hz), 0.87 (t, 3H, J = 6.8 Hz), *Anal*. Calcd. for $C_{21}H_{43}N$: C, 81.48; H, 14.00; N, 4.52. Found; C, 81.44; H, 14.03; N, 4.54.

(2*S*,6*R*)-Isosolenopsin C. HCl. (2*S*,6*R*)-Isosolenopsin C (1.0 g) in methanol (5 ml) was treated with HCl (0.5 ml) to yield its hydrochloride on recrystallization with methanol/ether, mp 144 - 145 °C; $[\alpha]_D^{24}$ = -8.2 (c 1.5, $CHCl_3$). ^{1}H nmr: δ 2.87 (m, 1H), 2.69 (m, 1H), 1.70 (m, 2H), 1.60 (m, 2H), 1.34-1.21 (m, 4H), 1.15 (d, 3H, J = 6.4 Hz), 1.00 (brs, 26H), 0.61 (t, 3H, J = 6.8 Hz).

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