

SYNTHESIS OF (±)-SOLENOPSIN A AND (±)-ISOLENOPSIN A
FROM 6-METHYL-2-PIPERIDINONE

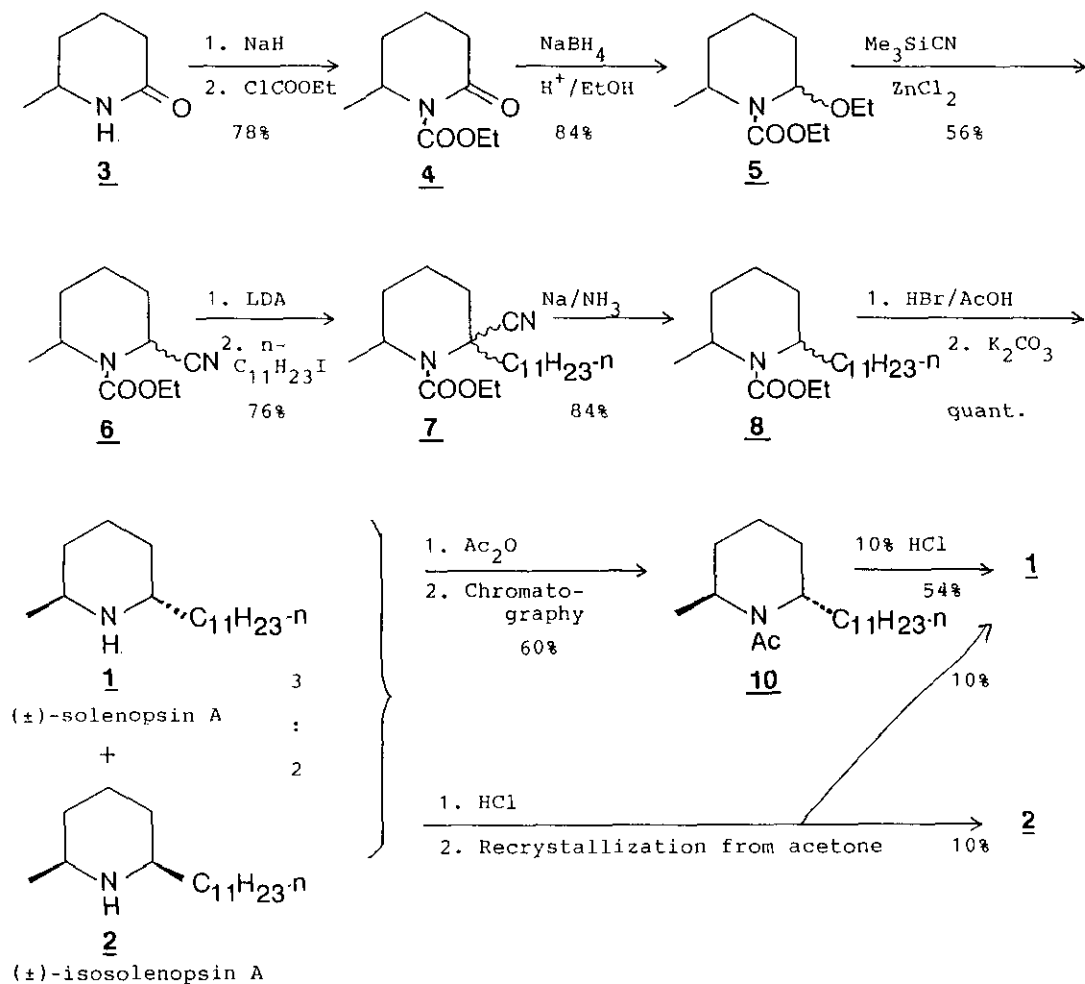
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Abstract -- (±)-Solenopsin A and (±)-isosolenopsin A were synthesized as a mixture in six steps from 6-methyl-2-piperidinone and they could be easily separated from each other as isomers.

The authors recently reported a method for converting lactams to α -substituted cyclic amines¹ and it has proved effective for the synthesis of a number of alkaloids and metabolites.² The present paper reports the synthesis of (±)-solenopsin A (1) and (±)-isosolenopsin A (2) from 6-methyl-2-piperidinone (3). Solenopsin A is obtained from the venom of the red fire ant, *Solenopsis saevissima*, in the United States.^{3a} Our purpose was to determine whether lactams having a substituent,⁴ such as compound (3), could be easily reduced with sodium borohydride, as a step to the stereoselective synthesis of these two compounds. Their synthesis was successfully achieved by the method in Scheme 1.

The Schmidt reaction of 2-methylcyclopentanone with hydrazoic acid is reported to give 6-methyl-2-piperidinone (3) in good yield.⁵ However, though this synthesis was carried out several times, the yield of 3 never exceeded 33%. The Grignard reaction^{4a} of glutarimide with methymagnesium iodide followed by reduction with sodium cyanoborohydride gave 3 in 79% yield on a milligram scale, but only 30% on a gram scale. The reaction of 3 with ethyl chloroformate in the presence of sodium hydride gave carbamate (4) in 78% yield. The reduction of 4 with sodium borohydride under controlled conditions^{1a} gave α -ethoxycarbamate (5) in 84% yield. This reduction required rigorous conditions for pH and temperature, since 1-ethoxycarbonyl-6-methyl-1,4,5,6-tetrahydropyridine (enamine) was produced as a major product in some cases. The reaction of 5 with trimethylsilyl cyanide^{2a} in the presence of zinc chloride gave α -cyanocarbamate (6) in 56% yield along with

Scheme 1



the enamine described above. Compounds 5 and 6 could not be distinguished from their isomers on the basis of their ^1H -nuclear magnetic resonance (nmr) spectra or thin layer chromatography (tlc). Treatment of 6 with lithium diisopropylamide (LDA) followed by *n*-undecyl iodide afforded α -cyano- α -*n*-undecylcarbamate^{2a} (7) in 76% yield, which was a mixture of isomers at a 3:2 ratio, according to gas chromatography.⁶ Hydrolysis of 7 (mixture) with hydrobromic acid in acetic acid followed by reduction with sodium borohydride^{2a} to obtain 1 and 2 unexpectedly provided amide (9) as a diastereomeric mixture in 39% yield. Removal of the cyano group from α -cyanocarbamates (12-18) by the Birch reductions was thus carried out and results are given in

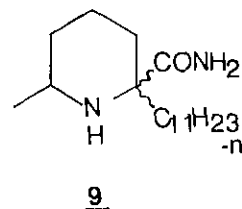
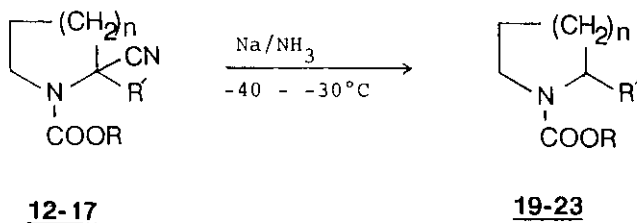
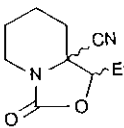


Table I. Generally, decyanation by Birch reactions of α -cyanocarbamates (12-16) having simple alkyl groups at the α -position was successfully carried out to give α -alkylcarbamates (19-23) in good yields. The decyanation of α -cyanocarbamates (17 and 18), however, having functional groups gave a large assortment of undesirable products. The Birch reduction of 7 (a mixture of isomers) with sodium-ammonia at

Table I. Decyanation of α -Cyanocarbamates (12-18) by Birch Reduction



Run	Starting Material	/	Product	Yield (%)
1	<u>12</u>	$n=1, R=\text{Et}, R'=\text{CH}_2\text{Ph}$	<u>19</u>	88
2	<u>13</u>	$n=2, R=\text{Me}, R'=\text{Me}$	<u>20</u>	88
3	<u>14</u>	$n=2, R=\text{Me}, R'=\text{n-C}_{11}\text{H}_{23}$	<u>21</u>	72
4	<u>15</u>	$n=2, R=\text{Me}, R'=\text{CH}_2\text{Ph}$	<u>22</u>	95
5	<u>16</u>	$n=2, R=\text{Me}, R'=\text{CH}_2\text{CH}=\text{CH}_2$	<u>23</u>	50
6	<u>17</u>	$n=2, R=\text{Me}, R'=\text{COEt}$	--	0
7	<u>18</u>		--	0

$-40 - -30^\circ\text{C}$ gave 1,6-dialkylcarbamate (8)^{3e} in 84% yield. Without separation, it was treated with a hydrobromic acid-acetic acid mixture to give a mixture in quantitative yield of (+)-solenopsin A (1) and (+)-isosolenopsin A (2) in a 3:2 ratio (by nmr). The isolation⁷ of 1 and 2 from this mixture was affected as follows: Several recrystallizations of a mixture of the hydrochlorides of 1 and 2 from acetone gave the pure hydrochloride of 2. The pure hydrochloride of 1 was obtained from the mother liquid. Acetylation of a mixture of 1 and 2, however, with acetic anhydride also gave a mixture of acetates (10 and 11) in quantitative yield, which, on chromatographic separation by elution with hexane-acetone (20:1), afforded 10 (trans) as a pure isomer. Refluxing of 10 in 10% hydrochloric acid gave the hydrochloride of 1, which was subsequently purified by recrystallization

from isopropyl ether to give the pure hydrochloride of 1 in 54% yield. The spectral data of (+)-solenopsin A (1) and (+)-isosolenopsin A (2) synthesized in this study showed complete agreement with those of authentic samples reported in the literature.³

In conclusion, the N-alkoxycarbonylation of 6-methyl-2-piperidinone (3), a lactam with a substituent at the ω -position, followed by controlled reduction and alkylation is shown to be an effective means for converting the lactam to α,ω -disubstituted cyclic amines. This reaction, however, is not stereoselective.

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on a Hitachi 200-10 spectrophotometer and a Hitachi M-80 spectrometer, respectively. ¹H-Nmr spectra were recorded on Varian EM-390 (90 MHz) and Bruker M-400 (400 MHz) instruments. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). Chromatographic separation was made using a silica gel (Wako gel C-200) column. Thin layer chromatography (TLC) was carried out with pre-coated silica gel plates (Kiesel 60 F-254, Merck).

6-Methyl-2-piperidinone (3) -- A solution of MeMgBr (1 mmol) in ether (Aldrich) was added to one of glutarimide (113 mg, 1 mmol) in THF (5 ml) under an argon atmosphere and the reaction mixture was stirred at room temperature for 30 min. A solution of the same Grignard reagent (2 mmol) in ether was added to this mixture followed by stirring at room temperature for 2 h and then the addition of EtOH (5 ml), NaBH₃CN (63 mg, 1 mmol), and bromocresol green (in a small amount as an indicator). The solution was neutralized with 1% HCl in EtOH till its color remained only yellow. The reaction mixture was stirred overnight, H₂O was added, and extraction was carried out with CHCl₃. The CHCl₃ extract was washed with H₂O, dried over MgSO₄, and evaporated to give a solid which, on chromatographic separation by elution with benzene-acetone (5:1) followed by recrystallization from EtOH, gave 89 mg (79%) of 3 as colorless needles, mp 87-88°C (lit.⁵ mp 87-88°C). Ms m/z: 113 (M⁺). Ir (CHCl₃) cm⁻¹: 3430, 1685. ¹H-Nmr (CDCl₃) δ : 1.20 (3H, d, $J=7$ Hz, Me), 1.20-2.10 (4H, m, CH₂ x 2), 2.20-2.40 (2H, m, CH₂CO), 3.50 (1H, m, CH), 6.35 (1H, br, NH).

1-Ethoxycarbonyl-6-methyl-2-piperidinone (4) -- Ethoxycarbonylation of 3 was

conducted by a previously described method¹ to give 4 in 55-78% yield, bp 90°C (3 mmHg). Ms m/z : 185 (M^+). Ir (neat) cm^{-1} : 1760, 1720. 1H -Nmr ($CDCl_3$) δ : 1.30 (3H, d, $J=6Hz$, $CHMe$), 1.33 (3H, t, $J=7Hz$, CH_2Me), 1.65-2.10 (4H, m, $CH_2 \times 2$), 2.40-2.70 (2H, m, $COCH_2$), 4.10 (1H, m, $CHMe$), 4.29 (2H, q, $J=7Hz$, OCH_2). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.24; H, 8.16; N, 7.53.

2-Ethoxy-1-ethoxycarbonyl-6-methylpiperidine (5) -- Reduction of 4 with $NaBH_4$ under controlled conditions¹ gave 5 in 84% yield, bp 92-95°C (4 mmHg). This reaction must not be allowed to take place at over 0°C under acidic conditions. Ms m/z : 215 (M^+-Me). Ir (neat) cm^{-1} : 1720. 1H -Nmr ($CDCl_3$) δ : 1.10-1.40 (9H, m, $Me \times 3$), 1.30-2.40 (6H, m, $CH_2 \times 3$), 3.46 (2H, q, $J=7Hz$, OCH_2Me), 4.17 (2H, d, $J=7Hz$, $COOCH_2Me$), 4.20 (1H, m, CHN), 5.50 (1H, br, $CHOEt$). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found: C, 61.35; H, 9.96; N, 6.54.

2-Cyano-1-ethoxycarbonyl-6-methylpiperidine (6) -- Me_3SiCN (1 g, 10 mmol) was added to a mixture of $ZnCl_2$ (580 mg, 4.2 mmol) and dry CH_2Cl_2 (142 ml) cooled at -30 - -40°C under an argon atmosphere followed by the addition of a solution of 5 (1.8 g, 8.37 mmol) in CH_2Cl_2 (34 ml) at the same temperature, stirring at -30 - -40°C for 5 h and then standing at room temperature overnight. H_2O was then added and the separated aqueous layer was extracted with CH_2Cl_2 several times. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated to give an oil which, on chromatographic separation by elution with hexane-acetone (30:1), gave 916 mg (56%) of 6 as a colorless oil, bp 83°C (3 mmHg). Ms m/z : 196 (M^+). Ir (neat) cm^{-1} : 1720. 1H -Nmr ($CDCl_3$) δ : 1.33 (3H, t, $J=7Hz$, CH_2Me), 1.40 (3H, d, $J=6Hz$, $CHMe$), 1.51-2.20 (6H, m, $CH_2 \times 3$), 4.20 (2H, q, $J=7Hz$, OCH_2Me), 4.41 (1H, m, CHN), 5.17 (1H, m, $CHCN$). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.40; H, 8.16; N, 14.10.

2-Cyano-1-ethoxycarbonyl-6-methyl-2-n-undecylpiperidine (7) -- A solution of $n-BuLi$ (5.3 mmol) in hexane was added at -78°C to a solution of diisopropylamine (1.41 g, 14 mmol) in THF (53 ml) under an argon atmosphere. Fifteen minutes later, a solution of 6 (916 mg, 4.67 mmol) and HMPA (840 mg, 4.67 mmol) in THF (5 ml) was then added followed by stirring -78°C for 30 min. A solution of n -undecyl iodide (3.96 g, 14 mmol) in THF (5 ml) was then added and the reaction mixture was stirred at -78°C for 1 h and then at room temperature for 1 h. The system was neutralized by aqueous saturated NH_4Cl and extraction was carried out with ether. The extract was washed with 5% HCl and brine, dried over $MgSO_4$, and evaporated. Chromatographic separation by elution with hexane-acetone (30:1) gave 1.24 g (76%)

of 7 as a colorless oil, bp 164°C (2 mmHg). Glc (column; 1.5% SE-30 on Chromosorb W, temperature; 170°C, N₂; 48 ml/min): t_R=2.2 and 3.2 min (2:3). Ms (CI) m/z: 351 (M⁺+1). Ir (neat) cm⁻¹: 1720. ¹H-Nmr (CDCl₃) δ: 0.88 (3H, br t, J=6Hz, undecyl-Me), 1.03-1.50 (26H, m, OCH₂Me, CHMe, CH₂ X 10), 1.50-2.25 (6H, m, CH₂ X 3), 4.20 (2H, q, J=7Hz, OCH₂Me), 4.31 (1H, m, CHN). Anal. Calcd for C₂₁H₃₈N₂O₂: C, 71.95; H, 10.93; N, 7.99. Found: C, 71.97; H, 10.94; N, 7.96.

2-Carbamoyl-2-n-undecyl-6-methylpiperidine (9) -- A solution of 7 (115 mg, 0.33 mmol) in 25% HBr solution in AcOH (10 ml) was stirred at room temperature for 3 h. The reaction mixture was evaporated to give an oil which was subsequently mixed with NaBH₄ (50 mg, 1.35 mmol) in EtOH (10 ml) and stirred at room temperature overnight. After evaporating the solvent, the residue was dissolved in a small amount of H₂O, basified with K₂CO₃ powder, and extracted with ether several times. The extract was washed with brine, dried over MgSO₄, and evaporated to give an oil (127 mg) whose chromatographic separation by elution with CHCl₃ gave the two isomers of 9 in a 3:2 ratio. Minor product (13 mg) from the first crop: Ms (CI) m/z: 297 (M⁺+1). Ir (CHCl₃) cm⁻¹: 3530, 3400, 1675. ¹H-Nmr (CDCl₃) δ: 0.86 (3H, m, undecyl-Me), 1.10-1.80 (29H, m, CH₂ X 13, Me), 2.20 (1H, m, CHN). Major product (25 mg) from the second crop: Ms (CI) m/z: 297 (M⁺+1). Ir (CHCl₃) cm⁻¹: 3500, 3370, 1670. ¹H-Nmr (CDCl₃) δ: 0.87 (3H, m, undecyl-Me), 1.05 (3H, d, J=6Hz, CHMe), 1.28 (20H, s, CH₂ X 10), 1.30-2.00 (6H, CH₂ X 3), 2.80 (1H, br, CHN), 5.40 (1H, br, NH).

General Procedure for Decyanation of α-Cyanocarbamates (7, 12-16) by Birch Reduction⁸ -- A typical procedure used for 2-benzyl-1-ethoxycarbonylpyrrolidine (19) is as follows: To a solution of α-cyanocarbamate (12, 65 mg, 0.25 mmol) in liq. NH₃ (2 ml) at -30°C was added Na (18 mg, 0.75 mmol) in a small amount at a time. The reaction mixture was stirred at -30 - -40°C for 1 h and then warmed to room temperature. After the evaporation of NH₃, H₂O was added to the residue and the solution was extracted with ether. The extract was washed with brine, dried over MgSO₄, and evaporated under reduced pressure to give crude 19 which, on distillation, gave 52 mg (88%) of 19 as a colorless oil, bp 135°C (2 mmHg). Ms (CI) m/z: 234 (M⁺+1). Ir (neat) cm⁻¹: 1680. ¹H-Nmr (CDCl₃) δ: 1.27 (3H, t, J=7.5Hz, OCH₂Me), 1.51-2.00 (4H, m, CH₂ X 2), 2.51 (2H, d, J=11Hz, CH₂Ph), 2.88-3.51 (2H, m, CH₂N), 4.12 (2H, q, J=7.5Hz, OCH₂Me), 4.10 (1H, m, CHN), 7.23 (5H, s, Ph). Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.81; H, 8.27; N, 6.28.

1-Ethoxycarbonyl-6-methyl-2-n-undecylpiperidine (8)^{3e}: Chromatography by elution

with hexane-acetone (40:1) gave an oil (84%) of 8, bp 149°C (4 mmHg). Ms (CI) m/z : 326 ($M^+ + 1$). Ir (neat) cm^{-1} : 1700. 1H -Nmr (400MHz) ($CDCl_3$) δ : 0.87 (3H, t, $J=7$ Hz, undecyl-Me), 1.01 (d, $J=7$ Hz, Me), 1.65 (d, $J=7$ Hz, Me), 1.16-1.32 (23H, m, OCH_2Me , $CH_2 \times 10$), 1.33-1.86 (6H, m, $CH_2 \times 3$), 3.82-3.95 (1H, m, MeCHN), 4.11 (2H, q, $J=7$ Hz, OCH_2Me), 4.29-4.39 (1H, m, CHN).

2-Methyl-1-methoxycarbonylpiperidine (20): Chromatography by elution with hexane-acetone (10:1) gave the oil (88%) of 20, bp 92°C (2 mmHg). Ms m/z : 157 (M^+). Ir (neat) cm^{-1} : 1680. 1H -Nmr ($CDCl_3$) δ : 1.02 (3H, d, $J=8$ Hz, Me), 1.27-1.94 (6H, m, $CH_2 \times 3$), 2.57-2.94 (1H, m, HCHN), 3.57 (3H, s, OMe), 3.66-4.00 (1H, m, HCHN), 4.09-4.45 (1H, m, MeCHN). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.21; H, 9.70; N, 8.62.

1-Methoxycarbonyl-2-n-undecylpiperidine (21): Chromatography by elution with hexane-acetone (40:1) gave the oil (72%) of 21, bp 145°C (2 mmHg). Ms m/z : 297 (M^+). Ir ($CHCl_3$) cm^{-1} : 1700. 1H -Nmr ($CDCl_3$) δ : 0.85 (3H, t, $J=7$ Hz, undecyl-Me), 1.25 (20H, s, $CH_2 \times 10$), 1.40-2.20 (6H, m, $CH_2 \times 3$), 2.90-3.20 (1H, m, CHN), 3.70 (3H, s, OMe), 3.90-4.30 (2H, m, CHN $\times 2$). Anal. Calcd for $C_{18}H_{35}NO_2$: C, 72.67; H, 11.86; N, 4.71. Found: C, 72.38; H, 11.89; N, 4.66.

2-Benzyl-1-methoxycarbonylpiperidine (22): Chromatography by elution with hexane-acetone (30:1) gave the oil (95%) of 22, bp 140°C (2 mmHg). Ms (CI) m/z : 234 ($M^+ + 1$). Ir (neat) cm^{-1} : 1690. 1H -Nmr ($CDCl_3$) δ : 1.40-1.85 (6H, m, $CH_2 \times 3$), 2.80 (2H, d, $J=6$ Hz, CH_2Ph), 2.80-3.80 (2H, m, CH_2N), 3.50 (3H, s, OMe), 3.82-4.15 (1H, m, HCN), 7.17 (5H, m, Ph). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.98; H, 8.20; N, 6.35.

2-Allyl-1-methoxycarbonylpiperidine (23): Chromatography by elution with hexane-acetone (20:1) gave the oil (50%) of 23, bp 90°C (2 mmHg). Ms m/z : 142 (M^+ -allyl). Ir (neat) cm^{-1} : 1690. 1H -Nmr ($CDCl_3$) δ : 1.55-1.80 (6H, m, $CH_2 \times 3$), 2.70-3.10 (1H, m, HCHN), 3.72 (3H, s, OMe), 3.90-4.20 (1H, m, HCHN), 4.21-4.60 (1H, m, CHN), 4.91-5.25 (4H, m, $CH_2CH=CH_2$), 5.55-6.05 (1H, m, $CH_2=CH$). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.32; H, 9.30; N, 7.85.

trans-1-Acetyl-6-methyl-2-n-undecylpiperidine (10) -- A solution of 8 (273 mg, 0.84 mmol) in 25% HBr solution in AcOH (10 ml) was refluxed for 10 h. Following removal of HBr-AcOH under reduced pressure, the residual oil was dissolved in H_2O , basified with K_2CO_3 powder, and extracted with ether several times. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give a mixture of 1 and 2 in a 3:2 ratio. A solution of these amines (200 mg) in Ac_2O (10 ml) was reflux-

ed for 2 h followed by evaporation to give a mixture of crude acetates (10 and 11) in quantitative yield. Their chromatographic separation by elution with hexane-acetone (20:1) gave 140 mg (60%) of the trans-acetate (10): Ms m/z : 295 (M^+). Ir ($CHCl_3$) cm^{-1} : 1620. 1H -Nmr ($CDCl_3$) δ : 0.88 (3H, br t, $J=7$ Hz, undecyl-Me), 1.26 (23H, br s, $CH_2 \times 10$, Me), 1.30-1.90 (6H, m, $CH_2 \times 3$), 2.04 (3H, s, COMe), 3.70-4.10 (2H, br, CHN $\times 2$). The cis-isomer (11) could not be isolated in pure form.

(±)-Solenopsin A (1) -- A suspension of 10 (19 mg) in 10% HCl (2 ml) was refluxed for 10 h and then extracted with $CHCl_3$ several times. The extract was dried over $MgSO_4$ and evaporated to give a solid which was recrystallized from isopropyl ether to give 10 mg (54%) of pure (\pm)-solenopsin A (1) $\cdot HCl$, mp $114^\circ C$ (lit. mp $114^\circ C^{3b, 3k}$, mp $146^\circ C^{3n}$). 1H -Nmr (400MHz) ($CDCl_3$) δ : 0.88 (3H, t, $J=6.8$ Hz, undecyl-Me), 1.25 (20H, s, $CH_2 \times 10$), 1.48 (3H, d, $J=6.8$ Hz, MeCHN), 1.50-2.05 (6H, m, $CH_2 \times 3$), 3.27 (1H, br, CHN), 3.54 (1H, br, CHN). Anal. Calcd for $C_{17}H_{36}ClN$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.86; H, 6.49; N, 3.94. The free base (7 mg) of 1 was obtained by basification of this hydrochloride (10 mg) with K_2CO_3 powder followed by extraction with ether. 1H -Nmr (400MHz) ($CDCl_3$) δ : 0.88 (3H, t, $J=6.7$ Hz, undecyl-Me), 1.09 (3H, d, $J=6.5$ Hz, MeCHN), 1.26 (20H, s, $CH_2 \times 10$), 1.40-2.10 (6H, m, $CH_2 \times 3$), 2.90 (1H, br, CHN), 3.09 (1H, br, CHN).

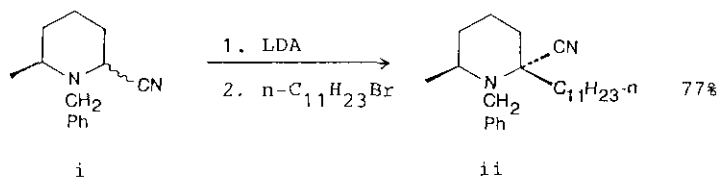
(±)-Isosolenopsin A (2) -- A mixture of 1 $\cdot HCl$ and 2 $\cdot HCl$ in a 3:2 ratio, prepared from 8 as described above, was recrystallized from acetone several times to give pure 2 $\cdot HCl$, mp $145-147^\circ C$ (lit. mp $155^\circ C^{3a}$, $154^\circ C^{3k}$). 1H -Nmr (400MHz) ($CDCl_3$) δ : 0.88 (3H, t, $J=6.9$ Hz, undecyl-Me), 1.25 (20H, s, $CH_2 \times 10$), 1.58 (3H, d, $J=6.4$ Hz, MeCHN), 1.60-2.20 (6H, m, $CH_2 \times 3$), 2.88 (1H, br, CHN), 3.06 (1H, br, CHN). Anal. Calcd for $C_{17}H_{36}ClN$: C, 70.43; H, 12.52; N, 4.83. Found: C, 70.00; H, 12.31; N, 4.81. From the mother liquid of the recrystallization, pure 1 $\cdot HCl$, mp $110-112^\circ C$, was obtained.

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ine (ii) in 77% yield; see reference 3g.



7. The trans- and cis-isomers (1 and 2) have been separated by column chromatography over alumina^{3a, 3b, 3g} or silica gel^{3h, 3l}; but recrystallization of hydrochlorides seems a more convenient means for this.
8. The syntheses of compounds (12-18) are reported in our previous paper.^{2a}

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