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

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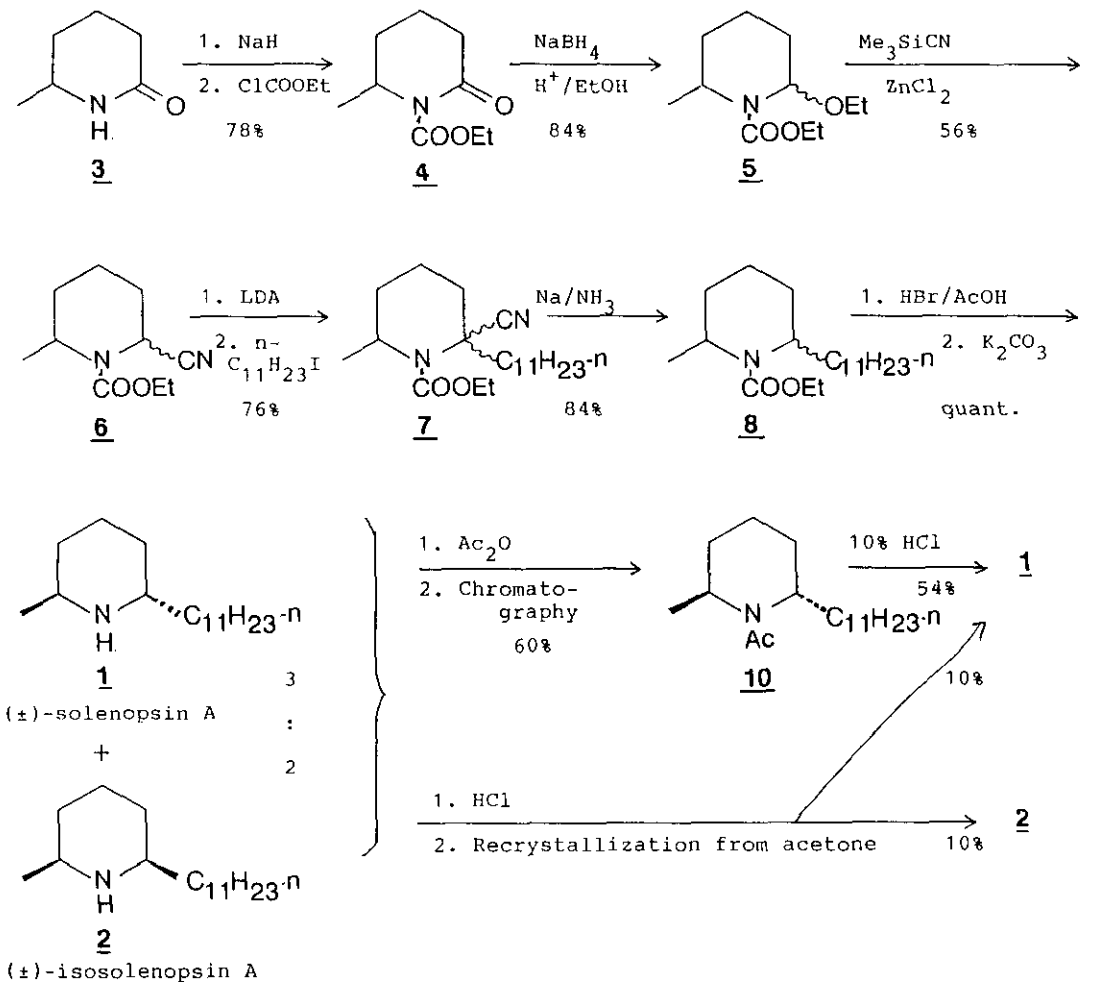
Abstract — (±)-Solenopsin A and (±)-isosolenopsin A were synthesized as a mixture in six steps from 6-methyl-2-piperidinone and they could be easily separated from each other as isomers.

The authors recently reported a method for converting lactams to α-substituted cyclic amines[1] 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-tetrehydropyridine (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 distingushed from their isomers on the basis of their ^{1}H-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 boro-hydride[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

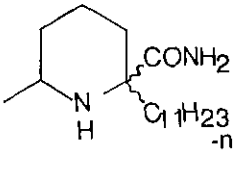


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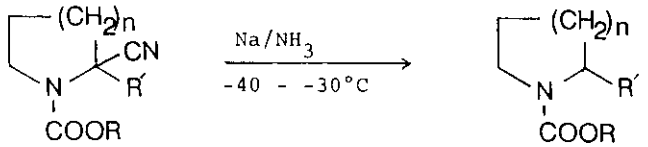
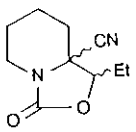
Table I. Generally, decyanation by Birch reactions of α-cyanocarbamates (12-16) having simple alkyl groups at the α-position was successfully carried out to give α-alkylcarbamates (19-23) in good yields. The decyanation of α-cyanocarbamates (17 and 18), however, having functional groups gave a large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



12-17 **19-23**

Run	Starting Material	/	Product	Yield (%)
1	12	n=1, R=Et, R'=CH_2Ph	19	88
2	13	n=2, R=Me, R'=Me	20	88
3	14	n=2, R=Me, R'=n-$C_{11}H_{23}$	21	72
4	15	n=2, R=Me, R'=CH_2Ph	22	95
5	16	n=2, R=Me, R'=$CH_2CH{=}CH_2$	23	50
6	17	n=2, R=Me, R'=COEt	--	0
7	18		--	0

-40 - -30°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 isolation[7] 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. ^{1}H-Nmr spectra were recorded on Varian EM-390 (90 MHz) and Brucker 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 precoated 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), $NaBH_3CN$ (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, H_2O was added, and extraction was carried out with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, 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 ($CHCl_3$) cm^{-1}: 3430, 1685. ^{1}H-Nmr ($CDCl_3$) δ: 1.20 (3H, d, J=7Hz, Me), 1.20-2.10 (4H, m, CH_2 x 2), 2.20-2.40 (2H, m, CH_2CO), 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 method[1] to give 4 in 55-78% yield, bp 90°C (3 mmHg). Ms m/z: 185 (M^+). Ir (neat) cm^{-1}: 1760, 1720. ^{1}H-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 x 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 conditions[1] 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. ^{1}H-Nmr ($CDCl_3$) δ: 1.10-1.40 (9H, m, Me x 3), 1.30-2.40 (6H, m, CH_2 x 3), 3.46 (2H, q, J=7Hz, OCH_2Me), 4.17 (2H, d, J=7Hz, $COOCH_2$Me), 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 atomosphere 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. ^{1}H-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 X 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 caried 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, N_2; 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. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, br t, J=6Hz, undecyl-Me), 1.03-1.50 (26H, m, OCH_2Me, CHMe, CH_2 X 10), 1.50-2.25 (6H, m, CH_2 X 3), 4.20 (2H, q, J=7Hz, OCH_2Me), 4.31 (1H, m, CHN). Anal. Calcd for $C_{21}H_{38}N_2O_2$: 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 solustion 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 $NaBH_4$ (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 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 an oil (127 mg) whose chromatographic separation by elution with $CHCl_3$ 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 ($CHCl_3$) cm^{-1}: 3530, 3400, 1675. ^{1}H-Nmr ($CDCl_3$) δ: 0.86 (3H, m, undecyl-Me), 1.10-1.80 (29H, m, CH_2 X 13, Me), 2.20 (1H, m, CHN). Major product (25 mg) from the second crop: Ms (CI) m/z: 297 (M^++1). Ir ($CHCl_3$) cm^{-1}: 3500, 3370, 1670. ^{1}H-Nmr ($CDCl_3$) δ: 0.87 (3H, m, undecyl-Me), 1.05 (3H, d, J=6Hz, CHMe), 1.28 (20H, s, CH_2 X 10), 1.30-2.00 (6H, CH_2 X 3), 2.80 (1H, br, CHN), 5.40 (1H, br, NH).

General Procedure for Decyanation of α-Cyanocarbamates (7, 12-16) by Birch Reduction[8] -- 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. NH_3 (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 NH_3, H_2O was added to the residue and the solution was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, 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. ^{1}H-Nmr ($CDCl_3$) δ: 1.27 (3H, t, J=7.5Hz, OCH_2Me), 1.51-2.00 (4H, m, CH_2 X 2), 2.51(2H, d, J=11Hz, CH_2Ph), 2.88-3.51 (2H, m, CH_2N), 4.12 (2H, q, J=7.5Hz, OCH_2Me), 4.10 (1H, m, CHN), 7.23 (5H, s, Ph). Anal. Calcd for $C_{14}H_{19}NO_2$: 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. ^{1}H-Nmr (400MHz) ($CDCl_3$) δ: 0.87 (3H, t, J=7Hz, undecyl-Me), 1.01 (d, J=7Hz, Me), 1.65 (d, J=7Hz, Me), 1.16-1.32 (23H, m, OCH_2Me, CH_2 X 10), 1.33-1.86 (6H, m, CH_2 X 3), 3.82-3.95 (1H, m, MeCHN), 4.11 (2H, q, J=7Hz,, 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 mHg). Ms m/z: 157 (M^+). Ir (neat) cm^{-1}: 1680. ^{1}H-Nmr ($CDCl_3$) δ: 1.02 (3H, d, J=8Hz, Me), 1.27-1.94 (6H, m, CH_2 X 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. ^{1}H-Nmr ($CDCl_3$) δ: 0.85 (3H, t, J=7Hz, undecyl-Me), 1.25 (20H, s, CH_2 X 10), 1.40-2.20 (6H, m, CH_2 X 3), 2.90-3.20 (1H, m, CHN), 3.70 (3H, s, OMe), 3.90-4.30 (2H, m, CHN X 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. ^{1}H-Nmr ($CDCl_3$) δ: 1.40-1.85 (6H, m, CH_2 x 3), 2.80 (2H, d, J=6Hz, 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. ^{1}H-Nmr ($CDCl_3$) δ: 1.55-1.80 (6H, m, CH_2 X 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. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, br t, J=7Hz, undecyl-Me), 1.26 (23H, br s, CH_2 X 10, Me), 1.30-1.90 (6H, m, CH_2 X 3), 2.04 (3H, s, COMe), 3.70-4.10 (2H, br, CHN X 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 (±)-solenopsin A (1)·HCl, mp 114°C (lit. mp 114°C[3b, 3k], mp 146°C[3n]). ^{1}H-Nmr (400MHz) ($CDCl_3$) δ: 0.88 (3H, t, J=6.8Hz, undecyl-Me), 1.25 (20H, s, CH_2 X 10), 1.48 (3H, d, J=6.8Hz, MeCHN), 1.50-2.05 (6H, m, CH_2 X 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. ^{1}H-Nmr (400MHz) ($CDCl_3$) δ: 0.88 (3H, t, J=6.7Hz, undecyl-Me), 1.09 (3H, d, J=6.5Hz, MeCHN), 1.26 (20H, s, CH_2 X 10), 1.40-2.10 (6H, m, CH_2 X 3), 2.90 (1H, br, CHN), 3.09 (1H, br, CHN).

(±)-Isosolenopsin A (2) -- A mixture of 1·HCl and 2·HCl in a 3:2 ratio, prepared from 8 as described above, was recrystallized from acetone several times to give pure 2·HCl, mp 145-147°C (lit. mp 155°C[3a], 154°C[3k]). ^{1}H-Nmr (400MHz) ($CDCl_3$) δ: 0.88 (3H, t, J=6.9Hz, undecyl-Me), 1.25 (20H, s, CH_2 X 10), 1.58 (3H, d, J=6.4Hz, MeCHN), 1.60-2.20 (6H, m, CH_2 X 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·HCl, mp 110-112°C, was obtained.

REFERENCES AND NOTES

1. a) T. Nagasaka, H. Tamano, and F. Hamaguchi, Heterocycles, 1986, 24, 1231. b) T. Nagasaka, H. Tamano, T. Maekawa, and F. Hamaguchi, Heterocycles, 1987, 26, 617.
2. a) T. Nagasaka, H. Hayashi, and F. Hamaguchi, Heterocycles, 1988, 27, 1685. b) T. Nagasaka, H. Yamamoto, A. Sugiyama, and F. Hamaguchi, Heterocycles, 1988, 27, 2219. c) T. Nagasaka, H. Yamamoto, H. Hayashi, M. Watanabe, and F.

Hamaguchi, Heterocycles, 1989, 29, 155. d) T. Nagasaka, Y. Koseki, and F. Hamaguchi, Tetrehedron Lett., 1989, 30, 1871. e) T. Nagasaka, H. Yamamoto, H. Hayashi, H. Kato, H. Kawaida, K. Yamaguchi, and F. Hamaguchi, Heterocycles, 1989, 29, 1209.

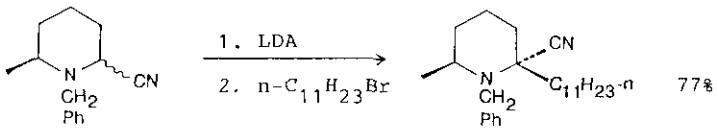
3. Reports on solenopsin A and isosolenopsin A syntheses: a) J. G. MacConnell, M. S. Blum, and H. M. Fales, Tetrahedron, 1971, 27, 1129. b) Y. Moriyama, D. Doan-Huynh, C. Monneret, and Q. Khuong-Huu, Tetrehedron Lett., 1977, 825. c) R. K. Hill and T. Yuri, Tetrahedron, 1977, 33, 1569. d) K. Fuji, K. Ichikawa, and E. Fujita, Chem. Pharm. Bull., 1979, 27, 3183. e) D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel, and S. M. Menchen, J. Org. Chem., 1980, 45, 2120. f) Y. Matsumura, K. Maruoka, and H. Yamamoto, Tetrahedron Lett., 1982, 23, 1929. g) M. Bonin, J. R. Romero, D. S. Grierson, and H. P. Husson, Tetrahedron Lett., 1982, 23, 3369. h) K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, J. Am. Chem. Soc., 1983, 105, 2831. i) Y. Nakazono, R. Yamaguchi, and M. Kawanishi, Chem. Lett., 1984, 1129. j) K. Abe, H. Okumura, T. Tsugoshi, and N. Nakamura, Synthesis, 1984, 597. k) W. Carruthers, M. J. Williams, and M. T. Cox, J. Chem. Soc., Chem. Comm., 1984, 1235. l) A. L. Meyres, P. D. Edwards, T. R. Bailey, and G. E. Jagdmann, Jr., J. Org. Chem., 1985, 50, 1019. m) K. Takahashi, H. Kurita, K. Ogura, and H. Iida, J. Org. Chem., 1985, 50, 4368. n) D. S. Grerson, J. Royer, L. Guerrier, and H. P. Husson, J. Org. Chem., 1986, 51, 4475. o) W. Carruthers and M. J. Williams, J. Chem. Soc., Chem. Comm., 1986, 1287. p) D. M. Ryckman and R. V. Stevens, J. Org. Chem., 1987, 52, 4274. q) R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata, and M. Kawanishi, Bull. Chem. Soc., Jpn, 1987, 60, 215. r) P. G. M. Wuts and Y. W. Jung, J. Org. Chem., 1988, 53, 1957.

4. The authors have found lactams with substituents to often exhibit behavior differing from that of simple lactams for this type reduction. Some examples of this reduction for lactams with substituents have been reported: a) K. H. Melching, H. Hiemstra, W. J. Klaver, and W. N. Speckamp, Tetrahedron Lett., 1986, 27, 4799. b) N. Langlois and R. Z. Andriamialisoa, Tetrahedron Lett., 1988, 29, 3259.

5. R. T. Conley, J. Org. Chem., 1958, 23, 1330.

6. The reaction of 1-benzyl-2-cyano-6-methylpiperidine (i) (whose stereochemistry has not been described) with n-undecyl bromide in the presence of LDA has been reported to provide exclusively 1-benzyl-2-cyano-cis-6-methyl-2-undecylpiperid-

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



i ii

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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