Pergamon

Tetrahedron, Vol. 53, No. 42, pp. 14247-14254, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00992-7

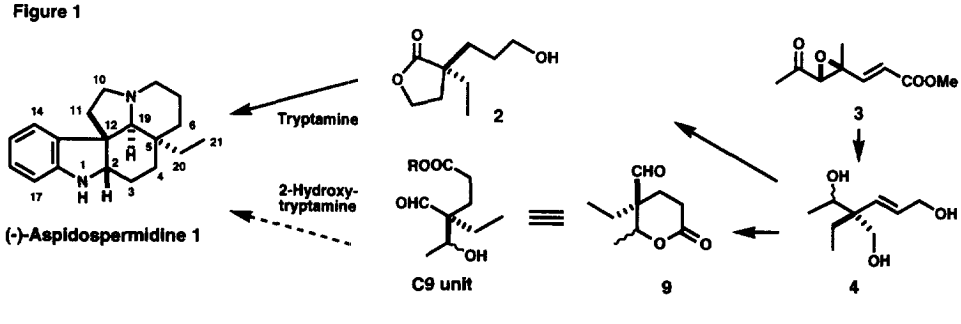
Asymmetric Synthesis of the Pentacyclic Ring System of *Aspidosperma* Alkaloids

Kunisuke Okada,* Kazumasa Murakami and Hideo Tanino
Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468, Japan

Abstract: The asymmetric synthesis of pentacyclic compound **13**, a known intermediate in the synthesis of 1-acetylaspidospermidine, was conducted *via* the condensation of 2-hydroxytryptamine with chiral C9 lactone **9**, readily available from triol **4**.© 1997 Elsevier Science Ltd.

The first asymmetric synthesis of aspidospermidine **1** was initially conducted through the elegant strategy by Fuji,[1] using the chiral C9 lactone **2** and tryptamine. The synthesis of **2** has been reported by Fukumoto.[2] The asymmetric synthesis of **2** was recently conducted by the authors from chiral triol **4** (76 % ee), involving a quaternary carbon bearing an ethyl group and C1, C2 and C3 units prepared *via* 1,2-acyl migration of optically active α,β-epoxy ketone **3** (90 % ee) followed by reduction.[3] This paper represents a new asymmetric synthesis of Ban's intermediate **13**, a useful intermediate in the synthesis of 1-acetylaspidospermidine.[4, 5] The key step of our method involves the condensation of 2-hydroxytryptamine with chiral C9 lactone **9**, derived from chiral synthon **4**.

Figure 1

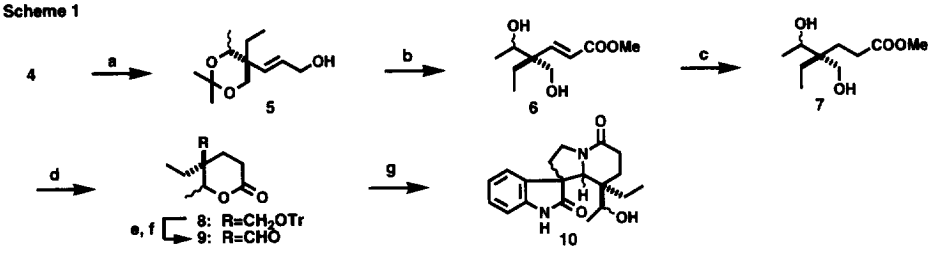


RESULTS AND DISCUSSION

The synthesis of chiral lactone **9** was initiated by the transformation of **4** to saturated ester **7** (66.8 % overall yield) as summarized in Scheme 1. Ester **7** was treated with trityl chloride in pyridine at 90 ℃ for 3 h, giving the desired lactone **8** in quantitative yield. Transformation of **8** to the lactone aldehyde **9**, equivalent to

the non-tryptamine C9 unit shown in Figure 1, was carried out in 57.5 % yield as an approximately 1:1 epimeric mixture by deprotection of the trityl group in **8** and successive oxidation of the hydroxymethyl moiety. Condensation of **9** with 2-hydroxytryptamine hydrochloride proceeded in pyridine at 80 ℃ to yield a mixture of stereoisomers of **10**, as a major fraction containing three close spots on TLC, in 47.4% yield.

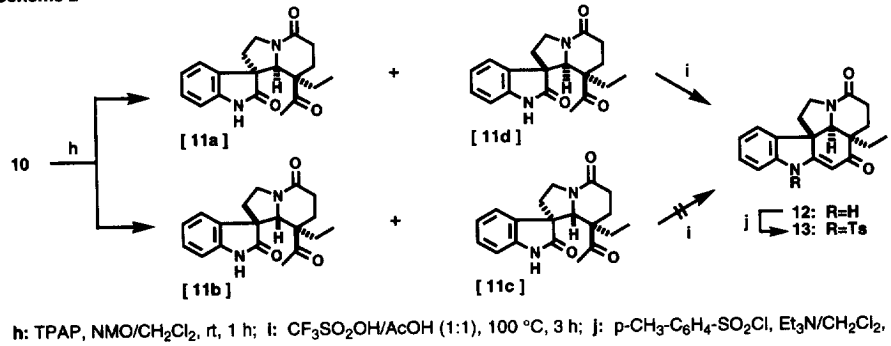
Scheme 1



a: 2,2-dimethoxypropane, CSA/DMF, 90 °C, 15 min; **b:** i) pyridinium chlorochromate/CH_2Cl_2, rt, 1 h, ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*tert*-BuOH-H_2O, rt, 1 h, iii) MeI, K_2CO_3/DMF, rt, 1 h, iv) 1N HCl/MeOH, rt, 1 h; **c:** H_2, Pd-C/EtOAc, rt, 30 min; **d:** ph_3CCl/pyridine, 90 °C, 3 h; **e:** 80 % AcOH, 60 °C, 1.5 h; **f:** SO_3-pyridine complex/ DMSO-Et_3N/CH_2Cl_2, rt, 20 min; **g:** 2-hydroxytryptamine-HCl/pyridine, 80 °C, 2 h

The oxidation of each fraction of **10** with tetrapropylammonium perruthenate (TPAP) in the presence of N-methylmorpholine N-oxide (NMO) in dichloromethane afforded four stereoisomers **11a**~**d** (in the order of decreasing polarity on TLC: **a**=16.2 %, **b**=15.9 %, **c**=16.3 %, **d**=19.8 % yield from **10**, respectively) following repeated purification on silica gel TLC using dichloromethane-methanol=100:5 and acetone-hexane=2:1 and recrystallization from ether.[6] (Scheme 2).

Scheme 2



h: TPAP, NMO/CH_2Cl_2, rt, 1 h; **i:** CF_3SO_2OH/AcOH (1:1), 100 °C, 3 h; **j:** p-CH_3-C_6H_4-SO_2Cl, Et_3N/CH_2Cl_2, rt, 2 h

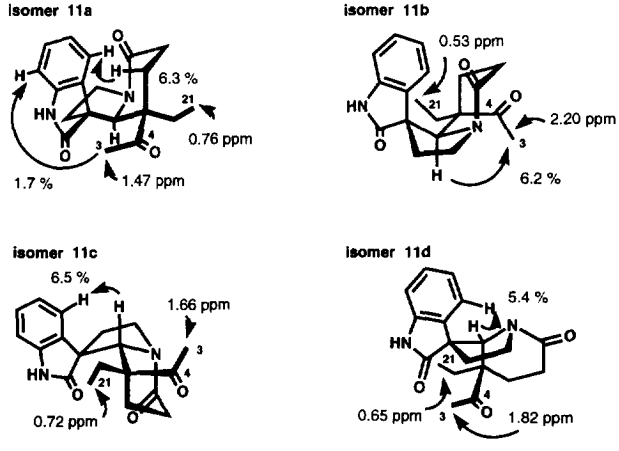
The stereochemistry of each isomer was tentatively assigned based on NMR data as follows. As the stereochemical features of the four isomers **11a**~**d** shown in Figure 2, chemical shifts of C3-methyl group in isomer **11a** and C21-methyl in isomer **11b** were observed in a extremely high field, compared to normal positions, such as 1.47 ppm and 0.53 ppm, respectively, indicating both methyl groups to be located over the the benzene ring in the 2-oxoindoline moiety. The structure of isomer **11a** was confirmed by NOE which was observed between the proton at C6-H (axial proton) and C14-H (6.3 %). Isomers **11c** and **11d** indicated NOE to be between C19-H (α-configuration) and C14-H as shown in Figure 2. However, identification of isomer **11c** and **11d** was difficult using only the data of the chemical shifts of C3-methyl and C21-methyl groups. These isomer **11c** and **11d** could be fully characerized based on the following:

treatment of the isomer **11d** [0.65 (3H, t, J=7.4 Hz), 1.82 (3H, s), 3.95 (1H, s, C19-H)] with a mixture of trifluoromethanesulfonic acid in acetic acid (1:1) at 100 ℃ for 3 h resulted in the formation of cyclized product **12** in almost quantitative yield. Thus, the stereochemistry at C12 and C19 of the isomer **11d** was concluded to be the natural configuration, with the C3-methyl group situated near the oxindolic ketone (Scheme 2).

Under similar conditions, isomer **11a** [0.76 (3H, t, J=7.4 Hz), 1.47 (3H, s), 4.01 (1H, s, C19-H)] gave **12** in about 75 % yield *via* recyclic treatment of the recovered material.[7] However, isomers **11b** [0.53 (3H, t, J=7.3 Hz), 2.20 (3H, s), 4.36 (1H, s, C19-H)] and **11c** [0.72 (3H, t, J=7.3 Hz), 1.66 (3H, s), 4.35 (1H, s, C19-H)] led to no cyclized product. The structure of the resulting pentacyclic compound was confirmed by chemical transformation to the N-tosylate **13** previously prepared by Ban. The ^{1}H-NMR spectrum of the tosylate was in good agreement with that reported.[4]

This paper thus presents a new method for the asymmetric synthesis of pentacyclic ring system of aspidospermidine *via* coupling reaction of C9-δ-lactone **9** and 2-hydroxytryptamine followed by oxidation of secondary alcohol and acid-catalyzed intramolecular aldol type condensation-dehydration reactions.[8]

Figure 2



EXPERIMENTAL

Melting points were not corrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Infrared (IR) spectra were recorded with a JASCO IR-A spectrometer. ^{1}H-NMR spectra were measured with a JNM-GX 270 or JNM-GX 400 spectrometer. The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as the internal standard. The following abbreviations were used: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), triplet of doublet (dt), doublet of doublet of doublet (ddd), multiplet (m), and broad (br). High resolution of mass spectra (HRMS) were obtained with a Hitachi M-80 (EI) or JEOL HX-110 (FAB) spectrometer. Column chromatography was performed on Kanto Chemical silica gel (over 100 mesh) or Wakogel C-300 (flash column chromatography). TLC was carried out on Kieselgel 60F254 plates (Art. 5744, Merck). Unless otherwise noted, all reaction mixtures were dried

after work up over anhydrous Na_2SO_4.

(E)-3-(5-ethyl-2,2,4-trimethyl-1,3-dioxa-5(R)-cyclohexyl)-2-propen-1-ol (5)

A mixture of **4** (854 mg, 4.91 mmol), 2,2-dimethoxypropane (3.0 ml, 24.4 mmol) and camphorsulfonic acid (CSA; 30 mg, 0.13 mmol) in dimethylformamide (DMF; 25 ml) was heated at 90 ℃ for 15 min under nitrogen atomosphere. After cooling, the mixture was diluted with ethyl acetate (300 ml) and the solution was successively washed with water (5 times) and brine, dried and concentrated. The residue was dissolved in a mixture of acetic acid-dichloromethane-methanol (1:15:4 v/v) and the mixture was warmed at 30 ℃ for 1 h. After the addition of dichloromethane (500 ml), the solution was washed with saturated aq. sodium bicarbonate and brine, dried and concentrated under reduced pressure to give a residue which was then subjected to column chromatography on silica gel. Elution with dichloromethane-methanol (10:1, v/v) afforded a diastereomeric mixture (1:1) of **5** (1.04 g, 99%) as an oil [IR (film): 3400, 2950, 1380, 1200, 970 cm^{-1}; HRMS m/z: calcd for $C_{12}H_{23}O_3$[MH^+] 215.1647, found 215.1626], small amount of which was carefully separated by silica gel TLC.
Less polar isomer: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.87 (3H, t, J=7.8 Hz), 1.05 (3H, d, J=6.4 Hz), 1.35～1.50 (2H, m), 1.40 (3H, s), 1.46 (3H, s), 3.71 (2H, s), 3.89 (1H, q, J=6.4 Hz), 4.14 (2H, d, J=5.7 Hz), 5.41 (1H, d, J=16.5 Hz), 5.60 (1H, dt, J=16.5, 5.7 Hz).
More polar isomer: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.81 (3H, t, J=7.8 Hz), 1.03 (3H, d, J=6.4 Hz), 1.20～1.55 (2H, m), 1.40 (3H, s), 1.46 (3H, s), 3.65 (1H, d, J=11.7 Hz), 3.78 (1H, d, J=11.7 Hz), 3.89 (1H, q, J=6.4 Hz), 4.19 (2H, d, J=5.4 Hz), 5.84 (1H, dt, J=16.1, 5.4 Hz), 5.92 (1H, d, J=16.1 Hz).

Methyl (4R)-4-ethyl-5-hydroxy-4-hydroxymethyl-2-hexenoate (6)

A mixture of **5** (969 mg, 4.53 mmol) and pyridinium chlorochromate (1.97g, 9.1 mmol) in dry dichloromethane (25 ml) was stirred at room temperature for 1 h. After dilution with ether (200 ml), it was passed through a short column of celite. The column was washed with ether (100 ml). The combined eluate was concentrated under reduced pressure to give a residue which was dissolved in a mixture of *tert*-butanol (35 ml), potassium dihydrogenphosphate (0.71 g) in water (9 ml), and 2-methyl-2-butene (2.1 ml). To the above solution was slowly added sodium chlorite (1.66 g, 18.3 mmol) with stirring at room temperature for 1 h. The mixture was cooled at 0 ℃, acidified with 1N hydrogen chloride and then extracted with dichloromethane (100 ml, 3 times). The combined extract was dried and concentrated under reduced pressure to give an oil which was dissolved in DMF (20 ml). To the solution in DMF was suspended anhydrous potassium carbonate (1.26 g) and methyl iodide (0.34 ml, 5.46 mmol) was added dropwise. After stirring at room temperature for 1 h, the reaction mixture was diluted with ethyl acetate (250 ml) which was washed with aqueous sodium thiosulfate solution (30 ml), water (50 ml, 5 times), brine and then dried. Evaporation of the solvent under reduced pressure gave a residue which was taken up into the 1N hydrogen chloride in methanol (20 ml) and the mixture was allowed to stand at room temperature for 1 h. To the cooled solution was added sodium bicarbonate powder and the mixture was further stirred at 0 ℃ for 15 min. After dilution with ethyl acetate (300 ml), the mixture was washed with water (50 ml, 2 times), brine, dried and concentrated. The residual oil was purified by flash column chromatography on silica gel with hexane-ethyl acetate (1:2, v/v) as the eluent to give a diastereomeric mixture (1:1) of **6** (708.5 mg, 77.4%) as an oil. IR (film): 3400, 2950, 1720, 1660, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.83, 0.86 (3H, t, J=7.4 Hz), 1,21, 1.24 (3H, d, J=6.7 Hz), 1.41～1.75 (2H, m), 3.74 (3H, s), 3.75 (1H, d, J=11.1 Hz), 3.86 (1H, d, J=11.1 Hz), 3.98 (1H, m), 5.81, 6.00 (1H, d, J=16.5 Hz), 6.87, 6.99 (1H, d, J=16.5 Hz), HRMS m/z: calcd for $C_{10}H_{19}O_4$

203.1282 [MH$^+$], found 203.1277.

Methyl (4R)-4-ethyl-5-hydroxy-4-hydroxymethylhexanoate (7)

To a solution of **6** (647 mg, 3.20 mmol) in ethyl acetate (30 ml) was added 10% Pd-C (647 mg). The mixture was stirred under hydrogen atmosphere for 30 min and passed through a short column of celite. The combined eluate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with hexane-ethyl acetate (2:3, v/v) as the eluent to afford a diastereomeric mixture (1:1) of **7** (569 mg, 87.2%) as an oil. IR (film): 3400, 2950, 1730, 1470, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.79, 0.85 (3H, t, J=7.4 Hz), 1.10～1.50 (2H,m), 1.21, 1.24 (3H, d, J=6.4 Hz), 1.76～2.07 (2H, m), 2.36 (2H, m), 3.37, 3.75 (1H, d, J=11.4 Hz), 3.48, 3.61 (1H, s), 3.68, 3.69 (3H, s), 3.71, 3.92 (1H, q, J=6.4 Hz); HRMS m/z: calcd for $C_{10}H_{21}O_4$ [MH$^+$] 205.1440, found 205.1453.

(4R)-4-ethyl-5-methyl-4-trityloxymethyl-δ-valerolactone (8)

A mixture of **7** (549 mg, 2.69 mmol) and trityl chloride (1.53 g, 5.49 mmol) was heated at 90 ℃ for 3 h under nitrogen and then concentrated under reduced pressure. The residue was taken up into dichloromethane (100 ml) and the solution was washed successively with 0.5 N hydrochloric acid, water, saturated aq. sodium bicarbonate and brine, dried and concentrated. The residue was purified by flash column chromatography on silica gel with hexane-ethyl acetate (3:1, v/v) as the eluent to give a diastereomeric mixture (1:1) of **8** (1.10 g, 98.8 %) as an oil [IR (film): 2950, 1740, 1600, 1495, 1450 cm^{-1}; HRMS m/z: calcd for $C_{28}H_{30}O_3$ [M$^+$] 414.2250, found 414.2250], a small amount of which was separated on silica gel TLC.

Less polar isomer: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.69 (3H, t, J=7.4 Hz), 1.12 (3H, d, J=6.7 Hz), 1.21～2.00 (4H, m), 2.50 (2H, m), 2.92 (1H, d, J=9.7 Hz), 3.15 (1H, d, J=9.7 Hz), 4.68 (1H, q, J=6.7 Hz), 7.25～7.43 (15H, m).

More polar isomer: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.81 (3H, t, J=7.4 Hz), 1.13 (3H, d, J=6.7 Hz), 1.45～1.88 (4H, m), 2.36 (2H, m), 2.98 (1H, d, J=9.4 Hz), 3.10 (1H, d, J=9.4 Hz), 4.40 (1H, q, J=6.7 Hz), 7.21～7.43 (15H, m).

(4S)-4-ethyl-4-formyl-5-methyl-δ-valerolactone (9)

A solution of **8** (228 mg, 0.55 mmol) in 80% acetic acid (6.0 ml) was heated at 60 ℃ for 1.5 h. After cooling, the mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane-ethyl acetate (1:2, v/v) as the eluent to give a diastereomeric mixture of primary alcohol derivative (78.7 mg, 83.2%) as an oil. IR (film): 3420, 2950, 1735, 1470, 1395 cm^{-1}; HRMS m/z: calcd for $C_9H_{15}O_3$ [MH$^+$] 173.1178, found 173.1168; ^{1}H-NMR $CDCl_3$, 270 MHz) δ: 0.92, 0.93 (3H, t, J=7.4 Hz), 1.20, 1.36 (3H, d, J=6.7 Hz), 1.33～1.92 (4H, m), 2.44～2.65 (2H, m), 3.53, 3.68 (1H, d, J=12.4 Hz), 4.05, 4.35 (1H, d, J=12.4 Hz), 4.38, 4.57 (1H, q, J=6.7 Hz). To a solution of the above lactone-alcohol (251 mg, 1.46 mmol), dimethyl sulfoxide (8.0 ml) and triehtylamine (3.2 ml) in dichloromethane (5.9 ml) was added sulfur trioxide-pyridine complex (2.32 g, 14.6 mmol). The mixture was stirred for 20 min at room temperature and poured into water (100 ml). The aqueous phase was thoroughly extracted with ethyl acetate (30 ml, 3 times). The combined organic phases were washed with 0.5 N hydrochloric acid, saturated aq. sodium hydrogencarbonate and brine, dried and concentrated. The residue was purified by silica gel column chromatography with hexane-ethyl acetate (2:3, v/v) as the eluent to give a diastereomeric mixture (1:1) of **9** (173.7 mg, 70.0%) as an oil. IR (film): 2950, 1740, 1470, 1400, 1220 cm^{-1}; HRMS m/z: calcd for $C_9H_{15}O_3$

[MH^+] 171.1021, found 171.1011; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.89, 0.90 (3H, t, J=7.4 Hz), 1.38, 1.50 (3H, d, J=6.7 Hz), 1.59 (1H, m), 1.64～1.93 (2H, m), 2.26 (1H, m), 2.46～2.79 (2H, m), 4.47, 4.70 (1H, q, J=6.7 Hz), 9.59, 9.73 (1H, s).

2,8-dioxo-4-hydroxy-2,3-seco-aspidospermidine isomers (10)

A mixture of **9** (158 mg, 0.93 mmol) and 2-hydroxytrypthamine hydrochloride (395 mg, 1.86 mmol) in pyridine (8 ml) was heated at 80 ℃ for 2 h under nitrogen and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with dichloromethane-methanol (100:7, v/v) as the eluent to afford a mixture of stereoisomers of **10** (144.6 mg, 47.4 % from **9**) as an amorphous solid, which was further separated into three fractions (about 1:2:1) by silica gel TLC (twice developed with dichloromethane-methanol =100:5).

2,4,8-trioxo-2,3-seco-aspidospermidine isomers (11)

To a mixture of the first fraction of **10** (37.0 mg, 0.113 mmol) and N-methylmorphorine N-oxide (NMO, 97% purity, 132 mg, 1.13 mmol) in dichloromethane (4.0 ml) was added tetrapropylammonium perrutenate (TPAP, 97% purity, 21 mg, 0.057 mmol). The mixture was stirred at room temperature for 1 h, passed through a short silica gel column. After washing the column with dichloromethane-methanol (10:1, v/v), the combined eluate was concentrated under reduced prssure. The residual oil was subjected to silica gel column chromatography with dichloromethane-methanol (100:5, v/v) as the eluent to give a fraction containing mainly **11a**, which was further purified on repeated silica gel TLC using a mixture of dichloromethane-methanol (100:5, v/v) and ethyl acetate-tetrahydrofuran (10:1, v/v) to pdoduce isomer **11a** and small amount of **11b**. In a similar way, the second fraction (72.2 mg, 0.22 mmol) afforded an isomer **11b** and **11d** and the third fraction (35.4 mg, 0.108 mmol) also gave **11c**, predominantly. Total amounts of **11a**, **11b**, **11c**, and **11d** [in the order of less porality on TLC with a mixture of dichloromethane-methanol (100:5, v/v)] thus obtained were 23.3 mg, 22.9 mg, 23.4 mg, and 28.5 mg, respectively. Total yield of **11a～d** from **10** was 68.2 %.

11a: mp 215～217 ℃ (from ether); $[\alpha]_D^{25}$ + 30.2° (c 0.39, $CHCl_3$); IR (KBr): 3400～3200, 2950, 1720, 1620, 1470, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.76 (3H, t, J=7.4 Hz), 1.47 (3H, s), 1.70～1.83 (2H, m), 1.85～2.00 (3H, m), 2.39 (1H, ddd, J=17.6, 10.6, 5.1 Hz), 2.42 (1H, m), 2.58 (1H, dt, J=17.6, 5.1 Hz), 3.66 (1H, ddd, J=12.5, 5.8, 2.9 Hz), 4.01 (1H, s), 4.10 (1H, dt, J=12.5, 8.0 Hz), 6.92 (1H, d, J=7.3 Hz), 6.99 (1H, t, J=7.3 Hz), 7.00 (1H, d, J=7.3 Hz), 7.25 (1H, dt, J=7.3, 1.5 Hz), 8.55 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 8.21, 24.85, 28.39, 28.73, 30.75, 35.88, 42.49, 50.38, 55.50, 70.93, 110.26, 122.38, 125.14, 129.00, 130.14, 140.92, 169.53, 178.21, 210.28.

11b: mp 269～271 ℃ (from ether); $[\alpha]_D^{25}$ +60.48° (c 0.58, $CDCl_3$); IR (KBr): 3400～3200, 2950, 1715, 1620, 1475, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.53 (3H, t, J=7.3 Hz), 1.09 (1H, m), 1.35 (1H, m), 1.90 (2H, m), 2.14 (1H, m), 2.20 (3H, s), 2.35 (1H, ddd, J=17.6, 11.0, 5.9 Hz), 2.40 (1H, m), 2.54 (1H, dt, J=17.6 5.9 Hz), 3.84 (1H, m), 4.02 (1H, m), 4.36 (1H, s), 6.97 (1H, d, J=7.3 Hz), 7.00 (1H, t, J=7.3 Hz), 7.05 (1H, d, J=7.3 Hz), 7.27 (1H, t, J=7.3 Hz), 8.44 (1H, s, NH-); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ:8.62, 21.35, 26.35, 26.59, 28.47, 36.33, 43.22, 53.51, 55.63, 66.97, 110.57, 122.44, 124.84, 128.62, 130.32, 139.70, 169.03, 177.29, 209.41.

11c: mp 223～226 ℃ (from ether); $[\alpha]_D^{25}$ +45.4°(c 0.84, $CDCl_3$); IR (KBr): 3400～3200, 2950, 1710, 1620, 1470, 1190. 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.72 (3H, t, J=7.3 Hz), 1.66 (3H, s), 1.76 (1H, m), 1.87 (1H, ddd, J=13.2, 5.9, 2.2 Hz), 2.02 (1H, m), 2.13 (1H, dt, J=13.2, 5.9 Hz), 2.19 (2H, m), 2.31 (1H,

ddd, J=18.3, 13.2, 5.9 Hz), 2.50 (1H, ddd, J=18.3, 5.9, 2.2 Hz), 3.84 (1H, m), 4.19 (1H, m), 4.35 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.02 (2H, m), 7.26 (1H, m), 8.88 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 8.89, 18.95, 26.18, 27.19, 28.14, 35.19, 43.74, 52.90, 54.39, 70.24, 110.18, 122.49, 123.08, 127.39, 129.28, 141.14, 168.34, 179.01, 209.15.

11d: mp 106~108 ℃ (from ether); $[\alpha]_D^{25}$ +63.0°(c 0.72, $CDCl_3$); IR (KBr): 3400, 3200, 2950, 1715, 1625, 1480, 1190, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, t, J=7.4 Hz), 1.50 (1H, m), 1.73 (2H, m), 1.82 (3H, s), 2.14 (1H, dt, J=12.5, 8.8 Hz), 2.20~2.35 (2H, m), 2.44 (1H, dt, J=17.6, 8.1 Hz), 2.62 (1H, dt, J=17.6, 6.6 Hz), 3.61 (1H, ddd, J=12.4, 8.8, 3.7 Hz), 3.95 (1H, s), 4.27 (1H, dt, J=12.4, 8.8 Hz), 6.92 (1H, d, J=7.3 Hz), 7.05 (1H, t, J=7.3 Hz), 7.16 (1H, d, J=7.3 Hz), 7.25 (1H, t, J=7.3 Hz), 8.61 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 8.28, 24.08, 28.65, 29.27, 29.67, 36.23, 42.84, 51.55, 54.28, 70.41, 110.33, 122.38, 122.72, 128.97, 129.46, 141.09, 169.31, 178.54, 208.13; HRMS m/z: calcd for $C_{19}H_{22}N_2O_3$ [M$^+$] 326.1627, found 326.1628.

(-)-2,3-dehydro-4,8-dioxoaspidospermidine (12)

A mixture of **11d** (15 mg, 0.046 mmol), trifluoromethanesulfonic acid (1 ml) and acetic acid (1 ml) was heated at 100 ℃ for 3 h. After cooling, the mixture was poured into cold saturated sodium bicarbonate solution and was extracted with dichloromethane. The extract was washed with brine, dried and concentrated. The residue was purified on silica gel TLC with dichloromethane-methanol (100:7) to give **12** (13.9 mg, 98.2 %): mp 269~273 ℃ (from ether, decomp); $[\alpha]_D^{25}$ -112.7°(c 0.11, $CHCl_3$); IR (KBr): 3200, 2950, 1640, 1615, 1470, 1360, 750 cm-1; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.71 (3H, t, J=7.3 Hz), 1.27 (1H, m), 1.45 (1H, m), 1.84 (1H, dt, J=14.0, 4.4 Hz), 1.91 (1H, ddd, J=12.5, 11.7, 7.3 Hz), 2.08 (1H, dd, 12.5, 5.1 Hz), 2.20 (1H, ddd, J=14.0, 11.7, 3.7 Hz), 2.31 (1H, ddd, J=16.1, 11.7, 4.4 Hz), 2.50 (1H, ddd, J=16.1, 4.4, 3.7 Hz), 3.34 (1H, dt, J=11.7, 5.1 Hz), 3.83 (1H, s), 4.09 (1H, dd, J=11.7, 7.3 Hz), 5.49 (1H, s), 6.92 (1H, d, J=8.1 Hz), 7.00 (1H, br.s), 7.03 (1H, t, J=8.1 Hz), 7.26 (1H, d, J=8.1 Hz), 7.27 (1H, t, J=8.1 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 8.56, 25.64, 30.40, 35.31, 42.11, 47.98, 49.49, 55.04, 61.46, 95.61, 110.03, 121.34, 122.11, 128.77, 129.00, 134.89, 169.35, 171.35, 197.81; HRMS m/z: calcd for $C_{19}H_{20}N_2O_2$ [M$^+$] 308.1523, found 308.1545.

(-)-2,3-dehydro-4,8-dioxoaspidospermidine N-tosylate (13)

To a solution of **12** (5 mg, 0.016 mmol) in dichloromerhane (1 ml) containing triethylamine (0.1 ml) was added tosyl chloride (9.2 mg, 0.048 mmol) and the system was stirred at room temperature for 1 h. After dilution with dichloromethane (20 ml), the solution was washed with 0.5N hydrochloric acid, water, saturated aq. sodium bicarbonate and brine, dried and concentrated under reduced pressure. The residue was purified on silica gel TLC with dichloromethane-methanol (100:5) to give **13** (7.0 mg, 94.7 %) as a crystal: mp 174~177 ℃ (from ether); IR (KBr): 1675, 1655, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.52 (3H, t, J=7.5 Hz), 0.87 (1H, m), 1.14 (1H, m), 1.67 (1H, dd, J=12.5, 4.8 Hz), 1.73 (1H. m), 2.23 (2H, m), 2.38 (3H, s), 2.47 (1H, ddd, J=15.7, 6.0, 3.3 Hz), 3.19 (1H, dt, J=11.7, 5.5 Hz), 3.70 (1H, s), 3.93 (1H, dd, J=11.7, 7.0 Hz), 6.48 (1H, s), 7.19 (2H, m), 7.25 (2H, d, J=8.1 Hz), 7.41 (1H, ddd, J=8.8, 7.3, 1.5 Hz), 7.74 (2H, d, J=8.1 Hz), 8.01 (1H, d, J=8.4 Hz).

REFERENCES AND NOTES

1. Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901-7903. Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517-521.
2. Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *Heterocycles,* **1990**, *31*, 1017-1020. Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1.* **1991**, 525-535.
3. Okada, K.; Katsura, T.; Tanino, H.; Kakoi, H.; Inoue, S. *Chemistry Lett.* **1994**, 157-160. Okada, K.; Murakami, M.; Tanino, H.; Kakoi, H.; Inoue, S. *Heterocycles*, **1996**, *43*, 1735-1750 and see ref.4.
4. Seki, K.; Ohnuma, T.; Oishi, T.; Ban, Y. *Tetrahedron Lett.* **1975**, 723-726. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990-6992. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron*, **1983**, *39*, 3657-3668.
5. For the other asymmetric synthesis of aspidospermidine, see: Desmae"le, D.; d'Angelo, J. J. Org. Chem., **1994**, *59*, 2292-2303.
6. Enantiomeric enrichment of **11a~d** might be performed at this stage.
7. Specific rotation of **12** {$[\alpha]_D^{25}$ -115.8° (c 0.14, $CHCl_3$)} obtained from **11a** was similar to that of **12** obtained from **11d**. Conversion of **11a** into **12** in acidic condition should proceed, without loss of the chirality at C5, as follows: 1) aldol type condensation-dehydration, 2) cleavage of C12-C19 bond promoted by protonation to the α,β-unsaturated carbonyl group and 3) recyclization through stable transition state.
8. Recently, similar acid-catalized cyclization was reported: Mirand, C.; Papa, M.; Cartier, D.; Le'vy, J. *Tetrahedron Lett.*, **1997**, *38*, 2263-2266 and references cited therein.

(*Received in Japan* 20 *June* 1997; *accepted* 11 *August* 1997)