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STEREOSELECTIVE REACTIONS. XIII.[1] TOTAL SYNTHESIS OF (+)-SESBANIME BY A HIGHLY STEREOSELECTIVE CYCLOANNELATION REACTION

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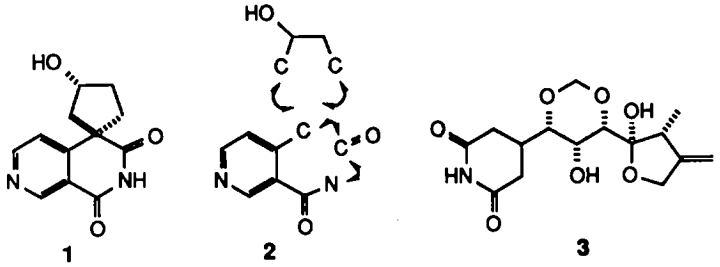
Abstract---An alkaloid sesbanine (1) was synthesized starting from l-malic acid as a chiral four-carbon unit. The key step was a highly stereoselective cycloannelation reaction to form a chiral quaternary carbon center. By this synthesis, the absolute configuration of natural sesbanine was established to 1. Furthermore, sesbanine, in both optically active and racemic forms, was found to be marginaly cytotoxic, contrary to remarkable cytotoxicity reported.

A novel alkaloid sesbanine (1) was isolated from Sesbania drummondii seed extracts and was reported to be endowed with remarkable antitumor activity.[2] The major component of antitumor activity of the plant extracts was later shown to be sesbanimide A (3).[3] Sesbanine was revealed by direct X-ray crystallography to have a previously unreported and highly unusual spirocyclic structure based on the 2,7-naphthylidine nucleus. Its absolute configuration was, however, remained undetermined due to the extremely limited amount of 1. Since the announcement of isolation of 1, many synthetic efforts have been reported.[4] Interested in the unique structure and reported biological activity of 1, we have also decided to synthesize and determine the absolute configuration of 1. As a result of efforts, the absolute configuration of 1 was determined to 1.[4b] To more important, sesbanine, in both optically active and racemic forms, was found to show only marginal cytotoxic activity. We describe here the detail of our highly stereoselective synthesis of (+)-1 with use of l-malic acid as a chiral four-carbon unit.

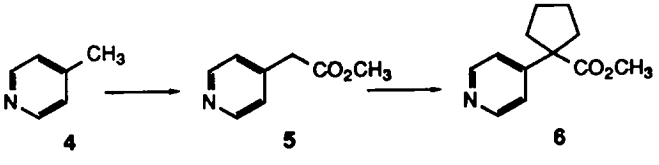


Synthetic Design

The general synthetic approach under consideration for 1 involves the three key steps as shown in 2, alkoxycarbonylation of 4-methylnicotinonitrile, cycloannelation with a chiral four-carbon unit, and cyclic-imide formation. Based on the strategy, the studies were begun to synthesize 6 from 4.

Synthesis of Deoxysesbanine

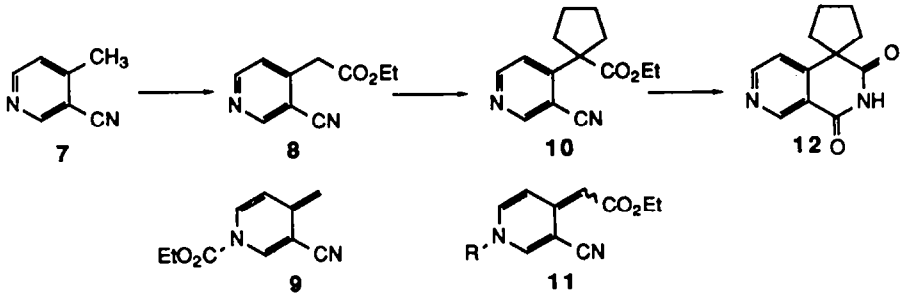
Treatment of γ-picoline (4) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C and then with methyl chloroformate afforded 5 in a quantitative yield. Cycloannelation was



carried out by treating **5** with 1,4-dibromobutane in dimethylformamide (DMF) in the presence of potassium tert-butoxide to afford **6** in 39% yield.

Then focus was turned to the synthesis of deoxysesbanine (**12**). On the contrary to the easy alkoxycarbonylation of **4**, treatment of **7** under the same reaction conditions with use of ethyl chloroformate lead to N-alkoxycarbonylation to afford **9**.[5] Fortunately, treatment of **7** with diethyl carbonate in the presence of sodium hydride in refluxing toluene afforded **8** in 53% yield. Cycloannelation of **8** under the same reaction conditions for **5** lead to the formation of **10** and **11**[5] in 40 and 20% yields, respectively. Use of sodium hydride in place of potassium tert-butoxide improved yield to give **10** and **11** in 61 and 30% yields, respectively.

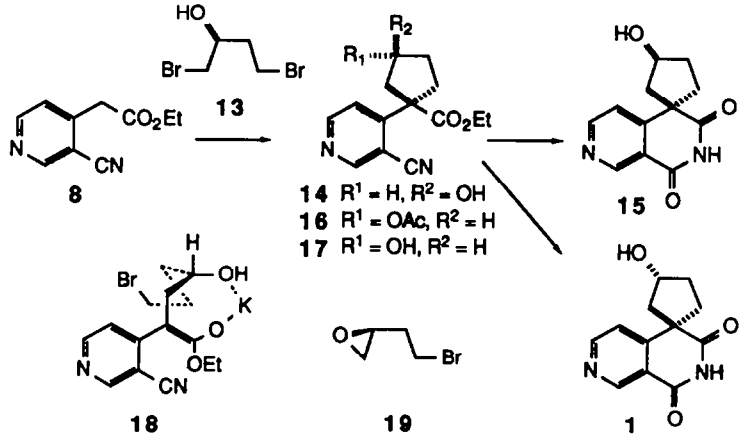
The stage was thus set for the cyclic-imide formation. Selective hydrolysis of the nitrile group of **10** was carried out by utilizing alkaline hydrogen peroxide in aqueous ethanol[6] at room temperature to give directly deoxysesbanine (**12**) in 83% yield.



Synthesis of (+)-Sesbanine

An optically active four-carbon unit (**13**) was prepared from l-malic acid according to the reported procedure.[7] Cycloannelation of **8** attempted with methoxymethylether of **13**, however, afforded methoxymethylether of **14** in only 0.5% yield, producing predominantly N-alkylation products. Fortunately, this problem was circumvented by using **13** as a four-carbon unit. Although the reaction of **8** with **13** in DMF in the presence of potassium carbonate lead to the N-alkylation, the reaction in ethanol[8] gave rise to the desired cycloannelation product (**14**) as a single stereoisomer in 27% yield.

The cycloannelation product (**14**) was then converted under the selective nitrile hydrolysis conditions to the cyclic-imide (**15**) in 57% yield. ^{1}H- and ^{13}C-NMR of **15** were completely different with those of sesbanine (**1**), but identical with those of episesbanine reported by Kende and Demuth.[4a]



The stereoinversion of the hydroxy group of **14** was carried out by applying Mitsunobu reaction[9] to afford **16**, which was then converted to **17** in 76% overall yield. Cyclic-imide

formation of **17** accomplished the total synthesis of sesbanine (**1**). Melting point, ^{1}H- and ^{13}C-NMR of the synthetic sesbanine were completely identical with those reported for natural sesbanine.[2] Since the sign of optical rotation of the synthetic **1** was identical with that of natural **1**, the absolute configuration of natural sesbanine was determined to **1**.[10]

Plausible Mechanism for Stereoselective Cycloannelation

It is quite important to note that cycloannelation reaction of **8** with **13** proceeded in a quite high stereoselectivity to afford **14** as a single stereoisomer. The chelation **18** would be responsible for the highly stereoselective alkylation in forming quaternary carbon.[11] This explanation is also in good agreement with the alkylation mechanism, i.e., in ethanol solvent the enolate of **8** would predominantly attack the terminal carbon of the epoxide (**19**), produced from **13**, in the first alkylation step.[8]

Conclusion

The total synthesis of (+)-sesbanine (**1**) was carried out in a highly efficient manner. The synthesis of (+)-**1** with definite absolute configuration determined the absolute configuration of natural sesbanine to **1**. The synthetic sesbanine and episesbanine, in both optically active and racemic forms, showed only a marginal cytotoxic activity.[12] Synthesis of sesbanimide A (**3**) is a next challenging goal.[13]

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Experimental Section

Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a Jasco DIP-181 Digital Polarimeter. IR spectra were taken with a Jasco Infrared Spectrometer Model DS-402G. ^{1}H-NMR spectra were taken with a Hitachi R-24 Spectrometer at 60 MHz, or with a JNM-PS 100 Spectrometer, or with a JEOL FX-100 Spectrometer at 100 MHz. ^{13}C NMR spectra were taken with JEOL FX-100 Spectrometer at 25 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS were taken with a JEOL DX-300 Mass Spectrometer.

Methyl 4-pyridylacetate (5)

To a cooled (-78 °C) solution of LDA (22 mmole) in THF (22 mL) and HMPA (3.83 mL, 22 mmole), prepared from diisopropyl amine (3.08 mL, 22 mmole) and a hexane solution of BuLi (12.5 mL, 22 mmole), was added γ-picoline (1.95 mL, 20 mmole). The mixture was stirred at -78 °C for 2 h and was poured into the solution of methyl chloroformate (1.86 mL, 24 mmole) in THF (5 mL) at -78 °C. The whole was stirred for 1 h at -78 °C and at room temperature for 2 h. The mixture was washed with satd. $NaHCO_3$ and then extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Concentration and distillation afforded **5** (3.2 g, quant) as a pale yellow oil (bp 130 °C/10 mmHg). NMR ($CDCl_3$) δ: 3.59 (s, CH_2, 2H), 3.66 (s, CH_3, 3H), 7.0-7.2 (m, 2H), 8.4-8.7 (m, 2H); IR (neat): 1730, 1600 cm^{-1}; Ms m/z; 151.

Methyl 1-(4-pyridyl)cyclopentanecarboxylate (6)

To a suspension of potassium tert-butoxide (247 mg, 2.2 mmole) in DMF (3 mL) was added a solution of **5** (151 mg, 1.0 mmole). After stirring for 20 min at room temperature, 1,4-dibromobutane (0.12 mL, 1.0 mmole) was added. The whole was stirred for 3 days at room temperature. The mixture was acidified with 10% HCl and washed with ether and then basified with satd. $NaHCO_3$ and extracted with ether. The extracts were washed with satd. $NaHCO_3$ and brine and dried over K_2CO_3. Concentration afforded a brown oil (80 mg), which was purified by silica gel column chromatography (ether) to give **6** (40 mg, 39%) as a colorless oil. NMR ($CDCl_3$) δ: 1.5-2.9 (m, 8H), 3.61 (s, 3H), 7.1-7.3 (m, 2H), 8.4-8.6 (m, 2H); IR (neat): 1730, 1600 cm^{-1}; Ms m/z: 205.

Ethyl 1-(3-cyano-4-pyridyl)acetate (8)

A suspension of 4-methylnicotinonitrile (118 mg, 1.0 mmole),[14] diethyl carbonate (1.21 mL, 10 mmole) and sodium hydride (200 mg, 5.0 mmole) in toluene (4 mL) was stirred under reflux for 9 h. The mixture was added by satd. NH_4Cl and basified with satd. $NaHCO_3$ and then extracted with ether. The extracts were washed with brine and dried over K_2CO_3. Concentration and silica gel column

chromatography (AcOEt:n-hexane/15:85) afforded **8** (100 mg, 53%) as a pale yellow oil. NMR ($CDCl_3$) δ: 1.31 (t, J=7 Hz, 3H), 3.89 (s, 2H), 4.20 (q, J=7 Hz, 2H), 7.43 (d, J=6 Hz, 1H), 8.72 (d, J=6 Hz, 1H), 8.84 (s, 1H); IR (neat): 2240, 1740, 1600 cm^{-1}; Ms m/z: Calcd for $C_{10}H_{10}N_2O_2$ 190.0739. Found 190.0732.

Ethyl 1-(3-cyano-4-pyridyl)cyclopentanecarboxylate (10)

A mixture of **8** (190 mg, 1.0 mmole), 1,4-dibromobutane (0.13 mL, 1.1 mmole), sodium hydride (2.2 mmole), and HMPA (0.38 mL, 2.2 mmole) in DMF (4 mL) was stirred at room temperature for 24 h and diluted with ether. The mixture was washed with brine and dried over K_2CO_3. Concentration gave a yellow solid (380 mg), which was purified by silica gel column chromatography (AcOEt:n-hexane/1:4) to afford **10** (150 mg, 62%) as a pale yellow oil. NMR ($CDCl_3$) δ: 1.20 (t, J=7 Hz, 3H), 1.5-3.0 (m, 8H), 4.20 (q, J=7 Hz, 2H), 7.37 (d, J=6 Hz, 1H), 8.72 (d, J=6 Hz, 1H), 8.83 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 14.0 (q), 24.5 (t), 36.6 (t), 58.5 (s), 61.8 (t), 110.1 (s), 116.5 (s), 121.6 (d), 152.9 (d), 154.0 (d), 155.9 (s), 173.5 (s); IR (neat): 2240, 1740 1600 cm^{-1}; Ms m/z: Calcd for $C_{14}H_{16}N_2O_2$ 244.1209. Found 244.1184.

Deoxysesbanine (12)

A solution of **10** (110 mg, 0.45 mmole), sodium hydroxide (4.4 mg, 0.11 mmole), and 30% hydrogen peroxide (0.36 mL, 3.2 mmole) in ethanol (3 mL) was stirred at room temperature for 2 h. After dilution with brine (10 mL), the mixture was extracted with chloroform. The extracts were washed with brine and dried over K_2CO_3. Concentration afforded a white solid, which was recrystallized from methanol to afford **12** (80 mg, 83%) as colorless needles of mp 204-205 °C. NMR (d_6-DMSO) δ: 1.5-2.5 (m, 8H), 7.53 (d, J=6 Hz, 1H), 8.78 (d, J=6 Hz, 1H), 9.08 (s, 1H), 11.5 (s, 1H); ^{13}C-NMR (d_6-DMSO) δ: 27.2 (t), 42.2 (t), 52.4 (s), 119.6 (s), 120.5 (d), 148.4 (d), 153.8 (d), 155.5 (s), 163.6 (s), 177.0 (s); IR (KBr): 3400, 1700, 1600 cm^{-1}; Ms m/z: 216. Anal. Calcd for $C_{12}H_{12}O_2N_2$ C 66.65, H 5.59, N 12.96. Found C 66.54, H 5.59, N 12.93.

(-)-(1R,3S)-Ethyl 1-(3-cyano-4-pyridyl)-3-hydroxycyclopentanecarboxylate (14)

A mixture of **8** (380 mg, 2.0 mmole), **13** (0.93 mL, 8.0 mmole: $[\alpha]_D^{19}$ -39.0 °(c 6.60, $CHCl_3$)),[7] and potassium carbonate (5.52 g, 40 mmole) in ethanol (40 mL) was stirred at 15 °C for 24 h and then filtered. The filtrate was diluted with chloroform and washed with brine and dried over K_2CO_3. Concentration and purification by silica gel column chromatography (acetone:chloroform/15:85) afforded **14** (140 mg, 27%) as a yellow oil. $[\alpha]_D^{20}$ -19.6 °(c 0.601, $CHCl_3$). NMR ($CDCl_3$) δ: 1.20 (t, J=7 Hz, 3H), 1.9-2.1 (m, 4H), 2.1-3.2 (m, 3H), 4.22 (q, J=7 Hz, 2H), 4.45 (m, 1H), 7.35 (d, J=6 Hz, 1H), 8.75 (d, J=6 Hz, 1H), 8.83 (s, 1H); IR (neat): 3400, 2240, 1735, 1580 cm^{-1}; Ms m/z: Calcd for $C_{14}H_{16}N_2O_3$ 260.1162. Found 260.1188.

(+)-Episesbanine (15)

According to the same procedure for deoxysesbanine (**12**), **14** was converted to the (+)-episesbanine (**15**) in 57% yield. Colorless fine needles of mp 249-252 °C (recrystallized from methanol). $[\alpha]_D^{20}$ +41.5 °(c 0.55, MeOH). NMR (d_6-DMSO) δ: 1.5-2.5 (m, 6H), 4.50 (m, 1H), 7.45 (d, J=6 Hz, 1H), 8.76 (d, J=6 Hz, 1H), 9.10 (s, 1H), 11.5 (s, 1H); ^{13}C-NMR (d_6-DMSO) δ: 35.4, 40.3, 47.2, 51.3, 72.6, 119.5, 120.6, 148.5, 153.9, 155.2, 163.6, 177.0; IR (KBr): 3400, 1715, 1605 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3$ C 62.06, H 5.21, N 12.06. Found C 61.83, H 5.21, N 11.96.

(-)-(1R,3R)-Ethyl 1-(3-cyano-4-pyridyl)-3-acetoxycyclopentanecarboxylate (16)

A mixture of **14** (50 mg, 0.19 mmole), triphenylphosphine (150 mg, 0.57 mmole), acetic acid (0.034 mL, 0.57 mmole), and diethyl azodicarboxylate (0.09 mL, 0.57 mmole) in THF (1.0 mL) was stirred at room temperature for 20 h. Concentration and purification by silica gel column chromatography (AcOEt:n-hexane/3:7) afforded **16** (52.4 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ -24.5 °(c 0.612, $CHCl_3$). NMR ($CDCl_3$) δ: 1.22 (t, J=7 Hz, 3H), 1.7-2.9 (m, 5H), 1.96 (s, 3H), 3.0-3.6 (m, 1H), 4.20 (q, J=7 Hz, 2H), 5.38 (m, 1H), 7.46 (d, J=5 Hz, 1H), 8.77 (d, J=5 Hz, 1H), 8.84 (s, 1H); IR (neat): 2240, 1735, 1585 cm^{-1}. Ms m/z: Calcd for $C_{16}H_{18}N_2O_4$ 302.1264. Found 302.1261.

(-)-(1R,3R)-Ethyl 1-(3-cyano-4-pyridyl)-3-hydroxycyclopentanecarboxylate (17)

A mixture of **16** (51 mg, 0.17 mmole) and potassium carbonate (15 mg) in ethanol (2.5 mL) was stirred at room temperature for 4 h and filtered. The filtrate was diluted with ether and washed with brine and dried over K_2CO_3. Concentration and purification by silica gel column chromatography (acetone:chloroform/4:6) afforded **17** (36 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ -17.4 °(c 0.726, $CHCl_3$). NMR ($CDCl_3$) δ: 1.19 (t, J=7 Hz, 3H), 1.6-2.8 (m, 6H), 3.05 (dd, J=6, 14 Hz, 1H), 4.19 (q, J=7 Hz, 2H), 4.60 (m, 1H), 7.52 (d, J=6 Hz, 1H), 8.73 (d, J=6 Hz, 1H), 8.80 (s, 1H); IR (neat): 3400, 2240, 1730, 1585 cm^{-1}. Ms m/z: Calcd for $C_{14}H_{16}N_2O_3$ 260.1158. Found 260.1156.

(+)-Sesbanine (1)

According to the same procedure for deoxysesbanine (**12**), **17** was converted to the (+)-sesbanine (**1**) in 67% yield. Colorless fine needles of mp 240-241 °C (recrystallized from methanol). $[\alpha]_D^{23}$ +43.1 °(c 0.52, MeOH). ^1H-NMR (d_6-DMSO) δ: 1.7-2.3 (m, 5H), 2.66 (dd, J=5, 14 Hz, 1H), 4.50 (m, 1H), 7.89 (d, J=6 Hz, 1H), 8.83 (d, J=6 Hz, 1H), 9.06 (s, 1H); ^{13}C-NMR (d_6-DMSO) δ: 36.3, 42.7, 48.6, 52.0, 72.6, 119.6, 121.7, 148.2, 153.8, 155.7, 163.7, 177.1; IR (KBr): 3510, 3490, 1710, 1690, 1600 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3$ C 62.06, H 5.21, N 12.06. Found C 62.00, H 5.19, N 11.91.

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(5) Typical NMR data for N-alkylation products. **9** ($CDCl_3$) δ: 1.40 (t, J=7 Hz, 3H), 4.20 (q, J=7 Hz, 2H), 4.57 (bs, 1H), 4.69 (bs, 1H), 5.83 (d, J=8 Hz, 1H), 6.82 (bd, J=8 Hz, 1H), 7.51 (bs, 1H); **11** ($CDCl_3$) δ: 1.21 (t, J=7 Hz, 3H), 1.5-2.3 (m, 4H), 3.2-3.9 (m, 4H), 4.10 (q, J=7 Hz, 2H), 5.18 (s, 1H), 6.64 (bd, J=8 Hz, 1H), 7.20 (bs, 1H), 7.78 (d, J=8 Hz, 1H).

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(10) Optical rotation of the synthetic **1** was higher than that of natural sesbanine reported by Powell,[2] probably due to the purity of natural sample.

(11) Asymmetric construction of quaternary carbon centers has been the subject of intensive studies. Review for the synthesis of quaternary carbon centers: S. F. Martin, Tetrahedron, **1980**, 36, 419.
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(12) Racemic sample was prepared in the same way using racemic **13**. Cytotoxic activity was evaluated against KB cell.

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