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AN EFFICIENT CHIRAL SYNTHESIS OF (+)-SESBANINE

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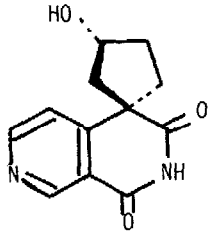
Summary: (+)-Sesbanine was effectively synthesized from 4-methylnicotinonitrile and l-malic acid.

A novel cytotoxic alkaloid sesbanine (1) was isolated from Sesbania drummondii seed extracts showing the potent antileukemic activity.[1,2] Although single crystal x-ray structure determination of 1 revealed a previously unreported and highly unusual spirocyclic structure based on the 2,7-naphthyridine nucleus, the absolute configuration of natural sesbanine was remained undetermined because of the extremely limited amount of sesbanine.[2]

As a consequence of our intention to engage in the total synthesis of 1 and further to determine the absolute configuration of natural sesbanine by the chiral synthesis starting from the component of the known absolute configuration, we have initiated our studies on the development of a simple and efficient methodology for the construction of the skeleton of 1.



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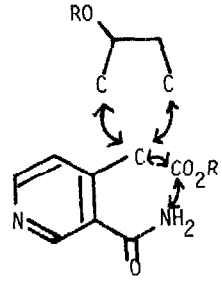

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The general synthetic approach under consideration involves the following three key steps as shown in 2, that is, first is the alkoxycarbonylation of 4-methylnicotinonitrile, second is the cycloannelation using appropriate optically active four carbon unit, and the last is the selective hydrolysis of nitrile group to primary amide group followed by simultaneous cyclic-imide formation. Since Kende and Demuth reported very recently the stereoselective synthesis of (±)-1 and its C-10 epimer based on the similar strategy described above,[3] we wish to report here our independent chiral synthesis of (+)-sesbanine.

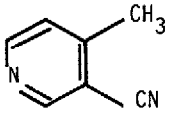
Based on the strategy cited above, the present studies were first begun to synthesize deoxysesbanine (4) as a model compound. Treatment of 3[4] with diethyl carbonate (10 eq.) in the

presence of sodium hydride (5 eq.) in boiling toluene for 9 hr gave the cyano ester (5), m/e 190 (M^+), in 53% yield.[5] Then 5 was treated with 1,4-dibromobutane (6) in the presence of sodium hydride (2 eq.) in DMF-HMPA (10:1) at room temperature for 24 hr to give the cyclized product (7), m/e 244 (M^+), in 62% yield. The last key step cyclic-imide formation of 7 was successfully achieved by the treatment of 7 with alkaline hydrogen peroxide (0.25 eq. of sodium hydroxide, 7 eq. of hydrogen peroxide)[6] in aqueous ethanol at room temperature for 2 hr to give directly deoxysesbanine (4), mp 204-205°, m/e 216 (M^+), PMR(DMSO-d_6) δ 1.5-2.5 (8H, m), 7.53 (1H, d, J=6 Hz), 8.78 (1H, d, J=6Hz), 9.08 (1H, s), IR(KBr) 1705, 1695 cm^{-1}, in 83% yield.

Applying above method the effort was focussed on the total synthesis of sesbanine. Cyclo-annelation of 5 with methoxymethyl ether of racemic 1,4-dibromobutan-2-ol (8) under the same condition described above, however, gave a trace of the desired product (9), m/e 304 (M^+). Fortunately this difficulty was circumvented by using racemic 8 as a four carbon unit (4 eq. of 8, 20 eq. of potassium carbonate, in ethanol at room temperature for 24 hr) to give the cyclized product (10) as a single isomer, m/e 260 (M^+), PMR($CDCl_3$) δ 1.20 (3H, t, J=7Hz), 1.6-2.1 (4H, m), 2.1-3.2 (3H, m), 4.22 (2H, q, J=7Hz), 4.45 (1H, m), 7.35 (1H, d, J=6Hz), 8.75 (1H, d, J=6Hz), 8.83 (1H, s), IR(neat) 3400, 2240, 1735 cm^{-1}, in 27% yield. Cyclic-imide formation of 10 was carried out as described for 7 to give 11, mp 235-237°, m/e 232 (M^+), PMR(DMSO-d_6) δ 4.5 (1H, m), 7.45 (1H, d, J=6Hz), 8.76 (1H, d, J=6Hz), 9.06 (1H, s), CMR(DMSO-d_6) 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, 1710, 1690, 1600 cm^{-1}, in 57% yield. Since PMR and CMR spectra were different with those of natural sesbanine, this product was decided to be C-10 epimer.[7] Therefore in order to achieve the synthesis of 1, the stereo-inversion of hydroxy group in 10 was necessary.

Then we turned our effort to the synthesis of optically active compound. Optically active 10 ($[\alpha]_D^{20}$ -19.6° ($CHCl_3$)) was synthesized as described for racemic 10 using optically active alcohol (8) ($[\alpha]_D^{19}$ -39.0° ($CHCl_3$)) prepared from l-malic acid according to the Seebach procedure.[8] The stereoinversion of hydroxy group in 10 was achieved applying Mitsunobu procedure (3 eq. of diethyl azodicarboxylate, 3 eq. of triphenylphosphine, and 3 eq. of acetic acid in THF at room temperature for 20 hr)[9] to give the corresponding acetate (12), $[\alpha]_D^{20}$ -24.5° ($CHCl_3$), m/e 302 (M^+), in 91% yield. Ester exchange reaction of 12 (catalytic amount of potassium carbonate in ethanol at room temperature for 4 hr) proceeded well to give desired 13, $[\alpha]_D^{20}$ -17.4° ($CHCl_3$), m/e 260 (M^+), PMR($CDCl_3$) δ 1.19 (3H, t, J=7Hz), 1.6-2.8 (6H, m), 3.05 (1H, d of d, J=14 and 5Hz), 4.19 (2H, q, J=7Hz), 4.60 (1H, m), 7.52 (1H, d, J=6Hz), 8.73 (1H, d, J= 6Hz), 8.80 (1H, s), IR(neat) 3400, 2240, 1730, 1585 cm^{-1}, in 98% yield. Cyclic-imide formation of 13 proceeded satisfactorily as described for 7 to give (+)-sesbanine (1), mp 240-241°, $[\alpha]_D^{23}$ +43.1° (MeOH),[10] m/e 232 (M^+), PMR(DMSO-d_6) δ 1.7-2.3 (5H, m), 2.66 (1H, d of d, J=14 and 5Hz), 4.50 (1H, m), 7.89 (1H, d, J=6Hz), 8.83 (1H, d, J=6Hz), 9.06 (1H, s), CMR(DMSO-d_6) 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}, in 67% yield.

IR, PMR, and CMR data of this synthetic (+)-sesbanine (1) were superimposable with those of natural sesbanine. And also melting point and sign of optical rotation were identical with those reported for natural sesbanine.[10] From these data it is concluded that natural sesbanine



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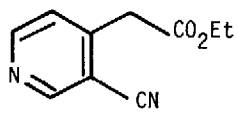

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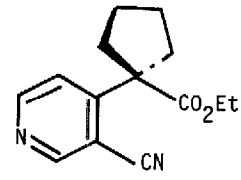

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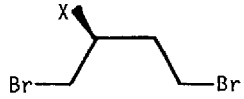
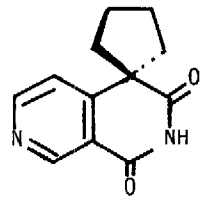


6 X=H

8 X=OH



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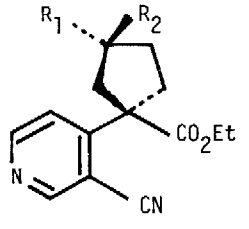
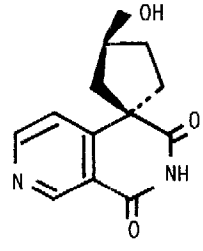


9 R_1, R_2=OCH_2OCH_3

10 R_1=H, R_2=OH



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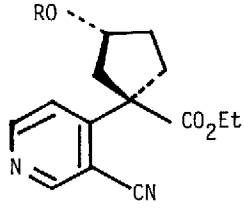
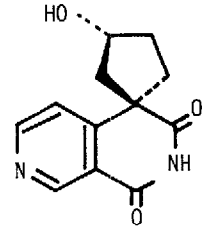


12 R=OAc

13 R=H



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has the absolute configuration shown in 1.

Further studies involving the synthesis of antipode of 1 are now in progress in our laboratory.

Acknowledgement

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REFERENCES AND NOTES

1 R. G. Powell, C. R. Smith, and R. V. Madrigal, Planta Med., 30, 1 (1976).

2 R. G. Powell, C. R. Smith, D. Weisleder, D. A. Muthard, and J. Clardy, J. Am. Chem. Soc., 101, 2784 (1979).

3 A. S. Kende and T. P. Demuth, Tetrahedron Letters, 21, 715 (1980).

4 J. M. Bobbitt and D. A. Scola, J. Org. Chem., 25, 560 (1960), W. Trommer and H. Blume, Tetrahedron Letters, 1447 (1973).

5 Satisfactory spectral and analytical data were obtained for all new compounds.

6 J. G. Wallace, "Hydrogen peroxide in organic chemistry", E. I. duPont Co., 1962, p. 42.

7 PMR and CMR data of 10 were also identical with those reported for (±)-episesbanine by Kende and Demuth. See reference 3.

8 B. Seuring and D. Seebach, Helv. Chim. Acta, 60, 1175 (1977).

9 O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Japan, 44, 3427 (1971).

10 Optical rotation of synthetic sesbanine was measured using combustion analysis sample. Although sign of optical rotation value was identical, the reported value ($[\alpha]_D^{23}$ +14.6° (MeOH)) was smaller than that of present synthetic (+)-sesbanine.

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