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STEREOSPECIFIC SYNTHESIS OF (±)-SESBANINE AND ITS C-10 EPIMER

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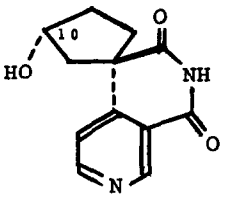
Abstract: A short, stereospecific total synthesis of (±)-sesbanine and its C-10 epimer from 4-methylnicotinonitrile is described.

Ethanolic seed extracts from Sesbania drummondii (Leguminosae) are known to possess antileukemic activity.[1] Powell, Clardy and their collaborators have recently described the isolation of a novel cytotoxic alkaloid, sesbanine, from these extracts.[2] Single crystal X-ray structure determination of sesbanine revealed the unusual tricyclic structure 1 featuring a cyclopentanol spiro-fused onto an oxygenated 2,7-naphthyridine framework. We now report a stereospecific total synthesis of (±)-sesbanine and its C-10 epimer.



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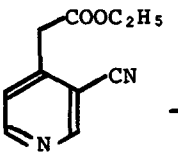

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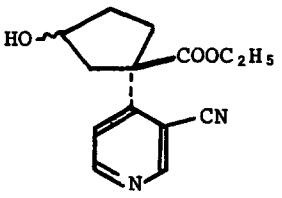
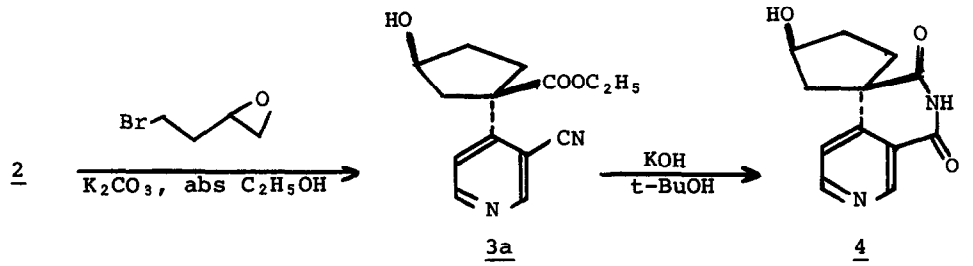


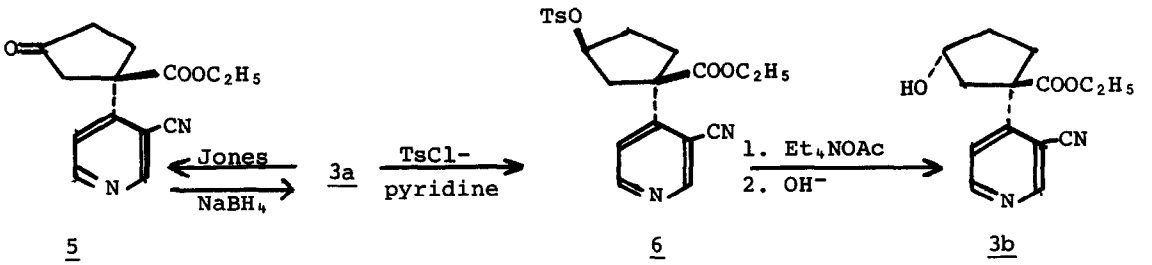
3

Our synthesis involves a key cycloannelation[3] which transforms the known cyanoester 2[4] to the substituted cyclopentanol 3. In our hands, 2 was most expeditiously prepared in 40% yield by the direct carbethoxylation of 4-methylnicotinonitrile[5] (2.1 eqt $NaN(SiMe_3)_2$, 1.0 eqt $(C_2H_5O)_2CO$, C_6H_6, rt, 18 hr). Treatment of cyanoester 2 in absolute ethanol under the conditions of Cruickshank[3] (3.0 eqt 1,2-epoxy-4-bromobutane, excess $NaOC_2H_5$, rt, 18 hr) gave instead of 3 a complex mixture of N- and C-alkylation products whose structures will be discussed in our full paper. In contrast, reaction of cyanoester 2 with 1,2-epoxy-4-bromobutane (3 eqt, abs. C_2H_5OH, rt, 18 hrs) using excess anhydrous K_2CO_3 as base gave a 40-45% yield of a new polar product which showed spectroscopic and analytical data consistent with the desired cyclopentanol system 3.[6] Moreover, these data showed that product 3 was obtained as a single racemic diastereomer rather than the expected cis/trans mixture.[7] This latter conclusion was verified by mild hydrolytic cyclization (KOH, t-BuOH, reflux, 90 min) to yield a single imide, mp 240-242°, in 40% yield. Although the physical properties of this imide were nearly identical to those of (+)-sesbanine, the ^{13}C nmr chemical shifts of several carbon atoms were sufficiently discrepant to differentiate our synthetic from the natural alkaloid.[8] Analytical characterization of our synthetic imide showed

it to be isomeric with sesbanine, leading to its identification as (±)-10-episesbanine 4.[8] Thus its cyclopentanol precursor was assigned the cis stereochemistry 3a shown below.



To bring this synthetic sequence into the trans series (cf. 3b), cyclopentanol 3a was oxidized with Jones reagent (rt, 4 hr, 89%) to the cyclopentanone 5.[9] However, reduction of this ketone with $NaBH_4$ (4 eqt, C_2H_5OH, 0° 1 hr) or with $Li(sec\text{-}Bu)_3BH$ (1.1 eqt, THF, -20°, 2 hr) merely converted it stereospecifically back to the precursor alcohol 3a. The desired stereoinversion was in turn successfully achieved by conversion of alcohol 3a to the crystalline tosylate 6[10] (1.1 eqt TsCl-pyridine, rt, 24 hr, 67% yd, mp 188.5-190°), followed by nucleophilic displacement with $(C_2H_5)_4N^+{}^-OCOCH_3$ (C_6H_6, reflux, 1 hr)[11] and subsequent mild hydrolysis (1N NaOH, 50% aq. CH_3OH, 0°, 30 min) to give 83% of the new cyclopentanol 3b, mp 104.5-106°.[12]



Alkaline cyclization of 3b proceeded as described for 3a to yield 60% of the crystalline imide 1, mp 241-243°.[13] Comparison with natural sesbanine showed the synthetic material to be identical by ^1H-nmr, ^{13}C-nmr, mp, mmp, mass spectrum and tlc behavior.

By the procedures outlined above, (±)-sesbanine becomes available in five simple synthetic operations from 4-methylnicotinonitrile.[14] Improvements in the current overall yield (5-6%) and the origins of the observed stereospecific formation of 3a are under investigation.

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is acknowledged with thanks. T.P.D. thanks the University of Rochester for a Sherman Clarke Fellowship.

References

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2. R. G. Powell, C. R. Smith Jr., D. Weisleder, D. A. Muthard and J. Clardy, J. Am. Chem. Soc., 101, 2784 (1979).
3. P. A. Cruickshank and M. Fishman, J. Org. Chem., 34, 4060 (1969).
4. W. Trommer and H. Blume, Tetrahedron Lett., 1447 (1973).
5. J. M. Bobbitt and D. A. Scola, J. Org. Chem., 25, 560 (1960)
6. Compound 3a: ^{1}H-nmr: δ9.00 (s, 1H); 8.90 (d, 1H, J = 5 Hz); 7.54 (d, 1H, J = 5 Hz); 4.46 (m, 1H); 4.28 (q, 2H, 5 = 7 Hz); 3.3 (br s, 1H); 2.96 (m, 2H); 1.8-2.4 (br m, 4H); 1.26 (t, 3H, J = 7 Hz). ir (neat): 3400 (br), 2218, 1712, 1580 cm^{-1}. ms (75 eV): 260 (M$^+$, 2%), 232 (4%), 215 (6%), 203 (7%), 187 (11%), 169 (100%), 145 (91%).
7. Careful examination of crude reaction mixtures from several bromoepoxide cyclizations, using tlc and nmr, showed no evidence for the presence of a second diastereomeric cyclopentanol. This was confirmed later by the independent synthesis of the second diastereomer (3b, see text), which is distinctly different in tlc and nmr properties from the cyclization product.
8. Compound 4: ^{1}H-nmr(d$_6$-DMSO): δ11.7 (br s, 1H), 9.26 (s, 1H); 8.96 (d, 1H, J = 6 Hz); 7.64 (d, 1H, J = 6 Hz); 5.0 (br s, 1H); 4.6 (m, 1H); 1.7-2.5 (br m, 6H). ir (KBr): 3400 (br), 2750 (br), 1712 (s), 1690 (s) cm^{-1}. ms (75 eV): 233 (M + 1, 2%), 232 (M$^+$, 2%), 214 (3%), 204 (97%), 199 (12%), 189 (8%), 175 (100%), 157 (31%), 131 (29%). ^{13}C-nmr (d$_6$-DMSO): ppm 177.1, 163.7, 155.3, 154.0, 148,6, 120.7, 119.5, 72.7, 51.4, 47.3, 40.3, 35.4. Elemental analysis. Calcd.: C, 62.06; H, 5.21; N, 12.06; Found: C, 61.83; H, 5.22; N, 11.95.
9. Compound 5: ^{1}H-nmr (CDCl$_3$): δ8.93 (s, 1H); 8.84 (d, 1H, J = 5 Hz); 7.38 (d, 1H, J = 5 Hz); 4.24 (q, 2H, J = 7 Hz); 3.44 (d, 1H, J = 17 Hz); 3.1 (m, 1H); 2.3-2.7 (m, 4H); 1.24 (t, 3H, J = 7 Hz). ir (neat): 2980, 2220, 1745 (br, s), 1590 cm^{-1}. ms (75 eV): 259 (M + 1, 4%), 258 (M$^+$, 4%), 230 (15%), 217 (5%), 202 (8%), 185 (100%), 178 (13%), 157 (38%),
10. Compound 6: ^{1}H-nmr (CDCl$_3$): δ8.83 (s, 1H); 8.75 (d, 1H, J = 5 Hz); 7.80 (d, 2H, J = 8 Hz); 7.39 (d, 1H, J = 5 Hz); 7.37 (d, 2H, J = 8 Hz); 5.06 (m, 1H); 4.18 (q, 2H, J = 7 Hz); 2.8-3.2 (m, 2H); 2.47 (s, 3H); 2.0-2.2 (m, 4H); 1.21 (t, 3H, J = 7 Hz). ir (KBr): 2980, 2220, 1736 (s), 1688, 1361, 1238, 1179 cm^{-1}.
11. G. W. Kirby and S. R. Massey, J. Chem. Soc. (C), 3047 (1971).
12. Compound 3b: ^{1}H-nmr (CDCl$_3$): δ8.92 (s, 1H), 8.74 (d, 1H, J = 6 Hz); 7.57 (d, 1H, 5 = 6 Hz); 4.60 (m, 1H); 4.16 (q, 2H, J = 7 Hz): 3.05 (d of d, 1H, J = 14, 5 Hz); 1.6-2.7 (br m, 6 H), 1.19 (t, 3H, J = 7 Hz).

ir ($CHCl_3$): 3400 (br); 2960, 2220, 1731 (s), 1586, 1235 cm^{-1}. ms (75 eV): 260 (M^{+}, 3%), 242 (2%), 231 (2%), 213 (11%), 202 (29%), 185 (29%), 168 (100%), 156 (23%).

13. Compound 1: ^{1}H-nmr (d_6-DMSO): δ11.5 (br s, 1H); 9.08 (s, 1H); 8.83 (d, 1H, J = 5 Hz); 7.90 (d, 1H, J = 5 Hz), 4.52 (m, 1H, w 1/2 = 12 Hz); 3.5 (br s, 1H); 2.67 (d of d, 1H, J = 14, 5 Hz); 1.7-2.3 (br m, 5H). ^{13}C-nmr (d_6-DMSO): ppm 177.2, 163.7, 155.9, 153.9, 148.3, 121.8, 119.7, 72.6, 52.0, 48.6, 42.9, 36.3. ir (KBr): 3490 (br), 2980, 2280 (br), 1708 (sh), 1690 (s), 1660, 1448, 1279 cm^{-1}. ms (75 eV): 232 (M^{+}, 21%) 214 (12%), 206 (8%), 204 (7%), 199 (6%), 188 (40%), 175 (100%), 171 (33%) 160 (30%), 147 (40%). Elemental analysis. Calcd.: C, 62.06; H, 5.21; N, 12.06; Found: C, 61.84; H, 5.47; N, 12.07.

14. An independent synthesis of (±)-sesbanine by an alternative route has recently been accomplished by J. Clardy and S. Donovan at Cornell University (private communication).

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