Total Synthesis of the Alkaloid (±)-Deoxyaspidodispermine

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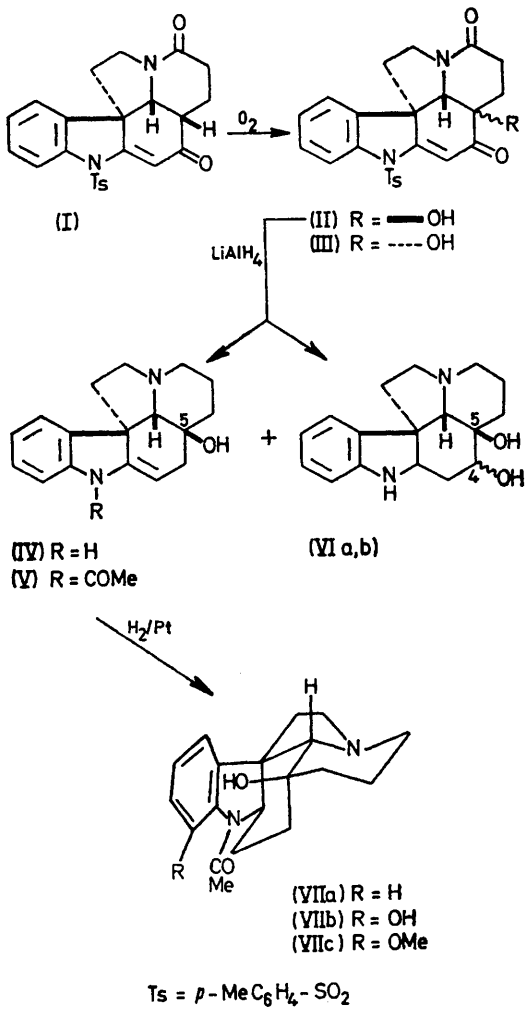
Summary (±)-Deoxyaspidodispermine, whose (−)-form was isolated from *Aspidosperma dispermum* and demonstrated as formula (VIIa) of a unique constitution among *Aspidosperma* alkaloids, was first synthesized under stereocontrol to directly prove the correctness of the proposed structure by chemical means.

(−)-DEOXYASPIDODISPERMINE was isolated together with (+)-aspidodispermine (VIIb) from *Aspidosperma dispermum* by Djerassi,[1] who suggested it had structure (VIIa) mainly by mass spectrometry. This initial proposal was later confirmed by *X*-ray analysis of (−)-17-*O*-methylaspidodispermine N^b-hydrobromide (VIIc, HBr).[2] This alkaloid, along with aspidodispermine (VIIb), occupies a unique position among a variety of *Aspidosperma* alkaloids, inasmuch as they possess a hydroxy-group instead of the two-carbon side chain at C-5 in the aspidospermine skeleton. We now report the first stereo-controlled total synthesis of (±)-deoxyaspidodispermine (VIIa) to prove the correctness of the proposed structure by chemical means.

Compound (I) (C/D ring junction *cis*, m.p. 240—241°) was prepared from 2-hydroxytryptamine and its stereochemistry fully elucidated.[3] It was treated with oxygen at −78° for 2 h in a solution of NaH in Bu^tOH and dimethylformamide containing triethyl phosphite,[4] and chromatography of the crude product on alumina gave the two α-ketols (II)† (C/D ring junction *cis*), needles (51%), m.p. 247—248° (decomp.), M^+ 450, and (III)† (C/D ring junction *trans*), prisms (5%), m.p. 277° (decomp.), M^+ 450. The orientation of the hydroxy-group at C-5 in the major product (II) should be the same as that of the hydrogen in substrate (I) which has been substituted, in agreement with known results;[4] this is also compatible with both kinetic and thermodynamic control of the present reaction. The assignment of structure (III) to the minor product is assumed by comparison of spectral data with those of major product. The ketol (II) was refluxed with $LiAlH_4$ in 1,2-dimethoxyethane for 1 h to give (IV) as a viscous



† Structure confirmed by elemental analysis, and i.r., u.v., and n.m.r. data.

oil (31%), M^+ 268, along with two 4,5-dihydroxy-isomers, (VIa), needles (28%), m.p. 240°, M^+286, and (VIb), prisms (29%), m.p. 174—177°, M^+ 286, as byproducts after chromatography on alumina. Acetylation of (IV) with acetyl chloride in 5% NaOH gave the *N*-acetyl derivative (V) as a viscous oil, M^+ 310, [picrate, m.p. 215—216° (decomp.)], which was hydrogenated at 56 p.s.i. with Adams' catalyst in ethanol containing dilute HCl. Preparative t.l.c. of the hydrogenated product gave a single spot due to a white amorphous solid (picrate, m.p. 239—240°) which showed a quartet (1H, 2-H) at δ 4·04, characteristic of the aspidospermine alkaloids,[5] and other signals with the same chemical shifts as described by Djerassi for the natural (−)-deoxyaspidodispermine (VIIa).[1] Furthermore, the mass [M^+, *m/e* 312, 140, and 112 (100%)] and u.v. spectra and R_f value on t.l.c. were identical with those of the natural product, and the i.r. spectrum of the natural product in chloroform solution was superimposable on that of synthetic (±)-deoxyaspidodispermine (VIIa), thus establishing the identity of the samples.

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[1] M. Ikeda and C. Djerassi, *Tetrahedron Letters*, 1968, 5837.
[2] N. C. Ling and C. Djerassi, *Tetrahedron Letters*, 1970, 3015.
[3] T. Ohnuma, T. Oishi, and Y. Ban, *J.C.S. Chem. Comm.*, 1973, 301; Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo, and T. Oishi, *Tetrahedron Letters*, 1972, 5023; Y. Ban, Y. Sendo, M. Nagai, and T. Oishi, *ibid.*, p. 5027; T. Oishi, M. Nagai, and Y. Ban, *ibid.*, 1968, 491; T. Oishi, M. Ochiai, M. Nagai, and Y. Ban, *ibid.*, p. 497.
[4] J. N. Gardner, F. E. Carlson, and O. Gnoj, *J. Org. Chem.*, 1968, 33, 3294.
[5] B. Gilbert, 'The Alkaloids, Chemistry and Physiology,' vol. VIII, ed. R. H. F. Manske, Academic Press, New York, 1965, p. 371.