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A TOTAL SYNTHESIS OF (±)-OBSCURINERVIDINE

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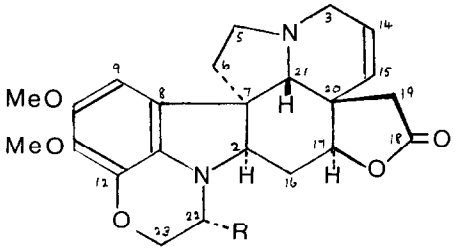
The first total synthesis of (±)-obscurinervidine is reported.

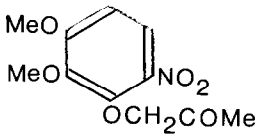
Obscurinervidine (1) and obscurinervine (2) belong to a relatively small group of heptacyclic Aspidosperma alkaloids which occur in A. obscurinervium Azambuja and A. neblinae Monachino.[1a] The structure and relative configuration of these alkaloids, elucidated in 1964,[1a] were confirmed in 1971 by the X-ray crystal structure determination of obscurinervine hydrobromide;[1b] the absolute configuration rests on the partial synthesis of dihydro-obscurinervidinol from depropionylaspidoalbine.[1a]

We now report the first total synthesis of (±)-obscurinervidine.

Condensation of the potassium salt of 2,3-dimethoxy-6-nitrophenol[2] with chloroacetone gave 2,3-dimethoxy-6-nitrophenacetol (3),[3] m.p. 55-56.5°, which on hydrogenation (H_2, Pd/C) and concomitant cyclization gave 7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (4), m.p. 71-71.5°. Nitrosation of (4), followed by reduction ($LiAlH_4$), gave the N-amino derivative (5), m.p. 75.5-76.5°. Attempted Fischer indolization of the isopropylidene derivative of (5) proved unsatisfactory, while the analogous cyclization of the methyl pyruvate derivative of (5) gave only 37% of 8,9-dimethoxy-5-methoxycarbonyl-3-methyl-3,4-dihydropyrrolo(1,2,3-de)-1,4-benzoxazine (6), m.p. 91-92°, which gave the corresponding carboxylic acid, m.p. 218-219.5°, on hydrolysis. Since the reduction of



Obscurinervidine (1); R = Me
Obscurinervine (2); R = Et



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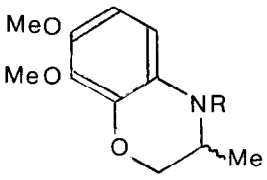
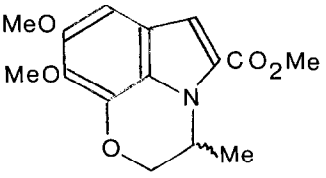


4; R = H
5; R = NH_2



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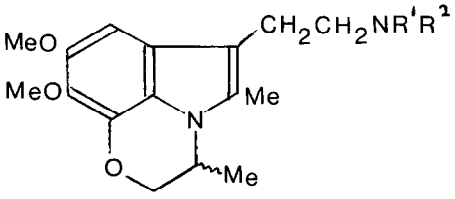
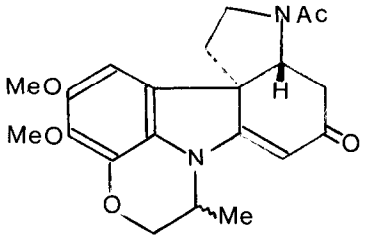


7; R^1R^2 = phthaloyl
8; R^1R^2 = H_2
9; R^1 = H; R^2 = $CH{=}C(CO_2Et)_2$



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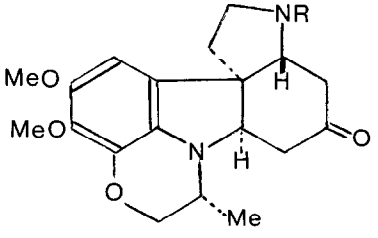
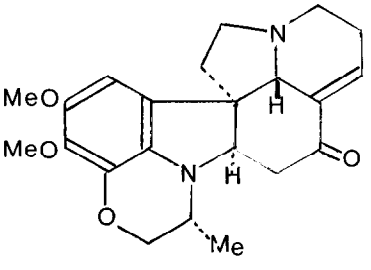


11; R = Ac
12; R = H



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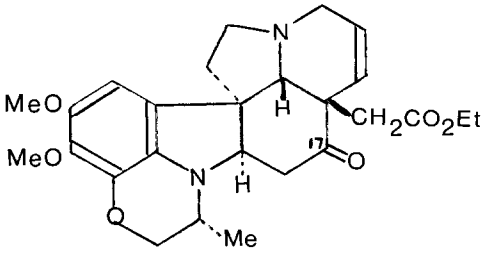

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the ester function in (6) to a methyl group could not be carried out efficiently, this route to the desired pyrrolobenzoxazine derivative was abandoned.

An attempt to prepare the tryptamine analogue (8) directly by the Grandberg synthesis[4] from (5) and 5-chloropentan-2-one also failed. However, Fischer cyclization of the derivative of (5) with 5-phthalimido-2-pentanone in glacial acetic acid gave 67% of 8,9-dimethoxy-3,5-dimethyl-6-(2-phthalimidoethyl)-3,4-dihydropyrrolo(1,2,3-de)-1,4-benzoxazine (7), m.p. 156.5-157.5°, which on hydrazinolysis gave the non-crystalline tryptamine analogue (8) (picrate, m.p. 214-214.5°). Condensation of (8) with diethyl ethoxymethylenemalonate, and Takano cyclization[5] of the enaminoester (9) so obtained (AcOH, Ac_2O, reflux, 4 days) afforded the pentacyclic enaminoketone (10) as a non-crystalline mixture of two racemates. Reduction of (10) (lithium-t-butanol-liquid ammonia) then gave a mixture of racemates, from which the desired stereoisomer[6] [(±)-11] (60%), m.p. 203.5-204.5°, was separated by fractional crystallization from ethanol.

Removal of the amide function in (11) by reaction with triethyloxonium tetrafluoroborate followed by aqueous sodium bicarbonate gave the secondary amine (12), which was converted into the non-crystalline hexacyclic enone (13) by Michael addition of acrolein, internal aldolization, and dehydration (CH_2=CH.CHO, NaOMe, then $MeSO_2Cl$ - pyridine).[7] Alkylation of the enone (13) by ethyl bromoacetate - potassium t-butoxide gave the ketoester (14) in modest (39%) yield. Finally, reduction ($NaBH_4$) of the ketone grouping in (14) and concomitant lactonization of the appropriate epimeric hydroxyester gave 55% of (±)-obscurinervidine (1), m.p. 209-210°, whose mass and ^1H n.m.r. spectra[8,9] were identical in virtually every detail with those of a sample of authentic (-)-obscurinervidine.[10] The reduction was not stereospecific, and a minor product was the 17α-hydroxyester derived from (14).

Acknowledgement: J.P.B. thanks the S.E.R.C. for a maintenance award.

References and notes

1. (a) K.S. Brown and C. Djerassi, J.Am.Chem.Soc., 1964, 86, 2451;
(b) J. Kahrl, T. Gebreyesus, and C. Djerassi, Tetrahedron Lett., 1971, 2527.

2. W. Baker and H.A. Smith, J.Chem.Soc., 1931, 2542. We thank Mr. I. Marlow for assistance in the preparation of this starting material.

3. Satisfactory infrared, n.m.r., microanalytical, and mass spectral data were obtained on all intermediates described in this communication.

4. B. Robinson: The Fischer Indole Synthesis. Wiley, New York, 1982, p. 487.

5. S. Takano, K. Shishido, M. Sato, and K. Ogasawara, Heterocycles, 1977, 6, 1699.

6. N.m.r. data for (±)-11 (numbering as in 1): δ ($CDCl_3$, 400 MHz) 6.30 (1H, s, C-9H), 4.18 (1H, dd, J 3.5, 3.0 Hz, C-2H),4.16 (1H, dd, J 3.0, 11.0 Hz, C-23H), 3.97 (1H, t, J 11 Hz, C-23H), 3.87 (3H, s, OMe), 3.84 (1H, m, C-5H), 3.80 (3H, s, OMe), 3.73 (1H, m, C-21H), 3.70 (1H, m, C-5H), 3.37 (1H, dd, J 3.5, 18.0 Hz, C-16H), 2.98 (1H, m, C-22H), 2.92 (1H, dd, J 3.0, 17.0 Hz, C-20H), 2.55 (1H, dd, J 3.0, 18.0 Hz, C-16H), 2.55 (1H, m, C-6H), 2.09 (3H, s, NAc), 2.06 (1H, m, C-6H), 1.20 (3H, d, J 6.4 Hz, C-24H); δ ($CDCl_3$) 207.70 (C-17), 169.94 (C-3), 148.71 (C-11), 137.11 (C-12), 136.84 (C-13), 132.67 (C-10), 124.00 (C-8), 99.14 (C-9), 72.92 (C-23), 72.43 (C-2), 63.71 (C-21), 60.95, 57.21 (2 x OMe), 54.44 (C-7), 52.66 (C-22), 47.56 (C-5), 43.28 (C-6), 38.73, 37.65 (C-20, C-16), 23.24 (C-14), and 16.79 ppm (C-24).

7. We are greatly indebted to Dr. G. Büchi (M.I.T.) for experimental details relating to the analogous annulation procedures used in the synthesis of vindoline and vindorosine.

8. N.m.r. data for (±)-1; δ ($CDCl_3$, 400 MHz) 6.36 (1H, s, C-9H), 5.725 (2H, m, C-14H and C-15H), 4.55 (1H, dd, J 5,0, 1.0 Hz, C-17H), 4.196 (1H, dd, J 1.5, 11.0 Hz, C-23H), 4.152 (1H, dd, J 2.0, 11.0 Hz, C-23H), 3.90, 3.85 (6H, 2s, 2 x OMe), 3.47 (2H, m, C-22H and C-3H), 3.28 (1H, m, C-2H), 3.25 (1H, s, C-21H), 2.73 (1H, br. d, J 16.0 Hz, C-3H), 2.56 (1H, d, J 18.5 Hz, C-19H), 2,33, 2.23 (3H, m, and 2H, m, C-16H, C-5H, C-6H), 2.09 (1H, d, J 18.5 Hz, C-19H), 1.80 (1H, m, C-6H), 1.06 (3H, d, J 6.4 Hz, C-24H); δ ($CDCl_3$) 176.01 (C-18), 147.84 (C-11), 137.33 (C-12), 135.60 (C-13), 133.76, 122.92 (C-14, C-15), 130.51 (C-10), 129.42 (C-8), 100.82 (C-9), 81.31 (C-17), 71.94 (C-23), 69.67, 65.01 (C-2, C-21), 61.00 (MeO), 57.75 (MeO), 54.28, 52.17 (C-3, C-5), 52.25 (C-7), 44.53 (C-22), 40.68 (C-20), 39.33, 38.68 (C-6, C-19), 23.84 (C-16), and 10.51 ppm (C-24).

9. We thank Dr. B.E. Mann (University of Sheffield for the 400 MHz n.m.r. spectra.

10. We thank Dr. C. Djerassi (Stanford University) for the generous gift of a sample of authentic (-)-obscurinervidine.

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