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TOTAL SYNTHESIS OF HEPTACYCLIC *ASPIDOSPERMA* ALKALOIDS. PART II. SYNTHESIS OF (±)-OBSCURINERVIDINE.[1]

James P. Brennan and J. Edwin Saxton*

Department of Organic Chemistry, The University, Leeds LS2 9JT.

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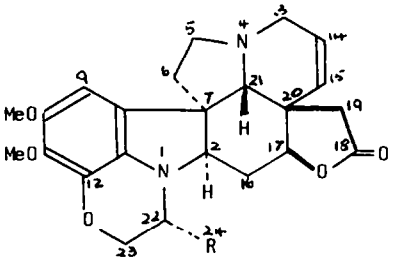
Summary: The first total synthesis of (±)-obscurinervidine, in 16 stages from pyrogallol, is described.

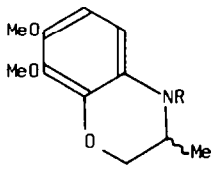
Obscurinervidine (1a) and obscurinervine (1b) belong to a relatively small group of heptacyclic *Aspidosperma* alkaloids which occur in *A. obscurinervium* Azambuja and *A. neblinae* Monachino.[2a] The structure and relative configuration of these alkaloids, elucidated in 1964,[2a] were confirmed in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



Obscurinervidine (1a) R = Me

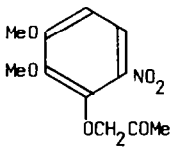
Obscurinervine (1b) R = Et

The construction of the obscurinervidine molecule (1a) by the route described in our earlier communication[3] requires, as essential starting material, the benzoxazine derivative (2), which we prepared from pyrogallol *via* partial methylation[4,5] to 2,3-dimethoxyphenol, followed by nitration[6] to 2,3-dimethoxy-6-nitrophenol. Condensation of the potassium salt of this nitrophenol with chloroacetone gave 2,3-dimethoxy-6-nitrophenacetol (3), which on hydrogenation and concomitant cyclization gave the required 7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (2). Nitrosation of (2), followed by reduction (by lithium aluminium hydride) gave the corresponding N-amino compound (4), from which it was necessary to prepare an appropriately substituted pyrrolobenzoxazine derivative.

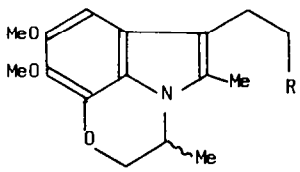


(2) R = H

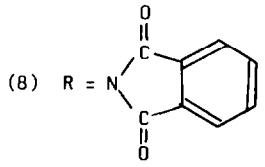
(4) R = NH_2



(3)



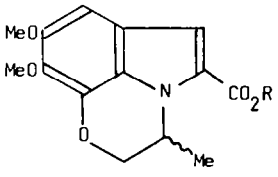
(5) R = NH_2



(8) R = N

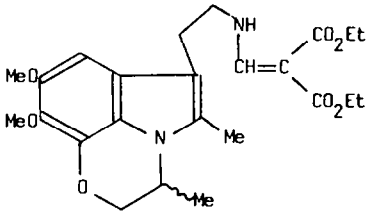
As a result of our experience in the model series[3] we first attempted to prepare the tryptamine analogue(5) by the Grandberg condensation-cyclization of the aminobenzoxazine derivative (4) with 5-chloro-2-pentanone, but to our disappointment no trace of (5) could be obtained under a variety of experimental conditions.

Concurrently with these experiments the Fischer indolization of the methyl pyruvate derivative of (4) was being studied. This gave the pyrrolobenzoxazine ester (6), but only in 37% yield; hydrolysis then gave the corresponding carboxylic acid (7). However, this approach was not further pursued, because it was found that the Fischer indolization of the derivative of (4) with 5-phthalimido-2-pentanone in glacial acetic acid gave the phthalimido derivative (8) of the desired tryptamine in acceptable (61%) yield. Hydrazinolysis then gave the tryptamine analogue (5).

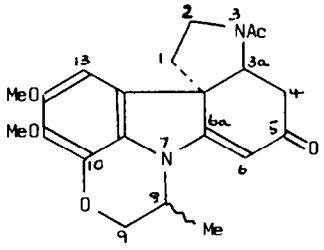


(6) R = Me

(7) R = H



(9)

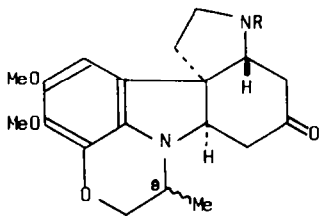


(10)

(10a); 8α-Me

Condensation of this tryptamine analogue (5) with diethyl ethoxymethylene-malonate in refluxing ethanol gave an essentially quantitative yield of the vinylogous urethane (9), which was cyclised by heating in acetic anhydride and acetic acid for four days. The product, the pentacyclic vinylogous amide (10), was isolated in 30-35% yield as an inseparable non-crystalline mixture of two racemates. Reduction of the double bond was then achieved with lithium-t-butanol in liquid ammonia to give an oily mixture of racemates, from which the desired racemate (11a) was isolated in 60% yield by fractional crystallisation from ethanol.

It had been anticipated that reduction of a vinylogous amide of the stereochemistry depicted in (10) would give exclusively a cis B/C ring junction, as observed in the model series.[3] However, the isolation of 60% of the pure racemate of (11a) from the reduction of the epimeric mixture of (10) was not expected, and it clearly indicates a preference in the Takano cyclization of (9) for a transition state leading to the α-methyl epimer (10a), a preference that was not predictable from a study of molecular models. Owing to uncertainty in the conformations adopted by the epimers (11) and the exact dihedral angles between groups, particularly between the C-8 methyl group and the C-6a hydrogen, the complete stereochemistry of the crystalline epimers of (11) could not be unequivocally deduced. The synthesis was therefore pursued with the pure, crystalline epimer, and its ultimate conversion into (±)-obscurinervidine (1a) is ample proof of the stereochemistry shown in (11a).

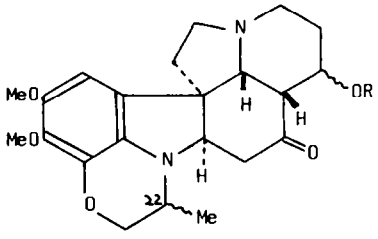


(11a), R = Ac; 8α-Me

(11b), R = Ac: 8β-Me

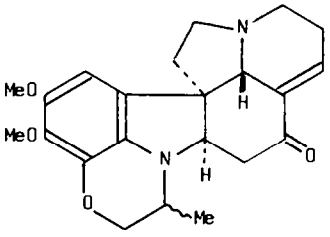
(12) R = H

(12a), R = H; 8α-Me



(13) R = Me

(15) R = H; α-Me at C-22



(14)

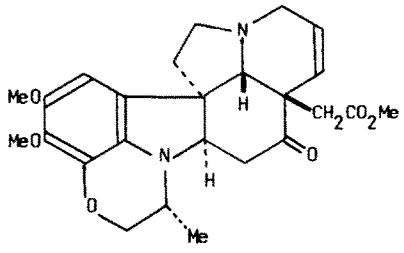
(14a), α-Me at C-22

The first stage in this final sequence of reactions involved the removal of the N-acetyl group, which was achieved by means of triethyloxonium tetrafluoroborate and sodium carbonate, followed by aqueous work-up. As in the model series[3] our first attempt to add ring D to the secondary aminoketone (12) using acrolein in the presence of sodium methoxide[7] led to a product (13) in which the elements of methanol had been added to the desired enone (14).* When milder conditions[8] were employed on the aminoketone derived from (11a) a mixture of ketols (15) was obtained, which were not purified, but immediately dehydrated by means of methane-

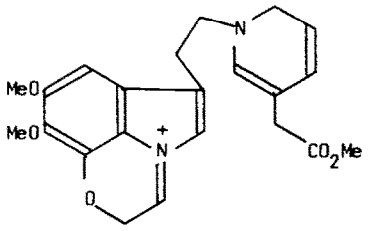
*In obscurinervidine (1a) and all the hexacyclic compounds reported in this paper the biogenetic numbering of the ring system is used.

sulphonyl chloride in pyridine to the enone (14a). Chromatography of the complex product mixture afforded the pure enone (14a) in 32% overall yield from the amino-ketone (12a).

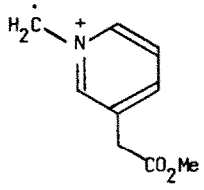
The penultimate stage of the synthesis involved stereospecific alkylation of the enone (14a) by means of methyl bromoacetate-potassium t-butoxide, which gave the ketoester (16) in a yield (not optimised) of 39%. This key ester gave carbonyl absorptions at 1732 (ester C=O) and 1711 cm^{-1} (ketone C=O) in the i.r. spectrum, and the 14,15-double bond gave rise to an absorption at 1615 cm^{-1}. The ^{13}C n.m.r. spectrum gave a clear indication that it was a single stereoisomer, which must have the stereochemistry shown in (16), since approach to C-20 via the α-face of the dienolate anion derived from the enone (14a) is severely hindered by the two carbon atoms (C-5 and C-6) of the ethanamine bridge. The mass spectrum was also consistent with this formulation. Reverse Diels-Alder fragmentation of ring C, characteristic of cis C/D compounds, with loss of ketene and also the methyl group (C-24), gives an ion (17) at m/z 397, which further cleaves at the benzylic position and aromatises with loss of hydrogen to give an ion (18) at m/z 165. Similar fragmentation of the parent molecular ion with retention of C-24 gives the ion (19) at m/z 246. Finally, loss of the elements of methyl acetate by a McLafferty mechanism gives the ion (20) at m/z 380.



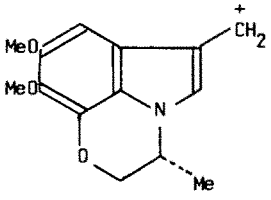
(16)



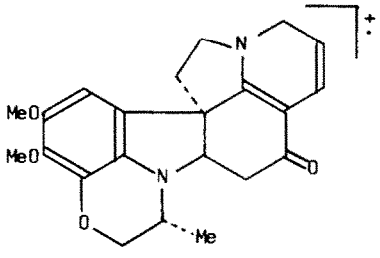
(17) m/z 397



(18) m/z 165



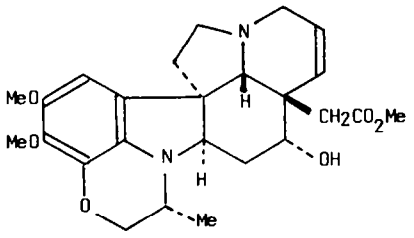
(19) m/z 246



(20) m/z 380

The synthesis of obscurinervidine was eventually completed by reduction of the ketoester (16), followed by lactonisation of the hydroxy ester so produced. Initially bulky reducing agents were employed in order to obtain exclusively, if possible, the 17β-hydroxyester required for lactonisation. However, in contrast to earlier experience in the vindoline series,[7] such reagents failed; even after a three-day reaction period no reduction was observed with lithium trisiamylboro-hydride or lithium tri-sec.-butylborohydride. Reduction by means of sodium borohydride was, as expected, not stereospecific but fortunately the C-17 β-hydroxyester lactonised spontaneously, and after 16 h the product was separated

into (±)-obscurinervidine (1a) (55%) and the C-17 α-hydroxyester (21) (38% yield). The i.r., mass and 400 MHz proton n.m.r. spectra of the synthetic (±)-obscurinervidine were identical in every detail with those of authentic (-)-obscurinervidine.[9,10]



(21)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultraviolet absorption spectra were recorded on either a Pye-Unicam SP800A or a PU8800 spectrometer. Infrared spectra were recorded on either a Perkin-Elmer 207 or a 1420 spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a Perkin-Elmer R32 instrument (^{1}H, 90 MHz), a Jeol FX90Q F.T. spectrometer (^{1}H, 90 MHz and ^{13}C, 22.5 MHz), or a Bruker WH400 spectrometer (^{1}H, 400 MHz). Solutions in deuteriochloroform with tetramethylsilane as internal standard were used unless otherwise stated. Chemical shifts are quoted in p.p.m. downfield from TMS. Mass spectra were recorded on a Kratos MS25 instrument. Accurate mass measurements were determined on an A.E.I.-Kratos MS902/50 instrument.

2,3-Dimethoxy-6-nitrophenacetol (3). — 2,3-Dimethoxy-6-nitrophenol (30.7 g, 0.15 mol)[5] was suspended in dry methanol (500 ml) and potassium hydroxide pellets (8.6 g, 0.15 mol) were slowly added. The mixture was heated on a steam bath for 45 min then cooled. The solvent was removed under reduced pressure to give the potassium salt of 2,3-dimethoxy-6-nitrophenol (38.4 g, 94%) which was recrystallised from acetone and obtained as orange prisms, m.p. 294-296°C.

To a slurry of this potassium salt (34.3 g, 0.14 mol) in dry acetone (200 ml) in an atmosphere of nitrogen freshly distilled chloroacetone (53.5 g, 0.58 mol) was added dropwise over 1 h with stirring. The mixture was heated at reflux for 16 h, then allowed to cool slightly after which decolourising charcoal (2.5 g) was added, and heating at reflux continued for a further 10 min. After the solution had cooled it was filtered through a pad of Celite and then concentrated under reduced pressure which gave 2,3-dimethoxy-6-nitrophenacetol (3) (45.0 g, 82%), which was recrystallised from absolute ethanol and obtained as pale green prisms, m.p. 55-56°C (Found: C, 51.95; H, 5.05; N, 5.2%, M^+, 255.07407. $C_{11}H_{13}NO_6$ requires C, 51.75; H, 5.10; N, 5.5%, M, 255.074279); $\nu_{max.}$ (Nujol) 1726, 1595, 1576, 1515, 1100, 825, 810, 740 cm^{-1}; δ_H 7.72 (1H, d, J 10 Hz), 6.75 (1H, d, J 10 Hz), 4.69 (2H, s), 3.96 (3H, s), 3.87 (3H, s), 2.32 (3H, s); $\lambda_{max.}$ (EtOH) 206,

215, 238, 296 nm; m/z (%) 255 (M^+, 6), 183 (16), 166 (33), 139 (10), 109 (11), 96 (14), 80 (22), 69 (19), 43 (100).

7,8-Dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (2). — A solution of 2,3-dimethoxy-6-nitrophenacetol (44.5 g, 0.17 mol) in absolute ethanol (750 ml) was hydrogenated at a pressure of 30 atmospheres and at 80-90°C for 90 min, employing 5% palladium on carbon (4.5 g) as catalyst. The reaction mixture was cooled, the catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure. The resulting oil was distilled under reduced pressure to give a clear oil which crystallised on cooling. Recrystallisation from ethanol gave 7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (2) 33.5 g, 92%) as colourless prisms, m.p. 71-71.5°C (Found: C, 63.35; H, 7.2; N, 6.9%, M^+, 209.1053. $C_{11}H_{15}NO_3$ requires C, 63.15; H, 7.2; N, 6.7%, M, 209.105186); $\nu_{max.}$ (Nujol) 3330, 1495, 1300, 1258, 1235, 1095, 790, 780 cm^{-1}; δ_H 6.36 (1H, d, J 9 Hz), 6.28 (1H, d, J 9 Hz), 4.26 (2H, dd, J 2.7, 9 Hz), 3.85 (3H, s), 3.76 (3H, s), 3.48 (1H, m), 3.46 (1H, br. s, exchanges with D_2O), 1.12 (3H, d, J 6 Hz); $\lambda_{max.}$ (EtOH) 215, 245, 300 nm; m/z (%) 209 (M^+, 100), 194 (91), 166 (9), 151 (12), 136 (7).

N-Nitroso-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine. — A solution of sodium nitrite (8.5 g, 0.12 mol) in water (40 ml) was added dropwise to a stirred solution of 7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (25.75 g, 0.12 mol) in concentrated hydrochloric acid (28.6 ml) while maintaining the reaction mixture temperature below 5°C. The mixture was stirred for 30 min, after which the precipitate which had formed was collected by filtration, washed with a minimum of ice-cold water, and dried over silica gel in vacuo. Recrystallation from ethanol then gave N-nitroso-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (26.9 g, 92%) as a pale yellow solid, m.p. 94-95.5°C (Found: C, 55.6; H, 5.9; N, 11.8%, M^+, 238.09523. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.76%, M, 238.095349); $\nu_{max.}$ (Nujol) 1605, 1500, 1440, 1115, 810, 770, 760, 735, 694 cm^{-1}; δ_H 7.76 (1H, d, J 9 Hz), 6.68 (1H, d, J 9 Hz), 5.16 (1H, ddq, J 1.5, 3, 8.5 Hz), 4.36 (1H, dd, J 1.5, 13 Hz), 4.02 (1H, dd, J 3, 13 Hz), 3.92 (3H, s), 3.90 (3H, s), 1.22 (3H, d, J 8.5 Hz); $\lambda_{max.}$ (EtOH) 206, 220, 252, 324 nm; m/z (%) (50 eV) no M^+ observed, 209 (78), 194 (79), 151 (16), 140 (26), 94 (28), 80 (37), 69 (100), 53 (60).

N-Amino-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (4). — To a solution of N-nitroso-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (26.6 g, 0.11 mol) in dry ether (600 ml) and dry tetrahydrofuran (100 ml) a solution of

lithium aluminium hydride (4.40 g, 0.11 mol) in dry ether (500 ml) was added dropwise with stirring, while maintaining the temperature below 10°C. The mixture was stirred at 5-10°C for a further 2 h after which the excess of lithium aluminium hydride was decomposed by the addition of 30% aqueous sodium hydroxide solution (100 ml). The aqueous phase was then extracted with ether (3 x 100 ml). The combined organic fractions were washed with water (200 ml), saturated brine (200 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave N-amino-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (4) (23.0 g, 92%), which was recrystallised from ethanol and obtained as yellow prisms, m.p. 75.5-76.5°C (Found: C, 58.8; H, 7.2; N, 12.55%, M^+, 224.11603. $C_{11}H_{16}N_2O_3$ requires C, 58.91; H, 7.19; N, 12.5%, M, 224.116084); $\nu_{max.}$ (Nujol) 3434, 1610, 1500, 1100, 1050, 890, 782, 731 cm^{-1}; δ_H 6.90 (1H, d, J 9 Hz), 6.45 (1H, d, J 9 Hz), 4.15 (2H, m), 3.87 (3H, s), 3.82 (3H, s), 3.5 (2H, br. s, exchanges with D_2O), 3.35 (1H, m), 1.16 (3H, d, J 7 Hz); $\lambda_{max.}$ ($\log_{10}$ ε) (MeOH) 213 (4.34), 245.5 (3.67), 292 nm (3.20); m/z (%) 224 (M^+, 100), 209 (65), 194 (35), 165 (11), 148 (11), 136 (22), 122 (9), 94 (14), 80 (24), 69 (27).

8,9-Dimethoxy-5-carbomethoxy-3-methyl-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine. — To a solution of N-amino-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (5.0 g, 0.023 mol) in ethanol (100 ml) methyl pyruvate (2.5 g, 0.025 mol) was added. The solution was stirred for 1 h and then concentrated under reduced pressure; this gave a red oil which was slowly heated to 130°C under reduced pressure (10-15 mmHg) for 1 h. The product was then allowed to distil slowly from the reaction mixture. The crude distillate was purified by chromatography on Kieselgel G (100 g), using benzene/ether (15%) as eluent. This gave 8,9-dimethoxy-5-carbomethoxy-3-methyl-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (2.40 g, 37%), which was recrystallised from dichloromethane/hexane, and obtained as colourless prisms, m.p. 91-92°C (Found: C, 61.55; H, 5.9; N, 4.7%, M^+, 291.11068. $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.9; N, 4.8%, M, 291.110664); $\nu_{max.}$ (Nujol) 1700, 1592, 1526, 1490, 1230, 1114, 1075, 1033, 981, 840, 819, 769, 710 cm^{-1}; δ_H 7.05 (1H, s), 6.64 (1H, s), 5.12 (1H, m), 4.36 (2H, m), 3.96 (3H, s), 3.87 (3H, s), 3.86 (3H, s), 1.42 (3H, d, J 10 Hz); $\lambda_{max.}$ $\log_{10}$ ε) (MeOH) 205 (4.32), 235 (4.16), 301 nm (4.20); m/z (%) 291 (M^+, 100) 276 (70), 244 (9), 216 (15), 204 (11), 160 (8), 133 (9), 104 (7), 73 (58), 59 (6).

8,9-Dimethoxy-3-methyl-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine-5-carboxylic acid (7). — A suspension of 8,9-dimethoxy-5-carbomethoxy-3-methyl-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (2.0 g, 6.9 mmol) in 2M sodium hydroxide solution (20 ml) was heated at reflux for 2 h, then cooled to 0°C. The

mixture was acidified by the addition of concentrated hydrochloric acid, then filtered. The solid was washed with ice-cold water and dried *in vacuo* over silica gel. Recrystallisation from ethanol gave 8,9-dimethoxy-3-methyl-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine-5-carboxylic acid (1.90 g, 100%) as colourless prisms, m.p. 218-219°C (Found: C, 60.35; H, 5.35; N, 4.9%, M^+, 277.09461. $C_{14}H_{15}NO_5$ requires C, 60.65; H, 5.45; N, 5.05%, M, 277.095014); $\nu_{max.}$ (Nujol) 2800-2300, 1660, 1590, 1532, 1497, 1255, 1230, 1116, 982, 825, 754, 640 cm^{-1}; δ_H (C_6D_6) 7.32 (1H, s), 6.74 (1H, s), 5.17 (1H, m), 4.15 (2H, m), 3.88 (3H, s), 3.69 (3H, s), 1.33 (3H, d, J 7.8 Hz); m/z (%) 277 (M^+, 100), 262 (64), 244 (4), 223 (11), 218 (12), 204 (18), 176 (5), 160 (6), 146 (4), 133 (3).

8,9-Dimethoxy-3,5-dimethyl-6-(2-phthalimidoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (8). — To N-amino-7,8-dimethoxy-3-methyl-3,4-dihydro-2H-1,4-benzoxazine (0.48 g, 2.2 mmol) in glacial acetic acid (20 ml) 5-phthalimido-2-pentanone (0.5 g, (2.2 mmol) was added. The mixture was heated at reflux for 4 h, then cooled. Water (20 ml) was added and the mixture was extracted with ether (3 x 60 ml). The combined ethereal layers were washed with water (2 x 30 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (100 g), using benzene/ether (20%) as eluent. This gave 8,9-dimethoxy-3,5-dimethyl-6-(2-phthalimidoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (8) (0.56 g, 61%), which was recrystallised from ethanol/ether, and obtained as pale green needles, m.p. 156.5-157.5°C (Found: 68.7; H, 5.7; N, 6.75%, M^+, 420.16982. $C_{24}H_{24}N_2O_5$ requires C, 68.55; H, 5.75; N, 6.6%, M, 420.168510); $\nu_{max.}$ (Nujol) 1712, 1598, 1120, 873, 808, 800, 728, 720 cm^{-1}; δ_H 7.57 (4H, m), 6.64 (1H, s), 4.30 (3H, m), 3.88 (3H, s), 3.83 (3H, s), 3.75 (2H, m), 2.98 (2H, m), 2.34 (3H, s), 1.34 (3H, d, J 6.3 Hz); $\lambda_{max.}$ ($\log_{10}$ ϵ) (MeOH) 213 (4.77), 270 (3.98), 296 nm (3.80); m/z (%) 420 (M^+, 0.3), 418 (27), 259 (100), 174 (12), 159 (110), 104 (6), 77 (9), 44 (18).

8,9-Dimethoxy-3,5-dimethyl-6-(2-aminoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (5). — To 8,9-dimethoxy-3,5-dimethyl-6-(2-phthalimidoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (12.6 g, 0.03 mol) in ethanol (450 ml) hydrazine hydrate (100% aq.sol.; 4.0 g, 0.03 mol) was added. After being heated at reflux for 20 h the solution became clear and on cooling deposited a white precipitate. The solvent was removed under reduced pressure and the residue was taken up in 3M hydrochloric acid solution (120 ml); the resulting solution was heated at reflux for 3 h, then cooled to 5°C. The phthalhydrazide which had been produced was filtered off, after which the filtrate was concentrated to 50 ml under reduced pressure, made alkaline by the addition of 2M sodium hydroxide

solution and then extracted with chloroform (4 x 75 ml). The combined extracts were washed with water (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure, which gave 8,9-dimethoxy-3,5-dimethyl-6-(2-aminoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (5) (7.6 g, 87%) as a clear, pale yellow oil (Found: M^+, 290.16384. $C_{16}H_{22}N_2O_3$ requires M, 290.163032); $\nu_{max.}$ (film) 3350 (br), 2965, 2920, 2870, 2840, 1640, 1590, 1500, 1478, 1370, 1340, 1250, 1115, 975, 750, 662 cm^{-1}; δ_H 6.60 (1H, s), 4.24 (3H, m), 3.92 (3H, s), 3.86 (3H, s), 2.85 (4H, m), 2.34 (3H, s), 1.54 (2H, br. s, exchanges with D_2O), 1.29 (3H, d, J 7.6 Hz); $\lambda_{max.}$ (EtOH) 221, 274 nm; m/z (%) 290 (M^+, 27), 260 (100), 244 (3), 175 (13), 77 (2). The picrate was recrystallised from ethanol and obtained as orange needles, m.p. 214-214.3°C (Found: C, 50.85; H, 5.0; N, 13.4. $C_{23}H_{28}N_2O_8$ requires C, 50.85; H, 4.85; N, 13.4%).

N_b-(2',2'-Dicarboethoxyvinyl)-8,9-dimethoxy-3,5-dimethyl-6-(2-aminoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (9). — A solution of 8,9-dimethoxy-3,5-dimethyl-6-(2-aminoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (3.8 g, 13 mmol) and diethyl ethoxymethylenemalonate (2.8 g, 13 mmol) in absolute ethanol (300 ml) was heated at reflux for 20 h, then cooled. Concentration under reduced pressure gave N_b-(2',2'-dicarboethoxyvinyl)-8,9-dimethoxy-3,5-dimethyl-6-(2-aminoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (5.90 g, 98%) as a colourless oil (Found: M^+, 460.22092. $C_{24}H_{32}N_2O_7$ requires M, 460.220935); $\nu_{max.}$ (film) 3360, 3278, 3190, 2980-2875, 1707, 1680, 1656, 1646, 1605, 1502, 1120, 1075, 802, 750, 684 cm^{-1}; δ_H 9.14 (1H, br, m), 7.75, 7.60 (1H, 2 s), 6.52 (1H, s), 4.30 (3H, m), 4.13 (4H, m), 3.93 (3H, s), 3.88 (3H, s), 3.52 (2H, m), 2.90 (2H, m), 2.22 (3H, s), 1.30 (9H, m); $\lambda_{max.}$ ($\log_{10}$ ϵ) (MeOH) 220 (4.44), 274.5 nm (4.60); m/z (%) 460 (M^+, 17), 414 (2), 260 (100), 175 (11), 154 (5), 109 (3), 83 (5).

3-Acetyl-2,3,3a,4,8,9-hexahydro-11,12-dimethoxy-8-methyl-[1,4]-oxazino[2,3,4-jk]pyrrolo-[2,3-d]-carbazol-5-(1H)-one (10). — A mixture of N_b-(2',2'-dicarboethoxyvinyl)-8,9-dimethoxy-3,5-dimethyl-6-(2-aminoethyl)-3,4-dihydropyrrolo[1,2,3-de]-2H-1,4-benzoxazine (9) (4.8 g, 0.01 mol) in glacial acetic acid (40 ml) and acetic anhydride (60 ml) was heated at reflux for 4 days. The solution was cooled, diluted to twice its volume with water, and 2M sodium hydroxide solution (200 ml) was added. After being stirred for 20 min the solution was extracted with chloroform (4 x 125 ml). The combined organic fractions were washed with 2M sodium hydroxide solution (2 x 75 ml), water (50 ml), 2M hydrochloric acid solution (2 x 75 ml), and then with water (2 x 75 ml). The solvent was removed from the dried (Na_2SO_4) solution under reduced pressure and the residue was

purified by chromatography on Kieselgel G (175 g) using chloroform/ethanol (0.3%) as eluent which gave 3-acetyl-2,3,3a,4,8,9-hexahydro-11,12-dimethoxy-8-methyl-[1,4]-oxazino[2,3,4-jk]pyrrolo-[2.3-d]-carbazol-5-(1H)-one (10) (1.20-1.40 g, 30-35%) as a yellow foam (Found: M^+, 384.16812. $C_{21}H_{24}N_2O_5$ requires M, 384.168510); $\nu_{max.}$ (Nujol) 1655, 1645, 1610, 1495, 1400, 1250, 1130, 833, 760, 733 cm^{-1}; δ_H 6.30, 6.29 (1H, 2 s), 5.47, 5.36 (1H, 2 s), 4.79 (0.5H, ap. t, J 9 Hz), 4.6-3.7 (5.5H, m), 3.93, 3.90 (3H, 2 s), 3.81, 3.79 (3H, 2 s), 3.22 (0.5H, dd, J 9, 18 Hz), 2.99 (0.5H, dd, J 9, 18 Hz), 2.6-2.1 (5H, m), 2.18, 2.16 (3H, 2 s), 1.46, 1.30 (3H, 2 d, J 9 Hz); $\lambda_{max.}$ ($\log_{10}$ ϵ) (MeOH) 218.5 (4.32), 245.5 (4.01), 297 (3.80), 353 nm (4.13); m/z (%) 384 (M^+, 89), 342 (39), 327 (17), 299 (40), 286 (70), 43 (100).

3-Acetyl-2,3,3a,4,6,6a,8,9-octahydro-11,12-dimethoxy-8-methyl-[1,4]-oxazino[2,3,4-jk]pyrrolo-[2,3-d]-carbazol-5-(1H)-one (11). — Liquid ammonia (200 ml) was distilled through a potassium hydroxide drying tower and condensed into a receiving flask containing a solution of the enaminoketone (10) (3.15 g, 8.20 mmol) in tetrahydrofuran (40 ml), cooled to -33°C. t-Butanol (608 mg, 8.20 mmol) was added to the reaction mixture followed by the slow addition of lithium metal wire (115 mg, 16.4 mmol). After 45 min at -33°C the ammonia was allowed to distil from the reaction mixture, which was then quenched with acetone (2 ml) and water (70 ml). The mixture was then extracted with chloroform (4 x 75 ml). The combined extracts were washed with saturated brine, dried (Na_2SO_4), and concentrated under reduced pressure which gave 3-acetyl-2,3,3a,4,6,6a,8,9-octahydro-11,12-dimethoxy-8-methyl-[1,4]-oxazino[2,3,4-jk]pyrrolo-[2,3-d]-carbazol-5-(1H)-one (11) (2.95 g, 93%) as a mixture of diastereoisomers. Recrystallisation from ethanol separated the two diastereoisomers.

3-Acetyl-2,3,3a,4,6,6a,8,9-octahydro-11,12-dimethoxy-8α-methyl-[1,4]-oxazino[2,3,4-jk]pyrrolo-[2,3-d]-carbazol-5-(1H)-one (11a) was obtained as colourless prisms (1.90 g, 60%), m.p. 203.5-204.5°C (Found: C, 65.35; H, 6.9; N, 7.15%, M^+, 386.18414. $C_{21}H_{26}N_2O_5$ requires C, 65.25; H, 6.8; N, 7.25%, M, 386.184159); $\nu_{max.}$ (Nujol) 1720, 1633, 1105, 1085, 791, 720 cm^{-1} δ_H ($CDCl_3$; 400 MHz) 6.30 (1H, s, 13-H), 4.18 (1H, t, J 3 Hz, 6a-H), 4.16 (1H, dd, J 3, 11 Hz, 9-H), 3.97 (1H, dd, J 8.5, 11 Hz, 9-H), 3.87 (3H, s, OMe), 3.84 (1H, m, 2-H), 3.80 (3H, s, OMe), 3.73 (1H, m, 3a-H), 3.70 (1H, m, 2-H), 3.37 (1H, dd, J 3.5, 18 Hz, 6-H), 2.98 (1H, m, 8-H), 2.92 (1H, dd, J 3, 17 Hz, 4-H), 2.55 (1H, m, J 3, 18 Hz, 6-H), 2.55 (1H, m, 1-H), 2.09 (3H, s, N-CO-CH_3), 2.06 (1H, m, 1-H), 1.20 (3H, d, J 6.4 Hz, 8a-H_3); δ_C 207.70 (C-5), 169.94 (C-1'), 148.71 (C-11), 137.11 (C-10), 136.84 (C-10a), 132.67 (C-12), 124.00 (C-13a), 99.14 (C-13), 72.92 (C-9), 72.43

and 63.71 (C-3a and C-6a), 60.95 (-OMe), 57.21 (-OMe), 54.44 (C-13b), 52.66 (C-8), 47.56 (C-2), 43.28, 38.73, and 37.65 (C-1, C-4, and C-6), 23.24 (C-2'), 16.79 (C-8a); $\lambda_{max.}$ ($\log_{10}$ ϵ) (MeOH) 216 (4.52), 247 (3.67), 300 nm (3.38); m/z (%) 386 ($\underline{M}^+$, 83), 371 (22), 300 (17), 260 (16), 246 (15), 43 (100).

The C-8 epimer (11b) was obtained as a pale yellow oil (0.94 g, 30%). The i.r. and mass spectra obtained on this material were similar to those reported for the diastereoisomer (11a). The following data were obtained by subtraction of the peaks due to the presence of the desired diastereoisomer (11a) from the spectrum obtained on enriched material; δ_H 6.25 (1H, s), 3.88 (3H, s), 3.78 (3H, s), 2.12 (3H, s), 1.11 (3H, d, $\underline{J}$ 6.4 Hz); δ_C 207.97 (C-5), 170.05 (C-1'), 147.68 (C-11), 137.39 (C-10), 135.98 (C-10a), 130.39 (C-12), 125.03 (C-13a), 100.55 (C-13), 72.16 (C-9), 66.80 and 61.27 (C-3a and C-6a), 61.00 (OMe), 57.59 (OMe), 53.90 (C-13b), 46.91 (C-2), 45.13 (C-8), 40.30, 38.41, and 36.73 (C-1, C-4, and C-6), 23.02 (C-2'), 12.30 (C-8a).

2,3,3a,4,6,6a,8,9-Octahydro-11,12-dimethoxy-8-methyl-[1,4]-oxazino[2,3,4-jk] pyrrolo-[2,3-d]-carbazol-5-(1H)-one (12). — To a solution of the acetylated aminoketone (11) (mixture of C-8 diastereoisomers) (580 mg, 1.5 mmol) in dichloromethane (25 ml) sodium bicarbonate (760 mg, 9.0 mmol) was added followed by triethyloxonium tetrafluoroborate (850 mg, 4.5 mmol). The resulting solution was stirred for 48 h at room temperature, then dilute sodium bicarbonate solution (10 ml) was added and stirring continued for 15 min. The aqueous phase was separated and extracted with chloroform (3 x 15 ml). The combined extracts were washed with water (25 ml) and extracted with 2M hydrochloric acid solution (3 x 25 ml). The combined acidic layers were made alkaline by the addition of 2M sodium hydroxide solution and the mixture was extracted with chloroform (3 x 40 ml). The combined organic fractions were washed with water (30 ml), saturated brine (30 ml), dried (Na_2SO_4), and then concentrated under reduced pressure. The yellow oily residue was purified by chromatography on Kieselgel G (60 g) using dichloromethane/methanol (2%)/concentrated ammonia solution (1%) (prepared by shaking the mixture vigorously and then discarding the aqueous phase) as eluent, which gave 2,3,3a,4,6,6a,8,9-octahydro-11,12-dimethoxy-8-methyl-[1,4]-oxazino [2,3,4-jk]pyrrolo-[2,3-d]-carbazol-5-(1H)-one (12) (420 mg, 81%) as a clear, pale yellow oil (Found: $\underline{M}^+$, 344.17378. $C_{19}H_{24}N_2O_4$ requires $\underline{M}$, 344.173596); $\nu_{max.}$ ($CHCl_3$) 3400 (br), 3000, 2980, 2915, 2812, 1707, 1610, 1480, 1100 cm^{-1}; δ_H 6.36, 6.33 (1H, 2 s), 4.22 (1H, m), 4.1 (1H, m), 3.89, 3.87 (3H, 2 s), 3.86, 3.85 (3H, 2 s), 3.7-1.7 (11H, m), 1.75 (1H, br. s, exchanges with D_2O), 1.18 and 1.08 (3H, 2 d, $\underline{J}$ 6.4 Hz); $\lambda_{max.}$ ($\log_{10}$ ϵ) (MeOH) 215 (4.41), 247 (3.70), 302 nm (3.40);

m/z (%) 344 (M^+, 95), 329 (17), 261 (8), 246 (100), 161 (14), 84 (11).

Hexacyclic methoxyketone (13). — A solution of the amine (12) (mixture of diastereoisomers) (190 mg, 0.55 mmol) in dry methanol (15 ml) containing sodium methoxide (prepared from 13 mg sodium) was stirred at room temperature for 15 min, then acrolein (34 mg, 0.6 mmol) was added. The mixture was stirred for 48 h at room temperature, then diluted with water (20 ml) and extracted with dichloromethane (4 x 40 ml). The combined organic extracts were washed with water (40 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residual yellow oil was purified by chromatography on Kieselgel G (40 g), using dichloromethane/methanol (3%) as eluent, which gave the hexacyclic methoxyketone (13) (27 mg, 12%) as a colourless oil (Found: M^+, 414.21564. $C_{23}H_{30}N_2O_5$ requires M, 414.215458); $\nu_{max.}$ ($CHCl_3$) 3000, 2920, 2840, 2810, 1700, 1610, 1475, 1100 cm^{-1}; δ_H 6.33 (1H, s), 4.10 (3H, m), 3.96 (3H, s), 3.84 (3H, s), 3.39 (1H, m), 2.8-1.6 (12H, m), 1.18 (3H, d, J 6.4 Hz); m/z (%) 414 (M^+, 100), 399 (15), 372 (1), 260 (6), 246 (27), 174 (7), 126 (48).

Hexacyclic enone (14a). — To a solution of the aminoketone (12a) (280 mg, 0.81 mmol) in dry methanol (50 ml) and dry benzene (5 ml) acrolein (68 mg, 1.2 mmol) was added followed by a solution of sodium metal (18.7 mg, 0.8 mmol) in dry methanol (5 ml). The mixture was stirred for 30 min and then more acrolein (23 mg, 0.41 mmol) was added. The solution was heated at reflux for 2 h, then cooled to 0°C, neutralised by the addition of 2M hydrochloric acid solution, and evaporated to dryness under reduced pressure. The residue was extracted with chloroform (4 x 50 ml), the combined organic fractions were washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was taken up in dry pyridine (10 ml) and cooled to 0°C. Methanesulphonyl chloride (230 mg, 2.0 mmol) was added to the mixture which was then stirred at 0°C for 1 h and at room temperature for 60 h. The solvent was then removed under reduced pressure which gave a red oil which was taken up in chloroform (30 ml). The resulting solution was washed with saturated sodium bicarbonate solution (15 ml), dried ($NaSO_4$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on Kieselgel G (50 g), using dichloromethane/methanol (0.3%) as eluent, which gave the hexacyclic enone (14a) (100 mg, 32%) as a colourless oil (Found: M^+, 382.18905. $C_{22}H_{26}N_2O_4$ requires M, 382.189245): $\nu_{max.}$ ($CHCl_3$) 3100, 3000, 2940, 2880, 2860, 1690, 1624, 1483, 1339, 1165, 1108 cm^{-1}; δ_H 6.99 (1H, m), 6.60 (1H, s), 4.29 (1H, dd, J 3, 11 Hz), 4.2-3.6 (4H, m), 3.87 (3H, s), 3.83 (3H, s), 3.3-2.0 (10H, m), 1.14 (3H, d, J 6.4 Hz); δ_C 197.79 (C-17), 147.95 (C-11), 136.84 (C-12),

136.36 (C-13), 135.22 (C-15), 134.14 (C-20), 130.61 (C-10), 129.26 (C-8), 100.76 (C-9), 72.27 (C-23), 67.77 and 63.76 (C-2 and C-21), 60.95 (OMe), 57.64 (OMe), 55.96 (C-7), 47.78, 45.78, and 43.34 (C-3, C-22, and C-5), 39.22 (C-6), 36.95 (C-16), 19.72 (C-14), 14.90 (C-24); $\lambda_{max.}$ (MeOH) 217, 150 (sh), 301.5 nm; m/z (%) 382 ($\underline{M}^+$, 100), 367 (34), 260 (10), 246 (15), 174 (24), 107 (11), 94 (4).

Hexacyclic ketoester (16). — To potassium t-butoxide (52 mg, 0.46 mmol) in dry t-butanol (8 ml) and dry dimethylformamide (2 ml), cooled to 0°C, a solution of the unsaturated aminoketone (14a) (88 mg, 0.23 mmol) in dry dimethylformamide (4 ml) was added, dropwise with stirring. After the addition was complete the mixture was stirred at 0°C for 30 min and then at room temperature for 60 min. Freshly distilled methyl bromoacetate (250 mg, 1.6 mmol) was added and stirring was continued for a further 1 h. Water (10 ml) was then added, and the solvents were removed under reduced pressure. The residue was taken up in chloroform (15 ml), washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (40 g) using dichloromethane/methanol (0.5%) as eluent, which gave the hexacyclic ketoester (16) (37 mg, 39%) as an orange solid, m.p. 173-174°C (Found: $\underline{M}^+$, 454.21055. $C_{25}H_{30}N_2O_6$ requires M, 454.210372); $\nu_{max.}$ ($CHCl_3$) 3000, 2940, 2880, 2850, 2800, 2740, 1732, 1711, 1615, 1489, 1350, 1345, 1170, 1150, 1123, 1096 cm^{-1}; δ_H 6.39 (1H, s), 5.79 (2H, m), 4.20 (2H, dd, J 1.6, 2.5 Hz), 3.88 (3H, s), 3.80 (3H, s), 3.8-3.2 (5H, m), 3.47 (3H, s), 2.86-1.8 (8H, m), 1.10 (3H, d, J 6.6 Hz); δ_C 209.55 (C-17), 170.92 (C-18), 147.90 (C-11), 137.33 (C-12), 135.43 (C-13), 130.51 (C-10), 128.77, 127.96, and 125.95 (C-14, C-8, and C-15), 101.52 (C-9), 72.11 (C-23), 70.97 and 69.83 (C-21 and C-2), 61.05 and 57.75 (2 x OMe), 53.47, 52.60, and 52.01 (C-3, C-7, and C-5), 51.19 (OMe), 50.81 (C-20), 44.96 (C-22), 39.38, 39,06, and 36.73 (C-6, C-19, and C-16), 11.0 (C-24); $\lambda_{max.}$ (EtOH) 215, 248 (sh), 304.5 nm; m/z (%) 454 ($\underline{M}^+$, 100), 439 (7), 397 (7), 380 (3), 261 (38), 260 (23), 246 (35), 179 (68), 165 (27), 151 (22), 106 (22), 92 (7), 79 (9).

(±)-Obscurinervidine (1a) and the Hexacyclic Hydroxyester (21). — To a solution of the hexacyclic ketoester (16) (30 mg, 0.07 mmol) in absolute ethanol (10 ml) sodium borohydride (12.5 mg, 0.33 mmol) was added. The mixture was stirred for 16 h at 35°C, then neutralised by the addition of 0.5M hydrochloric acid solution and concentrated under reduced pressure. The residue was taken up in chloroform (25 ml), washed with water (25 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (25 g) using dichloromethane/methanol (1%) as eluent, which gave (±)-obscurinervidine (1a) (15.5 mg, 55%). Recrystallisation from acetone/hexane gave colourless prisms,

m.p. 209-210°C (Found: M^+, 474.20041. $C_{24}H_{28}N_2O_5$ requires M, 424.199809); $\nu_{max.}$ ($CHCl_3$) 3000, 2974, 2941, 2880, 2850, 2795, 1615, 1486, 1373, 1343, 1186, 1153, 1127, 1100, 1026, 993 cm^{-1}; δ_H ($CDCl_3$; 400 MHz)[10] 6.36 (1H, s, 9-H), 5.72 (2H, m, 14-H + 15-H), 4.55 (1H, d, J 5 Hz, 17-H), 4.20 (1H, dd, J 1.5, 11 Hz, 23-H), 4.15 (1H, dd, J 2, 11 Hz, 23-H), 3.90 (3H, s, OMe), 3.85 (3H, s, OMe), 3.47 (2H, m, 22-H + 3-H), 3.28 (1H, m, 2-H), 3.25 (1H, s, 21-H), 2.73 (1H, d, J 16 Hz, 3-H), 2.56 (1H, d, J 18.5 Hz, 19-H), 2.33 and 2.23 (3H, m, and 2H, m, 16-H, 5-H, and 6-H), 2.09 (1H, d, J 18.5 Hz, 19-H), 1.80 (1H, m, 5-H or 6-H), 1.07 (3H, d, J 6.4 Hz, 24-H); δ_C 176.01 (C-18), 147.84 (C-11), 137.33 (C-12), 135.60 (C-13), 133.76 (C-14 or C-15), 130.51 (C-10), 129.42 (C-8), 122.92 (C-15 or C-14), 100.82 (C-9), 81.31 (C-17), 71.94 (C-23), 69.67 and 65.01 (C-21 and C-2), 61.00 (OMe), 57.75 (OMe), 54.28, 52.25, and 52.17 (C-3, C-7, and C-5), 44.53 (C-22), 40.68 (C-20), 39.33 and 38.68 (C-6 and C-19), 23.84 (C-16), 10.51 (C-24); $\lambda_{max.}$ ($\log_{10}\varepsilon$) (MeOH) 219 (4.45), 249.5 (3.70), 306 nm (3.34); m/z (%) 424 (M^+, 100) 409 (52), 260 (2), 246 (6), 244 (7), 216 (5), 198 (5), 107 (7).

The infrared, mass, proton and ^{13}C n.m.r. spectra were identical in every detail with those of authentic (-)-obscurinervidine kindly supplied by Dr. C. Djerassi.

Eluted from the column in a later fraction was the hexacyclic 17α-hydroxy-ester (21) (11.5 mg, 38%), which was obtained as a colourless gum (Found: M^+, 456.22572. $C_{25}H_{32}N_2O_6$ requires M, 456.226021); $\nu_{max.}$ ($CHCl_3$) 3000, 2940, 2885, 2856, 2700, 1733, 1612, 1485, 1348, 1109, 1092 cm^{-1}; δ_H 6.47 (1H, s), 6.00 (1H, ddd, J 10, 4.5, 1.6 Hz), 5.65 (1H, dt, J 10, 2 Hz), 4.30 (1H, dd, J 3, 10.7 Hz), 4.1-3.6 (3H, m), 3.87 (3H, s), 3.75 (3H, s), 3.61 (3H, s), 3.5-1.3 (13H, m), 1.16 (3H, d, J 6.2 Hz); $\lambda_{max.}$ (EtOH) 219, 253, 305 nm; m/z (%) 456 (M^+, 100), 441 (18), 424 (32), 409 (18), 260 (12), 246 (19), 179 (12), 106 (11).

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