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# A NEW SYNTHESIS OF THE CYLINDROCARINE GROUP OF ALKALOIDS.

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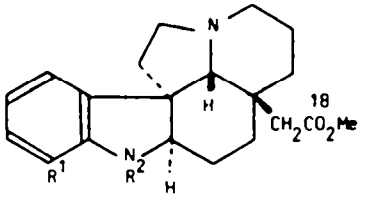
Summary: The Kuehne synthesis of anilinoacrylate alkaloids has been adapted to afford a new synthesis of (±)-12-demethoxy-N-acetylcylindrocarine, (±)-cylindrocarine, and (±)-N-formylcylindrocarine.

Several of the cylindrocarine group of alkaloids, including cylindrocarine (1), cylindrocarpidine (2), and cylindrocarpine (3) have already been synthesised,[1] as has limaspermine (4),[2] which may be considered in the same sub-group since it also contains a functionalised C-18.




Cylindrocarine (1) $R^1$ = OMe, $R^2$ = H

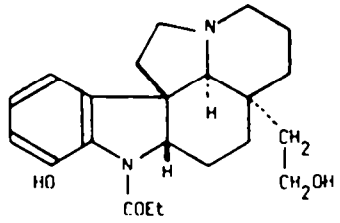
Cylindrocarpidine (1) $R^1$ = OMe, $R^2$ = Ac

Cylindrocarpine (3) $R^1$ = OMe, $R^2$ = COCH=CHPh

$N_a$-Formylcylindrocarine (37) $R^1$ = OMe, $R^2$ = CHO

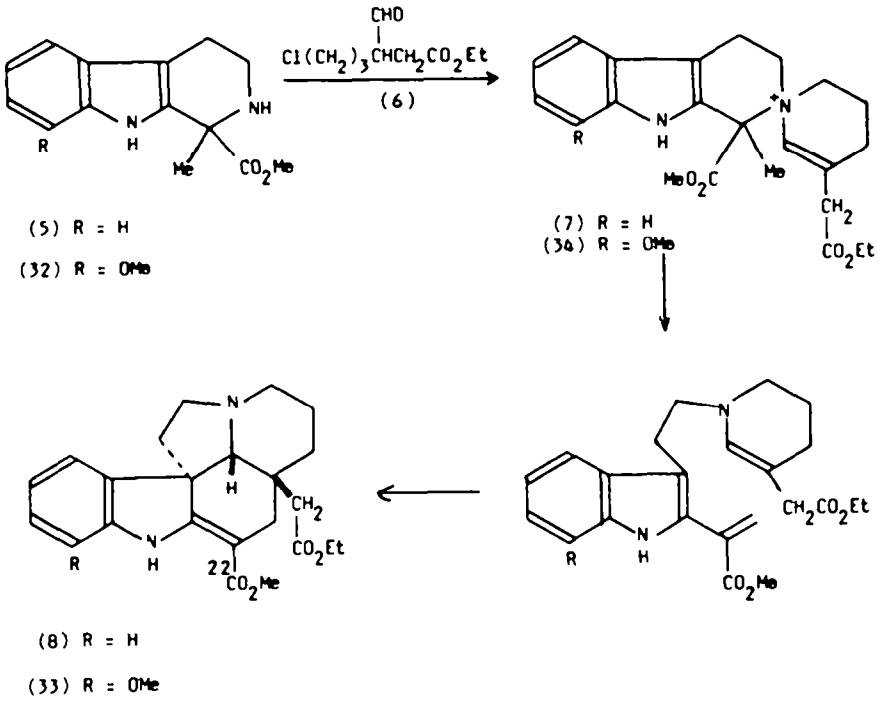
(30) $R^1$ = H, $R^2$ = Ac

(31) $R^1$ = $R^2$ = H



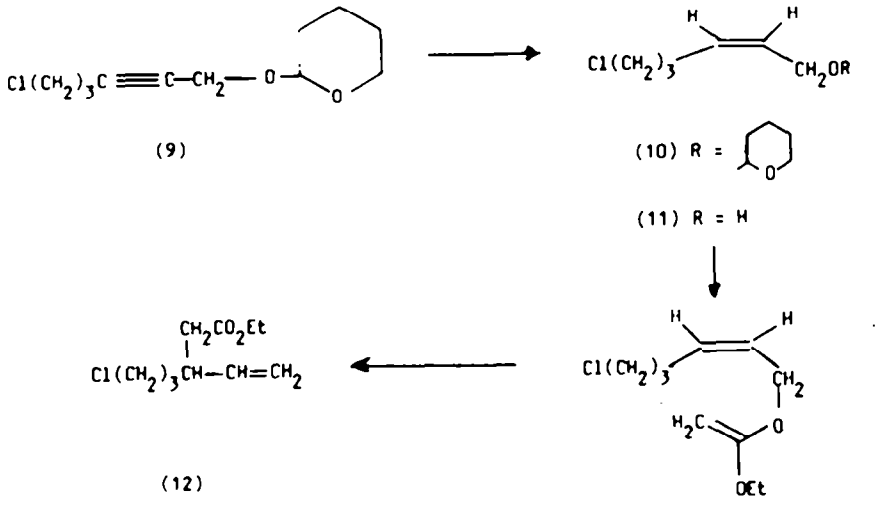

(4) Limaspermine

In developing this programme of synthesis, particularly with a view to extending it to more complex alkaloids such as dichotamine or alalakine, a much more direct synthesis was required, and for this purpose the Kuehne approach[3] seemed ideally suited. Thus, condensation of the tetrahydro-β-carboline ester (5) with an appropriate chloroaldehyde, e.g. (6), should yield the spirocyclic quaternary ammonium ion (7) which, by proton loss with concomitant fission of the 1,2 bond and recyclization, should afford the diester (8); this should be capable of conversion into a number of related alkaloids in the vincadifformine group, or into alkaloids of the cylindrocarine group, by obvious transformations. It was anticipated that the incorporation of two different ester alkoxy-groups in (8) should allow selective hydrolysis, as and when necessary.



(5) R = H
(32) R = OMe
(7) R = H
(34) R = OMe
(8) R = H
(33) R = OMe

6-Chlorohex-2-yn-1-ol tetrahydropyranyl ether (9)[4] was partially hydrogenated over the Lindlar catalyst to give the cis-alkene (10) which, without purification, was hydrolysed to the parent unsaturated chloroalcohol (11). When heated with triethyl orthoacetate in the presence of propionic acid as catalyst, followed by heating overnight at 135-140°C, Claisen rearrangement smoothly occurred, and the product was the desired unsaturated chloroester (12). Removal of the terminal



(9)
(10) R =
(11) R = H
(12)

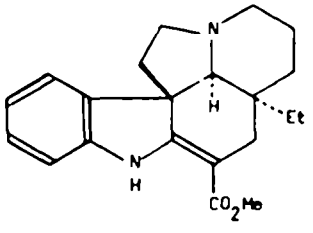
methylene group in (12) by ozonolysis then gave the chloroaldehydoester (6), in ~40% overall yield from propargyl alcohol.

Reaction of the tetrahydro-β-carboline ester (5)[3] with (6) in refluxing toluene for 110 h gave a complex mixture of products from which the required pentacyclic diester (8) was obtained in an optimum yield of 45%, following chromatographic separation. This ester showed the typical anilinoacrylate u.v. absorption at $\lambda_{max.}$ 234, 296, and 324 nm and i.r. absorption at 1603 and 1679 $cm^{-1}$ [cf. vincadifformine (13)]; the isolated ester carbonyl group gave rise to an additional absorption band at 1720 $cm^{-1}$. The $^{13}C$ n.m.r. spectrum (Table 1) compares well with the spectrum of vincadifformine (13),[5] and only the

TABLE 1

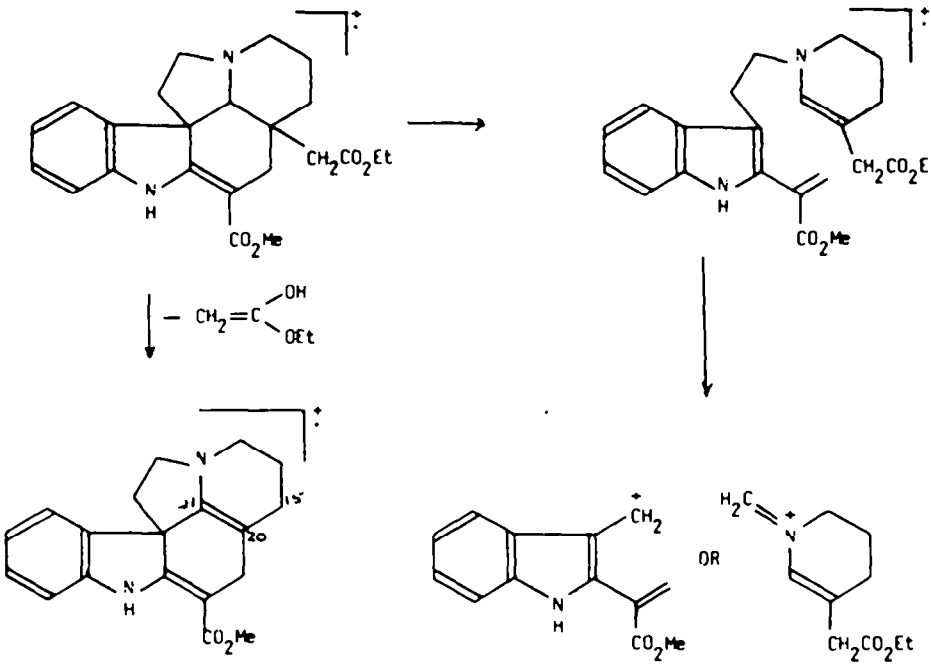
$^{13}C$ N.M.R. Data for Vincadifformine (13) and the Diesters (8) and (33).

| Carbon | Vincadifformine (13)[5] | Diester (8) | Diester (33) |
|---|---|---|---|
| 2 | 167.4 ppm | 166.8 ppm | 166.8 ppm |
| 3 | 50.4 | 50.9 | 50.8 |
| 5 | 51.6 | 51.6 | 51.6 |
| 6 | 45.1 | 45.4 | 45.3 |
| 7 | 55.4 | 55.4 | 56.1 |
| 8 | 137.7 | 137.2 | 132.1 |
| 9 | 121.0 | 121.0 | 110.2 |
| 10 | 120.5 | 120.6 | 113.6 |
| 11 | 127.3 | 127.6 | 121.2 |
| 12 | 109.2 | 109.4 | 144.3 |
| 13 | 143.7 | 143.3 | 138.1 |
| 14 | 21.9 | 22.1 | 22.1 |
| 15 | 32.3 | 33.5 | 33.5 |
| 16 | 92.4 | 93.1 | 93.4 |
| 17 | 25.6 | 26.8 | 26.9 |
| 18 | 7.0 | 171.5 | 171.3 |
| 19 | 29.3 | 41.5 | 41.4 |
| 20 | 38.1 | 38.5 | 38.5 |
| 21 | 72.4 | 71.4 | 71.5 |
| 22 | 168.9 | 169.1 | 168.7 |
| Me | 50.8 | 50.9 | 50.8 |
| $O\underline{C}H_2CH_3$ | | 59.9 | 59.8 |
| $OCH_2\underline{C}H_3$ | | 14.08 | 14.08 |



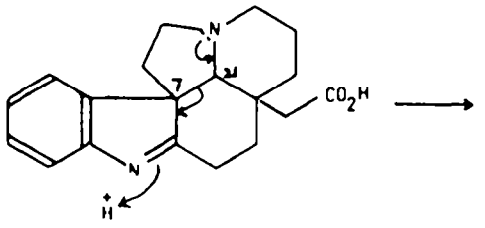

(-)-Vincadifformine (13)

expected substantial differences owing to C-18 and C-19 are observed. That this indicates a similarity of stereochemistry as well as structure is supported by the mass spectrum, which gives evidence for a retro Diels-Alder fragmentation of ring C, followed by fission of the 5,6 bond, to give ions at m/z 214 (14) and 182 (15) (base peak). An additional fragmentation, which has been observed in other compounds containing an ester group attached to C-19,[6] is the loss of the elements of ethyl acetate by a McLafferty mechanism, to give an important ion at m/z 308, owing to (16), or the $\Delta^{15,20}$ isomer.

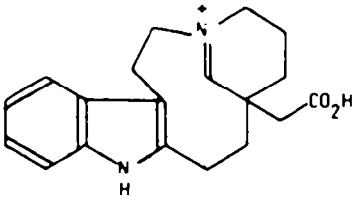


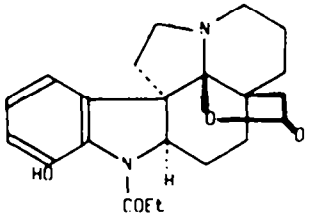

(16) m/z 308 (14) m/z 214 (15) m/z 182

For the completion of the demethoxycylindrocarine synthesis it was only necessary to hydrolyse and decarboxylate the ester group attached to C-16, reduce the indolenine double bond in the product, and re-esterify the carboxyl group released at C-18. Initially the diester (8) was hydrolysed by dilute ethanolic potassium hydroxide solution, after the method of Zsadon and Otta,[7] since these conditions seemed to afford the mildest of the known methods. After brief reaction times the product consisted of several components, but after 6 h a single product was obtained, which was neither the diacid related to (8) nor the desired indolenine (17) produced by decarboxylation. This product was clearly an indole derivative (u.v. spectrum) of molecular formula $C_{19}H_{22}N_2O_2$ (mass spectrum), which indicated that both ester groups had been hydrolysed, and C-22 had been lost. Since it was not acidic, and contained a sharp one-proton singlet at $\delta$ 5.18 in its n.m.r. spectrum, it was formulated as the carbinolamine lactone (18), obtained by reverse Mannich fission of the 7,21 bond in the indolenine (17), followed by lactonisation. The lactone function gave rise to a carbonyl absorption at $\nu_{max.}$ 1744 $cm^{-1}$ [cf. the carbonyl absorption at 1745 $cm^{-1}$ in cimicine (19)[8]].

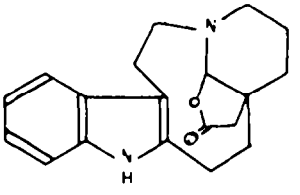


(17)



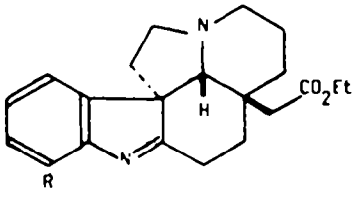


(19)



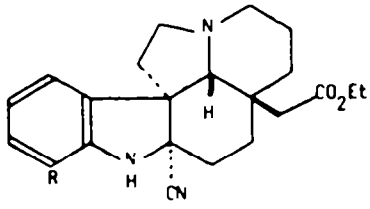
(18)

Since the attempts to reconvert this lactone into the indolenine acid (17), and thence into demethoxycylindrocarine, were unsuccessful a selective reagent was required which would hydrolyse and decarboxylate the anilinoacrylate function without simultaneously hydrolysing the isolated ethyl ester group. For this purpose a large excess of sodium cyanide in hexamethylphosphoramide[9] was employed. After 4 days at 90°C the diester (8) gave two products, which were shown to be the desired indolenine ester (20) (27%) and the aminonitrile ester (21) (57%), obtained by the addition of hydrocyanic acid to (20). Without complete characterisation the indolenine ester (20) was reduced by means of sodium borohydride in ethanol at 0°C to give 19-ethoxycarbonyl-19-demethylaspidospermidine (22). In consonance with structure (22), this ester exhibits the typical fragmentation of the aspidospermine ring system in the mass spectrometer. Loss of ethylene by retro Diels-Alder fission of ring C gives a major ion at m/z 312, which further fragments by fission of the 5,6 bond, to give ions at m/z 130 and 182 (15, base peak). McLafferty loss of the elements of ethyl acetate from (22) gives the ion (23) at m/z 252.



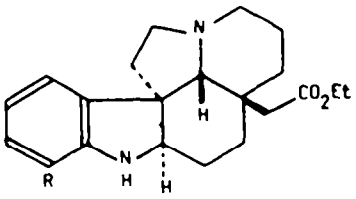
(20) R = H

(35) R = OMe



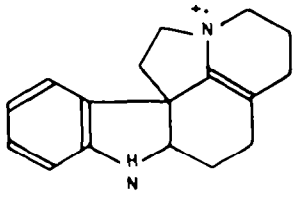
(21) R = H

(36) R = OMe



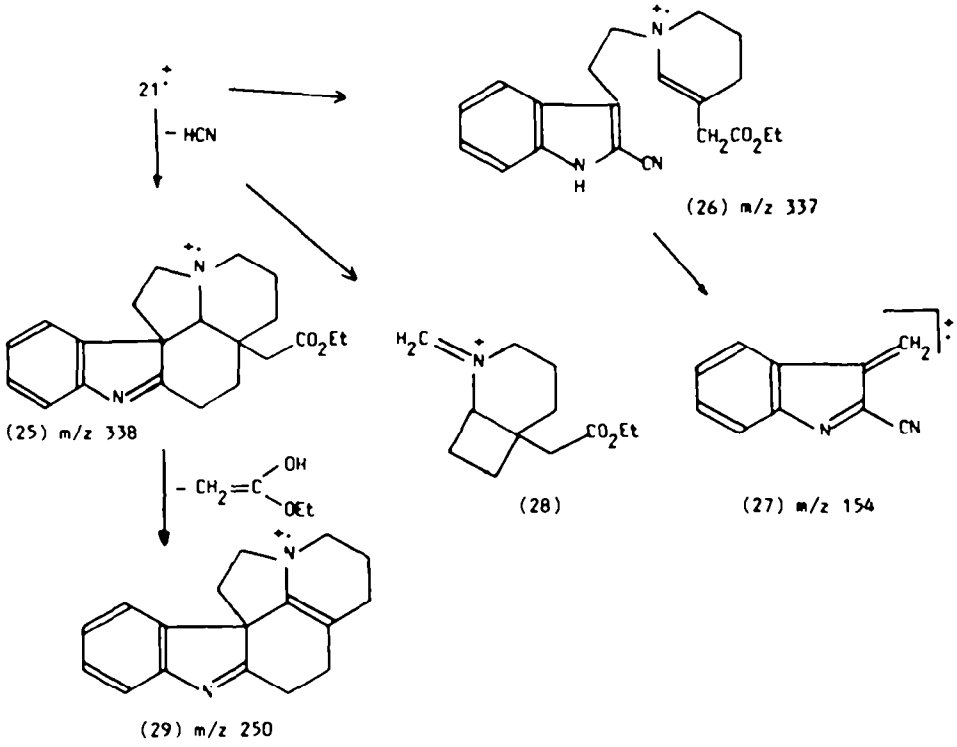
(22) R = H

(24) R = OMe



(23)

The stereochemistry of (22) is confirmed by the appearance in the proton n.m.r. spectrum of the signal owing to the C-2 hydrogen, the aspidospermine 'fingerprint', at δ 3.55, which occurs at significantly higher field in the cis B/C compounds than in the stereoisomeric trans series,[1] and by a comparison of the $^{13}C$ n.m.r. spectral data for (22) with those for its 12-methoxy derivative (24), which was subsequently converted into cylindrocarine (1) (see Table 2).



(25) m/z 338

(26) m/z 337

(27) m/z 154

(28)

(29) m/z 250

The major product from the hydrolysis and decarboxylation of the diester (8) with sodium cyanide gave a molecular ion at m/z 365, which readily lost HCN to give an ion (25) at m/z 338. Reverse Diels-Alder fragmentation of ring C in (21) with loss of ethylene gave the ion (26) at m/z 337, which further fragments to ions at m/z 154 (27) and 182 (15). A minor fragmentation pathway, also exemplified by aspidospermine,[10] affords the ion (28) at m/z 210. Again, McLafferty loss of the angular ester side-chain provides an important ion (29) at m/z 250. These data, and the $^{13}C$ n.m.r. data (Table 2), which reveal that the

additional carbon atom (δ 121.7 ppm) is quaternary, and its chemical shift is appropriate to that of a nitrile carbon, fully support the structure 21.

TABLE 2

$^{13}C$ N.M.R. Data for Esters (22) and (24) and the Nitrile-ester (21).

| Carbon | Ester (22) | Nitrile-ester (21) | Ester (24) |
|---|---|---|---|
| 2 | 64.8 ppm | 64.3 ppm | 65.4 ppm |
| 3 | 53.6 | 53.0 | 53.6 |
| 5 | 52.5 | 51.5 | 52.7 |
| 6 | 38.1 | 36.3 | 37.9 |
| 7 | 53.5 | 57.7 | 54.3 |
| 8 | 134.3 | 132.1 | 138.8 |
| 9 | 122.8 | 123.1 | 115.4 |
| 10 | 119.1 | 120.8 | 119.6 |
| 11 | 127.5 | 128.4 | 109.5 |
| 12 | 110.6 | 111.1 | 146.2 |
| 13 | 149.6 | 146.6 | 135.5 |
| 14 | 21.6 | 21.4 | 21.8 |
| 15 | 34.9 | 34.8 | 35.2 |
| 16 | 28.1 | 32.7 | 28.4 |
| 17 | 24.3 | 23.2 | 24.3 |
| 18 | 171.8 | 171.3 | 171.8 |
| 19 | 42.5 | 42.5 | 42.6 |
| 20 | 36.1 | 36.2 | 36.2 |
| 21 | 69.8 | 68.5 | 70.1 |
| $CH_2$ | 59.9 | 60.1 | 59.7 |
| $CH_3$ | 14.25 | 14.25 | 14.3 |
| OMe | | | 55.3 |
| CN | | 121.7 | |

The indoline ester (22) was finally converted into (±)-12-demethoxy-N-acetylcylindrocarine (30) by transesterification with sodium methoxide in methanol, followed by N-acetylation of the intermediate methyl ester (31). The spectroscopic data for (30) were identical with those reported by Milborrow and Djerassi (n.m.r. spectrum)[11] and by Achenbach (mass spectrum).[12]

The synthesis of the cylindrocarine group of alkaloids involved the repetition of the sequence of reactions described above, starting with the 8-methoxytetrahydro-β-carboline ester (32), prepared by the condensation of 7-methoxytryptamine with methyl pyruvate. Reaction of (32) with the chloroaldehydoester (6) in toluene with p-toluenesulphonic acid catalyst gave the desired diester (33) *via* the spirocyclic ammonium ion (34), in a one-pot reaction in 41% yield. As in the unmethoxylated series partial hydrolysis of (33), followed by decarboxylation, by means of sodium cyanide in HMPA, gave two products, which were identified as the required indolenine ester (35) (18%) and the aminonitrile ester (36) (60%). No attempt has so far been made to improve the yield of (35), or to convert the aminonitrile (36) into (35). Reduction of (35) by sodium borohydride in ethanol at 0°C gave the corresponding indoline ester

(24) (for $^{13}C$ n.m.r. data, see Table 2), which was subsequently converted into (±)-cylindrocarine (1) by transesterification with sodium methoxide in methanol. The spectroscopic data of the synthetic cylindrocarpine were identical with those reported by Milborrow and Djerassi[11] for the natural material (with the exception of m.p. and optical rotation), and with those reported earlier for synthetic material.[1] Finally, N-formylation of (±)-cylindrocarine afforded $N_a$-formyl-cylindrocarine (37), which is also a natural product.[11]

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultra-violet absorption spectra were recorded on either a Pye-Unicam SP800A or a PU8800 spectrometer. Infra-red spectra were recorded on either a Perkin-Elmer 297 or a 1420 spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a Perkin-Elmer R32 instrument ($^1H$, 90 MHz) or a Jeol FX90Q F.T. spectrometer ($^1H$, 90 MHz and $^{13}C$, 22.5 MHz). Solutions in deuteriochloroform ($CDCl_3$), with tetramethylsilane (TMS) as internal standard, were used unless otherwise stated. Chemical shifts are quoted in p.p.m. down-field from TMS. Mass spectra were recorded on a Kratos MS25 instrument with accurate mass measurement being carried out on an A.E.I.-Kratos MS902/50 machine.

6-Chloro-2-yn-1-ol tetrahydropyranyl ether (9). — To a solution of propargyl tetrahydropyranyl ether (125.0 g, 0.90 mol) in tetrahydrofuran (850 ml), cooled to -5°C, 1.6M n-butyl-lithium in hexane solution (566 ml, 0.9 mol) was added by syringe. The resulting solution was stirred for 1 h at -5°C and then added by syringe to a solution of 1-bromo-3-chloropropane (157 g, 1.0 mol) in tetrahydrofuran (150 ml), cooled to -40°C. After the addition was complete (40 min) the mixture was stirred at -40°C for a further 1 h and then heated to reflux (70-75°C) for 20 h. The volatile components were removed under reduced pressure and the residue was then distilled under reduced pressure which gave 6-chlorohex-2-yn-1-ol tetrahydropyranyl ether (156 g, 80%) as a colourless oil, b.p. 110-115°C/0.3 mmHg (Kugelrohr) (lit.[4] b.p. 110-114°C/0.14 mmHg); $\nu_{max.}$ (film) 3000-2820, 2220, 1140 $cm^{-1}$; $\delta_H$ 4.78 (1H, br. t), 4.24 (2H, m), 3.7 (2H, m), 3.64 (2H, t, J 6.3 Hz), 2.42 (2H, m), 1.96 (2H, m), 1.16 (6H, m); $\delta_C$ 96.92, 84.40, 72.28, 62.08, 54.55, 43.56, 31.58, 30,45, 25.57, 19.29, 16.41.

6-Chlorohex-2-en-1-ol (11). — A solution of 6-chlorohex-2-yn-1-ol tetrahydropyranyl ether (5.9 g, 0.02 mol) and freshly distilled quinoline (1 drop) in methanol (150 ml) was hydrogenated at room temperature and pressure using 5% palladium on calcium carbonate (100 mg) as catalyst. After one mol. equiv. of hydrogen had been taken up the reaction was stopped, and the catalyst removed by filtration through a pad of Celite. p-Toluenesulphonic acid (250 mg) was added to the filtrate and the solution was heated at reflux for 2 h. Concentration under reduced pressure followed by distillation (Kugelrohr) gave 6-chlorohex-2-en-1-ol (3.42 g, 93%) as a colourless oil, b.p. 70-72°C/0.3 mmHg (Found: $M^+$, 136.04728. Calc. for $C_6H_{11}{}^{37}ClO$, M, 136.046888. Found: $M^+$, 134.0498. Calc. for

$C_6H_{11}{}^{35}ClO$, M, 134.04938); $\nu_{max.}$ (film) 3360-3050, 3010-2800, 1658, 1443, 1030, 975, 725, 650 $cm^{-1}$; $\delta_H$ 5.60 (2H, m), 4.22 (2H, d, J 7.3 Hz), 3.54 (2H, t, J 6.0 Hz), 2.22 (2H, q, J 6.0 Hz), 1.84 (2H, m, J 0.9, 6.0 Hz), 1.53 (1H, s, exchanges with $D_2O$); $\delta_C$ 130.52, 130.23, 58.26, 44.31, 32.34, 24.70; m/z (%) 134 ($M^+$, 0.6), 85 (38), 71 (10), 58 (100), 43 (31).

Ethyl 3-vinyl-6-chlorohexanoate (12). — 6-Chlorohex-2-en-1-ol (10.0 g, 7.34 mmol), triethylorthoacetate (84.4 g, 0.52 mmol) and propionic acid (0.33 g, 4.5 mmol) were heated together at 130° for 3 h. During this period the ethanol produced was allowed to distil from the reaction mixture. The excess of triethyl orthoacetate was then removed under reduced pressure. The residue was stirred at 145°C (oil bath temperature) for 14 h and then cooled. Distillation of the residue under reduced pressure gave ethyl 3-vinyl-6-chlorohexanoate (10.2 g, 67%) as a colourless, mobile oil, b.p. 95-100°C/0.5 mmHg (Found: C, 58.45; H, 8.3; Cl, 17.05. $C_{10}H_{17}O_2Cl$ requires C, 58.7; H, 8.4, Cl, 17.3%. Found: m/z, 207.09641, 205.10019, 204.09227; $C_{10}H_{18}{}^{37}ClO_2$ ($M^+$ + 1) requires m/z, 207.096575; $C_{10}H_{18}{}^{35}ClO_2$ ($M^+$ + 1) requires m/z, 205.099525; $C_{10}H_{17}{}^{35}ClO_2$ requires M, 204.0917); $\nu_{max.}$ (film) 3080, 3000-2850, 1737, 1640, 1448, 1370, 1030, 920, 650 $cm^{-1}$; $\delta_H$ 5.15 (1H, m), 5.11 (1H, m), 4.96 (1H, m), 4.12 (2H, q, J 7.3 Hz), 3.45 (2H, t, J 6.4 Hz), 2.36 (3H, m), 1.7 (4H, m), 1.24 (3H, t, J 7.3 Hz); $\delta_C$ 171.89, 148.64, 115.44, 60.18, 44.75, 40.09, 39.93, 31.69, 30.28, 14.30; m/z (%) 207 ($M^+$ + 1, 0.5), 205 ($M^+$ + 1, 1.5), 204 ($M^+$), 169 (31), 159 (16), 127 (37), 122 (36), 95 (85), 94 (90), 88 (45), 81 (81), 68 (47), 55 (100).

Ethyl 3-formyl-6-chlorohexanoate (6). — A solution of ethyl 3-vinyl-6-chlorohexanoate (12) (2.0 g, 9.8 mmol) in methanol (60 ml) was cooled to -30°C and a stream of ozone in oxygen was bubbled through during 1 h while cooling the solution to -60°C. The addition of ozone was stopped when a slight blue colour was obtained in the reaction mixture, after which the solution was flushed with nitrogen gas. Dimethyl sulphide (0.80 g) was added to the solution which was then allowed to warm to -10°C and kept there for 1 h, then allowed to stand at 0°C for a further 1 h and then at room temperature for a further 2 h. The volatile materials were then removed under reduced pressure to give an oily residue, which was taken up in light petroleum (b.p. 40-60°) (50 ml), washed with water (4 x 30 ml), and then dried ($Na_2SO_4$). Concentration under reduced pressure then gave ethyl 3-formyl-6-chlorohexanoate (6) (85-90%) as a colourless oil which was unstable to distillation; $\nu_{max.}$ (film) 3000-2800, 2715, 1740, 1730, 1450, 1375, 1189, 1030, 650 $cm^{-1}$; $\delta_H$ 9.72 (1H, d, J 0.7 Hz), 4.15 (2H, q, J 7.1 Hz), 3.55 (2H, m), 2.6 (3H, m), 1.83 (4H, m), 1.26 (3H, t, J 7.1 Hz); $\delta_C$ 202.23, 171.62,

60.84, 47.62, 44.48, 33.21, 29.74, 25.79, 14.14; m/z (%) 207 ($\underline{M}^+$ + 1, 1.5), 206 ($\underline{M}^+$, 4), 205 (4), 204 (10), 179 (23), 177 (71), 141 (100), 115 (12), 113 (66), 99 (47), 88 (56), 71 (67), 55 (60).

19-Carboethoxy-19-demethylvincadifformine (8). — A solution of 1-carbomethoxy-1-methyl-1,2,3,4-tetrahydro-ß-carboline (5) (4.60 g, 18.8 mmol), ethyl 3-formyl-6-chlorohexanoate (5.0 g, 24.3 mmol) and p-toluenesulphonic acid (100 mg) in toluene (200 ml) was refluxed in a Dean and Stark apparatus for 110 h, while under an atmosphere of nitrogen. After 70 h and again after 90 h had elapsed further portions of ethyl 3-formyl-6-chlorohexanoate (2 x 1 g) were added to the reaction mixture. After removal of the solvent under reduced pressure, the residue was purified by chromatography on Kieselgel G (150 g), using dichloromethane/methanol (0.3%) as eluent. Recrystallisation from acetonitrile gave 19-carboethoxy-19-demethylvincadifformine (8) (3.40 g, 45%) as colourless plates, m.p. 167-168°C (Found: C, 69.7; H, 7.1; N, 7.3%, $\underline{M}^+$, 396.20458. $C_{23}H_{28}N_2O_4$ requires C, 69.7; H, 7.1; N, 7.1%, $\underline{M}$, 396.204894); $\nu_{max.}$ (Nujol) 3350, 1720, 1679, 1603, 750 $cm^{-1}$; $\delta_H$ 8.90 (1H, br. s), 7.10 (2H, m), 6.80 (2H, m), 3.94 (2H, q, $\underline{J}$ 7.5 Hz), 3.71 (3H, s), 3.2-1.4 (15H, m), 1.09 (3H, t, $\underline{J}$ 7.5 Hz); $\delta_C$ 171.46 (C-18), 169.08 (C-22), 166.80 (C-2), 143.34 (C-13), 137.17 (C-8), 127.63 (C-11), 121.02 (C-9), 120.59 (C-10), 109.43 (C-12), 93.12 (C-16), 71.45 (C-21), 59.92 ($O\underline{C}H_2CH_3$), 55.37 (C-7), 51.57 (C-5), 50.92 ($O\underline{C}H_3$), 50.92 (C-3), 45.45 (C-6), 41.50 (C-19), 38.52 (C-20), 33.53 (C-15), 26.82 (C-17), 22.10 (C-14), 14.08 ($OCH_2\underline{C}H_3$); $\lambda_{max.}$ ($\log_{10}$ ε) (MeOH) 324 (4.15), 296 (4.01), 224 nm (3.98); m/z (%) 396 ($\underline{M}^+$, 10), 365 (1), 351 (2), 309 (1), 308 (1), 182 (100), 154 (7).

Pentacyclic Lactone (18). — A solution of 19-carboethoxy-19-demethylvincadifformine (8) (400 mg, 1.0 mmol) in 0.5M ethanolic potassium hydroxide solution (8.0 ml) was heated at reflux for 6 h, then cooled to 0°C. The solution was neutralised by the addition of 0.5M hydrochloric acid and then extracted with cold ether (3 x 30 ml). The combined ethereal layers were washed with water (1 x 50 ml), dried ($Na_2SO_4$) at 0°C overnight, and then concentrated under reduced pressure, which gave the pentacyclic lactone (18) (236 mg, 75%) as a colourless oil (Found: $\underline{M}^+$, 310.16774. $C_{19}H_{22}N_2O_2$ requires $\underline{M}$, 310.168118); $\nu_{max.}$ ($CHCl_3$) 3480, 3110-2800, 1744, 1740, 1610, 1585, 1470, 1190, 900 $cm^{-1}$; $\delta_H$ 8.00 (1H, br. s), 7.5-7.05 (4H, m), 5.18 (1H, s), 3.4-1.2 (16H, m); $\lambda_{max.}$ (EtOH) 221, 270, 298 (sh) nm; m/z (%) 310 ($\underline{M}^+$, 100), 251 (43), 240 (47), 194 (43), 168 (27), 154 (48), 122 (47), 69 (79).

1,2-Dehydro-19-carboethoxy-19-demethylaspidospermidine (20) and 2-cyano-19-carbo-

ethoxy-19-demethylaspidospermidine (21). — To 19-carboethoxy-19-demethylvincadifformine (8) (400 mg, 1.0 mmol) in dry hexamethylphosphoramide (HMPA, 50 ml) sodium cyanide (1.0 g, 20.4 mmol) was added. The mixture was heated at 75-80°C for 4 days under a nitrogen atmosphere, and then cooled to room temperature. Water (100 ml) was added, then the solution was extracted with ether (5 x 50 ml). The combined ethereal layers were washed with water (5 x 100 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (100 g) using dichloromethane as eluent, which gave 1,2-dehydro-19-carboethoxy-19-demethylaspidospermidine (20) (92 mg, 27%) as a colourless oil; $\nu_{max.}$ 3000-2650, 1717, 1570, 1465, 1195, 1045, 920 $cm^{-1}$; $\delta_H$ 7.56-7.05 (4H, m), 3.90 (2H, q, J 7.05 Hz), 3.3-1.0 (17H, m), 1.08 (3H, t, J 7.05 Hz); $\lambda_{max.}$ (EtOH) 220, 226 (sh), 259.5 nm.

The remaining fractions were purified by a second chromatography on Kieselgel G (150 g) using chloroform as eluent. Recrystallisation from aqueous methanol gave 2-cyano-19-carboethoxy-19-demethylaspidospermidine (21) (237 mg, 65%) as colourless prisms, m.p. 114.5-115.7°C (Found: C, 72.05; H, 7.45; N, 11.4%, $M^+$, 365.21034. $C_{22}H_{27}N_3O_2$ requires C, 72.3; H, 7.45; N, 11.5%, M, 365.210315); $\nu_{max.}$ (Nujol) 3370, 3000-2750, 2219, 1604, 1590, 1481, 1174 $cm^{-1}$; $\delta_H$ 7.07 (2H, m), 6.70 (2H, m), 4.04 (2H, q, J 7.05 Hz), 3.42-1.2 (18H, m), 1.19 (3H, t, J 7.05 Hz); $\delta_C$ 171.35 (C-18), 146.60 (C-13), 132.08 (C-8), 128.45 (C-11), 123.08 (C-9), 121.73 (CN), 120.81 (C-10), 111.06 (C-12), 68.47 (C-21), 64.30 (C-2), 60.08 ($O\underline{C}H_2CH_3$), 57.75 (C-7), 52.98 (C-3), 51.46 (C-5), 42.47 (C-19), 36.29 (C-6), 36.19 (C-20), 34.83 (C-15), 32.67 (C-16), 23.24 (C-17), 21.40 (C-14), 14.25 ($CH_3$); $\lambda_{max.}$ (EtOH) 204, 239, 292 nm; m/z (%) 365 ($M^+$, 7), 338 (17), 320 (5), 277 (22), 250 (11), 210 (5), 182 (100), 154 (6), 109 (5).

19-Carboethoxy-19-demethylaspidospermidine (22). — To a solution of 1,2-dehydro-19-carboethoxy-19-demethylaspidospermidine (20) (72 mg, 0.21 mmol) in dry ethanol (20 ml) cooled to 0°C, sodium borohydride (95 mg, 2.5 mmol) was added. The mixture was kept at 0°C for 36 h, then water (40 ml) was added and the mixture extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with water (50 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure, which gave 19-carboethoxy-19-demethylaspidospermidine (22) (68 mg, 95%) as a colourless oil (Found: $M^+$, 340.21574. $C_{21}H_{28}N_2O_2$ requires M, 340.215066); $\nu_{max.}$ ($CHCl_3$) 3050-2750, 1724, 1608, 1464, 1177, 1030 $cm^{-1}$; $\delta_H$ 7.03 (2H, m), 6.67 (2H, m), 4.04 (2H, q, J 7.05 Hz), 3.55 (1H, dd, J 11, 10 Hz), 3.11 (2H, m), 2.5-1.2 (17H, m), 1.19 (3H, t, J 7.05 Hz); $\delta_C$ 171.79 (C-18), 149.63 (C-13), 134.30 (C-8), 127.53 (C-11), 122.76 (C-9), 119.13 (C-10), 110.58 (C-12), 69.83 (C-21),

64.79 (C-2), 59.86 ($O\underline{C}H_2CH_3$), 53.52 (C-7), 53.56 (C-3), 52.55 (C-5), 42.47 (C-19), 38.08 (C-6), 36.13 (C-20), 34.89 (C-15), 28.12 (C-16), 24.32 (C-17), 21.56 (C-14), 14.25 ($CH_3$); $\lambda_{max.}$ (EtOH) 205.5, 240, 293 nm; m/z (%) 340 ($\underline{M}^+$, 15), 312 (7), 295 (8), 252 (53), 210 (7), 182 (100), 144 (11), 130 (10).

(±)-12-Demethoxy-N-acetylcylindrocarine (30). — To 19-carboethoxy-19-demethyl-aspidospermidine (22) (91 mg, 0.27 mmol) in absolute methanol a solution of sodium methoxide (from 10 mg sodium) in absolute methanol (2 ml) was added. The solution was heated at reflux for 47 h, then cooled. Water (5 ml) was added to the mixture, which was then concentrated under reduced pressure. The residue was taken up in dichloromethane (25 ml), washed with water (20 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure to give (±)-12-demethoxy-cylindrocarine (31) as a yellow oil. This oil was dissolved in dry pyridine (8 ml) and acetic anhydride (2 ml) was added. The reaction mixture was stirred at 40°C for 2 h, then the volatile materials were removed under reduced pressure. The residue was taken up in dichloromethane (50 ml), washed with water (20 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (75 g) using dichloromethane/methanol (1.5%) as eluent, which gave (±)-12-demethoxy-N-acetylcylindrocarine (30) (52 mg, 53%) as a clear yellow oil (Found: $\underline{M}^+$, 368.20936. $C_{22}H_{28}N_2O_3$ requires $\underline{M}$, 368.209980); $\nu_{max.}$ ($CDCl_3$) 3050-2720, 1730, 1650, 1600, 1480, 1409, 1175 $cm^{-1}$; $\delta_H$ 8.12 (1H, m), 7.3-6.9 (3H, m), 4.04 (1H, dd, $\underline{J}$ 10.8, 8 (Hz), 3.57 (3H, s), 3.3-2.95 (2H, m), 2.53 (1H, s), 2.26 (3H, s), 2.5-1.2 (14H, m); $\delta_C$ 171.84 (C-18), 168.26 (N-$\underline{C}O$-$CH_3$), 141.12 (C-13), 137.44 (C-8), 127.96 (C-11), 124.33 (C-9), 122.32 (C-10), 118.59 (C-12), 69.85 (C-21), 67.61 (C-2), 53.52 (C-7), 53.04 (C-3), 52.22 (C-5), 51.03 (OMe), 42.36 (C-19), 39.33 (C-6), 36.03 (C-20), 34.83 (C-15), 29.74 (C-16), 24.59 (C-17), 23.19 (NCO-$\underline{C}H_3$), 21.61 (C-14); $\lambda_{max.}$ (MeOH) 212, 251, 278, 288 nm; m/z (%) 368 ($\underline{M}^+$, 17), 340 (4), 337 (5), 327 (1), 325 (5), 309 (4), 295 (22), 294 (58), 251 (4), 196 (7), 168 (100), 156 (5), 144 (9), 130 (7), 109 (6), 43 (27).

1-Carbomethoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (32). — A solution of 7-methoxytryptamine hydrochloride (3.20 g, 14.1 mmol) and methyl pyruvate (2.25 g, 22.0 mmol) in methanol (200 ml) was heated at reflux for 48 h. The solvent was then removed under reduced pressure to give a brown oily solid which was taken up in 1M hydrochloric acid (50 ml) and washed with chloroform (2 x 25 ml). The aqueous layer was cooled to 0°C and slowly adjusted to pH 12 by the addition of dilute ammonia solution. The precipitate was collected at the pump, washed with water and dried in air. Recrystallisation from aqueous ethanol gave 1-carbomethoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (32) (2.30 g, 60%)

as colourless prisms, m.p. 130-131°C (Found: C, 65.55; H, 6.6; N, 10.2%, $\underline{M}^+$, 274.13168. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%, $\underline{M}$, 274.131734); $\nu_{max.}$ (Nujol) 3330, 3180 (br), 1731, 1624, 1581 (sh), 1572, 1155, 1106, 1060, 810, 780, 739 $cm^{-1}$; $\delta_H$ 8.36 (1H, br. s), 7.24-6.57 (3H, m), 3.93 (3H, s), 3.74 (3H, s), 3.19 (2H, t, $\underline{J}$ 6 Hz), 2.73 (2H, m), 2.34 (1H, br. s, exchanges with $D_2O$), 1.70 (3H, s); $\lambda_{max.}$ ($\log_{10}$ $\epsilon$) (MeOH) 218 (4.49) 266 (3.84), 288 nm (sh) (3.55); m/z (%) 274 ($\underline{M}^+$, 7), 215 (100), 200 (21), 185 (8), 169 (4), 155 (3), 131 (3), 155 (5), 100 (4), 77 (3), 69 (7).

19-Carboethoxy-12-methoxy-19-demethylvincadifformine (33). — A mixture of 1-carbomethoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (32) (1.95 g, 7.11 mmol), ethyl 3-formyl-6-chlorohexanoate (6) (1.62 g, 7.83 mmol) and p-toluenesulphonic acid (50 mg) in toluene (200 ml) was heated at reflux in a Dean and Stark apparatus for 120 h, under a nitrogen atomsphere. The reaction mixture was cooled, and the solvent removed under reduced pressure. The residue was purified by chromatography on Kieselgel G (150 g) using dichloromethane/methanol (0-2%) as eluent, which gave 19-carboethoxy-12-methoxy-19-demethylvincadifformine (33) (1.25 g, 41%) as an orange oil (Found: $\underline{M}^+$, 426.21513. $C_{24}H_{30}N_2O_5$ requires $\underline{M}$, 426.215458); $\nu_{max.}$ (film) 3385 (br), 2946, 2860, 2781, 2730, 1732, 1680, 1618, 1498, 1460, 1440, 1276, 1050, 780, 760, 738 $cm^{-1}$; $\delta_H$ 8.83 (1H, br. s), 6.87-6.65 (3H, m), 3.96 (2H, q, $\underline{J}$ 7 Hz), 3.85 (3H, s), 3.76 (3H, s), 3.2-1.4 (15H, m), 1.13 (3H, t, $\underline{J}$ 7 Hz); $\delta_C$ 171.30 (C-18), 168.75 (C-22), 166.79 (C-2), 144.27 (C-12), 138.14 (C-13), 132.07 (C-8), 121.24 (C-11), 113.60 (C-10), 110.19 (C-9), 93.40 (C-16), 71.46 (C-21), 59.81 ($O\underline{C}H_2CH_3$), 56.12 (C-7), 55.42 (OMe), 51.57 (C-5), 50.76 (C-3), 50.76 (OMe), 45.29 (C-6), 41.39 (C-19), 38.46 (C-20), 33.48 (C-15), 26.87 (C-17), 22.10 (C-14), 14.08 ($OCH_2\underline{C}H_3$); $\lambda_{max.}$ ($\log_{10}$ $\epsilon$) (EtOH) 206 (4.77), 227 (4.65), 288 (4.36), 331 nm (4.68); m/z (%) 426 ($\underline{M}^+$, 14), 381 (2), 310 (1), 182 (100), 154 (4), 109 (3), 96 (2), 81 (2), 57 (3).

1,2-Dehydro-19-carboethoxy-12-methoxy-19-demethylaspidospermidine (35) and 2-cyano-19-carboethoxy-12-methoxy-19-demethylaspidospermidine (36). — A mixture of 19-carboethoxy-12-methoxy-19-demethylvincadifformine (33) (550 mg, 1.29 mmol), dry hexamethylphosphoramide (70 ml) and sodium cyanide (500 mg, 8.47 mmol) was heated at 80-90°C for 6 days, while under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature, diluted with water (150 ml), and extracted with ether (5 x 70 ml). The combined ethereal extracts were washed with water (5 x 150 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (150 g) using dichloromethane/methanol (1%) as eluent, which gave 1,2-dehydro-19-carboethoxy-12-methoxy-

19-demethylaspidospermidine (94 mg, 18%). Owing to its instability this compound was not characterised, but used immediately in the next reaction.

The second product eluted from the column was 2-cyano-19-carboethoxy-12-methoxy-19-demethylaspidospermidine (36) (306 mg, 60%), which was recrystallised from aqueous methanol and obtained as colourless plates, m.p. 136-137°C (Found: $M^+$, 395.22163. $C_{23}H_{29}N_3O_3$ requires $M$, 395.220879); $\nu_{max.}$ (Nujol) 3270 (sh), 2250, 1709, 1620, 1591, 1492, 1310, 1181, 1086, 733 $cm^{-1}$; $\delta_H$ 6.82-6.62 (3H, m), 4.04 (2H, q, $J$ 7.06 Hz), 4.04 (1H, br. s, exchanges with $D_2O$), 3.82 (3H, s), 3.45-1.3 (17H, m), 1.07 (3H, t, $J$ 7.06 Hz); $\lambda_{max.}$ ($\log_{10}$ $\epsilon$) (MeOH) 210 (4.51), 241 (3.81), 287 nm (3.41); m/z (%) 395 ($M^+$, 12), 368 (17), 350 (4), 307 (20), 298 (5), 281 (6), 225 (5), 210 (7), 182 (100), 154 (7), 109 (7), 81 (8).

Ethyl cylindrocarinate (24). — To a solution of 1,2-dehydro-19-carboethoxy-12-methoxy-19-demethylaspidospermidine (35) (90 mg, 0.24 mmol) in dry ethanol (25 ml) at 0°C, sodium borohydride (100 mg, 2.6 mmol) was added, with stirring. The reaction mixture was kept at 0°C for a further 48 h. Water (50 ml) was then added, and the solution was extracted with dichloromethane (3 x 60 ml). The combined dichloromethane extracts were washed with water (60 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure. Ethyl cylindrocarinate (24) (64 mg, 71%) was obtained as a yellow oil (Found: $M^+$, 370.22546. $C_{22}H_{30}N_2O_3$ requires $M$, 370.225630); $\nu_{max.}$ ($CHCl_3$) 1720, 1616, 1592, 1490, 1180 $cm^{-1}$; $\delta_H$ 6.78-6.65 (3H, m), 4.02 (2H, q, $J$ 7.3 Hz), 3.82 (3H, s), 3.58 (1H, dd, $J$ 10.2, 6.4 Hz), 3.2-1.1 (18H, m), 1.19 (3H, t, $J$ 7.3 Hz); $\delta_C$ 171.79 (C-18), 146.16 (C-12), 138.85 and 135.49 (C-8 and C-13), 119.62 (C-10), 115.39 (C-9), 109.54 (C-11), 70.07 (C-21), 65.44 (C-2), 59.75 ($O\underline{C}H_2CH_3$), 55.31 (OMe), 54.28 (C-7), 53.58 (C-3), 52.66 (C-5), 42.63 (C-19), 37.92 (C-6), 36.24 (C-20), 35.16 (C-15), 28.39 (C-16), 24.27 (C-17), 21.78 (C-14), 14.30 ($OCH_2\underline{C}H_3$); $\lambda_{max.}$ (MeOH) 211, 242, 286 nm; m/z (%) 370 (23), 342 (10), 325 (7), 282 (47), 254 (5), 210 (8), 182 (100), 160 (20).

(±)-Cylindrocarine (1). — To ethyl cylindrocarinate (24) (60.0 mg, 0.162 mmol) in absolute methanol (70 ml) a solution of sodium methoxide (from 50 mg sodium) in absolute methanol (20 ml) was added. The reaction mixture was then heated at reflux for 66 h, then cooled to room temperature. Water (5 ml) was added, and the mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane (30 ml), washed with water (15 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (50 g) using dichloromethane/methanol (0-1%) as eluent, which gave (±)-cylindrocarine (1) (54 mg, 93%) as a colourless oil (Found: $M^+$, 356.21065). $C_{21}H_{28}N_2O_3$ requires $M$, 356.209980); $\nu_{max.}$ ($CHCl_3$) 3365 (br), 1730, 1616, 1593,

1490, 1460, 1441, 1180 $cm^{-1}$; $\delta_H$ 6.8-6.61 (3H, m), 3.82 (3H, s), 3.55 (3H, s), 3.7-1.2 (18H, m); $\delta_C$ 172.27 (C-18), 146.22 (C-12), 138.90 and 135.49 (C-8 and C-13), 197.67 (C-10), 115.39 (C-9), 109.59 (C-11), 70.10 (C-21), 65.44 (C-2), 55.37 (-OMe), 54.33 (C-7), 53.63 (C-3), 52.66 (C-5), 50.87 ($CO_2$-Me), 42.47 (C-19), 37.92 (C-6), 36.24 (C-20), 35.27 (C-15), 28.44 (C-16), 24.27 (C-17), 21.83 (C-14); $\lambda_{max.}$ ($\log_{10}$ $\epsilon$) (MeOH) 212 (4.40), 242 (3.67), 286 nm (3.27); m/z (%) 356 ($M^+$, 42), 328 (16), 325 (6), 282 (36), 196 (8), 168 (100), 160 (12), 130 (5), 109 (5), 77 (5), 53 (4).

(±) N-Formylcylindrocarine (37). — Reaction of (±)-cylindrocarine (1) with acetic anhydride and formic acid according to the procedure of Milborrow and Djerassi[11] gave (±) N-formylcylindrocarine (37) (54 mg, 95%) as a colourless oil (Found: $M^+$, 384.20508. $C_{22}H_{28}N_2O_4$ requires M, 384.204894); $\nu_{max.}$ ($CHCl_3$) 2795, 2737, 1731, 1650, 1610, 1591, 1491, 1470, 1370, 1180 $cm^{-1}$; $\delta_H$ 9.33 (1H, d, J 0.9 Hz), 7.1-6.72 (3H, m), 4.54 (1H, dd, J 10.5, 6.1 Hz), 3.88 (3H, s), 3.56 (3H, s), 3.07 (2H, m), 2.46 (1H, s), 2.4-1.2 (15H, m); $\delta_C$ 172.00 (C-18), 161.38 (CHO), 148.60 (C-12), 140.26 (C-8), 127.80 (C-13), 124.82 (C-10), 115.88 (C-9), 111.00 (C-11), 69.40 (C-21), 63.60 (C-2), 55.58 (ar.-OMe), 53.4 (C-7), 52.76 (C-3), 52.11 (C-5), 51.03 ($CO_2$Me), 42.42 (C-19), 39.38 (C-6), 36.08 (C-20), 35.05 (C-15), 24.76 (C-16), 24.32 (C-17), 21.61 (C-14); $\lambda_{max.}$ ($\log_{10}$ $\epsilon$) (MeOH) 254 (3.99), 214.5 (4.34); $\lambda_{min.}$ 233 nm (3.73); m/z (%) 384 ($M^+$, 15), 356 (7), 353 (5), 310 (64), 281 (4), 196 (5), 168 (100), 160 (8), 149 (6), 109 (6), 69 (6).

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