HETEROCYCLES, Vol. 68, No. 11, 2006, pp. 2301 - 2317. © The Japan Institute of Heterocyclic Chemistry
Received, 25th July, 2006, Accepted, 1st September, 2006, Published online, 1st September, 2006. COM-06-10845

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART 106. AN EFFICIENT CONVERGENT SYNTHETIC PATHWAY TO BUILD UP THE IBOPHYLLIDINE SKELETON II. TOTAL SYNTHESIS OF (±)-DEETHYLIBOPHYLLIDINE AND (±)-14-EPI-DEETHYLIBOPHYLLIDINE

Flórián Tóth,[a] György Kalaus,[a,*] István Greiner,[b] Mária Kajtár-Peredy,[c] Ágnes Gömöry,[c] László Hazai,[a] and Csaba Szántay [a,c,*]

[a]Department for Organic Chemistry, Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, Gellért tér 4, H-1521 Budapest, Hungary. [b]Chemical Works of Gedeon Richter Ltd, Gyömrői út 19-21, H-1103 Budapest, Hungary. [c]Institute of Chemistry, Chemical Research Center, Hungarian Academy of Sciences, Pusztaszeri út 59-67, H-1025 Budapest, Hungary

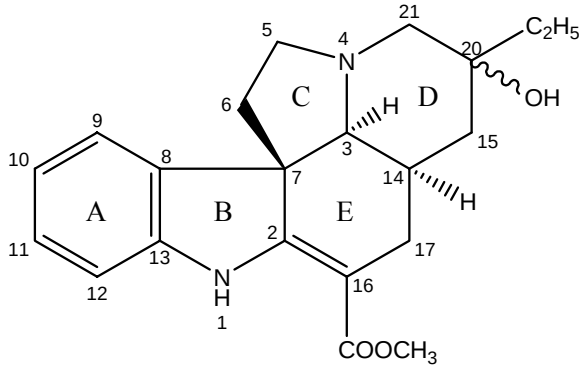
Corresponding author. Tel.: +36-1-463-1285; e-mail: kalaus@mail.bme.hu

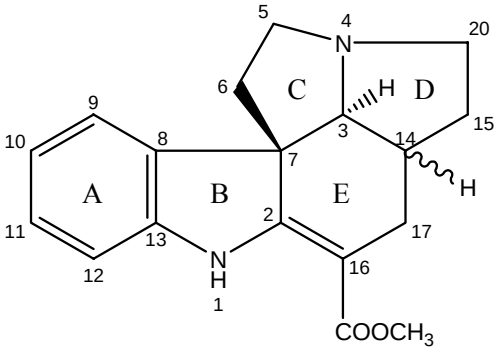
Abstract – Starting from 2,3-dihydrofuran **(7)** we prepared aldehyde **(5)** which, in a [4+2] cycloaddition reaction with the tryptamine derivative **(4)** gave, as a final step, compound **(10)** having a D-*seco*-aspidospermane skeleton. We synthesized (±)-14-epi-deethylibophyllidine **(3)** *via* the mesylate **(12)** of alcohol **(11)** which had been obtained from **10**, whereas the cyclization of the benzoate ester **(15)** resulted in (±)-deethylibophyllidine **(2)**. We have managed to build up (±)-**2** *via* the tetracyclic intermediates (**16**) and (**20**).

INTRODUCTION

The skeleton of indole alkaloids is characterized by a great deal of diversity. *Ibophyllidine* alkaloids, such as deethylibophyllidine **(2)** have a five-membered D-ring and biogenetically deduced from one group of the pseudoaspidospermane alkaloids (e.g. **1a** and **1b**) [1-4] (Figure 1). Deethylibophyllidine **(2)** was isolated in 1980 by French researchers from the bark of *Tabernaemontana albiflora*.[5] As compared to the *Aspidosperma* and *Strychnos* alkaloids,[6, 7] much less attention has been given to the investigation of

Ibophyllidine alkaloids. Therefore we aimed to achieve a simple synthetic route for the preparation of alkaloid **(2)** from *Ibophyllidine* family and its analogue compound **(3)**.[8] Our previous experiences [9-14] gave us a reason to regard this as a plausible objective.





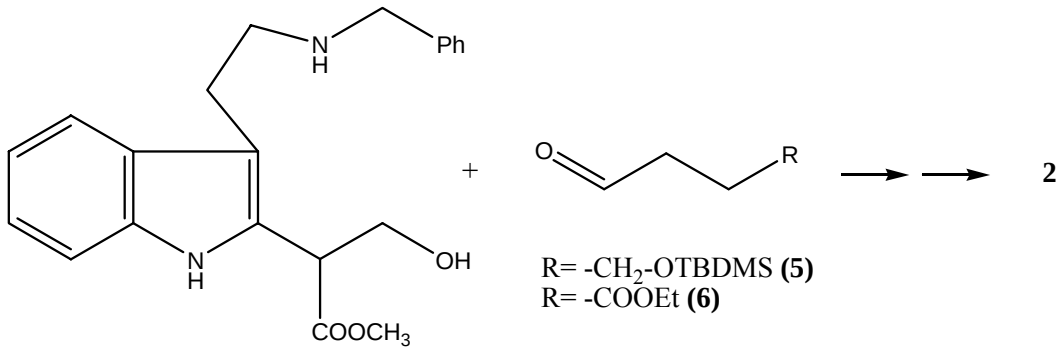
1a C20-βOH Pandoline
1b C20-αOH 20-Epi-pandoline

2 C14-αH Deethylibophyllidine
3 C14-βH 14-Epi-deethylibophyllidine

Figure 1

RESULTS AND DISCUSSION

As a substrate for the planned synthesis we utilized the tryptamine derivative **(4)** which we had used successfully in our earlier works.[9] We anticipated that the appropriately functionalized aldehydes **(5, 6)** and (**4**) would give, in several steps, molecules with D-*seco*-aspidospermane skeleton, from which the pentacyclic alkaloid **(2)** can be made to form easily (Figure 2).

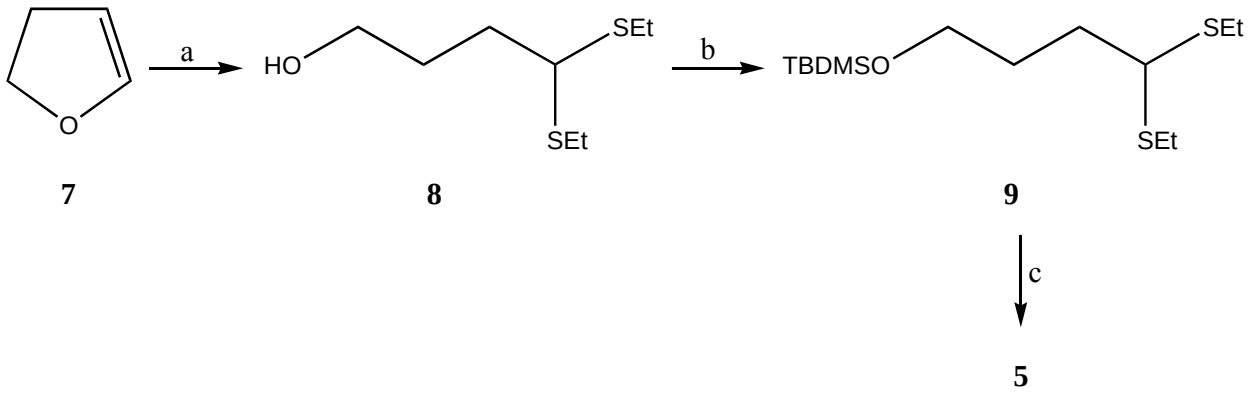


4

Figure 2

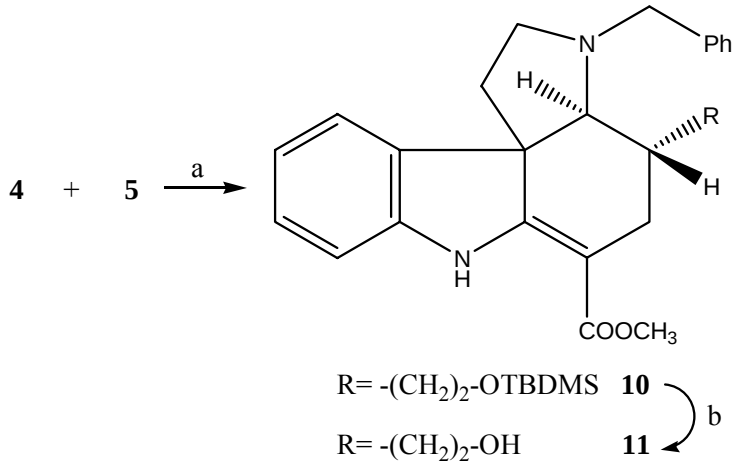
One of the reaction partners **(5)** was formed from 2,3-dihydrofuran **(7),** as a molecule containing a masked aldehyde function. In the first step, using a method known from the literature,[15] we opened up the ring of compound **(7)** by the application of boron trifluoride-diethyl etherate and ethanethiol **(8),** then we protected the alcohol **(8)** with *tert*-butyldimethylsilyl chloride in the presence of imidazole **(9)**. Finally,

after removing the dithioacetal protective group with mercury (II) chloride in the presence of calcium carbonate in aqueous acetonitrile at room temperature, we arrived at aldehyde **(5)** (Scheme 1).



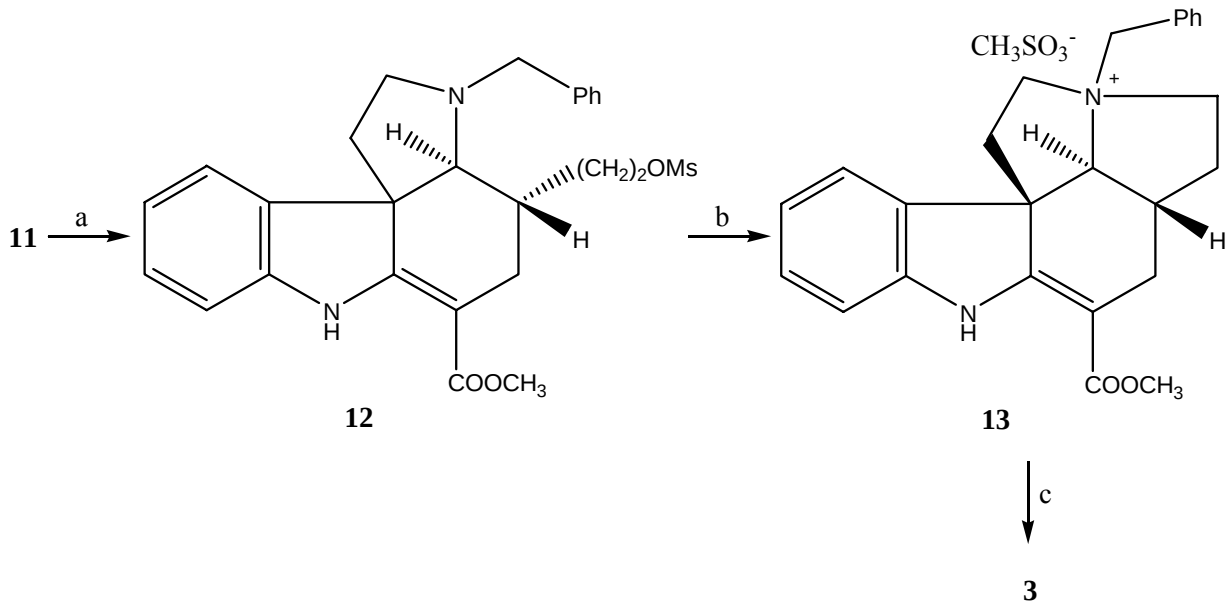
Scheme 1. Reagents and conditions: (a) EtSH, $BF_3 \cdot Et_2O$, $CHCl_3$, 0ºC, (86%); (b) TBDMSCl, imidazole, CH_2Cl_2, rt, (92%); (c) $HgCl_2$, $CaCO_3$, CH_3CN, H_2O, rt, (78%).

As a continuation, we allowed **5** to react with the tryptamine derivative **(4)** in boiling toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. From the reaction mixture the tertiary amine **(10)** was obtained in a good yield. We intended to construct the five-membered D-ring of the *Ibophyllidine* alkaloids by intramolecular alkylation, therefore, by hydrolysis of the derivative **(10)** containing the silyl moiety, we produced the alcohol **(11)** (Scheme 2).



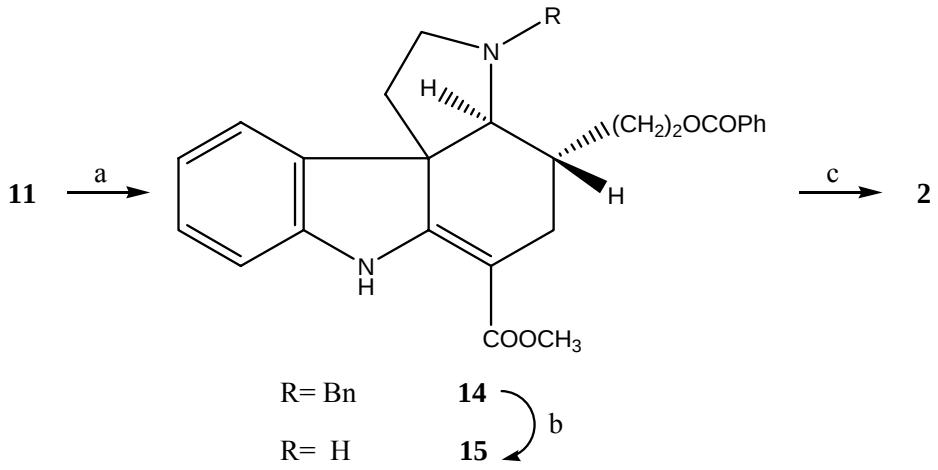
Scheme 2. Reagents and conditions: (a) *p*-$TsOH \cdot H_2O$, toluene, reflux, (67%); (b) 5M HCl, THF, rt, (88%).

Subsequently **11** was acylated with methanesulfonic acid chloride in the presence of triethylamine, then the mesylate **(12)** was converted to the quaternary salt **(13)** in boiling tetrahydrofuran from which, after catalytic debenzylation, the (±)-14-epi-deethylibophyllidine **(3)** was obtained in a good yield. The formation of the product with the trans D/E ring connection can be explained by the fact that under the conditions applied, prior to cyclization, the complete epimerization that had previously been observed by us,[16] and which would result in alkaloid **(2)**, does not take place (Scheme 3).



Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0°C, (82%); (b) THF, reflux, (69%); (c) H_2, Pd/C, CH_3COOH, rt, (83%).

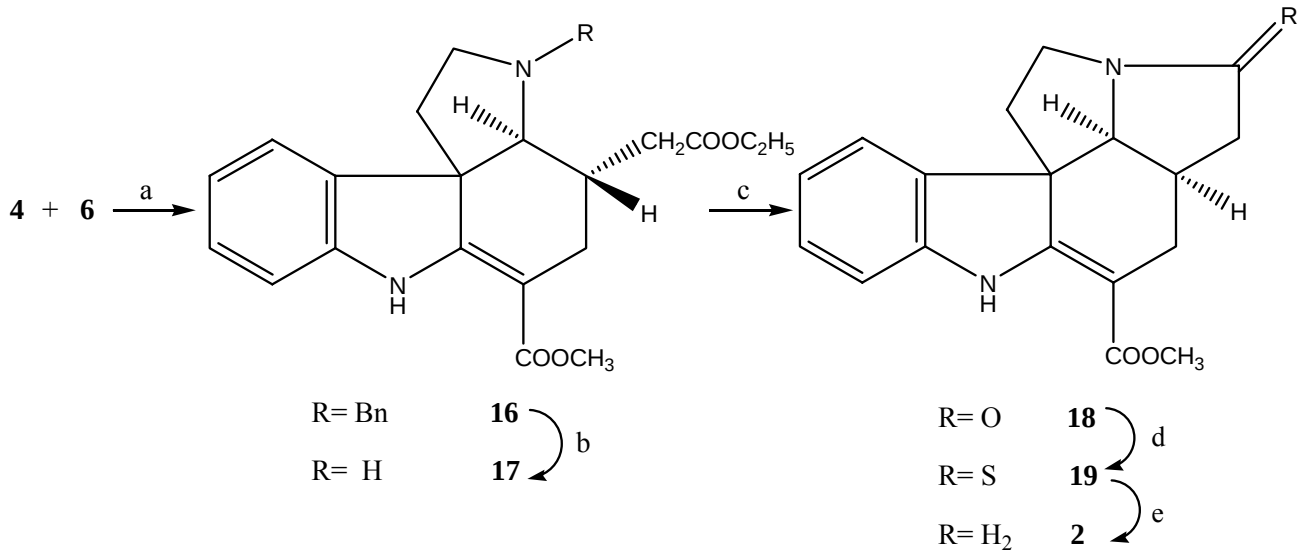
In the course of further studying the intramolecular alkylation reaction, we prepared the benzoate ester **(14)** of the alcohol **(11)** as well. The catalytic debenzylation of **14** in glacial acetic acid resulted in the expected molecule **(15)**. Boiling the secondary amine **(15)** in toluene, after full epimerization, according to our previous results and described mechanism,[16] we obtained racemic deethylibophyllidine **(2)** (Scheme 4).



Scheme 4. Reagents and conditions: (a) PhCOOH, DCC, DMAP, CH_2Cl_2, 0°C, (85%); (b) H_2, Pd/C, CH_3COOH, rt, (92%); (c) toluene, reflux, (71%).

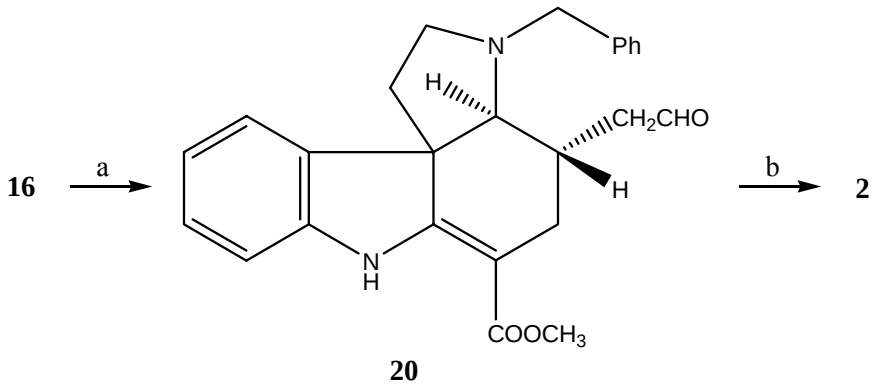
Utilizing our experiences from earlier syntheses,[9-14] we also synthesized the ibophyllidine skeleton *via* the lactam **(18)** known in the literature.[8c] We allowed the secondary amine **(4)** to react with ethyl-4-oxobutanoate **(6)**[17] in boiling toluene in the presence of *p*-toluenesulfonic acid monohydrate, yielding the tetracyclic ester **(16)**. Following catalytic debenzylation, by boiling the secondary amine **(17)**

in toluene we obtained the lactam **(18)** in a good yield. Further on, we converted **18** with phosphorus pentasulfide in tetrahydrofuran into thiolactam **(19)** and finally, the reductive desulfuration of the latter compound furnished (±)-deethylibophyllidine **(2)** (Scheme 5).



Scheme 5. Reagents and conditions: (a) *p*-TsOH·H_2O, toluene, reflux, (61%); (b) H_2, Pd/C, CH_3COOH, rt (95%); (c) toluene, reflux, (78%); (d) P_4S_{10}, THF, rt, (83%); (e) Raney Ni, THF, rt, (81%).

When ester **(16)** was reduced to aldehyde **(20)** with diisobutylaluminium hydride, the tertiary amine was catalytically debenzylated and under the reaction conditions applied (±)-**2** was obtained *via* epimerization, cyclization and reduction steps. (Scheme 6).



Scheme 6. Reagents and conditions: (a) DIBAL, CH_2Cl_2, -70°C, (66%); (b) H_2, Pd/C, CH_3COOH, rt, (82%).

CONCLUSION

Starting from 2,3-dihydrofuran **(7)** we produced aldehyde **(5)**, the reaction of which with the tryptamine derivative **(4)** yielded compound **(10)** with D-*seco*-aspidospermane skeleton. The intramolecular

alkylation reaction of the mesyl ester **(12)**, which had been prepared from alcohol **(11)** led to (±)-14-epi-deethylibophyllidine **(3)** as a final result, whereas the cyclization achieved *via* the benzoate ester **(15)** furnished (±)-deethylibophyllidine **(2)**. The synthesis of **(±)-2** from ester **(16)** was performed *via* two other reaction paths as well (see: **16→17→18→19→2**, and **16→20→2**, respectively).

EXPERIMENTAL

Melting points were determined on a hot-stage microscope Boetius and are uncorrected. IR spectra were recorded on a Specord JR-75 spectrophotometer. NMR spectra were recorded on a Varian Unity INOVA-400 instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All NMR spectra were recorded at rt. J_{1r}, long range coupling constant. Chemical shifts are relative to Me_4Si (δ=0 ppm). Mutual ^{1}H-^{1}H couplings are given only once, at the first occurrences. MS spectra were recorded on a PE Sciex API 2000 triple-quadrupole mass spectrometer equipped with a Turbo Ion Spray source and VG ZAB2-SEQ tandem mass spectrometer (high resolution mass spectra). Preparative TLC analyses were performed on silica gel F_{254} plates, and column chomatography was carried out on Merck Kieselgel 60 (0.063-0.200 mm).

4,4-Bis(ethylthio)butan-1-ol (8)

2,3-Dihydrofuran **(7)** (3.52 g, 3.8 mL, 50 mmol) was dissolved in dry $CHCl_3$ (50 mL) and EtSH (6.21 g, 7.4 mL, 100 mmol) was added to the solution. It was cooled to 0^{o}C and $BF_3{\cdot}OEt_2$ (6.38 g, 5.7 mL, 50 mmol) was added dropwise to the solution over 10 min period. After the addition, the reaction mixture was allowed to warm up to rt, and then stirred for 30 min. It was then poured into water (20 mL). The aqueous phase extracted with $CHCl_3$ (2×30 mL) and the combined organic phases were washed with 1 M aqueous solution of NaOH (20 mL) and brine (20 mL). It was dried ($MgSO_4$) and concentrated in vacuo, to yield **8** (8.36 g, 86%) as a colorless oil (TLC: acetone/hexane=1:2, R_f=0.72). IR (neat) ν_{max} 3352, 2928, 1452, 1264, 1060. MS m/z (%) (rel intensity) 194 (16.0, M^+), 133 (30.0), 115 (23.0), 87 (10.0), 71 (100.0). HRMS (EI) calcd for $C_8H_{18}OS_2$ 194.0799, found for 194.0805. ^{1}H NMR δ_H ($CDCl_3$): 1.26 (6H, t, J=7.4 Hz; 2×$SCH_2C\underline{H}_3$), 1.74 (1H, t, J=4.5 Hz; OH), 1.76-1.94 (4H, m; 2-H_2+3-H_2), 2.60+2.69 (2×2H, 2×dq, J_{gem}=12.5 Hz, J_{vic}=7.4 Hz; 2×$SC\underline{H}_2CH_3$), 3.67 (2H, td, J_{vic}=5.8 and 4.5 Hz; 4-H_2), 3.82 (1H, t, J=6.8 Hz; 1-H). ^{13}C NMR δ_C ($CDCl_3$): 14.50+24.18 (2×SCH_2CH_3), 30.57 (C3), 32.54 (C2), 51.19 (C1), 62.25 (C4).

(4,4-Bis(ethylthio)butoxy)(*tert*-butyl)dimetylsilane (9)

Imidazole (2.10 g, 31 mmol) was added to a solution of **8** (5.00 g, 26 mmol) in dry CH_2Cl_2 (50 mL). Then *tert*-butyldimethylsilyl chloride (4.65 g, 31 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the stirred solution. After the addition, the mixture was stirred for 2 h at rt. The salts were separated by

filtration and the organic phase was washed with water (2×15 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to give **9** (7.38 g, 92%) a colorless liquid (TLC: AcOEt/hexane=1:4, R_f=0.9). IR (neat) ν_{max} 2960, 2928, 1256, 1176, 840. MS m/z (%) (rel intensity) 308 (2.0, M^+), 247 (24.0), 189 (48.0), 115 (100.0), 73 (22.0). HRMS (EI) calcd for $C_{14}H_{32}OS_2Si$ 308.1664, found for 308.1665. ^{1}H NMR δ_H ($CDCl_3$): 0.07 (6H, s; $Si(C\underline{H}_3)_2$, 0.91 (9H, s; $SiC(C\underline{H}_3)_3$), 1.28 (6H, t, J=7.5 Hz; 2×$SCH_2C\underline{H}_3$), 1.73-1.93 (4H, m; 2-H_2+3-H_2), 2.61+2.70 (2×2H, 2×dq, J_{gem}=12.5 Hz, J_{vic}=7.5 Hz; 2×$SC\underline{H}_2CH_3$), 3.65 (2H, t, J=6.1 Hz; 4-H_2) 3.83 (1H, t, J=6.9 Hz; 1-H). ^{13}C NMR δ_C ($CDCl_3$): -5.28 ($Si(CH_3)_2$, 14.57+24.13 (2×SCH_2CH_3), 18.33 ($Si\underline{C}(CH_3)_3$), 25.97 ($SiC(\underline{C}H_3)_3$), 30.61 (C3), 32.52. (C2), 51.27 (C1), 62.53 (C4).

4-(*tert*-Butyldimethylsilanyloxy)butanal (5)

9 (2.00 g, 6.5 mmol) was dissolved in acetonitrile (50 mL) and water (5 mL) was added to the solution. $CaCO_3$ (2.60 g, 26 mmol) and mercury(II) chloride (7.10 g, 26 mmol) were added to a stirred solution. After the addition the mixture was stirred for 1 h. The salts were filtrated and the acetonitrile was removed at 40^{o}C under reduced pressure to leave a yellow oil. This was then taken up into CH_2Cl_2 (50 mL) and washed with 20 mL portion of aqueous solution of NaI, 20 mL portion of aqueous solution of $Na_2S_2O_8$ and brine (20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum, yielded 1.03 g (78 %) of **5** as a colorless oil (TLC: AcOEt/hexane=1:4, R_f=0.69). IR (neat) ν_{max} 2928, 1728, 1468, 1256, 1100. MS m/z (%) (rel intensity) 202 (2.0, M^+), 161 (12.0), 145 (17.0), 75 (100.0). HRMS (EI) calcd for $C_{10}H_{22}O_2Si$ 202.1389, found for 202.1392. ^{1}H NMR δ_H ($CDCl_3$): 0.06 (6H, s; $Si(CH_3)_2$), 0.91 (9H, s; $SiC(C\underline{H}_3)_3$), 1.88 (2H, m; 3-H_2), 2.52 (2H, td, J_{vic}=7.0 and 1.8 Hz; 2-H_2), 3.67 (2H, t, J=6.0 Hz; 4-H_2), 9.81 (1H, t, J=1.8 Hz; CHO). ^{13}C NMR δ_C ($CDCl_3$): -5.41 ($Si(CH_3)_2$), 18.29 ($Si\underline{C}(CH_3)_3$), 25.52 (C3), 25.90 ($SiC(\underline{C}H_3)_3$), 40.78 (C2), 62.09 (C4), 202.58 (C1).

3-Benzyl-4-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-2,3,3a,4,5,7-hexahydro-1H-pyrrolo[2,3-*d*]carb-azole-6-carboxylic acid methyl ester (10)

A solution of **4** (1.00 g, 2.85 mmol), **5** (0.69 g, 3.42 mmol), and *p*-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) in dry toluene (50 mL) was refluxed under argon over 24 h, then the reaction mixture was cooled and extracted with brine (2×40 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with AcOEt/hexane=1:4, R_f=0.65) to yield 0.99 g (67 %) of **10** as a yellow oil. IR (neat) ν_{max} 3384, 2928, 1676, 1612, 1464, 1440, 1248, 1104, 744. MS m/z (%) (rel intensity) 518 (33.0, M^+), 385 (65.0), 304 (100.0), 168 (11.0), 91 (74.0). HRMS (EI) calcd for $C_{31}H_{42}N_2O_3Si$ 518.2965, found for 518.2973. ^{1}H NMR δ_H ($CDCl_3$): -0.02+ -0.01 (2×3H, 2×s; $Si(CH_3)_2$), 0.85 (9H, s; $SiC(CH_3)_3$), 1.12 (2H, m; 15-H_2), 1.67+2.03 (2×1H, 2×ddd, J_{gem}=11.6 Hz, J_{vic}=4.9+<1 and 12.0+6.0 Hz; 6-H_2), 2.09 (1H, m; 14-H), 2.53+2.62 (2×1H,

2×dd, J_{gem}=15.0 Hz, J_{vic}=3.3 and 3.0 Hz; 17-H_2), 2.65+2.90 (2×1H, 2×ddd, J_{gem}=9.0 Hz, J_{vic}=12.0+4.9 and 6.0+<1 Hz; 5-H_2), 2.98 (1H, br s; 3-H), 3.49 (2H, m; 20-H_2), 3.72+4.13 (2×1H, 2×d, J_{gem}=13.0 Hz; NC$\underline{H}_2$Ph), 3.77 (3H, s; OCH_3), 6.80 (1H, d, J=7.7 Hz; 12-H), 6.82 (1H, ddd, J=7.5+7.4+1.4 Hz; 10-H), 6.94 (1H, br d, J=7.5 Hz; 9-H), 7.13 (1H, ddd, J=7.7+7.4+1.6 Hz; 11-H), 7.24-7.40 (5H, m; Ph), 8.94 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): -5.39 and -5.32 ($Si(CH_3)_2$), 18.34 ($Si\underline{C}(CH_3)_3$), 22.46 (C17), 25.99 ($SiC(\underline{C}H_3)_3$), 33.96 (C15), 35.28 (C14), 42.33 (C6), 50.40 (C5), 50.92 (OCH_3), 55.16 (C7), 58.02 (N$\underline{C}H_2$Ph), 61.11 (C20), 71.56 (C3), 90.87 (C16), 109.18 (C12), 120.51 (C9), 122.26 (C10), 127.77 (C11), 127.05+128.31+129.05+138.98 (Ph), 137.97 (C8), 143.08 (C13), 165.33 (C2), 169.08 (16-$\underline{C}OOCH_3$).

3-Benzyl-4-(2-hydroxyethyl)-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylic acid methyl ester (11)

5 M aqueous solution of HCl (0.75 mL) was added to a solution of **10** (1.00 g, 1.92 mmol) in 10 mL THF and the mixture was stirred for 45 min at rt. After stirring the mixture was concentrated in vacuo, then the residue was dissolved in CH_2Cl_2 (25 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=1:2, R_f=0.4) to yield a yellow oil, which was crystallized from CH_3OH to afford **11** (0.69 g, 88 %) as white crystals. IR (neat) ν_{max} 3376, 2952, 1676, 1608, 1464, 1440, 744. MS m/z (%) (rel intensity) 404 (10.0, M^+), 373 (4.0), 271 (4.0), 190 (36.0), 91 (100.0). HRMS (EI) calcd for $C_{25}H_{28}N_2O_3$ 404.2099, found for 404.2099. ^{1}H NMR δ_H ($CDCl_3$): 1.11+1.18 (2×1H, 2×dm, J_{gem}=13.8 Hz; 15-H_2), 1.68+2.05 (2×1H, 2×ddd, J_{gem}=11.7 Hz, J_{vic}=4.9+<1 and 12.0+6.0 Hz; 6-H_2), 2.04 (1H, m; 14-H), 2.55+2.63 (2×1H, 2×dd, J_{gem}=15.2 Hz, J_{vic}=3.3 and 3.0 Hz; 17-H_2), 2.68+2.96 (2×1H, 2×ddd, J_{gem}=9.0 Hz, J_{vic}=12.0+4.9 and 6.0+<1 Hz; 5-H_2), 2.98 (1H, br s; 3-H), 3.10 (1H, br s; OH), 3.50 (2H, t, J=6.7 Hz; 20-H_2), 3.79+4.11 (2×1H, 2×d, J_{gem}=13.0 Hz; NC$\underline{H}_2$Ph), 3.77 (3H, s; OCH_3), 6.81 (1H, br d, J=7.7 Hz; 12-H), 6.83 (1H, ddd, J=7.5+7.4+1.4 Hz; 10-H), 6.94 (1H, br d, J=7.5 Hz; 9-H), 7.13 (1H, ddd, J=7.7+7.4+1.6 Hz; 11-H), 7.25-7.40 (5H, m; Ph), 8.94 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 22.50 (C17), 33.94 (C15), 35.30 (C14), 42.17 (C6), 50.56 (C5), 51.02 (OCH_3), 55.20 (C7), 58.15 (N$\underline{C}H_2$Ph), 60.77 (C20), 71.72 (C3), 90.67 (C16), 109.25 (C12), 120.58 (C9), 122.22 (C10), 127.88 (C11), 127.21+128.36+129.16+138.64 (Ph), 137.74 (C8), 143.02 (C13), 165.02 (C2), 169.01 (16-$\underline{C}OOCH_3$). Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found C, 73.94; H, 6.87; N 7.00.

2-(9-(Methoxycarbonyl)-1-benzyl-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-11-yl)ethyl methanesulfonate (12)

11 (1.00 g, 2.47 mmol) was dissolved in dry CH_2Cl_2 (20 mL), triethylamine (0.41 mL, 0.30 g, 2.97 mmol) and 4-dimethylaminopyridine (35 mg, 0.3 mmol) were added to the solution. After the addition it was

cooled to 0°C and methanesulfonyl chloride (0.23 mL, 0.34 g, 2.97 mmol) was added dropwise at 0°C. The mixture was stirred 1 h and poured into water (5 mL). The phases were separated and the organic phase was washed with brine (10 mL). It was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (eluent: Et_2O/hexane=1:5, R_f=0.45) to afford 1.08 g (82 %) of the product **(12)** as a yellow oil. IR (neat) ν_{max} 3376, 2936, 1676, 1608, 1464, 1352, 1208, 746. MS m/z (FAB) (%) (rel intensity) 483 (10.0, $M+H^+$), 387 (45.0), 268 (12.0), 194 (13.0), 168 (15.0), 91 (100.0). HRMS (FAB) calcd for $C_{26}H_{31}N_2O_5S$ ($M+H^+$) 483.1958, found for ($M+H^+$) 483.1951. ^{1}H NMR δ_H ($CDCl_3$): 1.33 (2H, m; 15-H_2), 1.70+2.06 (2×1H, 2×ddd, J_{gem}=12.1 Hz, J_{vic}=4.8+<1 and 12.0+6.7 Hz; 6-H_2), 2.07 (1H, m; 14-H), 2.59+2.65 (2×1H, 2×dd, J_{gem}=15.5 Hz, J_{vic}=3.5 and 3.0 Hz; 17-H_2), 2.70+2.98 (2×1H, 2×m; 5-H_2), 2.93 (3H, s; OSO_2CH_3), 2.97 (1H, br s; 3-H), 3.78 (3H, s; OCH_3), 3.80+4.13 (2×1H, 2×d, J_{gem}=14.0 Hz; N$C\underline{H}_2$Ph), 4.00-4.14 (2H, m; 20-H_2), 6.82 (1H, d, J=7.7 Hz; 12-H), 6.85 (1H, ddd, J=7.5+7.2+1.0; 10-H), 6.96 (1H, br d; J=7.2 Hz; 9-H), 7.15 (1H, ddd, J=7.7+7.5+1.3 Hz; 11-H), 7.27-7.42 (5H, m; Ph), 8.94 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 21.94 (C17), 30.15 (C15), 35.11 (C14), 37.31 (OSO_2CH_3), 42.09 (C6), 50.58 (C5), 51.11 (OCH_3), 55.15 (C7), 58.16 (N$\underline{C}H_2$Ph), 68.13 (C20), 71.44 (C3), 90.14 (C16), 109.36 (C12), 120.75 (C9), 122.21 (C10), 128.04 (C11), 127.31+128.43+129.08+138.4 (Ph), 137.50 (C8), 142.88 (C13), 164.90 (C2), 168.73 (16-$\underline{C}OOCH_3$).

12-Benzyl-4-(methoxycarbonyl)1,2,2a,3,5,10,11,12a-octahydropyrrolizino[1,7-*cd*]carbazol-12-ium mesylate (13)

12 (0.50 g, 1 mmol) was dissolved in dry THF (10 mL) and it was refluxed over 12 h. Then it was cooled and the salt was separated by filtration. The crystals were washed with cold THF and dried in vacuo to give 345 mg (69 %) of **13** as white crystals. IR (KBr) ν_{max} 3320, 2944, 1680, 1608, 1464, 1204, 748. MS m/z (%) (rel intensity) 483 (100.0, M^+), 387 (10.0), 297 (35.0), 216 (4.0), 149 (5.0). HRMS (EI) calcd for $C_{26}H_{30}N_2O_5S$ 482.9272, found for 482.9269. ^{1}H NMR δ_H ($CDCl_3$): 1.95-2.06 (2H, m; 15-H_2), 2.15+2.80 (2×1H, 2×dd, J_{gem}=16.0 Hz, J_{vic}=12.0 and 4.5 Hz; 17-H_2), 2.22+3.12 (2×1H, 2×ddd, J_{gem}=13.8 Hz, J_{vic}=6.8+~1 and 12.6+8.0 Hz; 6-H_2), 2.55 (1H, m; 14-H), 2.82 (3H, s; $CH_3SO_3^-$), 3.74 (3H, s; OCH_3), 4.00 (1H, d, J=11.9 Hz; 3-H), 4.08+4.88 (2×1H, 2×ddd, J_{gem}=13.2 Hz, J_{vic}=12.4+5.6 and 7.0+<1 Hz; 20-H_2), 4.22+4.79 (2×1H, 2×ddd, J_{gem}=14.0 Hz, J_{vic}=12.6+6.8 and 8.0+<1 Hz; 5-H_2), 4.80+5.70 (2×1H, 2×d, J_{gem}=13.0 Hz; $N^+C\underline{H}_2$Ph), 6.92 (1H, d, J=8.0 Hz; 12-H), 6.97 (1H, ddd, J=7.9+7.2+1.5 Hz; 10-H), 7.29 (1H, ddd, J=8.0+7.2+1.0 Hz; 11-H), 7.44 (1H, d, J=7.9 Hz; 9-H), 9.48 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 26.54 (C17), 29.25 (C15), 39.65 ($CH_3SO_3^-$), 40.26 (C6), 42.12 (C14), 51.62 (OCH_3), 57.06 (C7), 67.93+68.75+6916 (C5+C20+$N^+\underline{C}H_2$Ph), 77.85 (C3), 98.57 (C16), 111.15 (C12), 121.34 (C10), 122.28 (C9), 129.98 (C11), 129.05+129.65+130.93+132.94 (Ph), 131.46 (C8), 145.23 (C13), 159.67 (C2), 167.96 (16-$\underline{C}OOCH_3$).

(±)-14-Epi-deethylibophyllidine (3)

A mixture of **13** (0.50 g, 1 mmol) and 10 % palladium/charcoal (0.25 g) in glacial AcOH (10 mL) was hydrogenated for 2 h at rt and then filtered. The filtrate was poured into ice-water (50 mL) and neutralized with saturated Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purufied by column chromatography (eluting with AcOEt/methanol=1:1, R_f=0.15) yielded 0.26 g (83 %) of **3** as a colorless oil. IR (neat) ν_{max} 3384, 2952, 1676, 1608, 1468, 1440, 1208, 744. MS m/z (%) (rel intensity) 296 (21.0, M^+), 202 (4.0), 167 (3.0), 91 (12.0), 82 (100.0), 44 (58.0). HRMS (EI) calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found for 296.1528. ^{1}H NMR δ_H ($CDCl_3$): 1.59+2.13 (2×1H, 2×dddd, J_{gem}=11.7 Hz, J_{vic}=12.6+9.8+9.0 and 5.6+7.5+1.0 Hz; 15-H_2), 1.82+2.63 (2×1H, 2×ddd, J_{gem}=12.5 Hz, J_{vic}=7.6+1.5 and 10.5+9.6 Hz; 6-H_2), 1.91 (1H, m; 14-H), 2.18+2.84 (2×1H, 2×dd, J_{gem}=15.7 Hz, J_{vic}=12.0 and 4.7 Hz; 17-H_2), 2.83+3.82 (2×1H, 2×ddd, J_{gem}=11.8 Hz, J_{vic}=9.6+1.5 and 10.5+7.6 Hz; 5-H_2), 2.93+3.77 (2×1H, 2×ddd, J_{gem}=11.7 Hz, J_{vic}=9.8+7.5 and 9.0+1.0 Hz; 20-H_2), 2.95 (1H, d, J=10.8 Hz; 3-H), 3.76 (3H, s; OCH_3), 6.78 (1H, d; 12-H), 6.86 (1H, dd; 10-H), 7.14 (1H, dd; 11-H), 7.42 (1H, d; 9-H), 9.18 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 27.30 (C17), 30.50 (C15), 39.67 (C6), 40.74 (C14), 51.20 (OCH_3), 56.41 (C7), 56.71 (C5), 58.57 (C20), 71.86 (C3), 96.73 (C16), 109.57 (C12), 120.99 (C10), 122.15 (C9), 128.13 (C11), 135.71 (C8), 144.34 (C13), 164.11 (C2), 168.88 (16-$\underline{C}OOCH_3$).

11-(2-(Benzoyloxy)ethyl)-1-benzyl-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylic acid methyl ester (14)

1,3-Dicyclohexylcarbodiimide (0.55 g, 2.6 mmol) and 4-dimethylaminopyridine (32 mg, 0.26 mmol) were added to a solution of benzoic acid (0.32 g, 2.6 mmol) in dry CH_2Cl_2 (10 mL). The mixture cooled to 0^{o}C and at this temperature **11** (1.00 g, 2.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The mixture was allowed to warm up to rt and then stirred for 3 h. The suspension was extracted with brine (2×10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (eluting with Et_2O/hexane=1:1, R_f=0.45) to afford 1.08 g (85 %) of the product **(14)** as white crystals after recrystallization from CH_3OH. IR (KBr) ν_{max} 3376, 2952, 1720, 1680, 1608, 1472, 1440, 1384, 1328, 748. MS m/z (%) (rel intensity) 508 (4.0, M^+), 386 (29.0), 367 (13.0), 149 (15.0), 91 (5.0), 82 (100.0). HRMS (EI) calcd for $C_{32}H_{32}N_2O_4$ 508.2362, found for 508.2357. ^{1}H NMR δ_H ($CDCl_3$): 1.34+1.40 (2×1H, 2×dm, J_{gem}=14.0 Hz; 15-H_2), 1.70+2.07 (2×1H, 2×ddd, J_{gem}=11.9 Hz, J_{vic}=5.0+<1 and 12.0+6.2 Hz; 6-H_2), 2.10 (1H, m; 14-H), 2.60+2.71 (2×1H, 2×dd, J_{gem}=15.5 Hz, J_{vic}=3.0 and 2.8 Hz; 17-H_2), 2.68+2.94 (2×1H, 2×ddd, J_{gem}=9.0 Hz, J_{vic}=12.0+5.0 and 6.2+<1 Hz; 5-H_2), 3.03 (1H, br s; 3-H), 3.76+4.11 (2×1H, 2×d, J_{gem}=13.4 Hz; NC$\underline{H}_2$Ph), 3.77 (3H, s; OCH_3), 4.14-4.26 (2H, m; 20-H_2), 6.82 (1H, br d, J=7.7 Hz; 12-H), 6.85 (1H, ddd, J=7.5+7.4+1.4 Hz; 10-H), 6.99 (1H, br d, J=7.5 Hz; 9-H),

7.15 (1H, ddd, J=7.7+7.4+1.6 Hz; 11-H), 7.20-7.42 (7H, m; Ph+3'-H+5'-H), 7.52 (1H, m; 4'-H), 7.96 (2H, m; 2'-H+6'-H), 8.99)1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 22.56 (C17), 29.95 (C15), 36.00 (C14), 42.27 (C6), 50.66 (C5), 51.04 (OCH_3), 55.23 (C7), 58.28 ($NC\underline{H}_2Ph$), 63.21 (C20), 71.58 (C3), 90.56 (C16), 109.30 (C12), 120.65 (C9), 122.29 (C10), 127.92 (C11), 127.14+128.33+128.95+138.88 (Ph), 128.36+129.56 (C2'+C3'+C5'+C6'), 130.37 (C1'), 132.84 (C4'), 137.76 (C8), 143.03 (C13), 165.08 (C2), 166.52 (O$\underline{C}$OPh), 169.02 (16-$\underline{C}OOCH_3$). Anal. Calcd for $C_{32}H_{32}N_2O_4 \cdot CH_3OH$: C, 73.13; H, 6.71; N, 6.39. Found C, 73.08; H, 6.55; N 5.38.

11-(2-(Benzoyloxy)ethyl)-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylic acid methyl ester (15)

A mixture of **14** (0.50 g, 0.98 mmol) and 10 % palladium/charcoal (0.25 g) in glacial AcOH (10 mL) was hydrogenated for 1 h at rt and then filtered. The filtrate was poured into ice-water (40 mL) and neutralized with saturated Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The main component was separated by preparative TLC (eluting with CH_2Cl_2/CH_3OH=20:1, R_f=0.32) yielded 0.38 g (92 %) of **15** as a yellow oil. IR (neat) ν_{max} 3368, 2952, 1720, 1676, 1608, 1464, 1440, 1276, 748. MS m/z (%) (rel intensity) 418 (3.0, M^+), 296 (27.0), 154 (5.0), 122 (16.0), 82 (100.0), 77 (12.0). HRMS (EI) calcd for $C_{25}H_{26}N_2O_4$ 418.1893, found for 418.1897. ^{1}H NMR δ_H ($CDCl_3$): 1.36-1.52 (2H, m; 15-H_2), 1.80-2.10 (3H, m; 6-H_2+14-H), 2.37 (1H, m; N4-H), 2.41+2.74 (2×1H, 2×dd, J_{gem}=15.5 Hz, J_{vic}=3.8 and 3.0 Hz; 17-H_2), 3.10-3.20 (2H, m; 5-H_2), 3.59 (1H, br s; 3-H), 3.77 (3H, s; OCH_3), 4.21+4.28 (2×1H, 2×dt, J_{gem}=11.1 Hz, J_{vic}=7.0 and 6.2 Hz; 20-H_2), 6.85 (1H, br d; 12-H), 6.90 (1H, ddd; 10-H), 7.17 (1H, ddd; 11-H), 7.24 (1H, br d; 9-H), 7.38-7.56 (3H, m; 3'-H+4'-H+5'-H), 7.98 (2H, m; 2-H+6'-H), 9.07 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 22.17 (C17), 30.47 (C15), 38.04 (C14), 44.20 (C6), 45.18 (C5), 51.08 (OCH_3), 55.71 (C7), 62.87 (C20), 66.32 (C3), 90.10 (C16), 109.37 (C12), 120.89 (C9), 121.95 (C10), 128.04 (C11), 128.33+129.57 (C2'+C3'+C5'+C6'), 130.32 (C1'), 132.87 (C4'), 137.48 (C8), 143.14 (C13), 165.22 (C2), 166.54 (O$\underline{C}$OPh), 168.87 (16-$\underline{C}OOCH_3$).

(±)-Deethylibophyllidine (2)

Method I.: A mixture of **15** (0.3 g, 0.72 mmol) and potassium iodide (0.12 g, 0.72 mmol) in dry DMF (7 mL) was refluxed 4 h, then was evaporated in vacuo. The main component was purified by preparative TLC (eluting with AcOEt/CH_3OH=1:1, R_f=0.15) to yield **2** (0.15 g, 71 %) as a yellow oil. IR (neat) ν_{max} 3376, 2944, 1676, 1608, 1248, 1112, 744. MS m/z (%) (rel intensity) 296 (24.0, M^+), 265 (4.0), 239 (5.0), 154 (30.0), 127 (13.0), 115 (6.0), 82 (100.). HRMS (EI) calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found for 296.1537. ^{1}H NMR δ_H ($CDCl_3$): 1.70+2.09 (2×1H, 2×ddd, J_{gem}=12.5 Hz, J_{vic}=5.5+1.2 and 12.0+7.5 Hz;

6-H_2), 1.80+2.16 (2×1H, 2×dddd, J_{gem}=12.8 Hz, J_{vic}=5.7+1.2+1.0 and 11.8+7.2+6.8 Hz; 15-H_2), 1.89+2.81 (2×1H, 2×ddd, J_{gem}=15.4 Hz, J_{vic}=12.0 and 5.9 Hz; 17-H_2), 2.07 (1H, m; 14-H), 2.77+3.33 (2×1H, 2×ddd, J_{gem}=9.5 Hz, J_{vic}=11.8+5.7 and 7.2+1.2 Hz; 20-H_2), 2.93+3.40 (2×1H, 2×ddd, J_{gem}=12.2 Hz, J_{vic}=7.5+1.2 and 12.0+5.5 Hz; 5-H_2), 3.77 (3H, s; OCH_3), 3.79 (1H, d, J=7.0 Hz; 3-H), 6.82 (1H, d; 12-H), 6.90 (1H, dd; 10-H), 7.18 (1H, dd; 11-H), 7.36 (1H, d; 9-H), 9.06 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 26.32 (C17), 31.82 (C15), 38.77 (C14), 38.94 (C6), 50.97 (OCH_3), 52.48 (C5), 55.13 (C20), 57.55 (C7), 73.10 (C3), 91.74 (C16), 109.19 (C12), 120.99 (C10), 122.58 (C9), 128. 13 (C11), 136.62 (C8), 143.55 (C13), 164.29 (C2), 168.54 (16-$\underline{C}OOCH_3$).

11-((Ethoxycarbonyl)methyl)-1-benzyl-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylic acid methyl ester (16)

A solution of **4** (1.00 g, 2.85 mmol), **6** (0.45 g, 3.42 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) in dry toluene (50 mL) was refluxed under argon over 24 h. The reaction mixture was extracted with brine (2×40 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with AcOEt/hexane=1:2, R_f=0.42) to yield a yellow oil, which was crystallized from methanol to afford **16** (0.78 g, 61 %) as white crystals. IR (KBr) ν_{max} 3376, 2976, 1736, 1680, 1612, 1464, 748. MS m/z (%) (rel intensity) 446 (25.0, M^+), 401 (9.0), 313 (59.0), 232 (98.0), 91 (100.0). HRMS (EI) calcd for $C_{27}H_{30}N_2O_4$ 446.2206, found for 446.2225. ^{1}H NMR δ_H ($CDCl_3$): 1.18 (3H, t, J=7.0 Hz; $COOCH_2C\underline{H}_3$), 1.67+2.04 (2×1H, 2×ddd, J_{gem}=11.8 Hz, J_{vic}=5.0+<1 and 12.0+6.1 Hz; 6-H_2), 1.90+2.03 (2×1H, 2×dd, J_{gem}=16.0 Hz, J_{vic}=8.4 and 6.0 Hz; 15-H_2), 2.51 (1H, m; 14-H), 2.63 (2H, m; 17-H_2), 2.63+2.89 (2×1H, 2×ddd, J_{gem}=9.0 Hz, J_{vic}=12.0+5.0 and 6.1+<1 Hz; 5-H_2), 3.04 (1H, br s; 3-H), 3.74+4.30 (2×1H, 2×d, J_{gem}=13.2 Hz; $NC\underline{H}_2Ph$), 3.76 (3H, s; OCH_3), 4.05 (2H, q, J=7.0 Hz; $COOC\underline{H}_2CH_3$), 6.81 (1H, d, J=7.6 Hz;12-H), 6.82 (1H, ddd; 10-H), 6.92 (1H, br d, J=7.2 Hz; 9-H), 7.14 (1H, ddd, J=7.6+7.4+1.7 Hz; 11-H), 7.24-7.42 (5H, m; Ph), 8.96 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 14.23 ($COOCH_2\underline{C}H_3$), 23.49 (C17), 35.76 (C14), 36.16 (C15), 42.23 (C6), 50.10 (C5), 50.96 (OCH_3), 55.02 (C7), 57.55 ($N\underline{C}H_2Ph$), 60.26 ($COO\underline{C}H_2CH_3$), 70.55 (C3), 90.72 (C16), 109.26 (C12), 120.62 (C9), 122.30 (C10), 127.88 (C12), 127.00+128.28+128.99+139.02 (Ph), 137.67 (C8), 142.99 (C13), 164.77 (C2), 168.91 (16-$\underline{C}OOCH_3$), 172.84 ($\underline{C}OOCH_2CH_3$). Anal. Calcd for $C_{27}H_{30}N_2O_4 \cdot CH_3OH$: C, 70.72; H, 6.04; N, 5.85. Found C, 70.79; H, 5.93; N 5.80.

11-((Ethoxycarbonyl)methyl)-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylic acid methyl ester (17)

16 (1.00 g, 2.24 mmol) was dissolved in 10 mL of glacial AcOH and 10 % palladium/charcoal (0.50 g) was added to the solution. It was hydrogenated for 2 h at rt and then filtered. The filtrtate was poured into

ice-water (50 mL) and neutralized with saturated Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 (3×70 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluent: CH_2Cl_2/CH_3OH=9:1, R_f=0.65) to yield 0.77 g (95 %) of the product **(17)** as a yellow oil. IR (neat) ν_{max} 3368, 2944, 1732, 1676, 1608, 1464, 1248, 747. MS m/z (%) (rel intensity) 356 (80.0, M^+), 313 (24.0), 311 (25.0), 287 (15.0), 280 (14.0), 238 (15.0), 215 (96.0), 168 (16.0), 154 (31.0), 142 (100.0), 96 (24.0).). HRMS (EI) calcd for $C_{20}H_{24}N_2O_4$ 356.1736, found for 446.2225. ^{1}H NMR δ_H ($CDCl_3$): 1.17 (3H, t, J=7.0 Hz; $COOCH_2C\underline{H}_3$), 1.84+1.99 (2×1H, 2×ddd, J_{gem}=12.2 Hz, J_{vic}=5.0+2.0 and 10.3+7.6 Hz; 6-H_2), 1.99+2.04 (2×1H, 2×dd, J_{gem}=16.0 Hz, J_{vic}=7.6 and 7.1 Hz; 15-H_2), 2.40 (1H, m; 14-H), 2.47+2.65 (2×1H, 2×dd, J_{gem}=15.5 Hz, J_{vic}=4.0 and 3.0 Hz; 17-H_2), 2.85 (1H, br s; N4-H), 3.16-3.24 (2H, m; 5-H_2), 3.57 (1H, br s; 3-H), 3.76 (3H, s; OCH_3), 4.04 (2H, q, J=7.0 Hz; $COOC\underline{H}_2CH_3$), 6.85 (1H, d, J=7.6 Hz; 12-H), 6.90 (1H, ddd, J=7.6+7.3+1.4 Hz; 10-H), 7.18 (1H, ddd, J=7.6+7.6+1.6 Hz; 11-H), 7.25 (1H, br d, J=7.3 Hz; 9-H), 9.05 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 14.12 ($COOCH_2\underline{C}H_3$), 23.15 (C17), 36.76 (C15), 37.65 (C14), 43.44 (C6), 44.84 (C5), 51.00 (OCH_3), 55.34 (C7), 60.34 ($COOC\underline{H}_2CH_3$), 65.59 (C3), 90.37 (C16), 109.34 (C12), 120.88 (C9), 122.02 (C10), 128.08 (C11), 137.12 (C8), 143.09 (C13), 164.39 (C2), 168.77 (16-$\underline{C}OOCH_3$), 172.47 ($\underline{C}OOCH_2CH_3$).

20-Oxodeethylibophyllidine (18)

A solution of **17** (0.50 g, 1.4 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) in 15 mL of dry toluene was refluxed under argon for 16 h. Then it was cooled and concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by preparative TLC (eluting with CH_2Cl_2/CH_3OH=9:1, R_f=0.85) to yield a colorless oil, which was crystallized from CH_3OH to afford 0.34 g (78 %) of **18** as white crystals. IR (KBr) ν_{max} 3384, 2944, 1696, 1608, 1440, 1252, 748. MS m/z (%) (rel intensity) 310 (27.0, M^+), 279 (3.0), 251 (6.0), 227 (44.0), 214 (100), 195 (46.0), 182 (21.0), 167 (20.0), 154 (40.0). HRMS (EI) calcd for $C_{18}H_{18}N_2O_3$ 310.3471, found for 310.3475. ^{1}H NMR δ_H ($CDCl_3$): 1.79+2.78 (2×1H, 2×dd J_{gem}=15.3 Hz, J_{vic}=12.0 and 5.0 Hz; 17-H_2), 1.84-1.94 (2H, m; 6-H_2), 2.15+2.86 (2×1H, 2×dd, J_{gem}=16.2 Hz, J_{vic}=<1 and 6.5 Hz; 15-H_2), 2.21 (1H, m; 14-H), 3.26+4.17 (2×1H, 2×dm, J_{gem}=12.0 Hz; 5-H_2), 3.77 (3H, s; OCH_3), 4.31 (1H, d, J=6.0 Hz; 3-H), 6.88 (1H, br d; J=7.9 Hz; 12-H), 6.94 (1H, ddd, J=7.6+7.4+1.0 Hz; 10-H), 7.22 (1H, ddd, J=7.9+7.6+1.2 Hz; 11-H), 7.27 (1H, br d, J=7.4 Hz; 9-H), 9.05 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 24.84 (C17), 36.10 (C14), 38.65 (C15), 42.60+43.19 (C5+C6), 51.14 (OCH_3), 54.95 (C7), 67.74 (C3), 92.86 (C16), 109.66 (C12), 121.25+121.72 (C9+C10), 128.70 (C11), 135.59 (C8), 143.39 (C13), 163.10 (C2), 168.04

(16-COOCH$_3$), 176.70 (C20). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found C, 69.57; H, 5.86; N 8.58.

20-Thioxodeethylibophyllidine (19)

To a solution of 20-oxodeethylibophyllidine **(18)** (0.50 g, 1.61 mmol) in dry THF (30 mL) was added 0.55 g (2.42 mmol) of phosphorus pentasulfide. The reaction mixture was stirred for 2 h at rt and then diluted with 30 mL of CH_2Cl_2. The solution was extracted with 20 mL of brine and the aqueous phase was extracted with 10 mL of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was purified by preparative TLC (eluting with acetone/hexane=1:2, R_f=0.35) to yield a yellow oil, which was crystallized from CH_3OH to afford **19** (0.44 g, 83 %) as white crystals. IR (KBr) ν_{max} 3384, 2944, 1672, 1624, 1608, 1456, 1176, 748. MS m/z (%) (rel intensity) 326 (100.0, M^+), 293 (10.0), 267 (4.0), 227 (70.0), 195 (67.0), 167 (48.0). HRMS (EI) calcd for $C_{18}H_{18}N_2O_2S$ 327.1167, found for 327.1206. ^{1}H NMR δ_H ($CDCl_3$): 1.78+2.78 (2×1H, 2×dd, J_{gem}=15.5 Hz, J_{vic}=12.0 and 5.0 Hz; 17-H$_2$), 1.94-2.05 (2H, m; 6-H$_2$), 2.28 (1H, m; 14-H), 2.88+3.27 (2×1H, 2×dd, J_{gem}=16.8 Hz, J_{vic}=<1 and 5.8 Hz; 15-H$_2$), 3.58+4.64 (2×1H, 2×dm, J_{gem}=12 Hz; 5-H$_2$), 3.77 (3H, s; OCH$_3$), 4.61 (1H, d, J=6.0 Hz; 3-H), 6.89 (1H, br d, J=7.9 Hz; 12-H), 6.97 (1H, ddd, J=7.6+7.4+1.0 Hz; 10-H), 7.24 (1H, ddd, J=7.9+7.6+1.2 Hz; 11-H), 7.31 (1H, br d, J=7.4 Hz; 9-H), 9.05 (1H, br s; N1-H). ^{13}C NMR δ_C ($CDCl_3$): 23.92 (C17), 38.43 (C14), 42.45 (C6), 47.25 (C15), 51.22 (OCH$_3$), 51.47 (C5), 53.99 (C7), 73.80 (C3), 93.26 (C16), 109.84 (C12), 121.38+121.46 (C9+C10), 128.96 (C11), 134.96 (C8), 143.39 (C13), 162.77 (C2), 168.00 (16-COOCH$_3$), 202.06 (C20). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found C, 66.32; H, 5.66; N 8.56; S, 9.76.

(±)-Deethylibophyllidine (2)

Method II.: To a solution of **19** (0.25 g, 0.77 mmol) in dry THF (20 mL) was added ca. 1 g of water, CH_3OH and dry THF-washed Raney Ni. The suspension was stirred for 10 h at rt and then filtered. The Raney Ni was washed with dry THF (10 mL) and the combined filtrates were concentrated in vacuo. The residue was purified by preparative TLC (eluent: AcOEt/CH_3OH=1:1, R_f=0.15) to afford 0.18 g (81 %) of the deethylibophyllidine **(2)** as a yellow oil. The analytical data were identified in the previous method.

1-Benzyl-11-(formylmethyl)-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylic acid methyl ester (20)

The ester **(16)** (1.00 g, 2.24 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to -78^{o}C. A solution of 1.0 M diisobutylaluminium hydride in hexane (2.91 mL, 2.91 mmol) was added dropwise, and the resulting solution was stirred at -78^{o}C for 1 h. Then saturated aqueous NH_4Cl (10 mL) was added, and the

solution was allowed to warm to rt. After stirring for 30 min the white precipitate was filtered, the solvent was extracted with water (2×20 mL) and brine (15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (eluting with Et_2O/hexane=1:1, R_f=0.41) to yield a colorless oil, which was crystallized from CH_3OH to afford **20** (0.77 g, 66 %) as white crystals. IR (KBr) ν_{max} 3384, 2944, 1720, 1676, 1608, 1448, 1248, 744. MS m/z (%) (rel intensity) 402 (20.0, M^+), 269 (46.0), 214 (10.0), 188 (69.0), 91 (100.0). HRMS (EI) calcd for $C_{25}H_{26}N_2O_3$ 402.1943, found for 402.1922. ^{1}H NMR δ_H ($CDCl_3$): 1.68 (1H, dd, J_{gem}=11.9 Hz, J_{vic}=5.0 Hz; 6-H_A), 2.05 (1H, m; 6-H_B), 2.05+2.16 (2×1H, 2×ddd, J_{gem}=18.0 Hz, J_{vic}=8.4+1.6 and 5.8+1.5 Hz; 15-H_2), 2.57 (1H, m; 14-H), 2.6-2.7 (3H, m; 17-H_2+5-H_A), 2.92 (1H, dd, J_{gem}=9.0 Hz, J_{vic}=6.7 Hz; 5-H_B), 2.98 (1H, br s; 3-H), 3.80+4.28 (2×1H, 2×d, J_{gem}=13.4 Hz; NC$\underline{H}_2$Ph), 3.77 (3H, s; OCH_3), 6.82 (1H, d; 12-H), 6.83 (1H, m; 10-H), 6.90 (1H, br d, J=7.1 Hz; 9-H), 7.14 (1H, ddd, J=7.6+7.4+1.7 Hz; 11-H), 7.25-7.42 (5H, m; Ph), 8.98 (1H, br s; N1-H), 9.58 (1H, t, J=1.5 Hz; 20-H). ^{13}C NMR δ_C ($CDCl_3$): 23.40 (C17), 33.33 (C14), 42.13 (C6), 45.79 (C15), 50.28 (C5), 51.03 (OCH_3), 55.10 (C7), 57.79 (N$\underline{C}H_2$Ph), 70.81 (C3), 90.67 (C16), 109.28 (C12), 120.72 (C9), 122.31 (C10), 127.97 (C11), 127.07+128.31+129.02+138.84 (Ph), 137.45 (C8), 142.88 (C13), 164.83 (C2), 168.81 (16-$\underline{C}OOCH_3$), 201.45 (C20). Anal. Calcd for $C_{25}H_{26}N_2O_3 \cdot 3/4CH_3OH$: C, 72.51; H, 6.38; N, 6.56. Found C, 72.53; H, 6.33; N 6.53.

(±)-Deethylibophyllidine (2)

Method III.: A mixture of the amino aldehyde **(20)** (0.50 g, 1.24 mmol) and 10 % palladium/charcoal catalyst (0.1 g) in 10 mL of CH_3COOH was stirred for 48 h under hydrogene at atmospheric pressure. The reaction mixture was filtered and the filtrate was poured into ice-water (40 mL) and neutralized with saturated Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluent: AcOEt/CH_3OH=1:1, R_f=0.15) to yield 0.31 g (82 %) of deethylibophyllidine **(2)** as a yellow oil. The analytical data were identified in the previous method.

ACKNOWLEDGEMENTS

The authors are grateful to the National Scientific Research Foundation (OTKA T046060) for financial support of this work.

REFERENCES

1. J. E. Saxton, The Ibogamine-Catharantine Group in *Monoterpenoid Indole Alkaloids*; ed. by J. E.

Saxton, In *The Chemistry of Heterocyclic Compounds*; ed. by E. C. Taylor, Wiley: New York 1994; Supplement to Vol. 25, Part 4, pp. 487-521.

2. (a) M. V. Kisakürek, A. J. M. Leewenberg, and M. A. Hesse, In *Alkaloids: Chemical and Biological Perspectives*, ed. by S. W. Pelletier, Wiley: New York, 1983; Vol. 1, pp. 211-376. (b) T. A. Van Beek, R. Verpoorte, A. Baerheim Svendsen, A. J. M. Leewenberg, and N. G. J. Bisset, *Ethnopharmacol.*, 1984, **10**, 1. (c) T. A. Van Beek and M. A. J. Van Gessel, Alkaloids of *Tabernaemontana* Species. In *Alkaloids: Chemical and Biological Perspectives*, ed. by S. W. Pelletier, Wiley: New York, 1988; Vol. 6, pp. 75-226.
3. For a general review of biogenetic and biosynthetic routes to indole alkaloids, see: (a) A. I. Scott, *Bioorg. Chem.*, 1974, **3**, 398. (b) M. E. Kuehne and J. B. Pitner, *J. Org. Chem.*, 1989, **54**, 4553.
4. The biogenetic numbering (J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.) is used throughout this paper, but the systematic nomenclature has been used in the Experimental Section.
5. C. Kan, H. P. Husson, H. Jacquemin, S. K. Kan, and M. Lounasmaa, *Tetrahedron Lett.*, 1980, **21**, 55.
6. D. Desmaële and J. d'Angelo, *J. Org. Chem.*, 1994, **59**, 2292.
7. (a) J. Bosch and J. Bonjoch, Pentacyclic *Strychnos* Indole Alkaloids. In *Studies Natural Products Chemistry*, ed. by Atta-úr-Rahman, Elsevier: Amsterdam, 1988; Vol. 1, pp. 31-88. (b) J. Bosch, J. Bonjoch, and M. Amat, *Strychnos* Alkaloids. In *The Alkaloids*; ed. by G. A. Cordell, Academic Press: New York, 1996; Vol. 48, pp. 75-189.
8. (a) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, L. Motyka, and D. Oliver-Smith, *J. Org. Chem.*, 1981, **46**, 2002. (b) M. C. Barsi, B. C. Das, J. L. Fourrey, and R. Sundaramoorthi, *J. Chem. Soc., Chem. Commun.*, 1985, **2**, 88. (c) M. E. Kuehne and J. B. Pitner, *J. Org. Chem.*, 1989, **54**, 4553. (d) J. Catena, N. Valls, J. Bosch, and J. Bonjoch, *Tetrahedron Lett.*, 1994, **35**, 4433. (e) J. C. Fernandez, N. Valls, J. Bocsh, and J. Bonjoch, *J. Chem. Soc., Chem. Commun.*, 1995, **12**, 2317. (f) J. Bonjoch, J. Catena, and N. Valls, *J. Org. Chem.*, 1996, **61**, 7106. (g) J. Bonjoch, J. C. Fernandez, and N. Valls, *J. Org. Chem.*, 1998, **63**, 7338. (h) A. Padwa, T. M. Heidelbaugh, J. T. Kuethe, M. S. McClure, and Q. Wang, *J. Org. Chem.*, 2002, **67**, 5928. (i) M. R. Tsai, P. P. Sun, M. Y. Chang, and N. C. Changa, *J. Chin. Chem. Soc.* 2004, **51**, 613.
9. Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Org. Chem.*, 1993, **58**, 1434.
10. Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Org. Chem.*, 1993, **58**, 6076.
11. Gy. Kalaus, I. Vágó, I. Greiner, M. Kajtár-Peredy, L Brlik, L. Szabó, and Cs. Szántay, *Nat. Prod. Lett.*, 1995, **7**, 197.
12. Gy. Kalaus, I. Greiner, and Cs. Szántay, *Synthesis of Some Aspidosperma and Related Alkaloids.*

Studies in Natural Products Chemistry, Vol. 19. Structure and Chemistry (Part E) ed. by Atta-ur-Rahman, Elsevier, 1997, pp. 89-116.

13. Gy. Kalaus, I. Juhász, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Org. Chem.*, 1997, **62**, 9188.
14. Gy. Kalaus, L. Léder, I. Greiner, M. Kajtár-Peredy, K. Vékey, L. Szabó, and Cs. Szántay, *Tetrahedron*, 2003, **59**, 5661.
15. Md. A. Rahim, T. Fujiwara, and T. Takeda, *Tetrahedron*, 2000, **56**, 763.
16. Gy. Kalaus, I. Juhász, J. Éles, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Heterocycl. Chem.*, 2000, **37**, 245.
17. E. J. Corey and A. Palani, *Tetrahedron Lett.*, 1997, **38**, 2397.