HETEROCYCLES, Vol. 71, No. 4, 2007, pp. 865 - 880. © The Japan Institute of Heterocyclic Chemistry
Received, 5th January, 2007, Accepted, 16th February, 2007, Published online, 16th February, 2007. COM-07-10991

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART 107. AN EFFICIENT CONVERGENT SYNTHETIC PATHWAY TO BUILD UP THE IBOPHYLLIDINE SKELETON III. TOTAL SYNTHESIS OF (±)-IBOPHYLLIDINE AND (±)-20-EPIIBOPHYLLIDINE

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

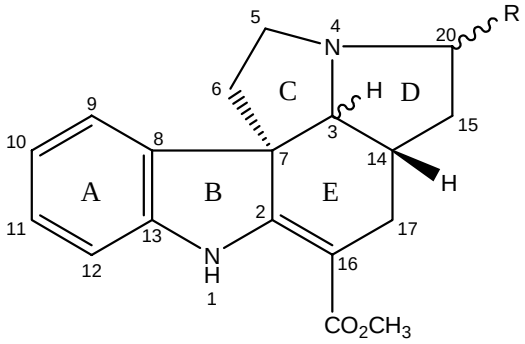
Abstract – Starting from 5-ethyldihydrofuran-2(3*H*)-one **(9)** we prepared aldehydes **(6** and **7)** which, in a [4+2] cycloaddition reactions with the tryptamine derivative **(8)** gave, as a final step, compounds **(13** and **22)** having D-*seco*-pseudoaspidospermane skeleton. We synthesized (±)-20-epiibophyllidine **(4)** *via* the benzoate ester **(15)** or the mesylate **(17)** of alcohol **(14)** which had been obtained from **13**, while the catalytic hydrogenation of **22** led to (±)-ibophyllidine **(3)** *via* full epimerization, cyclization and reduction steps in one operation.

INTRODUCTION

Recently, we reported a total synthesis of (±)-deethylibophyllidine **(1)** and its 14-epimer **(2)**, which demonstrated an efficient biomimetic synthetic route for the preparation of *ibophyllidine* alkaloids and alkaloid-like molecules.[1] In order to further evaluate this strategy we continued our research toward the construction of more complex structures, (±)-ibophyllidine **(3)** and (±)-20-epiibophyllidine **(4)**.[2,3]

Khuong-Huu and co-workers were the first to isolate the ibophyllidine **(3)** from the leaves of *Tabernaemontana iboga* and *Tabernaemontana subsessilis*.[4] Kan's research group found it also in

Tabernaemontana albiflora.[5] 20-Epiibophyllidine **(4)** was isolated from the bark of *Tabernaemontana albiflora* (Figure 1).[4]

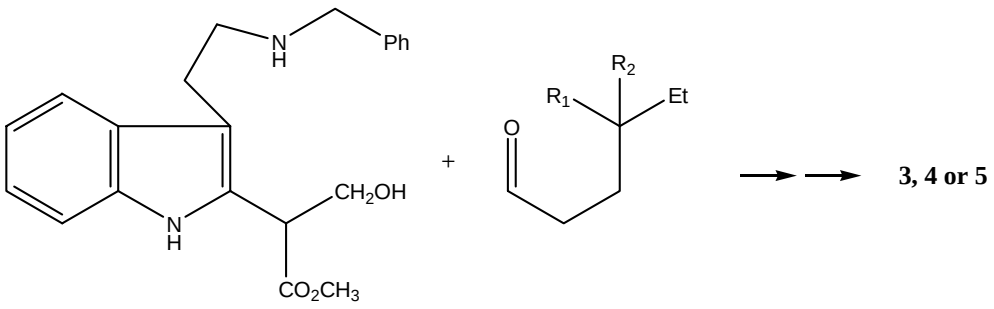


R=H C3-βH Deethylibophyllidine **(1)**
R=H C3-αH 14-Epi-deethylibophyllidine **(2)**
R= αC_2H_5 C3-βH Ibophyllidine **(3)**
R= βC_2H_5 C3-βH 20-Epiibophyllidine **(4)**
R= βC_2H_5 C3-αH 3,20-Diepiibophyllidine **(5)**

Figure 1

RESULTS AND DISCUSSION

As a substrate for the planned synthesis we utilized the tryptamine derivative **(8)** which we had used succesfully in our earlier works.[6] We anticipated that the appropriately functionalized aldehydes **(6, 7)** and **8** would give , in several steps, molecules with a D-*seco*-pseudoaspidospermane skeleton., from which the pentacyclic alkaloids **(3, 4)** and alkaloid-like molecule **(5)** can be made to form easily (Figure 2).[1,6-10]

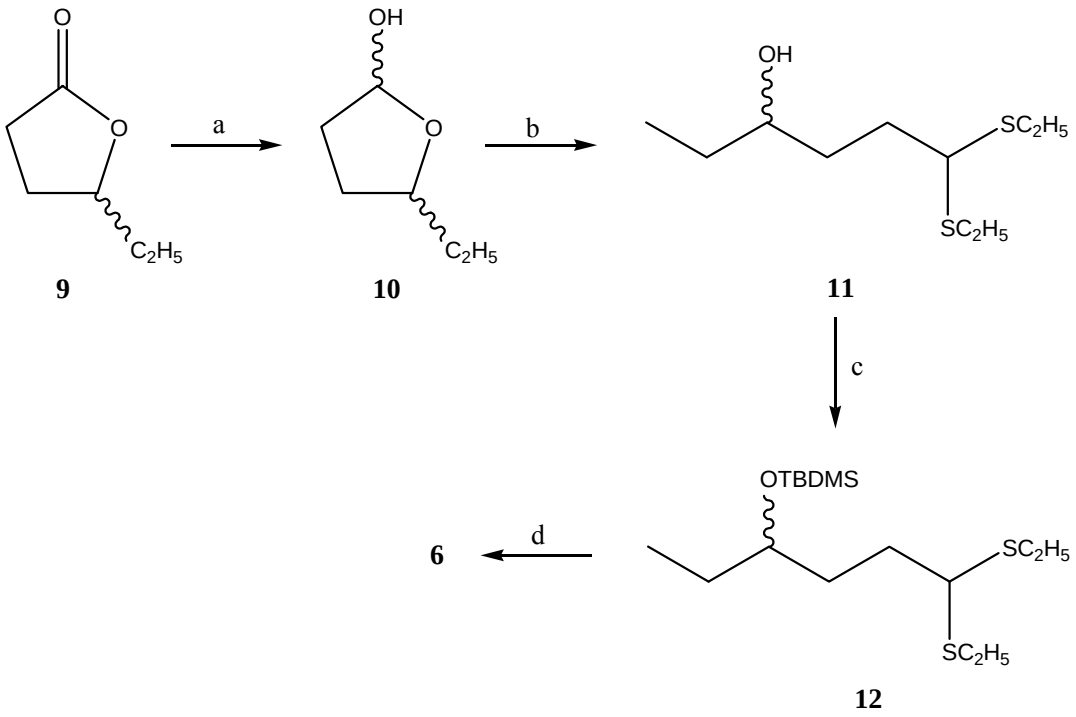


8

R_1= -OTBDMS, R_2=H **(6)**
R_1+R_2= =O **(7)**

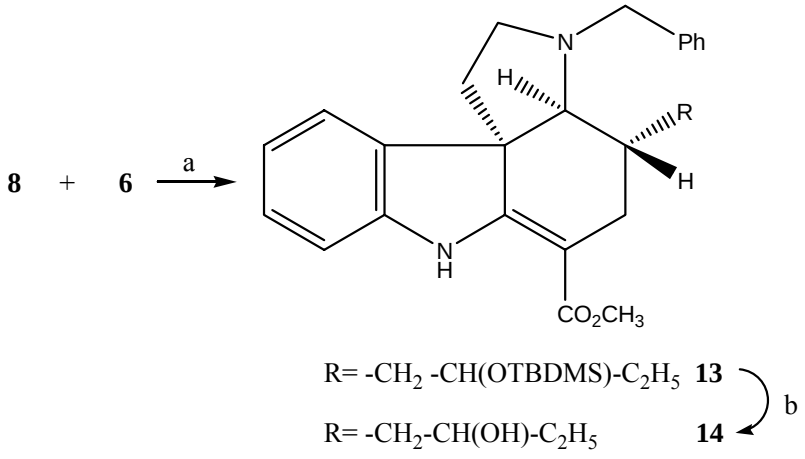
Figure 2

The reaction partners **(6** and **7)** were formed from 5-ethyldihydrofuran-2(3*H*)-one **(9)**. In the first step, using a method known from the literature,[1,11] we reduced the lactone **(9)** with diisobutylaluminium hydride, then we opened up the ring of compound **10** by the application of boron trifluoride-diethyl etherate and ethanethiol **(11)**. Afterwards, alcohol **11** was protected with *tert*-butyldimethylsilyl chloride in the presence of imidazole **(12)**. Finally, after removing of the dithioacetal protective group with mercury (II) chloride in the presence of calcium carbonate in aqueous acetonitrile at room temperature, we arrived at aldehyde **6** (Scheme 1).



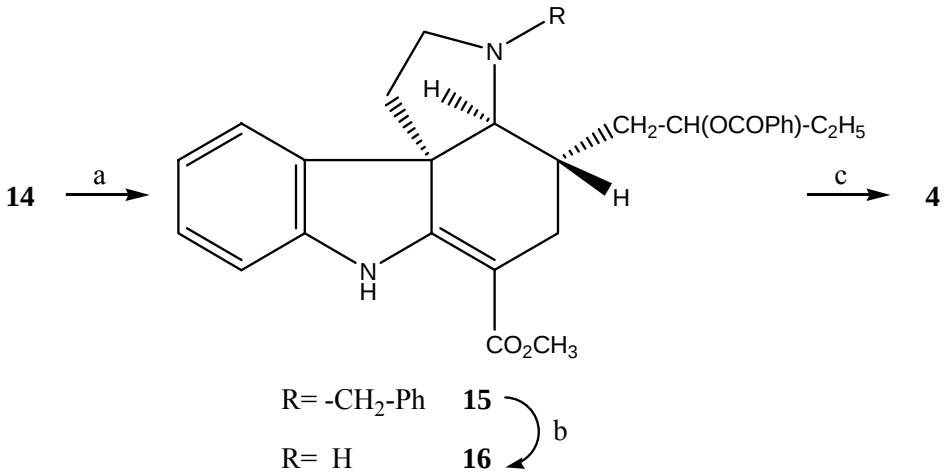
Scheme 1. (a) DIBAL, CH_2Cl_2, -70°C, (91%); (b) C_2H_5SH, $BF_3{\cdot}Et_2O$, $CHCl_3$, 0°C, (84%); (c)TBDMSCl, imidazole, CH_2Cl_2, rt, (88%); (d) $HgCl_2$, $CaCO_3$, CH_3CN, rt, (71%).

As a continuation, we allowed **6** to react with the tryptamine derivative **(8)** in boiling toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. From the reaction mixture the tetracyclic compound **13** was isolated. We intended to construct the five-membered D-ring of the ibophyllidine skeleton by intramolecular alkylation, therefore by hydrolysis of the derivative **13** containing the silyl moiety, we produced alcohol **14** (Scheme 2).



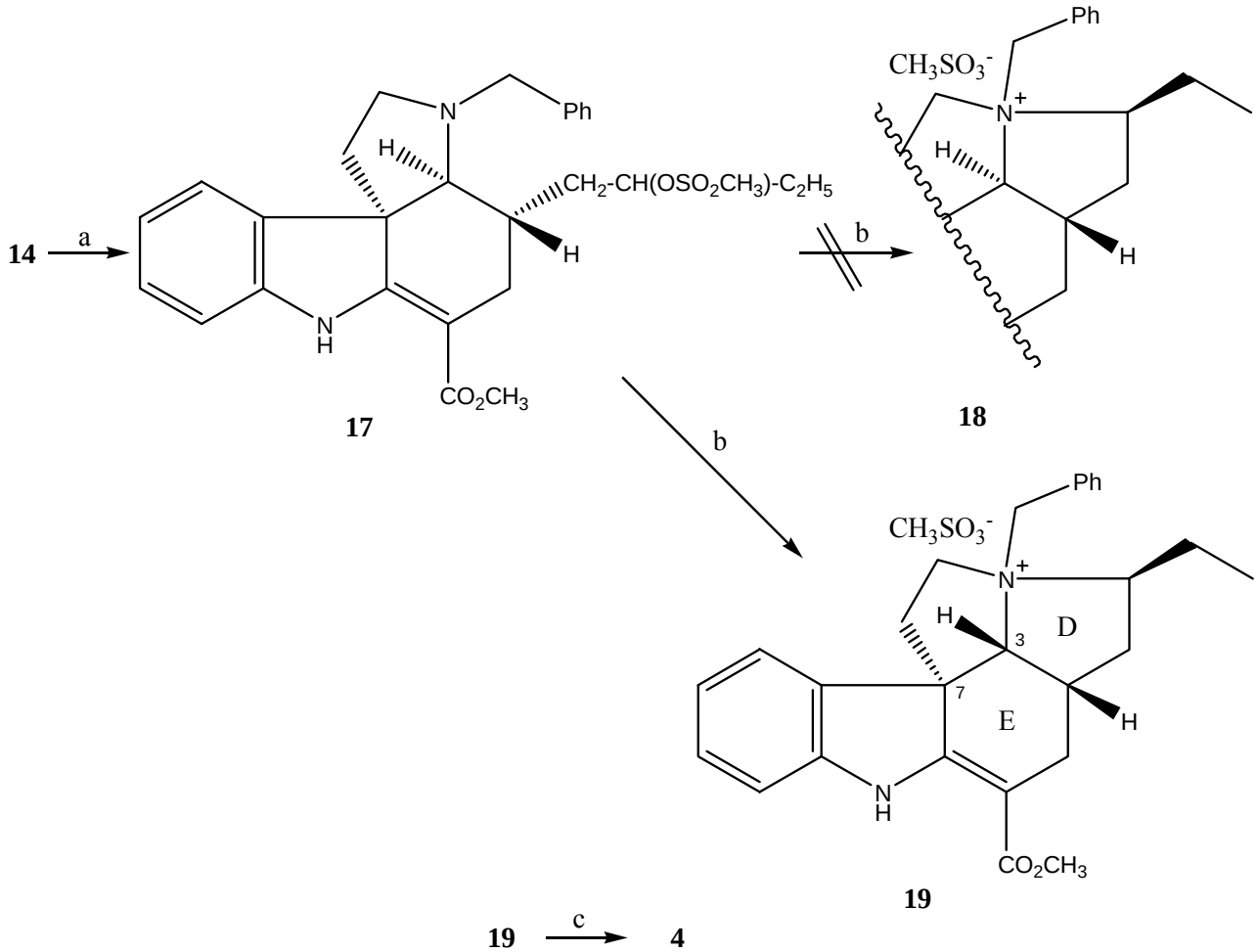
Scheme 2. (a) *p*-$TsOH{\cdot}H_2O$, toluene, Δ, (64%); (b) 5M HCl, THF, rt, (93%).

First of all we prepared the benzoate ester **(15)** of alcohol **14**. The catalytic debenzylation of **15** in glacial acetic acid resulted in the secondary amine **16**. Finally, amine **16** was boiled in dimethylformamide in the presence of potassium iodide. After full epimerization, according to our previous results and described mechanism,[12] we obtained (±)-20-epiibophyllidine **(4)** (Scheme 3).



Scheme 3. (a) $PhCO_2H$, DCC, DMAP, CH_2Cl_2, rt, (77%); (b) H_2, Pd/C, CH_3CO_2H, rt, (91%); (c) KI, DMF, Δ, (64%).

We tried to build up the alkaloid-like molecule **(5)** too.[1] For this reason **14** was mesylated with methanesulfonic acid chloride in the presence of triethylamine, then mesylate **17** was boiled in tetrahydrofuran for 96 h.



Scheme 4. (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C, (75%); (b) THF, Δ, (49%); (c) H_2, Pd/C, CH_3CO_2H, rt, (88%).

To our surprise, instead of the expected compound **(18)**, the pentacyclic quaternary salt **19** with cis D/E ring connection was proceeded, from which, after catalytic debenzylation, the (±)-**4** was also obtained (Scheme 4). This unusual epimerization can be explained by the pathway proposed in Figure 3. We assume that in the first step an intramolecular alkylation reaction occurs to give the kinetically controlled product **18**, which then undergoes cleavage of the C3/C7 bond, finally the transannular ring cyclization of the intermediate **(20)** results in the thermodinamically favourable quaternary salt with cis D/E ring connection **(19)**.

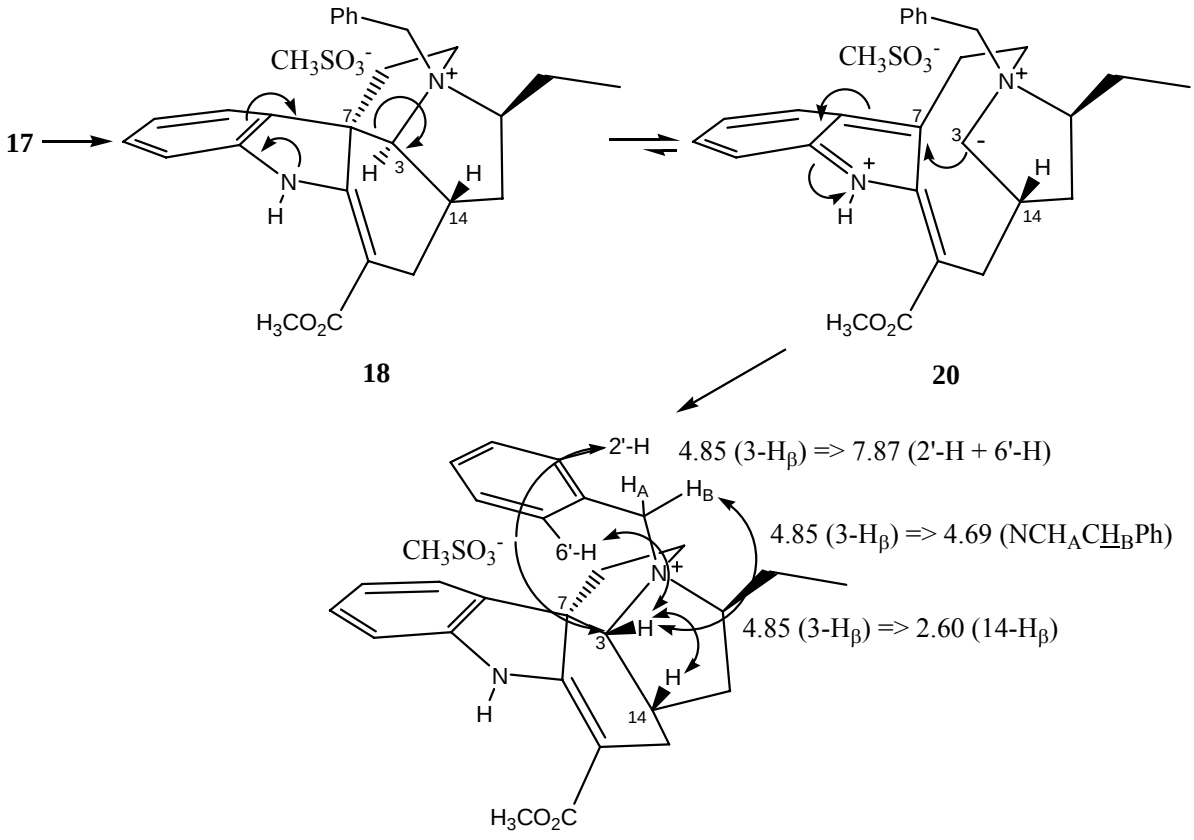
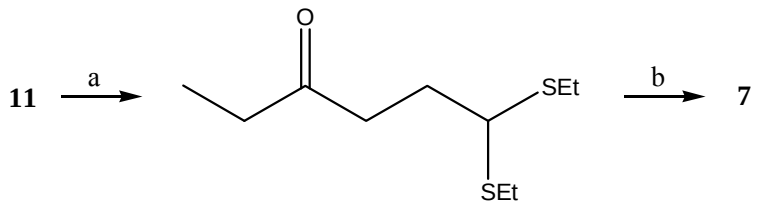


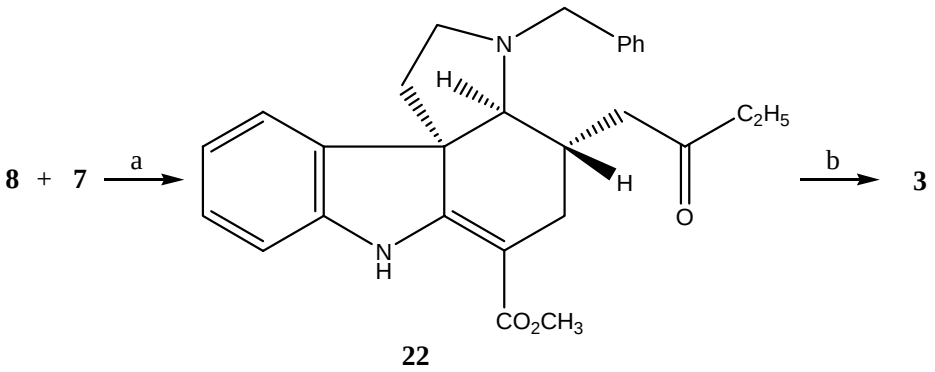
Figure 3

Utilizing our experiences from earlier syntheses, [1,6-10] we synthesized the (±)-ibophyllidine **(3)** *via* the tetracyclic amino ketone **(22)** known in literature.[3a]



Scheme 5. (a) PCC, CH_2Cl_2, rt, (79%); (b) $HgCl_2$, $CaCO_3$, CH_3CN, rt, (61%).

The stereoselective synthesis of (±)–**3** could be derived from the reaction of the tryptamine derivative **(8)** with 4-oxohexanal **7** which had been prepared from **11** by oxidation with pyridinium chlorochromate **(21)** and removal of the dithioacetal protective group (Scheme 5).



Scheme 6. (a) *p*-TsOH·H_2O, toluene, Δ, (59%); (b) H_2, Pd/C, CH_3CO_2H, rt, (81%).

Subsequently we allowed **7** to react with the tryptamine derivative **(8)** in boiling toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. From the reaction mixture the tertiary amine **22** was obtained in a good yield. Finally, hydrogenolysis of **22** resulted in (±)-ibophyllidine **(3)** *via* full epimerization, cyclization and reduction steps in one operation (Scheme 6).

CONCLUSION

In sum, we have described an efficient, biomimetic route for the synthesis of (±)-ibophyllidine **(3)** and (±)-20-epiibophyllidine **(4)**. Starting from 5-ethyldihydrofuran-2(3*H*)-one **(9)** we produced aldehydes **6** and **7** which, when allowed to react with the tryptamine derivative **8** yielded, compounds **13** and **22** with a D-*seco*-pseudoaspidospermane skeleton. The intramolecular alkylation reaction of the benzoate ester **16** which had been prepared from alcohol **14**, furnished (±)-20-epiibophyllidine **(4)**. To our surprise, the cyclization reaction achieved *via* the mesyl ester **17** also resulted in (±)-**4**. Finally, hydrogenolysis of **22** led to (±)-ibophyllidine **(3)** *via* full epimerization, cyclization and reduction steps in one operation.

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).

5-Ethyltetrahydrofuran-2-ol (10)

To a stirred solution of γ-caprolactone **(9)** (5.00 g, 44 mmol) in dichloromethane (50 mL) at -78°C was added gradually 1M diisobutylaluminum hydride in hexane (58 mL, 58 mmol) and the resulting solution was stirred at -78°C for 1 h. It was quenched with methanol (10 mL) and saturated aqueous NH_4Cl (10 mL) and the mixture was allowed to warm to rt. The layers were separeted, and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to yield the desired product **(10)** (4.63 g, 91 %) as a colorless oil (1:1 mixture of the diastereoisomers). The crude product was used directly for the next reaction without purification (TLC: acetone/hexane=1:2, R_f=0.45). IR (neat) ν_{max} 3400, 2968, 1024, 972. MS m/z (%) (rel intensity) 116 (100.0, $[M]^+$), 99 (76.0), 82 (4.0). HRMS (EI) calcd for $C_6H_{12}O_6$ 116.0837, found for 116.0841. ^{1}H NMR δ_H ($CDCl_3$):0.95 and 0.98 (3H, t, J=7.2 Hz; C(6)H_3), 1.45 (1H, br s; OH), 1.50-2.05 (6H, m; C(2)H_2+C(3)H_3+C(5)H_2), 3.25 (1H, dd, J_{gem}=12.0 Hz, J_{vic}=7.0 Hz; C(4)H), 3.93 and 4.15 (1H, dq, J_{gem}=12.5 Hz, J_{vic}=7.5 Hz; C<u>H</u>-OH). ^{13}C NMR δ_C ($CDCl_3$): 10.38 and 10.57 (C(6)), 28.59 and 28.92 (C(5)), 29.1 and 30.34 (C(2)), 33.19 and 34.12 (C(3)), 79.98 and 82.67 (C(4)), 98.44 and 98.63 (CH-OH).

6,6-bis(Ethylthio)hexan-3-ol (11)

10 (5.00 g, 43 mmol) was dissolved in dry chloroform (50 mL) and ethane thiol (5.34 g, 6.4 mL, 86 mmol) was added to the solution. It was cooled to 0°C and boron trifluoride-diethyl etherate (5.49 g, 49 mL, 43 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 chloroform (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 yielded 8.03 g (84%) **11** as a colorless oil (TLC: acetone/hexane=1:2, R_f=0.68). IR (neat) ν_{max} 3392, 2968, 1452, 1264. MS m/z (%) (rel intensity) 204 (4.0, $[M]^+$), 197 (2.0), 116 (100.0), 99 (24.0). HRMS (EI) calcd for $C_{10}H_{22}OS_2$ 222.1112, found for 222.1114. ^{1}H NMR δ_H ($CDCl_3$): 0.95 (3H, t, J=7.2 Hz; C(6)H_3), 1.26 (6H, t, J=7.5 Hz; 2×SCH_2C<u>H</u>$_3$), 1.40 (1H, br s; OH), 1.40-1.55 (2H, m; C(5)H_2), 1.62+1.76 (2×1H, 2×m; C(3)-H_2), 1.87+2.00 (2×1H, 2×m; C(2)H_2), 2.55-2.74 (4H, m; 2×S<u>H</u>$_2$$CH_3$), 3.55 (1H, m; C(4)H), 3.82 (1H, t, J=6.8 Hz; C(1)H). ^{13}C NMR δ_C ($CDCl_3$): 9.89 (C6), 14.54 (2×SCH_2C<u>H</u>$_3$), 24.17+24.31 (2×S<u>H</u>$_2$$CH_3$), 30.39 (C5), 32.32 (C3), 34.64 (C2), 51.48 (C1), 72.96 (C4).

***tert*-Butyl-(1-ethyl-4,4-bis(ethylsulfanylbutoxy))dimethylsilane (12)**

Imidazole (2.31 g, 34 mmol) was added to a solution of **11** (5.00 g, 22 mmol) in dry dichloromethane (50 mL). Then *tert*-butyldimethylsilyl chloride (5.08 g, 34 mmol) in dry dichloromethane (20 mL) was added dropwise to the stirred solution. After the addition, the mixture was stirred for 24 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 **12** (6.52 g, 88%) of a colorless liquid (TLC: ethyl acetate/hexane=1:4, R_f=0.96). IR (neat) ν_{max} 2960, 1468, 1256, 836. MS m/z (%) (rel intensity) 336 (2.0, $[M]^+$), 218 (17.0), 217 (100.0), 159 (20.0), 143 (88.0), 101 (42.0), 75 (39.0). HRMS (EI) calcd for $C_{16}H_{36}OS_2Si$ 336.1977, found for 336.1975. ^{1}H NMR δ_H ($CDCl_3$): 0.05 (6H, s; $Si(CH_3)_2$), 0.87 (3H, t, J=7.5 Hz; C(6)H_3), 0.89 (9H, s; $C(CH_3)_3$), 1.26 (6H, t, J=7.5 Hz; 2×$SCH_2C\underline{H}_3$), 1.46 (2H, qd, J=7.2 and 6.0 Hz; C(5)H_2), 1.58-1.94 (4H, m; C(3)H_2+C(2)H_2), 2.55-2.75 (4H, m; 2×$SC\underline{H}_2CH_3$), 3.61 (1H, m; C(4)H), 3.76 (1H, t, J=6.8 Hz; C(1)H). ^{13}C NMR δ_C ($CDCl_3$): -4.42 and -2.91 ($Si(CH_3)_2$), 9.62 (C6), 14.58 (2×$SCH_2\underline{C}H_3$), 18.16 ($Si\underline{C}(CH_3)_3$), 24.08+24.24 (2×$S\underline{C}H_2CH_3$), 25.96 ($SiC(\underline{C}H_3)_3$), 29.80 (C5), 31.76 (C3), 34.13 (C2), 51.76 (C1), 73.02 (C4).

4-(*tert*-Butyldimethylsilanyloxy)hexanal (6)

12 (3.00 g, 9 mmol) was dissolved in acetonitrile (70 mL) and water (7 mL) was added to the solution. Calcium carbonate (3.60 g, 36 mmol) and mercury(II) chloride (9.77 g, 36 mmol) were added to a stirred solution. After the addition the mixture was stirred for 2 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 dichloromethane (70 mL) and washed with 25 mL portion of aqueous solution of NaI, 25 mL portion of aqueous solution of $Na_2S_2O_3$ and brine (25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum, yielded 1.47 g (71 %) of **6** as a colorless oil (TLC: ethyl acetate/hexane=1:4, R_f=0.85). IR (neat) ν_{max} 2928, 1728, 1468, 1256, 1060. MS m/z (%) (rel intensity) 230 (1.0, $[M]^+$), 201 (11.0), 173 (97.0), 131 (20.0), 115 (14.0), 99 (22.0), 81 (17.0), 75 (100.0). HRMS (EI) calcd for $C_{12}H_{26}O_2Si$ 230.1402, found for 230.1407. ^{1}H NMR δ_H ($CDCl_3$): 0.05 (6H, s; $Si(C\underline{H}_3)_2$), 0.87 (3H, t; C(6)H_3), 0.89 (9H, s; $SiC(CH_3)_3$), 1.45 (2H, m; C(5)H_2), 1.65-1.85 (2H, m; (C(3)H_2), 2.46 (2H, t; C(2)H_2), 3.65 (1H, m; C(4)H), 9.78 (1H, t; C(1)HO). ^{13}C NMR δ_C ($CDCl_3$): -4.53 and -4.41 ($Si(CH_3)_2$), 9.52 (C6), 18.11 ($Si\underline{C}(CH_3)_3$), 25.90 ($SiC(\underline{C}H_3)_3$), 28.42 (C3), 29.67 (C5), 39.80 (C2), 72.35 (C4), 202.82 (C1).

3-Benzyl-4-[2-(*tert*-butyldimethylsilanyloxy)butyl]-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]-carbazole-6-carboxylic acid methyl ester (13)

A solution of **8** (1.50 g, 4.27 mmol), **6** (1.28 g, 5.55 mmol), and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in dry toluene (60 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 ethyl acetate/hexane=1:4, R_f=0.68) to yield 1.49 g (64 %) of **13** as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) ν_{max} 3384, 2928, 1680, 1612, 1464, 1248, 744. MS m/z (%) (rel intensity) 546 (38.0, $[M]^+$), 413 (29.0), 373

(100.0), 332 (90.0), 216 (24.0), 173 (27.0), 143 (21.0), 91 (73.0), 75 (27.0). HRMS (EI) calcd for $C_{33}H_{46}N_2O_3Si$ 546.3278, found for 546.3296. ^{1}H NMR δ_H ($CDCl_3$): -0.17, -0.07, -0.01 and 0.01 (6H, s; $Si(CH_3)_2$), 0.69 and 0.79 (3H, t, J=7.2 Hz; 18-H_3), 0.78 and 0.84 (9H, s; $C(CH_3)_3$), 0.85-1.55 (4H, m; 15-H_2+19-H_2), 1.67+2.02 (2×1H, 2×m; 6-H_2), 1.90 and 2.18 (1H, m; 14-H), 2.45-2.75 (3H, m; 17-H_2+5-H_A), 2.88 (1H, m; 5-H_B), 2.89 and 2.93 (1H, br s; 3-H), 3.45-3.60 (1H, m; 20-H), 3.70+4.12 (2×1H, 2×d; J_{gem}=13.2 Hz; NC$\underline{H}_2$Ph), 3.77 and 3.78 (3H, s; OCH_3), 6.78-6.86 (2H, m; 10-H+12-H), 6.97 and 6.99 (1H, m; 9-H), 7.13 (1H, m; 11-H), 7.24-7.40 (5H, m; Ph), 8.94 and 8.96 (1H, brs; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): -4.85, -4.75, -4.71 and -4.15 ($Si(CH_3)_2$), 9.26 and 9.41 (C18), 18.05 and 18.14 (Si$\underline{C}(CH_3)_3$), 21.98 and 22.12 (C17), 25.88 and 25.95 (SiC($\underline{C}H_3)_3$), 28.47 and 30.55 (C19), 35.06 and 35.32 (C14), 37.40 and 37.69 (C15), 42.29 and 42.55 (C6), 50.38 and 50.67 (C5), 50.85 and 50.92 (OCH_3), 55.20 and 55.23 (C7), 58.06 and 58.35 (N$\underline{C}H_2$Ph), 71.11 and 71.16 (C20), 72.40 and 72.77 (C3), 90.90 and 90.45 (C16), 109.18 and 109.15 (C12), 120.53 (C9), 122.21 and 122.28 (C10), 127.75 (C11), 127.03 and 127.07+128.29 and 128.34+128.92 and 129.03+139.03 (Ph), 137.88 and 138.02 (C8), 142.99 and 143.08 (C13), 165.42 and 165.65 (C2), 168.96 and 169.10 (16-$\underline{C}OOCH_3$).

Methyl 1-benzyl-2,3,8,10,11,11a-hexahydro-11-(2-hydroxybutyl)-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (14)

To a solution of **13** (1.00 g, 1.83 mmol) in tetrahydrofuran (10 mL) was added 5 M aqueous solution of HCl (0.75 mL) at rt and the mixture was stirred for 1 h. After stirring the mixture was concentrated in vacuo, then the residue was dissolved in dichloromethane (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=0.48) to afford 0.74 g (93 %) of the product **14** as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) ν_{max} 3384, 2928, 1676, 1608, 1464, 1440, 1248, 1204, 744. MS m/z (%) (rel intensity) 432 (4.0, $[M]^+$), 401 (3.0), 373 (12.0), 332 (7.0), 299 (35.0), 218 (80.0), 91 (100.0), 65 (8.0). HRMS (EI) calcd for $C_{27}H_{32}N_2O_3$ 432.5536, found for 432.5539. ^{1}H NMR δ_H ($CDCl_3$): 0.79 and 0.81 (3H, t, J=7.3 Hz; 18-H_3), 0.80-1.10 (2H, m; 15-H_2), 1.16-1.42 (2H, m; 19-H_2), 1.5 (1H, br s; OH), 1.68+2.05 (2×1H, 2×m; 6-H_2), 2.11 (1H, m; 14-H), 2.50-2.75 (3H, m; 17-H_2+5-H_A), 2.93 (1H, m; 5-H_B), 2.94 and 2.98 (1H, br s; 3-H), 3.40 and 3.45 (1H, m; 20-H), 3.76 and 3.77 (3H, s; OCH_3), 3.77+4.14 (2×1H, 2×d, J_{gem}=13.2 Hz; NC$\underline{H}_2$Ph), 6.81 (1H, br d, J=7.7 Hz; 12-H), 6.84 (1H, ddd, J=7.6+7.5+1.0 Hz; 10-H), 6.99 and 7.01 (1H, br d, J=7.6 Hz; 9-H), 7.14 (1H, ddd; 7.7+7.5+1.2 Hz; 11-H), 7.23-7.43 (5H, m; Ph), 8.92 and 8.95 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 9.73 and 9.92 (C18), 21.82 and 23.78 (C17), 30.19 and 30.91 (C19), 35.60 and 35.74 (C14), 38.00 and 38.67 (C15), 42.23 and 42.34 (C6), 50.64 and 50.79 (C5), 50.91 and 51.00 (OCH_3), 55.21 and 55.27 (C7), 58.32 and 58.37 (N$\underline{C}H_2$Ph), 71.11 (C20), 71.53 and 72.52 (C3), 90.69 and 90.95

(C16), 109.21 (C12), 120.52 and 120.57 (C10), 122.22 and 122.31 (C9), 127.81 (C11), 127.06+128.31+128.94 and 129.06+139.13 (Ph), 137.92 and 137.97 (C8), 143.02 (C13), 165.14 (C2), 169.06 (16-$\underline{C}OOCH_3$).

Methyl 11-(2-(benzoyloxy)butyl)-1-benzyl-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (15)

1,3-Dicyclohexylcarbodiimide (2.48 g, 12 mmol) and 4-dimethylaminopyridine (147 mg, 1.2 mmol) were added to a solution of benzoic acid (1.47 g, 12 mmol) in dry dichloromethane (20 mL). The mixture cooled to 0^{o}C and at this temperature **14** (1.00 g, 2.3 mmol) in dry dichloromethane (20 mL) was added dropwise. The mixture was allowed to warm up to rt and then stirred for 24 h. It was quenched with water (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1:1, R_f=0.52) to afford 0.95 g (77 %) of the product **15** as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) ν_{max} 3384, 2936, 1716, 1676, 1612, 1464, 1276, 1112, 744. MS m/z (%) (rel intensity) 536 (1.0, $[M]^+$), 433 (4.0), 329 (32.0), 225 (100.0), 204 (24.0), 91 (32.0). HRMS (EI) calcd for $C_{34}H_{36}N_2O_4$ 536.2675, found for 536.2678. ^{1}H NMR δ_H ($CDCl_3$): 0.80 (3H, t, J=7.3 Hz; 18-H_3), 1.10-1.42 (2H, m; 15-H_2), 1.45-1.65 (2H, m; 19-H_2), 1.66 (1H, m; 6-H_A), 1.98-2.08 (2H, m; 6-H_B+14-H), 2.45-2.80 (3H, m; 17-H_2+5-H_A), 2.88 (1H, m; 5-H_B), 3.00 and 3.04 (1H, br s; 3-H), 3.61 and 3.70+4.02 and 4.10 (2×1H, 2×d, J_{gem}=13.2 Hz; NC$\underline{H}_2$Ph), 3.76 and 3.78 (3H, s; OCH_3), 5.07 (1H, m; 20-H), 6.78-6.86 (2H, m; 12-H+10-H), 6.98 (1H, br d, J=7.6 Hz; 9-H), 7.10-7.16 (1H, m; 11-H), 7.18-7.36 (5H, m; $NCH_2\underline{Ph}$), 7.36-7.56+7.98 (3H, m+2H, m; COPh), 8.98 and 9.02 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 9.41 and 9.56 (C18), 22.34 and 23.61 (C17), 27.21 and 27.93 (C19), 35.20 and 35.26 (C15), 35.70 and 35.91 (C14), 42.19 and 42.43 (C6), 50.55 and 50.62 (C5), 50.96 (OCH_3), 55.14 and 55.20 (C7), 58.06 and 58.20 (N$\underline{C}H_2$Ph), 71.59 and 72.40 (C3), 74.04 and 74.75 (C20), 90.81 and 90.91 (C16), 109.26 (C12), 120.58 (C10), 122.22 and 122.30 (C9), 127.84 (C11), 126.96 and 127.03+128.32+128.91+138.93 and 139.14 ($NCH_2\underline{Ph}$), 128.26+129.58+130.77+132.68 and 132.74 (CO$\underline{Ph}$), 137.76 and 137.88 (C8), 143.03 and 143.07 (C13), 165.13 (C2), 166.19 and 166.26 ($\underline{C}OPh$), 169.08 and 169.17 (16-$\underline{C}OOCH_3$).

Methyl 11-(2-(benzoyloxy)butyl)-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (16)

A mixture of **15** (0.50 g, 0.93 mmol) and 10 % palladium/charcoal (0.25 g) in glacial acetic acid (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 dichloromethane (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 ethyl dichloromethane/methanol=20:1, R_f=0.34) to yield 0.38 g (91 %) of **16** as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) ν_{max} 3368, 2968, 1716, 1680, 1608, 1464, 1276, 1248, 1108, 748. MS m/z (%) (rel intensity) 447 (100.0, $[M]^+$), 342 (5.0), 325 (8.0), 218 (54.0), 91 (23.0), 65 (18.0). HRMS (EI) calcd for $C_{27}H_{30}N_2O_4$ 446.5381, found for 446.5378. ^{1}H NMR δ_H ($CDCl_3$): 0.80 and 0.82 (3H, t, J=7.3 Hz; 18-H_3), 1.00-2.15 (7H, m; 15-H_2+19-H_2+6-H_2+14-H), 2.29 and 2.42+2.61 and 2.82 (2×1H, 2×dd, J_{gem}=15.6 Hz, J_{vic}=3.5 and 3.0 Hz; 17-H_2), 3.04-3.22 (2H, m; 5-H_2), 3.50 and 3.66 (1H, br s; 3-H), 3.75 and 3.79 (3H, s; OCH_3), 5.02-5.17 (1H, m; 20-H), 6.76-6.92 (2H, m; 12-H+10-H), 7.10-7.26 (2H, m; 11-H+9-H), 7.38-7.58+8.00 (3H, m+2H, m; COPh), 9.04 and 9.11 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 9.51 and 9.56 (C18), 21.71 and 23.75 (C17), 27.39 and 27.88 (C19), 35.69 and 36.33 (C15), 37.90 and 38.18 (C14), 43.67 and 44.21 (C6), 44.95 and 45.22 (C5), 50.99 (OCH_3), 55.39 and 55.81 (C7), 65.45 and 67.31 (C3), 73.94 and 74.10 (C20), 90.27 and 90.62 (C16), 109.26 and 109.32 (C12), 120.77 and 120.82 (C10), 121.94 and 122.04 (C9), 127.91 and 127.96 (C11), 128.29 and 128.32+129.60+130.65+132.75 (CO<u>Ph</u>), 137.61 and 137.69 (C8), 143.20 (C13), 165.25 (C2), 166.27 and 166.41 (<u>C</u>OPh), 168.95 and 169.03 (16-<u>C</u>$OOCH_3$).

(±)-20-Epiibophyllidine (4)

Method I.: A mixture of **16** (0.2 g, 0.45 mmol) and potassium iodide (0.08 g, 0.45 mmol) in dry DMF (5 mL) was refluxed 5 h, then was evaporated in vacuo. The main component was purified by preparative TLC (eluting with ethyl acetate/methanol=4:1, R_f=0.31) to yield a yellow oil, which was crystallized from ether to afford **4** (93 mg, 64 %) as white crystals, mp 141-143 ^{o}C (mp 142-143 ^{o}C in lit., 3a). IR (KBr) ν_{max} 3376, 2928, 1676, 1612, 1464, 1440, 1244, 744. MS (FAB) m/z (%) (rel intensity) 326 (4.0), 325 (100.0, $[M]^+$), 296 (64.0), 181 (55.0), 168 (44.0). HRMS (FAB) calcd for $C_{20}H_{25}N_2O_2$ ($M+H^+$) 325.4168, found for 325.4172. ^{1}H NMR δ_H ($CDCl_3$): 0.93 (3H, t, J=7.5 Hz; 18-H_3), 1.38+1.96 (2×1H, 2×ddd, J_{gem}=12.5 Hz, J_{vic}=11.8+6.3 and 9.6+6.5 Hz; 15-H_2), 1.48+1.81 (2×1H, 2×dqd, J_{gem}=12.9 Hz, J_{vic}=8.8+7.3 and 7.5+5.6 Hz; 19-H_2)1.92+2.85 (2×1H, 2×dd, J_{gem}=15.0 Hz, J_{vic}=11.3 and 6.7 Hz; 17-H_2), 2.05 (1H, m; 14-H), 2.11+2.23 (2×1H, 2×ddd, J_{gem}=12.8 Hz, J_{vic}=8.8+8.3 and 9.7+4.5 Hz;6-H_2), 2.76 (1H, m; 20-H), 2.89+3.27 (2×1H, 2×dm, J_{gem}=9.8 Hz; 5-H_2), 3.62 (1H, d, J=8.6 Hz; 3-H), 3.76 (3H, s; OCH_3), 6.83 (1H, d, J=7.8 Hz; 12-H), 6.93 (1H, ddd, J=7.4+7.4+1.2 Hz; 10-H), 7.15 (1H, ddd, J=7.7+7.5+1.2 Hz; 11-H), 7.49 (1H, d, J=7.5 Hz; 9-H), 9.08 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 12.11 (C18), 24.48 (C19), 30.74 (C17), 34.83 (C15), 38.02 (C14), 41.17 (C6), 48.92 (C5), 50.98 (OCH_3), 56.39 (C7), 66.24 (C20), 75.10 (C3), 92.07 (C16), 109.18 (C12), 120.83 (C10), 122.32 (C9), 127.81 (C11), 137.93 (C8), 144.01 (C13), 165.32 (C2), 169.05 (16-<u>C</u>$OOCH_3$). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found C, 73.94; H, 7.41; N, 8.59.

1-(9-(Methoxycarbonyl)-1-benzyl-2,3,8,10,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-11-yl)-butan-2-yl methanesulfonate (17)

14 (1.00 g, 2.31 mmol) was dissolved in dry dichloromethane (20 mL) and 0.38 mL of triethylamine (0.28 g, 2.77 mmol) and 4-dimethylaminopyridine (35 mg, 0.3 mmol) were added to the solution. After the addition it was cooled to 0^{o}C and methanesulfonyl chloride (0.22 mL, 0.32 g, 2.77 mmol) was added dropwise at 0^{o}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: ether/hexane=1:4, R_f=0.57) to afford 0.88 g (75 %) of the product **17** as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) ν_{max} 3376, 2944, 1676, 1608, 1464, 1440, 1348, 1188, 912, 748. MS (FAB) m/z (%) (rel intensity) 511 (6.0, $[M+H^+]$), 393 (8.0), 330 (100.0), 149(19.0), 100(9.0), 91 (46.0), 65 (23.0). HRMS (FAB) calcd for $C_{28}H_{35}N_2O_5S$ 511.7438, found for 511.7441. ^{1}H NMR δ_H ($CDCl_3$): 0.78 and 0.87 (3H, t, J=7.3 Hz; 18-H_3), 1.16-1.25 (2H, m; 15-H_2), 1.42 (1H, m; 6-H_A), 1.50-1.62 (2H, m; 19-H_2), 1.82-1.95 (2H, m; 6-H_B+14-H), 2.47-2.76 (3H, m; 17-H_2+5-H_A), 2.84 (1H, m; 5-H_B), 2.91 (3H, s; OSO_2CH_3), 3.00+3.03(1H, br s; 3-H), 3.71 and 4.31 (2×1H, 2×d, J_{gem}=13.2 Hz; NC$\underline{H}_2$Ph), 3.76 and 3.78 (3H, s; OCH_3), 4.32-4.48 (1H, m; 20-H), 6.73-6.78 (2H, m; 12-H+10-H), 6.84 and 6.86 (1H, br d; J=7.5 Hz; 9-H), 7.19 (1H, ddd, J=7.6+7.4+1.2 Hz; 11-H), 7.28-7.43 (5H, m; Ph), 8.96 and 9.00 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 9.22 and 9.68 (C18), 21.27 and 22.46 (C17), 26.67 and 27.13 (C19), 31.75 ($OSO_2\underline{C}H_3$), 35.44 and 35.89 (C15), 37.72 and 38.38 (C14), 39.10 and 39.54 (C6), 51.00 and 51.06 (C5), 51.54 (OCH_3), 54.27 and 54.30 (C7), 57.86 and 57.94 (N$\underline{C}H_2$Ph), 66.45 and 66.82 (C3), 72.32 and 72.47 (C20), 91.56 and 91.63 (C16), 110.23 (C12), 121.19 (C10), 121.48 and 121.55 (C9), 128.01 and 128.12 (C11), 129.50+129.71+138.86 (Ph), 137.62 ans 137.69 (C8), 143.11 and 143.19 (C13), 165.17 (C2), 168.24 and 168.44 ($\underline{C}OOCH_3$).

12-Benzyl-1-ethyl-4-(methoxycarbonyl)-1,2,2a,3,5,10,11,12a-octahydropyrrolizino[1,7-*cd*]carbazol-12-ium mesylate (19)

17 (1.00 g, 1.96 mmol) in dry tetrahydrofuran (20 mL) was refluxed over 96 h. Then it was cooled and the salt was separated by filtration. The crystals were washed with cold tetrahydrofuran to give 0.49 g (49 %) of **19** as a white crystal. IR (KBr) ν_{max} 3376, 2952, 1688, 1616, 1252, 1216, 1056, 744. MS m/z (%) (rel intensity) 510 (2.0, $[M]^+$), 447 (12.0), 415 (100.0), 325 (17.0), 293 (10.0), 180 (10.0), 167 (11.0), 110 (54.0), 91 (73.0). HRMS (EI) calcd for $C_{28}H_{34}N_2O_5S$ 510.6450, found for 510.6448. ^{1}H NMR δ_H (DMSO-d_6): 1.09 (3H, t, J=7.2 Hz; 18-H_3), 1.82+2.58 (2×1H, 2×dm, J_{gem}=13.5 Hz; 6-H_2), 1.93+2.33 (2×1H, 2×dqd, J_{gem}=12.5 Hz, J_{vic}=7.2+10.5 and 7.2+3.0 Hz; 19-H_2), 2.23+2.52 (2×1H, 2×m; 15-H_2), 2.26+2.94 (2×1H, 2×dd, J_{gem}=15.8 Hz, J_{vic}=11.3 and 6.0 Hz; 17-H_2), 2.60 (1H, m; 14-H), 2.82 (3H, s; $CH_3SO_3^-$), 3.70+3.84 (2×1H, 2×ddd, J_{gem}=12.5 Hz, J_{vic}=13.5+5.5 and 6.4+1.0 Hz; 5-H_2), 3.71 (3H, s;

OCH_3), 3.98 (1H, m; 20-H), 4.56 (1H, d, J=7.8 Hz; 9-H), 4.60+4.69 (2×1H, 2×d, J_{gem}=12.9 Hz; $NC\underline{H}_2Ph$), 4.85 (1H, d, J=7.9 Hz; 3-H), 6.11 (1H, m; 10-H), 6.96-7.02 (2H, m; 11-H+12-H), 7.55-7.90 (5H, m; Ph), 9.95 (1H, br s; N(1)H). NOE: 4.85 (3-H_β)→ 2.60 (14-H_β), 7.87 (2'-H+6'-H), 4.56 (9-H), 4.69 ($NCH_A\underline{H}_BPh$); 1.09 (18-H_3)→ 1.93+2.33 (19-H_2), 2.23 (15-H_A), 3.98 (20-H); 4.56 (9-H)→ 6.11 (10-H), 7.55-7.90 (Ph), 4.85 (3-H), 3.70 (5-H_A). ^{13}C NMR δ_C (DMSO-d_6): 11.95 (C18), 21.44 (C19), 26.86 (C17), 33.07 (C15), 35.50 (C14), 37.80 (C6), 51.37 (OCH_3), 54.37 (C5), 55.49 (C7), 59.23 ($N\underline{C}H_2Ph$), 77.28 (C20), 80.36 (C3), 91.52 (C16), 110.56 (C12), 120.28 (C10), 121.93 (C9), 128.82 (C11), 129.23 (C1'), 130.24 (C3', C5'), 131.30 (C4'), 132.57 (C8), 135.57 (C2', C6'), 144.18 (C13), 157.83 (C2), 167.00 (16-$\underline{C}OOCH_3$).

(±)-20-Epiibophyllidine (4)

Method II.: A mixture of **19** (0.50 g, 0.98 mmol) and 10 % palladium/charcoal (0.25 g) in glacial acetic acid (10 mL) was hydrogenated for 4 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 dichloromethane (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 ethyl acetate/methanol=4:1, R_f=0.31) yielded 0.28 g (88 %) of **4** as a yellow oil. The analytical data were identified in the previous method.

6,6-Bis(ethylthio)hexan-3-one (21)

A solution of **11** (5.00 g, 23 mmol) in dichloromethane (50 mL) was added to a stirred suspension of pyridinium chlorochromate (7.27 g, 34 mmol), containing NaOAc (0.56 g, 7 mmol). After 2 h ether (100 ml) was added and the suspension was decanted. The black precipitate was washed with ether (2×50 mL). The combined organic phases were washed with 5% aqueous $NaHCO_3$ (50 mL), 1 M aqueous solution of HCl (50 mL) and water (50 mL), then dried ($MgSO_4$) and filtered over a layer of celite. Evaporation of the filtrate gave 4.00 g (79 %) of the title compound **(21)** as a colorless oil. The crude product was used directly for the next reaction without purification (TLC: acetone/hexane=1:2, R_f=0.84). IR (neat) ν_{max} 2968, 1716, 1452, 1376, 1264, 1112. MS m/z (%) (rel intensity) 220 (9.0, $[M]^+$),.205 (13.0), 159 (49.0), 143 (43.0), 103 (18.0), 99 (81.0), 81 (41.0), 57 (100.0). HRMS (EI) calcd for $C_{10}H_{20}OS_2$ 220.0956, found for 220.0963. ^{1}H NMR δ_H ($CDCl_3$): 1.07 (3H, t, J=7.3 Hz; C(6)H_3), 1.25 (6H, t, J=7.5 Hz; 2×$SCH_2C\underline{H}_3$), 2.09 (2H, td, J=7.1 and 7.0 Hz; C(2)H_2), 2.45 (2H, q, J=7.3 Hz; C(5)H_2), 2.59+2.67 (2×2H, 2×dq, J_{gem}=12.5 Hz, J_{vic}=7.5 Hz; 2×$SC\underline{H}_2CH_3$), 2.68 (2H, t, J=7.1 Hz; C(3)H_2), 3.83 (1H, t, J=7.0 Hz; C(1)H). ^{13}C NMR δ_C ($CDCl_3$): 7.88 (C6), 14.53 (2×$SCH_2\underline{C}H_3$), 24.41 (2×$S\underline{C}H_2CH_3$), 29.64 (C2), 36.19 (C5), 39.47 (C3), 50.54 (C1), 210.59 (C4).

4-Oxohexanal (7)

21 (4.00 g, 18 mmol) was dissolved in acetonitrile (100 mL) and water (10 mL) was added to the solution. Calcium carbonate (7.20 g, 72 mmol) and mercury(II) chloride (19.54 g, 72 mmol) were added to a stirred solution. After the addition the mixture was stirred for 30 min. The salts were filtrated and the acetonitrile was removed at 40°C under reduced pressure to leave a yellow oil. This was then taken up into dichloromethane (70 mL) and washed with 25 mL portion of aqueous solution of NaI, 25 mL portion of aqueous solution of $Na_2S_2O_3$ and brine (25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (eluting with acetone/hexane=1:1, R_f=0.72) to afford 1.25 g (61 %) of the product **7** as a colorless oil. IR (neat) ν_{max} 2976, 1712, 1416, 1168. MS m/z (%) (rel intensity) 114 (100.0, $[M]^+$), 81(21.0), 57 (38.0), 55 (13.0). HRMS (EI) calcd for $C_6H_{10}O_2$ 114.1425, found for 114.1429. ^{1}H NMR δ_H ($CDCl_3$): 1.08 (3H, t, J=7.5 Hz; C(6)H_3), 2.22 (2H, q, J=7.6 Hz; C(5)H_2), 2.48 (2H, qm, J=7.2 Hz; C(3)H), 2.75 (2H, q, J=7.2 Hz; C(4)H_2), 9.81 (1H, t, J=1.8 Hz; CHO). ^{13}C NMR δ_C ($CDCl_3$): 7.94 (C(6)), 34.35 (C(3)), 35.98 (C(5)), 37.64 (C(2)), 200.72 (CHO), 209.37 (C(4)O).

Methyl 2,3,8,10,11,11a-hexahydro-11-(2-oxobutyl)-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (22)

A solution of **8** (1.50 g, 4.27 mmol), **7** (0.73 g, 6.41 mmol), and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in dry toluene (60 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 ethyl acetone/hexane=1:2, R_f=0.64) to yield an yellow oil, which was crystallized from methanol to afford **22** (0.86 g, 59 %) as white crystals, mp 95-96 °C. IR (KBr) ν_{max} 3376, 2944, 1712, 1676, 1608, 1488, 1448, 1248, 748. MS m/z (%) (rel intensity) 430 (32.0, $[M]^+$), 373 (60.0), 297 (64.0), 228 (37.0), 216 (37.0), 91 (100.0). HRMS (EI) calcd for $C_{27}H_{30}N_2O_3$ 430.2246, found for 430.2244. ^{1}H NMR δ_H ($CDCl_3$): 0.93 (3H, t, J=7.5 Hz; 18-H_3), 1.65+2.02 (2×1H, 2×ddd, J_{gem}=12.2 Hz, J_{vic}=4.8+1.0 Hz and 12.3+6.5 Hz; 6-H_2), 1.97+2.13 (2×1H, 2×dd, J_{gem}=18.0 Hz, J_{vic}=8.5 and 5.5 Hz; 15-H_2), 2.17+2.22 (2×1H, 2×dq, J_{gem}=17.5 Hz, J_{vic}=7.5 Hz; 19-H_2), 2.52-2.66 (4H, m; 17-H_2+14-H+5-H_A), 2.89 (1H, m; 5-H_B), 2.94 (1H, br s; 3-H), 3.76+4.37 (2×1H, 2×d, J_{gem}=14.0 Hz; NC$\underline{H}_2$Ph), 3.77 (3H, s; OCH_3), 6.79-6.84 (2H, m; 12-H+10-H), 6.89 (1H, br d, J=7.6 Hz; 9-H), 7.14 (1H, ddd, J=7.7+7.5+1.4 Hz; 11-H), 7.23-7.45 (5H, m; Ph), 8.98 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 7.70 (C18), 23.51 (C17), 34.45 (C14), 36.62 (C19), 42.30 (C6), 43.72 (C15), 50.11 (C5), 50.98 (OCH_3), 55.05 (C7), 57.50 (N$\underline{C}H_2$Ph), 70.71 (C3), 90.99 (C16), 109.21 (C12), 120.66 (C10), 122.35 (C9), 127.87 (C11), 126.93+128.24+129.04+139.10 (Ph), 137.75 (C8), 142.91 (C13), 165.08 (C2), 169.04 (16-$\underline{C}OOCH_3$), 210.77 (C20). Anal. Calcd for $C_{27}H_{30}N_2O_3 \cdot 3/4CH_3OH$: C, 73.11; H, 6.71; N, 6.06. Found C, 73.00; H, 6.67; N, 6.01.

(±)-Ibophyllidine (3)

A mixture of the amino ketone **(22)** (0.50 g, 1.47 mmol) and 0.1 g of 10 % palladium/charcoal catalyst in glacial acetic acid (10 mL) was stirred for 72 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 dichloromethane (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluent: ethyl acetate/methanol=4:1, R_f=0.33) to yield a colorless oil, which was crystallized from ether to afford ibophyllidine **(3)** (0.39 g, 81 %) as white crystals, mp 114-115 ^oC (mp 109-111 ^oC in lit., 3a). IR (KBr) ν_{max} 3338, 2952, 1680, 1608, 1462, 1241, 748. MS m/z (%) (rel intensity) 324 (3.0, $[M]^+$), 295 (1.0), 180 (3.0), 110 (100.0), 82 (5.0). HRMS (EI) calcd for $C_{20}H_{24}N_2O_3$ 324.4168, found for 324.4162. ^1H NMR δ_H ($CDCl_3$): 1.04 (3H, t, J=7.5 Hz; 18-H_3), 1.32+2.23 (2×1H, 2×ddd, J_{gem}=12.8 Hz, J_{vic}=6.5+11.2 and 9.0+6.6 Hz; 15-H_2), 1.57+1.94 (2×1H, 2×dqd, J_{gem}=13.2 Hz, J_{vic}=7.5+8.9 and 7.5+5.8 Hz; 19-H_2), 1.83+3.13 (2×1H, 2×dd, J_{gem}=15.3 Hz, J_{vic}=11.1 and 6.9 Hz; 17-H_2), 2.08 (1H, m; 14-H), 2.21+2.29 (2×1H, 2×ddd, J_{gem}=13.6 Hz, J_{vic}=8.8+8.2 and 9.5+4.4 Hz; 6-H_2), 2.82+3.23 (2×1H, 2×dm, J_{gem}=10.0 Hz; 5-H_2), 3.30 (1H, m; 20-H), 3.60 (1H, d, J=8.8 Hz; 3-H), 3.76 (3H, s; OCH_3), 6.82 (1H, d, J=7.8 Hz; 12-H), 6.94 (1H, ddd, J=7.5+7.5+1.1 Hz; 10-H), 7.14 (1H, ddd, J=7.8+7.5+1.3 Hz; 11-H), 7.60 (1H, br d, J=7.5 Hz; 9-H), 9.16 (1H, br s; N(1)H). ^{13}C NMR δ_C ($CDCl_3$): 12.25 (C18), 25.33 (C19), 31.56 (C17), 34.84 (C15), 37.33 (C14), 41.11 (C6), 47.41 (C5), 50.86 (OCH_3), 55.73 (C7), 65.76 (C20), 75.30 (C3), 91.93 (C16), 108.76 (C12), 121.39 (C10), 123.32 (C9), 127.76 (C11), 137.98 (C8), 143.07 (C13), 164.40 (C2), 168.46 (16-$\underline{C}OOCH_3$). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found C, 73.98; H, 7.52; N, 8.57.

ACKNOWLEDGEMENTS

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

REFERENCES

1. F. Tóth, Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, Á. Gömöry, L. Hazai, and Cs. Szántay, *Heterocycles*, 2006, **68**, 2301.
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. (d) 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 Experimential Section.

3. (a) M. E. Kuehne and J. C. Bohnert, *J. Org. Chem.*, 1981, **46**, 3443. (b) M. E. Kuehne and J. B. Pitner, *J. Org. Chem.*, 1989, **54**, 4553. (c) W. G. Bornmann and M. E. Kuehne, *J. Org. Chem.*, 1992, **57**, 1752. (c) M. C. Barsi, B. C. Das, J. L. Fourrey, and R. Sundaramoorthi, *J. Chem. Soc., Chem. Commun.*, 1985, **2**, 88. (d) S. Jegham, J. L. Fourrey, and C. Das, *Tetrahedron Lett.*, 1989, **30**, 1959.
4. F. Khuong-Huu, M. Cesario, J. Guilhem, and R. Goutarel, *Tetrahedron*, 1976, **32**, 2539.
5. C. Kan, H. P. Husson, H. Jacquemin, S. K. Kan, and M. Lounasmaa, *Tetrahedron Lett.*, 1980, **21**, 55.
6. Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Org. Chem.*, 1993, **58**, 1434.
7. Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Org. Chem.*, 1993, **58**, 6076.
8. Gy. Kalaus, I. Vágó, I. Greiner, M. Kajtár-Peredy, L Brlik, L. Szabó, and Cs. Szántay, *Nat. Prod. Lett.*, 1995, **7**, 197.
9. 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.
10. Gy. Kalaus, I. Juhász, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Org. Chem.*, 1997, **62**, 9188.
11. Md. A. Rahim, T. Fujiwara, and T. Takeda, *Tetrahedron*, 2000, **56**, 763.
12. Gy. Kalaus, I. Juhász, J. Éles, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, *J. Heterocycl. Chem.*, 2000, **37**, 245.