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Synthesis of vinca alkaloids and related compounds. Part 102: Simple synthesis and ring transformation of (±)-minovincine. First synthesis of (±)-vincaminine☆

György Kalaus,*[,a] László Léder,[a,b] István Greiner,[b] Mária Kajtár-Peredy,[c] Károly Vékey,[c] Lajos Szabó[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*

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Dedicated to Professor G. Bernáth on the occasion of his 70th birthday

Abstract—A molecule with an indole skeleton, containing a latent acrylic ester function—acting as a diene—readily reacted with benzoic acid (4-bromomethylene-5-oxo)hexyl ester that had been built up from pentane-2,4-dione. Dehydration of the enamine and subsequent [4+2] cycloaddition supplied epimers having the D-secoaspidospermane skeleton. These compounds directly or after epimerization gave (±)-minovincine. Oxidative ring transformation of (±)-minovincine under different conditions led to (±)-16-acetyl-16-deethylapovincamine and (±)-vincaminine.

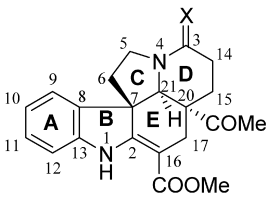
1. Introduction

In 1997 we reported the first synthesis of (±)-3-oxominovincine (**1**) from which we obtained (±)minovincine (**2**).[2] Building on our experience in synthesizing alkaloids with the aspidospermane skeleton as well as related compounds,[2–4] we saw a chance of producing **2** directly and performing subsequent ring transformation. The successful oxidative aspidospermane⟶eburnane skeleton transformation may allow production of both **3** and **4** (Fig. 1).

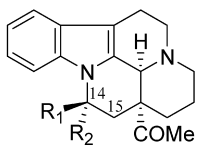
2. Results and discussion

As a result of a retrosynthetic analysis of our convergent synthetic strategies,[2,3] an activated vinyl halide derivative (aldehyde enol equivalent) was chosen as the reaction agent of the tryptamine derivative (**5**),[3] used earlier several times successfully, by which N_b-alkylation could be realized. We thought that benzoic acid (4-bromomethylene-5-oxo)hexyl ester (**10**) met all synthetic requirements.

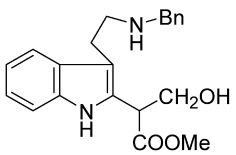
Molecule **10** was prepared from pentane-2,4-dione (**6**). Firstly **6** was alkylated with benzoic acid (3-iodo-propyl) ester,[5] then the diketoester (**7**) was allowed to react with aqueous formaldehyde in the presence of potassium



1 X = O
2 X = H_2



3 $\Delta^{14,15}$, R_2 = COOMe
4 R_1 = OH, R_2 = COOMe



5

Figure 1.

☆ Part 101, see Ref. 1.

Keywords: indoles; tryptamines; minovincine; vincaminine; alkaloids; natural products; cycloaddition; total synthesis.

* Corresponding authors. Address: Department for Organic Chemistry, Budapest University of Technology and Economics, Gellért tér 4, H-1111 Budapest, Hungary. Fax: +36-1-463-3297;
e-mail: szantay@mail.bme.hu

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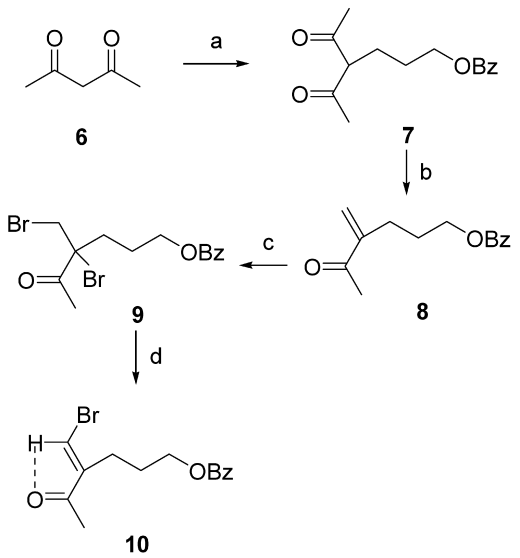
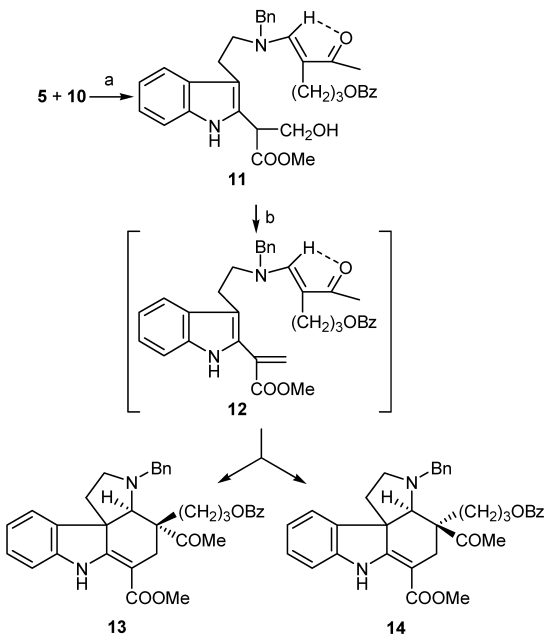


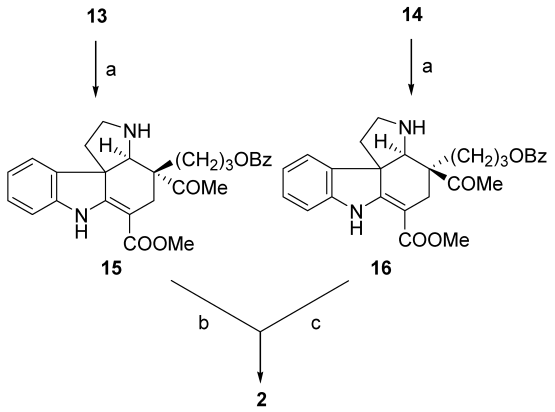
Scheme 1. *Reagents and conditions*: (a) **6**, $I(CH_2)_3OBz$, K_2CO_3, KI, acetone, △, 84%; (b) **7**, CH_2O, K_2CO_3, H_2O, rt, 43%; (c) **8**, Br_2, CH_2Cl_2, rt, 92%; (d) **9**, $(n\text{Bu})_4NF$, HMPA, rt, 63%.

carbonate at rt[6] giving the unsaturated derivative **8**. Addition of bromine to **8** led to **9** and subsequent elimination of hydrogen bromide[7] from **9** resulted in the expected compound **10** (Scheme 1).

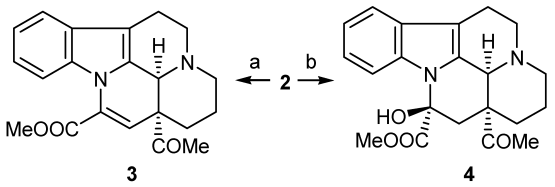
Subsequently, the secondary amine (**5**) was allowed to react with vinyl halide (**10**) in methanol at rt in the presence of *N*,*N*-diisopropyl-ethyl-amine. The expected[8] enamine (**11**) was obtained in 30% yield. The enamine **11** was refluxed in xylene in the presence of *p*-toluenesulphonic acid to give-via the non-isolable intermediate (**12**) as a [4+2] cyclo-addition-the tetracyclic compounds **13** and **14** having the D-secoaspidospermane skeleton. The starting enamine (**11**) disappeared from the reaction mixture on refluxing for 18 h,



Scheme 2. *Reagents and conditions*: (a) $(i\text{Pr})_2NEt$, MeOH, rt, 30%; (b) **11**, TsOH, xylene, △, 22% for **13**, 23% for **14**.



Scheme 3. *Reagents and conditions*: (a) H_2, Pd/C, CH_3COOH, rt, 95%; (b) **15**, KI, DMF, △, 2 h, 34%; (c) **16**, KI, DMF, △, 4 h, 34%.



Scheme 4. *Reagents and conditions*: (a) **2**, NCS, TFA, rt, 4 h then △, 3 h, Ar, 50%; (b) **2**, $(HOOC-(CH_2)_2-COO)_2$, MeOH, H_2O, cc. HCl, rt, dark, 39%.

a 1:1 mixture of the epimers (**13** and **14**) was isolated in 50% yield (Scheme 2).

The epimers **13** and **14** were separated by chromatography, and the benzyl-group was removed at rt by catalytic hydrogenolysis giving secondary amines **15** and **16**. Intramolecular *N*-alkylation (when boiling in the presence of potassium iodide in dimethylformamide) we obtained (±)-minovincine (**2**) directly or by epimerization[9] (Scheme 3).

Minovincine (**2**) was then converted, by ring transformation into the eburnane skeleton derivatives. When the reaction was carried out with *N*-chlorosuccinimide in refluxing trifluoroacetic acid,[10] (±)-16-acetil-16-deethylapovinc-amine (**3**) was obtained as the product. Using 4-(3-carboxy-propionylperoxy)-4-oxobutyric acid[11] in aqueous methanolic hydrocholic acid,[12] (±)-vincaminine[13] (**4**) was obtained as the product (Scheme 4).

3. Conclusion

By regioselective alkylation of the tryptamine derivative **5** with vinyl bromide **10**, the enamine **11** was obtained. Subsequent dehydration followed by intramolecular [4+2] cycloaddition resulted in compounds with the D-seco-aspidospermane skeleton (**13**, **14**). Hydrogenolysis of tertiary amines led to secondary amines (**15**, **16**), from which (±)-minovincine (**2**) could be obtained by intra-molecular alkylation. The aspidospermane→eburnane ring transformation was realized in two ways. In the first case we obtained compound **3**, and the second case resulted in the first synthesis of (±)-vincaminine (**4**).

4. Experimental

4.1. General

Melting points were determined with a hot-stage microscope Boëtius and are given uncorrected. IR spectra were recorded with a Specord JR-75 spectrophotometer. NMR spectra were recorded with a Varian Unity INOVA-400 instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All NMR spectra were registered at rt. The assignments denoted by x, + and ∗ may be interchanged. J_{lr}, 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 their first occurrences. MS spectra were determined on a VG ZAB2-SEQ tandem mass spectrometer using electron impact (70 eV) for ionization and direct probe for sample introduction at source temperature of 180°C. Mass range *m/z* 25–620 was considered in low resolution spectra. Exact mass measurements on molecular ions were carried out at resolution of 10000. Preparative TLC analyses were performed on silica gel F_{254} plates, and column chromatography was carried out on Merck Kieselgel 60 (0.063–0.200 mm). The organic layers were dried with $MgSO_4$.

4.1.1. Benzoic acid (4-acetyl-5-oxo)hexyl ester (7). To a solution of benzoic acid (3-iodopropyl) ester[5] (10.3 g, 35.5 mmol) in anhydrous acetone (120 mL) was added pentane-2,4dione (4.8 g, 48.0 mmol) and anhydrous K_2CO_3 (7.1 g, 51.6 mmol). The heterogeneous reaction mixture was refluxed for 48 h then was filtered and evaporated in vacuo. The main component was separated by column chromatography (eluent: hexane/acetone 5:1) to yield **7** (7.8 g, 84%) as a yellow oil (R_f=0.34). IR (neat) ν: 1720 (ester CO), 1715–1680 (CO) cm^{-1}; *oxo-form* δ_H ($CDCl_3$): 1.73 (m, 2H, CH_2CH$_2$O), 2.01 (m, 2H, CHCH_2), 2.20 (s, 6H, 2×COCH_3), 3.70 (t, J=7.2 Hz, 1H, CHCH$_2$), 4.33 (t, J=6.3 Hz, 2H, OCH$_2$), 7.4–7.6 (m, 3H, PhC(3)-H+PhC(5)-H+PhC(4)-H), 8.05 (m, 2H, PhC(2)-H+PhC(6)-H); *enol-form*: 1.89 (m, 2H, CH_2CH$_2$O), 2.17 (s, 6H, 2×CH$_3$), 2.41 (m, 2H, =C–CH$_2$), 4.36 (t, J=6.3 Hz, 2H, OCH$_2$), 7.4–7.6 (m, 3H, PhC(3)-H+PhC(5)-H+PhC(4)-H), 8.05 (m, 2H, PhC(2)-H+PhC(6)-H), 16.73 (enol-OH) ppm, (oxo-enol tautomeric ratio ~4:3); *oxo-form*: δ_C ($CDCl_3$): 24.71 (*C*H$_2$CH$_2$O), 26.70 (CH*C*H$_2$), 29.10 (2×CO*C*H$_3$), 64.15 (OCH$_2$), 68.29 (*C*HCH$_2$), 128.43 (PhC-3+PhC-5), 129.48 (PhC-2+PhC-6), 130.17 (PhC-1), 133.07 (PhC-4), 166.52 (O*C*OPh), 203.84 (2×*C*OCH$_3$); *enol-form*: 22.85 (2×CH$_3$), 24.22 (*C*H$_2$CH$_2$O), 29.68 (=C–*C*H$_2$), 64.18 (OCH$_2$), 109.36 (=*C*–CH$_2$), 128.48 (PhC-3+PhC-5), 129.57 (PhC-2+PhC-6), 130.15 (PhC-1), 133.04 (PhC-4), 166.54 (O*C*OPh), 191.09 (*C*OCH$_3$+ =*C*(OH)CH$_3$) ppm; MS *m/z* (rel inten): 262 (5.0), 219 (3.0), 140 (15.0), 125 (24.0), 105 (100.0), 98 (35.0), 83 (18.0), 77 (39.0), 43 (86.0); HRMS calcd for [$C_{15}H_{18}O_4$–H]$^+$ 263.1283; found 263.1268.

4.1.2. Benzoic acid (4-methylene-5-oxo)hexyl ester (8). To a mixture of **7** (6.0 g, 22.9 mmol) and 30% aqueous formaldehyde (4.6 mL) was added a solution of K_2CO_3 (6.3 g, 45.6 mmol) in water (4.3 mL) at rt. The heterogeneous reaction mixture was stirred for 12 h then diluted with water (60 mL), and the solution was extracted with ether (3×35 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The main component was separated by column chromatography (eluent: hexane/ether 1:1) to yield a colourless oil (R_f=0.59), which was crystallized from methanol to afford **8** (2.3 g, 43%) as white crystals. Mp 38–40°C; IR (KBr) ν: 1725 (ester CO), 1665 (CO), 1630 (C=C) cm^{-1}; δ_H ($CDCl_3$): 1.92 (m, 2H, CH_2CH$_2$O), 2.35 (s, 3H, COCH$_3$), 2.44 (t, J=7.0 Hz, 2H, =C–CH$_2$), 4.32 (t, J=6.3 Hz, 2H, OCH$_2$), 5.84+6.06 (2×d, J_{gem}=1.6 Hz, 2×1H, C=CH$_2$), 7.44 (m, 2H, PhC(3)-H+PhC(5)-H), 7.56 (m, 1H, PhC(4)-H), 8.05 (m, 2H, PhC(2)-H+PhC(6)-H) ppm; δ_C ($CDCl_3$): 25.90 (CO*C*H$_3$), 27.30+27.38 (=C–*C*H$_2$*C*H$_2$), 64.31 (OCH$_2$), 125.80 (C=*C*H$_2$), 128.35 (PhC-3+PhC-5), 129.55 (PhC-2+PhC-6), 130.31 (PhC-1), 132.90 (PhC-4), 147.96 (*C*=CH$_2$), 166.58 (O*C*OPh), 199.50 (*C*OCH$_3$) ppm; MS *m/z* (rel inten): 110 (48.0), 105 (100.0), 95 (25.0), 77 (51.0), 67 (28.0), 50 (8.0), 42 (23.0). Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; found C, 72.40; H, 7.01.

4.1.3. Benzoic acid (4-bromo-4-bromomethyl-5-oxo)-hexyl ester (9). To a solution of **8** (2.5 g, 10.8 mmol) in CH_2Cl_2 (50 mL) was added a solution of bromine (1.8 g, 0.6 mL, 11.7 mmol) in CH_2Cl_2 (5 mL) dropwise at rt. After the solution was stirred for 1 h the excess bromine was removed by washing with saturated $Na_2S_2O_3$ solution until the solution was discolored. The organic layer was separated and washed with water (20 mL), dried and concentrated in vacuo. The residue was crystallized from methanol to yield **9** (3.9 g, 92%) as white crystals. Mp 50–52°C; IR (KBr) ν: 1730 (ester CO), 1720 (CO) cm^{-1}; δ_H ($CDCl_3$): 1.90+2.04 (2×m, 2×1H, CH_2CH$_2$O), 2.34 (m, 2H, CH_2CH$_2$CH$_2$O), 2.47 (s, 3H, COCH_3), 3.85+4.09 (2×d, J_{gem}=10.7 Hz, 2×1H, C–CH$_2$–Br), 4.41 (m, 2H, OCH$_2$), 7.45 (m, 2H, PhC(3)-H+PhC(5)-H), 7.57 (m, 1H, PhC(4)-H), 8.05 (m, 2H, PhC(2)-H+PhC(6)-H) ppm; δ_C ($CDCl_3$): 24.36 (CO*C*H$_3$), 24.39 (*C*H$_2$CH$_2$O), 32.27 (*C*H$_2$CH$_2$CH$_2$O), 34.09 (C–*C*H$_2$–Br), 64.07 (OCH$_2$), 67.43 (Br–*C*–CH$_2$Br), 128.41 (PhC-3+PhC-5), 129.59 (PhC-2+PhC-6), 130.06 (PhC-1), 133.04 (PhC-4), 166.48 (O*C*OPh), 199.44 (*C*OCH$_3$) ppm; MS *m/z* (rel inten): 313 (11.0), 311 (11.0), 271 (3.0), 189 (10.0), 110 (35.0), 105 (100.0), 95 (20.0), 77 (52.0), 67 (23.0), 42 (42.0). Anal. calcd for $C_{14}H_{16}Br_2O_3$: C, 42.89; H, 4.11; Br, 40.76; found C, 42.92; H, 4.28; Br 40.75.

4.1.4. Benzoic acid (4-bromomethylene-5-oxo)hexyl ester (10). To a homogeneous solution of tetrabutylammonium fluoride monohydrate (2.6 g, 9.3 mmol) in HMPA (5 mL) was added a solution of **9** (3.0 g, 7.65 mmol) in HMPA (10 mL) over a 15 min period at 0°C. After being stirred for 12 h at rt, the brown mixture was cooled (0°C) and quenched with an aqueous solution of sulphuric acid (15 mL, 1 M) and then extracted with hexane (5×20 mL). The combined organic extracts were washed with water until neutrality of the aqueous layer. The organic layer was dried and concentrated in vacuo. The main component was separated by column chromatography (eluent: hexane/ether 1:1) to yield **10** (1.5 g, 63%) as a yellow oil (R_f=0.68). IR (neat) ν: 1710 (ester CO), 1665 (CO), 1590 (C=C) cm^{-1}; δ_H ($CDCl_3$): 1.90 (m, 2H, CH_2CH$_2$O), 2.33 (s, 3H, COCH$_3$), 2.66 (m, 2H, =C–CH$_2$), 4.32 (t, J=6.3 Hz, 2H, OCH$_2$), 7.44 (m, 2H, PhC(3)-H+PhC(5)-H), 7.55 (s, 1H, C=CH–Br), 7.56 (m, 1H, PhC(4)-H), 8.06 (m, 2H, PhC(2)-H+PhC(6)-H) ppm; *NOE*: 2.33 (COCH$_3$)→7.55

(C═C*H*Br) ppm; δ_C ($CDCl_3$): 25.63+26.81 (*C*H_2*C*H_2*C*H_2O), 26.13 (CO*C*H_3), 64.38 (O*C*H_2), 125.33 (C═*C*HBr), 128.36 (PhC-3+PhC-5), 129.59 (PhC-2+PhC-6), 130.41 (PhC-1), 132.87 (PhC-4), 146.58 (*C*═CHBr), 166.55 (O*C*OPh), 194.80 (*C*OCH$_3$) ppm; HRMS calcd for [$C_{14}H_{15}BrO_3$−H]$^+$ 311.0283; found 311.0267.

4.1.5. Enamine (11). To a mixture of **5**[3] (1.0 g, 2.84 mmol) and *N*,*N*-diisopropylethylamine (1.0 g, 7.75 mmol) in anhydrous methanol (200 mL) was added a solution of **10** (1.0 g, 3.21 mmol) in anhydrous methanol (20 mL) dropwise at rt. After being stirred for 48 h at rt the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (eluent: hexane/acetone 3:1) to yield **11** (0.49 g, 30%) as a yellow amorphous solid (R_f=0.31). IR (neat) *ν*: 3450−3260 (indole-NH+OH), 1735 (ester CO), 1720 (CO), 1630 (conj. ester CO), 1580 (C═C) cm^{-1}; δ_H ($CDCl_3$): 1.78 (m, 2H, C*H*$_2$CH$_2$O), 2.01 (s, 3H, COCH$_3$), 2.51 (m, 2H, ═C−CH$_2$), 2.92−3.07 (m, 2H, 3-CH$_2$), 3.50 (t, *J*=7.0 Hz, 2H, 3-CH$_2$C*H*$_2$N), 3.67 (s, 3H, OCH$_3$), 3.95−4.17 (m, 3H, 2-C*H*CH$_2$OH), 4.24 (t, *J*=6.3 Hz, 2H, OCH$_2$), 4.42 (s, 2H, NC*H*$_2$Ph), 7.08 (m, 1H, 5-H), 7.09 (m, 2H, 2″-H+6″-H), 7.17 (m, 1H, 6-H), 7.24 (s, 1H, C═CH), 7.25−7.42 (m, 7H, 4-H+7-H+3′-H+5′-H+3″-H+4″-H+5″-H), 7.50 (m, 1H, 4′-H), 7.89 (m, 2H, 2′-H+6′-H), 8.92 (br s, 1H, indole-NH) ppm; δ_C ($CDCl_3$): 21.04 (3-CH$_2$), 23.91[x] (*C*H$_2$CH$_2$O), 24.85 (CO*C*H$_3$), 29.93[x] (*C*H$_2$CH$_2$CH$_2$O), 44.77 (2-*C*H), 52.55 (OCH$_3$), 54.11 (3-CH$_2$*C*H$_2$N), 56.00 (NC*H*$_2$Ph), 63.80* (2-CH*C*H$_2$OH), 65.02* (*C*H$_2$OCOPh), 109.72$^+$ (NCH═*C*), 110.22$^+$ (C-3), 111.35 (C-7), 118.05 (C-4), 119.68 (C-5), 122.36 (C-6), 126.83 (C-2″+C-6″), 127.26 (C-3a), 127.73 (C-4″), 128.24 (C-3′+C-5′), 128.88 (C-3″+C-5″), 129.40 (C-2′+C-6′), 129.87 (C-2), 130.22 (C-1′), 132.73 (C-4′), 135.73 (C-7a), 137.18 (C-1″), 150.47 (N*C*H═C), 166.66 (O*C*OPh), 172.50 (*C*OOCH$_3$), 196.82 (*C*OCH$_3$) ppm; HRMS calcd for [$C_{35}H_{38}N_2O_6$−H]$^+$ 583.2808; found 583.2847.

4.1.6. (±)-20-Acetyl-4-benzyl-3-benzoyloxy-20-deethyl-2,16-didehydro-16-methoxycarbonyl-3,4-secoaspidospermidine (20*α*, 21*α*) (13) and (±)-20-acetyl-4-benzyl-3-benzoyloxy-20-deethyl-2,16-didehydro-16-(methoxycarbonyl)-3,4-secoaspidospermidine (20*β*, 21*α*) (14). A solution of **11** (1.0 g, 1.72 mmol) and *p*-toluenesulphonic acid monohydrate (0.01 g, 0.05 mmol) in xylene (50 mL) was refluxed under argon for 24 h. The reaction mixture was extracted with brine (2×50 mL) and the combined brine washes were extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried and evaporated in vacuo. The two main components were separated by column chromatography (eluent: hexane/ether 1:1). The more polar compound (*rac*-**13**, R_f=0.23) was obtained as a yellow amorphous solid (0.21 g, 22%). IR (neat) *ν*: 3398 (indole-NH), 1722 (ester CO), 1680 (CO), 1640 (conj. ester CO), 1620 (C═C) cm^{-1}; δ_H ($CDCl_3$): 1.61+1.82 (2×m, 2×1H, 14-H$_2$), 1.74+2.04 (2×ddd, J_{gem}=12.2 Hz, $J_{5,6}$=5.5+1.3, 11.9+6.6 Hz, respectively, 2×1H, 6-H$_2$), 1.99 (s, 3H, COCH$_3$), 1.93+2.35 (2×m, 2×1H, 15-H$_2$), 2.67+2.95 (2×d, J_{gem}=15.5 Hz, 2×1H, 17-H$_2$), 2.67+3.02 (2×ddd, J_{gem}=9.8 Hz, 2×1H, 5-H$_2$), 3.78+4.23 (2×d, J_{gem}=13.4 Hz, 2×1H, NC*H*$_2$Ph), 3.79 (s, 3H, OCH$_3$), 4.04 (d, J_{lr}=2.0 Hz, 1H, 21-H), 4.21 (t, *J*=6.5 Hz, 2H, 3-H$_2$), 6.81 (d, $J_{11,12}$=7.8 Hz, 1H, 12-H), 6.94 (ddd, $J_{9,10}$=7.5 Hz, $J_{10,11}$=7.3 , $J_{10,12}$=1.0 Hz, 1H, 10-H), 7.16 (ddd, $J_{9,11}$=1.2 Hz, 1H, 11-H), 7.19 (br d, 1H, 9-H), 7.20−7.60 (m, 8H, 2″-H+3″-H+4″-H+5″-H+6″-H+3′-H+4′-H+5′-H), 7.92 (m, 2H, 2′-H+6′-H), 8.74 (br s, 1H, N(1)-H) ppm; δ_C ($CDCl_3$): 25.31 (C-14), 26.00 (CO*C*H$_3$), 28.99 (C-17), 29.65 (C-15), 42.53 (C-6), 51.07 (OCH$_3$), 53.05 (C-5), 58.69[x] (C-7), 59.64[x] (C-20), 61.66 (N*C*H$_2$Ph), 64.83 (C-3), 68.35 (C-21), 89.84 (C-16), 109.51 (C-12), 121.19 (C-10), 122.04 (C-9), 127.18 (C-4″), 127.74 (C-11), 128.35 (C-3″+C-5″), 128.37 (C-3′+C-5′), 128.52 (C-2″+C-6″), 129.52 (C-2′+C-6′), 130.06 (C-1′), 132.89 (C-4′), 137.38 (C-8), 139.36 (C-1″), 142.52 (C-13), 166.52 (O*C*OPh), 167.11 (C-2), 167.90 (16-*C*OOCH$_3$), 211.74 (*C*OCH$_3$) ppm; HRMS calcd for [$C_{35}H_{36}N_2O_5$−H]$^+$ 565.2702; found 565.2734. The less polar compound (*rac*-**14**, R_f=0.42) was obtained as white crystals after crystallization from methanol (0.22 g, 23%). Mp 169−171°C; IR (KBr) *ν*: 3392 (indole-NH), 1720 (ester CO), 1688 (CO), 1648 (conj. ester CO), 1612 (C═C) cm^{-1}; δ_H ($CDCl_3$): 0.98+1.82 (2×ddd, J_{gem}=13.5 Hz, $J_{14,15}$=12.5+4.5, 4.0+12.0 Hz, respectively, 2×1H, 15-H$_2$), 1.33+1.51 (2×m, 2×1H, 14-H$_2$), 1.69+2.20 (2×dd, J_{gem}=12.1 Hz, $J_{5,6}$=5.5+1.0, 12.0+6.7 Hz, respectively, 2×1H, 6-H$_2$), 2.45 (s, 3H, COCH$_3$), 2.66+2.98 (2×ddd, J_{gem}=9.8 Hz, 2×1H, 5-H$_2$), 2.93+2.96 (2×d, J_{gem}=15.0 Hz, 2×1H, 17-H$_2$), 3.28 (br s, 1H, 21-H), 3.64+4.09 (2×d, J_{gem}=13.4 Hz, 2×1H, NC*H*$_2$Ph), 3.77 (s, 3H, COOCH$_3$), 4.04+4.13 (2×ddd, J_{gem}=10.6 Hz, $J_{3,14}$=5.7+6.8, 6.0+6.2 Hz, respectively, 2×1H, 3-H$_2$), 6.76−6.88 (m, 3H, 9-H+10-H+12-H), 7.10−7.47 (m, 8H, 11-H+2″-H+3″-H+4″-H+5″-H+6″-H+3′-H+5′-H), 7.54 (m, 1H, 4′-H), 7.95 (m, 2H, 2′-H+6′-H), 8.91 (br s, 1H, N(1)-H) ppm; δ_C ($CDCl_3$): 23.47 (C-14), 23.98 (C-17), 30.42 (C-15), 31.21 (CO*C*H$_3$), 40.78 (C-6), 51.10 (OCH$_3$), 51.85 (C-5), 56.87[x] (C-20), 57.84[x] (C-7), 61.06 (N*C*H$_2$Ph), 64.74 (C-3), 76.83 (C-21), 89.11 (C-16), 109.41 (C-12), 120.96 (C-10), 122.73 (C-9), 127.09 (C-4″), 128.13 (C-11), 128.25 (C-3″+C-5″), 128.31 (C-3′+C-5′), 129.13 (C-2″+C-6″), 129.54 (C-2′+C-6′), 130.39 (C-1′), 132.75 (C-4′), 136.84 (C-8), 138.41 (C-1″), 142.79 (C-13), 164.79 (C-2), 166.33 (O*C*OPh), 168.26 (16-*C*OOCH$_3$), 213.64 (*C*OCH$_3$) ppm; MS: *m*/*z* (rel inten): 564 (0.8) [M$^+$], 521 (0.4), 350 (16), 227 (9.0), 105 (45.0), 91 (100.0), 77 (15.0). Anal. calcd for $C_{35}H_{36}N_2O_5$: C, 74.45; H, 6.43; N, 4.96; found C, 74.32; H, 6.65; N, 5.02.

4.1.7. (±)-20-Acetyl-3-benzoyloxy-20-deethyl-2,16-didehydro-16-methoxycarbonyl-3,4-secoaspidospermidine (20*α*, 21*α*) (15). A mixture of *rac*-**13** (0.5 g, 0.89 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 (50 mL) and neutralized with saturated Na_2CO_3 solution. The solution was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried and evaporated in vacuo. The main component was separated by preparative TLC (eluting with CH_2Cl_2/methanol 20:1) to yield *rac*-**15** (0.40 g, 95%) as a yellow oil (R_f=0.42). IR (neat) *ν*: 3424 (indole-NH), 2928, 2880, 1716 (ester CO), 1680 (CO), 1652 (conj. ester CO), 1608 (C═C) cm^{-1}; δ_H ($CDCl_3$): 1.43+1.78 (2×m, 2×1H, 14-H$_2$), 1.80+1.88 (2×m, 2×1H, 6-H$_2$), 1.80+2.08 (2×m, 2×1H, 15-H$_2$), 1.97 (s, 3H, COCH$_3$), 2.44+2.86 (2×d, J_{gem}=15.4 Hz, 2×1H, 17-H$_2$), 3.14+3.23 (2×ddd, J_{gem}=9.5 Hz, $J_{5,6}$=6.2+1.2, 11.8+5.0 Hz, respectively, 2×1H, 5-H$_2$), 3.70 (br s, 1H, N(4)-H), 3.77 (s, 3H, OCH$_3$), 4.29 (t,

$J_{3,14}$=6.3 Hz, 2H, 3-H_2), 4.30 (d, J_{lr}=2.0 Hz, 1H, 21-H), 6.81 (d, 1H, 12-H), 6.95 (dd, 1H, 10-H), 7.18 (dd, 1H, 11-H), 7.28 (d, 1H, 9-H), 7.45 (m, 2H, 3′-H+5′-H), 7.58 (m, 1H, 4′-H), 8.02 (m, 2H, 2′-H+6′-H), 8.78 (br s, 1H, N(1)-H) ppm; δ_C ($CDCl_3$): 24.58 (C-14), 25.34 (CO*C*H_3), 28.09 (C-17), 29.72 (C-15), 44.46 (C-6), 45.14 (C-5), 51.05 (OCH_3), 57.12[x] (C-20), 58.41[x] (C-7), 60.82 (C-21), 64.78 (C-3), 89.33 (C-16), 109.50 (C-12), 121.18 (C-10), 121.34 (C-9), 127.64 (C-11), 128.45 (C-3′+C-5′), 129.54 (C-2′+C-6′), 130.22 (C-1′), 133.04 (C-4′), 137.88 (C-8), 142.56 (C-13), 166.58 (O*C*OPh), 167.85 (16-COO*C*H_3), 167.94 (C-2), 211.65 (*C*O*C*H_3) ppm; HRMS calcd for $C_{28}H_{30}N_2O_5$ 474.2155; found 474.2161.

4.1.8. (±)-20-Acetyl-3-benzoyloxy-20-deethyl-2,16-didehydro-16-methoxycarbonyl-3,4-secoaspidospermidine (20*β*, 21*α*) (16). The procedure was same as in the case of compound **15** to yield *rac*-**16** (0.40 g, 95%) as a yellow oil (R_f=0.48). IR (neat) *ν*: 3368 (indole-NH), 2928, 2880, 1716 (ester CO), 1670 (CO), 1645 (conj. ester CO), 1608 (C=C) cm^{-1}; δ_H ($CDCl_3$): 1.20+1.47 (2×ddd, J_{gem}=13.5 Hz, $J_{14,15}$=12.0+3.8, 12.0+2.8 Hz, respectively, 2×1H, 15-H_2), 1.30+1.57 (2×m, 2×1H, 14-H_2), 1.78+1.96 (2×m, 2×1H, 6-H_2), 1.80 (br s, 1H, N(4)-H), 2.28 (s, 3H, $COCH_3$), 2.59+2.93 (2×d, J_{gem}=15.8 Hz, 2×1H, 17-H_2), 3.03–3.13 (m, 2H, 5-H_2), 3.75 (d, J_{lr}=1.8 Hz, 1H, 21-H), 3.77 (s, 3H, OCH_3), 4.05+4.09 (2×ddd, J_{gem}=10.9 Hz, $J_{3,14}$=6.5+5.5, 6.3+5.5 Hz, respectively, 2×1H, 3-H_2), 6.80 (d, $J_{11,12}$=7.8 Hz, 1H, 12-H), 6.90 (ddd, $J_{9,10}$=7.5 Hz, $J_{10,11}$=7.6 Hz, $J_{10,12}$=1.0 Hz, 1H, 10-H), 7.17 (ddd, $J_{9,11}$=1.3 Hz, 1H, 11-H), 7.18 (br d, 1H, 9-H), 7.42 (m, 2H, 3′-H+5′-H), 7.55 (m, 1H, 4′-H), 7.91 (m, 2H, 2′-H+6′-H), 8.96 (br s, 1H, N(1)-H) ppm; δ_H ($CDCl_3$): 22.20 (C-14), 23.60 (C-17), 28.80 (CO*C*H_3), 29.93 (C-15), 44.37 (C-6), 45.22 (C-5), 51.11 (OCH_3), 56.82[x] (C-20), 58.00[x] (C-7), 64.45 (C-3), 68.95 (C-21), 89.61 (C-16), 109.49 (C-12), 120.96 (C-10), 121.82 (C-9), 128.16 (C-11), 128.32 (C-3′+C-5′), 129.50 (C-2′+C-6′), 130.21 (C-1′), 132.88 (C-4′), 137.31 (C-8), 143.03 (C-13), 165.58 (C-2), 166.28 (O*C*OPh), 168.53 (16-COO*C*H_3), 212.66 (*C*O*C*H_3) ppm; HRMS calcd for $C_{28}H_{30}N_2O_5$ 474.2155; found 474.2142.

4.1.9. (±)-Minovincine (2). *Method A*: A mixture of *rac*-**15** (0.20 g, 0.42 mmol) and KI (0.07 g, 0.42 mmol) in anhydrous DMF (10 mL) was refluxed for 2 h, then was evaporated in vacuo. The main component was purified by preparative TLC (eluting with hexane/acetone 3:1) to yield a yellow oil (R_f=0.41), which was crystallized from methanol to afford *rac*-**2** (0.05 g, 34%) as white crystals. *Method B*: A mixture of *rac*-**16** (0.20 g, 0.42 mmol) and KI (0.07 g, 0.42 mmol) in anhydrous DMF (10 mL) was refluxed for 4 h, then was worked up as in the case of compound **15** to yield *rac*-**2** (0.05 g, 34%) as white crystals.

In both cases the melting points and the spectroscopic data are agreement with those reported previously.[2]

4.1.10. (±)-16-Acetyl-16-deethyl-apovincamine (3). A mixture of *rac*-**2** (0.10 g, 0.28 mmol) and *N*-chlorosuccinimide (37 mg, 0.28 mmol) in dry trifluoroacetic acid (10 mL) was stirred under argon at rt for 4 h, then refluxed for 3 h. After that, the solution was evaporated in vacuo, the residue was diluted with ethylacetate (100 mL) and extracted with aqueous NaOH solution (2×50 mL, 2 M). The organic layer was dried and evaporated in vacuo. The residue was purified by preparative TLC (eluting with hexane/acetone 1:1) to yield a yellow oil (R_f=0.42), which was crystallized from ether to afford *rac*-**3** (49 mg, 50%) as pale-yellow crystals. Mp 154–156°C; IR (KBr) *ν*: 2920, 1736 (CO), 1712 (conj. ester CO), 1632, 1608 (C=C) cm^{-1}; δ_H ($CDCl_3$): 1.05+2.19 (2×ddd, J_{gem}=13.5 Hz, $J_{14,15}$=12.8+4.5, 3.3+2.8 Hz, respectively, 2×1H, 15-H_2), 1.39–1.54 (m, 2H, 14-H_2), 2.48 (s, 3H, $COCH_3$), 2.53+3.03 (2×m, 2×1H, 6-H_2), 2.60–2.66 (m, 2H, 3-H_2), 3.29–3.40 (m, 2H, 5-H_2), 3.95 (s, 3H, OCH_3), 4.90 (br s, 1H, 21-H), 6.01 (s, 1H, 17-H), 7.15 (m, 1H, 10-H), 7.18 (m, 1H, 11-H), 7.24 (m, 1H, 12-H), 7.48 (m, 1H, 9-H) ppm; δ_C ($CDCl_3$): 16.35 (C-6), 22.16 (C-14), 26.80 (CO*C*H_3), 28.47 (C-15), 44.70 (C-3), 51.46 (C-5), 51.88 (C-20), 52.75 (OCH_3), 53.53 (C-21), 109.78 (C-7), 112.58 (C-12), 118.41 (C-9), 120.74 (C-10), 121.21 (C-17), 122.35 (C-11), 129.24+129.32+129.75+134.07 (C-2+C-8+C-13+C-16), 163.29 (16-*C*OOCH$_3$), 208.79 (*C*O*C*H_3) ppm; HRMS calcd for $C_{21}H_{22}N_2O_3$ 350.1630; found 350.1647.

4.1.11. (±)-Vincaminine (4). To a mixture of *rac*-**2** (0.10 g, 0.28 mmol), water (2.5 mL) and methanol (7.5 mL) was added conc. HCl (56.5 μL, 0.68 mmol, 2.4 equiv.) and 4-(3-carboxy-propionylperoxy)-4-oxobutyric acid[11] (80.0 mg, 0.34 mmol, 1.2 equiv.). The solution was stirred for 24 h at rt, protecting from light, then the pH of the mixture was adjusted to 8 with 25% NH_4OH solution. After that, the solution was extracted with ether (2×20 mL) and with CH_2Cl_2 (2×20 mL). The combined organic layers were dried and evaporated in vacuo. The main component was separated by preparative TLC (eluting with hexane/acetone/triethylamine 2:1:0.1) to yield a yellow oil (R_f=0.35), which was crystallized from acetone to afford *rac*-**4** (40 mg, 39%) as pale-yellow crystals. Mp 203–205°C; (205–206°C, acetone[13a]); IR (KBr) *ν*: 3440 (OH), 2952, 2880, 1744 (ester CO), 1708 (CO) cm^{-1}; δ_H ($CDCl_3$): 1.45+1.55 (2×m, 2×1H, 14-H_2), 1.84+2.14 (2×dm, J_{gem}=14.2 Hz, 2×1H, 15-H_2), 2.16+2.39 (2×d, J_{gem}=13.8 Hz, 2×1H, 17-H_2), 2.40 (s, 3H, $COCH_3$), 2.52+2.63 (2×m, 2×1H, 3-H_2), 2.60+3.01 (2×dm, J_{gem}=16.0 Hz, 2×1H, 6-H_2), 3.35+3.39 (2×ddd, J_{gem}=14.0 Hz, $J_{5,6}$=6.8+1.0, 11.4+5.3 Hz, respectively, 2×1H, 5-H_2), 3.82 (s, 3H, OCH_3), 4.73 (br, 1H, 16-OH), 4.84 (br s, 1H, 21-H), 7.08 (m, 1H, 12-H), 7.02–7.17 (m, 2H, 10-H+11-H), 7.49 (m, 1H, 9-H) ppm; *NOE*: 4.84 (21-H_α)→2.40 ($COCH_3$), 2.39 (17-H_α), 3.39 (5-H_α); 4.72 (16-OH)→7.08 (12-H), 2.16 (17-H_β) ppm; δ_C ($CDCl_3$): 17.01 (C-6), 23.05 (C-14), 25.55 (C-15), 25.75 (CO*C*H_3), 42.97 (C-17), 44.32 (C-3), 49.88 (C-20), 50.84 (C-5), 54.52 (OCH_3), 54.69 (C-21), 81.86 (C-16), 106.77 (C-7), 110.35 (C-12), 118.59 (C-9), 120.54 (C-10), 121.98 (C-11), 129.15 (C-8), 130.62 (C-2), 134.24 (C-13), 173.68 (16-*C*OOCH$_3$), 210.34 (*C*O*C*H_3) ppm. Anal. calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60; found C, 68.39; H, 6.61; N, 7.31; HRMS calcd for $C_{21}H_{24}N_2O_4$ 368.1736; found 368.1729.

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