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Synthesis of vinca alkaloids and related compounds. Part 108: Efficient convergent synthetic pathway to the ibophyllidine skeleton IV. First synthesis of (±)-18-hydroxy-20-epiibophyllidine☆

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Abstract—The first total synthesis of the pentacyclic alkaloid (±)-18-hydroxy-20-epiibophyllidine was realized via an efficient preparation of the D-*seco*-pseudoaspidospermane molecule. The key step of the sequence involves an intramolecular [4+2] cycloaddition reaction of the dihydrosecodine intermediate, which was built up from the reaction of a tryptamine derivative with an aldehyde–ester. After full epimerization, the intramolecular N-alkylation of the tetracyclic ester gave the pentacyclic compound. Reduction of the latter molecule led to the title compound.

1. Introduction

The aspidospermane and pseudoaspidospermane families represent one of the largest group of indole alkaloids, with more than 300 compounds isolated from various biological sources. These alkaloids have been the target of synthetic studies for several years due to their structural complexity and diverse biological activities.[2] The basic framework of these compounds (ABCDE ring system) can be also found in the family of ibophyllidine alkaloids.[3] The continuation of our longstanding efforts in the biomimetic syntheses of these pentacyclic molecules was based on cyclization of the N_b-benzyltryptamine derivative **1** with appropriately functionalized aldehydes (or aldehyde equivalents).[4] In our earlier publications, we reported efficient synthetic routes involving intramolecular [4+2] cyclization for a wide range of ibophyllidine class alkaloids.[1,5]

In the next step of this work, (±)-18-hydroxy-20-epiibophyllidine **2** was chosen as our new target molecule (Fig. 1). This alkaloid was isolated from *Tabernaemontana albiflora* in 1980 by Kan et al.[6]

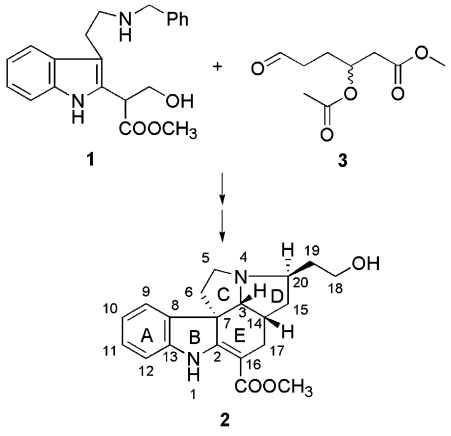

Figure 1. Planned synthesis of (±)-18-hydroxy-20-epiibophyllidine **2**.

2. Results and discussion

The preparation of the racemic alkaloid begin with the synthesis of the appropriately functionalized aldehyde **3**, which was realized from 4-(*tert*-butyl-dimethyl-silanyloxy)butanal **4**[1] as a starting material. Reformatsky reaction of the aldehyde **4** and methyl bromoacetate in the presence of zinc powder led to the hydroxy-ester **5** in a good yield. Acetylation of the alcohol **5** resulted in the expected diester **6**.

☆ See Ref. 1.
Keywords: 18-Hydroxy-20-epiibophyllidine; Ibophyllidine; Deethylibophyllidine; Indole alkaloids; Natural products.
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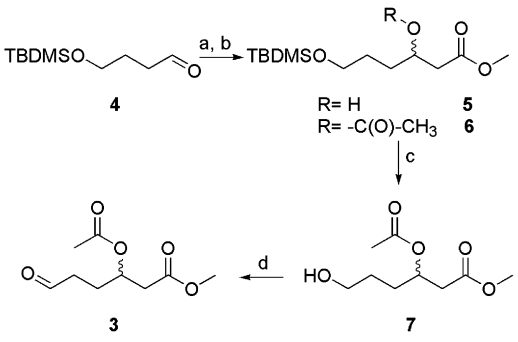
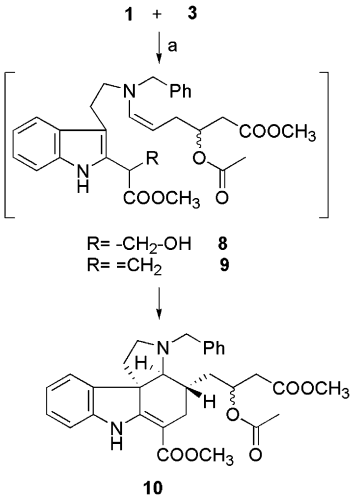
The *tert*-butyldimethylsilyl protecting group of **6** was removed by treatment with 1 M HCl solution in THF to give **7**. Afterwards, the alcohol **7** was oxidized with pyridinium chlorochromate to afford the corresponding aldehyde **3** (Scheme 1). Then, the N_b-benzyltryptamine derivative **1**[4a] was allowed to react with **3** in boiling toluene. From the reaction mixture only one product **10** was obtained (Scheme 2).

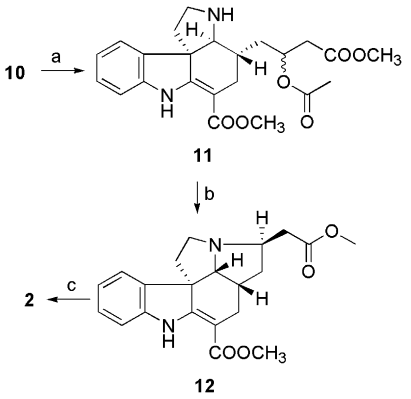


Scheme 1. Reagents and conditions: (a) Br-CH_2COOCH_3, Zn, benzene, Δ (81%); (b) $CH_3C(O)Cl$, $(C_2H_5)_3N$, DMAP, CH_2Cl_2, rt (73%); (c) 1 M HCl, THF, rt (76%); (d) PCC, $NaOOCH_3$, CH_2Cl_2, rt (67%).



Scheme 2. Reagents and conditions: (a) *p*-TsOH·H_2O, toluene, Δ (48%).

Hydrogenolysis of the tetracyclic compound **10** in glacial acetic acid at rt gave the secondary amine **11**. In our earlier work, a method was successfully used for the formation of ring D of the aspidospermane skeleton.[4] Accordingly, the tetracyclic secondary amine **11** was refluxed in dimethylformamide in the presence of potassium iodide. After full epimerization[1,4h] and cyclization of **11** we obtained the expected pentacyclic molecule **12** in low yield. For this reason we examined the N-alkylation step. We tried several reaction conditions, and under optimized parameters—using 1.2 equiv DBU in boiling THF—the intramolecular alkylation of the secondary amine **11** was completed in 96 h, and the pentacyclic ester **12** was obtained in 81% yield. Finally, by reduction of the ester **12** with $LiAlH_4$, we could isolate the target molecule, (±)-18-hydroxy-20-epiibophyllidine (**2**) (Scheme 3).



Scheme 3. Reagents and conditions: (a) 10% Pd/C, H_2, CH_3COOH, rt (91%); (b) KI, DMF, Δ (11%) or DBU, THF, Δ (81%); (c) $LiAlH_4$, THF, 0 °C (62%).

3. Conclusion

We have described the first synthesis of the pentacyclic alkaloid (±)-18-hydroxy-20-epiibophyllidine **2**. The tryptamine derivative **1** containing a latent acrylic ester function—acting as a diene—reacted with aldehyde–ester **3**, which had been built up from 4-(*tert*-butyl-dimethyl-silanyloxy)-butanal **4**. Formation and dehydration of enamine **8** and subsequent [4+2] cycloaddition led to the protected D-*seco*-pseudoaspidospermane molecule **10**. Debenzylation, full epimerization, intramolecular N-alkylation and reduction resulted in the (±)-18-hydroxy-20-epiibophyllidine **2**.

4. Experimental

4.1. General

Melting points were determined on a hot-stage microscope Boetius. 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 ^1H and 100 MHz for ^{13}C. All NMR spectra were recorded at rt. Chemical shifts are reported relative to Me_4Si (δ=0 ppm). Mutual ^1H–^1H couplings are given only once. 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 chromatography was carried out on Merck Kieselgel 60 (0.063–0.200 mm).

4.1.1. 6-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxy-hexanoic acid methyl ester (5). A 100 mL, three-necked flask fitted with a condenser, mechanical stirrer, and 100 mL dropping funnel was purged with nitrogen. Freshly activated zinc-powder (1.62 g, 24.7 mmol) and dry benzene (50 mL) were placed in the flask. Methyl bromoacetate (3.78 g, 24.7 mmol), 4-(*tert*-butyl-dimethyl-silanyloxy)-butanal (**4**) (5.00 g, 24.7 mmol), and dry benzene (50 mL) were placed in the dropping funnel. Without stirring, the solution (~10 mL) was added to the zinc suspension, the mixture was brought to reflux and the rest of the solution was

added at the boiling point of the benzene. After addition, the yellow reaction mixture was refluxed over 1 h. Then the reaction was cooled to rt and quenched with water (20 mL). The two-phase system was filtered to remove unchanged zinc and the phases were separated. The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography (eluting with ethyl acetate/hexane=1:4, R_f=0.29) to afford 5.21 g (81%) of product **5** as a colorless oil. IR (neat) 3424, 2952, 1740, 1100, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s; $Si(CH_3)_2$), 0.89 (9H, s; $C(CH_3)_3$), 1.48–1.72 (4H, m; 4-H_2+5-H_2), 2.46+2.50 (2×1H, 2×dd, J_{gem}=15.8 Hz, J_{vic}=7.5 and 4.6 Hz; 2-H_2), 3.34 (1H, brd, J=3.5 Hz; OH), 3.66 (2H, t, J=5.7 Hz; 6-H_2), 3.70 (3H, s; OCH_3), 4.04 (1H, m; 3-H); ^{13}C NMR ($CDCl_3$) δ −5.9 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 28.9 (C5), 33.7 (C4), 41.4 (C2), 51.6 (OCH_3), 63.2 (C6), 67.9 (C3), 173.2 (C1); MS *m/z* (relative intensity) 261 (1.0, $[(M+H)-H_2O]^+$), 219 (16.0), 187 (23.0), 145 (100.0), 127 (18.0), 105 (30.0), 85 (56.0), 75 (98.0); HRMS (CI) calcd for $C_{13}H_{29}O_4Si$ 277.1835, found for $[M+H^+]$ 277.1832.

4.1.2. 3-Acetoxy-6-(*tert*-butyl-dimethyl-silanyloxy)-hexanoic acid methyl ester (6). Compound **5** (5.00 g, 19.2 mmol) was dissolved in dry dichloromethane (80 mL) and 2.13 g (2.94 mL, 21.1 mmol) of triethylamine was added to the solution and it was cooled to 0 °C. Acetyl chloride (1.65 g, 1.49 mL, 21.1 mmol) and 4-(dimethylamino)pyridine (0.26 g, 2.11 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to rt, and then stirred for 1 h. It was then poured into water (20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3×30 mL) and the combined organic phases were washed with brine (25 mL). It was dried ($MgSO_4$) and concentrated in vacuo, yielding 4.24 g (73%) of **6** as a yellow oil (TLC: ethyl acetate/hexane=1:4, R_f=0.54). IR (neat) 2952, 1748, 1252, 1104, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (6H, s; $Si(CH_3)_2$), 0.89 (9H, s; $C(CH_3)_3$), 1.46–1.75 (4H, m; 4-H_2+5-H_2), 2.03 (3H, s; $OCOCH_3$), 2.56+2.60 (2×1H, 2×dd, J_{gem}=15.2 Hz, J_{vic}=7.2 and 5.5 Hz; 2-H_2), 3.61 (2H, t, J=6.1 Hz; 6-H_2), 3.67 (3H, s; OCH_3), 5.24 (1H, m; 3-H); ^{13}C NMR ($CDCl_3$) δ −5.3 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 21.1 ($OCOCH_3$), 25.9 ($C(CH_3)_3$), 28.4 (C5), 30.5 (C4), 39.1 (C2), 51.8 (OCH_3), 62.6 (C6), 70.4 (C3), 170.8+170.4 (C1+$OCOCH_3$); MS *m/z* (relative intensity) 319 (1.0, $[M+H]^+$), 261 (10.0), 227 (11.0), 202 (24.0), 201 (100.0), 119 (23.0), 95 (21.0); HRMS (CI) calcd for $C_{15}H_{31}O_5Si$ 319.1941, found for $[M+H^+]$ 319.1850.

4.1.3. 3-Acetoxy-6-hydroxy-hexanoic acid methyl ester (7). One mole aqueous HCl solution (2 mL) was added to a solution of **6** (5.00 g, 16.5 mmol) in THF (60 mL). The mixture was stirred for 30 min at rt. After stirring, the solution was concentrated in vacuo, then the residue was dissolved in dichloromethane (60 mL) and washed with water (20 mL) and brine (20 mL). The organic phases were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (eluent: acetone/hexane=1:2, R_f=0.36) to afford 2.56 g (76%) of the product **7** as a colorless oil. IR (neat) 3352, 2960, 1740, 1252, 1072 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52–1.78 (5H, m; 4-H_2+5-H_2+OH), 2.04 (3H, s; $OCOCH_3$), 2.56+2.62 (2×1H, 2×dd, J_{gem}=15.2 Hz, J_{vic}=7.2 and 5.5 Hz; 2-H_2), 3.66 (2H, t, J=6.3 Hz; 6-H_2), 3.68 (3H, s; OCH_3); ^{13}C NMR ($CDCl_3$) δ 21.1 ($OCOCH_3$), 28.2 (C5), 30.4 (C4), 39.0 (C2), 51.8 (OCH_3), 62.3 (C6), 70.2 (C3), 170.8+170.5 (C1+$OCOCH_3$); MS *m/z* (relative intensity) 204 (1.0, $[M]^+$), 143 (19.0), 114 (22.0), 101 (15.0), 71 (26.0), 59 (13.0), 42 (100.0); HRMS (CI) calcd for $C_9H_{17}O_5$ 205.1076, found for $[M+H^+]$ 205.1068.

4.1.4. 3-Acetoxy-6-oxo-hexanoic acid methyl ester (3). A solution of **7** (3.00 g, 14.7 mmol) in dry dichloromethane (50 mL) was added to a stirred suspension of pyridinium chlorochromate (4.75 g, 22.0 mmol), containing 1.80 g (22.0 mmol) sodium acetate. After 1 h, ether (25 mL) was added to the mixture and then it was decanted. The black precipitate was washed with ether (2×20 mL) and the combined solutions were washed with 5% aqueous solution of $NaHCO_3$ (25 mL), water (25 mL), and brine (25 mL). It was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluent: acetone/hexane=1:2, R_f=0.41) to give 1.99 g (67%) of the **3** as a yellow oil. IR (neat) 2952, 1740, 1440, 1376, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86–2.10 (2H, m; 4-H_2), 2.03 (3H, s; $OCOCH_3$), 2.53 (2H, td, J=7.0 and 1.0 Hz; 5-H_2), 2.56+2.63 (2×1H, 2×dd, J_{gem}=15.0 Hz, J_{vic}=7.2 and 6.0 Hz; 2-H_2), 3.69 (3H, s; OCH_3), 5.26 (1H, m; 3-H), 9.77 (1H, t, J=1.0 Hz; C(6)HO); ^{13}C NMR ($CDCl_3$) δ 20.9 ($OCOCH_3$), 26.3 (C4), 38.9 (C2), 39.7 (C5), 51.8 (OCH_3), 69.6 (C3), 170.4+170.4 (C1+$OCOCH_3$), 200.8 (C6); MS *m/z* (relative intensity) 203 (1.0, $[M]^+$), 159 (5.0), 142 (5.0), 129 (12.0), 114 (33.0), 85 (13.0), 55 (20.0), 43 (100.0); HRMS (CI) calcd for $C_9H_{15}O_5$ 203.0919, found for $[M+H^+]$ 203.0921.

4.1.5. 4-(2-Acetoxy-3-methoxycarbonyl-propyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylic acid methyl ester (10). A solution of 1.00 g (2.85 mmol) of N_b-benzyltryptamine derivative (**1**), **3** (0.69 g, 3.40 mmol), and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate were refluxed in dry toluene (50 mL) under argon over 24 h. Then the reaction mixture was extracted with brine (2×20 mL), and the combined aqueous phases were extracted with dichloromethane (2×30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluent: ether/hexane=4:1, R_f=0.6) to yield 0.69 g of (47%) **10** as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) 3376, 2952, 1740, 1712, 1680, 1608, 1464, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.31 (2H, m; 15-H_2), 1.68+2.03 (2×1H, 2×ddd, J_{gem}=11.8 Hz, J_{vic}=4.8+1.0 and 12.2+6.2 Hz; 6-H_2), 1.89 and 1.96 (1H, m; 14-H), 1.98 and 2.00 (3H, s; $OCOCH_3$), 2.30–2.71 (5H, m; 19-H_2+17-H_2+5-H_A), 2.91–3.01 (2H, m; 5-H_B+3-H), 3.46 and 3.59 (3H, s; 16-$COOCH_3$), 3.68 and 3.80 (3H, s; C19-$COOCH_3$), 3.75+4.09 (2×1H, 2×d, J_{gem}=13.5 Hz; NCH_2Ph), 5.13+5.17 (1H, m; 20-H), 6.79–6.86 (2H, m; 12-H+10-H), 6.96 and 6.98 (1H, d, J=7.5 Hz; 9-H), 7.12–7.16 (1H, m; 11-H), 8.98 and 9.01 (1H, br s; N(1)H); ^{13}C NMR ($CDCl_3$) δ 20.9 and 21.1 ($OCOCH_3$), 21.7 and 23.1 (C17), 35.5 and 35.6 (C14), 35.3 and 35.2 (C15), 39.6 and 38.9 (C19), 42.1 and 42.3 (C6), 50.6 and

50.7 (C5), 51.0 and 51.1 (16-COO*C*H_3), 51.7 and 51.9 (19-COO*C*H_3), 55.1 (C7), 58.2 and 58.1 (N*C*H_2Ph), 68.6 and 68.7 (C20), 72.1 and 71.3 (C3), 90.6 (C16), 109.3 and 109.3 (C12), 120.6 (C10), 122.2 (C9), 127.9 (C11), 127.1+128.4+128.9+138.9 (Ph), 137.6 (C8), 142.9 (C13), 164.9 (C2), 169.0 (16-*C*OOCH$_3$), 170.2 and 170.3 (O*C*OCH$_3$)$^{\times}$, 170.4 and 170.5 (C18)$^{\times}$; MS *m*/*z* (relative intensity) 518 (1.0, [M]$^+$), 429 (4.0), 415 (16.0), 355 (100.0), 236 (22.0), 91 (2.0); HRMS (EI) calcd for $C_{30}H_{34}N_2O_6$ 518.2539, found for [M$^+$] 518.2543.

4.1.6. 4-(2-Acetoxy-3-methoxycarbonyl-propyl)-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylic acid methyl ester (11). A mixture of **10** (1.00 g, 1.93 mmol) and 10% palladium/charcoal (0.50 g) in glacial acetic acid (15 mL) was hydrogenated for 1 h at rt 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 (3×70 mL) and the combined organic phases were dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by column chromatography (eluting with dichloromethane/methanol=9:1, R_f=0.58) to afford **11** (0.75 g, 91%) as a yellow oil (1:1 mixture of the diastereoisomers). IR (neat) 3376, 2952, 1740, 1704, 1680, 1608, 1440, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14–1.31 (2H, m; 15-H_2), 1.78+1.91 (2×1H, 2×ddd, J_{gem}=11.9 Hz, J_{vic}=4.6+1.1 and 12.4+6.1 Hz; 6-H_2), 1.85–1.89 (1H, m; 14-H), 1.99 and 2.00 (3H, s; OCOCH_3), 2.27–2.75 (6H, m; 19-H_2+17-H_2+5-H_A+N(4)H), 3.11–3.17 (2H, m; 5-H_B+3-H), 3.48 and 3.78 (3H, s; 16-COOCH_3), 3.60 and 3.79 (3H, s; 19-COOCH_3), 5.14+5.24 (1H, m; 20-H), 6.84 (1H, br d, J=7.2 Hz; 12-H), 6.90 (1H, ddd, J=7.6+7.3+1.2 Hz; 10-H), 7.17 (1H, ddd, J=7.4+7.2+1.0 Hz; 11-H), 7.27 (1H, d, J=7.3 Hz; 9-H), 9.04 and 9.09 (1H, br s; N(1)H); ^{13}C NMR ($CDCl_3$) δ 21.2 and 21.2 (OCO*C*H_3), 21.6 and 23.6 (C17), 36.1 and 36.4 (C14), 37.8 and 38.1 (C15), 39.3 and 39.7 (C19), 43.7 and 44.3 (C6), 45.0 and 45.3 (C5), 50.9 and 51.2 (16-COO*C*H_3), 51.8 and 51.9 (19-COO*C*H_3), 55.4 and 55.8 (C7), 65.2 and 67.1 (C20), 68.4 and 68.6 (C3), 90.3 and 90.5 (C16), 109.5 and 109.5 (C12), 120.9 (C10), 122.0 and 122.2 (C9), 128.1 and 128.1 (C11), 137.6 and 137.7 (C8), 143.2 and 143.3 (C13), 165.2 (C2), 169.1 (16-*C*OOCH$_3$), 170.5 (O*C*OCH$_3$)$^{\times}$, 170.6 (19-*C*OOCH$_3$)$^{\times}$; MS *m*/*z* (relative intensity) 429 (24.0, [M+H]$^+$), 421 (2.0), 418 (6.0), 417 (76.0), 369 (9.0), 360 (100.0), 311 (9.0), 226 (2.0), 148 (7.0), 102 (3.0), 91 (10.0); HRMS (FAB) calcd for $C_{23}H_{29}N_2O_6$ 428.9964, found for [M+H$^+$] 428.9961.

4.1.7. Methyl 1-(2-methoxy-2-oxoethyl)-1,2,2a,3,5,10,11,12a-octahydropyrrolizino[1,7-*cd*]carbazole-4-carboxylate (12).

4.1.7.1. Method I. A mixture of **11** (0.5 g, 1.17 mmol) and potassium iodide (0.20 g, 1.17 mmol) in dry DMF (7 mL) was refluxed over 3 h, and then evaporated in vacuo. The main component was purified by preparative TLC (eluting with dichloromethane/methanol=9:1, R_f=0.83) to yield **12** (47 mg, 11%) as a yellow oil. IR (neat) 3368, 2952, 1736, 1676, 1608, 1440, 1248, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67+2.68 (2×1H, 2×dd, J_{gem}=15.1 Hz; J_{vic}=12.3 and 5.3 Hz; 17-H_2), 1.85+2.22 (2×1H, 2×ddd, J_{gem}=12.6 Hz, J_{vic}=11.8+6.4 and 9.4+6.0 Hz; 15-H_2), 1.88–1.96 (2H, m; 6-H_2), 2.06 (1H, m; 14-H), 2.49 (2H, d, J_{gem}=7.5 Hz; 19-H_2), 2.79 (1H, dd, J_{gem}=12.8 Hz; J_{vic}=5.6 Hz; 5-H_A), 2.99 (1H, m; 20-H), 3.32–3.36 (2H, m; 3-H+5-H_B), 3.48 (1H, s; 19-COOCH_3), 3.76 (1H, s; 16-COOCH_3), 6.84 (1H, d, J=7.4 Hz; 12-H), 6.89 (1H, ddd, J=7.6+7.5+1.1 Hz; 10-H), 7.17 (1H, ddd, J=7.5+7.2+1.2 Hz; 11-H), 7.35 (1H, d, J=7.3 Hz; 9-H), 9.08 (1H, br s; N(1)H); ^{13}C NMR ($CDCl_3$) δ 26.6 (C15), 33.8 (C17), 38.4 (C14), 38.7 (C19), 39.1 (C6), 51.1 (19-COO*C*H_3), 51.8 (16-COO*C*H_3), 56.7 (C5), 57.9 (C7), 67.3 (C20), 73.6 (C3), 91.7 (C16), 109.3 (C12), 121.0 (C10), 122.7 (C9), 128.2 (C11), 136.6 (C8), 143.6 (C13), 162.4 (C2), 168.6 (16-*C*OOCH$_3$), 172.7 (19-*C*OOCH$_3$); MS *m*/*z* (relative intensity) 369 (19.0, [M+H]$^+$), 337 (17.0), 226 (43.0), 148 (26.0), 91 (100.0); HRMS (FAB) calcd for $C_{21}H_{25}N_2O_4$ 368.2479, found for [M+H$^+$] 368.2484.

4.1.7.2. Method II. Compound **11** (0.5 g, 1.17 mmol) was dissolved in dry THF (20 mL) and 1,8-diazabicyclo(5,4,0)undec-7-en (0.21 g, 1.40 mmol) was added to the solution and it was refluxed over 96 h. Then the solvent was evaporated in vacuo and the residue was dissolved in dichloromethane (50 mL) and washed with water (15 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The main component was separated by preparative TLC (eluting with dichloromethane/methanol=9:1, R_f=0.83) to yield **12** (0.35 g, 81%) as a yellow oil. The analytical data were identified in the previous method.

4.1.8. 18-Hydroxy-20-epiibophyllidine (2). To a solution of **12** (200 mg, 0.54 mmol) in dry THF (20 mL) at 0 °C was added $LiAlH_4$. The mixture was slowly warmed to rt and stirred 1 h. Then 1 M aqueous solution of NaOH (10 mL) was added to the suspension. After stirring for 15 min, the organic solvent was removed under reduced pressure. The residue was partitioned between dichloromethane (30 mL) and 1 M NaOH solution (10 mL). The aqueous phase was extracted with dichloromethane (3×15 mL) and the combined organic extracts were concentrated and the main component was separated by preparative TLC (eluent: dichloromethane/methanol=9:1, R_f=0.51) to afford **2** (114 mg, 62%) as a yellow oil. IR (neat) 3376, 2928, 1676, 1608, 1464, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77+2.21 (2×1H, 2×dm, J_{gem}=13.0 Hz; 15-H_2), 1.81+2.10 (2×1H, 2×dm, J=13.1 Hz; 19-H_2), 1.85+2.09 (2×1H, 2×dm, J=13.2 Hz; 6-H_2), 1.96+2.18 (2×1H, 2×dd, J_{gem}=15.0 Hz, J_{vic}=11.2 and 7.1 Hz; 17-H_2), 2.08 (1H, m; 14-H), 2.17 (1H, m; 18-OH), 2.88 (1H, dd, J_{gem}=12.5 Hz, J_{vic}=5.8 Hz; 5-H_A), 3.18 (1H, m; 20-H), 3.39 (1H, m; 5-H_B), 3.51 (1H, m; 3-H), 3.77 (3H, s; OCH_3), 4.06 (2H, m; 18-H_2), 6.84 (1H, d; J=7.4 Hz; 12-H), 6.91 (1H, ddd, J=7.5+7.5+1.2 Hz; 10-H), 7.19 (1H, ddd, J=7.6+7.4+1.3 Hz; 11-H), 7.36 (1H, br d, J=7.2 Hz; 9-H), 9.05 (1H, br s; N(1)H); ^{13}C NMR ($CDCl_3$) δ 26.9 (C19), 33.6 (C17), 35.8 (C15), 38.2 (C14), 38.6 (C6), 51.2 (C5), 51.5 (OCH_3), 57.2 (C7), 60.7 (C18), 66.2 (C20), 73.1 (C3), 91.9 (C16), 109.4 (C12), 121.5 (C10), 122.8 (C9), 128.6 (C11), 136.1 (C8), 143.5 (C13), 163.2 (C2), 168.4 (16-*C*OOCH$_3$); MS *m*/*z* (relative intensity) 340 (1.0, [M]$^+$), 322 (8.0), 295 (68.0), 149 (12.0), 91 (27.0), 75 (100.); HRMS (EI) calcd for $C_{20}H_{24}N_2O_3$ 340.3186, found for [M$^+$] 340.3185.

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