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Synthesis of vinca alkaloids and related compounds. Part 105: Efficient convergent synthetic pathway to the ibophyllidine skeleton and synthesis of (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine☆

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Abstract—Starting from methyl-5-oxohexanoate we produced the appropriately functionalized aldehyde, which, after having been allowed to react with the tryptamine derivative in a [4+2] cycloaddition reaction as the final step, yielded the molecule containing a D-seco-aspidospermane skeleton. From the latter we could successfully produce a 1:1 mixture of protected epimers, the desilylation reaction of the protected molecules gave the alkaloids (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine in good yield.
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1. Introduction

The ibophyllidine alkaloids, as pentacyclic monoterpenoid indole alkaloids, can be biogenetically classified into the ψ-aspidospermane skeleton group.[2,3] The precursors of their biosynthesis are pandoline (**1a**) and 20-epipandoline (**1b**)[4] (Fig. 1). The title alkaloids were isolated in 1980 by French researchers from the trunk of *Tabernaemontana albiflora*.[5] In our earlier publications we described an efficient convergent synthetic pathway to build up the aspidospermane and ψ-aspidospermane skeletons, in the course of which compounds with a D-seco-aspidospermane skeleton were obtained from an N_b-benzyltryptamine derivative (**3**) and appropriately built up aldehydes (or aldehyde equivalents), respectively. In the final reaction step involving intramolecular acylation or alkylation, the synthesis of several alkaloids and alkaloid-like molecules was achieved.[6,7]

2. Results and discussion

In the present synthesis we again used the well-proven tryptamine derivative **3**.[6] We anticipated that aldehyde **4**, used as a reaction partner would yield in a reaction with **3** a molecule with a D-seco-aspidospermane skeleton from which pentacyclic alkaloids can be easily formed (Fig. 2).

The starting material for the preparation of **4** was methyl-5-oxohexanoate (**5**) (Scheme 1).[8] In the first step, **5** was

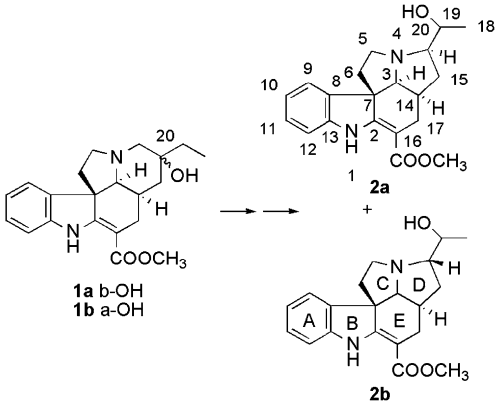

Figure 1. Biosynthesis of **2a** and **2b**.

☆ See Ref. 1.
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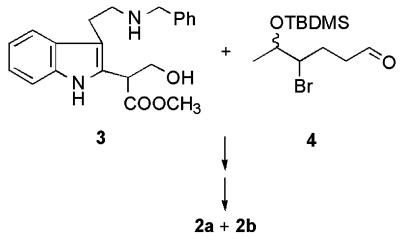
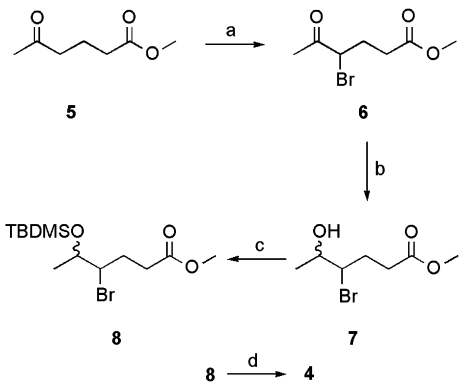
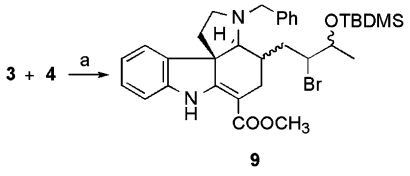


Figure 2. Planned synthesis of **2a** and **2b**.



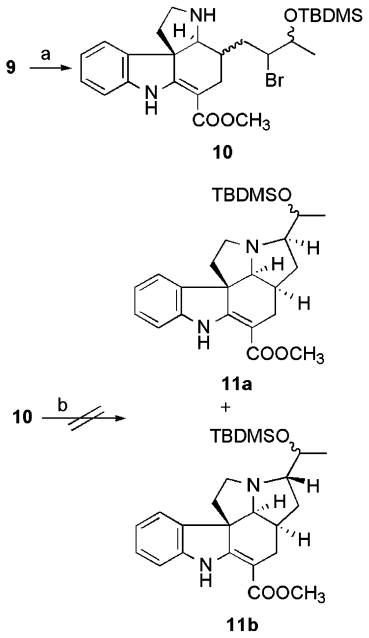
Scheme 1. Reagents and conditions: (a) Br_2, $(C_2H_5)_2O$, 0 °C (67%); (b) $NaBH_4$, CH_3OH, 0 °C (86%); (c) TBDMSCl, imidazole, CH_2Cl_2, Δ (78%); (d) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −60 °C (72%).

brominated to give **6**, then the ketone group was reduced with sodium borohydride to **7**. Subsequently, we protected the alcohol **7** in dichloromethane with *tert*-butyldimethylsilyl chloride in the presence of imidazole **8**. In the next step, ester **8** containing the protecting group was converted into aldehyde **4** in a good yield. The secondary amine **3** was allowed to react with aldehyde **4** in toluene in the presence of *p*-toluenesulfonic acid monohydrate (Scheme 2). From the reaction mixture the D-seco-aspidospermane **9** was isolated. As a continuation of the synthesis we intended to form the D-ring of the ibophyllidine skeleton. The benzyl group was removed from the tertiary amine **9** by catalytic hydrogenolysis, then **10** was boiled in toluene, xylene, or decalin, but the expected pentacyclic molecules (**11a** and **11b**) were not obtained in any of the cases (Scheme 3).



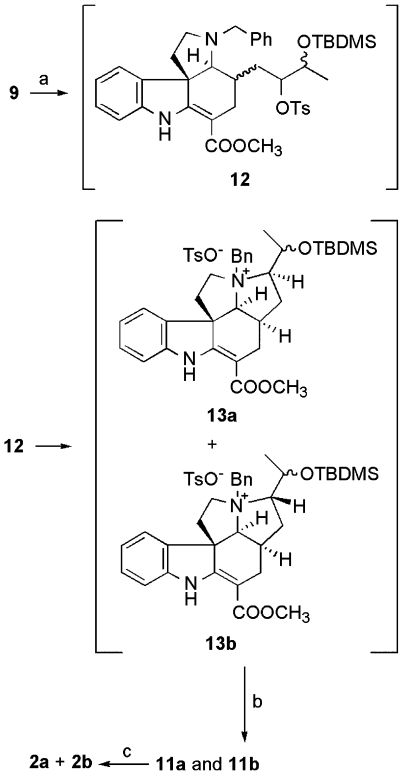
Scheme 2. Reagent and conditions: (a) *p*-TsOH·H_2O, toluene, Δ (47%).

Modifying our synthesis strategy, we intended to create the *p*-toluenesulfonyloxy group instead of the bromine function in the intramolecular alkylation reaction. We wished to achieve the halogen→tosyloxy change by boiling compound **9** in acetonitrile with silver *p*-toluenesulfonate, which is a method known in the literature (Scheme 4).[9] Surprisingly, the reaction did not result in the expected product mixture (**12**). In our opinion, during conversion, the tosyloxy group attaches to molecule **12**, resulting under the applied reaction conditions in the formation via alkylation of



Scheme 3. Reagents and conditions: (a) 10% Pd/C, H_2, CH_3COOH, (92%); (b) toluene, xylene or decalin, Δ.

a mixture of the quaternary salts **13a** and **13b**, accompanied by the earlier described full epimerization.[10] The salt mixture was catalytically debenzylated and in this step a mixture of the alcohols containing the protecting group (**11a** and **11b**) was obtained as a product. By removing the protecting group in the final step, (±)-19-hydroxy-ibophyllidine (**2a**) and (±)-19-hydroxy-20-epiibophyllidine (**2b**) can be isolated from the reaction mixture with a good yield.



Scheme 4. Reagents and conditions: (a) AgOTs, CH_3CN, Δ; (b) 10% Pd/C, H_2, CH_3COOH (48%); (c) 1 M HCl, THF (**2a**, 42%, **2b**, 39%).

3. Conclusion

We have worked out a new, biomimetic synthesis pathway for the construction of the ibophyllidine skeleton. Starting from methyl-5-oxohexanoate **5**, we produced aldehyde **4**, which was then used as a reaction partner in the course of the planned synthesis. In the final step the [4+2] cycloaddition reaction of the tryptamine derivative **3** and the aldehyde **4** resulted in **9** with a D-seco-aspidospermane skeleton. The hydrogenolysis of the tertiary amine **9** led to a mixture of the secondary amine epimers **10** from which the pentacyclic alkaloid skeleton was attempted to be formed by intramolecular alkylation. Due to lack of formation of the D-ring of the ibophyllidine skeleton we modified our strategy as a result of which a 1:1 mixture of the molecules containing the protective groups (**11a** and **11b**) was produced. As a final step, following removal of the protective group, we arrived at the (±)-19-hydroxy-ibophyllidine (**2a**) and (±)-19-hydroxy-20-epiibophyllidine (**2b**) alkaloids.

4. Experimental

4.1. General

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. Chemical shifts are reported relative to Me_4Si (δ=0 ppm). Mutual ^{1}H–^{1}H 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. Methyl 4-bromo-5-oxohexanoate (6). Compound **5** (2.00 g, 17.5 mmol) was dissolved in ether (50 mL) and it was cooled to 0 °C. Bromine (3.19 g, 20 mmol, 1.02 mL) was added to the solution at 0 °C over 20 min period. After the addition, the reaction mixture was allowed to warm up to rt and then stirred for 30 min. The suspension was extracted with 5% aqueous solution of $NaHCO_3$ (2×10 mL) and brine (2×10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1:2, R_f=0.45) to afford 1.33 g (67%) of the product **6** as a yellow oil: IR (neat) ν 2961, 1736, 1714, 1440, 1273, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.19+2.35 (2×1H, 2×m; CH–CH_2–CH_2), 2.39 (3H, s; $COCH_3$), 2.51+2.55 (2×1H, 2×ddd, J_{gem}= 16.6 Hz, J_{vic}=7.0+7.0 and 7.6+6.4 Hz; CH_2COOCH_3), 3.70 (3H, s; OCH_3), 4.43 (1H, dd, J=8.4+5.6 Hz; CH–Br); ^{13}C NMR ($CDCl_3$) δ 26.28 (COCH_3), 28.19+31.22 (CH_2CH_2COOCH_3), 51.86 (OCH_3), 52.75 (*C*H–Br), 172.74 (*C*OOCH_3), 201.30 (CH_3*C*O); MS *m/z* (relative intensity) 223 (40.0, [M]$^+$), 221 (41.0, [M]$^+$), 209 (29.0), 207 (29.0), 191 (26.0), 121 (45.0), 42 (100.0); HRMS (EI) calcd for $C_7H_{14}{}^{79}BrO_3$ 223.0658, found for [M$^+$] 223.0654.

4.1.2. Methyl 4-bromo-5-hydroxyhexanoate (7). $NaBH_4$ (0.40 g, 9 mmol) was added to a solution of **6** (2.00 g, 9 mmol) in dry methanol (50 mL) at 0 °C. After the addition, the reaction mixture was allowed to warm up to rt, and was stirred for 1 h. It was then poured into brine (20 mL) and extracted with dichloromethane (2×50 mL). The combined organic phases were 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 afford 1.74 g (86%) of the product **7** as a colorless oil (8:2 mixture of the diastereoisomers): IR (neat) ν 3472, 2952, 1736, 1440, 1260, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J=6.1 Hz; CHCH_3), 2.01 (1H, d, J=7.0 Hz; OH), 2.10–2.32 (2H, m; CHCH_2CH$_2$), 2.48–2.68 (2H, m; CH_2COOCH_3), 3.69 (3H, s; OCH_3), 3.77 (1H, m; C*H*OH), 4.07 (1H, td, J=10.0+4.0 Hz; CH–Br); ^{13}C NMR ($CDCl_3$) δ 21.3 (*C*H_3CH), 30.6 (CH*C*H_2CH$_2$), 32.1 (*C*H_2COOCH_3), 51.8 (OCH_3), 64.8 (*C*H–Br), 70.3 (*C*HOH), 173.2 (*C*OOCH_3); MS *m/z* (relative intensity) 227 (21.0, [M]$^+$), 225 (21.0, [M]$^+$), 209 (35.0), 207 (35.0), 181 (25.0), 179 (25.0), 127 (33.0), 74 (100.0); HRMS (EI) calcd for $C_7H_{14}{}^{79}BrO_3$ 225.0126, found for [M+H$^+$] 225.0143.

4.1.3. Methyl 4-bromo-5-(*tert*-butyl-dimethyl-silanyloxy) hexanoate (8). Imidazole (1.21 g, 17.8 mmol) was added to a solution of **7** (2.00 g, 8.9 mmol) in dry dichloromethane (40 mL). Then *tert*-butyldimethylsilyl chloride (2.68 g, 17.8 mmol) in 10 mL dry dichloromethane was added dropwise to a stirred solution at rt. After the addition the mixture was refluxed over 24 h. Then it was cooled, the salts were separated by filtration and the organic phase was washed with water (2×15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1:1, R_f=0.9) to afford 2.35 g (78%) of the product **8** as a colorless oil (8:2 mixture of the diastereoisomers): IR (neat) ν 2952, 2936, 1744, 1440, 1256, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07 (6H, s; $Si(CH_3)_2$), 0.90 (9H, s; $C(CH_3)_3$), 1.26 (3H, d, J=6.2 Hz; CH_3CH), 2.01+2.28 (2×1H, 2×m; CHCH_2CH$_2$), 2.49+2.63 (2×1H, 2×ddd, J_{gem}=16.4 Hz, J_{vic}=8.0+7.5 and 8.5+5.5 Hz; CH_2COOCH_3), 3.68 (3H, s; OCH_3), 3.92 (1H, td, J=10.6+3.5 Hz; C*H*Br), 3.98 (1H, qd, J=6.2 and 3.5 Hz; C*H*O–); ^{13}C NMR ($CDCl_3$) δ −4.8 and −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 19.6 (*C*H_3CH), 25.8 (C(CH_3)$_3$), 28.6 (CH*C*H_2CH$_2$), 32.5 (*C*H_2COOCH_3), 51.7 (OCH_3), 60.5 (CH–Br), 71.1 (*C*HO–), 173.3 (*C*OOCH_3); MS *m/z* (relative intensity) 341 (2.0, [M]$^+$), 339 (2.0, [M]$^+$), 309 (18.0), 307 (18.0), 283 (69.0), 281 (39.0), 259 (31.0), 209 (67.0), 207 (67.0), 159 (79.0), 127 (55), 85 (100.0); HRMS (EI) calcd for $C_{13}H_{28}{}^{79}BrO_3Si$ 339.0991, found for [M+H$^+$] 339.0986.

4.1.4. 4-Bromo-5-(*tert*-butyl-dimethyl-silanyloxy) hexanal (4). The ester **8** (2.00 g, 5.9 mmol) was dissolved in 50 mL dry dichloromethane and cooled to −60 °C. A solution of 1.0 M diisobutyl aluminum hydride in hexane (7.1 mL, 7 mmol) was added dropwise, and the resulting solution was stirred at −60 °C for 45 min. Then saturated aqueous NH_4Cl was added, and the solution was allowed to warm up to rt. After stirring for 30 min the white precipitate was filtered, and 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 ether/hexane=1:4, R_f=0.6) to afford 1.31 g (72%) of the product **4** as a colorless oil (8:2 mixture of the diastereoisomers): IR (neat) ν 2952, 2944, 1732, 1468, 1152, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07+0.08 (2×3H, 2×s; $Si(CH_3)_2$), 0.90 (9H, s; $C(CH_3)_3$), 1.26 (3H, d, J=6.2 Hz; CH_3CH), 2.00+2.32 (2×1H, 2×m; $CHCH_2CH_2$), 2.66+2.77 (2×1H, 2×m; CH_2COOCH_3), 3.89 (1H, td, J=10.6+3.5 Hz; CHBr), 3.99 (1H, qd, J=6.2 and 3.5 Hz; CHO–), 9.81 (1H, t, J=1.0 Hz; HC=O); ^{13}C NMR ($CDCl_3$) δ −4.8 and −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 19.5 (CH_3CH), 25.8 ($C(CH_3)_3$), 25.8 ($CHCH_2CH_2$), 42.5 (CH_2CHO), 60.4 (CHBr), 71.1 (CHO–), 201.1 (HC=O); MS m/z (relative intensity) 309 (4.0, $[M]^+$), 307 (4.0, $[M]^+$), 283 (15.0), 281 (15.0), 253 (25.0), 251 (32.0), 209 (56.0), 207 (56.0), 171 (23.0), 159 (82.0), 73 (100.0); HRMS (EI) calcd for $C_{12}H_{24}{}^{79}BrO_2Si$ 307.0729, found for $[M-H^+]$ 307.0744.

4.1.5. 3-Benzyl-4-[2-bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo [2,3-*d*]carbazole-6-carboxylic acid methyl ester (9). A solution of 1.00 g (2.85 mmol) of **3**, 1.08 g (3.45 mmol) **4**, and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 50 mL of dry toluene was refluxed under argon over 24 h. The reaction mixture was extracted with brine (2×40 mL), and the combined aqueous phases were extracted with dichloromethane (2×40 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluent: ethylacetate/hexane=1:4, R_f=0.6) to yield 0.84 g (47%) **9** as a yellow oil: IR (neat) ν 3381, 2928, 1680, 1612, 1464, 1440, 1248, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.19, −0.08, −0.03, and 0.07 (6H, 4×s; $Si(CH_3)_3$), 0.69 and 0.77 (9H, 2×s; $C(CH_3)_3$), 1.10 and 1.12 (3H, 2×d, J=6.5 Hz; CH_3CH), 1.17–1.57 (2H, m; 14-CH_2), 1.68+2.05 (2×1H, 2×m; 6-H_2), 2.22–2.40 (1H, m; 14-H), 2.50–2.75 (3H, m; 17-H_2+5-H_A), 2.85–3.03 (2H, m; 5-H_B+3-H), 3.76 and 3.78 (3H, 2×s; OCH_3), 3.65–3.90 (3H, m; CH–O+CH-Br+NCH_ACH_B), 4.18–4.32 (1H, 2×d; NCH_ACH_B), 6.76–6.86 (2H, m; 12-H+10-H), 6.95 (1H, br; 9-H), 7.09–7.16 (1H, m; 11-H), 7.26–7.45 (5H, m; Ph), 8.88 and 8.95 (1H, 2×br s; N1-H). ^{13}C NMR ($CDCl_3$) δ −4.9, −4.9, −4.8, and −4.7 ($Si(CH_3)_3$), 17.9 and 17.9 ($C(CH_3)_3$), 18.9 and 19.1 (CH_3CH), 20.7 and 24.8 (C17), 25.6 and 25.7 ($C(CH_3)_3$), 32.6 and 34.1 (C14–CH_2), 36.8 and 37.4 (C14), 42.3 and 42.5 (C6), 50.1 and 50.4 (C5), 50.9 (OCH_3), 55.2 (C7), 57.7 and 58.0 (NCH_2Ph), 59.3 and 59.6 (CH–Br), 69.9 and 72.3 (C3), 70.9 and 71.1 (CH–O), 90.1 and 91.3 (C16), 109.2 and 109.3 (C12), 120.6 and 120.7 (C10), 122.2 (C9), 127.1 (C4′), 127.9 and 127.9 (C11), 128.4 (C3′+C5′), 129.0 (C2′+C6′), 137.7 (C8), 139.1 (C1′), 142.9 and 143.0 (C13), 164.9 and 165.3 (C2), 168.7 and 168.9 ($COOCH_3$); MS m/z (relative intensity) 626 (12.0, $[M]^+$), 624 (12.0, $[M]^+$), 412 (40.0), 410 (31.0), 295 (11.0), 171 (16.0), 127 (45.0), 91 (100.0); HRMS (EI) calcd for $C_{33}H_{45}{}^{79}BrN_2O_3Si$ 624.2382, found for $[M^+]$ 624.2397.

4.1.6. 4-[2-Bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*] carbazole-6-carboxylic acid methyl ester (10). A mixture of **9** (0.5 g, 0.8 mmol) and 10% palladium/charcoal (0.25 g) in glacial acetic acid (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 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 dichloromethane/methanol=20:1, R_f=0.35) to yield **10** (0.39 g, 92%) as a yellow oil: IR (neat) ν 3376, 2952, 1680, 1608, 1464, 1440, 1248, 1204, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.18, −0.09, −0.07, and −0.03 (6H, 4×s; $Si(CH_3)_3$), 0.68 and 0.78 (9H, 2×s; $C(CH_3)_3$), 1.11 and 1.12 (3H, 2×d, J=6.3 Hz; CH_3CH), 1.14+1.41 (2×1H, 2×m; 14-CH_2), 1.82+1.92 (2×1H, 2×m; 6-H_2), 2.13 (1H, m;14-H), 2.33 and 2.43+2.64 and 2.70 (2×1H, 2×dd; 17-H_2), 3.10–3.20 (2H, m; 5-H_2), 3.47 and 3.49 (1H, 2×s; 3-H), 3.76 and 3.78 (3H, 2×s; OCH_3), 3.78–3.94 (2H, m; CH–O+CH–Br), 6.75–6.95 (2H, m; 12-H+10-H), 7.10–7.20 (1H, m; 11-H), 7.20–7.25 (1H, m; 9-H), 8.96 and 9.01 (1H, s; N1-H). ^{13}C NMR ($CDCl_3$) δ −5.0, −4.9, −4.8, and −4.7 ($Si(CH_3)_3$), 17.8 ($C(CH_3)_3$), 19.1 (CH_3CH), 20.4 and 24.4 (C17), 25.6 and 25.7 ($C(CH_3)_3$), 32.8 and 35.4 (C14-CH_2), 39.1 and 39.8 (C14), 44.1 and 44.5 (C6), 45.1 and 45.4 (C5), 51.0 (OCH_3), 55.9 and 56.0 (C7), 59.0 and 59.3 (CH–Br), 65.4 and 67.1 (C3), 70.6 and 70.9 (CH–O), 89.5 and 90.5 (C16), 109.2 and 109.3 (C12), 120.8 and 120.9 (C10), 121.9 (C9), 127.9 and 128.0 (C11), 137.5 (C8), 143.1 (C13), 165.2 and 165.6 (C2), 168.6 and 168.9 ($COOCH_3$); MS m/z (relative intensity) 536 (3.0, $[M]^+$), 534 (3.0, $[M]^+$), 456 (53.0), 295 (78.0), 242 (55.0), 215 (85.0), 168 (15.0), 154 (15.0), 110 (100.0); HRMS (EI) calcd for $C_{26}H_{39}{}^{79}BrN_2O_3Si$ 534.1913, found for $[M^+]$ 534.1897.

4.1.7. 19-(*tert*-Butyl-dimethyl-silanyloxy)-ibophyllidine (11a) and 19-(*tert*-butyl-dimethyl-silanyloxy)-20-epi-ibophyllidine (11b). Silver *p*-toluenesulfonate (0.45 g, 1.6 mmol) was added to a solution of **9** (0.5 g, 0.8 mmol) in acetonitrile (10 mL), and the mixture was refluxed for 48 h. After heating the solvent was evaporated in vacuo. The residue was dissolved in glacial acetic acid (10 mL) and 0.25 g 10% palladium/charcoal was added. The reaction mixture was hydrogenated for 4 h at rt and then filtrated. 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 purified by column chromatography (eluting with acetone/hexane=1:2, R_f=0.75) to afford 0.17 g (48%) of the mixture of **11a** and **11b** as a colorless oil: IR (neat) ν 3376, 2952, 2912, 1680, 1612, 1468, 1440, 1248, 744 cm^{-1}; **11a** component (~45%): ^1H NMR ($CDCl_3$) δ 0.092 and 0.10 (2×3H, 2×s; $Si(CH_3)_3$), 0.90 (9H, s; $C(CH_3)_3$), 1.38 (3H, d, J=6.0 Hz; 18-H_3), 1.50 (1H, ddd, J_{gem}=12.0 Hz, J_{vic}=11.8+6.7 Hz; 15-H_A), 1.82+3.15 (2×1H, 2×dd, J_{gem}=15.0 Hz, J_{vic}=11.0 and 7.00 Hz; 17-H_2), 2.04 (1H, m; 14-H), 2.10–2.32 (3H, m; 6-H_2+15-H_B), 2.83 (1H, m; 5-H_A), 3.08–3.15 (2H, m; 5-H_B+20-H), 3.51 (1H, br d, J=8.3 Hz; 3-H), 3.76 (3H, s; OCH_3), 3.99 (1H, m; 19-H), 6.81 (1H, d, J=8.0 Hz; 12-H), 6.93 (1H, m; 10-H), 7.14 (1H, m; 11-H), 7.51 (1H, br d, J=7.0 Hz; 9-H), 9.11 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ −4.6 and −3.8 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 23.4 (C18), 25.9

(C(CH_3)$_3$), 31.9 (C17), 32.6 (C15), 37.4 (C14), 41.7 (C6), 48.0 (C5), 50.9 (OCH_3), 55.4 (C7), 70.4 (C19), 70.8 (C20), 76.1 (C3), 92.2 (C16), 108.8 (C12), 121.4 (C10), 123.3 (C9), 127.7 (C11), 138.7 (C8), 143.3 (C13), 164.9 (C2), 168.6 (COOCH$_3$); **11b** component (~55%): ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s; Si(CH_3)$_3$), 0.90 (9H, s; C(CH_3)$_3$), 1.23 (3H, d, J=6.2 Hz; 18-H$_3$), 1.64+2.04 (2×1H, 2×ddd, J_{gem}=12.0 Hz, J_{vic}=5.2+~1 and 7.2+12.0 Hz; 6-H$_2$), 1.86–2.00 (4H, m; 17-H$_A$+15-H$_2$+14-H), 2.74 (1H, dd, J_{gem}=14.4 Hz, J_{vic}=4.6 Hz; 17-H$_B$), 2.85 (1H, ddd, J=6.0+7.1+8.1 Hz; 20-H$_\beta$), 2.98+3.36 (2×1H, 2×ddd, J_{gem}=12.4 Hz, J_{vic}=7.2+~1 and 5.2+12.0 Hz; 5-H$_2$), 3.70 (1H, qd, J=6.2 and 6.0 Hz; 19-H), 3.76 (3H, s; OCH_3), 3.84 (1H, d, J=6.2 Hz; 3-H), 6.83 (1H, d, J=8.0 Hz; 12-H), 6.89 (1H, m; 10-H), 7.16 (1H, m; 11-H), 7.32 (1H, d, J=7.3 Hz; 9-H), 9.05 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ −4.4 and −4.3 (Si(CH_3)$_2$), 18.2 (C(CH$_3$)$_3$), 21.9 (C18), 25.9 (C(CH$_3$)$_3$), 26.8 (C17), 34.9 (C15), 38.9 (C14), 39.4 (C6), 50.9 (OCH_3), 53.2 (C5), 57.9 (C7), 73.0 (C19), 73.3 (C20), 74.1 (C3), 91.9 (C16), 109.1 (C12), 120.9 (C10), 122.6 (C9), 127.9 (C11), 136.9 (C8), 143.6 (C13), 164.9 (C2), 168.6 (COOCH$_3$); MS m/z (relative intensity) 454 (6.0, [M]$^+$), 296 (22.0), 295 (100.0), 263 (9.0); HRMS (EI) calcd for $C_{26}H_{38}N_2O_3Si$ 454.2652, found for [M$^+$] 454.2652.

4.1.8. 19-Hydroxy-ibophyllidine (2a) and 19-hydroxy-20-epiibophyllidine (2b). Aqueous HCl solution (2N, 0.5 mL) was added to a solution of **11a** and **11b** (0.20 g, 0.44 mmol) in tetrahydrofuran (5 mL), and the mixture was stirred for 30 min at rt. After stirring the mixture was concentrated in vacuo, then the residue was dissolved in dichloromethane (20 mL) and worked with water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The two main components were separated by preparative TLC (eluting with acetone/hexane=2:1). The less polar compound (**2a**, R_f=0.53) was obtained (60 mg, 42%) as a colorless oil: IR (neat) ν 3376, 2952, 1672, 1612, 1480, 1464, 1248, 1224, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J=7.5 Hz; 18-H$_3$), 1.74+2.13 (2×1H, m; 15-H$_2$), 1.71+2.08 (2×1H, m; 6-H$_2$), 1.83+2.88 (2×1H, dm, dd, J_{gem}=11 Hz, J_{vic}=6.9 Hz; 17-H$_2$), 2.10 (1H, m; 14-H), 2.95+3.28 (2×1H, 2×dd, J_{gem}=11.5 Hz, J_{vic}=6.9 Hz; 5-H$_2$), 3.06 (1H, ddd, J=6.1+7.1+8.0 Hz; 20-H$_\alpha$), 3.81 (1H, br d, J=8.0 Hz; 3-H), 3.76 (3H, s; OCH_3), 3.89 (1H, m; 19-H), 6.85 (1H, d, J=8.0 Hz; 12-H), 7.01 (1H, m; 10-H), 7.19 (1H, m; 11-H), 7.49 (1H, br d, J=7.1 Hz; 9-H), 9.07 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 23.0 (C18), 29.5 (C17), 33.1 (C15), 37.8 (C14), 41.7 (C6), 48.2 (C5), 50.7 (OCH_3), 55.4 (C7), 70.8 (C19), 76.1 (C3), 91.5 (C16), 108.9 (C12), 121.4 (C10), 123.3 (C9), 128.0 (C11), 138.5 (C8), 143.2 (C13), 164.8 (C2), 168.7 (COOCH$_3$); MS (FAB) m/z (relative intensity) 341 (100.0, [M+H$^+$]), 327 (37.0), 149 (46.0). HRMS (FAB) calcd for $C_{20}H_{25}N_2O_3$ 341.1782, found for [M+H$^+$] 341.1772. The more polar component (**2b**, R_f=0.55) was obtained (55 mg, 39%) as a colorless oil: IR (neat) ν 3368, 2928, 1688, 1612, 1480, 1456, 1248, 1228, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, J=8.0 Hz; 18-H$_3$), 1.66+2.14 (2×1H, m; 15-H$_2$), 1.81+2.90 (2×1H, dm, dd, J_{gem}=12.0 Hz, J_{vic}=7.0 Hz; 17-H$_2$), 1.83+2.27 (2×1H, 2×dd, J_{gem}=11.9 Hz, J_{vic}=8.0 Hz; 6-H$_2$), 2.07 (1H, m; 14-H), 2.64+2.93 (2×1H, 2×dd, J_{gem}=12.0 Hz, J_{vic}=7.0 Hz; 5-H$_2$), 3.11 (1H, ddd, J=6.0+7.1+8.0 Hz; 20-H$_\beta$), 3.67 (1H, d, J=8.0 Hz; 3-H), 3.77 (3H, s; OCH_3), 3.84 (1H, qd, J=6.1 and 6.0 Hz; 19-H), 6.82 (1H, dm, J=8.0 Hz; 12-H), 6.98 (1H, m; 10-H), 7.14 (1H, m; 11-H), 7.38 (1H, d, J=7.5 Hz; 9-H), 9.05 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 22.2 (C18), 24.9 (C17), 34.6 (C15), 38.8 (C14), 41.7 (C6), 50.7 (OCH_3), 51.2 (C5), 55.4 (C7), 71.5 (C19), 73.4 (C20), 74.3 (C3), 90.3 (C16), 109.5 (C12), 120.8 (C10), 122.4 (C9), 128.1 (C11), 136.9 (C8), 143.2 (C13), 164.5 (C2), 169.1 (COOCH$_3$); MS (FAB) m/z (relative intensity) 341 (100.0, [M+H$^+$]), 327 (35.0), 149 (38.0); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_3$ 341.1782, found for [M+H$^+$] 341.1778.

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Supplementary data

Supplementary data contains ^{1}H, ^{13}C, and 2D NMR spectra of **6**, **7**, **8**, **4**, **9**, **10**, **11a**, **11b**, **2a**, and **2b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.079.

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