SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS.
PART 109. AN INTRAMOLECULAR [4+2] CYCLOADDITION
MEDIATED BIOMIMETIC SYNTHESIS OF (±)-IBOXYPHYLLINE

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Abstract – The pentacyclic alkaloid 1 could be synthesized by an intramolecular [4+2] cycloaddition reaction of intermediate 11, which had been obtained from tryptamine derivative 4 and aldehyde 5. After full epimerization of 13 the cyclization reaction furnished a mixture of 14a and 14b. Separation of the stereoisomers 14a and 14b and subsequent reduction with LiAlH4 resulted in (±)-iboxypylline (14a → 1) and its epimer, (±)-20-epiiboxypylline (14b → 15).

INTRODUCTION
Iboxyphylline (1) was isolated from the leaves of Tabernanthe iboga and Tabernanthe subsessilis in 1976. It can be classified as a D(21)-homopandoline type alkaloid and therefore the precursors of the biosynthesis are pandoline (2) and 20-epipandoline (3). The biogenetically unusual skeleton which contains a seven-membered D ring makes this compound an interesting synthetic target (Figure 1). Recently Kuehne and co-workers reported a synthetic route to the construction of 1 but their method gave a low yield. In our previous studies we used a [4+2] cyclization reaction as an expeditious synthetic
route to aspidospermane, \( \Psi \)-aspidospermane and ibophyllidine alkaloids.\(^{5-12}\) We now report the application of our biomimetic synthetic strategy to build up (±)-iboxyphylline (1).

![Chemical structures](image)

**Figure 1.**

**RESULTS AND DISCUSSION**

The key step of our synthesis was the reaction of tryptamine derivative 4\(^5\) with the appropriately functionalized aldehyde 5 (Figure 2).

![Chemical structures](image)

**Figure 2.**

Compound 5 was formed from 4-(\( \text{tert} \)-butyl-dimethyl-silyloxy)butanal (6).\(^{10}\) First step was a Reformatsky reaction of 6 with methyl 2-bromopropionate, which resulted in alcohol 7. Alcohol 7 was then acylated with acetyl chloride to afford the protected diester 8. Subsequent hydrolysis of 8 with 1M HCl solution in tetrahydrofuran led to 9. Finally, diester 9 was oxidized with pyridinium chlorochromate to give the expected aldehyde 5 (Scheme 1).
The secondary amine 4 was then allowed to react with 5 in boiling toluene in the presence of p-toluenesulfonic acid (10→11→12). Only one product (12) was obtained in a good yield (Scheme 2).

Scheme 1. Reagents and conditions: (a) Br-CH(CH₃)CO₂Me, Zn, benzene, reflux, (79%); (b) CH₃COCl, (C₂H₅)₃N, DMAP, CH₂Cl₂, rt., (84%); (c) 1M HCl, THF, rt., (82%); (d) PCC, NaOAc, CH₂Cl₂, rt., (71%).
Catalytic debenzylation in glacial acetic acid at room temperature of the tetracyclic compound 12 resulted in the expected secondary amine 13 (Scheme 3).

In our earlier works a method was succesfully used for the formation of the D ring of aspidospermane and ibophyllidine skeletons. Accordingly the tetracyclic secondary amine 13 was refluxed in toluene in the presence of p-toluenesulfonic acid. After full epimerization the intramolecular N-acylation reaction furnished two seven-membered D ring products (14a and 14b).

Separation of the stereoisomers 14a and 14b was carried out on a semipreparative Waters x-Terma RP18 column (Scheme 4). Finally, reduction of 14a and 14b with LiAlH4 furnished (±)-iboxyphylline (1) and (±)-20-epiboxyphylline (15) (Scheme 5).
CONCLUSION
In summary, we have accomplished a biomimetic total synthesis of (±)-iboxyphylline (1). Based on our efficient synthetic method, we built up from 4-(tert-butyldimethylsilyloxy)butanal (6) the aldehyde 5, which was then allowed to react with tryptamine derivative 4 and furnished compound 12. Catalytic hydrogenolysis, full epimerization, and cyclization reaction of the tetracyclic amine 12 then resulted in 14a and 14b. Finally, reduction of 14a and 14b with LiAlH₄ led to (±)-iboxyphylline (1) and its 20-epimer (15).

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 Brucker DRX-500 instrument at 500 MHz for ¹H and 100 MHz for ¹³C. All NMR spectra were recorded at rt. Chemical shifts are reported relative to Me₄Si (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 F₂₅₄ plates, and column chromatography was carried out on Merck Kieselgel 60 (0.063-0.200 mm).

6-(tert-Butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hexanoic acid methyl ester (7)
A 3-necked flask fitted with a condenser, mechanical stirrer, and 100 mL dropping funnel was purged with nitrogen. Freshly activated zinc powder (1.78 g, 27.2 mmol), and dry benzene (50 mL) were placed in the flask. Methyl 2-bromopropionate (4.13 g, 24.7 mmol), 4-(tert-butyldimethylsilyloxy)butanal (6)
(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 30 min. Then the reaction was cooled to rt and quenched with water (20 mL). The two-phases system were filtered to remove unchanged zinc and the phases were separated. The aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phases were washed with brine (30 mL), dried (MgSO₄) and evaporated in vacuo. The residue was purified by column chromatography (eluting with ethyl acetate/hexane=1:4, Rf=0.35) to afford 5.64 g (79%) of product 7 as a colorless oil (mixture of the diastereoisomers). IR (neat) νmax 3456, 2952, 1740, 1468, 1256, 1100, 836. ¹H NMR δH (CDCl₃): 0.06 (6H, s; Si(CH₃)₂), 0.90 (9H, s; C(CH₃)₃), 1.19 and 1.20 (3H, d; J=7.4 Hz; C₂-CH₃), 1.40-1.75 (4H, m; 4-H₂+5-H₂), 2.55 and 2.56 (1H, m; 2-H), 3.04 and 3.09 (1H, d; J=6.0 and 4.2 Hz; OH), 3.66 (2H, t; J=5.7 Hz; 6-H₂), 3.70 (3H, s; OCH₃), 3.88 (1H, m; 3-H). ¹³C NMR δC (CDCl₃): -5.36 (Si(CH₃)₂), 11.30 and 13.98 (C₂-CH₃), 18.31 (C(CH₃)₃), 25.93 (C(CH₃)₃), 28.86 and 29.29 (C₅), 31.21 and 31.49 (C₄), 44.73 and 45.44 (C₂), 51.66 and 51.70 (OCH₃), 63.22 (C₆), 71.83 and 73.05 (C₃), 176.35 (C₁). MS m/z (%) (rel intensity) 291 (52.0, M+H⁺), 233 (24.0), 203 (32.0), 201 (63.0), 159 (24.0), 105 (57.0), 71 (100.0). HRMS (Cl) calcd for C₁₄H₃₁O₄Si 291.1992, found for [M+H⁺] 291.1990.

3-Acetoxy-6-(tert-butyl-dimethyl-silanyloxy) -2-methyl-hexanoic acid methyl ester (8)

7 (5.00 g, 17.2 mmol) was dissolved in dry CH₂Cl₂ (80 mL) and triethylamine (3.48 g, 4.82 mL, 34.4 mmol) was added to the solution and it was cooled to 0°C. 2.70 g (2.44 mL, 34.4 mmol) of acetyl chloride, and 4-(dimethylamino)pyridine (0.42 g, 3.4 mmol) were added at 0°C. The reaction mixture was allowed to warm up to rt, and then stirred for 12 h. It was then poured into water (20 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3×30 mL) and the combined organic phases were washed with brine (25 mL). It was dried (MgSO₄) and concentrated in vacuo, yielding 5.36 g (84%) as a yellow oil (mixture of the diastereoisomers) (TLC: EtOAc/hexane=1:4, Rf=0.58). IR (neat) νmax 2952, 1744, 1464, 1236, 1100, 836. ¹H NMR δH (CDCl₃): 0.04 (6H, s; Si(CH₃)₂), 0.89 (9H, s; C(CH₃)₃), 1.15 and 1.16 (3H, d; J=7.0 Hz; C₂-CH₃), 1.40-1.78 (4H, m; 4-H₂+5-H₂), 2.03 and 2.04 (3H, s; OCOCH₃), 2.68 and 2.77 (1H, m; 2-H), 3.60 (2H, m; 6-H₂), 3.67 (3H, s; OCH₃), 5.13 and 5.17 (1H, m; 3-H). ¹³C NMR δC (CDCl₃): -5.31 (Si(CH₃)₂), 11.81 and 12.62 (C₂-CH₃), 18.31 (C(CH₃)₃), 20.93 and 20.99 (OCOCH₃), 25.94 (C(CH₃)₂), 28.42 and 27.39 + 28.78 and 28.36 (C₄+C₅), 43.15 and 43.25 (C₂), 51.72 and 51.78 (OCH₃), 62.52 and 62.55 (C₆), 73.95 and 74.37 (C₃), 170.33 and 170.48 (OCOCH₃), 173.96 and 174.23 (C₁). MS m/z (%) (rel intensity) 333 (4.0, M+H⁺), 275 (25.0), 215 (100.0), 183 (11.0), 141 (33.0), 119 (42.0), 75 (65.0). HRMS (Cl) calcd for C₁₆H₃₅O₄Si 333.2097, found for [M+H⁺] 333.2096.
3-Acetoxy-6-hydroxy-2-methyl-hexanoic acid methyl ester (9)

1M aqueous HCl solution (2 mL) was added to a solution of 8 (5.00 g, 15.0 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 CH₂Cl₂ (60 mL) and washed with water (20 mL) and brine (20 mL). The organic phases were dried (MgSO₄) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (eluent: acetone/hexane=1:2, Rf=0.53) to afford 2.69 g (82%) of the product 9 as a colorless oil (mixture of the diastereoisomers). IR (neat) ν max 3448, 2952, 1740, 1440, 1240, 1068. ¹H NMR δH (CDCl₃): 1.17 (3H, d, J=7.0 Hz; C2-CH₃), 1.48-1.78 (5H, m; 4-H₂+5-H₂+OH), 2.04 and 2.05 (3H, s; OCOCH₃), 2.69 and 2.78 (1H, m; 2-H), 3.65 (2H, t, J=6.0 Hz; 6-H₂), 3.68 (3H, s; OCH₃), 5.15 and 5.18 (1H, m; 3-H). ¹³C NMR δC (CDCl₃): 11.91 and 12.52 (C2-CH₃), 20.90 and 20.97 (OCOCH₃), 27.39 and 28.41 + 28.25 and 28.58 (C4+C5), 43.16 and 43.23 (C2), 51.78 and 51.85 (OCH₃), 62.21 and 62.28 (C6), 73.81 and 74.20 (C3), 170.62 (OCOCH₃), 173.93 and 174.24 (C1). MS m/z (%) (rel intensity) 219 (2.0, M+H⁺), 157 (14.0), 128 (13.0), 88 (49.0), 71 (76.0). HRMS (FAB) calcd for C₁₀H₁₉O₅ 219.1232, found for [M+H⁺] 219.1237.

3-Acetoxy-2-methyl-6-oxo-hexanoic acid methyl ester (5)

A solution of 9 (5.00 g, 23 mmol) in dry CH₂Cl₂ (80 mL) was added to a stirred suspension of pyridinium chlorochromate (7.45 g, 34.7 mmol), containing 2.86 g (34.7 mmol) of sodium acetate. After 1 h Et₂O (35 mL) was added to the mixture and then it was decanted. The black precipitate was washed with Et₂O (2×30 mL) and the combined solutions were washed with 5% aqueous solution of NaHCO₃ (40 mL), water (30 mL) and brine (30 mL). It was dried (MgSO₄) and evaporated in vacuo. The residue was purified by column chromatography (eluent: acetone/hexane=1:2, Rf=0.45) to give 3.53 g (71%) of 5 as an yellow oil (mixture of the diastereoisomers). IR (neat) ν max 2952, 1740, 1440, 1376, 1236, 1024. ¹H NMR δH (CDCl₃): 1.18 (3H, d, J=7.0 Hz; C2-CH₃), 1.80-2.00 (2H, m; 4-H₂), 2.04 and 2.05 (3H, s; OCOCH₃), 2.49 (2H, m; 5-H₂), 2.65-2.80 (1H, m; 2-H), 3.69 (3H, s; OCH₃), 5.10-5.20 (1H, m; 3-H), 9.75 (1H, m; 6H). ¹³C NMR δC (CDCl₃): 12.16 and 12.40 (C2-CH₃), 20.76 and 20.83 (OCOCH₃), 23.50 and 24.50 (C4), 39.82 and 40.14 (C5), 43.23 and 43.35 (C2), 51.87 and 51.93 (OCH₃), 73.22 and 73.38 (C3), 170.45 and 170.59 (OOCOCH₃), 173.64 and 173.91 (C1), 200.86 (C6). MS m/z (%) (rel intensity) 217 (1.0, M+H⁺), 173 (29.0), 143 (77.0), 128 (15.0), 88 (40.0), 69 (24.0). HRMS (FAB) calcd for C₁₀H₁₇O₅ 217.1232, found for [M+H⁺] 217.1237.

4-(2-Acetoxy-3-methoxycarbonyl-butyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylic acid methyl ester (12)
A solution of 1.00 g (2.85 mmol) of tryptamine derivative (4), 5 (0.74 g, 3.42 mmol) and p-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) 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 CH₂Cl₂ (2×30 mL). The combined organic phases were dried (MgSO₄) and evaporated in vacuo. The residue was purified by column chromatography (eluent: Et₂O/hexane=4:1, Rₑ=0.49) to yield 0.8 g (53%) 12 as an yellow oil (mixture of the diastereoisomers). IR (neat) νₘₐₓ 3368, 2952, 1740, 1712, 1680, 1612, 1480, 1280, 748. ¹H NMR δH (CDCl₃): 0.96 and 0.97 and 1.00 (3H, d, J=7.0 Hz; C₁₉-CH₃), 1.00-1.32 (2H, m; 15-H₂), 1.68 (1H, m; 6-Hₐ), 1.82-1.94 (1H, m; 14-H), 1.97 and 1.99 (3H, s; OCOCH₃), 4.06-4.15 (1H, m; NCH₃CH₃Ph), 5.08-5.24 (1H, m; 20-H), 6.78-7.18 (4H, m; 10-H+12-H+9-H+11-H), 7.22-7.42 (5H, m; Ph), 8.90 and 8.96 and 9.03 (1H, br s; N₁-H). ¹³C NMR δC (CDCl₃): 11.32 and 11.69 and 11.97 (C₁₉-CH₃), 20.05 and 20.93 and 20.96 (OCOCH₃), 21.24 and 21.42 and 23.60 and 24.20 (C₁₇), 31.54 and 31.98 and 32.92 and 33.75 (C₁₅), 35.34 and 35.40 and 35.59 and 35.64 (C₁₄), 41.96 and 42.38 (C₆), 42.45 and 43.05 and 43.12 and 43.48 (C₁₉), 50.30 and 50.55 (C₅), 50.94 and 51.03 (C₁₉-OCOCH₃), 51.43 and 51.57 and 51.79 (16-OCOCH₃), 55.11 and 55.16 (C₇), 57.49 and 57.83 and 58.25 (NCH₂Ph), 70.93+71.75 and 70.43+72.34 and 72.15 and 72.19 and 72.28 (C₃+C₂₀), 90.49 and 90.63 and 90.80 (C₁₆), 109.24 (C₁₂), 120.60 (C₉), 122.22 and 122.30 (C₁₀), 126.81-129.26 (C₁₁+C₂²+C₃³+C₄⁴+C₅⁵+C₆⁶), 137.69 (C₁'), 138.90 and 139.04 and 139.15 (C₈), 142.88 and 142.93 and 142.97 (C₁₃), 164.82 and 165.11 (C₂), 168.94 and 169.04 (16-OCOCH₃), 170.27 and 170.41 and 170.46 (OCOCH₃), 173.15 and 173.49 and 173.96 and 174.02 (C₂₁). MS m/z (%) (rel intensity) 532 (53.0, M⁺), 501 (10.0), 473 (8.0), 441 (22.0), 399 (100.0). HRMS (EI) calecd for C₃₁H₃₆N₂O₆ 532.2573, found for [M⁺] 532.2565.

4-(2-Acetoxy-3-methoxycarbonyl-butyl)-2,3,3a,4,5,7-hexahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylic acid methyl ester (13) A mixture of 12 (1.00 g, 1.87 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 Na₂CO₃ solution. The mixture was extracted with CH₂Cl₂ (3×70 mL) and the combined organic phases were dried (MgSO₄) and the solvent was removed in vacuo. The residue was purified by column chromatography (eluting with CH₂Cl₂/MeOH=9:1, Rₑ=0.61) to afford 13 (0.77 g, 93%) as a yellow oil (mixture of the diastereoisomers). IR (neat) νₘₐₓ 3368, 2952, 1736, 1708, 1676, 1608, 1440, 1244, 748. ¹H NMR δH (CDCl₃): 0.94 and 0.96 and 0.99 (3H, d, J=7.1 Hz; C₁₉-CH₃), 1.05-1.32 (2H, m; 15-H₂), 1.69 (1H, m; 6-Hₐ), 1.86-1.96 (1H, m; 14-H), 1.98 and 2.00 (3H, s; OCOCH₃),
2.01-2.12 (1H, m; 6-H_B), 2.27-2.75 (5H, m; 19-H+17-H_2+5-H_A+N4-H), 3.09-3.17 (2H, m; 5-H_B+3-H),
3.49 and 3.57 and 3.71 (3H, s; C21-OOCH_3), 3.78 and 3.81 (3H, s; 16-COOCH_3), 5.13 and 5.24 (1H, m; 20-H), 6.85 (1H, br d, J=7.3 Hz; 12-H), 6.90 (1H, ddd, J=7.6+7.4+1.2 Hz; 10-H), 7.16 (1H, ddd, J=7.4+7.2+1.0 Hz; 11-H), 7.23 (1H, d, J=7.3 Hz; 9-H), 8.98 and 9.04 (1H, br s; N1-H). 13C NMR δ_C (CDCl_3): 11.41 and 11.68 and 11.93 (C19-C_H_3), 20.97 and 21.22 and 21.24 (OCO-C_H_3), 21.26 and 21.47 and 23.58 and 24.22 (C17), 31.56 and 32.00 and 32.81 and 33.74 (C15), 35.35 and 35.41 and 36.07 and 36.46 (C14), 42.07 and 42.41 (C6), 43.05 and 43.17 and 43.49 and 44.01 (C19), 50.29 and 50.70 (C5), 51.78 and 51.92 (16-COOCH_3), 51.94 and 51.99 (C21OOCH_3), 55.47 and 55.87 (C7), 65.19 and 66.52 and 67.10 (C20), 68.44 and 68.62 and 68.98 (C3), 90.29 and 90.55 and 90.63 (C16), 109.47 (C12), 120.89 (C10), 122.09 and 122.22 (C9), 128.12 and 128.17 (C11), 137.61 and 137.82 (C8), 142.99 and 143.25 (C13), 160.11 and 160.21 (C2), 169.08 (16-COOCH_3), 170.56 (OOCOCH_3), 173.71 and 174.06 (C21). MS m/z (%) (rel intensity) 443 (27.0, M+), 399 (59.0), 173 (12.0), 128 (68.0), 88 (100.0). HRMS (EI) calcd for C_{24}H_{30}N_2O_5 442.9605, found for [M+] 442.9607.

21-Oxo-acetyl liberoxyphylline (14a) and 21-oxo-20-epi-acetyl liberoxyphylline (14b)

A solution of 13 (0.50 g, 1.13 mmol) and p-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) in 15 ml of dry toluene was refluxed under argon for 48 h. Then it was cooled and concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried (MgSO_4) and the solvent was removed in vacuo. The main components was separated by preparative TLC (eluent: aceton/hexane=1:1) 14 (R_f=0.71). The separation of the stereoisomers was carried out on a semipreparative Waters x-Terma RP_18 column (30mm×300mm), 40% MeOH/MeCN and H_2O, 18 mL/min flow rate provided 14a (0.214 g, 46 %) and 14b (0.163 g, 35 %). 14a: IR (neat) ν_{max} 3264, 2952, 1736, 1700, 1648, 1608, 1436, 1244. 1H NMR δ_H (CDCl_3): 1.18 (3H, d, J=6.6 Hz; C19-CH_3), 1.43 (1H, m, J=13.3 Hz; 15-H_B), 1.75 (1H, m; 14-H), 1.88+2.27 (2×1H, m; 6-H), 1.99+2.81 (2×1H, 2×dm, J=15.5 Hz; 17-H_2), 2.09 (3H, s; OCOCH_3), 2.17 (1H, m; 15-H_A), 2.96 (1H, m; 19-H), 3.75+3.98 (2H, m; 2-H), 3.77 (3H, s; OCH_3), 4.18 (1H, dm, J=8.9 Hz; 3-H), 5.13 (1H, ddd, J=10.7+6.0+6.0 Hz; 20-H), 6.87 (1H, br d, J=7.7 Hz; 12-H), 6.92 (1H, ddd, J=7.6+7.5+1.0 Hz; 10-H), 7.15 (1H, br d; J=7.6 Hz; 9-H), 7.22 (1H, ddd; 7.7+7.5+1.2 Hz; 11-H), 9.05 (1H, br s; N1-H). 13C NMR δ_C (CDCl_3): 11.32 (C18), 21.39 (OCOCH_3), 28.28 (C17), 33.51 (C14), 35.30 (C15), 35.67 (C6), 41.65 (C19), 44.19 (C5), 51.40 (16-OCOCH_3), 56.84 (C7), 62.86 (C3), 70.63 (C20), 93.10 (C16), 109.77 (C12), 121.68 (C10), 122.27 (C9), 129.11 (C11), 135.24 (C8), 143.50 (C13), 160.75 (C2), 168.29 (16-OCOCH_3), 170.91 (OCOCH_3), 171.13 (C21). MS m/z (%) (rel intensity) 410 (41.0, M+), 217 (11.0), 143 (54.0), 88 (49.0), 43 (100.0). HRMS (EI) calcd for C_{23}H_{26}N_2O_5 410.4629, found for [M+] 410.4630. 14b: IR (neat) ν_{max} 3264, 2952, 1736, 1700, 1648, 1608, 1436, 1244. 1H NMR δ_H (CDCl_3): 1.25 (3H, d, J=6.6 Hz; C19-CH_3),
1.54 (1H, dm, J=15.4 Hz; 15-Ha), 1.87 (1H, m; 14-H), 1.92 (2H, m; 6-Ha+17-Ha), 2.04 (3H, s; OCOCH3), 2.09 (1H, dm, J=15.4 Hz; 15-Ha), 2.27 (1H, m; 6-Ha), 2.71 (1H, dm, J=15.0 Hz; 17-Ha), 2.85 (1H, dq, J=6.6+6.6 Hz; 19-H), 3.74+3.88 (2×1H, m; 5-H2), 3.78 (3H, s; OCH3), 4.34 (1H, dm, J=8.5 Hz; 3-H), 4.92 (1H, ddd, J=8.0+3.1+3.0 Hz; 20-H), 6.88 (1H, br d, J=7.6 Hz; 12-H), 6.92 (1H, ddd, J=7.6+7.5+1.0 Hz; 10-H), 7.16 (1H, br d; J=7.6 Hz; 9-H), 7.22 (1H, ddd, J=7.6+7.5+1.2 Hz; 11-H), 9.01 (1H, br s; N1-H). 13C NMR δC (CDCl3): 14.44 (C18), 21.20 (OCOCH3), 27.59 (C17), 31.41 (C14), 34.25 (C15), 35.62 (C6), 43.83 (C19), 44.18 (C5), 51.29 (16-COOCH3), 56.66 (C7), 62.56 (C3), 74.43 (C20), 93.22 (C16), 109.59 (C12), 121.30 (C10), 121.93 (C9), 128.85 (C11), 135.27 (C8), 143.36 (C13), 160.92 (C2), 168.05 (16-COOCH3), 170.48 (OCOCH3), 171.00 (C21). MS m/z (%) (rel intensity) 410 (35.0, M+), 217 (11.0), 143 (54.0), 43 (100.0). HRMS (EI) calcd for C23H26N2O5 410.4629, found for [M+] 410.4626.

(±)-Iboxyphylline (1)

To a solution of 14a (200 mg, 0.54 mmol) in dry THF (20 mL) at 0°C was added LiAlH4 (61.6 mg, 1.62 mmol). The mixture was slowly warmed to rt and stirred 1 h. Then 1M 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 CH2Cl2 (30 mL) and 1M NaOH solution (10 mL). The aqueous phase was extracted with CH2Cl2 (3×15 mL) and the combined organic extracts were concentrated and the main component was separated by preparative TLC (eluent: CH2Cl2/MeOH=9:1, Rf=0.45) to afford 1 (114 mg, 61%) as an yellow oil. IR (neat) v_max 3384, 2928, 1676, 1608, 1448, 1204, 1104. 1H NMR δH (CDCl3): 0.88 (3H, d; J=7.4 Hz; C19-CH3), 1.21-1.38 (2H, m; 15-H2), 1.81+2.05 (2H, m; 6-H2), 1.82-1.94 (1H, m; 14-H), 2.24-2.26 (2H, m; 17-H2), 2.68+3.48 (2H, m; 21-H2), 2.77+3.53 (2H, m; 5-H2), 3.62 (1H, d, J=7.8 Hz; 3-H), 3.77 (3H, s; 16-COOCH3), 4.09 (1H, d, J=7.2 Hz; 20-H), 6.85-6.90 (2H, m; 10-H+12-H), 7.18-7.23 (2H, m; 9-H+11-H), 8.88 (1H, br s; N1-H). 13C NMR δC (CDCl3): 11.79 (C18), 28.11 (C17), 35.48 (C14), 33.06 (C15), 40.66 (C6), 44.92 (C19), 50.31 (C5), 51.43 (16-COOCH3), 56.99 (C7), 58.70 (C21), 67.32 (C3), 72.86 (C20), 93.49 (C16), 109.11 (C12), 120.55 (C10), 122.25 (C9), 128.74 (C11), 137.63 (C8), 142.86 (C13), 164.85 (C2), 168.10 (16-COOCH3). MS m/z (%) (rel intensity) 354 (34.0, M+), 278 (16.0), 217 (39.0), 140 (100.0), 128 (16.0). HRMS (EI) calcd for C21H26N2O3 354.4427, found for [M+] 354.4431.

(±)-20-Epiiboxyphylline (15)

To a solution of 14b (100 mg, 0.27 mmol) in dry THF (15 mL) at 0°C was added LiAlH4 (30.8 mg, 0.81 mmol). The mixture was slowly warmed to rt and stirred 1 h. Then 1M aqueous solution of NaOH (5 mL) was added to the suspension. After stirring for 15 min the organic solvent was removed under reduced pressure. The residue was partitioned between CH2Cl2 (20 mL) and 1M NaOH solution (10 mL). The
aqueous phase was extracted with CH$_2$Cl$_2$ (3×15 mL) and the combined organic extracts were concentrated and the main component was separated by preparative TLC (eluent: CH$_2$Cl$_2$/MeOH=9:1, R$_f$=0.46) to afford 15 (66 mg, 66%) as a yellow oil. IR (neat) $\nu_{\text{max}}$ 3384, 2936, 1680, 1608, 1452, 1440, 1204, 1108. $^1$H NMR $\delta$(CDCl$_3$): 0.92 (3H, d, J=7.4 Hz; C19-CH$_3$), 1.16-1.43 (2H, m; 15-H$_2$), 1.78-2.09 (2H, m; 6-H$_2$), 1.85-1.98 (1H, m; 14-H), 2.21-2.25 (2H, m; 17-H$_2$), 2.77+3.41 (2H, m; 21-H$_2$), 2.83+3.67 (2H, m; 5-H$_2$), 3.61 (1H, d, J=7.7 Hz; 3-H), 3.76 (3H, s; 16-COOCH$_3$), 4.13 (1H, d, J=7.3 Hz; 20-H), 6.81-6.88 (2H, m; 10-H+12-H), 7.17-7.25 (2H, m; 9-H+11-H), 8.96 (1H, br s; N1-H). $^{13}$C NMR $\delta$(CDCl$_3$): 10.82 (C18), 26.49 (C17), 32.72 (C15), 36.01 (C14), 42.32 (C6), 45.27 (C19), 50.48 (C5), 51.20 (16-COOCH$_3$), 56.77 (C7), 59.13 (C21), 68.09 (C3), 74.63 (C20), 96.94 (C16), 110.00 (C12), 120.42 (C10), 121.99 (C9), 128.73 (C11), 136.28 (C8), 142.81 (C13), 163.54 (C2), 168.02 (16-COOCH$_3$). MS m/z (%) (rel intensity) 354 (38.0, M$^+$), 278 (21.0), 140 (100.0), 128 (54.0). HRMS (EI) calcd for C$_{21}$H$_{26}$N$_2$O$_3$ 354.4427, found for [M$^+$] 354.4428.

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REFERENCES
4. The biogenetic numbering (J. Le Men and W. I. Taylor, *Experientia*, 1965, 21, 508.) is used throughout this paper, but the systematic nomenclature has been used in the Experimental Section.


