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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 (±)-iboxyphylline (**14a** → **1**) and its epimer, (±)-20-epiiboxyphylline (**14b** → **15**).

INTRODUCTION

Iboxyphylline (**1**) was isolated from the leaves of *Tabernanthe iboga* and *Tabernanthe subsessilis* in 1976.¹ 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**).²⁻⁴ 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.^{3b} In our previous studies we used a [4+2] cyclization reaction as an expeditious synthetic

route to aspidospermane, Ψ -aspidospermane and ibophyllidine alkaloids.⁵⁻¹² We now report the application of our biomimetic synthetic strategy to build up ($\pm$)-iboxyphylline (**1**).

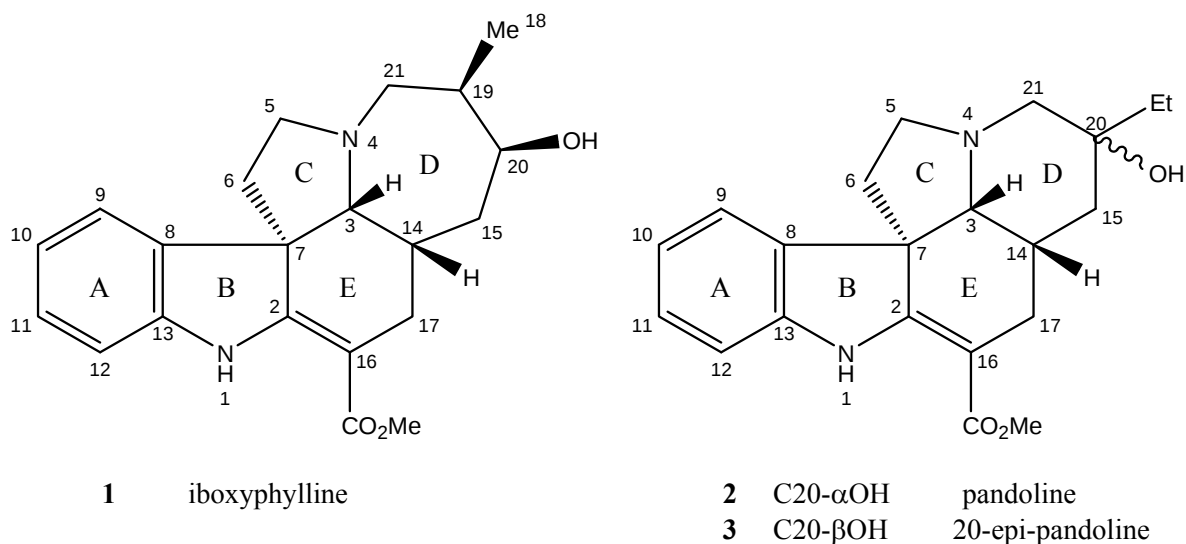


Figure 1.

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).

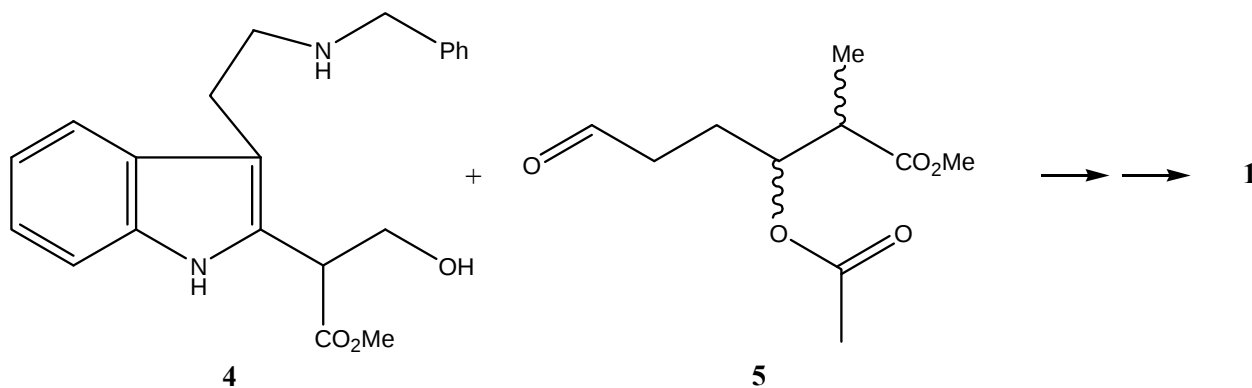
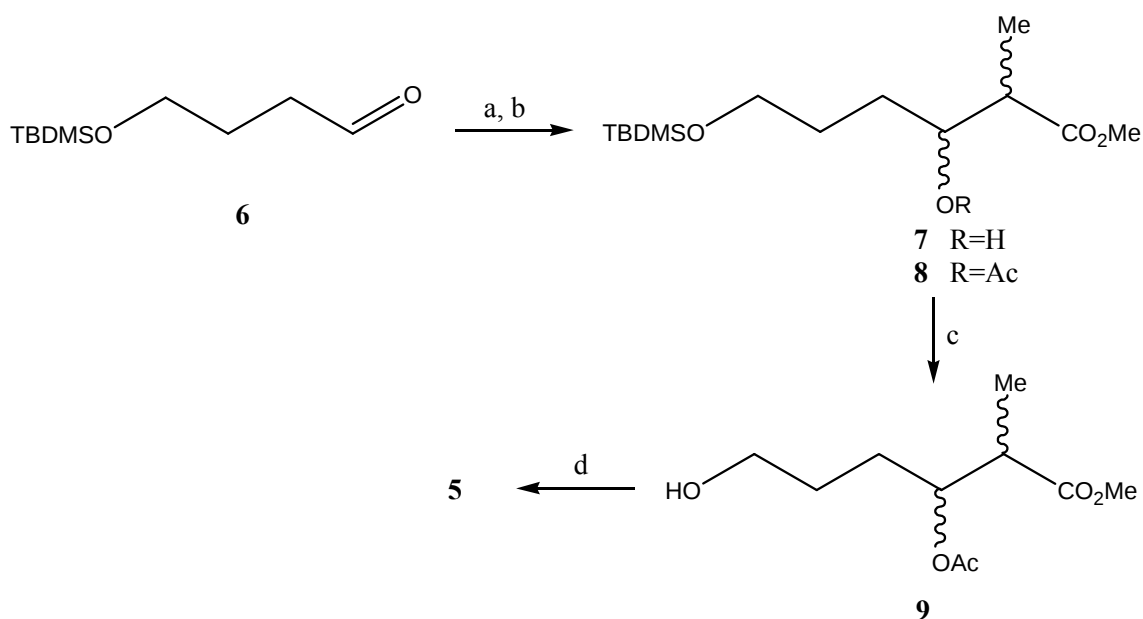


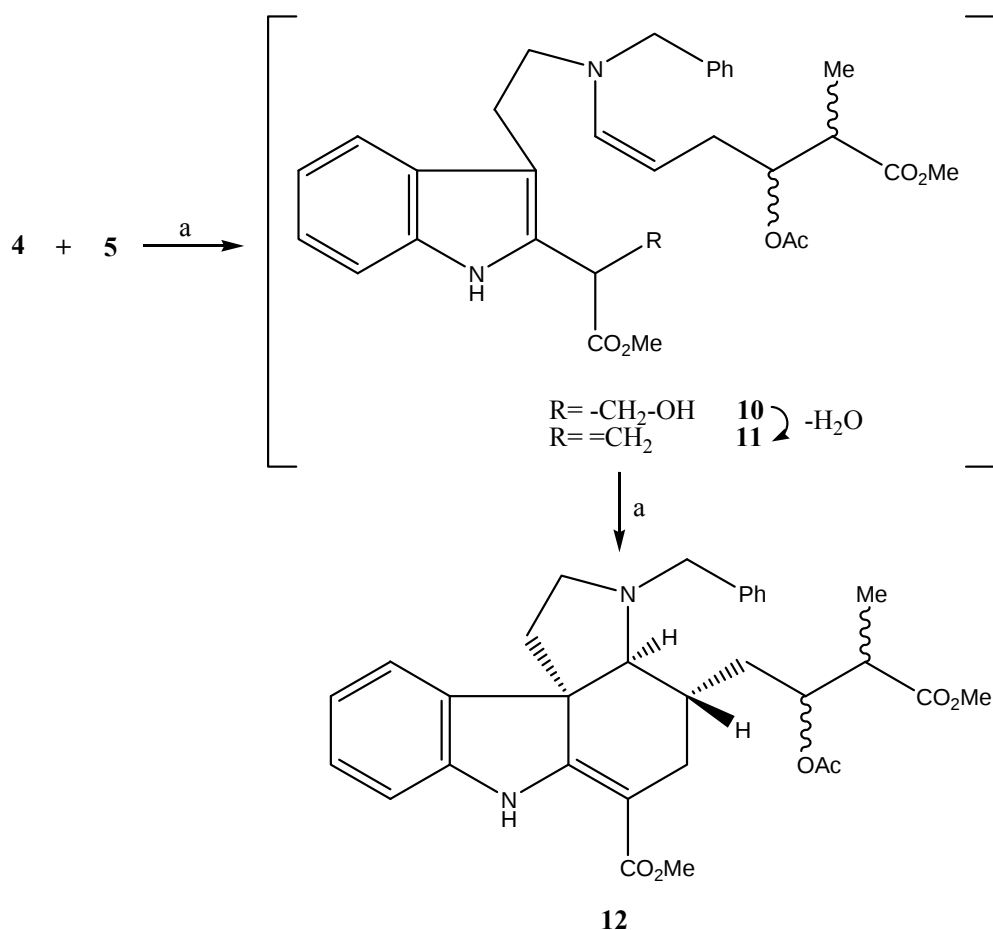
Figure 2.

Compound **5** was formed from 4-(*tert*-butyl-dimethyl-silanyloxy)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).



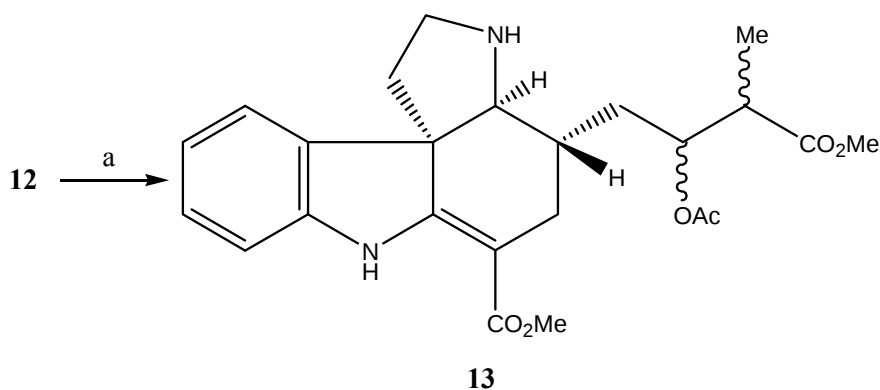
Scheme 1. Reagents and conditions: (a) $\text{Br-CH(CH}_3\text{)CO}_2\text{Me}$, Zn, benzene, reflux, (79%); (b) CH_3COCl , $(\text{C}_2\text{H}_5)_3\text{N}$, DMAP, CH_2Cl_2 , rt., (84%); (c) 1M HCl, THF, rt., (82%); (d) PCC, NaOAc, CH_2Cl_2 , rt., (71%).

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).



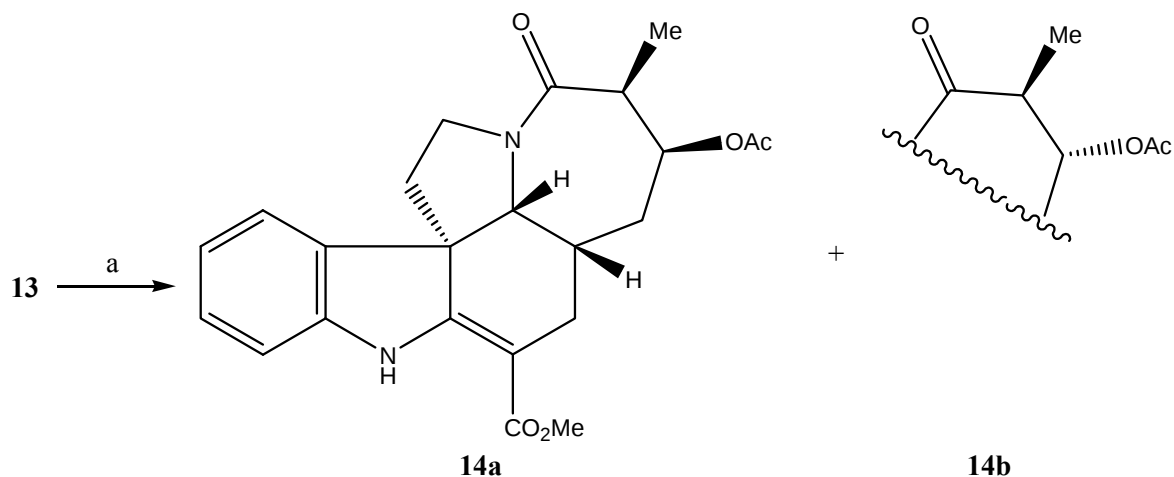
Scheme 2. Reagents and conditions: (a) *p*-TsOH, toluene, reflux, (53%).

Catalytic debenzoylation in glacial acetic acid at room temperature of the tetracyclic compound **12** resulted in the expected secondary amine **13** (Scheme 3).



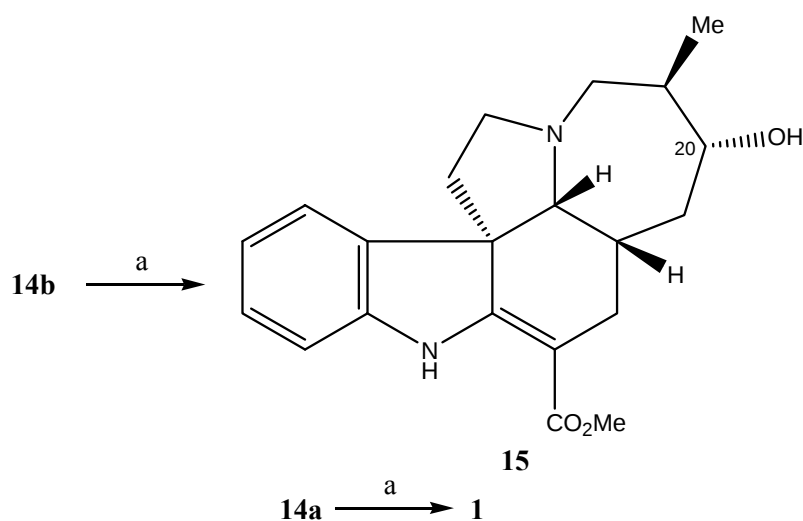
Scheme 3. Reagents and conditions: (a) 10% Pd/C, H₂, AcOH, rt., (93%).

In our earlier works a method was successfully used for the formation of the D ring of aspidospermane and ibophyllidine skeletons.⁵⁻¹² Accordingly the tetracyclic secondary amine **13** was refluxed in toluene in the presence of *p*-toluenesulfonic acid. After full epimerization¹³ the intramolecular N-acylation reaction furnished two seven-membered D ring products (**14a** and **14b**).



Scheme 4. Reagents and conditions: (a) *p*-TsOH, toluene, reflux, (46% (**14a**) and 35% (**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-epiiboxyphylline (**15**) (Scheme 5).



Scheme 5. Reagents and conditions: (a) LiAlH₄, THF, 0°C (61% (**1**) and 66% (**15**)).

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 Bruker 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-silyloxy)-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, R_f=0.35) to afford 5.64 g (79%) of product **7** as a colorless oil (mixture of the diastereoisomers). IR (neat) $\nu_{\max}$ 3456, 2952, 1740, 1468, 1256, 1100, 836. ¹H NMR δ_{H} (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 δ_{C} (CDCl₃): -5.36 (Si(CH₃)₃), 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 (CI) 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%) **8** as a yellow oil (mixture of the diastereoisomers) (TLC: EtOAc/hexane=1:4, R_f=0.58). IR (neat) $\nu_{\max}$ 2952, 1744, 1464, 1236, 1100, 836. ¹H NMR δ_{H} (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 δ_{C} (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 (CI) calcd for C₁₆H₃₃O₅Si 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, R_f=0.53) to afford 2.69 g (82%) of the product **9** as a colorless oil (mixture of the diastereoisomers). IR (neat) $\nu_{\max}$ 3448, 2952, 1740, 1440, 1240, 1068. ¹H NMR δ_{H} (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 δ_{C} (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, R_f=0.45) to give 3.53 g (71%) of **5** as a yellow oil (mixture of the diastereoisomers). IR (neat) $\nu_{\max}$ 2952, 1740, 1440, 1376, 1236, 1024. ¹H NMR δ_{H} (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 δ_{C} (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 (OCOCH₃), 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 217.1121, found for [M+H⁺] 217.1123.

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, R_f=0.49) to yield 0.8 g (53%) **12** as a yellow oil (mixture of the diastereoisomers). IR (neat) $\nu_{\max}$ 3368, 2952, 1740, 1712, 1680, 1612, 1480, 1280, 748. ¹H NMR δ_{H} (CDCl₃): 0.96 and 0.97 and 1.00 (3H, d, J=7.0 Hz; C19-CH₃), 1.00-1.30 (2H, m; 15-H₂), 1.68 (1H, m; 6-H_A), 1.82-1.94 (1H, m; 14-H), 1.97 and 1.99 (3H, s; OCOCH₃), 1.98-2.10 (1H, m; 6-H_B), 2.40-2.80 (4H, m; 19-H+17-H₂+5-H_A), 2.85-3.08 (2H, m; 5-H_B+3-H), 3.25 and 3.34 and 3.58 (3H, s; C21-OOCH₃), 3.66-3.80 (1H, m; NCH_AH_BPh), 3.80 3H, s; 16-COOCH₃), 4.06-4.15 (1H, m; NCH_ACH_BPh), 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 δ_{C} (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-COOCH₃), 51.43 and 51.57 and 51.79 (16-COOCH₃), 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+C2'+C3'+C4'+C5'+C6'), 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-COOCH₃), 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) calcd 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, R_f=0.61) to afford **13** (0.77 g, 93%) as a yellow oil (mixture of the diastereoisomers). IR (neat) $\nu_{\max}$ 3368, 2952, 1736, 1708, 1676, 1608, 1440, 1244, 748. ¹H NMR δ_{H} (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-H_A), 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-H₂+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-OOCH₃), 3.78 and 3.81 (3H, s; 16-COOCH₃), 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 (CDCl₃): 11.41 and 11.68 and 11.93 (C19-CH₃), 20.97 and 21.22 and 21.24 (OCOCH₃), 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-COOCH₃), 51.94 and 51.99 (C21OOCH₃), 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), 165.11 and 165.21 (C2), 169.08 (16-COOCH₃), 170.56 (OCOCH₃), 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 C₂₄H₃₀N₂O₅ 442.9605, found for [M⁺] 442.9607.

21-Oxo-acetyliboxyphylline (14a) and 21-oxo-20-epi-acetyliboxyphylline (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 CH₂Cl₂ (20 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried (MgSO₄) and the solvent was removed in vacuo. The main components was separated by preparative TLC (eluent: acetone/hexane=1:1) **14** (R_f=0.71). The separation of the stereoisomers was carried out on a semipreparative Waters x-Terra RP₁₈ column (30mm×300mm), 40% MeOH/MeCN and H₂O, 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 (CDCl₃): 1.18 (3H, d, J=6.6 Hz; C19-CH₃), 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-H₂), 1.99+2.81 (2×1H, 2×dm, J=15.5 Hz; 17-H₂), 2.09 (3H, s; OCOCH₃), 2.17 (1H, m; 15-H_A), 2.96 (1H, m; 19-H), 3.75+3.98 (2H, m; 5-H₂), 3.77 (3H, s; OCH₃), 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 (CDCl₃): 11.32 (C18), 21.39 (OCOCH₃), 28.28 (C17), 33.51 (C14), 35.30 (C15), 35.67 (C6), 41.65 (C19), 44.19 (C5), 51.40 (16-COOCH₃), 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-COOCH₃), 170.91 (OCOCH₃), 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 C₂₃H₂₆N₂O₅ 410.4629, found for [M⁺] 410.4630. **14b**: IR (neat) ν_{max} 3264, 2952, 1736, 1700, 1648, 1608, 1436, 1244. ¹H NMR δ_H (CDCl₃): 1.25 (3H, d, J=6.6 Hz; C19-CH₃),

1.54 (1H, dm, $J=15.4$ Hz; 15- H_B), 1.87 (1H, m; 14-H), 1.92 (2H, m; 6- H_B +17- H_B), 2.04 (3H, s; $OCOCH_3$), 2.09 (1H, dm, $J=15.4$ Hz; 15- H_A), 2.27 (1H, m; 6- H_A), 2.71 (1H, dm, $J=15.0$ Hz; 17- H_A), 2.85 (1H, dq, $J=6.6+6.6$ Hz; 19-H), 3.74+3.88 (2 $\times$ 1H, m; 5- H_2), 3.78 (3H, s; OCH_3), 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). ^{13}C NMR δ_C ($CDCl_3$): 14.44 (C18), 21.20 ($OCOCH_3$), 27.59 (C17), 31.41 (C14), 34.25 (C15), 35.62 (C6), 43.83 (C19), 44.18 (C5), 51.29 (16- $COOCH_3$), 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- $COOCH_3$), 170.48 ($OCOCH_3$), 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 $C_{23}H_{26}N_2O_5$ 410.4629, found for $[M^+]$ 410.4626.

($\pm$)-Iboxyphylline (1)

To a solution of **14a** (200 mg, 0.54 mmol) in dry THF (20 mL) at 0°C was added $LiAlH_4$ (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 CH_2Cl_2 (30 mL) and 1M NaOH solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 $\times$ 15 mL) and the combined organic extracts were concentrated and the main component was separated by preparative TLC (eluent: CH_2Cl_2 /MeOH=9:1, $R_f=0.45$) to afford **1** (114 mg, 61%) as a yellow oil. IR (neat) ν_{max} 3384, 2928, 1676, 1608, 1448, 1204, 1104. 1H NMR δ_H ($CDCl_3$): 0.88 (3H, d; $J=7.4$ Hz; C19- CH_3), 1.21-1.38 (2H, m; 15- H_2), 1.81+2.05 (2H, m; 6- H_2), 1.82-1.94 (1H, m; 14-H), 2.24-2.26 (2H, m; 17- H_2), 2.68+3.48 (2H, m; 21- H_2), 2.77+3.53 (2H, m; 5- H_2), 3.62 (1H, d, $J=7.8$ Hz; 3-H), 3.77 (3H, s; 16- $COOCH_3$), 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). ^{13}C NMR δ_C ($CDCl_3$): 11.79 (C18), 28.11 (C17), 35.48 (C14), 33.06 (C15), 40.66 (C6), 44.92 (C19), 50.31 (C5), 51.43 (16- $COOCH_3$), 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- $COOCH_3$). 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 $C_{21}H_{26}N_2O_3$ 354.4427, found for $[M^+]$ 354.4431.

($\pm$)-20-Epiiboxyphylline (15)

To a solution of **14b** (100 mg, 0.27 mmol) in dry THF (15 mL) at 0°C was added $LiAlH_4$ (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 CH_2Cl_2 (20 mL) and 1M NaOH solution (10 mL). The

aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were concentrated and the main component was separated by preparative TLC (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}=9:1$, $R_f=0.46$) to afford **15** (66 mg, 66%) as a yellow oil. IR (neat) ν_{max} 3384, 2936, 1680, 1608, 1452, 1440, 1204, 1108. ^1H NMR δ_{H} (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 δ_{C} (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 $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$ 354.4427, found for $[\text{M}^+]$ 354.4428.

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