A diastereoselective synthesis of (2*S*,5*R*)-5-hydroxypipericolic acid and 6-substituted derivatives

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Supporting Information

General information: Unless noted otherwise, materials were purchased from commercial suppliers and used without purification. Dichloromethane and acetonitrile were freshly distilled from calcium hydride. All air and moisture sensitive reactions were carried out under an inert atmosphere of dry argon. Column chromatography was performed using Acros silica gel (0.035-0.070 mm, 6 nm). TLC was performed using precoated silica gel (60 F254) plates and compounds were detected with UV light or with potassium permanganate. The optical rotation was measured with a Perkin-Elmer 21 polarimeter. Infrared spectra were recorded on an ATI Mattson Genesis FTI, with the splitPea™, Harrick. ¹H NMR and ¹³C NMR spectra were measured on a Bruker AM-300 (300 and 75 MHz, respectively) or a Varian 400 (400 and 100 MHz, respectively). Spectra are reported in units of ppm on the δ scale, relative to chloroform (7.26 ppm for ¹H NMR and 77.0 ppm for ¹³C NMR) or TMS (0.0 for ¹H NMR). ¹H NMR NOESY experiments are measured on a Varian 400 MHz. X-ray data are collected on a Nonius KappaCCD with area detector and ω scan. Mass spectra were measured using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Melting points are uncorrected.

(2*S*)-2-Benzoyloxycarbonylamino-5-[1,3]dioxolan-2-yl-pentanoic acid methyl ester (5)

(*S*)-2-Amino-5-[1,3]dioxolanyl-pentanoic acid **4**¹ (20.0 g, 105.7 mmol) was suspended in dioxane (50 mL) and cooled to 0 °C. A solution of 2N NaOH (53 mL) was slowly added, followed by NaHCO₃ (8.95 g, 106.5 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (Cbz-OSu) (26.8 g, 107.8 mmol). After stirring overnight, the solvent was removed under reduced pressure and a solution of 2.5% NaHCO₃ (500 mL) was added. The unreacted Cbz-OSu was extracted with Et₂O (3 x 100 mL). The aqueous solution was acidified by dropwise addition of 6M HCl (45 mL) to pH = 3 and the product was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*, to yield (*S*)-Cbz-**4** (33.5 g, 98%) as a white solid. To a solution of crude (*S*)-Cbz-**4** (30.5 g, 94.3 mmol) in DMF (100 mL) was added portionwise K₂CO₃ (13.0 g, 94.3 mmol) at 0 °C and the suspension was stirred vigorously at that temperature for 10 min. Then MeI (10.0 mL, 160.6 mmol) was added dropwise and stirring was continued for 2 h at rt. The reaction mixture was quenched by addition of water and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed

with aqueous $\text{Na}_2\text{S}_2\text{O}_5$ (2.5 wt%, 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (heptane:EtOAc = 2:1) yielded **5** (31.0 g, 91.9 mmol, 97%) as a slightly yellow oil. $[\alpha]_D^{20} + 5.9$ (c 1.20, CH_2Cl_2). ^1H NMR (CDCl_3 , 400 MHz) δ 7.18-7.23 (m, 5H), 5.72 (d, $J = 8.4$, 1H), 4.99 (s, 2H), 4.71 (t, $J = 4.5$, 1H), 4.26 (q, $J = 5.1$, 1H), 3.66-3.82 (m, 4H), 3.59 (s, 3H), 1.71-1.78 (m, 1H), 1.52-1.61 (m, 3H), 1.33-1.41 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.6, 155.7, 136.0, 128.0, 127.6, 66.4, 64.4, 53.5, 51.8, 32.8, 31.8, 19.5. IR ν 3330, 2945, 2876, 1717, 1518, 1454, 1432, 1212, 1134, 1043, 1030, 741, 697. HRMS (FAB⁺): calcd for $\text{C}_{17}\text{H}_{24}\text{O}_6\text{N}$ ($M+\text{H}^+$): 338.1604, found: 338.1605.

(2S,3,4-Dihydro-2H-pyridine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (6))

To a solution of **5** (5.0 g, 14.8 mmol) in toluene (50 mL) were added DMF (0.57 mL, 7.4 mmol) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.28 g, 1.48 mmol) and the reaction was stirred at 115 °C for 2 h. After cooling to room temperature the mixture was diluted with EtOAc (50 mL), washed with an aqueous saturated NaHCO_3 solution (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (heptane:EtOAc = 5:1→3:1) yielded **6** (4.0 g, 14.5 mmol, 98%) as a yellowish oil. $[\alpha]_D^{20} -29.8$ (c 0.75, CH_2Cl_2). ^1H NMR (CDCl_3 , 400 MHz, rotamers) δ 7.30-7.37 (m, 5H), 6.95 and 6.85 (2 x d, $J = 8.4$, 1H), 5.13-5.25 (m, 2H), 4.86-4.99 (m, 2H), 3.72 and 3.65 (2 x s, 3H), 2.31-2.38 (m, 1H), 1.85-2.00 (m, 3H). ^{13}C NMR (CDCl_3 , 100 MHz, rotamers) δ 171.4, 171.2, 153.2, 153.1, 136.0, 135.9, 128.4, 128.4, 128.1, 127.9, 127.8, 124.4, 124.1, 105.6, 105.3, 67.8, 67.8, 67.5, 67.5, 54.0, 53.6, 52.3, 52.3, 23.4, 23.3, 18.4, 18.2. IR ν 2950, 1748, 1701, 1653, 1407, 1333, 1299, 1199, 1070, 1044, 698. HRMS (FAB⁺): calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{N}$ ($M+\text{H}^+$): 276.1236, found: 276.1231.

(2S, 5R, 6R*)-5-Hydroxy-6-methoxy-piperidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (7)

To a suspension of Oxone® (11.3 g, 18.5 mmol) and NaHCO_3 (1.8 g, 21.2 mmol) in MeOH (28 mL) was added dropwise a solution of **6** (3.90 g, 14.2 mmol) in MeOH (28 mL) and the mixture was stirred overnight at room temperature. After removal of the solids by filtration, the remaining filtrate was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with an aqueous saturated NaHCO_3 solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (heptane:EtOAc:Et₃N = 1:1:0.05) yielded **7** (4.12 g, 12.7 mmol, 90%) as a colorless oil. ^1H NMR (CDCl_3 , 300 MHz, rotamers) δ 7.32-7.35 (m, 5H), 5.10-5.31 (m, 3H), 4.77-4.92 (m, 1H), 3.86-3.93 (m, 1H), 3.71 and 3.68 (2 x s, 3H), 3.37 and 3.27 (2 x s, 3H), 1.99-2.18 (m, 3H), 1.57-1.60 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz, rotamers) δ 171.8, 157.1, 156.6, 136.1, 136.0, 128.4, 128.4, 128.2, 128.0, 127.9, 127.7, 85.8, 85.5, 67.9, 67.7, 66.0, 65.9, 56.6, 56.1, 51.9, 51.2, 50.6, 22.5, 22.3, 18.5, 18.3. IR ν 3460, 2946, 1735, 1700, 1442, 1411, 1295, 1203, 1087, 1014, 957, 707. HRMS (FAB⁺): calcd for $\text{C}_{16}\text{H}_{21}\text{O}_6\text{N}$ ($M+\text{H}^+$): 324.1447, found: 324.1449.

(2S, 5R, 6R*)-5-Acetoxy-6-methoxy-piperidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (8)

To a solution of **7** (1.05 g, 3.25 mmol) in CH_2Cl_2 (20 mL) were added Et₃N (0.59 mL, 4.22 mmol), Ac₂O (0.37 mL, 3.90 mmol) and DMAP (40 mg, 0.32 mmol) and the resulting mixture was stirred for 1 h at room temperature. The organic phase was washed with an aqueous saturated NaHCO_3 solution (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (heptane:EtOAc:Et₃N = 3:1:0.05) yielded **8** (1.17 g, 3.22 mmol, 99%) as a colorless oil. ^1H NMR (CDCl_3 , 400 MHz, rotamers) δ 7.32-7.38 (m, 5H), 5.15-5.36 (m, 3H), 4.78-4.95 (m, 2H), 3.71 and 3.68 (2 x s, 3H), 3.37 and 3.28 (2 x s, 3H), 2.07-2.18 (m, 2H), 2.02 and 1.92 (2 x s, 3H), 1.88-1.98 (m, 1H), 1.62-1.68 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz, rotamers) δ 171.7, 171.7, 170.0, 170.0, 156.5, 156.1, 136.3, 136.2, 128.5, 128.5, 128.2, 128.1, 127.9, 127.7, 82.8, 82.7, 68.0, 68.0, 67.8, 67.6, 56.2, 52.0, 51.9, 51.1, 50.4, 21.0, 20.9, 20.3, 20.0, 19.3,

19.1. IR ν 2946, 1735, 1705, 1411, 1303, 1234, 1221, 1087, 1061, 1022. HRMS (FAB⁺): calcd for C₁₈H₂₄O₇N ($M+H^+$): 366.1553, found: 366.1561.

General procedure for *N*-acyliminium ion reactions:

A solution of **8** and TMS-nucleophile (5 equiv.) in MeCN (0.1M) was cooled to -30 °C and either Sn(OTf)₂ (10 mol%) or BF₃·OEt₂ (2 equiv.) was added. The mixture was kept at -30 °C for 30 min after which the reaction was stirred at room temperature for the indicated period. The progress was monitored with TLC and when completed, the reaction was diluted with EtOAc and quenched by addition of an aqueous saturated NaHCO₃ solution. The aqueous phase was isolated and extracted twice with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*.

General procedure for Cbz removal with Pd/C under hydrogen pressure

A suspension of the Cbz-protected amine and 10% Pd/C (10 mol% Pd) in the indicated solvent (0.05M) was stirred under hydrogen pressure (balloon). After stirring for the indicated period, the reaction mixture was filtered over Celite and the solvent was evaporated under pressure.

(2*S*, 5*R*)-5-Hydroxy-piperidine-2-carboxylic acid hydro chloride (**1**)

7 (200 mg, 0.62 mmol) was treated with Pd/C and hydrogen gas in MeOH for 1.5 h, according to the general procedure for Cbz removal. The crude product was purified by column chromatography (MeOH:EtOAc = 1:20→1:3) yielding the liberated amine (96 mg, 0.60 mmol, 97%). Refluxing the methyl ester (50 mg, 0.31 mmol) in 6M HCl (2 mL) for 2.5 h provided **1** (57 mg, 0.31 mmol, 100%) as a 96:4 mixture of diastereomers after removal of the solvent. Precipitation from aqueous acetone yielded diastereomerically pure **7** as a white solid. M.p. 212-215 °C. $[\alpha]_D^{20}$ -10.8 (*c* 0.31, H₂O) {*lit.*² $[\alpha]_D^{20}$ -10.9 (*c* 1.0, H₂O)}. Spectral data identical to the data reported in literature.^{2,3}

(2*S*, 5*R*, 6*S*)-5-Acetoxy-6-propyl-piperidine-2-carboxylic acid methyl ester (**9a**)

With allyltrimethylsilane: Reaction of **8** (100 mg, 0.27 mmol) in the presence of allyltrimethylsilane and Sn(OTf)₂ for 4 h according to the general procedure for *N*-acyliminium ion reactions. The crude product was treated with Pd/C under hydrogen pressure in EtOAc for 1.5 h, according to the general procedure for Cbz removal and the product was purified by column chromatography (heptane:EtOAc = 3:1) to yield **9a** (54 mg, 0.22 mmol, 82%) as a colorless oil.

With propargyltrimethylsilane: Reaction of **8** (70 mg, 0.19 mmol) in the presence of propargyltrimethylsilane and BF₃·OEt₂ for 5 h according to the general procedure for *N*-acyliminium ion reactions. The crude product was treated with Pd/C under hydrogen pressure in MeOH for 4 h, according to the general procedure for Cbz removal and the product was purified by column chromatography (heptane:EtOAc = 3:1) to yield **9a** (41 mg, 0.17 mmol, 90%) as a colorless oil. $[\alpha]_D^{20}$ -73.1 (*c* 1.45, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 4.38-4.45 (m, 1H), 3.73 (s, 3H), 3.36 (dd, *J* = 11.5, 2.8, 1H), 2.57-2.62 (m, 1H), 2.16-2.22 (m, 1H), 2.05-2.11 (m, 1H), 2.05 (s, 3H), 1.86 (br s, 1H), 1.26-1.62 (m, 6H), 0.92 (t, *J* = 7.0, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 172.9, 170.2, 73.4, 58.7, 58.1, 51.9, 34.2, 30.0, 28.5, 21.0, 18.5, 14.0. IR ν 3468, 2954, 2867, 1730, 1432, 1372, 1233, 1034. HRMS (FAB⁺): calcd for C₁₂H₂₂O₄N ($M+H^+$): 244.1549, found: 244.1547.

(2*S*, 5*R*, 6*S*)-**9a**

A ¹H NMR NOESY experiment showed a strong spatial relationship between proton H² and H⁶.

(2*S*, 5*R*, 6*S*)-Acetoxy-6-cyano-piperidine-2-carboxylic acid methyl ester and (2*S*, 5*R*, 6*R*)-5-Acetoxy-6-cyano-piperidine-2-carboxylic acid methyl ester (9b)

Reaction of **8** (100 mg, 0.27 mmol) in the presence of TMS-CN and Sn(OTf)₂ for 18 h according to the general procedure for *N*-acyliminium ion reactions. The crude product was treated with Pd/C under hydrogen pressure in EtOAc for 3 h, according to the general procedure for Cbz-removal and the product was purified by column chromatography (heptane:EtOAc = 2:1) to yield **(2*S*, 5*R*, 6*R*)-9b** (20 mg, 0.09 mmol, 32%) and **(2*S*, 5*R*, 6*S*)-9b** (35 mg, 0.16 mmol, 57%) as waxy solids. **(2*S*, 5*R*, 6*R*)-9b**: [α]_D²⁰ +79.6 (*c* 0.50, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 4.77-4.83 (m, 1H), 4.47 (d, *J* = 4.9, 1H), 3.77 (s, 3H), 3.66 (dd, *J* = 11.4, 2.8, 1H), 2.3-2.7 (br s, 1H), 2.18-2.24 (m, 1H), 2.11 (s, 3H), 2.10-2.14 (m, 1H), 1.79-1.90 (m, 1H), 1.58-1.69 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 171.6, 170.0, 116.7, 68.1, 53.6, 52.4, 49.8, 26.4, 26.3, 20.9. IR ν 3343, 2950, 1735, 1442, 1368, 1230, 1048. HRMS (FAB⁺): calcd for C₁₀H₁₅O₄N₂ (*M*+H⁺): 227.1032, found: 227.1031. **(2*S*, 5*R*, 6*S*)-9b**: [α]_D²⁰ -29.1 (*c* 0.31, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 4.81-4.88 (m, 1H), 3.77 (s, 3H), 3.72 (d, *J* = 9.2, 1H), 3.38 (dd, *J* = 10.5, 3.1, 1H), 2.29-2.35 (m, 1H), 2.09-2.15 (m, 1H), 2.11 (s, 3H), 1.64-1.75 (m, 1H), 1.42-1.52 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ 171.3, 169.6, 117.2, 69.7, 56.7, 52.4, 50.4, 28.7, 26.4, 20.9. IR ν 3312, 2950, 2924, 1735, 1441, 1372, 1230, 1053. HRMS (FAB⁺): calcd for C₁₀H₁₅O₄N₂ (*M*+H⁺): 227.1032, found: 227.1034.

(2*S*, 5*R*, 6*S*)-9b

A ¹H NMR NOESY experiment showed a strong spatial relationship between proton H² and H⁶.

(2*S*, 5*R*, 6*R*)-9b

A ¹H NMR NOESY experiment showed a strong spatial relationship between proton H⁵ and H⁶.

(2*S*, 5*R*, 6*S*)-5-Acetoxy-6-(2-oxo-2-phenyl-ethyl)-piperidine-2-carboxylic acid methyl ester (9c)

8 (100 mg, 0.27 mmol) was stirred for 18 h in the presence of the 1-phenyl-1-(trimethylsilyloxy)ethylene and Sn(OTf)₂ (20 mol%) according to the general procedure for *N*-acyliminium ion reactions. Purification by column chromatography (heptane:EtOAc = 3:1→1:1) yielded **9c** (120 mg, 0.26 mmol, 97%) as a colorless oil, which was treated with Pd/C and hydrogen pressure in MeCN for 1 h according to the general procedure for Cbz removal. The reaction was stopped before full conversion was reached to prevent reduction of the acetophenone carbonyl. Purification by column chromatography (heptane:EtOAc = 2:1→1:2) yielded **9c** (72 mg, 0.22 mmol, 82%, (92% based on recovered starting material)) as a glassy solid. [α]_D²⁰ -80.8 (*c* 0.25, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 7.94 (d, *J* = 7.4, 2H), 7.56-7.60 (m, 1H), 7.44-7.50 (m, 2H), 4.56-4.62 (m, 1H), 3.72 (s, 3H), 3.49 (dd, *J* = 11.5, 2.7, 1H), 3.26-3.33 (m, 2H), 3.02-3.10 (m, 1H), 2.71 (br s, 1H), 2.22-2.29 (m, 1H), 2.10-2.16 (m, 1H), 2.00 (s, 3H), 1.60-1.70 (m, 1H), 1.42-1.52 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ 198.8, 172.7, 170.3, 136.7, 133.4, 128.7, 128.0, 72.8, 58.1, 55.7, 52.1, 41.0, 30.0, 27.8, 21.1. IR ν 3343, 2954, 2846, 1731, 1675, 1446, 1372, 1295, 1238, 1035. HRMS (FAB⁺): calcd for C₁₇H₂₂O₅N (*M*+H⁺): 320.1498, found: 320.1489.

(3*S*, 6*R*)-{6-[Bis-(2,4-dimethoxy-phenyl)-methyl]-2-oxo-tetrahydro-pyran-3-yl}-carbamic acid benzyl ester (10)

A solution of **7** (200 mg, 0.62 mmol) and 1,3-dimethoxybenzene (0.41 mL, 3.10 mmol) was reacted with BF₃·OEt₂ for 3 h according to the general procedure for *N*-acyliminium ion reactions. Purification by column chromatography (heptane:EtOAc = 2:1) yielded **10** (166 mg, 0.31 mmol, 50%) as a colorless oil.

$[\alpha]_D^{20} +9.7$ (*c* 0.38, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz, rotamers) δ 7.24-7.37 (m, 7H), 6.39-6.44 (m, 4H), 5.53 (br s, 1H), 5.08-5.514 (m, 3H), 4.87 (d, *J* = 7.4, 1H), 4.05-4.10 (m, 1H), 3.73-3.76 (m, 12H), 2.40-2.44 (m, 1H), 1.72-1.94 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz, rotamers) δ 159.2, 159.2, 158.3, 157.9, 136.1, 129.8, 129.7, 128.6, 128.5, 128.1, 128.1, 122.2, 120.9, 104.2, 104.1, 98.9, 98.8, 83.6, 67.0, 55.6, 55.2, 55.2, 51.7, 41.1, 26.8. IR ν 3401, 3000, 2957, 2832, 1741, 1703, 1612, 1586, 1500, 1293, 1207, 1777, 1034, 914, 729. HRMS (FAB⁺): calcd for C₃₀H₃₄O₈N (*M*+H⁺): 536.2284, found: 536.2274.

(2*S*, 5*R*)-5-Acetoxy-2-benzyloxycarbonylamino-6,6-bis-(2,4-dimethoxy-phenyl)-hexanoic acid methyl ester (11)

A solution of **8** (55 mg, 0.15 mmol) and 1,3-dimethoxybenzene (0.20 mL, 1.5 mmol) was reacted with BF₃·OEt₂ in CH₂Cl₂ (0.1M) for 2 h according to the general procedure for *N*-acyliminium ion reactions. Purification by column chromatography (heptane:EtOAc = 3:1→1:1) yielded **11** (86 mg, 0.14 mmol, 94%) as a colorless oil. $[\alpha]_D^{20} +41.1$ (*c* 1.10, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 7.30-7.36 (m, 6H), 7.03 (d, *J* = 8.4, 1H), 6.33-6.44 (m, 4H), 5.72 (m, 1H), 5.21-5.25 (m, 1H), 5.07 (s, 2H), 4.83 (d, *J* = 9.03, 1H), 4.23-4.28 (m, 1H), 3.78, 3.76, 3.73, 3.71 and 3.64 (5 x s, 15H), 1.81-1.91 (m, 1H), 1.81 (s, 3H), 1.56-1.67 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 172.6, 170.7, 159.2, 159.0, 158.3, 158.0, 155.7, 136.2, 129.8, 129.4, 128.4, 128.0, 128.0, 122.0, 121.8, 98.6, 74.4, 66.8, 55.5, 55.4, 55.1, 53.9, 52.2, 39.7, 30.8, 28.6, 28.1. IR ν 3347, 2945, 2833, 1722, 1606, 1580, 1506, 1454, 1290, 1234, 1212, 1035, 732. HRMS (FAB⁺): calcd for C₃₃H₄₀O₁₀N (*M*+H⁺): 610.2652, found: 610.2646.

(2*S*, 5*R*, 6*R)-5-(3,5-Dimethoxy-benzyloxy)-6-methoxy-piperidine-1,2-(*S*)-dicarboxylic acid 1-benzyl ester 2-methyl ester (12)**

To a solution of **7** (500 mg, 1.58 mmol) in DMF (25 mL) was added NaH (69 mg of a 60% disp. in min. oil, 1.74 mmol) at 0 °C and the mixture was stirred for 15 min before 3,5-dimethoxybenzyl bromide (572 mg, 2.48 mmol) and (^tBu)₄NI (29 mg, 79 μ mol) were added. The mixture was stirred for 18 h at room temperature before the reaction was diluted with EtOAc (50 mL) and washed with an aqueous saturated NaHCO₃ solution (50 mL), brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (heptane:EtOAc:Et₃N = 4:1:0.05) yielded **12** (449 mg, 0.95 mmol, 60%) as a colorless oil. ¹H NMR (CDCl₃, 400 MHz, rotamers) δ 7.29-7.35 (m, 5H), 6.37-6.49 (m, 3H), 5.10-5.51 (m, 3H), 4.75-4.95 (m, 1H), 4.44-4.58 (m, 2H), 3.67, 3.70, 3.70, 3.73, 3.73, 3.75, 3.78 and 3.79 (8 x s, 9H), 3.53-3.60 (m, 1H), 3.27 and 3.37 (2 x s, 3H), 1.94-2.17 (m, 3H), 1.65-1.73 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz, rotamers) δ 171.6, 171.6, 160.4, 156.3, 156.0, 140.4, 140.3, 136.1, 135.9, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 105.1, 104.8, 99.5, 99.3, 83.4, 82.8, 72.9, 72.9, 7-.7, 70.4, 67.7, 67.5, 56.5, 56.0, 55.3, 55.2, 51.9, 51.9, 51.5, 50.8, 21.0, 20.5, 19.4, 19.2. IR ν 2940, 2832, 1739, 1704, 1592, 1449, 1432, 1411, 1294, 1203, 1156, 1091, 1061, 697. HRMS (FAB⁺): calcd for C₂₅H₃₂O₈N (*M*+H⁺): 474.2128, found: 474.2139.

(3*S*, 4*aR*, 10*aR*)-5,7-Dimethoxy-1,3,4,4a,9,10a-hexahydro-2H-10-oxa-4-aza-phenanthrene-3-carboxylic acid methyl ester (14)

A solution of **12** (100 mg, 0.21 mmol) in CH₂Cl₂ (4.2 mL) was cooled to 0 °C and Sn(OTf)₂ (9.0 mg, 21 μ mol) was added. After stirring for 1.5 h at 0 °C the reaction was quenched by addition of a few drops of Et₃N and the solvent was removed *in vacuo*. The reaction was stopped before full conversion was reached to prevent degradation of the product. Purification by column chromatography (heptane:EtOAc:Et₃N = 3:1:0.05) **13** (60 mg, 0.14 mmol, 66% (83% based on recovered starting material)) as a colorless oil. The Cbz-group was removed by treatment with Pd/C under hydrogen pressure in EtOAc for 1.5 h according to the general procedure in a quantitative manner to yield **14** as a colorless oil. $[\alpha]_D^{20} -94.9$ (*c* 1.75, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 6.31 (d, *J* = 2.2, 1H), 6.14 (d, *J* = 2.2, 1H), 4.90 (AB d, *J* = 15.2, H), 4.75

(AB d, $J = 15.2$, 1H), 3.99-4.01 (m, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.75-3.78 (m, 1H), 3.56-3.60 (m, 1H), 2.49 (br s, 1H), 2.12-2.22 (m, 1H), 1.98-2.04 (m, 2H), 1.77-1.86 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.6, 159.9, 158.5, 136.5, 117.3, 99.5, 96.7, 71.4, 68.6, 55.4, 55.3, 55.3, 51.7, 45.1, 26.4, 20.9. IR ν 3347, 3205, 2950, 2837, 1735, 1601, 1493, 1459, 1429, 1225, 1195, 1148, 1113, 1053, 827. HRMS (FAB^+): calcd for $\text{C}_{16}\text{H}_{22}\text{O}_5\text{N}$ ($M+\text{H}^+$): 308.1498, found: 308.1502.

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¹H NMR spectra of compounds **1**, **5**, **6**, **7**, **8**, **9a-c**, **10**, **11**, **12** and **14**.