

Supporting Information

Stereoselective Synthesis of (2*R*,3*R*,4*S*)-4,7-Diamino-2,3-dihydroxyheptanoic acid : A Novel Amino Acid of Callipeltins A and D

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General Methods. Materials were obtained from commercial suppliers and were used without further purification. Methylene chloride was distilled from calcium hydride immediately prior to use. Likewise, THF and benzene were distilled from sodium benzophenone ketyl. DMF and MeOH were dried with molecular sieves (4 Å). Air or moisture sensitive reactions were conducted under nitrogen atmosphere using oven-dried glassware and the standard syringe/septa technique. The reactions were monitored with a SiO₂ TLC plate under UV light (254 nm) followed by visualization with a molybdenum or a ninhydrin stain solution. Column chromatography was performed on silica gel 60 (70-230 mesh). Optical rotations were determined at ambient temperature with a digital polarimeter and are the average of five measurements. Films for IR were spin-coated on IR transparent silicon wafers. ¹H NMR spectra were measured at 300 MHz in CDCl₃ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, coupling constant in Hz, integration). ¹³C NMR spectra were measured at 75 MHz in CDCl₃ unless stated otherwise and data were reported in ppm (δ) from the internal standard (TMS, 0.0 ppm).

S-Ethyl**(S)-5-(Benzyloxycarbonyl)amino-2-(tert-**

butoxycarbonyl)aminopentanethioate (5). To a solution of acid **2** (1.099 g, 3.00 mmol) in dry DCM (10 mL) at 0 °C were added i-butylchloroformate (0.47 mL, 3.3 mmol) and triethylamine (0.36 mL, 3.0 mmol). After 5 min, EtSH (0.49 mL, 6.6 mmol) and triethylamine (0.36 mL, 3.0 mmol) were added. The mixture was stirred for another 15 min at 0 °C. The resulting mixture was washed with water (15 mL x 2) and the aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give thioester **5** (1.139 g, quantitative) as white solid. $[\alpha]_D^{22}$ -13.7 (*c* 1.12, CHCl₃); IR (film on a silicon wafer) 3369, 3335, 1705, 1701, 1697 cm⁻¹; ¹H NMR δ 1.24 (t, *J* = 7.4, 3H), 1.45 (s, 9H), 1.52-1.67 (m, 3H), 1.79-1.96 (m, 1H), 2.87 (q, *J* = 7.4, 2H), 3.21 (q, *J* = 6.1, 2H), 4.27-4.38 (m, 1H), 4.87 (br s, 1H), 5.05 (br s, 1H), 5.09 (s, 2H), 7.29-7.36 (m, 5H); ¹³C NMR δ 14.5, 23.2, 26.0, 28.3, 29.9, 40.5, 60.2, 66.6, 80.2, 128.1, 128.5, 136.5, 155.2, 156.5, 201.4; HRMS (CI) calcd for C₂₀H₃₁N₂O₅S (M⁺ + 1) 411.1954, found 411.1952; Anal. Calcd for C₂₀H₃₀N₂O₅S, C:58.51, H:7.37, N:6.82, S:7.81. Found C:58.29, H:7.23, N:6.74, S:7.62.

S-Ethyl (S)-5-(N-Benzyloxycarbonyl-N-tert-butoxycarbonyl)amino-2-(tert-butoxycarbonyl)aminopentanethioate (6a). To a solution of thioester **5** (0.574 g, 1.40 mmol) in MeCN (10 mL) at 0 °C were added Boc anhydride (0.350 g, 1.6 mmol), triethylamine (0.40 mL, 2.8 mmol) and DMAP (0.016 g, 0.14 mmol). The reaction mixture was stirred for 12 h. Then, additional Boc anhydride (0.122 g, 0.56 mmol) was added and the resulting mixture was stirred until the starting material disappeared. The reaction was quenched by adding a sat. aq. NH₄Cl solution (10 mL) and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 16:1) to give compound both **6a** (0.483 g, 68%) and **6b** (0.176 g, 21%) as colorless oil. **6a**: $[\alpha]_D^{22}$ -6.23 (*c* 0.80, CHCl₃); IR (film on a silicon wafer) 3369, 1719, 1706, 1701, 1696 cm⁻¹; ¹H NMR δ 1.24 (t, *J* = 7.4, 3H), 1.45 (s, 9H), 1.46 (s, 9H), 1.54-1.63 (m, 3H), 1.77-1.91 (m, 1H), 2.86 (q, *J* = 7.4, 2H), 3.65 (t, *J* = 7.0, 2H), 4.26-4.37 (m, 1H), 4.97 (d, *J* = 8.8, 1H), 5.22 (s, 2H), 7.31-7.41 (m, 5H); ¹³C NMR δ 14.5, 23.2, 24.9, 27.9, 28.3, 29.9, 45.9, 60.2, 68.4, 80.2, 83.0, 128.3, 128.4, 128.6, 135.5, 152.0, 153.8, 155.2, 201.2; HRMS (CI) calcd for C₂₅H₃₉N₂O₇S (M⁺ + 1) 511.2479, found 511.2463.

Methyl (2*R*,3*R*,4*S*)-7-(Benzyloxycarbonyl)amino-4-(diphenylmethylene)amino-2,3-*O*-isopropylidenedioxyheptanoate (10). To a solution of the crude diol **8** (116 mg, 0.230 mmol) in benzene (35 mL) was added 2,2-dimethoxypropane (5 mL, 40.33 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 12 mg, 0.046 mmol). The mixture was heated under reflux with a Dean-Stark apparatus for 3 h. After cooling the resulting solution, the solvent was evaporated under reduced pressure. The resulting mixture was dissolved in Et₂O (10 mL), and the resulting solution was washed with a sat. aq. NaHCO₃ solution (10 mL x 2). The organic layer was dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to give compound **10** as pale yellow oil (94 mg, 75%). ¹H NMR δ 1.11-1.23 (m, 1H), 1.36 (s, 3H), 1.41-1.54 (m, 1H), 1.62 (s, 3H), 1.58-1.72 (m, 2H), 2.81-2.92 (m, 1H), 3.00-3.09 (m, 1H), 3.33 (s, 3H), 3.32-3.38 (m, 1H), 4.49 (dd, *J* = 9.2, 6.3, 1H), 4.57 (d, *J* = 6.3, 1H), 4.85 (br s, 1H), 5.07 (s, 2H), 7.22-7.42 (m, 13H), 7.59-7.62 (m, 2H); ¹³C NMR δ 25.8, 26.0, 26.4, 29.4, 40.0, 51.7, 61.0, 66.5, 76.6, 80.4, 111.1, 127.97, 128.01, 128.04, 128.1, 128.2, 128.5, 128.75, 128.78, 130.0, 136.7, 136.9, 139.9, 156.3, 169.4, 171.3; HRMS (CI) calcd for C₃₂H₃₇N₂O₆ (M⁺ + 1) 545.2652, found 545.2656.

(3*R*,4*R*,5*S*)-5-(3-(*tert*-Butoxycarbonyl)amino)propyl-3,4-

isopropylidenedioxypyrrolidin-2-one (11 *cis*). To a solution of ester **10** (45 mg, 0.082 mmol) in MeCN (1.5 mL) were added Boc₂O (30 mg, 0.137 mmol) and DMAP (28 mg, 0.228 mmol). The reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with a sat. aq. NH₄Cl solution (5 mL) and the aqueous layer was extracted with DCM (5 mL x 2). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to give the Boc protected product (49 mg, 93%) at the terminal amine of **10**. Then the purified product was dissolved in MeOH (10 mL) and 10% Pd/C (50 mg) and HCO₂NH₄ (55 mg, 0.872 mmol) were sequentially added to the solution of MeOH. The mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and then filtered through a Celite pad that was rinsed with Et₂O (10 ml x 2). The filtrate was evaporated under reduced pressure to give the crude product that was purified by silica gel column chromatography (hexane:EtOAc = 1:4) to give pure **11 *cis*** as colorless oil (23 mg, 89%). [α]_D¹⁵ -11.9 (*c* 0.32, CHCl₃); IR (film on a silicon wafer) 3410, 3321, 3266, 1711, 1701, 983, 953 cm⁻¹; ¹H NMR (measured at 333K, deuterated with D₂O) δ 1.38 (s, 3H), 1.44 (s, 9H), 1.46 (s, 3H), 1.56-1.68 (m, 4H), 3.12-3.22

(m, 2H), 3.61-3.67 (m, 1H), 4.59 (d, $J = 5.6$, 1H), 4.66 (dd, $J = 5.6$, 4.6, 1H); ^{13}C NMR δ 26.1, 26.4, 27.0, 27.1, 28.4, 40.2, 54.8, 76.1, 77.8, 79.3, 112.7, 156.1, 174.2; HRMS (CI) calcd for $\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_5$ ($\text{M}^+ + 1$) 315.1921, found 315.1919.

(3*S*,4*S*,5*S*)-5-(3-(*tert*-Butoxycarbonyl)amino)propyl-3,4-

isopropylidenedioxypyrrolidin-2-one (11** *trans*).**¹⁵ $[\alpha]_{\text{D}}^{15} +5.71$ (c 0.46, CHCl_3); IR (film on a silicon wafer) 3412, 3325, 3288, 1706, 1701, 982, 956 cm^{-1} ; ^1H NMR δ 1.37 (s, 3H), 1.44 (s, 9H), 1.47 (s, 3H), 1.51-1.65 (m, 4H), 3.05-3.25 (m, 2H), 3.60-3.70 (m, 1H), 4.42 (d, $J = 5.8$, 1H), 4.61 (d, $J = 5.8$, 1H), 4.66 (br s, 1H), 7.18 (s, 1H); ^{13}C NMR δ 25.6, 26.3, 27.0, 28.4, 32.2, 40.0, 58.0, 76.5, 79.4, 79.6, 112.7, 156.1, 174.0; HRMS (CI) calcd for $\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_5$ ($\text{M}^+ + 1$) 315.1921, found 315.1917.







































