

ELECTRONIC SUPPLEMENTARY INFORMATION

Construction of macrocyclic thiodepsipeptides:

Synthesis of a nosiheptide 'southern hemisphere' model system

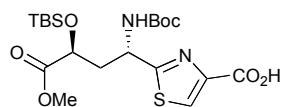
Marc C. Kimber and Christopher J. Moody

EXPERIMENTAL DETAILS FOR KEY COMPOUNDS

General

Commercially available reagents and solvents were used throughout without further purification, except tetrahydrofuran, dichloromethane and diethyl ether, which were freshly distilled. Light petroleum refers to the fraction with bp 40-60 °C. Thin layer chromatography was carried out on Merck Kieselgel 60 GF₂₅₄ aluminum foil backed plates. The plates were visualized under UV light or by vanillin stain. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrix silica 60, with the eluent specified. IR spectra were recorded using Perkin Elmer 1600 series FTIR spectrometer as solutions using chloroform as solvent. ¹H and ¹³C NMR spectra were recorded using Jeol EX270, Bruker AV400 and DRX500 machines (¹H frequencies 270, 400 and 500 MHz, ¹³C frequencies 75, 100 and 125 MHz respectively); chemical shifts are quoted in ppm. In the ¹³C spectra, signals corresponding to C, CH, CH₂ or CH₃ groups, as assigned from DEPT, are noted. High and low resolution mass spectra were carried out on a Bruker MicroTof high resolution mass spectrometer.

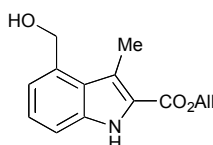
2-((5*S*,7*S*)-[3-(Methoxycarbonyl)-3-*tert*-butyldimethylsiloxy-1-*tert*-butoxycarbonylamino]propyl)thiazole-4-carboxylic acid **6**



To a solution of (2*S*,4*S*)-4-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethylsilyloxy)-4-methoxycarbonylbutanamide **5** (1.57 g, 4.02 mmol) in THF (130 mL) was added Lawsesson's reagent (0.82 g, 2.01 mmol) and the resultant solution stirred for 16 h under a nitrogen atmosphere. After this period the solvent was removed under reduced pressure and the residue purified by chromatography (2:1 light petroleum : ethyl acetate) yielding the thioamide as a white foam (1.32 g, 81 %) that was used immediately. To a solution of the thioamide (1.32 g, 3.25 mmol) in dry ethanol (60 mL) was added 3-bromopyruvic acid (0.79 g, 4.71 mmol) followed by CaCO₃ (0.95 g, 9.42 mmol) and the suspension stirred under nitrogen for 16 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with hydrochloric acid (1 M; 100 mL). The aqueous was then extracted with further ethyl acetate (100 mL) and the combined organic layers washed with brine (150 mL). The organic layer was then dried with Na₂SO₄, filtered and the solvent removed under reduced pressure. The resulting oil was then purified by chromatography (4:1, 3:2, 2:3, 1:4 light petroleum : ethyl acetate) yielding the title compound **6** as a white foam (0.89 g, 57 %); [α]_D²¹ = -28.0 (*c* 1.00, CHCl₃); [Found (ES): MNa⁺, 497.1754. C₂₀H₃₄N₂NaO₇SSi requires 497.1742]; IR (solution, CHCl₃) 3427, 3124, 2954, 2930, 2858, 1757, 1703, 1491, 1461, 1392, 1367, 1345, 1097, 1068, 1002, 906, 868, 839, 640 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.20 (1H, s), 5.96 (1H, d, *J* = 7.5 Hz), 5.17 (1H, s), 4.41 – 4.38 (2H, m), 3.69 (3H, s), 2.44 – 2.40 (2H, m), 1.38 (9H, s), 0.92 (9H, s), 0.05 (6H, s); ¹³C NMR (125 MHz; CDCl₃) δ 174.52 (C), 173.34 (C), 164.16 (C),

155.33 (C), 146.56 (C), 128.91 (CH), 80.38 (C), 69.50 (CH), 52.18 (CH₃), 50.29 (CH), 38.69 (CH₂), 28.31 (CH₃), 25.75 (CH₃), 18.14 (C), -5.04 (CH₃), -5.46 (CH₃).

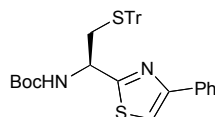
Allyl 4-hydroxymethyl-3-methyl-1*H*-indole-2-carboxylate **10**



A solution of allyl 3-methyl-4-(tetrahydro-2*H*-pyran-2-yloxy)methyl-1*H*-indole-2-carboxylate (463 mg, 1.407 mmol) and PPTS (35 mg, 0.140 mmol) in ethanol (40 mL) was heated to 55 °C for 2 h. The reaction mixture was cooled to room temperature diluted with ethyl acetate (60 mL) and washed with brine (50 mL). The aqueous was then further extracted with ethyl acetate (20.00 mL) and the combined organic extracts then dried with Na₂SO₄, filtered and the solvent removed under reduced pressure. The resulting solid was then purified by chromatography (8:2, 7:3, 6:4, 1:1, 4:6 light petroleum : ethyl acetate) yielding the title compound **10** as a colourless crystalline solid (300 mg, 87%); mp 136 - 138 °C; [Found (ES): MNa⁺, 268.0933. C₁₄H₁₅NNaO₃ requires 268.0950]; IR (solution, CHCl₃) 3605, 3462, 2932, 2890, 1714, 1693, 1383, 1341, 1022, 1077, 992 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.81 (1H, bs), 7.31 (1H, dd, *J* = 1.0, 8.5 Hz), 7.26 (1H, dd, *J* = 7.0, 8.5 Hz), 7.10 (1H, dd, *J* = 1.0, 7.0 Hz), 6.06 (1H, dddd, *J* = 5.5, 5.5, 10.5, 17.5 Hz), 5.43 (1H, ddd, *J* = 1.5, 1.5, 17.5 Hz), 5.31 (1H, ddd, *J* = 1.0, 1.0, 10.0 Hz), 5.07 (2H, s), 4.86 (2H, dt, *J* = 1.5, 5.5 Hz), 2.85 (3H, s); ¹³C NMR (125 MHz; CDCl₃) δ 162.17 (C), 136.61 (C), 135.59 (C), 132.17 (CH), 125.96 (C), 125.50 (CH), 123.38 (C), 121.00 (C), 120.40 (CH), 118.66 (CH₂), 112.07 (CH), 65.39 (CH₂), 63.78 (CH₂), 11.95 (CH₃); (Found: C, 68.42; H, 6.16; N, 5.94. C₁₄H₁₅NO₃ requires C, 68.56; H, 6.10; N, 5.71%).

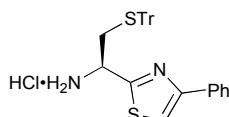
2-(1(*S*)-Amino-2-tritylthio)ethyl-4-phenylthiazole hydrochloride **13**

(a)



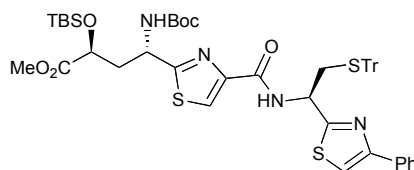
A solution of (*S*)-*N*-*tert*-butoxycarbonyl-*S*-tritylcysteine thioamide **12** (1.00 g, 2.09 mmol), 2-bromoacetophenone (0.50 g, 2.51 mmol) in ethanol (20 mL) was stirred at room temperature for 16 h. After this period the reaction mixture was diluted with dichloromethane (100 mL) and washed with aqueous NaHCO₃ (100mL), water (100 mL) and then brine (100 mL). The organic extracts were then dried with Na₂SO₄, filtered and the solvent removed under reduced pressure. The resulting solid was then purified by chromatography (95:5, 9:1, 85:15, 8:2, 3:1 light petroleum : ethyl acetate) yielding **2-(1(*S*)-*tert*-Butoxycarbonylamino-2-tritylthio)ethyl-4-phenylthiazole** as a white foam (0.94g, 78%); [α]_D²⁶ = -3.8 (*c* 1.00, CHCl₃); [Found (ES): MNa⁺, 601.1929. C₃₅H₃₄N₂NaO₂S₂ requires 601.1959]; IR (solution, CHCl₃) 3697, 3427, 2977, 2929, 1712, 1600, 1488, 1446, 1392, 1368, 1321, 1157, 1083, 1046, 869 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 7.89 (2H, dd, *J* = 1.5, 3.5 Hz), 7.46 - 7.43 (8H, m), 7.37 - 7.34 (2H, m), 7.31 - 7.21 (9H, m), 5.23 (1H, m), 5.01 (1H, m), 3.02 - 2.98 (1H, m), 2.85 - 2.82 (1H, m), 1.47 (9H, s); ¹³C NMR (125 MHz; CDCl₃) δ 171.26 (C), 155.62 (C), 154.94 (C), 144.54 (C), 134.54 (C), 129.66 (CH), 128.76 (CH), 128.16 (CH), 128.11 (CH), 129.92 (CH), 126.47 (CH), 112.81 (CH), 80.16 (C), 67.24 (C), 52.01 (CH), 37.25 (CH₂), 28.43 (CH₃); (Found: C, 72.21; H, 5.97; N, 4.75. C₁₄H₁₅NO₃ requires C, 72.63; H, 5.92; N, 4.84%).

(b)



To a solution of 2-(1(*S*)-*tert*-butoxycarbonylamino-2-tritylthio)ethyl-4-phenylthiazole (938 mg, 1.623 mmol) in 1,4-dioxane (10 mL) under a nitrogen atmosphere was added hydrogen chloride in 1,4-dioxane (4 M; 2.03 mL, 8.114 mmol) dropwise and the resultant solution stirred for 16 h at room temperature. After this period the milky solution was filtered and the solid washed with diethyl ether. This yielded the hydrochloride salt **13** as a white solid (623 mg, 75%) used without further purification; $[\alpha]_D^{24} = +4.5$ (*c* 1.00, CHCl₃); [Found (ES): MNa⁺, 501.1441. C₃₀H₂₆N₂NaS₂ requires 501.1435]; IR (solution, CHCl₃) 3379, 2925, 2359, 1713, 1596, 1490, 1446, 1321, 1083, 1027, 1001, 886 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 7.86 (2H,m), 7.48 – 7.45 (4H, m), 7.42 – 7.40 (4H, m), 7.34 – 7.27 (7H, m), 7.23 – 7.20 (4H, m), 3.86 (1H, dd, *J* = 4.5, 8.0 Hz), 2.88 (1H, dd, *J* = 4.5, 12.5 Hz), 2.76 (1H, dd, *J* = 8.0, 12.5 Hz); ¹³C NMR (125 MHz; CDCl₃) δ 174.00 (C), 155.31 (C), 144.68 (C), 134.53 (C), 129.69 (CH), 128.74 (CH), 128.25 (CH), 128.08 (CH), 126.87 (CH), 126.39 (CH), 112.78 (CH), 67.25 (C), 53.09 (CH), 40.29 (CH₂).

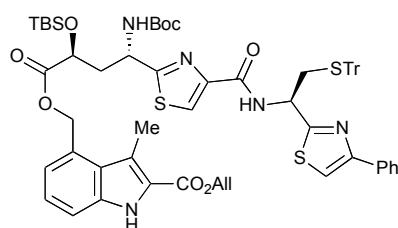
Bis-thiazole 14



To a solution of fragment **6** (510 mg, 1.076 mmol) and fragment **13** (514 mg, 1.076 mmol) in dry dichloromethane (20 mL) at 0 °C under nitrogen was added PyBOP[®] (784 mg, 1.506 mmol) followed by diisopropylethylamine (958 μ L, 5.378 mmol). The reaction mixture was then stirred at room temperature overnight. The reaction was then diluted with

dichloromethane (50 mL) and washed sequentially with hydrochloric acid (1 M; 50 mL), saturated NaHCO₃ (50 mL) and finally brine (50 mL). The organic layer was then dried with Na₂SO₄, filtered and the solvent removed under reduced pressure. The resulting oil was then purified by chromatography (9:1, 8:2, 7:3, 6:4 light petroleum : ethyl acetate) yielding the title compound **14** as a colourless white foam (814 mg, 81%); $[\alpha]_D^{24} = -32.7$ (*c* 1.00, CHCl₃); [Found (ES): MNa⁺, 957.3158. C₅₀H₅₈N₄NaO₆S₃Si requires 957.3185]; IR (solution, CHCl₃) 3398, 2929, 2856, 1730, 1672, 1540, 1490, 1462, 1373, 1300, 1273, 1098, 1046, 1002, 908, 840 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.04 (1h, s), 7.95 (1H, d, *J* = 8.5 Hz), 7.88 (2H, d, *J* = 7.0 Hz), 7.44 – 7.41 (5H, m), 7.37 (1H, s), 7.35 – 7.31 (1H, m), 7.28 – 7.25 (9H, m), 5.78 (1H, d, *J* = 7.5 Hz), 5.33 (1H, dd, *J* = 6.5, 8.5 Hz), 5.20 – 5.17 (1H, m), 4.43 – 4.40 (1H, m), 3.62 (3H, s), 3.11 – 3.05 (1H, m), 2.99 – 2.95 (1H, m), 2.49 – 2.44 (1H, m), 2.37 – 2.33 (1H, m), 1.45 (9H, s), 0.93 (9H, s), 0.06 (3H, s), 0.01 (3H, s); ¹³C NMR (125 MHz; CDCl₃) δ 173.80 (C), 173.30 (C), 169.13 (C), 160.26 (C), 155.25 (C), 149.49 (C), 144.54 (C), 134.43 (C), 129.69 (CH), 128.75 (CH), 128.17 (CH), 128.07 (CH), 126.85 (CH), 126.46 (CH), 124.05 (CH), 112.97 (CH), 80.33 (C), 69.59 (CH), 67.33 (C), 53.49 (C), 52.14 (CH₃), 50.52 (CH), 50.35 (CH), 38.90 (CH₂), 36.90 (CH₂), 28.35 (CH₃), 25.79 (CH₃), 18.18 (C), -4.99 (CH₃), -5.39 (CH₃).

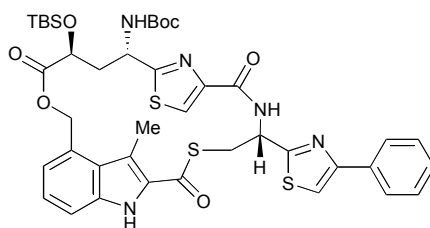
Macrocycle precursor 15



To a solution of amide **14** (481 mg, 0.515 mmol) in THF : methanol : water (15 mL, 2:2:1) was added LiOH (65 mg, 1.544 mmol) and the resultant mixture stirred at room temperature for 16 h. After this period the reaction was diluted with ethyl acetate (50 mL) and washed with hydrochloric acid (1 M; 50mL). The aqueous was further extracted with ethyl acetate (50 mL) and the combined organic layers washed with brine (100 mL), dried with Na₂SO₄, filtered and the solvent removed under reduced pressure yielding the crude acid as a white foam which was used without further purification (422 mg). To a solution of the crude acid (250 mg, 0.272 mmol) in dichloromethane (10.00 mL) at 0 °C under a nitrogen atmosphere was added DCC (1 M solution in dichloromethane; 326 μ L, 0.326 mmol) dropwise and the solution stirred at 0 °C for 1 h. After this period **10** (80 mg, 0.326 mmol) and DMAP (4 mg, 0.03 mmol) and HOAt (5 mg, 0.03 mmol) was added and the solution stirred at room temperature overnight. The mixture was filtered through Celite[®] and the filtrate concentrated under reduced pressure. The resulting solid was then purified by chromatography (9:1, 8:2, 7:3, 6:4, 1:1 light petroleum : ethyl acetate) yielding the title compound **15** as a white foam (216 mg, 69% from **14**); [α]_D²² = -41.4 (*c* 1.00, CHCl₃); [Found (ES): MH⁺, 1148.4150. C₆₃H₇₀N₅O₈S₃Si requires 1148.4150]; IR (solution, CHCl₃) 3460, 2929, 2857, 1715, 1673, 1490, 1368, 1340, 1309, 1103, 1046, 995, 908 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.83 (1H, bs), 8.02 (1H, s), 7.88 – 7.85 (3H, m), 7.42 – 7.32 (8H, m), 7.32 – 7.24 (8H, m), 7.20 – 7.17 (4H, m), 7.04 (1H, d, *J* = 6.5 Hz), 6.02 (1H, dddd, *J* = 5.5, 5.5, 10.5, 17.5 Hz), 5.67 (1H, d, *J* = 7.5 Hz), 5.57 (1H, d, *J* = 12.5 Hz), 5.43 (1H, d, *J* = 12.5 Hz), 5.40 (1H, ddd, *J* = 1.5, 1.5, 17.5 Hz), 5.31 – 5.28 (1H, m), 4.84 – 4.82 (2H, m), 4.43 – 4.42 (1H, m), 3.05 (1H, dd, *J* = 6.5, 12.5 Hz), 2.98 (1H, dd, *J* = 6.0, 12.5 Hz), 2.48 – 2.44 (1H, m), 2.73 (3H, s), 2.34 – 2.30 (1H, m), 1.42 (9H, s), 0.86 (9H, s), -0.04 (6H, s); ¹³C NMR (125 MHz; CDCl₃) δ 173.79 (C), 172.60 (C), 169.17 (C), 161.96 (C), 160.28 (C), 155.40 (C), 155.10 (C), 149.45 (C), 144.55 (C), 136.43 (C), 134.40 (C), 132.10 (CH), 129.69 (CH), 129.55 (C), 128.71 (CH), 128.11

(CH), 128.05 (CH), 126.82 (CH), 126.43 (CH), 126.26 (C), 125.32 (CH), 124.04 (CH), 123.62 (C), 122.34 (CH), 120.31 (C), 118.76 (CH₂), 112.94 (CH), 112.76 (CH), 80.32 (C), 77.29 (CH), 69.62 (CH), 67.35 (C), 65.44 (CH₂), 65.26 (CH₂), 50.47 (CH), 39.08 (CH₂), 36.83 (CH₂), 28.33 (CH₃), 25.73 (CH₃), 12.00 (CH₃), -4.98 (CH₃), 5.46 (CH₃).

The Southern Hemisphere Model Fragment 2



To a solution of **15** (85 mg, 0.074 mmol) in degassed dry THF (5.0 mL) was added PPh₃ (30 mg, 0.112 mmol), Pd(OAc)₂ (1.7 mg, 0.007 mmol) finally morpholine (7.8 μ L, 0.089 mmol) and the resultant mixture stirred at room temperature under nitrogen for 16 h. After this period the solvent was removed under reduced pressure and the resulting oil purified by PTLC (3:1 ethyl acetate : light petroleum) yielding the acid as a white foam and used without any further purification (76 mg, 93%). To a solution of the acid (97 mg, 0.0876 mmol) in dry methanol (5.0 mL) at 0 °C under nitrogen was added pyridine (25 μ L, 0.3067 mmol) followed by AgNO₃ (30 mg, 0.1753 mmol) and the reaction mixture stirred for a further 30 min at 0 °C. After this period 2-mercaptoethanol (71 μ L, 0.8762 mmol) was added and the mixture allowed to warm to room temperature and stirred for a further 1 h. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (10.0 mL) and filtered through Celite[®] to remove the silver salts. The solid was washed with further ethyl acetate (5.0 mL). The organics were then combined, solvent removed under reduced pressure and the

resulting oil purified by PTLC (1: 3, light petroleum : ethyl acetate) yielding the thiol-acid **3** as a white foam (56 mg, 75 %) and used directly in the next step.

Method A - To a solution of **3** (20 mg, 23.61 μmol) in THF (2.4 mL) at room temperature under a nitrogen atmosphere was added DCC (1 M solution in dichloromethane; 29 μL , 28.33 μmol) and the solution stirred for 1 h. After this period DMAP (3.5 mg, 28.33 μmol) was added and the reaction mixture stirred for a further 16 h at room temperature. The solvent was then removed under reduced pressure and the residue purified by PTLC (1:1 ethyl acetate : light petroleum) to give **2** as a colourless solid (10.5 mg, 52 %); mp 135 - 137 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{18} = -203.4$ (c 0.50, CHCl_3); [Found (ES): MNa^+ , 870.2436. $\text{C}_{41}\text{H}_{49}\text{N}_5\text{NaO}_7\text{S}_3\text{Si}$ requires 870.2456]; IR (solution, CHCl_3) 3444, 2930, 2858, 2358, 1756, 1715, 1670, 1489, 1461, 1368, 1126, 1045, 975, 906 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 8.77 (1H, bs), 8.06 (1H, d, $J = 9.0$ Hz), 7.98 (1H, s), 7.90 (2H, dd, $J = 1.5, 7.0$ Hz), 7.46 (1H, s), 7.41 (2H, t, $J = 7.2$ Hz), 7.36 (1H, m), 7.30 (1H, dd, $J = 0.8, 7.4$ Hz), 7.23 (1H, t, $J = 7.0$ Hz), 7.15 (1H, dd, $J = 0.8, 7.2$ Hz), 5.90 (1H, m), 5.68 (1H, d, $J = 12.0$ Hz), 5.48 – 5.46 (1H, m), 5.39 (1H, d, $J = 11.2$ Hz), 4.57 – 4.53 (1H, m), 4.44 (1H, dd, $J = 2.0, 8.8$ Hz), 4.21 (1H, dd, $J = 6.5, 14.0$ Hz), 4.11 (1H, dd, $J = 5.0, 14.0$ Hz), 2.94 (3H, s), 1.86 (1H, m), 1.66 (1H, m - obscured by water peak), 1.39 (9H, s), 0.91 (9H, s), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz; CDCl_3) δ 182.78, 172.85, 171.78, 170.13, 160.94, 155.64, 155.26, 149.12, 137.23, 134.29, 131.18, 129.71, 128.79, 128.28, 126.38, 126.02, 125.94, 124.68, 124.26, 119.83, 113.61, 113.29, 80.12, 68.85, 66.50, 50.85, 49.32, 40.59, 32.02, 28.32, 25.75, 18.18, 12.92, -4.91, -5.52.

Method B - To a solution of **3** (20 mg, 23.61 μmol) in THF (2.4 mL) at room temperature under nitrogen was added PyBOP[®] (15 mg, 28.33 μmol) followed by DIPEA (8.4 μL , 47.21 μmol) and the solution stirred for 16 h. After this period the solvent was removed under vacuum and the residue purified by PTLC (1:1 ethyl acetate : light petroleum) which gave **2** as a white solid; (9.4 mg, 47 %). Physical data was the same as above.