

Total Synthesis of Thiostrepton. Assembly of Key Building Blocks and Completion of the Synthesis.

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Supporting Information

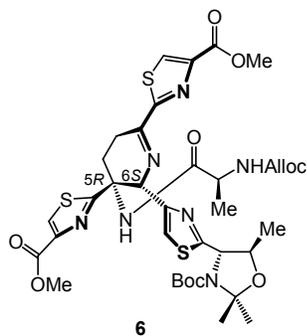
Experimental Data for Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et₂O), ethylene glycol dimethyl ether (DME), and methylene chloride (CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reagents were

purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, br = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

***N*-Alloc dehydropiperidine **6** (Scheme 1):**

To a solution of the less polar 5*R*,6*S* amine isomer **2**¹ (1.26 g, 1.68 mmol) in THF (26 mL) at 25 °C was added *i*-Pr₂NEt (2.9 mL, 16.9 mmol), allyl chloroformate (0.88 mL, 8.40 mmol), and 4-DMAP (21 mg, 0.17 mmol). The reaction mixture was stirred for 3 h at 25 °C and then diluted with ethyl acetate (200 mL). The organic layer was washed with aqueous 0.05 M KHSO₄ solution, saturated aqueous NaHCO₃ solution, and brine (50 mL each), then dried (Na₂SO₄) and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 60:40 → 30:70) to give *N*-Alloc dehydropiperidine **6** (1.28 g, 92%) as a yellow foam.

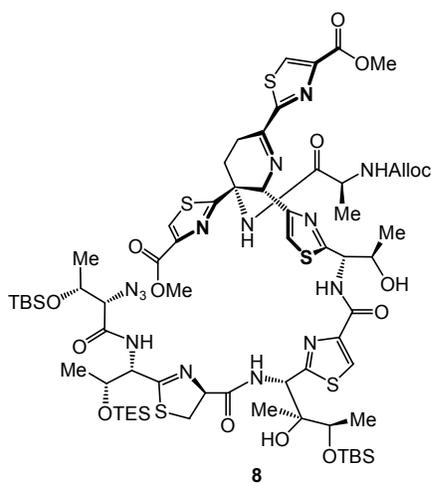


6: $R_f = 0.43$ (silica gel, hexanes:EtOAc, 2:8); $[\alpha]_D^{32} = +14.2$ (CHCl₃, $c = 1.00$); IR (film) ν_{\max} 3318, 3096, 2966, 2919, 1719, 1701, 1502, 1478, 1367, 1237, 1214, 1132, 1096, 991, 773 cm⁻¹;

^1H NMR (500 MHz, CD_3CN , 70 $^\circ\text{C}$) δ 8.27 (s, 1 H), 8.04 (s, 1 H), 7.13 (s, 1 H), 5.84 – 5.75 (m, 1 H), 5.68 (br s, 1 H), 5.35 (br s, 1 H), 5.20 (dq, $J = 17.3, 1.8$ Hz, 1 H), 5.11 (dq, $J = 11.6, 1.8$ Hz, 1 H), 4.75 (d, $J = 5.8$ Hz, 1 H), 4.30 (dd, $J = 13.2, 6.3$ Hz, 1 H), 4.31 – 4.17 (br, 2 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.41 (ddd, $J = 13.9, 7.0, 2.2$ Hz, 1 H), 3.14 (ddt, $J = 19.8, 6.3, 2.2$ Hz, 1 H), 2.97 – 2.86 (m, 1 H), 2.72 – 2.63 (m, 1 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 1.39 (d, $J = 6.3$ Hz, 3 H), 1.33 (br, 9 H), 1.31 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN , 70 $^\circ\text{C}$) δ 176.7, 174.3, 173.9, 170.7, 164.7, 162.7, 157.0, 153.5, 148.8, 147.8, 134.4, 131.9, 129.1, 120.3, 96.1, 81.8, 78.7, 67.7, 67.2, 66.5, 61.1, 53.4, 52.9, 52.8, 28.8, 28.4, 26.0, 19.1, 18.5; HRMS (ESI-TOF) calcd for $\text{C}_{36}\text{H}_{46}\text{N}_7\text{O}_{10}\text{S}_3^+$ [$\text{M} + \text{H}^+$] 832.2463, found 832.2459.

Seco diester **8** (Scheme 1):

To *N*-Alloc dehydropiperidine **6** (1.09 g, 1.31 mmol) in CH_2Cl_2 (42 mL) was added TFA (42 mL) at 0 $^\circ\text{C}$. After stirring for 10 min at 0 $^\circ\text{C}$, the reaction mixture was brought to 25 $^\circ\text{C}$ and



stirring was continued for a further 45 min. The reaction mixture was then concentrated and saturated aqueous NaHCO_3 solution (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 \times 30 mL), and the combined organic layers were then washed with brine (30 mL), dried (Na_2SO_4), and concentrated to give amino alcohol **7** which was used immediately and without further purification in the next step. The crude carboxylic acid **3**¹ and amino alcohol **7** were combined in a flask and dissolved in DMF (8.3 mL). The resulting pale yellow solution was cooled to

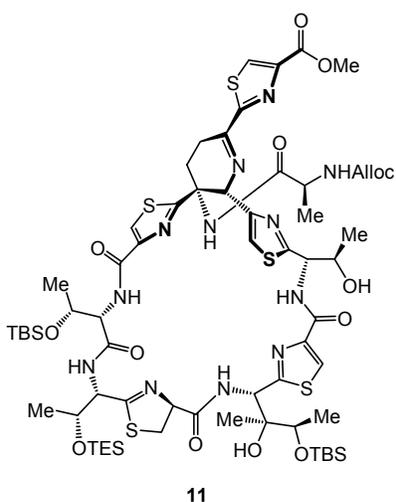
0 $^\circ\text{C}$ and then *i*- Pr_2NEt (0.69 mL, 3.39 mmol), HOAt (214 mg, 1.57 mmol), and HATU (597 mg, 1.57 mmol) were added. The reaction mixture was stirred for 30 min at 0 $^\circ\text{C}$, and then diluted with EtOAc (50 mL). The organic layer was washed with aqueous 0.01 M KHSO_4 solution, saturated aqueous NaHCO_3 solution, and brine (20 mL each), then dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:7) to give seco diester **8** (1.51 g, 73% over 2 steps from **6**) as a white foam.

8: $R_f = 0.42$ (silica gel, hexanes:EtOAc, 3:7); $[\alpha]_D^{32} = +15.6$ (CHCl_3 , $c = 1.00$); IR (film) ν_{max} 3387, 2953, 2837, 2112, 1737, 1677, 1508, 1247, 1101, 992, 843, 778 cm^{-1} ; ^1H NMR (600 MHz,

CD₃CN, 70 °C) δ 8.27 (br s, 1 H), 8.26 (s, 1 H), 8.23 (d, J = 8.8 Hz, 1 H), 8.03 (s, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.43 (d, J = 8.3 Hz, 1 H), 6.99 (s, 1 H), 6.46 – 6.41 (br, 1 H), 5.77 – 5.71 (m, 1 H), 5.37 (d, J = 8.3 Hz, 1 H), 5.34 (t, J = 1.3 Hz, 1 H), 5.29 (dd, J = 9.2, 3.1 Hz, 1 H), 5.17 (d, J = 17.1 Hz, 1 H), 5.07 (d, J = 10.6 Hz, 1 H), 5.02 (t, J = 8.8 Hz, 1 H), 4.72 – 4.69 (br, 1 H), 4.61 (d, J = 8.3 Hz, 1 H), 4.44 – 4.36 (m, 2 H), 4.26 (dd, J = 10.4, 6.8 Hz, 1 H), 4.14 – 4.11 (br, 1 H), 4.03 (q, J = 6.1 Hz, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.54 (dd, J = 11.0, 9.2 Hz, 1 H), 3.49 (dd, J = 11.4, 7.8 Hz, 1 H), 3.37 (ddd, J = 13.6, 6.6, 1.4 Hz, 1 H), 3.14 – 3.10 (m, 1 H), 2.92 – 2.83 (m, 1 H), 2.70 – 2.65 (m, 1 H), 1.34 (d, J = 6.5 Hz, 3 H), 1.30 (d, J = 7.4 Hz, 3 H), 1.29 (d, J = 6.5 Hz, 3 H), 1.24 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.6 Hz, 3 H), 1.03 (s, 3 H), 0.97 (t, J = 7.9 Hz, 9 H), 0.94 (s, 9 H), 0.91 (s, 9 H), 0.62 (dq, J = 7.9, 4.0 Hz, 6 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ¹³C NMR (125 MHz, CD₃CN, 70 °C) δ 176.8, 175.2, 174.7, 173.8, 173.0, 172.0, 171.7, 170.7, 170.3, 164.4, 162.7, 162.7, 162.6, 157.1, 153.9, 149.8, 148.8, 147.7, 134.3, 131.9, 129.1, 125.8, 119.8, 79.3, 77.1, 71.6, 71.0, 70.6, 70.4, 70.2, 69.9, 69.0, 67.9, 66.4, 61.1, 60.9, 59.8, 58.3, 57.5, 53.6, 52.9, 52.8, 37.3, 28.2, 26.7, 26.5, 25.7, 21.9, 21.5, 21.1, 19.5, 19.3, 18.9, 18.8, 18.4, 18.3, 7.2, 6.0, -3.2, -4.0, -4.2, -4.4; HRMS (ESI-TOF) calcd for C₆₆H₁₀₃N₁₄O₁₅S₅Si₃⁺ [M + H⁺] 1575.5633, found 1575.5609.

Thiazoline macrocycle **11** (Scheme 1):

Trimethyltin hydroxide (69 mg, 0.38 mmol) was added to seco diester **8** (300 mg, 0.19 mmol) in 1,2-dichloroethane (4.0 mL). The reaction mixture was heated at 50 °C for 4 h during which



time a further 69 mg (0.38 mmol) of trimethyltin hydroxide was added every hour (total amount of trimethyltin hydroxide added = 276 mg, 1.52 mmol). The reaction mixture was then cooled to 25 °C and concentrated, and the residue was purified by flash column chromatography (silica gel, CH₂Cl₂:MeOH, 96:4 → 88:12) to give regioisomeric monoacids **9** and **9'** (chromatographically inseparable mixture of regioisomers, 155 mg, 52%), recovered seco diester **8** (84 mg, 28%), and the corresponding diacid (42 mg, 14%). To the mixture of monoacids **9** and **9'** (155 mg, 0.10 mmol) in a 10:1 mixture of

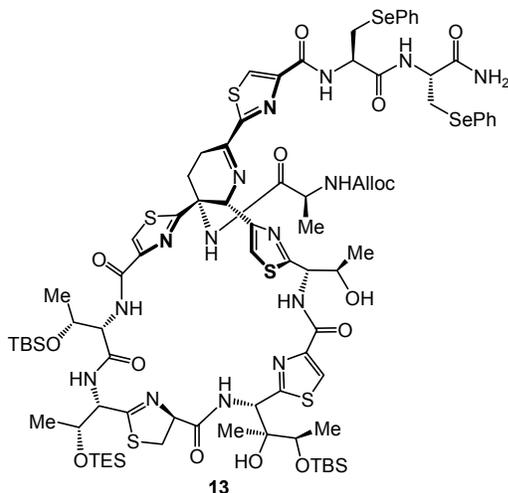
THF:water (0.50 mL) at 0 °C was added trimethylphosphine (1.0 M solution in THF, 0.30 mL,

0.30 mmol). The reaction mixture was stirred for 1 h at 0 °C and then a further 0.30 mL of 1.0 M Me₃P solution in THF (0.30 mmol) was added. Stirring was continued for 15 min at 0 °C, and then air was bubbled through the mixture for 15 min. Toluene (5 mL) was then added and the mixture was dried (Na₂SO₄) and concentrated to give crude regioisomeric amino acids **10** and **10'** which were used without purification in the next step. To the crude mixture of chromatographically inseparable amino acids **10** and **10'** was added DMF (50 mL, 0.002 M), followed by HATU (188 mg, 0.50 mmol), HOAt (67 mg, 0.50 mmol), and *i*-Pr₂NEt (0.11 mL, 0.60 mmol). The reaction mixture was stirred for 65 h at 25 °C, and then concentrated. The residue was taken up in EtOAc (50 mL) and the organic layer was washed with 0.01 M aqueous KHSO₄ solution, water, saturated aqueous NaHCO₃ solution, and brine (20 mL each), then dried (Na₂SO₄) and concentrated. The residue was purified first by flash column chromatography (silica gel, toluene:EtOAc, 1:1), and the resulting impure product was then repurified by preparative TLC (silica gel, hexanes:EtOAc, 4:6, eluted 2 ×) to give thiazoline macrocycle **11** (48 mg, 32% over 2 steps from mixture of monoacids **9** and **9'**) as a yellow foam.

11: $R_f = 0.37$ (silica gel, hexanes:EtOAc, 3:7); $[\alpha]_D^{32} = +16.9$ (CHCl₃, $c = 1.00$); IR (film) ν_{\max} 3394, 2927, 1718, 1670, 1528, 1483, 1256, 1101, 833, 757 cm⁻¹; ¹H NMR (500 MHz, CD₃CN, 70 °C) δ 8.30 (s, 1 H), 8.16 (s, 1 H), 7.87 (d, $J = 10.0$ Hz, 1 H), 7.77 (d, $J = 8.4$ Hz, 1 H), 7.37 (s, 2 H), 5.95 – 5.90 (br, 1 H), 5.80 – 5.71 (m, 1 H), 5.57 (d, $J = 8.8$ Hz, 1 H), 5.37 – 5.33 (m, 1 H), 5.27 – 5.22 (m, 1 H), 5.18 (dq, $J = 17.3, 1.5$ Hz, 1 H), 5.08 (dq, $J = 10.7, 1.5$ Hz, 1 H), 4.98 (dt, $J = 9.2, 1.9$ Hz, 1 H), 4.83 (d, $J = 8.8$ Hz, 1 H), 4.73 – 4.69 (br, 1 H), 4.64 – 4.59 (br, 1 H), 4.30 – 4.23 (br, 3 H), 4.10 (q, $J = 6.3$ Hz, 1 H), 3.95 (quin, $J = 7.0$ Hz, 1 H), 3.64 (dd, $J = 13.2, 7.4$ Hz, 1 H), 3.57 (d, $J = 9.2$ Hz, 2 H), 3.24 (d, $J = 16.5$ Hz, 1 H), 2.92 – 2.83 (m, 1 H), 2.49 – 2.42 (m, 1 H), 1.32 (d, $J = 6.2$ Hz, 3 H), 1.24 (d, $J = 6.3$ Hz, 3 H), 1.23 (d, $J = 7.0$ Hz, 3 H), 1.21 (d, $J = 6.6$ Hz, 3 H), 1.10 (d, $J = 6.3$ Hz, 3 H), 1.05 (s, 3 H), 0.98 (s, 9 H), 0.96 (t, $J = 8.1$ Hz, 9 H), 0.95 (s, 9 H), 0.64 (q, $J = 7.7$ Hz, 6 H), 0.20 (s, 3 H), 0.19 (s, 3 H), 0.12 (s, 3 H), 0.09 (s, 3 H); ¹³C NMR (150 MHz, CD₃CN, 70 °C) δ 174.2, 174.1, 171.1, 170.8, 170.1, 164.0, 162.8, 162.2, 162.0, 157.2, 156.0, 150.6, 150.1, 149.0, 134.3, 132.1, 126.3, 124.6, 120.2, 79.6, 78.0, 70.8, 70.7, 69.7, 69.6, 66.6, 59.5, 58.9, 58.1, 53.3, 53.0, 36.7, 32.9, 30.6, 30.4, 30.3, 30.2, 30.1, 29.2, 27.4, 26.8, 25.6, 21.0, 20.4, 19.5, 19.0, 18.9, 18.7, 18.3, 7.5, 6.1, -2.6, -3.9, -4.2; HRMS (ESI-TOF) calcd for C₆₅H₁₀₁N₁₂O₁₄S₅Si₃⁺ [M + H⁺] 1517.5466, found 1517.5432.

Bis-phenylselenium thiazoline macrocycle **13** (Scheme 2):

To thiazoline macrocycle **11** (40 mg, 0.027 mmol) in 1,2-dichloroethane (0.40 mmol) was added trimethyltin hydroxide (48 mg, 0.26 mmol). The reaction mixture was heated at 60 °C for 2.5 h



and then concentrated. The residue was taken up in EtOAc (15 mL) and washed with aqueous 0.01 M KHSO₄ solution (3 × 5 mL), and water (5 mL), then dried (Na₂SO₄) and concentrated to give carboxylic acid **12** (40 mg, 100%) as a yellow foam, which was used immediately and without further purification in the next step. To carboxylic acid **12** (40 mg, 0.027 mmol) in DMF (0.33 mL) at 0 °C was added bis-phenylselenium amine **4** (25 mg, 0.051 mmol), followed by HOAt (4.4 mg, 0.032 mmol), HATU

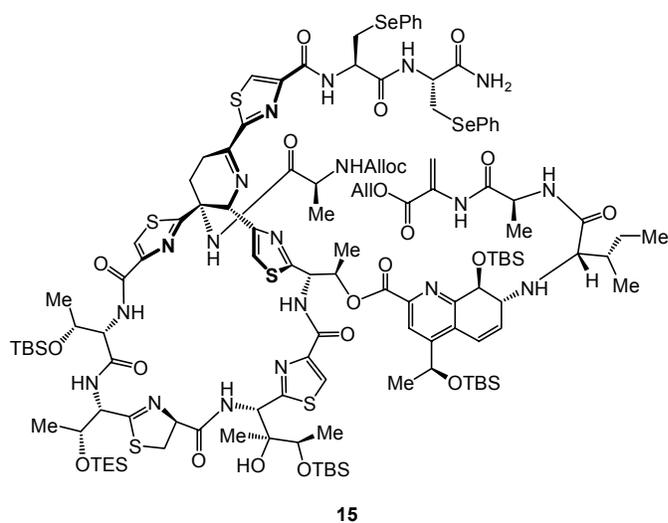
(12.0 mg, 0.032 mmol), and *i*-Pr₂NEt (14 μL, 0.081 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and then at 25 °C for 30 min. The reaction mixture was diluted with EtOAc (5 mL) and the organic layer was washed with 0.01 M KHSO₄ solution (2 × 1.5 mL), water (1.5 mL), and brine (1.5 mL), then dried (Na₂SO₄) and concentrated. The residue was purified by preparative TLC (silica gel, CH₂Cl₂:MeOH, 92.5:7.5) to give bis-phenylselenium thiazoline macrocycle **13** (42 mg, 83%) as a yellow foam.

13: $R_f = 0.40$ (silica gel, CH₂Cl₂:MeOH, 93:7); $[\alpha]_D^{32} = -14.1$ (CHCl₃, $c = 1.00$); IR (film) ν_{\max} 3398, 2927, 2860, 1664, 1529, 1482, 1384, 1256, 1100, 834, 778 cm⁻¹; ¹H NMR (600 MHz, CD₃CN, 70 °C) δ 8.16 (s, 1 H), 8.03 (d, $J = 7.0$ Hz, 1 H), 7.90 (d, $J = 9.2$ Hz, 1 H), 7.80 – 7.57 (m, 2 H), 7.56 – 7.52 (br, 1 H), 7.50 – 7.49 (m, 2 H), 7.39 (s, 1 H), 7.28 – 7.27 (m, 4 H), 7.24 – 7.23 (m, 3 H), 5.93 (br s, 1 H), 5.79 – 5.75 (m, 1 H), 5.58 (d, $J = 9.2$ Hz, 1 H), 5.39 – 5.38 (m, 1 H), 5.24 (br s, 1 H), 5.20 (dd, $J = 17.1, 1.3$ Hz, 1 H), 5.09 (dd, $J = 10.6, 1.1$ Hz, 1 H), 5.00 (dt, $J = 9.2, 1.4$ Hz, 1 H), 4.86 – 4.84 (m, 1 H), 4.72 – 4.65 (m, 2 H), 4.60 (br s, 1 H), 4.52 – 4.48 (m, 2 H), 4.32 – 4.25 (m, 4 H), 4.12 (q, $J = 6.1$ Hz, 1H), 4.00 (quin, $J = 6.6$ Hz, 1 H), 3.69 – 3.64 (m, 1 H), 3.58 (d, $J = 9.2$ Hz, 2 H), 3.44 – 3.19 (m, 6 H), 2.89 (br s, 1 H), 2.46 (br s, 1 H), 1.33 (d, $J = 6.1$ Hz, 3 H), 1.25 (d, $J = 6.6$ Hz, 3 H), 1.24 (d, $J = 6.0$ Hz, 3 H), 1.22 (d, $J = 6.6$ Hz, 3 H), 1.10 (d, $J = 6.1$ Hz, 3 H), 1.05 (s, 3 H), 0.98 (s, 9 H), 0.97 – 0.94 (m, 9 H), 0.95 (s, 9 H), 0.66 (q, $J = 7.9$ Hz, 6 H), 0.20 (s, 3 H), 0.19 (s, 3 H), 0.12 (s, 3 H), 0.089 (s, 3 H); ¹³C NMR (150 MHz,

dioxane-*d*₈, 70 °C) δ 173.6, 173.0, 172.0, 170.6, 169.7, 169.2, 161.1, 151.2, 149.6, 133.8, 133.2, 133.1, 131.0, 130.8, 129.7, 129.6, 127.6, 127.4, 119.4, 117.8, 71.1, 66.1, 61.6, 54.2, 53.8, 53.6, 52.1, 46.6, 33.8, 32.3, 30.1, 29.9, 29.8, 29.7, 29.6, 29.5, 28.9, 26.3, 26.2, 25.4, 25.2, 23.0, 18.4, 18.4, 17.8, 14.6, 14.0, 6.9, 5.4, -5.0; HRMS (ESI-TOF) calcd for C₈₂H₁₁₇N₁₅O₁₅S₅Se₂Si₃Na⁺ [M + Na⁺] 1978.4987, found 1978.4973.

Bis-phenylselenium seco compound **15** (Scheme 2):

To carboxylic acid **14**¹ (9.1 mg, 0.012 mmol) at 25 °C was added a solution of 2,4,6-trichlorobenzoyl chloride (3.7 μ L, 0.023 mmol) and Et₃N (0.010 mL, 0.071 mmol) in toluene



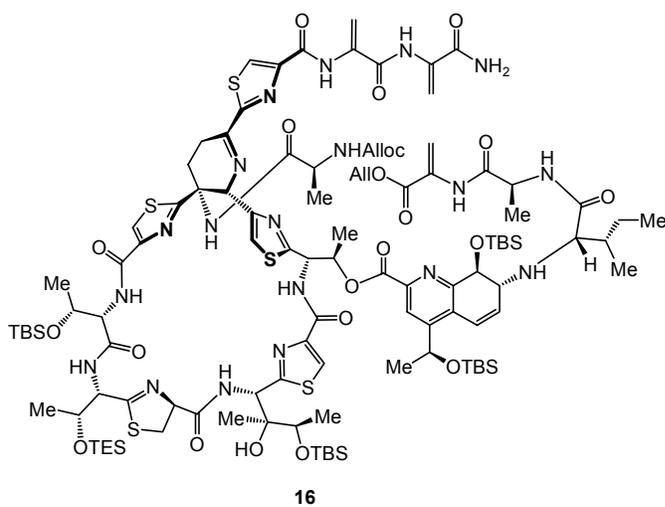
(0.10 mL). The reaction mixture was stirred for 16 h at 25 °C and then added to bis-phenylselenium thiazoline macrocycle **13** (11 mg, 0.0060 mmol) and 4-DMAP (11 mg, 0.090 mmol) and stirred for 35 min at 25 °C. The reaction mixture was then purified directly by preparative TLC (silica gel, EtOAc) to give bis-phenylselenium seco compound **15** as a yellow oil (12.8 mg, 84%).

15: R_f = 0.38 (silica gel, CH₂Cl₂:MeOH, 93:7); $[\alpha]_D^{32} = -50.0$ (CHCl₃, c = 0.70); IR (film) ν_{\max} 3366, 2926, 2854, 1718, 1684, 1654, 1541, 1522, 1490, 1474, 1376, 1252, 1098, 853, 779 cm⁻¹; ¹H NMR (500 MHz, CD₃CN, 70 °C) δ 8.46 (br s, 1 H), 8.18 (s, 1 H), 8.05 (s, 1 H), 8.02 (br s, 1 H), 8.01 (s, 1 H), 7.97 – 7.91 (m, 1 H), 7.75 (br s, 1 H), 7.67 (br s, 1 H), 7.60 – 7.56 (m, 2 H), 7.54 (s, 1 H), 7.51 – 7.47 (m, 1 H), 7.31 – 7.27 (m, 4 H), 7.26 – 7.21 (m, 4 H), 7.19 (d, J = 8.1 Hz, 1 H), 6.90 (d, J = 10.0 Hz, 1 H), 6.44 (s, 1 H), 6.37 (dd, J = 8.9, 4.7 Hz, 1 H), 6.02 – 5.97 (m, 1 H), 5.93 – 5.90 (br, 1 H), 5.85 (d, J = 1.0 Hz, 1 H), 5.81 – 5.74 (m, 1 H), 5.70 – 5.65 (br, 2 H), 5.44 (d, J = 8.8 Hz, 1 H), 5.37 (dq, J = 17.2, 1.5 Hz, 1 H), 5.26 (dq, J = 10.7, 1.5 Hz, 1 H), 5.22 – 5.18 (m, 2 H), 5.07 (d, J = 10.1 Hz, 1 H), 4.91 – 4.84 (m, 2 H), 4.74 – 4.68 (m, 3 H), 4.63 – 4.59 (m, 1 H), 4.51 – 4.42 (m, 3 H), 4.31 – 4.24 (m, 3 H), 4.06 – 4.02 (m, 2 H), 3.64 – 3.58 (m, 2 H), 3.46 – 3.37 (m, 4 H), 3.33 (dd, J = 12.9, 5.5 Hz, 1 H), 3.21 (dd, J = 12.9, 7.3 Hz, 1 H), 3.21 – 3.18 (m, 1 H), 3.10 (d, J = 5.9 Hz, 1 H), 2.99 – 2.92 (br, 1 H), 2.58 – 2.51 (br, 1 H), 1.36 –

1.34 (m, 12 H), 1.34 – 1.29 (m, 9 H), 1.13 (d, $J = 6.2$ Hz, 3 H), 0.99 – 0.89 (m, 36 H), 0.82 (d, $J = 7.0$ Hz, 3 H), 0.74 (s, 9 H), 0.65 (q, $J = 7.9$ Hz, 6 H), 0.21 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), -0.04 (s, 3 H), -0.16 (s, 3 H); ^{13}C NMR (125 MHz, dioxane- d_8 , 70 °C) δ 174.5, 173.7, 173.4, 172.2, 171.9, 170.7, 170.0, 169.6, 164.0, 161.2, 160.4, 158.9, 157.5, 151.3, 133.3, 133.1, 131.1, 133.0, 132.7, 129.8, 129.7, 127.7, 127.5, 118.6, 117.9, 75.4, 71.6, 71.2, 64.9, 62.5, 57.9, 54.0, 53.7, 52.4, 49.7, 46.8, 39.3, 34.0, 32.5, 30.2, 30.1, 29.8, 29.6, 29.5, 27.7, 26.5, 26.5, 26.2, 26.0, 25.5, 23.1, 18.9, 18.7, 18.6, 18.5, 18.4, 16.1, 14.2, 11.6, 7.1, 5.6, -3.2 , -3.9 , -4.6 , -4.7 ; HRMS (ESI-TOF) calcd for $\text{C}_{121}\text{H}_{179}\text{N}_{19}\text{O}_{22}\text{S}_5\text{Se}_2\text{Si}_5\text{Na}^+$ [$\text{M} + \text{Na}^+$] 2732.9144, found 2732.9132.

Triene seco compound **16** (Scheme 2):

To bis-phenylselenium seco compound **15** (12.5 mg, 0.0046 mmol) and NaHCO_3 (12 mg, 0.14 mmol) at 0 °C was added 1.0 mL of a 1:10 mixture of *t*-BuOOH (5 – 6 M in decane): CH_2Cl_2 .



The reaction mixture was stirred for 5 min at 0 °C and 30 min at 25 °C. A further 2.0 mL of the CH_2Cl_2 :*t*-BuOOH solution was added and stirring was continued for 45 min. The reaction mixture was cooled to 0 °C and quenched with a saturated aqueous 1:1 solution of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (6.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic

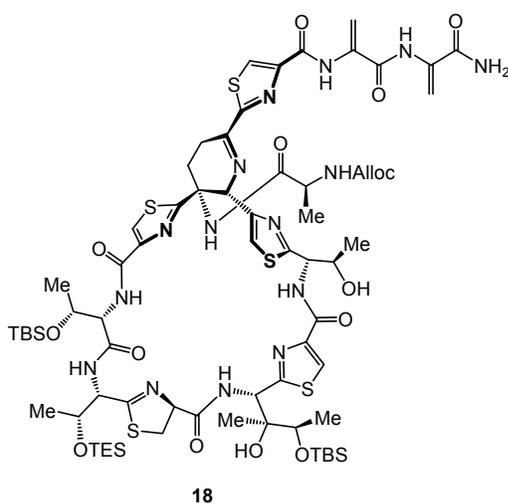
layers were dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC (silica gel, CH_2Cl_2 :MeOH, 92:8) to give triene seco compound **16** as a yellow oil (7.5 mg, 68%).

16: $R_f = 0.34$ (silica gel, CH_2Cl_2 :MeOH, 93:7); $[\alpha]_D^{32} = -33.0$ (CHCl_3 , $c = 1.00$); IR (film) ν_{max} 3362, 2922, 2852, 1701, 1655, 1522, 1459, 1255, 1101, 836, 756 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN , 70 °C) δ 9.76 (br s, 1 H), 8.89 (br s, 1 H), 8.45 (br s, 1 H), 8.27 (s, 1 H), 8.05 (s, 1 H), 8.01 (s, 1 H), 7.97 – 7.93 (m, 1 H), 7.90 (d, $J = 6.2$ Hz, 1 H), 7.75 (br s, 1 H), 7.68 (br s, 1 H), 7.54 (s, 1 H), 7.30 (d, $J = 6.6$ Hz, 1 H), 6.90 (d, $J = 10.0$ Hz, 1 H), 6.52 (d, $J = 0.8$ Hz, 1 H), 6.44 (s, 1 H), 6.39 – 6.34 (m, 1 H), 6.38 (s, 1 H), 6.00 – 5.96 (m, 1 H), 5.94 – 5.91 (br, 1 H), 5.85 (s,

1 H), 5.79 – 5.73 (m, 1 H), 5.69 – 5.65 (br, 2 H), 5.58 (s, 1 H), 5.56 (s, 1 H), 5.44 (d, $J = 8.3$ Hz, 1 H), 5.36 (d, $J = 17.5$ Hz, 1 H), 5.26 (d, $J = 10.6$ Hz, 1 H), 5.21 – 5.14 (m, 2 H), 5.07 (d, $J = 11.0$ Hz, 1 H), 4.91 – 4.84 (m, 2 H), 4.73 – 4.68 (m, 3 H), 4.63 – 4.59 (m, 1 H), 4.48 – 4.39 (m, 3 H), 4.29 – 4.21 (m, 3 H), 4.08 – 4.01 (m, 2 H), 3.66 – 3.58 (m, 3 H), 3.46 – 3.39 (m, 2 H), 3.27 (dd, $J = 12.9, 5.5$ Hz, 1 H), 3.09 (d, $J = 5.3$ Hz, 1 H), 3.01 – 2.95 (m, 1 H), 2.58 – 2.51 (br, 1 H), 1.38 – 1.34 (m, 9 H), 1.34 – 1.28 (m, 9 H), 1.25 (d, $J = 6.1$ Hz, 3 H), 1.13 (d, $J = 6.2$ Hz, 3 H), 0.98 (s, 9 H), 0.96 (t, $J = 7.9$ Hz, 9 H), 0.91 (s, 9 H), 0.88 (s, 9 H), 0.76 (d, $J = 5.7$ Hz, 3 H), 0.73 (s, 9 H), 0.64 (q, $J = 7.9$ Hz, 6 H), 0.21 (s, 6 H), 0.09 (s, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H), –0.04 (s, 3 H), –0.16 (s, 3 H); ^{13}C NMR (125 MHz, dioxane- d_8 , 70 °C) δ 173.9, 171.3, 169.0, 163.3, 162.4, 159.8, 159.1, 151.2, 135.3, 134.4, 132.1, 129.9, 129.8, 118.0, 117.1, 111.4, 102.0, 79.8, 74.8, 73.0, 71.0, 70.6, 70.5, 68.2, 64.3, 61.9, 61.4, 57.9, 54.0, 52.4, 49.1, 46.2, 38.7, 34.1, 33.4, 31.9, 29.6, 29.5, 29.4, 29.2, 27.1, 25.9, 25.8, 25.6, 25.4, 24.9, 23.2, 19.4, 18.3, 17.8, 17.7, 15.5, 13.5, 11.0, 6.5, 5.0, –4.6, –5.0, –5.2, –5.3; HRMS (ESI–TOF) calcd for $\text{C}_{109}\text{H}_{167}\text{N}_{19}\text{O}_{22}\text{S}_5\text{Si}_5\text{Na}^+$ [$\text{M} + \text{Na}^+$] 2416.9875, found 2416.9912.

Bis-dehydroalanine thiazoline macrocycle **18** (Scheme 3):

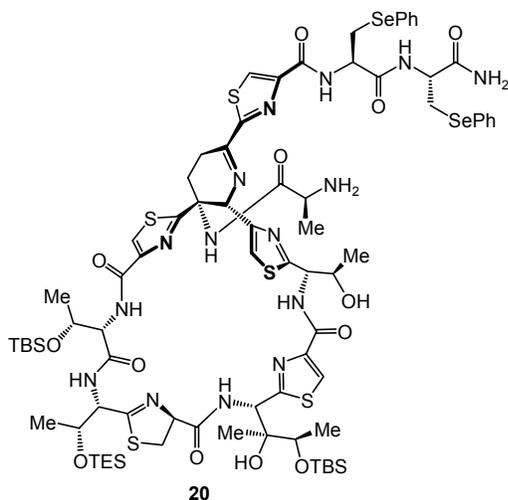
To a suspension of bis-phenylselenium macrocycle **13** (20 mg, 0.010 mmol) and NaHCO_3 (20 mg, 0.24 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added $t\text{-BuOOH}$ (0.10 mL of a 5 – 6 M solution



in decane). The reaction mixture was stirred for 5 min at 0 °C and then warmed to 25 °C. Stirring was continued for 1 h at 25 °C, then a further 0.10 mL of the 5 – 6 M decane solution of $t\text{-BuOOH}$ was added. Stirring was continued for 1 h, then the reaction mixture was cooled to 0 °C and EtOAc (12 mL) and a saturated aqueous 1:1 solution of $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 (7 mL) was added. The layers were separated and the aqueous phase was re-extracted with EtOAc (2×5 mL). The combined organic

layers were dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC (silica gel, $\text{CH}_2\text{Cl}_2\text{:MeOH}$, 93:7) to give bis-dehydroalanine thiazoline macrocycle **18** (14.1 mg, 84%) as a yellow oil.

18: $R_f = 0.35$ (silica gel, $\text{CH}_2\text{Cl}_2:\text{MeOH}$, 93:7); $[\alpha]_D^{32} = +15.0$ (CHCl_3 , $c = 1.00$); IR (film) ν_{max} 3367, 2927, 2855, 1683, 1528, 1484, 1382, 1256, 1101, 833 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN , 70 °C) δ 9.77 (br s, 1 H), 8.90 (br s, 1 H), 8.48 – 8.42 (br, 1 H), 8.26 (s, 1 H), 8.16 (s, 1 H), 7.89 (d, $J = 8.8$ Hz, 1 H), 7.80 (d, $J = 7.9$ Hz, 1 H), 7.60 – 7.52 (br, 1 H), 7.39 (s, 1 H), 6.52 (d, $J = 1.9$ Hz, 1 H), 6.38 (d, $J = 1.5$ Hz, 1 H), 5.97 – 5.91 (br, 1 H), 5.79 – 5.72 (m, 1 H), 5.58 (s, 1 H), 5.56 (t, $J = 1.8$ Hz, 1 H), 5.39 – 5.32 (m, 1 H), 5.27 – 5.23 (br, 1 H), 5.17 (dq, $J = 16.8, 1.9$ Hz, 1 H), 5.07 (dq, $J = 10.3, 1.1$ Hz, 1 H), 4.98 (dt, $J = 9.2, 1.4$ Hz, 1 H), 4.86 – 4.84 (m, 1 H), 4.72 – 4.68 (br, 1 H), 4.62 – 4.59 (br, 1 H), 4.29 – 4.26 (m, 4 H), 4.11 (q, $J = 6.3$ Hz, 1H), 3.97 (quin, $J = 7.0$ Hz, 1 H), 3.68 (dd, $J = 13.2, 6.3$ Hz, 1 H), 3.58 – 3.54 (m, 5 H), 3.31 – 3.24 (m, 1 H), 2.97 – 2.89 (m, 1 H), 2.47 (dt, $J = 12.5, 7.0$ Hz, 1 H), 2.26 (m, 1 H), 1.32 (d, $J = 6.1$ Hz, 3 H), 1.25 (d, $J = 6.6$ Hz, 6 H), 1.21 (d, $J = 6.6$ Hz, 3 H), 1.10 (d, $J = 6.3$ Hz, 3 H), 1.04 (s, 3 H), 0.98 (s, 9 H), 0.95 (s, 9 H), 0.94 (t, $J = 7.7$ Hz, 9 H), 0.64 (q, $J = 7.7$ Hz, 6 H), 0.20 (s, 3 H), 0.19 (s, 3 H), 0.12 (s, 3 H), 0.089 (s, 3 H); ^{13}C NMR (125 MHz, dioxane- d_8 , 70 °C) δ 174.5, 173.6, 173.1, 170.4, 169.7, 169.3, 166.2, 163.0, 159.6, 156.5, 151.6, 149.6, 135.8, 135.0, 134.0, 128.0, 119.5, 117.8, 102.6, 71.1, 52.1, 34.0, 32.5, 30.2, 30.1, 30.0, 29.9, 29.8, 26.5, 26.4, 25.5, 25.1, 23.1, 18.5, 17.9, 14.2, 7.0, 5.5, -3.3, -4.9; HRMS (ESI-TOF) calcd for $\text{C}_{70}\text{H}_{106}\text{N}_{15}\text{O}_{15}\text{S}_5\text{Si}_3^+$ $[\text{M} + \text{H}^+]$ 1640.5898, found 1640.5892.

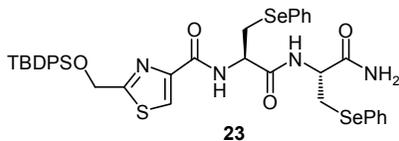


Bis-phenylselenium thiazoline macrocycle amine 20 (Scheme 3):

See below (preparation of seco ester **32**) for the deprotection conditions of bis-phenylselenium thiazoline macrocycle **13** to free amine **20**.

Bis-phenylselenium model system **23** (Scheme 4):

To thiazole **21**⁵ (1.0 g, 2.35 mmol) in 1,2-dichloroethane (12.0 mL) at 25 °C was added trimethyltin hydroxide (1.30 g, 7.05 mmol). The reaction mixture was refluxed for 1 h, then a further 1.30 g of trimethyltin hydroxide (7.05 mmol) was added and reflux was continued for a further hour. The reaction mixture was cooled to 25 °C and concentrated, and the residue was taken up in EtOAc (30 mL). The organic layer



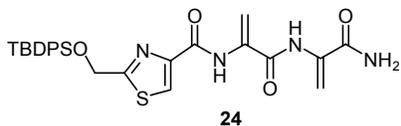
was washed with aqueous 5% HCl solution (5 × 30 mL) and brine (30 mL), then dried (Na₂SO₄) and concentrated to give pure carboxylic acid **22** as a white foam (932 mg, 100%). To carboxylic acid **22** (100 mg, 0.24 mmol) and amine **4**¹ (114 mg, 0.24 mmol) in DMF (1.2 mL) at 0 °C were added *i*-Pr₂NEt (0.13 mL, 0.72 mmol), HOAt (49 mg, 0.36 mmol), and HATU (137 mg, 0.36 mmol). The reaction mixture was stirred for 20 min at 0 °C and 2 h at 25 °C, then diluted with EtOAc (40 mL). The organic layer was washed with aqueous 5% HCl solution, water, saturated aqueous NaHCO₃ solution, and brine (20 mL each), then dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:8) to give bis-phenylselenium model system **23** (181 mg, 85%) as a clear oil.

23: $R_f = 0.49$ (silica gel, hexanes:EtOAc, 3:7); $[\alpha]_D^{32} = -82.4$ (CHCl₃, $c = 1.00$); IR (film) ν_{\max} 3365, 2931, 2849, 1654, 1559, 1474, 1111, 738, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09 (s, 1 H), 7.77 (d, $J = 6.3$ Hz, 1 H) 7.74 – 7.70 (m, 4 H), 7.49 – 7.41 (m, 10 H), 7.19 – 7.14 (m 6 H), 6.94 (d, $J = 8.1$ Hz, 1 H), 6.65 (br s, 1 H), 5.41 (br s, 1 H), 4.94 (s, 2 H), 4.65 (dt, $J = 8.1, 5.9$ Hz, 1 H), 4.52 (q, $J = 6.3$ Hz, 1 H), 3.43 (dd, $J = 13.2, 5.5$ Hz, 1 H), 3.26 (dd, $J = 12.9, 5.9$ Hz, 1 H), 3.15 (dd, $J = 13.2, 7.0$ Hz, 1 H), 3.12 (dd, $J = 13.2, 5.9$ Hz), 1.16 (s, 9 H); ¹³C NMR (150 MHz, CDCl₃) δ 173.3, 172.3, 170.1, 161.8, 148.8, 135.7, 135.6, 133.3, 133.2, 132.4, 132.3, 130.4, 129.4, 129.3, 128.6, 128.2, 127.7, 127.6, 124.2, 63.8, 53.8, 53.0, 38.8, 29.1, 29.0, 26.9, 19.4, 14.5; HRMS (ESI-TOF) calcd for C₃₉H₄₃N₄O₄SSe₂⁺ [M + H⁺] 851.1099, found 851.1085.

Bis-dehydroalanine model system **24** (Scheme 4):

To bis-phenylselenium model system **23** (90 mg, 0.11 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was added *t*-BuOOH (0.20 mL of a 5 – 6 M solution in decane). The reaction mixture was stirred for 10 min at 0 °C and 30 min at 25 °C, then a further 0.20 mL of the *t*-BuOOH solution was added. Stirring was continued for 30 min, then a third 0.20 mL portion of the *t*-BuOOH solution was

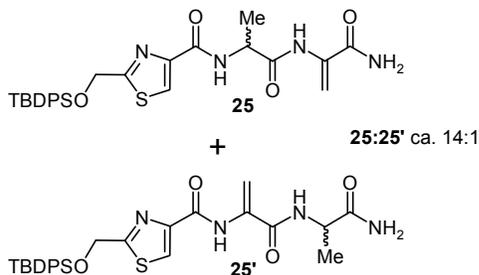
added and stirring was continued for 30 min. The reaction mixture was then cooled to 0 °C and quenched with a saturated aqueous 1:1 solution of NaHCO₃ and Na₂S₂O₃ (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:6) to give bis-dehydroalanine model system **24** (46 mg, 82%) as a white powder.



24: $R_f = 0.61$ (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{\max} 3366, 2931, 2847, 1658, 1486, 1427, 1192, 1111, 891, 823, 743, 701 cm^{-1} ; ^1H NMR (500 MHz, CDCl₃) δ 9.81 (br s, 1 H), 8.93 (br s, 1 H), 8.14 (s, 1 H), 7.71 – 7.68 (m, 4 H), 7.49 – 7.40 (m, 6 H), 6.73 (d, $J = 2.2$ Hz, 1 H), 6.61 (d, $J = 2.2$ Hz, 1 H), 6.15 (br, 1 H), 5.78 (br, 1 H), 5.50 (t, $J = 1.9$ Hz, 1 H), 5.38 (t, $J = 1.5$ Hz, 1 H), 4.98 (s, 2 H), 1.15 (s, 9 H); ^{13}C NMR (125 MHz, CDCl₃) δ 173.3, 165.6, 162.4, 160.1, 149.9, 135.7, 134.6, 133.1, 132.5, 130.4, 128.2, 123.9, 103.4, 102.9, 64.0, 26.9, 19.5; HRMS (ESI-TOF) calcd for C₂₇H₃₁N₄O₄SSi⁺ [M + H⁺] 535.1830, found 535.1829.

Reduced dehydroalanines **25** and **25'** (14:1 mixture of inseparable regioisomers) [Scheme 5]:

To bis-dehydroalanine model system **24** (22 mg, 0.041 mmol) in THF (0.40 mL) at 0 °C was added *n*-Bu₃SnH (0.28 mL, 1.03 mmol) and PdCl₂(PPh₃)₂ (2.9 mg, 0.0041 mmol). The reaction mixture was stirred for 10 min at 0 °C and then for 1 h at 25 °C. A further 2.9 mg of PdCl₂(PPh₃)₂ (0.0041 mmol) and 0.28 mL of *n*-Bu₃SnH (1.03 mmol) were then added and stirring was continued for 50 min. The crude reaction mixture was then purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:6) to give reduced dehydroalanines **25** and **25'** (18.9 mg, 85%) as a yellow oil and as a *ca* 14:1 mixture of chromatographically inseparable regioisomers.



25 and **25'** (*ca* 14:1 mixture of chromatographically inseparable regioisomers): $R_f = 0.48$ (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{\max} 3355, 2930, 2857, 1654, 1522, 1427, 1193, 1113, 823, 754, 701 cm^{-1} ; ^1H NMR (600 MHz, CDCl₃), major regioisomer **25** δ 8.76 (br s, 1 H), 8.07 (s, 1 H), 7.68 – 7.62 (m, 4 H), 7.47 – 7.37 (m, 6 H), 6.48 (d, $J = 1.7$ Hz, 1 H), 6.19 (br, 1 H), 5.91 (br,

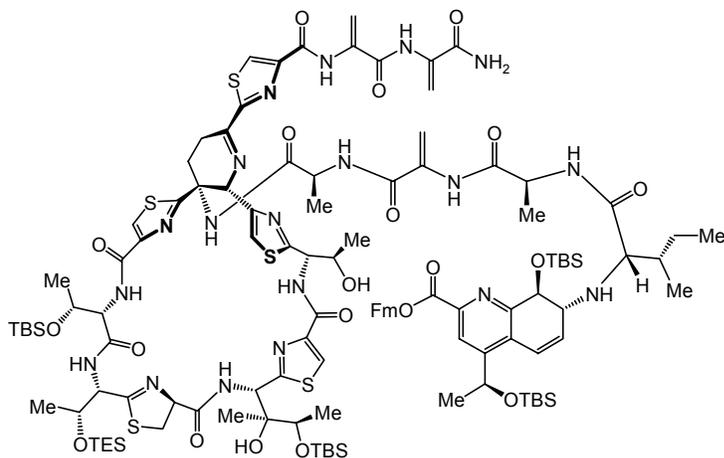
$J = 8.3$ Hz, 1 H), 7.84 – 7.82 (m, 2 H), 7.76 (d, $J = 7.9$ Hz, 1 H), 7.73 (d, $J = 7.0$ Hz, 1 H), 7.57 – 7.56 (m, 2 H), 7.50 – 7.48 (m, 2 H), 7.46 (br s, 1 H), 7.41 – 7.38 (m, 2 H), 7.32 (t, $J = 7.4$ Hz, 2 H), 7.26 – 7.15 (m, 9 H), 7.14 (d, $J = 4.0$ Hz, 1 H), 6.87 (s, 1 H), 6.86 (d, $J = 10.1$ Hz, 1 H), 6.36 (dd, $J = 10.1, 4.0$ Hz, 1 H), 5.56 (d, $J = 9.7$ Hz, 1 H), 5.37 (s, 1 H), 5.25 – 5.23 (m, 2 H), 4.97 (m, 1 H), 4.84 – 4.82 (m, 1 H), 4.77 (d, $J = 3.5$ Hz, 1 H), 4.72 – 4.60 (m, 5 H), 4.52 – 4.49 (m, 2 H), 4.41 (t, $J = 6.0$ Hz, 1 H), 4.38 – 4.31 (m, 2 H), 4.28 – 4.24 (m, 2 H), 4.19 (t, $J = 8.2$ Hz, 1 H), 4.10 – 4.05 (m, 2 H), 3.63 – 3.55 (m, 4 H), 3.48 – 3.45 (m, 1 H), 3.44 – 3.32 (m, 4 H), 3.30 – 3.10 (m, 2 H), 2.96 – 2.86 (br, 1 H), 2.45 (br s, 1 H), 1.35 (d, $J = 7.0$ Hz, 3 H), 1.32 (d, $J = 6.1$ Hz, 3 H), 1.24 – 1.21 (m, 9 H), 1.16 (d, $J = 6.1$ Hz, 3 H), 1.09 (d, $J = 6.1$ Hz, 3 H), 1.03 (s, 3 H), 0.97 – 0.90 (m, 27 H), 0.88 (s, 9 H), 0.82 (d, $J = 6.6$ Hz, 3 H), 0.75 (s, 9 H), 0.66 (q, $J = 7.9$ Hz, 6 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), –0.03 (s, 3 H), –0.11 (s, 3 H); ^{13}C NMR (150 MHz, dioxane- d_8 , 70 °C) δ 174.6, 173.6, 173.1, 172.7, 172.2, 171.1, 170.7, 170.6, 169.8, 169.3, 165.6, 161.1, 160.0, 151.5, 151.3, 149.8, 147.1, 145.3, 145.2, 142.2, 142.2, 133.5, 133.4, 133.2, 132.8, 132.8, 132.2, 131.2, 131.0, 130.7, 130.5, 130.5, 129.9, 129.8, 129.8, 129.9, 129.0, 128.3, 127.8, 127.7, 127.7, 127.6, 127.3, 126.2, 126.1, 122.6, 122.3, 120.6, 120.6, 75.5, 71.3, 68.0, 67.8, 64.9, 58.2, 53.9, 53.8, 50.5, 47.9, 39.3, 38.7, 34.0, 32.5, 30.4, 30.3, 30.2, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 27.8, 26.5, 26.3, 26.2, 26.0, 25.4, 24.9, 23.2, 18.8, 18.6, 17.9, 16.2, 14.2, 11.7, 7.1, 5.6, –4.0, –4.3, –4.7, –4.8; HRMS (ESI–TOF) calcd for $\text{C}_{134}\text{H}_{187}\text{N}_{19}\text{O}_{20}\text{S}_5\text{Se}_3\text{Si}_5^+$ $[\text{M} + \text{H}^+]$ 2922.9217, found 2922.9215.

Triene seco ester **33** (Scheme 7):

To seco ester **32** (3.0 mg, 0.0010 mmol) in CH_2Cl_2 (0.10 mL) at 0 °C was added *t*-BuOOH (60 μL of 5 – 6 M decane solution). The reaction mixture was stirred for 5 min at 0 °C and then warmed to 25 °C. Stirring was continued for 20 min, and then a further 60 μL of the above *t*-BuOOH solution was added. The resulting mixture was stirred for a further 30 min, cooled to 0 °C, quenched with a saturated aqueous 1:1 solution of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL), and then warmed to 25 °C and stirred for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 \times 2 mL) then dried (Na_2SO_4) and concentrated. The crude residue was purified by preparative TLC (silica gel, CH_2Cl_2 :MeOH, 92:8) to give triene seco ester **33** (1.9 mg, 74%) as a yellow foam.

33: $R_f = 0.42$ (silica gel, CH_2Cl_2 :MeOH, 93:7); $[\alpha]_D^{32} = -19.5$ (CHCl_3 , $c = 0.15$); IR (film) ν_{max} 3352, 2919, 2850, 1702, 1655, 1521, 1464, 1378, 1251, 1212, 1099, 835, 741 cm^{-1} ; ^1H NMR

(600 MHz, CD₃CN, 70 °C) δ 9.77 (s, 1 H), 8.90 (s, 1 H), 8.26 (s, 1 H), 8.14 (s, 1 H), 8.09 (s, 1 H), 7.91 (d, *J* = 8.3 Hz, 1 H), 7.83 (dd, *J* = 7.9, 4.4 Hz, 2 H), 7.77 – 7.71 (m, 3 H), 7.65 – 7.61 (br, 1 H), 7.58 (br s, 1 H), 7.41 (q, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 3 H), 7.22 (d, *J* = 8.1 Hz,



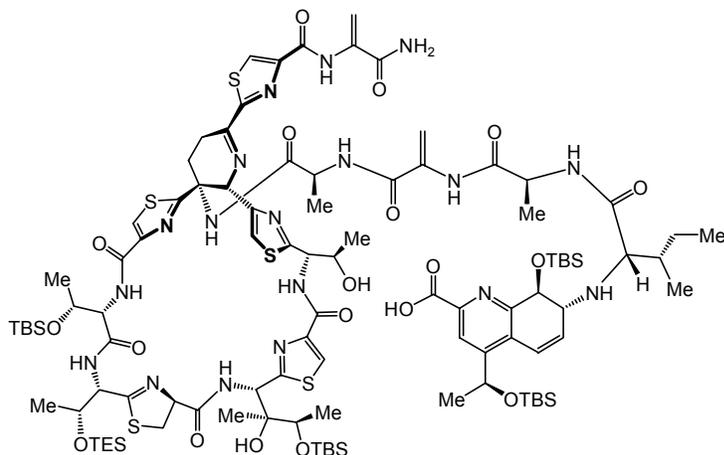
33

1 H), 6.87 (d, *J* = 10.0 Hz, 1 H), 6.51 (d, *J* = 1.8 Hz, 1 H), 6.39 – 6.34 (m, 1 H), 6.37 (d, *J* = 1.7 Hz, 1 H), 5.95 (s, 1 H), 5.59 – 5.52 (m, 3 H), 5.46 (s, 1 H), 5.39 (s, 1 H), 5.36 (t, *J* = 5.3 Hz, 1 H), 5.26 (q, *J* = 6.6 Hz, 1 H), 5.19 – 5.13 (m, 1 H), 4.95 (dt, *J* = 9.2, 1.7 Hz, 1 H), 4.85 – 4.81 (m, 1 H), 4.75 – 4.73 (m, 1 H), 4.72 (dd, *J* = 6.6, 4.0 Hz, 1 H), 4.66 (dd, *J* =

10.9, 7.0 Hz, 1 H), 4.52 – 4.49 (m, 2 H), 4.40 (t, *J* = 7.0 Hz, 1 H), 4.27 – 4.20 (m, 3 H), 4.07 (q, *J* = 7.0 Hz, 1 H), 3.29 – 3.21 (m, 2 H), 2.98 – 2.92 (br, 1 H), 2.52 – 2.44 (br, 1 H), 1.35 (d, *J* = 6.0 Hz, 3 H), 1.32 (d, *J* = 7.0 Hz, 3 H), 1.26 – 1.22 (m, 9 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 1.01 (s, 3 H), 0.96 – 0.89 (m, 36 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 0.74 (s, 9 H), 0.63 (q, *J* = 7.9 Hz, 6 H), 0.18 (s, 3 H), 0.17 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), –0.02 (s, 3 H), –0.13 (s, 3 H); ¹³C NMR (150 MHz, dioxane-*d*₈, 70 °C) δ 166.2, 165.3, 162.5, 162.4, 156.2, 144.4, 140.8, 133.6, 128.1, 126.3, 124.5, 119.1, 76.5, 69.3, 67.4, 66.5, 64.7, 56.6, 52.0, 49.3, 45.7, 40.3, 38.5, 37.5, 33.0, 29.4, 28.5, 25.8, 24.9, 17.6, 5.8, –3.2, –5.9, –7.2; HRMS (ESI–TOF) calcd for C₁₁₆H₁₇₀N₁₉O₂₀S₅Si₅⁺ [M + H⁺] 2449.0313, found 2449.0309.

Truncated hydroxy acid **34** (Scheme 7):

To triene seco ester **33** (1.9 mg, 0.00078 mmol) at 0 °C was added 0.10 mL of a 10:1 solution of CH₂Cl₂:Et₂NH. The reaction mixture was stirred for 5 min at 0 °C and for a further 2.5 h at 25 °C, then diluted with toluene (3 mL) and concentrated. The crude residue was purified by preparative TLC (silica gel, CH₂Cl₂:MeOH, 92:8) to give truncated hydroxy acid **34** (1.3 mg, 78%) as a yellow oil.



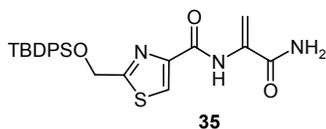
34

34: $R_f = 0.23$ (silica gel, $\text{CH}_2\text{Cl}_2:\text{MeOH}$, 93:7); $[\alpha]_D^{32} = -22.4$ (CHCl_3 , $c = 0.12$); IR (film) ν_{max} 3358, 2931, 2864, 1709, 1654, 1521, 1458, 1386, 1254, 1212, 1097, 831, 741 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CD_3CN , 70 °C) δ 9.88 (s, 1 H), 8.26 (s, 1 H), 8.20 (s, 1 H), 8.15 (s, 1 H), 7.95 (d, $J = 8.1$ Hz, 1 H), 7.81 – 7.78 (br, 1 H), 7.61 – 7.56 (br, 1 H), 7.49

(s, 1 H), 7.29 – 7.22 (m, 2 H), 6.90 (d, $J = 9.9$ Hz, 1 H), 6.55 (d, $J = 1.5$ Hz, 1 H), 6.38 – 6.34 (m, 1 H), 5.99 (s, 1 H), 5.59 – 5.52 (m, 3 H), 5.41 (s, 1 H), 5.37 (t, $J = 5.7$ Hz, 1 H), 5.29 (q, $J = 6.2$ Hz, 1 H), 5.21 – 5.18 (m, 1 H), 4.96 (d, $J = 9.3$ Hz, 1 H), 4.85 – 4.81 (m, 1 H), 4.76 (s, 1 H), 4.56 – 4.51 (m, 2 H), 4.41 – 4.37 (m, 1 H), 4.31 – 4.27 (m, 3 H), 4.11 – 4.06 (m, 1 H), 3.46 – 3.44 (m, 1 H), 3.29 – 3.21 (m, 2 H), 2.98 – 2.92 (br, 1 H), 2.52 – 2.44 (br, 1 H), 1.38 (d, $J = 6.6$ Hz, 3 H), 1.36 (d, $J = 7.0$ Hz, 3 H), 1.26 (d, $J = 6.2$ Hz, 3 H), 1.20 (d, $J = 6.3$ Hz, 3 H), 1.13 – 1.08 (m, 9 H), 1.03 (s, 3 H), 0.99 – 0.89 (m, 36 H), 0.86 (d, $J = 6.6$ Hz, 3 H), 0.72 (s, 9 H), 0.63 (q, $J = 7.9$ Hz, 6 H), 0.19 (s, 3 H), 0.18 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), –0.01 (s, 3 H), –0.12 (s, 3 H); HRMS (ESI–TOF) calcd for $\text{C}_{99}\text{H}_{157}\text{N}_{18}\text{O}_{19}\text{S}_5\text{Si}_5^+$ [$\text{M} + \text{H}^+$] 2201.9322, found 2201.9283.

Truncated dehydroalanine **35** (Scheme 8):

To bis-dehydroalanine model system **24** (20 mg, 0.040 mmol) at 0 °C was added 1.0 mL of a 6.3:1 solution of $\text{CH}_2\text{Cl}_2:\text{Et}_2\text{NH}$. The reaction mixture was stirred for 30 min at 0 °C and 2 h at 25 °C, then diluted in EtOAc (10 mL) and washed with aqueous 5% HCl solution, saturated aqueous NaHCO_3 solution, and brine (5 mL each), then dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:2) to give truncated dehydroalanine **35** (16.1 mg, 93%) as a white powder.



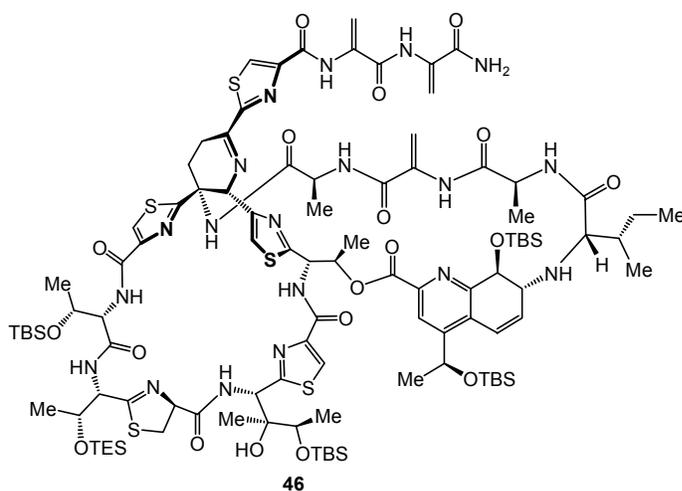
35

35: $R_f = 0.68$ (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{max} 3366, 2931, 2847, 1658, 1523, 1486, 1192, 743 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.78 (br s, 1 H), 8.13 (s, 1 H), 7.71 – 7.68

(m, 4 H), 7.49 – 7.40 (m, 6 H), 6.68 (d, $J = 2.2$ Hz, 1 H), 6.08 (br, 1 H), 5.75 (br, 1 H), 5.37 (t, $J = 1.5$ Hz, 1 H), 4.99 (s, 2 H), 1.15 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 173.3, 165.9, 160.1, 150.0, 135.7, 133.9, 132.5, 130.3, 128.2, 123.8, 103.2, 64.0, 26.9, 19.5; HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_3\text{SSi}^+$ [$\text{M} + \text{H}^+$] 465.1615, found 465.1619.

Macrolide triene **46** (Scheme 9):

To seco ester **32** (31 mg, 0.011 mmol) at 0 °C was added 4 mL of a 6.5:1 solution of $\text{CH}_2\text{Cl}_2:\text{Et}_2\text{NH}$, and the resulting mixture stirred for 5 min at 0 °C and then warmed to 25 °C.



After stirring for 2.5 h at 25 °C, toluene was added and the reaction mixture was concentrated. The residue was purified by preparative TLC (silica gel, $\text{CH}_2\text{Cl}_2:\text{MeOH}$, 92.5:7.5) to give carboxylic acid **44** (25 mg, 87%) as a tan foam. To carboxylic acid **44** (25 mg, 0.0091 mmol) in toluene (0.50 mL) at 25 °C was added triethylamine (51 μL , 0.36 mmol) and 2,4,6-trichlorobenzoyl

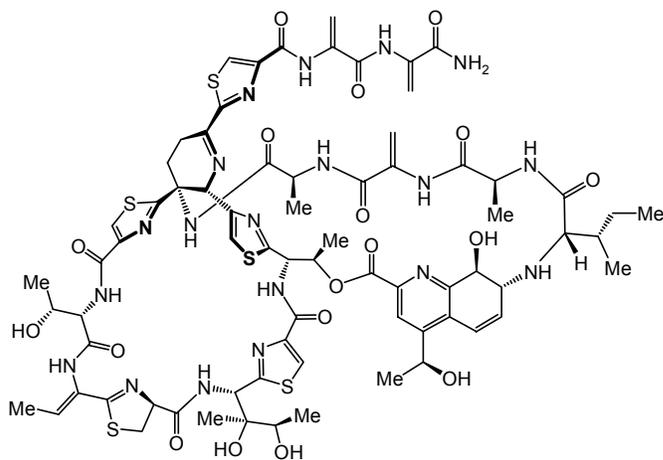
chloride (0.043 mL, 0.27 mmol). The reaction mixture was stirred for 24 h at 25 °C, then diluted with toluene (total volume = 4.25 mL) and added dropwise over the course of 12 h (syringe pump) to a solution of DMAP (33 mg, 0.27 mmol) in toluene (18.3 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH ~ 3 with an aqueous 10 mg/mL solution of KHSO_4 . The layers were separated and the aqueous layer was re-extracted with EtOAc (2×10 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous NaHCO_3 :brine (10 mL) and the aqueous layer was re-extracted with EtOAc (2×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC (silica gel, $\text{CH}_2\text{Cl}_2:\text{MeOH}$, 93:7) to give macrolide **45** as a pale yellow foam (10.7 mg, 42%). (Note: due to low solubility and extremely restricted rotation of the bulky phenylselenium and silyl protecting groups, no meaningful spectral data could be acquired for **45**.) To a suspension of macrolide **45** (10.7 mg, 0.0039 mmol) and NaHCO_3 (10.7 mg, 0.13 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was

added *t*-BuOOH (0.13 mL of a 5 – 6 M solution in decane). The reaction mixture was stirred for 5 min at 0 °C and then warmed to 25 °C. Stirring was continued for 1 h at 25 °C, then a further 0.13 mL of the 5 – 6 M decane solution of *t*-BuOOH was added. Stirring was continued for 1 h, then the reaction mixture was cooled to 0 °C, and EtOAc (12 mL) and a saturated aqueous 1:1 solution of Na₂S₂O₃ and NaHCO₃ (7 mL) were added. The layers were separated and the aqueous phase was re-extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by preparative TLC (silica gel, CH₂Cl₂:MeOH, 93:7) to give macrolide triene **46** (5.9 mg, 68%) as a pale yellow foam.

46: $R_f = 0.38$ (silica gel, CHCl₃:MeOH, 92:8); $[\alpha]_D^{32} = -23.6$ (CHCl₃, $c = 0.19$); IR (film) ν_{\max} 3354, 2924, 2852, 1705, 1658, 1501, 1464, 1381, 1250, 1219, 1098, 832, 779 cm⁻¹; ¹H NMR (600 MHz, CD₃CN, 70 °C) δ 9.72 (s, 1 H), 8.88 (s, 1 H), 8.25 (br s, 1 H), 8.24 (s, 1 H), 7.99 (br s, 1 H), 7.49 (br s, 1H), 7.34 (br s, 1 H), 7.12 (d, $J = 4.3$ Hz, 1 H), 6.90 (d, $J = 9.6$ Hz, 1 H), 6.50 (d, $J = 1.0$ Hz, 1 H), 6.34 (d, $J = 1.0$ Hz, 1 H), 6.31 – 6.29 (m, 1 H), 5.85 (br s, 1 H), 5.57 (s, 1 H), 5.55 (s, 1 H), 5.48 (t, $J = 7.1$ Hz, 1 H), 5.42 (d, $J = 7.7$ Hz, 1 H), 5.36 (s, 1 H), 5.21 (d, $J = 6.4$ Hz, 2 H), 4.89 – 4.82 (m, 2 H), 4.71 (s, 1 H), 4.56 (br s, 1 H), 4.39 – 4.22 (m, 4 H), 4.01 (d, $J = 6.8$ Hz, 1 H), 3.68 (t, $J = 7.4$ Hz, 1 H), 3.42 – 3.39 (m, 3 H), 3.04 (d, $J = 5.7$ Hz, 1 H), 2.53 – 2.48 (br, 1 H), 2.42 – 2.38 (br, 1 H), 1.36 (d, $J = 6.6$ Hz, 3 H), 1.26 (d, $J = 6.1$ Hz, 3 H), 1.23 – 1.20 (m, 9 H), 1.16 – 1.13 (m, 9 H), 1.10 (d, $J = 7.1$ Hz, 3 H), 0.92 – 0.88 (m, 36 H), 0.74 (s, 9 H), 0.63 (q, $J = 7.9$ Hz, 6 H), 0.18 (s, 3 H), 0.17 (s, 3 H), 0.14 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H), –0.05 (s, 3 H), –0.18 (s, 3 H); ¹³C NMR (150 MHz, dioxane-*d*₈, 70 °C) δ 172.4, 171.9, 171.0, 169.4, 168.9, 168.6, 167.8, 166.9, 166.8, 165.3, 163.7, 161.5, 160.5, 160.1, 159.5, 159.3, 159.2, 157.1, 156.2, 153.0, 151.8, 149.0, 148.9, 145.1, 142.0, 145.2, 133.2, 132.5, 131.4, 129.2, 127.9, 127.8, 127.6, 125.4, 125.3, 122.9, 122.7, 121.2, 120.5, 115.7, 100.0, 99.9, 77.8, 75.9, 70.8, 68.6, 58.1, 55.9, 54.3, 53.8, 50.1, 47.2, 37.0, 31.4, 29.9, 27.5, 27.2, 27.1, 25.1, 24.0, 22.9, 20.9, 20.5, 17.8, 17.0, 16.8, 16.5, 15.5, 14.8, 13.2, 13.0, 11.6, 8.9, –1.4, –5.3; HRMS (ESI–TOF) calcd for C₁₀₂H₁₅₈N₁₉O₁₉S₅Si₅⁺ [M + H⁺] 2252.9425, found 2252.9395.

Thiostrepton 1 (Scheme 9):

To macrolide triene **46** (5.9 mg, 0.0027 mmol) at 0 °C was added a 4:1 solution of THF:HF•py (6.0 mL). The reaction mixture was stirred for 5 min at 0 °C, and then for 24 h at 25 °C. The



1: thiostrepton

resulting mixture was then added to a saturated aqueous NaHCO₃ solution (45 mL) at 0 °C and the aqueous layer was extracted with CHCl₃ (3 × 25 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by preparative TLC (silica gel, CHCl₃:MeOH, 9:1) to give synthetic thiostrepton **1** (2.3 mg, 52%) as a white powder.

1 (synthetic and natural): $R_f = 0.34$

(silica gel, CHCl₃:MeOH, 92:8); $[\alpha]_D^{32} = -81.3$ (CHCl₃, $c = 0.17$); IR (film) ν_{\max} 3354, 2978, 2934, 1654, 1527, 1490, 1210, 1103, 1050, 938, 874, 755 cm⁻¹; ¹H NMR (600 MHz, THF-*d*₈, thiostrepton is more soluble and stable in this solvent than in CDCl₃; for proton numbering and abbreviations, see: ref 2f–h in the previous article¹): δ 10.03 (s, 1 H, CONH), 9.69 (s, 1 H, CONH), 9.30 (s, 1 H, CONH), 8.65 (s, 1 H, CONH), 8.39 (s, 1 H, Ar-H), 8.31 (br s, 1 H, OH or NH), 8.29 (s, 1 H, Ar-H), 8.20 (s, 1 H, Ar-H), 8.03 (br s, 1 H, CONH), 7.62 (d, $J = 5.6$ Hz, 1 H, CONH), 7.58 (d, $J = 10.3$ Hz, 1 H, CONH), 7.54 (br s, 1 H, Thstn C3-OH), 7.53 (s, 1 H, Ar-H), 7.48 (br s, 1 H, OH or NH), 7.42 (d, $J = 7.7$ Hz, 1 H, CONH), 7.32 (s, 1 H, Ar-H), 7.07 (d, $J = 7.7$ Hz, 1 H, QC8-OH), 6.99 (br s, 1 H, OH or NH), 6.92 (d, $J = 9.7$ Hz, Q H-5), 6.75 (d, $J = 2.0$ Hz, 1 H, Deala-H), 6.58 (d, $J = 7.5$ Hz, 1 H, CONH), 6.56 (s, 1 H, Deala-H), 6.45 (q, $J = 6.1$ Hz, 1 H, Thr(2) H-3), 6.32 (dd, $J = 9.7, 5.6$ Hz, 1 H, Q H-6), 6.13 (q, $J = 7.1$ Hz, 1 H, But H-3), 5.89 (d, $J = 9.8$ Hz, 1 H, Thr(2) H-2), 5.84 (d, $J = 9.2$ Hz, 1 H, Thstn H-2), 5.77 (s, 1 H, Deala-H), 5.55 (s, 1 H, Deala-H), 5.49 (s, 1 H, OH or NH), 5.47 – 5.46 (m, 1 H, Pip H-6 β), 5.30 (q, $J = 6.1$ Hz, 1 H, Q H-11), 5.20 (s, 1 H, Deala-H), 5.04 (dd, $J = 8.7, 4.1$ Hz, 1 H, Cys H-4 β), 4.84 (t, $J = 7.7$ Hz, 1 H, Ala(2) H-2), 4.73 (d, $J = 7.1$ Hz, 1 H, Q H-8), 4.35 (dd, $J = 7.9, 3.5$ Hz, 1 H, Thr(1) H-2), 4.29 (d, $J = 4.6$ Hz, 1 H, Q H-7 β), 4.20 – 4.15 (m, 2 H, Pip H-4 α , Thstn C4-OH), 3.90 (quin, $J = 6.5$ Hz, 1 H, Ala(1) H-2), 3.85 (quin, $J = 5.7$ Hz, 1 H, Thstn H-4), 3.24 (t, $J = 12.3$ Hz,

1 H, Cys H-5 α), 3.00 – 2.93 (m, 2 H, Ile H-2, Pip H-3 α), 2.39 – 2.35 (m, 1 H, Pip H-4 β), 1.60 (d, J = 7.2 Hz, 3 H, CH₃), 1.33 (d, J = 3.5 Hz, 3 H, CH₃), 1.32 (d, J = 3.1 Hz, 3 H, CH₃), 1.27 (d, J = 6.6 Hz, 3 H, CH₃), 1.16 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.06 (d, J = 6.1 Hz, 3 H, CH₃), 0.96 (t, J = 7.0 Hz, 3 H, CH₃), 0.88 (d, J = 6.6 Hz, 3 H, CH₃); ¹³C NMR (125 MHz, THF-*d*₈) δ 175.6, 173.6, 172.0, 171.9, 171.3, 170.5, 170.2, 169.5, 168.3, 166.6, 166.3, 164.3, 162.8, 162.7, 162.3, 162.1, 162.0, 159.9, 159.4, 155.9, 154.8, 152.1, 151.8, 147.9, 144.7, 136.3, 135.2, 134.3, 131.5, 131.4, 130.6, 128.3, 125.6, 125.4, 123.7, 123.5, 118.4, 102.2, 101.8, 101.7, 80.8, 78.8, 73.7, 65.6, 65.2, 61.1, 58.8, 57.3, 56.7, 54.2, 52.7, 50.0, 39.9, 35.8, 30.7, 27.1, 24.0, 20.9, 19.8, 19.6, 19.4, 18.1, 17.8, 16.1, 16.0, 12.0; HRMS (ESI-TOF) calcd for C₇₂H₈₆N₁₉O₁₈S₅⁺ [M + H⁺] 1664.4996, found 1664.4976.