Synthesis of macrocyclic precursors of the vioprolides

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Supplementary data:

Additional experimental procedures.

General experimental details

Flash column chromatography was performed using Merck silica gel (60H; 40-60μ, 230-240 mesh). Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled. Tetrahydrofuran was dried over sodium-benzophenone and was distilled under nitrogen. Dichloromethane was dried over CaH_2 and was distilled. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Mass spectra used electron impact ionisation (EI^+), chemical ionisation using ammonia (CI^+), electrospray ionisation in the positive mode (ES^+), atmospheric pressure chemical ionisation in the positive mode ($APCI^+$) and time of flight MS with electrospray ionisation (TOF ES^+). Low resolution and high resolution mass spectra were recorded using a Micromass Trio 200 and a Kratos Concept IS spectrometer, respectively. Characteristic groups of peaks were observed in mass spectra for compounds containing selenium and chlorine atoms. Accurate mass data correspond to compounds with the isotopes ^{80}Se and ^{35}Cl. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films. Nuclear magnetic resonance spectra were recorded using Varian Unity 500 (500 MHz), Varian INOVA 400 (400 MHz) and Varian Unity 300 (300 MHz) spectrometers at *ca.* 25 °C unless otherwise stated. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are relative to tetramethylsilane. Residual non-deuteriated solvent was used as the internal standard.

Prop-2-enyl *N*-[*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-serinyl]-*O*-*tert*-butyldimethylsilyl-L-threoninate (8). *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) (586 mg, 1.54 mmol) and hydroxybenzotriazole hydrate (HOBt) (60 mg, 0.44 mmol) were added to *N*-Fmoc-L-serine (360 mg, 1.10 mmol) in DMF (10 mL). The allyl ester of *O*-*tert*-butyldimethylsilyl-L-threonine **7**[31] (300 mg, 1.10 mmol) in DMF (5 mL) was added followed by di-isopropylethylamine (568 mg, 4.39 mmol), and the reaction mixture stirred at rt for 16 h then partitioned between saturated aqueous NH_4Cl (40 mL) and ether (60 mL). The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (20:80 light petroleum:ether) gave the *title compound* **8** (620 mg, 97%) as a pale yellow oil, R_f = 0.3 (20:80 light petroleum:ether), $[\alpha]_D^{20}$ −7.4 (*c* 2.0, $CHCl_3$) (Found: M^+ + H, 583.2837. $C_{31}H_{43}N_2O_7Si$ requires M, 583.2835); ν_{max}/cm^{-1} 3406, 3338, 2931, 2883, 2857, 1731, 1668, 1518, 1450, 1251, 1202, 1148, 1092, 1023, 969, 937, 838, 777, 759, 740 and 651; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.06 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.21 (3 H, d, *J* 6.3, threo 4-H_3), 3.34 (1 H, br. s, OH), 3.71 and 4.06 (each 1 H, m, ser 3-H), 4.23 (1 H, m, fluorenyl CH_2CH), 4.35-4.45 (3 H, m, ser 2-H, fluorenyl $CHCH_2$), 4.50-4.55 (2 H, m, threo 2-H, threo 3-H), 4.60 and 4.68 (each 1 H, m, CO_2CH), 5.31 (1 H, d, *J* 8.0, CH=CH*H*), 5.38 (1 H, d, *J* 16.0, CH=CH*H*), 5.80 (1 H, d, *J* 8.0, NH), 5.93 (1 H, m, $CH=CH_2$), 6.85 (1 H, d, *J* 8.0, NH), 7.33 (2 H, t, *J* 7.3, ArH), 7.42 (2 H, t, *J* 7.6, ArH), 7.61 (2 H, d, *J* 7.1, ArH) and 7.79 (2 H, d, *J* 7.6, ArH); δ_C (125 MHz, $CDCl_3$) −5.4, −4.4, 17.7, 21.2, 25.5, 47.1, 55.5, 58.6, 63.3, 66.6, 67.3, 68.1, 119.5, 119.9, 125.1, 127.0, 127.7, 131.1, 141.3, 143.8, 156.1, 170.8 and 171.6; *m*/*z* (ES^+) 605 (M^+ + 23, 100%).

Prop-2-enyl *N*-[*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-*O*-tri-isopropylsilyl-L-serinyl]-*O*-*tert*-butyldimethylsilyl-L-threoninate (9). Tri-isopropylsilyl trifluoromethylsulfonate (628 mg, 2.05 mmol) and 2,6-lutidine (293 mg, 2.73 mmol) were added to the alcohol **8** (796 mg, 1.37 mmol) in DCM (20 mL) at rt and the reaction mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (70:30 light petroleum:ether) gave the *title compound* **9** (564 mg, 56%) as a colourless gum, R_f = 0.3 (70:30 light petroleum:ether), $[\alpha]_D^{20}$ −18.7 (*c* 2.0, $CHCl_3$) (Found: M^+ + H, 739.4170. $C_{40}H_{63}N_2O_7Si_2$ requires M, 739.4168); ν_{max}/cm^{-1} 3432, 3345, 3065, 2943, 2891, 2865, 1731, 1681, 1593, 1579, 1504, 1463, 1541, 1376, 1310, 1251, 1223, 1199, 1094, 996, 882, 836, 773 and 739; δ_H (400 MHz, $CDCl_3$) −0.05 and 0.00 (each 3 H, s, $SiCH_3$), 0.80 [9 H, s, $SiC(CH_3)_3$], 1.05 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.15 (3 H, d, *J* 6.3, threo 4-H_3), 3.83 (1 H, dd, *J* 5.6, 9.6, ser 3-H), 4.21 (2 H, m, fluorenyl CH_2), 4.15-4.55 (7 H, m, ser 3-H′, threo 2-H, ser 2-H, threo 3-H, fluorenyl CH, CO_2CH_2), 5.24 (2 H, m, $CH=CH_2$), 5.69 (1 H, m, $CH=CH_2$), 5.87 and 7.09 (each 1 H, m, NH), 7.27 (2 H, t, *J* 7.3, ArH), 7.37 (2 H, t, *J* 7.1, ArH), 7.55 (2 H, m, ArH) and 7.74 (2 H, d, *J* 7.6, ArH); *m*/*z* (ES^+) 761 (M^+ + 23, 100%).

***N*-(2-Amino-5-nitrophenyl)-*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-prolinamide (12).** *N*-Methylmorpholine (0.38 mL, 2.96 mmol) was added to Fmoc-proline **11** (1.00 g, 2.96 mmol) in THF (25 mL) at −20 °C followed by isobutyl chloroformate (0.38 mL, 2.96 mmol). The mixture was stirred for 10 min, 4-nitro-*ortho*-phenylenediamine (0.45 g, 2.96 mmol) was added, and the mixture was stirred at −20 °C for 3 h and for a further 12 h at rt. After concentration under reduced pressure, the residue was dissolved in ethyl acetate (100 mL), and the solution was washed with saturated aqueous NH_4Cl (3 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL). It was then dried ($MgSO_4$) and concentrated under reduced pressure. Trituration (4:1 hexane:ethyl acetate, 25 mL) of the residue gave the *title compound* **12** as a yellow solid (1.10 g, 79%), $[\alpha]_D^{28}$ −124 (*c* 1.1, $CHCl_3$) (Found: M^+ + Na, 495.1627. $C_{26}H_{24}N_4O_5Na$ requires M, 495.1639); ν_{max}/cm^{-1} 3350, 2952, 1678,

1600, 1518, 1495, 1423, 1315, 1191, 1129 and 739; δ_H (500 MHz, DMSO-d_6, 100 °C) 1.68-1.78 (2 H, m, 4-H_2), 1.90 and 2.07 (each 1 H, m, 3-H), 2.97 (3 H, m, 5-H_2, fluorenyl CH), 3.78 (1 H, m, 2-H), 5.92 (2 H, br. s, NH_2), 6.21 (2 H, s, fluorenyl CH_2), 6.85 (1 H, d, *J* 9.0, ArH), 7.34 (2 H, t, *J* 7.5, ArH), 7.48 (2 H, t, *J* 7.5, ArH), 7.79-7.85 (5 H, m, ArH), 8.28 (1 H, d, *J* 2.5, ArH) and 9.31 (1 H, br. s, NH); δ_C (125 MHz, DMSO-d_6, 100 °C) 25.1, 29.6, 46.0, 60.4, 78.4, 108.1, 113.7, 119.2, 120.0, 120.5, 121.5, 126.5, 128.2, 137.0, 139.0, 142.3, 147.9 and 154.4; *m/z* (ES^+) 495.3 (M^+ + 23, 90%) and 261.2 (100).

_N_-(2-Amino-5-nitrophenyl)-_N_-(9_H_-fluoren-9-ylmethoxycarbonyl)-L-thioprolinamide (13).
A mixture of P_4S_{10} (0.20 g, 0.43 mmol) and Na_2CO_3 (0.40 g, 0.43 mmol) was stirred in THF (10 mL) under nitrogen until completely dissolved (1 h). The reaction mixture was cooled to 0 °C and the prolinamide **12** (0.40 g, 0.85 mmol) was added. The mixture was stirred at 0 °C for 30 min and at rt for 2.5 h, then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (60 mL), and the solution washed with saturated aqueous $NaHCO_3$ (60 mL), H_2O (60 mL) and brine (60 mL), and then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (1:1 light petroleum:EtOAc) gave the *title compound* **13** as a yellow foam (0.29 g, 71%), R_f = 0.5 (1:1 light petroleum:EtOAc), $[\alpha]_D^{28}$ −102 (*c* 1.1, $CHCl_3$) (Found: M^+ + H, 489.1584. $C_{26}H_{25}N_4O_4S$ requires M, 489.1591); ν_{max}/cm^{-1} 3341, 3227, 2952, 1679, 1633, 1604, 1587, 1515, 1492, 1414, 1309, 1191, 825 and 736; δ_H (500 MHz, DMSO-d_6) 1.88 (1 H, m, 4-H), 2.13 (2 H, m, 4-H′, 3-H), 2.35 (1 H, m, 3-H′), 3.53 and 3.62 (each 1 H, m, 5-H), 4.20 (1 H, m, fluorenyl CH), 4.30 (2 H, m, fluorenyl CH_2), 4.72 (1 H, m, 2-H), 6.37 (2 H, br. s, NH_2), 6.77 (1 H, d, *J* 9.0, ArH), 7.25-7.45 (4 H, m, ArH), 7.65-7.72 (2 H, m, ArH), 7.85-8.00 (4 H, m, ArH) and 11.26 (1 H, s, NH); δ_C (125 MHz, DMSO-d_6) 24.0, 32.7, 46.6, 47.1, 66.9, 67.3, 113.8, 120.2, 124.9, 125.2(2), 127.1, 127.7, 135.3, 140.7, 143.6, 143.8, 150.7, 154.7 and 206.5; *m/z* (ES^-) 487.2 ($[M - 1]^-$, 100%).

(9_H_-Fluoren-9-yl)methyl (_S_)-2-(6-nitro-1_H_-benzo[_d_][1,2,3]triazole-1-carbonothioyl)pyrrolidine-1-carboxylate (14).
Sodium nitrite (0.27 g, 3.99 mmol) was added to the thioprolinamide **13** (1.20 g, 2.46 mmol) in glacial acetic acid (30 mL) and H_2O (1.5 mL) at 0 °C and the reaction mixture stirred at 0 °C for 30 min and at rt for 1.5 h. Ice-water (100 mL) was added and the mixture was filtered. The filtrate was washed with EtOAc (80 mL) and concentrated under reduced pressure to afford the *title compound* **14** as a pale orange powder (1.06 g, 86%), a 2:1 mixture of rotamers (^{1}H NMR), $[\alpha]_D^{30}$ −57 (*c* 1.0, $CHCl_3$) (Found: M^+ + Na, 522.1203. $C_{26}H_{21}N_5O_4SNa$ requires M, 522.1206); ν_{max}/cm^{-1} 1703, 1536, 1416, 1347 and 758; δ_H (400 MHz, $CDCl_3$) 1.89 (1.8 H, m, 4-H, 3-H), 2.05-2.20 (1.2 H, m, 4-H′, 3-H), 2.46 (0.63 H, m, 3-H′), 2.70 (0.37 H, m, 3-H′), 3.57-3.85 (2 H, m, 5-H_2), 3.97 (0.63 H, t, *J* 4.0, fluorenyl CH), 4.31 (0.74 H, m, fluorenyl C*H*CH*H*), 4.54-4.63 (1 H, m, fluorenyl CH*H*), 4.77 (0.63 H, dd, *J* 11.0, 4.0, fluorenyl CH*H*), 5.64 (0.63 H, dd, *J* 9.0, 2.5, 2-H), 6.25 (0.37 H, dd, *J* 9.0, 3.0, 2-H), 6.81-6.84 (0.74 H, m, ArH), 6.99-7.03 (1.26 H, m, ArH), 7.11-7.15 (2 H, m, ArH), 7.32-7.47 (2.52 H, m, ArH), 7.67 (0.74 H, m, 7.5, ArH), 7.80 (0.74 H, dd, *J* 7.5, 3.6, ArH), 8.31 (0.37 H, d, *J* 9.0, ArH), 8.39 (0.63 H, d, *J* 9.0, ArH), 8.45 (0.37 H, dd, *J* 9.0, 2.0, ArH), 8.54 (0.63 H, dd, *J* 9.0, 2.0, ArH), 9.52 (0.63 H, d, *J* 2.0, ArH) and 9.71 (0.37 H, d, *J* 2.0, ArH); δ_C (125 MHz, $CDCl_3$) 20.6, 22.5, 23.7, 33.5, 34.0, 47.1, 47.2, 65.2, 67.2, 67.5, 68.1, 112.9, 113.3, 119.1, 119.2, 120.0(2), 121.1, 121.3, 122.0(2), 123.8, 124.0, 125.0, 125.2, 126.8(2), 127.0(2), 127.1, 127.7, 131.9, 132.0, 140.8(2), 141.3, 143.5(2), 143.7, 144.0, 148.6, 148.7, 149.3, 149.5, 153.8, 154.6, 175.6, 205.9 and 206.8; *m/z* (ES^+) 522.3 (M^+ + 23, 70%).

Prop-2-enyl L-thioprolinyl-(_O_-tri-isopropylsilyl-L-serinyl)-_O_-_tert_-butyldimethylsilyl-L-threoninate (15).
Piperidine (130 mg, 1.53 mmol) was added to the Fmoc-protected amine **9** (564 mg, 0.74 mmol) in DMF (10 mL) and the reaction mixture stirred at rt for 16 h then partitioned between water (20 mL) and ethyl acetate (20 mL). After concentration of the organic layer under reduced pressure, chromatography of the residue (20:80 light petroleum:ether) gave the aminodipeptide **10** (340 mg, 89%) as a colourless gum, R_f = 0.5 (20:80 light petroleum:ether), $[\alpha]_D^{20}$ +26.6 (*c* 2.0, $CHCl_3$) (Found: M^+ + H, 517.3488. $C_{25}H_{53}N_2O_5Si_2$ requires M, 517.3488); ν_{max}/cm^{-1} 3376, 2937, 2865, 1748, 1677, 1506, 1463, 1447, 1378, 1313, 1252, 1190, 1153, 1096, 1015, 993, 935, 882, 837, 777, 757 and 738; δ_H (500 MHz, $CDCl_3$) 0.00, 0.05, 0.06 and 0.08 (each 1.5 H, s, $SiCH_3$), 0.87 and 0.90 [each 4.5 H, s, $SiC(CH_3)_3$], 1.06 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.15 and 1.21 (each 1.5 H, d, *J* 6.3, threo 4-H_3), 1.71 (2 H, br. s, NH_2), 3.56 (1 H, m, ser 2-H), 3.80-4.00 (2 H, m, ser 3-H_2), 4.45-4.71 (4 H, m, threo 2-H, threo 3-H, CO_2CH_2), 5.25 and 5.34 (each 1 H, m, CH=CH*H*), 5.92 (1 H, m, C*H*=CH_2) and 8.23 (1 H, m, NH); *m/z* (ES^+) 517 (M^+ + 1, 35%) and 264 (100).

The amine **10** (340 mg, 0.66 mmol) was added dropwise over 5 min to a cooled solution of the benzotriazole **14** (340 mg, 0.66 mmol) in THF (6 mL) and the reaction mixture was stirred at rt for 6 h. After concentration under reduced pressure, chromatography of the residue (50:50 light petroleum:ether) gave the Fmoc-protected aminothioamide (375 mg, 60%) as a colourless gum, a mixture of rotamers, R_f = 0.5 (50:50 light petroleum:ether), $[\alpha]_D^{20}$ +31.1 (*c* 1.2, $CHCl_3$) (Found: $[M - H]^-$, 850.4313. $C_{45}H_{68}N_3O_7SSi_2$, requires M, 850.4322); ν_{max}/cm^{-1} 3346, 3064, 2937, 2864, 1749, 1710, 1681, 1511, 1449, 1407, 1346, 1253, 1192, 1096, 991, 936, 882, 837, 776, 755 and 738; δ_C (100 MHz, $CDCl_3$) −5.2, −4.4, 11.8, 12.5, 17.7, 18.0, 18.1, 25.7, 26.2, 44.8, 47.2, 55.0, 63.0, 66.1, 68.0, 68.8, 119.7, 120.0, 125.2, 125.5, 126.7, 127.1, 127.1, 127.7, 141.0, 141.3, 169.3, 203.6 and 204.9; *m/z* (ES^-) 850 ($[M - 1]^-$, 100%).

Piperidine (75 mg, 0.88 mmol) was added to the Fmoc-protected aminothioamide (375 mg, 0.44 mmol) in DMF (10 mL) and the reaction mixture was stirred at rt for 16 h then partitioned between water (20 mL) and ether (20 mL). The organic layer was concentrated under reduced pressure and chromatography of the residue (ether) gave the *title compound* **15** (184 mg, 66%) as a colourless gum, R_f = 0.2 (ether), $[\alpha]_D^{20}$ −44 (*c* 1.2, $CHCl_3$) (Found: M^+ + H, 630.3789. $C_{30}H_{60}N_3O_5SSi_2$ requires M, 630.3787); ν_{max}/cm^{-1}

3787, 3203, 2941, 2865, 1738, 1682, 1504, 1462, 1378, 1361, 1274, 1252, 1194, 1096, 993, 962, 921, 882, 836, 809, 776 and 740; δ_H (500 MHz, $CDCl_3$) –0.06 and 0.00 (each 3 H, s, $SiCH_3$), 0.80 [9 H, s, $SiC(CH_3)_3$], 1.02 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.11 (3 H, d, *J* 6.3, threo 4-H_3), 1.60-1.75 (4 H, m, thiopro 3-H_2, thiopro 4-H_2), 1.97 and 2.37 (each 1 H, m, thiopro 5-H), 2.93 and 3.02 (each 1 H, m, ser 3-H), 3.87 (1 H, dd, *J* 5.0, 9.8, thiopro 2-H), 4.22 (1 H, dd, *J* 5.4, 9.2, ser 2-H), 4.34 (1 H, dd, *J* 7.5, 3.0, threo 2-H), 4.41 (1 H, dq, *J* 1.9, 6.3, threo 3-H), 4.52 (1 H, m, CO_2CH*H*), 4.58 (2 H, m, NH, CO_2CH*H*), 5.11 (1 H, m, NH), 5.21 and 5.29 (each 1 H, m, CH=CH*H*), 5.87 (1 H, m, C*H*=CH_2) and 6.83 (1 H, d, *J* 9.1, NH); δ_C (100 MHz, $CDCl_3$) –4.4, –5.2, 11.8, 12.5, 17.9, 18.0, 20.8, 25.7, 26.1, 34.6, 47.5, 58.0, 59.0, 62.5, 68.3, 68.9, 119.0, 131.6, 169.3, 169.8 and 206.7; *m*/*z* (ES^+) 652 (M^+ + 23, 100%).

Prop-2-enyl (*N*-*tert*-butoxycarbonyl-D-leucinyl)-L-thioprolinyl-(*O*-tri-isopropylsilyl-L-serinyl)-*O*-*tert*-butyldimethylsilyl-L-threoninate (16).

HATU (156 mg, 0.41 mmol) and HOBt (17 mg, 0.12 mmol) were added to *N*-Boc-D-leucine (68 mg, 0.29 mmol) in DMF (2.5 mL). The L-threoninate **15** (184 mg, 0.29 mmol) in DMF (2.5 mL) was added followed by di-isopropylethylamine (151 mg, 1.17 mmol) and the reaction mixture stirred at rt for 16 h then partitioned between saturated aqueous NH_4Cl (20 mL) and ether (30 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (30:70 light petroleum:ether) gave the *title compound* **16** (207 mg, 85%) as a colourless gum, R_f = 0.6 (30:70 light petroleum:ether), $[\alpha]_D^{20}$ –20.0 (*c* 1.2, $CHCl_3$) (Found: M^+ + H, 843.5149. $C_{41}H_{79}N_4O_8SSi_2$ requires M, 843.5152); ν_{max}/cm^{-1} 3314, 2944, 2866, 1681, 1626, 1514, 1462, 1391, 1365, 1307, 1252, 1163, 1097, 990, 934, 881, 836 and 776; δ_H (400 MHz, $CDCl_3$) –0.05 and 0.00 (each 3 H, s, $SiCH_3$), 0.80 [9 H, s, $SiC(CH_3)_3$], 0.89 and 0.93 (each 3 H, d, *J* 6.6, either leu 4-CH_3 or leu 5-H_3), 1.03 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.11 (3 H, d, *J* 6.6, threo 4-H_3), 1.37 (2 H, m, leu 3-H_2), 1.53 [9 H, s, $CO_2C(CH_3)_3$], 1.65 (1 H, m, leu 4-H), 1.92 (1 H, m, thiopro 3-H), 2.12 (2 H, m, thiopro 4-H_2), 2.44 (1 H, m, thiopro 3-H′), 3.50 (1 H, m, threo 3-H), 3.77 and 3.91 (each 1 H, m, ser 3-H), 4.27 (1 H, m, leu 2-H), 4.39 (2 H, m, thiopro 5-H, ser 2-H), 4.48-4.62 (4 H, m, CO_2CH_2, thiopro 5-H′, threo 2-H), 4.83 (1 H, m, thiopro 2-H), 5.07 (1 H, m, NH), 5.18 and 5.28 (each 1 H, m, CH=CH*H*), 5.86 (1 H, m, C*H*=CH_2) and 7.13 and 8.84 (each 1 H, m, NH); δ_C (100 MHz, $CDCl_3$) –5.6, –5.1, –4.6, 11.6, 12.1, 17.7, 17.8, 19.9, 20.0, 21.6, 22.9, 24.1, 25.6, 25.7, 28.2, 46.9, 50.9, 58.0, 60.0, 62.5, 65.0, 67.2, 68.5, 68.6, 78.4, 117.9, 132.1, 155.2, 168.4, 169.1 and 204.4; *m*/*z* (ES^+) 865 (M^+ + 23, 100%).

Prop-2-enyl (*N*-*tert*-butoxycarbonyl-D-leucinyl)-L-thioprolinyl-(*O*-tri-isopropylsilyl-L-serinyl)-L-threoninate (17).

Tetra-*n*-butylammonium fluoride in THF (1 M, 300 μL, 0.3 mmol) was added to the *O*-TBS-threoninate **16** (207 mg, 0.25 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 16 h then concentrated under reduced pressure. Chromatography of the residue (95:5 ether:methanol) gave the corresponding diol (64 mg, 45%) as a white gum. This diol (64 mg, 0.11 mmol) was dissolved in THF (4 mL) and imidazole (46 mg, 0.68 mmol) and tri-isopropylsilyl chloride (108 mg, 0.56 mmol) were added. The reaction mixture was stirred at rt for 48 h then partitioned between water (10 mL) and ether (15 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (30:70 light petroleum-ether) gave the *title compound* **17** (54 mg, 68%) as a colourless gum, R_f = 0.3 (30:70 light petroleum-ether), $[\alpha]_D^{20}$ –15.6 (*c* 2.0, $CHCl_3$) (Found: M^+ + H, 729.4286. $C_{35}H_{65}N_4O_8SSi$ requires M, 729.4287); ν_{max}/cm^{-1} 3307, 2944, 1743, 1677, 1632, 1515, 1451, 1390, 1366, 1251, 1163, 1104, 1014, 991, 920, 882, 785 and 733; δ_H (400 MHz, $CDCl_3$) 0.89 and 0.91 (each 3 H, d, *J* 4.8, either leu 4-CH_3 or leu 5-H_3), 0.98 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.12 (3 H, d, *J* 6.1, threo 4-H_3), 1.36 (2 H, m, leu 3-H_2), 1.51 [9 H, s, $C(CH_3)_3$], 1.57 (1 H, m, leu 4-H), 1.95 (2 H, m, thiopro 4-H_2), 2.30 and 2.39 (each 1 H, m, thiopro 3-H), 3.54 (1 H, m, threo 3-H), 3.92 (1 H, m, ser 3-H), 4.10-4.24 (3 H, thiopro 5-H_2, leu 2-H), 4.27 (1 H, m, ser 3-H′), 4.47 (1 H, m, ser 2-H), 4.54-4.60 (2 H, m, CO_2CH_2), 4.94 (1 H, dd, *J* 4.3, 8.6, threo 2-H), 5.03 (1 H, m, thiopro 2-H), 5.15 and 5.27 (each 1 H, m, CH=CH*H*), 5.42 (1 H, br. m, NH), 5.86 (1 H, m, C*H*=CH_2), 7.16 (1 H, d, *J* 7.1, NH) and 8.28 (1 H, d, *J* 8.3, NH); δ_C (100 MHz, $CDCl_3$) 11.8, 17.9, 19.9, 21.9, 23.4, 23.8, 24.2, 24.7, 28.3, 31.0, 33.1, 51.1, 54.4, 62.2, 65.9, 67.7, 68.1, 69.6, 80.6, 118.5, 131.9, 149.0, 168.0, 168.5, 169.9 and 202.6; *m*/*z* (ES^+) 751 (M^+ + 23, 100%).

Prop-2-enyl 2-[(*N*-*tert*-butoxycarbonyl-D-leucinyl)-L-thioprolinyl-(*O*-tri-isopropylsilyl-L-serinyl)amino]-(*E*)-but-2-enoate (18).

A solution of the L-threoninate **17** (40 mg, 0.05 mmol), 1-ethyl-3-(3-methylaminopropyl)carbodi-imide (EDC) (17 mg, 0.11 mmol) and copper(II) chloride (1 mg, 0.01 mmol) in anhydrous toluene (2 mL) was stirred at 80 °C under nitrogen for 30 min. Water was added and the mixture was extracted with ethyl acetate (5 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (ether) gave the *title compound* **18** (23 mg, 65%) containing *ca*. 5% of its (*Z*)-isomer **21** (^{1}H NMR), as a colourless gum, R_f = 0.6 (30:70 light petroleum:ether), $[\alpha]_D^{20}$ –37.5 (*c* 2.0, $CHCl_3$) (Found: M^+ + H, 711.4189. $C_{35}H_{63}N_4O_7SSi$, requires M, 711.4182); ν_{max}/cm^{-1} 3294, 2943, 2867, 1682, 1645, 1507, 1447, 1386, 1366, 1251, 1163, 1106, 1066, 1046, 1014, 994, 920, 881 and 681; δ_H (400 MHz, $CDCl_3$) (*E*)-isomer **18** 0.89 and 0.91 (each 3 H, d, *J* 6.6, either leu 4-CH_3 or leu 5-H_3), 0.99 [21 H, m, 3 × $SiC(CH_3)_2$], 1.33 [9 H, s, $C(CH_3)_3$], 1.35-1.45 (2 H, m, leu 3-H_2), 1.64 (1 H, m, leu 4-H), 1.92 (1 H, m, thiopro 4-H), 1.98 (3 H, d, *J* 7.6, 4-H_3), 2.04 (1 H, m, thiopro 4-H′), 2.22 and 2.34 (each 1 H, m, thiopro 3-H), 3.51 (2 H, m, ser 3-H_2), 3.81 and 3.96 (each 1 H, m, thiopro 5-H), 4.21 (1 H, m, leu 2-H), 4.34 (1 H, m, ser 2-H), 4.61-4.66 (2 H, m, CO_2CH_2), 4.85 (1 H, m, thiopro 2-H), 5.08 (1 H, m, NH), 5.18 and 5.28 (each 1 H, m, CH=CH*H*), 5.9 (1 H, m, C*H*=CH_2), 6.68 (1 H, m, 3-H), 8.13 (1 H, br. s, NH) and 8.62 (1 H, br. d, *J* 7.3, NH); (*Z*)-isomer **21** 1.72 (3 H, d, *J* 7.5, 4-H_3); *m*/*z* (ES^+) 733 (M^+ + 23, 100%).

Prop-2-enyl 2-[(*N*-*tert*-butoxycarbonyl-D-leucinyl)-L-thioprolinyl-L-serinylamino]-(*E*)-but-2-enoate (19).

Tetra-*n*-butylammonium fluoride (1 M, 49 μL, 0.049 mmol)

was added to the silyl ether **18** (23 mg, 0.032 mmol) in THF (1 mL) and the reaction was stirred at rt for 16 h then concentrated under reduced pressure. Chromatography of the residue (ether) gave the *title compound* **19** (11 mg, 62%) as a white foam, R_f = 0.3 (ether), $[\alpha]_D^{20}$ −24 (*c* 2.0, $CHCl_3$) (Found: M^+ + Na, 577.2672. $C_{26}H_{42}N_4O_7SNa$ requires M, 577.2667); ν_{max}/cm^{-1} 3059, 2942, 2867, 1730, 1681, 1633, 1540, 1515, 1438, 1366, 1251, 1160, 1121, 999, 882, 851, 742 and 696; δ_H (300 MHz, $CHCl_3$) 0.80 and 0.81 (each 3 H, d, *J* 6.6, either leu 4-CH_3 or leu 5-H_3), 1.25 [9 H, s, $C(CH_3)_3$], 1.25-1.40 (2 H, m, leu 3-H_2), 1.55 (1 H, m, leu 4-H), 1.90 (3 H, d, *J* 7.5, 4-H_3), 1.85-1.95 (2 H, m, thiopro 4-H_2), 2.16 and 2.30 (each 1 H, m, thiopro 3-H), 2.96 (1 H, br. s, OH), 3.42 (1 H, m, ser 3-H), 3.65-3.85 (2 H, m, thiopro 5-H, ser 3-H′), 4.00 (1 H, m, thiopro 5-H′), 4.24 (1 H, m, leu 2-H), 4.50-4.60 (2 H, m, CO_2CH_2), 4.77 (1 H, m, ser 2-H), 4.92 (1 H, m, thiopro 2-H), 5.03 (1 H, br. m, NH), 5.10 and 5.21 (each 1 H, m, CH=CH*H*), 5.80 (1 H, m, C*H*=CH_2), 6.52 (1 H, m, 3-H), 8.20 (1 H, br. s, NH) and 8.71 (1 H, br. d, *J* 7.4, NH); δ_C (100 MHz, $CDCl_3$) 12.3, 14.2, 21.8, 23.4, 28.3, 30.3, 34.3, 40.8, 47.8, 50.9, 59.9, 65.9, 66.1, 68.0, 80.5, 118.8, 125.6, 128.5, 130.9, 131.8, 132.1, 132.2, 168.0 and 203.6; *m/z* (ES^+) 577 (M^+ + 23, 100%).

Prop-2-enyl 2-{(5*S*)-2-[*N*-(*N*-*tert*-butoxycarbonyl-D-leucinyl)-(2*S*)-pyrrolidin-2-yl]-4,5-dihydrothiazol-5-yl}carbonylamino-(*E*)-but-2-enoate (20).

Diethylaminosulfur trifluoride (10 mg, 0.06 mmol) was added dropwise over 1 min to the thioamide **19** (11 mg, 0.02 mmol) at −15 °C and the solution stirred at −15 °C for 1 h. Saturated aqueous $NaHCO_3$ was added and the reaction was allowed to warm to rt. DCM (5 mL) and water (5 mL) were added and the mixture was extracted with DCM (10 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (ether) gave the *title compound* **20** (8 mg, 75%) as a colourless gum, a ca. 70:30 mixture of rotamers (^{1}H NMR), R_f = 0.5 (ether), $[\alpha]_D^{20}$ −16 (*c* 1.0, $CHCl_3$) (Found: [M – H]$^-$, 535.2596. $C_{26}H_{39}N_4O_6S$ requires M, 535.2595); ν_{max}/cm^{-1} 3321, 2955, 702, 1682, 1643, 1510, 1425, 1366, 1343, 1250, 1162, 1015, 988, 932, 854 and 780; δ_H (400 MHz, $CDCl_3$) major rotamer 0.87 and 0.91 (each 3 H, d, *J* 6.6, either leu 4-CH_3 or leu 5-H_3), 1.35 [9 H, s, $C(CH_3)_3$], 1.35-1.45 (2 H, m, leu 3-H_2), 1.64 (1 H, m, leu 4-H), 1.85-2.00 (2 H, m, 4′′-H_2), 2.03 (3 H, d, *J* 7.6, 4-H_3), 2.05-2.15 (2 H, m, 3′′-H_2), 3.35-3.65 (3 H, m, 4'-H_2, 5′′-H), 3.88 (1 H, m, 5′′-H′), 4.44 (1 H, dt, *J* 4.8, 9.6, leu 2-H), 4.65-4.75 (2 H, m, CO_2CH_2), 4.84 (1 H, dd, *J* 4.0, 9.0, 5'-H), 5.03 (2 H, m, 2′′-H, NH), 5.20 and 5.30 (each 1 H, m, CH=CH*H*), 5.90 (1 H, m, C*H*=CH_2), 6.96 (1 H, q, *J* 7.8, 3-H) and 8.62 (1 H, br. s, NH); minor rotamer 0.74 and 0.80 (each 3 H, d, *J* 6.6, either leu 4-CH_3 or leu 5-H_3), 4.19 (1 H, dt, *J* 4.8, 9.6, leu 2-H) and 7.13 (1 H, q, *J* 7.8, 3-H); *m/z* (ES^-) 535 ([M – 1]$^-$, 100%); (ES^+) 559 (M^+ + 23, 100%).

Prop-2-enyl 2-[(*N*-*tert*-butoxycarbonyl-D-leucinyl)-L-thioprolinyl-(*O*-tri-isopropylsilyl-L-serinyl)amino]-(*Z*)-but-2-enoate (21).

Diethylaminosulfur trifluoride (7 mg, 0.04 mmol) was added dropwise over 1 min to the L-threoninate **17** (20 mg, 0.027 mmol) and pyridine (8 mg, 0.11 mmol) at 0 °C and the reaction mixture stirred at 0 °C for 2 h. Saturated aqueous $NaHCO_3$ was added, and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (30:70 light petroleum:ether) gave the *title compound* **21** (6 mg, 31%) as a colourless gum, R_f = 0.5 (30:70 light petroleum:ether), $[\alpha]_D^{20}$ −11 (*c* 2.0, $CHCl_3$) (Found: M^+ + H, 711.4184. $C_{35}H_{63}N_4O_7SSi$, requires M, 711.4182); ν_{max}/cm^{-1} 3323, 2943, 2867, 1686, 1641, 1509, 1450, 1366, 1250, 1163, 1068, 1046, 1015, 994, 921, 882, 757 and 682; δ_H (400 MHz, $CDCl_3$) 0.86 and 0.88 (each 3 H, d, *J* 6.6, either leu 4-CH_3 or leu 5-H_3), 0.99 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.30-1.45 [12 H, m, $C(CH_3)_3$, leu 3-H_2, leu 4-H), 1.72 (3 H, d, *J* 7.1, 4-H_3), 1.85-2.05 (2 H, m, thiopro 4-H_2), 2.20-2.35 (2 H, m, thiopro 3-H_2), 3.49-3.53 (2 H, m, thiopro 5-H_2), 3.55-4.00 (2 H, m, ser 3-H_2), 4.28 (1 H, m, leu 2-H), 4.39 (1 H, m, ser 2-H), 4.55-4.65 (2 H, m, CO_2CH_2), 4.85 (1 H, m, thiopro 2-H), 5.17 and 5.25 (each 1 H, m, CH=CH*H*), 5.84 (1 H, m, C*H*=CH_2), 6.79 (1 H, q, *J* 8.0, 3-H), 7.45 (1 H, br. d, *J* 8.6, NH), 7.97 (1 H, s, NH) and 8.48 (1 H, m, NH); *m/z* (ES^+) 733 (M^+ + 23, 100%).

Prop-2-enyl *N*-[*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-serinyl]-L-threoninate (25).

Toluene *p*-sulfonic acid (1.91 g, 10.04 mmol) and allyl alcohol (5.00 mL, 73.50 mmol) were added to threonine **24** (1.00 g, 8.39 mmol) in toluene (25 mL). The reaction mixture was heated to 110 °C for 16 h in a Dean-Stark apparatus and then concentrated under reduced pressure to give prop-2-enyl L-threoninate as its ammonium salt. This was dissolved in THF (100 mL) and Fmoc-L-serine (2.49 g, 7.63 mmol), HATU (2.50 g, 8.92 mmol), HOBt (0.41 g, 3.03 mmol) and di-isopropylethylamine (5.98 mL, 34.33 mmol) were added at 0 °C. The reaction mixture was stirred at rt for 16 h then concentrated under reduced pressure. The residue was dissolved in EtOAc (40 mL) and the solution washed with saturated aqueous NH_4Cl (25 mL), H_2O (25 mL) and brine (25 mL), then dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (1:1 light petroleum:EtOAc to EtOAc) gave the *title compound* **25** as a white foam (2.90 g, 74%), R_f = 0.5 (4:1 EtOAc:light petroleum), $[\alpha]_D^{22}$ −16.8 (*c* 0.95, MeOH) (Found: M^+ + H, 469.1960. $C_{25}H_{29}N_2O_7$ requires M, 469.1969); ν_{max}/cm^{-1} 3319, 1669, 1518, 1386, 1249, 1150, 1063, 839, 760 and 740; δ_H (500 MHz, $CDCl_3$) 1.12 (3 H, d, *J* 6.3, threo 4-H_3), 3.12 (2 H, br. s, OH), 3.61 (1 H, dd, *J* 11.2, 6.5, ser 3-H), 3.88 (1 H, m, ser 3-H′), 4.07 (1 H, t, *J* 7.0, fluorenyl CH), 4.25-4.29 (4 H, m, ser 2-H, threo 3-H, fluorenyl CH_2), 4.48-4.53 (3 H, m, CO_2CH_2, threo 2-H), 5.13 (1 H, d, *J* 10.4, CH=CH*H*), 5.21 (1 H, d, *J* 17.3, CH=CH*H*), 5.77 (1 H, m, C*H*=CH_2), 5.99 (1 H, br. s, NH), 7.18 and 7.28 (each 2 H, t, *J* 7.5, ArH), 7.36 (1 H, br. s, NH), 7.46-7.47 (2 H, m, ArH) and 7.64 (2 H, d, *J* 7.5, ArH); δ_C (125 MHz, $CDCl_3$) 20.1, 46.9, 55.7, 58.1, 63.1, 66.6, 67.4, 67.7, 119.1, 120.0, 125.0, 127.1, 127.7, 131.2, 141.2, 143.5, 143.7, 156.5, 170.9 and 171.5; *m/z* (ES^+) 469.2 (M^+ + 1, 90%) and 213.0 (100).

Prop-2-enyl *N*-[*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-*O*-*tert*-butyldimethylsilyl-L-serinyl]-L-threoninate (26).

Imidazole (0.38 g, 4.47 mmol, 1.60 mmol) and *tert*-butyldimethylsilyl chloride (0.77 g, 5.13 mmol) were

added to the hydroxydipeptide **25** (1.60 g, 3.42 mmol) in THF (60 mL) and the reaction mixture was stirred at rt for 16 h. EtOAc (60 mL) was added and the solution washed with saturated aqueous NH_4Cl (60 mL), H_2O (60 mL) and brine (60 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2:1 light petroleum:EtOAc) gave the *title compound* **26** as a colourless gum (1.58 g, 79%), $[\alpha]_D^{22}$ +24.9 (*c* 1.0, $CHCl_3$) (Found: M^+ + H, 583.2825. $C_{31}H_{43}N_2O_7Si$ requires M, 583.2834); ν_{max}/cm^{-1} 3310, 3066, 2942, 2865, 1725, 1683, 1520, 1463, 1450, 1384, 1257, 1107, 882, 758 and 740; δ_H (400 MHz, $CDCl_3$) 0.12-0.13 (6 H overlapping s, 2 × $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.23 (3 H, d, *J* 6.4, threo 4-H_3), 2.01 (1 H, br. s, OH), 3.61 (1 H, dd, *J* 9.5, 7.5, ser 3-H), 3.97 (1 H, dd, *J* 9.5, 3.8, ser 3-H′), 4.23-4.42 (5 H, m, fluorenyl $CHCH_2$, threo 3-H, ser 2-H), 4.62-4.65 (3 H, m, threo 2-H, CO_2CH_2), 5.25-5.37 (2 H, m, CH=CH_2), 5.75 (1 H, br. s, NH), 5.90 (1 H, m, C*H*=CH_2), 7.30-7.31 (2 H, m, ArH), 7.41-7.43 (3 H, m, ArH, NH), 7.60 (2 H, t, *J* 7.5, ArH) and 7.77 (2 H, d, *J* 7.5, ArH); δ_C (100 MHz, $CDCl_3$) –5.6, –5.5, 18.2, 20.0, 25.8, 47.0, 55.7, 57.5, 63.1, 66.2, 67.2, 67.9, 119.0, 120.0, 125.1, 127.0, 127.7, 131.3, 141.3, 143.6, 143.8, 156.1, 170.2 and 170.9; *m*/*z* (ES^-) 617.4 ($[M + 35]^-$, 100%).

Prop-2-enyl (*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninate (27).

Piperidine (0.35 mL, 3.37 mmol) was added to the Fmoc-protected dipeptide **26** (1.57 g, 2.25 mmol) in THF (80 mL) and the reaction mixture was stirred at rt for 3.5 h then concentrated under reduced pressure. Chromatography of the residue (1:1 light petroleum:EtOAc to 96:4 DCM:MeOH) gave the *title compound* **27** as a colourless gum (0.66 g, 68%), $[\alpha]_D^{32}$ –35.6 (*c* 1.3, MeOH) (Found: M^+ + H, 361.2158. $C_{16}H_{33}N_2O_5Si$ requires M, 361.2153); ν_{max}/cm^{-1} 3365, 2929, 2857, 1743, 1658, 1518, 1463, 1253, 1195, 1095, 1005, 988, 835 and 777; δ_H (400 MHz, $CDCl_3$) 0.06 and 0.08 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 1.20 (3 H, d, *J* 6.5, threo 4-H_3), 2.15 (3 H, br. s, OH, NH_2), 3.53 (1 H, t, *J* 4.6, ser 2-H), 3.81 and 3.90 (each 1 H, m, ser 3-H), 4.36 (1 H, qd, *J* 6.5, 2.7, threo 3-H), 4.60 (1 H, dd, *J* 9.0, 2.7, threo 2-H), 4.66-4.68 (2 H, m, CO_2CH_2), 5.26 (1 H, dd, *J* 10.5, 1.2, CH=CH*H*), 5.35 (1 H, dd, *J* 17.5, 1.2, CH=CH*H*), 5.88-5.96 (1 H, m, C*H*=CH_2) and 8.14 (1 H, d, *J* 9.0, NH); δ_C (100 MHz, $CDCl_3$) –5.5, 18.2, 19.9, 25.8, 56.6, 57.2, 65.1, 66.0, 68.1, 118.8, 131.5, 170.6 and 173.5; *m*/*z* (ES^+) 361.2 (M^+ + 1, 100%).

Prop-2-enyl [*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-thioprolinyl]-(*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninate (28).

The dipeptide **27** (0.52 g, 1.10 mmol) in THF (20 mL) was added dropwise to the benzotriazole **14** (0.54 g, 1.10 mmol) in THF (20 mL) at 0 °C and the reaction mixture stirred at rt for 16 h. EtOAc (50 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$ (30 mL), saturated aqueous NH_4Cl (30 mL), H_2O (30 mL) and brine (30 mL) then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (4:1 to 2:1 light petroleum:EtOAc) gave the *title compound* **28** as a pale yellow semi-solid (0.74 g, 98%), R_f = 0.8 (1:1 light petroleum:EtOAc), $[\alpha]_D^{30}$ –35.3 (*c* 1.3, MeOH) (Found: M^+ + H, 696.3125. $C_{36}H_{50}N_3O_7SSi$ requires M, 696.3133); ν_{max}/cm^{-1} 3350, 2951, 2929, 2883, 2856, 1746, 1675, 1520, 1413, 1347, 1292, 1258, 1193, 1102, 837, 779, 758 and 740; δ_H (400 MHz, $CDCl_3$) 0.03 and 0.07 (each 3 H, s, $SiCH_3$), 0.82 [9 H, s, $SiC(CH_3)_3$], 1.18 (3 H, d, *J* 5.8, threo 4-H_3), 1.89-1.98 (2 H, m, thiopro 4-H_2), 2.28 and 2.51 (each 1 H, m, thiopro 3-H), 3.58-3.59 (2 H, m, thiopro 5-H_2), 3.73 (1 H, dd, *J* 9.5, 4.0, ser 3-H), 4.22-4.67 (8 H, m, fluorenyl CH_2CH, ser 3-H′, threo 2-H, threo 3-H, CO_2CH_2), 4.88 (1 H, dd, *J* 8.8, 4.5, thiopro 2-H), 5.22 (2 H, m, ser 2-H, CH=CH*H*), 5.33 (1 H, dd, *J* 17.3, 1.3, CH=CH*H*), 5.91 (1 H, m, C*H*=CH_2), 7.18 (1 H, d, *J* 9.1, NH), 7.31-7.35 and 7.40-7.44 (each 2 H, m, ArH), 7.54 and 7.61 (each 1 H, d, *J* 7.5, ArH), 7.78 (2 H, d, *J* 7.5, ArH) and 8.50 (1 H, br. d, *J* 7.5, NH); δ_C (100 MHz, $CDCl_3$) –5.8, –5.6, 17.9, 20.1, 24.3, 25.6, 33.5, 46.9, 48.1, 58.3, 58.7, 61.7, 65.9, 68.2, 68.5, 68.7, 118.4, 120.0, 124.9, 127.1, 127.2, 127.9, 131.7, 141.2, 141.3, 143.1, 143.3, 156.6, 168.3, 169.6 and 202.2; *m*/*z* (ES^-) 694.7 ($[M – 1]^-$, 100%).

Prop-2-enyl L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninate (29).

Piperidine (0.10 mL, 1.06 mmol) was added to the Fmoc-protected thiotripeptide **28** (0.68 g, 0.98 mmol) in THF (30 mL) and the reaction mixture was stirred at rt for 3.5 h. More piperidine (0.05 mL, 0.50 mmol) was added and the reaction mixture stirred for a further 1.25 h before being concentrated under reduced pressure. Chromatography of the residue (1:1 light petroleum:EtOAc to 96:4 DCM:MeOH) gave the *title compound* **29** as an off-white semi-solid (0.44 g, 95%), R_f = 0.1 (2:1 EtOAc:light petroleum), $[\alpha]_D^{30}$ –58.5 (*c* 1.1, $CHCl_3$) (Found: M^+ + H, 474.2445. $C_{21}H_{40}N_3O_5SSi$ requires M, 474.2452); ν_{max}/cm^{-1} 3351, 2952, 2929, 2857, 1744, 1667, 1516, 1362, 1257, 1196, 1105, 1007, 989, 938, 838 and 779; δ_H (400 MHz, $CDCl_3$) 0.07 and 0.09 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.18 (3 H, d, *J* 6.5, threo 4-H_3), 1.58-1.74 (2 H, m, thiopro 4-H_2), 1.93 and 2.35 (each 1 H, m, thiopro 3-H), 2.94 and 3.05 (each 1 H, m, thiopro 5-H), 3.77 (1 H, dd, *J* 9.9, 6.5, ser 3-H), 4.15-4.22 (2 H, m, ser 3-H, thiopro 2-H), 4.34 (1 H, m, threo 3-H), 4.58 (1 H, dd, *J* 9.0, 2.5, threo 2-H), 4.63 (2 H, d, *J* 5.8, CO_2CH_2), 5.01 (1 H, dd, *J* 6.5, 4.3, ser 2-H), 5.22 (1 H, dd, *J* 10.4, 1.3, CH=CH*H*), 5.31 (1 H, dd, *J* 17.3, 1.3, CH=CH*H*), 5.88 (1 H, m, C*H*=CH_2) and 7.32 (1 H, d, *J* 8.9, NH); δ_C (100 MHz, $CDCl_3$) –5.7, –5.5, 18.0, 20.0, 25.6, 25.9, 34.4, 47.2, 57.4, 58.4, 61.7, 66.0, 67.7, 68.1, 118.7, 131.4, 169.9, 170.1 and 206.4; *m*/*z* (ES^+) 474.7 (M^+ + 1, 100%).

Prop-2-enyl [*N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-D-leucinyl]-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninate (30).

Di-isopropylethylamine (60 mg, 0.45 mmol) and HOBt (30 mg, 0.21 mmol) were added to the tripeptide **29** (68 mg, 0.15 mmol) and Fmoc-protected D-leucine (55 mg, 0.16 mmol) in DCM (2 mL). The solution was stirred at 0 °C for 10 min before EDC.HCl (40 mg, 0.21 mmol) was added and the mixture stirred at rt for 16 h. More DCM was added and the solution washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl, water and brine, then dried ($MgSO_4$) and concentrated under reduced pressure.

Chromatography of the residue (1:4 to 1:2 EtOAc:light petroleum) gave the *title compound* **30** (91 mg, 75%), R_f = 0.8 (1:1 light petroleum:EtOAc); ν_{max}/cm^{-1} 3295, 2955, 1683, 1635, 1522, 1450, 1259, 1105, 838 and 758; δ_H (400 MHz, $CDCl_3$) 0.05 and 0.06 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 0.96 and 0.98 (each 3 H, d, *J* 6.5, either leu 5-H_3 or leu 4-CH_3), 1.08 (3 H, d, *J* 7.0, 4-H_3), 1.40-1.70 [3 H, m, leu 3-H_2, leu 4-H), 1.95-2.10 (2 H, m, thiopro 4-H_2), 2.30-2.40 (2 H, m, thiopro 3-H_2), 3.63 and 4.05 (each 1 H, m, thiopro 5-H), 4.05-4.45 (8 H, m, 3-H, ser 3-H_2, leu 2-H, fluorenyl $CHCH_2$, OH), 4.55-4.70 (2 H, m, CO_2CH_2), 5.04 (1 H, m, thiopro 2-H), 5.21 (1 H, d, *J* 10.7, CH=CH*H*), 5.32 (1 H, d, *J* 17.3, CH=CH*H*), 5.43-5.55 (2 H, m, 2-H, ser 2-H), 5.90 (1 H, m, C*H*=CH_2), 7.22 (1 H, d, *J* 7.4, NH), 7.34, 7.41 and 7.60 (each 2 H, t, *J* 7.5, ArH), 7.75 (2 H, d, *J* 7.5, ArH) and 8.54 (1 H, d, *J* 7.0, NH); δ_C (100 MHz, $CDCl_3$) –5.4, 18.1, 19.8, 21.9, 23.2, 24.1, 24.9, 25.7, 32.9, 40.4, 46.9, 48.4, 51.4, 59.4, 60.0, 61.5, 65.8, 67.4, 67.9, 69.4, 118.5, 119.9, 120.0, 125.1, 127.1, 127.7, 131.7, 141.3, 143.3, 143.7, 157.0, 168.4, 170.0, 173.3 and 202.5.

A solution of the tetrapeptide **30** (0.42 g, 0.52 mmol) and piperidine (70 mg, 0.78 mmol) in THF (18 mL) was stirred at rt for 30 min. Concentration under reduced pressure and chromatography of the residue (1:1 EtOAc:light petroleum) gave a mixture of products. Attempts to couple a sample of the mixture (0.2 g) with Boc-alanine (80 mg, 0.42 mmol) using EDC.HCl (80 mg, 0.42 mmol), HOBt (50 mg, 0.39 mmol) and triethylamine (70 mg, 0.7 mmol) in DCM (3 mL) gave mixtures from which none of the required product **35** could be isolated. Using Boc-protected D-leucine, attempted deprotection of the intermediate using TMS-*O*-triflate for coupling with Boc-alanine led to a mixture of products and a sulfurous smell.

Prop-2-enyl (*N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninate (39).
Allyl alcohol (5.00 mL, 73.88 mmol) and *p*-TsOH (1.91 g, 10.04 mmol) were added to L-threonine **24** (1.00 g, 8.39 mmol) in toluene (25 mL). The reaction mixture was stirred at 110 °C for 16 h using a Dean-Stark apparatus, then allowed to cool to rt and concentrated under reduced pressure to give prop-2-enyl L-threoninate. HATU (3.19 g, 8.39 mmol) and HOBt (1.47 g, 10.88 mmol) were added to *N*-Boc-L-serine (1.89 g, 9.08 mmol) in THF (30 mL) at 0 °C followed by the prop-2-enyl L-threoninate in THF (40 mL). Di-isopropylethylamine (7.11 mL, 40.86 mmol) was added and the reaction mixture was stirred for 16 h at rt then concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and the solution washed with saturated aqueous NH_4Cl (40 mL), water (40 mL) and brine (40 mL). The aqueous washings were extracted with EtOAc (30 mL) and organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue through a short plug of silica (3:2 EtOAc:light petroleum) gave the dipeptide **38** as a foam, R_f = 0.5 (EtOAc), $[\alpha]_D^{30}$ –24.0 (*c* 1.0, MeOH), lit.[11b] –0.33 (*c* 0.6, EtOAc) (Found: M^+ + Na, 369.1624. $C_{15}H_{26}N_2O_7Na$ requires M, 369.1638); ν_{max}/cm^{-1} 3400, 2979, 1667, 1521, 1368, 1251, 1163, 1082 and 848; δ_H (500 MHz, $CDCl_3$) 1.24 (3 H, d, *J* 6.5, threo 4-H_3), 1.44 [9 H, s, $OC(CH_3)_3$], 3.59 (1 H, br. s, OH), 3.70 (1 H, m, ser 3-H), 3.92-3.97 (2 H, m, ser 3-H′, OH), 4.28 (1 H, m, ser 2-H), 4.36 (1 H, m, threo 3-H), 4.58 (1 H, dd, *J* 9.0, 2.5, threo 2-H), 4.66 (2 H, d, *J* 6.0, CO_2CH_2), 5.26 (1 H, dd, *J* 10.5, 1.5, CH=CH*H*), 5.34 (1 H, dq, *J* 17.0, 1.5, CH=CH*H*), 5.78 (1 H, br. s, NH), 5.90 (1 H, ddt, *J* 17.0, 11.5, 6.0, C*H*=CH_2) and 7.45 (1 H, br. s, NH); δ_C (125 MHz, $CDCl_3$) 20.0, 28.2, 55.3, 58.0, 63.0, 66.4, 67.8, 80.5, 119.0, 131.3, 156.0, 170.8 and 171.9; *m*/*z* (ES^+) 369.2 (M^+ + 23, 100%).

tert-Butyldimethylsilyl chloride (1.89 g, 12.59 mmol) and imidazole (0.91 g, 13.42 mmol) were added to this dipeptide **38** in THF (70 mL) at 0 °C and the reaction mixture was stirred at rt for 16 h then concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and the solution washed with saturated aqueous NH_4Cl (40 mL), water (40 mL) and brine (40 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (6:1 light petroleum:EtOAc) gave the *title compound* **39** as a viscous pale yellow oil (2.77 g, 72%), R_f = 0.7 (1:1 light petroleum:EtOAc), $[\alpha]_D^{30}$ +16.9 (*c* 1.1, $CHCl_3$) (Found: M^+ + Na, 483.2498. $C_{21}H_{40}N_2O_7SiNa$ requires M, 483.2503); ν_{max}/cm^{-1} 3550, 2953, 2930, 1667, 1501, 1391, 1367, 1253, 1169, 1112, 838 and 779; δ_H (400 MHz, $CDCl_3$) 0.08 (6 H, s, 2 × $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 1.20 (3 H, d, *J* 6.5, threo 4-H_3), 1.45 [9 H, s, $OC(CH_3)_3$], 2.49 (1 H, br. s, OH), 3.71 (1 H, dd, *J* 10, 6.5, ser 3-H) 4.03 (1 H, dd, *J* 10, 3.5, ser 3-H′), 4.23 (1 H, m, ser 2-H), 4.34 (1 H, m, threo 3-H), 4.62 (1 H, dd, *J* 9.0, 2.5, threo 2-H), 4.65 (2 H, d, *J* 6.0, CO_2CH_2), 5.24 (1 H, dd, *J* 10.5, 1.0, CH=CH*H*), 5.33 (1 H, dd, *J* 18.0, 1.0, CH=CH*H*), 5.37 (1 H, br. s, NH), 5.90 (1 H, m, *CH*=CH_2) and 7.29 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) –5.6, –5.5, 18.2, 19.9, 25.8, 28.2, 55.7, 57.4, 63.2, 66.1, 68.0, 80.2, 118.9, 131.4, 155.5, 170.2 and 171.1; *m*/*z* (ES^-) 495.3 ([M + 35]$^-$, 100%).

Prop-2-enyl 2-(*N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-(*E*)-but-2-enoate (40).
EDC (1.91 mL, 10.82 mmol) and copper(II) chloride (0.16 g, 1.20 mmol) were added to the dipeptide **39** (2.77 g, 6.01 mmol) in toluene (150 mL) and the reaction mixture was heated at 80 °C for 30 min then cooled to rt. EtOAc (60 mL) was added and the solution was washed with saturated aqueous NH_4Cl (60 mL), water (60 mL) and brine (60 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2:1 light petroleum:EtOAc) gave the *title compound* **40** as a yellow oil (2.19 g, 82%), R_f = 0.8 (2:1 light petroleum:EtOAc), $[\alpha]_D^{28}$ –9.1 (*c* 1.1, $CHCl_3$) (Found: M^+ + Na, 465.2404. $C_{21}H_{38}N_2O_6SiNa$ requires M, 465.2397); ν_{max}/cm^{-1} 3323, 2929, 2858, 1718, 1683, 1498, 1390, 1367, 1255, 1167, 1100, 838 and 779; δ_H (400 MHz, $CDCl_3$) 0.06 and 0.07 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.46 [9 H, s, $OC(CH_3)_3$], 2.11 (3 H, d, *J* 7.8, 4-H_3), 3.71 (1 H, dd, *J* 9.8, 6.0, ser 3-H), 4.06 (1 H, dd, *J* 9.8, 3.0, ser 3-H′), 4.19 (1 H, m, ser 2-H), 4.73 (2 H, d, *J* 5.8, CO_2CH_2), 5.28 (1 H, dd, *J* 10.5, 1.0, CH=CH*H*), 5.36 (1 H, dd, *J* 17.1, 1.0, CH=CH*H*), 5.36 (1 H, br. s, NH), 5.96 (1 H, m, C*H*=CH_2), 7.27 (1 H, m, 3-H) and 8.34 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) –5.6, –5.5, 14.4, 18.2, 25.7, 28.3, 56.5, 63.2, 66.0, 80.3, 118.8, 125.3, 128.4, 131.5, 155.4, 163.7

and 169.1; *m/z* (ES^+) 465.5 (M^+ + 23, 40%), 443.5 (M^+ + 1, 50) and 387.4 (100).

Methyl (*N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninyl-L-prolinate (41).

Phenylsilane (37 mg, 0.34 mmol) and $Pd(Ph_3P)_4$ (20 mg, 0.017 mmol) were added to the allyl ester **39** (80 mg, 0.17 mmol) in DCM and the mixture stirred in the dark at rt for 1 h. After concentration under reduced pressure, chromatography of the residue (4:1 to 1:1 light petroleum:EtOAc with traces of AcOH) gave the corresponding carboxylic acid. This was dissolved in DCM (3.3 mL) and methyl L-prolinate (31 mg, 0.19 mmol), HOBt (23 mg, 0.17 mmol), PyBOB (90 mg, 0.17 mmol) and NMM (34 mg, 0.34 mmol) were added. The solution was stirred at rt for 16 h, then diluted with more DCM (10mL) and washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL). After drying the solution ($MgSO_4$) and concentration under reduced pressure, chromatography of the residue (1:1 to 4:1 EtOAc:light petroleum) gave the *title compound* **41** (38 mg, 42%) as a pale yellow oil, R_f = 0.2 (4:1 EtOAc:light petroleum) (Found: M^+ + Na, 554.2890. $C_{24}H_{45}N_3O_8SiNa$ requires M, 554.2874); ν_{max}/cm^{-1} 3306, 2953, 2929, 2856, 1633, 1450, 1391, 1251, 1169, 1110, 837 and 779; δ_H (400 MHz, $CDCl_3$) 0.06(2) (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.16 (3 H, d, *J* 6.5, threo 4-H_3), 1.44 [9 H, s, $OC(CH_3)_3$], 1.95-2.10 (3 H, m, pro 3-H, pro 4-H_2), 2.20 (1 H, m, pro 3-H′), 3.15-3.35 (3 H, m, pro 5-H_2, ser 3-H), 3.73 (3 H, s, OCH_3), 4.10 (1 H, m, threo 3-H), 4.15-4.25 (2 H, m, ser 2-H, ser 3-H′), 4.50 (1 H, m, pro 2-H), 4.74 (1 H, m, threo 2-H), 5.31 (1 H, d, *J* 6.3, NH) and 7.23 (1 H, br. d, *J* 8.5, NH); δ_C (100 MHz, $CDCl_3$) −5.7 −5.5, 18.2, 18.5, 24.8, 25.8, 28.2, 28.9, 47.4, 52.4, 54.2, 56.0, 58.8, 63.1, 67.4, 80.4, 155.5, 170.0, 170.8 and 172.4; *m/z* (ES^+) 554.4 (M^+ + 23, 70%) and 532.4 (M^+ + 1, 100).

When the same procedure was applied to the (*E*)-dehydrobutyrine containing dipeptide **40** a complex mixture of products was obtained. The mass spectrum [*m/z* (ES^+) 514.4 (M^+ + 1, 100%)] and accurate mass (Found: M^+ + Na, 536.2776. $C_{24}H_{43}N_3O_7SiNa$ requires M, 536.2768) were consistent with some coupled product **42** being present, but the geometry of the dehydrobutyrine was not established nor was a pure sample of the required product isolated.

(3*S*,4*R*)-3-*tert*-Butoxycarbonylamino-4-methyloxetan-2-one (70).[26a]

PyBOP (1.42 g, 2.74 mmol) and Et_3N (0.95 mL, 6.84 mmol) were added to Boc-L-threonine (**69**) (0.50 g, 2.28 mmol) in DCM (45 mL) at 0 °C and the reaction mixture was stirred at rt for 2 h. Saturated aqueous NH_4Cl (20 mL) was added and the organic phase was washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2:1 light petroleum:EtOAc) gave the title compound **70** as a white semi-solid (0.34 g, 74%), R_f = 0.6 (1:1 light petroleum:EtOAc), $[\alpha]_D^{26}$ +36.1 (*c* 1.0, $CHCl_3$), lit.[26a] +29.4 (*c* 1.16, $CHCl_3$) (Found: M^+ + Na, 224.0901. $C_9H_{15}NO_4Na$ requires M, 224.0899); ν_{max}/cm^{-1} 3351, 1826, 1692, 1540, 1389, 1370, 1337, 1276, 1252, 1165, 1146, 1124, 1077, 1012 and 819; δ_H (500 MHz, $CDCl_3$) 1.44 [12 H, br. s, $OC(CH_3)_3$, 4-CH_3], 4.84 (1 H, quintet, *J* 6.0, 4-H), 5.41 (1 H, m, 3-H) and 5.65 (1 H, d, *J* 8.0, NH); δ_C (125 MHz, $CDCl_3$) 14.8, 28.1, 60.0, 75.0, 81.1, 154.6 and 169.5.

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-3-phenylselanylbutanoic acid (71).[26a]

Benzeneselenol (0.48 mL, 4.47 mmol) was added to the oxetanone **70** (0.60 g, 2.98 mmol) in DMF (6 mL) and the reaction was heated to 80 °C for 2 h then cooled to rt. Aqueous NaOH (1 M, 6 mL) and water (12 mL) were added and the mixture was extracted with Et_2O (3 × 15 mL). The aqueous layer was acidified to pH 3 with aqueous HCl (1 M) and then washed with EtOAc (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (4:1 to 1:1 light petroleum:EtOAc) gave the title compound **71** (0.89 g, 83 %), as a pale, yellow viscous oil, a mixture of rotamers (^1H NMR), R_f = 0.8 (1:1 light petroleum:EtOAc), $[\alpha]_D^{26}$ + 9.5 (*c* 1.0, $CHCl_3$), lit.[26a] +23.8 (*c* 1.0, $CHCl_3$) (Found: M^+ + Na, 382.0527. $C_{15}H_{21}NO_4SeNa$ requires M, 382.0533); ν_{max}/cm^{-1} 3314, 2978, 1717, 1657, 1395, 1368, 1160, 1077 and 741; δ_H (400 MHz, $CDCl_3$) 1.45-1.49 [12 H, narrow m, $OC(CH_3)_3$, 4-H_3], 3.69 (1 H, m, 3-H), 4.39 (0.3 H, m, 2-H), 4.53 (0.7 H, m, 2-H), 5.23 (0.7 H, d, *J* 8.5, NH), 6.22 (0.3 H, br. s, NH), 7.27-7.31 (3 H, m, ArH) and 7.60-7.62 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.1, 28.2, 40.6, 57.8, 80.5, 128.1, 128.2, 129.2, 135.3, 155.4 and 174.8; *m/z* (ES^-) 358.1 ([M − 1]$^-$, 100%) and 356.1 ([M – 1]$^-$, 50).

Methyl (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-3-phenylselanylbutanoate (72).

Trimethylsilyldiazomethane (2 M in hexanes, 1.38 mL, 2.77 mmol) was added dropwise to the acid **71** (0.74 g, 2.08 mmol) in toluene:MeOH (4:1, 23 mL) and the solution was stirred at rt for 2 h then concentrated under reduced pressure. Chromatography of the residue (1:1 light petroleum:EtOAc) gave the *title compound* **72** as a pale yellow viscous oil (0.77 g, *ca*. 100%), R_f = 0.7 (1:1 light petroleum:EtOAc), $[\alpha]_D^{26}$ +41.2 (*c* 1.25, $CHCl_3$) (Found: M^+ + Na, 396.0685. $C_{16}H_{23}NO_4SeNa$ requires M, 396.0690); ν_{max}/cm^{-1} 3361, 2976, 1744, 1714, 1499, 1366, 1210, 1161, 1020 and 741; δ_H (400 MHz, $CDCl_3$) 1.44 [12 H, br. s, $OC(CH_3)_3$, 4-H_3], 3.58 (1 H, m, 3-H), 3.73 (3 H, s, OCH_3), 4.53 (1 H, dd, *J* 8.5, 4.5, 2-H), 5.26 (1 H, d, *J* 8.5, NH), 7.27-7.30 (3 H, m, ArH) and 7.60-7.62 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.4, 28.2, 41.2, 52.4, 58.0, 80.1, 128.1, 128.2, 129.1, 135.3, 155.1 and 171.1; *m/z* (ES^+) 401.1 (50%), 374.1 (M^+ + 1, 55) and 257.0 (100).

Methyl (2*R*,3*S*)-2-[(*N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino]-3-phenylselanylbutanoate (73).

Trifluoroacetic acid (1.90 mL, 25.20 mmol) was added to the Boc-protected amino ester **72** (0.47 g, 1.26 mmol) in DCM (4.5 mL) at 0 °C and the reaction mixture was stirred at rt for 2 h. Water (10 mL) was added, the pH was adjusted to 7 with saturated aqueous $NaHCO_3$ and the reaction mixture was extracted with DCM (3 × 20 mL). The organic extracts were washed with water (20 mL)

and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding amine. *N-tert*-Butoxycarbonyl-*O-tert*-butyldimethylsilyl-L-serine (0.45 g, 1.39 mmol), HATU (0.67 g, 1.77 mmol), HOBt (0.19 g, 1.39 mmol) and di-isopropylethylamine (0.73 mL, 4.17 mmol) were added to this amine in DCM (12 mL) at 0 °C and the reaction mixture was stirred at rt for 16 h. DCM (15 mL) was added and the solution washed with saturated aqueous NH_4Cl (20 mL), water (20 mL) and brine (20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (4:1 to 1:1 light petroleum:EtOAc) gave the *title compound* **73** as a pale yellow foam (0.56 g, 77%), R_f = 0.8 (1:1 light petroleum:EtOAc), $[\alpha]_D^{28}$ +24.2 (*c* 1.2, $CHCl_3$) (Found: M^+ + H, 575.2031. $C_{25}H_{43}N_2O_6SeSi$ requires M, 575.2056); ν_{max}/cm^{-1} 3337, 2954, 2929, 2857, 1745, 1717, 1683, 1366, 1254, 1212, 1167, 1113, 838, 780 and 741; δ_H (400 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.39 (3 H, d, *J* 6.5, 4-H_3), 1.39 [9 H, s, $OC(CH_3)_3$], 3.55-3.67 (2 H, m, 3-H, ser 3-H), 3.67 (3 H, s, OCH_3), 3.93 (1 H, dd, *J* 10.0, 4.0, ser 3-H′), 4.07 (1 H, m, ser 2-H), 4.79 (1 H, dd, *J* 8.5, 4.5, 2-H), 5.27 (1 H, d, *J* 5.7, NH), 7.24-7.28 (4 H, m, ArH, NH) and 7.54-7.56 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.6, −5.4, 18.2, 25.7, 25.8, 28.2, 40.4, 52.3, 55.2, 56.7, 63.0, 80.0, 128.0, 128.1, 129.1, 135.4, 155.4, 170.2 and 170.3; *m/z* (ES^-) 609.2 ([M + 35]$^-$, 100%) and 607.2 ([M + 35]$^-$, 50).

Methyl (2*R*,3*S*)-2-[L-thioprolinyl-(*O-tert*-butyldimethylsilyl-L-serinyl)amino]-3-phenylselanylbutanoate (74).

Trifluoroacetic acid (1 mL) was added to the Boc-protected dipeptide **73** (0.55 g, 0.97 mmol) in DCM (4 mL) at 0 °C. and the reaction mixture stirred for 2 h at rt. DCM (10 mL) was added followed by saturated aqueous $NaHCO_3$ until the aqueous layer was at pH 8. The organic layer was washed with water (10 mL) and brine (10 mL) and the aqueous extracts were re-extracted with DCM (2 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the deprotected dipeptide that was dissolved in THF (7 mL). Et_3N (0.07 mL, 0.49 mmol) was added and the mixture cooled to 0 °C before the benzotriazole **14** (0.48 g, 0.97 mmol) in THF (7 mL) was added dropwise and the reaction mixture stirred at rt for 16 h. EtOAc (30 mL) was added and the mixture was washed with saturated aqueous NH_4Cl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The aqueous extracts were re-extracted with EtOAc (20 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (4:1 light petroleum:EtOAc) gave the Fmoc-protected tripeptide as a mixture of rotamers (0.53 g, 0.67 mmol), R_f = 0.8 (1:1 light petroleum:EtOAc) (Found: M^+ + H, 810.2537. $C_{40}H_{52}N_3O_6SSeSi$ requires M, 810.2511); ν_{max}/cm^{-1} 3349, 2952, 1745, 1685, 1526, 1450, 1410, 1347, 1302, 1258, 1212, 1106, 837 and 740; *m/z* (ES^+) 810.2 (M^+ + 1, 75%) and 237.2 (100).

Piperidine (0.20 mL, 0.20 mmol) was added to the Fmoc-tripeptide in THF (10 mL) and the reaction mixture was stirred at rt for 4 h. EtOAc (10 mL) was added and the mixture was washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:1 light petroleum:EtOAc to 96:4 CH_2Cl_2:MeOH) gave the *title compound* **74** as a viscous yellow wax (0.20 g, 35%), R_f = 0.1 (1:2 light petroleum:EtOAc), $[\alpha]_D^{29}$ −53.9 (*c* 1.1, $CHCl_3$) (Found: M^+ + H, 588.1839. $C_{25}H_{42}N_3O_4SSeSi$ requires M, 588.1831); ν_{max}/cm^{-1} 3317, 2952, 2928, 2856, 1745, 1687, 1509, 1258, 1212, 1108, 837 and 780; δ_H (500 MHz, $CDCl_3$) 0.14 and 0.15 (each 3 H, s, $SiCH_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 1.43 (3 H, d, *J* 7.0, 4-H_3), 1.67-1.78 (2 H, m, thiopro 4-H_2), 1.98 and 2.40 (each 1 H, m, thiopro 3-H), 2.99 and 3.10 (each 1 H, m, thiopro 5-H), 3.63 (1 H, m, 3-H), 3.69 (3 H, s, OCH_3), 3.70 (1 H, m, ser 3-H), 4.20 (1 H, dd, *J* 10.0, 4.1, ser 3-H′), 4.27 (1 H, dd, *J* 9.0, 6.0, thiopro 2-H), 4.83 (1 H, dd, *J* 8.5, 4.5, 2-H), 4.92 (1 H, dd, *J* 8.0, 4.1, ser 2-H), 7.27-7.31 (3 H, m, ArH), 7.40 (1 H, d, *J* 8.5, NH) and 7.57-7.58 (2 H, m, ArH); δ_C (125 MHz, $CDCl_3$) −5.5, −5.3, 18.2, 25.7, 25.8, 25.9, 34.5, 40.2, 47.3, 53.4, 56.8, 58.1, 61.3, 68.1, 128.0, 128.2, 129.1, 135.4, 169.5, 170.2 and 206.1; *m/z* (ES^+) 588.2 (M^+ + H, 95%) and 586.1 (100).

Methyl (2*R*,3*S*)-2-[(*N-tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O-tert*-butyldimethylsilyl-L-serinyl)amino]-3-phenylselanylbutanoate (75).

The tripeptide **74** (0.27 g, 0.45 mmol), HATU (0.22 g, 0.59 mmol), HOBt (0.06 g, 0.45 mmol) and di-isopropylethylamine (0.16 mL, 0.90 mmol) were added to the dipeptide **38** (0.15 g, 0.49 mmol) in DCM (25 mL) at 0 °C and the reaction mixture stirred at rt for 16 h. DCM (10 mL) was added and the solution was washed with saturated aqueous NH_4Cl (20 mL), water (20 mL) and brine (20 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (4:1 light petroleum:EtOAc) gave the *title compound* **75** as a pale yellow foam (0.38 g, 85%), R_f = 0.6 (1:1 light petroleum:EtOAc), $[\alpha]_D^{28}$ −32.6 (*c* 1.0, $CHCl_3$) (Found: [M – H]$^-$, 870.3414. $C_{39}H_{64}N_5O_8SSeSi$ requires M, 870.3410); ν_{max}/cm^{-1} 3316, 2954, 2931, 1746, 1715, 1656, 1513, 1213, 1102, 838 and 781; δ_H (400 MHz, $CDCl_3$) 0.13(2) (each 3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 0.94 (6 H, d, *J* 6.5, leu 4-CH_3, leu 5-H_3), 1.29 (3 H, d, *J* 7.0, ala 3-H_3), 1.40 [9 H, s, $OC(CH_3)_3$], 1.44 (3 H, d, *J* 7.0, 4-H_3), 1.55-1.62 (3 H, m, leu 3-H_2, leu 4-H), 1.84-1.93 (2 H, m, thiopro 4-H_2), 2.23-2.35 (2 H, m, thiopro 3-H_2), 3.57-3.88 (4 H, m, 3-H, thiopro 5-H_2, ser 3-H), 3.64 (3 H, s, OCH_3), 4.15-4.20 (2 H, m, ser 3-H′, ala 2-H), 4.72-4.75 (2 H, m, leu 2-H, 2-H), 4.91-4.99 (2 H, m, ser 2-H, thiopro 2-H), 5.57 and 7.22 (each 1 H, d, *J* 8.0, NH), 7.27-7.31 (3 H, m, ArH), 7.56-7.58 (2 H, m, ArH), 7.66 (1 H, d, *J* 8.5, NH) and 8.47 (1 H, d, *J* 7.0, NH); δ_C (101 MHz, $CDCl_3$) −5.5, −5.2, 17.3, 18.2, 18.4, 22.1, 23.1, 24.1, 24.5, 25.8, 28.2, 33.0, 39.4, 40.3, 47.6, 49.0, 49.7, 52.3, 57.2, 58.6, 61.0, 68.1, 79.8, 127.8, 128.2, 129.1, 135.3, 155.8, 169.9, 171.2, 173.3 and 202.7; *m/z* (ES^-) 908.3 ([M + 35]$^-$, 40%), 906.3 ([M + 35]$^-$, 100), 904.4 (60) and 870.4 ([M – 1]$^-$, 35).

Prop-2-enyl (2*S*)-3-{*N*-[(2*R*,3*S*)-2-(*N-tert*-butoxycarbonyl-L-alaninyl)-D-leucinyl-L-thioprolinyl-(*O-tert*-butyldimethylsilyl-L-serinyl)amino-3-

phenylselanylbutanoyl]-L-prolinyl-L-threoninyl-*N*-methyl-L-valinyloxy}-2-(2,2,2-trichloroethoxycarbonyloxy)propanoate (87).

The amine **86** was prepared from the Boc-protected dipeptidylglycerate **53** (24 mg, 0.037 mmol) using hydrogen chloride (4 N) in dioxane at 0 °C for 4.5 h as outlined for the preparation of the tripeptide **54**. The acid **81** (46 mg, 0.048 mmol) was prepared from the ester **80** as outlined for the preparation of the intermediate **83**. Isobutyl chloroformate (7.3 μL, 0.052 mmol) and NMM (16.1 μL, 0.15 mmol) were added to this acid **81** in THF (1 mL) at −15 °C and the mixture stirred for 10 min before the addition of the amine **86** in THF (0.75 mL). The mixture was stirred at rt for 17 h, then diluted using EtOAc, filtered through celite, and concentrated under reduced pressure. Chromatography of the residue (1:2 light petroleum:EtOAc to EtOAc) gave the *title compound* **87** (43 mg, 79%) as a pale, yellow foam, R_f 0.6 (EtOAc); δ_H (500 MHz, 120 °C, DMSO-d_6) 0.07 (6 H, s, 2 × $SiCH_3$), 0.84, 0.87 and 0.88 (each 3 H, d, *J* 6.8, val 3-CH_3, leu 4-CH_3, leu 5-H_3), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.99 (3 H, d, *J* 6.6, val 4-H_3), 1.10 (3 H, d, *J* 6.4, threo 4-H_3), 1.24 (3 H, d, *J* 6.9, ala 3-H_3), 1.41 [9 H, s, $OC(CH_3)_3$], 1.41 (3 H, d, *J* 6.8, 4′-H_3), 1.53 (2 H, m, leu 3-H_2), 1.60 (1 H, m, leu 4-H), 1.75-2.10 (7 H, m, pro 4-H_2, thiopro 4-H_2, thiopro 3-H_2, pro 3-H), 2.15-2.30 (2 H, m, val 3-H, pro 3-H′), 3.01 (3 H, s, NCH_3), 3.35-3.65 (6 H, m, pro 5-H_2, thiopro 5-H_2, 3′-H, ala 2-H), 3.94 (1 H, m, threo 3-H), 3.95-4.07 (3 H, m, leu 2-H, ser 3-H_2), 4.40-4.55 (2 H, m, pro 2-H, thiopro 2-H), 4.52 (1 H, dd, *J* 12.0, 5.5, 3-H), 4.63 (1 H, dd, *J* 12.0, 4.5, 3-H′), 4.65-4.72 (3 H, m, threo 2-H, CO_2CH_2), 4.73 (1 H, m, val 2-H), 4.92 (1 H, m, 2′-H), 4.93 and 4.95 (each 1 H, d, *J* 12.0, Cl_3CHCH), 5.13 (1 H, m, ser 2-H), 5.27 (1 H, dq, *J* 10.5, 1.0, CH=CH*H*), 5.34 (1 H, dq, *J* 16.5, 1.0, CH=CH*H*), 5.40 (1 H, dd, *J* 6.0, 4.5, 2-H), 5.93 (1 H, m, C*H*=CH_2), 6.19 (1 H, br. d, *J* 6.0, NH), 7.27-7.35 (3 H, m, ArH), 7.44 (2 H, m, 2 × NH), 7.56-7.64 (2 H, m, ArH), 7.73 (1 H, br. s, NH) and 9.13 (1 H, br. d, *J* 8.0, NH); δ_C (100 MHz, $CDCl_3$) −5.4, −5.2, 14.2, 17.7, 17.8, 18.3, 18.8, 19.1, 19.8, 22.1, 23.3, 24.2, 24.7, 25.0, 25.9, 27.4, 28.4, 29.7, 31.7, 32.9, 40.4, 47.7, 49.7, 53.1, 53.5, 54.8, 60.8, 61.3, 61.7, 62.4, 66.9, 67.7, 68.2, 73.9, 80.2, 93.9, 119.7, 127.6, 128.3, 129.2, 130.8, 136.1, 153.2, 155.9, 165.9, 169.2, 170.0, 171.3, 172.4, 173.4 and 203.2; *m/z* (ES^+) 1497.6 (M^+ + 23, 60%), 1496.7 (M^+ + 23, 65), 1495.7 (M^+ + 23, 100) and 1493.7 (M^+ + 23, 80).

Following the procedure outlined for the synthesis of the hydroxypropanoate **64**, the Troc-protected peptide **87** (165 mg, 0.12 mmol) and activated zinc (98 mg) in acetic acid-ether (2:1, 2 mL) at 0 °C to rt for 16 h, after dilution with ether-chloroform, filtration and concentration under reduced presure, gave the corresponding 2-hydroxyglycerate (170 mg, *ca*. 100%) as a pale yellow oil. Acetylation of a sample of this diol (123 mg, 0.095 mmol) using acetic anhydride (72 μL, 0.76 mmmol), pyridine (63 μL, 0.76 mmol) and DMAP (3 mg, 0.019 mmol) in DCM (2.5 mL) at 0 °C to rt for 4 h, after chromatography (1:4 light petroleum:EtOAc to EtOAc) gave the bis-acetate **83** (75 mg, 59%) identified by comparison of its spectroscopic data with those of a sample prepared earlier.

Methyl *N*-[(2*R*,3*S*)-2-(*N*-prop-2-enyloxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (88).

2,6-Lutidine (0.19 mL, 1.6 mmol) and trimethylsilyl trifluoromethanesulfonate (0.3 mL, 1.6 mmol) were added to the Boc-protected peptide **80** (0.2 g, 0.2 mmol) in DCM (10 mL) and the solution stirred at rt for 1.5 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the organic layer was extracted with DCM (15 mL). The organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Short column chromatography of the residue (1:1 light petroleum:EtOAc to 96:4 DCM:MeOH) gave the corresponding aminodipeptide (0.13 g, 0.15 mmol). Prop-2-enyl chloroformate (0.04 mL, 0.38 mmol), di-isopropylethylamine (0.13 mL, 0.75 mmol) and DMAP (1.80 μg, 15.00 μmol, 10 mol %) were added to this dipeptide in THF (1.85 mL) and the reaction mixture was stirred at rt for 16 h. EtOAc (15 mL) was added and the solution was washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL). The aqueous washings were re-extracted with EtOAc (10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2:1 to 1:1 light petrol:EtOAc) gave the *title compound* **88** as an off-white foam (0.11 g, 58%), R_f = 0.2 (1:1 light petroleum:EtOAc), $[\alpha]_D^{20}$ −63 (*c* 1.0, $CHCl_3$) (Found: M^+ + H, 953.3781. $C_{43}H_{69}N_6O_9SSeSi$ requires M, 953.3776); ν_{max}/cm^{-1} 3298, 2953, 2929, 1724, 1648, 1514, 1437, 1253, 1101, 838 and 753; δ_H (400 MHz, $CDCl_3$) 0.09 (6 H, s, 2 × $SiCH_3$), 0.88-0.95 [15 H, m, $SiC(CH_3)_3$, leu 4-CH_3, leu 5-H_3], 1.25-1.63 (9 H, m, ala 3-H_3, 4-H_3, leu 3-H_2, leu 4-H), 1.91-2.31 (8 H, m, pro 4-H_2, thiopro 4-H_2, pro 3-H_2, thiopro 3-H_2), 3.44-3.58 (4 H, m, pro or thiopro 5-H_2, thiopro or pro 5-H, 3-H), 3.67 (3 H, s, OCH_3), 3.87-3.91 (2 H, m, pro or thiopro 5-H′, ser 3-H), 4.17-4.33 (2 H, m, ser 3-H′, ala 2-H), 4.49-4.69 (4 H, m, leu 2-H, pro 2-H, CO_2CH_2), 4.89-5.04 (3 H, m, ser 2-H, 2-H, thiopro 2-H), 5.16 (1 H, d, *J* 10.5, CH=CH*H*), 5.26 (1 H, d, *J* 17.0, CH=CH*H*), 5.87 (1 H, ddt, *J* 17.0, 10.5, 5.5, C*H*=CH_2), 6.08 (1 H, d, *J* 8.0, NH), 6.97 (1 H, d, *J* 7.0, NH), 7.23-7.28 (3 H, m, ArH), 7.52 (1 H, d, *J* 8.5, NH), 7.62-7.69 (2 H, m, ArH) and 8.50 (1 H, d, *J* 6.5, NH); δ_C (100 MHz, $CDCl_3$) −5.4, −5.3, 17.7, 17.9, 18.2, 22.1, 23.1, 24.1, 24.6, 24.8, 25.8, 28.9, 32.9, 40.4, 40.7, 46.8, 47.6, 49.5, 49.9, 52.2, 54.6, 58.9, 59.5, 61.3, 65.8, 68.2, 117.8, 127.9, 129.0, 129.2, 132.7, 135.6, 156.2, 167.8, 169.2, 171.3, 172.2, 172.9 and 202.9; *m/z* (ES^-) 987.5 ($[M + 35]^-$, 100%) and 985.5 ($[M + 35]^-$, 45).

Prop-2-enyl (2*S*)-3-{*N*-[(2*R*,3*S*)-2-(*N*-prop-2-enyloxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinyl-(*O*-acetyl-L-threoninyl)-*N*-methyl-L-valinyloxy}-2-acetoxypropanoate (89).

The dipeptidyl glycerate **65** (0.03 g, 0.55 mmol) was stirred in hydrogen chloride in dioxane (4 M, 0.74 mL) at 0 °C for 4 h and then the solution was concentrated under reduced pressure to give the aminodipeptide **82** as its ammonium salt. Lithium hydroxide (1 M, 0.25 mL, 0.25

mmol) was added to the hexapeptide **88** (0.05 g, 0.05 mmol) in THF:*tert*-butanol (1:1, 0.6 mL) at 0 °C and the reaction mixture was stirred at rt for 2 h. Saturated aqueous NH_4Cl (15 ml) was added and the mixture was extracted with EtOAc. The organic extracts washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding acid. *N*-Methylmorpholine (0.07 mL, 0.60 mmol) was added to this acid in THF (1 mL) followed by isobutyl chloroformate (0.03 mL, 0.20 mmol) and the reaction mixture was stirred at −20 °C for 10 min. The amine **82** in THF (0.6 mL) was added dropwise and the reaction mixture stirred at rt for 14 h. EtOAc (15 mL) was added and the solution was washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:1 light petroleum:EtOAc to EtOAc) gave the *title compound* **89** as a pale yellow foam (0.1 g, 49%), R_f = 0.2 (EtOAc); $[\alpha]_D^{26}$ −70 (*c* 1.0, $CHCl_3$) (Found: M^+ + H, 1365.5627. $C_{62}H_{97}N_8O_{17}SSeSi$ requires M, 1365.5621); ν_{max}/cm^{-1} 3306, 2956, 1744, 1649, 1514, 1438, 1235, 1103 and 838; δ_H (500 MHz, $CDCl_3$) 0.08 and 0.10 (each 3 H, s, $SiCH_3$), 0.82-1.07 [21 H, m, leu 4-CH_3, leu 5-H_3, val 3-CH_3, val 4-H_3, $SiC(CH_3)_3$], 1.23-1.43 (9 H, m, threo 4-H_3, ala 3-H_3, 4'-H_3), 1.54-1.68 (3 H, m, leu 3-H_2, leu 4-H), 1.90-2.32 (15 H, m, pro CH_2CH_2, thiopro CH_2CH_2, 2 × CH_3CO, val 2-H), 2.81 (0.3 H, s, NCH_3), 3.09 (2.7 s, NCH_3), 3.44-3.60 (4 H, m, pro or thiopro 5-H_2, thiopro or pro 5-H, 3'-H), 3.87-3.88 (2 H, m, thiopro or pro 5-H', ser 3-H), 4.20 (1 H, dd, *J* 9.9, 6.1, ser 3-H'), 4.30 (1 H, m, ala 2-H), 4.43 (1 H, dd, *J* 12.1, 5.5, 3-H), 4.49-4.67 (7 H, m, threo 2-H, 3-H', leu 2-H, 2 × CO_2CH_2), 4.84 (1 H, d, *J* 10.1, val 2-H), 4.89-5.02 (3 H, m, pro 2-H, thiopro 2-H, 2'-H), 5.18 (1 H, d, *J* 10.8, ser 2-H), 5.27-5.36 (5 H, m, 2 × CH=CH_2, 2-H), 5.85-5.94 (2 H, m, 2 × C*H*=CH_2), 6.05 (1 H, d, *J* 6.6, NH), 6.97 (1 H, br. s, NH), 7.05 (1 H, br. d, *J* 8.2, NH), 7.27-7.29 (3 H, m, ArH), 7.51 (1 H, br. d, *J* 6.3, NH), 7.63-7.69 (2 H, m, ArH) and 8.55 (1 H, br. s, NH); *m/z* (ES^+) 1389.8 (M^+ + 23, 85%), 1387.8 (M^+ + 23, 100) and 1385.8 (M^+ + 23, 85).

2,2,2-Trichloroethyl *N*-[(2*R*,3*S*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (90).

Aqueous lithium hydroxide (1 M, 2.30 mL, 2.30 mmol) was added to the methyl ester **80** (0.44 g, 0.46 mmol) in THF:^{t}BuOH (1:1, 5.48 mL) at 0 °C and the solution stirred at rt for 2 h. Saturated aqueous NH_4Cl (15 mL) was added and the mixture extracted with EtOAc (3 × 15 mL). The organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the corrresponding acid. To this acid in DCM (1.55 mL) at 0 °C were added EDC·HCl (0.11 g, 0.55 mmol), DMAP (6 mg, 4.50 μmol) and Cl_3CCH_2OH (45 μL, 0.46 mmol), and the reaction mixture was stirred at rt for 16 h. More DCM (10 mL) was added and the solution was washed with saturated aqueous NH_4Cl (10 mL), H_2O (10 mL) and brine (10 mL). The aqueous washings were extracted with DCM (10 mL) and the organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography of the residue (2:1 to 1:1 light petroleum:EtOAc) gave the *title compound* **90** as a white foam (0.29 g, 58%), R_f = 0.4 (1:1 light petroleum:EtOAc), $[\alpha]_D^{19}$ −66 (*c* 1.1, $CHCl_3$) (Found: M^+ + H, 1085.3070. $C_{45}H_{72}N_6O_9Cl_3SSeSi$ requires M, 1085.3076); ν_{max}/cm^{-1} 3302, 2955, 1766, 1634, 1511, 1438, 1252, 1161, 1098, 838 and 755; δ_H (400 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × $SiCH_3$), 0.08-0.94 [15 H, m, $SiC(CH_3)_3$, leu 5-H_3, leu 4-CH_3], 1.30 (3 H, d, *J* 6.8, ala-CH_3), 1.39-1.45 [12 H, m, $OC(CH_3)_3$, 4-H_3], 1.54-1.63 (3 H, m, leu 4-H, leu 3-H_2), 1.91-2.08 (5 H, m, pro 3-H, pro 4-H_2, thiopro 4-H_2), 2.12-2.34 (3 H, m, pro 3-H', thiopro 3-H_2), 3.37-3.61 (4 H, m, pro 5-H_2, thiopro 5-H, 3-H), 3.78-3.89 (2 H, m, thiopro 5-H', ser 3-H), 4.15-4.23 (2 H, m, ser 3-H', ala 2-H), 4.60-4.78 (4 H, m, leu 2-H, pro 2-H, CH_2CCl_3), 4.92-5.00 (3 H, m, ser 2-H, 2-H, thiopro 2-H), 5.53 (1 H, d, *J* 7.8, NH), 7.13 (1 H, d, *J* 6.8, NH), 7.25-7.28 (3 H, m, ArH), 7.49 (1 H, d, *J* 8.5, NH), 7.62-7.64 (2 H, m, ArH) and 8.61 (1 H, d, *J* 6.5, NH); δ_C (100 MHz, $CDCl_3$) −5.5, −5.3, 17.7(2), 18.1, 22.0, 23.2, 24.1, 24.5, 24.7, 25.7, 28.2, 28.9, 32.8, 40.2, 40.4, 46.7, 47.6, 49.4, 49.6, 54.4, 58.7, 59.9, 61.3, 68.2, 73.7, 79.9, 94.8, 128.0, 128.7, 129.0, 135.7, 155.7, 168.0, 169.2, 170.0, 171.4, 173.2 and 203.0; *m/z* (ES^+) 1085.5 (M^+ + 1, 80%), 1083.6 (M^+ + 1, 40%), 929.6 (100) and 927.6 (95).

Following the procedure outlined for the removal of the Boc-group from the methyl ester **80**, the trichloroethyl ester **90** (0.26 g, 0.24 mmol) was deprotected using trimethylsilyl triflate (0.43 g, 1.9 mmol) and 2,6-lutidine 0.2 g, 1.9 mmol) in DCM (12 mL) at rt for 2 h to give, afer chromatography (1:1 light petroleum:EtOAc to 96:4 DCM:MeOH), the corresponding amine (0.21 g, 89%). Following the procedure used for the synthesis of the glyceramide **59**, this amine (80 mg, 0.083 mmol) was coupled with the acid **66** (46 mg, 0.09 mmol) using ByBOP (56 mg, 0.11 mmol) and NMM (34 mg, 0.03 mmol) in DCM (4.2 mL) to give the glyceramide **91** (70 mg, 69%). Reductive removal of the trichloroethyl ester using activated zinc and aqueous ammonium chloride in THF for 16 h at rt gave the corresponding acid but attempts to remove the Boc-group using trimethylsilyl triflate and 2,6-lutidine or hydrogen chloride in dioxane gave rise to the diketopiperazine **93**; δ_H (400 MHz, $CDCl_3$) 1.08 and 1.18 (each 3 H, d, *J* 7.0, 2 × val CH_3), 1.42 (3 H, d, *J* 7.0, threo 4-H_3), 2.06 (3 H, s, CH_3CO), 2.30 (1 H, m, val 3-H), 3.02 (3 H, s, NCH_3), 3.70 (1 H, d, *J* 6, val 2-H), 4.01 (1 H, dd, *J* 6.0, 4.0, threo 2-H), 5.25 (1 H, m, threo 3-H) and 6.10 (1 H, br s, NH).