Supporting Information

A Total Synthesis of Apratoxin A

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General Procedure ^1H NMR spectra were recorded on JEOL Model EX-270 (270 MHz) spectrometer and JEOL Model ECP-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration. FT-IR spectra were recorded on a Perkin-Elmer Spectrum OneTM spectrometer. Data are given in cm^{-1} with only significant diagnostic bands. Optical rotations were measured with a JASCO P-1020 polarimeter. Column chromatography was performed on Merck silica gel 60 (0.063 – 0.200 mm). HRMS (ESI-TOF) were measured on AppliedBioSystems Mariner TK3500 Biospectrometry Workstation (ESI-TOF) mass spectrometers and were calibrated with angiotensin I (SIGMA), bradykinin (SIGMA), and neurotensin (SIGMA) as an internal standard. Dry tetrahydrofuran, dry toluene and dry diethyl ether were distilled from sodium wire with a small amount of benzophenone. Dry CH_2Cl_2 was distilled from P_2O_5 . *N,N*-Dimethylformamide (peptide synthesis grade, Wako Pure Chemical Industries Inc.) was used without further purification.

(*E*)-(*S*)-5-(4-Methoxybenzyloxy)-3,6,6-trimethyl-2-hepten-1-ol (**9**)

To a solution of (*S*)-5,5-dimethyl-4-hydroxy-2-hexanone (**7**) [List, B.; Lerner, R. A.; Barbas, C. F.; III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; List, B. *Synlett* **2001**, 1675–1685; List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575.] (4.39 g, 30.4 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (12.1 g, 42.7 mmol) in tetrahydrofuran (71 mL) was added trifluoromethanesulfonic acid (0.027 mL, 0.304 mmol) at 0 °C under argon. After being stirred at the same temperature for 10 min, the reaction mixture was quenched with 1 M HCl and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. Addition of diethyl ether/hexane gave precipitation of trichloroacetamide. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15 % ethyl acetate in hexane) to give (*S*)-5,5-dimethyl-4-(4-methoxybenzyloxy)-2-hexanone (6.74 g, 27.4 mmol, 90%) as a colorless oil. TLC *R*_f 0.55 (hexane/ethyl acetate = 2/1); [α]_D³⁰ = –39.5 (*c* 1.08, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.47 (AB pattern, *J* = 10.6 Hz, 2H), 3.79 (s, 3H), 3.67 (dd, *J* = 7.7, 2.9 Hz, 1H), 2.67 (ABX pattern, *J* = 8.7, 7.7 Hz, 1H), 2.56 (ABX pattern, *J* = 8.7, 2.9 Hz, 1H), 2.18 (s, 3H), 0.92 (s, 9H); ¹³C NMR (67.8 MHz, CDCl₃) δ 208.6, 159.1, 131.2, 129.2, 113.7, 83.0, 73.9, 55.3, 45.4, 35.7, 31.4, 26.2; IR (neat cm^{–1}) 2958, 1717, 1614, 1515, 1248, 1074, 823; HRMS (ESI–TOF) calcd for [C₁₆H₂₄O₃+Na]⁺ 287.1618, found 287.1617.

To a solution of (*S*)-5,5-dimethyl-4-(4-methoxybenzyloxy)-2-hexanone (5.49 g, 22.3 mmol) in tetrahydrofuran (45 mL) was added dropwise vinyl magnesium bromide (45.0 mL, 1.0 M in tetrahydrofuran, 44.6 mmol) at 0 °C under argon. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous NH₄Cl and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with saturated aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude allylic alcohol in pyridine (35 mL) was added acetic anhydride (4.77 mL, 50.5 mmol) and 4-dimethylaminopyridine (740 mg, 6.06 mmol) at room temperature under argon. After being stirred at 50 °C for 24 h, the reaction mixture was poured into 1 M HCl at 0 °C and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with 1 M HCl, saturated aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The residue **8** was used for the next reaction without further purification.

To a solution of crude allylic acetate **8** in tetrahydrofuran (65 mL) was added PdCl₂(CH₃CN)₂ (176 mg, 0.680 mmol) at 0 °C under argon. After being stirred at room temperature for 2.0 h, the reaction mixture was diluted with diethyl ether. The solution was stirred with Florisil[®] at the same

temperature for 10 min. The mixture was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude allylic acetate in methanol (40 mL) was added potassium carbonate (2.82 g, 20.4 mmol) at 0 °C. After being stirred at the same temperature for 1.5 h, the reaction mixture was quenched with 1 M HCl and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20% to 25% ethyl acetate in hexane) to give (*E*)-**9** (3.29 g, 11.2 mmol, 50% in 4 steps) as a colorless oil and the (*Z*)-isomer (386 mg, 1.32 mmol, 6% in 4 steps) as colorless oil. (*E*)-**9**: TLC *R*_f 0.45 (hexane/ethyl acetate = 1/1); [α]_D²⁸ = +1.40 (*c* 0.990, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.54 (t, *J* = 7.7 Hz, 1H), 4.45 (AB pattern, *J* = 11.1 Hz, 1H), 4.42 (AB pattern, *J* = 11.1 Hz, 1H), 4.15 (ABX pattern, *J* = 16.1, 7.3 Hz, 1H), 4.13 (ABX pattern, *J* = 16.1, 6.8 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, *J* = 9.3, 3.0 Hz, 1H), 2.10-2.27 (m, 2H), 1.75 (s, 3H), 0.94 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 159.0, 137.8, 131.4, 129.1, 126.0, 113.7, 85.9, 74.4, 59.5, 55.3, 41.6, 36.2, 26.5, 16.9; IR (neat cm⁻¹) 3391, 2870, 1614, 1515, 1248, 1078, 1037, 822; HRMS (ESI-TOF) calcd for [C₁₈H₂₈O₃+Na]⁺ 315.1931, found 315.1930. the (*Z*)-isomer: TLC *R*_f 0.50 (hexane/ethyl acetate = 1/1); [α]_D²⁰ = +44.9 (*c* 2.44, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.71 (dd, *J* = 7.8, 6.8 Hz, 1H), 4.47 (AB pattern, *J* = 10.2 Hz, 1H), 4.42 (AB pattern, *J* = 10.2 Hz, 1H), 4.12 (ABX pattern, *J* = 12.2, 7.8 Hz, 1H), 3.87 (ABX pattern, *J* = 12.2, 6.8 Hz, 1H), 3.79 (s, 3H), 3.21 (dd, *J* = 11.2, 2.4 Hz, 1H), 2.63 (dd, *J* = 13.7, 11.2 Hz, 1H), 1.96 (dd, *J* = 13.7, 2.4 Hz, 1H), 1.84 (s, 3H), 0.98 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 138.2, 130.2, 129.4, 127.2, 113.7, 85.0, 75.2, 58.3, 55.2, 36.4, 33.4, 26.4, 23.8; IR (neat cm⁻¹) 3341, 2959, 2870, 1614, 1514, 1249, 1077, 1036, 822; HRMS (ESI-TOF) calcd for [C₁₈H₂₈O₃+Na]⁺ 315.1931, found 315.1921.

(3*S*,5*S*)-5-(4-Methoxybenzyloxy)-3,6,6-trimethylheptan-1-ol (10)

10

In a 50 mL of autoclave containing a glass tube was placed Ru(OAc)₂[(*S*)-binap] (89.0 mg, 106 μ mol), (*E*)-(*S*)-5-(4-methoxybenzyloxy)-3,6,6-trimethyl-2-hepten-1-ol (**9**) (1.55 g, 5.30 mmol) and degassed methanol (10 mL). The autoclave was filled with hydrogen (100 atm.) after repeated (3 times) filling and purging of hydrogen. The reaction was carried out under an appropriate hydrogen

pressure at 50 °C for 24 h. The reaction mixture was diluted with hexane. The solution was stirred with Florisil[®] at room temperature for 10 min. The mixture was filtered through a pad of Celite[®] and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give **10** (1.54 g, 5.23 mmol, quant.) as a colorless oil. TLC *R_f* 0.48 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{28} = -29.3$ (c 0.990, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 4.54 (s, 2H), 3.80 (s, 3H), 3.72 (m, 1H), 3.62 (m, 1H), 3.10 (dd, *J* = 6.8, 4.8 Hz, 1H), 1.72-1.83 (m, 2H), 1.39-1.42 (m, 2H), 1.29 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 159.0, 131.6, 129.1, 113.8, 85.5, 74.3, 61.2, 55.3, 39.4, 39.0, 36.2, 27.0, 26.6, 21.1; IR (neat cm⁻¹) 3392, 2955, 1615, 1587, 1515, 1464, 1302, 1249, 1039, 821; HRMS (ESI-TOF) calcd for [C₁₈H₃₀O₃+Na]⁺ 317.2087, found 317.2085.

(1R,3S,4S,6S,8S)-Benzoate-4-(tert-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-1,3,6,9,9-pentamethyl-2-oxo-decyl (12)

12

To a solution of oxalyl chloride (236 μL, 2.71 mmol) in CH₂Cl₂ (4.0 mL) was added dropwise a solution of dimethyl sulfoxide (319 μL, 4.51 mmol) in CH₂Cl₂ (5.0 mL) at -78 °C under argon. After being stirred at the same temperature for 2 h, a solution of **10** (531 mg, 1.80 mmol) in CH₂Cl₂ (9.0 mL) was added dropwise to the mixture at -78 °C and the reaction mixture was stirred at the same temperature for 1 h. Then, triethylamine (1.51 mL, 10.8 mmol) was added in one portion at -78 °C to the reaction mixture. After being stirred at -78 °C to 0 °C for 30 min, the reaction mixture was poured into saturated aqueous NH₄Cl at 0 °C and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give (3S,5S)-5-(4-methoxybenzyloxy)-3,6,6-trimethylheptanal (505 mg, 1.73 mmol, 96%) as a colorless oil. TLC *R_f* 0.60 (hexane/ethyl acetate = 2/1); $[\alpha]_D^{27} = -22.6$ (c 0.980, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.69 (m, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.57 (AB pattern, *J* = 10.6 Hz, 1H), 4.48 (AB pattern, *J* = 10.6 Hz, 1H), 3.80 (s, 3H), 3.05 (dd, *J* = 8.2, 2.3 Hz, 1H), 2.47 (m, 1H), 2.18 (m, 1H), 2.14 (m, 1H), 1.39-1.51 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 202.9, 159.2, 131.2, 129.3, 113.8, 85.3, 74.5, 55.3, 50.2,

38.8, 36.3, 26.6, 25.8, 21.6; IR (neat cm^{-1}) 2872, 1725, 1614, 1249, 1076, 1037, 822, 517; HRMS (ESI-TOF) calcd for $[\text{C}_{18}\text{H}_{28}\text{O}_3+\text{Na}]^+$ 315.1931, found 315.1928.

To a solution of dicyclohexylboron chloride (714 μL , 3.24 mmol) in diethyl ether (5.6 mL) was added *N,N*-dimethylethylamine (429 μL , 3.96 mmol) at 0 $^\circ\text{C}$ under argon. A solution of (*R*)-2-benzoyloxy-3-pentanone (**11**) (520 mg, 2.52 mmol) in diethyl ether (7.0 mL) was added via cannula and the mixture was stirred at 0 $^\circ\text{C}$ for 1.5 h before cooling to -78°C . Then, to the reaction mixture was added dropwise a solution of the above aldehyde (526 mg, 1.80 mmol) in diethyl ether (7.0 mL) at -78°C over 15 min. After the addition was complete, the reaction mixture was stirred at -78°C for 3 h, then stirred at -20°C for 12 h. The reaction mixture was quenched with methanol (8.0 mL), pH 7 buffer (8.0 mL) and hydrogen peroxide (8.0 mL, 30% aqueous) at 0 $^\circ\text{C}$, and stirred at room temperature for 1 h. The aqueous layer was extracted with CH_2Cl_2 , and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give aldol product as a colorless oil.

To a solution of the aldol product and 2,6-lutidine (839 μL , 7.20 mmol) in CH_2Cl_2 was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (827 μL , 3.60 mmol) at 0 $^\circ\text{C}$. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with methanol, then partitioned between H_2O and diethyl ether. The aqueous layer was extracted with diethyl ether, and the combined organic layer was washed with 1 M HCl, saturated aqueous NaHCO_3 , brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give silyl ether **12** (894 mg, 1.46 mmol, 81% in 2 steps) as a colorless oil. TLC *R_f* 0.55 (hexane/ethyl acetate = 2/1); $[\alpha]_D^{24} = -17.9$ (*c* 1.55, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.08 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.59 (m, 1H), 7.46 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.45 (q, *J* = 6.8 Hz, 1H), 4.62 (AB pattern, *J* = 11.1 Hz, 1H), 4.43 (AB pattern, *J* = 11.1 Hz, 1H), 4.16 (m, 1H), 3.79 (s, 3H), 3.13 (m, 1H), 3.04 (dd, *J* = 7.2, 3.9 Hz, 1H), 1.81 (m, 1H), 1.72 (m, 1H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.35-1.46 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.97 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.81 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.0, 165.8, 158.9, 133.5, 131.7, 129.9, 129.6, 128.7, 128.5, 113.6, 85.6, 74.4, 73.6, 69.5, 55.3, 49.0, 39.3, 36.2, 26.6, 26.5, 25.9, 20.6, 18.0, 16.1, 10.6, -4.4 , -4.6 ; IR (neat cm^{-1}) 2955, 1722, 1614, 1514, 1249, 1070, 836, 712; HRMS (ESI-TOF) calcd for $[\text{C}_{36}\text{H}_{56}\text{O}_6\text{Si}+\text{Na}]^+$ 635.3738, found 635.3733.

Pyrrolidine-1,2-dicarboxylic acid (2S)-2-[(1S,3S,5S,6S,8R)-8-benzoyloxy-1-tert-butyl-5-(tert-butyldimethylsilyloxy)-3,6-dimethyl-7-oxo-nonyl] ester 1-tert-butyl ester (13)

13

To a solution of **12** (894 mg, 1.46 mmol) in CH₂Cl₂ (13 mL) and pH 7 buffer (1.5 mL) was added 2,3-dichloro-5,6-dicyano-benzoquinone (397 mg, 1.75 mmol) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous NaHCO₃ and the aqueous layer was extracted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of *N*-Boc-L-proline (785 mg, 3.65 mmol) in tetrahydrofuran (23 mL) was added *N,N*-diisopropylethylamine (1.00 mL, 5.84 mmol) and 2,4,6-trichlorobenzoyl chloride (742 μL, 4.75 mmol) at room temperature under argon. After being stirred at the same temperature for 10 h, the reaction mixture was filtered through a pad of silica gel and concentrated *in vacuo*. To a solution of the residue in toluene (10 mL) was added a solution of crude xx in toluene (5.0 mL) and 4-dimethylaminopyridine (357 mg, 2.92 mmol) at room temperature under argon. After being stirred at the same temperature for 3 h, the reaction mixture was quenched with H₂O and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with 1 M HCl, saturated aqueous NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (14% ethyl acetate in hexane) to give **13** (786 mg, 1.14 mmol, 78% in 2 steps) as a colorless oil. TLC *R*_f 0.35 (hexane/ethyl acetate = 2/1); [α]_D²⁵ = −35.7 (*c* 1.04, CHCl₃); ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 8.07 (d, *J* = 7.8 Hz, 2H), 7.58 (m, 1H), 7.45 (dd, *J* = 7.8, 7.8 Hz, 2H), 5.44 (q, *J* = 6.8 Hz, 1H), 4.74 (m, 1H), 4.35 (dd, *J* = 8.8, 2.9 Hz, 0.5H), 4.30 (dd, *J* = 8.8, 2.4 Hz, 0.5H), 4.08 (m, 1H), 3.33–3.50 (m, 2H), 3.08 (dq, *J* = 6.8, 2.4 Hz, 1H), 1.80–2.15 (m, 4H), 1.65 (m, 1H), 1.54 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.46 (m, 1H), 1.45 (s, 4.5H), 1.42 (s, 4.5H), 1.30 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 1.5H), 1.24 (d, *J* = 6.8 Hz, 1.5H), 1.09 (m, 1H), 0.95 (d, *J* = 4.4 Hz, 3H), 0.87 (s, 4.5H), 0.86 (s, 4.5H), 0.83 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H), −0.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 209.2, 209.0, 172.6, 172.4, 165.8, 154.2, 154.0, 133.4, 133.3, 129.9, 129.7, 129.6, 128.5, 80.2, 80.1, 80.0, 79.5, 76.8, 74.8, 71.1, 70.5, 59.7, 59.4,

48.2, 47.9, 46.4, 46.2, 39.9, 35.2, 35.1, 31.0, 30.1, 28.6, 28.5, 27.2, 26.8, 26.0, 25.8, 24.3, 23.3, 20.6, 20.3, 18.1, 15.9, 12.0, 11.6, -4.3, -4.4, -4.6; IR (neat cm^{-1}) 2958, 1724, 1699, 1398, 1266, 1164, 1116, 837, 713; HRMS (ESI-TOF) calcd for $[\text{C}_{38}\text{H}_{63}\text{NO}_3\text{Si}+\text{Na}]^+$ 712.4215, found 712.4213.

Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (2*S*)-2-[(1*S*,3*S*,5*S*,6*S*)-1-*tert*-butyl-5-(*tert*-butyldimethylsilyloxy)-6-carboxy-3-methylheptyl] ester (6**)**

Dtena 6

To a solution of **13** (678 mg, 983 μmol) in methanol (20 mL) was added potassium carbonate (177 mg, 1.28 mmol) at room temperature. After being stirred at the same temperature for 1.5 h, the reaction mixture was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with saturated aqueous NH_4Cl , brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of the crude α -hydroxy ketone in 2-methyl-2-propanol (15 mL) and H_2O (7.5 mL) was added NaIO_4 (526 mg, 2.46 mmol) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was partitioned between saturated aqueous NH_4Cl and CH_2Cl_2 , and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to give **6** (445 mg, 798 μmol , 81% in 2 steps) as a colorless oil. TLC *R_f* 0.40 (hexane/ethyl acetate = 3/2); $[\alpha]_D^{28} = -55.4$ (*c* 0.825, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 4.79 (m, 0.6H), 4.72 (dd, $J = 8.7, 1.9$ Hz, 0.4H), 4.38 (dd, $J = 8.8, 2.9$ Hz, 0.6H), 4.33 (dd, $J = 8.8, 2.4$ Hz, 0.4H), 3.97 (m, 1H), 3.35-3.52 (m, 2H), 2.68 (m, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 1.84-1.92 (m, 2H), 1.60-1.70 (m, 1H), 1.47 (m, 2H), 1.45 (s, 5.4H), 1.43 (s, 3.6H), 1.24-1.40 (m, 2H), 1.23 (d, $J = 7.3$ Hz, 3H), 0.95 (d, $J = 5.8$ Hz, 3H), 0.91 (s, 9H), 0.89 (s, 3.6H), 0.87 (s, 5.4H), 0.17 (s, 1.2H), 0.16 (s, 1.8H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 177.7, 177.2, 172.5, 154.4, 154.0, 80.1, 79.8, 79.6, 76.8, 72.7, 72.4, 59.6, 59.3, 46.5, 46.3, 45.1, 44.9, 41.3, 39.4, 38.8, 35.0, 31.1, 30.1, 28.6, 28.5, 27.1, 26.4, 26.0, 25.9, 24.3, 23.4, 21.3, 21.1, 18.0, 13.1, 12.9, -4.2, -4.8; IR (neat cm^{-1}) 2959, 1739, 1705, 1465, 1398, 1167, 1121, 837, 774; HRMS (ESI-TOF) calcd for $[\text{C}_{29}\text{H}_{55}\text{NO}_7\text{Si}+\text{Na}]^+$ 580.3640, found 580.3635.

(E)-(R)-4-tert-Butoxycarbonylamino-2-methyl-5-(triphenylmethylthio)pentanoic acid ethyl ether (15)

To a solution of *N*-Boc-(*S*-Trt)-D-Cys-OH (**14**) (2.00 g, 4.32 mmol) in CH₂Cl₂ (22 mL) was added *N,N*-diisopropylethylamine (1.88 mL, 10.8 mmol), HOBT (760 mg, 5.62 mmol) and EDCI·HCl (1.08 g, 5.62 mmol) at room temperature. After being stirred at the same temperature for 2.5 h, the reaction mixture was quenched with 1 M HCl and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (35% ethyl acetate in hexane) to give (*R*)-*N*-methyl-*N*-methoxy-2-*tert*-butoxycarbonylamino-3-(triphenylmethylthio)propionamide (2.08 g, 4.10 mmol, 95%) as a white amorphous solid. TLC *R*_f 0.52 (hexane/ethyl acetate = 1/1); [α]²⁴_D = +17.3 (*c* 1.06, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (m, 6H), 7.25-7.29 (m, 6H), 7.20 (m, 3H), 5.11 (d, *J* = 8.7 Hz, 1H), 4.75 (m, 1H), 3.64 (s, 3H), 3.14 (s, 3H), 2.54 (ABX pattern, *J* = 12.1, 4.8 Hz, 1H), 2.37 (ABX pattern, *J* = 12.1, 7.7 Hz, 1H), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 155.2, 144.6, 129.6, 128.0, 126.8, 79.8, 66.7, 61.6, 49.8, 34.2, 32.2, 28.4; IR (neat cm⁻¹) 3314, 2976, 1713, 1661, 1489, 1249, 1167, 1022, 743, 700; HRMS (ESI-TOF) calcd for [C₂₉H₃₄N₂O₄S+Na]⁺ 529.2132, found 529.2135.

To a solution of the above Weinreb amide (2.08 g, 4.10 mmol) in toluene (41 mL) was added dropwise DIBAL (9.10 mL, 1.0 M in toluene, 9.11 mmol) at -78 °C over 15 min under argon. After being stirred at the same temperature for 15 min, the reaction mixture was poured into 10% aqueous potassium sodium tartrate at 0 °C, stirred at room temperature for 1 h and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude aldehyde in toluene (24 mL) was added Ph₃P=C(CH₃)CO₂Et (2.70 g, 7.54 mmol) at 0 °C under argon. After being at room temperature for 3.0 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (8% ethyl acetate in hexane) to give **15** (1.96 g, 3.69 mmol, 90% in 2 steps) as a white amorphous solid. TLC *R*_f 0.54 (hexane/ethyl acetate = 2/1); [α]²⁴_D = -16.3 (*c* 1.68, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.41 (m, 6H), 7.28 (m, 6H), 7.14-7.24 (m, 3H), 6.39 (dq, *J* = 9.2, 1.4 Hz, 1H), 4.55 (m, 1H), 4.38

(m, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 2.42 (ABX pattern, $J = 12.1, 7.2$ Hz, 1H), 2.35 (ABX pattern, $J = 12.1, 5.3$ Hz, 1H), 1.76 (d, $J = 1.4$ Hz, 3H), 1.41 (s, 9H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 154.9, 144.5, 140.1, 129.6, 128.1, 126.9, 79.8, 67.1, 60.8, 48.4, 36.5, 28.4, 14.3, 12.9; IR (solid cm^{-1}) 3356, 3060, 1956, 1700, 1488, 1366, 1250, 1160, 1032, 742, 699; HRMS (ESI-TOF) calcd for $[\text{C}_{32}\text{H}_{37}\text{NO}_4\text{S}+\text{Na}]^+$ 554.2336, found 554.2330.

Preparation of *N*-Boc derivative of **5**

N-Boc derivative of moCys-5

To a solution of **15** (526 mg, 1.06 mmol) in *tert*-butyl alcohol (8.0 mL), H_2O (2.0 mL) and THF (2.0 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (222 mg, 5.28 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer was extracted with CHCl_3 . The combined organic layer was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude acid in *N,N*-dimethylformamide (5.5 mL) was added potassium carbonate (293 mg, 522 mmol) and allyl bromide (128 μL , 522 μmol) at room temperature. After being stirred at the same temperature for 2.0 h, the reaction mixture was filtered through a pad of Celite[®], poured into 1 M HCl at 0 °C and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaHCO_3 , brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to give *N*-Boc protected **5** (502 mg, 899 μmol , 85% in 2 steps) as a white amorphous solid. TLC R_f 0.54 (hexane/ethyl acetate = 2/1); $[\alpha]_D^{24} = -17.3$ (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.39 (m, 6H), 7.25-7.30 (m, 6H), 7.21 (m, 3H), 6.43 (dq, $J = 9.2, 1.4$ Hz, 1H), 5.93 (m, 1H), 5.32 (dd, $J = 17.1, 1.5$ Hz, 1H), 5.23 (dd, $J = 14.8, 1.5$ Hz, 1H), 4.62 (d, $J = 5.9$ Hz, 2H), 4.56 (m, 1H), 4.38 (m, 1H), 2.42 (ABX pattern, $J = 12.2, 7.3$ Hz, 1H), 2.34 (ABX pattern, $J = 12.2, 5.8$ Hz, 1H), 1.78 (d, $J = 1.4$ Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 154.9, 144.5, 140.6, 132.4, 129.6, 128.1, 126.9, 118.2, 79.8, 77.3, 67.1, 65.5, 48.4, 36.4, 28.4, 12.9; IR (solid cm^{-1}) 3366, 2977, 1709, 1649, 1595, 1445, 1366, 1250, 1167, 1018, 743, 700; HRMS (ESI-TOF) calcd for

$[\text{C}_{33}\text{H}_{37}\text{NO}_4\text{S}+\text{Na}]^+$ 566.2336, found 566.2339.

Pyrrolidine-1,2-dicarboxylic acid (2S)-2-[(1R,3R,5S,6S)-6-[(E)-(R)-3-allyloxycarbonyl-3-methyl-1-[2-(triphenylmethylthio)ethyl]-2-propenylcarbamoyl]-1-tert-butyl-5-(tert-butyldimethylsilyloxy)-3-methylheptyl] ester 1-tert-butyl ester (16)

To a solution of *N*-Boc protected **5** (284 mg, 522 μmol) and 2,6-lutidine (366 μL , 3.14 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (284 μL , 1.57 mmol) at room temperature under argon. After being stirred at the same temperature for 3 h, the reaction mixture was quenched with methanol and H_2O . The aqueous layer was extracted with CHCl_3 . The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.0 mL). To this solution was added a solution of **6** (224 mg, 402 μmol) in CH_2Cl_2 (2.2 mL), *N,N*-diisopropylethylamine (140 μL , 804 μmol) and HATU (167 mg, 522 μmol) at room temperature. After being stirred at the same temperature for 10 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (26% ethyl acetate in hexane) to give **16** (372 mg, 378 μmol , 94%) as a white amorphous solid. TLC *R*_f 0.57 (hexane/ethyl acetate = 3/2); $[\alpha]_{\text{D}}^{26} = -39.8$ (*c* 0.940, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 7.37 (d, *J* = 7.3 Hz, 6H), 7.18-7.28 (m, 9H), 6.93 (d, *J* = 8.3 Hz, 0.5H), 6.85 (d, *J* = 8.3 Hz, 0.5H), 6.44 (dq, *J* = 9.3, 1.5 Hz, 1H), 5.88-5.98 (m, 1H), 5.32 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.22 (dd, *J* = 10.8, 1.4 Hz, 1H), 4.66-4.35 (m, 1H), 3.74 (m, 1H), 3.36-3.50 (m, 2H), 2.28-2.44 (m, 3H), 2.17 (m, 1H), 1.98 (m, 1H), 1.88 (m, 2H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.52 (m, 1H), 1.47 (m, 1H), 1.44 (s, 4.5H), 1.42 (s, 4.5H), 1.22-1.33 (m, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.84-0.87 (m, 2H), 0.09-0.15 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 174.3, 174.0, 172.7, 172.5, 167.3, 154.2, 154.0, 144.6, 139.8, 139.7, 132.4, 130.2, 129.6, 128.0, 126.8, 118.0, 80.2, 80.0, 79.8, 79.5, 73.9, 73.6, 66.9, 65.4, 59.5, 59.3, 46.5, 46.2, 45.9, 43.1, 43.0, 39.3, 36.4, 35.0, 34.9, 31.6, 31.1, 30.2, 28.6, 28.5, 27.5, 26.9,

26.1, 26.0, 25.9, 24.4, 23.3, 22.7, 22.4, 22.1, 18.0, 16.7, 16.5, 14.2, 13.2, -4.1, -4.6, -4.7; IR (solid cm^{-1}) 3339, 2955, 1697, 1397, 1254, 1162, 1086, 837, 743, 700; HRMS (ESI-TOF) calcd for $[\text{C}_{38}\text{H}_{63}\text{NO}_8\text{Si}+\text{Na}]^+$ 712.4215, found 712.4214.

Pyrrolidine-1,2-dicarboxylic acid (2S)-2-[(1R,3R,5S,6S)-6-{(E)-(R)-3-allyloxycarbonyl-3-methyl-1-[2-(triphenylmethylthio)ethyl]-2-propenylcarbamoyl}-1-tert-butyl-3-methyl-5-(2,2,2-trichloroethoxycarbonyloxy)heptyl] ester 1-(9-fluorenylmethyl) ester (4)

4

To a solution of **16** (372 mg, 378 μmol) in tetrahydrofuran (4.0 mL) was added TBAF (442 μl , 1.0 M in tetrahydrofuran, 442 μmol) at 0 $^{\circ}\text{C}$ under argon. After being stirred at the same temperature for 20 min, the reaction mixture was quenched with saturated aqueous NaHCO_3 and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (35% ethyl acetate in hexane) to give the *N*-Boc protected alcohol (312 mg, 359 μmol , 95%) as a white amorphous solid. TLC *R*_f 0.38 (hexane/ethyl acetate = 3/2); $[\alpha]_D^{25} = -30.1$ (*c* 1.39, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , major rotamer) δ 7.37 (m, 6H), 7.27 (m, 6H), 7.21 (m, 3H), 6.42 (dq, *J* = 9.3, 1.4 Hz, 1H), 5.92 (m, 1H), 5.30 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.22 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.85 (dd, *J* = 11.2, 1.4 Hz, 1H), 4.68 (m, 1H), 4.59-4.61 (m, 2H), 4.36 (dd, *J* = 8.3, 3.4 Hz, 1H), 3.63 (m, 1H), 3.34-3.55 (m, 2H), 2.49 (ABX pattern, *J* = 12.2, 7.3 Hz, 1H), 2.32 (ABX pattern, *J* = 12.2, 6.4 Hz, 1H), 1.96-2.28 (m, 2H), 1.78-1.90 (m, 3H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.53-1.63 (m, 2H), 1.41 (s, 9H), 1.40 (m, 1H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.09 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 175.4, 174.7, 172.4, 167.3, 154.6, 144.7, 144.5, 140.0, 139.9, 139.7, 132.4, 132.3, 130.2, 130.0, 129.7, 128.0, 127.9, 126.9, 126.8, 118.2, 118.1, 80.2, 79.9, 78.2, 76.8, 71.3, 71.2, 71.0, 67.1, 67.0, 65.5, 65.4, 59.6, 59.0, 47.8, 47.1, 46.9, 46.6, 46.3, 45.9, 40.5, 38.1, 37.2, 36.2,

36.1, 34.9, 34.6, 31.6, 31.1, 30.0, 28.5, 28.4, 26.2, 26.1, 26.0, 25.5, 25.4, 24.1, 23.3, 22.7, 21.2, 19.9, 14.7, 17.6, 14.2, 13.1, 13.0; IR (solid cm^{-1}) 3309, 2964, 1715, 1677, 1652, 1530, 1367, 1255, 1122, 962, 743, 701; HRMS (ESI-TOF) calcd for $[\text{C}_{51}\text{H}_{68}\text{N}_2\text{O}_8\text{S}+\text{Na}]^+$ 891.4589, found 891.4586.

To a solution of the *N*-Boc protected alcohol (328 mg, 377 μmol) and 2,6-lutidine (351 μL , 3.02 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (273 μL , 1.51 mmol) at room temperature under argon. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with methanol and H_2O . The aqueous layer was extracted with CHCl_3 . The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude amino alcohol and *N,N*-diisopropylethylamine (79.0 μL , 452 μmol) in CH_2Cl_2 (4.0 mL) and tetrahydrofuran (2.0 mL) was added FmocOSu (127 mg, 377 μmol) at 0 $^\circ\text{C}$. After being stirred at the same temperature for 40 min, the reaction mixture was quenched with 1 M HCl and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaHCO_3 , brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to give the *N*-Fmoc protected alcohol (359 mg, 362 μmol , 96% in 2 steps) as a white amorphous solid. TLC *R*_f 0.48 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{27} = -21.9$ (*c* 1.33, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , major rotamer) δ 7.76 (dd, *J* = 7.3, 2.4 Hz, 2H), 7.59 (dd, *J* = 10.2, 7.3 Hz, 2H), 7.13-7.42 (m, 19H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.43 (dq, *J* = 9.3, 1.4 Hz, 1H), 5.79-5.89 (m, 1H), 5.23 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.15 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.88 (dd, *J* = 10.7, 1.4 Hz, 1H), 4.60 (m, 1H), 4.48-4.51 (m, 2H), 4.43 (dd, *J* = 3.4, 3.4 Hz, 1H), 4.40 (m, 1H), 4.22-4.25 (m, 2H), 3.47-3.71 (m, 3H), 2.45 (ABX pattern, *J* = 12.2, 7.3 Hz, 1H), 2.29 (ABX pattern, *J* = 12.2, 6.4 Hz, 1H), 2.21 (dq, *J* = 6.8, 4.4 Hz, 1H), 1.92-2.18 (m, 4H), 1.85 (m, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.54-1.64 (m, 2H), 1.42 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.04 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 175.4, 172.2, 167.2, 155.3, 144.6, 144.5, 143.8, 141.3, 140.0, 132.4, 130.0, 129.7, 128.1, 128.0, 127.8, 127.2, 126.9, 126.8, 125.2, 125.1, 120.0, 118.0, 78.6, 71.1, 67.8, 67.1, 65.4, 59.6, 47.3, 47.2, 46.5, 46.3, 40.5, 37.2, 36.1, 34.9, 31.6, 29.9, 26.0, 25.5, 24.3, 22.7, 20.0, 15.3, 14.2, 13.0; IR (solid cm^{-1}) 3318, 2958, 2874, 1713, 1449, 1426, 1364, 1223, 1180, 758, 700; HRMS (ESI-TOF) calcd for $[\text{C}_{61}\text{H}_{70}\text{N}_2\text{O}_8\text{S}+\text{Na}]^+$ 1013.4745, found 1013.4734.

To a solution of the *N*-Fmoc protected alcohol (320 mg, 323 μmol), pyridine (157 μL , 1.94 mmol) and 4-dimethylaminopyridine (3.9 mg, 3.2 μmol) in CH_2Cl_2 (3.0 mL) was added TrocCl (130 μL , 969 μmol) at 0 $^\circ\text{C}$ under argon. After being stirred at room temperature for 1.0 h, the reaction mixture was quenched with H_2O and the aqueous layer was extracted with ethyl acetate. The

combined organic layer was washed with saturated aqueous NaHCO_3 , brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to give **4** (316 mg, 271 μmol , 84%) as a white amorphous solid. TLC R_f 0.56 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{26} = -34.6$ (c 1.35, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 7.74-7.78 (m, 2H), 7.69 (d, $J = 7.3$ Hz, 0.4H), 7.57-7.62 (m, 2H), 7.18-7.42 (m, 19H), 6.35-6.41 (m, 1H), 5.80-5.99 (m, 1H), 5.44 (d, $J = 7.8$ Hz, 0.6H), 5.32 (dd, $J = 17.6, 1.4$ Hz, 0.4H), 5.25 (dd, $J = 17.6, 1.5$ Hz, 0.6H), 5.23 (dd, $J = 10.2, 1.4$ Hz, 0.4H), 5.17 (dd, $J = 10.7, 1.5$ Hz, 0.6H), 4.97 (m, 1H), 4.84 (dd, $J = 8.2, 3.9$ Hz, 0.6H), 4.81 (AB pattern, $J = 12.2$ Hz, 0.6H), 4.80 (dd, $J = 10.2, 5.8$ Hz, 0.4H), 4.71 (AB pattern, $J = 12.2$ Hz, 0.4H), 4.48-4.67 (m, 3H), 4.36-4.42 (m, 1H), 4.19-4.30 (m, 2H), 3.46-3.66 (m, 2H), 2.09-2.54 (m, 5H), 1.89-2.02 (m, 3H), 1.73 (br s, 3H), 1.58-1.62 (m, 1H), 1.22-1.49 (m, 3H), 1.09 (d, $J = 6.8$ Hz, 1.8H), 1.06 (d, $J = 7.3$ Hz, 1.2H), 0.92 (d, $J = 6.8$ Hz, 1.8H), 0.87 (s, 3.6H), 0.85 (s, 5.4H), 0.73 (d, $J = 6.4$ Hz, 1.2H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 172.6, 172.2, 171.9, 167.2, 154.9, 154.5, 153.9, 153.8, 132.3, 130.4, 130.2, 129.7, 128.1, 128.0, 127.8, 127.2, 127.0, 126.9, 125.6, 125.3, 125.2, 120.0, 118.3, 118.1, 94.9, 79.3, 79.1, 78.8, 78.5, 67.9, 67.5, 67.2, 67.1, 65.6, 65.5, 59.8, 59.5, 47.3, 47.2, 47.1, 46.4, 45.3, 44.7, 38.1, 37.5, 36.8, 36.4, 35.8, 35.1, 34.8, 31.3, 30.1, 26.1, 25.9, 25.8, 24.3, 23.5, 20.4, 19.9, 13.5, 13.0, 12.9; IR (solid cm^{-1}) 3329, 2962, 1755, 1709, 1523, 1449, 1420, 1248, 1119, 946, 741; HRMS (ESI-TOF) calcd for $[\text{C}_{64}\text{H}_{71}\text{Cl}_3\text{N}_2\text{O}_{10}\text{S}+\text{Na}]^+$ 1187.3787, found 1187.3796.

Pyrrolidine-1,2-dicarboxylic acid (2S)-2-[(1R,3R,5S,6S)-6-[(E)-2-allyloxycarbonylpropenyl]-(S)-4,5-dihydro-thiazol-2-yl]-1-tert-butyl-5-hydroxy-3-methylheptyl] ester 1-(9-fluorenylmethyl) ester (18)

To a solution of triphenylphosphine oxide (72.0 mg, 257 μmol) in CH_2Cl_2 (1.0 mL) was added dropwise Tf_2O (22.0 μL , 129 μmol) at 0 $^\circ\text{C}$ under argon. After being stirred at the same temperature

for 10 min, to the mixture was added **4** (50.9 mg, 42.9 μ mol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, quenched with saturated aqueous NaHCO₃ at 0 °C and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of crude **17** in tetrahydrofuran (2.0 mL) and 1.0 M aqueous NH₄OAc (0.50 mL) was added Zn dust (28.0 mg, 429 μ mol) at room temperature. After being stirred at room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The solution was extracted with ethyl acetate. The combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to give **18** (28.2 mg, 38.6 μ mol, 90% in 2 steps) as a white amorphous solid. TLC *R*_f 0.37 (hexane/ethyl acetate = 2/1); $[\alpha]_D^{26} = -62.4$ (*c* 0.900, CHCl₃); ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.63 (dd, *J* = 6.8, 7.3 Hz, 2H), 7.39 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1.6H), 7.29 (d, *J* = 6.8 Hz, 0.6H), 6.78-6.82 (m, 1H), 5.84-6.00 (m, 1H), 5.16-5.35 (m, 3H), 4.90 (dd, *J* = 11.6, 1.9 Hz, 0.8H), 4.82 (dd, *J* = 10.6, 1.4 Hz, 0.2H), 4.59-4.66 (m, 2H), 4.33-4.53 (m, 3H), 4.19-4.31 (m, 1H), 3.80 (m, 0.8H), 3.69 (m, 0.2H), 3.62 (m, 1H), 3.52 (m, 1H), 3.43 (dd, *J* = 11.1, 8.7 Hz, 0.2H), 3.31 (dd, *J* = 11.2, 8.8 Hz, 0.8H), 2.92-3.02 (m, 1H), 2.65-2.72 (m, 1H), 2.25 (m, 1H), 2.02 (m, 1H), 1.97 (d, *J* = 1.5 Hz, 0.6H), 1.95 (d, *J* = 1.0 Hz, 2.4H), 1.86 (m, 0.8H), 1.61-1.74 (m, 2.0H), 1.48 (m, 0.2H), 1.27-1.38 (m, 1H), 1.25 (d, *J* = 7.3 Hz, 0.6H), 1.21 (d, *J* = 6.8 Hz, 2.4H), 0.99 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 2.4H), 0.88 (s, 9H), 0.79 (d, *J* = 6.4 Hz, 0.6H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 172.5, 167.3, 154.9, 154.4, 144.3, 144.1, 143.9, 141.4, 141.3, 140.3, 132.3, 127.7, 127.0, 125.5, 125.4, 125.3, 119.9, 118.3, 118.1, 79.4, 78.4, 74.1, 71.4, 67.9, 67.8, 65.6, 65.5, 59.6, 47.3, 47.2, 47.0, 46.5, 45.9, 45.3, 40.2, 39.1, 37.9, 37.6, 37.5, 34.8, 34.6, 31.6, 31.2, 30.0, 29.8, 26.1, 25.6, 25.0, 24.6, 23.3, 22.7, 20.6, 20.4, 16.2, 15.6, 14.2, 13.1; IR (solid cm⁻¹) 3475, 2960, 2874, 1712, 1610, 1451, 1419, 1362, 1245, 1089, 740; HRMS (ESI-TOF) calcd for [C₄₂H₅₄N₂O₇S+Na]⁺ 753.3544, found 753.3542.

Pyrrolidine-1,2-dicarboxylic acid (2*S*)-2-[(1*R*,3*R*,5*S*,6*S*)-6-[(*E*)-2-carboxypropenyl]-(*S*)-4,5-dihydro-thiazol-2-yl]-1-*tert*-butyl-5-hydroxy-3-methylheptyl] ester 1-(9-fluorenylmethyl) ester (2**)**

To a solution of **18** (28.2 mg, 38.6 μmol) and *N*-methylaniline (10.3 μL , 96.5 μmol) in tetrahydrofuran (2.5 mL) was added tetrakis(triphenylphosphine)palladium (4.5 mg, 3.9 μmol) at room temperature under argon. After being stirred at the same temperature for 40 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (3.0% methanol in CHCl_3) to give acid **2** (25.4 mg, 36.7 μmol , 95%) as a white amorphous solid. TLC *R_f* 0.40 (CHCl_3 /methanol = 9/1); $[\alpha]_D^{26} = -76.3$ (*c* 1.11, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 7.63 (d, *J* = 7.3 Hz, 2H), 7.63 (m, 2H), 7.38 (m, 2H), 7.30 (m, 2H), 6.84-6.89 (m, 1H), 5.14-5.28 (m, 1H), 4.90 (dd, *J* = 11.7, 1.5 Hz, 0.7H), 4.82 (br d, *J* = 10.3 Hz, 0.3H), 4.18-4.53 (m, 4H), 3.39-3.81 (m, 3H), 3.36 (dd, *J* = 10.8, 7.8 Hz, 0.3H), 3.30 (dd, *J* = 10.8, 8.8 Hz, 0.7H), 2.97 (m, 1H), 2.72 (m, 1H), 2.23 (m, 1H), 1.94-2.07 (m, 3H), 1.94 (br s, 0.9H), 1.92 (dd, *J* = 1.0 Hz, 2.1H), 1.84 (m, 1H), 1.29-1.78 (m, 2H), 1.24 (d, *J* = 7.3 Hz, 0.9H), 1.21 (d, *J* = 7.3 Hz, 2.1H), 0.96 (d, *J* = 6.4 Hz, 2.1H), 0.89 (s, 2.7H), 0.87 (s, 6.3H), 0.78 (d, *J* = 6.8 Hz, 0.9H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 173.0, 172.5, 172.0, 155.1, 155.0, 154.4, 144.3, 144.2, 144.1, 144.0, 143.8, 142.3, 141.4, 141.3, 141.2, 127.7, 127.6, 127.1, 125.5, 125.3, 119.9, 79.5, 78.6, 78.4, 71.5, 70.9, 67.9, 67.8, 59.6, 47.3, 47.2, 47.1, 47.0, 46.5, 46.0, 45.3, 40.1, 39.4, 39.0, 37.9, 37.6, 37.4, 34.8, 34.6, 31.2, 30.0, 26.0, 25.5, 25.1, 24.9, 24.6, 23.4, 20.5, 20.3, 16.2, 14.5, 12.9, 12.8; IR (solid cm^{-1}) 3464, 2957, 1962, 1607, 1419, 1359, 1178, 1124, 988, 758; HRMS (ESI-TOF) calcd for $[\text{C}_{39}\text{H}_{50}\text{N}_2\text{O}_7\text{S}+\text{Na}]^+$ 713.3231, found 713.3234.

Preparation of *N*-Fmoc derivative of tripeptide 3

N-Fmoc derivative of **3**

To Boc-(*N*-Me)Ile-OAllyl (2.30 g, 8.07 mmol) was added 4 M HCl in ethyl acetate (10 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was azeotroped with toluene and CH₂Cl₂ twice, then dissolved in CH₂Cl₂ (34 mL). To this solution was added Boc-(*N*-Me)Ala-OH (1.37 g, 6.72 mmol), *N,N*-diisopropylethylamine (2.93 mL, 16.8 mmol) and HATU (3.58 g, 9.41 mmol) at room temperature. After being stirred at the same temperature for 1.5 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to give dipeptide Boc-(*N*-Me)Ala-(*N*-Me)Ile-OAllyl (2.47 g, 6.68 mmol, quant.) as a colorless oil. TLC *R_f* 0.50 (hexane/ethyl acetate = 2/1); [α]_D²⁹ = -145 (*c* 1.09, CHCl₃); ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 5.21-5.33 (m, 2H); 5.12 (q, *J* = 6.8 Hz, 0.7H), 4.97 (d, *J* = 6.8 Hz, 0.12H), 4.52-4.69 (m, 2H), 4.29 (d, *J* = 10.2 Hz, 0.18H), 4.14 (d, *J* = 10.2 Hz, 0.12H), 3.02 (s, 2.1H), 2.96 (s, 0.36H), 2.84 (s, 0.54H), 2.76 (s, 2.1H), 2.64 (s, 0.54H), 2.58 (s, 0.36H), 1.92-2.18 (m, 1H), 1.49 (s, 1.08H), 1.46 (s, 6.3H), 1.45 (s, 1.62H), 1.33-1.40 (m, 1H), 1.28 (d, *J* = 10.6 Hz, 2.1H), 1.24-1.26 (m, 0.9H), 1.01-1.10 (m, 1H), 0.92-0.99 (m, 3H), 0.85-0.91 (m, 3H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 172.6, 172.1, 171.9, 171.2, 171.1, 170.9, 170.2, 170.1, 155.5, 155.1, 154.8, 153.9, 131.8, 119.6, 119.4, 118.7, 118.6, 80.4, 80.1, 66.1, 65.9, 65.3, 63.9, 63.7, 60.6, 52.4, 52.2, 50.7, 50.6, 34.5, 34.3, 33.6, 33.3, 31.1, 30.8, 29.7, 29.5, 29.2, 29.0, 28.7, 28.5, 28.4, 25.5, 25.3, 25.0, 24.8, 16.0, 15.8, 14.8, 14.7, 14.6; IR (neat cm⁻¹) 3525, 2937, 1739, 1694, 1661, 1456, 1392, 1183, 1077, 989, 772; HRMS (ESI-TOF) calcd for [C₁₉H₃₄N₂O₅+Na]⁺ 393.2360, found 393.2360.

To the above dipeptide (2.43 g, 5.83 mmol) was added 4 M HCl in ethyl acetate (10 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was azeotroped with toluene and CH₂Cl₂ twice, then dissolved in CH₂Cl₂ (25 mL). To this solution was added Fmoc-(*O*-Me)Tyr-OH (2.21 g, 5.30 mmol), *N,N*-diisopropylethylamine (2.77 mL, 15.9 mmol) and HATU (3.02 g, 7.95 mmol) at room temperature. After being stirred at the

same temperature for 12 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give the *N*-Fmoc derivative of tripeptide **3** (2.80 g, 4.18 mmol, 79%) as a white amorphous solid. TLC *R_f* 0.40 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{29} = -87.1$ (*c* 1.08, CHCl₃); ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.75 (m, 2H), 7.55 (m, 2H), 7.39 (m, 2H), 7.27-7.32 (m, 2H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 2H), 6.70-6.74 (m, 1H), 5.72-5.92 (m, 1H), 5.58 (d, *J* = 9.3 Hz, 1H), 5.42 (q, *J* = 7.4 Hz, 1H), 5.20-5.33 (m, 2H), 4.85-4.96 (m, 1H), 4.11-4.50 (m, 2H), 3.74 (s, 3H), 2.99-3.05 (m, 1H), 2.98 (s, 3H), 2.81-2.87 (m, 1H), 2.76 (s, 3H), 1.96 (m, 1H), 1.28 (d, *J* = 7.3 Hz, 3H), 1.23-1.27 (m, 1H), 1.00 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.84-0.90 (m, 3H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 171.9, 171.7, 170.7, 158.7, 155.8, 143.8, 141.3, 131.8, 130.5, 130.4, 128.0, 127.1, 125.2, 125.1, 120.0, 118.7, 114.0, 67.1, 65.4, 60.5, 55.2, 52.3, 49.8, 47.2, 38.1, 33.3, 31.0, 30.6, 25.1, 15.8, 14.4, 10.6; IR (solid cm⁻¹) 3296, 2965, 1718, 1636, 1512, 1243, 990, 741, 540; HRMS (ESI-TOF) calcd for [C₃₉H₄₇N₃O₇+Na]⁺ 692.3306, found 692.3314.

Pyrrolidine-1,2-dicarboxylic acid (2*S*)-2-[(1*R*,3*R*,5*S*,9*S*)-6-[(*S*)-4-[(*E*)-2-[(*S*)-1-[(*S*)-1-[(1*S*,2*S*)-1-allyloxycarbonyl-2-methylbutyl]-ethylcarbamoyl]ethyl)methylcarbamoyl]-2-(4-methoxyphenyl)ethylcarbamoyl]propenyl]-4,5-dihydro-thiazol-2-yl]-1-*tert*-butyl-5-hydroxy-3-methylheptyl] ester 1-(9-fluorenylmethyl) ester (19**)**

To a solution of the *N*-Fmoc derivative of tripeptide **3** (36.9 mg, 55.1 μmol) in CH₃CN (2.0 mL) was added *N,N*-diethylamine (1.0 mL) at room temperature. After being stirred at the same temperature for 20 min, the reaction mixture was concentrated *in vacuo*. The residue was azeotroped

with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (0.5 mL). To this solution was added a solution of acid **2** (25.4 mg, 36.7 μmol) in CH_2Cl_2 (1.5 mL), *N,N*-diisopropylethylamine (19.2 μL , 110 μmol) and HATU (17.6 mg, 55.1 μmol) at room temperature. After being stirred at the same temperature for 8.0 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (17% acetone in toluene) to give **19** (30.7 mg, 27.4 μmol , 75% in 2 steps) as a white amorphous solid. TLC *R_f* 0.60 ($\text{CHCl}_3/\text{MeOH} = 9/1$); $[\alpha]_{\text{D}}^{26} = -89.0$ (*c* 1.28, CHCl_3); ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.39 (dd, *J* = 7.7, 7.3 Hz, 2H), 7.31 (dd, *J* = 7.7, 7.3 Hz, 2H), 7.09 (d, *J* = 6.8 Hz, 2H), 6.78 (d, *J* = 6.8 Hz, 2H), 6.30 (d, *J* = 8.3 Hz, 1H), 5.87 (m, 1H), 5.37 (br d, *J* = 6.8 Hz, 1H), 5.19-5.32 (m, 2H), 5.18 (m, 1H), 5.11 (m, 1H), 4.80-4.94 (m, 2H), 4.59 (br d, *J* = 5.8 Hz, 2H), 4.15-4.20 (m, 3H), 3.77 (m, 1H), 3.75 (s, 3H), 3.64 (m, 1H), 3.53 (m, 1H), 3.24 (m, 1H), 2.98-3.06 (m, 2H), 2.95 (s, 3H), 2.78-2.93 (m, 2H), 2.73 (s, 3H), 2.66 (m, 1H), 2.23 (m, 1H), 1.91-2.20 (m, 4H), 1.92 (br s, 3H), 1.81 (m, 1H), 1.60-1.74 (m, 2H), 1.20-1.50 (m, 9H), 0.89-1.07 (m, 7H), 0.88 (s, 9H), 0.76-0.84 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 172.6, 171.9, 171.5, 170.7, 168.1, 158.7, 155.0, 144.1, 144.0, 142.9, 141.4, 141.3, 131.8, 127.7, 130.5, 127.7, 127.1, 125.4, 120.0, 118.7, 114.0, 78.4, 71.5, 67.9, 65.4, 60.5, 59.7, 59.6, 55.2, 49.7, 47.2, 46.6, 45.9, 39.1, 37.7, 37.6, 34.8, 39.1, 37.7, 37.6, 34.8, 33.3, 32.0, 31.0, 30.7, 30.6, 30.1, 30.0, 29.8, 29.7, 26.1, 25.1, 25.0, 23.4, 22.8, 20.4, 15.8, 14.5, 13.6, 10.7; IR (solid cm^{-1}) 3465, 3328, 2960, 2876, 1735, 1707, 1625, 1513, 1478, 1416, 1299, 1179, 1087, 988, 741, 545; HRMS (ESI-TOF) calcd for $[\text{C}_{63}\text{H}_{85}\text{N}_5\text{O}_{11}\text{S}+\text{Na}]^+$ 1142.5859, found 1142.5858.

Apratoxin A (1)

To a solution of **19** (30.7 mg, 27.4 μmol) and *N*-methylaniline (7.4 μL , 68.5 μmol) in tetrahydrofuran (2.0 mL) was added tetrakis(triphenylphosphine)palladium (3.2 mg, 2.7 μmol) at room temperature under argon. After being stirred at the same temperature for 15 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (4.0% methanol in CHCl_3) to give the *N*-Fmoc protected acid as a white amorphous solid.

To a solution of the *N*-Fmoc protected acid in CH_3CN (2.0 mL) was added diethylamine (1.0 mL) at room temperature. After being stirred at the same temperature for 30 min, the reaction mixture was concentrated *in vacuo*. The residue **20** was azeotroped with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (27 mL). To this solution was added *N,N*-diisopropylethylamine (31.9 μL , 247 μmol) and HATU (26.2 mg, 82.2 μmol) at room temperature under argon. After being stirred at the same temperature for 22 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (3.0% to 6.0% 2-propanol in CH_2Cl_2) and reverse-phase column chromatography (Bond Elut-C18) to give apratoxin A (**1**) (14.5 mg, 12.2 μmol , 53% in 3 steps) as a white amorphous solid. TLC *Rf* 0.33 (ethyl acetate); $[\alpha]_D^{25} = -161$ (*c* 0.625, methanol), lit. $[\alpha]_D^{25} -161$ (*c* 1.33, methanol); ^1H NMR (400 MHz, CDCl_3) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.35 (d, *J* = 9.8 Hz, 1H), 6.05 (d, *J* = 9.3 Hz, 1H), 5.25 (ddd, *J* = 9.8, 8.7, 4.3 Hz, 1H), 5.20 (d, *J* = 11.6 Hz, 1H), 5.05 (ddd, *J* = 10.7, 9.3, 4.9 Hz, 1H), 4.97 (dd, *J* = 12.6, 1.9 Hz, 1H), 4.70 (d, *J* = 10.6 Hz, 1H), 4.24 (m, 1H), 4.19 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 3.66 (m, 1H), 3.54 (m, 1H), 3.46 (dd, *J* = 11.1, 8.7 Hz, 1H), 3.28 (br q, *J* = 6.8 Hz, 1H), 3.14 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.11 (dd, *J* = 12.2, 10.7 Hz, 1H), 2.86 (dd, *J* = 12.2, 4.9 Hz, 1H), 2.81 (s, 3H), 2.71 (s, 3H), 2.64 (m, 1H), 2.24 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.97 (s, 3H), 1.88 (m, 1H), 1.79 (m, 1H), 1.57 (m, 1H), 1.31 (m, 1H), 1.25 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.06 (m, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.5, 172.7, 170.7, 170.1, 169.6, 158.7, 136.4, 130.7, 130.5, 128.3, 114.2, 114.0, 77.4, 72.5, 71.7, 60.8, 59.8, 56.7, 55.4, 50.6, 49.2, 47.7, 38.2, 37.7, 36.8, 35.0, 31.8, 30.6, 29.3, 26.1, 25.7, 24.3, 19.9, 16.7, 14.1, 14.0, 13.4, 9.1; IR (solid cm^{-1}) 3420, 2933, 2958, 2874, 1740, 1622, 1511, 1455, 1371, 1246, 1177, 1078; HRMS (ESI-TOF) calcd for $[\text{C}_{45}\text{H}_{69}\text{N}_5\text{O}_8\text{S}+\text{Na}]^+$ 862.4759, found 862.4749.

13-SEP-05 23:58:53

DFILE MASA9121

OBNUC 13C

EXMOD BCM

QPR 67.80 MHz

OBSET 135.00 kHz

OBFIN 5200.0 Hz

POINT 32768

FREQ 20000.0 Hz

SCANS 639

ACQTM 0.819 sec

PD 2.181 sec

PW1 5.1 us

IRNUC 1H

CTEMP 28.6 C

SLVNT CDCL3

EXREF 77.10 ppm

BF 1.22 Hz

RGAIN 24

OPERATOR :

9

¹³C NMR (CDCl₃)

400.0

300.0

200.0

100.0

(Millions)

7.0

X : parts per Million : 1H

5.0

4.0

3.0

2.0

1.0

0

15-SEP-05 11:14:07

DFILE SAVING

OBNUC 13C

EXMOD BCM

QFR 67.80 MHz

OBSET 135.00 KHz

OBFIN 5200.0 Hz

POINT 32768

FREQ 20000.0 Hz

SCANS 607

ACQTM 0.819 sec

PD 2.181 sec

PW1 5.1 us

IRNUC 1H

CTEMP 28.6 C

SLVNT CDCL3

EXREF 77.10 ppm

BF 1.22 Hz

RGAIN 24

OPERATOR :

¹³C NMR (CDCl₃)

10

¹³C NMR (CDCl₃)

12

¹H NMR (CDCl₃)

13

(Millions)

8.0

7.0

6.0

5.0

4.0

3.0

2.0

1.0

0

X : parts per Million : ¹H

^{13}C NMR (CDCl_3)

Dtena 6

¹³C NMR (CDCl₃)

N-Boc derivative of moCys-5

^{13}C NMR (CDCl_3)

18

(Billions)

190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0

X : parts per Million : ^{13}C

^1H NMR (CDCl_3)

N-Fmoc derivative of **3**

N-Fmoc derivative of **3**

^{13}C NMR (CDCl_3)

19

^{13}C NMR (CDCl_3)