Supporting Information

**Enantioselective Total Synthesis of the Protein Phosphatase
Inhibitor (-)-Motuporin**

Tao Hu and James S. Panek*

*Department of Chemistry, Metcalf Center for Science and Engineering,
590 Commonwealth Avenue, Boston University, Boston, MA 02215*

Experimental Section: ^1H and ^{13}C NMR spectra were taken in CDCl_3 at 400 MHz and 75 MHz respectively unless specified otherwise. Chemical shifts are reported in parts per million (ppm) using the solvent resonance internal standard (chloroform, 7.24 and 77.0 ppm for ^1H and ^{13}C NMR respectively, unless specified otherwise). NMR Data are reported as follows: chemical shift, multiplicity (app = apparent, par obsc = partially obscured, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, abq = ab quartet), coupling constant, and integration. Infrared Resonance (IR) spectra were recorded on a Perkin-Elmer 1800 series FTIR spectrophotometer. High resolution mass spectra were obtained on a Finnegan MAT-90 spectrometer in the Boston University Mass Spectrometry Laboratory. Reversed phase preparative HPLC was conducted on a Varian/Rainin SD-200 equipped with Dynamax PDA-2 Diode Array detector, using 22 x 250 mm Vydax C18 column (218TP1022). Methylene chloride (CH_2Cl_2), methanol (MeOH), *N,N*-dimethyl formamide (DMF), collidine, *N*-ethylmorpholine, and boron trifluoride etherate ($\text{BF}_3\cdot\text{OEt}_2$) were distilled from calcium hydride, Diisopropyl ethyl amine (DIPEA) was distilled from KOH, and tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. All other reagents were used as supplied. All reactions were carried out in oven-dried glassware under argon atmosphere unless otherwise noted. Analytical thin layer chromatography was performed on Whatman Reagent 0.25 mm silica gel 60-A plates. Flash chromatography was performed on E. Merck silica gel 230-400 mesh.

(E)-(5S, 6R)-Methyl 6-methoxy-7-phenyl-5-methylhept-3-enoate (16). A solution of phenyl acetaldehyde dimethyl acetal **15** (8.0 g, 48.1 mmol) and (*S*)-silane **7** (13.9 g, 52.9 mmol) in 100 mL of dry CH_2Cl_2 (0.48 M) was cooled to -78°C and treated with $\text{BF}_3 \cdot \text{OEt}_2$ (7.7 mL, 52.5 mmol). The reaction mixture was stirred at -78°C for 20 h, and then warmed to -50°C for 12 h before being diluted with a saturated aqueous solution of NaHCO_3 (100 mL). The resulting reaction mixture was stirred for 10 min before extraction with EtOAc (2 x 250 mL). The combined organic layers were dried with MgSO_4 , filtered, and concentrated under reduced pressure to yield crude product with 10:1 (*syn/anti*) diastereoselection as revealed by ^1H NMR analysis of the crude sample. The crude product was purified by flash chromatography on silica gel (5-10% EtOAc/hexanes as eluant) to afford pure *syn* diastereomer **16** (11.6 g, 91% yield) as a light yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.17 (m, 5H), 5.62-5.51 (m, 2H), 3.66 (s, 3H), 3.24-3.20 (par obsc m, 1H), 3.21 (s, 3H), 3.05 (d, $J = 5.7$ Hz, 2H), 2.75 (dd, $J = 4.5, 14.0$ Hz, 1H), 2.66 (dd, $J = 7.9, 14.0$ Hz, 1H), 2.38 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) 172.3, 139.5, 136.8, 129.3, 128.1, 125.8, 121.7, 86.4, 58.2, 51.8, 39.6, 37.9, 37.7, 15.3; IR (neat) 2952, 1740, 1496, 1436, 1167, 1098, 974, 746 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{16}\text{H}_{23}\text{O}_3$ $[\text{M} + \text{H}]^+$ 263.1647, found: 263.1606; $[\alpha]_D^{23} = -23.8$ (c 1.75, CHCl_3).

(3S, 4R)-1,1-Dibromo-4-methoxy-5-phenyl-3-methyl-pent-1-ene (18). To a precooled solution at -78°C of **16** (5.3 g, 20.22 mmol) and 2.0 mL of pyridine in MeOH (200 mL), ozone was bubbled through until the starting material was consumed as indicated by the blue coloration of the reaction mixture. Methyl sulfide (20 mL) was added dropwise, and the mixture

was warmed to ambient temperature and stirring was continued for 6 h. The reaction mixture was concentrated directly *in vacuo*. The remaining residue was diluted with Et₂O (300 mL), and washed with H₂O (200 mL) and aqueous NaHCO₃ (100 mL). The aqueous layers were back extracted with Et₂O (1 x 300 mL) and the combined organic extracts were washed with brine (1 x 200 mL), dried with Na₂SO₄, filtered, and concentrated *in vacuo* to afford the crude aldehyde **17** (3.95 g). This material was used in the following reaction without further purification.

A mixture of carbon tetrabromide (13.4 g, 40.5 mmol) and triphenylphosphine (21.2 g, 81.0 mmol) in 40 mL CH₂Cl₂ was stirred at 0 °C ice/water bath for 10 min. The crude aldehyde **17** (dissolved in 40 mL CH₂Cl₂) was added to this brown colored reaction mixture. The reaction mixture then turned to a dark-brown slurry mixture. The mixture was stirred at 0 °C for 4.0 h, then quenched with aqueous NH₄Cl (100 mL) and extracted with CH₂Cl₂ (3 x 150 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5% EtOAc in petroleum ether as eluant) to afford dibromo olefin **18** (6.18 g, 88% yield from **16**) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.18 (m, 5H), 6.34 (d, *J* = 9.2 Hz, 1H), 3.28 (m, 1H), 3.24 (s, 3H), 2.79 (dd, *J* = 7.3, 13.7 Hz, 1H), 2.72 (dd, *J* = 5.5, 13.7 Hz, 1H), 2.57 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃) δ 141.2, 138.6, 129.3, 128.3, 126.2, 88.7, 85.0, 58.6, 41.6, 37.9, 13.7; IR (neat) 3027, 2932, 2832, 2826, 1604, 1495, 1375, 1239, 1031, 821, 784, 768, 744 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₁₃H₂₀Br₂NO [M + H]⁺ 363.9912, found: 363.9954; [α]_D²³ = +8.0 (*c* = 1.3, CHCl₃).

(4R,5S)-4-Methyl-5-methoxy-6-phenyl-2-hexyne (5). Dibromo olefin **18** (2.8 g, 8.04 mmol) in THF (30 mL) was cooled to -78 °C and treated with ⁿBuLi (7.08 mL, 2.5 M in hexanes, 17.7 mmol). This reddish-purple solution was stirred at -78 °C for 30 min before being warmed to

0 °C (ice/water bath). After 30 min at 0 °C the reaction turned to a light yellow solution. The reaction solution was cooled back to -78 °C and methyl iodide (2.5 mL, 40.2 mmol) was added. The mixture was warmed slowly from -78 °C to rt over 12 h before being diluted with aqueous NH₄Cl (20 mL) and extracted with EtOAc (3 x 50 mL). The combined layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes as eluant) to provide alkyne **5** (1.60 g, 98% yield) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.16 (m, 5H), 3.24 (s, 3H), 3.21 (m, 1H), 2.95 (dd, *J* = 4.0, 14.1 Hz, 1H), 2.82 (dd, *J* = 7.9, 14.1 Hz, 1H), 2.52 (m, 1H), 1.80 (d, *J* = 2.4 Hz, 3H), 1.15 (d, *J* = 7.3, 3H); ¹³C NMR (67.5 MHz, CDCl₃) δ 139.1, 129.5, 128.1, 125.9, 85.8, 81.0, 77.5, 58.4, 37.8, 30.1, 17.3, 3.5 cm⁻¹; IR (neat) 3063, 2933, 2828, 1718, 1604, 1374, 1454, 1031, 749; HRMS (CI, NH₃) *m/z* calcd for C₁₄H₁₉O [M + H]⁺ 203.1436, found: 203.1412; [α]_D²³ = -59 (c 1.0, CHCl₃).

(1'R, 2R, 3S, 4R)-2-(1'-Azido)-3-dimethylphenylsilyl-4-methyl-tetrahydrofuran-2-acetic acid, methyl ester (21). A solution of (*S*)-trioxane (6.7 g, 75 mmol) and (*S, R*)-silane **8** (7.6 g, 25 mmol) in 75 mL dry CH₂Cl₂ was cooled to -78 °C and treated with BF₃•OEt₂ (9.3 mL, 75 mmol). The light-yellow reaction mixture was stirred at -78 °C for 1 h, then warmed to -50 °C and stirred for 36 h, and then warmed further to 0 °C for 2 h. The reaction mixture was quenched with aqueous NaHCO₃ solution (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (10% EtOAc in petroleum ether) to afford pure furan **21** (7.5 g, 91% yield) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.34 (m, 5H), 4.37 (dd, *J* = 2.0, 10.4 Hz, 1H), 3.84 (t, *J* = 7.6 Hz, 1H), 3.74 (s, 3H), 3.32 (t, *J* = 8.4 Hz, 1H), 2.96 (d, *J* = 2.0 Hz, 1H), 2.25 (m, 1H), 1.36 (t, *J* = 10.4 Hz, 1H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.39 (d, *J* = 7.4 Hz, 6H); ¹³C NMR (67.5 MHz, CDCl₃) δ 169.5, 136.6, 133.5, 129.5, 128.0, 83.2, 75.5, 63.6, 52.5, 37.6, 35.6,

17.3, -3.5, -5.2; IR (neat) 2940, 2102, 1740, 1425, 1250, 1195, 1100, 997, 832, 701 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}_3\text{O}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 334.1587, found: 334.1604; $[\alpha]_{\text{D}}^{23} = +44.7$ (c 1.15, CHCl_3).

(E)-(4R,5S)-Methyl 4-azido-6-hydroxy-5-methyl-hex-2-enoate (20). A solution of furan **21** (2.4 g, 7.2 mmol) in 145 mL dry CH_2Cl_2 (0.05 M) at -78°C was treated with SbCl_5 (1.2 mL, 9.36 mmol). This light yellow solution was warmed to -50°C and stirred for 15 h. The resulting reaction solution was diluted with 100 mL of distilled H_2O . The resulting white precipitate suspension solution was filtrated through a short plug of Celite and eluted with CH_2Cl_2 (200 mL). The resulting filtrate was collected and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). All organic extracts were combined and dried (MgSO_4), filtered and then concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30% EtOAc in petroleum ether as eluant) to afford pure alcohol **20** (1.38 g, 96% yield) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 6.78 (dd, $J = 7.3, 15.6$ Hz, 1H), 6.02 (dd, $J = 1.2, 15.6$ Hz, 1H), 4.12 (t, $J = 7.9$ Hz, 1H), 3.72 (s, 3H), 3.60 (dd, $J = 4.9, 10.8$ Hz, 1H), 3.50 (dd, $J = 6.2, 10.8$ Hz, 1H), 2.33 (br s, 1H), 1.86 (m, 1H), 0.88 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 166.1, 142.9, 124.0, 65.0, 64.2, 51.8, 39.4, 13.1; IR (neat) 3356, 2957, 2102, 1728, 1437, 1274, 1038 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_8\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 200.1035, found: 200.1031; $[\alpha]_{\text{D}}^{23} = +76.0$ ($c = 1.0$, CHCl_3).

(E)-(4R, 5S)-Methyl 4-azido-6-(tert-butyldimethylsilyloxy)-5-methyl-hex-2-enoate (22). Alcohol **20** (1.43 g, 7.18 mmol) was dissolved in DMF (10 mL) and cooled to 0°C ,

imidazole (1.22 g, 17.9 mmol) was added. The resulting reaction mixture was then stirred at 0 °C for 5 min before TBSCl (1.95 g, 12.9 mmol) was added. The reaction was warmed to rt over the period of 3.0 h and then diluted with 50 mL ether and 30 mL H₂O. The organic layer was separated and the aqueous layer was extracted with ether (2 x 60 mL). All ether extracts were combined and dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% EtOAc/Hexane as eluant) to afford **22** (2.75 g, 100% yield) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 6.81 (dd, *J* = 7.6, 15.5 Hz, 1H), 6.0 (dd, *J* = 1.2, 15.5 Hz, 1H), 4.14 (t, *J* = 7.7 Hz, 1H), 3.72 (s, 1H), 3.61 (dd, *J* = 4.9, 10.4 Hz, 1H), 3.43 (dd, *J* = 6.1, 10.4 Hz, 1H), 1.84 (m, 1H), 0.86 (s, 9H), 0.01 (d, *J* = 3.1 Hz, 6 H); ¹³C NMR (67.5 MHz, CDCl₃) δ 166.6, 143.2, 123.7, 64.5, 64.2, 51.7, 39.5, 25.8, 18.2, 12.8, -5.6; IR (neat) 2955, 2098, 1733, 1472, 1258, 1172, 1104, 838, 777 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₁₉H₃₈NO₅Si [M + H]⁺ 388.2519, found: 388.2559; [α]_D²³ = +46.9 (*c* 1.17, CHCl₃).

(E)-(4R,5S)-Methyl

4-(N-tert-butoxycarbonyl)amino-6-(tert-butyldimethyl-

silyloxy)-5-methyl-hex-2-enoate (**23**). Azido ester **22** (1.57 g, 5.0 mmol) was dissolved in 10 mL anhydrous methanol and stirred at 0 °C. To this was added SnCl₂ (1.9 g, 10 mmol) in one portion. The resulting reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to rt for an additional 6 h. The methanol was removed *in vacuo* to yield a light yellow-cream colored foam. Dioxane (20 mL) was added to this foam, followed by BOC₂O (2.18 g, 10 mmol) in one portion. Finally, a slurry of NaHCO₃ (1.68 g, 20 mmol) in 8 mL of distilled water was added while stirring the reaction mixture. The resulting white-cream slurry was stirred at rt for 14 h. This reaction mixture was diluted with 50 mL of EtOAc and 20 mL of H₂O and acidified to pH ~ 2 with 2N NaHSO₄. The organic layers were separated, and the aqueous layer was extracted with an additional 100 mL of EtOAc. The organic extracts were combined and dried (MgSO₄), and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (15%

EtOAc/hexanes as eluant) provided the desired *N*-protected carboximide **23** (1.62 g, 84% yield) as a colorless, viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 6.89 (dd, $J = 4.7, 15.8$ Hz, 1H), 5.94 (dd, $J = 1.8, 15.8$ Hz, 1H), 5.90 (par obsc br d, $J = 8.0$ Hz, 1H), 4.28 (br m, 1H), 3.71 (s, 3H), 3.71-3.67 (par obsc m, 1H), 3.44 (dd, $J = 3.9, 10.2$ Hz, 1H), 1.83 (br m, 1H), 1.40 (s, 9H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.88 (s, 9H), 0.01 (d, $J = 4.4$ Hz, 1H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 166.8, 155.7, 148.8, 120.6, 79.0, 65.0, 55.8, 51.5, 37.5, 28.3, 25.8, 18.0, 14.6, -5.7, -5.9; IR (neat) 3402, 2930, 1718, 1653, 1506, 1252, 1168, 838, 778 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{14}\text{H}_{28}\text{N}_3\text{O}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 314.1900, found: 314.1935; $[\alpha]_D^{23} = +18.8$ (c 1.3, CHCl_3);

(E)-(3*R*, 4*S*)-1-Iodo-3-(*N*-*tert*-butoxycarbonyl)amino-5-(*tert*-butyldimethylsilyloxy)-pent-1-ene (6). A solution of **23** (1.12 g, 2.9 mmol) and 0.5 mL of pyridine in anhydrous MeOH (29 mL) was stirred at -78 °C. Ozone was bubbled through until the starting material was totally consumed (monitored through TLC) and 4 mL Me_2S was added. After being stirred for 1 h at -78 °C, the reaction mixture was warmed to rt and stirred for an additional 4.0 h. The reaction mixture was concentrated directly *in vacuo*. The remaining organic residue was taken up with Et_2O (150 mL), and washed sequentially with H_2O (100 mL) and aqueous NaHCO_3 (100 mL). The aqueous layers were combined and back-extracted with ether (1 x 100 mL) and the combined organic extracts were washed with brine (1 x 150 mL), dried (Na_2SO_4), filtered and concentrated to afford crude aldehyde **23a** (970 mg, 101% crude yield from olefin **23**). This aldehyde was used immediately in the following reaction without further purification.

Flame-dried CrCl_2 (2.5 g, 20.3 mmol) was suspended in 15 mL dry THF at rt. To this green slurry, a solution of crude aldehyde **23a** (970 mg, 2.9 mmol) and CHI_3 (2.4 g, 6.1 mmol) in 20 mL THF (yellow homogeneous solution) was added via a cannula. The resulting brown colored reaction mixture was stirred at rt in the dark for 5.0 h, diluted with H_2O (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated

in vacuo. The resulting oil was purified by flash chromatography on silica gel (15% EtOAc in petroleum ether as eluant) to provide pure (*E*)-vinyl iodide **6** (973 mg, 74% yield from olefin **13**) as a yellow, viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 6.43 (dd, $J = 5.8, 14.3$ Hz, 1H), 6.2 (d, $J = 14.3$ Hz, 1H), 5.78 (br, 1H), 4.07 (br m, 1H), 3.73 (br d, $J = 8.6$ Hz, 1H), 3.44 (dd, $J = 3.7, 10.4$ Hz, 1H), 1.73 (m, 1H), 1.39 (s, 9H), 0.98 (d, $J = 7.3$ Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 155.6, 145.9, 79.0, 64.9, 59.0, 38.5, 37.6, 28.3, 25.8, 18.0, 14.3, -5.7; IR (neat) 3408, 2957, 2533, 1700, 1607, 1472, 1405, 1366, 1256, 1174, 1098, 838, 777 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{17}\text{H}_{35}\text{INO}_3\text{Si}$ [$\text{M} + \text{H}$] $^+$ 456.1431, found: 456.1390; $[\alpha]_{\text{D}}^{23} = +28.2$ (c 0.98, CHCl_3);

(*E, E*)-(2*S*, 3*S*, 8*S*, 9*S*)-3-(*N*-*tert*-butoxycarbonyl)amino-1-(*tert*-butyl-dimethylsilyloxy)-9-methoxy-10-phenyl-2, 6, 8-trimethyl-4, 6-decadiene (**25**). Alkyne **5** (125 mg, 0.68 mmol) and Cp_2ZrHCl (316 mg, 1.24 mmol) was dissolved in 1.5 mL THF and stirred at 50 $^\circ\text{C}$ under argon atmosphere. The mixture was stirred in the absence of light for 50 min, resulting in a blood-red reaction mixture. This mixture was brought to rt and stirred for 5 min, while the reaction turned to an orange-yellow solution. Anhydrous ZnCl_2 1 (141 mg, 1.03 mmol) dissolved in THF (1.5 mL) was added via a cannula, and the reaction then turned to a deep-dark colored mixture immediately. After this reaction mixture was stirred for 2 min at rt, a solution of (*E*)-vinyl iodide **6** (157 mg, 0.345 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (20 mg, 0.017 mmol) in THF (3.0 mL) was added via a cannula, followed by a wash with 1.5 mL of THF. The resulting reaction was allowed to stirred at rt for 5 min before being diluted with 10 mL H_2O and stirred for 10 min, and then extracted with EtOAc (3 x 30 mL). The organic extracts were combined and dried (Na_2SO_4), filtered, and

concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10% EtOAc / Hexanes as eluant) to afford coupling product **25** (154 mg, 84% yield, based on vinyl iodide **6**) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.14 (m, 5H), 6.15 (d, $J = 15.9$ Hz, 1H), 5.68 (br, 1H), 5.45 (dd, $J = 6.1, 15.9$ Hz, 1H), 5.32 (d, $J = 9.8$ Hz, 1H), 4.16 (br, 1H), 3.73 (br d, $J = 8.0$ Hz, 1H), 3.44 (dd, $J = 4.3, 9.8$ Hz, 1H), 3.20 (s, 3H), 3.15 (m, 1H), 2.79 (dd, $J = 4.6, 14.0$ Hz, 1H), 2.64 (dd, $J = 7.3, 14.0$ Hz, 1H), 2.56 (m, 1H), 1.73 (m, 1H), 1.61 (s, 3H), 1.41 (s, 9H), 1.00 (two ovrlp d, $J = 6.7$ Hz, 6H), 0.89 (s, 9H), 0.02 (d, $J = 2.0$ Hz, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 155.8, 139.4, 134.9, 132.6, 129.4, 129.1, 128.1, 127.1, 125.9, 87.1, 78.6, 65.1, 58.6, 56.2, 38.8, 38.3, 36.7, 28.4, 25.8, 18.1, 16.2, 14.2, 12.8, -5.7; IR (neat) 3420, 2929, 1718, 1496, 1365, 1251, 1174, 1082 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{31}\text{H}_{53}\text{NO}_4\text{Si}$ [$\text{M} + \text{H}$] $^+$ 531.3744, found: 531.3774; $[\alpha]_{\text{D}}^{23} = -13.0$ (c 1.0, CHCl_3).

(*E, E*)-(2*S*, 3*S*, 8*S*, 9*S*)-3-(*N*-*tert*-butoxycarbonyl)amino-9-methoxy-10-phenyl-2,6,8-trimethyl-4,6-decadien-1-ol (**25a**). A stirred solution of **25** (114 mg, 0.215 mmol) in THF (2.0 mL) at 0 °C was treated with $^n\text{Bu}_4\text{NF}$ (215 mL, 1.0 M in THF, 0.215 mmol) slowly. The resulting yellow solution was stirred at 0 °C for 10 min, and then warmed to rt and stirred for 1 h. The reaction was diluted with an aqueous solution of NH_4Cl (10 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30% EtOAc in hexane as eluant) to afford pure alcohol **25a** (89 mg, 100% yield) as a colorless, viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 6.19 (d, $J = 15.9$ Hz, 1H), 5.41 (par obsc dd, $J = 7.3, 15.9$ Hz, 1H), 5.37 (par obsc d, $J = 9.8$ Hz, 1H), 4.79 (br d, $J = 8.5$ Hz, 1H), 4.06 (q, $J = 7.9$ Hz, 1H), 3.71 (dd, $J = 2.4, 11.6$ Hz, 1H), 3.45 (br d, $J = 11.4$ Hz, 1H), 3.21 (s, 3H), 3.17 (m, 1H), 2.78 (dd, $J = 4.6, 14.0$ Hz, 1H), 2.66 (dd, $J = 7.3, 14.0$ Hz, 1H), 2.57 (m, 1H), 1.60 (s, 3H), 1.57 (par obsc m, 1H), 1.00, 0.97 (two ovrlp

d, $J = 6.7, 7.3$ Hz, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 156.4, 139.3, 137.0, 135.9, 132.4, 129.4, 128.1, 125.9, 125.6, 86.9, 79.8, 64.3, 58.6, 54.7, 40.8, 38.2, 36.7, 28.4, 16.2, 14.3, 12.7; IR (neat) 3400, 2929, 1685, 1559, 1457, 1366, 1251, 1172, 1107 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{25}\text{H}_{39}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 417.2879, found: 417.2865; $[\alpha]_{\text{D}}^{23} = -12.9$ (c 0.93, CHCl_3).

N-Boc Adda (3). To a stirred solution of alcohol **25a** (70 mg, 0.167 mmol) in DMF (1.5 mL) was added PDC (440 mg, 1.17 mmol) in one portion. The resulting red-dark reaction mixture was allowed to stir at ambient temperature for 20 h. It was quenched with H_2O (20 mL), and ether (10 mL) was added to dilute the reaction mixture. The resulting reaction mixture was extracted with Et_2O (2 x 15 mL) and then EtOAc (2 x 15 mL). The organic layers were combined and dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (40% EtOAc / hexanes as eluant) to provide N-Boc Adda **3** (62 mg, 86% yield) as a viscous, colorless oil: ^1H NMR (400 MHz, CDCl_3 , 7.26 ppm) δ 7.30-7.17 (m, 5H), 6.20 (d, $J = 15.8$ Hz, 1H), 5.47 (dd, $J = 6.4, 15.8$ Hz, 1H), 5.39 (d, $J = 9.7$ Hz, 1H), 5.25 (br s, 1H), 4.39 (br m, 1H), 3.23 (s, 3H), 3.19 (par obsc m, 1H), 2.82-2.55 (m, 4H), 1.61 (s, 3H), 1.45 (s, 9H), 1.26 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 179.6, 155.7, 139.4, 136.6, 136.1, 132.5, 129.4, 128.2, 126.0, 125.0, 87.0, 79.6, 58.6, 54.3, 44.0, 38.2, 36.7, 28.4, 16.2, 14.5, 12.7; IR (neat) 3428, 2978, 2934, 1717, 1496, 1246, 1169, 1083 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{25}\text{H}_{38}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 432.2750, found: 432.2776; $[\alpha]_{\text{D}}^{23} = -18.9$ ($c = 0.53$, CHCl_3).

(*E*)-(4*R*, 5*S*)-Methyl 4-azido-6-carboxyl-5-methyl-hex-2-enoic acid (**13**). To a stirred solution of alcohol **20** (500 mg, 2.51 mmol) in acetone (10 mL) at 0 °C was added Jones' reagent (1.9 M, *ca.* 4 mL) dropwise. The addition of the oxidant was continued until the starting material was consumed as determined by TLC analysis (*ca.* 20 min). The resulting yellow-brown reaction mixture was allowed to stir for an additional 2 h at 0 °C, before it was diluted with ¹PrOH (2 mL, to quench the excess of Jones' reagent) and warmed to rt for 10 min. The entire reaction mixture was then filtered through a short pad of Celite, with Et₂O (30 mL) used as eluant. The resulting filtrate was collected and concentrated *in vacuo*. The organic residue was dissolved in ether (150 mL), washed with saturated NaCl aqueous solution (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes as eluant) to afford the carboxylic acid **13** (473 mg, 88% yield) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 6.77 (dd, *J* = 7.7, 15.6 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 4.32 (t, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 2.67 (br m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.6, 165.8, 141.2, 125.2, 64.2, 52.0, 43.6, 13.5; IR (neat) 3200, 2955, 2104, 1727, 1248, 1174 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₈H₁₂N₃O₄ [M + H]⁺ 214.0828, found: 214.0819; [α]_D²³ = -24.33 (*c* 1.2, CHCl₃).

Dipeptide (26). To a solution of **14** (417 mg, 1.31 mmol) in CH₂Cl₂ (2.0 mL) was added TFA (2.0 mL). The reaction was stirred at rt for 30 min before it was diluted with toluene (5 mL) and concentrated *in vacuo* to afford the TFA salt of amine **14a**. The crude residue (**14a**) was dissolved in CH₂Cl₂ (3.0 mL) and treated with DIPEA (458 μL, 2.62 mmol). To this mixture was then added a solution of carboxylic acid **13** (280 mg, 1.31 mmol) and BOP reagent (593 mg, 1.35 mmol) in CH₂Cl₂ (1.0 mL) via cannula. The reaction mixture was stirred at rt for 14 h, loaded onto a short SiO₂ column, and purified by flash chromatograph (25% EtOAc/hexanes as eluant) to

afford dipeptide **26** (482 mg, 89% yield) as white crystalline moiety: ^1H NMR (400 MHz, CDCl_3) δ 6.75 (dd, $J = 7.9, 15.5$ Hz, 1H), 6.14 (br d, $J = 8.7$ Hz, 1H), 6.07 (d, $J = 15.5$ Hz, 1H), 4.53 (dd, $J = 4.7, 7.4$ Hz, 1H), 4.30 (t, $J = 8.3$ Hz, 1H), 4.22 (t, $J = 8.7$ Hz, 2H), 3.75 (s, 3H), 2.37 (m, 1H), 2.16 (m, 1H), 1.13 (d, $J = 7.1$ Hz, 3H), 1.00 (t, $J = 8.7$ Hz, 2H), 0.91 (d, $J = 6.7$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.6, 171.9, 165.8, 142.0, 124.9, 65.0, 63.9, 57.1, 52.0, 45.4, 31.4, 19.0, 17.8, 17.5, 15.0, -1.5; IR (neat) 3312, 2959, 2099, 1731, 1653, 1539, 1437, 1251, 1173, 861 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{18}\text{H}_{33}\text{N}_4\text{O}_8\text{Si}$ $[\text{M} + \text{H}]^+$ 413.2220, found: 413.2200; $[\alpha]_{\text{D}}^{23} = +25.0$ (c 1.0, CHCl_3).

(L)-Val- β -Me-Asp Dipeptide (10). To a vigorously stirred solution of olefin **26** (360 mg, 0.87 mmol) in CCl_4 / CH_3CN / H_2O solvent system (2:2:3, 7 mL) at rt was added NaIO_4 (784 mg, 3.65 mmol), followed with the addition of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (6.0 mg, 0.026 mmol) in one-portion. The resulting dark-brown reaction mixture was allowed to stir vigorously at rt for 2.5 h, before it was diluted with H_2O (10 mL) and CH_2Cl_2 (20 mL), and then acidified to pH 2 with 2% HCl aqueous solution. The organic layer was separated and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo* to afford the crude carboxylic acid (290 mg) as a yellow oil.

The crude carboxylic acid (290 mg) was dissolved in Et_2O (7 mL) and treated with diazomethane at 0 $^\circ\text{C}$ [the diazomethane was generated from a mixture of diazald (373 mg, 1.74 mmol) and KOH solid (2.2 g, 39.2 mmol) in 8.5 mL of 9:8 $\text{EtOH}/\text{H}_2\text{O}$ and was delivered to the acid, passed through a -78 $^\circ\text{C}$ dry ice/acetone trap, *via* a teflon tubing] over a period of 30 min. The reaction solution was concentrated *in vacuo* and purified by flash chromatography on silica gel (25% EtOAc /hexanes as eluant) to afford product **10** (263 mg, 78% yield) as clear colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 6.27 (br d, $J = 8.6$ Hz, 1H), 4.51 (dd, $J = 4.6, 8.9$ Hz, 1H), 4.20 (t, $J =$

8.7 Hz, 2H), 4.14 (d, $J = 7.6$ Hz, 1H), 3.79 (s, 3H), 2.84 (m, 1H), 2.16 (m, 1H), 1.24 (d, $J = 6.9$ Hz, 3H), 0.99 (t, $J = 8.7$ Hz, 2H), 0.91 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.8, 171.7, 169.6, 64.4, 63.8, 57.0, 52.8, 43.0, 31.4, 18.9, 17.6, 17.4, 14.9, -1.4; IR (neat) 3322, 2959, 2110, 1741, 1657, 1537, 1251, 1177, 861, 838 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{16}\text{H}_{31}\text{N}_4\text{O}_5\text{Si}$ $[\text{M} + \text{H}]^+$ 387.2073, found: 387.2085; $[\alpha]_{\text{D}}^{23} = +39.8$ (c 2.0, CHCl_3).

***N*-Boc(Me)-(D)-threonine-OBn (27).** To a solution of *N*-Boc-(D)-threonine-OBn **12** (972 mg, 3.14 mmol, Fluka) in THF (10 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 415 mg, 10.36 mmol) in one-portion. After stirring at 0 °C for 10 min, MeI (600 μL , 9.42 mmol) was added, followed by addition of DMF (500 μL). The reaction mixture was allowed to stir for 2h at 0 °C and additional 15h at rt. It was quenched with H_2O (10 mL), diluted with EtOAc (20 mL) and acidified to pH 2 by dropwise addition of 1N HCl aqueous solution. The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (2 x 30 mL). The organic extracts were combined and dried (MgSO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (30% EtOAc/hexanes as eluant) to afford pure *N*-methylated product **27** (862 mg, 85% yield) as a clear colorless oil: ^1H NMR (400 MHz, CDCl_3 , observed as a 2:1 mixture of rotamers) δ 7.31-7.22 (m, 5H), 4.85 (d, $J = 5.0$ Hz, 0.65H), 4.68 (d, $J = 5.0$ Hz, 0.35H), 4.51 (abq, $J = 11.5$ Hz, 2H), 4.30 (m, 0.65H), 4.21 (m, 0.35H), 3.0 (s, 1H), 2.99 (s, 2H), 1.46 (s, 6H), 1.42 (s, 3H), 1.23 (m, 3H); IR (neat) 2978, 1714, 1455, 1369, 1154, 1070 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 324.1811, found: 324.1827; $[\alpha]_{\text{D}}^{23} = -12.9$ (c 0.7, MeOH).

(2S, 3R)-N-Boc-N-methyl-O-benzyl-L-Threonine Benzyl Ester (28). ^1H NMR (400 MHz, CDCl_3 , observed as a 2:1 mixture of rotamers) δ 7.31-7.18 (m, 10H), 5.19-5.09 (m, 2H), 5.03 (d, $J = 4.9$ Hz, 0.67 H), 4.69 (d, $J = 5.5$ Hz, 0.33 H), 4.56 (d, $J = 11.6$ Hz, 0.33 H), 4.54 (d, $J = 11.6$ Hz, 0.67H), 4.34-4.22 (m, 2H), 3.01 (s, 1H), 3.00 (s, 2H), 1.46 (s, 6H), 1.40 (s, 3H), 1.23-1.20 (m, 3H); IR (neat) 2981, 1710, 1456, 1154 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{24}\text{H}_{32}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 414.2280, found: 414.2251.

N-Boc-(D)-glutamate α -methyl ester (30). A cooled (0 $^{\circ}\text{C}$) solution of *N*-Boc-(D)-glutamate-OBn **11** (1.25 gm, 3.7 mmol) in Et_2O (20 mL) was treated with diazomethane {the diazomethane was generated from a biphasic reaction mixture of diazald (1.59 mg, 3.64 mmol) and KOH (9.45 gm, 168 mmol) in 34 mL 9:8 $\text{EtOH}:\text{H}_2\text{O}$ and was delivered to the acid solution, passed through a -78 $^{\circ}\text{C}$ dry ice/acetone trap, *via* teflon tubing} over a period of 30 min. The reaction solution was concentrated *in vacuo* and flash chromatographed (10% EtOAc /hexanes as eluant) to afford the *N*-Boc-(D)-glutamate-(OBn) α -methyl ester (1.30 g, 100% yield) as clear colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.27 (m, 5H), 5.10 (s, 2H), 5.10 (ovrlp br s, 1H), 4.33 (m, 1H), 3.71 (s, 3H), 2.44 (m, 2H), 2.18 (m, 1H), 1.95 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.7, 172.5, 155.3, 135.7, 128.6, 128.3, 80.0, 66.5, 52.8, 52.4, 30.2, 28.3, 27.7; IR (neat) ν max: 3376, 2978, 1741, 1518, 1455, 1165 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_6$ [$\text{M} + \text{H}$] $^+$ 352.1760, found: 352.1749; $[\alpha]_{\text{D}}^{23} = -9.8$ (c 1.2, CHCl_3).

To a stirred solution of the above methylated product *N*-Boc-(D)-glutamate-(OBn) α -methyl ester (1.30 g, 3.70 mmol) in EtOAc (10 mL) was added Pd/C powder (activated, 260 mg, 10% w/w) in one-portion. The mixture was stirred under an atmosphere of H_2 (balloon pressure)

for 1.5 h before the reaction was filtered through a short plug of celite washing with 10 mL of EtOAc. The filtrate was collected and concentrated *in vacuo* to afford the debenzylated product **30** (966 mg, 100%) as a clear colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 5.13 (br d, $J = 7.6$ Hz, 1H), 4.33 (m, 1H), 3.72 (s, 3H), 2.43 (m, 2H), 2.16 (m, 1H), 1.92 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.9, 172.7, 155.5, 80.2, 52.6, 52.4, 30.0, 28.2, 27.5; IR (neat) 3350, 2980, 1715, 1521, 1439, 1394, 1369, 1168, 1054 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{11}\text{H}_{20}\text{NO}_6$ [$\text{M} + \text{H}$] $^+$ 262.1291, found: 262.1297; $[\alpha]_{\text{D}}^{23} = -3.4$ (c 5.3, CHCl_3).

(D)-Glu-NMe-(D)-Thr Dipeptide (9). To a solution of **28** (1.14 g, 2.8 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction was stirred at rt for 30 min before it was diluted with toluene (5 mL) and concentrated *in vacuo* to afford the TFA salt of amine **29**: ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.17 (m, 10H), 5.17 (s, 2H), 4.53 (d, $J = 11.6$ Hz, 1H), 4.31 (d, $J = 11.6$ Hz, 1H), 4.04 (m, 1H), 3.80 (d, $J = 4.9$ Hz, 1H), 2.78 (s, 3H), 1.33 (d, $J = 6.3$ Hz, 3H). This material was used immediately in the next reaction without further purification.

The crude **29** was dissolved in CH_2Cl_2 (10.0 mL) and treated with DIPEA (1.12 mL, 6.44 mmol). To this mixture was then added a solution of carboxylic acid **30** (953 mg, 3.64 mmol) and BOP reagent (1.3 g, 2.94 mmol) in CH_2Cl_2 (7.0 mL) via cannula. The reaction mixture was stirred at rt for 16 h, loaded onto a short SiO_2 column, and purified by flash chromatograph (35% EtOAc/hexanes as eluant) to afford (D)-Glu-NMe-(D)-Thr dipeptide **9** (1.28 g, 83% yield) as clear colorless, viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.15 (m, 10H), 5.51 (d, $J = 4.0$ Hz, 1H), 5.26 (br d, $J = 7.6$ Hz, 1H), 5.11 (ABq, $J = 12.2$ Hz, 1H), 4.53 (d, $J = 11.5$ Hz, 1H), 4.37-4.30 (m, 2H), 4.27 (d, $J = 11.5$ Hz, 1H), 3.72 (s, 3H), 3.12 (s, 3H), 2.84-2.40 (m, 2H), 2.21 (m, 1H), 1.92 (m,

1H), 1.41 (s, 9H), 1.16 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.6, 173.0, 169.8, 155.6, 138.4, 135.5, 128.6, 128.4, 128.3, 127.5, 127.2, 79.9, 75.5, 71.6, 66.9, 60.5, 53.1, 52.4, 34.3, 29.3, 28.3, 27.9, 16.0; IR (neat) 3351, 2977, 1745, 1714, 1644, 1171 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_8$ $[\text{M} + \text{H}]^+$ 557.2862, found: 557.2858; $[\alpha]_{\text{D}}^{23} = -21.2$ (c 0.95, CHCl_3).

Tetrapeptide (4). A suspension of Pd/C (100 mg, 10% w/w) in EtOAc (2 mL) was stirred vigorously under an atmosphere of hydrogen for 5 min at rt. To this mixture was added a solution of segment 9 (143 mg, 0.26 mmol) and 10 (70 mg, 0.18 mmol) in EtOAc (2 mL), followed by the addition of a catalytic amount of TFA (~15 μL). The resulting reaction mixture was stirred at room temperature for 15 h before being diluted with EtOAc (10 mL). The mixture was filtered through a short pad of Celite to eliminate the catalyst. The filtrate was concentrated *in vacuo* to afford a crude mixture of debenzylated hydroxy acid (derived from 9) and azido group reduced product (derived from 10).

The crude acid and amine were azeotroped with 2 mL of toluene. The resulting foam was then dissolved in DMF (1.5 mL) and to 0 $^{\circ}\text{C}$. To this was added collidine (71 μL , 0.54 mmol) followed by HATU (82 mg, 0.22 mmol). The resulting mixture was allowed to stir for 1 h at 0 $^{\circ}\text{C}$ and 15 h at rt. It was then diluted with EtOAc (10 mL), and washed with H_2O (10 mL) and 1N NaHCO_3 (10 mL). The aqueous phase was extracted with EtOAc (2 x 15 mL), and the combined organic layers were washed with saturated NaCl solution (20 mL), dried over MgSO_4 , filtrated, and concentrated *in vacuo*. ^1H NMR analysis of the crude sample revealed a 5:2 mixture of

diastereomers with the major isomer as the desired product. The crude product was purified by flash chromatography (100% EtOAc as eluant) to afford the tetrapeptide **4** (71 mg, 55% yield) as a clear colorless, viscous oil: ^1H NMR (400 MHz, CD_3OD) δ 8.25 (br d, $J = 8.6$ Hz, 1H), 7.05 (br d, $J = 7.9$ Hz, 1H), 4.95 (d, $J = 6.9$ Hz, 1H), 4.60 (d, $J = 5.9$ Hz, 1H), 4.34 (m, 1H), 4.31-4.19 (m, 4 H), 3.73 (s, 3H), 3.71 (s, 3H), 3.22 (m, 1H), 3.12 (s, 3H), 2.71 (dd, $J = 1.3, 10.5$ Hz, 1H), 2.63-2.52 (m, 2H), 2.18-2.12 (m, 2H), 1.94 (m, 1H), 1.44 (s, 9H), 1.23 (d, $J = 6.3$ Hz, 3H), 1.21 (d, $J = 7.3$ Hz, 3H), 1.03 (app t, $J = 8.6$ Hz, 1H), 0.94 (two ovrlp d, $J = 6.9$ Hz, 6H), 0.07 (s, 9H); ^1H NMR (400 MHz, CDCl_3) δ 7.22 (br d, $J = 8.6$ Hz, 1H), 6.26 (br d, $J = 8.3$ Hz, 1H), 5.61 (br d, $J = 8.9$ Hz, 1H), 5.13 (br d, $J = 4.6$ Hz, 1H), 4.73 (m, 1H), 4.49-4.37 (m, 3H), 4.19 (dd, $J = 7.5, 10.1$ Hz, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.48 (br s, 1H), 3.09 (br s, 3H), 3.00 (br m, 1H), 2.59-2.43 (m, 2H), 2.23 (m, 1H), 2.15 (m, 1H), 2.02 (m, 1H), 1.72 (br s, 1H), 1.40 (s, 9H), 1.20 (d, $J = 7.3$ Hz, 3H), 1.17 (d, $J = 6.3$ Hz, 3H), 0.99 (m, 2H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.6, 173.3, 173.1, 171.1, 170.8, 170.5, 155.6, 110.1, 80.8, 66.7, 65.8, 63.9, 60.1, 54.5, 52.6, 52.4, 41.4, 33.6, 31.3, 28.5, 28.4, 19.0, 17.7, 15.5, 15.1, -1.5; IR (neat) 3345, 2962, 1734, 1653, 1521, 1457, 1367, 1261, 1168, 1020, 801 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{32}\text{H}_{57}\text{N}_4\text{O}_{12}\text{Si}$ $[\text{M} + \text{H}]^+$ 719.3898, found: 719.3888; $[\alpha]_{\text{D}}^{23} = +9.3$ (c 0.28, CHCl_3).

Pentapeptide (31). To a solution of tetrapeptide **4** (28 mg, 0.38 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (1.0 mL). The reaction was stirred at rt for 30 min before being diluted with

toluene (2 mL) and concentrated *in vacuo*. The residue was taken up in CHCl_3 (20 mL) and washed with 2N Na_2CO_3 aqueous solution (10 mL). The aqueous phase was further extracted with CHCl_3 (2 x 10 mL), and the combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting crude tetrapeptide free amine was added *N*-Boc-(L)-valine-Adda **2** (12 mg, 0.027 mmol) as a solution in CH_2Cl_2 . The solution was concentrated *in vacuo* and then azeotroped from toluene (5 mL). To the resulting residue was added DMF (0.5 mL) and collidine (11 μL , 0.081 mmol). After cooling the solution in a 0 °C ice bath, HATU (12.5 mg, 0.032 mmol) was added. The resulting solution was allowed to stir for 1 h at 0 °C and 15 h at rt. It was then diluted with EtOAc (5 mL), and washed with H_2O (5 mL) and 1N NaHCO_3 (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic layers were washed with saturated NaCl solution (10 mL), dried over MgSO_4 , filtrated, and concentrated *in vacuo*. The crude product was flash chromatographed (40% THF/hexanes as eluant) to afford the pentapeptide **31** (16 mg, 70% yield) as a clear colorless, viscous oil: ^1H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 8.6 Hz, 2H), 8.12 (d, J = 8.6 Hz, 1H), 7.26-7.14 (m, 5H), 6.58 (br, 1H), 6.19 (d, J = 15.5 Hz, 1H), 5.51 (dd, J = 6.6, 15.5 Hz, 1H), 5.40 (d, J = 9.6 Hz, 1H), 4.94 (d, J = 6.9 Hz, 1H), 4.60 (m, 1H), 4.43 (m, 1H), 4.33 (m, 1H), 4.26 (par obsc m, 2H), 4.21 (app t, J = 8.6 Hz, 2H), 3.73 (par obsc m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.30 (m, 1H), 3.24-3.19 (par obsc m, 1H), 3.22 (s, 3H), 3.09 (s, 3H), 2.80 (dd, J = 4.6, 13.8 Hz, 1H), 2.65 (dd, J = 7.6, 13.8 Hz, 1H), 2.63-2.49 (m, 3H), 2.21-2.08 (m, 2H), 1.96 (m, 1H), 1.62 (s, 3H), 1.43 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.02 (par obsc t, J = 8.6 Hz, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.93 (two ovrlp d, J = 6.9 Hz, 6H), 0.05 (s, 9H); ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.15 (m, 5H), 7.10 (br, 1H), 6.36 (d, J = 8.9 HZ, 1H), 6.17 (d, J = 15.5 Hz, 1H), 5.81 (br s, 1H), 5.47 (m, 1H), 5.37 (d, J = 9.9 Hz, 1H), 5.05 (br s, 1H), 4.76 (dd, J = 4.9, 8.9 Hz, 1H), 4.60 (m, 1H), 4.43 (m, 2H), 4.23-4.14 (m, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.20 (s, 3H), 3.16-3.12 (m, 2H), 3.07 (s, 3H), 2.77 (dd, J = 3.6, 13.8 Hz, 1H), 2.64 (dd, J = 7.6, 13.8 Hz, 1H), 2.58-2.52 (m, 2H), 2.33 (br m, 1H), 2.12 (m, 2H), 1.65 (br, 2H), 1.58 (s, 3H), 1.41 (s, 9H), 1.17 (m, 9H), 0.98 (d, J = 6.3 Hz, 3H), 0.97 (obsc t, 2H), 0.90 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.03 (s, 9H); ^{13}C NMR (75 MHz,

CD₃OD) δ 177.4, 176.4, 175.8, 173.9, 173.3, 172.4, 172.1, 157.9, 140.8, 137.6, 137.1, 134.0, 136.6, 129.3, 127.2, 88.7, 80.8, 66.6, 64.6, 64.2, 59.3, 58.9, 57.9, 57.7, 57.2, 55.9, 53.6, 53.1, 52.9, 45.7, 41.9, 39.4, 38.0, 34.8, 32.0, 30.8, 29.2, 29.0, 28.2, 20.9, 19.7, 18.6, 16.6, 16.3, 15.6, 13.2, -1.4; IR (neat) 3343, 2968, 1740, 1653, 1521, 1457, 1218, 1175, 847, 755 cm⁻¹; LRMS (CI, NH₃) m/z calcd for C₅₂H₈₅N₅O₁₄Si [M + H]⁺ 1032.5, found: 1032.5; $[\alpha]_D^{23} = -4.9$ (c 0.45, MeOH).

Macrocycle (33). A stirred solution of TMSE-protected pentapeptide **31** (26 mg, 0.0252 mmol) in 1.0 mL of THF / DMF (5:1 v/v) at rt was treated with TBAF/SiO₂ (50 mg, 1.0-1.5 mmol/g, Aldrich Co.) in one-portion. The resulting reaction mixture was stirred at rt for 9 h. The reaction was diluted with 10% ⁱPrOH/CHCl₃ (10 mL), and filtered to remove SiO₂. The resulting filtrate was collected and carefully acidified with 1% HCl aqueous solution (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (75:25:2 EtOAc/Hexane/AcOH as eluant) to afford the pentapeptide free acid (15 mg, ~65% yield) as an off white residue. This carboxylic acid intermediate was contaminated with some derivatives or impurities (from the TBAF•SiO₂ reagent) which were difficult to separated.

To a solution of the above pentapeptide free acid (15 mg, 0.0161 mmol) in CH₂Cl₂ (1.0 mL) was added TFA (1.0 mL). The reaction was stirred at rt for 45 min before it was diluted with toluene (3 mL) and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (10.0 mL) and treated with DIPEA (39 μ L, 0.225 mmol), and allowed to stir for 5 min at rt. The resulting reaction solution was then added dropwise (over 4 h) to a vigorously stirred mixture of HATU (61 mg, 0.16

mmol) in CH_2Cl_2 (10.0 mL) at 0 °C. After stirring for 3 h at 0 °C and 16 h at rt, it was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 , loaded onto a short silica gel column and purified by flash chromatography (95:5 CHCl_3 :MeOH as eluant) to afford the desired macrocycle **33** (~1.9 mg, 9.6% yield based on pentapeptide **31**) as a white solid: ^1H NMR (400 MHz, CD_3OD , observed as a 7:3 mixture of rotamers) δ 7.26-7.14 (m, 5H), 6.24 (d, J = 15.5 Hz, 1H), 5.69 (dd, J = 8.3, 15.5 Hz, 0.3H), 5.66 (dd, J = 8.8, 15.5 Hz, 0.7H), 5.42 (d, J = 9.9 Hz, 0.7H), 5.06 (d, J = 5.8 Hz, 0.7H), 4.62 (dd, J = 4.6, 7.3 Hz, 0.3H), 4.49 (d, J = 5.0 Hz, 0.7H), 4.47-4.42 (m, 1.7H), 4.36 (m, 0.3H), 4.31-4.23 (m, 1.3H), 4.17 (d, J = 5.3 Hz, 0.3H), 4.13 (d, J = 5.6 Hz, 0.7H), 3.80 (s, 0.9H), 3.73 (s, 2.1H), 3.71 (s, 3H), 3.26-3.20 (par obsc m, 1H), 3.23 (s, 5.1H), 3.04 (par obsc m, 0.3H), 3.01 (s, 0.9H), 2.97 (m, 0.7H), 2.90-2.79 (m, 2H), 2.72-2.56 (m, 2H), 2.40-2.22 (m, 2H), 2.15-2.01 (m, 2H), 1.60 (s, 3H), 1.27 (d, J = 6.0 Hz, 0.9H), 1.23 (d, J = 7.2 Hz, 2.1H), 1.21 (d, J = 7.0 Hz, 2.1H), 1.09 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.95-0.85 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.5, 177.1, 176.6, 176.4, 175.7, 174.2, 174.0, 173.8, 172.3, 171.7, 171.6, 171.4, 140.7, 139.6, 139.3, 137.5, 137.3, 134.0, 133.9, 130.7, 129.4, 127.2, 125.7, 88.5, 67.3, 66.6, 66.2, 63.7, 59.7, 59.5, 58.9, 57.3, 57.0, 56.8, 56.3, 55.3, 53.5, 53.4, 52.9, 52.8, 46.3, 45.3, 41.2, 40.7, 39.1, 37.8, 34.2, 31.6, 30.6, 30.1, 29.6, 28.3, 26.9, 21.1, 20.8, 20.0, 19.9, 17.7, 17.0, 16.7, 16.1, 15.9, 13.1; IR (neat) 3369, 2924, 2851, 1739, 1653, 1522, 1456, 1373, 1241 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{42}\text{H}_{64}\text{N}_3\text{O}_{11}$ $[\text{M} + \text{H}]^+$ 814.4602, found: 814.4600; $[\alpha]_{\text{D}}^{23}$ = -24.2 (c 0.53, CHCl_3).

(E)-Vinyl Iodide (36). Alkyne **7** (40 mg, 0.2 mmol) and $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (103 mg, 0.4 mmol) was dissolved in THF (0.5 mL) and stirred at 50 °C under argon atmosphere. The mixture was stirred in the absence of light for 40 min, resulting in a orange-yellow homogeneous solution. The reaction was cooled to 0 °C and stirred for 2 min before a solution of I_2 (100 mg, 0.4 mmol) in THF (2.0 mL) was added via a cannula, and the reaction then turned to a dark-purple mixture

immediately. After this reaction mixture was stirred for 30 min at rt, it diluted with 5 mL of H₂O and 1.0 mL of saturated Na₂S₂O₃ aqueous solution. The resulting mixture was stirred at rt for 5 min before being extracted with 5% EtOAc/hexanes (3 x 10 mL). All organic extracts were combined and dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (5% EtOAc/Hexanes as eluant) to afford isomerically pure (E)-vinyl iodide **36** (66 mg, 93% yield) as a clear colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.17-7.30 (m, 5H), 6.10 (dd, *J* = 1.2, 10.1 Hz, 1H), 3.24 (s, 3H), 3.14-3.21 (m, 1H), 2.79 (dd, *J* = 4.9, 14.0 Hz, 1H), 2.68 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.42-2.48 (m, 1H), 2.23(d, *J* = 1.2 Hz, 3H), 1.00 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃) δ 143.8, 138.9, 129.4, 128.2, 126.1, 94.2, 86.0, 58.6, 39.1, 37.8, 27.8, 15.4; IR (neat) 3035, 2933, 1630, 1460, 1098 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₁₄H₁₉IO [M + H]⁺ 330.0440, found: 330.0448; [α]_D²³ = -46.4 (*c* 2.95, CHCl₃).

(E)-(4*R*, 5*S*)-Methyl 4-azido-6-(*tert*-butyldiphenylsilyloxy)-5-methyl-hex-2-enoate (20a). Alcohol **20** (2.03 g, 10.2 mmol) was dissolved in DMF (15 mL) and cooled to 0 °C, imidazole (1.39 g, 20.4 mmol) was added. The resulting reaction mixture was then stirred at 0 °C for 5 min before TBDPSCl (1.95 g, 12.9 mmol) was added. The reaction was warmed to rt over the period of 6.0 h and then diluted with Et₂O (50 mL) and then H₂O (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 60 mL). The combined extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was flash chromatographed on silica gel (10% EtOAc/hexanes as eluant) to afford pure **20a** (4.23 g, 95% yield) as a clear colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.36 (m, 10H), 6.82 (dd, *J* = 7.6, 15.6 Hz, 1H), 6.04 (d, *J* = 15.6 Hz, 1H), 4.27 (t, *J* = 7.6 Hz, 1H), 3.76 (s, 3H), 3.68 (dd, *J* = 4.9, 10.4 Hz, 1H), 3.51 (dd, *J* = 6.1, 10.4 Hz, 1H), 1.91 (m, 1H), 1.06 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.0, 142.9, 135.5, 133.2, 129.7, 127.7, 123.9, 64.9, 64.5, 51.8,

39.7, 26.8, 19.3, 12.9; IR (neat) 2932, 2858, 2096, 1730, 1428, 1274, 1112 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 438.2213, found: 438.2223; $[\alpha]_{\text{D}}^{23} = -9.1$ (c 1.0, CHCl_3).

Dipeptide (39). To a solution of azido ester **20a** (480 mg, 1.1 mmol) in 2 mL anhydrous methanol at 0 °C was added SnCl_2 (417 mg, 2.2 mmol) in one portion. The resulting reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to rt, stirring was continued for an additional 6 h. The methanol was removed *in vacuo* to yield a light yellow colored foam. This crude amine **37** was dissolved in dioxane (2 mL), followed by addition of a solution of *N*-Boc-(*L*)-Valine-OC₆F₅ **38** (890 mg, 2.2 mmol, dissolved in 1.0 mL of dioxane), and a saturated solution of NaHCO_3 (2 mL). The resulting biphasic reaction mixture was stirred at rt for 24 h. This reaction mixture was diluted with 10 mL of EtOAc and 10 mL of H_2O . The organic layers were separated, and the aqueous layer was extracted with an additional 20 mL of EtOAc. The organic extracts were combined and dried (MgSO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes as eluant) to afford dipeptide **39** (578 mg, 86% yield) as a colorless, viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.34 (m, 10H), 6.88 (dd, $J = 4.6, 15.8$ Hz, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 6.01 (d, $J = 15.8$ Hz, 1H), 5.05 (br d, $J = 7.9$ Hz, 1H), 4.74 (m, 1H), 3.82 (dd, $J = 6.6, 8.6$ Hz, 1H), 3.72 (par obsc m, 1H), 3.70 (s, 3H), 3.50 (dd, $J = 4.3, 10.6$ Hz, 1H), 2.02-1.83 (m, 2H), 1.42 (s, 9H), 1.07 (s, 9H), 1.04 (d, $J = 6.9$ Hz, 1H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.6, 166.5, 155.7, 146.9, 135.6, 132.6, 132.5, 130.0, 127.8, 121.2, 79.7, 65.8, 60.3, 53.8, 51.5, 37.8, 31.0, 28.2, 26.9,

19.5, 19.1, 17.8, 14.4; IR (neat) ν_{max} : 3322, 2964, 1726, 1516 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{34}\text{H}_{51}\text{N}_2\text{O}_6\text{Si}$ $[\text{M} + \text{H}]^+$ 611.3516, found: 611.3523; $[\alpha]_{\text{D}}^{23} = -10.7$ (c 1.0, CHCl_3).

Dipeptide (*E*)-Vinyl Iodide (41). A solution of **39** (500 mg, 0.82 mmol) and 5 mL of pyridine in anhydrous MeOH (30 mL) was stirred at $-78\text{ }^{\circ}\text{C}$. Ozone was bubbled through until the starting material was totally consumed (as determined by TLC analysis) and 5 mL Me_2S was added. After 1 h at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was warmed to rt, stirring was continued for an additional 6.0 h. The reaction mixture was directly concentrated *in vacuo*. The remaining organic residue was taken up in Et_2O (50 mL), and washed sequentially with H_2O (50 mL) and saturated aqueous NaHCO_3 (50 mL). The aqueous layers were combined and back-extracted with Et_2O (2 x 50 mL) and the combined organic extracts were washed with brine (1 x 50 mL), dried (Na_2SO_4), filtered and concentrated to afford crude aldehyde **40** (455 mg, 100% crude yield from olefin **39**). This aldehyde was used immediately in the following reaction without further purification: ^1H NMR (400 MHz, CDCl_3) δ 9.67 (s, 1H), 7.64-7.38 (m, 10H), 6.55 (d, $J = 8.0$ Hz, 1H), 5.0 (br, 1H), 4.64 (dd, $J = 3.2$ Hz, 1H), 3.98 (br s, 1H), 3.62 (dd, $J = 4.4, 10.7$ Hz, 1H), 3.38 (dd, $J = 8.3, 10.4$ Hz, 1H), 2.58 (m, 1H), 2.05 (m, 1H), 1.41 (s, 9H), 1.03 (s, 9H), 0.93-0.84 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.8, 160.3, 145.6, 127.7, 125.4, 123.1, 121.3, 79.5, 66.6, 62.9, 61.8, 41.5, 36.6, 34.1, 32.9, 26.5, 26.2, 24.8, 21.7; IR (neat) 3313, 2964, 1661, 1506 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_5\text{Si}$ $[\text{M} + \text{H}]^+$ 555.3254, found: 555.3253; $[\alpha]_{\text{D}}^{23} = -28.52$ (c 2.5, CHCl_3).

Flame-dried CrCl_2 (805 mg, 6.55 mmol) was suspended in 5 mL dry THF at rt. To this brown slurry, a solution of the crude aldehyde **40** (455 mg, 0.82 mmol) and CHI_3 (966 mg, 2.46 mmol) in dry THF (3 mL) was added via cannula. The resulting brown colored reaction mixture

was stirred at rt in the absence of light for 5.0 h. The reaction was diluted with H₂O (20 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel (15% EtOAc/hexanes as eluant) to provide pure dipeptide (*E*)-vinyl iodide **41** (973 mg, 74% yield from olefin **39**) as a clear colorless form: ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.37 (m, 10H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.43 (dd, *J* = 4.9, 14.5 Hz, 1H), 6.36 (d, *J* = 14.5 Hz, 1H), 5.03 (br d, *J* = 8.2 Hz, 1H), 4.55 (m, 1H), 3.75 (m, 2H), 3.49 (dd, *J* = 4.2, 10.3 Hz, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.43 (s, 9H), 1.08 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.91-0.86 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 155.8, 144.1, 135.6, 132.6, 129.9, 127.9, 79.8, 78.0, 65.7, 60.5, 57.0, 37.7, 30.9, 28.4, 27.0, 19.6, 19.2, 17.9, 14.2; IR (neat) 3306, 2962, 1654, 1520 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₃₂H₄₈IN₂O₄Si [M + H]⁺ 679.2428, found: 679.2436; [α]_D²³ = +14.5 (c 1.6, CHCl₃).

Dipeptide (E)-Vinyl Stannane (42). To a solution of vinyl iodide **41** (227 mg, 0.33 mmol) in 6 mL of benzene at rt was added DIPEA (17 μ L, 1.0 mmol) and hexamethylditin (200 μ L, 0.66 mmol) via syringe, followed by Pd(PPh₃)₄ (19 mg, 0.0165 mmol). The resulting yellow solution was heated to reflux (~ 80 °C), and the reaction gradually turned to black color. After 1 h at 80 °C, the reaction was directly concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (2:10:90 Et₃N/EtOAc/Hexanes as eluant) to afford pure vinyl stannane **42** (210 mg, 90% yield) as a clear colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.35 (m, 10 H), 6.52 (br d, *J* = 8.2 Hz, 1H), 6.19 (d, *J* = 19.3 Hz, 1H), 5.86 (dd, *J* = 4.3, 19.3 Hz, 1H), 5.13 (br d, *J* = 8.6 Hz, 1H), 4.59 (m, 1H), 3.88 (t, *J* = 7.3 Hz, 1H), 3.75 (dd, *J* = 3.8, 10.2 Hz, 1H), 3.49 (dd, *J* = 4.3, 10.2 Hz, 1H), 1.98 (m, 1H), 1.87 (m, 1H), 1.41 (s, 9H), 1.07 (s, 9H), 1.02 (d, *J* = 6.9 HZ, 3H), 0.88 (d, *J* = 6.9 HZ, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.08 (d, 9H); ¹³C NMR (75 MHz,

CDCl_3) δ 171.2, 155.8, 145.5, 135.5, 129.8, 128.9, 127.8, 79.3, 65.8, 60.0, 56.8, 46.2, 38.0, 31.6, 28.3, 27.0, 19.5, 19.2, 17.5, 14.4, 11.5, -9.5; IR (neat) 3323, 2964, 1659, 1521 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{35}\text{H}_{57}\text{N}_2\text{O}_4\text{SiSn}$ $[\text{M} + \text{H}]^+$ 717.3109, found: 717.3071; $[\alpha]_D^{23} = +6.0$ (c 0.5, CHCl_3).

(*E, E*)-Diene product (43). A solution of alkyne **5** (71 mg, 0.35 mmol) and Cp_2ZrHCl (181 mg, 0.7 mmol) in THF (1.0 mL) was stirred at 50 °C under argon atmosphere for 1 h. The resulting deep-brown homogeneous reaction solution was brought to rt and stirred for 2 min, while the reaction turned to an orange-yellow solution. Anhydrous ZnCl_2 (96 mg, 0.7 mmol) dissolved in THF (1.0 mL) was added via cannula, and the reaction then turned to a dark mixture immediately. This reaction mixture was stirred for 2 min at rt before a solution of dipeptide (*E*)-vinyl iodide **41** (120 mg, 0.176 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (20 mg, 0.017 mmol) in THF (1.0 mL) was added via cannula.² The resulting brown homogeneous reaction solution was allowed to stir at rt for 20 min before being diluted with H_2O (10 mL) and stirred for 5 min, and then extracted with EtOAc (3 x 30 mL). The organic extracts were combined and dried (MgSO_4), filtered, and concentrated *in vacuo*. The crude product was flash chromatographed on silica gel (15% EtOAc/hexanes as eluant) to afford coupling product **43** (108 mg, 81% yield, based on vinyl iodide **41**) as a colorless foam: ^1H NMR (400 MHz, CDCl_3) δ 7.65-7.15 (m, 15H), 6.54 (br d, $J = 8.5$ Hz, 1H), 6.21 (d, $J = 15.5$ Hz, 1H), 5.45 (dd, $J = 5.6, 15.5$ Hz, 1H), 5.38 (d, $J = 9.9$ Hz, 1H), 5.17 (m, 1H), 4.64 (m, 1H), 3.91 (t, $J = 6.8$ Hz, 1H), 3.76 (dd, $J = 4.0, 10.3$ Hz, 1H), 3.50 (dd, $J = 3.8, 10.3$ Hz, 1H), 3.21 (s, 3H), 3.17 (m, 1H), 2.80 (dd, $J = 4.3, 13.8$ Hz, 1H), 2.65 (dd, $J = 7.6, 13.8$ Hz, 1H), 2.58 (m, 1H), 2.01 (m, 1H), 1.86 (m, 1H), 1.58 (s, 3H), 1.42 (s, 9H), 1.07 (s, 9H), 1.03 (two overl d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 155.8,

139.3, 135.8, 135.5, 132.8, 132.7, 132.5, 129.8, 129.7, 129.4, 128.2, 127.8, 125.9, 125.5, 86.9, 79.3, 66.0, 59.8, 58.6, 54.3, 38.7, 38.2, 36.8, 31.9, 28.3, 26.9, 19.6, 19.1, 17.3, 16.4, 14.4, 12.8; IR (neat) 3322, 2962, 2932, 1660, 1496, 1112 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{46}\text{H}_{67}\text{N}_2\text{O}_5\text{Si}$ $[\text{M} + \text{H}]^+$ 755.4819, found: 755.4826; $[\alpha]_{\text{D}}^{23} = -20.9$ (c 0.75, CHCl_3).

Primary Alcohol (44). A stirred solution of silyl ether **43** (155 mg, 0.204 mmol) in THF (2.0 mL) at rt was treated with TBAF/ SiO_2 (511 mg, 1.0-1.5 mmol/g, Aldrich Co.) in one-portion. The resulting reaction mixture was stirred at rt for 4 h before it was diluted with 10% $^i\text{PrOH}/\text{CHCl}_3$ (15 mL), and filtered to remove SiO_2 . The resulting filtrate was collected and acidified with 1% HCl aqueous solution (10 mL). The layers were separated and the aqueous layer was extracted with 10% $^i\text{PrOH}/\text{CHCl}_3$ (2 x 15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50% EtOAc/hexane as eluant) to afford pure alcohol **44** (101 mg, 95% yield) as a pale yellow foam: ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.15 (m, 5H), 6.48 (br d, $J = 6.6$ Hz, 1H), 6.18 (d, $J = 15.7$ Hz, 1H), 5.43 (dd, $J = 7.3, 15.7$ Hz, 1H), 5.35 (d, $J = 9.6$ Hz, 1H), 5.02 (br s, 1H), 4.39 (m, 1H), 3.88 (dd, $J = 6.1, 8.4$ Hz, 1H), 3.71 (dd, $J = 3.0, 11.2$ Hz, 1H), 3.46 (dd, $J = 3.0, 11.2$ Hz, 1H), 3.21 (s, 3H), 3.16 (m, 1H), 3.16 (m, 1H), 2.77 (dd, $J = 4.6, 13.8$ Hz, 1H), 2.65 (dd, $J = 7.4, 13.8$ Hz, 1H), 2.58 (m, 1H), 2.14 (br m, 1H), 1.63 (par obsr m, 1H), 1.59 (s, 3H), 1.41 (s, 9H), 1.01-0.96 (m, 9H), 0.90 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.6, 155.9, 139.3, 137.4, 136.1, 132.4, 129.4, 128.1, 125.9, 125.1, 86.8, 80.0, 64.2, 60.2, 58.6, 54.2, 39.8, 38.2, 36.7, 30.5, 28.3, 19.5, 17.6, 16.2, 14.6, 12.7; IR (neat) 3314, 2966, 1650, 1526 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{30}\text{H}_{49}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 517.3641, found: 517.3629; $[\alpha]_{\text{D}}^{23} = -24.33$ (c 1.2, CHCl_3).

***N*-Boc-(*L*)-Valine Adda (34).** To a solution of alcohol **44** (18.0 mg, 0.035 mmol) and NMO (8 mg, 0.07 mmol) in anhydrous CH₃CN (0.5 mL), was added TPAP (1.2 mg, 0.0035 mmol) in one-portion. The resulting dark reaction mixture was allowed to stir at rt for 1h, before being treated with an additional portion of TPAP (1.0 mg) and NMO (8.0 mg). After which distilled H₂O (~5 μ L) was immediately added. The resulting reaction mixture was allowed to stir at rt for an additional 18 h before it was concentrated *in vacuo*. The remaining organic residue was taken up with CH₂Cl₂ (0.5 mL) and loaded on to a short silica gel column, and chromatographed (40:60:1 EtOAc/hexanes/AcOH as eluant) to afford acid **34** (16.2 mg, 87% yield) as a colorless, viscous oil: ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, *J* = 9.2 Hz, 1H), 7.26-7.15 (m, 5H), 6.21 (d, *J* = 15.5 Hz, 1H), 5.49 (dd, *J* = 6.9, 15.5 Hz, 1H), 5.35 (m, 2H), 4.66 (br s, 1H), 4.23 (m, 1H), 3.20 (s, 3H), 3.15 (m, 1H), 2.76 (dd, *J* = 4.5, 13.9 Hz, 1H), 2.64 (dd, *J* = 7.4, 13.9 Hz, 1H), 2.55 (m, 1H), 1.56 (s, 3H), 1.40 (s, 9H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.24 (par obsc m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.93-0.89 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 178.1, 171.5, 156.4, 139.3, 136.8, 136.1, 132.5, 129.4, 125.9, 124.9, 86.9, 80.4, 59.6, 58.6, 53.3, 43.3, 38.2, 36.6, 31.5, 28.3, 19.2, 18.0, 16.2, 15.7, 12.7; IR (neat) 3312, 2976, 1711, 1658, 1522, 1094 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₃₀H₄₇N₂O₆ [M + H]⁺ 531.3434, found: 531.3448; [α]_D²³ = -24.33 (*c* 1.2, CHCl₃).

(*E*)-(4*R*, 5*S*)-Methyl 4-azido-6-(trichloroethyl ester)-5-methyl-hex-2-enoate (53).

To a stirred solution of alcohol **20** (500 mg, 2.51 mmol) in acetone (10 mL) at 0 °C was added Jones' reagent (1.9 M, *ca.* 4 mL) dropwise. The addition of the oxidant was continued until the starting material was consumed as determined by TLC analysis (*ca.* 20 min). The resulting yellow-

brown reaction mixture was allowed to stir for an additional 2 h at 0 °C, before it was diluted with ⁱPrOH (2 mL, to quench the excess of Jones reagent) and warmed to rt for 10 min. The entire reaction mixture was then filtered through a short pad of celite, with Et₂O (30 mL) used as eluant. The resulting filtrate was collected and concentrated *in vacuo*. The organic residue was dissolved in ether (150 mL), washed with saturated NaCl aqueous solution (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was redissolved in 10 mL of toluene and concentrated *in vacuo* to afford crude acid as pale yellow oil (540 mg, 101% crude yield from alcohol **20**). This crude acid was used immediately in the following reaction without further purification: ¹H NMR (400 MHz, CDCl₃) δ 6.77 (dd, *J* = 7.7, 15.6 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 4.32 (t, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 2.67 (br m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.6, 165.8, 141.2, 125.2, 64.2, 52.0, 43.6, 13.5; IR (neat) 3200, 2955, 2104, 1727, 1248, 1174 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₈H₁₂N₃O₄ [M + H]⁺ 214.0828, found: 214.0819; [α]_D²³ = -24.33 (*c* 1.2, CHCl₃).

To a solution of the crude carboxylic acid (540 mg) and 2-trichloro ethanol (750 mg, 5.0 mmol) in CH₂Cl₂ (6.0 mL) at 0 °C was added DCC (543 mg, 2.64 mmol), followed with DMAP (16 mg, 0.13 mmol). The resulting reaction mixture was stirred at 0 °C for 1 h, and then warmed to rt and stirred for an additional 12 h. It was then filtered through a short pad of SiO₂, and eluted with CH₂Cl₂ (30 mL). The filtrate was collected and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% EtOAc/hexanes as eluant) to afford product **45** (715 mg, 82% yield, from alcohol **20**) as a clear colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 6.77 (dd, *J* = 7.9, 15.5 Hz, 1H), 6.11 (d, *J* = 15.6 Hz, 1H), 4.77 (abq, *J* = 11.8 Hz, 2H), 4.35 (t, *J* = 8.1 Hz, 1H), 3.75 (s, 3H), 2.75 (m, 1H), 1.20 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.4, 165.6, 140.9, 125.5, 94.6, 74.1, 64.3, 52.0, 43.8, 13.7; IR (neat) 2954, 2103, 1756, 1729, 1277, 1242, 1155 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₁₀H₁₃Cl₃N₃O₄ [M + H]⁺ 343.9972, found: 343.9961; [α]_D²³ = +21.1 (*c* 1.1, CHCl₃).

(2R, 3S)-Methyl 2-azido-3-(trichloroethyl ester)-3-methyl-but-2-anoate (46). To a vigorously stirred solution of olefin **45** (570 mg, 1.65 mmol) in $\text{CCl}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ solvent system (2:2:3, 14 mL) at rt was added NaIO_4 (1.49 g, 6.97 mmol), followed with the addition of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (9.0 mg, 0.04 mmol) in one-portion. The resulting dark-brown reaction mixture was allowed to stir vigorously at rt for 2.5 h, before it was diluted with H_2O (10 mL) and CH_2Cl_2 (20 mL), and then acidified to pH 2 with 2% HCl aqueous solution. The organic layer was separated and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo* to afford the crude carboxylic acid (506 mg) as a yellow oil. This material was used immediately in the following reaction without further purification: ^1H NMR (400 MHz, CDCl_3) δ 4.77 (abq, $J = 11.8$ Hz, 2H), 4.27 (d, $J = 5.6$ Hz, 1H), 3.24 (m, 1H), 1.39 (d, $J = 7.3$ Hz, 3H).

The crude carboxylic acid (506 mg) was dissolved in Et_2O (10 mL) and treated with diazomethane at 0 °C [the diazomethane was generated from a mixture of diazald (780 mg, 3.64 mmol) and KOH (4.64 g, 82.7 mmol) in 17 mL of 9:8 $\text{EtOH}/\text{H}_2\text{O}$ and was delivered to the acid, passed through a -78 °C dry ice/acetone trap, *via* a teflon tubing] over a period of 30 min. The reaction solution was concentrated *in vacuo* and flash chromatographed on silica gel (10% $\text{EtOAc}/\text{hexanes}$ as eluant) to afford product **46** (468 mg, 89% yield) as clear colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 4.74 (abq, $J = 11.9$ Hz, 2H), 4.20 (d, $J = 6.3$ Hz, 1H), 3.80 (s, 3H), 3.17 (m, 1H), 1.30 (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.5, 168.8, 94.5, 74.3, 63.7, 52.9, 41.4, 13.5; IR (neat) 2957, 2117, 1753, 1437, 1214 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_8\text{H}_{11}\text{Cl}_3\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 317.9815xx, found: 317.9808; $[\alpha]_{\text{D}}^{23} = +60.4$ (c 1.85, CHCl_3)

***N*-Boc-*N*-methyl-(*D*)-threonine-β-methyl aspartate α-methyl ester γ-trichloroethyl ester dipeptide (48).** To a stirred solution of azido ester **46** (1.05 g, 3.3 mmol) in anhydrous MeOH (20 mL) at 0 °C was added SnCl₂ (940 mg, 4.96 mmol). The resulting reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to rt for an additional 10 h, before it was concentrated *in vacuo*. The remaining foam like residue was taken up with CH₂Cl₂ (50 mL), and washed with saturated Na₂CO₃ aqueous solution (1 x 30 mL). The aqueous layer was back-extracted with CH₂Cl₂ (2 x 20 mL). The organic extracts were combined and dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the free amine **46a** (950 mg) as lemon-yellow oil. This crude amine was used immediately in the following reaction without further purification.

A suspension of Pd/C (250 mg, 10% w/w) in EtOH (10 mL) was stirred vigorously under an atmosphere of hydrogen for 5 min at rt. To this mixture was added a solution of *N*-Boc(Me)-(*D*)-threonine-OBn **27** (1.18 g, 3.65 mmol) in EtOH (10 mL), followed by the addition of a catalytic amount of TFA (~15 μL). The resulting reaction mixture was stirred at room temperature for 15 h before being diluted with EtOAc (10 mL). The mixture was filtered through a short pad of celite to eliminate the catalyst. The filtrate was concentrated *in vacuo* to afford the crude debenzylated product [*N*-Boc(Me)-(*D*)-threonine **47**, 846 mg] as a clear oil. This crude acid was used immediately in the following reaction without further purification: ¹H NMR (400 MHz, CDCl₃) δ 4.94 (br s, 1H), 4.44 (br m, 1H), 4.36 (br m, 1H), 2.96 (s, 3H), 1.46 (s, 9H), 1.25 (d, *J* = 6.4 Hz, 3H); HRMS (CI, NH₃) *m/z* calcd for C₁₀H₂₀NO₅ [M + H]⁺ 234.1341, found: 234.1328.

The crude amine **46a** (940 mg, 3.22 mmol), *N*-Boc(Me)-(*D*)-threonine **47** (846 mg, 3.63 mmol), and HOAT (540 mg, 4.0 mmol) were dissolved in THF (10 mL). To this was added EDCI (764 mg, 4.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h before it was warmed

to RT and stirred for an additional 12 h. This mixture was diluted with EtOAc (50 mL), and subsequently washed with 1N HCl (20 mL), 1N NaHCO₃ (20 mL), and brine solution (20 mL). The organic phase was dried with MgSO₄, filtrated, and concentrated *in vacuo* and flash chromatographed (40% EtOAc/hexanes as eluent) to afford the pure dipeptide **48** (1.48 g, 89% yield from **46**) as a pale yellow, viscous oil: ¹H NMR (400 MHz, CDCl₃) δ 7.04 (br d, *J* = 7.9 Hz, 1H), 4.94 (dd, *J* = 3.6, 9.6 Hz, 1H), 4.71 (abq, *J* = 12.0 Hz, 2H), 4.55 (d, *J* = 4.9 Hz, 1H), 3.72 (s, 3H), 4.46 (m, 1H), 2.92 (s, 3H), 1.46 (s, 9H), 1.28 (d, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.2, 171.4, 170.3, 157.1, 94.4, 80.9, 74.1, 66.7, 63.1, 53.0, 52.9, 40.8, 33.3, 28.3, 18.9, 13.8; IR (neat) $\bar{\nu}$ max: 3427, 2978, 1752, 1684, 1514, 1391, 1155 cm⁻¹; HRMS (CI, NH₃) *m/z* calcd for C₁₈H₃₀Cl₃N₂O₈ [M + H]⁺ 507.1068, found: 506.1070; [α]_D²³ = -24.0 (*c* 0.95, CHCl₃).

Tripeptide (35). To a solution of Boc protected dipeptide **48** (565 mg, 1.12 mmol) in CH₂Cl₂ (3.0 mL) was added TFA (3.0 mL). The reaction was stirred at rt for 30 min before it was diluted with toluene (5 mL) and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (3.0 mL) and treated with DIPEA (624 μL, 3.58 mmol). To this mixture was then added a solution of *N*-Boc-(D)-glutamate α-methyl ester **11** (321mg, 1.23 mmol) and BOP reagent (545 mg, 1.23 mmol) in CH₂Cl₂ (2.0 mL) via cannula. The reaction mixture was stirred at rt for 44 h, loaded onto a short SiO₂ column, and flash chromatographed (50% EtOAc/hexanes as eluant) to afford tripeptide **35** (601 mg, 83% yield) as a pale yellow, viscous oil: ¹H NMR (400 MHz, CDCl₃) δ 7.00 (br d, *J* = 9.1 Hz, 1H), 5.28 (br d, *J* = 8.1 Hz, 1H), 4.97 (d, *J* = 6.4 Hz, 1H), 4.91 (dd, *J* = 3.9,

9.4 Hz, 1H), 4.73 (abq, $J = 12.0$ Hz, 2H), 4.36 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.50 (br s, 1H), 3.42 (m, 1H), 3.08 (s, 3H), 2.52 (m, 1H), 2.40-2.32 (m, 2H), 1.84 (m, 1H), 1.41 (s, 9H), 1.25 (d, $J = 7.0$ Hz, 3H), 1.22 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.7, 173.1, 172.0, 170.5, 170.2, 155.6, 94.5, 80.2, 74.1, 65.6, 61.8, 53.1, 52.9, 52.6, 52.3, 41.1, 32.8, 28.8, 28.5, 28.3, 19.3, 13.8; IR (neat) 3355, 2978, 1746, 1519, 1367, 1166 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{24}\text{H}_{39}\text{Cl}_3\text{N}_3\text{O}_{11}$ $[\text{M} + \text{H}]^+$ 650.1650, found: 650.1655; $[\alpha]_{\text{D}}^{23} = +19.5$ (c 1.25, CHCl_3).

Pentapeptide (51). To a solution of tripeptide **35** (130 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (1.0 mL). The reaction was stirred at rt for 30 min before being diluted with toluene (2 mL) and concentrated *in vacuo*. The residue was taken up in CHCl_3 (20 mL) and washed with 2N Na_2CO_3 aqueous solution (10 mL). The aqueous phase was further extracted with CHCl_3 (2 x 10 mL), and the combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting crude tripeptide amine **50** was added *N*-Boc-(L)-valine-Adda **34** (82 mg, 1.54 mmol) as a solution in CH_2Cl_2 . The solution was concentrated *in vacuo* and then azeotroped from toluene (5 mL). To the resulting residue was added DMF (1.5 mL) and collidine (61 μL , 0.46 mmol). After cooling the solution in a 0 $^\circ\text{C}$ ice bath, HATU (70 mg, 0.18 mmol) was added. The resulting solution was allowed to stir for 1 h at 0 $^\circ\text{C}$ and 15 h at rt. It was then diluted with EtOAc (30 mL), and washed with H_2O (10 mL) and 1N NaHCO_3 (10 mL). The aqueous phase was extracted with EtOAc (2 x 20 mL), and the combined organic layers were washed with saturated NaCl solution (20 mL), dried over MgSO_4 , filtrated, and concentrated *in vacuo*. The

crude product was flash chromatographed (40% THF/hexanes as eluant) to afford the pentapeptide **51** (153 mg, 93.4% yield) as a clear colorless, viscous oil: ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, $J = 8.6$ Hz, 1H), 7.25-7.13 (m, 5H), 7.05 (d, $J = 9.6$ Hz, 1H), 6.51 (d, $J = 7.3$ Hz, 1H), 6.18 (d, $J = 15.8$ Hz, 1H), 5.48 (d, $J = 11.2$ Hz, 1H), 5.44 (par obsc dd, $J = 4.9, 15.8$ Hz, 1H), 5.32 (1H, $J = 9.6$ Hz, 1H), 4.94-4.88 (m, 2H), 4.71 (abq, $J = 11.9$ Hz, 2H), 4.70-4.60 (par obsc m, 2H), 4.36 (br, 1H), 4.01 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.60 (br s, 1H), 3.39 (m, 1H), 3.20 (s, 3H), 3.12 (m, 1H), 2.93 (s, 3H), 2.75 (dd, $J = 4.4, 13.9$ Hz, 1H), 2.64-2.50 (m, 3H), 2.40-2.07 (m, 3H), 1.63 (br m, 1H), 1.56 (s, 3H), 1.41 (s, 9H), 1.30 (d, $J = 6.3$ Hz, 3H), 1.21 (d, $J = 7.3$ Hz, 3H), 1.17 (d, $J = 6.9$ Hz, 3H), 0.96 (m, 6H), 0.90 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.3, 173.4, 172.9, 172.0, 171.9, 170.2, 170.0, 155.9, 139.2, 136.4, 135.8, 132.0, 129.4, 128.2, 126.0, 125.4, 94.5, 86.7, 79.4, 74.1, 68.0, 64.9, 62.1, 60.2, 58.6, 53.3, 53.1, 52.8, 52.7, 51.0, 44.0, 41.2, 38.1, 36.6, 32.0, 30.9, 28.5, 28.4, 25.6, 20.3, 19.6, 17.6, 16.3, 15.7, 13.7, 12.8; IR (neat) 3312, 2975, 1746, 1657, 1515 cm^{-1} ; LRMS (CI, NH_3) m/z calcd for $\text{C}_{49}\text{H}_{75}\text{Cl}_3\text{N}_5\text{O}_{14}$ $[\text{M} + \text{H}]^+$ 1062.4, found: 1062.4; $[\alpha]_{\text{D}}^{23} = +12.8$ (c 1.2, CHCl_3).

Pentapeptide free acid (52). To a solution of trichloroethyl ester-protected pentapeptide **51** (68 mg, 0.064 mmol) in AcOH (3.0 mL) at rt was added Zn dust (840 mg, 16.8 mmol) in one-portion. The resulting reaction mixture was vigorously stirred at rt for 4h before it was diluted with CH_2Cl_2 (20 mL), filtered through celite, diluted further with toluene (3 mL), and concentrated *in vacuo*. The residue was flash chromatographed ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$ 96:4:1) to afford the desired carboxylic acid **52** (56.5 mg, 95% yield) as a clear colorless glass: ^1H NMR (400 MHz, CD_3OD) δ 7.25-7.16 (m, 5H), 6.24 (d, $J = 15.6$ Hz, 1H), 5.54 (dd, $J = 5.9, 15.6$ Hz, 1H), 5.40 (d, J

= 9.9 Hz, 1H), 4.93 (d, $J = 7.6$ Hz, 1H), 4.70 (d, $J = 4.3$ Hz, 1H), 4.56 (m, 1H), 4.39 (m, 1H), 4.29 (m, 1H), 3.86 (m, 1H), 3.70 (two overl s, 6H), 3.20 (s, 3H), 3.20-3.07 (par obsc m, 2H), 3.07 (s, 3H), 2.78 (dd, $J = 4.6, 13.8$ Hz, 1H), 2.69 (par obsc m, 1H), 2.63 (dd, $J = 7.6, 14.0$ Hz), 2.58 (par obsc m, 1H), 2.47 (m, 1H), 2.08-2.18 (m, 2H), 1.95 (m, 1H), 1.60 (s, 1H), 1.43 (s, 9H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.16 (two overl d, $J = 7.3$ Hz, 6H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.3, 175.6, 174.3, 173.8, 172.4, 172.0, 158.2, 140.7, 137.4, 137.2, 134.0, 130.7, 129.4, 127.2, 126.2, 88.5, 80.7, 66.2, 63.6, 62.4, 59.0, 55.1, 55.0, 53.2, 53.0, 44.8, 42.3, 39.1, 37.8, 33.2, 31.6, 30.8, 28.9, 28.0, 20.9, 20.1, 18.6, 16.7, 15.9, 15.6, 14.5, 13.2; IR (neat) 3315, 2975, 1743, 1656, 1521, 1454 cm^{-1} ; LRMS (FAB, NBA/NaI) m/z calcd for $\text{C}_{47}\text{H}_{73}\text{N}_5\text{O}_{14}\text{Na}$ $[\text{M} + \text{Na}]^+$ 954, found: 954; $[\alpha]_{\text{D}}^{23} = +8.9$ (c 0.7, EtOH).

Dimethyl motuporin hydrate (33). To a solution of pentapeptide free acid **52** (7.8 mg, 0.84×10^{-3} mmol) in CH_2Cl_2 (2.0 mL) was added TFA (1.0 mL). The reaction was stirred at rt for 45 min before it was diluted with toluene (3 mL) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (8.0 mL) and treated with *N*-ethyl morpholine (15 μL , 0.117 mmol), and allowed to stir for 5 min at rt. The resulting reaction solution was then added dropwise (over 20 min) to a vigorously stirred mixture of HATU (32 mg, 0.084 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C. After stirring for 3 h at 0 °C and 21 h at rt, it was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 , loaded onto a short silica gel column and chromatographed (95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant) to afford the desired macrocycle **33** (5.4 mg, 79.3% yield) as a white crystalline residue: ^1H NMR (400 MHz, CD_3OD , observed as a 7:3 mixture of rotamers) δ 7.26-7.14 (m, 5H), 6.24 (d, $J =$

15.5 Hz, 1H), 5.69 (dd, $J = 8.3, 15.5$ Hz, 0.3H), 5.66 (dd, $J = 8.8, 15.5$ Hz, 0.7H), 5.42 (d, $J = 9.9$ Hz, 0.7H), 5.06 (d, $J = 5.8$ Hz, 0.7H), 4.62 (dd, $J = 4.6, 7.3$ Hz, 0.3H), 4.49 (d, $J = 5.0$ Hz, 0.7H), 4.47-4.42 (m, 1.7H), 4.36 (m, 0.3H), 4.31-4.23 (m, 1.3H), 4.17 (d, $J = 5.3$ Hz, 0.3H), 4.13 (d, $J = 5.6$ Hz, 0.7H), 3.80 (s, 0.9H), 3.73 (s, 2.1H), 3.71 (s, 3H), 3.26-3.20 (par obsc m, 1H), 3.23 (s, 5.1H), 3.04 (par obsc m, 0.3H), 3.01 (s, 0.9H), 2.97 (m, 0.7H), 2.90-2.79 (m, 2H), 2.72-2.56 (m, 2H), 2.40-2.22 (m, 2H), 2.15-2.01 (m, 2H), 1.60 (s, 3H), 1.27 (d, $J = 6.0$ Hz, 0.9H), 1.23 (d, $J = 7.2$ Hz, 2.1H), 1.21 (d, $J = 7.0$ Hz, 2.1H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.95-0.85 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.5, 177.1, 176.6, 176.4, 175.7, 174.2, 174.0, 173.8, 172.3, 171.7, 171.6, 171.4, 140.7, 139.6, 139.3, 137.5, 137.3, 134.0, 133.9, 130.7, 129.4, 127.2, 125.7, 88.5, 67.3, 66.6, 66.2, 63.7, 59.7, 59.5, 58.9, 57.3, 57.0, 56.8, 56.3, 55.3, 53.5, 53.4, 52.9, 52.8, 46.3, 45.3, 41.2, 40.7, 39.1, 37.8, 34.2, 31.6, 30.6, 30.1, 29.6, 28.3, 26.9, 21.1, 20.8, 20.0, 19.9, 17.7, 17.0, 16.7, 16.1, 15.9, 13.1; IR (neat) 3369, 2924, 2851, 1739, 1653, 1522, 1456, 1373, 1241 cm^{-1} ; HRMS (CI, NH_3) m/z calcd for $\text{C}_{42}\text{H}_{64}\text{N}_5\text{O}_{11}$ $[\text{M} + \text{H}]^+$ 814.4602, found: 814.4600; $[\alpha]_{\text{D}}^{23} = -24.2$ (c 0.53, CHCl_3).

(-)-Motuporin (1). To a suspension of macrocycle **33** (28.0 mg, 34.4×10^{-3} mmol) in 3.0 mL 9:1 $\text{H}_2\text{O}:\text{MeOH}$ was added dropwise saturated $\text{Ba}(\text{OH})_2$ aqueous solution (600 μL). The mixture was stirred at rt for 24 h. It was diluted with EtOAc (5 mL), and then acidified to pH 2 with 1N HCl aqueous solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). All the organic extracts were combined and concentrated *in vacuo*. The crude diacid was purified by preparative rpHPLC [69:31 MeOH:0.1% (V/V) aqueous TFA] to afford pure motuporin diacid **1** (13.8 mg, 52% yield) as a white crystalline powder after

lyophilization: ^1H NMR (diacid, 400 MHz, CD_3OD , observed as a 95:5 mixture of rotamers, only data for the major rotamer is reported) δ 8.87 (d, J = 6.9 Hz, 1H), 8.32 (d, J = 9.6 Hz, 1H), 7.26-7.14 (m, 5H), 6.99 (q, J = 7.2 Hz, 1H), 6.25 (d, J = 15.5 Hz, 1H), 5.50 (dd, J = 8.6, 15.5 Hz, 1H), 5.42 (d, J = 9.8 Hz, 1H), 4.68 (m, 1H), 4.57 (t, J = 9.9 Hz, 1H), 4.43 (dd, J = 4.0, 9.6 Hz, 1H), 4.38 (dd, J = 2.4, 6.6 Hz, 1H), 3.23 (s, 3H), 3.18 (par obsc m, 1H), 3.10 (s, 3H), 2.81 (dd, J = 4.6, 13.8 Hz, 1H), 2.72 (m, 1H), 2.65 (dd, J = 7.3, 13.8 Hz, 1H), 2.58 (m, 1H), 2.44 (m, 2H), 2.16 (m, 1H), 2.04 (m, 1H), 1.76 (d, J = 7.3 Hz, 3H), 1.59 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H); ^{13}C NMR (diacid, 75 MHz, CDCl_3) δ 177.0, 176.8, 176.2, 174.7, 174.4, 171.4, 165.8, 140.7, 139.5, 138.2, 137.5, 137.2, 133.9, 130.7, 129.3, 127.2, 126.2, 88.5, 58.9, 58.1, 57.8, 56.2, 52.2, 45.4, 39.8, 39.1, 37.9, 35.2, 30.1, 29.5, 27.8, 19.9, 16.9, 16.7, 16.4, 13.5, 13.0; IR (neat) 3313, 2970, 1640, 1510, 1199 cm^{-1} ; HRMS (FAB, NBA/NaI) m/z calcd for $\text{C}_{40}\text{H}_{57}\text{N}_5\text{O}_{10}\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 790.4008, found: 790.4012; $[\alpha]_{\text{D}}^{23}$ = -66.8 (diacid, c 0.38, MeOH). A portion of this diacid was converted to disodium salt form as described below.

To a solution of the motuporin diacid (7.0 mg, 9.1 μL) in MeOH was added 20 μL saturated NaHCO_3 aqueous solution. The mixture was stirred at rt for 20 min and then gel filtered through Sephadex LH20 (MeOH as eluant) to afford motuporin disodium salt (7.0 mg, 94.6% from diacid **1**, 49.2% from macrocycle **33**) as a glass: ^1H NMR (disodium salt, 400 MHz, CD_3OD) δ 7.26-7.13 (m, 5H), 6.93 (q, J = 7.2 Hz, 1H), 6.22 (d, J = 15.5 Hz, 1H), 5.61 (dd, J = 9.2, 15.5 Hz, 1H), 5.39 (d, J = 9.6 Hz, 1H), 4.59 (par obsc dd, J = 9.2, 10.5 Hz, 1H), 4.50 (br, 1H), 4.42 (d, J = 3.3 Hz, 1H), 4.20 (br d, J = 2.8 Hz, 1H), 3.23 (ovrlp m, 1H), 3.23 (s, 3H), 3.19 (m, 1H), 3.08 (s, 3H), 3.04 (par obsc m, 1H), 2.81 (dd, J = 4.7, 13.8 Hz, 1H), 2.76 (par obsc m, 1H), 2.65 (dd, J = 7.3, 13.8 Hz, 1H), 2.57 (m, 1H), 2.48 (m, 1H), 2.28 (m, 1H), 2.03 (m, 1H), 1.83 (m, 1H), 1.74 (d, J = 7.2 Hz, 3H), 1.61 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H), 1.04-0.98 (m, 6H), 0.84 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H); ^{13}C NMR (disodium salt, 75 MHz, CDCl_3) δ 178.3, 177.9, 177.3, 176.4, 175.4, 172.0, 165.7, 140.7, 138.5, 137.9, 136.7, 136.5, 134.3, 130.7, 129.3, 127.3, 127.2, 88.6, 60.5, 58.9, 57.8, 56.2, 54.4, 44.7, 40.9, 39.1, 37.8, 35.2, 30.2, 29.8, 28.6, 19.9, 16.7, 16.3, 13.3, 13.1; IR

(neat) 3296, 2960, 2925, 1660, 1600, 1523, 1455, 1395, 1220 cm^{-1} ; LRMS (FAB, NBA/NaI) m/z calcd for $\text{C}_{40}\text{H}_{57}\text{N}_5\text{O}_{10}\text{Na}_2$ $[\text{M} + 2\text{Na}]^+$ 813, found: 813; $[\alpha]_{\text{D}}^{23} = -73.3$ (disodium salt c 0.06, MeOH); $[\alpha]_{\text{D}}^{23}$ (ref.¹⁰³ = -73 (disodium salt, c 0.00718, MeOH); $[\alpha]_{\text{D}}$ (ref¹³ = -83.8 (specific conditions were not reported for this optical rotation measurement).

References and Notes

- 1 Zinc chloride, commercial available from Aldrich Inc., was fused by flame-drying under reduced pressure for 15 min before use.
- 2 Preparation of $\text{Pd}(\text{PPh}_3)_4$, see: Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121-124.