Supporting Information

Abbreviations used: DIPEA, diisopropylethylamine; HBTU, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOAT, N-hydroxy-5-azabenzotriazole; HMDS, hexamethyldisilazane; MSNT, 1-(mesitylene-2-sulfonyl)-3-nitro-1H-1,2,4-triazole; NMI, N-methylimidazole; NMM, N-methylmorpholine; NMP, N-methylpyrrolidinone.

General Methods. Conventional organic solvents were purchased from Fisher. All of the chemicals were purchased from Aldrich Chemical Co and used without further purification unless stated otherwise. Aminomethylated polystyrene (1.02 mmol/g, 100-200 mesh) was obtained from NovaBiochem (San Diego). [(COD)Rh(*S,S*)-Et-DuPHOS]OTf was purchased from Strem Chemical, Inc., (Newburyport, MA). Tetrahydrofuran (THF) was distilled under N_2 from sodium/benzophenone ketyl and methylene chloride from calcium hydride. Flash chromatography was performed with Merck silica gel (230-400 mesh). TLC plates (silica gel 60-F254) were purchased from VWR Scientific. All ^{1}H NMR spectra were recorded on Varian Gemini 300 MHz, Mercury 400, or Inova 500 spectrometers (75, 100, or 125 MHz for ^{13}C NMR spectra). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si) in parts per million (ppm). Compounds were visualized with a ninhydrin spray reagent or a UV/vis lamp. Mass spectra were recorded either on a VG Instrument VG70-250SE high-resolution mass spectrometer (EI and FAB) or on a Micromass Quattro II spectrometer (APCI).

4-Allyldimethylsilylbenzaldehyde (3).

(a) Preparation of 1-allyldimethylsilyl-4-bromobenzene. To a solution of 1,4-dibromobenzene (28.3 g, 120 mmol) in dried THF (300 mL) at –78 °C was added *n*-butyllithium (40.0 mL, 2.5 M solution in hexanes, 100 mmol) over a period of 20 min. After 30 min of further stirring at –78 °C, allylchlorodimethylsilane (13.5 g, 100 mmol) in THF (50 mL) was added dropwise over a period of 20 min, and the reaction mixture was warmed to room temperature. After being stirred for 1 h at room temperature, the reaction mixture was concentrated, and the residue was extracted

with ether and brine. The organic layer was dried (Na_2SO_4) and distilled under reduced pressure to provide a colorless liquid (21.9 g, 82 %, b.p. 72 °C/0.1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.31 (s, 6 H), 1.77 (d, J = 8.07 Hz, 2 H), 4.87 (m, 1 H), 4.92 (m, 1 H), 5.78 (ddt, J = 17.55, 9.51, and 8.07 Hz, 1 H), 7.41 (d, J = 8.28 Hz, 2 H), 7.52 (d, J = 8.28 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) -3.5 (2 C), 23.6, 113.8, 123.9, 130.9 (2 C), 134.2, 135.3 (2 C), 137.5; HRMS (EI) calcd for $C_{11}H_{15}BrSi$ 254.0127 and 254.0107, found 254.0128 and 256.0109.

(b) Preparation of 4-allyldimethylsilylbenzaldehyde (3). To a solution of 1-allyldimethylsilyl-4-bromobenzene (1.3 g, 5 mmol) in dried THF (70 mL) at -78 °C was added *tert*-butyllithium (3.0 mL, 1.7 M solution in pentane, 5.1 mmol) over a period of 10 min. After being stirred for 30 min at –78 °C, anhydrous DMF (750 μL, 10 mmol) was added dropwise, and the reaction mixture was stirred further for 1 h, then warmed to room temperature. Concentrated NH_4Cl (2 mL) was added to the solution, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate (20 mL) and brine (5 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (1:15 ethyl acetate/hexanes) to afford a colorless oil (860 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6 H), 1.78 (d, J = 8.10 Hz, 2 H), 4.84 (s, 1 H), 4.89 (m, 1 H), 5.76 (m, 1 H), 7.67 (d, J = 8.10 Hz, 2 H), 7.85 (d, J = 8.10 Hz, 2 H), 10.05 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) -3.4 (2C), 23.5, 114.2, 128.8 (2C) 133.7, 134.4, (2C), 136.9, 147.6, 192.8; HRMS (EI) calcd for $C_{12}H_{16}OSi$ 204.0971, found 204.0972

(2*Z*)-Methyl-2-acetamido-3-(4-allyldimethylsilylphenyl)prop-2-enoate (4). To a solution of methyl-2-acetamido-2-(dimethoxyphosphinyl)-acetate (4.8 g, 20.0 mmol) in THF (50 mL) at –78 °C was added tetramethylguanidine (3.2 mL, 26 mmol), and the mixture was stirred for 15 min. 4-Allyldimethylsilylbenzaldehyde (**3**, 4.1 g, 20.0 mmol) in THF (10 mL) was added, and the mixture was stirred for 1 h at –78 °C and 4 h at room temperature. The mixture was diluted with EtOAc, washed with 1 N HCl, 1 N $CuSO_4$, and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (1:3 ethyl acetate/CH_2Cl_2) to afford a white powder (5.5 g, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6 H), 1.76(d, J = 8.40 Hz, 2 H), 2.15 (s, 3 H), 3.85 (s, 3 H), 4.84 (s, 1 H), 4.89 (m, 1 H), 5.77

(m, 1 H), 7.12 (bs, NH, 1 H), 7.37 (s, 1 H), 7.44 (d, J = 7.80 Hz, 2 H), 7.52 (d, J = 7.80 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) –3.3, 23.3, 23.7, 52.8, 113.9, 125.1, 129.2, 132.8, 134.0, 134.3, 134.5, 141.1, 166.0, 169.8. HRMS (EI) calcd for $C_{17}H_{23}NO_3Si$ 317.1448, found 317.1451.

(*S*)-Methyl-2-acetamido-3-(4-allyldimethylsilylphenyl)propanoate. To a round bottomed flask containing (2*Z*)-methyl-2-acetamido-3-(4-allyldimethylsilylphenyl)prop-2-enoate (**4**, 3.2 g, 10 mmol) in deoxygenated CH_2Cl_2 (40 mL) was added [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf (7 mg). After eight vacuum/H_2 cycles, the reaction was stirred for 23 h at room temperature under H_2 (1 atm). Once the reaction was completed, the solution was passed through a short plug of silica gel and concentrated to afford a clear oil (3.2 g. 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 6 H), 1.72 (dd, J = 8.10 Hz, 2 H), 1.98 (s, 3 H), 3.10 (m, 2 H), 3.72 (s, 3 H), 4.81 (d, J = 1.2 Hz, 1 H), 4.83-4.92 (2 H), 5.76 (m, 1 H), 5.94 (bd, J = 7.80 Hz, NH, 1 H), 7.06 (d, J = 7.20 Hz, 2 H), 7.42 (d, J = 7.20 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) –3.2, 23.3, 23.9, 37.9, 52.6, 53.3, 113.7, 128.9, 134.1, 134.8, 136.9, 137.5, 170.1, 172.5; HRMS (EI) calcd for $C_{17}H_{25}NO_3Si$ 319.1600, found 319.1602.

(*S*)-Methyl-3-(4-allyldimethylsilylphenyl)-2-(*tert*-butoxycarbamido)propanoate (5). To a solution of (*S*)-methyl-2-acetamido-3-(4-allyldimethylsilylphenyl)propanoate (1.5 g, 4.7 mmol) and DMAP (115 mg, 0.94 mmol) in THF (16 mL) was added di-*tert*-butyl dicarbonate (2.0 g, 9.4 mmol), and the mixture was heated to reflux for 1 h. After the solution was cooled to room temperature, MeOH (15 mL) and hydrazine monohydrate (912 μL, 18.8 mmol) were added, and the mixture was stirred for 4 h at room temperature. The solvent was evaporated by rotary evaporation, and the residue was subjected to high vacuum to remove the remaining volatile materials. The oily residue was purified by column chromatography (1:7 ethyl acetate/hexanes) to afford a colorless oil (1.7 g, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6 H), 1.43 (s, 9 H), 1.76 (d, J = 7.80 Hz, 2 H), 3.09 (m, 2 H), 3.73 (s, 3 H), 4.62 (m, 1 H), 4.84 (s, 1 H), 4.88 (d J = 6.60 Hz, 1 H), 5.20 (bd, NH, 1 H), 5.78 (m, 1 H), 7.14 (d, J = 7.50 Hz, 2 H), 7.46 (d, J =

7.50 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) –3.2, 23.9, 28.5, 38.6, 52.5, 54.6, 80.1, 113.7, 129.0, 134.1, 134.8, 137.1, 137.3, 153.3, 172.6; HRMS (EI) calcd for $C_{20}H_{32}NO_4Si$ 378.2100, found 378.2101

3-Iodobenzamidomethylpolystyrene (6). To a pre-swelled aminomethylated polystyrene resin (7 g, 1.02 mmole/g) in DMF (100 mL) were added 3-iodobenzoic acid (12.4 g, 50 mmol), HOBT (6.8 g, 50 mmol), diisopropylethylamine (8.7 mL, 50 mmol), and 1,3-diisopropylcarbodiimide (7.8 mL, 50 mmol). The suspension was stirred for 2 days, and the resin was washed with DMF, MeOH, CH_2Cl_2, and MeOH, then dried under reduced pressure to provide the functionalized resin **6**.

Hydroboration and Suzuki coupling of (*S*)-methyl-3-(4-allyldimethylsilylphenyl)-2-(*tert*-butoxycarbamido)propanoate (5) to 6 to give building block 2. To a solution of (*S*)-methyl-3-(4-allyldimethylsilylphenyl)-2-(*tert*-butoxycarbamido)propanoate (**5**, 755 mg, 2 mmol) in dry THF (8 mL) under a N_2 atmosphere was added 9-BBN (4 mL, 0.5 M solution in THF, 2 mmol) dropwise at room temperature, and the mixture was stirred for 5 h. The resin (**6**, 5 g, 0.96 mmol/g), DMF (8 mL), and 2 N aqueous Na_2CO_3 (1.5 mL, 3 mmol) were added to the reaction mixture which was deaerated by bubbling with a slow stream of argon for 10 min. After the addition of $Pd(PPh_3)_4$ (130 mg), the reaction flask and reflux condenser were wrapped with aluminum foil, then stirred at 75 °C for 24 h. $Pd(PPh_3)_4$ (70 mg) was added to the reaction mixture, and stirring was continued for an additional 48 h.

After washing the resin product sequentially with CH_2Cl_2, DMF, 1 N HCl/THF (1:7, 16 mL, 30 min), MeOH, and CH_2Cl_2, an aliquot of the resin (200 mg) was treated with a solution of Br_2 (15 μL) in CH_2Cl_2 (8 mL) for 20 min. The cleavage solution was filtered and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave (*S*)-methyl-3-(4-bromophenyl)-2-(*tert*-butoxycarbamido)propanoate (**7**, 8.2 mg, thus the loading level of **2** was determined to be 0.12 mmol/g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 2.95-3.11 (2 H),

3.71 (s, 3 H), 4.57 (m, 1 H), 4.98 (bs, NH, 1 H), 6.99 (d, J = 8.1 Hz, 2 H), 7.41 (d, J = 8.1 Hz, 2 H); HRMS (EI) calcd for $C_{15}H_{20}BrNO_4$ 357.0576 and 359.0556, found 357.0582 and 359.0569.

Determination of the enantiopurity of 2 by MPTA amide derivatization. An aliquot of resin (**2**, 200 mg, 0.12 mmol/g) was treated with 2% thioanisole and 50% TFA in CH_2Cl_2 (8 mL) for 15 min, then washed with CH_2Cl_2, 0.1 N HCl, MeOH, and CH_2Cl_2. The washed resin was suspended in CH_2Cl_2 (8 mL), then treated with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride (3 eq) and DIPEA (4 eq) for 4 h. After successive washing with CH_2Cl_2, MeOH, and CH_2Cl_2, the resin was treated with a solution of Br_2 (15 μL) in CH_2Cl_2 (8 mL) for 20 min. The cleavage solution was filtered, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave MTPA amide **8** as a colorless oil (8.9 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (dd, J = 14.4, 7.2 Hz, 1 H), 3.11 (dd, J = 14.4, 5.6 Hz, 1 H), 3.45 (s, 3 H), 3.75 (s, 3 H), 4.98 (m, 1 H), 6.73 (d, J = 8.0 Hz, 2 H), 7.02 (bd, J = 8.4 Hz, NH, 1 H), 7.26 (d, J = 8.0 Hz, 2 H), 7.30-7.43 (5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.6, 52.7, 53.0, 55.1, 84.1, 121.3, 127.3, 128.7, 129.7, 131.0, 131.8, 132.7, 134.6, 166.2, 171.2; Analysis of the ^{1}H NMR and ^{19}F NMR spectral integration showed less than 1% of the minor diasteromer. HRMS (EI) calcd for $C_{20}H_{19}BrF_3NO_4$ 473.0450 and 475.0431, found 473.0453 and 475.0458.

Solid-phase synthesis of sansalvamide A using polymer-bound phenylalanine building block 2. A suspension of resin (**2**, 1.6 g, 0.12 mmol/g) and LiOH (5 eq) in THF/ H_2O (7:1, 20 mL) was stirred in a 50 mL round bottomed flask at room temperature for 16 h. The resin was collected and washed sequentially with THF, 0.1 N HCl, MeOH, THF, and NMP. The resin in NMP (17 mL) was allowed to react with **9** (4 eq), HBTU (4 eq), and DIPEA (4 eq) for 16 h. After being washed with DMF, MeOH, and CH_2Cl_2, the resin product was treated with 2% thioanisole and 50% TFA in CH_2Cl_2 (17 mL) for 15 min, then washed with CH_2Cl_2, 0.1 N HCl, MeOH, and NMP. The washed resin was suspended in NMP (17 mL), treated with Fmoc-Leu-

OH (4 eq), HBTU (4 eq), and DIPEA (4 eq) for 6 h. After being washed with DMF, 0.1 N HCl, MeOH, CH_2Cl_2, and NMP, the resin was treated with 20% piperidine in DMF (17 mL) for 40 min, and washed (DMF, 0.1 N HCl, MeOH, and $CHCl_3$). The washed resin was suspended again in NMP (17 mL), treated with Fmoc-Val-OH (4 eq), HBTU (4 eq), and DIPEA (4 eq) for 6 h, then washed successively with DMF, MeOH, and $CHCl_3$. To an argon agitated suspension of the resin in $CHCl_3$/AcOH/NMM (37:2:1, 18 mL) was added $Pd(PPh_3)_4$ (4 eq), and the reactor was sealed, then agitated for 3 h. After successive washing with CH_2Cl_2, DMF, 1 N HCl/THF (1:7, 16 mL, 30 min), MeOH, and DMF, the resin was treated with 20% piperidine in DMF (17 mL) for 40 min, washed with DMF, 1 N HCl/THF (1:7, 16 mL, 30 min), MeOH, CH_2Cl_2 and NMP. Cyclization was carried out by treatment of the resin in NMP (15 mL) with HBTU (4 eq), and DIPEA (4 eq) for 16 h followed by washing (DMF, MeOH, and CH_2Cl_2). An aliquot of the resin (400 mg) was treated with 50% TFA in CH_2Cl_2 (14 mL) for 36 h at room temperature. The cleavage solution was separated, and the resin was rinsed with CH_2Cl_2 (5 mL). Concentration of the combined filtrates gave sansalvamide A (**1**, 18 mg, 67%, purity was determined to be higher than 95% based on the ^1H NMR spectrum, which was identical to that of natural sansalvamide A donated by Professor William Fenical of Scripps Institution of Oceanography); ^1H NMR (400 MHz, CD_3OD) δ 0.83 (d, J = 6.4 Hz, 3 H), 0.85 (d, J = 6.4 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.95-0.97 (9 H), 0.99 (d, J = 6.4 Hz, 3 H), 1.00 (d, J = 6.4 Hz, 3 H), 1.39 (m, 1 H), 1.48 (m, 1 H), 1.64 (m, 2 H), 1.74 (m, 2 H), 1.83 (m, 2 H), 2.06 (m, 1 H), 3.08 (dd, J = 14.0, 11.6 Hz, 1 H), 3.25 (dd, J = 14.0, 4.4 Hz, 1 H), 3.68 (br dd, J = 9.2, 5,6 Hz, 1 H), 4.05 (d, J = 7.6 Hz, 1 H), 4.55 (dd, J = 10.8, 4.8 Hz, 1 H), 4.72 (dd, J = 9.6, 4.8 Hz, 1 H), 5.00 (dd, J = 9.2, 5.2 Hz, 1 H); HRMS (APCI, M+1) calcd for $C_{32}H_{51}N_4O_6$ 587.380, found 587.380.

Allyl (*S*)-(-)-2-hydroxyisocaproate (13). To a heterogeneous suspension of (*S*)-(-)-2-hydroxyisocaproic acid (6.0 g, 45 mmol) and powdered K_2CO_3 (12.4 g, 90 mmol) in 250 mL of acetone was added allyl bromide (4.7 mL, 54 mmol) in one portion, and the mixture was stirred at ambient temperature for 48 h. After filtration of the reaction mixture over Celite, the filtrate was

concentrated. The crude residue was dissolved in CH_2Cl_2, then passed through a short pad of silica gel column using CH_2Cl_2 as eluent. Concentration of the filtrate and washings afforded a colorless liquid (7.3 g, 95%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 0.95 (s, 3 H), 1.56 (m, 2 H), 1.90 (m, 1 H), 2.80 (bs, OH, 1 H), 4.23 (m, 1 H), 4.67 (d, J = 5.5 Hz, 2 H), 5.27 (d, J = 10.5 Hz, 1 H), 5.34 (d, J = 17.0 Hz, 1 H), 5.91 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7, 23.5, 24.6, 43.7, 66.2, 69.3, 119.1, 131.8, 175.8; HRMS (EI) calcd for $C_9H_{16}O_3$ 172.1099, found 172.1104

Boc-Leu-OLeu-Oallyl (14). To a mixture of *N*-Boc-leucine monohydrate (1.49 g, 6 mmol), **13** (860 mg, 5 mmol), and DCC (2.1 g, 10 mmol) in CH_2Cl_2 (40 mL) was added DMAP (100 mg), and the reaction mixture was stirred at room temperature for 2 days. The precipitated solid was filtered, and the filtrate was concentrated, purified by silica gel column chromatography using CH_2Cl_2 as the eluent to give a colorless oil (1.2 g, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91-0.94 (12 H), 1.40 (s, 9 H), 1.42-1.81 (6 H), 4.33 (m, 1 H), 4.59 (d, J = 5.2 Hz, 2 H), 4.87 (bd, NH, 1 H), 5.06 (m, 1 H), 5.22 (d, J = 11.0 Hz, 1 H), 5.29 (d, J = 17.0 Hz, 1 H), 5.85 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9, 22.1, 23.3, 23.4, 24.9, 25.1, 28.6, 40.0, 41.9, 52.1, 66.1, 71.8, 80.0, 119.0, 131.6, 155.5, 170.1, 173.3; HRMS (EI) calcd for $C_{20}H_{35}NO_6$ 385.2465, found 385.2464.

Leu-OLeu-Oallyl (9). A solution of Boc-Leu-OLeu-Oallyl (**14**, 430 mg, 1.1 mmol) in 50% TFA in CH_2Cl_2 (14 mL) was stirred at room temperature for 5 min, and concentrated. The residue was diluted in CH_2Cl_2 (10 mL), then evaporated again to give a colorless oil (440 mg, 100%). The TFA was removed just before use for solid-phase synthesis as follows: the residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate followed by brine, dried over sodium sulfate, and concentrated in vacuo to give a clear colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-0.99 (12 H), 1.70-1.95 (6 H), 4.12 (bs, 1 H), 4.62 (m, 2 H), 5.15 (m, 1 H), 5.26-5.34 (2 H), 5.97 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6, 21.8, 22.3, 23.1, 24.7,

24.9, 39.7, 39.9, 52.4, 66.9, 73.6, 119.8, 130.9, 169.6, 169.7; HRMS (EI) calcd for $C_{15}H_{28}NO_4$ 286.2018, found 286.2016.

Preparation of 11 using polymer-bound phenylalanine building block 2. A suspension of **2** (0.8 g, 0.12 mmol/g) and LiOH (5 eq) in THF/ H_2O (7:1, 20 mL) was stirred in a 50 mL round bottomed flask at room temperature for 16 h. The resin was collected by filtration and washed sequentially with THF, 0.1 N HCl, MeOH, THF, and NMP. The resin in NMP (17 mL) was allowed to react with *O*-allylleucine ester (4 eq), HBTU (4 eq), and DIPEA (4 eq) for 16 h. After being washed with DMF, MeOH, and CH_2Cl_2, the resin product was treated with 2% thioanisole and 50% TFA in CH_2Cl_2 (17 mL) for 15 min, then washed with CH_2Cl_2, 0.1 N HCl, MeOH, NMP. The washed resin was suspended in NMP (17 mL), treated with Fmoc-Leu-OH (4 eq), HBTU (4 eq), and DIPEA (4 eq) for 6 h. After being washed with DMF, 0.1 N HCl, MeOH, CH_2Cl_2, the resin was treated with 20% piperidine in DMF (17 mL) for 40 min, and washed (DMF, 0.1 N HCl, MeOH, and $CHCl_3$). The washed resin was suspended again in NMP (17 mL), treated with Fmoc-Val-OH (4 eq), HBTU (4 eq), and DIPEA (4 eq) for 6 h, then washed successively with DMF, MeOH, and $CHCl_3$. To the argon agitated suspension of the resin in $CHCl_3$/AcOH/NMM (37:2:1, 18 mL) was added $Pd(PPh_3)_4$ (4 eq), and the reactor was sealed, then agitated for 3 h. After successive washing with $CHCl_3$, DMF, and CH_2Cl_2, the resin in CH_2Cl_2 (17 mL) was allowed to react with **13** (4 eq), MSNT (4 eq), and *N*-methylimidazole (4 eq) for 16 h. The resin was filtered, washed with CH_2Cl_2, MeOH, and CH_2Cl_2, then dried under reduced pressure to afford **11**.