Supporting Information

Assignment of Absolute Stereochemistry and Total Synthesis of (-)-Spongidepsin

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All moisture sensitive reactions were carried out under nitrogen or argon atmosphere. Anhydrous solvents were obtained as follows: THF, diethyl ether, distilled from sodium and benzophenone; dichloromethane, distilled from P₂O₅; pyridine, toluene, benzene, and diisopropylethylamine, distilled from CaH₂. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 5-10 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 400 and 500 spectrometers. Infrared spectra were recorded on a Mattson Genesis II FTIR instrument. Optical rotations were measured using a Perkin-Elmer 341 polarimeter.

Compound 8. To the solution of *meso*-2,4-dimethyl 1,5-pentanediol (**7**) (350 mg, 2.31 mmol) and vinyl acetate (0.85 mL, 9.22 mmol) in DME (10 mL) was added lipase PS-30 (300 mg, 10% on celite). The reaction was stirred at 23°C for 1.5 h. The reaction mixture was filtered and the filter cake was washed with EtOAc. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel (30% EtOAc in Hexanes) to provide **8** (330 mg, 82%) [α]_D²³=12.1 (c= 10, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 3.96 (dd, J=5.3, 10.7 Hz, 1H), 3.84 (dd, J=7.9 10.7 Hz, 1H), 3.49 (dd, J=5.3, 10.5 Hz, 1H), 3.41 (dd, J=6.3, 10.4 Hz, 1H), 2.05 (s, 3H), 1.89 (m, 1H), 1.72 (m, 1H), 1.6-1.4 (bs, 1H), 1.44 (m, 1H), 0.99 (m, 1H), 0.95 (m, 6H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 171.3, 69.1, 68.0, 37.2, 33.0, 30.0, 21.0, 17.8, 17.2; IR (neat) 3438, 2959, 2925, 2878, 1739, 1463, 1371, 1240, 1038 cm⁻¹.

Compound 9. To a stirred solution of **8** (2.17 g, 12.4 mmol) in DMF (10 mL), imidazole (1.7 g, 25 mmol) and TBDPS-Cl (3.9 mL, 15 mmol) were added. The reaction mixture was stirred at 23°C for 4 h. EtOAc was added to the reaction and the organic layer was washed with water, 2% HCl and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography over silica gel (10% EtOAc in Hexanes) provided the TBDPS ether (5.14 g, quantitative).

To the above silyl ether (5.14 g) in DCM (35 mL) was added DIBAL-H (37 mL, 1 M, 37 mmol) at -78°C. The reaction mixture was stirred at that temperature for 1 h and then quenched with MeOH. Potassium sodium tartrate (25% in H₂O, 80 mL) was added to the mixture and it was stirred at 0°C for 2 h. The organic phase was washed with water, saturated aqueous NH₄Cl and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography over silica gel (30% EtOAc in Hexanes) provided **9** (4.32 g, 94%). [α]_D²³ 0.3 (c 0.4, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.67 (d, J=6.8 Hz, 4H), 7.40 (m, 6H), 3.52 (dd, J=5.3, 9.8 Hz, 1H), 3.48 (dd, J=5.2, 10.5 Hz, 1H), 3.43 (dd, J=5.3, 9.9 Hz, 1H), 3.35 (dd, J=6.6, 10.5 Hz, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 1.46 (m, 1H), 1.06 (s, 9H), 0.96 (d, J=6.6 Hz, 3H), 0.92 (m, 1H), 0.89 (d, J=6.9 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 135.6, 134.0, 129.5, 127.6, 68.7, 68.3, 37.1, 33.1, 26.9, 19.3, 17.9, 17.4; IR (neat) 3390, 3070, 3050, 2956, 2929, 2859, 1468, 1427, 1388, 1109, 1087, 702 cm⁻¹.

Compound 10. To a solution of **9** (4.34 g, 11.7 mmol) in CH₂Cl₂ (60 mL) at 0°C were added DMSO (2.9 mL, 41 mmol) and TEA (5.7 mL, 41 mmol). SO₃-Py complex (4.66 g, 29.3 mmol) was slowly added to the reaction mixture at 0°C. The reaction mixture was stirred at that temperature for 0.5 h and then quenched with saturated aqueous NH₄Cl. The organic layer was washed with pure water and then with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography over silica gel (5% EtOAc in Hexanes) provided the corresponding aldehyde (4.08 g, 94%).

To a suspension of methyltriphenylphosphonium bromide (10.17 g, 28.5 mmol) in THF (150 mL) at 0°C, *n*-BuLi (16.2 mL, 1.6 M in Hexanes, 25.4 mmol) was added slowly over a period of 1 min. The reaction mixture became clear and it was stirred for 15 min. Above aldehyde (2.10 g, 5.7 mmol) in THF (15 mL) was then slowly added to the red phosphorane solution. The reaction mixture was allowed to warm to 23°C and stirred for 30 min. The reaction was quenched with saturated aqueous NH₄Cl. The organic layer was washed with brine and dried over Na₂SO₄, filtered, concentrated under reduced pressure and chromatographed over silica gel (2% EtOAc in Hexanes) to give the olefin **10** (1.74 g, 83%). [α]_D²³ 5.1 (c 0.55, CHCl₃);

^1H NMR (CDCl_3 , 500 MHz) δ 7.67 (m, 4H), 7.39 (m, 6H), 5.60 (m, 1H), 4.94 (m, 2H), 3.45 (m, 2H), 2.20 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.06 (s, 9H), 1.02 (m, 1H), 0.96 (d, $J=6.7$ Hz, 3H), 0.91 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 144.7, 135.6, 134.1, 129.5, 127.5, 112.5, 69.2, 40.4, 35.4, 33.4, 26.9, 21.3, 19.3, 16.7; IR (neat) 3071, 3050, 2997, 2958, 2929, 2858, 1427, 1111, 1086, 701 cm^{-1} .

Compound 5. To a solution of **10** (1.74 g, 4.75 mmol) in THF (20 mL), TBAF (9.5 mL, 1 M in THF, 9.49 mmol) was added. The resulting mixture was stirred at 23°C for 2 h and then quenched with saturated aqueous NH_4Cl . EtOAc was added and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was dissolved in DMF (35 mL). PDC (17.8 g, 47.5 mmol) was added and the reaction mixture was stirred at 23°C for 24 h. Water was added to the reaction mixture and EtOAc was added. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. This product **5** (513 mg, 76%) is quite pure and it was used for the next coupling reaction without further purification. $[\alpha]_D^{23}$ -6.4 (c 2.2, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 11-10 (bs, 1H), 5.62 (m, 1H), 4.95 (m, 2H), 2.49 (m, 1H), 2.21 (m, 1H), 1.73 (m, 1H), 1.36 (m, 1H), 1.17 (d, $J=6.9$ Hz, 3H), 1.02 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 183.8, 143.4, 113.6, 39.9, 37.2, 35.8, 20.6, 16.6; IR (neat) 3078, 2972, 2934, 2881, 2660, 2584, 1708, 1462, 1417, 1287, 1243, 1216 cm^{-1} .

Compound 12. To a stirred solution of 4-penten-1-ol **11** (530 mg, 6.2 mmol) and imidazole (470 mg, 6.9 mmol) in a mixture of CH_2Cl_2 (150 mL) and DMF (50 mL) at 0°C, tetra-butylchlorodiphenylsilane (1.7 g, 76.9 mmol) was added. The resulting mixture was allowed to warm to 23°C and stirred at that temperature for 12 h. After this period, the reaction was diluted with EtOAc. The organic layer was washed with 2% HCl, water, and brine. The organic phase was dried over Na_2SO_4 , and the solvent was removed under reduced pressure. Chromatography over silica gel (2% EtOAc in Hexanes) afforded **12** (1.97 g, 98%) as a colorless oil. ^1H NMR (CDCl_3 , 300 MHz) δ 7.69 (m, 4H), 7.41 (m, 6H), 5.81 (m, 1H), 4.98 (m, 1H), 3.69 (t, $J=6.6$ Hz, 2H), 2.14 (m, 2H), 1.69 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 138.6, 135.6, 134.0, 129.5, 127.6, 114.5, 63.3, 31.8, 30.0, 26.8, 19.2; IR (neat) 3098, 2989, 2880, 2842, 1428, 1108, 703 cm^{-1} .

Compound 13. To a stirred solution of above alkene **12** (320 mg, 1 mmol) in CH_2Cl_2 (12 mL), allyl chloride (334 mg, 4.5 mmol) and 2nd generation Grubbs's catalyst (43 mg, 0.5 mmol) were added. The resulting mixture was refluxed for 12 h. After this period, the solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (2% EtOAc/Hexanes) to provide the corresponding allylic chloride (0.25g, 68%; *E/Z* ratio 15:1). *E* isomer: ^1H NMR (CDCl_3 , 300 MHz) δ 7.72 (m, 4H), 7.46 (m, 6H), 5.79 (m, 1H), 5.75 (m, 1H), 4.04 (d, $J=6.9$ Hz, 2H), 3.74 (t, $J=6.3$ Hz, 2H), 2.22 (m, 2H), 1.71 (m, 2H), 1.12 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 135.6, 133.9, 129.6, 127.7, 126.3, 63.0, 45.4, 31.7, 28.4, 26.9, 19.3; IR (neat) 3067, 3047, 2955, 2936, 2862, 1427, 1108 cm^{-1} .

Above allylic chloride (150 mg, 0.4 mmol) and NaI (150 mg, 1 mmol) were dissolved in acetone (2.5 mL) and was stirred overnight at 23°C . Hexanes was added to the reaction mixture and the organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Chromatography over silica gel (2% EtOAc in Hexanes) gave the product **13** (171 mg, 92%). ^1H NMR (CDCl_3 , 500 MHz) δ 7.67 (m, 4H), 7.44-7.38 (m, 6H), 5.72 (m, 2H), 3.85 (d, $J=6.8$ Hz, 2H), 2.16 (m, 2H), 1.64 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 135.6, 134.6, 133.9, 129.6, 128.1, 127.6, 62.9, 31.6, 28.3, 26.9, 19.2, 6.8 ppm; IR (neat) 3069, 2953, 2930, 2856, 1471, 1427, 1149, 1108 cm^{-1} ; HRMS (ESI) m/z 487.0926 (calcd for $\text{C}_{22}\text{H}_{29}\text{IO}_4\text{Si}+\text{Na}^+$ 487.0930).

Compound 15. To a stirred solution of (R)-(-)-4-benzyl-2-oxazolidinone (5.37 g, 30.3 mmol) in THF (100 mL) at -78°C , *n*-BuLi (20.8 mL, 1.6 M in Hexanes, 33.3 mmol) was added and the mixture was stirred for 10 min. Propionyl chloride (2.9 mL, 33.3 mmol) was added to this solution at -78°C . The reaction mixture was warmed to 0°C and stirred at 0°C for 30 min. After this period, the reaction was quenched with saturated aqueous NH_4Cl . The organic layer was washed with brine and dried over Na_2SO_4 , concentrated under reduced pressure. The residue was chromatographed over silica gel to give oxazolidinone **14** (6.72 g, 95%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.4-7.2 (m, 5H), 4.67 (m, 1H), 4.17 (m, 2H), 3.28 (dd, $J=3.3, 13.5$ Hz, 1H), 2.95 (m, 2H), 2.77 (dd, $J=9.3, 13.5$ Hz, 1H), 1.20 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 173.8, 153.3, 135.1, 129.2, 128.7, 127.1, 66.0, 54.9, 37.6, 28.9, 8.0.

To a stirred solution of **14** (1.0 g, 4.3 mmol) in THF (5 mL) at -78°C , LiHMDS (4.74 mL, 1M in THF, 4.74 mmol) was added. The reaction mixture was allowed to warm to -40°C

and stirred for 30 min. After this period, a solution of the iodide **13** (2.4 g, 5.16 mmol) in THF (5 mL) was added and the resulting mixture was warmed to 0°C and stirred for 3 h. Reaction was quenched with saturated aqueous NH₄Cl and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed over silica gel to provide **15** (2.21 g, 90%, 96% de). $[\alpha]_D^{23}$ 14.85 (c 2.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.65 (m, 4H) 7.43-7.19 (m, 11H), 5.52-5.39 (m, 2H), 4.68 (m, 2H), 4.16 (m, 2H), 3.78 (m, 1H), 3.66 (t, J=6.3 Hz, 2H), 3.28 (dd, J=13.3, 3.2 Hz, 1H), 2.67 (dd, J=9.8 13.3 Hz, 1H), 2.44 (m, 1H), 2.15 (m, 1H), 2.09 (m, 2H), 1.61 (m, 2H), 1.14 (d, 6.8 Hz, 3H), 1.03 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.7, 135.6, 135.3, 134.0, 132.9, 129.5, 129.4, 128.9, 127.6, 127.3, 126.8, 66.0, 63.3, 55.3, 38.1, 37.6, 36.8, 32.3, 28.8, 26.8, 19.2, 16.3; IR (neat) 3069, 2931, 2857, 1781, 1699, 1385, 1209, 1109 cm⁻¹; HRMS (ESI) m/z 592.2867 (calcd for C₃₅H₄₃NO₄Si+Na⁺ 592.2859).

Compound 16. To a stirred solution of **15** (9.94 g 17.44 mmol) in a mixture of dimethyl ether (100 mL) and H₂O (100 mL) at 0°C, NBS (3.42 g, 18.2 mmol) was added and the reaction mixture was stirred for 30 min. After this period, organic layer was washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄, concentrated under reduced pressure. The residue was chromatographed over silica gel (8% EtOAc in Hexanes) to provide **16** (7.72 g, 90%). $[\alpha]_D^{23}$ -15.9 (c 2.08, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.67 (m, 4H), 7.46-7.39 (m, 6H), 4.53 (m, 1H), 4.10 (m, 1H), 3.72 (t, J=5.8 Hz, 2H), 2.79 (dt, J=9.6, 7.3 Hz, 1H), 2.45 (m, 1H), 2.14 (m, 1H), 2.06 (dt, J=13.2, 7.7 Hz, 1H), 1.87 (m, 2H), 1.70 (m, 1H), 1.31 (d, J=7.4 Hz, 3H), 1.07 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 179.3, 135.6, 133.7, 129.7, 127.7, 79.3, 62.9, 57.4, 34.1, 33.4, 33.3, 29.9, 26.9, 19.2, 16.5; IR (neat) 2932, 2858, 1780, 1427, 1178, 1108 cm⁻¹; HRMS (ESI) m/z 511.1282 (calcd for C₂₅H₃₃BrO₃Si+Na⁺ 511.1280).

Compound 17. To a solution of **16** (5.2 g, 10.6 mmol) in a mixture of benzene (50 mL) and *t*-butanol (50 mL) at 23°C, AIBN (170 mg 1.06 mmol), Bu₃SnCl (431 μL, 1.59 mmol) and NaBH₃CN (1.07 g, 17.0 mmol) were added. The reaction mixture was refluxed for 2 h and then cooled and washed with brine. The organic layer was dried over Na₂SO₄, and concentrated under

reduced pressure. The residue was chromatographed over silica gel (15% EtOAc in Hexanes) to provide **17** (4.17 g, 96%). $[\alpha]_D^{23}$ -17.8 (c 3.2, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.68 (m, 4H), 7.44-7.38 (m, 6H), 4.48 (m, 1H), 3.69 (t, J=6.2 Hz, 2H), 2.68 (m, 1H), 2.08 (m, 1H), 1.98 (dt, J=12.8, 7.5 Hz, 1H), 1.69 (m, 1H), 1.60 (m, 1H), 1.53 (m, 2H), 1.47 (m, 1H), 1.28 (d, J=7.3 Hz, 3H), 1.08 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 180.1, 135.6, 133.9, 129.6, 127.7, 78.4, 63.5, 35.4, 35.1, 34.0, 32.1, 26.9, 21.8, 19.2, 15.9; IR (neat) 3069, 3048, 2934, 2859, 1173, 1427, 1187, 1110 cm⁻¹; HRMS (ESI) m/z 433.2160 (calcd for C₂₄H₃₄O₃Si+Na⁺ 433.2175).

Compound 6. To a solution of **17** (2.81 g, 6.84 mmol) in CH₂Cl₂ (100 mL) at -78°C, DIBAL-H (12.2 mL, 1 M in Hexanes, 12.2 mmol) was added and the resulting mixture was stirred for 2 h. The reaction mixture was quenched with MeOH and potassium sodium tartrate was added and the resulting mixture was stirred for 1h. The organic layer was washed with saturated aqueous NH₄Cl, brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was dried under vacuum and used directly for the next reaction.

To a suspension of PPh₃P⁺CH₃Br⁻ (12.21 g, 34.2 mmol) in THF (120 mL) at 0°C, *n*-BuLi (19.2 mL, 1.6 M in Hexanes) was added slowly over a period of 3 min. The reaction mixture was stirred for 30 min at 0°C. After this period, a solution of above crude lactol in THF (10 mL) was added at 0°C. The reaction mixture was warmed up to 23°C and then stirred for 1.5 h. Reaction was quenched with saturated aqueous NH₄Cl and washed with brine. The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The residue was chromatographed over silica gel to provide **6** (2.1 g, 74%). $[\alpha]_D^{23}$ +7.17 (c 1.91, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.78 (m, 4H), 7.50-7.43 (m, 6H), 5.75 (m, 1H), 5.08 (m, 2H), 3.77 (t, J=6.4 Hz, 2H), 3.69 (m, 1H), 2.49 (m, 1H), 1.86 (br s, 1H), 1.67 (m, 2H), 1.57 (m, 1H), 1.50 (m, 4H), 1.45 (m, 1H), 1.16 (s, 9H), 1.10 (d, J=6.8 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 144.3, 135.7, 134.1, 129.6, 127.7, 113.5, 69.6, 63.9, 44.3, 37.7, 34.8, 32.6, 27.0, 21.9, 21.4, 19.3; IR (neat) 3382, 3070, 2931, 2860, 1469, 1427, 1180, 1109 cm⁻¹; HRMS (ESI) m/z 433.2521 (calcd for C₂₆H₃₈O₂Si+Na⁺ 433.2539).

Compound 18. To a solution of N-Boc-L-phenylalanine (0.30 g, 1.13 mmol) in THF (6 mL) at 0°C, NaH (158 mg, 60%, 4.0 mmol) followed by CH₃I (563 μ L, 9.05 mmol) were added. The reaction mixture was stirred at 23°C for 24 h. After this period, H₂O (100 mL) was added slowly and the water layer was extracted with diethyl ether. The aqueous layer was acidified to pH=3 with citric acid and then extracted with EtOAc. The EtOAc layer was washed with H₂O, brine, dried over Na₂SO₄, and concentrated under reduced pressure to give compound **4** [α]_D²³ -70.7 (c 2.3, CHCl₃). The product contains 2 rotamers. ¹H NMR (CDCl₃, 500 MHz) δ 9.0-7.5 (bs, 1H), 7.30-7.18 (m, 5H), 4.85 (dd, J=5.0, 11.0 Hz, 0.5H), 4.63 (dd, J=4.2, 10.9 Hz, 0.5H), 3.32 (m, 1H), 3.12 (dd, J=11.2, 14.2 Hz, 0.5H), 3.04 (dd, J=11.2, 14.0 Hz, 0.5H), 2.76 (s, 1.5H), 2.69 (s, 1.5H), 1.40 (s, 4.5H), 1.34 (s, 4.5H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.9, 176.5, 156.8, 155.4, 137.8, 137.5, 129.4, 129.3, 129.0, 128.9, 127.2, 127.1, 81.2, 61.9, 61.1, 35.7, 35.1, 33.4, 33.0, 28.7, 28.6.

To a stirred solution of N-Boc-N-methyl-L-phenylalanine (**4**) (192 mg, 0.69 mmol) and the alcohol **6** (94 mg, 0.23 mmol) in diethyl ether (15 mL) at 23°C, Ph₃P (180 mg, 0.69 mmol), diethylazodicarboxylate (108 μ L, 0.69 mmol) were added. The reaction mixture was stirred at 23°C for 2 h and was concentrated under reduced pressure. The residue was chromatographed over silica gel to provide **18** (111 mg, 72.4%). The product contains two rotamers from the amide. [α]_D²³ -25.4 (c 2, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 7.29-7.19 (m, 5H), 5.73 (m, 1H), 5.00-4.76 (m, 4H), 3.66-3.65 (m, 2H), 3.32 (m, 1H), 2.99 (m, 1H), 2.79 (s, 1.6H), 2.72 (s, 1.44), 2.19 (m, 1H), 1.71 (m, 1H), 1.69 (m, 1H), 1.55 (m, 4H), 1.47-1.33 (m, 12H), 1.07 (s, 9H), 1.01 (m, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.0, 170.7, 155.7, 155.1, 143.9, 143.7, 137.6, 137.5, 134.0, 133.7, 129.6, 129.0, 128.9, 128.5, 128.3, 127.6, 126.6, 126.4, 113.1, 112.8, 80.1, 79.8, 73.7, 73.4, 63.6, 60.8, 59.8, 40.7, 40.6, 35.2, 35.1, 34.9, 34.3, 33.9, 33.8, 32.4, 28.3, 28.2, 26.9, 21.4, 20.3, 20.1, 19.2; IR (neat) 3069, 2956, 2932, 2860, 1735, 1699, 1391, 1109 cm⁻¹; HRMS (ESI) m/z 694.3907 (calcd for C₄₁H₅₇NO₅Si+Na⁺ 694.3904).

Compound 3. A solution of **18** (422 mg, 0.628 mmol) in a mixture of TFA (2 mL) and CH₂Cl₂ (2 mL) was stirred at 0°C for 1h. After this period, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and the organic layer was washed with 5% NaHCO₃ and brine and then dried over Na₂SO₄, and concentrated under reduced pressure to provide the corresponding amine. This amine was used directly for the next reaction.

To a stirred solution of above amine and 2,4-dimethyl-hex-5-enoic acid (251 mg, 1.76 mmol) in CH₂Cl₂ (30 mL) at 23°C, EDCI (1.12 g, 5.86 mmol) and HOBt (33 mg, 0.23 mmol) were added. The reaction mixture was stirred at 23°C for 2 h. After this period, the reaction was quenched with saturated aqueous NH₄Cl solution. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was chromatographed over silica gel (10% EtOAc in Hexanes) to give **3** (374 mg, 86% overall). Product contains 2 rotamers of the amide: $[\alpha]_D^{23}$ -36.1 (c 1.6, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.67 (m, 4H), 7.42-7.37 (m, 6H), 7.26-7.10 (m, 5H), 5.72-5.67 (m, 1H), 5.50-5.45 (m, 1.8H), 4.99-4.82 (m, 5H), 4.58 (m, 0.2H), 3.65 (m, 2H), 3.36 (dd, J=15.07, 5.4 Hz, 0.8H), 3.24 (dd, J=14.0, 4.6 Hz, 0.2H), 2.96 (dd, J=14.4, 11.4 Hz, 1H), 2.89 (s, 0.6H), 2.80 (s, 2.4H), 2.54 (m, 1H), 2.20-2.09 (m, 1H), 1.86 (m, 1H), 1.66 (m, 1H), 1.56 (m, 4H), 1.42-1.22 (m, 5H), 1.06 (s, 2.6H), 1.05 (s, 7.3H), 1.02 (d, J=6.7 Hz, 2.4H), 1.00 (d, J=6.7 Hz, 2.4H), 0.92 (d, J=6.7 Hz, 0.7H), 0.76 (d, J=6.7 Hz, 2.4H), 0.58 (d, J=6.4 Hz, 0.6H); ¹³C NMR (CDCl₃, 125 MHz) δ 177.3, 177.0, 170.8, 169.8, 143.9, 143.8, 143.43, 143.38, 137.1, 136.7, 135.5, 134.0, 133.9, 129.5, 129.2, 128.9, 128.7, 128.4, 127.6, 127.0, 126.6, 114.1, 113.2, 113.0, 112.9, 74.2, 73.6, 63.6, 63.5, 61.4, 57.6, 40.8, 40.6, 40.2, 35.6, 35.5, 35.3, 34.8, 34.4, 33.8, 33.2, 32.7, 32.4, 29.6, 26.9, 21.4, 21.1, 20.3, 20.2, 20.0, 19.2, 16.7, 15.7; IR (neat) 3070, 2956, 2930, 2859, 1734, 1651, 1460, 1205, 1110 cm⁻¹; HRMS (ESI) m/z 718.4291 (calcd for C₄₄H₆₁NO₄Si+Na⁺ 718.4268).

Compound 19. To a solution of **3** (301 mg, 0.43 mmol) in CH₂Cl₂ (650 mL), second generation Grubbs's catalyst (37 mg, 0.04 mmol) was added. The resulting mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the crude mixture was purified by silica gel chromatography to give **19** (269 mg, 93%). $[\alpha]_D^{23}$ -113.8 (c 1.21, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.66 (m, 4H), 7.43-7.37 (m, 6H), 7.28-7.12 (m, 5H), 5.19 (m, 2H), 5.07 (m, 1H), 3.66 (t, J=6.3 Hz, 2H), 3.56 (dd, J=4.1, 11.2 Hz, 1H), 3.48 (dd, J=13.6, 11.2 Hz, 1H), 3.33 (dd, J=4.1, 13.6 Hz, 1H), 2.77 (m, 1H), 2.62 (s, 3H), 2.46 (m, 1H), 2.12 (m, 1H), 1.89 (t, J=12.5 Hz, 1H), 1.60-1.26 (m, 8H), 1.15 (m, 1H), 1.10 (d, J=6.7 Hz, 3H), 1.05 (s, 9H), 0.99 (t, J=6.7 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.6, 170.0, 138.7, 136.2, 135.7, 134.0, 129.6, 129.5,

128.4, 127.6, 126.5, 73.3, 66.9, 63.6, 44.2, 43.1, 39.4, 35.2, 34.5, 33.7, 32.5, 30.2, 26.9, 26.8, 21.6, 20.0, 19.4, 19.2, 18.6; IR (neat) 2956, 2930, 2858, 1737, 1640, 1273, 1109 cm^{-1} ; HRMS (ESI) m/z 690.3947 (calcd for $\text{C}_{42}\text{H}_{57}\text{NO}_4\text{Si}+\text{Na}^+$ 690.3955).

Compound 20. To a solution of **19** (230 mg, 0.34 mmol) in THF (40 mL), TBAF (0.7 mL, 0.69 mmol) was added. The resulting reaction mixture was stirred for 2 h at 23°C. After this period, reaction was quenched with NH_4Cl and washed with brine. The organic layer was dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (40% EtOAc in Hexanes) to afford the corresponding alcohol (156 mg, 92%). $[\alpha]_D^{23}$ -161.9 (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 7.29-7.15 (m, 5H), 5.19 (dd, $J=9.0$, 12.6 Hz, 1H), 5.15 (dd, $J=9.0$, 12.6 Hz, 1H), 5.05 (m, 1H), 3.64 (t, $J=6.5$ Hz, 2H), 3.60 (dd, $J=11.2$, 4.4 Hz, 1H), 3.46 (dd, $J=11.2$, 13.7 Hz, 1H), 3.33 (dd, $J=4.4$, 13.8 Hz, 1H), 2.76 (m, 1H), 2.65 (s, 3H), 2.45 (m, 1H), 2.09 (m, 1H), 1.87 (t, $J=12.6$ Hz, 1H), 1.62-1.31 (m, 8H), 1.14 (m, 1H), 0.90 (d, $J=6.7$ Hz, 3H), 0.98 (d, $J=6.6$ Hz, 3H), 0.96 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 176.6, 170.2, 138.7, 136.1, 135.7, 129.5, 128.4, 126.5, 73.2, 66.9, 62.6, 44.2, 43.1, 39.5, 35.2, 34.5, 33.7, 32.6, 30.2, 29.7, 26.8, 21.5, 20.0; IR (neat) 3430, 2955, 2930, 2869, 1734, 1630, 1456, 1220, 1077 cm^{-1} ; HRMS (ESI) m/z 452.2786 (calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_4+\text{Na}^+$ 452.2777).

To a solution of alcohol (96 mg) in MeOH (30 mL), $\text{Pd}(\text{OH})_2$ (30 mg, 20% on charcoal) was added. The reaction mixture was hydrogenated under a H_2 filled balloon at 23°C for 12 h. After this period, the reaction mixture was filtered and the filter cake was washed with EtOAc. Evaporation of the solvent under reduced pressure gave a residue which was purified by chromatography over silica gel to provide **20** (82 mg, 85%). $[\alpha]_D^{23}$ -191 (c 1.02, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 7.28 (t, $J=7.2$ Hz, 2H), 7.21 (t, $J=7.3$ Hz, 1H), 7.15 (d, $J=7.1$ Hz, 2H), 5.14 (m, 1H), 3.66 (t, $J=6.4$ Hz, 2H), 3.57 (dd, $J=4.2$, 11.2 Hz, 1H), 3.49 (dd, $J=13.4$, 11.2 Hz, 1H), 3.29 (dd, $J=4.2$, 13.4 Hz, 1H), 2.79 (m, 1H), 2.63 (s, 3H), 1.98 (t, $J=12.5$ Hz, 1H), 1.62-1.34 (m, 12H), 1.11 (d, $J=6.6$ Hz, 3H), 1.02 (m, 2H), 0.89 (d, $J=6.4$ Hz, 6H), 0.85 (m, 1H), 0.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 176.8, 170.2, 138.8, 129.5, 128.4, 126.5, 73.2, 66.9, 62.7, 39.6, 39.1, 37.0, 35.6, 34.4, 33.3, 32.6, 32.3, 31.4, 27.3, 24.0, 22.3, 21.7, 21.4, 18.8; IR (neat) 3434, 3027, 2926, 2856, 1734, 1631, 1457, 1277, 1210, 1076 cm^{-1} ; HRMS (ESI) m/z 454.2931 (calcd for $\text{C}_{26}\text{H}_{41}\text{NO}_4+\text{Na}^+$ 454.2933).

Preparation of Ohira-Bestmann Reagent: To a suspension of NaN₃ (682 mg, 10.5 mmol) in a mixture of acetone (25 mL) and H₂O (25 mL) at 0°C, TsCl (2.0 g, 10.5 mmol) was added. The resulting reaction mixture was stirred for 2 h at 0°C. After this period, 20 mL H₂O was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over Na₂SO₄, and concentrated under reduced pressure to give the crude TsN₃ (1.97g). This product was used for the next reaction.

To a stirred suspension of NaH (400 mg, 60% in oil, 10 mmol) in a mixture of benzene (30 mL) and THF (5 mL) was added (MeO)₂P(O)CH₂CH(O)CH₃ (1.17 mL, 8.5mmol) in benzene (5 mL) in a dropwise manner at 0°C. The mixture was stirred for 1.5 h at 0°C. The reaction mixture was filtered through a Celite pad. The solvent was removed under reduced pressure and crude product was purified by silica gel chromatography (60% EtOAc in Hexanes) to give the Ohira-Bestmann Reagent (1.2 g, 74%). ¹H NMR (CDCl₃, 500 MHz) δ 3.59 (d, J=11.9 Hz, 6H), 2.00 (s, 3H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 189.5, 189.4, 53.3, 26.8 ppm; IR (neat) 3552, 3495, 3300, 3006, 2958, 2854, 2122, 1660, 1272, 1023 cm⁻¹.

Synthetic (-)-Spongidepsin 2. To a stirred solution of alcohol **20** (61.4 mg, 0.14 mmol) in CH₂Cl₂ (2 mL) at 0°C, DMSO (0.26 mL, 3.56 mmol) and DIPEA (0.26 mL, 1.42 mmol) were added. To this solution at 0°C, SO₃·Py complex (112 mg, 0.71 mmol) was added and the resulting reaction mixture was stirred at that temperature for 1 h. the reaction was quenched with saturated aqueous NH₄Cl solution. The layers were separated and the organic layer was washed with brine dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by chromatography over silica gel (25% EtOAc in Hexanes) to provide the aldehyde (56.2 mg, 92%). [α]_D²³ -227.2 (c 0.93, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.77 (t, J=1.4 Hz, 1H), 7.28 (m, 2H), 7.22 (m, 1H), 7.15 (d, J=7.1 Hz, 2H), 5.15 (m, 1H), 3.58 (ddd, J=2, 4.2, 11.1 Hz, 1H), 3.40 (dd, J=13.6, 11.2 Hz, 1H), 3.29 (dd, J=13.6, 4.2 Hz, 1H), 2.80 (m, 1H),

2.63 (s, 3H), 2.49 (m, 1H), 2.38 (m, 1H), 1.98 (t, $J=12.5$ Hz, 1H), 1.66-1.51 (m, 7H), 1.43 (m, 1H), 1.32 (m, 1H), 1.11 (d, $J=6.6$ Hz, 3H), 1.01 (m, 2H), 0.88 (d, $J=6.4$ Hz, 6H), 0.83 (m, 1H), 0.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 202.2, 176.8, 170.1, 138.7, 129.4, 128.4, 126.5, 72.6, 66.8, 43.6, 39.6, 39.1, 37.0, 35.1, 34.4, 33.3, 32.2, 31.4, 27.3, 24.0, 22.3, 21.4, 18.8, 17.8; IR (neat) 2955, 2925, 2853, 2734, 1638, 1454, 1211, 1173 cm^{-1} ; HRMS (ESI) m/z 452.2774 (calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_4+\text{Na}^+$ 452.2777).

Above aldehyde (33.7 mg, 0.08 mmol) and Ohira-Bestmann reagent (213 mg, 1.06 mmol) were dissolved in MeOH (20 mL) at 23°C. To this mixture, K_2CO_3 (136 mg, 0.94 mmol) was added at 23°C. The reaction mixture was stirred at 23°C for 2 h. After this period, the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The resulting residue was purified by chromatography over silica gel to provide synthetic spongidepsin **2** (29.3 mg, 88%). $[\alpha]_D^{23}$ -198 (c 0.29, CH_3OH); ^1H NMR (CD_3OD , 500 MHz) δ 7.28 (t, $J=7.3$ Hz, 2H), 7.22 (t, $J=7.3$ Hz, 1H), 7.18 (d, $J=7.0$ Hz, 2H), 5.15 (m, 1H), 3.98 (dd, $J=4.8, 11.1$ Hz, 1H), 3.40 (dd, $J=11.2, 13.6$ Hz, 1H), 3.24 (dd, $J=4.7, 13.6$ Hz, 1H), 2.92 (m, 1H), 2.71 (s, 3H), 2.24 (m, 1H), 2.22 (m, 1H), 1.90 (m, 1H), 1.66 (m, 4H), 1.54 (m, 4H), 1.38 (m, 1H), 1.07 (d, $J=6.6$ Hz, 3H), 1.05 (m, 1H), 0.92 (d, $J=6.4$ Hz, 3H), 0.87 (d, $J=6.3$ Hz, 3H), 0.77 (m, 1H); ^{13}C NMR (CD_3OD , 125 MHz) δ 181.9, 174.4, 142.1, 133.1, 132.0, 130.2, 87.2, 76.5, 72.5, 70.1, 42.9, 42.8, 40.5, 38.3, 37.8, 37.0, 35.9, 35.0, 30.9, 28.0, 27.7, 25.0, 24.2, 21.5; IR (neat) 3027, 2955, 2872, 2852, 2359, 2340, 1736, 1640, 1455, 1275, 1210, 1172, 1071 cm^{-1} ; HRMS (ESI) m/z 448.2835 (calcd for $\text{C}_{29}\text{H}_{39}\text{NO}_4+\text{Na}^+$ 448.2828).

Compound 21 (2S,4S,7R,9R,16S). ^1H NMR (CDCl_3 , 500 MHz) δ 7.26-7.23 (m, 4H), 7.18 (m, 1H), 5.89 (dd, $J=8.1, 8.6$ Hz, 1H), 4.81 (m, 1H), 3.23 (dd, $J=8.9, 14.0$ Hz, 1H), 2.95 (s, 3H), 2.89 (dd, $J=7.8, 14.0$ Hz, 1H), 2.09-2.00 (m, 2H), 1.91 (t, $J=2.6$ Hz, 1H), 1.75 (m, 1H), 1.63-1.52 (m, 4H), 1.25-1.02 (m, 9H), 0.96 (d, $J=6.7$ Hz, 3H), 0.88 (d, $J=6.0$ Hz, 3H), 0.85 (d, $J=6.4$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz) δ 178.2, 171.0, 136.9, 129.6, 128.8, 127.0, 84.4, 75.0, 69.0, 55.7, 44.8, 41.0, 35.0, 34.6, 34.4, 34.1, 33.7, 30.9, 30.6, 29.3, 24.1, 22.1, 20.6, 19.6, 18.5 ppm; $[\alpha]_D^{23}$ -97.0 (c 0.65, CHCl_3); HRMS (ESI) m/z 448.2808 (calcd for $\text{C}_{29}\text{H}_{39}\text{NO}_4+\text{Na}^+$ 448.2828).

Compound 22 (2S,4S,7R,9S,16S). ¹H NMR (CDCl₃, 500 MHz) δ 7.26-7.05 (m, 5H), 5.96 (dd, J=4.9, 12.2 Hz, 1H), 5.03 (m, 1H), 3.56 (dd, J=5.0, 15.3 Hz, 1H), 2.92 (dd, J=12.4, 15.2 Hz, 1H), 2.89 (s, 3H), 2.56 (m, 1H), 2.25 (m, 2H), 1.98 (t, J=2.5 Hz, 1H), 1.80 (m, 2H), 1.74 (m, 2H), 1.57-1.18 (m, 9H), 0.92 (d, J=6.8 Hz, 3H), 0.88 (m, 1H), 0.85 (d, J=6.6 Hz, 3H), 0.73 (d, J=6.8 Hz, 3H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 179.0, 171.9, 137.2, 128.8, 127.0, 84.3, 75.1, 69.3, 56.2, 43.2, 37.4, 36.1, 35.3, 35.1, 34.5, 31.9, 31.7, 30.1, 29.1, 25.2, 23.1, 21.7, 20.4, 18.8 ppm; [α]_D²³ -24.0 (c 0.24, CHCl₃); HRMS (ESI) m/z 464.2565 (calcd for C₂₉H₃₉NO₄+K⁺ 464.2567).

Compound 23 (2S,4S,7S,9R,16S). ¹H NMR (CDCl₃, 500 MHz) δ 7.26-7.17 (m, 5H), 5.85 (dd, J=8.3, 3.4 Hz, 1H), 4.96 (m, 1H), 3.21 (dd, J=8.0, 14.2 Hz, 1H), 2.93 (s, 3H), 2.89 (dd, J= 8.7, 14.2 Hz, 1H), 2.61 (m, 1H), 2.11 (m, 2H), 1.94 (t, J=2.6 Hz, 1H), 1.80 (dt, J=10.0, 13.7Hz, 1H), 1.63-1.57 (m, 4H), 1.41-1.15 (m, 8H), 0.91 (d, J=6.9 Hz, 3H), 0.88 (m, 1H), 0.85 (d, J=6.9 Hz, 3H), 0.84 (d, J=7.2 Hz, 3H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 177.8, 170.9, 136.9, 129.6, 128.7, 127.0, 84.4, 73.5, 69.1, 55.6, 44.1, 39.8, 36.2, 36.1, 35.1, 34.6, 34.3, 32.7, 31.0, 29.2, 24.6, 23.6, 22.3, 20.0, 18.6 ppm; [α]_D²³ -86.5 (c 0.84, CHCl₃); HRMS (ESI) m/z 448.2822 (calcd for C₂₉H₃₉NO₄+Na⁺ 448.2828).

Compound 24 (2R,4R,7R,9S,16S). ^1H NMR (CDCl_3 , 500 MHz) δ 7.30-7.16 (m, 5H), 5.05 (m, 1H), 4.78 (dd, $J=3.6, 11.3$ Hz, 1H), 3.48 (dd, $J=3.5, 14.3$ Hz, 1H), 2.98 (dd, $J=11.3, 14.2$ Hz, 1H), 2.93 (s, 3H), 2.24 (m, 3H), 1.98 (t, $J=2.6$ Hz, 1H), 1.83 (m, 1H), 1.79-1.45 (m, 6H), 1.40-1.05 (m, 6H), 0.92 (d, $J=6.9$ Hz, 3H), 0.88 (m, 1H), 0.84 (d, $J=6.6$ Hz, 3H), 0.36 (d, $J=6.7$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz) δ 179.0, 170.2, 137.1, 129.1, 128.9, 127.1, 83.6, 73.4, 69.0, 63.0, 42.6, 37.3, 35.8, 35.6, 34.9, 33.7, 33.6, 32.4, 31.0, 30.0, 24.3, 22.0, 21.8, 20.1, 18.3 ppm; $[\alpha]_D^{23}$ -45.1 (c 0.42, CHCl_3); HRMS (ESI) m/z 448.2830 (calcd for $\text{C}_{29}\text{H}_{39}\text{NO}_4 + \text{Na}^+$ 448.2828).

^1H NMR (600MHz, CD_3OD)
of natural Spongidepsin
(From Prof. Riccio)

^1H NMR (500MHz, CD_3OD)
of synthetic Spongidepsin

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(2S,4S,7R,9R,16S)