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Total Synthesis and Structural Assignment of Spongidepsin via a Stereodivergent RCM Strategy

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General: Unless noted otherwise, all oxygen and moisture-sensitive reactions were executed in oven-dried glassware sealed under a positive pressure of dry argon or nitrogen and moisture-sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. Unless stated otherwise, all commercial reagents were used as received. All reaction solvents were dried under nitrogen atmosphere: THF and diethyl ether were distilled over Na-benzophenone; CH_2Cl_2, Et_3N, and pyridine were distilled from CaH_2. Flash chromatography was performed using Baker Flash silica gel 60 (40 μM); analytical TLC was performed using 0.25 mm EM silica gel 60 F_{254} plates that were visualized by irradiation (254 nm) or by staining (450 mL of 95% EtOH, 25 mL conc. H_2SO_4, 15 mL acetic acid, and 25 mL anisaldehyde). Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. IR spectra were recorded using a Perkin-Elmer 683 infrared spectrophotometer. NMR spectra were obtained using INOVA 500 and 300 MHz Varian instruments. High-resolution mass spectrometric data were obtained using a VG Analytical Sector-Field or Bruker BioTOF II (ESI) mass spectrometers.

(*S*)-1-(4-Methoxy-benzyloxy)-5-methyl-hex-5-en-3-ol (8). To a suspension of Mg (0.47 g, 19 mmol) in THF (5 mL) was added 1,2-dibromoethane (100 μL) and 2-bromopropene (1.28 mL, 14.4 mmol). The mixture was heated at reflux for 15 min. After the mixture was cooled to rt, it was transferred dropwise to a solution of epoxide **6** (1.00 g, 4.8 mmol) and CuI (0.47 g, 2.4 mmol) in THF (10 mL) at -60 ºC. The reaction mixture was maintained at -60 ºC for 30 min before saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was extracted with diethyl ether (20 mL) and the organic layer was washed with brine (10 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 7:1, v/v) of the residue gave **8** (1.03 g, 86%) as a colorless oil: R_f 0.31 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ –3.56, (*c* 1.79, $CHCl_3$); IR (neat, cm^{-1}) 3450, 2936, 2862, 1613, 1514, 1248, 1093, 1035, 821; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.7 Hz, 2H), 6.88 (d, *J*=8.7 Hz, 2H), 4.84 (m, 1H), 4.77 (m, 1H), 4.46 (s, 2H), 3.96 (m, 1H), 3.79 (s, 3H), 3.69

(m, 1H), 3.62 (m, 1H), 2.79 (br, 1H), 2.22 (dd, *J*=7.5, 13.5 Hz, 1H), 2.16 (dd, *J*=5.5, 13.5 Hz, 1H), 1.76 (s, 3H), 1.74 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 159.0, 142.6, 129.9, 129.2, 113.6, 112.9, 72.8, 68.3, 68.2, 55.1, 45.9, 36.1, 22.4; HRMS (ESI) calcd for $[C_{15}H_{22}O_3Na]^+$ 273.1461, found 273.1479.

(*S*)-{1-[2-(4-methoxy-benzyloxy)-ethyl]-3-methyl-but-3-enyloxy}-triethylsilane (9). To a solution of alcohol **8** (400 mg, 1.6 mmol) in CH_2Cl_2 (8 mL) was added imidazole (0.327 g, 4.8 mmol), 4-dimethylaminopyridine (19.5 mg, 0.16 mmol) and triethylsilyl chloride (0.40 mL, 2.4 mmol). The resulting reaction mixture was stirred at rt for 30 min before water (10 mL) was added. The mixture was extracted with diethyl ether (15 mL) and the organic layer was washed with brine (5 mL). The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Silica gel column chromatography (hexanes-ethyl acetate, 25:1, v/v) of the residue gave the corresponding silyl ether **9** (565 mg, 97%) as a colorless oil: R_f 0.81 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ –6.27, (*c* 1.72, $CHCl_3$); IR (neat, cm^{-1}) 2953, 2876, 1514, 1248, 1098, 1040, 1009, 743; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.7 Hz, 2H), 6.88 (d, *J*=8.7 Hz, 2H), 4.78 (m, 1H), 4.72 (m, 1H), 4.44 (dd, *J*=11.7, 15 Hz, 2H), 4.01 (m, 1H), 3.82 (s, 3H), 3.55 (m, 2H), 2.24 (dd, *J*=5.4, 13.2 Hz, 1H), 2.15 (dd, *J*=7.5, 13.2 Hz, 1H), 1.85 (m, 1H), 1.74 (s, 3H), 1.64 (m, 1H), 0.97 (t, *J*=7.8 Hz, 9H), 0.61 (q, *J*=7.8 Hz, 6H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 158.9, 142.4, 130.6, 129.0, 113.6, 112.9, 72.4, 67.9, 66.7, 55.1, 46.5, 36.7, 22.9, 6.8, 4.9; HRMS (ESI) calcd for $[C_{21}H_{36}O_3SiNa]^+$ 387.2328, found 387.2336.

Alcohols (10a and **10b)**. To a solution of alkene **9** (0.528 g, 1.45 mmol) in THF (14 mL) was added BH_3-THF complex (1.0 M in THF, 3.2 mL, 3.19 mmol) at 0 ºC. The resulting reaction mixture was maintained at the same temperature for 2 h before NaOH (3 M in H_2O, 3.5 mL) and H_2O_2 (2 mL) were added. The mixture was allowed to stir at 0 ºC for another 2 h before it was partitioned between Et_2O (20 mL) and brine (15 mL). The aqueous layer was extracted with diethyl ether (4 x 20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Silica gel column chromatography (hexanes-ethyl acetate, 4:1, v/v) of the residue gave two inseparable

diastereoisomers **10a** and **10b** in a 1:1 ratio (526 mg, 95% combined) as a colorless oil: R_f 0.21 (hexanes-ethyl acetate, 4:1, v/v); IR (neat, cm^{-1}) 3352, 2958, 2934, 1514, 1464, 1248, 1073, 1042; ^{1}HNMR(500 MHz, $CDCl_3$) δ 7.25 (d, *J*=8 Hz, 1H), 7.24 (d, *J*=8 Hz, 1H), 6.88 (d, *J*=8 Hz, 1H), 6.87 (d, *J*=8 Hz, 1H), 4.40 (m, 2H), 4.02 (m, 0.5H), 3.92 (m, 0.5H), 3.78 (s, 3H), 3.48 (m, 2H), 3.44 (m, 0.5H), 3.40 (m, 1H), 3.31 (m, 0.5H), 2.09 (br, 1H), 1.79 (m, 2H), 1.49 (m, 2H), 1.22 (m, 1H), 0.94 (t, *J*=7 Hz, 4.5H), 0.93 (t, *J*=7 Hz, 4.5H), 0.88 (d, *J*=7 Hz, 1.5H), 0.83 (d, *J*=7 Hz, 1.5H), 0.61 (q, *J*=7 Hz, 3H), 0.57 (q, *J*=7 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 159.14, 159.12, 130.50, 130.45, 129.35, 129.30, 113.85, 113.73, 72.66, 72.64, 68.63, 68.50, 68.38, 68.27, 66.61, 62.54, 55.25, 42.61, 41.32, 38.03, 36.03, 34.82, 32.51, 31.89, 18.9, 18.29, 17.27, 13.85, 6.92, 6.82, 5.10, 4.82; HRMS (ESI) calcd for $[C_{21}H_{38}O_4SiNa]^+$ 405.2433, found 405.2426.

(3*R*,5*R/S*)-1-(4-Methoxy-benzyloxy)-5-methyl-hept-6-en-3-ol (12a and **12b)**. To a solution of **10a** and **10b** (ca. 1:1, mol/mol, 0.46 g, 1.2 mmol) in CH_2Cl_2 (12 mL) was added 4 Å MS (600 mg), 4-methyl morpholine *N*-oxide (0.212 g, 1.8 mmol) and tetra-*n*-propylammonium perruthenate (42.2 mg, 0.096 mmol) at rt. The resulting mixture was allowed to stir at rt for 10 min before it was passed through a pad of silica gel. The filtrate was concentrated for next step without further purification. The resulting aldehyde was dissolved in CH_2Cl_2 (5 mL) and treated with excess Lombardo's reagent (Zn, CH_2Br_2, $TiCl_4$)[1] at rt for 10 min before ethyl ether (20 mL) and saturated aqueous $NaHCO_3$ solution (10 mL) were added. The resulting mixture was allowed to stir until the two layers were separated. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was redissolved in THF (5 mL) and tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.8 mL) was added. The reaction mixture was allowed to stir at rt for 30 min before water (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 4:1, v/v) of the resulting residue gave two inseparable diastereoisomers **12a** and **12b** (1:1, mol/mol, 0.235 g, 74% over three steps) as a colorless oil: R_f 0.23 (hexanes:ethyl acetate, 4:1, v/v); IR (neat, cm^{-1}) 3443, 2955, 2932, 1613,

1514, 1248, 1093, 1036; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J*=8 Hz, 2H), 6.88 (d, *J*=8 Hz, 2H), 5.77 (ddd, *J*=8, 10.5, 17 Hz, 0.5H), 5.66 (ddd, *J*=8, 10.5, 17 Hz, 0.5H), 4.97 (m, 2H), 4.46 (s, 1H), 4.44 (s, 1H), 3.85 (m, 1H), 3.81 (s, 1.5H), 3.79 (s, 1.5H), 3.69 (m, 1H), 3.62 (m, 1H), 2.81 (br, 1H), 2.41 (m, 0.5H), 2.32 (m, 0.5H), 1.73 (m, 2H), 1.57 (m, 0.5H), 1.49 (m, 0.5H), 1.32 (m, 1H), 1.02 (d, *J*=6 Hz, 1.5H), 1.01 (d, *J*=6 Hz, 1.5H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 159.3, 144.9, 144.2, 130.1, 129.3, 129.2, 113.8, 113.3, 112.5, 73.0, 72.9, 69.5, 69.2, 68.8, 55.3, 44.4, 44.2, 36.9, 36.6, 34.7, 34.5, 21.2, 20.0; HRMS (ESI) calcd for $[C_{16}H_{24}O_3Na]^+$ 287.1618, found 287.1612.

2-(tert-Butoxycarbonyl-methyl-amino)-(S)-3-phenyl-propionic acid 1-[2-(4-methoxy-benzyloxy)-ethyl]-3-methyl-pent-4-enyl ester (13a and **13b)**. To a solution of triphenyl phosphine (89 mg, 0.34 mmol) in THF (3 mL) was added di-*iso*-propyl azadicarboxylate (68 μL, 0.34 mmol). The resulting mixture was allowed to stir at rt for 10 min before a solution of **12a** and **12b** (1:1, mol/mol, 29.9 mg, 0.113 mmol) in THF (1 mL) was added. After stirring at rt for 10 min, *N*-methyl-*N*-Boc phenylalanine (47.4 mg, 0.136 mmol) was added. The mixture was stirred at rt for 10 min before saturated aqueous $NaHCO_3$ solution (5 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 12:1, v/v) of the resulting residue gave two inseparable diastereoisomers **13a** and **13b** (54 mg, 91%, 7*R* and 7*S* epimers in a 1:1 ratio and as *N*-carbamate rotamers) as a colorless oil: R_f 0.46 (hexanes-ethyl acetate, 4:1, v/v); IR (neat, cm^{-1}) 2971, 2930, 1737, 1697, 1513, 1248, 1173, 1036; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.16-7.29 (m, 7H), 6.88 (m, 2H), 5.71 (m, 1H), 5.15 (m, 1H), 4.99 (m, 2H), 4.81 (m, 1H), 4.39 (s, 1H), 4.37 (s, 1H), 3.79 (s, 3H), 3.41 (m, 2H), 3.22 (m, 1H), 2.92 (m, 1H), 2.75 (m, 3H), 2.18 (m, 1H), 1.85 (m, 2H), 1.72 (m, 1H), 1.68 (m, 1H), 1.38 (m, 4.5H), 1.31 (m, 4.5H), 1.01 (m, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 170.4, 158.9, 155.5, 143.7, 143.4, 142.9, 137.3, 130.3, 130.1, 129.2, 128.8, 128.7, 128.3, 128.1, 126.4, 126.3, 113.6, 112.9, 112.7, 79.9, 79.6, 72.5, 71.5, 71.3, 71.2, 70.9, 66.6, 66.1, 60.5, 60.2, 59.5, 55.1, 41.3, 40.9, 35.4, 34.9, 34.8, 34.7, 34.3, 34.1, 31.8, 28.1, 28.0, 20.6, 20.5, 20.2, 19.9; HRMS (ESI) calcd for $[C_{31}H_{43}NO_6Na]^+$ 548.2983, found 548.2984.

2-Methylamino-3-phenyl-propionic acid 1-[2-(4-methoxy-benzyloxy)-ethyl]-3-methyl-pent-4-enyl ester (4a and **4b)**. To a solution of **13a** and **13b** (1:1, mol/mol, 13 mg, 25.4 μmol) in CH_2Cl_2 (0.75 mL) was added 2,6-lutidine (9.9 μL 76.2 μmol) and *tert*-butyldimethylsilyl trifluromethane sulfonate (11.6 μL, 51 μmol) at rt. The resulting reaction mixture was allowed to stir for 1.5 h before saturated aqueous NH_4Cl solution (1 mL) was added. The aqueous mixture was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in THF (1 mL) and was treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 26 μL). The reaction mixture was allowed to stir at rt for 1 h before saturated aqueous NH_4Cl solution (1 mL) was added. The aqueous mixture was extracted with ethyl acetate (8 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 2:1, v/v) of the resulting residue gave two inseparable diastereomeric amines **4a** and **4b** (9.2 mg, 85%, 7*R* and 7*S* epimers in a 1:1 ratio) as a colorless oil: R_f 0.14 (hexanes-ethyl acetate, 2:1, v/v); IR (neat, cm^{-1}) 2957, 2859, 1728, 1613, 1513, 1248, 1179, 1096; ^{1}HNMR(500 MHz, $CDCl_3$) δ 7.26 (m, 5H), 7.20 (m, 2H), 6.86 (m, 2H), 5.69 (ddd, *J*=7, 10, 17 Hz, 0.5H), 5.62 (ddd, *J*=7, 10.5 Hz, 0.5H), 5.11 (m, 1H), 4.95 (m, 2H), 4.36 (m, 2H), 3.79 (s, 3H), 3.40 (m, 1H), 3.27 (m, 2H), 2.90 (m, 3H), 2.35 (s, 1.5H), 2.33 (s, 1.5H), 2.14 (m, 1H), 1.75 (m, 2H), 1.65 (m, 1H), 1.44 (m, 1H), 0.99 (d, *J*=7 Hz, 1.5H), 0.98 (d, *J*=7 Hz, 1.5H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 174.1, 174.0, 159.2, 143.8, 143.2, 137.4, 137.3, 130.5, 129.4, 129.3, 129.2, 128.5, 126.7, 113.8, 112.9, 72.7, 71.2, 70.9, 66.2, 66.1, 64.8, 63.7, 55.3, 41.3, 40.9, 39.5, 34.8, 34.7, 34.6, 34.5, 34.3, 20.8, 19.9; HRMS (ESI) calcd for $[C_{26}H_{35}NO_4Na]^+$ 448.2458, found 448.2452.

5-(tert-Butyl-diphenyl-silanyloxy)-2,4-dimethyl-pentan-1-ol (15). To a solution of alcohol **7** (0.21 g, 1.2 mmol) in CH_2Cl_2 (12 mL) was added imidazole (0.164 g, 2.42 mmol), 4-*N,N*-dimethylaminopyridine (14.7 mg, 0.121 mmol) and *tert*-butyldiphenylsilyl chloride (0.47 mL, 1.8 mmol) at rt. The resulting reaction mixture was allowed to stir at rt for 1.5 h before diethyl ether (20 mL) and water (10 mL) were added. The aqueous mixture was extracted with ethyl ether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was redissolved in a

suspension of K_2CO_3 (0.333 g, 2.42 mmol) in methanol (6 mL) at rt. The reaction mixture was stirred at rt for 4 h before it was partitioned between diethyl ether (20 mL) and saturated aqueous NH_4Cl solution (5 mL). The aqueous mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 8:1, v/v) of the resulting residue gave alcohol **15** (363 mg, 81% over two steps) as a colorless oil: R_f 0.39 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +1.1 (*c* 0.72, $CHCl_3$); IR (neat, cm^{-1}) 3351, 2957, 2932, 1472, 1428, 1112, 739, 704; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.42 (m, 6H), 3.53 (dd, *J*=4.5, 10 Hz, 1H), 3.48 (dd, *J*=5, 10 Hz, 1H), 3.44 (dd, *J*=6.5, 10 Hz, 1H), 3.36 (dd, *J*=7, 10.5 Hz, 1H), 1.76 (m, 1H), 1.65 (m, 1H), 1.46 (m, 2H), 1.43 (br, 1H), 1.08 (s, 9H), 0.96 (d, *J*=7 Hz, 3H), 0.90 (d, *J*=7 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 135.7, 134.8, 129.6, 127.6, 68.7, 68.3, 37.2, 33.1, 26.9, 19.3, 17.9, 17.5; HRMS (ESI) calcd for $[C_{23}H_{34}O_4SiNa]^+$ 393.2300, found 393.2287.

(*2R*,*4R*)-*2*,4-Dimethyl-hex-5-en-1-ol (17b). To a solution of alcohol **15** (0.184 g, 0.497 mmol) in CH_2Cl_2 (5 mL) was added 4 Å MS (249 mg), 4-methylmorpholine *N*-oxide (87.6 mg, 0.746 mmol) and tetra-*n*-propylammonium perruthenate (14.0 mg, 40 μmol) at rt. The resulting mixture was allowed to stir at rt for 10 min before it was passed through a pad of silica gel and concentrated. The residual aldehyde was dissolved in CH_2Cl_2 (2 mL) and an excess of Lombardo's reagent (Zn, CH_2Br_2, $TiCl_4$)[1] was added. After stirring at rt for 10 min, diethyl ether (10 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) were added. The resulting mixture was allowed to stir until two layers separated. The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was redissolved in THF (2.5 mL) and tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.75 mL) was added. The reaction mixture was allowed to stir at rt for 3 h before water (5 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 7:1, v/v) of the residue gave alkene **17b** (37 mg, 58% over three steps) as a colorless oil: R_f 0.42 (hexanes-ethyl

acetate, 4:1, v/v); $[\alpha]_D^{25}$ +11.2 (*c* 1.35, $CHCl_3$); IR (neat, cm^{-1}) 3345, 2960, 2923, 1418, 1034, 995, 910; ^{1}HNMR (500 MHz, $CDCl_3$) δ 5.62 (ddd, *J*=8.4, 9.9, 17.4 Hz, 1H), 4.94 (m, 2H), 3.44 (m, 3H), 2.23 (m, 1H), 1.68 (m, 1H), 1.38 (m, 1H), 1.07 (m, 1H), 0.99 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.6 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 144.3, 112.9, 68.7, 40.3, 35.5, 33.4, 21.5, 16.3; HRMS (ESI) calcd for $[C_8H_{16}ONa]^+$ 151.1093, found 151.1091.

(*2R*,*4R*)-*2,4*-Dimethylhex-5-enoic acid (5b). To a solution of alcohol **17b** (37 mg) in acetone (2 mL) was added Jones reagent until a red solution persisted. The red solution was allowed to stir for 30 min before it was titrated with 2-propanol. The mixture was extracted with diethylether (4 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give crude carboxylic acid **5b**, which was used for the next step without further purification.

2-[(2,4-Dimethyl-hex-5-enoyl)-methyl-amino]-3-phenyl-propionic acid 1-[2-(4-methoxy-benzyloxy)-ethyl]-3-methyl-pent-4-enyl ester (3a and **3b)**. To a solution of acid **5b** (4.84 mg, 34.1 μmol) in DMF (0.5 mL) was added di-*iso*-propylethyl amine (17.6 μL, 0.102 mmol) and (7-azabenzotriazole-1-yloxy) tripyrrodino-phosphonium hexafluorophosphate (19.3 mg, 36.92 μmol). The resulting mixture was allowed to stir at rt for 2 min before diastereomeric amine mixtures **4a** and **4b** (12.1 mg, 28.4 μmol) in DMF (0.5 mL) were added. The reaction mixture was stirred at rt for 24 h before it was partitioned between ethyl ether (10 mL) and saturated aqueous $NaHCO_3$ solution (1 mL). The organic layer was washed with brine (2 mL). The combined aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 8:1, v/v) of the resulting residue gave two inseparable amides **3a** and **3b** (1:1, mol/mol, 13.6 mg, 87%) as a colorless oil: R_f 0.69 (hexanes-ethyl acetate, 2:1, v/v); IR (neat, cm^{-1}) 2961, 2866, 1737, 1650, 1644, 1514, 1248, 1094, 914; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.26 (m, 5H), 7.18 (m, 2H), 6.87 (m, 2H), 5.67 (m, 0.5H), 5.61 (m, 0.5H), 5.48 (m, 0.5H), 5.36 (m, 0.5H), 5.13 (m, 1H), 4.98 (m, 2H), 4.83 (m, 2H), 4.39 (s, 1H), 4.38 (s, 1H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.43 (m, 3H), 3.31 (m, 1H), 2.91 (m,

1H), 2.79 (s, 1.5H), 2.77 (s, 1.5H), 2.53 (m, 1H), 2.17 (m, 1H), 1.85 (m, 3H), 1.63 (m, 1H), 1.46 (m, 0.5H), 1.24 (m, 1H), 1.06 (m, 0.5H), 1.04 (d, *J*=7 Hz, 1.5H), 1.03 (d, *J*=7 Hz, 1.5H), 1.01 (d, *J*=7 Hz, 1.5H), 0.99 (d, *J*=7 Hz, 1.5H), 0.95 (m, 0.5H), 0.78 (d, *J*=7 Hz, 1.5H), 0.76 (d, *J*=7 Hz, 1.5H), 0.57 (m, 0.5H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 176.8, 170.4, 158.9, 143.8, 143.6, 142.9, 136.9, 130.2, 129.3, 129.2, 129.0, 128.6, 128.5, 128.2, 126.4, 113.9, 113.7, 113.6, 112.9, 112.8, 71.3, 71.1, 66.1, 66.0, 57.6, 55.1, 41.3, 40.9, 40.0, 35.4, 35.2, 35.1, 34.7, 34.6, 34.2, 33.1, 32.5, 32.4, 21.1, 20.6, 20.2, 20.1, 16.6; HRMS (ESI) calcd for $[C_{34}H_{47}NO_5Na]^+$ 572.3347, found 572.3347.

(2*R*,4*S*,7*S*,9S)-(5*E*)-18a. To a solution of **3a** and **3b** (1:1, mol/mol, 15 mg, 27.3 μmol) in toluene (135 mL) at reflux was added 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexylphosphine) ruthenium[2] (2.44 mg, 2.73 μmol) in toluene (1 mL) via syringe pump over 15 min. Upon completion of catalyst addition, the reaction mixture was placed in a 0° C bath for 20 min. The reaction mixture was then passed through a pad of silica gel and concentrated *in vacuo*. The residue was purified by preparative TLC to afford four macrocyclic alkene isomers (2*R*,4*S*,7*S*,9S)-(5*E*)-**18a** (33%), (2*R*,4*S*,7*R*,9S)-(5*E*)-**18b** (ca. 33%), (2*R*,4*S*,7*S*,9S)-(5*Z*)-**18zs** (ca. 3%) and (2*R*,4*S*,7*R*,9S)-(5*Z*)-**18zr** (ca. 3%). **18a**: R_f 0.57 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{25}$ –84 (*c* 0.58, $CHCl_3$); IR (neat, cm^{-1}) 2960, 1737, 1638, 1514, 1249, 1103, 911, 736; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.06 (d, *J*=7.2 Hz, 2H), 6.89 (d, *J*=9 Hz, 2H), 5.20 (m, 1H), 5.17 (dd, *J*=8, 19 Hz, 1H), 5.14 (dd, *J*=9.5, 19 Hz, 1H), 4.41 (dd, *J*=9.5, 11.5 Hz, 2H), 3.81 (s, 3H), 3.54 (m, 4H), 3.26 (dd, *J*=2, 11.5 Hz, 1H), 2.74 (ddq, *J*=2.5, 6, 13 Hz, 1H), 2.59 (s, 3H), 2.44 (m, 1H), 2.12 (m, 1H), 1.88 (m, 2H), 1.77 (m, 1H), 1.49 (m, 1H), 1.35 (m, 1H), 1.14 (m, 1H), 1.07 (d, *J*=7 Hz, 3H), 0.99 (d, *J*=7 Hz, 3H), 0.96 (d, *J*=7 Hz, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 176.4, 169.9, 158.9, 138.5, 135.9, 135.5, 130.4, 129.3, 129.0, 128.2, 126.3, 113.6, 72.5, 71.2, 67.1, 66.6, 55.1, 44.1, 43.6, 39.2, 35.6, 34.3, 33.5, 30.1, 26.6, 19.8, 19.2, 18.5; HRMS (ESI) calcd for $[C_{32}H_{43}NO_5Na]^+$ 544.3034, found 544.3039.

Diol 22. To a solution of **18a** (14 mg, 0.027 mmol) in CH_2Cl_2 (1 mL), *tert*-butanol (0.1 mL) and pH 7 phosphate buffer (0.1 mL) was added 2,3-dichloro-5,6-dicyanoquinone

(36.5 mg, 0.162 mmol). The reaction flask was immersed in a water-filled sonication bath for 10 min at rt. The reaction mixture was diluted with ethyl acetate (5 mL) before saturated aqueous $NaHCO_3$ solution (2 mL) was added. The aqueous layer was extracted with ethyl acetate (5 x 3 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 3:1, v/v) of the residue gave the corresponding primary alcohol **19** as colorless oil: R_f 0.21 (hexanes-ethyl acetate, 2:1, v/v). The primary alcohol **19** was dissolved in CH_2Cl_2 (1 mL) and imidazole (3.65 mg, 0.054 mmol), *tert*-butyldiphenylsilyl chloride (11.1 mg, 0.041 mmol) and 4-*N,N*-dimethylaminopyridine were added. The reaction mixture was allowed to stir at rt for 3 h before water (1 mL) was added. The aqueous layer was extracted with diethyl ether (5 x 3 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave the corresponding silyl ether **20** as a colorless oil: R_f 0.71 (hexanes-ethyl acetate, 2:1, v/v). Through a -78º C solution of **20** in methanol (1 mL) was bubbled O_3 for 20 min then O_2. After 10 min, $NaBH_4$ (3 mg) was added and the reaction mixture was allowed to stir at -78 ºC for another 10 min before it was warmed to rt slowly. After 2 h, water (0.5 mL) was added and the mixture was extracted with ethyl ether (5 x 3 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude diol **21** as a colorless oil: R_f 0.14 (hexanes-ethyl acetate, 1:2, v/v). To a solution of crude diol **21** in *tert*-butanol (0.3 mL) and water (0.1 mL) was added LiOH (5 mg) at rt. The resultant mixture was stirred at rt for 1 h before it was diluted with ethyl acetate (2 mL) and water (0.5 mL). The separated aqueous layer was extracted with ethyl acetate (5 x 2 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 3:2, v/v) of the residue gave **22** as colorless oil: R_f 0.59 (hexanes-ethyl acetate, 1:2, v/v); ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=7.2 Hz, 4H), 7.42 (t, *J*=7.2 Hz, 2H), 7.39 (t, *J*=7.2 Hz, 4H), 4.04 (m, 1H), 3.88 (m, 2H), 3.57 (dd, *J*=4.5, 11.5 Hz, 1H), 3.42 (dd, *J*=8, 11.5 Hz, 1H), 1.88 (m, 1H), 1.80 (dddd, *J*=6.5, 7.5, 7.5, 14 Hz, 1H), 1.63 (dddd, *J*=2.5, 3.5, 4.5, 14 Hz, 1H), 1.54 (ddd, *J*=7.5, 9.5, 14 Hz, 1H), 1.40 (ddd, *J*=2.5, 5.5, 14 Hz, 1H), 1.05 (s, 9H), 0.93 (d, *J*=7 Hz, 3H).

Lactone 23. To a solution of diol **22** (1.2 mg) in CH_2Cl_2 (0.1 mL) was added iodobenzene diacetate (7 mg) and 2,2,6,6-tetramethyl-1-piperidinyloxy (1 mg) at rt. The resultant mixture was allowed to stir at rt for 3 h before 10% aqueous $NaHSO_3$ solution was added. The aqueous layer was extracted with diethyl ether (5 x 2 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 7:1, v/v) of the resulting residue gave lactone **23** as colorless oil: R_f 0.53 (hexanes-ethyl acetate, 2:1, v/v); ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J*=7.2 Hz, 4H), 7.41 (t, *J*=7.2 Hz, 2H), 7.39 (t, *J*=7.2 Hz, 4H), 4.59 (dddd, *J*=5.5, 5.5, 7.5, 10.5 Hz, 1H), 3.86 (ddd, *J*=5.5, 7.5, 10 Hz, 1H), 3.78 (ddd, *J*=5.5, 5.5, 10.0 Hz, 1H), 2.67 (ddq, *J*=7.0, 8.5, 12.5 Hz, 1H), 2.48 (ddd, *J*=5.5, 8.5, 12.5 Hz, 1H), 1.97 (dddd, *J*=5.5, 5.5, 7.5, 10 Hz, 1H), 1.86 (dddd, *J*=5.5, 5.5, 7.5, 10 Hz, 1H), 1.51 (ddd, *J*=10.5, 12.5, 12.5 Hz, 1H), 1.21 (d, *J*=7 Hz, 3H), 1.05 (s, 9H). The *cis*-relative stereochemistry of **23** was assigned on the basis of positive NOE's between α– and γ-lactone substituents (spectra reproduced in Figure 1. below) and comparison of ^{1}HNMR data with analogous lactones as summarized in Tables 1 and 2 below.

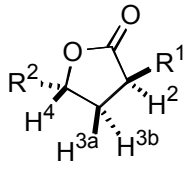

Table 1. Coupling Constants for *trans*-Lactones. [a]

entry	R_1	R_2	*J*(Hz) H_2, H_{3a}	*J*(Hz) H_2, H_{3b}	*J*(Hz) H_{3a}, H_4	*J*(Hz) H_{3b}, H_4	*J*(Hz) H_{3a}, H_{3b}
1	CH_3	C_6H_5	7.0	9.0	7.5	5.5	12.8
2	CH_3	C_6H_5	8.0	8.6	8.1	4.6	12.9
3	CH_3	CH_2OTBS	8.9	9.4	8.9	2.9	12.5
4	CH_3	CH_2OBn	8.8	9.3	8.8	3.2	12.7
5	$CH_2C_6H_5$	C_6H_5	7.5	8.4	7.5	4.3	12.8
6	$CH_2C_6H_5$	C_6H_5	8.1	8.5	8.1	4.2	12.9
7	$CH_2C_6H_5$	CH_2OH	8.7	9.5	8.7	3.6	13.0
8	$CH_2C_6H_5$	CH_2OBn	9.0	9.4	9.0	3.3	12.8

[a] The coupling constant data for comparative *trans*- and *cis*-five-membered lactones were obtained from Myers and McKinstry.[3]

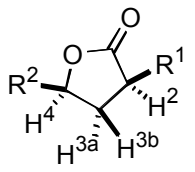

Table 2. Coupling Constants for *cis*-Lactones.[a]

entry	R_1	R_2	*J*(Hz) H_2, H_{3a}	*J*(Hz) H_2, H_{3b}	*J*(Hz) H_{3a}, H_4	*J*(Hz) H_{3b}, H_4	*J*(Hz) H_{3a}, H_{3b}
1	CH_3	C_6H_5	8.1	12.9	5.8	10.8	12.4
2	CH_3	C_6H_5	8.2	11.9	5.5	10.9	11.6
3	CH_3	CH_2OTBS	9.2	11.9	6.3	10.2	12.5
4	CH_3	CH_2OBn	8.9	11.9	6.2	10.3	12.4
5	$CH_2C_6H_5$	C_6H_5	9.3	11.9	5.6	10.6	12.2
6	$CH_2C_6H_5$	C_6H_5	8.0	12.9	5.7	10.6	12.2
7	$CH_2C_6H_5$	CH_2OH	9.0	11.8	6.3	10.0	12.9
8	$CH_2C_6H_5$	CH_2OBn	9.0	11.6	6.3	10.1	12.6
9[b]	*CH_3*	*CH_2CH_2O TBDPS*	*8.5*	*12.5*	*5.5*	*10.5*	*12.5*

[a] The coupling constant data for entries 1-8 were obtained from Myers and McKinstry.[3]
[b]Entry 9 is for lactone **23**, derived from **18a** as detailed above.

3-Benzyl-13-(2-hydroxy-ethyl)-4,6,8,11-tetramethyl-1-oxa-4-aza-cyclotridecane-2,5-dione (2a). To a solution of alkene **18a** (16.6 mg, 31.8 μmol) in ethyl acetate (1 mL) was added Pd (10% on carbon, 10.2 mg, 9.55 μmol). The reaction solution was placed under 1 atm of H_2 for 8 h before it was passed through a pad of silica gel and concentrated *in vacuo*. The residue was purified with silica gel chromatography (hexanes-ethyl acetate, 3:1, v/v) to give alcohol **2a** (11.3 mg, 88%) as colorless oil: R_f 0.22 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{25}$ –159 (*c* 0.31, $CHCl_3$); IR (neat, cm^{-1}) 3485 (br), 2961, 2926, 1733, 1634, 1264, 1053, 759; ^{1}HNMR (500 MHz, CD_3OD) δ 7.31 (t, *J*=7.3 Hz, 2H), 7.25 (t, *J*=7.3 Hz, 1H), 7.21 (d, *J*=7.3 Hz, 2H), 5.25 (q, *J*=6.5 Hz, 1H), 3.99 (dd, *J*=4.8, 11.1 Hz, 1H), 3.60 (t, *J*=6.9 Hz, 2H), 3.41 (dd, *J*=11.1, 13.8 Hz, 1H), 3.24 (dd, *J*=4.8, 13.8 Hz, 1H), 2.95 (m, 1H), 2.71 (s, 3H), 1.91 (m, 1H), 1.79 (m, 2H), 1.68 (m, 1H), 1.66 (m, 1H), 1.56 (m, 1H), 1.55 (m, 1H), 1.43 (m, 1H), 1.08 (d, *J*=7 Hz, 3H), 1.07 (m, 1H), 1.06 (m, 1H), 0.93 (d, *J*=7 Hz, 3H), 0.91 (m, 1H), 0.90 (d, *J*=7 Hz, 3H), 0.79 (m, 1H); ^{13}CNMR (75 MHz, CD_3OD) δ 177.8, 170.4, 138.0, 128.9, 127.9, 126.1, 70.6, 66.1, 58.1, 38.9, 38.8, 38.2, 36.8, 33.7, 32.9, 31.9, 30.9, 26.8, 23.7, 20.9, 20.1, 17.4; HRMS (ESI) calcd

for $[C_{24}H_{37}NO_4Na]^+$ 426.2615, found 426.2636. Macrolides **2b-h** were prepared in similar fashions from RCM products **18b-h** (see text). Comparative ^{1}HNMR data of **2a-h** are summarized in Table 3.

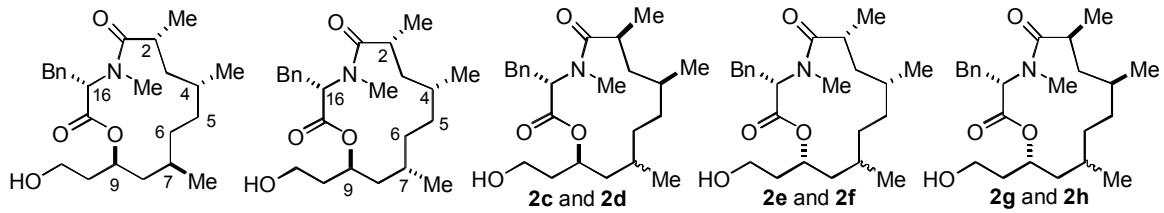

Table 3. Comparison of the eight synthetic macrolide isomers 2a-h with the natural product spongidepsin via ^{1}HNMR spectroscopic data.[a]

Compound	Chemical Shift (ppm) C9-H	Chemical Shift (ppm) C16-H	Chemical Shift (ppm) C24-H	Chemical Shift (ppm) C25-H	Chemical Shift (ppm) C26-H
2a(2*R*, 4*R*, 7*R*, 9*R*, 16*S*)	**5.25**	**3.99**	**1.08**	**0.93**	**0.90**
2b(2*R*, 4*R*, 7*S*, 9*R*, 16*S*)	5.39	4.81	0.99	0.90	0.88
2c(2*S*, 4*S*, 7*R*, 9*R*, 16*S*)	5.10	5.89	0.98	0.89	0.86
2d(2*S*, 4*S*, 7*S*, 9*R*, 16*S*)	4.95	5.79	0.82	0.76	0.75
2e(2*R*, 4*R*, 7*R*, 9*S*, 16*S*)	5.08	4.81	0.94	0.85	0.38
2f(2*R*, 4*R*, 7*S*, 9*S*, 16*S*)	5.22	5.09	0.93	0.84	0.33
2g(2*S*, 4*S*, 7*R*, 9*S*, 16*S*)	5.10	5.57	0.97	0.88	0.85
2h(2*S*, 4*S*, 7*S*, 9*S*, 16*S*)	5.21	5.77	0.95	0.89	0.86
Spongidepsin[4]	**5.18**	**4.00**	**1.10**	**0.95**	**0.92**

[a] Data are of ^{1}HNMR chemical shifts in ppm of selected protons in $CDCl_3$. Data for spongidepsin are from the literature[4] and corroborated by comparison spectra (see Figures 2 and 3 below).

Alkene 25. To a solution of alcohol **2a** (11 mg, 27 μmol) in THF (1 mL) was added sequentially imidazole (9.2 mg, 0.14 mmol), triphenylphosphine (10.8 mg, 40.9 μmol) and iodine (8.4 mg, 33 μmol). The resulting mixture was allowed to stir at rt for 5 min before saturated aqueous $NaHCO_3$ solution (2 mL) was added. The organic layer was washed with brine (1 mL). The combined aqueous phase was extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 15:1, v/v) of the residue gave the corresponding unstable iodide **24** (11.5 mg, 82%). To a

solution of allyl tri-*n*-butyltin (54 mg, 0.16 mmol) and 2,2'-azobisbutyronitrile (17.9 mg, 0.109 mmol) in benzene (1 mL) at reflux was added iodide **24** (11.5 mg) dropwise. The reaction mixture was allowed to stir at reflux for 4 h before it was cooled to rt and concentrated with N_2. The resulting residue was purified with silica gel chromatography (hexanes-ethyl acetate, 15:1, v/v) to give alkene **25** as a colorless oil (9.9 mg, 85%): R_f 0.51 (hexanes-ethyl acetate, 5:1, v/v); $[\alpha]_D^{25}$ -125, (*c* 0.445, $CHCl_3$); IR (neat, cm^{-1}) 2956, 2925, 1737, 1640, 1455, 1224, 1211, 911; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J*=7.5 Hz, 2H), 7.23 (t, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 2H), 5.81 (dddd, *J*=6.5, 7, 10, 17.5 Hz, 1H), 5.15 (q, *J*=6.5 Hz, 1H), 4.99 (dd, *J*=2, 17.5 Hz, 1H), 4.96 (dd, *J*=2, 10 Hz, 1H), 3.57 (dd, *J*=4, 11.5 Hz, 1H), 3.52 (dd, *J*=11.5, 13 Hz, 1H), 3.31 (dd, *J*=3.5, 13 Hz, 1H), 2.80 (ddq, *J*=2.5, 6, 13 Hz, 1H), 2.65 (s, 3H), 2.07 (dd, *J*=7.0, 7.0 Hz, 2H), 1.99 (t, *J*=12 Hz, 1H), 1.65 (m, 1H), 1.59 (m, 3H), 1.55 (m, 3H), 1.41 (m, 2H), 1.34 (m, 1H), 1.12 (d, *J*=7 Hz, 3H), 1.04 (m, 1H), 0.90 (d, *J*=7 Hz, 3H), 0.89 (d, *J*=7 Hz, 3H), 0.88 (m, 1H), 0.77 (ddd, *J*=2, 11, 13 Hz, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 176.6, 169.9, 138.7, 138.4, 129.3, 128.2, 126.3, 114.6, 73.1, 66.8, 39.5, 39.0, 36.8, 35.1, 34.3, 33.6, 33.2, 32.2, 31.3, 30.2, 27.1, 24.6, 23.9, 22.1, 21.2, 18.7; HRMS (ESI) calcd for $[C_{27}H_{41}NO_3Na]^+$ 450.2979, found 450.2985.

(**2*R*,4*R*,7*R*,9*R*,16*S***)-**1**. To a solution of alkene **25** (4.65 mg, 10.9 μmol) in THF (0.5 mL) and water (0.25 mL) was added K_2OsO_4-$2H_2O$ (0.4 mg, 1 μmol) at rt. After 10 min stirring at rt, $NaIO_4$ (13.97 mg, 65.28 μmol) was added. The resulting mixture was allowed to stir at rt for 30 min before it was partitioned between diethyl ether (2 mL) and aqueous pH 7 phosphate buffer (1 mL). The aqueous layer was extracted with diethyl ether (3 x 3 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 8:1, v/v) of the residue gave the corresponding aldehyde in 87% yield. To a solution of aldehyde (4.1 mg, 9.6 μmol) in methanol (0.5 mL) was added K_2CO_3 (3.96 mg, 28.7 μmol) and dimethyl-1-diazo-2-oxopropylphosphonate (3.7 mg, 19.1 μmol). The resulting reaction mixture was allowed to stir at rt for 3 h before saturated aqueous NH_4Cl solution (0.5 mL) was added. The aqueous layer was extracted with diethyl ether (5 x 3 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 15:1, v/v) of the residue gave (2*R*,4*R*,7*R*,9*R*,16*S*)-**1** as an amorphous solid: R_f 0.62 (hexanes-ethyl acetate, 3:1, v/v); $[\alpha]_D^{25}$ –67.3, (*c* 1.00, MeOH) [literature[4] $[\alpha]_D^{25}$ –61.8, (*c* 1.4, MeOH)]; ^{1}HNMR (500 MHz, CD_3OD) δ 7.30 (t, *J*=7.5 Hz, 2H), 7.23 (t, *J*=7.5 Hz, 1H), 7.20 (d, *J*=7.5 Hz, 2H), 5.16 (m, 1H), 3.99 (dd, *J*=5, 11.5 Hz, 1H), 3.40 (dd, *J*=11. 13.5 Hz, 1H), 3.25 (dd, *J*=5, 13.5 Hz, 1H), 2.94 (ddq, *J*=3, 6, 13 Hz, 1H), 2.72 (s, 3H), 2.24 (m, 3H), 1.92 (m, 1H), 1.69 (m, 1H), 1.67 (m, 2H), 1.63 (m, 1H), 1.57 (m, 1H), 1.54 (m, 2H), 1.51 (m, 1H), 1.41 (m, 1H), 1.08 (d, *J*=7 Hz, 3H), 1.07 (m, 1H), 1.06 (m, 1H), 0.93 (d, *J*=7 Hz, 3H), 0.91 (m, 1H), 0.90 (d, *J*=7 Hz, 3H), 0.79 (ddd, *J*=3, 11.5, 14 Hz, 1H); ^{13}CNMR (75 MHz, CD_3OD) δ 179.6, 172.1, 139.7, 130.7, 129.7 127.8, 84.8, 74.1, 70.1, 67.7, 40.6, 40.5, 38.2, 35.9, 35.4, 34.7, 33.6, 32.7, 28.5, 25.7, 25.4, 22.6, 21.8, 19.1, 18.9; HRMS (ESI) calcd for $[C_{27}H_{39}NO_3Na]^+$ 448.2822, found 448.2823. Comparative ^{1}HNMR spectra are provided below.

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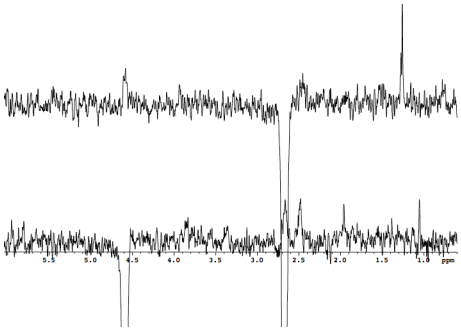

Figure 1. NOE plots for lactone 23.
Top: Irradiation of the resonance of C7-H (δ 2.68) enhanced the resonances of C9-H (δ 4.6). Bottom: Irradiation of the resonance of C9-H (δ 2.68) enhanced the resonances of C7-H (δ 2.68) and C8-H (δ 2.5).

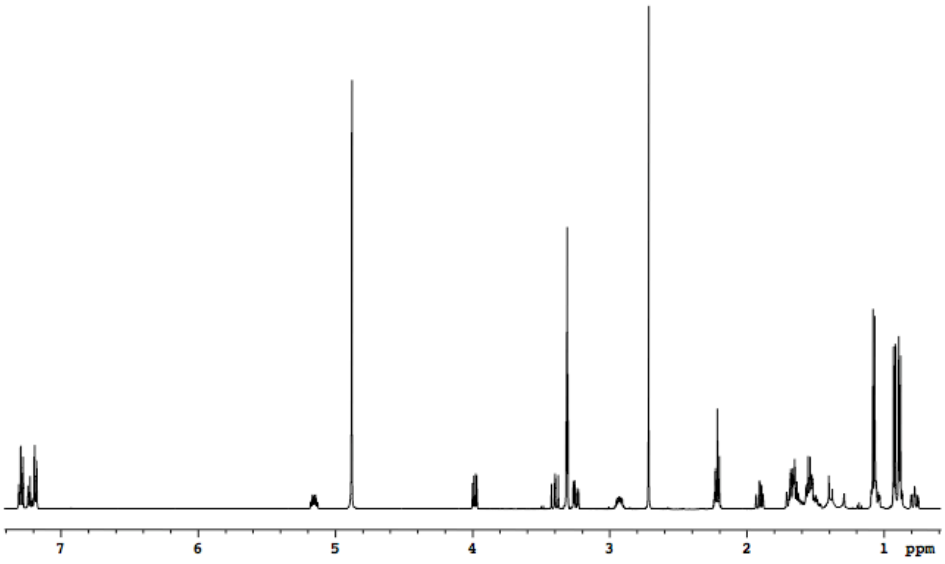

Figure 2. ^{1}**HNMR spectrum of synthetic (2*R*,4*R*,7*R*,9*R*,16*S*)-1**.

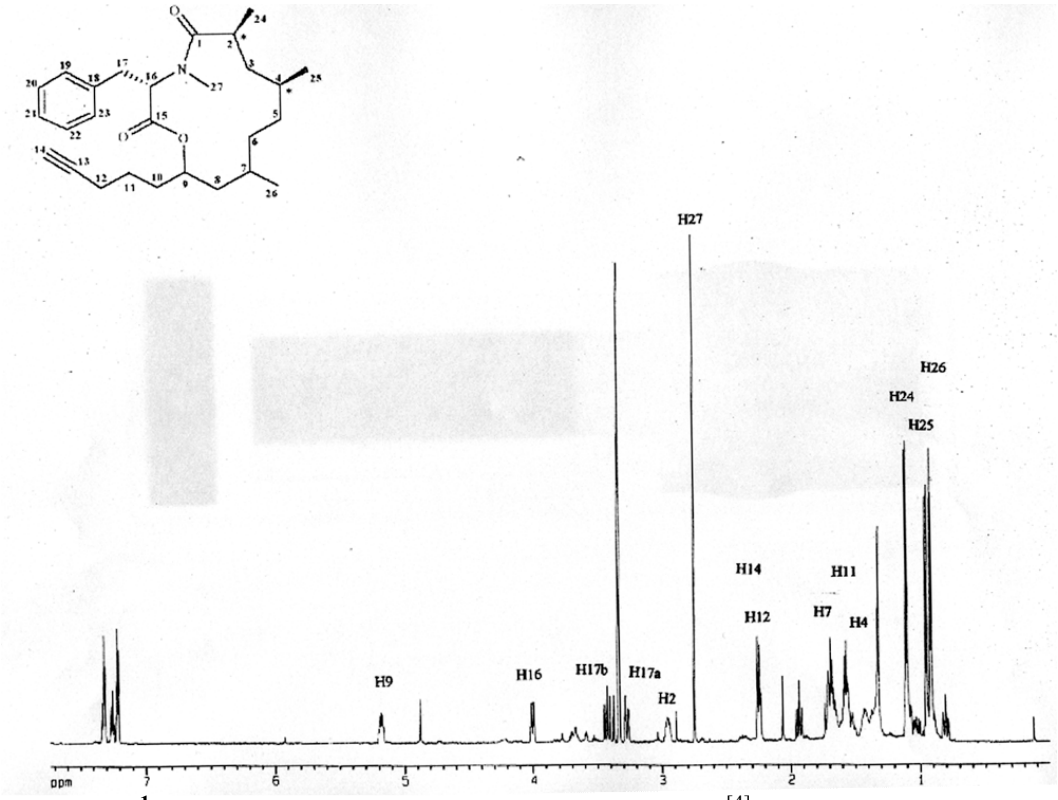

Figure 3. ^{1}**HNMR spectrum of natural spongidepsin**.[4]

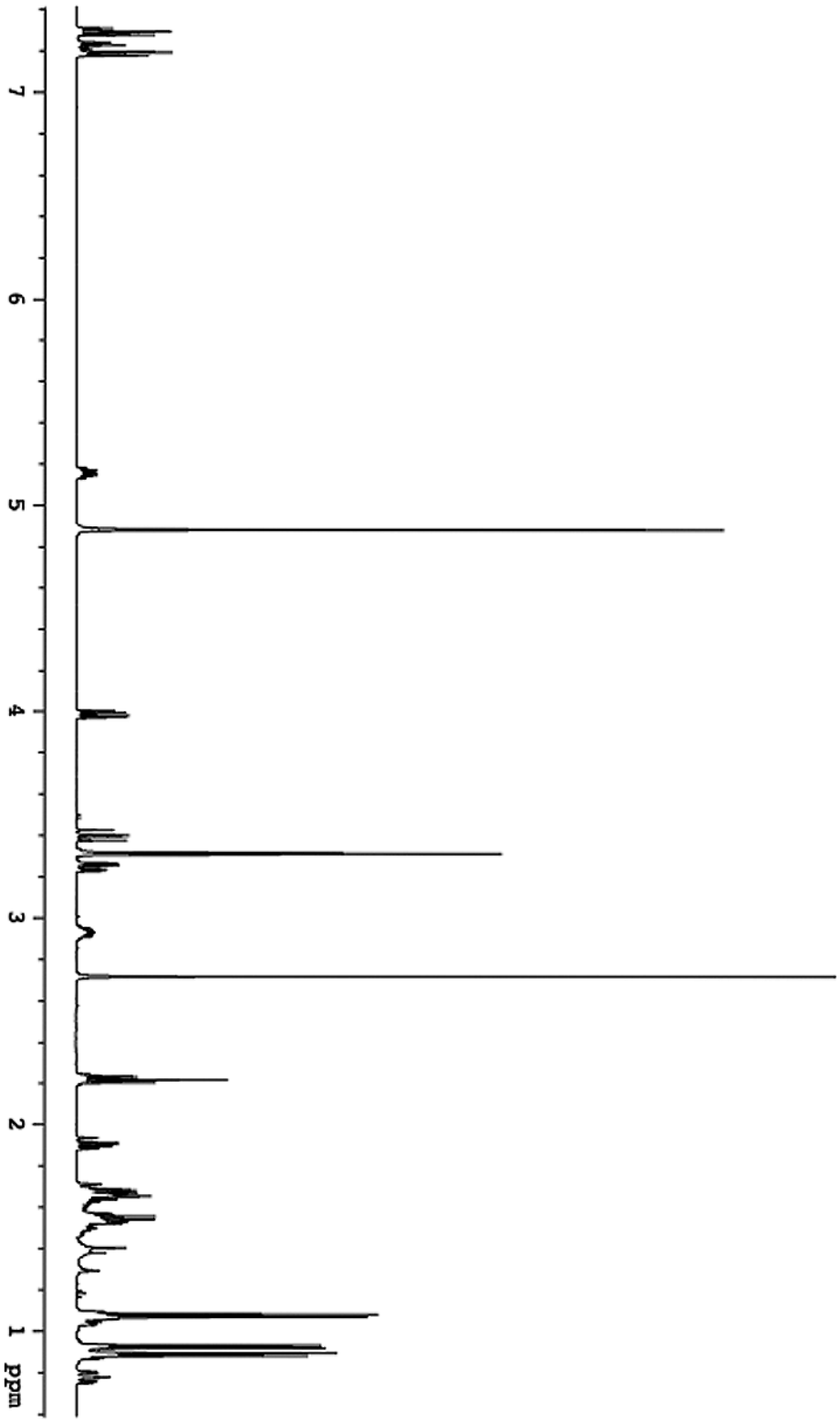

Figure 4. Enlarged ^{1}HNMR spectrum of synthetic (2*R*,4*R*,7*R*,9*R*,16*S*)-1.

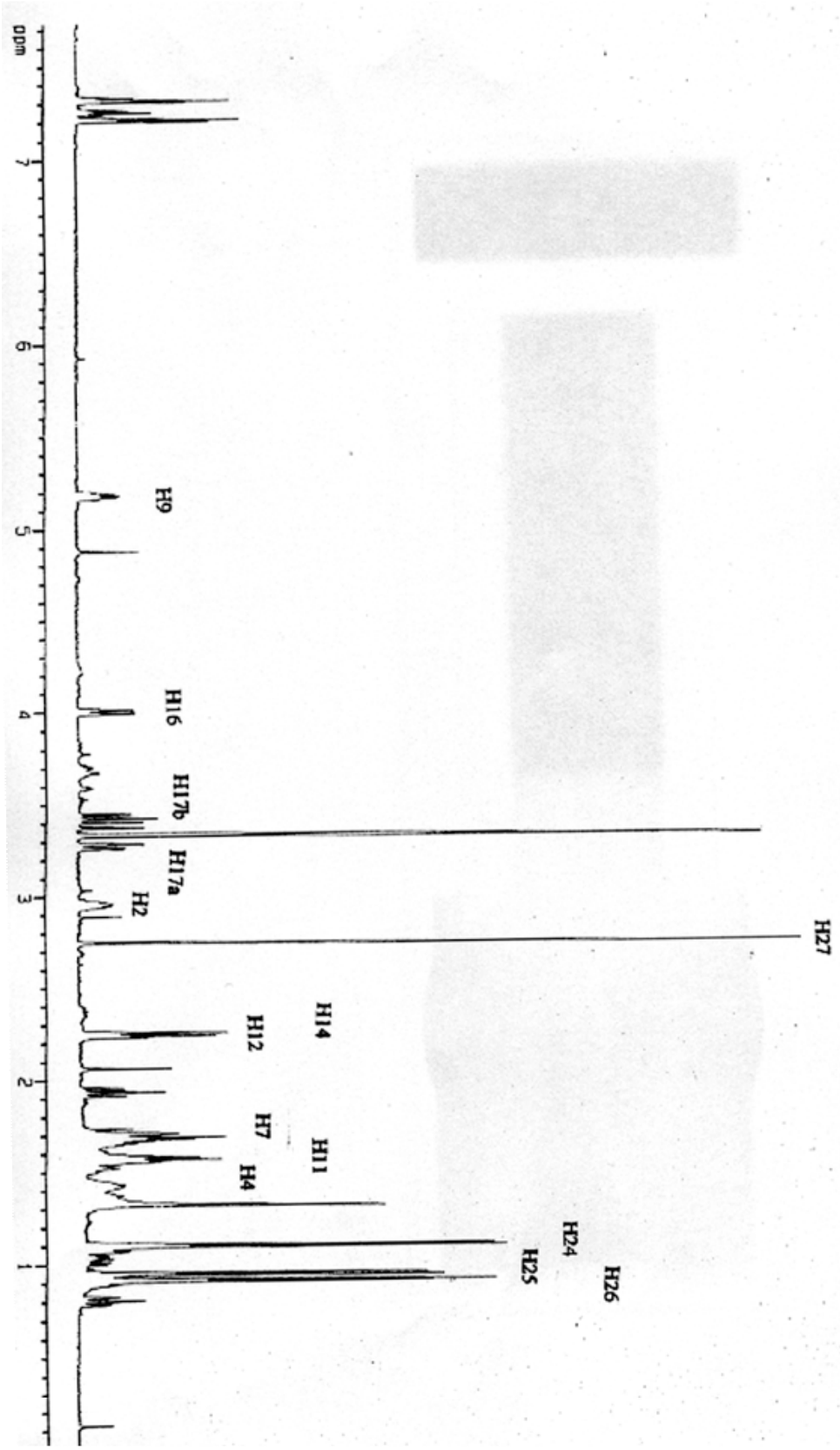

Figure 5. Enlarged ^{1}HNMR spectrum of natural (2*R*,4*R*,7*R*,9*R*,16*S*)-1.