Supporting Information

The Total Synthesis of (+)-Migrastatin

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Analytical Equipment: Optical rotations were measured on a JASCO DIP-370 digital polarimeter at rt. Concentration (*c*) in g/100 ml and solvent are given in parentheses. ¹H- and ¹³C-NMR spectra were recorded on a Bruker AMX-400 MHz or a Bruker Advance DRX-500 MHz spectrometer in CDCl₃ (referenced to 7.26 ppm (δ) for ¹H-NMR and 77.0 ppm for ¹³C-NMR). Coupling constants (*J*) (H,H) are given in Hz, spectral splitting patterns are designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet or more overlapping signals (m), apparent (app), broad signal (br). Low resolution mass spectra (ionspray, a variation of electrospray) were acquired on a Perkin-Elmer Sciex API 100 spectrometer. Samples were introduced by direct infusion. High resolution mass spectra (fast atom bombardment, FAB) were acquired on a Micromass 70-SE-4F spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer as a film in CHCl₃ (NaCl plates). Absorption bands are noted in cm⁻¹.

Compound 4: $[\alpha]_D +31.0^\circ$ (c 1.77, CHCl_3); IR (neat) 3454, 3078, 2982, 2936, 2824, 1643, 1420, 1192, 1102, 992, 973, 925; ^1H -NMR (500 MHz, CDCl_3) δ 5.77-5.71 (m, 2H), 5.36-5.32 (m, 4H), 3.81 (app t, $J = 6.3$, 2H), 3.76 (d, $J = 5.5$, 2H), 3.32 (s, 6H), 2.96 (br s, 2H); ^{13}C -NMR (125 MHz, CDCl_3) δ 135.08, 119.27, 86.65, 71.23, 57.15; MS (ESI) 225 $[\text{M}+\text{Na}^+]$; HRMS (FAB) calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}^+]$ 225.1103, found 225.1079.

Compound 7: $[\alpha]_D +77.1^\circ$ (c 2.00, CHCl_3); IR (neat) 2980, 2938, 2883, 2827, 1785, 1671, 1622, 1602, 1460, 1387, 1305, 1214, 1176, 1085, 1010, 924, 697; ^1H -NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 5.63-5.54 (m, 1H), 5.48-5.43 (m, 2H), 4.25 (dd, $J = 8.6, 2.9$, 1H), 3.88 (app t, $J = 8.5$, 1H), 3.37 (s, 3H), 2.44 (dq, $J = 7.2, 2.9$, 1H), 1.68 (s, 3H), 1.07 (d, $J = 7.2$, 3H); ^{13}C -NMR (125 MHz, CDCl_3) δ 198.99, 160.75, 131.79, 122.06, 112.51, 82.69, 81.99, 56.37, 40.62, 10.42, 9.96; MS (ESI) 219 $[\text{M}+\text{Na}^+]$; HRMS (FAB) calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}^+]$ 219.0997, found 219.0991.

Compound 10: $[\alpha]_D +3.8^\circ$ (c 1.85, CHCl_3); IR (neat) 3352, 2957, 2930, 2857, 1472, 1462, 1250, 1127, 1081, 1028, 1006, 929, 834, 776; ^1H -NMR (500 MHz, CDCl_3) δ 5.73-5.66 (m, 1H), 5.30-5.24 (m, 3H), 4.12 (dd, $J = 11.8, 4.9$, 1H), 4.00 (dd, $J = 11.7, 6.5$, 1H), 3.48-3.43 (m, 2H), 3.22 (s, 3H), 2.69-2.61 (m, 1H), 1.78 (d, $J = 1.1$, 3H), 1.68-1.66 (m, 1H), 0.91 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C -NMR (125 MHz, CDCl_3) δ 135.15, 133.05, 118.54, 85.89, 78.28, 61.76, 56.12, 34.23, 26.11, 25.64, 21.53, 18.49, 15.32, -3.88 , -4.70 ; MS (ESI) 337 $[\text{M}+\text{Na}^+]$; HRMS (FAB) calcd. for $\text{C}_{17}\text{H}_{34}\text{O}_3\text{NaSi}$ $[\text{M}+\text{Na}^+]$ 337.2175, found 337.2162.

Compound 14: $[\alpha]_D +10.9^\circ$ (c 2.38, CHCl_3); IR (neat) 3460, 2970, 2930, 2880, 1460, 1380, 1250, 1130, 1060, 1020, 840, 740; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 5.60-5.53 (m, 1H), 5.35-5.26 (m, 3H), 4.31 (d, $J = 9.1$, 1H), 3.68-3.60 (m, 2H), 3.42-3.34 (m, 2H), 3.20 (s, 3H), 3.13 (app d, $J = 7.0$, 1H), 2.63-2.60 (m, 1H), 1.94-1.90 (m, 1H), 1.67 (d, $J = 1.2$, 3H), 0.94 (t, $J = 8.1$, 9H), 0.91 (m, 12H), 0.70 (d, $J = 7.1$, 3H), 0.58 (q, $J = 8.0$, 6H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 135.10, 133.66, 133.46, 118.84, 86.46, 78.30, 76.58, 68.33, 56.08, 38.87, 33.24, 26.13, 18.58, 17.70, 14.25, 12.64, 6.75, 4.74, -3.85 , -4.89 ; MS (ESI) 509 $[\text{M}+\text{Na}^+]$; HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{54}\text{O}_4\text{NaSi}_2$ $[\text{M}+\text{Na}^+]$ 509.3458, found 509.3468.

Compound 18: ^1H -NMR (500 MHz, CDCl_3) δ 8.22 (br s, 1H), 5.63-5.56 (m, 1H), 5.48 (d, $J = 9.3$, 1H), 5.33 (dd, $J = 10.3$, 1.7, 1H), 5.27 (dd, $J = 17.2$, 1.3, 1H), 4.95 (d, $J = 9.8$, 1H), 4.41-4.35 (m, 2H), 3.19 (s, 3H), 2.79-2.63 (m, 4H), 2.58-2.54 (m, 2H), 2.29-2.23 (m, 2H), 2.18-2.10 (m, 1H), 1.95 (br s, 1H), 1.66 (d, $J = 1.0$, 3H), 1.66-1.59 (m, 2H), 1.42-1.37 (m, 2H), 0.90 (s, 9H), 0.88 (d, $J = 6.6$, 3H), 0.87 (d, $J = 7.1$, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C -NMR (125 MHz, CDCl_3) δ 214.01, 172.21, 135.51, 134.72, 131.56, 119.19, 86.30, 78.26, 71.69, 55.98, 48.87, 42.70, 37.73, 37.70, 34.08, 33.26, 30.32, 26.11, 20.07, 18.55, 17.35, 13.87, 13.63, -3.79, -4.90; MS (ESI) 546 $[\text{M}+\text{Na}^+]$; HRMS (FAB) calcd. for $\text{C}_{28}\text{H}_{49}\text{NO}_6\text{NaSi}$ $[\text{M}+\text{Na}^+]$ 546.3227, found 546.3227.

Ester **20** (19.5 mg, 0.0309 mmol, 1 equiv) was dissolved in dry toluene (65 mL) and heated to reflux before adding second-generation Grubbs catalyst (5.5 mg, 0.00665 mmol, 0.2 equiv). After 10 minutes at reflux, the reaction mixture was cooled to room temperature, passed through a silica plug (25% EtOAc/Hexanes) and concentrated. The residual oil was further purified by flash chromatography (silica gel, gradient elution, 16-50% EtOAc/Hexanes) to afford the desired macrocycle (13 mg, 0.0215 mmol, 70% yield). The macrocycle (13 mg, 0.0215 mmol, 1 equiv) was dissolved in THF (1.25 mL) and treated with HF-pyridine (0.25 mL). The reaction mixture was stirred at room temperature for 7.5 hours before being quenched by addition of MeOTMS (2.5 mL). Evaporation and purification by flash chromatography (silica gel, gradient elution, 33-66% EtOAc/Hexanes) afforded migrastatin (**1**, 10 mg, 0.0204 mmol, 95% yield) as a white solid.

Compound 1 (Migrastatin): $[\alpha]_D +12.6^\circ$ (*c* 0.50, MeOH); lit. $[\alpha]_D +17.9^\circ$ (*c* 3.18, MeOH); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.82 (br s, 1H), 6.49 (ddd, $J = 15.7, 10.5, 3.7$, 1H), 5.64 (dd, $J = 10.7, 1.2$, 1H), 5.58 (dd, $J = 15.8, 1.2$, 1H), 5.54-5.48 (m, 1H), 5.24 (dd, $J = 15.5, 4.7$, 1H), 5.08 (d, $J = 10.0$, 1H), 3.47 (dd, $J = 8.7, 4.8$, 1H), 3.30 (s, 3H), 3.03 (dd, $J = 8.7, 1.7$, 1H), 2.99-2.87 (m, 2H), 2.80 (br s, 1H), 2.73-2.68 (m, 2H), 2.50 (app t, $J = 6.9$, 2H), 2.44-2.39 (m, 2H), 2.28-2.18 (m, 4H), 2.15-2.08 (m, 1H), 1.86 (d, $J = 1.2$, 3H), 1.69-1.55 (m, 2H), 1.41-1.30 (m, 2H), 1.12 (d, $J = 7.2$, 3H), 0.96 (d, $J = 6.9$, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 210.88, 171.78, 163.86, 150.01, 132.99, 131.17, 130.46, 127.87, 122.08, 82.39, 77.92, 76.92, 56.93, 51.18, 39.88, 37.68, 37.66, 34.12, 31.93, 31.08, 30.34, 25.99, 20.09, 13.39; MS (ESI) 512 $[\text{M}+\text{Na}^+]$; HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{39}\text{NO}_7\text{Na}$ $[\text{M}+\text{Na}^+]$ 512.2604, found 512.2624.

Spectral Comparison of Synthetic Migrastatin and Natural Migrastatin.