Supporting Information:

*Synthesis of Epothilone A Cyclopropane **8***

5: To a solution of epothilone C (**3)** (500 mg, 1.05 mmol; the preparation of epothilone C and D from the corresponding epothilone A and B has been previously disclosed: Kim, Soong-Hoon; Johnson, James A. *A process for the reduction of oxiranyl epothilones to olefinic epothilones.* WO 9928324) in CH_2Cl_2 (30 mL) at 0 °C was added lutidine (0.61 mL, 5.3 mmol) followed by dropwise addition of TBSOTf (0.9 mL, 4.1 mmol). The reaction mixture was stirred for 1 hr and then poured into saturated $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed with 10% EtOAc/hexane to give 509 mg (69%) of **5** as a white solid. ^{1}H NMR (400 MHz, [D_1] $CHCl_3$, 25 °C, TMS): δ = 6.96 (s, 1H), 6.57 (s, 1H), 5.53 (dt, ^3J(H,H) = 3.5, 11.1 Hz, 1H), 5.37 (dd, ^3J(H,H) = 6.5, 10.1 Hz, 1H), 4.99 (d, ^3J(H,H) = 10.4 Hz, 1H), 4.01 (d, ^3J(H,H) = 9.7 Hz, 1H), 3.88 (d, ^3J(H,H) = 8.8 Hz, 1H), 3.00 (dq, ^3J(H,H) = 8.7, 6.9 Hz, 1H), 2.82 (d, ^3J(H,H) = 16.3 Hz, 1H), 2.60-2.80 (m, 2H), 2.70 (s, 3H), 2.36 (q, ^3J(H,H) = 10.2 Hz, 1H)), 2.03-2.15 (m, 1H), 2.11 (s, 3H), 1.80-1.92 (m, 1H), 1.45-1.64 (m, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.10-1.15 (m, 1H), 1.08 (d, ^3J(H,H) = 6.8Hz, 3H), 0.95 (d, ^3J(H,H) = 7.1 Hz, 3H), 0.93 (s, 9H), 0.83-0.92 (m, 1H), 0.84 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), -0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.0, 171.3, 164.6, 152.4, 138.5, 135.1, 122.7, 119.5, 116.0, 79.6, 77.2, 76.4, 53.3, 48.0, 38.8, 37.7, 31.8, 31.3, 29.1, 28.4, 26.3, 26.2, 25.0, 24.2, 19.2, 18.6, 18.6, 17.7, 15.2, -3.2, -3.3, -3.7, -5.8. (overlapped CH_3); HR-MS (ESI, M+H) calcd for $C_{38}H_{68}NO_5Si_2S$: 706.4356; found: 706.4362.

6: To a solution of **5** (225 mg, 0.32 mmol) in bromoform (2.7 mL) was added benzyltriethylammonium chloride (7 mg, 0.032mmol), EtOH (0.02 mL), and then 50% $NaOH_{(aq)}$ (0.45 mL). The reaction mixture was stirred vigorously at 45 °C for 18 hr. The reaction mixture was cooled to RT, and then poured into saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed twice with 5% EtOAc/hexane, then recrystallized from hexane to give 33 mg (12%) of **6** as a pale yellow solid. ^{1}H NMR (400 MHz, [D_1] $CHCl_3$, 25 °C, TMS): δ = 6.99 (s, 1H), 6.55 (s, 1H), 5.12 (d, ^3J(H,H) = 8.4 Hz, 1H), 4.00 (d, ^3J(H,H) = 9.6 Hz, 1H), 3.88 (d, ^3J(H,H) = 9.2 Hz, 1H), 2.96 (dq, ^3J(H,H) = 9.4, 6.8 Hz, 1H), 2.80 (d, ^3J(H,H) = 15.6 Hz, 1H), 2.70 (s, 3H), 2.65 (dd, ^3J(H,H) = 16.4, 10.4 Hz, 1H), 2.13-2.20 (m, 1H), 2.11 (s, 3H), 1.31- 1.76 (m, 8H), 1.15-1.27 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.07 (d, ^3J(H,H) = 6.8 Hz, 3H), 0.96 (d, ^3J(H,H) = 7.2 Hz, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.8, 171.3, 164.8, 152.0, 138.3, 119.6, 116.3, 79.8, 79.1, 77.2, 53.2, 48.6, 38.9, 36.8, 35.0, 34.9, 32.2, 31.9, 31.1, 28.7, 27.1, 26.4, 26.1, 24.8, 24.2, 19.8, 19.2, 18.7, 18.6, 17.9, 15.4, -3.2, -3.5, -3.8, -5.9; HR-MS (ESI, M+H) calcd for $C_{39}H_{68}NO_5Si_2SBr_2$: 876.2723; found: 876.2727.

7: To a solution of **6** (26 mg, 0.03 mmol) in hexane (0.5 mL) was added tri-*n*-butyltin hydride (0.080 mL, 0.3 mmol) followed by AIBN (1.0 mg, 0.006 mmol). The reaction mixture was heated at reflux for 9 hr. The reaction mixture was cooled to RT, concentrated, and the residue chromatographed with 2-8 % EtOAc/hexane to give 16 mg (76%) of **7** as a white solid. ^{1}H NMR (400 MHz, [D_1] $CHCl_3$, 25 °C, TMS): δ = 6.96 (s, 1H), 6.54 (s, 1H), 5.08 (d, ^3J(H,H) = 9.1Hz, 1H), 4.04 (dd, ^3J(H,H) = 9.6, 1.7 Hz, 1H), 3.87 (d, ^3J(H,H) = 9.3 Hz, 1H), 3.01 (dq, ^3J(H,H) = 9.2, 6.9 Hz, 1H), 2.69-2.86 (m, 2H), 2.70 (s, 3H), 2.04-2.11 (m, 1H), 2.08 (s, 3H), 1.36-1.76 (m, 5H),

1.22-1.33 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 1.04-1.08 (m, 1H), 1.07 (d, ^3J(H,H) = 6.8 Hz, 3H), 0.96 (d, ^3J(H,H) = 6.9 Hz, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.71-0.82 (m, 1H), 0.57-0.63 (m, 2H), 0.13 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), -0.02 (s, 3H), -0.31-(-0.39) (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.1, 171.8, 164.6, 152.4, 139.5, 119.0, 115.8, 81.1, 79.9, 77.2, 53.3, 48.5, 38.9, 36.8, 33.6, 31.4, 29.9, 28.0, 26.3, 26.2, 24.6, 24.1, 19.8, 19.1, 18.7, 18.6, 17.9, 17.6, 15.4, 15.3, 9.3, -3.3, -3.5, -3.6, -5.9; HR-MS (ESI, M+H) calcd for $C_{39}H_{70}NO_5Si_2S$: 720.4513; found: 720.4537.

8: To a vial charged with **7** (13 mg, 0.018 mmol) at –15 °C was added 20% TFA/CH_2Cl_2 (0.55 mL). The reaction mixture was warmed to 0 °C and stirred for 2 hr. The reaction mixture was concentrated, and the residue was chromatographed with 40% EtOAc/hexane to give 8 mg (90 %) of cyclopropyl epothilone A (**8)** as a white solid. ^{1}H NMR (400 MHz, [D_1] $CHCl_3$, 25 °C, TMS): δ = 6.95 (s, 1H), 6.55 (s, 1H), 5.27 (dd, ^3J(H,H) = 9.2, 3.7 Hz, 1H), 4.05-4.15 (m, 1H), 3.88 (t, ^3J(H,H) = 4.3 Hz, 1H), 3.84 (bs, 1H), 3.20 (dq, ^3J(H,H) = 4.2, 6.8 Hz, 1H), 2.69 (s, 3H), 2.65 (bs, 1H), 2.53 (dd, ^3J(H,H) = 15.0, 9.0 Hz, 1H), 2.47 (dd, ^3J(H,H) = 15.0, 3.6 Hz, 1H), 2.03-2.08 (m, 1H), 2.06 (s, 3H), 1.65-1.77 (m, 1H), 1.40-1.60 (m, 4H), 1.36 (s, 3H), 1.22-1.34 (m, 2H), 1.17 (d, ^3J(H,H) = 7.6 Hz, 3H), 1.16 (s, 3H), 1.05-1.15 (m, 1H), 0.99 (d, ^3J(H,H) = 7.0 Hz, 3H), 0.67-0.77 (m, 2H), 0.58-0.66 (m, 1H), -0.31 (dd, ^3J(H,H) = 5.5, 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 220.8, 171.1, 165.0, 152.1, 138.9, 119.8, 115.9, 81.2, 77.2, 73.3, 52.4, 42.9, 39.2, 36.3, 32.2, 31.4, 29.4, 27.0, 22.5, 20.6, 19.1,17.3, 16.9, 15.3, 13.9, 13.3, 10.1; HR-MS (ESI, M+H) calcd for $C_{27}H_{42}NO_5S$: 492.2783; found: 492.2804.

Molecular Modeling

The modeling was performed on an SGI Octane workstation. The crystallographic coordinates of the X-ray structure of epothilone A (in-house data) was used as the starting geometry for modeling both epothilone A and the cyclopropane analog. The cyclopropane was built by modifying the appropriate atoms of model of epothilone A using the Sybyl program[a]. The conformational profiles of epothilone A and analogs were examined by a 10,000 step Monte Carlo (MC) conformational search in Macromodel[b] (version 7.0) using the Merck molecular mechanics force field[c-f] (MMFF) and the GB/SA water continuum model[g]. The trial conformation from each MC step was subjected to conjugate gradient minimization using the Polak-Ribiere first derivative method until a derivative convergence criterion of 0.01 kcal/mol-Å was reached or until a maximum of 400 iterations had been performed. The resulting unique conformations (a conformation was deemed unique if it met a heavy atom RMS criterion of >0.25 Å compared to an existing conformer) within a 10 kcal/mol energy window were further subjected to 500 steps of conjugate gradient minimization. The pool of unique conformations of epothilone A (352 conformers) and the cyclopropane analog (380 conformers) within an energy window of 5 kcal/mol were compared to each other. The global minimum of epothilone A was found 8 times and the global minimum of the cyclopropane analog was found 7 times. The X-ray structure of epothilone A was also minimized using the same protocol as above and found to be 7.4 kcal/mol- Å above the global minimum.

[a] SYBYL, Version 6.5, Tripos Associates, St. Louis, MO, 1994.

[b] MACROMODEL c/o Prof. W.C. Still, Columbia University, New York, NY.

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[e] T. A. Halgren, R .B. Nachbar, *J. Comp. Chem*., **1996**, *17*, 553-586.

[f] T. A. Halgren, *J. Comp. Chem*., **1996**, *17*, 616-641.

[g] W.C. Still, A. Tempczyk, R.C. Hawley, T. Hendrickson,. *J. Am. Chem. Soc*. **1990,** 112, 6127-6129.