Complex Target-Oriented Total Synthesis in the Drug Discovery Process: The Discovery of a Highly Promising Family of Second Generation Epothilones

Alexey Rivkin, Fumihiko Yoshimura, Ana E. Gabarda, Ting-Chao Chou, Huajin Dong, William P. Tong, and Samuel J. Danishefsky

General Methods: Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. The following solvents were obtained from a dry solvent system (passed through a prepacked column of alumina) and used without further drying: tetrahydrofuran, methylene chloride, diethyl ether, benzene, and toluene. All air and water sensitive reactions were performed in flame-dried glassware under a positive pressure of prepurified argon gas. NMR ($^1$H and $^{13}$C) spectra were recorded on Bruker AMX-400 MHz or Bruker Advance DRX-500 MHz as noted individually, referenced to CDCl$_3$ (7.27 ppm for $^1$H and 77.0 ppm for $^{13}$C). Infrared spectra (IR) were obtained on a Perkin-Elmer FT-IR model 1600 spectrometer. Optical rotations were obtained on a JASCO model DIP-370 digital polarimeter at 22 ± 2 °C. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Compounds which were not UV active were visualized by dipping the plates in a ceric ammonium molybdate or $para$-anisaldehyde solution and heating. Silica gel chromatography was performed using the indicated solvent on Davisil® (grade 1740, type 60A, 170-400 mesh) silica gel.

Acronyms and Abbreviations
TES, triethylsilyl; TBS, Dimethyltertbutylsilyl; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HF-PY, hydrogen fluoride in pyridine; DMAP, 4-$N$, $N$-dimethylaminopyridine; DCM, dichloromethane; DMF, $N$, $N$-dimethylformamide; THF, tetrahydrofuran.

Experimental
**Compound 7**: To a solution of freshly prepared LDA (11.6 mmol) in THF (25 mmol) was added dropwise a solution of ketone 5 (2.40 g, 10.4 mmol) in THF (6.8 mL) at –78 °C. After stirring at –40 °C for 0.5 h, the mixture was cooled to –90 °C. A solution of aldehyde 6 (1.38 g, 7.72 mmol) in THF (6.8 mL) was added dropwise. After stirring at –90 °C for 35 min, the reaction was quenched with sat. aq. NH₄Cl (15 mL) and extracted with EtOAc (50 mL x 3). The combined organic extracts were dried over Na₂SO₄ and concentrated. Purification by flash column chromatography (SiO₂, hexane/EtOAc = 15:1 to 12:1) gave 7 (2.09 g, 66%) and isomer (0.39 g, 12%) both as yellow oils. 7: [α]D° 13.1 (c 1.22, CHCl₃); IR (film) ν 3494, 2972, 2932, 1708, 1454, 1380, 1329, 1120, 998, 734 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.98 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.10 (3H, d, J = 6.1 Hz), 1.14 (3H, d, J = 6.9 Hz), 1.15 (3H, s), 1.17 (3H, d, J = 6.2 Hz), 1.18 (3H, s), 1.20 (3H, d, J = 6.2 Hz), 1.81-1.92 (1H, m), 3.33 (1H, qd, J = 7.0, 2.2 Hz), 3.51 (1H, dd, J = 8.9, 6.3 Hz), 3.64 (1H, d, J = 1.8 Hz), 3.66-3.71 (2H, m), 3.78-3.86 (2H, m), 4.51 (1H, d, J = 12.0 Hz), 4.54 (1H, d, J = 12.0 Hz), 4.58 (1H, s), 7.25-7.35 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 10.0, 14.3, 20.5, 21.3, 21.9, 22.5, 23.5, 23.6, 36.4, 42.1, 54.1, 69.8, 71.2, 72.8, 73.3, 73.4, 103.8, 127.6, 127.7 (2C), 128.5 (2C), 138.9, 221.6; LRMS (ESI) calcd for C₂₄H₄₀O₇Na [M+Na⁺] 431.3, found 431.4.

**Compound 7a (not shown)**: To a cooled (–40 °C) solution of alcohol 7 (1.01 g, 2.47 mmol) and 2,6-lutidine (691 µL, 5.93 mmol) was added TBSOTf (681 µL, 3.00 mmol), and the mixture was warmed to –20 °C over 3.5 h. The reaction was quenched with sat. aq. NaHCO₃ (10 mL). After extraction with hexane (50 mL x 3), the combined organic extracts were dried over Na₂SO₄ and concentrated. Purification by flash column chromatography (SiO₂, hexane/EtOAc = 50:1) gave 7a (1.25 g, 2.39 mmol, 97%) as a colorless oil; [α]D° –19.7 (c 0.58, CHCl₃); IR (film) ν 2966, 2931, 1696, 1455, 1378, 1320, 1255, 1091, 1044, 991, 873, 838, 773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.08
(6H, s), 0.89 (9H, s), 0.99 (3H, d, J = 7.0 Hz), 1.04 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.07 (3H, s), 1.14 (3H, d, J = 6.1 Hz), 1.17 (3H, s), 1.17 (3H, d, J = 6.0 Hz), 1.20 (3H, d, J = 6.2 Hz), 1.76-1.85 (1H, m), 3.21 (1H, dd, J = 9.2, 7.3 Hz), 3.32 (1H, quint, J = 7.4 Hz), 3.62 (1H, dd, J = 9.2, 5.7 Hz), 3.78-3.85 (2H, m), 3.87 (1H, dd, J = 7.7, 2.0 Hz), 4.46 (1H, d, J = 12.1 Hz), 4.50 (1H, d, J = 12.1 Hz), 4.73 (1H, s), 7.24-7.37 (5H, m); 13C NMR (100 MHz, CDCl3) δ –3.6, -3.3, 15.6, 16.8, 18.7, 18.8, 21.8, 22.1, 22.5, 23.5, 23.7, 26.4 (3C), 39.0, 46.2, 54.0, 69.7, 70.9, 72.1, 73.4, 76.7, 103.1, 127.6, 127.8 (2C), 128.5 (2C), 139.0, 218.9; LRMS (ESI) calcd for C30H54O5SiNa [M+Na+] 545.4, found 545.4.

**Compound 8:** The mixture of 7a (3.03 g, 5.79 mmol) and p-TsOH-H2O (286 mg) in aqueous THF (64 mL, THF/H2O = 4:1) was heated under reflux for 6.5 h. The reaction mixture was cooled to rt and poured into sat. aq. NaHCO3 (25 mL). After extraction with EtOAc (100 mL + 50 mL x 2), the combined organic layers were washed with brine, dried over Na2SO4 and concentrated. Purification by flash column chromatography (SiO2, hexane/EtOAc = 50:1 to 30:1) gave 8 (2.37 g, 5.64 mmol, 98%) as a colorless oil: [α]D25 25.8 (c 0.515, CHCl3); IR (film) ν 2955, 2931, 1731, 1696, 1455, 1360, 1255, 1091, 1026, 873, 826, 767 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 0.06 (3H, s), 0.07 (3H, s), 0.90 (9H, s), 0.95 (3H, d, J = 7.1 Hz), 1.03 (3H, d, J = 7.0 Hz), 1.28 (3H, s), 1.33 (3H, s), 1.73-1.82 (1H, m), 3.16 (1H, dd, J = 9.2, 6.1 Hz), 3.28 (1H, quint, J = 7.3 Hz), 3.55 (1H, dd, J = 9.2, 6.7 Hz), 3.91 (1H, dd, J = 7.8, 2.1 Hz), 4.46 (2H, s), 7.27-7.36 (5H, m), 9.58 (1H, s); 13C NMR (100 MHz, CDCl3) δ –3.6, -3.5, 15.7, 16.3, 18.6, 19.8, 20.1, 26.3 (3C), 39.1, 47.0, 61.1, 71.9, 73.4, 75.8, 127.7, 128.0 (2C), 128.5 (2C), 138.6, 201.3, 213.3; LRMS (ESI) calcd for C30H54O5SiNa [M+Na+] 545.4, found 545.4.
**Compound 9:** To a solution of freshly prepared LDA (18 mL of a 0.5 M solution in Et₂O, 9.0 mmol) in Et₂O (20 mL) was added t-butyl acetate (1.16 mL, 8.61 mmol) at −78 °C. After stirring for 50 min, CpTiCl(OR)₂ (100 mL of a 0.1 M solution in Et₂O, 10.0 mmol) was added dropwise over 65 min via syringe pump. After stirring for 20 min, the reaction mixture was warmed to −30 °C, stirred for 50 min, and re-cooled to −78 °C. A solution of 8 (2.42 g, 5.75 mmol) in Et₂O (9 mL) was added dropwise over 10 min, and the resulting mixture was stirred at −78 °C. After stirred for 2 h, the reaction was quenched with aqueous THF (5 M H₂O, 37 mL) and stirred at rt for 2 h. After addition of water (40 mL), the mixture was stirred for further 1 h. The precipitate formed was filtered off by Celite (Et₂O rinse), and the filtrate was washed with water (40 mL). The aqueous layer was extracted with Et₂O (100 mL x 2) and the combined organic layers were washed with brine (40 mL), dried over Na₂SO₄ and concentrated. Purification by flash column chromatography (SiO₂, hexane/EtOAc = 10:1) gave 9 (2.65 g, 4.94 mmol, 86%) as a pale yellow oil; [α]D₂⁵ −20.3 (c 1.0, CHCl₃); IR (film) ν 3523, 2957, 2930, 2856, 1732, 1700, 1472, 1368, 1252, 1152, 1091, 1042, 986, 834, 774 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.07 (3H, s), 0.07 (3H, s), 0.90 (9H, s), 0.99 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.10 (3H, s), 1.14 (3H, s), 1.47 (9H, s), 1.77-1.83 (1H, m), 2.26 (1H, dd, J = 16.0, 10.0 Hz), 2.34 (1H, dd, J = 15.9, 2.7 Hz), 3.23 (1H, dd, J = 9.2, 7.1 Hz), 3.35 (1H, d, J = 2.7 Hz, -OH), 3.36 (1H, quint, J = 7.0 Hz), 3.61 (1H, dd, J = 9.2, 5.9 Hz), 3.88 (1H, dd, J = 7.6, 2.0 Hz), 4.17 (1H, dt, J = 10.0, 2.7 Hz), 4.48 (2H, s), 7.27-7.36 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ −3.5, -3.4, 16.3, 16.7, 18.7, 20.1, 21.6, 26.4 (3C), 28.3 (3C), 38.0, 39.1, 45.8, 51.8, 72.2, 72.9, 73.5, 76.7, 81.4, 127.7, 128.0 (2C), 128.5 (2C), 138.8, 172.7, 219.6; LRMS (ESI) calcd for C₃₀H₅₂O₆SiNa [M+Na⁺] 559.3, found 559.4.

**Compound 9a (Not Shown):** To a mixture of alcohol 9 (10.2 g, 18.9 mmol) and
imidazole (2.70 g, 39.7 mmol) in DMF (25 mL) was added TESCl (3.3 mL, 19.8 mmol) at 0 °C, and the mixture was stirred at rt for 2 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL). After extraction with hexane (500 mL + 120 mL x 2), the combined organic extracts were washed successively water (30 mL x 2) and brine (30 mL), dried over Na₂SO₄ and concentrated. Purification by flash column chromatography (SiO₂, hexane/EtOAc = 40:1) gave 9a (12.1 g, 18.5 mmol, 98%) as a colorless oil: [α]₀²⁵ –38.0 (c 0.46, CHCl₃); IR (film) v 2955, 2877, 1733, 1697, 1456, 1367, 1298, 1251, 1155, 1099, 988, 835, 742 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.05 (6H, s), 0.57-0.68 (6H, m), 0.89 (9H, s), 0.95 (9H, t, J = 7.9 Hz), 0.99 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.04 (3H, s), 1.13 (3H, s), 1.45 (9H, s), 1.67-1.79 (1H, m), 2.16 (1H, dd, J = 17.0, 7.0 Hz), 2.40 (1H, dd, J = 17.0, 3.1 Hz), 3.22 (1H, dd, J = 9.1, 7.5 Hz), 3.31 (1H, quint, J = 6.9 Hz), 3.61 (1H, dd, J = 9.1, 5.4 Hz), 3.83 (1H, d, J = 7.3, 2.3 Hz), 4.30 (1H, dd, J = 6.9, 3.1 Hz), 4.48 (2H, s), 7.27-7.36 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ –3.5, -3.4, 5.3 (3C), 7.3 (3C), 15.3, 16.9, 18.7, 20.1, 23.4, 26.4 (3C), 28.3 (3C), 39.1, 41.1, 46.2, 53.4, 72.2, 73.4, 74.3, 76.7, 80.6, 127.6, 127.9 (2C), 128.5 (2C), 138.9, 171.5, 218.4; LRMS (ESI) calcd for C₃₆H₆₆O₆Si₂Na [M+Na⁺] 673.4, found 673.5.

**Compound 9b (Not Shown):** To a stirred solution of 9a (242.5 mg, 0.373 mmol) in EtOH (5.7 mL) was added Pd/C (10%wt, 24.2 mg) and the mixture was stirred under an atmosphere of H₂. After stirred for 30 min, the mixture was filtered through a pad of Celite, which was rinsed with EtOH. The filtrate was concentrated and purified by flash column chromatography (SiO₂, hexane/EtOAc = 10:1) gave 9b (172.6 mg, 0.308 mmol, 83%) as a colorless oil; [α]₀²⁵ –16.1 (c 0.62, CHCl₃); IR (film) v 3543, 2956, 1732, 1696, 1472, 1368, 1299, 1252, 1155, 1100, 988, 837, 775, 742 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.10 (3H, s), 0.12 (3H, s), 0.60-0.68 (6H, m), 0.93 (9H, s), 0.96 (9H, t, J = 8.0 Hz), 0.99 (3H, d, J = 7.1 Hz), 1.10 (3H, d, J = 6.9 Hz), 1.14 (3H, s), 1.20 (3H, s), 1.45 (9H, s), 1.46-1.55 (1H, m), 2.21 (1H, dd, J = 17.2, 7.1 Hz), 2.39 (1H, dd, J = 17.2, 2.8 Hz), 2.54 (1H, t, J = 5.8 Hz, -OH), 3.30 (1H, quint, J = 6.9 Hz), 3.58 (1H, dt, J =
11.5, 5.5 Hz), 3.66 (1H, dt, J = 11.3, 5.4 Hz), 3.92 (1H, dd, J = 8.0, 2.1 Hz), 4.32 (1H, dd, J = 7.1, 2.9 Hz); 13C NMR (100 MHz, CDCl3) δ –3.6, -3.5, 5.3 (3C), 7.2 (3C), 16.0, 16.1, 18.6, 20.0, 23.4, 26.4 (3C), 28.3 (3C), 40.0, 40.9, 46.9, 53.7, 64.8, 73.3, 78.1, 80.9, 171.7, 218.5; LRMS (ESI) calcd for C29H60O6Si2Na [M+Na+] 583.4, found 583.5.

**Compound 9c (Not shown):** To a stirred mixture of alcohol 9b (644.1 mg, 1.15 mmol) and powdered MS4A (1.14 g) in CH2Cl2 (22 mL) were added NMO (403.5 mg, 3.44 mmol) followed by TPAP (28.2 mg, 80.4 µmol). After stirred at rt for 48 min, the mixture was filtered through a silica gel column (hexane/Et2O = 5:1) gave 9c (610.1 mg, 1.09 mmol, 95%) as a colorless oil; [α]D25 –69.6 (c 0.25, CHCl3); IR (film) ν 2955, 2878, 1732, 1696, 1472, 1368, 1253, 1155, 1097, 989, 837 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 0.09 (3H, s), 0.10 (3H, s), 0.59-0.68 (6H, m), 0.89 (9H, s), 0.95 (9H, t, J = 8.0 Hz), 1.08 (3H, s), 1.11 (3H, d, J = 6.9 Hz), 1.14 (3H, d, J = 7.1 Hz), 1.24 (3H, s), 1.45 (9H, s), 2.19 (1H, dd, J = 17.0, 6.7 Hz), 2.33 (1H, qt, J = 7.1, 2.2 Hz), 2.41 (1H, dd, J = 17.0, 3.3 Hz), 3.28 (1H, quint, J = 7.5 Hz), 4.07 (1H, dd, J = 7.9, 2.2 Hz), 4.32 (1H, dd, J = 6.7, 3.2 Hz), 9.74 (1H, d, J = 2.0 Hz); 13C NMR (100 MHz, CDCl3) δ –3.8, -3.5, 5.3 (3C), 7.2 (3C), 12.6, 15.6, 18.5, 20.5, 23.3, 26.2 (3C), 28.3 (3C), 41.1, 46.9, 51.1, 53.5, 74.0, 76.5, 80.7, 171.1, 204.3, 218.0; LRMS (ESI) calcd for C29H58O6Si2Na [M+Na+] 581.3, found 581.3.

**Compound 10:** MePPh3I (197.4 mg, 0.488 mmol) in THF (4.0 mL) was treated with n-BuLi (287 µL of a 1.6 M solution in hexane, 0.460 mmol) at 0 °C. After stirred at 0 °C for 0.5 h, the resulting suspension was cooled to –78 °C and a solution of aldehyde 9c (160.6 mg, 0.2873 mmol) was added. The mixture was allowed to warm to –5 °C
over 4 h. The reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with Et₂O (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (SiO₂, hexane/Et₂O = 20:1) gave 10 (125.3 mg, 0.225 mmol, 78%) as a colorless oil; [α]D25 –33.6 (c 0.250, CHCl₃); IR (film) ν 2956, 2878, 1733, 1696, 1472, 1367, 1299, 1253, 1156, 1100, 988, 837, 774 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.08 (3H, s), 0.08 (3H, s), 0.60-0.68 (6H, m), 0.93 (9H, s), 0.96 (9H, t, J = 8.0 Hz), 1.04 (6H, d, J = 7.0 Hz), 1.09 (3H, s), 1.20 (3H, s), 1.45 (9H, s), 2.08-2.15 (1H, m), 2.29 (1H, dd, J = 17.0, 7.0 Hz), 2.41 (1H, dd, J = 17.0, 3.1 Hz), 3.08 (1H, quint, J = 7.0 Hz), 3.84 (1H, dd, J = 7.0, 2.1 Hz), 4.32 (1H, dd, J = 7.0, 3.1 Hz), 5.02 (1H, dd, J = 17.9, 1.0 Hz), 5.06 (1H, dd, J = 10.5, 1.0 Hz), 5.93 (1H, ddd, J = 17.9, 10.5, 7.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ –3.6, -3.3, 5.4 (3C), 7.2 (3C), 15.2, 18.7, 19.0, 20.2, 23.6, 26.4 (3C), 28.3 (3C), 41.1, 43.8, 46.4, 53.5, 73.9, 76.6, 80.6, 115.5, 140.2, 171.5, 218.5; LRMS (ESI) calcd for C₃₀H₆₀O₅Si₂Na [M+Na⁺] 579.4, found 579.4.

**Compound 11:** To a solution of t-butyl ester 10 (1.79 g, 3.21 mmol) and 2,6-lutidine (1.5 mL, 12.8 mmol) in CH₂Cl₂ (21 mL) was added TESOTf (1.45 mL, 6.42 mmol) at 0 °C. After stirred at 0 °C for 20 min, the mixture was stirred at rt for 3 h. The mixture was diluted with Et₂O (300 mL), washed with successively 5% aq. KHSO₄ (30 mL x 2) and brine (40 mL), dried over Na₂SO₄, and concentrated. The residue was dried under high vacuum to give silylester (2.31 g). The crude silylester (2.31 g) was dissolved in aqueous THF (35 mL, THF/H₂O = 6:1) and treated with sat. aq. NaHCO₃ (5 mL). After stirred at rt for 20 min, the resulting suspension was diluted with Et₂O (300 mL) and acidified with aqueous 5% KHSO₄ (30 mL). After layers were separated, the aqueous layer was extracted with Et₂O (60 mL) and the combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄ and concentrated. The residue was dried under high vacuum to give crude acid 11 (1.89 g, contaminated with TESOH) as a colorless oil, which was used for next reaction without further purification.
Compound 14: The 3-O-TES-6-O-TBS protected acid 11 was dried through azeotropic distillation from benzene. Freshly dried alcohol 12 (200 mg, 1.19 mmol) is dissolved in DCM (10 mL) and cooled to 0 °C, at which point solid DMAP (167 mg, 1.37 mmol) and solid EDCI (261 mg, 1.37 mmol) are added. After stirring the reaction mixture at 0 °C for 15 min, a solution of acid 11 (425 mg, 0.85 mmol) in DCM (2 mL) is added dropwise. The cooling bath is removed and stirring continued for another 2 hours. The crude reaction mixture is diluted with DCM (10 mL) and stripped onto silica and purified using silica gel chromatography employing 10% EtOAc/Hexanes as the eluent yielding ester 14 (380 mg, 81% yield, two steps, starting from 10) as a clear oil: [α]_D -15.1 (c 1.2, CDCl₃); IR (neat) 2955, 2932, 2877, 1743, 1732, 1694, 1474, 1461, 1417, 1380, 1360, 1295, 1252, 1169, 1094, 1043, 988.3, 912.9, 871.4, 836.5, 774.8, 741.6 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 0.08 (3H, s), 0.08 (3H, s), 0.60-0.68 (6H, m), 0.93 (9H, s), 0.95 (9H, t, J = 8.0 Hz), 1.04 (3H, d, J = 6.9 Hz), 1.05 (3H, d, J = 6.9 Hz), 1.10 (3H, s), 1.25 (3H, s), 1.69 (3H, s), 2.08-2.15 (2H, m), 2.16 (3H, s), 2.38 (1H, dd, J = 17.0, 7.0 Hz), 2.48 (2H, t, J = 6.5 Hz), 2.57 (1H, dd, J = 17.0, 2.7 Hz), 2.71-2.76 (2H, m), 3.07 (1H, quint, J = 7.0 Hz), 3.83 (1H, d, J = 7.2 Hz), 4.36 (1H, dd, J = 7.0, 2.7 Hz), 4.97-5.07 (4H, m), 5.19 (1H, t, J = 7.0), 5.73 (1H, td, J = 15.4, 5.9 Hz), 5.92 (1H, dd, J = 15.7, 8.0 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 218.4, 205.4, 172.1, 140.1, 137.4, 135.4, 119.1, 115.8, 115.6, 78.7, 76.5, 73.9, 53.3, 46.3, 43.7, 39.6, 36.6, 29.2, 26.7, 26.4, 23.8, 23.7, 19.9, 18.9, 18.7, 15.4, 7.06, 5.30, -3.29, -3.62; LRMS (ESI) calcd for C₃₆H₆₆O₆Si₂Na [M+Na⁺] 673.4, found 673.5.
**Compound 15**: To a solution of compound 14 (20 mg, 0.031 mmol) in dry toluene (60 mL) at reflux was added in one portion a solution of tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (5.2 mg, 0.0061 mmol) in dry toluene (2 mL) and heated for 10 minutes. The reaction mixture was cooled immediately in ice bath and stripped onto silica and purified using silica gel chromatography employing 4-10% EtOAc/pentane gradient as the eluent to furnish compound 15 (15 mg, 78% yield) as an oil: $[\alpha] -28.6$ (c 1.2, CHCl$_3$); IR (neat) 2955, 2933, 2878, 1745, 1731, 1695, 1471, 1462, 1380, 1361, 1251, 1159, 1104, 1080, 1019, 985.0, 876.1, 835.5, 774.7, 743.1, 670.1 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 0.07 (3H, s), 0.10 (3H, s), 0.59-0.68 (6H, m), 0.91 (9H, t, $J = 8.0$ Hz), 0.93 (9H, s), 1.04 (3H, d, $J = 7.0$ Hz), 1.10 (3H, s), 1.11 (3H, d, $J = 7.0$ Hz), 1.17 (3H, s), 1.71 (3H, s), 2.21 (3H, s), 2.27-2.32 (1H), 2.38 (1H, dd, $J = 14.6$, 6.8 Hz), 2.51-2.61 (2H, m), 2.57 (1H, dd, $J = 15.5$, 3.3 Hz), 2.93-3.1 (3H, m), 3.94 (1H, d, $J = 8.5$ Hz), 4.28 (1H, dd, $J = 8.6$, 3.0 Hz), 5.04 (1H, dd, $J = 8.7$, 2.4), 5.16 (1H, t, $J = 7.5$), 5.73 (1H, tdd, $J = 12.8$, 9.94, 6.9 Hz), 5.92 (1H, ddd, $J = 18.0$, 10.3, 7.8 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 215.9, 204.8, 171.3, 140.0, 132.7, 129.2, 118.6, 79.1, 78.2, 75.4, 54.0, 48.2, 41.7, 40.3, 35.0, 29.2, 26.6, 26.5, 23.5, 22.8, 20.6, 18.8, 17.5, 14.3, 7.19, 5.53, -3.36; LRMS (ESI) calcd. for C$_{34}$H$_{62}$O$_6$Si$_2$ 645.4, found 645.4 (M+Na$^+$).
**Compound 15a (not shown):** To a solution of Wittig reagent (19.1 mg, 54.7 µmol) in THF (0.4 mL) was added KHMDS (109 µL of a 0.5 M solution in toluene, 54.7 µmol) at 0 °C. The mixture was added immediately and then cooled to –78 °C. The mixture was added dropwise to the mixture at –20 °C over 1.5 h. The reaction was quenched with sat. aq. NH₄Cl (2 mL) and extracted with EtOAc (7 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (SiO₂, hexane/Et₂O = 10:1) gave 5.6 mg of inseparable olefin mixture (E/Z = 9:1). The mixture was purified by preparative TLC (hexane/Et₂O = 4:1) gave pure 15a (5.0 mg, 6.96 µmol, 76%) as a colorless oil; [α]D²⁵
-41.5 (c 0.715, CHCl₃); IR (film) ν 2955, 2884, 1737, 1690, 1467, 1378, 1249, 1179, 1102, 1014, 979, 879, 826, 773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.08 (3H, s), 0.12 (3H, s), 0.57 (6H, q, J = 7.8 Hz), 0.89 (9H, t, J = 8.0 Hz), 0.93 (9H, s), 1.04 (3H, s), 1.06 (3H, d, J = 7.1 Hz), 1.12 (3H, s), 1.17 (3H, d, J = 7.1 Hz), 1.68 (3H, s), 2.15 (3H, d, J = 0.8 Hz), 2.14-2.27 (2H, m), 2.45 (1H, dd, J = 14.0, 4.8 Hz), 2.50 (1H, dd, J = 14.9, 3.2 Hz), 2.64-2.74 (2H, m), 2.72 (3H, s), 3.02 (1H, quint, J = 7.0 Hz), 3.10 (1H, dd, J = 14.4, 7.3 Hz), 3.96 (1H, d, J = 8.7 Hz), 4.43 (1H, dd, J = 8.3, 2.9 Hz), 5.22 (1H, dd, J = 9.8, 5.7 Hz), 5.33-5.42 (2H, m), 5.69 (1H, dd, J = 15.8, 8.2 Hz), 6.57 (1H, s), 6.96 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ -3.3, -3.2, 5.6 (3C), 7.1 (3C), 15.0, 17.2, 18.8, 19.4, 21.4, 21.7, 23.8, 24.3, 26.5 (3C), 33.2, 35.6, 41.3, 41.8, 48.2, 54.0, 74.4, 77.4, 79.3, 116.4, 120.5, 121.0, 129.3, 132.1, 137.8, 138.0, 152.7, 164.8, 170.7, 216.8; LRMS (ESI) calcd for C₃₉H₆₈NO₅SSi₂ [M+H⁺] 718.4, found 718.3.

**Compound 3:** To a solution of 15a (298.8 mg, 0.416 mmol) in THF (6.5 mL) in a
plastic tube was added HF-pyridine (3.2 mL) at 0 °C, and the mixture was stirred at rt for 3 h. The reaction was quenched with dropwise addition of TMSOMe (30 mL) at 0 °. After concentrated and dried under high vacuum, the residue was purified by flash column chromatography (SiO₂, hexane/EtOAc = 1:1) gave 3 (196.6 mg, 0.402 mmol, 97%) as a white solid; [α]D25 –96.6 (c 0.235, CHCl₃); IR (film) ν 3502, 2970, 2927, 1733, 1685, 1506, 1375, 1251, 1152, 1040, 977 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.06 (3H, s), 1.11 (3H, d, J = 7.0 Hz), 1.22 (3H, d, J = 6.8 Hz), 1.28 (3H, s), 1.72 (3H, s), 2.10 (3H, s), 2.31-2.40 (2H, m), 2.43 (1H, dd, J = 16.0, 3.7 Hz), 2.49 (1H, dd, J = 16.0, 9.2 Hz), 2.55-2.68 (2H, m), 2.71 (3H, s), 2.98 (1H, dd, J = 14.4, 6.4 Hz), 3.16 (1H, quint, J = 6.2 Hz), 3.76 (1H, dd, J = 5.9, 3.2 Hz), 4.30 (1H, dd, J = 9.2, 3.7 Hz), 5.18 (1H, brt, J = 7.3 Hz), 5.32 (1H, dd, J = 8.4, 2.5 Hz), 5.63 (1H, dd, J = 15.7, 6.4 Hz), 5.60 (1H, ddd, J = 15.7, 6.9, 5.1 Hz), 6.60 (1H, s), 6.98 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 15.1, 16.0, 17.7, 19.2, 19.5, 22.5, 23.6, 32.0, 35.0, 39.6, 40.3, 44.8, 53.3, 71.8, 75.6, 78.3, 116.1, 119.6, 120.5, 129.9, 131.3, 137.5, 138.2, 152.2, 165.0, 170.7, 218.8; LRMS (ESI) calcd for C₂₇H₄₀NO₅S [M+H⁺] 490.3, found 490.2.

**dEpoB (1):** To a solution of 3 (1.2 mg, 2.5 µmol) and TrisNHNH₂ (29.3 mg, 98 µmol) in CH₂Cl₂ (0.7 mL) at 50 °C was added Et₃N (13.7 µL, 98 µmol). The reaction was monitored by HPTLC (hexane/EtOAc/CH₂Cl₂ = 1/1/2). After stirred for 7 h, the mixture was cooled to rt, diluted with EtOAc and filtered through a pad of silica gel, which was rinsed with EtOAc. After concentrated, the residue was purified by preparative TLC (hexane/EtOAc/CH₂Cl₂ = 1/1/2) gave 1 (1.1 mg, 2.2 µmol, 91%) as a white solid. The spectral data of 1 was identical to those reported of dEpoB.