Supplementary Information

A scalable approach for the synthesis of epothilone thiazole fragment (C_{12}-C_{21} unit) via Wacker oxidation.

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**General Remarks**

All reactions needing inert atmosphere were carried out under a nitrogen atmosphere. All reagents and solvents were purchased from commercial suppliers and used without further purification. All metal catalysts were purchased from Aldrich and used without further purification. Thin layer chromatography was carried out on aluminum backed silica plates. The plates were visualized under UV (254 nm) light, followed by staining with phosphomolybdic acid dip or potassium permanganate and gentle heating. Organic layers were routinely dried with anhydrous NaSO₄ and concentrated using a Büchi rotary evaporator.

**Synthetic procedures:**

**Preparation of ((R)-3,5-bis(tert-butylidimethylsilyloxy)pentanenitrile (3):**

To a stirred solution of compound 2 (100 g, 0.64 mol) in methanol (500 mL) was slowly added sodium borohydride (48 g, 1.27 mol) at 0-5°C. The reaction mixture was stirred for 8 h at ambient temperature and after completion of reaction, acidified the reaction mixture to pH 5-6 using acetic acid. The resulted reaction mixture was concentrated under reduced pressure and diluted with dichloromethane (500 mL). The resulted by-product was filtered off under vacuum and the filtrate was concentrated under reduced pressure. The resulted crude was diluted with N,N-dimethylformamide (600 mL) and added Imidazole (212.8 g, 3.12 mol) followed by tert-butylidimethyl silylchloride (235 g, 1.56 mol). The reaction mixture was stirred for 7 h at 75°C. After completion of reaction chilled water (1 L) was added to reaction mixture and product was extracted with methyl tert-butyl ether. The separated organic layer washed with brine solution and the solvent was removed under reduced pressure at 40°C. The residue dried at 55°C under 0.2 mm Hg vacuum pressure to get compound 3 (201 g, 92%) as an oily liquid. MS: m/z 344.4 [M+H]; [α]²⁵D -18.0 (c 1.0, CHCl₃); IR (CCl₄) νmax: 2251, 2955 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.050 (s, 6H), 0.091 (s, 3H), 0.123 (s, 3H), 0.889, 0.906 (2s, 18H), 1.749-1.794 (m, 2H), 2.516-2.576 (m, 2H), 3.672-3.702 (m, 2H), 4.122-4.150 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 4.6, -5.4, 17.8, 25.6, 26.3, 39.6, 58.6, 65.7, 117.6; Elem. Anal. Found: C 59.5; H 10.75; N 4.20; Calcd. for C₁₇H₃₇NO₂Si₂: C 59.42; H 10.85; N 4.08.

**Preparation of (R)-3,5-bis(tert-butylidimethylsilyloxy)pentan-1-ol (4):**

DIBAL-H (664 mL, 1.5 M solution, 989 mmol) was added to a solution of nitrile 3 (170 gm, 494 mmol) in dichloromethane (1 L) at -78°C and stirred for 2 hours. After complete consumption of the 3, reaction was quenched with dilute HCl solution and extracted with methyl tertiary butyl ether. Organic layer concentrated under vacuum at below 35°C. The obtained residue dissolved in methanol (725 mL) and added with sodium borohydride (23.7 gm, 627 mmol) at 0°C. Reaction mixture was stirred for 2 h at ambient temperature and added with 10% ammonium chloride solution (725 mL). The resulted reaction mixture extracted twice with methyl tertiary butyl ether and concentrated under reduced pressure to afford alcohol 7 as liquid (120 gm, 70% yield). MS: m/z 349.4 [M+H]; IR (CCl₄) νmax: 2295, 3368 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.041 (s, 6H), 0.096 (s, 6H), 0.911 (s, 18H), 1.609-1.939 (m, 4H), 2.486-2.520 (t, J=5.1, 1H), 3.635-3.677 (t, J=6.3, 2H), 3.692-3.892 (m, 2H), 4.060-4.136 (m, 1H).

**Preparation of (S)-5-(2-iodoethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxo-3,9-disila undecane (5):**

To a stirred solution of compound 4 (113 gm, 324 mmol) in dichloromethane (1 L) was added Imidazole (66 gm, 970 mmol) followed by triphenylphosphine (170 gm, 648 mmol) at 0°C. To the resulting reaction mixture was slowly added iodine (164 gm, 646 mmol) at 0°C. The reaction mixture was stirred at ambient temperature for 1 hr and quenched with 10% sodium thiosulphate solution (565 mL). The separated aqueous layer was extracted with dichloromethane and washed with brine solution (565 mL). The resulting organic layer was evaporated under vacuum.
and co-evaporated with cyclohexane. Silica and cyclohexane was added to the resulting mixture and filtered the silica and washed thoroughly with cyclohexane. Concentrated the filtrate under vacuum to yield iodo compound 5 as colorless liquid (138 gm, 93% yield). MS: m/z 459.2 [M+H]; [α]D30 13.5 (c 1.0, CHCl3); IR (CCl4) νmax: 2857, 2954 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ -0.05 - 0.05 (m, 12H), 0.85 (s, 18H), 1.60-1.65 (m, 2H), 1.94-1.99 (m, 2H), 3.15-3.18 (m, 2H), 3.60-3.62 (t, J=6.3, 2H), 3.82-3.87 (m, 1H); 13C NMR (100 MHz, CDCl3): δ -7.76, -6.80, -0.004, 15.75, 15.58, 24.50, 37.31, 38.90, 56.83, 67.17; Elem. Anal Found: C 44.52; H 8.45; Calcd for C44H39BrI: C 44.53; H 8.57.

Preparation of (S)-2,2,3,3,9,10,10-octamethyl-5-vinyl-4,8-dioxo-3,9-disilaundecane (6):

To a stirred solution of compound 5 (138 gm, 300 mmol) in tetrahydrofuran (1400 mL) potassium tertiary butoxide (67.6 gm, 602 mmol) was added at 0°C and stirred at same temperature for 2hr. After complete conversion of 5, the mixture was deuterated with methyl tertiary butyl ether (690mL) and quenched with sat. ammonium chloride solution (690 mL). The separated organic layer was washed with water and added with silica (276 gm). The resulted organic layer evaporated under reduced pressure and extracted the compound from slurry with ether followed by evaporation of solvent afforded the compound 6 as colorless oil (65.6 gm, 66% yield). MS: m/z 329.2 [M-H]; IR (CCl4) νmax: 775, 1644, 2255 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 0.094(s, 12H), 0.893-0.897 (2s, 18H), 1.594-1.783 (m, 2H), 3.618-3.709 (m, 2H), 4.246-4.308 (m, 1H), 4.997-5.040 (m, 1H), 5.111-5.178 (m, 1H), 5.759-5.871 (m, 1H).

Preparation of (S)-3,5-bis(tert-butylidimethylsilyloxy)pentan-2-one (7):

The alkene 6 (30 gm, 91 mmol) was added with stirring to a mixture of PdCl2 (8 mol %) and Cu(OAc)2.H2O (3.6 gm, 18 mmol) in N,N-dimethyl acetamide/water (7:1, 210 mL), and the ambient environment was replaced with oxygen. After complete consumption of the alkene (30 h, TLC), reaction mixture diluted with ether and filtered through celite employing ether to wash the filter cake. The resulted filtrate was washed with brine solution and separated organic layer was separated and concentrated under reduced pressure. The crude mixture diluted with N,N-dimethylformamide (150 mL) and added with imidazole (10.9 gm, 181 mmol), TBSCI (13.7 gm, 91 mmol) and N,N-dimethyl-4-aminopyridine (10 mol %). The reaction mixture heated to 75°C for 2 hrs and N,N-dimethylformamide was removed under reduced pressure. The crude mixture added with ice cold water and extracted with ether. The solvent was removed under reduced pressure and diluted with hexane. The resulted mixture diluted with hexane and filtered through silica bed. The resulted hexane filtrate on evaporation yielded the pure methyl ketone 7 as liquid (138 gm, 75% yield). MS: m/z 347.4 [M+H]; [α]D30 -10.9 (c 1.0, CHCl3); IR (CCl4) 1720, 2955 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 0.03-0.06 (m, 12H), 0.88-0.91 (2s, 18H), 1.765-1.846 (m, 2H), 2.16 (t, J=5.4, 1.2 Hz, 3H), 3.627-3.761 (m, 2H), 4.134-4.174 (dd, J=5.4, 1.2 Hz, 1H).

Preparation of (S,E)-4-(3,5-bis(tert-butylidimethylsilyloxy)-2-methylpent-1-enyl)-2-methylthiazole (8):

Under inert atmosphere Sodium bis(trimethylsilyl)amide (NaHMDS) (115gm, 627 mmol) was added at -78°C to the solution of diethyl (2-methylthiazol-4-yl)methylphosphonate, 10 (105gm, 418mmol) in tetrahydrofuran (1300 mL) and maintained for 1hr. This reaction mixture was added with compound 7 (100 gm, 288mmol) in tetrahydrofuran (900 mL). The resulting mixture was stirred at ambient temperature for 12 hr. After completion of reaction the mixture was quenched with sat ammonium chloride solution (800 mL) and extracted with ether. The organic layer was evaporated under reduced pressure to yield 8 as colorless liquid (96 gm, 75% yield). MS: m/z 442.4 [M+H]; [α]D30 -0.7 (c 0.5, CH2Cl2); IR (CCl4) νmax: 1472, 2856, 2955 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 0.007-0.063 (2s, 12H), 0.897 (s, 18H), 1.752-1.835 (m, 2H), 2.024 (s, 3H), 2.713 (s, 3H), 3.591-3.718(m, 2H), 4.192-4.234 (m, 1H), 6.491(s, 1H), 6.940 (s, 1H).

Preparation of ((S,E)-3-(tert-butylidimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)pent-4-enal (9):

D-camphor sulphonic acid (53 gm, 226mmol) was slowly added to a mixture of compound 8 (100 gm, 226mmol) dissolved methanol (1500mL) and dichloromethane (1500 mL) at 0°C and stirred for 4 hrs. After completion of reaction, resulting mixture was diluted with dichloro methane (500 mL) and quenched with 5% sodium bi carbonate solution (1 L). The solvent was evaporated from the resulted organic layer under reduced pressure. The crude mixture
was diluted with dichloromethane (195 mL) and added at 0°C to a mixture of des-martin periodinane (126 gm, 297 mmol), sodium bicarbonate (33 gm, 393 mmol) in dichloromethane (325 mL). The resulted mixture was stirred at ambient temperature for 2 hr and solvent was removed under reduced pressure. The crude mixture was diluted with petrol ether and filtered. The filtrate was concentrated under reduced pressure to yield title compound 9 as light-yellow color liquid (62 gm, 84% yield).

**MS:** m/z 326.4 [M+H]; [α]_D^25 -11.9 (c 1.0, CHCl_3); IR (CCl_4) ν~max: 778, 1720, 2955 cm^{-1}; _1H NMR (300 MHz, CDCl_3): δ 0.007-0.063 (2s, 6H), 0.897 (s, 9H), 2.027 (s, 3H), 2.754 (s, 3H), 3.591-3.718 (m, 2H), 4.192-4.234 (t, J = 6.3, 1H), 6.491 (s, 1H), 6.940 (s, 1H), 9.433-9.674 (m, 1H); HRMS (EI): calcd for C_{16}H_{28}O_2NSSi [M+H] 326.1604, found 326.1608.

**Preparation of 4-((S,1E,5Z)-3-(tert-butyldimethylsilyloxy)-6-iodo-2-methylhepta-1,5-dienyl)-2-methylthiazole (1):**

Under inert atmosphere n-butyl lithium (1.6M, 480 mL, 770 mmol) was added to the solution of ethyltriphenylphosphonium iodide (193 gm, 460 mmol) in tetrahydrofuran (1500 mL) at -10°C and stirred at ambient temperature for 30 min. This reaction mixture was slowly added to a solution of iodine (117 gm, 460 mmol) in tetrahydrofuran (2 L) at -78°C and stirred for 30 min at -30°C. Sodium hexamethyldisilazane (2M, 300 mL, 600 mmol) was slowly added to above reaction mixture and stirred for 15 min. the resulted reaction mixture was added with compound 9 (50 gm, 153 mmol) in tetrahydrofuran (500 mL) at -30°C stirred for 1 hr. After conversion of compound 9, reaction mixture was quenched with sat. ammonium chloride solution and extracted with ether. The solvent was removed from organic layer and co evaporated with petroleum ether. The resulting crude mixture was extracted with petroleum ether and concentrated under reduced pressure to yield the compound 1 as color less liquid (52 gm, 73% yield). MS: m/z 464.2 [M+H]; [α]_D^{25} +14.2 (c 1.0, CHCl_3); IR (CCl_4) ν~max: 2927, 1071, 771 cm^{-1}; _1H NMR (300 MHz, CDCl_3): δ 0.063 (2s, 6H), 0.897 (s, 9H), 2.024 (s, 3H), 2.359-2.409 (m, 2H), 2.482 (s, 2H), 2.713 (s, 3H), 4.192-4.234 (m, 1H), 5.433-5.481 (m, 1H), 6.491 (s, 1H), 6.940 (s, 1H); HRMS (EI): calcd for C_{18}H_{31}ONISSi [M+H] 464.0934, found 464.0935.