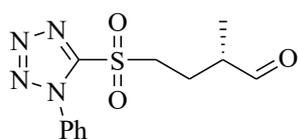


Synthesis of the acyclic precursor of an epothilone D analogue

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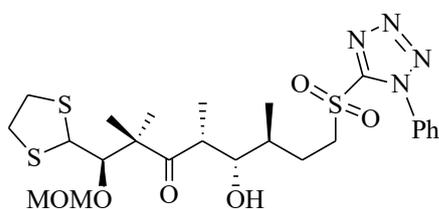
General

Solvents were purified and dried by standard procedures. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 mesh pre-coated foil plates. Column chromatography was carried out using 210–280 mesh silica gel. Optical rotations were measured using the sodium D line at 589 nm on a Perkin Elmer, Model 241 MC polarimeter. IR (infrared spectra) were recorded on a Shimadzu IRPrestige-21 spectrometer in Nujol mulls. ^1H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^1H and 500 MHz for ^{13}C) as solutions in CDCl_3 (Aldrich Chemical Company; spectra grade). Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer.



(2*S*)-2-Methyl-4-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]butanal (**8**)

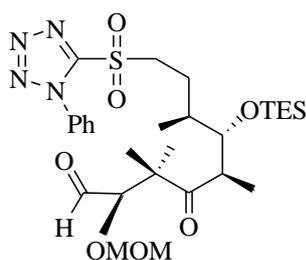
To a stirred solution of alcohol **6** (1.18 g, 4.0 mmol) in dry dichloromethane (80 mL) was added $\text{PhI}(\text{OAc})_2$ (1.93 g, 4.0 mmol) and catalytic amounts of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 10 mol%). The mixture was stirred at room temperature until completion of the reaction (TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (10% EtOAc/petroleum ether) to give product **8** (1.03 g, 88%) as a light yellow oil; [Found: C, 49.10; H, 4.88; N, 18.96; S, 10.83. $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3\text{S}$ requires C, 48.97; H, 4.79; N, 19.04; S, 10.89%]; R_f (30% ethyl acetate/petroleum ether) 0.32; $[\alpha]_D^{20}$ -28.0, (c 1.56, CH_2Cl_2); ν_{max} (Nujol mull) 2967, 2917, 2849, 1723, 1498, 1341, 1152, 765, 690 cm^{-1} ; δ_{H} (300 MHz, CDCl_3) 1.24 (3H, d, $J=7.1$ Hz), 2.01–2.08 (1H, m), 2.29–2.36 (1H, m), 2.63–2.70 (1H, m), 3.72–3.89 (2H, m), 7.62 (3H, br s), 7.67–7.70 (2H, m), 9.65 (1H, s); δ_{C} (500 MHz, CDCl_3) 13.5, 22.7, 44.4, 53.6, 125.0, 129.7, 131.5, 132.9, 153.2, 202.4.



(1*R*,4*R*,5*S*,6*S*)-1-(1,3-Dithiolan-2-yl)-5-hydroxy-1-methoxymethoxy-2,2,4,6-tetramethyl-8-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]octan-3-one (**9**)

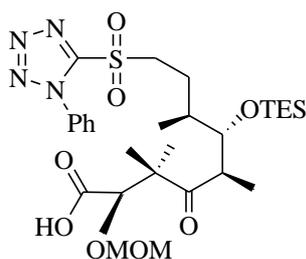
A THF solution of LiHMDS (1 M, 8.5 mL, 8.50 mmol) was added at -78°C with stirring to a solution of hydroxy sulfone **7** (1.18 g, 4.25 mmol) in THF (100 mL). The mixture was stirred for 2.5 h at $+5^\circ\text{C}$, then a solution of aldehyde **8** (0.5 g, 1.70 mmol) in THF (50 mL) was added dropwise at -78°C , and the resulting solution was stirred for 20 min at the same temperature. The cooling bath was removed, and a saturated NH_4Cl (150 mL, aq.) was added, the layers were separated, the aqueous one was extracted with EtOAc (3 \times 50 mL). The combined organic phase was dried over MgSO_4 , filtered, and evaporated. Purification of the

residue by column chromatography (15% EtOAc/petroleum ether) afforded product **9** (0.70 g, 72%) as a light yellow oil; [Found: C, 50.46; H, 6.41, N, 9.59, S, 16.85. C₂₄H₃₆N₄O₆S₃ requires C, 50.33; H, 6.34, N, 9.78; S, 16.80%]; R_f (30% ethyl acetate/petroleum ether) 0.33; $[\alpha]_D^{20} +14.3$, (*c* 1.35, CH₂Cl₂); ν_{\max} (Nujol mull) 3512, 2971, 2936, 1684, 1498, 1465, 1342, 1152, 1027, 764, 690, 545 cm⁻¹; δ_H (300 MHz, CDCl₃) 0.95 (3H, d, *J*=6.8 Hz), 1.07 (3H, d, *J*=6.8 Hz), 1.25 s (6H, s), 1.77-1.93 (2H, m), 2.22-2.26 (1H, m), 3.11-3.25 (5H, m), 3.41 (3H, s), 3.48 (1H, d, *J*=9.5 Hz), 3.80-3.93 (2H, m), 4.10-4.15 (1H, m), 4.48 (1H, d, *J*=5.6 Hz), 4.78 (1H, d, *J*=5.6 Hz), 4.92 d (1H, d, *J*=6.1 Hz), 7.61-7.69 (5H, m); δ_C (500 MHz, CDCl₃) 10.0, 16.3, 20.0, 23.5, 26.5, 34.5, 38.1, 38.3, 41.4, 53.6, 54.6, 55.5, 56.8, 75.0, 85.5, 99.6, 125.0, 129.6, 129.4, 131.4, 133.0, 153.4, 219.5.



(2R,5R,6S,7S)-2-Methoxymethoxy-3,3,5,7-tetramethyl-4-oxo-9-[(1-phenyl-1H-tetrazol-5-yl)sulfonyl]-6-(triethylsilyloxy)nonanal (10)

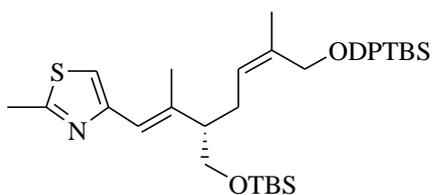
To a stirred solution of alcohol **9** (0.3 g, 0.52 mmol) in dry dichloromethane (40 mL) was added 2,6-lutidine (0.3 mL, 2.62 mmol). The resulting solution was cooled to 0°C, and Et₃SiOTf (0.23 mL, 1.05 mmol) was added dropwise. The mixture was stirred at 0°C until completion (TLC). The cooling bath was removed, and a saturated aqueous solution of NaHCO₃ (30 mL) was added, the layers were separated, the aqueous one was extracted with dichloromethane (3 × 20 mL), the combined organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was diluted with Me₂CO-H₂O (4:1, 40 mL) and CaCO₃ (0.16 g, 1.57 mmol) was added to the mixture under vigorous stirring. The solution was heated under reflux, and MeI (0.33 mL, 5.24 mmol) was added dropwise within 8 h. The reaction mixture was stirred under reflux over 8 h, until the starting material was consumed (TLC). The mixture was filtered, diluted with EtOAc (30 mL), dried over MgSO₄, filtered again, and evaporated. Purification of the residue by column chromatography (15% ethyl acetate/petroleum ether) afforded product **10** (0.22 g, 69%) as a light yellow oil; [Found: C, 55.17; H, 7.64; N, 9.05; S, 5.18; Si, 4.51. C₂₈H₄₆N₄O₇SSi requires C, 55.06; H, 7.59; N, 9.17; S, 5.25; Si, 4.60]; R_f (25% ethyl acetate/petroleum ether) 0.45; $[\alpha]_D^{20} +3.5$, (*c* 0.87, CH₂Cl₂); ν_{\max} (Nujol mull) 2958, 2915, 2878, 1727, 1696, 1498, 1462, 1341, 1153, 1041, 1004, 987, 740 cm⁻¹; δ_H (300 MHz, CDCl₃) 0.61-0.68 (6H, m), 0.97 (9H, t, *J*=8.0 Hz), 1.03 (3H, d, *J*=6.8 Hz), 1.13 (3H, d, *J*=6.9 Hz), 1.30 (3H, s), 1.35 (3H, s), 1.51-1.56 (2H, m), 1.99-2.08 (1H, m), 3.06-3.11 (1H, m), 3.40 (3H, s), 3.53-3.65 (1H, m), 3.78-3.92 (3H, m), 4.64-4.71 m (2H, m), 7.63-7.72 (5H, m), 9.72 (1H, s); δ_C (500 MHz, CDCl₃) 5.4, 7.0, 16.0, 17.9, 22.0, 22.5, 22.8, 36.0, 45.1, 54.3, 54.6, 56.3, 78.4, 86.7, 97.7, 125.0, 129.7, 131.4, 133.0, 153.3, 202.33, 216.5.



(2R,5R,6S,7S)-2-Methoxymethoxy-3,3,5,7-tetramethyl-4-oxo-9-[(1-phenyl-1H-tetrazol-5-yl)sulfonyl]-6-(triethylsilyloxy)nonanoic acid (11)

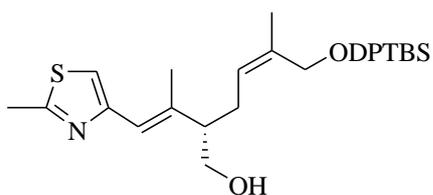
To a stirred solution of aldehyde **10** (0.3 g, 0.49 mmol) in *t*-BuOH-THF-H₂O mixture (5:5:1, 30 mL) was added 2,3-dimethylbut-2-ene (7.5 mL), Na₂HPO₄ (0.2 g, 1.23 mmol) and NaClO₂ (0.23 g, 2.55 mmol). The mixture was stirred at room temperature over 16 h and then filtered. The filter cake was washed with EtOAc (30 mL), the filtrate was dried over

MgSO₄, and concentrated. Purification of the residue by column chromatography (25% *t*-BuOH/chloroform) afforded product **11** (0.25 g, 81%) as a yellow oil; [Found: C, 53.51; H, 7.48; N, 9.04; S, 4.96; Si, 4.39. C₂₈H₄₆N₄O₈SSi requires C, 53.65; H, 7.40; N, 8.94; S, 5.12; Si, 4.48%]; R_f (ethyl acetate) 0.1; $[\alpha]_D^{20}$ +3.1, (*c* 1.23, CH₂Cl₂); ν_{\max} (Nujol mull) 2959, 2878, 1743, 1697, 1498, 1463, 1342, 1153, 1046, 994, 764, 740, 689 cm⁻¹; δ_H (300 MHz, CDCl₃) 0.60-0.66 (6H, m), 0.94 (9H, t, *J*=8.0 Hz), 1.12 (3H, d, *J*=6.8 Hz), 1.25 (3H, d, *J*=6.9 Hz), 1.30 (3H, s), 1.34 (3H, s), 1.59 (1H, br.s), 1.80-1.82 (1H, m), 2.01-2.07 (1H, m), 3.14-3.17 (1H, m), 3.37 (3H, s), 3.58-3.64 (1H, m), 3.82-3.90 (2H, m), 4.40 (1H, s), 4.62-4.67 (2H, m), 7.57-7.62 (3H, m), 7.68-7.70 (2H, m); δ_C (500 MHz, CDCl₃) 5.1, 5.37, 5.5, 5.6, 7.1, 16.3, 17.9, 20.6, 22.7, 22.9, 36.0, 45.2, 51.4, 54.6, 56.7, 76.8, 77.1, 77.3, 78.3, 80.7, 97.4, 125.0, 128.3, 129.7, 131.4, 133.0, 153.3, 175.4, 216.7.



4-((1*E*,3*S*,5*Z*)-3-[*tert*-Butyl(dimethyl)-silyloxymethyl]-7-[*tert*-butyl(diphenyl)silyloxy]-2,6-dimethylhepta-1,5-dien-1-yl)-2-methyl-1,3-thiazole (12**)**

Compound **5** (0.35 g, 0.92 mmol) was dissolved in CH₂Cl₂ (40 mL), and to this solution were added imidazole (0.14 g, 2.02 mmol), DMAP (0.06 g, 0.46 mmol) and *t*-BuPh₂SiCl (0.31 mL, 1.19 mmol). The mixture was stirred for 12 h, concentrated, and the residue was purified by column chromatography (6% EtOAc/petroleum ether) to provide product **12** (0.57 g, quant) as a colorless liquid; [Found: C, 69.68; H, 8.50; N, 2.17; S, 5.26; Si, 8.90. C₃₆H₅₃NO₂SSi₂ requires C, 69.73; H, 8.62; N 2.26; S, 5.17; Si, 9.06%]; R_f (20% ethyl acetate/petroleum ether) 0.81; $[\alpha]_D^{20}$ +0.9, (*c* 5.2, CH₂Cl₂); ν_{\max} (Nujol mull) 2957, 2930, 2857, 1472, 1428, 1114, 822, 701, 505 cm⁻¹; δ_H (300 MHz, CDCl₃) 0.86 (6H, s), 1.08 (9H, s), 1.10 (9H, s), 1.82 (3H, s), 1.90 (3H, s), 2.15-2.28 (2H, m), 2.35-2.39 (1H, m), 2.69 (3H, s), 3.48-3.61 (2H, m), 4.22 (2H, s), 5.19-5.23 (1H, m), 6.30 (1H, s), 6.81 (1H, s), 7.37-7.43 (6H, m), 7.70-7.75 (4H, m); δ_C (500 MHz, CDCl₃) -5.4, 16.5, 18.3, 19.3, 21.3, 25.9, 26.9, 27.6, 52.3, 62.7, 65.6, 114.4, 124.4, 127.7, 129.7, 134.9, 135.4, 135.7, 140.9, 152.4, 164.8.

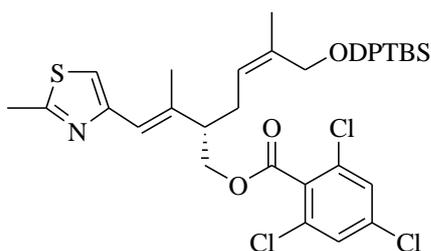


(2*S*,4*Z*)-6-[*tert*-Butyl(diphenyl)silyloxy]-5-methyl-2-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)vinyl]hex-4-en-1-ol (13**)**

To an ice-bath cooled solution of compound **12** (0.44 g, 0.71 mmol) in MeOH-CH₂Cl₂ (1:1, 40 mL) was added TsOH (0.04 g, 0.21 mmol). The mixture was stirred at 15°C for 12 h, then the mixture was quenched with solid NaHCO₃ and filtered. The filtrate was evaporated and the residue was purified by column chromatography (30% EtOAc/petroleum ether) to provide product **13** (0.33 g, 92%) as a light yellow oil; [Found: C, 71.15; H, 7.63; N, 2.72; S, 6.27; Si, 5.63. C₃₀H₃₉NO₂SSi requires C, 71.24; H, 7.77; N, 2.77; S, 6.34; Si, 5.55%]; R_f (50% ethyl acetate/petroleum ether) 0.32; $[\alpha]_D^{20}$ +4.7, (*c* 1.94, CH₂Cl₂); ν_{\max} (Nujol mull) 3386, 2956, 2931, 2857, 1472, 1428, 1112, 1070, 824, 740, 702, 615, 504 cm⁻¹; δ_H (300 MHz, CDCl₃) 1.05 (9H, s), 1.80 (3H, s), 1.89 (3H, s), 1.95-1.98 (2H, m), 2.26-2.30 (1H, m), 2.70 (3H, s), 3.50 (2H, d, *J*=6.5 Hz), 4.11-4.18 (2H, m), 5.16-5.20 (1H, m), 6.32 (1H, s), 6.85 (1H, s), 7.38-7.41 (6H, m), 7.68-

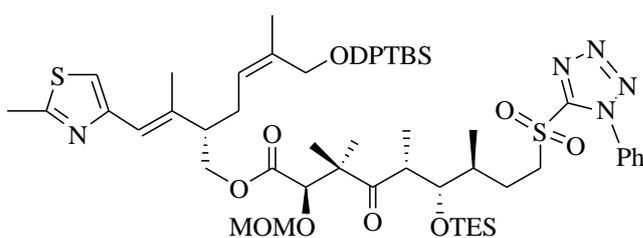
7.70 (4H, m); δ_C (500 MHz, CDCl_3) 15.5, 19.0, 19.2, 21.3, 26.8, 27.6, 52.3, 62.6, 63.8, 115.1, 121.2, 124.0, 127.6, 129.6, 133.7, 135.6, 135.8, 140.2, 152.7, 164.6.

General procedure for the Yamaguchi esterification. To a stirred solution of acid **11** (0.31 g, 0.49 mmol) in dry THF (25 mL) were added Et_3N (0.14 mL, 0.99 mmol) and 2,4,6-trichlorobenzoyl chloride (0.08 mL, 0.49 mmol). The mixture was stirred for 1 h, followed by successive addition of solution of alcohol **13** (0.25 g, 0.49 mmol) in THF (5 mL) and catalytic amounts of DMAP. The stirring was continued for 3 h, and then the solid was isolated by filtration. The filtrate was concentrated and the residue was purified by column chromatography (15% ethyl acetate/petroleum ether) to give products **15** (0.12 g, 35%) and **4** (0.33 g, 60%) as a light yellow oils.



(2S,4Z)-6-[*tert*-Butyl(diphenyl)silyloxy]-5-methyl-2-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)vinyl]hex-4-en-1-yl 2,4,6-trichlorobenzoate (15**)**

[Found: C, 62.37; H, 5.53; Cl, 14.83; N, 1.89; S, 4.37; Si, 3.99. $\text{C}_{37}\text{H}_{40}\text{Cl}_3\text{NO}_3\text{SSi}$ requires C, 62.31; H, 5.65; Cl, 14.91; N, 1.96; S, 4.50; Si, 3.94%]; R_f (15% ethyl acetate/petroleum ether) 0.74; $[\alpha]_D^{20}$ -4.4, (c 0.9, CH_2Cl_2); ν_{max} (Nujol mull) 2930, 2958, 2857, 1741, 1581, 1428, 1372, 1273, 1115, 822, 703, 504 cm^{-1} ; δ_H (300 MHz, CDCl_3) 1.04 (9H, s), 1.81 (3H, s), 1.93 (3H, s), 1.99-2.12 (2H, m), 2.53-2.57 (1H, m), 2.70 (3H, s), 4.17 (2H, d, $J=2.0$ Hz), 4.27-4.38 (2H, m), 5.16-5.20 (1H, m), 6.31 (1H, s), 6.82 (1H, s), 7.27 (2H, s), 7.37-7.44 (6H, m), 7.66-7.68 (4H, m); δ_C (500 MHz, CDCl_3) 15.5, 19.1, 19.2, 21.3, 26.8, 27.8, 48.5, 62.5, 67.6, 115.1, 122.9, 127.6, 127.7, 129.6, 132.1, 132.5, 133.7, 135.6, 136.0, 136.5, 141.4, 152.1, 164.0, 164.4.



(2S,4Z)-6-[*tert*-Butyl(diphenyl)-silyloxy]-5-methyl-2-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)vinyl]-hex-4-en-1-yl (2*R*,5*R*,6*S*,7*S*)-2-methoxymethoxy-3,3,5,7-tetramethyl-4-oxo-9-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]-6-(triethylsilyloxy)nonanoate (4**)**

[Found: C, 62.55; H, 7.61; N, 6.22; S, 5.63; Si, 5.10. $\text{C}_{58}\text{H}_{83}\text{N}_5\text{O}_9\text{S}_2\text{Si}_2$ requires C, 62.50; H, 7.51; N, 6.28; S, 5.75; Si, 5.04%]; R_f (15% ethyl acetate/petroleum ether) 0.28; $[\alpha]_D^{20}$ -2.3, (c 1.13, CH_2Cl_2); ν_{max} (Nujol mull) 2958, 2934, 2878, 1744, 1696, 1499, 1464, 1341, 1153, 1112, 1045, 997, 741, 703, 504 cm^{-1} ; δ_H (300 MHz, CDCl_3) 0.59-0.67 (6H, m), 0.95 (9H, t, $J=8.0$ Hz), 1.0 (3H, d, $J=6.9$ Hz), 1.04 (9H, s), 1.07 (3H, s), 1.08 (3H, d, $J=7.0$ Hz), 1.24 (3H, s), 1.54-1.58 (1H, m), 1.80 (3H, s), 1.87 (3H, s), 1.94-1.99 (4H, m), 2.43-2.47 (1H, m), 2.69 (3H, s), 3.09-3.14 (1H, m), 3.26 (3H, s), 3.56-3.65 (1H, m), 3.83-3.87 (2H, m), 4.04-4.15 (4H, m), 4.33 (1H, s), 4.50 (2H, s), 5.12-5.17 (1H, m), 6.26 (1H, s), 6.81 (1H, s), 7.38-7.40 (5H, m), 7.59-7.71 (10H, m); δ_C (500 MHz, CDCl_3) 5.4, 7.1, 15.24, 16.4, 17.9, 19.2, 19.8, 21.2, 22.8, 23.0, 26.8, 27.8, 36.0, 45.1, 48.7, 51.0, 54.6, 56.5, 62.5, 66.2, 78.3, 80.4, 96.9, 115.1, 123.0, 125.0, 127.6, 129.6, 129.7, 131.4, 133.0, 133.7, 135.6, 136.4, 139.9, 152.8, 153.4, 164.3, 170.8, 216.6.