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Synthesis of the C^6–C^{21} fragment of epothilone analogues

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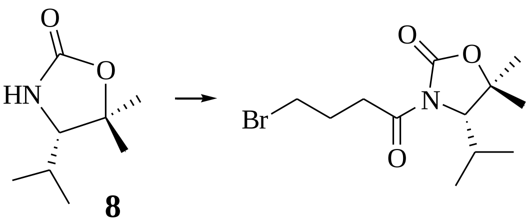
List of abbreviations

APCI	atmospheric pressure chemical ionization
DMAP	4-(dimethylamino)pyridine
KHMDS	potassium hexamethyldisilazide
NaHMDS	sodium hexamethyldisilazide
p-TSA	*p*-toluenesulfonic acid
TBSCl	*tert*-butyldimethylsilyl chloride
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TLC	thin-layer chromatography

Experimental

General

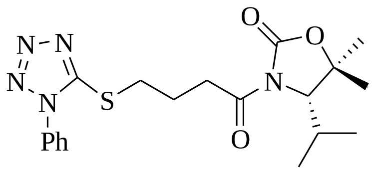
Solvents were purified and dried before used by standard procedures. Reagents were generally the best quality commercial grade and used without further purification unless indicated. All reactions were carried in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 mesh precoated 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) was recorded on a Shimadzu IRPrestige-21 spectrometer as a nujol mull. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^{1}H and 75.47 MHz for ^{13}C) as solutions in $CDCl_3$ (Aldrich Chemical Company; spectra grade). Mass spectra were recorded on Shimadzu LCMS QP-2010EV (APCI) spectrometer. Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer.



8

(4*S*)-3-(4-bromobutanoyl)-4-isopropyl-5,5-dimethyl-1,3-oxazolidin-2-one (9)

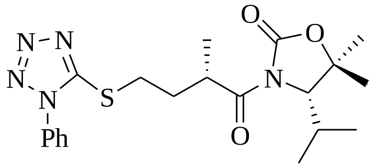
A 2.0 M solution of *n*-butyllithium in hexane (3.2 ml, 6.37 mmol) was added to a stirred solution of oxazolidinone **8** (0.50 g, 3.18 mmol) in dry tetrahydrofuran (20 ml) under Ar at -80 ^{o}C, the mixture was stirred for 40 min, and a solution of 4-bromobutyryl chloride (0.77 g, 4.15 mmol) in tetrahydrofuran (5 ml) was added dropwise. The reaction mixture was stirred for 2 h at -80 ^{o}C and then allowed to warm to -60 ^{o}C, followed by addition of a solution of tetrahydrofuran-water (4:1, 20 ml). The mixture was allowed to reach room temperature and then was treated with a saturated solution of ammonium chloride. The organic phase was separated, the aqueous phase was extracted with ethyl acetate (2 × 30 ml), the extracts were combined with the organic phase and dried over $MgSO_4$, filtered, and evaporated. Purification of the product by column chromatography (30% ethyl acetate/light petroleum) afforded product **9** (0.81 g, 84%) as a light yellow oil; [Found: C, 46.9; H, 6.6; Br 26.0; N, 4.4. $C_{12}H_{20}BrNO_3$ requires C, 47.07; H, 6.58; Br, 26.10; N, 4.57%]; R_f (25% ethyl acetate/light petroleum) 0.51; $[\alpha]_D^{20}$ +29.3 (*c* 3.94, CH_2Cl_2); ν_{max} (Nujol mull) 2971, 2933, 2880, 1774, 1701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.94 (3H, d, *J*=7.0 Hz), 1.01 (3H, d, *J*=7.0 Hz), 1.38 (3H, s), 1.50 (3H, s), 2.11-2.15 (1H, m), 2.20-2.25 (2H, m), 3.05-3.18 (2H, m), 3.49 (2H, t, *J*=6.7 Hz), 4.13 (1H, d, *J*=3.1 Hz); δ_C (75 MHz, $CDCl_3$) 17.1, 21.4, 21.6, 27.3, 28.9, 29.6, 32.7, 33.9, 66.4, 83.0, 153.5, 172.5; *m/z* (APCI) 307 (68, MH$^+$), 227 (100%).



(4*S*)-4-isopropyl-5,5-dimethyl-3-{4-[(1-phenyl-1*H*-tetrazol-5-yl)thio]butanoyl}-1,3-oxazolidin-2-one (10)

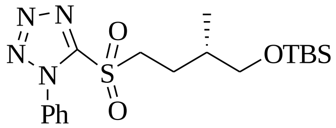
Compound **9** (0.78 g, 2.55 mmol) was added to a stirred solution of 1-phenyl-1*H*-tetrazole-5-thiol (0.59 g, 3.31 mmol) and anhydrous potassium carbonate (0.57 g, 5.38 mmol) in acetone (30 ml) and stirred overnight at room temperature. The mixture was then filtered, concentrated and the residue was purified by column chromatography (15% ethyl acetate/light petroleum) to provide product **10** (0.91 g, 88%) as a colorless liquid; [Found: C, 56.33; H, 6.09; N, 17.14; S, 7.86. $C_{19}H_{25}N_5O_3S$ requires C, 56.56; H, 6.24; N, 17.36; S, 7.95%]; R_f (25% ethyl acetate/light petroleum) 0.22; $[\alpha]_D^{20}$ +21.8 (*c* 2.49, CH_2Cl_2); ν_{max} (Nujol mull) 2976, 2934, 2879, 1768, 1736, 1701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, d, *J*=7.0 Hz), 1.01 (3H, d, *J*=7.0 Hz), 1.38 (3H, s), 1.50 (3H, s), 2.11-2.15 (1H, m), 2.21-2.26 (2H, m), 3.05-3.18 (2H, m), 3.47-3.50

(2H, m), 4.13 (1H, d, *J*=3.1 Hz), 7.53-7.57 (5H, m); δ$_C$ (75 MHz, $CDCl_3$) 17.0, 21.4, 23.9, 28.8, 29.5, 32.4, 34.0, 66.3, 83.0, 123.9, 129.8, 130.1, 133.6, 153.5, 154.1, 172.4; *m/z* (APCI) 404 (51, MH^+), 178 (100%).



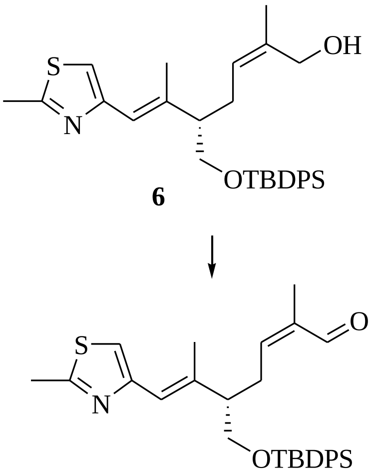
(4*S*)-4-isopropyl-5,5-dimethyl-3-{(2*S*)-2-methyl-4-[(1-phenyl-1*H*-tetrazol-5-yl)thio]butanoyl}-1,3-oxazolidin-2-one (11)

A 1 M solution of NaHMDS in tetrahydrofuran (4.3 ml, 4.32 mmol) was added at -78 °C with stirring to a solution of compound **10** (0.87 g, 2.16 mmol) in dry tetrahydrofuran (30 ml). The reaction mixture was stirred for 1 h, then a solution of MeI (0.94 ml, 15.1 mmol) in tetrahudrofuran (10 ml) was added dropwise at -78 °C. The reaction mixture was stirred for 2 h at -70 °C, the cooling bath was removed, and the mixture was allowed to warm to room temperature. Saturated aqueous solution of NH_4Cl (40 ml) was added, the layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 30 ml), the combined organic phase was dried over $MgSO_4$, filtered and evaporated. Purification of the residue by column chromatography (15% ethyl acetate/light petroleum) afforded product **11** (*dr* 10:1) (0.77 g, 85%) as a colorless liquid; [Found: C, 57.27; H, 6.54; N, 16.82; S, 7.51. $C_{20}H_{27}N_5O_3S$ requires C, 57.53; H, 6.52; N, 16.77; S, 7.68%]; R$_f$ (25% ethyl acetate/light petroleum) 0.31; $[\alpha]_D^{20}$ +37.8 (*c* 1.95, CH_2Cl_2); ν_{max} (Nujol mull) 2971, 2931, 2878, 2853, 1772, 1730, 1698 cm^{-1}; δ$_H$ (300 MHz, $CDCl_3$) 0.92 (3H, d, *J*=7.0 Hz), 0.98 (3H, d, *J*=7.0 Hz), 1.31 (3H, d, *J*=6.7 Hz), 1.36 (3H, s), 1.48 (3H, s), 1.89-1.94 (1H, m), 2.11-2.15 (1H, m), 2.29-2.33 (1H, m), 3.34-3.37 (1H, m), 3.43-3.48 (1H, m), 3.88-3.91 (1H, m), 4.17 (1H, d, *J*=3.1 Hz), 7.51-7.55 (5H, m); δ$_C$ (75 MHz, $CDCl_3$) 16.9, 18.5, 21.4, 21.6, 28.8, 29.6, 31.0, 31.9, 37.1, 66.1, 82.8, 124.0, 129.8, 130.2, 133.7, 153.0, 154.5, 176.4; *m/z* (APCI) 418 (34, MH^+), 241 (100%). The given NMR description for compound **11** is the one of the obtained major isomer.



5-[((3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylbutyl)sulfonyl]-1-phenyl-1*H*-tetrazole (5)

A 1 M solution of $LiAlH_4$ in tetrahydrofuran (1.8 ml, 1.76 mmol) was added to a solution of compound **11** (0.61 g, 1.46 mmol) in dry tetrahydrofuran (25 ml) at 5 °C within 30 min. The mixture was stirred at room temperature for 1 h and then quenched by addition of THF-H_2O (1:1, 40 ml). The layers were separated, the aqueous layer was extracted with ether (3 × 30 ml), the combined organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in ethanol (25 ml) and to this solution, cooled to 0 °C, a solution of $(NH_4)_6Mo_7O_{24}\cdot4H_2O$ (0.36 g, 0.29 mmol) in 35% aqueous H_2O_2 (2.13 g, 21.9 mmol) was added. The cooling bath was removed, and the mixture was stirred for 12 h. The mixture was poured onto brine (25 ml), extracted with ether (3 × 30 ml), the combined organic phase was dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in dichloromethane (25 ml) and to this solution were added imidazole (0.22 g, 3.22 mmol), DMAP (0.09 g, 0.73 mmol) and TBSCl (0.33 g, 2.19 mmol). The mixture was stirred for 8 h, concentrated and the residue was purified by column chromatography (6% ethyl acetate/light petroleum) to provide product **5** (0.39 g, 65%) as a colorless liquid; [Found: C, 52.76; H, 7.07; N, 13.46; S, 7.58. $C_{18}H_{30}N_4O_3SSi$ requires C, 52.65; H, 7.36; N, 13.64; S, 7.81%]; R_f (10% ethyl acetate/light petroleum) 0.52; $[\alpha]_D^{20}$ -5.4 (*c* 1.73, CH_2Cl_2); ν_{max} (Nujol mull) 3445, 2957, 2929, 2898, 2857, 1472, 1344, 1258, 1154, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 (6H, s), 0.87 (9H, s), 0.93 (3H, d, *J*=7.0 Hz), 1.77-1.86 (2H, m), 2.02-2.08 (1H, m), 3.39-3.44 (1H, m), 3.52-3.57 (1H, m), 3.79-3.84 (2H, m), 7.57-7.69 (5H, m); δ_C (75 MHz, $CDCl_3$) -3.0, 16.3 18.2, 25.6, 25.9, 34.7, 54.5, 66.6, 125.1, 129.7, 131.4, 133.1, 153.5; *m/z* (APCI) 409 (38, $[M-H]^-$), 339 (100), 325 (74%).



6

(2*Z*,5*S*,6*E*)-5-{[*tert*-butyl(diphenyl)silyloxy]methyl}-2,6-dimethyl-7-(2-methyl-1,3-thiazol-4-yl)hepta-2,6-dienal (7)

Iodosobenzene diacetate (0.95 g, 2.96 mmol) and TEMPO (0.05 g, 0.32 mmol) were added to a solution of **6** (0.75 g, 1.48 mmol) in dichloromethane (25 ml) and the mixture was stirred at room temperature until the starting compound was consumed (~6 h, TLC monitoring). The solution was then concentrated and the residue was purified by column chromatography (10% ethyl acetate/light petroleum) to provide **7** (0.70 g, 93%) as a light yellow oil; [Found: C, 71.50; H, 7.28; N, 2.62; S, 6.15. $C_{30}H_{37}NO_2SSi$ requires C, 71.53; H, 7.40; N, 2.78; S, 6.37%]; R_f (25% ethyl acetate/light petroleum) 0.43; $[\alpha]_D^{20}$ +0.8 (*c* 0.84, CH_2Cl_2); ν_{max} (Nujol mull) 2956, 2929, 2857, 1678, 1112, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.05 (9H, s), 1.73 (3H, s), 1.93 (3H, s), 2.46-2.53 (1H, m), 2.65-2.67 (1H, m), 2.70 (3H, s), 2.94-3.01 (1H, m), 3.65-3.79 (2H, m), 6.32 (1H, s), 6.47 (1H, t, *J*=7.0 Hz), 6.85 (1H, s), 7.37-7.43 (6H, m), 7.64 (4H, d, *J*=6.7 Hz), 10.13 (1H, s); δ_C (75 MHz, $CDCl_3$) 16.5, 16.7, 19.2, 20.6, 26.9, 29.7, 52.2, 66.0, 115.2, 121.3, 127.7, 129.8, 133.5, 135.6, 136.7, 139.1, 147.4, 154.8, 164.4, 191.1; *m/z* (APCI) 505 (18, MH^+), 475 (100%).