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Synthesis of a Chiral Building Block for the C^6–C^9 Fragment of Epothilones

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Abstract—A procedure has been developed for the synthesis of a new chiral building block for epothilone analogs starting from L-malic acid.

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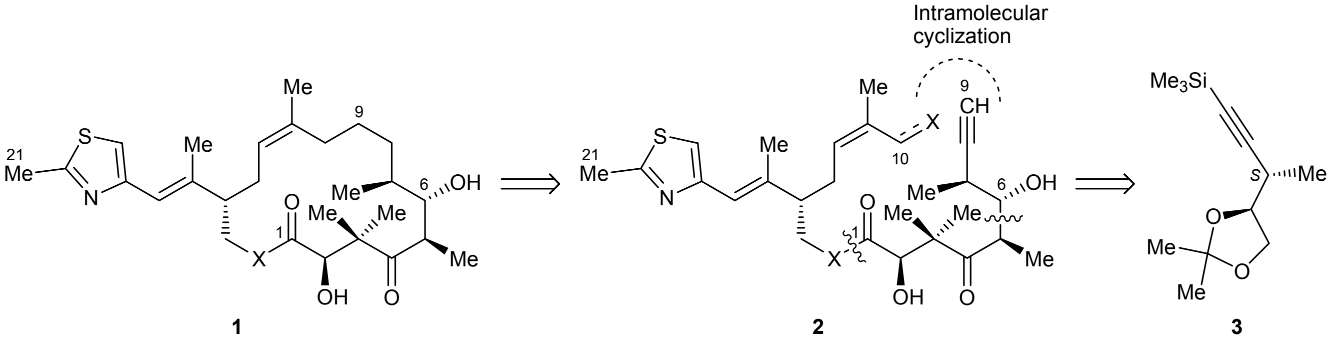
Much attention is given to the preparation of individual isomers of chiral building blocks (synthons) for directed synthesis [1]. While developing a synthetic approach to epothilone D analogs **1** [2, 3] through key acyclic precursor **2**, it was necessary to obtain building block **3** containing *S*-configured CHMe fragment. We planned to use compound **3** for the construction of the C^6–C^9 fragment of epothilone **1** molecule (Scheme 1).

We have developed a simple and efficient synthesis of individual diastereoisomer **3** starting from L-malic acid (**4**) (Scheme 2). The alkylation of diester **5** derived from L-malic acid (**4**) [4] gave a mixture of diastereoisomers at a ratio of 6 : 1 (GLC) in favor of the desired isomer **6** [5], which could not be separated by silica gel chromatography. Thew reduction of **6** with $LiAlH_4$, $(i\text{-}Bu)_2AlH$, or $BH_3 \cdot THF$ afforded triol **7** in very poor yield (10–20%), whereas compound **7** was smoothly obtained in 89% yield by heating diester **6** with $NaBH_4$ in EtOH [6]. Selective protection of vicinal hydroxy groups in **7** was achieved by acetalization with acetone according to [7]. Swern oxidation of primary alcohol **8** gave aldehyde **9** which was subjected to Corey–Fuchs olefination [8]. Geminal dibromide **10** thus obtained was treated in succession with butyllithium and chloro(trimethyl)silane. The resulting compound **3** was separated from minor diastereoisomer by column chromatography on silica gel. The diastereoisomeric purity of **3** was 99% (GLC).

EXPERIMENTAL

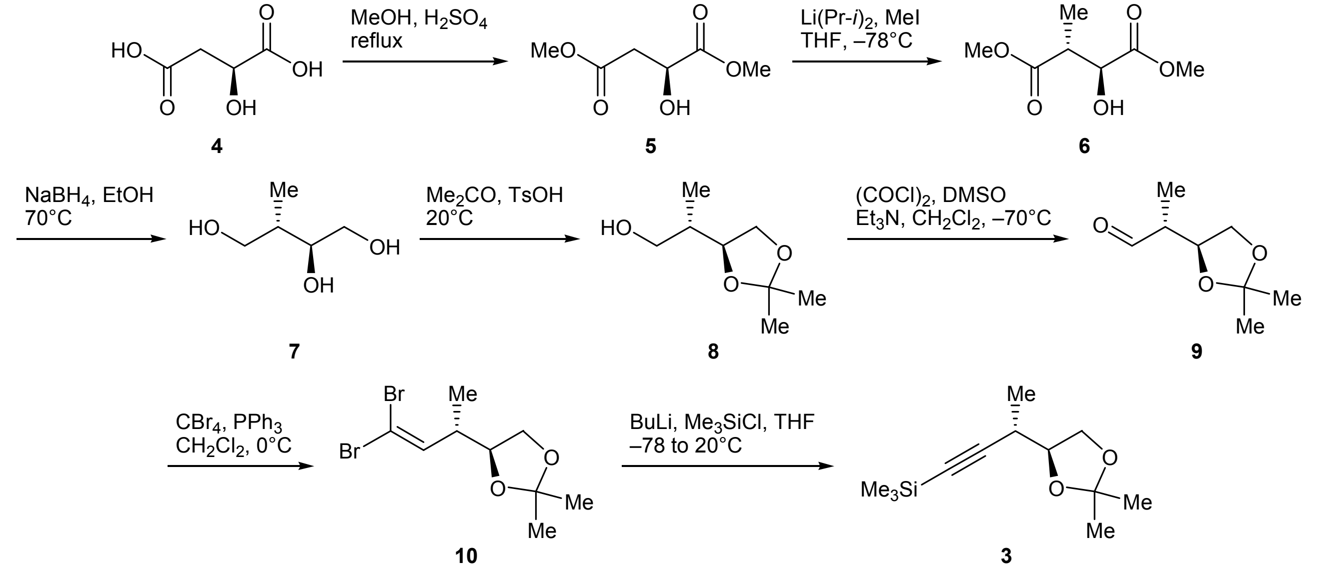
The IR spectra were recorded on a UR-20 spectrometer from thin films or Nujol mulls. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively,

Scheme 1.



1, X = O, NH; **2**, X = O, I.

Scheme 2.



using $CDCl_3$ as solvent and tetramethylsilane as internal standard. The mass spectra were obtained on a Shimadzu LCMS-2010 EV instrument. Analytical TLC was performed on Sorbfil plates (Russia). Silica gel (Lancaster, UK) was used for column chromatography. The optical rotations were measured using a Perkin-Elmer 241 MS polarimeter. The purity of the isolated compounds was checked by GLC on a Chrom 5 chromatograph.

Dimethyl (2*S*,3*R*)-2-hydroxy-3-methylbutanedioate (6). A solution of 18.7 mL (133 mmol) of diisopropylamine in 100 mL of THF was cooled to –78°C, 39.7 mL (111 mmol) of a 2.8 N solution of butyllithium in hexane was added dropwise under stirring, and the mixture was stirred for 30 min at –10°C. The mixture was cooled to –78°C, a solution of 6.0 g (37.0 mmol) of diester **5** in 30 mL of THF was added dropwise, and the mixture was allowed to warm up to –20°C over a period of 45 min. The mixture was cooled again to –78°C, 11.5 mL (185 mmol) of methyl iodide was added dropwise, and the mixture was stirred for 30 min at 0°C and treated with a 1 M solution of citric acid. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (2×50 mL), the extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated, and the residue was subjected to silica gel chromatography using petroleum ether–ethyl acetate (4:1) as eluent. Yield 5.21 g (80%), light yellow liquid, *de* 86% (GLC). IR spectrum, ν, cm^{-1}: 3492, 2988, 2956, 1742, 1439, 1212, 1143. ^1H NMR spectrum, δ, ppm: 1.26 d (3H, CH_3, *J* = 6.7 Hz), 2.99–3.02 m (1H, 3-H), 3.12 br.s (1H, OH), 3.65 s (3H, OCH_3), 3.76 s (3H, OCH_3), 4.25 d (1H, 2-H, *J* = 3.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.0, 43.1, 51.9, 52.6, 72.4, 173.3, 173.6. Found, %: C 47.68; H 6.71. $C_7H_{12}O_5$. Calculated, %: C 47.72; H 6.87.

(2*S*,3*S*)-3-Methylbutane-1,2,4-triol (7). A solution of 5.1 g (29.0 mmol) of **6** in 20 mL of ethanol was added dropwise under stirring to a solution of 2.2 g (58.0 mmol) of $NaBH_4$ in 50 mL of ethanol. The mixture was stirred for 5 h at 70°C, cooled to 0°C, acidified to pH ~2 with 35% aqueous HCl, and filtered. The filtrate was diluted with 150 mL of methanol and evaporated, the residue was dissolved in methylene chloride, sodium hydrogen carbonate was added to neutral reaction, and the solution was dried over $MgSO_4$ and evaporated under reduced pressure. Yield 3.09 g (89%), light yellow liquid, *de* 86% (GLC). IR spectrum, ν, cm^{-1}: 3350, 2966, 2935, 2882, 1428, 1340, 1040. ^1H NMR spectrum, δ, ppm: 0.87 d (3H, CH_3, *J* = 6.7 Hz), 1.81–1.91 m (1H, 3-H), 3.56–3.68 m (2H, 1-H, 2-H), 3.72–3.79 m (2H, 4-H), 4.24–4.34 m (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 13.6, 37.2, 65.0, 67.2, 74.0. Found, %: C 49.81; H 10.11. $C_5H_{12}O_3$. Calculated, %: C 49.98; H 10.07.

(2*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-propan-1-ol (8). A catalytic amount of *p*-toluenesulfonic acid was added under stirring to a solution of 2.95 g (24.6 mmol) of **7** in 60 mL of acetone. The mixture was stirred for 6 h at room temperature, neutralized with sodium hydrogen carbonate, filtered, and evaporated, and the residue was purified by silica gel chromatography (petroleum ether–EtOAc, 5:1).

Yield 3.38 g (86%), light yellow liquid, *de* 86% (GLC). IR spectrum, ν, cm^{-1}: 3398, 2986, 2936, 2880, 1380, 1371, 1216, 1063, 1043. ^{1}H NMR spectrum, δ, ppm: 0.82 d (3H, CH_3, *J* = 7.0 Hz), 1.36 s and 1.41 s [3H each, $C(CH_3)_2$], 1.81–1.89 m (1H, 2-H), 3.57–3.75 m (4H, 1-H, 5′-H), 4.06–4.11 m (1H, 4′-H). ^{13}C NMR spectrum, δ_C, ppm: 13.0, 25.7, 26.6, 39.2, 67.4, 68.7, 80.7, 109.4. Found, %: C 59.94; H 9.95. $C_8H_{16}O_3$. Calculated, %: C 59.97; H 10.07.

(2*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-propanal (9). A solution of 3.2 mL (37.5 mmol) of oxalyl chloride in 60 mL of methylene chloride was cooled to –60°C, a solution of 5.3 mL (75.0 mmol) of dimethyl sulfoxide in 10 mL of methylene chloride was added dropwise under stirring, and the mixture was stirred for 10 min at –60°C. The mixture was cooled to –78°C, a solution of 3.0 g (18.8 mmol) of **8** in 10 mL of methylene chloride was added, the mixture was stirred for 15 min at –60°C and cooled to –78°C, 13.0 mL (93.8 mmol) of triethylamine was added, and the mixture was stirred for 10 min at –78°C. The mixture was then allowed to warm up to room temperature, treated with water, and saturated with sodium chloride, the organic layer was separated, and the aqueous phase was extracted with methylene chloride (2×50 mL). The extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by silica gel chromatography (petroleum ether–EtOAc, 5:1). Yield 2.28 g (77%), light yellow liquid, *de* 86% (GLC). IR spectrum, ν, cm^{-1}: 2986, 2938, 1729, 1381, 1371, 1214, 1162, 1062. ^{1}H NMR spectrum, δ, ppm: 1.07 d (3H, CH_3, *J* = 7.0 Hz), 1.35 s and 1.41 s [3H each, $C(CH_3)_2$], 2.56–2.61 m (1H, 2-H), 3.64–3.73 m (2H, 5′-H), 4.10–4.14 m (1H, 4′-H), 9.77 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 9.9, 25.3, 26.5, 49.6, 67.4, 75.9, 109.9, 203.2. Found, %: C 60.80; H 8.79. $C_8H_{14}O_3$. Calculated, %: C 60.74; H 8.92.

(4*S*)-4-[(2*S*)-4,4-Dibromobut-3-en-2-yl]-2,2-dimethyl-1,3-dioxolane (10). A solution of 16.6 g (63.3 mmol) of triphenylphosphine in 40 mL of methylene chloride was added dropwise under stirring to a solution of 10.5 g (31.6 mmol) of carbon tetrabromide in 40 mL of methylene chloride, cooled to 0°C. The mixture was stirred for 10 min at 0°C, a solution of 2.0 g (12.7 mmol) of **9** in 20 mL of methylene chloride was added, and the mixture was stirred for 15 min at 0°C and neutralized with a solution of sodium hydrogen carbonate. The organic phase was separated, the aqueous phase was extracted with methylene chloride (2×50 mL), the extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by silica gel chromatography (petroleum ether–EtOAc, 10:1). Yield 3.38 g (85%), light yellow liquid, *de* 86% (GLC). IR spectrum, ν, cm^{-1}: 2985, 2933, 2875, 1438, 1197, 1120, 721, 695, 541. ^{1}H NMR spectrum, δ, ppm: 1.01 d (3H, CH_3, *J* = 7.0 Hz), 1.29 s and 1.36 s [3H each, $C(CH_3)_2$], 2.54–2.60 m (1H, 2′-H), 3.54–3.56 m (1H, 5-H), 3.91–3.99 m (2H, 4-H, 5-H), 6.32 d (1H, $Br_2C{=}CH$, *J* = 9.4 Hz). ^{13}C NMR spectrum, δ_P, ppm: 15.6, 25.3, 26.3, 41.2, 67.2, 78.3, 90.2, 108.8, 139.5. Found, %: C 34.51; H 4.44; Br 50.78. $C_9H_{14}Br_2O_2$. Calculated, %: C 34.42; H 4.49; Br 50.89.

(4*S*)-2,2-Dimethyl-4-[(2*S*)-4-(trimethylsilyl)but-3-yn-2-yl]-1,3-dioxolane (3). A solution of 3.0 g (9.55 mmol) of **10** in 60 mL of THF was cooled to –78°C, 7.8 mL (22.0 mmol) of a 2.8 N solution of butyllithium in hexane was added dropwise under stirring, the mixture was stirred for 30 min at –30°C and cooled to –78°C, and 2.4 mL (19.1 mmol) of freshly distilled chloro(trimethyl)silane was added dropwise. The mixture was allowed to warm up to 0°C and neutralized with aqueous $NaHCO_3$, the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2×50 mL). The extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated, and the residue was subjected to silica gel chromatography (petroleum ether–EtOAc, 40:1). Yield 1.64 g (76%), colorless liquid, $[\alpha]_D^{20}$ = +8.0 (*c* = 0.23, CH_2Cl_2), *de* 99% (GLC). IR spectrum, ν, cm^{-1}: 2958, 2925, 2850, 1456, 1379, 1250, 1067, 844. ^{1}H NMR spectrum, δ, ppm: 0.15 s [9H, $Si(CH_3)_3$], 0.97 d (3H, CH_3, *J* = 7.0 Hz), 1.37 s and 1.44 s [3H each, $C(CH_3)_2$], 2.68–2.73 m (1H, 3-H), 3.82–3.87 m and 4.01–4.04 m (1H each, 5′-H), 4.11–4.15 m (1H, 4′-H). ^{13}C NMR spectrum, δ_C, ppm: 0.0, 16.0, 25.5, 26.3, 29.6, 66.7, 77.6, 81.5, 106.4, 109.8. Mass spectrum: *m/z* 227 $[M + H]^+$. Found, %: C 63.80; H 9.84; Si 12.52. $C_9H_{14}O_2Si$. Calculated, %: C 63.66; H 9.80; Si 12.41. *M* 226.39.

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