Total Synthesis of Epothilone A: The Macrolactonization Approach**

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Dedicated to Professor Stephen Hanessian on the occasion of his 60th birthday

The novel molecular structures of the epothilones, for example epothilone A (**1**, Figure 1), coupled with their antifungal[1, 2] and antitumor activities[1–4] and microtubule binding properties[4] promise an exciting new chapter in chemistry, biology, and medicine. Particularly intriguing is the ability of these compounds to displace taxol from its binding site on microtubules,[4] towards which epothilones exhibit much higher affinity than taxol.[5] An indication of the intense interest in this field is the flurry of activity[6] directed toward their total synthesis within the relatively short time since their structural elucidation.[2] While our first total synthesis[6f] of **1** enjoys the benefits of the olefin metathesis reaction, the one we wish to report here relies on a macrolactonization process for constructing the main ring skeleton. In addition, the reported synthesis is highly convergent and flexible and therefore allows entry into a large library of epothilones, including epothilone B and all of the 2^6 stereoisomers of **1**.

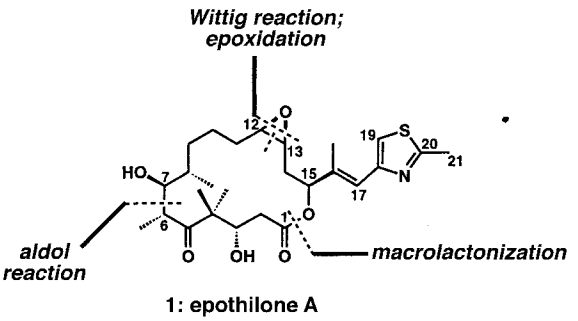
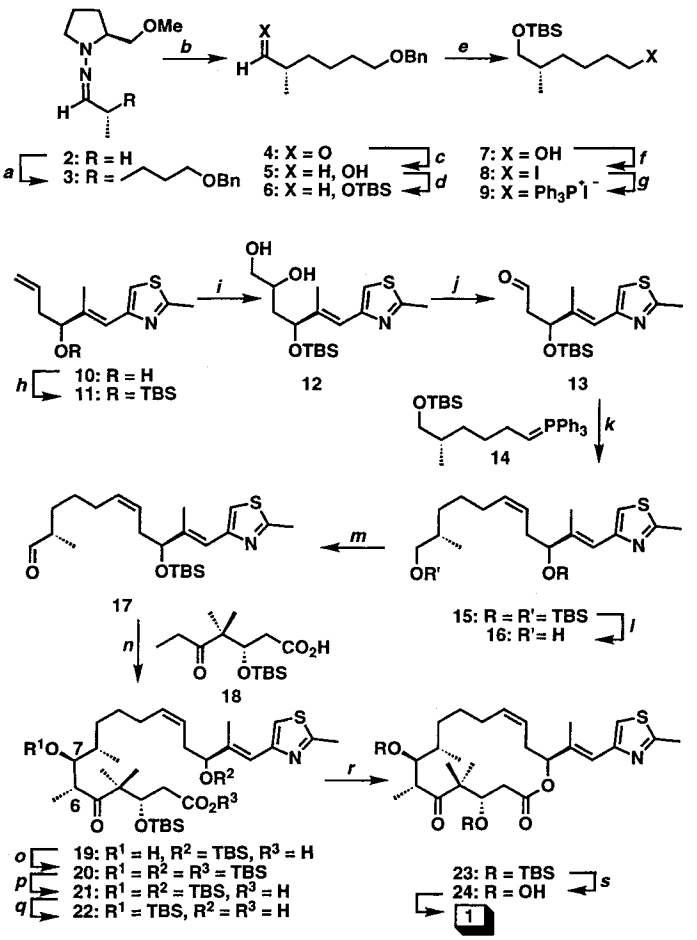


Figure 1. Structure and retrosynthetic analysis of epothilone A (**1**).

By the macrolactonization approach to **1** (Figure 1), three fragments (C1–C6, C7–C12, and C13–C21), each containing a stereogenic center, are to be constructed stereoselectively by asymmetric synthesis procedures, united, and elaborated to the final target. A Wittig and an aldol reaction will be used for the coupling of these fragments, whereas the C(O)–O bond formation is reserved for the macrocycle forming process, in the form of a macrolactonization. It is important to note that this strategy allows for the preparation of all the possible stereoisomers of **1**, since the configuration of each stereocenter can easily be reversed.

The execution of this rather simple strategy proceeded smoothly for **1** (Scheme 1). The SAMP derivative **2**, obtained by reaction of SAMP[7] with propionaldehyde, was alkylated with 4-iodo-1-benzyloxybutane in the presence of LDA in THF at $-100\,^{\circ}C$ according to the method of Enders et al.[7] to produce **3** in 92% yield and greater than 98% *ee*.[8] Ozonolysis of **3** followed by treatment with $NaBH_4$ furnished alcohol **5**, via aldehyde **4**, in 77% overall yield. Protection of the hydroxyl group in **5** as a *tert*-butyldimethylsilyl (TBS) ether, followed by standard elaboration of the other end of the molecule (hydrogenolysis of benzyl ether, iodonation, and phosphonium salt formation) yielded the desired fragment **9** in 79.5% overall yield (from **5**).



Scheme 1. Total synthesis of epothilone A (**1**): a) 1.1 equiv LDA, THF, 0 °C, 8 h; then 1.5 equiv 4-iodo-1-benzyloxybutane in THF at −100 to 0 °C, 6 h, 92%; b) O_3, CH_2Cl_2, −78 °C, 77%; c) 3.0 equiv $NaBH_4$, MeOH, 0 °C, 15 min, 98%; d) 1.5 equiv TBSCl, 2.0 equiv Et_3N, CH_2Cl_2, 0 to 25 °C, 12 h, 95%; e) H_2, $Pd(OH)_2$ cat, THF, 15 min, 40 psi, 25 °C, 95%; f) 1.5 equiv I_2, 3.0 equiv imidazole, 1.5 equiv Ph_3P, Et_2O/CH_3CN (3:1), 0 °C, 0.5 h, 91%; g) Ph_3P, neat, 100 °C, 2 h, 92%; h) 1.5 equiv TBSCl, 2.0 equiv imidazole, THF, 0 to 25 °C, 1 h, 99%; i) 1 mol% OsO_4, 1.1 equiv NMO, 25 °C, 14 h, 95%; j) 1.1 equiv $Pb(OAc)_4$, EtOAc, 0 °C, 10 min, 99%; k) 1.2 equiv **9**, 1.2 equiv NaHMDS, THF, 0 °C, 0.25 h, then addition 1.0 equiv aldehyde **13** at 0 °C, 15 min, 69% (*Z*:*E* ≈ 9:1); l) 1.0 equiv CSA in portions over 1 h, CH_2Cl_2/MeOH (1:1), 0 °C, then 25 °C, 0.5 h, 86%; m) 2.0 equiv SO_3·pyridine, 10.0 equiv DMSO, 5.0 equiv Et_3N, CH_2Cl_2, 25 °C, 0.5 h, 82%; n) 3.0 equiv LDA, THF, 0 °C, 0.25 h, then 1.2 equiv **18** in THF at −78 to −40 °C, 0.5 h, then 1.0 equiv **17** in THF at −78 °C, high yield of **19** and its 6*S*,7*R*-diasteromer (ca. 1:1 ratio); o) 3.0 equiv TBSOTf, 5.0 equiv 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; p) 2.0 equiv K_2CO_3, MeOH, 25 °C, 15 min, 31% of **21** and 30% of its 6*S*,7*R*-diasteromer from **17**; q) 6.0 equiv TBAF, THF, 25 °C , 8 h, 79%; r) 5 equiv 2,4,6-trichlorobenzoylchloride, 6.0 equiv Et_3N, THF, 25 °C, 15 min, then addition to a solution of 10.0 equiv 4-DMAP in toluene (0.002 M based on **22**), 25 °C, 0.5 h, 90%; s) 20% CF_3COOH (v/v) in CH_2Cl_2, 0 °C, 1 h, 92%. LDA = lithium diisopropylamide; 4-DMAP = 4-dimethylaminopyridine; TBS = *tert*-butyldimethylsilyl; NaHMDS = sodium bis(trimethylsilyl)amide; DMSO = dimethylsulfoxide; Tf = triflate; NMO = *N*-methylmorpholine *N*-oxide.

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The second requisite fragment, thiazoline aldehyde **13**, was rapidly constructed from the thiazoline derivative **10**[6f] by silylation (TBSCl, imidazole, 99%), selective 1,2-dihydroxylation[9] (OsO_4, NMO, 95%), and $Pb(OAc)_4$ cleavage (99%). Generation of the phosphorane **14** from the phosphonium salt **9** with sodium bis(trimethylsilyl)amide (NaHMDS), followed by addition of aldehyde **13**, led predominently to the (*Z*)-olefin **15** in 69% yield ($Z:E \approx 9:1$). The primary TBS group was selectively removed from **15** with camphorsulfonic acid (CSA) in MeOH to give alcohol **16** (86% yield), which was oxidized to the corresponding aldehyde (**17**) by the action of SO_3·pyridine (82% yield). Condensation of the dilithio derivative of **18**[6f] (2.6 equiv of LDA, THF, −78 to −40 °C) with aldehyde **17** proceeded at −78 °C to afford a mixture of diastereomers (**19** + 6*S*,7*R*-diastereomer; ca. 1:1 to 1:2 ratio depending on precise conditions) in good yield. This mixture was carried through the sequence until compound **21**, at which stage it was separated into its components by silica gel chromatography. Thus, the aldol products (**19** + diastereomer) were fully silylated with TBSOTf/2,6-lutidine. The resulting mixture of *tetra*-TBS derivatives (compound **20** + diastereomer) was briefly exposed to K_2CO_3 in MeOH to afford, after preparative thin layer chromatography, pure carboxylic acid **21** (31% overall yield) and its 6*S*,7*R*-diastereomer (30% overall yield from **17**; **21**: $R_f = 0.61$, 6*S*,7*R*-diastereomer: $R_f = 0.70$, silica gel, 5% MeOH in CH_2Cl_2, for spectroscopic details of **21**, see Table 1). The indicated stereochemical assignment for the slower moving isomer **21** was based on its successful conversion to macrolactone **24**[6f] and **1**.

Table 1. Selected physical properties of compounds **21**–**23**.

21: $R_f = 0.61$ [silica gel, methanol:dichloromethane (5%)]; $[\alpha]_D^{22} = -8.8$ ($c = 0.8$ in chloroform); IR (film): $\tilde{\nu} = 2931, 2856, 1712, 1466, 1254, 1083, 836\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H, −C=CHS−), 6.61 (s, 1H, −C=CH−C=), 5.44–5.41 (m, 2H, −CH=C*H*−CH$_2$−, −C*H*=CH−CH$_2$−), 4.40 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 6.5$ Hz, −(CH$_3$)$_2$C−C*H*−), 4.11 (dd, 1H, $J_1 = 5.9$ Hz, $J_2 = 6.5$ Hz, −C*H*(OSi(CH$_3$)$_2$*t*Bu)−), 3.75 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.5$ Hz, TBSO−C*H*−CH(Me)), 3.12 (dq, 1H, $J_1 = 7.0$ Hz, $J_2 = 6.5$ Hz, −C(O)C*H*(CH$_3$)−), 2.69 (s, 3H, −S−C(CH$_3$)=N−), 2.48 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 16.0$ Hz, −C*H*$_2$−COOH), 2.35 (dd, 1H, $J_1 = 6.7$ Hz, $J_2 = 16.0$ Hz, −C*H*$_2$−COOH), 2.31–2.28 (m, 2H, −C*H*$_2$CH=CH), 2.10–2.00 (m, 2H, −C*H*$_2$−CH=CH), 1.95 (s, 3H, −C(C*H*$_3$)=CH−C=), 1.42–1.30 (m, 5H), 1.18 (s, 3H, −C(C*H*$_3$)$_2$), 1.10 (s, 3H, −C(C*H*$_3$)$_2$), 1.06 (d, 3H, $J = 7.0$ Hz, −C(O)−CH(C*H*$_3$)−), 0.90–0.85 (m, 30H, −C(O)−CH(C*H*$_3$)−, 3× −SiC(C*H*$_3$)$_3$(CH$_3$)$_2$), 0.12 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.09 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.07 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.05 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.04 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.03 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$): $\delta = 218.2, 176.1, 164.9, 152.7, 142.8, 131.4, 126.0, 118.5, 114.7, 78.7, 73.3, 53.7, 44.7, 40.0, 39.0, 34.7, 30.8, 28.0, 27.8, 26.2, 26.0, 25.8, 23.6, 19.0, 18.8, 18.5, 18.2, 17.2, 15.8, 13.8, −3.8, −3.9, −4.2, −4.6, −4.7, −4.9$; HRMS: calcd for $C_{44}H_{83}NO_6SSi_3$ ($M + Cs^+$) 970.4303, found 970.4318.

22: $R_f = 0.40$ [silica gel, methanol:dichloromethane (5%)]; $[\alpha]_D^{22} = -19.2$ ($c = 0.1$ in chloroform); IR (film): $\tilde{\nu} = 3358$ (br, OH), 2932, 2857, 1701, 1466, 1254, 1088, 988, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.95$ (s, 1H, −C=CHS−), 6.61 (s, 1H, −C=CH−C=), 5.58–5.54 (m, 1H, −CH=C*H*−CH$_2$−), 5.43–5.39 (m, 1H, −C*H*=CH−CH$_2$−), 4.39 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 6.7$ Hz, −(CH$_3$)$_2$C−C*H*−), 4.18 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 7.5$ Hz, −C*H*(OH)−), 3.78 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.9$ Hz, −SiO−C*H*−CH(Me)), 3.11 (dq, 1H, $J_1 = 6.9$ Hz, $J_2 = 6.7$ Hz, −C(O)−C*H*(CH$_3$)−), 2.70 (s, 3H, −S−C(CH$_3$)=N−), 2.43 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 16.2$ Hz, −C*H*$_2$−COOH), 2.40–2.35 (m, 2H, −C*H*$_2$−CH=), 2.35 (dd, 1H, $J_1 = 6.7$ Hz, $J_2 = 16.2$ Hz, −C*H*$_2$−COOH), 2.15–2.10 (m, 1H, −C*H*$_2$−CH=), 2.00 (s, 3H, −C(C*H*$_3$)=CH−C=), 1.99–1.95 (m, 1H, −C*H*$_2$−CH=), 1.48–1.30 (m, 5H), 1.18 (s, 3H, −C(C*H*$_3$)$_2$−), 1.08 (s, 3H, −C(C*H*$_3$)$_2$), 1.05 (d, 3H, $J = 6.7$ Hz, −C(O)−CH(C*H*$_3$)−), 0.89–0.84 (m, 21H, −C(O)−CH(C*H*$_3$)−, −SiC(C*H*$_3$)$_3$(CH$_3$)$_2$), 0.09 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.05 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.04 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.03 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$): $\delta = 218.9, 175.4, 166.3, 152.8, 134.4, 125.7, 119.5, 115.9, 74.4, 74.3, 54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8, 27.0, 26.9, 24.4, 22.0, 21.4, 20.0, 19.6, 19.3, 19.1, 17.9, 17.1, 15.5, 8.6, −2.9, −3.1, −3.3, −3.8$; HRMS: calcd for $C_{38}H_{69}NO_6SSi_2$ ($M + Cs^+$) 856.3439, found 856.3459.

23: $R_f = 0.37$ [silica gel, hexane:ether (2:1)]; $[\alpha]_D^{22} = -22.9$ ($c = 0.3$ in chloroform); IR (film): $\tilde{\nu} = 2926, 2854, 1734, 1693, 1463, 1381, 1252, 1099, 829\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, −C=CHS−), 6.58 (s, 1H, −C=CH−C=), 5.53 (m, 1H, −CH=C*H*−CH$_2$−), 5.43–5.34 (m, 1H, −C*H*=CH−CH$_2$), 5.00 (d, 1H, $J = 6.0$ Hz, −O−CH), 4.03 (d, 1H, $J = 10.0$ Hz, −C*H*(OH)−), 3.89 (d, 1H, $J = 9.0$ Hz, −C*H*(OH)), 3.04–2.98 (m, 1H, −C(O)−CH−), 2.85 (d, 1H, $J = 15.0$ Hz, OOC−C*H*$_2$−), 2.72 (s, 3H, −S−C(C*H*$_3$)=N−), 2.66 (dd, 1H, $J_1 = 15.0$ Hz, $J_2 = 10.0$ Hz, OOC−C*H*$_2$−), 2.42–2.31 (m, 2H), 2.11 (s, 3H, −C(C*H*$_3$)=), 1.92–1.83 (m, 1H), 1.66–1.38 (m, 4H), 1.20 (s, 3H, −C(C*H*$_3$)$_2$−), 1.16 (s, 3H, −C(C*H*$_3$)$_2$), 1.09 (d, 3H, $J = 7.0$ Hz, −C(O)−CH(C*H*$_3$)−), 0.95 (d, 3H, $J = 7.0$ Hz, −CH(C*H*$_3$)−), 0.94 (s, 9H, −SiC(C*H*$_3$)$_3$(CH$_3$)$_2$), 0.85 (s, 9H, −SiC(C*H*$_3$)$_3$(CH$_3$)$_2$), 0.12 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.10 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), 0.08 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$), −0.10 (s, 3H, −SiC(CH$_3$)$_3$(C*H*$_3$)$_2$). ^{13}C NMR (600 MHz, C_6D_6): $\delta = 215.0, 171.3, 135.1, 122.7, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.0, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, −3.1, −3.2, −3.7, −5.8$; HRMS: calcd for $C_{38}H_{67}NO_5SSi_2$ ($M + H^+$) 706.4357, found 706.4382.

At this stage, it was necessary to deprotect the C15 hydroxyl group selectively for the intended macrolactonization reaction. This task was successfully accomplished with tetra-*n*-butylammonium fluoride (TBAF) in THF at 25 °C, leading to the desired hydroxy acid **22** in 78% yield (Table 1). Steric hindrance at the sites of the other TBS groups was presumed to be responsible for this selectivity. The key ring closure of **22** was smoothly effected under Yamaguchi conditions[10] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP, THF/toluene, 25 °C), furnishing the 16-membered ring lactone **23** in 90% yield (Table 1). Finally, exposure of **23** to CF_3COOH (20% by volume) in CH_2Cl_2 at 0 °C led to the targeted olefinic diol **24** (92% yield). The latter compound was then converted into **1** by exposure to *m*CPBA as already described.[6f]

This expedient route to epothilone A (**1**) may easily be extended to epothilone B and a variety of analogs of these naturally occurring compounds for biological investigations. Indeed, the molecular design, chemical synthesis, and biological screening of such analogs should be among the next priorities in this field.[11]

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[8] Only one diastereomer is detected in the 500 MHz ^{1}H NMR spectrum ($CDCl_3$) of **3**.

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[11] All new compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data.