Synthesis toward Epothilone A: Coupling Reaction between the Sulfone of C1-C10 and the Allylic Bromide of C11-C21

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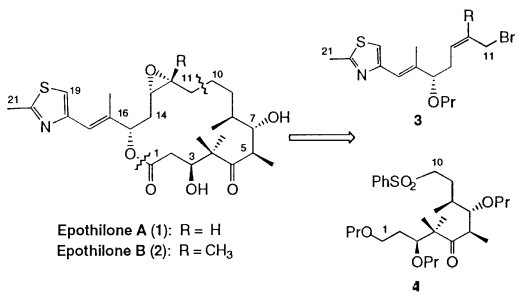
Macrolide epothilones **1** and **2**, isolated by Höfle *et al.* from the myxobacterium *Sorangium cellulosum*, have been drawing considerable attention because of their novel structural features and paclitaxel (Taxol®)-like antitumor activity.[1] The biological activity of epothilones came from their binding and stabilization of the microtubule assembly.[2] But epothilones differ from paclitaxel in respect of retaining activity against multidrug-resistant cells, solubility in water, and their easy availability by fermentation.

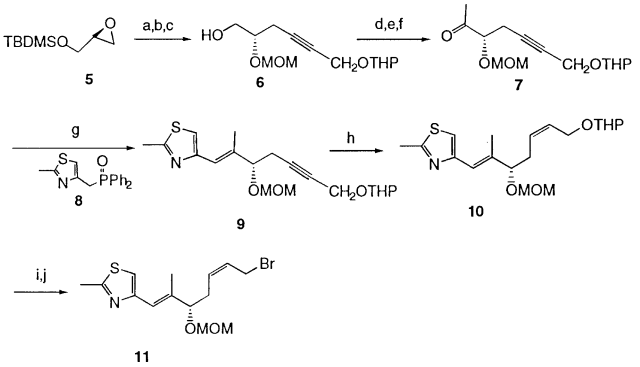
The synthetic studies have been recently exploited by many organic chemists.[3] Our retrosynthetic analysis of epothilones suggests disconnection at C10-C11 bond and lactonic bond. Thus, our synthetic plans require two building blocks **3** and **4** with appropriate protecting groups (Scheme 1). The coupling reaction between the allylic bromide **3** and a carbanion of the sulfone **4** will lead to the key intermediate, which can be further cyclized into a macrolide.

The subunit of allylic bromide can be constructed from protected (*R*)-(+)-glycidol as its *t*-butyldimethylsilyl ether (TBDMS). As a candidate for the sulfonyl subunit we decided to use the sulfone derivative from 1,10-decanediol in order to examine our approach.

According to our synthetic plan, the TBDMS ether **5** of (*R*)-(+)-glycidol was reacted with acetylenic carbanion of tetrahydropyranyl (THP) ether of propargyl alcohol in the presence of a Lewis acid, BF_3·Et_2O (Scheme 2). The subsequent removal of the TBDMS group of the intermediate with *n*-Bu_4NF following the protection of a secondary hydroxyl group as methyloxymethyl (MOM) ether furnished alcohol **6**. The next step was the conversion of primary alcohol to methyl ketone. Accordingly, a series of reactions including oxidation of the hydroxyl group to the aldehyde, methylation of the aldehyde with methylmagnesium bromide, and oxidation of the secondary hydroxyl group gave the desired methyl ketone **7** from **6**. For the introduction of a thiazole ring, Emmons reaction of phosphine oxide **8** with methyl



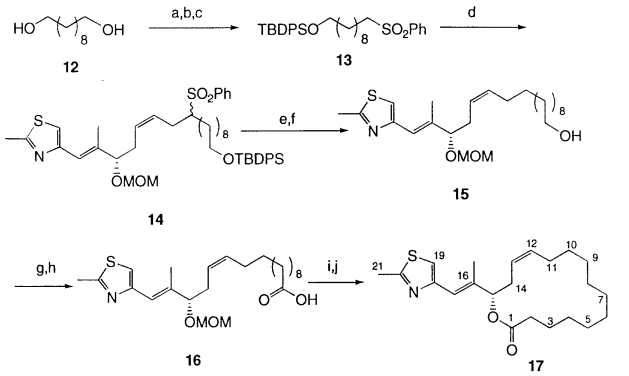
Scheme 1



Scheme 2. (a) $LiCCH_2OTHP$, BF_3-OEt_2, THF, 93%; (b) MOMCl, $(i\text{-Pr})_2NEt$, $ClCH_2CH_2Cl$, 97%; (c) *n*-Bu_4NF, THF, 92%; (d) Swern Ox., 95%; (e) CH_3MgBr, THF, 83%; (f) TPAP, NMO, CH_2Cl_2, 86%; (g) *n*-BuLi, **8**, THF, 95%; (h) Pd/$CaCO_3$, H_2, Quinoline, MeOH, 98%; (i) aq. MeOH, *p*-TsOH, 82%; (j) PPh_3, CBr_4, CH_2Cl_2, 94%.

ketone **7** was utilized to obtain compound **9**.[3j] The triple bond of **9** was partially hydrogenated with Lindlar catalyst to furnish *Z*-alkene **10**. The resulting **10** was hydrolyzed to the allylic alcohol under the acidic condition and the resulting alcohol was further converted into bromide **11** by treating with PPh_3 and CBr_4.

The coupling of **11** with sulfone **13** was accomplished as shown in Scheme 3. The sulfone **13** was prepared from readily available 1,10-decanediol (**12**) *via* monosilylation and sulfonation by Hata's method.[4] Compound **11** was coupled with a carbanion of **13** generated by treatment of *n*-



Scheme 3. (a) TBDPSCl, Et_3N, DMF, 62%; (b) PhSSPh, Bu_3P; (c) mcpba, $NaHCO_3$, 98% (2 steps); (d) LDA, THF, **11**, -78 °C, 68%; (e) 5% Na(Hg), Na_2HPO_4, MeOH, RT, 75%; (f) *n*-Bu_4NF, THF, 96%; (g) Swern Ox., 92%; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 97%; (i) TMSBr, CH_2Cl_2, -30 °C → 0 °C, 92%; (j) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; dmap, Toluene, RT, 30 min, 75%.

BuLi. The reductive removal of phenylsulfonyl group of the resulting **14** under condition of buffered sodium amalgam and treatment of the intermediate with *n*-Bu_4NF afforded primary alcohol **15**. The conversion of the alcohol **15** to carboxylic acid **16** was performed by subsequent reactions consisting of Swern oxidation and treatment with $NaClO_2$. MOM group was removed from the secondary hydroxyl group using TMSBr.[5] The lactonization of the intermediate hydroxy carboxylic acid using Yamaguchi's method[6] finally furnished the desired macrolide **17**. The structure of the product was confirmed by its spectroscopic data.[7] Our synthetic approach seems appropriate for the preparation of the simple analogs of a macrolide with a thiazole fragment.

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7. Spectral data for **17**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25-1.36 (m,13H), 1.66-1.70 (m, 3H), 1.99 (dt, J = 13.7, 6.8 Hz, 1H), 2.09 (s, 3H), 2.12 (dt, J = 13.7, 6.8 Hz, 1H), 2.28 (dt, J = 14.3, 7.1 Hz, 1H), 2.34 (dt, J = 14.3, 7.1 Hz, 1H), 2.37-2.42 (m, 1H), 2.59-2.65 (m, 1H), 2.71 (s, 3H), 5.29-5.34 (m, 2H), 5.52 (qt, J = 8.8, 1.8 Hz, 1H), 6.55 (s, 1H), 6.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.92, 19.20, 24.23, 25.94, 26.19, 26.34, 26.42, 26.55, 26.76, 27.83, 31.21, 34.62, 78.21, 116.15, 120.52, 124.34, 132.61, 137.35, 152.35, 152.52, 164.60, 173.14; IR (neat) 2928, 2856, 1732, 1458 cm^{-1}; HRMS Calcd. for $C_{22}H_{33}NOS$: 375.2232. Found 375.2234: $[\alpha]_D^{20}$ = -25.3 (c 1.90, $CHCl_3$).