Synthesis of the C11-C21 and C13-C21 Fragments of Epothilones from *D*-Glucose

Hyo Won Lee,* Ihl-Young Choi Lee,† and Yong Deog Hong

Department of Chemistry, Chungbuk National University, Cheongju 361-763, Korea
†Korea Research Institute of Chemical Technology, Daejeon 305-606, Korea
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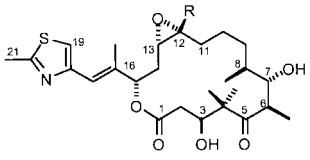
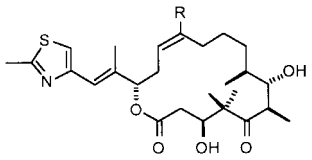
Macrolide epothilones **1** and **2**, isolated by Höfle *et al.* from the myxobacterium *Sorangium cellulosum*, have evoked intensive interest and excitement due to their potent antitumor activity.[1] Epothilones promote the polymerization of tubulins and stabilize microtubule assembly.[2] In this aspect epothilones have almost identical mode of action to that of paclitaxel (Taxol®) and furthermore, are superior to paclitaxel in retaining activity in multidrug-resistant cells, solubility in water, and their easy availability from fermentation. These significant biological properties along with their structural features have prompted synthetic investigation of organic chemists.[3]



Epothilone A (**1a**): R = H
Epothilone B (**1b**): R = CH_3

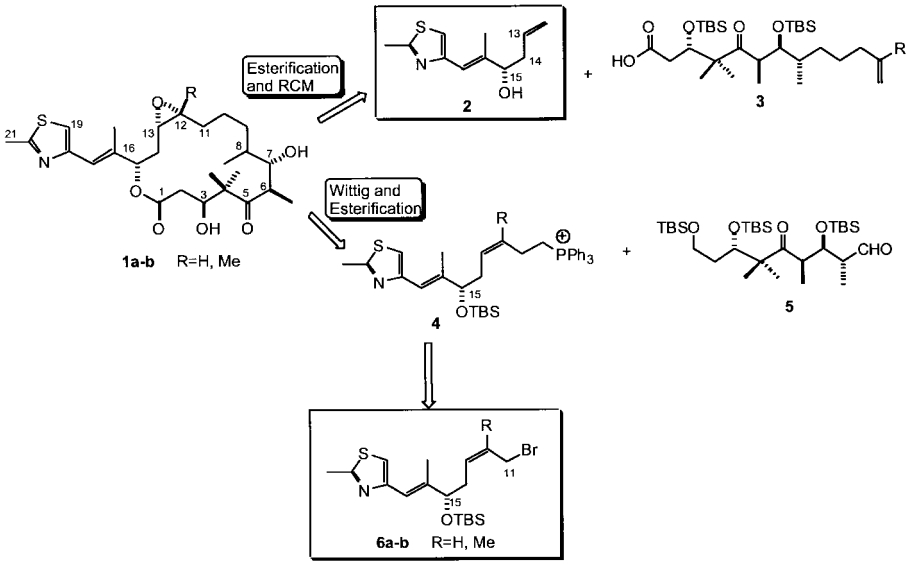


Epothilone C (**1c**): R = H
Epothilone D (**1d**): R = CH_3

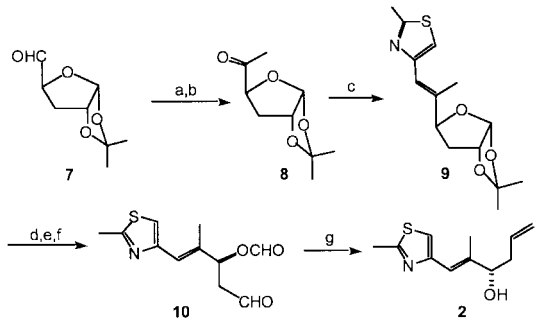
Our synthetic plan toward epothilones A-D (**1a-d**) comprises of two pathways as shown in Scheme 1. The first approach implies a key transforamtion of the ring closing metathesis (RCM) on an ester intermediate derivived from alcohol **2** and acid **3** toward epothilones. The other approach encompasses a key reaction of Wittig reagent **4** derived from compound **6** and aldehyde **5**. Herewith, we would like to report the successful synthesis of these two compounds **2** and **6b**.

Each subunit of **2** and **6b** was prepared from the common aldehyde **9**, originated from the chiral template of *D*-glucose. As for fragment **2**, aldehyde **7** of furanose was easily prepared from the deoxygenation of *D*-glucose according to a procedure reported in the literature (Scheme 2).[4] Thus, compound **7** was treated with methylmagnesium bromide to give a secondary alcohol, which was subsequently oxidized with PCC in the presence of molecular seives to ketone **8** (92% in two steps). The requisite thiazole ring was introduced by Horner-Emmons reaction of diethyl phosphonate reagent upon **8**. The resulting compound **9** was obtained as a mixture of *E* and *Z* isomer (76% and 13%, respectively). After chromatographic separation of *E* isomer of **9**, the removal of acetonide group was accomplished by employing the mild reaction condition of $BF_3 \cdot Et_2O$ in acetic anhydride at -30 °C for 10 to 30 min.[5] In this way, the diacetate intermediate was obtained in quantitative yield. The diacetate was converted to α-hyroxyhemiacetal by treating with K_2CO_3 in methanol (88%). The subsequent oxidative cleaveage of α-hydroxyhemiacetal with $NaIO_4$ yielded quantitatively the key compound **10** with a formylated hydroxy group. The Wittig reaction of **10** gave the desired compound **2** with a terminal vinyl group (72%). Slightly excess of *n*-BuLi for this reaction removed a formyl group and released free hydroxy group. The derivatization of **2** to MTPA ester with Mosher's reagent showed more than 99% ee of **2** ($[\alpha]_D^{24}$ = -20.1°, *c* 0.35, $CHCl_3$). Otherwise the conventional treatment of **8** under the acidic conditions such as 50% aqueous acetic acid required heating of reaction mixture and this

Scheme 1. Retrosynthetic Analysis for the Synthesis of Epothilones

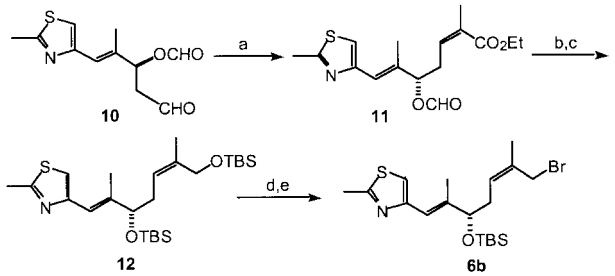


Scheme 2. Synthesis of Fragment **2** of Epothilones



Reagents: (a) CH_3MgBr, THF, 0 °C, (b) PCC, MS 4 Å, CH_2Cl_2; (c) *n*-BuLi, THF, -78 °C, Diethyl (2-methylthiazol-4-yl)methanephosphonate; (d) Ac_2O, $BF_3{\cdot}OEt$, -30 °C; (e) K_2CO_3, MeOH; (f) $NaIO_4$, MeOH; (g) Ph_3PCH_3Br, *n*-BuLi, THF, RT.

Scheme 3. Synthesis of Fragment **6b** of Epothilone B



Reagents: (a) $(CF_3CH_2O)_2POCHCH_3COOEt$, KHMDS, 18-Crown-6, THF; (b) Dibal, toluene; (c) TBSCl, Et_3N DMF; (d) CSA, CH_2Cl_2:MeOH=1 : 1; (e) Ms_2O, Et_3N, CH_2Cl_2, Acetone; LiBr.

harsh reaction condition ended up to 82% ee of **2** at best.

The successful synthesis of **2** prompted us to prepare the fragment of **6b**, which is the precusor for Wittig reagent in White's synthesis of Epothilone B.[3j]

Further utilization of compound **10** toward subunit of **6b** according to the second approach was accomplished (Scheme 2). Compound **10** was treated with Still's phosphaester reagent[6] to obtain single *Z*-isomeric selectivity for compound **11** (72 %). In this reaction, we could not observe any *E*-isomer of **11**. The reduction of **11** with DIBAL furnished allylic alcohol (96%) and subsequent protection of two hydroxy groups of this compound as TBS ethers yielded compound **12** (94%). The selective deprotection of TBS ether of primary hydroxy group under the acidic condition of camphorsulfonic acid provided primary alcohol (92%), which was converted into a mesylated and subsequently to the desired allyl derivative **6b**, using bromide-mesylate exchange reaction (95%).

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