Synthesis of the C11-C21 Fragments of Epothilones A and B Using Ring-Closing Metathesis

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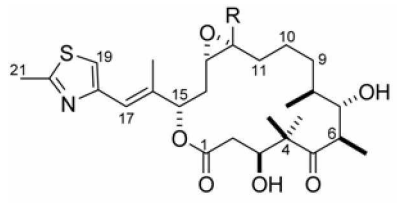
Epothilones A (**1**) and B (**2**) are cytotoxic 16-membered macrolides, isolated from a cultured strain of the cellulose-degrading myxobacterium *Sorangium cellulosum*.[1] The biological activity of these compounds shows a similar mechanism as that of paclitaxel (Taxol®) in inhibition of cancer cell proliferation *via* promoting microtubule assembly and stabilization.[2] Especially, *in vitro* study indicates that they are also active against the multi-drug resistant cancer cell lines. In contrast to structurally complex paclitaxel, epothilones allow easy access to their synthesis. Enticed from their biological activity as well as structural novelty, many organic chemists have reported the extensive synthesis of epothilones.[3]

The subunit comprising the C11-C21 fragment is one of the important building blocks of epothilones. As an approach to this subunit, Evans oxazolidinone protocol as a key transformation was utilized by White *et al.*[4] Differently Mulzer *et al.* prepared this subunit from commercially available (2*S*)-hydroxybutyrolactone and (*S*)-malic acid, respectively.[5,6] Previously we reported the synthesis of the C11-C21 fragment using (*R*)-glycidol and D-glucose as starting materials.[7] Herein we would like to describe our results in the concise and efficient synthesis of the C11-C21 fragments of epothilones A and B. Our synthetic method is appropriate to prepare the derivatives of C11-C21 fragments of epothilones because numerous acrylic acid derivatives are readily available.

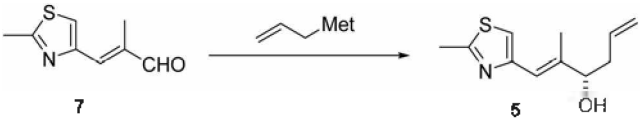


Epothilone A (**1**, R= H) and **B** (**2**, R=CH_3)

Our synthetic strategy as shown in the retrosynthetic analysis (Scheme 1) for the C11-C21 fragment **3** of epothilones suggests the double bond at C12-C13 be constructed from the reductive ring opening of 5,6-dihydropyran-2-one ring in compound **4**, which can be prepared utilizing intramolecular ring-closing metathesis (RCM)[8] of an intermediate ester from the reaction **5** with **6**.

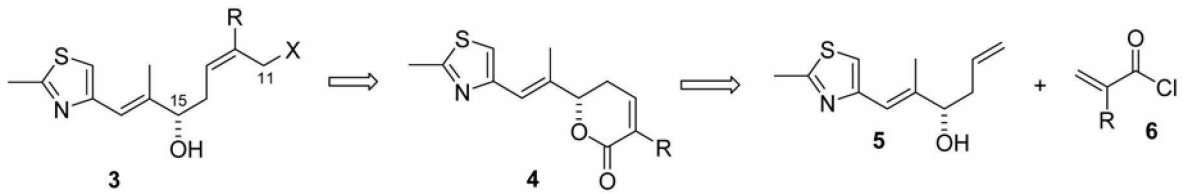
For the synthesis of **5** from compound **7** we have examined several approaches for asymmetric allylation as shown in Table 1. Among these the utilization of (+)-*B*-allyldiisopinocamphenylborane and allyltributylstannane-(*S*)-BINOL-Ti(OPr^i)$_4$ for the allylation was well documented in the literature.[9,10] We obtained good results using allylbutyltin-Zr(OBu^t)$_4$-(*S*)-BINOL (entry 1) and 2-bromo-4,5-diphenyl-1,3-bis(toluene-4-sulfonyl)[1,3,2]-diazaborolidine (entry 2).[11,12] By contrast, the boronate of diisopropyl tartrate and Ag(I) with chiral phosphine ligands did not yield any satisfactory results.[13,14]

Table 1. Asymmetric allylation reactions of aldehyde **7**

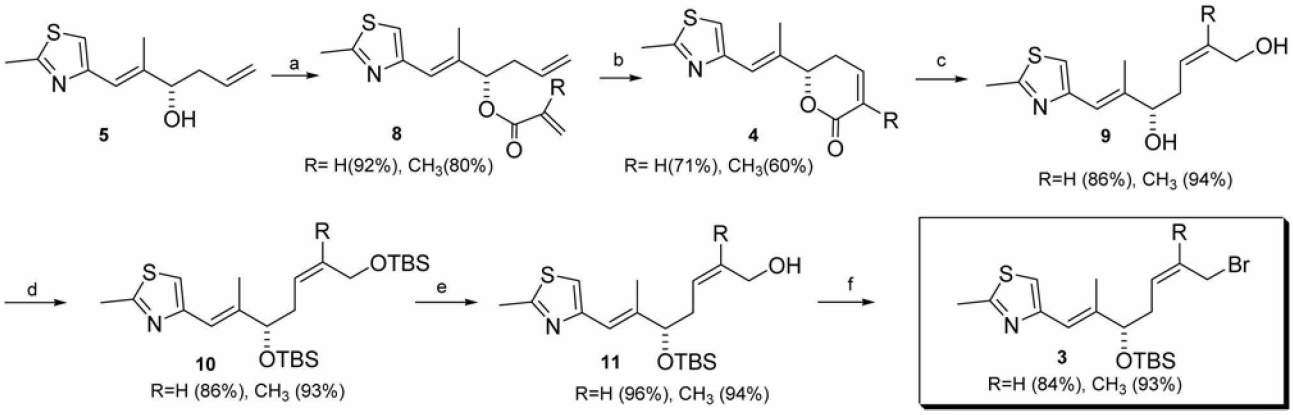


Entry	Chiral reagent	Reaction condition	%ee[a]	Yield
1	Zr(OBu^t)$_4$, (*S*)-BINOL, allyltributyltin	0 °C, 8 h	94	94
2	(*S,S*)-Stien, BBr$_4$, allyltributyltin	−78 °C, 10 min	98	95
3	Diisopropyl L-tartrate boronate	−78 °C, 1 h	32	92
4	AgOTf, (*S*)-BINAP, allyltributyltin	−20 °C, 48 h	6	82

[a]Enantiomeric excess was determined from the ^{1}H NMR data of MTPA esters.

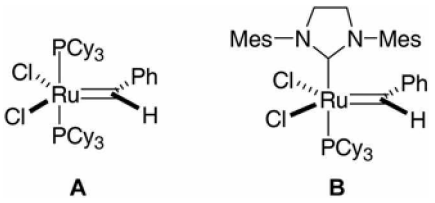


Scheme 1



Scheme 2. *Reagents and conditions*: a. **6**, Et_3N, 0 °C; b. Grubbs catalyst, CH_2Cl_2; c: Dibal, THF, 0 °C; d. TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; e. CSA, MeOH:CH_2Cl_2=1:1, 0 °C; f. Ms_2O, NEt_3, CH_2Cl_2, 0 °C; LiBr, acetone

With homoallyl alcohol **5** in our hands, the esterification with α,β-unsaturated carboxylic chloride **6** provided ester **8** (Scheme 2). The subsequent RCM reaction using Grubbs catalyst upon **8** furnished the cyclized product **4**. Then the resulting ester **8** was converted to the lactonic product **4** by the RCM in the presence of Grubbs catalysts. When R is hydrogen, the utilization of Grubbs first generation catalyst **A** gave 71% yield of lactonic product after stirring at room temperature for 12 h. But when R is methyl, Grubbs second generation catalyst **B** was used because of the lack of reactivity to Grubbs first generation catalyst **A**. The yield of methyl derivative was 60% after stirring of the reaction mixture in the presence of the Grubbs catalyst at room temperature for 24 h. The opening of lactone ring of **4** was performed by the reduction with DIBAL. The next step was the protection of two hydroxyl groups as TBS ethers. The treatment of **9** with TBSOTf in the presence of 2,6-lutidine provided compound **10**. And the following selective deprotection of TBS ether of primary hydroxy group of **10** under the acidic condition furnished the monoprotected alcohol **11**. The conversion of the hydroxy group of **11** to the bromide to obtain the desired product **3** was performed via mesylation and subsequent displacement the mesylate with LiBr. Thus we were able to prepare the C11-C21 fragment **3** of epothilones A and B utilizing RCM reaction as a key transformation.



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