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Synthesis of the acyclic precursor of an epothilone D analogue

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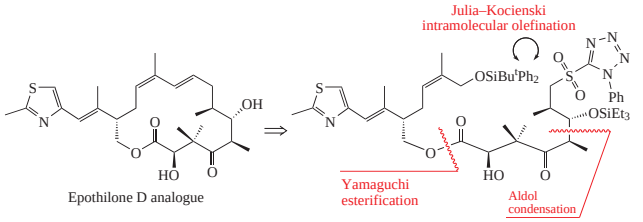
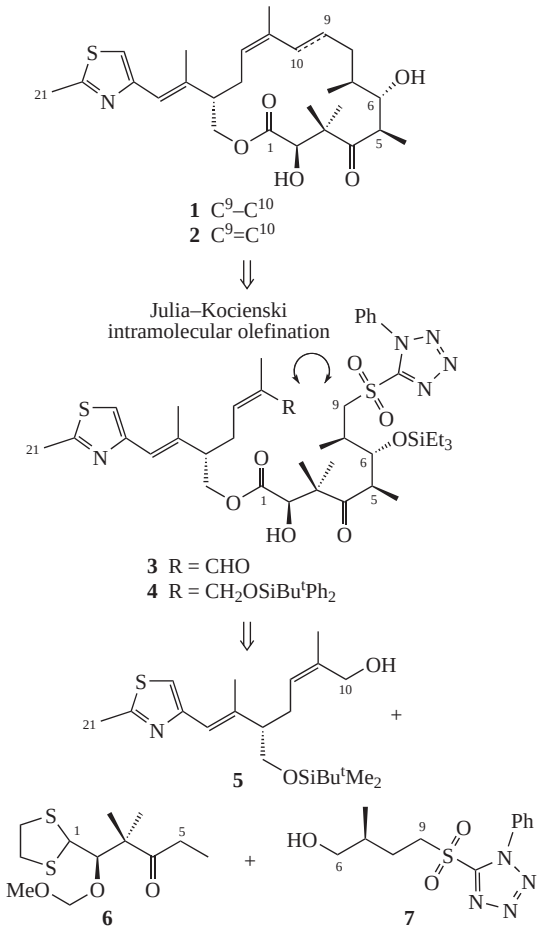
Condensation of separately obtained C^1–C^9 and C^{10}–C^{21} chiral blocks under Yamaguchi conditions affords the corresponding ester, an acyclic precursor of an epothilone D analogue. The reaction is accompanied by the formation of a side product of acylation of the starting alcohol by the Yamaguchi reagent.



Epothilones (Epo), polyfunctional macrolides, and their analogues are the promising compounds in the search for anticancer agents with toxol-like action mechanism.[1–3] The intramolecular lactonization performed according to the Yamaguchi protocol (comprising mixed anhydride with 2,4,6-trichlorobenzoic acid) in the majority of examples[4–6] is the key stage in the Epo syntheses. In continuation of our studies towards an Epo analogue Epo D **1**,[7] we present a synthesis of acyclic block **4** for the Epo diene precursor **2** from the blocks **5**, **6** and **7** reported previously[7–9] (Scheme 1).



Scheme 1

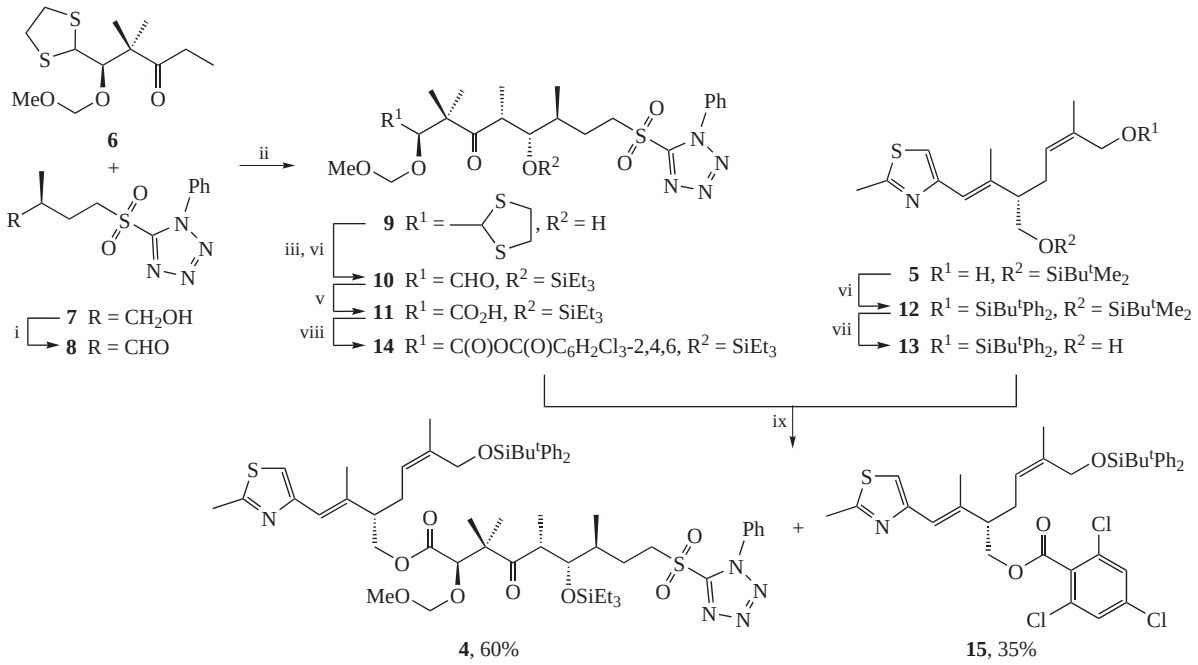
The approach to the target structure **2** that we planned implies the use of intramolecular Julia–Kocienski cyclization of α,ω-sulfo aldehyde **3**.[8] Taking into consideration that this version of cyclization ensures the most chemorational approach to the diene structure **2**, our efforts were aimed at the synthesis of acyclic block **4**.

The initial stage of our synthetic strategy involves the coupling of the C^1–C^5 and C^6–C^9 blocks. To this end, alcohol **7** was oxidized with $PhI(OAc)_2$[10] and the thus obtained aldehyde **8** reacted with the enolate of compound **6** generated *in situ* (Scheme 2). We succeeded in diastereoselective performance of this stage. The yield of compound **9** was 72% after purification on SiO_2. The stereochemical assignments of the newly formed chiral centers in it were made on the basis of reported data where predominant formation of diastereomers with the configuration shown above was observed under similar conditions for analogous compounds.[11–14]

The next stage involves the construction of the C^1–C^{21} block. Here the key stage is the Yamaguchi esterification of the alcohol and acid components prepared from the corresponding blocks **5** and **9**. For this purpose, the C^1–C^9 block in **9** was converted in three steps into acid **11**, while silyl ether **5** was converted into block **13**.

The resulting blocks **11** and **13** were subjected to intermolecular Yamaguchi reaction using the standard technique. The coupling was performed in stages. First, acid **11** was activated with 2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent) in THF in the presence of Et_3N to afford compound **14**. After addition of alcohol **13** and a catalytic amount of DMAP, the formation of two products was detected by TLC. Work up of the reaction mixture after 5 h followed by purification on SiO_2 gave the target product **4** and side ester **15**.

Apparently, the decomposition of the intermediate mixed anhydride **14** follows two competitive pathways to result in compounds **4** and **15**. This fact should be taken into account when one plans to work with the Yamaguchi reagent. Nevertheless, the yield of the desired product **4** was 60%, which is acceptable. Thus, it follows from the data obtained that the above synthetic



Scheme 2 *Reagents and conditions:* i, $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 88%; ii, LiHMDS (2 equiv.), 5 °C, 2.5 h, then **8**, –78 °C, THF, 72%; iii, Et_3SiOTf, CH_2Cl_2, –78 °C; iv, $CaCO_3$, MeI, $Me_2CO–H_2O$ (4 : 1), 69% for two steps; v, $NaClO_2$, 2,3-dimethylbut-2-ene, Na_2HPO_4, $Bu^tOH–THF–H_2O$ (5 : 5 : 1), 81%; vi, Bu^tPh_2SiCl, imidazole, DMAP, CH_2Cl_2, quantitative yield; vii, TsOH, CH_2Cl_2, 92%; viii, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 1 h; ix, DMAP, THF.

method is most preferable for a successful access to the target structures **1** and **2**.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.007.

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