Total Synthesis of Paclitaxel

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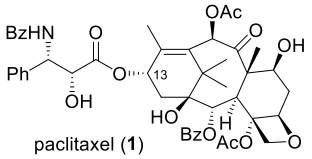
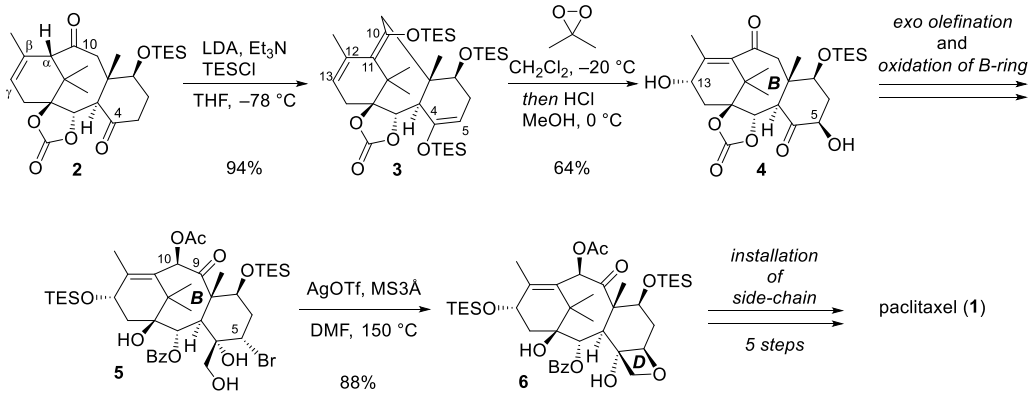


Paclitaxel (Taxol, **1**) is a well-known natural diterpenoid that has been efficacious as an anticancer drug. The structural features of **1** are bridgehead olefin and an oxetane ring which are embedded in highly oxidized tetracyclic framework. Moreover, **1** includes nine stereo centers including a quaternary carbon. In 2015, we achieved the formal synthesis of **1** via Takahashi's intermediate.[1,2] However, many steps were required for the installation of the bridgehead olefin, oxidation of the taxane framework, and formation of the oxetane-ring. To solve these problems, we investigated the 2nd generation synthesis of **1** (Scheme 1). Treatment of β,γ-unsaturated diketone **2** with TESCl and LDA gave bis(silyl enol ether) **3**. Epoxidation of **3** with DMDO and following acidic workup constructed a bridgehead olefin and two hydroxy groups at C-5 and C-13, simultaneously, through double Rubottom oxidation to generate diol **4**. Subsequently, **4** was transformed to oxetane precursor **5**. Treatment of **5** with AgOTf provided oxetane **6** in 88% yield. Finally, installing of a side-chain at C-13 and the removing of silly-group, we accomplished the total synthesis of paclitaxel (**1**) (47 steps, LLS from 3-methoxy toluene).[3]



Scheme 1. Synthesis of paclitaxel (**1**)

1) T. Takahashi *et al*, *Chem*. *Asian*. *J*. **2006**, *1*, 370–383. 2) N. Chida *et al*, *Org*. *Lett*. **2015**, *17*, 2570–2573; *Org*. *Lett*. **2015**, *17*, 2574–2577. 3) N. Chida *et al*, *Org*. *Lett*. **2021**, doi.org/10.1021/acs.orglett.1c03851