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A Concise Synthetic Approach to Optically Active Taxol C-Ring Fragment

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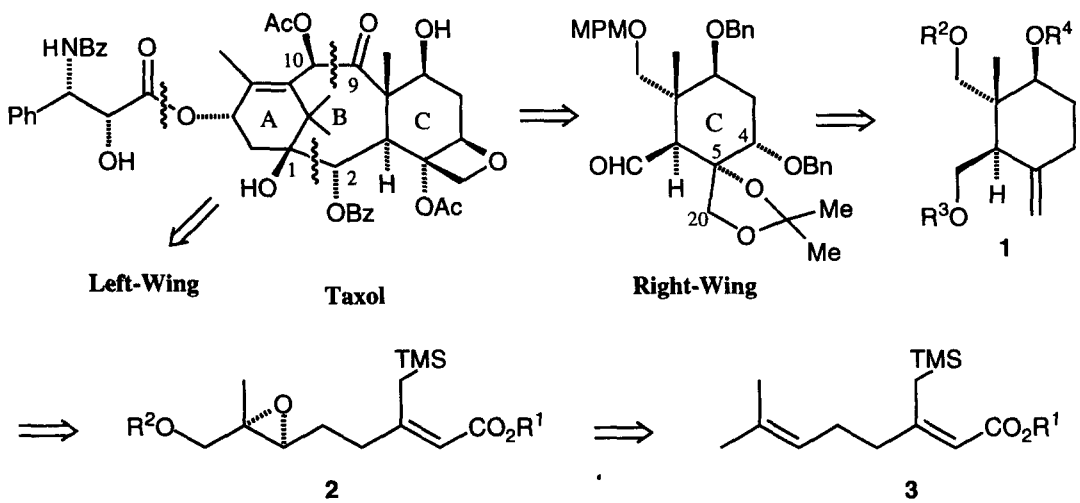
Abstract: A concise synthetic approach to an optically active taxol C-ring fragment starting from a readily available compound is described. Lewis acid promoted-cyclization of optically active epoxy trimethylsilane **7** affords the key intermediate **8** in 69% yield (at 91% conversion). Further transformation of **8** to our taxol C-ring fragment is successfully achieved in a stereoselective manner.

Taxol[1] has long attracted the attention of synthetic chemists because of its challenging structure and potent anticancer activity[2]. Although some total syntheses were reported[3], many synthetic chemists have continued work on the total synthesis of taxol since it is a fascinating synthetic target. Three years have passed since the first total synthesis was achieved. Hence, the next stage should be to investigate an efficient, short synthetic approach to taxol.

We therefore started a project to investigate a convergent, facile synthesis of the taxol carbon framework, which is advantageous for further synthetic study on the taxol family. In this paper we wish to report a concise synthetic approach to an optically active taxol C-ring fragment starting from a readily available compound.

As shown in **Scheme 1**, our retrosynthetic analysis is convergent, and bond disconnections between C1



Left-Wing **Taxol** **Right-Wing**

Scheme 1. Retrosynthetic Analysis of Taxol and Right-Wing

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and C2, C9 and C10 were planned to afford the taxol A-ring fragment, Left-Wing and taxol C-ring fragment, Right-Wing. C4, C5, C20 hydroxy groups of the taxol-C ring were anticipated to be introduced into compound **1** by diastereoselective allylic oxidation and subsequent dihydoxylation of the double bond. Hence we planned the synthesis of **1** first, and we selected Lewis acid-promoted cyclization[4] of the acyclic epoxy trimethylsilane **2** to prepare **1** because **2** should be obtained in optically active form by asymmetric epoxidation[5] of the corresponding allyl alcohol, which apparently could be readily obtained from the already reported **3** by allylic oxidation. Lewis acid promoted-cyclization of epoxy trimethylsilanes has been developed to synthesize terpenoid[4], and the methodology was also successfully applied to the synthesis of taxol A- and C-ring moieties by Frejd *et al.*[6] The yield of their synthesis of the C-ring moiety by this methodology was only 30%. However, we believed that the yield of the cyclization would be improved by modifying our substrate or optimizing the reaction condition.

According to the known procedure[7] a large amount of **4**, which was purified by distillation, was readily prepared in 3 steps using commercially available compounds. Allylic oxidation of **4** has never been reported as far as we know, but the catalytic SeO_2 oxidation system[8] was found to be superior to other methods including stoichiometric use of SeO_2. The yield did not change when the reaction was stopped after the starting material disappeared. Maximum yield based on the consumed starting material was 72% at 78% conversion and the recovered starting material was recycled. Allylic oxidation of derivatives of the allyl alcohol obtained from **4** afforded a considerable amount of undefined polar by-products even under the catalytic oxidation condition. Asymmetric epoxidation[9] of **5** proceeded smoothly to afford epoxy alcohol **6** in 93% yield.

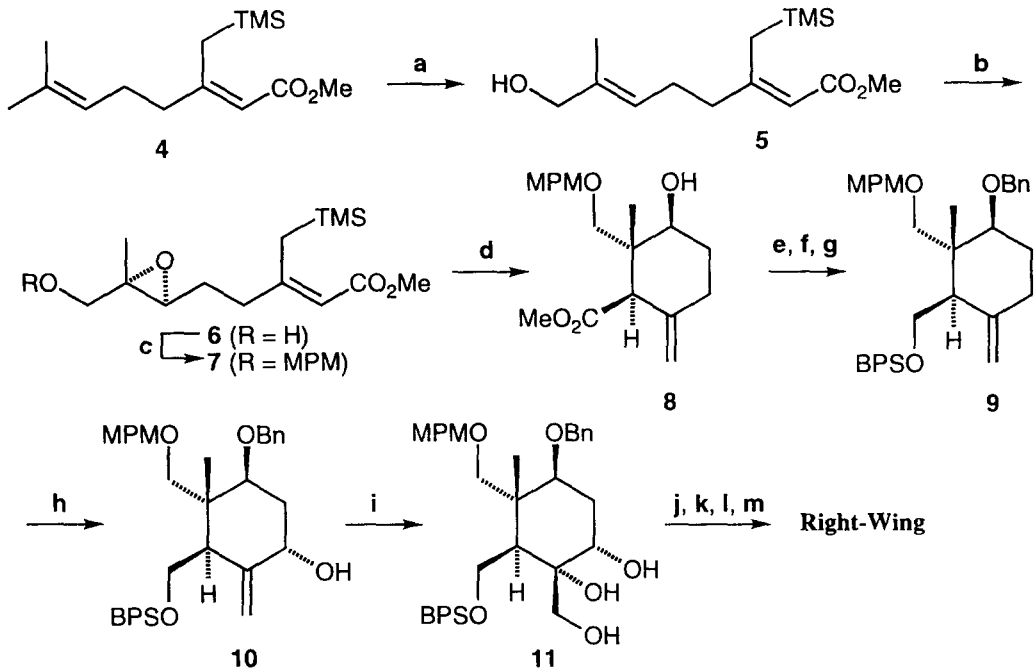
Next, functional groups necessary for Lewis acid-promoted cyclization were set in the substrate, and the epoxy alcohol **6** was treated with $BF_3{\cdot}OEt_2$ (1eq.) in CH_2Cl_2 at -60°C to afford the cyclized product in 34% yield. This result was promising, but the hydroxy group of **6** should be protected for subsequent functional group conversions. The yield of the cyclization reaction seemed to be better when the hydroxy group of **6** could be protected because the hydroxy group must react with the cationic reactive species. However, introduction of the protective group was limited due to the existing acid or base sensitive groups such as allylsilane, ester, epoxide. TBS ether of **6** was then examined and the yield of the cyclized product was improved to 42%, but a desilylated product was also obtained[10]. Derivatives possessing electron-withdrawing protective groups such as benzoate, *N*-phenyl carbamate of **6** gave no cyclized product. These results prompted us to investigate a less bulky, electron-donating MPM protecting group. The preparation method of MPM ether reported by Yonemitsu *et al.*[11] was successfully applied to afford MPM ether **7** in 85% yield. Lewis acid promoted-cyclization of **6** was investigated and the condition described in **Scheme 2** was found to give **8** in 69% yield (at 91% conversion)[12]. Reaction temperature higher than -60°C and prolonged reaction time resulted in lower yield. Among Lewis acids examined, $BF_3{\cdot}OEt_2$ recorded the best result. Further optimization of this cyclization condition is now underway. $LiAlH_4$ reduction of **8** followed by selective BPS(*tert*-butyldiphenylsilyl) protection of the primary alcohol and benzyl ether formation afforded **9** in 96% yield (3 steps). Allylic oxidation of **9** using a catalytic amount of SeO_2[8] cleanly furnished the desired α-alcohol **10** as an almost single isomer in 84% yield (at 78% conversion). The stereoselectivity was obviously attributed to the steric hindrance caused by β-oriented BnO, Me, and $BPSOCH_2$ groups during the second pericyclic step of the SeO_2 oxidation. Catalytic dihydroxylation of **10** using the OsO_4-$Me_3N^+O^-$ system[13] proceeded sluggishly but afforded the desired triol **11** exclusively. The stereoselective catalytic dihydroxylation should occur at the less hindered α-face of the double bond of **10**[3a].

The triol **11** was converted to the crystalline derivative **12**, as described in **Scheme 3**, which was subjected to X-ray crystallographic analysis to confirm the whole structure constructed so far. The result clearly showed that all the asymmetric centers of **11** had been constructed as expected (**Figure 1**).

Acetonide formation of the triol **11**, followed by benzyl ether formation, deprotection of BPS, and Swern

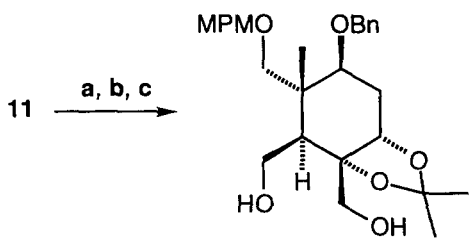
oxidation[14] of the resulting alcohol finally afforded Right-Wing (**Scheme 2**).

In conclusion, enantioselective synthesis of our taxol C-ring fragment, Right-Wing, was completed in 13steps (16% overall yield) starting from **4**, which was readily prepared using commercially available materials.



Reagents and Conditions; **a**. SeO_2 (0.05 eq.), 70% TBHP (3.6 eq.), salicylic acid (0.1 eq.), CH_2Cl_2, r.t., 36h, 72% (at 78% conv.); **b**. TBHP, L(+)-DET, $Ti(Oi\text{-}Pr)_4$, MS4A, CH_2Cl_2, -20°C, 3.5h, 93%; **c**. $MPMOCCCl_3NH$, PPTS, CH_2Cl_2, r.t., 24h, 85%; **d**. $BF_3{\cdot}OEt_2$ (1.0 eq.), MS4A, CH_2Cl_2, -60°C, 1h, 69% (at 91% conv.); **e**. $LiAlH_4$, Et_2O, 0°C→r.t., 1h, 100%; **f**. BPSCl, imidazole, CH_2Cl_2, 0°C→r.t., 97%; **g**. BnBr, $nBu_4N^+I^-$, KH, THF, r.t., 99%; **h**. SeO_2 (0.05 eq.), 70% TBHP (3.6 eq.), salicylic acid (0.1 eq.), CH_2Cl_2, r.t., 12h, 84% (at 78% conv.); **i**. OsO_4 (0.05 eq.), $Me_3N^+O^-$ (2.2 eq.), acetone, H_2O, r.t., 36h, 82% (at 87% conv.); **j**. 2,2-dimethoxypropane, CSA, CH_2Cl_2, r.t., 73%; **k**. BnBr, $nBu_4N^+I^-$, KH, THF, r.t., 93%; **l**. $nBu_4N^+I^-$, THF, reflux, 96%; **m**. Swern oxidation, 96%

Scheme 2. Synthesis of Taxol C Ring Fragment, Right-Wing



Reagents and Conditions; **a**. Pivaloyl chloride, DMAP, CH_2Cl_2, 0°C → r.t., 97%; **b**. 2,2-dimethoxypropane, CSA, CH_2Cl_2, r.t., 96%; **c**. $LiAlH_4$, Et_2O, 0°C→r.t., 1h; then $nBu_4N^+F^-$, THF, reflux, 95% (2 steps).

Scheme 3. Synthesis of Crystalline Derivative

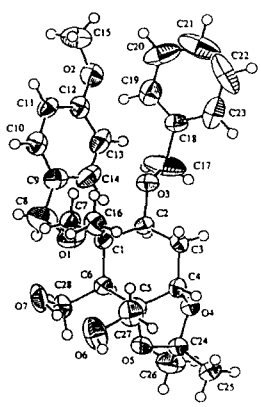


Figure 1. X-ray crystal structure of 12

Lewis acid promoted-cyclization of MPM ether **7** and stereoselective introduction of hydroxy groups to **9** using a catalytic amount of SeO_2 and OsO_4 were crucial to this concise synthesis. Related synthetic studies on the taxol A-, B-ring moiety will be reported in due course.

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