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Synthesis of Paclitaxel. 1. Synthesis of the ABC Ring of Paclitaxel by SmI_2-Mediated Cyclization

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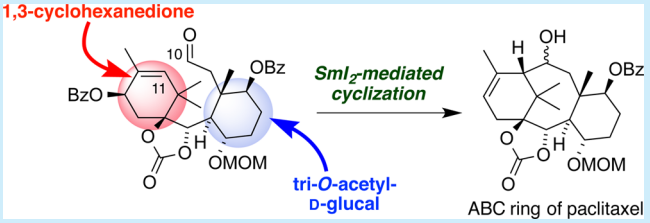
Supporting Information

ABSTRACT: A convergent synthesis of the ABC ring of antitumor natural product paclitaxel (Taxol) is described. SmI_2-mediated reductive cyclization of an allylic benzoate possessing an aldehyde function, synthesized from tri-*O*-acetyl-D-glucal and 1,3-cyclohexanedione, smoothly afforded the highly strained 6−8−6 tricarbocyclic structure in 66% yield.



Paclitaxel (Taxol, **1**) is a well-documented natural diterpenoid that has been used as an anticancer drug.[1−3] The challenging structure, a highly strained 6−8−6 tricarbocyclic framework with a bridgehead olefin and an oxetane ring, as well as important biological activities of **1** have naturally attracted much attention from the synthetic community, and many studies toward the synthesis of **1** have been reported.[4] Although nine successful total and formal syntheses of **1** have been documented to date,[5−13] for the creation of novel anticancer agents, development of an efficient synthetic route to chiral **1** and its derivatives starting from readily available materials is still an important issue in the field of organic and medicinal chemistry. In this paper, we report the convergent synthesis of the ABC ring **3** of paclitaxel starting from tri-*O*-acetyl-D-glucal and 1,3-cyclohexanedione employing the SmI_2-mediated cyclization reaction as the key step.

Our retrosynthetic analysis of **1** based on the chiral pool approach utilizing D-glucal as the starting material[14] suggested that Takahashi's oxetane intermediate **2**[12] would be a suitable target molecule for the paclitaxel synthesis (Figure 1). For the preparation of **2**, the ABC ring intermediate **3** was expected to be a potential precursor. Construction of the strained 6−8−6 tricarbocyclic structure **3** was perceived to be the most challenging issue, and we reasoned that bond formation between C10 and C11 by the SmI_2-mediated reaction[15,16] of allylic benzoate **4** having an aldehyde function would provide a feasible approach to **3**.[17]

The pioneering work of Molander[18a] and Matsuda[18b,c] has revealed that the SmI_2-mediated reductive cyclization of carbonyl compounds possessing allylic acetate or allylic chloride functionalities is a powerful reaction for the construction of eight-membered carbocycles. Their successful results, as well as previous syntheses of ABC rings of paclitaxel by a C10−C11 closure, suggested the possibility of our approach.[18,19] The substrate for the SmI_2-mediated cyclization, ABC precursor **4**, in turn was planned to be obtained by the Shapiro coupling of the A-ring hydrazone **5** with C-ring **6**.

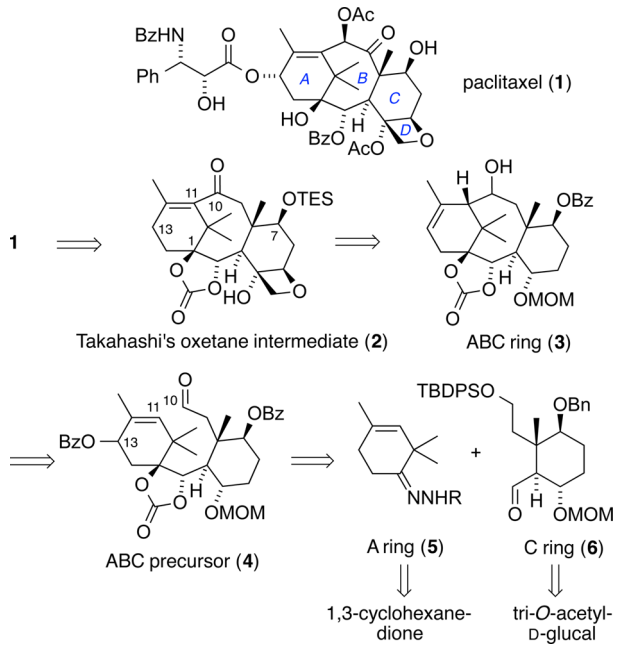


Figure 1. Retrosynthetic analysis of paclitaxel (**1**).

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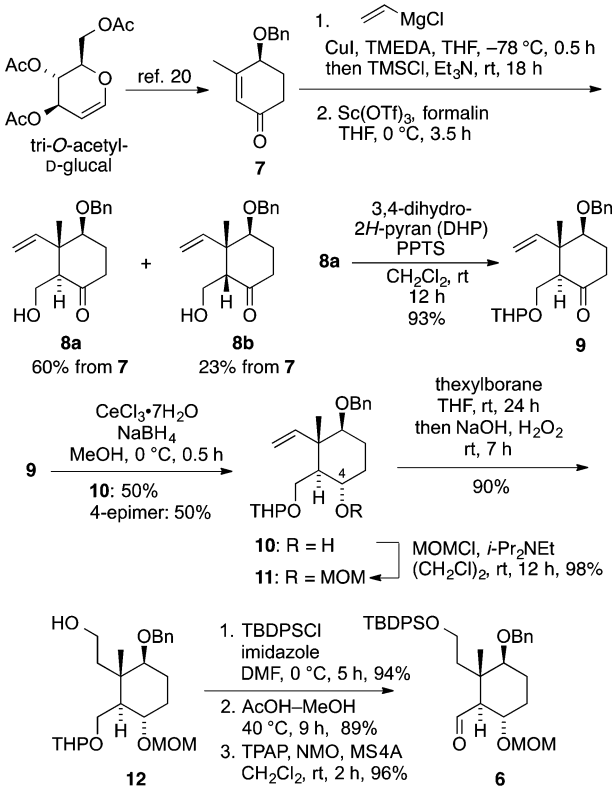
Our synthetic endeavors started with the synthesis of the C ring (Scheme 1). Treatment of optically pure cyclohexenone **7**,

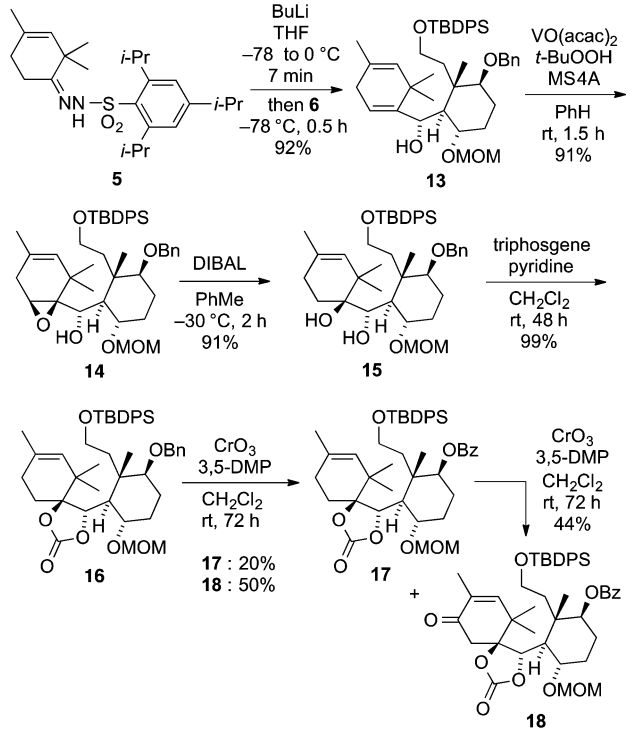
Scheme 1. Synthesis of the C Ring of Paclitaxel



prepared from tri-*O*-acetyl-D-glucal,[20] with vinylmagnesium chloride in the presence of CuI afforded a 1,4-addition product, which was trapped with TMSCl to give a TMS enol ether. Without purification, the enol ether was treated with formalin and $Sc(OTf)_3$[21] to give **8a** and **8b** in 60% and 23% isolated yields, respectively.[22] Protection of the primary hydroxy group in **8a** as a THP ether afforded **9** (93% yield), whose ketone carbonyl was reduced to give secondary alcohol **10** (50% yield) and its 4-epimer (50% yield).[23] After conversion of the secondary alcohol in **10** to a MOM ether, hydroboration–oxidation of the resulting **11** afforded primary alcohol **12** in 88% yield from **10**. Formation of the *O*-TBDPS ether, removal of the THP group, and subsequent oxidation of the resulting primary alcohol with Pr_4NRuO_4 (TPAP) provided C-ring **6** in 80% yield from **12**.

Coupling of C-ring **6** with A-ring **5** was achieved by the Shapiro reaction, which had been employed for the coupling of similar A and C rings in the synthesis of paclitaxel reported by Nicolaou,[6] Danishefsky,[7] and Takahashi.[12] Thus, treatment of hydrazone **5**, synthesized from 1,3-cyclohexanedione in six steps,[24] with BuLi afforded a vinyl anion species, which was then reacted with C-ring **6** (Scheme 2). The reaction proceeded under chelation control[6c] to produce **13** in 92% yield as a single isomer. The hydroxy-directed epoxidation[6c] of **13** gave *β*-epoxide **14** as the sole product in 91% yield. Regioselective reduction of **14** with DIBAL afforded diol **15**, which was then treated with triphosgene to give cyclic carbonate **16** in 90% yield from **14**. Reaction of **16** with CrO_3 in the presence of 3,5-dimethylpyrazole (3,5-DMP)[25] in CH_2Cl_2 first oxidized a benzylic carbon to give benzoate **17** and

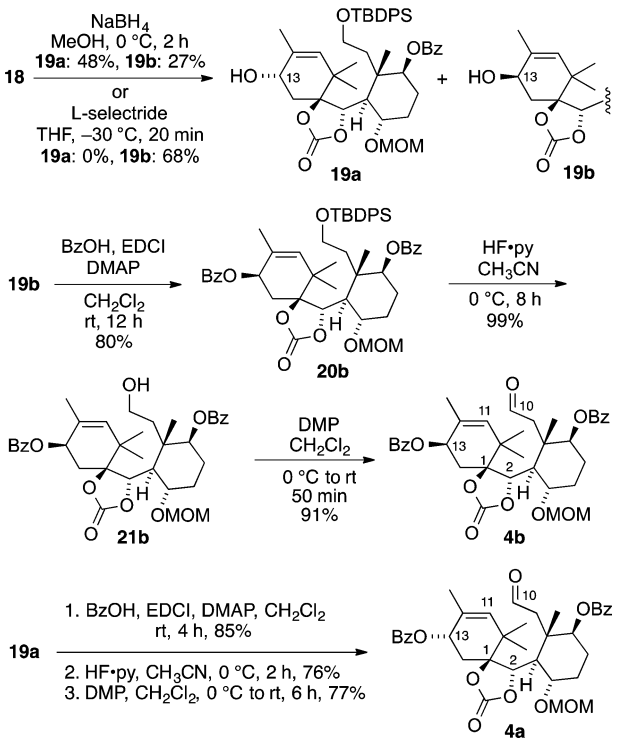
Scheme 2. Preparation of the A–C Rings of Paclitaxel



then the allylic position to provide cyclohexenone **18** in 20% and 50% yields, respectively. Reoxidation of benzoate **17** under the same reaction conditions afforded an additional amount of **18** in 44% yield.

With the appropriately functionalized AC ring of paclitaxel in hand, transformation of **18** into the cyclization precursor **4** was carried out (Scheme 3). While reduction of **18** with $NaBH_4$

Scheme 3. Preparation of the ABC Precursor 4



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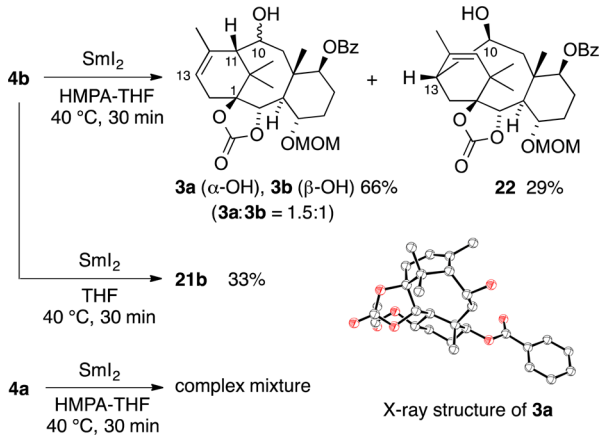
afforded a mixture of allylic alcohols **19a** and **19b** (75% yield, 1.8:1), reaction with L-Selectride stereoselectively generated **19b** in 68% yield. Esterification of the allylic alcohol in **19b** with benzoic acid cleanly provided benzoate **20b** (80% yield), whose TBDPS group was removed to give **21b** in 99% yield. The structure of **21b** was unambiguously confirmed by X-ray analysis.[26,27] Oxidation of **21b** with Dess–Martin periodinane (DMP) furnished cyclization precursor **4b** (91% yield). The same reaction sequence was applied to **19a** to provide another precursor, epimeric benzoate **4a**, in 50% overall yield.

Next, the crucial SmI_2-mediated cyclization was investigated (Scheme 4). After many attempts, it was found that when

Scheme 4. Construction of ABC Ring of Paclitaxel 3



compound **4b** was treated with SmI_2 in HMPA–THF at 40 °C, the desired reductive cyclization took place to generate the eight-membered carbocycle, ABC ring **3**, in 66% yield as an epimeric mixture (**3a**:**3b** = 1.5:1). The isomeric tricarbocycle **22** in which carbon–carbon bond formation occurred between C10 and C13 was also isolated in 29% yield. The structures of **3a** and **3b** were fully confirmed by X-ray analyses,[27,28] and the structure of **22** was assigned on the basis of ^{1}H NMR experiments. In the SmI_2-mediated reaction of **4b**, the use of HMPA as a cosolvent was found to be essential for the successful cyclization: the reaction in the absence of HMPA gave no cyclized product but afforded primary alcohol **21b**. The configuration of the allylic benzoate was also an important factor. Under the same reaction conditions as employed for **4b**, epimeric benzoate **4a** gave many unidentified products, and no cyclized product (**3** nor **22**) was detected in the reaction mixture.

Although the detailed mechanism of the cyclization reaction has been unclear so far, the reaction of **4b** would proceed via an allylic organosamarium species (Barbier-type reaction) and/or a biradical intermediate (coupling of ketyl and allylic radicals).[15,29] In the absence of HMPA, the less reactive SmI_2 did not affect the allylic benzoate but reduced only the aldehyde function.[30] The striking difference in the experimental results between **4a** and **4b** implied that the chelation of SmI_2 might be important for cyclization. In compound **4b**, having a *syn* relationship of the benzoate group at C13 and the oxygen at C1, chelation between SmI_2 and the C13-benzoyl/C1-oxygen would be possible, whereas epimeric **4a** would be unlikely to have a stable chelated structure due to its *anti* relationship of the C13-benzoate and the C1-oxygen. The chelation pathway in **4b** might have accelerated the rate of the reduction of the allylic benzoate to generate an allylic radical or allylic samarium species smoothly,[31] which afforded eight-membered carbocycles **3** and **22** with high efficiency (95% combined yield).

In summary, the ABC ring of paclitaxel **3**, based on the chiral pool approach using tri-*O*-acetyl-D-glucal as the starting material, has been synthesized. The key SmI_2-mediated reductive cyclization of allylic benzoate possessing an aldehyde function **4b** proved to be a powerful reaction for the construction of the eight-membered ring and successfully provided the highly strained 6–8–6 tricarbocycle **3** in 66% yield. Since compound **3** has the basic framework of paclitaxel with appropriate functionalities, it is expected to be a promising intermediate for the synthesis of paclitaxel. Efforts for conversion of **3** to paclitaxel are the subject of the following paper.[4d]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; copies of ^{1}H and ^{13}C NMR spectra of new compounds; the crystallographic data of **3a**, **3b**, and **21b**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01173.

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Notes

The authors declare no competing financial interest.

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