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Synthesis of Paclitaxel. 2. Construction of the ABCD Ring and Formal Synthesis

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Supporting Information

ABSTRACT: A formal synthesis of the antitumor diterpenoid paclitaxel (Taxol) is described. The ABC ring of paclitaxel, synthesized starting from 1,3-cyclohexanedione and tri-*O*-acetyl-D-glucal by SmI_2-mediated cyclization as the key transformation, was successfully converted to Takahashi's tetracyclic oxetane intermediate. A double Chugaev reaction was employed for introduction of the strained bridgehead olefin, and stereoselective formation of the oxetane ring afforded the known synthetic intermediate, completing the formal synthesis of paclitaxel.

In the preceding paper, a synthesis of the ABC ring of paclitaxel **3** was reported via SmI_2-mediated cyclization of an allylic benzoate possessing an aldehyde function.[1] It had been prepared from 1,3-cyclohexanedione and tri-*O*-acetyl-D-glucal. The ABC ring **3**, possessing the 6−8−6 tricyclic core of paclitaxel with proper functionalities, was expected to be a promising compound for the synthesis of paclitaxel (Taxol, **1**) and its congeners.[2,3] In this paper, we report the conversion of **3** to Takahashi's oxetane intermediate **2**[4] through a reaction sequence involving introduction of a bridgehead olefin by way of a double-Chugaev reaction, one-carbon elongation by a Peterson olefination, and construction of an oxetane ring.

Our synthetic plan for Takahashi's oxetane intermediate (ABCD ring of paclitaxel)[4] **2** from ABC ring **3** is shown in Figure 1. We reasoned that compound **4** possessing a taxane framework with an *exo*-methylene at C4 would be a suitable intermediate for the synthesis of **2**, since the previous successful synthesis of paclitaxel by Takahashi[4] and Nakada[5] revealed that allylic oxidation followed by dihydroxylation of similar taxane skeletons stereoselectively provided their oxetane precursors. The major requisite transformations for the synthesis of **4** from **3** would be (1) introduction of a bridgehead olefin between C11 and C12 and (2) one-carbon elongation and formation of an exomethylene at C4.

First, formation of the bridgehead olefin by the isomerization of the C12/C13 olefin in **3** was examined (Scheme 1).

Oxidation of the hydroxy group in ABC ring **3a**[1] with Pr_4NRuO_4 (TPAP) afforded ketone **5** in 77% yield.[6] A variety of reaction conditions for isomerization of a double bond (acidic,[7] basic,[8] and metal-catalyzed conditions[9]) were applied to β,γ-unsaturated ketone **5**. However, all attempted reactions resulted in the recovery and/or decomposition of the starting material, and the formation of isomerized α,β-unsaturated ketone **6** was not detected.

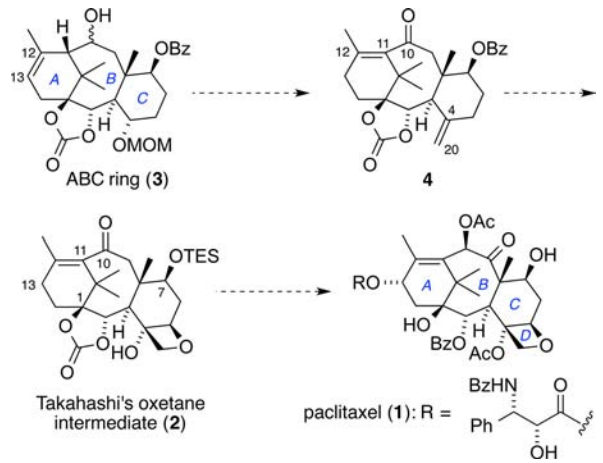

Figure 1. Synthetic plan for paclitaxel (**1**) from ABC ring (**3**).

Recognizing the difficulty in the direct isomerization of the double bond in **5**,[10] we decided to adopt a stepwise oxidation/elimination procedure. Reduction of the ketone carbonyl in **5** with $NaBH_4$ afforded **3b** in a stereoselective manner, whose hydroxy group was protected as a benzyl ether to give **7** in 96% yield over two steps. OsO_4 oxidation of **7**, followed by treatment with aqueous $NaHSO_3$, stereoselectively generated diol **8** in 87% yield. Since compound **8** has a *syn* relationship

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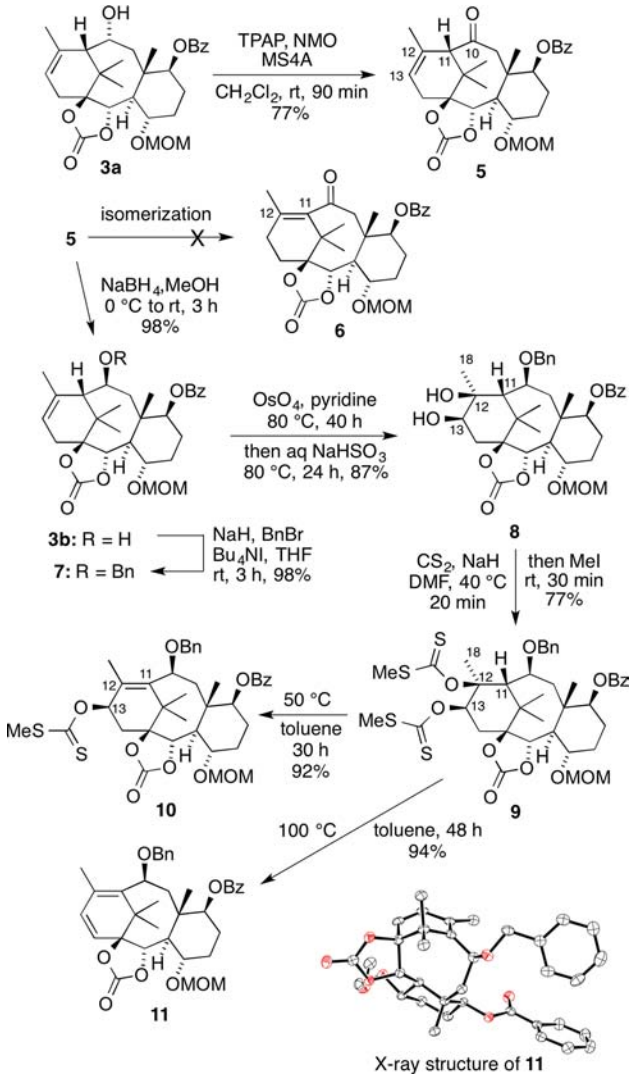
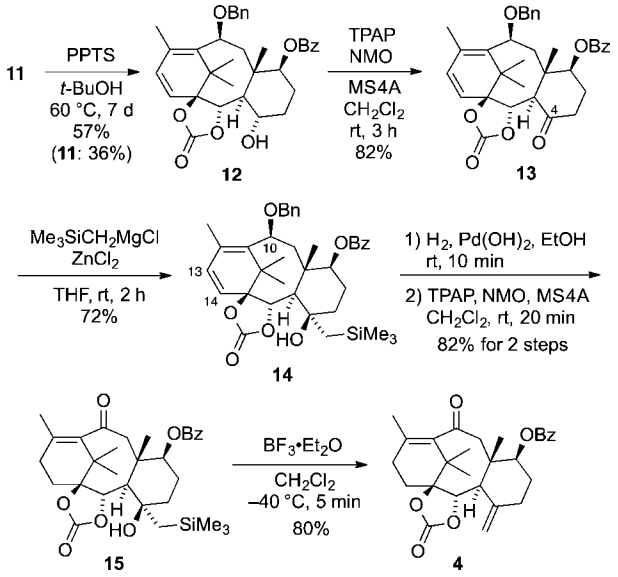
Scheme 1. Construction of a Bridgehead Olefin by Chugaev Reaction



between the tertiary alcohol at C12 and H11 and an *anti* relationship between C12-tertiary alcohol and H13, it was expected that *syn*-elimination of the oxygen function at C12 would generate the C11/C12 bridgehead olefin. For this purpose, the Chugaev reaction[11] was attempted. Thus, diol **8** was converted into bis-xanthate **9** by the action of NaH and CS_2, followed by MeI treatment (77% yield). Gratifyingly, when a toluene solution of bis-xanthate **9** was heated at 50 °C, Chugaev elimination between the tertiary xanthate at C12 and H11 smoothly occurred to provide compound **10** with a bridgehead olefin as the sole product in 92% yield, and the formation of an exomethylene isomer with C12/C18 olefin was not observed.[12] It should be noted that the Chugaev reaction took place at relatively low temperature (50 °C) to generate the strained bridgehead olefin in excellent yield with high regioselectivity. The same reaction at an elevated temperature (100 °C) induced elimination of the second xanthate at C13 to provide the product of double Chugaev reaction, diene **11**, also in high yield (94%). The structure of **11** was unambiguously confirmed by X-ray analysis.[13]

With the tricarbocyclic compound possessing the bridgehead olefin **11** in hand, conversion of **11** to the taxane skeleton **4** was next investigated (Scheme 2). Treatment of **11** with PPTS in *t*-

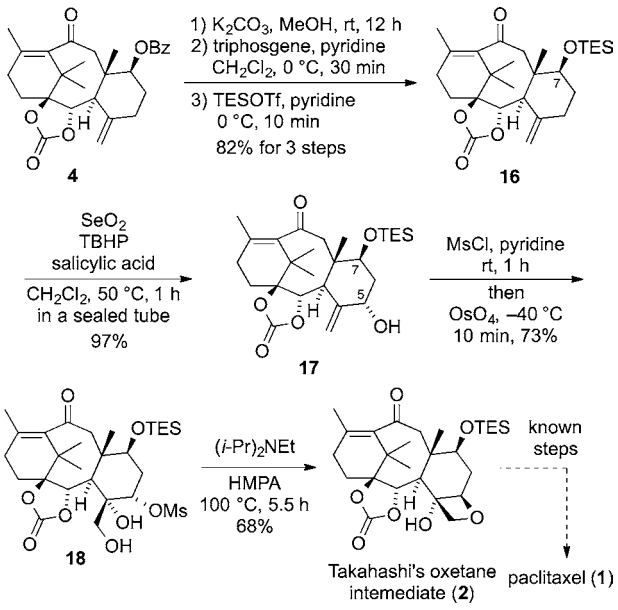
Scheme 2. Synthesis of Taxoid 4



BuOH removed the MOM protecting group to give **12** in 57% yield (**11** was recovered in 36% yield), whose hydroxy group was oxidized by the action of TPAP to provide ketone **13** (82% yield). For one-carbon elongation, ketone **13** was reacted with $TMSCH_2MgCl$ in the presence of $ZnCl_2$[14] to provide **14** as a single isomer in 72% yield. When **14** was treated with H_2 gas in the presence of Pearlman catalyst, selective hydrogenation of the double bond at C13/C14 as well as hydrogenolysis of the *O*-benzyl group at C10 took place to provide an unstable allylic alcohol, which was immediately oxidized with TPAP to give ketone **15** in 82% yield over 2 steps. Reaction of **15** with BF_3·OEt_2 at −40 °C induced the Peterson-type olefination[15] to cleanly afford the desired taxoid **4** in 80% yield.

Final functionalization and introduction of the oxetane ring started with the exchange of the protecting group at C7 in **4** (Scheme 3). Treatment of **4** with K_2CO_3 in MeOH removed both the *O*-benzoyl group at C7 and the cyclic carbonate to

Scheme 3. Synthesis of Takahashi's Oxetane Intermediate



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give a triol, whose vicinal diol moiety was again protected as a cyclic carbonate. The resulting secondary alcohol was protected as a TES ether to afford **16** in 82% yield from **4**. Allylic oxidation of **16** with SeO_2 in the presence of TBHP and salicylic acid[4,16] introduced a hydroxy group at C5 to afford **17** with high stereoselectivity and chemical yield (97%). Reaction of **17** with MsCl in pyridine provided the corresponding C5 mesylate; however, this mesylate was found to be highly unstable: attempted isolation via silica gel chromatography resulted in the complete decomposition of the product. To overcome this difficulty, dihydroxylation of the crude mesylate in a one-pot process was carried out. Thus, after confirmation of the consumption of the starting alcohol **17** in the mesylation step by TLC analysis, OsO_4 (5 equiv) was added to the reaction mixture. Fortunately, dihydroxylation took place smoothly to give diol mesylate **18** as a relatively stable compound, which could be isolated in 73% yield from **17**. Finally, according to the reported procedure by Takahashi,[4] mesylate **18** was reacted with *N*,*N*-diisopropylethylamine in HMPA at 100 °C to provide Takahashi's oxetane intermediate of paclitaxel **2** in 68% yield. The spectral data of synthetic **2** were identical to those reported by Takahashi.[4] Since compound **2** had been converted to paclitaxel in nine more steps,[4,17,18] a formal synthesis of paclitaxel has been achieved.

In conclusion, a synthesis of Takahashi's oxetane intermediate of paclitaxel **2** has been completed. The double-Chugaev reaction of bis-xanthate **9** derived from the ABC ring effectively generated the strained bridgehead olefin in excellent yield. Allylic oxidation of **16**, followed by one-pot mesylation/dihydroxylation and subsequent base treatment, successfully constructed the oxetane ring to furnish the known synthetic intermediate **2**. All stereochemistry of compound **2** flowed from a single stereogenic center at C-7, which came from readily available tri-*O*-acetyl-D-glucal. We believe that this successful synthesis revealed the effectiveness of the methodology based on the chiral pool approach from carbohydrates for the preparation of structurally complex natural products.[19] The new and convergent synthetic pathway to paclitaxel from readily available starting materials, established in this work, should enable the preparation of various paclitaxel congeners, which are expected to be potential candidates for novel anticancer agents. Further efforts for reducing the number of synthetic steps and improving the yields of each step are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; copies of ^1H and ^{13}C NMR spectra of new compounds; crystallographic data of **5** and **11**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01174.

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Notes

The authors declare no competing financial interest.

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(10) The structure optimization of simplified model compounds (**i**, **ii**, and **iii**) by DFT calculations (B3LYP/6-31G*) revealed that conjugated isomer **ii** with a bridgehead olefin is an unstable isomer. Isomer **i** with a C12/C13 olefin is more stable than isomer **ii** (with C11/C12 olefin) by 12.55 kcal/mol, suggesting that the isomerization of **i** to **ii** would be unlikely to occur under thermodynamic conditions. It was also shown that exomethylene isomer **iii** (with C12/C18 olefin) is more stable than isomer **ii** by 5.28 kcal/mol. For details of the calculation, see the Supporting Information.

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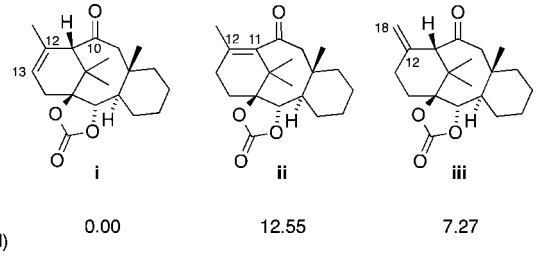

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(12) In the ^{1}H NMR spectra of **8** and **9**, the chemical shifts of the methine proton at H11 and CH_3 at C18 in diol **8** were observed at δ 2.32 and 1.11 (in C_6D_6 at 79 °C), whereas those in bis-xanthate **9** resonated at δ 4.56−4.65 and 1.37−1.59 (in C_6D_6 at rt; the chemical shifts of some protons in **9** could not be fully determined due to the signal broadening caused by the presence of conformational isomers), respectively. The remarkable downfield shift of H11 (δ 2.32 in **8** → δ ca. 4.6 in **9**), which was assumed to be caused by the anisotropic effect of a thiocarbonyl group, indicated that the C═S moiety of C12-xanthate in compound **9** was in close proximity to H11. These observations suggested that in the Chugaev reaction of **9**, *syn* elimination between C12-xanthate and H11, rather than between C12 and H18, might be favorable under kinetic conditions.

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