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A semisynthesis of paclitaxel via a 10-deacetylbaccatin III derivative bearing a β-keto ester appendage

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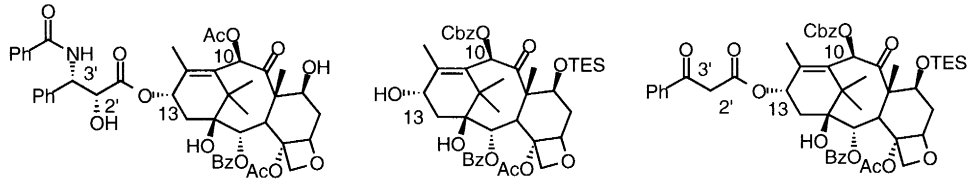
Abstract

A semisynthesis of paclitaxel has successfully been accomplished starting from a newly developed baccatin III derivative bearing a β-keto ester appendage on C-13.

Keywords: β-keto ester appendage; 10-deacetylbaccatin III; paclitaxel; semisynthesis.

In the preceding paper, we reported a remarkably efficient preparative method for a 10-deacetylbaccatin III derivative **3** by the transesterification of ethyl benzoylacetate with a protected 10-deacetylbaccatin III (**2**). Here we wish to describe a new semisynthetic method for paclitaxel (**1**)[1] from **3** via a regio- and diastereoselective construction of the 2′-α-OH-3′-α-NH_2 alignment requisite for **1**.



Our protocol is outlined in Scheme 1. The key intermediate **3** was treated with *O*-benzylhydroxylamine hydrochloride in pyridine at room temperature for 3 h to give oxime ether **4** in a quantitative yield. Then, introduction[2] of 2′-OH of **4** was extensively examined. However, all the efforts were unfruitful, which involved the oxidation with *m*-CPBA, the air oxidation of the carbanion, and the bromination with NBS and ensuing acetoxylation. To our great delight, an elegant synthetic method for α-acyloxyketone by

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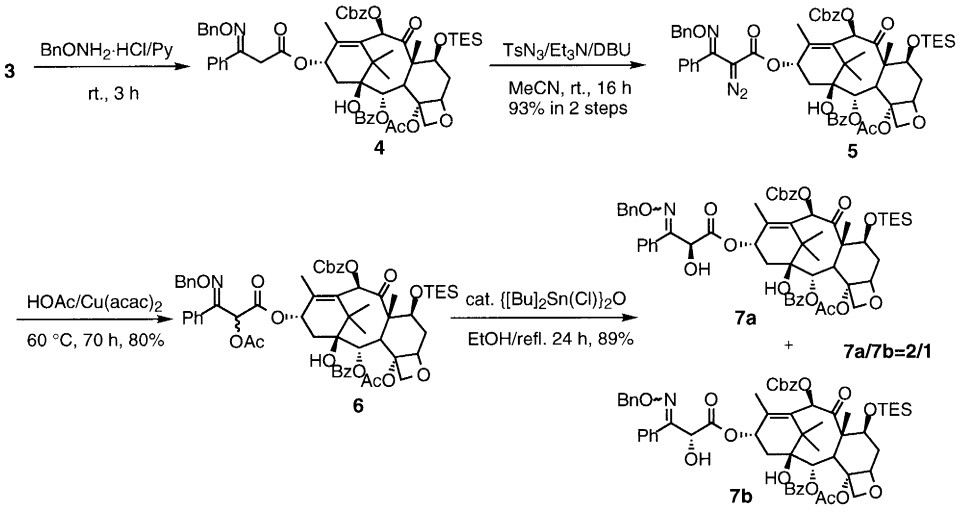
$Cu(acac)_2$-catalyzed insertion reaction of α-diazoketone to carboxylic acid has been reported by Shinada and Ohfune.[3] Their protocol stimulated us to synthesize diazo compound **5**, which was uneventfully prepared in 93% yield based on **3** by the treatment of **4** with a combination of TsN_3/Et_3N/cat. DBU (1.1/1.3/0.3 equiv. each) in acetonitrile at room temperature for 16 h. The insertion reaction of **5** thus obtained was carried out according to their standard procedure, whereas the reaction was very sluggish with a slight excess of acetic acid in toluene at room temperature. Compound **5**, stabilized by both the C=N and C=O bonds, seemed much less reactive than α-diazoketones. Consequently, the reaction of **5** in HOAc as the solvent proceeded at 60°C for 70 h at a reasonable rate to give acetate **6** in 80% yield. The diastereoselectivity of the reaction was ambiguous at this stage since **6** was found to be an inseparable mixture of four diastereomers composed of both *E*/*Z* isomers of the oxime, and α and β-OAc. Next, attempted alkaline hydrolysis of the 2′-OAc of **6** using weak bases did not proceed chemoselectively, the other acetoxy group on C-4 position being damaged. To overcome this crucial problem, **6** was subjected to bis(dibutylchlorotin)oxide-catalyzed transesterification[4] in boiling ethanol for 24 h, giving rise to a chromatographically separable mixture of alcohols **7a** and **7b** in 89% combined yield. Eventually, the diastereoselectivity of the insertion reaction of **5** was unambiguously determined to be 2/1.[5]

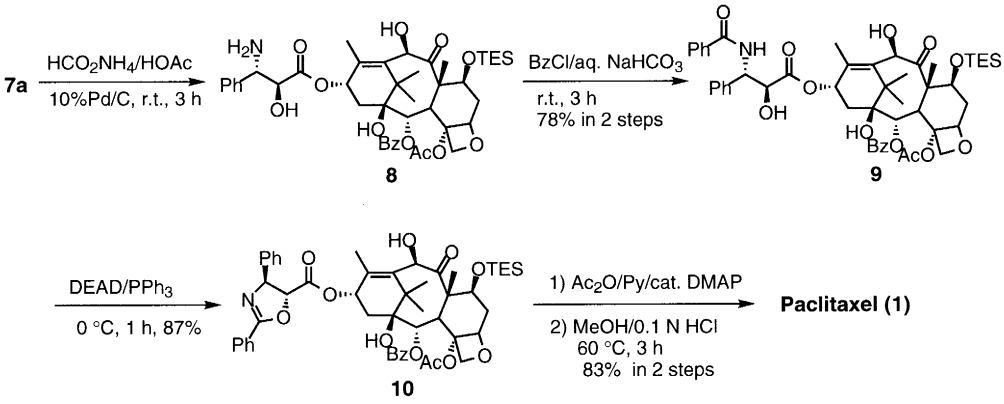


Scheme 1.

At first, the minor isomer **7b** seemed to be an ideal intermediate, if the stereoselective reduction of the oxime to α-NH_2 could be realized. However, all the attempted reductions with various metal hydrides[6] were entirely unsuccessful because the baccatin III nucleus was fatally damaged. Furthermore, the attempted catalytic hydrogenation[7] using Pd/C (10%), Pd black, PtO_2, Rh/Al_2O_3, Rh/C (5%), or Raney-nickel resulted in either the entire recovery of **7b** or at most the deprotection of 10-Cbz. Fortunately, the oxime was only amenable to reduction using HCO_2NH_4/cat. Pd/C (10%)[8] in acetic acid[9] to provide β-NH_2 smoothly with simultaneous deprotection of 10-Cbz.

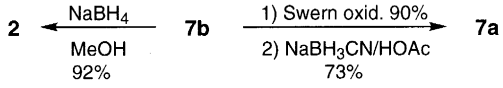
From these observations, we turned our attention to the major isomer **7a**, examining its efficient transformation into **1** (Scheme 2). Simultaneous deprotection of 10-Cbz and reduction of the oxime ether of **7a** were affected with a combination of HCO_2NH_4/cat. Pd/C (10%)/HOAc at room temperature for 3 h to provide **9** in 78% yield in two steps via protection of 3′-NH_2 of **8** as a benzamide. The relative configuration of the 2′-OH and 3′-*N*-Bz in **9** was found to be *anti*, with none of the *syn* isomer being detected. Inversion of the stereochemistry of the β-OH in **9** was successfully achieved via oxazoline formation and ensuing acid hydrolysis. Namely, **9** was treated with DEAD/PPh_3 at 0°C for 1 h to give

oxazoline **10**[10] in 87% yield. Acetylation of **10** (Ac_2O/py/cat. DMAP) followed by the acid-mediated hydrolysis of the oxazoline moiety[10] (0.1N HCl in methanol at 60°C for 3 h) provided paclitaxel (**1**) in 83% yield in two steps.



Scheme 2.

From a synthetic point of view, we examined the transformation of **7b** into **7a** (Scheme 3). Swern oxidation (90%) of **7b** followed by the reduction with $NaBH_3CN$/HOAc provided **7a** (73%) accompanied by **7b** (20%). In addition, **7b** was amenable to the reduction with $NaBH_4$/MeOH to give rise to **2** (92%), which can be reused.



Scheme 3.

In summary, a new semisynthesis of paclitaxel has successfully been accomplished starting from a readily available protected 10-deacetylbaccatin III, which involves both introduction of β-keto ester appendage into C-13 position via catalysis-free transesterification with β-keto ester and construction of 2′-OH-3′-NH_2 in regio- and diastereoselective manners without any asymmetric auxiliaries. We believe this protocol would be helpful for a large scale production of paclitaxel from 10-deacetylbaccatin III.

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5. The absolute configuration of 2′-OH of **7a** and **7b** was determined by converting to **1** and its diastereomer.

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9. When methanol was used as the solvent according to Ref. 8, a cleavage of the side chain was considerably observed probably due to the attack of NH_3 in situ generated to the 1′-ester carbonyl of **8**. Acetic acid may work to suppress the cleavage as the buffer.
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