A Mild and Convenient Semi-Synthesis of Docetaxel from 10-Deacetyl Baccatin III

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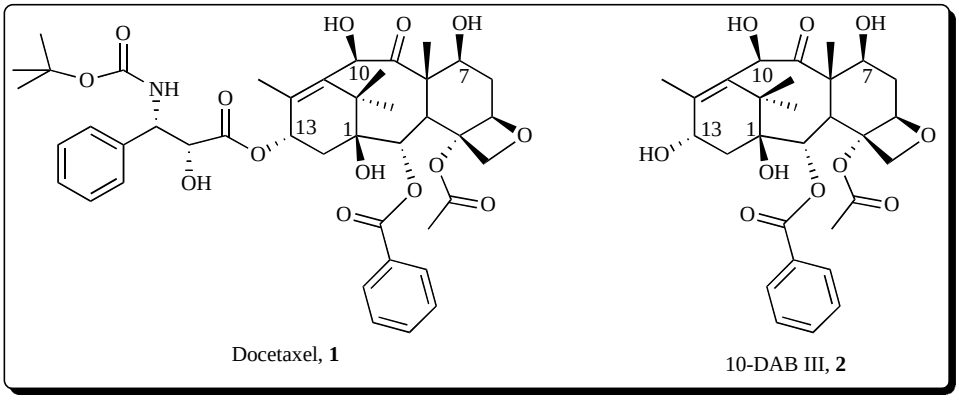
Abstract: A novel protocol for the semi-synthesis of docetaxel was achieved in four steps from 10-deacetyl baccatin III with an overall yield of 50%. The key step is the selective protection of the C(7) and C(10) hydroxyl groups of 10-deacetyl baccatin III, utilizing benzyl chloromate as a selective protecting reagent, which are capable of being conveniently removed by Pd/C under hydrogen atmosphere.

Keywords: Docetaxel, semi-synthesis, 10-DAB III, benzyl chloromate.

INTRODUCTION

Docetaxel is a semi-synthetic, second-generation taxane. It displays potent and broad antineoplastic properties [1,2]. Docetaxel is considered a more effective cytotoxic antimicrotuble agent than doxorubicin, paclitaxel, and fluorouracil [1]. In view of the significance of docetaxel in cancer therapy, a demand of large quantity of docetaxel is expected. At the same time, the total synthesis of docetaxel is not commercially practical due to the lengthy synthetic steps as well as the high cost involved. Thus, highly efficient and practical semi-synthesis is a favorable solution. Semi-synthesis of docetaxel generally utilizes a key coupling reaction of a suitably protected baccatin III derivative with a chiral C(13) side chain [6]. 10-Deacetyl baccatin III(10-DAB III) [3], which possesses the skeleton of taxol and is commercially extracted from the needle of *Taxus baccata L.*, the European yew, is the most readily available and abundant taxane. Its conversion to docetaxel first requires selective protection of the C(7) and C(10) hydroxyl groups. And the selective protecting groups are required to be easily introduced and removed under mild conditions, especially in the extremely sensitive taxane skeleton.

Currently, triethylsilyl(TES) [4], trichloroethoxycarbonyl (Troc) [5], tribromoacetyl [6] have been reported as the protecting groups for the C(7) and C(10) hydroxyl groups of 10-DAB III. However, always a series of by-products were obtained when using TES and Troc as the protecting group. This led to the difficulty of purification. Sisti's group [7] has developed a method utilizing the benzyloxycarbonyl (Cbz) group to protect the C(7) and C(10) hydroxyl groups, but it requires the low temperature of -78 ^{o}C and 1.5 equivalent of n-butyl lithium, which is very sensitive to moisture. Herein, we wish to report benzyl chloromate as a practical selective protecting reagent for 10-DAB III under a mild condition and its application in the semi-synthesis of docetaxel.



Docetaxel, **1** 10-DAB III, **2**

RESULTS AND DISCUSSIONS

In the preliminary study, we investigated the selective protection of 10-DAB III utilizing benzyl chloromate in the presence of 4-(dimethylamino)pyridine (DMAP). Fortunately, the desired C(7), C(10) carbonate was obtained in high yield and purity (Table **1**, entry 1). In addition, p-NO_2-benzyl chloromate was investigated as the protecting reagent.

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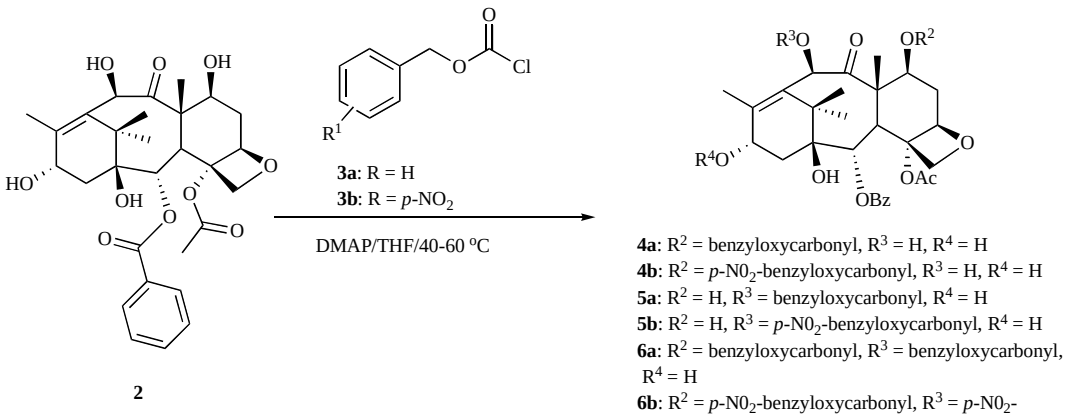
Table 1. The Selective Protection of 10-DAB III[a]



2

4a: R^2 = benzyloxycarbonyl, R^3 = H, R^4 = H
4b: R^2 = *p*-$N0_2$-benzyloxycarbonyl, R^3 = H, R^4 = H
5a: R^2 = H, R^3 = benzyloxycarbonyl, R^4 = H
5b: R^2 = H, R^3 = *p*-$N0_2$-benzyloxycarbonyl, R^4 = H
6a: R^2 = benzyloxycarbonyl, R^3 = benzyloxycarbonyl, R^4 = H
6b: R^2 = *p*-$N0_2$-benzyloxycarbonyl, R^3 = *p*-$N0_2$-benzyloxycarbonyl, R^4 = H
7a: R^2 = benzyloxycarbonyl, R^3 =benzyloxycarbonyl, R^4 =benzyloxycarbonyl
7b: R^2 = *p*-$N0_2$-benzyloxycarbonyl, R^3 = *p*-$N0_2$-benzyloxycarbonyl, R^4 = *p*-$N0_2$-benzyloxycarbonyl

Entry	Protecting Reagent	Ratio (%)[b]			
		4	**5**	**6**	**7**
1	**3a**	2.4(**4a**)	0.3(**5a**)	97.3(**6a**)	N.D.[c](**7a**)
2	**3b**	1.0(**4b**)	0.2(**5b**)	98.8(**6b**)	N.D.(**7b**)

[a]Reaction was conducted with **2**(28 mmol) in THF(150 mL) with DMAP(28 mmol) and **3**(0.37 mol/L in THF, 150 mL) at 40-60 °C.
[b]Determined by HPLC.
[c]N. D. = Not Detected.

Similar results were obtained (Table **1**, entry 2) and therefore we selected benzyl chloromate to continue on with.

Subsequently, several organic bases have been examined. The results are summarized in Table **2**. When aliphatic tertary amine, triethyl amine, was used instead of DMAP, many by-products were found without any desired products (Table **2**, entry 1). When pyridine was used, only mono-protection of C(7) or C(10) hydroxyl of 10-DAB III were found(Table **2**, entry 2). When inorganic bases such as Na_2CO_3 or NaOH were mixed with 10-DAB III, many by-products were formed, therefore DMAP was the base of choice. And the desired C(7), C(10) carbonate was obtained with the isolated yield of 81%.

In light of our success in developing selective protection of 10-DAB III, we decided to apply it into the synthesis of docetaxel. The reaction conditions and their results were summarized in Scheme **1**. Coupling of 7,10-diprotected baccatin III(**6a**) with commercially available side-chain **10** was carried out by using $NaN(TMS)_2$ and NaH to afford **8** in 80% yield *via* column chromatography. Upon treatment of **8** with Pd/C under a hydrogen atmosphere, gave pure **9** in 98% yield after filtration and concentration. Finally, the removal of 2'-acetal with $AcOH/H_2O$ afforded the desired docetaxel in 78% yield.

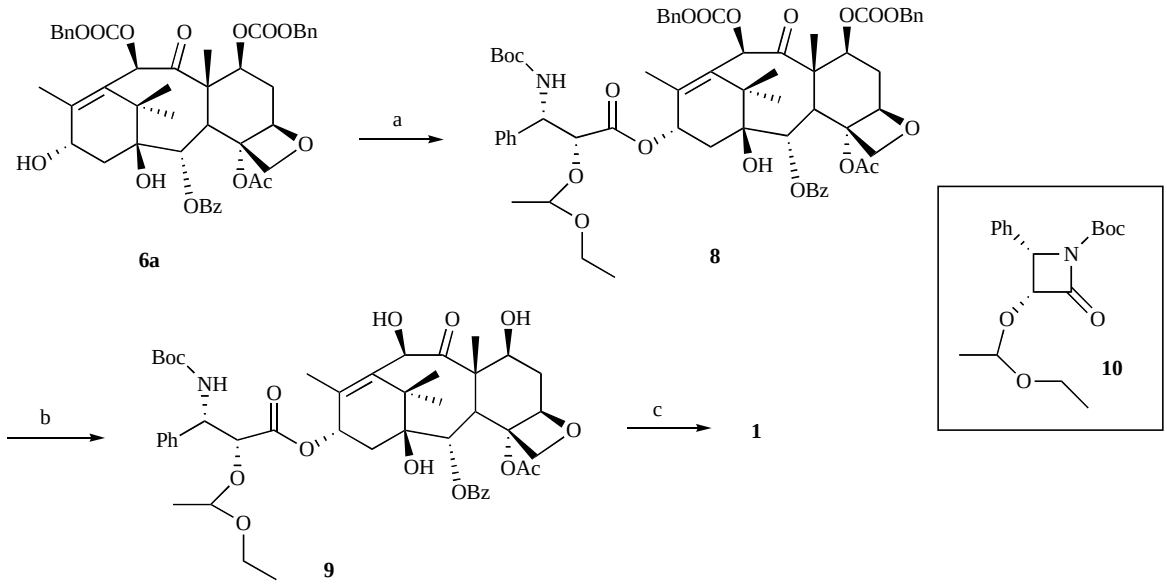
In conclusion, we have developed a new method for docetaxel with an overall yield of 50% from 10-DAB III. The key step is the highly selective protection of the C(7) and C(10) hydroxyl groups of 10-DAB III, utilizing benzyl chloromate as a selective protecting reagent and DMAP as coupling reagents in a mild condition. The method will

Table 2. The Selective Protection of 10-DAB III with Different Bases[a]

2 $\xrightarrow{\textbf{3}/\text{base/THF/40-60 °C}}$ **4a** + **5a** + **6a** + **7a**

Entry	Base	Ratio(%)[b]			
		4a	**5a**	**6a**	**7a**
1	Et_3N	N.D.[c]	N.D.	N.D.	N.D.
2	Pyridine	3.02	1.03	N.D.	N.D.
3	DMAP	2.35	0.31	97.20[d]	N.D.

[a]Reaction was conducted with **2**(28mmol) in THF(150 mL) with a certain base(28 mmol) and **3**(0.37 mol/L in THF, 150 mL) at 40-60 °C.
[b]Determined by HPLC.
[c]N. D. = Not Detected.
[d]The isolated yield is 81%.



Scheme 1. Semi-synthesis of Docetaxel.

Reagents and conditions: (a) **10**, NaH, $NaN(TMS)_2$, -40 ^oC, THF, 2.5h, 80%; (b) Pd/C, H_2, THF, r.t., 5h, 98%; (c) $AcOH/H_2O$(4:1, v/v), r.t., 4h, 78%.

benefit from the easy handle, high yield and the high purity[8] of docetaxel.

EXPERIMENTAL SECTION

C-7, C-10-dibenzyloxycarbonyl-10-Deacetyl baccatin III (6a)

10-DAB III (15g, 28mmol) and DMAP (3.4g, 28mmol) were dissolved in anhydrous THF (150 mL) and the solution was warmed to 40 ^oC. Benzyl chloromate (0.37 mol/L in THF, 150 mL) was added dropwise over 1h, and the solution was warmed to 60 ^oC, and stirred for an additional 30 min. The mixture was then cooled to r.t., filtrated, and washed with THF. The combined filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography to obtain pure **6a** as a white solid (18g, 81%). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.6, 15.4, 20.1, 22.6, 25.6, 26.6, 33.4, 38.4, 42.7, 47.4, 56.3, 68.0, 68.0, 69.9, 70.1, 74.3, 75.6, 76.4, 78.7, 79.0, 80.6, 83.9, 128.3, 128.3, 128.4, 128.44, 128.5, 128.6, 128.7, 129.3, 130.1, 131.5, 133.7, 135.2, 135.3, 145.6, 154.2, 154.2, 167.0, 170.7, 202.0; ESI-MS calcd. for $C_{45}H_{48}O_{14}Na$ $[M+Na]^+$: 835.3, found 835.6.

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[8] The purity of docetaxel synthesized by our method was 99.6% which was determined by HPLC. (YMC C18(150×46mm,5μm), Methanol/Acetonitrile/H_2O = 33/25/42, flow rate 1.5 mL/min, detection at 232 nm, t_R 14.8 min).