Development of New Efficient Synthetic Methods for Docetaxel

Jae Ho Heo, Sung Jun Park,† Joo Hi Kang, In Suk Lee,† Jin Seo Lee,†
Young Jun Park,† Kyoung Soo Kim,†,* and Jae Yeol Lee*

*Research Institute for Basic Sciences and Department of Chemistry, College of Sciences, Kyung Hee University, Seoul 130-701, Korea. *E-mail: ljy@khu.ac.kr*
*†Chirogenix Co., Ltd., Kowoon Institute of Technology Innovation, Suwon University, Whasung, Kyunggi 445-743, Korea. *E-mail: kskimpc@chirogenix.com*
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Docetaxel is a clinically well established anti-mitotic chemotherapy medication used mainly for the treatment of breast, ovarian, and non-small cell lung cancer.[1,2] Docetaxel is considered better than doxorubicin, paclitaxel and fluorouracil as a cytotoxic antimicrotubule agent (Figure 1).[1] Docetaxel is marketed worldwide under the name of Taxotere® by Sanofi-Aventis.[3] Docetaxel is of the chemotherapy drug class (taxane) and is a semi-synthetic analogue of paclitaxel (Taxol®), an extract from the rare Pacific yew tree *Taxus brevifolia*.[2] As shown in Figure 1, docetaxel differs from paclitaxel at two positions in its chemical structure: (1) It has a hydroxyl functional group on carbon-10, whereas paclitaxel has an acetate ester; (2) a *tert*-butyloxylcarbonyl group exists on the nitrogen atom of phenylpropionate side chain rather than benzoyl group. The carbon-10 functional group change causes docetaxel to be more water soluble than paclitaxel.[2] However, great difficulty exists in the total synthesis of docetaxel because of its complex structure. Since 10-deacetyl baccatin III (10-DAB III) was extracted in large scale from the renewable and readily available European yew tree *Taxus baccata*,[4] however, the effective semi-synthesis of docetaxel was started to reduce synthetic difficulty and cost of docetaxel dramatically.[5]

As a result, a number of semi-synthetic methods for docetaxel have been reported up to date.[6-15] Among them, the method comprised of the coupling reaction of 10-deacetylbaccatin III (10-DAB III) with commercially available (2*R*, 3*S*)-phenylisoserine seems to be an effective and cheap way to synthesize docetaxel, in particular, for large-scale commercial production.[16] Herein, we describe the efficient synthetic methods of docetaxel for large scale-up preparation by using new protecting groups and a mild de-protecting condition.

After a number of trials, we decided to protect both C-3' NH_2 and C-2' OH groups of (2*R*, 3*S*)-phenylisoserine (**1**) with 1,1-dichloroacetone or chloral ethylate in the presence of PPTS to

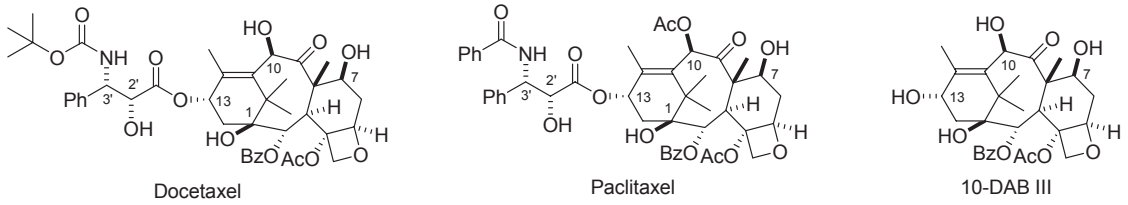
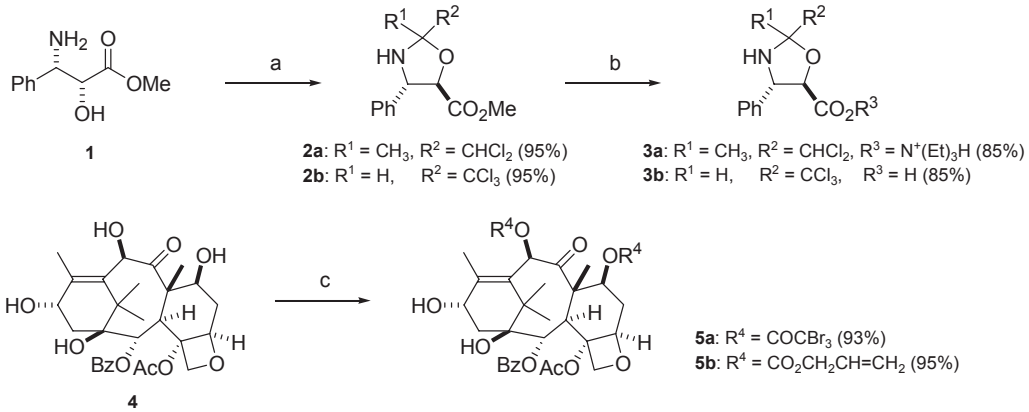
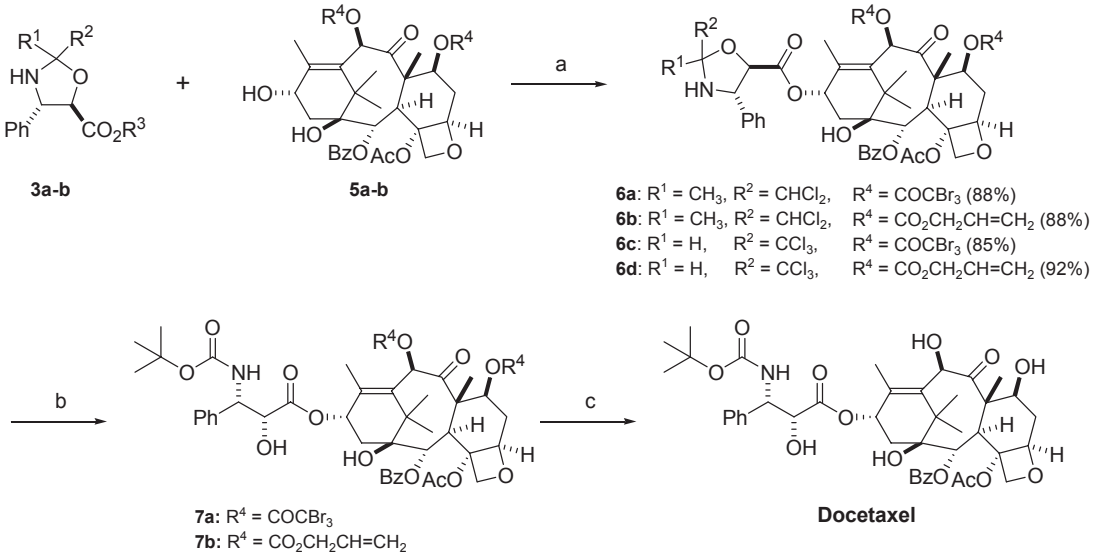


Figure 1. Structures of docetaxel, paclitaxel, and 10-DAB III



Scheme 1. Reagents and conditions: (a) $CH_3COCHCl_2$ (for **2a**) or $CCl_3CH(OH)OEt$ (for **2b**), PPTS, toluene, reflux, 3 h; (b) 3N LiOH, MeOH, rt, 30 min, then 3N HCl (for **3b**) and Et_3N (for **3a**); (c) CBr_3COCl (for **5a**) or $ClCO_2CH_2CH{=}CH_2$ (for **5b**), pyridine, $CHCl_3$, 0°C to rt, 3 h.



Scheme 2. Reagents and conditions: (a) DCC, DMAP, toluene/DMF, 0°C to rt, 3 h; (b) *c*-HCl, EtOAc, rt, 20 min to 12 h, then $NaHCO_3$ and $(^tBoc)_2O$, rt, 2.5-3 h; (c) see Table 1.

Table 1. Yield of compound **7,** reaction condition c in Scheme 2, and its yield

Entry	Compound	Yield (%) of **7**	Reaction condition c	Yield (%) of docetaxel
1	**6a**	**7a**[a]	$AcONH_4$, MeOH/THF (1:1), rt, 3 h	90[b]
2	**6b**	**7b** (95)	$Pd(PPh_3)_4$, aniline, CH_2Cl_2, rt, 30 min	84
3	**6c**	**7a** (96)	$AcONH_4$, MeOH/THF (1:1), rt, 3 h	92
4	**6d**	**7b** (92)	Pd/C, $HCONH_4$, MeOH, rt, 40 min	85

[a] Not purified and used for next reaction. [b] Two-step yield

afford the *trans*-oxazolidine intermediates **2a** and **2b** as a diastereomeric mixture in 95% yields, respectively, which were hydrolyzed with 3N LiOH and treated with 3N HCl to provide the corresponding carboxylic acids in 85% yields. In the case of **3a**, the carboxylic acid was converted into triethylamine salt due to its low stability at room temperature (Scheme 1).

With respect to 10-DAB (**4**), both hydroxyl groups of C-7 and C-10 were protected with tribromoacetyl chloride or allyl chloroformate in the presence of pyridine as a base to afford the corresponding **5a-b** in 93 and 95% yields, respectively. Coupling of acid **3a-b** with 7,10-diprotected baccatin III (**5a-b**) was carried out by using DCC and catalytic amount of DMAP as coupling reagents to afford **6a-d** in 85-92% yields *via* column chromatography and recrystallization. Treatment of **6a-d** with *c*-HCl, followed by the introduction of ^tBoc into C-3' NH_2 of phenylisoserine side chain provided the corresponding 7,10-diprotected docetaxels **7a-b** in 92-96% yields. Finally, the removal of tribromoacetyl group with ammonium acetate or allyloxycarbonyl group with palladium catalyst afforded the desired docetaxel in 84-92% yields (Scheme 2). The reaction conditions and their results were summarized in Table 1. The spectroscopic data of synthetic docetaxels were exactly coincided with those of authentic docetaxel.

In conclusion, we have developed new synthetic methods for docetaxel, especially for large scale-up process. By employing one methodology as follows: 1,1-dichloroacetone for phenylisoserine, tribromoacetyl chloride for 10-DAB III, and $AcONH_4$ for de-protection, the synthesis of 100 g of docetaxel has been carried out three times with an overall yield up to 60% and 99.4% purity for real scale-up study.

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