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Synthesis of new baccatin III derivatives through transesterification of β-keto esters with a protected 10-deacetylbaccatin III

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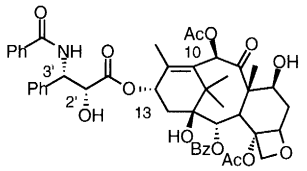
Abstract

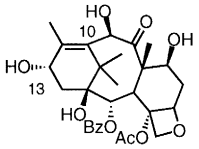
Synthesis of a new array of baccatin III derivatives bearing a β-keto ester appendage on C-13 is successfully achieved through transesterification of a wide range of β-keto esters with a protected baccatin III.

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

Paclitaxel (**1**) has been a challenging target for synthetic organic chemists because of its unique and complex structure.[1] In spite of a recent great success in total syntheses of **1** by six groups,[2] a semisynthesis is still definitely more advantageous in a practical sense owing to readily available 10-deacetylbaccatin III (**2**).



Paclitaxel (1)



10-Deacetyl baccatin III (2)

Semisyntheses of **1** reported so far include procedures for attaching the C-13 side chain to a protected derivative of **2** through esterification of suitably protected phenylisoserine (**A**), [3] ring opening of β-lactam (**B**),[4] and transesterification of thiol ester (**C**).[5] Chiral epoxy carboxylic acid (**D**)[6] is also utilized as the

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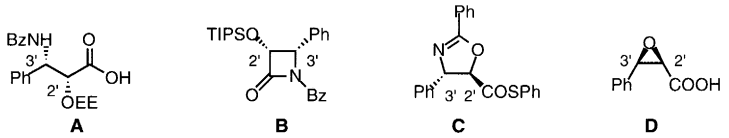
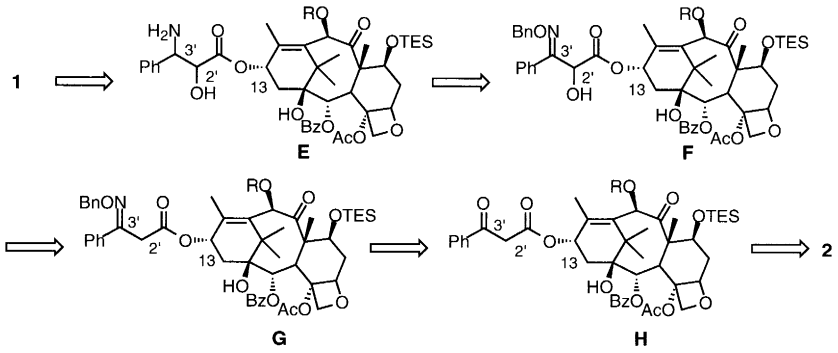
precursor, wherein the requisite NH_2 should be introduced stereoselectively after the esterification. In any case, costly chiral auxiliaries or asymmetric catalysts were used inevitably for the preparation of enantiomerically enriched side chain precursors **A**–**D**.



A **B** **C** **D**

We have been intrigued to establish a new semisynthetic method for paclitaxel (**1**) from **2**, which would be adaptable for industrial scale production. Our synthetic strategy is fundamentally different from conventional methods described above on the point that none of a costly chiral auxiliary is used for the preparation of the side chain through the semisynthesis. As can be seen from the retrosynthetic analysis of **1** shown in Scheme 1, 2′-hydroxy-3′-oxime ether **F** would be one of ideal precursors. 3′-Oxime ether **G** would become an excellent intermediate of **F** if a diastereoselective introduction of 2′-hydroxyl group is feasible. For this purpose, we envisaged to take advantage of baccatin III nucleus in **G** as a promising chiral auxiliary. Thus, we started our project to prepare a baccatin III derivative **H** bearing a β-keto ester appendage which easily leads to the intermediate **G**.

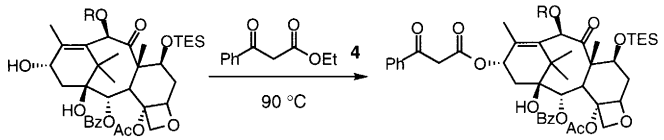


Scheme 1.

To attach the β-keto ester appendage on the C-13 position of **2**, we examined the transesterification[7] of commercially available ethyl benzoylacetate (**4**) with suitably protected derivatives of baccatin III (**3a**–**c**). To our surprise, the present transesterification proceeded very smoothly without catalyst[8] regardless of the sterically hampered α-oriented 13-OH, the results being listed in Table 1. Initially, heating **3a** with an excess (20 equiv.) of **4** without any solvent at 90°C for 24 h provided **5a** in 82% yield (entry 1). The reaction was found to be accelerated markedly by a continuous removal of ethanol formed in vacuo (entry 2). The reaction proceeded at a reasonable rate at 70°C (entry 3). The reaction was, however, very slow at 50°C (entry 4) even under reduced pressure. More than 5 equiv. of **4** seems to be required for the smooth transesterification due to the low solubility of **3a** in **4** even at 90°C (entries 5 and 6).

This protocol is applicable to a wide range of β-keto esters **6** as shown in Table 2. In cases where R is aromatic, the reactivity and the yields are not affected by the substituents (entries 1–6). As for the cyclic and acyclic substituents, the reaction proceeded very smoothly to give **7** in excellent yields (entries 7–9). 2-Carbethoxy cyclopentanone also provided **7** efficiently (entry 10), whereas methyl-substituted ethyl benzoylacetate gave **7** in lower yield (entry 11).

Table 1
Transesterification[a] of ethyl benzoylacetate (**4**) with protected derivatives of baccatin III (**3a–c**)



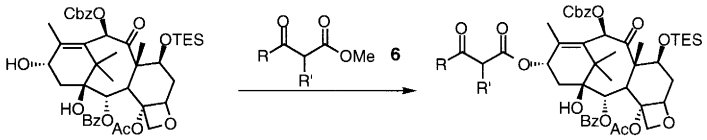
3a: R=Cbz
3b: R=Ac
3c: R=Alloc

5a: R=Cbz
5b: R=Ac
5c: R=Alloc

Entry	3	4 (eq)	Pressure (mmHg)	Time(h)	%Yield[b] of 5	
1	**3a**	20	760	24	**5a**	82 (14)
2	**3a**	20	<1	3	**5a**	97
3[c]	**3a**	20	<1	27	**5a**	90 (5)
4[d]	**3a**	20	<1	21	**5a**	9 (90)
5	**3a**	5	20	10	**5a**	94
6	**3a**	2	20	24	**5a**	43 (54)
7	**3b**	20	<1	3	**5b**	91
8	**3c**	20	<1	3	**5c**	96

a) **3** (0.1 mmol) was reacted at 90 °C. b) Isolated yields and recovered **3** in parentheses. c) Carried out at 70 °C. d) Carried out at 50 °C.

Table 2
Transesterification[a] of β-keto esters **6** with a protected 10-deacetylbaccatin III (**3a**)



3a **7**

Entry	6			Time	Yield (%)[b]
	R	R'	(eq)	(h)	**7**
1	*p*-MeOC$_6$H$_4$-	H	10	7	99
2	*m*-F-C$_6$H$_4$-	H	10	6	88
3	*o*-F-C$_6$H$_4$-	H	10	6	92
4	*p*-F-C$_6$H$_4$-	H	10	6	94
5	*m*-CF$_3$C$_6$H$_4$-	H	10	6	90
6	2-furyl-	H	20[c]	8	99
7	cyclohexyl-	H	10	6	95
8	cyclopropyl-	H	10	6	94
9	n-C$_9$H$_{19}$-	H	10	6	95
10	-(CH$_2$)$_3$-		20[c]	5	93
11	Ph	Me	20	25	20[d]

a) The compound **3a** (0.1 mmol) was reacted at 90 °C under 20 mmHg. b) Isolated yields. c) When 10 eq of **6** was used, the product deposited during the reaction. d) 78% of **3a** was recovered.

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