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Synthetic Studies with 13-Deoxybaccatin III

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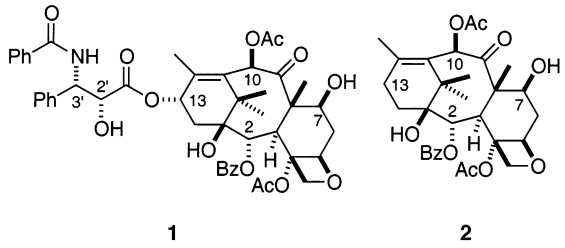
Abstract: An efficient synthesis of 13-*epi*-7-*O*-(triethylsilyl)-baccatin III from 13-deoxybaccatin III is described. Oxidation of 13-deoxy-7-*O*-(triethylsilyl)baccatin III with *tert*-butyl peroxide, followed by reduction with SmI_2, produced 13-*epi*-7-*O*-(triethylsilyl)baccatin III in good overall yield. The preparation of 13-oxo-7-*O*-(triethylsilyl)baccatin III from 13-*epi*-7-*O*-(triethylsilyl)baccatin III using tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide is also reported.

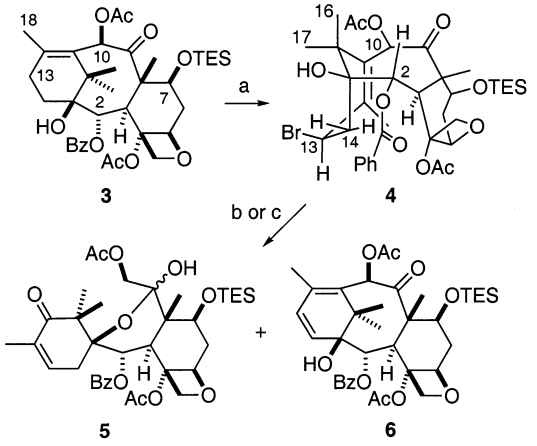
Paclitaxel (**1**, Figure 1), a complex diterpene isolated from the bark of *Taxus brevifolia* (Pacific Yew),[1,2] is a chemotherapeutic agent with impressive antitumor activity.[3,4] Paclitaxel is available only in small quantities from natural sources;[1,2] however, semisynthetic approaches toward paclitaxel synthesis and analogue development have been developed, utilizing 10-deacetylbaccatin III, a more readily available paclitaxel-related natural product.[5−7] A major advantage of using 10-deacetylbaccatin III is that it can be obtained from a regenerable source, the needles of *Taxus baccata*.[8] As paclitaxel becomes widely used for the treatment of several types of cancers, plant cell culture represents an alternative method for paclitaxel production. The major goal of plant cell culture is to produce paclitaxel in high yield, minimizing the formation of other taxane diterpenes.[9] However, certain byproducts can become useful if appropriate synthetic routes can be developed to convert these intermediates to paclitaxel or its derivatives. We now report on the chemistry of such a byproduct, 13-deoxybaccatin III (**2**, Figure 1), which is produced in high quantity from plant cell cultures.[9]



1 **2**

FIGURE 1. Structures of paclitaxel (**1**) and 13-deoxybaccatin III (**2**).

SCHEME 1[a]



[a] Conditions: (a) NBS, benzoyl peroxide, CCl_4, reflux, 8 h, 94%; (b) NaN_3, DMF, 40 °C, 7 h, 79% (**5**:**6** = 1:1); (c) AgOAc, DMF, 40 °C, 7 h, 85% (**5**:**6** = 2:1).

The 7-hydroxy group of 13-deoxybaccatin III was protected with triethylsilyl chloride (TESCl) to provide 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**)[10,11] in 95% yield. Then, 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**) was treated with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide producing the corresponding 13β-bromo derivative **4** in 94% yield (Scheme 1). Bromo compound **4** was found to be unstable on silica gel and was therefore not subjected to purification via column chromatography. The stereochemistry at C13 of **4** was determined through NOE experiments. Irradiation of H16 (δ 1.14) strongly enhanced H2, but not H13, and irradiation of H17 (δ 1.24) significantly enhanced H14β, but not H13. Therefore, the stereochemistry of the 13-bromo group was assigned as 13β. This bromide is unsuitable for further elaboration into bioactive compounds. When reacted with sodium azide and silver acetate, the bromide produced a mixture of 10,11-seco derivative **5**[12] and diene **6** (Scheme 1).[13]

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(12) Kingston and co-workers reported compound **5** as the only product when 13β-chloro-13-deoxy-7-*O*-(triethylsilyl)baccatin III was reacted with sodium azide in DMF. The structure of **5** was identical in all respects to the compound reported in the literature. Chordia, M. D.; Gharpure, M. M.; Kingston, D. G. I. *Tetrahedron* **1995**, *51*, 12963−12970.

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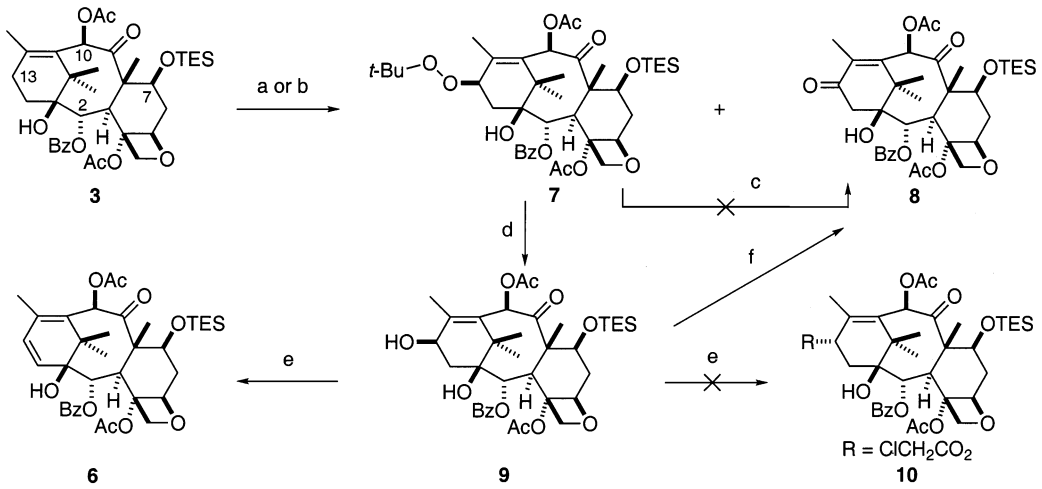
SCHEME 2[a]



[a] Conditions: (a) *tert*-BuOOH, benzene, 60 °C, 7 h, 78% for product **7**; (b) oxidants, *tert*-BuOOH, benzene, rt, 22−26 h, gave **7** and **8**, 0−31% for product **7**; (c) PDC, CuBr, or CuCl, *tert*-BuOOH, benzene, 50−55 °C, 18−23 h; (d) SmI_2, THF, rt, 3.5 h, 86%; (e) DEAD, Me_3P, $ClCH_2CO_2H$, toluene, from 0 to 90 °C, 24 h, 43% for product **6**; (f) TPAP, NMO, CH_2Cl_2, rt, 2 h, 81%.

TABLE 1. Oxidation of 3 with Various Oxidants in the Presence of *tert*-Butyl Hydroperoxide in Benzene

					relative product ratio (%)[a] (isolated yield, %)		
entry	substrate	reagents[b]	time (h)	*T* (°C)	**3**	**7**	**8**
1	**3**	PDC/*t*-BuOOH	20	25	18	43(31)	37
2	**3**	CrO_3/*t*−BuOOH	23	25	5	31(14)	64
3	**3**	SeO_2/*t*−BuOOH	25	25	100	0	0
4	**3**	PCC/*t*-BuOOH	23	25	25	30(23)	45
5	**3**	CuBr/*t*-BuOOH[c]	22	55	37	63(43)	0
6	**3**	CuCl/*t*-BuOOH[c]	26	50	0	100(72)	0
7	**3**	*t*-BuOOH	22	25	19	55(34)	26
8	**3**	*t*-BuOOH	7	60	0	100(78)	0
9	**7**	PDC/*t*-BuOOH	23	50	0	100(>95)[d]	0
10	**7**	CuBr/*t*-BuOOH[c]	18	55	0	100(>95)[d]	0
11	**7**	CuCl/*t*-BuOOH[c]	20	55	0	100(>95)[d]	0

[a] Obtained from integration of signals in the ^{1}H NMR of unpurified reaction products. [b] Ratio of **3**:oxidants:*t*-BuOOH = 1:10:10. [c] CuBr and CuCl were used as catalysts. [d] Starting material **7** was recovered quantitatively.

We also carried out allylic oxidation reactions with compound **3**[14] using various oxidants (Scheme 2 and Table 1) in the presence of *tert*-butyl hydroperoxide. Thus, 7-protected 13-deoxybaccatin III **3** was subjected to oxidants (PCC, PDC, MnO_2, CrO_3, and SeO_2) in the presence of *tert*-butyl hydroperoxide in order to obtain ketone **8**. However, the oxidations gave a mixture of starting material **3**, *tert*-butylperoxy product **7**, and 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**) (Scheme 2, Table 1, entries 1−4). When CuCl and CuBr were used as catalysts in the *tert*-butyl hydroperoxide oxidation reactions,[15,16] none of the ketone **8** was obtained (Table 1, entries 5 and 6). Furthermore, treatment of **3** with only *tert*-butyl hydroperoxide in benzene at 60 °C resulted in the formation of the *tert*-butylperoxy derivative **7** in good yield (78%) as the exclusive product (Scheme 2 and Table 1, entry 8).

The *tert*-butylperoxy compound **7** could be a potential intermediate in the pathway leading to the ketone **8**. Thus, the *tert*-butylperoxy compound **7** was further reacted with *tert*-butyl hydroperoxide and PDC,[17] CuBr, and CuCl[15,16] in order to produce 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**); however, none of the desired product was formed, and the *tert*-butylperoxy compound **7** was recovered in all cases (Scheme 2 and Table 1, entries 9−11).

The stereochemistry at C13 of the *tert*-butylperoxy compound **7** was determined through NOE studies as described above for bromo compound **4**. Since the same results were obtained, the sterochemistry of the 13-*tert*-butylperoxy group was assigned as 13β.

(13) The structure of diene **6** was confirmed by HMQC and HMBC NMR experiments. The protons at C13 and C14 resonate as doublets at 6.09 and 5.60 ppm, respectively ($J_{13,14}$ = 9.4 Hz). In an HMQC experiment, H13 and H14 have correlations with carbon signals at 133.6 and 133.0 ppm, respectively. Therefore, we assigned the signal at 133.6 ppm to C13 and the 133.0 ppm signal to C14. In an HMBC experiment, we found that the proton at C13 showed three bond couplings to the carbons at C12 and C14 and a long-range coupling to C18. The proton at C14 showed three bond couplings to the carbons at C1 and C13. The diene **6** was subjected to epoxidation and dihydroxylation reagents such as *m*CPBA, oxone, OsO_4, and $VO(acac)_2$. However, starting material was recovered in all cases.

(14) Nicolaou and co-workers reported that compound **3** can also be converted to enone **8** by oxidation using excess of pyridiniumchlorochromate (30 equiv) in refluxing benzene (75% yield). See also refs 10 and 11.

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To effect the reductive cleavage of the oxygen−oxygen bond in *tert*-butylperoxy compound **7** to form 13-*epi*-baccatin III **9**, a variety of hydride delivering reagents were used, including $LiAlH_4$, $NaBH_4$, $LiBH_4$, and L-Selectride. However, none of these reagents provided the desired product. The results of these reactions included multiple ester cleavage products or recovery of the starting taxane diterpene. Dimethyl sulfide, triphenylphosphine, and trimethoxyphosphine were also unsuccessfully employed in the attempted reductive cleavage of the oxygen−oxygen bond of peroxide **7**.[18] Therefore, we turned our attention to SmI_2,[19] as a reducing reagent, which cleanly reacted with **7** to generate the desired product, 13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**) in excellent yield (86%, Scheme 2). The coupling constants between H13 and both H14α and H14*β* of 13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**) show 9.7 and 3.5 Hz, respectively, which are similar to those reported before for 13-*epi*-paclitaxel.[20]

In 1995, the syntheses of 13-*epi*-paclitaxel and 4-deacetyl-13-*epi*-baccatin III via removal of the 4-acetyl group of a 13-ketobaccatin III derivative were published.[20] The free 4-hydroxy group assisted in the transannular delivery of a hydride [$Me_4NBH(OAc)_3$] to the 13-ketone moiety yielding the corresponding 4-deacetyl-13-*epi*-baccatin III. The new two-step preparation of 13-*epi*-baccatin III from 13-deoxy-7-*O*-(triethylsilyl)baccatin III by *tert*-butyl hydroperoxide oxidation followed by SmI_2 reduction avoids the deacetylation and reacetylation at C4.

Mitsunobu conditions were then utilized in an attempt to invert the C13 stereochemistry of 13-*epi*-baccatin III **9**; however, starting material was recovered in all cases investigated.[21] These results are in agreement with the observation that the cup-shaped conformation of the taxane diterpene ring disfavors reactions at C13 from the concave side of the molecule.[10,11]

13-*epi*-7-*O*-(Triethylsilyl)baccatin III (**9**) was treated with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) to obtain 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**) in 81% yield (Scheme 2). The structure of **8** was identical in all respects to the compound described in the literature.[10,11] Compound **8** can be converted regio- and stereoselectively to 7-*O*-(triethylsilyl)baccatin III by reduction with $NaBH_4$.[10,11]

In conclusion, an efficient synthetic pathway has been developed to prepare 13-*epi*-baccatin III by oxidation of 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**) with *tert*-butyl peroxide, followed by reduction with SmI_2. 13-*epi*-7-*O*-(Triethylsilyl)baccatin III (**9**) was oxidized to 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**) using TPAP/NMO conditions.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz, and 100 MHz, respectively. High-resolution mass spectrometry (HRMS) spectra were obtained on a VG instrument ZAB double-focusing mass spectrometer. Column chromatography was carried out employing silica gel (EM-9385-9, 230−400 mesh). Analytical thin-layer chromatography (TLC) was performed on a silica gel $60F_{254}$ plate (EM-5717, Merck). SmI_2 was freshly prepared from samarium metal and 1,2-diiodoethane using the procedure described by Kagan.[22] THF and CH_2Cl_2 were distilled before use, and anhydrous solvents were purchased commercially.

13-Deoxy-7-*O*-(triethylsilyl)baccatin III (3). To a solution of 13-deoxybaccatin III (**2**, 102 mg, 0.18 mmol) in DMF (3 mL) were added TESCl (300 μL, 10 equiv) and 4-(dimethylamino)-pyridine (catalytic amount). The reaction mixture was stirred at room temperature for 17 h and then poured into ice water (10 mL) and extracted with CH_2Cl_2. The organic phase was washed with 10% HCl, saturated $NaHCO_3$, and brine solution. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (2:1 EtOAc/hexane) to give **3** (117 mg, 95%) as a white solid: mp 208−209 °C; R_f 0.74 (1:1 EtOAc/hexane); $[\alpha]^{20}_D$ −6.32 (*c* 0.590, $CHCl_3$). The structure of **3** was identical in all respects to the compound described in the literature.[10,11]

13-Deoxy-13*β*-*tert*-butylperoxy-7-*O*-(triethylsilyl)baccatin III (7). To a solution of 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**, 80 mg, 0.12 mmol) in benzene (5 mL) in an ice−water bath was added *tert*-butyl hydroperoxide (400 μL, 70 wt % in water). The reaction mixture was heated at 60 °C for 7 h; the reaction was quenched with water (5 mL), and the mixture was and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, and then the solvent was evaporated. The residue was purified by flash silica gel column chromatography (1:4 EtOAc/hexane) to give **7** (72 mg, 78%) as a white solid: mp 169−170 °C; R_f 0.54 (1:2 EtOAc/hexane); IR (KBr) υ 3500 (br), 2960, 2875, 1745, 1724, 1716, 1370, 1238, 1102 cm^{-1}; ^1H NMR δ 8.13 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 6.49 (s, 1H), 5.65 (d, J = 6.8 Hz, 1H), 4.99 (d, J = 8.0 Hz, 1H), 4.47 (dd, J = 6.9 10.0 Hz, 1H), 4.34 (A of AB, d, J = 8.4 Hz, 1H), 4.29 (dd, J = 3.0, 9.0 Hz, 1H), 4.18 (B of AB, d, J = 8.4 Hz, 1H), 3.60 (d, J = 6.8 Hz, 1H), 2.63 (dd, J = 9.6, 16.0 Hz, 1H), 2.56 (m, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 2.16 (dd, J = 2.5, 16.0 Hz, 1H), 1.89 (m, 1H), 1.69 (s, 3H), 1.28 (s, 9H), 1.25 (s, 3H), 1.19 (s, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.59 (dq, J = 2.2, 7.9 Hz, 6H); ^{13}C NMR δ 202.0, 170.6, 169.9, 167.2, 140.5, 138.2, 134.0, 130.5, 129.7, 129.0, 84.3, 83.6, 81.7, 81.0, 80.6, 76.7, 76.4, 73.4, 72.8, 59.5, 47.3, 42.6, 37.8, 33.9, 32.0, 27.1, 22.5, 21.4, 19.4, 10.1, 7.2, 5.7; HRMS (FAB) *m*/*z* calcd for $C_{41}H_{64}O_{12}SiN$ $[M + NH_4]^+$ 790.4198, found 790.4215; $[\alpha]^{20}_D$ −3.64 (*c* 0.560, $CHCl_3$).

13-Oxo-7-*O*-(triethylsilyl)baccatin III (8). To a solution of 13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**, 1 mg, 0.0014 mmol) in CH_2Cl_2 (0.3 mL) were added TPAP (catalytic amount) and NMO (2 mg). The reaction mixture was stirred at room temperature for 2 h. The solution was purified by filtration over silica gel (1:3 EtOAc/hexane) to give **8** (0.8 mg, 81%) as a white solid: R_f 0.36 (1: EtOAc/hexane). The structure of **8** was identical in all respects to the compound described in the literature.[10,11]

13-*epi*-7-*O*-(Triethylsilyl)baccatin III (9). To a solution of **7** (20 mg, 0.026 mmol) in dry THF (2 mL) under argon was added SmI_2 (0.1 M solution in THF) until the color of the reaction

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(21) Treatment of **9** with diethyl azodicarboxylate (DEAD), trimethylphosphine, and chloroacetic acid (or *p*-nitrobenzoic acid) in toluene at 90 °C resulted in the formation of elimination product **6** instead of providing baccatin III **10** (Scheme 2). Other conditions for the Mitsunobu reaction of **9** were investigated ((a) triphenylphosphine, *p*-nitrobenzoic acid, DEAD, at room temperature in THF; (b) triphenylphosphine, *p*-nitrobenzoic acid, DEAD, at 90 °C in toluene; (c) trimethylphosphine, *p*-nitrobenzoic acid, DEAD, at room temperature in THF).

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became dark blue. The reaction mixture was stirred at room temperature for 3.5 h. The reaction solution was diluted with methylene chloride (10 mL), and the solution was washed with 10% $Na_2S_2O_3$. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by filtration over silica gel (5:1 EtOAc/hexane) to give **9** (15.5 mg, 86%) as a white solid: mp 201−202 °C dec; R_f 0.15 (1:2 EtOAc/hexane); IR (KBr) υ 3491 (br), 2956, 2877, 1723, 1371, 1248, 1108 cm^{-1}; ^1H NMR δ 8.11 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 6.46 (s, 1H), 5.66 (d, J = 7.0 Hz, 1H), 4.96 (d, J = 8.3 Hz, 1H), 4.46 (dd, J = 6.8, 10.4 Hz, 1H), 4.32 (A of AB, d, J = 8.4 Hz, 1H), 4.17 (B of AB, d, J = 8.4 Hz, 1H), 3.97 (dd, J = 3.5, 9.7 Hz, 1H), 3.76 (s, 1H), 3.62 (d, J = 7.1 Hz, 1H), 2.73 (dd, J = 9.8, 15.7 Hz, H), 2.54 (m, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 2.16 (dd, J = 3.4, 8.4 Hz, 1H), 1.89 (m, 1H), 1.69 (s, 3H), 1.29 (s, 9H), 1.27 (s, 3H), 1.19 (s, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.59 (dq, J = 2.2, 7.9 Hz, 6H); ^{13}C NMR δ 202.0, 170.5, 169.7, 167.3, 140.8, 138.2, 134.1, 130.4, 129.7, 129.0, 84.4, 83.8, 81.7, 76.7, 76.6, 73.4, 72.7, 70.0, 68.4, 59.4, 47.4, 42.5, 37.7, 36.8, 32.0, 30.1, 22.6, 21.4, 19.6, 18.7, 10.1, 7.1, 5.7; HRMS (FAB) m/z calcd for $C_{37}H_{53}O_{11}Si$ $[M + H]^+$ 701.3357, found 701.3383; $[\alpha]^{20}_D$ −3.61 (*c* 0.815, $CHCl_3$).

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Supporting Information Available: Experimental procedures for formation of compounds **4**−**6**, reaction of **4** with sodium azide or silver acetate, and attempted Mitsunobu reactions with compound **9** and ^1H and ^{13}C NMR spectra for compounds **3**−**7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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