HETEROCYCLES, Vol. 53, No.12, 2000, pp. 2759 - 2768, Received, 13th September, 2000

HIGH REGIO- AND STEREOSELECTIVITY IN FACILE ONE-POT CONVERSION OF TAXOIDS TO THE PRIMARY ALCOHOLS: PRECURSORS FOR THE SYNTHESIS OF 4-DEACETOXYPACILITAXEL AND ANALOGUES

Qian Cheng, Tohru Horiguchi, Marina Yamaguchi, and Takayuki Oritani*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan. Email: oritani@biochem.tohoku.ac.jp

Abstract-The conversion of alkali metal hydroxy base sensitive taxoids bearing ester groups to the corresponding primary alcohols in a facile one-pot protocol has been reported. This process which involves two steps of hydroboration and oxidation, using a mixture of NMO and TBHP (2:1), which possesses high regio- and stereoselectivity was first established. Proof of the chemistry used in the preparation of a precursor for the synthesis of a 4-deacetoxypaclitaxel analogue has also been presented.

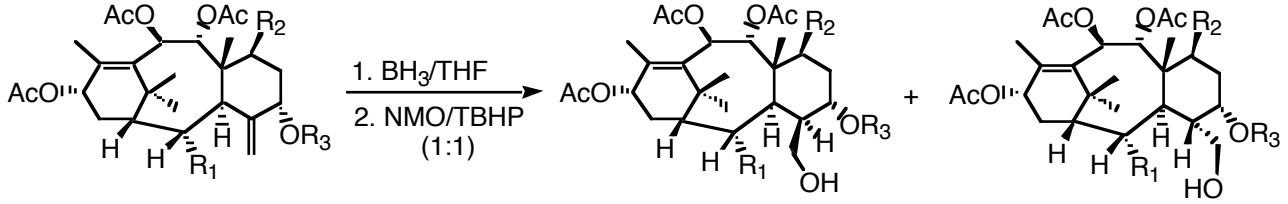
INTRODUCTION

Diterpenoid paclitaxel[1] (Taxol®) has been proven to be a powerful therapeutic drug for cancer chemotherapy, and also exhibits potent antitumor activity against various cancers that have been uneffectively treated by existing chemotherapeutic drugs.[2,3] Paclitaxel was approved by the FDA for the treatment of advanced ovarian cancer and breast cancer in 1994 and also for the second-line treatment of AIDS related Kaposi's sarcoma in 1997.[4] Since its discovery in 1960's, a large amount of paclitaxel analogues have been synthesized for biological and medicinal research,[5] as well as structure-activity relationship (SAR) studies.[6] Due to our studies on chemical conversions of natural taxoids to paciltaxel and analogues for pharmaceutical uses,[7] a facile one-pot protocol for the conversion of alkali metal hydroxy base sensitive taxoids bearing functional groups to the corresponding primary alcohols has been established and presented here. This process involves hydroboration and oxidation, using 4-methylmorpholine *N*-oxide (NMO) and *t*-butyl hydroperoxide (TBHP) two steps which possess high regio- and stereoselectivity.

DISCUSSION AND RESULTS

Hydroboration, in particular a regio- and stereoselective hydroboration, of a carbon double bond with borane and boron compounds leading to organoboranes, which were subsequently oxidized with hydrogen peroxide under an aqueous NaOH condition in order to give primary alcohols, has been widely used in

organic synthesis.[8] Unfortunately, this reaction has not been efficient in the hydroboration-oxidation of taxoids bearing ester groups due to ester hydrolysis.[9] In addition, trimethylamine *N*-oxide was also observed to be uneffective for oxidation of the organoborane taxoids to primary alcohol in our experiments due to the comparatively lower product yield.[10] However, it was interesting to find that 4-methylmorpholine *N*-oxide (NMO) accompanied by *t*-butyl hydroperoxide (TBHP) was efficient in the oxidation reaction of organoborane taxoids to the corresponding primary alcohols. And the hydroboration of taxoids with borane-tetrahydrofuran complex followed by oxidation with NMO and TBHP two steps could be performed in one-pot protocol. The experimental results are shown in Scheme 1 and Table 1.



1: R_1 = H, R_2 = OAc, R_3 = $COCH_2CHNMe_2Ph$ — **1a** — **1b**
2: R_1 = H, R_2 = OAc, R_3 = Ac — **2a** — **2b**
3: R_1 = H, R_2 = OAc, R_3 = TES — **3a** — **3b**
4: R_1 = H, R_2 = OAc, R_3 = TBDMS — **4a** — **4b**
5: R_1 = OAc, R_2 = H, R_3 = Ac — **5a** — **5b**
6: R_1 = OAc, R_2 = H, R_3 = TES — **6a** — **6b**

Scheme 1

Table 1. One-pot coversion of taxoids to the corresponding primary alcohols.

Compound	β-CH_2OH : α-CH_2OH (**a**) : (**b**)[a]	Isolated yield (%)
1	99 : 1	66[c]
2	5 : 1	84
3	9 : 1	81
4	20 : 1	77
5	100 : 0[b]	78
6	100 : 0[b]	73

a: The ratio of α- and β-isomers was determined by ^{1}H-NMR (500 MHz) of a crude mixture.

b: α-Isomers (**5b**) and (**6b**) were not found by ^{1}H-NMR (500 MHz) of a crude mixture

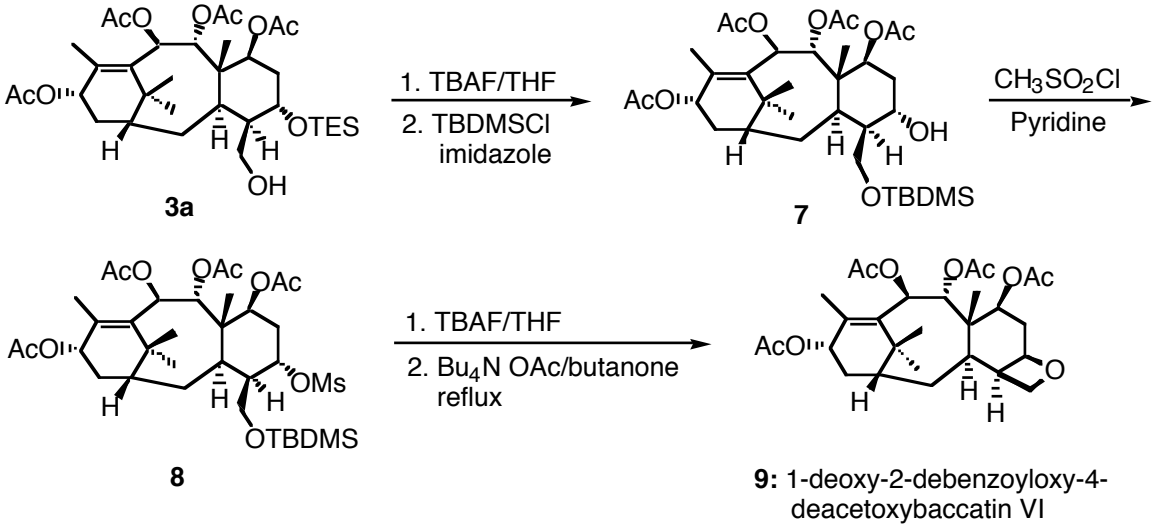
c: Hydroboration was completed in 3 h.

Several kinds of taxoids were introduced in the experiment. The results, shown in Table 1, indicate that the hydroboration with borane took place only at C-4(20) double bond and that the β-isomers as major products were obtained in all experimental examples. The ratio of β- and α-isomers of the products was influenced by the substituents of 2- and 5- positions as well the stereoskeleton of taxinine and derivatives. 2-Deacetoxy taxinine J derivatives (**1**) and (**4**), bearing the bulk substituents at the C-5 position, gave high stereoselectivity in the 99:1 and 20:1 ratios of products respectively, while compounds (**2**) and (**3**) afforded mediate stereoselectivity in both 5:1 and 9:1 ratios of products. This may arise from the fact that the α-face is most likely favorble to be attacked by boron reagents in a specially rigid taxinine skeleton. In fact, similar stereochemistry has been observed in both dihydroxylation and epoxidation of C4(20) double bond in taxoids using osmium tetroxide (OsO_4)[11] and *m*-chloroperoxybenzoic acid (*m*CPBA)[12] respectively. All

products were unambiguously identified by NMR studies including 2D-NMR experiments. NOESY correlations of H-20a to H-2β, H-5 and H_3-19, and H-3 to H-4α were observed in all major isomers bearing 4β-hydroxymethylene group. Whereas all minor isomers bearing 4α-hydroxymethylene group gave NOESY correlations of H-4α to H-2β, H-5, H-6β and H_3-19, and H-3 to H-20b. Similarly, respective taxinine derivatives (**5**) and (**6**) afforded only the β-isomers (**5a**) and (**6a**) as the reaction products which were further confirmed by NOESY correlations of H-20a to H-2β and H_3-19, and H-3 to H-4α. Formation of only the β-isomers (**5a**) and (**6a**) from taxinine derivatives (**5**) and (**6**) respectively might be due to an acetoxy group possessing α-orientation located at C-2 which is not likely to be attacked by boron reagents from β-face in a rigid taxinine skeleton.[13]

The hydroboration of taxoid (**1**) using a bulk 9-BBN instead of borane resulted in the recovery of the starting material probably due to the hinderance of the C4(20) double bond which was not likely to be attacked by the bulk reagent 9-BBN.[14] Whereas taxoid (**2**) was treated with 9-BBN followed by the addition of NMO and TBHP under refluxing for 2 h to furnish only (**2a**) in a 48% yield. In addition, we observed that the oxidiation of organoborane taxoid in the 1,4-dioxane or THF-1,4-dioxane (1:2) was preferable to that of in THF at the refluxing temperature. This might indicate that a higher refluxing temperature quickens the oxidation process.

A large number of paciltaxel analogues having been synthesized for structure-activity relationships (SAR) studies. It is known that the removal of a 4-acetyl group leads to a marked decrease in the bioactivity of paclitaxel.[6] Although the synthesis of 4-deacetoxypaclitaxel derived from paclitaxel has been reported by Kingston and his co-workers,[15] in depth chemical and medicinal studies on 4-deacetoxypaclitaxels have not yet appeared in literature due to the fact that 4-deacetoxypaclitaxel analogues are difficult to prepare. The above-demonstrated chemistry was proposed in order to provide a useful method for the synthesis of 4-deacetoxypaclitaxels from available natural taxoids. Proof of the preparation of 1-deoxy-2-debenzoyloxy-4-deacetoxybaccatin VI (**9**), a useful precursor for the synthesis of 4-deacetoxypaclitaxel analogue, from the 4β-hydroxymethylene taxoid (**3a**) is shown below. (Scheme 2).



9: 1-deoxy-2-debenzoyloxy-4-deacetoxybaccatin VI

Scheme 2

Deprotection of **3a** with tetrabutylammonium fluoride (TBAF, 1.0 *M* in THF) followed by a selective protection using *tert*-butyldimethylsilyl chloride gave 5α-hydroxy taxoid (**7**) in an 81% yield, which was subsequently mesylated by methanesulfonyl chloride to afford the protected taxoid (**8**) in a 74% yield. The desired compound (**9**) was successfully obtained in a 61% yield from (**8**) following the previously established methods.[7c] The structure and stereochemistry of (**9**) were unambiguously determined by wide NMR studies including COSY and NOESY.

In summary, the facile conversion of the alkali metal hydroxy base sensitive taxoids bearing ester groups to the corresponding primary alcohols in a highly regio- and stereoselective one-pot protocol which involves two steps of hydroboration and oxidation using NMO and TBHP has been established.

EXPERIMENTAL

All anhydrous reactions were performed in oven-dried glassware under nitrogen. Tetrahydrofuran and ether were distilled from sodium and benzophenone. Dichloromethane was refluxed and distilled from CaH_2 under nitrogen. Chromatography was carried out on Merck silica gel 60 (230-400 mesh). Preparative TLC was performed on Merck silica gel 60 F_{254} plates (0.85 mm thickness). ^{1}H-NMR (500 MHz), ^{13}C-NMR (125 MHz) and 2D-NMR were performed on Varian Unity INOVA 500 spectrometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants *(J)* are given in Hertz(*Hz*). Optical rotation was recorded by a Horiba SEPA-300 polarimeter. HRMS (EI and FAB) were measured by a JEOL JMS-700 spectrometer. All commercially available reagents were used without further purification. The natural 2-deacetoxy-5-(3'-dimethylamino-3'-phenylpropionoxy)taxinine J[16] 2-deacetoxydecinnamoyltaxinine J[17] and 5-decinnamoyltaxinine E[18] were isolated from the Japanese yew *Taxus cuspidata* following the standard method[19] in our laboratory. Taxoids (**2-4**) and (**5-6**) were prepared from 2-deacetoxydecinnamoyltaxinine J and 5-decinnamoyltaxinine E through acetylation with Ac_2O, silylation with TESCl and TBDMSCl, respectively, according to the known established methods.[7,11]

Typical procedure of one-pot hydroborlation and oxidation of taxoids (1-6) to corresponding alcohols as follows:

A solution of taxoid (0.1 mmol) in THF (8 mL) was slowly injected BH_3-THF complex (0.2 mL, 1.0*M* in THF) under nitrogen at 0°C. The mixture was stirred for an additional 1-2 h (the reaction was monitored by TLC) at 0°C and then allowed to warm to rt, and methanol (0.2 mL) was added. After removal of THF, the residue was resolved in 1,4-dioxane (10 mL) followed by the addition of NMO (0.3 mmol) and TBHP (0.035 mL, 4.2*M* in toluene). The resulting mixture was refluxed for 2 h and cooled to rt. The mixture was extracted with EtOAc, and the combined organic phase was washed with water, brine, and drived over $MgSO_4$. After removal of the solvent, chromatography on silica gel with EtOAc-hexane (1:1) gave the product alcohols which are shown in Table 1.

1a: a colorless amorphous solid, $[\alpha]_D^{25}$ +65.7° (c 1.10, $CHCl_3$). ^{1}H NMR δ_H 7.32-7.30 (m, 5H, Ph), 6.23 (d, 1H, *J* =10.8 Hz, H-10), 5.83 (d, 1H, *J* =10.8 Hz, H-9), 5.71(dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.67 (dd, 1H, *J* =11.6, 5.3 Hz, H-7), 4.87 (m, 1H, H-5), 3.85(t, 1H, *J* =7.0 Hz, H-3'), 3.62(dd, 1H, *J* =10.1, 2.6 Hz, H-20), 3.17 (dd, 1H, *J* =5.4, 4.8 Hz, H-3), 3.10 (dd, 1H, *J* =10.1, 3.5 Hz, H-20), 2.92 (dd, 1H,

J =16.0, 7.0 Hz, H-2'), 2.78 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.53 (dd, 1H, *J* =16.0, 7.0 Hz, H-2'), 2.22(s, 6H, NMe_2), 2.20(m, 1H, H-4), 2.16 (s, 3H, H_3-18), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.99 (m, 1H, H-6), 1.98 (s, 3H, Ac), 1.89 (m, 1H, H-2), 1.78 (m, 1H, H-1), 1.72-1.70 (m, 2H, H-6, H-2), 1.60 (s, 3H, H_3-16), 1.10 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.06 (s, 3H, H_3-17), 0.89 (s, 3H, H_3-19). ^{13}C NMR δ_c 171.32 (s, C=O), 170.31, 170.00, 169.62, 169.20 (4×s, 4×Ac), 138.50 (s), 137.73 (s), 135.89 (s), 129.72 (d), 128.24 (d), 127.60 (d), 76.67 (d), 73.89 (d), 72.15 (d), 70.05 (d), 69.82 (d), 66.72 (t), 66.71 (d), 51.62 (d), 46.52 (s), 42.37 (q), 42.35 (q), 39.62 (d), 39.21 (d), 39.01 (s), 38.51 (t), 36.12 (t), 32.31 (t), 32.14 (q), 26.94 (t), 26.12 (q), 21.45, 21.01, 20.92, 20.81 (4×q, 4×Ac), 15.92 (q), 12.70 (q). HMRS (FAB) calcd for $C_{39}H_{56}O_{11}$(M^++1) 700.3819, found 700.3821.

2a: a colorless amorphous solid, $[\alpha]_D^{25}$ +71.2° (c 0.52, $CHCl_3$). ^{1}H NMR δ_H 6.21 (d, 1H, *J* =10.5 Hz, H-10), 5.84 (d, 1H, *J* =10.5 Hz, H-9), 5.71 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.67 (dd, 1H, *J* =11.6, 5.3 Hz, H-7), 4.64 (m, 1H, H-5), 3.64 (dd, 1H, *J* =10.2, 2.6 Hz, H-20), 3.21 (dd, 1H, *J* =5.4, 4.8 Hz, H-3), 3.13 (dd, 1H, *J* =10.2, 3.5 Hz, H-20), 2.76 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.21 (m, 1H, H-4), 2.16 (s, 3H, H_3-18), 2.09 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.01 (s, 3H, Ac), 2.00 (s+m, 4H, Ac+H-6), 1.98 (s, 3H, Ac), 1.88 (m, 1H, H-2), 1.79 (m, 1H, H-1), 1.71-1.69 (m, 2H, H-6, H-2), 1.60 (s, 3H, H_3-16), 1.11 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.05 (s, 3H, H_3-17), 0.88 (s, 3H, H_3-19). ^{13}C NMR δ_c 170.54, 170.21, 170.01, 169.54, 169.20 (5×s, 5×Ac), 137.69 (s), 135.92 (s), 76.84 (d), 73.92 (d), 72.23 (d), 70.24 (d), 69.92 (d), 65.48 (t), 51.27 (d), 45.78 (s), 39.72 (d), 39.40 (s), 38.91 (d), 36.15 (t), 32.15 (t), 31.98 (q), 26.56 (t), 26.17 (q), 21.40, 21.21, 20.93, 20.87, 20.81 (5×q, 5×Ac), 16.10 (q), 13.01 (q). HMRS (EI) calcd for $C_{30}H_{44}O_{11}$ (M^+) 580.2881, found 580.2287. **2b**: a colorless amorphous solid, $[\alpha]_D^{25}$ +114.3° (c 0.10, $CHCl_3$). ^{1}H NMR δ_H 6.21 (d, 1H, *J* =10.5 Hz, H-10), 5.83 (d, 1H, *J* =10.5 Hz, H-9), 5.70 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.65 (dd, 1H, *J* =11.6, 5.4 Hz, H-7), 4.75 (m, 1H, H-5), 3.94 (dd, 1H, *J* =10.1, 2.1 Hz, H-20), 3.58 (dd, 1H, *J* =10.1, 4.5 Hz, H-20), 3.07 (dd, 1H, *J* =9.5, 5.4 Hz, H-3), 2.76 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.20 (m, 1H, H-4), 2.16 (s, 3H, H_3-18), 2.09 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.01 (s, 6H, 2Ac), 1.98 (s+m, 4H, Ac+H-6), 1.90 (m, 1H, H-2), 1.78 (m, 1H, H-1), 1.72-1.69 (m, 2H, H-6, H-2), 1.61 (s, 3H, H_3-16), 1.24 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.07 (s, 3H, H_3-17), 0.89 (s, 3H, H_3-19). ^{13}C NMR δ_c 170.51, 170.32, 170.00, 169.89, 169.24 (5×s, 5×Ac), 138.23 (s), 135.84 (s), 76.57 (d), 73.79 (d), 72.19 (d), 70.19 (d), 70.01 (d), 66.15 (t), 53.52 (d), 46.02 (s), 40.12 (d), 39.84 (d), 38.90 (s), 36.24 (t), 32.26 (t), 32.24 (q), 26.72 (t), 26.59 (q), 21.39, 21.27, 20.93, 20.90, 20.85 (5×q, 5×Ac), 16.10 (q), 12.89 (q). HMRS (FAB) calcd for $C_{30}H_{45}O_{11}$ (M^++1) 581.2959, found 581.2963.

3a: a colorless amorphous solid, $[\alpha]_D^{25}$ +53.4° (c 1.17, $CHCl_3$). ^{1}H NMR δ_H 6.24 (d, 1H, *J* =10.7 Hz, H-10), 5.84 (d, 1H, *J* =10.7 Hz, H-9), 5.71 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.67 (dd, 1H, *J* =11.6, 5.3 Hz, H-7), 3.61 (dd, 1H, *J* =10.2, 2.5 Hz, H-20), 3.37 (m, 1H, H-5), 3.15 (dd, 1H, *J* =5.4, 4.8 Hz, H-3), 3.08 (dd, 1H, *J* =10.2, 3.5 Hz, H-20), 2.78 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.36 (m, 1H, H-4), 2.18 (s, 3H, H_3-18), 2.07 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.97 (m, 1H, H-6), 1.89 (m, 1H, H-2), 1.78 (m, 1H, H-1), 1.71-1.69 (m, 2H, H-6, H-2), 1.57 (s, 3H, H_3-16),

1.09 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.04 (s, 3H, H_3-17), 0.97 (m, 9H, $3CH_3$), 0.83 (s, 3H, H_3-19), 0.62 (m, 6H, $3CH_2$). ^{13}C NMR δ_c 170.46, 170.08, 169.70, 169.29 (4×s, 4×Ac), 140.63 (s), 136.02 (s), 76.69 (d), 73.56 (d), 72.37 (d), 71.29 (d), 69.92 (d), 65.85 (t), 51.56 (d), 46.71 (s), 40.63 (d), 39.75 (d), 39.01 (s), 36.12 (t), 32.42 (q), 32.40 (t), 26.84 (t), 25.89 (q), 21.43, 21.02, 20.87, 20.81 (4×q, 4×Ac), 16.14 (q), 13.04 (q), 6.74 (q), 4.34 (t). HMRS (EI) calcd for $C_{34}H_{56}O_{10}Si$ (M^+) 652.3639, found 652.3632. **3b**: a colorless amorphous solid, $[\alpha]_D^{25}$ +87.3° (c 0.23, $CHCl_3$). ^{1}H NMR δ_H 6.23 (d, 1H, *J* =10.8 Hz, H-10), 5.83 (d, 1H, *J* =10.8 Hz, H-9), 5.70 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.65 (dd, 1H, *J* =11.6, 5.4 Hz, H-7), 3.87 (dd, 1H, *J* =10.3, 2.2 Hz, H-20), 3.54 (m, 1H, H-5), 3.52 (dd, 1H, *J* =10.3, 4.6 Hz, H-20), 3.02 (dd, 1H, *J* =9.8, 5.4 Hz, H-3), 2.76 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.29 (m, 1H, H-4), 2.18 (s, 3H, H_3-18), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.98 (s+m, 4H, Ac+H-6), 1.91 (m, 1H, H-2), 1.79 (m, 1H, H-1), 1.71-1.69 (m, 2H, H-2, H-6), 1.54 (s, 3H, H_3-16), 1.24 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.05 (s, 3H, H_3-17), 0.98 (t, 9H, *J* =7.0 Hz, $3CH_3$), 0.86 (s, 3H, H_3-18), 0.62 (q, 6H, *J* =7.0Hz, $3CH_2$). ^{13}C NMR δ_c 170.31, 170.01, 169.87, 169.34 (4×s, 4×Ac), 138.72 (s), 136.57 (s), 76.64 (d), 73.57 (d), 72.49 (d), 71.12 (d), 69.89 (d), 65.79 (t), 53.49 (d), 46.82 (s), 40.54 (d), 39.79 (d), 39.52 (s), 36.17 (t), 32.45 (q), 32.41 (t), 26.81 (t), 26.01 (q), 21.37, 21.07, 20.96, 20.86 (4×q, 4×Ac), 16.11 (q), 12.98 (q), 6.71 (q), 4.54 (t). HMRS (EI) calcd for $C_{34}H_{56}O_{10}Si$ (M^+) 652.3639, found 652.3645.

4a: a colorless amorphous solid, $[\alpha]_D^{25}$ +60.1° (c 0.90, $CHCl_3$). ^{1}H NMR δ_H 6.24 (d, 1H, *J* =10.7 Hz, H-10), 5.84 (d, 1H, *J* =10.7 Hz, H-9), 5.70 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.67 (dd, 1H, *J* =11.6, 5.4 Hz, H-7), 3.63 (dd, 1H, *J* =10.2, 2.5 Hz, H-20), 3.42 (m, 1H, H-5), 3.17 (dd, 1H, *J* =5.5, 4.8 Hz, H-3), 3.10 (dd, 1H, *J* =10.2, 3.5 Hz, H-20), 2.79 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.19 (m, 1H, H-4), 2.18 (s, 3H, H_3-18), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.97 (m, 1H, H-6), 1.90 (m, 1H, H-2), 1.77 (m, 1H, H-1), 1.70-1.69 (m, 2H, H-6, H-2), 1.57 (s, 3H, H_3-16), 1.10 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.06 (s, 3H, H_3-17), 0.88 (s, 9H, $3CH_3$), 0.84 (s, 3H, H_3-19), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3). ^{13}C NMR δ_c 170.47, 170.05, 169.89, 169.41 (4×s, 4×Ac), 139.27 (s), 136.40 (s), 76.80 (d), 73.26 (d), 72.17 (d), 71.59 (d), 69.82 (d), 66.71 (t), 50.04, (d), 46.19 (s), 40.11 (d), 39.91 (d), 39.45 (s), 36.15 (t), 32.41 (t), 32.17 (q), 26.84 (t), 25.94 (q), 25.90 (q), 25.89 (q), 25.88 (q), 21.84, 21.56, 20.90, 20.78 (4×q, 4×Ac), 17.92 (s), 16.12 (q), 12.94 (q), -3.32 (q), -3.21 (q). HMRS (EI) calcd for $C_{34}H_{56}O_{10}Si$ (M^+) 652.3639, found 652.3633. **4b**: a colorless amorphous solid, $[\alpha]_D^{25}$ +96.4° (c 0.14, $CHCl_3$). ^{1}H NMR δ_H 6.23 (d, 1H, *J* =10.8 Hz, H-10), 5.84 (d, 1H, *J* =10.8 Hz, H-9), 5.70 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.66 (dd, 1H, *J* =11.6, 5.4 Hz, H-7), 3.86 (dd, 1H, *J* =10.3, 2.1 Hz, H-20), 3.52 (dd, 1H, *J* =10.3, 4.8 Hz, H-20), 3.51 (m, 1H, H-5), 3.04 (dd, 1H, *J* =10.0, 5.4 Hz, H-3), 2.78 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.18 (s, 3H, H_3-18), 2.13 (m, 1H, H-4), 2.08 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.98 (s+m, 4H, Ac+H-6), 1.86 (m. 1H, H-2), 1.78 (m, 1H, H-1), 1.71 (m, 1H, H-2), 1.67 (m, 1H, H-6), 1.58 (s, 3H, H_3-16), 1.09 (dd, 1H, J =15.6, 4.5 Hz, H-14), 1.05 (s, 3H, H_3-17), 0.89 (s, 9H, $3CH_3$), 0.85 (s, 3H, H_3-19), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3). ^{13}C NMR δ_c 170.56, 170.07, 169.90, 169.34 (4×s, 4×Ac), 138.81 (s), 135.94 (s), 76.91 (d), 74.01 (d), 72.37 (d), 70.58 (d), 69.89 (d), 65.29 (t), 53.41 (d), 45.94 (s), 39.98 (d), 39.87 (d), 38.94 (s), 36.21 (t),

32.19 (t), 32.15(q), 26.79 (t), 26.01 (q), 25.91 (q), 25.90 (q), 25.88 (q), 21.45, 21.10, 20.86, 20.42 (4×q, 4×Ac), 17.94 (s), 15.98 (q), 13.02 (q), -3.21 (q), -3.17 (q). HMRS (EI) calcd for $C_{34}H_{56}O_{10}Si$ (M^+) 652.3639, found 652.3641.

5a: a colorless amorphous solid, $[\alpha]_D^{25}$ +102.3° (c 0.31, $CHCl_3$). ^1H NMR δ_H 6.07 (d, 1H, *J* =10.4 Hz, H-10), 5.76 (dd, 1H, *J* =10.4, 5.0 Hz, H-9), 5.72 (d, 1H, *J* =10.4 Hz, H-13), 5.62 (dd, 1H, *J* =6.0, 2.3 Hz, H-2), 4.76 (m, 1H, H-5), 3.67 (dd, 1H, *J* =10.2, 2.5 Hz, H-20), 3.20 (dd, 1H, *J* =6.0, 4.5 Hz, H-3), 3.14 (dd, 1H, *J* =10.2, 3.5 Hz, H-20), 2.68 (ddd, 1H, *J* =15.7, 10.4, 8.6Hz, H-14), 2.13 (s, 3H, Ac), 2.11 (s, 3H, H_3-18), 2.08 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.98 (dd, 1H, *J* =8.6, 2.3 Hz, H-1), 1.89 (m, 1H, H-7), 1.79 (m, 1H, H-6), 1.64 (s, 3H, H_3-16), 1.60 (m, 2H, H-7, H-6), 1.45 (dd, 1H, *J* =15.7, 5.0 Hz, H-14), 1.05 (s, 3H, H_3-17), 0.89 (s, 3H, H_3-19). ^{13}C NMR δ_c 170.67, 170.34, 169.98, 169.88, 169.34 (5×s, 5×Ac), 140.01 (s), 136.59 (s), 75.82 (d), 73.62 (d), 72.84 (d), 71.68 (d), 69.89 (d), 65.13 (t), 51.27 (d), 45.64 (s), 40.10 (d), 40.01 (d), 39.21 (s), 32.21 (t), 32.17 (q), 28.18 (t), 27.46 (t), 25.98 (q), 21.65, 21.43, 21.07, 20.92, 20.34 (5×q, 5×Ac), 15.94 (q), 12.32 (q). HMRS (FAB) calcd for $C_{30}H_{45}O_{11}$ (M^++1) 518.2959, found 518.2954.

6a: a colorless amorphous solid, $[\alpha]_D^{23}$ +93.5° (c 0.64, $CHCl_3$). ^1H NMR δ_H 6.08 (d, 1H, *J* =10.4 Hz, H-10), 5.75 (dd, 1H, *J* =10.4, 5.0 Hz, H-9), 5.72 (d, 1H, *J* =10.4 Hz, H-13), 5.61 (dd, 1H, *J* =6.1, 2.2 Hz, H-2), 3.65 (dd, 1H, *J* =10.2, 2.5 Hz, H-20), 3.36 (m, 1H, H-5), 3.17 (dd, 1H, J =6.1, 4.5 Hz, H-3), 3.10 (dd, 1H, J =10.2, 3.5 Hz, H-20), 2.67 (ddd, 1H, J =15.7, 10.4, 8.5 Hz, H-14), 2.12 (s, 3H, H_3-18), 2.08 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.97 (dd, 1H, J =8.5, 2.2 Hz, H-1), 1.90 (m, 1H, H-7), 1.80 (m, 1H, H-6), 1.64 (s, 3H, H_3-16), 1.61-1.59 (m, 2H, H-7, H-6), 1.44 (dd, 1H, J =15.7, 5.0 Hz, H-14), 1.06 (s, 3H, H_3-17), 0.98 (t, 9H, *J* =7.0 Hz, $3CH_3$), 0.90 (s, 3H, H_3-19), 0.61 (q, 6H, *J* =7.0 Hz, $3CH_3$). ^{13}C NMR δ_c 170.41, 170.00, 169.92, 169.36 (4×s, 4×Ac), 139.89 (s), 136.56 (s), 75.67 (d), 73.45 (d), 72.89 (d), 71.09 (d), 69.70 (d), 66.37 (t), 51.21 (d), 45.72 (s), 40.17 (d), 40.13 (d), 38.91 (s), 33.41 (q), 32.84 (t), 28.46 (t), 27.56 (t), 25.97 (q), 21.44, 21.06, 20.87, 20.40 (4×q, 4×Ac), 16.17 (q), 13.12 (q), 6.76 (q), 4.36 (t). HMRS (EI) calcd for $C_{34}H_{56}O_{10}Si$ (M^+) 652.3639, found 652.3646.

Preparation of 1-deoxy-2-debenzoyloxy-4-deacetoxybaccatin VI (9) from compound (3a)

A solution of **3a** (163 mg, 0.25 mmol) in THF (2 mL) was added tetrabutylammonium fluoride in THF (1.0*M*, 1 mL). The reaction mixture was stirred for 1 h at rt. Ethyl acetate (20 mL) was added and the organic layers were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was used for next step reaction without further purification.

A solution of imidazole (245 mg, 3.6 mmol) and *tert*-butyldimethylsilyl chloride (226 mg, 1.5 mmol) in dry DMF (2 mL) was stirred for 15 min at rt followed by an addition of the above residue in dry DMF (1 mL). The resulting reaction mixture was stirred for an additional 3 h, diluted with a solution of 10% aqueous citric acid (10 mL), and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel

(ethyl acetate:hexane=1:2 v/v) to give 132 mg (81%) of **7** as an oil. ^{1}H nmr δ_H 6.23 (d, 1H, *J*=10.8 Hz, H-10), 5.84 (d, 1H, *J* =10.8 Hz, H-9), 5.71 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.66 (dd, 1H, *J* =11.6, 5.4 Hz, H-7), 4.15 (dd, 1H, *J* =10.5, 2.1 Hz, H-20), 3.58 (m, 1H, H-5), 3.54 (dd, 1H, *J* =10.5, 3.5 Hz, H-20), 2.76 (ddd, 1H, *J* =15.6, 10.2, 8.5 Hz, H-14), 2.67 (dd, 1H, *J* =5.5, 4.5 Hz, H-3), 2.20 (m, 1H, H-4), 2.17 (s, 3H, H_3-18), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac), 20.1 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.97 (m, 1H, H-6), 1.89 (m, 1H, H-2), 1.78 (m, 1H, H-1), 1.70 (m, 2H, H-2. H-6), 1.58 (s, 3H, H_3-16), 1.09 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.07 (s, 3H, H_3-17), 0.87 (s, 9H, 3CH_3), 0.84 (s, 3H, H_3-19), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3). HMRS (EI) calcd for $C_{34}H_{56}O_{10}Si$ (M^+) 652.3639, found 652.3645.

A solution of **7** (130 mg, 0.2 mmol) in pyridine (2 mL) at 0°C was added MsCl (0.1 mL). The reaction mixture was stirred for 20 h at rt and CH_2Cl_2 (15 mL) was added. The resulting solution was washed with a solution of 10% aqueous citric acid (7 mL), saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silics gel (ethyl acetate:hexane =1:2 v/v) to give 108 mg (74%) of **8** as an oil. ^{1}H NMR δ_H 6.24 (d, 1H, *J* =10.8 Hz, H-10), 5.84 (d, 1H, *J* =10.8 Hz, H-9), 5.71 (dd, 1H, *J* =10.3, 4.5 Hz, H-13), 5.64 (dd, 1H, *J* =11.6, 5.4 Hz, H-7), 4.84 (m, 1H, H-5), 4.17 (dd, 1H, *J* =10.5, 2.1 Hz, H-20), 3.56 (dd, 1H, *J* =10.5, 3.5 Hz, H-20), 2.97 (s, 3H, CH_3), 2.78 (ddd, 1H, *J* =15.6, 10.2, 8.5 Hz, H-14), 2.66 (dd, 1H, *J* =5.5, 4.5 Hz, H-3), 2.20 (m, 1H, H-4), 2.18 (s, 3H, H_3-18), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.01 (m, H-6), 2.00 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.90 (m, 1H, H-2), 1.78 (m, 1H, H-1), 1.70-1.69 (m, 2H, H-2, H-6), 1.54 (s, 3H, H_3-16), 1.10 (dd, 1H, *J* =15.6, 4.5 Hz, H-14), 1.07 (s, 3H, H_3-17), 0.85 (s, 9H, 3CH_3), 0.83 (s, 3H, H_3-19), 0.05 (s, 3H, CH_3), 0.03 (s, 3H, CH_3). HMRS (FAB) calcd for $C_{35}H_{58}O_{12}NaSSi$ (M^++Na) 753.3312, found 753.3317.

A solution of **8** (73 mg, 0.1 mmol) in THF (1.5 mL) was added tetrabutylammonium fluoride in THF (1.0*M*, 0.7 mL). The reaction mixture was stirred for 1 h at rt. Ethyl acetate (10 mL) was added and the organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in butanone (2 mL) and then tetrabutylammonium acetate (270 mg, 0.9 mmol) was added. The resulting mixture was refluxed for 20 h and diluted with ethyl acetate (10 mL). The resulting solution was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silics gel (ethyl acetate:hexane =1:2 v/v) to give 31 mg (61%) of **9** as a colorless oil. $[\alpha]_D^{25}$ +83.2° (c 0.03, $CHCl_3$). ^{1}H NMR δ_H 6.21 (d, 1H, *J* =10.7 Hz, H-10), 5.86 (d, 1H, *J* =10.7 Hz, H-9), 5.72 (dd, 1H, *J* =10.3, 5.0 Hz, H-13), 5.68 (dd, 1H, *J* =11.6, 5.0 Hz, H-7), 5.20 (m, 1H, H-5), 4.35 (d, 1H, *J* =8.1 Hz, H-20), 4.27 (d, 1H, *J* =8.1 Hz, H-20), 3.82 (m, 1H, H-4), 3.27 (dd, 1H, *J* =6.0, 5.7 Hz, H-3), 2.79 (ddd, 1H, *J* =15.6, 10.3, 8.5 Hz, H-14), 2.48 (m, 1H, H-6), 2.17 (s, 3H, H_3-18), 2.09 (s, 3H, Ac), 2.08 (m, 1H, H-6), 2.07 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.89 (m, 1H, H-2), 1.80 (m, 1H, H-1), 1.72 (m, 1H, H-2), 1.57 (s, 3H, H_3-16), 1.12 (dd, 1H, *J* =15.6, 5.0 Hz, H-14), 1.05 (s, 3H, H_3-17), 0.87 (s, 3H, H_3-19). ^{13}C NMR δ_c 170.61, 170.01, 169.94, 169.32 (4×s, 4×Ac), 139.68 (s), 136.24 (s), 82.56 (d), 77.64 (d), 74.68 (t), 72.57 (d), 71.62 (d), 70.89 (d), 56.27 (d), 45.14 (s), 41.15 (d), 39.87 (d), 39.41 (s), 37.68 (t), 33.07 (q), 32.56 (t), 26.96 (t), 25.89 (q), 21.32, 21.26, 20.91, 20.24 (4×q, 4×Ac), 16.12 (q), 14.17 (q). HMRS (EI) calcd for $C_{28}H_{40}O_9$ (M^+) 520.2670, found 520.2677.

ACKNOWLEDGEMENT

Financial support in part by Grant-in-Aid for scientific research from the Ministry of Education, Science, Sports, and Culture of Japan and a fellowship to Q. C. from the Japan Society of the Promotion for Science are acknowledged.

REFERENCE

1. M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.
2. M. C. Bissery, D. Guénard, F. Guéritte-Vogelein, and F. Lavelle, *Cancer Res.*, 1991, **51**, 4845; D. Guénard, F. Guéritte-Vogelein, and P. Potier, *Acc. Chem. Res.*, 1993, **26**, 160.
3. P. B. Schiff, J. Fant, and S. B. Horwitz, *Nature*, 1979, **227**, 665.
4. I. Ojima, T. Wang, M. L. Miller, S. Lin, C. P. Borella, X. Geng, P. Pera, and R. Bernacki, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3423.
5. K. C. Nicolaou, W.-M. Dai, and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; D. Guenard, F. Gueritte-Voegelein, and F. Lavelle, *Curr. Pharm. Design*, 1995, **1**, 95.
6. F. Guéritte-Voegelein, D. Guénard, J. Dudois, A. Wahl, R. Marder, R. Muller, M. Lund, L. Bricard, and P. Potier, 'In Taxane Anticancer Agents: Basic Science and Current Status,' ed. by G. I. Georg, T. T. Chen, I. Ojima, and D. M. Vyas, ACS Symposium Series 583, American Chemical Society, Washington, DC, 1995, pp. 189-202; D. G. I. Kingston, 'In Taxane Anticancer Agents: Basic Science and Current Status,' ed. by G. I. Georg, T. T. Chen, I. Ojima, and D. M. Vyas, ACS Symposium Series 583, American Chemical Society, Washington, DC, 1995, pp. 203-216; J. Kant, 'In The Chemistry and Pharmacology of Taxol and Its Derivatives,' ed. by V. Farina, Elsevier, Amsterdam, 1995, pp. 255-300.
7. Q. Cheng, T. Oritani, and T. Horiguchi, *Tetrahedron*, 1999, **55**, 12099; Q. Cheng, T. Oritani, T. Horiguchi, T. Yamada, and A. Hassner, *Tetrahedron*, 2000, **56**, 1181; Q. Cheng, T. Oritani, T. Horiguchi, T. Yamada, and Y. Mong, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 517; T. Horiguchi, Q. Cheng, and T. Oritani, *Tetrahedron Lett.*, 2000, **41**, 3907.
8. F. A. Carey and R. J. Sundberg, 'Advanced Organic Chemistry, Part B: Reactions and Synthesis,' Plenum Press: New York, 1990, pp. 200-211 and references cited therein
9. No major products were isolated in experiment. T. Oritani, and Q. Cheng, unpublished results.
10. G. W. Kabalka and H. C. Hedgecock, *J. Org. Chem.*, 1975, **40**, 1776. In our experiments, less than 30% in all yield of products **2a** and **2b**.
11. In the all dihydroxylation of C4(20) double bond using OsO_4 for the synthesis of paclitaxel analogues, for example, see H. Poujol, A. A. Mourabit, A. Ahoud, C. Poupat, and P. Potier, *Tetrahedron*, 1997, **53**, 12575.
12. H. Hosoyama, H. Shigemori, Y. In, T. Ishida, and J. Kobayashi, *Tetrahedron*, 1998, **54**, 2521.
13. These were supported by the studies on the molecular models and preferred conformations of taxinines based on minimum energy calculations which were performed on Macintosh computer

using CS Chem 3D Pro. 3.2.

14. T. Horiguchi, unpublished results in Ph.D Thesis, Tohoku University, 2000. Morever, simliar result of the recovery of starting material was also obtained in the usage of 2-deacetoxytaxinine J as a starting material. On the other hand, 2-deacetoxytaxinine J could be hydroborated by borane-THF complex.
15. M. D. Chordia, A. G. Chaudhary, and D. G. H. Kingston, *Tetrahedron Lett.*, 1994, **35**, 6843.
16. L. Ettouati, A. Ahond, O. Convert, D. Laurent, C. Poupat, and P. Potier, *Bull. Soc. Chim. Fr.*, 1988, 749.
17. G. Appendino, 'In The Chemistry and Pharmacology of Taxol and Its Derivatives,' ed. by V. Farina, Elsevier, Amsterdam, 1995, pp. 55-101 and references cited therein.
18. Y.-J. Chen, C.-Y. Chen, and Y.-C. Shen, *J. Nad. Prod.*, 1999, **62**, 149.
19. Q.-W. Shi, T. Oritani, T. Sugiyama, H. Kiyota, and H. Horiguchi, *Heterocycles*, 1999, **51**, 841; Q. Cheng, T. Oritani, and T. Horiguchi. *Biosci. Biotech. Biochem.*, 2000, **64**, 894.