A New Method for Synthesis of 7-Deoxytaxane Analogues by Hydrogenation of $\Delta^{6,7}$-Taxane Derivatives

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A new method for the synthesis of 7-deoxytaxane analogues has been established through hydrogenation of $\Delta^{6,7}$-taxane derivatives. Among several catalysts examined, Pd–C was found to be a most effective catalyst for the preparation of target compound.

Key words 7-deoxytaxane analogue; hydrogenation; new efficient method

Paclitaxel (**1**, Taxol®)[1] and docetaxel (**2**, Taxotere®)[2] are currently considered to be some of the most important drugs used in cancer chemotherapy. Since their discovery, structure–activity relationships of taxane analogues have been extensively studied, and these studies have established that the C-13 side chain, the ester groups at C-2 and C-4, and the rigid core are essential for biological activity.[3,4] In contrast, it was shown that the C-7 hydroxyl group was not essential for antitumor activity[5] and that modifications of this moiety could lead to improvements in the cytotoxicity against drug-resistant cancer cell lines.[6,7] On the basis of these findings, we focused on the 7-deoxytaxane analogues and thus have established a new method for the synthesis of these compounds.

Chemistry

Some groups have already reported the synthesis of 7-deoxytaxane analogues by employing the Barton deoxygenation procedure[5,8] or the electrochemical reduction of 7α-iodo docetaxel,[9] however, those yields were relatively low. In our previous paper, we achieved the synthesis of 7-deoxytaxane analogue in satisfactory yield, but still using the organotin reagent.[10] To avoid using the toxic organotin reagent, we planned to prepare the 7-deoxytaxane analogues by hydrogenation of $\Delta^{6,7}$-taxanes. Application of a modified Johnson's protocol (Tf_2O/DMAP/DMF)[11] for the attempted triflation of 10-deacetylbaccatin III (**3**) was found to provide 10-*O*-formyl-10-deacetylbaccatin III (**4**) unexpectedly.[10,12] Treatment of **4** with triflic anhydride in a mixture of pyridine and CH_2Cl_2 afforded 10-*O*-formyl-7-*O*-triflate **5**. After removal of the formyl group at the C-10 position with Me_2NH in THF,[13] the resulting compound was treated with DBU to generate the key intermediate 6,7-dehydro-10-deacetylbaccatin III **6** (Chart 1).

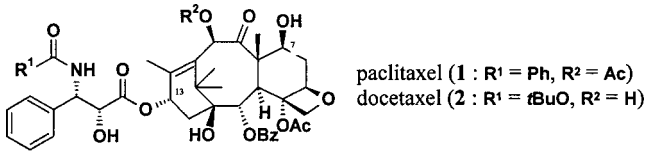
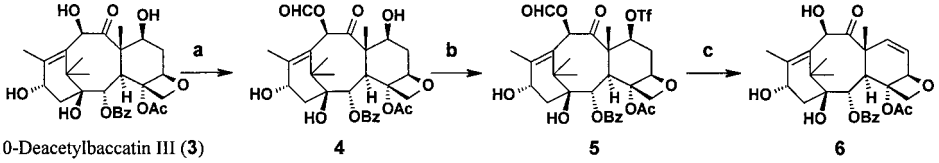


Fig. 1. Structures of Paclitaxel and Docetaxel

With this olefin **6**, hydrogenation using various catalysts were carried out (Table 1). With PtO_2, both the phenyl ring at C-2 and 6,7-double bond were smoothly reduced to afford **8** in high yield (entry 1). As with PtO_2, the hydrogenation of **6** over Pt–C (100 wt%) generated **8** in good yield (entry 3). By using Rh–Al_2O_3 (50 wt%), the target compound **7** was obtained along with unreacted **6** (entry 4). When the amount of the catalyst was increased, however, hydrogenation of aromatic nuclei occurred to provide a mixture of **7** and **8** (entry 5). Therefore, it might be possible to obtain the target compound **7** by controlling the amount of Rh–Al_2O_3 and the reaction time. In contrast to the above catalysts, Pd–C was found effective to produce the target compound **7** selectively (entry 6). Moreover, the hydrogenation of **6** with this catalyst proceeded smoothly without reducing the aromatic nuclei and/or decomposing of starting material, irrespective of an increase in the amount of catalyst and elongation of the reaction time (entries 7, 8, 9) and was successfully applied to the direct scale up (entry 10). By the use of $Pd(OH)_2$, the target compound **7** was obtained as a major product, together with an unknown byproduct (entry 11).

We recently reported the synthesis of novel 9β-dihydro-9,10-*O*-acetal taxane analogues. Potier *et al.* had already prepared 9α-dihydro-9,10-*O*-isopropylidene-7-deoxydocetaxel from natural taxine B and isotaxine B, and its cytotoxicity was reported to be the same as that of docetaxel.[14] On the other hand, our novel analogues, 9β-isomer, showed stronger activity against several tumor cell lines than did docetaxel.[10,15] Therefore, we applied this newly developed method to the synthesis of their 7-deoxy analogues. 9,10-*O*-



Reagents : (a) Tf_2O, DMAP, DMF (95%); (b) Tf_2O, pyridine, CH_2Cl_2; (c) (i) Me_2NH, THF, (ii) HCO_2Me, (iii) DBU, THF, 1,4-dioxane (79% from **4**)

Chart 1

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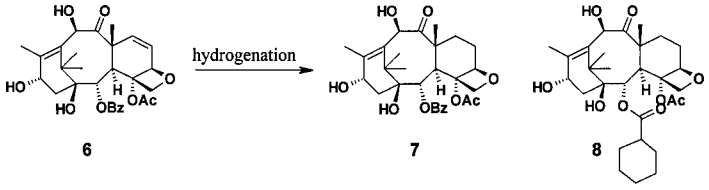
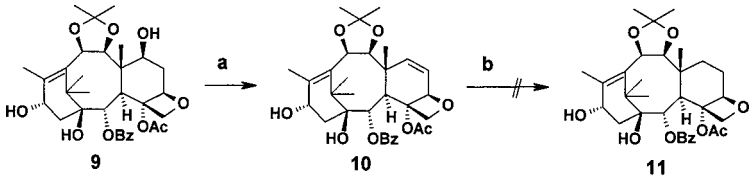
Table 1. Hydrogenation of **6** Using Several Catalysts



6 **7** **8**

Entry	Scale (g)	Catalyst (Amount)	Solvent	Time (h)	Product	Yield (%)[a]
1	0.1	PtO_2 (50 wt%)	AcOEt	1.5	**8**	89
2	0.1	Pt–C (50 wt%)	EtOH	14	**7** and **8** (5 : 6)[b]	—
3	0.1	Pt–C (100 wt%)	EtOH	41	**8**	79
4	0.1	Rh–Al_2O_3 (50 wt%)	EtOH	1.5	**6** and **7** (1 : 3)[b]	—
5	0.1	Rh–Al_2O_3 (100 wt%)	EtOH	2	**7** and **8** (3 : 2)[b]	—
6	0.1	Pd–C (50 wt%)	EtOH	14	**7**	99
7	0.1	Pd–C (100 wt%)	EtOH	14	**7**	99
8	0.1	Pd–C (100 wt%)	EtOH	62	**7**	94
9	0.1	Pd–C (100 wt%)	AcOEt	45	**7**	82
10	10	Pd–C (20 wt%)	EtOH	24	**7**	99
11	0.1	$Pd(OH)_2$ (50 wt%)	EtOH	15	**7**	—[c]

a) Isolated yield. *b*) Ratios determined by ^{1}H-NMR analysis of the crude mixture. *c*) **7** was obtained as a mixture of unknown by-product.



9 **10** **11**

Reagents : (a) Tf_2O, DMAP, CH_2Cl_2 (43%); (b) Pd-C or Rh-Al_2O_3, H_2, EtOH

Chart 2

Acetonide **9**[10] was treated with triflic anhydride in CH_2Cl_2 in the presence of DMAP, elimination of 7-*O*-triflate occurred to afford the 6,7-olefin **10**. Attempts to reduce the 6,7-double bond of **10** by using Pd–C or Rh–Al_2O_3, however, resulted in the decomposition of the starting material (Chart 2). Highly strained architecture of **10** in which the cyclic acetal at C-9/C-10 causes angle distortion may be responsible for this unfavorable reaction. Though an efficient method to obtain the target compound **11** has not been developed, the hydrogenation of other $\Delta^{6,7}$-taxanes to prepare the various 7-deoxytaxane analogues are presently under investigation.

In conclusion, we have developed a new method for the synthesis of 7-deoxytaxane analogues. Although the applicability might be limited, we believe that this synthetic method should provide efficient and practical routes to obtain 7-deoxytaxane analogues.

Experimental

All chemicals and solvents used in the synthesis were reagent-grade products and were used without additional purification. The following abbreviations are used for the solvent and reagent names: ethyl acetate (AcOEt), 1,8-diazabicylo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), triflic anhydride (Tf_2O). Melting points were obtained on a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL EX-400 spectrometer, with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm, δ units). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on a Hitachi 270-30 spectrometer with KBr disks. Elementary analysis was carried out with a Perkin-Elmer Model 240C elemental analyzer. Optical rotations were measured with a Horiba SEPA-200 polarimeter. Mass spectra were recorded on a JEOL JMS-HX-100, AX505W, JMS-D300 or JMS-700 spectrometer. Merck Kieselgel 60 (70—230 mesh) was used for column chromatography.

(1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*S*,10*R*,13*S*)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-10-formyloxy-9-oxo-1,7,13-trihydroxytax-11-ene (4) To a solution of (1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*S*,10*R*,13*S*)-4-acetoxy-2-benzoyloxy-5,20-epoxy-9-oxo-1,7,10,13-tetrahydroxytax-11-ene (10-Deacetylbaccatin III, **3**) (10 g, 18.4 mmol) and DMAP (4.5 g, 36.8 mmol) in DMF (100 ml) was added Tf_2O (5.0 ml, 29.7 mmol) dropwise with ice cooling, and the mixture was stirred at the same temperature for 10 min. The reaction mixture was poured into a mixture of AcOEt and water, and the layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was triturated with $CHCl_3$–*n*-hexane. The resulting precipitate was collected by filtration to give the title compound (10.0 g, 95%) as a white powder, mp 250—253 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, s), 1.13 (3H, s), 1.68 (3H, s), 1.76 (1H, br s), 1.80—1.93 (1H, m), 2.05 (3H, s), 2.20—2.45 (4H, m), 2.26 (3H, s), 2.56 (1H, ddd, J=6.8, 9.8, 15.1 Hz), 3.88 (1H, d, J=7.1 Hz), 4.15 (1H, d, J=8.3 Hz), 4.31 (1H, d, J=8.3 Hz), 4.40—4.50 (1H, m), 4.88 (1H, br s), 4.98 (1H, d, J=7.8 Hz), 5.63 (1H, d, J=7.1 Hz), 6.45 (1H, s), 7.48 (2H, t, J=7.4 Hz), 7.61 (1H, t, J=7.4 Hz), 8.10 (2H, d, J=7.4 Hz), 8.22 (1H, s); FAB-MS (*m*/*z*): 573 $(M+H)^+$; *Anal.* Calcd for $C_{30}H_{36}O_{11}\cdot 0.75H_2O$: C, 61.48; H, 6.45. Found: C, 61.52; H, 6.27; IR: 3540, 2940, 2898, 1710, 1452 cm^{-1}; $[\alpha]_D^{24}$ −90.6° (c=0.54, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*S*,10*R*,13*S*)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-10-formyloxy-1,13-dihydroxy-9-oxo-7-trifluoromethanesulfonyloxytax-11-ene (5) To a solution of **4** (9.5 g, 16.6 mmol) in a mixture of pyridine (10 ml) and CH_2Cl_2 (100 ml) was added Tf_2O (4.2 ml, 24.9 mmol) with ice cooling, and the mixture was stirred at the same temperature for 1 h. After adding saturated aqueous $NaHCO_3$ and AcOEt to the reaction mixture, the layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was triturated with $CHCl_3$–*n*-hexane. The resulting precipitate was collected by filtration to

give the title compound (11.5 g) as a white solid, which contained a small amount of pyridine and was used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, s), 1.20 (3H, s), 1.61 (1H, br s), 1.88 (3H, s), 2.05—2.40 (4H, m), 2.25 (3H, s), 2.31 (3H, s), 2.80—2.95 (1H, m), 4.01 (1H, d, J=7.1 Hz), 4.16 (1H, d, J=8.5 Hz), 4.35 (1H, d, J=8.5 Hz), 4.80—4.90 (1H, br s), 4.95 (1H, d, J=8.8 Hz), 5.53 (1H, dd, J=7.8, 10.3 Hz), 5.69 (1H, d, J=7.1 Hz), 6.73 (1H, s), 7.50 (2H, t, J=7.8 Hz), 7.63 (1H, t, J=7.8 Hz), 8.10 (2H, d, J=7.8 Hz), 8.20 (1H, s); FAB-MS (m/z): 705 $(M+H)^+$.

(1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*R*,10*R*,13*S*)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-9-oxo-1,10,13-trihydroxytax-6,11-diene (6) To a solution of **5** (11.5 g) in THF (115 ml) was added Me_2NH (2.0 M in THF, 12.3 ml, 24.5 mmol), and the mixture was stirred at room temperature for 1.5 h. After adding ethyl formate (2.0 ml, 24.5 mmol) to the reaction mixture, the resulting mixture was stirred at the same temperature for further 15 min. The reaction mixture was concentrated under reduced pressure and the residue was suspended in a mixture of THF (5 ml) and 1,4-dioxane (50 ml). To this suspension was added DBU (5 ml), and the mixture was stirred at 100 °C for 30 min. The reaction mixture was poured into a cold mixture of 1 N HCl and AcOEt. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel eluted with $CHCl_3$–AcOEt (1 : 1 (v/v)). The eluate was concentrated under reduced pressure, and the residue was triturated with *n*-hexane–AcOEt. The resulting precipitate was collected by filtration to give the title compound (6.8 g, 79%) as a white solid, mp 160—162 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, s), 1.13 (3H, s), 1.66 (1H, br s), 1.92 (3H, s), 1.95—2.35 (3H, m), 2.00 (3H, d, J=1.0 Hz), 2.31 (3H, s), 4.18 (1H, d, J=6.5 Hz), 4.23 (1H, d, J=1.5 Hz), 4.30 (1H, d, J=8.3 Hz), 4.43 (1H, d, J=8.3 Hz), 4.82—4.93 (1H, br s), 5.02 (1H, s), 5.10 (1H, d, J=5.4 Hz), 5.76 (1H, d, J=9.8 Hz), 5.81 (1H, d, J=6.5 Hz), 6.04 (1H, dd, J=5.4, 9.8 Hz), 7.49 (2H, t, J=7.8 Hz), 7.62 (1H, t, J=7.8 Hz), 8.14 (2H, d, J=7.8 Hz); FAB-MS (m/z): 527 $(M+H)^+$; *Anal.* Calcd for $C_{29}H_{34}O_9 \cdot 0.5H_2O$: C, 65.03; H, 6.59. Found: C, 65.07; H, 6.64; IR: 3461, 2991, 2898, 1710, 1488 cm^{-1}; $[\alpha]_D^{24}$ −89.4° (c=0.17, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*R*,10*R*,13*S*)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-9-oxo-1,10,13-trihydroxytax-11-ene (7) (General Procedure, Entry 7) **6** (100 mg, 190 μmol) was hydrogenated (balloon) in EtOH (3 ml) over 10% Pd–C (100 mg) for 14 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel eluted with $CHCl_3$–MeOH (50 : 1 (v/v)). The eluate was concentrated under reduced pressure to give the title compound (100 mg, 99%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, s), 1.09 (3H, s), 1.50—1.55 (1H, m), 1.61 (1H, br s), 1.80 (3H, s), 1.90—2.41 (6H, m), 2.06 (3H, s), 2.29 (3H, s), 3.92 (1H, d, J=7.3 Hz), 4.17 (1H, d, J=1.5 Hz), 4.22 (1H, d, J=8.3 Hz), 4.33 (1H, d, J=8.3 Hz), 4.82—4.92 (1H, m), 4.96 (1H, dd, J=3.2, 9.6 Hz), 5.24 (1H, d, J=1.5 Hz), 5.62 (1H, d, J=7.3 Hz), 7.48 (2H, t, J=7.3 Hz), 7.61 (1H, t, J=7.3 Hz), 8.12 (2H, d, J=7.3 Hz); FAB-MS (m/z): 529 $(M+H)^+$; HR-MS Cacld for $C_{29}H_{37}O_9$: 529.2438. Found, 529.2448; IR: 3451, 2956, 1714, 1600, 1488 cm^{-1}; $[\alpha]_D^{25}$ −25.2° (c=1.04, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*R*,10*R*,13*S*)-4-Acetoxy-2-cyclohexanecarbonyloxy-5,20-epoxy-9-oxo-1,10,13-trihydroxytax-11-ene (8) (General Procedure, Entry 1) **6** (100 mg, 190 μmol) was hydrogenated (balloon) in AcOEt (3 ml) over PtO_2 (50 mg) for 1.5 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure and the residue was triturated with $CHCl_3$. The resulting powder was collected by filtration to give the title compound (90 mg, 89%) as a white powder, mp 127—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, s), 1.07 (3H, s), 1.21—1.56 (7H, m), 1.64 (1H, m), 1.74 (3H, s), 1.78—1.80 (1H, m), 1.93—2.32 (8H, m), 2.02 (3H, m), 2.18 (3H, s), 3.78 (1H, d, J=7.1 Hz), 4.12 (1H, d, J=1.5 Hz), 4.19 (1H, d, J=8.0 Hz), 4.47 (1H, d, J=7.3 Hz), 4.84 (1H, m), 4.97 (1H, d, J=9.5 Hz), 5.19 (1H, s), 5.38 (1H, d, J=7.0 Hz); FAB-MS (m/z): 535 $(M+H)^+$; HR-MS Calcd for $C_{29}H_{43}O_9$: 535.2907. Found, 535.2916; IR: 3442, 2929, 2856, 1720, 1685, 1450 cm^{-1}; $[\alpha]_D^{23}$ −37.3° (c=0.65, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*,5*R*,8*R*,9*S*,10*R*,13*S*)-4-acetoxy-2-benzoyloxy-1,13-dihydroxy-5,20-epoxy-9,10-(isopropylidenedioxy)tax-6,11-diene (10) To a solution of **9** (1.0 g, 1.71 mmol) and DMAP (2.1 g, 17.1 mmol) in CH_2Cl_2 (30 ml) was added Tf_2O (1.15 ml, 6.83 mmol) with ice cooling, and the mixture was stirred at the same temperature for 6 h. The reaction mixture was poured into a mixture of AcOEt and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel eluted with $CHCl_3$–acetone (50 : 1 (v/v)). The eluate was concentrated under reduced pressure, and the residue was triturated with $CHCl_3$–*n*-hexane. The resulting powder was collected by filtration to give the title compound (0.42 g, 43%) as a white powder, mp 143—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.42 (3H, s), 1.53 (3H, s), 1.54 (3H, s), 1.59 (3H, s), 1.73 (1H, s), 1.91 (3H, s), 2.09 (1H, dd, J=7.3, 15.1 Hz), 2.16 (1H, d, J=8.1 Hz), 2.32—2.39 (1H, m), 2.34 (3H, s), 3.22 (1H, d, J=5.8 Hz), 4.03 (1H, d, J=7.3 Hz), 4.26 (1H, d, J=8.0 Hz), 4.34 (1H, d, J=8.1 Hz), 4.78—4.81 (1H, m), 4.82 (1H, d, J=4.1 Hz), 5.53 (1H, d, J=7.5 Hz), 5.67 (1H, dd, J=3.2, 10.2 Hz), 5.92 (1H, d, J=6.0 Hz), 6.10 (1H, d, J=10.2 Hz), 7.48 (2H, t, J=7.8 Hz), 7.60 (1H, t, J=7.8 Hz), 8.15 (2H, d, J=7.8 Hz); FAB-MS (m/z): 569 $(M+H)^+$; HR-MS Calcd for $C_{32}H_{41}O_9$: 569.2751. Found, 569.2764; IR: 3507, 2975, 1725, 1689, 1482 cm^{-1}; $[\alpha]_D^{24}$ −12.9° (c=1.04, $CHCl_3$).

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