New Oxetane-type Taxanes from *Taxus wallichiana* Zucc.†

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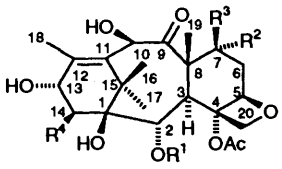
The needles of *Taxus wallichiana* Zucc. gave the novel oxetane-type taxane diterpenoids **2** and **5**, whose structures have been established on the basis of spectroscopic data and chemical reactions. The acid-catalysed rearrangement of 10-deacetylbaccatin III has been investigated.

As part of a study on renewable sources of taxol and related compounds, we reported the isolation of 14-β-hydroxy-10-deacetylbaccatin III **1** from the needles of the Himalayan yew (*Taxus wallichiana* Zucc.).[1] Compound **1** can be used as a synthetic precursor of hydroxylated derivatives of taxol,[2] and this prompted us to investigate further this plant for the presence of additional compounds potentially useful for the synthesis of antitumour taxoids. In the course of these studies, two new taxanes of the oxetane-type (**2** and **5**) were obtained from fractions less polar than those containing **1**.



	R^1	R^2	R^3	R^4
1	Bnz	H	OH	OH
2	H	H	OH	OBnz
3	Bnz	OH	H	OH

(Bnz = benzoyl)

The isolation of **2** was difficult on account of its instability on silica gel and in solution, especially in halogenated solvents. Only small amounts of pure **2** could eventually be obtained by a combination of HPLC and crystallization, and therefore its structural elucidation was based exclusively on spectroscopic data. The NMR spectra of **1** and **2** were similar, as were their mass spectra, which showed the same molecular ion and fragmentation model; the compounds are thus isomers, differing in the acylation pattern and/or the stereochemistry. The lower polarity of **2** and its good solubility in halogenated solvents were surprising, and suggested the presence of several intramolecular hydrogen bonds. This was confirmed by the presence of five exchangeable signals, unaffected by dilution, in the ^{1}H NMR spectrum. In baccatin III derivatives, the epimerization of the hydroxy group at C-7 is known to cause a marked decrease in polarity, on account of a strong intramolecular hydrogen bond between the epimerized hydroxy group and the tertiary acetate at C-4.[3] However, this was ruled out for **2** by spectroscopic considerations [chemical shift of C-19 (δ 10.1); splitting pattern of 7-H (dd, *J* 11.5, 6.5 Hz)],[4] and by direct comparison with a sample of **3**, the C-7 epimer of **1**, prepared by base-induced isomerization of the natural compound. A comparison of the ^{1}H NMR spectra of **2** and **1** showed a marked upfield shift for the signal of 2-H (Δδ −1.77 ppm), and a downfield shift for that of 14-H (Δδ +1.20 ppm), suggesting that in **2** the hydroxy group at C-2 is free and that at C-14 is instead acylated. This was confirmed by a series of 2D NMR experiments, which unambiguously located the benzoate group at C-14 and the acetate at C-4. This acylation pattern is unusual, since in all baccatin III derivatives isolated to date the hydroxy group at C-2 is esterified. However, O(2)-deacyl derivatives of baccatin III are unstable[5,6] and might have easily escaped detection, especially if present in trace amounts; as a result their occurrence might thus have been underestimated.

It has been suggested that the acylation pattern of taxanes plays a role in the intracellular trafficking of these metabolites.[7] In this context it is worth noting that in oxetane-type taxanes benzoylation is found preferentially at the C-2 hydroxy group, whereas in brevifoliol-type derivatives ($\Delta^{4,20}$, free hydroxy at C-5) is occurs instead mainly at the C-7 hydroxy group. On the other hand, no benzoyl group has been found so far in taxine B and taxicin-type derivatives [$\Delta^{4,20}$, hydroxy at C-5 esterified with phenylpropanoic (amino)acids].[8] The specificity of the acyl transferases involved in the biosynthesis of taxanes seems thus strongly related to the functionalization of the C-4–(C-20)–C-5 moiety.

The rearranged taxane **5** was isolated as a colourless oil. The mass spectrum showed a molecular weight of 526, corresponding to the loss of a water molecule from 10-deacetylbaccatin III **4**. This loss could be accounted for by the formation of an ether bridge between two hydroxylated carbons; indeed, the ^{1}H NMR spectra of **4** and **5** showed the same spin systems, and their ^{13}C NMR spectra the same multiplicity patterns, thus implying an identical substitution for the 20 carbons of the taxane system. The loss of two exchangeable protons was further demonstrated by the presence of only two acylable hydroxy [TAI (trichloroacetyl isocyanate) experiments].[9] Acylation shifts were observed for 7-H and 13-H (ΔTAI +0.70 and +1.06 ppm respectively), whereas the signal of 10-H was virtually unaffected and no tertiary hydroxy was present. This showed that the ether bridge is between C-10 and a tetrasubstituted carbon. In the ^{13}C NMR spectrum, some chemical shift values were highly unusual for baccatin III derivatives; **5** showed, in fact, four signals of sp^3-hybridized tetrasubstituted carbons: those at δ 81.0 and 54.5 are typical of C-4 and C-8 in oxetane-type taxanes, but the remaining resonances (δ 68.0 and 85.7) have no counterpart in baccatin III derivatives. Besides, only one of these carbons was oxygenated (obviously that resonating at δ 85.7), since all the remaining oxygens were already accounted for by other resonances. Thus, the signal at δ 68.00 belonged to a non-

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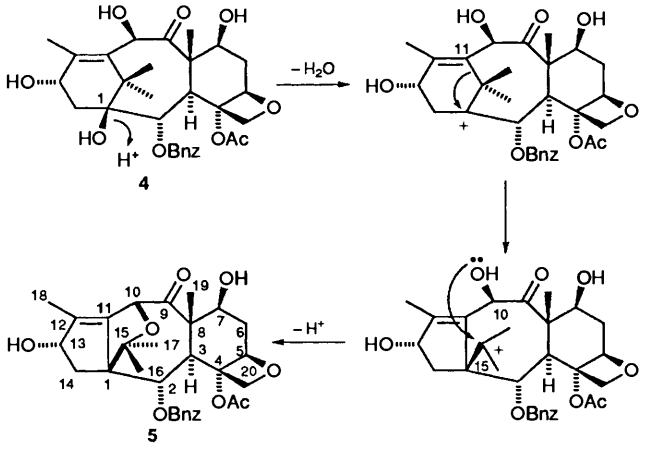
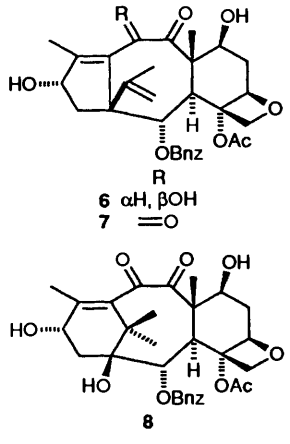
oxygenated carbon. In taxane derivatives, unusually downfield shifts (δ 65–70) for non-oxygenated quaternary carbons have been reported in baccatin VI derivatives (C-15)[7] and in 11(15->1)*abeo*-taxanes (C-1).[6] A rearranged structure of this type was in accordance with all the spectroscopic features of **5**, and could easily accommodate an ether bridge between C-10 (a methine) and C-15 (a tertiary carbon). In unrearranged taxanes an ether bridge involving C-10 is impossible, since the tertiary hydroxy at C-1 is not within bonding distance with C-10.

Further proof for structure **5** came from a study of the acid-catalysed rearrangement of 10-deacetylbaccatin III **4**. The conversion of 7,10-diprotected derivatives of **4** into 11(15->1)*abeo*-taxanes has been successfully achieved,[6,10] but no study on the rearrangement of **4** itself has been reported to date. The high polarity of **4** prevented the use of the reaction conditions employed for its more lipophilic derivatives, but the rearrangement took place in acidic methanol. Under these relatively mild conditions no epimerization at C-7 could be observed, whereas some related taxanes (including **1**) were stable. From the mixture of the rearranged taxanes, **5** was obtained, along with **6** and **7**. A possible rationalization for the formation of **5** from **4** is depicted in Scheme 1. Protonation of



Scheme 1 Possible mechanism for the rearrangement of **4** to **5**



the tertiary hydroxy group at C-1 followed by loss of water can generate a bridgeheaded cation, triggering the 1,2-anionotropic migration of C-11. The resulting tertiary carbenium ion at C-15 might then be trapped by the hydroxy group at C-10. Since C-15 and the hydroxy group at C-10 are spatially close, the whole process depicted in Scheme 1 might take place in a concerted way.

The major reaction product from the acidic rearrangement of **4** was the α-diketone **7**. This compound was not the result of the air oxidation of the corresponding α-ketol **6**, which failed to give **7** under the reaction conditions. Therefore, the oxidation at C-10 must occur before the rearrangement, and presumably takes place *via* the acid-catalysed tautomerization of the acyloin system of **4** to an enediol. The oxidation of the latter would eventually give the α-diketone **8** as the ultimate precursor of **7**. Since the yield of **7** was much higher than that of **5** and **6**, the presence of a carbonyl adjacent to C-11 apparently favours the anionotropic migration of this carbon to C-1, thus driving the reaction towards the formation of the rearranged and oxidized product. A possible explanation might be a better conjugation between the endocyclic double bond and the carbonyl at C-10; on account of severe conformational constraints, no conjugation can, in fact, take place in taxane derivatives between a double bond at C-11–C-12 and a keto group at C-10.[11] Conjugation is instead fully possible in 11(15->1)-*abeo*-taxanes, and this might provide an extra bonus for the rearrangement. The α-diketone **7** was also formed if the reaction was carried out under nitrogen in carefully degassed solvents, suggesting that a dismutation reaction is probably responsible for the oxidation at C-10. Indeed, besides the rearrangement of products, the reaction also gave a complex mixture of polar compounds, but we were unable to isolate any pure product from it. It is worth noting that in **4**, the hydrogen-bonded and sterically hindered hydroxy group at C-10 is the most difficult to oxidize, and its chemoselective oxidation failed with a variety of oxidants (Cr^{6+} salts, MnO_2, $BaMnO_4$, activated dimethyl sulfoxide).[12]

The production of **5** from the treatment of **4** with acids supports the assignment of an *abeo*-taxane structure for **5**, but also raises the question as to whether this compound is a natural product or an artefact. Although no 11(15->1)*abeo*-taxane derivatives have been isolated to date, an enzymatic origin for **5** is supported by the absence in the plant extract of **6** and **7**, the major reaction products of the acidic degradation of **4**, and by the exclusive epimerization at C-7, without skeletal rearrangement, upon treatment of **4** with silica gel. Some ring A-contracted taxol analogues show excellent tubulin-binding activity,[6,10] but when one of these compounds was studied for antitumour activity, no cytotoxicity was found.[10] The availability of ring-A contracted and variously functionalized baccatin III derivatives should allow a systematic investigation of this remarkable observation, that is of great interest in the context of the structure–activity relationships within antitumour taxoids.

Experimental

M.p.s were determined on a Büchi SMP 20 apparatus and are uncorrected; optical rotations were measured on a Perkin-Elmer 141 automatoc polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. UV Spectra were recorded on a Beckman DB-GT spectrophotometer. IR Spectra were recorded on a Perkin-Elmer model 127 spectrophotometer. Chemical ionization (CI) mass spectra were recorded on a VG EQ 70/70 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer (300 and 75.4 MHz respectively), with $SiMe_4$ as reference. NMR Data for compounds **2**, **3** and **5**–**7** are given in Tables 1 and 2. Silica gel 60 (70–230 mesh, Merck) was used for column chromatography. All solvents used for chromatography were bought as technical grade, and distilled before use. A Waters microporasil column (0.8 × 30 cm) was used for preparative HPLC, with detection by a Waters differential refractometer 7401.

T. wallichiana Zucc. was collected in Western Himalaya, and was identified by Dr U. Boni (Indena S.p.A., Milano). A voucher specimen is kept at Indena S.p.A., Milano.

Isolation of **2** *and* **5**.—An extract from the needles was obtained and separated as previously described.[1] After removal

Table 1 ^{1}H NMR data (300 MHz, $SiMe_4$, $CDCl_3$, *J*-values in Hz)

H	2[a]	3	5	ΔTAI	6	7
2	3.77 (t, 7.0)	5.85 (d, 8.0)	6.23 (d, 10.2)	−0.08	5.66 (d, 8.1)	5.74 (d, 7.7)
3	3.52 (d, 6.8)	3.94 (d, 7.6)	3.14 (d, 10.2)	+0.11	3.56 (d, 8.1)	3.47 (d, 7.7)
5	4.90 (br d, 8.7)	4.93 (dd, 8.6, 4.5)	4.73 (br d, 8.0)	+0.12	5.06 (br d, 9.2)	5.01 (br d, 7.9)
6a	2.28 (m)	2.32 (m)	2.42 (m)	+0.20	2.64 (m)	2.60 (m)
6b	1.65 (br t, 12.5)	[b]	[b]		[b]	1.92 (m)
7	4.07 (ddd, 11.5, 6.9, 6.5)	3.66 (m)	4.88 (dd, 9.9, 4.4)	+0.70	4.36 (m)	4.28 (m)
10	5.13 (d, 2.7)	5.46 (s)	4.69 (s)	−0.03	5.29 (s)	—
13	4.77 (br t, 6.0)	4.73 (dd, 7.0, 1.5)	4.52 (m)	+1.06	4.60 (br t, 8.0)	4.62 (br t, 7.8)
14	4.99 (d, 6.0)	3.99 (d, 6.7)	[b]		2.36 (m)	2.66 (m)
	—	—	[b]		[b]	1.86 (m)
16	1.12 (s)	1.11 (s)	1.78 (s)	+0.12	4.94 (br s)	4.79 (br s)
17	0.89 (s)	1.09 (s)	1.71 (s)	−0.13	4.71 (br s)	4.70 (br s)
18	1.90 (br s)	1.98 (br s)	1.90 (br s)	+0.16	1.80 (s)	1.71 (s)
19	1.49 (s)	1.70 (s)	1.08 (s)	−0.06	1.99 (br s)	2.33 (br s)
20a	4.48 (d, 9.1)	4.35 (d, 8.8)	4.58 (d, 8.1)	−0.01	1.65 (s)	1.76 (s)
20b	4.43 (d, 9.1)	4.36 (d, 8.8)	4.24 (d, 8.1)	−0.01	4.33 (d, 8.1)	4.30 (br s)
Bnz	8.00 (d, 7.5)	8.08 (d, 7.5)	8.20 (d, 7.3)	+0.02	4.25 (d, 8.1)	
	7.65 (t, 7.5)	7.61 (t, 7.5)	7.63 (t, 7.3)	+0.03	8.02 (d, 7.3)	8.05 (d, 7.5)
	7.52 (t, 7.5)	7.48 (t, 7.5)	7.49 (t, 7.3)	+0.08	7.61 (t, 7.3)	7.63 (t, 7.5)
Ac	2.07 (s)	2.38 (s)	2.15 (s)	+0.07	7.47 (t, 7.3)	7.49 (t, 7.5)
					2.24 (s)	2.19 (s)

[a] [$^2H_6$]Dimethyl sulfoxide; 1-OH, 4.36 (s); 2-OH, 4.20 (d, 7.0), 7-OH 4.92 (d, 6.9); 10-OH, 4.76 (d, 2.7); 13-OH, 5.69 (d, 6.0). [b] Could not be observed owing to overlapping.

Table 2 ^{13}C NMR data (75.4 MHz, $SiMe_4$, $CDCl_3$)

C	2[a]	3	5	6	7
1	77.7 s	75.4 s	68.0 s	63.9 s	59.7 s
2	73.6 d	74.1 d	69.2 d	70.2 d	68.4 d
3	47.7 d	39.2 d	44.5 d	44.4 d	43.7 d
4	81.7 s	81.2 s	81.0 s	79.0 s	78.6 s
5	83.7 d	81.4 d	85.5 d	84.7 d	84.8 d
6	37.3 t	35.0 t	35.4 t	37.2 t	36.3 t
7	71.7 d	77.8 d	71.0 d	71.0 d	71.2 d
8	57.9 s	56.7 s	54.5 s	55.7 s	56.1 s
9	210.9 s	214.5 s	211.1 s	210.9 s	206.2 s
10	74.3 d	75.2 d	84.3 d	75.9 d	194.2 s
11	136.4 s	134.9 s	135.8 s	136.6 s	135.2 s
12	138.8 s	138.6 s	144.6 s	145.6 s	165.3 s
13	72.7 d	72.6 d	80.8 d	71.9 d	75.7 d
14	77.5 d	72.2 d	33.7 t	42.3 t	41.8 t
15	43.0 s	41.4 s	85.7 s	147.0 s	145.1 s
16	27.1 q	25.8 q	25.6 q	112.6 t	113 6 t
17	21.1 q	21.2 q	22.7 q	20.8 q	20.8 q
18	15.4 q	14.9 q	11.3 q	11.5 q	14.5 q
19	10.1 q	16.6 q	10.2 q	9.0 q	7.9 q
20	77.6 t	76.7 t	76.4 t	74.6 t	74.2 t
Bnz	166.9 s	165.4 s	164.3 s	165.4 s	165.8 s
	133.6 d	133.2 d	133.7 d	133.6 d	133.8 d
	130.6 s	129.6 s	130.1 s	128.7 s	130.0 s
	129.9 d	129.7 d	129.3 d	129.7 d	129.8 d
	129.0 d	128.6 d	128.6 d	128.6 d	128.8 d
Ac	170.2 s	171.8 s	169.8 s	170.6 s	170.4 s
	22.7 q	22.3 q	21.8 q	21.9 q	21.7 s

[a] [$^2H_6$]Dimethyl sulfoxide.

of **1** by crystallization from methanol, the mother liquors (12 g) were purified by column chromatography ($CHCl_3$–EtOH 9:1) to give fractions containing **2** (2.1 g) and fractions containing **5** (700 mg). Further purification of each fraction by HPLC ($CHCl_3$–EtOH 95:5) gave **5** as a colourless oil (84 mg) and crude **2** (210 mg). The latter was further purified by crystallization (acetone–diethyl ether) to give 64 mg of a white powder.

2-*Debenzoyl*-14β-*benzoyloxy*-10-*deacetylbaccatin III* **2**. White powder, m.p. 160 °C; $[\alpha]_D^{25}$ −30 (MeOH, *c* 0.37); λ_{max}(EtOH)/nm 230, 263; ν_{max}(KBr disc)/cm^{-1} 3420, 1730, 1700, 1300, 1260, 1000, 725; *m/z* (Cl, NH_3) 561 $[(M + H)^+(C_{29}H_{36}O_{11})^+$, 100%]; *m/z* [electron impact (EI), 70 eV] 560.2261 $(M)^+$ ($C_{29}H_{36}O_{11}$ requires 560.2258) (9%), 542 $[(M - H_2O)^+$, 35%], 420 $[(M - H_2O\text{-}PhCO_2H)^+$, 80%], 360 $[(M - H_2O\text{-}HOAc\text{-}PhCO_2H)^+$, 50%], 105 (100%).

10,15-*Epoxy*-11(15- > 1)abeo-10-*deacetylbaccatin III* **5**. Colourless oil, $[\alpha]_D^{25}$ −18 (CH_2Cl_2, *c* 1.2); λ_{max}(EtOH)/nm 230, 265; ν_{max}(liquid film)/cm^{-1} 3500, 1730, 1700, 1250, 980, 760; *m/z* (Cl, NH_3) 527 $[(M + H)^+(C_{29}H_{34}O_9 + H)^+$, 100%]; *m/z* (EI, 70 eV) 508.2092 $(M - H_2O)^+$ ($C_{29}H_{32}O_8$ requires 508.2097 (12%), 326 $[(M\text{-}H_2O\text{-}HOAc - PhCO_2H)^+$, 62%], 105 (100%).

14β-*Hydroxy*-10-*deacetylbaccatin V* **3**.—A sample of **1** (500 mg) was dissolved in methanol (25 cm^3) and basic alumina (500 mg, Merck) was added. After stirring at room temp. for 14 days, the reaction mixture was worked up by filtration, and the solvent was evaporated. The residue was purified by column chromatography (5 g silica gel, $CHCl_3$–EtOH 9:1 as eluent) to give **3** (154 mg, 31%) and 200 mg unchanged **1**. White powder, m.p. 229 °C; $[\alpha]_D^{25}$ −46 (CH_2Cl_2, *c* 0.80); λ_{max}(EtOH)/nm 222 and 260; ν_{max}(KBr disc)/cm^{-1} 3400, 1720, 1700, 1360, 1240, 1170, 1080, 900; *m/z* (Cl,NH_3) 578 $[(M + NH_4)^+$, $(C_{29}H_{36}O_{11} + NH_4)^+$, 100%)]; *m/z* (EI, 70 eV) 542.2157 $(M - H_2O)^+$ ($C_{29}H_{34}O_{10}$ requires 542.2152) (6%), 482 $[(M\text{-}H_2O\text{-}HOAc)^+$, 20%], 360 $[(M - H_2O\text{-}HOAc\text{-}PhCO_2H)^+$, 46%], 105 (100).

Acid Catalysed Rearrangement of 10-*Deacetylbaccatin III* **4**.—A sample of **4** (2.0 g) was dissolved in methanol (150 cm^3), and toluene-*p*-sulfonic acid (150 mg) was then added. The solution was stirred under a nitrogen atmosphere for 48 h, and then worked up by the addition of powdered $NaHCO_3$ (1 g) and filtration. After removal of the solvent, the residue was purified by column chromatography (30 g silica gel). Fractions eluted with CH_2Cl_2–EtOH 95:5 gave 253 mg **7** (12%) and 107 mg (*ca.* 5%) of a 1:2 mixture (^{1}H NMR analysis) of **5** and **6**, that could be separated by HPLC ($CHCl_3$–EtOH) 95:5). Fractions eluted with $CHCl_3$–EtOH 9:1 gave unchanged **4** (438 mg) and 622 mg of a mixture of more polar products that could not be further characterized.

15(16)-*Anhydro*-11(15- > 1)abeo-10-*deacetylbaccatin III* **6**. Colourless oil, $[\alpha]_D^{25}$ −26 (CH_2Cl_2, *c* 1.0); λ_{max}(EtOH)/nm 230, 266; ν_{max}(liquid film)/cm^{-1} 3500, 1730, 1700, 1280, 1120, 1000, 960, 760; *m/z* (Cl, NH_3) 527 $[(M + H)^+$ $(C_{29}H_{34}O_9 + H)^+$,

100%]; *m/z* (EI, 70 eV) 508.2092 $(M-H_2O)^+$ ($C_{29}H_{32}O_8$ requires 508.2097) (6%), 326 [$(M-H_2O-HOAc-PhCO_2H)^+$, 54%], 105 (100%).

15(16)-*Anhydro*-11(15->1)abeo-10-*deacetyl*-10-*dehydrobaccatin III* **7**. Colourless needles (acetone–diethyl ether), m.p. 195 °C; $[\alpha]_D^{25}$ +9.2 (CH_2Cl_2, *c* 1.1); λ_{max}(EtOH)/nm 230, 268; ν_{max}(KBr disc)/cm^{-1} 3480, 1725, 1580, 1370, 1250, 1090, 920; *m/z* (Cl, NH_3) 542 [$(M + NH_4)^+$($C_{29}H_{32}O_9$ + H)$^+$, 100%]; *m/z* (EI, 70 eV) 524.2043 $(M)^+$ ($C_{29}H_{32}O_9$ requires 524.2046) (6%), 506 [$(M-H_2O)^+$, 13%], 324 [$(M-H_2O-HOAc - PhCO_2H)^+$, 68%], 105 (100).

Treatment of **4** *with silica gel*.—A sample of **4** (300 mg) was dissolved in methanol, and silica gel (70–230 mesh, Merck, 6 g) was added. After stirring 96 h at room temp., the suspension was filtered and the residue purified by column chromatography ($CHCl_3$–EtOH 9:1) to give 10-deacetylbaccatin V (162 mg)[13] and unchanged **4** (96 mg).

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