Revised Structure of Brevifoliol and some Baccatin VI Derivatives

Giovanni Appendino,*[a] Luciano Barboni,[b] Pierluigi Gariboldi,*[b] Ezio Bombardelli,[c] Bruno Gabetta[c] and Davide Viterbo[d]

[a] *Dipartimento di Scienza e Tecnologia del Farmaco, via Giuria 9, 10125 Torino, Italy*
[b] *Dipartimento di Scienze Chimiche, Via S. Agostino 1, 62032 Camerino (MC), Italy*
[c] *Indena S.p.A., via Ripamonti 99, 20141 Milano, Italy*
[d] *Dipartimento di Chimica Inorganica, Chimica Fisica e Chimica dei Materiali, Via Giuria 7, 10125 Torino, Italy*

Brevifoliol and some baccatin VI derivatives have been shown to have a rearranged 11(15→1)*abeo*-taxane skeleton and not a taxane skeleton as originally reported, making *abeo*-taxanes an emerging major structural type of taxoids.

The ring *A* of taxane derivatives can rearrange in acidic medium giving two types of ring *A* contracted taxoids: 11(15→1)*abeo*-taxanes (**A**)[1] and 1(15→11)*abeo*-taxanes (**B**).[2] The type of rearrangement depends on the oxidation state of C-1; C-1 hydroxylated compounds give 11(15→1)*abeo*-derivatives *via* a cation at C-1,[1] whereas their non-oxygenated counterparts afford 1(15→11)*abeo*-derivatives *via* a cation at C-13.[2] Both types of rearrangement are documented, and two examples of 11(15→1)*abeo*-taxanes have recently been reported as natural products.[3,4] In a recent review summarizing our work on the constituents of yew needles, we pointed out that in 11(15→1)*abeo*-taxanes C-1 resonates at unusually low field (δ 60–70) for a tetrahedral carbon not bearing heteroatoms.[5] A literature survey showed that values of this type have also been reported for a non-oxygenated quaternary carbon in a series of baccatin VI[6,7] and brevifoliol[7–10] derivatives. This signal was attributed either to C-8 or to C-15.

We have isolated baccatin VI (**1a**)[11] from various parts of yew trees. A thorough spectroscopic investigation on this compound, for which only low-field ^{1}H NMR data were available,[11] confirmed the structure assigned, but also revealed that some compounds reported as derivatives of **1a**[6,7] had spectral features inconsistent with those of the parent compound. Similar conclusions were drawn comparing the spectroscopic features of brevifoliol and some of its derivatives.[7–10]

In baccatin VI (**1a**) the chemical shift of the non-oxygenated quaternary carbons (C-8 and C-15) is that expected for taxane derivatives (δ 45.73 and 42.74). In a compound originally formulated as **1b**,[7] these resonances are instead at δ 67.66 and 43.72. Acetylation of this compound afforded a pentaacetylated taxane different from baccatin VI,† and having the resonances of the quaternary non-oxygenated carbons at δ 68.52 and 45.53. The detection of a ROE effect between the tertiary hydroxy proton and H-9 and of a long-range ^{1}H–^{13}C coupling between H-10 and the benzoate carbonyl suggested the 11(15→1)*abeo*-taxane structure **2c** for this product. The

† **1a**: m.p. 265–268 °C; $[\alpha]_D^{25}$ −8.7 ($CHCl_3$, *c* 0.90). **2c**: m.p. 240–241 °C; $[\alpha]_D^{25}$ −52.3 ($CHCl_3$, *c* 0.35). **3c**: m.p. 260–263 °C; $[\alpha]_D^{25}$ + 126 ($CHCl_3$, *c* 0.11). **4c**: oil, $[\alpha]_D^{25}$ −58.1 ($CHCl_3$, *c* 0.45).

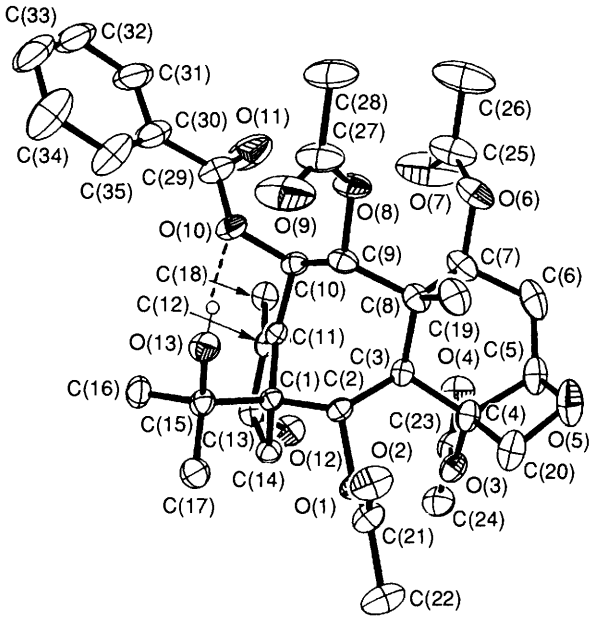
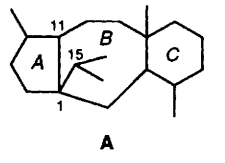


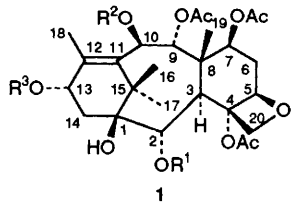
Fig. 1 Molecular structure of **2d**

X-ray analysis of the natural tetraacetate showed that this compound has indeed the structure **2d** (Fig. 1),‡ confirming that both the skeletal type and the acylation pattern should be revised. The presence of diagnostic long-range correlations (H-10, H-16, H-17) assigned the downfield singlet at δ 68.52 to C-1.

The tetraacetate **3a** and the diacetate **3b** were both reported[7] as derivatives of brevifoliol (**3d'**).[8] These compounds showed different resonances of the quaternary non hydroxylated carbons (δ 46.95 and 43.12 in **3a**; 61.30 and 45.11 in **3b**), and gave different acetylation products (**3c** and **4c**).† The presence of a ROE effect between H-9 and the tertiary hydroxy established an *abeo*-taxane structure for **4c**; the natural diacetate has thus the formula **4b**. In a similar way brevifoliol[8] and four other compounds reported as its derivatives[7,9,10] were proved to be rearranged taxanes of the 11(15→1)*abeo* type. Furthermore, 2D NMR experiments (long-range ^1H–^{13}C correlations) showed that in brevifoliol and its 2α-acetoxy- and 13-acetyl derivatives, the benzoate is located at C-10 and not at C-7. The structure of these compounds is thus represented by **4d–h** and not **3d',e',f',g,h** as originally reported.[7–10] All these compounds show a downfield signal (δ 60–70) for C-1,[7–10] a resonance well distinct from those of the quaternary non oxygenated carbons (C-8 and C-15) of taxanes, that resonate at higher fields [δ 37–45 for C-15, and 40–47 (55–58 when a keto group is present at C-9) for C-8]. This rather unusual and remarkable spectroscopic feature seems typical of C-15 hydroxylated *abeo*-taxanes, and is difficult to rationalize. It must be noticed however, that in **2d** the C-1–C-15 and the C-1–C-2 bonds are rather long [1.582(4) Å and 1.569(4) Å respectively]; the unusual chemical shift value of C-1 in *abeo*-taxanes might thus be the result of considerable linear strain. Besides the examples discussed here, also the structure of other compounds reported as baccatin VI derivatives[6] should be revised.

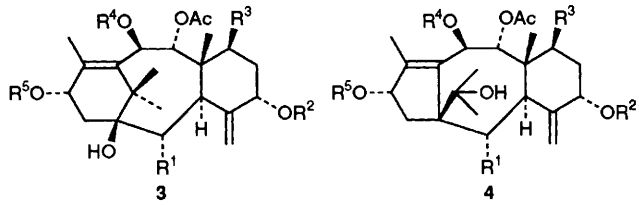
‡ *Crystal data*: $C_{35}H_{44}O_{13}$, M_r = 672.7, monoclinic, space group $P2_1$, a = 9.982(2), b = 11.634(2), c = 15.862(4) Å, β = 104.43(2), V = 1784.0(7) Å^3, Z = 2, μ = 0.096 mm^{-1}, $F(000)$ = 716, Mo-Kα radiation, λ = 0.71073 Å. 5379 independent reflections were collected on a Siemens P4 diffractometer; 3944 with $F > 4\sigma(F)$ were used in the structure solution (direct methods) and refinement (full-matrix least-squares). Final R = 0.054, R_w = 0.070. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.





1 2

	R¹	R²	R³
a	Bz	Ac	Ac
b	Bz	Ac	H
c	Ac	Bz	Ac
d	Ac	Bz	H



3 4

	R¹	R²	R³	R⁴	R⁵
a	H	H	OAc	Ac	Ac
b	H	H	OAc	H	H
c	H	Ac	OAc	Ac	Ac
d	H	H	OAc	Bz	H
d'	H	H	OBz	Ac	H
e	OAc	H	OAc	Bz	H
e'	OAc	H	OBz	Ac	H
f	H	H	OAc	Bz	Ac
f'	H	H	OBz	Ac	Ac
g	OAc	H	H	H	H
h	H	H	H	H	H

Abeo-taxanes with an isopropenyl side-chain at C-1 are easily recognized, since their proton spin system and ^{13}C multiplicity pattern are peculiar. The ^1H NMR spectra of C-1 hydroxylated taxanes and C-15 hydroxylated *abeo*-taxanes are instead similar, and their ^{13}C NMR spectra show the same carbon multiplicities. Since the molecular topology is similar, J pattern and ROEs effects of all the non-exchangeable protons are also comparable. The close similarity of the ROEs can be rationalized in terms of a preferred orientation of the hydroxyisopropyl group, that in *abeo*-taxanes adopts a conformation having one of the methyls pointing towards the five-membered ring (dipolar interactions with H-13 and H-14β) and the other directed towards the seven membered ring (strong interaction with H-2). This arrangement is also found in the solid-state conformation of **2d** (Fig. 1), and mimics the gem-dimethyl substituted bridgeheaded A,B-junction of taxanes. A 15-hydroxy-11(15→1)*abeo*-taxane structure is strongly suggested by the low-field resonance (δ 60–70) of one of the aliphatic non-oxygenated quaternary carbons; this structural assignment can be confirmed by the analysis of the ROE effects associated to the tertiary hydroxy proton. Furthermore, when the tertiary hydroxy is the only acylable group, useful indications can also come from inspection of the trichloroacetylisocyanate (TAI)-induced shifts;[13] *in situ* acylation of the C-1 hydroxy of taxanes causes in fact a dramatic

downfield shift of H-14β (Δδ + 1.44 in **1a**), whereas acylation of the C-15 hydroxy of *abeo*-taxanes has no effect on this proton, and instead causes shifts of H-9 (upfield, Δδ − 0.20 in **2c**) and the gem-dimethyl groups (downfield, Δδ + 0.50 and + 0.47 in **2c**), that are spatially close to the tertiary hydroxy. When the C-10 hydroxy of *abeo*-taxanes is acylated, a fairly strong intramolecular hydrogen bonding exists between the 'ethereal' ester oxygen and the tertiary hydroxy at C-15 (Fig. 1; distance O-13···O-10, 2.952 Å. This is the only intra- or inter-molecular hydrogen bonding observed in **2d**). As a result, the hydroxy proton resonates as a singlet at δ *ca.* 2.6 ($CDCl_3$). This signal has never been observed in C-1 hydroxylated taxanes, even when C-2 is oxygenated, and the possibility of an alternative intramolecular hydrogen bonding exists. It is also worth noting that the tricyclic ring system of *abeo*-taxanes is apparently more flexible than its bridgeheaded taxane counterpart, since some *abeo*-taxanes exist in solution as mixtures of conformers.[7,9]

^{13}C NMR data are not available for many C-1 hydroxylated taxanes, and other structural revisions besides those reported or suggested here might be possible. As a result, *abeo*-taxanes might emerge as one major structural class of taxoids. In all *abeo*-taxanes isolated to date C-15 is hydroxylated, whereas the acidic treatment of C-1 hydroxylated taxanes gives mixtures of 15,16-unsaturated and C-15 hydroxylated rearranged products.[1,12] It is thus likely that C-15 hydroxylated *abeo*-taxanes are natural products and not artefacts, a view also supported by the peculiar acylation pattern of some *abeo*-taxanes, that has no counterpart within C-1 hydroxylated taxanes. Biological studies on 15-hydroxy-11(15→1)*abeo*-taxol derivatives showed a tubulin-binding activity[1,12] but no *in vitro* cytotoxicity,[1] an interesting observation in the context of structure–activity relationships with antitumor taxoids.

Received, 8th June 1993; Com. 3/03287F

References

1 G. Samaranayake, N. F. Magri, C. Jitrangsri and D. G. I. Kingston, *J. Org. Chem.*, 1991, **56**, 5114.
2 W. R. Chan, T. G. Halsall, G. M. Hornby, A. W. Oxford, W. Sabel, K. Bjamer, G. Ferguson and J. M. Robertson, *Chem. Commun.*, 1966, 923.
3 K. Fuji, K. Tanaka, B. Li, T. Shingu, H. Sun and T. Taga, *Tetrahedron Lett.*, 1992, 7915.
4 G. Appendino, H. Ç. Özen, P. Gariboldi, E. Torregiani, B. Gabetta, R. Nizzola and E. Bombardelli, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1563.
5 G. Appendino, P. Gariboldi, B. Gabetta and E. Bombardelli, *Fitoterapia*, 1993, **64**, 37.
6 A. Chu, J. Zajicek, L. B. Davin, N. G. Lewis and R. B. Croteau, *Phytochemistry*, 1992, **31**, 4249.
7 L. Barboni, P. Gariboldi, E. Torregiani, G. Appendino, B. Gabetta and E. Bombardelli, *Phytochemistry*, 1993, **33**, 145.
8 F. Balza, S. Tachibana, H. Barrios and G. H. N. Towers, *Phytochemistry*, 1991, **30**, 1613.
9 G. Appendino, H. Ç. Özen, S. Tagliapietra, P. Gariboldi, B. Gabetta and E. Bombardelli, *J. Nat. Prod.*, 1993, **56**, 514.
10 G. Appendino, H. Ç. Özen, P. Gariboldi, B. Gabetta and E. Bombardelli, *Fitoterapia*, 1993, **64**, 47.
11 P. Della Casa de Marcano and T. G. Halsall, *J. Chem. Soc., Chem. Commun.*, 1975, 365.
12 A. Wahl, F. Guéritte-Voegelein, D. Guénard, M. T. le Goff and P. Potier, *Tetrahedron*, 1992, **48**, 6965.
13 Z. Samek and M. Buděšínský, *Collect. Czech. Chem. Commun.*, 1979, **44**, 558.