Taxagifine: New Taxane Derivative from *Taxus baccata* L. (Taxaceae)

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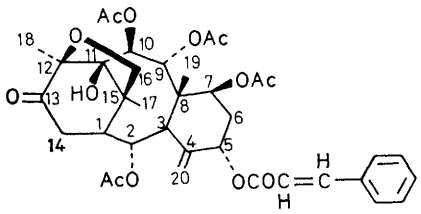
Chemical investigation of *Taxus baccata* L. in conjunction with biological evaluation led to the isolation and full characterization of a new taxane derivative: 12β,16β-epoxy-11β-hydroxy-12,12-dihydrotaxinin E, named taxagifine.

Constituents of the yew tree *Taxus baccata* L. have been the subjects of phytochemical[1a] and synthetic[1b] work since the discovery of terpenes belonging to the taxane group. Among them, taxol, formerly isolated from the stem bark of *Taxus brevifolia* Nutt. by Wani *et al.*[2] has been recognized as being a strong antimitotic agent. This important biological activity has been related to the *in vitro* inhibition by taxol and some of its derivatives of the depolymerisation process of tubulin.[3] We have used this property to follow the fractionation of active metabolites of *T. baccata*.

Ethanolic (80%) extracts from yew leaves were subjected to H_2O–$CHCl_3$ partitioning and h.p.l.c. (SiO_2) leading to the isolation of a less bioactive compound than taxol (ID_{50} 5×10^{-5} M, *cf.* 10^{-6} for taxol), *i.e.* taxagifine (**1**): m.p. 265—267 °C (MeOH); $[\alpha]_D$ +7.5° (MeOH, *c* 10 g l^{-1}).†

† Spectral data: i.r., ν 3450, 1750, 1720, and 1640 cm^{-1}; u.v. (EtOH), λ 282 nm, ε 25 000 dm^3 mol^{-1} cm^{-1}; mass spectrum, *m/e* 696 (weak molecular ion) and 548 (base peak due to loss of cinnamic acid); ^1H n.m.r. ($CDCl_3$, 250 MHz), δ 2.34 [*J*(1,14β) 11, *J*(1,14α) 0, and *J*(1,2) 6 Hz, H-1], *ca.* 5.40 [m, *J*(2,3) 8 Hz, H-2], 3.36 (H-3), *ca.* 5.40 (m, H-5), 2.2 (H-6α), 1.64 [*J*(6α,6β) 14 Hz, H-6β], 5.40 (m, H-7), 4.92 [*J*(9,10) 2.5 Hz, H-9], 5.36 (H-10), 2.5 (H-14α), 3.0 [*J*(14α,14β) 18 Hz, H-14β], 1.08 (H-17), 1.52 (H-18), 1.2 (H-19), 3.66 and 4.16 [*J*(19,19′) 8 Hz, H-19 and H-19′], and 4.56 and 5.4 (H-20).



(1)

The structure of (1) has been established by *X*-ray diffraction.

Crystal data: orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 20.204$, $b = 18.902$, and $c = 9.089$ Å. 2583 structure factors with $I > 2\sigma(I)$ were derived from 3015 intensities collected using a four-circle diffractometer operating with Cu-K_α radiation. The structure was solved by the use of the multisolution technique[5] and anisotropically refined to an *R*-factor of 8.5%. Hydrogen atoms were introduced at calculated positions with an isotropic thermal vibration parameter equal to that of the bonded carbon atom but not refined (Figure 1). The absolute configuration displayed is that of taxane derivatives.‡

Taxagifine differs from taxol by, *inter alia*, the presence of an –O– bridge between C-12 and C-16 and the absence of the oxetan-type bridge between C-20 and C-5 leading to important conformational changes. The changes were also indicated by the unusual coupling constants between H-9 and H-10 (2.5 instead of 10 Hz found for taximine derivatives), in agreement with the corresponding angle of 114° in the *X*-ray

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

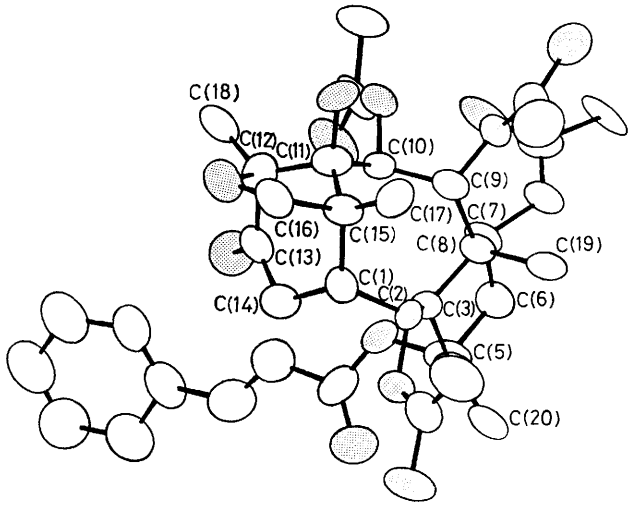


Figure 1

structure. The conformational consequence of these structural modifications is an unusual folding of the molecule which might lead to a diminution in biological activity compared to taxol itself.

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