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# Synthesis of Azetidine-type Taxanes[1]

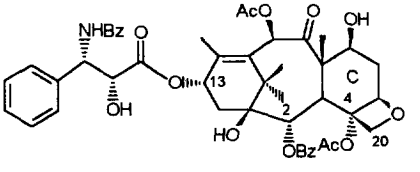
**Ivana Fenoglio,[a]* Gian Mario Nano,[a] David G. Vander Velde[b] and Giovanni Appendino[a]***

[a] Dipartimento di Scienza e Tecnologia del Farmaco, via Giuria 9, 10125 Torino, Italy

[b] Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, U.S.A.

***Abstract***: *Starting from the alkaloid 2'-deacetoxyaustrospicatine (2) azetidine isosteres of the oxetane-type taxane 1-deoxy-2-debenzoyloxy-4-deacetylbaccatin VI were synthesised.*


The isolation of paclitaxel (= taxol®) (**1**) and paclitaxel-equivalent compounds (e.g. 10-deacetylbaccatin III, taxols B - D) from biomass derived from cultivation (needles, twigs) has solved the much hyped 'paclitaxel dilemma', paving the way to the commercialisation of this anticancer agent and making the yew tree (*Taxus* sp. vv.) an important commodity for the pharmaceutical industry.[2] Paclitaxel and paclitaxel-equivalent compounds generally make up less than 0.1 % of the dried plant material, and large amounts of potentially useful compounds remain in the side-cuts and left-overs of the industrial processing.[3] Indeed, the major terpenoid constituent of the needles of several yew species is a mixture of basic alkaloids collectively referred to as 'taxine'.[4] The possibility of using this easily available material for the synthesis of antitumor taxoids or of model compounds did not go unnoticed, and, starting from a constituent of taxine from the European yew, 7-deoxybaccatin VI analogues were synthesised.[5] This seminal sequence featured the first conversion of a taxane of the 5-hydroxy-$\Delta^{4(20)}$-type into a 4-acetyloxy-5(20)-oxetane derivative, a committed step in all the three total syntheses of paclitaxel reported to date.[6] We report the use of taxine to address another problem, namely the synthesis of oxetane isosteres.

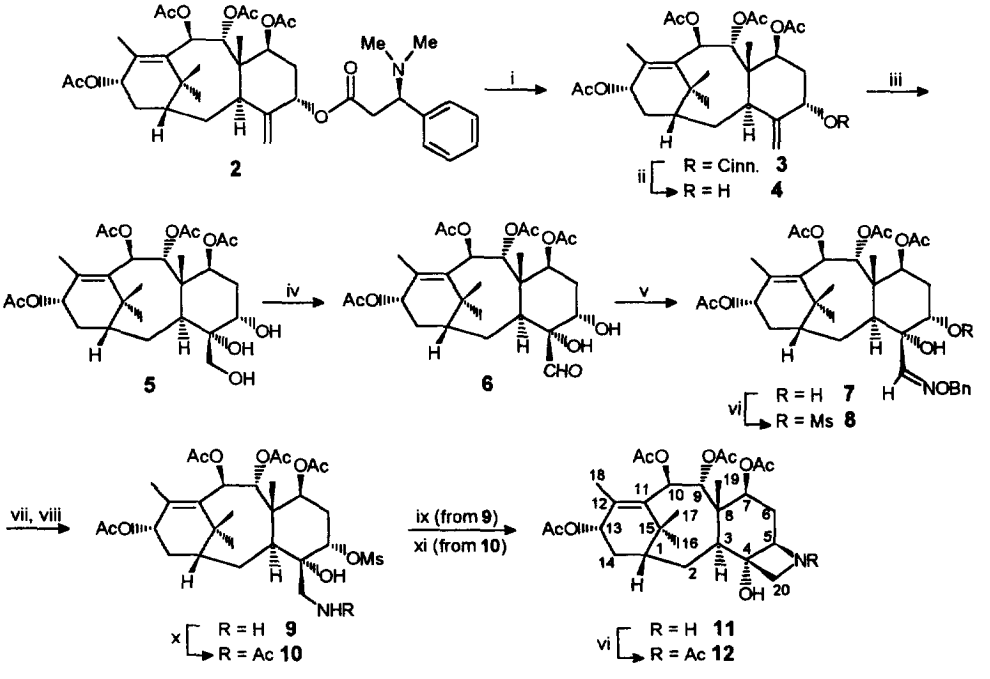



**1**

The structure-activity relationships of antitumor taxoids have been an active area of research.[7] Many studies have highlighted the importance of the oxetane moiety on ring C and the ester groups at C-13, C-2 and C-4 for a significant activity.[7] The pattern of ester substitution has been rationalised in terms of hydrophobic clustering,[8] but the role of the oxetane ring is essentially unknown. It might either act as a local conformational constraint, locking ring C in a sofa conformation, or, alternatively, be directly involved in receptor binding, acting as a hydrogen bonding acceptor. These alternatives might be distinguished replacing the oxetane oxygen with isosteric groups (-NH-, -NAc-, -$CH_2$-, -S-) so as to dissect the electronic and the conformational contributions of the four-membered heterocyclic ring. Since the oxygen functions at C-2 and C-20 can be involved in several intramolecular reactions (acyl migration, ether formation),[9] we decided to use **2**[10], a compound lacking an oxygen function at C-2, as starting material. In this way the heavy armour of protecting

groups typical of most taxane manipulations could be avoided, focusing instead on the basic chemistry underlying the synthesis of the oxetane isosteres. **2** (2'-deacetoxyaustrospicatine) can be obtained by direct crystallisation of crude taxine from *T.* x *media* Rehd cv. Hicksii, one of the major sources of cultivated yew biomass.[2]

Cope elimination of the *N*-oxide of **2** (formed *in situ*)[11] gave the *E*-cinnamate **3** (Scheme 1), which was chemoselectively deacylated with hydroxylamine[12] and osmilated to give the 4,5,20-triol **5**. Attempts to introduce a nitrogen function at C-20 by nucleophilic displacement of a 20-tosylate failed, since intramolecular attack by the 4-hydroxyl prevailed, giving the 4α,20-epoxide instead. Protection of the 4,5-diol system as acetonide was of no avail, since the 20-tosylate proved essentially unreactive under Sn2-type conditions.[13] A stronger electrophylic group at C-20 was needed to introduce a nitrogen function, and the synthesis of the aldehyde **6** was attempted. The chemoselective oxidation of the primary hydroxyl of **5** failed or gave mixture of products with several oxidants ($Cr^{6+}$-based reagents, TPAP-NMO, IBX, DCC, NBS- and $SO_3$-pyridine activated DMSO), but could be eventually be achieved in satisfactory yield using the Swern procedure or $P_4O_{10}$-activated DMSO.[14] In both cases, the reaction was plagued by the formation of the 20-*nor* formate **14**, presumably derived from the fragmentation of the sulfoxonium ion **13** (Scheme 2).[15]

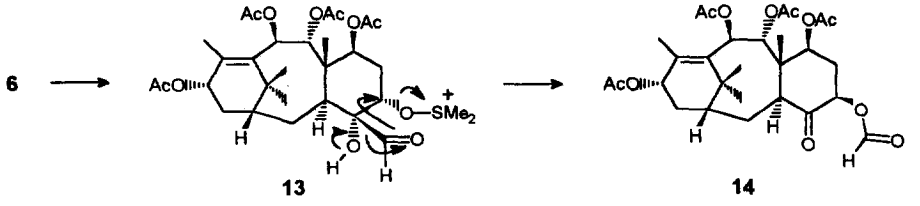



***Reagents:*** *i) MCPBA, THF/$H_2O$, RT, 18h. ii) Hydroxylamine sulfate, THF/$H_2O$/EtOH, Δ, 36 h, 94% from* **2** *based on 90% of conversion yield in (ii). iii) NMO, $OsO_4$, Acetone/$H_2O$, RT, 6 h, 94%. iv) a: DMSO, oxalyl chloride, $CH_2Cl_2$, -60°C, 1h. b: TEA, RT, 30 min, 66%* **6**, *13%* **14**. *v) O-Benzyl hydroxylamine hydrochloride, anhydrous $Na_2SO_4$, $CH_2Cl_2$, RT, 1h, 78%. vi) MsCl, pyridine, RT, 18h, 82%. vii) $H_2$, Pd/C, EtOH, viii) $NaBH_3CN$, $TiCl_3$, MeOH, 4h, 68% from* **8**. *ix) Dioxane, Δ, 90%. x) $Ac_2O$, $CH_2Cl_2$, RT, 5 min, 79%. xi) DMSO, KOH, RT, 30 min, 42%.*

*Scheme 1. Synthesis of the azetidines* **11** *and* **12**.

The aldehyde **6** was unreactive toward amines, precluding reductive amination strategies, but condensation products could be obtained with hydroxylamine-type nucleophyles. Thus, formation of the protected,

stereochemically homogeneous, oxime 7, mesylation of the axial 5-hydroxyl and deprotection were uneventful, but the oxime to amine reduction turned out to be a difficult task, failing with the reagents commonly employed for this purpose [catalytic hydrogenation, dissolving metal reduction (Al(Hg), Zn-HOAc), $NiCl_2$-$NaBH_4$]. After considerable experimentation, a procedure using the couple $NaBH_3CN$-$TiCl_3$[16] was eventually established.[17] The amino-mesylate **9** was surprisingly stable, and the azetidine **11**[18] was only formed after refluxing in dioxane. Alternatively, the 20-acetamido mesylate **10** was smoothly cyclised by treatment with KOH in DMSO, affording the *N*-acetyl azetidine **12**.[19] As a side product, the 13-deacetyl derivative of **12** was also obtained (28 %). Both these *N*-acyl azetidines exist at room temperature as a mixture of amide rotamers.[20]




*Scheme 2. Possible mechanism for the formation of* **14**.

In taxane chemistry, mechanistic understanding generally lags behind synthetic advances,[7] and the synthesis of **11** and **12** is no exception. The difficulties encountered are undoubtedly related to the special features of the taxane skeleton. However, the way they were overcome (choice of reagents and amination strategies) will prove useful to the many ongoing projects devoted to the study of the chemical modification of antitumor taxoids.

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13. Also the 4,20-epoxide was refractory to nucleophilic opening in basic medium (*Cf.* Holton, R. *et al.* "Total Synthesis of Paclitaxel from Camphor" in *Taxane Anticancer Agents: Basic Science and Current Status* Georg, I. G.; Chen, T. T.; Ojima, I.; Vyas, D. M. Ed.; ACS Symposium Series 583, American Chemical Society, Washington D.C., **1995**, pp. 288-301). The poor electrophilicity of the primary C-20 carbon in the 4,20-epoxide and 20-tosylate is reminiscent of the poor nucleophilicity of the 19-hydroxyl (Margraff, R. M.; Bezard, D.; Bourzat, J.D.; Commerçon, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 233-236). The underlying cause is presumably a 1,3-diaxial interaction between C-19 and C-20. This contrasts to the easy opening of the 20(5)-oxetane, which is, however, an anchimerically assisted (4-acetyl) process (7).

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15. To further confirm the results of the spectroscopic assignment of **14**, the formyl group was chemoselectively hydrolysed ($NaHCO_3$) and the product compared with the C-5α alcohol obtained by treatment of the triol **5** with LTA in $CH_3CN$ (*Cf.* Chen, S.-H.; Huang, S.; Wei, J,; Farina, V. *Tetrahedron*, **1993**, *49*, 2805-2828.)
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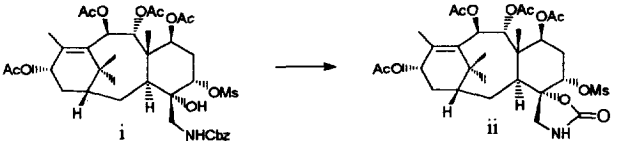
17. To a solution of oxime **7** (520 mg, 0.71 mmol) in ethanol (30 mL), Pd/C 10% (600 mg) was added. After stirring overnight at room temp. under hydrogen atmosphere, the suspension was filtered on celite and the solvent evaporated to give crude **8**. The latter was dissolved in methanol (20 mL), and $NaBH_3CN$ (162 mg, 2.6 mmol, 3.6 eq) and $NH_4Ac$ (500 mg) were added. A 15% solution of $TiCl_3$ (1.8 mL, 1.70 mmol, 2.4 eq) was then added dropwise. After stirring 4 h at room temp., the reaction was worked up by dilution with water and extraction with $CHCl_3$. The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallised ($CHCl_3$/ether) to give 302 mg **9** (68%) as a white solid.
18. All the $^1H$ and $^{13}C$ NMR spectra were assigned with the aid of NOE difference, HMQC and the HMBC spectra. **11**: $^1H$ NMR (500 MHz, $CDCl_3$, TMS as reference): δ 6.03 (d, J=11.0 Hz, H-10) 5.83 (d, J=11.0 Hz, H-9), 5.64 (brd, J=10.0 Hz, H-13), 5.24 (dd, J=7.4, 9.6 Hz, H-7), 3.84 (dd, J=10.0, 3.0 Hz, H-5), 3.42 (d, J=10.3, H-20a), 3.38 (d, J=10.3, H-20b), 2.80 (m, H-14a), 2.29 (m, H-6a), 2.18 (br s, H-3), 2.19 (s, H-18), 2.06 (m, H-2a), 1.99, 2.07, 2.09, 2.11 (s, Ac), 1.85 (m, H-6b), 1.80 (m, H-14b), 1.77 (m, H-1), 1.59 (m, H-2b), 1.58 (s, H-17), 1.44 (s, H-19), 0.96 (s, H-16); $^{13}C$ NMR δ 39.2 (d, C-1), 27.5 (t, C-2), 44.2 (d, C-3), 76.6 (s, C-4), 62.8 (d, C-5), 35.9 (t, C-6), 72.9 (d, C-7), 45.4 (s, C-8), 75.6 (d, C-9), 71.6 (d, C-10), 138.2 (s, C-11), 136.5 (s, C-12), 70.0 (d, C-13), 31.8 (t, C-14), 38.8 (s, C-15), 33.7 (q, C-16), 25.7 (q, C-17), 16.3 (q, C-18), 13.0 (q, C-19), 53.2 (t, C-20), 21.4, 21.1, 21.0, 20.8 (q, Ac), 170.4, 170.3, 169.0, 168.9 (s, Ac).
19. Attempts to cyclise **12** with other bases (NaH/cat.TBAI, KO*t*Bu/18-crown-6) afforded mainly the 13-deacetyl derivative of **10**. Under these conditions, the *N*-Cbz derivative (i) of **9** gave the 4,20 cyclic carbamate (ii).




20. Data for the 13-deacetyl derivative of **12** as representative. Major amide rotamer (57%): $^1H$ NMR (500 MHz, $CDCl_3$, TMS as reference): δ 6.03 (d, J=11.0 Hz, H-10), 5.80 (d, J=10.7 Hz, H-9), 5.25 (dd, J=7.0, 10.7 Hz, H-7), 4.33 (br d, J=9.5 Hz, H-13), 4.17 (dd, J=3.7, 10.3 Hz, H-5), 3.95 (d, J=8.5, H-20a), 3.75 (d, J=9.6, H-20b), 2.78 (m, H-14a), 2.60 (d, J=5.5 Hz, H-3), 2.43 (m, H-6a), 2.16 (br s, H-18), 2.06, 2.05, 1.98, 1.85 (s, Ac), 2.00 (m, H-6b), 1.94 (m, H-14b), 1.75 (m, H-1), 1.54 (s, H-17), 1.38 (m, H-2), 1.14 (s, H-19), 0.92 (s, H-16); $^{13}C$ NMR δ 39.4 (d, C-1), 27.6 (t, C-2), 42.5 (d, C-3), 72.5 (s, C-4), 65.4 (d, C-5), 31.9 (t, C-6), 72.1 (d, C-7), 45.1 (s, C-8), 75.3 (d, C-9), 72.1 (d, C-10), 136.7 (s, C-11), 136.7 (s, C-12), 68.0 (d, C-13), 33.5 (t, C-14), 38.3 (s, C-15), 35.1 (q, C-16), 25.4 (q, C-17), 17.2 (q, C-18), 12.9 (q, C-19), 59.0 (t, C-20), 21.3, 21.1, 20.8, 19.4 (q, Ac), 170.1, 169.3, 170.5, 171.2 (s, Ac); Minor amide rotamer (43%): $^1H$ NMR: δ 6.02 (d, J=11.0 Hz, H-10), 5.81 (d, J=11.0 Hz, H-9), 5.30 (dd, J=6.6, 10.7 Hz, H-7), 4.32 (br d, J=9.5 Hz, H-13), 4.22 (dd, J=3.3, 9.2 Hz, H-5), 3.84 (d, J=10.3, H-20a), 3.67 (d, J=11.0, H-20b), 2.78 (m, H-14a), 2.60 (d, J=5.5 Hz, H-3), 2.43 (m, H-6a), 2.16 (s, H-18), 2.10, 2.05, 1.98, 1.87 (s, Ac), 2.00 (m, H-6b), 1.94 (m, H-14b), 1.75 (m, H-1), 1.55 (s, H-17), 1.38 (m, H-2), 1.13 (s, H-19), 0.92 (s, H-16); $^{13}C$ NMR δ 39.2 (d, C-1), 27.5 (t, C-2), 42.5 (d, C-3), 72.6 (s, C-4), 67.1 (d, C-5), 33.2 (t, C-6), 72.1 (d, C-7), 45.0 (s, C-8), 75.2 (d, C-9), 72.9 (d, C-10), 136.9 (s, C-11), 136.9 (s, C-12), 68.1 (d, C-13), 33.5 (t, C-14), 38.4 (s, C-15), 35.0 (q, C-16), 25.4 (q, C-17), 17.1 (q, C-18), 13.2 (q, C-19), 56.7 (t, C-20), 21.3, 21.1, 20.8, 19.8, (q, Ac), 171.5, 170.3, 170.1, 169.4 (s, Ac).

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