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Taxol Structure–Activity Relationships: Synthesis and Biological Evaluation of 10-Deoxytaxol

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Summary: 10-Deoxytaxol **2** was prepared from taxol (**1**) in four steps via the intermediate dienone **5b**; the key reaction in the sequence is a Yarovenko reagent-mediated dehydration at the C-10 hydroxyl group. Compound **2** was found to possess comparable antitumor activity with respect to taxol. This confirms that the functional group at C-10 in taxol is not involved in receptor binding.

The novel diterpenoid taxol (**1**), a promising anticancer agent,[1] is isolated from a variety of yew trees in only limited quantities. The exciting therapeutic profile of this compound, combined with its limited availability, have made it the subject of intensive synthetic investigations, including structure–activity relationship (SAR) studies.[2] On the basis of the assumption that not all the functional groups in the heavily oxygenated taxol core are involved in its binding to microtubules, we have initiated a systematic program aimed at deleting some of the oxygen-containing functionalities in order to assess their contribution to binding.[3] In this paper we would like to report the synthesis and biological evaluation of 10-deoxytaxol **2**.

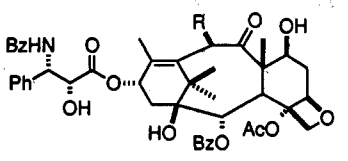
Our synthesis began with 10-desacetyltaxol (**3**) (see Scheme I) which was obtained by Lewis acid-promoted methanolysis of taxol.[4] Compound **3** was then treated with a slight excess of trichloroethyl chloroformate to give the doubly protected derivative **4** in modest yield, accompanied by some unreacted starting material (25%), as well as traces of the triply protected compound.

After extensive efforts to effect functionalization at C-10, we found that treatment of **4** with Yarovenko's reagent[5] ($ClFHCCF_2NEt_2$) in dichloromethane at rt cleanly yielded dienone **5a**, together with a small amount of fluorinated enone **6a**. This reaction is remarkable since Yarovenko's reagent is a fluorinating agent, and dehydration products are rarely obtained.[6] Furthermore, no 10-fluoro derivative

Table I. Biological Evaluation of Taxol Analogs

compd	tubulin polymerization: rel initial slope[a] (%)	HCT116 IC_{50}[b] (μM)
taxol	100	0.004
5b	106	0.030
6b	125	0.031
2	143	0.007

[a] Relative initial slope = 100 × initial slope (analog)/initial slope (10 μM taxol). Employed in assay: 1.5 mg/mL of microtubule protein, 10 μM drug (1% DMSO). [b] Drug concentration required to inhibit cell proliferation to 50% vs untreated cells (incubated at 37 °C for 72 h). All data are the average of three determinations.

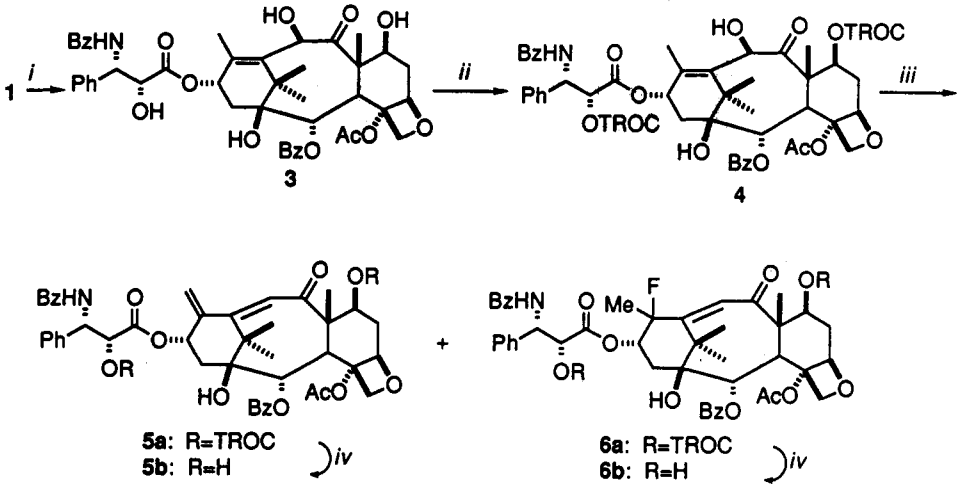


1: R=OAc, *Taxol*
2: R=H, *10-deoxy taxol*

(1) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.
(2) For a review on the chemistry of taxol, see: Kingston, D. G. I. *Pharm. Ther.* **1991**, *52*, 1.
(3) For the synthesis of 2-deoxytaxol, see: Chen, S. H.; Wei, J. M.; Farina, V. *Tetrahedron Lett.*, in press.
(4) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114. See also: Chen, S. H.; Huang, S.; Farina, V. *Tetrahedron*, in press.
(5) Yarovenko, N. N.; Raksha, M. A. *J. Gen. Chem. USSR* **1959**, *29*, 2125. For a review, see: Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 125.

0022-3263/93/1958-2927$04.00/0

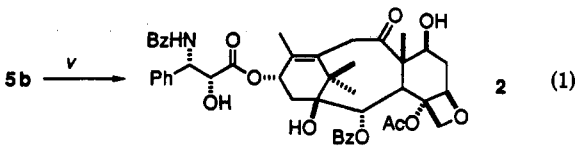
Scheme I[a]



[a] Reagents and conditions: (i) $ZnBr_2$/MeOH/rt (36%); (ii) TROCCl/pyr/CH_2Cl_2/0 °C (46%); (iii) Et_2NCF_2CHFCl/CH_2Cl_2 (47% of **5a**; 13% of **6a**); (iv) Zn/MeOH + AcOH/40 °C (81% of **5b**; 80% of **6b**).

was obtained, fluorination taking place with allylic transposition at C-12, apparently in a stereospecific fashion.[7] Removal of the protecting group from **5a** and **6a** was accomplished with zinc in a mixture of acetic acid[8] and methanol, to afford **5b** and **6b** in high yields.

Finally, **5b** was found to readily absorb 1 molar equiv of hydrogen under palladium catalysis to afford directly 10-deoxytaxol **2** in good yield (eq 1).



(1)

Reagents and conditions: (v) H_2(1 atm)/Pd/C/EtOAc/R.T.(68%).

Biological evaluation of the new taxanes was carried out by measuring the initial rate of tubulin polymerization in a spectrophotometric assay,[9] as well as by a standard cytotoxicity assay in a sensitive cell line (HCT 116, a human colon carcinoma). The data are shown in Table I. The three new compounds described in this paper, and especially **2**, have the ability to polymerize tubulin at equal or faster rate than taxol, on an equimolar basis. The cytotoxicity of **5b** and **6b**, however, is slightly diminished with respect to taxol. On the other hand, 10-deoxytaxol is essentially as cytotoxic as taxol, confirming that the functional group at C-10 is not involved in interactions at the binding site. Previous structure–activity studies[2] at this position are very limited but are compatible with our findings. The above results also suggest that modification in the C-11/C-12 segment of the core may lead to slightloss of biological activity. Further SAR studies are in progress and will be reported shortly.

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Supplementary Material Available: Full experimental details and ^{1}H-NMR data for all new compounds (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6) Examples of dehydration in the steroid field are reported in: Knox, L. H.; Velarde, E.; Berger, S.; Cuadriello, D.; Cross, A. D. *J. Org. Chem.* **1964**, *29*, 2187.

(7) The product was homogeneous by NMR spectroscopy, but the configuration at C-12 was not established.

(8) Without acetic acid, epimerization at C-7 is a serious side reaction. Acetic acid is used to prevent this side reaction.

(9) The assay was performed using methods described in: Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176.