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TAXOL STRUCTURE-ACTIVITY RELATIONSHIPS: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-DEOXYTAXOL

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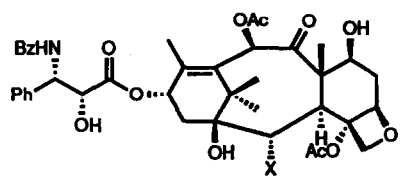
Abstract: *2-Deoxy taxol 2 was prepared in nine steps from baccatin III; the key step of the synthesis is a Barton-type deoxygenation at C-2. The compound was found to possess much reduced antitumor activity with respect to taxol.*

The anticancer drug taxol (1) has shown excellent clinical activity against a number a tumors, [1] but structure-activity relationship studies in this area have been few. [2] Guided by the assumption that not all the functional groups in this densely oxygenated molecule are involved in binding to the microtubule receptor, we have begun a program aimed at systematically removing selected substituents in the tetracyclic core in order to evaluate their contribution to the biological activity. So far, no information is available concerning the role of the C-2 benzoate in receptor binding, since no derivatives at this position have been described. We describe here the first member of this class of taxol analogs, *i.e.* 2-deoxy taxol.

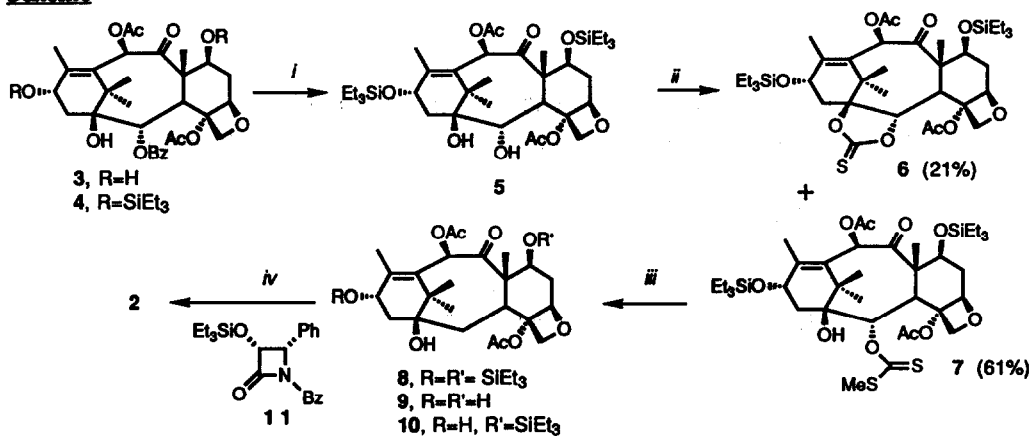


1, X= OCOPh (taxol)
2, X=H

Silylation of Baccatin III, 3, led to 4 (see Scheme), which was debenzoylated in low yield[3] to produce 5. Formation of the C-2 xanthate 7 was complicated by the formation of cyclic thionocarbonate 6, but under carefully controlled conditions, the production of 6 could be minimized. [4] Treatment of 7 with tributyltin hydride [5] led cleanly to 2-deoxy derivative 8. Unfortunately, selective desilylation at C-13 was not successful, and therefore two steps were necessary to obtain 10, the substrate for side-chain attachment. Acylation according to the method of Holton,[6] followed by desilylation, finally gave the desired 2.

Our synthetic 2 showed modest *in vitro* cytotoxicity in a human colon cancer line (HCT116: IC_{50}, 0.48 μg/ml, taxol 0.004 μg/ml). Its ability to polymerize tubulin *in vitro* was below measurable levels. We can therefore conclude that the C-2 benzoate plays an essential role in the binding of taxol to its receptor. Studies aimed at further C-2 modifications are in progress.

Scheme



Conditions: 3 to 4: Et_3SiCl, imidazole, rt (90%); (i) MeONa, MeOH, rt (25%); (ii) NaH (1.2 eq.), THF/CS_2 5:1, then MeI, rt; (iii) 0.05M 7, Bu_3SnH (2 eq.), AIBN, PhMe, 100°C (89% of 8); then Bu_4NF,THF, rt (85% of 9); then Et_3SiCl,imidazole, DMF, 0°C (85% of 10); (iv) BuLi (1.1 eq.), THF, -40°C, then 11, 0°C; then Bu_4NF, THF, rt (63% overall).

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