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Synthesis, biology, and modeling of a C-4 carbonyl C,D-*seco*-taxoid

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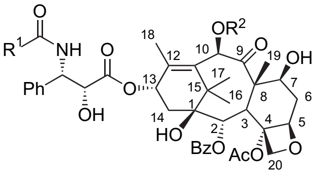
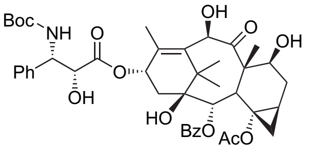
Dedicated with profound respect and affection to the memory of Professor Pierre Potier

Abstract—A C,D-*seco*-paclitaxel derivative **26** was prepared from taxine and tested for biological activity. Chemical reactivity of the *seco*-compounds proved to be substantially modified, with respects to taxoids. The corresponding C,D-*seco*-taxoid does not show tubulin stabilizing activity or cytotoxicity. Explanation of these observations based on molecular modeling is provided.

1. Introduction



1 Paclitaxel R^1=Ph, R^2=Ac
2 Docetaxel R^1=O^{t}Bu, R^2=H



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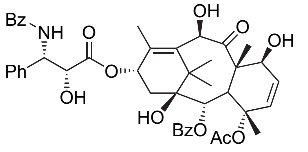

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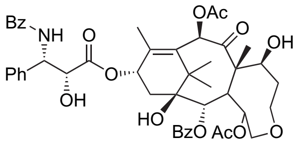

5 C,D-*seco*-Paclitaxel

Taxol **1**[1,2] and Taxotere **2**[2,3] are currently considered as the most efficient therapeutic agents for the treatment of several types of cancer. In order to understand better their unique mechanism of action, which would allow for design of the analogs of reduced structural complexity, yet with improved properties (i.e., higher activity, better solubility, activity against multidrug-resistant (MDR) tumors, etc.), extensive structure–activity relationship (SAR) studies have been performed. These studies indicated that the oxetane ring may be one of the crucial structural units of biologically active taxoids; its exact role, however, remained a matter of debate.[4] According to one explanation, the four-membered ring may serve purely as a rigidifying element, that imposes a proper conformational bias to the taxane core, thus forcing the functional groups at C-2, C-4, and C-13 to assume the appropriate positions for productive interactions with tubulin receptor. Alternatively, electronic effects may be important, with the heteroatom being involved in stabilizing dipolar, or hydrogen bonding, interactions with tubulin protein. For both hypotheses—'conformational' and 'electronic'—experimental support exists, as well as some contradictory data. Thus, substitution of oxygen in ring D by nitrogen,[5] sulfur,[6] or selenium[6b] results in the loss of activity, although the geometries of the corresponding azetidine, thietane, and selenetane derivatives do not differ very much, as compared to the parent oxetane. These findings infer the prevalence of the electronic factors. On the other hand, the lack of bioactivity of most of D-*seco*-taxoids with various degree of oxygenation at positions C-4, C-5, and C-20, suggests that the role of the oxetane ring may be 'the conformational lock' of the diterpene scaffold.[7,4b] In line with this hypothesis, a taxoid **3**, containing cyclopropane ring in place of oxetane, showed the tubulin polymerizing activity comparable to that of docetaxel.[8] Recently, it was shown that, contrary to long

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lasting belief, no ring D is required for tubulin polymerizing activity of taxoids: on the basis of molecular modeling it was predicted that **4** would have a strong microtubule stabilizing activity, which was subsequently experimentally confirmed.[9] However, it should be noted that both **3** and **4** are at least by two orders of magnitude less cytotoxic with respect to paclitaxel or docetaxel; thus, while not necessary for the tubulin stabilizing activity, the oxetane ring still might be essential for cytotoxicity.

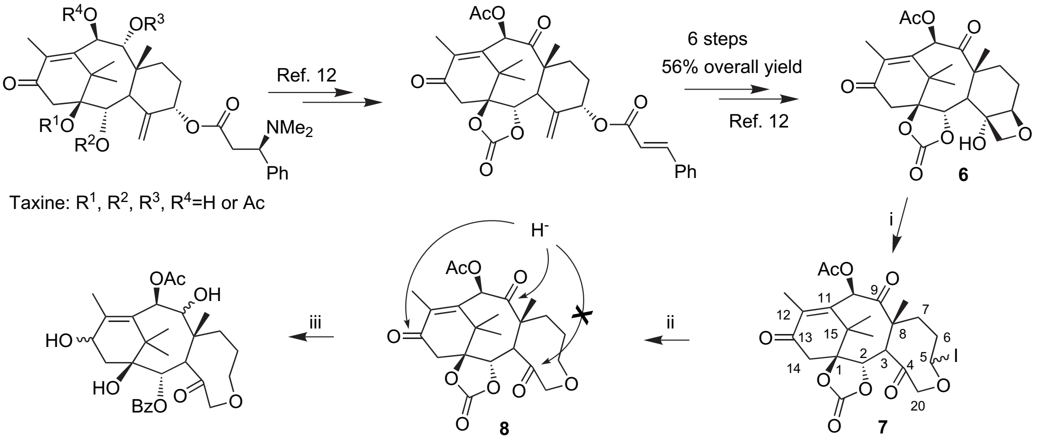
2. Results and discussion

In order to discern between the conformational and electronic effects of the oxetane ring, we endeavored to synthesize a C,D-*seco*-taxoid of type **5** and to evaluate its biological activity. While conformationally more flexible, the *seco*-derivative maintains the functionalization pattern of paclitaxel. The lack of biological activity of the compound would point to a conformational constraint as the principal (if not the sole) effect of the oxetane ring; on the contrary, eventual cytotoxicity of the *seco*-derivative would indicate the importance of the oxygenation pattern (i.e., the electronic effect of the oxetane oxygen atom). We decided to perform our study on 7-deoxy-taxoids: given that a 7-hydroxyl group is not required for cytotoxicity,[10] synthetic transformations could be performed on derivatives that require less protective group manipulation. In addition, others[11] and we[12] have shown that taxine B[13]—a pseudoalkaloid readily isolated from the renewable needles of the European yew (*Taxus baccata*)—constitutes a suitable starting material, amenable to structural patterns relevant for this study.[14]

Our initial plan called for the scission of the central C-4–C-5 bond in previously described alcohol **6**,[12] via a fragmentation of the corresponding alkoxyl radical (Scheme 1). After some experimentation, the iodine-transfer fragmentation was cleanly effected using diacetoxyiodobenzene (DIB)/iodine reagent under photolytic conditions.[15] Subsequent reduction with tributyltin hydride (TBTH) afforded the desired intermediate **8** in good yield. For the reaction to proceed efficiently, a high concentration and an excess of TBTH are needed (under the conventional conditions for reductions with TBTH, rearrangements occur and unidentified products are formed). This skeletal transformation reversed the order of reactivity of carbonyl groups, with respect to the parent taxane: while C-9 carbonyl group in paclitaxel is resistant even to $LiAlH_4$,[16] in 4,5-*seco*-derivative it underwent rapid, but stereorandom reduction with $NaBH_4$, as well as C-13 carbonyl. On the contrary, the newly formed ketone at C-4 proved resistant toward $NaBH_4$, $NaBH_4/CeCl_3$, or $NaBH_3CN$, while a large excess of $NaBH_4$ resulted in decomposition of material.

In order to overcome this difficulty, the target structure was modified by substituting the C-9 α-acetate for the C-9 carbonyl group: a change that should simplify the synthetic procedure without affecting the biological activity of the final product (Scheme 2).[17] After the acetylation of a mixture of cinnamoyltaxicines **9** and **10**, selective removal of the cinnamoyl side chain in **10**, in the presence of two acetate units and a cyclic carbonate, was accomplished using our previously developed procedure:[12] dihydroxylation of **11** with OsO_4 resulted in stereoselective introduction of two requisite hydroxyl groups into the taxane core, while simultaneously activating (by intramolecular hydrogen bonding in **12**) the intermediate 2,3-dihydroxy-3-phenylpropanoate side chain toward alcoholysis in a buffered methanolic solution. The resulting triol **13** was converted into oxetane **17** by a slightly modified four-step protocol developed by the CNRS group[11a] (the cyclization step had to be performed with DIPEA in refluxing toluene; the reagents described in the literature proved unsuccessful). Alternatively, the conversion of **11** into the advanced cyclization precursor **16** could be effected via a three-step procedure based on hydroxylamine promoted selective cinnamate cleavage.[6a,18] The latter route is shorter and avoids the use of protective groups; however, the overall yield of **17** is lower (calculated yields for the transformation **11**→**17**, via tetraol **12**: 38%; via allylic alcohol **18**: 23%).

With compound **17** in hand, several reagents for the generation of tertiary alkoxyl radicals were tried for the fragmentation step. Surprisingly, the major product in the reaction with DIB/iodine was acetate **19** (29%), accompanied by the desired iodide **20** (17%); this is in sharp contrast to the same reaction with **6**, which proceeded in 73% yield without



Scheme 1. Reagents and conditions: (i) $PhI(OAc)_2$ (1.5 equiv), I_2 (1.5 equiv), benzene, 15 °C, 250 W Xenophot lamp, 73%; (ii) Bu_3SnH (10 equiv, 0.4 M), benzene, 15 °C, 250 W Xenophot lamp, 80%; (iii) $NaBH_4$, $CeCl_3$, EtOH, rt.