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The Chemistry of the Taxane Diterpene: Stereoselective Synthesis of 10-Deacetoxy-11,12-epoxypaclitaxel

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Abstract: Epoxidation of the olefin in 10-deacetoxybaccatin III (**6**) and 10-deacetoxypaclitaxel (**9**) was accomplished with *meta*-chloroperbenzoic acid leading to a novel pentacyclic ring system. Hydroxyl directed delivery of the epoxidizing agent did not appear to play a role in the stereoselectivity of the reaction as epoxidation occurred at the β-face of the molecule. 10-Deacetoxy-11,12-epoxypaclitaxel (**10**) proved to be more active than paclitaxel (**1**) in the microtubule assembly assay and three-fold less cytotoxic than paclitaxel against B16 melanoma cells.

The highly functionalized naturally occurring diterpene paclitaxel (**1**) was isolated from the bark of the Pacific yew tree in 1971.[1] Paclitaxel has been successfully used in the treatment of several forms of cancer including cisplatin refractory ovarian cancer, metastatic breast cancer, head and neck cancer, and a wide variety of other forms of cancer.[2-4] The search for the paclitaxel pharmacophore continues in hopes of finding second generation taxanes with outstanding biological properties.[5,6]

Chemistry of this complex molecule has been reported for all areas of the molecule[4,7-9] including the *N*-benzoyl-3-phenylisoserine side chain at C13, the esters at C2, C4 and C10, the hydroxyl at C7, reduction of the C9 ketone, but chemistry at the C11/C12 olefin of paclitaxel has not been pursued extensively. Due to steric hindrance, the double bond has proven to be fairly resistant to chemical modification. For example, catalytic (Pt/C) hydrogenation of paclitaxel and baccatin III results in the reduction of the aromatic rings but leaves the C11 double bond intact.[10,11] However, recently it was reported that the double bond of 13-oxobaccatin III can be reduced with zinc in acetic acid.[12,13] The C11 double bond of the baccatin moiety is also inert to ozonolysis.[14]

The chemistry of the 11,12-olefin of the A-ring of paclitaxel continues to be an area of interest for synthetic manipulations. The two planar sp^2 carbons lock this ring into a pseudoboat-like conformation, contributing significantly to the overall cage- or cup-like conformation of the diterpene ring system.[15,16] The A-ring also appears to play an important role in the positioning of the *N*-benzoyl-3-phenylisoserine side chain underneath the diterpene in close proximity to the C2 benzoate and the C4 acetate, a functionality that is crucial for biological activity.[17,18] Synthetic manipulations at the 11,12-olefinic centers would allow for a significant change in the overall conformation of the molecule. We herein report on the chemistry of the 11,12-olefin of the taxane diterpene.

Initially our goal was to utilize the naturally occurring paclitaxel precursor baccatin III (**2**) as the starting diterpene for the formation of the targeted 11,12-epoxypaclitaxel. We envisioned that the epoxidation could be directed by the allylic 13-hydroxyl group leading to the formation of an α-oxirane. On the other hand

utilization of 10-deacetylbaccatin III (**3**), another naturally occurring diterpene which has two allylic hydroxyls, one on the top face of the olefin (at C10) and one on the bottom face of the olefin (at C13), could provide α- and/or β-oxiranes. When baccatin III (**2**) was reacted with 60% *meta*-chloroperbenzoic acid (MCPBA) 13-oxobaccatin III (**4**) was formed quantitatively via allylic oxidation (Scheme 1). No products resulting from reaction at the 11,12-olefin were detected. Treatment of 10-deacetylbaccatin III (**3**) with 60% MCPBA also caused allylic oxidation to the 13-keto product **5**. In order to invoke reaction at the sterically hindered tetrasubstituted olefin, we targeted 10-deacetoxybaccatin III (**6**) for reaction with MCPBA. Facile deoxygenation of baccatin III was accomplished with SmI_2 resulting in the quantitative formation of **6**.[19] Reaction of **6** with 60% MCPBA in EtOAc provided 10-deacetoxy-11,12-epoxy-7-*epi*-baccatin III (**7**) in quantitative yield. No Baeyer-Villiger products were detected. Epimerization at the 7-position can be attributed to an acid catalyzed retro-aldol reaction[20,21] initiated by the 60% MCPBA/benzoic acid mixture. It is of note that a substituent at C10 apparently prevents this facile epimerization, since no C7 epimerized products were observed in the reaction of baccatin III (**2**) and 10-deacetylbaccatin II (**3**) with the 60% MCPBA/benzoic acid mixture. Use of 100% MCPBA accelerated reaction rates, 15 h utilizing 60% MCPBA vs. 3 h with the purified reagent. Under these conditions the acid catalyzed epimerization at C7 did not take place and epoxide **8** was formed. The absolute stereochemistry of epoxide **7** was verified through NOE studies, which showed that the oxirane resided on the β-face of the molecule.[22] The stereochemistry of the oxirane suggests that the epoxidation is not directed by the allylic hydroxyl, but controlled by the approach of the reagent from the least hindered β-face of the 11,12-olefin. Oxiranes **7** and **8** proved to be unstable and decomposed slowly at room temperature. We believe that the instability of the oxiranes may be due to side reactions as a result of a Pane rearrangement (attack of the 13-hydroxyl group at the epoxide moiety).

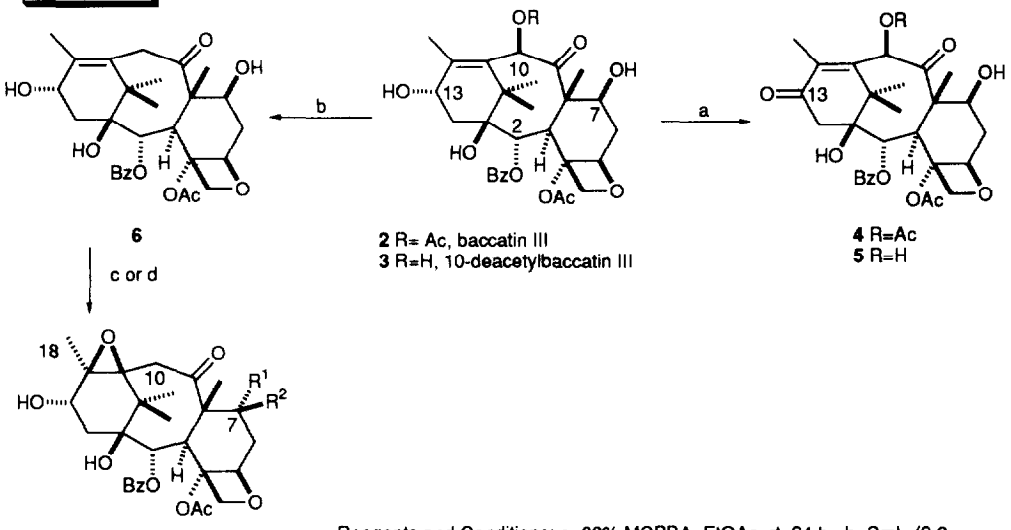
In order to avoid this problem and to arrive at the product more directly, we applied the chemistry to paclitaxel (**1**). Deacetoxylation of paclitaxel was accomplished in 90% yield using SmI_2 to afford 10-deacetoxypaclitaxel (**9**),[19] which possesses bioactivity similar to paclitaxel.[5] Reaction of **9** with 100% MCPBA resulted in the formation of stable 10-deacetoxy-11,12-epoxypaclitaxel (**10**), quantitatively.[22,23] No Baeyer-Villiger or 7-epimerization products were detected. Oxiranes **7**, **8** and **10** are the first taxane 11,12-epoxides which are functionalized at C13 and possess the paclitaxel CD-moiety.[24,25]

An overlay of minimized structures[26,27] of taxol and epoxide **10** (Figure) suggested that no significant conformational changes should occur as a result of the epoxidation of the 11,12-double bond. The results of our calculations were found to be in agreement with NOE's and coupling constant values of **10**, which are very similar to those found in paclitaxel.[17]

Epoxypaclitaxel **10** was tested for its bioactivity in two assays. Compound **10** was found to be more active ($ED_{50}/ED_{50(paclitaxel)} = 0.66$) than paclitaxel in the microtubule assembly assay and about three-fold less cytotoxic ($ED_{50}/ED_{50(paclitaxel)} = 3.2$) against murine B16 melanoma cells in comparison to paclitaxel.[28]

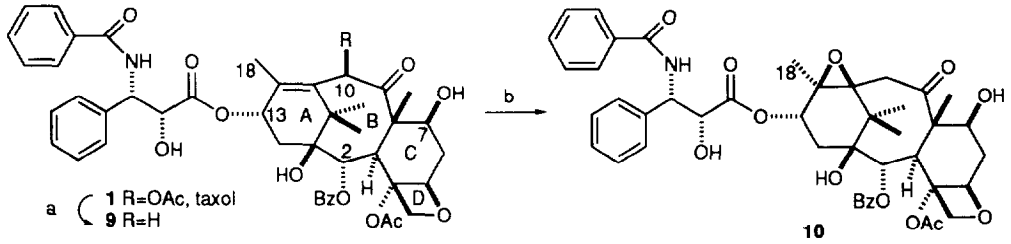
The study demonstrated that epoxidation at the C11 double did not change the overall conformation of the taxane moiety and that additional bulk on the β-face at C11/C12 is tolerated at the taxol binding site on tubulin. The reduced cytotoxicity of **10** against B16 melanoma cells suggests that uptake or metabolism of **10** is different from paclitaxel for this cell line.

Scheme 1



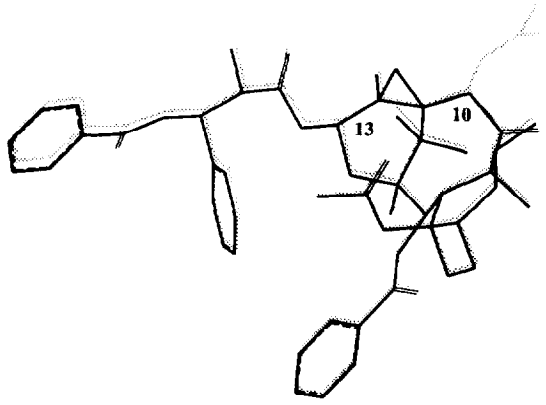
Reagents and Conditions: a. 60% MCPBA, EtOAc, rt, 24 h. b. SmI_2 (2.2 equiv), HOAc (1.5 equiv), anhydrous THF, rt,10 min. c. 60% MCPBA (10 equiv), EtOAc, rt, 15 h. d. 100% MCPBA (10 equiv), EtOAc, rt, 3 h.

Scheme 2



Reagents and Conditions: a. SmI_2 (2.2 equiv), HOAc (1.5 equiv), anhydrous THF, rt, 10 min.
b. 100% MCPBA (10 equiv), EtOAc, rt, 3 h.

Figure. Overlay of minimized taxol (**1**) and epoxide **10** (bold). Hydrogens and oxygens are omitted for clarity.



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