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A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol® Analogues

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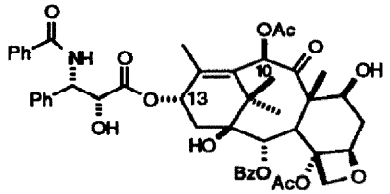
Abstract : *A chemoselective approach to functionalize the C-10 position of 10-deacetyl baccatin III, a key intermediate for the semi-synthesis of paclitaxel, is described. The chemistry provides an easy access to a variety of C-10 hydroxyl derivatives, such as, ethers, esters, carbonates, carbamates, and sulfonates under mild conditions. The C-10 modified baccatin derivatives were further employed in the synthesis of novel biologically active Taxol® analogues.*

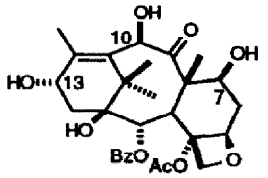
Taxol ® (paclitaxel) (**1**), a complex antineoplastic diterpene isolated from *Taxus brevifolia*,[1] has recently been approved for the treatment of metastatic carcinoma of the ovary.[2] Paclitaxel inhibits cell replication in the mitotic phase of the cell cycle by promoting polymerization of microtubules which are stable and abnormally resistant to depolymerization.[3] In recent years, the clinical importance of paclitaxel has prompted the synthesis of novel analogues with the goal of designing more effective antitumor drugs.[4]

With the aim of obtaining drugs having more desirable properties than the prototype, we were interested in replacing the C-10 acetate moiety with other functionalities. Recently, few publications have appeared in the literature describing the chemistry at the C-10 position of paclitaxel or on its naturally occuring semi-synthetic precursor, 10-deacetyl baccatin III (10-DAB) (**2**). The C-10 hydroxyl group has been deoxygenated under Barton's condition to synthesize 10-deoxy analogues of paclitaxel;[5] simple carbamates have been prepared by reacting C-10 trichloroethyloxy carbonyl (TROC) derivative of paclitaxel with primary amines [6]; other studies include: acetylation and protection (as a TROC ester) of the C-10 hydroxyl group in 10-DAB.[7]

For our planned studies, 10-DAB (**2**) was envisioned to be the ideal starting material. The synthetic manipulations at C-10 appeared to be much easier without the C-13 phenylisoserine side chain, furthermore, the side chain can always be introduced at a later stage by using a variety of published procedures.[4] This letter describes our studies on 10-DAB, which includes: chemoselective approach to functionalize the C-10 position; synthesis and biological evaluations of novel paclitaxel analogues.



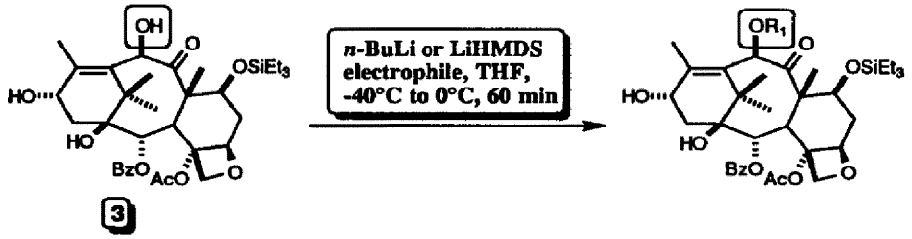
Paclitaxel (1)



10-DAB (2)

In view of the NMR studies and molecular mechanics calculations it is reasonable to assume that the C-13 hydroxyl group is sterically congested due to its location inside the skeletal concavity of 2. The study has also revealed the possibility of a hydrogen bonding between the C-13 hydroxyl group and the C-4 acetate moiety.[8] Hence, with the more reactive C-7 hydroxyl protected, an opportunity was available to *selectively deprotonate* the C-10 hydroxyl to generate an alkoxylithium anion which upon treatment with various electrophiles might afford the C-10 derivatives. To demonstrate this concept, 3 [9] was treated with 1.05 equiv of *n*-BuLi at -40°C in THF followed by the addition of 1.2 equiv of acetyl chloride. After 60 min at 0°C the reaction afforded 7-triethylsilyl baccatin III (4). This method was an improvement over existing Greene's acetylation method[7c] which employed an excess of reagents and longer reaction time. The reaction was found to be quite general allowing us to introduce a variety of functionalities (esters, ethers, carbonates, carbamates, and sulfonates) at the C-10 position of baccatin in moderate to high yields by simply treating the C-10 alkoxyanion with different electrophiles (Table I).

Table I



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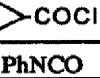
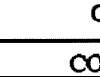
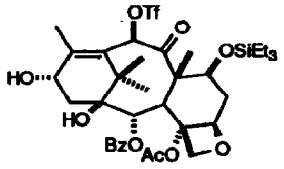
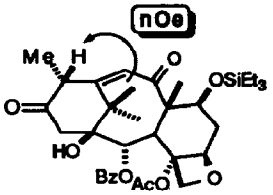
Baccatin	Electrophile	R_1	Yield %
4	AcCl	$COCH_3$	90
5	BzCl	COC_6H_5	85
6	*n*-C_4H_9COCl	COC_4H_9	75
7	Me_2SO_4	Me	85
8			78
9	PhNCO	$CONHC_6H_5$	78
10	Me_2NCOCl	$CON(Me)_2$	72
11	$MeSO_2Cl$	SO_2CH_3	68
12	MeOCOCl	CO_2Me	75



13



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An attempt to isolate the triflate **13** by reacting the C-10 alkoxy anion with *N*-phenyltrifluoromethanesulfonimide was unsuccessful under our reaction protocol. Instead, the reaction afforded the enone **14**, presumably arising from the labile triflate **13** *via* an allylic carbocationic intermediate. The stereochemistry at the C-12 position was assigned based on nOe experiments. A strong interaction was observed between the C-12 proton and C-17 methyl protons which led us to assign α-methyl configuration at the C-12 position. To synthesize our target analogues, the C-10 baccatin derivative was treated with 1.10 equiv of LiHMDS or *n*-BuLi followed by the addition of β-lactam at low temperature.[10] After isolating the C-13 acylated paclitaxel derivative, the analogue was subjected to acidic conditions to remove the two silyl (2' & 7) protecting groups. Following this protocol, a variety of C-10 paclitaxel analogues were synthesized (Scheme I, Table II).[9] All new analogues were evaluated in tubulin polymerization [3] and *in-vitro* cytotoxicity assays performed using the HCT 116 human colon carcinoma cell lines (Table II).[11]

Scheme 1

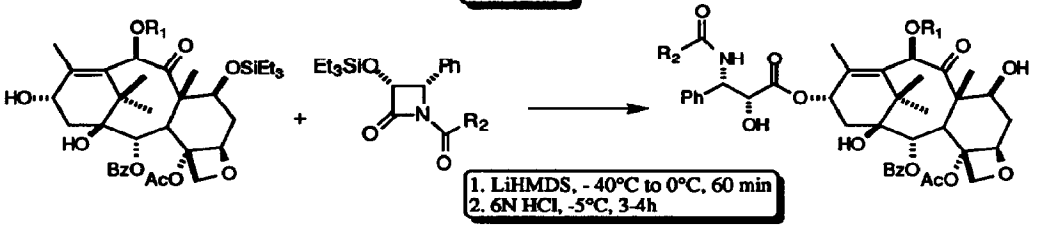

Table II

Paclitaxel Analogue	R_1	R_2	% Yield	Tubulin Ratio[a]	IC_{50} (nM)[b] HCT 116
Taxol®	Ph	Ph	-	1.0	2.0
15	COMe	OBu^t	80	0.7	2.0
16	COBu	Ph	78	1.5	3.4
17		Ph	85	1.1	2.3
18	$CON(Me)_2$	Ph	88	1.0	1.1
19	Me	Ph	73	1.0	12.0
20	Me	OBu^t	83	0.3	1.3
21	CO_2Me	Ph	76	1.1	3.0
22	CO_2Me	OBu^t	83	0.8	1.5
23	COPh	Ph	82	19	2.2
24	COPh	OBu^t	74	2.1	2.0

a=Ratio of analogue relative to paclitaxel ($EC_{0.01}$ @ 5 μM).

b=Drug concentration required to inhibit cell proliferation to 50% vs. untreated cells (incubated at 37°C for 72 h).

All new compounds displayed cytotoxic properties (Table II). Analogues with C-10 methyl ether (**20**) or methyl carbonate (**22**) with Taxotere™ side chain (*i.e.*, 3'-NHBOC) were found to be more cytotoxic than paclitaxel (**1**) or 10-acetyl taxotere (**15**). These compounds also exhibited better tubulin binding properties. However, with the paclitaxel side chain, the corresponding C-10 modifications resulted in analogues (**19** & **21**) exhibiting tubulin binding similar to paclitaxel but less cytotoxic than the parent compound, with the exception of C-10 carbamate (**18**), which was found to be more potent than paclitaxel. The analogue with cyclopropyl ester (**17**) was as active as paclitaxel, but other esters, such as the *n*-butyl ester, displayed reduced cytotoxicity. Similarly, analogues with the C-10 benzoate ester (**23** & **24**) also exhibited cytotoxicity comparable to paclitaxel, especially with Taxotere™ side chain. In view of our studies, it is reasonable to suggest that the functional group present at the C-10 position does modulate the antitumor activity, which is quite contrary to some of the earlier predictions.[4] Further studies are in progress and full details will be published in due time.

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References and Notes

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9. Treatment of **2** with 3.0 equiv triethylsilyl chloride and imidazole in DMF at ambient temperature for 3h afforded **3** in 80% yield. Also see reference 7c for an alternate preparation. All new compounds were characterized fully by NMR, HRMS, and CHN analysis. We thank our Analytical Department for the services.

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