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Stereoselective Synthesis of 9β-Hydroxytaxanes via Reduction with Samarium Diiodide

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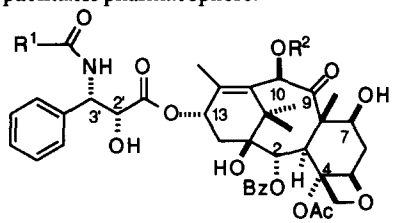
Abstract: Reaction of baccatin III and paclitaxel with samarium diiodide yielded the corresponding 10-deacetyl-9β-hydroxy derivatives. When 10-deacetylbaccatin III and docetaxel were subjected to the same reaction conditions the corresponding 9β-hydroxy and 10-dehydroxy-9β-hydroxy analogues were isolated.

The discovery of the potent anticancer agent paclitaxel (**1**),[1] recently approved by the FDA for the treatment of drug refractory ovarian cancer and advanced breast cancer, has not only stimulated further in-depth clinical evaluation[2] but also detailed chemical and biological studies[3] and investigations directed at the elucidation of the paclitaxel pharmacophore.[4-7]



R^1=Ph, R^2=Ac paclitaxel (**1**)
R^1=Bu^{t}O, R^2=H docetaxel (**2**)

Structure-activity studies have established that both the diterpene moiety and the C-13 phenylisoserine side chain are essential for the anticancer activity of paclitaxel.[1] The C-3' phenyl group or a closely related functional group is essential for strong cytotoxicity and the natural stereochemistry at the C-13 phenylisoserine side chain (2'*R*,3'*S*) is optimal for activity.[7-9] An *N*-acyl moiety such as benzoyl (paclitaxel) or *tert*-butoxycarbonyl (docetaxel) and others are needed for bioactivity.[7-9] Recent SAR studies have revealed that modifications at the northern part of the diterpene moiety (C-7 to C-10) are typically tolerated better than changes at the southern part (C-2 and C-4) of the molecule.[4-7,10]

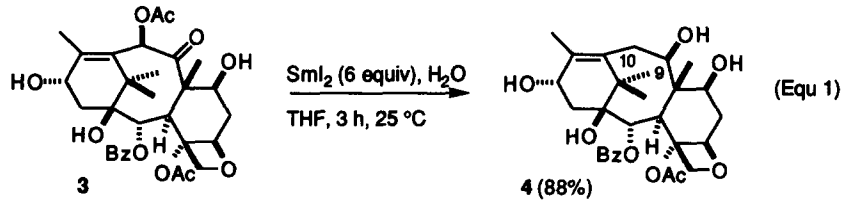
Only limited information has been available until very recently on the importance of the C-9 carbonyl group on biological activity. This is due to the fact that the sterically encumbered C-9 carbonyl group was found to be highly unreactive.[5] For example, the carbonyl group could not be reduced with sodium borohydride[5] or lithium aluminum hydride.[11]

The first report on a C-9 reduced paclitaxel derivative was provided by the Abbott group, which detailed the semisynthesis of 9α-hydroxypaclitaxel and related analogues.[12] These taxanes, obtained by semisynthesis from naturally occurring, C-9 reduced 13-acetyl-9α-hydroxybaccatin III,[12] displayed potent antitumor activity. This group was also able to prepare 9-deoxotaxane analogues from this natural product.[13] It was shown that 9-

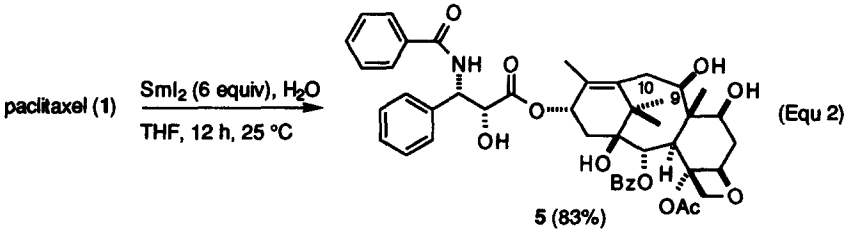
deoxotaxanes possess considerable cytotoxicity.[13] We recently reported on the synthesis of the first chemically modified C-9 carbonyl analogue, a cyclic carbonate, which was found to be inactive.[14] Py and collaborators were able to reduce the carbonyl group in a 7-epi-baccatin III derivative with diborane.[15] However, they were not able to effect the same transformation with baccatin derivatives possessing the natural C-7β stereochemistry. The recent reports by Commercon and collaborators[16] on the electrochemical reduction of docetaxel to the corresponding 9α- and 9β-hydroxy derivatives prompted us to disclose our findings on the samarium diiodide-mediated reduction of baccatin III, 10-deacetylbaccatin III, paclitaxel and docetaxel.

We[17] and Holton[18] have recently reported on the samarium diiodide-mediated,[15] one step deoxygenation of paclitaxel to yield 10-deacetoxypaclitaxel. This reaction proceeds in five minutes and in excellent yield (91%). Since this reaction must involve the participation of the C-9 carbonyl group, we rationalized that it might be possible to reduce the C-9 keto group of 10-deacetoxypaclitaxel with the same reagent.

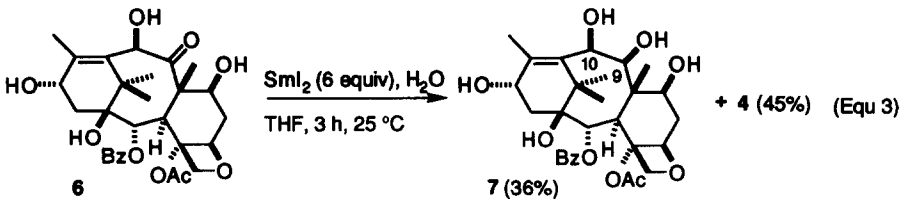
In our initial study we reacted baccatin III (**3**) with samarium diiodide in the presence of water[19] and first observed (five min) the formation of 10-deacetoxybaccatin III. However, after a reaction time of 3 h, we were able to isolate C-9 reduced 10-deacetoxy-9β-hydroxybaccatin III (**4**) in 88% yield (Equ 1). As a side product we also isolated 10-deacetoxy-7-epi-baccatin III in 3% yield.



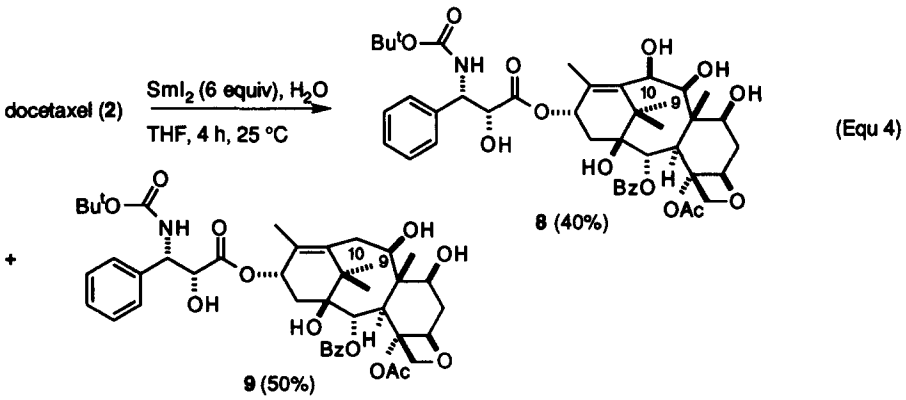
This reaction was successfully extended to the reduction of paclitaxel. Exposure of paclitaxel to samarium diiodide for 12 h provided the novel paclitaxel analogue 10-deacetoxy-9β-hydroxypaclitaxel (**5**) in 83% yield (Equ 2).



During our samarium diiodide-mediated deoxygenation studies we had noticed that reaction of 10-deacetylbaccatin III (**6**) to 10-deacetoxybaccatin III was a slow process. Since this is due to the poor leaving group characteristics of the hydroxy group, we reasoned that if the reduction of the C-9 carbonyl group proceeds at a similar or faster rate than the deoxygenation, we would be able to obtain the C-9 reduced derivative while retaining the C-10 hydroxy group. After treating 10-deacetylbaccatin III (**6**) with samarium diiodide for 3 h, we obtained 36% of the desired 10-deacetyl-9β-hydroxybaccatin III (**7**) together with 45% of 10-deacetoxy-9β-hydroxybaccatin III (**4**) (Equ 3).



Similarly, reaction of docetaxel with samarium diiodide for 4 h resulted in the formation of 40% 9β-hydroxydocetaxel (**8**) and 50% 10-dehydroxy-9β-hydroxydocetaxel (**9**) (Equ 4). It is of interest to note that all reductions proceeded with excellent stereoselectivity to provide the 9β-derivatives.[20,21]



The biological activities of compounds **5**, **8**, and **9** were evaluated in the microtubule assembly assay and for their cytotoxicities against B16 melanoma cells, in comparison to paclitaxel.[22] It was found that the docetaxel analogs **8**, and **9** displayed activity (**Table**) in both tests comparable to paclitaxel. Paclitaxel analogue **5** was almost as active in the microtubule assembly assay, but showed reduced cytotoxicity against B16 melanoma cells in comparison to paclitaxel.

Table. *In vitro* biological evaluation of 9β-hydroxy analogues **5**, **8**, and **9**.[a]

compound	microtubule assembly[b] ED_{50}/ED_{50}(paclitaxel)	B16 melanoma cytotoxicity[c] ED_{50}/ED_{50}(paclitaxel)
1	1.0	1.0
2	0.45	0.41
5	1.4	12
8	0.97	1.1
9	1.7	1.8

[a]For experimental procedures see ref. 22. [b]ED_{50} is the concentration which causes polymerization of 50% of the tubulin present in 15 min at 37 °C. [c]ED_{50} refers to the concentration which produces 50% inhibition of proliferation after 40 h of incubation.

In summary, we have developed a stereoselective procedure for the synthesis of 9β-hydroxypaclitaxel analogs via a SmI_2-mediated reduction. We also have demonstrated that 9β-hydroxytaxanes possess significant biological activity. The hydroxy group at C-9 provides a site for further transformations at C-9. Investigations to this effect are in progress.

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