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A ONE-STEP SYNTHESIS OF A DEUTERATED PACLITAXEL ANALOGUE: 10-DEACETOXY-(10α-^{2}H)PACLITAXEL

Dinah Dutta,[a] Harry Hadd,[b,1] David G. Vander Velde,[a] and Gunda I. Georg[a,*]

[a]*Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, U.S.A.*
[b]*Northwest Center for Medical Education, Indiana University School of Medicine, 3400 Broadway, Gary, IN 46408, U.S.A.*

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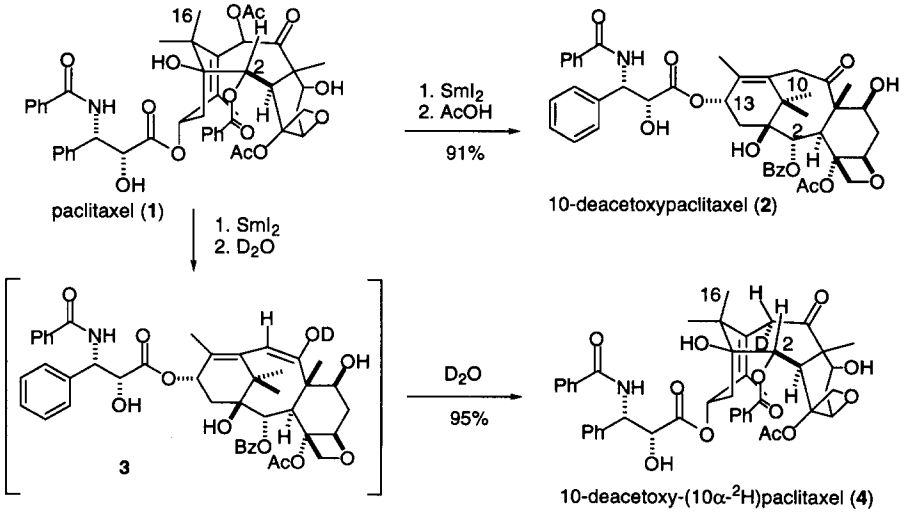
Abstract: 10-Deacetoxy-(10α-^{2}H)paclitaxel was prepared in one step via the samarium diiodide mediated deoxygenation of paclitaxel in the presence of D_2O.

Paclitaxel (**1**, Scheme 1, Taxol®), a complex natural product isolated from the bark of *Taxus brevifolia*, is an effective agent for the treatment of a variety of cancers.[2] As a result of its clinical success as an antitumor agent, paclitaxel has been the subject of intense chemical, biological and clinical investigations.[3–6] During structure–activity studies[4–6] we and others found that 10-deacetoxypaclitaxel (**2**) and related analogues can be prepared from paclitaxel in one step and in excellent yield without the need for protecting groups (Scheme 1).[7–9] 10-Deacetoxypaclitaxel is a highly active paclitaxel analogue.[7–10]

We are now communicating a study aimed at investigating the stereochemical course of the protonation of the intermediate enol **3** (Scheme 1), generated during the SmI_2-mediated deoxygenation. The first step of the SmI_2-mediated deoxygenation is the formation of a ketyl that is immediately protonated and then further reduced by a second equivalent of SmI_2, producing a carbanion, which induces the β-elimination of the acetoxy group. Tautomerization of the enol provides the ketone.

Scheme 1



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A number of proton sources can be used in this reaction, including water. In order to study the stereochemical outcome of the protonation of enol **3**, we used D_2O as the proton source. The reaction was carried out as described by us before,[7] replacing acetic acid with D_2O to obtain a 6:4 mixture of 10-deacetoxy-(10α-^{2}H)paclitaxel (**4**) and its protonated derivative 10-deacetoxypaclitaxel in a combined yield of 95%. When the reaction was carried out using baccatin III as the starting material, employing the same reaction conditions, a 9:1 mixture of 10-deacetoxy-(10α-^{2}H)baccatin III and 10-deacetoxy-baccatin III (reaction not shown) was obtained in 85% yield (unoptimized, 15% starting material was recovered). We concluded that exchangeable C13 side-chain protons may be responsible for the lower deuterium incorporation into **4**, compared to baccatin III. This assumption was verified when we carried out the reaction with 2'-O-TBS-protected paclitaxel and obtained a 9:1 ratio of deuterated and protonated product. In another experiment, we performed a deuterium exchange ($CHCl_3/D_2O$ for 3 h) with paclitaxel prior to the deoxygenation. In that case, we observed quantitative incorporation of deuterium for the product 10-deacetoxy-(10α-^{2}H)paclitaxel (**4**) in an unoptimized yield of 60%.

As judged by ^{2}H NMR, the deuteration of **4** was completely stereoselective: the only detectable signal above natural abundance came at 3.5 δ. The stereochemistry of the remaining proton at H10 was established by an NOE difference experiment. Irradiation of H16 gave the expected strong enhancement at H2, and also strongly enhanced H10, showing they are both on the β-face of the molecule. The added deuterium is therefore on the α-face.

The exclusive protonation of enol **3** from the sterically more hindered α-face of the molecule is surprising. It is, however, possible that deuterium oxide forms deuterium bonds with the C2 and C4 acyl groups, located in the α-face of the molecule, and thus facilitates delivery of the deuterium oxide from the bottom face of the molecule.

The method described herein could find applications for the facile, one-step synthesis of tritiated paclitaxel analogues using readily available and inexpensive tritiated water as the tritium source. This procedure could also be of utility for the facile introduction of deuterium and tritium into other molecules.

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References and Notes

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