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Deacetylation of Paclitaxel and Other Taxanes

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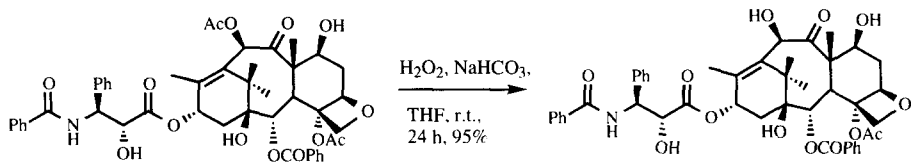
Abstract: 10-Deacetyltaxol is prepared from paclitaxel in 95% yield by using H_2O_2 in the presence of $NaHCO_3$.

Deacetylation of paclitaxel and other taxanes has appeared in recent years to be an important step in the synthesis of paclitaxel analogues for SAR studies.[1-8] There are acetyl groups at the 4 and 10 positions of the naturally existing paclitaxel skeleton. Selective removal of the 10-acetyl group from paclitaxel results in formation of 10-deacetyltaxol (10-DAT), and this is a starting material for many newly developed analogues.[9-15] Even though 10-DAT can be obtained by isolation from *Taxus brevifolia*,[16] the amount in the natural biomass is limited and the isolation process is complicated and difficult. Some methodologies have been developed aimed at the selective removal of acetyl groups from taxanes, but currently available methods are problematic. For example, when a strong base such as sodium methoxide was used, a low yield of deacetyltaxanes resulted due to the low selectivity.[4] It is also well known that strong bases will cause side chain cleavage. Use of Lewis acids is an alternative approach that results in formation of the 7-epimer of paclitaxel.[3,17] In order to increase the availability of the deacetyl type taxane compounds, a synthetic method that is capable of removing the acetyl group with high selectivity and high yield is still in demand.

The report herein describes a facile method for deacetylation and deacylation of paclitaxel and paclitaxel analogues with high yield and high selectivity. This mild method results in the selective removal of the 10-acetyl group from paclitaxel in 95% yield in a single step as illustrated in Scheme 1.

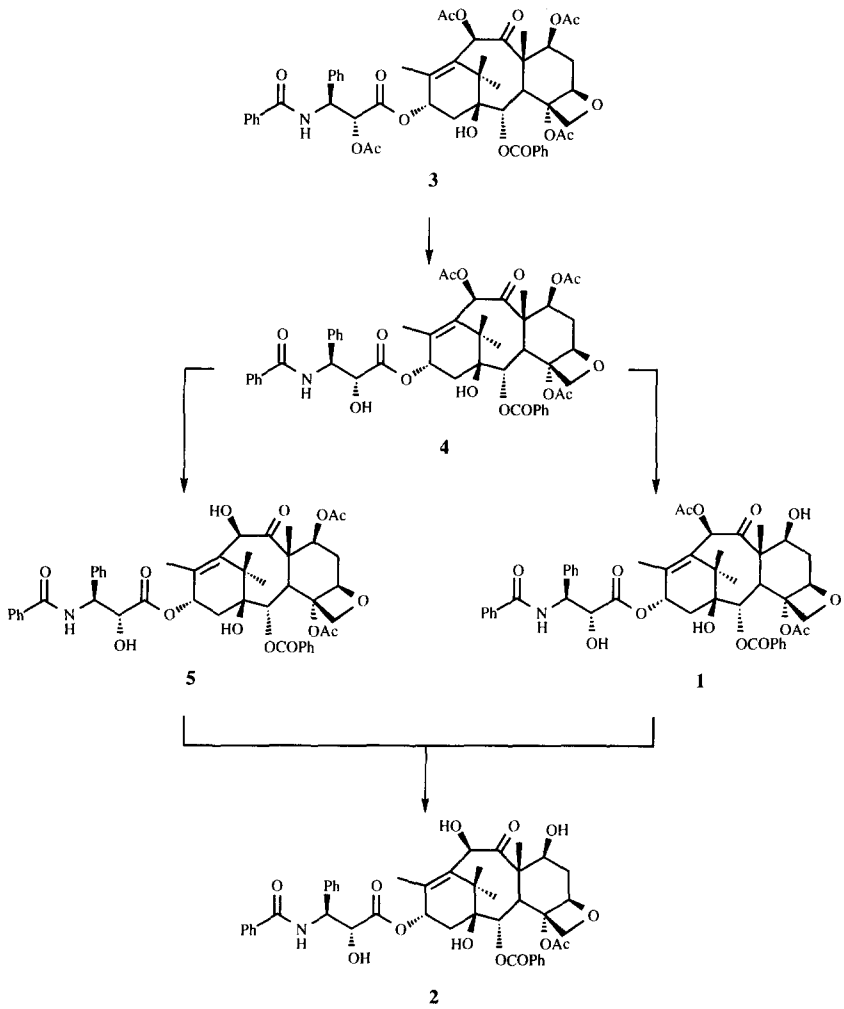


1 2

Scheme 1. Deacetylation of paclitaxel.

When paclitaxel **1** was treated with hydrogen peroxide (30%) in the presence of a base such as sodium bicarbonate at room temperature in tetrahydrofuran (THF) for 24 hours, 10-deacetyltaxol **2** was formed as a single product in 95% yield. Many peroxides were examined. Hydrogen peroxide appears to be the best peroxide compared with tBuOOH, MCPBA, and MMPP. Organic solvents such as THF, CH_2Cl_2, MeOH, and acetone work well but THF is the best of these solvents. Many bases were examined for this method such as $NaHCO_3$, Na_2CO_3, NaOH, K_2CO_3, $CaCO_3$, Cs_2CO_3, LiOH, $Ca(OH)_2$ and $BaCO_3$. Among all the bases tried,

$NaHCO_3$ and $CaCO_3$ were the mildest for paclitaxel and other taxanes. The 7-OH epimerization is not a problem, even with prolonged hydrolysis in the presence of the $NaHCO_3$ or $CaCO_3$. Other bases, such as NaOH and LiOH, under the same conditions are too strong and result in decomposition of the taxane compounds.[18]

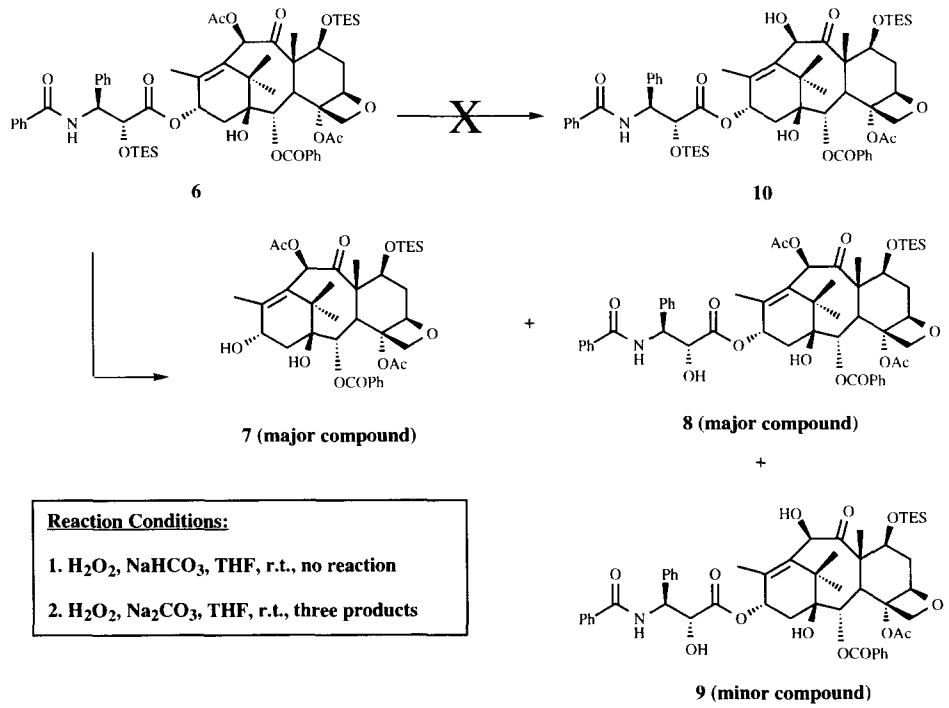


Scheme 2. Selectivity of the deacetylation of paclitaxel.

In order to determine the selectivity of this method, 2',7-bis acetyltaxol **3** was prepared. As shown in Scheme 2 under the same reaction conditions mentioned above, the order of reactivity of the fully acetylated

taxanes is 2'-OAc > 10-OAc > 7-OAc > 4-OAc. The 2'-acetyl group was removed within 30 minutes in 92% yield.[19] However, there is only a slight selectivity between the 10-OAc and 7-OAc groups. After the 10-OAc is removed, the 7-OAc group also is removed, resulting in the formation of 10-DAT. The 4-OAc is stable under these reaction conditions.

When both 2'-OH and 7-OH are protected by a triethylsilyl group, removal of the 10-acetyl group becomes difficult as shown in Scheme 3.[4] There was no reaction under the typical reaction conditions (H_2O_2, $NaHCO_3$). When a stronger base, Na_2CO_3, was used, three products were formed. Compound **7** and **8** are the two major products. Compound **9** is the minor product. Compound **10** was not formed.



Scheme 3. Deacetylation of 2',7-bis(Et_3Si) taxol.

Examples of deacetylation of some taxanes under different conditions are listed in Table 1. 10-Deacetyltaxol B **12** was prepared from cepalomannine **11** in 72% yield (Entry 2, i). In a control experiment, lacking either H_2O_2 or $NaHCO_3$ present, no 10-deacetyl products were found even after 72 hours reaction time when cephalomannine **11** was used as the starting material (Entry 2, iii, iv). Therefore, both peroxide and base are necessary for this method. Docetaxel **14** was also prepared from 10-acetyldocetaxel **13** in 79-81% yield. These reactions were run only 16 hours because longer reaction times resulted in some decomposition of the product. Preparation of 10-deacetylbaccatin III **16** from baccatin III **15** under these conditions resulted in one major product. The lower yield is due to the loss of 10-deacetylbaccatin III **16** in an aqueous phase during the workup.

Table 1. Experiments of deacetylation of paclitaxel.

Entry	Starting Material	Product	Reaction Condition[a]	Chemical Yield[d] (%)
1	paclitaxel (**1**)	10-deacetyltaxol (**2**)	i ii	95 92
2	cephalomannine (**11**)	10-deacetyltaxol B (**12**)	i iii iv	72 0 0
3	10-acetyldocetaxel (**13**)	docetaxel (**14**)	i[b] ii[b]	81 79
4	baccatin III (**15**)	10-deacetylbaccatin III (**16**)	i ii	54[c] 57[c]

[a]i. H_2O_2, $NaHCO_3$, THF, r.t., 24 h; ii. H_2O_2, $CaCO_3$, THF, r.t., 72 h; iii. $NaHCO_3$, THF/H_2O, r.t., 72 h; iv. H_2O_2, THF, r.t., 72 h. [b]Reaction time was 16 hours. [c]Low yield is due to the loss of 10-deacetylbaccatin III in an aqueous solution during the workup. [d]Isolated yield.

This method works well with systems that have a carbonyl group at either the α or β position to the hydroxyl carbon. Transition state involving the carbonyl group may be required for the deacetylation. In conclusion, we have developed an efficient and highly selective method for deacetylation of paclitaxel and other taxanes. This method is mild enough that it may be used as a general method for other natural product synthesis.

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