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THE CHEMISTRY OF TAXANES: UNEXPECTED REARRANGEMENT OF BACCATIN III DURING CHEMOSELECTIVE DEBENZOYLATION WITH $Bu_3SnOMe/LiCl$

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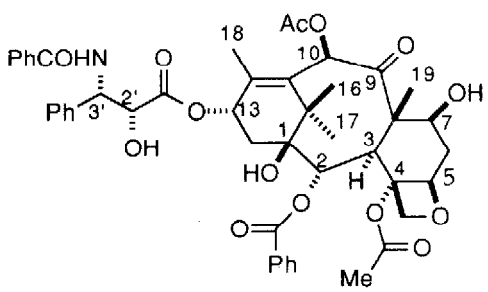
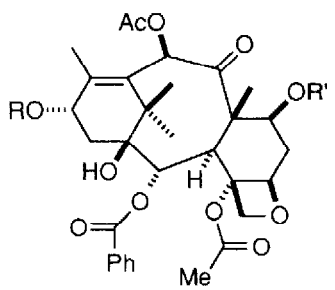
Summary: *Chemoselective debenzoylation of 7,13-diacetyl baccatin III was achieved with tributyltin methoxide in NMP in the presence of lithium chloride as an activating agent. Surprisingly, the debenzoylation reaction was followed by rapid intramolecular cleavage of the oxetane ring to produce a novel taxane structure featuring a tetrahydrofuran ring.*

The antitumor agent taxol **1** , isolated from the bark of the yew tree [1] is generating much excitement due to its clinical efficacy against a growing number of tumors. [2] Systematic modification of the various functional groups in this complex molecule has been carried out primarily by Kingston and coworkers. [3] In order to establish a thorough Structure-Activity Relationship (SAR) data base in the taxol area, it seemed to us of primary importance to be able to effect selective esterifications/de-esterifications at the various ring positions. We have focused mostly on the chemistry of baccatin III (**2a**), which is structurally simpler than taxol, and which can be converted to taxol by acylation . [4]



1 TAXOL

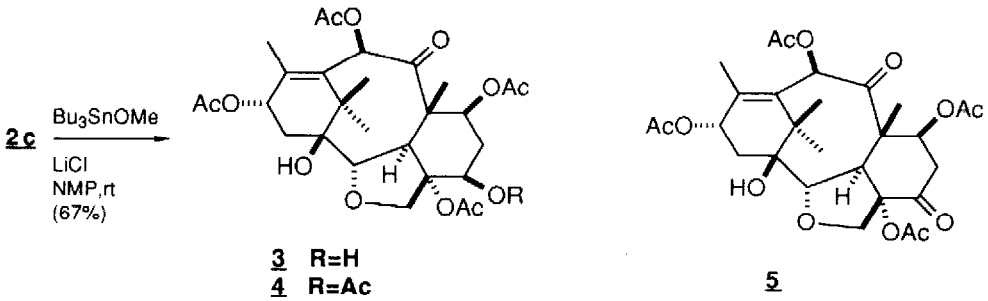


2 **a) R=R'=H**
b) R=H R'=Ac
c) R=R'=Ac

It has been reported by Kingston that the acetyl group at the C-10 position can be removed by hydrolysis using Lewis acids in methanol, [5] but no method has yet been reported that effects selective debenzoylation at C-2. One of the strategies that we have adopted consists of using organotin alkoxides or oxides. These reagents have been used to hydrolyze esters under aprotic conditions, [6] and in polyfunctional derivatives often display high chemoselectivity, due to the

ability of neighboring groups to coordinate the tin and direct the reagent intramolecularly.

When we treated taxol **1** or baccatin **2a** with tributyltin methoxide or hexabutylditin oxide under typical conditions, [6] either no reaction took place or epimerization of the C-7 hydroxyl group was observed. [5] However, when 7,13-diacetyl baccatin was employed as substrate and lithium chloride was added as an activator, [7] tributyltin methoxide in NMP induced clean debenzoylation at room temperature. The product, however, displayed an unusual ^{1}H-NMR spectrum. The most striking feature was the geminal coupling constant of the C-20 hydrogens, which increased from 8.3 to 11.6 Hz, suggesting that the oxetane ring was not intact. After complete spectral characterization, we assigned structure **3** to the product. In particular, the shift of the signal due to C-2 in the ^{13}C-NMR spectrum from δ 74.4 to δ 85.2 suggests the formation of a cyclic ether, while the shift for C-5 (from δ 83.9 to 70.9) shows that the ether bond at this site has been cleaved. That the free hydroxyl group is now at C-5 was confirmed by acetylation to yield **4**, as well as PCC oxidation, that cleanly produced **5**. A COLOC [8] experiment also established the presence of a three bond carbon-proton coupling between H-20 and C-2. Selected NMR data for compounds **2c** and **3** are summarized in Table 1.



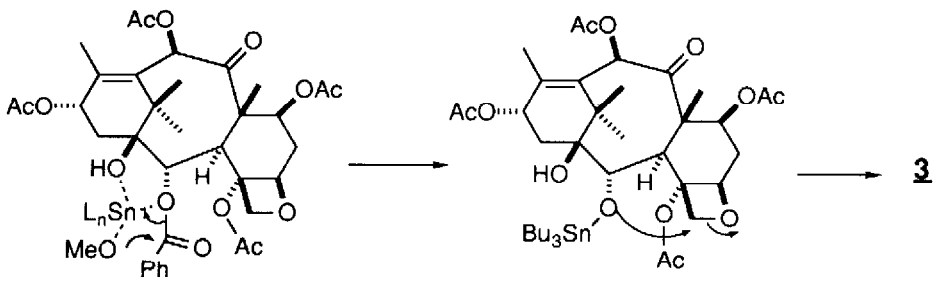
Conditions: **3** *to* **4**: Ac_2O *(10 eq)* CH_2Cl_2, *Py, rt , 51%.* **3** *to* **5** : *PCC (2 eq),* CH_2Cl_2, *rt, 87%.*

Several features of this reaction are worthy of comment. The selectivity of the reaction was essentially complete, [9] *none of the four other acyl groups being affected to any appreciable extent.* When even a single free hydroxyl group was present in the molecule, as in **2b**, the reaction was much slower and complex, very low yields of the desired product being obtained. The use of highly polar aprotic solvents is crucial. No product was obtained in benzene, and the reaction was extremely slow in THF, while use of NMP led to clean and fast reaction (typically less than 1 h at RT). DMSO was also acceptable as a solvent. The tin reagent was preferentially tributyltin methoxide, which led to smooth reaction at 25°C, while hexabutyltin oxide also led to reaction, but only in 3-5 days at 50°C. The use of an "activator" was also crucial, as very little reaction was seen otherwise. We found chloride ion to be the optimum: tetrabutylammonium chloride was as effective as lithium chloride, while iodide was ineffective and fluoride (as KF) or LiBr were satisfactory, but required 50°C overnight to achieve complete reaction. Alcoholic solvents [6a] were unsuitable, and methanol was actually found to strongly retard the reaction even when

added in small amounts to the NMP solution of the reactants. Finally, the benzoyl group that is removed from C-2 was present at the end of the reaction as methyl benzoate, no benzoic acid being detected by HPLC.

The above features clearly point to the involvement of the C-1 hydroxyl group in directing the tin reagent to the neighboring benzoyl group. Since this hydroxyl group is tertiary and highly hindered, the reaction is possible only when all the other hydroxyl groups in the molecule are protected to prevent non-productive coordination. The deleterious effects of added alcohols can be explained similarly. Our mechanistic ideas are summarized in **Scheme 1**. It is interesting to observe the rapid intramolecular rearrangement of putative intermediate **6**, which we were unable to trap under a variety of conditions. This is consistent with literature reports describing the enhanced nucleophilicity of tin alkoxides. [10] Dreiding models show that the reactive tin alkoxide is rigidly situated in an ideal position for backside attack onto C-20, leading to oxetane opening with retention at C-5.

SCHEME 1



6

Our mechanism does not explicitly take into account the role of the chloride. Harpp has reported previously on the activating effect of fluoride in a variety of Sn-X reagents (X=O, S. Se) [11] and in his studies as well the precise nature of the activation remains unclear. That chloride does not simply generate LiOMe was shown by ^{119}Sn-NMR studies and by the complete lack of reactivity of preformed LiOMe under our standard conditions. Most likely chloride ion loosely associates with tin, thereby promoting the higher (penta- or hexa-) coordination level necessary to induce reaction. [12]

In any case, the nature of the new reagent $Bu_3SnOMe/LiCl$ deserves further study, and we are currently examining its use in other deacylation chemistries. The unexpected finding that the hydroxyl group at C-2 has such a high tendency to participate in an intramolecular S_N2 reaction leading to oxetane ring opening has important implications both in the context of SAR studies in this area and in relation to total synthetic efforts aimed at Taxol.

Table 1. Diagnostic Carbon and Proton NMR data on **2c** *and* **3** *($CDCl_3$).* [13]

H (Position)	**2c**	**3**	C (Position)	**2c**	**3**
H-10	6.23 (s)	6.23 (s)	C-5	83.9	70.9
H-13	6.14 (br t)	6.11 (br t)	C-1	78.7	76.3
H-2	5.63 (d, J=7.0)	4.02 (J =6.6)	C-20	76.3	71.0
H-7	5.56 (dd, J = 10.5; 7.1)	5.07 (dd, J = 12.4; 4.1)	C-10	75.4	75.9
H-5	4.94 (d, J=8.0)	4.30 (m)	C-2	74.4	85.2
H-20 β	4.13 (d, J=8.3)	3.63(d,J= 11.6)	C-7	71.4	69.4
H-20 α	4.29 (d, J=8.3)	4.32 (dd, J = 11.6; 1.0)	C-13	69.5	70.1
H-3	3.93 (d, J=7.0)	3.37 (dd, J = 6.6; 1.0)	C-3	47.2	51.1

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13. Assignments were carried out by Proton-Proton and Carbon-Proton correlations and by DEPT. **Experimental**: **2c** (104 mg, 0.158 mmol) was dissolved in dry NMP (1.0 mL) and stirred with anhydrous LiCl (16.6 mg, 2.5 equiv) and tributyltin methoxide (0.091 mL, 2 equiv) for 2h at RT. Addition of saturated aqueous KF and EtOAc, filtration, then SiO_2 chromatography gave **3** as a white foam (60.1 mg, 67%). The compound was characterized by NMR and mass spectroscopy.

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