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# Selective Protection of the C(7) and C(10) Hydroxyl Groups in 10-Deacetyl Baccatin III

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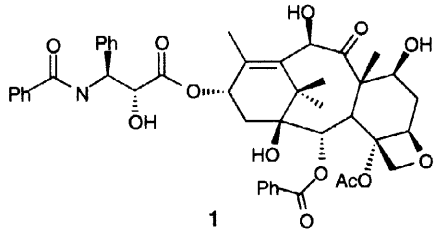
**Abstract**

New protocols for the selective protection of the C(7) and C(10) hydroxyl groups of 10-deacetyl baccatin III are described, leading to more efficient semisyntheses of taxol and taxol analogs. The C(10) hydroxyl group of 10-DAB can be highly selectively acylated or silylated, and subsequent selective protection of the C(7) hydroxyl group then becomes straightforward. 

*Keywords:* Acylation, Lanthanides, Protecting groups, Taxoid

The emergence of taxol (**1**) as an important anticancer agent has resulted from extensive chemical, biological, and medical research.[1,2a] The commercial production of semisynthetic taxol currently utilizes a key coupling reaction of a suitably protected baccatin III derivative with a synthetic β-lactam precursor of the C(13) side chain.[2] 10-Deacetyl baccatin III (10-DAB)[3] (**2**), which possesses the skeleton of taxol and is commercially extracted from the needles of *Taxus baccata* L., the English yew, is the most readily available and abundant taxane. Its conversion to taxol and taxol analogs first requires the differentiation of its similarly reactive C(7) and C(10) hydroxyl groups. Preliminary studies conducted by Potier demonstrated that the relative reactivity of the four hydroxyl groups of 10-DAB toward acetic anhydride in pyridine was C(7)-OH > C(10)-OH > C(13)-OH > C(1)-OH,[4] and Greene's group in 1988 reported the selective silylation of the C(7) hydroxyl group with triethylsilyl chloride in pyridine to give 7-triethylsilyl-10-deacetyl baccatin (III) (**3**) in 85% yield.[5] While Potier's and Greene's studies provided some important insight regarding the relative reactivity of the hydroxyl groups in 10-DAB, their results failed to fully reveal the subtle reactivity difference of the C(7) and C(10) hydroxyl groups.

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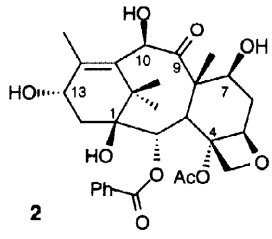


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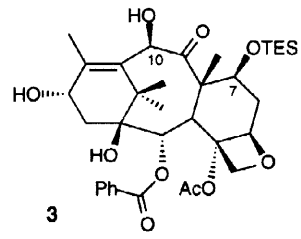


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We have found that, under different reaction conditions, the C(10) hydroxyl group of 10-DAB can be highly selectively acylated or silylated. Subsequent selective protection of the C(7) hydroxyl group then becomes straightforward, leading to more efficient and flexible protocols for the semisynthesis of taxol and taxol analogs.

Upon treatment of 10-DAB with $Ac_2O$ in THF at room temperature *in the absence of pyridine*, baccatin III (**6**) was very slowly produced. The reaction did not proceed to completion even after several days. However,

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10-DAB reacted much faster with dibenzyl dicarbonate (20 equiv, THF, 25 °C, 24 h) to give 10-cbz-10-DAB (**4**) in almost quantitative yield (98%). Diallyl dicarbonate reacted more slowly with 10-DAB under the same conditions; after 48 h 10-allyloxycarbonyl-10-DAB (**5**) was formed in 95% yield at 70% conversion.

Various conditions were investigated with the goal of enhancing the reaction rate while retaining high selectivity. Addition of a base to the reaction mixture induced the formation of some 7-acetyl-10-DAB and 7-acetyl baccatin III as side products. However, treatment of 10-DAB with $Ac_2O$ in the presence of $ZnCl_2$ for 4 h gave baccatin III in 93% yield.[6] It should be noted that no 7-acetyl-10-DAB was produced under these conditions. Using this procedure, 10-DAB was also converted to the corresponding 10-chloroacetate **7** and the 10-propionate **8**, both in 93% yield. Other Lewis acids were also found to be effective promoters of the formation of C(10) esters and carbonates, and among these, lanthanides, particularly $CeCl_3$, proved to be efficient catalysts for the acylation. C(10) carbamates **16-19**, however, were formed most selectively and efficiently in the presence of CuCl. Conditions and results are summarized in **Table 1**.

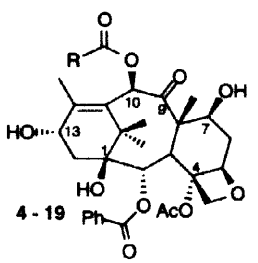
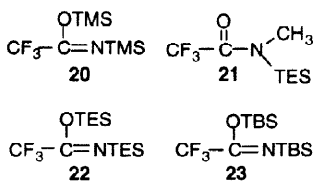



**Table 1**. Formation of 10-acyl-10-DAB from 10-DAB**

| Product | R | Reagent (eq) | Promoter (eq) | Time | Yield(%) |
|---|---|---|---|---|---|
| **4** | BnO | $(PhCH_2O_2C)_2O$ (20) | none | 24 h | 98 |
| **4** | BnO | $(PhCH_2O_2C)_2O$ (3) | $CeCl_3$ (0.7) | 1 h | 98 |
| **5** | $C_3H_5O$ | $(CH_2=CHCH_2O_2C)_2O$ (40) | none | 48 h | 95* |
| **5** | $C_3H_5O$ | $(CH_2=CHCH_2O_2C)_2O$ (5) | $CeCl_3$ (0.1) | 1 h | 96 |
| **6** | $CH_3$ | $(CH_3CO)_2O$ (20) | $ZnCl_2$ (2) | 4 h | 93 |
| **6** | $CH_3$ | $(CH_3CO)_2O$ (10) | $CeCl_3$ (0.1) | 1.5 h | 95 |
| **7** | $ClCH_2$ | $(ClCH_2CO)_2O$ (78) | $ZnCl_2$ (2) | 5 h | 93 |
| **8** | $C_3H_7$ | $(C_3H_7CO)_2O$ (40) | $ZnCl_2$ (2) | 5 h | 93 |
| **8** | $C_3H_7$ | $(C_3H_7CO)_2O$ (10) | $CeCl_3$ (0.1) | 3 h | 100 |
| **9** | *i*-$C_3H_7$ | (*i*-$C_3H_7CO)_2O$ (10) | $CeCl_3$ (0.1) | 4.5 h | 100 |
| **10** | Ph | $(PhCO)_2O$ (10) | $CeCl_3$ (0.1) | 21 h | 94 |
| **11** | *c*-$C_3H_5$ | (*c*-$C_3H_5CO)_2O$ (10) | $CeCl_3$ (0.1) | 20.5 h | 94 |
| **12** | $C_3H_5$ | $(C_3H_5CO)_2O$ (10) | $CeCl_3$ (0.1) | 20 h | 91 |
| **13** | $C_2H_5O$ | $(C_2H_5OCO)_2O$ (5) | $CeCl_3$ (0.1) | 3 h | 99 |
| **14** | $CH_3O$ | $(CH_3O\,CO)_2O$ (5) | $CeCl_3$ (0.1) | 3 h | 98 |
| **15** | *t*-BuO | (*t*-$BuOCO)_2O$ (10) | $CeCl_3$ (0.7) | 24 h | 94 |
| **16** | $C_2H_5NH$ | $C_2H_5NCO$ (1.1) | CuCl (1) | 0.5 h | 88 |
| **17** | $C_3H_5NH$ | $CH_2=CHCH_2NCO$ (1.1) | CuCl (1) | 0.5 h | 88 |
| **18** | $C_4H_9NH$ | $C_4H_9NCO$ (1.1) | CuCl (1) | 0.5 h | 87 |
| **19** | PhNH | PhNCO (1.1) | CuCl (1) | 3 h | 94 |

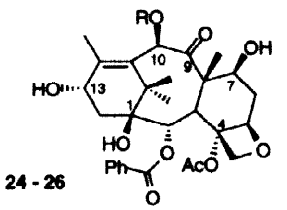
*At 70% conversion. **All reactions were conducted in THF (0.05M) at 25 °C.

Selective silylation of the C(10) hydroxyl group of 10-DAB is also possible. The silylating reagents[7] selected for this study were N,O-bis(trimethylsilyl)trifluoroacetamide (**20**) (commercially available), N-methyl-N-triethylsilyltrifluoroacetamide (**21**), N,O-bis(triethylsilyl)trifluoroacetamide (**22**), and N,O-bis(*t*-butyldimethyl-silyl)trifluoroacetamide (**23**).[8] As shown in **Table 2**, N,O-bis(trimethylsilyl)trifluoroacetamide (**20**) reacted with 10-DAB in THF at 0 °C to give 10-TMS-10-DAB (**24**) in 91% yield. N-Methyl-N-triethylsilyltrifluoroacetamide (**21**) reacted with 10-DAB in THF at 25 °C to afford 10-TES-10-DAB (**25**) in 85% yield. It has been reported that a trace amount of fluoride ion



dramatically catalyzes the reaction of N,O-bis(*t*-butyldimethylsilyl)trifluoroacetamde (**23**) with hydroxyl groups.[9] We were disappointed to find that addition of a small amount of tetrabutylammonium fluoride to a mixture of 10-DAB and N,O-bis(triethylsilyl)trifluoroacetamide (**22**) in THF at 0 °C gave 10-TES-10-DAB (**25**) in only 70% yield. However, when a catalytic amount of LHMDS was added to a solution of 10-DAB and 10 equiv of N,O-bis(triethylsilyl)trifluoroacetamide (**22**) in THF at 0 °C, 10-TES-10-DAB (**25**) was formed immediately in 95% yield. The mechanism of this catalysis is not yet clear, and we are also currently studying the general application of this method. Treatment of 10-DAB with N,O-bis(*t*-butyldimethylsilyl)-trifluoroacetamide (**23**) and a catalytic amount of LHMDS at 0 °C for 5 h afforded 10-TBS-10-DAB (**26**) in 70% yield. We have not been able to prepare 10-TBS-10-DAB cleanly under various other reaction conditions.

**Table 2.** Formation of 10-silyl-10-DAB from 10-DAB



**24 - 26**

| Product | R | Reaction Conditions | Yield(%) |
|---|---|---|---|
| **24** | TMS | **20**, THF, 0 °C, 5 h | 91 |
| **25** | TES | **21**, THF, rt, 24 h | 85 |
| **25** | TES | **22**, LHMDS(cat), THF, 0 °C, 10 min | 95 |
| **26** | TBS | **23**, LHMDS(cat), THF, 0 °C, 5 h | 70 |

In addition to the methods previously described by Greene and Potier for protection of the C(7) hydroxyl group of 10-DAB,[4,5] we have found that *t*-butyldimethylsilyl (TBS),[6] tribenzylsilyl, dimethylphenylsilyl, and dimethylisopropylsilyl groups can all be attached with high selectivity and yield under controlled conditions (**Table 3**). The C(7) hydroxyl groups of 10-acyl-10-DAB, baccatin III, and 10-TES-10-DAB can also be protected selectively,[11] and some illustrative additional examples from our laboratory are listed in **Table 3**.

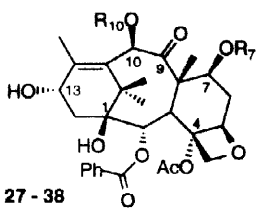


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**Table 3.** Protection of the C(7)-OH Group of Baccatin III derivatives

| Substrate | Product | $R_{10}$ | $R_7$ | Reaction Conditions | Yield(%) |
|---|---|---|---|---|---|
| **2** | **3** | H | $(Et)_3Si$ | TESCl, pyridine, rt, 10 h | 91[10] |
| **2** | **27** | H | $t$-$Bu(CH_3)_2Si$ | TBSCl, imidazole, DMF, rt, 24 h | 90[6] |
| **2** | **28** | H | $(CH_3)_2i$-PrSi | $(CH_3)_2i$-PrSiCl, pyridine, -10 °C, 3 h | 93 |
| **2** | **29** | H | $(CH_3)_2PhSi$ | $(CH_3)_2PhSiCl$, pyridine/THF, -20 °C, 1 h | 92 |
| **2** | **30** | H | $(PhCH_2)_3Si$ | $(PhCH_2)_3SiCl$, imidazole, DMF, rt, 3 h | 91 |
| **6** | **31** | Ac | cbz | $(PhCH_2O_2C)_2O$, $CH_2Cl_2$, DMAP, rt, 4 h | 95 |
| **6** | **32** | Ac | $C_3H_5OCO$ | $(CH_2{=}CHCH_2O_2C)_2O$, $CH_2Cl_2$, DMAP, rt, 1 h | 97 |
| **6** | **33** | Ac | $(CH_3)_2PhSi$ | $(CH_3)_2PhSiCl$, pyridine/THF, -10 °C, 1 h | 98 |
| **6** | **34** | Ac | $(CH_3)_2i$-PrSi | $(CH_3)_2i$-PrSiCl, pyridine, 0 °C, 3 h | 97 |
| **6** | **35** | Ac | $(PhCH_2)_3Si$ | $(PhCH_2)_3SiCl$, imidazole, DMF, rt, 3 h | 94 |
| **6** | **36** | Ac | Troc | $Cl_3CCH_2O_2CCl$, DMAP, pyridine, rt | 95[11] |
| **25** | **37** | TES | cbz | $PhCH_2O_2CCl$, $CHCl_3$, DMAP, rt, 4 h | 93 |
| **25** | **38** | TES | Troc | $Cl_3CCH_2O_2CCl$, $CH_2Cl_2$, DMAP, rt, 1 h | 97 |

The methods we describe here provide new flexibility which should prove to be of wide utility to those attempting either the synthesis of taxanes or the chemical modification of substituents on the baccatin nucleus.

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