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A Simple Synthesis of 10-Deacetoxytaxol Derivatives

Robert A. Holton,* Carmen Somoza, and Ki-Byung Chai

Dittmer Laboratory of Chemistry
Florida State University
Tallahassee, Florida 32306

Abstract: The C-10 oxygen substituent can be reductively removed in high yield by reaction of taxol, baccatin III, or 10-deacetylbaccatin III with samarium diiodide. This reaction pathway can be completely shut down by protection of the C-7 hydroxyl group of baccatin III as the triethylsilyl ether.

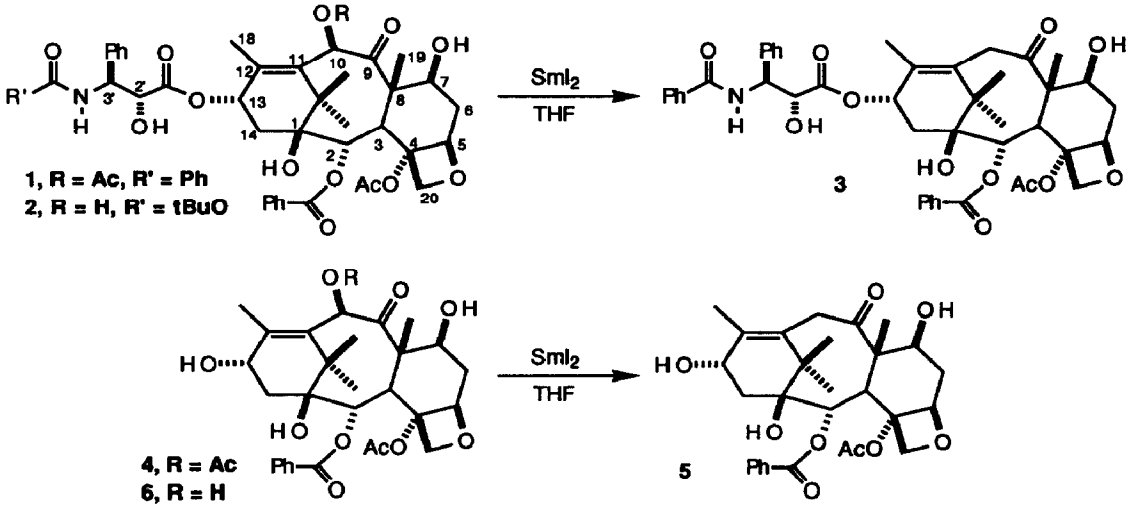
Taxol (**1**) and the semisynthetic analog, taxotere (**2**), continue to be the subject of intense interest in the chemical, biological, and medical communities. Taxol is currently marketed for treatment of refractory ovarian cancer, and it continues to show impressive clinical activity against other cancers, particularly breast and lung cancer.[1] Since its isolation by Wall and Wani in 1971,[2] it has been the subject of extensive chemical and biological studies, which have recently been summarized in several reviews.[3]

The chemistry of taxol has been found to be particularly challenging, and unexpected rearrangements to produce unusual structures are frequently encountered.[4] The dense array of nine reactive functional groups sprinkled around the perifery of the unusual taxane skeleton provides a unique challenge, and, as a result, the pharmacophore of taxol remains to be completely defined. Selective manipulation of this array of functional groups is also an important issue which must be addressed before a total synthesis of taxol can be realized.

An ongoing program in our laboratory has dual objectives: (a) to achieve a total synthesis of baccatin III (**4**), and therefore taxol,[5] and (b) to define the taxol pharmacophore as a first step in developing a detailed understanding of its mechanism of biological action. In the course of these endeavors we have discovered a simple and direct high yield route to 10-deacetoxytaxol (**3**) and 10-deacetoxybaccatin III (**5**), and the results of these studies are reported herein.

Farina, et. al. have recently reported a synthesis of 10-deacetoxytaxol from taxol, and have found its biological activity to be approximately equivalent to that of taxol.[6] Independently, Kingston, et. al. have reported an alternative synthesis of 10-deacetoxytaxol and 10-deoxytaxotere (**11**) from 10-deacetylbaccatin III, and have found 10-deoxytaxotere to possess superior activity.[7] Both of these synthetic routes required several steps and proceeded in low overall yield.

We have found that taxol (**1**) undergoes smooth reduction in the presence of 2.5 mol equiv of samarium diiodide in THF solution at 0 °C for 45 min. Examination of the crude reaction mixture by ^{1}H NMR indicated that a small amount of epimerization at C-7 had occurred (the ratio of **3** to 7-epi-**3** ranged from 6:1 to 9:1). Upon flash chromatography, the mixture partially epimerized back to **3**, and, typically, **3** could be obtained in ca. 91-92% yield along with 7-8% of 7-epi-**3**.



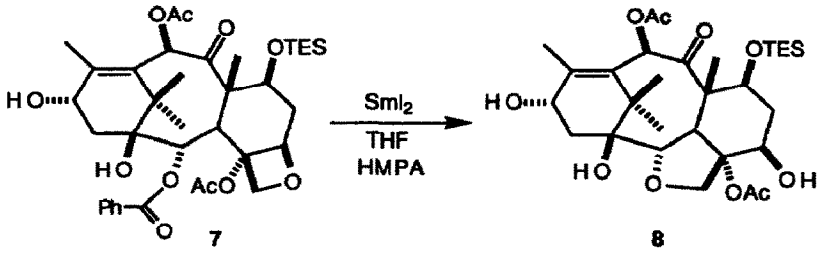
When baccatin III (**4**) was subjected to identical conditions, similar results were obtained. The crude reaction mixture contained **5** and 7-epi-**5** in ratios ranging from 3.6:1 to 20:1. After flash chromatography the yield of **5** was ca. 92% and the yield of 7-epi-**5** was ca. 8%. Interestingly, after purification, no epimerization of 7-epi-**3** to **3** or 7-epi-**5** to **5** was observed. Perhaps the epimerization during chromatography is due to the presence of chelated Sm (+3) salts. When the reduction was carried out at 25 °C, more epimerization (5:4 ratio of **5** to 7-epi-**5**) was observed. Upon chromatography, a 2:1 ratio of **5** to 7-epi-**5** was obtained.

The reduction of 10-deacetylbaccatin III (**6**) was, as expected, more difficult, and the reaction was very slow at 0 °C. Reduction of **6** was achieved with 5 mol equiv of samarium diiodide in THF solution at 25 °C for 4 h, providing a crude mixture of **5** and 7-epi-**5** in ratios ranging from 2.5:1 to 2:3. After chromatography the yield of **5** was 60% to 75%. The undesired C-7 epimerization appeared to be promoted by higher reaction temperatures. Therefore, **6** was treated with 2.5 mol equiv of samarium diiodide in a mixture of 10:1 THF:HMPA at -23 °C for 0.5 h, and **5** was obtained in 94% yield at 85% conversion with only a small amount (ca. 5% or less) of C-7 epimerization.

Unexpectedly, 7-triethylsilyl baccatin III (**7**) remained unchanged in the presence of

samarium diiodide in THF at either 0 °C or 25 °C. Under relatively harsh conditions (3.5 mol equiv of samarium diiodide in THF solution at reflux for 5 h), only a small amount of unreacted **7** (20%) was recovered, along with many (>10) other products. The lack of reactivity of **7** is reminiscent of that observed by Chen, et. al. during studies of the Lewis acid promoted methanolysis of the C-10 acetoxy group of baccatin III and 7-triethylsilyl baccatin III.[8]

Surprisingly, when **7** was treated with 4 mol equiv of samarium diiodide in a 10:1 mixture of THF:HMPA at 25 °C for 1 h, the tetrahydrofuran **8** was obtained in 96% yield. An analogous conversion of the oxetane to a 2-20 tetrahydrofuran has previously been observed as a consequence of attempted basic methanolysis of baccatin derivatives.[9] It has been noted that the oxygen at C-2 is almost perfectly aligned for backside opening of the oxetane. In this case, we suspect that the reaction is promoted by Sm (+3) complexation with the oxetane oxygen after reduction of the C-2 benzoate.[10]



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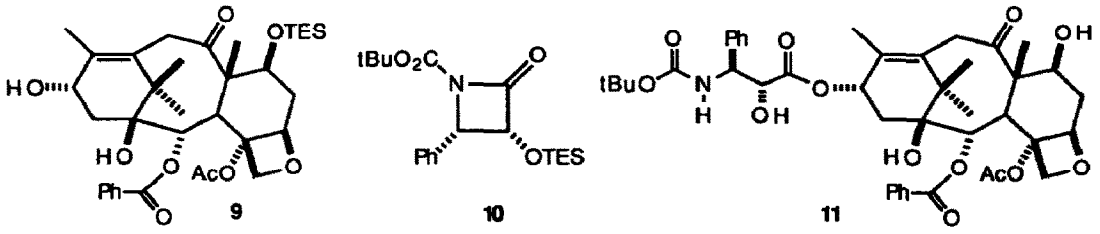
10-Deacetoxybaccatin III (**5**) was converted to 10-deoxytaxotere (**11**) in ca. 80% overall yield via a three step sequence:[5] (a) protection of **5** as the 7-TES derivative **9** (TESCl, pyridine, 25 °C), (b) esterification of **9** with racemic β-lactam **10** (LHMDS, THF, **10**, 0 °C), and (c) removal of 7 and 2' TES groups (HF, pyridine, acetonitrile, 25 °C). 10-Deoxytaxotere (**11**) showed slightly better *in vitro* cytotoxicity than taxotere in a human colon cancer cell line (HCT116: IC_{50}, 0.002 μg/mL; taxotere, 0.003 μg/mL), and its ability to polymerize tubulin was about twice that of taxotere. These results are consistent with those reported by Kingston in the P-388 cell culture system.[7]



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10. Although we are aware of no literature precedent, we have observed that simple esters, e.g. methyl benzoate, are reduced by samarium diiodide in THF/HMPA. Further exploration of this observation is warranted.

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