Internal Nucleophile Assisted Selective Deesterification Studies on Baccatin III. Synthesis of 2-Debenzoyl- and 4-Deacetylbaccatin III Analogues

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Received April 28, 1994

The naturally occurring diterpenoid Taxol (**1**) (Figure 1) is one of the most exciting discoveries in the field of cancer chemotherapy.[1] Its chemistry and clinical activity have been the focus of intense investigations involving a diverse segment of the scientific community worldwide.[2] Structure–activity studies of taxol derivatives are of interest to elucidate the taxol pharmacophore, thus providing valuable information for the design of second generation taxol analogues.[2–6] 10-Deacetylbaccatin III (**2**) and baccatin III (**3**), diterpenes more readily available than taxol, are known synthetic precursors of taxol and its analogues.[5,7] Since they have less structural complexity than taxol, they are also valuable starting materials for structural modifications at the diterpene part of the taxol molecule.

In continuation of our ongoing program in taxol research, we decided to investigate the selective deesterification of baccatin III at C-2 and C-4. These baccatin III derivatives will provide insight concerning the contribution of these acyl groups to biological activity and will offer additional sites for further structure–activity studies.

Deacylation studies[8–12] with baccatin III analogues, involving alkaline hydrolysis or methanolysis or metal hydride reductions, resulted in the formation of varying mixtures of 2-, 4-, and 10-deacylated products along with oxetane ring rearranged products in some cases. Only one successful attempt to remove the 2-benzoate group selectively has been reported recently. Treatment of 7,13-bis(triethylsilyl)baccatin III with Red-Al provided the corresponding 2-debenzoyl derivative in 78% yield.[13]

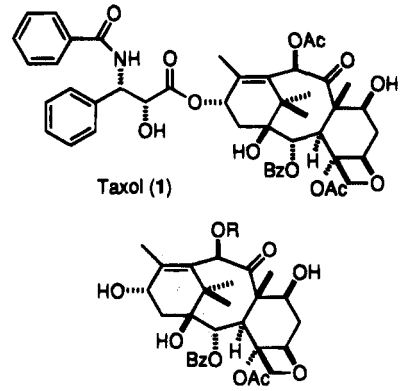

Figure 1. Structures of taxanes.

Studies from the Kingston group with 7-(triethylsilyl)-hexahydrobaccatin III have shown that the C-10 acetyl group is hydrolyzed first (sodium methoxide), followed by the C-4 acetyl group. The C-2 benzoyl group is hydrolyzed last.[11] The surprising outcome that the tertiary ester is hydrolyzed preferentially in the presence of the secondary ester at C-2 can be explained via an intramolecular assistance from the C-13 hydroxyl group. Related results were also reported by the Potier group.[9] On the basis of high-resolution NMR, X-ray diffraction, and molecular modeling studies, the overall conformations of the diterpene ring skeleton of taxol and baccatin III have been described to be a "cup or cage like". This places the C-13 hydroxyl and the C-4 acetyl group in baccatin III in close proximity.[6] Thus, the ready hydrolysis of the tertiary C-4 acetoxy group was rationalized to be due to the "neighboring group" effect of the C-13 hydroxy group, which either acts as a nucleophile in the deacylation or helps in delivering the nucleophile to the carbonyl center of the acetoxy group resulting in hydrolysis. In light of these observations, we reasoned that under suitable conditions it might be possible to utilize the strategically located C-1 and C-13 hydroxy groups in effecting selective deacylations at C-2 and C-4.

Our investigation thus started with the known 7-(triethylsilyl)baccatin III (**4**).[7] Initial deprotonation studies using a variety of bases (*viz.* NaH, BuLi, LDA, NaHMDS) and reaction conditions failed to yield any deacylated product. However, when the reaction was carried out using potassium *tert*-butoxide (1.1 equiv) as base in THF at −25 °C → 0 °C, TLC monitoring showed the formation of a major product along with some unreacted starting material. Workup and purification of the crude mixture afforded the product as a white solid [58% (81%)].[14] To our great satisfaction, the product formed was found to be the 4-deacylated baccatin III analogue **5** (Scheme 1). As mentioned earlier, the probable mechanism of formation can be viewed as an initial deprotonation of the C-13 hydroxy group followed by an intramolecular transfer of the acetyl group from the C-4 to the C-13 oxygen and subsequent hydrolysis of the allylic C-13 acetate, resulting in the formation of **5**. Attempts to increase the conversion of **4** to **5** by using excess base or varying

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(14) Yields in parentheses are based on recovered starting material.

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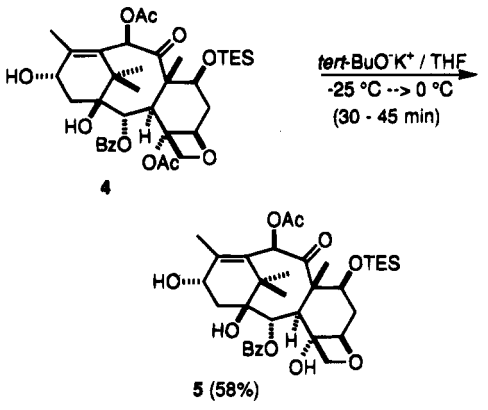
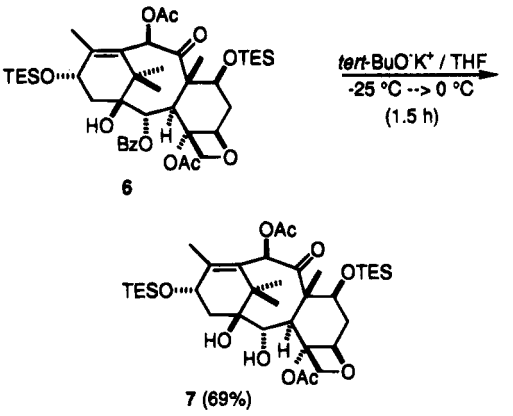
Scheme 1



Scheme 2



reaction conditions resulted in the formation of complex mixture of products which were not identified.

Having successfully performed the selective removal of the C-4 acetyl group, we next proceeded to extend the above methodology to study the selective debenzoylation at C-2. We reasoned that a selective removal of the benzoyl group at C-2 might be possible through the assistance of an oxyanion generated at the neighboring C-1 hydroxyl group. For this study the more reactive C-13 hydroxy group was first protected as its triethylsilyl ether using a known procedure.[11] 7,13-Bis(triethylsilyl)-baccatin III (**6**) was then treated with potassium *tert*-butoxide (1.1 equiv) as above. Subsequent purification of the crude mixture afforded a light yellow oil [69% (79%)][14] which was found to be the expected 2-debenzoylated baccatin III analogue **7** (Scheme 2).

In conclusion, our strategy of effecting selective deesterification on baccatin III derivatives, using the free hydroxy groups of the molecule as internal nucleophiles has proved to be quite efficient, affording the products in reasonably good yields. The ready availability of derivatives **5** and **7** by our method should now make it possible to develop and evaluate additional interesting taxol analogues.

Experimental Procedures[15]

4-Deacetyl-7-(triethylsilyl)baccatin III (5). To a stirred solution of 7-(triethylsilyl)baccatin III (**4**) (70 mg, 0.1 mmol) in dry THF (7 mL) at −20 °C under argon was added potassium *tert*-butoxide (12 mg, 0.11 mmol) in THF (3 mL) dropwise, and the mixture was allowed to reach 0 °C in 30−45 min. The reaction was then quenched with saturated NH_4Cl solution, and the solution was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water and brine and then dried (Na_2SO_4). After the solvent was evaporated under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, hexane/EtOAc = 3/1 to 3/2) to yield **5** as a colorless solid (38 mg, 58%; starting material recovered = 21 mg): mp 119−122 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, J = 8 Hz, 6H), 0.90 (t, J = 8 Hz, 9H), 0.99 (s, 3H), 1.19 (s, 3H), 1.55 (s, 3H), 1.98 (m, 1H), 2.19 (br s, 6H), 2.42 (m, 2H), 2.58 and 2.64 (2d, J = 2.5 Hz, 1H), 3.40 (br d, J = 9 Hz, 1H, (exchangeable with D_2O)), 3.62 (d, J = 9 Hz, 1H), 4.01 (s, 1H, (exchangeable with D_2O)), 4.09 (dd, J = 6 Hz, 1H), 4.16 and 4.36 (2d, J = 9 Hz, 2H), 4.58 (br t, J = 8 Hz, 1H), 4.76 (dd, J = 3.6 and 9 Hz, 1H), 5.61 (d, J = 5 Hz, 1H), 7.44 (t, J = 7 Hz, 2H), 7.57 (t, J = 7 Hz, 1H), 8.05 (d, J = 7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.18, 6.72, 9.77, 16.91, 18.35, 20.96, 29.32, 37.09, 37.51, 42.13, 50.67, 58.84, 68.85, 72.29, 73.57, 75.81, 76.01, 80.43, 88.17, 128.65, 129.17, 129.96, 133.67, 135.06, 142.96, 166.73, 169.39, 201.91; IR (neat) 3500, 1715 (br), 1600 cm^{-1}; MS (FAB+) m/e 658 (M+); $[\alpha]^{25}_D$ −148.5° (c = 0.7, $CHCl_3$). Anal. Calcd for $C_{35}H_{50}O_{10}Si$: C, 63.80; H, 7.65. Found: C 63,63; H, 8.00.

2-Debenzoyl-7,13-bis(triethylsilyl)baccatin III (7). To a stirred solution of 7,13-bis(triethylsilyl)baccatin III (**6**) (100 mg, 0.12 mmol) in dry THF (8 mL) at −20 °C under argon was added potassium *tert*-butoxide (15 mg, 0.13 mmol) in THF (2 mL) dropwise, and the mixture was allowed to reach 0 °C in 90 min. The reaction was then quenched with a saturated NH_4Cl solution, and the solution was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water and brine and then dried (Na_2SO_4). After the solvent was evaporated under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, hexane/EtOAc, 3/1 to 3/2) to yield **7** as a light yellow viscous liquid (60 mg, 68%; starting material recovered = 13 mg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (m, 12H), 0.95 (m, 18H), 1.08 (s, 3H), 1.13 (s, 3H), 1.63 (s, 3H), 1.90 (m, 1H), 2.04 (s, 3H), 2.06 (m, 2H), 2.15 (s, 3H), 2.17 (s, 3H), 2.50 (m, 1H), 3.42 (d, J = 7 Hz, 1H), 3.88 (br d, J = 7 Hz, 1H), 4.41 (dd, J = 3.5 and 7 Hz, 1H), 4.59 (dd, J = 7 and 16 Hz, 2H), 4.95 (m, 2H), 6.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.79, 5.22, 6.75, 6.95, 10.24, 14.77, 20.95, 21.11, 22.37, 26.11, 37.26, 40.53, 42.45, 46.80, 58.24, 68.45, 72.22, 74.89, 75.75, 77.79, 78.54, 82.01, 83.74, 131.73, 145.02, 169.25, 169.55, 202.86; IR (neat) 3480, 1740, 1715, 1450 cm^{-1}; MS (FAB+) m/e 711 (M + 1); $[\alpha]^{25}_D$ −43° (c = 0.65, $CHCl_3$).

Acknowledgment. These studies were supported by a grant from Oread Laboratories (Grant No. 5339). Partial support to G.I.G. from the National Institutes of Health is acknowledged. The authors would like to thank Dr. D. G. Vander Velde for his help with the structural assignments by NMR.

Note Added in Proof: While this manuscript was undergoing review, a facile debenzoylation of taxol was reported: Chaudhary, A. G.; Gharpure, M. M.; Rimoldi, J. M.; Chordia, M. D.; Gunatilaka, A. A. L.; Kingston, D. G. I.; Grover, S.; Lin, C. M.; Hamel, E. *J. Am. Chem. Soc.* **1994**, *116*, 4097−4098.

Supplementary Material Available: Copies of the ^1H NMR of **5** and **7** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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