Synthesis of 7-Deoxy- and 7,10-Dideoxytaxol via Radical Intermediates

Shu-Hui Chen,* Stella Huang, Joydeep Kant, Craig Fairchild, Jianmei Wei, and Vittorio Farina*

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492-7660

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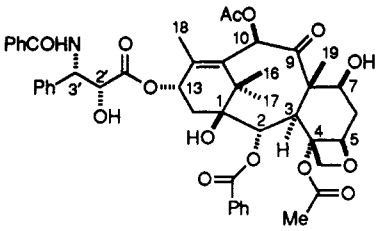
Summary: 7-Deoxytaxol and 7,10-dideoxytaxol were prepared from baccatin III, employing the Barton deoxygenation procedure and the Holton acylation method at C-13.

The important anticancer agent taxol,[1] recently approved for the treatment of ovarian cancer, has been the target of several structure–activity studies.[2] We have recently shown that, while the benzoate moiety at C-2 of the taxol core is essential for its biological activity,[3] the acetate group at C-10 contributes very little to receptor binding.[4] In this paper we wish to report the synthesis of another deoxygenated taxol analog, 7-deoxytaxol, together with its congener, 7,10-dideoxytaxol. Our studies confirm that the C-7 hydroxyl group is also not essential for antitumor activity.



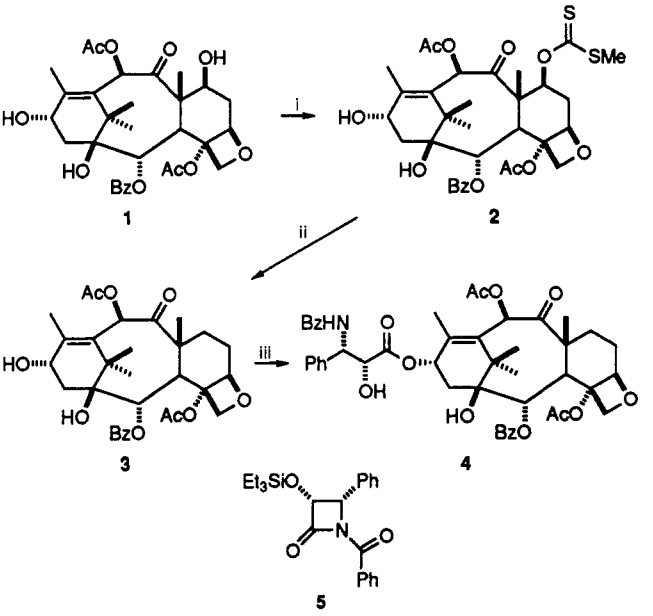
taxol

Our approach is illustrated in Scheme I. Treatment of baccatin with carbon disulfide and sodium hydride in THF produced xanthate **2** in modest yield. This compound was too insoluble in hydrocarbon solvents and had to be silylated at C-13 prior to deoxygenation. Tin hydride reduction and desilylation at C-13 afforded 7-deoxybaccatin **3**. Acylation according to the Holton protocol[5] gave the desired **4**.

Since deoxygenation at C-10 is not accompanied by loss of bioactivity, we were interested in examining the effect of defunctionalization at both the C-7 and C-10 position on the antitumor activity.

The known 7-(triethylsilyl)baccatin **6** (Scheme II)[6] was functionalized to give thionocarbonate **7**, which was reduced with tin hydride in high yield. Xanthate introduction at C-7 was then followed by treatment with tin hydride. Upon heating in toluene, two compounds were cleanly produced. Separation was difficult but was

Scheme I[a]



[a] Conditions: (i) NaH (1.5 equiv), THF/CS_2 (5:1), imidazole (0.05 equiv), 1.5 h, rt, then MeI (3 equiv), rt, 40 min (57%); (ii) Et_3SiCl, imidazole, DMF, rt (74%); Bu_3SnH, PhMe, 110 °C (83%); then TBAF (2 equiv), THF, rt (73%); (iii) BuLi (1.5 equiv), THF, −40 °C, then **5** (1.5 equiv), 0 °C, 45 min; then HCl, CH_3CN, −5 °C, 15 min (53% overall).

achieved by semipreparative HPLC. Along with the expected dideoxy compound **10**, which could be converted in low yield to the desired **12** (Scheme II), we obtained an isomer featuring a ^{1}H-NMR spectrum that was completely different from the ones typical of taxanes. Extensive NMR analysis[7] established that the isomer had structure **11**.

The formation of this isomer can be rationalized by invoking a cascade of radical rearrangements. The initially formed radical, **13** (Scheme III), is a β-keto radical[8] and can isomerize via alkoxy radical **14** to the isomeric **15**.

This places the radical-bearing carbon in close vicinity with the C11,C12 double bond, and 5-exo cyclization[9] to **16** occurs. This radical is not quenched by the tin hydride but undergoes a remote hydrogen atom transfer from C-3, as in our recently published photochemical rearrangement.[10] The resulting **17** apparently undergoes a novel

(1) Review: Kingston, D. G. I. *Pharm. Ther.* **1991**, *52*, 1.
(2) For recent, very interesting work, see: Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176. Also: Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M. T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992.
(3) Chen, S. H.; Wei, J. M.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 3205.
(4) Chen, S. H.; Fairchild, C.; Mamber, S. M.; Farina, V. *J. Org. Chem.* **1993**, *58*, 2927.
(5) Holton, R. A. Presented at the 203rd Meeting of the American Chemical Society, San Francisco, 1991; Abstract ORGN 0355. See also: Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985 and references cited therein.
(6) Denis, J. N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
(7) Connectivity was established by standard H–H and C–H correlation. The stereochemistry at C-8 and C-12 was demonstrated by NOE experiments. Especially diagnostic is the singlet in the proton spectrum for H-2 (indicating H-3 is missing), the olefinic nature of C-4 and C-3 (δ 143.0 and 126.2, respectively), and three-bond couplings between H-19 and C-11 and between H-12 and C-8. COSY and NOE data are shown in the supplementary material.
(8) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans 2*, **1992**, 1777 and references cited therein.
(9) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.
(10) Chen, S. H.; Combs, C. M.; Hill, S. E.; Farina, V.; Doyle, T. W. *Tetrahedron Lett.* **1992**, *33*, 7679.

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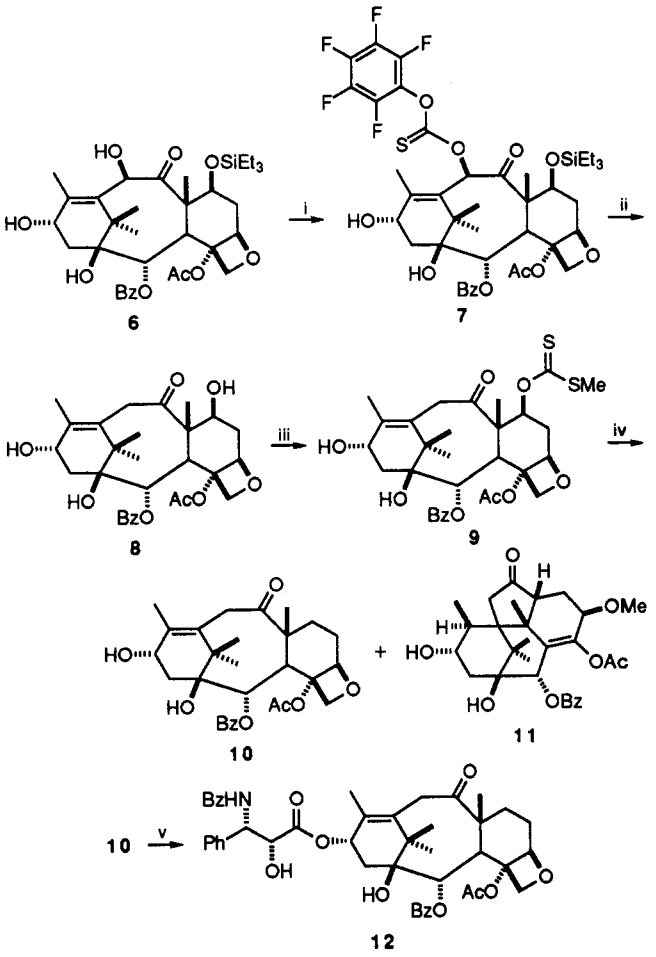
Scheme II[a]



[a] Conditions: (i) BuLi (1.25 equiv), THF, then C_6F_5CSCl, −20 °C, 90 min (74%); (ii) Bu_3SnH (1.5 equiv), AIBN, PhMe, 90 °C, 1 h (99%); then HCl, CH_3CN, −10 °C, 30 min (76%); (iii) NaH (1.5 equiv), THF/CS_2 (4:1), rt, 2 h, then MeI (3 equiv), rt, 16 h (53%); (iv) Bu_3SnH (5 equiv), AIBN, PhH, 80 °C, 3h (56% yield of **10**, 22% yield of **11**); (v) BuLi (1.15 equiv), THF, −40 °C, then **5** (2 equiv), 0 °C, 45 min; then TBAF, THF, 0 °C (30% overall).

oxetane fragmentation reaction,[11] leading to α-alkoxy radical **18**, which is finally trapped by hydride. When the reducing agent employed was tributyltin deuteride, the product was specifically labeled only at the methoxy group. This spectacular rearrangement[12] highlights the highly crowded topology of the taxol core and the tendency of the functionalities in the concave face of the molecule to strongly interact with each other. When the reaction mixture yielding **3** was carefully scrutinized for a similar

Scheme III

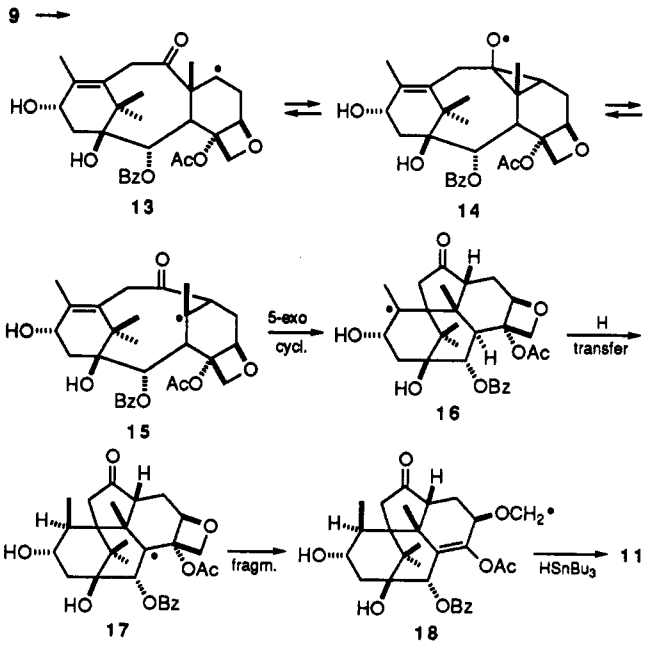


Table I

compd	HCT116IC_{50}[a] (μM)
taxol	0.004
7-deoxytaxol (**4**)	0.004
7,10-dideoxytaxol (**12**)	0.029

[a] Drug concentration required to inhibit cell proliferation to 50% vs untreated cells (incubated at 37 °C for 72 h).

rearrangement product, none was found. Evidently, the C-10 acetate function acts as a deterrent with respect to the radical cascade. Although the nature of this effect is not obvious at this stage, this phenomenon is once again an illustration of the subtle interplay of the various functions in the molecule.

The cytotoxicity of **4** was essentially identical to that of taxol, while **12** was slightly less active. Detailed cytotoxicity data for compound **4** and **12** are listed in Table I.[13] A more complete biological profile of these and related deoxygenated taxanes will be reported separately.

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Supplementary Material Available: Experimental details and ^{1}H-NMR spectra of key compounds (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) For the related epoxide fragmentation, see: Sabatino, E. C.; Gritter, R. J. *J. Org. Chem.* **1963**, *28*, 3437. For the fragmentation of cyclobutylcarbinyl radicals, see: Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1083.

(12) For a review see: Beckwith, A. L. J.; Ingold, K. U. In *Free Radical Rearrangements*; De Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 161.

(13) The results are the average of three determinations. For details of the *in vitro* cytotoxicity assay: Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827.