Modified Taxols. 10. Preparation of 7-Deoxytaxol, a Highly Bioactive Taxol Derivative, and Interconversion of Taxol and 7-*epi*-Taxol[1]

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Received May 4, 1993

Summary: Deoxygenation of taxol at C-7 can be achieved through its *S*-methyldithiocarboxy derivative **3** to yield a product which is more cytotoxic than taxol to P-388 cells.

Taxol (**1**) is an important new anticancer agent with clinical activity against several human cancers. First isolated in the late 1960's by Wall and co-workers,[2] it has recently been shown to have excellent clinical activity against ovarian and breast cancers and also to have some activity against lung cancer; clinical trials in other cancers are ongoing.[3] Extensive studies on its chemistry and structure–activity relationships have appeared, both from our group[4] and from other groups,[5] and it continues to be the focus of several on-going studies.[6]

One of the early results obtained both with taxol and its close relative cephalomannine was that the hydroxyl group at the 7-position is readily epimerized when either compound is treated with mild base; this epimerization is thought to occur by a facile retro-aldol reaction followed by recyclization by an aldol condensation.[7] As normally carried out on taxol in hydroxylic solvents this reaction gives a mixture of taxol and 7-*epi*-taxol, which can be separated to yield both epimers. 7-*epi*-Taxol has not been tested extensively for biological activity, but it appears to be slightly less active than taxol.[6b,c] Further studies of the effect of the 7-hydroxyl group on taxol's activity were carried out by preparation of 7-acetyltaxol[8c,8] and other 7-acyltaxols.[9] These derivatives also showed activities which were only slightly less than those of taxol in several bioassay systems.

On the basis of these data, it appeared that the C-7 hydroxyl group has only a secondary effect on the activity of taxol, since epimerizing it or acylating it cause only modest decreases in taxol's activity. *We now report the surprising finding that removal of the C-7 hydroxyl group yields a taxol analogue which is more cytotoxic than taxol to P-388 leukemia cells.*

Initial attempts to deoxygenate taxol at C-7 through a 7-thionobenzoate derivative[10] or a 7-(phenyloxy)thionyl derivative[11] were unsuccessful,[12] as were attempts to deoxygenate it through its 7-(pentafluorophenyl) thiocarbonate[13] and its 7-(2,4,6-trichlorophenyl) thiocarbonate[13] derivatives. Deoxygenation was, however, finally achieved through the *S*-methyl xanthate **3**. Treatment of taxol (**1**) with triethylchlorosilane and imidazole gave 2′-(triethylsilyl)taxol (**2**) in quantitative yield, and treatment of **2** with 1–2 equiv of sodium hydride in dry THF, followed by excess carbon disulfide and iodomethane, yielded **3** in 60% yield. Formation of **3** was accompanied by the formation of lesser amounts of a second product tentatively identified as 1-benzoyl-2-debenzoyl-2′-(triethylsilyl)-2,7-bis(*S*-methyldithiocarboxy)taxol (**4**), together with some unreacted starting material. Deoxygenation of **3** with tributyltin hydride in the presence of AIBN in toluene at 75 °C[14] gave the 7-deoxy derivative **5**, and deprotection of **5** with dilute acid gave 7-deoxytaxol (**6**) in 49% yield from **3**. On the basis of unrecovered starting material, the conversion of **1** to **6** can be carried out in approximately 37% yield.

*Compound **6** is more cytotoxic than taxol in the P-388 leukemia system, showing ED_{50} 1×10^{-4} μg/mL as compared with 4×10^{-3} μg/mL for taxol.* This compound thus represents an important new derivative for future development, and it also suggests that introduction of a hydroxyl group at C-7 may not be necessary for the synthesis of taxol analogues, thus simplifying the synthetic problem.

(1) Part 9: see ref 9.

(2) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.

(3) For reviews: (a) Rowinsky, E. K.; Donehower, R. C., *J. Natl. Cancer Inst.* **1991**, *83*, 1778–1781. (b) Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *Ibid.* **1991**, *83*, 1797–1805. (c) Slichenmyer, W. J.; Von Hoff, D. D. *Anti-Cancer Drugs*, **1991**, *2*, 519–530. (d) Rowinsky, E. K.; Donehower, R. C. *Pharmac. Ther.* **1991**, *52*, 35–84.

(4) Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.* **1986**, *51*, 797–802. (b) Magri, N. F.; Kingston, D. G. I.; Jitrangsri, C.; Piccariello, T. *J. Org. Chem.* **1986**, *51*, 3239–3242. (c) Kingston, D. G. I.; Gunatilaka, A. A. L.; Ivey, C. A. *J. Nat. Prod.* **1992**, *55*, 259–261. (d) Magri, N. F.; Kingston, D. G. I. *J. Nat. Prod.* **1988**, *51*, 298–306. (e) Samaranayake, G.; Magri, N. F., Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114–5119. (f) Samaranayake, G.; Neidigh, K.; Kingston, D. G. I. *J. Nat. Prod.*, in press.

(5) Gueritte-Voegelein, F.; Guenard, D.; Lavelle, F.; Le Goff, M. T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992–998. (b) Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *Ibid.* **1991**, *34*, 1176–1184. (c) Lataste, H.; Senilh, V.; Wright, M.; Guenard, D.; Potier, P., *Proc. Nat. Acad. Sci. U.S.A.* **1984**, *81*, 4090–4094. (d) Chen, S.-H.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805–2828. (e) Klein, L. L. *Tetrahedron Lett.*, **1993**, *34*, 2047–2050. (f) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 295–298. (g) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R., Burke, C. T. *J. Med. Chem.* **1992**, *35*, 4230–4237.

(6) For reviews on the chemistry and structure –activity relationships of taxol: (a) Suffness, M.; Cordell, G. A. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 25, pp 3–355. (b) Kingston, D. G. I.; Samaranayake, G.; Ivey, C. A. *J. Nat. Prod.* **1990**, *53*, 1–12. (c) Blechert, S.; Guenard, D. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195–238. (d) Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1–34. (e) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1–188.

(7) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, R.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469–1474. (b) Huang, C.-H. O.; Kingston, D. G. I.; Magri, N. F.; Samaranayake, G.; Boettner, F. E. *J. Nat. Prod.* **1986**, *49*, 665–669. (c) Ringel, I.; Horwitz, S. B. *J. Pharmac. Exp. Ther.* **1987**, *242*, 692–698.

(8) Mellado, W.; Magri, N. F.; Kingston, D. G. I.; Garcia-Arenas, R.; Orr, G. A.; Horwitz, S. B. *Biochem. Biophys. Res. Commun.* **1984**, *124*, 329–335. (b) Chenu, J.; Takoudju, M.; Wright, M.; Senilh, V.; Guenard, D. *J. Labeled Compd Radiopharm.* **1987**, *24*, 1245–1255.

(9) Rimoldi, J. M.; Kingston, D. G. I.; Chaudhary, A. G.; Samaranayake, G.; Grover, S.; Hamel, E. *J. Nat. Prod.*, in press.

(10) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.

(11) Robbins, M. J.; Wilson, J. S.; Hansske, F., *J. Am. Chem. Soc.*, **1983**, *105*, 4059–4065.

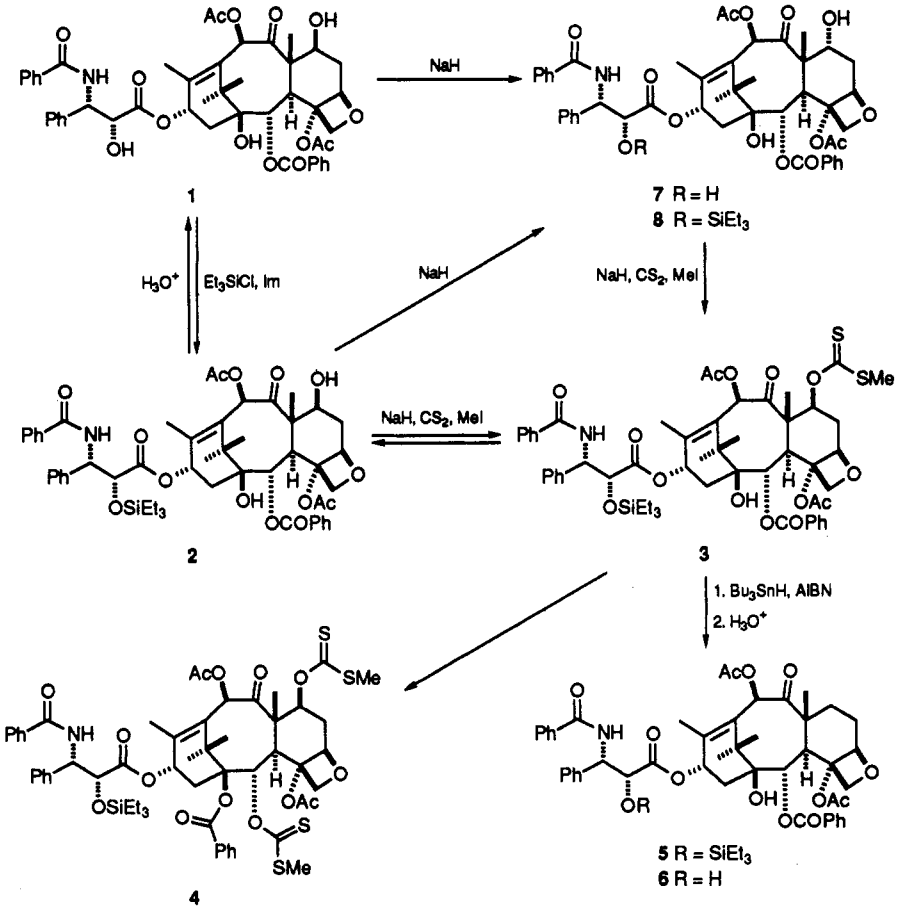
(12) Magri, N. F. Ph.D. Dissertation, Virginia Polytechnic Institute and State University, 1985.

(13) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619–2622. (b) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *43*, 8969–8984.

(14) For reviews see: (a) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15–31. (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609–2645.

0022-3263/93/1958-3798$04.00/0

Scheme I



In the course of these studies, we also developed efficient methods to convert taxol into 7-*epi*-taxol and 7-*epi*-taxol to taxol. Treatment of taxol (1) or 2′-(triethylsilyl)taxol (2) with sodium hydride in dry THF led to rapid epimerization at C-7 to yield 7-*epi*-taxol (7) or 2′-(triethylsilyl)-7-*epi*-taxol (8) in 70–80% yield. This method of formation of 7-*epi*-taxol is superior to the one reported earlier,[7b] which has proved to give very variable results and has failed completely in some cases in our hands, although it originally worked very well. It thus seems probable that the original purified batch of AIBN was contaminated with base in some way and that epimerization was due to this contaminant rather than to the AIBN.

Conversion of 7-*epi*-taxol to taxol could be achieved through the 7-(*S*-methylthiocarboxy)taxol 3. Treatment of 2′-(triethylsilyl)-7-*epi*-taxol 8 with sodium hydride, carbon disulfide, and methyl iodide converted it into the *S*-methylthiocarboxy derivative 3 of the *normal* series, together with some of the putative dixanthate 4. The pathway for this reaction, which was verified by TLC analysis of the course of the reaction, involves equilibration of the *epi*-taxol derivative 8 and the taxol derivative 2, with 8 being the major epimer. Compound 2, however, can react with carbon disulfide and methyl iodide to form the S-methyl xanthate 3, while compound 8 is unreactive to these reagents (presumably because of steric crowding around the 7-*epi*-hydroxyl group). Conversion of 8 to 3 thus occurs under the indicated conditions, in an unoptimized yield of 62%.

Hydrolysis of 3 could be achieved by treatment with tributyltin hydride and AIBN in wet toluene[10] to yield 2′-(triethylsilyl) taxol (2), which could be hydrolyzed quantitatively to taxol (1), thus completing the cycle. The overall conversion of 3 to 1 occurred in 95% yield. These reaction sequences thus provide pathways for the conversion of taxol to 7-*epi*-taxol and of 7-*epi*-taxol to taxol.

Acknowledgment. Financial support for this work was provided by the National Cancer Institute, grant CA-55131. Mass spectra were obtained by the Midwest Center for Mass Spectrometry with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262). We thank Dr. K. Snader, National Cancer Institute, for a gift of crude taxol-containing fractions which were used as the source of taxol for this work.

Supplementary Material Available: Experimental procedures and NMR data for compounds 2, 3, 6, and 8 (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm edition of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.