Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.16; H, 10.57.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Purchase of a preparative liquid chromatograph was made possible by a grant from the National Science Foundation.

Registry No. 7, 22628-06-4; 8, 100207-72-5; 9, 100207-75-8; 10, 100207-77-0; 11, 100207-78-1; 12, 100207-79-2; 13, 100207-80-5; 14, 100207-81-6; 15, 100296-06-8; *trans*-16, 937-99-5; *cis*-16, 937-98-4; 17 (isomer 1), 100207-73-6; 17 (isomer 2), 100207-74-7; 18, 100207-76-9; bromomagnesium isopropylcyclohexylamide, 100207-82-7.

Modified Taxols. 2.[1] Oxidation Products of Taxol

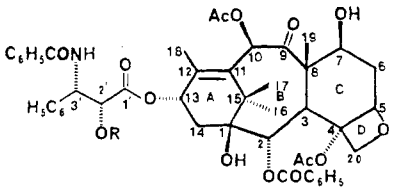
Neal F. Magri and David G. I. Kingston*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received September 26, 1985

Oxidation of taxol (1) or substituted taxols with Jones' reagent under appropriate conditions yielded 7-oxotaxol (6), 2',7-dioxotaxol (9), or 2'-oxo-7-acetyltaxol (12). Treatment of 7-oxotaxol with DBU or silica gel yielded a *D*-secotaxol derivative 14. Hydrogenation of the 2'-acetate derivative of 14 yielded the unstable diketone 16, while hydrogenation of 14 itself followed by workup in methanol gave the lactone 17.

The complex diterpene taxol (1) was reported in 1971 as the major cytotoxic and antileukemic constituent of *Taxus brevifolia* Nutt.[2] It shows activity in several of the National Cancer Institute's in vivo screens, including the P-388, L-1210, and P-1534 mouse leukemias, the B-16 melanocarcinoma, the CX-1 colon xenograft, the LX-1 lung xenograft, and the MX-1 breast xenograft,[3] and it also shows strong cytotoxicity in KB cell culture.[2] Taxol blocks



1 R = H

4 R = $COCH_3$

7 R = $COOCH_2CCl_3$

cell replication in HeLa cells, predominantly in the mitotic phase of the cell cycle, and studies with purified microtubule protein have demonstrated that it promotes the assembly of unusually stable microtubles in vitro and in cells.[4] The ability to promote the assembly of microtubules in the absence of GTP is a unique feature of this drug,[5] and studies done in vitro with [^{3}H]taxol have indicated that at saturation the drug binds reversibly to polymerized tubulin with an approximate stoichiometry of 1 mol of taxol per mol of polymerized dimer.[6]

Because of its promising anticancer activity and its unusual structure and mechanism of action, taxol is currently undergoing clinical tests as a potential cancer chemotherapeutic agent. However, taxol is obtainable only in relatively low yield by extraction and isolation from *Taxus brevifolia*.[7] In an attempt to address this problem we have initiated a study of structure–activity relationships in the taxol area, in order to determine which parts of the molecule are essential for activity. The ultimate goal of this work (which may or may not be attainable) is to design a simpler analogue of taxol which would be accessible either by synthesis or by modification of such readily available taxanes as *O*-cinnamoyltaxicin-I triacetate (2)[9] or taxusin (3).[10]

(1) Mellado, W.; Magri, N. F.; Kingston, D. G. I.; Garcia-Arenas, R.; Orr, G. A.; Horwitz, S. B. *Biochem. Biophys. Res. Commun.* **1984** *124*, 329–336. This reference is considered Part 1 of this series.

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

(3) Lomax, N. R., Narayanan, V. L. "Chemical Structures of Interest to the Division of Cancer Treatment"; U.S. Government Printing Office: Washington, DC, 1983; Vol. III, p 17.

(4) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561–1565. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature (London)* **1979**, *277*, 665–667. Kumar, N. *J. Biol. Chem.* **1981**, *256*, 10435–10551. DeBrabander, M.; Geuens, G.; Nuydens, R.; Willebrods, R.; DeMey, J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5608–5612.

(5) Schiff, P. B.; Horwitz, S. B. *Biochemistry* **1981**, *20*, 3247–3252.

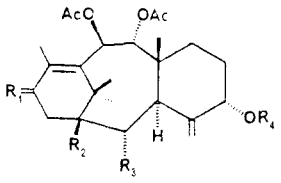
(6) Parness, J.; Horwitz, S. B. *J. Cell. Biol.* **1981**, *91*, 479–487.

(7) Recent large-scale extractions gave yields of 0.004% and 0.016% of taxol from *T. brevifolia* bark wood. Boettner, F. E.; Williams, T. M.; Boyd, R.; Halpern, B. D. Preparation Report 9, Polysciences, Inc.: Paul Valley Industrial Park, Warrington, PA 18976, Nov 24, 1974; Boettner, F. E.; Tara, D.; Forsyth, G.; Murphy, D.; Epling, B.; Halper, B. D. Preparation Report 36, Polysciences, Inc.: Paul Valley Industrial Park, Warrington, PA 18976, Feb 22, 1985.

(8) A number of synthetic approaches to the taxane ring system have been published: Kato, T.; Takayanagi, H.; Suzuki, T.; Uyehara, T. *Tetrahedron Lett.* **1978**, 1201–1204. Kitigawa, I.; Shibuya, H.; Fujioka, H.; Kejiwara, A.; Tsujii, S.; Yamamoto, Y.; Takagi, A. *Chem. Lett.* **1980**, 1001–1004. Inouye, Y.; Fukaya, C.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1117–1125. Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190–3192. Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886–887. Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732–3732. Shea, K. J.; Davis, P. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 419–420. Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, 253–255. Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731–5732. Neh, H.; Blechest, S.; Schnick, W.; Jansen, M. *Ang. Chem., Int. Ed. Engl.* **1984**, *23*, 905–906. Andriamialisoa, R. Z.; Fetizon, M.; Hanna, I.; Pascard, C.; Prange, T. *Tetrahedron* **1984**, *40*, 4285–4295. Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 5389–5392. Trost, B. M.; Fray, J. *Tetrahedron Lett.* **1984**, *25*, 4605–4608. Swindell, C. S.; deSolms, S. J. *Tetrahedron Lett.* **1984**, *25*, 3801–3804. Jackson, C. B.; Pattenden, G. *Tetrahdedron Lett.* **1985**, *26*, 3393–3396. Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3397–3400. Kojima, T.; Inouye, Y.; Kakisawa, H.; *Chem. Lett.* **1985**, 323–326. Berkowitz, W. F.; Amaresekara, A. S. *Tetrahedron Lett.* **1985**, *26*, 3663–3664. Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *Tetrahedron Lett.* **1985**, *26*, 3665–3668.

(9) Lythgoe, B. In "The Alkaloids"; Manske, R. F. H., Ed.; Academic Press: New York, 1968; Vol. 10, Chapter 14, pp 597–626.

0022-3263/86/1951-0797$01.50/0



2 R_1 = O; R_2 = OH; R_3 = $OCOCH_3$; R_4 = $COCH{=}CHC_6H_5$

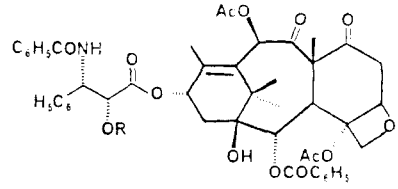
3 R_1 = endo-$OCOCH_3$, exo-H; R_2 = R_3 = H; R_4 = $COCH_3$

We have previously reported on the preparation and biological activity of some acetate derivatives of taxol,[1] and in this paper we discuss the oxidation of taxol and its consequences. Biological data on the compounds discussed in this paper will be presented in a subsequent paper in the series.

Results and Discussion

Taxol possesses three free hydroxyl groups, at positions 1, 2′, and 7. Selective oxidation of the 7-hydroxyl group would be of interest since we have shown that 7-acetyltaxol retains the effects of taxol on cell replication and on in vitro microtubule polymerization,[1] and further modifications of this group would thus assist in determining the importance of substitution at C7 for the activity of taxol. Oxidation at the C2′ position would also be of interest, since one of the hypotheses for the mechanism of action of taxol is that the C13 ester linkage, activated by the 2′-hydroxyl group, acts as an acylating agent.[11]

Our initial studies were carried out on taxols protected at the 2′-position. Oxidation of 2′-acetyltaxol (**4**)[1] with Jones' reagent yielded the 7-oxo derivative **5** in essentially quantitative yield. Attempted deacylation of **5** to 7-



5 R = $COCH_3$

6 R = H

8 R = $COOCH_2CCl_3$

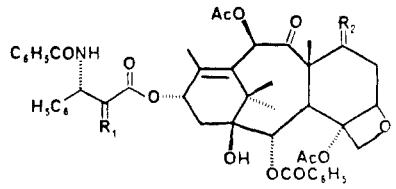
oxotaxol (**6**) could not be effected under mild conditions (0.025% aqueous methanolic $NaHCO_3$[1] or KCN in ethanol[12]), due to the base sensitivity of the 7-oxo derivative; reaction in each case yielded a complex mixture of products.

Deprotection of an oxidized 2′-derivative of taxol was effected by use of the [(2,2,2-trichloroethyl)oxy]carbonyl (troc) protecting group. Preparation of 2′-troc-taxol (**7**) was carried out by reaction of taxol with 2,2,2-trichloroethyl chloroformate under milder conditions than those previously reported;[13] the desired product was obtained in 85% yield together with small amounts of taxol and 2′,7-ditroc-taxol.

Oxidation of 2′-troc-taxol with Jones' reagent followed by deprotection of the resulting 2′-troc-7-oxotaxol (**8**) with zinc in methanolic acetic acid gave 7-oxotaxol (**5**) in 94% yield. The product was characterised by its method of preparation and its spectroscopic properties. Its molecular weight, as shown by FAB mass spectrometry, was 851 (MH^+ at m/z 852), two units less than that of taxol. Its ^1H NMR spectrum showed an absence of signals for the C7 proton and a shift in the signals for the C6 proton from a two-proton multiplet at 2.0 ppm in taxol to a one-proton doublet at 3.10 ppm (J = 19 Hz) and a one-proton doublet of doublets at 2.59 ppm (J = 6, 19 Hz). Irradiation of the doublet at 2.59 ppm caused the doublet at 3.10 ppm to collapse to a singlet and also caused the doublet for the C5 proton at 5.06 ppm (J = 6 Hz) to collapse to a singlet.

Having established the structure of 7-oxotaxol by unambiguous synthesis, we were then able to prepare it more efficiently by direct oxidation of taxol. Oxidation of taxol (**1**) with Jones' reagent yielded 7-oxotaxol (**6**) as the major product, and pure material was obtained by preparative HPLC in 50% yield; the material obtained in this way was identical with that obtained by the route described above. The lack of reactivity of the 2′-hydroxyl group under these mild conditions is an expected consequence of the fact that it is adjacent to a carbonyl group.

Oxidation of taxol with excess Jones' reagent for an extended period yielded 2′,7-dioxotaxol (**9**) as the major product, as judged by ^1H NMR and TLC evidence. This material was purified by preparative reverse-phase HPLC using methanol–water as eluant, and the ^1H NMR spectrum of the isolated product showed that it was approximately a 70:30 mixture of 2′,7-dioxotaxol and a new substance. Analysis of the purified 2′,7-dioxotaxol by HPLC showed the presence of an additional less polar compound which had not been present during the initial isolation. A



9 R_1 = R_2 = O

10 R_1 = OH, OCH_3; R_2 = O

11 R_1 = OH, OH; R_2 = O

12 R_1 = O; R_2 = α-H, β-$OCOCH_3$

solution of the mixture of 2′,7-dioxotaxol and the new product was allowed to stand in $CDCl_3$ solution, and after 12 h its ^1H NMR spectrum indicated that essentially complete reversion to 2′,7-dioxotaxol had occurred. The ^1H NMR spectrum of the new product (obtained by subtraction of the spectrum of 2′,7-dioxotaxol from that of the mixture) showed as its most prominent feature a new three-proton singlet at 4.42 ppm; the other signals were very similar to those of 2′,7-dioxotaxol. These data indicate that the unstable new compound is a hemiketal derivative of 2′,7-dioxotaxol and most probably the methanol adduct **10**. The stereochemistry of the new chiral center is unknown, but the observation of a single sharp methoxy resonance at 4.42 ppm suggests that **10** is a single diastereomer.

The ready formation of the adduct **10** raises the question as to whether 2′,7-dioxotaxol esists as such or as its hydrate **11**. The mass spectrum of the substance showed an apparent protonated molecular ion peak at m/z 850, corresponding to structure **9**, but this is not conclusive evidence since the observed peak could correspond to $(MH - H_2O)^+$, with MH^+ being unobserved. However, the ready conversion of **10** to **9** on standing in $CDCl_3$ suggests that 2′,7-dioxotaxol is correctly formulated at **9**, since the same

(10) Miyazaki, M.; Shimizu, K.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546–548.
(11) Fujita, E.; Nagao, Y. *Bioorg. Chem.* **1977**, *6*, 287–309.
(12) Mori, K.; Sasoki, M. *Tetrahedron Lett.* **1979**, 1329–1332.
(13) Sénilh, V.; Blechert, S.; Colin, M.; Guénard, D.; Picot, F.; Potier, P.; Varenne, P. *J. Nat. Prod.* **1984**, *47*, 131–137.

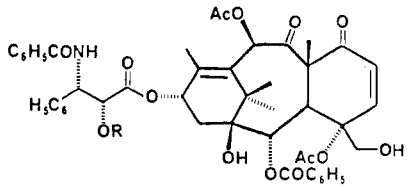
factors causing decomposition of the hemiketal **10** to **9** would also presumably cause any hydrate **11** to revert to **9**.

Oxidation of 7-acetyltaxol with excess Jones' reagent at room temperature for 24 h yielded 2′-oxo-7-acetyltaxol (**12**) in good yield. Isolation by preparative TLC without the use of alcohol solvents assured that conversion to a hemiketal did not occur. The product showed the same shift of the C-3′ proton as 2,7-dioxotaxol to 6.47 (d, J = 9 Hz), and its FAB mass spectrum showed a protonated molecular ion at m/z 894, indicating a molecular weight of 893 for this compound, two units less than that of 7-acetyltaxol.

These reactions indicate that taxol is a generally stable molecule in dilute sulfuric acid solution, since it withstands the long exposure of the Jones' reagent oxidations. The reactivity of the two secondary hydroxyl groups is in line with expectations from general principles, but it is noteworthy that the reactivity difference is such that the 7-hydroxyl group can be selectively oxidized in the presence of a free 2′-hydroxyl group. We saw no evidence of epimerization at C3′ in the 2′-oxotaxols under the mild conditions of our work. Finally, these studies reinforce the usefulness of the [(2,2,2-trichloroethyl)oxy]carbonyl protecting group for taxol, since it can be cleanly removed even from a labile intermediate such as 2′-troc-7-oxotaxol (**8**).

With the methods of preparation of 7-oxotaxol and its derivatives now established, we next turned to an investigation of the reactivity of the 7-oxo group.

Treatment of 2′-acetyl-7-oxotaxol (**5**) with mild aqueous bases led to a complex mixture of products, as described earlier. However, treatment with 1,8-diazabicycloundecene (DBU) in dichloromethane at 25 °C rapidly gave the D-seco product **13** in quantitative yield. The structure of



13 R = $COCH_3$

14 R = H

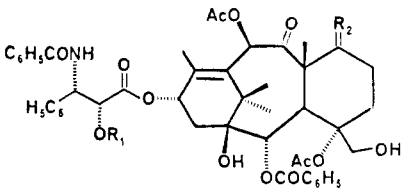
13 was deduced from its spectral data. Its FAB mass spectrum showed a protonated molecular ion at m/z 894 unchanged from that of 2′-acetyl-7-oxotaxol **5**. The ^1H NMR spectrum of **13** showed sharp signals for two new vinyl protons at 6.01 (d, J = 10 Hz) and 7.00 (d, J = 10 Hz) ppm for the α- and β-protons of the new enone system, H-6 and H-5, respectively. In addition, the geminal coupling constant for the C20 protons is 12 Hz, as compared with 8 Hz in taxol and related compounds with an intact oxetane ring. This change in coupling constant corresponds to that expected from the hybridization changes on opening up the oxetane ring.[14]

The ring-opening reaction to form D-secotaxol derivatives occurs very readily and even occurs on silica gel under some conditions. We were thus able to prepare 7-oxo-6-dehydro-5,O-secotaxol (**14**) in 70% yield in a one-step reaction involving oxidation of taxol with Jones' reagent and purification of the product by preparative TLC on silica gel. Samples of 7-oxotaxol (**6**) which were stored as solids at room temperature were converted to the D-seco derivative **14** over a period of several months.

(14) Mathieson, D. W., Ed. "Nuclear Magnetic Resonance for Organic Chemists"; Academic Press: London, 1967; p 135.

One significant consequence of the ring-opening to form D-secotaxols such as **13** and **14** is that the resulting tricyclic ring system is considerably more flexible than the tetracyclic ring system of taxol, which is locked into a rigid inverted cup shape by the constraints of its tetracyclic nature. One indication of this increased flexibility and the conformational changes associated with it is that the signals for the protons of the A ring undergo noticeable shifts on opening the D ring. Thus, the C13 proton is observed as a broad triplet at about 6.2 ppm (J = 7 Hz) in all the tetracyclic taxol derivatives that we have encountered. In the spectra of the D-secotaxol derivatives, however, it occurs as a doublet of doublets at about 5.9 ppm (J = 4, 11 Hz). The C14 protons also change from a complex multiplet near 2.4 ppm to two doublets of doublets at 3.0 (J = 4, 16 Hz) and 2.4 ppm (J = 11, 16 Hz).

In view of the potential importance of D-secotaxol derivatives in understanding the factors governing the activity of taxol, we desired to carry out the reduction of these derivatives to a derivative such as the D-secotaxol **15** in which the only structural differences between the compound and taxol lies in the fact that the oxetane ring is opened in **15**. Unfortunately the secotaxol **14** could not



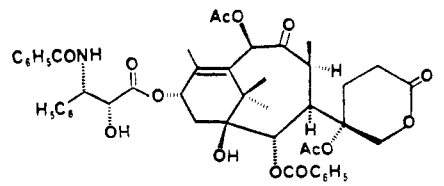
15 R_1 = H; R_2 = α-H, β-OH

16 R_1 = $COCH_3$; R_2 = O

be reduced to the tetrahydro derivative **15** under any conditions that did not also reduce other functional groups in the molecule, and our attempts in this direction were thus abandoned. We did, however, succeed in preparing the dihydro derivative **16**, as outlined below.

Attempted reduction of the D-secotaxol **13** with hydrogen or formic acid in the presence of palladium on alumina gave no reduced product, but hydrogenation in ethyl acetate over platinum on carbon with a workup that did not involve heat or exposure to hydroxylic solvents yielded the unstable dihydro derivative **16**. Structural assignment of **16** was made primarily on the basis of its ^1H NMR spectrum, which showed the expected disappearance of the two enone doublets at 6.00 and 7.00 ppm and the appearance of new multiplets at 2.3–2.5 ppm. Other signals in the spectrum were all consistent with the assigned structure.

Hydrogenation of the D-secotaxol **14** in methanol, followed by a workup which involved warming to 40 °C on a rotary evaporator, yielded a new product identified as the lactone **17**. Structure assignment of **17** was made on



17

the basis of its ^1H NMR and mass spectrum. Its FAB mass spectrum showed a protonated molecular ion at m/z 854, and exact mass measurement confirmed the composition $C_{47}H_{52}NO_{14}$ for this ion. The ^1H NMR spectrum showed

a three-proton doublet at 1.39 ppm (J = 7 Hz) for the methyl group at C8. Double resonance experiments showed that the methyl protons were coupled to a proton resonating at 3.10 ppm (dd, J = 1, 7 Hz), which in turn was coupled to the C3 proton at 3.77 ppm (dd, J = 2, 7 Hz). The C20 protons occur as a pair of doublets at 4.43 (J = 11 Hz) and 4.68 ppm (J = 11 Hz), downfield from their position in **15** due to acylation. The stereochemistry at C8 was assigned as β-methyl on the basis of the observed coupling constant of 2 Hz between H8 and H3, since an analysis of a Dreiding model showed that the dihedral angle between these protons is in the range 70–100 °C for accessible conformations with a β-methyl but 120–165 °C for conformations with an α-methyl. The lactone **17** could arise either from intramolecular attack of the C20 hydroxyl group on the C7 carbonyl group, followed by a retro-Claisen reaction or by an initial retro-Claisen reaction catalyzed by methanol, followed by lactonization.

The work reported in this paper shows that it is possible to manipulate the structure of taxol in a reasonably precise fashion provided that nonbasic conditions are employed. Previous work on taxol has shown that the compound rapidly hydrolyzes and epimerizes in basic solution to yield complex mixtures of products,[15] but in our hands the compound is relatively stable in nonnucleophilic acids such as dilute sulfuric acid and in neutral solution. The conformational change observed on opening of the oxetane ring may have important implications for the biological activity of taxol derivatives, since it indicates that taxol itself is in a fixed rigid conformation. This rigid conformation of taxol may in part explain why it is essentially unique in its biological activity.

Experimental Section

General Methods. Analytical TLC was performed on silica gel 60 F_{254} plates (E. Merck), 0.2-mm layer. Preparative TLC was on silica gel GF plates, 20 × 20 cm × 1000 μm thick (Analtech). HPLC analysis was carried out on an apparatus consisting of a Waters Associates M-6000A pump, a Valco injection valve, and a Waters Associates Model 441 absorbance detector set at 254 nm. Analytical HPLC was carried out either on an RP-8 column, 4.6 × 250 mm (Alltech), or on a Resolve-C_8 Radial-Pak cartridge (Waters). Preparative HPLC was on LiChrosorb RP-8, 10 × 250 mm (E. Merck). ^{1}H NMR spectra were obtained on an IBM WP-270 spectrometer operating at 270 MHz; spectra were obtained at room temperature in $CDCl_3$, and chemical shifts are reported by using the residual proton signal at 7.24 ppm as internal standard. Mass spectra were obtained by the fast atom bombardment (FAB) method on Kratos MS 50 instruments at the Midwest Center for Mass Spectrometry at the University of Nebraska, a National Science Foundation Regional Instrumentation Facility (Grant CHE 82-11164); a few spectra were also obtained at the Middle Atlantic Mass Spectrometry Laboratory at Johns Hopkins University, a National Science Foundation Regional Instrumentation Facility (Grant CHE 78-18386). The designation (M – RCOOH)$^+$ in the listing of mass spectral data indicates an ion formed by loss of the C13 ester side chain as an acid. IR spectra were obtained in KBr and rotations on a Perkin-Elmer 241 polarimeter.

The phrase "worked up by standard methods" means dilution of the reaction mixture with an excess of CH_2Cl_2 or other organic solvent, washing with 1 N HCl, 5% $NaHCO_3$, and H_2O, drying over $MgSO_4$, filtration through a cotton plug in a Pasteur pipet, and evaporation of solvent in vacuo. Oxidation reactions were worked up by stopping the reaction with a few drops of 2-propanol, filtering through a 0.45-μm filter to remove precipitated chromium salts, dilution with CH_2Cl_2, washing with 5% $NaHCO_3$ and water, drying with $MgSO_4$, filtration of the solution, and evaporation of the solvent in vacuo.

Crude taxol preparations were supplied by Polysciences, Inc., and pure taxol was a gift of the National Cancer Institute.

2′-Acetyl-7-oxotaxol (5). 2′-Acetyltaxol (**4**)[1] (19 mg) was dissolved in acetone (0.3 mL) and treated with Jones' reagent[16] (11 μL) at room temperature. The reaction was worked up by standard methods after 30 min to yield 2′-acetyl-7-oxotaxol (**5**) as the only product, homogeneous on TLC: R_f 0.54 (EtOAc–hexane, 6:4) [2′-acetyltaxol has R_f 0.35 in this system]; FABMS, m/z 916 (MNa$^+$), 894 (MH$^+$) 567, 549, 507; IR 1765, 1755, 1675, 1535, 1505, 1475, 1390, 1250, 1195, 1125 cm^{-1}; ^{1}H NMR, see Table I; $[\alpha]_D$ −26.0° (c 0.004, MeOH).

Attempted Deacylations of 2′-Acetyl-7-oxotaxol. (A) With $NaHCO_3$. 2′-Acetyl-7-oxotaxol (**5**) (0.5 mg) was treated with 3.0 mL of a solution of 3:1:0.01 MeOH–H_2O–$NaHCO_3$, as was previously used on 2′,7-diacetyltaxol.[1] The reaction was monitored by HPLC (RP-8; MeOH–H_2O, 65:35); after 1.5 h at room temperature all the material had decomposed to a complex mixture of polar products.

(B) With KCN/EtOH. 2′-Acetyl-7-oxotaxol (1 mg) was dissolved in 0.3 mL EtOH containing 0.75% KCN. HPLC indicated that a variety of polar products was formed immediately, and conversion of the starting material to these products was largely complete after 45 min at 0 °C.

2′-[((2,2,2-Trichloroethyl)oxy)carbonyl]taxol (7). Taxol (50 mg) in CH_2Cl_2 (1.0 mL) and pyridine (0.1 mL) was cooled to −23 °C and treated with 2,2,2-trichloroethyl chloroformate (0.008 mL) over 45 min. Workup by standard methods yielded a mixture of **7** (R_f 0.34; EtOAc–hexane, 1:1) together with small amounts of taxol, R_f 0.11, and a product assumed to be 2′,7-bis[((2,2,2-trichloroethyl)oxy)carbonyl]taxol, R_f 0.74. The product was isolated by PTLC with EtOAc–hexane (1:1) as solvent: yield, 51 mg (85%); FABMS, m/z 1028 (MH$^+$), 509; IR 1780, 1740, 1690, 1675, 1530, 1505, 1390, 1290, 1255 cm^{-1}; ^{1}H NMR, see Table I.

7-Oxotaxol (6). (A) From 2′-[((2,2,2-Trichloroethyl)oxy)carbonyl]taxol (7). Compound **7** (51 mg) in acetone (3.0 mL) was treated with Jones' reagent (0.05 mL) for 11 min at room temperature; standard workup gave 2′-[((2,2,2-trichloroethyl)oxy)carbonyl]-7-oxotaxol (**8**) as a homogeneous material, R_f 0.69 (EtOAc–hexane, 1:1). Compound **8** was dissolved in MeOH–AcOH (9:1) (2.0 mL) and zinc dust (40 mg) added. The mixture was stirred for 10 min at room temperature and was then filtered to remove excess zinc, evaporated to small volume, and worked up by standard methods. The resulting 7-oxotaxol (**6**) was homogeneous on TLC: R_f 0.22 (EtOAc–hexane, 3:2); yield, 39.8 mg (94%); FABMS, m/z 890 (MK$^+$), 874 (MNa$^+$), 852 (MH$^+$), 788 (MH$^+$ – AcOH), 774 (MH$^+$ – AcOH – H_2O), 589 (MNa$^+$ – RCOOH), 567 (MH$^+$ – RCOOH), 549 (MH$^+$ – RCOOH – H_2O), 507 (MH – RCOOH – AcOH)$^+$; IR 1750, 1730, 1685, 1665, 1535, 1510, 1395, 1290, 1260, 1120–1060 cm^{-1}, ^{1}H NMR, see Table I.

(B) From Taxol. Taxol (20 mg) in acetone (0.1 mL) was treated with Jones' reagent (0.02 mL). The reaction was allowed to proceed for 20 min at room temperature, and was then worked up by standard methods. The crude product was purified by preparative HPLC (RP-8 column; MeOH–H_2O, 7:3) to yield 7-oxotaxol (10 mg, 50%), identical with the sample prepared by method A.

2′,7-Dioxotaxol (9). Taxol (24 mg) in acetone (0.40 mL) was treated with Jones' reagent (0.05 mL) and the mixture allowed to stand for 24 h. Workup by standard methods yielded a mixture of which the major component, as judged by ^{1}H NMR, was 2′,7-dioxotaxol (**9**). Purification by preparative HPLC (RP-8 column; MeOH–H_2O, 70:30) followed by evaporation of the methanol in vacuo and extraction of the product into ethyl acetate gave two products as judged by ^{1}H NMR. A solution of the mixture was allowed to stand in $CDCl_3$ for 12 h, and the resulting solution was homogeneous as judged by ^{1}H NMR. The isolated material had the following: FABMS m/z 850 (MH$^+$), 790 (MH$^+$ – AcOH), 772 (MH$^+$ – AcOH – H_2O), 507 (MH – RCOOH$^+$ –

(15) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, A.; Clardy, J. J. Org. Chem. 1981, 46, 1469–1474.

(16) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. J. Chem. Soc. 1946, 39–45. Bladon, P.; Fabian, J. M.; Henbest, H. B.; Koch, H. P.; Wood, G. W. J. Chem. Soc. 1951, 2402–2411. Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. J. Chem. Soc. 1953, 2548–2560.

(17) Kingston, D. G. I.; Hawkins, D. R.; Ovington, L. J. Nat. Prod. 1982, 45, 466–470.

Table I. ^{1}H NMR Spectra of Modified Taxols[a]

protons on	1[b]	4	5	7	6
C2	5.62 (d, 7)	5.69 (d, 7)	5.77 (d, 6)	5.56 (d, 7)	5.74 (d, 7)
C3	3.80 (d, 7)	3.81 (d, 7)	4.29 (d, 6)	3.79 (d, 7)	3.78 (d, 7)
C5	4.92 (dd, 2, 8)	4.97 (dd, 2, 7)	5.08 (d, 5)	4.95 (d, 9)	5.06 (br d, 6)
C6		2.3–2.5 (m)	2.84 (d, 19)	2.4 (m)	3.10 (d, 19)
			3.09 (dd, 1, 19)		2.59 (dd, 6, 19)
C7	4.33 (m)	4.43 (dd, 6, 10)		4.41 (m)	
C10	6.26 (s)	6.29 (s)	6.42 (s)	6.27 (s)	6.18 (s)
C13	6.15 (t)	6.25 (br t, 8)	6.19 (br t, 8)	6.27 (br t, 8)	6.06 (br t, 9)
C14	2.5 (m)	2.3–2.5 (m)	2.3–2.4 (m)	2.4 (m)	2.45 (m)
C16	1.25 (s)	1.14 (s)	1.16 (s)	1.11 (s)	1.10 (s)
C17	1.14 (s)	1.27 (s)	1.18 (s)	1.21 (s)	1.07 (s)
C18	1.78 (s)	1.68 (s)	1.88 (br s)	1.65 (s)	1.41 (s)
C19	1.67 (s)	1.93 (br s)	2.05 (s)	1.87 (s)	1.78 (br, s)
C20	4.17 (d, 8)	4.15 (d, 8)	4.28 (d, 8)	4.19 (d, 8)	4.43 (d, 8)
	4.27 (d, 8)	4.24 (d, 8)	4.47 (d, 8)	4.21 (d, 8)	4.67 (d, 8)
C2′	4.71 (d, 3)	5.51 (d, 3)	5.53 (d, 3)	5.51 (d, 2.5)	4.91 (d, 2)
C3′	5.72 (dd, 3, 9)	5.95 (dd, 3, 9)	5.94 (dd, 9, 3)	6.03 (dd, 2.5, 9)	5.87 (dd, 2, 9)
NH	7.00 (d, 9)	6.88 (d, 9)	6.88 (d, 9)	6.91 (d, 9)	7.16 (d, 9)
OAc	2.23 (s)	2.16 (s)	2.43 (s)	2.20 (s)	1.90 (s)
	2.38 (s)	2.23 (s)	2.20 (s)	2.44 (s)	2.10 (s)
		2.38 (s)	2.14 (s)		
2-OBz	8.11 (dd)	8.10 (d, 7)	8.14 (d, 8)	8.13 (d, 8)	8.17 (d, 8)
	7.4 (m)	7.4 (m)	7.64 (t, 7)	7.60 (t, 8)	7.4 (m)
			7.4 (m)	7.4 (m)	
3′-NBz	7.7 (dd)	7.74 (d, 7)	7.73 (d, 7)	7.74 (d, 7)	7.79 (d, 8)
	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)
3′-Ph	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)
other				4.73 (d, 11)[c]	
				4.79 (d, 11)[c]	

protons on	9	12	13	14	17	16
C2	5.72 (d, 6)	5.65 (d, 7)	5.62 (d, 6)	5.60 (d, 6)	5.73 (d, 7)	5.57 (d, 5)
C3	4.72 (d, 6)	3.96 (d, 7)	4.17 (d, 6)	4.18 (d, 6)	3.77 (dd, 2, 7)	4.10 (d, 5)
C5	5.04 (br d, 7)	4.97 (d, 9)	7.00 (d, 10)	7.00 (d, 10)	2.3–2.5 (m)	4.3–2.5 (m)
C6	2.82 (dd, 1, 19)	2.2–2.5 (m)	6.01 (d, 10)	6.00 (d, 10)	2.3–2.5 (m)	2.3–2.5 (m)
	3.07 (dd, 7.19)					
C7		5.0 (dd, 6,10)				
C10	6.42 (s)	6.72 (s)	6.38 (s)	6.37 (s)	6.18 (s)	6.51 (s)
C13	6.12 (dd, 8, 10)	6.18 (br t, 9)	5.87 (br d, 11)	5.95 (br dd, 4, 10)	6.05 (br dd, 4, 10)	5.87 (br d, 10)
C14	2.15 (m)	2.2–2.4 (m)	2.46 (dd, 16, 4)	3.04 (dd, 4, 16)	2.2–2.5 (m)	3.10 (dd, 4, 15.5)
			2.44 (dd, 16, 11)			2.45 (br d, 15.5)
C16	1.15 (s)	1.18 (s)	1.06 (s)	1.20 (s)	1.08 (s)	1.14 (s)
C17	1.14 (s)	1.14 (s)	1.20 (s)	1.08 (s)	1.05 (s)	1.05 (s)
C18	1.84 (s)	1.77 (s)	1.55 (s)	1.83 (br s)	1.77 (br s)	2.02 (br s)
C19	2.00 (s)	1.96 (s)	1.90 (br s)	1.56 (s)	1.39 (d, 7)	1.60 (s)
C20	4.22 (d, 8)	4.12 (d, 8)	4.12 (d, 12)	4.35 (d, 12)	4.68 (br d, 11)	4.05 (d, 11.5)
	4.41 (d, 8)	4.28 (d, 8)	4.37 (d, 12)	4.18 (d, 12)	4.43 (d, 11)	4.56 (d, 11.5)
C2′			5.31 (d, 2)	4.87 (br s)	4.91 (dd, 2.5)	5.30 (d, 2)
C3′	6.41 (d, 6)	6.47 (d)	6.31 (dd, 2, 9)	6.08 (d, 9)	5.87 (dd, 2, 9)	6.30 (dd, 2, 9)
NH	7.12 (d, 6)	7.22 (d)	7.00 (d, 9)	7.12 (d, 9)	7.14 (d, 9)	7.03 (d, 9)
OAc	2.14 (s)	2.16 (s)	1.70 (s)	2.20 (s)	2.18 (s)	2.21 (s)
	2.19 (s)	2.13 (s)	2.17 (s)	1.77 (s)	1.89 (s)	2.16 (s)
		2.02 (s)	2.21 (s)			1.80 (s)
2-OBz	8.04 (d, 8)	7.73 (d)	8.22 (d, 8)	8.20 (d, 8)	8.14 (dd, 1, 8)	8.18 (d, 8)
	7.62 (t, 8)	7.4 (m)	7.20 (t, 8)	7.11 (t, 8)	7.58 (t, 8)	7.20 (t, 8)
	7.4 (m)		7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)
3′-NBz	7.80 (d, 8)	7.53 (d)	7.80 (d, 8)	7.79 (d, 8)	7.78 (dd, 1, 8)	7.79 (d, 8)
	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)
3′-Ph	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)	7.4 (m)
other			4.6 (s)[d]	4.60 (s)[d]	3.10 (qd, 2, 7)[e]	4.34 (br s)[d]
					3.44 (d, 5)[f]	

[a] Multiplicity and coupling constants in Hertz in parentheses. [b] Data from ref 17; measured at 200 MHz. [c] CH_2 protons of the 2,2,2-[(trichloroethyl)oxy]carbonyl group. [d] C20 hydroxy proton. [e] C8 proton. [f] C2′ hydroxyl proton.

AcOH); m/z 850.2861 (MH^+; $C_{47}H_{48}NO_{14}$ requires 850.3075); IR 1745, 1730, 1670, 1500, 1475, 1280, 1250, 1120, 1085, 1060, 720 cm^{-1}; ^{1}H NMR, see Table I.

Methanol Adduct of 2′,7-Dioxotaxol (10). A solution of 2′,7-dioxotaxol (**9**; 10 mg) in $CDCl_3$ (0.5 mL) was treated with CD_3OD (1.0 mL) and the solution heated at 50 °C for 3.5 h. The ^{1}H NMR spectrum of the resulting solution showed the presence of a mixture of 2′,7-dioxotaxol (**9**) and the adduct **10b** (R_1 = OD, OCD_3). The same adduct (**10a**, R_1 = OH, OCH_3) was observed in the mixture described above formed on evaporation of an aqueous methanolic solution of 2′,7-dioxotaxol. The adduct **10a** showed ^{1}H NMR absorptions distinguishable from those of **9** at δ 8.14 (d, 7, 20 Bz), 7.73 (d, 8, 3′ NBz), 6.30 (s, H10), 6.02 (br t, 7, H13), 5.73 (d, 7, C2), 4.45 (d, 6, H20 α (or β)), 3.42 (s, 2′-OCH_3).

2′-Oxo-7-acetyltaxol (12). 7-Acetyltaxol[1] (10 mg) in acetone (0.3 mL) was treated with Jones' reagent (0.05 mL) and the mixture allowed to stand 24 h at room temperature. Workup by standard methods yielded crude product, which was purified by preparative TLC (ethyl acetate–hexane, 3:2) to yield 2′-oxo-7-acetyltaxol (**12**) (6.5 mg, 65%): FABMS, m/z 894 (MH^+), 834 (MH^+ – AcOH), 611 (MH^+ – RCOOH), 551 (MH^+ – RCOOH-AcOH); m/z 894.3322 (MH^+; $C_{49}H_{52}NO_{15}$ requires 894.3338); ^{1}H NMR, see Table I.

2′-Acetyl-7-oxo-5,6-dehydro-5,*O*-secotaxol (13). 2′-

Acetyl-7-oxotaxol (150 mg) was dissolved in CH_2Cl_2 (0.5 mL) containing 0.5% DBU. Reaction occurred immediately, and workup by standard methods gave the secotaxol **13** (143 mg, 95%): FABMS, m/z 916 (MNa^+) 894 (MH^+), 876 ($MH^+ - H_2O$), 834 (MH^+ - AcOH), 549 (MH^+ - RCOOH - H_2O), 507 (MH^+ - RCOOH - AcOH); m/z 894.3236 (MH^+; $C_{49}H_{53}NO_{15}$ requires 894.3338); IR 1760, 1745, 1675, 1530, 1505, 1470, 1390, 1280, 1240, 1105, 1085, 1075, 720, cm^{-1}; ^1H NMR, see Table I. $[\alpha]^{21}_D$ - 77.2° (c 0.004 MeOH).

7-Oxo-5,6-dehydro-5,*O*-secotaxol (14). Taxol (50 mg) in acetone (0.5 mL) was treated with Jones' reagent (0.02 mL) at room temperature and the mixture allowed to stand for 20 min. Standard workup gave 7-oxotaxol (**6**), which was purified by preparative TLC with elution by ethyl acetate–hexane (1:1). Opening of the oxetane ring occurred on the TLC plate, and 7-oxo-5,6-dehydro-5,*O*-secotaxol (**14**) was isolated (35 mg, 70%): FABMS, m/z 890 (MK^+), 874 (MH^+), 834 ($MH^+ - H_2O$), 549 (MH^+ - RCOOH - H_2O), 507 (MH^+ - RCOOH - AcOH); IR 1765, 1745, 1685, 1695, 1530, 1505, 1470, 1380, 1265, 1230, 1100, 1075, 1045 cm^{-1}; ^1H NMR, see Table I.

Reaction of 2′-Acetyl-7-oxotaxol with Borohydride. 2′-Acetyl-7-oxotaxol (**5**; 14 mg) and tetrabutylammonium borohydride (6 mg) were dissolved in dry CH_2Cl_2 (0.3 mL) and the mixture stirred at room temperature. All the starting material had disappeared after 8 min, reaction was stopped by adding several drops of acetone, and the mixture was worked up by standard methods. Analysis by ^1H NMR and TLC showed the major product to be 2′-acetyl-7-oxo-5,6-dehydro-5,*O*-secotaxol (**13**), with no evidence of reduction of either carbonyl group or the double bond.

Hydrogenation of 13 with Palladium Catalyst. A sample of 2′-acetyl-7-oxo-5,6-dehydro-5,*O*-secotaxol (**13**; 10 mg) was hydrogenated in ethyl acetate over 5% palladium on carbon (4 mg). No reaction was detected by TLC over a period of 12 h.

Hydrogenation of 7-Oxo-5,6-dehydro-5,*O*-secotaxol with Platinum Catalyst. 7-Oxo-5,6-dehydro-5,*O*-secotaxol (**14**; 35 mg) and 5% platinum on carbon (17 mg) in methanol (10 mL) was hydrogenated at room temperature for 3 h, at which point HPLC analysis showed the absence of starting material. The catalyst was filtered off, the methanol evaporated, and the lactone product **17** isolated by preparative HPLC: yield, 27 mg (77%); FABMS, m/z 876 (MNa^+), 854 (MH^+), 509 (MH^+ - RCOOH - AcOH), 286 ($RCOOH^+$); m/z 854.3246 (MH^+; $C_{47}H_{52}NO_{14}$ requires 854.3389); IR 1800, 1765, 1753, 1740, 1690, 1667, 1643 cm^{-1}; ^1H NMR, see Table I; $[\alpha]^{21}_D$ - 38.6° (c 0.002, MeOH).

2′-Acetyl-7-oxo-5,*O*-secotaxol (16). 2′-Acetyl-7-oxo-5,6-dehydro-5,*O*-secotaxol (**13**; 39 mg) and 5% platinum on carbon (23 mg) in ethyl acetate (5 mL) was hydrogenated for 3 h at room temperature. The catalyst was filtered off and the solvent removed on a rotary evaporator at 30 °C, followed by drying in a vacuum desiccator for several hours. ^1H NMR of the crude product showed the presence of two compounds, but on standing in $CDCl_3$ for 24 h only the major product **16** could be detected by ^1H NMR, together with minor impurities estimated at 10% or less of the mixture. Compound **16** was obtained as an unstable substance: FABMS m/z 551 (MH^+ - RCOOH - H_2O), 509 (MH^+ - RCOOH - AcOH), 328 ($RCOOH_2^+$), 268 ($RCOOH^+$ - AcOH), 105; IR 1745, 1720, 1675, 1530, 1500, 1470, 1385, 1280, 1240, 1105, 1085, 1050 cm^{-1}; ^1H NMR, see Table I.

Acknowledgment. We thank Dr. F. Boettner (Polysscience, Inc.) and Dr. M. Suffness (National Cancer Institute) for gifts of partially purified taxol fractions and of pure taxol, respectively. We acknowledge the assistance of the staffs of the Midwest Center for Mass Spectrometry and the Middle Atlantic Mass Spectrometry Laboratory, for mass spectral determinations. Financial support from the American Cancer Society (Grant CH-268) is gratefully acknowledged.

Transannular Acetal Synthesis: Studies Related to the Synthesis of Oxide-Bridged Terpenes

M. S. Jelenick and T. A. Bryson*[1]

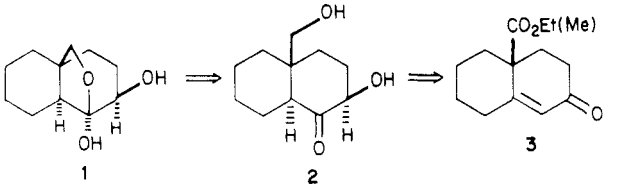
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received May 6, 1985

Synthesis of a transannular acetal model for oxide-bridged terpenoid systems was investigated. The use of Lewis acid catalyzed epoxide opening/rearrangement to generate the desired keto diol **2** was unsuccessful. However, Brönsted acid catalyzed intramolecular cyclization between a hydroxyl group and an enol ether gave the acetal **13** which could be hydrolyzed to the target hemiacetal **1**.

Several very challenging synthetic targets possess acetals and hemiacetals as key structural features.[2] The exploration of possible synthetic methods for the preparation of bridged hemiacetals and the reactivity of these units was of interest to us. Disclosed herein is a strategy for formation of this functional group, along with some stereochemical and chemical aspects of this naturally occurring unit.

Scheme I



The basic source of our model is illustrated in Scheme I.

It was reasoned that if *trans*-keto diol **2** was formed, it would close to the desired model, hemiacetal **1**. In turn, diol **2** would seem readily accessible from ester **3**.[3] Se-

(1) To whom all correspondence should be addressed.

(2) The terms ketal and hemiketal have been abandoned in favor of the terms acetal and hemiacetal (IUPAC. "Nomenclature of Organic Chemistry"; Pergamon Press: New York, 1979; Section C, Rule 331.1). Quassinoids: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101. Botryodiplodin: Moreau, S.; Lablanche-Combier, A.; Biguet, J.; Foulon, C.; Delfosse, M. *J. Org. Chem.* **1982**, *47*, 2358. 2-Desoxylemnacarnol: Izac, R. R.; Schneider, P.; Swain, M.; Fenical, W. *Tetrahedron Lett.* **1982**, *3*, 817. Palytoxin: More, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491. Lineatin: Slessor, K. N.; Oehlschlager, A. C.; Johnston, B. D.; Pierce, H. C., Jr.; Grewal, S. K.; Wichremesinghe, L. K. G. *J. Org. Chem.* **1980**, *45*, 2290. Humistratin: Nishio, S.; Blum, M. S.; Silverton, J. V.; Highet, R. J. *Ibid.* **1982**, *47*, 2154. α-Multistriatin: Sherk, A. E.; Fraser-Reid, B. *Ibid.* **1982**, *47*, 941.

(3) Marshall, J. A.; Greene, A. E. *J. Org. Chem.* **1971**, *36*, 2035 and references cited therein.

0022-3263/86/1951-0802$01.50/0