Modified Taxols. 5.[1] Reaction of Taxol with Electrophilic Reagents and Preparation of a Rearranged Taxol Derivative with Tubulin Assembly Activity[2]

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Received May 15, 1990

Reaction of the antineoplastic natural product taxol (1) with Meerwein's reagent leads to a product 4 with an opened oxetane ring. Reaction of taxol with acetyl chloride yields a product 16 in which the oxetane ring is opened and the A ring is contracted; a taxol derivative with a contracted A ring alone (22) can be prepared from taxol on treatment with mesyl chloride. The ring-contracted taxol derivative 22 shows comparable activity to taxol in a tubulin disassembly assay, but does not show significant cytotoxicity against KB cells in a cell culture assay; the derivatives 4 and 16 are inactive in both assays.

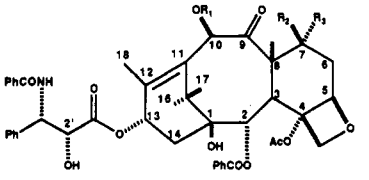
The unique diterpenoid taxol (1) was isolated from the western yew *Taxus brevifolia* by the group at Research Triangle Institute.[3] It has potent anticancer and antileukemic properties, showing good activity in several test systems,[4] and also showing very promising activity in clinical trial, particularly against ovarian cancer.[5] An additional feature of interest is that taxol acts in an unusual way, binding to polymerized tubulin and stabilizing it to disassembly, thus disrupting the tubulin–microtubule equilibrium and consequently inhibiting mitosis.[6] Because of its importance as an anticancer drug, we have been studying structure–activity relationships of its derivatives in order to determine which structural features are necessary for its biological activity; previous papers in this series have reported on our studies on taxol acetates,[7] oxidation products of taxol,[8] baccatin III derivatives,[9] and taxols modified in the C-13 ester side chain.[1]

One of the unusual features of the taxol structure is the oxetane ring at the C-4, C-5 positions. A study of Dreiding models indicated to us that the taxane skeleton of taxol is very rigid and inflexible, but that a taxol analogue in which the oxetane ring is opened is relatively flexible. It thus seemed that the oxetane ring might play a key role in the binding of taxol to the presumed receptor site on polymerized tubulin.

The oxetane ring is susceptible to ring opening by reaction with electrophilic reagents, and we report herein the results of our studies on the reactions of taxol with the three electrophiles zinc bromide, triethyloxonium tetrafluoroborate (Meerwein's reagent), and acetyl chloride. These studies have led to taxol derivatives in which the oxetane ring is opened and to those in which ring A is contracted; these derivatives thus provide information on the importance not only of an intact oxetane ring but also of an intact ring A to the activity of taxol.

Results and Discussion

The mildest conditions we tested were those of zinc bromide in methanol at ambient temperature. Under these conditions taxol simply underwent epimerization of the C-7 hydroxyl group and cleavage of the 10-acetyl group to yield 10-deacetyltaxol (2) and 10-deacetyl-7-epitaxol (3), with the latter being the major product. The structures



1 R_1 = Ac, R_2 = OH, R_3 = H
2 R_1 = H, R_2 = OH, R_3 = H
3 R_1 = H, R_2 = H, R_3 = OH

of these compounds were established for 2 by comparison with literature data[10] and for 3 by comparison of spectroscopic data with those for 2 and for 7-epitaxol.[11] The mechanism of the epimerization probably involves a Lewis acid catalyzed retroaldol reaction followed by recyclization, and the formation of the epitaxol derivative as the major product under the equilibrium conditions of the reaction suggests that it is the thermodynamic product of the reaction, presumably because the 7-epihydroxyl group can form a hydrogen bond to the 4-acetoxy group.[12] It should be noted that reaction of taxol with zinc chloride has been carried out by Potier under the more vigorous conditions of zinc chloride in toluene; under these conditions a rearrangement occurred similar to that discussed below.[12]

A more significant reaction occurred on treatment of taxol with excess triethyloxonium tetrafluoroborate (Meerwein's reagent) followed by an aqueous quench. Under these conditions taxol was largely (51%) converted to a single product 4 with a lower R_f on TLC. This product gave a mass spectrum that showed a molecular ion at m/z 871, corresponding to taxol + H_2O, and its ^1H NMR

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(2) Presented in part as a plenary lecture at the Research Congress on Natural Products and 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August 1989. Kingston, D. G. I.; Samaranayake, G.; Ivey, C. A. *J. Nat. Prod.* **1990**, *53*, 1–12.
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(8) Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.* **1986**, *51*, 797–802.
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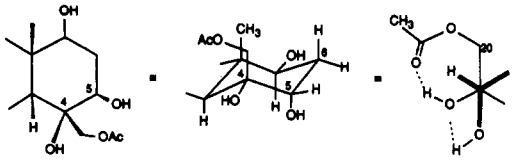


Figure 1. Hydrogen bonding in compound 4.

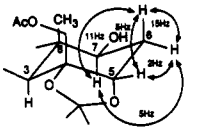
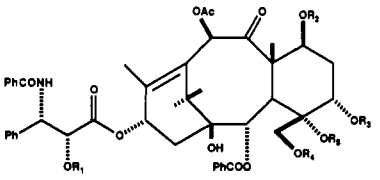


Figure 2. Coupling constants of protons in the C ring of acetonide 8.

spectrum showed that ethylation of taxol had not occurred. The major changes in the ^1H NMR spectrum of 4 as compared to taxol occurred at C-5 and C-20, and these changes are consistent with the assignment of structure 4 to the product. Thus, the chemical shift of the C-5 proton changed from 4.92 ppm in taxol to 3.70 ppm in 4, consistent with opening of the oxetane ring, while the chemical shift of the C-20 protons changed from 4.17 to 3.85 ppm consistent with ring opening and acetylation at C-20.[13] The alternate structure 5, which had been considered at one time,[14] was excluded both by the chemical shift arguments presented above and by the fact that mild acetylation of 4 did not cause acetylation at C-20; instead, the 2′,7-diacetyl derivative 6 was obtained.

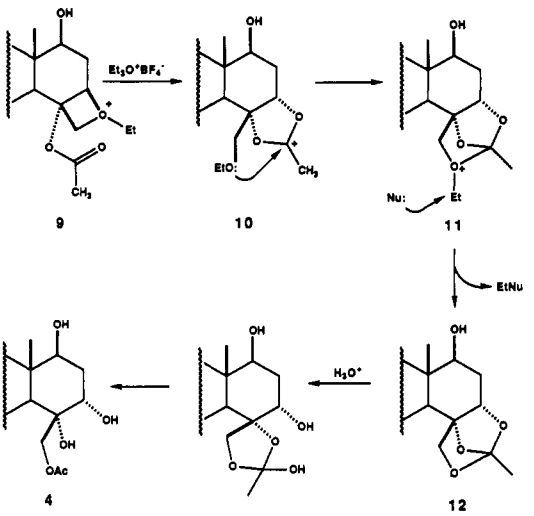


4 $R_1 = R_2 = R_3 = R_5 = H$ $R_4 = Ac$
5 $R_1 = R_2 = R_3 = R_4 = H$ $R_5 = Ac$
6 $R_1 = R_2 = R_4 = Ac$ $R_3 = R_5 = H$
7 $R_1 = R_2 = R_3 = R_4 = Ac$ $R_5 = H$

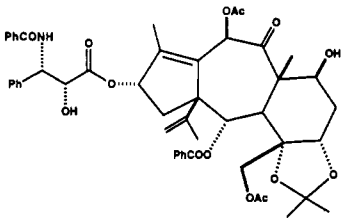
The secondary hydroxyl group at C-5 in the Meerwein product 4 proved surprisingly difficult to acetylate. Reaction was finally achieved by the use of Ac_2O/DCC/4-pyrrolidinopyridine at 60 °C, and the 2′,5,7-triacetyl derivative 7 was obtained. This product had a very similar ^1H NMR spectrum to that of 4 with the exception of the expected acylation shifts at positions 2′, 5, and 7 and smaller shifts of protons on adjacent carbons. The difficulty of acetylation of the C-5 hydroxyl group is presumably due in part to intramolecular hydrogen bonding with the C-4 hydroxyl group and in part to its hindered location on the inside of the "cup-shaped" molecule. A similar lack of reactivity is seen for the C-13 hydroxyl group of baccatin III.[9] Hydrogen bonding of the C-4 hydroxyl group with the C-20 acetoxy group is evident from the fact that the ^1H NMR spectrum of 4 shows a large chemical shift difference between the C-20 protons, suggestive of hindered rotation. Such bonding might well make the C-4 oxygen more negative, assisting bonding to the C-5 OH group (Figure 1). The acetonide 8 (see below), which lacks a

(13) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; pp 164, 199.
(14) Kingston, D. G. I.; Magri, N. F.; Jitrangsri, C. In *New Trends in Natural Products Chemistry 1986 (Studies in Organic Chemistry Vol. 26)*, Atta-ur-Rahman, LeQuesne, P. W., Eds.; Elsevier Science Publishers: Amsterdam, 1986; pp 219–235.

Scheme I



hydroxyl group to form a hydrogen bond with the C-20 acetoxy group, shows a very similar chemical shift to that of taxol for the C-20 protons.



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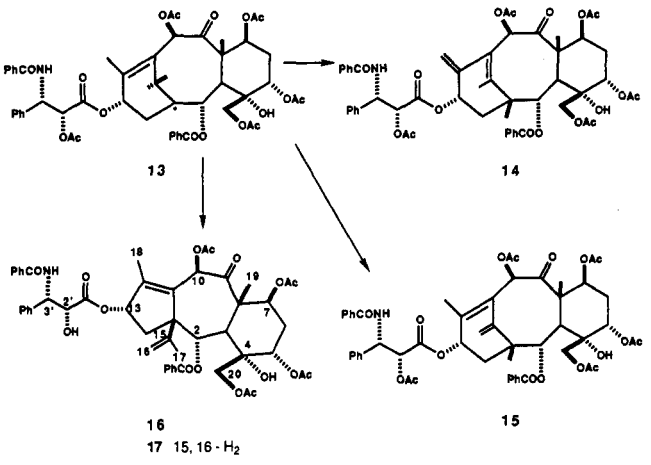
The stereochemistry of the C-5 hydroxyl group of 4 was established by conversion of 4 to the acetonide derivative 8. This conversion also caused a rearrangement of ring A to occur; this rearrangement will be discussed in more detail below. The coupling constants of all the protons in the C ring of 8 were determined by specific proton decoupling and are shown in Figure 2. The small coupling constants of 5 and 2 Hz between the C-5 proton and the two C-6 protons establish that the C-5 proton is equatorial and that the C ring has the chair conformation: an alternate structure in which the C ring is in the boat conformation would require a large antiperiplanar coupling between the C-5 and one of the C-6 protons. The observed coupling constants also establish that the C-7 hydroxyl group retains its configuration; this is probably because hydrogen bonding to the C-4 acetoxy group is no longer possible in the products 4 and 8, but it may also be due to the different and nonequilibrating conditions of the reaction with Meerwein's reagent.

One additional point concerning the Meerwein product 4 deserves mention. As noted earlier, Dreiding models of taxol show that the ring system is essentially rigid, locked into one conformation by the geometry of the tetracyclic structure. The product 4, on the other hand, is much more flexible. This evidence from models is supported by the ^1H NMR spectrum of 4, since the ring-A protons show significant differences from the corresponding protons in taxol. The C-13 proton in 4, for example, appears as a broad doublet of doublets (J_1 = 11 Hz, J_2 = 4 Hz); in taxol this proton appears as an apparent triplet with $J_1 \approx J_2$ = 8 Hz. This change in coupling constants is indicative of a change in the conformation of ring A on opening the oxetane ring.

The mechanism of the reaction with Meerwein's reagent is not known, but one possible pathway is shown in Scheme

Scheme II



I. Ethylation of the oxetane oxygen of taxol to give 9 followed by participation of the neighboring acetoxy group as proposed by Raber[15] would yield the cation 10. Intramolecular trapping of 10 by the ether oxygen would lead to 11, which could then form the ortho ester 12 by reaction with a nucleophile or on aqueous workup. The ortho ester 12 would hydrolyze to the stable final product 4 under the acidic workup conditions.

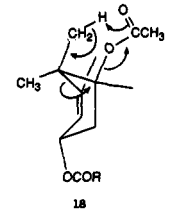
The third electrophilic reagent studied was acetyl chloride. This has been shown to give oxetane ring-opened products in other cases,[16] but reaction of taxol with refluxing acetyl chloride yielded a product that had clearly undergone a more drastic change than simple oxetane ring opening. The product 16 had a ^{1}H NMR spectrum that showed the presence of two new vinyl protons at 4.69 and 4.82 ppm, and a ^{13}C NMR INEPT spectrum showed the presence of two additional vinyl carbons at 112.8 and 144.2 ppm; the signal at 112.8 ppm was a triplet indicating the presence of a terminal methylene group. As expected, the C-2′, C-7, and C-10 hydroxyl groups were acetylated, and signals for two additional acetate groups were observed. The mass spectrum of 16 showed that it had a molecular weight of 979, corresponding to taxol plus three acetates.

Important additional evidence for the structure of 16 came from our studies of the Meerwein product 4. Acetylation of 4 in the presence of acetyl chloride and triethylamine yielded a single product identical with the product 16 obtained with acetyl chloride. Since the Meerwein product 4 is formed by an overall hydration of taxol, this implies that conversion of taxol to 16 must involve *both* the overall hydration of the oxetane ring and a dehydration to yield a methylene group.

Three possible products of such a dehydration reaction are shown in Scheme II. The Meerwein product 4 would yield the cation 13[17] on acetylation of the 2′ and 7 hydroxyl groups and loss of the C-1 hydroxyl group (possibly after acetylation). Cation 13 could then rearrange via a 1,2-methyl migration followed by loss of a proton to give either of the methylene derivatives 14 and 15. Alternatively, migration of the 11,15 bond, possibly through the intermediacy of a cyclopropylcarbinyl cation, would lead to the isopropenyl derivative 16 in which the A-ring of taxol has contracted to a cyclopentene structure.

A distinction between the possible rearrangement products 14–16 was made on the basis of the COSY spectrum of the product. This spectrum showed a clear long-range coupling between H-13 and a vinyl methyl group, which must therefore be the C-18 methyl group; this evidence excludes structure 14. Additionally, the vinyl protons at 4.69 and 4.82 ppm showed a long-range coupling to a vinyl methyl group that is not C-18 and must thus be C-17; this evidence is only consistent with structure 16. Final support for structure 16 was obtained by hydrogenation (Pt/H_2), which converted the isopropenyl group in 16 to an isopropyl group (17). The ^{1}H NMR spectrum of 17 showed two new methyl doublets at 0.76 and 0.78 ppm and a methine multiplet at 1.60 ppm; these assignments were confirmed by selective proton decoupling experiments. A similar rearrangement has been reported for a taxinine derivative by Chan and co-workers.[18]

The mechanism of the conversion of taxol to the rearranged product 16 presumably involves separate reactions of acetyl chloride with the oxetane ring and with ring A. Opening of the oxetane ring could occur by a pathway analogous to those suggested for formation of the Meerwein product 4, and rearrangement of 4 to 16 could occur either as indicated in Scheme II or by a concerted pathway such as that shown on partial structure 18 (arrows). The



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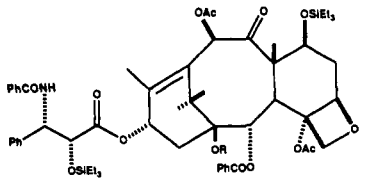
stability of the tertiary C-4 hydroxyl group of 16 under the vigorous reaction conditions is surprising and must be due in part to its hindered location, which prevents acetylation and subsequent loss of acetate.

The acetonide derivative 8, prepared as described earlier from the Meerwein product 4, was also found to have undergone the same ring-A rearrangement as 16, as evidenced by its ^{1}H NMR spectrum and in particular by the appearance of vinyl proton signals at 4.67 and 4.75 ppm. It is noteworthy that the Meerwein product 4 underwent rearrangement to 8 under relatively mild conditions (*p*-toluenesulfonic acid, 1 h, room temperature). Similar conditions have no effect on taxol; thus, taxol survived oxidation with Jones' reagent for 24 h without any rearrangement occurring.[8] This evidence tends to support a carbocation mechanism, since presumably the rigid oxetane ring is holding taxol in a conformation that does not permit cation formation at C-1, while the more flexible ring-opened derivative 4 can form a cation at C-1 relatively easily.

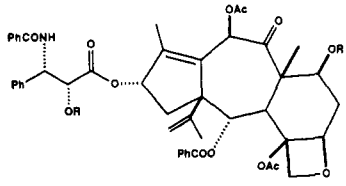
Although as noted above the rearrangement of the Meerwein product 4 occurs under relatively mild conditions, the presence of acid raises the possibility that some undetected deep-seated rearrangement is occurring and that the product might therefore not have the structure 16.[19] We thus elected to carry out rearrangement of ring A under basic conditions so as to eliminate this possibility. Reaction of taxol with triethylsilyl chloride in the presence of imidazole yielded 2′,7-bis(triethylsilyl)taxol (19). Treatment of 19 with methanesulfonyl chloride and triethylamine in dichloromethane at −15 to 0 °C, followed by a quench with aqueous triethylamine, yielded as the

(15) Raber, D. J.; Guida, W. C. *Synthesis* **1974**, 808–809.
(16) Kovacs, O.; Weisz, I.; Zoller, P.; Fodor, G. *Helv. Chim. Acta* **1956**, *39*, 99–110.
(17) The cation 13 is shown as an intermediate simply for clarity of exposition. The actual mechanism of formation of 16 may well be a concerted process, as discussed later.
(18) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W. *Chem. Commun.* **1966**, 923–929.
(19) We thank Professor R. M. Coates for this suggestion.



19 R = H
20 R = SO_2CH_3

major product the rearranged derivative **21**, presumably



21 R = $SiEt_3$
22 R = H

formed via the mesylate **20**, which proved to be too labile to isolate. The structure of **21** was confirmed by its ^1H NMR spectrum, which showed inter alia resonances for two vinyl protons at 4.66 and 4.75 ppm, and by its mass spectrum (M^+ at m/z 1063, corresponding to the overall loss of water from the silyltaxol **19**).

Deprotection of the silyl ether **21** yielded a mixture of products when tetrabutylammonium fluoride was used, but pyridinium hydrofluoride[20] at 0 °C converted it smoothly to the A-nortaxol **22**. The structure of **22** follows from its ^1H NMR spectrum and its mass spectrum.

Biological activities of the isolated compounds were determined in both the KB cell culture assay[21] and a tubulin depolymerization assay;[22] these activities are summarized in Table I. The Meerwein product **4** was essentially inactive in the KB cell culture assay and was also inactive in the tubulin depolymerization assay. This important result indicates that an intact oxetane ring (or some functional equivalent thereof) is necessary for the full activity of taxol. It is not known, however, whether the oxetane ring is necessary per se (for example, to provide a site for hydrogen bonding from polymerized tubulin), or whether its function is simply to hold the taxane skeleton in a favorable conformation for access to the binding site on polymerized tubulin.

The product **16** from reaction with acetyl chloride is also inactive in KB cell culture: it was not tested in the tubulin depolymerization assay since 2'-acetyltaxol derivatives have been shown to be inactive in promoting the polymerization of tubulin.[7] The inactivity of **16** in cell culture is consistent with the lack of an intact oxetane ring.

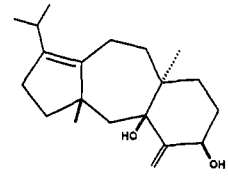
The assay results on the ring-contracted taxol derivative **22** proved most informative, since this compound was *almost as active as taxol in the tubulin depolymerization assay*. This result is surprising, since **22** has such a highly modified A ring and since molecular models indicate that the shape of **22** is significantly different from the shape of taxol itself. It is thus suggested that taxol may have two key binding regions on tubulin, one involving the C-13 ester side chain and the other involving the oxetane ring; changes at either end of the molecule would thus destroy its activity, but changes in the central A/B rings could be tolerated to a greater degree.

Table I. Bioactivity of Modified Taxols

compd	ED_{50} (μg/mL) in KB cell culture[a]	ID_{50} (μM) in tubulin depolymerization assay[b]
taxol (1)	0.000 01	0.3
4	2.3	>6.3
16	2.5	
22	2.0	0.9

[a] Cytotoxicity assays were performed at the University of Miami by Dr. W. Lichter. [b] The tubulin depolymerization assay was carried out at Virginia Polytechnic Institute and State University by the method of Lataste et al.[22] Cow brain tubulin was prepared by the method of Williams and Lee[23] to yield material that was 85% pure as determined by SDS-polyacrylamide gel electrophoresis. All buffers were filtered and degassed before use, and samples were dissolved in DMSO. The rate of depolymerization was determined as previously described,[22] and the data were plotted as described on a dose response curve. ID_{50} values were determined from this curve. The ID_{50} value is defined as that concentration of drug that reduces the rate of depolymerization of tubulin to 50% of the rate in the absence of drug.

In spite of the activity of **22** in the tubulin depolymerization assay, it proved to be essentially inactive in the KB cytotoxicity assay. This could be explained either by the failure of **22** to gain access to the cells or by some biotransformation of **22** to an inactive metabolite. It may thus prove profitable to prepare analogues of **22** for further exploration of structural effects on reactivity in this area. In this connection it is also worth noting that the ring system of **22** is synthetically more accessible than is that of taxol, having been made recently, for example, in a synthesis of the dolastane diterpene isoamijiol (**23**).[24] If analogues of **22** should prove to be active in vivo, they might well also be easier to prepare than any similar taxol derivatives.



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Experimental Section

General Methods. General methods were the same as previously described[8] except that low-resolution mass spectra were obtained on a VG7070E-HF mass spectrometer. Exact mass measurements were performed at the Midwest Center for Mass Spectrometry, an NSF Regional Instrumentation Facility (Grant CHE-8211164). Standard workup means extraction with a suitable solvent (EtOAc unless specified otherwise), washing the extract with H_2O, drying over $MgSO_4$ or Na_2SO_4, and evaporation in vacuo. ^1H NMR spectra were obtained in $CDCl_3$ and were assigned primarily by comparison of chemical shifts and coupling constants with those of related compounds and by appropriate decoupling experiments and COSY spectra; ^{13}C NMR spectra were assigned by HETCOSY and INEPT spectra. Product purity was determined by reversed-phase HPLC (C18 column, 70:30 MeOH/H_2O, UV detector at 254 nm), and all compounds gave a single peak unless otherwise stated. ^1H NMR spectra showed the presence of traces of ethyl acetate and hydrocarbon impurities in most samples purified by PTLC. Taxol and its derivatives retain ethyl acetate very tightly, and it cannot be removed completely even on prolonged treatment in vacuo at 38 °C. The hydrocarbon impurities persisted even though the PTLC plates

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Table II. ^{1}H NMR Spectral Data of Taxol Derivatives

protons on carbon	1	4	7	8
2	5.62 (d, 7)	5.56 (d, 6)	5.63 (3, 5)	5.34 (d, 8)
3	3.80 (d, 7)	4.03 (d, 6)	4.04 (d, 5)	3.06 (d, 8)
5	4.92 (dd, 2, 8)	3.70 (br s)	5.26 (m)[c]	4.34 (m)
6	[a]	[a]	[a]	6_{ax} 1.95 (ddd, 5, 11, 15)[b] 6_{eq} 2.36 (ddd 2, 5, 15)
7	4.33 (m)	4.49 (dd, 4, 11)	5.43 (br d, 9)	4.48 (dd, 5, 11)
10	6.26 (s)	6.57 (s)	6.42 (s)	6.38 (d, 2)
13	6.15 (t, 8)	6.01 (br dd, 4, 11)	6.03 (m)	5.68 (m)
14	2.5 (m)	2.45 (dd, 11, 16), 3.08 (dd, 4.16)	2.40 (dd, 9, 15), 3.07 (dd, 5, 15)	2.57 (AB part of ABX, 9, 14, $\Delta\nu_{AB}$ = 62)
15				
16	1.25 (s)	1.12 (s)	1.13 (s)	4.67 (s), 4.75 (s)
17	1.14 (s)	1.12 (s)	1.11 (s)	1.63 (s)
18	1.78 (s)	2.10 (s)[b]	2.24 (s)	1.67 (s)[b]
19	1.67 (s)	1.22 (s)	1.38 (s)	1.62 (s)
20	4.17 (ABq, 8, $\Delta\nu_{AB}$ = 31)	3.85 (ABq, 11, $\Delta\nu_{AB}$ = 86)	4.01 (ABq, 12, $\Delta\nu_{AB}$ = 57)	4.15 (ABq, 12, $\Delta\nu_{AB}$ = 26)
2′	4.71 (d, 8)	4.70 (br s)	5.26 (m)[c]	4.50 (d, 3)
3′	5.72 (dd, 3, 9)	5.92 (dd, 2, 9)	6.12 (dd, 3, 10)	5.60 (dd, 3, 8)
NH	7.00 (d, 9)	7.19 (br d, 9)	7.20 (br d, 9)	6.98 (br d, 8)
OAc	2.23 (s), 2.38 (s)	1.65 (s), 2.25 (s)	1.98 (s), 2.13 (s), 2.16 (s), 2.19 (s), 2.20 (s)	1.83 (s), 2.17 (s)
2-OBz	8.11 (dd), 7.3–7.6 (m)[c]	8.03 (m), 7.3–7.6 (m)[c]	8.20 (m), 7.2–7.6 (m)[c]	8.10 (m), 7.3–7.4 (m)[c]
3′-NBz	7.7 (m), 7.3–7.6 (m)[c]	7.80 (m), 7.3–7.6 (m)[c]	7.8 (m), 7.2–7.6 (m)[c]	7.73 (m), 7.3–7.4 (m)[c]
3′-Ph	7.3–7.6 (m)[c]	7.3–7.6 (m)[c]	7.2–7.6 (m)[c]	7.3–7.4 (m)[c]
OH		3.91 (s)		
Other				1.30 (s)[d]

protons on carbon	19	20	22	24	25
2	5.35 (d, 7)	5.17 (d, 8)	5.71 (m)	5.54 (d, 8)	5.49 (d, 8)
3	3.54 (d, 7)	3.68 (d, 8)	3.88 (d, 6)	3.53 (d, 8)	3.48 (d, 8)
5	5.28 (br s)	4.94 (br d, 11)	4.94 (br d, 11)	5.02 (d, 8)	5.04 (d, 8)
6	[a]	[a]	[a]	1.90 (m)	1.86 (dd, 11, 15), 2.59 (ddd, 8, 9, 15)
7	5.54 (dd, 4, 13)	5.54 (dd, 5, 11)	4.48 (dd, 6, 14)	4.53 (33, 8, 5)	4.63 (dd, 9, 11)
10	6.38 (s)	6.36 (s)	6.44 (s)	6.39 (s)	6.32 (s)
13	5.67 (t,m 7)	5.72 (m)	6.20 (m)	5.81 (br t, 7)	5.71 (m)[c]
14	2.64 (m)	2.48 (AB part of AABX, 14, 16, $\Delta\nu_{AB}$ = 65)	[a]	2.40 (m), 2.60 (m)	2.04 (dd, 8, 13), 2.42 (dd, 13, 6)
15		1.60 (m)			
16	4.69 (s), 4.82 (s)	0.76 (d, 7)	1.22 (s)	4.66 (s), 4.75 (s)	4.69 (br s), 4.76 (br s)
17	1.62 (s)	0.78 (d, 7)	1.18 (s)	1.65 (s)	1.59 (s)
18	1.82 (s)	1.83 (s)	2.02 (s)	1.62 (s)	1.61 (s)
19	1.53 (s)	1.53 (s)	1.70 (s)	1.73 (s)	1.64 (s)
20	4.15 (ABq, 12, $\Delta\nu_{AB}$ = 55)	4.11 (ABq, 11, $\Delta\nu_{AB}$ = 78)	4.27 (ABq, 11, $\Delta\nu_{AB}$ = 63)	4.15 (ABq, 12, $\Delta\nu_{AB}$ = 26)	4.24 (ABq, 8 $\Delta\nu_{AB}$ = 34)
2′	5.52 (d, 2)	5.40 (d, 3)	4.71 (d, 3)	4.60 (d, 2)	4.67 (d, 2)
3′	6.02 (dd, 2, 9)	5.95 (dd, 3, 8)	5.71 (m)	5.64 (dd, 2, 11)	5.71 (dd, 11, 2)[c]
NH	7.03 (d, 9)	7.02 (d, 8)	7.12 (d, 9)	7.15 (d, 11)	6.89 (d, 11)
OAc	1.85 (s), 2.00 (s), 2.13 (s), 2.17 (s), 2.22 (s)	1.17 (s), 1.18 (s), 2.00 (s), 2.13 (s), 2.17 (s)	2.17 (s), 2.55 (s)	2.02 (s), 2.40 (s)	2.17 (s), 2.36 (s)
2-OBz	7.93 (m), 7.2–7.9 (m)[c]	7.91 (m), 7.2–7.6 (m)[c]	8.12 (m), 7.2–7.5 (m)[c]	8.01 (m), 7.2–7.5 (m)[c]	8.10 (m), 7.2–7.6 (m)[c]
3′-NBz	7.85 (m), 7.2–7.9 (m)[c]	7.83 (m), 7.2–7.6 (m)[c]	7.79 (m), 7.2–7.5 (m)[c]	7.70 (m), 7.2–7.5 (m)[c]	7.66 (m), 7.2–7.6 (m)[c]
3′-PH	7.2–7.9 (m)[c]	7.2–7.6 (m)[c]	7.2–7.5 (m)[c]	7.2–7.5 (m)[c]	7.2–7.6 (m)[c]
OH	3.75 (s)				
other			0.48 (6 H, m)[e]	0.38 (6 H, m)[e]	
			0.57 (6 H, m)	0.60 (6 H, m)	
			0.81 (9 H, t, 8)	0.75 (9 H, t, 8)	
			0.91 (9 H, t, 8)	0.90 (9 H, t, 8)	

[a] Peak concealed under signals from methyl group. [b] Determined by decoupling experiment. [c] Overlapping peaks. [d] Signals of the methyl groups of the acetonide. [e] Signals of the ethyl groups of the TES groups.

were washed prior to use and the best available solvents were used. IUPAC nomenclature[25] for taxol derivatives is used for title compounds.

Reaction of Taxol with $ZnBr_2$. 10-Deacetyltaxol (2) and 10-Deacetyl-7-epitaxol (3). A mixture of taxol (1; 100 mg, 0.117 mmol) and $ZnBr_2$ (3.3 g, 0.41 mmol) in $CHCl_3$/MeOH (1:4, 10 mL) was stirred for 24 h at 40 °C. Water was added, and standard workup yielded a white solid that was purified by PTLC (EtOAc/hexane (1:1)) to obtain two compounds that were identified as 10-deacetyltaxol (2; 12 mg, mp 169–171.5 °C) and 10-deacetyl-7-epitaxol (3, 49 mg, mp 167–169 °C) by comparison of published data.[10,11]

Reaction of Taxol with Meerwein's Reagent. Formation of 20-Acetoxy-4-deacetyl-5-epi-20,*O*-secotaxol (the Meerwein Product, 4). To a cooled (0 °C) and stirred solution of taxol (1; 100 mg, 0.117 mmol) in dry CH_2Cl_2 (28 mL) was added dropwise triethyloxonium tetrafluoroborate (200 μL, 1 M in CH_2Cl_2) from a freshly opened bottle. After 30 min, the reaction was quenched with ethereal HCl (3 mL of a 1:2 mixture of 1 N HCl/ether) and the mixture was stirred for 10 min. Standard workup gave a crude solid that was further purified by flash chromatography and PTLC (EtOAc/hexane (80:20)) to yield 53 mg (51%) of product 4, purity >95% by HPLC: mp 160–164 °C (amorphous solid); IR (KBr) 1745 (s), 1670 (m), 1535 (w), 1505 (w), 1474 (w), 1395 (m), 1120 (m), 1080 (m), 1060 (m) cm^{-1}; ^{1}H NMR, see Table II; ^{13}C NMR (HetJRES, 50 Mz, $CDCl_3$) δ 10.16 (q, 19), 15.77 (q, 18), 18.41, 19.46, 20.23 (each q, 10-OAc, 20-OAc, 17), 27.42 (q, 16), 31.04, 34.66 (each t, 14, 6), 42.08 (s, 15), 45.34 (d, 3), 54.03 (d, 3′), 60.01 (s, 8), 63.66 (t, 20), 68.20 (d, 13), 71.41, 72.42, 73.16, 74.18, 75.14 (each d, 2, 7, 5, 10, 2′), 74.14 (s, 1), 126.19–132.67 (aromatics), 133.79 (s, 11), 134.68 (s, 1′ of Ph at 3′), 138.36 (s, 1′ of NBz), 139.89 (s, 12), 209.15 (s, 9); MS (FAB) *m/z* (relative intensity), 872 (MH^+, 100), 854 ($MH^+ - H_2O$); high-resolution mass spectrum calcd for $C_{47}H_{54}NO_{15}$ (MH^+) 872.3493, obsd 872.3463.

20-Acetoxy-4-deacetyl-2′,7-diacetyl-5-epi-20,*O*-secotaxol (6). Compound 4 (5 mg, 0.0057 mmol) was dissolved in pyridine (100 μL), and excess CH_3COCl (300 μL) was added. After 30 min at rt, the solution was warmed to 60 °C for 1 h. The reaction was

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quenched by addition of water, and then standard workup yielded a crude material that was purified on PTLC (EtOAc/hexane (60:40)) to yield 3 mg (55%) of chromatographically homogeneous 6; ^{1}H NMR, see Table II.

20-Acetoxy-4-deacetyl-2',5,7-triacetyl-5-epi-20,*O*-secotaxol (7). To a solution of 6 (8 mg, 0.008 mmol) in THF (750 μL) was added dicyclohexylcarbodiimide (5 mg, 2.5 equiv), Ac_2O (4 μL, 5 equiv), and a catalytic amount of 4-pyrrolidinopyridine. The solution was stirred and heated at 60 °C for 7.5 h, and the solvent was then evaporated and the residue extracted into ethyl acetate. Standard workup yielded a crude mixture that was purified by PTLC with 1% MeOH/$CHCl_3$ to yield 3 mg (38% yield at 63% conversion) of triacetate 7: IR (KBr) 1740 (s), 1720 (s), 1676 (m), 1625 (s), 1225 (s) cm^{-1}; ^{1}H NMR, see Table II; MS (FAB) *m/z* (relative intensity) 998 (MH^+, 13), 980 (MH^+, 12), 936 (6), 848 (23), 650 (100).

Acetonide 8. A solution of 4 (6 mg, 0.007 mmol) and 2,2-dimethoxypropane (200 μL) in dry CH_2Cl_2 (500 μL) was treated with a catalytic amount of *p*-toluenesulfonic acid and stirred for 1 h; complete conversion of starting material to the product was observed. Standard workup yielded a crude product that was further purified by PTLC (EtOAc/hexane (70:30)) to obtain 6 mg (95%) of pure acetonide 8: ^{1}H NMR, see Table II; MS (FAB) *m/z* (relative intensity), 916 (MNa^+, 100), 855 (MNa^+ - HOAc - H, 25), 832 (MNa^+ - CH_3CO - C_3H_5, 50), 761 (40).

(1α)-20-Acetoxy-2',5,7-triacetyl-15(16)-anhydro-4-deacetyl-11(15→1)-*abeo*-5-epi-20,*O*-secotaxol (16). Method A. Taxol (1; 200 mg, 0.23 mmol) was dissolved in acetyl chloride (2 mL) and the solution refluxed for 1 h. The reaction was quenched with ice–water and ethyl acetate and stirred for 30 min. Standard workup yielded a white solid. Recrystallization of this solid from EtOAc and hexanes yielded the acetylated taxol derivative 16 as white needles (156 mg, 68%): mp 140–142 °C; IR ($CHCl_3$) 1750 (s), 1660 (m), 1606 (m), 1372 (m), 1282 (m), 1156 (m) cm^{-1}; ^{1}H NMR, see Table II; ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.28, 11.29 (18, 19), 20.09–21.05 (five OAc methyls, 17), 29.65 (6), 38.01 (14), 45.37 (3), 52.85 (3'), 55.59 (8), 63.79 (1), 64.71 (20), 70.37 (10), 70.50 (2'), 71.71 and 71.84 (7, 5), 73.19 (4), 74.26 (2), 80.36 (13), 112.84 (16), 126–130 (aromatics), 131.92 (*p*-NBz), 133.85 (*p*-OBz), 136.92 (12), 137.45 (1' of 3'-Ph), 144.27 (15), 145.29 (11), 165.99, 167.16, 167.63, 169.29 169.60, 170.07 (ester carbonyls), 201.26 (9); MS (FAB) *m/z* (relative intensity) 1002 (MNa^+, 35), 676 (MNa^+ - side chain, 15), 616 (657 - HOAc, 30), 554 (676 - PhCOOH, 20), 494 (616 - PhCOOH, 30), 411 (24), 372 (24), 177 (100); high-resolution mass spectrum calcd for $C_{53}H_{57}NO_{17}Na$(MNa^+) 1002.3524, obsd 1002.3557.

Method B. Treatment of compound 4 (50 mg) with excess CH_3COCl in $CHCl_3$ with catalytic 4-pyrrolidinopyridine and excess Et_3N for 5 h, followed by an aqueous quench and standard workup, yielded compound 16 in 18% yield after purification by PTLC.

Hydrogenation of (1α)-20-Acetoxy-2',5,7-triacetyl-15(16)-anhydro-4-deacetyl-11(15→1)-*abeo*-5-*epi*-20,*O*-secotaxol (16) to Its Dihydro Derivative 17. Compound 16 (24 mg, 0.023 mmol) was dissolved in EtOAc (2.5 mL) and hydrogenated over 5% Pd/C. After 24 h, the catalyst was filtered off and the solvent was evaporated to yield a crude solid that consisted of product and unreacted starting material, which was not separable from the product. The crude product was dissolved in CH_2Cl_2 (5 mL) and treated with *m*-chloroperoxybenzoic acid (58%, 5 mg) at room temperature for 3 h to convert the starting material to its separable epoxide. The solvent was evaporated and the residue subjected to PTLC with 4% MeOH/$CHCl_3$ to yield pure reduced product 17 (8 mg, 35%) along with a mixture of diastereomeric epoxides (11 mg). Compound 17 was recrystallized from ethyl acetate and hexanes: mp 148–150 °C; IR (KBr) 1740 (s), 1720 (m), 1640 (m), 1220 (m), 910 (m) cm^{-1}; ^{1}H NMR, see Table II; MS (FAB) *m/z* (relative intensity) 1004 (MNa^+, 100), 962 (MNa^+ - C_3H_6, 10), 944 (MNa^+ - HOAc, 15).

2',7-Bis(diethylsilyl)taxol (19). To a solution of taxol (1; 200 mg, 0.234 mmol) in DMF (2.5 mL) under argon was added solid imidazole (238 mg, 10 equiv). Triethylsilyl chloride (196 μL, 10 equiv) was added to the stirred solution at room temperature in one portion, and the solution was warmed to 45–50 °C. Reaction was complete after 2 h, and the solution was diluted with water and extracted with EtOAc. The crude solid obtained after evaporation of the solvent was purified on a silica gel flash column (EtOAc/hexane (20:80)) to yield 242 mg (96%) of pure 2',7-bis(triethylsilyl)taxol (19): mp 122–123 °C; IR 1740 (s), 1720 (s), 1660 (s), 1640 (m), 1240 (s), 810 (m), cm^{-1}; ^{1}H NMR, see Table II; MS (FAB) *m/z* (relative intensity) 1104 (MNa^+, 100), 1003 (30), 981 (MNa^+ - PhCOOH, 10).

(1α)-15(16)-Anhydro-2',7-bis(triethylsilyl)-11(15→1)-abeotaxol (21). A solution of taxol derivative 19 (30 mg, 0.028 mmol) in dry CH_2Cl_2 (3 mL) was cooled to −15 °C under argon and treated with NEt_3 (600 μL, 154 equiv), followed by MsCl (300 μL, 138 equiv) in CH_2Cl_2 (1 mL) during 5 min. The system was allowed to warm to −5 to 0 °C and maintained at this temperature for a total reaction time of 2.5 h; 50% conversion of the starting material was observed at this point. The solution was cooled again to −15 °C, and additional amounts of Et_3N (1 mL) and MsCl (500 μL) were added. This procedure was repeated one additional time, and the reaction was then stopped by adding 2 mL of Et_3N, water (5 mL), and EtOAc (5 mL). Standard workup yielded a crude material that was purified by PTLC (EtOAc/hexane (30:70)) to give 6 mg (20%) of rearranged taxol 21, along with starting material (2 mg) and (1α)-15(16)-anhydro-7-(triethylsilyl-11(15→1)-abeotaxol (2 mg): ^{1}H NMR, see Table II; MS (FAB) *m/z* (relative intensity) 1086 (MNa^+, 45), 1064 (MH^+, 75), 1005 (MH^+ - OAc, 25), 975 (MH^+ - OAc - CH_2O, 15), 963 (MH^+ - OAc - C_3H_6, 15), 820 (MH^+ - PhCOOH - $PhCONH_2$ - H, 100).

(1α)-15(16)-Anhydro-11(15→1)-abeotaxol 22. Compound 21 (67 mg, 0.07 mmol) in dry THF (1 mL) under argon was cooled to 0 °C and treated with pyridinium hydrofluoride (70% in pyridine, 100 μL). After 3 h, the cooling bath was removed, and the reaction was allowed to proceed for an additional 45 h at room temperature. Then the reaction was quenched with aqueous pyridine (10% v/v pyridine, 2 mL). Standard workup gave a crude solid that was purified by PTLC with 8% MeOH/$CHCl_3$ as the eluent. (1α)-15(16)-Anhydro-11(15→1)-abeotaxol (22) was obtained as an amorphous white solid in 55% yield (29 mg): ^{1}H NMR, see Table II; MS (FAB) *m/z* (relative intensity) 836 (MH^+, 100), 776 (MH^+ - HOAc, 30), 551 (836 - side chain - H, 10), 307 (20); high-resolution mass spectrum calcd for $C_{47}H_{50}NO_{13}$ (MH^+) 836.3282, obsd 836.3272.

Acknowledgment. Partial financial support for this work was provided by the American Cancer Society (Grant CH 268). We acknowledge gifts of crude taxol-containing fractions from PolySciences, Inc., through the courtesy of Dr. Matthew Suffness and Dr. Gordon Cragg of the National Cancer Institute, and we thank Professor Tomas Hudlicky for helpful discussions.

Supplementary Material Available: ^{1}H NMR spectra for compounds 4, 7, 8, 16, 17, and 22 (6 pages). Ordering information is given on any current masthead page.