Synthesis of Ring B-Rearranged Taxane Analogs

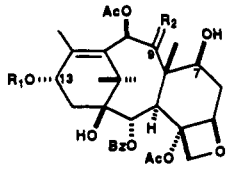
Larry L. Klein,* Clarence J. Maring, Leping Li, Clinton M. Yeung, Sheela A. Thomas, David J. Grampovnik, Jacob J. Plattner, and Rodger F. Henry†

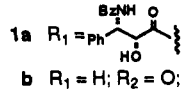
Anti-Infective Division, D-47M, and Analytical Research Division, D-418, Abbott Laboratories, Abbott Park, Illinois 60064

Received November 29, 1993•

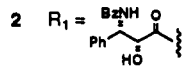
Reaction of the C-7 hydroxyl group on the 9-dihydrotaxane skeleton with triflic anhydride causes a major skeletal rearrangement to occur leading to contraction of ring B. In addition the formation of a ring C-fused cyclopropane structure occurs. The requisite C-13 phenylisoserinate side chains are appended via an initial deacylation of the C-13 acetate followed by reacylation and deprotection. These rearranged compounds show very similar structural features with the parent 9-dihydrotaxane skeleton and also retain biological activity.

Increased interest in the naturally-occurring antitumor agent taxol (**1a**) has encouraged numerous chemical modifications,[1] though until recently, few reports have focused on the polycyclic carbon skeleton.[2] This is primarily due to the poor accessibility of reagents to this sterically crowded and highly functionalized molecule. Furthermore, attempts to utilize conditions of low or high pH are limited by opening of the oxetane ring in the former case or epimerization of C-7 in the latter case.[3] Without appropriate protection even mildly basic conditions cause C-7 epimerization to occur in compounds bearing the C-9 carbonyl e.g. taxol or baccatin III (**1b**), presumably due to a reversible retro-aldol reaction.



1a R_1 =  R_2 = O; **Taxol**

b R_1 = H; R_2 = O; **Baccatin III**

2 R_1 = 

R_2 = H, α-OH; **9-Dihydrotaxol**

The few taxane derivatives that incorporate a modified ring B have arisen from new isolates such as a transannular product bearing a C-3–C-11 bond[4] or from the known rearrangement of ring A via activation of the C-1 hydroxyl group.[5] This latter rearrangement, which involves cleavage of the *gem*-dimethyl bridge, results in the contraction of both rings A and B. These bicyclo[5.3.0]decene derivatives exhibit little or no antitumor activity.

We have recently reported[6] the preparation of 9-dihydrotaxol (**2**) which shares the conformation and biological activity with that of taxol. The presence of the C-9 reduced center in this molecule not only enhances its stability relative to the parent molecule, but also allows for a different reactivity profile at the surrounding centers. We report the preparation of a novel ring B-contracted system via an unprecedented rearrangement reaction of this 9-dihydrotaxane skeleton.

Chemistry

Initial efforts to effect a displacement of the C-7 hydroxyl group as its corresponding mesylate returned starting material or, under forcing conditions, afforded decomposition products.[7] In an attempt to further activate this center, compound **3**[6b] was treated with triflic anhydride; however, new products were formed that did not contain the trifluoromethanesulfonyl moiety. The ^{1}H NMR spectrum of the major product exhibited an aldehydic proton and a methyl doublet in place of one of the methyl singlets. Crystallization of this material from methanol afforded a sample for X-ray analysis (Figure 1)[8], and the data proved that a major rearrangement of the carbon skeleton had taken place. This new taxane derivative **4** contained a bicyclo[4.3.1]decene ring bearing a C-7 methyl and C-8 aldehyde group both positioned onto the β-face.

A mechanism for this transformation was postulated as involving an initial dissociation of the triflate to form a C-7 carbocation (Scheme 1). A Wagner–Meerwein shift of the C-8 methyl group to C-7 then leads to a new tertiary carbocation at C-8. A pinacol-type rearrangement involving the C-9 hydroxyl group can then take place with subsequent transfer of the C-10 carbon. According to molecular models, the migration of the C-10 center should lead to the expected β-stereochemistry of the pendent aldehyde group; however, the preceding methyl migration would seem to be syn-facial. One possible explanation is that the C-4 acetyl group may block any approach to the C-7 cationic center from the α-face thus allowing for the β-migration of this methyl group to take place. This rearrangement has not been observed in the C-9 carbonyl system and should be inaccessible since it relies on

† Analytical Research Division.

• Abstract published in *Advance ACS Abstracts*, April 1, 1994.

(1) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1–206.

(2) (a) Chen, S.-H.; Fairchild, C.; Mamber, S. W.; Farina, V. *J. Org. Chem.* **1993**, *58*, 2927–2928. Chaudhary, A. G.; Rimoldi, J. M.; Kingston, D. G. I. *J. Org. Chem.* **1993**, *58*, 3798–3799. Chen, S.-H.; Wei, J.-M.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 3205–3206. (b) Chen, S.-H.; Huang, S.; Wei, J.-M.; Farina, V. *J. Org. Chem.* **1993**, *58*, 4520–4521.

(3) (a) Chen, S.-H.; Huang, S.; Wei, J.-M.; Farina, V. *Tetrahedron* **1993**, *49*, 2805–2828. (b) Ringel, I.; Horwitz, S. B. *J. Pharm. Exper. Ther.* **1987**, *242*, 692–698.

(4) Graf, E.; Kirfel, A.; Wolff, G.-J.; Breitmaier, E. *Liebigs Ann. Chem.* **1982**, 376. Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J.C.S. Chem. Commun.* **1966**, 923. Chiang, H. C.; Woods, M. C.; Nakadaira, Y.; Nakanishi, K. *J.C.S. Chem. Commun.* **1967**, 1201. Chen, S.-H.; Combs, C. M.; Hill, S. E.; Farina, V.; Doyle, T. W. *Tetrahedron Lett.* **1992**, *33*, 7679–7680.

(5) Samaranayake, G.; Magri, N. F.; Jitransgri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114–5119. Ref 3a.

(6) (a) Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047–2050. (b) Gunawardana, G. P.; Premachandran, U.; Burres, N. S.; Whittern, D. N.; Henry, R.; Spanton, S.; McAlpine, J. B. *J. Nat. Prod.* **1992**, *55*, 1686–1689.

(7) The C-7 trifluoroethanesulfonate (tresylate) exhibits optimal stability/reactivity. Klein, L. L. Unpublished results.

(8) Johnson, C. K. ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, TN (1976).

0022-3263/94/1959-2370$04.50/0

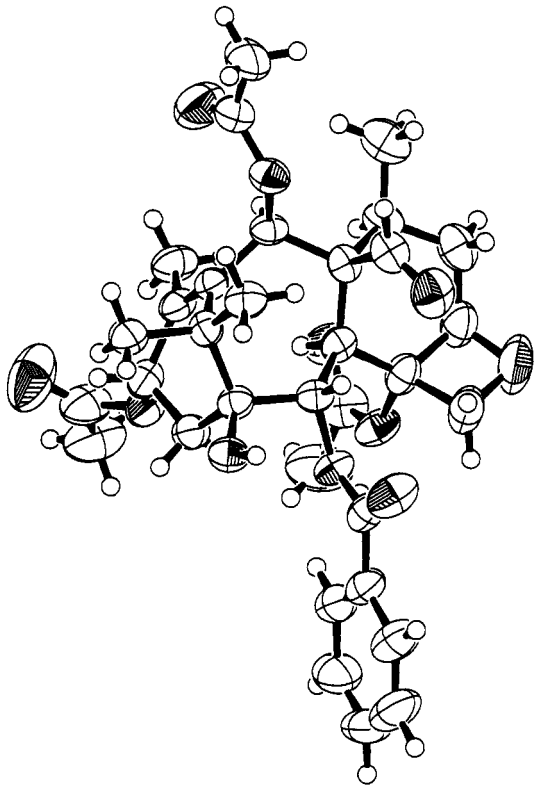
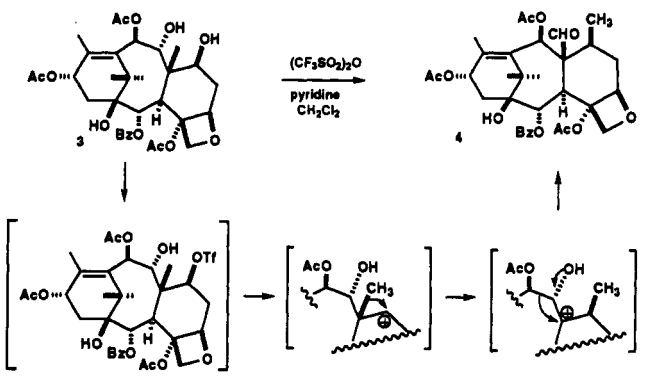
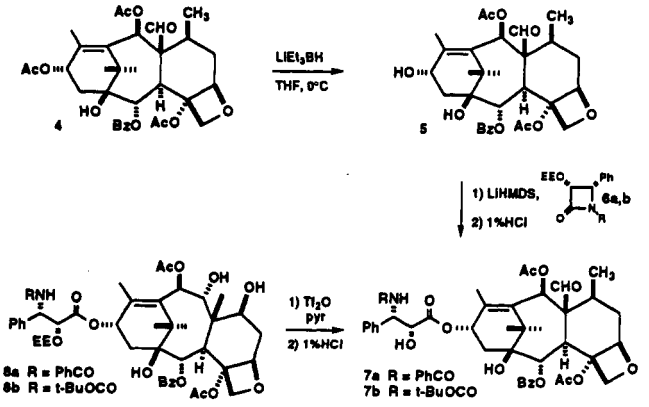


Figure 1. Crystal structure of compound 4.[8]

Scheme 1



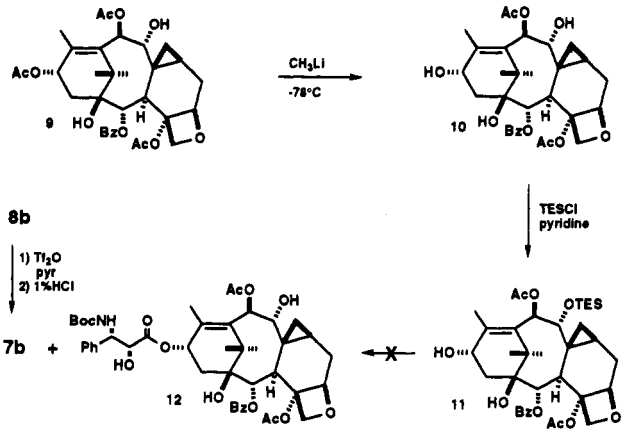
Scheme 2



formation of the C-8 α-carbocation, a species which would be disfavored.

Inspection of crystal structures and molecular models demonstrates that this new ring system overlaps quite well with that of the parent 9-dihydrotaxane system. Figure 2[9] represents the crystal structure of compound **3** (grey)

Scheme 3



superimposed onto the corresponding structure for compound **4** (black). This illustration was formed by allowing the atoms in ring A, ring C, C-2, along with the first atom out from each of these two rings to fit optimally on both structures. It is apparent that C-10 in **4** nearly bisects the C-9–C-10 bond in **3**. While the distance between C-11 and C-8 in **4** has certainly decreased, the optimal fit displayed in Figure 1 shows that the functionalities on the "lower" half of the taxane system (C-2 benzoate, C-4 acetate, C-4,5-oxetane ring) can retain their general positions relative to those in compound **3**. Furthermore, although gross functional changes have occured in the "upper" C-7–C-10 portion, reasonable overlap of the C-7 methyl and C-8 aldehyde carbons in **4** with the C-7 hydroxyl and C-8 methyl carbons in **3**, respectively, is still possible.

In order to ascertain the level of biological activity of this new series, we needed to remove the C-13 acetate present in **4** and append the C-13 phenylisoserinate side chain since it is required for activity. Our previous report on the preparation of 9-dihydrotaxol described the use of nucleophilic reagents such as *n*-butyllithium[6] for the first selective deacylation of a taxane C-13 acetate. For compound **4** we found that lithium triethylborohydride deacylates equally well, effecting the selective cleavage of this acetate not only in the presence of the C-4, C-10 acetates and C-2 benzoate, but also in the presence of the C-9 aldehyde group. This C-13 hydroxyl group could then be reacylated using lithium hexamethyldisilazide and the corresponding β-lactams **6a,b**.[10] Simple deprotection of the C-2′ ethoxyethyl groups using 1% HCl in ethanol gave the two side-chain-bearing products, **7a** and **7b**. We later found that direct triflation of the 2′-*O*-ethoxyethyl derivative of 9-dihydrotaxol **8**[6] also provided a direct, though lower yield source of **7a** following deprotection.

In the rearrangement reaction one of the minor products was isolated and, while not showing an aldehyde proton by NMR analysis as in **4**, did also result from a loss of water (mass spectral analysis). From X-ray analysis of a sample crystallized from methanol, we found this compound to be the cyclopropane analog **9** (Figure 3).[8] This product could arise from a trapping of the carbocation center formed at C-7 as described above by the C-8 methyl followed by loss of a proton. Recently, this same reaction was found to occur in the 9-carbonyl system.[2b] There is

(9) SYBYL 6.03, Tripos Associates, St. Louis, MO.
(10) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron*, **1992**, *34*, 6985–7012.

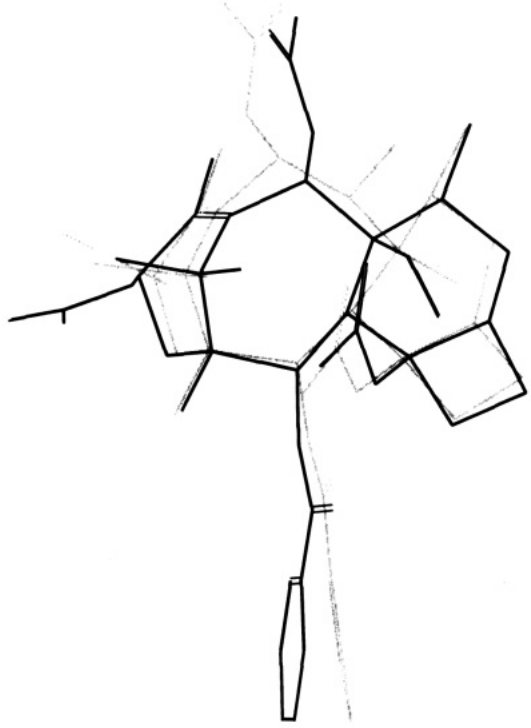


Figure 2. Superposition of crystal structure of compound **4** (black) and compound **3** (grey)(refs 6b, 9).

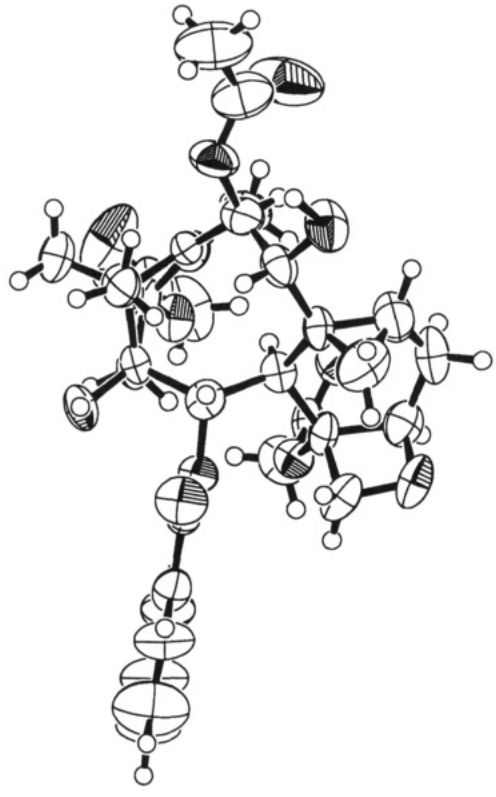


Figure 3. Crystal structure of compound **9**.[8]

little precedent for such a ring closure in organic chemistry, and although it is as yet unclear what the driving force for this cyclization is, it may merely attest to the peculiar conformation of ring C in these compounds.

The bonds lengths of the new ring in **9** are 1.47, 1.53, and 1.7 Å for C-7/C-8, C8/C19, and C7/C19, respectively, as compared to corresponding distances of 1.6, 1.5, and 2.6 Å in compound **3**. The exceptionally long bond length for the newly formed bond between C7/C19 in **9** reflects an asymmetric, and possibly strained, cyclopropane ring.

Table 1. Tumor Cell Cytotoxicity[a]

compd	IC_{50} (μg/mL) vs tumor cell lines[b]		
	HT29	B16F10	P388
1a, taxol	0.0024	0.0041	0.0096
7a	0.076	0.046	0.032
7b	0.0054	0.0046	0.0083
12	0.0012	0.0005	0.0011

[a] Determined by MTT-colorimetric microtiter assay.[12] [b] HT29 = human colon adenocarcinoma, B16F10 = mouse melanoma, P388 = mouse leukemia.

In order to determine the effect of this cyclopropane structure on bioactivity, compound **9** was deacylated at the C-13 acetate as before; however, attempts to reacylate product **10** with the isoserinate lactam **6b** afforded mixtures resulting from the mono- and diacylation of both C-13 and C-9 hydroxyl groups. Initial protection of **9** with triethylsilyl chloride also led to similar silylated regioisomers. Although the desired silyl ether **11** could be isolated from this mixture, the subsequent reacylation of C-13 hydroxyl of **11** still failed to provide our desired product. The seemingly greater accessibility of the C-9 hydroxyl group in **10** may reflect a different conformation of this strained compound. Fortunately the desired product could be obtained as a minor constituent from the direct triflation of **8b** and, following deprotection as before, was isolated as the fully functionalized cyclopropane analog **12**.

Although the aldehyde group in rearrangement product **4** was considered as a potential site for modifications, it was found to be resistant to various reagents, presumably due to its hindered nature. Nucleophiles such as *n*-BuLi or Super Hydride could be used as described above to deacylate the C-13 acetate in **4** without affecting this group; however, treatment with sodium borohydride in ethanol did succeed in slow reduction to the corresponding hydroxymethyl analog.[11] Even so, it was shown that this new primary hydroxyl group was less reactive than that of the C-13 hydroxyl and thus, a different strategy for further functionalization of this center is being studied.

Interestingly, these rearranged structures exhibited much of the in vitro antitumor activity of taxol when tested against several tumor cell lines (Table 1). The derivative bearing the 3′-*N*-benzoyl group, **7a**, exhibited 4- to 40-fold less activity than taxol against the cell lines while the 3′-*N*-Boc derivative, **7b**, exhibited nearly equal potency to taxol. The activity of the cyclopropyl analog **12** was even better than **7b** though it should be noted that analogs bearing this Boc group generally exhibit 10-fold greater potency than the corresponding benzamide analogs. The potencies of **7** and **12** would lead one to conclude that, since the changes in these molecules do not greatly effect the conformation, the functional groups present on the C-7 to C-10 portion are not absolutely required for cytotoxic activity. These results should encourage further modifications in this area of the molecule.

Experimental Section

^{1}H NMR spectra were recorded on a General Electric QE300 spectrometer using Me_4Si as an internal standard and the high-

(11) Klein, L. L. Anti-Infective Division, Abbott Laboratories. Unpublished results.
(12) Mosmann, T. *J. Immunol. Meth.* **1983**, *65*, 55.

resolution MS were obtained on a Kratos MS50 instrument. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY. Methylene chloride was distilled from calcium hydride, and tetrahydrofuran was distilled from sodium. Unless otherwise noted, materials were obtained from commercial sources and used without further purification.

Rearrangement of 3 (4). To 13-acetyl-9-dihydrobaccatin III (**3**) (25 mg) dissolved in methylene chloride (1 ml) and pyridine (0.064 ml, 20 eq.) at 0 °C under nitrogen was added a 10% solution of trifluoromethanesulfonic anhydride in methylene chloride dropwise with stirring until an orange color persists. The ice bath was removed and the mixture allowed to stir 1 h at which time the reaction was complete by thin-layer chromatographic analysis. The reaction was quenched by the addition of pH 7 phosphate buffer and the organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography using ethyl acetate:hexane (1:1, R_f = 0.4) to give 13.6 mg of aldehyde **4** (56%): ^{1}H NMR ($CDCl_3$) δ 10.24 (d, 1H), 8.18 (d, 2H), 7.61 (t, 1H), 7.5 (t, 2H), 6.28 (s, 1H), 6.07 (t, 1H), 5.83 (d, 1H), 5.21 (d, 1H), 4.9 (dd, 1H), 4.19 (d, 1H), 2.45–2.44 (m, 1H), 2.48 (d, 1H), 2.25 (s, 3H), 2.2 (s, 3H), 2.23–2.1 (m, 2H), 2.18 (s, 3H), 2.0 (dd, 1H), 1.94 (d, 3H), 1.62 (ddd, 1H), 1.22 (d, 3H), 1.15 (s, 3H), 1.1 (s, 3H); MS (DCI/NH_3) m/z 613 (M^+ + 1), 630 (M^+ + NH_4^+). Recrystallized from MeOH:water (1:1) for X-ray analysis.

Second component from ethyl acetate:hexane column chromatography (1:1, R_f = 0.18) gave 1.9 mg of cyclopropane **9** (8%): ^{1}H NMR ($CDCl_3$; trace D_2O) δ 8.12 (d, 2H), 7.61 (t, 1H), 7.48 (t, 2H), 6.12 (t, 1H), 5.84 (d, 1H), 5.77 (d, 1H), 4.82 (t, 1H), 4.27 (d, 1H), 4.22 (d, 1H), 4.17 (d, 1H), 3.48 (d, 1H), 2.46 (dt, 1H), 2.3–2.1 (m, 2H), 2.29 (s, 3H), 2.2 (s, 3H), 2.13 (s, 3H), 1.95 (dt, 1H), 1.92 (d, 3H), 1.63 (m, 4H, H-7), 1.35 (t, 1H), 1.2 (s, 3H), 1.02 (dd, 1H). Recrystallized from MeOH:water (1:1) for X-ray analysis.

Deacetylation of Aldehyde 4 (5). To a solution of **4** (27 mg) in tetrahydrofuran (5 mL) stirred at −78 °C under nitrogen was added Super Hydride ($LiEt_3BH$, 1 M in THF, 0.128 mL) dropwise. After 10 min the reaction was shown to be complete by thin-layer chromatographic analysis. The reaction was quenched by the addition of pH 7 phosphate buffer and methylene chloride, and the organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography using methylene chloride:methanol (95:5) to give 18 mg of the desired product **5** (72%): ^{1}H NMR ($CDCl_3$) δ 10.28 (d, 1H), 8.18 (d, 2H), 7.6 (t, 1H), 7.48 (t, 2H), 6.28 (s, 1H), 5.79 (d, 1H), 5.21 (d, 1H), 4.9 (dd, 1H), 4.86 (t, 1H), 4.18 (d, 1H), 5.21 (d, 1H), 2.5–2.4 (m, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 2.25–2.0 (m, 3H), 2.09 (d, 3H), 1.62 (ddd, 1H), 1.23 (d, 3H), 1.1 (s, 3H), 1.0 (s, 3H); MS (DCI/NH_3) m/z 588 (M^+ + NH_4^+).

Reacylation of C-13 (7b). To a solution of **5** (18 mg) in THF (2 mL) stirred under nitrogen at −78 °C was added lithium hexamethyldisilazide (LiHMDS, 1 M in THF, 0.063 mL, 2 equiv) dropwise and after 15 min lactam **6b** was added in THF (1 mL, 2 equiv). The mixture was warmed to 0 °C and after 15 min the reaction was complete by thin-layer chromatographic analysis. The reaction was quenched by the addition of pH 7 phosphate buffer and methylene chloride, and the organic layer was separated, dried, and evaporated. The residue was treated with 1% HCl in ethanol (2 mL) and stirred at 25 °C for 4 h at which time the reaction was complete by thin-layer chromatographic analysis. The mixture was quenched by the addition of pH 7 phosphate buffer and concentrated before partitioning between water and methylene chloride. The organic layer was separated, dried, and evaporated, and the residue was purified by silica gel column chromatography using methylene chloride:methanol (95:5, R_f = 0.36) to give 13 mg of the desired product **7b** (50%): ^{1}H NMR ($CDCl_3$) δ 10.25 (d, 1H, J = 1.1 Hz), 8.24 (d, 2H, J = 7.14 Hz), 7.6–7.3 (m, 10H), 6.3 (s, 1H), 6.3 (t, 1H), 5.92 (d, 1H, J = 9.89 Hz), 5.4 (d, 1H, J = 9.89 Hz), 5.31 (br d, 1H, J = 9.89 Hz), 5.17 (d,1H, J = 7.14 Hz), 4.84 (dd, 1H, J = 6.59, 9.89 Hz), 4.62 (br s, 1H), 4.15 (d, 1H, J = 7.14 Hz), 3.18 (d, 1H, J = 3.3 Hz), 2.56 (d, 1H, J = 9.89 Hz), 2.35–2.5 (m, 1H), 2.38 (s, 3H), 2.2 (s, 3H), 2.2–2.1 (m, 3H), 1.91 (br s, 3H), 1.65 (dt, 1H, J = 6.59, 14.29 Hz), 1.27 (d, 3H, J = 7.69 Hz), 1.23 (s, 9H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.3, 204.4, 172.2, 170.9, 169.3, 167.7, 154.9, 139.6, 138.8, 135.9, 133.4, 130.5, 129.4, 128.8, 128.5, 127.8, 126.5, 83.8, 83.4, 80.3, 79.9, 78.9, 75.1, 73.8, 72.3, 57.1, 55.6, 46.2, 41.9, 39.5, 37, 36.3, 28.1, 25.7, 22.4, 22.3, 21.1, 16.3, 15.1. Anal. Calcd for $C_{45}H_{55}NO_{14}\cdot H_2O$: C, 63.44; H, 6.74; N, 1.64. Found: C, 63.32; H, 6.53; N, 1.74.

Rearrangement of 8a (7a). 9-Dihydrotaxol-2′-OEE (**8a**) (10 mg) was treated as for **3** above to give the corresponding rearranged product. After similar workup the crude product was treated with 1% HCl in EtOH for 4 h at 25 °C, quenched with buffer and methylene chloride, and purified by silica column chromatography using methylene chloride:methanol (95:5, R_f = 0.4) to give 1.8 mg of the desired product, **7a** (20%): ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 8.31 (d, 2H, J = 7.69 Hz), 7.7–7.3 (m, 13H), 7.0 (d, 1H, J = 9.34 Hz), 6.29 (s, 1H), 6.23 (t, 1H, J = 8.24 Hz), 5.92 (d, 1H, J = 10 Hz), 5.85 (br d, 1H, J = 9.35 Hz), 5.2 (d, 1H, J = 7.69 Hz) 4.83 (dd, 1H, J = 6,9.34 Hz), 4.77 (br s, 1H), 4.16 (d, 1H, J = 7.14 Hz), 3.34 (d, 1H, J = 3.85 Hz), 2.58 (d, 1H, J = 10 Hz), 2.5 (m, 1H), 2.4 (s, 3H), 2.26 (dd, 1H, J = 7.69, 15.93 Hz), 2.2 (s, 3H), 2.25–2.0 (m, 2H), 1.92 (br s, 3H), 1.62 (dt, 1H, J = 6, 14.28 Hz), 1.27 (d, 3H, J = 7.14 Hz), 1.16 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.4, 172.3, 171.3, 169.4, 167.6, 166.6, 139.4, 138.4, 136, 133.8, 133.4, 131.7, 130.6, 129.5, 128.9, 128.5, 128.5, 128.1, 127, 126.7, 83.9, 83.3, 80.2, 79, 75, 73.4, 72.6, 57.1, 54.4, 46.2, 41.8, 39.5, 37, 36.3, 25.8, 22.4, 22.3, 21.1, 16.3, 15; Anal. Calcd for $C_{47}H_{51}NO_{13}\cdot 1.5H_2O$: C, 65.27; H, 6.29; N, 1.62. Found: C, 65.39; *H, 5.85*; N, 1.8.

Rearrangement of 8b (12). 9-Dihydro-10-acetyl-2′-OEE-3′-*N*-debenzoyl-3′-*N*-(*tert*-butoxycarbonyl)taxol (**8b**) (50 mg) was treated as for **3** above to give, after similar workup, 16 mg of the corresponding rearranged product **7b** and 7 mg of 2′-OEE **12**. Product 2′-OEE **12** was treated with 1% HCl in EtOH for 1.5 h at 25 °C, quenched with buffer and methylene chloride, and purified by silica gel column chromatography using methylene chloride:methanol (95.5, R_f = 0.3) to give 4 mg of the desired product, **12** (8%, total from **8b**); ^{1}H NMR ($CDCl_3$) δ 8.11 (d, 2H, J = 7.69 Hz), 7.62–7.3 (m, 8H), 6.12 (t, 1H, J = 8.24 Hz), 5.8 (m, 2H, H-10), 5.58 (d, 1H, J = 9.89 Hz), 5.31 (br d, 1H), 4.8 (t, 1H, J = 4.4 Hz), 4.63 (br s, 1H), 4.27 (d, 2H, J = 8.24 Hz), 4.2 (d, 1H, J = 8.24 Hz), 4.0 (br s, 1H), 3.47 (d, 1H, J = 6.6 Hz), 2.36 (dd, 1H, J = 9.89, 15.39), 2.27 (s, 3H), 2.12 (s, 3H), 1.83 (s, 3H), 1.65 (s, 3H), 2.3–1.3 (m, 5H), 1.39 (s, 9H), 1.21 (s, 3H), 1.1 (dd, 1H, J = 6.04, 9.34 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4, 170.9, 169.9, 167.3, 155.1, 138.3, 133.7, 130.1, 129.3, 128.7, 128.6, 127.8, 126.9, 112.3, 85.1, 85.0, 84.0, 79.9, 78.9, 77.7, 76.8, 76.5, 74.1, 73.9, 72.0, 55.9, 42.7, 39.6, 36.0, 28.2, 27.6, 26.7, 25.5, 22.5, 22.2, 21.2, 15.0, 14.4, 12.5; high resolution MS calcd for $C_{45}H_{55}NO_{14}$ (M^+ + 1) 834.3701, found 834.3696.

X-ray Crystallographic Study of 4 and 9. Data for both compounds were collected on a Rigaku AFC5 diffractometer with a rotating anode and using Ni-filtered Cu K_α radiation (λ = 1.5418 Å)[13a] Crystal data for **4** are as follows: $C_{33}H_{40}O_{11}$; space group $P2_1$; a = 15.935(3) Å, b = 12.749(1) Å, c = 15.902(2) Å, β = 97.746(9)°; V = 3201.1(6) Å^3; Z = 4; D_{calc} = 1.27 g/cm^3; μ(Cu K_α) = 7.94 cm^{-1}; total of 3460 reflections within 2Θ = 120.2° and $I > 3\sigma(I)$. The final R factor was 0.045 (R_W = 0.047). Crystal data for **9** are as follows: $C_{33}H_{40}O_{11}\cdot 2H_2O$; space group $P2_1$; a = 8.475(1) Å, b = 16.460(3) Å, c = 12.7068(9) Å, β − 97.7839)°; V = 1746.8(4) Å^3, Z = 2; D_{calc} = 1.23 g/cm^3; μ(Cu K_α) = 7.98 cm^{-1}; total of 1335 reflections within 2Θ = 90.1° and $I > 3\sigma(I)$. The final R factor was 0.044 (R_W = 0.041). Both structures were solved by direct method using Shelxs86.[13b] All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were geometrically calculated or taken from a difference Fourier map. The hydrogen atoms were included in calculations but not refined.

(13) (a) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) Sheldrick, G. M. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goodard, R., Eds.; Oxford University Press: New York, 1985; pp 175–189. TeXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1992).