Antitumor Activity of 9(*R*)-Dihydrotaxane Analogs

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A novel reduced taxane, 13-acetyl-9(*R*)-dihydrobaccatin III (**1**) has been isolated from *Taxus canadensis*. The selective C-13 deacetylation of this isolate has allowed for the preparation of a wide variety of 9(*R*)-dihydrotaxane analogs. In general, this series has shown greater stability and water solubility than the 9-carbonyl series while retaining antimicrotubule and tumor cell cytotoxicity activities relative to taxol. Placement of polar functionalities at the C-7 position results in loss of activity whereas alkylation or acylation of either C-7 or C-9 hydroxyl groups ameliorate the activity.

Introduction

The remarkable antitumor activity of taxol[1] has led to its approval in 1992 as a useful therapeutic agent for ovarian cancer.[2] Due to its novel mode of action,[3] this drug shows promise in combination therapy[4] and is currently being studied as an agent in first line cancer therapy. On the other hand, taxol exhibits very poor water solubility and requires an inordinate amount of a relatively toxic vehicle, Cremophor EL, for administration.[5] The identification of new taxol analogs which exhibit broader spectrum, enhanced *in vivo* activity, or improved water solubility will be important in the continued evolution of this class of agents.[6]

The isolation of the novel component, 13-acetyl-9(*R*)-dihydrobaccatin III (**1**) (Figure 1) was reported by several laboratories in 1992.[7] It is found as a constituent in *Taxus canadensis*, a bush common to the northeastern United States and southern Quebec but has also been found to a minor extent in other species such as *Taxus chinensis* in China.[7c] Since the majority of **1** is contained within the needles of *T. canadensis*, this plant serves as a cultivatable and renewable resource for this novel starting material. The content of **1** in these needles is similar to the content of 10-deacetylbaccatin III (10DAB), the starting material for taxotere, in *Taxus baccata*.[8]

We have recently reported[9] the preparation of 9-dihydrotaxol (**2**) which shares the conformation and microtubule binding activity with that of taxol. The X-ray crystal structure of **1** shows excellent overlap with that of the corresponding baccatin III derivative due to the fact that the C-9 carbonyl in the latter series bisects the C-9 carbinol center in **1**.[7a] Several advantages and opportunities afforded by this novel structure are apparent: (1) the presence of the C-9 hydroxyl serves as an additional site for modifications; (2) the presence of this hydroxyl serves to increase the water solubility of these analogs; and (3) the lack of a C-9 carbonyl serves to stabilize the system relative to the base-catalyzed C-7 epimerization[10] and also allows for a different reactivity profile at the surrounding centers.

In this paper we report the synthesis and antitumor activities of a variety of 9-dihydrotaxane analogs bearing modified ring functionalities.

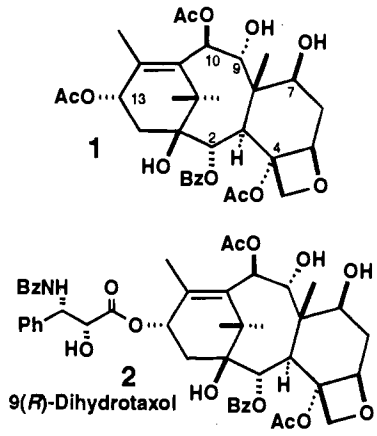

Figure 1.

Chemistry

In order to ascertain the effect of the C-9 hydroxyl on the antitumor activity of this system, we needed to cleave the C-13 acetyl group present in **1** and reacylate this center with an appropriate side chain. While many ways of conducting the latter reaction have been reported, no method for selective removal of the C-13 acetate from the taxane nucleus was known prior to our work.

C-13 Deacetylation. Initial attempts toward this end involved hydrolytic deacetylation and succeeded only in rapid, selective, and high-yield removal of the C-10 acetate, giving **3** (Scheme 1). Further mild hydrolysis afforded complicated mixtures arising from competitive deacylation of the C-2, C-4, and C-13-*O*-acetyl groups. Formation of the 7,9-acetonide **4** under standard conditions and use of this substrate under these hydrolytic conditions resulted in slowing the C-10 deacylation but failed to enhance selectivity toward the C-13 ester. Under more vigorous conditions, complete deacylation of the C-2 benzoate occurred and was accompanied by facile ring opening of the oxetane ring with concomitant formation of the tetrahydrofuran side product **5**. This ring system was also reported in the C-9 carbonyl series and has been shown to lead to inactive compounds.[11]

Although hydrolytic approaches proved unsatisfactory, we found that the deacetylation could be successfully accomplished via treatment of protected substrates such as 4 with strongly nucleophilic agents such as

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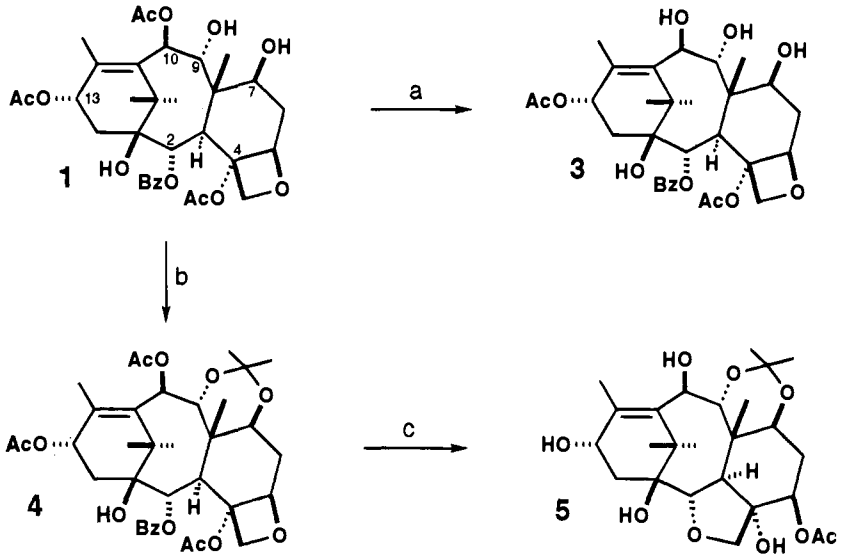
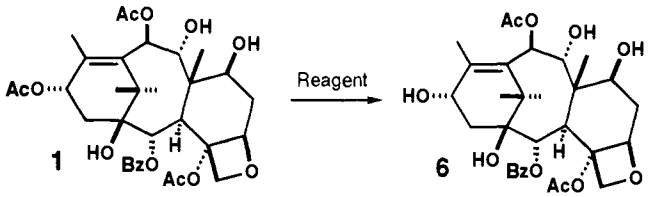
Scheme 1[a]



[a] (a) 1 N NaOH, MeOH, 0 °C; (b) DMP/acetone, CSA, 25 °C; (c) 1 N NaOH, 50 °C; Ac_2O, pyridine.

Table 1. Deacylation of the C-13 Acetate of 1



entry	reagent[a]	conditions[b]	result[c]
1	*n*-BuLi (2.5 M in hexane)	5 equiv	56%
2	CH_3Li (1.4 M in ether)	5 equiv	82%
3	PhLi (1.8 M in C_6H_{12}/ether)	5 equiv	50%
4	*s*-BuLi (1.3 M in C_6H_{12})	5 equiv	decomposition
5	BuMgCl (2 M in ether)	30 equiv	incomplete
6	MeMgBr (3 M in ether)	30 equiv	incomplete
7	$LiBEt_3H$ (1 M in THF)	5 equiv	60%[d]
8	$NaBH_4$ (MeOH)	excess	no reaction

[a] All reagents were purchased from Aldrich Co. and used as received. [b] All reactions run in THF at −78 °C except for $NaBH_4$ which was run at 0 °C in MeOH. [c] Reactions complete after 1 h, except entries 5 and 6 which stopped after 3 h. [d] Conversion. Product was in the form of a 7,9-ethyl borinate, with 20% 1 recovered.

n-BuLi.[9] Further advantage of this process is attained by reacting the resultant C-13 oxyanion directly with azetidinone **9**[12] to afford a one-pot deacetylation/side chain acylation process.

Recent work has characterized both the scope and optimal conditions for this reaction. First, protection of the C-7 or C-9 hydroxyls is unnecessary, and excellent results are obtained with **1** by simply increasing the equivalents of nucleophile added (Table 1). Second, this selective deacylation was found to be of general utility for taxanes, applicable to rearranged ring systems,[13] to deoxygenated compounds,[14] and even to the C-9 carbonyl series.[15] Finally, Table 1 lists many reagents which can produce **6**, though methyllithium was found to be the reagent of choice producing 82% yield of the desired product from **1** on a multigram scale.

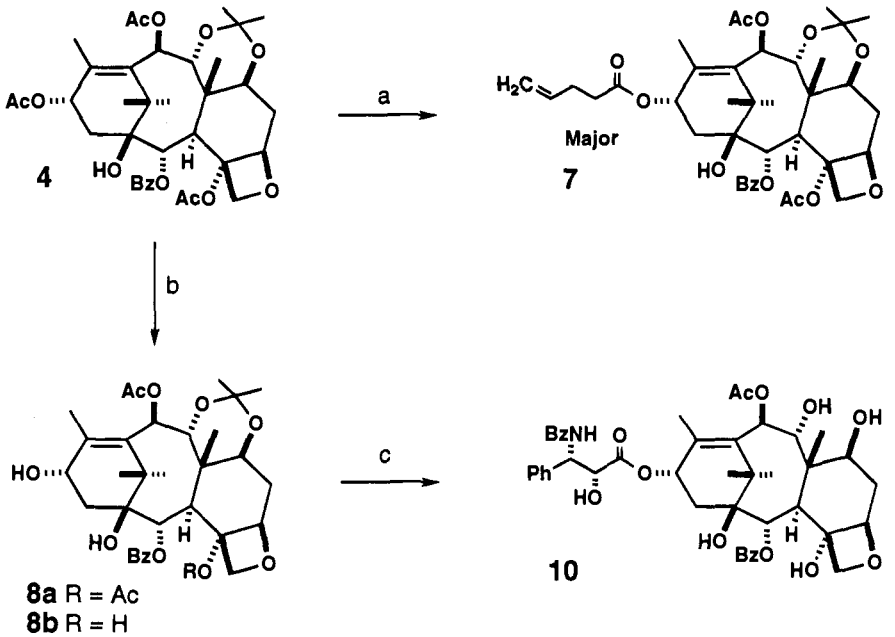
Rationale for this unexpected selectivity is suggested by the result of treatment of the acetonide **4** with lithium hexamethyldisilazide (LHMDS) and allyl bromide at −78 °C. The major product was the 13-(4-pentenoyloxy) analog **7** which obviously arose from the enolization and subsequent allylation of the C-13 acetyl group (Scheme 2). In addition to demonstrating that condensation of the C-13 enolate with electrophiles is a viable process,[16] the presence of this enolate allows for a mechanism, i.e., a ketene elimination, to lead to this deacetylation; however, such eliminations rarely occur at −20 °C. Why this presumably less accessible ester is the site for deprotonation should be conformationally related and is cause for further study.

One minor product isolated from the deacetylation of the acetonide **4** was the 4,13-dideacetyl analog **8b**. In order to study the effect of the functionality at C-4 on activity, the side chain was added to **8b**. This involved low-temperature deprotonation of the C-13 hydroxyl group with LHMDS followed by treatment with the azetidinone **9a**. Deprotection of both the ethoxyethyl protecting group and the acetonide afforded 4-deacetyl-9(*R*)-dihydrotaxol (**10**).[17]

C-13 Side Chain Addition. The previously described hydrolytic deacetylation attempts using methanolic 1 N NaOH established the capability of an efficient and selective removal of the C-10 acetyl group. In general, removal of the C-10 acetyl group has minimal effect on the cytotoxicity,[18] but a desirable effect on the water solubility of these lipophilic compounds. The general approach toward the preparation of derivatives (Scheme 3) was therefore planned to proceed through a common intermediate which would allow access to both the 10-acetyl and 10-deacetyl series. Through variation of the N-substituent on the azetidinone moiety, ready access to a wide range of analogs is possible.

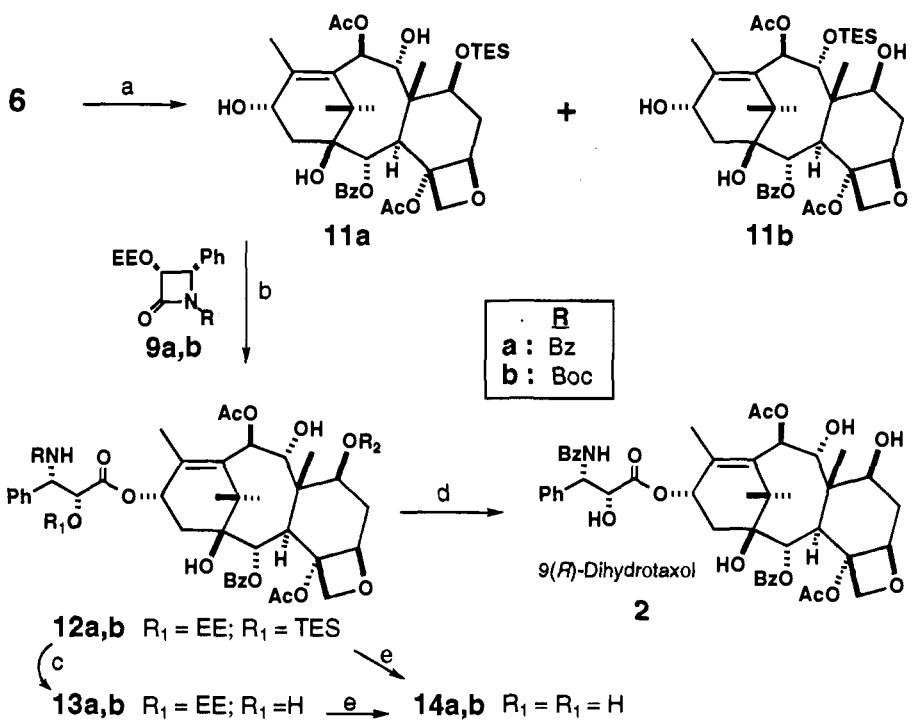
Previous attempts to acylate the unprotected 9-dihydrotaxane nucleus of **6** have resulted in reaction at the more accessible C-7 hydroxyl group; therefore, just as in the C-9 carbonyl series, this hydroxyl was initially protected with triethylsilyl chloride. The use of triethylamine as base in the silylation reaction with **6** produced both the C-7 **11a** and the C-9 **11b** triethylsilyl (TES) ethers (**11a**:**11b**, 5:1) which could be separated. Whereas silyl ether **11a** was stable to conditions required for subsequent side chain addition (LHMDS, THF, −78 °C), **11b** underwent partial isomerization to **11a**, suggesting a less sterically hindered environment at C-7. The

Scheme 2[a]



[a] (a) LiHMDS, THF, allyl bromide, −78 °C; (b) *n*-BuLi, THF, −78 °C; (c) NaH, THF, **9a**, 0 °C/1% HCl, EtOH.

Scheme 3[a]



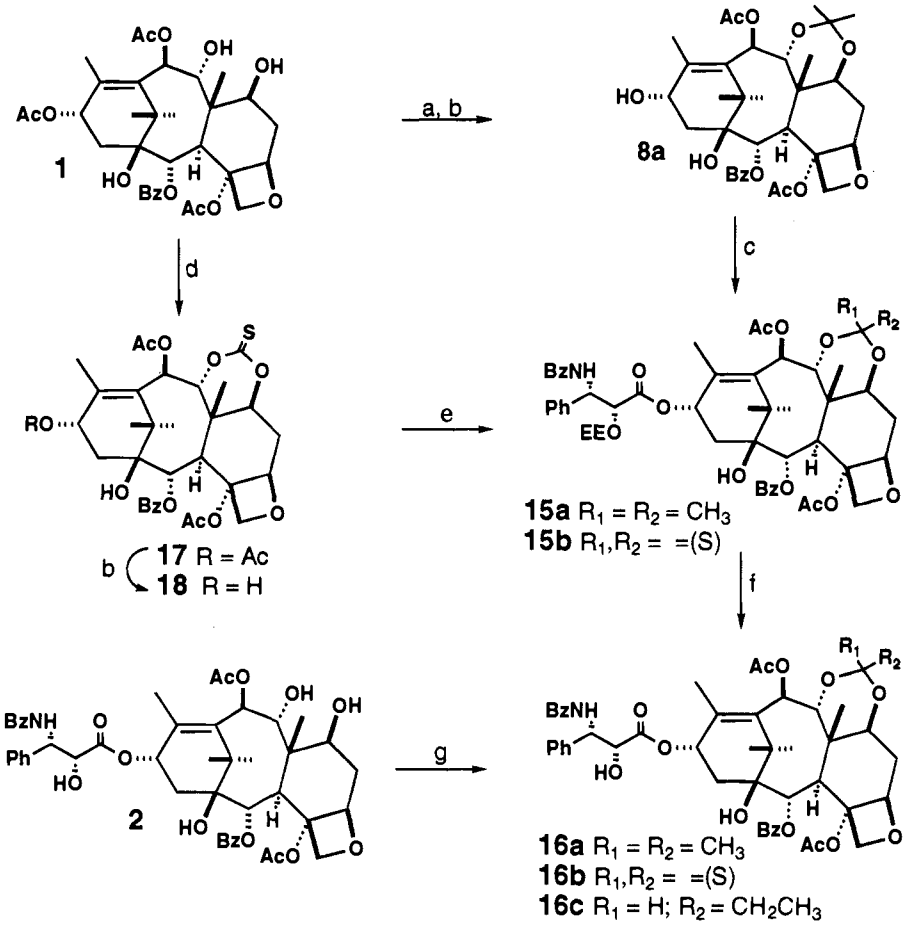
[a] (a) TESCl, pyridine, 0 °C; (b) LiHMDS, THF, −78 °C, **9a**; (c) HF−pyridine/MeOH/TEA, 0 °C; (d) 1% HCl, EtOH; (e) 1 N KOH, MeOH, 0 °C/1% HCl, EtOH.

formation of this side product could be partially overcome through the use of pyridine as base, thereby leading to a 75% yield of **11a** with only traces of **11b**.

Several early studies established that the 9-dihydrotaxane nucleus was slightly less reactive at C-13 toward acylating agents than the C-9 carbonyl system and, therefore, was subsequently coupled via the use of strong bases. Similar to several other studies,[19] LHMDS was found to be optimal in the deprotonation and acylation of **11a** as compared to NaHMDS, KHMDS, LDA, and NaH, although the latter reagent had been used in preliminary studies. Azetidinones **9** were added in standard fashion leading to the optimally protected 2′-OEE-7-OTES intermediates **12**. At this stage we were able to directly deprotect the C-2′/C-7 groups with acid to give 9(*R*)-dihydro analogs such as **2** or cleave the C-10/C-7 groups with 1 N NaOH prior to the acid quench to afford the 10-deacetyl-9(*R*)-dihydro analogs **14**. It was also possible to selectively deprotect only the 7-*O*-silyl group with HF/pyridine to give **13**. Alternatively, removal of only the 2′-*O*-EE group was possible with HCl/$CHCl_3$.[20]

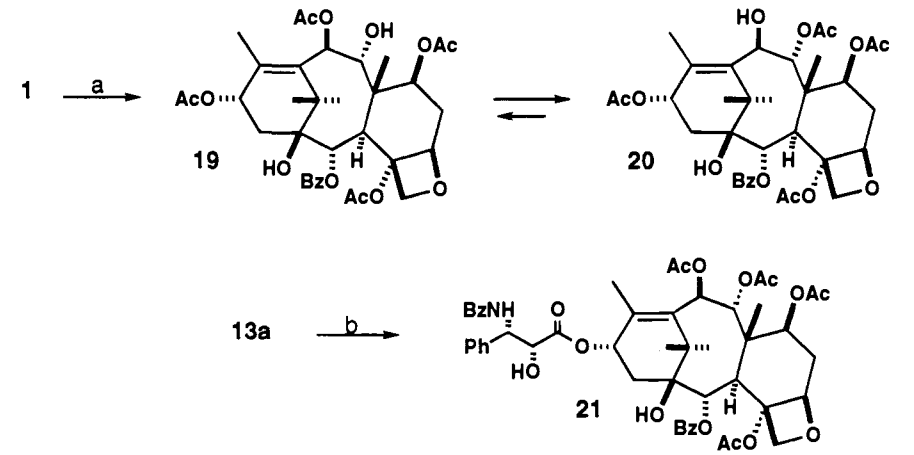
C-7−C-9 Chemistry. The pseudoequatorial placement of the C-7 and C-9 hydroxyl groups on the ring backbone facilitated the formation of 7,9-bridged analogs, e.g., 7,9-acetals could be formed under standard

Scheme 4[a]



[a] (a) DMP/acetone, CSA, 25 °C; (b) *n*-BuLi, THF, −44 °C; (c) b, then **9a**; (d) TCDI, DMAP, PhMe, reflux; (e) NaH, THF, **9a**; (f) 1% HCl, EtOH; (g) CH_3CH_2CHO, TsOH, 25 °C.

Scheme 5[a]



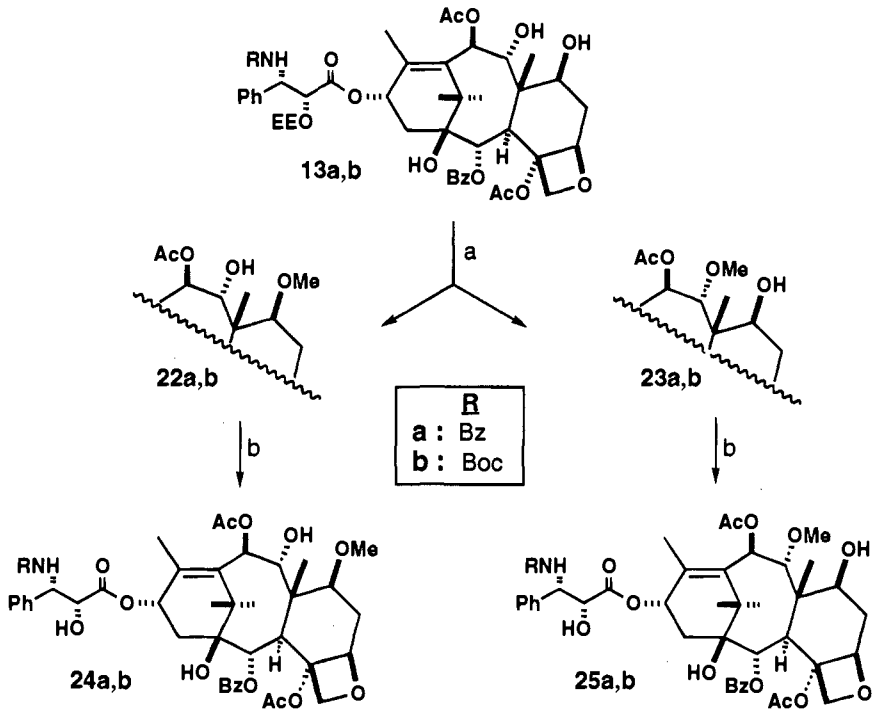
[a] (a) Ac_2O, TEA; (b) Ac_2O, pyridine, cat. DMAP.

conditions. The ketals such as acetonide **16a** or acetals such as the propylidene compound **16c** were prepared by treating **1** and **2** with excess dimethoxypropane or propionaldehyde, respectively, in the presence of acid over several hours (Scheme 4). The major limitation to the formation of these derivatives was the acid instability of the oxetane ring which, in most cases, was slowly cleaved under these conditions; therefore, these reactions were not always run to completion in order to acquire useful quantities of the products.

Treatment of **1** with thiocarbonyl agents bearing two leaving groups such as thiophosgene, thiocarbonyldiimidazole (TCDI), or phenyl chlorothionoformate all led to formation of the 7,9-thionocarbonate **17**.[14] Deacetylation of the C-13 acetate as before followed by addition of azetidinone **9** and deprotection afforded the thionocarbonate **16b**.

When simple acylation of the C-7 hydroxyl was carried out, two products were typically observed (Scheme 5). In addition to the expected 7-*O*-acyl compound **19**, the other product was characterized as the C-7-*O*-acyl 9-acetate **20** arising from migration of the C-10 acetyl group from the C-10 to the C-9 hydroxyl group.[21] Interestingly, this did not occur during the previously

Scheme 6[a]



[a] (a) CH_3I, Ag_2O, THF, reflux; (b) 1% HCl, EtOH.

described silylation conditions nor was this migration observed during or following alkylation of the C-7 hydroxyl group. Furthermore the C-7 or C-9 acyl products were unstable relative to silica gel and underwent interconversion upon standing in chloroform. In order to study the effect of acylation of C-7 on activity, it was necessary to acylate both C-7 and C-9 under standard conditions. This was carried out on the 2′-OEE-protected 9-dihydrotaxol **13a** using acetic anhydride, pyridine, and 4-(dimethylamino)pyridine. Following deprotection with 1% HCl, the triacetate **21** was obtained.

In contrast to the sensitivity of the C-9 carbonyl series under basic conditions, the 9(*R*)-dihydro system can be treated directly with base in order to alkylate the C-7 or the C-9 hydroxyl groups (Scheme 6). For methylation of **13** many conditions were studied in order to obtain selective products. No selectivity was observed under standard conditions (Ag_2O, CH_3I), leading to both the 7-*O*- and 9-*O*-methyl derivatives **22** and **23** in equal quantities; however, no dimethylated products were observed. These products were then deprotected with acid to give the final 7- and 9-*O*-methyl products, **24** and **25**, in both the *N*-benzoyl and *N*-Boc series for comparative purposes.

Taking advantage of its increased stability, isolate **1** could be directly treated with strong base (NaH or LiHMDS) and alkylated with allyl bromide to obtain the corresponding 7-*O*-allyl ether, **26** (Scheme 7). Deacetylation of **26** as before followed by side chain addition led to product **28**. From this compound, a variety of derivatives were available through standard manipulations. For example, hydroxylation with osmium tetraoxide afforded the diastereomeric diols **30** following deprotection with acid. Allyl ether **28** could, in turn, be oxidatively cleaved to give aldehyde **31**, which was directly reduced to alcohol **32** and acetylated to give **33** or reductively aminated with diethylamine to give **34**.

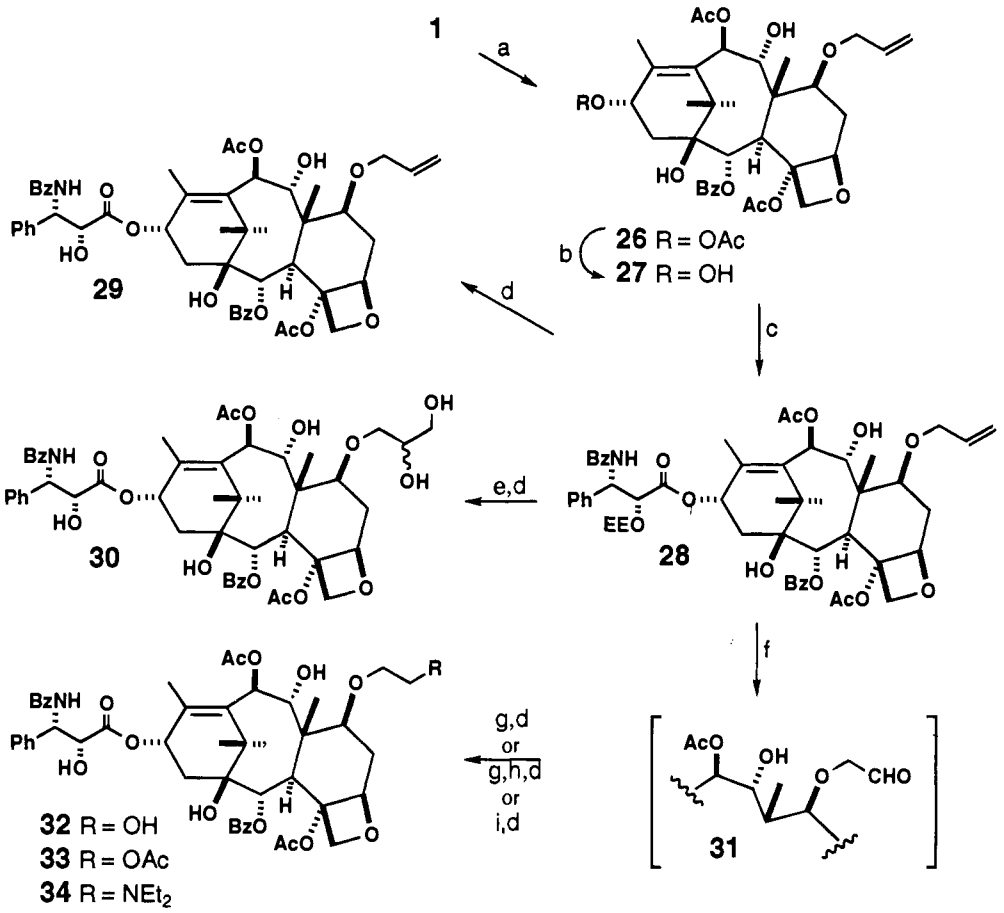
Biological Activity

Biological activity for these compounds was measured using both a tubulin assembly assay[22] and a tumor cell cytotoxicity assay[23] employing four tumor cell lines (Table 3). In general, a reasonable correlation of data from these assays was observed although several exceptions are noted. In order to determine which compounds would be further evaluated relative to the *in vivo* models, we depended heavily on the *in vitro* activity. Paramount to this work was the fact that 9(*R*)-dihydrotaxol (**2**) exhibited potent tubulin binding activity and cytotoxicity similar to, though 3–8-fold weaker than, that of taxol. This was the first example of a biologically active taxane lacking the C-9 carbonyl. These compounds show greater water solubility and stability and therefore may also exhibit modified pharmacokinetics. In fact, the *in vivo* antitumor activity shown by **2** in several mouse models was found to be increased relative to taxol.[24]

The two deacetyl analogs of **2**, i.e., **10** and **14a**, are very different in terms of their effect on microtubule assembly and whole cell activity. It has been shown in other cases that the presence of the 10-acetyl group has little effect on activity,[28] and this is also true for **14a**; however, removal of the 4-acetyl group as in **10** resulted in loss of activity. This result may reflect the importance of the 4-acetyl group's interaction with the C-13 side chain.[17] Comparison of the X-ray crystal structures of **8b** and **1** reveals no significant conformational variance due to loss of acetyl from the concave "pocket" of the taxane ring system. The fact that conditions for C-13 acetyl cleavage can also result in C-4 acetyl cleavage may be further evidence for the proposed interaction of C-13 hydroxyl and C-4 acetate promoted by others.[25]

Another general correlation is the 10-fold increased *in vitro* potency of the 3′-*N*-Boc analogs relative to their

Scheme 7[a]



[a] (a) NaH, Bu_4NI, allyl bromide, 0 °C; (b) *n*-BuLi, THF −44 °C; (c) NaH, THF, **9a**; (d) 1% HCl, EtOH; (e) OsO_4, NMMO, aqueous THF; (f) O_3, MeOH, −78 °C; (g) $NaBH_4$, MeOH; (h) Ac_2O, pyridine, 25 °C; (i) Et_2NH, $NaCNBH_3$.

Table 2. Characterizations of 9(*R*)-Dihydrotaxol Analogs

		HRMS		
compd	MS (FAB) *m/z*	calculated	measured	HPLC[a] %/t_R
2	ref 9	$C_{47}H_{53}NO_{14}$: 856.3544	856.3531	96.6/6.9
3	–	$C_{31}H_{41}O_{11}$: 589.2649	589.2628	–
4	ref 9	$C_{36}H_{47}O_{12}$: 671.3068	671.3055	–
6	589 [M + H^+]	$C_{31}H_{41}O_{11}$: 589.2649	589.2636	89.5/5.5
7	711 [M + H^+]	$C_{39}H_{51}NO_{12}$: 711.3381	711.3381	–
8a	ref 9	$C_{34}H_{45}O_{11}$: 629.2962	629.2964	–
8b	604 [M + NH_4^+]	x-ray analysis[b]		
10	814 [M + H^+]	$C_{45}H_{52}NO_{13}$: 814.3439	814.3444	93.5/8.8
11a	703 [M + H^+]	$C_{37}H_{55}O_{11}Si$: 703.3514	703.3500	88.7/17.5
14a	814 [M + H^+]	$C_{45}H_{52}NO_{13}$: 814.3439	814.3425	97.7/10.2
14b	848 [M + K^+]	$C_{43}H_{56}NO_{14}$: 810.3701	810.3691	97.4/7.1
16a	896 [M + H^+]	$C_{50}H_{58}NO_{14}$: 896.3857	896.3872	96.9/15.4
16b	936 [M + K^+]	$C_{48}H_{52}NO_{14}S$: 898.3109	898.3100	87.9/14.7
16c	896 [M + H^+]	$C_{50}H_{58}NO_{14}$: 896.3857	896.3872	88.2/16.9
17	673 [M + H^+]	$C_{34}H_{41}O_{12}S$: 673.2319	673.2312	96.4/12.1
18	631 [M + H^+]	$C_{32}H_{39}O_{11}S$: 631.2213	631.2218	85.6/10.6
21	978 [M + K^+]	$C_{51}H_{58}O_{16}N$: 940.3756	940.3765	95/14.6
24a	908 [M + K^+]	$C_{48}H_{56}NO_{14}$: 870.3701	870.3695	98.7/5.9
24b	904 [M + K^+]	$C_{46}H_{56}NO_{15}$: 866.3963	866.3920	99.7/14.6
25a	908 [M + K^+]	$C_{48}H_{56}NO_{14}$: 870.3701	870.3712	90.2/5.8
25b	904 [M + K^+]	$C_{46}H_{56}NO_{15}$: 866.3963	866.3978	93.4/14.2
29	934 [M + K^+]	$C_{50}H_{57}NO_{14}Na$: 918.3677	918.3690	88.5/14.3
30	968 [M + K^+]	$C_{50}H_{59}NO_{15}Na$: 852.3732	952.3743	96.2/3.5
32	938 [M + H^+]	$C_{49}H_{57}NO_{15}Na$: 922.3626	922.3644	89.2/6.1
33	942 [M + H^+]	$C_{51}H_{59}NO_{16}Na$: 964.3732	961.3730	92/4.8
34	955 [M + H^+]	$C_{53}H_{67}N_2O_{14}$; 955.4952	955.4609	89.7/5.3

[a] HPLC conditions: reverse phase Dynamax 300-A C-18 column; mobile phase: CH_3CN:H_2O at 1 mL/min; detection: UV 230 nm; %/t_R = percentage/retention time in min. [b] Supplementary material.

3′-*N*-Bz parents. This is clearly shown for 10-deacetyltaxol and taxotere, and in this series for **14a** vs **14b** (9(*R*)-dihydrotaxotere), with the latter exhibiting cytotoxicity equivalent to taxotere. Previous work in the 9(*R*)-dihydrotaxane series has shown that, similar to the 9-carbonyl series, the 3′-*N*-Boc analogs exhibit the

Table 3. Biological Activity of 9(*R*)-Dihydrotaxane Analogs

compd	tumor cell[a] cytotoxicity (ng/mL) A549	HT-29	$B_{16}F_{10}$	P_{388}	tubulin assembly:[b] ED_{50}/ED_{50} taxol
Taxol	2.5–4.3	1.8–3.5	3.4–6.3	8.8–11	1.00
Taxotere	0.18	0.21	0.6	1.5	0.7
2	16–22	6.4–9.6	25	49–57	0.75
10	>1000	>1000	>1000	>1000	>10
14a	11	1.9	39	140	0.83
14b	0.26	0.65	0.4	2.8	1.31
16a	34	29	34	42	0.76
16b	19	11	20	35	2.78
16c	23	16	15	22	–
21	15	3.3	13	22	0.91
24a	1.2	1.4	1.5	3.9	0.92
25a	4.7	3.1	4.8	7.8	1.74
24b	0.27	0.15	0.2	0.6	0.35
25b	0.1	0.5	0.9	1.3	0.51
29	1.0	1.2	2.7	5.3	1.4
30	626	310	>1000	>1000	2.02
32	39	10	119	170	1.77
33	120	31	43	79	2.47
34	400	108	110	310	2.61

[a] Method: see the Experimental Section. A_{549}, human lung carcinoma; HT-29, human colon adenocarcinoma; B16F10, mouse melanoma; P388, mouse lymphocytic leukemia. [b] Assay performed by Dr. R. Himes, University of Kansas, Department of Biochemistry (ref 22).

greatest potency as compared to other tested analogs such as other amides, ureas, and carbamates.[26]

Methylation of the C-7 (**24a**) or of the C-9 (**25a**) hydroxyl group is shown to increase potency (Table 3). The corresponding 3′-*N*-Boc analogs, **24b** and **25b**, which show 10-fold greater activity, are the most potent compounds tested in both assays. These results are in accordance with previous results in that removal of polarity, either by excision (7-deoxytaxanes refs 14 and 27) or alkylation, improves activity. The size of the C-7 substituent is not limited to methyl since others such as the allyl analog **29** are equally active.

The activity of analogs bearing both C-7 and C-9 substituents is also reported in Table 3. The cytotoxicity of diacetate **21** supports the general trend described above as do the cyclic derivatives **16a–c**; however, the poor tubulin data for **16b** is difficult to understand.

Compound **28** also served as a versatile intermediate for the introduction of solubilizing groups at this position; however, in every case, the addition of polar substituents to this quadrant of the molecule resulted in loss of activity, e.g., **30**, **32**, and **34**. Acetoxyethyl analog **33** is certainly the least polar among these derivatives, and so its lower activity may reflect some steric component. In summary, masking of the C-7 or C-9 hydroxyls leads to analogs of greater potency whereas the presence of hydroxyl or amino groups in this quadrant produced compounds of lesser activity.

The water solubility measurements for these analogs were determined by standard equilibration/filtration techniques and analyzed by HPLC.[28] The water solubility of several of the 9(*R*)-dihydrotaxane compounds were measured, and in every case, the 9-dihydro analogs show greater solubility than the corresponding 9-carbonyl series; however, both classes exhibit relatively low solubility (<1 mg/mL). 9(*R*)-Dihydrotaxol (**2**) exhibits nearly 7-fold greater water solubility than taxol perhaps not only due to the presence of the C-9 hydroxyl group, but also due to the lack of the C-9 carbonyl–C-7 hydroxyl interaction. Alkylation or acylation of the C-7 hydroxyl group causes expected decreases in solubility and only small increases are noted for the hydroxyalkyl or aminoalkyl-functionalized analogs in this series (4–10-fold increase vs taxol). Much greater effects can be seen via modifications involving removal of the C-10 acetate and exchange of the C-3′ *N*-benzoyl for *N*-Boc (**14b**, 70-fold increase vs taxol). We have also found improvements in water solubility upon exchange of the C-3′ phenyl for isobutyl group.[29]

Conclusion

The 9(*R*)-dihydrotaxanes show great promise as a second generation class of agents in that they have greater stability and water solubility while exhibiting similar *in vitro* activity to their C-9 carbonyl analogs. Addition of polar functionality at C-7 or C-9 generally decreases the biological activity, while alkylation or acylation of these groups increases activity.

Experimental Section

Proton NMR spectra were recorded on a General-Electric QE300 or a QE500 spectrometer unless otherwise stated with chemical shift values listed in parts per million (ppm) downfield from tetramethylsilane. The high-resolution MS were obtained on a Kratos MS50 instrument, and the low-resolution data was obtained on a Finnigan SSQ7000. All reaction mixtures were stirred under nitrogen atmosphere, and progress was followed by thin layer chromatography using analytical plates (0.25 mm, EM Separations). The terms "buffer" refers to pH 7 phosphate buffer, and "dried" refers to stirring with sodium sulfate followed by filtering or decanting. Purification by chromatography refers to flash chromatography using silica gel (230–400 mesh ASTM, EM Science) unless otherwise stated. Reagents obtained from commercial sources were purified where necessary, e.g., methylene chloride (CH_2Cl_2) was distilled from calcium hydride and tetrahydrofuran (THF) was distilled from sodium. The starting material, isolate 1, was used in partially pure form (>85%) for most reactions. Taxol was obtained from NaPro Biotherapeutics, Inc., Boulder, CO. Taxotere was synthesized as described in ref 19.

Common abbreviations include MeOH (methanol), EtOH (ethanol), LHMDS (lithium hexamethyldisilazide), THF (tetrahydrofuran), and EtOAc (ethyl acetate). High-resolution mass spectral data along with HPLC data for each new compound are listed in Table 2.

10-Deacetyl-13-acetyl-9(*R*)-dihydrobaccatin III (3). A solution of isolate 1[5] (31 mg, 0.049 mmol) in MeOH (2 mL) was cooled to 0 °C, and to this solution was added 1 N NaOH (0.25 mL). The reaction progress was followed by TLC until complete (ca. 2 h) at which time CO_2 was bubbled in to acidify to pH 8–9, and the solvent was evaporated. The crude residue was purified via chromatography with 7.5% MeOH in CH_2Cl_2 to give **3** as a solid (26.4 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 8.1 (d, 2H), 7.61 (t, 1H), 7.48 (t, 2H), 6.2 (t, 1H), 5.78 (d, 1H), 4.95 (d, 1H), 4.93 (d, 1H), 4.4 (dd, 1H), 4.35 (d, 1H), 4.32 (d, 1H), 4.19 (d, 1H), 3.75 (brs, OH), 3.08 (d, 1H), 2.56 (ddd, 1H), 2.3 (s, 3H), 2.25–2.0 (m, 2H), 2.2 (s, 3H), 1.94 (dd, 1H), 1.87 (d, 3H), 1.84 (s, 3H), 1.72 (s, 3H), 1.32 (s, 3H); HRMS calcd for $C_{31}H_{41}O_{11}$ 589.2649, found 589.2628.

13-Acetyl-9(*R*)-dihydrobaccatin III 7,9-Acetonide (4).[9b] To a suspension of 1 (103 mg, 0.16 mmol) in acetone/dimethoxypropane (3 mL, 2:1) at 25 °C was added (±)-camphorsulfonic acid (CSA) (10 mg), and this mixture was stirred under nitrogen for 2 h. The reaction was quenched with saturated $NaHCO_3$ (1 mL), and the mixture was extracted three times with EtOAc (10 mL). The collected organic layers were washed with brine, dired, and evaporated to give the crude product. Purification via chromatography using 2.5% MeOH in CH_2Cl_2 gave **4** as a solid (104.4 mg, 97%): ^{1}H NMR ($CDCl_3$) δ 8.1 (dt,2H), 7.62 (tt, 1H), 7.5 (bt, 2H), 6.48 (d, 1H), 6.11 (ddd, 1H), 5.84 (brd, 1H), 4.92 (brd, 1H), 4.54 (d, 1H), 4.24 (brt, 1H), 4.2 (s, 2H), 3.14 (d, 1H), 2.46 (ddd, 1H), 2.31

(dd, 1H), 2.3 (s, 3H), 2.21 (ddd, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 1.98 (d, 3H), 1.76 (s, 3H), 1.7 (ddd, 1H), 1.56 (s, 3H), 1.5 (s, 3H), 1.4 (s, 3H), 1.15 (s, 3H); MS (DCl/NH_3) *m/z* 671 (M^+ + H^+).

Tetrahydrofuran Rearrangement Product (5).[9b] Acetonide **4** (15 mg, 0.022 mmol) was combined with K_2CO_3 (5 mg, 1.6 equiv) in MeOH (1 mL) and heated to 50 °C for 12 h. Carbon dioxide gas was bubbled in for 15 min, and the solvent was evaporated. The crude residue was dissolved in CH_2Cl_2 (2 mL), and triethylamine (0.5 mL) and acetic anhydride (0.25 mL) were added. After 24 h the solvents were evaporated, and the product was purified via chromatography using 5% MeOH in CH_2Cl_2 to give **5** as a solid (8.8 mg, 80%): ^1H NMR (CD_3OD) δ 5.2 (dd, 1H), 5.13 (d, 1H), 4.36 (br d, 1H), 4.25 (dd, 1H), 4.05 (d, 1H), 3.94 (dd, 1H), 3.69 (dd, 1H), 3.66 (d, 1H), 2.9 (dd, 1H), 2.51 (dd, 1Hz), 2.34 (ddd, 1H), 2.13 (ddd, 1H, 2.02 (s, 3H), 1.89 (d, 3H), 1.58 (ddd, 1H), 1.5 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.07 (s, 3H).

9(*R*)-Dihydrobaccatin III (6). To a solution of 1 (5 g, 7.93 mmol) in THF (500 mL) at −78 °C was added methyllithium (36.8 mL, 1.4 M in ether, 6.5 equiv) over 10 min, and the reaction was followed by TLC until complete. This mixture was quenched by pouring into buffer (2 L) and extracted with EtOAc. The organic layer was washed with brine and dried, and the solvent was evaporated. The residue was purified by chromatography using 10% MeOH in $CHCl_3$ to give **6** as a solid (4.8 g, 82%): ^1H NMR ($CDCl_3$) δ 8.1 (d, 2H), 7.6 (t, 1H), 7.49 (t, 2H), 6.15 (d, 1H), 5.75 (d, 1H), 4.93 (d, 1H), 4.8 (br t, 1H), 4.5−4.4 (m, 2H), 4.32 (d, 1H), 4.19 (d, 1H), 3.11 (d, 1H), 2.55 (ddd, 1H), 2.35−1.87 (m, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 2.12 (d, 3H), 1.82 (s, 3H), 1.65 (s, 3H), 1.1 (s, 3H); MS (DCl/NH_3) *m/z* 589 (M^+ + H^+).

13-(4-Pentenoyl)-9(*R*)-dihydrobaccatin III 7,9-Acetonide (7). To a solution of **4** (22 mg, 0.033 mmol) in THF (3 mL) at −78 °C was added LHMDS (0.09 mL, 3 equiv). After 20 min allyl bromide (8 mg, 2 equiv) was added. After 2 h the mixture was diluted with EtOAc and the reaction quenched with 1 N H_2SO_4. The organic layer was dried and the solvent evaporated. The crude residue was purified by chromatography to give **7** as a solid (8.5 mg, 37%) along with some recovered **4** (4 mg): ^1H NMR ($CDCl_3$) δ 8.08 (d, 2H), 7.6 (t, 1H), 7.48 (t, 2H), 6.49 (d, 1H), 6.15 (d, 1H), 5.92−5.79 (m, 2H), 5.12 (d, 1H), 5.07 (d, 1H), 4.9 (d, 1H), 4.51 (d, 1H), 4.3 (d, 1H), 4.22 (dd, 1H), 4.19 (d, 1H), 3.13 (d, 1H), 2.6−2.4 (m, 5H), 2.3 (s, 3H), 2.2 (d, 2H), 2.13 (d, 3H), 2.02 (d, 3H), 1.85−1.79 (m, 1H), 1.78 (s, 3H), 1.6 (s, 3H), 1.53 (s, 3H), 1.47 (s, 3H), 1.2 (s, 3H).

9-Dihydrobaccatin III 7,9-Acetonide (8a).[9b] The acetonide **4** (39 mg, 0.058 mmol) was dissolved in THF (5 mL) and cooled to −44 °C (acetonitrile/carbon dioxide). To this solution was added dropwise *n*-butyllithium (*n*-BuLi) (0.11 mL, 3 equiv, 1.6 M in hexanes) over 10 min. The reaction was quenched with buffer, and the mixture was extracted with CH_2Cl_2, dried, and purified via chromatography with 5% MeOH in CH_2Cl_2 to give **8a** (27 mg, 74%) and a minor amount of 4-deacetyl-9(*R*)-dihydrobaccatin III 7,9-acetonide (**8b**) as solids (3.4 mg, 10%). 8a: ^1H NMR (CD_3OD) δ 8.13 (d, 2H), 7.62 (t, 1H), 7.51 (t, 2H), 6.49 (d, 1H), 5.79 (dd, 1H), 4.91 (dd, 1H), 4.7 (m, 1H), 4.5 (d, 1H), 4.26 (dd, 1H), 4.2 (br d, 1H), 4.18 (dd, 1H), 3.2 (d, 1H), 2.44 (ddd, 1H), 2.35 (dd, 1H), 2.2 (s, 3H), 2.2 (m, 1H), 2.09 (d, 3H), 2.07 (s, 3H), 1.74 (s, 3H), 1.68 (ddd, 1H), 1.51 (s, 3H), 1.5 (s, 3H), 1.39 (s, 3H), 1.04 (s, 3H); HRMS calcd for $C_{34}H_{45}O_{11}$ 629.2962, found 629.2964. 8b: a sample was crystallized from methanol for X-ray analysis; ^1H NMR (CD_3OD) δ 8.13 (d, 2H), 7.63 (t, 1H), 7.49 (t, 2H), 6.44 (d, 1H), 5.78 (dd, 1H), 4.76 (br d, 1H), 4.68 (dd, 1H), 4.48 (br d, 1H), 4.44 (d, 1H), 4.38 (d, 1H), 4.16 (d, 1H), 3.99 (dd, 1H), 2.96 (d, 1H), 2.76 (dd, 1H), 2.42−2.32 (m, 2H), 2.14 (s, 3H), 2.11 (s, 3H), 1.82 (ddd, 1H), 1.63 (s, 3H), 1.48 (d, 3H), 1.4 (s, 3H), 0.98 (s, 3H).

4-Deacetyl-9(*R*)-dihydrotaxol (10). To a solution of **8b** (15 mg, 0.023 mmol) in THF (2 mL) were added NaH (9 mg 60% dispersion in mineral oil, 10 equiv) and **9a** (17 mg, 1 equiv), the mixture was stirred at 0 °C for 1 h, and the reaction quenched with acetic acid (0.016 mL). The mixture was diluted with EtOAc, the organic layer was separated and washed with brine, and the solvent was evaporated. The crude residue was directly combined with EtOH (3 mL) and 1% HCl (1 mL) as for **2**, and the mixture was stirred at 25 °C for 30 h before diluting with EtOAc and washing with saturated $NaHCO_3$. The organic layer was separated, and the solvent was evaporated. The crude residue was purified by chromatography with 4% MeOH in CH_2Cl_2 to give **10** as a solid (9 mg, 46%): ^1H NMR (CD_3OD) δ 8.15 (d, 2H), 7.9 (d, 2H), 7.6−7.28 (m, 11H), 6.16 (d, 1H), 5.93 (br d, 1H), 5.88 (d, 1H), 5.78 (d, 1H), 4.84 (dd, 1H), 4.67 (d, 1H), 4.46 (d, 1H), 4.18 (d, 1H), 4.17 (t, 1H), 3.06 (dd, 1H), 2.72 (d, 1H), 2.47 (ddd, 1H), 2.25 (dd, 1H), 2.12 (s, 3H), 1.96 (s, 3H), 1.96−1.86 (m, 1H), 1.67 (s, 3H), 1.6 (s, 3H), 1.1 (s, 3H); MS (DCl/NH_3) *m/z* 814 (M^+ + H^+).

7-*O*-(Triethylsilyl)-9(*R*)-dihydrobaccatin III (11a). To a solution of **6** (4.5 g, 7.65 mmol) in pyridine (10 mL) at 0 °C was added triethylsilyl chloride (1.9 mL, 1.5 equiv). The ice bath was removed, and the mixture was stirred for 3 h. This reaction was quenched by pouring the mixture into buffer (650 mL) and extracting with EtOAc. The organic layer was washed with brine and dried. The solvent was evaporated, and the residue was purified by chromatography using EtOAc:hexane (1:2) to give **11a** as a solid (4.03 g, 75%): ^1H NMR ($CDCl_3$) δ 8.1 (d, 2H), 7.6 (t, 1H), 7.48 (t, 2H), 6.12 (d, 1H), 5.72 (d, 1H), 5.32 (d, 1H), 4.91 (d, 1H), 4.79 (m, 1H), 4.57 (dd, 1H), 4.32 (br s, OH), 4.31 (t, 1H), 4.19 (d, 1H), 3.11 (d, 1H), 2.5 (ddd, 1H), 2.3−1.93 (m, 3H), 2.27 (s, 3H), 2.14 (s, 3H), 2.11 (d, 3H), 1.81 (s, 3H), 1.68 (s, 3H), 1.11 (s, 3H), 1.02 (t, 9H), 0.74 (m, 6H); MS (DCl/NH_3) *m/z* 703 (M^+ + H^+).

The use of triethylamine as base and CH_2Cl_2 as solvent at 25 °C led to the production of 64% of **11a** and 13% of solid **11b**: ^1H NMR ($CDCl_3$) δ 8.1 (d, 2H), 7.61 (t, 1H), 7.49 (t, 2H), 5.9 (d, 1H), 5.72 (d, 1H), 4.93 (d, 1H), 4.77 (m, 1H), 4.7 (d, 1H), 4.37 (br t, 1H), 4.32 (d, 1H), 4.14 (d, 1H), 3.11 (d, 1H), 2.59 (ddd, 1H), 2.35−2.1 (m, 2H), 2.26 (s, 3H), 2.19 (d, 3H), 2.13 (s, 3H), 1.84 (dd, 1H), 1.72 (s, 3H), 1.61 (s, 3H), 1.09 (s, 3H), 1.05 (t, 9H), 0.79 (m, 6H); MS (DCl/NH_3) *m/z* 720 (M^+ + NH_4^+), 703 (M^+ + H^+).

9(*R*)-Dihydrotaxol (2).[9b] i. To a solution of **11a** (2.6 g, 3.7 mmol) in THF (260 mL) at −78 °C was added LHMDS (6.29 mL, 1 M in THF, 1.7 equiv), and the mixture was stirred for 20 min. A solution of lactam **9a** (2.13 g, 1.7 equiv) in THF (4 mL) was added dropwise at −78 °C, and the mixture was warmed to 0 °C for 1 h, quenched by pouring into buffer (1.6 L), and extracted with EtOAc. The organic layer was washed with brine and dried, and the solvent was evaporated. The residue was purified by chromatography using EtOAc:hexane (2:3) to give **12a** (3.51 g, 91%) as a mixture of diastereomers.

ii. **Method A.** To **12a** (85 mg, 0.082 mmol) in MeOH (2 mL) at 0 °C was added HF/pyridine:methanol:triethylamine (0.75 mL, 1:9:4), and this mixture was stirred for 45 min before diluting with EtOAc. The organic layer was washed with buffer, and the solvent was evaporated. The crude residue was purified by chromatography using EtOAc:hexanes (1:1) to give **13a** (51 mg, 70%). Product **13a** could be deprotected with 1% HCl as before or, alternatively, a one-pot deprotection scheme could be applied.

iii. **Method B: One-Pot Deprotection.** To a solution of **12a** (1.2 g, 1.15 mmol) in MeOH (30 mL) at 25 °C was added 1% HCl (7 mL) dropwise over 15 min, and this mixture was stirred for 1 h before pouring into buffer (400 mL) and brine (400 mL). The organic layer was extracted with EtOAc and dried, and the solvent was evaporated. The residue was purified by gravity chromatography using 10% MeOH in $CHCl_3$ to give **2** as a solid (0.9 g, 91%): ^1H NMR (CD_3OD) δ 8.11 (br d, 2H), 7.83 (br d, 2H), 7.66−7.28 (m, 16H), 6.17 (d, 1H), 6.15 (ddd, 1H), 5.75 (d, 1H), 5.67 (d, 1H), 4.93 (br d, 1H), 4.75 (d, 1H), 4.49 (d, 1H), 4.35 (dd, 1H), 4.19 (d, 1H), 4.16 (br d, 1H), 3.03 (d, 1H), 2.43 (ddd, 1H), 2.3 (s, 3H), 2.26 (dd, 1H), 2.09 (s, 3H), 2.09 (m, 1H), 1.87 (d, 3H), 1.81 (ddd, 1H), 1.76 (s, 3H) 1.64 (s, 3H), 1.22 (s, 3H); HRMS calcd for $C_{47}H_{54}NO_{14}$ 856.3544, found 856.3531.

10-Deacetyl-9(*R*)-dihydrotaxol (14a). To a solution of **12a** (2.1 g, 2.01 mmol) in MeOH (70 mL) at 0 °C was added 1 N KOH (4 mL) dropwise, and the mixture was stirred for 1.5 h. Upon completion of the reaction, 1% HCl (8 mL) was added as for **2** for 4 h at 0 °C, and the mixture was worked up and

purified as above using 5% MeOH in $CHCl_3$ to give **14a** as a solid (1.4 g, 85%): ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 2H), 7.8 (d, 2H), 7.6 (t, 1H), 7.51–7.3 (m, 11H), 6.1 (br t, 1H), 5.83 (dd, 1H), 5.75 (d, 1H), 4.9 (br d, 1H), 4.85–4.79 (m, 2H), 4.74 (t, 1H), 4.48 (d, 1H), 4.32–4.18 (m, 4H), 3.69 (br s, 1H), 3.3 (s, 1H), 2.99 (d, 1H), 2.53 (ddd, 1H), 2.36 (dd, 1H), 2.29 (s, 3H), 2.05 (dd, 1H), 1.9 (dd, 1H), 1.68 (s, 3H), 1.5 (s, 3H), 1.25 (s, 3H); MS (DCl/NH_3) *m/z* 814 ($M^+ + H^+$).

3′-*N*-Debenzoyl-*N*-Boc-10-deacetyl-9(*R*)-dihydrotaxol (14b). i. Similar to the procedure for preparing **12**, **11a** (1.2 g, 1.7 mmol) in THF (120 mL) was treated with LHMDS (3 mL, 1.7 equiv) and lactam **9b** (1.03 g, 1.8 equiv) in THF (3 mL) to give **12b** (1.75 g, 99%) as a mixture of diastereomers.

ii. To a solution of **12b** (0.94 g, 0.9 mmol) in MeOH (25 mL) at 25 °C was added HF/pyridine:methanol:triethylamine (6 mL, 1:9:4), and this mixture was stirred for 30 min before diluting with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, and the solvent was evaporated. The crude residue was purified by chromatography to give **13a** (0.75 g, 89%) as a mixture of diastereomers

iii. Similar to the procedure for preparing **14a**, **13a** (1.1 g, 1.2 mmol) was treated with KOH in MeOH to effect the 10-deacetylation, and this material was treated directly with 1% HCl in EtOH to give **14b** as a solid (0.753 g, 78%): ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 2H), 7.61 (t, 1H), 7.48 (t, 2H), 7.42 (d, 2H), 7.37 (t, 2H), 7.31 (t, 1H), 6.13 (br t, 1H), 5.78 (d, 1H), 5.66 (d, 1H), 5.27 (br d, 1H), 4.9 (d, 2H), 4.62 (br s, 1H), 4.32 (d, 1H), 4.3 (d, 1H), 4.21 (d, 1H), 3.03 (d, 1H), 2.53 (ddd, 1H), 2.38 (dd, 1H), 2.26 (s, 3H), 2.1–1.7 (m, 3H), 1.83 (s, 3H), 1.71 (s, 3H), 1.68 (br s, 3H), 1.41 (br s, 9H), 1.29 (s, 3H); MS (DCl/NH_3) *m/z* 848 ($M^+ + K^+$).

9(*R*)-Dihydrotaxol 7,9-Acetonide (16a).[9b] i. Acetonide 4 (360 mg, 0.54 mmol) was deacetylated as above to form **8a**, except, following the *n*-BuLi addition, the −44 °C mixture was stirred for 30 min before a THF solution of lactam **9a** (270 mg, 1.5 equiv) was added dropwise. The mixture was warmed to 0 °C for 1 h, quenched with buffer, and extracted three times with CH_2Cl_2. The organic layer was washed with brine and dried, and the solvent was evaporated to give the ethoxyethyl ether (400 mg, 76% crude yield) as a mixture of diastereomers.

ii. **Deprotection.** The ethoxyethyl ether **15a** (11 mg, 0.011 mmol) was dissolved in EtOH (1 mL), and to this solution was added 1% HCl (0.1 mL). The mixture was stirred at 25 °C for 24 h and worked up by combining it with CH_2Cl_2 and buffer. The organic layer was dried and the solvent evaporated. Purification by chromatography gave **16a** as a solid (3.1 mg, 35%): ^{1}H NMR (CD_3OD) δ 8.1 (d, 2H), 7.84 (d, 2H), 7.64 (t, 1H), 7.7–7.3 (m, 10H), 6.43 (d, 1H), 6.12 (ddd, 1H), 5.81 (br d, 1H), 5.64 (d, 1H), 4.88 (br d, 1H), 4.73 (d, 1H), 4.54 (d, 1H), 4.14–4.21 (m, 3H), 3.08 (d, 1H), 2.42 (ddd, 1H), 2.31 (s, 3H), 2.26 (dd, 1H), 2.21 (br dd, 1H), 2.07 (s, 3H), 1.91 (d, 3H), 1.74 (s, 3H), 1.69 (ddd, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.14 (s, 3H); MS (DCl/NH_3) *m/z* 896 ($M^+ + H^+$).

13-Acetyl-9(*R*)-dihydrobaccatin III 7,9-Thionocarbonate (17). To a solution of **1** (50 mg, 0.079 mmol) in toluene (8 mL) was added thionocarbonyl diimidazole (TCDI) (62 mg, 4.4 equiv) and a catalytic amount of 4-(dimethylamino)pyridine, and this mixture was refluxed for 1 h. The cooled mixture was washed with buffer and the solvent evaporated. The crude residue was purified by chromatography using 2.5% MeOH in CH_2Cl_2 to give **17** as a solid (49.5 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 2H), 7.63 (t, 1H), 7.5 (t, 2H), 6.3 (d, 1H), 6.15 (t, 1H), 5.84 (d, 1H), 5.15 (d, 1H), 4.94 (d, 1H), 4.82 (dd, 1H), 4.35 (d, 1H), 4.14 (d, 1H), 3.3 (d, 1H), 2.81 (ddd, 1H), 2.25–2.0 (m, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 2.19 (s, 3H), 1.95 (d, 3H), 1.8 (s, 3H), 1.57 (s, 3H), 1.26 (s, 3H); MS (DCl/NH_3) *m/z* 673 ($M^+ + H^+$).

9(*R*)-Dihydrotaxol 7,9-Thionocarbonate (16b). i. **Deacetylation.** To a solution of **17** (11 mg, 16.2 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (64 μL, 1M in hexanes, 4 eq) as before for **8a**. Following workup the residue was purified by chromatography using 5% MeOH in CH_2Cl_2 to give **18** (4.5 mg, 44%): ^{1}H NMR ($CDCl_3$) δ 8.1 (d, 2H), 7.62 (t, 1H), 7.5 (t, 2H), 6.29 (d, 1H), 5.81 (d, 1H), 5.12 (d, 1H), 4.94 (d, 1H), 4.85 (dd, 1H), 4.8 (br t, 1H), 4.35 (d, 1H), 4.12 (d, 1H), 3.33 (d, 1H), 2.81 (ddd, 1H), 2.3–2.0 (m, 3H), 2.26 (s, 3H), 2.2 (s, 3H), 2.1 (d, 3H), 1.8 (s, 3H), 1.61 (s, 3H), 1.12 (s, 3H); MS (DCl/NH_3) *m/z* 631 ($M^+ + H^+$).

ii. **Acylation/Deprotection.** To a solution of **18** (12.5 mg, 0.02 mmol) in THF (3 mL) at 0 °C was added NaH (38 mg, 60% dispersion in mineral oil, 40 equiv), and this mixture was stirred for 30 min. A solution of lactam **9a** (20 mg, 3 quiv) in THF (1 mL) was added dropwise to the suspension, and the ice bath was removed. After 36 h this mixture was recooled to −78 °C and carefully quenched with buffer. The mixture was extracted with CH_2Cl_2 and dried, and the solvent was evaporated to give **15b** as a mixture of diastereomers.

iii. This crude residue was combined with EtOH (2 mL) and 1% HCl (5 drops), the mixture was stirred at 25 °C for 16 h, and the reaction was quenched with buffer. This mixture was extracted with CH_2Cl_2, washed with water, and dried, and the solvent was evaporated. The crude residue was purified by chromatography using EtOAc:hexanes (1:1) to give **16b** as a solid (7.8 mg, 44% for ii, iii): ^{1}H NMR (CD_3OD) δ 8.1 (d, 2H), 7.83 (d, 2H), 7.7–7.3 (m, 11H), 6.31 (d, 1H), 6.15 (t, 1H), 5.84 (d, 1H), 5.62 (d, 1H), 5.28 (d, 1H), 4.99 (d, 1H), 4.8 (t, 1H), 4.72 (d, 1H), 4.2 (AB q, 2H), 3.23 (d, 1H), 2.75 (ddd, 1H), 2.32 (s, 3H), 2.25–1.9 (m, 3H), 2.15 (s, 3H), 1.9 (s, 3H), 1.78 (d, 3H), 1.63 (s, 3H), 1.23 (s, 3H); MS (DCl/NH_3) *m/z* 936 ($M^+ + K^+$).

9(*R*)-Dihydrotaxol 7,9-Propylidene Acetal (16c). A solution of **2** (4 mg, 0.0047 mmol) in propionaldehyde (0.5 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid, and the mixture was stirred at 25 °C for 4 h. The mixture was quenched with CH_2Cl_2 and saturated $NaHCO_3$, the organic layer was separated, and the solvent was evaporated. The crude product was purified by chromatography using EtOAc/hexanes to give **16c** as a solid (2.6 mg, 62%). Only one isomer by NMR/HPLC: ^{1}H NMR (CD_3OD) δ 8.11 (br d, 2H), 7.85 (br d, 2H), 7.69 (t, 1H), 7.6–7.27 (m, 11H), 6.78 (d, 1H), 6.12 (t, 1H), 5.8 (d, 1H), 4.97–4.85 (m, 2H), 4.72 (d, 1H), 4.5 (d, 1H), 4.19 (s, 2H), 4.0 (t, 1H), 3.02 (d, 1H), 2.45 (ddd, 1H), 2.3 (s, 3H), 2.22 (dd, 1H), 2.06 (s, 3H), 2.05–1.95 (m, 1H), 1.88 (s, 3H), 1.76 (s, 3H), 1.75–1.5 (m, 3H), 1.6 (s, 3H), 1.2 (s, 3H), 0.89 (t, 3H); MS (DCl/NH_3) *m/z* 896 ($M^+ + H^+$).

7,9-Diacetyl-9(*R*)-dihydrotaxol (21). To a solution of **13a** (6 mg, 0.006 mmol) in pyridine (0.3 mL) were added acetic anhydride (0.1 mL) and a catalytic amount of 4-(dimethylamino)pyridine. The reaction mixture was stirred at 25 °C for 16 h, diluted with EtOAc, and washed with buffer and brine, and the solvent was evaporated. The crude residue was purified by chromatography using EtOAc:hexanes (1:1) to give **21** as a solid (5.3 mg, 87%): ^{1}H NMR (CD_3OD) δ 8.14 (d, 2H), 7.83 (d, 2H), 7.64 (d, 1H), 7.57–7.3 (m, 10H), 6.18 (d, 1H), 6.16 (t, 1H), 6.1 (d, 1H), 5.89 (d, 1H), 5.64 (d, 1H), 5.52 (t, 1H), 4.97 (d, 1H), 4.78 (d, 1H), 4.23 (d, 1H), 4.12 (d, 1H), 3.15 (d, 1H), 2.41 (ddd, 1H), 2.32 (s, 3H), 2.27 (dd, 1H), 2.11 (s, 3H), 2.1 (dd, 1H), 2.09 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.8 (dd, 1H), 1.73 (s, 3H), 1.6 (s, 3H), 1.2 (s, 3H); MS (DCl/NH_3) *m/z* 978 ($M^+ + K^+$).

7- and 9-*O*-Methyl-9(*R*)-dihydrotaxol (24a and 25a). A solution of **13a** (20 mg, 0.02 mmol) in THF (1 mL), methyl iodide (0.8 mL), and Ag_2O (12 mg, 4.4 equiv) was refluxed for 6 h, cooled, and filtered. The filtrate was combined with EtOAc and buffer, washed with water and brine, and evaporated. Chromatographic separation could be carried out at this stage using 10% MeOH in CH_2Cl_2 to give **22a** and **23a**; or the crude mixture could be treated with 1% HCl and purified using EtOAc:hexanes (1:1) to give **24a** (5.1 mg, 27%) and **25a** (4.9 mg, 26%) as solids from **13a**.

24a: ^{1}H NMR (CD_3OD) δ 8.12 (d, 2H), 7.83 (d, 2H), 7.64 (t, 1H), 7.55 (t, 1H), 7.52 (t, 2H), 7.41 (t, 2H), 7.36 (m, 4H), 7.28 (t, 1H), 6.17 (d, 1H), 6.17 (br t, 1H), 5.72 (d, 1H), 5.67 (d, 1H), 4.98 (d, 1H), 4.75 (d, 1H), 4.37 (d, 1H), 4.2 (d, 1H), 4.16 (d, 1H), 3.96 (dd, 1H), 3.44 (s, 3H), 3.05 (d, 1H), 2.69 (ddd, 1H), 2.32 (s, 3H), 2.25 (dd, 1H), 2.1 (dd, 1H), 2.09 (s, 3H), 1.87 (s, 3H), 1.78 (s, 3H), 1.75 (ddd, 1H), 1.65 (s, 3H), 1.53 (s, 9H), 1.24 (s, 3H); MS (DCl/NH_3) *m/z* 908 ($M^+ + K^+$).

25a: ^{1}H NMR (CD_3OD) δ 8.12 (d, 2H), 7.83 (d, 2H), 7.65 (t, 1H), 7.55 (t, 1H), 7.55–7.42 (m, 4H), 7.52 (t, 2H), 7.41 (t, 2H), 7.38 (t, 1H), 6.21 (d, 1H), 6.15 (br t, 1H), 5.77 (d, 1H), 5.67 (d, 1H), 4.92 (d, 1H), 4.75 (d, 1H), 4.36 (d, 1H), 4.22 (t, 1H), 4.2 (d, 1H), 4.16 (d, 1H), 3.75 (s, 3H), 2.95 (d, 1H), 2.46 (ddd, 1H),

2.29 (s, 3H), 2.25 (dd, 1H), 2.13 (s, 3H), 2.1 (dd, 1H), 1.85 (s, 3H), 1.73 (s, 6H), 1.72 (ddd, 1H), 1.53 (s, 9H), 1.23 (s, 3H); MS (DCl/NH_3) *m/z* 908 ($M^+ + K^+$).

3′-*N*-Debenzoyl-*N*-Boc-7- and -9-*O*-methyl-9(*R*)-dihydrotaxol (24b and 25b). Similar to the procedure for preparing **24a** and **25a**, a solution of **13b** (26 mg, 0.028 mmol) in THF (1 mL) was treated with methyl iodide (0.9 mL) and Ag_2O (18 mg, 4.4 equiv) to give **22b** and **23b** which were subsequently deprotected with 1% HCl to give **24b** (10.8 mg, 44%) and **25b** (4.1 mg, 17%) as solids following chromatographic separation by using EtOAc:hexanes (1:1).

24b: ^1H NMR (CD_3OD) δ 8.12 (d, 2H), 7.64 (t, 1H), 7.52 (t, 2H), 7.42–7.35 (m, 4H), 7.28 (t, 1H), 6.17 (d, 1H), 6.17 (br t, 1H), 5.72 (d, 1H), 5.14 (br s, 1H), 4.99 (d, 1H), 4.55 (br s, 1H), 4.39 (d, 1H), 4.2 (d, 1H), 4.16 (d, 1H), 4.02 (dd, 1H), 3.49 (s, 3H), 3.06 (d, 1H), 2.75 (ddd, 1H), 2.32 (s, 3H), 2.25 (dd, 1H), 2.1 (dd, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.79 (s, 3H), 1.77 (ddd, 1H), 1.66 (s, 3H), 1.4 (s, 9H), 1.26 (s, 3H); MS (DCl/NH_3) *m/z* 904 ($M^+ + K^+$).

25b: ^1H NMR (CD_3OD) δ 8.1 (d, 2H), 7.64 (t, 1H), 7.52 (t, 2H), 7.36 (m, 4H), 7.28 (t, 1H), 6.17 (d, 1H), 6.17 (br t, 1H), 5.78 (d, 1H), 5.47 (br s, 1H), 4.94 (d, 1H), 4.55 (brs, 1H), 4.37 (d, 1H), 4.27 (t, 1H), 4.2 (d, 1H), 4.16 (d, 1H), 3.75 (s, 3H), 2.98 (d, 1H), 2.53–2.46 (m, 1H), 2.28 (s, 3H), 2.25 (dd, 1H), 2.14 (s, 3H), 2.1 (dd, 1H), 1.92 (s, 3H), 1.78–1.72 (m, 1H), 1.74 (s, 3H), 1.73 (s, 3H), 1.4 (s, 9H), 1.25 (s, 3H); MS (DCl/NH_3) *m/z* 904 ($M^+ + K^+$).

7-*O*-Allyl-9(*R*)-dihydrotaxol (29). i. To a solution of 1 (1.06 g, 1.7 mmol) in THF (50 mL) at 0 °C were added NaH (0.6 mg, 60% dispersion in mineral oil, 10 equiv), tetrabutylammonium iodide (62 mg, 0.1 equiv), and allyl bromide (0,17 mL, 1.1 equiv). After 12 h at 25 °C the reaction was quenched with buffer and EtOAc, the organic layer was dried, and the solvent was evaporated. The crude residue was purified using EtOAc:hexane (1:1) to give **26** (518 mg, 46%).

ii. **Deacetylation.** Compound **26** (0.51 g, 0.76 mmol) in THF (40 mL) was deacetylated at −44 °C with *n*-BuLi (2.6 mL, 1.6 M in hexanes, 6 equiv) as for 8a. The crude residue was purified by chromatography using hexane:EtOAc (1:2) to give the deacetyl derivative **27** (225 mg, 47%).

iii. To a solution of **27** (175 mg, 0.28 mmol) in THF (10 mL) at 0 °C was added NaH (160 mg, 60% dispersion in mineral oil, 15 equiv), and mixture was stirred for 30 min before the addition of lactam **9a** (113 mg, 1.2 equiv). This mixture was stirred for 21 h and quenched with acetic acid and dilute with EtOAc. The organic layer was separated and washed with $NaHCO_3$ and brine, and the solvent was evaporated. The crude residue was purified by chromatography using hexane:EtOAc (1:1) to give **28** (188 mg, 70%) as a mixture of diastereomers.

iv. Treatment of **28** (6.8 mg, 0.007 mmol) with 1% HCl in ethanol as before produced **29** as a solid (5 mg, 79%): ^1H NMR (500 MHz, CD_3OD) δ 8.12 (d, 2H), 7.83 (d, 2H), 7.65 (t, 1H), 7.6–7.3 (m, 10H), 6.28 (d, 1H), 6.16 (t, 1H), 5.98 (ddd, 1H), 5.78 (d, 1H), 5.68 (d, 1H), 5.3 (d, 1H), 5.23 (d, 1H), 4.93 (br d, 1H), 4.76 (d, 1H), 4.54 (d, 1H), 4.5–4.05 (m, 5H), 2.98 (d, 1H), 2.48 (ddd, 1H), 2.3 (s, 3H), 2.28 (m, 1H), 2.1 (s, 3H), 2.09 (m, 1H), 1.88 (s, 3H), 1.74 (m, 1H), 1.73 (s, 6H), 1.23 (s, 3H); MS (DCl/NH_3) *m/z* 934 ($M^+ + K^+$).

7-*O*-(2,3-Dihydroxypropyl)-9(*R*)-dihydrotaxol (30). To a solution of **28** (4 mg, 0.004 mmol) in THF:water (1.2 mL, 5:1) was added *N*-methylmorpholine *N*-oxide (1 mg, 2 equiv) and a catalytic amount of Os_4O_4. After 2 h this reaction was quenched by the addition of excess sodium thiosulfate and Celite, and the reaction mixture was filtered and evaporated to give the crude protected diol. Direct treatment of this material with 1% HCl as above afforded of **30** as a solid (3.5 mg, 91%): ^1H NMR (CD_3OD) (mixture of 2 diastereomers) δ 8.12 (d, 2H), 7.84 (d 2H), 7.65 (t, 1H), 7.58–7.28 (m, 10H), 6.22 (d, 1H), 6.15 (br t, 1H), 5.79 (d, 1H), 5.68 (d, 1H), 4.93 (d, 1H), 4.76 (d, 1H), 4.44 (dd, 1H), 4.3–4.0 (m, 5H), 3.9–3.5 (m, 3H), 2.98 (d, 1H), 2.49 (ddd, 1H), 2.3 (s, 3H), 2.28 (m, 1H), 2.14 (d, 3H), 2.09 (m, 1H), 1.88 (s, 3H), 1.75 (s, 3H), 1.75 (m, 1H), 1.72 (s, 3H), 1.22 (s, 3H); MS (DCl/NH_3) *m/z* 968 ($M^+ + K^+$).

7-*O*-(2-Hydroxyethyl)-9(*R*)-dihydrotaxol (32). i. Into a solution of **29** (41 mg, 0.042 mmol) in MeOH:CH_2Cl_2 (4 mL, 1:1) at −78 °C was bubbled a stream of ozone for 30 s. The reaction mixture was purged with oxygen for 5 min before dimethyl sulfide (15 equiv) was added, and the mixture was warmed to 25 °C over 1 h. The solvents were evaporated, and the crude residue was purified by chromatography using EtOAc:hexanes (1:3 to pure EtOAc) to give the relatively unstable aldehyde **31**(38 mg, 93%).

ii. To a solution of **31** (5 mg, 0.0052 mmol) in MeOH (1 mL) was added excess $NaBH_4$. After 1 h the reaction was quenched with buffer, the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, and dried, and the solvent was evaporated.

iii. This crude residue was directly treated with 1% HCl as above to afford, after purification using 5% MeOH in CH_2Cl_2, **32** as a solid (2.9 mg, 63%): ^1H NMR (CD_3OD) δ 8.12 (d, 2H), 7.83 (d, 2H), 7.64 (t, 1H), 7.6–7.3 (m, 10H), 6.22 (d, 1H), 6.14 (br t, 1H), 5.79 (d, 1H), 5.69 (d, 1H), 4.93 (d, 1H), 4.76 (d, 1H), 4.47 (d, 1H), 4.28 (d, 1H), 4.22 (d, 1H), 4.13 (d, 1H), 4.1–4.0 (m, 1H), 3.92–3.85 (m, 1H), 3.72–3.68 (m, 2H), 2.98 (d, 1H), 2.5 (ddd, 1H), 2.3 (s, 3H), 2.28 (dd, 1H), 2.12 (s, 3H), 2.1–2.02 (m, 1H), 1.88 (s, 3H), 1.75 (s, 3H), 1.74 (m, 1H), 1.71 (s, 3H), 1.23 (s, 3H); MS (DCl/NH_3) *m/z* 938 ($M^+ + H^+$).

7-*O*-(2-Acetoxyethyl)-9(*R*)-dihydrotaxol (33). A portion of the alcohol from paragraph ii above could be directly acetylated by treatment with excess acetic anhydride in pyridine for 3 h. Following evaporation of the solvents, the crude product was treated as before with 1% HCl and purified using 5% MeOH in CH_2Cl_2 to give **33** as a solid (5.6 mg): ^1H NMR (CD_3OD) δ 8.12 (d, 2H), 7.85 (d, 2H), 7.66 (t, 1H), 7.6–7.3 (m, 10H), 6.26 (d, 1H), 6.15 (br t, 1H), 5.78 (d, 1H), 5.68 (d, 1H), 4.92 (d, 1H), 4.77 (d, 1H), 4.5 (d, 1H), 4.5–4.4 (m, 1H), 4.3–4.1 (m, 4H), 4.0 (m, 1H), 2.98 (d, 1H), 2.5 (ddd, 1H), 2.3 (s, 3H), 2.29 (dd, 1H), 2.17 (s, 3H), 2.17–2.0 (m, 1H), 2.1 (s, 3H), 1.88 (s, 3H), 1.8–1.7 (m, 1H), 1.73 (s, 3H), 1.71 (s, 3H), 1.24 (s, 3H); MS (DCl/NH_3) *m/z* 942 ($M^+ + H^+$).

7-*O*-[2-(Dimethylamino)ethyl]-9(*R*)-dihydrotaxol (34). To a solution of **31** (8 mg, 0.0083 mmol) in EtOH (2 mL) was added diethylamine (0.02 mL, 10 equiv) and acetic acid (0.03 mL, 30 equiv) followed by excess sodium cyanoborohydride. After 2 h, the reaction mixture was directly treated with 1% HCl as before and washed with saturated $NaHCO_3$ to give the free amine **34** as a solid (5.4 mg, 69%): ^1H NMR (CD_3OD) δ 8.12 (d, 2H), 7.85 (d, 2H), 7.65 (t, 1H), 7.6–7.3 (m, 10H), 6.2 (d, 1H), 6.16 (br t, 1H), 5.78 (d, 1H), 5.68 (d, 1H), 4.96 (d, 1H), 4.77 (d, 1H), 4.43 (d, 1H), 4.22 (d, 1H), 4.15–4.05 (m, 2H), 3.9 (br s, 1H), 2.98 (d, 1H), 2.71 (br s, 6H), 2.5 (ddd, 1H), 2.31 (s, 3H), 2.29 (dd, 1H), 2.16 (s, 3H), 2.08 (dd, 1H), 1.89 (s, 3H), 1.8–1.65 (m, 1H), 1.74 (s, 6H), 1.23 (s, 3H), 1.1 (t, 6H); MS (DCl/NH_3) *m/z* 955 ($M^+ + H^+$).

Biological Assay

The human lung carcinoma line A549, the human colon adenocarcinoma line HT-29, the mouse lymphocytic leukemia line P388, and the mouse melanoma line B16-F10 were obtained from the American Type Culture Collection, Rockville, MD. Cells were grown in RPMI 1640 supplemented with 10% fetal calf serum. Test compounds are dissolved in dimethyl sulfoxide (DMSO) and diluted first with Earle's Balanced Salt Solution, followed by culture medium, to twice the highest concentration of compound to be tested. From this concentrated stock, 2-fold serial dilutions are prepared in 96-well microtiter trays. Each concentration is tested in triplicate and compared to triplicated drug-free controls. A 100 mL aliquot of cells (2.5×10^3 cells) was added to the wells of the microtiter plate containing 0.1 mL of growth medium with or without test drugs. Plates were incubated for 72 h at 37 °C in a humidified atmosphere containing 5% CO_2. After 72 h, 0.02 mL of 5 mg/mL MTT (MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added, and cells were incubated for 90 min to allow reduction of the formasan

by the surviving cells. Following washing and solubilization by DMSO, the absorbance of each well was measured spectrophotometrically at 570 nm. The IC_{50} is determined as the concentration of compound tested required to reduce the absorbance to 50% of non-drug-treated control values.

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Supplementary Material Available: X-ray structure report for **8b**, including data collection, data reduction, and structure solution and refinement, experimental details, atomic coordinates, anisotropic displacement parameters, bond angles, and bond lengths (28 pages). Ordering information is given on any current masthead page.

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