# Synthesis and Biological Evaluation of C-3′-Modified Analogs of 9(*R*)-Dihydrotaxol

Leping Li,* Sheela A. Thomas, Larry L. Klein, Clinton M. Yeung, Clarence J. Maring, David J. Grampovnik, Paul A. Lartey, and Jacob J. Plattner

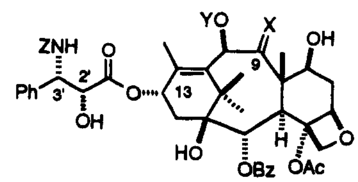
*Anti-Infective Research Division, D47M, AP9A, Abbott Laboratories, Abbott Park, Illinois 60064-3500*

*Received June 16, 1994*[⊗]

Taxol (1) is considered a most exciting new drug in cancer chemotherapy. The promising antitumor activity of 9(*R*)-dihydrotaxol (**3**) encouraged us to further explore the structure–activity relationship of this new member of the taxane family. Studies indicated that the C-13 side chain of taxol is indispensable for antitumor activity and that the natural substitution pattern of a 2′(*R*)-hydroxy and a 3′(*S*)-acylamino group might be optimal. However, relatively little is known about the effects of the 3′-phenyl ring on activity. The synthesis and biological evaluation of analogs of **3** modified at the C-3′ position are described. This study revealed that the 3′-phenyl ring was not required for activity and identified several compounds which had equal or greater *in vitro* and *in vivo* activity than taxol.

## Introduction

Taxol (1) was isolated in 1971 from the bark of western yew *Taxus brevifolia* by Wani *et al.*[1] and has been shown to be clinically efficacious against several tumors which are refractory to other antitumor drugs. A semisynthetic analog, Taxotere (**2**), is also receiving extensive clinical evaluation.[2] However, both agents had drawbacks. Problems concerning toxicity and low aqueous solubility have accelerated the search for new analogs with more desirable physicochemical properties and higher potency.[3] Studies showed that the side chain at the C-13 position of taxol was indispensable for antitumor activity[1] and that the natural substitution pattern of a 2′-hydroxy and a 3′-*N*-acylamino group in the 2′*R*,3′*S* configuration was required for optimal activity.[4,5] Owing to its important role in the binding of taxol to microtubules, the side chain was also a target of intensive molecular modeling and NMR studies.[6] Synthetic modifications have focused on the 3′-*N*-acyl and the 3′-phenyl groups, and results from these investigations are described.[7] We were interested in probing the role of the taxol side chain in searching for crucial information on the structure–activity relationship (SAR) for the design of agents with more favorable therapeutical profiles. In addition, the efficient synthesis and the interesting antitumor activity of 9(*R*)-dihydrotaxol (**3**), prepared from 13-acetyl-9(*R*)-dihydrobaccatin III (**4**),[8] encouraged us to explore the SAR of this new member of the taxane family.[9] A systematic examination of the 3′-*N*-acyl substituent on this new 9-dihydro template identified 10-acetyl-9(*R*)-dihydrotaxotere (**5**) as having optimum activity in that series.[10] In this paper, we describe the synthesis and biological evaluation of C-3′-modified analogs of 9(*R*)-dihydrotaxol.[11]




| | X | Y | Z |
|---|---|---|---|
| taxol (**1**) | O | Ac | Bz |
| taxotere (**2**) | O | H | Boc |
| 9(*R*)-dihydrotaxol (**3**) | α-OH | Ac | Bz |
| 10-acetyl-9(*R*)-dihydrotaxotere (**5**) | α-OH | Ac | Boc |

## Chemistry

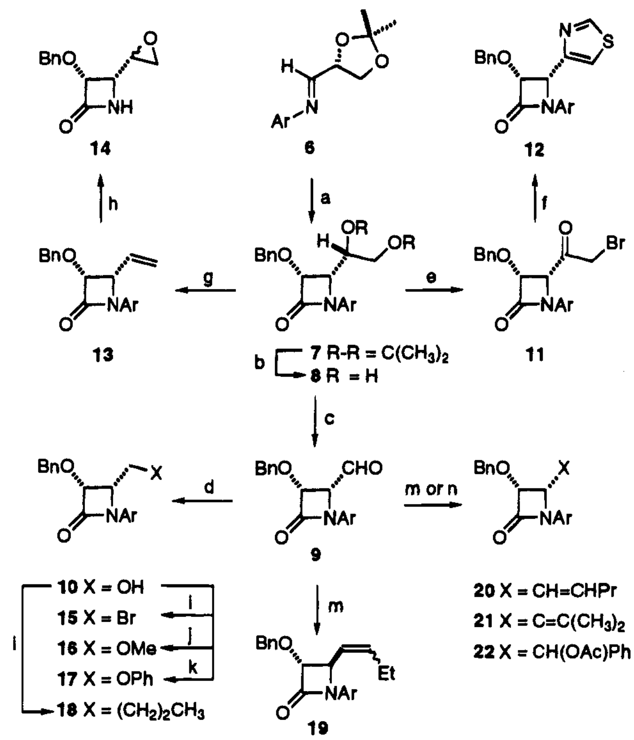
The use of a *β*-lactam as the acylating agent for the semisynthesis of taxol was well studied.[12] This method was employed in our study because it was efficient and would simplify the synthesis of C-3′ analogs to the 4-substituted 2-azetidinones. Accordingly, we devised a flexible synthetic strategy which allowed for the introduction of a variety of substituents to the 4-position of the 2-azetidinone.

A Staudinger reaction between a chiral Schiff base, **6**, prepared from D-glyceraldehyde acetonide and *p*-anisidine, and the ketene from benzyloxyacetyl chloride and triethylamine produced *β*-lactam **7** with very high diastereoselectivity.[13] In this reaction, the chiral center in **6** determined the stereochemical outcome of the two newly formed centers, which possessed the correct relative and absolute configurations of the taxol side chain. The acetonide group was removed by treatment with an acid to give diol **8**, which was converted to alcohol **10** via aldehyde **9** by oxidative cleavage with $NaIO_4$ and reduction with $NaBH_4$. Compounds **8–10** were versatile intermediates for further manipulations as shown in Scheme 1. Selective oxidation of diol **8** with *n*-$Bu_2SnO$ and $Br_2$[14] and treatment of the resulting α-hydroxy ketone with carbon tetrabromide–triphenylphosphine yielded α-bromo ketone **11**, which gave thiazole **12** in excellent yield on refluxing with thioformamide in acetone. A Corey–Winter olefination process from **8** yielded the 4-vinyl compound **13**, which was also the precursor for epoxide **14**. The hydroxy group in compound **10** could be removed (by conversion to a bromo group, **15**) or extended through etherifications to **16** and **17**. Carbon chain elongations were achieved in several ways. When **10** was converted to its triflate, chain extension to **18** was achieved through a cross-coupling reaction with organometallic reagents.[15] Wittig chemistry furnished compounds **19–21**. When the reaction of aldehyde **9** and phenylmagnesium bro-

⊗ Abstract published in *Advance ACS Abstracts*, August 1, 1994.

**Scheme 1**[a]




[a] Reagents: (a) $BnOCH_2COCl$–TEA; (b) TsOH, $THF/H_2O$; (c) $NaIO_4$; (d) $NaBH_4$; (e) (i) *n*-$Bu_2SnO$, $Br_2$, (ii) $CBr_4$–$PPh_3$; (f) $CH(S)NH_2$; (g) (i) 1,1′-thiocarbonyldiimidazole, (ii) $P(OMe)_3$; (h) (i) $Ce(NH_4)_2NO_3)_6$, (ii) MCPBA; (i) $CBr_4$–$PPh_3$; (j) $CH_3I$–$Ag_2O$; (k) PhOH, $EtO_2CN{=}NCO_2Et$, $PPh_3$; (l) (i) $Tf_2O$, TEA, (ii) PrMgBr–CuBr; (m) Wittig reactions to **19**–**21**; (n) PhMgBr, AcCl.

mide was quenched with acetyl chloride, a diastereomeric mixture of acetates **22** was obtained. Deacetoxylation occurred in a subsequent debenzylation step by hydrogenolysis.

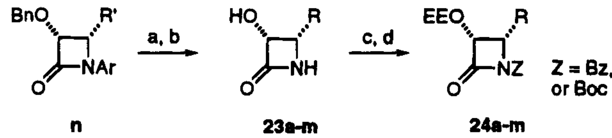
Once the desired (or precursory) substituents R′ were introduced (**7**, **12**–**22**), oxidative cleavage of the *N*-anisyl group with ceric ammonium nitrate in $CH_3CN$–$H_2O$[16] and debenzylation by hydrogenolysis over Pd/C–$HCO_2NH_4$ in methanol or treatment with $BCl_3$ in $CH_2Cl_2$ gave 3-hydroxy lactams **23a**–**l**. 3-Cyclohexyl-2-azetidinone (**23m**) was obtained from the hydrogenation of 3-phenyl-2-azetidinone, which was prepared following literature procedures.[12c] Reprotection of the 3-hydroxy group as an α-ethoxyethyl ether and acylation of the nitrogen as benzamide or *tert*-butoxycarbamate yielded β-lactams **24a**–**m** in proper form ready for coupling.

The suitably protected taxane moiety **25** was obtained in two steps from **4**, via a regioselective 13-deacylation with methyllithium in THF at −78 °C and a triethylsilylation of the C-7 hydroxyl group.[17] The coupling of **25** with the respective β-lactams **24a**–**m** and the subsequent removal of protecting groups at C-2′ and C-7 were carried out following similar procedures reported by Ojima to afford C-3′-modified 9(*R*)-dihydrotaxol) compounds **26a**–**m** in good yields (15–65% unoptimized). The cleavage of the acetonide group in **26** under acidic conditions led to **27**. The diastereomeric isomers (**26b,b′**) due to the C-4′ chiral center were separated, but the absolute configurations were not determined. Compound **28** came from hydrogenation of **26h**.[18]

## Results and Discussion

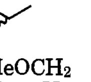
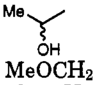
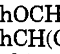
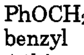
9(*R*)-Dihydrotaxol analogs were evaluated in cytotoxicity assays against four tumor cell lines,[19] a tubulin

**Scheme 2**[a]



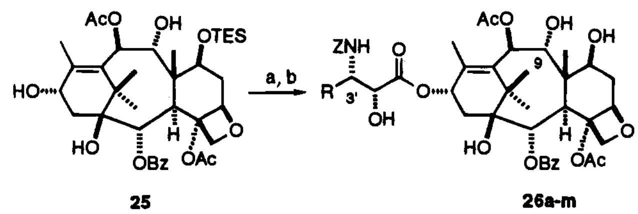

[a] Reagents: (a) $Ce(NH_4)_2(NO_3)_6$; (b) Pd/C, $HCO_2NH_4$; (c) EVE, PPTS; (d) BzCl, TEA, DMAP, or $Boc_2O$, TEA.

**Table 1.** Synthesis of β-Lactams **23** and **24**

| compound | | compound | | | compound | | |
|---|---|---|---|---|---|---|---|
| no. | R′ | no. | R | yield (%) | no. | Z | yield (%) |
| **7** |  | **23a** |  | 67 | **24a** | Boc | 63 |
| **14** |  | **23b** |  | 51[a] | **24b** | Boc | 94 |
| **16** | $MeOCH_2$ | **23c** | $MeOCH_2$ | 50 | **24c** | Bz | 21 |
| **17** | $PhOCH_2$ | **23d** | $PhOCH_2$ | 47 | **24d** | Bz | 81 |
| **22** | PhCH(OAc) | **23e** | benzyl | 83 | **24e** | Boc | 75 |
| **12** | 4-thiazolyl | **23f** | 4-thiazolyl | 75[b] | **24f** | Boc | 50 |
| **15** | bromomethyl | **23g** | methyl | 61 | **24g** | Boc | 80 |
| **13** | vinyl | **23h** | vinyl | 48[b] | **24h** | Boc | 49 |
| **18** | butyl | **23h** | butyl | 75 | **24i** | Boc | 53 |
| **19** | (4*R*)-1-butenyl | **23j** | (4*R*)-butyl | 68 | **24j** | Boc | 49 |
| **20** | 1-pentenyl | **23k** | pentyl | 78 | **24k** | Boc | 78 |
| **21** | isobutenyl | **23l** | isobutyl | 69 | **24l** | Boc | 86 |
| | | **23m** | cyclohexyl | 83 | **24m** | Boc | 75 |

[a] Treatment of **14** (a pair of diastereomers) with Pd/C and $HCO_2NH_4$ affected the debenzylation and the oxirane ring cleavage to give **23b**. [b] Debenzylation was achieved with $BCl_3$ in $CH_2Cl_2$.

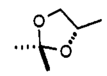
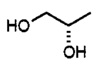
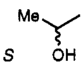
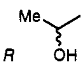
**Scheme 3**[a]




[a] Reagents: (a) $LiN(TMS)_2$, β-lactam **24a**–**m**; (b) 1% HCl–EtOH.

assembly assay (Table 3),[20] and, in several cases, an *in vivo* study against M109 murine lung tumor. In general, the tubulin assembly assay showed a good correlation with the cytotoxicity data. We found that replacement of the C-3′ phenyl with oxygenated groups was not tolerated. Compound **26a** was inactive in both *in vitro* assays, possibly due to the presence of oxygen atoms and the bulkiness of the 2,2-dimethyl-1,3-dioxolo group. Compounds **26b,b′** and **27** bearing free hydroxy groups at C-3′ or C-4′ had increased water solubility but exhibited diminished cytotoxicity. Loss of activity was also observed with 3′-methoxymethyl and 3′-phenoxymethyl analogs (**26c,d**). We were surprised to find that the C-3′ benzyl analog was also devoid of activity. On the other hand, replacement of the C-3′ phenyl ring with an isosteric heteroaromatic ring such as a 4-thiazolyl group resulted in retention of activity. Lipophilic alkyl or alkenyl groups were allowed at this position, with potency increasing in the order of size from methyl to isobutyl. The *n*-pentyl and cyclohexyl compounds (**26k,m**) were both very active but slightly less potent than the isobutyl derivative **26l**. Compound **26j** having the unnatural 3′*R* configuration was inactive; this result confirmed the importance of the stereochemistry at C-3′ even in the non-phenyl case.

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

| compound | | | | | HRMS | | |
|---|---|---|---|---|---|---|---|
| no. | R | Z | yield (%) | MS (FAB) *m/z* | calculated | measured | HPLC[a] %/$t_R$ |
| **26a** |  | Boc | 63 | 914 [M + K$^+$] | $C_{44}H_{62}NO_{17}Na$ 898.3854 | 898.3837 | 100/16.1 |
| **27** |  | Boc | 19[b] | 874 [M + K$^+$] | $C_{41}H_{58}NO_{17}$ 836.3705 | 836.3721 | 91/3.1 |
| **26b** |  *R* or *S* | Boc | 23 | 924 [M + K$^+$] | $C_{41}H_{57}NO_{16}Na$ 842.3575 | 842.3574 | 82/5.1 |
| **26b'** |  *S* or *R* | Boc | 19 | 924 [M + K$^+$] | $C_{41}H_{57}NO_{16}Na$ 842.3575 | 842.3572 | 93/5.7 |
| **26c** | $MeOCH_2$ | Bz | 53 | 862 [M + K$^+$] | $C_{43}H_{54}NO_{15}$ 824.3493 | 824.3481 | 96/5.7 |
| **26d** | $PhOCH_2$ | Bz | 48 | 924 [M + K$^+$] | $C_{48}H_{55}NO_{15}Na$ 908.3469 | 908.3471 | 96/33.4 |
| **26e** | benzyl | Boc | 67 | 904 [M + K$^+$] | $C_{46}H_{60}NO_{15}$ 866.3963 | 866.3964 | 94/45.6 |
| **26f** | 4-thiazolyl | Boc | 52 | 897 [M + K$^+$] | $C_{42}H_{55}N_2O_{15}S$ 859.3323 | 859.3315 | 97/11.5 |
| **26g** | methyl | Boc | 52 | 828 [M + K$^+$] | $C_{40}H_{56}NO_{15}$ 790.3650 | 790.3647 | 96/9.7 |
| **26h** | vinyl | Boc | 36 | 840 [M + K$^+$] | $C_{41}H_{55}NO_{15}$ 802.3650 | 802.3669 | 94/12.4 |
| **28** | ethyl | Boc | 80[c] | 842 [M + K$^+$] | $C_{41}H_{58}NO_{15}$ 804.3806 | 804.3801 | 99/14.2 |
| **26i** | butyl | Boc | 34 | 870 [M + K$^+$] | $C_{43}H_{62}NO_{15}$ 832.4119 | 832.4134 | 96/52.7 |
| **26j** | (3'*R*)-butyl | Boc | 15 | 870 [M + K$^+$] | $C_{43}H_{61}NO_{15}K$ 870.3678 | 870.3681 | 90/48.9 |
| **26k** | pentyl | Boc | 46 | 884 [M + K$^+$] | $C_{44}H_{63}NO_{15}$ 846.4276 | 846.4258 | 97/102.3 |
| **26l** | isobutyl | Boc | 56 | 870 [M + K$^+$] | $C_{43}H_{61}NO_{15}$ 832.4119 | 832.4138 | 94/41.9 |
| **26m** | cyclohexyl | Boc | 34 | 896 [M + K$^+$] | $C_{45}H_{65}NO_{15}$ 858.4276 | 858.4277 | 97/85.6 |

[a] HPLC conditions: reverse phase YMC cartridge C-8 column; mobile phase, 30:5:65 $CH_3CN$:MeOH:0.01 M TMAP/0.1% TFA at 1 mL/min; detection, UV 205 nm; reported as percentage/retention time in min. [b] Compound **27** was isolated as a minor product in the synthesis of **26a**. [c] From hydrogenation of **26h** over Pd/C in methanol.

Two of C-3' analogs, **26l,m**, were further evaluated in an *in vivo* study in the M109 murine lung tumor model.[21] Preliminary data showed that the efficacy of both compounds paralleled their excellent cytotoxicity results. Significant protection was produced with optimal delays in tumor growth of 15.6 days for **26l** and 8.8 days for **26m** as compared to that of 0.2 days for taxol. Inhibition of tumor growth by both agents was severalfold greater than inhibition by taxol, and their toxicity was seen to be less than taxol. The detailed data from this and other tumor models will be reported in the future.

Two models on the bioactive conformations of the taxol side chain have been proposed on the basis of information from NMR and molecular modeling study. One model features a networking of hydrogen bonding between the 1'-ester carbonyl, the 2'-hydroxyl, and the 3'-NH.[6a,b] An alternative model relies on a hydrophobic collapse consideration.[6c] The key feature of the latter is a hydrophobic clustering of the 2-benzoyl, 3'-phenyl, and 4-acetyl groups. The nonpolar side chain amide groups are believed not to be involved. The fact that compounds with hydrophobic 3'-substituents are generally active while 3'-substituents bearing hydrophilic groups lead to less active compounds is in support of the notion that there exists a hydrophobic binding pocket on the microtubules to interact with the 3'-substituent of the taxol-type side chain. The lack of activity with 3'-benzyl compound **26e** suggests that such a pocket has a limited size. Further study by X-ray crystallography, NMR, and molecular modeling methods of the C-3' 9(*R*)-dihydrotaxol analogs should provide valuable information regarding the taxol binding site on microtubules.

## Conclusion

A versatile strategy for the preparation of chiral 3-hydroxy-2-azetidinones varying the 4-substituent was developed. A series of novel 9(*R*)-dihydrotaxol analogs were synthesized, and their biological activities were evaluated. This detailed investigation expanded our SAR knowledge and further defined the structural requirements for activity at the C-3' position of taxol-like compounds. We showed that the 3'-phenyl ring was not required for activity, with heteroaromatic rings and alkyl and alkenyl groups serving as acceptable replacements. Several analogs were identified to have equal or greater potency than taxol. We found that an oxygen atom at this position generally led to less active compounds. The stereochemistry at C-3' was confirmed to be optimal in the natural *S* configuration. The isobutyl derivative **26l** was identified as the most potent compound in the series and showed superior activity to taxol in both the tumor cell line cytotoxicity assays and the *in vivo* study.

## Experimental Section

$^1H$ NMR spectra were recorded on a General Electric QE300 or QE500 spectrometer with chemical shifts given in parts per

**Table 3.** Cytotoxicity and Tubulin Assembly Activity of 9(*R*)-Dihydrotaxol Analogs

| | tumor cell cytotoxicity $IC_{50}$ (ng/mL)[a] | | | | tubulin[b] |
|---|---|---|---|---|---|
| compd | A549 | HT-29 | B16F10 | P388 | $ED_{50}/ED_{50taxol}$ |
| **3** | 19 | 80 | 25 | 53 | 0.86 |
| **5** | 3 | 0.16 | 0.4 | 2.5 | 0.87 |
| **26a** | >100 | >100 | 86 | >100 | 7.91 |
| **27** | >100 | >100 | >100 | >100 | 2.71 |
| **26b** | >100 | >100 | >100 | >100 | 0.80 |
| **26b′** | >100 | >100 | >100 | >100 | 1.20 |
| **26c** | >100 | 79 | >100 | >100 | 3.14 |
| **26d** | 92 | 39 | 84 | >100 | 5.81 |
| **26e** | >100 | >100 | >100 | >100 | >17.1 |
| **26f** | 6.3 | 0.92 | 0.3 | 1.4 | 1.36 |
| **26g** | 15 | 8.3 | 19 | 43 | 1.08 |
| **26h** | 1.1 | 1.8 | 4.4 | 16 | 0.92 |
| **28** | 0.83 | 1.4 | 3.2 | 11 | 0.61 |
| **26i** | 9.5 | 8.8 | 9.7 | 18 | 2.15 |
| **26j** | >100 | 67 | >100 | >100 | 9.74 |
| **26k** | 12 | 16 | 14 | 16 | 2.00 |
| **26l** | 0.12 | 0.38 | 0.9 | 0.36 | 0.95 |
| **26m** | 6.5 | 5 | 5.7 | 14 | 0.57 |

[a] A549—human lung carcinoma; HT-29—human colon adenocarcinoma; B16F10—mouse melanoma; P388—mouse leukemia. $IC_{50}$ is described as the concentration of agent required to inhibit cell proliferation to 50% vs untreated cells (incubated at 37 °C for 72 h) determined by MTT colorimetric microtiter assay.[19] [b] $ED_{50}$ is the concentration of agent which reduces the supernatent protein concentration (tubulin, 1 mg/mL) by 50% in 15 min at 37 °C.[20]

million (ppm) downfield from an interal tetramethylsilane standard. MS were recorded with a Finnigan SSQ 7000 instrument, and high-resolution MS were obtained on a Kratos MS 50 instrument. All melting points were recorded on a Mel-Temp II capillary melting point apparatus and are uncorrected. Column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) under low pressure. Thin layer chromatography (TLC) was carried out on E. Merck precoated plates, silica gel 60 $F_{254}$, with a thickness of 0.25 or 0.50 mm. Methylene chloride ($CH_2Cl_2$) was distilled from calcium hydride, and tetrahydrofuran (THF) was distilled from sodium–benzophenone. Unless otherwise noted, materials were obtained from commercial sources and used without further purification.

**Synthesis of 1-(4-Methoxyphenyl)-3-(benzyloxy)-2-azetidinones. (3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(4-thiazolyl)-2-azetidinone (12).** i. A suspension of diol **8**[13] (5.03 g, 14.7 mmol) and di-*n*-butyltin oxide (11.0 g, 88.9 mmol) in methanol (100 mL) was refluxed for 5 h. The solvent was evaporated, and the residue was dried under vacuum overnight. The resultant solid and pulverized molecular sieves were suspended in $CH_2Cl_2$ (100 mL), and to this mixture was added a solution of $Br_2$ in $CH_2Cl_2$ until the reaction was complete as indicated by TLC analysis. The entire reaction mixture was poured onto a silica gel column and initially eluted with chloroform ($CHCl_3$) to wash out the tin species followed by further elution with $CHCl_3$/ethyl acetate (AcOEt) which gave the desired hydroxy ketone. This product was further purified by crystallization from $CH_2Cl_2$/ether/hexane (4.13 g, 83%).

ii. **α-Bromo Ketone (11).** The mixture of triphenylphosphine (7.62 g, 29.1 mmol) and carbon tetrabromide (4.82 g, 14.5 mmol) in $CH_2Cl_2$ (100 mL) was stirred for 10 min, and to this mixture was added a solution of the hydroxy ketone from i (4.13 g, 12.1 mmol) in $CH_2Cl_2$ (50 mL). After stirring at 25 °C for 2 h, the reaction mixture was poured into a vigorously stirred mixture of ether and hexanes (1:1, 100 mL). Precipitates were removed by filtration, and more precipitates came out on concentration of the filtrate, which were removed again by filtration. The oily residue from the filtrate was purified by chromatography using 10:1 hexanes/AcOEt and produced **11** (4.15 g, 85%). $^1$H NMR ($CDCl_3$): $\delta$ 7.35 (m, 5H), 7.25 (d, $J$ = 9.3 Hz, 2H), 6.88 (d, $J$ = 9.3 Hz, 2H), 5.05 (s, 2H), 4.85 (d, $J$ = 11.7 Hz, 1H), 4.74 (d, $J$ = 11.7 Hz, 1H), 4.16 (d, $J$ = 14.4 Hz, 1H), 3.95 (d, $J$ = 14.4 Hz, 1H), 3.80 (s, 3H). MS (DCI/$NH_3$): $m/z$ 421, 423 (M + $NH_4^+$) (100).

iii. A portion of 11 (2.72 g, 6.75 mmol) was refluxed with thioformamide (5 equiv) in acetone for 4 h. The solvent was evaporated to give a solid which was loaded onto a silica gel column with 5% methanol/$CH_2Cl_2$ and eluted with hexanes/AcOEt (2:1–1:1) to yield crude product. Crystallization from ether–hexanes gave **12** as a yellow solid (1.90 g, 77%), mp 158–160 °C. $^1$H NMR ($CDCl_3$): $\delta$ 8.77 (d, $J$ = 2.4 Hz, 1H), 7.36 (d, $J$ = 2.4 Hz, 1H), 7.30 (d, $J$ = 9.0 Hz, 2H), 7.25 (m, 4H), 7.06 (m, 1H), 6.80 (d, $J$ = 9.0 Hz, 2H), 5.60 (d, $J$ = 4.5 Hz, 1H), 5.09 (d, $J$ = 4.5 Hz, 1H), 4.45 (ABq, $J$ = 10.8 Hz, 2H), 3.75 (s, 3H). MS (DCI/$NH_3$): $m/z$ 384 (M + $NH_4^+$) (80), 367 (M + $H^+$) (100). HRMS-FAB: calcd for $C_{20}H_{19}N_2O_3S$, 367.116; measured, 367.1112.

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-vinyl-2-azetidinone (13).** i. The mixture of diol **8** (7.40 g, 21.6 mmol) and 1,1′-thiocarbonyldiimidazole (1.0 equiv) in toluene (100 mL) was heated at 100 °C for 1 h. The mixture was cooled, the reaction quenched with water, and the mixture evaporated. Crystallization from methanol/$H_2O$ gave pure product which was washed with water and dried to yield the thionocarbonate (7.73 g, 93%).

ii. A mixture of the thionocarbonate from i (7.60 g) and $(MeO)_3P$ (80 mL) was refluxed for 5 h, cooled, and evaporated. The residue was purified by recrystallization from methanol/$H_2O$ to give **13** (5.71 g, 94%), mp 104–105 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.36 (m, 5H), 7.38 (d, $J$ = 9.0 Hz, 2H), 6.83 (d, $J$ = 9.0 Hz, 2H), 6.01 (ddd, $J$ = 17.5, 10.0, 7.8 Hz, 1H), 5.56 (d, $J$ = 17.5 Hz, 1H), 5.49 (d, $J$ = 10.0 Hz, 1H), 4.86 (d, $J$ = 4.8 Hz, 1H), 4.72 (d, $J$ = 12.0 Hz, 1H), 4.71 (d, $J$ = 12.0 Hz, 1H), 4.59 (dd, $J$ = 7.8, 4.8 Hz, 1H), 3.78 (s, 3H). MS (DCI/$NH_3$): $m/z$ 327 (M + $NH_4^+$) (100), 310 (M + $H^+$) (40).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(hydroxymethyl)-2-azetidinone (10).** To a solution of diol **8** (7.16 g, 20.9 mmol) in 100 mL of methanol at 0 °C was added a solution of $NaIO_4$ (8.93 g, 41.8 mmol) in $H_2O$ (100 mL). The reaction mixture was stirred for 30 min, and the white precipitate was filtered and washed with water (3 × 25 mL). The filtrate was extracted with AcOEt (400 mL), and this extract was dried over $MgSO_4$, filtered, and evaporated to give the aldehyde **9** as a white solid (6.50 g, 100%).

To aldehyde **9** (3.30 g, 10.6 mmol) in methanol (50 mL) at 0 °C was added in portions $NaBH_4$ until the reduction was complete as indicated by TLC analysis. The reaction mixture was partitioned between AcOEt and dilute NaCl, and the organic layer was dried over $MgSO_4$, filtrated, and evaporated. The crude product was purified by chromatography to give alcohol **10** (3.3 g, 99%). $^1$H NMR ($CDCl_3$): $\delta$ 7.40 (m, 5H), 7.38 (d, $J$ = 9.0 Hz, 2H), 6.80 (d, $J$ = 9.0 Hz, 2H), 5.02 (d, $J$ = 11.5 Hz, 1H), 4.87 (d, $J$ = 5.6 Hz, 1H), 4.78 (d, $J$ = 11.5 Hz, 1H), 4.24 (m, 1H), 4.05 (m, 2H), 3.79 (s, 3H), 2.31 (bt, 1H). MS (DCI/$NH_3$): $m/z$ 331 (M + $NH_4^+$) (100), 314 (M + $H^+$) (40).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(bromomethyl)-2-azetidinone (15).** A mixture of triphenylphosphine (2.40 g, 9.16 mmol) and carbon tetrabromide (1.50 g, 4.52 mmol) in $CH_2Cl_2$ was stirred for 10 min, and to this mixture was added a solution of alcohol **10** (700 mg, 2.24 mmol). After being stirred at 25 °C for 2 h, the reaction mixture was poured into a stirred solvent mixture (1:1 $Et_2O$/hexanes, 100 mL). Precipitates were removed by filtration, and more precipitates came out on concentration of the filtrate, which was removed again by filtration. The oily residue from the filtrate was purified by chromatography with 10:1 hexanes/AcOEt as eluent to give product **15** (0.73 g, 83%). $^1$H NMR ($CDCl_3$): $\delta$ 7.31–7.50 (m, 5H), 7.35 (d, $J$ = 8.4 Hz, 2H), 6.90 (d, $J$ = 8.4 Hz, 2H), 4.90 (s, 2H), 4.86 (d, $J$ = 5.2 Hz, 1H), 4.52 (dt, $J$ = 6.6, 5.2 Hz, 1H), 3.80 (s, 3H), 3.71 (dd, $J$ = 10.5, 6.6 Hz, 1H), 3.70 (dd, $J$ = 10.5, 5.2 Hz, 1H). MS (DCI/$NH_3$): $m/z$ 393 (M + $NH_4^+$) (100), 376 (M + $H^+$) (35).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(methoxymethyl)-2-azetidinone (16).** Alcohol **10** (403 mg, 1.29 mmol), $Ag_2O$ (600 mg, 2.59 mmol), and iodomethane (3 mL) were refluxed until the completion of the reaction. The solid was removed by filtration, and the filtrate was evaporated. Purification by chromatography gave **16** (330 mg, 78%). $^1$H

NMR ($CDCl_3$): δ 7.50 (d, $J$ = 9.2 Hz, 2H), 7.35 (m, 5H), 6.87 (d, $J$ = 9.2 Hz, 2H), 4.83 (d, $J$ = 5.1 Hz, 1H), 4.81 (ABq, $J$ = 11.8 Hz, 2H), 4.32 (dt, $J$ = 5.8, 5.1 Hz, 1H), 3.79 (s, 3H), 3.78 (dd, $J$ = 10.7, 5.1 Hz, 1H), 3.71 (dd, $J$ = 10.7, 5.8 Hz, 1H), 3.38 (s, 3H). MS (DCI/$NH_3$): $m/z$ 345 (M + $NH_4^+$) (100), 328 (M + $H^+$) (85).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(phenoxymethyl)-2-azetidinone (17).** To the stirred solution of alcohol **10** (1.372 g, 4.38 mmol), phenol (618 g, 6.57 mmol), and triphenylphosphine (1.72 g, 6.57 mmol) in THF (10 mL) was added diethyl azodicarboxylate (1.14 g, 6.57 mmol) dropwise. The mixture was heated at 60 °C for 5 h and then cooled and evaporated. The residue was purified by chromatography with 4:1 hexanes/AcOEt to give **17** (1.10 g, 65%). $^1$H NMR ($CDCl_3$): δ 7.55 (d, $J$ = 9.3 Hz, 2H), 7.32 (m, 7H), 6.95 (t, $J$ = 7.2 Hz, 1H), 6.88 (m, 3H), 4.92 (d, $J$ = 5.4 Hz, 1H), 4.87 (d, $J$ = 11.4 Hz, 1H), 4.77 (d, $J$ = 11.4 Hz, 1H), 4.56 (dt, $J$ = 5.4, 5.3 Hz, 1H), 4.39 (dd, $J$ = 9.3, 5.4 Hz, 1H), 4.30 (dd, $J$ = 9.3, 5.3 Hz, 1H), 3.80 (s, 3H). MS (DCI/$NH_3$): $m/z$ 407 (M + $NH_4^+$) (100), 390 (M + $H^+$) (30).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-butyl-2-azetidinone (18).** i. Alcohol **10** (2.39 g, 7.64 mmol) was treated with triflic anhydride (4.31 g, 15.3 mmol) and triethylamine (3.40 g, 33.6 mmol) in $CH_2Cl_2$ (20 mL) at −20 °C to give, following chromatography with hexanes/AcOEt (5:1), the product trifilate (2.54 g, 76%).

ii. Propylmagnesium bromide (3.80 mL, 2.0 M in ether) was added to a stirred suspension of CuBr (120 mg) in THF at 0 °C and stirred for 10 min. To this mixture was added a solution of the freshly prepared triflate from i (840 mg, 1.92 mmol) in THF (2 mL). The reaction was quenched in 3 h by diluting with ether and washing with 10% $NaHSO_4$. After chromatographic separation, the desired product **18** was obtained (275 mg, 41%) along with **10** (220 mg, 37%) and **15** (80 mg, 12%). **18**: $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H), 7.32 (d, $J$ = 8.8 Hz, 2H), 6.87 (d, $J$ = 8.8 Hz, 2H), 4.96 (d, $J$ = 11.8 Hz, 1H), 4.76 (d, $J$ = 11.8 Hz, 1H), 4.75 (d, $J$ = 5.2 Hz, 1H), 4.15 (dt, $J$ = 5.2, 4.2 Hz, 1H), 3.79 (s, 3H), 1.89 (m, 2H), 1.37 (m, 4H), 0.89 (t, $J$ = 6.9 Hz, 3H); MS (DCI/$NH_3$) $m/z$ 357 (M + $NH_4^+$) (100), 340 (M + $H^+$) (90).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(2-methylpropen-1-yl)-2-azetidinone (21).** To a suspension of isopropyltriphenylphosphonium iodide (15.4 g, 35.7 mmol) at −78 °C in THF (250 mL) was added *n*-BuLi (1.6 M in hexane, 21.2 mL, 33.9 mmol). The mixture was stirred for 20 min and for an additional 40 min at −30 °C. A solution of aldehyde **10** in THF (100 mL) was added to the *in situ* formed ylide. The temperature was allowed to rise to 25 °C gradually, and the reaction was quenched in 3 h with 1 N HCl and ether (500 mL). Two layers were separated; the aqueous phase was extracted with ether once. The combined organic phase was evaporated to give a tar, which was taken up with ether and filtered, and the filtrate was washed with saturated NaCl, dried over $MgSO_4$, refiltered, and evaporated. The crude product was purified by chromatography with gradient elution using hexanes/AcOEt (4:1−2:1). Further purification by recrystallization from hexanes−AcOEt afforded pure product **21** as a white solid (4.70 g, 59%), mp 101−103 °C. $^1$H NMR ($CDCl_3$): δ 7.35 (m, 5H), 7.32 (d, $J$ = 9.0 Hz, 2H), 6.85 (d, $J$ = 9.0 Hz, 2H), 5.38 (bd, $J$ = 8.4 Hz, 1H), 4.82 (m, 2H), 4.67 (d, $J$ = 12.0 Hz, 1H), 4.63 (d, $J$ = 12.0 Hz, 1H), 3.77 (s, 3H), 1.86 (s, 3H), 1.82 (d, $J$ = 2.0 Hz, 3H). MS (DCI/$NH_3$): $m/z$ 355 (M + $NH_4^+$) (100), 338 (M + $H^+$) (75).

**(3*R*,4*R*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(buten-1-yl)-2-azetidinone (19).** Use of propyltriphenylphosphonium bromide following similar procedures as described above produced a complicated mixture from which was isolated the 4*R* isomer **19** in 9% yield. $^1$H NMR ($CDCl_3$): δ 7.35 (m, 5H), 7.32 (d, $J$ = 9.0 Hz, 2H), 6.85 (d, $J$ = 9.0 Hz, 2H), 5.72 (dt, $J$ = 10.5, 7.5 Hz, 1H), 5.35 (dd, $J$ = 10.5, 10.0 Hz, 1H), 4.85 (d, $J$ = 12.0 Hz, 1H), 4.70 (d, $J$ = 12.0 Hz, 1H), 4.68 (ddd, $J$ = 10.0, 2.0, 2.0 Hz, 1H), 4.50 (d, $J$ = 2.0 Hz, 1H), 3.78 (s, 3H), 2.20 (m, 2H), 1.07 (t, $J$ = 6.6 Hz, 3H). MS (DCI/$NH_3$): $m/z$ 355 (M + $NH_4^+$) (75), 338 (M + $H^+$) (100).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(penten-1-yl)-2-azetidinone (20).** A mixture of diastereomers (in 2:1 ratio), which were inseparable by chromatography but distinguishable by NMR, was obtained in 32% yield. **Major isomer**: $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H), 7.35 (d, $J$ = 9.0 Hz, 2H), 6.85 (d, $J$ = 9.0 Hz, 2H), 5.90 (m, 1H), 5.62 (m, 1H), 4.92 (ddd, $J$ = 9.3, 4.8, 0.9 Hz, 1H), 4.85 (d, $J$ = 4.8 Hz, 1H), 4.70 (s, 2H), 3.78 (s, 3H), 2.25 (m, 2H), 1.55 (m, 2H), 1.02 (t, $J$ = 7.5 Hz, 3H). **Minor isomer**: $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H), 7.35 (d, $J$ = 9.0 Hz, 2H), 6.85 (d, $J$ = 9.0 Hz, 2H), 5.90 (m, 1H), 5.62 (m, 1H), 4.84 (d, $J$ = 4.8 Hz, 1H), 4.70 (s, 2H), 4.58 (dd, $J$ = 8.7, 4.8 Hz, 1H), 3.78 (s, 3H), 2.10 (ABq, $J$ = 6.6 Hz, 2H), 1.42 (q, $J$ = 7.5 Hz, 2H), 0.89 (t, $J$ = 7.5 Hz, 3H). MS (DCI/$NH_3$): $m/z$ 369 (M + $NH_4^+$) (100), 352 (M + $H^+$) (80).

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(α-acetoxybenzyl)-2-azetidinone (22).** To a stirred solution of aldehyde **9** (1.00 g, 3.22 mmol) in THF (30 mL) at −40 °C was added phenylmagnesium bromide (1 M in THF, 3.50 mL). The reaction mixture was stirred for 2 h, at which time an excess of acetyl chloride (*ca.* 10 equiv) was added, and the temperature was allowed to rise to 0 °C over 30 min. The mixture was diluted with AcOEt and washed with dilute HCl, $NaHCO_3$, and saturated NaCl solution. A mixture of diastereomers **22** (0.91 g, *ca.* 8:1) was obtained after chromatography. $^1$H NMR ($CDCl_3$): δ 7.10−7.45 (m, 12H), 6.85 (d, $J$ = 9.0 Hz, 2H), 6.25 (d, $J$ = 8.1 Hz, 1H), 4.72 (dd, $J$ = 8.1, 5.8 Hz, 1H), 4.68 (d, $J$ = 5.8 Hz, 1H), 4.58 (d, $J$ = 12.0 Hz, 1H), 4.41 (d, $J$ = 12.0 Hz, 1H), 3.80 (s, 3H), 1.70 (s, 3H). MS (DCI/$NH_3$): $m/z$ 449 (M + $NH_4^+$) (100), 432 (M + $H^+$) (10).

**General Procedures for Preparation of 3-Hydroxy-2-azetidiones. i. Dearylation.**[16] Ceric ammonium nitrate (2.2 equiv) in $H_2O$ (30 mL) was added to a stirred solution of 1-(methoxyphenyl)-3-(benzyloxy)-2-azetidinone (7.09 mmol) in acetonitrile/$H_2O$ (2:1, 60 mL) at 0 °C. The mixture was stirred for 1 h, at which time AcOEt (100 mL) was added, the organic phase was washed with $NaHCO_3$, $H_2O$, and saturated NaCl solutions sequentially and dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by chromatography with AcOEt−hexanes mixtures to give 3-(benzyloxy)-2-azetidinone.

ii. **Debenzylation.** A mixture of the benzyl ether described in i (2.60 mmol), ammonium formate (600 mg), 10% Pd/C (300 mg), and methanol (20 mL) was refluxed until TLC indicated complete disappearance of starting material. The mixture was filtered through a Celite pad, which was washed with a 1:1 mixture of AcOEt and methanol and evaporated. The residue was purified by chromatography with AcOEt−hexanes mixtures to yield desired product **23**.

**(3*R*,4*S*)-3-Hydroxy-4-(2,2-dimethyl-1,3-dioxol-4-yl)-2-azetidinone (23a)** was prepared as above from 7, mp 143−145 °C. $^1$H NMR ($CDCl_3$): δ 6.05 (bs, 1H), 4.90 (ddd, $J$ = 10.8, 5.4, 1.5 Hz, 1H), 4.40 (m, 1H), 4.22 (dd, $J$ = 9.0, 6.5 Hz, 1H), 3.81 (m, 2H), 3.65 (d, $J$ = 10.8 Hz, 1H, OH), 1.58 (s, 3H), 1.35 (s, 3H). MS (DCI/$NH_3$): $m/z$ 205 (M + $NH_4^+$) (100), 188 (M + $H^+$) (25).

**(3*R*,4*S*)-3-Hydroxy-4-(1-hydroxyethyl)-2-azetidinone Diastereomers 23b.** i. 3-(Benzyloxy)-4-ethenyl-2-azetidinone was prepared from **13** via above dearylation in 86% yield.

ii. **Epoxidation.** A solution of 3-(benzyloxy)-4-ethenyl-2-azetidinone (0.74 g, 3.65 mmol) in 1,2-dichloroethane (25 mL) was treated with MCPBA (1.40 g, 8.1 mmol) and refluxed for 2 h. The mixture was diluted with $CH_2Cl_2$, washed with saturated $NaHSO_3$, $NaHCO_3$, water, and brine, and finally evaporated. The crude product was purified by chromatography to give the isomers **14** (0.552 g, 69%). **14a**: $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H), 6.15 (bs, 1H, NH), 4.90 (d, $J$ = 12.0 Hz, 1H), 4.81 (dd, $J$ = 5.6, 2.4 Hz, 1H), 4.68 (d, $J$ = 12.0 Hz, 1H), 3.31 (dd, $J$ = 7.5, 5.6 Hz, 1H), 3.20 (ddd, $J$ = 7.5, 4.5, 2.7 Hz, 1H), 2.85 (t, $J$ = 4.5 Hz, 1H), 2.48 (dd, $J$ = 4.5, 2.7 Hz, 1H). **14b**: $^1$H NMR ($CDCl_3$) δ 7.38 (m, 5H), 5.80 (bs, 1H, NH), 4.85 (dd, $J$ = 4.8, 2.4 Hz, 1H), 4.79 (d, $J$ = 12.0 Hz, 1H), 4.77 (d, $J$ = 12.0 Hz, 1H), 3.71 (t, $J$ = 4.8 Hz, 1H), 3.15 (ddd, $J$ = 5.4, 4.8, 3.0 Hz, 1H), 2.87 (dd, $J$ = 5.4, 4.5 Hz, 1H), 2.77 (dd, $J$ = 4.5, 3.0 Hz, 1H). MS (DCI/$NH_3$): $m/z$ 237 (M + $NH_4^+$) (100), 220 (M + $H^+$) (10).

iii. Debenzylation of **14** also affected cleavage of the epoxide and afforded diastereomeric mixture **23b** in a 1:1 ratio inseparable by chromatography but distinguishable by NMR.

$^1$H NMR ($CD_3OD$): δ 4.86 (d, J = 4.5 Hz, 1H), 4.79 (d, J = 4.5 Hz, 1H), 3.93 (m, 1H), 3.84 (m, 1H), 3.47 (dd, J = 6.6, 4.5 Hz, 2H), 1.22 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.0 Hz, 3H). MS (DCI/$NH_3$): m/z 149 (M + $NH_4^+$) (100), 132 (M + $H^+$) (10).

**(3*R*,4*S*)-3-Hydroxy-4-(methoxymethyl)-2-azetidinone (23c)** was prepared as described in the general procedure above from **16**. $^1$H NMR ($CDCl_3$): δ 5.90 (bs, 1H), 4.91 (dd, J = 5.4, 1.5 Hz, 1H), 3.87 (dt, J = 5.4, 3.3 Hz, 1H), 3.76 (d, J = 3.3 Hz, 1H), 3.75 (d, J = 3.3 Hz, 1H). MS (DCI/$NH_3$): m/z 149 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-Hydroxy-4-(phenoxymethyl)-2-azetidinone (23d)** was prepared as described in the general procedure above from **17**. $^1$H NMR ($CDCl_3$): δ 7.30 (m, 2H), 7.02 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 7.9 Hz, 2H), 6.11 (bs, 1H), 5.08 (dd, J = 5.7, 2.4 Hz, 1H), 4.35 (dd, J = 10.2, 3.0 Hz, 1H), 4.24 (dd, J = 10.2, 5.4 Hz, 1H), 4.14 (m, 1H). MS (DCI/$NH_3$): m/z 211 (M + $NH_4^+$) (15).

**(3*R*,4*S*)-3-Hydroxy-4-benzyl-2-azetidinone (23e)** was prepared as described in the general procedure above from **22**. $^1$H NMR ($CDCl_3$): δ 7.21–7.38 (m, 5H), 6.05 (bs, 1H, NH), 5.02 (m, 1H), 4.00 (ddd, J = 14.0, 10.1, 5.1 Hz, 1H), 3.51 (d, J = 6.3 Hz, 1H, OH), 3.12 (dd, J = 14.0, 5.1 Hz, 1H), 2.85 (dd, J = 14.0, 10.1 Hz, 1H). MS (DCI/$NH_3$): m/z 195 (M + $NH_4^+$) (100), 178 (M + $H^+$) (6).

**(3*R*,4*S*)-3-Hydroxy-4-(4-thiazolyl)-2-azetidinone (23f).** Dearylation of **12** was carried out as above. The subsequent debenzylation was performed using $BCl_3$. A solution of the benzyl ether (46.5 mg) was treated with boron trichloride (1 M in $CH_2Cl_2$) in $CH_2Cl_2$ at 0 °C for 2 h. Upon completion of the reaction as determined by TLC analysis, a $NaHCO_3$ solution was added and the mixture was stirred for an additional 30 min. Ethanol was added to aid the azeotropical removal of water. The crude product was purified by chromatography by eluting with 5% MeOH/$CH_2Cl_2$ and gave **23f** (18.2 mg, 92% yield). $^1$H NMR ($CD_3OD$): δ 9.01 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 5.12 (d, J = 4.5 Hz, 1H), 5.05 (d, J = 4.5 Hz, 1H). MS (DCI/$NH_3$): m/z 190, 188 (M + $NH_4^+$) (100), 172, 171 (M + $H^+$) (80).

**(3*R*,4*S*)-3-Hydroxy-4-methyl-2-azetidinone (23g)** was prepared as described in the general procedure above from **15**. Hydrogenolysis of the bromine also occurs in this reaction. $^1$H NMR ($CD_3OD$): δ 6.25 (bs, 1H), 4.90 (dd, J = 5.2, 2.4 Hz, 1H), 3.91 (dq, J = 5.3, 5.2 Hz, 1H), 2.29 (s, 1H), 1.32 (d, J = 6.3 Hz, 3H). MS (DCI/$NH_3$): m/z 119 (M + $NH_4^+$) (100), 102 (M + $H^+$) (22).

**(3*R*,4*S*)-3-Hydroxy-4-ethenyl-2-azetidinone (23h).** Dearylation of **13** (i in **23b**) gave 3-(benzyloxy)-4-ethenyl-2-azetidinone, and subsequent debenzylation was performed using $BCl_3$ as for **23f**. The crude product was purified by chromatography by using 5% methanol/$CH_2Cl_2$ and gave **23h** (35 mg, 56%). $^1$H NMR ($CD_3OD$): δ 5.91 (m, 1H), 5.33 (m, 2H), 4.21 (m, 1H), 1.27 (bs, 1H, OH), 4.21 (m, 1H), 1.27 (bs, 1H, OH), 0.89 (b, 1H). MS (DCI/$NH_3$): m/z 131 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-Hydroxy-4-butyl-2-azetidinone (23i)** was prepared as described in the general procedure above from **18**. $^1$H NMR ($CD_3OD$): δ 4.79 (d, J = 5.4 Hz, 1H), 3.63 (ddd, J = 7.5, 6.0, 5.4 Hz, 1H), 1.60 (m, 1H), 1.52 (m, 1H), 1.37 (m, 4H), 0.92 (t, J = 6.1 Hz, 3H). MS (DCI/$NH_3$): m/z 161 (M + $NH_4^+$), (100).

**(3*R*,4*R*)-3-Hydroxy-4-butyl-2-azetidinone (23j)** was prepared as described in the general procedure above from **19**. $^1$H NMR ($CD_3OD$): δ 4.28 (d, J = 1.8 Hz, 1H), 3.37 (td, J = 6.6, 1.8 Hz, 1H), 1.60 (m, 2H), 1.38 (m, 4H), 0.95 (t, J = 6.0 Hz, 3H). MS (DCI/$NH_3$): m/z 161 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-Hydroxy-4-pentyl-2-azetidinone (23k)** was prepared as described in the general procedure above from **20**. $^1$H NMR ($CD_3OD$): δ 4.80 (d, J = 5.4 Hz, 1H), 3.60 (m, 1H), 1.60 (m, 1H), 1.52 (m, 1H), 1.37 (m, 6H), 0.92 (t, J = 6.0 Hz, 3H). MS (DCI/$NH_3$): m/z 175 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-Hydroxy-4-(2-methylpropyl)-2-azetidinone (23l)** was prepared as described in the general procedure above from **21**. $^1$H NMR ($CDCl_3$): δ 6.09 (bs, 1H), 4.93 (m, 1H), 3.84 (dt, J = 8.7, 4.8 Hz, 1H), 3.01 (bd, 1H, OH), 1.42–1.76 (m, 3H), 0.97 (d, J = 6.3 Hz, 6H). MS (DCI/$NH_3$): m/z 161 (M + $NH_4^+$) (100), 144 (M + $H^+$) (30).

**(3*R*,4*S*)-3-Hydroxy-4-cyclohexyl-2-azetidinone (23m)** was prepared from 3-hydroxy-4-phenyl-2-azetidinone via hydrogenation,[12c] mp 175–178 °C. $^1$H NMR ($CDCl_3$): δ 6.20 (bs, 1H), 4.95 (dd, J = 5.0, 2.0 Hz, 1H), 3.48 (dd, J = 9.5, 5.0 Hz, 1H), 3.05 (bs, 1H), 1.86 (m, 1H), 1.55–1.80 (m, 4H), 1.15–1.40 (m, 4H), 0.81–1.02 (m, 2H). MS (DCI/$NH_3$): m/z 187 (M + $NH_4^+$) (100), 170 (M + $H^+$) (40).

**General Procedure for Protection and N-Acylation of the Azetidinones 23a–m.** The azetidinones were treated with excess ethyl vinyl ether and a catalytic amount of pyridinium *p*-tosylate in $CH_2Cl_2$ (30 mL) at 25 °C for 2 h. The reaction was quenched with saturated $NaHCO_3$, and the organic phase was separated, dried, and evaporated to give a crude oil. This residue was treated with either *tert*-butoxycarbonic anhydride or benzoyl chloride (1.2 equiv) along with triethylamine (2.4 equiv) and a catalytic amount of 4-(dimethylamino)pyridine in $CH_2Cl_2$ at 25 °C for 2 h. Following evaporation of the solvent, the crude residue was purified by chromatography using AcOEt–hexanes mixtures to give the product **24**.

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2,2-dimethyl-1,3-dioxol-4-yl)-*N*-Boc-2-azetidinone (24a)** was prepared as described in the general procedure above from **23a**. $^1$H NMR ($CD_3OD$): δ 5.09 (d, J = 6.0 Hz, 0.5H), 5.07 (d, J = 6.0 Hz, 0.5H), 4.9–4.85 (m, 1H), 4.92 (q, J = 4.8 Hz, 0.5H), 4.37–4.3 (m, 1H), 4.3–4.23 (m, 1H), 4.17–4.05 (m, 2H), 3.88–3.48 (m, 2H), 1.51 (s, 9H), 1.4 (s, 3H), 1.35–1.3 (m, 3H), 1.32 (s, 3H), 1.2 (t, J = 7.0 Hz, 3H). MS (DCI/$NH_3$): m/z 377 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-[1-(1-ethoxyethoxy)ethyl]-*N*-Boc-2-azetidinone (24b)** was prepared as described in the general procedure above from **23b**. $^1$H NMR ($CDCl_3$): δ 5.01–4.85 (m, 2H), 4.85–4.75 (m, 1H), 4.37–4 (m, 2H), 3.9–3.78 (m, 0.5H), 3.75–3.45 (m, 3.5H), 1.52 (s, 9H), 1.4–1.25 (m, 9H), 1.25–1.15 (m, 6H). MS (DCI/$NH_3$): m/z 393 (M + $NH_4^+$) (55).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(methoxymethyl)-*N*-benzoyl-2-azetidinone (24c)** was prepared as described in the general procedure above from **23c**. $^1$H NMR ($CDCl_3$): δ 7.96 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 5.11 (d, J = 6.3 Hz, 0.5H), 5.08 (d, J = 6.3 Hz, 0.5H), 4.96 (q, J = 4.8 Hz, 0.5H), 4.92 (q, J = 4.8 Hz, 0.5H), 4.55 (m, 1H), 3.87 (m, 2.5H), 3.73 (m, 0.5H), 3.55 (m, 1H), 3.41 (s, 3H), 1.42 (d, J = 5.7 Hz, 1.5 H), 1.37 (d, J = 5.7 Hz, 1.5 H), 1.23 (t, J = 6.9 Hz, 3H). MS (DCI/$NH_3$): m/z 325 (M + $NH_4^+$) (65), 308 (M + $H^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(phenoxymethyl)-*N*-benzoyl-2-azetidinone (24d)** was prepared as described in the general procedure above from **23d**. $^1$H NMR ($CDCl_3$): δ 8.17 (d, J = 7.6 Hz, 0.5H), 7.96 (m, 1.5 H), 7.7–7.25 (m, 5H), 6.95 (m, 3H), 5.22 (d, J = 6.3 Hz, 0.5H), 5.18 (d, J = 6.3 Hz, 0.5H), 4.95 (p, J = 4.8 Hz, 1H), 4.78 (m, 1H), 4.56–3.8 (m, 2H), 3.93–3.47 (m, 2H), 1.37 (t, J = 5.7 Hz, 3H), 1.23 (q, J = 6.9 Hz, 3H). MS (DCI/$NH_3$): m/z 387 (M + $NH_4^+$) (100), 370 (M + $H^+$) (50).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-benzyl-*N*-Boc-2-azetidinone (24e)** was prepared as described in the general procedure above from **23e**. $^1$H NMR ($CD_3OD$): δ 7.16–7.31 (m, 5H), 5.08 (d, J = 4.8 Hz, 0.5H), 5.04 (d, J = 4.8 Hz, 0.5H), 4.65 (q, J = 5.7 Hz, 0.5H), 4.50 (q, J = 5.7 Hz, 0.5H), 4.48 (m, 1H), 3.66 (m, 1H), 3.36 (m, 1H), 3.23 (dd, J = 14.0, 4.2 Hz, 0.5H), 3.16 (dd, J = 14.0, 4.8 Hz, 0.5H), 3.11 (dd, J = 14.0, 8.4 Hz, 0.5H), 3.00 (dd, J = 14.0, 8.4 Hz, 0.5H), 1.45 (s, 4.5H), 1.41 (s, 4.5 H), 1.26 (d, J = 5.7 Hz, 1.5H), 1.17 (d, J = 5.7 Hz, 1.5H), 1.11 (t, J = 6.6 Hz, 1.5H), 1.05 (t, J = 6.6 Hz, 1.5H). MS (DCI/$NH_3$): m/z 367 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(4-thiazolyl)-*N*-Boc-2-azetidinone (24f)** was prepared as described in the general procedure above from **23f**. $^1$H NMR ($CD_3OD$): δ 9.00 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 5.42 (d, J = 5.4 Hz, 1H), 5.33 (d, J = 5.4 Hz, 1H), 4.68 (q, J = 5.7 Hz, 0.5H), 4.58 (q, J = 5.7 Hz, 0.5H), 3.40–3.60 (m, 2H), 1.39 (s, 4.5H), 1.37 (s, 4.5H), 1.10 (t, J = 6.6 Hz, 3H), 1.06 (d, J = 5.7 Hz, 1.5H), 1.05 (d, J = 5.7 Hz, 1.5 H). MS (DCI/$NH_3$): m/z 360 (M + $NH_4^+$) (10), 343 (M + $H^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-methyl-*N*-Boc-2-azetidinone (24g)** was prepared as described in the general procedure above from **23g**. $^1$H NMR ($CD_3OD$): δ 5.00 (d, J = 5.6

Hz, 1H), 4.80 (q, $J$ = 6.0 Hz, 1H), 4.22 (m, 1H), 3.82–3.47 (m, 2H), 1.50 (s, 9H), 1.34 (d, $J$ = 6.3 Hz, 3H), 1.32 (d, $J$ = 6.0 Hz, 1.5H), 1.29 (d, $J$ = 6.0 Hz, 1.5H), 1.19 (t, $J$ = 7.5 Hz, 3H). MS (DCI/$NH_3$): $m/z$ 291 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-ethenyl-*N*-Boc-2-azetidinone (24h)** was prepared as described in the general procedure above from **23h**. $^1$H NMR ($CDCl_3$): $\delta$ 5.95–5.8 (m, 1H), 5.47–5.39 (m, 2H), 5.04 (d, $J$ = 5.2 Hz, 0.5H), 5.01 (d, $J$ = 5.2 Hz, 0.5H), 4.9 (q, $J$ = 5.2 Hz, 0.5H), 4.82 (q, $J$ = 5.2 Hz, 0.5H), 4.56–3.98 (m, 1H), 3.8 (m, 0.5H), 3.7–3.4 (m, 1.5H), 1.5 (s, 9H), 1.37 (d, $J$ = 5.2 Hz, 1.5H), 1.27 (d, $J$ = 5.2 Hz, 1.5H), 1.2 (t, $J$ = 7.0 Hz, 1.5H), 1.19 (t, $J$ = 7.0 Hz, 1.5H). MS (DCI/$NH_3$): $m/z$ 303 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-butyl-*N*-Boc-2-azetidinone (24i)** was prepared as described in the general procedure above from **23i**. $^1$H NMR ($CDCl_3$): $\delta$ 4.95 (q, $J$ = 4.8 Hz, 0.5H), 4.91 (d, $J$ = 1.5 Hz, 0.5H), 4.89 (d, $J$ = 1.5 Hz, 0.5H), 4.85 (q, $J$ = 4.8 Hz, 0.5H), 4.07 (m, 1H), 3.85–3.45 (m, 2H), 1.81 (m, 2H), 1.53 (s, 9H), 1.37 (m, 7H), 1.22 (t, $J$ = 7.5 Hz, 3H), 0.95 (m, 3H). MS (DCI/$NH_3$): $m/z$ 333 (M + $NH_4^+$) (100).

**(3*R*,4*R*)-3-(1-Ethoxyethoxy)-4-butyl-*N*-Boc-2-Azetidinone (24j)** was prepared as described in the general procedure above from **23j**. $^1$H NMR ($CDCl_3$): $\delta$ 4.95 (q, $J$ = 5.4 Hz, 0.5H), 4.87 (q, $J$ = 5.4 Hz, 0.5 H), 4.51 (d, $J$ = 2.4 Hz, 0.5H), 4.48 (d, $J$ = 2.4 Hz, 0.5H), 3.85–3.45 (m, 2H), 2.10 (m, 2H), 1.51 (s, 9H), 1.37 (m, 7H), 1.21 (t, $J$ = 6.6 Hz, 1.5H), 1.20 (t, $J$ = 6.6 Hz, 1.5H), 0.92 (m, 3H). MS (DCI/$NH_3$): $m/z$ 333 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-pentyl-*N*-Boc-2-azetidinone (24k)** was prepared as described in the general procedure above from **23k**. $^1$H NMR ($CDCl_3$): $\delta$ 4.95 (q, $J$ = 4.8 Hz, 0.5H), 4.91 (d, $J$ = 1.5 Hz, 0.5H), 4.89 (d, $J$ = 1.5 Hz, 0.5H), 4.85 (q, $J$ = 4.8 Hz, 0.5H), 4.07 (m, 1H), 3.67 (m, 2H), 1.79 (m, 2H), 1.53 (s, 9H), 1.37 (m, 9H), 1.22 (t, $J$ = 7.5 Hz, 3H), 0.89 (m, 3H). MS (DCI/$NH_3$): $m/z$ 347 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-methylpropyl)-*N*-Boc-2-azetidinone (24l)** was prepared as described in the general procedure above from **23l**. $^1$H NMR ($CDCl_3$): $\delta$ 5.03 (t, $J$ = 5.2 Hz, 0.5H), 4.90 (q, $J$ = 5.2 Hz, 0.5H), 4.83 (q, $J$ = 5.2 Hz, 0.5H), 4.22 (m, 1H), 3.85–3.45 (m, 2H), 1.77 (m, 1H), 1.68–1.6 (m, 2H), 1.5 (s, 9H), 1.34 (d, $J$ = 5.2 Hz, 1.5H), 1.31 (d, $J$ = 5.2 Hz, 1.5H), 1.19 (t, $J$ = 7.0 Hz, 3H), 0.98 (d, $J$ = 6.6 Hz, 6H). MS (DCI/$NH_3$): $m/z$ 333 (M + $NH_4^+$) (100).

**(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-cyclohexyl-*N*-Boc-2-azetidinone (24m)** was prepared as described in the general procedure above from **23m**. $^1$H NMR ($CDCl_3$): $\delta$ 4.95 (q, $J$ = 5.7 Hz, 0.5H), 4.92 (d, $J$ = 4.5 Hz, 0.5 h), 4.90 (d, $J$ = 4.5 Hz, 0.5H), 4.85 (q, $J$ = 5.7 Hz, 0.5H), 3.92 (m, 1H), 3.71–3.46 (m, 2H), 1.70 (m, 6H), 1.52 (s, 9H), 1.39 (d, $J$ = 5.7 Hz, 1.5H), 1.34 (d, $J$ = 5.7 Hz, 1.5H), 1.31–1.15 (m, 5H) 1.22 (t, $J$ = 7.5 Hz, 3H). MS (DCI/$NH_3$): $m/z$ 359 (M + $NH_4^+$) (100).

**General Coupling Procedure for Synthesis of 9(*R*)-Dihydrotaxol Analogs.** To the stirred solution of the 7-*O*-(triethylsilyl)-9(*R*)-dihydrobaccatin III (**25**) (0.017 mmol) in THF (2 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (1 M in THF, 4 equiv). After 30 min, a solution of azetidinone **24** in THF (1 mL) was added. The mixture was warmed to 0 °C and stirred for an additional 30 min, at which time TLC analysis indicated the completion of the coupling reaction. The mixture was diluted with AcOEt (10 mL) and washed with pH 5 phosphate buffer and saturated NaCl solution. After drying with $MgSO_4$, filtration, and evaporation of the solvent, a yellow oil was obtained. This crude product was dissolved in ethanol (3 mL) and treated with 1% HCl (1.5 mL) at 0 °C for 3 h. The mixture was neutralized with $NaHCO_3$, saturated with solid NaCl, and twice extracted with AcOEt. The combined extracts were dried over $Na_2SO_4$, filtered, and evaporated. The crude product was purified by chromatography. Elution with 5% methanol/$CH_2Cl_2$ or AcOEt–hexanes mixtures gave product **26**.

**26a**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.0 Hz, 2H), 7.63 (t, $J$ = 7.6 Hz, 1H), 7.51 (dd, $J$ = 7.6, 7.0 Hz, 2H), 6.20 (d, $J$ = 10.5 Hz, 1H), 6.08 (bt, $J$ = 8.7 Hz, 1H), 5.78 (d, $J$ = 6.4 Hz, 1H), 4.96 (d, $J$ = 8.7 Hz, 1H), 4.50 (d, $J$ = 10.5 Hz, 1H), 4.42 (d, $J$ = 2.9 Hz, 1H), 4.39 (dd, $J$ = 9.3, 7.6 Hz, 1H), 4.28 (dt, $J$ = 6.4, 5.8 Hz, 1H), 4.22 (d, $J$ = 8.2 Hz, 1H), 4.16 (d, $J$ = 8.2 Hz, 1H), 4.13 (d, $J$ = 5.8, 2.9 Hz, 1H), 4.06 (dd, $J$ = 8.2, 6.4 Hz, 1H), 3.90 (dd, $J$ = 8.2, 6.4 Hz, 1H), 3.07 (d, $J$ = 6.4 Hz, 1H), 2.46 (ddd, $J$ = 15.1, 8.7, 7.6 Hz, 1H), 2.37 (s, 3H), 2.33 (dd, $J$ = 15.1, 8.7 Hz, 1H), 2.31 (dd, $J$ = 15.1, 8.7 Hz, 1H), 2.10 (s, 3H), 1.93 (s, 3H), 1.82 (ddd, $J$ = 15.1, 9.3, 1.7 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.42 (s, 3H), 1.40 (s, 9H), 1.34 (s, 3H), 1.23 (s, 3H).

**26b**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.1 Hz, 2H), 7.63 (t, $J$ = 7.5 Hz, 1H), 7.51 (dd, $J$ = 7.5, 7.1 Hz, 2H), 6.21 (d, $J$ = 10.6 Hz, 1H), 6.06 (bt, $J$ = 9.1 Hz, 1H), 5.82 (d, $J$ = 6.1 Hz, 1H), 4.97 (d, $J$ = 9.1 Hz, 1H), 4.49 (d, $J$ = 10.6 Hz, 1H), 4.49 (d, $J$ = 2.3 Hz, 1H), 4.39 (dd, $J$ = 9.7, 7.7 Hz, 1H), 4.22 (d, $J$ = 8.1 Hz, 1H), 4.16 (d, $J$ = 8.1 Hz, 1H), 3.97 (dq, $J$ = 6.4, 5.3 Hz, 1H), 3.07 (d, $J$ = 6.1 Hz, 1H), 2.85 (d, $J$ = 4.0, 2.3 Hz, 1H), 2.46 (ddd, $J$ = 15.0, 9.1, 7.7 Hz, 1H), 2.37 (s, 3H), 2.34 (d, $J$ = 8.7 Hz, 2H), 2.10 (s, 3H), 1.92 (s, 3H), 1.82 (ddd, $J$ = 15.0, 9.7, 1.6 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.40 (s, 9H), 1.23 (d, $J$ = 6.4 Hz, 3H), 1.22 (s, 3H).

**26b'**: $^1$H NMR ($CD_3OD$) $\delta$ 8.15 (d, $J$ = 7.7 Hz, 2H), 7.63 (t, $J$ = 7.3 Hz, 1H), 7.51 (dd, $J$ = 7.7, 7.3 Hz, 2H), 6.21 (d, $J$ = 10.8 Hz, 1H), 6.05 (dd, $J$ = 9.3, 8.2 Hz, 1H), 5.77 (d, $J$ = 6.1 Hz, 1H), 4.96 (d, $J$ = 8.4 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, 1H), 4.42 (dd, $J$ = 9.7, 7.7 Hz, 1H), 4.75 (d, $J$ = 1.7 Hz, 1H), 4.21 (d, $J$ = 8.2 Hz, 1H), 4.16 (d, $J$ = 8.2 Hz, 1H), 3.83 (dq, $J$ = 9.7, 6.2 Hz, 1H), 3.73 (d, $J$ = 9.7, 1.7 Hz, 1H), 3.07 (d, $J$ = 6.1 Hz, 1H), 2.46 (m, 1H), 2.42 (dd, $J$ = 15.1, 8.2 Hz, 1H), 2.41 (s, 3H), 2.30 (dd, $J$ = 15.1, 9.3 Hz, 1H), 2.10 (s, 3H), 1.95 (s, 3H), 1.80 (m, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.38 (s, 9H), 1.22 (s, 3H), 1.22 (d, $J$ = 6.2 Hz, 3H).

**26c**: $^1$H NMR ($CD_3OD$) $\delta$ 8.13 (d, $J$ = 7.1 Hz, 2H), 7.80 (d, $J$ = 7.1 Hz, 2H), 7.63 (t, $J$ = 7.7 Hz, 1H), 7.52 (dd, $J$ = 7.7, 7.1 Hz, 2H), 7.51 (t, $J$ = 7.1 Hz, 1H), 7.41 (t, $J$ = 7.1 Hz, 2H), 6.21 (d, $J$ = 10.8 Hz, 1H), 6.10 (bt, $J$ = 8.8 Hz, 1H), 5.77 (d, $J$ = 6.0 Hz, 1H), 4.96 (d, $J$ = 8.8 Hz, 1H), 4.85 (m, 1H), 4.61 (d, $J$ = 1.9 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, 1H), 4.38 (dd, $J$ = 9.4, 7.5 Hz, 1H), 4.22 (d, $J$ = 7.7 Hz, 1H), 4.16 (d, $J$ = 7.7 Hz, 1H), 3.70 (dd, $J$ = 9.0, 9.0 Hz, 1H), 3.55 (dd, $J$ = 9.0, 7.0 Hz, 1H), 3.41 (s, 3H), 3.06 (d, $J$ = 6.0 Hz, 1H), 2.45 (m, 1H), 2.41 (s, 3H), 2.41 (d, $J$ = 15.1, 8.8 Hz, 1H), 2.27 (d, $J$ = 15.1, 9.1 Hz, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.83 (ddd, $J$ = 15.1, 9.4, 1.1 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.22 (s, 3H).

**26d**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.1 Hz, 2H), 7.80 (d, $J$ = 7.1 Hz, 2H), 7.63 (t, $J$ = 7.7 Hz, 1H), 7.52 (dd, $J$ = 7.7, 7.1 Hz, 2H), 7.52 (t, $J$ = 7.1 Hz, 1H), 7.44 (dd, $J$ = 7.7, 7.1 Hz, 2H), 7.31 (t, $J$ = 7.1 Hz, 2H), 7.02 (d, $J$ = 7.7 Hz, 2H), 6.98 (t, $J$ = 7.1 Hz, 1H), 6.20 (d, $J$ = 11.0 Hz, 1H), 6.08 (bt, $J$ = 8.8 Hz, 1H), 5.78 (d, $J$ = 5.5 Hz, 1H), 4.97 (m, 1H), 4.95 (d, $J$ = 9.3 Hz, 1H), 4.77 (d, $J$ = 2.9 Hz, 1H), 4.51 (d, $J$ = 11.0 Hz, 1H), 4.38 (dd, $J$ = 9.3, 7.7 Hz, 1H), 4.34 (dd, $J$ = 9.3, 4.6 Hz, 1H), 4.21 (d, $J$ = 8.2 Hz, 1H), 4.17 (d, $J$ = 8.2 Hz, 1H), 4.15 (dd, $J$ = 9.3, 6.0 Hz, 1H), 3.08 (d, $J$ = 5.5 Hz, 1H), 2.45 (m, 1H), 2.41 (s, 3H), 2.30 (dd, $J$ = 15.1, 8.8 Hz, 1H), 2.27 9dd, $J$ = 15.1, 9.9 Hz, 1H), 2.09 (s, 3H), 1.92 (s, 3H), 1.77 (s, 3H), 1.83 (ddd, $J$ = 15.1, 11.0, 1.1 Hz, 1H), 1.65 (s, 3H), 1.22 (s, 3H).

**26e**: $^1$H NMR ($CD_3OD$) $\delta$ 8.12 (d, $J$ = 7.1 Hz, 2H), 7.64 (t, $J$ = 7.1 Hz, 1H), 7.52 (t, $J$ = 7.1 Hz, 2H), 7.32 (m, 4H), 7.23 (t, $J$ = 7.1 Hz, 1H), 6.21 (d, $J$ = 11.0 Hz, 1H), 6.01 (bt, $J$ = 9.3 Hz, 1H), 5.74 (d, $J$ = 6.0 Hz, 1H), 4.96 (d, $J$ = 8.8 Hz, 1H), 4.48 (d, $J$ = 11.0 Hz, 1H), 4.34 (dd, $J$ = 9.3, 7.7 Hz, 1H), 4.21 (d, $J$ = 8.0 Hz, 1H), 4.18 (d, $J$ = 1.9 Hz, 1H), 4.17 (d, $J$ = 8.0 Hz, 1H), 4.13 (dd, $J$ = 6.9, 1.9 Hz, 1H), 3.06 (d, $J$ = 6.0 Hz, 1H), 3.00 (dd, $J$ = 13.2, 7.7 Hz, 1H), 2.85 (dd, $J$ = 13.2, 7.1 Hz, 1H), 2.41 (ddd, $J$ = 14.8, 8.8, 7.7 Hz, 1H), 2.27 (dd, $J$ = 9.3, 2.2 Hz, 2H), 2.09 (s, 3H), 1.90 (s, 3H), 1.89 (s, 3H), 1.74 (s, 3H), 1.83 (dd, $J$ = 15.0, 9.3 Hz, 1H), 1.64 (s, 3H), 1.34 (s, 9H), 1.20 (s, 3H).

**26f**: $^1$H NMR ($CD_3OD$) $\delta$ 8.95 (d, $J$ = 2.0 Hz, 1H), 8.13 (d, $J$ = 7.3 Hz, 2H), 7.62 (t, $J$ = 7.5 Hz, 1H), 7.51 (dd, $J$ = 7.5, 7.3 Hz, 2H), 7.47 (d, $J$ = 2.0 Hz, 1H), 6.22 (d, $J$ = 10.8 Hz, 1H), 6.14 (dd, $J$ = 10.0, 8.4 Hz, 1H), 5.78 (d, $J$ = 5.9 Hz, 1H), 5.42 (bs, 1H), 4.95 (d, $J$ = 9.3 Hz, 1H), 4.94 (bs, 1H), 4.45 (d, $J$ = 10.8 Hz, 1H), 4.40 (dd, $J$ = 9.7, 7.7 Hz, 1H), 4.21 (d, $J$ = 8.1 Hz, 1H), 4.17 (d, $J$ = 8.1 Hz, 1H), 3.05 (d, $J$ = 5.9 Hz, 1H), 2.46 (ddd, $J$ = 14.8, 9.3, 7.7 Hz, 1H), 2.41 (s, 3H), 2.40 (dd, $J$ = 15.0, 8.4 Hz, 1H), 2.33 (dd, $J$ = 15.0, 10.0 Hz, 1H), 2.15 (s, 3H), 1.96 (s, 3H), 1.83 (ddd, $J$ = 15.0, 9.9, 1.5 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.42 (s, 9H), 1.24 (s, 3H).

**26g**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.5 Hz, 2H), 7.63 (t, $J$ = 7.5 Hz, 1H), 7.52 (t, $J$ = 7.5 Hz, 2H), 6.21 (d, $J$ = 10.8 Hz, 1H), 6.07 (t, $J$ = 8.0 Hz, 1H), 5.78 (d, $J$ = 5.8 Hz, 1H), 4.96 (d, $J$ = 8.6 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, 1H), 4.38 (dd, $J$ = 9.4, 7.5 Hz, 1H), 4.21 (d, $J$ = 8.0 Hz, 1H), 4.18 (d, $J$ = 1.9 Hz, 1H), 4.17 (d, $J$ = 8.0 Hz, 1H), 4.13 (d, $J$ = 6.9, 1.9 Hz, 1H), 3.06 (d, $J$ = 5.8 Hz, 1H), 2.46 (ddd, $J$ = 15.0, 8.6, 7.5 Hz, 1H), 2.35 (m, 2H), 2.35 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H), 1.83 (ddd, $J$ = 15.0, 9.4, 1.4 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.38 (s, 9H), 1.25 (d, $J$ = 7.1 Hz, 3H), 1.23 (s, 3H).

**26h**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.1 Hz, 2H), 7.63 (t, $J$ = 7.1 Hz, 1H), 7.52 (t, $J$ = 7.1 Hz, 2H), 6.21 (d, $J$ = 10.8 Hz, 1H), 6.10 (bt, 1H), 5.94 (ddd, $J$ = 17.6, 10.4, 5.5 Hz, 1H), 5.77 (d, $J$ = 6.0 Hz, 1H), 5.28 (d, $J$ = 17.6 Hz, 1H), 5.25 (dd, $J$ = 10.4, 1.7 Hz, 1H), 4.96 (d, $J$ = 8.2 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, 1H), 4.38 (dd, $J$ = 9.9, 7.7 Hz, 1H), 4.37 (d, $J$ = 2.2 Hz, 1H), 4.22 (d, $J$ = 8.2 Hz, 1H), 4.16 (d, $J$ = 8.2 Hz, 1H), 4.13 (b, 1H), 3.07 (d, $J$ = 6.0 Hz, 1H), 2.46 (ddd, $J$ = 14.8, 8.2, 7.7 Hz, 1H), 2.35 (s, 3H), 2.34 (m, 2H), 2.10 (s, 3H), 1.94 (s, 3H), 1.83 (ddd, $J$ = 14.8, 9.9, 1.7 Hz, 1H), 1.83 (ddd, $J$ = 14.8, 9.9, 1.7 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.40 (s, 9H), 1.23 (s, 3H).

**26i**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.1 Hz, 2H), 7.64 (t, $J$ = 7.1 Hz, 1H), 7.52 (t, $J$ = 7.1 Hz, 2H), 6.21 (d, $J$ = 11.0 Hz, 1H), 6.07 (bt, $J$ = 8.9 Hz, 1H), 5.77 (d, $J$ = 6.0 Hz, 1H), 4.95 (d, $J$ = 8.8 Hz, 1H), 4.50 (d, $J$ = 11.0 Hz, 1H), 4.38 (dd, $J$ = 9.9, 7.7 Hz, 1H), 4.24 (d, $J$ = 1.7 Hz, 1H), 4.22 (d, $J$ = 8.2 Hz, 1H), 4.16 (d, $J$ = 8.2 Hz, 1H), 3.97 (m, 1H), 3.06 (d, $J$ = 6.0 Hz, 1H), 2.46 (ddd, $J$ = 14.8, 8.8, 7.7 Hz, 1H), 2.35 (s, 3H), 2.35 (m, 2H), 2.09 (s, 3H), 1.93 (d, $J$ = 1.1 Hz, 3H), 1.83 (ddd, $J$ = 14.8, 9.9, 1.1 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.58 (m, 2H), 1.38 (s, 9H), 1.22−1.45 (m, 4H), 1.22 (s, 3H), 0.94 (t, $J$ = 6.0 Hz, 3H).

**26j**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.1 Hz, 2H), 7.64 (t, $J$ = 7.1 Hz, 1H), 7.52 (t, $J$ = 7.1 Hz, 2H), 6.21 (d, $J$ = 11.0 Hz, 1H), 6.16 (bt, $J$ = 8.9 Hz, 1H), 5.78 (d, $J$ = 6.0 Hz, 1H), 4.95 (d, $J$ = 8.8 Hz, 1H), 4.50 (d, $J$ = 11.0 Hz, 1H), 4.39 (dd, $J$ = 9.5, 7.7 Hz, 1H), 4.26 (d, $J$ = 4.8 Hz, 1H), 4.23 (d, $J$ = 8.2 Hz, 1H), 4.17 (d, $J$ = 8.2 Hz, 1H), 3.97 (ddd, $J$ = 9.6, 4.8, 4.8 Hz, 1H), 3.09 (d, $J$ = 6.0 Hz, 1H), 2.46 (ddd, $J$ = 14.8, 8.8, 7.7 Hz, 1H), 2.35 (m, 1H), 2.35 (s, 3H), 2.21 (m, 1H), 2.09 (s, 3H), 1.96 (d, $J$ = 1.1 Hz, 3H), 1.83 (ddd, $J$ = 14.8, 9.5, 1.1 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.55 (m, 2H), 1.44 (s, 9H), 1.22−1.45 (m, 4H), 1.22 (s, 3H), 0.94 (t, $J$ = 6.0 Hz, 3H).

**26k**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.1 Hz, 2H), 7.64 (t, $J$ = 7.7 Hz, 1H), 7.52 (dd, $J$ = 7.7, 7.1 Hz, 2H), 6.22 (d, $J$ = 11.0 Hz, 1H), 6.06 (bt, $J$ = 8.9 Hz, 1H), 5.77 (d, $J$ = 5.5 Hz, 1H), 4.95 (d, $J$ = 8.8 Hz, 1H), 4.50 (d, $J$ = 11.0 Hz, 1H), 4.38 (dd, $J$ = 9.3, 7.7 Hz, 1H), 4.24 (d, $J$ = 2.2 Hz, 1H), 4.22 (d, $J$ = 8.2 Hz, 1H), 4.16 (d, $J$ = 8.2 Hz, 1H), 3.97 (m, 1H), 3.06 (d, $J$ = 5.5 Hz, 1H), 2.46 (ddd, $J$ = 14.8, 8.8, 7.7 Hz, 1H), 2.35 (m, 2H), 2.35 (s, 3H), 2.09 (s, 3H), 1.93 (d, $J$ = 1.1 Hz, 3H), 1.83 (ddd, $J$ = 14.8, 9.3, 1.1 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.55 (m, 2H), 1.38 (s, 9H), 1.22−1.45 (m, 6H), 1.22 (s, 3H), 0.93 (t, $J$ = 6.6 Hz, 3H).

**26l**: $^1$H NMR ($CD_3OD$) $\delta$ 8.13 (d, $J$ = 7.1 Hz, 2H), 7.63 (t, $J$ = 7.7 Hz, 1H), 7.52 (dd, $J$ = 7.7, 7.1 Hz, 2H), 6.21 (d, $J$ = 10.8 Hz, 1H), 6.07 (bt, $J$ = 8.8 Hz, 1H), 5.77 (d, $J$ = 6.0 Hz, 1H), 4.96 (d, $J$ = 8.8 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, 1H), 4.38 (dd, $J$ = 9.4, 7.5 Hz, 1H), 4.22 (d, $J$ = 7.7 Hz, 1H), 4.18 (d, $J$ = 1.9 Hz, 1H), 4.16 (d, $J$ = 7.7 Hz, 1H), 4.13 (dd, $J$ = 6.9, 1.9 Hz, 1H), 3.06 (d, $J$ = 6.0 Hz, 1H), 2.46 (ddd, $J$ = 15.1, 8.8, 7.7 Hz, 1H), 2.36 (d, $J$ = 8.8 Hz, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H), 1.83 (ddd, $J$ = 15.1, 9.4, 1.1 Hz, 1H), 1.77 (s, 3H), 1.72 (m, 1H), 1.66 (s, 3H), 1.42 (m, 1H), 1.40 (s, 9H), 1.23 (m, 2H), 1.22 (s, 3H), 0.95 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR ($CD_3OD$) $\delta$ 175.0, 172.1, 171.4, 167.6, 158.0, 158.0, 140.2, 136.7, 134.5, 131.3, 131.2, 129.5, 85.6, 83.4, 80.3, 78.7, 78.2, 77.6, 75.0, 74.9, 74.8, 74.6, 74.4, 73.1, 61.5, 52.9, 52.8, 48.0, 45.8, 44.6, 41.8, 38.6, 36.4, 28.8, 28.7, 28.6, 26.0, 23.9, 23.8, 23.4, 22.2, 21.2, 14.9, 14.4, 13.2.

**26m**: $^1$H NMR ($CD_3OD$) $\delta$ 8.13 (d, $J$ = 7.7 Hz, 2H), 7.63 (t, $J$ = 7.7 Hz, 1H), 7.52 (t, $J$ = 7.7, Hz, 2h), 6.21 (d, $J$ = 11.0 Hz, 1H), 6.07 (bt, $J$ = 8.2 Hz, 1H), 5.78 (d, $J$ = 5.5 Hz, 1H), 4.96 (d, $J$ = 8.8 Hz, 1H), 4.50 (d, $J$ = 11.0 Hz, 1H), 4.49 (d, $J$ = 1.7 Hz, 1H), 4.38 (dd, $J$ = 9.3, 7.7 Hz, 1H), 4.22 (d, $J$ = 7.7 Hz, 1H), 4.15 (d, $J$ = 7.7 Hz, 1H), 4.13 (d, $J$ = 9.9, 1.7 Hz, 1H), 3.06 (d, $J$ = 5.5 Hz, 1H), 2.45 (ddd, $J$ = 15.1, 8.8, 7.7 Hz, 1H), 2.37 (s, 3H), 2.32 (dd, $J$ = 15.2, 8.2 Hz, 2H), 2.09 (s, 3H), 1.93 (s, 3H), 1.90 (m, 1H), 1.83 (ddd, $J$ = 15.1, 9.3, 1.1 Hz, 1H), 1.76 (s, 3H), 1.66 (s, 3H), 1.65 (m, 4H), 1.37 (s, 9H), 1.23 (m, 4H), 1.22 (s, 3H), 0.95 (m, 3H); $^{13}$C NMR ($CD_3COD$) $\delta$ 175.8, 172.1, 171.6, 167.6, 158.2, 140.2, 136.7, 134.5, 131.3, 129.6, 85.6, 83.3, 80.3, 78.8, 78.2, 77.6, 75.0, 74.8, 74.6, 75.0, 74.8, 74.6, 73.4, 71.4, 59.3, 48.0, 45.8, 44.6, 40.1, 38.6, 36.4, 31.3, 31.3, 38.7, 27.4, 27.3, 23.9, 23.6, 21.2, 14.9, 13.2.

**27**: $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, $J$ = 7.0 Hz, 2H), 7.63 (t, $J$ = 7.6 Hz, 1H), 7.51 (dd, $J$ = 7.6, 7.0 Hz, 2H), 6.21 (d, $J$ = 11.1 Hz, 1H), 6.08 (bt, $J$ = 8.7 Hz, 1H), 5.78 (d, $J$ = 5.8 Hz, 1H), 4.95 (d, $J$ = 8.7 Hz, 1H), 4.54 (d, $J$ = 2.3 Hz, 1H), 4.50 (d, $J$ = 11.1 Hz, 1H), 4.39 (dd, $J$ = 9.3, 7.6 Hz, 1H), 4.21 (d, $J$ = 8.2 Hz, 1H), 4.16 (d, $J$ = 8.2 Hz, 1H), 4.14 (dd, $J$ = 4.0, 2.3 Hz, 1H), 3.85 (dt, $J$ = 5.8, 4.1 Hz, 1H), 3.58 (d, $J$ = 5.8 Hz, 2H), 3.07 (d, $J$ = 5.8 Hz, 1H), 2.46 (ddd, $J$ = 15.1, 8.7, 7.6 Hz, 1H), 2.37 (s, 3H), 2.33 (dd, $J$ = 15.1, 8.7 Hz, 1H), 2.31 (dd, $J$ = 15.1, 8.7 Hz, 1H), 2.10 (s, 3H), 1.80 (ddd, $J$ = 15.1, 9.3, 1.7 Hz, 1H), 1.95 (s, 3H), 1.77 9s, 3H), 1.66 (s, 3H), 1.41 (s, 9H), 1.23 (s, 3H).

**28.** Compound **26h** (6.0 mg, 7.5 $\mu$mol) was hydrogenated over Pd/C with a hydrogen balloon in methanol (1 mL). The mixture was filtered through a Celite pad, washed with methanol. The filtrate was evaporated, and the residue was purified by chromatography to give **28** (4.8 mg, 80%). $^1$H NMR ($CD_3OD$): $\delta$ 8.14 (d, $J$ = 7.7 Hz, 2H), 7.63 (t, $J$ = 7.7 Hz, 1H), 7.52 (t, $J$ = 7.7 Hz, 2H), 6.21 (d, $J$ = 11.0 Hz, 1H), 6.10 (bt, $J$ = 10.0 Hz, 1H), 5.78 (d, $J$ = 6.0 Hz, 1H), 4.95 (d, $J$ = 8.6 Hz, 1H), 4.50 (d, $J$ = 11.0 Hz, 1H), 4.38 (dd, $J$ = 9.9, 7.7 Hz, 1H), 4.27 (d, $J$ = 1.6 Hz, 1H), 4.22 (d, $J$ = 8.0 Hz, 1H), 4.16 (d, $J$ = 8.0 Hz, 1H), 3.88 (d, $J$ = 6.6, 1.6 Hz, 1H), 3.06 (d, $J$ = 6.0 Hz, 1H), 2.46 (ddd, $J$ = 15.0, 8.3, 7.7 Hz, 1H), 2.35 (s, 3H), 2.29−2.35 (m, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.83 (ddd, $J$ = 15.0, 9.9, 1.1 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.62−1.66 (m, 2H), 1.38 (s, 9H), 1.22−1.30 (m, 1H), 1.23 (s, 3H), 0.98 (t, $J$ = 7.7 Hz, 3H).

**Acknowledgment.** We thank Dr. G. Gunawardana for supplying the 13-acetyl-9(*R*)-dihydrobaccatin III used in this work. We are grateful to Dr. Jeff Alder and Ms. Darlene Balli in the General Microbiology Department for performing the *in vivo* study and cytotoxicity measurement, respectively.

## References

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. Plant Antitumor Agent. VI. The Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor Agent from *Taxus Brevifolia*. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.

(2) For a recent review on the preclinical and clinical development of taxol and taxotere, see Rothenberg, M. Taxol, Taxotere, and Other New Taxanes. *Curr. Opin. Invest. Drugs* **1993**, *2*, 1269−1277.

(3) For recent reviews on the chemistry and structure−activity relationships of taxol, see (a) Swindell, C. S. Taxane Diterpene Synthesis Strategies. A Review. *Org. Prep. Proced. Int.* **1991**, *23*, 465−543. (b) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. The Texane Diterpenoids. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1−188. (c) Kingston, D. G. I. The Chemistry of Taxol. *Pharmacol. Ther.* **1991**, *52*, 1−34. (d) Guenard, D.; Gueritte-Voegelein, F.; Potier, P. Taxol and Taxotere: Discovery, Chemistry, and Structure-Activity Relationships. *Acc. Chem. Res.* **1993**, *26*, 160−167. (e) Suffness, M. Taxol: From Discovery to Therapeutic Use. In *Annual Report in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1993; Vol. 28, Chapter 32, pp 305−314. (f) Georg, G. I.; Ali, S. M.; Zygmunt, J.; Jayasinghe, L. R. Taxol: A Novel Antitumor Agent. *Curr. Opin. Ther. Pat.* **1994**, *4*, 109−112. (g) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. Chemistry and Biology of Taxol. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44.

(4) Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M.-T.; Mangatal, L.; Potier, P. Relationship between the Structure of Taxol Analogues and Their Antimitotic Activity. *J. Med. Chem.* **1991**, *34*, 992−998.

(5) Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. Biologically Active Taxol Analogues with Deleted A-Ring Side Chain Substituents and Variable C-2′ Configurations. *J. Med. Chem.* **1991**, *34*, 1176−1184.

(6) (a) Williams, H. J.; Scott, A. I.; Dieden, R. A.; Swindell, C. S.; Chirlan, L. E.; Francl, M. M.; Heerding, J. M.; Krauss, N. E. NMR and Molecular Modeling Study of the Conformations of Taxol and its Side Chain Methylester in Aqueous and Non-Aqueous Solution. *Tetrahedron* **1993**, *49*, 6645–6560. (b) Dubois, J.; Guénard, D.; Guéritte-Voegelein, F.; Guedira, N.; Potier, P.; Gillet, B.; Beloeil, J.-C. Conformation of Taxotere® and Analogues Determined By NMR Spectroscopy and Molecular Modeling Study. *Tetrahedron* **1993**, *49*, 6533–6544. (c) Vander Velde, D. G.; Georg, G.; Grunewald, G. L.; Gunn, C. W.; Mitscher, L. A. "Hydrophobic *Collapse*" of Taxol and Taxotere Solution Conformations in Mixtures of Water and Organic Solvent. *J. Am. Chem. Soc.* **1993**, *115*, 11650–11651.

(7) (a) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H.; Himes, R. H. Schotten-Baumann Acylation of N-Debenzoyltaxol; An Efficient Route to N-Acyl Taxol Analogues and Their Biological Evaluation. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335–338. (b) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R. Semisynthesis and Biological Activity of Taxol Analogues: Baccatin III 13-(N-benzoyl-(2'*R*,3'*S*)-3'-(p-tolyl)isoserinate), Baccatin III 13-(N-(p-toluoyl)-(2'*R*,3'*S*)-3'-phenylisoserinate), Baccatin III 13-(N-benzoyl-(2'*R*,3'*S*)-3'-(p-trifluoromethylphenyl)isoserinate), and Baccatin III 13-(N-(p-trifluoromethylbenzoyl)-(2'*R*,3'*S*)-3'-phenylisoserinate). *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1751–1754. (c) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. Synthesis of Biologically Active Taxol Analogues with Modified Phenylisoserine Side Chains. *J. Med. Chem.* **1992**, *35*, 4230–4237. (d) Bourzat, J. D.; Commercon, A. A. Practical Access to Chiral Phenylisoserinates, Preparation of Taxotere® Analogs. *Tetrahedron Lett.* **1993**, *34*, 6049–6052.

(8) (a) Gunawardana, G.; Premachandran, U.; Burres, N. S.; Whitten, D.; Henry, R.; Spanton, S.; McAlpine, J. B. Isolation of 9-Dihydro-13-acetylbaccatin III from *Taxus canadensis*. *J. Nat. Prod.* **1992**, *55*, 1686–1689. (b) Zamir, L. O.; Nedea, M. E.; Belair, S.; Sauriol, F.; Mamer, O.; Jacqmain, E.; Jean, F. I.; Carneau, F. X. Taxanes Isolated from *Taxus canadensis*. *Tetrahedron Lett.* **1992**, *33*, 5173–5176. (c) Zhang, S.; Chen, W.-M.; Chen, Y.-H. Isolation and Identification of Two New Taxane Diterpenes from *Taxus chinensis* (Pilger) Rehd. *Yaoxue*, Xuebao **1992**, *27*, 268–272.

(9) Klein, L. L. Synthesis of 9-Dihydrotaxol: A Novel Bioactive Taxane. *Tetrahedron Lett.* **1993**, *34*, 2047–2050.

(10) Maring, C. J.; Grampovnik, D. J.; Klein, L. L.; Yeung, C. M.; Li, L.; Thomas, S. A.; Plattner, J. J. C-3'-N-Acyl Analogs of 9(*R*)-Dihydrotaxol: Synthesis and Structure-Activity Relationships. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1429–1432.

(11) Preliminary disclosure: Li, L.; Thomas, S. A.; Klein, L. L.; Yeung, C. M.; Maring, C. J.; Grampovnik, D. J.; Plattner, J. J. Structure-Activity Relationship Study at the C-3' Position of 9-(*R*)-Dihydrotaxol. 207th American Chemical Society National Meeting, San Diego, CA, March 13–17, 1994; Abstracts MEDI 103.

(12) (a) Holton, R. A. Method for the Preparation of Taxol. EP 0400971A2, 1990; *Chem. Abstr.* **1991**, *114*, 164568q. (b) Ojima, I.; Zucco, M.; Duclos, O.; Kuduk, S. D.; Sun, C. M.; Park, Y. H. N-Acyl-3-Hydroxy-β-Lactams as Key Intermediates for Taxotere for its Analogs. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2479–2482. (c) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. New and Efficient Approaches to the Semisynthesis of Taxol and its C-13 Side Chain Analogs by Means of β-Lactam Synthon Method. *Tetrahedron* **1992**, *48*, 6985–7012. (d) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. An Efficient Semisynthesis of Taxol from (3*R*,4*S*)-*N*-Benzoyl-3-[t-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone and 7-(Triethylsilyl)baccatin III. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467–2470.

(13) (a) Hubschwerlen, C.; Schmidt, G. An Enantioselective β-Lactam Synthesis Starting from L-(*S*)-Glyceraldehyde Acetonide. Helv. *Chim. Acta* **1983**, *66*, 2206–2209. (b) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. Studies on Lactams. 81. Enantiospecific Synthesis and Absolute Configuration of Substituted β-Lactams from D-Glyceraldehyde Acetonide. *J. Org. Chem.* **1988**, *53*, 4227–4236. (c) For a review, see Georg, G. I.; Ravikumar, V. T. *Stereocontrolled* Ketene-Imine Cycloaddition Reactions. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; pp 295–368.

(14) Tsuda, Y.; Hanajima, M.; Matsuhiru, N.; Okuno, Y.; Kanemitsu, K. Regioselective Monooxidation of Non-protected Carbohydrates by Brominolysis of the Tin Intermediates. *Chem. Pharm. Bull.* **1989**, *37*, 2344–2350 and references cited therein.

(15) Kosuki, H.; Kadota, I.; Ochi, M. A Novel Carbon-Carbon Bond-Forming Reaction of Triflates with Copper-Catalyzed Grignard Reagents. A New Concise and Enantiospecific Synthesis of (+)-exo-Brevicomin, (5*R*,6*S*)-(−)-6-Acetoxy-5-hexadecanolide, and L-Factor. *J. Org. Chem.* **1990**, *55*, 4417–4422.

(16) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. Oxidative N-Dearylation of 2-Azetidinones. *p*-Anisidine as a Source of Azetidinone Nitrogen. *J. Org. Chem.* **1982**, *47*, 2765–2768.

(17) Klein, L. L. *et al.*, Abbott Laboratories. Unpublished results.

(18) All new 9(*R*)-dihydrotaxol analogs were fully characterized by NMR, MS, and HRMS and in agreement with their structures. The purity of the final compounds was verified by HPLC analysis.

(19) $IC_{50}$ is described as the concentration of agent required to inhibit cell proliferation to 50% vs untreated cells (incubated at 37 °C for 72 h) measured by colorimetry as in Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. Immunol. Methods* **1983**, *65*, 55–63.

(20) Tubulin assembly data were provided by Professor Richard Himes at the University of Kansas. $ED_{50}$ is the concentration of agent which reduces the supernatent protein concentration (tubulin, 1 mg/mL) by 50% in 15 min at 37 °C. For details of the assay, see ref 7c.

(21) The compounds were dosed once every 4 days for a total of three doses (q4dX3) by the IP route on days 1, 5, and 9 postinoculation. Dr. Jeff Alder, D47T, Abbott Laboratories. Unpublished results.