

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

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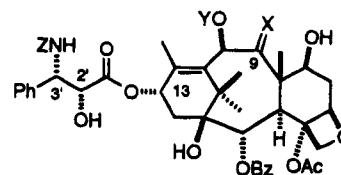
Taxol (1) is considered a most exciting new drug in cancer chemotherapy. The promising antitumor activity of 9(*R*)-dihydrotaxol (3) encouraged us to further explore the structure–activity relationship of this new member of the taxane family. Studies indicated that the C-13 side chain of taxol is indispensable 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 activity¹ 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*)-dihydro-taxotere (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

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







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

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 NaIO₄ and reduction with NaBH₄. Compounds 8–10 were versatile intermediates for further manipulations as shown in Scheme 1. Selective oxidation of diol 8 with *n*-Bu₂SnO and Br₂¹⁴ 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-

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

no.	compound		yield (%)	MS (FAB) <i>m/z</i>	HRMS		HPLC ^a %/ <i>t_R</i>
	R	Z			calculated	measured	
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		Boc	23	924 [M + K ⁺]	C ₄₁ H ₅₇ NO ₁₆ Na 842.3575	842.3574	82/5.1
26b'		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 ₂ O 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 <i>R</i>)-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 CH₃CN: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

compd	tumor cell cytotoxicity IC ₅₀ (ng/mL) ^a				tubulin ^b ED ₅₀ /ED _{50taxol}
	A549	HT-29	B16F10	P388	
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. IC₅₀ 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 ED₅₀ is the concentration of agent which reduces the supernatant protein concentration (tubulin, 1 mg/mL) by 50% in 15 min at 37 °C.²⁰

million (ppm) downfield from an internal 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 F₂₅₄, with a thickness of 0.25 or 0.50 mm. Methylene chloride (CH₂Cl₂) 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. (3R,4S)-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 CH₂Cl₂ (100 mL), and to this mixture was added a solution of Br₂ in CH₂Cl₂ 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 (CHCl₃) to wash out the tin species followed by further elution with CHCl₃/ethyl acetate (AcOEt) which gave the desired hydroxy ketone. This product was further purified by crystallization from CH₂Cl₂/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 CH₂Cl₂ (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 CH₂Cl₂ (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%). ¹H NMR (CDCl₃): δ 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/NH₃): *m/z* 421, 423 (M + NH₄⁺) (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/CH₂Cl₂ 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. ¹H NMR (CDCl₃): δ 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/NH₃): *m/z* 384 (M + NH₄⁺) (80), 367 (M + H⁺) (100). HRMS-FAB: calcd for C₂₀H₁₉N₂O₃S, 367.116; measured, 367.1112.

(3R,4S)-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/H₂O 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/H₂O to give **13** (5.71 g, 94%), mp 104–105 °C. ¹H NMR (CDCl₃): δ 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/NH₃): *m/z* 327 (M + NH₄⁺) (100), 310 (M + H⁺) (40).

(3R,4S)-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 NaIO₄ (8.93 g, 41.8 mmol) in H₂O (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 MgSO₄, 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 NaBH₄ 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 MgSO₄, filtrated, and evaporated. The crude product was purified by chromatography to give alcohol **10** (3.3 g, 99%). ¹H NMR (CDCl₃): δ 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/NH₃): *m/z* 331 (M + NH₄⁺) (100), 314 (M + H⁺) (40).

(3R,4S)-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 CH₂Cl₂ 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 Et₂O/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%). ¹H NMR (CDCl₃): δ 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/NH₃): *m/z* 393 (M + NH₄⁺) (100), 376 (M + H⁺) (35).

(3R,4S)-1-(4-Methoxyphenyl)-3-(benzyloxy)-4-(methoxymethyl)-2-azetidinone (16). Alcohol **10** (403 mg, 1.29 mmol), Ag₂O (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%). ¹H

NMR (CDCl₃): 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/NH₃): m/z 345 (M + NH₄⁺) (100), 328 (M + H⁺) (85).

(3R,4S)-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%). ¹H NMR (CDCl₃): 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/NH₃): m/z 407 (M + NH₄⁺) (100), 390 (M + H⁺) (30).

(3R,4S)-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 CH₂Cl₂ (20 mL) at -20 °C to give, following chromatography with hexanes/AcOEt (5:1), the product triflate (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% NaHSO₄. After chromatographic separation, the desired product **18** was obtained (275 mg, 41%) along with **10** (220 mg, 37%) and **15** (80 mg, 12%). **18**: ¹H NMR (CDCl₃): 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/NH₃): m/z 357 (M + NH₄⁺) (100), 340 (M + H⁺) (90).

(3R,4S)-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 MgSO₄, 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. ¹H NMR (CDCl₃): 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/NH₃): m/z 355 (M + NH₄⁺) (100), 338 (M + H⁺) (75).

(3R,4R)-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 4R isomer **19** in 9% yield. ¹H NMR (CDCl₃): 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/NH₃): m/z 355 (M + NH₄⁺) (75), 338 (M + H⁺) (100).

(3R,4S)-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:** ¹H NMR (CDCl₃): 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:** ¹H NMR (CDCl₃): 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/NH₃): m/z 369 (M + NH₄⁺) (100), 352 (M + H⁺) (80).

(3R,4S)-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, NaHCO₃, and saturated NaCl solution. A mixture of diastereomers **22** (0.91 g, *ca.* 8:1) was obtained after chromatography. ¹H NMR (CDCl₃): 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/NH₃): m/z 449 (M + NH₄⁺) (100), 432 (M + H⁺) (10).

General Procedures for Preparation of 3-Hydroxy-2-azetidinones. i. **Dearylation.**¹⁶ Ceric ammonium nitrate (2.2 equiv) in H₂O (30 mL) was added to a stirred solution of 1-(methoxyphenyl)-3-(benzyloxy)-2-azetidinone (7.09 mmol) in acetonitrile/H₂O (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 NaHCO₃, H₂O, and saturated NaCl solutions sequentially and dried over MgSO₄, 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**.

(3R,4S)-3-Hydroxy-4-(2,2-dimethyl-1,3-dioxol-4-yl)-2-azetidinone (23a) was prepared as above from **7**, mp 143-145 °C. ¹H NMR (CDCl₃): 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/NH₃): m/z 205 (M + NH₄⁺) (100), 188 (M + H⁺) (25).

(3R,4S)-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 CH₂Cl₂, washed with saturated NaHSO₃, NaHCO₃, water, and brine, and finally evaporated. The crude product was purified by chromatography to give the isomers **14** (0.552 g, 69%). **14a:** ¹H NMR (CDCl₃): 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:** ¹H NMR (CDCl₃): 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/NH₃): m/z 237 (M + NH₄⁺) (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.

¹H NMR (CD₃OD): 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/NH₃): m/z 149 (M + NH₄⁺) (100), 132 (M + H⁺) (10).

(3R,4S)-3-Hydroxy-4-(methoxymethyl)-2-azetidinone (23c) was prepared as described in the general procedure above from 16. ¹H NMR (CDCl₃): 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/NH₃): m/z 149 (M + NH₄⁺) (100).

(3R,4S)-3-Hydroxy-4-(phenoxyethyl)-2-azetidinone (23d) was prepared as described in the general procedure above from 17. ¹H NMR (CDCl₃): 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/NH₃): m/z 211 (M + NH₄⁺) (15).

(3R,4S)-3-Hydroxy-4-benzyl-2-azetidinone (23e) was prepared as described in the general procedure above from 22. ¹H NMR (CDCl₃): 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/NH₃): m/z 195 (M + NH₄⁺) (100), 178 (M + H⁺) (6).

(3R,4S)-3-Hydroxy-4-(4-thiazolyl)-2-azetidinone (23f). Dearylation of 12 was carried out as above. The subsequent debenzoylation was performed using BCl₃. A solution of the benzyl ether (46.5 mg) was treated with boron trichloride (1 M in CH₂Cl₂) in CH₂Cl₂ at 0 °C for 2 h. Upon completion of the reaction as determined by TLC analysis, a NaHCO₃ solution was added and the mixture was stirred for an additional 30 min. Ethanol was added to aid the azeotropic removal of water. The crude product was purified by chromatography by eluting with 5% MeOH/CH₂Cl₂ and gave 23f (18.2 mg, 92% yield). ¹H NMR (CD₃OD): 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/NH₃): m/z 190, 188 (M + NH₄⁺) (100), 172, 171 (M + H⁺) (80).

(3R,4S)-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. ¹H NMR (CD₃OD): 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/NH₃): m/z 119 (M + NH₄⁺) (100), 102 (M + H⁺) (22).

(3R,4S)-3-Hydroxy-4-ethenyl-2-azetidinone (23h). Dearylation of 13 (i in 23b) gave 3-(benzyloxy)-4-ethenyl-2-azetidinone, and subsequent debenzoylation was performed using BCl₃ as for 23f. The crude product was purified by chromatography by using 5% methanol/CH₂Cl₂ and gave 23h (35 mg, 56%). ¹H NMR (CD₃OD): 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/NH₃): m/z 131 (M + NH₄⁺) (100).

(3R,4S)-3-Hydroxy-4-butyl-2-azetidinone (23i) was prepared as described in the general procedure above from 18. ¹H NMR (CD₃OD): 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/NH₃): m/z 161 (M + NH₄⁺) (100).

(3R,4R)-3-Hydroxy-4-butyl-2-azetidinone (23j) was prepared as described in the general procedure above from 19. ¹H NMR (CD₃OD): 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/NH₃): m/z 161 (M + NH₄⁺) (100).

(3R,4S)-3-Hydroxy-4-pentyl-2-azetidinone (23k) was prepared as described in the general procedure above from 20. ¹H NMR (CD₃OD): 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/NH₃): m/z 175 (M + NH₄⁺) (100).

(3R,4S)-3-Hydroxy-4-(2-methylpropyl)-2-azetidinone (23l) was prepared as described in the general procedure above from 21. ¹H NMR (CDCl₃): 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/NH₃): m/z 161 (M + NH₄⁺) (100), 144 (M + H⁺) (30).

(3R,4S)-3-Hydroxy-4-cyclohexyl-2-azetidinone (23m) was prepared from 3-hydroxy-4-phenyl-2-azetidinone via hydrogenation,^{12c} mp 175–178 °C. ¹H NMR (CDCl₃): 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/NH₃): m/z 187 (M + NH₄⁺) (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 CH₂Cl₂ (30 mL) at 25 °C for 2 h. The reaction was quenched with saturated NaHCO₃, and the organic phase was separated, dried, and evaporated to give a crude oil. This residue was treated with either *tert*-butoxycarbonyl anhydride or benzoyl chloride (1.2 equiv) along with triethylamine (2.4 equiv) and a catalytic amount of 4-(dimethylamino)pyridine in CH₂Cl₂ 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.

(3R,4S)-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. ¹H NMR (CD₃OD): 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/NH₃): m/z 377 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-[1-(1-ethoxyethoxy)ethyl]-N-Boc-2-azetidinone (24b) was prepared as described in the general procedure above from 23b. ¹H NMR (CDCl₃): 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/NH₃): m/z 393 (M + NH₄⁺) (55).

(3R,4S)-3-(1-Ethoxyethoxy)-4-(methoxymethyl)-N-benzoyl-2-azetidinone (24c) was prepared as described in the general procedure above from 23c. ¹H NMR (CDCl₃): 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/NH₃): m/z 325 (M + NH₄⁺) (65), 308 (M + H⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-(phenoxyethyl)-N-benzoyl-2-azetidinone (24d) was prepared as described in the general procedure above from 23d. ¹H NMR (CDCl₃): 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/NH₃): m/z 387 (M + NH₄⁺) (100), 370 (M + H⁺) (50).

(3R,4S)-3-(1-Ethoxyethoxy)-4-benzyl-N-Boc-2-azetidinone (24e) was prepared as described in the general procedure above from 23e. ¹H NMR (CD₃OD): 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/NH₃): m/z 367 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-(4-thiazolyl)-N-Boc-2-azetidinone (24f) was prepared as described in the general procedure above from 23f. ¹H NMR (CD₃OD): 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/NH₃): m/z 360 (M + NH₄⁺) (10), 343 (M + H⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-methyl-N-Boc-2-azetidinone (24g) was prepared as described in the general procedure above from 23g. ¹H NMR (CD₃OD): 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/NH₃): m/z 291 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-ethenyl-N-Boc-2-azetidinone (24h) was prepared as described in the general procedure above from **23h**. ¹H NMR (CDCl₃): δ 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/NH₃): m/z 303 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-butyl-N-Boc-2-azetidinone (24i) was prepared as described in the general procedure above from **23i**. ¹H NMR (CDCl₃): δ 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/NH₃): m/z 333 (M + NH₄⁺) (100).

(3R,4R)-3-(1-Ethoxyethoxy)-4-butyl-N-Boc-2-Azetidinone (24j) was prepared as described in the general procedure above from **23j**. ¹H NMR (CDCl₃): δ 4.95 (q, $J = 5.4$ Hz, 0.5H), 4.87 (q, $J = 5.4$ Hz, 0.5H), 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/NH₃): m/z 333 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-pentyl-N-Boc-2-azetidinone (24k) was prepared as described in the general procedure above from **23k**. ¹H NMR (CDCl₃): δ 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/NH₃): m/z 347 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-(2-methylpropyl)-N-Boc-2-azetidinone (24l) was prepared as described in the general procedure above from **23l**. ¹H NMR (CDCl₃): δ 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/NH₃): m/z 333 (M + NH₄⁺) (100).

(3R,4S)-3-(1-Ethoxyethoxy)-4-cyclohexyl-N-Boc-2-azetidinone (24m) was prepared as described in the general procedure above from **23m**. ¹H NMR (CDCl₃): δ 4.95 (q, $J = 5.7$ Hz, 0.5H), 4.92 (d, $J = 4.5$ Hz, 0.5H), 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/NH₃): m/z 359 (M + NH₄⁺) (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 MgSO₄, 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 NaHCO₃, saturated with solid NaCl, and twice extracted with AcOEt. The combined extracts were dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by hexanes chromatography. Elution with 5% methanol/CH₂Cl₂ or AcOEt–hexanes mixtures gave product **26**.

26a: ¹H NMR (CD₃OD) δ 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: ¹H NMR (CD₃OD) δ 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': ¹H NMR (CD₃OD) δ 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: ¹H NMR (CD₃OD) δ 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: ¹H NMR (CD₃OD) δ 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: ¹H NMR (CD₃OD) δ 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: ¹H NMR (CD₃OD) δ 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: ^1H NMR (CD_3OD) δ 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: ^1H NMR (CD_3OD) δ 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: ^1H NMR (CD_3OD) δ 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: ^1H NMR (CD_3OD) δ 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: ^1H NMR (CD_3OD) δ 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: ^1H NMR (CD_3OD) δ 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) δ 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: ^1H NMR (CD_3OD) δ 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_3OD) δ 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: ^1H NMR (CD_3OD) δ 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 μmol) 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%). ^1H NMR (CD_3OD) δ 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).

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- (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.