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New Highly Active Taxoids from 9 β -Dihydrobaccatin-9,10-acetals. Part 4

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Abstract—It was shown that a new taxane analogue **3**, which exhibited both in vitro antitumor activity and in vivo efficacy by both iv and po administration, was prone to be metabolized by human liver microsomes. We identified a major metabolite, M-1, generated by human liver microsomes as **20a**, a hydroxylated compound at the pyridine ring of **3**. To improve the metabolic stability of **3**, we designed and synthesized new taxane analogues based on the structure of M-1, and obtained some compounds that maintained excellent antitumor activity and were scarcely metabolized by human liver microsomes.

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Introduction

Paclitaxel (**1**, Taxol®) was isolated from the bark of the western yew *Taxus brevifolia* by Wani et al. in 1971¹ and has been shown to be clinically efficacious against several tumors that are refractory to other antitumor drugs. Paclitaxel is an antimetabolic agent with a unique mode of action; it promotes the assembly of stable microtubules, which cannot be depolymerized by calcium, a variation of temperature, or microtubule-disassembling agents.² The excellent clinical activity of paclitaxel prompted intense research aimed at understanding the influence of structural modifications of the paclitaxel molecule on its biological activity and searching for new analogues with more desirable physicochemical properties and higher potency, such as docetaxel (**2**, Taxotere®).³ The search for novel taxane analogues has focused on regions such as the side chain at the C-13 position, C-2 benzoate and C-4 acetate, which interact directly with tubulin,⁴ and the modifications of such regions influenced the biological activity

significantly. On the other hand, modifications at the position C-7–C-10 regions of the diterpene moiety are tolerated very well,⁵ because these regions do not interact directly with tubulin. Under these circumstances, we focused on the C-7–C-10 region and, as a result, found that some of the new taxane analogues, 9- β -dihydro-9,10-*O*-acetal taxanes, showed activity against several tumor cell lines stronger than that of docetaxel.⁶ Following an extensive study, we discovered the compound **3**, which exhibited marked in vitro antitumor activity as well as in vivo efficacy by both iv and po administration (Fig. 1).⁷

During the exploration of the biological property of **3**, however, it was elucidated that the metabolic stability of **3** differed among species; compound **3** was scarcely metabolized by mouse or dog liver microsomes. On the other hand, the incubation of **3** with monkey or human liver microsomes provided the metabolite M-1 rapidly. Hence, it was considered that the excellent antitumor efficacy of **3** obtained by both po and iv administration in mouse might not be assured in the case of oral administration in humans. For this reason, we started to prepare taxane analogues that maintained antitumor efficacy but would be less prone to be metabolized (Fig. 2).

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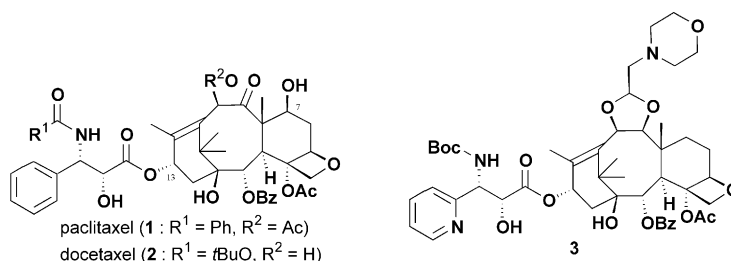


Figure 1. Structures of taxane analogues.

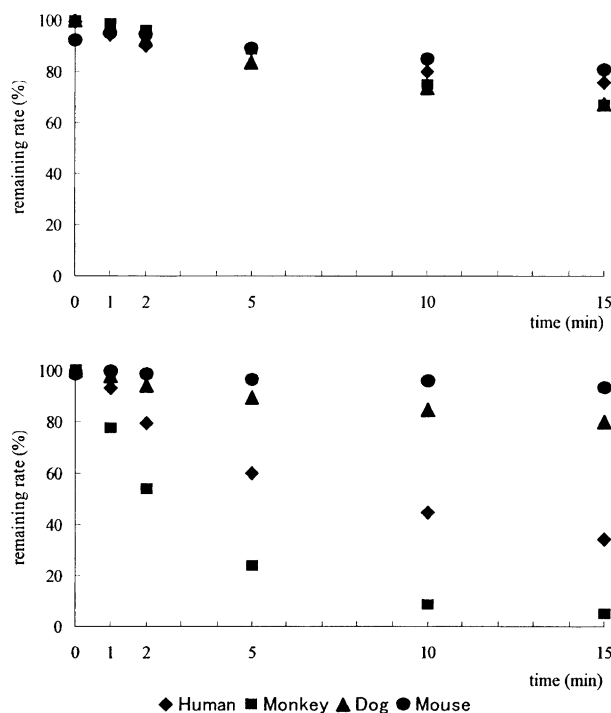


Figure 2. Remaining rates of docetaxel (upper) and **3** (lower) after incubation with human, monkey, dog, and mouse liver microsomes.

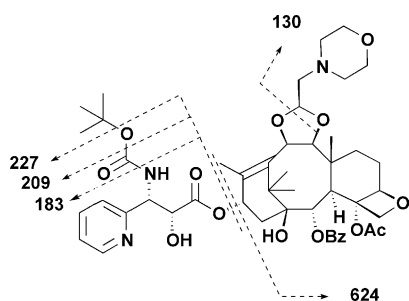


Figure 3. Mass fragment patterns of **3**.

Chemistry

Before beginning to synthesize new taxane analogues, we tried to identify the structure of M-1. The chemical structure of M-1 was partially determined by LC/MS/MS analysis. As a result of the LC/MS/MS analysis, M-1 gave a strong signal at m/z 922, that is 16 mass units greater than the protonated molecular ion ($M+H$)⁺ of **3** at m/z 906. Subsequently, LC/MS/MS analysis of **3** at m/z 906 and that of M-1 at m/z 922 were performed,

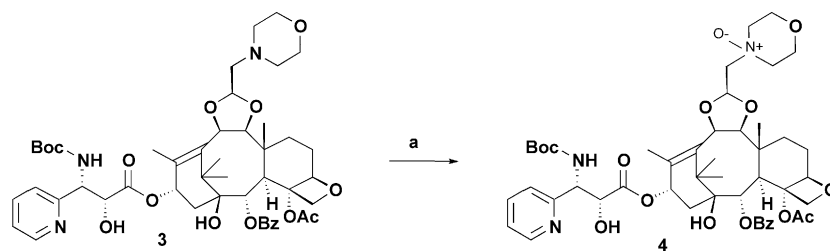
and both fragmentation patterns gave product ions at m/z 130 and 624, which corresponded to the core taxane ring. Therefore, the core taxane ring was assumed to be unchanged in M-1. The fragment ions at m/z 183, 209, and 227 were found in the spectrum of **3**, but were not present in the spectrum of M-1. These were replaced by new ions at m/z 199, 225, and 243, which were 16 mass unit greater than the respective corresponding ions. These results suggested that M-1 is the oxygenated compound of **3** and that the oxidation occurred on the pyridine ring moiety. Then, we tried to synthesize the pyridine *N*-oxide at first (Fig. 3).

Treating **3** with *m*-chloroperbenzoic acid (*m*CPBA) in CHCl_3 afforded the morpholine *N*-oxide **4** in good yield but not the pyridine *N*-oxide (Scheme 1).

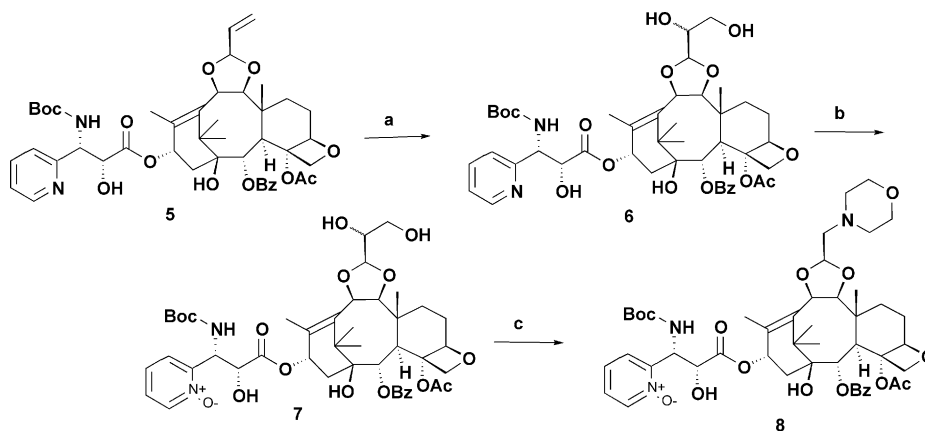
Oxidation of **5**,⁷ the precursor of **3**, with OsO_4 gave the diol **6**; then oxidation with *m*CPBA afforded the pyridine *N*-oxide **7**. Cleavage of the diol moiety of **7** with NaIO_4 gave the aldehyde, to which the morpholine moiety was introduced by reductive amination to afford the targeted pyridine *N*-oxide **8** (Scheme 2).

As shown by HPLC analysis, the retention time of *N*-oxide **8** did not agree with that of M-1. Therefore, it was assumed that M-1 was oxidized onto the pyridine ring. Then, we tried to synthesize compounds possessing the hydroxypyridine rings at the C-13 side chain. The synthesis of the key β -lactam intermediates (**14a**, **14b**) is shown in Scheme 3. Protection of the phenol moiety of **9** with benzyl bromide gave the benzyl ether **10**, which was converted to the aldehyde **11a** in four steps according to a procedure similar to that reported by Blantz and co-workers.⁸ The 3-benzyloxypyridyl aldehyde **11b** was synthesized from **12** via the protection followed by oxidation. Aldehydes **11a** and **11b** were converted to β -lactams (**13a**, **13b**) by the method of chiral enolate-imine cyclocondensation.^{9,10} Acylations of **13a** and **13b** were accomplished with di-*tert*-butyl dicarbonate [(Boc)₂O] and 4-dimethylaminopyridine (DMAP) to afford the respective targeted β -lactams (**14a**, **14b**) in high yield.

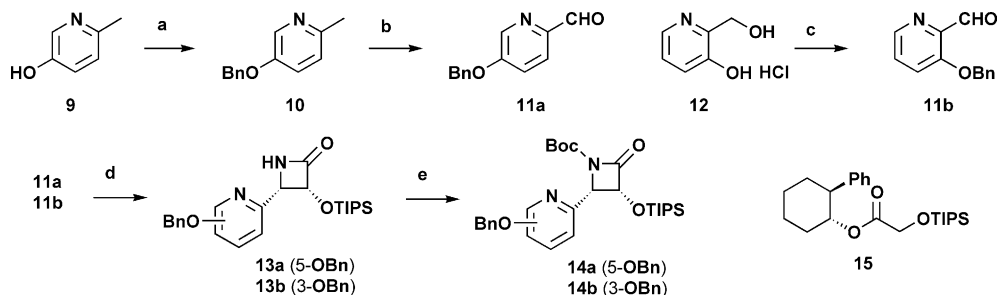
The coupling of **16**⁷ with the respective β -lactams (**14a**, **14b**) and the subsequent removal of the protecting group at C-2' were carried out following procedures similar to those reported by Ojima et al.⁹ to give the compounds **18a** and **18b**. Oxidation of **18a** and **18b** with OsO_4 followed by cleavage with NaIO_4 gave the aldehydes, which were converted to the compounds **19a** and **19b** by reductive amination. Finally, cleavage of the



Scheme 1. Reagents: (a) *m*CPBA, CHCl₃ (92%).



Scheme 2. Reagents: (a) OsO₄, NMO, THF, acetone, H₂O (90%); (b) *m*CPBA, CHCl₃ (51%); (c) (1) NaIO₄, THF, MeOH, H₂O; (2) morpholine, AcOH, NaBH₃CN, EtOH (39%).



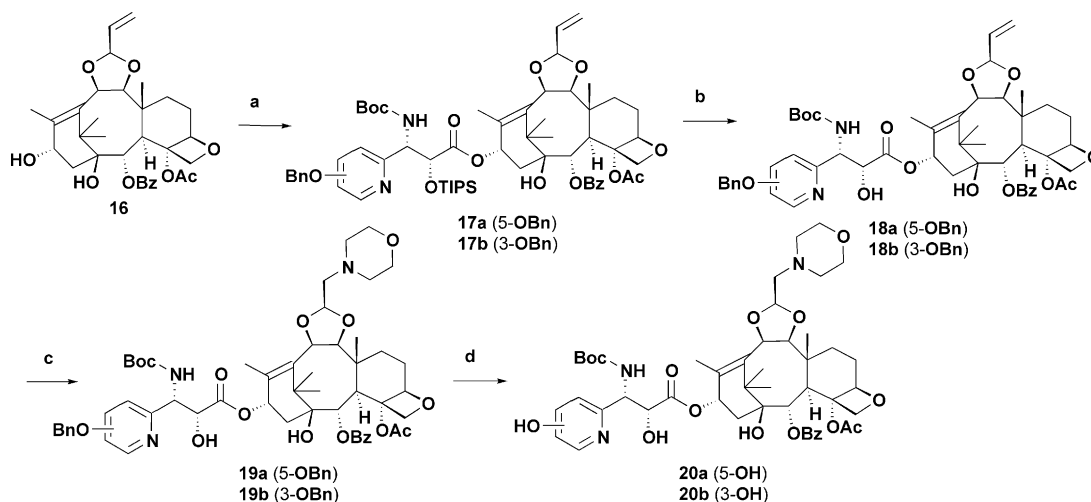
Scheme 3. Reagents: (a) BnBr, NaH, THF, DMF (82%); (b) (1) *m*CPBA, CHCl₃ (96%); (2) Ac₂O (77%); (3) NaOH, EtOH, H₂O (75%); (4) MnO₂, CHCl₃ (77%); (c) (1) BnBr, KOH, EtOH (66%); (2) MnO₂, CHCl₃ (73%); (d) (1) LiHMDS, TMSCl, THF; (2) **15**, LDA, THF (39% for **13a**, 37% for **13b**); (e) (Boc)₂O, DMAP, THF (88% for **14a**, 83% for **14b**).

benzyl moiety of **19a** and **19b** by catalytic hydrogenation gave the targeted compounds **20a** and **20b** (Scheme 4). As a result of LC/MS/MS analysis, compound **20a** was found to give the same mass fragmentation patterns and the same retention time in HPLC chromatograms as those of M-1 generated by human liver microsomes. Therefore, it was elucidated that the metabolite of **3** produced by human liver microsomes was the compound oxidized onto the 5-position of the pyridine ring of **3**.

The cytotoxicity of four oxidized compounds (**4**, **8**, **20a**, **20b**) was compared with those of paclitaxel (**1**), docetaxel (**2**), and **3** (Table 1). All compounds, with the exception of **20a** exhibited decreased cytotoxicity. Although the cytotoxicity of **20a** against cancer cell lines expressing P-glycoprotein (PC-12, PC-6/VCR29-9 and PC-6/VP1-1) was weak compared with that of **3**, **20a** retained the activity against P388 and PC-6. It was

therefore considered that the introduction of the substituent onto the 5-position of the pyridine ring would not significantly alter the cytotoxicity of **3** but would effectively block hydroxylation. On this assumption, we synthesized the taxane analogues possessing the pyridine ring substituted at its 5-position at the C-13 side chain.

Synthesis of the β -lactams (**23a–23f**) possessing the pyridine ring with the introduced substituents on their 5-positions was depicted in Scheme 5. Acylations of chiral β -lactams (**22a–22f**) with (Boc)₂O afforded the desired β -lactams (**23a–23f**) in good yield. The β -lactams (**22a–22f**) were derived from the corresponding pyridylaldehydes (**21a–21f**) in various ways. The β -lactams (**24a**, **24d**, **24e**) were synthesized by the Staudinger reaction between the imine, which was derived from the corresponding aldehydes (**21a**, **21d**, **21e**) and *p*-anisidine, and the ketene derived in situ from 2-acetoxyacetyl



Scheme 4. Reagents: (a) LiHMDS, β -lactams (90% for **17a**, 82% for **17b**); (b) TBAF, THF (100% for **18a**, 94% for **18b**); (c) (1) OsO_4 , NMO, THF, acetone, H_2O ; (2) NaIO_4 , THF, MeOH, H_2O ; (3) morpholine, AcOH, NaBH_3CN , EtOH (74% for **19a**, 69% for **19b**); (d) H_2 , $\text{Pd}(\text{OH})_2$, EtOH (64% for **20a**, 84% for **20b**).

Table 1. Cytotoxicity and metabolic stability of 7-deoxy-9,10-*O*-acetal taxane analogues

Compd	Cytotoxicity GI_{50} (ng/mL) ^a					Remaining rate (%) ^b
	P388	PC-6	PC-12	PC-6/VCR29-9	PC-6/VP1-1	
1	2.93	1.27	539	455	1000	NT
2	0.78	0.26	19.1	62.1	442	88.7
3	0.18	0.26	0.13	2.43	19.3	60.2
4	10	4.45	4.12	30.5	NT	NT
8	42.4	17.1	331	> 1000	NT	NT
20a	0.05	0.02	2.66	54.3	585	NT
20b	11.3	7.31	40.5	199	NT	NT
35a	0.06	0.34	0.05	0.97	14.1	28.8
35b	3.69	3.97	4.66	14.6	74.2	NT
35c	0.05	0.31	0.11	1.11	13.5	98.8
35d	0.14	0.78	0.43	4.4	39.3	87.8
35e	9.2	5.84	10.5	38	209	NT
35f	0.16	0.07	0.14	1.13	28.7	87.8

NT, not tested.

^aConcentration that inhibited the growth of cells by 50% at 72 h continuous exposure for the five cell lines [mouse leukemia (P388), human lung cancer cell lines (PC-6 and PC-12), and resistant cancer cell lines (PC-6/VCR29-9 and PC-6/VP1-1)].¹²

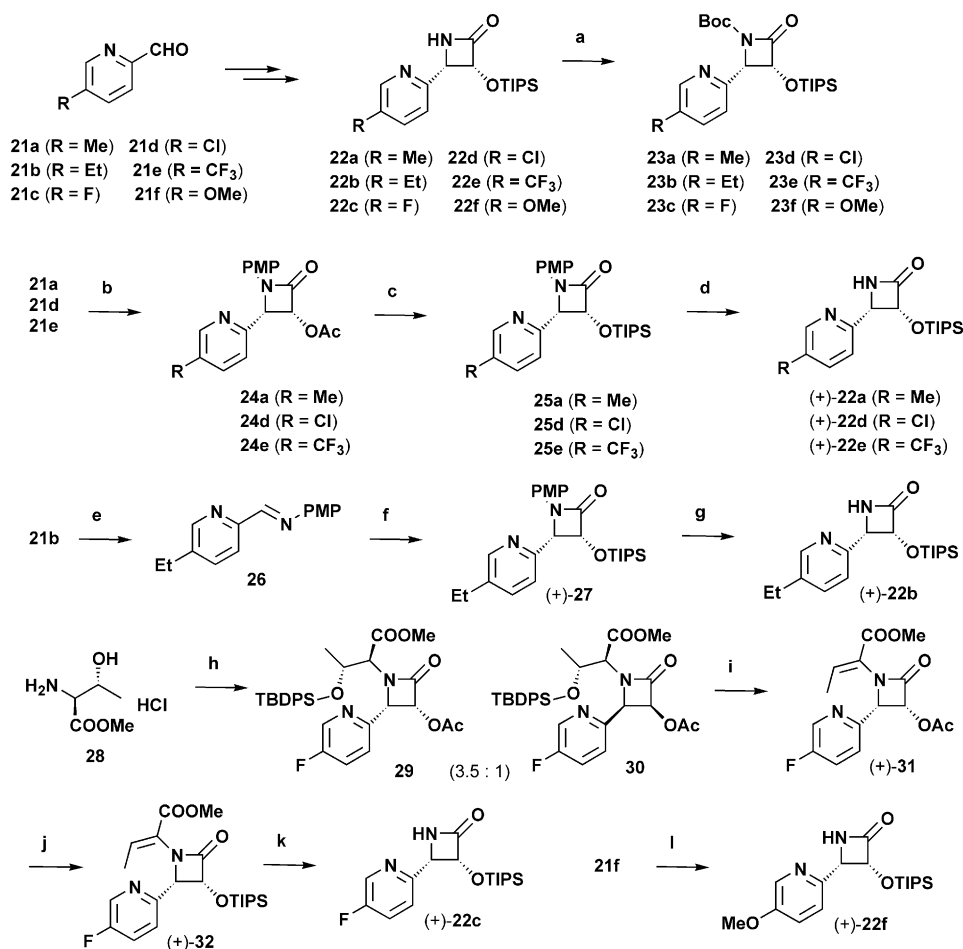
^bRemaining rate of the substrate after 5 min of incubation with human liver microsomes.

chloride. Sequential deacetylation and silylation gave the β -lactams (**25a**, **25d**, **25e**). After removal of the *p*-methoxyphenyl moieties, the racemic mixtures were resolved by using a chiral HPLC column to afford the optically pure β -lactams [(+)-**22a**, (+)-**22d**, (+)-**22e**]. Formation of (+)-**27** was achieved via chiral ester-enolate imine cyclocondensation utilizing **15** as a chiral auxiliary and the imine **26** derived from the aldehyde **21b**. Finally, the *p*-methoxyphenyl moiety was removed with ceric ammonium nitrate (CAN) to afford the desired β -lactam (+)-**22b**, whose enantiomeric excess was 79% ee. Synthesis of (+)-**22c** was accomplished according to a published procedure utilizing L-threonine methyl ester (**28**) as a chiral auxiliary,¹¹ and its enantiomeric excess was 54% ee. The β -lactam (+)-**22f**,¹⁰ possessing the methoxyl group, was synthesized by following a procedure analogous to that for the preparation of **13a**, possessing the benzyloxy group.

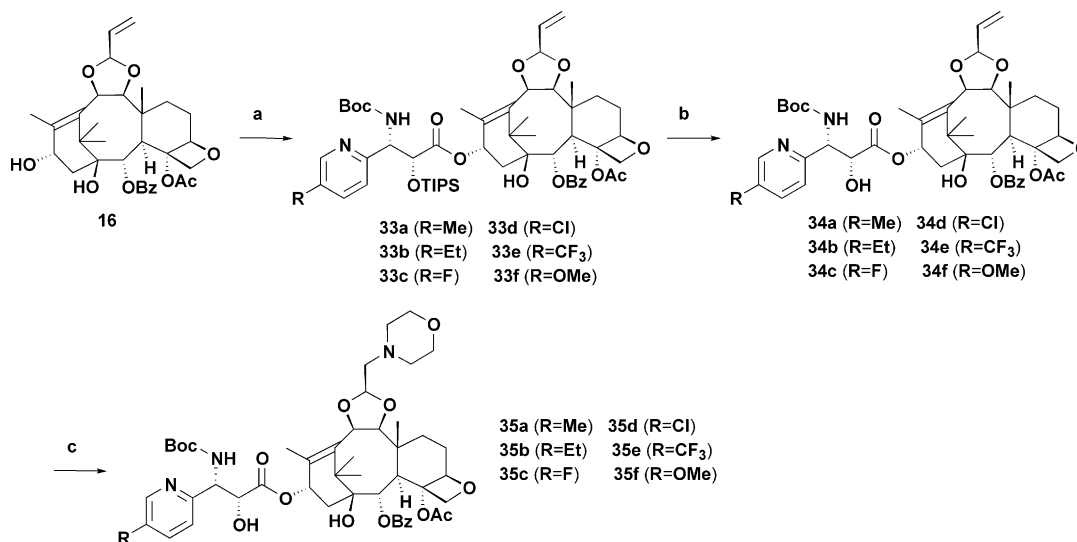
The targeted compounds (**35a–35f**) were synthesized according to a procedure similar to that described for the preparation of **19a** utilizing **16** and the corresponding β -lactams (**23a–23f**) (Scheme 6).

Results and Discussion

Activities of the synthetic compounds were evaluated in cytotoxicity assays against five cell lines (P388, PC-6, PC-12, PC-6/VCR29-9 and PC-6/VP1-1), and activities were compared with those of paclitaxel and docetaxel. The activities of **35a**, **35c**, and **35f**, which possessed, respectively, a methyl, fluoro, and methoxyl group on the pyridine ring, were similar to that of **3** against all cell lines, and **35d** possessing the chloro moiety showed slightly weaker cytotoxicity compared with that of these three compounds. On the other hand, **35b** and **35e**,



Scheme 5. Reagents: (a) (Boc)₂O, DMAP, THF (96% for **23a**, 92% for **23b**, 93% for **23c**, 100% for **23d**, 99% for **23e**, 91% for **23f**); (b) (1) 4-anisidine, Na₂SO₄, benzene; (2) AcOCH₂COCl, Et₃N, CH₂Cl₂ (88% for **24a**, 61% for **24d**, 23% for **24e**); (c) (1) K₂CO₃, THF, MeOH; (2) TIPSCl, imidazole, DMF (85% for **25a**, 78% for **25d**, 36% for **25e**); (d) (1) CAN, CH₃CN, H₂O; (2) Chiralcel OD or AD (27% for **22a**, 25% for **22d**, 33% for **22e**); (e) 4-anisidine, Na₂SO₄, benzene (84%); (f) **15**, LDA, THF (30%); (g) CAN, CH₃CN, H₂O (59%); (h) (1) TBDPSCl, imidazole, DMAP, CH₂Cl₂; (2) **21c**, benzene; (3) AcOCH₂COCl, Et₃N, CH₂Cl₂ (72%); (i) TBAF, THF (85%); (j) (1) K₂CO₃, THF, MeOH; (2) TIPSCl, imidazole, DMF (61%); (k) NaHCO₃, KMnO₄, acetone, H₂O (35%); (l) (1) LiHMDS, TMSCl, THF; (2) **15**, LDA, THF (57%).



Scheme 6. Reagents: (a) LiHMDS, β -lactams (80% for **33a**, 95% for **33b**, 74% for **33c**, 71% for **33d**, 92% for **33e**, 100% for **33f**); (b) TBAF, THF (94% for **34a**, 85% for **34b**, 99% for **34c**, 100% for **34d**, 76% for **34e**, 91% for **34f**); (c) (1) OsO₄, NMO, THF, acetone, H₂O; (2) NaIO₄, THF, MeOH, H₂O; (3) morpholine, AcOH, NaBH₃CN, EtOH (58% for **35a**, 61% for **35b**, 64% for **35c**, 77% for **35d**, 81% for **35e**, 51% for **35f**).

which possessed, respectively, an ethyl and trifluoromethyl group on the pyridine ring, gave significantly decreased cytotoxicity. This reduction of cytotoxicity might be due to a steric hindrance.

The metabolic stability of **35a**, **35c**, **35d**, and **35f**, which all showed nearly the same cytotoxicity as **3**, was examined, and the results were shown as the remaining rate of substrate after 5 min of incubation with human liver microsomes. All compounds, except **35a**, exhibited good metabolic stability compared with **3**, as we had expected. Compound **35a** possessing a methyl group might be oxidized at its methyl moiety of the pyridine ring.

In conclusion, to improve the metabolic stability of **3**, we designed and synthesized taxane analogues based on the structure of M-1, the major metabolite of **3**. Some compounds maintained the strong cytotoxicity and were scarcely metabolized by human liver microsomes. Further study to improve the metabolic stability of **3** is in progress, and we expect that this study will lead us to obtain a compound that will exhibit good antitumor activity not only in mice but also in humans.

Experimental

All chemicals and solvents used in synthesis were reagent-grade products and were used without additional purification. The solvent and reagent names are abbreviated as follows: acetic anhydride (Ac₂O), ethyl acetate (AcOEt), benzyl bromide (BnBr), di-*tert*-butyl dicarbonate [(Boc)₂O], ceric ammonium nitrate (CAN), 4-dimethylaminopyridine (DMAP), *N,N*-dimethylformamide (DMF), diethyl ether (Et₂O), lithium bis(trimethylsilyl)amide (LiHMDS), *m*-chloroperbenzoic acid (*m*CPBA), *N*-methylmorpholine-*N*-oxide (NMO), tetrabutylammonium fluoride (TBAF), *tert*-butyldiphenylsilyl chloride (TBDPSCl), tetrahydrofuran (THF), triisopropylsilyl chloride (TIPSCl), and trimethylsilyl chloride (TMSCl). Melting points were obtained on a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL EX-400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm, δ units). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Infrared (IR) spectra were obtained on a Hitachi 270-30 spectrometer with KBr disks. Mass spectra were recorded on a JEOL AX-505W, or a JMS-700 spectrometer. Elementary analysis was carried out with a Perkin-Elmer Model 240C elemental analyzer. Optical rotations were measured with a Horiba SEPA-200 polarimeter. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography. The HPLC system consisted of a model L-6200, L-6000 system (Hitachi) with a 717 plus autosampler (Waters), a model L-7400 UV detector (Hitachi), and a 250×4.6 mm Symmetry C₁₈ column (Waters) maintained at 30 °C. The conditions for LC/MS/MS were as follows: mass spectrometry, TSQ LC/MS/MS system (ThermoQuest); HPLC system, an Alliance 2690 (Waters); column, 150×2.1 mm Symmetry C₁₈ (Waters); mobile phase, 0.2% AcOH

and acetonitrile [70:30 (v/v)]; flow rate, 0.2 mL/min; column temperature, 30 °C; detection, ESI/MS/MS (positive mode); capillary temperature, 225 or 275 °C; sheath gas (N₂), 70–80 psi; auxiliary gas (N₂), 5–10 units; collision energy, –40 eV; collision gas (Ar), 1.8 m torr; electron multiplier, 1000 or 1200 V.

Identification of M-1

As a result of the LC/MS analysis of **8**, **20a** and **20b**, all samples gave a strong signal at *m/z* 922, and LC/MS/MS spectrum of them at *m/z* 922 gave product ions at *m/z* 199, 225, and 243, which were consistent with that of M-1. The HPLC analysis was performed using two diverse mobile phases, 0.01 M AcONa (pH 3.8) and acetonitrile [55:45 (v/v)] (condition A) and 0.01 M AcONa (pH 5.0) and acetonitrile [50:50 (v/v)] (condition B) at a constant flow rate of 1.0 mL/min. The retention times of **3**, M-1, **8**, **20a** and **20b** of each mobile phase were as follows: Condition A; **3** (about 17.2 min), M-1 (about 9.5 min), **8** (about 6.4 min), **20a** (about 9.5 min), **20b** (10.3 min). Condition B; **3** (about 27.3 min), M-1 (about 14.6 min), **8** (about 10.3 min), **20a** (about 14.6 min), **20b** (about 17.7 min). And the mixture of the extracts from human liver microsomes and **20a** gave a single peak in both conditions.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino-*N*-oxide)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-(2-pyridyl)propionate (4). To a solution of **3** (100 mg, 0.119 mmol) in CHCl₃ (2 mL) was added *m*CPBA (21 mg, 0.12 mmol) with ice cooling, and the mixture was stirred at the same temperature for 1 h. After saturated aqueous NaHCO₃ was added to the reaction mixture, the whole was extracted with AcOEt. The extract was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by preparative TLC (CHCl₃–MeOH = 10:1) and lyophilized with 1,4-dioxane to give the title compound (93 mg, 92%) as a white amorphous powder, mp 159–164 °C. ¹H NMR (CDCl₃) δ : 1.25 (3H, s), 1.45 (9H, s), 1.49 (3H, s), 1.60 (3H, s), 1.74 (3H, s), 1.89–2.04 (3H, m), 2.20–2.37 (1H, m), 2.47 (3H, s), 2.94 (1H, d, *J* = 5.5 Hz), 3.37–3.78 (8H, m), 4.19 (2H, m), 4.33 (1H, d, *J* = 8.3 Hz), 4.39–4.48 (2H, m), 4.94 (1H, s), 4.98 (1H, d, *J* = 2.0 Hz), 5.36 (2H, d, *J* = 8.0 Hz), 5.94–6.00 (2H, m), 6.05 (1H, t-like, *J* = 8.3 Hz), 7.19 (1H, dd, *J* = 2.0, 7.5 Hz), 7.45–7.49 (3H, m), 7.60 (1H, d, *J* = 8.0 Hz), 8.13 (2H, d, *J* = 8.0 Hz), 8.55 (1H, d, *J* = 5.0 Hz); FAB-MS (*m/z*): 922 (M + H)⁺. Anal. calcd for C₄₈H₆₃N₃O₁₅·2H₂O: C, 60.18; H, 7.05; N, 4.39. Found: C, 60.33; H, 6.93; N, 4.28; IR: 3423, 2971, 1712, 1592, 1569, 1490 cm^{–1}; [α]_D²⁶ –2.9° (*c* 0.11, CHCl₃).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2,3-dihydroxypropylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-(2-pyridyl)propionate (6). To a solution of **5** (40 mg, 0.048 mmol) in a mixture of THF (1 mL), acetone (1 mL), and H₂O (1 mL) were added NMO (28 mg, 0.24 mmol) and OsO₄ (2.5 mg),

and the mixture was stirred at room temperature for 1 h. After AcOEt and 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with saturated aqueous NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CHCl_3 – MeOH = 10:1) to give the title compound (37.5 mg, 90%) as a white amorphous powder. ^1H NMR (CDCl_3) δ : 1.27 (3H, s), 1.44 (9H, s), 1.50 (3H, s), 1.57 (3H, s), 1.73 (3H, s), 1.84–2.17 (3H, m), 2.36 (3H, s), 2.93 (1H, d, J = 5.4 Hz), 3.75–3.88 (3H, m), 4.20–4.22 (2H, m), 4.32 (1H, d, J = 7.8 Hz), 4.84–4.92 (3H, m), 5.28 (2H, d, J = 7.0 Hz), 5.35 (1H, d, J = 9.5 Hz), 5.96 (2H, m), 6.10 (1H, br t, J = 8.0 Hz), 7.23 (1H, dd, J = 2.0, 6.0 Hz), 7.41–7.61 (3H, m), 7.72 (1H, dd, J = 2.0, 8.0 Hz), 8.11 (2H, d, J = 8.0 Hz), 8.53 (1H, d, J = 4.5 Hz); HR-MS calcd for $\text{C}_{45}\text{H}_{59}\text{N}_2\text{O}_{15}$: 867.3915. Found, 867.3887.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2,3-dihydroxypropylenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(2-pyridyl-*N*-oxide)propionate (7). Compound **7** was obtained from **6** as a white amorphous powder (51%) by following a procedure analogous to that described for the preparation of **4** from **3**. ^1H NMR (CDCl_3) δ : 1.27 (3H, s), 1.41 (9H, s), 1.50 (3H, s), 1.58 (3H, s), 1.81 (3H, s), 1.84–2.32 (2H, m), 2.39 (3H, s), 2.92 (1H, d, J = 5.4 Hz), 3.76–3.88 (3H, m), 4.19–4.24 (2H, m), 4.32 (1H, d, J = 7.8 Hz), 4.87–4.91 (2H, m), 5.15 (1H, s), 5.30–5.36 (2H, m), 5.97 (1H, d, J = 4.0 Hz), 6.19 (1H, t, J = 8.0 Hz), 7.23–7.28 (1H, m), 7.36 (1H, t, J = 8.0 Hz), 7.44–7.48 (3H, m), 7.59 (1H, t, J = 8.0 Hz), 8.12 (2H, d, J = 8.0 Hz), 8.17 (1H, d, J = 6.5 Hz); HR-MS calcd for $\text{C}_{45}\text{H}_{59}\text{N}_2\text{O}_{16}$: 883.3865. Found, 883.3840.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(2-pyridyl-*N*-oxide)propionate (8). To a solution of **7** (19 mg, 0.021 mmol) in a mixture of THF (1 mL), MeOH (1 mL), and H_2O (1 mL) was added NaIO_4 (44 mg, 0.21 mmol), and the mixture was stirred at room temperature for 30 min. After AcOEt and water were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with saturated aqueous NaHCO_3 , and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was dissolved in EtOH (2 mL). To this solution were added morpholine (0.02 mL, 0.23 mmol), AcOH (0.012 mL, 0.23 mmol), and NaBH_3CN (13.5 mg, 0.23 mmol) with ice cooling, and the mixture was stirred at room temperature for 10 min. After AcOEt, saturated aqueous NaHCO_3 , and water were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure. The

residue was purified by preparative TLC (CHCl_3 – MeOH = 10:1) and lyophilized with 1,4-dioxane to give the title compound (7.5 mg, 39%) as a white amorphous powder, mp 165–168 °C. ^1H NMR (CDCl_3) δ : 1.27 (3H, s), 1.41 (9H, s), 1.48 (3H, s), 1.60 (3H, s), 1.80 (3H, s), 1.85–2.11 (2H, m), 2.29–2.31 (1H, m), 2.35 (3H, s), 2.59–2.68 (4H, m), 2.71 (1H, dd, J = 5.4, 13.2 Hz), 2.79 (1H, dd, J = 4.0, 13.2 Hz), 2.93 (1H, d, J = 4.9 Hz), 3.75 (4H, t, J = 4.5 Hz), 4.12 (1H, d, J = 7.3 Hz), 4.23 (1H, d, J = 8.3 Hz), 4.32 (1H, d, J = 8.3 Hz), 4.91 (1H, s), 5.05 (1H, t, J = 4.5 Hz), 5.14 (1H, d, J = 2.5 Hz), 5.25 (1H, d, J = 7.3 Hz), 5.77 (1H, d, J = 9.8 Hz), 6.00 (1H, d, J = 4.9 Hz), 6.05 (1H, d, J = 8.9 Hz), 6.18 (1H, t, J = 8.0 Hz), 7.24–7.28 (1H, m), 7.34 (1H, t, J = 7.0 Hz), 7.42–7.49 (3H, m), 7.60 (1H, t, J = 7.0 Hz), 8.12 (2H, d, J = 8.0 Hz), 8.20 (1H, d, J = 7.0 Hz); FAB-MS (m/z): 922 ($M+H$)⁺; HR-MS calcd for $\text{C}_{48}\text{H}_{64}\text{N}_3\text{O}_{15}$: 922.4337. Found, 922.4382; IR: 3430, 2952, 1714, 1602, 1488, 1452, 1432 cm^{-1} ; $[\alpha]_D^{25}$ –22.0° (c 0.03, CHCl_3).

5-Benzyloxy-2-methylpyridine (10). To a suspension of NaH (60% in oil, 2.05 g, 51.2 mmol) in THF (100 mL) was added a solution of **9** (5.0 g, 45.8 mmol) in DMF (50 mL) with ice cooling, and the mixture was stirred at the same temperature for 30 min. After BnBr (6.0 mL, 50.5 mmol) was added to the reaction mixture, the whole was stirred overnight at room temperature. To the reaction mixture was added saturated aqueous NaHCO_3 , and the mixture was extracted with AcOEt. The extract was washed with water, brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give the title compound (7.5 g, 82%) as a yellow oil. ^1H NMR (CDCl_3) δ : 2.49 (3H, s), 5.08 (2H, s), 7.05 (1H, d, J = 8.3 Hz), 7.16 (1H, dd, J = 2.5, 8.3 Hz), 7.34–7.41 (5H, m), 8.26 (1H, d, J = 2.5 Hz).

5-Benzyloxy-2-formylpyridine (11a). (i) To a solution of **10** (7.5 g, 37.6 mmol) in CHCl_3 (200 mL) was added *m*CPBA (7.14 g, 41.4 mmol) with ice cooling, and the mixture was stirred at the same temperature for 1 h. To the reaction mixture was added 5% aqueous Na_2CO_3 and the whole was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure to give 5-benzyloxy-2-methylpyridine *N*-oxide (7.8 g, 96%) as colorless crystals.

(ii) To Ac_2O (39 mL) was added 5-benzyloxy-2-methylpyridine *N*-oxide (7.8 g, 36.2 mmol) at 80 °C and the mixture was stirred at 130 °C for 30 min. The reaction mixture was poured into ice-water and the whole was stirred at room temperature for 2 h. The mixture was extracted with AcOEt and the extract was washed with saturated aqueous NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give 2-acetoxy-methyl-5-benzyloxypyridine (7.2 g, 77%) as a yellow oil.

(iii) To a solution of 2-acetoxymethyl-5-benzoyloxypyridine (7.2 g, 28.0 mmol) in a mixture of EtOH (72 mL) and water (18 mL) was added NaOH (2.0 g, 50 mmol), and the mixture was stirred under reflux for 1.5 h. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was extracted with CHCl_3 . The extract was washed with water, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was crystallized from *n*-hexane–AcOEt. The resulting precipitate was collected by filtration to give 5-benzoyloxy-2-hydroxymethylpyridine (4.5 g, 75%) as brown crystals.

(iv) To a solution of 5-benzoyloxy-2-hydroxymethylpyridine (4.5 g, 20.9 mmol) in CHCl_3 (225 mL) was added MnO_2 (22.5 g) and the mixture was stirred under reflux for 5 min. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (4:1). The eluate was concentrated under reduced pressure to give the title compound (3.45 g, 77%) as colorless crystals. ^1H NMR (CDCl_3) δ : 5.21 (2H, s), 7.34–7.45 (6H, m), 7.95 (1H, d, $J=8.8$ Hz), 8.50 (1H, d, $J=3.0$ Hz), 9.99 (1H, d, $J=1.0$ Hz).

3-Benzoyloxy-2-formylpyridine (11b). (i) To a suspension of **12** (5.0 g, 26.3 mmol) in EtOH (100 mL) were added KOH (3.5 g, 53 mmol) and BnBr (3.15 mL, 26.5 mmol), and the mixture was stirred under reflux for 24 h. After cooled to room temperature, the reaction mixture was diluted with water and the whole was extracted with AcOEt. The extract was washed with water, brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with CHCl_3 –MeOH (20:1). The eluate was concentrated under reduced pressure to give 3-benzoyloxy-2-hydroxymethylpyridine (3.76 g, 66%) as yellow crystals.

(ii) To a solution of 3-benzoyloxy-2-hydroxymethylpyridine (3.75 g, 17.4 mmol) in CHCl_3 (100 mL) was added MnO_2 (15 g) and the mixture was stirred under reflux for 80 min. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (1:1). The eluate was concentrated under reduced pressure to give the title compound (2.7 g, 73%) as a yellow oil. ^1H NMR (CDCl_3) δ : 5.26 (2H, s), 7.34–7.47 (7H, m), 8.41 (1H, t, $J=2.5$ Hz), 10.40 (1H, s).

(3R, 4S)-4-(5-Benzoyloxy-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (13a). (i) To a 1.0 M solution of LiHMDS in THF (5.0 mL, 5.0 mmol) was added a solution of **11a** (1.0 g, 4.69 mmol) in THF (2.5 mL) at -78°C , and the mixture was stirred at the same temperature for 5 min and then at 0°C for 30 min. Then, to the reaction mixture was added TMSCl (0.68 mL, 5.51 mmol) and the mixture was stirred at the same temperature for 30 min to give a solution of *N*-trimethylsilylaldimine.

(ii) To a solution of diisopropylamine (0.7 mL, 5.0 mmol) in THF (5 mL) was added a 1.58 M solution of

*n*BuLi in *n*-hexane (3.2 mL, 5.0 mmol) at 0°C . The solution was stirred at the same temperature for 15 min and then cooled to -78°C . To the mixture was added a solution of **15** (1.83 g, 4.69 mmol) in THF (5 mL). The solution was stirred for 2 h followed by addition of a solution of *N*-trimethylsilylaldimine, described above. The mixture was slowly allowed to warm to room temperature and further stirred overnight. After saturated aqueous NaHCO_3 and AcOEt were added to the reaction mixture, the layers were separated. The aqueous layer was extracted with AcOEt and the combined extract was washed with water, brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give the title compound (780 mg, 39%) as a yellow oil. ^1H NMR (CDCl_3) δ : 0.88–1.00 (21H, m), 4.94 (1H, d, $J=4.4$ Hz), 5.12 (2H, s), 5.22 (1H, dd, $J=2.9, 4.4$ Hz), 6.24 (1H, br s), 7.25–7.43 (7H, m), 8.30 (1H, d, $J=2.9$ Hz); HR-MS calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_3\text{Si}$: 427.2417. Found, 427.2390.

(3R, 4S)-4-(3-Benzoyloxy-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (13b). Compound **13b** was obtained from **11b** as a yellow oil (37%) by following a procedure analogous to that described for the preparation of **13a** from **11a**. ^1H NMR (CDCl_3) δ : 0.85–0.99 (21H, m), 5.07 (2H, ABq, $J=12.0$ Hz), 5.30 (2H, ABq, $J=5.0$ Hz), 6.35 (1H, br s), 7.15–7.19 (2H, m), 7.34–7.40 (5H, m), 8.23 (1H, dd, $J=2.0, 2.5$ Hz); HR-MS calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_3\text{Si}$: 427.2417. Found, 427.2390.

(3R, 4S)-4-(5-Benzoyloxy-2-pyridyl)-1-(tert-butoxycarbonyl)-3-triisopropylsilyloxy-2-azetidinone (14a). To a solution of **13a** (780 mg, 1.83 mmol) and (Boc) $_2$ O (0.50 mL, 2.17 mmol) in THF (15.6 mL) was added DMAP (45 mg, 0.37 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (9:1). The eluate was concentrated under reduced pressure to give the title compound (850 mg, 88%) as a colorless syrup. ^1H NMR (CDCl_3) δ : 0.87–1.00 (21H, m), 1.42 (9H, s), 5.12 (2H, s), 5.20 (2H, s), 7.25–7.43 (7H, m), 8.33 (1H, d, $J=3.0$ Hz); HR-MS calcd for $\text{C}_{29}\text{H}_{43}\text{N}_2\text{O}_5\text{Si}$: 527.2941. Found, 527.2924.

(3R, 4S)-4-(3-Benzoyloxy-2-pyridyl)-1-(tert-butoxycarbonyl)-3-triisopropylsilyloxy-2-azetidinone (14b). Compound **14b** was obtained from **13b** as a colorless syrup (83%) by following a procedure analogous to that described for the preparation of **14a** from **13a**. ^1H NMR (CDCl_3) δ : 0.87–1.01 (21H, m), 1.43 (9H, s), 5.05 (2H, ABq, $J=11.5$ Hz), 5.21 (1H, d, $J=5.0$ Hz), 5.61 (1H, br s), 7.12–7.19 (2H, m), 7.33–7.42 (5H, m), 8.21 (1H, d, $J=3.0$ Hz); HR-MS calcd for $\text{C}_{29}\text{H}_{43}\text{N}_2\text{O}_5\text{Si}$: 527.2941. Found, 527.2983.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenyldenedioxy]tax-11-en-13-yl (2R, 3S)-3-(5-benzoyloxy-2-pyridyl)-3-(tert-butoxycarbonylamino)-2-triisopropylsilyloxypropionate (17a). To a solution of **16** (100 mg,

0.175 mmol) in THF (2 mL) was added LiHMDS (1.0 M in THF, 0.21 mL, 0.21 mmol) at -55°C , and the mixture was stirred at the same temperature for 30 min. To the reaction mixture was added a solution of **14a** (140 mg, 0.265 mmol) in THF (2 mL) at -55°C , and the whole was stirred with ice cooling for 30 min. After saturated aqueous NaHCO_3 and AcOEt were added to the reaction mixture with ice cooling, the two layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane– AcOEt (4:1). The eluate was concentrated under reduced pressure to give the title compound (157 mg, 82%) as a white amorphous powder. ^1H NMR (CDCl_3) δ : 0.86–0.93 (21H, m), 1.31 (3H, s), 1.41 (9H, s), 1.52 (3H, s), 1.65 (3H, s), 1.79–2.07 (2H, m), 1.81 (3H, s), 2.26–2.30 (2H, m), 2.50 (3H, s), 2.97 (1H, d, $J=5.4$ Hz), 4.19–4.22 (2H, m), 4.33 (1H, d, $J=7.8$ Hz), 4.96 (1H, br s), 5.12 (2H, s), 5.21 (1H, d, $J=6.0$ Hz), 5.28 (2H, m), 5.44–5.60 (4H, m), 5.96–6.03 (2H, m), 6.11 (1H, br t, $J=8.0$ Hz), 7.20–7.47 (9H, m), 7.57 (1H, t, $J=7.8$ Hz), 8.13 (2H, d, $J=7.8$ Hz), 8.31 (1H, d, $J=2.5$ Hz); HR-MS calcd for $\text{C}_{61}\text{H}_{83}\text{N}_2\text{O}_{14}\text{Si}$: 1095.5614. Found, 1095.5623.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenyldenedioxy]tax-11-en-13-yl (2R, 3S)-3-(3-benzoyloxy-2-pyridyl)-3-(tert-butoxycarbonylamino)-2-triisopropylsilyloxypropionate (17b). Compound **17b** was obtained as a white amorphous powder (90%) by following a procedure analogous to that described for the preparation of **17a** from **16** by replacing **15a** with **15b**. ^1H NMR (CDCl_3) δ : 0.86–0.91 (21H, m), 1.36 (3H, s), 1.37 (9H, s), 1.53 (3H, s), 1.64 (3H, s), 1.75–2.30 (6H, m), 1.79 (3H, s), 2.45 (3H, s), 2.95 (1H, d, $J=6.0$ Hz), 4.19–4.22 (2H, m), 4.30 (1H, d, $J=7.8$ Hz), 4.87 (1H, s), 5.12 (1H, d, $J=3.0$ Hz), 5.19–5.27 (3H, m), 5.45 (1H, d, $J=10.5$ Hz), 5.57 (1H, d, $J=17.0$ Hz), 5.70 (1H, d, $J=3.0$, 10.0 Hz), 5.95–6.04 (2H, m), 6.13 (1H, d, $J=10.0$ Hz), 6.19 (1H, br t, $J=8.0$ Hz), 7.08–7.15 (2H, m), 7.31–7.46 (7H, m), 7.57 (1H, t, $J=7.8$ Hz), 8.13–8.17 (3H, m); HR-MS calcd for $\text{C}_{61}\text{H}_{83}\text{N}_2\text{O}_{14}\text{Si}$: 1095.5614. Found, 1095.5537.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenyldenedioxy]tax-11-en-13-yl (2R, 3S)-3-(5-benzoyloxy-2-pyridyl)-3-(tert-butoxycarbonylamino)-2-hydroxypropionate (18a). To a solution of **17a** (150 mg, 0.137 mmol) in THF (3 mL) was added TBAF (1.0 M in THF, 0.27 mL, 0.27 mmol) with ice cooling, and the mixture was stirred at the same temperature for 15 min. After AcOEt and brine were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by preparative TLC (*n*-hexane– AcOEt = 1:1) to give the title compound (128 mg, 100%) as a white amorphous powder. ^1H NMR (CDCl_3) δ : 1.26 (3H, s), 1.43 (9H, s), 1.49 (3H, s), 1.63 (3H, s), 1.70 (3H, s), 1.83–2.11 (2H, m), 2.34 (3H,

s), 2.93 (1H, d, $J=5.4$ Hz), 4.17 (1H, d, $J=7.0$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.77 (1H, br s), 4.85 (1H, s), 4.92 (1H, s), 5.10 (2H, s), 5.23–5.27 (2H, m), 5.46 (1H, d, $J=10.3$ Hz), 5.57 (1H, d, $J=17.0$ Hz), 5.91 (1H, d, $J=10.3$ Hz), 5.96–6.02 (2H, m), 6.08 (1H, t, $J=8.0$ Hz), 7.28–7.48 (9H, m), 7.59 (1H, t, $J=7.8$ Hz), 8.12 (2H, d, $J=7.8$ Hz), 8.28 (1H, d, $J=2.5$ Hz); HR-MS calcd for $\text{C}_{52}\text{H}_{63}\text{N}_2\text{O}_{14}$: 939.4279. Found, 939.4293.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenyldenedioxy]tax-11-en-13-yl (2R, 3S)-3-(3-benzoyloxy-2-pyridyl)-3-(tert-butoxycarbonylamino)-2-hydroxypropionate (18b). Compound **18b** was obtained from **17b** as a white amorphous powder (94%) by following a procedure analogous to that described for the preparation of **18a** from **17a**. ^1H NMR (CDCl_3) δ : 1.28 (3H, s), 1.40 (9H, s), 1.50 (3H, s), 1.64 (3H, s), 1.86 (3H, s), 1.82–2.24 (5H, m), 2.24 (3H, s), 2.44–2.50 (1H, m), 2.94 (1H, d, $J=5.5$ Hz), 4.19–4.23 (2H, m), 4.30 (1H, d, $J=8.3$ Hz), 4.37 (1H, br s), 4.78 (1H, br s), 4.89 (1H, s), 5.22 (2H, s), 5.25 (1H, d, $J=5.9$ Hz), 5.32 (1H, d, $J=6.0$ Hz), 5.46 (1H, d, $J=10.5$ Hz), 5.68 (1H, d, $J=17.0$ Hz), 5.83 (1H, d, $J=10.3$ Hz), 5.97–6.09 (3H, m), 6.25 (1H, t, $J=9.0$ Hz), 7.17–7.48 (9H, m), 7.58 (1H, t, $J=7.8$ Hz), 8.11 (2H, d, $J=7.8$ Hz), 8.18 (1H, d, $J=4.5$ Hz); HR-MS calcd for $\text{C}_{52}\text{H}_{63}\text{N}_2\text{O}_{14}$: 939.4279. Found, 939.4351.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(5-benzoyloxy-2-pyridyl)-3-(tert-butoxycarbonylamino)-2-hydroxypropionate (19a). To a solution of **18a** (128 mg, 0.136 mmol) in a mixture of THF (1.3 mL), acetone (1.3 mL), and H_2O (1.3 mL) were added NMO (80 mg, 0.68 mmol) and OsO_4 (7 mg), and the mixture was stirred at room temperature for 2.5 h. After AcOEt and 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt , and the combined organic layer was washed with saturated aqueous NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was dissolved in a mixture of THF (1.5 mL), MeOH (1.5 mL), and H_2O (1.5 mL). To this solution was added NaIO_4 (192 mg, 0.9 mmol) and the mixture was stirred at room temperature for 0.5 h. After AcOEt and water were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt , and the combined organic layer was washed with saturated aqueous NaHCO_3 , and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was dissolved in EtOH (3 mL). To this solution were added morpholine (0.079 mL, 0.9 mmol), AcOH (0.051 mL, 0.9 mmol), and NaBH_3CN (56 mg, 0.9 mmol), and the mixture was stirred at room temperature for 15 min. After AcOEt , saturated aqueous NaHCO_3 , and water were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt , and the combined organic layer was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CHCl_3 –MeOH = 20:1) to

give the title compound (82 mg, 74%) as a white amorphous powder. ^1H NMR (CDCl_3) δ : 1.26 (3H, s), 1.43 (9H, s), 1.48 (3H, s), 1.60 (3H, s), 1.68 (3H, s), 1.82–2.11 (5H, m), 2.30–2.37 (1H, m), 2.34 (3H, s), 2.58–2.70 (4H, m), 2.69 (1H, d, $J=3.9$, 13.5 Hz), 2.77 (1H, d, $J=4.9$, 13.5 Hz), 2.91 (1H, d, $J=5.4$ Hz), 3.74 (4H, t, $J=4.5$ Hz), 4.11 (1H, d, $J=7.3$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.75 (1H, br s), 4.84 (1H, d, $J=2.0$ Hz), 4.92 (1H, s), 5.05 (1H, t, $J=4.5$ Hz), 5.10 (2H, s), 5.21 (1H, d, $J=7.0$ Hz), 5.28 (1H, d, $J=8.9$ Hz), 5.98 (1H, d, $J=5.0$ Hz), 6.07 (1H, t, $J=8.3$ Hz), 7.28–7.49 (9H, m), 7.59 (1H, t, $J=8.3$ Hz), 8.12 (2H, d, $J=8.3$ Hz), 8.28 (1H, d, $J=2.5$ Hz); HR-MS calcd for $\text{C}_{55}\text{H}_{70}\text{N}_3\text{O}_{15}$: 1012.4807. Found, 1012.4884.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(3-benzoyloxy-2-pyridyl)-3-(tert-butoxycarbonylamino)-2-hydroxypropionate (19b). Compound **19b** was obtained from **18b** as a white solid (69%) by following a procedure analogous to that described for the preparation of **19a** from **18a**. ^1H NMR (CDCl_3) δ : 1.27 (3H, s), 1.40 (9H, s), 1.48 (3H, s), 1.60 (3H, s), 1.84 (3H, s), 1.82–2.07 (5H, m), 2.24 (3H, s), 2.42–2.48 (1H, m), 2.58–2.68 (4H, m), 2.69 (1H, d, $J=3.9$, 14.0 Hz), 2.77 (1H, d, $J=4.5$, 14.0 Hz), 2.93 (1H, d, $J=5.5$ Hz), 3.75 (4H, t, $J=4.5$ Hz), 4.14 (1H, d, $J=7.3$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.29 (1H, d, $J=8.3$ Hz), 4.34 (1H, br s), 4.77 (1H, s), 4.88 (1H, s), 5.05 (1H, t, $J=4.5$ Hz), 5.21 (2H, s), 5.25 (1H, d, $J=8.0$ Hz), 5.82 (1H, d, $J=8.9$ Hz), 5.98 (1H, d, $J=5.0$ Hz), 6.07 (1H, t, $J=8.3$ Hz), 6.24 (1H, d, $J=9.0$ Hz), 7.17–7.49 (9H, m), 7.58 (1H, t, $J=8.3$ Hz), 8.10 (2H, d, $J=8.3$ Hz), 8.17 (1H, d, $J=3.5$ Hz); HR-MS calcd for $\text{C}_{55}\text{H}_{70}\text{N}_3\text{O}_{15}$: 1012.4807. Found, 1012.4775.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-hydroxy-2-pyridyl)propionate (20a). **19a** (82 mg, 0.081 mmol) was hydrogenated over 10% Pd(OH) $_2$ (40 mg) in EtOH (3 mL) at atmospheric pressure for 1 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CHCl_3 –MeOH = 20:1) and lyophilized from 1,4-dioxane to give the title compound (48 mg, 64%) as a white amorphous powder, mp 163–165 °C. ^1H NMR (CDCl_3) δ : 1.25 (3H, s), 1.44 (9H, s), 1.48 (3H, s), 1.59 (3H, s), 1.69 (3H, s), 1.81–2.10 (5H, m), 2.33–2.36 (1H, m), 2.33 (3H, s), 2.60–2.70 (4H, m), 2.71 (1H, d, $J=3.9$, 13.5 Hz), 2.78 (1H, d, $J=4.9$, 13.5 Hz), 2.90 (1H, d, $J=5.4$ Hz), 3.75 (4H, t, $J=4.5$ Hz), 4.11 (1H, d, $J=7.3$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.84 (1H, s), 4.92 (1H, s), 5.04 (1H, t, $J=4.5$ Hz), 5.21–5.26 (2H, m), 5.96–5.98 (2H, m), 6.08 (1H, t, $J=8.3$ Hz), 7.05 (1H, dd, $J=2.5$, 8.3 Hz), 7.19 (1H, d, $J=8.3$ Hz), 7.47 (2H, t, $J=8.3$ Hz), 7.60 (1H, t, $J=8.3$ Hz), 8.02 (1H, d, $J=2.5$ Hz), 8.12 (2H, d, $J=8.3$ Hz); FAB-MS (m/z): 922 ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{48}\text{H}_{63}\text{N}_3\text{O}_{15}\cdot 1.25\text{H}_2\text{O}$: C, 61.04; H, 6.99; N, 4.45. Found: C, 61.05; H, 6.97; N, 4.28; IR: 3409, 2960, 1712, 1581, 1490, 1454 cm^{-1} ; $[\alpha]_{\text{D}}^{24}$ –13.4° (c 0.1, CHCl_3).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(3-hydroxy-2-pyridyl)propionate (20b). Compound **20b** was obtained from **19b** as a white amorphous powder (84%), mp 168–171 °C, by following a procedure analogous to that described for the preparation of **20a** from **19a**. ^1H NMR (CDCl_3) δ : 1.30 (3H, s), 1.43 (9H, s), 1.48 (3H, s), 1.61 (3H, s), 1.77 (3H, s), 1.88–2.31 (5H, m), 2.36 (3H, s), 2.59–2.68 (4H, m), 2.69 (1H, d, $J=3.9$, 14.0 Hz), 2.77 (1H, d, $J=4.5$, 14.0 Hz), 2.94 (1H, d, $J=5.5$ Hz), 3.74 (4H, t, $J=4.5$ Hz), 4.13 (1H, d, $J=7.3$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.34 (1H, d, $J=8.3$ Hz), 4.92 (1H, s), 4.93 (1H, s), 4.96 (1H, d, $J=2.5$ Hz), 5.04 (1H, t, $J=4.5$ Hz), 5.23 (1H, d, $J=7.3$ Hz), 5.30 (1H, dd, $J=2.5$, 8.0 Hz), 5.98 (1H, d, $J=5.5$ Hz), 6.17 (1H, t, $J=8.3$ Hz), 6.48 (1H, d, $J=8.0$ Hz), 7.19–7.22 (1H, m), 7.30–7.33 (1H, m), 7.48 (2H, t, $J=8.3$ Hz), 7.61 (1H, t, $J=8.3$ Hz), 8.03 (1H, dd, $J=1.5$, 4.5 Hz), 8.13 (2H, d, $J=8.3$ Hz); FAB-MS (m/z): 922 ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{48}\text{H}_{63}\text{N}_3\text{O}_{15}\cdot 1.25\text{H}_2\text{O}$: C, 61.04; H, 6.99; N, 4.45. Found: C, 60.91; H, 6.89; N, 4.35; IR: 3411, 2956, 1712, 1600, 1579, 1488, 1452 cm^{-1} ; $[\alpha]_{\text{D}}^{23}$ –28.0° (c 0.03, CHCl_3).

Compounds **23a–f** were obtained by following a procedure analogous to that described for the preparation of **14a** from **13a** by replacing **13a** with the corresponding β -lactams **22a–f**.

(3R, 4S)-1-(tert-Butoxycarbonyl)-4-(5-methyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (23a). A pale yellow syrup (96%); ^1H NMR (CDCl_3) δ : 0.87–0.98 (21H, m), 1.43 (9H, s), 2.32 (3H, s), 5.21 (1H, d, $J=4.9$ Hz), 5.25 (1H, d, $J=4.9$ Hz), 7.22 (1H, d, $J=7.8$ Hz), 7.49 (1H, d, $J=7.8$ Hz), 8.39 (1H, s); HR-MS calcd for $\text{C}_{23}\text{H}_{39}\text{N}_2\text{O}_4\text{Si}$: 435.2629. Found, 435.2661.

(3R, 4S)-1-(tert-Butoxycarbonyl)-4-(5-ethyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (23b). A colorless syrup (92%); ^1H NMR (CDCl_3) δ : 0.86–1.02 (21H, m), 1.22 (3H, t, $J=7.3$ Hz), 1.43 (9H, s), 2.64 (2H, q, $J=7.3$ Hz), 5.22 (2H, s), 7.25 (1H, d, $J=8.0$ Hz), 7.51 (1H, dd, $J=2.0$, 8.0 Hz), 8.41 (1H, s); HR-MS calcd for $\text{C}_{24}\text{H}_{41}\text{N}_2\text{O}_4\text{Si}$: 449.2836. Found, 449.2843.

(3R, 4S)-1-(tert-Butoxycarbonyl)-4-(5-fluoro-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (23c). A colorless syrup (93%); ^1H NMR (CDCl_3) δ : 0.88–1.01 (21H, m), 1.44 (9H, s), 5.20 (1H, d, $J=4.9$ Hz), 5.25 (1H, d, $J=4.9$ Hz), 7.33–7.45 (2H, m), 8.44 (1H, d, $J=2.9$ Hz); HR-MS calcd for $\text{C}_{22}\text{H}_{36}\text{FN}_2\text{O}_4\text{Si}$: 439.2428. Found, 439.2400.

(3R, 4S)-1-(tert-Butoxycarbonyl)-4-(5-chloro-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (23d). A colorless syrup (100%); ^1H NMR (CDCl_3) δ : 0.88–1.02 (21H, m), 1.44 (9H, s), 5.20 (1H, d, $J=4.9$ Hz), 5.24 (1H, d, $J=4.9$ Hz), 7.29 (1H, d, $J=8.3$ Hz), 7.68 (1H, dd, $J=8.3$ Hz, 2.4 Hz), 8.54 (1H, d, $J=2.4$ Hz); HR-MS calcd for $\text{C}_{22}\text{H}_{36}\text{ClN}_2\text{O}_4\text{Si}$: 455.2133. Found, 455.2133.

(3R, 4S)-1-(tert-Butoxycarbonyl)-4-(5-trifluoromethyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (23e). A

colorless syrup (99%); ^1H NMR (CDCl_3) δ : 0.86–1.00 (21H, m), 1.46 (9H, s), 5.27 (1H, d, $J=5.4$ Hz), 5.33 (1H, d, $J=5.4$ Hz), 7.47 (1H, d, $J=8.3$ Hz), 7.95 (1H, d, $J=8.3$ Hz), 8.86 (1H, s); HR-MS calcd for $\text{C}_{23}\text{H}_{36}\text{F}_3\text{N}_2\text{O}_4\text{Si}$: 489.2396. Found, 489.2364.

(3R, 4S)-4-(5-Methoxy-2-pyridyl)-1-(tert-butoxycarbonyl)-3-triisopropylsilyloxy-2-azetidinone (23f). A colorless syrup (91%); ^1H NMR (CDCl_3) δ : 0.88–1.01 (21H, m), 1.43 (9H, s), 3.85 (3H, s), 5.18 (1H, d, $J=5.8$ Hz), 5.24 (1H, d, $J=5.8$ Hz), 7.18–7.28 (2H, m), 8.27 (1H, d, $J=3.0$ Hz); HR-MS calcd for $\text{C}_{23}\text{H}_{39}\text{N}_2\text{O}_5\text{Si}$: 451.2635. Found, 451.2635.

cis-(±)-Acetoxy-1-(4-methoxyphenyl)-4-(5-methyl-2-pyridyl)-2-azetidinone (24a). A mixture of **21a** (0.79 g, 6.55 mmol), 4-anisidine (0.81 g, 6.62 mmol), and Na_2SO_4 (2.0 g) in benzene (15 mL) was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and to this solution were added Et_3N (1.07 mL, 7.69 mmol) and 2-acetoxyacetyl chloride (0.57 mL, 5.1 mmol) at -78°C , and the mixture was allowed to come to room temperature overnight. To the reaction mixture was added water and the whole was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give the title compound (1.5 g, 88%) as a pale orange solid. ^1H NMR (CDCl_3) δ : 1.77 (3H, s), 2.34 (3H, s), 3.75 (3H, s), 5.45 (1H, d, $J=5.0$ Hz), 6.09 (1H, d, $J=5.0$ Hz), 6.80 (2H, m), 7.22 (1H, d, $J=7.8$ Hz), 7.27 (2H, m), 7.43 (1H, dd, $J=1.9$ Hz, 8.3 Hz), 8.42 (1H, dd, $J=1.5$ Hz); FAB-MS (m/z): 327 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.03; H, 5.55; N, 8.50.

Compounds **24d** and **24e** were obtained by following a procedure analogous to that described for the preparation of **24a** from **21a** by replacing **21a** with the corresponding β -lactams **21d** and **21e**.

cis-(±)-Acetoxy-4-(5-chloro-2-pyridyl)-1-(4-methoxyphenyl)-2-azetidinone (24d). Colorless crystals (61%); ^1H NMR (CDCl_3) δ : 1.81 (3H, s), 3.76 (3H, s), 5.46 (1H, d, $J=5.3$ Hz), 6.11 (1H, d, $J=5.3$ Hz), 6.80–6.84 (2H, m), 7.23–7.27 (2H, m), 7.29 (1H, d, $J=8.3$ Hz), 7.66 (1H, dd, $J=8.3$ Hz, 2.4 Hz), 8.59 (1H, d, $J=2.4$ Hz); HR-MS calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_2\text{O}_4$: 347.0799. Found, 347.0771.

cis-(±)-3-Acetoxy-4-(5-trifluoromethyl-2-pyridyl)-1-(4-methoxyphenyl)-2-azetidinone (24e). A pale orange solid (23%); ^1H NMR (CDCl_3) δ : 1.78 (3H, s), 3.77 (3H, s), 5.56 (1H, d, $J=5.3$ Hz), 6.17 (1H, d, $J=5.3$ Hz), 6.83 (2H, d, $J=8.3$ Hz), 7.25 (2H, d, $J=8.3$ Hz), 7.47 (1H, d, $J=7.8$ Hz), 7.93 (1H, d, $J=7.8$ Hz), 8.91 (1H, s).

cis-(±)-1-(4-Methoxyphenyl)-4-(5-methyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (25a). To a solution of **24a** (1.5 g, 4.5 mmol) in a mixture of MeOH (15 mL) and THF (15 mL) was added K_2CO_3 (2.5 mg) with ice

cooling, and the mixture was stirred at room temperature for 1 h. To the reaction mixture was added Dowex 50 (H^+ form) and the whole was stirred at room temperature for 5 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (10 mL) and to this solution were added imidazole (0.73 g, 10.8 mmol) and TIPSCl (1.15 mL, 5.39 mmol) with ice cooling, and the mixture was stirred at room temperature for 14 h. The reaction mixture was poured into ice-water and the mixture was extracted with Et_2O . The extract was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (3:1). The eluate was concentrated under reduced pressure to give the title compound (1.65 g, 85%) as a white powder. ^1H NMR (CDCl_3) δ : 0.90–1.02 (21H, m), 2.32 (3H, s), 3.74 (3H, s), 5.30 (1H, d, $J=4.8$ Hz), 5.31 (1H, d, $J=4.8$ Hz), 6.78–6.79 (2H, m), 7.23–7.28 (2H, m), 7.43 (1H, dd, $J=1.9$ Hz, 8.3 Hz), 8.42 (1H, dd, $J=1.5$ Hz); FAB-MS (m/z): 441 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_3\text{Si}$: C, 68.14; H, 8.23; N, 6.36. Found: C, 67.99; H, 7.95; N, 6.31.

Compounds **25d** and **25e** were obtained by following a procedure analogous to that described for the preparation of **25a** from **24a** by replacing **24a** with the corresponding β -lactams **24d** and **24e**.

cis-(±)-4-(5-Chloro-2-pyridyl)-1-(4-methoxyphenyl)-3-triisopropylsilyloxy-2-azetidinone (25d). Colorless crystals (78%); ^1H NMR (CDCl_3) δ : 0.91–1.02 (21H, m), 3.75 (3H, s), 5.30 (1H, d, $J=4.9$ Hz), 5.32 (1H, d, $J=4.9$ Hz), 6.78–6.82 (2H, m), 7.23–7.28 (2H, m), 7.30 (1H, d, $J=8.3$ Hz), 7.61 (1H, dd, $J=8.3$ Hz, 2.4 Hz), 8.57 (1H, d, $J=2.4$ Hz); FAB-MS (m/z): 461 ($\text{M}+\text{H}$) $^+$; HR-MS calcd for $\text{C}_{24}\text{H}_{33}\text{ClN}_2\text{O}_3\text{Si}$: 460.1949. Found, 460.1955.

cis-(±)-1-(4-Methoxyphenyl)-4-(5-trifluoromethyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (25e). A white powder (36%); ^1H NMR (CDCl_3) δ : 0.89–1.02 (21H, m), 3.75 (3H, s), 5.37 (1H, d, $J=4.9$ Hz), 5.41 (1H, d, $J=4.9$ Hz), 6.81 (2H, d, $J=8.8$ Hz), 7.25 (2H, d, $J=8.8$ Hz), 7.47 (1H, d, $J=8.3$ Hz), 7.86 (1H, dd, $J=1.9$, 8.3 Hz), 8.88 (1H, s). Anal. calcd for $\text{C}_{25}\text{H}_{33}\text{F}_3\text{N}_2\text{O}_3\text{Si}$: C, 60.71; H, 6.72; N, 5.66; F, 11.52. Found: C, 60.81; H, 6.81; N, 5.59; F, 11.24.

(3R,4S)-4-(5-Methyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (22a). To a solution of **25a** (0.98 g, 2.2 mmol) in CH_3CN (40 mL) was added a solution of CAN (3.82 g, 6.6 mmol) in H_2O (30 mL) with ice cooling, and the mixture was stirred at the same temperature for 1.5 h. After saturated aqueous NaHCO_3 , saturated aqueous Na_2SO_3 , and AcOEt were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (1:1). The eluate was concentrated under reduced pressure to give the racemic compound, which was resolved by using a chiral HPLC

column (Daicel Chiralcel OD, with *n*-hexane–2-propanol [94:6 (v/v)] as the solvent) to give the title compound (434 mg, 27%) as a white solid. ^1H NMR (CDCl_3) δ : 0.88–1.01 (21H, m), 2.33 (3H, s), 4.95 (1H, d, $J=4.9$ Hz), 5.25 (1H, dd, $J=2.4, 4.9$ Hz), 6.11 (1H, br s), 7.37 (1H, d, $J=8.3$ Hz), 7.51 (1H, dd, $J=1.5, 8.3$ Hz), 8.37 (1H, s); FAB-MS (m/z): 335 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_2\text{Si}$: C, 64.63; H, 9.04; N, 8.37. Found: C, 64.37; H, 8.90; N, 8.16; $[\alpha]_{\text{D}}^{25} + 80.8^\circ$ (c 1.0, CHCl_3).

Compounds **22d** and **22e** were obtained by following a procedure analogous to that described for the preparation of **22a** from **25a** by replacing **25a** with the corresponding β -lactams **25d** and **25e**. A Daicel Chiralcel AD, with *n*-hexane–2-propanol [95:5 (v/v)] as the solvent, was used for the resolution of ($\pm$)-**22d**, and a Daicel Chiralcel OD, with *n*-hexane–2-propanol [96:4 (v/v)] as the solvent, was used for the resolution of ($\pm$)-**22e**.

(3R, 4S)-4-(5-Chloro-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (22d). Colorless crystals (25%); mp: 106–108 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ : 0.88–1.01 (21H, m), 4.98 (1H, d, $J=4.9$ Hz), 5.25 (1H, dd, $J=4.9$ Hz, 3.0 Hz), 6.85 (1H, br s), 7.45 (1H, d, $J=8.3$ Hz), 7.69 (1H, dd, $J=8.3$ Hz, 2.4 Hz), 8.50 (1H, d, $J=2.4$ Hz); FAB-MS (m/z): 355 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{17}\text{H}_{27}\text{ClN}_2\text{O}_2\text{Si}$: C, 57.52; H, 7.67; N, 7.89; Cl, 9.99. Found: C, 57.69; H, 7.65; N, 7.76; Cl, 10.23; IR: 2942, 2865, 1743 cm^{-1} ; $[\alpha]_{\text{D}}^{23} + 93.0^\circ$ (c 0.52, EtOH).

(3R, 4S)-4-(5-Trifluoromethyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (22e). A white solid (33%); ^1H NMR (CDCl_3) δ : 0.87–1.01 (21H, m), 5.08 (1H, d, $J=4.9$ Hz), 5.32 (1H, dd, $J=4.9, 3.0$ Hz), 6.31 (1H, br s), 7.63 (1H, d, $J=8.3$ Hz), 7.94 (1H, d, $J=8.3$ Hz), 8.83 (1H, s); FAB-MS (m/z): 389 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{18}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_2\text{Si}$: C, 55.65; H, 7.00; N, 7.21. Found: C, 55.64; H, 7.06; N, 7.08; $[\alpha]_{\text{D}}^{24} + 75.7^\circ$ (c 0.17, CHCl_3).

N-(4-Methoxyphenyl)-(5-ethyl-2-pyridyl)methanaldimine (26). A mixture of **21b** (3.0 g, 22.2 mmol), 4-anisidine (2.75 g, 22.3 mmol), and Na_2SO_4 (10 g) in benzene (60 mL) was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was crystallized from *n*-pentane to give the title compound (4.5 g, 84%) as yellow crystals. ^1H NMR (CDCl_3) δ : 1.30 (3H, t, $J=7.3$ Hz), 2.72 (2H, q, $J=7.3$ Hz), 3.84 (3H, s), 6.93–6.97 (2H, m), 7.30–7.34 (2H, m), 7.63 (1H, dd, $J=2.0, 8.0$ Hz), 8.10 (1H, d, $J=8.0$ Hz), 8.53 (1H, d, $J=2.0$ Hz), 8.61 (1H, s).

(3R, 4S)-4-(5-Ethyl-2-pyridyl)-1-(4-methoxyphenyl)-3-triisopropylsilyloxy-2-azetidinone (27). To a solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (4 mL) was added a 1.59 M solution of *n*BuLi in *n*-hexane (1.57 mL, 2.5 mmol) at 0 $^\circ\text{C}$. The solution was stirred at the same temperature for 15 min and then cooled to -78°C . To the mixture was added a solution of **15** (0.92 g, 2.35 mmol) in THF (3.5 mL). The solution was stirred for 2 h followed by addition of a solution of **26** (565 mg, 2.35 mmol) in THF (3.5 mL). The mixture was slowly allowed to warm to room temperature and

further stirred overnight. After saturated aqueous NaHCO_3 and AcOEt were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with water, brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (9:1). The eluate was concentrated under reduced pressure to give the title compound (316 mg, 30%) as a yellow oil. ^1H NMR (CDCl_3) δ : 0.89–1.03 (21H, m), 1.22 (3H, t, $J=7.3$ Hz), 2.63 (2H, q, $J=7.3$ Hz), 3.74 (3H, s), 5.31 (2H, s), 6.77–6.81 (2H, m), 7.25–7.30 (3H, m), 7.45 (1H, dd, $J=2.0, 8.0$ Hz), 8.44 (1H, d, $J=2.0$ Hz); HR-MS calcd for $\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_3\text{Si}$: 454.2652. Found, 454.2668.

(3R, 4S)-4-(5-Ethyl-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (22b). To a solution of **27** (315 mg, 0.69 mmol) in CH_3CN (12.6 mL) was added a solution of CAN (1.14 g, 2.07 mmol) in H_2O (6.3 mL) with ice cooling, and the mixture was stirred at the same temperature for 10 min. After saturated aqueous NaHCO_3 , saturated aqueous Na_2SO_3 , and AcOEt were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt and the combined extract was washed with saturated aqueous NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give the title compound (143 mg, 59%, 79% ee) as yellow crystals. Enantiomeric purity was determined by HPLC analysis on a chiral column, Daicel Chiralcel OD, with *n*-hexane–2-propanol as the solvent. ^1H NMR (CDCl_3) δ : 0.87–1.00 (21H, m), 1.22 (3H, t, $J=7.3$ Hz), 2.64 (2H, q, $J=7.3$ Hz), 4.97 (1H, d, $J=4.5$ Hz), 5.25 (1H, dd, $J=3.0, 4.5$ Hz), 6.35 (1H, br s), 7.39 (1H, d, $J=8.0$ Hz), 7.53 (1H, dd, $J=2.0, 8.0$ Hz), 8.30 (1H, d, $J=2.0$ Hz). Anal. calcd for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_2\text{Si}$: C, 65.47; H, 9.25; N, 8.04. Found: C, 65.27; H, 9.18; N, 7.94.

Methyl (2S,3R)-2-[(3R,4S)-3-acetoxy-4-(5-fluoro-2-pyridyl)-2-oxo-1-azetidinyl]-3-(tert-butylphenylsilyloxy)butyrate (29), methyl (2S,3R)-2-[(3S,4R)-3-acetoxy-4-(5-fluoro-2-pyridyl)-2-oxo-1-azetidinyl]-3-(tert-butylphenylsilyloxy)butyrate (30). To a suspension of **28** (0.5 g, 2.95 mmol) in CH_2Cl_2 (10 mL) were added imidazole (0.44 g, 6.5 mmol), DMAP (5 mg), and TBDPSCl (0.85 mL, 3.3 mmol), and the mixture was stirred at room temperature for 72 h. After AcOEt and water were added to the reaction mixture, the two layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with water, saturated aqueous NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was dissolved in benzene (20 mL). To this solution was added **21c** (0.37 g, 2.95 mmol) and the mixture was stirred under reflux for 1 h. Then, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (12 mL). To this solution were added Et_3N (0.45 mL, 3.2 mmol) and 2-acetoxyacetyl chloride (0.35 mL, 3.2 mmol) at -40°C

and the whole was stirred at -40°C to room temperature overnight. After removal of the solvent, water and AcOEt were added to the residue and the two layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with water, saturated aqueous NH_4Cl , saturated aqueous NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (3:1). The eluate was concentrated under reduced pressure to give the mixture of the title compounds (1.23 g, 72%, **29/30** = 3.5:1) as a yellow oil. ^1H NMR (CDCl_3) δ : 0.86 (9H, s), 1.07 (3H, d, J = 6.4 Hz), 1.74 and 1.76 (total 3H, each s), 3.33 and 3.65 (total 3H, each s), 4.31 and 4.38 (total 1H, each m), 4.45–4.49 (1H, m), 5.41 and 5.67 (total 1H, each d, J = 4.9 Hz), 5.96 and 6.08 (total 1H, each d, J = 4.9 Hz), 7.06–7.08 (2H, m), 7.23–7.67 (10H, m), 8.37 and 8.52 (total 1H, each d, J = 2.4 Hz).

Methyl 2-[(3R,4S)-3-Acetoxy-4-(5-fluoro-2-pyridyl)-2-oxo-1-azetidinyl]-2-butenate (31). To a solution of the mixture of **29** and **30** (3.5:1) (1.23 g, 2.12 mmol) in THF (12.3 mL) was added TBAF (1.0 M in THF, 2.25 mL, 2.25 mmol) with ice cooling, and the mixture was stirred at the same temperature for 15 min. To the reaction mixture was added saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The extract was washed with water, brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give the title compound (0.58 g, 85%) as a colorless syrup. ^1H NMR (CDCl_3) δ : 1.80 (3H, s), 2.12 (3H, d, J = 6.8 Hz), 3.75 (3H, s), 5.73 (1H, d, J = 5.4 Hz), 6.02 (1H, d, J = 5.4 Hz), 6.95 (1H, q, J = 6.8 Hz), 7.25–7.31 (1H, m), 7.39 (1H, dd, 1H, J = 2.9, 8.3 Hz), 8.45 (1H, d, J = 2.9 Hz).

Methyl 2-[(3R,4S)-4-(5-fluoro-2-pyridyl)-2-oxo-3-triisopropylsilyloxy-1-azetidinyl]-2-butenate (32). To a solution of **31** (0.57 g, 1.76 mmol) in a mixture of THF (6.75 mL) and MeOH (6.75 mL) was added K_2CO_3 (15 mg) and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added Dowex 50 (H^+ form) and the mixture was stirred at room temperature for 5 min. The whole was filtered and the filtrate was concentrated under reduced pressure. After drying in vacuo, the residue was dissolved in DMF (6.8 mL) and to this solution were added imidazole (0.18 g, 2.64 mmol) and TIPSCl (0.56 mL, 2.61 mmol) with ice cooling. The whole was stirred at room temperature for 72 h and poured into ice-water. The mixture was extracted with AcOEt and the extract was washed with water, brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (4:1). The eluate was concentrated under reduced pressure to give the title compound (0.47 g, 61%) as a colorless syrup. ^1H NMR (CDCl_3) δ : 0.90–1.05 (21H, m), 2.04 (3H, d, J = 7.3 Hz), 3.73 (3H, s), 5.32 (1H, d, J = 4.9 Hz), 5.55 (1H, d, J = 4.9 Hz), 6.86 (1H, q, J = 7.3 Hz), 7.37–7.40 (2H, m), 8.41 (1H, s).

(3R,4S)-4-(5-Fluoro-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (22c). To a solution of **32** (0.47 g, 1.09 mmol) in a mixture of acetone (9.4 mL) and water (3 mL) were added NaHCO_3 (458 mg, 5.45 mmol) and KMnO_4 (181 mg, 1.14 mmol) at -20°C , and the mixture was stirred at the same temperature for 20 min. To the reaction mixture was added water and the whole was extracted with AcOEt. The extract was washed with water, saturated aqueous NH_4Cl , brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (2:1). The eluate was concentrated under reduced pressure to give the title compound (128 mg, 35%, 54% ee) as colorless crystals. Enantiomeric purity was determined by HPLC analysis on a chiral column, Daicel Chiralcel AD, with *n*-hexane–2-propanol as the solvent. ^1H NMR (CDCl_3) δ : 0.89–1.02 (21H, m), 5.00 (1H, d, J = 4.9 Hz), 5.26 (1H, dd, J = 2.9, 4.9 Hz), 6.32 (1H, br s), 7.41–7.52 (2H, m), 8.41 (1H, d, J = 2.9 Hz). Anal. calcd for $\text{C}_{17}\text{H}_{27}\text{FN}_2\text{O}_2\text{Si}$: C, 60.32; H, 8.04; N, 8.28; F, 5.61. Found: C, 60.40; H, 7.97; N, 8.14; F, 5.47.

(3R,4S)-4-(5-Methoxy-2-pyridyl)-3-triisopropylsilyloxy-2-azetidinone (22f). Compound **22f** was obtained from **21f** as yellow crystals (57%) by following a procedure analogous to that described for the preparation of **13a** from **11a**. ^1H NMR (CDCl_3) δ : 0.89–1.02 (21H, m), 3.86 (3H, s), 4.95 (1H, d, J = 4.9 Hz), 5.23 (1H, dd, J = 2.4, 4.9 Hz), 6.20 (1H, br s), 7.23 (1H, dd, J = 2.9, 8.3 Hz), 7.42 (1H, d, J = 8.3 Hz), 8.30 (1H, d, J = 2.9 Hz); HR-MS calcd for $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_3\text{Si}$: 351.2104. Found, 351.2138.

Compounds **33a–f** were obtained by following a procedure analogous to that described for the preparation of **17a** from **16** by replacing **14a** with the corresponding β -lactams **23a–f**.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-methyl-2-pyridyl)-2-triisopropylsilyloxypropionate (33a). A white amorphous powder (80%); ^1H NMR (CDCl_3) δ : 0.83–0.93 (21H, m), 1.32 (3H, s), 1.42 (9H, s), 1.52 (3H, s), 1.65 (3H, s), 1.82 (3H, s), 1.59–1.78 (2H, m), 1.87 (1H, s), 2.04–2.13 (1H, m), 2.32 (3H, s), 2.51 (3H, s), 2.26–2.32 (1H, m), 2.97 (1H, d, J = 5.4 Hz), 4.20 (1H, d, J = 7.8 Hz), 4.22 (1H, d, J = 7.3 Hz), 4.33 (1H, d, J = 7.8 Hz), 4.96 (1H, br s), 5.21 (1H, d, J = 6.4 Hz), 5.28 (1H, d, J = 7.3 Hz), 5.44–5.48 (2H, m), 5.58 (1H, d, J = 17.1 Hz), 5.78 (1H, s), 5.97–6.00 (2H, m), 6.09 (1H, br t), 7.42–7.46 (3H, m), 7.56 (1H, m), 7.60 (1H, t, J = 7.8 Hz), 8.13 (2H, dd, J = 1.0, 7.3 Hz), 8.38 (1H, d, J = 1.5 Hz); HR-MS calcd for $\text{C}_{55}\text{H}_{79}\text{N}_2\text{O}_{13}\text{Si}$: 1003.5351. Found, 1003.5289.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-ethyl-2-pyridyl)-2-triisopropylsilyloxypropionate (33b). A white amorphous powder (95%); ^1H NMR (CDCl_3) δ : 0.86–1.05 (21H, m), 1.22 (3H, t, J = 7.5 Hz), 1.32 (3H, s), 1.42 (9H, s), 1.43 (3H, s), 1.65

(3H, s), 1.82 (3H, s), 1.91–1.99 (1H, m), 2.23–2.35 (2H, m), 2.53 (3H, s), 2.61–2.67 (3H, m), 2.97 (1H, d, $J=5.5$ Hz), 4.19–4.23 (2H, m), 4.34 (1H, d, $J=8$ Hz), 4.97 (1H, s), 5.21 (1H, d, $J=5.5$ Hz), 5.24–5.31 (2H, m), 5.43–5.60 (3H, m), 5.96–6.05 (2H, m), 6.12 (1H, t, $J=8$ Hz), 7.24–7.31 (1H, m), 7.42–7.58 (4H, m), 8.13 (2H, d, $J=7$ Hz), 8.41 (1H, d, $J=2$ Hz); HR-MS calcd for $C_{56}H_{81}N_2O_{13}Si$: 1017.5508. Found, 1017.5532.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-(5-fluoro-2-pyridyl)-2-triisopropylsilyloxypropionate (33c). A white amorphous powder (74%); 1H NMR($CDCl_3$) δ : 0.87–0.94 (21H, m), 1.20–1.70 (2H, m), 1.31 (3H, s), 1.42 (9H, s), 1.52 (3H, s), 1.65 (3H, s), 1.82 (3H, s), 1.75–2.07 (2H, m), 2.26–2.32 (2H, m), 2.49 (3H, s), 2.97 (1H, d, $J=5.4$ Hz), 4.19–4.23 (2H, m), 4.33 (1H, d, $J=8$ Hz), 4.96 (1H, s), 5.21 (1H, d, $J=5.9$ Hz), 5.27–5.32 (2H, m), 5.43–5.49 (3H, m), 5.58 (1H, d, $J=17.5$ Hz), 5.96–6.04 (2H, m), 6.12 (1H, t, $J=8$ Hz), 7.36–7.47 (4H, m), 7.57 (1H, t, $J=7.3$ Hz), 8.13 (2H, d, $J=7.3$ Hz), 8.43 (1H, d, $J=2.4$ Hz); HR-MS calcd for $C_{54}H_{76}FN_2O_{13}Si$: 1007.5101. Found, 1007.5144.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-chloro-2-pyridyl)-2-triisopropylsilyloxypropionate (33d). A white amorphous powder (71%); 1H NMR ($CDCl_3$) δ : 0.87–0.94 (21H, m), 1.18–1.69 (2H, m), 1.31 (3H, s), 1.41 (9H, s), 1.52 (3H, s), 1.65 (3H, s), 1.82 (3H, s), 1.72–2.05 (2H, m), 2.24–2.34 (2H, m), 2.48 (3H, s), 2.97 (1H, d, $J=5.4$ Hz), 4.19–4.23 (2H, m), 4.33 (1H, d, $J=7.8$ Hz), 4.95 (1H, s), 5.21 (1H, d, $J=5.8$ Hz), 5.27–5.31 (2H, m), 5.42–5.47 (3H, m), 5.58 (1H, d, $J=17.5$ Hz), 5.96–6.04 (2H, m), 6.11 (1H, t, $J=8.8$ Hz), 7.38 (1H, d, $J=8.3$ Hz), 7.44 (2H, t, $J=7.3$ Hz), 7.57 (1H, t, $J=7.3$ Hz), 7.65 (1H, dd, $J=2.5, 8.3$ Hz), 8.13 (2H, d, $J=7.3$ Hz), 8.53 (1H, d, $J=2.5$ Hz); HR-MS calcd for $C_{54}H_{76}ClN_2O_{13}Si$: 1023.4805. Found, 1023.4785.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-trifluoromethyl-2-pyridyl)-2-triisopropylsilyloxypropionate (33e). A white amorphous powder (92%); 1H NMR ($CDCl_3$) δ : 0.85–0.92 (21H, m), 1.31 (3H, s), 1.43 (9H, s), 1.52 (3H, s), 1.65 (3H, s), 1.83 (3H, s), 1.60–1.66 (3H, m), 1.92–1.95 (1H, m), 2.04–2.09 (1H, m), 2.26–2.40 (2H, m), 2.51 (3H, s), 2.98 (1H, d, $J=5.4$ Hz), 4.19–4.23 (2H, m), 4.34 (1H, d, $J=8.3$ Hz), 4.96 (1H, s), 5.21 (1H, d, $J=5.9$ Hz), 5.29 (1H, d, $J=6.8$ Hz), 5.38 (1H, d, $J=9.3$ Hz), 5.45–5.51 (3H, m), 5.58 (1H, d, $J=17.1$ Hz), 5.96–6.05 (2H, m), 6.13 (1H, t, $J=8.8$ Hz), 7.45 (2H, t, $J=7.8$ Hz), 7.55–7.59 (2H, m), 7.93 (1H, d, $J=8.3$ Hz), 8.13 (2H, d, $J=7.3$ Hz), 8.86 (1H, s); HR-MS calcd for $C_{55}H_{76}F_3N_2O_{13}Si$: 1057.59. Found, 1057.5068.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbo-

nylamino)-3-(5-methoxy-2-pyridyl)-2-triisopropylsilyloxypropionate (33f). A white amorphous powder (100%); 1H NMR ($CDCl_3$) δ : 0.89–0.95 (21H, m), 1.32 (3H, s), 1.33–1.62 (2H, m), 1.41 (9H, s), 1.52 (3H, s), 1.65 (3H, s), 1.82 (3H, s), 1.92–2.32 (3H, m), 2.49 (3H, s), 2.98 (1H, d, $J=4.9$ Hz), 3.85 (3H, s), 4.20 (1H, d, $J=7.4$ Hz), 4.22 (1H, d, $J=6.8$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.95 (1H, s), 5.21 (1H, d, $J=5.8$ Hz), 5.26–5.29 (2H, m), 5.39–5.47 (3H, m), 5.57 (1H, d, $J=17.6$ Hz), 5.96–6.02 (2H, m), 6.11 (1H, t-like, $J=8.3$ Hz), 7.15 (H, dd, $J=2.4, 8.8$ Hz), 7.31 (1H, d, $J=8.8$ Hz), 7.44 (2H, t, $J=7.8$ Hz), 7.56 (1H, t, $J=7.8$ Hz), 8.13 (2H, d, $J=7.8$ Hz), 8.26 (1H, d, $J=3.0$ Hz); HR-MS calcd for $C_{55}H_{79}N_2O_{14}Si$: 1019.5301. Found, 1019.5260.

Compounds **34a–f** were obtained by following a procedure analogous to that described for the preparation of **18a** from **17a**.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-methyl-2-pyridyl)propionate (34a). A pale yellow amorphous powder (94%); 1H NMR ($CDCl_3$) δ : 1.27 (3H, s), 1.43 (9H, s), 1.49 (3H, s), 1.64 (3H, s), 1.75 (3H, s), 1.59–1.78 (2H, m), 1.88 (1H, s), 1.91 (1H, m), 2.04–2.13 (2H, m), 2.33 (3H, s), 2.35 (3H, s), 2.33–2.38 (1H, m), 2.94 (1H, d, $J=4.9$ Hz), 4.19 (1H, d, $J=7.3$ Hz), 4.22 (1H, d, $J=8.3$ Hz), 4.33 (1H, d, $J=8.3$ Hz), 4.89 (1H, br s), 4.91 (1H, br s), 4.89–4.91 (1H, m), 5.23 (1H, d, $J=5.9$ Hz), 5.30 (2H, m), 5.46 (1H, d, $J=9.8$ Hz), 5.58 (1H, d, $J=17.1$ Hz), 5.92 (1H, d, $J=9.8$ Hz), 5.96–6.05 (2H, m), 6.09 (1H, t, $J=8.3$ Hz), 7.30 (1H, d, $J=8.3$ Hz), 7.47 (1H, t, $J=7.8$ Hz), 7.45–7.49 (1H, m), 7.52 (1H, dd, $J=1.5, 7.8$ Hz), 7.60 (1H, t, $J=7.8$ Hz), 8.13 (2H, d, $J=7.3$ Hz), 8.35 (1H, s); HR-MS calcd for $C_{46}H_{59}N_2O_{13}$: 847.4017. Found, 847.4095.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-ethyl-2-pyridyl)-2-hydroxypropionate (34b). A white amorphous powder (85%); 1H NMR ($CDCl_3$) δ : 1.23–1.27 (6H, m), 1.43 (9H, s), 1.50 (3H, s), 1.63 (3H, s), 1.74 (3H, s), 1.84–1.89 (2H, m), 2.03–2.13 (1H, m), 2.32–2.38 (1H, m), 2.35 (3H, s), 2.65 (2H, q, $J=7.5$ Hz), 2.93 (1H, d, $J=5$ Hz), 4.17–4.22 (2H, m), 4.32 (1H, d, $J=8.0$ Hz), 4.87–4.92 (3H, m), 5.23 (1H, d, $J=6.5$ Hz), 5.28–5.33 (2H, m), 5.46 (1H, d, $J=10.5$ Hz), 5.58 (1H, d, $J=7.0$ Hz), 5.93–6.05 (3H, m), 6.09 (1H, t, $J=8.0$ Hz), 7.32 (1H, d, $J=7.5$ Hz), 7.46 (1H, t, $J=8.0$ Hz), 7.48–7.61 (2H, m), 8.11 (2H, d, $J=8.0$ Hz), 8.37 (1H, s); HR-MS calcd for $C_{47}H_{61}N_2O_{13}$: 861.4174. Found, 861.4095.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-fluoro-2-pyridyl)-2-hydroxypropionate (34c). A white amorphous powder (99%); 1H NMR ($CDCl_3$) δ : 1.27 (3H, s), 1.20–1.68 (2H, m), 1.44 (9H, s), 1.49 (3H, s), 1.64 (3H, s), 1.74 (3H, s), 1.75–2.05 (2H,

m), 2.30–2.39 (2H, m), 2.34 (3H, s), 2.93 (1H, d, $J=4.9$ Hz), 4.18 (1H, d, $J=6.8$ Hz), 4.23 (1H, d, $J=8.3$ Hz), 4.33 (1H, d, $J=8.3$ Hz), 4.62 (1H, d, $J=2.5$ Hz), 4.90–4.92 (2H, m), 5.24 (1H, d, $J=5.8$ Hz), 5.30 (1H, d, $J=6.8$ Hz), 5.37 (1H, d, $J=9.3$ Hz), 5.46 (1H, d, $J=10.2$ Hz), 5.58 (1H, d, $J=17$ Hz), 5.90 (1H, d, $J=10.2$ Hz), 5.96–6.05 (2H, m), 6.10 (1H, t, $J=7.8$ Hz), 7.40–7.49 (4H, m), 7.60 (1H, t, $J=7.3$ Hz), 8.12 (2H, d, $J=7.3$ Hz), 8.41 (1H, s); HR-MS calcd for $C_{45}H_{56}FN_2O_{13}$: 851.3766. Found, 851.3793.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-chloro-2-pyridyl)-2-hydroxypropionate (34d). A white amorphous powder (100%); 1H NMR ($CDCl_3$) δ : 1.26 (3H, s), 1.22–1.65 (2H, m), 1.43 (9H, s), 1.49 (3H, s), 1.64 (3H, s), 1.74 (3H, s), 1.75–2.09 (2H, m), 2.30–2.39 (2H, m), 2.33 (3H, s), 2.94 (1H, d, $J=4.9$ Hz), 4.18 (1H, d, $J=5.3$ Hz), 4.22 (1H, d, $J=8.3$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.61 (1H, br s), 4.92 (2H, m), 5.24 (1H, d, $J=6.3$ Hz), 5.30 (1H, d, $J=6.8$ Hz), 5.36 (1H, d, $J=9.3$ Hz), 5.46 (1H, d, $J=10.5$ Hz), 5.58 (1H, d, $J=17.5$ Hz), 5.87 (1H, d, $J=9.3$ Hz), 5.96–6.05 (2H, m), 6.11 (1H, t, $J=7.8$ Hz), 7.39 (1H, d, $J=8.3$ Hz), 7.47 (2H, t, $J=7.3$ Hz), 7.60 (1H, t, $J=7.3$ Hz), 7.69 (1H, dd, $J=2.4, 8.3$ Hz), 8.12 (2H, d, $J=7.3$ Hz), 8.51 (1H, d, $J=2.4$ Hz); HR-MS calcd for $C_{45}H_{56}ClN_2O_{13}$: 867.3471. Found, 867.3503.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-trifluoromethyl-2-pyridyl)propionate (34e). A white amorphous powder (76%); 1H NMR ($CDCl_3$) δ : 1.27 (3H, s), 1.44 (9H, s), 1.49 (3H, s), 1.64 (3H, s), 1.75 (3H, s), 1.60–1.91 (3H, m), 2.04–2.09 (2H, m), 2.33–2.40 (2H, m), 2.34 (3H, s), 2.93 (1H, d, $J=4.9$ Hz), 4.18 (1H, d, $J=7.3$ Hz), 4.23 (1H, d, $J=8.3$ Hz), 4.33 (1H, d, $J=8.3$ Hz), 4.65 (1H, br s), 4.92 (1H, s), 4.98 (1H, s), 5.25 (1H, d, $J=6.3$ Hz), 5.31 (1H, d, $J=7.8$ Hz), 5.46 (1H, d, $J=10.8$ Hz), 5.58 (1H, d, $J=17.1$ Hz), 5.90 (1H, d, $J=9.3$ Hz), 5.97–6.05 (2H, m), 6.13 (1H, t, $J=7.8$ Hz), 7.47 (2H, t, $J=7.8$ Hz), 7.57–7.62 (2H, m), 7.96 (1H, d, $J=7.8$ Hz), 8.13 (2H, d, $J=7.8$ Hz), 8.84 (1H, s); HR-MS calcd for $C_{46}H_{55}F_3N_2O_{13}Na$: 923.3554. Found, 923.3472.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-propenylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-methoxy-2-pyridyl)propionate (34f). A white amorphous powder (91%); 1H NMR ($CDCl_3$) δ : 1.26 (3H, s), 1.43 (9H, s), 1.50 (3H, s), 1.60–1.91 (3H, m), 1.64 (3H, s), 1.74 (3H, s), 1.91 (1H, s), 2.04–2.16 (2H, m), 2.32–2.37 (1H, m), 2.34 (3H, s), 2.93 (1H, d, $J=5.3$ Hz), 3.85 (3H, s), 4.18 (1H, d, $J=7.3$ Hz), 4.22 (1H, d, $J=8.3$ Hz), 4.33 (1H, d, $J=8.3$ Hz), 4.79 (1H, br s), 4.85 (1H, br s), 4.92 (1H, br s), 5.23 (1H, d, $J=5.8$ Hz), 5.29–5.30 (2H, m), 5.46 (1H, d, $J=10.3$ Hz), 5.58 (1H, d, $J=17.1$ Hz), 5.90 (1H, d, $J=9.7$ Hz), 5.96–6.03 (2H, m), 6.09 (1H, t-like, $J=8.4$ Hz), 7.22 (1H, dd, $J=2.4, 8.8$ Hz), 7.34 (1H, d, $J=8.8$ Hz), 7.47

(2H, t, $J=7.8$ Hz), 7.60 (1H, t, $J=7.8$ Hz), 8.13 (2H, d, $J=7.8$ Hz), 8.22 (1H, d, $J=2.4$ Hz); HR-MS calcd for $C_{46}H_{59}N_2O_{14}$: 863.3966. Found, 863.4012.

Compounds **35a–f** were obtained by following a procedure analogous to that described for the preparation of **19a** from **18a**.

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-methyl-2-pyridyl)propionate (35a). Colorless small needles (58%), mp 166–168 °C. 1H NMR ($CDCl_3$) δ : 1.26 (3H, s), 1.43 (9H, s), 1.48 (3H, s), 1.60 (3H, s), 1.74 (3H, s), 1.74–2.13 (6H, m), 2.33 (3H, s), 2.34 (3H, s), 2.31–2.36 (1H, m), 2.58–2.68 (4H, m), 2.72 (1H, dd, $J=4.9, 13.2$ Hz), 2.79 (1H, dd, $J=4.9, 13.2$ Hz), 2.93 (1H, d, $J=4.9$ Hz), 3.74 (4H, dd, $J=4.4, 4.9$ Hz), 4.13 (1H, d, $J=6.8$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.86 (1H, d, $J=2.0$ Hz), 4.86–4.92 (1H, br s), 4.92 (1H, br s), 5.04 (1H, t, $J=4.9$ Hz), 5.23 (1H, d, $J=6.8$ Hz), 5.31 (1H, d, $J=9.3$ Hz), 5.91 (1H, d, $J=9.3$ Hz), 5.98 (1H, d, $J=4.9$ Hz), 6.09 (1H, t, $J=8.3$ Hz), 7.30 (1H, d, $J=8.3$ Hz), 7.45–7.53 (1H, t, $J=7.3$ Hz), 7.60 (1H, t, $J=7.3$ Hz), 8.12 (2H, d, $J=7.3$ Hz), 8.35 (1H, s); FAB-MS (m/z): 920 ($M+H$)⁺. Anal. calcd for $C_{49}H_{65}N_3O_{14} \cdot 0.5H_2O$: C, 63.75; H, 7.16; N, 4.52. Found: C, 63.30; H, 7.16; N, 4.42; IR: 3559, 2952, 1724, 1698, 1602, 1575, 1486, 1452 cm^{-1} ; $[\alpha]_D^{25}$ –6.8° (c 0.3, $CHCl_3$).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-ethyl-2-pyridyl)-2-hydroxypropionate (35b). A white powder (61%), mp 148–151 °C. 1H NMR ($CDCl_3$) δ : 1.23–1.26 (6H, m), 1.43 (9H, s), 1.48 (3H, s), 1.60 (3H, s), 1.72 (3H, s), 1.87–1.90 (2H, m), 1.98–2.18 (2H, m), 2.31–2.37 (1H, m), 2.35 (3H, s), 2.57–2.68 (6H, m), 2.72 (1H, dd, $J=4.9, 13.2$ Hz), 2.79 (1H, dd, $J=4.9, 13.2$ Hz), 3.74 (4H, t, $J=4.5$ Hz), 4.12 (1H, d, $J=7.0$ Hz), 4.21 (1H, d, $J=8.0$ Hz), 4.32 (1H, d, $J=8.0$ Hz), 4.86 (1H, d, $J=3.5$ Hz), 4.92 (1H, s), 5.04 (1H, t, $J=4.5$ Hz), 5.22 (1H, d, $J=7.5$ Hz), 5.31 (1H, d, $J=9.0$ Hz), 5.92 (1H, d, $J=9.0$ Hz), 5.98 (1H, d, $J=5.0$ Hz), 6.09 (1H, t, $J=8.0$ Hz), 7.32 (1H, d, $J=8.0$ Hz), 7.47 (2H, t, $J=8.0$ Hz), 7.54 (1H, dd, $J=2.0, 8.0$ Hz), 7.60 (1H, t, $J=8.0$ Hz), 8.12 (1H, d, $J=8.0$ Hz), 8.36 (1H, s); FAB-MS (m/z): 934 ($M+H$)⁺. Anal. calcd for $C_{50}H_{67}N_3O_{14} \cdot 0.75H_2O$: C, 63.38; H, 7.29; N, 4.43. Found: C, 63.32; H, 7.28; N, 4.24; IR: 3423, 2964, 1712, 1600, 1571, 1484, 1452 cm^{-1} ; $[\alpha]_D^{25}$ –5.9° (c 0.15, $CHCl_3$).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-fluoro-2-pyridyl)-2-hydroxypropionate (35c). A white powder (64%), mp 148–152 °C. 1H NMR ($CDCl_3$) δ : 1.26 (3H, s), 1.20–1.69 (2H, m), 1.43 (9H, s), 1.48 (3H, s), 1.62 (3H, s), 1.72 (3H, s), 1.75–2.02 (2H, m), 2.33 (3H, s), 2.30–2.39 (2H, m), 2.59–2.69 (4H, m), 2.71 (1H, dd, $J=5.4, 13.2$ Hz), 2.79 (1H, dd, $J=3.9, 13.2$ Hz), 2.92 (1H, d, $J=4.9$ Hz), 3.74

(4H, t, $J=4.9$ Hz), 4.12 (1H, d, $J=7.3$ Hz), 4.22 (1H, d, $J=8.3$ Hz), 4.32 (1H, d, $J=8.3$ Hz), 4.60 (1H, br s), 4.90–4.92 (2H, m), 5.04 (1H, t, $J=4.9$ Hz), 5.24 (1H, d, $J=6.8$ Hz), 5.36 (1H, d, $J=9.3$ Hz), 5.89 (1H, d, $J=9.8$ Hz), 5.99 (1H, d, $J=4.9$ Hz), 6.09 (1H, t, $J=8.0$ Hz), 7.42–7.49 (3H, m), 7.60 (1H, t, $J=7.3$ Hz), 7.60 (1H, t, $J=7.3$ Hz), 8.12 (2H, d, $J=7.3$ Hz), 8.40 (1H, s); FAB-MS (m/z): 924 ($M+H$)⁺. Anal. calcd for C₄₈H₆₂FN₃O₁₄·H₂O: C, 61.19; H, 6.85; N, 4.46; F, 2.02. Found: C, 61.16; H, 6.85; N, 4.36; F, 2.05; IR: 3438, 2958, 1716, 1600 cm⁻¹; $[\alpha]_D^{25}$ -6.7° (c 0.25, CHCl₃).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-3-(5-chloro-2-pyridyl)-2-hydroxypropionate (35d). A white powder (77%), mp 146–150 °C. ¹H NMR (CDCl₃) δ : 1.26 (3H, s), 1.20–1.72 (2H, m), 1.43 (9H, s), 1.48 (3H, s), 1.63 (3H, s), 1.73 (3H, s), 1.75–2.03 (2H, m), 2.33 (3H, s), 2.30–2.38 (2H, m), 2.59–2.69 (4H, m), 2.72 (1H, dd, $J=5.4$, 13.2 Hz), 2.79 (1H, dd, $J=3.9$, 13.2 Hz), 2.92 (1H, d, $J=4.9$ Hz), 3.74 (4H, t, $J=4.9$ Hz), 4.12 (1H, d, $J=7.9$ Hz), 4.22 (1H, d, $J=8.8$ Hz), 4.32 (1H, d, $J=8.8$ Hz), 4.59 (1H, br s), 4.91 (2H, m), 5.05 (1H, t, $J=4.4$ Hz), 5.24 (1H, d, $J=6.8$ Hz), 5.35 (1H, d, $J=9.3$ Hz), 5.87 (1H, d, $J=9.8$ Hz), 5.99 (1H, d, $J=4.9$ Hz), 6.10 (1H, t, $J=8.0$ Hz), 7.39 (1H, d, $J=8.3$ Hz), 7.47 (2H, t, $J=7.3$ Hz), 7.60 (1H, t, $J=7.3$ Hz), 7.69 (1H, dd, $J=2.5$, 8.3 Hz), 8.12 (2H, d, $J=7.3$ Hz), 8.50 (1H, d, $J=2.5$ Hz); FAB-MS (m/z): 940 ($M+H$)⁺. Anal. calcd for C₄₈H₆₂ClN₃O₁₄·H₂O: C, 60.15; H, 6.73; N, 4.38; Cl, 3.70. Found: C, 60.15; H, 6.74; N, 4.20; Cl, 3.63; IR: 3430, 2956, 1714, 1602 cm⁻¹; $[\alpha]_D^{24}$ -3.0° (c 0.16, CHCl₃).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-trifluoromethyl-2-pyridyl)propionate (35e). A white powder (81%), mp 148–151 °C. ¹H NMR (CDCl₃) δ : 1.26 (3H, s), 1.44 (9H, s), 1.48, 1.61, 1.73 (each 3H, all s), 1.63–1.94 (3H, m), 2.03–2.08 (2H, m), 2.34–2.39 (2H, m), 2.34 (3H, s), 2.59–2.68 (4H, m), 2.70–2.82 (2H, m), 2.92 (1H, d, $J=5.3$ Hz), 3.75 (4H, t, $J=4.4$ Hz), 4.12 (1H, d, $J=7.3$ Hz), 4.23 (1H, d, $J=8.3$ Hz), 4.33 (1H, d, $J=8.3$ Hz), 4.62 (1H, br s), 4.91 (1H, s), 4.98 (1H, d, $J=1.9$ Hz), 5.06 (1H, s), 5.24 (1H, d, $J=7.4$ Hz), 5.46 (1H, d, $J=8.8$ Hz), 5.89 (1H, d, $J=8.8$ Hz), 6.00 (1H, d, $J=4.9$ Hz), 6.12 (1H, t, $J=7.8$ Hz), 7.47 (2H, t, $J=8.3$ Hz), 7.57–7.62 (2H, m), 7.96 (1H, d, $J=8.3$ Hz), 8.12 (2H, d, $J=8.3$ Hz), 8.83 (1H, s), FAB-MS (m/z): 974 ($M+H$)⁺. Anal. calcd for C₄₉H₆₂F₃N₃O₁₄·0.75H₂O: C, 59.60; H, 6.48; N, 4.25; F, 5.77. Found: C, 59.71; H, 6.65; N, 3.96; F, 5.47; IR: 3423, 2954, 1712, 1606, 1577, 1488, 1452, 1367 cm⁻¹; $[\alpha]_D^{23}$ -3.2° (c 0.4, CHCl₃).

(1S, 2S, 3R, 4S, 5R, 8R, 9S, 10R, 13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-1-hydroxy-9,10-[(1S)-2-(morpholino)ethylidenedioxy]tax-11-en-13-yl (2R, 3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-(5-methoxy-2-pyridyl)propionate (35f). Colorless small needles (51%), mp 160–161 °C. ¹H NMR (CDCl₃) δ : 1.27 (3H, s), 1.43 (9H,

s), 1.48 (3H, s), 1.60 (3H, s), 1.72 (3H, s), 1.78–2.12 (6H, m), 2.31–2.38 (1H, m), 2.34 (3H, s), 2.58–2.68 (4H, m), 2.71 (1H, dd, $J=5.4$, 13.2 Hz), 2.79 (1H, dd, $J=3.9$, 13.2 Hz), 2.93 (1H, d, $J=5.3$ Hz), 3.75 (4H, t, $J=4.9$ Hz), 3.86 (3H, s), 4.12 (1H, d, $J=7.3$ Hz), 4.21 (1H, d, $J=8.3$ Hz), 4.33 (1H, d, $J=8.3$ Hz), 4.76 (1H, br s), 4.85 (1H, br s), 4.92 (1H, s), 5.04 (1H, t, $J=4.6$ Hz), 5.23 (1H, d, $J=6.9$ Hz), 5.29 (1H, d, $J=8.8$ Hz), 5.90 (1H, d, $J=9.3$ Hz), 5.98 (1H, d, $J=4.9$ Hz), 6.08 (1H, t-like, $J=8.3$ Hz), 7.22 (1H, dd, $J=2.9$, 8.8 Hz), 7.34 (1H, d, $J=8.8$ Hz), 7.47 (2H, t, $J=7.8$ Hz), 7.60 (1H, t, $J=7.8$ Hz), 8.13 (2H, d, $J=7.8$ Hz), 8.22 (1H, d, $J=2.9$ Hz), FAB-MS (m/z): 936 ($M+H$)⁺. Anal. calcd for C₄₉H₆₅N₃O₁₅: C, 62.87; H, 7.00; N, 4.49. Found: C, 62.66; H, 7.08; N, 4.28; IR: 3542, 2950, 1729, 1720, 1600, 1581, 1481, 1450 cm⁻¹; $[\alpha]_D^{24}$ -2.1° (c 0.77, CHCl₃).

In vitro cytotoxicity. To examine the direct growth-inhibitory effects of the test compounds against P388 mouse leukemia, PC-6 and PC-12 human non-small cell lung cancer cell lines, and resistant cell lines PC-6/VCR29-9 and PC-6/VP1-1, the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide] assay was performed. The concentration giving a growth inhibition of 50% (GI₅₀) was calculated according to a published procedure.¹³

In vitro metabolic stability. The reaction mixture consisted of 4 mM MgCl₂, 10 mM disodium glucose-6-phosphate, 1 unit/mL glucose-6-phosphate dehydrogenase, 1 mM β -NADPH, 10 μ M test compound, and 1 mg protein/mL liver microsomes of each animal in 0.1 M potassium phosphate buffer (pH 7.4) at a final volume of 0.5 mL. This mixture was preincubated for 2 min at 37 °C and the reaction was started by the addition of 10 μ L (to the 0.49 mL of mixture) β -NADPH. After incubation at 37 °C, the reaction was stopped by adding 1 mL of acetonitrile. After centrifugation, the supernatant fraction was applied for analysis.

References and Notes

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