Flexible Enantiodivergent Synthesis and Biological Activity of Mannostatin Analogues, New Cyclitol Glycosidase Inhibitors

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Received June 21, 1995[⊗]

Mannostatin A (**1**) is a new cyclitol inhibitor of glycoprotein processing. 2-Epimannostatin A (**12**) and its enantiomer (**13**) as well as their positional isomers (**14**, **15**) were designed for probing structure−activity relationships in this class of glycosidase inhibitors. The analogues have been synthesized from (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-cyclopentenone by an enantiodivergent strategy in a totally stereospecific fashion. Compound **13** showed inhibition against almond β-glucosidase and is shown to be a topographical analogue of β-D-glucopyranoside.

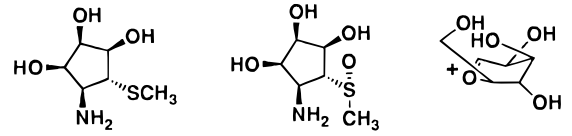
Introduction

Oligosaccharides, in the form of glycoproteins, are involved in a variety of biological functions such as immune response, oncogenesis, metastasis of tumors, and viral infection, *etc.* Specific inhibitors of the glycosidases involved in the biosynthesis of the oligosaccharide chains of glycoproteins have been useful in unraveling how glycosidases catalyze hydrolysis[1] and how they produce beneficial pharmaceutical effects in their roles as antiviral,[2] antimetastatic,[3] antitumor,[4] or immunoregulatory agents.[3a,5]

In 1989, mannostatins A [**1**, (1*R*,2*R*,3*R*,4*S*/5*R*)-4-amino-5-(methylthio)-1,2,3-cyclopentanetriol] and B (**2**) were isolated from the culture filtrate of *Streptoverticillium verticillus* var. *quintum* ME3-AG3 and were shown to be potent competitive inhibitors of the rat epididymal α-mannosidase.[6] Compound **1** also competitively and potently inhibited jack bean, mung bean, and rat liver lysosomal α-mannosidases and proved to be a potent inhibitor of the Golgi glycoprotein-processing enzyme mannosidase II but was inactive against the processing mannosidase I.[7] In cell culture, **1** blocked the normal processing of influenza viral glycoproteins, resulting in the accumulation of hybrid types of oligosaccharides.[7]

The structure of **1** is quite distinct from the usual glycohydrolase inhibitors, which are polyhydroxylated monocyclic or bicyclic alkaloids resembling the corresponding glycose, such as nojirimycin,[8] galactostatin,[9] castanospermine,[10] swainsonine,[11] and their congeners.[12] The structure−activity relationship of **1** is unclear since the structure of an aminocyclopentanetriol bearing sulfur has little resemblance either to D-mannose or to the mannosyl cation **3** (Chart 1), the transition-state intermediate in this enzymatic hydrolysis.[13] It is even more ambiguous that the antipode of **1**, rather than **1** itself, more closely resembles **3**.[14]

Chart 1



Mannostatin A (1) Mannostatin B (2) Mannopyranosyl cation (3)

Due to its intriguing chemical structure and inhibitory mechanism, **1** has become an attractive synthetic target, resulting in four independent syntheses[14,15] and an improved synthesis.[16] Several analogues and derivatives of **1** have also been designed and synthesized for a mechanistic investigation.[17] Our need for specific glucosidase inhibitors arose in connection with projects on antitumor metastasis and anti-AIDS studies. The observation that some glucosidase inhibitors show antitumor metastasis[3a,e] and anti-HIV[18] activities prompted us to rationally design specific glucosidase inhibitors modeled after **1**. Here we report a flexible enantiodivergent synthesis of analogues of **1** that exhibit glucosidase inhibition.

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1996.

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Scheme 1

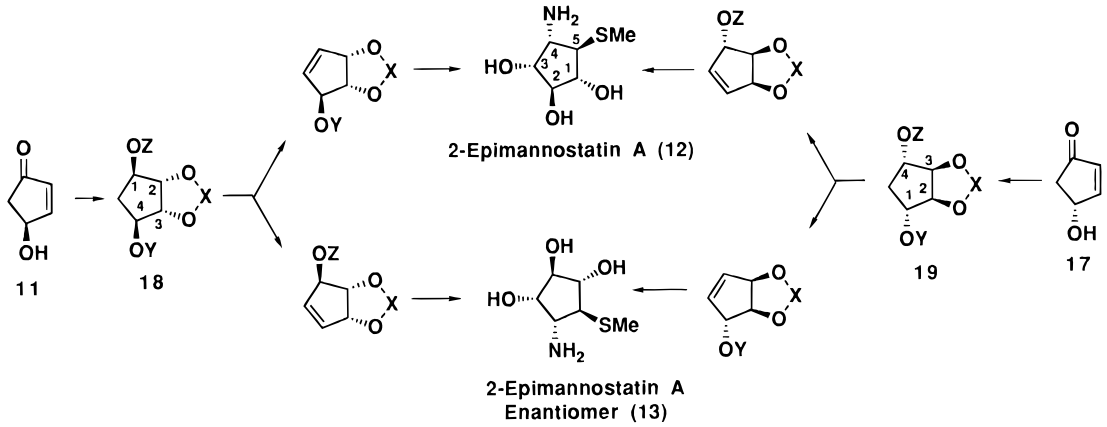


Chart 2

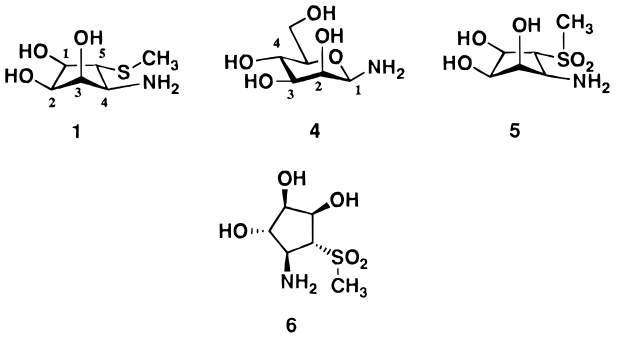
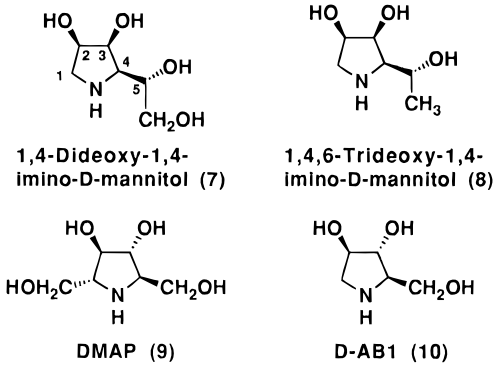


Chart 3



Results and Discussion

The structure of **1** is different from other well-documented mannosidase inhibitors such as 1-deoxymannojirimycin,[19] swainsonine,[11] kifunensine,[20] and mannoamidrazone[21] which closely resemble D-mannose or mannopyranosyl cation **3**. King and Ganem[17] have noted that **1** resembles β-D-mannopyranosylamine (**4**), a competitive inhibitor of mannosidase (Chart 2). They also found that mannostatin sulfone **5** showed the similar activity to **1** for jack bean α-mannosidase. They synthesized 3-epimannostatin sulfone **6** for the purpose of transforming **1** from a mannosidase inhibitor to a glucosidase inhibitor. However, **6** showed no significant inhibition against almond β-glucosidase or jack bean α-mannosidase. A synthetic antipode of **1** also had little affect on the α-mannosidases.[17] While the synthetic polyhydroxylated pyrrolidines, 1,4-dideoxy-1,4-imino-D-mannitol (**7**) and 1,4,6-trideoxy-1,4-imino-D-mannitol (**8**), show the specific inhibitory activity against mannosidases, the natural ones, DMAP (**9**) and D-AB1 (**10**), are specific glucosidase inhibitors (Chart 3).[22] It is now clear that both **7** and **8** superimpose very well on the energy-minimized mannosyl cation, but **10** lacks the OH group equivalent to the cation's C2-OH.[22b] This suggests that epimerization of the C2 hydroxy group of **1**, which equates to C3 of **7** and **8** and C2 of D-mannose or mannosyl cation, would instill inhibitory activity against the glucosidases.

On the basis of this supposition, 2-epimannostatin A (**12**) and its enantiomer **13**, as well as their positional isomers **14** and **15**, were targeted as specific glucosidase inhibitors and as tools to probe the roles of methylthio and amino substituents on the inhibition of enzymatic hydrolysis.

Since our interest in this class of inhibitors encompassed both enantiomerically pure stereoisomers and positional isomers, we developed a highly flexible enantiodivergent strategy utilizing both (*S*)-4-hydroxy-2-cyclopentenone (**11**) and its 4*R*-isomer **17**,[23] as outlined in Scheme 1. Our approach to the desired analogues involves, as the key steps, the regio- and stereoselective introduction of three different heteroatom functions on each carbon of the same mesointermediates, **18** and **19**, by differentiation of these positions. We report an enantiodivergent route to the desired compounds starting from (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-cyclopentenone (**16**).[23]

Reduction of **16** with diisobutylaluminum hydride followed by protection gave **21** (Scheme 2). Compound **21** was effectively converted to the pivotal intermediate, mesotetrol **23**, by the sequence of Woodward reaction,[24] methanolysis and protection with an isopropylidene group. Assignment of the relative stereochemistry of **23** was based on nuclear Overhauser effects (NOEs), which were evident between 7-CH_3 and 2-H, 7-CH_3 and 3-H,

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(23) Optically pure **16** ($[\alpha]^{23}_D$ −65.4° (*c* 0.96, CH_3OH)) and its 4*R*-isomer ($[\alpha]^{22}_D$ +67.4° (*c* 0.4, CH_3OH)) were kindly donated from Institute for Bio-medical Research, Teijin Limited: (a) Tanaka, T. Jpn. Pat. 54-163510; Japan Kokai 56-86128. (b) Tanaka, T.; Kurozumi, S.; Toru, T.; Miuya, S.; Kobayashi, M.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1713.
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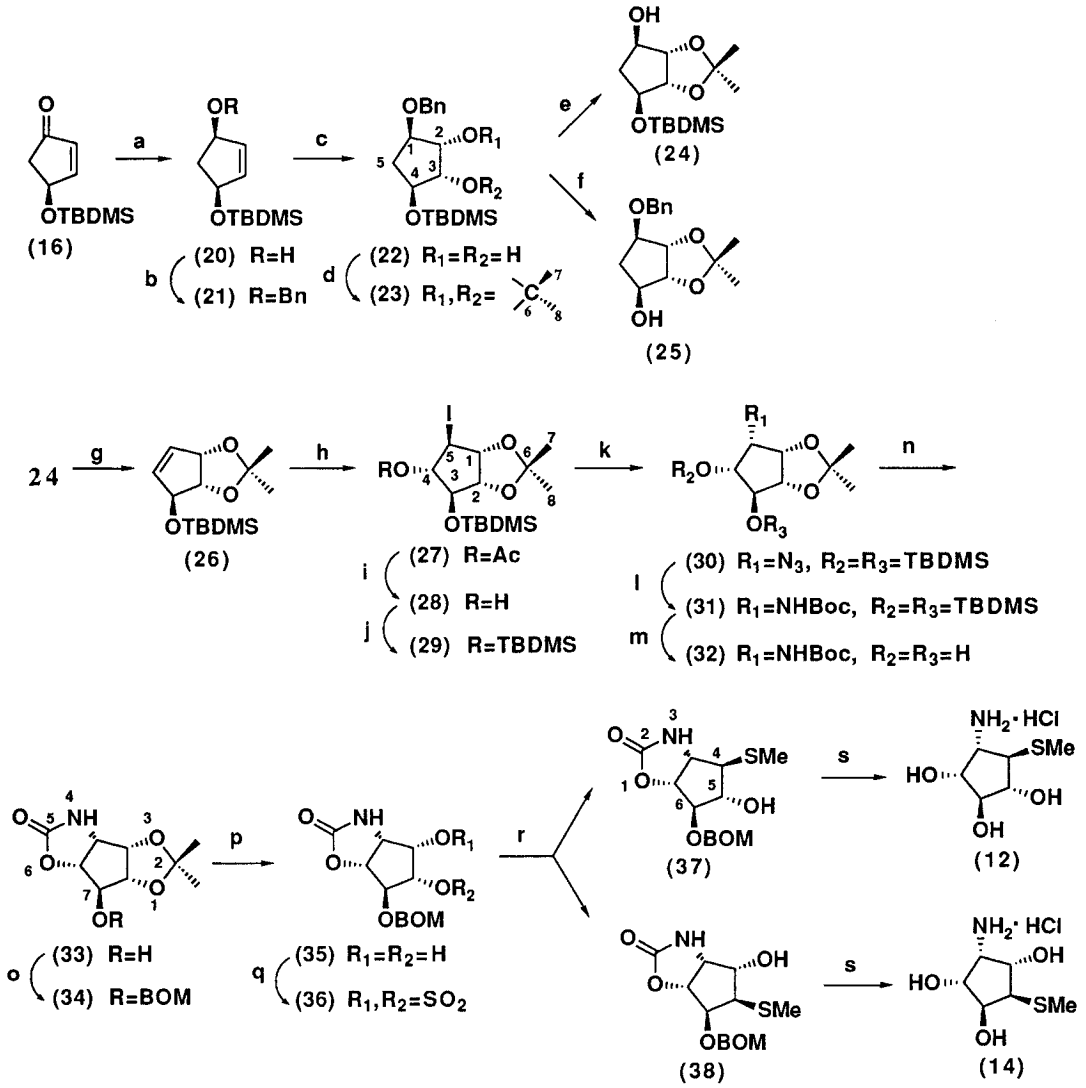
Scheme 2



a) DIBALH, benzene b) BnBr, NaH, Bu_4NI, THF c) AgOAc, I_2, wet AcOH; MeONa, MeOH d) $Me_2C(OMe)_2$, D-camphor-10-sulfonic acid, CH_2Cl_2 e) H_2, Pd/C, MeOH f) Bu_4NF, THF g) Ph_3P, DEAD, benzene h) AgOAc, I_2, benzene i) NH_3/MeOH j) TBDMSCl, imidazole, DMF k) NaN_3, DMSO l) H_2, Pd/C, AcOEt-MeOH; $(t\text{-BuOCO})_2O$, EtN*i*-Pr_2, CH_2Cl_2 m) Bu_4NF, THF n) NaH, DMF o) BOMCl, EtN*i*-Pr_2, DMF p) aq. AcOH q) $SOCl_2$, py, CH_2Cl_2; $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O r) NaSMe, DMF; H_2SO_4, H_2O-THF s) $Ba(OH)_2$, H_2O; HCl/dioxane

8-CH_3 and 1-H, and 8-CH_3 and 4-H. The differentiation of C1 and C4 of meso **23** was accomplished by selective removal of each protecting group. Catalytic hydrogenolysis of **23** with Pd/C afforded 1-hydroxy derivative **24** in good yield, while treatment with tetrabutylammonium fluoride gave 4-hydroxy derivative **25** quantitatively. Treatment of **24** with triphenylphosphine and diethyl azodicarboxylate smoothly eliminated the hydroxy group to provide **26**. The amino-hydroxylation of **26** was successfully achieved by a silver acetate−iodine reaction,[25] displacement of the iodo group of the appropriately protected derivative with an azido group, and hydrogenolysis, in good yield. The stereochemistry of **27** was established by NOE experiments, which revealed enhancements between 4-H and 1-H, 4-H and 2-H, 3-H and 5-H, 7-CH_3 and 1-H, 7-CH_3 and 2-H, 8-CH_3 and 3-H, and 8-CH_3 and 5-H. This stereochemical assignment was later confirmed by X-ray crystallographic analysis of **47** (*vide infra*).

The last issue was the introduction of the methylthio group to the desired position of thus obtained aminocyclitol **31**. A problem arose, however, as removal of the isopropylidene group of **31** proceeded without chemoselectivity, and substitution of sulfonates of the corresponding monocyclic aminocyclitol with nucleophiles such as methylthio or thioacetyl was accompanied by elimination of the hydroxy group at the position under consideration. This was circumvented by nucleophilic substitution of the cyclic sulfate function of the fused tricyclic system with sodium thiomercaptide. The desired compound **36** was effectively obtained by the successive removal of the *O-tert*-butyldimethylsilyl group, cyclic carbamate formation with NaH, protection of the hydroxy group, acid hydrolysis, and cyclic sulfate formation[26] by treatment

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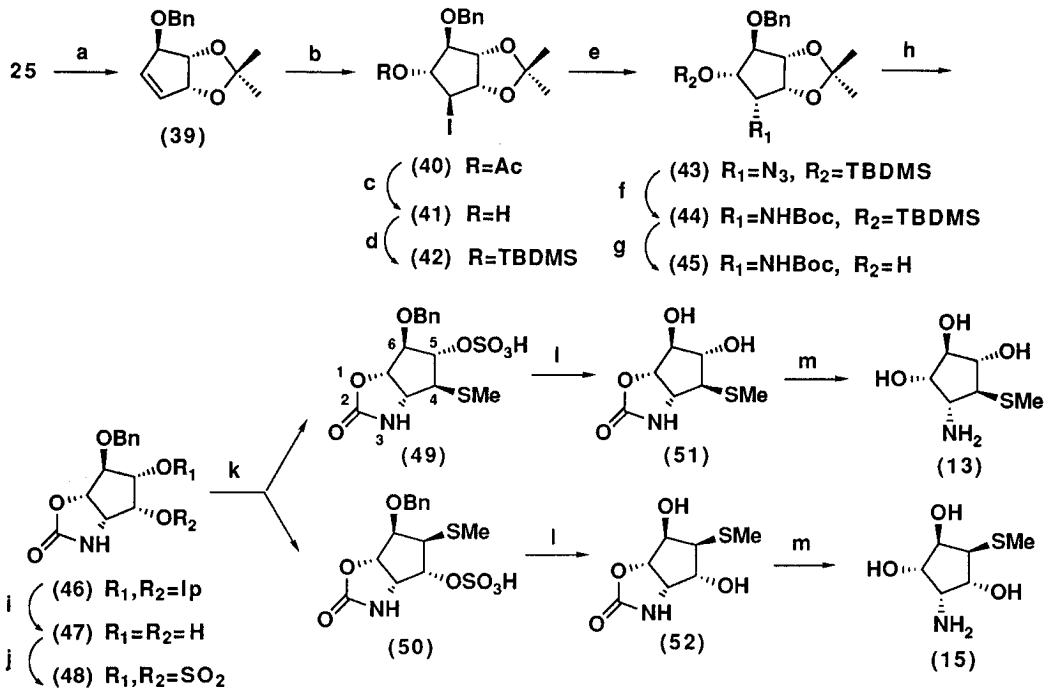
Scheme 3



a) Ph_3P, DEAD, benzene b) AgOAc, I_2, benzene c) NH_3/MeOH d) TBDMSCl, imidazole, DMF e) NaN_3, DMSO f) H_2, Pd/C, AcOEt-MeOH; (t-BuOCO)$_2$O, EtNi-Pr$_2$, CH_2Cl_2 g) Bu_4NF, THF h) NaH, DMF i) aq. AcOH j) $SOCl_2$, py, CH_2Cl_2; $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O k) NaSMe, DMF l) H_2SO_4, H_2O-THF; Me_3SiI, CH_2Cl_2 m) $Ba(OH)_2$, H_2O

with $SOCl_2$ and pyridine in CH_2Cl_2, followed by oxidation with $RuCl_3$ and $NaIO_4$ in $CCl_4-CH_3CN-H_2O$. The sulfate **36** smoothly underwent the nucleophilic displacement with sodium thiomercaptide to generate **37** and **38** in a 1:1 ratio after hydrolysis with catalytic H_2SO_4 in THF. The mixture was easily separated by preparative thin-layer chromatography. The regiochemistry of **37** was determined by the aid of $^1H-^1H$ shift correlation (COSY), $^1H-^{13}C$ COSY and heteronuclear multiple bond correlation (HMBC) experiments. The strong correlations between SCH_3-H (2.21 ppm) and C-4 (55.54 ppm) and between 4-H (2.88 ppm) and SCH_3-C (14.27 ppm) were observed in the HMBC, while no correlations between SCH_3-H and C-5 and between 5-H and SCH_3-C were observed. Removal of the protecting groups of **37** and **38** by alkaline and acid hydrolysis resulted in 2-epimannostatin hydrochloride **12** and its positional isomer **14**, respectively. Their enantiomers **13** and **15** were also successfully obtained from **25** by a similar sequence of reactions varying in the removal of the *O*-benzyl group of **49** and **50** with trimethylsilyl iodide. Part of a series of enantiomers, cyclic carbamate **47** was crystallized from ethyl acetate−methanol to give a single crystal for X-ray diffraction analysis. The X-ray analysis clearly indicated the desired absolute stereochemistry.[27] The regiochemistry of **49** and **50** was also clarified by HMBC experiments, which showed strong correlations between SCH_3-H (C) and C-4 (4-H) and between SCH_3-H (C) and C-5 (5-H), respectively. HMBC spectra of **13** and **15** also showed strong correlations between SCH_3-H (C) and C-5 (5-H), indicative of the regiochemistries shown in Scheme 3.

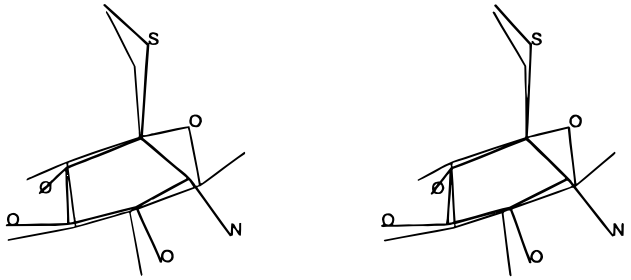
(27) The authors have deposited atomic coordinates for structure **47** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 IEZ, U.K.

To determine whether epimerization at C2 and inversion of absolute stereochemistry of **1** lead to an alteration of enzyme specificity, **12** and its antipode **13** as well as **1** were assayed against bakers' yeast α-glucosidase, almond β-glucosidase, jack bean α-mannosidase, snail β-mannosidase, *Escherichia coli* α-galactosidase, *Saccharomyces fragilis* β-galactosidase, and bovine liver β-glucuronidase. The antipode **13** only affected almond β-glucosidase (IC_{50} 8 μg/mL). Neither **12** nor **13** significantly inhibited any of these enzymes (IC_{50} >100 μg/mL). The position isomers **14** and **15** also showed no inhibitory activity against these enzymes. Compound **1** proved to be a specific inhibitor for jack bean α-mannosidase (IC_{50} 0.04 μg/mL).

Clearly, the configuration at C2 as well as the absolute stereochemistry of **1** plays an important role in mannosidase inhibition. Molecular modeling was undertaken to understand the structure-inhibition relation of **13**. The structures were optimized first with molecular mechanics (MM2) and then with PM3 in MOPAC. Molecular modeling revealed that **13** superimposes well on the chair form of β-D-glucopyranose and has its three hydroxyl groups lying in the same region of space as C2, C3, and C4 of the glucose. The C4-NH_2 group of **13** would interact with the amino acid residue of the enzyme instead of the water molecule which participates in hydrolysis[26] (Chart 4). These results would suggest that **13** mimics glucopyranoside in ground-state binding to glucosidases and thereby inhibits the enzymatic reaction.

The enantiodivergent route to mannostatin A analogues presented here should offer a useful approach to these multifunctionalized cyclopentanes which can behave as carbohydrate mimics, promising to be potent glycosidase inhibitors. The synthetic intermediates are

Chart 4. Superimposition of 2-Epimannostatin A Enantiomer (13) and β-D-Glucopyranose. Hydrogen Atoms Are Omitted for Clarity



highly flexible in terms of alteration of the diastereo- and enantiomerism and the regioplacement of the functionality.

Experimental Section

(1*R*,4*S*)-4-*O*-(*tert*-Butyldimethylsilyl)cyclopent-2-ene-1,4-diol (20). To a solution of **16** (4.87 g, 23 mmol) in dry benzene (97 mL) was added dropwise a solution of diisobutylaluminum hydride (DIBALH) in toluene (1 M, 23 mL, 23 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. After the reaction was quenched with a large excess of saturated aqueous Na_2SO_4 solution, the resulting insoluble matters were filtered off. Evaporation of the solvent gave an oil, which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with chloroform−methanol (70:1) gave a colorless liquid of **20** (4.4 g, 90%): $[\alpha]^{28}_D$ −33.6° (*c* 0.35, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 0.09 (6H, s), 0.89 (9H, s), 1.52 (1H, dt, J = 4.4 and 13.7 Hz), 1.68 (1H, broad d, J = 8.8 Hz), 2.69 (1H, dt, J = 6.8 and 13.7 Hz), 4.59 (1H, broad m), 4.66 (1H, m), 5.89 (1H, broad d with small couplings, J = 5.4 Hz), and 5.95 (1H, broad d with small couplings, J = 5.4 Hz); mass spectrum (FAB^+) *m*/*z* (relative intensity) 215 $(M + H)^+$ (11), 197 (57), 107 (28), 73 (100).

(1*R*,4*S*)-1-*O*-Benzyl-4-*O*-(*tert*-butyldimethylsilyl)cyclopent-2-ene-1,4-diol (21). To a solution of **20** (4.3 g, 20 mmol) in dry THF was added NaH (60% in oil, 1.7 g, 42 mmol) at −10 °C. After the mixture was stirred at room temperature for 30 min, tetrabutylammonium iodide (3.4 g, 9.2 mmol) and benzyl bromide (7.1 mL, 60 mmol) were added to the mixture. Then the resulting mixture was stirred at room temperature for 1 h. After quenching with a small amount of water at −10 °C, evaporation of the solvent gave an oil, which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with dichloromethane gave a liquid of **21** (6 g, 98%): $[\alpha]^{27}_D$ −2.2° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.08 (6H, broad s), 0.90 (9H, s), 1.65 (1H, dt, J = 5.4 and 13.2 Hz), 2.68 (1H, dt, J = 6.6 and 13.2 Hz), 4.45 (1H, m), 4.52 and 4.57 (2H, ABq, J = 11.9 Hz), 4.59 (1H, m), 5.89 (1H, m), 5.96 (1H, m,) and 7.1−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 305 $(M + H)^+$ (9), 197 (100), 165 (31), 91 (76), 75 (60), 73 (62).

(1*R*,2*R*,3*S*,4*S*)-1-*O*-Benzyl-4-*O*-(*tert*-butyldimethylsilyl)cyclopentane-1,2,3,4-tetrol (22). To a solution of **21** (5.9 g, 19 mmol) in acetic acid (120 mL) were added CH_3CO_2-Ag (14 g, 84 mmol) and iodine (9.7 g, 38 mmol), and the mixture was stirred at room temperature for 1.5 h. After addition of 4% aqueous acetic acid solution, the mixture was further stirred at 50 °C for 4 h. After removal of insoluble matters by filtration, the filtrate was evaporated to give an oil. The oil was dissolved in $CHCl_3$, and the solution was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with chloroform−methanol (100:1) gave an oil (6.1 g). The oil was dissolved in dry methanol (92 mL), and sodium methoxide in methanol (1 M, 5 mL) was added to the mixture. After being stirred at room temperature for 30 min, evaporation of the solvent gave an oil, which was subjected to column chromatography on silica gel. Elution with chloroform−methanol (70:1) gave an oil of **22** (5.4 g, 83%): $[\alpha]^{25}_D$ −2.9° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.05 and 0.06 (each 3H, s), 0.88 (9H, s), 1.53 (1H, dt, J = 7.0 and 13.5 Hz), 2.3−2.5 (3H, m), 3.82 (1H, dt, J = 4.3 and 7.0 Hz), 4.01 (1H, dt, J = 5.0 and 7.0 Hz), 4.55 (2H, t, J = 11.9 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 339 $(M + H)^+$ (61), 91 (100), 73 (81).

(1*R*,2*S*,3*S*,4*S*)-1-*O*-Benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (23). To a solution of **22** (3.3 g, 9.8 mmol) in CH_2Cl_2 (40 mL) were added 2,2-dimethoxypropane (4 mL, 32 mmol) and D-camphor-10-sulfonic acid (160 mg, 0.69 mmol), and the mixture was stirred at room temperature for 30 min. After addition of a saturated aqueous $NaHCO_3$ solution (10 mL) and dilution with CH_2Cl_2 (100 mL), the mixture was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the solvent gave an oil, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave an oil of **23** (3.5 g, 95%): $[\alpha]^{25}_D$ −4.6° (*c* 0.9, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.07 and 0.09 (each 3H, s), 0.88 (9H, s), 1.29 and 1.43 (each 3H, s), 1.88 (1H, dt with small couplings, J = 5.4 and 13.9 Hz), 2.21 (1H, dt, J = 5.4 and 13.9 Hz), 3.82 (1H, dt, J = 2.0 and 5.4 Hz), 4.15 (1H, dt, J = 2.0 and 5.4 Hz), 4.46 (1H, broad d with a small coupling, J = 6.6 Hz), 4.56 (2H, t, J = 12.5 Hz), 4.63 (1H, broad d with small couplings, J = 6.6 Hz), and 7.15−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 379 $(M + H)^+$ (25), 229 (53), 129 (53), 91 (100), 73 (91).

(1*R*,2*S*,3*S*,4*S*)-4-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (24). The solution of **23** (1.85 g, 4.9 mmol) in a mixture of ethyl acetate (30 mL) and methanol (60 mL) was stirred with 10% Pd/C (1 g) under a hydrogen atmosphere for 7 h. The catalysts were filtered off, and the filtrate was evaporated to give an oil of **26** (1.46 g, 100%): $[\alpha]^{25}_D$ −4.5° (*c* 0.98, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 0.12 and 0.13 (each 3H, s), 0.89 (9H, s), 1.29 and 1.39 (each 3H, s), 1.77 (1H, broad d with small couplings, J = 14.2 Hz), 2.09 (1H, broad dt with small couplings, J = 4.1 and 14.2 Hz), 3.21 (1H, d, J = 10.9 Hz), 4.09 (1H, broad dd, J = 4.1 and 10.9 Hz), 4.13 (1H, broad d, J = 4.1 and 5.4 Hz), 4.51 (1H, dd, J = 1.5 and 5.4 Hz), 4.66 (1H, dd, J = 2.0 and 5.4 Hz); mass spectrum (FAB^+) *m*/*z* (relative intensity) 289 $(M + H)^+$ (100), 231 (30), 173 (24), 73 (37).

(1*R*,2*S*,3*R*,4*S*)-1-*O*-Benzyl-2,3-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (25). To a solution of **23** (1.7 g, 4.5 mmol) in THF (18 mL) was added tetrabutylammonium fluoride in THF (1 M, 6.8 mL, 6.8 mmol). After stirring at room temperature for 30 min, evaporation of the solvent gave an oil. The oil was dissolved in CH_2Cl_2, and the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with chloroform−methanol (150:1) gave an oil of **25** (1.3 g, 100%): $[\alpha]^{25}_D$ 0° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 1.21 and 1.30 (each 3H, s), 1.87 (1H, broad d, J = 14.7 Hz), 2.02 (1H, dt, J = 4.4 and 14.7 Hz), 2.80 (1H, broad d, J = 10.9 Hz), 3.91 (1H, broad d, J = 4.4 Hz), 4.02 (1H, broad dd, J = 4.4 and 10.9 Hz), 4.46 and 4.55 (2H, ABq, J = 11.9 Hz), 4.53 (1H, dd, J = 1.6 and 5.6 Hz), 4.64 (1H, dd, J = 1.7 and 5.6 Hz), and 7.1−7.3 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 265 $(M + H)^+$ (37), 107 (25), 91 (100).

(1*S*,2*S*,3*S*)-3-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidenecyclopent-4-ene-1,2,3-triol (26). To a solution of **24** (2.8 g, 9.7 mmol) in dry benzene (77 mL) were added triphenylphosphine (10.2 g, 39 mmol) and diethyl azodicarboxylate (6.1 mL, 39 mmol), and the mixture was stirred at room temperature overnight. After addition of water, evaporation of the solvent gave an oil. The oil was dissolved in $CHCl_3$, and the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave a liquid of **7** (1.9 g, 72%): $[\alpha]^{23}_D$ −116°

(*c* 0.48, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.09 and 0.12 (each 3H, s), 0.89 (9H, s), 1.24 and 1.29 (each 3H, s), 4.44 (1H, d, J = 5.4 Hz), 4.74 (1H, m), 5.26 (1H, broad d with small couplings, J = 5.4 Hz), 5.78 (1H, broad d with small couplings, J = 5.9 Hz), and 5.90 (1H, broad d with small couplings, J = 5.9 Hz); mass spectrum (FAB^+) m/z (relative intensity) 271 $(M + H)^+$ (45), 213 (88), 73 (100).

(1*R*,2*S*,3*R*,4*S*,5*S*)-4-*O*-Acetyl-3-*O*-(*tert*-butyldimethylsilyl)-5-iodo-1,2-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (27). To a solution of **26** (2.3 g, 8.5 mmol) in dry ether (75 mL) were added iodine (3.4 g, 13 mmol) and CH_3CO_2Ag (3.2 g, 19 mmol), and the mixture was stirred at room temperature for 48 h. After removal of insoluble matters, evaporation of the solvent gave an oil. The oil was dissolved in CH_2Cl_2, and the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with toluene−acetone (40:1) gave an oil of **27** (3.5 g, 90%): $[\alpha]^{23}_D$ −12.8° (*c* 0.91, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.10 and 0.11 (each 3H, s), 0.90 (9H, s), 1.28 and 1.49 (each 3H, s), 2.09 (3H, s), 4.04 (1H, dd, J = 4.0 and 6.3 Hz), 4.11 (1H, dd, J = 2.3 and 4.6 Hz), 4.44 (1H, dd, J = 2.3 and 6.8 Hz), 4.98 (1H, dd, J = 4.0 and 6.8 Hz), 5.33 (1H, dd, J = 4.6 and 6.3 Hz); mass spectrum (FAB^+) m/z (relative intensity) 457 $(M + H)^+$ (21), 399 (81), 281 (28), 117 (100), 73 (95).

(1*R*,2*S*,3*S*,4*S*,5*R*)-3-*O*-(*tert*-Butyldimethylsilyl)-5-iodo-1,2-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (28). Compound **27** (3.1 g, 6.8 mmol) was dissolved in methanol saturated with NH_3 (31 mL), and the solution was allowed to stand at room temperature overnight. Evaporation of the solvent gave an oil, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$−CH_3OH (25:1) gave an oil of **28** (2.5 g, 89%): $[\alpha]^{23}_D$ −12.2° (*c* 0.36, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.10 and 0.11 (each 3H, s), 0.80 (9H, s), 1.27 and 1.47 (each 3H, s), 2.45 (1H, broad d, J = 5.8 Hz), 3.99 (1H, dd, J = 5.3 and 7.9 Hz), 4.00 (1H, dd, J = 3.1 and 5.8 Hz), 4.08 (1H, broad dt, J = 5.8 and 7.9 Hz), 4.35 (1H, dd, J = 3.1 and 7.1 Hz), and 4.82 (1H, dd, J = 5.3 and 7.1 Hz), mass spectrum (FAB^+) m/z (relative intensity) 415 $(M + H)^+$ (15), 257 (21), 215 (37), 73 (100), 59 (21).

(1*R*,2*R*,3*R*,4*S*,5*S*)-3,4-Bis-*O*-(*tert*-butyldimethylsilyl)-5-iodo-1,2-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (29). To a solution of **28** (2.0 g, 4.8 mmol) in dry DMF (1.8 mL) were added imidazole (1.3 g, 19 mmol) and *tert*-butyldimethylsilyl chloride (2.2 g, 14 mmol), and the mixture was stirred at room temperature for 2 h. After dilution with $CHCl_3$ (200 mL), the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to column chromatography on silica gel. Elution with chloroform gave an oil of **29** (2.1 g, 82%): $[\alpha]^{25}_D$ +11.6° (*c* 1.8, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 0.09, 0.10, 0.12, and 0.17 (each 3H, s), 0.90 and 0.91 (each 9H, s), 1.25 and 1.56 (each 3H, s), 3.87 (1H, dd, J = 5.4 and 7.8 Hz), 3.93 (1H, dd, J = 2.5 and 5.4 Hz), 4.15 (1H, dd, J = 5.4 and 7.8 Hz), 4.27 (1H, dd, J = 2.5 and 7.0 Hz), and 4.83 (1H, dd, J = 5.4 and 7.0 Hz); mass spectrum (FAB^+) m/z (relative intensity) 529 $(M + H)^+$ (5), 413 (66), 285 (74), 229 (76), 215 (98), 147 (100), 133 (91), 81 (87), 75 (89), 59 (90).

(1*S*,2*S*,3*R*,4*R*,5*R*)-5-Azido-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (30). To a solution of **29** (2.0 g, 3.8 mmol) in dry dimethyl sulfoxide (30 mL) was added NaN_3 (4 g, 62 mmol), and the mixture was stirred at 150 °C for 2.5 h. After dilution with ether (500 mL), the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to column chromatography on silica gel. Elution with chloroform gave an oil of **30** (1.1 g, 66%): $[\alpha]^{25}_D$ −69.4° (*c* 0.96, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 0.07, 0.10, 0.13, and 0.15 (each 3H, s), 0.85 and 0.94 (each 9H, s), 1.30 and 1.52 (each 3H, s), 3.34 (1H, t, J = 5.4 Hz), 4.02 (1H, broad dd, J = 3.0 and 5.4 Hz), 4.05 (1H, d with a small coupling, J = 3.0 Hz), 4.30 (1H, d with a small coupling, J = 5.8 Hz), and 4.76 (1H, t, J = 5.8 Hz); mass spectrum (FAB^+) m/z (relative intensity) 444 $(M + H)^+$ (8), 386 (38), 147 (76), 73 (100).

(1*S*,2*S*,3*R*,4*R*,5*R*)-5-((*tert*-Butoxycarbonyl)amino)-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (31). The solution of **30** (1.0 g, 2.3 mmol) in a mixture of ethyl acetate (25 mL) and methanol (25 mL) was stirred with 10% Pd/C (1 g) under a hydrogen atmosphere for 3 h. The catalysts were filtered off, and the filtrate was evaporated to give a residue, which was dissolved in dry CH_2Cl_2 (21 mL). To the solution were added *N*,*N*-diisopropylethylamine (5.6 mL, 32 mmol) and di-*tert*-butyl dicarbonate (2.5 mL, 11 mmol), and the mixture was stirred at room temperature overnight. Evaporation of the solvent gave an viscous oil, which was dissolved in CH_2Cl_2. The solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to column chromatography on silica gel. Elution with chloroform gave an oil of **31** (920 mg, 79%): $[\alpha]^{25}_D$ +2.5° (*c* 1.3, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 0.07, 0.08, 0.09 and 0.10 (each 3H, s), 0.87 and 0.91 (each 9H, s), 1.28 and 1.45 (each 3H, s), 1.45 (9H, s), 3.92 (1H, broad d, J = 4.4 Hz), 3.97 (1H, s), 4.24 (1H, broad dt, J = 5.9 and 9.8 Hz), 4.32 (1H, dd, J = 1.0 and 5.9 Hz), 4.64 (1H, t, J = 5.9 Hz), and 5.16 (1H, broad d, J = 9.8 Hz); mass spectrum ($FAB^{+)}$ m/z (relative intensity) 518 $(M + H)^+$ (6), 418 (70), 404 (28), 73 (100), 57 (48).

(1*S*,2*R*,3*S*,4*R*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-1,2-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (32). To a solution of **31** (900 mg, 1.7 mmol) in dry THF (18 mL) was added tetrabutylammonium fluoride in THF (1 M, 4 mL, 4 mmol), and the mixture was stirred at room temperature for 3 h. Evaporation of the solvent gave an oil, which was dissolved in CH_2Cl_2. The solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to column chromatography on silica gel. Elution with chloroform−methanol (30:1) gave a solid of **32** (430 mg, 86%), which was crystallized from ethyl acetate to give colorless crystals: mp 156−157 °C; $[\alpha]^{24}_D$ −18.3° (*c* 1.4, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 1.32 and 1.48 (each 3H, s), 1.47 (9H, s), 2.34 (1H, broad d, J = 8.8 Hz), 3.01 (1H, broad s), 3.95 (1H, broad dd, J = 4.4 and 8.8 Hz), 4.18 (1H, broad s), 4.27 (1H, broad dt, J = 4.4 and 8.8 Hz), 4.52 (1H, dd, J = 1 and 5.4 Hz), 4.71 (1H, t, J = 5.4 Hz), and 5.33 (1H, broad d, J = 8.8 Hz); mass spectrum (FAB^+) m/z (relative intensity) 290 $(M + H)^+$ (51), 234 (67), 190 (100), 57 (42). Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01; N, 4.58. Found: C, 53.69; H, 8.30; N, 4.31.

(3a*R*,3b*R*,6a*R*,7*S*,7a*R*)-7-Hydroxy-2,2-dimethyl[1,3]-dioxolo[4,5-*d*]cyclopent[4,5-*d*]oxazolidin-5-one (33). To a solution of **32** (398 mg, 1.4 mmol) in dry DMF (8 mL) was added NaH (60% in oil, 165 mg, 4.1 mmol) at −20 °C, and the mixture was stirred at room temperature overnight. After quenching with saturated aqueous NH_4Cl solution, evaporation of the solvent gave a viscous solid. The solid was dissolved in chloroform, and the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the solvent gave a solid. The solid was subjected to column chromatography on silica gel. Elution with chloroform−methanol (7:1) gave a solid of **33** (263 mg, 89%), which was crystallized from chloroform to give colorless crystals: mp 125−126 °C: $[\alpha]^{23}_D$ −36° (*c* 0.66, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 1.35 and 1.50 (each 3H, s), 4.25 (1H, t, J = 6.6 Hz), 4.54 (1H, s), 4.63 (1H, d, J = 5.6 Hz), 4.69 (1H, t, J = 5.6 Hz), 4.88 (1H, d, J = 7.0 Hz), 5.17 (1H, broad s); mass spectrum (FAB^+), m/z (relative intensity) 216 $(M + H)^+$ (52), 107 (100), 89 (80), 77 (67). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 49.97; H, 6.25; N, 6.73.

(3a*S*,3b*R*,6a*R*,7*S*,7a*S*)-7-((Benzyloxy)methoxy)-2,2-dimethyl[1,3]dioxolo[4,5-*a*]cyclopent[4,5-*d*]oxazolidin-5-one (34). To a solution of **33** (236 mg, 4.6 mmol) in dry DMF (2.5 mL) were added *N*,*N*-diisopropylethylamine (1.5 mL, 8.6 mmol) and (benzyloxy)methyl chloride (0.31 mL, 2.2 mmol), and the mixture was stirred at room temperature for 48 h. After quenching with water, evaporation of the solvent gave an oil. The oil was dissolved in chloroform, and the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with

chloroform−methanol (15:1) gave a solid of **34** (215 mg, 58%), which was crystallized from ether to give colorless crystals: mp 114−115 °C; $[\alpha]^{24}_D$ −43.2° (*c* 0.93, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 1.32 and 1.50 (each 3H, s), 4.16 (1H, dd with a small coupling, J = 5.9 and 7.8 Hz), 4.46 (1H, s), 4.58 (1H, t, J = 5.9 Hz), 4.63 (2H, s), 4.70 (1H, d, J = 5.9 Hz), 4.83 (2H, s), 4.84 (1H, d, J = 7.8 Hz), 5.25 (1H, broad s), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 336 $(M + H)^+$ (56), 138 (94), 107 (56), 91 (100). Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.61; H, 6.52; N, 4.33.

(3a*R*,4*S*,5*S*,6*R*,6a*R*)-6-((Benzyloxy)methoxy)-4,5-dihydroxycyclopent[*d*]oxazolidin-2-one (35). Compound **34** (107 mg, 0.32 mmol) was dissolved in 50% aqueous acetic acid (3 mL), and the mixture was stirred at 70 °C for 2 h. Evaporation of the solvent gave a solid of **35** (77 mg, 82%), which was crystallized from methanol−water (5:1) to give colorless crystals: mp 155−156 °C; $[\alpha]^{23}_D$ −16.4° (*c* 0.55, CH_3OH); NMR (CD_3OD, 400 MHz) δ 3.94 (1H, dd, J = 4.6 and 5.4 Hz), 4.01 (1H, t, J = 4.6 Hz), 4.16 (1H, dd, J = 4.6 and 8.3 Hz), 4.25 (1H, dd, J = 2.2 and 5.4 Hz), 4.64 (2H, t, J = 12.2 Hz), 4.78 (1H, dd, J = 2.2 and 8.3 Hz), 4.86 (2H, s), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 296 $(M + H)^+$ (64), 107 (86), 91 (100), 89 (68). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.71; H, 6.04; N, 4.59.

(3a*S*,3b*S*,6a*R*,7*S*,7a*R*)-7-((Benzyloxy)methoxy)[1,3,2]-dioxathiolo[4,5-*a*]cyclopent[4,5-*d*]oxazolidine-2,2,5-trione (36). To a solution of **35** (78 mg, 0.26 mmol) in dry CH_2Cl_2 (3 mL) were added dry pyridine (0.15 mL, 1.9 mmol) and $SOCl_2$ (0.024 mL, 0.33 mmol), and the mixture was stirred at room temperature for 2 h. After dilution with CH_2Cl_2 (10 mL), the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was dissolved in CCl_4−CH_3CN−H_2O (2:2:3, 4.5 mL). To the solution were added $RuCl_3$ (13 mg, 0.063 mmol) and $NaIO_4$ (95 mg, 0.44 mmol), and the mixture was stirred at room temperature for 1 h. After dilution with CH_2Cl_2 (10 mL), the solution was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to preparative thin-layer chromatography (PTLC) on silica gel developed with chloroform−methanol (10:1) to give a solid of **36** (69 mg, 73%), which was crystallized from methanol to give colorless crystals: mp 122−123 °C; $[\alpha]^{24}_D$ −41.3° (*c* 0.75, CH_3OH); NMR (CD_3OD, 400 MHz) δ 4.61 (1H, dd, J = 5.9 and 7.8 Hz), 4.65 (1H, d, J = 2.0 Hz), 4.64 and 4.68 (2H, ABq, J = 12.2 Hz), 4.91 (2H, s), 4.98 (1H, d with small couplings, J = 7.8 Hz), 5.28 (1H, dd with small coupling, J = 2.0 and 5.9 Hz), 5.40 (1H, t, J = 5.9 Hz) and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 358 $(M + H)^+$ (26), 107 (71), 91 (100), 89 (58), 77 (50). Anal. Calcd for $C_{14}H_{15}NO_8S$: C, 47.05; H, 4.23; N, 3.92. Found: C, 46.89; H, 4.41; N, 3.67.

(3a*S*,4*R*,5*R*,6*R*,6a*R*)-6-((Benzyloxy)methoxy)-5-hydroxy-4-(methylthio)cyclopent[*d*]oxazolidin-2-one (37) and (3a*S*,4*S*,5*R*,6*S*,6a*R*)-6-((Benzyloxy)methoxy)-4-hydroxy-5-(methylthio)cyclopent[*d*]oxazolidin-2-one (38). A mixture of **36** (52 mg, 0.15 mmol) and $NaSCH_3$ (51 mg, 0.73 mmol) in dry DMF (0.6 mL) was stirred under argon at room temperature for 1 h. Evaporation of the solvent gave a viscous solid, which was dissolved in $CHCl_3$. The solution was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was dissovled in a solution (1 mL) of a mixture of THF (46.4 mL), H_2O (15 μL), and H_2SO_4 (10 μL), and the solution was stirred at room temperature overnight. After being stirred with excess $NaHCO_3$, the mixture was filtered through a Celite. Evaporation of the filtrate gave an oil. The oil was subjected to PTLC on silica gel developed with toluene−acetone (3:1) to give a foam of **37** (18 mg, 38%) and a foam of **38** (19 mg, 40%).

37: $[\alpha]^{23}_D$ +34° (*c* 0.7, $CHCl_3$); H NMR ($CDCl_3$, 400 MHz) δ 2.21 (3H, s), 2.89 (1H, dd, J = 7.3 and 10.3 Hz), 3.76 (1H, dd, J = 8.0 and 10.3 Hz), 3.82 (1H, broad s), 3.96 (1H, broad t, J = ~8.3 Hz), 4.02 (1H, dd, J = 4.9 and 8.0 Hz), 4.65 and 4.75 (2H, ABq, J = 11.7 Hz), 4.79 (1H, dd, J = 4.9 and 10.3 Hz), 4.85 and 4.95 (2H, ABq, J = 7.3 Hz), 6.52 (1H, s), and 7.25−7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.27, 55.54, 57.79, 70.41, 76.75, 81.64, 89.26, 95.15, 128.10, 128.20, 128.26, 136.56, 158.40; mass spectrum (FAB^+) *m*/*z* (relative intensity) 326 $(M + H)^+$ (90), 137 (98), 91 (100).

38: $[\alpha]^{23}_D$ +64.6° (*c* 0.8, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 2.22 (3H, s), 3.06 (1H, dd, J = 4.4 and 10.3 Hz), 3.57 (1H, broad s), 4.16 (1H, dd, J = 5.9 and 10.3 Hz), 4.2−4.3 (2H, m), 4.62 and 4.77 (2H, ABq, J = 11.7 Hz), 4.81 (1H, dd, J = 6.8 and 14.7), 4.83 and 4.85 (2H, ABq), 6.38 (1H, s), and 7.25−7.40 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 348 $(M + Na)^+$ (25), 326 $(M + H)^+$ (30), 296 (33), 218 (82), 91 (100).

(1*R*,2*S*,3*R*)-1-*O*-Benzyl-2,3-O-isopropylidenecyclopent-4-ene-1,2,3-triol (39). Procedures used were similar to those used for the preparation of **26** from **24** described above; the yield was 95%; $[\alpha]^{25}_D$ +101° (*c* 0.96, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 1.37 and 1.41 (each 3H, s), 4.57 (1H, m), 4.57 and 4.70 (2H, ABq, J = 11.7 Hz), 4.65 (1H, d, J = 5.6 Hz), 5.28 (1H, broad d with small couplings, J = 5.6 Hz), 5.93 (1H, broad d with small couplings, J = 5.1 Hz), 6.05 (1H, broad d with small couplings, J = 5.1 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 247 $(M + H)^+$ (6), 189 (76), 91 (100), 69 (51), 55 (58).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-*O*-Acetyl-2-*O*-benzyl-5-iodo-3,4-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (40). Procedures used were similar to those used for the preparation of **27** from **26**; the yield was 82%; $[\alpha]^{23}_D$ −1.6° (*c* 0.48,$CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 1.29 and 1.49 (each 3H, s), 2.09 (3H, s), 3.93 (1H, dd, J = 2.0 and 4.8 Hz), 4.07 (1H, dd, J = 4.3 and 6.4 Hz), 4.60 (1H, dd, J = 2.0 and 6.6 Hz), 4.64 (2H, s), 4.98 (1H, dd, J = 4.3 and 6.6 Hz), 5.54 (1H, dd, J = 4.8 and 6.4 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 433 $(M + H)^+$ (31), 375 (36), 91 (100).

(1*R*,2*S*,3*S*,4*S*,5*S*)-2-*O*-Benzyl-5-iodo-3,4-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (41). Procedures used were similar to those used for the preparation of **28** from **27**; the yield was 85%; $[\alpha]^{25}_D$ −2.9° (*c* 0.8, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 1.31 and 1.51 (each 3H, s), 2.55 (1H, broad d, J = 4.6 Hz), 3.84 (1H, dd, J = 3.3 and 6.9 Hz), 3.94 (1H, dd, J = 6.0 and 9.2 Hz), 4.24 (1H, m), 4.51 (1H, dd, J = 3.3 and 6.9 Hz), 4.64 and 4.72 (2H, ABq, J = 11.7 Hz), 4.82 (1H, dd, J = 6.0 and 6.9 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 391 $(M + H)^+$ (23), 107 (24), 91 (100), 89 (33).

(1*R*,2*S*,3*S*,4*S*,5*R*)-2-*O*-Benzyl-1-*O*-(*tert*-butyldimethylsilyl)-5-iodo-2,3-isopropylidenecyclopentane-1,2,3,4-tetrol (42). Procedures used were similar to those used for the preparation of **29** from **28**; the yield was 95%; $[\alpha]^{23}_D$ −5.2° (*c* 0.35, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.09 and 0.16 (each 3H, s), 0.90 (9H, s), 1.30 and 1.53 (each 3H, s), 3.71 (1H, dd, J = 3.6 and 7.3 Hz), 3.88 (1H, dd, J = 7.3 and 9.9 Hz), 4.19 (1H, dd, J = 7.3 and 9.9 Hz), 4.40 (1H, dd, J = 3.6 and 7.3 Hz), 4.55 and 4.68 (2H, ABq, J = 11.4 Hz), 4.77 (1H, t, J = 7.3 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 505 $(M + H)^+$ (18), 107 (33), 91 (100), 73 (85).

(1*S*,2*S*,3*R*,4*R*,5*S*)-5-Azido-2-*O*-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (43). Procedures used were similar to those used for the preparation of **30** from **29**; the yield was 81%; $[\alpha]^{23}_D$ −86.5° (*c* 0.45, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.12 and 0.13 (each 3H, s), 0.92 (9H, s), 1.33 and 1.56 (each 3H, s), 3.39 (1H, t, J = 4.9 Hz), 3.80 (1H, dd, J = 1.6 and 4.9 Hz), 4.07 (1H, t, J = 4.9 Hz), 4.37 (1H, dd, J = 1.6 and 5.0 Hz), 4.62 (1H, broad t, J = 5.0 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 420 $(M + H)^+$ (4), 362 (36), 91 (100), 73 (91).

(1*S*,2*S*,3*R*,4*R*,5*S*)-2-*O*-Benzyl-5-((*tert*-butoxycarbonyl)-amino)-1-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (44). Procedures used were similar to those used for the preparation of **31** from **30**; the yield was 84%; $[\alpha]^{24}_D$ −1.4° (*c* 0.97, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ 0.03 and 0.06 (each 3H, s), 0.89 (9H, s), 1.46 (9H, s), 3.72 (1H, broad s), 4.12 (1H, broad d, J = 5.3 Hz), 4.22 (1H, dt, J = 5.3 and 9.9 Hz), 4.45−4.60 (3H, m), 4.64 (1H, broad t, J = 5.3 Hz), 5.15 (1H, broad d, J = 9.9 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 494 $(M + H)^+$ (10), 394 (87), 380 (50), 91 (100).

(1*S*,2*S*,3*R*,4*R*,5*R*)-2-*O*-Benzyl-5-((*tert*-butoxycarbonyl)-amino)-3,4-*O*-isopropylidenecyclopentane-1,2,3,4-tetrol (45). Procedures used were similar to those used for the preparation of **32** from **31**; the yield was 98%; $[\alpha]^{26}_D$ +16.1° (*c* 0.45, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 1.32 (3H, s), 1.47 (12H, s), 2.20 (1H, d, J = 9.8 Hz), 3.90 (1H, s), 4.12 (1H, dd, J = 4.4 and 9.8 Hz), 4.26 (1H, m), 4.5−4.65 (3H, m), 4.71 (1H, t, J = 5.4 Hz), 5.28 (1H, broad d, J = 8.3 Hz), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 380 $(M + H)^+$ (19), 280 (100), 91 (85), 57 (35).

(3a*R*,3b*S*,6a*R*,7*R*,7a*R*)-7-Benzoxy-2,2-dimethyl[1,3]-dioxolo[4,5-*a*]cyclopent[4,5-*d*]oxazoliden-5-one (46). Procedures used were similar to those used for the preparation of **33** from **32**; the yield was 64%: mp 137−138 °C; $[\alpha]^{27}_D$ +47.1° (*c* 0.45, $CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 1.34 and 1.50 (each 3H, s), 4.21 (1H, d, J = 6.8 Hz), 4.24 (1H, broad s), 4.64 (2H, s), 4.66 (1H, d, J = 5.6 Hz), 4.71 (1H, d, J = 5.6 Hz), 4.94 (1H, d, J = 6.8 Hz), 5.00 (1H, broad s), and 7.2−7.4 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 306 $(M + H)^+$ (100), 137 (36), 91 (88). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.65; H, 6.48; N, 4.73.

(3a*S*,4*S*,5*R*,6*R*,6a*S*)-6-Benzoxy-4,5-dihydroxycyclopent-[*d*]oxazolidin-2-one (47). Procedures used were similar to those used for the preparation of **35** from **34**; the yield was 72%; crystallized from ethyl acetate−methanol (5:1): mp 178−179 °C; $[\alpha]^{27}_D$ +3.5° (*c* 0.5, $CHCl_3$); NMR (CD_3OD, 400 MHz) δ 3.97 (1H, dd, J = 4.3 and 5.4 Hz), 4.02 (1H, t, J = 4.3 Hz), 4.04 (1H, dd, J = 2.0 and 5.4 Hz), 4.18 (1H, dd, J = 4.3 and 8.6 Hz), 4.62 and 4.69 (2H, ABq, J = 11.7 Hz), 4.81 (1H, dd, J = 2.0 and 8.5 Hz), and 7.25−7.45 (5H, m); mass sepctrum (FAB^+) *m*/*z* (relative intensity) 266 $(M + H)^+$ (35), 120 (100), 107 (93), 91 (93), 90 (83), 77 (86). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.57; H, 5.83; N, 5.39.

(3a*R*,3b*R*,6a*S*,7R,7a*S*)-7-Benzoxy[1,3,2]dioxathiolo[4,5-*a*]cyclopent[4,5-*d*]oxazolidin-2,2,5-trione (48). Procedures used were similar to those used for the preparation of **36** from **35**; the yield was 89%; crystallized from ethanol; mp 150−151 °C; $[\alpha]^{23}_D$ +46.6° (*c* 0.57, CH_3OH); NMR (CD_3OD, 400 MHz) δ 4.45 (1H, broad t, J = 2.0 Hz), 4.65 (1H, dd, J = 5.9 and 7.8 Hz), 4.71 (2H, s), 5.06 (1H, dt, J = 1.0 and 7.8 Hz), 5.40 (1H, dd, J = 2.0 and 5.9 Hz), 5.45 (1H, t, J = 5.9 Hz), and 7.25−7.45 (5H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 328 $(M + H)^+$ (83), 107 (99), 91 (100), 89 (71), 77 (71).

(3a*R*,4*S*,5*S*,6*R*,6a*S*)-6-Benzoxy-4-(methylthio)-5-(sulfooxy)cyclopent[*d*]oxazolidin-2-one (49) and (3a*S*,4*R*,-5*R*,6*R*,6a*R*)-6-Benzoxy-5-(methylthio)-4-(sulfooxy)cyclopent[*d*]oxazolidin-2-one (50). A mixture of **48** (49 mg, 0.15 mmol) and $NaSCH_3$ (53 mg, 0.76 mmol) in dry DMF (0.5 mL) was stirred under argon at room temperature for 1 h. Evaporation of the solvent gave a viscous solid, which was dissolved in $CHCl_3$. The solution was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave a foam. The foam was subjected to PTLC on silica gel developed with chloroform−methanol to give a foam of **49** (26 mg, 46%) and a foam of **50** (25 mg, 44%).

49: $[\alpha]^{22}_D$ +20.3° (*c* 1.7, CH_3OH); NMR (CD_3OD, 400 MHz) δ 2.23 (3H, s), 3.39 (1H, m), 4.29 (1H, m), 4.32 (1H, dd, J = 1.9 and 7.8 Hz), 4.62 and 4.75 (2H, ABq, J = 11.7 Hz), 4.92 (1H, m), 5.00 (1H, d with a small coupling, J = 7.8 Hz), and 7.20−7.45 (5H, m); ^{13}C NMR (CD_3OD) δ 15.89, 57.66, 63.93, 73.39, 85.28, 86.38, 88.87, 160.44; mass spectrum (FAB^+) *m*/*z* (relative intensity) 398 $(M+Na)^+$ (9), 176 (100), 107 (57), 87 (48).

50: $[\alpha]^{22}_D$ −65.5° (*c* 2.0, CH_3OH); NMR (CD_3OD, 400 MHz) δ 2.21 (3H, s), 3.17 (1H, dd, J = 4.9 and 9.8 Hz), 3.99 (1H, d, J = 4.9 Hz), 4.56 (1H, dd, J = 5.7 and 7.8 Hz), 4.61 and 4.69 (2H, ABq, J = 12.0 Hz), 4.78 (1H, dd, J = 5.7 and 9.8 Hz), 4.93 (1H, d, J = 7.8 Hz), and 7.20−7.40 (5H, m); ^{13}C NMR (CD_3OD) δ 15.18, 51.87, 57.21, 73.40, 81.61, 83.14, 83.45, 160.94; mass spectrum (FAB^-) *m*/*z* (relative intensity) 374 $(M - H)^-$ (100), 306 (39), 199 (30), 153 (94).

(3a*R*,4*S*,5*S*,6*S*,6a*S*)-5,6-Dihydroxy-4-(methylthio)cyclopent[*d*]oxazolidin-2-one (51). Compound **49** (19 mg, 0.05 mmol) was dissolved in a solution (0.5 mL) of a mixture of THF (46.4 mL), H_2O (15 μL) and H_2SO_4 (10 μL), and the solution was stirred at room temperature overnight. After being stirred with excess $NaHCO_3$, the mixture was filtered through a Celite. Evaporation of the filtrate gave an oil, which was suspended in CH_2Cl_2 (2 mL). To a suspension was added CH_3SiI (37 μL, 0.2 μmol), and the mixture was stirred at room temperature for 3 h. After addition of methanol, evaporation of the solvent gave a solid. The solid was subjected to PTLC on silica gel to give an amorphous solid of **51** (8 mg, 77%): $[\alpha]^{23}_D$ +11° (*c* 0.2, CH_3OH); NMR (CD_3OD) δ 2.19 (3H, s), 2.75 (1H, dd, J = 6.3 and 9.3 Hz), 3.63 (1H, dd, J = 8.3 and 9.3 Hz), 3.94 (1H, dd, J = 4.9 and 8.3 Hz), 4.02 (1H, dd, J = 6.3 and 9.3 Hz), and 4.66 (1H, dd, J = 4.9 and 9.3 Hz); mas spectrum (FAB^+) *m*/*z* (relative intensity) 228 $(M + Na)^+$ (22), 206 $(M + H)^+$ (80), 176 (100), 107 (73), 89 (62).

(3a*S*,4*R*,5*S*,6*R*,6a*S*)-4,6-Dihydroxy-5-(methylthio)cyclopent[*d*]oxazolidin-2-one (52). Procedures used were similar to those used for the preparation of **51** from **49**; the yield was 70%; $[\alpha]^{23}_D$ −71° (*c* 0.27, CH_3OH); NMR (CD_3OD, 400 MHz) δ 2.20 (3H, s), 2.89 (1H, dd, J = 3.9 and 10.3 Hz), 4.06 (1H, d, J = 3.9 Hz), 4.09 (1H, dd, J = 5.9 and 10.3 Hz), 4.25 (1H, dd, J = 5.9 and 7.8 Hz), and 4.73 (1H, d, J = 7.8 Hz); ^{13}C NMR (CD_3OD) δ 14.97, 54.82, 58.44, 75.15, 77.02, 84.26 and 161.47; mass spectrum (FAB^+) *m*/*z* (relative intensity) 228 $(M + Na)^+$ (40), 206 $(M + H)^+$ (100), 176 (80), 107 (41).

2-Epimannostatin A Hydrochloride (12). Compound **37** (13 mg, 0.04 mmol) was dissolved in a solution (2 mL) of water (10 mL) containing $Ba(OH)_2 \cdot 8H_2O$ (100 mg, 0.32 mmol), and the solution was stirred at 100 °C for 1 h. After introduction of CO_2 gas, the resulting precipitates were filtered off. Evaporation of the filtrate gave a foam. The foam was dissolved in 4 M HCl−dioxane (0.5 mL), and the mixture was stirred at room temperature for 4 h. The resulting precipitates were taken by centrifugation and washed thoroughly with ether to give a colorless amorphous solid of hydrochloride of **12** (8 mg, 97%): mp 149−151 °C dec; $[\alpha]^{26}_D$ +16° (*c* 0.27, H_2O); H NMR (D_2O, 400 MHz) δ 1.56 (3H, s), 2.28 (1H, t, J = 9.3 Hz), 2.83 (1H, dd, J = 6.8 and 9.3 Hz), 3.18 (1H, dd, J = 6.8 and 9.3 Hz), 3.29 (1H, dd, J = 4.9 and 6.8 Hz), and 3.45 (1H, dd, J = 4.9 and 6.8 Hz); mass spectrum (FAB^+) *m*/*z* (relative intensity) 180 $(M + H)^+$ (100), 115 (57), 75 (83).

(1*S*,2*R*,3*R*,4*S*,5*R*)-3-Amino-5-(methylthio)cyclopentane-1,2,4-triol Hydrochloride (14). Compound **38** (15 mg, 0.046 mmol) was dissolved in a solution (2 mL) of water (10 mL) containing $Ba(OH)_2 \cdot 8H_2O$ (100 mg, 0.32 mmol), and the solution was stirred at 100 °C for 1 h. After introduction of CO_2 gas, the resulting precipitates were filtered off. Evaporation of the filtrate gave a foam. The foam was dissolved in 4 M HCl−dioxane (0.5 mL), and the mixture was stirred at room temperature for 4 h. Evaporation of the solvent gave an oil, which was washed thoroughly with ether to give a viscous solid. The resulting viscous solid was subjected to column chromatography on Diaion HP-20 (Nippon Rensui Co.). Elution with water gave a hygroscopic amorphous solid of hydrochloride of **14** (8 mg, 84%): $[\alpha]^{26}_D$ +36.4° (*c* 0.53, H_2O); NMR (D_2O, 400 MHz) δ 2.04 (3H, s), 3.13 (1H, t, J = 5.4 Hz), 3.73 (1H, t, J = 6.6 Hz), and 4.0−4.2 (3H, m); mass spectrum (FAB^+) *m*/*z* (relative intensity) 180 $(M + H)^+$ (100), 115 (99), 75 (56).

2-Epimannostatin A Enantiomer (13). Compound **51** (6 mg, 0.029 mmol) was dissolved in a solution (1 mL) of water (10 mL) containing $Ba(OH)_2 \cdot 8H_2O$ (100 mg, 0.32 mmol), and the solution was stirred at 100 °C for 6 h. After introduction of CO_2 gas, the resulting precipitates were filtered off. Evaporation of the filtrate gave a solid. The solid was subjected to PTLC on silica gel developed with chloroform−methanol−ammonia (2:1:0.3) to give **13** (3 mg, 57%): $[\alpha]^{24}_D$ −11° (*c* 0.1, H_2O); NMR (D_2O, 400 MHz) δ 2.00 (3H, s), 2.52 (1H, t, J = 9.0 Hz), 2.99 (1H, dd, J = 6.8 and 9.2 Hz), 3.57 (1H, dd, J = 6.3 and 8.8 Hz), 3.68 (1H, dd, J = 4.9 and 6.3 Hz), and 3.76 (1H, dd, J = 4.9 and 6.8 Hz); mass spectrum (FAB^+) *m*/*z* 180 $(M + H)^+$ (92), 115 (100), 75 (91).

(1*R*,2*S*,3*R*,4*R*,5*S*)-3-Amino-5-(methylthio)cyclopentane-1,2,4-triol (15). Procedures used were similar to those used for the preparation of **14** from **51** described above; the yield

was 61%: $[\alpha]^{24}_D$ −30.8° (*c* 0.14, H_2O); NMR (D_2O, 500 MHz) δ 2.19 (3H, s), 3.24 (1H, t, J = 6.4 Hz), 3.48 (1H, dd, J = 5.4 and 6.5 Hz), 4.02 (1H, dd, J = 3.9 and 5.4 Hz), 4.03 (1H, t, J = 6.4 Hz), and 4.20 (1H, dd, J = 3.9 and 6.4 Hz); ^{13}C NMR (D_2O) δ 14.05, 53.37, 55.14, 74.40, 75.42 and 76.52; mass spectrum (FAB^+) *m*/*z* (relative intensity) 180 $(M + H)^+$ (54), 115 (100), 75 (38).

Molecular Modeling of 13. Force field calculation MM2[28] and semiempirical calculation PM3 incorporated in the MOPAC (ver. 6.0)[29] package were performed on BIOCES[E][30] system in one high performance desk top workstation (NEC EWS 4800/330).

X-ray Analysis of 47. Crystal data: $C_{13}H_{15}NO_5$, orthorhombic $P2_12_12_1$, a = 7.198(2) Å, b = 29.587(3) Å, c = 5.971(2) Å, V = 1271.6(5) Å, Z = 4. Data were collected at 20 °C on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation giving 1172 unique reflections. The structure was solved by a direct method (SHEL XS86) to yield R = 0.050 for 896 independent reflections with $I > 2\sigma(I)$.[27]

Acknowledgment. We are grateful to Dr. S. Ohuchi of the Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., and Dr. C. Imada of Institute of Microbial Chemistry for the biological evaluation of the derivatives. We also thank Ms. R. Shinei and Y. Fukurose for their technical assistance.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and HMBC spectra of compounds **12**−**15** and **20**−**52** (80 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951126V

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