Stereocontrolled Syntheses of 6-*epi*-Trehazolin and 6-*epi*-Trehalamine from D-Ribonolactone

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6-*epi*-Trehazolin was synthesized in a stereocontrolled manner, and this synthesis proved that an oxazine structural isomer of 6-*epi*-trehazolin does not exist.

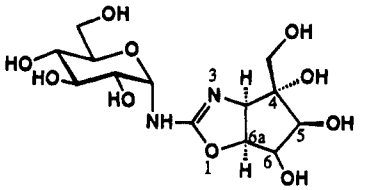
Introduction

For a long time carbohydrates were generally regarded solely as energy storage vehicles and structural units in cells. However, nowadays it is recognized that carbohydrates govern a wide range of biological recognition phenomena: they are blood group determinants; they provide cell surface receptors for proteins, toxins, pathogens, viruses, etc.; and they can be the binding site for cell-adhesion molecules such as glycoconjugates.

Moreover, in recent years interest in the use of enzyme inhibitors as terapoitic agents has been growing. In particular, glycosidase inhibitors have become an important group of enzyme inhibitors. During the last 20 years, many glycosidase inhibitors have been discovered.[1]

Recently, it has also been recognized that trehalase is an enzyme of paramount ecological importance in the control of insects and certain fungi. In 1991, groups from both Sankyo[2] and Suntory[3] independently isolated a powerful trehalase inhibitor, trehazolin (**1**), from culture broths produced by *Micromonospora* sp. SANK 62390 and *Amicolatopsis trehalostatica*, respectively. On the basis of spectral data analyses, a pseudodisaccharide structure, consisting of an α-glucosyl group and a unique aglycon moiety, was elucidated for **1**. The structure and absolute configuration of **1** were confirmed by us[4] and Ogawa *et al.*[5] through synthetic studies.

We were interested in the biological activity of trehalase, particularly in the inhibitory activity of trehazolin and trehazolin analogues, namely, 5-*epi*-trehazolin (trehalostatin), 6-*epi*-trehazolin, and other epimers, as well as 5,6-ring-fused structural isomers, toward the trehalase enzyme itself. In this paper, we describe in detail the synthesis, from D-ribonolactone, of 6-*epi*-trehazolin (**2**),[6] whose absolute configuration is [3a*R*-(3aα,4α,5β,6β,6aα)]. We also provide proof that the oxazine (5,6-ring fused) structural isomer **43** does not exist.



Trehazolin (**1**): C-6 = ·····
6-*epi*-Trehazolin (**2**): C-6 = —

Figure 1.

Synthesis of 6-*epi*-Trehazolin

Treatment of D-(+)-ribonolactone (**3**) first with 2,2-dimethoxypropane using pyridinium *p*-toluenesulfonate as a catalyst and then with 1 M HCl aqueous in THF gave 2,3-*O*-isopropylidene-D-ribonolactone (**4**)[7] (Scheme 1). Pfitzner–Moffat oxidation of **4** with dicyclohexylcarbodiimide and a catalytic amount of phosphoric acid in dimethyl sulfoxide[8] or Dess–Martin oxidation of **4** gave aldehyde **5**. Treatment of **5** with *tert*-butyldimethylsilyl chloride and 1,4-diazabicyclo[2.2.2]octane in *N*,*N*-dimethylformamide gave (*Z*)-silyl enol ether **6** (mp 94–96 °C). The *Z*-geometry of **6** was confirmed from the observation of a nuclear Overhauser effect between the C-3 proton and the C-5 olefinic proton. A tandem Aldol–Wittig type reaction of **6** with α-(lithiomethylene)triphenylphosphorane ($LiCH{=}PPh_3$)[9] in THF gave cyclopentenone **7** in one pot. This reaction should have synthetic utility for one-step syntheses of cyclic α,β-unsaturated ketones from cyclic enol ester-type deriva-

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(5) (a) Ogawa, S.; Uchida, C. *Chem. Lett.* **1993**, 173–176. (b) Uchida, C.; Yamagishi, T.; Ogawa, S. *Chem. Lett.* **1993**, 971–974.

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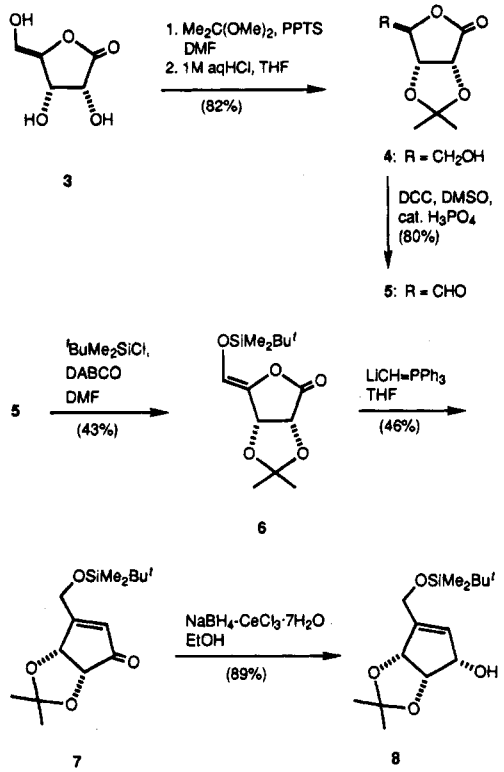
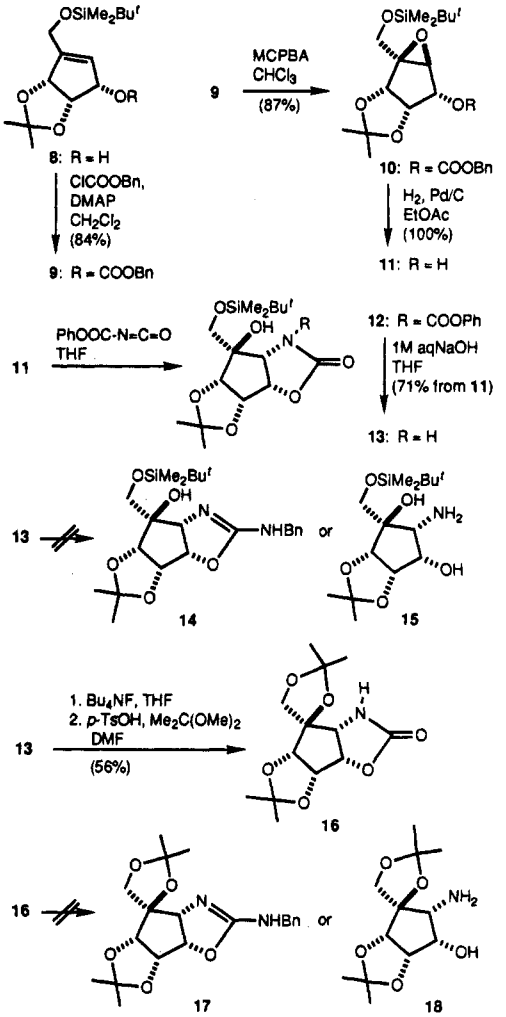
Scheme 1



tives.[10,11] Selective reduction of ketone **7** with sodium borohydride and cerium trichloride,[12] to leave the double bond intact, gave alcohol **8** exclusively.

Treatment of **8** with 5 equiv of both benzyloxycarbonyl chloride and 4-(dimethylamino)pyridine gave **9** in 84% yield (Scheme 2). Excess ClCOOBn was required to elevate the yield because a fairly large amount of ClCOOBn decomposed during the reaction. This protection of the secondary alcohol of **8** made the subsequent epoxidation stereospecific; when the alcohol is not protected, the epoxidation gives a mixture of α,β-epoxides. Epoxidation of **9** with *m*-chloroperoxybenzoic acid gave **10** (mp 74–74.5 °C) in 87% yield as a single isomer with the epoxide trans to all the substituents on the cyclopentane ring. Hydrogenolysis of **10** with 10% Pd on carbon gave alcohol **11** quantitatively. Treatment of **11** with phenoxycarbonyl isocyanate[13] gave a mixture of phenyl carbamate and bicyclic *N*-(phenoxycarbonyl)-oxazolone alcohol **12** (mp 176–177 °C), which arose from attack of the nitrogen of the intermediate *N*-(phenoxycarbonyl)urethane on the epoxide during silica gel chromatography. Treatment of **12** with 1 M NaOH yielded **13** (mp 120.5–121.5 °C) in 71% yield from **11**. Next, the Trost method[14] was employed in an attempt to form aminooxazoline **14** from **13**, and saponification of **13** to aminocyclitol **15** was tried. However, both of these reactions failed. Therefore, compound **13** was converted

Scheme 2



to **16** through a vicinal diol. Deprotection of the silyl group of **13** with tetrabutylammonium fluoride in THF was performed, and treatment of the concentrated residue with 2,2-dimethoxypropane–DMF (2:1) and a catalytic amount of *p*-toluenesulfonic acid monohydrate gave diacetonide **16** in 56% yield. The same reactions attempted for the conversion of **13** to **14** and **15** were employed to convert **16** to **17** and **18**. These reactions also failed. Therefore, we attempted another route to the title compound.

Methoxybenzylation of **8** with sodium hydride and *p*-methoxybenzyl chloride gave **19** in 69% yield (Scheme 3). It was necessary to change the silyl protecting group of **19** to a benzyl group because of the desilylation that occurred during the epoxy-opening azidation of **11** by NaN_3–NH_4Cl in DMF. Deprotection of the silyl ether of **19** with Bu_4NF afforded **20** in 93% yield. Reprotection of liberated alcohol of **20** with a benzyl group by treatment with NaH and benzyl chloride gave **21** quantitatively. Epoxidation of **21** with MCPBA gave stereospecifically epoxide **22** in 55% yield. The oxygen attacked the double bond from the least crowded face of the cyclopentene ring, trans to the three substituents on the ring. Treatment of **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[15] and H_2O afforded alcohol **23** in 99% yield. Reaction of **23** with sodium azide and ammonium chloride[16] in DMF at 100 °C for 16 h gave azide diol **24** in

(10) Compare with the Fujimoto–Belleau reaction: (a) Fujimoto, G. I. *J. Am. Chem. Soc.* **1951**, *73*, 1856. (b) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251. (c) Review: Weill-Raynal, J. *Synthesis* **1969**, 49–56.

(11) Compare with: (a) Marquez, V. E.; Lim, M.-I.; Tseng, C. K.-H.; Markovac, A.; Priest, M. A.; Khan, M. S.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709–5714. (b) Altmann, K.-H.; Kesselring, R.; Francottes, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331–2334.

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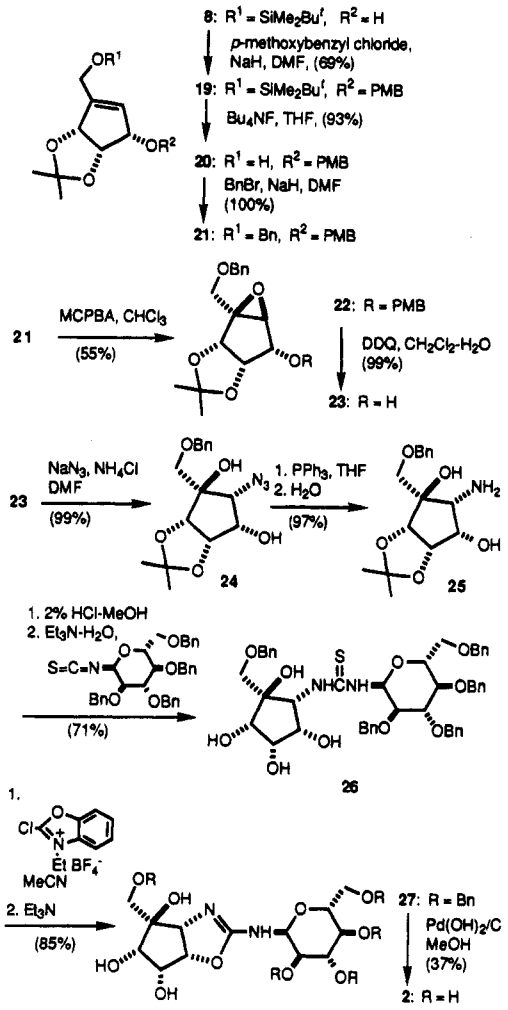
Scheme 3



99% yield. The azide group was introduced exclusively at the secondary position of the expoxide. Treatment of the azide group of **24** first with triphenylphosphine[17] and then with H_2O gave amine **25** (mp 86–87 °C) in 97% yield. The structure of **25** was confirmed by single-crystal X-ray structure analysis (Figure 2).

Treatment of **25** first with 2% HCl in MeOH to remove the acetonide and then with triethylamine and 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate[18] gave α-D-glucopyranosylthiourea **26** in 71% yield. Formation of 2-aminooxazoline **27** from **26** was accomplished in 85% yield with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate[18] and Et_3N. The IR spectrum of compound **27** showed the characteristic absorption band of 2-aminooxazoline at 1672 cm^{-1}. Since the primary alcohol was protected by a benzyl group, compound **26** cyclized predominantly to 5,5-ring-fused tetrahydro-4*H*-cyclopentoxazole **27**.

In the DQF-COSY and HOHAHA spectra of **27**, spin systems corresponding to the aglycon and glucose parts and the five pairs of benzyl protons were identified. The identification of these protons led automatically to the assignments of ^{13}C resonances with directly bound protons in the HMBC spectrum, except for the resonance for C_{3a}, which could not be located, probably because of the extreme broadening. Then, the partial structures separated by the quaternary carbons were combined on the basis of $^1H-^{13}C$ long-range couplings derived from the HMBC spectrum. An isolated methylene unit that exhibited a ^1H resonance around 3.86 ppm and long-range coupling to C_4 at 81.3 ppm was assigned to the hydroxy group attached to C_4; thus, the aglycon part was completed. The relative configurations of the aglycon were assigned by the analysis of NOEs observed among H_{3a}, H_5, H_6, and H_{6a} and the vicinal couplings among them. Proof that the 1-amino glucose part was attached to the aglycon part in the trehazolin-like manner arose from the long-range coupling of the anomeric proton of the glucose part to C_2 (160.4 ppm), which, in turn, showed long-range couplings to H_{3a} and H_{6a} of the aglycon part. It should be noted here that the explicit conformation of sites at which the protective benzyl groups were introduced were given by the long-range $^1H-^{13}C$ couplings of the benzyl protons to the respective carbons to which they are attached via oxygen.

Deprotection of the four benzyl groups on the 1-amino-1-deoxy-α-D-glucoside of **27** was accomplished by hydrogenolysis with $Pd(OH)_2$ on carbon as a catalyst and gave tetrahydro-4*H*-cyclopentoxazole **2** in 37% yield. The IR absorption of the 2-aminooxazoline part of **2** appeared at 1671 cm^{-1}.

The structure of **2** was also confirmed in the manner outlined above. After liberation of the benzyl groups at C_2, C_3, C_4, and C_6 and the hydroxy methyl at C_4, all of the ^{13}C resonances of the glucose part were shifted to higher field by ca. 8~9 ppm. The stereochemistry of the aglycon part assigned by analysis of the NOEs and was supported by the four-bond long-range couplings between H_{3a} and H_5 and between H_{6a} and H_5 due to the W-shaped geometry.

An alternative route to **2** from compound **11** via compound **36** was investigated to determine the influence of steric circumstances on the overall yields of **2** (Scheme 4). Azide formation of **11** with NaN_3 and NH_4Cl gave silyl group-deprotected triol **28** in 92% yield. Protection of the vicinal diol group of **28** as an isopropylidene gave bis-isopropylidene **29** (mp 75.5–76.5 °C) in 80% yield. The structure of **29** was confirmed by X-ray analysis (Figure 3).

The remaining alcohol of **29** was reprotected with a *p*-methoxybenzyl group to give **30** in 90% yield. One of the acetonides of **30** was again removed regioselectively by treatment with 85% acetic acid to give **31** in 64% yield. Dibenzylation of **31** with NaH and benzyl bromide gave **32** in 89% yield. Removal of the *p*-methoxybenzyl group from **32** with DDQ–H_2O in CH_2Cl_2 gave alcohol **33** in 92% yield. Conversion of the azide group of **33** to an amine was performed using PPh_3 and then H_2O to give **34**, which was further treated with 2% HCl–MeOH and then Et_3N and 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate[17] to give triol thiourea **35** in 17% yield in two steps. The low yield may be due to the steric hindrance caused by the vicinal dibenzyl groups neighboring the reacting amine.

Treatment of **35** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate[19] gave oxazoline **36** in 90% yield. Hydrogenolysis of **36** with $Pd(OH)_2$ on carbon gave **2** in 46% yield. Compound **2** obtained from **36** was identical in all respects to that obtained from **27**.

(16) VanderWerf, C. A.; Heisler, R. Y.; McEwen, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 1231–1235.
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(19) (a) Takeda, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 163–166. (b) Review: Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707–721.

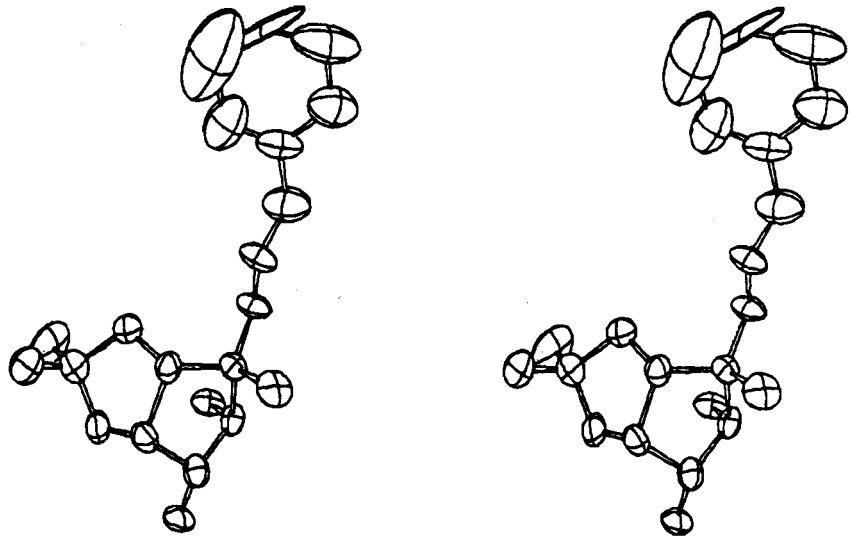
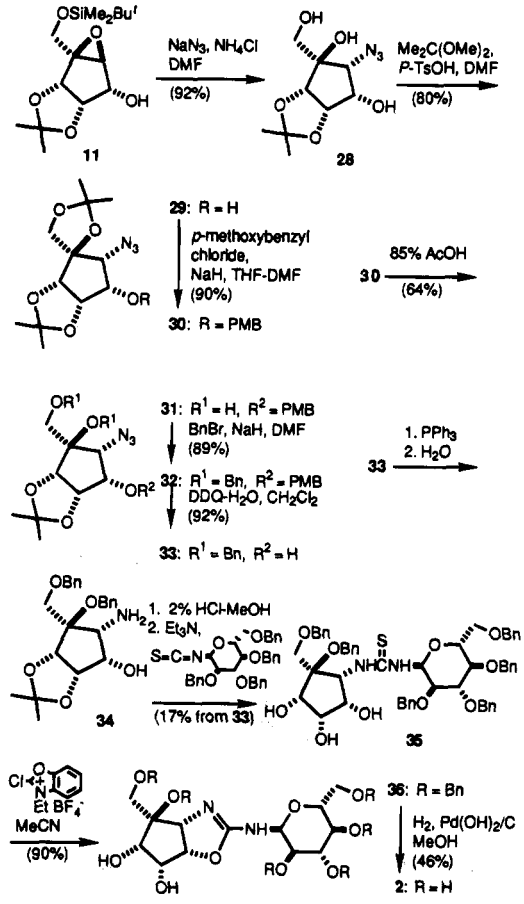


Figure 2. X-ray structure of compound **25**.

Scheme 4



If the unprotected amine of **18** were used, an improvement in the overall yield of **2** would be expected on the basis of the result (the low yield of **35** from **33**). Therefore, another route from **29** was investigated.

Treatment of **29** with PPh_3 and then H_2O gave amine **18** in 94% yield (Scheme 5). Treatment of the bis-acetonide of **18** with 2% HCl–MeOH and then Et_3N and 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate[18] afforded pentaol thiourea **37** in 84% yield. Oxazoline formation from **37** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate gave **38** in 84% yield. Hydrogenolysis of **38** with $Pd(OH)_2$ on carbon gave **2** in 43% yield. Compound **2** obtained from **38** was identical in all respects to that obtained from **27** and **36**. In addition, this third route was more effective and consisted of fewer steps than the previous methods.

It was obvious judging from the yields of compounds **26**, **35**, and **37** that the benzyl groups suppressed the formation of thiourea from amines and glucosyl isothiocyanate in accordance with the increase in the number of benzyl groups.

An Attempted Synthesis of a 5,6-Ring-Fused Structural Isomer of 6-*epi*-Trehazolin

Additionally we attempted to synthesize 5,6-ring-fused structural isomer **43**. Treatment of **29** with benzyl bromide and sodium hydride yielded **39** quantitatively (Scheme 6). Compound **39** was subjected to the procedure described above: (i) reduction of azide to amine **40**, (ii) deprotection of the bis-isopropylidene groups and then formation of thiourea **41**, and (iii) 2-aminooxazine formation gave hexahydrocyclopent[*d*][1,3]oxazine **42** in 51% yield. The existence of a 2-aminooxazine framework in compound **42** was indicated by the IR absorption band at 1660 cm^{-1} and by ^1H NMR data.

To our surprise, removal of the benzyl groups of **42** by hydrogenolysis gave **2** in 42% yield. It seems that the unstable **43** underwent transformation to intermediate **44**, and **44** was converted to the most stable isomer, **2**. The physical data for **2** thus obtained were identical to those of **2** obtained from compounds **27**, **36**, and **38**.

Synthesis of 6-*epi*-Trehalamine

6-*epi*-Trehalamine **47**, which is the aglycon part of 6-*epi*-trehazolin, was synthesized as follows. Reaction of **25** first with 2% HCl in MeOH and then with Et_3N and benzyl isothiocyanate afforded **45** in 48% yield (Scheme 7). The reaction of **45** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate gave oxazoline **46** in 45% yield. Hydrogenolysis of **46** with $Pd(OH)_2$ on carbon gave **47** in 45% yield.

In the ^1H NMR spectrum of **47**, nonequivalent methylene protons at 3.52 and 3.70 ppm and a coupled four-spin system corresponding to H_{3a}, H_{6a}, H_6, and H_5 were identified. These two spin systems could be combined via C_4 (82.1 ppm), which showed long-range coupling to H_{3a} and H_{6a} and via a nonequivalent methylene proton pair at 3.52 and 3.70 ppm in the HMBC spectrum. H_{3a} and H_{6a} exhibited long-range coupling to C_2 at 162.2 ppm.

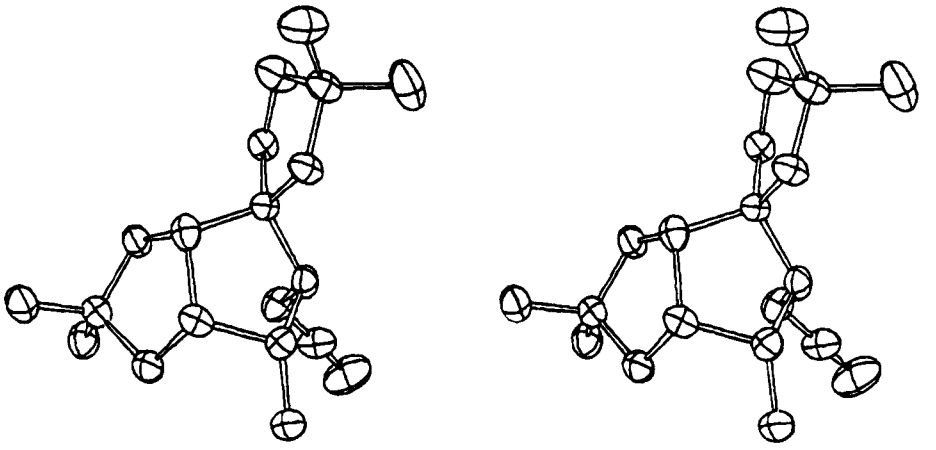
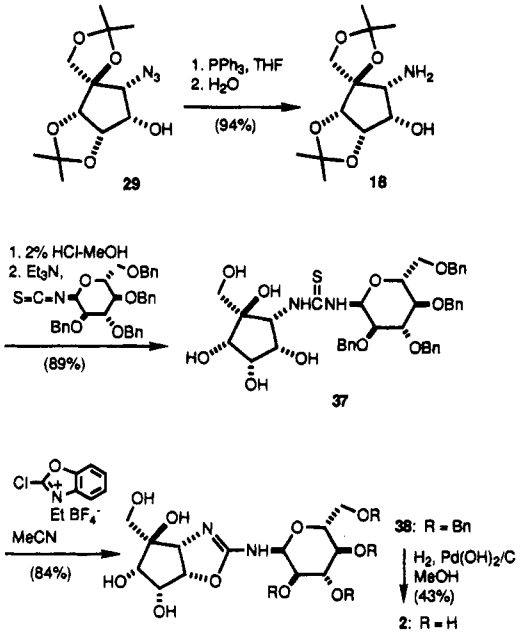
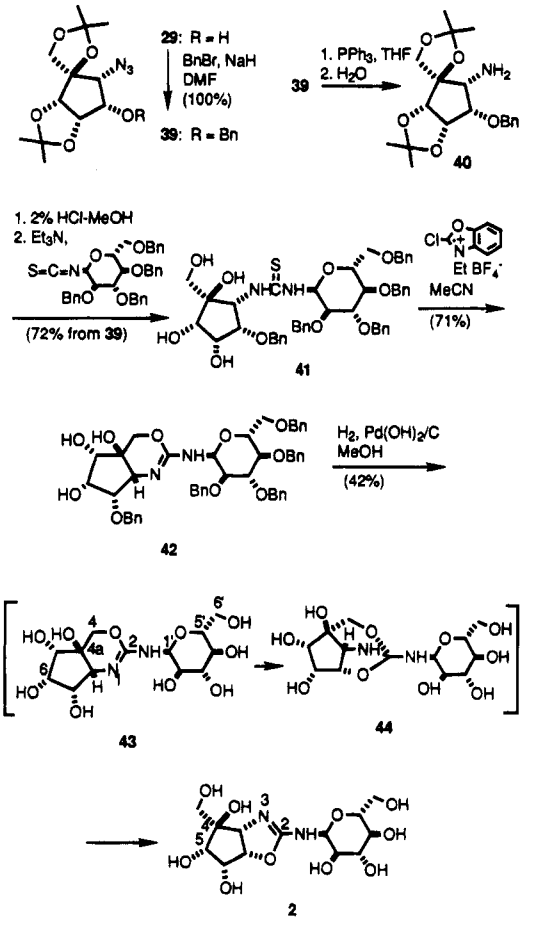


Figure 3. X-ray structure of compound **29**.

Scheme 5



Scheme 6



Since the configurations of **47** were assigned on the basis of the NOEs among H_{3a}, H_{6a}, H_6, and H_5 and the W-shaped long-range coupling between H_{3a} and H_5, **47** could be confirmed as being 6-*epi*-trehalamine.

An alternative route to **47** from compound **18** was investigated to determine the steric influence of bis-isopropylidene groups on **18** (Scheme 8).

Treatment of **18** with BnN=C=S gave thiourea **48** quantitatively. Reaction of **48** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate gave carbodiimide **49** in 11% yield. However, all attempts to convert **49** to **50** failed. The IR absorption of the carbodiimide of **49** appeared at 2125 cm^{-1}.

It is obvious that the intramolecular migration of the neighboring alcohol to the carbodiimide was sterically hindered by the bis-isopropylidene groups. At any rate, the existence of carbodiimide **49** provided proof that the intermediate for the formation of the oxazoline with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate was a carbodiimide.

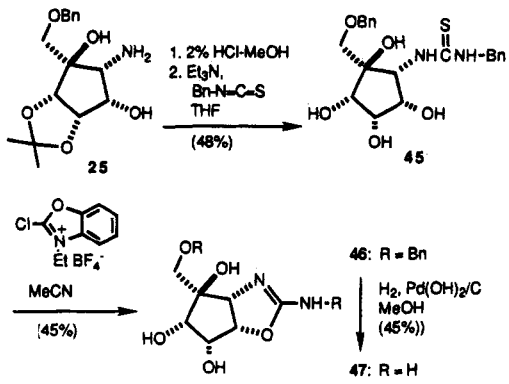
Discussion

The benzyl protecting groups on the aminocyclitol moiety neighboring the reacting amine strongly affected the formation of glycosylthiourea, and isopropylidene groups hindered the migration required for aminooxazoline formation from the intermediate carbodiimide. The alcohol protecting groups on the cyclopentane ring must strongly affect the formation of the bicyclic aminooxazoline ring system. Because of the nonexistence of the 5,6-ring-fused structural isomer, synthesis of 6-*epi*-trehazolin via the unprotected aminocyclitol will be better than that via the protected compound.

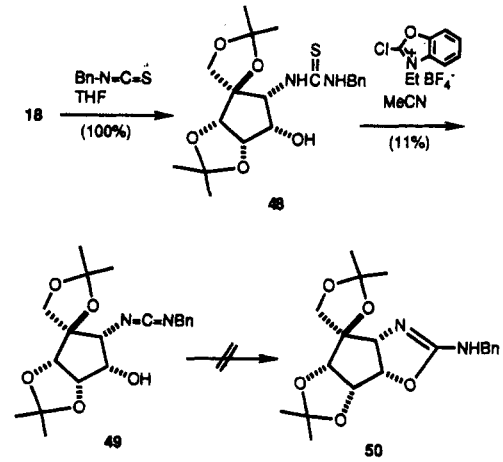
Conclusion

6-*epi*-Trehazolin (**2**) and 6-*epi*-trehalamine (**47**) were synthesized in a stereocontrolled manner through a tandem Aldol–Wittig type reaction of cyclic enol ester **6**. And structural isomer **43**, which has a tetrahydrocyclopent[*d*][1,3]oxazine skeleton, was proved not to exist.

Scheme 7



Scheme 8



Experimental Section

Melting points were uncorrected. ^{1}H NMR spectra (270, 400, and 500 MHz) were recorded using TMS as an internal standard. Elemental analyses were performed by the Institute of Science and Technology, Inc. Preparative TLC was performed on silica gel plates (Merck, Silica Gel 60 F_{245}), and column chromatography was carried out on columns packed with Merck Silica Gel 60 (230–400 mesh) using a slightly increased pressure (1.2 atoms) for elution. THF was distilled from $LiAlH_4$ and used immediately. CH_2Cl_2 was dried by being passed through ICN Alumina B-Super I. DMF and pyridine were dried by storage over 4A molecular sieves. MeCN was dried by storage over 3A molecular sieves.

2,3-*O*-Isopropylidene-D-ribonolactone (4). To a suspension of D-(+)-ribonolactone (**3**, 49.2 g, 0.332 mol) in 2,2-dimethoxypropane (200 mL) was added pyridium *p*-toluenesulfonate (1.50 g). The mixture was stirred for 1 h at 50 °C and was concentrated in vacuo. The residue was diluted with EtOAc, then it was washed with aqueous $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give an oily residue, which was dissolved in THF (200 mL). To this solution was added 1 M HCl (50 mL), and the mixture was stirred for 1 h at 24–25 °C. The solution was concentrated to half volume in vacuo to give a residue, which was diluted with EtOAc. The solution was washed with aqueous $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give an oily residue. Recrystallization of the residue from hexane–EtOAc gave **4** (51.3 g, 82% yield): mp 138–141 °C; IR ν_{max} (KBr) 3470, 1776 cm^{-1}, MS *m/z* 189 ($M^+ + 1$); ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, s), 1.48 (3H, s), 2.54 (1H, bs, OH), 3.81 (1H, dd, J = 2.0, 12.5 Hz), 4.00 (1H, dd, J = 2.0, 12.5 Hz), 4.64 (1H, t, J = 2.0 Hz), 4.78 (1H, d, J = 5.9 Hz), 4.84 (1H, d, J = 5.3 Hz). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.95; H, 6.44.

3,4-*O*-Isopropylidene-*aldehydo*-L-*ribo*-penturono-5,2-lactone (5). (a) To a solution of **4** (12.3 g, 64.5 mmol) in DMSO (100 mL) and CH_2Cl_2 (30 mL) were added DCC (40.5 g, 196.1 mmol) and H_3PO_4 (1.0 mL). After the mixture was stirred for 5 h at room temperature, the reaction mixture was filtered, and the filter cake was washed with a small amount of DMSO. The filtrate was diluted with EtOAc (1.5 L); it was then washed three times with H_2O, which was reextracted with EtOAc. The combined EtOAc layer was dried over $MgSO_4$, filtered, and concentrated in vacuo, and chromatographed quickly. Elution with hexane–EtOAc (1:1, then 1:2) gave an oily aldehyde **5** (9.5 g, 80% yield), which was employed for the next reaction without further purification: IR ν_{max} (KBr) 3425, 1787 cm^{-1}; MS *m/z* 187 ($M^+ + 1$), 171 (M^+ – Me); ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, J = 0.5 Hz), 1.47 (3H, J = 0.5 Hz), 1.96 (1.8H, bs, OH), 4.44–5.40 (3H, m), 9.77 (0.1H, s, CHO). Anal. Calcd for $C_8H_{10}O_5 \cdot H_2O$: C, 47.04; H, 5.93. Found: C, 47.10; H, 6.02.

(b) To a solution of Dess–Martin reagent (4.47 g, 10.5 mmol) in CH_2Cl_2 (80 mL) was added a solution of **4** (1.52 g, 8.09 mmol) in CH_2Cl_2 (80 mL) with stirring at room temperature under nitrogen. After 30 min, Et_2O (300 mL) was added to this reaction mixture, and the mixture was filtered on Celite. The filtrate was concentrated in vacuo and chromatographed quickly. Elution with hexane–EtOAc (1:1, then 1:2) gave an oily aldehyde **5** (1.43 g, 95% yield).

(*Z*)-5-*O*-(*tert*-Butyldimethylsilyl)-4,5-didehydro-2,3-*O*-isopropylidene-D-*erythro*-penturono-1,4-lactone (6). To a solution of aldehyde **5** (1.23 g, 6.61 mmol) in DMF (20 mL) were added *tert*-butyldimethylsilyl chloride (1.49 g, 9.91 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.97 g, 7.93 mmol) with stirring at 0–5 °C. After 1 h, the reaction mixture was neutralized with aqueous 1 M HCl at 0–5 °C and then extracted with EtOAc; it was then washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with hexane–EtOAc (3:1) gave **6** (850 mg, 43% yield) as a crystalline solid: mp 94–96 °C (from hexane); $[\alpha]^{25}_D$ +59.0° (c = 1.2, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1811, 1731 cm^{-1}; MS *m/z* 300 (M^+), 285, 243, 199, 169, 157, 129, 111; ^{1}H NMR ($CDCl_3$) δ: 0.19 (3H, s), 0.20 (3H, s), 0.94 (9H, s), 1.41 (3H, s), 1.48 (3H, s), 4.81 (1H, d, J = 5.9 Hz), 5.04 (1H, d, J = 5.9 Hz), 6.09 (1H, s). Anal. Calcd for $C_{14}H_{24}O_5Si$: C, 55.97; H, 8.05. Found: C, 56.16; H, 8.08.

(4*S*,5*R*)-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-one (7). To a suspension of (bromomethyl)triphenylphosphonium bromide (4.80 g, 11 mmol, azeotropically dried with 50 mL × 3 portions of toluene) in dry THF (60 mL) at −78 °C was added *t*-BuOK (1.0 M THF solution, 12 mL) under nitrogen. After 1.5 h at −78 °C of stirring, a solution of *t*-BuLi (1.7 M pentane solution, 18 mL) was added dropwise over a 10-min period. The resulting orange suspension was maintained for 5 h at −78 °C with stirring; it was then treated with a solution of silyl enol lactone **6** (3.0 g, 9.99 mmol) in THF (15 mL). The mixture was stirred for 15 min at −78 °C and then for an additional 17 h at 24 °C; it was then diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with hexane–EtOAc (4:1, then 3:1) gave **7** (1.37 g, 46% yield) as an oil: $[\alpha]^{25}_D$ −9.3° (c = 0.76, $CHCl_3$); IR ν_{max} (film) 1725, 1628 cm^{-1}; MS *m/z* 299 ($M^+ + 1$); ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.95 (9H, s), 1.43 (6H, s), 4.47, 4.67 (2H, AB-q, J = 1.3–1.9, 18.9 Hz, CH_2OSi), 4.52 (1H, d, J = 5.3 Hz, C4–H), 5.07 (1H, d, J = 5.3 Hz), 6.19 (1H, t, J = 1.3–1.9 Hz, C2–H). Anal. Calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78. Found: C, 60.22; H, 8.89.

[1*S*-(1α,4α,5α)]-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-ol (8). To a solution of **7** (1.20 g, 4.02 mmol) and $CeCl_3 \cdot 7H_2O$ (1.57 g, 2.10 mmol) in EtOH (99.5%, 40 mL) was added $NaBH_4$ (80 mg, 2.10 mmol) at room temperature. The mixture was stirred for 30 min; it was then concentrated in vacuo to one-third volume, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give **8** (1.10 g, 99% yield) as an oil: $[\alpha]^{25}_D$ +22.6° (c = 0.80, $CHCl_3$); IR ν_{max} (film) 3500 (broad) cm^{-1}; MS *m/z* 300 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.92 (9H, s), 1.40 (3H, s), 1.43 (3H, s), 2.68 (1H, bs, OH), 4.24 (1H, dt, J = 1.0, 15.2 Hz, C3–CHOSi), 4.35 (1H, d, J = 15.2 Hz, C3–CHOSi), 4.56 (1H, bs, C1–H), 4.77 (1H, t, J = 5.3–5.9 Hz, C5–H), 4.90 (1H, d, J = 5.9 Hz, C4–H), 5.74 (1H, bs, olefinic C2–H). Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 59.81; H, 9.52.

[1*S*-(1α,4α,5α)]-1-[(Benzyloxycarbonyl)oxy]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4,5-(isopropylidenedioxy)-2-cyclopentene (9). To a solution of **8** (674 mg, 2.24 mmol) and DMAP (1.37 g, 11.2 mmol) in CH_2Cl_2 (18 mL) was added benzyl chloroformate (1.91 g, 11.2 mmol) at 0–5 °C. The mixture was stirred for 1 h at 0 °C and then at room temperature for 30 min. The reaction mixture was diluted with EtOAc; it was then washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (9:1) gave **9** [819 mg, 84% yield, R_f = 0.326 (cyclohexane–EtOAc = 9:1)] as an oil and dibenzylcarbonate (R_f = 0.465). Physical data of **9**: $[\alpha]^{25}_D$ −28.5° (*c* = 0.48, $CHCl_3$); IR ν_{max} (film) 1742 cm^{-1}; MS *m/z* 419 (M^+ − Me), 377, 319; ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.91 (9H, s), 1.37 (6H, s), 4.27 (1H, dt, *J* = 1.0, 15.2 Hz), 4.39 (1H, d, *J* = 15.2 Hz), 4.89 (1 H, d, *J* = 5.3 Hz), 4.96 (1H, t, *J* = 5.3–5.9 Hz), 5.21 (2H, s), 5.29 (1H, m, *J* ≤ 1.0–2.0 Hz), 5.75 (1H, s), 7.32–7.41 (5H, m). Anal. Calcd for $C_{23}H_{34}O_6Si$: C, 63.56; H, 7.89. Found: C, 63.34; H, 7.83.

[1*R*-(1α,2α,3α,4α,5α)]-4-[(Benzyloxycarbonyl)oxy]-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-6-oxabicyclo[3.1.0]hexane (10). A solution of **9** (798 mg, 1.84 mmol) and *m*-chloroperoxybenzoic acid (85% purity, 3.43 g, 1.69 mmol) in $CHCl_3$ (40 mL) was stirred in the dark for 4 days at room temperature. The mixture was diluted with EtOAc. The solution was washed with 10% Na_2SO_3 three times and with saturated $NaHCO_3$ two times; it was then dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (5:1) gave **10** (740 mg, 89% yield) as a solid: mp 74–74.5 °C (prisms, from hexane); $[\alpha]^{25}_D$ −50.0° (*c* = 0.94, $CHCl_3$); IR ν_{max} (film) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 1.31 (3H, s), 1.36 (3H, s), 3.66 (1H, s), 3.79, 4.26 (2H, AB-q, *J* = 12.5 Hz), 4.58 (1H, t, *J* = 5.3 Hz), 4.68 (1H, d, *J* = 5.3 Hz), 4.93 (1H, d, *J* = 5.3 Hz), 5.15, 5.23 (2H, AB-q, *J* = 12.5 Hz), 7.36 (5H, bs); MS *m/z* 435 (M^+ − Me), 393 (M^+ − Bu), 301, 183. Anal. Calcd for $C_{23}H_{34}O_7Si$: C, 61.31; H, 7.61. Found: C, 61.19; H, 7.43.

[1*R*-(1α,2α,3α,4α,5α)]-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-6-oxabicyclo[3.1.0]hexan-4-ol (11). A solution of **10** (691 mg, 1.53 mmol) in EtOAc (50 mL) containing 10% Pd on carbon (200 mg) was stirred with hydrogen under atmospheric pressure at room temperature for 30 min. The mixture was filtered and concentrated in vacuo to give **11** (486 mg, quantitatively, R_f = 0.51 [cyclohexane–EtOAc = 3:1)] as a syrup: $[\alpha]^{25}_D$ +0.45° (*c* = 0.2, $CHCl_3$); IR ν_{max} (film) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.39 (3H, s), 1.52 (3H, s), 3.58 (1H, s), 3.75, 4.25 (2H, AB-q, *J* = 12.5 Hz), 4.09 (1H, d, *J* = 5.3 Hz), 4.52 (1H, t, *J* = 5.3–5.9 Hz), 4.70 (1H, d, *J* = 5.3 Hz); MS *m/z* 301 (M^+ − Me), 259, 241, 201, 183, 171, 155. Anal. Calcd for $C_{15}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 56.92; H, 8.74.

[3a*R*-(3aα,4α,5β,6β,6aα)]-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5,6-(isopropylidenedioxy)-2-oxo-3-(phenoxycarbonyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazol-4-ol (12). (a) To a solution of **11** (76 mg, 0.240 mmol) in THF (3 mL) was added phenoxycarbonyl isocyanate[12] (50 mg, 0.307 mmol), with stirring at room temperature. After 10 min, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture of three compounds ([1*R*-(1α,2α,3α,4α,5α)]-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-4-[[(phenoxycarbonyl)carbamoyl]oxy]-6-oxabicyclo[3.1.0]hexane (R = CONHCOOPh in **11**), **12**, and $PhOOCNH_2$). The mixture was chromatographed. During chromatography on the silica gel column, [1*R*-(1α,2α,3α,4α,5α)]-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-4-[[(phenoxycarbonyl)carbamoyl]oxy]-6-oxabicyclo[3.1.0]-hexane changed to compound **12**. Elution with hexane–EtOAc (2:1) gave 112 mg of a mixture of **12** and phenyl carbamate. Both compounds had the same R_f value (0.275). This mixture was employed for the next reaction without further purification. (b) An alternative route to compound **12**. (i) To a solution **8** (270 mg, 0.899 mmol) in THF (10 mL) was added phenoxycarbonyl isocyanate (175 mg, 1.07 mmol) at room temperature with stirring. After 30 min, the reaction mixture was concentrated in vacuo and chromatographed. Elution with cyclohexane–EtOAc (2:1) gave [1*S*-(1α,4α,5α)]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4,5-(isopropylidenedioxy)-1-[[(phenoxycarbonyl)carbamoyl]oxy]-2-cyclopentene (379 mg, 91% yield, R_f = 0.447) as a powder: MS *m/z* 448 (M^+ − Me), 406, 354, 312, 294, 254, 225, 210, 209, 167; ^1H NMR ($CDCl_3$) δ 0.09 (6H, s), 0.92 (9H, s), 1.39 (3H, s), 1.42 (3H, s), 4.27, 4.41 (2H, AB-q, *J* = 15.8 Hz), 4.92 (1H, d, *J* = 5.9 Hz), 4.99 (1H, t, *J* = 5.9 Hz), 5.52 (1H, m, *J* < 2.0 Hz), 5.73 (1H, s), 7.17–7.41 (5H, m), 7.93 (1H, s, NH). Anal. Calcd for $C_{23}H_{33}NO_7Si$: C, 59.59; H, 7.18, N, 3.02. Found: C, 58.65; H, 7.14; N, 2.92. (ii) The compound (379 mg, 0.818 mmol) obtained in procedure i and *m*-chloroperoxybenzoic acid (3.5 g, purity >85%) were dissolved in CH_2Cl_2 (35 mL) and allowed to stand at room temperature for 16 h in the dark. The mixture was diluted with EtOAc, it was then washed with three times with aqueous 10% Na_2SO_3, three times with saturated $NaHCO_3$ and with brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with *n*-hexane–EtOAc (2:1) gave the starting material (194 mg, 51% recovery), and elution with (1:1) gave **12** (94 mg, 24% yield) as a solid: mp 176–177 °C (from EtOAc–*n*-hexane); IR ν_{max} (Nujol) 3480 (w), 2570 (w), 1805, 1725 (w) cm^{-1}; MS *m/z* 466, 465, 464 (M^+ − Me), 423, 422; ^1H NMR ($CDCl_3$) δ 0.08 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 1.36 (3H, s), 1.56 (3H, s), 3.15 (1H, bs, OH), 3.96 (2H, s), 4.46 (1H, d, *J* = 4.0 Hz), 4.68 (1H, d, *J* = 8.6 Hz), 4.83 (1H, t, *J* = 5.3 Hz), 5.02 (1H, dd, *J* = 5.9, 7.9 Hz), 7.16–7.44 (5H, m). Anal. Calcd for $C_{23}H_{33}NO_8Si$: C, 57.60; H, 6.94; N, 2.92. Found: C, 57.54; H, 6.97; N, 2.93.

[3a*R*-(3aα,4α,5β,6β,6aα)]-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5,6-(isopropylidenedioxy)-2-oxo-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazol-4-ol (13). To a solution of a mixture (112 mg) of phenyl carbamate and **12**, as they were obtained above in procedure (a), in THF (8 mL), was added 1 M NaOH (1.5 mL). After 10 min of stirring at room temperature, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with hexane–EtOAc (1:1, then 1:2) gave **13** (61 mg, 71% yield from **11**) as a solid: mp 120.5–121.5 °C (from EtOAc–*n*-hexane); IR ν_{max} (Nujol) 3440, 3360 (shoulder), 1747 cm^{-1}; MS *m/z* 360 (M + 1), 344 (M − Me), 302, 284, 244; ^1H NMR ($CDCl_3$) δ 0.13 (6H, s), 0.92 (9H, s), 1.32 (3H, s), 1.50 (3H, s), 2.73 (1H, bs, OH), 3.87 (2H, s), 4.08 (1H, d, *J* = 7.3 Hz), 4.41 (1H, d, *J* = 5.3 Hz), 4.84 (1H, t, *J* = 5.3–5.9 Hz), 5.00 (1H, dd, *J* = 5.3, 7.3 Hz), 5.20 (1H, bs, NH). Anal. Calcd for $C_{16}H_{29}NO_6Si$: C, 53.46; H, 8.13; N, 3.90. Found: C, 53.81; H, 8.25; N, 3.91.

[3a*R*-(3aα,4α,5β,6β,6aα)]-4,1′:5,6-bis(isopropylidenedioxy)-4-methyl-2-oxo-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole (16). (i) To a solution of **13** (27 mg, 0.075 mmol) in THF (2 mL) was added a solution of 1 M Bu_4NF (0.10 mL, 0.10 mmol) in THF. After 15 min of stirring at room temperature, the reaction mixture was concentrated in vacuo to give a mixture, which was dissolved in dimethoxypropane (2 mL) and DMF (1 mL) containing *p*-TsOH·H_2O (15 mg, 0.08 mmol). The solution was refluxed for 1 h; it was then diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude solid, which was chromatographed. Elution with hexane–EtOAc (1:2) gave **16** (12 mg, 56% yield) as a solid: mp 223–224 °C (from EtOAc); IR ν_{max} (Nujol) 3220, 3150, 1760–1740 cm^{-1}; MS *m/z* 287 (M + 2), 286 (M + 1), 285 (M), 271, 270; ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s), 1.39 (3H, s), 1.42 (3H, s), 1.48 (3H, s), 4.11, 4.33 (2H, AB-q, *J* = 9.9 Hz), 4.17 (1H, d, *J* = 7.3 Hz), 4.47 (1H, d, *J* = 5.3 Hz), 4.78 (1H, t, *J* = 5.9 Hz), 4.96 (1H, t, *J* = 6.6–7.3 Hz), 6.54 (1H, bs, NH). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.57; H, 6.98; N, 4.93.

[1*S*-(1α,4α,5α)]-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(isopropylidenedioxy)-1-[(4-methoxybenzyl)oxy]-2-cyclopentene (19). To a solution of **8** (560 mg, 1.86 mmol) in DMF (5 mL) were added 4-methoxybenzyl chloride (350 mg, 2.24 mmol) and NaH (55% oil dispersion, 98 mg, 2.24 mmol), at room temperature. The mixture was stirred for 3 h; it was then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (5:1) gave **19** (538

mg, 69% yield, R_f = 0.470 [cyclohexane–EtOAc = 4:1)] as an oil and [1*S*-(1α,4α,5α)]-4,5-(isopropylidenedioxy)-1-[(4-methoxybenzyl)oxy]-3-[(4-methoxybenzyl)oxy]methyl-2-cyclopentene (127 mg, 16% yield, R_f = 0.200). Physical data of **19**: $[\alpha]^{25}_D$ −7.9° (*c* = 0.87, $CHCl_3$); IR ν_{max} (film) 1610 cm^{-1}; MS *m/z* 405 (M^+ − Me); ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 1.40 (3H, s), 1.45 (3H, s), 3.80 (6H, s), 4.20–4.40 (3H, m), 4.54, 4.75 (2H, AB-q, *J* = 11.9 Hz), 4.78 (1H, d, *J* = 5.9 Hz, C4-H), 4.83 (1H, t, *J* = 5.9 Hz, C5-H), 5.69 (1H, s, olefinic C2-H), 6.88 (2H, d, *J* = 9.6 Hz), 7.34 (2H, d, *J* = 9.6 Hz). Anal. Calcd for $C_{23}H_{36}O_5Si$: C, 65.06; H, 8.55. Found: C, 65.04; H, 8.70.

[1*S*-(1α,4α,5α)]-3-(Hydroxymethyl)-4,5-(isopropylidenedioxy)-1-[(4-methoxybenzyl)oxy]-2-cyclopentene (20). To a solution of **19** (533 mg, 1.27 mmol) in THF (10 mL) was added *n*-Bu_4NF (1M solution in THF, 1.52 mL, 1.52 mmol). The mixture was stirred for 3 h at room temperature; it was then diluted with EtOAc (250 mL), washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (1:2) gave **20** (360 mg, 93% yield) as a gum: $[\alpha]^{25}_D$ −14.2° (*c* = 0.39, $CHCl_3$); IR ν_{max} (film) 3440, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (3H, s), 1.47 (3H, s), 3.80 (6H, s), 4.25, 4.33 (2H, AB-q, *J* = 14.5 Hz), 4.35 (1H, dd, *J* = 2.0, 5.3 Hz), 4.54, 4.73 (2H, AB-q, *J* = 11.2 Hz), 4.80 (1H, d, *J* = 5.3 Hz), 4.91 (1H, d, *J* = 5.3 Hz), 5.71 (1H, s), 6.88 (2H, d, *J* = 8.6 Hz), 7.33 (2H, d, *J* = 8.6 Hz). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.42; H, 7.27.

[1*S*-(1α,4α,5α)]-3-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-1-[(4-methoxybenzyl)oxy]-2-cyclopentene (21). To a solution of **20** (365 mg, 1.05 mmol) in DMF (5 mL) were added BnBr (270 mg, 1.58 mmol) and NaH (55% oil dispersion, 60 mg, 1.3 equiv), with stirring at room temperature. The mixture was stirred for 2 h at room temperature; it was then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (3:1) gave **21** (461 mg, quantitatively) as a gum: $[\alpha]^{25}_D$ −2.4° (*c* = 0.47, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 1.40 (3H, s), 1.45 (3H, s), 3.79 (3H, s), 4.16 (2H, s, C1–CH_2O), 4.36 (1H, dd, *J* = 2.0, 5.3 Hz, C–H), 4.55 (2H, s), 4.56, 4.73 (2H, AB-q, *J* = 11.2 Hz), 4.79 (1H, t, *J* = 5.3–5.9 Hz, C–H), 4.91 (1H, d, *J* = 5.9 Hz), 5.78 (1H, s, C–H), 6.87 (2H, d, *J* = 8.6 Hz), 7.29–7.34 (7H, m). Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.69; H, 7.08.

[1*R*-(1α,2α,3α,4α,5α)]-1-[(Benzyloxy)methyl]-2,3-(isopropylidenedioxy)-4-[(4-methoxybenzyl)oxy]-6-oxabicyclo[3.1.0]hexane (22). A solution of **21** (444 mg, 1.12 mmol) and *m*-chloroperoxybenzoic acid (85% purity, 1.27 g, 6.25 mmol) in $CHCl_3$ (15 mL) was allowed to stand in the dark for 24 h at room temperature. The mixture was diluted with EtOAc. The solution was washed with 10% Na_2SO_3 three times and with saturated $NaHCO_3$ two times, and then it was dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (4:1) gave **22** (254 mg, 55% yield) as a gum: $[\alpha]^{25}_D$ −53.4° (*c* = 0.3, $CHCl_3$); IR ν_{max} (film) 1613, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (3H, s), 1.51 (3H, s), 3.51 (1H, s, C5–H), 3.53, 4.18 (2H, AB-q, *J* = 11.9 Hz, C1–CH_2O), 3.80 (3H, s), 3.88 (1H, d, *J* = 5.3 Hz, C4–H), 4.44, 4.76 (2H, AB-q, *J* = 11.9 Hz), 4.57 (1H, t, *J* = 5.3 Hz, C3–H), 4.61 (2H, s), 4.70 (1H, d, *J* = 5.3 Hz, C2–H), 6.88 (2H, d, *J* = 8.6 Hz), 7.27–7.35 (7H, m). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.86; H, 7.09.

[1*R*-(1α,2α,3α,4α,5α)]-1-[(Benzyloxy)methyl]-2,3-(isopropylidenedioxy)-6-oxabicyclo[3.1.0]hexan-4-ol (23). A mixture of **22** (220 mg, 0.533 mmol), H_2O (1.5 mL), and DDQ (240 mg, 1.06 mmol) in CH_2Cl_2 (15 mL) was stirred for 3 h at 24 °C, and then it was concentrated in vacuo to one-third volume, diluted with EtOAc, washed with $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (3:1) gave **23** (154 mg, 99% yield) as a gum: $[\alpha]^{25}_D$ +9.7° (*c* = 1.2, $CHCl_3$); IR ν_{max} (film) 3470, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (3H, s), 1.52 (3H, s), 2.86 (1H, d, *J* = 4.6 Hz, OH), 3.54, 4.17 (2H, AB-q, *J* = 11.9 Hz, C1–CH_2O), 3.57 (1H, s, C5–H), 4.11 (1H, dd, *J* = 4.6, 5.9 Hz, C4–H), 4.53 (1H, t, *J* = 5.9 Hz, C3–H), 4.62 (2H, s), 4.78 (1H, d, *J* = 5.9 Hz), 7.28–7.36 (5H, m). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.86; H, 7.01.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1-[(benzyloxy)methyl]-2,3-(isopropylidenedioxy)-1,4-cyclopentanediol (24). A mixture of **23** (117 mg, 0.400 mmol), NaN_3 (315 mg, 4.85 mmol), and NH_4Cl (225 mg, 4.77 mmol) in DMF (6 mL) was stirred for 16 h at 100 °C with attachment of a glass stopper to prevent the generated HN_3 gas from leaking. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (3:2) gave **24** (133 mg, 99% yield) as a gum: $[\alpha]^{25}_D$ −54.0° (*c* = 0.07, $CHCl_3$); IR ν_{max} (film) 3450, 2110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, s), 1.50 (3H, s), 2.88 (1H, s, C1–OH), 2.92 (1H, d, *J* = 11.2 Hz, OH), 3.68, 3.86 (2H, AB-q, *J* = 9.2 Hz, C1–CH_2O), 3.83 (1H, dd, *J* = 1.0, 7.3 Hz, C5–H), 4.29 (1H, dd, *J* = 1.0, 5.3 Hz, C2–H), 4.53 (1H, t, *J* = 5.9 Hz, C3–H), 4.62 (2H, s), 4.78 (1H, d, *J* = 5.9 Hz), 7.28–7.36 (5H, m); MS *m/z* 320 (M^+ − Me). Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.22; H, 5.97; N, 12.37.

[1*R*-(1α,2β,3β,4β,5β)]-5-Amino-1-[(benzyloxy)methyl]-2,3-(isopropylidenedioxy)-1,4-cyclopentanediol (25).[20] A solution of **24** (141 mg, 0.420 mmol) and Ph_3P (330 mg, 1.26 mmol) in THF (10 mL) was stirred for 9 days at room temperature, and then H_2O (1.0 mL) was added to this solution. After 16 h, the reaction mixture was concentrated in vacuo, and chromatographed. Elution with EtOAc, and then with EtOAc–MeOH (9:1), gave amine **25** (126 mg, 97% yield) as a solid: mp 86–87 °C (from diethyl ether–hexane); $[\alpha]^{25}_D$ −10.1° (*c* = 1.17, $CHCl_3$); IR ν_{max} (film) 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3H, s), 1.46 (3H, s), 3.04 (1H, dd, *J* = 1.0, 5.9 Hz, C5–H), 3.78, 3.83 (2H, AB-q, *J* = 9.6 Hz, C1–CH_2O), 4.28 (1H, t, *J* = 5.3–5.9 Hz, C4–H), 4.33 (1H, dd, *J* = 1.0, 5.3 Hz, C2–H), 4.59, 4.66 (2H, AB-q, *J* = 11.9 Hz), 4.64 (1H, t, *J* = 5.3 Hz, C3–H), 7.35 (5H, bs). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.32; H, 7.44; N, 4.42. X-ray analysis of **25** was carried out in order to confirm the stereochemistry. From the result, the stereochemistry of **25** was determined to be as shown in Figure 2.

[1*R*-(1α,2β,3β,4β,5β)]-[1-[(Benzyloxy)methyl]-1,2,3,4-tetrahydroxycyclopentane-5-yl]amino (2,3,4,6-Tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino Thioketone (26). A solution of **25** (53 mg, 0.172 mmol) in 2% HCl in MeOH (2 mL) was stirred for 3 h at 50 °C. The reaction mixture was concentrated in vacuo to give [1*R*-(1α,2β,3β,4β,5β)]-5-amino-1-[(benzyloxy)methyl]-1,2,3,4-cyclopentanetetraol hydrochloride, which was dissolved in a mixture of THF (5 mL), H_2O (1 mL), and Et_3N (140 mg). To this mixture, a solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate (140 mg, 0.24 mmol, 1.4 equiv) in THF (3 mL) was added. After 2 h of stirring at room temperature, the reaction mixture was concentrated in vacuo and chromatographed. Elution with EtOAc gave a thiourea **26** (104 mg, 71% yield) as a gum: $[\alpha]^{25}_D$ + 117.6° (*c* = 1.13, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3400, 3310, 3010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34–3.79 (8H, m), 4.09–4.18 (2H, m), 4.25 (1H, t, *J* = 4.6–5.3 Hz), 4.37–4.94 (10H, m), 5.05–5.07 (1H, m, anomeric H), 6.65 (1H, s, NH), 7.15–7.18 (2H, m), 7.22–7.40 (23H, m), 7.78 (1H, d, *J* = 7.3 Hz, NH). Anal. Calcd for $C_{48}H_{54}N_2O_{10}S \cdot {}^1/_2H_2O$: C, 67.03; H, 6.45; N, 3.26; S, 3.72. Found: C, 67.06; H, 6.51; N, 3.09; S, 3.38.

[3a*R*-(3aα,4α,5β,6β,6aα)]-4-[(Benzyloxy)methyl]-2-[(2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino]-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole-4,5,6-triol (27). To a solution of **26** (55 mg, 0.065 mmol) in MeCN (4 mL) was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (70 mg, 0.260 mmol, 4 equiv), at 0 °C under nitrogen with stirring. After 2 h of stirring at 0 °C, Et_3N (150 mg) was added with stirring to this mixture. After further stirring for 30 min at 0 °C, the reaction mixture was concentrated in vacuo to give a residue (the R_f value of product **27** was exactly the

(20) The author has deposited atomic coordinates for **25** and **29** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

same as that of the starting **26**), which was chromatographed. Elution with cyclohexane–EtOAc (1:4) gave **27** (45 mg, 85% yield) as a gum: $[\alpha]^{24}_D$ +53.8° (*c* = 3.97, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3550, 3430, 1672 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 3.17 (1H, dd, *J* = 9.4, 9.1 Hz), 3.27 (1H, dd, *J* = 8.8, 9.9 Hz), 3.56 (1H, dd, *J* = 1.5, 9.9 Hz), 3.61 (1H, dd, *J* = 5.1, 9.6 Hz), 3.63 (1H, d, *J* = 3.8 Hz), 3.79 (1H, ddd, *J* = 9.1, 1.5, 8.8 Hz), 3.86 (1H, dd, *J* = 9.6, 9.4 Hz), 3.86 (2H, s), 4.17 (1H, d, *J* = 6.5 Hz), 4.30 (1H, dd, *J* = 3.8, 5.8 Hz), 4.98 (1H, dd, *J* = 5.8, 6.5 Hz), 5.20 (1H, d, *J* = 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 69.4 (t), 69.7 (t), 70.2 (d), 72.6, 73.6, 73.7, 73.8 (d), 75.0, 75.8, 76.8 (d), 77.9 (d), 77.9 (d), 78.2 (d), 81.3 (s), 81.4 (d), 84.6 (d), 160.4 (s). (Chemical shifts are given to internal $CDCl_3$ [^1H δ 7.24 and ^{13}C δ 77.0] as a reference.) Anal. Calcd for $C_{48}H_{52}N_2O_{10}$ (816.9): C, 70.56; H, 6.42; N, 3.43. Found: C, 70.34; H, 6.53; N, 3.27.

[3a*R*-(3aα,4α,5β,6β,6aα)]-2-[(1-Deoxy-α-D-glucopyranos-1-yl)amino]-4-(hydroxymethyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole-4,5,6-triol (2). (a) To a solution of **27** (36 mg, 0.044 mmol) in MeOH (7 mL) was added $Pd(OH)_2$ on carbon (moist, Pearlman's catalyst, Pd content 20%, dry weight basis H_2O content <50%, 730 mg), and the mixture was stirred under hydrogen atmosphere (1 atom) at 60 °C for 30 min. After completion of the reaction, the reaction mixture was filtered and concentrated in vacuo to give a crude product, which was chromatographed on Amberlite CG-50 (NH_4^+ type/H^+ type = 3:2, 5 mL). Elution with 0.5 M aqueous NH_3 gave **2** (6.0 mg, 37% yield) as a powder: $[\alpha]^{24}_D$ +111.7° (*c* = 0.7, H_2O); FT-IR ν_{max} (KBr) 3371, 2929, 1671, 1549, 1103, 1048 cm^{-1}; 400-MHz ^1H NMR (D_2O) δ 3.21 (1H, dd, *J* = 9.6, 9.8 Hz), 3.37 (1H, ddd, *J* = 9.8, 2.4, 5.3 Hz), 3.46 (1H, dd, *J* = 9.6, 9.6 Hz), 3.54 (1H, dd, *J* = 5.3, 12.3 Hz), 3.56 (1H, dd, *J* = 5.3, 9.6 Hz), 3.73 (1H, dd, *J* = 1.0, 4.4 Hz), 3.98 (1H, dd, *J* = 1.0, 6.8 Hz), 4.26 (1H, dd, *J* = 4.4, 6.6 Hz), 4.88 (1H, dd, *J* = 6.0, 6.8 Hz), 5.13 (1H, d, *J* = 5.3 Hz), 5.61 (1H, dd, *J* = 2.4, 12.3 Hz); ^{13}C NMR (D_2O) δ 60.6 (t), 61.5 (t), 69.6 (d), 69.8 (d), 71.8 (d), 72.5 (d), 72.6 (d), 72.9 (d), 75.9 (d), 80.5 (d), 82.2 (s), 83.5 (d), 161.0 (s) (^1H chemical shifts are given to external TMS as a reference δ 0.00, and ^{13}C chemical shifts are given to internal dioxane as a reference δ 66.5); FAB MS (positive) *m/z* 367 $(M + 1)^+$; (negative) *m/z* 365 $(M - 1)^-$; FAB HRMS (positive) 367.0699; calcd for $C_{13}H_{23}N_2O_{10}$ 367.0691. Anal. Calcd for $C_{13}H_{22}N_2O_{10}{}^{5}/_{2}H_2O$ (366.3 + 45.1): C, 37.96; H, 6.61; N, 6.81. Found: C, 37.68; H, 6.25; N, 6.77.

(b) By using the above-mentioned procedure for making **2** from **27**, **38** (8 mg) was converted to **2** (1.5 mg, 46%), which was identical to that obtained from **27** in all respects: $[\alpha]^{24}_D$ +130.0° (*c* = 0.2, H_2O).

(c) By using the above-mentioned procedure for making **2** from **27**, **42** (36 mg) was converted to **2** (8.0 mg, 43%), which was identical to the one obtained from **27** in all respects; $[\alpha]^{24}_D$ +121.3° (*c* = 0.7, H_2O).

(d) By using the above-mentioned procedure for making **2** from **27**, **36** (21 mg) was converted to **2** (3.9 mg, 42%), which was identical to the one obtained from **27** in all respects: $[\alpha]^{24}_D$ +125.9° (*c* = 0.4, H_2O).

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1-(hydroxymethyl)-2,3-(isopropylidenedioxy)-1,4-cyclopentanediol (28). A mixture of **11** (377 mg, 1.19 mmol), NaN_3 (930 mg, 14.3 mmol), and NH_4Cl (765 mg, 14.3 mmol) in DMF (18 mL) was stirred for 16 h at 100 °C with attachment of a glass stopper to prevent the generated HN_3 gas from leaking. The reaction mixture was filtered, and the filtrate was concentrated in vacuo with a pump to remove DMF. The residue was chromatographed. Elution with cyclohexane–EtOAc (3:1, and then 1:2) gave [1*R*-(1α,2β,3β,4β,5β)]-5-azido-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-1,4-cyclopentanediol [20 mg, 5% yield, R_f = 0.863 (cyclohexane–EtOAc = 1:2)] and **28** [269 mg, 92% yield, R_f = 0.250 (cyclohexane–EtOAc = 1:2)] as a gum: IR ν_{max} (film) 3390, 2120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3H, s), 1.52 (3H, s), 2.48 (3H, bs, OH × 3), 3.84 (1H, d, *J* = 5.3 Hz, C5–H), 3.89, 3.98 (2H, AB-q, *J* = 11.2 Hz, C1–CH_2O), 4.32 (1H, d, *J* = 4.6 Hz, C2–H), 4.48 (1H, dd, *J* = 5.3, 5.9 Hz, C4–H), 4.67 (1H, t, *J* = 5.9 Hz, C3–H). Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.28; H, 6.04; N, 17.04.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1,1′:2,3-bis(isopropylidenedioxy)-1-methylcyclopentan-4-ol (29).[20] To a solution of **28** (260 mg, 1.06 mmol) in DMF (5 mL) and 2,2-dimethoxypropane (10 mL) was added p-TsOH·H_2O (20 mg), and the mixture was stirred for 16 h at room temperature to give a mixture of two conformational isomers. The reaction mixture was concentrated in vacuo with a pump and chromatographed. During the chromatography on a silica gel column, the upper R_f conformer (R_f = 0.540, cyclohexane–EtOAc = 3:1) changed to the lower R_f one (R_f = 0.405). Elution with cyclohexane–EtOAc (4:1) gave **29** (248 mg, 82% yield) as a solid: mp 75.5–76.5 °C (prisms, from hexane); $[\alpha]^{24}_D$ −64.1° (*c* = 1.2, $CHCl_3$); IR ν_{max} (Nujol) 3520, 2110 cm^{-1}; MS *m/z* 286 $(M^+ + 1)$, 270, 263, 242, 212, 199, 171, 157, 143; ^1H NMR ($CDCl_3$) δ 1.31 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.51 (3H, s), 2.87 (1H, d, *J* = 5.2 Hz, OH), 3.82 (1H, d, *J* = 5.3 Hz, C5–H), 4.26 (2H, s), 4.30–4.36 (1H, m, C4–H), 4.38 (1H, d, *J* = 5.9 Hz, C2–H), 4.61 (1H, t, *J* = 5.9 Hz, C3–H). Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.52: H, 6.71; N, 14.73. Found: C, 50.63; H, 6.99; N, 14.85.

X-ray analysis of **29** was carried out in order to confirm the stereochemistry. From the result, the configuration of **29** was determined as to be shown in Figure 3.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1,1′:2,3-bis(isopropylidenedioxy)-4-[(4-methoxybenzyl)oxy]-1-methylcyclopentane (30). To a mixture of **29** (90 mg, 0.315 mmol) in DMF–THF (1:1, 5 mL) and NaH (55% oil dispersion, 60 mg, 1.38 mmol), was added 4-methoxybenzyl chloride (120 mg, 0.766 mmol) at room temperature. The mixture was stirred for 16 h; it was then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (5:1) gave **30** (115 mg, 90% yield, R_f = 0.333) as an oil: $[\alpha]^{24}_D$ −38.4° (*c* = 2.47, $CHCl_3$); IR ν_{max} (film) 2101, 1610 cm^{-1}; MS *m/z* 405 (M^+), 390, 376, 348, 319, 304; ^1H NMR ($CDCl_3$) δ 1.29 (3H, s), 1.35 (6H, s), 1.53 (3H, s), 3.72 (1H, dd, *J* = 0.5, 4.6 Hz, C5–H), 3.81 (3H, s), 4.05 (1H, t, *J* = 4.6–5.3 Hz, C4–H), 4.21 (2H, s, C1–CH_2O), 4.32 (1H, dd, *J* = 0.5, 5.3 Hz), 4.63, 4.72 (2H, AB-q, *J* = 11.9 Hz, OCH_2Ar), 4.69 (1H, dt, *J* = 0.5, 5.3 Hz, C3–H), 6.89 (2H, d, *J* = 8.6 Hz), 7.34 (2H, d, *J* = 8.6 Hz). Anal. Calcd for $C_{20}H_{27}N_3O_6$: C, 59.24; H, 6.71; N, 10.37. Found: C, 59.04; H, 6.90; N, 10.29.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1-(hydroxymethyl)-2,3-(isopropylidenedioxy)-4-[(4-methoxybenzyl)oxy]cyclopentan-1-ol (31). A solution of **30** (115 mg, 0.284 mmol) in 85% AcOH was warmed to 40–45 °C for 24 h with stirring. The mixture was concentrated in vacuo and chromatographed. Elution with cyclohexane–EtOAc (4:1) gave the recovered **30** (5 mg), and elution with EtOAc gave **31** (66 mg, 64%) as a solid: Mp 138–139 °C (from EtOAc–cyclohexane); $[\alpha]^{24}_D$ −36.2° (*c* = 1.1, $CHCl_3$); IR ν_{max} (Nujol) 3525, 2350 (w), 2115 cm^{-1}; MS *m/z* 336 $(M^+ - 29)$; ^1H NMR ($CDCl_3$ + D_2O) δ 1.29 (3H, s), 1.56 (3H, s), 3.77 (1H, dd, *J* = 0.5, 11.2 Hz), 3.93 (1H, d, *J* = 11.2 Hz), 3.76 (1H, d, *J* = 5.9 Hz, C5–H), 3.81 (3H, s), 4.20 (1H, t, *J* = 5.3 Hz, C3–H), 4.23 (1H, dd, *J* = 0.5, 5.9 Hz, C2–H), 4.64, 4.70 (2H, AB-q, *J* = 12.5 Hz, OCH_2Ar), 4.72 (1H, t, *J* = 5.3–5.9 Hz, C4–H), 6.90 (2H, d, *J* = 8.6 Hz), 7.34 (2H, d, *J* = 8.6 Hz). Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.35; N, 11.50. Found: C, 55.74; H, 6.12; N, 11.51.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1-(benzyloxy)-1-[(benzyloxy)methyl]-2,3-(isopropylidenedioxy)-4-[(4-methoxybenzyl)oxy]cyclopentane (32). A mixture of **31** (55 mg, 0.151 mmol), BnBr (154 mg, 0.903 mmol), and NaH (55% oil dispersion, 50 mg) in DMF (2 mL) was stirred for 16 h at 10 °C; it was then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (4:1) gave **32** (73 mg, 89%) as an oil: $[\alpha]^{25}_D$ −7.9° (*c* = 2.9, $CHCl_3$); IR ν_{max} (film) 2105, 1612 cm^{-1}; MS *m/z* 516. ^1H NMR ($CDCl_3$) δ 1.26 (3H, s), 1.57 (3H, s), 3.81 (3H, s, OCH_3), 3.85, 3.94 (2H, AB-q, *J* = 11.2 Hz, C1–CH_2O), 4.07 (1H, dd, *J* = 0.5, 5.3 Hz), 4.13 (1H, t, *J* = 4.6–5.3 Hz), 4.29 (1H, dd, *J* = 0.5, 5.9 Hz), 4.42, 4.55 (2H, AB-q, *J* = 11.2 Hz), 4.54, 4.66 (2H, AB-q, *J* = 10.6 Hz), 4.64 (1H, td, *J* = 5.9, 0.5 Hz), 4.66 (2H, s), 6.88 (2H, d, *J* = 8.6 Hz), 7.09–7.12 (2H, m), 7.26–7.36 (10H, m). Anal. Calcd for $C_{31}H_{35}N_3O_6$: C, 68.24; H, 6.47; N, 7.70. Found: C, 68.37; H, 6.31; N, 7.61.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-1-(benzyloxy)-1-[(benzyloxy)methyl]-2,3-(isopropylidenedioxy)cyclopentan-4-ol (33). A mixture of **32** (70 mg, 0.135 mmol), H_2O (0.7 mL), and DDQ (100 mg, 0.441 mmol) in CH_2Cl_2 (7 mL) was stirred for 4 h at room temperature; it was then diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (4:1) gave a mixture (50 mg) of *p*-methoxybenzaldehyde and **33** as an oil, which was employed for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, s), 1.53 (3H, s), 2.89 (1H, d, J = 11.9 Hz, OH), 3.90, 3.99 (2H, AB-q, J = 11.2 Hz, C1–CH_2O), 4.19 (1H, d, J = 5.9 Hz, C5–H), 4.37–4.45 (2H, m, C2–H, C4–H), 4.53, 4.70 (2H, AB-q, J = 11.9 Hz), 4.56, 4.64 (2H, AB-q, J = 11.2 Hz), 4.57 (1H, t, J = 5.9 Hz, C3-H), 7.21–7.42 (10H, m).

[1*R*-(1α,2β,3β,4β,5β)]-5-Amino-1-(benzyloxy)-1-[(benzyloxy)methyl]-2,3-(isopropylidenedioxy)cyclopentan-4-ol (34). A solution of the above-obtained mixture (50 mg) of *p*-methoxybenzaldehyde and **33** and Ph_3P (100 mg) in THF (6 mL) was stirred for 7 days at room temperature, and then H_2O (0.5 mL) was added to this solution. After 2 h, the reaction mixture was concentrated in vacuo and chromatographed. Elution with cyclohexane–EtOAc (4:1), and then with 5% MeOH in EtOAc, gave a mixture (72 mg) of triphenylphosphine oxide and amine **34** as a solid, which was employed for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, s), 1.47 (3H, s), 3.46 (1H, dd, J = 2.0, 5.9 Hz, C5–H), 3.92, 4.03 (2H, AB-q, J = 11.2 Hz, C1–CH_2O), 4.27 (1H, t, J = 5.9 Hz, C4–H), 4.42 (1H, dd, J = 2.0, 5.9 Hz, C2–H), 4.52, 4.63 (2H, AB-q, J = 11.2 Hz), 4.58 (1H, t, J = 5.9 Hz, C3–H), 4.58–4.61 (2H, m), 7.13–7.75 (10H, m).

[1*R*-(1α,2β,3β,4β,5β)]-[1-(Benzyloxy)-1-[(benzyloxy)methyl]-2,3,4-trihydroxycyclopent-5-yl]amino (2,3,4,6-Tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino Thioketone (35). The mixture (72 mg) of triphenylphosphine oxide and **34** in 2% HCl in MeOH (8 mL) was stirred for 4 h at 50 °C. The reaction mixture was concentrated in vacuo to give a mixture (70 mg) of triphenylphosphine oxide and [1*R*-(1α,2β,3β,4β,5β)]-5-amino-1-(benzyloxy)-1-[(benzyloxy)methyl]-2,3,4-cyclopentanetriol hydrochloride, which was dissolved in a mixture of THF (8 mL), H_2O (1.6 mL), and Et_3N (160 mg). To this mixture was added a solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate (140 mg) in THF (3 mL). After 2 h of stirring at room temperature, the reaction mixture was concentrated in vacuo and chromatographed. Elution with EtOAc gave a thiourea **35** (27 mg, 22% yield from **32**) as a gum: $[\alpha]^{25}_D$ +59.4° (c = 1.8, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3600–3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.69 (1H, bs, OH), 3.16 (2H, bs, 2 × OH), 3.40–3.80 (16H, m), 4.11–5.16 (9H, m), 6.60 (1H, bs, NH), 7.14–7.50 (30 H, m), 7.78 (1H, d, J = 9.3 Hz, NH). Anal. Calcd for $C_{55}H_{60}N_2O_{10}S$: C, 70.19; H, 6.43; N, 2.98; S, 3.41. Found: C, 70.01; H, 6.89; N, 2.77; S, 3.04.

[3a*R*-(3aα,4α,5β,6β,6aα)]-4-(Benzyloxy)-4-[(benzyloxy)methyl]-2-[(2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino]-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole-5,6-diol (36). To a solution of **35** (15 mg, 0.016 mmol) in MeCN (1 mL) was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (30 mg, 0.111 mmol) at 0 °C under nitrogen with stirring. After 1 h of stirring at 0 °C, Et_3N (50 mg) was added with stirring to this mixture. After a further 15 min of stirring at 0 °C, and a further 30 min at room temperature, the reaction mixture was diluted with EtOAc; it was then washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (4:1) was performed to remove the higher R_f material; and then elution with cyclohexane–EtOAc (1:1) gave **36** (13 mg, 90% yield) as a gum; $[\alpha]^{25}_D$ +60.5° (c = 1.2, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3420, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.90 (3H, bs, NH, 2 × OH), 3.25–3.50 (2H, m), 3.60–3.90 (4H, m), 3.95–4.15 (2H, m), 4.30–5.00 (14H, m), 5.36 (1H, d, J = 4.0 Hz), 7.09–7.15 (2H, m), 7.20–7.50 (30H, m). Anal. Calcd for $C_{55}H_{58}N_2O_{10}$: C, 72.83; H, 6.44; N, 3.09. Found: C, 72.55; H, 6.59; N, 2.91.

[1*R*-(1α,2β,3β,4β,5β)]-5-Amino-1,1′:2,3-bis(isopropylidenedioxy)-1-methylcyclopentan-4-ol (18). A solution of **29** (120 mg, 0.421 mmol) and PPh_3 (240 mg, 0.914 mmol) in THF (25 mL) was allowed to stand for 5 days. To this solution was added H_2O (2 mL) with stirring at room temperature. After 5 h, the solution was concentrated in vacuo and chromatographed. Elution with EtOAc gave **18** (99 mg, 91%) as a solid: mp 113–113.5 °C (needles, from hexane–EtOAc); $[\alpha]^{24}_D$ −15.9° (c = 1.5, $CHCl_3$); IR ν_{max} (Nujol) 3600–3000, 1587 (w) cm^{-1}; MS m/z: 260 (M^+ + 1), 270, 244, 201; ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.50 (3H, s), 2.44 (3H, broad, NH_2, OH), 3.24 (1H, d, J = 5.3 Hz, C5–H), 4.21 (1H, t, J = 5.3–5.9 Hz, C4–H), 4.30, 4.34 (2H, AB-q, J = 9.5 Hz, C1–CH_2O), 4.43 (1H, d, J = 5.9 Hz, C2–H), 4.63 (1H, t, J = 5.9 Hz, C3–H). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.37; H, 8.13; N, 5.34.

[1*R*-(1α,2β,3β,4β,5β)]-[1-(Hydroxymethyl)-1,2,3,4-tetrahydroxycyclopent-5-yl]amino (2,3,4,6-Tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino Thioketone (37). A solution of **18** (37 mg, 0.143 mmol) in 2% HCl in MeOH (8 mL) was stirred for 2 h at 50 °C. The reaction mixture was concentrated in vacuo to give [1*R*-(1α,2β,3β,4β,5β)]-5-amino-1-(hydroxymethyl)-1,2,3,4-cyclopentanetetraol hydrochloride, which was dissolved in in a mixture of THF (3 mL), H_2O (0.6 mL), and Et_3N (68 mg). To this mixture was added a solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate (120 mg, 0.206 mmol) in THF (2 mL). After 2 h of stirring at room temperature, the reaction mixture was concentrated in vacuo and chromatographed. Elution with EtOAc, or with 5% MeOH in EtOAc, gave a thiourea **37** (96 mg, 89% yield) as a powder: $[\alpha]^{25}_D$ +131.4° (c = 1.0, $CHCl_3$); IR ν_{max} (Nujol) 3500–3200 (broad) cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O) δ 3.44–3.81 (9H, m), 4.00 (1H, d, J = 5.3 Hz), 4.13–4.23 (2H, m), 4.41–4.92 (8H, m, benzyl CH_2 × 4), 5.21 (1H, bs, anomeric H), 6.87 (1H, bs, NH), 7.10–7.13 (2H, m), 7.21–7.48 (20H, m), 7.71 (1H, d, J = 7.3 Hz, NH). Anal. Calcd for $C_{41}H_{48}N_2O_{10}S$: C, 64.72; H, 6.36; N, 3.68; S, 4.21. Found: C, 64.32; H, 6.49; N, 3.66; S, 3.88.

[3a*R*-(3aα,4α,5β,6β,6aα)]-2-[(2,3,4,6-Tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino]-4-(hydroxymethyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole-4,5,6-triol (38). To a solution of **37** (30 mg, 0.039 mmol) in MeCN (2 mL) was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (20 mg, 0.074 mmol) at 0 °C under nitrogen with stirring. After 1 h of stirring at 0 °C, Et_3N (35 mg) was added to this mixture with stirring. After a further 5 min of stirring at 0 °C, the reaction mixture was concentrated in vacuo and chromatographed. Elution with 10% MeOH in EtOAc gave **38** (24 mg, 84% yield) as a powder: $[\alpha]^{24}_D$ + 73.5° (c = 1.0, MeOH); IR ν_{max} (Nujol) 3350, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.18 (1H, bs, NH, D_2O exchanged), 3.31 (1H, t, J = 9.2 Hz), 3.41 (1H, dd, J = 6.2, 9.9 Hz), 3.60–4.02 (7H, m, containing OH), 4.20 (1H, d, J = 6.6 Hz), 4.34 (1H, dd, J = 4.6, 5.3 Hz), 4.38–4.69 (6H, m, containing OH), 4.72–4.92 (5H, m), 5.36 (1H, d, J = 4.6 Hz, anomeric H), 7.07–7.09 (2H, m), 7.24–7.33 (23H, m); MS m/z 635 (M^+ − Bn), 540, 539, 527, 474. Anal. Calcd for $C_{41}H_{46}N_2O_{10}$: C, 67.75; H, 6.38; N, 3.85. Found: C, 67.65; H, 6.35; N, 4.00.

[1*R*-(1α,2β,3β,4β,5β)]-5-Azido-4-(benzyloxy)-1,1′:2,3-bis(isopropylidenedioxy)-1-methylcyclopentane (39). To a solution of **29** (100 mg, 0.351 mmol) in DMF (1 mL) were added BnBr (120 mg, 0.701 mmol) and NaH (55% oil dispersion, 31 mg, 0.701 mmol) with stirring at room temperature. After 1 h of stirring at room temperature, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed. Elution with cyclohexane–EtOAc (4:1) gave **39** (131 mg, quantitatively) as a gum: $[\alpha]^{25}_D$ −52.3° (c = 0.47, $CHCl_3$); IR ν_{max} (film) 2101 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, s), 1.36 (6H, s), 1.54 (3H, s), 3.77 (1H, d, J = 4.6 Hz, C5–H), 4.08 (1H, t, J = 4.6 Hz, C4–H), 4.23 (2H, s, C1–CH_2O), 4.33 (1H, d, J = 5.3 Hz, C2–H), 4.70, 4.80 (2H, AB-q, J = 12.5 Hz), 4.72 (1H, t, J = 4.6–5.3 Hz, C3–H), 7.37–7.45 (5H, m). Anal. Calcd for $C_{19}H_{25}N_3O_5$: C, 60.79; H, 6.71; N, 11.19. Found: C, 60.55; H, 6.56; N, 11.20.

[1*R*-(1α,2β,3β,4β,5β)]-5-Amino-4-(benzyloxy)-1,1′:2,3-bis(isopropylidenedioxy)-1-methylcyclopentane (40). A solution of **39** (110 mg, 0.293 mmol) and PPh_3 (230 mg, 0.877 mmol) in THF (11 mL) was allowed to stand for 7 days. To this solution was added H_2O (1.5 mL) with stirring at room temperature. After 3–15 h, the solution was concentrated in

vacuo and chromatographed. Elution with EtOAc gave **40** (174 mg, containing a small amount of Ph_3PO) as a solid. The analytical sample was purified on a silica gel TLC plate by development with cyclohexane–EtOAc (1:3). The R_f values of **40** and Ph_3PO (cyclohexane–EtOAc = 1:3) were 0.392 and 0.322, respectively: $[\alpha]^{25}_D$ −21.0° (c = 0.2, $CHCl_3$); IR ν_{max} (film) 3600–3200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3H, s), 1.35 (3H, s), 1.39 (3H, s), 1.49 (3H, s), 1.59 (2H, bs, NH_2), 3.08 (1H, d, J = 4.6 Hz, C5–H), 3.90 (1H, t, J = 5.3 Hz, C4–H), 4.32 (3H, s), 4.38 (1H, d, J = 5.9 Hz, C2–H), 4.64, 4.76 (2H, AB-q, J = 11.9–12.5 Hz), 4.71 (1H, t, J = 5.3–5.9 Hz, C3–H), 7.35–7.42 (5H, m). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 64.85; H, 7.47; N, 4.13.

[1*R*-(1α,2β,3β,4β,5β)]-[4-(Benzyloxy)-1-(hydroxymethyl)-1,2,3-trihydroxycyclopent-5-yl]amino (2,3,4,6-*O*-Tetrabenzyl-1-deoxy-α-D-glucopyranos-1-yl)amino Thioketone (41). A solution of **40** (68 mg, containing a small amount of Ph_3PO obtained above) in 2% HCl in MeOH (10 mL) was stirred for 4 h at 50 °C. The reaction mixture was concentrated in vacuo to give [1*R*-(1α,2β,3β,4β,5β)]-5-amino-4-(benzyloxy)-1-(hydroxymethyl)-1,2,3-cyclopentanetriol hydrochloride, which was dissolved in a mixture of THF (3 mL), H_2O (1 mL), and Et_3N (100 mg). To this mixture, was added a solution of 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate (100 mg, 0.172 mmol) in THF (2 mL). After 2 h of stirring at room temperature, the reaction mixture was concentrated in vacuo and chromatographed. Elution with cyclohexane–EtOAc (1:2) gave a thiourea **41** (72 mg, 72% yield) as a gum: $[\alpha]^{25}_D$ +120.2° (c = 1.1, $CHCl_3$). IR ν_{max} (film) 3410, 3325 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (1H, d, J = 3.3 Hz, OH), 3.19 (1H, d, J = 5.3 Hz, OH), 3.41–3.83 (12H, m, containing 2 × OH), 4.24 (1H, t, J = 6.6 Hz), 4.36 (1H, dd, J = 5.3–5.9, 11.2–11.9 Hz), 4.42 (2H, s), 4.45 (2H, s), 4.47 (1H, d, J = 9.9 Hz), 4.54 (2H, s), 4.75–4.89 (4H, m), 4.97 (1H, dd, J = 2.6, 4.6 Hz), 6.68 (1H, d, J = 2.6 Hz, NH), 7.12–7.14 (2H, m), 7.22–7.42 (23H, m), 7.73 (1H, d, J = 9.2 Hz, NH). Anal. Calcd for $C_{48}H_{54}N_2O_{10}S$: C, 67.75; H, 6.40; N, 3.29; S, 3.77. Found: C, 67.99; H, 6.47; N, 3.13; S, 3.54.

[4a*R*-(4aα,5β,6β,7β,7aα)]-2-[(2,3,4,6-Tetra-*O*-benzyl-1-deoxy-α-D-glucopyranos-1-yl)amino]-7-(benzyloxy)-4,4a,5,6,7,7a-hexahydro-4a,5,6,7a-tetrahydroxycyclopent-[*d*][1,3]oxazine (42). To a solution of **41** (95 mg, 0.112 mmol) in MeCN (5 mL) was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (56 mg, 0.208 mmol) at 0 °C under N_2 with stirring. After 1 h of stirring at 0 °C, Et_3N (110 mg) was added to this mixture with stirring. After a further 15 min of stirring at 0 °C, the reaction mixture was concentrated in vacuo and chromatographed. Elution with EtOAc and then with 15% MeOH in EtOAc and concentration in vacuo gave a residue, which was dissolved in EtOAc. The solution was washed with H_2O and brine to remove the contaminated silica gel; it was then dried over $MgSO_4$ and concentrated in vacuo to give **42** (65 mg, 71% yield) as a gum: $[\alpha]^{24}_D$ +59.1° (c = 0.6, $CHCl_3$); IR ν_{max} (film) 3300–3200, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29–3.80 (8H, m), 4.01–4.95 (14H, m), 5.47 (1H, bs, anomeric), 7.10 (2H, bs), 7.17–7.40 (23H, m). Anal. Calcd for $C_{48}H_{52}N_2O_{10}$: C, 70.57; H, 6.42; N, 3.43. Found: C, 70.18; H, 6.24; N, 3.56.

[1*R*-(1α,2β,3β,4β,5β)]-[1-[(Benzyloxy)methyl]-1,2,3,4-tetrahydroxycyclopent-5-yl]amino Benzylamino Thioketone (45). The intermediate in the course of the formation of compound **26** from **25**, that is, [1*R*-(1α,2β,3β,4β,5β)]-5-amino-1-[(benzyloxy)methyl]-1,2,3,4-cyclopentanetetraol hydrochloride, obtained from 29 mg (0.094 mmol) of **25**, was dissolved in THF–H_2O (5:1, 3.6 mL). To this solution were added Et_3N (27 mg, 0.267 mmol) and benzyl isothiocyanate (41 mg, 0.275). The mixture was stirred for 2 h at 22 °C, concentrated in vacuo, and then chromatographed. Elution with EtOAc gave **45** (19 mg, 48% yield) as a powder: $[\alpha]^{25}_D$ +12.0° (c = 0.6, MeOH); IR ν_{max} (Nujol) 3300 cm^{-1}; ^1H NMR (DMF-d_7) δ 3.67, 3.77 (2H, AB-q, J = 9.2–9.9 Hz), 3.87 (1H, d, J = 4.6 Hz, C2–H), 4.15–4.26 (2H, m, C3–H, C4–H), 4.51 (2H, s), 4.65–4.99 (3H, m, C5–H, CH_2Ph), 7.21–7.45 (8H, m), 7.50–7.77 (4H, m). Anal. Calcd for $C_{21}H_{26}N_2O_5S$: C, 60.27; H, 6.26; N, 6.69; S, 7.66. Found: C, 60.10; H, 6.38; N, 6.60; S, 7.59.

[3a*R*-(3aα,4α,5β,6β,6aα)-4-[(Benzyloxy)methyl]-2-(benzylamino)-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole-4,5,6-triol (46). To a solution of **45** (17 mg, 0.041 mmol) in CH_2Cl_2 (3 mL) and Et_3N (1.5 mL) was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (55 mg, 0.204 mmol) at 0–5 °C under nitrogen with stirring. After 1.5 h of stirring at 0–5 °C, the reaction mixture was concentrated in vacuo and chromatographed on a silica gel column. Elution with 5% MeOH in EtOAc gave **46** (7 mg, 45% yield) as a powder: $[\alpha]^{24}_D$ −14.8° (c = 0.8, MeOH); IR ν_{max} (Nujol) 3300, 1660 cm^{-1}; ^1H NMR (DMF-d_7) δ 3.69, 3.92 (2H, AB-q, J = 10.3 Hz, C4–CH_2O), 3.88 (1H, bs, C2-H), 4.14 (1H, d, J = 6.5 Hz, C5–H), 4.30, 4.45 (2H, AB-q, J = 15.8 Hz, CH_2Ph), 4.37 (3H, bs, 2H exchanged and a triplet, J = 4.6 Hz, appeared on addition of D_2O, C3–H), 4.56 (2H, s, CH_2Ph), 4.80 (2H, bs, exchanged on addition of D_2O), 4.88 (1H, m, changed to a triplet on addition of D_2O, J = 6.5 Hz, C4–H), 7.21–7.48 (10H, m). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.27; H, 6.44; N, 7.20.

[3a*R*-(3aα,4a,5β,6β,6aα)]-2-Amino-4-(hydroxymethyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopentoxazole-4,5,6-triol (47). By using the above-mentioned procedure for making **2** from **27**, **46** (6 mg) was converted to **47** (1.0 mg, 31%) as a powder: $[\alpha]^{23}_D$ +34.0° (c = 0.1, H_2O); IR ν_{max} (KBr) 3380, 2926, 2855, 1680 cm^{-1}; 400-MHz ^1H NMR (D_2O) δ 3.52, 3.70 (2H, AB-q, J = 12.4 Hz, C4–CH_2O), 3.69 (1H, dd, J = 1.1, 4.4 Hz, C5–H), 3.93 (1H, dd, J = 1.1, 7.3 Hz, C3a–H), 4.22 (1H, dd, J = 4.4, 5.7 Hz, C6–H), 4.87 (1H, dd, C6a–H); ^{13}C NMR (D_2O) δ 162.2 (s, C2), 72.1 (d, C3a), 82.1 (s, C4), 75.7 (d, C5), 72.4 (d, C6), 84.0 (d, C6a), 61.3 (t, C4–*C*–O) (^1H and ^{13}C chemical shifts are given to internal dioxane as a reference δ 3.53 and δ 66.5, respectively); FAB HRMS (positive) $[M + H]^+$, found 205.0822, calcd for $C_7H_{12+1}N_2O_5$ 205.0824.

[1*R*-(1α,2β,3β,4β,5β)]-5-[[(Benzylamino)thiocarbonyl]amino]-1,1′:2,3-bis(isopropylidenedioxy)-1-methylcyclopentan-4-ol (48). To a solution of **18** (26 mg, 0.10 mmol) in THF (2 mL) was added benzyl isothiocyanate (41 mg, 0.275). The mixture was stirred for 4 h at 24 °C; it was then concentrated in vacuo and chromatographed. Elution with cyclohexane–EtOAc (1:1) gave **48** (40 mg, 98% yield) as a gum: ^1H NMR ($CDCl_3$) δ 1.26 (3H, s), 1.34 (3H, s), 1.36 (3H, s), 1.58 (3H, s), 2.60 (1H, bs, OH), 4.04–4.16 (2H, m), 4.22–4.27 (2H, m), 4.87 (1H, bd, J = 14.5 Hz), 6.58 (1H, bs, NH), 6.82 (1H, bs, NH), 7.27–7.39 (5H, m). Anal. Calcd for $C_{20}H_{28}N_2O_5S$: C, 58.80; H, 6.91; N, 6.86; S, 7.85. Found: C, 58.71; H, 7.02; N, 6.83; S, 7.79.

[1*R*-(1α,2β,3β,4β,5β)]-[1,1′:2,3-Bis(isopropylidenedioxy)-4-hydroxy-1-methylcyclopent-5-yl]benzylcarbodiimide (49). To a solution of **48** (30 mg, 0.07 mmol) in MeCN (2 mL) was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (40 mg, 0.15 mmol) under N_2 at 0 °C with stirring. After 1 h, Et_3N (22 mg, 0.218 mmol) was added to this solution. The mixture was stirred for 10 min at 0 °C; it was then concentrated in vacuo and chromatographed quickly on a short column. Elution with cyclohexane–EtOAc (1:1) gave **49** (3 mg, 11% yield) as a gum: IR ν_{max} (Nujol) 3330, 2125, 1635 (broad), 1558 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3H, s), 1.44 (6H, s), 1.48 (3H, s), 2.55 (1H, d, J = 9.2 Hz, OH), 3.64 (1H, d, J = 3.3 Hz, C5–H), 3.91 (1H, dd, J = 3.3, 6.0, 9.2 Hz, C4–H), 4.08, 4.16 (2H, AB-q, J = 8.6 Hz, C1–CH_2), 4.39–4.51 (4H, m, C2–H, C3–H, CH_2Ph), 7.26–7.33 (5H, m). Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.16; H, 7.00; N, 7.48. Found: C, 63.91; H, 7.10; N, 7.31.

Supplementary Material Available: Details of X-ray studies of **25** and **29**, modeling studies of **43** and **2**, and NMR studies of **27** and **2** (6 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.