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Synthesis of a Novel Azapseudodisaccharide Related to Allosamidin Employing *N,N'*-Diacetylchitobiose as a Key Starting Material

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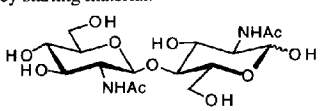
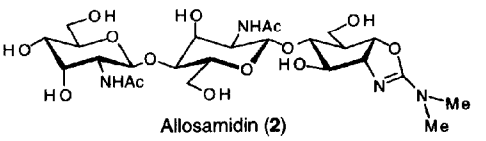
Abstract: Design and synthesis of a potential chitinase inhibitor **4**, related to allosamidin (**2**), is described. Radical cyclization mediated by tributyltin hydride was applied for the first time to chitobiose-derived oxime ethers **9a,b** to give four stereoisomers of an aminocyclopentane derivative connected to an *N*-acetyl-D-glucosamine residue at C-1 position. The major isomer **10b** was efficiently converted into a novel pseudodisaccharide **4** *via* a series of cyclic-guanidine formation reaction.

Keywords: Carbohydrate mimetics; enzyme inhibitors; guanidines; radicals and radical reactions.

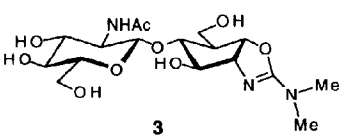
In the course of our studies on the utilization of oligosaccharides as key starting materials for the syntheses of biologically active compounds,[1] we have established an efficient method for the preparation of β-(1→4)-linked amino sugar disaccharide, *N,N'*-diacetylchitobiose (**1**),[2] and achieved total synthesis of a natural chitinase inhibitor, allosamidin (**2**)[3] therefrom.[4] Furthermore, we have continued to prepare artificial analogues of **2** in order to develop new chitinase inhibitors as insecticides and antifungal agents.[5] Recently, allosamidin-like pseudodisaccharides have been synthesized and reported to inhibit some chitinases,[6] i. e., a pseudodisaccharide **3** obtained by acidic hydrolysis of a congener of **2** was a potent inhibitor against the chitinase from a pathogenic yeast, *Candida albicans*.[6a] Independently, cyclic guanidine derivatives carrying hydroxyl groups resembling an amino cyclitol moiety of **2** have been shown to be good competitive inhibitors for glycosidases.[7] These findings prompted us to design a novel pseudodisaccharide **4** containing *N,N*-dimethylguanidine as a potential chitinase inhibitor. The *N,N*-dimethylguanidine moiety was expected to show a stronger affinity for a carboxyl group in an active site in the enzyme than the core structure of **2**. Described herein is a facile synthesis of **4** employing **1** as a key starting material.[8]



N,N-Diacetylchitobiose (**1**)



Allosamidin (**2**)



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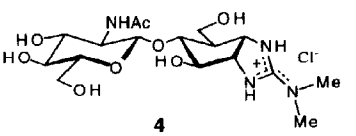
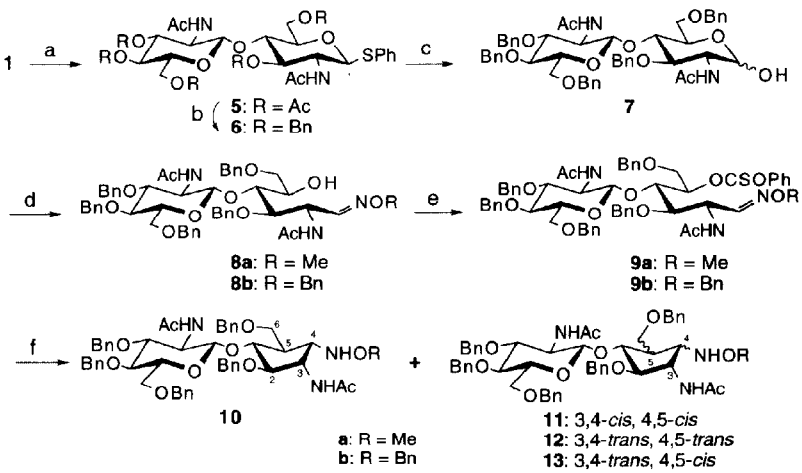


4

PII: S0040-4020(99)00972-2

Our synthetic strategy directed toward **4** involved an installation of *N,N*-dimethylguanidine on a 3,4-*cis*;4,5-*trans* diaminocyclopentane derivative such as **10** as a key step. In order to prepare this key intermediate, we have planned to utilize an intramolecular radical cyclization of oxime ethers. Radical cyclization of monosaccharide-derived oximes[9] have been well recognized as an efficient method for preparation of an aminocyclitol, while no paper has appeared dealing with such reaction of oligosaccharide derivatives. Therefore, we began to study a cyclization of chitobiose-derived oximes **9a,b**, which were prepared as follows (Scheme 1). Thioglycoside **5** prepared from **1**[2b,4a] was de-*O*-acetylated, and then benzylated to give a benzyl ether **6** in 69% yield. After removing an anomeric protection, the resulting hemiacetal **7** was condensed with *O*-methylhydroxylamine hydrochloride to afford oxime methylethers **8a** as an unseparable mixture of stereoisomers (*E*/*Z* = 80/20, ^{1}H NMR analyses) in 82% yield. Upon treatment with phenyl chlorothionoformate, **8a** gave the corresponding thiocarbonates **9a** in 74% yield. Similarly, the benzyl analogues **9b** were also prepared from **7**. Condensation of **7** with *O*-*t*-butyldimethylsilylhydroxylamine failed even when under drastic conditions.



Scheme 1: a) ref. 2b, 4a; b) NaOMe, MeOH-CH_2Cl_2, 40 °C, and then BnBr, BaO, $Ba(OH)_2{\cdot}7H_2O$, DMF, rt, 69%; c) NBS, aq. THF, 0 °C, 70%; d) $MeONH_2{\cdot}HCl$ or $BnONH_2{\cdot}HCl$, pyridine-CH_2Cl_2, rt, 82% for **8a**, 87% for **8b**; e) PhOCSCl, pyridine-CH_2Cl_2, 0 °C-rt, 74% for **9a**, 71% for **9b**; f) Bu_3SnH, AIBN or Et_3B (see Table 1).

Tributyltin hydride (Bu_3SnH) promoted radical cyclization reaction of **9a,b** was conducted at 0~110 °C by using a radical initiator {azobis(isobutylonitrile) (AIBN)[9] or triethylborane (Et_3B)[10]}, and the results are shown in Table 1. As seen from the Table, the isomer ratio varied in moderate range depending on the initiator and solvent employed; there was no significant difference concerning the protecting group of oxime moieties. Preferential formation of 4,5-*trans* isomers (**10** and **12**) in all entries would be explained by the severe steric interaction between the ring substituents on C-4 and C-5 in the transition state.[11] On the other hand, a moderate 3,4-*cis*:4,5-*cis* selectivity observed in entry 5-7 suggests a freezing effect on the conformation by coordination of Et_3B. Of a variety of conditions examined, reaction of **9b** in the presence of AIBN in toluene at 110 °C (entry 2)

Table 1 Tributyltin hydride[a] induced cyclization of oxime ethers **9a,b**

Entry	Oxime	Initiator	Solvent (M)[b]	Temp (°C)	Ratio of diastereomer (**10/11/12/13**)[c]	Yield[d] (%)
1	**9a**	AIBN	toluene (0.01)	110	41 / 6 / 35 / 18	57
2	**9b**	AIBN	toluene (0.01)	110	**44** / 3 / 32 / 21	71
3	**9a**	Et_3B	THF (0.06)	23	45 / 10 / 15 / 30	59
4	**9b**	Et_3B	THF (0.06)	23	38 / 8 / 24 / 30	66
5	**9a**	Et_3B	toluene-THF (0.06)	23	43 / 22 / 16 / 19	67
6	**9b**	Et_3B	toluene-THF (0.06)	23	35 / 21 / 23 / 21	69
7	**9b**	Et_3B	toluene-hexane (0.06)	0	31 / 26 / 26 / 17	69

[a] 2.0-4.0 mol eq. of Bu_3SnH in the presence of a catalytic amount of AIBN or 2.0 mol eq. of Et_3B was employed. [b]The values in parentheses denote the substrate concentration (mol/l). [c] Ratios were determined by the integrated intensity of each *N*-acetyl siganl in the ^1H NMR (400 and 500 MHz) spectra. [d]Combined yield of purified isomers.

furnished a desired 3,4-*cis*; 4,5-*trans* product **10b** in 31% yield after chromatography on silica gel.[12] This yield was of little concern regarding synthesis of the target **4** because of the simple procedure to give **10b** from **1**. The three isomers **11b** (~2%), **12b** (23%), and **13b** (15%) may also be useful intermediates for the preparation of new glycosidase inhibitors.

The stereochemistry of each isomer prepared during this study, was established by the NMR analyses together with the difference NOE experiment (Table 2) and by chemical derivations such as an acetonide formation. For example, in **10a**, irradiation of H_5 results in the enhancement of N*H*Ac, H_1, and H_2 peaks. Likewise, irradiation of H_4 caused enhancement of signal due to H_3. In **10b**, a strong NOE was observed for the signals of N*H*Ac, N*H*OBn, and H_6 upon irradiation of H_5. Similar signal enhancement for H_3 was seen by irradiating H_4. These data are consistent with the assigned 3,4-*cis*: 4,5-*trans* structure for **10a,b**. Comparison of ^{13}C chemical shifts of C_1-C_6 also shows same stereochemical relationship between **10a** and **10b**.

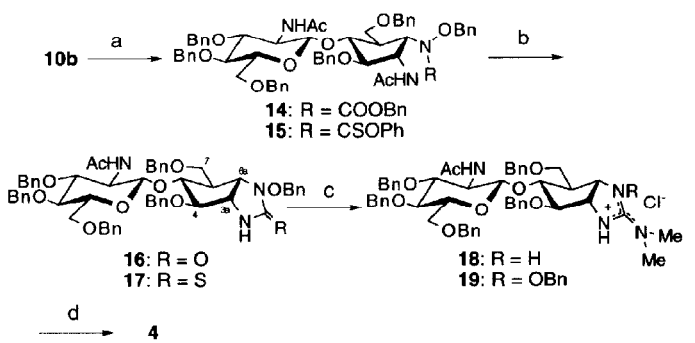
Table 2 Selected NOEs and ^{13}C-NMR chemical shift for cyclopentane derivatives (**10-13**)[a]

Comp.	NOE[b]	C-1	C-2	C-3	C-4	C-5	C-6
10a	$H_4 \rightarrow H_3$; $H_5 \rightarrow$ N*H*Ac, H_1, H_2	85.3	86.5	54.0	62.6	48.1	71.9
10b	$H_4 \rightarrow H_3$; $H_5 \rightarrow$ N*H*Ac, N*H*OBn, H_{6a}	85.2	86.3	53.9	62.7	48.0	71.9
11a	$H_5 \rightarrow H_1$	81.9	88.7	55.9	61.4	44.7	65.2
11b	$H_4 \rightarrow H_3$, H_5; $H_5 \rightarrow H_1$, H_4	82.1	88.9	56.1	62.0	44.7	65.3
12a	$H_4 \rightarrow$ N*H*Ac	80.9	86.2	56.4	69.8	46.1	67.5
12b	$H_4 \rightarrow$ N*H*Ac, H_{6a}, H_{6b}; $H_5 \rightarrow H_1$	81.0	86.3	56.3	70.0	45.9	67.5
13a	$H_4 \rightarrow H_5$; $H_{6a} \rightarrow H_1$	85.9	86.2	55.8	66.1	46.3	69.2
13b	$H_4 \rightarrow$ N*H*Ac, H_5; $H_{6a} \rightarrow H_1$, H_3, H_5	85.7	86.5	55.9	66.3	46.3	68.9

[a]The assignment of protons and carbons was conducted according to the numbering shown in the Scheme 1. [b]Irradiation of the proton on the left of the arrow causes NOE of the one on the right.

Next our attention was focused on the construction of a cyclic guanidine in **10b**. As attempts to remove selectively acetyl and benzyloxy groups in the nitrogen functions of this ring were unsuccessful, we adopted a stepwise procedure as follows (Scheme 2). Initially, reaction of **10b** with benzyl chloroforamte provided a benzyl carbamate **14** in 74% yield. When this was treated with sodium hydride in DMF, a cyclization concomitant with de-*N*-acetylation took place to give an urea **16** in 87% yield. Formation of a cyclic guanidine starting from **16**, however, turned out more difficult.[13] In 1977, Kishi et al. had reported that reaction of a cyclic thioiminoether with ammonium propionate at the elevated temperature proceeded smoothly to give the corresponding guanidine in good yield.[14] This paper have turned our attention to a thioanalogue **17**, which was prepared from **10b** *via* a thiocarbamate **15** according to the preparation of the urea **16**. As anticipated, the thiourea **17** was smoothly transformed into guanidine derivatives (**18** and **19**). Thus, a solution of **17** in methyl iodide was heated under reflux, and then concentrated *in vacuo*. The resulting syrup was treated with dimethylammonium acetate at 120 °C under an argon atmosphere, giving the guanidine **18** in 69 % yield along with its *N*-benzyloxy derivative **19** (12%). Both compounds were not obtained under other conditions (e. g., dimethylamine hydrochloride-triethylamine, rt). These structures were confirmed by the 2D-NMR spectra and high resolution FAB-MS. In particular, the cross peaks between aminomethyl groups and amidino carbon as well as those between amidino carbon and H-3a or H-6a were observed in the HMBC spectrum of **18**, indicating that the *N,N*-dimethylguanidine ring fused at C-3a, 6a positions of the cyclopentane ring. Finally, all benzyl groups in **18** were removed by hydrogenation in aqueous ethanol-acetic acid to give a desired pseudodisaccharide **4** in high yield. This compound was also obtained from the benzyl analogue **19** in good yield. Since the pseudodisaccharide **4** is structurally related to allosamidin (**1**), the chitinase inhibitory activities were expected to be comparable to that of **1**. However, disappointingly, the inhibitory activity of **4** was shown to be weak (13 ~ 20% inhibition at 50 μM concentration) against an insect chitinase (*Bombyx mori*).

In conclusion, the facile synthesis of a novel pseudodisaccharide **4** without glycosidation reaction was achieved employing *N,N'*-diacetylchitobiose (**1**) as a key starting material.



Scheme 2: a) BnOCOCl, aq. Na_2CO_3-CH_2Cl_2, 0 °C→rt, or PhOCSCl, Et_3N, CH_2Cl_2, 0 °C→rt, 72% for **14**, 74% for **15**; b) NaH, DMF, 0 °C, 87% for **16**, 83% for **17**; c) MeI, 40 °C and then $Me_2NH_2^+OAc^-$, 120 °C, 69% for **18**, 12% for **19**; d) 10% Pd/-C, H_2, AcOH-EtOH-H_2O, rt, 99% from **18**, 75% from **19**.

Experimental

General Procedures. Melting points were determined in a capillary with an Ishii melting-point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter at 23±2 °C. IR spectra were recorded with a JASCO VALOR-III spectrophotometer. ^{1}H-NMR spectra were recorded with JEOL α 400 (400 MHz) or GX 500 (500 MHz) spectrometers in $CDCl_3$ using tetramethylsilane as the internal standard, unless otherwise noted. ^{13}C-NMR spectra were recorded at 100 MHz with JEOL JNM-α 400 spectrometer. The assignment of protons and carbons in the NMR spectra of cyclitol derivatives was conducted according to the numbering shown in the Schemes. Column chromatography was performed on silica gel 60 (230-400 mesh; E. Merck, Darmstadt, Germany). Merck precoated silica gel 60 F_{254} plates, 0.25 or 1.0 mm thickness, were used for analytical or preparative thin-layer chromatography respectively.

Phenyl 2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (6). To a stirred suspension of the pentaacetate **5** (8.0 g, 10.8 mmol) in dichloromethane-methanol (1: 2; 270 ml) was added sodium methoxide (355 mg, 6.57 mmol) and then the mixture was stirred at 40 °C for 2 h, cooled to room temperature, made neutral with Dowex 50W X-8 (H^+) resin. The mixture was filtered, and the filtrate evaporated, co-evaporated with toluene and *N,N*-dimethylformamide (DMF) to give a crude pentaol (7.0 g). To a stirred suspension of the above pentaol (7.0 g, ca. 10.8 mmol), barium oxide (50 g, 0.33 mol) and barium hydroxide heptahydrate (50 g, 0.16 mol) in DMF (250 ml) was added dropwise benzyl bromide (43.1 g, 0.25 mol) at room temperature. The mixture was stirred at room temperature for 3 d, diluted with chloroform, filtered through a pad of Celite, and then the filtrate evaporated. The residue was dissolved in chloroform, washed with water, and brine, dried, and evaporated to dryness. The residue was treated with ethanol to give the pentabenzyl ether **6** (5.30 g) as crystalline solids. The mother liquid was purified by chromatography on silica gel with chloroform-ethyl acetate (5:1 → 3:1) as the eluent, giving additional **6** (1.90 g). The total amount of **6** was 7.20 g (69% from **5**), mp 217 °C (dec.); $[\alpha]_D^{25}$ -32.2° (*c* 0.92 in $CHCl_3$); δ_H (400 MHz) 1.48, 1.96 (each 3H, 2s, 2 × Ac), 3.28 (1H, td, $J_{4',5'}$ = 9.3 Hz, $J_{5',6'a}$ = 2.9 Hz, $J_{5',6'b}$ = 2.3 Hz, H-5'), 3.43 (1H, dd, $J_{2',3'}$ = 10 Hz, $J_{3',4'}$ = 8.8 Hz, H-3'), 3.61-3.76 (8H, m, H-3, 5, 6, 4', 5', 6'), 3.79 (1H, q, $J_{1',2'}$ = 8.3 Hz, $J_{2',3'}$ = 10 Hz, $J_{2',NH'}$ = 7.8 Hz, H-2'), 4.06 (1H, dd, $J_{3,4}$ = 2.9 Hz, $J_{4,5}$ = 4.9 Hz, H-4), 4.17 (1H, ddd, $J_{1,2}$ = 8.8 Hz, $J_{2,3}$ = 3.8 Hz, $J_{2,NH}$ = 9.3 Hz, H-2), 4.26 (1H, d, $J_{1',2'}$ = 8.3 Hz, H-1'), 4.48-4.81 (10H, m, CH_2Ph), 4.63 (1H, d, $J_{1,2}$ = 8.8 Hz, H-1), 4.76 (1H, d, $J_{2',NH'}$ = 7.8 Hz, NH'), 6.43 (1H, d, $J_{2,NH}$ = 9.3 Hz, NH), 7.20-7.46 (30H, m, Ph).

Found: C, 70.57; H, 6.45; N, 2.94; S, 3.19%. Calcd for $C_{57}H_{62}O_{10}N_2S$: C, 70.79; H, 6.46; N, 2.90; S, 3.31%.

2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranose (7). To a stirred mixture of the thioglycoside **6** (4.2 g, 4.35 mmol) in tetrahydrofuran-water (5 : 1; 120 ml) was added *N*-bromosuccinimide (2.33 g, 13.1 mmol) at 0 °C and then the mixture was stirred at 0 °C → room temperature for 9 h. After addition of aq. $Na_2S_2O_3$ solution, the resulting mixture was extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated to dryness. Chromatography on silica gel with chloroform-methanol

(50:1) as the eluent yielded the hemiacetal **7** (2.65 g, 70%), $[\alpha]_D^{17}$ +27.5° (*c* 1.0 in $CHCl_3$) {lit., $[\alpha]_D^{18}$ +28.1 (*c* 0.53 in $CHCl_3$)[15] }, whose spectral data were consistent with those of an authentic sample.[15]

2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-D-glucose *O*-Methyl Oximes (8a). A mixture of the hemiacetal **7** (2.65 g, 3.03 mmol) and *O*-methyl hydroxylamine hydrochloride (507 mg, 6.07 mmol) in dichloromethane-pyridine (3:1; 20 ml) was stirred at room temperature for 18 h, and then diluted with dichloromethane. The resulting solution was washed with water, aqueous cupric sulfate, aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated to dryness. Chromatography on silica gel with chloroform-methanol (100:1→20:1) as the eluent yielded the oxime ethers **8a** (2.24 g, 82%) as a stereoisomeric mixture (*E*/*Z* = 4/1), δ_H (400 MHz) 1.78 [0.60H, s, Ac (*Z*)], 1.79 [2.40H, s, Ac (*E*)], 1.81 [2.40H, s, Ac (*E*)], 1.82 [0.60H, s, Ac (*Z*)], 2.80 [1H, brd, OH (*E* and *Z*)], 3.18 [0.80H, q, $J_{1',2'}$ = 8.3 Hz, $J_{2',3'}$ = 9.8 Hz, $J_{2',NH'}$ = 7.8 Hz, H-2' (*E*)], 3.42-3.70 [5.40H, m, H-6 (*E* and *Z*), 2' (*Z*), 4' (*Z*), 5' (*E* and *Z*), 6' (*E* and *Z*)], 3.45 [0.80H, dd, $J_{3',4'}$ = 8.8 Hz, $J_{4',5'}$ = 8.3 Hz, H-4' (*E*)], 3.82 [0.60H, s, MeO (*Z*)], 3.83 [2.40H, s, MeO (*E*)], 3.80-4.08 [3H, m, H-3 (*E* and *Z*), 4 (*E* and *Z*), 5 (*E* and *Z*)], 4.26 [0.80H, dd, $J_{2',3'}$ = 9.8 Hz, $J_{3',4'}$ = 8.8 Hz, H-3' (*E*)], 4.40-4.83 [10.20H, m, H-3' (*Z*), CH_2Ph], 4.95 [0.20H, d, $J_{1',2'}$ = 8.3 Hz, H-1' (*Z*)], 5.05 [0.80H, d, $J_{1',2'}$ = 8.3 Hz, H-1' (*E*)], 5.19 [0.80H, td, $J_{1,2}$ = 5.4 Hz, $J_{2,3}$ = 5.4 Hz, $J_{2,NH}$ = 8.3 Hz, H-2 (*E*)], 5.53 [0.20H, br q, $J_{1,2}$ = 6.3 Hz, $J_{2,3}$ = 6.3 Hz, $J_{2,NH}$ = 7.8 Hz, H-2 (*Z*)], 5.65 [0.20H, d, $J_{2',NH'}$ = 7.8 Hz, NH' (*Z*)], 5.71 [0.80H, d, $J_{2',NH'}$ = 7.3 Hz, NH' (*E*)], 6.71 [0.20H, d, $J_{2,NH}$ = 7.8 Hz, NH (*Z*)], 6.76 [0.80H, d, $J_{2,NH}$ = 8.3 Hz, NH (*E*)], 7.02 [0.20H, d, $J_{1,2}$ = 6.3 Hz, H-1 (*Z*)], 7.13-7.37 [30H, m, Ph (*E* and *Z*)], 7.63 [0.80H, d, $J_{1,2}$ = 5.4 Hz, H-1 (*E*)].

Found: C, 68.54; H, 6.72; N, 4.58. $C_{52}H_{61}O_{11}N_3 \cdot 0.5H_2O$ requires C, 68.40; H, 6.84; N, 4.60%

2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-D-glucose *O*-Benzyl Oximes (8b). Treatment of the hemiacetal **7** (3.00 g, 3.43 mmol) with *O*-benzylhydroxylamine hydrochloride (1.10 g, 6.86 mmol) as described above yielded the corresponding benzyl analogues **8b** (2.91 g, 87%) as a stereoisomeric mixture, δ_H (400 MHz) 1.76 [0.54H, s, Ac (*Z*)], 1.78 [2.46H, s, Ac (*E*)], 1.80 [3H, s, Ac (*Z* and *E*)], 2.76 [0.18H, d, $J_{5,OH}$ = 5.9 Hz, OH (*Z*)], 2.80 [0.82H, d, $J_{5,OH}$ = 6.8 Hz, OH (*E*)], 3.17 [0.82H, q, $J_{1',2'}$ = 8.3 Hz, $J_{2',3'}$ = 9.8 Hz, $J_{2',NH'}$ = 7.3 Hz, H-2' (*E*)], 3.41 [0.18H, m, H-2' (*Z*)], 3.42-3.52 [4H, m, H-6 (*E* and *Z*), 4' (*E* and *Z*), 5' (*E* and *Z*)], 3.58-3.68 [2H, m, H-6' (*E* and *Z*)], 3.90 [0.18H, m, H-5 (*Z*)], 3.93 [0.82H, m, H-5 (*E*)], 3.98-4.08 [2H, m, H-3 (*E* and *Z*), 4 (*E* and *Z*)], 4.28 [0.82H, dd, $J_{2',3'}$ = 9.8 Hz, $J_{3',4'}$ = 7.8 Hz, H-3' (*E*)], 4.35-5.05 [12.18H, m, H-3' (*Z*), CH_2Ph], 4.90 [0.18H, d, $J_{1',2'}$ = 8.3 Hz, H-1' (*Z*)], 5.06 [0.82H, d, $J_{1',2'}$ = 8.3 Hz, H-1' (*E*)], 5.20 [0.82H, td, $J_{1,2}$ = 4.9 Hz, $J_{2,3}$ = 5.4 Hz, $J_{2,NH}$ = 8.3 Hz, H-2 (*E*)], 5.30 [0.18H, br q, $J_{1,2}$ = 6.3 Hz, $J_{2,3}$ = 6.3 Hz, $J_{2,NH}$ = 7.3 Hz, H-2 (*Z*)], 5.63 [0.18H, d, $J_{2',NH'}$ = 7.8 Hz, NH' (*Z*)], 5.72 [0.82H, d, $J_{2',NH'}$ = 7.3 Hz, NH' (*E*)], 6.72 [0.18H, d, $J_{2,NH}$ = 7.3 Hz, NH (*Z*)], 6.77 [0.82H, d, $J_{2,NH}$ = 8.3 Hz, NH (*E*)], 7.05 [0.18H, d, $J_{1,2}$ = 6.3 Hz, H-1 (*Z*)], 7.13-7.37 [30H, m, Ph (*E* and *Z*)], 7.70 [0.82H, d, $J_{1,2}$ = 4.9 Hz, H-1 (*E*)].

Anal. Found: C, 70.83; H, 6.67; N, 4.19. $C_{58}H_{65}O_{11}N_3$ requires C, 71.07; H, 6.68; N, 4.29%.

2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-5-*O*-phenoxy(thiocarbonyl)-D-glucose *O*-Methyl Oximes (9a). To a stirred solution of the oxime ethers **8a** (2.03 g, 2.25 mmol) in dichloromethane-pyridine (4 : 1; 25 ml) was added

dropwise phenyl chlorothioformate (0.62 ml, 4.50 mmol) at 0 °C under Ar, and then the mixture was stirred for 3 h at 0 °C → room temperature. Ice and water were added and the resulting mixture was vigorously stirred for 1 h. The mixture was extracted with dichloromethane and the extracts were washed with water, aqueous cupric sulfate, aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated to dryness. The residue was passed through a short column of silica gel with toluene-acetone (10 : 1) to give the unstable thiocarbonates **9a** as an isomeric mixture (1.72 g, 74%), which was employed to the next step without further purification, δ_H(400 MHz) 1.77 [2.40H, s, Ac (*E*)], 1.79 [0.60H, s, Ac (*Z*)], 1.80 [2.40H, s, Ac (*Z*)], 1.81 [0.60H, s, Ac(*E*)], 3.14-3.23 [1H, m, H-2' (*E* and *Z*)], 3.42-3.98 [5.0H, m, H-3 (*E* and *Z*), 6a (*E* and *Z*), 4' (*E* and *Z*), 5' (*E* and *Z*), 6' (*E* and *Z*)], 3.76 [0.60H, s, MeO (*Z*)], 3.83 [2.40H, s, MeO (*E*)], 3.92 [0.2H, dd, $J_{5,6b}$ = 2.4 Hz, $J_{6a,6b}$ = 12 Hz, H-6b (*Z*)], 4.02 [0.8H, dd, $J_{5,6b}$ = 2.4 Hz, $J_{6a,6b}$ = 12 Hz, H-6b (*E*)], 4.25-4.32 [1H, m, H-3' (*E* and *Z*)], 4.34-4.83 [11.2H, m, H-4 (*E* and *Z*), H-1' (*Z*), C*H*$_2$Ph], 5.13 [0.80H, d, $J_{1',2'}$ = 8.3 Hz, H-1' (*E*)], 5.24 [0.80H, td, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 4.9 Hz, $J_{2,NH}$ = 8.3 Hz, H-2 (*E*)], 5.45 [0.20H, d, $J_{2',NH'}$ = 8.3 Hz, NH' (*Z*)], 5.47 [0.20H, m, H-2 (*Z*)], 5.60 [0.20H, m, H-5 (*Z*)], 5.64 [0.80H, m, H-5 (*E*)], 5.66 [0.80H, d, $J_{2',NH'}$ = 7.8 Hz, NH' (*E*)], 6.64 [0.20H, d, $J_{2,NH}$ = 8.3 Hz, NH (*Z*)], 6.74 [0.80H, d, $J_{2,NH}$ = 8.8 Hz, NH (*E*)], 6.92 [0.20H, d, $J_{1,2}$ = 5.4 Hz, H-1 (*Z*)], 7.00-7.40 [30H, m, Ph (*E* and *Z*)], 7.59 [0.80H, d, $J_{1,2}$ = 4.4 Hz, H-1(*E*)]; HR-FABMS Found: $(M+Na)^+$, 1062.4169. $C_{59}H_{65}O_{12}N_3SNa$ requires *m/z*, 1062.4187.

2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-5-*O*-phenoxy(thiocarbonyl)-D-glucose *O*-Benzyl Oximes (9b). Treatment of the oximes **8b** (460 mg, 0.47 mmol) as described above yielded the corresponding benzyl analogues **9b** (370 mg, 71%) as a stereoisomeric mixture, which was employed to the next step without further purification, δ_H(400 MHz) 1.76 [2.46H, s, Ac (*E*)], 1.77 [0.54H, s, Ac (*Z*)], 1.79 [3H, s, Ac (*Z* and *E*)], 3.14-3.23 [1H, m, H-2' (*E* and *Z*)], 3.41-3.73 [6H, m, H-6a (*E* and *Z*), 3' (*E* and *Z*), 4' (*E* and *Z*), 5' (*E* and *Z*), 6' (*E* and *Z*)], 3.87 [0.18H, dd, $J_{5,6b}$ = 2.9 Hz, $J_{6a,6b}$ = 8.8 Hz, H-6b (*Z*)], 3.98-4.01 [1H, m, H-3 (*E* and *Z*)], 4.02 [0.82H, dd, $J_{5,6b}$ = 2.4 Hz, $J_{6a,6b}$ = 8.7 Hz, H-6b (*E*)], 4.33-5.17 [13H, m, H-4 (*E* and *Z*), C*H*$_2$Ph], 4.82 [0.18H, d, $J_{1',2'}$ = 7.8 Hz, H-1' (*Z*)], 5.16 [0.82H, d, $J_{1',2'}$ = 8.3 Hz, H-1' (*E*)], 5.26 [0.82H, td, $J_{1,2}$ = 4.9 Hz, $J_{2,3}$ = 4.8 Hz, $J_{2,NH}$ = 8.3 Hz, H-2 (*E*)], 5.47 [0.18H, d, $J_{2',NH'}$ = 7.8 Hz, NH' (*Z*)], 5.52 [0.18H, td, $J_{1,2}$ = 6.3 Hz, $J_{2,3}$ = 3.9 Hz, $J_{2,NH}$ = 7.8 Hz, H-2 (*Z*)], 5.60 [0.18H, m, H-5 (*Z*)], 5.63 [0.82H, m, H-5 (*E*)], 5.71 [0.82H, d, $J_{2',NH'}$ = 7.3 Hz, NH' (*E*)], 6.64 [0.18H, d, $J_{2,NH}$ = 7.8 Hz, NH (*Z*)], 6.77 [0.82H, d, $J_{2,NH}$ = 8.8 Hz, NH (*E*)], 7.00 [0.18H, d, $J_{1,2}$ = 6.3 Hz, H-1 (*Z*)], 7.00-7.40 [35H, m, Ph (*E* and *Z*)], 7.68 [0.82H, d, $J_{1,2}$ = 4.9 Hz, H-1 (*E*)]; HR-FABMS Found: $(M+Na)^+$, 1138.4504. $C_{65}H_{69}O_{12}N_3SNa$ requires *m/z*, 1138.4500.

3-Acetamido-2-benzyloxy-4-(methoxy)amino-5-[(benzyloxy)methyl]cyclopentyl 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosides (10a-13a) and 3-Acetamido-2-benzyloxy-4-(benzyloxy)amino-5-[(benzyloxy)methyl]cyclopentyl 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosides (10b-13b)

i) Typical procedure with Bu_3SnH-AIBN. To a stirred solution of the thiocarbonates **9b** (480 mg, 0.43 mmol) in toluene (40 ml) was added dropwise slowly a mixture of tributyltin hydride (0.46 ml, 1.72 mmol) and azobis(isobutyronitrile) (14 mg, 0.08 mmol) in toluene (10 ml) at 110 °C and the mixture was stirred for 2 h at the same temperature. After cooling, the reaction mixture was concentrated *in vacuo*. Chromatography on

silica gel with toluene-acetone (3:1) as the eluent yielded the amine **10b** (84 mg, 20%), the isomer **11b** (7 mg, 2%), and a mixture of three stereoisomers **10b**, **12b**, and **13b**. The mixture was further separated by chromatography on silica gel with chloroform-methanol (20:1) as the eluent to give additional **10b** (34 mg, 11%), **12b** (95 mg, 23%), and **13b** (62 mg, 15%).

ii) Typical procedure with Bu_3SnH-Et_3B. To a stirred solution of the thiocarbonates **9b** (176 mg, 0.16 mmol) in toluene (2 ml) was added a solution of triethylborane in tetrahydrofuran (1.0 M solution; 0.32 ml), and then tributyltin hydride (0.09 ml, 0.32 mmol) was added dropwise to the resulting mixture at room temperature. After stirring at ambient temperature for 7 h, the reaction mixture was concentrated *in vacuo*. Chromatography on silica gel with toluene-acetone (4:1 → 2:1) as the eluent yielded a mixture of four stereoisomers **10b**, **11b**, **12b**, and **13b** (106 mg, 69% ; **10b** : **11b** : **12b** : **13b** = 35 : 21 : 23 : 21 by the ^1H NMR analyses).

(1R,2R,3S,4S,5S)-Methoxyamine (**10a**); $[\alpha]_D^{23}$ -8.0 (*c* 0.75 in $CHCl_3$); δ_H(400 MHz) 1.74, 2.03 (each 3H, 2s, 2 × Ac), 2.03 (1H, m, H-5), 3.30-3.68 (5H, m, H-3', 4', 5', 6'), 3.33 (1H, t, $J_{3,4}$ = 7.3 Hz, $J_{4,5}$ = 6.8 Hz, H-4), 3.43 (1H, dd, $J_{6a,6b}$ = 9.3 Hz, $J_{5,6}$ = 5.4 Hz, H-6a), 3.45 (3H, s, OMe), 3.60 (1H, dd, $J_{6a,6b}$ = 9.3 Hz, $J_{5,6}$ = 5.9 Hz, H-6b), 3.73 (1H, q, 2'-H), 3.92 (1H, $J_{1,2}$ = 3.0 Hz, $J_{2,3}$ = 2.5 Hz, H-2), 3.97 (1H, dd, $J_{1,2}$ = 3.0 Hz, $J_{1,5}$ = 3.9 Hz, H-1), 4.43-4.78 (11H, m, H-1', CH_2Ph), 4.46 (1H, ddd, $J_{3,4}$ = 7.3 Hz, $J_{2,3}$ = 2.5 Hz, $J_{3,NH}$ = 8.3 Hz, H-3), 5.09 (1H, d, $J_{2',NH'}$ = 8.8 Hz, NH'), 5.85-5.95 (1H, br s, NH), 6.18 (1H, d, $J_{3,NH}$ = 8.3 Hz, NH), 7.20-7.35 (25H, m, Ph).

Anal. Found: C, 70.07; H, 6.95; N, 4.62. $C_{52}H_{61}O_{10}N_3$ requires C, 70.33; H, 6.92; N, 4.73%.

(1R,2R,3S,4S,5S)-Benzyloxyamine (**10b**); $[\alpha]_D^{23}$ -6.2 (*c* 0.41 in $CHCl_3$); δ_H(500 MHz) 1.68, 1.96 (each 3H, 2s, 2 × Ac), 2.04 (1H, m, H-5), 3.31 (1H, m, H-5'), 3.35 (1H, dd, *J* = 7.6 and 7.0 Hz, H-4), 3.41 (1H, t, $J_{5,6a}$ = $J_{6a,6b}$ = 8.9 Hz, H-6a), 3.43 (1H, dd, $J_{2',3'}$ = 8.5 Hz, $J_{3',4'}$ = 10 Hz, H-3'), 3.57 (1H, dd, $J_{5,6b}$ = 6.1 Hz, $J_{6a,6b}$ = 8.9 Hz, H-6b), 3.61-3.66 (2H, m, H-6'), 3.66 (1H, dd, $J_{3',4'}$ = 10 Hz, $J_{4',5'}$ = 9.2 Hz, H-4'), 3.72 (1H, q, $J_{1',2'}$ = 8.2 Hz, $J_{2',3'}$ = 8.5 Hz, $J_{2',NH'}$ = 8.6 Hz, H-2'), 3.95 (2H, br s, H-1, 2), 4.41-4.77 (12H, m, CH_2Ph), 4.46 (1H, d, $J_{1',2'}$ = 8.2 Hz, H-1'), 4.47 (1H, m, H-3), 5.12 (1H, d, $J_{2',NH'}$ = 8.6 Hz, NH'), 5.76-5.88 (1H, br s, NH), 6.11 (1H, d, $J_{3,NH}$ = 7.9 Hz, NH), 7.19-7.33 (30H, m, Ph), HR-FABMS Found: $(M+H)^+$, 964.4758. $C_{58}H_{66}O_{10}N_3$ requires *m/z*, 964.4748.

Anal. Found: C, 71.44; H, 6.74; N, 4.30. $C_{58}H_{65}O_{10}N_3 \cdot 0.5H_2O$ requires C, 71.58; H, 6.84; N, 4.32%

(1R,2R,3S,4S,5R)-Methoxyamine (**11a**); $[\alpha]_D^{24}$ -1.0 (*c* 0.11 in $CHCl_3$); δ_H(500 MHz) 1.69, 1.91 (each 3H, 2s, 2 × Ac), 2.55 (1H, m, H-5), 3.34-3.40 (2H, m, H-3', 5'), 3.38 (3H, s, OMe), 3.52 (1H, brd, $J_{6a,6b}$ = 8.9 Hz, H-6a), 3.60 (1H, brd, $J_{6a,6b}$ = 8.9 Hz, H-6b), 3.63-3.75 (3H, m, H-4', 6'), 3.65 (1H, t, *J* = 7.8 Hz, H-4), 3.78 (1H, brs, H-2), 3.84 (1H, q, *J* = 9.3 Hz, H-2'), 4.12 (1H, brd, *J* = 3.7 Hz, H-1), 4.21 (1H, d, $J_{1',2'}$ = 8.1 Hz, H-1'), 4.26-4.83 (11H, m, NH', CH_2Ph), 4.48 (1H, m, H-3), 5.93 (1H, brs, NH), 6.49 (1H, d, $J_{4,NH}$ = 9.0 Hz, NH), 7.21-7.34 (25H, m, Ph).

Anal. Found: C, 70.01; H, 6.98; N, 4.51. $C_{52}H_{61}O_{10}N_3$ requires C, 70.33; H, 6.92; N, 4.73%.

(1R,2R,3S,4S,5R)-Benzyloxyamine (**11b**); $[\alpha]_D^{24}$ -1.0 (*c* 0.75 in $CHCl_3$); δ_H(500 MHz) 1.60, 1.82 (each 3H, 2s, 2 × Ac), 2.52 (1H, m, H-5), 3.37 (1H, m, H-5'), 3.39 (1H, dd, $J_{2',3'}$ = 8.9 Hz, $J_{3',4'}$ = 10 Hz, H-3'), 3.54 (1H, brd, $J_{6a,6b}$ = 9.8 Hz, H-6a), 3.57 (1H, dd, $J_{5,6}$ = 4.3 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6b), 3.63 (1H, q, $J_{3,4}$ = 7.0 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,NH}$ = 10 Hz, H-4), 3.64 (1H, dd, $J_{5',6'}$ = 2.1 Hz, $J_{6'a,6'b}$ = 11 Hz, H-6'a), 3.68 (1H, dd, $J_{3',4'}$ = 10 Hz, $J_{4',5'}$ = 9.4 Hz, H-4'), 3.71 (1H, dd, $J_{5',6'}$ = 4.3 Hz, $J_{6'a,6'b}$ = 11 Hz, H-6'b), 3.76 (1H, dd, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.6 Hz, H-2), 3.81 (1H, q, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 8.9 Hz, $J_{2',NH'}$ = 8.2 Hz, H-

2'), 4.10 (1H, brd, $J_{1,2}$ = 1.3 Hz, $J_{1,5}$ = 4.9 Hz, H-1), 4.22 (1H, d, $J_{2',NH'}$ = 8.2 Hz, NH'), 4.24-4.81 (12H, m, CH_2Ph), 4.45 (1H, m, H-3), 4.56 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.90 (1H, d, $J_{4,NH}$ = 10 Hz, NH), 6.44 (1H, d, $J_{3,NH}$ = 9.2 Hz, NH), 7.20-7.35 (30H, m, Ph); HR-FABMS Found: $(M+H)^+$, 964.4744. $C_{58}H_{66}O_{10}N_3$ requires *m/z*, 964.4748.

(1R,2R,3S,4R,5R)-Methoxyamine (**12a**); $[\alpha]_D^{24}$ -6.0 (*c* 0.34 in $CHCl_3$); δ_H(500 MHz) 1.64, 1.95 (each 3H, 2s, 2 × Ac), 2.55 (1H, m, H-5), 2.85 (1H, dd, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.34 (1H, m, H-5'), 3.36 (1H, dd, $J_{2',3'}$ = 7.8 Hz, $J_{3',4'}$ = 10 Hz, H-3'), 3.49 (1H, t, J = 9.3 Hz, H-6a), 3.52 (3H, s, MeO), 3.57 (1H, dd, $J_{5,6}$ = 3.9 Hz, $J_{6a,6b}$ = 9.3 Hz, H-6b), 3.60-3.74 (4H, m, H-2', 4', 6'), 3.74 (1H, brs, H-2), 4.17 (1H, d, $J_{1',2'}$ = 8.3 Hz, H-1'), 4.20 (1H, brd, J = 1.9 Hz, H-1), 4.23-4.80 (11H, m, NH', CH_2Ph), 4.38 (1H, m, H-3), 5.76 (1H, brs, NH), 6.66 (1H, d, $J_{3,NH}$ = 8.7 Hz, NH), 7.21-7.33 (25H, m, Ph).

Anal.Found: C, 70.22; H, 7.01; N, 4.58. $C_{52}H_{61}O_{10}N_3$ requires C, 70.33; H, 6.92; N, 4.73%.

(1R,2R,3S,4R,5R)-Benzyloxyamine (**12b**); $[\alpha]_D^{24}$ -2.9 (*c* 0.42 in $CHCl_3$); δ_H(500 MHz) 1.61, 1.95 (each 3H, 2s, 2 × Ac), 2.54 (1H, m, H-5), 2.82 (1H, dd, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.34 (1H, m, H-5'), 3.36 (1H, dd, $J_{2',3'}$ = 8.5 Hz, $J_{3',4'}$ = 10 Hz, H-3'), 3.41 (1H, t, $J_{5,6}$ = 9.7 Hz, $J_{6a,6b}$ = 9.0 Hz, H-6a), 3.46 (1H, dd, $J_{5,6}$ = 4.9 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6b), 3.60-3.72 (3H, m, H-2', 4', 6'), 3.73 (1H, brs, H-2), 4.14 (1H, d, $J_{1',2'}$ = 8.3 Hz, H-1'), 4.20 (1H, brs, H-1), 4.23-4.81 (12H, m, CH_2Ph), 4.46 (1H, m, H-3), 4.51 (1H, d, $J_{2',NH'}$ = 8.3 Hz, NH'), 6.65 (1H, d, $J_{3,NH}$ = 9.5 Hz, NH), 7.19-7.33 (30H, m, Ph); HR-FABMS Found: $(M+H)^+$, 964.4747. $C_{58}H_{66}O_{10}N_3$ requires *m/z*, 964.4748.

(1R,2R,3S,4R,5S)-Methoxyamine (**13a**); $[\alpha]_D^{22}$ -8.7 (*c* 0.47 in $CHCl_3$); δ_H(500 MHz) 1.75, 1.93 (each 3H, 2s, 2 × Ac), 2.38 (1H, m, H-5), 3.30-3.36 (2H, m, H-3', 5'), 3.37 (1H, dd, $J_{3,4}$ = 6.2 Hz, $J_{4,5}$ = 8.8 Hz, H-4), 3.44 (3H, s, OMe), 3.57 (1H, t, $J_{5,6}$ = 9.8 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6a), 3.65 (1H, t, J = 9.3 Hz, H-4'), 3.64-3.67 (2H, m, H-6'), 3.77 (1H, brt, H-2), 3.78 (1H, m, H-2'), 3.81 (1H, dd, $J_{5,6}$ = 5.5 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6b), 4.18 (1H, t, $J_{1,2}$ = 3.4 Hz, $J_{1,5}$ = 3.5 Hz, H-1), 4.20 (1H, brq, H-3), 4.41-4.80 (11H, m, H-1', CH_2Ph), 5.13 (1H, d, $J_{2',NH'}$ = 8.8 Hz, NH'), 5.78 (1H, d, $J_{3,NH}$ = 7.8 Hz, NH), 5.99-6.05 (1H, brs, NH), 7.20-7.36 (25H, m, Ph).

Anal. Found: C, 70.01; H, 6.89; N, 4.58. $C_{52}H_{61}O_{10}N_3$ requires C, 70.33; H, 6.92; N, 4.73%.

(1R,2R,3S,4R,5S)-Benzyloxyamine (**13b**); $[\alpha]_D^{24}$ -9.6 (*c* 0.53 in $CHCl_3$); δ_H(500 MHz) 1.73, 1.92 (each 3H, 2s, 2 × Ac), 2.38 (1H, m, H-5), 3.34 (1H, m, H-5'), 3.37 (1H, dd, $J_{2',3'}$ = 8.5 Hz, $J_{3',4'}$ = 10 Hz, H-3'), 3.42 (1H, dd, $J_{3,4}$ = 8.4 Hz, $J_{4,5}$ = 6.3 Hz, H-4), 3.53 (1H, t, $J_{5,6}$ = 9.5 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6a), 3.63-3.69 (3H, m, H-4', 6'), 3.74 (1H, q, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 8.5 Hz, $J_{2',NH'}$ = 8.5 Hz, H-2'), 3.75 (1H, dd, $J_{5,6}$ = 3.3 Hz, $J_{6a,6b}$ = 9.8 Hz, H-6b), 3.78 (1H, t, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 4.3 Hz, H-2), 4.18 (1H, t, $J_{1,2}$ = 4.0 Hz, $J_{1,5}$ = 3.7 Hz, H-1), 4.28 (1H, brq, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 8.4 Hz, $J_{3,NH}$ = 8.2 Hz, H-3), 4.41-4.78 (12H, m, CH_2Ph), 4.45 (1H, d, $J_{1',2'}$ = 7.9 Hz, H-1'), 5.15 (1H, d, $J_{2',NH'}$ = 8.5 Hz, NH'), 5.86 (1H, d, $J_{2,NH}$ = 8.2 Hz, NH'), 6.00-6.20 (1H, brs, NH), 7.20-7.36 (30H, m, Ph); HR-FABMS Found: $(M+H)^+$, 964.4709. $C_{58}H_{66}O_{10}N_4$ requires *m/z*, 964.4748.

***(1R,2R,3S,4S,5S)*-3-Acetamido-2-benzyloxy-4-(*N*-benzyloxy-*N*-benzyloxycarbonyl) amino-5-[(benzyloxy)methyl]cyclopentyl 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-gluco pyranoside (14).** To a stirred suspension of the amine **10b** (92 mg, 0.10 mmol) in dichloromethane-aqueous sodium carbonate solution [2:1 (v/v), 3 ml] was added benzyloxycarbonyl chloride (0.09 ml, 0.63 mmol) at 0 °C and the mixture was stirred at 0 °C → room temperature for 15 h under Ar. After ammonium hydroxide solution

had been added with vigorous stirring, the reaction mixture was poured into ice-water, and then extracted with dichloromethane. The extract was washed with cold hydrochloric acid solution, aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated to dryness. Chromatography on silica gel with hexane-ethyl acetate (1 : 2) as the eluent yielded the carbamate **14** (75 mg, 72%), $[\alpha]_D^{25}$ -2.8° (*c* 0.11 in $CHCl_3$); ν_{max} ($CHCl_3$): 3320, 1735, 1678, 1540, 1470, 1380, 1080 cm^{-1}; δ_H(400 MHz) 1.60, 1.71 (each 3H, 2s, 2 × Ac), 2.55 (1H, m, H-5), 3.32-3.36 (2H, m, H-3', 5'), 3.43 (1H, t, J = 8.8 Hz, H-6a), 3.53-3.71 (4H, m, H-6b, 4', 6'), 3.80 (1H, q, $J_{1',2'}$ = 7.3 Hz, $J_{2',3'}$ = 8.8 Hz, $J_{2',NH'}$ = 9.2 Hz, H-2'), 3.91 (1H, brt, $J_{1,2}$ = 5.9 Hz, $J_{2,3}$ = 6.8 Hz, H-2), 4.00 (1H, brt, $J_{1,2}$ = 5.9 Hz, $J_{1,5}$ = 5.4 Hz, H-1), 4.29 (1H, t, J = 7.8 Hz, H-4), 4.42-5.20 (14H, m, CH_2Ph), 4.52 (1H, m, H-3), 4.58 (1H, d, $J_{1',2'}$ = 7.3 Hz, H-1'), 5.05 (1H, d, $J_{2',NH'}$ = 9.2 Hz, NH'), 5.56 (1H, d, J = 8.8 Hz, NH), 7.15-7.38 (35H, m, Ph).

Anal. Found: C, 72.04; H, 6.31; N, 3.88. $C_{66}H_{71}O_{12}N_3$ requires C, 72.18; H, 6.52; N, 3.83%.

***(3aS,4R,5R,6S,6aS)*-6-Benzyloxymethyl-1,4-dibenzyloxy-2-oxo-2,3,3a,5,6,6a-hexahydro-4*H*-cyclopentimidazole-5-yl Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (16).** To a stirred solution of the carbamate **14** (37 mg, 0.04 mmol) in DMF (0.5 ml) was added sodium hydride (60% dispersion in mineral oil, 12 mg, 0.30 mmol) at 0 °C and then the mixture was stirred for 2 h. After ammonium chloride solution had been added with vigorous stirring, the reaction mixture was poured into ice-water, and then extracted with dichloromethane. The extract was washed with water, and brine, dried, and evaporated to dryness. The residue was purified by preparative TLC on silica gel [chloroform-methanol (20 : 1)] to yield the urea **14** (29 mg, 87%), $[\alpha]_D^{25}$ +29.0° (*c* 0.10 in $CHCl_3$); ν_{max} ($CHCl_3$): 3310, 1743, 1660, 1483, 1078 cm^{-1}; δ_H(400 MHz) 1.79 (3H, s, NAc), 2.53 (1H, m, H-5), 3.29-3.37 (3H, m, H-7, 2'), 3.46 (1H, td, $J_{4',5'}$ = 9.3 Hz, $J_{5',6'}$ = 3.4 Hz, $J_{5',6'}$ = 2.9 Hz, H-5'), 3.58 (1H, dd, $J_{3',4'}$ = 8.8 Hz, $J_{4',5'}$ = 9.3 Hz, H-4'), 3.64 (2H, brd, H-6'), 3.70 (1H, dd, $J_{3a,6a}$ = 8.3 Hz, $J_{3a,4}$ = 2.4 Hz, H-3a), 3.77 (1H, dd, $J_{3a,6a}$ = 8.3 Hz, $J_{6,6a}$ = 3.9 Hz, H-6a), 3.89 (1H, dd, $J_{3a,4}$ = 2.4 Hz, $J_{4,5}$ = 3.9 Hz, H-4), 4.06 (1H, dd, $J_{2',3'}$ = 9.8 Hz, $J_{3',4'}$ = 8.8 Hz, H-3'), 4.18 (1H, dd, $J_{4,5}$ = 3.9 Hz, $J_{5,6}$ = 4.9 Hz, H-5), 4.39-4.88 (13H, m, NH, CH_2Ph), 4.77 (1H, d, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.60 (1H, d, $J_{2',NH}$ = 7.3 Hz, NH'), 7.17-7.39 (30H, m, Ph).

Anal. Found: C, 72.10; H, 6.47; N, 4.28. $C_{57}H_{61}O_{10}N_3$ requires C, 72.21; H, 6.49; N, 4.43%.

***(1R,2R,3S,4S,5S)*-3-Acetamido-2-benzyloxy-4-(*N*-benzyloxy-*N*-phenoxythiocarbonyl)amino-5-[(benzyloxy)methyl]cyclopentyl 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (15).** To a stirred solution of the amine **10b** (370 mg, 0.38 mmol) and triethylamine (0.53 ml, 3.80 mmol) in dichloromethane (3 ml) was added chloro phenylthionoformate (0.27 ml, 1.95 mmol) at 0 °C and the mixture was stirred at 0 °C → room temperature under Ar. After 18 h, additional triethylamine (0.53 ml, 3.80 mmol) and chloro phenylthionoformate (0.27 ml, 1.95 mmol) were added, and stirring was continued for more 1 d. The reaction mixture was poured into ice-water, and then extracted with dichloromethane. The extract was washed with water, aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated to dryness. Chromatography on silica gel with toluene-ethyl acetate (4 : 1) as the eluent yielded the carbamate **15** (313 mg, 74%), $[\alpha]_D^{23}$ +14.5° (*c* 0.87 in $CHCl_3$); ν_{max} ($CHCl_3$): 3330, 1680, 1540, 1475, 1380, 1080 cm^{-1}; δ_H(400 MHz) 1.58, 1.83 (each 3H, 2s, 2 × Ac), 2.76 (1H, m, H-5), 3.35-3.48 (2H, m, H-3', 5'), 3.58 (1H, t, $J_{5,6}$ = 8.8 Hz, $J_{6a,6b}$ = 8.3 Hz, H-6a), 3.52-3.78 (4H, m, H-6b, 4', 6'), 3.82 (1H, q, $J_{1',2'}$ = 8.3 Hz, $J_{2',3'}$ = 9.8 Hz, $J_{2',NH'}$ = 8.8 Hz, H-2'), 4.04 (1H, brt, $J_{1,2}$ = 5.2 Hz, $J_{2,3}$ = 6.3 Hz, H-2), 4.12 (1H, brt, $J_{1,2}$ = 5.2

Hz, $J_{1,5}$ = 5.4 Hz, H-1), 4.45-4.80 (13H, m, H-4, CH_2Ph), 4.62 (1H, d, $J_{1',2'}$ = 8.3 Hz, H-1'), 4.83 (1H, m, H-3), 4.99 (1H, d, $J_{2',NH'}$ = 8.8 Hz, NH'), 5.64 (1H, br s, NH), 7.20-7.53 (35H, m, Ph).

Anal. Found: C, 70.95; H, 6.55; N, 3.77; S, 2.72. $C_{65}H_{69}O_{11}N_3S$ requires C, 70.95; H, 6.32; N, 3.82; S, 2.91%.

***(3aS,4R,5R,6S,6aS)*-6-Benzyloxymethyl-1,4-dibenzyloxy-2-thio-2,3,3a,5,6,6a-hexahydro-4*H*-cyclopentimidazole-5-yl Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (17).** To a stirred solution of the thiocarbamate **15** (270 mg, 0.25 mmol) in DMF (5 ml) was added sodium hydride (60% dispersion in mineral oil, 110 mg, 2.75 mmol) at 0 °C and then the mixture was stirred for 2 h. After ammonium chloride solution had been added with vigorous stirring, the reaction mixture was poured into ice-water, and then extracted with dichloromethane. The extract was washed with water, and brine, dried, and evaporated to dryness. Chromatography on silica gel with chloroform-ethyl acetate (10 : 1) as the eluent yielded the thiourea **17** (198 mg, 83%), $[\alpha]_D^{25}$ -10.0 (*c* 0.62 in $CHCl_3$); ν_{max} ($CHCl_3$): 3310, 1670, 1570, 1510, 1465, 1380, 1080 cm^{-1}; δ_H(400 MHz) 1.76 (3H, s, NAc), 2.72 (1H, m, H-5), 3.04 (1H, q, *J* = 7.6 Hz, H-2'), 3.28 (1H, dd, $J_{6,7a}$ = 7.9 Hz, $J_{7a,7b}$ = 9.5 Hz, H-7a), 3.34 (1H, dd, $J_{6,7b}$ = 7.0 Hz, $J_{7a,7b}$ = 9.5 Hz, H-7b), 3.54 (2H, brd, H-4', 5'), 3.66 (2H, brs, H-6'), 3.95 (1H, brs, H-4), 3.96 (1H, brd, $J_{3a,6a}$ = 8.2 Hz, H-3a), 4.05 (1H, dd, $J_{3a,6a}$ = 8.2 Hz, $J_{6,6a}$ = 2.5 Hz, H-6a), 4.22 (1H, brs, H-5), 4.37-4.79 (11H, m, H-3', CH_2Ph), 4.90 (1H, d, $J_{1',2'}$ = 8.2 Hz, H-1'), 5.00 (2H, brs, CH_2Ph), 5.70 (1H, brs, NH), 6.16 (1H, d, $J_{2',NH}$ = 7.0 Hz, NH'), 7.17-7.36 (30H, m, Ph).

Anal. Found: C, 71.23; H, 6.46; N, 4.26; S, 3.06. $C_{57}H_{61}O_9N_3S$ requires C, 71.01; H, 6.38; N, 4.36; S, 3.33%.

***(3aS,4R,5R,6S,6aS)*-4-Benzyloxy-6-benzyloxymethyl-2-dimethylamino-3a,5,6,6a-tetrahydro-4*H*-cyclopentimidazole-5-yl Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (18) and *(3aS,4R,5R,6S,6aS)*-6-Benzyloxymethyl-1,4-dibenzyloxy-2-dimethylamino-3a,5,6,6a-tetrahydro-4*H*-cyclopentimidazole-5-yl Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (19).** A solution of the thiourea **17** (143 mg, 0.15 mmol) in iodomethane (4 ml) was heated under reflux with stirring for 1.5 h under Ar and then evaporated to dryness to give a syrup (140 mg). This was heated with dimethylammonium acetate (ca. 4 ml) at 120 °C with stirring under Ar for 3 h. After cooling, the resulting mixture was poured into water, and then extracted with chloroform. The extracts were washed with dil. HCl solution, water, and brine, dried, and concentrated. Chromatography on silica gel with chloroform-methanol (50 : 1) as the eluent yielded the guanidine **18** (92 mg, 69%) and its benzyl analogue **19** (20 mg, 13%).

18; $[\alpha]_D^{24}$ -14.5 (*c* 0.53 in CH_2Cl_2); ν_{max} ($CHCl_3$): 3280, 1690, 1560, 1465, 1080 cm^{-1}; δ_H(400 MHz) 1.86 (3H, s, NAc), 2.80 (1H, m, H-6), 2.97 (6H, s, NMe), 3.41 (1H, m, H-5'), 3.50-3.65 (6H, m, H-7, 2', 4', 6'), 3.75 (1H, t, *J* = 8.8 Hz, H-3'), 4.11 (1H, brs, H-4), 4.23 (2H, brs, H-3a, 6a), 4.28 (1H, brt, H-5), 4.38-4.79 (11H, m, NH', CH_2Ph), 4.65 (1H, d, $J_{1',2'}$ = 7.8 Hz, H-1'), 7.15-7.31 (25H, m, Ph); δ_C(100 MHz): 23.5 (AcN), 39.2 (NMe), 51.1 (C-6), 55.8 (C-2'), 62.1 (C-6a), 65.1 (C-3a), 68.8 (C-7), 68.9 (C-6'), 71.8 (CPh), 73.0 (CPh), 73.3 (CPh), 74.5 (C-5'), 74.6 (CPh), 75.3 (CPh), 78.3 (C-4'), 82.6 (C-3'), 83.3 (C-5), 88.4 (C-4), 99.4 (C-1'), 127.7 (Ph), 127.8 (Ph), 128.0 (Ph), 128.4 (Ph), 128.5 (Ph), 137.8 (Ph),

138.1 (Ph), 138.2 (Ph), 158.6 (C=N), 171.1 (C=O); Anal. Found: $(M+H)^+$, 869.4492. $C_{52}H_{61}O_8N_4$ requires *m/z*, 869.4489.

19; $[\alpha]_D^{24}$ +52.0 (*c* 0.18 in $CHCl_3$); ν_{max} ($CHCl_3$): 3300, 1655, 1580, 1470, 1385, 1080 cm^{-1}; δ_H(400 MHz) 1.69 (3H, s, NAc), 2.28 (1H, m, H-6), 2.98 (6H, s, NMe), 3.42 (1H, m, H-5'), 3.54-3.65 (6H, m, H-7, 2', 4', 6'), 3.74 (1H, t, J = 8.8 Hz, H-3'), 3.97 (1H, dd, $J_{3a,4}$ = 3.1 Hz, $J_{4,5}$ = 5.8 Hz, , H-4), 4.04-4.10 (2H, m, H-5, 6a), 4.32 (1H, dd, $J_{3a,6a}$ = 7.9 Hz, $J_{3a,4}$ = 3.1 Hz, H-3a), 4.41-4.77 (12H, m, CH_2Ph), 4.71 (1H, d, $J_{1',2'}$ = 8.3 Hz, H-1'), 5.40 (1H, brs, NH'), 7.17-7.37 (30H, m, Ph); δ_C(100 MHz): 23.4 (AcN), 39.1 (NMe), 48.3 (C-6), 56.2 (C-2'), 67.7 (C-6a), 68.2 (C-7), 68.9 (C-6'), 71.7 (CPh), 71.8 (C-3a), 73.3 (CPh), 73.4 (CPh), 74.4 (CPh), 74.6 (C-5'), 74.8 (CPh), 75.7 (CPh), 78.4 (C-4'), 81.3 (C-3'), 83.7 (C-5), 89.0 (C-4), 100.0 (C-1'), 127.4 (Ph), 127.5 (Ph), 127.7 (Ph), 127.9 (Ph), 128.0 (Ph), 128.1 (Ph), 128.2 (Ph), 128.3 (Ph), 128.4 (Ph), 128.5 (Ph), 128.8 (Ph), 135.4 (Ph), 138.1 (Ph), 138.4 (Ph), 138.7 (Ph), 163.1 (C=N), 170.0 (C=O); HR-FABMS Found: $(M+H)^+$, 975.4914. $C_{59}H_{67}O_9N_4$ requires *m/z*, 975.4908.

***(3aS,4R,5R,6S,6aS)*-2-Dimethylamino-3a,5,6,6a-tetrahydro-4-hydroxy-6-hydroxymethyl-4*H*-cyclopentimidazole-5-yl 2-Acetamido-2-deoxy-β-D-glucopyranoside hydrochloride (4).**

i) From **18.** To a stirred solution of the guanidine **18** (49 mg, 0.05 mmol) in AcOH-H_2O-EtOH (1 : 1 : 1, v/v/v, 3 ml) was added 10% Pd-C (24 mg) and the mixture was stirred at room temperature for 18 h under a hydrogen atmosphere. The catalyst was then filtered off and washed with aq. methanol. The filtrate and washings were combined and concentrated *in vacuo*, and the residual syrup was chromatographed in a column of Sephadex-G 10 equilibrated with H_2O. The amine fractions, eluted with H_2O, were combined and concentrated *in vacuo*. The residue was dissolved in water, and lyophilized to give **4** (24 mg, 99%) as a hygroscopic powder.

ii) From **19.** Treatment of the benzyl ether **19** (9 mg, 9 mmol) as described above yielded the guanidine **4** (3 mg, 75%), $[\alpha]_D^{24}$ +13.0 (*c* 0.20 in H_2O); ν_{max} (KBr): 3300, 1680, 1650, 1541, 1433, 1110 cm^{-1}; δ_H (400 MHz; D_2O, DHO=4.80): 2.07 (3H, s, NAc), 2.24 (1H, m, H-6), 3.02 (6H, brs, NMe_2), 3.44 (1H, dd, $J_{3',4'}$ = 8.8 Hz, $J_{4',5'}$ = 9.8 Hz, H-4'), 3.52 (1H, ddd, $J_{4',5'}$ = 9.8 Hz, $J_{5',6a'}$ = 6.6 Hz, $J_{5',6b'}$ = 2.2 Hz, H-5'), 3.58 (1H, dd, $J_{2',3'}$ = 10 Hz, $J_{3',4'}$ = 8.8 Hz, H-3'), 3.64 (1H, dd, $J_{6,7a}$ = 6.3 Hz, $J_{7a,7b}$ = 11 Hz, H-7a), 3.73 (1H, dd, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 10 Hz, H-2'), 3.74 (1H, dd, $J_{5',6'}$ = 6.6 Hz, $J_{6'a,6'b}$ = 12 Hz, H-6'a), 3.79 (1H, dd, $J_{6,7b}$ = 4.4 Hz, $J_{7a,7b}$ = 11 Hz, H-7b), 3.82 (1H, dd, $J_{4,5}$ = 4.8 Hz, $J_{5,6}$ = 8.7 Hz, H-5), 3.98 (1H, dd, $J_{5',6'}$ = 2.2 Hz, $J_{6'a,6'b}$ = 12 Hz, H-6'b), 4.18 (1H, dd, $J_{3a,4}$ = 4.8 Hz, $J_{3a,6a}$ = 9.6 HJz, H-3a), 4.20 (1H, t, $J_{3a,4}$ = 4.8 Hz, $J_{4,5}$ = 4.8 Hz, H-4), 4.31 (1H, dd, $J_{3a,6a}$ = 9.6 Hz, $J_{6.6a}$ 6.0 Hz, H-6a), 4.55 (1H, d, $J_{1',2'}$ = 8.5 Hz, H-1'); δ_C(100MHz, D_2O, dioxane=67.4): 22.0 (AcN), 37.8 (NMe), 52.1 (C-6), 55.5 (C-2'), 57.5 (C-6a), 59.5 (C-7), 60.7 (C-6'), 63.2 (C-3a), 70.0 (C-4'), 73.4 (C-3'), 75.7 (C-5'), 81.5 (C-4), 84.8 (C-5), 101.7 (C-1'), 158.2 (C=N), 174.4 (C=O); HR-FABMS Found: $(M+H)^+$, 419.2138. $C_{17}H_{31}O_8N_4$ requires *m/z*, 419.2142.

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12. Cyclization reaction of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-5-*O*-phenoxy(thiocarbonyl)-D-glucose *O*-benzyl oximes under the same conditions gave a mixture of the corresponding cyclopentane derivatives in 63% yield with the stereoselectivity as follows (**10** : **11** : **12** : **13** = 51 : 13 : 20 : 16).

13. For example, Appel. R, *Angew. Chem., Int. Ed.*, **1975**, *14*, 801. Reaction of **16** with alkylating reagents such as Meerwein reagent and methyl trifrate also gave unsatisfactory results. In addition, treatment of **10b** with dichloromethylenedimethyliminium chloride led to a intractable mixture.
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