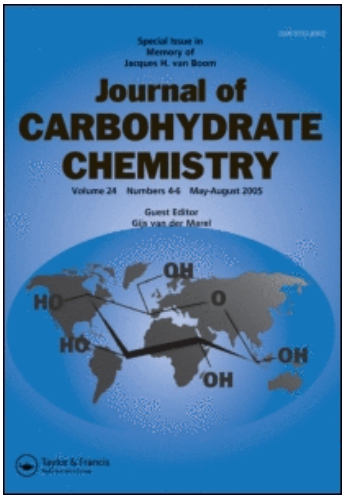

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Preparation of a Highly Functionalized Cyclopentane Derivative Suitable for the Synthesis of Allosamidin Analogs

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PREPARATION OF A HIGHLY FUNCTIONALIZED CYCLOPENTANE DERIVATIVE SUITABLE FOR THE SYNTHESIS OF ALLOSAMIDIN ANALOGS

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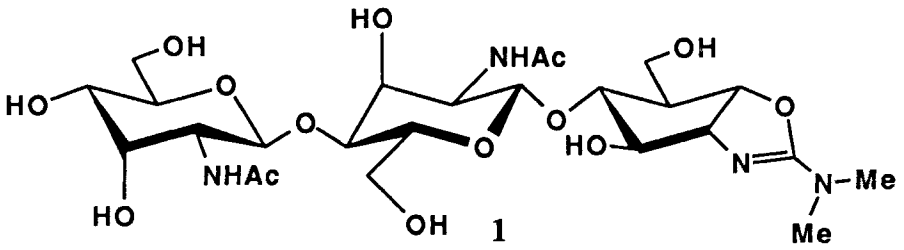
ABSTRACT

Methyl 3,6-di-*O*-benzyl-4-*O*-benzoyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (**8**) was prepared from D-glucosamine via its 4,6-*O*-benzylidene derivative. The methyl glycoside moiety of **8** was hydrolyzed in the presence of *d*-camphorsulfonic acid in acetic acid to give hemiacetal **12**. The oxime **14** derived from the latter was subjected to the radical cyclization mediated by tributyltin hydride, providing three types of cyclopentane derivatives. One isomer, **15**, having an allosamizoline (**2**)-like configuration was converted into the *N,N'*-isopropylidene derivative **3**, which is a potential intermediate for the syntheses of analogs of chitinase inhibitor allosamidin (**1**).

INTRODUCTION

Since the discovery of a chitinase inhibitor allosamidin (**1**),[1-3] several congeners of **1** have been isolated from various fungi.[4-6] The unique common pseudotrisaccharide structure of these molecules is composed of two β-1,4-linked *N*-acetyl aminosugar residues connected to an aminocyclitol termed allosamizoline (**2**) (or its *N*-monomethyl analog). These inhibitors have recently attracted much attention of many biochemists[7-10] because of their different inhibitory spectra against various chitinases from different

sources. Furthermore, total syntheses of **1** have been reported by several groups.[11-13] In regard to the structure-activity relationship study of **1**, there has been considerable interest in the preparation and inhibitory activity of unnatural analogs of **1**.[14] For example, Corbett et al. have synthesized a 6-membered carbocyclic ring analog of **2**[15a] and showed that the pseudodisaccharide derived therefrom has a rather weak inhibitory activity against yeast chitinase.[15b] Some chemical modifications of the allosamizoline moiety in **1** and inhibitory activities of analogs prepared thereby have been also reported by Kinoshita et al., suggesting that the aminooxazoline structure plays an important role in chitinase inhibition.[16] These reports prompted us to synthesize a novel type of allosamizoline analog in which the oxygen atom in the oxazoline moiety is replaced by nitrogen. Here we describe a preparation of a highly functionalized cyclopentane derivative **3** suitable for the synthesis of new allosamidin analogs.



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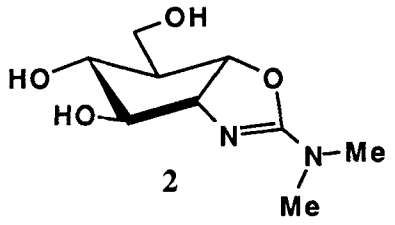

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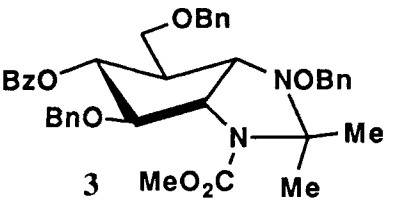

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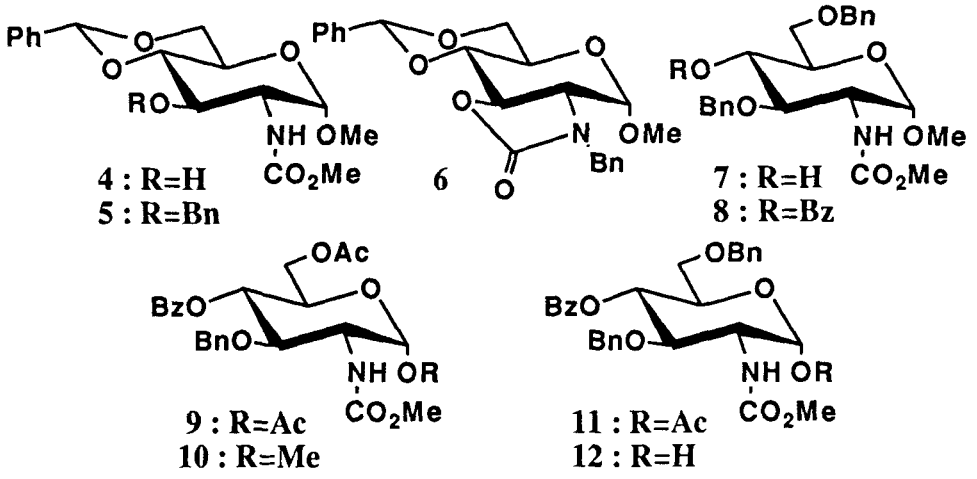
RESULTS AND DISCUSSION

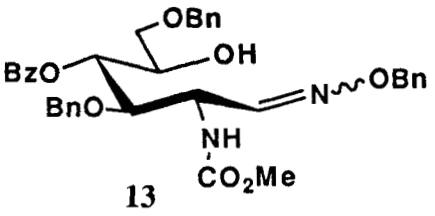
Our synthetic effort toward **3** starting from D-glucosamine hydrochloride was targeted to accomplishing three major tasks; i) selective protection of D-glucosamine to prepare dibenzyl ether **8**, ii) ring-opening of the protected D-glucosamine into an open chain oxime **13**, iii) construction of the cyclopentane ring system by ring-closure of an acyclic thiocarbonate **14** by a radical cyclization.[17] Methyl 4,6-*O*-benzylidene-2-deoxy-2-

methoxycarbonylamino-α-D-glucopyranoside (**4**), prepared from D-glucosamine hydrochloride,[18] was benzylated with benzyl bromide and barium hydroxide-barium oxide in *N,N*-dimethylformamide at room temperature, giving the benzyl ether **5** in good yield. The use of potassium hydroxide instead of barium hydroxide-barium oxide afforded the cyclic carbonate **6** as a major product (50% yield). Benzyl ether **5** reacted with borane-trimethylamine complex and aluminium chloride[19] in the presence of molecular sieves 4A in tetrahydrofuran at room temperature to give alcohol **7** in 85% yield. The hydroxyl group in **7** was protected by treatment with benzoyl chloride in pyridine, giving the benzoate **8** in 95% yield. This protection enabled us to discriminate the OH group at C-4 from other hydroxyls. To obtain the open-chain substance, we required selective hydrolysis of the methyl glycoside moiety in **8**. Initially we examined acetolysis of



8 because an acetyl group at C-1 position of a glycosyl acetate was well known to be selectively cleaved by the action of amines such as butylamine without affecting other ester-functions. Attempted acetolysis of methyl glycoside **8** with ca. 4% H_2SO_4 in acetic acid-acetic anhydride at 0 °C for 3.5 hours gave undesirable diacetate **9** in high yield. Even when the amount of H_2SO_4 was diminished to ca. 0.05%, the product was not the desired glycosyl acetate **11** but methyl glycoside **10**. The acetolysis under moderate acidic conditions (ca. 0.5%H_2SO_4) resulted in the formation of a mixture of **9** and **10**. These results clearly indicated that the benzyloxy group at C-6 in **8** is more reactive than the

methyl glycoside moiety at C-1 under the conditions of the acetolysis. Therefore, direct hydrolysis of **8** was examined. After some experimentations, *d*-camphorsulfonic acid (CSA) was found to be a superior catalyst instead of a usual proton acid such as hydrochloric acid or sulfuric acid. Compound **8** was treated with 70% acetic acid in the presence of 2.5 mole equivalents of CSA at 110 °C for 31 hours to afford the desired hemiacetal **12** in 47% yield; the starting material **8** was recovered (31% yield).



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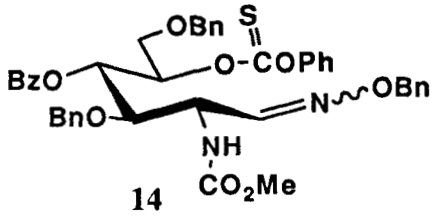

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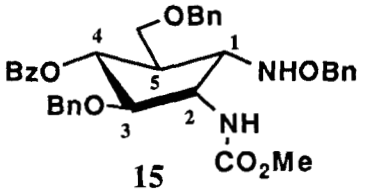

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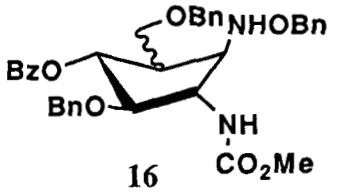

16

Upon obtaining multigram quantities of hemiacetal **12**, the conversion of the pyranose form into the cyclopentane derivative was performed according to Bartlett's procedure.[17] Thus, compound **12** was reacted with *O*-benzylhydroxylamine in pyridine-dichloromethane to afford the oxime **13** as an inseparable mixture of two stereoisomers (anti : syn = 4 : 1, ^{1}H NMR analysis). The latter was converted to thiocarbonate **14** by treatment with phenyl chlorothionoformate in pyridine-dichloromethane at 0 °C. Radical cyclization reaction was executed by adding a mixture of tributyltin hydride and 2,2'-azobis(isobutyronitrile) in toluene into a solution of **14** in refluxing toluene, giving **15** and **16** in 54% combined yield. It was established by ^{1}H, ^{13}C NMR and difference NOE spectra that the isomer **15** isolated in 19% yield had the allosamizoline (**2**)-like configuration, e. g., 1,2-*cis*,1,5-*trans* relationship. For example, in the ^{1}H NMR spectrum of **15**, irradiation of H_5 resulted in enhancements of H_1, H_3, H_4, and CH_2OBn peaks. Likewise, irradiation of H_3 caused enhancement of signal due to H_5. A strong

NOE was also observed upon irradiation of H_1 for signals from H_2 and H_4. On the other hand, **16** was an inseparable mixture of two stereoisomers (ca. 8 : 5, ^{1}H NMR analysis). The structure of this inseparable mixture was mainly estimated based on the previous results of Bartlett et al.[17] and Simpkins et al.[20] In the ^{13}C NMR spectra of **16**, two signals due to C_5 were observed at 42.2 and 44.4 ppm and one signal derived from C_2 was observed at 58.4 ppm which shifted to a lower field than that from **15**, suggesting **16** was a diastereomeric mixture at C-5 with a 1,2-*trans* relationship.[21] The full assignment of proton and carbon signals in the NMR spectra of **16** and from NOE experiments, however, could not be attained due to the complexity of the spectra. Both NH groups in **15** were protected as the acetonide by treatment of **15** with isopropenyl methyl ether in the presence of CSA in acetone-dichloromethane, giving the *N,N'*-isopropylidene derivative **3** in high yield. Syntheses of allosamidin analogs using **3** are now under investigation.

EXPERIMENTAL

General Procedures. Melting points were determined in a capillary with an Ishii melting-point apparatus and are reported uncorrected. Optical rotations were determined with a JASCO DIP-370 polarimeter. IR spectra were recorded with a Shimadzu-FTIR-8100M spectrophotometer. NMR spectra were recorded on JEOL JNM-GSX 400 or 500 spectrometers in a $CDCl_3$ solution (unless otherwise specified), using tetramethylsilane as internal standard. In the NMR assignment of cyclopentane derivatives, the numbering system shown is used for ease of comparison between the sugar and the cyclitol. 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.

Methyl 4,6-*O*-Benzylidene-3-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (5). To a vigorously stirred suspension of **4** (20.0 g, 0.06 mol), barium oxide (36.2 g, 0.24 mol) and barium hydroxide octahydrate (37.2 g, 0.12 mol) in *N,N*-dimethylformamide (300 mL) was added dropwise benzyl bromide (14.0 g, 0.12 mol) at room temperature (rt) and the mixture was stirred for 8 h at rt. Methanol (5 mL) was added to the reaction mixture, and then the resulting suspension was diluted with chloroform and filtered through a Celite pad. The filtrate was washed with

water, brine, dried ($MgSO_4$), and then concentrated *in vacuo* to give a crystalline solid, which was recrystallized from ethanol to give **5** (24.4 g, 96%): mp 202-203 °C (from ethanol); $[\alpha]_D^{23}$ +60.5° (*c* 0.72, $CHCl_3$); ν_{max}(KBr) 1700, 1540 cm^{-1}; ^1H NMR δ 3.36 (3H, s, OMe), 3.69 (3H, s, OMe), 3.64-3.85 (4H, m), 3.99 (1H, brt, H-2), 4.29 (1H, brd, H-6), 4.66 (1H, d, J = 12Hz, C*H*HPh), 4.71 (1H, d, J = 3.4 Hz, H-1), 4.76 (1H, d, J = 9.3Hz, NH), 4.90 (1H, d, J = 12Hz, C*H*HPh), 5.59 (1H, s, C*H*Ph), 7.26-7.51 (10H, m, Ph).

Anal. Calcd for $C_{23}H_{27}O_7N$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.04; H, 6.30; N, 3.35.

Methyl 2-Benzylamino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside 2,3-Carbamate (6). To a stirred suspension of **4** (300 mg, 0.88 mmol) and powdered potassium hydroxide (148 mg, 2.64 mmol) in *N,N*-dimethylformamide (3 mL) was added dropwise benzyl bromide (0.21 mL, 1.76 mmol) at rt and the mixture was stirred for 4 h at rt. Work up as with **5** gave a crystalline solid, which was recrystallized from ethanol-chloroform to give **6** (138 mg, 44%). The mother liquor was concentrated *in vacuo* and then applied to a column of silica gel employing toluene-ethyl acetate (10:1 v/v) as the eluant to give additional **6** (19 mg, 6%) and **5** (52 mg, 14%). **6**. mp 217.5-218.5 °C (from ethanol-chloroform); $[\alpha]_D^{19}$ +10.3° (*c* 1.03, $CHCl_3$); ν_{max}(KBr) 1761 cm^{-1}; ^1H NMR δ 3.18 (3H, s, OMe), 3.33 (1H, dd, $J_{1,2}$ = 2.8 Hz and $J_{2,3}$ = 11 Hz, H-2), 3.79 (1H, ddd, $J_{4,5}$ = 8.6 Hz, $J_{6,5}$ = 8.4 Hz, $J_{6',5}$ = 3.7 Hz, H-5), 3.81 (1H, dd, $J_{6,6'}$ = 9.2 Hz, H-6), 3.96 (1H, dd, $J_{3,4}$ = 10 Hz, H-4), 4.21 (1H, dd, H-6'), 4.42 (1H, d, J = 15 Hz, C*H*HPh), 4.45 (1H, d, J = 15 Hz, C*H*HPh), 4.56 (1H, d, H-1), 4.67 (1H, dd, H-3), 5.56 (1H, s, C*H*Ph), 7.29-7.40 (8H, m, Ph), 7.45-7.50 (2H, m, Ph).

Anal. Calcd for $C_{22}H_{23}O_6N$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.32; H, 6.07; N, 3.52.

Methyl 3, 6-Di-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (7). To a stirred solution of **5** (10 g, 23 mmol), borane-trimethylamine complex (10 g, 0.14 mol) and molecular sieves 4A (31 g) in tetrahydrofuran (450 mL) was added finely ground aluminum chloride (18.4 g, 0.14 mol) at 0 °C under argon . The mixture was stirred at 0 °C→rt under Ar for 15 h and then diluted with diethyl ether (200 mL). The resulting suspension was filtered through a Celite pad

and the filtrate was diluted with chloroform. The chloroform solution was washed with dil HCl solution, satd $NaHCO_3$ solution, water and brine, and dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was applied to a column of silica gel employing dichloromethane→dichloromethane-methanol (20:1 v/v) as the eluant to give **7** (8.54 g, 85 %): mp 101.5-102.5 °C (from isopropyl ether); $[\alpha]_D^{21}$ +66.4° (*c* 0.72, $CHCl_3$); ν_{max}(KBr) 3340, 3314, 1697, 1540 cm^{-1}; ^1H NMR δ 2.61 (1H, br s, OH), 3.35 (3H, s, OMe), 3.51 (1H, dd, J = 10 Hz, J = 7.9 Hz, H-3), 3.66 (3H, s, OMe), 3.67-3.76 (4H, m), 3.95 (1H, brt, H-2), 4.55 (1H, d, J = 12 Hz, C*H*HPh), 4.61 (1H, d, J = 12 Hz, C*H*HPh), 4.67 (1H, d, J = 2.1 Hz, H-1), 4.71 (1H, d, J = 12 Hz, C*H*HPh), 4.74 (1H, d, J = 12 Hz, C*H*HPh), 4.83 (1H, d, J = 9.7 Hz, NH), 7.27-7.34 (10H, m, Ph).

Anal. Calcd for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.04; H, 6.80; N, 3.19.

Methyl 4-*O*-Benzoyl-3,6-di-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (8). To a stirred solution of **7** (7.15 g, 17 mmol) in pyridine (70 mL) was added benzoyl chloride (2.96 mL, 25.5 mmol) at 0 °C. The mixture was stirred overnight and poured into ice-water. The resulting solution was extracted with chloroform. The combined extracts were successively washed with water, dil HCl solution, satd $NaHCO_3$ solution, water and brine, dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was treated with ether to give **8** (8.54 g, 95%) as a crystalline solid: mp 100-101 °C (from isopropyl ether); $[\alpha]_D^{21}$ +37.3° (*c* 0.8, $CHCl_3$); ν_{max}(KBr) 3326, 1725, 1700, 1547 cm^{-1}; ^1H NMR δ 3.42 (3H, s, OMe), 3.59 (2H, brs, H-6), 3.66 (3H, s, OMe), 3.84 (1H, brs, H-3), 3.99 (1H, m, H-5), 4.12 (1H, brt, H-2), 4.49 (2H, s, CH_2Ph), 4.57 (2H, s, CH_2Ph), 4.78 (2H, brs, H-1, NH), 5.39 (1H, brt, H-4), 7.10-7.30 (10H, m, Ph), 7.44 (2H, t, J = 7.8 Hz, Ph), 7.58 (1H, t, J = 7.8 Hz, Ph), 7.99 (2H, brd, Ph).

Anal. Calcd for $C_{30}H_{33}O_8N$: C, 67.27; H, 6.21; N, 2.62. Found: C, 67.29; H, 6.30; N, 2.69.

1,6-Di-*O*-acetyl-4-*O*-benzoyl-3-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranose (9). To a stirred solution of **8** (535 mg, 1.0 mmol) in acetic anhydride (3 mL) was added a mixture of acetic acid (6 mL), acetic anhydride (3 mL) and concd H_2SO_4 (0.4 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The

reaction mixture was poured into a solution of sodium acetate in ice-water. The mixture was extracted with chloroform. The combined extracts were washed with water, satd $NaHCO_3$ solution, water and brine, dried ($MgSO_4$) and then concentrated *in vacuo*, giving a solid, which was recrystallized from ethanol to give **9** (300 mg, 58%): mp 178.5-179 °C (from ethanol); $[\alpha]_D^{21}$ +44.5° (*c* 0.65, $CHCl_3$); ν_{max}(KBr) 3285, 1755, 1744, 1727, 1696, 1557 cm^{-1}; ^1H NMR δ 2.03, 2.18 (3H×2, each s, Ac), 3.68 (3H, s, OMe), 3.88 (1H, brt, H-3), 4.10 (1H, m, H-5), 4.12 (1H, brd, $J_{6,6'}$ = 12 Hz, H-6), 4.22 (1H, dd, $J_{6',5}$ = 4.3 Hz, H-6'), 4.20-4.30 (1H, m, H-2), 4.51 (1H, brd, J = 8.2 Hz, NH), 4.58 (1H, d, J = 11 Hz, C*H*HPh), 4.63 (1H, d, J = 11 Hz, C*H*HPh), 5.49 (1H, brt, H-4), 6.23 (1H, brd, $J_{1,2}$ = 3.4 Hz, H-1), 7.10-7.25 (5H, m, Ph), 7.45-7.48 (2H, t, J = 7.8 Hz, Ph), 7.59-7.62 (1H, t, J = 7.8 Hz, Ph), 8.03-8.06 (2H, brd, Ph).

Anal. Calcd for $C_{26}H_{29}O_{10}N$: C, 60.57; H, 5.67; N, 2.72. Found: C, 60.35; H, 5.67; N, 2.68.

Methyl 6-*O*-Acetyl-4-*O*-benzoyl-3-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (10). To a stirred mixture of acetic acid-acetic anhydride-concd H_2SO_4 (1:4:2.5×10^{-3} v/v/v, 3 mL) was added **8** (268 mg, 0.5 mmol) at 0 °C and the mixture was stirred at 0 °C for 3.5 h. The reaction mixture was poured into a solution of sodium acetate in ice-water. The mixture was extracted with chloroform. The combined extracts were washed with water, satd $NaHCO_3$ solution, water, brine and dried ($MgSO_4$), and then concentrated *in vacuo*. The residue was purified by preparative TLC (hexane-ethyl acetate, 2:1 v/v, 5 developments) to give **10** (182 mg, 75%). The starting material **8** (66 mg) was also recovered. **10**. $[\alpha]_D^{19}$ +30.6° (*c* 1.27, $CHCl_3$); ν_{max}(KBr) 3308, 1722, 1705, 1550 cm^{-1}; ^1H NMR δ 2.04 (3H, s, Ac), 3.42 (3H, s, OMe), 3.67 (3H, s, OMe), 3.84 (1H, brt, H-3), 4.02 (1H, m, H-5), 4.14 (1H, m, H-2), 4.16 (1H, brd, $J_{6,6'}$ = 12 Hz, H-6), 4.22 (1H, dd, $J_{5,6'}$ = 4.9 Hz, H-6'), 4.57 (2H, brt, C*H*$_2$Ph), 4.77 (1H, brs, H-1), 4.82 (1H, d, J = 8.6 Hz, NH), 5.40 (1H, brt, H-4), 7.11-7.15 (5H, m, Ph), 7.43-7.46 (2H, m, Ph), 7.56-7.60 (1H, m, Ph), 8.01-8.03 (2H, m, Ph).

Anal. Calcd for $C_{25}H_{29}O_9N \cdot 0.5H_2O$: C, 60.48; H, 6.09; N, 2.82. Found: C, 60.43; H, 5.98; N, 2.83.

4-*O*-Benzoyl-3,6-di-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranose (12). A mixture of **8** (3.35 g, 6.3 mmol) and *d*-camphorsulfonic acid (3.13 g, 13.5 mmol) in 70 % acetic acid (98 mL) was stirred at 110 °C for 31 h under argon. The reaction mixture was directly concentrated *in vacuo* and the residue was diluted with chloroform. The chloroform solution was washed with water, satd $NaHCO_3$ solution, water, brine and dried ($MgSO_4$), and then concentrated *in vacuo*. The residual oil was applied to a column of silica gel employing hexane-ethyl acetate (1:1 v/v) as the eluant to give a hemiacetal **12** (1.54 g, 47%) as a solid. The starting material **8** (1.03 g) was also recovered. **12**. mp 136.5-139 °C (from ethanol); $[\alpha]_D^{20}$ +5.8° (*c* 2.43, $CHCl_3$); ν_{max}(KBr) 3500-3250, 3300, 1728, 1533 cm^{-1}; ^1H NMR δ 3.52 (1H, dd, $J_{6,6'}$ = 11 Hz, $J_{5,6}$ = 3.3 Hz, H-6), 3.57 (1H, brd, H-6'), 3.65 (3H, s, OMe), 3.70-3.80 (1H, brs, OH), 3.95 (1H, brt, H-3), 4.02 (1H, m, H-2), 4.27 (1H, m, H-5), 4.45 (1H, d, J = 12 Hz, C*H*HPh), 4.50 (1H, d, J = 12 Hz, C*H*HPh), 4.57 (2H, brs, CH_2Ph), 4.86 (1H, d, J = 9.3 Hz, NH), 5.20-5.40 (1H, m, H-1), 5.31 (1H, brt, J = 10 Hz, H-4), 7.15-7.33 (10H, m, Ph), 7.44 (2H, t, J = 8 Hz, Ph), 7.59 (1H, t, J = 8 Hz, Ph), 7.99 (2H, brd, J = 8 Hz, Ph); ^{13}C NMR δ 52.4 (Me), 54.5 (C-2), 69.1 (C-5), 69.4 (C-6), 71.5 (C-4), 73.5 (CH_2Ph), 92.1 (C-1), 127.6, 127.7, 127.9, 128.2, 128.4, 129.5, 129.7, 133.2, 137.3 (Ph), 156.6 (CO_2Me), 165.2 (COPh).

Anal. Calcd for $C_{29}H_{31}O_8N$: C, 66.78; H, 5.99; N, 2.69. Found: C, 66.38; H, 5.99; N, 2.80.

4-*O*-Benzoyl-3,6-di-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-D-glucose *O*-benzyl oxime (13). To a stirred solution of **12** (5.61 g, 0.01 mol) in pyridine-dichloromethane (1:1 v/v, 100 mL) was added *O*-benzylhydroxylamine hydrochloride (3.19 g, 0.02 mol). The mixture was stirred at rt for 4 h, and then poured into ice-water, and extracted with chloroform. The extracts were washed with water, satd $NaHCO_3$ solution, water, brine and dried ($MgSO_4$), and then concentrated *in vacuo*. The residual oil was applied to a column of silica gel employing hexane-ethyl acetate (3:1 v/v) as the eluant to give **13** (5.77 g, 86%): ν_{max}(film) 3630-3250, 3422, 1724, 1510 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 3.43-3.59 (5H, m, H-6, OMe), 4.05-4.11 (1H, m, H-5), 4.24-4.26 (1H, m, H-3), 4.40-4.44 (2H, m, CH_2Ph), 4.52-4.54 (0.8H, m, H-2 of *anti*-isomer), 4.65 (2H, s, CH_2Ph), 4.83 (0.8H, d, J = 12Hz, C*H*HPh of *anti*-isomer), 4.91

(0.8H, d, J = 12Hz, C*H*HPh of *anti*-isomer), 4.95 (0.2H, d, J = 12Hz, C*H*HPh of *syn*-isomer), 5.00 (0.2H, d, J = 12Hz, C*H*HPh of *syn*-isomer), 5.02-5.08 (0.2H, m, H-2 of syn isomer), 5.07 (0.2H, d, J = 6.0 Hz, OH of *syn*-isomer), 5.11 (0.8H, d, J = 6.3 Hz, OH of *anti*-isomer), 5.24-5.26 (1H, m, H-4), 6.70-6.90 (1H, m, NH), 6.79 (0.2H, d, J = 5.9 Hz, H-1 of *syn*-isomer), 7.21-7.38 (15H, m, Ph), 7.44 (0.8H, d, J = 5.9 Hz, H-1 of *anti*-isomer), 7.45-7.50 (2H, m, Ph), 7.58-7.65 (1H, m, Ph), 7.88-7.95 (2H, m, Ph).

Anal. Calcd for $C_{36}H_{38}O_8N_2 \cdot H_2O$: C, 67.07; H, 6.25; N, 4.35. Found: C, 67.26; H, 6.02; N, 4.27.

4-*O*-Benzoyl-3,6-di-*O*-benzyl-2-deoxy-2-methoxycarbonylamino-5-*O*-phenoxythiocarbonyl-D-glucose *O*-benzyl oxime (14). To a stirred solution of **13** (5.27 g, 8.41 mmol) in dichloromethane-pyridine (3:1 v/v, 52 mL) was added phenyl chlorothionoformate (2.33 mL, 16.82 mmol) at 0 °C under Ar. The mixture was stirred under ice-bath cooling for 18 h, poured into ice-water and then extracted with chloroform. The extracts were washed with satd $CuSO_4$ solution, satd $NaHCO_3$ solution, water, brine and dried ($MgSO_4$), and then concentrated *in vacuo*. The residue was passed through a short column of silica gel employing hexane-ethyl acetate (4:1 v/v) as the eluant to give **14** (5.14 g, 80%), which was employed without further purification in the next step: ν_{max}(film) 3422, 1728, 1491, 1206 cm^{-1}.

Radical cyclization of the *O*-benzyl oxime derivative 14. To a stirred solution of **14** (4.97 g, 6.5 mmol) in toluene (325 mL) was added slowly a mixture of tributyltin hydride (10.3 mL, 40 mmol) and 2,2'-azobis(isobutyronitrile) (0.42 g, 2.6 mmol) in toluene (11 mL) at 110 °C under Ar. The mixture was stirred for 4 h at 110 °C and then cooled, concentrated *in vacuo*, and dissolved in acetonitrile. The acetonitrile solution was washed with hexane 3 times, and then concentrated *in vacuo*. The residual oil was applied to a column of silica gel employing chloroform-ethyl acetate (10:1 v/v) as the eluant to give **15** (767 mg, 19%) and **16** as a diastereomeric mixture (1.4 g, 35%). **15**. $[\alpha]_D^{19}$ -20.5° (*c* 1.12, $CHCl_3$); ν_{max} (film) 3400, 1717, 1271 cm^{-1}; ^1H NMR δ 2.31 (1H, m, H-5), 3.50-3.80 (3H, m, H-1,6), 3.67 (3H, s, OMe), 4.15-4.30 (2H, m, H-2,3), 4.48 (2H, brs, C*H*$_2$Ph), 4.60-4.75 (4H, m, C*H*$_2$Ph), 5.22 (1H, brs, H-4), 5.53 (1H, brs, NH), 5.90-6.40 (1H, brs, NH), 7.20-7.35 (15H, m, Ph), 7.40 (2H, t, J = 8.0 Hz, Ph), 7.54 (1H, t, J = 8.0 Hz, Ph), 7.90-8.10 (2H, m, Ph). ^{13}C NMR δ 45.6 (C-5),

52.1 (OMe), 56.1 (C-2), 63.7 (C-1), 71.4 (C-6), 71.8, 73.3, 76.4 (Ph), 78.6 (C-4), 85.7 (C-3), 127.5, 127.6, 127.9, 128.0, 128.3, 128.4, 128.7, 129.8, 133.2, 137.2, 137.9, 138.1 (Ph), 156.9 (*C*O_2Me), 165.8 (*C*OPh).

Anal. Calcd for $C_{36}H_{38}O_7N_2 \cdot 0.5H_2O$: C, 69.77; H, 6.34, N, 4.52. Found: C, 69.98; H, 6.18; N, 4.54.

16 (mixture of isomers), ν_{max} (film) 3341, 1721, 1700, 1273 cm^{-1}; ^1H NMR δ 2.58 (0.62H, m, H-5 of major isomer), 2.78 (0.38H, m, H-5 of minor isomer), 3.35-3.45 (0.38H, m), 3.50-3.75 (2H, m), 3.63, 3.65 (3H, each s, OMe), 3.86 (0.62H, dd, J = 9.3 and 6.6 Hz), 3.90-4.30 (2H, m), 4.35-4.75 (6H, m, C*H*$_2$Ph), 4.90-5.05 (1H, brd, NH), 5.50 (1H, brt, H-4), 6.00-6.20 (1H, brs), 7.10-7.60 (18H, m, Ph), 7.80-8.03 (2H, m, Ph). ^{13}C NMR δ 42.2 (C-5 of minor isomer), 44.4 (C-5 of major isomer), 52.0 (O*Me*), 58.4 (C-2), 63.3, 67.9, 68.1, 68.3, 71.6, 71.8, 73.3, 76.4, 78.6, 84.2, 85.7, 127.5, 127.6, 127.7, 128.2, 128.4, 128.5, 128.6, 129.6, 129.8, 133.0, 137.5, 137.9, 156.4, 165.6, 165.8.

Anal. Calcd for $C_{36}H_{38}O_7N_2 \cdot 0.5H_2O$: C, 69.77; H, 6.34, N, 4.52. Found: C, 69.60; H, 6.15; N, 4.48.

Isopropylidenation of the cyclopentane derivative 15. To a stirred solution of **15** (29 mg, 0.05 mmol) in acetone-dichloromethane-isopropenyl methyl ether (4:2:1 v/v/v, 0.35 mL) was added a catalytic amount of *d*-camphorsulfonic acid at 0 °C and then the mixture was stirred under ice-bath cooling for 6 h. After adding satd $NaHCO_3$ solution, the resulting mixture was directly concentrated *in vacuo*, and diluted with chloroform. The chloroform suspension was washed with dil NaOH solution, water, brine and dried ($MgSO_4$), and then concentrated *in vacuo*. The residue was purified by preparative TLC (hexane-ethyl acetate, 4:1 v/v) to give **3** (25 mg, 81%): $[\alpha]_D^{23}$ +31° (*c* 0.10, $CHCl_3$); ν_{max} (film) 1714, 1271 cm^{-1}; ^1H NMR (DMSO-d_6, 80 °C) δ 1.33, 1.66 (3H×2, each s, acetonide), 2.64 (1H, m, H-5), 3.58 (2H, brd, H-6), 3.61 (3H, s, OMe), 3.69 (1H, brd, $J_{1,2}$ = 7.6 Hz, H-1), 4.17 (1H, dd, $J_{2,3}$ = 4.6 Hz, $J_{3,4}$ = 4.3 Hz, H-3), 4.23 (1H, dd, H-2), 4.51 (2H, brs, C*H*$_2$Ph), 4.60 (1H, d, J = 12 Hz, C*H*HPh), 4.64 (1H, d, J = 12 Hz, C*H*HPh), 4.82 (1H, d, J = 11 Hz, C*H*HPh), 4.86 (1H, d, J = 12 Hz, C*H*HPh), 5.37 (1H, dd, $J_{4,5}$ = 3.7 Hz, H-4), 7.27-7.37 (15H, m, Ph), 7.55 (2H, t, J = 8.0 Hz, Ph), 7.67 (1H, t, J = 8.0 Hz, Ph), 7.99 (2H, m, Ph).

Anal. Calcd for $C_{39}H_{42}O_7N_2$: C, 71.98; H, 6.51, N, 4.30. Found: C, 71.93; H, 6.54; N, 4.23.

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