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NOTES

Synthesis of 1,6-Anhydro-4-*O*-benzyl-2-deoxy-3-*O*-*p*-methoxybenzoyl-2-phthalimido-β-D-glucopyranose and Its Oligomer

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Regioselectively substituted polysaccharides such as glycosaminoglycans show important biological activities.[1-3] The relationship between the chemical structure of bioactive polysaccharides and the biological activity has been reported in detail. For the function such as biological activity and for the chemical modification of polysaccharides, a lot of regioselectively substituted (1→6)-linked polysaccharides had been synthesized.

Glucosamine residues in oligosaccharide or polysaccharide play important roles *in vivo*. Since amino group is not suitable for the cationic polymerization, phthalimido[4] or azido[5] group is used as a precursor of the amino group in the monomer. The polymerization of 1,6-anhydro-3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-glucopyranose with phosphorus pentafluoride-benzoyl fluoride complex as initiator at low temperature gave a highly stereoregular (1→6)-α-D-glucopyranan derivative with high molecular weight, though the polymerization of 1,6-anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose and 1,6-anhydro-4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose provided only oligomers. Reduction of 3-azido-3-deoxy-(1→6)-α-D-glucopyranan derivative with lithium aluminum hydride gave amino-group containing *O*-benzylated (1→6)-α-D-glucopyranan which was then debenzylated with sodium in liquid ammonia to give 3-amiono-3-deoxy-(1→6)-α-D-glucopyranan.[5] On the other hand, we reported the synthesis of 2-acetamide-2-deoxy-(1→6)-β-D-glucopyranan by the cationic ring-opening polymerization of 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranose.[4] In this report, the author aimed at the design and synthesis of a new glucosamine compound with two kinds of protective groups at regioselective position.

EXPERIMENTAL

General Methods

200-MHz ^{1}H NMR spectra were recorded on a VARIAN EX-200 spectrometer in $CDCl_3$ using tetramethylsilane as internal reference. Gel-permeation chromatography was carried out on 1% solutions of the polymer in tetrahydrofuran with a Shimadzu liquid chromatograph (model LC-9A, columns: GPC-802, 803, and 804).

1,6-Anhydro-2,3-O-(S)-p-methoxybenzylidene-β-D-mannopyranose

1,6-Anhydro-β-D-mannopyranose (3 g, 18.5 mmol) and *p*-anisaldehyde dimethyl acetal (20.2 g, 111 mmol) were dissolved in 50 ml of dimethylformamide. After adding *p*-toluenesulfonic acid (3.18 g, 1.85 mmol), the reaction mixture was stirred at 50°C for 30 min. The reaction mixture was diluted with chloroform and neutralized with aqueous $NaHCO_3$. The chloroform layer was washed with water, dried on anhydrous sodium sulfate, and evaporated. 1,6-Anhydro-2,3-*O*-(*S*)-*p*-methoxybenzylidene-β-D-mannopyranose was purified by column chromatography of silica gel followed by crystallization. Yield 2.70 g (52.1%).

1,6-Anhydro-4-O-benzyl-2,3-O-(S)-p-methoxybenzylidene-β-D-mannopyranose

1,6-Anhydro-2,3-*O*-(*S*)-*p*-methoxybenzylidene-β-D-mannopyranose (2.67 g, 9.54 mmol) was dissolved in a suspension of sodium hydride (0.915 g, 20.8 mmol) in dimethylformamide (100 ml) at room temperature over a period of 5 h. After 1 h, benzyl chloride (2.16 ml, 19.1 mmol) in dimethylformamide (10 ml) was added to the mixture. The reaction mixture was stirred for 16 h, and quenched by adding methanol. The residue was extracted with chloroform, and the chloroform layer was repeatedly washed with water. Crystallization of 1,6-anhydro-4-*O*-benzyl-2,3-*O*-(*S*)-*p*-methoxybenzylidene-β-D-mannopyranose was achieved from a solution of ether. Yield 3.30 g (93.5%).

1,6-Anhydro-4-O-benzyl-3-O-p-methoxybenzoyl-β-D-mannopyranose

Into a solution of 1,6-anhydro-4-*O*-benzyl-2,3-*O*-(*S*)-*p*-methoxybenzylidene-β-D-mannopyranose (1.8 g, 4.86 mmol) in dichloromethane (20 ml), 2 ml of water was poured, under an atmosphere of nitrogen. After adding 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ, 1.54 g, 6.80 mmol), the reaction mixture was vigorously stirred at room temperature for 20 h. The residue was neutralized by aqueous $NaHCO_3$ and the organic layer was washed with water, dried on sodium sulfate, and evaporated. Compound 1,6-anhydro-4-*O*-benzyl-3-*O*-*p*-methoxybenzoyl-β-D-mannopyranose was obtaind as colorless syrup. Yield 1.72 g (91.7%).

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1,6-Anhydro-4-O-benzyl-2-deoxy-3-O-p-methoxybenzoyl-2-phthalimido-β-D-glucopyranose (**1**)

To a cooled (−10°C) dichloromethane (5 ml) solution of 1,6-anhydro-4-*O*-benzyl-3-*O*-*p*-methoxybenzoyl-β-D-mannopyranose (1.55 g, 4.02 mmol), trifluoromethanesulfonic anhydride (1.5 ml) and pyridine (1.5 ml) in dichloromethane (20 ml) were added under a nitrogen atmosphere. After raising the temperature to 0°C, the reaction mixture was stirred for 2 h. The chloroform solution of the product was washed with water. After concentration of the organic layer, a crude syrup was obtained. The syrup was dissolved in dimethylformamide (10 ml). After adding potassium phthalimide (5.0 g), the reaction mixture was vigorously stirred. After 2 days, the mixture was diluted with chloroform and filtered. The filtrate was washed with water and chromatographed on silica-gel (benzene : ethyl acetate = 2 : 3). Compound **1** was crystallized from diethyl ether (several times). Yield 512 mg (26.2%). ^{1}H NMR: 3.45 (dd, 1H, H-4, $J_{3,4}$ = 6.02 Hz), 3.72 (s, 4H, H-6 and –Ph–OCH_3), 4.26 (d, 1H, H-2, $J_{2,3}$ = 9.44 Hz), 4.68 (dd, 2H, J_{gem} = 12.45 Hz, $-CH_2Ph$), 4.78 (m, 1H, H-5), 5.67 (s, 1H, H-1), 5.85 (dd, 1H, H-3), 6.85, 7.24, 7.70 and 7.78 (m, 14H, aromatic protons).

Polymerization of **1**

Ring-opening polymerization of **1** was carried out with phosphorus pentafluoride as an initiator as described previously.[4]

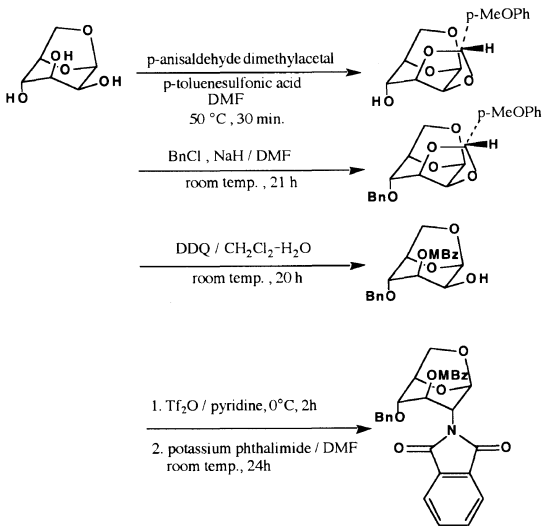
RESULTS AND DISCUSSION

1,6-Anhydro-4-O-benzyl-2-deoxy-3-O-p-methoxybenzoyl-2-phthalimido-β-D-glucopyranose (**1**)

1,6-Anhydro-4-*O*-benzyl-2-deoxy-3-*O*-*p*-methoxybenzoyl-2-phthalimido-β-D-glucopyranose was synthesized from 1,6-anhydro-β-D-mannopyranose[6] by 5 steps as shown in Scheme 1. 1,6-Anhydro-4-*O*-benzyl-2,3-*O*-(*S*)-*p*-methoxybenzylidene-β-D-mannopyranose was prepared by introducing *p*-methoxybenzylidene group into the *cis* hydroxyl groups at C-2 and C-3 of 1,6-anhydro-β-D-mannopyranose followed by benzylation of 4-OH. ^{1}H–^{1}H Nuclear Overhauser effect (NOE) experiment of *p*-methoxybenzylidene product was carried out in order to confirm the configuration of *p*-methoxybenzylidene group. The large NOE from the acetal proton of *p*-methoxybenzylidene group to H-2 and H-3 protons was observed, suggesting that the acetal proton was exo-binding against the pyranose-ring. Consequently, it was concluded that the configuration of *p*-methoxybenzylidene was endo-type. Oxidation of the (*S*)-*p*-methoxybenzylidene derivative with DDQ selectively yielded 1,6-anhydro-4-*O*-benzyl-3-*O*-*p*-methoxybenzoyl-β-D-mannopyranose. In this oxidation reaction, the acetal carbon of methoxybenzylidene group was oxidized by the oxygen atom of water, and consequent addition of hydrogen atom to acetal oxygen yielded methoxybenzoylester. The selectivity of acetal bond cleavage may be influenced by reaction conditions. For example, the reduction of 1,6-anhydro-4-*O*-benzyl-2,3-*O*-benzylidene-β-D-mannopyranose with lithium aluminum hydride and aluminum chloride selectively cleaves the acetal bond at C-3, giving 1,6-anhydro-3,4-di-*O*-benzyl-β-D-mannopyranose.[4] In the present case, acetal bond at C-2 was selectively cleaved. Trifluoromethanesulfonylation of 1,6-anhydro-4-*O*-benzyl-3-*O*-*p*-methoxybenzoyl-β-D-mannopyranose gave 1,6-anhydro-4-*O*-benzyl-3-*O*-*p*-methoxybenzoyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose. S_N2 substitution reaction of 1,6-anhydro-4-*O*-benzyl-3-*O*-*p*-methoxybenzoyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose with potassium phthalimide gave 1,6-anhydro-4-*O*-benzyl-2-deoxy-3-*O*-*p*-methoxybenzoyl-2-phthalimido-β-D-glucopyranose (**1**). The S_N2 substitution reaction hardly occurs at equatorial position. Therefore, in order to synthesize glucosamine derivatives by S_N2 substitution reaction, the conformational change from C1 to 1C by forming anhydro ring. In 1C conformation, nucleophilic S_N2 substitution reaction occurs at axial position to give glucosamine derivatives.

Oligomerization

Cationic ring-opening polymerization of **1** with phosphorus pentafluoride as an initiator gave oligosaccharide derivatives, which is confirmed by GPC, consisting of 4-*O*-benzyl-2-deoxy-3-*O*-*p*-methoxybenzoyl-2-phthal-



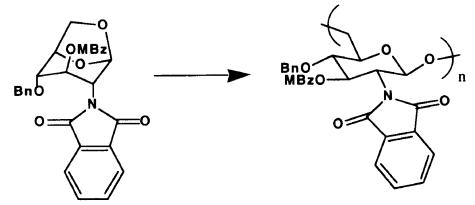
Scheme 1.

Table I. Ring-opening oligomerization of 1,6-anhydro-4-*O*-benzyl-2-deoxy-3-*O*-*p*-methoxybenzoyl-2-phthalimido-β-D-glucopyranose (**1**)[a]

No.	Solvent / ml	Initiator / mol%	Temp / °C	Time / h	Yield / %	Main product[b]
1	2.0	10	0	48	11	trimer
2	1.0	30	0	48	47	trimer

[a] Monomer, 100 mg; solvent, dichloromethane; initiator PF_5. [b] Determined by GPC (polystyrene standard).

imido-D-glucopyranose. The results are shown in Table I. ^{1}H NMR spectrum of the oligomer showed that the coupling constant between H-1 and H-2 was $J_{1,2}=8.27$ Hz. The large $J_{1,2}$ value means that the configuration between H-1 and H-2 protons is *anti*. Thus, it was concluded that the oligomer was (1→6)-β linked 4-*O*-benzyl-2-deoxy-3-*O*-*p*-methoxybenzoyl-2-phthalimido-D-glucopyranan. The previous report[4] showed that the reaction of 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranose with its derived cation (propagating chain end) was restricted by steric hindrance. Therefore, the reaction of **1** with its derived cation may be also restricted by steric hindrane. Moreover, carbonyl groups of **1** may complex with Lewis acids to decrease the polymerizability.[7]



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