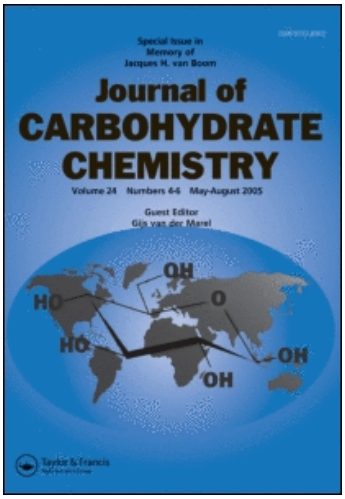

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Itsuo Fujimaki[a]; Hiroyoshi Kuzuhara[a]
[a] The Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan

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SYNTHESIS OF POTENTIAL ANTIMICROBIAL AGENTS FROM MALTOSE. III. INTRODUCTION OF AN AMINO GROUP INTO THE 3'-POSITION OF 1,6-ANHYDRO-DISACCHARIDES

Itsuo Fujimaki and Hiroyoshi Kuzuhara*

The Institute of Physical and Chemical Research
Wako-shi, Saitama 351, Japan

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ABSTRACT

Regioselective cleavage of 1,6-anhydro-maltose (1) with periodate and the subsequent recyclization with nitromethane gave 1,6-anhydro-3'-deoxy-3'-nitro-disaccharides (3). Three diastereomers, prepared by benzylidenation of 3, were separated by column chromatography. Each of 4',6'-O-benzylidene derivatives successively underwent debenzylidenation, reduction of the nitro group, and peracetylation to give 3'-acetamido-3'-deoxy-disaccharide derivatives (7, 8, and 9). The configurations of the 3-amino sugar moieties in 7 (D-gluco), 8 (D-manno) and 9 (D-galacto) were determined on the basis of the ^{1}H NMR data. The main product (7) was further modified to the 6-deoxy-6-nitro derivative.

INTRODUCTION

In a series of studies on the chemical conversion of maltose into the aminated α-linked pseudodisaccharides as potential antibacterial agents, we have developed a couple of procedures for transformation of the reducing monosaccharide constituent of maltose

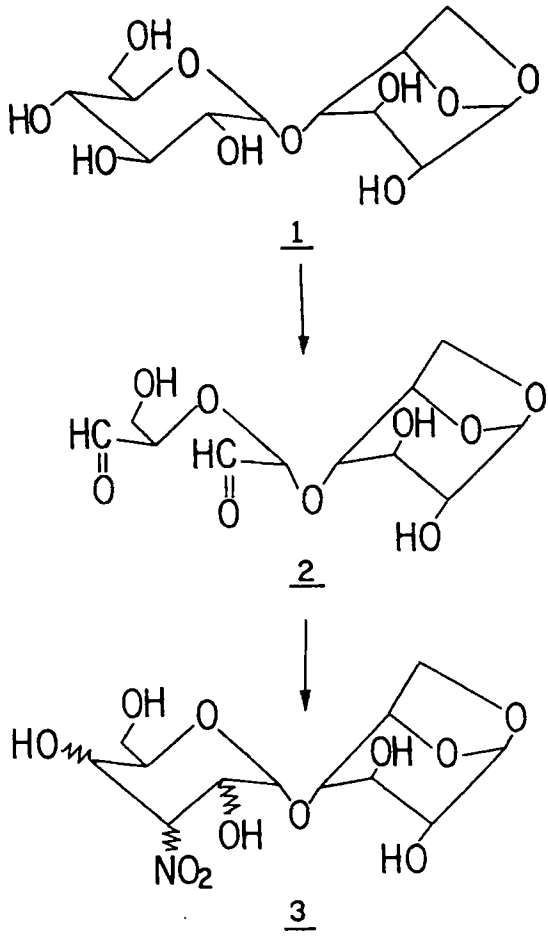
into several aminocyclitols,[1,2] employing 1,6-anhydro-maltose 1[3] as a key intermediate. All pseudodisaccharides so far obtained through these procedures kept the nonreducing α-D-glucopyranosyl moiety derived from maltose as a common constituent. Our attention was next directed towards the chemical modification of the α-D-glucopyranosyl moiety in 1 in order to get a new key intermediate for preparation of more functionalized pseudodisaccharides.

This paper deals with the preparation of three diastereomers of 3'-amino-1,6-anhydro-3'-deoxy-disaccharides from 1,6-anhydro-maltose (1) and some preliminary modification of one of the products for further transformation into the corresponding pseudodisaccharides.

RESULTS AND DISCUSSION

When 1,6-anhydro-maltose (1)[3] was treated with two equimolar amounts of periodate, only one monosaccharide moiety of $^4C_1$(D) conformation was oxidatively cleaved to give the dialdehyde (2). Without purification, 2 was soon recyclized through condensation with nitromethane in ethanol in the presence of sodium methylate as the catalyst. The yield of the resulting 1,6-anhydro-4-O-(3-deoxy-3-nitro-α-D-hexopyranosyl)-β-D-glucopyranose (3) was almost quantitative on the basis of 1. Attempts to separate each of the diastereoisomeric forms of 3 failed. However, benzylidenation of 3 revealed three separable O-benzylidene derivatives on a thin-layer chromatogram. In fact, each of the components (4, 5, and 6) was separated by column chromatography, in the approximate ratio of 45:9:13. Then 4, 5 and 6 were each subjected to benzylidene group removal with aqueous acetic acid, catalytic reduction of the nitro group with Raney Ni, and peracetylation

SCHEME 1



with acetic anhydride and pyridine. The structures of the resulting products, 7, 8, and 9, were elucidated on the basis of their ^{1}H NMR spectra, amenable to first-order analysis at 270 or 400 MHz. Those data are presented in Table I. The values of $J_{2',3'}$ and $J_{3',4'}$ from these compounds indicated that 7 had a 3-amino-3-deoxy-α-D-glucopyranosyl component, 8 a

SCHEME 2

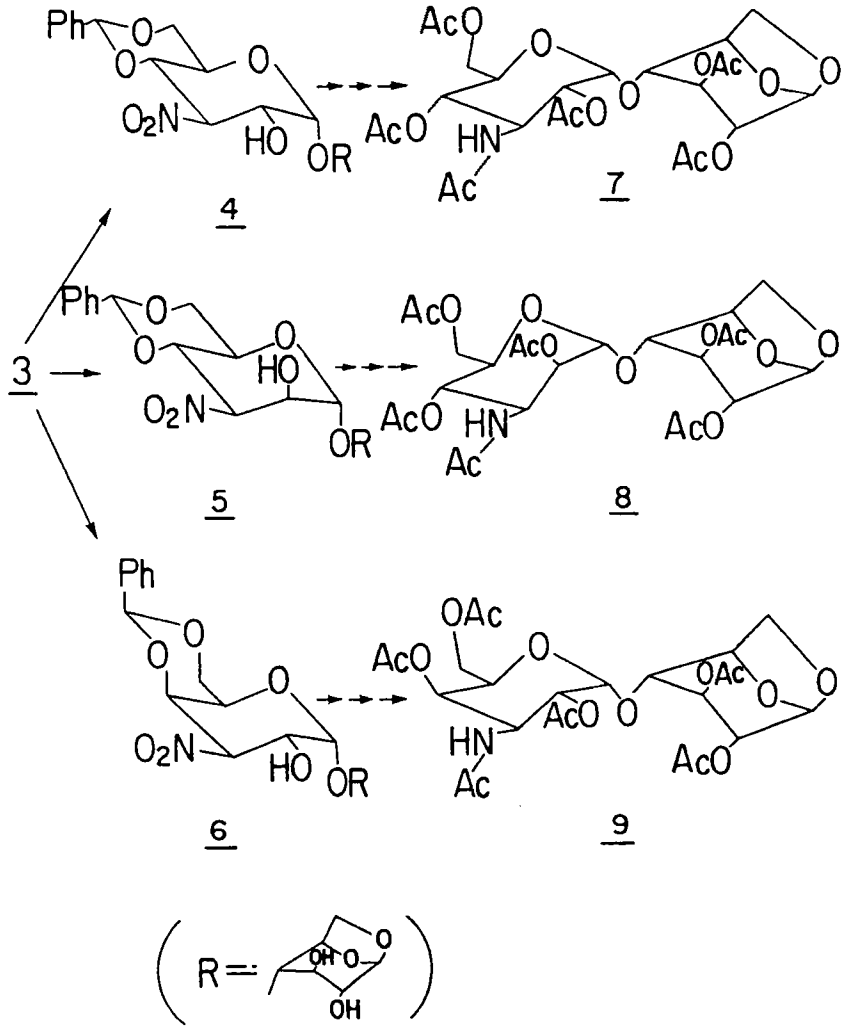


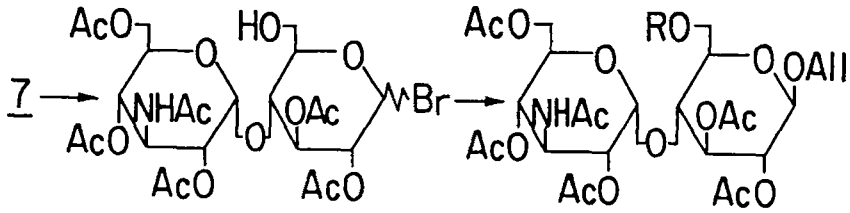
TABLE I

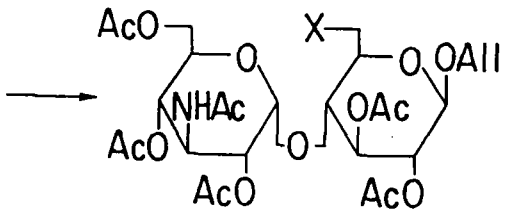
^{1}H NMR Spectral Data for Compounds 7-9

	7[a]	8[b]	9[b]
NH	6.96 (d, $J_{NH,3'}$=10 Hz)	7.09 (d, $J_{NH,3'}$=9.8 Hz)	7.28 (d, $J_{NH,3'}$=8.3 Hz)
H-1	5.44 (s)	5.42 (s)	5.41 (s)
H-1'	5.25 (d, $J_{1',2'}$=3.5 Hz)	5.14 (broad s)	5.28 (d, $J_{1',2'}$=3.4 Hz)
H-2'	—— (overlapped)	4.96 (q, $J_{1',2'}$=1.4 Hz $J_{2',3'}$=3.4 Hz)	4.92 (q, $J_{1',2'}$=3.4 Hz $J_{2',3'}$=11.7 Hz)
H-3'	4.64 (q, $J_{2',3'}$=10 Hz $J_{3',4'}$=10 Hz $J_{3',NH}$=10 Hz)	4.76 (hex, $J_{NH,3'}$=10 Hz $J_{3',4'}$=10 Hz $J_{2',2'}$=3.4 Hz)	4.72 (oct. $J_{2',3'}$=11.7 Hz $J_{3',4'}$=2.8 Hz $J_{3',NH}$=8.3 Hz)
H-4'	4.96 (t, $J_{3',4'}$=10 Hz $J_{4',5'}$=10 Hz)	5.05 (t, $J_{3',4'}$=10 Hz $J_{4,5'}$=10 Hz)	5.40 (broad d, $J_{3',4'}$=2.8 Hz $J_{4',5'}$=0 Hz)
H-5'	4.39 (hex, $J_{4',5'}$=10 Hz $J_{5',6'a}$=3.5 Hz $J_{5',6'b}$=3.5 Hz)	4.35 (oct, $J_{4',5'}$=10 Hz $J_{5',6'a}$=5.0 Hz $J_{5',6'b}$=3.0 Hz)	4.60 (broad t, $J_{4',5'}$=0 Hz $J_{5',6'a,b}$=6.4Hz)

a. Bruker WH-270; in $(CD_3)_2C$=0. b. JEOL JNM-FX 400; in $(CD_3)_2C$=0.

SCHEME 3





3-amino-3-deoxy-α-D-mannopyranosyl component, and 9 a 3-amino-3-deoxy-α-D-galactopyranosyl component. Only 7 crystallized readily.

As preliminary model treatments for the transformation of these new intermediates into the corresponding aminocyclitol glycosides, the main product 7 was further modified according to our previous experiments with the peracetate of 1.[1] Thus, opening of the 1,6-anhydro ring in 7 was performed by treatment with titanium tetrabromide to give the bromide 10, which was soon changed into allyl β-glycoside 11 through the Koenigs-Knorr reaction. After the hydroxyl group

at the 6-position of 11 had been mesylated, the resulting 12 was treated with sodium iodide to give the 6-iodo derivative (13). When 13 was treated with sodium nitrite in the presence of phloroglucinol[4] in a mixture of DMSO and DMF,[5] the iodine atom was substituted with a nitro group to give allyl 2,3-di-O-acetyl-6-deoxy-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-β-D-glucopyranosyl)-6-nitro-β-D-glucopyranoside (14). Further transformation of the nitrosugar moiety into the aminocyclitols also will be performed according to our previous paper.[1]

EXPERIMENTAL

General Procedures. Solutions were evaporated under diminished pressure; solvent extracts were dried with anhydrous sodium sulfate or magnesium sulfate. Column chromatography was performed on Merck silica gel 60 with solvent systems specified. Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 241MC polarimeter. IR spectra were recorded with a Shimadzu IR-27 instrument. ^{1}H NMR spectra were recorded with a Bruker WH-270 or a JEOL JNM-FX 400 spectrometer, for solutions in deuterioacetone containing tetramethylsilane as the internal standard.

A Diastereomeric Mixture of 1,6-Anhydro-4-O-(3-deoxy-3-nitro-α-D-hexopyranosyl)-β-D-glucopyranose (3). To an ice-cooled solution of 1 (14 g) in water (170 mL) was added $NaIO_4$ (19.5 g) in portions. The mixture was stirred for 2 h, adjusted to pH 6 by addition of $NaHCO_3$ (2.3 g), and diluted with ethanol (250 mL). After the precipitate had been filtered off, the filtrate was evaporated to dryness and the residue was extracted with ethanol (150 mL). To the extract cooled in an ice-bath were added nitromethane (10 mL)

and a methanolic solution of sodium methylate (18.3 mL, prepared from 1.05 g of sodium metal and 119 mL of methanol). The mixture was stirred for 1 h, diluted with water (60 mL), neutralized with Dowex 50 (H^+ form, 60 mL), and filtered. The filtrate was evaporated to give 3 (15 g, quantitative yield); ν_{max}^{KBr} 1550, 1370 (NO_2) cm^{-1}.

2,3-Di-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-α-D-glucopyranosyl)-1,6-anhydro-β-D-glucopyranose (7), 2,3-Di-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-α-D-manno-pyranosyl)-1,6-anhydro-β-D-glucopyranose (8), and 2,3-di-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-α-D-galacto-pyranosyl)-1,6-anhydro-β-D-glucopyranose (9). A mixture of 3 (14 g), fused $ZnCl_2$ (14 g), and freshly distilled benzaldehyde (60 mL) was shaken for 20 h in a tightly stoppered flask and poured onto ice-water (300 mL) with vigorous stirring. Separated syrupy product was washed with petroleum ether (200 mL x 6 times), dissolved in methanol (100 mL), and adjusted to weakly basic conditions by addition of Na_2CO_3. After evaporation, the residue was chromatographed using chloroform-methanol (9:1 v/v) as the eluant to give three diastereomers (4, 5, and 6). The order of moving speeds determined from the chromatogram was 5<4<6. Product yields were 0.9 g (5), 4.5 g (4), and 1.3 g (6) respectively. Each of 4, 5, and 6 successively underwent debenzylation, reduction and peracetylation as described for 4. A solution of the main component 4 (300 mg) in 80% aqueous acetic acid (10 mL) was heated for 3 h at 70°C under nitrogen gas and evaporated to dryness. The residue was dissolved in water and the solution was shaken in a hydrogen atmosphere with Raney Ni (W-4) until the absorption of the gas stopped. After filtration, the filtrate

was evaporated to dryness and the residue was acetylated in a mixture of acetic anhydride and pyridine. Usual work-up and agitation in methanol gave crystalline 7, which was recrystallized from ethanol; yield 120 mg (30% from 4); mp. 240-242 °C; $[\alpha]_D^{25}$ +35° (c 1.01, $CHCl_3$); ν_{max}^{KBr} 1740 (OCO), 1670, 1545 (NHCO) cm^{-1}; ^1H NMR data are in Table 1.

Anal. Calc. for $C_{24}H_{33}NO_{15}$: C, 50.09; H, 5.78; N, 2.43. Found: C, 49.96; H, 5.72; N. 2.53.

Compound 5 was treated as described for 4 except for the method for purification of the final product. The peracetylated product was chromatographed using chloroform-ethanol (19:1 v/v) as the eluant to give 8 as an amorphous material in 31% yield from 5; $[\alpha]_D^{20}$ -10° (c 0.11, $CHCl_3$); ν_{max}^{KBr} 1745 (OCO), 1660, 1550 (NHCO) cm^{-1}; ^1H NMR data are in Table 1.

Anal. Calc. for $C_{24}H_{33}NO_5$: C, 50.09; H, 5.78; N, 2.43. Found: C, 50.14; H, 5.66; N, 2.65.

Compound 6 was treated as described for 5, giving 9 as an amorphous material in 30% yield from 6; $[\alpha]_D^{21}$ +49° (c 0.31, $CHCl_3$); ν_{max}^{KBr} 1740 (OCO) 1670, 1540 (NHCO) cm^{-1}; ^1H NMR data are in Table 1.

Anal. Calc. for $C_{24}H_{33}NO_{15}$: C, 50.09; H, 5.78; N, 2.43. Found: C, 49.52; H, 5.71; N, 2.62.

Allyl 2,3-Di-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-α-D-glucopyranosyl)-β-D-glucopyranoside (11). To a solution of $TiBr_4$ (25 g) in ethanol-free chloroform (80 mL) was added in portions a solution of 7 (6 g) in chloroform (40 mL). The mixture was refluxed with stirring for 7 h and poured onto ice-water. The chloroform solution of 10 was separated, and dried (finally by addition of molecular sieve 4A). To the solution were added allyl alcohol (35 mL) and Ag_2CO_3 (5.5 g) and the mixture was stirred for 2 days in the dark at room temperature.

After filtration, the filtrate was evaporated. When the residue was triturated in ethanol, a moderate amount of 7 (1 g), that was formed through an intramolecular glycosidation, was separated as crystals and filtered off for recycling. The filtrate was evaporated and chromatographed using chloroform-ethanol (95:5 v/v) as the eluant to give 11 (1.4 g); $[\alpha]_D^{22}$+36° (c 0.28, $CHCl_3$); ν_{max}^{KBr} 3350-3450 (NH, OH), 1740 (OCO), 1670, 1540 (NHCO), cm^{-1}.

Anal. Calc. for $C_{27}H_{39}NO_{16}$: C, 51.18; H, 6.21; N, 2.21. Found: C, 50.62; H, 6.10, N, 2.23.

Allyl 2,3-Di-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-α-D-glucopyranosyl)-6-deoxy-6-iodo-β-D-glucopyranoside (13). To an ice-cooled solution of 11 (1.9 g) in pyridine (30 mL) was added methanesulfonyl chloride (8 mL) and the resulting mixture was kept for several hours at 0-5 °C. After the usual work-up, the resulting amorphous 12 was dissolved in a solution of sodium iodide (1.95 g) in butan-2-one (25 mL), and the mixture heated under reflux for 13 h. After evaporation, the residue was extracted with chloroform, washed with water, dried, and the solvent evaporated to give crystalline 13, which was recrystallized from ethanol (1.2 g, 55% from 11); mp. 172-173 °C; $[\alpha]_D^{21}$ +28° (c 0.12, $CHCl_3$); ν_{max}^{KBr} 1745 (OCO), 1670, 1535 (NHCO) cm^{-1}.

Anal. Calc. for $C_{27}H_{38}INO_{15}$: C, 43.62; H, 5.15; I, 17.07; N, 1.88. Found: C, 43.56; H, 5.10; I, 17.11; N, 1.86.

Allyl 2,3-Di-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-acetamido-3-deoxy-α-D-glucopyranosyl)-6-deoxy-6-nitro-β-D-glucopyranoside (14). To a solution of 13 (900 mg) in a mixture of DMSO and DMF (4:1 v/v) were added sodium nitrite (400 mg) and phloroglucinol (300 mg). The mixture was stirred for 65 h at room temperature,

diluted with water, and extracted with ether several times. The combined extracts were evaporated and the resulting residue was chromatographed with chloroform-ethanol (95:5 v/v) as the eluant, giving 14 (327 mg, 41%); mp. 197-199 °C; $[\alpha]_D^{21}$ +14° (c 0.14, $CHCl_3$); ν_{max}^{KBr} 1740 (OCO), 1670, 1535 (NHCO), 1560 (NO_2) cm^{-1}.

Anal. Calc. For $C_{27}H_{38}N_2O_{17}$: C, 48.94; H, 5.78; N, 4.23. Found: C, 48.89; H, 5.75; N, 4.03.

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