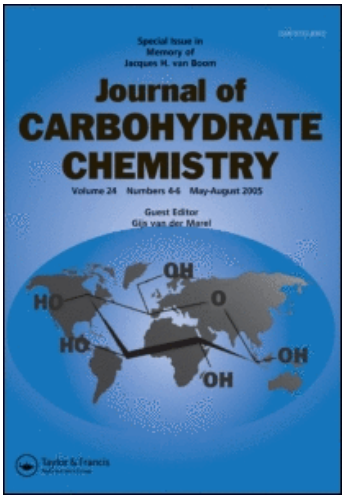

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SYNTHESIS OF RISTRIOSE[1]

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ABSTRACT

A new reducing trisaccharide D-α-D-arabinofuranosyl-(1⟶2)-D-α-D-mannopyranosyl-(1⟶2)-D-D-glucopyranose (11), named ristriose, has been synthesized in twenty one steps, starting from D-glucose, D-mannose and D-arabinose, with an overall yield of 3.5 %.

INTRODUCTION

The antibiotic ristomycin, a member of the vancomycin-group of antibiotics,[3] is a glycopeptide type compound containing a hetero-tetrasaccharide side-chain named ristotetrose.[4,5] Partial acid hydrolysis of the antibiotic followed by acetolysis degraded the tetrasaccharide moiety into two reducing disaccharides and two reducing trisaccharides. One of the disaccharides was identified as rutinose.[6,7] The other three compounds have been isolated for the first time by our research group and are named ristobiose, ristotriose and ristriose,[8] respectively. The structures of ristobiose and ristotriose were elucidated by chemical degradation experiments and confirmed by syntheses.[9]

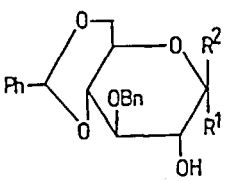
We now report the synthesis of ristriose (11).

RESULTS AND DISCUSSION

Glycosyl acceptors 1 and 2 were prepared[10] from D-glucose and analytical samples obtained by column chromatography. The configuration of the D-glycosidic bonds was proven from the one-bond ^{13}C-^{1}H coupling constants[11] and values of 168.5 Hz and 158 Hz for 1 and 2, respectively. Glycosyl donor 3 was synthesized essentially according to Garegg's procedure,[12] but with some modifications. This product was formed in better yield and purity than previously reported, and used directly for the glycosylation reaction.

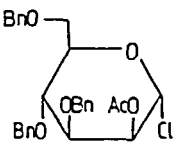
Silver triflate-promoted glycosylation[13] of 1 with 3 afforded the disaccharide derivative 4 in 78 % yield. Zemplén deacetylation of 4 gave 5 in 81 % yield.

Glycosylation of 5 with 2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl bromide[14] under similar conditions as for the synthesis of 4, gave the trisaccharide derivative 6 in an excellent yield of 91 %.



1 R^1 = OCH_2-CH=CH_2; R^2 = H

2 R^1 = H; R^2 = OCH_2-CH=CH_2



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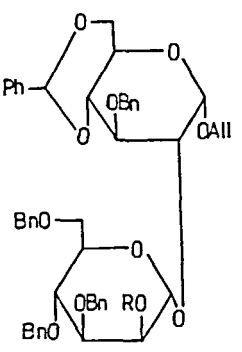
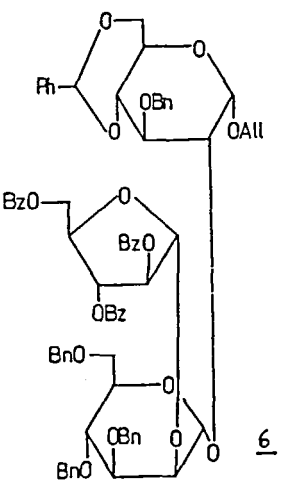


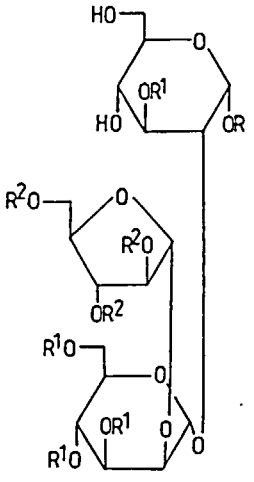
4 R = Ac

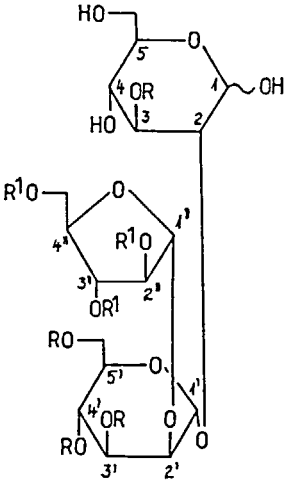
5 R = H



6

By treatment of 6 with trifluoroacetic acid in dichloromethane, the O-benzylidene group was removed and the trisaccharide derivative 7 was obtained in 86 % yield. Isomerisation of the O-allyl group using tris(triphenylphosphine) rhodium(I) chloride[15,16] as the catalyst gave the prop-1-enyl ether derivative 8 which was converted into 9 (85 %) by mercury(II) chloride hydrolysis[17] of the prop-1-enyl group.





7 R = $CH_2CH{=}CH_2$; R^1 = Bn ; R^2 = Bz

8 R = CH=CH-CH_3 ; R^1 = Bn ; R^2 = Bz

9 R = Bn ; R^1 = Bz

10 R = Bn ; R^1 = H

11 R = R^1 = H

The ^{13}C NMR spectrum of 9 contained two C-1 signals at 90.32 and 96.76 ppm for the α- and β-forms, respectively.[15] The other anomeric carbon pairs appeared double as expected (Table I). The estimated α/β ratio is 1:1 based on the ^{13}C NMR spectrum. Zemplén O-debenzoylation of 9 followed by removal of O-benzyl groups (Pd/C) afforded the target compound (11) in a quantitative yield.

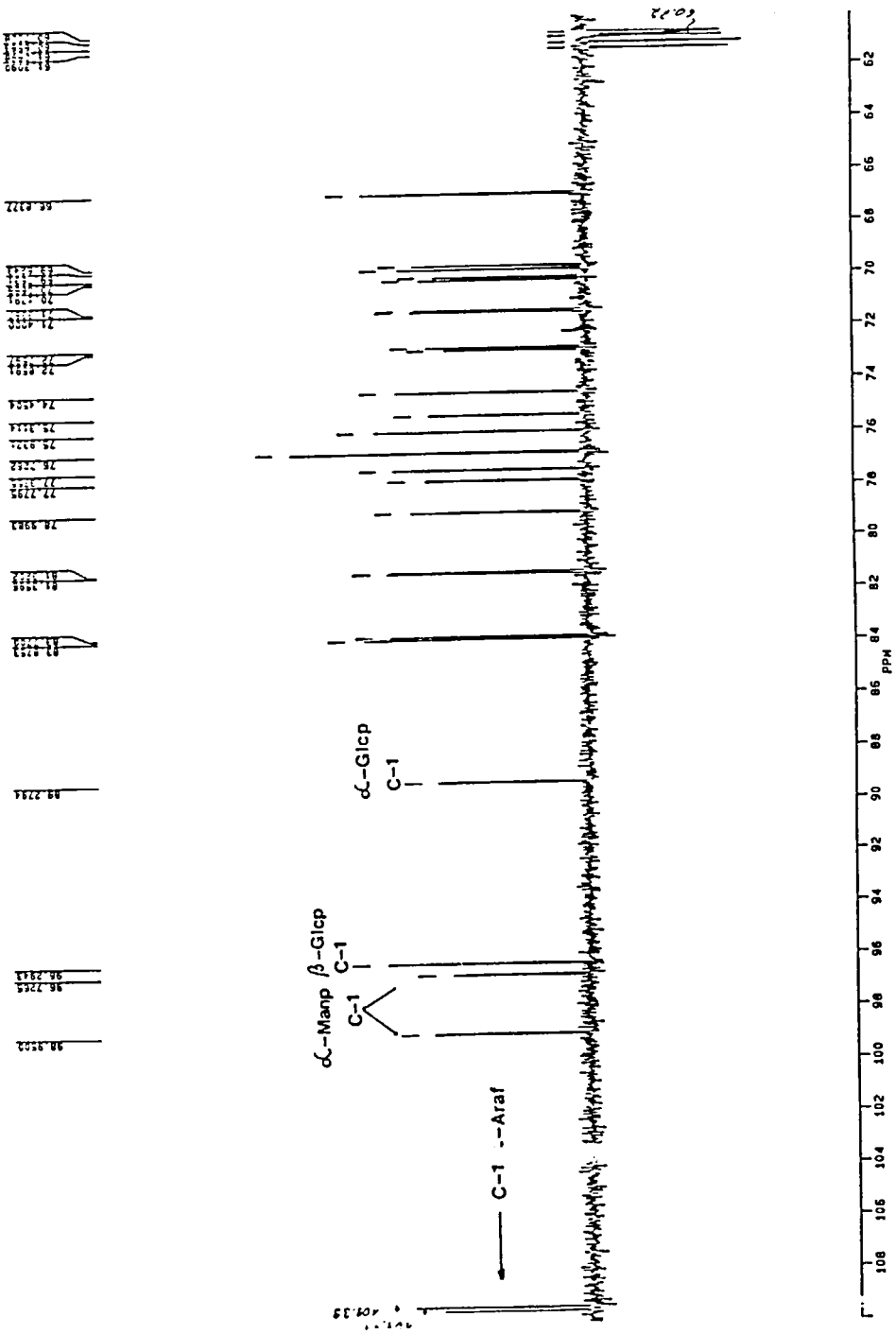


Fig. 1. ^{13}C-NMR I-Modulated Spectrum of 11 (D_2O, r.t)

Table I. ^{13}C NMR Data for the Anomeric Carbons of 9 and Ristriose (11)

Compound		C-1	C-1'	C-1''
9[a]	α	90.32	98.71, 99.54	107.61, 107.91
	β	96.76		
11[b]	α	89.27	96.72, 98.95	109.39, 109.54
			(172.9), (171,3)	(174)
	β	96.29 (162.2)[c]		

a. in CD_3OD (reference solvent signal 49.0 ppm)
b. in D_2O
c. $^1J_{C,H}$ coupling constants (Hz) in parentheses

In the ^1H NMR spectrum of 11 the α- and β-forms were easily recognized because of the two well-separated doublets at 5.41 ppm ($^3J_{1,2}$ = 3.5 Hz) and 4.70 ppm ($^3J_{1,2}$ = 7.5 Hz), respectively. The ^{13}C NMR spectrum of 11 showed six signals for the three anomeric carbons (Fig. 1.). Comparison with literature data,[18] as well as the ^1H-^{13}C shift correlated spectrum enabled us to assign C-1 of the α-anomer (89.27 ppm) and the anomeric carbon of the α-D-arabinofuranosyl unit (109.39, 109.54). At the same time it was difficult to distinguish between the C-1 signal of the β-anomer and one of the signals for C-1' of the α-D-mannopyranosyl unit, appearing in very close proximity (96.29, 96.72; Table I). This problem was solved by measuring one-bond ^{13}C-^1H coupling constants for the anomeric centers. On the basis of the values of $^1J_{C\text{-}1,H\text{-}1}$ = 162.2 Hz for the carbon atom at 96.3 ppm and $^1J_{C\text{-}1,H\text{-}1}$ = 172.9 Hz for the carbon at 96.7 ppm, the former one was assigned as the β-anomer of compound 11. Data from the integration showed that the α/β ratio is ca. 1:1.

EXPERIMENTAL

Optical rotations were measured with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded with a Bruker WP-200 SY spectrometer at 50.3 and 200.13 MHz for ^{13}C and ^{1}H respectively, including 2D correlation measurements. Solutions in organic solvents were dried with sodium sulfate, and evaporations were performed *in vacuo* at 30 °C (bath). TLC were performed on Kieselgel 60 F_{254} (Merck), and Kieselgel G (Reanal, Budapest) was used for short-column chromatography. TLC detection was effected with UV light and/or by charring with sulfuric acid. The purity of syrupy compounds for which elemental analyses were not performed, was carefully ascertained by TLC and NMR.

2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl chloride (3). A solution of 3,4,6-tri-O-benzyl-1,2-O-(methoxyethylidene)-β-D-mannopyranose[12] (200 mg, 0.39 mmol) in HCl-saturated diethyl ether (4 mL) was kept at 0-5 °C for 15 min. The solution was concentrated to a syrup and evaporated three times with dry diethyl ether to afford 3 (200 mg) as a white foam in a quantitative yield: $[\alpha]_D$ +85.4° (c 0.8, chloroform); R_F 0.71 (toluene-ethyl acetate, 3:1); Lit.[12] $[\alpha]_D$ +73°; ^{1}H NMR ($CDCl_3$ + CCl_4) δ 2.15 (s, 3H, $COCH_3$), 4.43-4.87 (6d, 3 x 2H, 3 x $PhCH_2$), 6.03 (d, 1H, H-1, $J_{1,2}$ = 2 Hz), 7.09-7.36 (m, 15H, 3Ph).

Allyl O-(2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (4). A mixture of allyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside[10] (1, 300 mg, 0.75 mmol), 4Å molecular sieves powder (1.0 g) and silver triflate (920 mg, 3.59 mmol) in dry dichloromethane (10 mL) was stirred under argon for 30 min. at room temperature and afterwards cooled to -40 °C. A solution of 3 (750 mg, 1.47 mmol) in dry dichloromethane (5 mL) was added and stirring was continued at -40 °C for 2 h. A solution of pyridine (2 mL) in dichloromethane (4 mL) was added, the mixture slowly attained room temperature and was then diluted with dichloromethane (100 mL),

filtered through Celite, and the solids washed with dichloromethane. The filtrate was washed with 10 % aqueous sodium hydrogen carbonate, water, 10 % sulfuric acid, 10 % aqueous sodium hydrogen carbonate, water, dried and concentrated. Column chromatography of the residue with toluene-ethyl acetate (96:4) gave 4 (513 mg, 78 %): $[\alpha]_D$ +40.0° (c 0.8, chloroform); R_F 0.50 (toluene-ethyl acetate 3:1); ^{1}H NMR ($CDCl_3$ + CCl_4) δ 2.15 (s, 3H, $COCH_3$), 4.95 (d, 1H, H-1, $J_{1,2}$ = 1.5 Hz, D-Manp), 5.01 (d, 1H, H-1, $J_{1,2}$ = 3 Hz, D-Glcp), 5.51 (s, 1H, PhCH=), 5.95 (m, 1H, OCH_2-CH=CH_2), 6.90-7.70 (m, 25H, 5Ph); ^{13}C NMR ($CDCl_3$ + CCl_4) δ 20.99 ($COCH_3$), 68.05 (OCH_2-CH=CH_2), 68.75 (C-6, C-6'), 71.81, 73.08, 75.10, 75.59 (4 x CH_2-benzylic), 94.55 (C-1, D-Manp), 94.94 (C-1, D-Glcp), 101.36 (PhCH=), 118.66 (OCH_2-CH=CH_2), 137.58-138.92 (5 x quaternary arom. carbon), 170.02 ($COCH_3$).

Anal. Calcd for $C_{52}H_{56}O_{12}$: C, 71.55; H, 6.46. Found: C, 71.70; H, 6.48.

Allyl O-(3,4,6-Tri-O-benzyl-α-D-mannopyranosyl)-(1⟶2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (5). To a solution of 4 (300 mg, 0.34 mmol) in dry methanol (25 mL) was added dropwise 0.1 M methanolic sodium methoxide (pH 8) and this mixture was kept at room temperature for 24 h. After neutralization with AG^R 50W-X12 (H^+) resin, the solution was filtered and concentrated. Column chromatography (toluene-ethyl acetate, 8:2) gave 5 (242 mg, 81 %): $[\alpha]_D$ +55.6° (c 0.6, chloroform); R_F 0.47 (chloroform-ethyl acetate, 7:3); ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 1H, OH), 4.30-4.86 (8d, 4 x 2H, 4CH_2Ph), 5.03 (d, 1H, H-1, $J_{1,2}$ = 2 Hz, D-Manp), 5.09 (d, 1H, H-1, $J_{1,2}$ = 3 Hz, D-Glcp), 5.54 (s, 1H, PhCH=), 6.0 (m, 1H, OCH_2-CH=CH_2), 7.0-7.60 (m, 25 H, 5Ph); ^{13}C NMR ($CDCl_3$) δ 95.0 (C-1, D-Glcp), 95.9 (C-1, D-Manp), 101.2 (PhCH=), 118.6 (OCH_2-CH=CH_2), 137.4-138.7 (5 x quaternary arom. carbon).

Anal. Calcd for $C_{50}H_{54}O_{11}$: C, 72.27; H 6.55. Found: C, 72.17; H, 6.58.

Allyl O-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-(1→2)-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (6). A mixture of 5 (124 mg, 0.15 mmol), 4Å molecular sieves powder (0.6 g) and silver triflate (190 mg, 0.74 mmol) in dry dichloromethane (10 mL) was stirred under argon at room temperature for 30 min and then cooled to -40 °C. A solution of 2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl bromide[14] (170 mg, 0.32 mmol) in dry dichloromethane (4 mL) was added and stirring was continued for 2 h at -40 °C. A solution of pyridine (2 mL) in dichloromethane (4 mL) was added, the mixture slowly attained room temperature, and the solids were washed with dichloromethane. The combined filtrate and washings was washed with 10 % aqueous hydrogen carbonate, 10 % sulfuric acid, 10 % aqueous sodium hydrogen carbonate, water, dried and concentrated. Column chromatography of the residue with toluene-ethyl acetate (96:4) gave 6 (174 mg, 91 %): $[\alpha]_D$ +24.8° (c 0.8, chloroform); R_F 0.46 (toluene-ethyl acetate, 9:1); ^{13}C NMR ($CDCl_3$) δ 72.2, 72.6, 75.0, 75.5 (4 x CH_2-benzylic), 94.7 (C-1, D-Glcp), 95.6 (C-1, D-Manp), 101.2 (PhCH=), 106.8 (C-1, D-Araf), 118.5 ($O-CH_2-CH=CH_2$), 125.9 ($OCH_2-CH=CH_2$); ^1H NMR ($CDCl_3$) δ 5.01 (d, 1H, H-1, $J_{1,2}$ = 3 Hz, D-Glcp), 5.10 (d, 1H, H-1, $J_{1,2}$ = 1.7 Hz, D-Manp), 5.64 (s, 1H, H-1, D-Araf).

Anal. Calcd for $C_{76}H_{74}O_{18}$: C, 71.57; H, 5.85. Found: C, 71.42; H, 6.06.

Allyl O-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-(1→2)-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3-O-benzyl-α-D-glucopyranoside (7). To a solution of 6 (165 mg, 0.13 mmol) in dichloromethane (22.5 mL), trifluoroacetic acid containing 3 % of water was added (2.5 mL) and this solution was kept at room temperature for 5 min. Toluene was added (20 mL) and the solution concentrated to one half of its volume. Toluene was added again and the above procedure repeated. After the third addition of toluene, the solution was concentrated and the residue subjected to

column chromatography (toluene-ethyl acetate, 3:1) to afford 7 (132 mg, 86 %): $[\alpha]_D$ +44.3° (c 0.4, chloroform); R_F 0.51 (dichloromethane-methanol, 98:2); ^{13}C NMR ($CDCl_3$) δ 69.1 ($O\underline{C}H_2$-CH=CH_2), 72.1, 72.8, 74.9, 75.8 (4 x $\underline{C}H_2$-benzylic), 94.01 (C-1, D-Glcp), 95.5 (C-1, D-Manp), 106.7 (C-1, D-Araf), 118.3 (OCH_2-CH=$\underline{C}H_2$), 161.1, 165.7, 166.1 (3 x Ph$\underline{C}$O); ^1H NMR ($CDCl_3$) δ 5.04 (d, 1H, H-1, $J_{1,2}$ = 3 Hz, D-Glcp), 5.16 (d, 1H, H-1, $J_{1,2}$ = 1.7 Hz, D-Manp), 5.68 (s, 1H, H-1, D-Araf).

Anal. Calcd for $C_{69}H_{70}O_{18}$: C, 69.80; H, 5.94. Found: C, 69.87; H, 6.12.

O-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-(1 ⟶ 2)-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3-O-benzyl-D-glucopyranose (9). A solution of 7 (98 mg, 0.082 mmol) in ethanol-toluene-water (7:3:1, 5 mL), containing diazobicyclo [2.2.2.]octane (20 mg, 0.18 mmol) and tris(triphenylphosphine)rhodium(I) chloride (20 mg, 0.022 mmol) was boiled under reflux for 1 h. TLC (toluene-ethyl acetate, 2:1, twice developed) showed complete conversion of the allyl ether 7 (R_F 0.34) into the prop-1-enyl ether 8 (R_F 0.44). The mixture was cooled to room temperature and concentrated. The residue was dissolved in acetone (5 mL), mercury(II) oxide added (20 mg), followed by the addition of a solution of mercury(II) chloride (100 mg) in acetone-water (9:1, 1 mL) with vigorous stirring at room temperature. After 30 min, TLC (dichloromethane-methanol, 94:4) showed complete conversion of 8 into 9 (R_F 0.25). The mixture was concentrated, the residue was taken up with dichloromethane (100 mL), the solution was washed with 30 % aqueous potassium bromide (2 x 20 mL), and with water (20 mL), dried and concentrated. Column chromatography of the residue (dichloromethane-methanol; 96:4) gave 9 (80.8 mg, 85.5 %): $[\alpha]_D$ +28.6° (c 0.78, methanol; constant value for 24 h); R_F 0.57 (dichloromethane-methanol, 9:1); ^{13}C NMR data (Table I).

O-α-D-Arabinofuranosyl-(1 ⟶ 2)-O-α-D-mannopyranosyl-(1 ⟶ 2)-O-D-glucopyranose (11). To a solution of 9 (73.4 mg, 0.064 mmol) in dry methanol (25 mL), 0.1 M methanolic sodium

methoxide was dropwise added (up to pH 8) and this mixture was kept at room temperature for 20 h. After neutralization with AG^{R} 50W-X12 (H^+) resin, the solution was filtered and concentrated. The residue was washed with (1:1) mixture of ether-n-hexane (3 x 1 mL). The debenzoylated compound 10 (TLC R_F 0.38, dichloromethane-methanol, 85:15) was obtained as a colourless amorphous substance.

10 % Pd/C (100 mg) in dry methanol was stirred at room temperature under hydrogen atmosphere for 5 h. A solution of 10 (from the above described experiment) in dry methanol (15 mL) was added and stirring was continued at room temperature under hydrogen atmosphere for additional 18 h. The mixture was filtered through Celite, and the solids washed with methanol and water. The solvent was evaporated and water removed by co-evaporation with dry toluene and ethanol. After drying in vacuo (P_2O_5/wax) the pure colourless amorphous trisaccharide 11 ($C_{17}H_{30}O_{15}.2H_2O$) was obtained in a quantitative yield (32 mg); $[\alpha]_D$ +46.0° $\xrightarrow{24\ h}$ 46.6° (c 1.0, water): R_F 0.29 (chloroform-methanol-25 % aqueous NH_4OH, 1:3:1); ^{13}C NMR data (Table I).

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