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Note

A facile synthesis of 2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranosides ☆

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During the preparation of simple mannopyranosides using the Koenigs–Knorr type reaction, we observed that a significant amount of disaccharide glycoside was produced when the alcohol was used in amounts less than equivalent of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide ("acetobromomannose"). The disaccharide product turned out to be almost exclusively of one isomeric structure, i.e., that of α-D-Man-(1→2)-α-D-Man.

Mannose was converted to acetobromomannose according to the method of Kartha and Jennings [1], which proceeded smoothly, and TLC indicated the presence of essentially a single product. Subsequent repeated evaporation with toluene produced a brown syrup, which was used in the glycoside formation without crystallization. Helferich and Zirner [2] reported formation of 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose and -galactopyranose from their respective acetobromo derivatives by a controlled hydrolysis. It appears that in their reactions the acetyl group at the 2-position migrated to the 1-OH. Deferrari et al. [3] extended the procedure to mannose to obtain 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose. In our reactions, however, the 2-*O*-deacetylated derivative must have been generated without the loss of the bromine atom, since we obtained the α-D-Man-(1→2)-α-D-Man disaccharide exclusively as the per-*O*-acetylated glycoside and not as its 1-acetate. Also, in our reaction negligible amounts of trisaccharides or higher saccharides were produced. Therefore, we suspect that partial and specific

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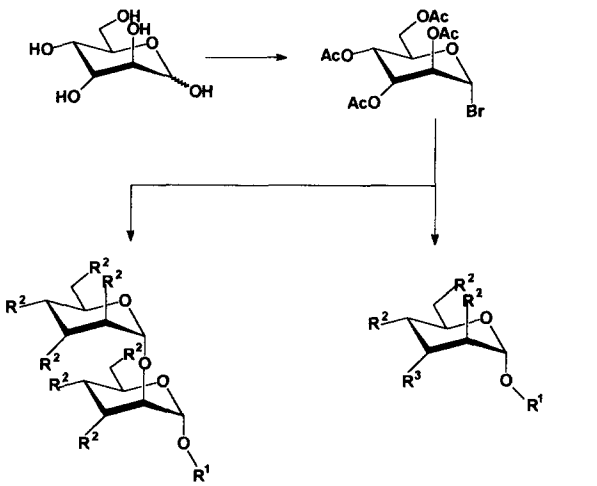

	R^1	R^2		R^1	R^2	R^3
1	$(CH_2)_6NHCOCF_3$	OAc	2	$(CH_2)_6NHCOCF_3$	OAc	OAc
3	$(CH_2)_6NHCOCF_3$	OH	4	$(CH_2)_6NHCOCF_3$	OH	OH
5	$(CH_2)_6NH_2$	OH	6	$(CH_2)_6NH_2$	OH	OH
7	$(CH_2)_3CH=CH_2$	OAc	8	$(CH_2)_3CH=CH_2$	OAc	OAc
			9	$(CH_2)_3CH=CH_2$	OAc	OH

mono-deacetylation occurred during our synthetic operation to yield the 2-*O*-deacetylated mannopyranoside that served as a glycosyl acceptor to form the corresponding glycoside, α-D-Man-(1→2)-α-D-Man.

We exploited this phenomenon and synthesized 6-(trifluoroacetamido)hexyl (TFAAH) and 4-pentenyl glycosides of α-D-Man-(1→2)-α-D-Man without any site-specific protection/deprotection steps. The disaccharide glycoside can be easily separated from the monosaccharide product by gel filtration on a column of Sephadex LH-20. The disaccharide glycoside, which eluted first, was almost totally in the per-*O*-acetylated form, while the monosaccharide fractions contained both per-*O*-acetylated and mono-*O*-deacetylated products. Interestingly, the major isomer of the mono-*O*-deacetylated products lacked an acetyl group at the 3-OH and not at the 2-position. It is likely that the 2-*O*-deacetylated product served almost exclusively and efficiently as the glycosyl acceptor. Some 3-*O*-deacetylated material may also have formed by *O*-acyl migration. In our reaction scheme, disaccharide glycosides were obtained in ~ 20% overall yield based on the amount of alcohol which was present in limiting quantity. This translates to the yield of ~ 40% in terms of mannose, and is quite favorable in comparison with the reported yield of 37% for 2-*O*-α-D-mannopyranosyl-β-D-mannopyranose octaacetate [4], if the desired product is a glycoside of this disaccharide. Moreover, in our reaction a large amount of monosaccharide glycoside is produced simultaneously. The disaccharide

formation presented here makes use of a glycosyl acceptor formed in situ, so that the process is considerably simpler than the traditional method, such as that of Reichert [5], of preparing a proper glycosyl acceptor separately.

1. Experimental

4-Penten-1-ol, acetic anhydride and 30% HBr in acetic acid were purchased from Aldrich Chemical Co. (Milwaukee, WI). Preparation of acetobromomannose [1] and 6-(trifluoroacetamido)hexanol (TFAAHol) [6] has been reported.

TLC was done on Silica Gel-60 F-254 layers on aluminum backing, and silica gel column chromatography was carried out with Silica Gel-60 (packed size of 2.5 × 25 cm) (EM Industries, Inc., Gibbstown, NJ). Solvents used were: (A) toluene–ethyl acetate (1:1, v/v); (B) toluene–ethyl acetate (2:1, v/v); (C) toluene–ethyl acetate (4:1, v/v); (D) ethyl acetate–2-propanol–water (9:4:2, v/v). A Sephadex LH-20 column (5 × 190 cm) was equilibrated and eluted with 95% ethanol, 20-mL fractions being collected.

The phenol–sulfuric acid assay for sugars [7] and the trinitrobenzene sulfonic acid (TNBS) assay for amino groups [7] were by the described method. Elemental analyses were done by Galbraith Laboratories, Inc. (Knoxville, TN), and ^{1}H NMR spectra were recorded using a Bruker AMX 300 spectrometer.

*6-(Trifluoroacetamido)hexyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**1**) *and 6-(trifluoroacetamido)hexyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-mannopyranoside* (**2**).—Syrupy tetra-*O*-acetyl-α-D-mannopyranosyl bromide [1], obtained by repeated coevaporation with toluene, was dissolved in ether and precipitated as syrup by addition of hexanes. After overnight storage in the cold, the supernatant was discarded, and the syrupy residue was briefly dried in an evacuated desiccator. Acetobromomannose thus obtained (from 10 g, 55.5 mmol of D-mannose) was dissolved in 100 mL of toluene–nitromethane (1:1, v/v), and to this solution were added Drierite (5 g), 6-(trifluoroacetamido)hexanol (9.6 g, 45 mmol) and mercury(II) cyanide (12 g, 47.5 mmol). The mixture was stirred overnight at room temperature, filtered, and the filtrate was evaporated. The residue was dissolved in chloroform, undissolved solid was filtered, and the chloroform solution was washed with aqueous M NaCl and M KBr. The chloroform solution was dried (anhyd Na_2SO_4), filtered and evaporated. The syrupy residue was dissolved in 95% ethanol (~ 20 mL) and fractionated on a Sephadex LH-20 column in two batches. The elution profile was similar to that of the 4-pentenyl glycoside preparation shown in Fig. 1. The disaccharide region contained one major compound (**1**) of R_f 0.31 in solvent A, while the monosaccharide region contained two major components of R_f 0.49 (**2**) and 0.27. The fractions of the disaccharide region (fraction numbers 100–109) were combined and evaporated. A fraction containing only **2** (fraction number 114) was evaporated for the purpose of ^{1}H NMR spectral determination. The remaining fractions of monosaccharide region (fraction numbers 111–127) were also combined and evaporated. Overall yield of syrupy **1** was 6.2 g [7.45 mmol, 16.6% based on 6-(trifluoroacetamido)hexanol].

A trial *O*-deacetylation of **1** produced a product (**3**) with R_f 0.43 in solvent D, while the two components of the monosaccharide region both produced the same material of

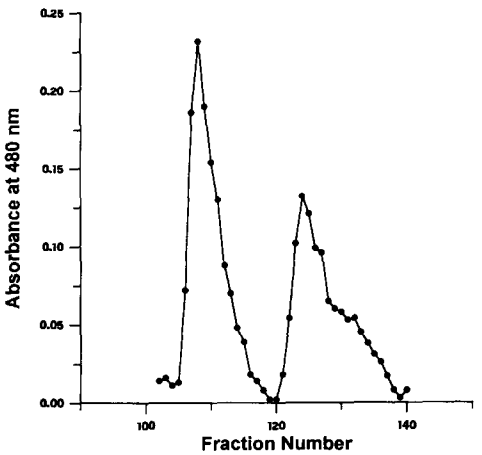

Fig. 1. Elution profile of the 4-pentenyl glycoside mixture on a column of Sephadex LH-20 (5 × 190 cm). The column was eluted with 95% ethanol, and 20-mL fractions were collected. For the phenol–sulfuric acid assay, 10 μL of 20-fold diluted effluent fractions was used.

R_f 0.65, which was 6-(trifluoroacetamido)hexyl α-D-mannopyanoside (**4**). This suggests that the lower R_f material in the monosaccharide region (R_f 0.27 in solvent A) is a partially *O*-deacetylated **2**. The two components in the monosaccharide region were not fractionated, but they were *O*-deacetylated together (see below).

^{1}H NMR of **1** ($CDCl_3$): δ 1.409 (m, 4 H, 2 CH_2); 1.615 (m, 4 H, 2 CH_2); 2.017 (s, 3 H, $COCH_3$); 2.043 (s, 3 H, $COCH_3$); 2.049 (s, 3 H, $COCH_3$); 2.093 (s, 6 H, 2 $COCH_3$); 2.147 (s, 3 H, $COCH_3$); 2.160 (s, 3 H, $COCH_3$); 3.336–3.404 (m, 2 H, CH_2); 3.430–3.482 (m, 1 H, 0.5 CH_2); 3.678–3.751 (m, 1 H, 0.5 CH_2); 3.90–3.94 (m, 1 H, H-5′); 4.009 (t, 1 H, *J* 2.19, 2.19 Hz, H-2); 4.121–4.262 (m, 5 H, H-5, H-6s and H-6′s); 4.924 (s, 2 H, H-1 and H-1′); 5.2688 (dd, 1 H, *J* 3.33, 1.92 Hz, H-2′); 5.299–5.370 (m, 3 H, H-3, H-4 and H-4′); 5.4136 (dd, 1 H, *J* 9.96, 3.36 Hz, H-3′). Decoupling at 4.924 ppm caused both signals at 4.009 and 5.2688 to change to a doublet, indicating that the two mannose residues in **1** are linked α-(1→2). ^{1}H NMR of **2** ($CDCl_3$): δ 1.346 (m, 4 H, 2 CH_2); 1.552 (s, 4 H, 2 CH_2); 1.942 (s, 3 H, $COCH_3$); 1.9914 (s, 3 H, $COCH_3$); 2.046 (s, 3 H, $COCH_3$); 2.102 (s, 3 H, $COCH_3$); 3.2735–3.3407 (m, 2 H, CH_2); 3.3563–3.4293 (m, 1 H, 0.5 CH_2); 3.612–3.6852 (m, 1 H, 0.5 CH_2); 3.8905–3.9378 (8, 1 H, H-5); 4.047 (dd, 1 H, *J* 12.3, 2.48 Hz, H-6b); 4.221 (dd, 1 H, *J* 12.2, 5.21 Hz, H-6a); 4.739 (d, 1 H, *J* 1.58 Hz, H-1); 5.148 (dd, 1 H, *J* 2.49, 1.78 Hz, H-2); 5.209 (t, 1 H, *J* 9.7, 9.6 Hz, H-4); 5.265 (dd, 1 H, *J* 10, 3.31 Hz, H-3). Anal. for **2** Calcd for $C_{34}H_{48}F_3NO_{19} \cdot 0.6H_2O$: C, 48.47; H, 5.89; N, 1.66. Found: C, 48.52; H, 5.90; N, 1.62.

6-(Trifuoroacetamido)hexyl 2-O-(α-D-mannopyranosyl)-α-D-mannopyranoside (**3**) *and 6-(trifluoroacetamido)hexyl α-D-mannopyranoside* (**4**).—A small portion of **1** (~ 100 mg) was dissolved in abs ethanol and coevaporated with toluene. Zemplén *O*-deacetylation with 10 mM NaOMe in dry methanol for 2 h at room temperature, followed by deionization (Dowex 50, H^+ form) and evaporation, produced pure **3** in quantitative yield; TLC (R_f 0.45 in solvent D).

Fractions containing fully and partially acetylated monosaccharide glycosides were combined and *O*-deacetylated in a similar fashion to yield 6.5 g (17.3 mmol, 38.5% overall yield) of syrupy **4**, which corresponded to the standard in the TLC (R_f 0.67 in solvent D). A portion of **4** was crystallized out from ethyl acetate–ether; mp 101–102° C (lit. [8]: 105–106° C).

To confirm further that compound **3** is a disaccharide glycoside, ~ 50 mg each of **3** and **4** was *N*-detrifluoroacetylated by treating them in an aqueous solution containing 10% triethylamine and 10% ethanol at room temperature overnight [9] to yield the corresponding 6-aminohexyl glycosides **5** and **6**. Mannose content and amino content of the two compounds were determined using the phenol–sulfuric acid assay and TNBS assay, respectively [9]. On the basis of amino content, **5** contained 2 mols of mannose per mol, while **6** contained 1 mol per mol. Anal. for **3** Calcd for $C_{20}H_{34}F_3NO_{12}\cdot 1.5H_2O$: C, 42.55; H, 6.61; N, 2.48. Found: C, 42.84; H, 6.65; N, 2.36.

4-Pentenyl 3,4,6-tri-O-*acetyl-2*-O-*(2,3,4,6-tetra*-O-*acetyl-α*-D-*mannopyranosyl)-α*-D-*mannopyranoside* (**7**), *4-pentenyl 2,3,4,6-tetra*-O-*acetyl-α*-D-*mannopyranoside* (**8**) and *4-pentenyl 2,4,6-tri*-O-*acetyl-α*-D-*mannopyranoside* (**9**).—The preparation of 4-pentenyl glycosides was similar to that of **1** and **2**, except for scaling the reaction down by 50% and using 4-penten-1-ol at 0.7 equivalence of mannose. The reaction mixture was processed similarly, and the ethanolic solution was applied to the LH-20 column in one batch. The column fractions were monitored by the phenol–sulfuric acid assay (Fig. 1) and by TLC with solvent A. The first peak (fraction number 106–115) consisted almost exclusively of **7** (R_f 0.35), yielding 2.73 g (3.87 mmol, 19.9% yield) of syrupy product upon evaporation. The second peak was composed of three components which were not totally separated from each other: fractions 122–128 contained **8** (R_f 0.55), fractions 127–133 contained **9** (R_f 0.32) and fractions 131–138 contained an unidentified byproduct (R_f 0.43).

Crude preparations of **7**, **8**, and **9** were further purified by silica gel chromatography: solvent A for **7**, solvent C for **8**, and solvent B for **9**. The TLC monitoring (solvent A) of silica gel chromatography revealed that the crude preparation of **7** contained a small amount of a second component of slightly lower R_f (R_f 0.33) which did not separate from **7** in the silica gel chromatography. The minor component, which was estimated to account for no more than ~ 5% of the total, could be separated from the major component after *O*-deacetylation. NMR examination of per-*O*-acetylated minor component suggests that it has the same inter-mannose linkage as the major component [α-D-Man-(1→2)-D-Man] but with the β-pentenyl aglycon [4.1166 (d, 1 H, 2.73 Hz, H-2); 4.5377 (S, 1 H, H-1); 4.9844 (d, 1 H, 1.83 Hz, H-1′)]. Similarly, crude **9** contained two components (R_f 0.32 and 0.30 in solvent A) which did not separate completely by column chromatography; yield 0.32 g (0.85 mmol). A small portion of the major component (**9**, R_f 0.32) was obtained in a reasonably pure form for NMR examination. The yields of purified glycosides were as follows: **7**, 2.16 g (3.1 mmol, 16% yield); **8**, 1.51 g (3.63 mmol, 18.7% yield). ^{1}H NMR examination indicated **7**, **8**, and **9** to be the compounds as shown in the title.

^{1}H NMR of **7** ($CDCl_3$): δ 1.698–1.744 (m, 2 H, CH_2); 2.0156 (s, 3 H, $COCH_3$); 2.0419 (s, 3 H, $COCH_3$); 2.0478 (s, 3 H, $COCH_3$); 2.0894 (s, 6 H, 2 $COCH_3$); 2.1470 (s, 3 H, $COCH_3$); 2.1603 (s, 3 H, $COCH_3$); 3.414–3.504 (m, 2 H, CH_2); 3.674–3.750

(m, 2 H, CH_2); 3.908–3.934 (m, 1 H, H-5′); 4.0342 (t, 1 H, *J* 1.92, 1.92 Hz, H-2); 4.091–4.262 (m, 5 H, H-5, H-6s, H-6′s); 4.9285 (d, 2 H, *J* 1.62 Hz, H-1 and H-1′); 4.981, 5.0132 and 5.0658 (m, 2 H, $=CH_2$); 5.246–5.334 (m, 4 H, H-3, H-4, H-4′ and H-2′); 5.4179 (dd, 1 H, *J* 9.99, 3.36 Hz, H-3′); 5.733–5.869 (m, 1 H, CH =). Other than signals for aglycon portion, the NMR spectrum of **7** was similar to that of **1**, indicating the linkage between the two mannose residues is also α-(1→2) in **7**. Anal. Calcd for $C_{31}H_{44}O_{18}$: C, 52.84; H, 6.29. Found: C, 52.66; H, 6.33.

^{1}H NMR of **8** ($CDCl_3$): δ 1.67–1.78 (m, 2 H, CH_2); 2.0025 (s, 3 H, $COCH_3$); 2.0522 (s, 3 H, $COCH_3$); 2.1097 (s, 3 H, $COCH_3$); 2.1644 (s, 3 H, $COCH_3$); 3.43–3.505 (m, 2 H, CH_2); 3.667–3.744 (m, 2 H, CH_2); 3.962--4.019 (8, 1 H, H-5); 4.1053 (dd, 1 H, *J* 12.2 and 2.3 Hz, H-6b); 4.2851 (dd, 1 H, *J* 12.2 and 5.34 Hz, H-6a); 4.807 (d, 1 H, *J* 1.59 Hz, H-1); 4.983, 5.0159 and 5.074 (m, 2 H, $=CH_2$); 5.2412 (dd, 1 H, *J* 3.36 and 1.73 Hz, H-2); 5.2933 (d, 1 H, *J* 9.72 Hz, H-4); 5.3572 (dd, 1 H, *J* 9.96 and 3.34 Hz, H-3); 5.742–5.877 (m, 1 H, CH =). Anal. Calcd for $C_{19}H_{28}O_{10}$: C, 54.80; H, 6.78. Found: C, 54.95; H, 6.94.

^{1}H NMR of **9** (D_2O exchanged in $CDCl_3$): δ 1.64–1.73 (m, 2 H, CH_2); 2.099 (s, 3 H, $COCH_3$); 2.131 (s, 3 H, $COCH_3$); 2.170 (s, 3 H, $COCH_3$); 3.430–3.462 (m, 2 H, CH_2); 3.635–3.690 (m, 2 H, CH_2); 3.88–3.96 (8, 1 H, H-5); 4.0747 (dd, 1 H, *J* 9.78 and 3.7 Hz, H-3); 4.1089 (dd, 1 H, *J* 12.1 and 2.28 Hz, H-6b); 4.2854 (dd, 1 H, *J* 12.2 and 5.34 Hz, H-6a); 4.8496 (d, 1 H, *J* 1.56 Hz, H-1); 4.965 (m, 1 H, 0.5 $=CH_2$); 4.999 (m, 1 H, 0.5 $=CH_2$); 5.0514 (m, 1 H, H-2); 5.0514 (t, 1 H, *J* 9.96 and 9.96 Hz, H-4); 5.72–5.87 (m, 1 H, CH =).

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