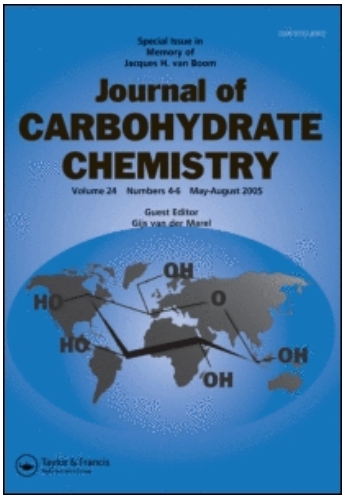

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Synthesis of 4-Octuloses from a Derivative of d-Fructose

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SYNTHESIS OF 4-OCTULOSES FROM A DERIVATIVE OF D-FRUCTOSE

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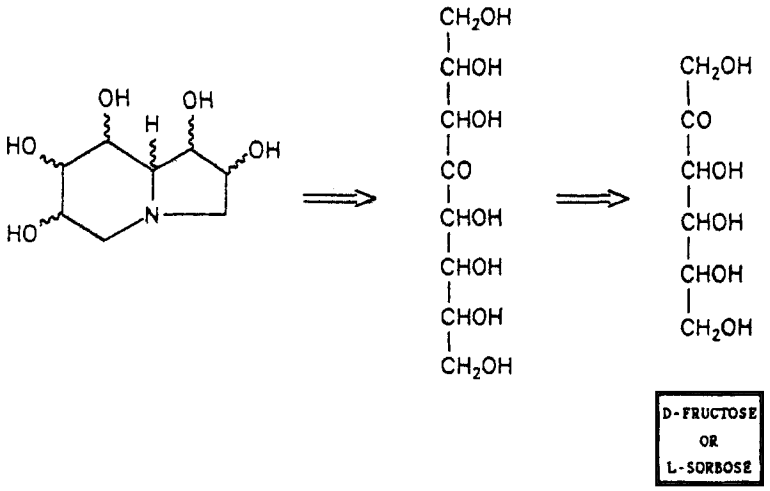
ABSTRACT

Reaction of 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulo-2,6-pyranose (**1**) with (methoxycarbonylmethylene)triphenylphosphorane in either dichloromethane or methanol gave methyl (*E*)-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-oct-2-ene-4-ulo-4,8-pyranosonate (**2**) or a 1:2.3 mixture of **2** and its *Z*-isomer (**3**), respectively. Bishydroxylation of **2** with osmium tetraoxide gave a mixture of methyl 4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*- (**4**) and -D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranosonate (**5**) which were carefully resolved by column chromatography. Compound **4** was transformed into its 2,3-di-*O*-methyl derivative (**6**) which was deacetonated to **7** and subsequently degraded to dimethyl 2,3-di-*O*-methyl-(+)-L-tartrate (**8**). On the other hand, acetonation of a mixture of **4** and **5** gave the corresponding tri-*O*-isopropylidene derivatives (**9**) and (**10**). Compounds **4** and **5** were reduced with $LiAlH_4$ to the related 4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*- (**11**) and -β-D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranose (**12**). Treatment of **11** and **12** with acetone/PTSA/$CuSO_4$ only produced the acetonation at the C-2,3 positions. Finally, compounds **11** and **12** were deacetonated to the corresponding D-*glycero*-D-*galacto*- (**15**) and D-*glycero*-D-*ido*-oct-4-ulose (**16**).

INTRODUCTION

According to Richardson *et al.*[1] retrosynthetic analysis (see Scheme) of polyhydroxyindolizidines (potent inhibitors of different glycosidases[2]), clearly



Scheme

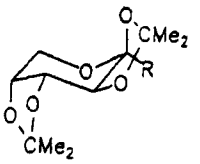
demonstrates that they could be built up from a 4-octulose, which in its turn could be synthesized from a hexulose by extension of the sugar chain by two more carbon atoms at C-1, insertion, in a stereocontrolled manner, of two hydroxy groups in the extended chain and finally, introduction of the amine function required for the formation of the indolizidine skeleton. The readily available hexuloses, such as D-fructose and L-sorbose, can be considered excellent starting chiral templates for the enantioselective synthesis of such inhibitors, the choice depending on the required stereoisomers. We report herein the synthesis of some 4-octulose derivatives from D-fructose and their configurational assignments.

RESULTS AND DISCUSSION

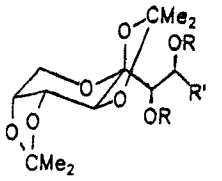
Reaction of aldehyde **1** with (methoxycarbonylmethylene)triphenylphosphorane in dichloromethane and methanol gave mixtures of methyl (*E*)- (**2**) and (*Z*)-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-oct-2-ene-4-ulo-4,8-pyranosonate (**3**) in a 1:traces and a 1:2.3 ratio (GLC analysis), respectively, depending upon reaction conditions employed. The structures of **2** and **3** were established on the basis of their analytical and spectroscopic data, while their configurations at the double bond were

concluded from the observed $J_{2,3}$ values of 15.5 and 12.3 Hz, respectively. The difference in the stereoselectivity found in the reaction of **1** with the above ylide is in accord with previous data,[3] where the yield of the *Z* isomer was improved by the use of a solvent of higher polarity.

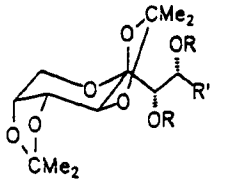
Bishydroxylation of **2** with osmium tetraoxide gave a mixture of methyl 4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*- (**4**) and -D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranosonate (**5**) in a 5.6:1 ratio (GLC evidence) which could be resolved by column chromatography.



1 R = CHO
2 R = (E)-HC=CHCO$_2$Me
3 R = (Z)-HC=CHCO$_2$Me



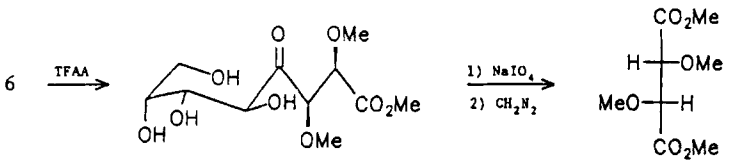
4 R = H; R' = CO$_2$Me
6 R = Me; R' = CO$_2$Me
9 R = >CMe$_2$; R' = CO$_2$Me
11 R = H; R' = CH$_2$OH
13 R = >CMe$_2$; R' = CH$_2$OH



5 R = H; R' = CO$_2$Me
10 R = >CMe$_2$; R' = CO$_2$Me
12 R = H; R' = CH$_2$OH
14 R = >CMe$_2$; R' = CH$_2$OH

The configurations of the osmylation products of an unsaturated compound with an adjacent chiral centre bearing either a hydroxy or alkoxy group, can be predicted by application of the empirical Kishi's rule,[4] which states "that the relative stereochemistry

between the pre-existing hydroxy or alkoxy group at the adjacent chiral centre and the new-introduced hydroxy group, of the major product, is *erythro*", which involves a preferential *anti* approach of OsO_4 to such adjacent groups. In the present case the existence of two α-alkoxy groups at C-4 in **2** would introduce some uncertainty about which of the two faces of the carbon-carbon double bond, in the less compressed conformation of $\mathbf{2}^{5-7}$ (see Fig.) would be preferably attacked according to such a rule. Thus, it was necessary to make a stereochemical correlation between the two new-formed hydroxy groups of the main isomer with a compound of well known alsolute configuration, in our case, dimethyl 2,3-di-*O*-methyl-(+)-L-tartrate (**8**). Thus, compound **4** was transformed into the corresponding 2,3-di-*O*-methyl derivative (**6**) which was hydrolyzed to methyl 2,3-di-*O*-methyl-oct-4-ulosonate (**7**), and subsequently oxidized with $NaIO_4$ to the not isolated methyl 2,3-di-*O*-methyl-(+)-L-tartrate which after treatment with diazomethane gave **8**, indicating 2*R*,3*R* configurations for the two new-formed chiral centres in **4**. Hence the pyranose ring oxygen atom leads the attack of the osmylation reagent.



7 8

A mixture of compounds **4** and **5**, enriched in **4**, was acetonated with acetone/PTSA/$CuSO_4$ affording crystalline methyl 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonate (**9**) and the -D-*glycero*-D-*ido*- isomer (**10**), respectively. On the other hand, compounds **4** and **5**, separately, were reduced with $LiAlH_4$ to the corresponding octulose derivatives (**11**) and (**12**). Attempts to isomerize compounds **11** and **12** by treatment with acetone/PTSA/$CuSO_4$ only gave acetonation products at the 2,3 positions to afford 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose (**13**) and the -D-*glycero*-D-*ido*- isomer (**14**), respectively. The positions of acetonation was confirmed by obtaining the latter products after

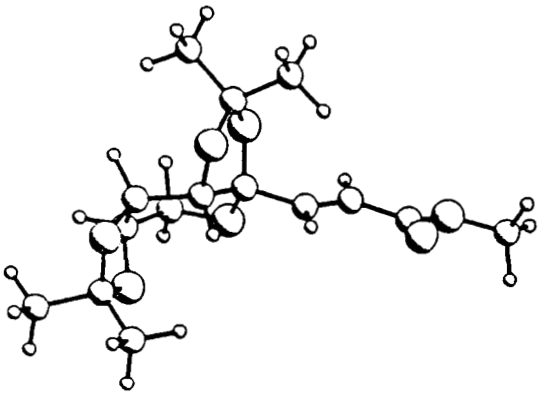
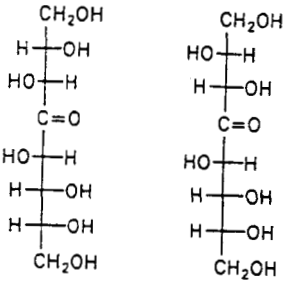


Fig. Less compressed conformation for **2**

reduction into a mixture of esters **9** and **10**. Finally, hydrolysis of **11** and **12** lead to the corresponding D-*glycero*-D-*galacto*- (**15**) and D-*glycero*-D-*ido*-oct-4-ulose (**16**).



15 16

EXPERIMENTAL

General Methods. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Hewlett-Packard HP-5988-A mass spectrometer. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Perkin-Elmer 8410 gas chromatograph equipped with a flame-ionisation detector and a

steel column (2 m x 0.125 in. i.d.) packed with 5% OV-17 on Chromosorb W (100-120 mesh): (*A*) at 200 °C; (*B*) at 230 °C; (*C*) at 160 °C. The He flow rate was 30 mL/min, the injection port and the zone-detector temperatures were (*A*) and (*B*) 280 °C; (*C*) 200 °C. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR and mass spectrometry.

Methyl (*E*)- (2) and (*Z*)-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-oct-2-ene-4-ulo-pyranosonate (3). To a stirred solution of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[8] (13 g, 50 mmol) in dry CH_2Cl_2 (150 mL) were added pyridinium chlorochromate (20 g, 92 mmol) and molecular sieve (4 Å, 20 g). Stirring was continued for 3 h at room temperature. GLC (*A*) showed that the starting material (T_R 4.83 min) had almost disappeared and that aldehyde **1** (T_R 3.08 min) was present. (Methoxycarbonylmethylene)triphenylphosphorane (25 g, 75 mmol) in this solvent (50 mL) was added and the mixture stirred overnight at room temperature. GLC (*A*) then showed the presence of a main product (T_R 7.08 min). The mixture was concentrated and then diluted with ether (300 mL), filtered through silica gel G, and concentrated. Chromatography (1:5 ether-hexane) of the residue gave syrupy **2** (9 g, 57%); $[\alpha]_D^{23}$ +28° (*c* 0.9); ν_{max}^{film} 1730 (C=O, conjugated), 1672 (C=C, conjugated), 1384 and 1374 cm^{-1} (CMe_2). NMR data: ^1H, δ 6.85 (d, 1 H, $J_{2,3}$ 15.5 Hz, H-3), 6.28 (d, 1 H, H-2), 4.58 (dd, 1 H, $J_{6,7}$ 8 Hz, H-6), 4.22 (ddd, 1 H, H-7), 4.18 (d, 1 H, $J_{5,6}$ 2.6 Hz, H-5), 3.88 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 13 Hz, H-8), 3.77 (dd, 1 H, $J_{7,8'}$ 0.8 Hz, H-8'), 3.72 (s, 3 H, OMe), 1.54, 1.46, 1.35, and 1.32 (4 s, 12 H, 2 CMe_2); ^{13}C, δ 166.61 (C-1), 145.77 (C-3), 122.29 (C-2), 109.32 and 108.94 (2 CMe_2), 101.28 (C-4), 73.39 (C-5), 70.43 and 70.12 (C-6,7), 61.36 (C-8), 51.81 (OMe), 26.19, 25.93, 24.87, and 24.24 (2 CMe_2).

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 56.98; H, 7.14.

Reaction of **1** (3.38 g, 13 mmol) in methanol (10 mL) with the same ylide (5 g, 15 mmol) in this solvent (20 mL) for 1 h afforded a mixture of **2** and **3** (T_R 5.98 min) in a 1:2.3 ratio [GLC analysis (*A*)]. Work-up of the reaction as above gave, after column chromatography (1:7 ether-hexane), **2** (1.13 g, 28%) and syrupy **3** (2.5 g, 61%); $[\alpha]_D^{26}$ -

12° (*c* 0.9); ν_{max}^{film} 1740 (C=O, conjugated), 1665 (C=C, conjugated), 1385 and 1374 cm^{-1} (CMe_2). NMR data: ^1H, δ 5.91 (d, 1 H, $J_{2,3}$ 12.3 Hz, H-3), 5.85 (d, 1 H, H-2), 4.59 (dd, 1 H, $J_{5,6}$ 2.6, $J_{6,7}$ 8 Hz, H-6), 4.21 (d, 1 H, H-5), 4.19 (ddd, 1 H, H-7), 3.84 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 13 Hz, H-8), 3.74 (dd, 1 H, $J_{7,8'}$ 0.9 Hz, H-8'), 3.71 (s, 3 H, OMe), 1.49, 1.47, 1.32, and 1.29 (4 s, 12 H, 2 CMe_2); ^{13}C, δ 168.02 (C-1), 134.91 (C-3), 122.16 (C-2), 109.33 and 109.16 (2 *C*Me_2), 100.94 (C-4), 73.70 (C-5), 70.47 and 70.18 (C-6,7), 61.58 (C-8), 51.70 (OMe), 26.33, 25.83, 24.36, and 24.32 (2 C*Me*$_2$).

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.52 ; H, 6.87.

Bishydroxylation of 2. To a stirred solution of **2** (1.2 g, 4 mmol) in acetone (10 mL) was added a solution of potassium chlorate (490 mg, 4 mmol) in water (10 mL) and aqueous 1% osmium tetraoxide (3 mL), and the mixture left at room temperature overnight. GLC (*B*) then revealed the presence of two new products in a 5.6:1 ratio. The mixture was concentrated to a residue that was extracted with ethyl acetate, then concentrated. Cautious column chromatography (2:1 ether-hexane → ether) afforded first, crystalline methyl 4,5:6,7-di-*O*-isopropy-lidene-*β*-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonate (**4**, 815 mg, 59%), (T_R 6.37 min), mp 106-107 °C; $[\alpha]_D^{23}$ -26° (*c* 1); ν_{max}^{KBr} 3509 and 3476 (OH), 1763 and 1745 (C=O), 1387, 1383, and 1373 cm^{-1} (CMe_2). NMR data: ^1H, δ 4.81 (s, 1 H, H-2), 4.63 (dd, 1 H, $J_{5,6}$ 2.7, $J_{6,7}$ 7.9 Hz, H-6), 4.52 (d, 1 H, H-5), 4.24 (dd, 1 H, H-7), 4.08 (s, 1 H, H-3), 3.94 (dd, 1 H, $J_{7,8}$ 1.8, $J_{8,8'}$ 12.9 Hz, H-8), 3.79 (s, 3 H, OMe), 3.80 (d, 1 H, H-8'), 1.55, 1.47, 1.42, and 1.34 (4 s, 12 H, 2 CMe_2); ^{13}C, δ 173.52 (C-1), 109.62 and 109.29 (2 *C*Me_2), 103.27 (C-4), 71.91, 70.83, 70.14, and 69.47 (C-2,3,5,6,7), 61.76 (C-8), 52.79 (OMe), 26.74, 25.68, 25.47, and 24.12 (2 C*Me*$_2$).

Anal. Calcd for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 52.12; H, 7.22.

The product eluted second was crystalline methyl 4,5:6,7-di-*O*-isopropylidene-*β*-D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranosonate (**5**, 165 mg, 12%), (T_R 7.94 min), mp 158-159 °C; $[\alpha]_D^{24}$ -18° (*c* 0.6); ν_{max}^{KBr} 3461 (OH), 1748 (C=O), 1386 and 1377 cm^{-1} (CMe_2). NMR data: ^1H, δ 4.68 (s, 1 H, H-2), 4.58 (dd, 1 H, $J_{5,6}$ 2.4, $J_{6,7}$ 7.8 Hz, H-6), 4.47 (d, 1 H, H-5), 4.23 (dd, 1 H, H-7), 4.03 (s, 1 H, H-3), 3.89 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 13.2 Hz, H-8), 3.80 (bs, 1 H, OH), 3.78 (d, 1 H, H-8'), 3.76 (s, 3 H, OMe), 3.08 (bs, 1 H, OH), 1.52, 1.49, 1.40, and 1.34 (4 s, 12 H, 2 CMe_2); ^{13}C, δ 172.25 (C-1), 109.38

and 108.91 (2 CMe_2), 104.42 (C-4), 74.83, 71.13, 70.60, 70.25, and 70.15 (C-2,3,5,6,7), 61.24 (C-8), 52.51 (OMe), 26.28, 25.62, 25.37, and 23.68 (2 CMe_2).

Anal. Calcd for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 51.60; H, 6.47.

A small quantity (220 mg) of unreacted **2** was also isolated.

Methyl 4,5:6,7-di-*O*-isopropylidene-2,3-di-*O*-methyl-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonate (6). To a stirred solution of NaH (80% oil dispersion) (300 mg, 10 mmol)) in dry Me_2SO (3 mL) and imidazole (50 mg) under Ar, a solution of **4** (520 mg, 1.5 mmol) in dry THF (7 mL) was added dropwise at room temperature for 30 min. Then iodomethane (0.66 mL, 12 mmol) was added and the mixture stirred for 30 min. TLC (ether) then showed a faster-running product, the excess of hydride was destroyed by cautious addition of ether saturated with water and then with water. After separation of the organic phase, the aqueous phase was extracted with ether. The extracts were washed with brine and concentrated. Column chromatography (1:3 ether-hexane) of the residue afforded syrupy **6** (460 mg, 81.5%), $[\alpha]_D^{26}$ +4° (*c* 1.5); ν_{max}^{film} 1751 (C=O), 1384 and 1373 cm^{-1} (CMe_2). NMR data: ^1H, δ 4.59 (dd, 1 H, $J_{5,6}$ 2.7, $J_{6,7}$ 7.8 Hz, H-6), 4.33 (d, 1 H, H-5), 4.18 (bdd, 1 H, H-7), 4.11 (d, 1 H, $J_{2,3}$ 6.4 Hz, H-2), 3.83 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 12.9 Hz, H-8), 3.71 (s, 3 H, CO_2Me), 3.66 (d, 1 H, H-3), 3.60 (bd, 1 H, H-8'), 3.53 and 3.43 (2 s, 6 H, 2 OMe), 1.49, 1.39, and 1.33 (3 s, 12 H, 2 CMe_2); ^{13}C, δ 171.63 (C-1), 109.28 and 109.21 (2 CMe_2), 103.05 (C-4), 82.29 and 80.90 (C-2,3) 71.03, 70.42, and 70.37 (C-5,6,7), 61.56 (C-8), 61.50 and 58.78 (2 OMe), 51.88 (CO_2Me), 26.69, 25.85, 25.56, and 24.38 (2 CMe_2). Mass spectrum (c.i., CH_4): *m/z* 377 (12.6%, M^++1), 361 (12.7, M^+-Me), 319 (21.9, M^++1-Me_2HO), 303 (6.3, M^+-Me-Me_2CHO), 287 (80.8, M^++1-Me_2CO-MeOH), 255 (41.2), 173 (100, M^++1-Me_2CO-MeOH-$C_5H_6O_3$), 155 (46.5), and 71 (34.5).

Dimethyl 2,3-di-*O*-methyl-(+)-L-tartrate [dimethyl (2*R*,3*R*)-2,3-dimethoxysuccinate] (8). Dimethyl (+)-L-tartrate (535 mg, 3 mmol) was methylated with NaH (80% oil dispersion) (330 mg, 11 mmol), imidazole (100 mg), and iodomethane (2 mL, 32 mmol) in dry Me_2SO (3 mL) as above. Work-up of the reaction mixture afforded, after column chromatography (1:2 ether-hexane), pure **8**, T_R 2.93 min (*C*), $[\alpha]_D^{23}$ +71° (*c* 1.3, methanol) [lit.[9] $[\alpha]_D$ +81° (*c* 6.26, methanol); ν_{max}^{film} 1770 and 1735 cm^{-1} (C=O). NMR data: ^1H, δ 4.18 (s, 2 H, H-2,3), 3.76 (s, 6 H, 2 CO_2Me), and 3.41 (s, 6 H, 2 OMe).

Degradation of 6 to 8. A solution of **6** (500 mg, 1.33 mmol) in aqueous 70% trifluoroacetic acid (5 mL) was heated at 40 °C for 10 h. TLC (ether) then revealed a non-mobile compound. The mixture was concentrated and repeatly codistilled with water and the residue chromatographed (10:1 chloroform-methanol) to afford a colourless solid foam (340 mg), presumably methyl 2,3-di-*O*-methyl-D-*glycero*-D-*galacto*-oct-4-ulonosonate (**7**) that was not further characterized but oxidized in water (5 mL) with a solution of $NaIO_4$ (1.12 g, 5.2 mmol) in the same solvent (10 mL). The reaction was monitorized by polarimetry to a constant rotation. The mixture was concentrated and the residue extracted with ethyl acetate. Concentration of the extracts gave a residue that was dissolved in dry methanol (10 mL) and saturated with a stream of CH_2N_2 until a slight yellow colour remained and the mixture left at room temperature for 30 min. GLC (*C*) then revealed a main product with same T_R as that of an authentic sample of **8**. The reaction mixture was concentrated and the residue chromatographed (1:2 ether-hexane) to afford **8** (60 mg) which had $[\alpha]_D^{28}$ +60° (*c* 1.9, methanol) and spectral data were identical to those of an authentic sample.

Methyl 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto* (9) and D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranosonate (10). To a stirred solution of a mixture of **4** and **5** [in a ≈15:1 ratio, GLC (*B*)] (840 mg, 2.41 mmol)] in dry acetone (20 mL), PTSA (100 mg) and anhydrous copper sulfate (1 g) were added at room temperature. The stirring was continued overnight. TLC (ether) then revealed a faster-running product. The mixture was neutralized (K_2CO_3), filtered through a Celite pad, and then concentrated to a crystalline residue. Recrystallization (ether-hexane) yielded pure **9** (510 mg), T_R 12.8 min (*A*), mp 137-139 °C; $[\alpha]_D^{26}$ -26° (*c* 1.1); ν_{max}^{KBr} 1749 (C=O), 1387 and 1371 cm^{-1} (CMe_2). NMR data (400 MHz): ^1H, δ 4.66 (d, 1 H, $J_{2,3}$ 6.7 Hz, H-2), 4.59 (dd, 1 H, $J_{5,6}$ 2.8, $J_{6,7}$ 7.8 Hz, H-6), 4.47 (d, 1 H, H-3), 4.41 (d, 1 H, H-5), 4.19 (dd, 1 H, H-7), 3.85 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 12.9 Hz, H-8), 3.73 (s, 3 H, OMe), 3.67 (d, 1 H, H-8'), 1.52, 1.46, 1.45, 1.40, 1.39 and 1.32 (6 s, 18 H, 3 CMe_2); ^{13}C, δ 171.40 (C-1), 112.06, 109.39 and 109.23 (3 CMe_2), 102.35 (C-4), 79.46 (C-3), 75.81 (C-2), 71.10 (C-7), 70.75 (C-5), 70.27 (C-6), 61.75 (C-8), 52.46 (OMe), 26.60, 26.57, 26.26, 25.79, 27.70, and 24.49 (3 CMe_2).

Anal. Calcd for $C_{18}H_{28}O_9$: C, 55.66; H, 7.27. Found: C, 55.84; H, 7.05.

Column chromatography (1:4 ether-hexane) of the mother liquors gave, first **9** (90 mg), a mixture of **9** and **10** (110 mg), and finally pure **10** (50 mg) as white needles, T_R 13.8 min (*A*), mp 96-98 °C; $[\alpha]_{405}^{27}$ +3° (*c* 1.2); ν_{max}^{KBr} 1752 (C=O) and 1387 cm^{-1} (CMe_2). NMR data (400 MHz): ^1H, δ 4.92 (d, 1 H, $J_{2,3}$ 6.3 Hz, H-2), 4.60 (d, 1H, H-3), 4.51 (dd, 1 H, $J_{5,6}$ 2.1, $J_{6,7}$ 8.0 Hz, H-6), 4.39 (d, 1 H, H-5), 4.19 (dd, 1 H, H-7), 3.87 (dd, 1 H, $J_{7,8}$ 2.0, $J_{8,8'}$ 13.0 Hz, H-8), 3.75 (s, 3 H, OMe), 3.75 (d, 1 H, H-8'), 1.50, 1.49, 1.41, 1.39, and 1.32 (5 s, 18 H, 3 CMe_2); ^{13}C, δ 171.61 (C-1), 111.83, 108.88 and 108.50 (3 CMe_2), 104.11 (C-4), 79.73 (C-3), 75.36 (C-2), 70.37 (C-7), 70.20 (C-5), 70.04 (C-6), 61.04 (C-8), 52.47 (OMe), 26.68, 26.56, 26.25, 25.82, 25.65, and 23.60 (3 CMe_2).

Anal. Calcd for $C_{18}H_{28}O_9$: C, 55.66; H, 7.27. Found: C, 55.49 ; H, 7.01.

4,5:6,7-Di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose (11). To a stirred solution of **4** (348 mg, 1 mmol) in dry THF (10 mL) $LiAlH_4$ (115 mg, 3 mmol) was added portionwise and the mixture left at room temperature overnight. TLC (ethyl acetate) then showed the presence of a slower-running product. The excess of hydride was destroyed by cautious addition of aqueous saturated ammonium chloride solution, filtered, concentrated and the residue extracted with ethyl acetate. Concentration of the extracts gave a residue that was chromatographed to afford **11** (270 mg, 84%) as a colourless syrup, $[\alpha]_D^{24}$ -23° (*c* 1.2); ν_{max}^{film} 3479 (OH), 1384 and 1375 cm^{-1} (CMe_2). NMR data (400 MHz): ^1H, δ 4.58 (dd, 1 H, $J_{5,6}$ 2.7, $J_{6,7}$ 7.8 Hz, H-6), 4.55 (d, 1 H, H-5), 4.26 (bt, 1 H, H-2), 4.20 (dd, 1 H, H-7), 3.87 (dd, 1 H, $J_{7,8}$ 1.8, $J_{8,8'}$ 12.9 Hz, H-8), 3.72 (d, 1 H, H-8'), 3.70 (dd, 1H, $J_{1,2}$ 6.2, $J_{1,1'}$ 11.5 Hz, H-1), 3.65 (dd, 1 H, $J_{1',2}$ 4.7 Hz, H-1'), 3.61 (d, 1 H, $J_{2,3}$ 1 Hz, H-3), 3.05 (s, 3 H, HO-1,2,3), 1.50, 1.41, 1.40, and 1.30 (4 s, 12 H, 2 CMe_2); ^{13}C, δ 109.10 (2 CMe_2), 104.17 (C-4), 71.30 (C-3), 70.78 (C-7), 70.12 (C-5,6), 69.34 (C-2), 64.77 (C-1), 61.39 (C-8), 26.58, 25.78, 25.58, and 23.96 (2 CMe_2).

Anal. Calcd for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55. Found: C, 52.47; H, 7.23.

4,5:6,7-Di-*O*-isopropylidene-β-D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranose (12). Reduction of **5** (348 mg, 1 mmol) in dry THF (10 mL) with $LiAlH_4$ (115 mg, 3 mmol) as above gave **12** (250 mg, 78%) that crystallized on standing, mp 107-109 °C; $[\alpha]_D^{26}$ -19° (*c* 1.1); ν_{max}^{KBr} 3450 (OH), 1384 and 1377 cm^{-1} (CMe_2). NMR data (400 MHz): ^1H,

δ 4.59 (dd, 1 H, $J_{5,6}$ 2.5, $J_{6,7}$ 7.9 Hz, H-6), 4.49 (d, 1 H, H-5), 4.24 (dd, 1 H, H-7), 4.14 (ddd, 1 H, H-2), 3.89 (dd, 1 H, $J_{7,8}$ 2.1, $J_{8,8'}$ 13.2 Hz, H-8), 3.77 (d, 1 H, H-8'), 3.74 (dd, 1 H, $J_{1,2}$ 7.2, $J_{1,1'}$ 11.3 Hz, H-1), 3.65 (dd, 1 H, $J_{1',2}$ 4.5 Hz, H-1'), 3.59 (d, 1 H, $J_{2,3}$ 1.7 Hz, H-3), 2.99 (bs, 3 H, HO-1,2,3), 1.52, 1.51, 1.40, and 1.35 (4 s, 12 H, 2 CMe_2); ^{13}C, δ 109.32 and 108.65 (2 CMe_2), 104.76 (C-4), 73.42 (C-3), 70.73 (C-7), 70.34 (C-5), 70.15 (C-6), 69.65 (C-2), 64.42 (C-1), 60.99 (C-8), 26.35, 25.42, 25.41, and 23.58 (2 CMe_2).

Anal. Calcd for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55. Found: C, 52.14; H, 7.48.

2,3:4,5:6,7-Tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose (13). A stirred solution of **11** (155 mg, 0.48 mmol) in dry acetone (5 mL) was treated with PTSA (50 mg) and anhydrous copper sulfate (500 mg) at room temperature for 2 h. TLC (ether) then revealed the presence of a faster-running compound. Work-up of the reaction mixture as above afforded, after column chromatography (1:1 ether-hexane), **13** (145 mg, 84%), that crystallized on standing, T_R 3.94 min (*B*), mp 90-92 °C; $[\alpha]_D^{26}$ -26° (*c* 2); ν_{max}^{film} 3507 (OH), 1384 and 1373 cm^{-1} (CMe_2). NMR data (400 MHz): ^1H, δ 4.60 (dd, 1 H, $J_{5,6}$ 2.8, $J_{6,7}$ 7.9 Hz, H-6), 4.43 (d, 1 H, H-5), 4.29 (dt, 1 H, H-2), 4.21 (dd, 1 H, H-7), 3.96 (d, 1 H, $J_{2,3}$ 8.3 Hz, H-3), 3.88 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 12.9 Hz, H-8), 3.81 (dd, 1 H, $J_{1,2}$ 4.2, $J_{1,1'}$ 11.6 Hz, H-1), 3.62 (dd, 1 H, $J_{1',2}$ 4.2 Hz, H-1'), 3.70 (d, 1 H, H-8'), 2.10 (bs, 1 H, HO-1), 1.53, 1.45, 1.41, 1.39, and 1.32 (5 s, 18 H, 3 CMe_2); ^{13}C, δ 109.53, 109.29, and 109.26 (3 CMe_2), 102.41 (C-4), 78.21 (C-3), 77.80 (C-2), 71.17 (C-5), 70.98 (C-7), 70.20 (C-6), 63.35 (C-1), 61.60 (C-8), 27.52, 26.79, 26.68, 25.95, 25.77, and 24.29 (3 CMe_2).

Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83. Found: C, 56.24; H, 7.71.

2,3:4,5:6,7-Tri-*O*-isopropylidene-β-D-*glycero*-D-*ido*-oct-4-ulo-4,8-pyranose (14). Compound **12** (140 mg, 0.44 mmol) in dry acetone (5 mL) was treated with PTSA (50 mg) and anhydrous copper sulfate (500 mg) at room temperature for 2 h. Work-up of the reaction mixture as above gave **13** (140 mg, 89%) as a colourless syrup, T_R 4.24 min (*B*), $[\alpha]_D^{27}$ -10° (*c* 0.9); ν_{max}^{film} 3516 (OH), 1384 and 1374 cm^{-1} (CMe_2). NMR data: ^1H, δ 4.50 (dd, 1 H, $J_{5,6}$ 2.0, $J_{6,7}$ 8.0 Hz, H-6), 4.46 (d, 1 H, H-5), 4.42 (bdt, 1 H, H-2), 4.19 (dd, 1 H, H-7), 4.02 (d, 1 H, $J_{2,3}$ 8.5 Hz, H-3), 3.87 (dd, 1 H, $J_{7,8}$ 1.9, $J_{8,8'}$ 13.2 Hz, H-8), 3.80 (dd, 1 H, $J_{1,2}$ 3.7, $J_{1,1'}$ 11.6 Hz, H-1), 3.74 (d, 1 H, H-8'), 3.68

(dd, 1 H, $J_{1',2}$ 4.8 Hz, H-1'), 2.05 (bs, 1 H, HO-1), 1.49, 1.47, 1.43, 1.40, and 1.31 (5 s, 18 H, 3 CMe_2); ^{13}C, δ 109.24, 108.79, and 108.15 (3 CMe_2), 103.99 (C-4), 78.68 (C-3), 77.06 (C-2), 70.29 (C-7), 70.20 (C-5), 70.11 (C-6), 63.43 (C-1), 60.66 (C-8), 27.32, 27.03, 26.51, 25.79, 25.18, and 23.38 (3 CMe_2).

Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83. Found: C, 56.38; H, 8.01.

A small amount (7 mg) of a faster-running crystalline product identified as the 1,2:4,5:6,7-tri-*O*-isopropylidene isomer could be also isolated, mp 95-97 °C; $[\alpha]_D^{26}$ +7.7° (*c* 0.3). NMR data: ^1H, δ 4.59 (dd, 1 H, $J_{5,6}$ 2.5, $J_{6,7}$ 7.9 Hz, H-6), 4.48 (d, 1 H, H-5), 4.39 (bdt, 1 H, H-2), 4.28 (dd, 1 H, H-7), 4.11 (dd, 1 H, $J_{1,2}$ 6, $J_{1,1'}$ 8.8 Hz, H-1), 3.85 (dd, 1 H, $J_{7,8}$ 2.0, $J_{8,8'}$ 13.2 Hz, H-8), 3.79 (dd, 1 H, $J_{1',2}$ 7.7 Hz, H-1'), 3.76 (d, 1 H, H-8'), 3.59 (d, 1 H, $J_{2,3}$ 8.3 Hz, H-3), 2.29 (bs, 1 H, HO-1), 1.55, 1.53, 1.45, 1.41, 1.40, and 1.38 (6 s, 18 H, 3 CMe_2).

Reduction of 9 and 10. A mixture of **9** and **10** (110 mg, 0.28 mmol) was reduced with $LiAlH_4$ (50 mg) in dry THF as usual to give a mixture of **13** and **14** (90 mg, 90%) (GLC and ^1H NMR evidence).

D-*Glycero*-D-*galacto*-oct-4-ulose (15). A solution of **11** (62 mg, 0.2 mmol) in aqueous 30% acetic acid (2.5 mL) was left at room temperature for 50 h and then at 40 °C for 48 h. TLC (ethyl acetate) then revealed that **11** had disappeared and that a non-mobile substance was present. The mixture was concentrated and residual acetic acid was removed by codistillation with water to afford **15** (47 mg, quantitative) that was homogeneous by TLC [R_F 0.32 (precoated Cellulose sheet Eastman 13254) (28:7:13 1-butanol-ethanol-water) and detection with silver nitrate[10]] and had $[\alpha]_D^{27}$ +63° (*c* 2.5 methanol).

D-*Glycero*-D-*ido*-oct-4-ulose (16). Hydrolysis of **12** (62 mg, 0.2 mmol) in aqueous 30% acetic acid (2.5 mL), as described above yielded syrupy **16** (47 mg, quantitative) that was homogeneous by TLC (as above) R_F 0.23, and had $[\alpha]_D^{26}$ +32.6° (*c* 2.4 methanol).

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