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Synthesis of 3-deoxy-2-octulosonic acid derivatives and characterisation of their 3-deoxyoctitols †

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ABSTRACT

The diethyl dithioacetals of D-altrose, D-idose, and D-talose were used to synthesise the respective *O*-benzyl aldehydo-sugars as intermediates for the synthesis of 3-deoxy-D-*glycero*-D-*gluco* / *manno*-, 3-deoxy-D-*glycero*-L-*gulo* / *ido*-, and 3-deoxy-D-*glycero*-L-*allo* / *altro*-octonate derivatives, respectively. After reduction and deprotection, the respective 3-deoxyoctitols were obtained. For the synthesis of 3-deoxy-D-*glycero*-L-*galacto* / *talo*-octitol, 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone was transformed by reduction and selective oxidation at C-1 to the *aldehydo*-D-gulose, from which the 3-deoxy-D-*glycero*-L-*galacto* / *talo*-octonate was synthesised. Carboxyl- and carbonyl-reduction and deprotection gave the 3-deoxyoctitol. The 3-deoxyoctitols were characterised by GLC and GLC–MS in the acetylated and methylated form. The data presented here and the data published earlier [T. Krülle, O. Holst, H. Brade, and R.R. Schmidt, *Carbohydr. Res.*, 247 (1993) 145–158] showed that methylated 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol can be distinguished by GLC from the other 3-deoxy-D-octitols and thus allows the identification of the *manno* configuration of 3-deoxy-D-*manno*-octulosonic acid (Kdo) in natural products such as the lipopolysaccharides of different Gram-negative bacteria, where Kdo is a generally occurring constituent.

INTRODUCTION

3-Deoxy-D-*manno*-octulopyranosonic acid[1] (Kdo) is a common constituent of the core region[2] of Gram-negative bacterial lipopolysaccharides (LPS) and has been identified in some capsular polysaccharides[3] and cell walls of plants[4]. In general, the stereochemistry of Kdo was not determined. In the latter report[4], the *manno* configuration for the Kdo was proposed based on the observation that the trimethylsilylated derivatives obtained after methanolysis of the cell-wall polysaccharide comigrated in GLC with similarly derivatised authentic Kdo. However, it was not shown that the methanolysis derivatives possessed different retention

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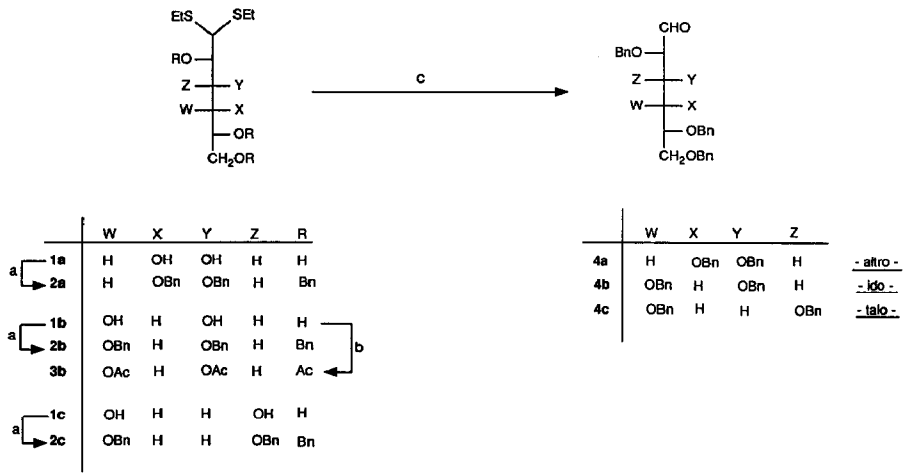
times to those of the respective derivatives of the other octulosonic acid stereoisomers. In addition, the absolute configuration was determined to be D as shown by GLC of the trimethylsilylated (+)-2-butyl glycoside.

In order to find a simple GLC and GLC–MS method to identify the *manno* configuration of Kdo, we started to synthesise the 3-deoxyoctitols of the D series, for which a Wittig reaction of *O*-protected aldehydo-sugars[5,6] with [(benzyloxy)(benzyloxycarbonyl)methyl]triphenylphosphonium bromide was used. In a first report[6], we described the synthesis of 3-deoxy-D-*glycero*-D-*allo* / *altro*-, 3-deoxy-D-*glycero*-L-*gluco* / *manno*-, 3-deoxy-D-*glycero*-D-*gulo* / *ido*-, and 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol from *O*-benzyl-protected D-allose, D-galactose, D-glucose, and D-mannose, respectively, and showed that the methylated octitol derivatives could be distinguished in GLC. Here, we report the synthesis of the other four 3-deoxyoctitols, namely 3-deoxy-D-*glycero*-D-*gluco* / *manno*-, 3-deoxy-D-*glycero*-L-*gulo* / *ido*-, 3-deoxy-D-*glycero*-L-*allo* / *altro*-, and 3-deoxy-D-*glycero*-L-*galacto* / *talo*-octitol, and their characterisation by GLC and GLC–MS.

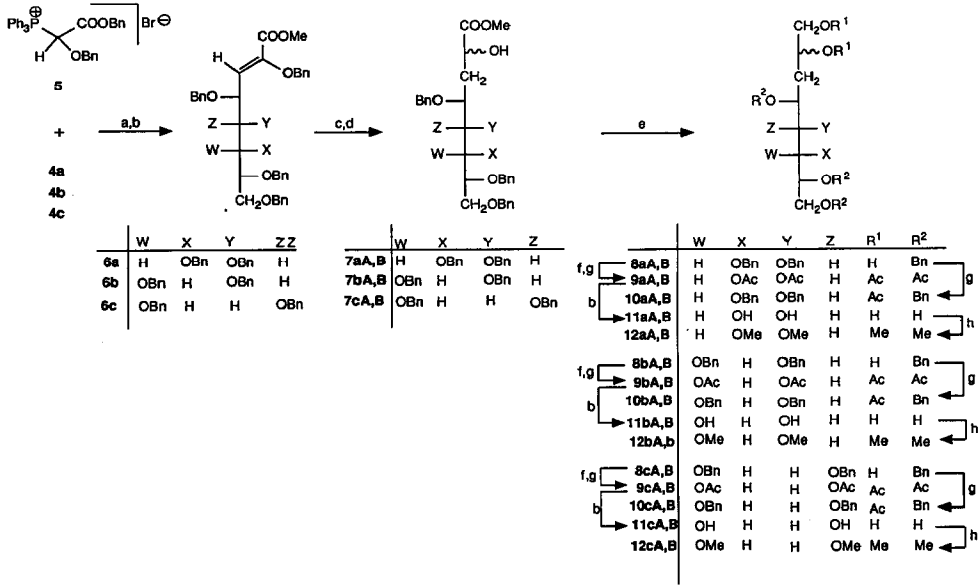
RESULTS AND DISCUSSION

The diethyl dithioacetals of D-altrose[7] **1a**, D-idose **1b**, and D-talose[8] **1c** (Scheme 1) were the starting materials for the preparation of the aldehydes **4a**, **4b**, and **4c**, respectively. In the case of D-idose, the diethyl dithioacetal **1b** was unknown. It was obtained in the usual manner from D-idose[9] by reaction with ethanethiol in concentrated hydrochloric acid[10,11]. The ^{1}H NMR spectral data of the acetylated compound **3b** were identical with those reported for the corresponding L isomer[10]. Perbenzylation of the diethyl dithioacetals with sodium hydride and benzyl bromide led to the protected acetals **2a–c**, which were hydrolysed in aqueous acetone in the presence of mercuric chloride–mercuric oxide to afford the *aldehydo*-D-altrose **4a**, *aldehydo*-D-idose **4b**, and *aldehydo*-D-talose **4c**, respectively. Wittig reaction of **4a–c** with the ylid derived from [(benzyloxy)(benzyloxycarbonyl)methyl]triphenylphosphonium bromide[5] (**5**) (Scheme 2) and then transesterification in methanol completed the synthetic sequence to Kdo derivatives **6a–c** which were obtained exclusively as the (*Z*)-isomers. It has been shown[6] that benzyl enol ethers of this kind are more reactive than aliphatic benzyl ethers to hydrogenolysis with palladium as catalyst. Palladium-on-calcium carbonate, a weak *O*-debenzylation catalyst, in tetrahydrofuran as solvent, enabled the selective cleavage of the enol ether functions in compounds **6a–c**. Subsequent reduction of the liberated keto groups led to the stable derivatives **7aA,B**, **7bA,B**, and **7cA,B** which were obtained as diastereomeric mixtures. Further reduction with sodium borohydride afforded the partly *O*-benzylated standard molecules **8aA,B**, **8bA,B**, and **8cA,B**. Small samples of these 3-deoxyoctitols were acetylated in order to establish their structures by ^{1}H NMR spectroscopy of their di-*O*-acetyl derivatives **10aA,B**, **10bA,B**, and **10cA,B**. The penta-*O*-benzyl-3-deoxyoctitols were hydrogenated with palladium-on-carbon in methanol. After acetylation of the crude products, the hepta-

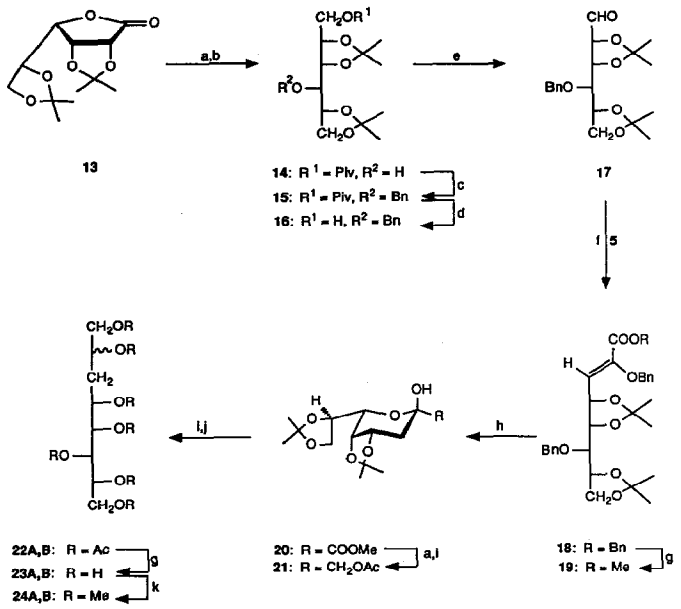


Scheme 1. (a) BnBr, NaH, DMF; (b) Ac_2O, Py; (c) $HgCl_2$, HgO, acetone–water.

O-acetyl-3-deoxyoctitols **9aA,b**, **9bA,B**, and **9cA,B** were obtained. Final treatment with traces of sodium methoxide in methanol yielded the pure, completely *O*-deprotected 3-deoxyoctitols **11aA,B**, **11bA,B**, and **11cA,B**. Methylation gave the hepta-*O*-methyl-3-deoxyoctitols **12aA,B**, **12bA,B**, and **12cA,B**.



Scheme 2. (a) BuLi, THF; −78 to 40°C; (b) NaOMe, MeOH; (c) Pd–$CaCO_3$, H_2, THF; (d) $NaBH_4$, MeOH, −10°C; (e) $NaBH_4$, EtOH; (f) Pd–C, H_2, MeOH; (g) Ac_2O, Py: (h) MeI, NaOH.



Scheme 3. (a) $LiAlH_4$, THF; (b) Piv-Cl, Py; (c) BnBr, NaH, DMF; (d) NaOMe, MeOH, 60°C; (e) DCC, Me_2SO, ether; (f) BuLi, THF, −78 to 40°C; (g) NaOMe, MeOH; (h) Pd–C, H_2, EtOAc; (i) Ac_2O, Py; (j) $NaBH_4$, EtOH, HCl; (k) MeI, NaOH.

In the case of the D-*gulo* isomers, a different strategy was chosen, although the diethyl dithioacetal is known[12]. Readily available 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone[13] (**13**) (Scheme 3) appeared to be an attractive starting material for the synthesis of an open-chain derivative of D-gulose. After reduction with lithium aluminium hydride, the primary alcoholic function was selectively protected with pivaloyl chloride to obtain compound **14**. *O*-Benzylation in dry dimethyl-formamide afforded the fully protected gulitol **15**, which was then treated with sodium methoxide in methanol. Oxidation of the resulting alcohol **16** in a dicyclohexylcarbodiimide(DCC)/dimethyl sulphoxide system furnished aldehyde **17**. The *aldehydo*-D-gulose was converted via Wittig reaction with **5** into enolether **18** [(*Z*)-isomer]; ensuing transesterification (with NaOMe–MeOH) afforded methyl ester **19**. Hydrogenolytic *O*-debenzylation of **19** led to the cyclic D-*gulo*-Kdo derivative **20**; its ^1H NMR data support the assignment of the β configuration[14]. To our surprise, $LiAlH_4$ in tetrahydrofuran reduced mainly the ester group of **20** while the keto group was retained. Therefore *O*-acetylation under the usual conditions led to the monoacetylated ketose **21**. Sodium borohydride treatment in ethanol permitted the reduction of the keto function of **21**. Subsequent acid-catalysed *O*-deisopropylidenation and then *O*-acetylation afforded diastereomers **22A,B** which were transformed into the *O*-deprotected 3-deoxyoctitols **23A,B** with a small amount of sodium methoxide in methanol. Methylation gave the hepta-*O*-methyl-3-deoxyoctitols **24A,B**.

TABLE I

Retention times (t_R) in GLC of acetylated **9aA,B**, **9bA,B**, **9cA,B**, and **22A,B**, and methylated **12aA,B**, **12bA,B**, **12cA,B**, and **24A,B** (relative to α-D-glucopyranose pentaacetate, t_R 1.00)

Compound	Separating phase	
	SE-54	SP-2380
Acetylated compounds [a]		
9aA,B	2.78/2.83	1.44/1.46
9bA,B	2.87/2.93	1.59/1.60
9cA,B	2.79/2.84	1.45/1.47
22A,B	2.78/2.87	1.52/1.53
Methylated compounds [b]		
12aA,B	0.29/0.31	0.13/0.14
12bA,B	0.37 [c]	0.21 [c]
12cA,B	0.32/0.35	0.16/0.17
24A,B	0.33/0.34	0.18 [c]

Temperature programmes: [a] SE-54, 140°C for 3 min, then 3°C min^{-1} to 250°C; SP-2380, 200°C for 5 min, then 5°C min^{-1} to 270°C; [b] SE-54, 130°C for 5 min, then 5°C min^{-1} to 250°C; SP-2380, 180°C for 5 min, then 5°C min^{-1} to 250°C. [c] Isomers not separated.

The relative retention times in GLC of the acetylated derivatives **9aA,B**, **9bA,B**, **9cA,B**, and **22A,B** are listed in Table I. The two isomers resulting from the reduction could be separated on both columns for each of the four compounds. On SE-54, derivatives **9aA,B** and **22A,B** had similar relative retention times, but all four acetylated derivatives could be separated on SP-2380 [the relative retention times of **9aA,B** and **9cA,B** on SP-2380 also look similar; however, both derivatives were separated, as is better illustrated by their absolute retention times of 18.55/18.85 min (**9aA,B**) and 18.73/18.94 min (**9cA,B**)]. The mol wt of 520 was determined in CI(ammonia)-MS [m/z 538, $(M + 18)^+$]. Despite differences in the intensities of the ions, the mass spectra of the acetylated 3-deoxyoctitols were very similar and corresponded to the reported[6] fragmentation pattern and m/z values. However, the ion at m/z 69 was the base peak in all spectra, whereas in the spectra of acetylated 3-deoxy-D-*glycero*-L-*gluco* / *manno*- and 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol, the ion at m/z 123, and in those of acetylated 3-deoxy-D-*glycero*-D-*allo* / *altro*- and 3-deoxy-D-*glycero*-D-*gulo* / *ido*-octitol, the ion at m/z 129, were base peaks[6]. The comparison of the relative retention times of all acetylated 3-deoxyoctitols (this work and ref 6) revealed that the 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol could not be identified unambigously on SE-54 or on SP-2380.

The relative retention times of the methylated derivatives **12aA,b**, **12bA,B**, **12cA,B**, and **24A,B** are also listed in Table I. The isomers of **12bA,B** could neither be separated on SE-54 nor on SP-2380, and the isomers of **24A,B** were not separated on SP-2380. The mol wt of 324 was determined in CI(ammonia)-MS [m/z 325 $(M + 1)^+$, m/z 342 $(M + 18)^+$]. The EIMS data were also very similar, and corresponded to the published[6] fragmentation pattern and m/z values.

Except for the spectrum of one diastereomer of **12cA,B**, which had *m/z* 101 as the base peak, the ion at *m/z* 89 was the base peak in all spectra. The comparison of the relative retention times of the eight methylated octitol derivatives (this work and ref 6) showed that the 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol could not be separated from the 3-deoxy-D-*glycero*-L-*allo* / *altro*-octitol on SP-2380, but was clearly distinguished from the latter and the other derivatives with SE-54 as the separating phase.

To validate the usefulness of this method for the chemical analysis of natural products, we selected three LPS of enteric Gram-negative bacteria, i.e., *Escherichia coli* K-12 strain W3100 (ref 15), *E. coli* F515-207 (ref 16), and *Salmonella minnesota* R5 (chemotype RcP$^-$, ref 17). Kdo was released by hydrolysis, reduced and methylated, and compared by GLC with the authentic methylated 3-deoxyoctitols. The retention times (SE-54) of the 3-deoxyoctitols from the LPS were identical to that of methylated 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol and different to those of the other derivatives, especially to that of methylated 3-deoxy-D-*glycero*-L-*allo* / *altro*- and 3-deoxy-D-*glycero*-D-*gluco* / *manno*-octitol which, due to their relative retention times, were neighbouring the 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol. The EI- and CI(ammonia)-mass spectra of the octitols from the LPS were identical to that obtained from methylated 3-deoxy-D-*glycero*-D-*galacto* / *talo*-octitol. Thus, the *manno* configuration of the Kdo from these LPS was proved.

The analytical determination of the stereochemistry of tetroses, pentoses, and hexoses is a relatively simple process. However, in the case of heptoses, octoses, and higher monosaccharides, this determination is most often not possible due to the lack of standards. By combination of the method described herein and the method[4] for the determination of the absolute configuration of Kdo, the unequivocal identification of 3-deoxy-D-*manno*-octulosonic acid is possible and thus should be included in sugar analysis when 3-deoxyoctulosonic acid is present.

EXPERIMENTAL

General methods.—Solvents were purified in the usual way; the petroleum ether (PE) used had a boiling range of 30–70°C. ^{1}H NMR spectra: Bruker AC 250 Cryospec; internal standard, tetramethylsilane. Protons designated H-Xa resonate at higher field than those designated H-Xb. With the exception of acetylated octitols, protons which are part of a wide multiplet are not listed. Flash chromatography: Silica Gel 60 (Merck; 40–60 mm). Medium-pressure liquid chromatography (MPLC): silica gel LiChroPrep RP 8 (Merck; 40–60 mm). Thin-layer chromatography (TLC): foil plates, Silica Gel 60 F254 (Merck; layer thickness, 0.2 mm). Optical rotations: Perkin–Elmer polarimeter 241/MS, 1-dm cell.

Methylation was performed according to the method of Ciucanu and Kerek[18], and methylated products were purified[19] on a SEP-PAK C18 cartridge.

GLC was done on a Varian model 3700 gas chromatograph equipped with a flame-ionisation detector. For analysis of the acetylated and methylated 3-de-

oxyoctitols, fused-silica columns with chemically bonded SE-54 (25 m × 0.32 mm, 0.25-μm film thickness, Weeke, Mühlheim) at 0.15 MPa H2, and SP-2380 (30 m × 0.25 mm, 0.20-μm, Supelco, Inc.) at 0.15 MPa H2, were used. The temperature programs are given in Table I. GLC–MS was carried out on a Hewlett–Packard 5985 instrument, equipped with an SE-54 capillary column and an HP-1000 data system. EI-mass spectra were recorded at 70 eV, and CI-mass spectra were obtained with ammonia as reactant gas.

Preparation of methylated 3-deoxyoctitols from LPS.—A sample (20 mg) of each of the LPS from *E. coli* K-12 strain W3100 (ref 15), *E. coli* F515-207 (a recombinant strain bearing[16] the *Chlamydia*-specific LPS-epitope), and *S. minnesota* R5 (RcP^- chemotype)[17] was hydrolysed (1 h, 100°C) in sodium acetate buffer (0.1 M, pH 4.4), and the hydrolysate was dialysed against water (3 × 50 mL). In the case of *E. coli* F515-207, the combined diffusates were fractionated by gel-permeation chromatography on a column (2.5 × 40 cm) of TSK HW40 (S) (Merck) in water, and in the case of *E. coli* K-12 and *S. minnesota* R5 by using a column (1 × 100 cm) of Bio-Gel P2 (Bio-Rad) in water. The fractions containing Kdo monosaccharide (as revealed by high-voltage paper chromatography at pH 2.8) were reduced ($NaBH_4$), methylated[18], purified[19], carboxyl-reduced[20], methylated and purified, and analysed by GLC and GLC–MS.

2,3,4,5,6-Penta-O-benzyl-D-altrose diethyl dithioacetal (**2a**).—To a solution of D-altrose diethyl dithioacetal[7] (**1a**; 2.5 g, 8.7 mmol) and benzyl bromide (9.9 g, 58 mmol) in dry DMF (40 mL) was added NaH (1.8 g, 75 mmol) in 4 portions during 1 h. The reaction temperature should not exceed 30°C. After 2 h, the mixture was poured onto ice (150 g) and extracted with ether (3 × 50 mL). The organic layer was dried with $MgSO_4$ and concentrated. After purification of the residue by flash chromatography (11 : 1 PE–EtOAc), **2a** was obtained as a colourless oil (5.8 g, 91%); TLC (6 : 1 PE–EtOAc): R_f 0.58; $[\alpha]_D^{20}$ −7.8° (*c* 2.68, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.70 (dd, 1 H, $J_{5,6a}$ 4.3, $J_{6a,6b}$ 10.4 Hz, H-6a), 3.81 (dd, 1 H, $J_{5,6b}$ 2.4 Hz, H-6b), 4.10 (dd, 1 H, $J_{1,2}$ 3.3, $J_{2,3}$ 7.0 Hz, H-2), 4.27 (dd, 1 H, $J_{3,4}$ 3.1 Hz, H-3). Anal. Calcd for $C_{45}H_{52}O_5S_2$ (737.04): C, 73.33; H, 7.11. Found: C, 73.39; H, 7.12.

2,3,4,5,6-Penta-O-benzyl-aldehydo-D-*altrose* (**4a**).—To a solution of **2a** (5.7 g, 7.7 mol) in acetone (40 mL) and water (6 mL) was added HgO (5.7 g). To this mixture was added dropwise a solution of $HgCl_2$ (5.7 g) in acetone (40 mL) with vigorous stirring. After 12 h, the suspension was filtered through Celite and concentrated in vacuo. A solution of the residue in $CHCl_3$ (150 mL) was washed with warm water (4 × 50 mL) and aq KI (30%, 3 × 30 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by flash chromatography (6 : 1 PE–EtOAc) to yield 3.9 g (81%) of aldehyde **4a**; TLC (6 : 1 PE–EtOAc): R_f 0.44; $[\alpha]_D^{20}$ −13.9° (*c* 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.16 (dd, 1 H, $J_{2,3}$ 4.2, $J_{3,4}$ 6.0 Hz, H-3), 9.63 (d, 1 H, $J_{1,2}$ 1.6 Hz, CHO). Anal. Calcd for $C_{41}H_{42}O_6$ (630.79): C, 78.07; H, 6.71. Found: C, 78.11; H, 6.83.

Methyl 2,4,5,6,7,8-hexa-O-benzyl-3-deoxy-D-altro-oct-2-enosonate (**6a**).—To a suspension of [(benzyloxy)(benzyloxycarbonyl)methyl]triphenylphosphonium

bromide[5] (**5**; 4.5 g, 7.5 mmol) in dry THF (40 mL) was added dropwise butyllithium (4 mL of a 1.6 M solution in hexane) at −78°C under N_2. After 20 min, **4a** (2.9 g, 4.6 mmol) in 20 mL of dry THF was added, and the cooling bath was removed. The mixture was stirred for an additional 12 h at 40°C. Then it was partitioned between 1:1 ether–water (100 mL). The aqueous layer was extracted three times with 30 mL of ether. The combined ethereal extracts were dried over $MgSO_4$, concentrated in vacuo, and filtered through a short column of silica gel (3:1 PE–EtOAc). The solvent was removed by rotary evaporation, and the residue was dissolved in 1:4 toluene–MeOH (100 mL). $NaBH_4$ (100 mg) was added with vigorous stirring for the reduction of the aldehyde. After 1 h, sodium (50 mg) was dissolved to complete the transesterification (controlled by TLC). The solution was diluted with water (100 mL), neutralised with M HCl, and extracted with ether (3 × 70 mL). The organic layer was dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (5:1 PE–EtOAc) yielded **6a** (2.6 g, 72%); TLC (6:1 PE–EtOAc): R_f 0.40; $[\alpha]_D^{20}$ −5.6° (*c* 0.86, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.59 (dd, 1 H, $J_{4,5}$ 3.6, $J_{5,6}$ 7.5 Hz, H-5), 3.76 (s, 3 H, COOMe), 3.99 (dd, 1 H, $J_{6,7}$ 2.7 Hz, H-6), 6.33 (d, 1 H, $J_{3,4}$ 9.2 Hz, H-3). Anal. Calcd for $C_{51}H_{52}O_8$ (792.98): C, 77.25; H, 6.61. Found: C, 77.52; H, 6.66.

*Methyl 4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D-glycero-D-gluco-*octonate and methyl 4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D-glycero-D-manno-*octonate* (**7aA,B**).—Pd–$CaCO_3$ (5%, 250 mg) in dry THF (20 mL) was activated for 12 h under H_2. A solution of **6a** (2.1 g, 2.7 mmol) in THF (15 mL) was added. Debenzylation was carried out until compound **6a** disappeared in TLC. The suspension was filtered through Celite and washed several times with THF. The filtrate was evaporated to dryness and the residue redissolved in MeOH (50 mL). After cooling to −10°C, $NaBH_4$ (100 mg) was added with vigorous stirring. After 1.5 h, the solution was neutralised with M HCl, diluted with water (50 mL), and extracted with ether 3 × 75 mL). The ethereal extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography (3:1 PE–EtOAc): 1.4 g (75%) of **7aA,B** was obtained as a colourless oil (diastereomer ratio 1.6:1); TLC (5:1 PE–EtOAc): R_f 0.28; ^1H NMR ($CDCl_3$) major product: δ 3.32 (d, 1 H, *J* 4.0 Hz, OH), 3.53 (s, 3 H, COOMe); minor product: δ 2.77 (d, 1 H, *J* 6.7 Hz, OH), 3.66 (s, 3 H, COOMe). Anal. Calcd for $C_{44}H_{48}O_8$ (704.86): C, 74.98; H, 6.86. Found: C, 74.79; H, 6.91.

*4,5,6,7,8-Penta-*O*-benzyl-3-deoxy-*D-glycero-D-gluco-*octitol, 4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D-glycero-D-manno-*octitol* (**8aA,B**) *and 1,2-di-*O*-acetyl-4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D-glycero-D-gluco-*octitol, 1,2-di-*O*-acetyl-4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D-glycero-D-manno-*octitol* (**10aA,B**).—To a solution of **7aA,B** (950 mg, 1.35 mmol) in EtOH (60 mL) was added $NaBH_4$ (500 mg). After 12 h, the solution was neutralised with M HCl and concentrated to half of the original volume. The solution was diluted with water and extracted with ether (3 × 70 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. After purification of the residue by flash chromatography (1:1 PE–EtOAc), 840 mg (92%) of **8aA,B** was obtained as an oil; TLC (1:1 PE–EtOAc): R_f 0.31.

A sample of **8aA,B** (50 mg) was acetylated with pyridine (10 mL) and Ac_2O (10 mL). After the usual work-up, the syrupy acetate was purified by flash chromatography (3:1 PE–EtOAc); **10aA,B** was obtained quantitatively; TLC (3:1 PE–EtOAc): R_f 0.42; ^1H NMR ($CDCl_3$) major product: δ 1.89, 1.96 (2 s, 6 H, 2 OAc), 5.08 (m, 1 H, H-2); minor product: δ 1.87, 1.98 (2 s, 6 H, 2 OAc), 4.18 (dd, 1 H, $J_{1a,1b}$ 11.8, $J_{1b,2}$ 3.6 Hz, H-1b), 5.28 (m, 1 H, H-2). Anal. Calcd for $C_{47}H_{52}O_9$ (acetylated compounds): C, 74.19; H, 6.89. Found: C, 74.16; H, 6.89.

*1,2,4,5,6,7,8-Hepta-*O*-acetyl-3-deoxy-*D*-glycero-*D*-gluco-octitol and 1,2,4,5,6,7,8-hepta-*O*-acetyl-3-deoxy-*D*-glycero-*D*-manno-octitol* (**9aA,B**).—A sample of **8aA,B** (750 mg, 1.1 mmol) in MeOH (25 mL) was hydrogenated in the presence of Pd–C (10%, 100 mg). After 12 h, the suspension was filtered through Celite and washed several times with MeOH. The filtrate was evaporated to dryness and the residue was acetylated with pyridine (10 mL) and Ac_2O (10 mL). After 1 day at room temperature, the mixture was concentrated under high vacuum with a rotary evaporator, and the residue was purified by flash chromatography (1:1 PE–EtOAc) to yield 570 mg (quant.) of **9aA,B** as an oil; TLC (1:1 PE–EtOAc): R_f 0.33; ^1H NMR ($CDCl_3$) major product: δ 1.77 (m, 2 H, H-3a,3b), 2.01–2.15 (m, 21 H, 7 OAc), 4.07–4.32 (m, 4 H, H-1a,1b,8a,8b), 5.03–5.31 (m, 5 H, H-2,4,5,6,7); minor product: δ 1.65–1.91 (2 m, 2 H, H-3a,3b), 1.98–2.14 (m, 21 H, OAc), 3.92 (dd, 1 H, $J_{1a,2}$ 5.5, $J_{1a,1b}$ 12.0 Hz, H-1a), 4.03–4.32 (m, 3 H, H-1b,8a,8b), 4.88–5.31 (2 m, 5 H, H-2,4,5,6,7). Anal. Calcd for $C_{22}H_{32}O_{14}$ (520.49): C, 50.77; H, 6.20. Found: C, 50.74; H, 6.26.

*3-Deoxy-*D*-glycero-*D*-gluco-octitol and 3-deoxy-*D*-glycero-*D*-manno-octitol* (**11aA, B**).—A solution of **9aA,B** (560 mg, 1.08 mmol) in MeOH (25 mL) was treated with NaOMe (90 mL, 2.8 M solution in dry MeOH). After 24 h, the solution was neutralised with Amberlite IR-120 (H^+) resin. Then the resin was removed by filtration. The filtrate was concentrated in vacuo to a syrup which was purified by MPLC (1:20 acetone–water). The aqueous solution was concentrated and freeze-dried to give **11aA,B** (213 mg, 87%); TLC (5:4:1 $CHCl_3$–MeOH–water): R_f 0.37. Acetylation of **11aA,B** under the usual conditions led to **9aA,B** in quantitative yield.

D-Idose diethyl dithioacetal (**1b**) *and 2,3,4,5,6-penta-*O*-acetyl-D-idose diethyl dithioacetal* (**3b**).—A mixture of syrupy D-idose[9] (18.2 g, 100 mmol), concd HCl (35 mL), and ethanethiol (50 mL) was agitated vigorously for 1 h at 0°C. The mixture was diluted with water (150 mL) and neutralised by addition of $NaHCO_3$. Continuous extraction with $CHCl_3$ yielded the crude dithioacetal, which was recrystallised from EtOAc–EtOH to give **1b** (9.8 g, 34%); mp 98°C; TLC (7:1 $CHCl_3$–MeOH): R_f 0.38; $[\alpha]_D^{20}$ +5.9° (*c* 1.3, MeOH); lit.[21], L isomer: mp 96–97°C; $[\alpha]_D^{22}$ −7.0° (*c* 1.0, MeOH).

A sample of **1b** (200 mg) was acetylated in 1:1 pyridine–Ac_2O (10 mL). After purification by flash chromatography (2:1 PE–EtOAc), **3b** was obtained quantitatively; TLC (2:1 PE–EtOAc): R_f 0.33; $[\alpha]_D^{20}$ +3.9° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.00 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1), 4.04 (dd, 1 H, $J_{5,6a}$ 5.6, $J_{6a,6b}$ 12.2 Hz,

H-6a), 4.35 (dd, 1 H, $J_{5,6b}$ 3.9 Hz, H-6b), 5.39 (dd, 1 H, $J_{3,4}$ 4.7, $J_{4,5}$ 6.1 Hz, H-4), 5.70 (dd, 1 H, $J_{2,3}$ 5.6 Hz, H-3). Anal. Calcd for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.50. Found: C, 48.42; H, 6.65.

*2,3,4,5,6-Penta-*O*-benzyl-*D*-idose diethyl dithioacetal* (**2b**).—Benzylation of **1b** (2.5 g, 8.7 mmol) was carried out as described for **2a**, to yield 5.5 g (86%) of **2b** as a colourless oil; TLC (6:1 PE–EtOAc): R_f 0.62; $[\alpha]_D^{20}$ −7.6° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.48 (dd, 1 H, $J_{5,6a}$ 5.5, $J_{6a,6b}$ 10.3 Hz, H-6a), 3.58 (dd, 1 H, $J_{5,6b}$ 4.0 Hz, H-6b), 3.81 (m, 1 H, H-4), 4.24 (m, 1 H, H-3), 4.36, 4.40 (2 d, 2 H, *J* 12.0 Hz, OCH_2Ph). Anal. Calcd for $C_{45}H_{52}O_5S_2$ (737.04): C, 73.33; H, 7.11. Found: C, 73.29; H, 7.08.

*2,3,4,5,6-Penta-*O*-benzyl-*aldehydo-D-*idose* (**4b**).—Hydrolysis of the diethyl dithioacetal **2b** (5.2 g, 7.1 mmol) was carried out as described for **4a**, to yield 3.9 g (87%) of aldehyde **4b** as a colourless oil; TLC (3:1 PE–EtOAc): R_f 0.59; $[\alpha]_D^{20}$ −4.3° (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.95, 4.02 (2 m, 2 H, H-3,4), 9.50 (d, 1 H, $J_{1,2}$ < 1.0 Hz, CHO). Anal. Calcd for $C_{41}H_{42}O_6$ (630.79): C, 78.07; H, 6.71; Found: C, 77.58; H, 6.68.

*Methyl 2,4,5,6,7,8-hexa-*O*-benzyl-3-deoxy-*D*-*ido*-oct-2-enosonate* (**6b**).—[(Benzyloxy)(benzyloxycarbonyl)methyl]triphenylphosphonium bromide (**5**; 4.5 g, 7.5 mmol), butyllithium (4 mL of a 1.6 M solution in hexane), and aldehyde **4b** (3 g, 4.8 mmol) were used as described for **6a**, to yield 1.6 g (42%) of **6b** as a colourless oil; TLC (6:1 PE–EtOAc): R_f 0.35; $[\alpha]_D^{20}$ −31.2° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.45 (dd, 1 H, $J_{7,8a}$ 5.8, $J_{8a,8b}$ 9.8 Hz, H-8), 3.79 (s, 3 H, COOMe), 6.32 (d, 1 H, $J_{3,4}$ 9.1 Hz, H-3). Anal. Calcd for $C_{51}H_{52}O_8$ (792.98): C, 77.25; H, 6.61. Found: C, 76.94; H, 6.75.

*Methyl 4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D*-glycero-*L*-gulo-octonate and methyl 4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D*-glycero-*L*-ido-octonate* (**7bA,B**).—Debenzylation and reduction of **6b** (1.35 g, 1.7 mmol) were carried out as described for **7aA,B**; Pd–$CaCO_3$ (5%, 205 mg) and $NaBH_4$ (104 mg) were used. After purification by flash chromatography (3:1 PE–EtOAc), 800 mg (67%) of **7bA,B** was obtained as a colourless oil (diastereomer ratio 1.3:1); TLC (5:1 PE–EtOAc): R_f 0.19; ^1H NMR ($CDCl_3$) major product: δ 2.98 (d, 1 H, *J* 4.2 Hz, OH), 3.55 (s, 3 H, COOMe), 4.10 (m, 1 H, H-2); minor product: δ 2.61 (d, 1 H, *J* 6.5 Hz, OH), 3.67 (s, 3 H, COOMe), 4.27 (m, 1 H, H-2). Anal. Calcd for $C_{44}H_{48}O_8$ (704.86): C, 74.98; H, 6.86. Found: C, 74.83; H, 6.90.

*4,5,6,7,8-Penta-*O*-benzyl-3-deoxy-*D*-glycero-*L*-gulo-octitol, 4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D*-glycero-*L*-ido-octitol* (**8bA,B**) *and 1,2-di-*O*-acetyl-4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D*-glycero-*L*-gulo-octitol, 1,2-di-*O*-acetyl-4,5,6,7,8-penta-*O*-benzyl-3-deoxy-*D*-glycero-*L*-ido-octitol* (**10bA,B**).—Treatment of **7bA,B** (610 mg, 0.87 mmol) with $NaBH_4$ (300 mg) under the same conditions as described for **8aA,B** yielded 520 mg (89%) of **8bA,B** as an oil; TLC (1:1 PE–EtOAc): R_f 0.26.

A sample of **8bA,B** (50 mg) was acetylated with pyridine (10 mL) and Ac_2O (10 mL). After the usual workup, the syrupy acetate was purified by flash chromatography (3:1 PE–EtOAc); **10bA,B** was obtained quantitatively; TLC (3:1 PE–

EtOAc): R_f 0.36; ^{1}H NMR ($CDCl_3$), major product: δ 1.89, 1.96 (2 s, 6 H, 2 OAc), 4.00 (dd, 1 H, $J_{1b,2}$ 3.1, $J_{1a,1b}$ 12.1 Hz, H-1b), 4.97 (m, 1 H, H-2); minor product: δ 1.92, 1.99 (2 s, 6 H, 2 OAc), 4.19 (dd, 1 H, $J_{1b,2}$ 3.5, $J_{1a,1b}$ 11.9 Hz, H-1b), 5.23 (m, 1 H, H-2). Anal. Calcd for $C_{47}H_{52}O_9$ (acetylated compounds): C, 74.19; H, 6.89. Found: C, 74.26; H, 7.03.

*1,2,4,5,6,7,8-Hepta-O-acetyl-3-deoxy-*D-glycero-L-gulo-*octitol and 1,2,4,5,6,7,8-hepta-O-acetyl-3-deoxy-*D-glycero-L-ido-*octitol* (**9bA,B**).—Compound **8bA,B** (470 mg, 0.69 mmol) was debenzylated and acetylated as described for **9aA,B**; 320 mg (91%) of **9bA,B** was obtained as an oil; TLC (1:1 heptane–EtOAc): R_f 0.2; ^{1}H NMR ($CDCl_3$), major product: δ 1.73–1.87 (m, 2 H, H-3a,3b), 2.04–2.09 (m, 21 H, 7 OAc), 3.95–4.06 (m, 2 H, H-1a,8a), 4.12–4.24 (m, 2 H, H-1b,8b), 4.99–5.31 (m, 5 H, H-2,4,5,6,7); minor product: δ 1.73–1.87 (m, 2 H, H-3a,3b), 2.02–2.09 (m, 21 H, 7 OAc), 3.90–4.06 (m, 2 H, H-1a,8a), 4.12–4.24 (m, 2 H, H-1b,8b), 4.99–5.31 (m, 4 H, H-2,4,5,6), 5.38 (m, 1 H, H-7). Anal. Calcd for $C_{22}H_{32}O_{14}$ (520.49): C, 50.77; H, 6.20. Found: C, 50.87; H, 6.30.

*3-Deoxy-*D-glycero-L-gulo-*octitol and 3-deoxy-*D-glycero-L-ido-*octitol* (**11bA,B**).—Compound **9bA,B** (280 mg, 0.54 mmol) was deprotected and purified as described for **11aA,B**, to give **11bA,B** (105 mg, 87%); TLC (5:4:1 $CHCl_3$–MeOH–water): R_f 0.34. Acetylation of **11bA,B** under the usual conditions led to **9bA,B** in quantitative yield.

*2,3,4,5,6-Penta-O-benzyl-*D-*talose diethyl dithioacetal* (**2c**).—Benzylation of **1c**[8] (2.6 g, 9.1 mmol) was carried out as described for **2a**, to yield 5.3 g (79%) of **2c** as a colourless oil; TLC (6:1 PE–EtOAc): R_f 0.62; $[\alpha]_D^{20}$ −24.3° (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.57 (dd, 1 H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 10.6 Hz, H-6a), 3.65 (dd, 1 H, $J_{5,6b}$ 3.7 Hz, H-6b), 3.79 (m, 1 H, H-5). Anal. Calcd for $C_{45}H_{52}O_5S_2$ (737.04): C, 73.33; H, 7.11. Found: C, 73.35; H, 7.15.

*2,3,4,5,6-Penta-O-benzyl-*aldehydo-D-*talose* (**4c**).—Hydrolysis of the diethyl dithioacetal **2c** (5.2 g, 7.1 mmol) was carried out as described for **4a**, to yield 3.8 g (85%) of aldehyde **4c** as a colourless oil; TLC (6:1 PE–EtOAc): R_f 0.38; $[\alpha]_D^{20}$ −9.3° (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.46 (d, 1 H, $J_{1,2} < 1.0$ Hz, CHO). Anal. Calcd for $C_{41}H_{42}O_6$ (630.79): C, 78.07; H, 6.31. Found: C, 77.80; H, 6.80.

*Methyl 2,4,5,6,7,8-hexa-O-benzyl-3-deoxy-*D-talo-*oct-2-enosonate* (**6c**).—[(Benzyloxy)(benzyloxycarbonyl)methyl]triphenylphosphonium bromide (**5**; 4.5 g, 7.5 mmol), butyllithium (4 mL of a 1.6 M solution in hexane), and aldehyde **4c** (3 g, 4.8 mmol) were used, as described for **6a**, to yield 1.83 g (48%) of **6c** as a colourless oil; TLC (6:1 PE–EtOAc): R_f 0.40; $[\alpha]_D^{20}$ −6.6° (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3 H, COOMe), 6.34 (d, 1 H, $J_{3,4}$ 9.4 Hz, H-3). Anal. Calcd for $C_{51}H_{52}O_8$ (792.98): C, 77.25; H, 6.61. Found: C, 77.09; H, 6.69.

*Methyl 4,5,6,7,8-penta-O-benzyl-3-deoxy-*D-glycero-L-allo-*octonate and methyl 4,5,6,7,8-penta-O-benzyl-3-deoxy-*D-glycero-L-altro-*octonate* (**7cA,B**).—Debenzylation and reduction of **6c** (1.30 g, 1.64 mmol) were carried out as described for **7aA,B**; Pd–$CaCO_3$ (5%, 200 mg) and $NaBH_4$ (190 mg) were used. After purification by flash chromatography (3:1 PE–EtOAc), 740 mg (64%) of **7cA,B** was

obtained as a colourless oil (diastereomer ratio 1.3:1); TLC (5:1 PE–EtOAc): R_f 0.25; ^{1}H NMR ($CDCl_3$), major product: δ 3.26 (d, 1 H, J 3.8 Hz, OH), 3.49 (s, 3 H, COOMe); minor product: δ 2.96 (d, 1 H, J 6.2 Hz, OH), 3.68 (s, 3 H, COOMe). Anal. Calcd for $C_{44}H_{48}O_8$ (704.86): C, 74.98; H, 6.86. Found: C, 74.86; H, 6.86.

4,5,6,7,8-Penta-O-*benzyl-3-deoxy*-D-glycero-L-allo-*octitol, 4,5,6,7,8-penta*-O-*benzyl-3-deoxy*-D-glycero-L-altro-*octitol* (**8cA,B**) *and 1,2-di*-O-*acetyl-4,5,6,7,8-penta*-O-*benzyl-3-deoxy*-D-glycero-L-allo-*octitol, 1,2-di*-O-*acetyl-4,5,6,7,8-penta*-O-*benzyl-3-deoxy*-D-glycero-L-altro-*octitol* (**10cA,B**).—Treatment of **7cA,B** (640 mg, 0.91 mmol) with $NaBH_4$ (300 mg), under the same conditions as described for **8aA,B**, yielded 560 mg (91%) of **8cA,B** as an oil; TLC (1:1 PE–EtOAc): R_f 0.35. A sample of **8cA,B** (50 mg) was acetylated with pyridine (10 mL) and Ac_2O (10 mL). After the usual workup, the syrupy acetate was purified by flash chromatography (3:1 PE–EtOAc); **10cA,B** was obtained quantitatively; TLC (3:1 PE–EtOAc): R_f 0.41; ^{1}H NMR ($CDCl_3$), major product: δ 1.91, 1.96 (2 s, 6 H, 2 OAc), 4.15 (dd, 1 H, $J_{1b,2}$ 2.6, $J_{1a,1b}$ 11.9 Hz, H-1b), 5.27 (m, 1 H, H-2); minor product: δ 1.79, 2.02 (2 s, 6 H, 2 OAc), 4.28 (dd, 1 H, $J_{1b,2}$ 3.4, $J_{1a,1b}$ 11.9 Hz, H-1b), 5.34 (m, 1 H, H-2). Anal. Calcd for $C_{47}H_{52}O_9$ (acetylated compounds): C, 74.19; H, 6.89. Found: C, 74.12; H, 6.98.

1,2,4,5,6,7,8-Hepta-O-*acetyl-3-deoxy*-D-glycero-L-allo-*octitol and 1,2,4,5,6,7,8-hepta*-O-*acetyl-3-deoxy*-D-glycero-L-altro-*octitol* (**9cA,B**).—Compound **8cA,B** (504 mg, 0.74 mmol) was debenzylated and acetylated as described for **9aA,B**; 300 mg (78%) of **9cA,B** was obtained as an oil; TLC (1:1 heptane–EtOAc): R_f 0.27; ^{1}H NMR ($CDCl_3$), major product: δ 1.94–2.15 (m, 23 H, H-3a,3b, 7 OAc), 3.82–3.99 (m, 2 H, H-1a,8a), 4.17–4.25 (m, 2 H, H-1b,8b), 4.95–5.09 (m, 2 H, H-2,4), 5.22–5.33 (m, 3 H, H-5,6,7); minor product: δ 1.82–2.15 (m, 23 H, H-3a,3b, 7 OAc), 3.82–4.01 (m, 2 H, H-1a,8a), 4.17–4.29 (m, 2 H, H-1b,8b), 4.91–5.09 (m, 2 H, H-2,4), 5.18–5.33 (m, 3 H, H-5,6,7). Anal. Calcd for $C_{22}H_{32}O_{14}$ (520.49): C, 50.77; H, 6.20. Found: C, 50.81; H, 6.28.

3-Deoxy-D-glycero-L-allo-*octitol and 3-deoxy*-D-glycero-L-altro-*octitol* (**11cA,B**).—Compound **9cA,B** (250 mg, 0.48 mmol) was deprotected and purified as described for **11aA,B**, to give **11cA,B** (95 mg, 88%); TLC (5:4:1 $CHCl_3$–MeOH–water): R_f 0.39. Acetylation of **11cA,B** led to **9cA,B** in quantitative yield.

2,3:5,6-Di-O-*isopropylidene-1*-O-*pivaloyl*-D-*gulitol* (**14**).—A solution of the D-gulono-1,4-lactone **13**[13] (5.2 g, 20.1 mmol) in dry THF (50 mL) was added dropwise to a refluxing suspension of $LiAlH_4$ (1 g, 26.4 mmol) in ether (50 mL). The mixture was heated for 1 h. Careful addition of EtOAc destroyed the excess of $LiAlH_4$. In order to get a filterable precipitate, water (1 mL), then aq 10% NaOH (1 mL), and finally water (2 mL) were added. After filtration of the suspension through Celite, the filtrate was evaporated to dryness (5.4 g). The residue was redissolved in CH_2Cl_2 (50 mL), and pyridine (4 mL) and pivaloyl chloride (3.2 g, 26.4 mmol) were added. After 12 h at room temperature, the mixture was diluted with CH_2Cl_2 (100 mL), washed twice with water, dried with $MgSO_4$, and concentrated. Purification of the residue by flash chromatography (2:1 PE–EtOAc) yielded 6 g (86%) of **14**

as a colourless oil; TLC (2:1 PE–EtOAc): R_f 0.5; $[\alpha]_D^{20}$ +5.2° (*c* 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.18 (s, 9 H, Piv), 1.32, 1.34, 1.41, 1.48 (4 s, 12 H, 4 Me), 2.40 (d, 1 H, *J* 6.8 Hz, OH), 3.65 (m, 1 H, H-4), 3.79 (dd, 1 H, $J_{5,6a}$ 6.6 Hz, $J_{6a,6b}$ 8.3 Hz, H-6a), 4.03 (dd, 1 H, $J_{5,6b}$ 6.6 Hz, H-6b), 4.08 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.0 Hz, H-3), 4.19 (m, 1 H, H-5). Anal. Calcd for $C_{17}H_{30}O_7$ (346.42): C, 58.94; H, 8.73. Found: C, 58.92; H, 8.66.

4-O-Benzyl-2,3:5,6-di-O-isopropylidene-1-O-pivaloyl-D-gulitol (**15**).—The gulitol **14** (5.7 g, 16.5 mmol) and benzyl bromide (2.2 mL, 18.5 mmol) dissolved in dry DMF (50 mL) were treated with NaH (480 mg, 20 mmol). After 1 h, the mixture was poured onto ice (100 g) and extracted three times with ether (50 mL). The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by flash chromatography (6:1 PE–EtOAc) yielded 5.3 g (73%) of **15** as a colourless oil; TLC (3:1 PE–EtOAc): R_f 0.66; $[\alpha]_D^{20}$ −6.3° (*c* 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.21 (s, 9 H, Piv), 1.35, 1.37, 1.44, 1.50 (4 s, 12 H, 4 Me), 3.63 (dd, 1 H, $J_{3,4} = J_{4,5} \approx 5.2$ Hz), 3.87 (dd, 1 H, $J_{5,6a} \sim 7.9$, $J_{6a,6b}$ 8.2 Hz, H-6a), 4.03 (dd, 1 H, $J_{5,6b}$ 6.5 Hz, H-6b), 4.76, 4.84 (2 d, 2 H, *J* 11.9 Hz, OCH_2Ph). Anal. Calcd for $C_{24}H_{36}O_7$ (436.55): C, 66.03; H, 8.31. Found: C, 65.96; H, 8.34.

4-O-Benzyl-2,3:5,6-di-O-isopropylidene-D-gulitol (**16**).—A solution of **15** (5.3 g, 12.1 mmol) in MeOH (70 mL) was treated with NaOMe (5 mL of a 2.5 M solution in MeOH) at 60°C with stirring. After 2 h, the solution was concentrated to half of the original volume and diluted with $CHCl_3$ (150 mL). The organic layer was washed with water and saturated aq NaCl, dried over $MgSO_4$, and evaporated to dryness. The residual oil was purified by flash chromatography (2:1 PE–EtOAc) to yield 3.2 g (75%) of **16** as a colourless oil; TLC (3:1 PE–EtOAc): R_f 0.15; $[\alpha]_D^{20}$ −6.4° (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.35, 1.37, 1.44, 1.51 (4 s, 12 H, 4 Me), 2.44 (dd, 1 H, $J_1 = J_2 \approx 2$ Hz, OH), 3.74 (dd, 1 H, $J_{3,4} = J_{4,5} \approx 5.5$ Hz, H-4), 3.91 (dd, 1 H, $J_{5,6a} \sim 8.0$, $J_{6a,6b}$ 8.4 Hz, H-6a), 4.03 (dd, 1 H, $J_{5,6b}$ 6.5 Hz, H-6b), 4.74, 4.78 (2 d, 2 H, *J* 11.7 Hz, OCH_2Ph). Anal. Calcd for $C_{19}H_{28}O_6$ (352.43): C, 64.75; H, 8.01. Found: C, 64.82; H, 8.05.

4-O-Benzyl-2,3:5,6-di-O-isopropylidene-D-gulose (**17**).—Compound **16** (2.9 g, 8.2 mmol), dicyclohexylcarbodiimide (8.6 g, 41.7 mmol), and Me_2SO (3.5 mL, 49.3 mmol) were dissolved in ether (60 mL). After cooling in an ice bath, the solution was treated with pyridine (0.52 mL) and CF_3CO_2H (0.52 mL) and stirred for 12 h at 0°C. Then oxalic acid dihydrate (4 × 1 g) was added at lower temperature. The mixture was stirred for an additional 1 h and then filtered through Celite. The filtrate was washed three times with aq $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness. After purification by flash chromatography (5:2 PE–EtOAc), 2.35 g (82%) of aldehyde **17** was obtained; TLC (2:1 PE–EtOAc): R_f 0.69; ^1H NMR ($CDCl_3$): δ 1.36, 1.43, 1.58, 1.61 (4 s, 12 H, 4 Me), 3.49 (dd, 1 H, J_1 2.3, J_2 7.1 Hz, H-4), 3.77 (dd, 1 H, $J_{5,6a} = J_{6a,6b} \approx 8.1$ Hz, H-6a), 4.09 (dd, 1 H, $J_{5,6b}$ 6.2 Hz, H-6b), 4.24, 4.96 (2 d, 2 H, *J* 11.5 Hz, OCH_2Ph), 4.34 (dd, 1. H, $J_{1,2}$ 2.0, $J_{2,3}$ 8.0 Hz, H-2), 9.51 (d, 1 H, CHO).

*Benzyl 2,6-di-O-benzyl-3-deoxy-4,5 : 7,8-di-O-isopropylidene-*D-gulo-*oct-2-enosonate* (**18**).—The Wittig reaction was carried out in the same way as described for **6a**. Phosphonium bromide **5** (5.8 g, 9.7 mmol), butyllithium (5.1 mL of a 1.6 M solution in hexane), and aldehyde **17** (2.1 g, 6 mmol) were used to yield 3.1 g (88%) of **18** as a colourless oil. In this example, separation of aldehyde and olefin was possible; TLC (3:1 PE–EtOAc): R_f 0.62; $[\alpha]_D^{20}$ +47.5° (*c* 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.21, 1.29, 1.41, 1.49 (4 s, 12 H, 4 Me), 3.21 (dd, 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 5.9 Hz, H-6), 3.65 (dd, 1 H, $J_{7,8a} = J_{8a,8b} = 7.9$ Hz, H-8a), 3.94 (dd, 1 H, $J_{7,8b}$ 6.3 Hz, H-8b), 4.12 (dd, 1 H, $J_{4,5}$ 6.6 Hz, H-5), 4.23 (m, 1 H, H-7), 4.51, 4.83 (2 d, 2 H, *J* 11.8 Hz, OCH_2Ph), 4.86, 5.04 (2 d, 2 H, *J* 11.2 Hz, OCH_2Ph), 4.99 (dd, 1 H, $J_{3,4}$ 8.2 Hz, H-4), 5.09, 5.18 (2 d, 2 H, *J* 12.3 Hz, OCH_2Ph), 6.43 (d, 1 H, H-3). Anal. Calcd for $C_{35}H_{40}O_8$ (588.7): C, 71.41; H, 6.85. Found: C, 71.47; H, 6.85.

*Methyl 2,6-di-O-benzyl-3-deoxy-4,5 : 7,8-di-O-isopropylidene-*D-gulo-*oct-2-enosonate* (**19**).—A solution of **18** (2.8 g, 4.8 mmol) in MeOH (60 mL) was treated with NaOMe (0.2 mL of a 2.5 M solution in MeOH). After 12 h, the solution was neutralized with Amberlite IR-120 (H^+) resin. The resin was removed by filtration, and the filtrate was concentrated in vacuo to a syrup, which was purified by flash chromatography (5:1 PE–EtOAc). Removal of the solvent afforded 2 g (81%) of **19** as a colourless oil; TLC (5:1 PE–EtOAc): R_f 0.43; $[\alpha]_D^{20}$ +59.1° (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.28, 1.31, 1.41, 1.52 (4 s, 12 H, 4 Me), 3.23 (dd, 1 H, $J_{5,6}$ 4.1, $J_{6,7}$ 5.6 Hz, H-6), 3.68 (s, 3 H, COOMe), 3.94 (dd, 1 H, $J_{7,8b}$ 6.4, $J_{8a,8b}$ 7.9 Hz, H-8b), 4.16 (dd, 1 H, $J_{4,5}$ 6.5 Hz, H-5), 4.22 (m, 1 H, H-7), 4.57, 4.85 (2 d, 2 H, *J* 11.8 Hz, OCH_2Ph), 4.84, 5.03 (2 d, 2 H, *J* 11.2 Hz, OCH_2Ph), 5.00 (dd, 1 H, $J_{3,4}$ 8.5 Hz, H-4), 6.37 (d, 1 H, H-3). Anal. Calcd for $C_{29}H_{36}O_8$ (512.61): C, 67.95; H, 7.08. Found: C, 67.94; H, 6.99.

*Methyl 3-deoxy-4,5 : 7,8-di-O-isopropylidene-β-*D-gulo-*2-octulopyranosonate* (**20**). —The ester **19** (840 mg, 1.64 mmol) in EtOAc (25 mL) was hydrogenated in the presence of Pd–C (10%, 81 mg). After 2 h, the mixture was filtered and the filtrate concentrated. The residue was purified by flash chromatography (1:1 PE–EtOAc) to yield 520 mg (95%) of **20** as crystals; mp 148°C; TLC (1:1 PE–EtOAc): R_f 0.28; $[\alpha]_D^{20}$ −37.5° (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.29, 1.37, 1.41, 1.45 (4 s, 12 H, 4 Me), 1.90, 2.36 (2 dd, 2 H, $J_{3a,3e}$ 14.0, $J_{3a,4}$ 5.4, $J_{3e,4}$ 7.7 Hz, H-3*a*, H-3*e*), 3.74 (s, 1 H, OH), 3.76 (dd, 1 H, $J_{7,8}$ 7.7, $J_{8a,8b}$ 8.2 Hz, H-8a), 3.80 (s, 3 H, COOMe), 3.96 (dd, 1 H, $J_{4,5}$ 6.0, $J_{5,6}$ 2.4 Hz, H-5), 4.06 (dd, 1 H, $J_{6,7}$ 8.1 Hz, H-6), 4.14 (dd, 1 H, $J_{7,8b}$ 6.3 Hz, H-8b), 4.38 (m, 1 H, H-7), 4.46 (m, 1 H, H-4). Anal. Calcd for $C_{15}H_{24}O_8$ (332.35): C, 54.21; H, 7.28. Found: C, 54.45; H, 7.21.

*1-O-Acetyl-3-deoxy-4,5 : 7,8-di-O-isopropylidene-β-*D-gulo-*2-octulopyranose* (**21**). —To a suspension of $LiAlH_4$ (100 mg) in dry THF (20 mL) was slowly added a solution of **20** (445 mg, 1.34 mmol) in dry THF (10 mL). The mixture was stirred at 50°C for 1.5 h. Then EtOAc (0.5 mL), water (100 mL), aq 10% NaOH (100 mL), and finally water (200 mL) were carefully added. After filtration through Celite, the solution was evaporated to dryness. The residue was acetylated with pyridine (20 mL) and Ac_2O (15 mL). After the usual workup, the syrupy residue was

purified by flash chromatography (1 : 1 PE–EtOAc); 203 mg (44%) of crystalline **21** was obtained; mp 110°C; TLC (1 : 1 PE–EtOAc): R_f 0.22; $[\alpha]_D^{20}$ −34.1° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.26, 1.37, 1.41, 1.42 (4 s, 12 H, 4 Me), 1.70 (m, 1 H, H-3*a*), 2.09 (s, 3 H, OAc), 2.28 (dd, 1 H, $J_{3a,3e}$ 15.4, $J_{3e,4}$ 4.2 Hz, H-3*e*), 2.99 (s, 1 H, OH), 3.73 (dd, 1 H, $J_{7,8a}$ 7.3, $J_{8a,8b}$ 8.2 Hz, H-8a), 3.79 (dd, 1 H, $J_{6,7}$ 8.1 Hz, H-6), 4.12 (dd, 1 H, $J_{7,8b}$ 6.3 Hz, H-8b), 4.29 (m, 1 H, H-7). Anal. Calcd for $C_{16}H_{26}O_8$ (346.38): C, 55.48; H, 7.57. Found: C, 55.83, H, 7.61.

*1,2,4,5,6,7,8-Hepta-O-acetyl-3-deoxy-*D-glycero-L-galacto-*octitol and 1,2,4,5,6,7,8-hepta-O-acetyl-3-deoxy-*D-glycero-L-talo-*octitol* (**22A,B**).—Compound **21** (87 mg, 0.25 mmol) was dissolved in EtOH (10 mL) and reduced with $NaBH_4$ (52 mg). After 12 h at room temperature, the solution was acidified with M HCl to pH 1 and stirred for 1.5 h at 70°C. The mixture was passed down a column of Amberlite IR-120 (H^+) resin (10 mL), and the eluate and washings, after concentration to dryness, were distilled with MeOH (5 × 20 mL) to remove boric acid. The residue was acetylated (1 : 1 Ac_2O–pyridine). After purification by flash chromatography (1 : 1 PE–EtOAc), 120 mg (92%) of **22A,B** was obtained as an oil (diastereomer ratio 1.2 : 1); TLC (1 : 1 PE–EtOAc): R_f 0.26; ^1H NMR ($CDCl_3$), major product: δ 1.69–2.12 (2 m, 23 H, H-3a,3b, 7 OAc), 3.88–4.31 (2 m, 4 H, H-1a,1b,8a,8b), 4.84 (m, 1 H, H-4), 5.05 (m, 1 H, H-2), 5.14–5.38 (m, 3 H, H-5,6,7); minor product: δ 1.84–2.12 (m, 23 H, H-3a,b, 7 OAc), 3.88–4.31 (2 m, 4 H, H-1a,1b,8a,8b), 4.93 (m, 1 H, H-4), 5.05 (m, 1 H, H-2), 5.14–5.38 (m, 3 H, H-5,6,7). Anal. Calcd for $C_{22}H_{32}O_{14}$ (520.49): C, 50.77; H, 6.20. Found: C, 50.62; H, 6.40.

*3-Deoxy-*D-glycero-L-galacto-*octitol and 3-deoxy-*D-glycero-L-talo-*octitol* (**23A,B**). —Compound **22A,B** (110 mg, 0.21 mmol) was deprotected and purified as described for **11aA,B**, to give **23A,B** (38 mg, 80%); TLC (5 : 4 : 1 $CHCl_3$–MeOH–water): R_f 0.32. Acetylation of **23A,B** led to **22A,B** in quantitative yield.

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