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Note

Synthesis of methyl D- and L-*glycero*-α-D-*manno*-heptofuranosides

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Abstract

Methyl L-*glycero*-α-D-*manno*- and D-*glycero*-α-D-*manno*-heptofuranosides (**1** and **2**) have been synthesized using two-carbon-atom elongation of a lyxofuranoside system. A new method for the synthesis of **2** has been developed based on the reaction of protected methyl α-D-*manno*-hexodialdo-1,4-furanoside with benzyloxymethylmagnesium chloride.

Keywords: Methyl L-*glycero*-α-D-*manno*-heptofuranoside; Methyl D-*glycero*-α-D-*manno*-heptofuranoside; Synthesis

1. Introduction

Practical methods for the synthesis of heptoses, particularly of the D- and L-*glycero*-D-*manno* configuration, are of importance since these sugars are components of the inner core part of Gram-negative bacterial lipopolysaccharides [1,2]. In most cases studied up to now, these sugars occur in the pyranose form. Accordingly, convenient methods for their synthesis have been elaborated [3–7].

It was suggested that L-*glycero*-D-*manno*-heptose might occur within the *Hafnia alvei* LPS in the furanose form (E. Romanowska, *personal communication*). In order to obtain model compounds, suitable for the structural confirmation, we have synthesized methyl heptofuranosides of the L-*glycero*-D-*manno* and D-*glycero*-D-*manno* configuration (**1** and **2**) using Brimacombe two-carbon-atom elongation of a lyxofuranose system [8,9]. For the synthesis of **2**, a new method has been developed based on one-carbon atom homologation of suitably blocked methyl α-D-mannofuranoside.

2. Results and discussion

The syntheses of **1** and **2** followed essentially the method elaborated by Brimacombe [8], replacing benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside by the methyl analogue **3**. Some changes in the procedures allowed to increase the stereoselectivity and to obtain the final products in high purity.

Methyl (methyl *Z*- and *E*-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hept-5-enofuranosid)uronate (**5** and **6**, 3:1) were prepared by the Wittig reaction between methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**4**) and (methoxycarbonylmethylene)-triphenylphosphorane (Scheme 1). *Cis*-hydroxylation of **5** gave methyl (methyl 2,3-*O*

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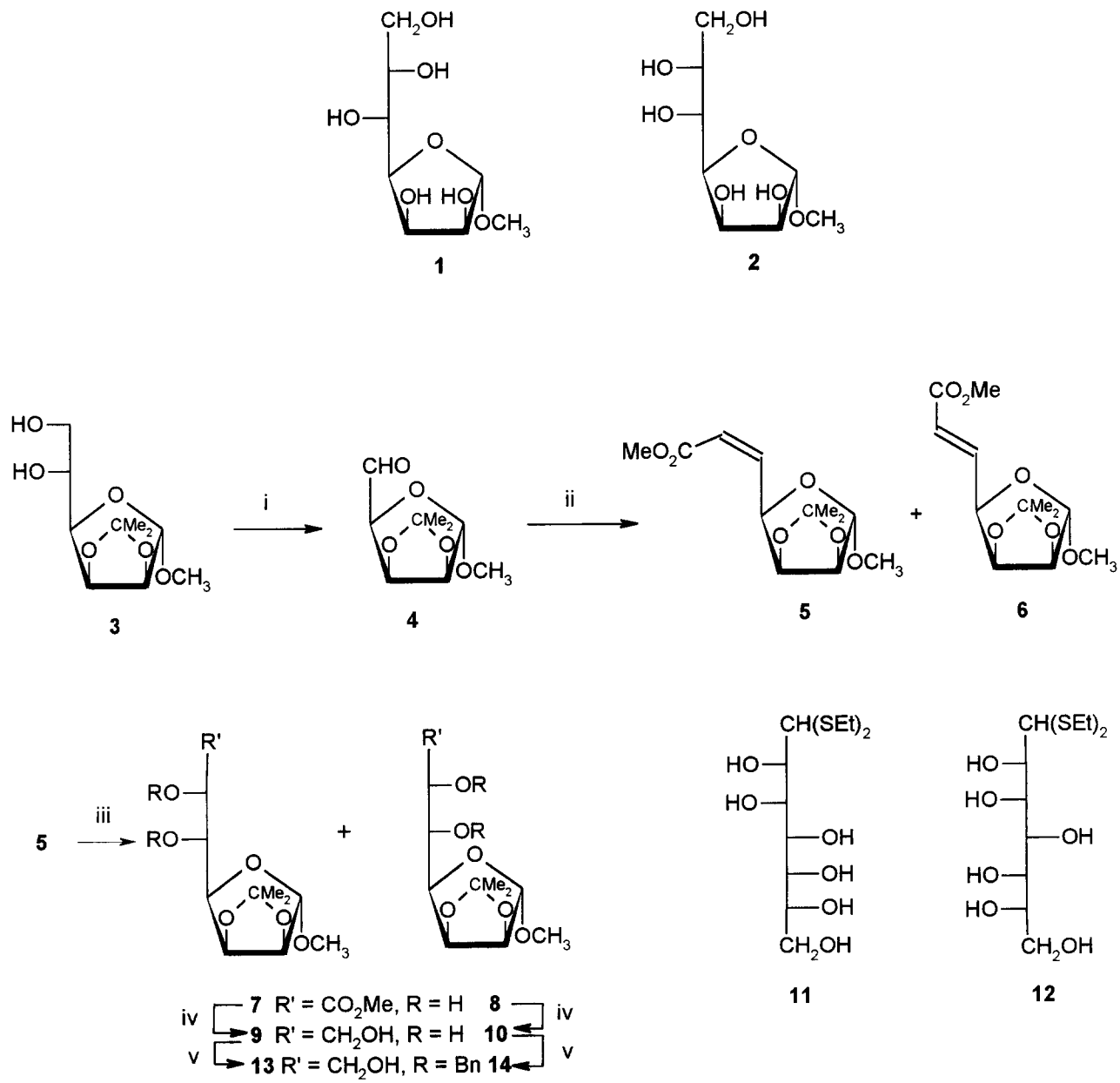
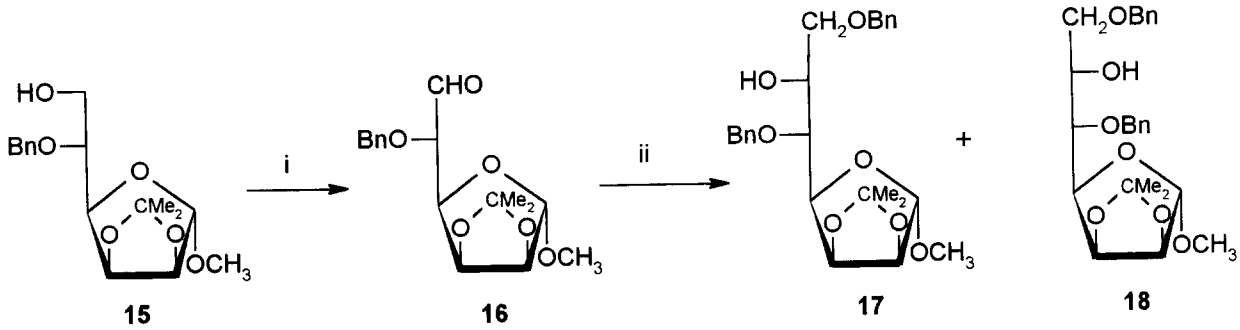


Scheme 1. i, $NaIO_4$; ii, Ph_3PCHCO_2Me, C_6H_6, refl.; iii, NMMO, OsO_4, 1:1 tert-BuOH-H_2O; iv, DIBAH, −5 °C; v, NaH, BnBr, THF.

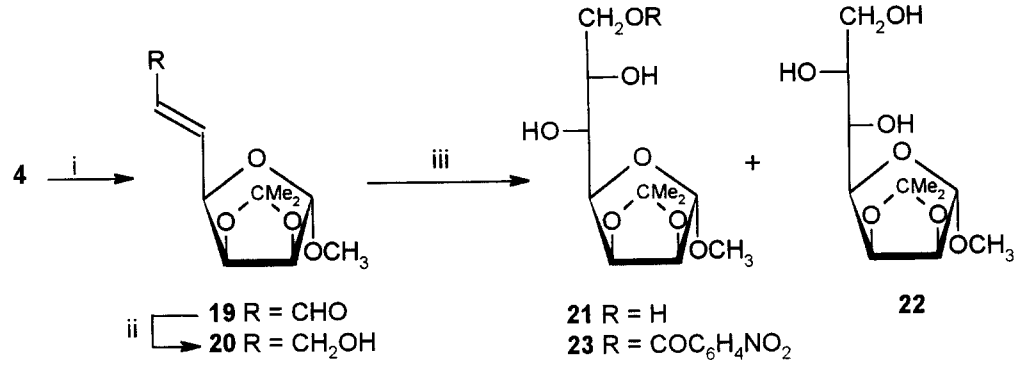
-isopropylidene-D-*glycero*-α-D-*manno*-heptofurano-sid)uronate (**7**) and the L-*glycero*-β-L-*gulo* stereoisomer (**8**) in a ratio 9:1. Diisobutylammonium hydride reduction of **7** + **8** led to methyl heptofuranosides **9** and **10** in the same proportion and in a good overall yield (89%). The configuration of both products was confirmed after hydrolysis to free sugars and conversion to the crystalline diethyl dithioacetals **11** and **12**. The configurational assignments were also confirmed [10] by the recently developed CD method [11].

Separation of **9** and **10** could be achieved after conversion to the 5,6,7-tri-*O*-benzyl derivatives **13** and **14**. Pure **13** was hydrogenolyzed again to **9**. Hydrolytic cleavage of the isopropylidene grouping in **9** under typical conditions (80% CH_3COOH or formic acid) was achieved with the loss of the anomeric methoxy grouping. Eventually methyl D-*glycero*-α-D-*manno*-heptofuranoside (**2**) was obtained in 30% yield after hydrolysis with 50% trifluoro-acetic acid in MeOH.

A new approach to **2** was based on one-carbon-atom chain elongation [3] of protected methyl α-D-mannofuranoside (**15**) (Scheme 2). Swern oxidation of **15** to methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-α-



i. Swern oxid., ii. $BnOCH_2MgCl$.



Scheme 2. i, $Ph_3PCHCHO$, C_6H_6, refl.; ii, DIBAH, −5 °C; iii, NMMO, OsO_4, t-BuOH-H_2O 1:1.

D-*manno*-hexodialdo-1,4-furanoside (**16**) and its reaction with benzyloxymethylmagnesium chloride furnished 65% of methyl 5,7-di-*O*-benzyl-2,3-*O*-isopropylidene-heptofuranosides of the D-*glycero*-α-D-*manno* (**17**) and L-*glycero*-β-L-*gulo* (**18**) configuration in 7:1 proportion. These products were identified after hydrogenation to **9** and **10** (Scheme 1). Configuration of **18** was additionally proved by the formation and isolation of the diethyl dithioacetal identical in every respect with **12**. Isolation of **18** instead of the L-*glycero*-α-D-*manno* stereoisomer was unexpected. The formation of **18** was undoubtedly preceded by epimerization at C-5 in the aldehyde **16** before reacting with the Grignard reagent. The stereochemical outcome of the Grignard reaction leading to both products can be interpreted with the non-chelated Felkin–Anh model [12,13].

Methyl L-*glycero*-α-D-*manno*-heptofuranoside (**1**) was obtained from **4**, via aldehyde **19** and allylic alcohol **20**, using the Brimacombe approach [8] shown in Scheme 2. Methyl 2,3-*O*-isopropylidene-heptofuranosides of the L-*glycero*-α-D-*manno* (**21**) and L-*glycero*-β-L-*gulo* (**22**) configuration were obtained with an improved (9:1) stereoselectivity and a good (79%) overall yield. Chromatographic separation of both stereoisomers was achieved after conversion of the mixture to their 7-*O*-(*p*-nitrobenzoates). The major ester **23** was next hydrolysed with sodium hydrogen carbonate in MeOH to pure **21** and the isopropylidene grouping was again removed with 50% trifluoroacetic acid in MeOH to give 53% of **1**. This product was also converted to the diethyl dithioacetal **24** having physical data identical with the literature.

^1H and ^{13}C NMR spectral data of intermediate and final products are collected in Tables 1 and 2.

3. Experimental

General methods.—^1H NMR spectra were recorded with Varian AC-200 (200 MHz) and Bruker AM-500 (500 MHz) spectrometers using $CDCl_3$ or

Table 1
^{1}H and ^{13}C NMR data for L- and D-*glycero*-α-D-*manno*- and L-*glycero*-β-L-*gulo*-heptofuranosides and their derivatives

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	CH_2Ph	OCH_3	CMe_2
	H-1	H-2	H-3	H-4	H-5	H-6	$H_{7A,7B}$	C	C	C
	($J_{1,2}$ Hz)	($J_{2,3}$ Hz)	($J_{3,4}$ Hz)	($J_{4,5}$ Hz)	($J_{5,6}$ Hz)	($J_{6,7}$ Hz)	($J_{7A,7B}$ Hz)	H($J_{H,H''}$ Hz)	H	H
1	110.36	78.54	72.88	80.20	70.01	72.20	64.71		56.02	
	4.81 (d)	4.05 (dd)	4.32 (dd)	4.09 (dd)	4.01 (dd)	3.88 (td)	3.69 (m)		3.36	
	(3.1)	(4.9)	(3.9)	(8.2)	(1.7)	(5.7)	(10.9)			
2	109.98	77.90	72.91	80.12	73.98	71.77	63.93		55.67	
	4.82 (d)	3.79 (dd)	4.30 (dd)	4.09 (dd)	3.83 (dd)	3.96 (m)	3.75, 3.64		3.37	
	(3.2)	(4.6)	(3.9)	(6.9)	(5.6)	(3.5) (6.7)	(11.5)			
9	107.42	84.30	80.16	79.31	72.77	70.65	63.18		54.78	25.86, 24.52
	4.93 (s)	4.58 (d)	4.87 (dd)	4.07 (dd)	4.05 (dd)	3.89	3.78 (m)		3.32	1.47, 1.33
		(5.9)	(3.3)	(8.2)	(5.0)					
10	106.56	85.12	81.17	79.30	71.71	71.33	63.73		54.66	25.74, 24.14
	4.97 (s)	4.60 (d)	4.82 (dd)	4.14 (m)	4.10 (m)	3.90	3.78 (m)		3.34	1.48, 1.31
		(5.9)	(3.6)	(7.3)						
11	56.82	75.33	70.10	72.74	73.78	75.07	64.98	25.96, 25.76		15.11, 15.01
	4.96 (d)	4.91 (bd)	5.09 (bd)	5.10 (dd)	4.70 (dd)	4.66 (m)	4.52, 4.40	2.94, 2.76)		1.25, 1.20
	(1.7)	(9.2)	(< 0.5)	(6.4)	(7.0)	(3.6)(5.6)	(AB)(11.1)	($2\times SCH_2$		($2\times CH_3$)
12	56.09	75.23	75.54	69.02	76.34	73.04	64.76	25.62, 25.41		14.84, 14.63
	4.90 (bs)	4.91 (bd)	4.79 (dd)	5.25 (dd)	4.57 (dd)	4.62 (m)	4.74, 4.32	2.94, 2.73		1.28, 1.18
		(8.6)	(1.4)	(2.3)	(7.6)	(4.0)(5.8)	(AB)(11.0)	($2\times SCH_2$)		($2\times CH_3$

13	107.16 4.83 (s)	84.45 4.49 (d) (5.9)	80.03 4.76 (dd) (3.2)	78.20 4.01 (dd) (9.2)	77.39 4.12 (dd) (1.5)	79.71 4.07 (m) (4.9)	70.43 3.81 (m) (10.6)	73.99,73.15, 72.52 4.80, 4.50, 4.76 (12.0)	54.26 3.17	26.16, 25.03 1.44, 1.32
14	106.69 4.90 (s)	85.11 4.49 (d) (5.9)	81.12 4.61 (dd) (2.8)	78.65 4.08 (dd) (8.7)	78.56 4.12 (dd) (2.0)	79.93 3.93 (m) (6.3)	69.91 3.76 (ABq) (10.2)	74.29,73.32, 71.57 4.80, 4.63, 4.51 (11.6)	54.39 3.32	26.10, 24.83 1.44, 1.25
17	107.54 4.85 (s)	84.38 4.50 (d) (5.8)	80.09 4.76 (dd) (3.3)	79.14 3.95 (dd) (9.3)	77.11 4.00 (dd) (3.9)	72.23 4.17 (m) (7.3)	70.56 3.68 (ABq)(10.0)	74.17, 73.36 4.71, 4.58 (12)	54.54 3.19	26.23, 25.06 1.46, 1.31
18	106.74 4.91 (s)	85.08 4.58 (d) (5.8)	81.89 4.76 (dd) (3.3)	80.43 4.02 (dd) (8.1)	79.13 4.07 (dd) (3.3)	71.01 3.98 (m) (5.3)	70.76 3.98 (ABq) (9.6)	74.57, 73.34 4.71, 4.60 (11.2)	54.51 3.35	26.19, 24.92 1.47, 1.28
21	107.0 64.92 (s)	84.61 4.58 (d) (5.9)	80.11 4.85 (dd) (3.8)	78.69 4.08 (dd) (8.0)	71.51 3.99 (dd) (2.8)	72.23 3.87 (dd) (4.6)	64.92 3.83 (m) (11.0)		54.65 3.32	25.85, 24.49 1.48, 1.34
22	106.89 4.96 (s)	85.09 4.59 (d) (5.9)	80.04 4.80 (dd) (3.1)	79.12 4.13 (m) (8.6)	70.79 4.11 (m) (2.7)	71.47 3.82	64.42 3.75 (m)		54.72 3.33	25.97, 24.31 1.46, 1.30
23	107.01 4.92 (s)	84.62 4.59 (d) (5.9)	80.01 4.86 (dd) (3.8)	78.74 4.11 (dd) (8.1)	69.70 4.02 (dd) (2.7)	70.00 4.19 (m) (5.8)	67.03 4.56 (7.1)		54.66 3.30	25.84, 24.50 1.46, 1.33
24	56.99 4.97 (d) (1.7)	75.73 4.90 (dd) (9.2)	71.70 5.14 (dd) (0.8)	70.73 5.08 (dd)	72.23 4.66 (dd) (2.0)	72.38 4.88 (6.2)(6.0)	65.28 4.37, 4.34 (AB)(10.8)	25.95, 25.77 2.93, 2.76 ($2\times SCH_2$)		15.07, 15.00 1.26, 1.17 ($2\times CH_3$)

Table 2
^{1}H and ^{13}C NMR data for intermediate products in the synthesis of methyl L- and D-*glycero*-D-*manno*-heptofuranosides

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	CH_2Ph	OCH_3	CMe_2
	H-1	H-2	H-3	H-4	H-5	H-6	H-7	C	C	C
	($J_{1,2}$ Hz)	($J_{2,3}$ Hz)	($J_{3,4}$ Hz)	($J_{4,5}$ Hz)	($J_{5,6}$ Hz)	($J_{6,7}$ Hz)	($J_{7A,7B}$ Hz)	H($J_{H,H''}$ Hz)	H	H
5	107.36	81.64	77.28	85.08	120.67	45.16	165.94	51.56	54.69	26.11, 24.76
	4.96 n(s)	4.60 (d)	5.03 (dd)	5.41 (m)	6.35 (dd)	6.35 (dd)		3.73	3.33	1.45, 1.29
		(5.8)	(3.7)	(1.5)	(11.7)	(6.8)				
6	107.27	81.12	79.02	85.21	122.99	141.43	166.34	51.70	54.89	26.10, 5.05
	4.95 (s)	4.60 (d)	4.76 (dd)	4.55 (m)	6.14 (dd)	6.98 (dd)		3.75	3.34	1.43, 1.30
		(5.8)	(3.8)	(1.6)	(15.8)	(5.5)				
7	107.43	84.12	80.01	77.64	70.84	71.81		52.92	54.85	25.96, 24.70
	4.95 (s)	4.60 (d)	4.81 (dd)	4.08 (dd)	4.24 (dd)	4.44 (dd)		3.85		1.47, 1.33
		(5.9)	(3.8)	(8.8)	(1.9)					
8	106.95	84.85	79.82	78.06	71.26	70.43		52.64	54.39	25.88, 24.58
	4.91 (s)	4.58 (d)	4.83 (dd)	4.09 (dd)	4.27 (dd)	4.44 (dd)		3.83	3.31	1.49, 1.33
		(5.9)	(3.7)	(8.6)	(1.6)					
19	107.35	81.12	79.02	85.22	133.47	149.79	193.36		54.99	26.07, 25.02
	4.91 (s)	4.56 (d)	4.75 (dd)	4.62 (m)	6.8 (dd)	6.32 (dd)	9.57 (dd)		3.34	1.41, 1.29
		(5.8)	(3.8)	(5.1)	(15.9)	(7.9)	(7.9)			
20	107.21	81.47	80.28	85.39	125.22	134.75	63.04		54.82	26.18, 24.96
	4.90 (s)	4.58 (d)	4.66 (dd)	4.42 (dd)	5.87 (qt)	6.04 (dt)	4.20		3.34	1.47, 1.31
		(5.8)	(3.5)	(7.1)	(15.6)	(4.8)	(9.6)			

CH_3OD as solvents and Me_4Si as internal standard. ^{13}C NMR spectra were recorded in the DEPT mode. The assignment of signals was based on ^1H, ^{13}C-COSY spectra. High resolution mass spectra (HRMS) were measured in the FAB^+ ion mode with AMD-604 mass spectrometer. Optical rotations were measured at 20 ± 2 °C with a Jasco DIP 360 polarimeter.

Tetrahydrofuran was distilled from lithium aluminum hydride under argon. TLC was performed on E. Merck Silica Gel HF-254 plates and column chromatography on Silica Gel 230–400 mesh. The intermediate products were obtained according to published methods: Methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**3**) [14], methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**4**) [15] and methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannofuranoside (**15**) [16].

*Methyl (methyl Z- and E-5,6-dideoxy-2,3-O-isopropylidene-α-*D-lyxo-*hept-5-eno-furanosid)uronates* (**5**)*and* (**6**).—To a soln of **4** (2 g, 9.9 mmol) in abs benzene (50 mL), (methoxycarbonylmethylene)-triphenylphosphorane (3.3 g, 10.2 mmol) was added and the mixture was refluxed. After 3 h the mixture was cooled, concentrated to dryness, and the residue was purified by column chromatography with 6:1 hexane–EtOAc. A mixture of **5** + **6**, (1.94 g 76%) was obtained. Repeated chromatography with 8:1 hexane–EtOAc gave pure compounds: **5** (1.3 g), oil, $[\alpha]_D$ −100° (*c* 2.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 6.97. Found: C, 55.80; H, 7.02; and **6** (0.42 g), mp 88–89 °C, $[\alpha]_D$ +9° (*c* 0.8, $CHCl_3$). Anal. Found: C, 55.90; H, 7.15.

Cis-*hydroxylation of* (**5**).—To a soln of **5** (0.65 g, 2.51 mmol) in 1:1 *tert*-butanol–water (17 mL) *N*-methylmorpholine *N*-oxide (NMMO, 0.72 g, 5.33 mmol) and osmium tetraoxide (69.5 mg, 0.4 mL of a 2% solution in toluene) was added and the mixture was stirred in the dark at room temperature. After 16 h, $CHCl_3$ (150 mL) was added, the soln was washed with 5 M HCl (8 mL) followed by 45% aqueous sodium metabisulfite (10 mL), the organic layer was dried and concentrated to dryness. The residue was dissolved in EtOAc (10 mL), filtered through a silica gel pad, and concentrated. A mixture of **7** and **8** (0.51 g, 68%) in the proportion 9:1 (^1H NMR) was obtained.

*Methyl 2,3-*O*-isopropylidene-*D-glycero-α-D-manno-*and* L-glycero-β-L-gulo-*heptofuranosides* (**9**) *and* (**10**).—To a cooled (−5 °C) soln of the mixture **7** + **8** (0.43 g, 1.4 mmol) in CH_2Cl_2 (10 mL) diisobutylaluminum hydride (DIBAH, 5 mL of a 1 M solution in hexane) was slowly added. After 3 h of stirring at 0 °C, MeOH (5 mL) was added, the soln was filtered, and the filtrate was concentrated to afford a mixture of **9** and **10** (0.346 g, 89%) in 9:1 proportion.

Separation of this mixture, also in the form of its 5,6,7-tri-*O*-acetyl derivatives, did not succeed. The mixture was benzylated (sodium hydride, BnBr, Me_2NCHO, 88%) and 5,6,7-tri-*O*-benzyl derivatives **13** and **14** could be separated by chromatography. Compound **13**: $[\alpha]_D$ +26° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{32}H_{38}O_7$: C, 71.90; H, 7.11. Found: C, 71.77; H, 7.14. **14**: $[\alpha]_D$ +15° (*c* 1.2, $CHCl_3$). HRMS: *m/z* 519.2383, Calcd for $[M - CH_3]^+$ ($C_{31}H_{35}O_7$): 519.2402. Separated compounds were hydrogenated (hydrogen gas, palladium on carbon) to afford homogeneous triols: **9**, $[\alpha]_D$ +42° (*c* 1.6, $CHCl_3$). HRMS: *m/z* 249.0972, Calcd for $[M - CH_3]^+$ ($C_{10}H_{17}O_7$): 249.0974; and **10**, $[\alpha]_D$ +22° (*c* 1.2, $CHCl_3$). HRMS: Found for $[M - CH_3]^+$ ($C_{10}H_{17}O_7$): 249.0966.

D-glycero-D-manno-*heptose and* L-glycero-L-gulo-*heptose diethyl dithioacetals* (**11**), (**12**).—A sample of the mixture **9** + **10** was hydrolyzed with 80% acetic acid and to the mixture of free heptoses dissolved in concd HCl, ethanethiol was added [18]. The diethyl dithioacetals were separated by preparative TLC yielding: **11**, mp 156 °C, lit. 155–156 °C [18]; $[\alpha]_D$ +30.1° (*c* 0.8, water), lit. +29.6° (*c* 2.1, water) [18]; and **12**, mp 154–155 °C, $[\alpha]_D$ +7.7° (*c* 0.88, C_5H_5N). Anal. Calcd for $C_{11}H_{24}O_6S_2$: C, 41.75; H, 7.64; S, 20.24. Found: C, 41.98; H, 7.93; S, 20.10. The diethyl dithioacetal, prepared from commercial D-*glycero*-D-*gulo*-heptose, had mp 153–154 °C, $[\alpha]_D$ −7.8° (*c* 2.81, C_5H_5N).

Methyl D-glycero-α-D-manno-*heptofuranoside* (**2**).—To a solution of **9** (144 mg, 0.54 mmol) in MeOH (10 mL), 50% aq trifluoroacetic acid (0.6 mL) was added and the mixture was refluxed. The reaction was stopped after 8 h, after approximately half of the substrate has reacted. TLC showed the substantial formation of a strongly polar (free heptose) product. The soln was neutralized with Amberlite IRA 410/OH^- resin, concentrated, and the residue was chromatographed with 6:1 $CHCl_3$–MeOH to recover 48 mg (33%) of the unreacted substrate, and then with 3:1 chloroform–MeOH to obtain **2** (24.8 mg, 30.4% after subtraction of the recovered substrate), $[\alpha]_D$ +41.5° (*c* 1.6, MeOH). HRMS: *m/z* 193.0726, Calcd for $[M - OCH_3]^+$ ($C_7H_{13}O_6$): 193.0712.

*Methyl 5,7-di-*O*-benzyl-2,3-*O*-isopropylidene-*D-glycero-α-D-manno-*and* L-glycero-β-L-gulo-*heptofuranosides* (**17**) and (**18**).—Dry magnesium

turnings (0.75 g) were covered with abs tetrahydrofuran (2 mL) and sublimed mercury(II) chloride (30 mg) was added. The mixture was cooled to −15 °C and a few drops of neat, freshly prepared benzyloxymethyl chloride was added while stirring. When formation of the Grignard reagent started, a soln of benzyloxymethyl chloride (4.85 g) in abs tetrahydrofuran (5 mL) was slowly added at −25 to −20 °C. After completion of the Grignard reagent formation (2 h), a soln of methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-α-D-*manno*-hexodialdo-1,4-furanoside (**16**, 2.5 g, freshly prepared from **15** by Swern oxidation) in abs tetrahydrofuran (10 mL) was slowly added (~2 h) at the same temperature and afterwards, the reaction mixture was allowed to attain room temperature. After additional stirring for 12 h the mixture was cooled to 0 °C and poured to cold aq ammonium chloride (150 mL). The mixture was extracted with ether, dried over MgSO4, and concentrated to dryness. The residue was purified by column chromatography with toluene–acetone (95:5) as eluent; a mixture of **17** and **18** (2.23 g, 64%) was obtained in 7:1 proportion.

*Methyl 2,3-*O*-isopropylidene-*D-glycero-α-D-manno-*heptofuranoside* (**9**).—Debenzylation of **17** + **18** under conventional conditions (H_2, 10% palladium on carbon, EtOH, reaction time, 18 h) yielded a mixture of methyl 2,3-*O*-isopropylidene-heptofuranosides (~8.5:1, 96%) identical (^{1}H NMR) with **9** and **10**.

Methyl E-*5,6-dideoxy-2,3-*O*-isopropylidene-α-D-lyxo-hepto-5-enodialdo-1,4-furanoside* (**19**).—To a soln of **4** (1.81 g, 9 mmol) in dry benzene (60 mL) was added (formylmethylene)triphenylphosphorane (3.0 g, 10 mmol) and the mixture was refluxed. After 6 h the soln was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column with 1:1 hexane–EtOAc as eluent. Compound **19** (1.74 g, 85%) was obtained as a colorless oil, $[\alpha]_D$ +23° (*c* 2.4, $CHCl_3$).

Methyl E-*5,6-dideoxy-2,3-*O*-isopropylidene-α-D-lyxo-hepto-5-enofuranoside* (**20**).—To a cooled (−10 °C) and stirred soln of aldehyde **19** (1.13 g, 4.95 mmol) in anhyd CH_2Cl_2 (15 mL) under argon was gradually added a 1 M solution of diisobutylaluminum hydride in hexane (7.5 mL, 7.45 mmol) maintaining the internal temperature at −5 °C. The mixture was stirred at 0 °C for 2 h, the excess of the reagent was destroyed with saturated aq ammonium chloride, and CH_2Cl_2 (200 mL) was added. The organic layer was filtered through a Celite pad, the filtrate was washed with water, dried ($MgSO_4$), and concentrated under diminished pressure. Chromatography of the residue on a silica gel column with 1:2 hexane–EtOAc yielded **20** (0.9 g, 82%), oil, $[\alpha]_D$ +36° (*c* 1.8, $CHCl_3$).

Cis-*hydroxylation of* (**20**).—A soln of **20** (0.62 g, 2.69 mmol), *N*-methylmorpholine *N*-oxide (0.73 g, 5.4 mmol) and osmium tetraoxide (0.68 mL of a 1% solution in toluene) in 1:1 *tert*-butanol–water (15 mL) was stirred in the dark at room temperature until TLC indicated the disappearance of the substrate (~6 h). The mixture was diluted with $CHCl_3$ (150 mL), washed with 5 M HCl (10 mL) and shaken vigorously for several min with 45% aq sodium metabisulfite (10 mL). The chloroform soln was dried, concentrated, the residue was dissolved in a small portion of EtOAc, and passed through a silica gel column. The eluent was concentrated under reduced pressure to furnish a 7:1 mixture of **21** and **22** (0.52 g, 73%) (500 MHz ^{1}H NMR).

Separation of the mixture of **21** + **22** was not successful. Column chromatography, HPLC, and preparative TLC of the free triols as well as of their tri-*O*-acylated, tri-*O*-trimethylsilylated and tri-*O*-benzylated derivatives did not provide any separation of the stereoisomeric products.

*Methyl 2,3-*O*-isopropylidene-7-*O*-(p-nitrobenzoyl)-*L-glycero-α-D-manno-*heptofuranoside* (**23**).—The mixture of triols **21** and **22** (0.176 g, 0.66 mmol) was dissolved in pyridine (5 mL) and *p*-nitrobenzoyl chloride (0.148 g, 0.79 mmol, 15% molar excess) was added at room temperature and the soln was stirred for 12 h. The solvent was evaporated and the residue (containing several products, TLC) was separated on TLC preparative plates with 4:1 hexane–EtOAc. The major product **23** (0.118 g, 43%) was obtained after elution as a colorless foam, $[\alpha]_D$ +39° (*c* 1.8, $CHCl_3$). Treatment of this product with $NaHCO_3$ in MeOH yielded **21** (72 mg, 96%).

L-glycero-D-manno-heptose diethyl dithioacetal (**24**).—Compound **24** was prepared from **21** as described for **11** and **12**: mp 202–203 °C, lit. 202–203 °C [17]; $[\alpha]_D$ +11.6° (*c* 1.6, C_5H_5N), lit. $[\alpha]_D$ +10.2° (*c* 1.2, C_5H_5N) [17].

Methyl L-glycero-α-D-manno-*heptofuranoside* (**1**).—Obtained from **21** (88 mg, 0.33 mmol) as described for **2**; 20.7 mg (23.5%) of the unreacted substrate was recovered. **1**, 30.4 mg (53.2%), after subtraction of the unreacted substrate, 20.7 mg (53.2%); $[\alpha]_D$ +52.3° (*c* 1.3, MeOH). HRMS: *m/z* 193.0712, calcd for $[M - OMe]^+$ ($C_7H_{13}O_6$): 193.0712.

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