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The synthesis of five L-*glycero*-D-*manno*-heptose monophosphates

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Abstract

From suitably protected benzyl α-D-mannopyranosides, five benzyl L-*glycero*-α-D-*manno*-heptopyranosides were synthesized by chain-elongation at C-6. By regiospecific protection–deprotection procedures five *O*-benzylated heptosides having 'isolated' free OH groups at C-2, C-3, C-4, C-6, or C-7 were obtained. These substrates were phosphorylated and the products were converted into free monophosphates or monophosphate cyclohexylammonium salts (**1–5**) which were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectra and high-performance anion-exchange chromatography. © 1996 Elsevier Science Ltd.

Keywords: Bacterial sugars; L-*glycero*-D-*manno*-Heptose monophosphate; Heptose synthesis

1. Introduction

L-*glycero*-D-*manno*-Heptopyranose (LD-manHep*p*) residues occurring within the inner core region of lipopolysaccharides of Enterobacteriaceae are often esterified by a phosphate, 2-aminoethyl-phosphate or -pyrophosphate residue [1]. Their location is often difficult to determine because phosphates are able to migrate under various experimental conditions and phosphodiesters or pyrophosphates may be removed during degradation processes. As a part of a larger programme, we decided to synthesize monophosphates of L-*glycero*-D-*manno*-heptopyranose having the $PO(OH)_2$ moiety at O-2, -3, -4, -6, and -7 (**1–5**). These compounds serve as models for the structure determination of oligoheptose fragments of inner core oligosaccharides by NMR.

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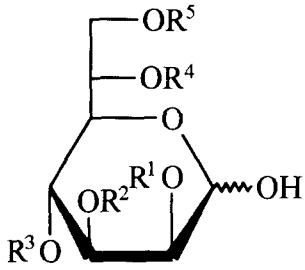
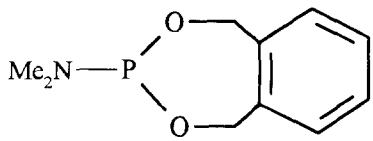
2. Results

To ensure an unambiguous introduction of a phosphoryl group at a particular oxygen atom of the L-*glycero*-D-*manno*-heptopyranose system we decided to employ derivatives of LD-manHep*p* blocked with only benzyl-type protecting groups. It is known that these groups can be removed hydrogenolytically without inducing any migration of the phosphoryl group [2,3]. Therefore, although a synthesis of a derivative of L-*glycero*-D-*manno*-heptose has already been elaborated, permitting selective access to free OH groups at C-2, -3, -4, -6, and -7 [4], we decided to synthesize separately five benzyl-protected L-*glycero*-D-*manno*-heptopyranoses having a free OH group at these positions. For chain-elongation of the D-mannose system the well-established procedure of the Grignard-type addition of an $ROCH_2$ equivalent to the aldehyde group obtained by oxidation of the 6-CH_2OH was employed. Although the desired products of the L-*glycero*-D-*manno* configuration were the dominating products some quantities of the alternative D-*glycero*-D-*manno* stereoisomer and, more often, of benzyl heptosides derived from C-5-epimerized aldehydes were also isolated.

The compounds of L-*glycero*-D-*manno* configuration were subsequently phosphitylated with 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane (DMABDP, **6**) [5] and the phosphites were then oxidized to phosphate esters. The products obtained were purified, hydrogenated in the presence of 10% Pd–C catalyst in an ethanol–ethyl acetate mixture, and converted into di(cyclohexylammonium) salts as final, non-hygroscopic products.





6 (DMABDP)

1 $R^1 = PO(OH)_2$, $R^2=R^3=R^4=R^5=H$ (cyclohexylammonium salt)

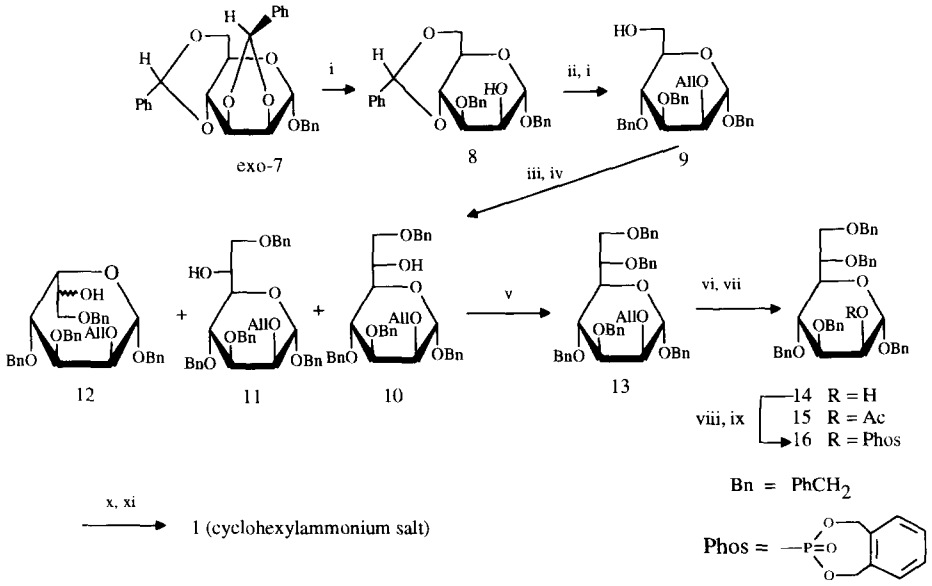
2 $R^2 = PO(OH)_2$, $R^1=R^3=R^4=R^5=H$ (cyclohexylammonium salt)

3 $R^3 = PO(OH)_2$, $R^1=R^2=R^4=R^5=H$

4 $R^4 = PO(OH)_2$, $R^1=R^2=R^3=R^5=H$

5 $R^5 = PO(OH)_2$, $R^1=R^2=R^3=R^4=H$ (cyclohexylammonium salt)

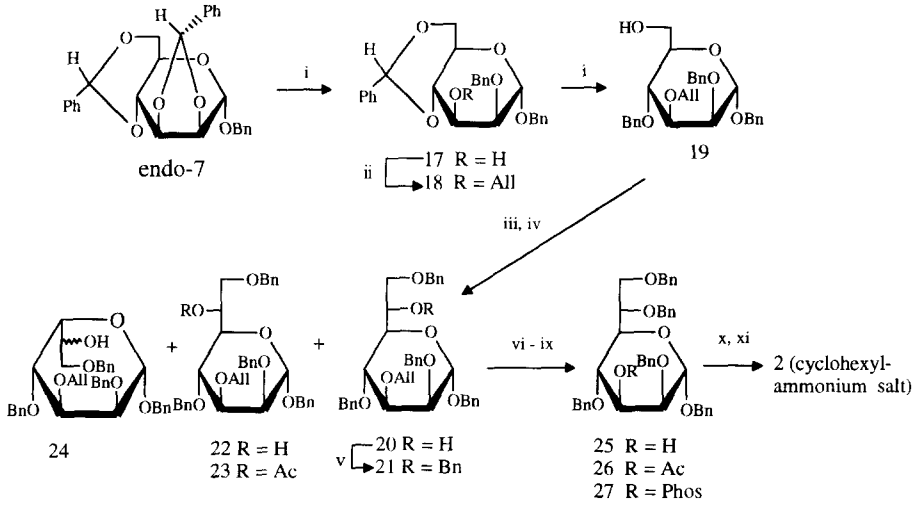
The first two phosphates having the phosphoryl group at O-2 or O-3 were synthesized starting from benzyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**7**). The mixture of



Scheme 1. Reagents: i. $LiAlH_4$–$AlCl_3$; ii. NaH, AllBr, DMF; iii. Swern oxid.; iv. $BnOCH_2MgCl$, THF; v. NaH, BnCl, DMF; vi. $(PPh_3)_3RhCl$, Dabco; vii. HgO, $HgCl_2$; viii. DMABDP; ix. MCPBA; x. H_2, Pd/C; xi. $C_6H_{11}NH_2$.

exo and *endo* isomers was separated, and *exo*-**7** was reduced to yield benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**8**) as described by Lipták et al. [6]. The free OH group was allylated and the benzylidene ring was reduced again with the $LiAlH_4$–$AlCl_3$ reagent to yield benzyl 2-*O*-allyl-3,4-di-*O*-benzyl-α-D-mannopyranoside (**9**) as described in ref. [6]. For the chain-elongation reaction, **9** was oxidized according to Swern, and the resulting aldehyde was treated with benzyloxymethylmagnesium chloride to yield 85% of a 4.2:1.2:1 mixture of benzyl 2-*O*-allyl-3,4,7-tri-*O*-benzyl-L-*glycero*-D-*manno*- and -D-*glycero*-D-*manno*-heptopyranoside (**10** and **11**, respectively) and a stereoisomer (**12**) of **10** and **11** derived from the aldehyde having inverted configuration at C-5. The configuration of **12** is unknown but, assuming a Cram-type cyclic transition state during the Grignard reaction, the D-*glycero*-L-*gulo* configuration would be expected. The mixture was separated by chromatography and **10** was benzylated at O-6 to yield **13**. *O*-Deallylation of **13** led to the derivative **14** having a free OH-2 group which was phosphitylated, and the resulting phosphite was oxidized in situ to give phosphate **15**. Exhaustive hydrogenolysis of **15** removed all protecting groups in one step and yielded L-*glycero*-D-*manno*-heptose 2-(dihydrogen phosphate) which was converted into the di(cyclohexylammonium) salt **1** (Scheme 1).

endo-**7** Was converted into benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) which was exposed to an analogous series of reactions: allylation (→ **18**), $LiAlH_4$–$AlCl_3$ reduction of **18** (→ **19**) as described by Lipták [6], Swern oxidation of **19**, and chain elongation with benzyloxymethylmagnesium chloride to give LD-manHep*p* (**20**) together with DD-manHep*p* (**22**) and stereoisomer **24**. Separation of the mixture,



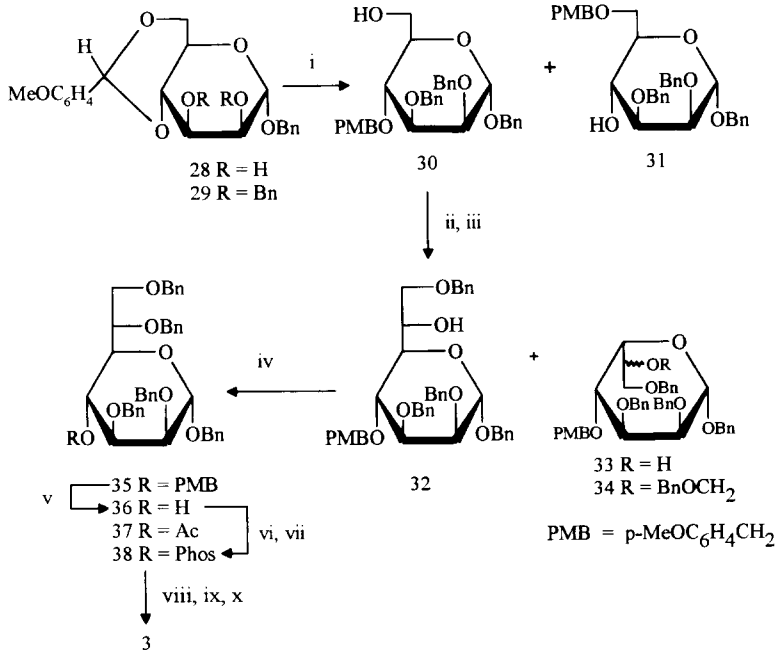
Scheme 2. Reagent sequence as in Scheme 1.

benzylation of **20** (→ **21**), *O*-deallylation (→ **25**), phosphitylation of **25**, oxidation to phosphate, and hydrogenation afforded L-*glycero*-D-*manno*-heptose 3-(dihydrogen phosphate), which was isolated as the di(cyclohexylammonium) salt **2** (Scheme 2).

For the synthesis of the 4-phosphate **3**, benzyl 4,6-*O*-(*p*-methoxybenzylidene)-α-D-mannopyranoside (**28**) was used as the substrate. Benzylation of the free OH groups at C-2 and C-3 (→ **29**) followed by reduction of **29** with sodium cyanoborohydride [7] led to a 4.5:1 mixture of benzyl 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-α-D- and 2,3-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-α-D-mannopyranoside (**30** and **31**). This mixture was separated and **30** was oxidized by the Swern method; the aldehyde obtained was subjected to reaction with benzyloxymethylmagnesium chloride to yield a 12:1 mixture of the corresponding LD-manHep*p* derivative **32** and an 'inverted' product **34** [1] in 95% yield. The mixture was separated by chromatography; pure **32** was benzylated (→ **35**), the *p*-methoxybenzyl group was oxidatively removed, and the product **36** with free 4-OH group was phosphitylated and oxidized to yield the protected 4-phosphate (**38**) (Scheme 3). Hydrogenolytic deprotection of **38** followed by neutralization with cyclohexylamine yielded a mixture of products. Gel permeation chromatography led to two fractions. The first contained the 4-phosphate **3** as the free acid and the second a ketosidic artefact as a cyclohexylammonium salt (vide infra).

Scheme 4 shows the synthesis of the 6-phosphate **4**. Benzyl 2,3,4,7-tetra-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (**39**) was obtained as described earlier [8]. We have found that the main product **39** was accompanied by a minute amount of 'inverted' stereoisomer **40**. Reaction of **39** with phosphitylating reagent **6** yielded a phosphite which was oxidized in situ to give the protected phosphate **42** in 70% yield. Hydrogena-

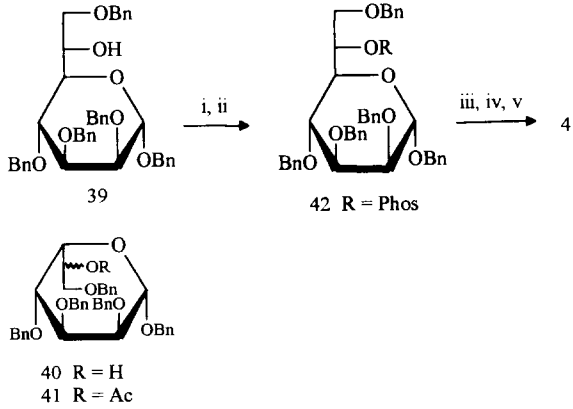
[1] The benzyloxymethyl acetal was presumably derived from the alcohol **33** by alkylation in situ with excess of the chloride.



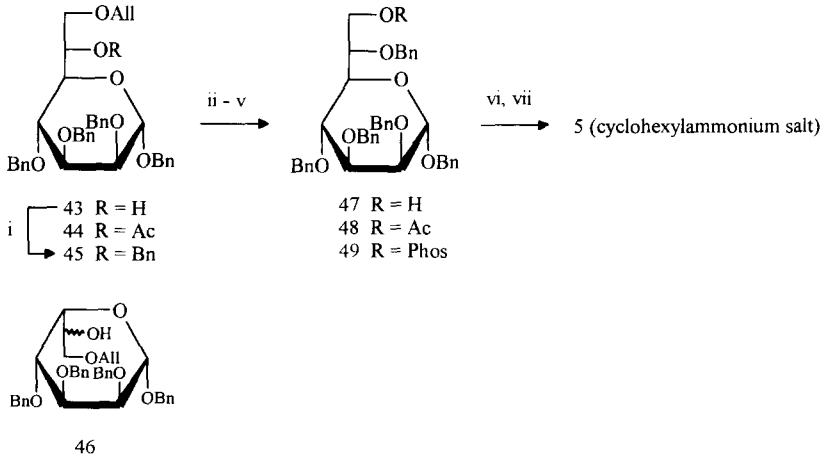
Scheme 3. Reagents: i. $NaBH_3CN$, Me_3SiCl; ii. Swern oxid.; iii. $BnOCH_2MgCl$, THF; iv. NaH, BnBr, DMF; v. $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O; vi. DMABDP; vii. MCPBA; viii. H_2, Pd/C; ix. $C_6H_{11}NH_2$; x. GPC.

tion of **42** followed by addition of aqueous cyclohexylamine furnished again a mixture of products which was separated by gel permeation chromatography. The first of these was, as in case of the 4-phosphate, the free 6-phosphate **4**, and the second was a ketosidic artefact in the form of a cyclohexylammonium salt.

Neither ketosidic product was investigated further. However, their identification was



Scheme 4. Reagents: i. DMABDP; ii. MCPBA; iii. H_2, Pd/C; iv. $C_6H_{11}NH_2$; v. GPC.



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Scheme 5. Reagents: i. NaH, BnCl, DMF; ii. $(PPh_3)_3RhCl$, Dabco; iii. HgO, $HgCl_2$; iv. DMABDP; v. MCPBA; vi. H_2, Pd/C; vii. $C_6H_{11}NH_2$.

based on NMR data. In the ^1H NMR spectra no signals of anomeric protons could be detected and no anomeric coupling could be seen in the GATED spectrum; also, no anomeric carbon atom signal was discernible in the DEPT spectrum. The ketosidic derivatives in both these cases could be formed by the Amadori rearrangement of the heptosylamine phosphates initially formed from sugar phosphates and cyclohexylamine. Such a rearrangement was observed many years ago for D-glucopyranose 4,6-(hydrogen phosphate) when the compound was treated with cyclohexylamine [9].

The last LD-manHep*p* derivative having the phosphate grouping at O-7 was synthesized from the known benzyl 7-*O*-allyl-2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (**43**) [8]. Here again a small amount of a corresponding 'inverted' product **46** was isolated. Benzylation of **43** (→ **45**) and deallylation of **45** furnished the 7-OH product **47** which was phosphitylated and oxidized to give the protected phosphate **49**. Hydrogenation, as in the previous cases, followed by neutralization with cyclohexylamine, yielded L-*glycero*-D-*manno*-heptose 7-phosphate as its di(cyclohexylammonium) salt **5** (Scheme 5).

Two comments on the syntheses performed appear to be relevant. Firstly, the Grignard-type chain elongation at C-6 of the D-mannoside system bearing various protecting groups is efficient and leads to compounds of the desired L-*glycero*-D-*manno* configuration in good to very good yields. It is remarkable, however, that besides rather small quantities of the expected DD-manHep*p* stereoisomer, more often a heptoside derived from the C-5-inverted aldehyde is formed. It is probable that all five side products of this type (i.e., **12**, **24**, **33**, **40**, and **46**) have the D-*glycero*-L-*gulo* configuration. Under the synthesis conditions, formation of these side products is limited and they can be separated from the main product by careful chromatography. Secondly, even if the Amadori products have not been observed in the synthesis of **1**, **2**, and **5**, neutralization of the free heptose phosphates with an excess of amine should be avoided.

All the phosphates occur in water solution as mixtures of α- and β-pyranose forms

Table 1
NMR data [a] for L-*glycero*-D-*manno*-heptopyranose monophosphates

Phosphate	Chemical shifts (δ)							
	H-1 C-1	H-2 C-2 2-P	H-3 C-3 3-P	H-4 C-4 4-P	H-5 C-5	H-6 C-6 6-P	H-7a C-7 7-P	H-7b
α-Hep 2P (**1**)	5.26 94.47 [b]	4.28 74.83 [c] 3.34	3.80 71.73	3.90 68.04	3.73 72.50	4.02 69.92	3.64 64.23	3.64
β-Hep 2P (**1**)	4.91 95.74 [d]	4.38 75.35 [e] 4.99	3.62 74.41	3.83 67.50	3.32 76.00	3.99 69.89	3.68 64.03	3.68
α-Hep 3P (**2**)	5.17 95.21 [f]	4.08 71.40	4.26 75.43 [g] 2.95	3.97 67.26	3.81 72.29	4.04 70.14	3.69 64.25	3.69
β-Hep 3P (**2**)	4.91 95.06 [h]	4.08 71.82	4.08 77.78 3.11	3.92 66.94	3.39 75.73	4.04 70.05	3.73 63.98	3.73
α-Hep 4P (**3**)	5.15 95.13 [i]	3.92 71.88 [j]	3.97 71.88 [j]	4.25 70.74 [k] 4.60	3.79 71.68 [l]	4.12 69.64	3.66 63.76	3.66
β-Hep 4P (**3**)	4.86 95.28 [m]	3.93 71.47	3.82 74.56	4.20 70.40 [n] 4.79	3.38 75.65°	4.07 69.54	3.70 63.50	3.70
α-Hep 6P (**4**)	5.16 95.69 [p]	3.90 71.04 [q]	3.86 72.45 [q]	3.92 67.16	3.84 74.22 [r]	4.40 72.63 [s] 5.04	3.66 63.18	3.66
β-Hep 6P (**4**)	4.85 95.56 [t]	3.93 71.91 [q]	3.67 73.55	3.89 66.87	3.37 76.23 [u]	4.35 72.74 [v] 5.14	3.74 62.71	3.74
α-Hep 7P (**5**)	5.17 95.50 [w]	3.91 71.89 [x]	3.84 71.82 [x]	3.82 67.44	3.92 72.42	4.16 68.99 [y]	3.88 66.66 [z] 3.13	3.88
β-Hep 7P (**5**)	4.89 95.15 [aa]	3.94 71.73 [x]	3.65 74.50	3.79 67.13	3.38 75.63	4.12 68.91 [y]	3.88 66.69 [ab] 3.05	3.88

[a] Spectra were measured on samples in D_2O at 23 °C under the following conditions: ^1H, 360 MHz, relative to acetone (δ 2.225); ^{13}C, 90.6 MHz, relative to acetone (δ 31.45); ^{31}P, 145 MHz, relative to 85% phosphoric acid (δ 0.00). The samples possessed the following pD: Hep 2P (**1**): 6.6; Hep 3P (**2**): 6.5; Hep 4P (**3**): 7.0; Hep 6P (**4**): 7.0; Hep 7P (**5**): 6.6. Phosphates **3** and **4** were measured in the protonated form. For **1**, **2**, and **5** the cyclohexylammonium group signals were: ^1H, δ 3.14 (=C*H*–N), 1.96, 1.88, 1.62, 1.32, 1.26 (10 H, 5 –CH_2–); ^{13}C, δ 51.53 (=*C*H–N), 31.58, 25.52, 25.03 (–*C*H_2C–). In ^{31}P NMR measurements the samples contained 2 nM EDTA.

[b] $J_{C\text{-}1,H\text{-}1}$ 173.8 Hz; $J_{C\text{-}1,P}$ 2.8 Hz. [c] $J_{C\text{-}2,P}$ 3.9 Hz. [d] $J_{C\text{-}1,H\text{-}1}$ 163.2 Hz. [e] $J_{C\text{-}2,P}$ 3.2 Hz. [f] $J_{C\text{-}1,H\text{-}1}$ 171.2 Hz. [g] $J_{C\text{-}3,P}$ 2.1 Hz. [h] $J_{C\text{-}1,H\text{-}1}$ 160.5 Hz. [i] $J_{C\text{-}1,H\text{-}1}$ 169.8 Hz. [j] Non-resolved. [k] $J_{C\text{-}4,P}$ 5.3 Hz. [l] $J_{C\text{-}5,P}$ 6.6 Hz. [m] $J_{C\text{-}1,H\text{-}1}$ 160.6 Hz. [n] $J_{C\text{-}4,P}$4.0 Hz. [o] $J_{C\text{-}5,P}$ 6.6 Hz. [p] $J_{C\text{-}1,H\text{-}1}$ 171.2 Hz. [q,x,y] Assignments interchangeable. [r] $J_{C\text{-}5,P}$ 5.3 Hz. [s] $J_{C\text{-}6,P}$ 5.3 Hz. [t] $J_{C\text{-}1,H\text{-}1}$ 161.0 Hz. [u] $J_{C\text{-}5,P}$ 5.3 Hz. [v] $J_{C\text{-}6,P}$ 5.3 Hz. [w] $J_{C\text{-}1,H\text{-}1}$ 171.2 Hz. [z] $J_{C\text{-}7,P}$ 5.3 Hz. [aa] $J_{C\text{-}1,H\text{-}1}$ 160.6 Hz. [ab] $J_{C\text{-}7,P}$ 5.3 Hz.

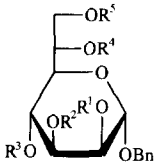
Table 2
Elution times of L-*glycero*-D-*manno*-heptose monophosphates in high-performance anion-exchange chromatography [a]

α,β-Hep phosphate	Elution time (min)
2P	17.53
3P	18.13 [b]
4P	18.00 [b]
6P	16.87
7P	15.73

[a] cf. Experimental section.
[b] Heptose phosphates 3P and 4P could not be separated as a mixture.

[10]. Their NMR (^{1}H, ^{13}C, and ^{31}P) data are collected in Table 1. Identification of LD-manHep*p* monophosphates was possible on the basis of the ^{1}H spectra [downfield shift of proton signals due to phosphorylation (+0.2 to +0.3 ppm)] and the ^{13}C NMR

Table 3
^{13}C NMR data of protected benzyl L-*glycero*-D-*manno*-heptopyranosides [a]



Compound	R^1	R^2	R^3	R^4	R^5	C-1	C-2	C-3	C-4	C-5	C-6	C-7
10	All	Bn	Bn	H	Bn	97.57	74.70	80.12	74.23	71.06	67.81	68.95
13	All	Bn	Bn	Bn	Bn	97.09	74.91	80.49	74.22	71.54	74.17	70.03
14	H	Bn	Bn	Bn	Bn	98.45	68.21	80.86	74.91	70.96	73.74	69.95
15	Ac	Bn	Bn	Bn	Bn	96.97	68.60	78.88	74.88	71.33	73.85	69.95
20	Bn	All	Bn	H	Bn	97.40	74.50	80.00	74.18	71.00	67.82	68.87
21	Bn	All	Bn	Bn	Bn	96.91	74.94	80.42	74.17	71.53	74.07	70.0
25	Bn	H	Bn	Bn	Bn	95.96	78.41	72.28	75.20	70.86	75.41	70.14
26	Bn	Ac	Bn	Bn	Bn	97.02	75.89	73.59	73.49	71.49	75.02	70.16
32	Bn	Bn	PMB	H	Bn	97.42	74.65	80.34	74.06	71.17	67.91	68.92
35	Bn	Bn	PMB	Bn	Bn	96.96	75.03	80.73	74.32	71.73	73.96	68.84
36	Bn	Bn	H	Bn	Bn	97.16	74.95	80.08	66.28	71.71	73.76	68.88
37	Bn	Bn	Ac	Bn	Bn	97.20	74.88	77.79	67.79	69.68	73.72	68.86
39	Bn	Bn	Bn	H	Bn	97.49	74.70	80.40	74.37	71.21	67.98	71.51
43	Bn	Bn	Bn	H	All	97.49	74.83	80.40	74.40	71.19	67.93	68.94
44	Bn	Bn	Bn	Ac	All	96.95	74.06	80.65	73.91	69.70	68.88	67.55
45	Bn	Bn	Bn	Bn	All	97.03	74.63	80.76	74.35	71.63	75.04	69.86
47	Bn	Bn	Bn	Bn	H	97.26	74.51	80.48	74.46	73.54	76.05	62.59
48	Bn	Bn	Bn	Bn	Ac	97.00	74.09	80.61	73.84	71.27	74.29	62.54

[a] Carbon atom signals of acetyl, allyl, and benzyl groups occurred at their normal positions and are omitted.

Table 4
^{13}C NMR spectra of benzyl-protected, phosphorylated benzyl L-*glycero*-D-*manno*-heptopyranosides [a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7
16	97.71 (3.2) [b]	73.46 (5.4)	78.65 (4.5)	73.83	71.60	75.32	70.05
27	97.24	76.98 (n.d.) [c]	79.05 (5.8)	74.09 (6.5)	71.51	75.13	70.00
38	96.94	74.39	78.41 (1.8)	74.37 (5.2)	70.65 (5.7)	73.98	69.01
42	97.16	73.97	80.87	75.11	70.32 (5.9)	74.67 (5.5)	68.79 (1.6)
49	97.14	74.00 [d]	80.60	74.25 [d]	70.94	74.80 (7.7)	66.06 (5.7)

[a] Signals of carbon atoms belonging to benzyl and 5,6-benzo-2-oxo-1,3,2-dioxaphosphepanyl groups are omitted.
[b] $^{3}J_{C,P}$ or $^{2}J_{C,P}$.
[c] n.d. = Not determined.
[d] Can be interchanged.

spectra in which the phosphate substitution was indicated by a substantial α-effect ($+3.0 \pm 0.5$ ppm) and characteristic $J_{C,P}$ coupling constants. The ^{31}P NMR spectra (recorded in the presence of EDTA) revealed characteristic chemical shifts of the monophosphates. Each phosphate exhibits two signals (for α and β anomers) which are specific for a given location of the $-OPO(OH)_2$ grouping in the LD-Hep skeleton. The regioisomeric phosphates could also be differentiated (except for Hep 3P and 4P) by elution times in high-performance anion-exchange chromatography (Table 2).

The ^{13}C NMR data of protected LD-Hep derivatives are tabulated in Tables 3 and 4.

We are currently continuing the synthesis of an analogous series of methyl L-*glycero*-D-*manno*-heptopyranoside phosphates.

3. Experimental

Optical rotations were measured at 20 ± 2 °C with a Jasco DIP 360 automatic polarimeter. NMR spectra of protected sugar derivatives were recorded with a Varian Gemini AC-200 (200 MHz), Bruker AM-500 (500 MHz), or Bruker 360 MHz spectrometer. ^{1}H NMR signals of aromatic, benzyl CH_2, and allyl groups occurred at the expected chemical shifts and are omitted in the description of spectra. ^{13}C NMR spectra were recorded in the DEPT mode. The NMR spectra of phosphorylated free heptoses were measured in D_2O at 23 °C at 360 MHz: ^{1}H, relative to acetone (δ 2.225), at 90.6 MHz: ^{13}C, relative to acetone (δ 31.45), at 145 MHz: ^{31}P, relative to 85% phosphoric acid (δ 0.00) and pD values of 6.6 (2- and 7-phosphates), 6.5 (3-phosphate), 7.0 (4- and 6-phosphates). Spectra were assigned by $^{1}H,^{1}H$-correlation spectroscopy (COSY) and relayed coherence transfer COSY, $^{1}H,^{13}C$-COSY, $^{1}H,^{31}P$-COSY, and 1D ^{13}C-DEPT and GATED spectra.

TLC was performed on Silica Gel HF-254 ready plates and column chromatography on Silica Gel 230–400 or 70–230 mesh (Merck). Gel permeation chromatography of 4- and 6-phosphates was performed on a column (165 × 1.5 cm) of Bio-Gel P2 (Bio-Rad, Germany) in water. Fractions were detected using a differential refractometer (Knauer, Germany). High-performance anion-exchange chromatography was carried out on a

Dionex DX 300 system equipped with an AS3500 autoinjector (Thermo Separation Products) and a column (4 × 250 mm) of CarboPac Pa-100 (Dionex) at 1 mL min^{-1} in the eluents (*A*) 0.1 M NaOH and (*B*) eluent *A* containing 1 M NaOAc, using a linear gradient of 0–53% in 30 min. The eluate was monitored with a pulsed amperometric detector (Dionex).

*Benzyl 4,6-O-(*p*-methoxybenzylidene)-α-*D*-mannopyranoside* (**28**).—To stirred anisaldehyde (100 mL), anhyd $ZnCl_2$ (10 g) was added and, after 10 min, benzyl α-D-mannopyranoside (10 g) was added. After 4 days of stirring at room temperature the mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aq 5% NaOH and water, dried over $MgSO_4$, the solution was concentrated to dryness, and the residue was separated by chromatography with 4:1 hexane–EtOAc to yield the 2,3:4,6-di-*O*-(*p*-methoxybenzylidene) derivative {$[\alpha]_D$ +25.5° (*c* 1.0, $CHCl_3$), *exo:endo* mixture 1:1} and **28** (6.55 g); mp 150–151 °C, $[\alpha]_D$ +70.7° (*c* 1.9, $CHCl_3$); ^1H NMR (200 MHz) ($CDCl_3$): inter alia, δ 5.53 (s, 1 H, acetal CH), 4.96 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1), 3.8–4.3 (m, 6 H, H-2,3,4,5,6a,6b), 3.80 (s, 3 H, OMe). Anal. Calcd for $C_{21}H_{24}O_7 \cdot 0.5H_2O$: C, 63.46; H, 6.34. Found: C, 63.32; H, 6.32.

*Benzyl 2,3-di-*O*-benzyl-4-O-(*p*-methoxybenzyl)-α-*D*-mannopyranoside* (**30**).—Compound **28** (5.4 g) was benzylated by the conventional method (NaH, BnBr, DMF, 0 °C) to yield **29** (6.12 g).

A solution of **29** (3.2 g) in MeCN (115 mL) was stirred with molecular sieves 3 Å for 10 min. The solution was cooled (ice–water), $NaBH_3CN$ (2.17 g) was added, and after a few minutes a solution of trimethylsilyl chloride (4.36 mL) in MeCN (4.4 mL) was added dropwise. After completion of the reduction (TLC) the reaction mixture was filtered through a Celite pad, poured into dil aq $NaHCO_3$, extracted with CH_2Cl_2, dried, and concentrated. The residue was chromatographed with 9:1 → 4:1 hexane–ether.

Eluted first was **31** (0.35 g); $[\alpha]_D$ +25.5° (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$): inter alia, δ 4.97 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1), 4.07 (t, 1 H, $J_{4,3} \approx J_{4,5} \approx 9.0$ Hz, H-4). Anal. Calcd for $C_{35}H_{38}O_7$: C, 73.66; H, 6.71. Found C, 73.65; H, 6.79.

Eluted second was **30** (1.57 g); $[\alpha]_D$ +49° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): inter alia, δ 4.89 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 3.6–4.0 (m, 6 H, H-2,3,4,5,6a,6b), 3.79 (s, 3 H, OMe). Anal. Found: C, 73.78; H, 6.55.

Synthesis of protected derivatives of benzyl L-glycero-α-D-manno-*heptopyranoside. —General method.* A solution of oxalyl chloride (1 mL, 11 mmol) in CH_2Cl_2 (25 mL) was cooled (−50 to −60 °C) and a solution of Me_2SO (1.7 mL, 22 mmol) in CH_2Cl_2 (5 mL) was slowly added. After 5 min a solution of the protected benzyl mannopyranoside with 6-OH group (10 mmol) in CH_2Cl_2 (20 mL) was slowly added dropwise. Stirring at −60 °C was continued for 1 h whereupon Et_3N (7 mL, 50 mmol) was added. After 5 min of stirring the reaction mixture was allowed to attain room temperature. To the solution was added water (50 mL), and the mixture was extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and concentrated. The remaining oil was additionally dried by azeotropic distillation (3–4 times) with small portions of anhyd benzene and was used in the next step without any additional purification.

To dry Mg turnings (583 mg, 24 mmol) under freshly distilled THF (1.5 mL) was added sublimed $HgCl_2$ (50 mg), and a few drops of neat pure alkoxymethyl chloride, (freshly distilled before the reaction) were added while lowering the temperature to −15

°C (for allyloxymethyl chloride) or 0 to −5 °C (for benzyloxymethyl chloride). When the formation of the Grignard reagent had started, the rest of the alkoxymethyl chloride (24 mmol) in THF (3 mL) was added at −18 to −20 °C ($AllOCH_2Cl$) or at 0 to 5 °C ($BnOCH_2Cl$) and the stirring was continued for 2 h. The temperature was then lowered to −30 °C ($AllOCH_2MgCl$) or −20 °C ($BnOCH_2MgCl$) and a solution of aldehyde (4 mmol) in abs THF (10 mL) was added dropwise. The mixture was stirred at these temperatures for 2 h and was slowly brought to room temperature while stirring for another 12 h. Cold (0 °C) aq NH_4Cl (150 mL) was added and the products were extracted with ether. The ether extract was dried and concentrated, and the residue was chromatographed with hexane–EtOAc (9:1 or 85:15) to give the derivatives of benzyl heptosides in the order: 'inverted' first, followed by DD- and LD-manHep*p* as the last.

Benzyl 2-O-*allyl-3,4,7-tri*-O-*benzyl*-D(L)-glycero-L-gulo-*heptopyranoside* (**12**), 13.5%; $[\alpha]_D$ +6.0° (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$): inter alia, δ 4.84 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 3.82 (dd, 1 H, $J_{5,6}$ 9.3, $J_{5,4}$ 1.3 Hz, H-5), 3.81 (t, 1 H, $J_{3,2}$ 3.2, $J_{3,4}$ 3.6 Hz, H-3), 3.74 (dd, 1 H, H-4), 3.67 (dd, 1 H, $J_{7a,6}$ 3.1, $J_{7a,7b}$ 9.6 Hz, H-7a), 3.60 (dd, 1 H, $J_{7b,6}$ 5.4 Hz, H-7b), 3.53 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ 100.6 (C-1), 76.37, 75.11, 74.20, 72.68, 68.07 (C-2,3,4,5,6), 71.23 (C-7).

Benzyl 2-O-*allyl-3,4,7-tri*-O-*benzyl*-D-glycero-D-manno-*heptopyranoside* (**11**), 15.7%; $[\alpha]_D$ +34° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): inter alia, δ 4.88 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 3.74 (t, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 3.67 (dd, 1 H, $J_{7a,6}$ 6.7, $J_{7a,7b}$ 10.1 Hz, H-7a), 3.60 (dd, 1 H, $J_{7b,6}$ 3.1 Hz, H-7b); ^{13}C NMR ($CDCl_3$): δ 97.40 (C-1), 80.38 (C-3), 76.37, 74.92, 72.29, 71.36 (C-2,4,5,6), 70.96 (C-7).

Benzyl 2-O-*allyl-3,4,7-tri*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**10**), 56.1%; $[\alpha]_D$ +39° (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.85 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.18 (dt, 1 H, $J_{6,7a}$ 7.2, $J_{6,7b}$ 6.1 Hz, H-6), 4.13 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.95 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.76 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 3.75 (dd, 1 H, $J_{5,6}$ 1.0 Hz, H-5), 3.64 (dd, 1 H, $J_{7a,7b}$ 9.4 Hz, H-7a), 3.55 (dd, 1 H, H-7b) ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{38}H_{42}O_7 \cdot H_2O$: C, 72.59; H, 7.06. Found: C, 72.69; H, 6.86.

Benzyl 3-O-*allyl-2,4,7-tri*-O-*benzyl*-D(L)-glycero-L-gulo-*heptopyranoside* (**24**), 5.9%; $[\alpha]_D$ +7.5° (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.84 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 3.78 (dd, 1 H, $J_{5,6}$ 9.1, $J_{5,4}$ 1.4 Hz, H-5), 3.72 (dd, 1 H, $J_{4,5}$ 1.3, $J_{4,3}$ 3.6 Hz, H-4), 3.69 (dd, 1 H, $J_{7a,6}$ 3.1, $J_{7a,7b}$ 9.6 Hz, H-7a), 3.65 (t, 1 H, $J_{3,2}$ 3.3 Hz, H-3), 3.63 (dd, 1 H, H-2), 3.61 (dd, 1 H, $J_{7b,6}$ 5.5 Hz, H-7b); ^{13}C NMR ($CDCl_3$): δ 100.6 (C-1), 75.76, 74.96, 73.80, 72.60, 67.95 (C-2,3,4,5,6), 71.13 (C-7).

The D-*glycero*-D-*manno* stereoisomer **22** was characterized as its 6-*O*-acetyl derivative **23**:

Benzyl 6-O-*acetyl-3*-O-*allyl-2,4,7-tri*-O-*benzyl*-D-glycero-D-manno-*heptopyranoside* (**23**), 5.3%; $[\alpha]_D$ +45° (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$): inter alia, δ 5.56 (ddd, 1 H, $J_{6,5}$ 2.0, $J_{6,7a}$ 4.7, $J_{6,7b}$ 6.9 Hz, H-6), 4.89 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 3.97 (dd, 1 H, $J_{4,3}$ 9.0, $J_{4,5}$ 9.9 Hz, H-4), 3.89 (dd, 1 H, $J_{5,4}$ 9.9 Hz, H-5), 3.81 (dd, 1 H, $J_{3,2}$ 3.1, $J_{3,4}$ 9.0 Hz, H-3), 3.77 (dd, 1 H, H-2), 3.74 (dd, 1 H, $J_{7a,7b}$ 10.7 Hz, H-7a), 3.70 (dd, 1 H, H-7b); ^{13}C NMR ($CDCl_3$): δ 97.0 (C-1), 80.12 (C-3), 74.87, 74.74, 71.96, 71.92 (C-2,4,5,6), 68.32 (C-7).

Benzyl 3-O-*allyl-2,4,7-tri*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**20**) [11], 54.5%; $[\alpha]_D$ +31° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.88 (d, 1 H, $J_{1,2}$ 1.6 Hz,

H-1), 4.18 (dt, 1 H, $J_{6,7a}$ 7.1, $J_{6,7b}$ 6.1 Hz, H-6), 4.15 (t, 1 H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.7 Hz, H-4), 3.83 (dd, 1 H, $J_{3,2}$ 3.0 Hz, H-3), 3.73 (dd, 1 H, H-2), 3.74 (dd, 1 H, $J_{5,6}$ 0.9 Hz, H-5), 3.64 (dd, 1 H, $J_{7a,7b}$ 9.4 Hz, H-7a), 3.55 (dd, 1 H, H-7b); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93. Found: C, 74.32; H, 6.84.

Benzyl 2,3,7-tri-O-*benzyl-6*-O-*benzyloxymethyl-4*-O-(p-*methoxybenzyl*)-D(L)-glycero-L-gulo-*heptopyranoside* (**34**), 7.3%; $[\alpha]_D$ +6° (*c* 0.78, $CHCl_3$); ^{1}H NMR (C_6D_6): inter alia, δ 5.23 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.37 (ddd, 1 H, $J_{6,5}$ 8.9, $J_{6,7a}$ 3.2, $J_{6,7b}$ 5.6 Hz, H-6), 4.15 (dd, 1 H, $J_{5,4}$ 1.4 Hz, H-5), 4.00 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 3.95 (t, 1 H, $J_{3,4}$ 3.8 Hz, H-3), 3.95, 3.87 (ABq, 2 H, J_{AB} 9.8 Hz, OCH_2OBzl), 3.64 (dd, 1 H, $J_{7a,7b}$ 9.9 Hz, H-7a), 3.59 (dd, 1 H, H-7b); ^{13}C NMR ($CDCl_3$): δ 100.6 (C-1), 76.13, 74.92, 73.36, 72.29, 68.04 (C-2,3,4,5,6), 71.58 (C-7).

Benzyl 2,3,7-tri-O-*benzyl-4*-O-(*p-methoxybenzyl*)-L-glycero-D-manno-*heptopyranoside* (**32**), 87.9%; $[\alpha]_D$ +28° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.89 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.18 (dt, 1 H, $J_{6,7a}$ 7.3, $J_{6,7b}$ 6.1 Hz, H-6), 4.18 (t, 1 H, $J_{4,5}$ 9.6, $J_{4,3}$ 9.6 Hz, H-4), 3.95 (dd, 1 H, $J_{3,2}$ 3.0 Hz, H-3), 3.79 (dd, 1 H, H-2), 3.74 (dd, 1 H, $J_{5,6}$ 9.7 Hz, H-5), 3.64 (dd, 1 H, $J_{7a,7b}$ 9.4 Hz, H-7a), 3.54 (dd, 1 H, H-7b). ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{43}H_{48}O_7$: C, 74.76; H, 6.71. Found: C, 74.36; H, 6.74.

Stereoisomer **40** was characterized as the 6-*O*-acetyl derivative **41**:

Benzyl 6-O-*acetyl-2,3,4,7-tetra*-O-*benzyl*-D(L)-glycero-L-gulo-*heptopyranoside* (**41**), 17.5%; $[\alpha]_D$ +17.5° (*c* 1.14, $CHCl_3$); ^{1}H NMR (C_6D_6): inter alia, δ 5.71 (ddd, 1 H, $J_{6,5}$ 8.6 $J_{6,7a}$ 2.0, $J_{6,7b}$ 4.8 Hz, H-6), 5.25 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 3.89 (dd, 1 H, $J_{5,4}$ 1.2, $J_{5,6}$ 8.5 Hz, H-5), 3.99 (dd, 1 H, $J_{3,2}$ 3.3, $J_{3,4}$ 3.3 Hz, H-3), 3.94 (dd, 1 H, H-2), 3.91 (dd, 1 H, $J_{7a,7b}$ 11.1 Hz, H-7a), 3.82 (dd, 1 H, H-7b); ^{13}C NMR ($CDCl_3$): inter alia, δ 100.80 (C-1), 75.97, 74.38, 73.63, 70.31, 70.10 (C-2,3,4,5,6), 68.30 (C-7).

Benzyl 2,3,4,7-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**39**) [8], 46.0%; $[\alpha]_D$ +24° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.89 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1), 4.18 (dt, 1 H, $J_{6,7a}$ 7.3, $J_{6,7b}$ 6.1 Hz, H-6), 4.20 (t, 1 H, $J_{4,5}$ 9.8, $J_{4,3}$ 9.6 Hz, H-4), 3.95 (dd, 1 H, $J_{3,2}$ 3.0 Hz, H-3), 3.79 (dd, 1 H, H-2), 3.77 (dd, 1 H, H-5), 3.59 (dd, 1 H, $J_{7a,7b}$ 9.4 Hz, H-7a), 3.50 (dd, 1 H, H-7b); ^{13}C NMR: Table 3. MS/LSIMS: $(M + Na)^+$ 683, $(M + H)^+$ 661.

Benzyl 7-O-*allyl-2,3,4-tri*-O-*benzyl*-D(L)-glycero-L-gulo-*heptopyranoside* (**46**), 23.6%; $[\alpha]_D$ +5.3° (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): inter alia, δ 4.93 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 3.81 (dd, 1 H, $J_{5,6}$ 9.0, $J_{5,4}$ 1.1 Hz, H-5), 3.63 (dd, 1 H, $J_{4,3}$ 3.2 Hz, H-4), 3.56 (dd, 1 H, $J_{7b,6}$ 5.5, $J_{7a,7b}$ 9.7 Hz, H-7b); ^{13}C NMR ($CDCl_3$): δ 100.6 (C-1), 76.09, 74.96, 73.84, 72.70, 67.91 (C-2,3,4,5,6), 71.15 (C-7).

Benzyl 7-O-*allyl-2,3,4-tri*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**43**) [8], 52.4%; $[\alpha]_D$ +40° (*c* 2.6, $CHCl_3$). lit. [8] +35° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.86 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 4.20 (t, 1 H, $J_{4,5}$ 9.6, $J_{4,3}$ 9.5 Hz, H-4), 4.16 (dt, 1 H, H-6), 3.96 (dd, 1 H, $J_{3,2}$ 3.1 Hz, H-3), 3.81 (dd, 1 H, H-2), 3.76 (dd, 1 H, $J_{5,6}$ 1.1 Hz, H-5), 3.59 (dd, 1 H, $J_{7a,6}$ 7.3, $J_{7a,7b}$ 9.4 Hz, H-7a), 3.50 (dd, 1 H, $J_{7b,6}$ 6.2 Hz, H-7b); ^{13}C NMR: Table 3.

Benzyl 6-O-*acetyl-7*-O-*allyl-2,3,4-tri*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**44**); $[\alpha]_D$ +19° (*c* 0.7, $CHCl_3$), lit. [8] +18° (*c* 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): inter alia, δ 5.63 (dt, 1 H, $J_{6,7a} \approx J_{6,7b} \approx 5.9$, $J_{6,5}$ 1.1 Hz, H-6), 5.02 (d, 1 H,

$J_{1,2}$ 1.8 Hz, H-1), 3.92 (t, 1 H, $J_{4,3} \approx J_{4,5} \approx 9.0$ Hz, H-4), 3.82 (dd, 1 H, $J_{2,3}$ 2.4 Hz, H-2), 3.62-3.72 (m, 2 H, H-7a,7b); ^{13}C NMR: Table 3.

Benzylation at O-6 in benzyl L-glycero-D-manno-*heptopyranosides* **10**, **20**, **32**, and **43**.—To a cooled (0 °C) solution of benzyl heptopyranoside (1 mmol) in abs DMF (10 mL) was added NaH (2 mmol). The suspension was stirred for 10 min and a solution of benzyl chloride (2 mmol) in abs DMF (1 mL) was added. Stirring was continued for 8 h whereupon the excess of the hydride was decomposed with MeOH and the mixture was poured into ice–water. The product was extracted with ether, and the organic extract was dried and concentrated to dryness. The residue was purified by chromatography in 95:5 or 9:1 hexane–EtOAc.

Benzyl 2-O-allyl-3,4,6,7-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**13**), 72.1%; $[\alpha]_D$ +45° (*c* 2.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{45}H_{48}O_7 \cdot 0.5H_2O$: C, 76.14; H, 6.96. Found: C, 75.97; H, 6.83.

Benzyl 3-O-allyl-2,4,6,7-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**21**) [11], 86.2%; $[\alpha]_D$ +33° (*c* 0.8, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{45}H_{48}O_7$: C, 77.12; H, 6.90. Found: C, 77.00; H, 6.81.

Benzyl 2,3,6,7-tetra-O-*benzyl-4*-O-(p-*methoxybenzyl)*-L-glycero-D-manno-*hepto-pyranoside* (**35**), 82.6%; $[\alpha]_D$ +30° (*c* 1.1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.95; H, 6.67.

Benzyl 7-O-allyl-2,3,4,6-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**45**) [11], 85.9%; mp 60–61 °C, lit. [8] 63–64 °C; $[\alpha]_D$ +45° (*c* 1.4, $CHCl_3$): lit. [8] +43° (*c* 2.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. On chromatographic purification of **45** a small amount of D-*glycero*-D-*manno* stereoisomer was also isolated, and characterized by NMR data only: ^{1}H NMR ($CDCl_3$): inter alia, δ 4.94 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 4.07 (t, 1 H, $J_{4,3}$ 9.3, $J_{4,5}$ 9.7 Hz, H-4), 3.80 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 3.76 (dd, 1 H, $J_{7a,6}$ 4.5, $J_{7a,7b}$ 10.5 Hz, H-7a), 3.70 (dd, 1 H, $J_{7b,6}$ 6.7 Hz, H-7b); ^{13}C NMR ($CDCl_3$): δ 96.34 (C-1), 80.55 (C-3), 78.25, 75.05, 74.76, 72.67 (C-2,4,5,6), 70.67 (C-7).

De-allylation of **13**, **22**, and **44**.—To a solution of heptopyranoside derivative **13**, **22**, or **44** (0.65 mmol) in a mixture of EtOH (9 mL), benzene (3 mL), and water (1 mL) was added 1,4-diazabicyclo[2.2.2]octane (Dabco, 15 mg), and the solution was heated to 80 °C. Wilkinson's catalyst (42 mg) was added and the mixture was refluxed for 3 h and left at room temperature overnight. The mixture was filtered and the filtrate was concentrated under lowered pressure. The remaining oil was dissolved in 15:1 acetone–water, and HgO (149 mg) and $HgCl_2$ (187 mg) were added. The suspension was stirred (0.5 h) at room temperature, then filtered, the filtrate was concentrated, and the residue was dissolved in ether. The ether solution was washed with aq 50% KI, aq 10% $NaHSO_3$, and aq 1% $NaHCO_3$, dried, and concentrated. The products were chromatographed with 7:3 light petroleum–ether.

Benzyl 3,4,6,7-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**14**), 96.5%; $[\alpha]_D$ +56° (*c* 1.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 76.23; H, 6.80. 2-*O*-Acetyl derivative (**15**): $[\alpha]_D$ +24° (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{44}H_{46}O_8 \cdot H_2O$: C, 73.31; H, 6.71. Found: C, 73.51; H, 6.51.

Benzyl 2,4,6,7-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**25**) [11], 70.8%; $[\alpha]_D$ +34° (*c* 1.0, $CHCl_3$), lit. [11] +29° (*c* 1.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3.

Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 75.92; H, 6.70. 3-*O*-Acetyl derivative (**26**): $[\alpha]_D$ +20° (*c* 2.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{44}H_{46}O_8$: C, 75.19; H, 6.60. Found: C, 74.92; H, 6.64.

Benzyl 2,3,4,6-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**47**) [11], 83.1%; $[\alpha]_D$ +52° (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. 7-*O*-Acetyl derivative (**48**): $[\alpha]_D$ +30° (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. MS/LSIMS: $(M-H)^+$ 701, $(M+Na)^+$ 725.

Benzyl 2,3,6,7-tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**36**).—To a solution of **35** (464 mg) in MeCN–water (9:1, 10 mL) was added ammonium cerium(IV) nitrate (669 mg), and the mixture was stirred at room temperature. After 1 h (TLC in 2:1 hexane–ether) the mixture was diluted with CH_2Cl_2 (15 mL) and poured into satd aq $NaHCO_3$ (30 mL). The organic extract was dried and concentrated to dryness. The residue was chromatographed with 3:1 hexane–ether to yield **36** (331 mg, 84%); $[\alpha]_D$ +17° (*c* 1.31, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 75.89; H, 6.89. 4-*O*-Acetyl derivative (**37**): $[\alpha]_D$ +37° (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 3. Anal. Calcd for $C_{44}H_{46}O_8 \cdot 0.5H_2O$: C, 74.23; H, 6.66; Found: C, 74.23; H, 6.69.

Phosphorylation of benzyl tetra-O-*benzyl*-L-glycero-D-manno-*heptopyranosides using 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane* (**6**).—*General method.* To a solution of benzyl tetra-*O*-benzyl-L-*glycero*-D-*manno*-heptopyranoside (661 mg, 1 mmol) in abs CH_2Cl_2 (10 mL) was added tetrazole (210 mg, 3 mmol) and the mixture was stirred. After 10 min a solution of **6** (253 mg, 1.2 mmol) in CH_2Cl_2 (1 mL) was added and the mixture was again stirred. After 2 h at room temperature (TLC in 1:1 hexane–ether) the solution was cooled to −60 °C and a solution of *m*-$ClC_6H_4CO_3H$ (MCPBA) (1.8 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was complete in 15 min (TLC in 1:1 hexane–EtOAc). The reaction mixture was diluted with EtOAc (20 mL), and washed with aq 1% $NaHCO_3$ and aq 1% $NaHSO_3$. The organic layer was dried and concentrated to dryness. The residue was chromatographed with 4:1 hexane–EtOAc to yield pure phosphates.

Benzyl 2-O-*(5,6-benzo-2-oxo-1,3,2-dioxaphosphepan-2-yl)-3,4,6,7-tetra*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**16**), 91.1%; mp 128–129 °C; $[\alpha]_D$ −2.3° (*c* 1.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 4. Anal. Calcd for $C_{50}H_{51}O_{10}P$: C, 71.24; H, 6.10. Found: C, 71.04; H, 6.14.

Benzyl 3-O-*(5,6-benzo-2-oxo-1,3,2-dioxaphosphepan-2-yl)-2,4,6,7-tetra*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**27**), 85.9%; oil; $[\alpha]_D$ +36° (*c* 0.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 4. Anal. Found: C, 71.35; H, 6.25.

Benzyl 4-O-*(5,6-benzo-2-oxo-1,3,2-dioxaphosphepan-2-yl)-2,3,6,7-tetra*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**38**), 96.7%; oil; $[\alpha]_D$ +27° (*c* 0.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 4. Anal. Found: C, 70.87; H, 5.94.

Benzyl 6-O-*(5,6-benzo-2-oxo-1,3,2-dioxaphosphepan-2-yl)-2,3,4,7-tetra*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**42**), 70.1%; mp 138–139 °C; $[\alpha]_D$ +6.4° (*c* 0.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 4. Anal. Found: C, 71.16; H, 5.97.

Benzyl 7-O-*(5,6-benzo-2-oxo-1,3,2-dioxaphosphepan-2-yl)-2,3,4,6-tetra*-O-*benzyl*-L-glycero-D-manno-*heptopyranoside* (**49**), 97.7%; oil; $[\alpha]_D$ +31° (*c* 1.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$): Table 4. Anal. Found: C, 71.06; H, 6.06.

Hydrogenation of benzyl O-*(5,6-benzo-2-oxo-1,3,2-dioxaphosphepan-2-yl)-tetra*-O-*benzyl*-L-glycero-D-manno-*heptopyranosides.*—To a solution of phosphate (**16**, **27**, **38**, **42**, or **49**) (421 mg, 0.5 mmol) in 7:3 EtOH–EtOAc was added 10% Pd–C catalyst (420 mg), and the suspension was hydrogenated overnight. Filtration through a Celite pad and concentration of the filtrate left a foam which was dissolved in 0.3 M aq cyclohexylamine (2 mL). The solution was lyophilized, leaving the di(cyclohexylammonium) salt (in case of the 2-, 3-, and 7-phosphates) or a mixture of products (in case of the 4- and 6-phosphates) as a colourless or slightly yellow foam. The ^{1}H, ^{13}C, and ^{31}P NMR data of the phosphates and salts are collected in Table 1. Products from hydrogenation of **38** and **42** were purified by gel permeation chromatography (GPC).

L-glycero-D-manno-*Heptopyranose 2-[di(cyclohexylammonium) phosphate]* (**1**), 84.4%; $[\alpha]_D$ +2.6° (*c* 1.1, H_2O).

L-glycero-D-manno-*Heptopyranose 3-[di(cyclohexylammonium) phosphate]* (**2**), 82.9%; $[\alpha]_D$ +12.5° (*c* 0.25, H_2O).

L-glycero-D-manno-*Heptopyranose 4-(dihydrogen phosphate)* (**3**), 84.1%; $[\alpha]_D$ −14.2° (*c* 0.9, H_2O).

L-glycero-D-manno-*Heptopyranose 6-(dihydrogen phosphate* (**4**), 93.7%; $[\alpha]_D$ +6° (*c* 0.2, H_2O).

L-glycero-D-manno-*Heptopyranose 7-[di(cyclohexylammonium) phosphate]* (**5**), 74.1%; $[\alpha]_D$ +7.5° (*c* 0.9, H_2O).

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