A New Route for Preparation of 5-Deoxy-5-(hydroxyphosphinyl)-D-mannopyranose and -L-gulopyranose Derivatives

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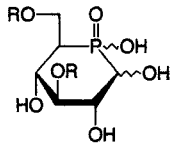
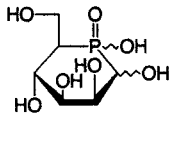
Dedicated to Professor *Wolfgang Pfleiderer* on the occasion of his 75th birthday

Starting from methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**5**), methyl 6-*O*-benzyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose (**12**) was prepared in three steps. The addition reaction of dimethyl phosphonate to **12**, followed by deoxygenation of 5-OH group, provided the 5-deoxy-5-dimethoxyphosphinyl-α-D-mannofuranoside derivative **15a** and the β-L-gulofuranoside isomer **15b**. Reduction of **15a** and **15b** with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by the action of HCl and then H_2O_2, afforded the D-mannopyranose (**17**) and L-gulopyranose analog **21**, each having a phosphinyl group in the hemiacetal ring. These were converted to the corresponding 1,2,3,4,6-penta-*O*-acetyl-5-methoxyphosphinyl derivatives **19** and **23**, respectively, structures and conformations ($^4C_1$ or $^1C_4$, resp.) of which were established by ^{1}H-NMR spectroscopy.

Introduction. – We have prepared various sugar analogs having a P-atom in the hemiacetal ring (phospha sugars) [1] because of considerable interest in the physicochemical properties and potential biological activity, as in the case of aza sugars [2] and thia sugars [3]. Thus, a large number of phospha sugars were synthesized, such as those of D-glucose (**1a**,**b**) [4][5], D-mannose (**2**) [6], D-galactose (**3**) [7], and L-fucose (**4**) [8].



1a R =H
1b R =Bn



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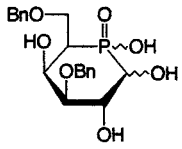

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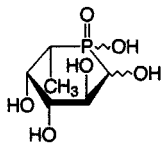

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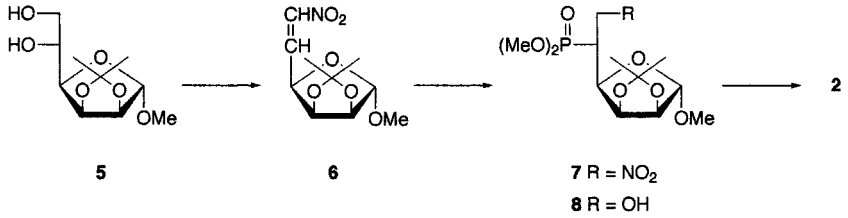
For example, the first synthesis of 5-deoxy-5-(hydroxyphosphinyl)-D-mannopyranose (**2**) was performed starting from methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**5**) by the sequence of **5** → **6** → **7** → **8** → **2** in ten steps (*Scheme 1*) [6]. Although the introduction of a phosphinyl group at C(5) was accomplished by the addition of dimethyl phosphonate to the nitro olefin **6** with relatively good diastereoselectivity (86:14), the conversion of the 6-NO_2 group of the major isomer **7** to a 6-OH group

Scheme 1



resulted in a low yield of **8** because of the simultaneous production of various by-products.

We have recently found an alternative new procedure to introduce a phosphinyl group into a sugar skeleton: namely, addition of a phosphonate to hexofuranos-5-ulose derivatives and the subsequent deoxygenation of 5-OH group [5][7]. As the use of such procedures was proved to be effective for preparation of D-glucopyranose and D-galactopyranose analogs, **1b** and **3**, respectively, we have decided to employ the new method for preparation of D-mannopyranose analogs, **2**, as a series for systematic investigation of the stereoselectivity and synthetic efficiency for dehydroxylation of various α-hydroxyphosphonates (5-hydroxy-5-phosphinylhexofuranoses).

Results and Discussion. – Methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**5**) served as the starting material for preparation of an important key intermediate **12** for the introduction of a phosphinyl group at C(5) (*Scheme 2*). The epoxidation of **5** under *Mitsunobu*'s conditions afforded the 5,6-*O*-anhydro derivative **9**[1]) (89%) which was treated with BnOH and NaH in 1,2-dimethoxyethane (DME) to give the 6-*O*-benzyl compound **11**[2]) in 94% yield. As an alternative way for preparation of **11**, compound **5** was converted to the 6-*O*-Ts derivative **10** [8] in 96% yield. The treatment of **10** with BnOH and NaH in DME afforded **11** by a one-pot procedure, without isolation of the intermediate **9**, in 93% yield.

The addition reaction of dimethyl phosphonate to **12** in the presence of DBU afforded the (5*R*)-5-(dimethylphosphinyl)-D-*lyxo*-hexofuranoside derivative **13a** (76%) and its (5*S*)-epimer **13b** (19%). The major (5*R*)-epimer **13a** was converted to the methoxalyl esters **14a** with methoxalyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) and then reduced with Bu_3SnH in the presence of AIBN [11], affording an 81:19 mixture of the 5-deoxy products. On structural assignment of the resulting two separable diastereoisomers by ^{1}H-NMR, it turned out that the major isomer was not the expected 5-deoxy-5-(dimethylphosphinyl)-α-D-mannofuranoside derivative **15a** (16% from **13a**) but the β-L-gulofuranoside isomer **15b** (70%).

The α-D-*manno* configuration for **15a** was assigned on the basis of the large J(4,5) value (10.7 Hz) and the presence of long-range coupling, ^5J(1,P) (1.5 Hz) [8][12] (*Fig. 1*

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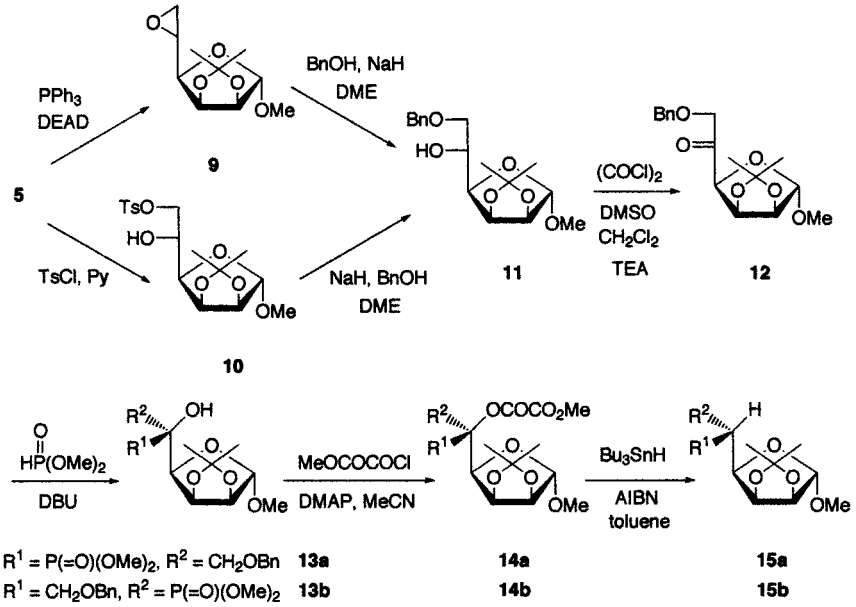
[1]) Compound **9** had been obtained from **5** *via* the 6-*O*-naphthalenesulfonyl derivative in 45% overall yield [9].

[2]) Compound **11** had been obtained as a minor product (35% yield) from **5** in two-phase BnBr/aq. NaOH system [10].

Scheme 2



and *Table 1*). Similarly, the *β*-L-*gulo* configuration for **15b** was derived from the large $J(4,5)$ value (10.4 Hz), and the presence of $^5J(2,P)$ (1.2 Hz) and $^4J(3,P)$ (1.1 Hz). Although 5-OH compounds **13a** and **13b** have no H-atom at C(5), their configurations at C(5) were assigned by comparison to the corresponding 5-deoxy compounds **15a** and **15b**, respectively, because the similar characteristic tendency of the corresponding coupling constants and the chemical shifts is expected due to almost identical conformations[3]). Thus, (5*R*)-configuration for **13a** and (5*S*)-configuration for **13b** were derived from the presence of $^5J(1,P)$ (for **13a**), and $^5J(2,P)$ and $^4J(3,P)$ (for **13b**).

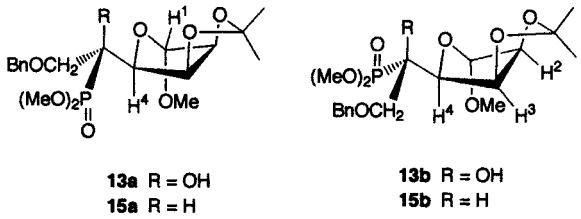


Fig. 1. *The most favorable conformations for* **13a**,**b** *and* **15a**,**b**

[3]) The *antiperiplanar* orientation of H–C(4) and H–C(5) in **15a**,**b** is due to steric interaction around C(4)–C(5) bond, whereas the same orientation of H–C(4) and HO–C(5) in **13a**,**b** could be explained in terms of the intramolecular H-bond between the OH group, and O(3) and/or O(4) [13].

Table 1. *Selected ^{1}H-NMR Parameters for Compounds* **13a**,**b** *and* **15a**,**b** *in $CDCl_3$*

	δ/ppm							
	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H–C(5)			
13a	4.91	4.57	5.00	4.32	–			
13b	4.97	4.49	4.85	4.32	–			
15a	4.81	4.54	4.77	4.29	2.71			
15b	4.88	4.48	4.59	4.29	2.62			
	J/Hz							
	J(1,2)	^5J(1,P)	*J*(2,3)	^5J(2,P)	*J*(3,4)	^4J(3,P)	*J*(4,P)	*J*(4,5)
13a	0	2.1	5.8	0	2.8	0	1.0	–
13b	0	0	5.8	1.0	3.4	0.9	4.2	–
15a	0	1.5	5.5	0	3.1	0	5.8	10.7
15b	0	0	5.5	1.2	3.1	1.1	7.3	10.4

Similarly, the minor (5*S*)-epimer **13b** was converted to **14b**, which afforded **15a**,**b** in almost the same ratio and yields as those from **13a**. These results, therefore, indicated that an epimerization took place at C(5) *via* a radical intermediate during the reduction of the methoxalyl esters **14a**,**b** [5][7].

As for the predominant production of the L-gulofuranoside (**15b**) by the radical reduction of **14a**,**b**, we propose transition state **A** of the radical intermediate from the viewpoint of electronic factors (*Fig. 2*). Namely, the opposition of the phosphinyl group and electronegative O-atom in the furanose ring reduces intramolecular electrostatic repulsion [14]. Moreover, the alignment of the σ(C(4)–C(3)) bond with the radical p orbital stabilizes the transition state [15]. Although the mechanistic proposals have been reported for the radical-mediated reduction of α-bromo-β-alkoxycarboxylates [16], no report seems to exist, to the best of our knowledge, for the corresponding β-alkoxyphosphonate derivatives. Systematic mechanistic studies concerning stereoselectivity of the reduction for 5-phosphinylhexofuranoses are in progress.

The minor α-D-mannofuranoside **15a** was then reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) to give the 5-phosphino derivative **16**, which, with HCl in aq. i-PrOH followed by oxidation with H_2O_2, afforded 6-*O*-benzyl-5-deoxy-5-(hydroxyphosphinyl)-α/β-D-mannopyranoses **17** (*Scheme 3*). For the purpose of purification and characterization, compounds **17** were converted to the corresponding

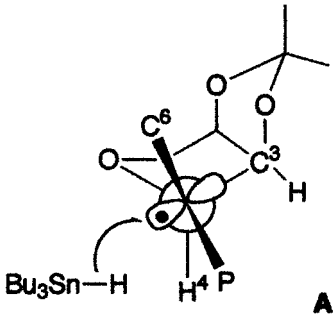
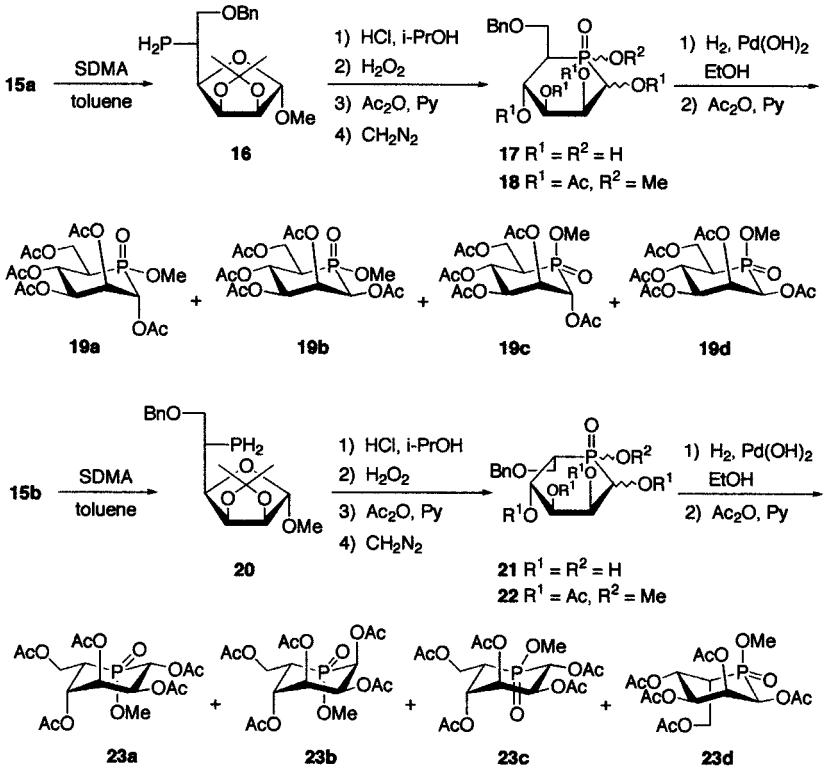


Fig. 2. *A plausible conformation for the radical intermediate* **A** *and the direction of reduction*

Scheme 3



5-(methoxyphosphinyl) 1,2,3,4-tetra-*O*-acetates **18** by treatment with Ac_2O/pyridine and then ethereal CH_2N_2. As the separation of a diastereoisomeric mixture of **18** was still difficult, unambiguous structural assignment was made by further conversion of **18** to the 1,2,3,4,6-penta-*O*-acetyl derivatives **19**[4]). Namely, debenzylation[5]) of **18** by the catalytic hydrogenation over 20% $Pd(OH)_2$/C, followed by acetylation, afforded the pentaacetates **19**. After chromatographic purification, 1,2,3,4,6-penta-*O*-acetyl-5-deoxy-5-[(*R*)-methoxyphosphinyl]-α-D-mannopyranose (**19a**; 6.2% from **15a**), its β-anomer **19b** (8.3%), the 5-[(*S*)-methoxyphosphinyl]-α-isomer **19c** (4.7%), and its β-isomer **19d** (5.9%) were obtained[6]).

The similar treatment of the major β-L-gulofuranoside **15b** afforded 6-*O*-benzyl-5-deoxy-5-(hydroxyphosphinyl)-α/β-L-gulopyranoses (**21**) *via* the 5-phosphino compound **20**. The L-gulopyranose analogs **21** were also converted to 5-(methoxyphos-

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[4]) Penta-*O*-acetates are apparently more valuable in view of synthesizing unsubstituted phospha sugars, because it is easy to convert them to deacetylated compounds with MeONa/MeOH.

[5]) On debenzylation of crude **17** by catalytic hydrogenation, a considerable amount of starting material remained unchanged despite many trials. However, the same reaction of **18**, which had been purified by column chromatography, proceeded with quantitative yield.

[6]) Compounds **19c/d**, **23a/d**, and **23b/c** were obtained as inseparable mixtures. The yield of each product was based on the ^{1}H-NMR.

phinyl) pentaacetates **23** *via* **22**: 1,2,3,4,6-penta-*O*-acetyl-5-deoxy-5-[(*R*)-methoxyphosphinyl]-β-L-gulopyranose (**23a**; 12% from **15b**), its α-anomer **23b** (5.1%), the 5-[(*S*)-methoxyphosphinyl]-β-isomer **23c** (11%), and its α-anomer **23d** (6.5%)[6].

The precise parameters were obtained for these eight isomers, **19a–d**, **23a–d** by the analysis of their 500-MHz ^{1}H-NMR spectra (*Table 2*). Some characteristic features of new products **19b** and **23a–d** are discussed here in detail for comparison with those of the previously reported isomers **19a**,**c**, and **d** [6].

Table 2. *Selected ^{1}H-NMR Parameters for Compounds* **19a–d** *and* **23a–d** *in $CDCl_3$*

	δ/ppm								
	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H–C(5)	H–C(6)	H′–C(6)	MeO–P	
19a	5.45	5.36	5.34	5.63	2.65	4.49	4.41	3.75	
19b	5.32	5.61	5.14	5.62	2.47	4.50	4.47	3.82	
19c	5.35	5.42	5.25	5.52	2.74	4.58	4.31	3.85	
19d	5.42	5.67	5.11	5.56	2.49	4.58	4.33	3.95	
23a	5.78	5.40	5.44	5.30	2.83	4.40	4.35	3.94	
23b	5.63	5.45	5.37	5.46	2.99	4.41	4.38	3.86	
23c	5.49	5.57	5.53	5.36	2.71	4.40	4.40	3.79	
23d	5.61	5.67	5.52	5.49	2.81	4.43	4.39	3.87	
	J/Hz								
	J(1,2)	*J*(1,P)	*J*(2,3)	*J*(2,P)	*J*(3,4)	*J*(4,5)	*J*(4,P)	*J*(5,P)	others
19a	6.4	8.8	2.8	21.6	8.6	9.9	8.3	15.4	
19b	3.1	8.6	2.5	24.4	8.9	10.8	6.8	13.3	
19c	5.5	10.1	3.0	25.1	9.3	10.8	4.8	14.6	
19d	3.6	5.9	2.9	28.9	9.9	11.1	3.9	13.3	
23a	11.3	3.4	2.7	3.1	4.6	3.7	35.4	15.1	[a]
23b	3.4	14.4	3.0	7.3	6.0	4.3	26.0	18.9	[b]
23c	11.0	4.9	2.6	4.9	5.5	3.7	33.6	15.0	[c]
23d	3.4	9.8	3.1	20.1	8.6	4.2	11.0	22.1	

[a]) ^4J(3,P) = 1.8 Hz. [b]) ^4J(1,3) = 1.3 Hz. [c]) ^4J(3,P) = 1.9 Hz.

The large *J*(4,5) values (10–11 Hz) of **19a–d** and the small *J*(4,5) values (*ca.* 4 Hz) of **23a–d** indicate the D-mannopyranose configuration of the former and the L-gulopyranose configuration of the latter. Conformations of these compounds (in $CDCl_3$ solution) are derived from the magnitudes of *J*(2,P) (20–29 Hz for **19a–d** and **23d** *vs.* 3–7 Hz for **23a–c**) and *J*(4,P) (4–11 Hz for **19a–d** and **23d** *vs.* 26–35 Hz for **23a–c**) with respect to the corresponding vicinal dihedral angles. Thus, **19a–d** and **23d** are assigned to be predominantly in the $^4C_1$ conformation, whereas **23a–c** exist in the $^1C_4$ conformation. Compounds **19a** and **23d** have smaller *J*(2,P) (21.6 and 19.8 Hz) and larger *J*(4,P) values (8.3 and 11.0 Hz) than those of **19b–d**, indicating that they exist as a conformational mixture of $^4C_1$ and $^1C_4$ forms (*Fig. 3*). By employing the additivity rule for vicinal coupling constants [17], the equilibrium population of $^4C_1$ and $^1C_4$ conformers were estimated to be 76:24 for **19a** and 81:19 for **23d**[7]).

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[7]) The ratios of the conformers were estimated by means of the following values: **19a**: $J(1,2) = 4.0$, $J(2,3) = 3.1$, $J(3,4) = 9.8$, $J(4,5) = 11.55$ for the pure $^4C_1$ form; $J(1,2) = 11.3$, $J(2,3) = 3.1$, $J(3,4) = 3.6$, $J(4,5) = 3.5$ for the pure $^1C_4$ form. **23d**: $J(1,2) = 3.5$, $J(2,3) = 3.1$, $J(3,4) = 9.8$, $J(4,5) = 4.5$ for the pure $^4C_1$ form; $J(1,2) = 2.7$, $J(2,3) = 3.1$, $J(3,4) = 3.6$, $J(4,5) = 3.0$ for the pure $^1C_4$ form [17].

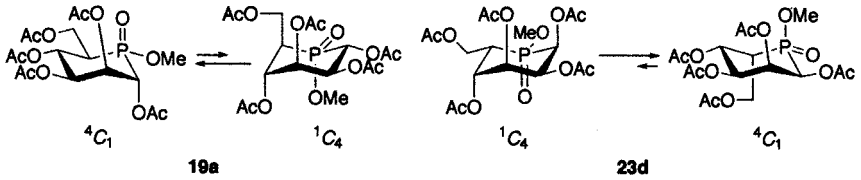

Fig. 3. *Conformational equiliblia for* **19a** *and* **23d**

As for the D-mannopyranose derivative, the H–C(3) and H–C(5) signals of **19a**,**c** appear downfield from those of **19b**,**d**, thus indicating that the orientation of AcO–C(1) group of **19a**,**c** is axial and that of **19b**,**d** equatorial. For the L-gulopyranose derivatives, the large magnitudes of $J(1,2)$ indicate axial H–C(1) orientation for **23a**,**c**, whereas the smaller $J(1,2)$ value points out the equatorial H–C(1) orientation for **23b**.

A slight downfield shift of H–C(4) signal of **19a**,**b** compared with those of **19c**,**d** indicates the axial P=O orientation for **19a**,**b** and the equatorial P=O orientation for **19c**,**d**. Likewise, a similar downfield shift of H–C(2) signal of **23c** compared with those of **23a**,**b** indicates the axial P=O orientation for **23c** and the equatorial P=O orientation for **23a**,**b**. An appreciable downfield shift observed for H–C(2) of **23d** could be explained by its equatorial orientation (contrary to the axial H–C(2) for **23a–c**).

The conformation of **23d** in favor of $^4C_1$ is most likely ascribed to the presence of strong destabilizing interactions between 1,3-*syn*-diaxial P=O and AcO–C(4) group in the $^1C_4$ form as well as those between AcO–C(1) and AcO–C(3) group. The electronic destabilizing effects of axial P=O group for **23d** seems to be much stronger than those of the corresponding P–OMe group for **23b**, because the latter exists in the $^1C_4$ form.

Such a difference in the destabilization effect between P=O and P–OMe group is also observed between **19a** and **19c**. Namely, the repulsion between the axial P–OMe and AcO–C(2) groups of **19c** (in the $^4C_1$ form) scarcely affects the inversion of the chair conformer, while the repulsion between axial P=O and AcO–C(2) group of **19a** (in the $^4C_1$ form) causes interconversion into the $^1C_4$ form at a considerable rate (but still in favor of the $^4C_1$ form).

For β-D-mannopyranose **19b** and β-L-gulopyranose **23c**, both having the equatorial AcO–C(1) group, notable conformational equiliblia are not observed, although there exist destabilizing interactions between the 1,3-*syn*-diaxial P=O and AcO groups.

These precise ^{1}H-NMR parameters of eight diastereoisomers obtained by the present study are thought to be of high value in determining configurations and conformations for other hexopyranose phospha sugars. Although the desired D-mannofuranose precursor was not obtained as a major product for introduction of phosphinyl group, total reaction steps of the present work are fewer, and yields of the ring-transposition products were higher than by the method previously employed. Extension of this work, including investigation of stereoselectivity of the dehydroxylation for α-hydroxyphosphonates, having other hexopyranose structures, as well as biological evaluation of D-manno- and L-gulopyranose phospha sugars, is anticipated to be of interest.

Experimental Part

General. All reactions were monitored by TLC (*Merck* silica gel *60F*, 0.25 mm) with an appropriate solvent system. Column chromatography (CC) was performed with *Katayama* silica gel *60K070*. Components were detected by exposing the plates to UV light and/or spraying them with 20% H_2SO_4/EtOH (with subsequent heating). The NMR spectra were measured in $CDCl_3$ with *Varian VXR-500* (500 MHz for ^1H) and *VXR-200* (81 MHz for ^{31}P) spectrometers at 22°; chemical shifts are reported as δ values [ppm] relative to TMS (internal standard for ^1H) and 85% phosphoric acid (external standard for ^{31}P). The MS spectra were recorded on a *VG-70SE* instrument and are given in terms of *m*/*z* (relative intensity) compared with the base peak.

Methyl 5,6-Anhydro-2,3-O-*isopropylidene-α*-D-*mannofuranoside* (**9**) [9]. To a soln. of **5** (1.04 g, 4.44 mmol) and Ph_3P (1.20 g, 4.57 mmol) in dry toluene (10 ml) was added diethyl azodicarboxylate (DEAD; 0.750 ml, 4.82 mmol). The mixture was refluxed for 8 h and evaporated *in vacuo*. The residue was purified by CC with AcOEt/hexane 1:4 → 1:2 to give **9** (854 mg, 89%). Colorless syrup. R_f (AcOEt/hexane 1:2) 0.48. ^1H-NMR (500 MHz): 1.32, 1.47 (2*s*, Me_2C); 2.77 (*dd*, $J(6,6')=5.2$, $J(5,6')=2.8$, H′–C(6)); 2.90 (*dd*, $J(5,6)=4.0$, H–C(6)); 3.29 (*ddd*, $J(4,5)=6.1$, H–C(5)); 3.30 (*s*, MeO–C(C(1)); 3.64 (*dd*, $J(3,4)=3.7$, H–C(4)); 4.57 (*d*, $J(2,3)=5.8$, $J(1,2)=0$, H–C(2)); 4.81 (*dd*, H–C(3)); 4.90 (*s*, H–C(1)).

Methyl 6-O-*Benzyl-2,3*-O-*isopropylidene-α*-D-*mannofuranoside* (**11**) [10]. a) *From* **9**. To a suspension of NaH (60% in mineral oil, 250 mg, 6.25 mmol) and BnOH (1.30 ml, 1.26 mmol) in DME (2.0 ml), a soln. of **9** (270 mg, 1.25 mmol) in DME (1.0 ml) at 0° was added. The mixture was stirred at 60° for 5 h, diluted with sat. NH_4Cl (20 ml), and extracted with $CHCl_3$ three times. The combined org. layers were washed with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC with AcOEt/hexane 1:1 to give **11** (380 mg, 94%). Colorless syrup. R_f (AcOEt/hexane 1:2) 0.33. ^1H-NMR (500 MHz): 1.32, 1.47 (2*s*, Me_2C); 2.75 (br. *s*, HO–C(5)); 3.28 (*s*, MeO–C(1)); 3.65 (*dd*, $J(6,6')=9.8$, $J(5,6)=5.8$, H′–C(6)); 3.76 (*dd*, $J(5,6)=3.7$, H–C(6)); 3.96 (*dd*, $J(4,5)=8.2$, $J(3,4)=3.7$, H–C(4)); 4.14 (*ddd*, H–C(5)); 4.55 (*d*, $J(2,3)=5.8$, $J(1,2)=0$, H–C(2)); 4.57, 4.62 (2*d*, $^2J=11.9$, 1 H each, CH_2O–C(6)); 4.83 (*dd*, H–C(3)); 4.88 (*s*, H–C(1)); 7.30 (*m*, H_p of Ph); 7.35 (*m*, 2 H_o, 2 H_m of Ph).

b) *From* **10** [18]. To a soln. of **10** (4.01 g, 10.4 mmol) dissolved in DME (40 ml), NaH (60% in mineral oil, 450 mg, 11.2 mmol) at 0° was added. After stirring for 10 min, BnOH (8.60 ml, 83.1 mol) and then NaH (1.70 g, 42.5 mmol) were added. The mixture was stirred at 60° for 4 h and worked up by employing the same procedures described above to give **11** (3.12 g, 93%).

Methyl 6-O-*Benzyl-2,3*-O-*isopropylidene-α*-D-lyxo-*hexofuranosid-5-ulose* (**12**). To a soln. of oxalyl chloride (2.00 ml, 22.9 mmol) in CH_2Cl_2 (20 ml), a soln. of DMSO (3.30 ml, 46.5 mmol) in CH_2Cl_2 (10 ml) at −60° was added under Ar, and then a soln. of **11** (2.91 g, 8.98 mmol) in CH_2Cl_2 (10 ml) was added. The mixture was stirred at −60° for 8 h, and then Et_3N (TEA; 8.0 ml, 57 mmol) was added, followed by stirring at 0–10° for 0.5 h. The mixture was diluted with $CHCl_3$ (30 ml) and washed with aq. NaCl soln. The aq. layer was extracted twice with $CHCl_3$. The combined org. layers were washed once with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by CC to give **12** (2.72 g, 94%). Colorless prisms. M.p. 66–67° (AcOEt/hexane 1:2). R_f (AcOEt/hexane 1:2) 0.52. ^1H-NMR (500 MHz): 1.27, 1.34 (2*s*, Me_2C); 3.33 (*s*, MeO–C(1)); 4.34 (*s*, CH_2O–C(6)); 4.54 (*d*, $J(2,3)=5.8$, $J(1,2)=0$, H–C(2)); 4.61 (*d*, $^2J=11.9$, H′–C(6)); 4.64 (*d*, H–C(6)); 4.66 (*d*, $J(3,4)=4.3$, H–C(4)); 5.01 (*s*, H–C(1)); 5.07 (*dd*, H–C(3)); 7.32 (*m*, H_p of Ph); 7.34–7.38 (*m*, 2 H_o and 2 H_m of Ph). FAB-MS: 323 (7.8, $[M+1]^+$), 307 (5.6), 291 (11), 233 (22), 201 (35), 181 (56), 91 (100). HR-MS: 323.1480 ($[M+1]$, $C_{17}H_{23}O_6^+$; calc. 323.1495). Anal. calc. for $C_{17}H_{22}O_6$ (322.36): C 63.34, H 6.88; found: C 63.22, H 6.95.

*Methyl (5*R*)- and (5*S*)-6*-O-*Benzyl-5-(dimethoxyphosphinyl)-2,3*-O-*isopropylidene-α*-D-lyxo-*hexofurano-sides* (**13a**,**b**). DBU (0.800 ml, 5.25 mmol) was dropwise added to a soln. of **12** (1.21 g, 3.75 mmol) in dimethyl phosphonate (10.0 ml, 90 mmol) at 0°, and the soln. was stirred at this temp. for 0.5 h under Ar. The mixture was treated with sat. NH_4Cl at 20° for 4 h and extracted with $CHCl_3$ three times. The combined org. layers were washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was separated by CC with AcOEt/hexane 1:1 → 2:1 to give **13a** and **13b**.

Data of **13a**: Colorless needles (1.31 g, 76%). M.p. 85–86° (AcOEt/hexane 2:1). R_f (AcOEt/hexane 2:1) 0.25. ^1H-NMR (500 MHz): see *Table 1*; additionally, 1.32, 1.48 (2*s*, Me_2C); 3.26 (*s*, MeO–C(1)); 3.76, 3.81 (2*d*, $J(P,Me)=10.7$, $P(OMe)_2$); 3.82 (*dd*, $J(6',P)=12.8$, $J(6,6')=8.6$, H′–C(6)); 3.88 (*dd*, $J(6,P)=26.6$, H–C(6)); 4.45, 4.63 (2*d*, $^2J=11.9$, 1 H each, CH_2O–C(6)); 4.75 (*s*, HO–C(5)); 7.24 (*m*, H_p of Ph); 7.30 (*m*, 2 H_m of Ph); 7.32 (*m*, 2 H_o of Ph). ^{31}P-NMR (81 MHz): 25.2. FAB-MS: 433 (35, $[M+1]^+$), 401 (11), 201 (18), 91 (100). HR-MS: 433.1641 ($[M+1]^+$, $C_{19}H_{30}O_9P^+$; calc. 433.1628). Anal. calc. for $C_{19}H_{29}O_9P$ (432.41): C 52.78, H 6.76; found: C 52.66, H 6.89.

Data of **13b**: Colorless syrup (322 mg, 20%). R_f (AcOEt/hexane 1:2) 0.18. ^{1}H-NMR (500 MHz): see *Table 1*; additionally, 1.23, 1.46 (2*s*, Me_2C); 3.36 (*s*, MeO–C(1)); 3.80, 3.85 (2*d*, J(P,Me) = 10.7, $P(OMe)_2$); 3.85 (*dd*, J(6′,P) = 19.8, J(6,6′) = 9.8, H′–(6)); 3.96 (*t*, J(6,P) = 10.0, H–C(6)); 4.36 (br. *s*, HO–C(5)); 4.58, 4.64 (2*d*, ^2J = 11.9, 1 H each, CH_2O–C(6)); 7.28 (*m*, H_p of Ph); 7.33 (*m*, 2 H_m of Ph); 7.35 (*m*, 2 H_o of Ph). ^{31}P-NMR (81 MHz): 24.1. FAB-MS: 433 (24, $[M+1]^+$), 401 (13), 201 (15), 91 (100). HR-MS: 433.1651, ($[M+1]^+$, $C_{19}H_{30}O_9P^+$; calc. 433.1628).

*Methyl 6-*O*-Benzyl-5-(dimethoxyphosphinyl)-2,3-*O*-isopropylidene-α-*D*-manno- and β-*L*-gulofuranoside* (**15a** and **15b**, resp.). Methoxalyl chloride (1.00 ml, 10.9 mmol) was added to a soln. of **13a** (1.19 g, 2.75 mmol) and DMAP (1.34 g, 11.0 mmol) in dry MeCN (10 ml) at 0°. The mixture was stirred at 0° for 0.5 h under Ar, and the most of solvent was distilled off *in vacuo*. The residue was treated with aq. NH_4Cl and extracted with $CHCl_3$ three times. The combined org. layer was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo* to give the (5*R*)-5-*O*-methoxalyl derivative **14a** as a pale yellow syrup: R_f (AcOEt/hexane 2:1) 0.35.

The crude **14a** was co-evaporated with dry toluene and dissolved in the same solvent (10 ml). Bu_3SnH (1.10 ml, 4.09 mmol) and AIBN (80 mg, 0.49 mmol) were added under Ar. The mixture was stirred at 80° for 2 h and then concentrated *in vacuo*. The residue was separated by CC with AcOEt/hexane 1:1 → 2:1 to give **15a** and **15b**.

Data of **15a**: Colorless syrup (187 mg, 16%). R_f (AcOEt/hexane 2:1) 0.33. ^{1}H-NMR (500 MHz): see *Table 1*; additionally, 1.31, 1.42 (2*s*, Me_2C); 2.71 (*dddd*, J(5,P) = 19.2, J(4,5) = 10.7, J(5,6′) = 4.9, J(5,6) = 2.8, H–C(5)); 3.26 (*s*, MeO–C(1)); 3.71, 3.73 (2*d*, J(P,Me) = 10.7, $P(OMe)_2$); 3.94 (*ddd*, J(6′,P) = 29.3, J(6,6′) = 9.2, H′–C(6)); 3.98 (*ddd*, J(6,P) = 15.3, H–C(6)); 4.55, 4.61 (2*d*, ^2J = 11.9, 1 H each, CH_2O–C(6)); 7.26 (*m*, H_p of Ph), 7.32 (*m*, 2 H_m of Ph), 7.35 (*m*, 2 H_o of Ph). ^{31}P-NMR (81 MHz): 31.3. FAB-MS: 417 (21, $[M+1]^+$), 401 (12), 385 (11), 177 (19), 137 (11), 91 (100). HR-MS: 417.1691 ($[M+1]^+$, $C_{19}H_{30}O_8P^+$; calc. 417.1679).

Data of **15b**: Colorless syrup (803 mg, 70%). R_f (AcOEt/hexane 2:1) 0.26. ^{1}H-NMR (500 MHz): see *Table 1*; additionally, 1.25, 1.40 (2*s*, Me_2C); 2.62 (*ddt*, J(5,P) = 18.3, J(4,5) = 10.4, J(5,6) = 4.0, J(5,6′) = 3.7, H–C(5)); 3.32 (*s*, MeO–C(1)); 3.74, 3.76 (2*d*, J(P,Me) = 10.7 Hz, $P(OMe)_2$); 3.82 (*ddd*, J(6′,P) = 28.1, J(6,6′) = 9.8, H′–C(6)); 3.88 (*ddd*, J(6,P) = 10.6, H–C(6)); 4.51, 4.57 (2*d*, ^2J = 11.9, 1 H each, CH_2O–C(6)); 7.28 (*m*, H_p of Ph); 7.33 (*m*, 2 H_o and 2 H_m of Ph). ^{31}P-NMR (81 MHz): 32.4. FAB-MS: 417 (32, $[M+1]^+$), 401 (18), 385 (15), 177 (15), 91 (100). HR-MS: 417.1682 ($[M+1]^+$, $C_{19}H_{30}O_8P^+$; calc. 417.1679).

By the same procedures described above, **13b** (262 mg) was converted to **15a** (38.3 mg, 15%) and **15b** (172 mg, 68%) *via* intermediate **14b**.

*1,2,3,4,6-Tetra-*O*-acetyl-5-deoxy-5-[(*R*)- and (*S*)-methoxyphosphinyl]-α/β-*D*-mannopyranoses* **19a**–**d**. To a soln. of **15a** (196 mg, 0.471 mmol) in dry toluene (2.0 ml) was added, with stirring, a soln. of sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA; 70% in toluene, 2.5 ml, 0.85 mmol) in dry toluene (1.0 ml) in small portions during 30 min at −10° under Ar. The stirring was continued at this temp. for 30 min. Then, H_2O (0.2 ml) was added to decompose excess SDMA, and the mixture was centrifuged. The precipitate was extracted with several portions of toluene. The org. layers were combined and evaporated *in vacuo* to give *methyl 6-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-5-phosphino-α-*D*-mannofuranoside* (**16**) as a colorless syrup.

This syrup was immediately treated with i-PrOH/0.5M HCl 2:1 (3.0 ml) at 90° for 2 h under Ar. After cooling, the mixture was evaporated *in vacuo*. The residue was dissolved in i-PrOH (2.0 ml), treated with 35% H_2O_2 (0.8 ml, 9.3 mmol) at 20° for 12 h and then concentrated *in vacuo* to give crude *6-*O*-benzyl-5-deoxy-5-(hydroxyphosphinyl)-α/β-*D*-mannopyranoses* (**17**) as a colorless syrup. This was dissolved in dry pyridine (2.0 ml), and Ac_2O (1.0 ml, 11 mmol) was added at 0°. The mixture was stirred at r.t. for 12 h, diluted with a small amount of cold H_2O, and concentrated *in vacuo*. The residue was dissolved in EtOH and passed through a column of *Amberlite IR-120(H$^+$)* (20 ml). The eluent was evaporated *in vacuo*, and the residue was methylated with ethereal CH_2N_2 in dry CH_2Cl_2 (2.0 ml) at 0°. After evaporation of the solvent, the residue was separated by CC with AcOEt/hexane 2:1 → AcOEt to give 1,2,3,4-tetra-O-*acetyl-6-*O*-benzyl-5-deoxy-5-[(*R*)-* and *(*S*)-methoxyphosphinyl]-α/β-*D*-mannopyranoses* (**18**; 72 mg) as a colorless syrup containing a small amounts of unidentified products (R_f (AcOEt) 0.59–0.52).

Compounds **18** dissolved in EtOH (2.0 ml) was hydrogenated in the presence of $Pd(OH)_2$/C (25 mg) at 20° under atmospheric pressure of H_2. After 12 h, the catalysts was filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in dry pyridine (1.0 ml), and Ac_2O (0.25 ml) was added. After stirring at 20° for 12 h, cold H_2O was added. The mixture was evaporated *in vacuo*, and the residue was separated by CC with AcOEt/hexane 2:1 → AcOEt into three *Fractions A–C*.

Fraction A (R_f(AcOEt) 0.41) gave the 5-[(*R*)-methoxyphosphinyl]-α-*D*-mannopyranose **19a** [6] as a colorless syrup (13.2 mg, 6.2% from **15a**; [6]: 6.1% from **8**). ^{31}P-NMR (81 MHz): 39.3.

Fraction B (R_f 0.36) gave a colorless syrup (22.6 mg), which consisted of 5-[(*S*)-methoxyphosphinyl]-α-isomer **19c** (4.7% from **15a**; [6]: 2.4% from **8**) and its β-isomer **19d** (5.9%; [6]: 3.6% from **8**), the ratio being estimated by ^{1}H-NMR. ^{31}P-NMR (81 MHz): 38.8 (for **19c**), 37.7 (for **19d**).

Fraction C (R_f 0.23) gave 5-[(*R*)-methoxyphosphinyl]-β-isomer **19b** as a colorless syrup (17.7 mg, 8.3% from **15a**). ^{1}H-NMR (500 MHz): see *Table 2*; additionally, 2.03, 2.07, 2.08, 2.15, 2.18 (5*s*, 5 AcO); 3.82 (*d*, *J*(P,Me) = 11.0, MeO–P); 4.47 (*ddd*, *J*(6′,P) = 13.5, *J*(6,6′) = 11.8, *J* (5,6′) = 6.6, H′–C(6)); 4.50 (*ddd*, *J*(6,P) = 11.1, *J*(5,6) = 6.9, H–C(6)). ^{31}P-NMR (81 MHz): 38.0. FAB-MS: 453 (8.2, $[M+1]^+$), 410 (11), 393 (6), 368 (8), 351 (48), 321 (28), 309 (80), 207 (75), 188 (100), 164 (36). HR-MS: 453.1163 ($[M+1]^+$, $C_{17}H_{36}O_{12}P^+$; calc. 453.1162).

1,2,3,4,6-Tetra-O-*acetyl-5-deoxy-5-[(*R*)- and (*S*)-methoxyphosphinyl]-*α/β*-*L*-*gulopyranoses* (**23a–d**). The procedures similar to those for the preparation of compounds **19** from substrates **15a** were employed. Thus, compound **15b** (210 mg, 0.504 mmol) was converted to *1,2,3,4-tetra*-O-*acetyl-6*-O-*benzyl-5-deoxy-5-[(*R*)-* and *(*S*)-methoxylphosphoninyl]-*α/β*-L-gulopyranoses (**22**) *via* intermediates **20** and **21**. The diastereoisomeric mixture **22** was debenzylated and then acetylated again to give **23**. The crude product **23** was separated by CC into *Fractions A* and *B*.

Fraction A (R_f (AcOEt) 0.44) gave a colorless syrup (41.1 mg), which consisted of 5-[(*R*)-methoxyphosphinyl]-β-isomer **23a** (12% from **15b**) and 5-[(*S*)-methoxyphosphinyl]-α-isomer **23d** (6.5%), the ratio being estimated by ^{1}H-NMR. ^{1}H-NMR (500 MHz) of **23a**: see *Table 2*; additionally, 1.98, 2.05, 2.14, 2.15, 2.175 (5*s*, 5 AcO); 3.84 (*d*, *J*(P,Me) = 10.7, MeO–P); 4.35 (*ddd*, *J*(6,6′) = 11.3, *J*(5,6′) = 9.8, *J*(6′,P) = 7.0, H′–C(6)); 4.40 (*dt*, *J*(6,P) = 5.9, *J*(5,6) = 5.2, H–C(6)). ^{1}H-NMR (500 MHz) of **23d**: see *Table 2*; additionally, 2.04, 2.11, 2.12, 2.135, 2.17 (5*s*, 5 AcO); 3.87 (*d*, *J*(P,Me) = 10.7, MeO–P); 4.39 (*m*[8]), *J*(5,6′) = 5.2, H′–C(6)); 4.43 (*dt*, *J*(6,P) = 19.2, *J*(6,6′) = 11.6, *J*(5,6) = 3.7, H–C(6)). ^{31}P-NMR (81 MHz): 38.4 (for **23a**); 37.7 (for **23d**). FAB-MS: 453 (5.2, $[M+1]^+$), 410 (9.8), 393 (6), 351 (48), 321 (18), 309 (80), 230 (39), 207 (79), 188 (100), 164 (32). HR-MS: 453.1169 ($[M+1]^+$, $C_{17}H_{36}O_{12}P^+$; calc. 453.1162).

Fraction B (R_f 0.39) gave a colorless syrup (36.1 mg), which consisted of 5-[(*R*)-methoxyphosphinyl]-α-isomer **23b** (5.1% from **15b**) and 5-[(*S*)-methoxyphosphinyl]-β-isomer **23c** (11%), the ratio being estimated by ^{1}H-NMR. ^{1}H-NMR (500 MHz) for **23b**: see *Table 2*; additionally, 2.06, 2.10, 2.115, 2.12, 2.175 (5*s*, 5 AcO); 3.86 (*d*, *J*(P,Me) = 11.0, MeO–P); 4.40 (*ddd*, *J*(6,6′) = 11.6, *J*(5,6′) = 8.5, *J*(6′,P) = 6.7, H′–C(6)); 4.41 (*ddd*, *J*(6,P) = 9.9, *J*(5,6) = 4.5, H–C(6)). ^{1}H-NMR (500 MHz) for **23c**: see *Table 2*; additionally, 2.00, 2.07, 2.16, 2.18, 2.19 (5*s*, 5 AcO); 3.79 (*d*, *J*(P,Me) = 11.0, MeO–P); 4.40 (*dd*, *J*(6,P) = *J*(6′,P) = 9.8, *J*(5,6′) = *J*(5,6) = 7.3, CH_2(6)). ^{31}P-NMR (81 MHz): 37.8 (for **23b**); 39.1 (for **23c**). FAB-MS: 453 (4.2, $[M+1]^+$), 410 (11), 393 (10), 351 (38), 321 (15), 309 (69), 230 (32), 207 (68), 188 (100), 164 (39). HR-MS: 453.1173 ($[M+1]^+$, $C_{17}H_{36}O_{12}P^+$; calc. 453.1162).

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