Synthesis and Structural Analysis of 5-Deoxy-5-[(*R*)- and (*S*)- methylphosphinyl]-α,β-D-manno- and -L-gulopyranoses

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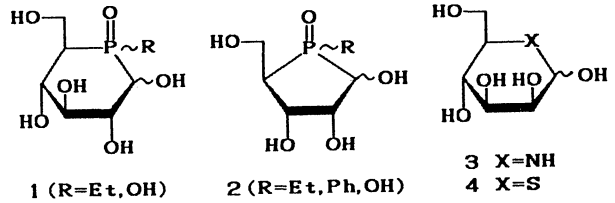
Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-α-D-*lyxo*-hex-5-enofuranoside (**10**) was prepared from D-mannose in 7 steps. Addition of methyl methylphosphinate to **10**, followed by the catalytic hydrogenation and diazotization, afforded methyl 5-deoxy-2,3-*O*-isopropylidene-5-[(methoxy)methylphosphinyl]-α-D-*lyxo*-hexofuranoside, which was then converted into 6-*O*-triphenylmethyl and 6-*O*-tetrahydropyranyl derivatives (**14**, **15**). By reduction with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by acid hydrolysis, both **14** and **15** provided the D-mannopyranoses (together with a minor proportion of L-gulopyranoses) having a methylphosphinylidene group in place of the ring oxygen. These were converted into 1,2,3,4,6-penta-*O*- acetyl derivatives, whose structures and conformations were established by spectroscopy.

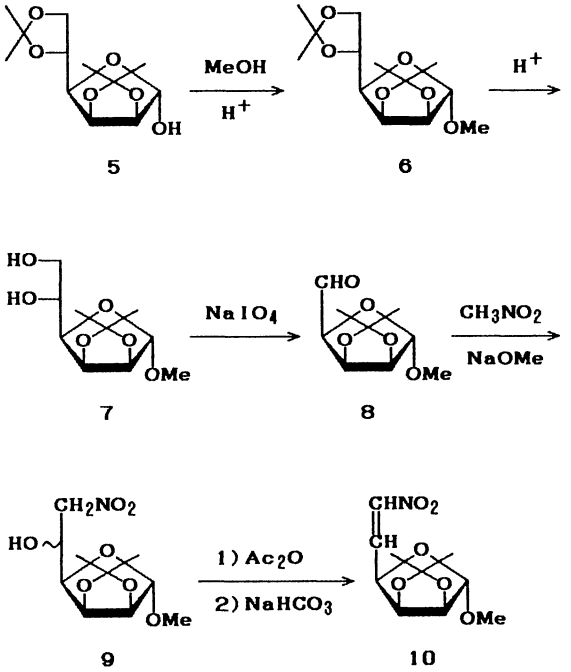
Sugar analogues possessing a phosphorus atom in place of oxygen in the hemiacetal ring[1] have not been found in nature. However, these P-in-ring sugars have drawn interest owing to their physicochemical properties as well as potential biological activity. Accordingly, various such analogues have been prepared in recent years: e.g., 5-deoxy-5-phosphinyl-D-glucopyranoses[2-5] (**1**) and 4-deoxy-4-phosphinyl-D-ribofuranoses[6-8] (**2**). In the meantime, 5-amino-5-deoxy-D-mannopyranose[9] (**3**) has been proven to inhibit β-D-glucosidase and α,β-D-mannosidase, whereas the first, naturally occurring S-in-ring thiosugar has turned out to possess D-mannopyranose structure **4**.[10] We report herein a detailed study on the first synthesis and characterization of P-in-ring D-mannopyranoses, as well as the L-gulopyranoses, by placing methylphosphinylidene in the hemiacetal ring as a model functional group.[11]



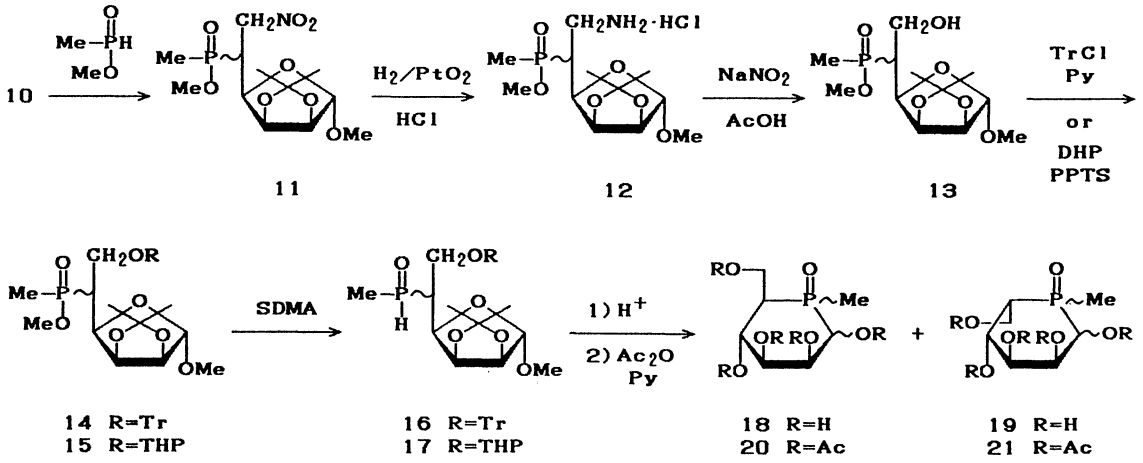
Results and Discussion

2,3 : 5,6-Di-*O*-isopropylidene-α-D-mannofuranose[12] (**5**) (available from D-mannose in two steps) served as the starting material for preparation of the important key intermediate, methyl 5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-α-D-*lyxo*-hex-5-enofuranoside (**10**), by the sequence illustrated in Scheme 1. Glycosidation of **5** using an ion-exchange resin Amberlite IR-120(H^+) in methanol was found to furnish, with simpler procedures, a higher yield of the methyl α-D-mannofuranoside (**6**) than that by the previously reported method (MeI-Ag_2O in DMF).[12] Selective deprotection of **6** with acid afforded methyl 2,3-*O*-isopropulidene-α-D-mannofuranoside (**7**), which was then treated with sodium periodate to give methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside[13] (8). Addition of nitromethane to **8** in the presence of sodium methoxide gave a mixture of methyl (5*R* and 5*S*)-6-deoxy-2,3-*O*-isopropylidene-6-nitro-α-D-*lyxo*-hexofuranosides (**9**), which in turn was immediately converted into **10**.

Addition of methyl methylphosphinate[14] to **10** afforded methyl 5,6-dideoxy-2,3-*O*-isopropylidene-5-[(methoxy)methylphosphinyl]-6-nitro-α-D-*lyxo*-hexofuranoside (**11**) (Scheme 2). Catalytic hydrogenation of **11** over platinum oxide (to convert into the 6-amino derivative **12**), followed by diazotization and then hydrolysis, gave methyl 5-deoxy-2,3-*O*-isopropylidene-5-[(methoxy)methylphosphinyl]-α-D-*lyxo*-



Scheme 1.



Scheme 2.

hexofuranoside (**13**). Compound **13** was subsequently converted into the 6-*O*-triphenylmethyl (Tr) and 6-*O*-tetrahydropyranyl (THP) derivative (**14** and **15**).

Compound **14** was then reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) to give the unstable 5-deoxy-5-methylphosphinyl derivative **16**, which was immediately treated with ethanolic 0.5 M hydrochloric acid (1 M=1 mol dm^{-3}) at 80 °C under nitrogen, thus affording a crude mixture of 5-deoxy-5-(methylphosphinyl)-D-manno- (**18**) and -L-gulopyranoses (**19**) as shown in Scheme 2. These products were characterized after conversion into the corresponding penta-*O*-acetyl derivatives **20** and **21** by the usual method. By purification on a silica-gel column, the presence of the following eight penta-*O*-acetyl diastereomers were confirmed (Chart 1), although some of the minor products were not completely separable, whereupon the product ratio was based on the NMR (see the Experimental section): 5-[(*R*)-methylphosphinyl]-α-D-mannopyranose (**20a**, 6.0% overall yield from **14**), the β-anomer (**20b**, 0.9%), the [(*S*)-*P*]-α-isomer (**20c**, 4.6%), the β-anomer (**20d**, 0.4%), 5-[(*R*)-methylphosphinyl]-β-L-gulopyranose (**21a**, 1.7%), the α-anomer (**21b**, 0.9%), 5-[(*S*)-*P*]-β-isomer (**21c**, 3.2%), and the α-anomer (**21d**, 2.0%). Structures and the preferable conformations (in solution) of these products were established on the basis of high-resolution mass spectrometry (HR-MS) and 500 MHz ^{1}H NMR spectral data (see below). The ratio of D-manno- to L-gulo-type compounds obtained under these conditions turned out to be 6:4 in favor of the former (**20a—d**).

Similar treatments of the 6-*O*-THP derivative **15** afforded, via 5-methylphosphinyl intermediate **17**, a mixture of **18** and **19**. These were also led to **20a—d** and **21a—d** and the overall yields from **15** were close to those derived from **14**: namely, the ratio of the D-manno- to L-gulopyranose was approximately 6:4.

These results significantly contrast to the fact that high selectivity in the product ratios has been achieved,[2-4] when 6-*O*-Tr- and 6-*O*-THP derivatives of 5-deoxy-5-phosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose were subjected to the same ring-transposition procedures, furnishing either 5-deoxy-5-phosphinyl-D-gluco- (**1**) or -L-idopyranose.

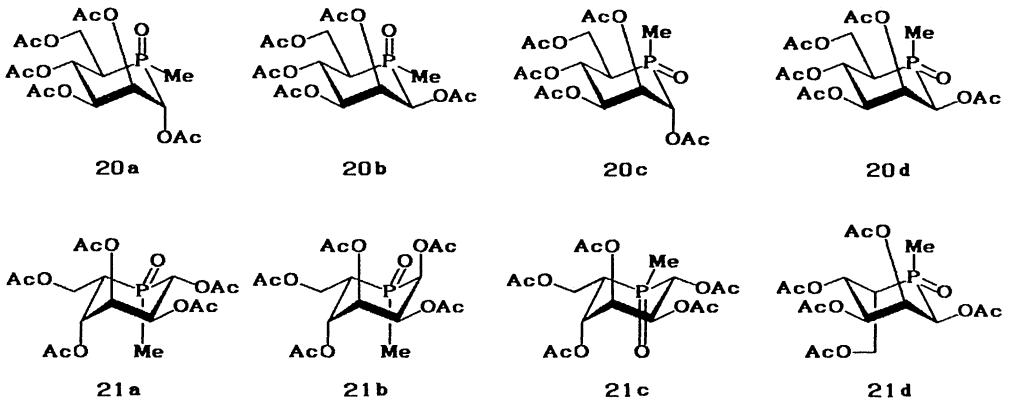
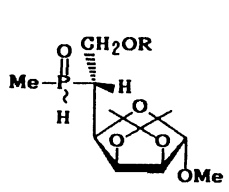
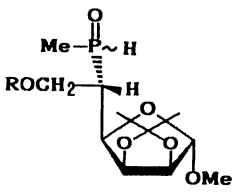


Chart 1. Structures of 1,2,3,4,6-penta-*O*-acetyl-5-deoxy-5-methylphosphinyl-D-manno- and -L-gulopyranoses and their conformations.

The unpreponderating but only slightly favorable formation of D-mannopyranoses **18** (over L-gulopyranoses **19**) from **13** via **14** (or **15**) could be rationalized in terms of the absence of a significant difference in the steric congestion between the key intermediates D-mannofuranoside **16a** (or **17a**) and L-gulofuranoside **16b** (or **17b**) that are expected to be produced as the result of thermodynamical equilibration[4] at C-5 caused by the strongly basic SDMA during the reduction. Once the reaction mixture is worked up with cold water after the reduction, the ratio of the C-5 epimers **16a** (**17a**) to **16b** (**17b**) would correspond to that of the final product **20** to **21**, because no epimerization takes place during the following reactions (acid-catalyzed deprotection with simultaneous ring-transposition and per-*O*-acetylation). It is unlikely that the ratio of the D-manno- to L-gulofuranoside component in **13**, which, however, was not possible to specify by NMR, affects the final product ratio of **20** to **21**, taking into account the well-established reaction mechanism of similar ring enlargement.[2-4,6]



16a R=Tr
17b R=THP



16b R=Tr
17b R=THP

^{1}H NMR Spectral Analysis of Penta-*O*-acetyl-5-deoxy-5-(methylphosphinyl)-D-manno- and -L-gulopyranoses. For structural assignments of these eight new products **20a—d** and **21a—d** having the same molecular composition ($C_{17}H_{25}O_{11}P$ by HR-MS), the chemical shift of each proton signal of their NMR spectra and the dependence of the $^2J_{H,P}$, $^3J_{H,P}$, $^3J_{H,H}$, and $^4J_{H,H}$ values on their dihedral angles were carefully taken into consideration. The precise parameters thereby obtained for these compounds are summarized in Table 1. Since the parameters for 5-deoxy-5-phosphinyl-D-manno and -L-gulopyranoses have been obtained for the first time in the present study, some characteristic features of **20a—d** and **21a—d** are discussed here in detail. These parameters are instructive in determining the structures of other similar phosphinyl-in-ring sugar analogues, preparation of which is currently under investigation.

(1) The D-mannopyranose configuration is assignable to **20a—d** on the basis of their relatively large values of $J_{4,5}$ (9—12 Hz). In contrast, the smaller values ($J_{4,5}$=4—5 Hz) of **21a—d** suggest the structure of L-gulopyranose type as in the case employed for distinction between 5-deoxy-5-phosphinyl-D-gluco- (**1**) and -L-idopyranoses.[2-5] Conformations of these compounds (in $CDCl_3$ solution) are derived by the analysis of the values of $J_{2,P}$ (17—27 Hz for **20a—d** vs. 3—5 Hz for **21a—c**) and $J_{4,P}$ (3—9 Hz for **20a—d** vs. 25—28 Hz for **21a—c**) with respect to the corresponding vicinal dihedral angles (namely, whether in the anti or gauche connection). As a result, **20a—d** and **21a—c** are respectively assigned to exist predomi-

Table 1. ^{1}H NMR (500 MHz) Parameters for **20** and **21** in $CDCl_3$

Compd	Chemical shift (δ)								
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	Ac-1,2,3,4,6[a]	PMe
20a	5.63	5.35	5.32	5.67	2.57	4.59	4.48	2.18, 2.14, 2.09, 2.09, 2.06	1.67
20b	5.14	5.68	5.12	5.76	2.28	4.58	4.47	2.18, 2.17, 2.11, 2.07, 2.01	1.68
20c	5.38	5.52	5.27	5.41	2.71	4.72	4.31	2.24, 2.18, 2.08, 2.05, 1.99	1.85
20d	5.48	5.71	5.16	5.45	2.46	b)	b)	2.19, 2.13, 2.12, 2.04, 1.98	1.84
21a	5.92	5.17	5.42	5.32	2.98	4.46	4.44	2.20, 2.15, 2.15, 2.07, 1.99	1.77
21b	5.68	5.34	5.33	5.50	3.07	4.47	4.41	2.21, 2.13, 2.13, 2.11, 2.07	1.76
21c	5.44	5.73	5.57	5.36	2.45	4.50	4.44	2.20, 2.20, 2.16, 2.08, 1.99	1.72
21d	5.73	5.72	5.62	5.40	2.83	4.52	4.51	2.21, 2.14, 2.13, 2.12, 2.02	1.84

Compd	Coupling constant (Hz)												
	$J_{1,2}$	$J_{1,P}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{4,5}$	$J_{4,P}$	$J_{5,6}$	$J_{5,6'}$	$J_{5,P}$	$J_{6,6'}$	$J_{6,P}$	$J_{6',P}$	J_{PMe}
20a	6.8	7.7	2.8	16.9	8.5	9.2	9.3	7.5	7.1	7.0	11.7	8.9	13.5	13.6
20b	3.1	2.0	2.5	22.7	9.9	10.3	3.4	8.0	6.0	4.3	11.5	10.5	5.0	13.5
20c	4.9	9.8	3.2	25.4	9.8	11.7	3.6	4.2	2.7	20.0	12.1	22.6	9.5	13.6
20d	3.3	12.5	2.8	27.0	10.2	11.7	3.5	2.5	4.1	19.3	b)	b)	b)	13.6
21a	11.6	11.2	2.6	3.3	5.2	3.3	27.7	5.9	8.4	21.0	11.8	13.6	6.2	13.2
21b	3.8	7.0	2.9	4.5	5.0	4.0	25.4	4.1	8.0	22.1	11.7	12.8	5.4	13.2
21c	11.5	3.9	2.6	4.3	5.0	3.4	27.5	7.2	7.8	5.4	11.7	7.2	11.9	13.2
21d	3.9	11.2	2.8	23.4	9.9	5.1	5.3	3.4	3.9	16.8	11.8	10.0	18.0	13.6

a) The assignments of acetoxyl groups may have to be interchanged. b) Values uncertain because of overlapping with other signals.

nantly in the $^4C_1$(D) and $^1C_4$ (L) conformations. As **21d** shows $J_{2,P}$=23.4 Hz and $J_{4,P}$=5.3 Hz, it is considered to exist mainly in the $^4C_1$ (L) form.

(2) The orientation of the ring P=O group can be established by the δ values of H-4 (for **20a—d**) and H-2 (for **21a—d**). An appreciable down field shift (0.3—0.5 Hz) is observed for **20a,b** and **21c**, thus showing the axial orientation of the ring P=O for these compounds. The small values of $J_{5,P}$ support the anti orientation of H-C(5)-P=O for **20a,b** and **21c**. Because of the absence of these characteristic features, the equatorial P=O orientation is assigned to the rest of the products (**20c,d** and **21a,b**). The appreciable downfield shift observed for H-2 of **21d** could be explained by its equatorial orientation (contrary to the axial H-2 for all other products); for a possible reasoning, see later.

(3) The anomeric orientation of C-1 is derived from the values of $J_{1,2}$ and $J_{1,P}$ as well as from the presence (or absence) of an NOE effect among H-1, H-3, and H-5 signals. The small values of $J_{1,P}$ of **20b** and **21c** suggest the anti connection of H-C(1)-P=O for these compounds. The large values of $J_{1,2}$ (11.5—11.6 Hz) indicate axial H-1 orientation for **21a,c**, whereas the smaller $J_{1,2}$ value (3.8 Hz) points out the equatorial H-1 configuration for **21b**. As H-2 of **20a—d** and **21d** is in equatorial orientation, all of $J_{1,2}$ of these compounds show similar, small values, thus making the assignment of their anomeric AcO-1 orientation rather difficult. However, NOE difference studies on **20a,c** show no enhancement for H-1 although 7—8% enhancement for H-3 upon irradiation of H-5, supporting the assignment of the equatorial orientation of H-1 in **20a** and **20c**. Similarly, the presence of an NOE effect between H-1 and H-5 observed for **21a,c** is in conformity with the diaxial orientation of H-1 and H-5 in these compounds.

As for the more precise conformation of **20a**, it is noted that the values of $J_{2,P}$ (16.9 Hz) and $J_{4,P}$ (9.3 Hz) tend to become appreciably closer to intermediate values, suggesting an equilibrium mixture of $^4C_1$(D) and $^1C_4$(D) conformers (but still in favor of the former). Such an averaging between these conformers would allow minimization of a nonbonded interaction between 1,3-*syn*-diaxial P=O and AcO-2 groups (Scheme 3). On the other hand, the conformation of **21d** in favor of exceptional $^4C_1$(L) is most likely ascribed to the presence of much stronger destabilizing interactions between the 1,3-*syn*-oriented P=O and AcO-4 groups in addition to the two acetoxyl groups (AcO-1,3) in the alternative $^1C_4$(L) conformation of **21d**, compared with the only one 1,3-diaxial repulsive influence exerted by AcO-2 and P-Me groups in the $^4C_1$(L) conformation (Scheme 3).

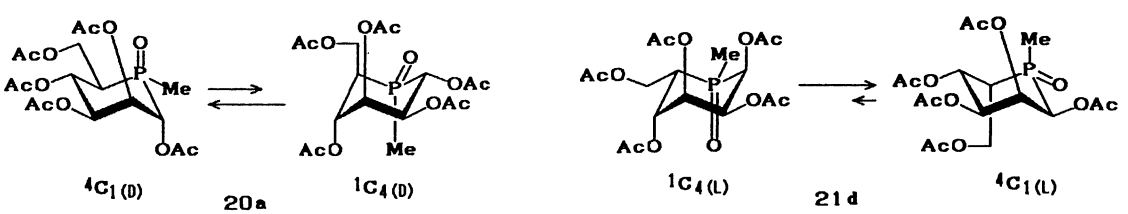
Although the yields of some steps and the stereoselectivity of the ring-transposition reaction remain to be improved, present work demonstrates a possible way for preparation of 5-deoxy-5-phosphinyl-D-mannopyranoses from appropriate intermediates. Extension of this work including preparative studies on improved product ratios of the ring-transposition products in relation to various kinds of substituents at P-5 and O-6 of the intermediates (corresponding to **14** and **15**), as well as biological evaluation of the compounds, is in progress.

Experimental

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1 : 1 AcOEt-hexane and (*B*) 9 : 1 AcOEt-EtOH]; components were detected with 20% sulfuric acid-ethanol (with subsequent heating). Column chromatography was performed with Wako C-200 silica gel. The ^{1}H NMR spectra were measured in $CDCl_3$ with a Hitachi-Perkin-Elmer R-600 (60 MHz, FT) or Varian VXR-500 instrument (500 MHz, the SC-NMR Lab., Okayama Univ.) at 23 °C. Chemical shifts are recorded as δ values relative to tetramethylsilane as internal standard. The assignments of all signals were made by employing a first-order analysis with the aid of decoupling technique and, if necessary, two-dimensional COSY or NOEDS measurements. The parameters were confirmed by a computer-assisted simulation analysis. The mass spectra were taken on an A.E.I. MS 50 ultrahigh resolution instrument and were given in terms of *m/z* (rel intensity) compared with the base peak.

Methyl 2,3-*O*-Isopropylidene-α-D-mannofuranoside[12] (7). A mixture of 19.8 g of **5**[12] and Amberlite IR-120(H^+) ion-exchange resin (50 ml) in abs methanol (200 ml) was refluxed for 2 h. After cooling, the resin was filtered off and the filtrate was evaporated in vacuo, giving crude methyl 2,3 : 5,6-di-*O*-isopropylidene-α-D-mannofuanoside[12] (**6**) (which contained a small amount of **7**) as a colorless syrup: R_f=0.72 (A).

This was dissolved in methanol (160 ml) and 0.2 M H_2SO_4 (40 ml). The mixture was stirred at 20 °C for 24 h and then neutralized with solid barium carbonate. The precipitate was filtered through an active carbon bed, and the filtrate was evaporated in vacuo. The residue was purified by short-path column chromatography, giving **7** as a colorless syrup (12.7 g, 71% overall yield from **5**, lit,[12] 58%): R_f=0.15



Scheme 3. Conformational equilibria for **20a** and **21d**.

(*A*); ^{1}H NMR (500 MHz) δ=1.33, 1.47 (3H each, 2s, CMe_2), 2.28 (1H, br s, HO-6), 2.91 (1H, br s, HO-5), 3.30 (3H, s, MeO-1), 3.72 (1H, dd, $J_{6,6'}$=10.8, $J_{5,6'}$=5.9 Hz, H-6'), 3.86 (1H, dd, $J_{5,6}$=3.3 Hz, H-6), 3.93 (1H, dd, $J_{4,5}$=7.9, $J_{3,4}$=3.8 Hz, H-4), 4.02 (1H, ddd, H-5), 4.57 (1H, d, $J_{2,3}$=5.9 Hz, H-2), 4.83 (1H, dd, H-3), and 4.91 (1H, s, H-1).

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-6-nitro-α-D-*lyxo*-hex-5-enofuranoside (10). Although compound **8** and its ^{1}H NMR spectral data (60 MHz) have been reported,[13] no preparative procedures are given. Thus, we prepared **8** as follows: A solution of sodium periodate (13.5 g, 63.1 mmol) in water (100 ml) was dropwise added to a solution of **7** (12.3 g, 52.5 mmol) in methanol (100 ml) at 0 °C. The solution was then stirred at room temp for 1 h and concentrated in vacuo. The residue was extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated in vacuo, giving crude **8** as a colorless syrup in a quantitative yield: R_f=0.38 (*A*).

A solution of **8** in abs methanol (120 ml) was treated with nitromethane (9.77 g, 160 mmol) and 25% sodium methoxide-methanol (34.0 ml, 149 mmol) at 0 °C. After 2 h, the solution was neutralized with methanol-washed Amberlite IR-120(H^+) ion-exchange resin at 0 °C. The solvent was evaporated in vacuo, giving **9** as a pale yellow syrup in a quantitative yield: R_f=0.53 (*A*); ^{1}H NMR (60 MHz) δ=1.34, 1.50 (3H each, 2s, CMe_2), 3.25 (1H, m, HO-5, D_2O exchangeable), 3.35, 3.42 (3H, 2s, MeO-1), 3.92 (1H, m, H-5), 4.50—4.85 (2H, m, H-3,4), 4.60 (1H, d, $J_{2,3}$=6.0 Hz, H-2), 4.68 (2H, m, H-6,6'), and 4.94 (1H, br s, H-1).

To a solution of **9** in acetic anhydride (25 ml, 265 mmol) was added, at 0 °C, sodium acetate (11.0 g, 134 mmol). The suspension was stirred for 12 h at room temp and then the mixture was poured into cold saturated aq $NaHCO_3$ (700 ml). The resulting solution was stirred for 2 h at 5 °C and then extracted with $CHCl_3$. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography, giving **10** (7.60 g, 59% overall yield from **8**) as a colorless syrup: R_f=0.64 (*A*); ^{1}H NMR (500 MHz) δ=1.30, 1.41 (3H each, 2s, CMe_2), 3.35 (3H, s, MeO-1), 4.62 (1H, d, $J_{2,3}$=5.8 Hz, H-2), 4.70 (1H, td, $J_{3,4}$=4.0, $J_{4,5}$=3.8, $J_{4,6}$=1.1 Hz, H-4), 4.83 (1H, dd, H-3), 4.97 (1H, s, H-1), 7.23 (1H, dd, $J_{5,6}$=13.2 Hz, H-6), and 7.28 (1H, dd, H-5); MS *m/z* 245 (M^+; 0), 230 (M−CH_3, 15), 214 (4), 187 (11), 173 (6), 167 (6), 158 (7), 149 (18), 129 (8), 115 (9), 97 (14), 85 (55), and 59 (100). Found: *m/z* 230.0658. Calcd for $C_9H_{12}NO_6$: M−CH_3, 230.0665.

Methyl (5*R* and 5*S*)-5,6-Dideoxy-2,3-*O*-isopropylidene-5-[(*R* and *S*)-(methoxy)methylphosphinyl]-6-nitro-α-D-*lyxo*-hexofuranosides (11). A mixture of **10** (720 mg, 2.93 mmol), methyl methylphosphinate[14] (0.74 ml, 8.8 mmol), and dry benzene (0.5 ml) was stirred for 12 h at 70 °C under nitrogen. The excess phosphinate was distilled off at ca. 50 °C/0.2 Torr (1 Torr=133.322 Pa). The residue was diluted with $CHCl_3$, washed with aq $NaHCO_3$ and then with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by silica-gel column chromatography, giving **11** as a colorless syrup (580 mg, 58%): R_f=0.45—0.40 (*B*); ^{1}H NMR (500 MHz) for the main component of **11** δ=1.30, 1.46 (3H each, 2s, CMe_2), 1.69 (3H, d, $J_{P,Me}$=14.6 Hz, PCH_3), 3.16 (1H, dddd, $J_{5,P}$=13.2, $J_{4,5}$=9.6, $J_{5,6}$=6.6, $J_{5,6'}$=4.0 Hz, H-5), 3.33 (3H, s, MeO-1), 3.74 (3H, d, J_{POMe}=10.7 Hz, POMe), 4.32 (1H, ddd, $J_{4,P}$=5.8, $J_{3,4}$=3.4 Hz, H-4), 4.57 (1H, d, $J_{2,3}$=5.8 Hz, H-2), 4.74 (1H, dd, H-3), 4.77 (1H, td, $J_{6',P}$=15.3, $J_{6,6'}$=14.5 Hz, H-6'), 4.81 (1H, ddd, $J_{6,P}$=17.2 Hz, H-6), and 4.92 (1H, s, H-1); MS *m/z* 340 (M+1; 0.6), 324 (M−CH_3; 33), 308 (5), 250 (4), 222 (9), 217 (21), 196 (64), 192 (15), 175 (25), 149 (77), 121 (24), 111 (34), and 93 (100). Found: *m/z* 324.0850. Calcd for $C_{11}H_{19}NO_8P$: M−CH_3, 324.0848.

Methyl (5*R* and 5*S*)-5-Deoxy-2,3-*O*-isopropylidene-5-[(*R* and *S*)-(methoxy)methylphosphinyl]-α-D-*lyxo*-hexofuranosides (13). Compound **11** (203 mg, 0.60 mmol) was dissolved in methanol (10 ml) containing 2 M HCl (0.30 ml, 0.60 mmol) and hydrogenated in the presence of platinum oxide (40 mg) at room temp under atmospheric pressure of H_2. After 20 h, disappearance of the starting material was confirmed by TLC. The catalyst was filtered off and the filtrate was evaporated in vacuo, giving the 6-aminohexofuranoside hydrochloride derivative (**12**) as an amorphous solid: R_f<0.05 (*B*).

To a solution of **12** in water (2 ml) was added, at 0 °C, acetic acid (0.12 ml, 2.2 mmol) and then sodium nitrite (200 mg, 2.9 mmol), followed by stirring at this temp. After 5 h, the mixture was extracted with $CHCl_3$. The combined organic layers were washed with aq $NaHCO_3$ and then with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography, giving **13** (90 mg, 48% from **11**) as a colorless syrup. R_f=0.26—0.22 (*B*); ^{1}H NMR (60 MHz) δ=1.30, 1.45 (3H each, 2s, CMe_2), 1.58, 1.65 (3H, 2d, J_{PMe}=14.8 Hz, PCH_3), 2.0—2.8 (1H, m, H-5), 3.31, 3.35 (3H, 2s, MeO-1), 3.4—3.8 (1H, m, HO-6), 3.76, 3.78, 3.82 (3H, 3d, J_{POMe}=10.8 Hz, POMe), 3.8—4.1 (2H, m, H-6,6'), 4.1—4.3 (1H, m, H-4), 4.56 (1H, d, $J_{2,3}$=6.0 Hz, H-2), 4.70 (1H, m, H-3), and 4.88 (1H, br s, H-1); MS *m/z* 310 (M^+; ≃0), 295 (M−CH_3; 7), 293 (40), 279 (72), 261 (22), 232 (6), 221 (10), 217 (15), 203 (15), 175 (27), 167 (36), 151 (24), 149 (35), 137 (44), 121 (33), and 93 (100). Found: *m/z* 295.0964. Calcd for $C_{11}H_{20}O_7P$: M−CH_3, 295.0947.

Methyl (5*R* and 5*S*)-5-Deoxy-2,3-*O*-isopropylidene-5-[(*R* and *S*)-(methoxy)methylphosphinyl]-6-*O*-triphenylmethyl-α-D-*lyxo*-hexofuranosides (14). A solution of **13** (570 mg, 1.83 mmol) and triphenylmethyl chloride (1.02 g, 3.66 mmol) in dry pyridine (7 ml) was stirred at 50 °C for 30 h. The mixture was cooled, diluted with water (1 ml), stirred at 20 °C for 1 h, and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on a column of silica gel, giving **14** (435 mg, 43%) as a colorless syrup: R_f=0.58—0.55 (*B*); ^{1}H NMR (60 MHz) δ=1.11, 1.13, 1.31, 1.35 (6H, 4s, CMe_2), 1.52, 1.58, 1.67 (3H, 6d, J_{PMe}=15.0 Hz, PCH_3), 2.2—3.2 (1H, m, H-5), 3.29, 3.34 (3H, 2s, MeO-1), 3.62, 3.68, 3.74, 3.80 (3H, 4d, J_{POMe}=11.0 Hz, POMe), 3.5—4.2 (2H, m, H-6,6'), 4.15—4.65 (2H, m, H-3,4), 4.58 (1H, d, $J_{2,3}$=6.0 Hz, H-2), 4.85 (1H, br s, H-1), and 7.25—7.65 (15H, m, CPh_3); MS *m/z* 552 (M^+; ≃0), 537 (M−CH_3; 0.5), 475 (M−C_6H_5; 1.0), 350 (2.4), 309 (34), 277 (11), 251 (10), 244 (26), 243 (100), 165 (32), and 93 (17). Found: *m/z* 475.1883. Calcd for $C_{25}H_{32}O_7P$: M−C_6H_5, 475.1886.

Methyl (5*R* and 5*S*)-5-Deoxy-2,3-*O*-isopropylidene-5-[(*R* and S)-(methoxy)methylphosphinyl]-6-*O*-(tetrahydropyran-2-yl)-α-D-*lyxo*-hexofuranosides (15). A solution of **13** (194 mg, 0.625 mmol) and dihydropyran (160 mg, 1.90 mmol) in dry CH_2Cl_2 (4 ml) containing pyridinium *p*-toluenesulfonate (47 mg, 0.187 mmol) was stirred for 12 h at

room temp. The solution was diluted with ether, washed once with half-saturated brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by short-path column chromatography, giving **15** (217 mg, 88%) as a colorless syrup: R_f=0.42—0.33 (*B*); ^{1}H NMR (60 MHz) δ=1.32, 1.45 (3H each, 2s, CMe_2), 1.45—1.80 [6H, m, C-$(CH_2)_3$-C-O-6], 2.3—3.09 (1H, m, H-5), 3.32, 3.39, 3.40 (3H, 3s, MeO-1), 3.5—4.2 (4H, m, CH_2-O-C-O-6, H-6,6′), 3.78 (3H, br d, J_{POMe}=10.8 Hz, POMe), 4.2—4.5 (1H, m, H-4), 4.58 (1H, d, $J_{2,3}$=6.0 Hz, H-2), 4.6—4.8 (1H, m, H-3), 4.62 (1H, br s, CH-O-6), and 4.93 (1H, br s, H-1); MS *m/z* 394 (M^+; ≃0), 379 (M−CH_3, 5), 363 (3), 323 (5), 311 (16), 309 (16), 295 (16), 279 (16), 252 (11), 221 (14), 205 (13), 192 (24), 176 (33), 167 (100), 137 (37), 111 (45), and 93 (66). Found: *m/z* 379.1519. Calcd for $C_{16}H_{28}O_8P$: M−CH_3, 379.1522.

1,2,3,4,6-Penta-*O*-acetyl-5-deoxy-5-[(*R*)-methylphosphinyl]-α-D-mannopyranose (20a), the β-Anomer (20b), the [(*S*)-Methylphosphinyl]-α-D-mannopyranose (20c), the β-Anomer (20d), the [(*R*)-Methylphosphinyl]-β-L-gulopyranose (21a), the α-Anomer (21b), the [(*S*)-Methylphosphinyl]-β-L-gulopyranose (21c), the α-Anomer (21d). To a solution of **14** (590 mg, 1.07 mmol) in dry benzene (8 ml) was added, with stirring, a solution of SDMA (70% in toluene, 0.70 ml, 2.4 mmol) in dry benzene (2 ml) in small portions at 5 °C under argon. The stirring was continued at this temp for 1 h. Water (1 ml) was added at 0 °C and the mixture was stirred for 30 min. The precipitate was centrifuged and washed with several portions of benzene. The organic layer was combined and evaporated in vacuo, giving **16** as a colorless syrup.

This syrup was immediately dissolved in ethanol (4 ml) and 0.5 M HCl (4 ml). The mixture was degassed with argon and then stirred at 90 °C for 3 h. After cooling, the reactant was neutralized by adding enough Amberlite IRA-45. The resin was filtered off and washed with aq ethanol. The filtrate combined with washings was evaporated in vacuo, giving a mixture of 5-deoxy-5-(methylphosphinyl)-D-mannopyranose (**18**) and -L-gulopyranose (**19**) as a colorless syrup.

This was dissolved in dry pyridine (4 ml) and acetic anhydride (2 ml) at 0 °C. The mixture was stirred at room temp overnight, diluted with a small amount of cold water, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo, giving a mixture of pentaacetates (**20a—d**, **21a—d**), which were separated by column chromatography with a gradient eluant of AcOEt →19:1 AcOEt-EtOH into four fractions A—D.

Fraction A [R_f=0.40 (*B*)] gave **20a** as a colorless syrup: 28.0 mg (6.0% overall yield from **14**); ^{1}H NMR (500 MHz), see Table 1; NOEDS experiment[15] [obsd NOEs (%) by irradiation of H-5] H-3=6.9, H-4=5.2, and H-6=H-6′=3.0; MS *m/z* 436 (M^+; 0.5), 394 (11), 377 (8), 352 (I6), 335 (70), 293 (76), 275 (33), 264 (14), 251 (18), 233 (56), 214 (47), 191 (34), 172 (54), and 43 (100). Found: *m/z* 436.1154. Calcd for $C_{17}H_{25}O_{11}P$: M^+, 436.1135.

Fraction B [R_f=0.36 (*B*)] gave a colorless syrup (31.3 mg) which consisted of **20c** (4.6% from **14**), **21a** (1.7%), and **20d** (0.4%), the relative amounts of these isomers being determined from the integral ratios of their H-5 and P-CH_3 signals: ^{1}H NMR (500 MHz) , see Table 1; NOEDS experiment [obsd NOEs (%) by irradiation of H-5 for **20c**] H-3=8.4, H-4=3.8, H-6=3.8, and H-6′=2.6, (for **21a**) H-1=8.5, H-4 13.5, and H-6=H-6′=4.9.

Fraction C [R_f=0.32 (*B*)] gave a colorless syrup (19.1 mg) which consisted of **21c** (3.2% from **14**) and **20b** (0.9%): ^{1}H NMR (500 MHz), see Table I; NOEDS experiment [obsd NOEs (%) by irradiation of H-5 for **21c**] H-1=6.0, H-4=9.7, and H-6=H-6′=3.4; MS *m/z* 437 (M+1; 5), 394 (M−CH_2CO; 4), 383 (9), 377 (5), 352 (20), 351 (27), 335 (100), 309 (14), 293 (93), 275 (44), 251 (37), 233 (98), 214 (16), 207 (28), 191 (82), 172 (92), 135 (21), and 111 (39). Found: *m/z* 437.1213. Calcd for $C_{17}H_{26}O_{11}P$: M+1, 437.1213.

Fraction D [R_f=0.28 (*B*)] gave a colorless syrup (13.6 mg) which consisted of **21d** (2.0% from **14**) and **21b** (0.9%): ^{1}H NMR (500 MHz), see Table 1.

When **15** was subjected to the same procedures described above, **20** and **21** were also obtained in yields similar to those described above: **20a**, 5.7% from **15**; **20b**, 1.3%; **20c**, 4.2%; **20d**, 0.3%; **21a**, 1.8%; **21b**, 1.2%; **21c**, 3.0%; **21d**, 2.3%.

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