

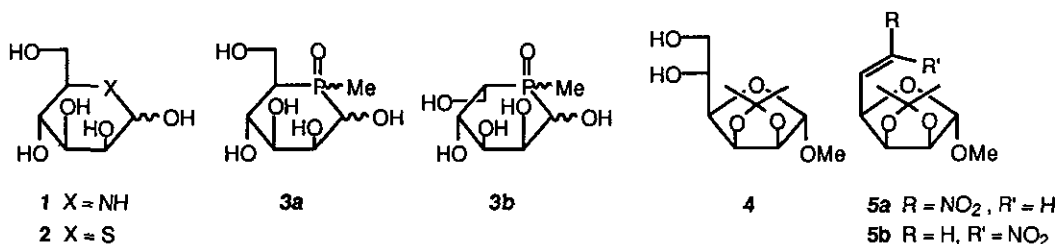
SYNTHESIS OF 5-DEOXY-5-HYDROXYPHOSPHINYL-D-MANNOPYRANOSIDES

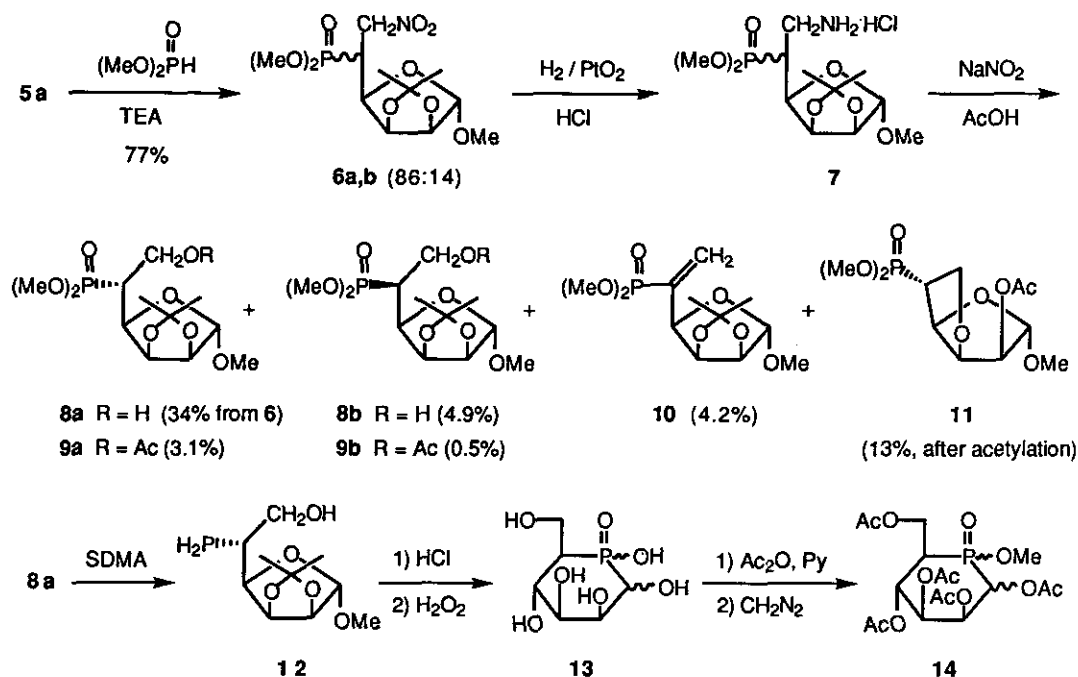
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Abstract - The title sugar analogues (**13**) were synthesized by starting with known methyl (*E*)-5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro- α -D-lyxo-hex-5-enofuranoside (**5a**) in six steps through the key intermediate, methyl 5-deoxy-5-dimethoxyphosphinyl-2,3-*O*-isopropylidene- α -D-mannofuranoside (**8a**). The products (**13**) were converted into the corresponding penta-*O*-acetyl-5-methoxyphosphinyl derivatives (**14**), whose structures and conformations (mostly 4C_1) were established by spectroscopy.

There has been considerable interest in the synthesis of sugar analogues containing nitrogen,¹ sulfur,² phosphorus,³⁻⁵ instead of oxygen in the hemiacetal ring. In a modification of D-mannose, 5-amino-5-deoxy-D-mannopyranose (**1**)⁶ has been shown to act as an inhibitor of β -D-glucosidase and α,β -D-mannosidase,^{6,7} whereas 5-thio-D-mannopyranose (**2**)⁸ has been isolated from the marine sponge *Clathria pyramida*⁹ as the first naturally occurring example of S-in-the-ring sugars. An analogue of P-in-the-ring D-mannose, 5-deoxy-5-methylphosphinyl-D-mannopyranose (**3a**), was recently prepared but as a mixture with the corresponding L-gulopyranose (**3b**).¹⁰ We wish to describe herein an unambiguous synthesis of D-mannopyranose analogue having a hydroxyphosphinyl group in the ring; it should be noticed that the PO(OH)-in-the ring sugar analogues^{4,5} are generally more difficult to prepare than those having an alkyl- or phenylphosphinyl group in the ring but are expected to be interesting in view of biological activities.

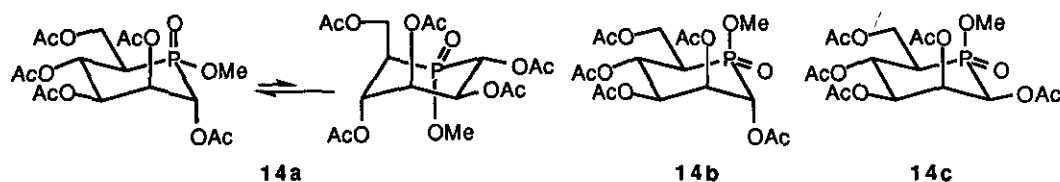




Scheme 1

The starting material (**5a**) was prepared from D-mannofuranoside (**4**) by the previous method;^{10,11} a trace amount of unreported (*Z*)-isomer (**5b**) was presently noted to accompany the main product (**5a**). The olefinic structures of **5a** and **5b** were readily perceived by the magnitude of the $J_{5,6}$ values (13.2 Hz¹⁰ for **5a** vs. 8.9 Hz for **5b**). An addition reaction of dimethyl phosphonate to **5a** in the presence of triethylamine (TEA)¹¹ gave an inseparable mixture (86:14) of the α -D-mannofuranoside (**6a**) and β -L-gulofuranoside (**6b**) in 77% yield.

Catalytic hydrogenolysis of **6a,b** over platinum oxide converted them into the 6-amino derivatives (**7**). Diazotization of **7** and then hydrolysis provided α -D-mannofuranoside (**8a**) (34% yield from **6a,b**), β -L-gulofuranoside (**8b**) (4.9%), their 6-*O*-acetyl compounds (**9a**) (3.1%) and (**9b**) (0.5%), and 5,6-dideoxy-hex-5-enofuranoside (**10**) (4.2%),¹² as well as 3,6-anhydro- α -D-mannofuranoside (**11**) (after acetylation, 13%). The last product was presumably formed as the result of acetonide cleavage under acidic conditions and subsequent intramolecular etherification with 3-OH group at the stage of the deamination. By considering the anti relationship of H-4/H-5 derived from the large $J_{4,5}$ values (9.7-10.3 Hz), the *D-manno* configuration was assignable to **8a** and **9a** by the presence of $^5J_{1,P}$ (1.5 Hz), whereas the *L-gulo* configuration of **8b** and **9b** was based on the presence of $^5J_{2,P}$ (1.0 Hz) and $^4J_{3,P}$ (1.2 Hz).^{11,12}

Table 1. ^1H and ^{31}P Nmr Parameters for Compounds (14a—c) in CDCl_3

Com- pound	Chemical shifts / δ										31p			
	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	POMe	AcO-1,2,3,4,5 ^a					
14a	5.43	5.36	5.33	5.63	2.65	4.49	4.41	3.75	2.18, 2.17, 2.08, 2.08, 2.05		37.6			
14b	5.35	5.42	5.25	5.52	2.74	4.58	4.31	3.85	2.22, 2.16, 2.08, 2.06, 2.01		37.1			
14b	5.42	5.68	5.11	5.56	2.49	4.58	4.33	3.93	2.19, 2.12, 2.07, 2.05, 2.00		35.0			
Coupling constants / 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_{POMe}
14a	6.4	8.8	2.8	21.6	8.6	9.9	8.3	6.6	6.3	15.4	11.7	12.0	13.7	11.1
14b	5.4	10.1	3.0	25.2	9.4	10.8	4.6	5.5	5.2	14.6	11.8	15.6	11.9	10.8
14c	3.6	5.9	2.9	28.9	9.9	11.1	3.9	5.5	5.5	13.3	11.8	15.6	11.6	10.8

^a The assignment of acetyl signals may have to be interchanged.

The major product (8a) was then reduced with sodium dihydrobis(2-methoxyethoxy)aluminum (SDMA) to give the 5-phosphino derivative (12) which, by the action of hydrochloric acid and then peroxide oxidation, afforded 5-deoxy-5-hydroxyphosphinyl-D-mannopyranoses (13). The separation and structural assignment of compounds (13) were made by converting them into the 5-methoxyphosphinyl pentaacetates (14): after chromatographic purification, the 5-deoxy-5-[(*R*)-methoxyphosphinyl]- α -D-mannopyranose (14a) (6.1% from 8a), the 5-[(*S*)-methoxyphosphinyl]- α -isomer (14b) (2.4%), and its β -isomer (14c) (3.6%) were obtained.

The structural assignments of 14a–c are made by the analysis of the ^1H nmr spectra (see Table 1). The $^4\text{C}_1$ conformation of 14b,c is derived from the large $J_{2,P}$ (25–29 Hz) and the small $J_{4,P}$ values (4–5 Hz).^{4,10,12} Compound (14a) has smaller $J_{2,P}$ (21.6 Hz) and larger $J_{4,P}$ values (8.3 Hz) than those of 14b,c, indicating to exist

as an equilibrium mixture (ca. 4:1) of 4C_1 and 1C_4 conformers. As H-3 and H-5 signals of **14a,b** appear at downfield compared with those of **14c**, the orientation of AcO-1 group of **14a,b** are assigned to be axial and that of **14c** is equatorial; the large $J_{1,P}$ value of **14a,b** and the small value of **14c** support these orientation.^{4,12} A slight downfield shift of H-4 signal of **14a** compared with those of **14b,c** indicates the axial P=O orientation for **14a** and the equatorial P=O for **14b,c**. Improvement of the yields of each step in the present scheme and applications of these findings in synthesizing other P-in-the-ring sugar analogous are in progress.

EXPERIMENTAL SECTION

All reaction were monitored by tlc (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(A) 1:9 AcOEt-hexane; (B) AcOEt; (C) 5:3:1 2-propanol-AcOEt-H₂O]. Column chromatography was performed by Wako C-200 silica gel. Optical rotations were measured in CHCl₃ solution with a Nihon-Bunko DIP-370 polarimeter at 21 °C. The nmr spectra were measured in CDCl₃ with Varian VXR-500 (500 MHz for 1H , 126 MHz for ${}^{13}C$) and VXR-200 (81 MHz for ${}^{31}P$) spectrometers at 22 °C. Chemical shift are reported as δ values relative to tetramethylsilane (internal standard for 1H and ${}^{13}C$) and 85% phosphoric acid (external standard for ${}^{31}P$). The mass spectra were taken on an A.E.I. MS 50 ultra-high resolution instrument and are given in terms of m/z (relative intensity) compared with the base peak.

*Methyl (E)-5,6-Dideoxy-2,3-O-isopropylidene-6-nitro- α -D-lyxo-hex-5-enofuranoside (5a)*¹⁰ and Its (Z)-Isomer (**5b**). Following the reported procedures,^{10,11} methyl 2,3-O-isopropylidene- α -D-mannofuranoside (**4**) was converted into **5a** and **5b** in three steps.

5a: Colorless needles (61% yield from **4**); R_f = 0.14 (A); physical data, see refs. 10 and 11.

5b: Colorless syrup (2% yield from **4**); R_f = 0.18 (A); 1H nmr δ = 1.29, 1.44 (3H each, 2s, CMe₂), 3.34 (3H, s, MeO-1), 4.62 (1H, d, $J_{2,3}$ = 5.8, Hz, H-2), 4.97 (1H, s, H-1), 5.13 (1H, dd, $J_{2,3}$ = 5.8, $J_{3,4}$ = 3.9 Hz, H-3), 5.36 (1H, ddd, $J_{4,5}$ = 6.2, $J_{3,4}$ = 3.9, $J_{4,6}$ = 1.8 Hz, H-4), 6.30 (1H, dd, $J_{5,6}$ = 8.9, $J_{4,5}$ = 6.2 Hz, H-5), 7.00 (1H, dd, $J_{5,6}$ = 8.9, $J_{4,6}$ = 1.8 Hz, H-6); FAB ms m/z 246 (M+1; 49), 230 (17), 215 (14), 199 (15), 185 (79), 93 (100). Found: m/z 246.2413. Calcd for C₁₀H₁₆NO₆: M+1, 246.2400.

Methyl 5,6-Dideoxy-5-dimethoxyphosphinyl-2,3-O-isopropylidene-6-nitro- α -D-manno- and β -L-Gulofuranoside (6a,b).¹¹ The same procedures described in ref. 11 were employed. Thus, **5a** gave **6a** and **6b** as an inseparable mixture (86:14): 77% yield [lit.,¹¹ 67% yield (87:13)]; ${}^{13}C$ nmr for **6a** δ = 24.87, 25.70 [C(CH₃)₂], 34.11 (${}^1J_{5,P}$ = 140.7 Hz, C-5), 53.03 (${}^2J_{C,P}$ = 6.7 Hz, MeOP), 53.32 (${}^2J_{C,P}$ = 6.5 Hz, MeOP), 54.75 (CH₃O-1), 71.82 (C-6), 75.96 (${}^2J_{4,P}$ = 2.8 Hz, C-4), 80.13 (${}^3J_{3,P}$ = 3.9 Hz, C-3), 85.03 (C-2), 106.66 (C-1), 112.85

(CMe₂), for **6b** δ = 24.39, 25.79 [C(CH₃)₂], 36.08 (¹J_{5,P} = 144.7 Hz, C-5), 52.99 (²J_{C,P} = 7.0 Hz, MeOP), 53.46 (²J_{C,P} = 6.5 Hz, MeOP), 54.83 (CH₃O-1), 71.45 (²J_{6,P} = 3.8 Hz, C-6), 75.57 (C-4), 79.77 (³J_{3,P} = 5.3 Hz, C-3), 84.87 (C-2), 106.73 (C-1), 112.82 (CMe₂); other physical data, see Ref. 11.

Methyl 5-Deoxy-5-dimethoxyphosphinyl-2,3-O-isopropylidene- α -D-mannofuranoside (8a) and β -L-Gulofuranoside (8b), Their 6-O-Acetyl Derivatives (9a,b), Methyl 5,6-Dideoxy-5-dimethoxyphosphinyl-2,3-O-isopropylidene- α -D-lyxo-hex-5-enofuranoside (10), and Methyl 2-O-Acetyl-3,6-O-anhydro-5-dimethoxyphosphinyl- α -D-mannofuranoside (11). Compounds (**6a,b**) (850 mg, 2.48 mmol) dissolved in a mixture of methanol (5 ml) and 2 M hydrochloric acid (1.24 ml, 2.48 mmol) were hydrogenolyzed in the presence of platinum oxide (170 mg, 0.75 mmol) at 20 °C under an atmospheric pressure of H₂. After 30 h, the catalyst was filtered off, and the filtrate was evaporated in vacuo to give 6-aminohexofuranoside hydrochloride (**7**): R_f = 0.48 (C). To a stirred solution of **7** in water (10 ml) at 0 °C were added acetic acid (0.53 ml, 9.3 mmol) and then sodium nitrite (855 mg, 12.4 mmol). After 2 h, the mixture was extracted with CHCl₃. The combined organic layers were washed with saturated aq. NaHCO₃ and water, dried (Na₂SO₄), and evaporated in vacuo. The residue was separated by column chromatography, giving six fractions A–F.

Fraction A [R_f = 0.50 (B)] gave **10**¹² as a colorless syrup: 32 mg (4.2% from **6**).

Fraction B [R_f = 0.35 (B)] gave **9a** as a colorless syrup: 28 mg (3.1% from **6**); ¹H nmr δ = 1.32, 1.44 (3H each, 2s, CMe₂), 2.06 (3H, s, AcO-6), 2.82 (1H, dddd, $J_{5,P}$ = 19.7, $J_{4,5}$ = 10.3, $J_{5,6}$ = 5.2, $J_{5,6'}$ = 3.7 Hz, H-5), 3.27 (1H, s, MeO-1), 3.77 [6H, d, J_{POMe} = 10.9 Hz, P(OMe)₂], 4.19 (1H, ddd, $J_{4,5}$ = 10.3, $J_{4,P}$ = 6.3, $J_{3,4}$ = 3.2 Hz, H-4), 4.52 (1H, d, $J_{2,3}$ = 5.7 Hz, H-2), 4.54–4.57 (2H, m, H-6,6'), 4.77 (1H, dd, $J_{2,3}$ = 5.7, $J_{3,4}$ = 3.2 Hz, H-3), 4.82 (1H, d, $J_{1,P}$ = 1.5 Hz, H-1); ³¹P nmr δ = 27.7.

Fraction C [R_f = 0.29 (B)] gave **9b** as a colorless syrup: 4.5 mg (0.5% from **6**); ¹H nmr δ = 1.30, 1.43 (3H each, 2s, CMe₂), 2.07 (3H, s, AcO-6), 2.75 (1H, dddd, $J_{5,P}$ = 19.4, $J_{4,5}$ = 10.2, $J_{5,6'}$ = 5.1, $J_{5,6}$ = 4.0 Hz, H-5), 3.35 (3H, s, MeO-1), 3.77, 3.81 [3H each, 2d, J_{POMe} = 10.9 Hz, P(OMe)₂], 4.23 (1H, ddd, $J_{4,5}$ = 10.2, $J_{4,P}$ = 6.6, $J_{3,4}$ = 3.3 Hz, H-4), 4.32 (1H, ddd, $J_{6,6'}$ = 11.7, $J_{6,P}$ = 9.9, $J_{5,6'}$ = 5.1 Hz, H-6'), 4.55 (1H, dd, $J_{2,3}$ = 5.6, $J_{2,P}$ = 1.0 Hz, H-2), 4.60 (1H, ddd, $J_{6,P}$ = 24.4, $J_{6,6'}$ = 11.7, $J_{5,6}$ = 4.0 Hz, H-6), 4.72 (1H, ddd, $J_{2,3}$ = 5.6, $J_{3,4}$ = 3.3, $J_{3,P}$ = 1.2 Hz, H-3), 4.91 (1H, s, H-1); ³¹P nmr δ = 28.3.

Fraction D [R_f = 0.18 (B)] gave **8a** as a colorless syrup: 278 mg (34% from **6**); [α]_D +44 ° (c 1.24); ¹H nmr δ = 1.32, 1.45 (3H each, 2s, CMe₂), 2.50 (1H, br s, HO-6), 2.74 (1H, ddt, $J_{5,P}$ = 20.0, $J_{4,5}$ = 9.7, $J_{5,6}$ = 5.7, $J_{5,6'}$ = 5.0 Hz, H-5), 3.32 (3H, s, MeO-1), 3.78, 3.785 [3H each, 2d, J_{POMe} = 10.9, 10.8 Hz, P(OMe)₂], 4.01 (1H, ddd, $J_{6,P}$ = 17.4, $J_{6,6'}$ = 11.7, $J_{5,6'}$ = 5.0 Hz, H-6'), 4.05 (1H, ddd, $J_{6,P}$ = 14.7, $J_{6,6'}$ = 11.7, $J_{5,6}$ = 5.7 Hz,

H-6), 4.21 (1H, ddd, $J_{4,5} = 9.7$, $J_{4,P} = 7.1$, $J_{3,4} = 3.3$ Hz, H-4), 4.55 (1H, d, $J_{2,3} = 5.8$ Hz, H-2), 4.74 (1H, dd, $J_{2,3} = 5.8$, $J_{3,4} = 3.3$ Hz, H-3), 4.87 (1H, d, $^5J_{1,P} = 1.6$ Hz, H-1); ^{31}P nmr $\delta = 29.1$; ms m/z 327 ($M+1$; 2.4), 311 (33), 295 (15), 277 (4.8), 251 (7.9), 237 (14), 221 (17), 208 (20), 183 (92), 153 (100). Found: m/z 327.1204. Calcd for $\text{C}_{12}\text{H}_{24}\text{O}_8\text{P}$: $M+1$, 327.1208.

Fraction E [$R_f = 0.12$ (B)] gave **8b** as a colorless syrup: 40 mg (4.9% from **6**); $[\alpha]_D +62^\circ$ (c 1.10); ^1H nmr $\delta =$ 1.31, 1.44 (3H each, 2s, CMe_2), 2.45 (1H, br s, HO-6), 2.58 (1H, dddd, $J_{5,P} = 17.6$, $J_{4,5} = 10.0$, $J_{5,6'} = 5.0$, $J_{5,6} = 3.6$ Hz, H-5), 3.325 (3H, s, MeO-1), 3.80, 3.82 [3H each, 2d, $J_{\text{POMe}} = 10.7$, 10.8 Hz, P(OMe)_2], 3.97 (1H, ddd, $J_{6',P} = 25.7$, $J_{6,6'} = 11.9$, $J_{5,6'} = 5.0$ Hz, H-6'), 4.01 (1H, ddd, $J_{6,P} = 17.3$, $J_{6,6'} = 11.9$, $J_{5,6} = 3.6$ Hz, H-6), 4.26 (1H, ddd, $J_{4,5} = 10.0$, $J_{4,P} = 7.3$, $J_{3,4} = 3.3$ Hz, H-4), 4.55 (1H, dd, $J_{2,3} = 5.9$, $^5J_{2,P} = 1.0$ Hz, H-2), 4.78 (1H, ddd, $J_{2,3} = 5.9$, $J_{3,4} = 3.3$, $^4J_{3,P} = 1.2$ Hz, H-3), 4.90 (1H, s, H-1); ^{31}P nmr $\delta = 31.6$; ms m/z 327 ($M+1$; 0.5), 311 (21), 295 (11), 251 (4.5), 237 (11), 221 (15), 183 (81), 153 (100). Found: m/z 327.1201. Calcd for $\text{C}_{12}\text{H}_{24}\text{O}_8\text{P}$: $M+1$, 327.1208.

Fraction F [$R_f = 0.08\text{--}0.04$ (B)] gave a colorless syrup (106 mg). This was treated with 1:2 acetic anhydride-pyridine. After purification by column chromatography, 2-*O*-acetyl-3,6-anhydro compound **11** was obtained as a colorless syrup: 99 mg (13% from **6**); $R_f = 0.24$ (B); $[\alpha]_D +146^\circ$ (c 0.56); ^1H nmr $\delta =$ 2.12 (3H, s, AcO-2), 2.69 (1H, dddd, $J_{5,P} = 17.3$, $J_{5,6'} = 6.9$, $J_{5,6} = 3.1$, $J_{4,5} = 1.3$ Hz, H-5), 3.35 (3H, s, MeO-1), 3.78, 3.785 [3H each, 2d, $J_{\text{POMe}} = 10.8$ Hz, P(OMe)_2], 4.05 (1H, ddd, $J_{6',P} = 27.8$, $J_{6,6'} = 9.2$, $J_{5,6'} = 6.9$ Hz, H-6'), 4.26 (1H, ddd, $J_{6,P} = 15.8$, $J_{6,6'} = 9.2$, $J_{5,6} = 3.1$ Hz, H-6), 4.82 (1H, ddd, $J_{2,3} = 5.7$, $J_{3,4} = 5.1$, $^4J_{3,P} = 1.0$ Hz, H-3), 4.91 (1H, ddd, $J_{4,P} = 9.8$, $J_{3,4} = 5.1$, $J_{4,5} = 1.3$ Hz, H-4), 4.99 (1H, dd, $J_{2,3} = 5.7$, $J_{2,P} = 1.2$ Hz, H-2), 5.00 (1H, s, H-1); ^{31}P nmr $\delta = 28.0$; FAB ms m/z 311 ($M+1$; 39), 279 (100), 237 (18), 195 (21), 93 (30). Found: m/z 311.2475. Calcd for $\text{C}_{11}\text{H}_{20}\text{O}_8\text{P}$: $M+1$, 311.2486.

1,2,3,4,6-Penta-O-acetyl-5-deoxy-5-methoxyphosphinyl-D-mannopyranoses (14a-c). To a solution of **8a** (140 mg, 0.429 mmol) in dry benzene (1.5 ml) was added a solution of SDMA (3.4 M in toluene, 0.45 ml, 3.5 equiv.) in dry benzene (1 ml), in small portions at 5°C under argon. The mixture was stirred at 5°C for 1 h, and then water (0.5 ml) was added. The mixture was centrifuged and the precipitate was extracted with several portions of benzene. The combined organic layers were evaporated in vacuo, giving methyl 5-deoxy-2,3-*O*-isopropylidene-5-phosphino- α -D-mannofuranoside (**12**) as a colorless syrup: $R_f = 0.72$ (B). This syrup was immediately treated with 1:1 2-propanol-0.5 M hydrochloric acid (3 ml) at 100°C for 1 h under argon. The reactants were neutralized at 5°C with Amberlite IRA-45. The resin was filtered off and washed with aqueous ethanol. The filtrate was evaporated in vacuo. The residue was dissolved in water (3 ml), treated with 30% hydrogen peroxide (0.5 ml) at

20 °C for 10 h, and then concentrated under reduced pressure to give crude 5-deoxy-5-hydroxyphosphinyl-D-mannopyranose (**13**) as a colorless syrup: $R_f = 0.23$ (C). This was acetylated with acetic anhydride (0.5 ml) and dry pyridine (1 ml) at 20 °C for 18 h. The mixture was concentrated in vacuo. The residue dissolved in ethanol was passed through a column of Amberlite IR-120B (30 ml). The eluant was evaporated in vacuo and the residue dissolved in dry CH_2Cl_2 (1 ml) was methylated with ethereal diazomethane at 0 °C. The solvent was evaporated in vacuo and the residue was separated by column chromatography with a gradient eluent of 3:1 AcOEt-hexane $\rightarrow$ AcOEt, into two fractions.

The faster-eluting fraction [$R_f = 0.25$ (B)] gave the 5-[(R)-methoxyphosphinyl]- α -D-mannopyranose (**14a**) (11.9 mg, 6.1% from **8a**) as a colorless syrup: ^1H and ^{31}P nmr, see Table 1; ms m/z 453 (M+1; 2.7), 410 (8.8), 393 (4.9), 368 (10), 351 (44), 321 (26), 309 (87), 280 (34), 249 (73), 207 (72), 188 (100), 164 (27). Found: m/z 453.1166. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_{12}\text{P}$: M+1, 453.1162.

The slower-eluting fraction [$R_f = 0.18$ (B)] gave a colorless syrup (11.5 mg) which consisted of 5-[(S)-P]- α -D-mannopyranose (**14b**) (2.4% from **8a**) and its β -anomer (**14c**) (3.6%), the relative amounts being determined by the integral ratio of ^{31}P nmr signals; ^1H and ^{31}P nmr, see Table 1; ms m/z 453 (M+1; 4.8), 410 (2.4), 393 (5.8), 351 (39), 321 (28), 309 (82), 230 (34), 207 (88), 188 (100), 164 (42). Found: m/z 453.1166. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_{12}\text{P}$: M+1, 453.1162.

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