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SYNTHESIS OF 5-DEOXY-5-PHOSPHINYL-D-GALACTOPYRANOSE DERIVATIVES: NEW PHOSPHA-SUGAR ANALOGS OF D-GALACTOSE

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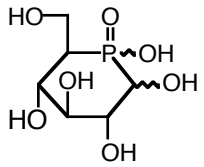
Abstract – The addition reaction of dimethyl phosphonate to 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-L-*arabino*-hexofuranos-5-ulose (**11**), followed by deoxygena tion of 5-hydroxyl group, provided 5-deoxy-5-dimethoxyphosphinyl-D-galacto-furanose derivative (**13a**). Reduction of **13a** with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by the action of hydrochloric acid and then hydrogen peroxide, afforded the first D-galactopyranose analog (**15**) having a phosphinyl group in the hemiacetal ring. This was converted into the 1,2,4-tri-*O*-acetyl-5-methoxyphosphinyl derivatives (**16**), whose structure and confor-mation were established by ^{1}H-NMR spectroscopy.

We have prepared various sugar analogs having a phosphorus atom in the hemiacetal ring (phospha-sugar) because of a considerable interest in their chemical and biochemical properties.[1] As for phospha-sugars of the hexopyranose type, analogs of D-glucose (**1**),[2] D-mannose (**2**),[3] and L-fucose (**3**)[4] have been synthesized. Although all of these sugar analogs contain a hydroxyphosphinyl group in the ring of the important naturally occurring hexoses, no example of phospha-sugar analogs having a D-galactose skeleton have been prepared so far. In the meantime, D-galactose-type azasugar (**4**)[5] and the thiasugar (**5**)[6] were prepared and they have been proven to inhibit D-galactosidase.



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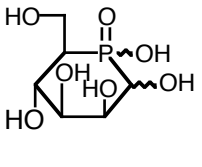

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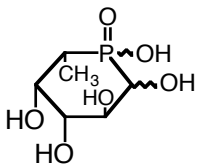

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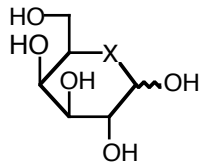
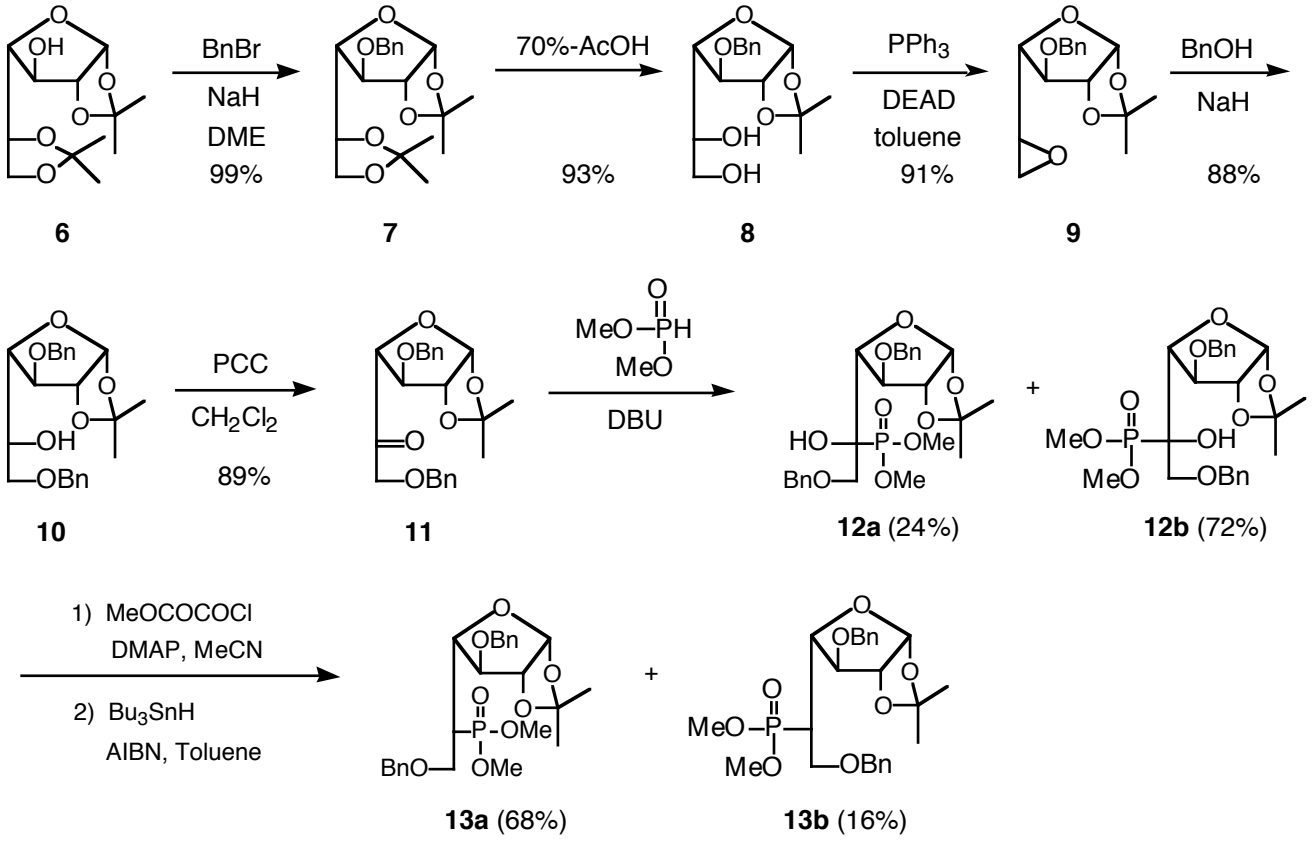


4 X = NH
5 X = S

In the synthesis of **1** and **2**, the stereoselective introduction of a phosphinyl group into the C–5 position was accomplished by the addition of dimethyl phosphonate to the 5,6-dideoxy-6-nitrohex-5-enofuranose

derivatives.[2,3] However, this procedure turned out to unsuitable for the synthesis of D-galactose-type phospha-sugar because of the preponderant production of the undesirable epimer.[7] We describe herein a convenient synthesis of 3,6-di-*O*-benzyl-5-deoxy-5-hydroxyphosphinyl-D-galactopyranose (**14**) as a first example of a D-galactose-type phospha-sugar, by using our alternative procedure[8] to introduce a phosphinyl group onto a sugar skeleton, namely, addition of phosphonate to the 5-ulose derivatives and the subsequent deoxygenation.

1,2:5,6-Di-*O*-isopropylidene-α-D-galactofuranose (**6**) (available from D-glucose in 4 steps)[9–12] served as the starting material for preparation of the key intermediate, 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-L-*arabino*-hexofuranos-5-ulose (**11**), as illustrated in Scheme 1. The 5,6-anhydro-3-*O*-benzyl derivative (**9**) was prepared by 3-*O*-benzylation of **6**, selective acid-hydrolysis of **7**, and epoxidation of the diol (**8**) under Mitsunobu's conditions. The reported procedures[10,11] for these steps were slightly modified to give **7–9** in higher yields. The treatment of **9** with benzyl alcohol and sodium hydride in DME afforded the 6-*O*-benzyl derivative (**10**), which was oxidized with pyridinium chlorochromate (PCC) to provide **11**.

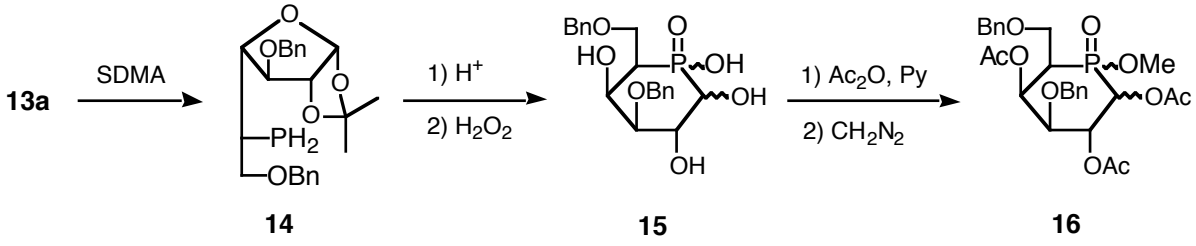


Scheme 1

The addition reaction of dimethyl phosphonate to **11** in the presence of DBU gave the (5*R*)-5-dimethoxyphoshinyl-L-*arabino*-hexofuranose derivative (**12a**) (24%) and its (5*S*)-epimer (**12b**) (72%). The deoxygenation of 5-hydroxyl group of **12a** and **12b** was achieved by application of the Dolan and MacMilan's procedure.[13] Namely, esterification of the (5*S*)-epimer (**12b**) with methyl oxalyl chloride in

the presence of 4-dimethylaminopyridine (DMAP), followed by reduction with tributyltin hydride, mainly afforded the 5-deoxy-5-phosphinyl-D-galactofuranose derivative (**13a**) (68%) together with the L-altrofuranose isomer (**13b**) (16%). The L-*altro* configuration for **13b** and the (5*S*)-cofiguration for **12b** were assigned on the basis of the presence of the characteristic long-range coupling ($^5J_{1,P}$ = 1.0–1.5 Hz).[4,7,8] When the minor (5*R*)-epimer (**12a**) was subjected to the same reduction, **13a** and **13b** were obtained notably in almost the same ratio and yields as those from **12b**. These results therefore indicated that an epimerization took place at C–5 *via* a radical intermediate during the reduction of the methyl oxalyl esters. Detailed mechanism concerning stereoselectivity of this reduction is under investigation.[14]

The major product (**13a**) was then reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) to give the 5-phosphino derivative (**14**), which was immediately treated with hydrochloric acid at 90 °C and then oxidized with hydrogen peroxide to afford 3,6-di-*O*-benzyl-5-deoxy-5-hydroxyphosphinyl-α,β-D-galactopyranoses (**15**) (Scheme 2). These products were characterized after having been converted into the corresponding 5-methoxyphosphinyl-1,2,4-tri-*O*-acetates (**16**) by treatment with acetic anhydride-pyridine and then ethereal diazomethane. By purification on a silica gel column, the 5-deoxy-5-[(*R*)-methoxyphosphinyl]-α-D-galactopyranose (**16a**) (10.5% overall yield from **13a**), its β-anomer (**16b**) (9.1%), 5-[(*S*)-methoxyphosphinyl]-α-D-galactopyranose (**16c**) (8.1%), and its β-anomer (**16d**) (10.5%) were obtained.



14 **15** **16**

Scheme 2

The precise structures of **16a–d** were established by the analysis of their 500-MHz ^{1}H-NMR spectra; for all the assignments of the signals, see Table 1. The $^4C_1$ conformation of **16a-d** are derived from the large values of $J_{4,P}$ (34–36 Hz) and $J_{2,3}$ (*ca.* 10 Hz).[2-4] As for anomeric orientation of C-1, the large $J_{1,2}$ values (11 Hz) of **16b,d** indicate the axial H-1 orientation, whereas the small $J_{1,2}$ values (3 Hz) of **16a,c** show the equatorial H-1 configuration.[15] With regard to the orientation of the ring P=O group, a down-field shift (0.2–0.3 ppm) of H-2 for **16a,b** compared with those of **16c,d** indicates the axial P=O orientation for the former and the equatorial P=O orientation for the latter.

Present work thus demonstrates a convenient way for preparation of 5-deoxy-5-phosphinyl-D-galactopyranose from appropriate intermediates. Extension of this work including applications of these findings in synthesizing other phospha-sugar analogs, as well as biological evaluation of D-galactopyranose phospha-sugar, is anticipated to be highly of interest.

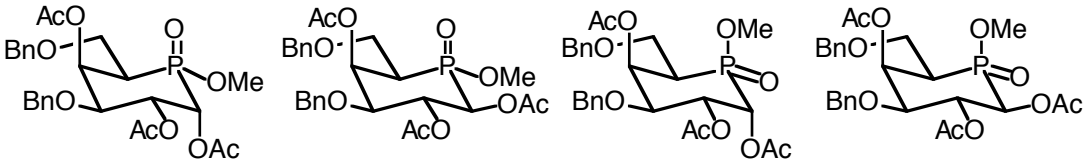


Table 1. ^{1}H and ^{31}P NMR Parameters for Compounds (**16a–d**) in $CDCl_3$

Compound	Chemical shifts / δ										
	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	POMe	AcO-1,2,4[a]	CH_2O-3,6[b,c]	^{31}P
16a	5.61	5.69	3.80	5.98	2.52	3.78	3.62	3.65	2.13, 2.11, 1.98	4.75, 4.46; 4.52, 4.48	39.6
16b	5.24	5.69	3.49	5.90	2.26	3.84	3.65	3.66	2.16, 2.13, 1.95	4.72, 4.41; 4.53, 4.49	39.7
16c	5.68	5.38	3.76	5.99	2.67	3.89	3.59	3.78	2.12, 2.03, 1.98	4.735, 4.46; 4.49, 4.49	39.2
16d	5.40	5.50	3.49	5.96	2.37	3.91	3.54	3.85	2.10, 2.06, 1.94	4.73, 4.39; 4.495, 4.48	39.2

	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}
16a	2.8	14.6	10.4	0.5	2.9	2.8	34.5	4.9	9.2	15.9	9.8	5.8	9.5	11.0
16b	10.7	5.5	9.8	2.7	2.5	2.7	35.5	5.8	8.5	13.8	9.8	6.1	10.7	11.0
16c	3.0	15.6	10.4	0.5	3.0	2.9	33.9	3.5	9.2	16.6	9.5	9.5	4.0	11.0
16d	10.9	3.7	9.9	1.8	2.9	2.9	36.0	3.6	9.5	14.5	9.5	7.3	4.0	10.7

[a] The assignment of acetyl signals may be interchanged. [b] ^{2}J = 11.6–11.9 Hz: the assignment of CH_2O-3 or -6 may be interchanged. [c] Ph: δ = 7.23–7.38 (10H, m).

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1:3 and (*B*) 1:1 AcOEt-hexane, (*C*) AcOEt]. Column chromatography was performed by Katayama Silica Gel 60K070. Components were detected by exposing the plates to UV light and/or spraying them with 20% sulfuric acid–ethanol (with subsequent heating). Optical rotations were measured with a JASCO P-1020 polarimeter at 26 °C in $CHCl_3$. The NMR spectra were measured in $CDCl_3$ with Varian VXR-500 (500 MHz for ^{1}H) and VXR-200 (81 MHz for ^{31}P) spectrometers at 22 °C. Chemical shifts are reported as δ values relative to tetramethylsilane (internal standard for ^{1}H) and 85% phosphoric acid (external standard for ^{31}P). The MS spectra were taken on a VG-70SE instrument and are given in terms of *m/z* (relative intensity) compared with the base peak.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (7).[10]

The following modification of the literature procedures[10] was made. To a solution of **6** (721 mg, 2.77

mmol) in dry DME (5 mL) was added, with stirring, sodium hydride (60% in mineral oil, 185 mg, 4.63 mmol) and then benzyl bromide (0.700 mL, 5.90 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 h. After addition of methanol (2 mL), the mixture was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evapolated *in vacuo*. The residue was purified by column chromatography with 1:5 AcOEt-hexane as an eluant to give **7** [960 mg, 99%, lit.,[10] 73% (by using benzyl chloride and DMF)] as a colorless syrup: R_f = 0.49 (*A*); $[\alpha]_D$ –47.1 ° (*c* 1.01); ^{1}H NMR δ = 1.36, 1.38, 1.42, 1.55 (3H each, 4s, Me_2C), 3.72 (1H, dd, $J_{6,6'}$ = 8.3, $J_{5,6'}$ = 7.1 Hz, H'-6), 3.88 (1H, dd, $J_{3,4}$ = 5.0, $J_{2,3}$ = 1.3 Hz, H-3), 3.91 (1H, dd, $J_{5,6}$ = 6.5 Hz, H-6), 3.92 (1H, dd, $J_{4,5}$ = 7.0 Hz, H-4), 4.26 (1H, q, H-5), 4.53, 4.68 (1H each, 2 d, ^2J = 11.7 Hz, CH_2O-3), 4.65 (1H, dd, $J_{1,2}$ = 4.0 Hz, H-2), 5.86 (1H, d, H-1), 7.32–7.38 (5H, m, Ph).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-galactofuranose (8).[10,11]

Compound (**7**) (700 mg, 2.00 mmol) was dissolved in 70% aqueous acetic acid (10 mL) and the solution was stirred at 25 °C for 5 h. The mixture was concentrated *in vacuo* and the residue was coevaporated with xylene twice. The residue was purified by recrystalization from AcOEt-hexane and the mother liquid was chromatographed with 1:1 AcOEt-hexane to give **8** (total 576 mg, 93%): Colorless needles [mp 104–105 °C (from 1:1 AcOEt-hexane)], $[\alpha]_D$ –28.4 ° (*c* 1.40) [lit.,[10] mp 104–104.5 °C, $[\alpha]_D$ –32.6° (*c* 1.10), 80% yield, lit.,[11] mp 102 °C, $[\alpha]_D$ –28.6 ° (*c* 1.0), 75% yield (by using H_2SO_4 as an acid)]; R_f = 0.32 (*B*); ^{1}H-NMR δ = 1.35, 1.53 (3H each, 2s, CMe_2), 2.27 (2H, br s, 2H, HO-5,6), 3.59 (1H, dd, $J_{6,6'}$ = 11.7, $J_{5,6'}$ = 4.8 Hz, H'-6), 3.69 (1H, dd, $J_{5,6}$ = 3.9 Hz, H-6), 3.80 (1H, dt, $J_{4,5}$ = 6.7 Hz, H-5), 4.01 (1H, dd, $J_{3,4}$ = 3.5, $J_{2,3}$ = 0.8 Hz, H-3), 4.13 (1H, dd, H-4), 4.57, 4.65 (1H each, 2d, ^2J = 11.7 Hz, CH_2O-3), 4.69 (1H, d, $J_{1,2}$ = 4.1 Hz, H-2), 5.92 (1H, d, H-1), 7.31–7.38 (5H, m, Ph).

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-galactofuranose (9).[11]

To a solution of **8** (672 mg, 2.17 mmol) and triphenylphosphine (681 mg, 2.60 mmol) in dry toluene (15 mL) was added DEAD (0.400 mL, 2.57 mmol). The mixture was refluxed for 6 h and evapolated *in vacuo*. The residue was purified by column chromatography with 1:1 AcOEt-hexane as an eluant to give **9** (575 mg, 91%) as colorless prisms: mp 62-64 °C (from 1:1 AcOEt-hexane), $[\alpha]_D$ –27.5 ° (*c* 1.02) [lit.,[11] mp 55 °C; $[\alpha]_D$ –29.4 ° (*c* 1.4), 80% yield]; R_f = 0.34 (*A*); ^{1}H-NMR δ = 1.37, 1.55 (3H each, 2s, CMe_2), 2.65 (1H, dd, $J_{6,6'}$ = 5.0, $J_{5,6'}$ = 2.7 Hz, H'-6), 2.79 (1H, t, $J_{5,6}$ = 4.1 Hz, H-6), 3.21 (1H, ddd, $J_{4,5}$ = 6.2 Hz, H-5), 3.81 (1H, dd, $J_{3,4}$ = 3.7 Hz, H-4), 4.01 (1H, dd, $J_{2,3}$ = 1.0 Hz, H-3), 4.55, 4.66 (1H each, 2d, ^2J = 11.8 Hz, CH_2O-3), 4.66 (1H, dd, $J_{1,2}$ = 4.0 Hz, H-2), 5.90 (1H, d, H-1), 7.31-7.39 (5H, m, Ph).

3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-galactofuranose (10).

To a solution of sodium hydride (60% in mineral oil, 100 mg, 2.50 mmol) in benzyl alcohol (2.0 mL, 19.3 mmol) was added a solution of **9** (388 mg, 1.25 mmol) in benzyl alcohol (2.0 mL) at 0 °C. The mixture was stirred at 50 °C for 12 h, diluted with saturated NH_4Cl (20 mL), and extracted with $CHCl_3$ three times. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography with 1:4 AcOEt-hexane as an eluant to give **10** (442 mg,

88%) as colorless needles: mp 64-65 °C (from cyclohexane); $[\alpha]_D$ –15.2 ° (*c* 1.00); R_f = 0.17 (*A*); ^{1}H-NMR δ = 1.34, 1.53 (3H each, 2s, CMe_2), 3.51 (1H, dd, $J_{6,6'}$ = 9.9, $J_{5,6'}$ = 5.3 Hz, H'-6), 3.55 (1H, dd, $J_{5,6}$ = 5.8 Hz, H-6), 3.94 (1H, q, $J_{4,5}$ = 6.4 Hz, H-5), 4.08 (1H, dd, $J_{3,4}$ = 3.4, $J_{2,3}$ = 0.8 Hz, H-3), 4.15 (1H, dd, H-4), 4.40 (1H, br s, HO-5), 4.50, 4.58 (2H each, 2d, ^2J = 11.7 Hz, CH_2O-3), 4.54 (2H, s, CH_2O-6), 4.67 (1H, dd, $J_{1,2}$ = 4.1 Hz, H-2), 5.91 (1H, d, H-1), 7.27–7.35 (10H, m, Ph). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.10; H, 7.01.

3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-L-*arabino*-hexofuranos-5-ulose (11).

To a suspension of PCC (560 mg, 2.60 mmol) and finely powdered molecular sieves 3A (1.1 g) in dry CH_2Cl_2 (10 mL) was added a solution of **10** (410 mg, 1.02 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred at 20 °C for 12 h. After addition of 2-propanol (3 mL), the mixture was diluted with ether. The precipitates were filtered off through celite and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography with 1:3 AcOEt-hexane as an eluant to give **11** (360 mg, 89%) as a colorless syrup: $[\alpha]_D$ +3.42 ° (*c* 1.02); R_f = 0.35 (*A*); ^{1}H-NMR δ = 1.26, 1.32 (3H each, 2s, CMe_2), 4.38, 4.70 (1H each, 2d, $J_{6,6'}$ = 18.3 Hz, H_2-6), 4.53 (1H, br s, $J_{3,4}$ = 0.5, $J_{2,3}$ = 0 Hz, H-3), 4.58, 4.63 (1H each, 2d, ^2J = 11.6 Hz, CH_2O-3), 4.59 (2H, s, CH_2O-6), 4.62 (1H, d, $J_{1,2}$ = 4.0 Hz, H-2), 4.62 (1H, br s, H-4), 5.98 (1H, d, H-1), 7.28-7.37 (10H, m, Ph). *Anal.* Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.09; H, 6.70.

(5*R*)- and (5*S*)-3,6-Di-*O*-benzyl-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-β-L-*arabino*-hexofuranoses (12a,b).

DBU (0.495 mL, 3.31 mmol) was dropwise added to a solution of **11** (1.10 g, 2.76 mmol) in dimethyl phosphonate (11.4 mL, 124 mmol) at 0 °C and the solution was stirred at this temperature for 30 min under argon. The mixture was treated with saturated NH_4Cl at rt for 1 h and extracted with $CHCl_3$ three times. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was separated by column chromatography with a gradient eluant of 1:1 AcOEt–hexane → AcOEt to give **12a** and **12b**.

12a: Colorless prisms (338 mg, 24%); mp 94–95 °C (from 2:1 AcOEt-hexane); $[\alpha]_D$ –15.2 ° (*c* 1.21); R_f = 0.39 (*C*), ^{1}H-NMR δ = 1.34, 1.57 (3H each, 2s, Me_2C), 3.51 (1H, br d, $J_{P,OH}$ = 2.8 Hz, HO-5), 3.58 (1H, dd, $J_{6',P}$ = 21.4, $J_{6,6'}$ = 9.8 Hz, H'-6), 3.775, 3.78 [3H each, 2d, J_{POMe} = 10.7 Hz, $P(OMe)_2$], 3.83 (1H, t, $J_{6,P}$ = 9.8 Hz, H-6), 4.31 (1H, dd, $J_{3,4}$ = 4.3, $J_{2,3}$ = 1.2 Hz, H-3), 4.46, 4.56 (1H each, 2d, ^2J = 11.6 Hz, CH_2O-3), 4.52 (2H, s, CH_2O-6), 4.64 (1H, dd, $J_{1,2}$ = 4.0 Hz, H-2), 4.69 (1H, dd, $J_{4,P}$ = 2.5 Hz, H-4), 5.91 (1H, d, H-1), 7.24–7.34 (10H, m, Ph); ^{31}P-NMR δ = 25.7.

12b: Colorless syrup (1.01 g, 72%); $[\alpha]_D$ –7.56 ° (*c* 1.65); R_f = 0.55 (*C*); ^{1}H-NMR δ = 1.34, 1.53 (3H each, 2s, Me_2C), 3.50 (1H, m, HO-5), 3.76, 3.77 [3H each, 2d, J_{POMe} = 10.7 Hz, $P(OMe)_2$], 3.80 (2H, d, $J_{6,P}$ = 17.1 Hz, H_2-6), 4.60 (2H, s, CH_2O-6), 4.60 (1H, m, H-3), 4.62 (2H, m, H-2,4), 4.625, 4.66 (1H each, 2d, ^2J = 11.3 Hz, CH_2O-3), 5.87 (1H, dd, $J_{1,2}$ = 3.7, $^5J_{1,P}$ = 1.0 Hz, H-1), 7.25–7.37 (10H, m, Ph); ^{31}P- NMR δ = 25.8; FAB MS *m/z* 509 (M+1; 11), 451 (12), 419 (3), 361 (4), 181 (16), 91 (100). Found: *m/z* 509.1959. Calcd for $C_{25}H_{34}O_9P$: M+1, 509.1941.

3,6-Di-*O*-benzyl-5-deoxy-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-α-D-galacto- and β-L-altrofuranose (13a,b).

Methyl oxalyl chloride (1.10 mL, 11.9 mmol) was added to a solution of **12a,b** (1.21 g, 2.38 mmol) and DMAP (1.45 g, 11.9 mmol) in dry acetonitrile (20 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min under argon, poured into water, and extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was coevaporated with dry toluene and dissolved in the same solvent (20 mL). Tributyltin hydride (0.96 mL, 3.56 mmol) and AIBN (59 mg, 0.36 mmol) were added under argon. The mixture was stirred at 80 °C for 6 h and then concentrated *in vacuo*. The residue was separated by column chromatography with a gradient eluant of 1:1 AcOEt–hexane → AcOEt to give **13a** and **13b**.

13a: Colorless needles (798 mg, 68%); mp 68–69 °C (from 2:1 AcOEt-hexane); $[\alpha]_D$ –20.7 ° (*c* 1.51); R_f = 0.45 (*C*); ^{1}H-NMR δ = 1.33, 1.55 (3H each, 2s, Me_2C), 2.61 (1H, dddd, $J_{5,P}$ = 20.4, $J_{4,5}$ = 9.2, $J_{5,6}$ = 5.5, $J_{5,6'}$ = 4.0 Hz, H-5), 3.73, 3.75 [3H each, 2d, J_{POMe} = 11.0 Hz, $P(OMe)_2$], 3.78 (1H, ddd, $J_{6',P}$ = 16.6, $J_{6,6'}$ = 9.2 Hz, H'-6), 3.795 (1H, dd, $J_{6,P}$ = 13.1 Hz, H-6), 4.32 (1H, dd, $J_{3,4}$ = 3.1, $J_{2,3}$ = 1.0 Hz, H-3), 4.45, 4.47 (1H each, 2d, ^2J = 11.9 Hz, CH_2O-3), 4.46 (1H, ddd, $J_{4,P}$ = 11.3 Hz, H-4), 4.51 (2H, s, CH_2O-6), 4.61 (1H, dd, $J_{1,2}$ = 4.0 Hz, H-2), 5.87 (1H, d, H-1), 7.26–7.33 (10H, m, Ph); ^{31}P-NMR δ = 30.5; FAB MS *m/z* 493 (M+1; 10), 435 (12), 345 (6), 237 (9), 185 (16), 91 (100). Found: *m/z* 493.2001. Calcd for $C_{25}H_{34}O_8P$: M+1, 493.1992.

13b: Colorless syrup (188 mg, 16%); $[\alpha]_D$ –6.02 ° (*c* 2.47); R_f = 0.55 (*C*); ^{1}H-NMR δ = 1.30, 1.44 (3H each, 2s, Me_2C), 2.61 (1H, ddt, $J_{5,P}$ = 20.5, $J_{4,5}$ = 10.1, $J_{5,6}$ = 3.7, $J_{5,6'}$ = 3.4 Hz, H-5), 3.64, 3.67 [3H each, 2d, J_{POMe} = 11.0 Hz, $P(OMe)_2$], 3.93 (1H, ddd, $J_{6',P}$ = 11.9, $J_{6,6'}$ = 9.2 Hz, H'-6), 3.99 (1H, ddd, $J_{6,P}$ = 28.7 Hz, H-6), 4.43 (1H, dd, $J_{3,4}$ = 1.8, $J_{2,3}$ = 0.8 Hz, H-3), 4.55, 4.59 (1H each, 2d, ^2J = 11.9 Hz, CH_2O), 4.58 (1H, ddd, $J_{4,P}$ = 3.7 Hz, H-4), 4.59, 4.63 (1H each, 2d, ^2J = 11.9 Hz, CH_2O), 4.64 (1H, dd, $J_{1,2}$ = 4.0 Hz, H-2), 5.94 (1H, dd, $^5J_{1,P}$ = 1.5 Hz, H-1), 7.24–7.37 (10H, m, Ph); ^{31}P-NMR δ = 31.6; FAB MS *m/z* 493 (M+1; 18), 435 (16), 237 (14), 185 (26), 91 (100). Found: *m/z* 493.1981. Calcd for $C_{25}H_{34}O_8P$: M+1, 493.1992.

1,2,4-Tri-*O*-acetyl-3,6-di-*O*-benzyl-5-deoxy-5-methoxyphosphinyl-D-galactopyranose (16a–d).

To a solution of **13a** (208 mg, 0.422 mmol) in dry toluene (2.0 mL) was added, with stirring, a solution of 0.34 M SDMA in toluene (2.5 mL, 0.85 mmol) in small portions during 30 min at 0 °C under argon. The stirring was continued at this temperature for 30 min. Then, water (0.08 mL) was added to decompose excess SDMA and the mixture was centrifuged. The precipitate was extracted with several portions of toluene. The organic layers were combined and evaporated *in vacuo*, giving 3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-5-phosphino-α-D-galactofuranose (**14**) as a colorless syrup.

This syrup was immediately treated with 1:1 2-propanol–0.5 M hydrochloric acid (5.0 mL) at 90 °C for 2 h under argon. After cooling, the reactants were neutralized with Amberlite IRA-93ZU. The resin was filtered off and washed with aqueous ethanol. The filtrate was evaporated *in vacuo*. The residue was dissolved in 2-propanol (2.0 mL), treated with 30% hydrogen peroxide (0.6 mL, 5.9 mmol) at rt for 12 h

and then concentrated *in vacuo* to give crude 3,6-di-*O*-benzyl-5-deoxy-5-hydroxyphosphinyl-α,β-D-galactopyranoses (**15**) as a colorless syrup. This was dissolved in dry pyridine (2.0 mL), and acetic anhydride (1.0 mL, 11 mmol) was added at 0 °C. The mixture was stirred at rt for 16 h, diluted with a small amount of cold water, and concentrated *in vacuo*. The residue was dissolved in ethanol 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 diazomethane in dry CH_2Cl_2 (2.0 mL) at 0 °C. After evaporation of the solvent, the residue was separated by column chromatography with a gradient eluent of 1:1 AcOEt-hexane → AcOEt into three fractions A–C.

Fraction A [R_f = 0.62 (*C*)] gave the 5-[(*R*)-methoxyphosphinyl]-α-D-galactopyranose (**16a**) as colorless needles (24.3 mg, 11% from **13a**): mp 150–151 °C (from 3:1 AcOEt-hexane); $[\alpha]_D$ +4.02 ° (*c* 1.79); ^1H and ^{31}P NMR, see Table 1; FAB MS *m/z* 549 (M+1; 11), 507 (4), 441 (6), 181 (12), 93 (100). Found: *m/z* 549.1885. Calcd for $C_{27}H_{34}O_{10}P$: M+1, 549.1890 *Anal.* Calcd for $C_{27}H_{33}O_{10}P$: C, 59.12; H, 6.06. Found: C, 59.29; H, 6.12.

Fraction B (R_f = 0.53–0.50) gave a colorless syrup (43.2 mg) which consisted of 5-[(*S*)-P]-a-isomer (**16c**) (8.1% from **13a**) and its b-isomer (**16d**) (11%), the ratio being estimated by ^1H NMR: ^1H and ^{31}P NMR, see Table 1.

Fraction C (R_f = 0.43) gave 5-[(*R*)-P]-β-isomer (**16b**) as colorless prisms (21.1 mg, 9.1% from **13a**): mp 145–146 °C (from 3:1 AcOEt-hexane); $[\alpha]_D$ +27.2 ° (*c* 0.82); ^1H and ^{31}P NMR, see Table 1; FAB MS *m/z* 549 (M+1; 12), 507 (6), 459 (6), 369 (8), 181 (18), 93 (100). Found: *m/z* 549.1901. Calcd for $C_{27}H_{34}O_{10}P$: M+1, 549.1890. *Anal.* Calcd for $C_{27}H_{33}O_{10}P$: C, 59.12; H, 6.06. Found: C, 59.03; H, 6.19.

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