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Synthesis and structural analysis of 6-deoxy-6-hydroxyphosphinyl-D-fructopyranose derivatives

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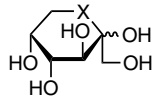
Abstract—3,4-Di-*O*-benzyl-6-deoxy-6-diethoxyphosphinyl-1,2-*O*-isopropylidene-β-D-fructofuranose (**13**) was prepared from the known 1,2-*O*-isopropylidene-6-*O*-tosyl-β-D-fructofuranose in five steps. Reduction of **13** with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by the action of hydrochloric acid and then hydrogen peroxide, afforded the 6-deoxy-6-hydroxyphosphinyl-D-fructopyranose derivative. This was converted into the 1,2,3,4,5-penta-*O*-acetyl-6-deoxy-6-methoxyphosphinyl-D-fructopyranoses, whose structure and conformation were established by ^{1}H NMR spectroscopy.

Keywords: Phospho sugar; 6-Deoxy-6-phosphinyl-D-fructopyranose; Hydroxyphosphinyl group; Acetyl migration; Conformational analysis

Various sugar analogs containing a heteroatom instead of oxygen in the hemiacetal ring have been prepared because of the wide interest in their chemical and biochemical properties.[1,2] Heteroatom-in-the-ring sugar analogs of D-fructopyranose, one of the most abundant ketoses in nature, have also attracted considerable interest, along with those of aldoses such as D-glucose and D-mannose. Meanwhile, thio sugar (**1**)[3] and imino sugar (**2**)[4] analogs of D-fructopyranose have been synthesized by chemoenzymatic procedures and various antiradiation properties of the former have been reported.[5]



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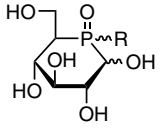

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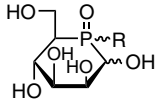

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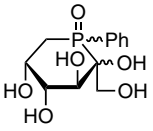

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With the general objective of a chemical modification by heteroatoms, we have prepared various sugar analogs having a phosphorus atom in the ring (phospho sugar),[6] in the D-glucopyranose (**3**)[7] and D-mannopyranose (**4**) analogs.[8] As the first example of a P-in-the-ring ketose, D-fructopyranose having a phenylphosphinyl group (**5**)[9] has been prepared, although the further synthesis, and characterization of other ketose analogs remained to be performed. Hydroxyphosphinyl-in-the-ring sugar analogs are usually more difficult to prepare and to assign than those having alkyl- or phenylphosphinyl group in the ring, but are expected to be of interest in view of potential biological activities.[6–10] We describe herein a convenient synthesis and an unambiguous structural assignment of D-fructopyranose analogs having a hydroxyphosphinyl group in the ring.

The 6-deoxy-6-phosphinyl-D-fructofuranose derivatives can be perceived as key intermediates in the preparation of the D-fructopyranose-type phospho sugars, and we chose benzyl group for protection of the 3,4-hydroxy groups, based on the previous study on the synthesis of various phospho sugars.[7–10]

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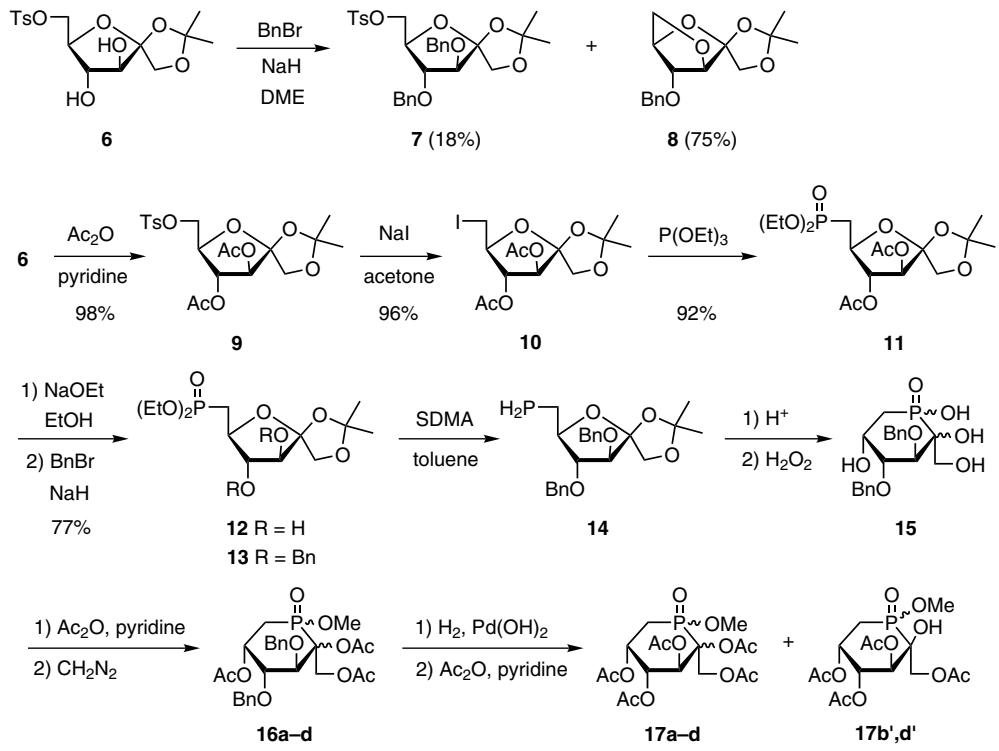

Scheme 1.

The starting material, 1,2-*O*-isopropylidene-6-*O*-tosyl-β-D-fructofuranose (**6**)[9a] was prepared from D-fructose according to the reported method. Benzylation of **6** with benzyl bromide and sodium hydride in DMF resulted in formation of mainly a 3,6-anhydro-4-*O*-benzyl derivative **8** (75%), along with the desired 3,4-di-*O*-benzyl compound **7** (18%) (Scheme 1). As the location of 3-hydroxy and 6-tosyloxy groups of **6** appears to favor an intramolecular substitution reaction, we employed another approach for the preparation of the key intermediate **13**; namely, introduction of a phosphinyl group at C-6 before 3,4-*O*-benzylation of **6**.

Thus, compound **6** was treated with acetic anhydride–pyridine to provide the 3,4-di-*O*-acetyl derivative (**9**), which was converted into the 6-iodo compound (**10**).[9a] Michaelis–Arbuzov reaction of **10** with triethyl phosphite afforded 6-deoxy-6-diethoxyphosphinyl derivative (**11**) in 92% yield. Treatment of **11** with sodium ethoxide in ethanol gave the deacetylated compound (**12**), which was converted into the 3,4-di-*O*-benzyl derivative (**13**) by use of benzyl bromide and sodium hydride in 77% overall yield from **11**.

Compound (**13**) was then reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) to give the 6-deoxy-6-phosphino derivative (**14**), whose 6-PH_2 group was confirmed on the basis of characteristic values of ^{1}H NMR ($^1J_{P,H}$ = 197.3 and 198.6 Hz) and ^{31}P NMR data (δ 1.5). The unstable **14** was immediately treated with hydrochloric acid at 90 °C under argon and then oxidized with hydrogen peroxide to afford 3,4-di-*O*-benzyl-6-deoxy-6-hydroxyphosphinyl-α,β-D-fructopyranoses (**15**).

These products were characterized after having been converted into the corresponding 6-methoxyphosphinyl-1,2,5-triacetates (**16**) by treatment with acetic anhydride–pyridine and then ethereal diazomethane. By purification on a silica gel column, the crude product was separated into two fractions. The faster-eluting fraction gave an inseparable mixture of 6-deoxy-6-[(*R*)-methoxyphosphinyl]-α-D-fructopyranose (**16a**) (4.1% overall yield from **13**) and its 6-[(*S*)-methoxyphosphinyl] β-isomer (**16d**) (10%), whereas the slower-eluting fraction gave an inseparable mixture of the 6-[(*R*)-methoxyphosphinyl] β-isomer (**16b**) (16%) and the 6-[(*S*)-methoxyphosphinyl] α-isomer (**16c**) (11%). The molecular composition of these compounds was confirmed by FAB-mass spectra, which gave the $(M+1)^+$ ions at *m*/*z* 549 corresponding to $C_{27}H_{34}O_{10}P$.

The precise structures of **16a–d** were established by the analysis of their 600 MHz ^{1}H NMR spectra; for all signals assignments, see Figure 1 and Table 1. The $^5C_2$ conformation of **16a–d** are assigned from the large values of $J_{3,P}$ (20–36 Hz) and $J_{5,6S}$ (11–13 Hz) and the small values of $J_{5,P}$ (6–14 Hz) and $J_{3,4}$ (5–6 Hz).[6a,8–10] The presence of a long-range W-coupling ($J_{4,6R}$ = 1.0–1.5 Hz) in **16a–d** further supports the $^5C_2$ conformation having the equatorial-oriented H-4 and H^R-6. It has been reported that β-D-fructopyranose derivatives exist

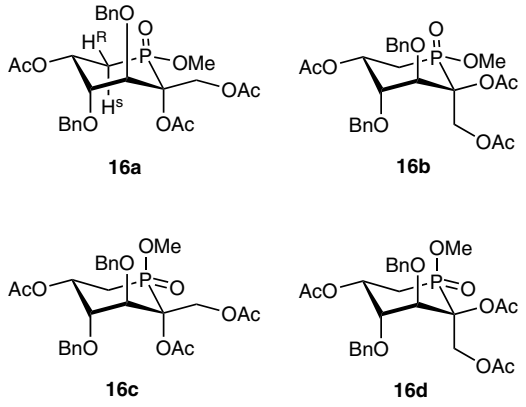

Figure 1. Structures and favored conformations for **16a**–**d**.

in the $^{2}C_{5}$ conformation, whereas α-D-fructopyranose derivatives exist mainly in the $^{5}C_{2}$ conformation.[11] It should be noted therefore that **16a**–**d** all exist predominantly in the $^{5}C_{2}$ conformation. The $^{5}C_{2}$ preference of **16a**–**d** is most likely attributable to avoidance of the unfavorable 1,2-*trans* steric repulsion that would arise if two benzyloxy groups at C-3 and C-4 were oriented equatorially in the $^{2}C_{5}$ form. Such conformational flips of the pyranose rings having two bulky substituents at the 1,2-*trans* position have been observed; namely, benzyloxy,[12] tosyloxy,[13] *tert*-butyldimethylsilyloxy groups.[14]

With regard to the orientation of the ring P=O group, a downfield shift (0.15–0.25 ppm) of H-5 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.[6a] Similarly, the axial orientations (α anomers) of AcO-2 in **16a**,**c** are established by the downfield shift (0.15–0.25 ppm) of H^{S}-6 from those of **16b**,**d** (β anomers) having the equatorial AcO groups.[6a]

To separate of diastereomeric mixtures **16a**,**d** and **16b**,**c** and for their more detailed characterization, compounds **16** were converted into the corresponding 1,2,3,4,5-tetraacetates **17**. Debenzylation of the mixture of **16a**,**d** by catalytic hydrogenation over 20% $Pd(OH)_2$–C, followed by acetylation, afforded 1,2,3,4,5-penta-*O*-acetyl-6-deoxy-6-[(*R*)-methoxyphosphinyl]-α-D-fructopyranose (**17a**) (83% from **16a**), its 6-[(*S*)-phosphinyl]β-isomer (**17d**) (18% from **16d**), and the corresponding 1,3,4,5-tetra-*O*-acetyl-6-[(*S*)-phosphinyl]β-analog (**17d′**) (66% from **16d**). Meanwhile, similar treatment of the other mixture, **16b**,**c**, afforded 1,2,3,4,5-penta-*O*-acetyl-6-deoxy-6-[(*S*)-methoxyphosphinyl]-α-D-fructopyranose (**17c**) (81% from **16c**), its 6-[(*R*)-phosphinyl] β-isomer (**17b**) (24% from **16b**), and the corresponding 1,3,4,5-tetra-*O*-acetyl-6-[(*R*)-phosphinyl] β analog (**17b′**) (59% from **16b**).

The precise ^{1}H NMR parameters for **17a**–**d** and **17b′**,**d′** and their favored conformations in $CDCl_3$ are shown in Table 2 and Figure 2. Compounds **17a**,**b′**,**c**,**d′** exhibit opposite magnitudes of the corresponding coupling constants in comparison with those of **16a**–**d**: that is, the small values of $J_{3,P}$ (1–10 Hz) and $J_{5,6S}$ (5–7 Hz) and the large values of $J_{5,P}$ (26–35 Hz) and $J_{3,4}$ (9–10 Hz), indicating the $^{2}C_{5}$ conformation. Compounds **17b**,**d** have moderate or intermediate magnitudes of $J_{3,P}$ (15 Hz), $J_{5,6S}$ (9 Hz), and $J_{5,P}$ (19 Hz), and $J_{3,4}$ (7 Hz), suggesting an equilibrium mixture of $^{2}C_{5}$ and $^{5}C_{2}$ conformers in almost equal ratio.[15] The ^{1}H NMR spectrum of **17b** in a polar solvent (Me_2SO-d_6) exhibited

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

Compound	Chemical shifts/δ											
	H-1	H-1′	H-3	H-4	H-5	H^{R}-6	H^{S}-6	POMe	AcO-1,2,5[a]	CH_2O-3[b,c]	CH_2O-4[b,c]	^{31}P
16a	5.05	4.76	5.00	3.93	5.55	2.14[d]	2.67	3.79	2.04, 2.00, 1.70	4.66, 4.62[e]	4.41, 4.37[f]	42.5
16b	4.93	4.50	4.30	3.93	5.56	2.29	2.40	3.82	2.11, 2.02, 1.95	4.80, 4.68[g]	4.49, 4.38[e]	39.9
16c	4.92	4.77	4.86	3.87	5.31	2.08[d]	2.65	3.80	2.08, 2.005, 1.87	4.68, 4.62[g]	4.56, 4.50[f]	40.9
16d	5.09	4.67	4.75	4.02	5.41	2.17	2.51	3.82	2.07, 2.01, 2.005	4.65, 4.61[e]	4.63, 4.41[h]	38.7

	Coupling constants/Hz												
	$J_{1,1'}$	$J_{1,P}$	$J_{1',P}$	$J_{3,4}$	$J_{3,P}$	$J_{4,5}$	$J_{4,6R}$	$J_{5,6R}$	$J_{5,6S}$	$J_{5,P}$	$J_{6R,6S}$	$J_{6R,P}$	$J_{6S,P}$	J_{POMe}
16a	12.0	20.8	6.2	4.6	27.3	2.5	1.5	3.6	12.7	5.6	14.1	[i]	13.5	11.0
16b	12.9	3.7	6.6	5.6	23.7	2.7	1.2	3.9	11.7	9.0	14.7	22.7	13.2	11.1
16c	11.7	15.4	10.0	5.9	19.8	2.5	1.0	3.4	10.5	13.7	14.5	[i]	14.5	10.9
16d	12.9	7.1	12.5	5.1	22.4	2.7	1.2	3.7	11.4	8.8	14.6	22.3	10.9	10.5

[a] The assignment of acetyl signals may be interchanged.
[b] The assignment of CH_2O-3 or -4 may be interchanged.
[c] Ph: δ = 7.16–7.38 (10H, m).
[d] The chemical shifts were confirmed by 2D-COSY measurement.
[e] ^{2}J = 11.7 Hz.
[f] ^{2}J = 11.2 Hz.
[g] ^{2}J = 12.0 Hz.
[h] ^{2}J = 10.7 Hz.
[i] Uncertain because of overlapping with other signals.

Table 2. ^{1}H and ^{31}P NMR parameters for compounds (**17a**–**d**, **17b′**,**d′**) in $CDCl_3$

Compound	Chemical shifts/δ										
	H-1	H-1′	H-3	H-4	H-5	H^R-6	H^S-6	POMe	AcO-1,2,3,4,5[a]	HO-2	^{31}P
17a	4.51	4.37	5.54	5.40	5.48	2.21	2.54	3.91	2.15, 2.14, 2.13, 2.10, 2.05		42.5
17b	4.89	4.59	5.76	5.40	5.51	2.47	2.38	3.84	2.13, 2.12, 2.10, 2.07, 2.04		38.5
17b[b]	4.79	4.51	5.61	5.27	5.34	2.59	2.57	3.72	2.09, 2.06, 2.05, 2.00, 1.98		
17b′	4.52	4.28	5.64	5.38	5.46	2.49	2.31	3.82	2.13, 2.11, 2.10, 1.98[c]	5.24	43.7
17c	4.89	4.50	6.07	5.42	5.35	2.13[d]	2.59	3.84	2.15, 2.14, 2.13, 2.10, 2.04		39.1
17d	4.95	4.89	5.97	5.41	5.47	2.20	2.56	3.87	2.13, 2.11, 2.10, 2.07, 2.065		40.2
17d[b]	4.81	4.85	5.90	5.29	5.30	2.36	2.58	3.77	2.08, 2.07, 2.065, 2.05, 2.00		
17d′	4.48	4.44	5.78	5.36	5.42	2.34	2.36	3.84	2.16, 2.14, 2.13, 2.03[c]	3.26	42.9

	Coupling constants/Hz												
	$J_{1,1'}$	$J_{1,P}$	$J_{1',P}$	$J_{3,4}$	$J_{3,P}$	$J_{4,5}$	$J_{4,6R}$	$J_{5,6R}$	$J_{5,6S}$	$J_{5,P}$	$J_{6R,6S}$	$J_{6R,P}$	$J_{6S,P}$	J_{POMe}
17a	11.5	15.4	9.5	8.6	9.6	2.7	0	3.6	7.1	25.7	15.4	16.0	17.1	10.5
17b	12.7	4.9	8.1	7.6	15.1	2.7	0.8	3.2	9.0	18.6	14.9	20.0	14.9	11.2
17b[b]	12.5	7.6	7.6	8.8	9.3	2.9	0	3.9	6.6	25.4	16.1	16.6	15.9	11.0
17b′	12.2	7.3	14.2	10.3	1.0	3.2	0	3.4	4.9	34.7	16.4	13.7	17.0	10.7
17c	11.0	9.0	17.1	9.3	7.1	2.9	0	3.2	7.1	28.1	15.6	[e]	18.3	11.2
17d	11.7	13.0	11.0	7.1	15.4	2.9	0.8	3.7	9.3	18.8	15.6	19.1	15.3	11.0
17d[b]	11.7	14.4	10.3	6.1	18.3	2.9	0.9	3.8	10.0	16.0	14.9	19.3	15.1	11.0
17d′	12.2	4.9	16.1	9.8	3.4	2.9	0	3.4	5.6	32.7	15.4	15.4	17.6	10.7

[a] The assignment of acetyl signals may be interchanged.
[b] In Me_2SO-d_6.
[c] AcO-1,3,4,5.
[d] The chemical shift was confirmed by 2D-COSY measurement.
[e] Uncertain because of overlapping with other signals.

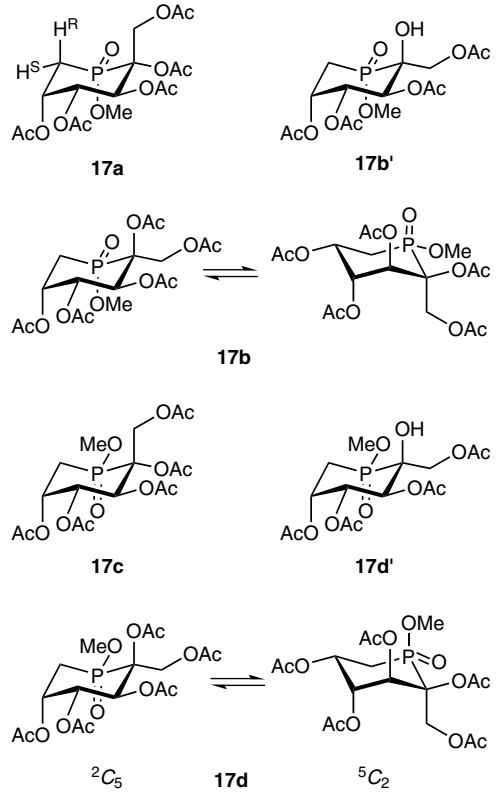

Figure 2. Structures and favored conformations for **17a**–**d** and **17b′**,**d′**.

an equilibrium shift in favor of the $^2C_5$ form, whereas **17d** in Me_2SO-d_6 was shown to exist as a conformational mixture in a ratio similar to that observed in $CDCl_3$ (but with a slight increase of the $^5C_2$ form).

The axial P=O orientations (in the $^2C_5$ form) of **17c**,**d**,**d′** are confirmed by the downfield shift (0.2–0.5 ppm) of H-3 from those of the corresponding P-epimers **17a**,**b**,**b′**, respectively. An appreciable downfield shift of H^R-6 is observed for **17b**,**b′**,**d**,**d′** having the axial AcO-2 (or HO-2), as compared with those of **17a**,**c** having the equatorial AcO-2.

The tetraacetates (**17b′**,**d′**) appear to be formed as the results of migration of the 2-*O*-acetyl group to the debenzylated 3-hydroxy group in the *cis*-relationship, and subsequent acetylation. However, the axial 2-hydroxy groups of 6-deoxy-6-phosphinyl-β-D-fructopyranose derivatives being in the $^2C_5$ form do not undergo acetylation under such a conditions as acetic anhydride–pyridine in a manner similar to those of β-D-fructopyranose and 5-thio-β-D-fructopyranose.[3c,16] In contrast, both an axial and an equatorial 2-hydroxy group of 6-deoxy-6-phosphinyl-β-D-fructopyranose derivatives, being in the $^5C_2$ form, are readily converted into the 2-acetates (**16a**–**d**). The reactivity of these tertiary hydroxy groups, seemingly depending upon their conformations, remains to be further studied.

The present work thus demonstrates a convenient way for preparation and structural assignment of 6-deoxy-6-hydroxyphosphinyl-D-fructopyranose derivatives. Extension of this work, including applications of these findings for synthesizing and characterizing phospho sugar analogs of other ketoses, as well as the

biological evaluation of D-fructopyranose phospho sugars, is of interest.

1. Experimental

1.1. General methods

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(A) 1:2 and (B) 2:1 EtOAc–hexane, (C) EtOAc, (D) 1:19 EtOH–EtOAc]. Column chromatography was performed on 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). Optical rotations were measured with a Jasco P-1020 polarimeter at 28 °C in $CHCl_3$. The NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz for ^1H) and Mercury 300 (121 MHz for ^{31}P) spectrometers at 23 °C. Chemical shifts are reported as δ values relative to Me_4Si (internal standard for ^1H) 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.

1.2. 3,4-Di-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-tosyl-β-D-fructofuranose (7) and 3,6-anhydro-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructofuranose (8)

To a solution of **6**[9a] (149 mg, 0.398 mmol) in dry DMF (1.0 mL) was added, with stirring, sodium hydride (60% in mineral oil, 35 mg, 0.88 mmol) and then benzyl bromide (0.100 mL, 0.921 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Water (2 mL) was added and then products were extracted with $CHCl_3$ three times. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was separated by column chromatography with 1:3 EtOAc–hexane as an eluent to give **7** and **8**.

Compound **7**: colorless needles (39.8 mg, 18%); mp 83–84 °C (from 1:1 EtOAc–hexane); $[\alpha]_D^{28}$ −11.2 (*c* 1.44); R_f 0.50 (A); ^1H NMR: δ 1.35, 1.40 (2s, 3H each, Me_2C), 2.43 (s, 3H, MeC_6–S), 3.89, 3.98 (2d, 1H each, $J_{1,1'}$ 9.5 Hz, H,H′-1), 3.95 (d, 1H, $J_{3,4}$ 6.1 Hz, H-3), 4.03–4.11 (m, 4H, H-4,5,6,6′), 4.56, 4.565 (2d, 2H each, ^2J 11.7 Hz, CH_2O-3 or 4), 4.655 (s, 1H, CH_2O-3 or 4), 7.28–7.36 (m, 5H, Ph), 7.33, 7.77 (2d, 2H each, *J* 8.3 Hz, C_6H_4–S). FAB MS: 555 (M+1; 8), 539 (12), 497 (15), 185 (25), 91 (100). Anal. Calcd for $C_{30}H_{34}O_8S$: C, 64.96; H, 6.18. Found: C, 65.01; H, 6.19.

Compound **8**: colorless syrup (87.4 mg, 75%); $[\alpha]_D^{28}$ −6.14 (*c* 3.42); R_f 0.32 (*A*); ^1H NMR: δ 1.46, 1.52 (2s, 3H each, CMe_2), 3.94 (dd, 1H, $J_{6,6'}$ 8.6, $J_{5,6'}$ 1.2 Hz, H-6′), 4.00 (d, 1H, $J_{5,6}$ 0 Hz, H-6), 4.01 (d, 1H, $J_{3,4}$ 2.4 Hz, H-3), 4.015, 4.065 (2d, 1H each, $J_{1,1'}$ 10.3 Hz, H,H′-1), 4.18 (dd, 1H, $J_{4,5}$ 0.7 Hz, H-4), 4.43 (d, 1H, H-5), 4.52, 4.62 (2d, 1H each, ^2J 11.7 Hz, CH_2O-4), 7.30–7.37 (m, 5H, Ph). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.81; H, 6.88.

1.3. 3,4-Di-*O*-acetyl-6-deoxy-6-diethoxyphosphinyl-1,2-*O*-isopropylidene-β-D-fructofuranose (11)

A mixture of **10**[9a] (620 mg, 1.50 mmol) and triethyl phosphite (3.0 mL, 17.5 mmol) was heated at 150 °C for 18 h with stirring under nitrogen; after 10 h, an additional amount of triethyl phosphite (2.0 mL) was added. After removal of an excess of phosphite in vacuo, the residue was purified by column chromatography with 3:1 EtOAc–hexane as an eluent to give **11** (585 mg, 92%) as colorless prisms: mp 32–33 °C (from 1:4 EtOAc–hexane); $[\alpha]_D^{28}$ −38.3 (*c* 2.98); R_f 0.51 (C); ^1H NMR: δ 1.30, 1.31 (2t, 3H each, J_{Et} 7.1 Hz, $POCCH_3$), 1.35, 1.49 (2s, 3H each, CMe_2), 2.07, 2.11 (2s, 3H each, AcO-3,4), 2.315 (ddd, 1H, $J_{6',P}$ 17.8, $J_{6,6'}$ 15.4, $J_{5,6'}$ 8.1 Hz, H-6′), 2.36 (ddd, 1H, $J_{6,P}$ 18.8, $J_{5,6}$ 5.6 Hz, H-6), 4.05, 4.10 (2d, 1H each, $J_{1,1'}$ 9.5 Hz, H,H′-1), 4.09, 4.11* (2dq, 2H each, $^3J_{H,P}$ 17.1, 14.2* Hz, $POCH_2$), 4.30 (tdd, 1H, $J_{5,P}$ 8.1, $J_{4,5}$ 4.6 Hz, H-5), 5.27 (d, 1H, $J_{3,4}$ 6.4 Hz, H-3), 5.30 (dd, 1H, H-4); ^{31}P NMR: δ 27.0. Anal. Calcd for $C_{17}H_{29}O_{10}P$: C, 48.11; H, 6.89. Found: C, 48.08; H, 6.91.

1.4. 3,4-Di-*O*-benzyl-6-deoxy-6-diethoxyphosphinyl-1,2-*O*-isopropylidene-β-D-fructofuranose (13)

To a solution of **11** (806 mg, 1.90 mmol) in dry EtOH (5.0 mL) was added, with stirring, a 21% ethanolic solution of NaOMe (0.05 mL, 0.13 mmol) at 0 °C. After stirring for 1 h, the mixture was diluted with EtOH (10 mL) and neutralized with Amberlite IR-120(H^+). The resin was filtered off and washed with EtOH. The filtrate was evaporated in vacuo to give 6-deoxy-6-diethoxyphosphinyl-1,2-*O*-isopropylidene-β-D-fructofuranose (**12**) as a pale yellow syrup (640 mg): R_f 0.10 (C); ^1H NMR: δ 1.33, 1.34 (2t, 3H each, J_{Et} 7.1 Hz, $POCCH_3$), 1.40, 1.49 (2s, 3H each, CMe_2), 2.06 (ddd, 1H, $J_{6',P}$ 16.8, $J_{6,6'}$ 14.7, $J_{5,6'}$ 11.0 Hz, H′-6), 2.34 (ddd, 1H, $J_{6,P}$ 20.2, $J_{5,6}$ 3.9 Hz, H-6), 3.15 (br s, 2H, HO-3,4), 3.94 (ddt, 1H, $J_{4,5}$ 6.6, $J_{5,P}$ 3.7 Hz, H-5), 3.97 (d, 1H, $J_{3,4}$ 8.3 Hz, H-3), 4.01 (dd, 1H, H-4), 4.035, 4.04 (2d, 1H each, $J_{1,1'}$ 9.3 Hz, H,H′-1), 4.07–4.17 (m, 4H, $POCH_2$); ^{31}P NMR: δ 28.5.

This syrup was dissolved in DMF (5.0 mL) and, with stirring, sodium hydride (60% in mineral oil, 230 mg, 5.75 mmol) and then benzyl bromide (0.700 mL, 5.90 mmol) was added at 0 °C under argon. The mixture was stirred at 20 °C for 2 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 2:1 EtOAc–hexane as an eluent to give **13** (762 mg, 77% from **11**) as colorless needles: mp 52–53 °C (from 2:1 EtOAc–hexane); $[\alpha]_D^{28}$ −22.5 (*c* 2.00); R_f 0.28 (B); ^{1}H NMR: δ 1.29, 1.30 (2t, 3H each, J_{Et} 7.1 Hz, $POCCH_3$), 1.46, 1.51 (2s, 3H each, CMe_2), 2.18 (ddd, 1H, $J_{6',P}$ 18.8, $J_{6,6'}$ 15.4, $J_{5,6'}$ 5.9 Hz, H-6′), 2.25 (ddd, 1H, $J_{6,P}$ 17.8, $J_{5,6}$ 7.8 Hz, H-6), 3.94, 4.02 (2d, 1H each, $J_{1,1'}$ 9.5 Hz, H,H′-1), 3.945 (d, 1H, $J_{3,4}$ 5.9 Hz, H-3), 4.090, 4.091* (2dq, 2H each, $^3J_{H,P}$ 20.2, 21.9* Hz, $POCH_2$), 4.15 (dd, 1H, $J_{4,5}$ 4.6 Hz, H-4), 4.27 (ddd, 1H, $J_{5,P}$ 8.1 Hz, H-5), 4.64, 4.65 (2d, 1H each, ^2J 12.2 Hz, CH_2O-3 or 4), 4.67, 4.72 (2d, 1H each, ^2J 11.7 Hz, CH_2O-3 or 4), 7.28–7.36 (m, 10H, Ph); ^{31}P NMR: δ 27.5. FAB MS: 521 (M+1; 8), 377 (10), 337 (12), 287 (15), 247 (28), 215 (19), 181 (24), 91 (100). Anal. Calcd for $C_{27}H_{37}O_8P$: C, 62.30; H, 7.16. Found: C, 62.26; H, 7.14.

1.5. 1,2,5-Tri-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-6-methoxyphosphinyl-D-fructopyranose (16a–d)

To a solution of **13** (192 mg, 0.369 mmol) in dry toluene (2.0 mL) was added, with stirring, a solution of SDMA (70% in toluene, 0.25 mL, 0.90 mmol) in small portions at −10 °C under argon. The mixture was stirred at this temperature for 1 h. Then, water (0.2 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 3,4-di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-phosphino-β-D-fructofuranose (**14**) as a colorless syrup: R_f 0.78 (B); ^{1}H NMR: δ 1.47, 1.51 (2s, 3H each, CMe_2), 1.82 (ddq, 1H, $J_{6,6'}$ 14.5, $^3J_{6',PH'}$ 10.0, $^2J_{6',P}$ 5.7, $J_{5,6'}$ 5.9, $^3J_{6',PH}$ 4.7 Hz, H-6′), 1.95 (dddt, 1H, $^3J_{6',PH}$ 9.7, $^2J_{6,P}$ 7.9, $^3J_{6,PH'}$ 5.5, $J_{5,6}$ 5.3 Hz, H-6), 2.63 (dddd, 1H, $^1J_{P,H'}$ 197.3, $^2J_{H,H'}$ 12.1 Hz, H′–P), 2.74 (dddd, 1H, $^1J_{P,H}$ 198.6 Hz, H–P), 3.91 (dq, 1H, $J_{5,P}$ 8.3, $J_{4,5}$ 5.1 Hz, H-5), 3.97, 4.03 (2d, 1H each, $J_{1,1'}$ 9.4 Hz, H,H′-1), 4.00 (d, 1H, $J_{3,4}$ 6.4 Hz, H-3), 4.06 (dd, 1H, H-4), 4.62, 4.70 (2d, 1H each, ^2J 11.7 Hz, CH_2O-3 or 4), 4.66, 4.74 (2d, 1H each, ^2J 11.7 Hz, CH_2O-3 or 4), 7.27–7.37 (m, 10H, Ph); ^{31}P NMR: δ 1.5.

This syrup was immediately dissolved in 1:1 2-propanol–0.5 M HCl (3.0 mL) and solution was stirred at 90 °C for 2 h under argon. After cooling, the mixture was evaporated in vacuo. The residue was dissolved in 2-propanol (2.0 mL), treated with 30% H_2O_2 (0.6 mL, 5.9 mmol) at rt for 12 h and then concentrated in vacuo to give crude 3,4-di-*O*-benzyl-6-deoxy-6-hydroxyphosphinyl-α,β-D-fructopyranoses (**15**) as a colorless syrup: R_f 0 (*C*). This was dissolved in dry pyridine (1.5 mL), and Ac_2O (0.70 mL, 7.4 mmol) was added at 0 °C. The mixture was stirred at rt for 24 h 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 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 2:1 EtOAc–hexane to EtOAc into two fractions.

The faster-eluting fraction [R_f 0.49 (D)] gave a colorless syrup (29.4 mg), which consisted of 6-[(*R*)-methoxyphosphinyl]-α-D-fructopyranose (**16a**) (4.1% from **13**) and its 6-[(*S*)-P]-β-isomer (**16d**) (10%), the ratio being estimated by ^{1}H NMR: ^{1}H and ^{31}P NMR, see Table 1. FAB MS *m*/*z* 549 (M+1; 20), 507 (18), 521 (11), 181 (12), 91 (100). Found: *m*/*z* 549.1871. Calcd for $C_{27}H_{34}O_{10}P$: M+1, 549.1890.

The slower-eluting fraction [R_f 0.42 (D)] gave a colorless syrup (53.9 mg), which consisted of 6-[(*R*)-methoxyphosphinyl]-β-D-fructopyranose (**16b**) (16% from **13**) and its 6-[(*S*)-P]-α-isomer (**16c**) (11%), the ratio being estimated by ^{1}H NMR: ^{1}H and ^{31}P NMR, see Table 1. FAB MS *m*/*z* 549 (M+1; 22), 507 (15), 521 (13), 181 (24), 91 (100). Found: *m*/*z* 549.1878. Calcd for $C_{27}H_{34}O_{10}P$: M+1, 549.1890.

1.6. 1,2,3,4,5-Penta-*O*-acetyl-6-deoxy-6-methoxyphosphinyl-D-fructopyranose (17a–d) and 1,3,4,5-tetra-*O*-acetyl-6-deoxy-6-methoxyphosphinyl-D-fructopyranose (17b′,d′)

A 28:72 mixture of **16a** and **16d** (22.0 mg, 0.0401 mmol) dissolved in EtOH (1.0 mL) was hydrogenated in the presence of 20% $Pd(OH)_2$–C (8.0 mg) at 25 °C under an atmospheric pressure of H_2. After 10 h, the catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was separated by column chromatography with a gradient eluent of 3:1 EtOAc–hexane to EtOAc into two fractions.

The faster-eluting fraction [R_f 0.45 (D)] gave 6-[(*S*)-methoxyphosphinyl]-β-D-fructopyranose pentaacetate (**17d**) (2.4 mg, 18% from **16d**) as a colorless syrup: ^{1}H and ^{31}P NMR, see Table 2. FAB MS *m*/*z* 453 (M+1; 100), 411 (84), 393 (37), 381 (30), 369 (41), 248 (53), 219 (62), 189 (49). Found: *m*/*z* 453.1151. Calcd for $C_{17}H_{26}O_{12}P$: M+1, 453.1162.

The slower-eluting fraction [R_f 0.36 (D)] gave a colorless syrup (12.2 mg), which consisted of 6-[(*R*)-P]-α-D-fructopyranose pentaacetate (**17a**) (4.2 mg, 83% from **16a**) and 6-[(*S*)-P]-β-D-fructopyranose tetraacetate (**17d′**) (8.0 mg, 66% from **16d**), the ratio being estimated by ^{1}H NMR:^{1}H and ^{31}P NMR, see Table 2. Compound **17d′** was crystallized from EtOAc: mp 91–92 °C. Anal. Calcd for $C_{15}H_{23}O_{11}P$: C, 43.91; H, 5.65. Found: C, 43.86; H, 5.66.

By use of the same procedures described above, a 60:40 mixture of **16b** and **16c** (33.0 mg, 0.0602 mmol) was converted into the corresponding acetyl derivatives,

which were separated by column chromatography into two fractions.

The faster-eluting fraction [R_f 0.49 (D)] gave 6-[(*S*)-methoxyphosphinyl]-α-D-fructopyranose pentaacetate (**17c**) (8.8 mg, 81% from **16c**) as a colorless syrup: ^{1}H and ^{31}P NMR, see Table 2. FAB MS *m/z* 453 (M+1; 100), 411 (78), 393 (30), 381 (32), 369 (26), 248 (45), 219 (44), 189 (32). Found: *m/z* 453.1140. Calcd for $C_{17}H_{26}O_{12}P$: M+1, 453.1162.

The slower-eluting fraction [R_f 0.41 (D)] gave a colorless syrup (12.6 mg), which consisted of 6-[(*R*)-P]-β-D-fructopyranose pentaacetate (**17b**) (24% from **16b**) and 6-[(*R*)-P]-β-D-fructopyranose tetraacetate (**17b′**) (59% from **16b**), the ratio being estimated by ^{1}H NMR:^{1}H and ^{31}P NMR, see Table 2.

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