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Synthesis of 6-Deoxy-4-*O*-methyl-6-phenylphosphinyl-D-fructopyranoses. The First P-in-the-Ring Analogs of a Ketose

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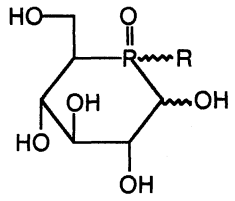
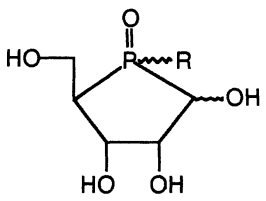
Treatment of D-fructose with 2-methoxypropene-TsOH, followed by tosylation, gave 1,3-*O*-isopropylidene-6-*O*-tosyl-α-D-fructofuranose (**5**). Methyl 6-deoxy-6-[(ethoxy)phenylphosphinyl]-4-*O*-methyl-α-D-fructofuranoside (**8**) was derived from **5** in a 3 step sequence (67% overall yield). Compound **8** was converted into the title compounds, which were characterized as the 1,3,5-tri-*O*- and 1,2,3,5-tetra-*O*-acetyl derivatives.

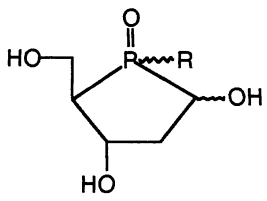
Various sugar analogs possessing a phosphorus atom in the hemiacetal ring have been prepared.[1] Such compounds are of interest in view of their physicochemical and biochemical properties. Although a number of the aldose-type analogs having a phosphinyl group in the ring, such as D-glucopyranoses (**1**),[2] D-ribofuranoses (**2**),[3] and 2-deoxy-D-ribofuranoses (**3**),[4] have been synthesized, no such analogs of a ketose-type have been re-



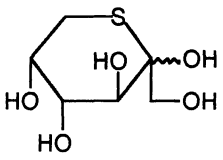
1 R=OH,Et,Ph



2 R=OH,Et,Ph



3 R=OH,Me



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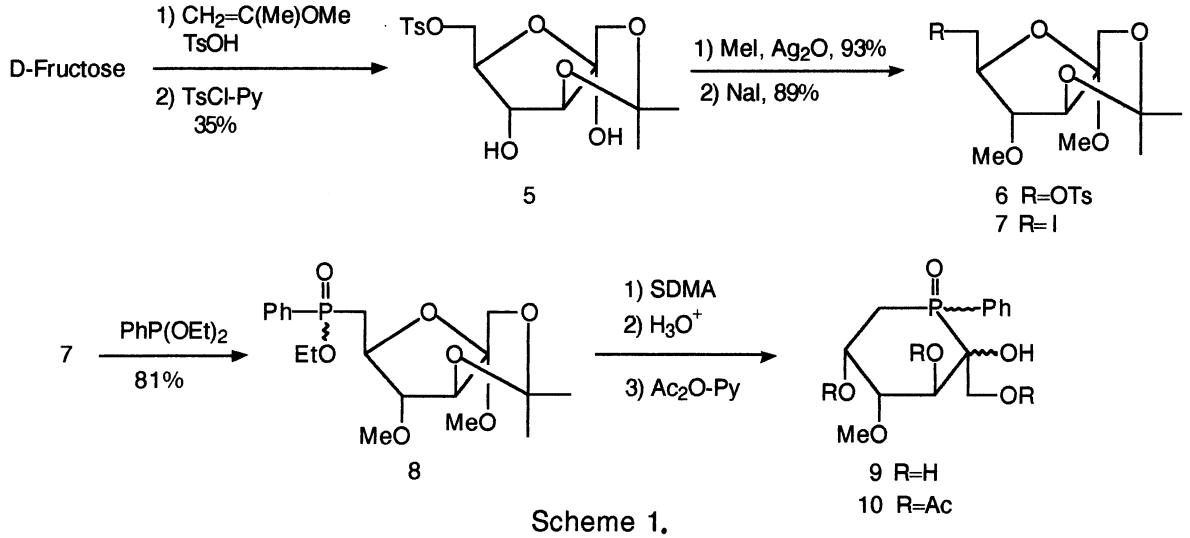
ported yet. Meanwhile, an S-in-the-ring analog of D-fructopyranose (**4**) showing various antiradiation activity have been reported.[5] We now describe a convenient synthesis of 6-deoxy-4-*O*-methyl-6-phenylphosphinyl-D-fructopyranoses, the first P-in-the-ring ketose analogs having a phenylphosphinyl as a model functional group.

Thus, D-fructose was first converted into 1,3-*O*-isopropylidene-6-*O*-tosyl-α-D-fructofuranose (**5**) by treatment with 2-methoxypropene in the presence of *p*-tolylsulfonic acid[6] and then with tosyl chloride in pyridine

as illustrated in Scheme 1.[7] Protection of the anomeric 2-hydroxyl as well as 4-hydroxyl group of **5** (to facilitate characterization of the products in the subsequent steps) was performed by the use of MeI-Ag_2O, providing the methyl 4-*O*-methyl furanoside **6**. This was converted to 6-iodo compound **7**, which was led to the key intermediate 6-deoxy-6-[(ethoxy)phenylphosphinyl] derivative **8** by the Michaelis-Arbuzov reaction[8] with diethyl phenylphosphonite. Compound **8** was then reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA), followed by acid hydrolysis, affording 6-deoxy-4-*O*-methyl-6-phenylphosphinyl-D-fructopyranose (**9**) as a mixture of diastereomers (with regard to anomeric C-2 and ring-P). Compound **9** was converted by the usual method into the per-*O*-acetyl derivative **10** for characterization (Scheme 1). Rechromatography of **10** on a column of silica gel with 19:1 (v/v) ethyl acetate-ethanol as the eluant afforded 1,3,5-tri-*O*-acetyl-6-deoxy-4-*O*-methyl-6-[(*S*)-phenylphosphinyl]-β-D-fructopyranose (**10a**) (13% overall yield from **8**), its 6-[(*R*)-*P*] analog **10b** (16% yield, mp 182-183 °C), 6-[(*R*)-phenylphosphinyl]-α- isomer **10c** (4.7% yield), its 6-[(*S*)-*P*] analog **10d** (3.2% yield). A small amount of 1,2,3,5-tetra-*O*-acetyl-6-deoxy-4-*O*-methyl-6-[(*S*)-phenylphosphinyl]-α-D-fructopyranose (**10e**) was also isolated (4.1% yield).



Scheme 1.

The precise configuration and conformation of **10a** (in a 1:1 equilibrium mixture of $^2C_5$ and $^5C_2$ forms), **10b** (in the $^2C_5$ form), and **10c**, **10d**, and **10e** (all in the $^5C_2$ form) were established by analysis of their 500-MHz ^1H NMR spectra; see Table 1 for the assignments of all signals.[9] These NMR data are expected to be highly versatile in determining the structures of a series other 6-deoxy-6-phosphinyl-D-fructopyranoses, which are to be prepared.

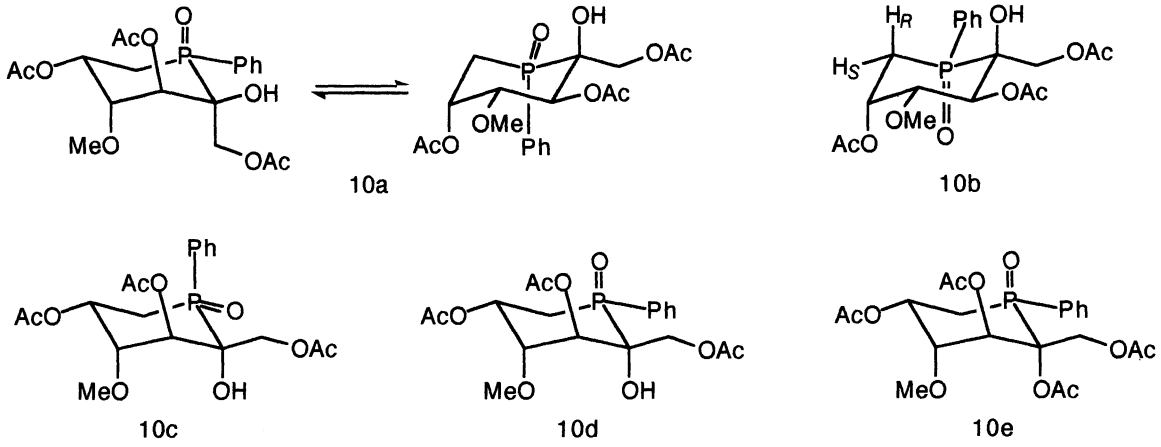


Table 1. ^{1}H and ^{31}P NMR Parameters for **10a—e** in $CDCl_3$[a)]

	Chemical shifts / δ											
Compd	H-1	H-1'	H-3	H-4	H-5	H_S-6	H_R-6	MeO-4	AcO-1,3,5[b)]	HO-2	Ph[c)]	^{31}P
10a	4.27	3.87	5.73	3.93	5.69	2.74	2.54	3.49	1.89, 2.21, 2.08	4.29	d)	32.4
10b	4.58	4.45	5.91	3.83	5.68	2.46	2.44	3.44	1.32, 2.20, 2.17	4.02	e)	29.8
10c	4.20	4.05	5.61	3.79	5.56	2.89	2.64	3.63	1.85, 2.17, 2.03	4.43	f)	31.9
10d	4.64	4.03	5.43	4.01	5.75	2.94	2.29	3.70	1.81, 2.20, 2.10	4.64	g)	32.7
10e	4.64	4.60	6.11	3.90	5.76	2.85	2.39	3.59	1.86, 2.23, 2.09, 2.04[h)]		i)	29.0

	Coupling constants / Hz											
	$J_{1,1'}$	$J_{1,P}$	$J_{1',P}$	$J_{3,4}$	$J_{3,P}$	$J_{4,5}$	$J_{4,6R}$	$J_{5,6S}$	$J_{5,6R}$	$J_{5,P}$	$J_{6S,6R}$	$J_{6S,P}$	$J_{6R,P}$
10a	11.9	8.8	6.8	7.0	14.0	2.7	0.8	6.2	3.9	16.2	14.9	9.2	19.9
10b	12.5	17.3	2.9	10.0	0.5	3.0	0	4.4	3.4	29.4	15.3	14.0	7.5
10c	11.8	6.8	5.8	6.0	19.7	2.3	1.0	11.4	3.9	8.0	14.6	18.6	13.7
10d	12.1	7.0	3.0	4.2	22.2	2.0	1.5	12.8	3.8	3.5	14.5	4.7	18.6
10e	12.6	5.6	8.5	5.1	21.9	1.9	1.5	12.5	3.9	4.4	14.4	3.3	19.7

a) Measured with a Varian VXR-500 or -200 instrument (at 500 MHz for ^{1}H with TMS as internal standard, or at 81 MHz for ^{31}P with 80% phosphoric acid as external standard). b) The assignment of acetoxyl signals may be interchanged. c) For protons of Ph(*o*), Ph(*m*), Ph(*p*). d) 7.88, 7.54, 7.62. e) 7.92, 7.50, 7.56. f) 7.91, 7.54, 7.61. g) 7.93, 7.50, 7.58. h) For AcO-1,2,3,5.[b)] i) 7.75, 7.50, 7.55.

The present work thus demonstrates that P-in-the-ring ketose analogs can readily be prepared from appropriate precursors. Extension of this work including preparative studies on improved yields of intermediates without protection of the 4-hydroxyl group is in progress.

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6) D-Fructose has been reported to give 2,4,6-tri-*O*-acetyl-1,3-*O*-isopropylidene-α-D-fructofuranose in 55% yield by treatment with 2-methoxypropene-TsOH and then acetic anhydride-pyridine but without detailed experimental procedure: E. Fanton, J. Celas, and D. Horton, *J. Chem. Soc., Chem. Commun.*, **1980**, 21.

7) MS (high-resolution) and ^{1}H NMR data (mostly at 500 MHz) of the products described in this paper were in agreement with the structures proposed.

8) See e.g. G. M. Kosolapoff, *Org. React.*, **6**, 273 (1951); D. Redmore, *Chem. Rev.*, **71**, 317 (1971).

9) For structural assignments of these products, the chemical shift of each proton signal and the dependence of the $^2J_{H,P}$, $^3J_{H,P}$, $^3J_{H,H}$, and $^4J_{H,H}$ values on the dihedral angles were carefully taken into consideration.

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