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Synthesis of 5-Deoxy-5-[(R and S)-methylphosphinyl]-α,β-D-mannopyranoses. The First P-in-Ring Sugar Analogues of D-mannose Type

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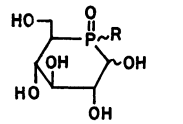
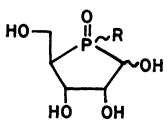
Starting with methyl 2,3-O-isopropylidene-α-D-lyxo-pentodialdo-1,4-furanoside, methyl 5-deoxy-2,3-O-isopropylidene-5-[(methoxy)methylphosphinyl]-α-D-lyxo-hexofuranoside (**8**) was prepared (in 5 steps, 16% overall yield). The hexose **8** was converted into the title compounds, which were characterized as the 1,2,3,4,6-pentaacetates.

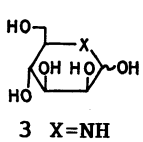
Various sugar analogues possessing a phosphorus atom in the hemiacetal ring, e.g., D-glucopyranoses **1**[1] and D-ribofuranoses **2**,[2] have been prepared in recent years.[3] These compounds are of interest in view of their physico-chemical properties and potential biological activity. Meanwhile, 5-amino-5-deoxy-D-mannopyranose[4] (**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 be D-mannopyranose (**4**).[5] We now describe a convenient synthesis of the first P-in-ring sugar analogues with D-mannopyranose structure having an alkylphosphinyl group in the ring.



1 R=Et,OH

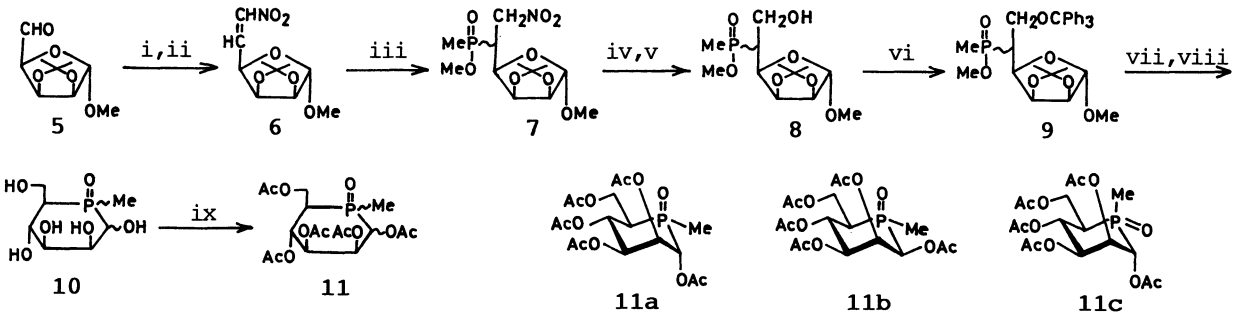


2 R=Et,Ph,OH



3 X=NH
4 X=S

Thus, compound **5**[6] was converted into the key intermediate 6-O-(triphenylmethyl) derivative **9** by sequence of **5** → **6** → **7** → **8** → **9** (6 steps, 7% overall yield) as illustrated in Scheme 1.[7] Then, **9** was reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA), followed by acid hydrolysis, affording 5-deoxy-5-(methylphosphinyl)-D-lyxo-hexopyranoses (**10**), which were converted into their



Scheme 1. Reagents: i, $MeNO_2$-MeONa/MeOH; ii, Ac_2O-AcONa; iii, MePH(=O)OMe in benzene, 80 °C; iv, H_2-PtO_2; v, $NaNO_2$/AcOH; vi, Ph_3CCl/Py; vii, SDMA; viii, 0.5 M HCl-EtOH, 80 °C; ix, Ac_2O-Pyridine.

pentaacetates (**11**) by the usual method (Scheme 1). Rechromatography of **11** in a column of silica gel with 19:1 (v/v) ethyl acetate-ethanol as the eluant afforded pure 1,2,3,4,6-penta-O-acetyl-5-deoxy-5-[(R)-methylphosphinyl]-α-D-mannopyranose (**11a**) (6.0% overall yield from **9**), its β-anomer **11b** (0.9% yield), and 5-[(S)-methylphosphinyl]-α- analogue **11c** (4.6%).[8] The configuration of **11a-c**, all predominantly in the $^4C_1$(D) conformation, was established by analysis of their 500-MHz ^{1}H NMR spectra (see Table 1), by taking into account the known parameters of structurally related compounds obtained before, e.g., pentaacetates[1] of **1**. Those parameters for **11a-c** are considered to be highly versatile in determining the structures of other 5-deoxy-5-phosphinyl-D-mannopyranoses, preparation of which is currently under investigation.

Table 1. ^{1}H NMR (500 MHz) Parameters for **11a-c** in $CDCl_3$[a]

	Chemical Shifts (δ)													
Compd	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	Ac-1,2,3,4,6[b]						Me-P
11a	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
11b	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
11c	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
	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_{PMe}
11a	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
11b	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
11c	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

a) Measured with a Varian VXR-500 instrument. b) The assignments of acetoxyl groups may have to be interchanged.

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5) R.J. Capton and J.K. MacLead, J. Chem. Soc., Chem. Commun., 1987, 1200. The first synthesis of **4** has recently been presented: T. Fujimori, Y. Izukawa, H. Yuasa, and H. Hashimoto, 58th National Meeting of the Chemical Society of Japan, Kyoto, April 1989, Abstr., No. 3IL11.
6) J.M.J. Tronchet, B. Gentile, A.P. Bonenfant, and O.R. Martin, Helv. Chim. Acta, 62, 696 (1979).
7) MS (high-resolution) and ^{1}H NMR data (mostly at 500 MHz) were in agreement with the products described in this paper. The complete data for the newly isolated products as well as a result of a more precise conformational study will be presented in a future paper.
8) The fractions of the last two compounds **11b,c** contained minor proportions of β-anomer of **11c** as well as the analogues of L-gulopyranose type (by NMR). Their complete separation and the characterization are in progress. Improvement of the synthetic route to the key intermediate **9** as well as optimization of the conversion of **9** to **11** is being studied.

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