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An Efficient Synthesis of 4-Deoxy-4-(hydroxyphosphinyl)-D-ribofuranoses. The First D-Ribofuranose Analogues Having Hydroxyphosphinyl Group in the Hemiacetal Ring

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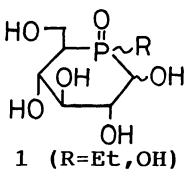
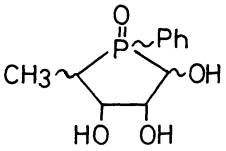
Methyl 2,3-O-isopropylidene-β-D-ribopyranoside was converted (in 4 steps) into methyl 4-deoxy-4-[(dimethoxy)phosphinyl]-2,3-O-isopropylidene-β-D-ribopyranoside (**10a**, 30% overall yield). The title compounds were readily derived from **10a** and characterized as the 4-deoxy-4-(methoxyphosphinyl) tetraacetates.

Various sugar analogues having a phosphorus atom in the hemiacetal ring, e.g., D-glucopyranoses **1**,[1] have been prepared in recent years;[2] these compounds are of interest in view of their physicochemical properties as well as their potential biological activity. As for analogues of D-ribofuranose type, **2**[3] and **3**[4] have been prepared in lengthy steps as a mixture with their L-lyxofuranoses. We wish to report herein an efficient synthesis of the first D-ribofuranose analogues having a hydroxyphosphinyl group in the ring; the PO(OH)-in-ring sugar analogues are generally more difficult to prepare than those having an alkyl- or arylphosphinyl group in the ring[1,2] but are apparently of considerable biological interest.[2] Moreover, the present synthesis clarifies the ambiguity concerning the epimerization that took place for some intermediates during the hydride reduction in the previous synthetic schemes.[3,4]



1 (R=Et,OH)



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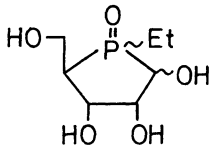

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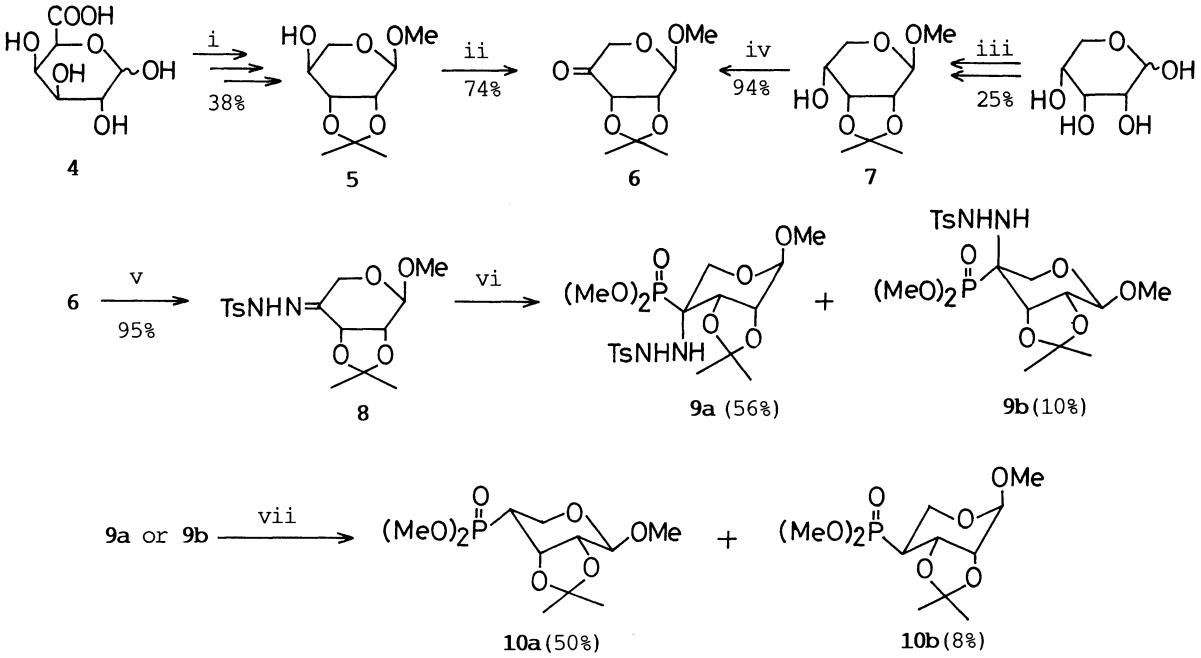
Although L-lyxopyranoside **5** (obtained,[5] with some difficulty, from D-galacturonic acid **4** in 4 steps) was used as the starting material for synthesis of **3**,[4] we have now found it more convenient to utilize D-ribopyranoside **7**[6] instead, which is readily available in quantities, though along with the separable 3,4-O-isopropylidene isomer, from D-ribose in 2 steps (Scheme 1). Oxidation of **7** with pyridinium chlorochromate (PCC) in the presence of molecular sieves (3A) afforded 4-ulose **6** more effectively than the previous oxidation procedure for **5** (see Scheme 1). **6** was then converted to tosylhydrazone **8**, which in turn was treated with an excess (8 equiv) of dimethyl phosphonate in the presence of trifluoromethanesulfonic acid (0.3 equiv), giving a ca. 85:15 mixture of the (4S)-phosphonate **9a** and (4R)-isomer **9b**; the assignment of their structures and preferred conformations (in

$CDCl_3$) (see Scheme 1) was made on the basis of ^1H NMR spectral data,[7,8] and this is the first time that both diastereomers of the phosphonate addition products have been isolated and characterized in this type of synthetic scheme of C—P bond formation.[2]

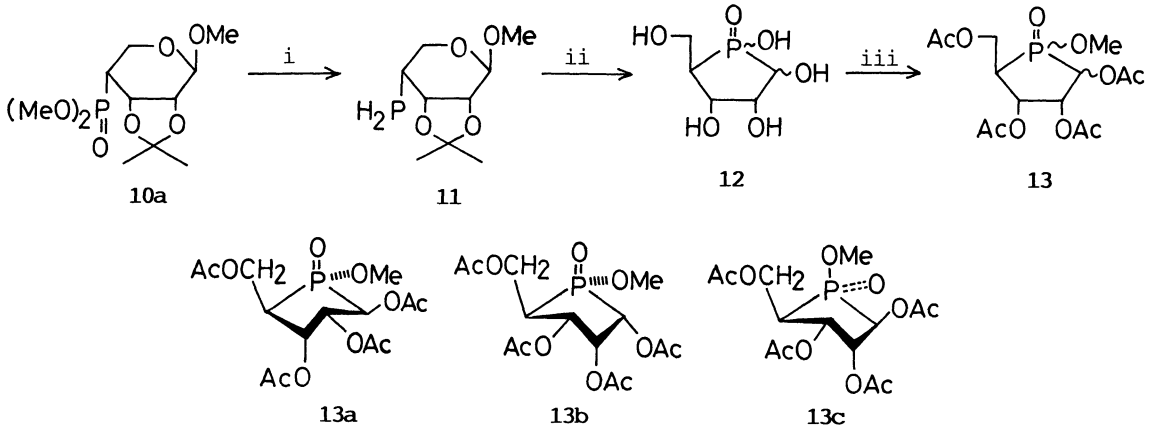
Reduction of the major product **9a** with sodium borohydride preponderantly afforded the D-ribopyranoside **10a** together with a small proportion of L-lyxopyranoside **10b**.[7,9,10] When the epimer **9b** was subjected to the same reduction, **10a** and **10b** were obtained in almost the same respective yields, thus indicating that an epimerization took place at C-4 during the borohydride reduction of both **9a** and **9b** to give presumably the thermodynamically controlled major product **10a** along with the minor product **10b**; both most likely have conformations in which the phosphonate group is predominantly linked equatorial (in $CDCl_3$)[10] (see Scheme 1).



Scheme 1. Synthesis of methyl 4-deoxy-4-[(dimethoxy)phosphinyl]-2,3-O-isopropylidene-β-D-ribopyranoside and α-L-lyxopyranoside. Reagents: i, Refs. 4,5; ii, DMSO-$(COCl)_2$-TEA (Ref. 4); iii, Ref. 6; iv, PCC/CH_2Cl_2, 25 °C, 4 h; v, $TsNHNH_2$/MeOH, 25 °C, 6 h; vi, $HP(O)(OMe)_2/CF_3SO_3H$, 25 °C, 5 h; vii, $NaBH_4$/THF, 25 °C, 12 h.

Then, the D-ribose type precursor **10a** was reduced with an excess (3 equiv) of sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) to give solely methyl 4-deoxy-2,3-O-isopropylidene-4-phosphino-β-D-ribopyranoside **11**[7] (Scheme 2); the unstable phosphine intermediate **11** has been isolated and characterized for the first time in this ring-transposition scheme of conversion to P-in-ring compounds. It should be noticed that no epimerization occurs at C-4 of **10a** with SDMA. Compound **11** was then hydrolyzed with mineral acid at 90 °C, affording 4-deoxy-4-(hydroxyphosphinyl)-α,β-D-ribofuranose (**12**). For isolation and characterization, **12** was converted into its 4-(methoxyphosphinyl) tetraacetates **13** by the usual method (in 17% overall yield from **10a**) (Scheme 2). Rechromatography of **13** in a column of silica gel with 19:1 (v/v) ethyl acetate-ethanol as the eluant afforded pure 1,2,3,5-tetra-O-

acetyl-4-deoxy-4-[(R)-methoxyphosphinyl]-β-D-ribofuranose (**13a**, colorless syrup, 6% yield from **10a**), its α-anomer **13b** (colorless syrup, 3% yield), and the 4-[(S)-P]-β- isomer (**13c**, colorless syrup, 2.5%).[11] The configurations of **13a** [approximately in the $^{2}T_{3}$(D) conformation] and **13b** and **13c** [both in $^{3}T_{2}$(D)] were established by analysis of their 500-MHz ^{1}H NMR spectra (see Table 1).



Scheme 2. Synthesis of 4-deoxy-4-[(R)- and (S)-methoxyphosphinyl]-α- and β-D-ribofuranoses. Reagents: i, SDMA/C_6H_6, 5 °C, 1 h; ii, 0.5 M HCl-iPrOH (1:1), 90 °C, 1 h, then aq H_2O_2, 25 °C, 1 d; iii, CH_2N_2/MeOH-DMSO, 0 °C, then Ac_2O-Pyridine.

Table 1. ^{1}H NMR (500 MHz) Parameters for **13a-c** in $CDCl_3$[a]

	Chemical shift (δ)							
Compd	H-1	H-2	H-3	H-4	H-5	H'-5	Ac-1,2,3,5[b]	POMe
13a	4.94	5.58	5.42	2.66	4.43	4.28	2.19, 2.10, 2.10, 2.09	3.92
13b	5.20	5.72	5.24	2.76	4.36	4.36	2.14, 2.09, 2.09, 2.06	3.90
13c	5.03	5.43	5.27	2.84	4.33	4.22	2.15, 2.13, 2.11, 2.08	3.80

	Coupling constant (Hz)													
	$J_{1,2}$	$J_{1,4}$	$J_{1,P}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{3,P}$	$J_{4,5}$	$J_{4,5'}$	$J_{4,P}$	$J_{5,5'}$	$J_{5,P}$	$J_{5',P}$	J_{POMe}
13a	6.4	0.5	6.6	3.9	11.1	5.7	18.0	6.7	7.2	16.7	11.8	12.8	13.2	11.5
13b	4.7	0	7.7	3.3	31.0	11.1	2.5	6.8	6.8	17.7	—	15.8	15.8	11.2
13c	3.8	0.5	5.5	3.7	21.3	8.3	8.7	7.0	8.0	18.8	11.3	10.0	9.8	10.7

a) Measured with a Varian VXR-500 instrument (the SC-Lab., Okayama Univ.). b) The assignments of acetoxyl groups may have to be interchanged.

These findings are believed to have clearly proved the equilibrated epimerization (caused by the hydride reagents) in favor of the formation of the key intermediate methyl 4-deoxy-4-phosphinyl-β-D-ribopyranoside, and therefore this synthetic scheme is expected to be readily applicable for preparation of D-ribofuranose analogues having various other kinds of phosphinyl or phosphino group in the ring, which is currently under intensive investigation.

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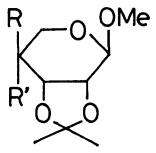
7) MS (high-resolution) and ^{1}H NMR data (mostly at 500 MHz) were in agreement with the products described in this paper (with the conformations shown in the structural formulas). The complete data for the newly isolated products will be presented in a future paper.

8) For distinction between the diastereomers **9a** and **9b**, the following ^{1}H NMR data were in particular taken into consideration: δ 4.85 (H-1), $J_{1,2}$ = 1.9 Hz, and $J_{2,P}$ = 1.2 Hz for **9a** ($^1\underline{C}_4$) vs. δ 4.17 (H-1), $J_{1,2}$ = 7.2 Hz, and $J_{3,5e}$ = 1.5 Hz for **9b** ($^4\underline{C}_1$).

9) Besides **10a,b**, a minor proportion of hydrazino compounds **10c**[7] (12%) and **10d**[7] (7%) were obtained from **9a** and **9b**, respectively. An effort to suppress these byproduct formation is currently being made.



10c: R=PO(OMe)$_2$ R'=NHNH$_2$
10d: R=NHNH$_2$ R'=PO(OMe)$_2$

10) The following characteristic ^{1}H NMR data served for distinction between the epimers **10a** and **10b**: δ 4.37 (H-1), $J_{3,4}$ = 3.0 Hz, and $J_{3,5e}$ = 0.8 Hz for **10a** ($^4\underline{C}_1$) vs. δ 4.79 (H-1), $J_{1,5e}$ = 2.0 Hz, $J_{2,P}$ = 1.6 Hz, and $J_{3,4}$ = 8.4 Hz for **10b** ($^1\underline{C}_4$).

11) Besides these pure compounds, another product, presumably α-anomer of **13c** was obtained in an extremely low yield (<0.5%). Improvement of the synthetic route to the key intermediate **10a** as well as optimization of the conversion of **10a** to **13** is being studied.

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