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Preliminary Communication

An efficient synthesis of 2,4-dideoxy-4-hydroxyphosphinyl-D-*erythro*-pentofuranose

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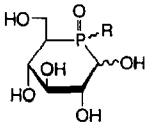
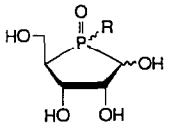
The interesting chemical and biochemical properties of sugars[1] containing phosphorus as the ring heteroatom have led in recent years to several examples of their preparation, for instance, such sugar analogs as 5-deoxy-5-phosphinyl-D-glucopyranoses[2] (**1**) and 4-deoxy-4-phosphinyl-D-ribofuranoses[3] (**2**). Analogs of the 2-deoxy-D-*erythro*-pentofuranose type are expected to be of considerable interest in view of their potential derivatization to the corresponding nucleosides and nucleotides. Thus far, there have been only brief reports of the low-yield formation of 2,4-dideoxy-4-methyl-(or 4-cyclohexyl-)phosphinyl-D-*erythro*-pentofuranoses as a mixture with their 4-epimers, the L-*threo*-pentofuranoses[4]. We now describe an efficient and unequivocal synthesis of the potentially more bioactive hydroxyphosphinyl-in-the-ring sugar analogs having the 2-deoxy-D-*erythro*-pentofuranose structure. Also reported are n.m.r.-spectral data of their 4-methoxyphosphinyl triacetates for the structural and conformational analysis, as these provide an effective way for establishing the structures of the rather complex 2,4-dideoxy-4-phosphinylfuranoses.



1 R = CH,Et



2 R = CH,Ph,Et

Addition of dimethyl phosphonate to 3,5,6-trideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*erythro*-hex-5-enofuranose[5] (**3**) in the presence of triethylamine at 25° gave an inseparable 2:1 mixture of the α-D-*ribo*- and β-L-*lyxo*-hexofuranoses (**4**) in 94% yield. Catalytic hydrogenation of **4** over platinum oxide in methanol, followed by deamination with nitrous acid, afforded mainly a mixture of the 3,5-dideoxyhexofuranoses **5** (in 61% yield), along with a minor amount of dehydrated product **6** (12%).

Compounds **5** were treated with acetic anhydride–sulfuric acid for 4 h at 25° (to

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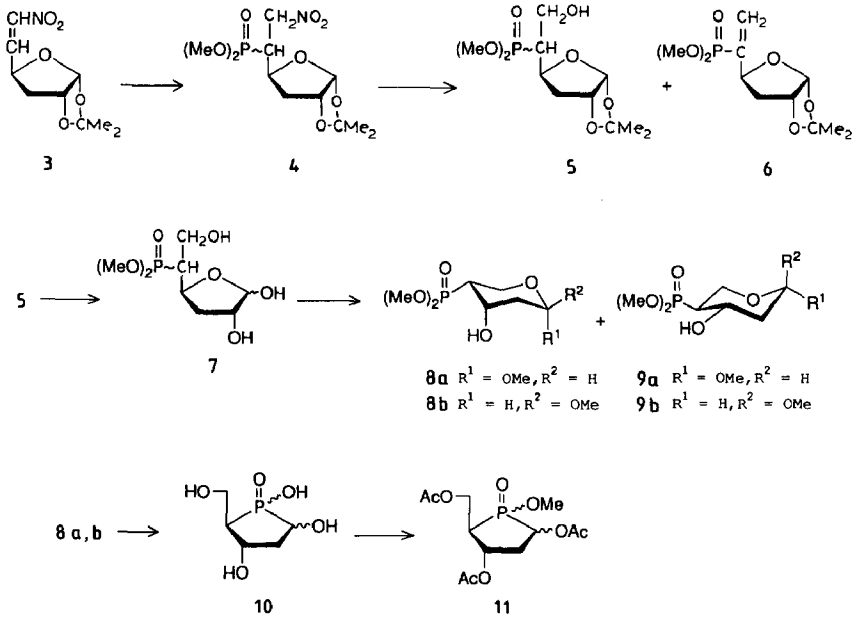

afford the 1,2,6-tri-*O*-acetyl derivative of **7**) and then with sodium methoxide in methanol to give the hexofuranoses **7**. Periodate oxidation of **7**, followed by treatment with methanol in the presence of an acidic ion-exchange resin and then separation of the products by silica gel chromatography with 1:19 methanol–chloroform, afforded methyl 2,4-dideoxy-4-dimethoxyphosphinyl-α-D-*erythro*-pentopyranoside (**8a**, 13% overall yield from **7**), its β anomer **8b** (26%), the β-L-*threo*-pentopyranoside **9a** (3.4%), and its α anomer **9b** (14%).

Reduction of the major, α,β-D-*erythro* products **8a,b** with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by treatment with hydrochloric acid in aqueous ethanol and then oxidation with hydrogen peroxide, gave 2,4-dideoxy-4-hydroxyphoshinyl-D-*erythro*-pentofuranose (**10**), which contained many inseparable byproducts. Crude **10** was therefore converted into the 4-methoxyphosphinyl triacetates **11** by treatment with diazomethane and then acetic anhydride–pyridine. Chromatography of

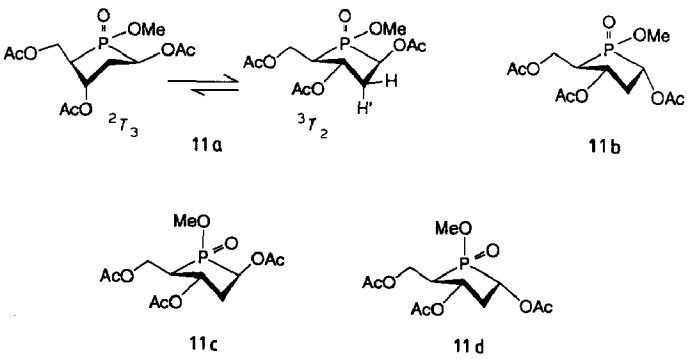

TABLE I

500-MHz, ^{1}H-N.m.r. parameters for 2,4-dideoxy-4-methoxyphosphinyl-D-*erythro*-pentofuranoses in $CDCl_3$[a]

Compounds	*Chemical shifts (δ)*									*Coupling constants (Hz)*			
	H-1	*H-2*	*H-2'*	*H-3*	*H-4*	*H-5*	*H-5'*	*POMe*	*AcO-1,3,5*[b]	$J_{1,2}$	$J_{1,2'}$	$J_{1,P}$	$J_{1,4}$
11a	5.07	2.45	2.13[c]	5.28	2.39	4.39	4.28	3.87	2.16, 2.07, 2.07	5.0	7.2	4.9	0.5
11b	5.03	2.73	1.95	5.13	2.44	4.35	4.35	3.83	2.13, 2.07, 2.06	5.1	7.2	7.0	0
11c	5.12	2.42	2.18	5.20	2.50	4.31	4.22	3.79	2.12, 2.08, 2.07	3.3	4.9	5.8	0.5
11d	4.82	2.69	2.05[c]	4.98	2.59	4.33	4.24	3.88	2.17, 2.08, 2.07	5.0	8.8	8.8	0

Coupling constants (Hz)

	$J_{2,3}$	$J_{2,P}$	$J_{2,2'}$	$J_{2',3}$	$J_{2',P}$	$J_{3,4}$	$J_{3,P}$	$J_{4,5}$	$J_{4,5'}$	$J_{4,P}$	$J_{5,P}$	$J_{5',P}$	$J_{5,5'}$	$^3J_{POMe}$
11a	5.3	19.0	14.3	7.1	[d]	7.4	10.6	7.0	7.8	16.3	9.9	13.8	11.7	11.2
11b	6.9	28.7	14.2	7.9	7.0	8.0	5.9	7.3	7.3	17.0	12.7	12.7		10.9
11c	5.6	27.1	14.4	9.6	7.4	8.4	5.3	7.4	7.9	16.4	16.4	8.8	11.3	10.8
11d	6.5	28.1	14.0	8.5	[d]	9.3	5.3	7.2	7.6	15.8	15.8	8.8	11.4	10.9

[a] Signals were assigned by first-order analysis with the aid of decoupling and, if necessary, by computer-assisted analysis. [b] Acetoxyl assignments may be interchanged. [c] Chemical shifts were confirmed by 2D COSY experiments, despite the presence of overlapping acetoxyl signals. [d] Values are uncertain because of overlapping with acetoxyl signals.

11 over silica gel with ethyl acetate–hexane yielded 1,3,5-tri-*O*-acetyl-2,4-dideoxy-4-[(*R*)-methoxyphosphinyl]-β-D-*erythro*-pentofuranose **11a** (6.1% overall yield from **8**), its α anomer **11b** (3.9%), the 4-[(*S*)-methoxyphosphinyl]-β-isomer **11c** (7.5%), and its α anomer **11d** (5.2%).

The molecular composition of these compounds was confirmed by their e.i., high-resolution mass spectra, which gave the (M + 1) ions at *m/z* 322 (0.2–4.2%) corresponding to $C_{12}H_{20}O_8P$. The precise configurations and conformations of **11a** (in a 2:3 equilibrium mixture of $^2T_3$ and $^3T_2$ forms) and **11b–d** (all in the $^3T_2$ conformation) were established by analysis of their 500-MHz ^{1}H-n.m.r. spectra; see Table I for the assignments of all signals. As the C-4 configuration (D-*erythro*) of **11a–d** is maintained during the transformation from **8a,b**, careful analysis of the δ values of H-4 and H-1 in combination with the $J_{3,4}$, $J_{4,P}$, $J_{1,P}$, and $J_{1,4}$ values, as well as the relative magnitudes of $J_{2,P}$ and $J_{3,P}$, leads to establishment of the orientation of the ring P=O group, the anomeric orientation of C-1, and the favored conformations of the furanoid ring of **11a–d**. The specific n.m.r. parameters for the four diastereoisomers of **11** were obtained notably by the effective use of the $J_{1,4}$ long-range coupling constants, despite the frequently encountered difficulty[3] in determining the exact configurations of compounds of the 4-deoxy-4-methoxyphosphinyl type, in comparison with their 4-alkyl- or 4-arylphosphinyl congeners.

The present work thus demonstrates an effective way for preparation and structural analysis of 2,4-dideoxy-4-hydroxyphosphinyl-D-*erythro*-pentofuranoses.

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