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A FACILE ROUTE TO METHYLENEPHOSPHONATE SUGARS SUBSTITUTED AT THE ANOMERIC CARBON

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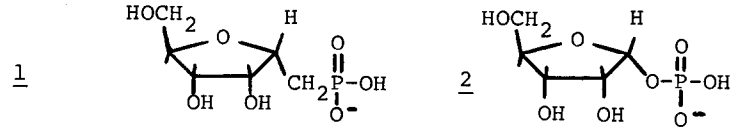
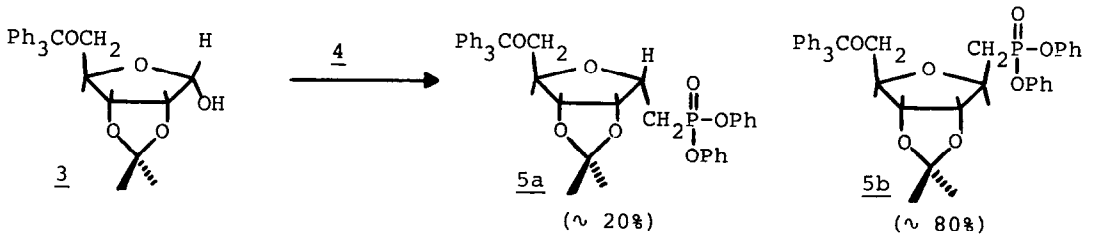
Abstract: A single-step approach to the synthesis of aldose sugar phosphonates substituted at C-1, the anomeric carbon, is demonstrated through the example of the isosteric methylene analog of α-D-ribose-1-phosphate.

Phosphonate analogs of several classes of biological compounds have been the object of significant efforts in synthetic chemistry and enzymology.[1,2] Sugar phosphonates substituted at the C-5 or C-6 position can be readily synthesized,[3,4] but the placement of a methylenephosphonate moiety onto the anomeric carbon (C-1 in aldoses or C-2 in ketoses) is a much more difficult synthetic problem. For example, Chmielewski et al. recently reported a six-step synthesis which led to a protected analog of galactose-1-phosphate although the free phosphonate was not described.[5] Such analogs are of particular biochemical interest since the scissile C-O bond would be replaced with a non-hydrolyzable C-C bond and enzymatic glucosyl- or ribosyl-group transfer (as examples) would be prevented. Likely candidates include analogs of α-D-galactose-1-phosphate (already attempted[5]), α-D-glucose-1-phosphate[5], α-D-ribose-1-phosphate and its derivative 5-phosphoribosyl-1-pyrophosphate. In this communication I illustrate a one-step approach to such compounds by describing the synthesis of 1 the isosteric methylene analog of 2, α-D-ribose-1-phosphate:

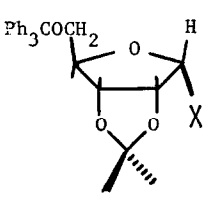


The protected ribose 5-trityl-2,3-isopropylidene-D-ribose[6] (3) is reacted with the stabilized ylid diphenyl triphenylphosphoranylidenemethylphosphonate[7] (4) to yield[8] both the α and β "anomers" (epimers) of 5:



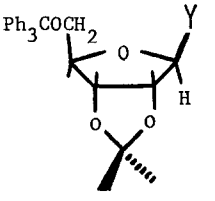
The products, 5a (R_f=0.34)[9] and 5b (R_f=0.25)[9], and the starting material 3 (R_f=0.57)[9] were separated by silica gel chromatography using petroleum ether/ethyl acetate (4/1) as solvent; the products are named using the nomenclature of Ohrui et al.[10]: diphenyl D-altro-2,5-anhydro-3,4-isopropylidene-6-trityl-deoxyhexanophosphonate (5a), and diphenyl D-allo-2,5-anhydro-3,4-isopropylidene-6-trityl-deoxyhexanophosphonate (5b). This reaction is analogous to that described by Ohrui et al.[10] for the syntheses of precursors to C-glycosidic nucleosides, and applies the ylid described by Jones et al.[7] for the synthesis of phosphono sugars[3,4] and nucleotides at the C-6 or C-5 positions of the sugar moiety.[11] As predicted by the analogous results of Ohrui et al.[10] the intermediate olefin undergoes a spontaneous Michael-type addition to reclose the sugar ring at the newly-formed "anomeric" carbon; this ring-closure is evidenced by a lack of vinyl protons and a predictable double doublet in the ^{1}H-NMR for the C-1 protons of 5b.[12]

The assignments of absolute configuration to the two epimers 5a and 5b were made from a detailed comparison of the ^{1}H- and ^{13}C-NMR data for 5a, 5b and a series of three pairs of closely related altro and allo "anomers" described by Ohrui et al.[10] (6a,6b,7a,7b,8a,8b); their assignments were based on an exact correlation to the structure (as determined by x-ray crystallography) of one isomer.[10] As reported by Ohrui et al.[10] and seen in Table 1, the methyl and ketal carbons of the isopropylidene groups show significant downfield shifts for the α (altro) isomers (5a,6a, 7a,8a) compared to the shifts of the β (allo) isomers (5b,6b,7b,8b). Also, the anomeric carbon shows an upfield shift for all of the altro compounds ($\Delta\delta$=2.6±0.3 ppm) consistent with the data of Ohrui et al.[10] The ^{1}H-NMR downfield shifts for the C-2, C-3, and C-4 protons are greater for the altro isomers (5a etc.) than for the allo isomers, and the value of $\Delta\delta$ for the two isopropylidene methyls is significantly greater for 5b (allo) as is true for 6b, 7b, and 8b (Table 2). Similar compounds described by Secrist[13] yield NMR data which are in agreement with these assignments.



altro (α)

6a,X = $-CH_2CN$ = Y,6b
7a,X = $-CH_2C(O)Me$ = Y,7b
8a,X = $-CH[C(O)OEt]_2$ = Y,8b



allo (β)

Two other observations are consistent with the configurational assignments for 5a and 5b. First, the altro ("α") isomer is less polar than the allo isomer in agreement with Ohrui et al.[10] Second, the allo isomer (5b) was found to be the kinetic product,[14] also in agreement with Ohrui et al.[10] It should be noted that for the compounds described, the only NMR data that do not correlate exactly with the assignments made by Ohrui et al.[10] are that the C-1 protons of 5a are equivalent and 5b non-equivalent (see Table 2).

The altro isomer (5a) has been readily hydrolyzed[15] to yield D-altro-2,5-anhydro-deoxyhexanophosphonate(1). This compound is a non-metabolizable isosteric[1] analog of α-D-ribose-1-phosphate (2), a substrate for the various nucleoside phosphorylases that catalyze the synthesis

of nucleosides using pyrimidine or purine bases. Studies of the ability of 1 to inhibit nucleoside phosphorylases are in progress and will be described elsewhere. In addition, 1 is a precursor to various analogs of PRPP, which is a key metabolite in the de novo and "salvage" biosynthetic pathways to nucleotides.[16] The syntheses and enzymatic studies of such analogs are also now in progress.

Table 1. Comparison of ^{13}C - NMR data[a] for 5a, 5b and Related Compounds

	Chemical Shift (downfield from TMS)			
Compound	Me(1)[b]	Me(2)[b]	ketal[c]	epimeric C
5a	25.06	26.27	112.47	76.76[f]
6a[d]	24.90	26.14	113.23	77.76
7a[d]	25.19	26.33	112.58	78.25
8a[d]	25.00	26.24	112.61	80.27
altro, $\bar{x}\pm\sigma$[e]	25.04±0.12	26.24±0.08	112.72±0.34	-
5b	25.70	27.53	114.46	79.64[f]
6b[d]	25.55	27.44	114.89	79.97
7b[d]	25.75	27.63	114.37	81.08
8b[d]	25.68	27.57	114.21	82.74
allo, $\bar{x}\pm\sigma$[e]	25.67±0.09	27.54±0.08	114.48±0.29	-

[a]obtained using a Bruker WM250 spectrometer at 62.89 MHz, [b]isopropylidene methyl groups, [c]isopropylidene ketal carbon, [d]data from Ohrui et al.[10], [e]mean ± standard deviation for compounds 5 - 8, [f]approximate center of peaks split by nearby ^{31}P.

Table 2. Comparison of ^{1}H-NMR data[a] for 5a, 5b, and Related Compounds

Compound	$C(1)H_a$	$C(1)H_b$	C(2)H	C(3)H	C(4)H	Methyls($\Delta\delta$)[b]
5a	2.65(ddd)	2.58(ddd)	4.81(m)[c]	4.86(m)[c]	4.74(d)	0.16
5b	2.51(dd)		4.45(m)	4.61-4.66(m)[c]		0.21
6a[d]	2.67(d)		4.50(dt)	4.79(dd)	4.71(d)	0.17
6b[d]	2.58(dd)	2.77(dd)	4.12(m)	4.50(dd)	4.65(dd)	0.19
7a[d]	2.75(d)		4.61(dt)	4.82(dd)	4.68(d)	0.17
7b[d]	2.62(dd)	2.78(dd)	4.31(dt)	4.63(dd)	4.55(dd)	0.20
8a[d]	4.29(d)	-	5.27(dd)	5.08(dd)	4.43(dd)	0.19
8b[d]	~ 4.0	-	4.84(dd)	4.98(dd)	4.68(dd)	0.20

[a]obtained using a Bruker WM250 spectrometer at 250.13 MHz, [b]$\Delta\delta$ for the two isopropylidene methyls, [c]tightly coupled AB system, [d]data from Ohrui et al.[10] (for the sake of comparison the C(2) of these compounds is the epimeric carbon).

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8. Compound 3 was heated with 2 equivalents of 4 in acetonitrile at reflux for 40 hours. The product was dissolved in petroleum ether/ethyl acetate and chromatographed on silica gel.

9. TLC on silica gel, solvent: petroleum ether/ethyl acetate (4/1).

10. H. Ohrui, G.H. Jones, J.G. Moffatt, M.L. Maddox, A.T. Christensen, and S.K. Byram (1975) J. Am. Chem. Soc. 97, 4602.

11. G.H. Jones and J.G. Moffatt (1968) J. Am. Chem. Soc., 90, 5337.

12. The quartet is centered at 2.51 ppm with the following coupling constants: $-P-CH_2-$, 19 Hz; CH_2-CH(anomeric), 6.5 Hz. These protons are non-equivalent in 5a (see Table 2).

13. J.A. Secrist (1978) J. Org. Chem. 43, 2925.

14. This was determined by ending a reaction after about 50% completion (18 hr.); the ratio of 5b/5a was about 4, consistent with the prediction of Ohrui et al.[10] As predicted, 5b was converted to 5a (thermodynamically favored) in the presence of anhydrous base (PhO^-).

15. The compound was treated with glacial acetic acid containing 7% 12 M HCl for one hour at 22°. The neutralized solution was chromatographed on DEAE-cellulose (0 to 0.5 M gradient of triethylammonium bicarbonate). Three fractions were recovered: the diphenyl ester of 1 (about 40%), the monophenyl ester of 1 (about 5%), and 1 (about 55%). The ^1H-NMR of 1 was satisfactory.

16. A. Kornberg (1980) "DNA Replication," Chapter 2, W.H. Freeman, San Francisco.

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