Regio- and Stereoselective Synthesis of Glycosyl Phosphinic Acids

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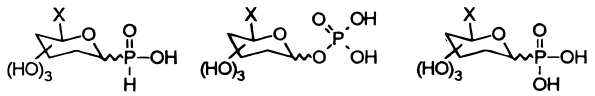
Glycosyl phosphinic acids **1** are glycose derivatives carrying a phosphonyl group at the anomeric center. These nonisosteric phosphinate analogues of the naturally occurring glycosyl phosphates **2** are not known.



1 **2** **3**

X = H or CH_2OH

During attempts to prepare the analogs by 1,6-anhydroglycose ring opening with phosphinic acid, Nifant'ev et al.[1] obtained glycose 6-deoxy-6-phosphinic acids. Glycosylphosphinic acids **1** can be readily oxydized to glycosyl phosphonates **3**, the latter being accessible only by elaborate protective group manipulations.[2,3] Sugar phosphinic and phosphonic acids **1** and **3** are resistant to enzymes involved in glycosyl group transfer from/to phosphates, thus providing mechanistic possibilities for metabolic regulations.[4]

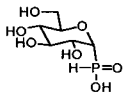
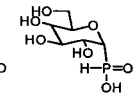
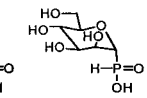
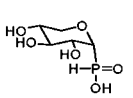
We report herein a convenient and high yielding regio- and stereoselective synthesis of glycosylphosphinic acids, based on the reaction of phosphinic acid with unprotected glycoses in the presence of propylene oxide as a condensation agent. The scope of the reaction was demonstrated for glucose, galactose, mannose, and xylose as glycosyl donors.

Glycosyl phosphinic acids **1** were prepared by reacting equimolar amounts (0.02 mol) of crystalline phosphinic acid, glycose, and propylene oxide in dried dioxane (20 mL). After being stirred at 40−60 °C for 1 h, the reaction mixture was evaporated to dryness. The residue was dissolved in water and chromatographed first on a column (1 × 30 cm) of Dowex 1W-8X(OH^-) with 0.02 M NaCl and then on a column (1 × 30 cm) of Dowex 50W-8X(H^+) with water to give pure product. Physical characteristics for these new glycosyl derivatives are shown in Table 1.

Assignments of the structures and configurations at the anomeric centers of the isolated products were based on their spectroscopic and chemical properties. In both ^1H and ^{31}P NMR spectra, a doublet with J ca. 540 Hz is characteristic of the PH proton in nonionized alkylphosphonic acids.[5,6] This doublet seen in the ^1H spectrum of each isolated product (Table 1) disappears upon addition of I_2, indicating oxidation of the compounds to glycosylphosphonic acids. The products are anomerically pure as evidenced by a single PH doublet. Assignment of the anomeric configuration was based on the known spectral properties of α- and β-D-glycopyranosylphosphonic acids.[2] A dd signal for the geminal (anomeric) and a ddd signal for the vicinal (H-C(2)) protons (Table 1) are diagnostic for α-anomers. Another indication comes from $^3J_{2P}$ values (Table 1), suggesting an appropriate H−C2−C1−P torsion angle. The presumed structure is also consistent with the chemical properties of the products. In marked contrast to the instability of alkyl phosphinates,[7] they were stable throughout the purification procedures by ion-exchange chromatography and were easily oxidized by I_2 to dibasic P-containing acids.

When phosphinic acid was reacted in dioxane with propylene oxide in the absence of a hydroxy compound, the ^{31}P NMR spectrum of the reaction mixture contained a triplet signal at 18.8 ppm and J_{PH} = 581 Hz, $^3J_{POCH}$ = 10 Hz.[8] These values are characteristic of alkyl phosphinates and have been used by Gallagher and Honegger[7] to demonstrate the rapid transesterification that phosphinates undergo with alcohols even at room temperature. This suggests that, in the presence of a glycose, the initially formed β-hydroxypropyl phosphinate **4** rapidly reacts with the anomeric hydroxyl group to give glycosyl phosphinate **6** instead of isomerizing to β-hydroxypropyl phosphinic acid **5**. The phosphinate exchange reaction **4** ⇌ **6** is additionally accelerated by the

Table 1. Physical Data and Chemical Yields of the Glycopyranosyl Phosphinic Acids[a]

Parameter	Phosphinic Acid			
				
	α-D-Gluco	α-D-Galacto	α-D-Manno	α-D-Xylo
^1H-NMR[b]				
$\delta_{H1\alpha}$	4.07 (dd)	4.15 (dd)	4.01 (dd)	4.04 (m)
J_{12}	3.9	3.50	1.67	
J_{1P}	17.8	15.9	18.30	
δ_{H2}	3.61 (ddd)	3.59 (ddd)	3.83 (ddd)	3.69 (ddd)
J_{21}	3.9	3.50	1.67	3.51
J_{23}	8.3	11.52	9.17	13.74
$^3J_{2P}$	29.0	26.39	3.33	36.72
δ_{H5}	3.7 (m)	3.66 (m)	3.65 (dd)	3.66 (m)[c]
J_{45}			12.5	
$J_{56a}=J_{56b}$			6.78	
δ_{HP}	7.05 (d)	7.06 (d)	7.05 (d)	7.07 (d)
J_{PH}	538.6	543.7	544.9	532.6
Acid number[d]	246/238	246/244	246/242	283/286
R_f[e]	0.20	0.18	0.20	0.19
P(%)[d]	13.6/13.52	13.6/13.85	13.6/13.49	15.7/15.54
Yield(%)	85	89	80	85

[a] Purified product. [b] Selected signals; measured in D_2O at 250 MHz on a Bruker WM-250 spectrometer; δ (ppm), J_{ij} (MHz). [c] Two protons. [d] Neutralization equivalent, calcd/found. [e] Silica gel plates, nBuOH/MeOH 1:4 (v/v) system.

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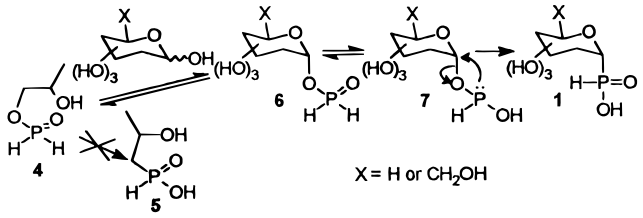
anchimeric assistance of the vicinal hydroxy group in **4**. The mechanism of this reaction is obscure[7] but probably congruent to the mechanism of the transesterification reaction, catalyzed by ribozyme (group I intron).[9,10]



Alkyl phosphinates like **6** are thermally unstable[7] and are easily alkylated on phosphorus by carbonium ions.[5,11] This reactivity is attributed to the enhanced nucleophilicity of phosphorus on its trivalent tautomer in **7**, the equilibrium **6** ⇌ **7** being rapidly attained under acidic conditions.[5] An intramolecular attack by the phosphorus nucleophile on the anomeric center in **7** would result in the formation of the glycosylphosphinic acids **1** with retention of the configuration. Such a $D_N + D + A_N$ or S_Ni rearrangement has been proposed for alkynyl[12] and alkyl phosphinates.[8] It has not been proved experimentally, however. Thus, the regio- and stereoselective synthesis of glycosylphosphinic acids reported here could be explained by the S_Ni rearrangement **7** ⇌ **1** provided the phosphinate exchange reaction **4** ⇌ **6** is regio- and stereoselective as expected since electronegative substituents at the anomeric center like the phosphonoxy group in **6** prefer the axial configuration due to the thermodynamic anomeric effect.[13]

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Supporting Information Available: Procedures and characterization data (2 pages).

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