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SYNTHESIS OF CARBOHYDRATE PHOSTONES AS POTENTIAL GLYCOMIMETICS

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Abstract: A series of stereoisomeric monosaccharide δ-phostones (cyclic phosphonate esters) were prepared and their structures were confirmed by single crystal X-ray analysis. Esterification of the D-*gluco* phostonic acid with appropriate sugar alcohols gave the first 1→6 and 1→4 disaccharide glycomimetics with phosphorus at the anomeric carbon of the non-reducing unit. Their structures and configuration at phosphorus were established by X-ray analysis.

In spite of a long-standing interest in the synthesis[1] and biological activity[2] of carbohydrates containing a hetero-atom in the ring instead of oxygen,[3] relatively little is known of analogs in which the anomeric carbon atom has been modified. A logical choice would involve a pentacovalent phosphorus atom which would correspond to a cyclic phosphonate (2-alkoxy-1,2λ^5-oxaphosphorinan-2-one, or a "phosphone").[4,5] Thiem[6] and Wroblewski[7] have described the synthesis of pyranose, and furanose phostones respectively using the Abramov-reaction[8] under mildly basic conditions. Phostone analogs of KDO have also been reported.[9] Very recently, Darrow and Drueckhammer[10] reported the preparation of cyclic phosphonate analogs of D-glucopyranose and D-mannopyranose via an acid-catalyzed Abramov reaction. These products were characterized by detailed ^{1}H and ^{31}P NMR studies. Analogs of simple cyclic phosphonates have shown different biological profiles compared to corresponding lactones.[11]

We describe herein our studies on the synthesis and characterization of a number of monosaccharide and disaccharide phostones. Unequivocal structural and stereochemical assignments have been secured from single crystal X-ray analysis of several phostone analogs.

As in the preceding reports,[6,7] we relied on the Abramov reaction[8] to prepare the isomeric monosaccharide phostones from the appropriate pentose derivatives. Thus, treatment of 2,3,5-tri-O-benzyl-D-arabinose **1**, with dibenzylphosphite in the presence of DBU in toluene gave a mixture of four compounds **2-4** in a ratio of 3:1:1:0.5 respectively [12] (Scheme 1). These were separated by silica gel column chromatography to afford the α-D-*gluco* **2**, β-D-*gluco* **3**, β-D-*manno* **4**, and α-D-*manno* **5** phostone isomers several of which were crystalline products suitable for X-ray analysis. The X-ray crystal structures of **3** and **5** are shown in Scheme 1.

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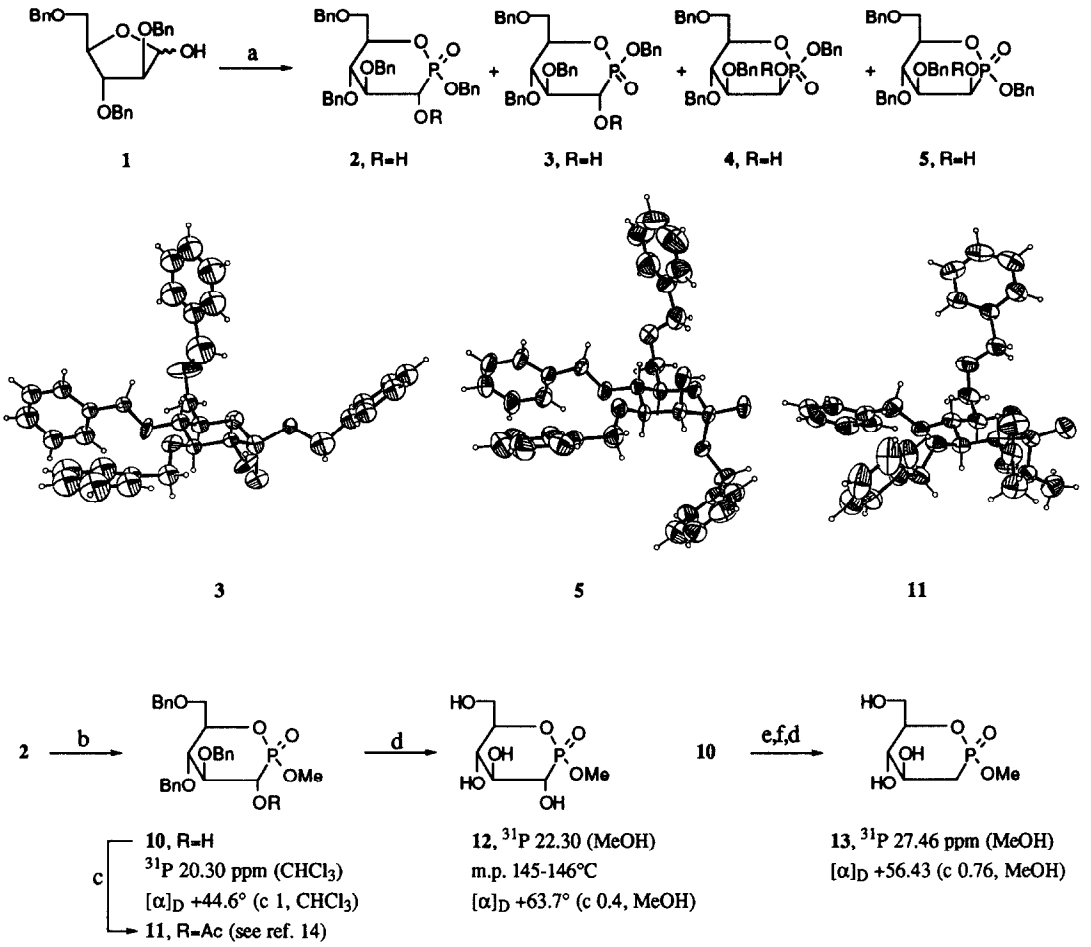
Scheme 1



a) $HPO(OBn)_2$, DBU, toluene, 20 h, 78%; b) MeONa/MeOH, 7h, 64%; c) Ac_2O,Et_3N, DMAP, CH_2Cl_2, 96%; d) $Pd(OH)_2/C$, H_2, THF; e) Cl-CSO-Ph, DMAP, CH_3CN, 30min., 62%; f) n-Bu_3Sn, AIBN, toluene, 2h,76%.

Acetylation of the original mixture offered an alternative method for the separation of the isomers, and a structural assignment to the α-D-*gluco* isomer **6** by X-ray crystallography. The acetate esters could be selectively cleaved to give the parent phostones **2-4** by treatment with KCN[13] in THF/EtOH. Thus, all four possible C-1 isomeric phostone benzyl esters could be isolated and characterized as the C-1 hydroxy derivative or the corresponding acetate.

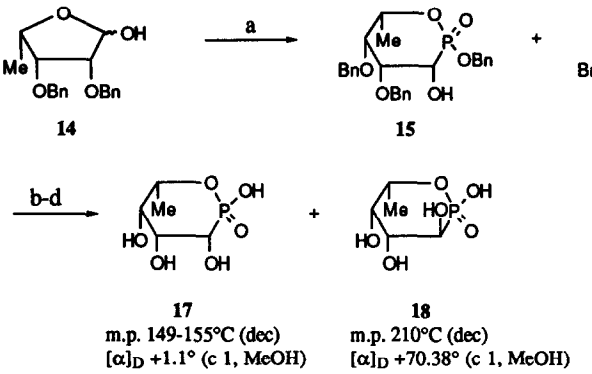
Utilizing dimethylphosphite in the Abramov reaction also gave the four possible isomers corresponding to **2-4**, which could be separated chromatographically as such or as the corresponding acetates. The X-ray crystal structure of the acetylated α-D-*gluco* analog **11** is shown in Scheme 1.[14] It was also possible to effect a transesterification reaction from the individual benzyl esters **2-4** with the formation of phostone methyl esters.

Thus, treatment of **2** with sodium methoxide gave the α-methyl phostone derivative **10** as the major product (α/β:75/25) which is separated from the minor β-isomer by chromatography. Catalytic debenzylation of **10** gave the α-methyl phostone **12** as a crystalline solid. It is noteworthy that **12** and its β-isomer were previously obtained as an inseparable mixture.[10]

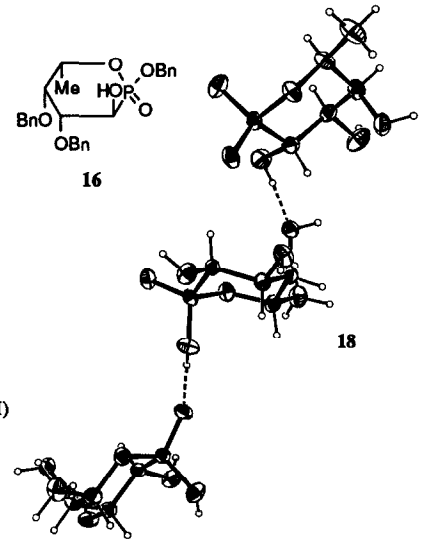
Having had access to **10** (and its β-isomer) either directly from an Abramov reaction, or via transesterification, it was of interest to obtain the corresponding C-1 deoxy phostone. Thus, **10** was transformed into the corresponding phenoxythiocarbonate derivative which was subjected to radical-mediated deoxygenation.[15] The resulting C-1 deoxy compound was catalytically debenzylated to give the α-methyl 1-deoxy phostone **13** (Scheme 1).

An alternative route to the methyl and benzyl phostones shown in Scheme 1, involved treatment of 4-O-t-butyldimethylsilyl 2,3,5-tri-O-benzyl-*aldehydo*-D-arabinose with either dibenzyl or dimethylphosphite under base- catalyzed conditions. The acyclic diastereomeric products which were separable by chromatography, were individually converted to the corresponding benzyl phostones (ex. **2-4** and their methyl analogs) by removal of the silyl protective group followed by base catalyzed closure. A recent report[10] described the acid-catalyzed addition of dimethylphosphite on a 4-formate ester related to the above mentioned acyclic sugar derivative.

Scheme 2



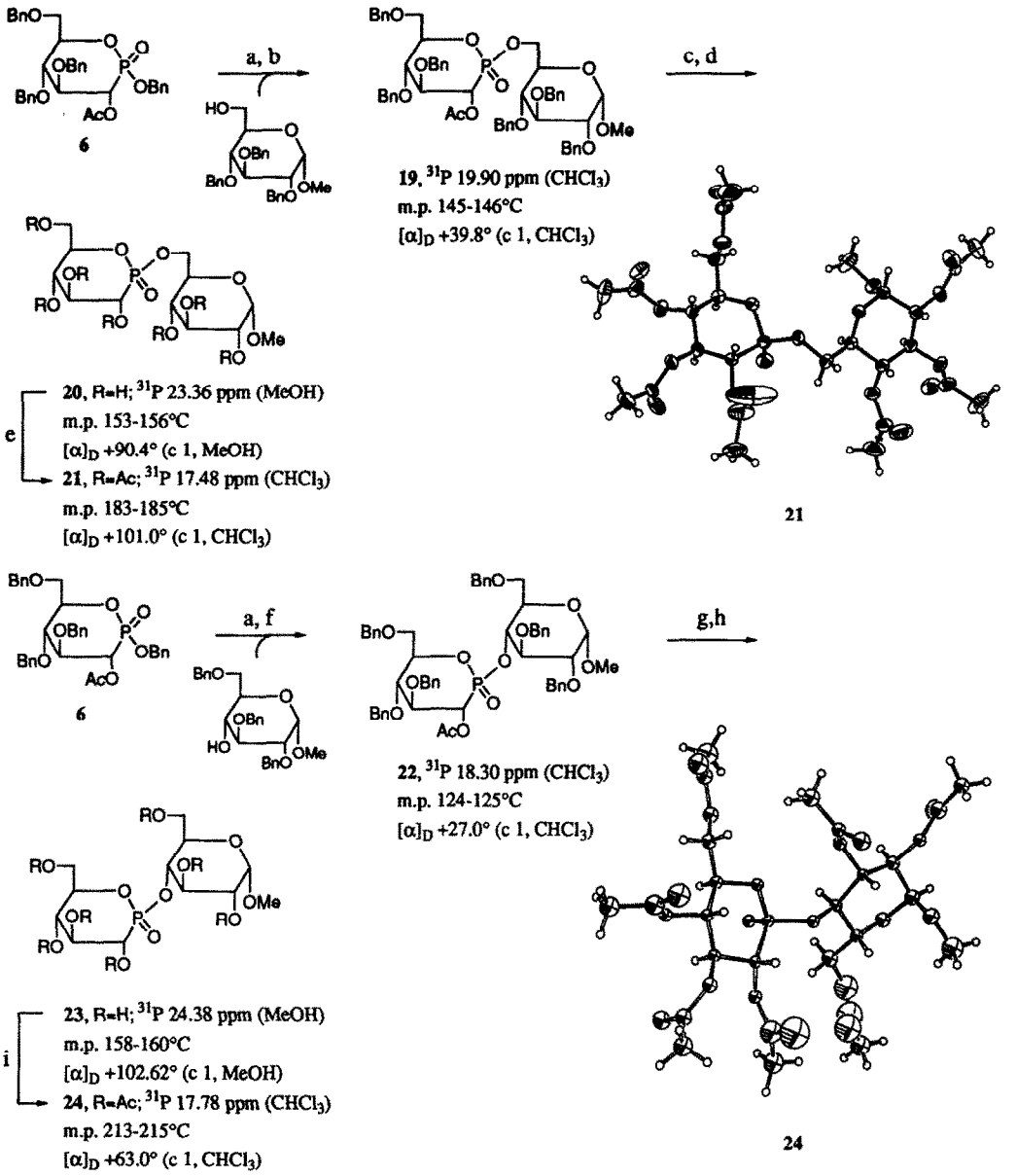
a) $HPO(OBn)_2$, toluene, DBU; b) Ac_2O, pyr.;
c) KCN, EtOH, THF; d) Pd/C, H_2.



Applying the Abramov reaction to 5-deoxy-2,3-di-O-benzyl-L-lyxose **14** led to the formation and isolation of the L-*talo* **15** and L-*fuco* **16** phostones in a 15:1 ratio after separation of the corresponding acetate esters by preparative HPLC (Scheme 2). The corresponding methyl phostones were formed in a 4:1 ratio. Treatment with potassium cyanide followed by catalytic debenzylation gave the free phostones **17** and **18**. The structure of the L-*fuco* analog **18** was established by X-ray crystallographic analysis. Interestingly, a H-bond was found to link the P-hydroxyl group of one L-*fuco* phostone unit to the P=O group of another (Scheme 2).

Utilizing the same protocol, the α-methyl 2,3,5-tri-O-benzyl-D-*galacto*-phostone and the corresponding D-*talo* derivatives were prepared from 2,3,5-tri-O-benzyl-D-lyxose, further showing the generality of the reaction.[16]

Scheme 3



a) Me_3SiBr, THF, 6 h, 90%; b) BOP, DIEA, CH_2Cl_2, 12 h, 60%, β/α: 88/12; c) MeONa/MeOH, 0°C, 4 h, 75%; d) H_2, $Pd(OH)_2/C$, THF, 4 h, 95%; e) Ac_2O, Et_3N, DMAP, DMF, 1 h, 95%; f) BOP, DIEA, CH_2Cl_2, 12 h, 54%; g) MeONa/MeOH, 0°C, 8 h, 85%; h) H_2, $Pd(OH)_2/C$, THF, 3 h, 89%; i) Ac_2O, $BF_3.Et_2O$, 30 min., 94%.

In view of the unique nature of these molecules with regard to the presence of a pentacovalent phosphorus atom at the anomeric center, and the potential for a number of biological applications,[17] we deemed it necessary to extend our methodology to include disaccharide formation with the D-*gluco* phostones as illustrated in Scheme 3.

Thus, treatment of **6** with TMSiBr in THF produced an anomeric mixture of phostonic acids which were esterified with appropriate alcohols in the presence of BOP.[18] The 1→6-linked phostone disaccharide **19** was obtained as the major component in an 88:12 mixture of isomers. Crystallographic separation, debenzylation and acetylation gave a crystalline product **21** (Scheme 3). The structure and β-1→6 anomeric configuration of **21**, hence of **20**, was established by single crystal X-ray crystallography.

The β-1→4 phostone disaccharide **22** was obtained as a major product from the esterification of **6** in the presence of BOP. Deacetylation, catalytic debenzylation, and reacetylation gave a crystalline product which was assigned the structure **24**, by single crystal X-ray analysis (Scheme 3). All the δ-phostone rings reported in this study, adopt a chair-like conformation.[19] It is also of interest that pseudo-axial and pseudo-equatorial P=O groups are encountered in the X-ray structures of the monosaccharide phostones **2-4** and their analogs, which offers an opportunity to study the individual stereoelectronic properties[20] of the deprotected analogs as well as their biological effects.

The above described phostones and their configurationally defined α- and β-ester analogs are interesting candidates for evaluation as substrates for a variety of enzymatic reactions implicating carbohydrate substrates in general, and the anomeric carbon in particular, such as glycosyl transferases, glycosidases, oxidases and kinases.[21]

Extensions of these observations, as well as results pertaining to enzymatic reactions, will be reported in due course. It is also noteworthy that these unusual carbohydrate phostones can be interesting substrates for the generation of new types of catalytic antibodies,[22] as glycomimetics,[23] and other carbohydrate-based therapeutic applications.[24,25]

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methoxy-1,2λ^5-oxaphosphorinan-2-one. The α- and β-designations refer to (2*R*)- and (2*S*)-configurations at phosphorus in analogy to the corresponding α- and β-D-glycosides.

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