Cyclic Phosphonate Analogs of Hexopyranoses

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Acyclic and cyclic analogs of D-glucopyranose and D-mannopyranose have been prepared in which the anomeric carbon has been replaced with a phosphorus. Base-catalyzed addition of dimethyl phosphite to di-*O*-isopropylidene-D-arabinose followed by recrystallization yields only the acyclic *gluco*-isomer, through what appears to be a selective recrystallization process. The use of diethyl phosphite under similar conditions yielded only the acyclic *manno*-isomer. The stereochemistry of each was ascertained through comparison of the pentaacetylated derivatives **11** and **12**. For the cyclic analogs **1** and **2**, synthesis consists of acid-catalyzed trimethyl phosphite addition to the carbonyl of a hydroxyl-protected open-chain D-arabinose derivative, removal of a formate ester from the 4-hydroxyl group, and base-catalyzed transesterification/cyclization. All four possible cyclic α-hydroxy phosphonate diastereomers were synthesized in roughly equal amounts. Complete separation of the *gluco*- and *manno*-isomers was accomplished, and Homonuclear two-dimensional *J*-spectroscopy was used to supplement standard NMR analysis in order to completely characterize the isolated diastereomers **21** and **22** and assign *gluco*- and *manno*-stereochemistry, respectively.

Introduction

Carbohydrates are a ubiquitous class of biomolecules, with a great array of diversity, both in structure and biological function. The functions of carbohydrates include their roles as energy-rich metabolites and storage compounds, as structural components of a large number of natural products, and as cellular recognition and intercellular communication elements.[1] Analogs of the natural and common sugars have the potential to modify many biological events. As a result, sugar analogs are recognized as having a variety of possible medical applications including the treatment of obesity[2] and diabetes[3] and use as antiviral,[4] antibiotic,[5] and antitumor[6] agents.

Most of the chemical and enzymatic reactions of sugars involve the anomeric carbon. Thus, sugar analogs modified in the structure and reactivity of the anomeric carbon are of special interest. Probably the largest group of known sugar analogs are those that mimic the half-chair conformation and/or positive charge character of the glycosyl cation, a proposed high-energy intermediate in many if not all glycosidase and glycosyl transfer reactions.[5,7,8] Many of these compounds are natural products or components of natural products and act as inhibitors of glycosidase and glycosyltransferase enzymes. Interest in another class of sugar analogs, the C-glycosides,[9-11] has also grown, in part from studies of natural products containing C-glycosidic linkages. Several carbon-linked disaccharide and trisaccharide analogs have been synthesized and the conformational properties of these compounds studied in some detail.[9]

Sugar analogs containing phosphorus have received continued attention in the literature. Several cyclic sugar analogs were prepared in which a phosphorus atom replaces the ring oxygen.[12] A few hydroxyl-protected acyclic sugar analogs containing a phosphorus atom in place of the carbonyl carbon have been prepared.[13-15] A number of five-membered ring cyclic phosphonates with phosphorus in place of the anomeric carbon are reported in the literature,[16-18] although, with the exception of a few hydroxylated compounds, most bear little similarity to sugars. A six-membered ring phosphonate analog of a seven-carbon sugar with phosphorus in the "anomeric" position has also been reported, albeit in protected form.[19,20] Unlike the glycosyl cation mimics and C-glycosides, these compounds appear to have no precedence in natural systems.

There is substantial precedence for synthesis of phosphonate analogs of biological compounds, especially phosphonate analogs of amides and esters, which have received much attention as inhibitors of enzymes that catalyze the

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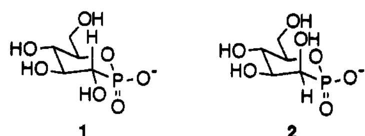
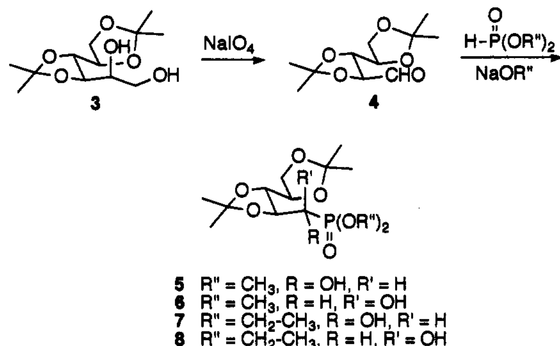


Figure 1. Cyclic α-hydroxy phosphonate glucose analog 1 and mannose analog 2.

Scheme 1



hydrolysis of amide and ester bonds,[21,22] and phosphonate isosteres of natural phosphate esters.[23,24] However, general methods have not been developed for the synthesis of cyclic phosphonate analogs of biologically important sugars, and these compounds have not been explored for potentially interesting biological characteristics. We are interested in studying the chemistry and biological properties of cyclic phosphonate analogs of some of the common sugars. We report here an efficient synthesis of the cyclic phosphonate glucose analog 1 and the corresponding mannose analog 2 (Figure 1) both having phosphorus in place of the anomeric carbon atom.

Results

Dialkyl Phosphite Additions to Di-*O*-isopropylidene-D-arabinose. Initial attempts at synthesis of 1 and 2 began with di-*O*-isopropylidene-D-arabinose (4), prepared by oxidative cleavage of 1,2:3,4-di-*O*-isopropylidene-D-mannitol (3).[25,26] (Di-*O*-isopropylidene-D-mannitol was prepared by partial hydrolysis of the triisopropylidene species.)[27] Base-catalyzed addition of dimethyl phosphite and diethyl phosphite to 4 was performed as shown in Scheme 1. No stereoselective phosphite addition was observed with either the dimethyl or the diethyl phosphite; NMR analysis of the crude products, 5, 6 and 7, 8, showed the presence of nearly equal amounts of the two diastereomers in both reactions. However, recrystallization in each case gave predominantly only one of the two possible diastereomers. In order to determine the stereochemistry of the crystallized phosphonate products, derivatives were prepared by acid-catalyzed hydrolysis of the isopropylidene groups from each of the crystallized products (Scheme 2) to give 9 and 10, followed by acetylation to

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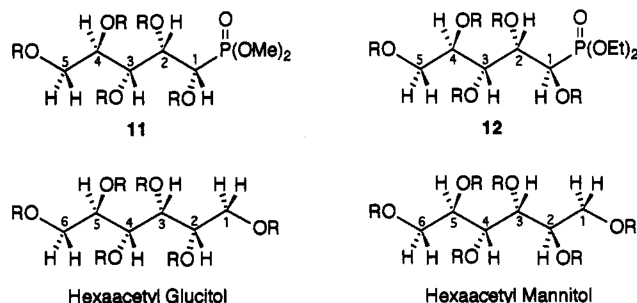


Figure 2. Structures for acetylated compounds 11 and 12 (R = Ac) shown in comparison with hexaacetylated glucitol and hexaacetylated mannitol (see ref 31b). Coupling constants are given in Table 1 according to the numbering scheme indicated for each compound and compared by relative position. Accordingly, the value of $J_{H\text{-}1/H\text{-}2}$ of compound 11 is compared with $J_{H\text{-}2/H\text{-}3}$ of hexaacetylglucitol.

Scheme 2

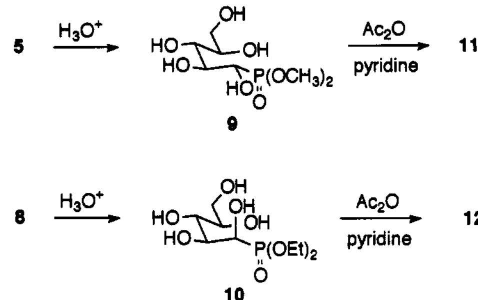


Table 1. Comparison of *J*-Values between Acetylated Acyclic Phosphonates 11 and 12 and Acetylated Glucitol and Mannitol

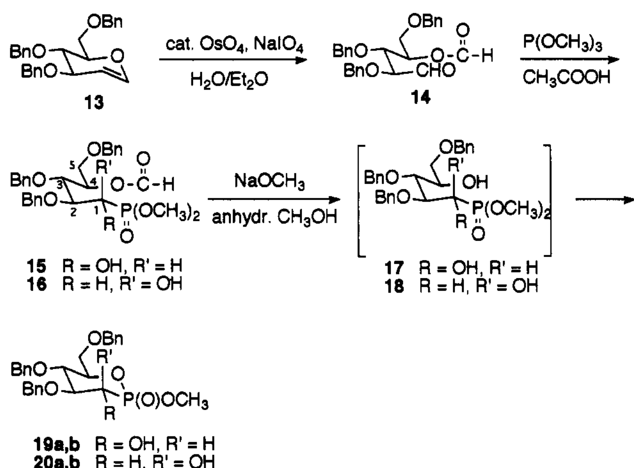
11	$J_{1,2}$ 5.6 Hz	$J_{2,3}$ 4.9	$J_{3,4}$ 6.0	$J_{4,5}$ 4.3	$J_{4,5'}$ 6.0
hexaacetyl-glucitol[a]	$J_{2,3}$ 6.4 Hz	$J_{3,4}$ 4.3	$J_{4,5}$ 6.8	$J_{5,6}$ 3.6	$J_{5,6'}$ 5.6
12	$J_{1,2}$ 10.1 Hz	$J_{2,3}$ 2.0	$J_{3,4}$ 9.1	$J_{4,5}$ 2.8	$J_{4,5'}$ 4.8
hexaacetyl-mannitol[a]	$J_{2,3}$ 9.0 Hz	$J_{3,4}$ 2.2	$J_{4,5}$ 9.0	$J_{5,6}$ 2.6	$J_{5,6'}$ 5.3

[a] See ref 31b.

give the pentaacetylated compounds 11 and 12. The large C-1/P coupling constants (approximately 160 Hz) found in the ^{13}C-NMR for 9 and 10 indicated that the phosphorus–carbon bond remained intact during the hydroxyl deprotection reaction. The stereochemistry of the crystallized products was determined by NMR analysis of the pentaacetyl derivatives 11 and 12, as shown in Figure 2. The coupling constants for the pentaacetylated compounds 11 and 12 were compared to those reported for hexaacetylglucitol and hexaacetylmannitol (Figure 2).[31d] 11 gave an H-1 to H-2 coupling constant of 5.6 Hz (Table 1), supporting assignment of the glucose (1*S*) configuration at C-1 while 12 gave an H-1 to H-2 coupling constant of 10.1 Hz, indicating the mannose (1*R*) configuration at C-1. As Table 1 indicates, the other coupling constants for 11 and 12 were also consistent with these assignments. Thus, by inference, the crystallized dimethyl phosphonate product 5 was determined to possess the glucose (*S*) configuration at C-1, while the crystallized diethyl phosphonate product 8 possessed the mannose (*R*) configuration.

Base-catalyzed cyclization of the fully deprotected phosphonate diesters 9 and 10 was attempted by reaction of 9 with sodium methoxide or triethylamine in methanol and reaction of 10 with sodium ethoxide or triethylamine in ethanol. In both cases, complex mixtures of products

Scheme 3



were obtained. Purification and analysis of individual products were not successful.

Synthesis of Protected Derivatives of 1 and 2 from Tri-*O*-benzyl-D-glucal. An alternate synthetic route to hydroxyl-protected derivatives of **1** and **2** was undertaken as shown in Scheme 3. Tri-*O*-benzyl-D-glucal (**13**) was reacted with $OsO_{4cat.}$/ $NaIO_4$ to oxidatively cleave the olefin, yielding the protected D-arabinose derivative **14**.[28] **14** was reacted with 1.5 equiv of trimethyl phosphite in glacial acetic acid at room temperature for 36 h to form a mixture of the glucose-like (**15**) and mannose-like (**16**) diastereomeric phosphonates. **15** and **16**, present in approximately a 1:1 ratio by NMR analysis, were separable on analytical reversed-phase HPLC but were not separated preparatively, as the elution times were too close for practical preparative resolution. The mixture of **15** and **16** was reacted with catalytic sodium methoxide in methanol for 4 h at room temperature to cleave the formate ester. The intermediate products **17** and **18** cyclized in situ to form the pyranose analogs **19** and **20**. (It was possible to isolate the mixture of acyclic 4-hydroxyl-deprotected products **17** and **18** by refluxing a solution of **15** and **16** in methanol for 48 h in the absence of base.) Reversed-phase HPLC analysis of the crude cyclization product showed four compounds present in nearly equal quantities, presumably due to the two epimers at phosphorus of both **19** and **20**.

Separation and Stereochemical Assignment of 19a,b and 20a,b. Reaction of the mixture of **19a,b** and **20a,b** with sodium iodide gave a mixture of only two products as indicated by reversed-phase HPLC. These two compounds, assigned the demethylated structures **21** and **22** (Scheme 4), were separated by preparative reverse phase HPLC. The isomer with the shorter retention time was assigned the mannose configuration **22** based on an H-1/H-2 coupling constant of 1.9 Hz, consistent with an H-1/H-2 equatorial–axial relationship. The longer retention time isomer was assigned the glucose configuration **21** based on an H-1/H-2 coupling constant of 10.2 Hz, consistent with an H-1/H-2 trans diaxial relationship. Important to this assignment was the use of "homonuclear two-dimensional *J*" value spectra (HOM2D*J*) to separate and identify the H-1/P coupling constant for **22** (10.94 Hz), the H-2/P constant for **22** (3.56 Hz), the H-1/P constant for **21** (10.20 Hz), and the H-2/P constant for **21** (1.40 Hz) from the proton–proton coupling constants for each compound.

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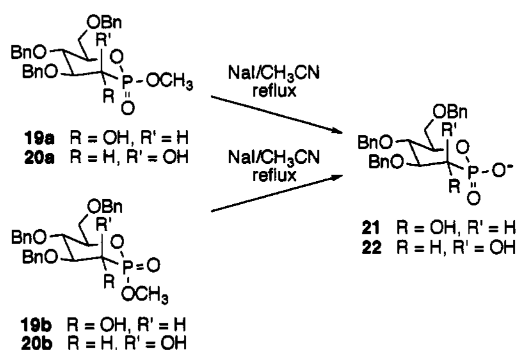
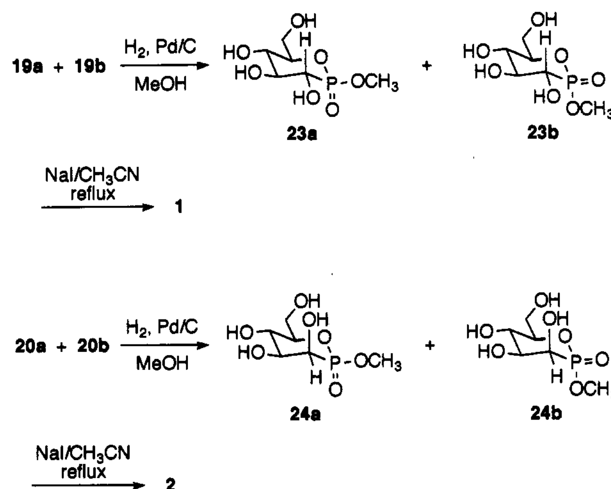
Scheme 4



Scheme 5



Chromatography of the mixture of cyclic products **19a,b** and **20a,b** on silica gel with ethyl acetate successfully separated the mixture into three fractions (bands A, B, and C; $R_{fA} = 0.50$, $R_{fB} = 0.45$, $R_{fC} = 0.40$). Band A contained two components of the original mixture as indicated by HPLC, while bands B and C each contained one component, which differed from each other as well as from the band A material, although complete resolution of band B was difficult. Upon demethylation using sodium iodide, band A gave a single product by HPLC and NMR which was identified as the glucose analog **21**. Reaction of each of the two lower R_f fractions, B and C, with sodium iodide gave a single identical product by HPLC, which differed by HPLC and NMR from the product of band A and was identified as the mannose analog **22**.

Deprotection of 19a,b and 20a,b. Debenzylation of **21** and **22** by catalytic hydrogenolysis was slow and gave a mixture of partially debenzylated products, even when the reaction proceeded over the course of 5–8 days at 4 atm pressure. The use of additional catalyst or varying reaction temperatures (20–40 °C), solvents (0–25% H_2O in methanol, 0–25% H_2O in ethanol), concentrations of reactants and catalyst, or catalyst type (10% Pd on C, 10% Pd on C Degussa type, PtO_2) improved neither rate nor yield of the reaction significantly. Debenzylation of the methyl phosphonates **19a,b** and **20a,b**, separated by chromatography on silica gel (band A and combined bands B and C, respectively) as described above, proceeded much more smoothly (Scheme 5). The debenzylated products **23** and **24** were each isolated as a mixture of isomers at phosphorus. Subsequent demethylation of **23** and **24** with sodium iodide in refluxing acetonitrile gave the target compounds **1** and **2**.

Discussion

α-Hydroxy phosphonates are readily prepared by base-catalyzed addition of a dialkyl phosphite to an aldehyde or ketone. While some furanose forms of hydroxyl-protected ribose[19] and mannose[20] compounds have been reacted with dialkyl phosphites to form α-hydroxy phosphonates, the yields reported are low.[29] We thus chose to utilize sugar derivatives locked in the open-chain form by hydroxyl protection in order to facilitate phosphite addition to the carbonyl carbon. In general, sugars may be protected in the open-chain form by dithioacetal formation at the carbonyl carbon, hydroxyl protection (*e.g.*, by isopropylidene formation), and dithioacetal cleavage.[30] However, in the case of arabinose, the precursor for the desired glucose and mannose analogs, the diisopropylidene-protected compound **4** was more easily prepared by oxidative carbon–carbon bond cleavage of 1,2:3,4-di-*O*-isopropylidenemannitol. Dimethyl and diethyl phosphite additions to **4** proceeded well, similar to previously published results for dialkyl phosphite additions to diisopropylidene-D-arabinose.[26] In both cases, crystallized product was obtained in 42–45% yield for the addition step.

Confirmation of the stereochemistry was accomplished through NMR analysis of the pentaacetate derivatives. It has been demonstrated previously that this technique can be used to assign relative stereochemistry in polyols and related compounds.[31] By this method, completely acetylated sugars predominantly exist in a zig–zag conformation, placing the protons attached to the backbone in a single preferred orientation relative to one another. A comparison of the structures of **11** and **12** and the hexaacetylated glucitol and mannitol derivatives is shown in Figure 2, and a comparison of the associated coupling constants is given in Table 1.[31d] Compound **11** gave an H-1 to H-2 coupling constant of 5.6 Hz, which is consistent with a *gauche* relationship between H-1 and H-2 and supports the glucose configuration assignment. The other vicinal proton coupling constants are also in good agreement between **11** and the glucitol derivative, supporting assignment of the glucose configuration at C-1 of the dimethyl phosphonate analog. The coupling constants for compound **12**, on the other hand, are very similar to those found for the pentaacetyl mannitol derivative. Most importantly, the 10.1-Hz coupling constant for H-1 to H-2 of **12** is consistent with an *anti* relationship akin to that found in the mannose configuration. The diethyl phosphonate compound was thus assigned the mannose configuration at C-1.

Other researchers have obtained selectively the (1*S*) phosphonate upon crystallization (in diethyl ether) of the crude dialkyl phosphonate product from the addition of phosphite to diisopropylidene-D-arabinose.[26] Our results agreed with this finding for the reaction of dimethyl phosphite with diisopropylidene-D-arabinose; the isolated product was found to be the glucose analog **5**. However, when diethyl phosphite was used, the opposite stereochemistry in the crystallized product was observed; the mannose analog **8** was isolated in pure form. This apparent inconsistency in the selectivity from the reported results led us to examine more closely the crude products. Analysis of the crude products from both reactions, before crystallization, indicated that in both cases the (1*R*) and (1*S*) addition products had been formed in roughly equal amounts. The isolation of almost pure isomers from the dialkyl phosphite addition reaction was in fact due to a selective crystallization process, rather than a stereoselective addition of the phosphite to the carbonyl. However, selective crystallization provided, conveniently and reproducibly, each of the two diastereomeric products in high purity. Subsequent recrystallization from diethyl ether gave products with no detectable amounts of the contaminating diastereomers.

Attempts at base-catalyzed cyclization reactions of the deprotected sugar analog phosphonate diesters **9** and **10** gave mixtures of unidentifiable products.[32] This is perhaps due to formation of five-, six-, and seven-membered rings as well as the two possible stereochemistries at phosphorus of the cyclic products. The highly polar nature of these hydroxyl-deprotected products and the complexities of the mixtures, with no predominant compounds evident, made purification difficult and unsuccessful. Although this synthetic route was successful for construction of acyclic phosphonate sugar analogs, an alternative route was chosen for the synthesis of the target hexopyranose analogs which would allow only six-membered ring formation and would facilitate chromatographic purification by leaving hydrophobic protecting groups intact until the final steps in the reaction sequence.

Most previous syntheses of cyclic α-hydroxy phosphonates have employed aldehydes or ketones having a β-hydroxyl group but no γ- or δ-hydroxyl.[16–18] These compounds thus cannot form five- or six-membered ring cyclic hemiacetals, so that the carbonyl group is free for phosphite addition. After phosphite addition to the carbonyl, the phosphonate γ-OH is induced to react at phosphorus to form a five-membered ring product. Synthesis of cyclic phosphonate analogs of most of the common sugars, including hexopyranose analogs, is more complex. For the synthesis of hexopyranose analogs from five-carbon aldose sugars, the 3-, 4-, and 5-hydroxyls of the substrate for phosphite addition need to be protected, since free 4- and 5-hydroxyls will form cyclic hemiacetals making the carbonyl resistant to phosphite addition while a free 3-hydroxyl is likely to result in five-membered ring cyclic phosphonate formation after phosphite addition to the carbonyl.

The protected arabinose derivative **14** was chosen as a practical synthon for synthesis of the target compounds. To our knowledge, **14** is not a previously known compound but was readily prepared from the commercially available tri-*O*-benzyl D-glucal **13** using standard conditions for oxidative cleavage of carbon–carbon double bonds.[28] Protection of all of the hydroxyl groups at this point maintains the compound in the open-chain aldehyde form. This permits efficient phosphite addition to the free aldehyde to form the key carbon–phosphorus bond. Furthermore, the 4-hydroxyl can subsequently be selec-

(29) Attempts to react arabinopyranose systems directly with dimethyl or diethyl phosphite failed; in all cases, we recovered primarily starting material.

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(32) After synthesis and characterization of glucose analogs **23a,b** and mannose analogs **24a,b**, the NMR data for the attempted base-catalyzed cyclization of materials **9** and **10** was reexamined for possible correlations. Compounds **23a,b**, as well as the corresponding ethyl ester analogs of **24a,b**, appear to be present in the mixtures resulting from the attempted cyclization of materials **9** and **10**, respectively, but are not the major products observed.

tively deprotected with base followed by cyclization to form specifically the desired six-membered ring products.

Previous addition of dialkyl phosphites to aldehydes have been achieved by base catalysis, with[13,14] and without an alcohol solvent.[26] However, under such conditions the formate ester of **14** was rapidly removed prior to phosphite addition, with the resulting alcohol forming a cyclic hemiacetal to which phosphite addition is inefficient. When this reaction with **14** was attempted, only the deformylated hemiacetal material was obtained. Acid-catalyzed phosphite addition was thus attempted, following the precedence of acid-catalyzed conjugate addition of a trialkyl phosphite to the β position of α,β-unsaturated carbonyl compounds.[33] This reaction was quite successful and to our knowledge, this is the first report of acid-catalyzed phosphite addition directly to a carbonyl group.

While analytical reversed-phase HPLC and ^{13}C-NMR clearly showed the presence of two isomers **15** and **16** in comparable quantities, chromatography on silica gel was unsuccessful in separating the two isomers. It was thus decided to forego separation at this point and carry on to cyclic product, at which point the isomers might be more readily separated. As expected, the cyclization reaction gave a mixture of four similar products **19a,b** and **20a,b** (presumably the four diastereomers due to the stereochemistry at C-1 and at phosphorus), as indicated by ^{13}C-NMR and analytical reversed-phase HPLC. Again, the four products were present in nearly equal quantities, but the HPLC elution times for the four compounds were too close for good preparative resolution at this stage. Analysis of these mixtures, as well as the completely isolable materials **20a** and **20b**, by mass spectrometry and elemental analysis strongly indicated that cyclization had occurred. Analysis of ^{13}C-NMR data indicated that large (approximately 160 Hz) C-1/P coupling was still evident; therefore, the carbon–phosphorus bond remained intact. The ^{13}C-NMR and APT spectra also identified the C-5 carbon or carbons in each case, which were found to be doublets due to C-5/P coupling. Such C-5/P coupling indicated that a new bond had formed between the C-5 hydroxyl oxygen and the phosphorus; thus, cyclization had formed the desired six-membered ring system. Determination of the stereochemistry at phosphorus is possible, in principle, by examining the H-1/P splitting to determine the dihedral angle between the proton and the phosphoryl oxygen. We would expect to see a larger coupling between H-1 and P if the phosphoryl oxygen and H-1 are *syn* relative to one another than if they are *trans*.[15] As can be seen in the Newman projections for each of the two glucose analogs, looking down the C-1/P bond, phosphorus oxide in the axial position is *trans* to the axial H-1 (180° dihedral angle) and should result in a smaller coupling than the *syn* axial H-1/equatorial phosphoryl oxygen arrangement (60° dihedral angle). Unfortunately, this analysis necessitates pure diastereomers, and separation of the two glucose isomers at this stage was not successful. In the mannose analog case, where separation was successful, both *syn* and *trans* relationships between the two groups result in a 60° dihedral angle, and thus the two phosphorus epimers would be expected to have similar H-1/P coupling constants.

Demethylation of **19a,b** and **20a,b** by reaction with sodium iodide, as expected, destroyed the phosphorus stereocenter and simplified the mixture to two products as indicated by analytical reversed-phase HPLC. Preparative reversed-phase HPLC was successful in separation of sufficient quantities of the demethylated products **21** and **22** for rigorous analysis. Disappearance of the phosphonate methyl ester peaks in both the ^{1}H- and ^{13}C-NMR spectra indicated successful methyl cleavage in both cases, which was confirmed by mass spectroscopy and elemental analysis. ^{31}P NMR of isolated **21** and **22** indicated that only one phosphorus-containing product was present in each case after HPLC purification, whereas each of the starting material mixtures **19a,b** and **20a,b** initially had two ^{31}P peaks present, as did the mixture of **21** and **22**. Product **21** differed significantly from **22** by NMR analysis, yet mass spectroscopy and elemental analysis results were identical, presenting strong evidence for a stereoisomeric relationship. Verification that both **21** and **22** had not experienced ring opening during the sodium iodide reaction was done primarily by analysis of the ^{13}C-NMR and APT data much like that described for **19a,b** and **20a,b**, although mass spectroscopy and elemental analysis results also strongly corroborated these results.

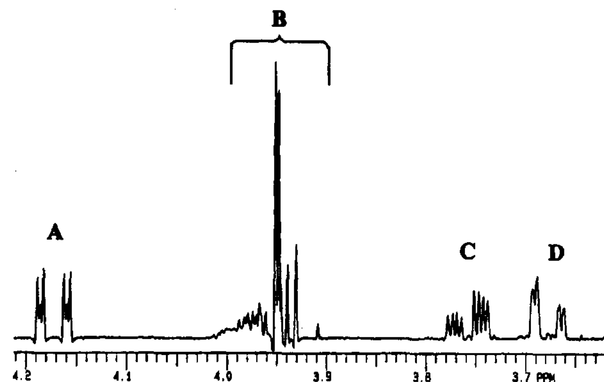

Figure 3. Resolved ^{1}H spectrum for compound **22** showing the key peak regions for assignment of stereochemistry at the C-1 position. Regions A, B, C, and D are assigned to protons H-4, (H-3/H-5/H-5′), H-2, and H-1, respectively, and their assignment explained more fully in the text.

Determination of the stereochemistry at the C-1 position for **22** relied primarily on analysis of the ^{1}H NMR data shown in Figure 3. The H-1 signal, identification of which was essential for the stereochemical assignment, was predicted to be two doublets, as this proton would be split by H-2 as well as the geminal phosphorus. Accordingly, signal D at 3.68 ppm (Figure 3), which integrates as one proton, was assigned to H-1 and its splitting measured to be 1.90 Hz and 10.94 Hz. In order to assign stereochemistry, it was necessary to determine which splitting was due to phosphorus and which was due to H-2. In other systems,[13–20,26] geminal proton–phosphorus coupling is relatively large, which leads to the prediction that the larger coupling in this case corresponds to the H-1/P coupling. The H-1/H-2 coupling of only 1.9 Hz predicts (*R*) assignment at C-1 due to *syn* rather than *trans* diaxial coupling. Signal C at 3.76 ppm integrates as one proton, and the splitting of the signal was determined to be 1.90, 10.53, and 3.56 Hz. This led to the tentative assignment of signal C as arising from H-2, with $J_{H\text{-}1,H\text{-}2} = 1.90$ Hz, and supported the assignment of the mannose (*R*) configuration at C-1. Unfortunately, neither of the two remaining signals appeared to have $J = 10.5$ or 3.56, although signal B (3.91–4.02 ppm) was a complex multiplet integrating as three protons and could easily possess such splitting. Without additional information there was no way to verify the

(33) Dixon, H. B. F.; Sparkes, M. J. *Biochem. J.* **1974**, *141*, 715–719.
(34) Bax, A. *Two Dimensional Nuclear Magnetic Resonance in Liquids*; Delft University Press: Delft, Holland, 1982; pp 110–128.

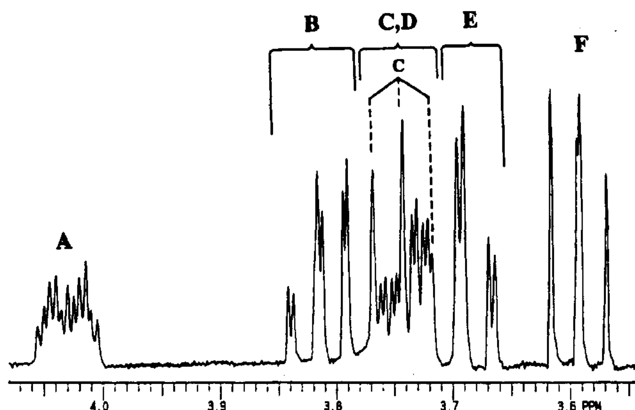

Figure 4. Resolved ^{1}H spectrum for compound **21** showing the key peak regions for assignment of stereochemistry at the C-1 position. Regions A, B, C, D, E, and F are assigned to protons H-4, H-2, H-1 (indicated by dashed lines), H-5′, H-5, and H-3, respectively, and their assignment explained more fully in the text.

assignments of H-1 and H-2. A COSY experiment was then used to identify the remaining signals by correlation of proton–proton coupling. The multiplet at 3.91–4.10 ppm, signal B, was assigned to H-3, H-5, and H-5′, and signal A at 4.18, split by the three neighboring protons as well as phosphorus, was found to be due to H-4. This assignment agrees well with the prediction that the H-4 proton should be shifted downfield relative to the other sugar protons due to the significant deshielding effect of the phosphorus-bonded ring oxygen. Protons H-1 and H-2 were confirmed by COSY to give rise to the signals at 3.68 ppm and 3.76 ppm, respectively, and the assignment of (*R*) to the C-1 postion was verified. While it was expected that **21** must thus have the glucose (*S*) configuration at C-1, direct stereochemical assignment was necessary.

The stereochemical assignment of **21** was initially approached in the same manner, although the ^{1}H spectrum (Figure 4) for **21** is considerably more complex than that for **22**. As with **22**, the nonbenzyl signal furthest downfield (4.03 ppm) integrates as one proton and corresponds to H-4, again due to the deshielding effect of the geminal phosphorus-bound ring oxygen. The complexity of the splitting found with this signal (triplet of doublet of doublets, tdd) supports this assignment, as H-4 is the only proton in the molecule with this level of coupling possible. Proton decoupling experiments, using a 1610-Hz pulse to decouple all protons coupled to H-4, identified the signals at 3.59, 3.68, and 3.75 ppm as corresponding to H-3, H-5, and H-5′. Interpretation of the COSY data allowed us to positively assign the signal at 3.59 ppm to be H-3; COSY's usefulness was somewhat limited by the large extent of signal overlap in this complex region. Unfortunately, these signals were too close together to be discernible using proton decoupling. A different approach was therefore required to identify specific signals within the complex region between 3.55 ppm and 3.85 ppm, a region integrating as four protons and containing H-1, H-2, H-5, and H-5′.

At this point we utilized a form of two-dimensional correlation NMR spectroscopy, homonuclear two-dimensional *J*-spectroscopy (HOM2D*J*),[33] which possessed a number of qualities we thought useful for addressing this problem. A HOM2D*J* spectrum of the 3.55–3.85 region of **21** is shown in Figure 5. In this spectrum, the proton spectrum is plotted along the *x*-axis, and the proton–proton couplings are plotted along the *y*-axis. Below the center

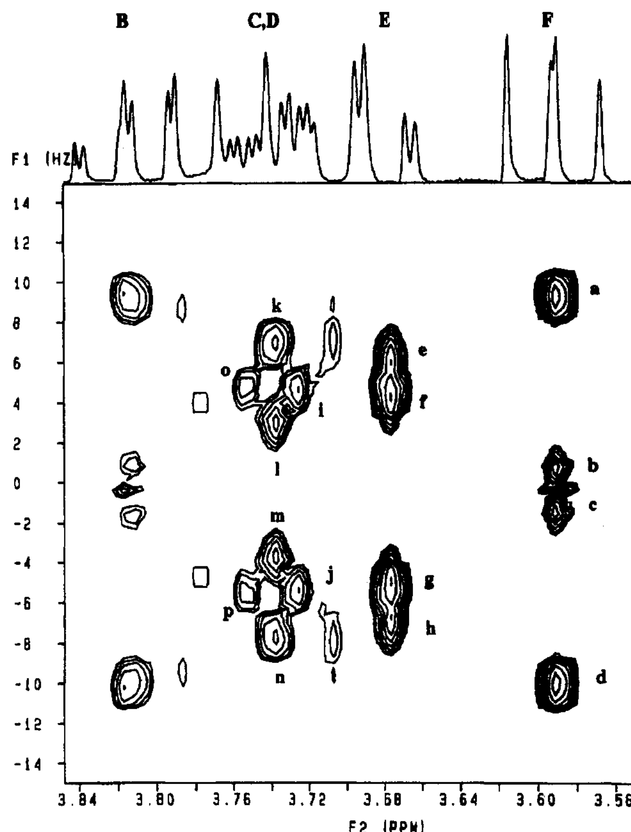

Figure 5. Key region of the homonuclear two-dimensional *J*-spectrum (HOM2D*J*) for compound **21**, showing the resolved ^{1}H spectrum along the *x*-axis and the proton–proton coupling values for each signal along the *y*-axis. Cross peaks are shown as contour line drawings, similar to more conventional 2D spectra.

of each signal in the proton spectrum lies a series of contour "cross peaks." These cross peaks correspond to all the couplings associated with the proton signal immediately above on the *x*-axis. In order to measure the individual couplings, the distance vertically between the centers of the contour cross peaks is measured and compared to the Hertz coupling scale along the *y*-axis. For example, signal F in Figure 4 gives rise to four cross peaks below signal F in the HOM2D*J* spectrum, Figure 5. This pattern corresponds to a doublet of doublets (dd), where the coupling constants can be directly measured as 8.8 Hz between cross peaks a and b and 10.2 Hz between peaks a and c. This correlates very well with the results obtained directly from the resolved proton spectrum shown in Figure 4.

More directly beneficial for analysis of compound **21**, however, was another important feature of the HOM2D*J* spectrum, namely that the center of each signal can be identified precisely. Under ideal circumstances, this provides the equivalent of a fully "proton-decoupled" proton spectrum. Thus, HOM2D*J* is especially practical in the case of Figure 4, where a number of proton signals overlap. From analysis of Figure 5, the center of the signal corresponding to signal E in Figure 4 is 3.68 ppm, indicating that these four peaks make up a doublet of doublets, rather than two-thirds of a triplet of doublets (where two of the peaks could be buried under the multiplet at 3.71–3.77 ppm). The coupling constants for signal E are determined to be 3.5 Hz (peaks e and f, or g and h) and 10.6 Hz (peaks e and g, or f and h). Signal B is confirmed as a doublet of doublet of doublets centered at 3.82 ppm, also integrating as one proton, and corresponds to H-2.

Interpretation of the multiplet at 3.71–3.77 ppm is complicated by the presence of proton–phosphorus coupling. In the absence of phosphorus decoupling experiments, the proton–proton coupling constants may first be determined by identifying nearly matching *J* values found for different signals, and any remaining coupling values are ascribed to proton–phosphorus coupling (within coupling range). However, this could lead to an undesired level of ambiguity in the stereochemical assignments. Using HOM2D*J*, we observed that, while proton–proton coupling is displayed on the *y*-axis of the plot, proton–phosphorus coupling is displayed on the *x*-axis. Thus, in Figure 4 the multiplet at 3.71–3.77 ppm is divided into two signals, C and D. Cross peaks i, j, o, and p represent a single proton (signal *C*) with the horizontal distance between i and o (or j and p) providing the H/P coupling constant (J = 10.0 Hz) while that between i and j (or o and p) gives proton–proton coupling (10.5 Hz). Peaks k, l, m, and n correlate to a doublet of doublet of doublets integrating as a single proton (signal D), with a coupling constant of 4.0 Hz between peaks k and l (or m and n), and a coupling constant of 11.0 Hz between peaks k and m (or l and n). Peaks k, l, m, and n are broadened due to 1.6-Hz coupling to phosphorus. In this manner, it is possible to isolate proton–phosphorus coupling constants from a large number of proton–proton interactions. The relative magnitudes of the now isolated proton–phosphorus couplings gives information about the relative distances of each proton from the phosphorus atom in question. Here this identifies signal C as H-1, since H-1, of all the protons in compound **21**, will have the largest magnitude of coupling with the phosphorus atom. Signal C (designated by dashed lines in Figure 4) appears as a triplet rather than as a doublet of doublets, since the two coupling constants to H-1 are of almost the same magnitude. The doublet of doublet of doublets at 3.75 is therefore due to signal D, and the coupling constants determined from both Figure 4 and Figure 5 support this assignment.

Having confirmed signal C in Figure 4 as H-1, and identified the value for H-1/P coupling, we have thus confirmed the H-1/H-1 coupling constant to be 10.2 Hz. We can now go back and assign the signals due to H-2 (3.82 ppm), H-5 (3.68 ppm), and H-5′ (3.75 ppm) making use of ^{1}H, HOM2D*J*, and COSY spectra. Now that the number and type of signals have been identified, we can, in principle, return to the resolved proton spectrum shown in Figure 4 to calculate precise couplings. The coupling constants measured from the 1-D spectrum are in good agreement with those measured from the HOM2D*J* spectrum. The stereochemical assignment of **21** at the C-1 position, based on this analysis, is (*S*), as a diaxial arrangement of vicinal protons (as with H-1/H-2 in the glucose configuration) would be predicted to split each other by approximately 10–12 Hz.

The relatively small H-2 to P coupling constants of 1.40 Hz for **21** and 3.56 Hz for **22** indicate that both **21** and **22** exist in the chair configuration. Six-membered phosphonate ring systems known to be in twist-boat or boat conformations have H-2 to P coupling constants in the range of 30–35 Hz.[19,20]

With stereochemical assignments accomplished, the next step was the removal of the protecting groups. Debenzylation of **21** and **22** by catalytic hydrogenolysis was surprisingly sluggish, even with large quantities of catalyst and under a variety of conditions. We reasoned that the catalyst was perhaps being poisoned by some component or product of the demethylation reaction, and thus hydrogenolysis was attempted on the mixture of four methylated products **19a,b** and **20a,b**. This hydrogenolysis proceeded smoothly. However, in order to perform debenzylation before demethylation on a preparative scale, it was necessary to separate the glucose and mannose isomers at the stage of **19a,b** and **20a,b**. Due to the high polarities of the debenzylated products, separation of **23a,b** and **24a,b** was not feasible. Chromatography of **19a,b** and **20a,b** on silica gel with ethyl acetate gave a clear separation into three bands (bands A, B, and C, R_{fA} = 0.50, R_{fB} = 0.45, R_{fC} = 0.40). Band A was shown by HPLC and NMR to contain two components of the original mixture. Bands B and C each contained a single component, although complete resolution of band B was difficult. Though it was not readily predictable whether the separation was based on configuration at C-1 or at phosphorus, destruction of the stereochemistry at phosphorus by demethylation of the material from band A gave a single product by HPLC and NMR. The demethylation of the materials from bands B and C yielded identical products, yet different from that of band A. Through comparison of NMR data and HPLC retention times for each demethylated product to the previously separated products, band A was found to contain a mixture of the two glucose analogs, while bands B and C each contained one of the two mannose analogs. This indicated that the silica gel chromatography had successfully separated the glucose and mannose isomers. Debenzylation of the mixture of the glucose analogs **19a** and **19b** gave cleanly a mixture of **23a** and **23b**. Likewise, debenzylation of the mannose analogs **20a** and **20b** gave cleanly the mixture of products **24a** and **24b**. Reaction of each of these mixtures with sodium iodide in acetonitrile, to cleave the methyl ester from the phosphonate, gave the desired products **1** and **2**. ^{31}P NMR of **1** and **2** each gave one signal, whereas the starting mixtures each gave two signals. As with **21** and **22**, ^{13}C-NMR was used to verify that the cyclic systems remained intact after treatment with sodium iodide.

Conclusion

A short, versatile approach for the synthesis of α-hydroxy phosphonate sugar analogs **1** and **2** from hydroxyl-protected glucal **13** has been described. The key feature of this strategy is the acid-catalyzed trimethyl phosphite addition to the unprotected carbonyl of an acyclic carbohydrate compound, **14**, to yield the critical carbon–phosphorus bond. It is anticipated that compound **14** may serve as a general synthon for a variety of glucose and mannose analogs having the anomeric carbon replaced with another functionality. Furthermore, the chemistry described here should be useful for the synthesis of cyclic phosphonate analogs of other sugars, starting from the readily accessible protected glycals.

Homonuclear two-dimensional *J*-spectroscopy (HOM2D*J*) was used to supplement standard NMR analysis in order to completely characterize the isolated diastereomers **21** and **22** and assign *gluco*- and *manno*-stereochemistry respectively. Efforts are now underway to explore the interaction of **1** and **2** and related compounds with enzymes which catalyze reactions at the anomeric carbon or the anomeric hydroxyl of glucose and mannose, including glycosidases and glycosyltransferases which proceed with inversion of the anomeric center. The chemistry is also being further developed to prepare disaccharide analogs, proceeding from the demethylated

benzyl protected analogs **21** and **22**. This may provide entry into a novel class of disaccharide and oligosaccharide analogs which are resistant to the action of glycosidases and may have interesting conformational properties.

Experimental Section

General. Unless otherwise noted, all starting materials and solvents were obtained from commercial suppliers and used without further purification. Pyridine used was predried with potassium hydroxide and distilled over calcium hydride immediately prior to use. Reactions were monitored by thin-layer chromatography using precoated glass plates of 250-mm-thickness silica gel with 254-nm fluorescent indicator and dyed with *p*-anisaldehyde stain unless otherwise indicated. Preparative TLC was carried out on precoated glass plates of 500-mm-thickness silica gel with 254-nm fluorescent indicator. Flash chromatography was carried out using silica gel (32–63 mm, 60-Å pore). HPLC columns employed were analytical C-18 (4.6-mm i.d. × 25 cm), semipreparative C-18 (10.0-mm i.d. × 25 cm), and preparative C-8 column (17.5-mm i.d. × 48 cm).

NMR and Analytical Data. 400-MHz ^{1}H-NMR, 200-MHz ^{1}H-NMR, 100.6-MHz ^{13}C-NMR, 50.3-MHz ^{13}C-NMR, 162.0-MHz ^{31}P-NMR, and two-dimensional NMR spectra were determined in $CDCl_3$ unless otherwise noted. Low-resolution mass spectroscopy experiments were performed by the Mass Spectroscopy Facility, Department of Chemistry, University of California, San Francisco. High-resolution exact mass data were obtained by the Mass Spectroscopy Facility, Department of Chemistry, University of California, Riverside. Elemental analysis experiments was carried out by E+R Microanalytical Laboratory, Inc., 96-34 Corona Ave, Corona, NY.

2,3:4,5-Di-*O*-isopropylidene-D-arabinose (4). To a solution of **3**[27] (0.50 g, 1.91 mmol) in 2 mL of ethanol (95%) was added powdered $NaHCO_3$ (0.36 g, 4.38 mmol, 2.25 equiv). To this reaction mixture stirring at rt was added 2 mL of an aqueous solution of $NaIO_4$ (0.8 g, 4.96 mmol, 2.6 equiv). The cleavage was monitored by TLC (4:1 hexanes:ethyl acetate, R_f **3** = 0.0, brown-green, R_f **4** = 0.20, pink-red; ethyl acetate, R_f **3** = 0.40, R_f **4** = 0.55). After 2–4 h at rt, the reaction mixture was evaporated to a white solid, H_2O (15 mL) was added, and the aqueous solution was extracted five times with 30 mL of ethyl acetate. The ethyl acetate layers were pooled and back-extracted with brine (25 mL). The organic layers were then dried over $MgSO_4$, filtered, and evaporated down to a pale yellow oil. Great care was taken during evaporation, as the concentrated aldehyde product rapidly polymerized at elevated temperatures. Polymerization also occured upon standing at 0 °C: yield 85% of a viscous oil; 200-MHz ^{1}H-NMR ($CDCl_3$) δ 9.78 ppm (d, 1H, J = 0.6 Hz), 4.41 (dd, 1H, J = 0.6, 3.0 Hz), 3.94–4.24 (m, 7H), 1.35–1.49 (8 singlets, each 3H) (hydrated aldehyde present); 50.3-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 200.32 ppm, 111.92, 110.08, 83.22, 77.63, 76.35, 66.86, 26.73, 26.48, 25.99, 24.84.

(1*S*,*R*)-2,3:4,5-Di-*O*-isopropylidene-D-arabinose 1-(Dimethylphosphonate) (5 and 6). Dimethyl phosphite (0.59 mL, 6.43 mmol) was added to **4** (0.46 g, 1.98 mmol) with stirring at rt. Four drops of sodium methoxide (25% in methanol) were then added with stirring, and the reaction was stirred overnight at rt. The reaction solution solidified into a white mass during the course of the reaction. The crude solidified material was then analyzed by NMR. **5 and 6: mixed (1*R*) and (1*S*) isomers:** 200 MHz ^{1}H-NMR ($CDCl_3$) δ 3.6–4.3 ppm (m, 12H), includes signals at 3.85 (d, J = 10.52 Hz), 3.84 (d, J = 10.48 Hz), 3.83 (d, J = 10.60 Hz), and 3.82 (d, J = 10.58 Hz), 1.44 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); 50.3-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 110.38 ppm, 109.92, 109.82, 109.65, 80.07 (d, J = 12.07 Hz), 78.88 (d, J = 22.64 Hz), 76.81, 76.17, 76.08, 75.90, 68.93 (d, J = 154.66 Hz), 65.68 (d, J = 151.08 Hz), 67.50, 66.66, 53.34, 53.22, 53.13, 52.99, 52.85, 52.72, 52.58, 26.75, 26.58, 26.31, 26.23, 25.91, 24.78;162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 25.01 ppm, 24.90.

The solid residue was recrystallized from diethyl ether: methanol (10:1), and the resulting rodlike crystals were filtered and washed with 0 °C diethyl ether. A second crop of crystals was obtained from the filtrate similarly. Total yield of crystals was 0.31 g (45%). Recrystallized material **5**: 200-MHz ^{1}H-NMR ($CDCl_3$) δ 4.29 ppm (ddd, 1H, J = 1.8, 2.8 Hz, J = 7.8 Hz), 3.93–4.40 (m, 5H), 3.85 (d, 3H, J = 10.44 Hz), 3.83 (d, 3H, J = 9.04 Hz), 2.65 (dd, 1H, J = 2.4, 10.2 Hz), 1.43 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H); 50.3-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 110.21 ppm, 109.98, 78.77, 76.20, 76.75 (d, J = 27.67 Hz), 67.85, 65.92 (d, J = 161.5 Hz), 53.64 (d, J = 6.40 Hz), 52.79 (d, J = 7.38 Hz), 26.94, 26.60, 26.49, 25.03; 162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 24.86 ppm; MS (MH^+) exact mass 341.14 with error magnitude <5.7 ppm (calcd for $C_{13}H_{26}O_8P^+$, 341.14). Anal. Calcd for $C_{13}H_{25}O_8P$: C, 45.9; H, 7.41; O, 37.6; P, 9.11. Found: C, 45.78; H, 7.20; P, 8.83.

(1*S*,*R*)-2,3:4,5-Di-*O*-isopropylidene-D-arabinose 1-(Diethylphosphonate) (7 and 8). Diethyl phosphite (0.67 mL, 5.22 mmol) was added to **4** (0.37 g, 1.61 mmol) with stirring at rt. Four drops of sodium ethoxide (21% in ethanol) were then added with stirring, and the reaction was stirred overnight at rt. The reaction solution solidified into a white mass during the course of the reaction. The crude solidified material was then analyzed by NMR. **7 and 8: mixed (1*R*) and (1*S*) isomers:** 200-MHz ^{1}H-NMR ($CDCl_3$) δ 3.88–4.32 ppm (m, 10H), 1.30–1.48 (m, 18H); 50.3-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 110.96 ppm, 110.56, 110.50, 110.32, 80.97, 80.80, 79.82, 79.26, 77.42, 76.87, 76.69, 70.64, 68.43, 68.17, 67.53, 65.47, 63.12, 63.03, 62.93, 62.85, 62.76, 62.14, 62.06, 27.27, 27.22, 27.09, 26.93, 26.82, 26.48, 25.39, 25.30, 16.63, 16.56, 16.48, 16.39; 162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 22.50 ppm, 22.35.

The solid residue was recrystallized from diethyl ether: methanol (10:1) as above for compound **4**. Total yield of rodlike crystals was 0.26 g (44%). Recrystallized material **8**: 200-MHz ^{1}H-NMR ($CDCl_3$) δ 3.88–4.32 ppm (m, 10H), 3.75 (dd, 1H, J = 4.0, 17.0 Hz), 1.30–1.48 (m, 18H); 50.3-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 110.54 ppm, 110.20, 80.68 (d, J = 13.02 Hz), 79.42, 76.27, 69.19 (d, J = 166.71 Hz), 67.29, 62.65, 62.60, 62.52, 26.82, 26.68, 26.11, 24.92, 16.31, 16.19; 162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 22.33 ppm; MS (MH^+) exact mass 369.17 with error magnitude < 4.4 ppm (calcd for $C_{15}H_{30}O_8P^+$, 369.16). Anal. Calcd for $C_{15}H_{29}O_8P$: C, 48.9; H, 7.94; O, 34.8; P, 8.41. Found: C, 48.76; H, 7.92; P, 8.53.

(1*S*)-D-Arabinose 1-(Dimethylphosphonate) (9). Crystalline **5** (0.50 g, 1.474 mmol) was suspended in H_2O (10 mL) and stirred at rt. Methanol (2.0 mL) was then added to increase the solubility of **5**. To this was added Dowex-H^+ resin (1.0 g, prewashed with H_2O, 50W-X8, 20–50 mesh) and the reaction heated to 50 °C. Stirring was continued at 50 °C for 5–6 h, and progress of cleavage was monitored by TLC (9:1 methylene chloride:methanol, diacetonide R_f = 0.60, monoacetonide R_f = 0.30, product R_f = 0.0; pink-red spots). The Dowex was removed by filtration, and the filtrate was evaporated, leaving the product as a white solid in near-quantitative yields. NMR analysis of the white solid indicated a high degree of purity. The crude product was used directly for subsequent reactions: 200-MHz ^{1}H-NMR (D_2O) δ 4.30 ppm (dd, 1H, J = 5.86, 9.20 Hz), 4.09 (m, 1H), 3.58–3.90 (m, 10H, contains signals at 3.85 (d, J = 10.62 Hz) and 3.83 (d, J = 10.66 Hz); 50.3-MHz ^{13}C-NMR (D_2O) (assisted by APT experiments) δ72.39 ppm (d, J = 7.81 Hz), 72.09, 69.20 (d, J = 162.34 Hz), 70.09 (d, J = 6.51 Hz), 63.80, 55.19 (d, J = 7.05 Hz), 54.60 (d, J = 7.27 Hz).

(1*R*)-D-Arabinose 1-(Diethylphosphonate) (10). Formation of **10** via the deprotection of crystalline **8** was done via the procedure for the formation of **9** from **5**. NMR analysis of the white solid product indicated a high degree of purity. The crude product was used directly for subsequent reactions: 200-MHz ^{1}H-NMR (D_2O) δ4.04–4.30 ppm (m, 6H), 3.60–3.90 (m, 4H), 1.33 (td, 6H, J = 2.0, 7.0 Hz); 50.3-MHz ^{13}C-NMR (D_2O) (assisted by APT experiments) δ72.76 ppm, 71.18 (d, J = 11.18 Hz), 71.16 (d, J = 1.95 Hz), 68.87 (d, J = 165.16 Hz), 66.34 (d, J = 9.66 Hz), 66.20 (d, J = 8.89 Hz), 65.62, 17.97 (d, J = 5.10 Hz).

(1*S*)-1,2,3,4,5-Penta-*O*-acetyl-D-arabinose 1-(Dimethylphosphonate) (11). To a solution of **9** (0.16 g, 0.69 mmol, white crystals) in dry pyridine (5 mL) was added acetic anhydride (0.75 mL, 0.812 g, 7.50 mmol). The reaction flask was evacuated and flushed twice with dry N_2 and the reaction then purged and stirred under N_2. TLC analysis indicated the reaction was complete

after 36 h at rt (ethyl acetate, R_f 9 = 0.0, R_f 11 = 0.50). The reaction solution was evaporated and dissolved in ethyl acetate (15 mL) and washed with H_2O (2 × 10 mL). The water layer was extracted with ethyl acetate (3 × 15 mL), and the organic layers were pooled and washed with brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated down to a viscous oil. Yield was 60%. Analysis results were found similar to those given in literature:[31d] 200-MHz ^{1}H-NMR ($CDCl_3$) δ 5.52 ppm (dd 1H, J = 4.9, 5.0, 10.54 Hz), 5.36 (dd, 1H, J = 5.0, 12.3 Hz), 5.29 (dd, 1H, J = 4.9, 6.0 Hz), 4.89 (dt, J = 4.3, 6.0, 6.0 Hz), 4.16 (dd, 1H, J = 4.3, 12.2 Hz), 3.92 (dd, 1H, J = 6.0, 12.2 Hz), 3.65 (d, 6H, J = 10.9 Hz), 2.02, 1.96, 1.94, 1.92, 1.88 (five singlets, each 3H); 50.3-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 170.47 ppm, 169.83, 169.66, 169.44, 169.38, 169.30, 69.18 (d J = 7.65 Hz), 68.57, 67.44 (d, J = 5.01 Hz), 65.48 (d, J = 167.9 Hz), 61.28, 53.55, 53.42, 53.29, 20.24, 20.14, 20.03, 19.94.

(1*R*)-1,2,3,4,5-Penta-*O*-acetyl-D-arabinose 1-(Diethylphosphonate) (12). Formation of 12 from a solution of 10 was done via the procedure outlined for formation of 11 from 9: 200-MHz ^{1}H-NMR ($CDCl_3$) δ 5.73 ppm (dt, 1H, J = 2.0, 10.1, 10.1 Hz), 5.44 (ddd, 1H, J = 1.1, 2.0, 9.1 Hz), 5.28 (dd, 1H, J = 7.0, 10.1 Hz), 5.05 (ddd, 1H, J = 2.8, 4.8, 9.1 Hz), 4.12 (m, 6H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.31 (t, 3H, J = 13.0 Hz), 1.32 (t, 3H, J = 13.0 Hz); 50.3-MHz ^{13}C-NMR ($CDCl_3$) δ 170.84 ppm, 170.15, 170.06, 169.73, 169.38, 169.30, 67.61, 67.20, 66.99, 66.69, 66.65, 64.86, 63.25, 63.25, 63.12, 62.93, 61.71, 61.51, 20.63, 20.47, 20.36, 16.09, 16.03, 15.98, 15.91.

Attempted Cyclization of 9 or 10. Representative Procedure. To a solution of 9 (0.10 g, 0.43 mmol) in methanol (3 mL) was added several drops of sodium methoxide (25% in methanol). The reaction was stirred at rt and monitored by TLC (2:5 ethanol:ethyl acetate, starting material R_f 9 = 0.30). After 15 min, loss of discrete starting material spot was observed and broad streaking around R_f = 0.30 occurred, with several novel discrete spots appearing within the streak (R_f = 0.28–0.32). ^{1}H and ^{13}C NMR of the crude material indicated a number of materials were present. Chromatographic purification of the crude material was unsuccessful. Similar results were obtained using triethylamine in methanol or using triethylamine as solvent.

2,3,5-Tri-*O*-benzyl-4-*O*-formyl-D-arabinose (14). 3,4,6-Tri-*O*-benzyl-D-glucal (13) (1.00 g, 2.40 mmol) was dissolved in 2 mL of diethyl ether. To this was added 18 mL of H_2O, followed by sodium *meta*-periodate (3.08 g, 14.41 mmol). While the mixture was stirred vigorously at rt, osmium tetraoxide solution (0.1 mL, 4% in H_2O) was added, and the reaction mixture immediately turned black. The flask was covered and stirred vigorously overnight. Progress of the reaction was monitored by TLC in 1:1 ethyl acetate:hexanes (glucal R_f = 0.50, UV active/stained red; sugar–osmium complex R_f = 0.30, UV active/stained black; and aldehyde product 4 R_f = 0.70, UV active/stained green-brown). After several hours, white material began to form between the two layers, although starting material and osmium complex were still present in significant amounts. After 12 h, neither starting material nor osmium complex was observed by TLC. Filtration of this solid, followed by water wash and recrystallization from diethyl ether (0 °C) afforded pure product as a white fibrous material in 70–75% yield. However, greater than 97% yields of pure material were obtained through extraction of the combined reaction bilayers with ethyl acetate. The organic layers were pooled, dried over $MgSO_4$, filtered and evaporated at low temperature (less than 40 °C) to yield white fibrous solid. The aldehyde product, like compound 4, had to be used immediately for the next step, as the compound was unstable and was prone to polymerization. Excessive or prolonged heating during the evaporation stages led to formation of a brownish solid. Storage at rt, or even 0 °C, also led to polymerization: 400-MHz ^{1}H-NMR ($CDCl_3$) (assisted by COSY experiments) δ 9.65 ppm (d, 1H, J = 0.64 Hz), 7.85 (s, 1H), 5.30 (ddd, 1H, J = 3.01, 4.42, 7.32 Hz), 4.40–4.70 (m, 6H), 4.24 (dd, 1H, J = 3.05, 7.32 Hz), 3.93 (dd, 1H, J = 0.64, 3.05 Hz), 3.81 (dd, 1H, J = 3.01, 11.13 Hz), 3.76 (dd, 1H, J = 4.42, 11.13 Hz); 100.6-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 202.61 ppm, 159.50, 137.18, 136.61, 136.09, 128.30, 128.11, 128.06, 127.89, 127.77, 127.63, 127.53, 82.03, 76.30, 73.96, 73.14, 72.99, 71.03, 67.29; MS (MNH_4^+) exact mass 466.22 with error magnitude < 5.0 ppm (calcd for $C_{27}H_{32}NO_6^+$, 466.22). Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.3; H, 6.54; O, 21.4. Found: C, 72.29; H, 6.54.

(1*S*,*R*)-2,3,5-Tri-*O*-benzyl-4-*O*-formyl-D-arabinose 1-(Dimethyl phosphonate) (15, 16). 2,3,5-Tribenzyl-4-formyl-D-arabinose (14) (0.50 g, 1.12 mmol) was suspended in glacial acetic acid (5.0 mL), and trimethyl phosphite (0.14 mL, 0.15 g, 1.20 mmol) was added. 14 dissolved completely upon addition of the phosphite. The reaction then stirred at rt for 36 h until predominantly product was observed by TLC (1:1 ethyl acetate: hexanes, starting material 14 R_f = 0.70, UV active/stained green-brown: product R_f = 0.25, UV active/stained red). A 1:1 mixture of 15 and 16 was obtained in 75% yield after flash chromatography in 1:1 ethyl acetate:hexanes: 400-MHz ^{1}H-NMR ($CDCl_3$) δ 8.05 ppm (s, 1H), 8.02 (s, 1H), 7.30 (m, 30H), 5.40 (m, 2H), 4.40–3.62 (m, 10H), 3.82 (d, 3H, J = 10.44 Hz), 3.77 (d, 3H, J = 10.40 Hz), 3.75 (d, 3H, J = 10.48 Hz), 3.73 (d, 3H, J = 10.68 Hz), 3.17 (m, 2H); 100.6-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT experiments) δ 160.49 ppm, 160.41, 138–127 (aromatic), 79.99 (d, J = 6.5 Hz), 78.92 (d, J = 14.0 Hz), 77.91, 77.06, 76.55, 74.63, 74.46, 74.41, 73.26, 73.22, 72.99, 72.77 (d, J = 196 Hz), 68.34, 68.12, 67.50 (d, J = 163 Hz), 53.56 (d, J = 7.33 Hz), 52.93 (d, J = 7.73 Hz), 52.80 (d, J = 7.73 Hz); 162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 26.44 ppm, 25.16; MS (MH^+) 559.2 by FAB (calcd for $C_{29}H_{36}O_9P^+$, 559.2). Anal. Calcd for $C_{29}H_{35}O_9P$: C, 62.3; H, 6.31; O, 25.8; P, 5.54. Found: C, 62.13; H, 6.34; P, 5.31.

(1*S*,*R*)-2,3,5-Tribenzyl-D-arabinose 1-(Methyl phosphonate) (19a,b and 20a,b). The mixture of 15 and 16 was dissolved in methanol (2–4 mL) and stirred at rt. Four drops of sodium methoxide (25% in methanol) were added, and the reaction immediately darkened slightly. Monitoring of reaction progress by TLC was unsuccessful, as the product compounds were observed to have the same R_f values as the starting material. The reaction was monitored by analytical reversed-phase HPLC and was complete after stirring for 2.0–2.5 h at rt. Material containing all four diastereomers, but free of other contaminants, was obtained by flash chromatography with 1:1 ethyl acetate:hexanes. Preparative TLC in ethyl acetate was used to isolate and purify **20a**, **20b** and the mixture of **19a** and **19b**.

19a and 19b, (1*S*)-Isomers. Glucose analogs, mixed phosphorus anomers: 400-MHz ^{1}H-NMR ($CDCl_3$) δ 7.12–7.38 ppm (m, 30H), 4.50–4.95 (m, 12H), 3.70–4.00, 4.05–4.15, 4.25–4.31 (three multiplets, 18H, includes two signals at 3.90 (d, J = 10.32 Hz) and 3.88 ppm (d, J = 11.07 Hz)); 100.6-MHz ^{13}C-NMR ($CDCl_3$) (assisted by APT): δ 138.16, 138.02, 137.67, 137.60, 137.56, 128.65, 128.41, 128.37, 128.21, 128.05, 127.94, 127.87, 127.76, 84.71 (d, J = 12.62 Hz), 84.22 (d, J = 9.16 Hz), 77.44, 77.32, 76.84 (d, J = 1.01 Hz), 76.27, 76.10, 75.60, 75.49, 75.30, 73.62, 73.50, 69.62 (d, J = 142.4 Hz), 68.92 (d, J = 139.0 Hz), 68.53 (d, J = 9.78 Hz), 68.19 (d, J = 8.55 Hz), 53.97 (d, J = 4.23 Hz), 53.78 (d, J = 7.33 Hz); 162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 24.10 ppm, 20.26 ppm; MS (MH^+) 499.3 (calcd for $C_{27}H_{32}O_7P^+$, 499.2). Anal. Calcd for $C_{27}H_{31}O_7P$: C, 65.0; H, 6.47; O, 22.5; P, 6.21. Found: C, 65.05; H, 6.47; P, 6.19.

20a and 20b, (1*R*)-Isomers. Mannose analogs, mixed phosphorus anomers: MS (MH^+) 499.3 (calcd for $C_{27}H_{32}O_7P^+$, 499.2). Anal. Calcd for $C_{27}H_{31}O_7P$: C, 65.0; H, 6.47; O, 22.5; P, 6.21. Found: C, 64.72; H, 6.52.

20(a or b), (1*R*)-Isomer. Mannose analog; purified single diastereomer from middle R_f band (band b) on preparative TLC: 400-MHz ^{1}H-NMR ($CDCl_3$) δ 7.25 ppm (m, 15H), 4.86 (d, 1H, J = 10.7 Hz), 4.70 (s, 1H), 4.69 (s,1H), 4.65 (d, 1H, J = 12.1 Hz), 4.58 (d, 1H, J = 10.7 Hz), 4.52 (d, 1H, J = 12.1 Hz), 4.43 (dd, 1H, J = 2.32 Hz, J = 9.89 Hz), 4.30 (m, 1H), 4.12 (m, 1H), 3.95 (d, 3H, J = 10.64 Hz), 3.90 (dd, 1H, J = 3.20, 11.32 Hz), 3.88 (dd, 1H, J = 3.36, 11.32 Hz), 3.72 (dd, 1H, J = 2.16, 11.32 Hz); 100.6-MHz ^{13}C-NMR ($CDCl_3$) δ 137.89 ppm, 137.88, 137.06, 128.65, 128.62, 128.55, 128.31, 128.21, 128.05, 127.97, 127.74, 127.64, 81.55 (d, J = 6.32 Hz), 75.99 (d, J = 1.75 Hz), 75.40, 73.41, 72.51, 73.62, 68.58 (d, J = 9.38 Hz), 64.85 (d, J = 146.47 Hz), 54.74 (d, J = 5.91 Hz); MS (MH^+) 499.3 (calcd for $C_{27}H_{32}O_7P^+$, 499.2).

20(b or a), (1*R*)-Isomer. Mannose analog; purified single diastereomer from lowest R_f band (band c) on preparative TLC: 400-MHz ^{1}H-NMR ($CDCl_3$) (assignments and coupling constant measurements were assisted by APT, COSY, HETCOR, and ^{1}H-decoupling experiments) δ 7.25 ppm (m, 15H), 4.85 (d, 1H, J = 10.7 Hz), 4.71 (s, 2H), 4.63 (d, 1H, J = 12.1 Hz), 4.56 (d, 1H, J

= 10.7 Hz), 4.56 (d, 1H, J = 12.1 Hz), 4.27 (ddd, 1H, J = 3.0, 3.1, 8.2 Hz), 4.09 (t, 1H, J = 9.0 Hz), 4.05 (m, 1H), 3.90 (ddd, 1H, J = 3.0, 9.0, 3.1 Hz), 3.77 (d, 3H, J = 10.6 Hz), 3.11 (dd, 1H, J = 3.0, 15.6 Hz), 3.82 (dd, 1H, J = 4.0, 11.1 Hz), 3.81 (dd, 1H, J = 3.9, 11.1 Hz); 100.6-MHz ^{13}C-NMR ($CDCl_3$) δ 137.89 ppm, 137.69, 137.31, 128.55, 128.41, 128.37, 128.07, 128.01, 127.96, 127.89, 127.74, 127.64, 80.93 (d, J = 4.7 Hz), 77.66 (d, J = 5.9 Hz), 75.34, 73.55, 72.36, 73.18, 69.01 (d, J = 9.0 Hz), 63.65 (d, J = 146 Hz), 52.35 (d, J = 5.9 Hz); 162.0-MHz ^{31}P-NMR ($CDCl_3$) (vs H_3PO_4 in $CDCl_3$ external ref δ 0.0 ppm) δ 19.91 ppm; MS (MH^+) 499.3 (calcd for $C_{27}H_{32}O_7P^+$, 499.2).

(1*S*)-2,3,5-Tri-*O*-benzyl-D-arabinose 1-Phostone (21). The mixture of **19a** and **19b** (0.06 g, 0.112 mmol) was dissolved in acetonitrile (5 mL), and sodium iodide (0.019 g, 0.128 mmol, 1.1 equiv) was added. The reaction was heated at reflux for 12 h until reaction was complete as indicated by TLC (ethyl acetate; starting compounds R_f = 0.70, product R_f = 0.0). The cloudy white solution was then evaporated, taken up in methanol, and purified by reversed-phase HPLC. Yield was 0.052 g (92%): 400-MHz ^{1}H-NMR (CD_3OD) (assignments and coupling constant measurements were assisted by COSY, HOM2DJ, and ^{1}H-decoupling experiments) δ 7.25 ppm (m, 15H, aromatic), 4.03 (ddt, 1H, J = 9.92, 2.13, 3.94 Hz), 3.82 (ddd, 1H, J = 1.40, 8.80, 10.2 Hz), 3.75 (ddd, J = 1.64, 3.94, 10.8 Hz), 3.74 (t, 1H, J = 10.2 Hz), 3.68 (dd, 1H, J = 2.13, 10.8 Hz), 3.59 (dd, 1H, J = 8.80, 9.92 Hz); 100.6-MHz ^{13}C-NMR (CD_3OD) δ 139.93 ppm, 139.21, 139.04, 129.39, 129.24, 129.15, 129.03, 128.99, 128.87, 128.75, 128.67, 127.55, 87.18 (d, J = 10.8 Hz), 79.93, 76.87, 75.97, 74.20, 75.15, 71.80 (d, J = 143 Hz), 70.26 (d, J = 8.76 Hz); 162.0-MHz ^{31}P-NMR (CD_3OD) (vs H_3PO_4 in CD_3OD external ref δ 0.0 ppm) δ 12.75 ppm; MS (MNa^+) exact mass 507.16 with error magnitude < 5.6 ppm (calcd for $C_{26}H_{29}O_7PNa^+$, 507.16).

(1*R*)-2,3,5-Tri-*O*-benzyl-D-arabinose 1-Phostone (22). Mannose analog. The mixture of **20a** and **20b** was demethylated via the procedure for formation of **21** via demethylation of **19a** and **19b**. Yield was 0.051 g (90%). **20a** and **20b** were also demethylated individually, with similar yields and identical analytical results: 400-MHz ^{1}H-NMR (CD_3OD) (assignments and coupling constant measurements were assisted by COSY, HOM2DJ, and ^{1}H-decoupling experiments) δ 7.25 ppm (m, 15H, aromatic), 4.82 (d, 1H, J = 10.8 Hz), 4.78 (d, 1H, J = 11.8 Hz), 4.60 (d, 1H, J = 11.9 Hz), 4.59 (d, 1H, J = 11.7 Hz), 4.48 (d, 1H, J = 12.1 Hz), 4.45 (d, 1H, J = 10.9 Hz), 4.19 (dt, 1H, J = 3.67, 4.18 Hz), 3.91–4.10 (m, 3H), 3.76 (ddd, 1H, J = 1.90, 3.56, 10.53 Hz), 3.68 (dd, 1H, J = 1.90, 10.94 Hz); 100.6-MHz ^{13}C-NMR (CD_3OD) δ 140.58 ppm, 139.81, 139.63, 129.47, 129.39, 129.32, 129.05, 128.87, 128.71, 128.68, 128.49, 128.16, 127.93, 87.56 (d, J = 11.1 Hz), 76.52, 75.87, 74.09, 80.27, 75.03 (d, J = 2.93 Hz), 72.08 (d, J = 141 Hz), 70.90 (d, J = 10.8 Hz); 162.0-MHz ^{31}P-NMR (CD_3OD) (vs H_3PO_4 in CD_3OD external ref δ 0.0 ppm) δ 11.77 ppm; MS (MNa^+) exact mass 507.16 with error magnitude < 4.2 ppm (calcd for $C_{26}H_{29}O_7PNa^+$, 507.16).

Attempted Hydrogenolysis of 21 or 22. Representative Procedure (Vigorous). A solution of **21** (0.1 g, 0.114 mmol) was dissolved in ethanol (20 mL, 180 proof) and palladium added (0.1 g, 10% on carbon, Degussa type, 0.25 equiv of Pd). The reaction vessel was evacuated and purged with N_2 and then evacuated and purged with H_2 twice. The system was placed under 4 atm of H_2 and was shaken vigorously for 8 days at rt. After this time the reaction vessel was purged with N_2 and the solution examined by TLC (2:5 ethanol:ethyl acetate, starting material **21** R_f = 0.55). Completely debenzylated product (R_f = 0.0) was observed in a very small amount. Starting material was the predominant component, although partially debenzylated materials (R_f = 0.35, R_f = 0.15) were also present as minor components. Similar reaction conditions using platinum(IV) oxide (Adam's catalyst) as catalyst gave identical results.

D-Arabinose (1*S*)-1-(Methylphostone) (23a and 23b). Glucose Analogs. The mixture of glucose analogs **19a** and **19b** (0.10g, 0.201 mmol) was dissolved in 5 mL of methanol and 1 mL of H_2O added. To this was added palladium on carbon (0.10 g, 10% by wt, Degussa type) and the reaction vessel evacuated, flushed twice with dry N_2, and then evacuated and sealed. The system was purged with H_2, and the reaction was run at rt under H_2 at atmospheric pressure while being stirred vigorously. The reaction was complete after 12 h. (TLC in ethyl acetate: starting material R_f = 0.60, product R_f = 0.0). The mixture was filtered through celite to remove the Pd/C and the filtrate evaporated to yield 0.045 g of the product (99%): 400-MHz ^{1}H-NMR (CD_3OD) δ 3.88–4.10 ppm (m), 3.89–3.85 (m, includes two signals at 3.88 (d, 3H, J = 10.22 Hz) and 3.86 (d, 3H, J = 10.99 Hz)), 3.65–3.80 (m), 3.62 (td, J = 9.50, 1.53 Hz), 3.41–3.45 (td, J = 9.04, 1.02); 100.6-MHz ^{13}C-NMR (CD_3OD) δ 81.84, 81.79, 80.64, 78.42, 78.32, 78.12, 77.99, 72.26, 71.95, 71.93, 70.48, 70.46, 69.01, 63.64, 63.55, 63.50, 63.39; 162.0-MHz ^{31}P-NMR (D_2O) (vs H_3PO_4 in D_2O external ref δ 0.0 ppm) δ 25.77 ppm, 22.31; MS (MH^+) exact mass 229.05 with error magnitude < 1.8 ppm (calcd for $C_6H_{14}O_7P^+$, 229.05). Anal. Calcd for $C_6H_{13}O_7P$: C, 31.6; H, 5.75; O, 49.1; P, 13.6. Found: C, 31.24; H, 5.96; P, 13.25.

D-Arabinose (1*R*)-1-(Methylphostone) (24a and 24b). Mannose Analogs. The mixture of mannose analogs **20a** and **20b** (0.10 g, 0.201 mmol) was debenzylated analogously to the reaction forming **23a** and **23b**. The mixture was filtered through celite to remove the Pd/C and the filtrate evaporated to yield 0.045 g of the product (99%). Similar results were obtained using the isolated **20a** or **20b**. **24a,b:** MS (MH^+) exact mass 229.05 with error magnitude < 5.7 ppm (calcd for $C_6H_{14}O_7P^+$, 229.05). Anal. Calcd for $C_6H_{13}O_7P$: C, 31.6; H, 5.75; O, 49.1; P, 13.6. Found: C, 31.29; H, 5.98; P, 13.12. **24a** or **b** (band b material from separation of **19a,b** and **20a,b**): 400-MHz ^{1}H-NMR (CD_3OD) δ 4.22 ppm (dd, 1H), 3.70–4.04 (m, 8H), within 3.70–4.04 is a signal at 3.93 (d, 3H, J = 10.3 Hz); 100.6-MHz ^{13}C-NMR (CD_3OD) δ 80.65 (d, J = 3.25 Hz), 74.50 (d, J = 9.88 Hz), 68.68 (d, J = 143.02 Hz), 67.70, 62.93 (d, J = 9.76 Hz), 55.95 (d, J = 7.38 Hz); 162.0-MHz ^{31}P-NMR (CD_3OD) (vs H_3PO_4 in CD_3OD external ref δ 0.0 ppm) δ 21.21 ppm. **24b** or **a** (band c material from separation of **19a,b** and **20a,b**): 400-MHz ^{1}H-NMR (CD_3OD) δ 4.14–4.18 ppm (m), 3.88–3.94 (m), 3.70–3.87 (m), within 3.70–3.87 is a signal at 3.80 (d, 3H, J = 10.47 Hz); 100.6-MHz ^{13}C-NMR (CD_3OD) δ 81.52 (d, J = 5.29 Hz), 74.50 (d, J = 8.15 Hz), 67.32, 67.10 (d, J = 147.66 Hz), 63.08 (d, J = 9.34 Hz), 52.68 (d, J = 7.13 Hz); 162.0-MHz ^{31}P-NMR (CD_3OD) (vs H_3PO_4 in CD_3OD external ref δ 0.0 ppm) δ 21.84 ppm.

D-Arabinose (1*S*)-1-Phostone (1). Glucose Analog. The mixture of **23a** and **23b** (0.11 g, 0.482 mmol) was dissolved in 5 mL of acetonitrile, and sodium iodide (0.080 g, 0.531 mmol, 1.1 equiv) was added. The reaction was heated to reflux and stirred for 12 h until reaction was complete by NMR. The reaction solution was evaporated: 400-MHz ^{1}H-NMR (D_2O) δ 4.21–4.30 (m, 2H), 4.17–4.21 (m, 1H), 4.12 (td, 1H, J = 10.0, 1.75 Hz), 4.05 (t, 1H, J = 9.9 Hz), 3.93 (t, 1H, J = 9.7); 100.6-MHz ^{13}C-NMR (D_2O) δ 77.20 (d, J = 9.58 Hz), 76.68 (d, J = 3.67 Hz), 71.27, 70.55 (d, J = 144.39), 64.24 (d, J = 9.16 Hz); 162.0-MHz ^{31}P-NMR (CD_3OD) (vs H_3PO_4 in CD_3OD external ref δ 0.0 ppm) δ 16.38 ppm; MS (M^-) exact mass 213.02 with error magnitude < 2.7 ppm (calcd for $C_5H_{10}O_7P^-$, 213.02).

D-Arabinose (1*R*)-1-Phostone (2). Mannose Analog. The mixture of **23a** and **23b** was reacted with sodium iodide as per the formation of **1**: 400-MHz ^{1}H-NMR (D_2O) δ 4.03 (dd, 1H, J = 1.1, 5.5 Hz), 3.30–3.95 (m, 5H); 100.6-MHz ^{13}C-NMR (D_2O) δ 76.65 (d, J = 4.24 Hz), 73.80 (d, J = 7.94 Hz), 69.65 (d, J = 209.82 Hz), 67.17 (d, J = 6.05 Hz), 61.98 (d, J = 9.02 Hz); MS (M^-) exact mass 213.02 with error magnitude < 5.7 ppm (calcd for $C_5H_{10}O_7P^-$, 213.02).

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