Synthesis of Glycophostones: Cyclic Phosphonate Analogues of Biologically Relevant Sugars

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Analogues of L-fucose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-mannosamine, and *N*-acetyl neuraminic acid in which the anomeric carbon atom was replaced by a phosphonyl group (phostones or cyclic phosphonates) were synthesized by stereocontrolled methods relying on the Abramov reaction.

Introduction

Aminodeoxy and deoxy sugars are important components of biologically relevant natural products such as antibiotics and other anti-infective agents.[1] They also play a critical role in conferring specificity in the interaction of oligosaccharide components of glycoproteins with proteins, for example.[2] The relevance of such interactions is manifested by vital physiological effects related to health issues for mankind.

As a result, the field of glycobiology has emerged as an important area of research on many fronts.[3] Concurrently, much attention has been focused on synthetic methods for the stereocontrolled synthesis of glycosides and oligosaccharides[4] to be used as tools and probes to elucidate interactions at the molecular level. As in peptide and oligonucleotide chemistry, carbohydrate-based substrates are subject to degradation under physiological conditions through the action of specific glycosidases.[5] The modification of amide bonds in certain peptide sequences[6] and the internucleotidic linkages in oligonucleotides[7] has been successfully accomplished,

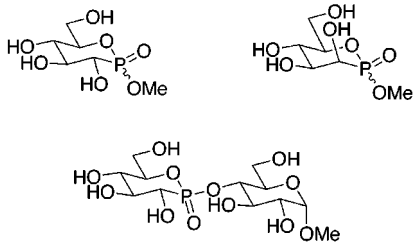

Figure 1.

with dramatic results, often culminating with the discovery of new therapeutic agents. Because of the fidelity of the interactions of carbohydrates with proteins, their chemical modification to glycomimetics has been investigated to a lesser degree.[8] Invariably, conformation, configuration, the nature of the functional groups, as well as stereochemistry play critical roles in such recognition phenomena. Therefore, it is not surprising that even subtle modifications such as configurational inversion, deoxygenation, etc. may result in a loss of the original effect with a biological target.

It occurred to us some years ago that the replacement of the anomeric carbon atom of a sugar by a pentacovalent phosphorus atom would be of interest in the search for anomerically modified glycomimetics.[9] Such molecules would correspond to functionalized versions of cyclic phosphonates also known as phostones (Figure 1). Following earlier reports of simple phostones,[10] we disclosed our syntheses of D-gluco, D-manno, and disaccharide phostones, including X-ray crystal structures that revealed interesting functional features at phosphorus.[9] Cyclic phosphonates in the D-gluco- and D-manno series were also reported by Drueckammer,[11] Withers,[12] and their respectives co-workers.

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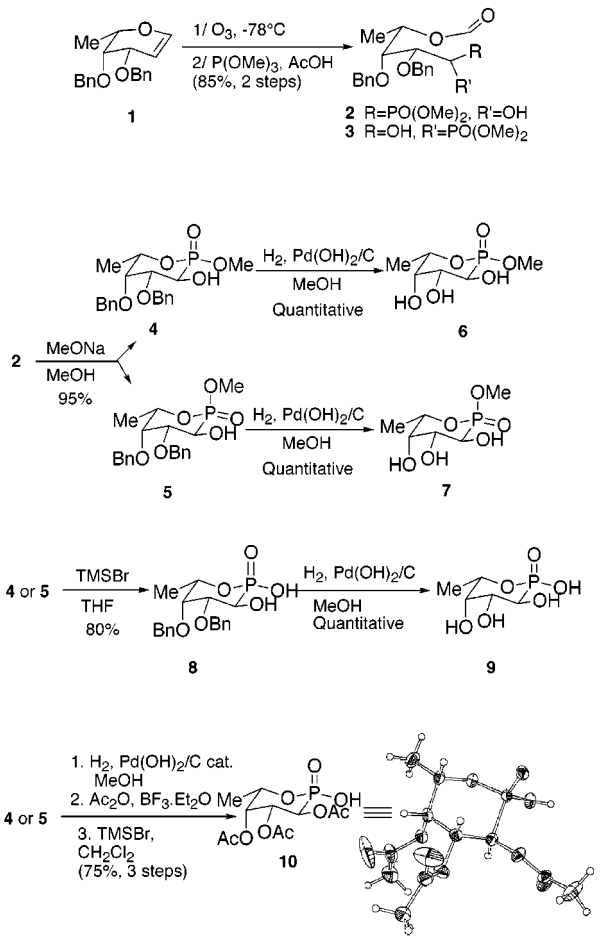
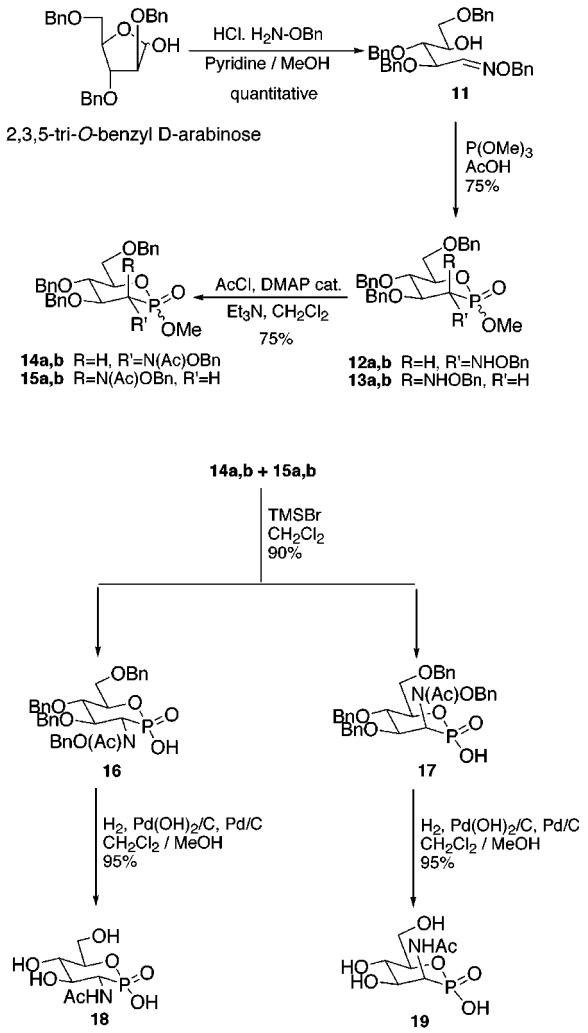
Scheme 1



We now extend our studies to the synthesis of phostones corresponding to L-fucose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-mannosamine, and *N*-acetyl neuraminic acid. In each case, we obtained the anomeric methyl phosphonate esters as well as the free acids. The synthesis protocol for each analogue consisted of the oxidative cleavage of the corresponding O-benzylated glycal to the aldehydo sugar bearing a formate ester at C-5 (originally the anomeric carbon atom), followed by condensation with trimethyl phosphite in glacial acetic acid[11] to introduce the dimethylphosphonyl moiety (Abramov reaction).[13]

The synthesis of the acyclic L-talo and L-fuco dimethylphosphonates **2** and **3**, which were obtained in a 2:3 ratio, respectively, is shown in Scheme 1. In view of the greater potential relevance of the L-fuco isomer, we focused on the synthesis of the corresponding phostone. Nevertheless, it was of interest that there was a modest level of selectivity in the Abramov reaction favoring the desired L-fuco isomer. Treatment of **2** with sodium methoxide led to the two methyl phosphonates **4** and **5** in a ratio of 3:2. The L-fuco isomers **4** and **5** showed H-2 coupling constants of $J_{H3,H4}$ = 8.1 Hz and $J_{H3,P}$ = 10.5 Hz for a doublet of doublets, reflecting on a trans diaxial orientation. For comparison, the corresponding L-talo analogues had $J_{H3,H4}$ = 4.0 Hz and $J_{H3,P}$ = 10.5 Hz, respectively.

Scheme 2



The stereochemistry at the phosphorus atom in compounds **6** and **7** was deduced from NMR proton signals. Protons on the same face of the ring as the P═O bond are deshielded.[14] For instance, ring protons H4, H5 and H6 are deshielded if the P═O bond is axial, and H3 is deshielded if the P═O is equatorial. The H4, H5, and H6 signals of **6** have extra upfield shifts of 0.08, 0.04, and 0.11 ppm, respectively, compared to the shifts in **7**. The stereochemistry at the phosphorus atom in compound **9** was assumed to be as shown based on the X-ray structure obtained from the polyacetylated derivative **10**.

The synthesis of the *N*-acetyl-D-glucosamine and *N*-acetyl-D-mannosamine phostones **18** and **19** presented a new challenge in the application of the Abramov reaction (Schemes 2). Addition of *O*-benzyl hydroxylamine to 2,3,5-tri-*O*-benzyl D-arabinose[15] led to the corresponding oxime **11** in quantitative yield. We were pleased to find that the addition of trimethyl phosphite in acetic acid proceeded smoothly giving a mixture D-gluco and D-manno isomers each consisting of a pair of two isomeric phosphonate esters. In this case, cyclization to the phostones was spontaneous under the reaction conditions. Flash

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chromatography allowed the isolation of the D-gluco isomer with the *R*-methoxy configuration **12a**, and a mixture of the D-gluco *S*-methoxy isomer **12b**, along with the corresponding D-manno *R*- and *S*-methoxy isomers **13a**,**b** in 75% overall yield.

It was found practical to continue the synthesis with the D-gluco isomer **12a** and the mixture of D-manno isomers **13a**,**b** (containing residual amounts of **12b**). Acetylation of **12a** gave the corresponding *N*-acetyl D-gluco derivative **14a**, while acetylation of the remaining mixture of isomers led to the other D-gluco phosphonate ester **14b** and D-manno analogues **15a**,**b**.

Hydrolysis[16] of the methyl esters **14a,b** and **15a,b** gave the corresponding free acids **16** and **17** which were separated chromatographically. Finally, hydrogenolysis of each isomer gave *N*-acetyl-D-glucosamine phostone **18** and *N*-acetyl-D-mannosamine phostone **19** as the free acids.

Although the *N*-acetyl neuraminic acids have been known as components of glycoproteins, their role as chemotherapeutic agents was not appreciated until recently.[17] Two major areas of interest are concerned with influenza virus A and B and cell adhesion molecules in relation to inflammation. Haemagglutinin[18] and neuraminidase[19] are two major glycoproteins expressed by influenza A and B viruses. Since neuraminidase has been implicated in enhancing viral infectivity as well as in other processes dealing with the movement of viruses, it has been considered as a suitable target to inhibit.[20] Several analogues of *N*-acetyl neuraminic acid have been synthesized in the search for effective anti-influenza agents.[21] Zanamivir,[22] a 2,3-unsaturated 4-guanidino-4-*N*-acetyl neuraminic acid, is a potent inhibitor of neuraminidase (Figure 2). Inhibition has also been reported with the phosphonic acid analogue[23] of *N*-acetyl neuraminic acid and its 2-deoxy phosphonic acid.[24] Surprisingly potent compounds have resulted from the replacement of the trihydroxypropyl side chain with an isopentyl group and the substitution of the 4-hydroxy group with an amine as in GS 4074.[25]

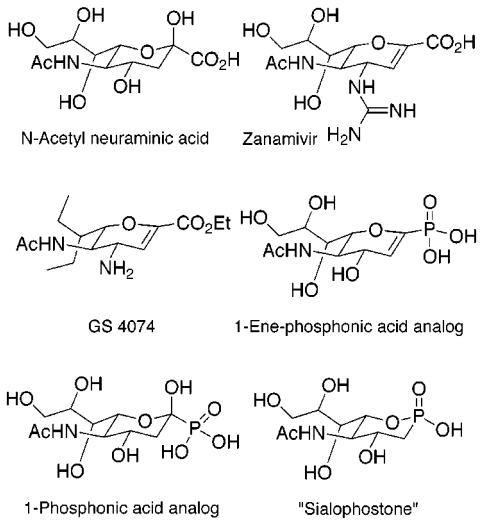

Figure 2.

The cyclic phosphonate analogue of *N*-acetyl neuraminic acid (sialophostone) (Figure 2) presented interesting features that included among others the presence of a phosphonic acid at the anomeric carbon. Sialophostone can be regarded as an anomerically truncated hybrid of the natural compound and its 1-phosphonic acid analogue. A related phostone analogue of phosphoramidon,[26] an inhibitor of endothelin converting enzyme, was recently synthesized in our laboratory.[27]

As in the synthesis of the glycophostones described above, it was more practical to excise the anomeric carbon from a suitably O-protected 5-*N*-acetyl neuraminic acid and to apply the conditions of the Abramov reaction. For practical reasons, it was decided to start with the known tetra-*O*-benzyl derivative **20**.[28] In our hands, the benzylation of the precursor tetrol proceeded best with sodium hydride as base, rather than with barium hydroxide[29] although the yield was still modest. Ozonolysis of **20** and treatment of the corresponding aldehydo ester with trimethyl phosphite in acetic acid gave a 3:2 ratio of the epimeric phosphonates **21** and **22**. Several attempts to deoxygenate the hydroxy group in these molecules resulted in inseparable mixtures possibly due to concominant deoxygenation of the oxalate ester.[30] We therefore converted each isomer to the corresponding cyclic phosphonate. Treatment of **21** with aqueous sodium hydroxide led to a 1:2 mixture of methyl esters **23** and **24**. Similar treatment of **22** led to the corresponding cyclic phosphonate as an inseparable mixture of methyl esters **25**.

The successful application of the Barton−McCombie deoxygenation reaction[31] to highly functionalized 2-hy-

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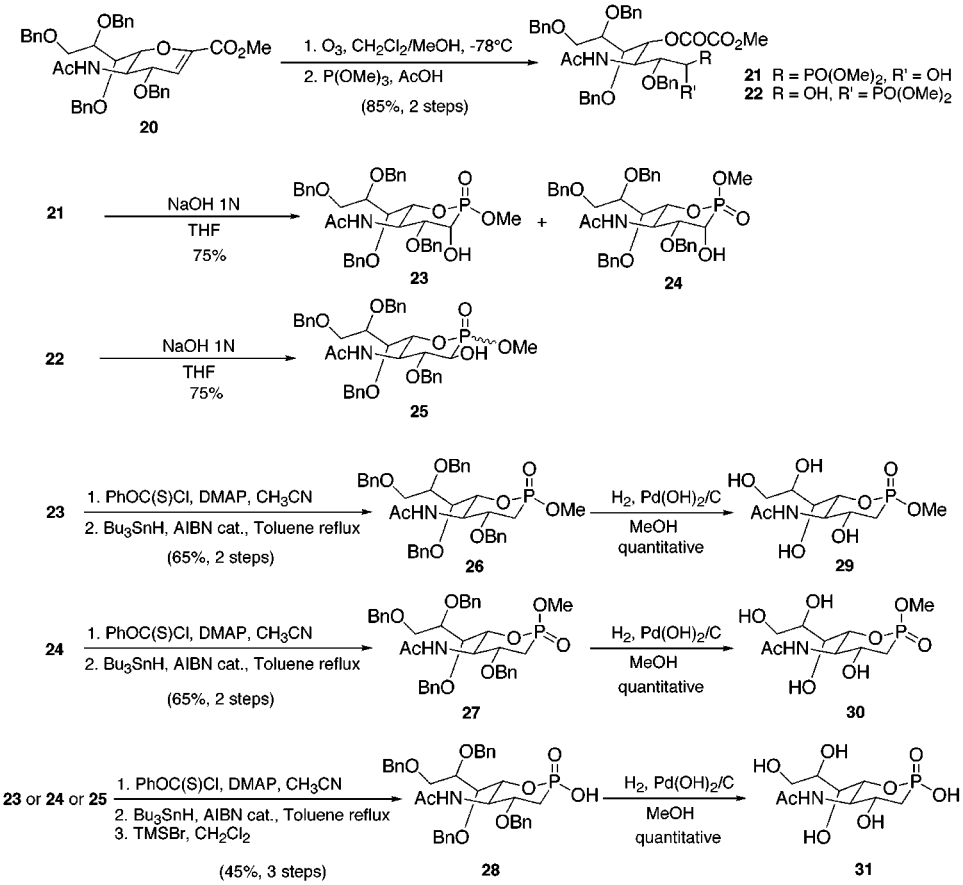
Scheme 3



droxyphosphonates exemplified by compounds **23**−**25** was a rewarding result, in view of the lack of precedents. Thus, formation of the phenylthionocarbonate from **23** and **24** individually, followed by treatment with tributyltin hydride under standard conditions, led to the expected deoxygenated phosphonates **26** and **27** in 65% yield in each case. Similarly, deoxygenation of the mixture of esters **25** gave the corresponding deoxy phosphonates **26** and **27** (Scheme 3).

Hydrogenolysis of each of the esters **26** and **27** gave the corresponding methyl phosphonates **29** and **30**. The stereochemistry of the phosphorus atom in compounds **29** and **30** was assigned on the basis of the observation of an anisotropic effect of the P═O on the protons located on the same face of the ring (vide supra).

Cleavage of the ester with trimethylsilyl bromide[16] gave the phosphonic acid **28**, which could be obtained from **26** or **27**. Hydrogenolysis of the benzyl ethers in **28** led to the sialophostone acid **31**. Unfortunately, compounds **29**, **30**, and **31** were found to be inactive when tested for neuraminidase B (Memphis 3/89) inhibiting activity (<10% at 1 μM).

Experimental Section

General Methods. Unless otherwise noted, all starting materials and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography was performed on 230−240 mesh silica gel. Thin-layer chromatography (TLC) was performed on glass plates coated with 0.02 mm layer of silica gel 60 F_{254}. All solvents were freshly distilled before use.

NMR and Analytical Data. ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz), and ^{31}P NMR spectra (162.0 MHz) were determined in $CDCl_3$ unless otherwise noted. Wherever necessary, ^{1}H NMR assignments were supported by appropriate homonuclear correlation experiments (COSY). Optical rotations were measured at 25 °C at the sodium line.

3,4-Di-*O*-benzyl-L-fucal (1). Sodium hydride (60% dispersion in mineral oil, 120 mg, 3 equiv) was added to a stirred solution of L-fucal (130 mg, 1 mmol) in dry DMF (5 mL), and the slurry was stirred at room temperature for 1 h. The mixture was cooled in an ice bath, and benzyl bromide (595 μL, 5 equiv) was added gradually. When the intensive evolution of hydrogen ceased the clear solution was kept for 1 h at room temperature and then poured into ice−water (20 mL), sulfuric acid 1 M (1 mL), and chloroform (20 mL). The organic layer was dried (sodium sulfate), filtered, and evaporated under diminished pressure. Flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:9, gave **1** as a syrup (295 mg, 95%): $[\alpha]_D$ +76.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45−7.22 (m, 10H), 6.40 (dd, 1H, J = 4.5, 6.2 Hz), 5.01 (d, 1H, J = 11.9 Hz), 4.90−4.87 (m, 1H), 4.78−4.65 (m, 3H), 4.30−4.28 (m, 1H), 4.09 (q, 1H, J = 6.6 Hz), 3.75−3.73 (m, 1H), 1.33 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 144.3, 138.1, 138.0, 128.2−127.3, 99.4, 73.6, 73.1, 72.8, 72.1, 70.7, 16.5; HMRS calcd for $C_{20}H_{23}O_3$ (M^+) 311.30670, found 311.30790.

2,3-Di-*O*-benzyl-5-deoxy-1-dimethylphosphonyl-4-*O*-formyl-L-fucose (2) and 2,3-Di-*O*-benzyl-5-deoxy-1-dimethylphosphonyl-4-*O*-formyl-L-talose (3). A stream of O_3/O_2 was passed into a cooled solution of **1** (200 mg, 0.64 mmol) in dichloromethane (10 mL) at −78 °C until the color turned blue (15 min). Methyl sulfide (10 μL) was added, and the solution was purged at 0 °C with nitrogen (10 min). The clear solution was evaporated under diminished pressure, the residue was dissolved in glacial acetic acid (10 mL) at room temperature, and trimethyl phosphite (152 μL, 2 equiv) was added gradually. After the reaction mixture was stirred overnight, evaporation and flash chromatography on silica gel (eluting with ethyl acetate/hexanes 1:1) gave **2** (93 mg) and **3** (140 mg). For **2**: $[\alpha]_D$ −2.35 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$)

δ 8.35 (s, 1H), 7.68−7.53 (m, 10H), 5.64−5.62 (m, 1H), 5.14 (d, 1H, J = 9.9 Hz), 5.05 (d, 1H, J = 11.2 Hz), 4.96 (d, 1H, J = 11.2 Hz), 4.68 (d, 1H, J = 9.9 Hz), 4.53 (t, 1H, J = 10.7 Hz), 4.25 (dd, 1H, J = 5.3, 8.5 Hz), 4.09 and 4.07 (2d, 6H, J = 10.7, 10.1 Hz), 3.94 (dd, 1H, J = 1.2, 8.3 Hz), 3.56 (dd, 1H, J = 3.2, 10.3 Hz), 1.62 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 160.5, 137.3, 137.0, 128.5−127.98, 79.3 (d, J = 11.9 Hz), 77.3, 75.4, 74.0, 69.4, 66.2 (d, J = 162.9 Hz), 53.5 (d, J = 7.2 Hz), 52.89 (d, J = 7.2 Hz), 16.9; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 25.5; HMRS calcd for $C_{22}H_{30}O_8P$ (M^+) 426.30670, found 426.30790. For **3**: $[\alpha]_D$ −6.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.37−7.25 (m, 10H), 5.40 (t, 1H, J = 6.4 Hz), 4.82−4.65 (m, 5H), 4.39 (dd, 1H, J = 5.0, 10.4 Hz), 4.00 (ddd, 1H, J = 5.0, 6.2, 17.0 Hz), 3.71 (d, 3H, J = 10.4 Hz), 3.68 (d, 3H, J = 10.4 Hz), 1.33 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 160.7, 137.7, 137.5, 128.3−127.7, 81.1 (d, J = 6.9 Hz), 79.6, 74.6, 74.0, 70.2, 68.1 (d, J = 160.8 Hz), 53.3 (d, J = 6.6 Hz), 52.9 (d, J = 6.9 Hz), 17.1; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 26.8; HMRS calcd for $C_{22}H_{30}O_8P$ (M^+) 426.30670, found 426.30790.

4,5-Di-*O*-benzyl-6-methyl-L-*galacto*-(2*R*)-methoxy-1,-2λ^5-oxaphosphorinan-2-one (4) and 4,5-Di-*O*-benzyl-6-methyl-L-*galacto*-(2*S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (5). A quantity of **2** (100 mg, 0.23 mmol) was dissolved in dry methanol (10 mL), and a few drops of freshly prepared sodium methoxide in methanol were added with stirring. After 2 h, the pH was made neutral by addition of Amberlite IR-120 (H^+). The filtered solution was evaporated to give a white foam. Preparative TLC in ethyl acetate was used to isolate and purify **4** (52 mg) and **5** (35 mg) in 95% yield as syrups. For **4**: $[\alpha]_D$ −36.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.26 (m, 10H), 4.97 (d, 1H, J = 11.5 Hz), 4.85 (d, 1H, J = 11.7 Hz), 4.74 (d, 1H, J = 11.7 Hz), 4.66 (d, 1H, J = 11.5 Hz), 4.60 (dd, 1H, J = 8.1, 11.5 Hz), 4.21−4.19 (m, 1H), 3.89 (d, 3H, J = 10.2 Hz), 3.82 (td, 1H, J = 2.3, 10.5 Hz), 3.66−3.39 (m, 1H), 1.30 (dd, 3H, J = 1.5, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 138.2, 137.8, 128.4−127.6, 82.9 (d, J = 10.1 Hz), 78.0, 74.9, 74.6 (d, J = 5.7 Hz), 74.2, 67.4 (d, J = 143.0 Hz), 53.6 (d, J = 7.0 Hz), 17.8 (d, J = 10.8 Hz); ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 19.8; HMRS calcd for $C_{20}H_{26}O_6P$ (M^+) 393.30981, found 393.31130. For **5**: $[\alpha]_D$ −35.3 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.26 (m, 10H), 4.97 (d, 1H, J = 11.4 Hz), 4.78 (q, 2H, J = 11.7 Hz), 4.67 (d, 1H, J = 11.4 Hz), 4.44−4.39 (m, 2H), 3.94 (td, 1H, J = 3.1, 10.6 Hz), 3.84 (d, 3H, J = 11.0 Hz), 3.69 (s, 1H), 1.31 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 137.7, 137.6, 128.5−127.7, 83.1 (d, J = 8.0 Hz), 75.0, 73.8 (d, J = 3.3 Hz), 73.7, 66.1 (d, J = 138.6 Hz), 53.9 (d, J = 6.5 Hz), 17.8 (d, J = 10.9 Hz); ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 24.1; HMRS calcd for $C_{20}H_{26}O_6P$ (M^+) 393.30981, found 393.31130.

6-Methyl-L-*galacto*-(2*R*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (6). A solution of **4** (17 mg, 0.04 mmol) in methanol (2 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated to give **7** as a syrup (9 mg, quant); $[\alpha]_D$ −45.8 (*c* 0.9, MeOH); ^{1}H NMR (CD_3OD) δ 4.48 (qdd, 1H, J = 0.9 Hz, 2.8, 6.4, 9.3 Hz), 4.13 (dd, 1H, J = 8.0, 10.2 Hz), 3.92 (td, 1H, J = 2.7, 10.7 Hz), 3.83 (d, 3H, J = 10.9 Hz), 3.79−3.78 (m, 1H), 1.37 (dd, 3H, J = 1.5, 6.5 Hz); ^{13}C NMR (CD_3OD) δ 75.7 (d, J = 3.0 Hz), 75.0 (d, J = 13.0 Hz), 74.8, 65.9 (d, J = 142.6 Hz), 54.4 (d, J = 6.7 Hz), 17.9 (d, J = 10.9 Hz); ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 26.3; HMRS calcd for $C_6H_{14}O_6P$ (M^+) 213.28480, found 213.28320.

6-Methyl-L-*galacto*-(2*S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (7). A solution of **5** (14 mg, 0.037 mmol) in methanol (2 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated to give **6** as a syrup (8 mg, quant): $[\alpha]_D$ −77.4 (*c* 0.7, MeOH); ^{1}H NMR (CD_3OD) δ 4.35 (qdd, 1H, J = 1.1, 2.3, 6.5 Hz), 4.11 (dd, 1H, J = 9.3, 9.8 Hz), 3.86 (d, 3H, J = 10.2 Hz), 3.83 (td, 1H, J = 2.6, 9.8 Hz), 3.74 (dd, 1H, J = 2.3, 2.6 Hz), 1.37 (dd, 3H, J = 1.6, 6.5 Hz); ^{13}C NMR (CD_3OD) δ 79.1 (d, J = 5.5 Hz), 78.1 (d, J = 10.4 Hz), 77.1, 70.3 (d, J = 144.8 Hz), 56.3 (d, J = 7.8 Hz), 20.4 (d, J = 10.8 Hz); ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 22.5; HMRS calcd for $C_6H_{14}O_6P$ (M^+) 213.28480, found 213.28320.

4,5-Di-*O*-benzyl-6-methyl-L-galacto-(2*R*)-hydroxy-1,2λ5-oxaphosphorinan-2-one (8). Compound **4** and/or **5** (112 mg, 0.28 mmol) was dissolved in dichloromethane (10 mL), and trimethylsilyl bromide (190 μL, 5 equiv) was added. The solution was stirred overnight at room temperature with protection from atmospheric moisture. Water (50 μL) was added, and the solution was stirred for 30 min. After concentration, the residue was purified by precipitation (ethyl acetate/pentane) to give **8** as an amorphous powder (87 mg, 80%): $[\alpha]_D$ −54.4 (*c* 1.0, $CHCl_3$); mp 248−250 °C; ^{1}H NMR (DMSO-d_6) δ 7.40−7.25 (m, 10H, arom.), 4.83 (d, 1H, J = 10.5 Hz), 4.75 (s, 2H), 4.56 (d, 1H, J = 10.5 Hz), 4.17 (br, 1H), 3.78−3.50 (m, 2H), 3.38 (br, 1H), 1.16 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 140.3, 140.0, 129.1−128.2, 85.1 (d, J = 9.0 Hz), 80.4, 75.6, 73.3, 71.4 68.6 (d, J = 136.2 Hz), 19.1; ^{31}P NMR (DMSO-d_6) (H_3PO_4 in DMSO-d_6 external reference δ 0.0 ppm) δ 20.1; HMRS calcd for $C_{19}H_{24}O_6P$ (M^+) 379.08484, found 379.08410.

6-Methyl-L-*galacto*-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (L-Fucophostone) (9). A solution of **8** (30 mg, 0.08 mmol) in methanol (2 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated to give **9** as a syrup (15 mg, quant): $[\alpha]_D$ −64.4 (*c* 0.7, MeOH); ^{1}H NMR (CD_3OD) δ 4.38 (l, 1H), 4.04 (l, 1H), 3.86 (l, 1H), 3.76 (l, 1H), 1.36 (d, 3H, J = 5.0 Hz); ^{13}C NMR (CD_3OD) δ 74.7 (d, J = 8.9 Hz), 74.4, 74.0, 66.9 (d, J = 146.9 Hz), 17.1 (d, J = 10.6 Hz); ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 20.1; HMRS calcd for $C_5H_{12}O_6P$ (M^+) 199.01154, found 199.01230.

3,4,5-Tri-*O*-acetyl-6-methyl-L-galacto-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (10). A solution of **4** and/or **5** (40 mg, 0.1 mmol) in methanol (2 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated. The residue was dissolved in acetic anhydride (5 mL) and cooled at 0 °C, $BF_3{\cdot}Et_2O$ (20 μL) was added, and the mixture was stirred at room temperature overnight. The solution was poured into aqueous saturated sodium bicarbonate, and the solution was extracted with chloroform (2 × 5 mL) and concentrated. The residue was dissolved in dichloromethane (5 mL), and trimethylsilyl bromide (90 μL, 5 equiv) was added. The solution was stirred overnight at room temperature with protection from atmospheric moisture. Water (50 μL) was added, and the solution was stirred for 30 min. After concentration, the residue was purified by crystallization (ethyl acetate/pentane) to give **10** as fine needles (20 mg, 75%): mp 80−82 °C; $[\alpha]_D$ −43.5 (*c* 0.8, MeOH); ^{1}H NMR (CD_3OD) δ 5.41 (t, 1H, J = 10.9 Hz), 5.27 (s, 1H), 5.23 (td, 1H, J = 3.3 et 6.5 Hz), 4.56−4.54 (m, 1H), 3.19−3.18 (m, 1H), 2.08 1.99 1.84 (3s, 9H), 1.17 (d, 3H, J = 6.3 Hz); ^{13}C NMR (CD_3OD) δ 171.9, 171.5, 171.1 (d, J = 4.5 Hz), 73.9 (d, J = 5.4 Hz), 73.5 (d, J = 11.5 Hz), 73.2, 66.4 (d, J = 147.8 Hz), 20.6, 20.5, 20.4, 17.6 (d, J = 10.5 Hz); ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 12.9.

2,3,5-Tri-*O*-benzyl-D-arabinose-*O*-benzyloxime (11). To a suspension of 2,3,5-tri-*O*-benzyl-D-arabinose (3 g, 7.14 mmol) in dry methanol (50 mL) were added *O*-benzylhydroxylamine hydrochloride (2.5 g, 2 equiv) and pyridine (2.5 mL). After being stirred overnight, the clear solution was concentrated, and dichloromethane (20 mL) was added. After filtration and concentration, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:4, to give **11** as a colorless oil (3.81 g, quant): $[\alpha]_D$ −34.36 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.14 (m, 20H), 5.27−5.19 (m, 2H), 4.76−4.44 (m, 5H), 4.21−4.04 (m, 1H), 3.85−3.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 149.1, 138.0−127.6, 80.2, 79.1, 76.5, 76.4, 76.0, 74.2, 74.1, 74.5, 73.4, 72.4, 72.3, 71.2, 71.0, 70.8, 70.0, 69.9; HRMS calcd for $C_{33}H_{36}NO_5$ (M^+) 526.25934, found 526.26040.

4,5-Di-*O*-benzyl-3-benzyloxyamino-3-deoxy-6-benzyloxymethyl-D-*gluco*-(2*R/S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (12a,b) and 4,5-Di-*O*-benzyl-3-benzyloxyamino-3-deoxy-6-benzyloxymethyl-D-*manno*-(2*R/S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (13a,b). To a solution of **11** (2 g, 3.8 mmol) in glacial acetic acid (20 mL) was added trimethyl phosphite (1.34 mL, 3 equiv). After being stirred at room temperature for 36 h, the solution was evaporated, and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:1 to give the D-glucophostone isomer **12a** as a pale yellow solid (300 mg) and the other isomers (**12b**, **13a**,**b**) as a yellow oil (1.45 g) for an overall yield of 75%. For **12a**: $[\alpha]_D$ +55.2 (*c* 0.5, $CHCl_3$); ^1H NMR (C_6D_6) δ 7.31−7.00 (m, 20H), 4.79 (d, 1H, J = 11.4 Hz), 4.73 (d, 1H, J = 11.1 Hz), 4.70 (d, 1H, J = 15.7 Hz), 4.68 (d, 1H, J = 6.9 Hz), 4.59 (d, 1H, J = 11.0 Hz), 4.47 (d, 1H, J = 11.1 Hz), 4.34 (d, 1H, J = 9.5 Hz), 4.20 (dd, 2H, J = 12.0, 50.3 Hz), 3.97 (t, 1H, J = 10.3 Hz), 3.81 (t, 1H, J = 19.2 Hz), 3.57 (td, 1H, J = 2.6, 11.5 Hz), 3.49 (d, 3H, J = 11.2 Hz), 3.43 (dd, 1H, J = 1.4, 10.9 Hz), 2.05 (s, 3H); ^{13}C NMR (C_6D_6) δ 135.5, 139.2, 138.8, 138.6, 129.3−128.1, 81.3 (d, J = 10.0 Hz), 79.0, 75.5, 77.0, 76.3, 75.6, 73.9, 69.3 (d, J = 9.7 Hz), 62.2 (d, J = 130.0 Hz), 53.3 (d, J = 5.3 Hz); ^{31}P NMR (C_6D_6) (H_3PO_4 in C_6D_6 external reference δ 0.0 ppm) δ 25.4; HRMS calcd $C_{34}H_{39}NO_7P$ (M^+) 604.24640, found 604.24810. For **12b**, **13a**,**b**: ^1H NMR ($CDCl_3$) δ 7.43−7.22 (m, 20H), 6.45−6.10 (m, total 1H), 4.90−4.55 (m, 9H), 4.35−4.0 (m, 3H), 3.92 3.90 3.78 (3d, total 3H, J = 11.0, 10.7 and 10.8 Hz); ^{13}C NMR ($CDCl_3$) δ 138.0−137.2, 128.8−127.6, 79.5, 79.4, 78.9, 78.7, 78.4, 76.6, 76.5, 76.4, 76.3, 75.7, 75.2, 74.4, 74.0, 73.9, 73.7, 73.6, 73.5, 73.4, 73.3, 72.7, 69.4 (d, J = 6.9 Hz), 68.9 (d, J = 8.2 Hz), 68.7 (d, J = 9.7 Hz), 61.2 (d, J = 142.3 Hz), 57.1 (d, J = 140.5 Hz), 56.5 (d, J = 139.1 Hz), 53.4 (d, J = 5.4 Hz), 52.7 (d, J = 7.0 Hz), 52.3 (d, J = 6.4 Hz); ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 22.0, 20.5 and 19.6 (ratio 1:2:3.3); HRMS calcd $C_{34}H_{38}NO_7P$ (M^+) 604.24640, found 604.24810.

3-*N*-Acetyl-4,5-di-*O*-benzyl-3-*N*-benzyloxyamino-3-deoxy-6-benzyloxymethyl-D-*gluco*-(2*R/S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (14a,b) and 3-*N*-Acetyl-4,5-di-*O*-benzyl-3-*N*-benzyloxyamino-3-deoxy-6-benzyloxymethyl-D-*manno*-(2*R/S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (15a,b). Representative Procedure. To a stirred solution of **12a** (200 mg, 0.33 mmol) at 0 °C in dry dichloromethane (10 mL) was added a catalytic amount of DMAP and triethylamine (92 μL, 2 equiv) followed by acetyl chloride (50 μL, 3 equiv) under nitrogen. The solution was stirred overnight at room temperature and poured into a separatory funnel containing cold water (20 mL). After extraction and washing with a saturated solution of sodium hydrogencarbonate and brine, the organic layer was concentrated and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:1, to give **14a** (160 mg, 75%) as an oil. The same procedure was applied to **12b/13a**,**b** (1 g, 1.65 mmol) to give **14b/15a**,**b** (800 mg, 75%). For **14a**: $[\alpha]_D$ −6.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.48−7.11 (m, 20H), 5.7 (br, 1H), 5.15 (t, 1H, J = 10.5 Hz), 4.90 (d, 1H, J = 9.3 Hz), 4.78 (d, 2H, J = 10.8 Hz), 4.67−4.60 (m, 4H), 4.55 (d, 1H, J = 12.0 Hz), 4.41−4.36 (m, 2H), 4.02 (t, 1H, J = 9.6 Hz), 3.94−3.90 (m, 4H), 3.78 (dd, 1H, J = 2.0, 11.2 Hz), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 138.2, 137.6, 137.5, 134.6, 129.8−126.9, 79.4, 79.0 (d, J = 13.5 Hz), 78.7, 75.4 (d, J = 2.0 Hz), 75.3, 74.6, 73.4, 68.2 (d, J = 9.9 Hz), 54.8 (d, J = 132.2 Hz), 54.2 (d, J = 6.8 Hz), 20.3; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 20.5; HRMS calcd for $C_{36}H_{41}NO_8P$ (M^+) 646.25696, found 646.25850. For **14b**, **15a**,**b**: ^1H NMR ($CDCl_3$) δ 7.43−7.22 (m, 20H), 4.90−4.55 (m, 9H), 4.35−4.0 (m, 3H), 3.92 3.90 3.78 (3d, total 3H, J = 11.0, 10.7 and 10.8 Hz), 2.09 (3s, total 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 176.1, 176.0, 138.0−137.2, 128.8−127.6, 79.5, 79.4, 78.9, 78.7, 78.4, 76.6, 76.5, 76.4, 76.3, 75.7, 75.2, 74.4, 74.0, 73.9, 73.7, 73.6, 73.5, 73.4, 73.3, 72.7, 69.4 (d, J = 6.9 Hz), 68.9 (d, J = 8.2 Hz), 68.7 (d, J = 9.7 Hz), 61.2 (d, J = 142.3 Hz), 57.1 (d, J = 140.5 Hz), 56.5 (d, J = 139.1 Hz), 53.4 (d, J = 5.4 Hz), 52.7 (d, J = 7.0 Hz), 52.3 (d, J = 6.4 Hz), 20.3, 20.2, 20.1; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 22.1, 20.6 and 19.7 (ratio 1:2:3.3); HRMS calcd for $C_{36}H_{41}NO_8P$ (M^+) 646.25696, found 646.25850.

3-*N*-Acetyl-4,5-di-*O*-benzyl-3-*N*-benzyloxyamino-3-deoxy-6-benzyloxymethyl-D-*gluco*-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (16) and 3-*N*-Acetyl-4,5-di-*O*-benzyl-3-*N*-benzyloxyamino-3-deoxy-6-benzyloxymethyl-D-*manno*-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (17). A mixture containing **14a**,**b** and **15a**,**b** (100 mg, 0.16 mmol) was dissolved in dichloromethane (10 mL), and trimethylsilyl bromide (5 equiv, 100 μL) was added. The solution was stirred overnight at room temperature with protection from atmospheric moisture. Water (20 μL) was added, and the solution was stirred for 30 min. After concentration, the residue was purified by flash chromatography on silica gel, eluting with chloroform/methanol 95:5, to give **16** (55 mg) and **17** (35 mg) as white powders after precipitation (chloroform/pentane) for an overall yield of 90%. For **16**: $[\alpha]_D$ +33.5 (*c* 1.0, $CHCl_3$); mp 116−118 °C; ^1H NMR (DMSO-d_6) δ 7.73−7.06 (m, 20H), 5.84 (d, 1H, J = 9.7 Hz), 4.87 (d, 1H, J = 9.7 Hz), 4.77−4.62 (m, 2H), 4.56−4.36 (m, 5H), 4.11−4.02 (m, 2H), 3.73−3.54 (m, 3H), 1.98 (s, 3H);^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6, 139.6−127.9, 82.0, 81.5, 77.9, 75.0, 74.7, 74.3, 73.8, 73.2, 70.6, 56.9 (d, J = 121.5 Hz), 21.1; ^{31}P NMR (162 MHz, DMSO-d_6) (H_3PO_4 in DMSO external reference δ 0.0 ppm) δ 7.8; HRMS calcd for $C_{35}H_{39}NO_8P$ (M^+) 632.24133, found 632.23930. For **17**: $[\alpha]_D$ +27.0 (*c* 1.0, $CHCl_3$); mp 120−122 °C; ^1H NMR (DMSO-d_6) δ 7.5−7.0 (m, 20H), 5.69 (d, 1H, J = 9.4 Hz), 4.76 (d, 1H, J = 9.5 Hz), 4.66 (d, 1H, J = 10.4 Hz), 4.57 (d, 1H, J = 10.4 Hz), 4.50 (s, 2H), 4.30 (dd, 2H, J = 11.0 and 16.9 Hz), 4.16 (s, 1H), 3.89 (t, 1H, J = 9.4 Hz), 3.59−3.39 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 174.8, 139.3−128.1, 82.6, 78.1, 77.5, 75.0, 73.4, 72.4, 71.5 (d, J = 8.9 Hz), 53.1 (d, J = 136.5 Hz), 21.2;^{31}P NMR (162 MHz, DMSO-d_6) (H_3PO_4 in DMSO external reference δ 0.0 ppm) δ 5.9; HRMS calcd for $C_{35}H_{39}NO_8P$ (M^+) 632.24133, found 632.23930.

3-*N*-Acetyl-3-deoxy-6-hydroxymethyl-D-*gluco*-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (*N*-Acetyl-D-glucosaminophostone) (18). A solution of **16** (20 mg, 0.03 mmol) in methanol (2 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) and palladium on carbon 30% (10 mg) at 60 psi for 2 days. The solution was filtered over Celite and evaporated to give **18** after precipitation (methanol/ethyl acetate) as a white powder (8 mg, 95%): $[\alpha]_D$ +8.5 (*c* 0.5, MeOH); mp 120−122 °C; ^1H NMR (CD_3OD) δ 4.34 (dd, 1H, J = 11.1, 14.4 Hz), 4.03−3.98 (m, 1H), 3.90−3.87 (m, 1H), 3.86−3.78 (m, 1H), 3.72 (td, 1H, J = 1.9, 9.1 Hz), 3.54 (t, 1H, J = 9.1 Hz), 2.01 (d, 3H, J = 1.3 Hz); ^{13}C NMR (CD_3OD) δ 175.1 (d, J = 3.5 Hz), 81.5 (d, J = 3.2 Hz), 76.4 (d, J = 11.1 Hz), 73.6, 64.2 (d, J = 9.9 Hz), 50.6 (d, J = 136.9 Hz), 24.1; ^{31}P NMR (CD_3OD) (H_3PO_4in CD_3OD external reference δ 0.0 ppm) δ 15.5; HRMS calcd for $C_7H_{15}NO_7P$ (M^+) 256.05862, found 256.05960.

3-*N*-Acetyl-3-deoxy-6-hydroxymethyl-D-*manno*-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (*N*-Acetyl-D-mannosaminophostone) (19). A solution of **17** (20 mg, 0.03 mmol) in methanol (2 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) and 10 mg of palladium on carbon 30% at 60 psi for 2 days. The solution was filtered over Celite and evaporated to give **19** after precipitation (methanol/ethyl acetate) as a white powder (8 mg, 95%): $[\alpha]_D$ +7.7 (*c* 0.5, MeOH); mp 130−132 °C; ^1H NMR (CD_3OD) δ 4.40 (dd, 1H, J = 10.7, 16.9 Hz), 3.91−3.73 (m, 3H), 3.59−3.56 (m, 1H), 3.50 (t, 1H, J = 9.4 Hz), 2.00 (d, 3H, J = 1.2 Hz); ^{13}C NMR (CD_3OD) δ 175.2 (d, J = 3.1 Hz), 82.6 (d, J = 5.4 Hz), 77.1 (d, J = 9.2 Hz), 73.4, 64.4 (d, J = 6.6 Hz), 51.9 (d, J = 140.2 Hz), 24.2; ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 15.3; HRMS calcd for $C_7H_{15}NO_7P$ (M^+) 256.05862, found 256.05960.

3-Acetamido-2,5,6,7-tetra-*O*-benzyl-2-deoxy-4-*O*-(methyloxalyl)-1-dimethyl phosphonyl-D-*erythro*-L-*manno*-heptitol (21) and 3-Acetamido-2,5,6,7-tetra-*O*-benzyl-2-deoxy-4-*O*-(methyloxalyl)-1-dimethylphosphonyl-D-*erythro*-L-*gluco*-heptitol (22). A stream of O_3/O_2 was passed into a

cooled solution of **20** (450 mg, 0.67 mmol) in dichloromethane (20 mL) at −78 °C until the color turned blue (15 min). The solution was purged with nitrogen (10 min) and evaporated to give a foam, which was suspended in glacial acetic acid (20 mL), and trimethyl phosphite (400 μL, 5 equiv) was added. The reaction was stirred at room temperature (24 h) and concentrated, and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 4:1, to give **21** (279 mg) and **22** (185 mg) as syrups for an overall yield of 85%. For **21**: $[\alpha]_D$ +1.4 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41−7.06 (m, 20H), 6.44 (d, 1H, *J* = 8.7 Hz), 5.47 (dd, 1H, *J* = 2.8, 10.1 Hz), 5.38 (dd, 1H, *J* = 6.2, 24.7 Hz), 4.96 (d, 1H, *J* = 9.9 Hz), 4.65 (d, 1H, *J* = 11.0 Hz), 4.56 (d, 2H, *J* = 10.2 Hz), 4.44−4.37 (m, 4H), 4.28 (d, 1H, *J* = 9.9 Hz), 4.12−4.07 (m, 2H), 3.88 (d, 3H, *J* = 10.2 Hz), 3.75 (d, 3H, *J* = 10.2 Hz), 3.73 (s, 3H), 3.72−3.56 (m, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 157.3, 157.2, 137.9, 137.5, 137.1, 128.4−127.6, 79.4, 76.8 (d, *J* = 3.1 Hz), 74.5, 74.4, 73.1, 72.3, 72.0, 67.1, 66.3 (d, *J* = 170.5 Hz), 54.0 (d, *J* = 6.9 Hz), 53.4, 52.5 (d, *J* = 7.1 Hz), 52.2 (d, *J* = 12.7 Hz), 22.3; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 26.8; HMRS calcd for $C_{42}H_{51}NO_{13}P$ (M^+) 808.30981, found 808.31130. For **22**: $[\alpha]_D$ +9.0 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39−7.17 (m, 20H), 6.05 (d, 1H, *J* = 9.4 Hz), 5.49 (dd, 1H, *J* = 3.1, 9.4 Hz), 4.88 (d, 1H, *J* = 10.2 Hz), 4.70−4.62 (m, 3H), 4.53−4.47 (m, 4H), 4.13−4.07 (m, 2H), 3.79 (d, 3H, *J* = 10.5 Hz), 3.77 (d, 3H, *J* = 10.5 Hz), 3.73 (s, 3H), 3.63 (dd, 1H, *J* = 3.5, 10.4 Hz), 3.28 (t, 1H, *J* = 10.2 Hz), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 157.5, 157.2, 137.8, 137.7, 137.2, 128.7−127.6, 78.6, 75.1, 74.9 (d, *J* = 4.5 Hz), 74.8, 74.1, 73.5, 73.2, 72.4, 67.9 (d, *J* = 161.8 Hz), 67.8, 53.7 (d, *J* = 7.7 Hz), 53.3, 53.0 (d, *J* = 7.2 Hz), 52.2 (d, *J* = 10.4 Hz), 23.0; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 24.8; HMRS calcd for $C_{41}H_{51}NO_{13}P$ (M^+) 808.30981, found 808.31130.

5-Acetamido-4-*O*-benzyl-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-gluco-(2*R*/*S*)-methoxy-1,2λ⁵-oxaphosphorinan-2-one (23) and (24). A quantity of **21** (200 mg, 0.25 mmol) was dissolved in THF (10 mL), and sodium hydroxide 1 N (800 μL) was added dropwise. After 10 min, the solution was poured into hydrochloric acid 1 N (10 mL) and chloroform (20 mL). The organic solution was dried (sodium sulfate), filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:2, to give **23** (80 mg) and **24** (45 mg) as syrups for an overall yield of 75%. For **23**: $[\alpha]_D$ +6.4 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41−7.23 (m, 20H), 5.28 (d, 1H, *J* = 9.2 Hz), 4.73 (d, 1H, *J* = 11.0 Hz), 4.65−4.39 (m, 1H), 3.79−3.73 (m, 4H), 3.75 (d, 3H, *J* = 10.9 Hz), 3.62 (dd, 1H, *J* = 3.5, 10.9 Hz), 1.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 138.2, 137.9, 137.8, 137.0, 128.6−127.5, 79.3, 76.5, 74.9 (d, *J* = 8.5 Hz), 74.6, 74.0, 73.3, 72.7, 71.2, 67.8, 64.1 (d, *J* = 146.2 Hz), 55.3 (d, *J* = 7.3 Hz), 46.7, 23.5; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 19.9; HMRS calcd for $C_{38}H_{45}NO_9P$ (M^+) 690.28480, found 690.28320. For **24**: $[\alpha]_D$ −5.6 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36−7.22 (m, 20H, arom.), 5.32 (d, 1H, *J* = 7.5 Hz), 4.93 (d, 1H, *J* = 10.5 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.61 (s, 2H), 4.54−4.50 (m, 4H), 4.41−4.37 (m, 2H), 4.16−4.13 (m, 1H), 3.95−3.85 (m, 3H), 3.77 (dd, 1H, *J* = 2.5, 11.0 Hz), 3.64−3.60 (m, 1H), 3.54 (d, 3H, *J* = 10.5 Hz), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 138.2, 138.0, 137.9, 137.4, 128.9−127.3, 77.3, 76.4, 75.0, 74.2 (d, *J* = 8.4 Hz), 73.2, 73.0, 71.9, 71.6, 68.0, 63.2 (d, *J* = 145.9 Hz), 52.2 (d, *J* = 6.9 Hz), 48.7, 23.4; ^{31}P NMR (162 MHz, $CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 20.4; HMRS calcd for $C_{38}H_{45}NO_9P$ (M^+) 690.28480, found 690.28320.

5-Acetamido-4-*O*-benzyl-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-manno-(2*R*/*S*)-methoxy-1,2λ⁵-oxaphosphorinan-2-one (25). A quantity of **22** (200 mg, 0.25 mmol) was dissolved in THF (10 mL), and sodium hydroxide 1 N (800 μL) was added dropwise. After 10 min, the solution was poured into hydrochloric acid 1 N (10 mL) and chloroform (20 mL). The organic layer was dried (sodium sulfate), filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:2, to give **25** (125 mg, 75%) as an inseparable mixture of phosphonates: ^1H NMR ($CDCl_3$) δ 7.63−7.17 (m, 20H), 4.90−3.81 (m, 15H), 3.78 and 3.76 (d, total 3H, POMe minor *J* = 11.0 Hz and POMe major *J* = 10.2 Hz), 3.75−3.61 (m, 2H), 1.78 and 1.64 (s, total 3H); ^{13}C NMR ($CDCl_3$) δ 170.3 (minor), 170.1 (maj), 138.4−137.7, 128.9−127.7, 80.9 (minor), 80.5 (major), 77.2, 75.1, 74.7, 74.5, 73.9, 73.3, 73.3, 72.3, 71.0 (d, *J* = 143 Hz), 67.6 (minor), 67.4 (major), 54.1 (d, *J* = 6.9 Hz), 54.0 (d, *J* = 6.5 Hz), 52.2 (major), 50.9 (minor), 23.4 (major), 23.3 (minor); ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 23.9 and 19.8 (ratio 2:5); HMRS calcd for $C_{38}H_{45}NO_9P$ (M^+) 690.28190, found 690.28320.

5-Acetamido-4-*O*-benzyl-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-lyxo-(2*R*)-methoxy-1,2λ⁵-oxaphosphorinan-2-one (26). Phenyl thiochloroformate (3 equiv, 50 μL) was added to a solution of compound **23** (50 mg, 0.072 mmol) and DMAP (5 equiv, 45 mg) in dry acetonitrile (10 mL). After the mixture was stirred for 16 h at room temperature, water (1 mL) was added and the mixture stirred for a further 30 min. Ethyl acetate (20 mL) was added, and the organic phase was washed with 5% sodium hydrogen carbonate (2 × 10 mL) and hydrochloric acid 1 N (10 mL), dried (sodium sulfate), and filtered. The solvent was evaporated to give a yellow solid. The solid was dissolved in dry toluene, and then AIBN (0.1 equiv, 2 mg) and tributyltin hydride (3 equiv, 60 μL) were added. The mixture was stirred for 2 h at 110 °C. The solvent was evaporated, acetonitrile (15 mL) added, and the solution washed with hexanes (15 mL). After concentration of the layer, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:2, to give **26** as a syrup (30 mg, 65%): $[\alpha]_D$ −7.5 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.57−7.13 (m, 20H, arom.), 5.13 (d, 1H, *J* = 9.7 Hz), 4.83−4.31 (m, 10H), 4.00−3.93 (m, 1H), 3.89−3.85 (m, 1H), 3.80−3.69 (m, 2H), 3.75 (d, 3H, *J* = 9.4 Hz), 3.64 (dd, 1H, *J* = 4.0, 11.3 Hz), 2.59−2.49 (m, 1H), 2.04−1.84 (m, 1H), 1.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1, 138.0, 137.9, 137.8, 137.5, 128.6−127.6, 75.8, 75.1, 75.0, 74.5, 74.2, 73.3, 72.7, 70.7, 67.7, 53.0 (d, *J* = 6.5 Hz), 51.3, 27.6 (d, *J* = 120.7 Hz), 23.6; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 26.6; HMRS calcd for $C_{38}H_{45}NO_8P$ (M^+) 674.28827, found 674.28660.

5-Acetamido-4-*O*-benzyl-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-lyxo-(2*S*)-methoxy-1,2λ⁵-oxaphosphorinan-2-one (27). Phenyl thiochloroformate (3 equiv, 50 μL) was added to a solution of compound **24** (50 mg, 0.072 mmol) and DMAP (5 equiv, 45 mg) in dry acetonitrile (10 mL). After the mixture was stirred for 16 h at room temperature, water (1 mL) was added and the mixture stirred for a further 30 min. Ethyl acetate (20 mL) was then added and the organic phase washed with 5% sodium hydrogen carbonate (2 × 10 mL) and hydrochloric acid 1 N (10 mL), dried (sodium sulfate), and filtered. The solvent was evaporated to give a yellow solid that was dissolved in dry toluene and heated for 2 h at 110 °C with AIBN (0.1 equiv, 2 mg) and tributyltin hydride (3 equiv, 60 μL). The solvent was evaporated, acetonitrile (15 mL) was added, and the solution was washed with hexanes (15 mL). After concentration of the layer, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:2 gave **27** as a syrup (30 mg, 65%): $[\alpha]_D$ −34.4 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.45−7.13 (m, 20H), 4.84 (d, 1H, *J* = 8.5 Hz), 4.71−4.65 (m, 2H), 4.62 (d, 2H, *J* = 4.5 Hz), 4.58−4.50 (m, 4H), 4.36 (d, 1H, *J* = 11.7 Hz), 4.09 (td, 1H, *J* = 2.6, 9.5 Hz), 3.89 (s, 2H), 3.85−3.67 (m, 3H), 3.55 (d, 3H, *J* = 10.8 Hz), 2.47−2.38 (m, 1H), 1.91−1.78 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.0, 137.9, 137.8, 137.5, 128.6−127.6, 77.3, 74.8, 74.2, 73.3, 71.8, 71.0, 67.4, 52.9, 51.5 (d, *J* = 6.4 Hz), 27.9 (d, *J* = 120.6 Hz), 23.5; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 24.8; HMRS calcd for $C_{38}H_{45}NO_8P$ (M^+) 674.28827, found 674.28660.

5-Acetamido-4-*O*-benzyl-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-lyxo-(2*R*)-hydroxy-1,2λ⁵-oxaphosphorinan-2-one (28). The deoxygenation of **25** (50 mg, 0.074 mmol) gave an inseparable mixture of **26** and **27** that was dissolved in dichloromethane (10 mL), and trimethylsilyl bromide (5 equiv, 145 μL) was added. The solution was stirred overnight at room temperature with protection from atmospheric moisture. Water (50 μL) was added, and the solution was stirred

for 30 min. After concentration, the residue was purified by precipitation (ethyl acetate/pentane) to give **28** (46 mg, 95%) as an amorphous powder: $[\alpha]_D$ −10.0 (*c* 1.0, $CHCl_3$); mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 7.50−7.14 (m, 20H), 4.70−4.63 (m, 3H), 4.59−4.56 (m, 4H), 4.49−4.46 (m, 2H), 4.33 (t, 1H, J = 4.9 Hz), 3.88−3.84 (m, 3H), 3.70 (dd, 1H, J = 3.1, 10.7 Hz), 2.63−2.53 (m, 1H), 1.95 (s, 3H), 1.89−1.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.5, 78,4, 78.1, 76.7 (d, J = 8.3 Hz), 76.0, 75.6, 74.3, 73.6, 72.1, 68.9, 52.6, 30.3 (d, J = 119.7 Hz), 23.1; ^{31}P NMR ($CDCl_3$) (H_3PO_4 in $CDCl_3$ external reference δ 0.0 ppm) δ 18.6; HMRS calcd for $C_{37}H_{43}NO_8P$ (M^+) 660.27264, found 660.27430.

5-Acetamido-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-lyxo-(2*R*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (29). A solution of **26** (65 mg, 0.01 mmol) in methanol (3 mL) was hydrogenated in the presence of 20 mg of palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated to give **29** as an amorphous powder (30 mg, quantitative): $[\alpha]_D$ −7.5 (*c* 0.7, MeOH); mp 118−120 °C; ^{1}H NMR (CD_3OD) δ 4.34 (ddd, 1H, J = 1.1, 2.9, 10.6 Hz), 4.10−4.05 (m, 1H), 3.96 (t, 1H, J = 10.3 Hz), 3.83−3.73 (m, 1H), 3.82 (d, 3H, J = 11.3 Hz), 3.66−3.58 (m, 2H), 3.54 (ddd, 1H, J = 1.1, 4.0 and 9.3 Hz), 3.29−3.27 (m, 1H), 2.00 (s, 3H), 1.99−1.86 (m, 1H); ^{13}C NMR (CD_3OD) δ 176.6, 78.3, 72.5, 71.9 (d, J = 9.1 Hz), 70.3, 66.6, 56.4, 55.9, 33.0 (d, J = 120.9 Hz), 24.4; ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 29.4; HMRS calcd for $C_{10}H_{21}NO_8P$ (M^+) 314.10049, found 314.09960.

5-Acetamido-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-lyxo-(2*S*)-methoxy-1,2λ^5-oxaphosphorinan-2-one (30). A solution of **27** (65 mg, 0.01 mmol) in methanol (3 mL) was hydrogenated in the presence of 20 mg palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated to give **30** as an amorphous powder (30 mg, quantitative): $[\alpha]_D$ −34.4 (*c* 0.8, MeOH); mp 130−132 °C; ^{1}H NMR (CD_3OD) δ 4.22 (ddd, 1H, J = 1.0, 2.8 and 10.3 Hz), 4.01−3.86 (m, 2H), 3.75 (d, 3H, J = 10.9 Hz), 3.77−3.72 (m, 1H), 3.69−3.54 (m, 3H), 2.51−2.42 (m, 1H), 1.99 (s, 3H), 1.89−1.84 (m, 1H); ^{13}C NMR (CD_3OD) δ 176.7, 79.2 (d, J = 5.7 Hz), 72.9, 71.5 (d, J = 9.2 Hz), 70.5, 66.6, 56.1, 53.9 (d, J = 6.8 Hz), 33.0 (d, J = 122.9 Hz), 24.4; ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 27.9; HMRS calcd for $C_{10}H_{21}NO_8P$ (M^+) 314.10049, found 314.09860.

5-Acetamido-5-deoxy-6-[(1*S*,2*S*)-1,2,3-tribenzyloxypropyl]-L-lyxo-(2*R*)-hydroxy-1,2λ^5-oxaphosphorinan-2-one (Sialophostone) (31). A solution of **28** (13 mg, 0.02 mmol) in methanol (3 mL) was hydrogenated in the presence of 10 mg of palladium hydroxide on carbon (Degussa) at 60 psi overnight. The solution was filtered over Celite and evaporated to give **31** after precipitation as an amorphous powder (6 mg, quantitative): $[\alpha]_D$ −7.0 (*c* 0.3, MeOH); mp 178−180 °C; ^{1}H NMR (CD_3OD) δ 4.11−4.08 (m, 1H), 3.98−3.91 (m, 1H), 3.88−3.82 (m, 1H), 3.80−3.75 (m, 2H), 3.62 (q, 1H, J = 5.5 Hz), 3.45 (d, 1H, J = 7.5 Hz), 2.23 (t, 1H, J = 17.5 Hz), 2.02 (s, 3H), 1.76−1.72 (m, 1H); ^{13}C NMR (CD_3OD) δ 174.8, 75.0, 70.9, 70.1, 65.0, 55.2, 34.2 (d, J = 120.4 Hz), 22.7; ^{31}P NMR (CD_3OD) (H_3PO_4 in CD_3OD external reference δ 0.0 ppm) δ 20.7; HMRS calcd for $C_9H_{18}NO_8P$ (M^+) 300.08484, found 300.08410.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P NMR spectra for **6**, **7**, **10**, **12a**, **14a**, **16**−**19**, **23**, **24**, and **26**−**31** and the X-ray crystal structure data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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