Stereoselective Synthesis of the Isosteric Phosphono Analogues of *N*-Acetyl-α-D-glucosamine 1-Phosphate and *N*-Acetyl-α-D-mannosamine 1-Phosphate

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The isosteric phosphono analogues of *N*-acetyl-α-D-glucosamine 1-phosphate and *N*-acetyl-α-D-mannosamine 1-phosphate (**1** and **2**) are stereoselectively synthesized starting from 2,3,5-tri-*O*-benzyl-D-arabinose (**3b**). Reaction of **3b** with divinylzinc stereoselectively affords the glucoenitol **4c**, the mercuriocyclization and subsequent iododemercuriation of which stereoselectively afford the α-C-glucopyranosyl iodide **6b** with a free hydroxyl group at C-2. Temporary protection of the hydroxyl group and treatment with triethyl phosphite converts **6b** into the corresponding phosphonate **7b**. The free hydroxyl group of **7b** is then converted into an acetamido group by oximation, acetylation of the oxime, reduction, and subsequent acetylation. The reduction of the oxime with diborane stereoselectively affords the gluco isomer, whereas catalytic hydrogenation gives the manno isomer. Acetylation and deprotection afford the desired products **1** and **2**.

Glycosyl phosphates play a central role in the metabolism of carbohydrates. They act as glycosyl donors in the biosynthesis of oligo- and polysaccharides and glycoconjugates, and in some cases they also perform the role of metabolic regulators.[1]

N-acetyl-α-D-glucosamine 1-phosphate is a glycosyl phosphate of particular interest, being the key intermediate in the biosynthesis of the N-linked glycoproteins, a class of glycoproteins involved in many important cell−cell and cell−pathogen recognition phenomena. Pharmacologically important examples of these phenomena are HIV-lymphocyte T adhesion or tumor cells−selectin adhesion. The first step in the biosynthesis of the N-linked glycoproteins is the conversion of *N*-acetyl-α-D-glucosamine 1-phosphate into UDP-GlcNAc which is then converted into the dolichyl-*N*-acetyl-α-D-glucosamine 1-diphosphate. Further glycosylations afford a dolichyl diphosphate oligosaccharide which is then transferred to an asparagine residue of the protein. Other important processes involving *N*-acetyl-α-D-glucosamine 1-phosphate are the biosynthesis of mureine and teichoic acids, the main components of the bacterial cell walls. Moreover, it has been recently shown that *N*-acetyl-α-D-glucosamine 1-phosphate is involved in a glycosylation−deglycosylation of some proteins, an abundant and dynamic process the role of which is not clear[2] and is presently under investigation. In light of this evidence, there is a great interest in the synthesis of inhibitors or regulators of the metabolic processes in which *N*-acetyl-α-D-glucosamine 1-phosphate is involved. These molecules could interfere in the cell−pathogen adhesion phenomena and in the formation of bacterial cell wall. Furthermore, they could spread light on the recently discovered dynamic glycosylation process.

N-acetyl-α-D-mannosamine 1-phosphate is another glycosyl phosphate of great interest. It is involved in the biosynthesis of *N*-acetylneuraminic acid, a component of many tumor-associated oligosaccharides and in the biosynthesis of many bacterial polysaccharides repeating units.

Antimetabolites of natural phosphates have been obtained by substituting the oxygen of the phosphoesteric linkage with a carbon atom. The geometry of the so modified molecules, defined isosteric phosphono analogues, is approximately the same of that of the parent natural phosphate.[3] So, these analogues fit the active sites or receptors of the parent substrate. However, they cannot undergo the cleavage of the phosphoesteric bond, which is the main metabolic transformation, and this often results in an inhibition of the metabolic process.

The synthesis of isosteric phosphono analogues of glycosyl phosphates requires the formation of a C-glycosidic bond with the desired stereochemistry. Many examples have been described by us[4] and others,[5] but the analogue of *N*-acetyl-α-D-glucosamine 1-phosphate has never been synthesized, despite its biological importance.

We recently described the synthesis of the phosphono analogue **2** of *N*-acetyl-α-D-mannosamine 1-phosphate,[6] the first example of a phosphono analogue of an aminosugar. Now we describe our efforts in the synthesis of the phosphono analogues of *N*-acetyl-α-D-glucosamine 1-phosphate (**1**) and *N*-acetyl-α-D-mannosamine 1-phos-

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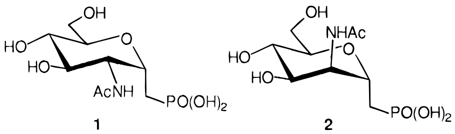
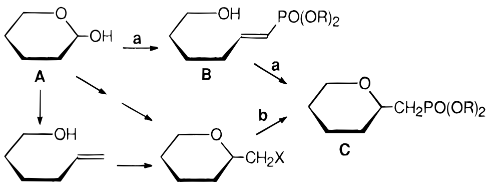
Chart 1



Scheme 1



phate (**2**), affording alternatively each of the two molecules in a stereoselective manner (Chart 1).

Results and Discussion

The most straightforward way to prepare the isosteric phosphono analogue of a glycosyl phosphate is the reaction of the protected aldose **A** with the ylide (diphenylphosphoranylidine)methanephosphonate[5b] or with the anion of a tetraalkyl methylenediphosphonate.[5c] This reaction affords directly the desired C-glycosyl methylenephosphonate **C** by spontaneous Michael cyclization of the α,*β*-phosphonate intermediate **B** (Scheme 1, path a). Unfortunately, this process lacks stereoselection and it is not generally applicable.[5c] So, after some preliminary attempts to apply this reaction to glucosamino derivatives, we decided to effect the synthesis of the phosphono analogue of *N*-acetyl-α-D-glucosamine 1-phosphate following the more general procedure which requires the preparation of a C-glycosyl halide **E** and its conversion into a phosphonate **C** by reaction with a trialkyl phosphite (Scheme 1, path b).

The synthesis of a C-glycosyl halide **E** can be easily and stereoselectively effected by reaction of a properly protected aldose **A** with methylenetriphenylphosphorane and subsequent electrophilic cyclization of the obtained glycoenitol **D** (Scheme 1).[7] In the case of glucosamine this procedure is troublesome: in fact, the reaction of methylenetriphenylphosphorane with properly protected glucosamino derivatives did not afford the desired aminoglucoenitol.[8] An interesting alternative to obtain an aminoglucoenitol is the reaction of *N*-benzyl-*N*-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)amine (**3a**) with vinylmagnesium bromide (Scheme 2).[9] The reaction affords stereoselectively the aminoglucoenitol **4a**, the cyclization of which with mercuric trifluoroacetate gives the α-C-glucopyranoside **5a**.[10] We made different attempts to convert the mercurio derivative **5a** into the corresponding halide. Br_2 or I_2 in CH_2Cl_2, in THF−$NaHCO_3$, or in THF−H_2O−pH 4 (citric buffer) and NBS and NIS in CH_2Cl_2 gave unsatisfactory results. In addition, the direct

Scheme 2

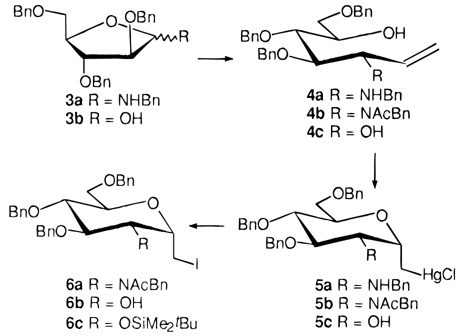
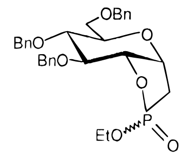


Chart 2



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halocyclization of **4a**, tested with the reagents reported above, was unsuccessful. In the hypothesis that the nucleophilic character of the amino function of **5a**, adjacent to the electrophilic carbon of the desired halide, interferes in the reaction,[10] we also lowered its nucleophilicity by conversion into an acetamide. This required the selective acetylation of the open chain precursor **4a** and the subsequent mercuriocyclization of the obtained product **4b**, as **5a** was inert to acetylation, also under drastic conditions (Ac_2O, Et_3N, DMAP, in toluene). Unfortunately, the *N*-acetylated mercurio derivative **5b** also gave unsatisfactory results in the halodemercuriation, whereas treatment of **4b** with iodine in THF at pH 4 afforded the very labile iodo derivative **6a**, which decomposes when refluxed with $P(OEt)_3$.

To overcome all these difficulties, we decided to follow a different synthetic strategy, in which the amino function is introduced in the molecule after the phosphono function. The strategy requires the synthesis of an α-C-glucopyranoside with a deprotected hydroxyl group at C-2, which is converted into an amino function at the end of the synthesis. This can be done by stereoselective vinylation of 2,3,5-tri-*O*-benzyl-D-arabinose (**3b**) with divinylzinc and subsequent stereoselective cyclization of the obtained enitol **4c**. We observed that the direct iodocyclization of a glucoheptenitol such as **4c** occurs with a debenzylation to afford a furanosidic product.[11] The cyclization of **4c** was then effected with mercuric acetate, and the α-C-glucopyranosyl mercurio derivative **5c**[12] was easily converted into the corresponding stabile iodide **6b.** The conversion of **6b** into the corresponding phosphonate required the temporary protection of the free hydroxyl group at C-2; in fact, direct treatment with $P(OEt)_3$ under reflux afforded **11** (Chart 2). So, the free hydroxyl group of **6b** was protected as *tert*-butyldimethylsilyl ether **6c**, and the Arbuzov reaction afforded the phosphonate **7a**. Desilylation of **7a** by treatment with trifluoroacetic acid gave the desired α-C-glucopyranosylmethanephosphonate **7b**, with a free hydroxyl group at C-2 (Scheme 3).

The conversion of a free hydroxyl group at C-2 of a glucopyranoside into an amino function is a well-

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(8) We tested unfruitfully the reaction on 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranose and 2-amino-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranose.

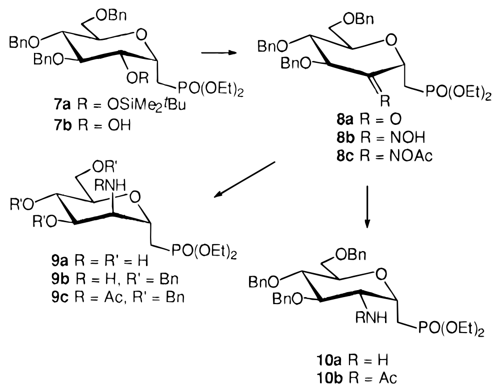
(9) (a) Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 297. (b) Lay, L.; Nicotra, F.; Panza, L.; Verani, A. *Gazz. Chim. Ital.* **1992**, *122*, 345.

(10) The *β*-anomer of **5a**, in which the two functional groups are trans related, easily affords the corresponding iodo derivative by treatment with I_2 and $NaHCO_3$.

(11) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1987**, *171*, 49.

(12) Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181.

Scheme 3



established process; it can be effected by oxidation, oximation, and reduction of the oxime to the corresponding amine by catalytic hydrogenation or treatment with diborane. It is also established that the process affords stereoselectively a 2-aminosugar with the manno configuration if the anomeric center of the starting ketone is β, whereas starting from the α-anomer, the gluco isomer is preferentially formed.[13] In our case, starting from an α-C-glucopyranoside **7b**, we expected the formation of the amino derivative with a gluco configuration.

7b was oxidized with DMSO−Ac_2O to afford the ketone **8a**[14] which was converted into the oxime **8b** by treatment with hydroxylamine at pH 4.5. The reduction of the oxime was first effected by catalytic hydrogenation and surprisingly afforded the product with the manno configuration. When $Pd(OH)_2$ was used as catalyst the debenzylated manno derivative **9a** was recovered quantitatively, whereas when Ni-Raney was used the benzylated manno derivative **9b** was obtained in 60% diastereomeric excess. Yields and stereoselection did not change when the corresponding methyloxime was reduced. These results suggest a coordination of the α-oriented phosphonic group with the metal catalyst, which favors the attack of the hydrogen from the α-face. The reduction of the acetyloxime **8c** with diborane in THF afforded on the contrary the expected 2-amino-2-deoxy-α-C-glucopyranoside **10a** in 64% diastereomeric excess. The diastereomeric excesses were determined by ^{13}C-NMR analysis of the crude reaction mixture, and the pure isomers were isolated after acetylation. The configuration of the new stereocenter was easily attributed in view of the ^{1}H-coupling constants obtained by decoupling experiments effected on the final deprotected products (see below).

The acetates **9c** and **10b** were deprotected by treatment with Me_3SiI to afford the phosphono analogues of *N*-acetyl-α-D-glucosamine 1-phosphate and *N*-acetyl-α-D-mannosamine 1-phosphate (**1** and **2**). The gluco isomer **1** shows a 10.5 Hz coupling constant between H-2 and H-3, which indicates the axial orientation of these hydrogen atoms, as required for a glucopyranosidic structure in a $^4C_1$ conformation. The manno isomer **2** shows on the contrary a 3.2 Hz coupling constant between H-2 and H-3 and a 8.1 Hz coupling constant between H-3 and H-4. This indicates the axial orientation of H-3 and the equatorial orientation of H-2, as required for a mannopyranosidic structure in a $^4C_1$ conformation.

(13) Lichtentaler, F. W.; Kaji, E. *Liebigs Ann. Chem.* **1985**, 1659 and references cited therein.

(14) No epimerization occurred during the oxidation, as the reduction of **8a** with $NaBH_4$ gave back the starting compound **7b**.

In conclusion, the phosphono analogue of *N*-acetyl-α-D-glucosamine 1-phosphate and *N*-acetyl-α-D-mannosamine 1-phosphate (**1** and **2**), glycomimetics of great biological interest, can be obtained following a procedure in which the amino function is introduced at the end of the synthesis. The procedure allows us to obtain stereoselectively the product with the gluco or the manno configuration just by changing the reduction agent.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded with TMS as internal reference. The signals of the aromatic carbons in the ^{13}C NMR spectra are not reported. $[\alpha]_D$ values were measured at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed with the flash procedure using silica gel 60 (230−400 mesh). TLC was performed on silica gel 60 F_{254} plates and visualised by spraying with a solution containing H_2SO_4 (31 mL), ammonium molibdate (21 g), and $Ce(SO_4)_2$ (1 g) in water (500 mL) and then heating at 110 °C for 5 min.

4,5,7-Tri-*O*-benzyl-D-gluco-1-heptenitol (4c). To a 1 M solution in THF of the commercially available (Aldrich) vinylmagnesium bromide (36 mL, 36.0 mmol) was added a solution in dry THF (10 mL) of dried $ZnBr_2$ (4.01 g, 18.0 mmol). The reaction mixture was stirred under N_2 until the complete formation of divinylzinc (30 min); via a double-ended needle a solution of 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**3b**) (3.0 g, 17.8 mmol) in dry THF (10 mL) was added to the organometallic reagent. After 4 h the reaction was quenched with a saturated NH_4Cl solution; the organic phase was diluted with CH_2Cl_2 and sequentially washed with 5% HCl, saturated $NaHCO_3$ solution, and water. The organic layer was then dried over Na_2SO_4, filtered, and evaporated, giving **4c** (quantitative) as a yellow oil that was used in the next step without further purification.

***C*-(2-Hydroxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-chloromercuriomethane (5c).**[15] To a solution of the glucoenitol **4c** (3.2 g, 7.1 mmol) in dry THF (15 mL), under N_2, was added $Hg(OAc)_2$ (2.3 g, 7.1 mmol) dissolved in 25 mL of dry THF. The solution was stirred until the complete disappearance of **4c** (6 h), and then KCl (797 mg, 10.7 mmol) dissolved in the minimum amount of water was added. After 30 min, the reaction mixture was diluted with EtOAc and washed twice with water; the organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure, yielding 4.9 g of crude product. Purification by flash chromatography, eluting with 7:3 hexane:EtOAc, afforded **5c** (80%) as a pale yellow oil.

***C*-(2-Hydroxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-iodomethane (6b).** Under N_2, to a solution of **5c** (2.9 g, 4.2 mmol) in dry CH_2Cl_2 (10 mL), was added 65 mL of a solution prepared dissolving iodine in dry CH_2Cl_2 (20 g/L). After 3 h the reaction was recovered by adding 20 mL of water and $Na_2S_2O_3$ and stirred until the organic layer became colorless. The reaction mixture was then washed first with brine and after with water; the organic phase was dried over Na_2SO_4 and filtered and the solvent evaporated. The residual mercury salts were removed by a simple filtration over a short column of 70−230 mesh silica gel (h = 5 cm, eluent 7:3 hexane:EtOAc). After purification, **6b** (2.4 g, quantitative) was obtained as a colorless oil: $[\alpha]_D$ +25.4° (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (d, 1H, J = 9.1 Hz), 3.30 (t, 1H, J = 10.2 Hz), 3.40 (dd, 1H, J = 10.2, 5.5 Hz), 3.63 (t, 1H, J = 4.0 Hz), 3.72−3.79 (m, 2H), 3.80−3.88 (m, 2H), 4.03 (ddd, 1H, J = 8.2, 5.8, 2.2 Hz), 4.11 (bdt, 1H, J = 4.5, 3.5, Hz), 4.53−4.63 (m, 6H), 7.20−7.35 (m, 15H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 4.42, 68.42, 68.94, 72.35, 73.16, 73.67, 73.98, 74.61, 75.00, 77.02. Anal. Calcd for $C_{28}H_{31}O_5I$: C, 58.52; H, 5.44. Found: C, 58.36; H, 5.53.

(15) We named C-glycoside by semisystematic names generally accepted for this class of compounds; this allows an easier comparison with the parent sugar.

***C*-(2-*O*-(*tert*-Butyldimethylsilyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)iodomethane (6c).** **6b** (2.4 g, 4.2 mmol) was dissolved in dry DMF (20 mL) under N_2, and then imidazole (850 mg, 12.5 mmol) and TBDMSCl (940 mg, 6.2 mmol) were added; the mixture was stirred overnight. Solvent was removed and the residue diluted with CH_2Cl_2. The remaining solids were removed by filtration and the filtrate concentrated, yielding 2.86 g of **6c** (quantitative) as a yellow oil that was used in the next step without further purification. For the characterization an analytical sample was purified by flash chromatography (eluent 8:2 hexane:EtOAc): $[\alpha]_D$ +61.4° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 3.38 (t, 1H, *J* = 11.8 Hz), 3.49 (dt, 1H, *J* = 9.6, 3.2 Hz), 3.58 (dd, 1H, *J* = 11.8, 4.3 Hz), 3.61−3.68 (m, 2H), 3.75 (dd, 1H, *J* = 21.4, 10.7 Hz), 3.76 (dd, 1H, *J* = 21.4, 10.7 Hz), 3.88 (dd, 1H, *J* = 9.6, 6.4 Hz), 4.02−4.12 (m, 1H), 4.44 (d, 1H, *J* = 10.7 Hz), 4.55 (d, 1H, *J* = 12.3 Hz), 4.64−4.84 (m, 4H), 7.00−7.35 (m, 15H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ −4.06 (2C), 2.73, 18.50, 26.46 (3C), 69.42, 72.05, 73.54, 74.26, 75.55, 75.94, 77.76, 78.53, 83.37. Anal. Calcd for $C_{34}H_{45}O_5ISi$: C, 59.29; H, 6.59. Found: C, 58.98; H, 6.55.

Diethyl *C*-(2-*O*-(*tert*-Butyldimethylsilyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)methanephosphonate (7a). A solution of **6c** (3.3 g, 4.8 mmol) in triethyl phosphite (30 mL) was refluxed for 5 h. The solvent was removed under reduced pressure, and the crude product (3.5 g) was purified by flash chromatography eluting with a gradient of hexane:EtOAc 7:3 to 6:4 affording 2.6 g of **7a** (77%) as a white solid: $[\alpha]_D$ +28.4° (*c* 1, $CHCl_3$); mp 75−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.20−1.30 (m, 6H), 2.12−2.25 (m, 2H), 3.49 (t, 1H, *J* = 8.6 Hz), 3.61−3.68 (m, 3H), 3.75 (dd, 1H, *J* = 10.5, 2.5 Hz), 3.89 (ddd, 1H, *J* = 8.7, 6.0, 2.7 Hz), 4.07 (q, 2H, *J* = 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.35−4.40 (m, 1H), 4.45 (d, 1H, *J* = 10.4 Hz), 4.46 (d, 1H, *J* = 12.1 Hz), 4.62 (d, 1H, *J* = 12.1), 4.74 (d, 1H, *J* = 10.4 Hz), 4.80 (d, 1H, *J* = 12.1 Hz), 4.84 (d, 1H, *J* = 12.1 Hz), 7.15−7.38 (m, 15H); ^{13}C NMR (50.29 MHz, $CDCl_3$) δ −4.00, −3.93, 17.05, 17.08, 18.57, 22.45 (J_{C-P} = 146.0 Hz), 26.56, 62.04, 62.16, 62.33, 62.45, 69.57, 72.65, 73.20 (J_{C-P} = 6.0 Hz), 73.51, 74.33, 75.59, 76.03, 78.79, 83.54; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 29.94. Anal. Calcd for $C_{38}H_{55}O_8PSi$: C, 65.30; H, 7.93. Found: C, 65.53; H, 7.89.

Diethyl *C*-(3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl)methanephosphonate (7b). A solution in CH_2Cl_2 (40 mL) of **7a** (2.6 g, 3.7 mmol) was cooled to 0 °C, and a mixture of 9:1 CF_3COOH/H_2O (1.5 mL) was added. The reaction was stirred overnight; the mixture was then sequentially washed with saturated $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4 and filtered and the solvent evaporated. The crude product was purified by flash chromatography (eluent hexane:EtOAc 2:8), and **7b** was obtained (2.0 g, 93%) as a white solid: $[\alpha]_D$ +38.3° (*c* 0.76, $CHCl_3$); mp 79−81 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 1.02−1.08 (m, 6H), 2.26 (ddd, 1H, *J* = 18.0, 15.5, 7.7 Hz), 2.41 (ddd, 1H, *J* = 18.0, 15.6, 5.9 Hz), 3.71 (t, 1H, *J* = 5.5 Hz), 3.77 (t, 1H, *J* = 5.5 Hz), 3.81−3.91 (m, 4H), 3.94−4.05 (m, 4H), 4.14 (dd, 1H, *J* = 4.9, 9.8 Hz), 4.38−4.59 (m, 6H), 4.61−4.66 (m, 1H), 7.01−7.30 (m, 15H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 16.96, 27.00 (J_{C-P} = 142.6 Hz), 62.47 (2C), 62.75, 67.91, 68.88, 69.90 (J_{C-P} = 9.0 Hz), 73.40, 73.76, 73.97, 74.71, 74.96, 77.63; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 30.08. Anal. Calcd for $C_{32}H_{41}O_8P$: C, 65.74; H, 7.07. Found: C, 65.71; H, 6.99.

Diethyl C-(3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexosulopyranosyl)methanephosphonate (8a). A mixture of **7b** (2.0 g, 3.4 mmol) and 3:2 DMSO:Ac_2O (15 mL) was stirred overnight. The reaction was quenched by adding ice-cold water and extracted with CH_2Cl_2. The organic phase was then washed with saturated $NaHCO_3$ and water to neutrality, dried over Na_2SO_4, and filtered and the solvent evaporated. The crude product (2.0 g) was purified by flash chromatography eluting with 2:8 hexane:EtOAc affording ketone **8a** (1.6 g, 81%) as oil: $[\alpha]_{578}$ +32.7° (*c* 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.30 (t, 3H, *J* = 7.1 Hz), 2.20 (ddd, 1H, *J* = 17.0, 15.0, 6.3 Hz), 2.29 (ddd, 1H, *J* = 17.0, 15.0, 5.5 Hz), 3.59 (dd, 1H, *J* = 10.8, 3.6 Hz), 3.68 (dd, 1H, *J* = 10.8, 2.5 Hz), 3.98 (t, 1H, *J* = 7.5 Hz), 4.02−4.18 (m, 6H), 4.37 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.55−4.74 (m, 3H), 4.83 (d, 1H, *J* = 11.5 Hz), 5.01 (d, 1H, *J* = 11.5 Hz), 7.17−7.46 (m, 15H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 17.00 (2C), 28.45 (J_{C-P} = 143.6 Hz), 62.51, 62.67, 70.39, 76.13, 76.45, 76.74, 77.31, 77.72, 78.14, 84.71, 207.70; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 27.05. Anal. Calcd for $C_{32}H_{39}O_8P$: C, 65.97; H, 6.75. Found: C, 65.32; H, 6.48.

Diethyl *C*-(3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexosulopyranosyl)methanephosphonate Oxime (8b). A solution of the ketone **8a** (125 mg, 0.21 mmol) in THF/MeOH 1:1 (4 mL) was treated with a buffer solution (1.7 mL) prepared with 1 g of $AcONa{\cdot}3H_2O$ and 0.5 g of $NH_2OH{\cdot}HCl$ (the pH is eventually adjusted to 4.5 by adding AcOH dropwise). After 1 h the mixture was extracted with CH_2Cl_2, and the organic layer washed sequentially with water, saturated $NaHCO_3$, and water to neutrality. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product (116 mg) was purified by flash chromatography eluting with 2:8 hexane: EtOAc, affording 106 mg of oxime **8b** (82%), in a mixture of *E* and *Z* isomers as white solid. NMR data refer to the more abundant isomer: ^{1}H NMR (300MHz, $CDCl_3$) δ 1.28 (t, 3H, *J* = 7.4 Hz), 1.30 (t, 3H, *J* = 7.4 Hz), 2.36 (ddd, 1H, *J* = 19.4, 10.0, 3.9 Hz), 2.49 (dt, 1H, *J* = 15.5, 10.5 Hz), 3.57 (dd, 1H, *J* = 10.1, 5.1 Hz), 3.66 (dd, 1H, *J* = 10.1, 5.0 Hz), 3.83 (t, 1H, *J* = 6.0 Hz), 4.01−4.15 (m, 5H), 4.29 (d, 1H, *J* = 6.0 Hz), 4.51−4.54 (m, 4H), 4.67 (d, 1H, *J* = 11.5 Hz), 4.80 (d, 1H, *J* = 11.9 Hz), 5.45 (dt, 1H, *J* = 10.5, 3.9 Hz), 7.10−7.32 (m, 15H), 9.92 (bs, 1H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 16.97 (2C), 26.42 (J_{C-P} = 140.9 Hz), 62.56 (2C), 66.59, 70.85, 72.18, 72.54, 73.51, 74.31, 76.80, 77.80, 155.34; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 28.13, 30.97 for the *E* and *Z* isomers. Anal. Calcd for $C_{32}H_{40}NO_8P$: C, 64.31; H, 6.75; N, 2.34. Found: C, 64.01; H, 6.83; N, 2.45.

Diethyl *C*-(3,4,6-Tri-*O*-benzyl-α-D-*arabino*-hexosulopyranosyl)methanephosphonate Acetyloxime (8c). To a solution of **8b** (300 mg, 0.50 mmol) in dry CH_2Cl_2 (5 mL) were added catalytic DMAP, pyridine (324 μL, 4.0 mmol), and Ac_2O (190 μL, 2.0 mmol). After 1 h the solvent was evaporated and the crude product purified by flash chromatography (eluent hexane:EtOAc 3:7), affording 320 mg of **8c** (quantitative). NMR data refer to the more abundant isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14−1.32 (m, 6H), 2.20 (s, 3H), 2.41−2.57 (m, 2H), 3.58 (dd, 1H, *J* = 10.4, 5.2 Hz), 3.64 (dd, 1H, *J* = 10.4, 5.2 Hz), 3.89 (dd, 1H, *J* = 6.5, 5.2 Hz), 4.01−4.15 (m, 4H), 4.44 (d, 1H, *J* = 6.5 Hz), 4.49−4.54 (m, 4H), 4.57 (d, 1H, *J* = 11.7 Hz), 4.70 (d, 1H, *J* = 11.6 Hz), 4.88 (d, 1H, *J* = 11.7 Hz), 5.41 (dt, 1H, *J* = 10.4, 4.3 Hz), 7.12−7.40 (m, 15H); ^{13}C NMR (54.29 MHz, $CDCl_3$) δ 16.71 (2C), 19.65, 23.80 (J_{C-P} = 126.9 Hz), 62.30 (2C), 67.11, 70.73, 72.96, 73.88 (2C), 74.62, 77.00, 77.70, 158.00, 167.98. Anal. Calcd for $C_{34}H_{42}NO_9P$: C, 63.84; H, 6.62; N, 2.19. Found: C, 63.57; H, 6.79; N, 2.34.

Diethyl *C*-(2-Amino-2-deoxy-α-D-mannopyranosyl)methanephosphonate (9a). Product **8b** (76 mg, 0.13 mmol) dissolved in MeOH (5 mL) was hydrogenated, in the presence of HCl 2N (0.13 mmol, 65 μL), using $Pd(OH)_2$ as catalyst (10% in weight, 8 mg). The reaction was monitored by TLC using as eluent 2:8 hexane:EtOAc to detect the starting material and 7:3:1 EtOAc:*n*-PrOH:H_2O to detect the formation of the product. The suspension was then filtered over a Celite pad, and the solvent evaporated affording 46 mg of **9a**·HCl (quantitative) as a hygroscopic white solid: $[\alpha]_{578}$ +18.3° (*c* 0.6, H_2O); ^{1}H NMR (300 MHz, Py-d_5) δ 1.28 (t, 6H, *J* = 7.0 Hz), 2.84 (dt, 1H, *J* = 15.5, 7.4 Hz), 2.93 (dt, 1H, *J* = 15.5, 5.2 Hz), 4.05−4.47 (m, 9H), 4.49 (bd, 1H, *J* = 3.9 Hz), 4.61 (t, 1H, *J* = 8.1 Hz), 4.91 (dd, 1H, *J* = 8.1, 3.9 Hz), 5.47 (m, 1H), 6.65 (bs, 3H); ^{13}C NMR (75.43 MHz, D_2O) δ 16.41 (2C), 25.86 (J_{C-P} = 141.0 Hz), 55.69 (J_{C-P} = 14.6 Hz), 61.01 (2C), 64.61, 66.89, 67.61, 70.11, 74.50; ^{31}P NMR (80.96 MHz, D_2O) δ 29.85. Anal. Calcd for $C_{11}H_{25}ClNO_7P$: C, 37.78; H, 7.20; N, 4.00. Found: C, 37.54; H, 7.12; N, 3.87.

Diethyl *C*-(2-Amino-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)methanephosphonate (9b). To a solution of **8b** (112 mg, 0.18 mmol) in MeOH (10 mL) was added a Ni-Raney suspension (20 mg) in water. The solution was stirred under hydrogen atmosphere overnight. The TLC of the reaction mixture (eluent EtOAc:CH_2Cl_2:MeOH 7:5:1) revealed the presence of two products, the manno and the gluco isomers, in a 4:1 ratio, determined by ^{1}H NMR spectra of the mixture. The suspension was filtered over a Celite pad and the crude product (120 mg) used in the next step. The two C-2 epimers were separated after acetylation of the amino group.

Diethyl *C*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)methanephosphonate (9c). The crude product **9b** (120 mg) was dissolved in dry CH_2Cl_2, and pyridine (48 μL, 0.60 mmol), Ac_2O (26 μL, 0.30 mmol), and a catalytic amount of DMAP were added. After 1 h the reaction was recovered by evaporating the solvent; the residue (110 mg) was purified by flash chromatography (eluent EtOAc:CH_2Cl_2:MeOH 5:5:0.5), affording 59 mg of the acetylated mannosamine **9c** and 14 mg of the acetylated glucosamine **10b** as byproduct, in a 65% overall yield from **8b**. Both products are white solids: $[\alpha]_D$ +19.9° (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 1.04 (t, 3H, *J* = 7.3 Hz), 1.09 (t, 3H, *J* = 7.3 Hz), 1.53 (s, 3H), 2.12−2.20 (m, 2H), 3.70−4.09 (m, 9H), 4.31−4.70 (m, 7H), 4.83 (m, 1H), 5.94 (d, 1H, *J* = 10.5 Hz), 7.00−7.30 (m, 15H); ^{13}C NMR (54.29 MHz, $CDCl_3$) δ 16.90, 17.01 23.93, 29.16 (J_{C-P} = 141.0 Hz), 49.67 (J_{C-P} = 13.7 Hz), 62.62, 62.74, 69.07, 69.27, 72.53, 73.01, 73.64, 74.03, 74.27, 76.90, 170.41; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 29.03. Anal. Calcd for $C_{34}H_{44}NO_8P$: C, 65.27; H, 7.09; N, 2.24. Found: C, 65.42; H, 7.04; N, 2.43.

Diethyl *C*-(2-Amino-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)methanephosphonate (10a). A solution of **8c** (320 mg, 0.50 mmol) in dry THF (5 mL) was cooled to −5 °C, and under N_2, a 1 M solution of diborane in THF (2 mL) was added. The reaction was allowed to warm to room temperature and after complete disappearance of the starting material MeOH was added dropwise until the borane in excess was destroyed. The solution was concentrated and the residue diluted with CH_2Cl_2; the organic phase was washed with water, dried over Na_2SO_4, filtered, and evaporated. The crude product (290 mg), a mixture of the gluco and manno isomers in a 4.5:1 ratio (de 64%), determined by ^{1}H NMR, was used for the acetylation.

Diethyl *C*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)methanephosphonate (10b). The procedure was the same used for the acetylation of product **9c**. Crude product **10a** (290 mg) afforded 95 mg of **10b** and 21 mg of **9c** as byproduct in 37% overall yield from **8c**: $[\alpha]_D$ −0.9° (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 1.06 (t, 3H, *J* = 6.9 Hz), 1.11 (t, 3H, *J* = 6.9 Hz), 1.49 (s, 3H), 2.15 (ddd, 1H, *J* = 15.0, 15.6 4.6 Hz), 2.27 (dt, 1H, *J* = 15.6, 8.4 Hz), 3.57 (d, 1H, *J* = 2.3 Hz), 3.75 (bt, 1H, *J* = 2.3 Hz), 3.91−4.01 (m, 3H), 4.07−4.14 (m, 3H), 4.17−4.50 (m, 7H), 4.58 (dd, 1H, *J* = 9.6, 2.3 Hz), 4.82 (dddd, 1H, *J* = 8.4, 7.0, 4.6, 1.7 Hz), 6.45 (d, 1H, *J* = 9.6 Hz) 7.03−7.32 (m, 15H); ^{13}C NMR (50.29 MHz, $CDCl_3$), δ 16.90, 17.00, 23.81, 29.60 (J_{C-P} = 142.8 Hz), 49.06 (J_{C-P} = 13.8 Hz), 61.95, 62.51, 65.04, 68.92, 72.56, 72.76, 73.70, 74.05, 75.06, 76.05, 170.52; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 29.89. Anal. Calcd for $C_{34}H_{44}NO_8P$: C, 65.27; H, 7.09; N, 2.24. Found: C, 65.18; H, 7.52; N, 2.05.

***C*-(2-Acetamido-2-deoxy-α-D-glucopyranosyl)methanephosphonic Acid (1).** Fifty mg (0.08 mmol) of **10b** was dissolved in dry CCl_4 (2 mL), and TMSI (163 μL, 1.20 mmol) was added. After 15 min the reaction was complete, the solvent evaporated, and the residue washed with Et_2O. The product was purified by crystallization (EtOH/EtOAc) (24 mg, quantitative) and then dissolved in water and lyophilized, affording a white hygroscopic solid: $[\alpha]_D$ +51.0° (*c* 1, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 2.08 (ddd, 1H, H-1a′, *J* = 21.2, 17.5, 2.5 Hz), 2.12 (s, 3H, C*H*$_3$CO), 2.40 (dt, 1H, H-1b′, *J* = 17.5, 11.3 Hz), 3.57 (t, 1H, H-4, *J* = 9.1 Hz), 3.71 (dt, 1H, H-5, *J* = 9.1, 3.4 Hz), 3.78 (dd, 1H, H-3, *J* = 10.5, 9.1 Hz), 3.83−3.92 (m, 2H, H-6a, H-6b), 4.04 (dd, 1H, H-2, *J* = 10.5, 5.0 Hz), 4.52−4.57 (m, 1H, H-1); ^{13}C NMR (75.43 MHz, D_2O) δ 22.76, 24.60 (J_{C-P} = 139.1 Hz), 54.19, (J_{C-P} = 12.1 Hz), 61.37, 70.36, 71.06 (2C), 73.81, 175.36; ^{31}P NMR (80.96 MHz, D_2O) δ 27.83. Anal. Calcd for $C_9H_{18}NO_8P$: C, 36.13; H, 6.06; N, 4.68. Found: C, 36.43; H, 6.25; N, 4.54.

***C*-(2-Acetamido-2-deoxy-α-D-mannopyranosyl)methanephosphonic Acid (2).** The same procedure described for the preparation of **1** was used for the hydrolysis of **10b** (quantitative yield from 55 mg, 0.09 mmol of **9c**): $[\alpha]_D$ +9.0° (*c* 0.5, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 2.20 (s, 3H, C*H*$_3$CO), 2.24−2.45 (m, 2H, H-1a′, H-1b′), 3.77−3.79 (m, 2H, H-4, H-5), 3.94 (dd, 1H, H-6a, *J* = 9.7, 2.6 Hz), 4.00 (dd, 1H, H-6b, *J* = 9.7, 3.9 Hz), 4.15 (dd, 1H, H-3, *J* = 8.1, 3.2 Hz), 4.33−4.41 (m, 1H, H-1), 4.50 (t, 1H, H-2, *J* = 3.2 Hz); ^{13}C NMR (75.43 MHz, D_2O) δ 22.85, 28.44 (J_{C-P} = 135.9 Hz), 53.55 (J_{C-P} = 12.8 Hz), 61.10, 67.98, 69.84, 72.51, 75.05, 175.29; ^{31}P NMR (80.96 MHz, D_2O) δ 26.68. Anal. Calcd for $C_9H_{18}NO_8P$: C, 36.13; H, 6.06; N, 4.68. Found: C, 36.28; H, 6.12; N, 4.76.

11. A solution of **6b** (979 mg, 1.7 mmol) in triethyl phosphite (10 mL) was refluxed for 5 h. The solvent was removed under reduced pressure, and the crude product, purified by flash chromatography eluting with $CHCl_3$−EtOAc 10:3, afforded two products, corresponding to the diastereoisomers of **11** at the chiral phosphorus (267 of **11a** R_f 0.34 and 252 mg of **11b** R_f 0.24; 56% overall yield). **11a**: white solid; $[\alpha]_D$ +54.6° (*c* 1.4, $CHCl_3$); mp 57.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H), 2.07 (ddd, 1H, $J_{1'a,P}$ = 13.3, $J_{1'a,1}$ = 8.5, $J_{1'a,1'b}$ = 15 Hz, H-1′a), 2.18 (dt, 1H, $J_{1'b,P}$ = 15, $J_{1'b,1}$ = 8.5, $J_{1'a,1'b}$ = 15 Hz, H-1′b), 3.59−3.73 (m, 4H), 3.94 (dt, 1H, $J_{3,2}$ = 6.5, $J_{3,4}$ = 6.5, $J_{3,P}$ = 2.5 Hz, H-3), 4.17 (dd, 2H), 4.22 (dd, 2H), 4.35 (ddd, 1H, $J_{1,2}$ = 6.5, $J_{2,P}$ = 13.0, $J_{2,3}$ = 6.5 Hz, H-2), 4.80 (dq, 1H, $J_{1,P}$ = 8.5 Hz, H-1), 4.80−5.00 (m, 6H, OCHPh); ^{13}C NMR (75.43 MHz,$CDCl_3$) δ 17.00, 24.2 ($J_{C,P}$ = 121 Hz), 63.24, 70.07, 72.90, 74.60, 75.59, 82.35, 83.77, 74.1, 74.94, 75.4; ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 42.55. Anal. Calcd for $C_{30}H_{35}O_7P$: C, 66.90; H, 6.55. Found: C, 66.77; H, 6.87. **11b**: white hygroscopic solid; $[\alpha]_D$ = +62.6° (*c* 1.3, $CHCl_3$); (300 MHz, $CDCl_3$) δ 1.30 (q, 3H), 2.08 (dt, 1H, *J* = 15.5, 6.7 Hz), 2.18 (ddt, 1H, *J* = 15.5, 7.3, 2.18 Hz), 3.64−3.69 (m, 4H), 3.94 (dt, 1H, *J* = 7 Hz), 4.20 (m, 4H,), 4.49 (dt, 1H, $J_{2,1}$ = 6.5, $J_{2,3}$ = 6.5, $J_{2,P}$ = 13 Hz, H-2), 4.81 (m, 1H, $J_{1,1'a}$ = 7.3, $J_{1,1'b}$ = 6.7, $J_{1,2}$ = 6.5, $J_{1,P}$ = 14Hz, H-1), 4.40−4.58 (m, 3H), 4.73−4.95 (m, 3H); ^{13}C NMR (75.43 MHz,$CDCl_3$) δ 17.06, 24.95 ($J_{C,P}$ = 122 Hz), 63.7, 69.94, 72.52, 75.18 (2C), 82.75, 82.63, 74.15, 74.32, 75.43. ^{31}P NMR (80.96 MHz, $CDCl_3$) δ 44.30. Found: C, 66.69; H, 6.40.

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