Synthesis of Selectively Labeled D-Fructose and D-Fructose Phosphate Analogues Locked in the Cyclic Furanose Form

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2,5-Anhydroglucitol and 2,5-anhydromannitol and their 6-phosphate and 1,6-diphosphate derivatives are cyclic analogues of the α and β anomers of D-fructofuranose, D-fructofuranose-6-phosphate, and D-fructofuranose-1,6-diphosphate. They were synthesized from protected D-mannose or D-glucose. The synthetic method was developed with emphasis on selective ^2H labeling of these compounds, as a model for ^3H incorporation, which will be used for further biochemical studies. A key cyclization step, based on a benzyl ether nucleophilic attack on an activated alcohol, constructed the ring system. The stereochemistry at C_2 (α/β anomers) and at C_5 (D sugar) was controlled by selective epimerizations. Mono- and diphosphate analogues were obtained from the same intermediate by changing the sequence of deprotection and phosphorylation steps.

Introduction

Substrate analogues are useful tools in the study of enzyme reaction mechanisms. Such analogues could help in the identification of the active substrate conformation or configuration or in the stabilization of reaction intermediates. Thus, discrete changes, at the molecular level, of the substrate during the catalytic reaction could be detected and characterized. This approach was found to be useful in the study of a few sugar metabolizing enzymes.[1]

D-Fructose and its phosphorylated derivatives, D-fructose-1-phosphate, D-fructose-6-phosphate, and D-fructose-1,6-diphosphate, are substrates and products of a few key enzymes, such as phosphoglucoisomerase, phosphofructokinase and aldolase (of the glycolytic pathway), invertase and sucrose synthetase, fructokinase and ketose-1-phosphate aldolase (in the liver), and transaldolase and transketolase.[2] D-Fructose-6-phosphate is also suggested as a possible substrate for the initial step in the biosynthesis of neplanocin A and aristeromycin, two biologically active secondary metabolites of some streptomyces.[3] Therefore, analogues of fructose derivatives, with specifically tailored features, are of interest in the mechanistic study of these and other enzymes.

For fructose and its 6-phosphate and 1,6-diphosphate derivatives in aqueous solution there is a dynamic equilibrium between the α and β anomers of the hemiketal structure (mainly the furanose form) and the open ketone form. 2,5-Anhydroglucitol **5a** and 2,5-anhydromannitol **5b** (Chart 1) are cyclic fructose analogues lacking the anomeric C_2 hydroxy substituent, and therefore, they are locked either in the α (the former) or in the β (the latter) anomeric form of the cyclic fructofuranose. Therefore, they (and their phosphorylated derivatives **8** and **9**, Chart 1) can be used as mechanistic tools to study the anomeric specificity of enzymes, the importance of the anomeric hydroxy group, isolation of reaction intermediates, etc. One approach is to utilize their selectively labeled form. They can help follow and identify the catalytic products, obtain mechanistic information or, in the case of affinity labeling, provide a means to follow the inactivated enzyme. Such labeling has the distinct advantage of strictly maintaining the stereoelectronic character of the unlabeled compound. Alas, it may require special synthetic methodologies, different from those utilized in the synthesis of its unlabeled equivalent.

2,5-Anhydroglucitol **5a**[4,5] and 2,5-anhydromannitol **5b**[4,6] and their corresponding 6-phosphate and 1,6-diphosphate derivatives **8** and **9**[4] were previously synthesized by various methods.[7] Construction of the anhydro ring system in these and related compounds was achieved by diazotation of glucosamine,[6,8] acid-catalyzed dehydration,[5,9] silicon-directed cyclization,[10] silylation and reductive cleavage,[11] and an intramolecular displacement of a mesylated hydroxyl group.[12] Phosphorylation

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(1) For a few recent examples, see: (a) Shoucheng, D.; Faiger, H.; Belakhov, V.; Baasov, T. *Bioorg. Med. Chem.* **1999**, *7*, 2671−2682. (b) Baasov, T.; Belakhov, V. *Recent Res. Devel. Org. Chem.* **1999**, *3*, 195−206. (c) Lauhon, C. T.; Bartlett, P. A. *Biochemistry* **1994**, *33*, 14100−14108. (d) Bender, S. L.; Widlanski, T.; Knowles, J. R. *Biochemistry* **1989**, *28*, 7560−7572. (e) Widlanski, T.; Bender, S. L.; Knowles, J. R. *Biochemistry* **1989**, *28*, 7572−7582.

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(3) Jenkins, G. N.; Turner, N. J. *Chem. Soc. Rev.* **1995**, 169−176. (b) Parry, R. J.; Bornemann, V.; Subramanian, R. *J. Am. Chem. Soc.* **1989**, *111*, 5819−5824.

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(6) Bera, B. C.; Foster, A. B.; Stacey, M. *J. Chem. Soc.* **1956**, 4531−4535.

(7) 2,5-Anhydromannitol is now commercially available.

(8) (a)Horton, D.; Phillips, K. D. *Carbohydr. Res.* **1973**, *30*, 367−374. (b) Otero, D. A.; Simpson, R. *Carbohydr. Res.* **1984**, *128*, 79−86.

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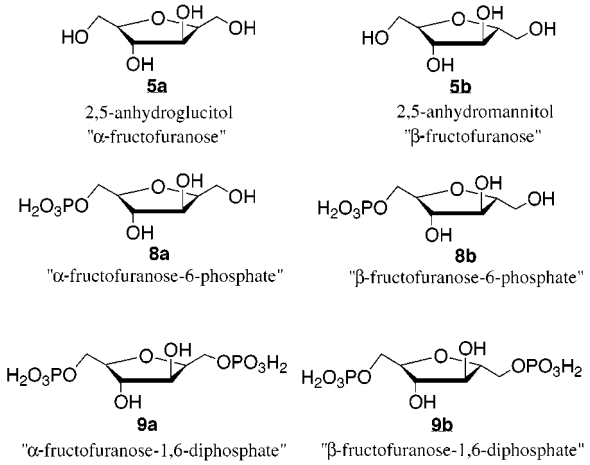
Chart 1. Fructose Derivatives Locked in the Cyclic Furanose Form



involved either chemical[13,14] or enzymatic[14] procedures. These and related compounds were utilized in enzymatic studies of aldolase,[13a] phosphofructokinase,[14,15] and fructose-1,6-diphosphatase.[4,16] However, these synthetic methods could not be applied in a straightforward manner for efficient selective radiolabeling.

In the present study, we describe an alternative synthetic method for the above six compounds (α- and *β*-fructofuranose analogues, **5a** and **5b**, and their 6-phosphate and 1,6-diphosphate derivatives, Chart 1). This synthetic approach was developed specifically in order to enable efficient selective incorporation of labeling (tritium or deuterium) into as many as four positions of the sugar skeleton (C_1, C_2, C_5, and C_6). Furthermore, this approach can also be applied to the synthesis of other ketohexose analogues.

Results and Discussion

Synthesis. The synthesis of the α and *β* anomers of the cyclic analogues proceeds in parallel lines. The starting material was either protected D-mannose or protected D-glucose. These have the desired stereochemistry of the hydroxy substitutions at C_3 and C_4. The other two chiral centers, at C_2 and C_5, could be manipulated to control the family of D sugars (C_2 of the starting material, see below) and the α/*β* anomerism (C_5 of the starting material). While the α anomer is prepared directly from protected D-mannose or D-glucose, the *β* anomer requires epimerization at the C_5 position of the starting material (L sugar) followed by the same protocol of the α anomer. All three fructose derivatives (the "free sugar" and its mono- and diphosphates) are obtained from a common key intermediate by changing the sequence of deprotection and phosphorylation steps.

Ring Construction. The construction of the locked cyclic skeleton of the sugar analogues is described in Schemes 1−3. It is based on a key regio- and stereoselective cyclization step (yielding cyclic olefins **2**), previously described by Martin et al.[17] Oxidation of the olefin functionality of **2**, yielding aldehyde **3**, was carried out by a variety of methods: ozonolysis under various conditions,[18,19] *m*-CPBA epoxidation followed by periodate oxidation,[20] one-pot OsO_4/HIO_4 oxidation,[21] and two-step OsO_4/4-methylmorpholine *N*-oxide and HIO_4 oxidation.[22] The latter proved to be the most effective in our hands. $NaBH_4$ reduction of the aldehyde to the corresponding alcohol **4** completed the construction of the cyclic system.

The C2 symmetry of the cyclic systems **4**, in respect to the C_3 and C_4 substitution pattern, allowed us to "rotate" the compounds, transforming the C_2 position of the starting material into the C_5 position of the final fructofuranose analogues and C_5 of the starting material into the C_2 of the products (Schemes 1 and 3). This simplified the following phosphorylation steps (for the production of the monophosphate analogues), circumventing laborious protection and deprotection steps, and enabled introduction of selective labeling at the C_5 and C_6 positions of the analogues (see below).

Starting from 2,3,4,6-tetra-*O*-benzyl mannose, this procedure provided cyclic alcohol **4a**, which bears the correct stereochemistry of α-D-fructofuranose at all its chiral centers (Scheme 1). Aldehyde **3a** could also be prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucose by a similar procedure (Scheme 2). Thus, cyclic olefin **2c** was oxidized to the cyclic aldehyde **3c**, bearing an opposite absolute configuration at C_2, in comparison with aldehyde **3a**, derived from the mannose derivative starting material. This chiral center was inverted under basic conditions (Et_3N, DMF), yielding the desired epimer **3a** as the major constituent (**3a**/**3c** 4:1).

Comparison of the synthetic efficiency toward **3a** from protected glucose and mannose shows comparable total yields, despite a step longer procedure from the glucose derivative. Considering the price difference of the starting materials (the 2,3,4,6-tetra-*O*-benzyl mannose is 2.5-fold more expensive than the corresponding glucose derivative) and the possibility of introduction of selective labeling at the epimerization step (see below) makes the glucose route more attractive.

The chiral center at C_5 of the sugar starting material should be epimerized in order to obtain the *β*-fructofuranose analogues. Therefore, the linear olefin **1a**, derived from protected mannose and bearing a free hydroxy group at C_5, underwent a Mitsunobu reaction[23,24] to yield its isomer **1b**. The new olefin was subject to a set of reactions similar to those described for **1a**, yielding the

(13) (a) Hartman, F. C.; Barker, R. *Biochemistry* **1965**, *4*, 1068−1075. (b) Koerner, T. A. W., Jr.; Voll, R. J.; Younathan, E. S. *Carbohydr. Res.* **1979**, *70*, 165−168.

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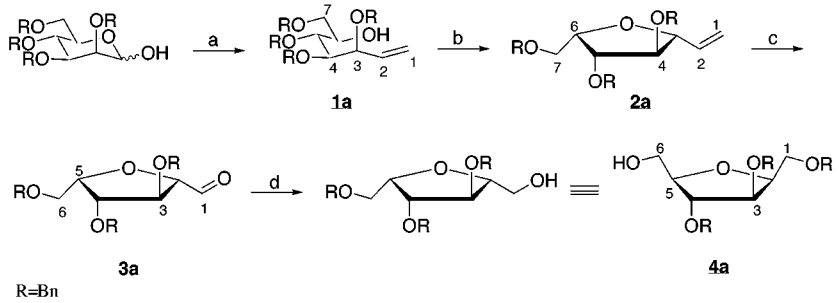
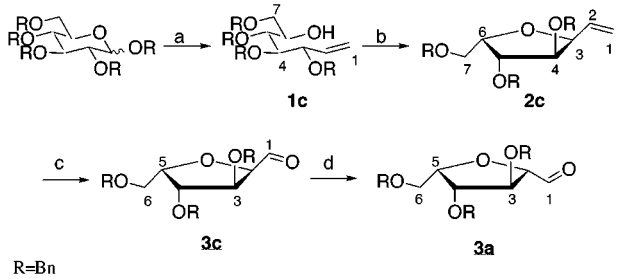
Scheme 1. Construction of the α-Furanose Analogue Ring System from Protected Mannose[a]



[a] Key: (a) $Ph_3P^+CH_3Br^-$, BuLi, $(CH_3OCH_2)_2$; (b) Tf_2O, py; (c) (i) OsO_4, NMO, (ii) $NaIO_4$, THF-H_2O; (d) $NaBH_4$, EtOH.

Scheme 2. Construction of the α-Furanose Analogue Ring System from Protected Glucose[a]



[a] Key: (a) $Ph_3P^+CH_3Br^-$, BuLi, $(CH_3OCH_2)_2$; (b) Tf_2O, py; (c) (i) OsO_4, NMO, (ii) $NaIO_4$, THF−H_2O; (d) Et_3N, DMF.

cyclic alcohol **4b** key intermediate (Scheme 3). This intermediate, or rather its precursor **3b**, could also be prepared from the corresponding glucose derivative **1c** in a similar manner, following a Mitsunobu epimerization at C_5 (**1d**), ring closure (**2d**), and unmasking of the aldehyde functionality (**3d**) and its epimerization under basic conditions.

The relative stereochemistry of the various cyclic olefins **2** and aldehydes **3** was supported by NOESY experiments. Since the C_3 and C_4 positions do not undergo any changes throughout the synthesis and their protons do not become labile, their absolute configuration in the intermediates **2** and **3** (as well as in all other intermediates and products) is defined. Therefore, this set of measurements confirmed the absolute stereochemistry of these compounds (Scheme 4).

Phosphorylation. Selective mono- and diphosphorylation were achieved by a similar set of reactions, carried out in a different order.

D-Fructofuranose-6-phosphate Analogues. Phosphorylation of the only free alcohol of **4a** and **4b** by diphenyl chlorophosphate afforded the fully protected derivatives **6a** and **6b**, respectively. A two-step deprotection, first removal of the benzyl protecting groups from the hydroxyls by catalytic hydrogenation over Pd/C and then removal of the phenyl protecting groups of the phosphate by catalytic hydrogenation over PtO_2, afforded the α and the *β* anomers of the fructofuranose-6-phosphate analogues **8a** and **8b**, respectively (Scheme 5).

The *β*-D-fructofuranose-6-phosphate analogue **8b** is also a *β*-D-fructofuranose-1-phosphate analogue (by "180° rotation"). Therefore, it could be used in the study of both enzymes utilizing fructose-6-phosphate and enzymes utilizing fructose-1-phosphate as substrates.

D-Fructofuranose and D-Fructofuranose-1,6-diphosphate Analogues. The three benzyl protecting groups of **4a** were removed by catalytic hydrogenation, yielding 2,5-anhydroglucitol (the α-D-fructofuranose analog) **5a**. Selective phosphorylation of the two primary alcohols,[25] followed by deprotection (catalytic hydrogenation) afforded the α-D-fructofuranose-1,6-diphosphate analogue **9a** (Scheme 5).[13,14] **9b** can be similarly prepared from **5b**.

It should be noted that compounds **5b**, **7b**, and **9b** could be easily distinguished from their corresponding α analogues **5a**, **7a**, and **9a** by NMR spectroscopy. The formers have C_2 symmetry. Therefore, they exhibit very simplified NMR spectra.[26] This is especially evident in their ^{13}C NMR spectra, exhibiting only three peaks (besides the phenyl carbons of the phosphate esters of **7b**). In contrast, the α-fructofuranose analogues **5a**, **7a**, and **9a** exhibit much more complex NMR spectra, due to the lack of symmetry.

Selective Labeling. To probe the possibilities of introducing ^3H labeling into the fructofuranose analogues **5**, **8**, and **9**, we studied the incorporation of its stable isotope deuterium into various positions by two methods. Incorporation of the deuterium atom was confirmed by ^1H and ^{13}C NMR and by mass spectroscopy.

^{2}H-Labeling at C_1/C_6. Aldehyde **3d** was reduced with NaB^2H_4, yielding a diastereomeric mixture of (6-*R*,*S*)-[6-^{2}H]-**4d** (an analogue of protected [1-^{2}H]-α-D-mannopyranose).

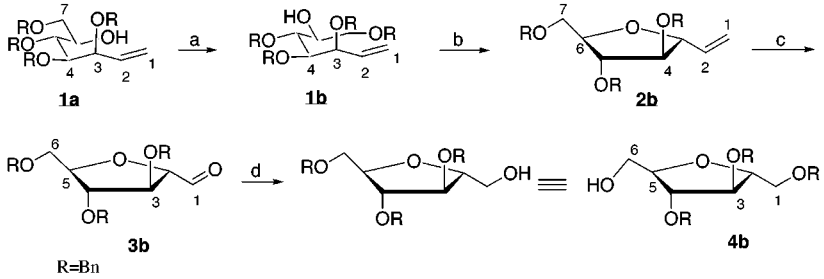
This approach can be used for the synthesis of a variety of selectively labeled derivatives. NaB^3H_4 reduction of aldehyde **3a** to alcohol **4a** will further lead to [6-^{3}H]-α-fructofuranose-6-phosphate and [6-^{3}H]-α-fructofuranose-1,6-diphosphate analogues. The same procedure applied to aldehyde **3d** will provide, in addition to the [1-^{3}H]-α-fructofuranose analogue described above, [1-^{3}H]-α-fructofuranose-1-phosphate and [1-^{3}H]-α-fructofuranose-1,6-diphosphate analogues. Similar manipulation of aldehyde **3b** will yield [6-^{3}H]-*β*-fructofuranose-6-phosphate, [1-^{3}H]-*β*-fructofuranose-1-phosphate and [1,6-^{3}H]-*β*-fructofuranose-1,6-diphosphate analogues.

^{2}H-Labeling at C_5. Selective incorporation of ^2H labeling into the C_5 position was achieved by proton exchange with ^2H_2O during the epimerization step of aldehyde **3c** to aldehyde **3a**. To mimic conditions of ^3H_2O handling for radioactive labeling, the reaction was based on exchange with only 2 molar equiv of ^2H_2O, to avoid large excess of "radioactive" manipulations. This reaction was explored in order to maximize label incorporation and equilibrium isomeric ratio of **3a**/**3c**. Various solvents

(25) Phosphorylation was carried out according to ref 13a, with slight modifications.

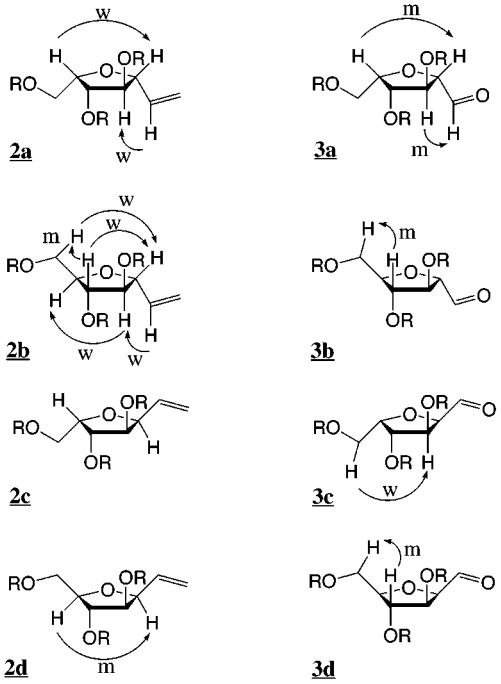
(26) Koerner, T. A. W., Jr.; Voll, R. J.; Cary, L. W.; Younathan, E. S. *Biochemistry* **1980**, *19*, 2795−2801.

Scheme 3. Construction of the *β*-Furanose Analogue Ring System from Protected Mannose[a]



[a] Key: (a) Ph_3P, DEAD, $O_2NC_6H_4CO_2H$, Et_3N, $PhCH_3$; (b) Tf_2O, py, CH_2Cl_2; (c) (i) OsO_4, NMO, (ii) $NaIO_4$, $THF-H_2O$; (d) $NaBH_4$, EtOH.

Scheme 4. Confirmation of Substitution Pattern of the Ring Systems 2 and 3 by NOESY

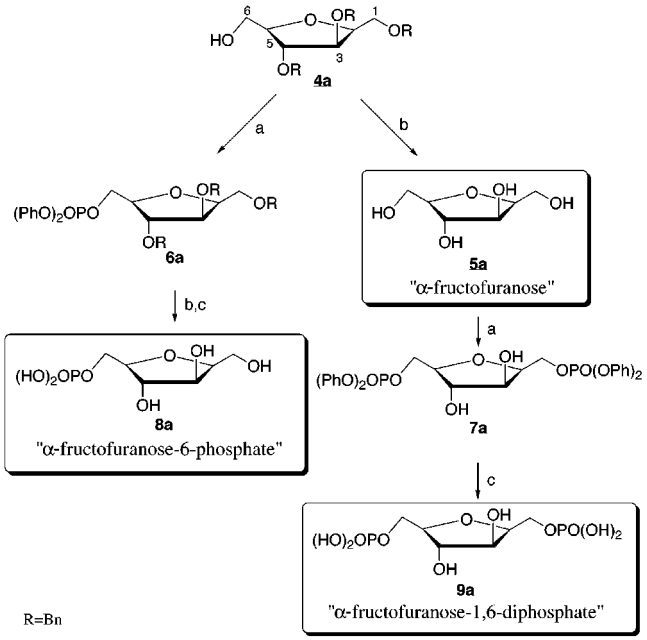


and bases were tested. The equilibrium **3a**/**3c** ratio and the extent of ^2H incorporation from ^2H_2O are summarized in Table 1.

It shows little dependence of the equilibrium isomeric ratio on the solvent. The extent of the label incorporation, on the other hand, is highly dependent. While very little ^2H incorporation from two molar equivalents of ^2H_2O present in the reaction solution was observed when carried out in CH_2Cl_2, very efficient incorporation was observed when the reaction was carried out in DMF. This may be the result of solvent polarity, leading to the formation of a tight ion pair of the triethylammonium − **3**$^-$ in the nonpolar CH_2Cl_2, and much better solvation of the "naked" charges in the polar DMF. The tight ion pair exchanges its labile proton with the small amount of water present very slowly. Therefore, the original proton is returned from the base to the aldehyde **3** (both **3a** and **3c**) and no labeling is observed. When dissolved well (in DMF), efficient exchange of the C_2 proton with the water takes place, leading to ^2H incorporation into C_2. The extent of labeling in DMF as a solvent reaches the expected value.

This method will yield [5-^{3}H]-α-fructofuranose-6-phosphate and [5-^{3}H]-α-fructofuranose-1,6-diphosphate analogues from aldehyde **3a**. Aldehyde **3b** can provide

Scheme 5. Final Stages of the Synthesis of 2,5-Anhydroglucitol (α-Fructofuranose Analogue) and its 6-P and 1,6-P_2 Derivatives[a]



[a] Key: (a) $(PhO)_2POCl$, DMAP, Py; (b) H_2, Pd/C, MeOH; (c) H_2, PtO_2, MeOH.

Table 1. Epimerization of Aldehyde 3c. Isomeric Ratio and Extent of ^2H Incorporation

solvent	base	**3a**:**3c** ratio	^2H incorporation (%)
CH_3CN	Na_2CO_3	*a*	
CH_2Cl_2	Et_3N	2	20
THF	Et_3N	3	40
DMF	Et_3N	4	83

[a] An unidentified mixture of condensation and other products was obtained.

access to [5-^{3}H]-*β*-fructofuranose-6-phosphate, [2-^{3}H]-*β*-fructofuranose-1-phosphate and [2,5-^{3}H]-*β*-fructofuranose-1,6-diphosphate analogues.

Conclusions

The present study describes the synthesis of 2,5-anhydroglucitol and 2,5-anhydromannitol, cyclic analogues of fructose, and their phosphorylated derivatives, 6-phosphate and 1,6-diphosphate. These analogues are "locked" in a cyclic configuration, either in the α- or in the *β*- furanose form. The focus of the synthetic method is the efficient selective incorporation of radioactive (^{3}H) labeling into various positions of the different sugar

analogues for further biochemical studies. These compounds will be used as conformational and mechanistic probes for enzymatic catalytic reactions.

Experimental Section

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 600, 150, and 81 MHz, respectively, in $CDCl_3$ (TMS as an internal standard) or, when specified, in D_2O (MeOH as an internal standard). Multiplicity "d" refers to a doublet-like second-order peak. ^{1}H NMR assignments were supported by COSY experiments, while ^{13}C NMR assignments were supported by hetero COSY (HMQC and HMBC) experiments. Mass spectra were recorded in DCI mode with methane or ammonia as the reagent gas. TLC was performed on E. Merck 0.2 mm precoated silica gel F-254 plates and viewed by UV, vanillin,[27] or malachite green.[28] Chromatography refers to flash column chromatography,[29] carried out on silica gel 60 (230−400 mesh ASTM, E. Merck). Anhydrous solvents were dried and freshly distilled (THF and toluene from sodium/benzophenone, pyridine and triethylamine from CaH_2, CH_2Cl_2 from $CaCl_2$ and DMF from 4 Å molecular sieves).

Manno open olefin **1a** and gluco open olefin **1c** were prepared from the corresponding 2,3,4,6-tetra-*O*-benzyl aldohexose as previously described.[17] They were purified by chromatography (ether/hexane 1:3).

Mitsunobu Epimerization. The open olefin (2.69 g, 5 mmol), triphenyl phosphine (2.62 g, 10 mmol), *p*-nitrobenzoic acid (1.67 g, 10 mmol), and triethylamine (3.5 mL, 25 mmol) were dissolved in 100 mL of dry toluene at 0 °C. DEAD (1.6 mL, 10 mmol) was added dropwise. After 10 min, the solution was allowed to warm to room temperature. After the solution was stirred for 5−15 h, the solvent was evaporated, CH_2Cl_2 (100 mL) was added, and the organic phase was extracted consecutively with 100 mL of 1 M HCl, saturated $NaHCO_3$, and water, dried over $MgSO_4$, filtered, and evaporated to dryness. (The *p*-nitrobenzoyl ester could be chromatographed with ether/hexane 1:5. Spectroscopic analysis at this stage is much more informative than after the methanolysis step.[24]) The *p*-nitrobenzoate was dissolved in methanol (150 mL) and 10 molar equiv of NaOH were added. After 1 h, the methanol was partially evaporated, CH_2Cl_2 added and the organic phase was extracted twice with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Chromatography (EtOAc/hexane 1:4) afforded the clean product.

Open olefin 1b: 79% yield; ^{1}H NMR δ 3.39 (dd, J = 9.6, 6.0 Hz, 1H, C7H$_2$), 3.43 (dd, J = 9.6, 6.2 Hz, 1H, C7H$_2$), 3.72 (dd, J = 6.1, 3.0 Hz, 1H, C5H), 3.83 (dd, J = 6.1, 5.1 Hz, 1H, C4H), 3.92 (ddd, J = 6.2, 6.0, 3.0 Hz, 1H, C6H), 4.04 (bdd, J = 7.9, 5.1 Hz, 1H, C3H), 4.31 (d, J = 11.8 Hz, 1H, Bn), 4.38 (d, J = 11.9 Hz, 1H, Bn), 4.42 (d, J = 11.9 Hz, 1H, Bn), 4.45 (d, J = 11.1 Hz, 1H, Bn), 4.58 (d, J = 11.1 Hz, 1H, Bn), 4.60 (d, J = 11.8 Hz, 1H, Bn), 4.68 (d, J = 11.1 Hz, 1H, Bn), 4.73 (d, J = 11.1 Hz, 1H, Bn), 5.33 (ddd, J = 17.5, 1.7, 0.8 Hz, 1H, C1H$_2$), 5.35 (ddd, J = 10.4, 1.7, 0.8 Hz, 1H, C1H$_2$), 5.96 (ddd, J = 17.5, 10.4, 7.9 Hz, 1H, C2H), 7.22−7.28 (m, 20H, Ph); ^{13}C NMR δ 70.14 (C6/Bn), 70.17 (C6/Bn), 71.21 (C7), 73.19, 74.32, 74.87 (Bn), 78.64 (C5), 81.12 (C3), 81.75 (C4), 119.61 (C1), 127.48−129.56 (Ph), 135.53 (C2), 138.05−138.45 (Ph); HRMS calcd for $C_{35}H_{39}O_5$ (MH^+) 539.2798, found 539.2841; MS *m*/*z* 539 (MH^+, 8), 431 (22), 323 (19), 91 (84).

Open olefin 1d: 72% yield; ^{1}H NMR δ 2.60 (d, J = 6.5 Hz, 1H, OH), 3.39 (dd, J = 9.4, 5.9 Hz, 1H, C7H$_2$), 3.46 (dd, J = 9.4, 6.3 Hz, 1H, C7H$_2$), 3.77 (dd, J = 7.1, 3.9 Hz, 1H, C4H), 3.85 (m, 1H, C6H), 3.86 (m, 1H, C5H), 4.05 (bdd, J = 7.4, 3.9 Hz, 1H, C3H), 4.34 (d, J = 11.9 Hz, 1H, Bn), 4.42 (d, J = 12.0 Hz, 1H, Bn), 4.46 (d, J = 12.0 Hz, 1H, Bn), 4.55 (d, J = 11.3 Hz, 1H, Bn), 4.63 (d, J = 11.9 Hz, 1H, Bn), 4.66 (d, J = 11.3 Hz, 1H, Bn), 4.69 (d, J = 11.3 Hz, 1H, Bn), 4.76 (d, J = 11.3 Hz, 1H, Bn), 5.31 (ddd, J = 10.6, 1.6, 1.0 Hz, 1H, C1H$_2$), 5.31 (ddd, J = 17.0, 1.6, 1.0 Hz, 1H, C1H$_2$), 5.94 (ddd, J = 17.0, 10.6, 7.4 Hz, 1H, C2H), 7.20−7.40 (m, 20H, Ph); ^{13}C NMR δ 69.63 (C6), 70.53 (Bn), 71.27 (C7), 73.21, 74.82, 74.97 (Bn), 78.76 (C5), 79.82 (C3), 82.11 (C4), 118.86 (C1), 127.60−128.34 (Ph), 135.30 (C2), 138.09, 138.25, 138.32, 138.48 (Ph); HRMS calcd for $C_{35}H_{39}O_5$ (MH^+) 539.2798, found 539.2760; MS *m*/*z* 539 (MH^+, 4.4), 393 (8), 91 (100).

Cyclization: Cyclic olefins **2a**−**d** were prepared from the opened olefins **1a**−**d**, respectively, as previously described[17,30] and purified by chromatography with ether/hexane 1:5.

2a: 47% yield; ^{1}H NMR δ 3.75 (dd, J = 10.0, 6.2 Hz, 1H, C7H$_2$), 3.80 (dd, J = 10.0, 5.5 Hz, 1H, C7H$_2$), 3.84 (dd, J = 3.8, 1.6 Hz, 1H, C4H), 4.00 (dd, J = 4.2, 1.6 Hz, 1H, C5H), 4.26 (ddd, J = 6.2, 5.5, 4.2 Hz, 1H, C6H), 4.31 (ddt, J = 7.4, 3.8, 1 Hz, 1H, C3H), 4.43 (d, J = 12.0 Hz, 1H, Bn), 4.47 (d, J = 12.0 Hz, 1H, Bn), 4.49 (d, J = 12.0 Hz, 1H, Bn), 4.50 (d, J = 12.0 Hz, 1H, Bn), 4.53 (d, J = 12.0 Hz, 1H, Bn), 4.59 (d, J = 12.0 Hz, 1H, Bn), 5.13 (ddd, J = 10.3, 1.6, 1.0 Hz, 1H, C1H$_2$), 5.32 (ddd, J = 17.2, 1.6, 1.0 Hz, 1H, C1H$_2$), 5.95 (ddd, J = 17.2, 10.3, 7.4 Hz, 1H, C2H), 7.26−7.33 (m, 15H, Ph); ^{13}C NMR δ 68.30 (C7), 71.52, 71.62, 73.34 (Bn), 79.92 (C6), 82.83 (C5), 85.00 (C3), 87.18 (C4), 116.87 (C1), 127.44−128.35 (Ph), 136.98 (C2), 137.57, 137.82, 138.11 (Ph); HRMS calcd for $C_{28}H_{31}O_4$ (MH^+) 431.2222, found 431.2243, calcd for $C_{21}H_{23}O_4$ (MH^+ − CH_3Ph) 339.1596, found 339.1565; MS *m*/*z* 431 (MH^+,7), 339 (10), 91 (100).

2b: 75% yield; ^{1}H NMR δ 3.58 (dd, J = 10.1, 5.5 Hz, 1H, C7H$_2$), 3.60 (dd, J = 10.1, 5.5 Hz, 1H, C7H$_2$), 3.95 (dd, J = 5.1, 3.6 Hz, 1H, C4H), 4.09 (dd, J = 4.6, 3.6 Hz, 1H, C5H), 4.22 (td, J = 5.5, 4.6 Hz, 1H, C6H), 4.45 (ddt, J = 7.0, 5.1, 1.1 Hz, 1H, C3H), 4.51 (d, J = 11.8 Hz, 1H, Bn), 4.52 (d, J = 12.2 Hz, 1H, Bn), 4.55 (d, J = 12.2 Hz, 1H, Bn), 4.57 (s, 2H, Bn), 4.57 (d, J = 11.8 Hz, 1H, Bn), 5.20 (ddd, J = 10.4, 1.4,1.3 Hz, 1H, C1H$_2$), 5.35 (dt, J = 17.2, 1.4 Hz, 1H, C1H$_2$), 5.95 (ddd, J = 17.2, 10.4, 7.0 Hz, 1H, C2H), 7.25−7.34 (m, 15H, Ph); ^{13}C NMR δ 70.28 (C7), 71.92, 72.02, 73.37 (Bn), 81.36 (C6), 83.51 (C3), 84.90 (C5), 88.11 (C4), 117.17 (C1), 127.59−128.40 (Ph), 136.65 (C2), 137.89−139.25 (Ph); HRMS calcd for $C_{28}H_{31}O_4$ (MH^+) 431.2222, found 431.2198; MS *m*/*z* 448 (MNH_4^+,100), 431 (MH^+, 47), 339 (43).

2c: 56% yield; ^{1}H NMR δ 3.69 (dd, J = 9.7, 6.2 Hz, 1H, C7H$_2$), 3.74 (dd, J = 9.7, 6.3 Hz, 1H, C7H$_2$), 3.92 (d, J = 4.0 Hz, 1H, C4H), 4.05 (d, J = 4.1 Hz, 1H, C5H), 4.42 (td, J = 6.3, 4.1 Hz, 1H, C6H), 4.46 (d, J = 12.3 Hz, 2H, Bn), 4.49 (d, J = 12.3 Hz, 1H, Bn), 4.51 (d, J = 12.0 Hz, 1H, Bn), 4.52 (d, J = 12.3 Hz, 1H, Bn), 4.56 (dd, J = 7.5, 4.0 Hz, 1H, C3H), 4.60 (d, J = 12.0 Hz, 1H, Bn), 5.24 (dd, J = 10.3, 0.9 Hz, 1H, C1H$_2$), 5.34 (dd, J = 17.3, 0.9 Hz, 1H, C1H$_2$), 6.02 (ddd, J = 17.3, 10.3, 7.5 Hz, 1H, C2H), 7.23−7.33 (m, 15H, Ph); ^{13}C NMR δ 68.39 (C7), 72.02, 72.25, 73.36 (Bn), 78.83 (C6), 81.65 (C3), 81.85 (C5), 83.15 (C4), 118.03 (C1), 127.4−129.7 (Ph), 134.08 (C2), 137.8−138.2 (Ph); HRMS calcd for $C_{28}H_{31}O_4$ (MH^+) 431.2222, found 431.2230; MS *m*/*z* 431 (MH^+, 8), 339 (10), 233 (5), 215 (8), 107 (17), 91 (100).

2d; 77% yield; ^{1}H NMR δ 3.54 (dd, J = 10.0, 6.5 Hz, 1H, C7H$_2$), 3.63 (dd, J = 10.0, 5.8 Hz, 1H, C7H$_2$), 3.88 (dd, J = 4.0, 1.5 Hz, 1H, C4H), 3.94 (dd, J = 3.4, 1.5 Hz, 1H, C5H), 4.07 (ddd, J = 6.5, 5.8, 3.4 Hz, 1H, C6H), 4.41 (d, J = 12.1 Hz, 1H, Bn), 4.43 (ddt, J = 7.4, 4.0, 1 Hz, 1H, C3H), 4.44 (d, J = 12.1 Hz, 1H, Bn), 4.46 (d, J = 12.0 Hz, 1H, Bn), 4.49 (d, J = 12.0 Hz, 1H, Bn), 4.50 (d, J = 12.1 Hz, 1H, Bn), 4.56 (d, J = 12.1 Hz, 1H, Bn), 5.25 (ddd, J = 10.3, 1.8, 0.8 Hz, 1H, C1H$_2$), 5.36 (ddd, J = 17.3, 1.8, 1.0 Hz, 1H, C1H$_2$), 6.02 (ddd, J = 17.3, 10.3, 7.4 Hz, 1H, C2H), 7.22−7.30 (m, 15H, Ph); ^{13}C NMR δ 70.51 (C7), 71.53, 71.64, 73.31 (Bn), 82.31 (C6), 82.63 (C3), 84.27 (C5), 84.31 (C4), 118.74 (C1), 127.54−128.42 (Ph), 133.57 (C2), 137.79,137.88,138.23 (Ph); HRMS calcd for $C_{28}H_{31}O_4$ (MH^+) 431.2222, found 431.2230; MS *m*/*z* 431 (MH^+, 20), 339 (47), 91 (100).

Oxidation (Osmilation−Periodination): Cyclic Aldehydes 3a−d. To a solution of the cyclic olefin (**2a**−**d**, respec-

(27) Stahl E. *Thin-Layer Chromatography*, 2nd ed., Springer-Verlag: Berlin, 1969; p 217−218.

(28) Stahl E. *Thin-Layer Chromatography*, 2nd ed.; Springer-Verlag: Berlin, 1969; p 618.

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(30) ^{13}C NMR spectra can be compared with those at ref 17.

tively) (4.3 g, 10 mmol) in 50 mL of 1:1 THF/H_2O was added 4-methylmorpholine *N*-oxide (234 mg, 10 mmol), followed by OsO_4 (0.04 mmol). After the solution was stirred at room temperature for 2−15 h, $NaIO_4$ (642 mg, 30 mmol) in MeOH (50 mL) was added and stirring was continued for additional 2 h. The solution was then partially evaporated (to remove MeOH and THF) and the remaining aqueous phase was extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. Chromatography with CH_2Cl_2 afforded the clean aldehyde.

3a: 48% yield; ^{1}H NMR δ 3.77 (dd, J = 10, 5.5 Hz, 1H, C6H_2), 3.79 (dd, J = 10, 6.5 Hz, 1H, C6H_2), 3.97 (dd, J = 3.4, 1.3 Hz, 1H, C4H), 4.19 (dd, J = 1.3, 1.0 Hz, 1H, C3H), 4.30 (d, J = 11.8 Hz, 1H, Bn), 4.37 (t, J = 1.0 Hz, 1H, C2H), 4.44 (d, J = 11.8 Hz, 1H, Bn), 4.50 (ddd, J = 6.5, 5.5, 3.4 Hz, 1H, C5H), 4.51 (d, J = 12.0 Hz, 1H, Bn), 4.53 (d, J = 12.0 Hz, 1H, Bn), 4.61 (d, J = 12.0 Hz, 1H, Bn), 4.62 (d, J = 12.0 Hz, 1H, Bn), 7.25−7.35 (m, 15H, Ph), 9.59 (d, J = 1.0 Hz, 1H, C1HO); ^{13}C NMR δ 68.19 (C6), 71.57, 71.65, 73.40 (Bn), 80.11 (C4), 81.01 (C5), 84.76 (C3), 87.07 (C2), 127.62−128.49, 136.98, 137.04, 137.93 (Ph), 203.17 (C1). HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.1978; MS *m*/*z* 433 (MH^+, 2), 341 (51), 313 (54), 163 (80).

3b; 76% yield; ^{1}H NMR δ 3.59 (dd, J = 9.9, 6.4 Hz, 1H, C6H_2), 3.65 (dd, J = 9.9, 6.4 Hz, 1H, C6H_2), 4.02 (dd, J = 2.4, 1.8 Hz, 1H, C4H), 4.20 (t, J = 1.8 Hz, 1H, C3H), 4.40 (td, J = 6.4, 2.4 Hz, 1H, C5H), 4.42 (d, J = 11.8 Hz, 1H, Bn), 4.45 (d, J = 11.8 Hz, 1H, Bn), 4.46 (dd, J = 1.8, 1.0 Hz, 1H, C2H), 4.47 (d, J = 11.8 Hz, 1H, Bn), 4.52 (d, J = 12.1 Hz, 1H, Bn), 4.57 (d, J = 11.8 Hz, 1H, Bn), 4.59 (d, J = 12.1 Hz, 1H, Bn), 7.25−7.94 (m, 15H, Ph), 9.68 (d, J = 1.0 Hz, 1H, C1HO); ^{13}C NMR δ 69.87 (C6), 71.45, 71.90, 73.36 (Bn), 82.61 (C4), 83.90 (C5), 84.75 (C3), 87.57 (C2), 127.70−128.52, 136, 137.11, 137.97 (Ph), 202.60 (C1); HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.2028; MS *m*/*z* 433 (MH^+, 0.4), 91 (100).

3c: 44% yield; ^{1}H NMR δ 3.74 (dd, J = 10.8, 6.1 Hz, 1H, C6H_2), 3.77 (dd, J = 10.8, 6.1 Hz, 1H, C6H_2), 4.02 (dd, J = 3.6, 1.3 Hz, 1H, C4H), 4.31 (dd, J = 4.8, 1.3 Hz, 1H, C3H), 4.37 (d, J = 12.0 Hz, 1H, Bn), 4.42 (d, J = 12.1 Hz, 1H, Bn), 4.43 (d, J = 12.0 Hz, 1H, Bn), 4.48 (d, J = 12.1 Hz, 1H, Bn), 4.49 (dd, J = 4.8, 2.0 Hz, 1H, C2H), 4.53 (d, J = 12.0 Hz, 1H, Bn), 4.58 (td, J = 6.1, 3.6 Hz, 1H, C5H), 4.63 (d, J = 12.0 Hz, 1H, Bn), 7.2−7.4 (m, 15H, Ph), 9.67 (d, J = 2.0 Hz, 1H, C1HO); ^{13}C NMR δ 67.97 (C6), 72.35, 72.41, 73.53 (Bn), 80.89 (C4), 81.06 (C5), 83.71 (C3), 84.72 (C2), 127.54−128.49, 136.87, 137.35, 137.97 (Ph), 201.88 (C1); HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.2000; MS *m*/*z* 433 (MH^+, 1), 341 (13), 107 (50), 91 (100).

3d: 50% yield; ^{1}H NMR δ 3.61 (dd, J = 9.9, 6.8 Hz, 1H, C6H_2), 3.72 (dd, J = 9.9, 6.0 Hz, 1H, C6H_2), 4.02 (dd, J = 2.7, 1.4 Hz, 1H, C4H), 4.29 (ddd, J = 6.8, 6.0, 2.7 Hz, 1H, C5H), 4.31 (dd, J = 4.7, 1.4 Hz, 1H, C3H), 4.35 (d, J = 11.9 Hz, 1H, Bn), 4.40 (d, J = 11.9 Hz, 1H, Bn), 4.43 (dd, J = 4.7, 1.9 Hz, 1H, C2H), 4.47 (d, J = 12.0 Hz, 1H, Bn), 4.50 (d, J = 12.0 Hz, 1H, Bn), 4.53 (d, J = 12.1 Hz, 1H, Bn), 4.61 (d, J = 12.1 Hz, 1H, Bn), 7.25−7.34 (m, 15H, Ph), 9.68 (d, J = 1.9 Hz, 1H, C1HO); ^{13}C NMR δ 70.03 (C6), 71.64, 72.00, 73.41 (Bn), 82.89 (C4), 83.93 (C5), 84.68 (C3), 85.36 (C2), 127.74−128.52, 137.0−138.0 (Ph), 200.94 (C1); HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.2015; MS *m*/*z* 433 (MH^+, 20), 341 (46), 91 (100).

Epimerization. To a solution of the aldehyde **(3c** or **3d)** (430 mg, 1 mmol) in 20 mL of dry DMF were added Et_3N (0.14 mL, 1 mmol) and 36 μL (2 mmol) water. After the solution was stirred at room temperature for 18 h, CH_2Cl_2 was added and extracted with 1 M HCl. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness, affording a mixture of two epimers.

3a and **3c** (4:1) were obtained from **3c** in 40% yield.

3b and **3d** (1:1) were obtained from **3d** in 68% yield.

Reduction. Aldehyde (**3a** or **3b**) (2.16 g, 5 mmol) in EtOH (10 mL) was treated with $NaBH_4$ (285 mg, 7.5 mmol). Water was added after 2 h, and the solution was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. Chromatography with ether/hexane 1:2 afforded the corresponding clean alcohol (**4a** or **4b**).

4a: 92% yield; ^{1}H NMR δ 2.38 (dd, J = 7.4, 4.4 Hz, 1H, OH), 3.64 (ddd, J = 11.8, 7.4, 3.9 Hz, 1H, C6H_2), 3.72 (dd, J = 10.1, 6.2 Hz, 1H, C1H_2), 3.75 (dd, J = 10.1, 5.2 Hz, 1H, C1H_2), 3.80 (ddd, J = 11.8, 4.5, 2.0 Hz, 1H, C6H_2), 3.99 (d, J = 3.8 Hz, 1H, C3H), 4.05 (bs, 2H, C4H, C5H), 4.25 (ddd, J = 6.2, 5.2, 3.9 Hz, 1H, C2H), 4.42 (d, J = 11.8 Hz, 1H, Bn), 4.49 (d, J = 11.8 Hz, 1H, Bn), 4.52 (d, J = 12.0 Hz, 1H, Bn), 4.53 (d, J = 11.8 Hz, 1H, Bn), 4.57 (d, J = 11.8 Hz, 1H, Bn), 4.61 (d, J = 12.0 Hz, 1H, Bn), 7.23−7.34 (m, 15H, Ph); ^{13}C NMR δ 62.95 (C6), 68.16 (C1), 71.65, 71.87, 73.46 (Bn), 79.96 (C2), 82.33 (C3), 82.80 (C4), 84.48 (C5), 126.91−128.49, 137.43, 137.58, 137.97 (Ph); HRMS calcd for $C_{27}H_{31}O_5$ (MH^+) 435.2171, found 435.2140; MS *m*/*z* 435 (MH^+, 26), 343 (15), 107 (29), 91 (94).

4b: 80% yield; ^{1}H NMR δ 3.51 (dd, J = 10.0, 6.0 Hz, 1H, C6H_2), 3.56 (dd, J = 10.0, 6.0 Hz, 1H, C6H_2), 3.63 (dd, J = 11.8, 5.3 Hz, 1H, C1H_2), 3.70 (dd, J = 11.8, 3.6 Hz, 1H, C1H_2), 4.05 (dd, J = 4.6, 2.6 Hz, 1H, C3H), 4.06 (t, J = 3 Hz, 1H, C4H), 4.12 (td, J = 5, 3.7 Hz, 1H, C2H), 4.25 (td, J = 6.0, 3.5 Hz, 1H, C5H), 4.51 (d, J = 12.0 Hz, 1H, Bn), 4.53 (s, 2H, Bn), 4.54 (d, J = 12.1 Hz, 2H, Bn), 4.57 (d, J = 12.1 Hz, 1H, Bn), 7.22−7.30 (m, 15H, Ph); ^{13}C NMR δ 62.80 (C6), 70.10 (C1), 71.67, 72.13, 73.44 (Bn), 81.98 (C3), 83.24 (C4), 84.18 (C2/C5), 84.68 (C2/C5), 127.72−128.47, 137−138 (Ph); HRMS calcd for $C_{27}H_{31}O_5$ (MH^+) 435.2171, found 435.2172; MS *m*/*z* 452 (MNH_4^+, 100), 435 (MH^+, 41), 343 (30).

Catalytic Hydrogenation of Benzyl Ethers. Pd/C (10%, 100 mg) was added to a solution of the protected alcohol (**4a** or **4b**) (1 g, 2.3 mmol) in MeOH (10 mL), and the reaction mixture was stirred at room temperature under atmospheric pressure of H_2 for 18 h. Filtration and evaporation to dryness afforded the free alcohol (2,5-anhydroglucitol **5a** or 2,5-anhydromannitol **5b**, respectively).[31]

5a: 61% yield; ^{1}H NMR (D_2O) δ 3.70 (dd, J = 12.1, 6.0 Hz, 1H, C1H_2), 3.74 (dd, J = 11.9, 7.0 Hz, 1H, C6H_2), 3.77 (dd, J = 12.1, 3.8 Hz, 1H, C1H_2), 3.83 (dd, J = 11.9, 4.3 Hz, 1H, C6H_2), 3.84 (ddd, J = 6.0, 4.3, 3.8 Hz, 1H, C2H), 4.02 (dd, J = 4.3, 2.5 Hz, 1H, C3H), 4.12 (dt, J = 7.0, 4.4 Hz, 1H, C5H), 4.18 (dd, J = 4.4, 2.5 Hz, 1H, C4H); ^{13}C NMR (D_2O) δ 60.72 (C1/C6), 62.31 (C1/C6), 77.51, 78.60, 81.55, 85.2 (C2, C3, C4, C5); HRMS calcd for $C_6H_{13}O_5$ (MH^+) 165.0723, found 165.0771; MS *m*/*z* 165 (MH^+, 100), 147 (16), 129 (32), 111 (20).

5b: 100% yield; ^{1}H NMR (D_2O) δ 3.70 (dd, J = 12.4, 5.6 Hz, 2H, C1H_2/C6H_2), 3.78 (dd, J = 12.4, 3.1 Hz, 2H, C1H_2/C6H_2), 3.90 (m, 2H, C2H/C5H), 4.06 (m, 2H, C3H/C4H); ^{13}C NMR (D_2O) δ 61.80 (C1,C6), 77.06 (C3,C4), 82.96 (C2,C5); HRMS calcd for $C_6H_{13}O_5$ (MH^+) 165.0723, found 165.0780; MS *m*/*z* 182 (MNH_4^+, 100), 165 (MH^+, 26).

Phosphorylation. The alcohol (either mono-, **4a** or **4b**, or tetraol **5a**) (1.5 mmol) was dissolved in dry pyridine (7 mL) under argon atmosphere. DMAP (10 mg) was added, and the solution was cooled to 0 °C. Diphenyl chlorophosphate (1.3 g, 5 mmol) was added, and the solution was allowed to warm to room temperature. After 18 h, EtOAc (for the diphosphates) or CH_2Cl_2 (for the monophosphates) was added and extracted consecutively twice with 1 M HCl, saturated $NaHCO_3$, and water. The solution was dried over $MgSO_4$, filtered, and evaporated to dryness. Chromatography with EtOAc/hexane (1:1 for the monophosphates and 2:1 for the diphosphate) afforded the clean products.

Protected monophosphate **6a** was obtained from **4a** in 55% yield: ^{1}H NMR δ 3.68 (dd, J = 10.0, 6.4 Hz, 1H, C1H_2), 3.73 (dd, J = 10.0, 5.5 Hz, 1H, C1H_2), 3.97 (dd, J = 3.9, 1.2 Hz, 1H, C3H), 4.00 (dd, J = 2.3, 1.2 Hz, 1H, C4H), 4.19 (ddd, J = 7.2, 5.7, 2.3 Hz, 1H, C5H), 4.27 (ddd, J = 10.2, 6.8, 7.2 Hz, 1H, C6H_2), 4.30 (ddd, J = 6.4, 5.5, 3.9 Hz, 1H, C2H), 4.35 (ddd, J = 10.2, 6.8, 5.7 Hz, 1H, C6H_2), 4.37 (d, J = 11.9 Hz, 1H, Bn), 4.40 (d, J = 11.8 Hz, 1H, Bn), 4.43 (d, J = 11.8 Hz, 1H, Bn), 4.49 (d, J = 12.0 Hz, 1H, Bn), 4.50 (d, J = 11.9 Hz, 1H, Bn), 4.59 (d, J = 12.0 Hz, 1H, Bn), 7.19−7.32 (m, 25H, Ph); ^{13}C NMR δ 68.10 (d, J = 5.8 Hz, C6), 68.20 (C1), 71.57, 71.79,

(31) Spectra can be compared with refs 9−12 and 26.

73.44 (Bn), 80.45 (C2), 81.70 (d, $J = 8.4$ Hz, C5), 82.05 (C3), 82.87 (C4), 120.11 (d, $J = 4.9$, 120.55 (d, $J = 4.7$ Hz), 123.58−129.84, 137.40, 137.53, 138.01, 150.44 (d, $J = 7.4$ Hz), 152.12 (d, $J = 5$ Hz) (Ph); ^{31}P NMR δ −11.58 (t, $J = 6.8$ Hz); HRMS calcd for $C_{39}H_{40}O_8P$ (MH^+) 667.2461, found 667.243; MS *m/z* 667 (MH^+, 4), 107 (100), 91 (41).

Protected monophosphate **6b** was obtained from **4b** in 51% yield: ^{1}H NMR δ 3.53 (dd, $J = 10.1$, 5.8 Hz, 1H, C1H$_2$), 3.56 (dd, $J = 10.1$, 5.8 Hz, 1H, C1H$_2$), 4.06 (dd, $J = 3.5$, 2.6 Hz, 1H, C4H), 4.07 (dd, $J = 3.6$, 2.6 Hz, 1H, C3H), 4.21 (td, $J = 5.8$, 3.6 Hz, 1H, C2H), 4.28 (td, $J = 6.8$, 3.5 Hz, 1H, C5H), 4.33 (t, $J = 6.8$ Hz, 2H, C6H$_2$), 4.42 (d, $J = 11.8$ Hz, 1H, Bn), 4.45 (d, $J = 11.8$ Hz, 1H, Bn), 4.47 (d, $J = 11.8$ Hz, 1H, Bn), 4.49 (d, $J = 11.8$ Hz, 1H, Bn), 4.52 (d, $J = 12.0$ Hz, 1H, Bn), 4.55 (d, $J = 12.0$ Hz, 1H, Bn), 7.16−7.32 (m, 25H, Ph); ^{13}C NMR δ 67.90 (d, $J = 7.1$ Hz, C6), 70.03 (C1), 71.84, 71.94, 73.35 (Bn), 81.07 (d, $J = 8.1$ Hz, C5), 82.30 (C2), 84.08 (C4), 84.36 (C3), 120.07 (d, $J = 4.5$ Hz), 125.35, 127.68−128.44, 129.76, 137.45, 137.59, 138.10, 150.50 (d, $J = 2.3$ Hz) (Ph); ^{31}P NMR (CD_3OD) δ −11.61 (t, $J = 6.8$ Hz); HRMS calcd for $C_{39}H_{40}O_8P$ (MH^+) 667.2461, found 667.246; MS *m/z* 667 (MH^+, 39), 577 (13), 107 (29), 91 (100).

Protected diphosphate **7a** was obtained from **5a** in 45% yield: ^{1}H NMR δ 3.98 (td, $J = 5.6$, 2.7 Hz, 1H, C2H), 4.00 (dd, $J = 3.7$, 1.8 Hz, 1H, C4H), 4.08 (dd, $J = 2.7$, 1.8 Hz, 1H, C3H), 4.23 (ddd, $J = 6.4$, 5.7, 3.7 Hz, 1H, C5H), 4.28 (td, $J = 10.8$, 5.7 Hz, 1H, C6H$_2$), 4.30 (ddd, $J = 10.8$, 8.9, 5.6 Hz, 1H, C1H$_2$), 4.35 (ddd, $J = 10.8$, 8.0, 5.6 Hz, 1H, C1H$_2$), 4.47 (ddd, $J = 10.8$, 8.4, 6.5 Hz, 1H, C6H$_2$); ^{13}C NMR δ 67.15 (d, $J = 5.9$ Hz, C1/C6), 68.92 (d, $J = 6.3$ Hz, C1/C6), 76.96 (C3/C4), 78.35 (C3/C4), 79.56 (d, $J = 6.9$ Hz, C2/C5), 83.43 (d, $J = 7.0$ Hz, C2/C5), 120.1 (d, $J = 4$ Hz), 125.6, 129.9, 150.3 (d, $J = 9.0$ Hz) (Ph); ^{31}P NMR δ −11.47 (t, $J = 8.4$ Hz), −10.80 (dd, $J = 10.8$, 8.4 Hz); HRMS calcd for $C_{30}H_{31}O_{11}P_2$ (MH^+) 629.1342, found 629.1345; MS *m/z* 629 (MH^+, 39), 535 (9), 379 (9), 95 (100).

Catalytic Hydrogenation of Phenyl Phosphate Esters. The protected diphosphate **7a** (1 mmol) was dissolved in MeOH (7 mL). PtO_2 (10 mg) was added and the mixture was stirred under atmospheric pressure of H_2 for 18 h. Filtration and evaporation afforded the clean diphosphate **9a** in quantitative yield. It could be further purified by ion exchange chromatography on DEAE-cellulose (2.5 × 22 cm column), eluted by a step gradient of 100 mL of H_2O, followed by 100 mL of 1 M $NH_4^+HCO_2^-$.[32]

The protected monophosphate (**6a** or **6b**) was first hydrogenated with Pd/C as described above and then with PtO_2, affording the monophosphate (**8a** or **8b**, respectively).[32]

Monophosphate **8a**: 74% yield; ^{1}H NMR (D_2O) δ 3.59 (m, 1H, C1H$_2$), 3.61 (m, 1H, C6H$_2$), 3.82 (m, 1H, C2H), 3.89 (m, 1H, C6H$_2$), 3.95 (m, 1H, C1H$_2$), 3.95 (m, 1H, C3H), 3.99 (m, 1H, C5H), 4.05 (dd, 1H, C4H).

Monophosphate **8b**; 61% yield; ^{1}H NMR (D_2O) δ 3.61 (dd, $J = 11.8$, 5.3 Hz, 1H, C1H$_2$), 3.70 (dd, $J = 11.8$, 3.4 Hz, 1H, C1H$_2$), 3.82 (ddd, $J = 6.1$, 5.3, 3.4 Hz, 1H, C2H), 3.97 (dt, $J = 5.6$, 3.4 Hz, 1H, C5H), 3.99 (t, $J = 5.9$ Hz, 1H, C3H), 4.02 (dd, $J = 5.9$, 3.4 Hz, 1H, C4H), 4.16 (ddd, $J = 10.8$, 6.7, 5.6 Hz, 1H, C6H$_2$), 4.24 (ddd, $J = 10.8$, 6.1, 3.4 Hz, 1H, C6H$_2$); ^{13}C NMR (D_2O) δ 63.96 (C1), 69.28 (d, $J = 5.7$ Hz, C6), 79.20 (C3/C4), 79.27 (C3/C4), 83.95 (C5), 86.01 (C2); ^{31}P NMR (CD_3OD) δ 0.65 (t, $J = 6$ Hz); MS FAB$^-$ *m/z* 243 ($M - H^+$, 19), 183 (23).

Diphosphate **9a**: ^{1}H NMR (D_2O) δ 3.99 (dt, $J = 6.0$, 4.4 Hz, 1H, C5H), 4.07 (ddd, $J = 10.8$, 7.4, 6.4 Hz, 2H, C1H$_2$, C6H$_2$), 4.11 (dd, $J = 4.4$, 3.2 Hz, 1H, C4H), 4.14 (ddd, $J = 10.8$, 6.1, 4.4 Hz, 1H, C6H$_2$), 4.19 (ddd, $J = 10.8$, 6.5, 3.8 Hz, 1H, C1H$_2$), 4.28 (dd, $J = 4.8$, 3.2 Hz, 1H, C3H), 4.31 (ddd, $J = 6.9$, 4.8, 3.8 Hz, 1H, C2H); ^{13}C NMR (D_2O) δ 64.19 (d, $J = 7.4$ Hz, C1/C6), 65.64 (d, $J = 8.1$ Hz, C1/C6), 77.38 (C3/C4), 78.33 (C3/C4), 80.60 (d, $J = 12.4$ Hz, C2/C5), 84.05 (d, $J = 12.4$ Hz, C2/C5); ^{31}P NMR (D_2O) δ 1.37 (t, $J = 6.5$ Hz), 1.65 (t, $J = 7$ Hz); MS FAB$^-$ *m/z* 323 ($M - H^+$, 12).

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Supporting Information Available: Figures showing ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) ^{13}C NMR spectra can be compared with those at ref 26.