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Synthesis of Three *C*-Glycoside Analogues of UDP-Galactopyranose as Conformational Probes for the Mutase-Catalyzed Furanose/Pyranose Interconversion

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Dedicated to Professor Alain Krief

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UDP-galactopyranose mutase (UGM) catalyzes the isomerization of UDP-galacto*pyranose* (UDP-Gal*p*) into UDP-galacto*furanose* (UDP-Gal*f*), an essential step of the mycobacterial cell wall biosynthesis. In order to probe the UGM binding pocket, we synthesized the α- and β-*C*-glycosidic analogues of UDP-galacopyranose along with the corresponding UDP-*exo*-galactal. Preliminary inhibition evaluation indicated that UDP-*exo*-galactal inhibits UGM with a binding affinity similar to that of UDP-α-*C*-galactopyranose.

Introduction

Although tuberculosis can be effectively treated by antibiotic therapy, it remains a life-threatening infection, not only in Third World Countries but also in western countries.[1] Notably, the identification of extreme drug-resistant tuberculosis strains has recently raised considerable alarm.[2] The unusual structure of the cell wall of *Mycobacterium tuberculosis*, the causative agent of tuberculosis, is now acknowledged to be a key target for the development of new therapeutics.[3] This cell wall insures the survival of the mycobacteria by acting both as a permeability barrier to the passage of antibiotics and also as a modulator of the host immune system. Oligo-galacto*furanosides* (Gal*f*) are conserved cell wall glycoconjugates of all mycobacteria whose biosynthesis has attracted much attention for the discovery of novel classes of molecules that would be developed for the treatment of tuberculosis.[4]

The search for the biosynthetic origin of the Gal*f* residues has led to the discovery of an unusual enzymatic ring contraction: the interconversion of UDP-galactopyranose (UDP-Gal*p*) **1** into UDP-galactofuranose (UDP-Gal*f*) **2**, the universal Gal*f* donor for all oligo-galactofuranosides (Figure 1). Such an enzymatic isomerization is a key biocatalytic process not only because it is essential for the survival of mycobacteria, but also because its mechanism addresses questions that are at the heart of enzymology and the chemistry of carbohydrates. UDP-galactopyranose mutase (UGM), the enzyme catalyzing this reaction, is a flavoenzyme whose FAD cofactor plays an unprecedented role in biochemistry.[5,6] Moreover, the binding mode of the galactose residue within the UGM catalytic pocket has raised many questions and led to different investigations: potentiometric analysis,[6] STD-NMR experiments correlated with computational studies,[7] mutagenesis,[8] as well as inhibition studies with analogues of its substrate.[9–13]

In preliminary studies, our approach was to probe the UGM binding site with conformationally locked molecules such as **3**[11,14] and **4** but also with acyclic iminogalactitol derivatives.[15] Moreover, we found that UDP-*exo*-glycals derived from galacto*furanose* displayed interesting time-dependent inactivation properties.[12,13] All these molecules were analogues of the product UDP-Gal*f* **2**. Therefore, to have a global and comparative overview of the binding mode of the galactose moiety with UGM we need now to assess the inhibition profiles of *C*-glycosidic analogues of UDP-galacto*pyranose* **1** and compare them to boat-locked galactoside **3** and furanoside **4**.

Here, we report the synthesis of UDP-*C*-α-Gal*p* **5** and UDP-*C*-β-Gal*p* **6**, the phosphonate analogues of UDP-galactopyranose, with respectively α and β configurations at the anomeric position, as well as the synthesis of UDP-(*Z*)-*exo*-galactal **7**. Preliminary inhibition profiles are also described.

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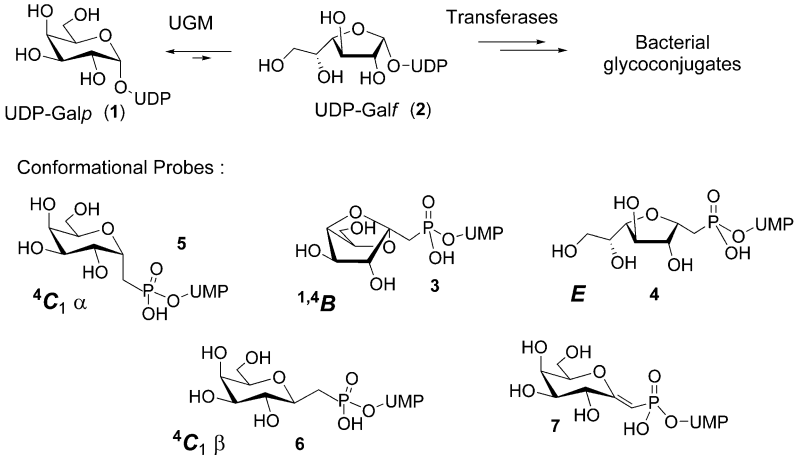
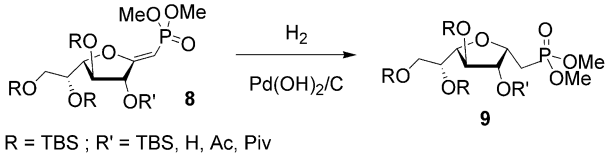


Figure 1. *C*-Glycosidic analogues of UDP-galactose.

Results and Discussion

Synthesis of UDP-*C*-β-Gal*p*

In a previous study,[11] we reported a short synthetic sequence allowing the preparation of UDP-*C*-α-Gal*f* **4** (5 steps, 21% global yield) by exploiting the stereoselective hydrogenation of protected *exo*-glycals **8** (Scheme 1). Whatever the protective group at the 2-position, we always observed high "α" (or 1,2-*cis*) selectivity.[11,16]



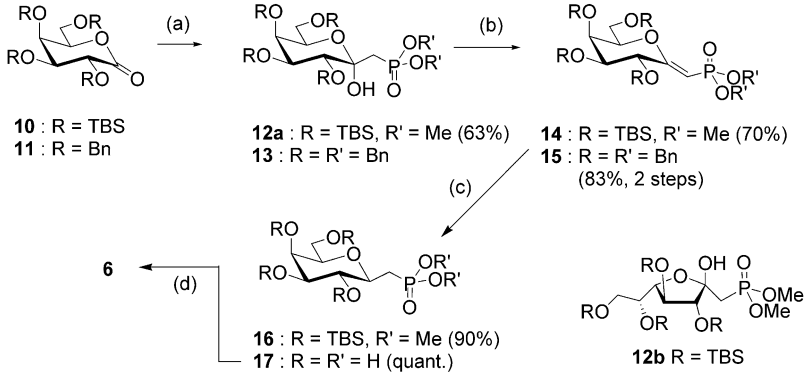
Scheme 1. Stereoselective preparation of "α"-*C*-galactofuranosides.

Considering the results obtained in the furanose series, we reasoned that it should be interesting to develop the same strategy in the pyranose series to obtain the corresponding α-phosphonate.

Persilylated *exo*-glycal **14** was first synthesized in two steps from persilylated 1,5-galactonolactone **10**[17] by condensing the lithium anion of dimethyl methylphosphonate at –78 °C in anhydrous THF to yield intermediate lactol **12a** in 63% yield after purification on silica gel (Scheme 2). We observed that it was important to keep the temperature at –78 °C during the course of the reaction (30 min) to minimize the parallel formation of *furano*-lactol **12b**. This surprising side reaction was in fact a transsilylation of pyranose **12** through an acyclic intermediate resulting in furanose formation.

Lactol **12a** was then subjected to an elimination reaction achieved through a procedure described by Lin et al.[18] As expected, this procedure exclusively gave *exo*-glycal **14** with the (*Z*) configuration in 70% yield. When *exo*-glycal **14** was submitted to the hydrogenation conditions we had optimized for the synthesis of α-*C*-galactofuranosides (Pearlman's catalyst in EtOAc),[11] the reaction was highly stereoselective, but this time, in favor of the β-phosphonate (compound **16**) with a global yield of 90%. At first sight, this result surprised us given the α selectivity observed for the same reaction performed on the corresponding furanose (Scheme 1).

The β configuration was established by the coupling constant between H-1 and H-2 (J = 8.7 Hz), showing a *trans* relationship between these two protons. In this case, the ste-



Scheme 2. Reagents and conditions: (a) $(R'O)_2POCH_2Li$, THF, –78 °C, 30 min; (b) $(CF_3CO)_2O$, Py, THF, 0 °C, 1 h; (c) H_2, Pd-$(OH)_2$/C, EtOAc, room temp., 8 h; (d) UMP-*N*-methylimidazolium, molecular sieves 4 Å, CH_3CN, 0 °C, 5 h then NH_4^+, AcO^- (pH = 7; 250 mM).

ric hindrance at the 2-position, which was likely the origin of the α stereospecificity in the furanose series,[11] did not operate. Instead, it might be argued that the β face of pyranose **14** is hindered by the two TBS groups at the 4- and 6-positions, thus directing the hydrogen addition from the α face. As such a remote control is rather unusual for the addition on exocyclic double bonds, electronic or even stereoelectronic effects may also be at the origin of this total "β" stereoselectivity.

Considering this result, we reasoned that it would be judicious to realize this sequence on a perbenzylated *exo*-glycal to obtain the *C*-β-phosphonate in order to shorten the synthesis and make the complete deprotection of the final phosphonate sugar easier. We thus synthesized (*Z*)-*exo*-glycal **15** in 83% yield in a one-pot sequence from perbenzylated D-galactono-1,5-lactone **11** by following the procedure described above. The hydrogenation of intermediate **15**, catalyzed by $Pd(OH)_2$ yielded β-configured phosphonate **17** as sole product in quantitative yield. This novel sequence from **11** to **17** was, indeed, much shorter and efficient than the previous one starting from **10**, notably because ring isomerization/expansion could not occur.

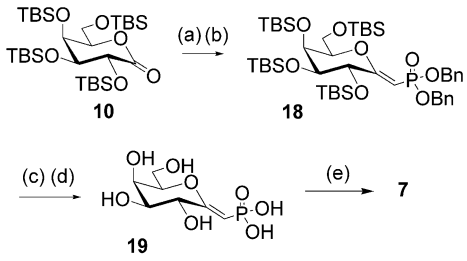
A survey of the literature showed us that similar stereoselectivities had been observed with pyranosides bearing an exocyclic enol ether functionality,[19,20] but the origin of the selectivity is still obscure. To summarize, hydrogenation reactions of *exo*-glycals lead to 1,2-*cis* adducts from furanosides and 1,2-*trans* adducts from pyranosides.

Deprotected β-phosphonate **17** was then coupled to activated UMP in CH_3CN by following a procedure described by Bogachev[21] for the synthesis of nucleosides triphosphates and by Kiessling[22] for the challenging synthesis of UDP-galactofuranose.[23–25] UDP-*C*-β-Gal*p* **1** was obtained in 54% yield after size exclusion chromatography and semi-preparative HPLC purification.

Synthesis of UDP-*exo*-Galactal 7

In previous work,[12] we presented the synthesis of UDP-*exo*-galactofuranosylglycal with a (*Z*) configuration that displayed an interesting time-dependent inactivation of UDP-galactopyranose mutase. We then prepared their fluorinated analogues,[13] whose UGM inactivation kinetics ruled out single-electron transfers from the FAD cofactor. Considering these results, we naturally turned our attention to the synthesis of the same molecule in the pyranose series.

To synthesize UDP-*exo*-galactal **7**, we used the same strategy as that for the preparation of UDP-*exo*-glycalGal*f* previously described in our group.[12] *exo*-Glycal **18** was synthesized in two steps from lactone **10** (Scheme 3). Then, the complete deprotection was achieved first by selective debenzylation under standard conditions, directly followed by a tetradesilylation with the use of an excess amount of tetrabutylammonium fluoride to give phosphonate **19** in 78% yield over two steps after ion-exchange chromatography. As in the case of the furanose series,[12] the sequence of deprotection is important and cannot be inverted: the TBS groups prevent saturation of the double bond during the hydrogenolysis step.



Scheme 3. Reagents and conditions: (a) $(BnO)_2POCH_2Li$, THF, –78 °C, 30 min (55%); (b) $(CF_3CO)_2O$, Py, THF, 0 °C, 2 h (91%); (c) H_2, Pd/C, Et_3N, CH_2Cl_2, room temp., 1 h 30 min; (d) nBu$_4$NF·3H$_2$O, THF, room temp., 4 h (78%, 2 steps); (e) UMP-*N*-methylimidazolium, CH_3CN, room temp., 12 h then NH_4^+, AcO^- (pH = 7, 250 mM) (67%).

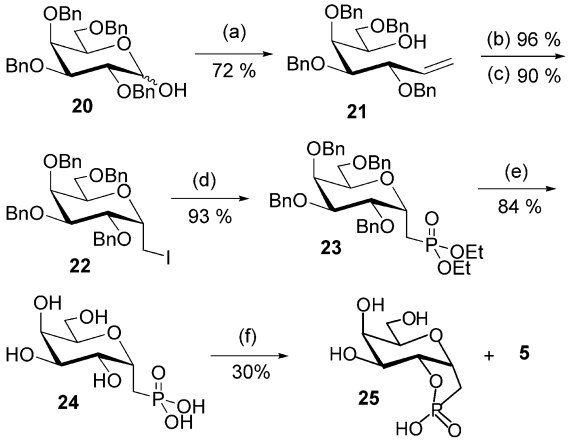
exo-Glycal **19** was then coupled to UMP by using the Bogachev procedure and target *exo*-glycal **3** was efficiently obtained in 67% yield after purification. Compound **7** was obtained in five steps in 26% global yield from persilylated D-galactono-1,5-lactone **10** (Scheme 3).

In 2004, Schmidt et al. reported the synthesis of novel UDP-glycal derivatives, such as **3**, as transition-state analogue inhibitors of UDP-GlcNAc 2-epimerase.[20] From a purely synthetic point of view, we managed to improve the global yield of the synthesis of **3** by appropriate choice of the protecting groups on the sugar (silyl ethers instead of acetyl groups) and by proper choice of the coupling procedure with UMP. On the one hand, the Bogachev procedure was found to be much more efficient than the standard morpholidate coupling, because the short reaction times and the mild conditions avoided side reactions or decomposition of the sensitive enol ether functionality. On the other hand, it should be mentioned that the Bogachev procedure is, technically, much more demanding than the classical morpholidate coupling, as it requires extremely pure and anhydrous reagents as well as the preparation of several intermediate solutions for the activation of UMP.

Synthesis of UDP-*C*-α-Gal*p* 5

To achieve the synthesis of α-*C*-galactosyl derivative **5** (Scheme 4), we used a multistep sequence developed in the literature by Nicotra et al. for the synthesis of the phosphonate analogues of D-glucose and D-mannose 1-phosphates.[26] The key step of this strategy is an α-stereospecific mercurio-cyclization of a 1,2-dideoxy heptenitol pioneered by Sinaÿ and collaborators.[27]

The reaction of 2,3,4,6 tetra-*O*-benzyl-D-galactose **20** with methylenetriphenylphosphorane gave compound **21** in 72% yield according to a known procedure.[28] Enitol **21** was thus converted into its mercuric derivative with mercuric acetate. As expected, this reaction proceeded stereospecifically to afford the 1,2-*cis* *C*-glycoside [J(1-2) = 3.7 Hz]. When this intermediate was treated with diiode, we gener-



Scheme 4. Reagents and conditions: (a) **20**, then (PPh_3CH_3Br, BuLi), THF, 0 °C to room temp., 8 h; (b) $Hg(OAc)_2$, THF, room temp., 20 h then KCl (aq.), room temp., 1 h; (c) I_2, DCM, room temp., 6 h; (d) $(EtO)_3P$, 160 °C, 12 h; (e) TMSI, CCl_4, 0 °C, 4 h; (f) UMP-*N*-methylimidazolium, CH_3CN, 0 °C, 1.5 h then NH_4^+, AcO^- (pH = 7; 250 mM).

ated **22** in 90% yield, which was heated at reflux with triethyl phosphite to afford phosphonate **23** in 93% yield after chromatography on silica gel. Deprotection of both benzyl ether and ethyl ester groups could be easily performed with an excess amount of iodotrimethylsilane at 0 °C in CCl_4 to afford expected phosphonate **24** in 84% yield after ion-exchange chromatography.

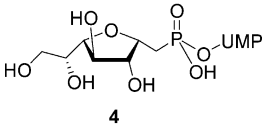
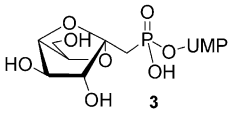
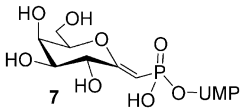
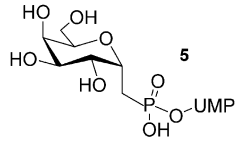
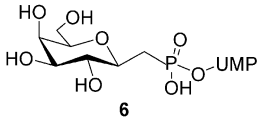
The Bogachev coupling of **24** with UMP completed the synthesis of target molecule **5**. As in the case of UDP-*C*-α-Gal*f* we previously synthesized,[11] compound **5** was found to be unstable: its decomposition into cyclic phosphonate **25** during the course of the reaction and its purification explained the rather poor, but optimized, yield. In pure water, a decomposition of 10% of nucleotide sugar **5** was observed when it was kept for 2 h at room temperature. A reaction time of 1.5 h and a temperature of 0 °C were required to minimize this side reaction, and desired nucleotide sugar **5** was isolated after size-exclusion chromatography and semipreparative HPLC purification in a triethylammonium acetate buffer.

Enzymatic Assay

As a preliminary biological evaluation, we measured inhibition percentages of the interconversion of UDP-Gal*f* and UDP-Gal*p* catalyzed by UDP-galactopyranose mutase from *E. coli*. Table 1 compares the inhibition levels of nucleotide sugars **5**, **6**, and **7** to those of two *C*-glycosidic analogues of UDP-Gal*f* we previously described: [11] UDP-*C*-Gal*f* **4** and constrained analogue **3** locked in a $^{1,4}B$ boat conformation.

The inhibitory activities of the *C*-glycosides were evaluated by HPLC following the procedure developed by Liu et al.:[10] all molecules were tested at a concentration of 1 mM by using UDP-Gal*f* (1 mM) as substrate under reducing (upon addition of sodium dithionite) and nonreducing

Table 1. Inhibition percentages of UGM from *E. coli* at [UDP-Gal*f*] = [inhibitor] = 1 mM under nonreducing conditions.

Entry	Molecule	Inhibition percentage [%]
1	 **4**	91
2	 **3**	53
3	 **7**	42
4	 **5**	36
5	 **6**	8

(native enzyme) conditions. We had applied the same conditions for the measurements of inhibition and/or inactivation properties of molecules **3** and **4**.[11,12] Under reducing conditions, all pyranosides **5**, **6**, and **7** displayed poor inhibition properties (<10%). Therefore, in the whole series depicted in Scheme 1, constrained analogue **3** remains the best inhibitor.[11]

Inhibition percentages under nonreducing conditions are reported in Table 1, from the best inhibitor (Entry 1) to the weakest (Entry 5). As expected, β-pyranoside **6** with the wrong anomeric configuration displayed the lowest inhibition percentage (8%, Entry 5). Not surprisingly, UDP-*C*-α-Gal*p* **5** exhibited lower inhibition percentages (Entry 4) than UDP-*C*-α-Gal*f* **4** (Entry 1), as expected from their relative K_m values for UGM and the 92:8 pyranose/furanose ratio at the equilibrium (Figure 1, equilibrium between **1** and **2**).[25]

Very surprisingly, *exo*-glycal **7** and α-*C*-pyranoside **5** exhibited similar inhibition profiles despite their significant structural differences. Moreover, *exo*-glycal **7** did not inactivate UGM in a time-dependent manner, which is in deep contrast with the inactivation we observed with all *exo*-glycals in the furanose series.[12,13] This result indicates that *exo*-glycal **7** adopts a specific binding mode within the catalytic cavity that prevents its reaction with the enzyme. Docking and cocrystallization experiments with UGM are in progress to explain why this molecule possesses a similar affinity to the *C*-glycosidic analogue of natural substrate **1**.

Conclusions

In conclusion, we described the synthesis of three *C*-glycosidic analogues of UDP-galacto*pyranose* and compared their inhibition properties, against UGM, with known *C*-glycosides in the UDP-galacto*furanose* series. The binding affinities of these nucleotide-sugars for UGM significantly increase in the order: β-galactopyranose < α-galactopyranose ≈ *exo*-glycalpyranose < boat-locked galactose < α-galactofuranose. Surprisingly, UDP-*exo*-galactal derivative **7** was a competitive inhibitor, whereas time-dependent inactivation was expected.

Experimental Section

Materials and Procedures: All chemicals were purchased from Sigma, Aldrich, or Fluka and used without further purification. Tetrahydrofuran, diethyl ether, and toluene were freshly distilled from sodium benzophenone, dichloromethane over P_2O_5, and acetonitrile over CaH_2. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded with Bruker AC-250 and AMX-400 spectrometers. All compounds were characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy as well as by ^1H–^1H and ^1H–^{13}C correlation experiments. Specific optical rotations were measured with a Perkin–Elmer 241 Polarimeter in a 1 dm cell. Melting points were determined with a Büchi 535 apparatus. Column chromatography was performed on silica gel Kieselgel Si 60 (40–63 μm). Size-exclusion chromatography was accomplished on a Sephadex G15 column (2.5 × 60 cm) by using a Pharmacia Biotech Äkta FPLC apparatus, and the fractions containing uridine derivatives were detected by UV. When required, purifications of nucleotide-sugars were realized by semipreparative HPLC by using a Waters Delta prep 4000 chromatography system equipped with a NovaPack C18 (1 × 10 cm) column (eluent: triethylammonium acetate 50 mM, pH 6.8). For enzymatic assays, a Waters 600 E analytical apparatus equipped with a Zorbax C18-SB column (25 × 0.46 cm, 5 μm) was used (eluent: triethylammonium acetate 50 mM, pH 6.8). UDP-Gal*f* was prepared according to known procedures.[22,24,25]

Atom and Position Numberings: We systematically numbered the phosphonate methylene group 1′ and adopted the usual numbering for carbohydrates from 1 to 6 with 1 for the anomeric position. For nucleotide-sugars, we used the conventional ribose and pyrimidine numberings: 1′ for the anomeric position, 1′′ for the nitrogen atom linked to the ribose.

Preparation and Purification of UGM: UGM from *E. coli* was overexpressed and purified following our procedure.[11]

Enzyme Kinetics and Inhibition Assays: Conditions described by Liu et al. were followed.[10] All assays were performed by using a potassium phosphate buffer (100 mM, pH 6.8) at T = 21 °C. Under reductive conditions, freshly prepared sodium dithionite solutions were used to allow a final concentration of 20 mM. When native mutase was used (without sodium dithionite), reactions were conducted in the dark under aerobic conditions. All inhibition studies consisted in measuring the conversion of pure starting UDP-Gal*f* into UDP-Gal*p* (compared with a commercially available sample) by analytical HPLC (C18 column, elution by triethylammonium acetate 50 mM, pH 6.8, detection at 262 nm). Substrate and inhibitor concentrations were adjusted at 1 mM from titrated mother solutions. Incubation times were always 12 h at 21 °C. As a control, the relative concentrations of any species in the reaction mixtures could be titrated by using UMP as an internal standard. Enzyme concentrations were adjusted to allow a conversion of UDP-Gal*p* between 15 and 25%. Reactions were stopped by freezing the solution in liquid nitrogen. Residual enzyme activities were then measured in the presence of inhibitors at three different times, compared with the same experiment conducted without inhibitors, and averaged.

Uridine Diphosphate-*C*-α-D-Galactopyranose (5): The Bogachev procedure detailed below for the synthesis of molecule **6** was strictly followed.

The final crude mixture was purified by size-exclusion chromatography (Sephadex G15). Eluent was a 50 mM triethylammonium acetate buffer (pH 6.8) to avoid decomposition of compound **5** into UMP and cyclic phosphonate **25**. The appropriate fractions were pooled and freeze-dried. Compound **5** was further purified by HPLC by using a C18 column (elution: 1% MeCN in 50 mM triethylammonium acetate buffer pH 6.8 as eluent; flow rate: 1 mL min^{-1}). Fractions containing **5** were pooled and lyophilized. This protocol afforded compound **5** as a white solid (31 mg, triethylammonium salt) in 30% yield. ^1H NMR (400 MHz, D_2O): δ = 7.96 [d, J(5′′-6′′) = 8.0 Hz, 1 H, 6′′-H], 5.99 [d, J(1′-2′) = 4.2 Hz, 1 H, 1′-H], 5.98 [d, J(5′′-6′′) = 8.0 Hz, 1 H, 5′′-H], 4.47 (m, 1 H, 1-H), 4.40–4.35 (m, 2 H, 2′-H, 3′-H), 4.29 (m, 2 H, 1-H, 4′-H), 4.28–4.18 (m, 2 H, 5′-Ha, 5′-Hb), 3.99 [dd, J(2-3) = 6.1 Hz, 1 H, 2-H], 3.98 (m, 1 H, 4-H), 3.93 [ddd, J(4-5) = 2.0 Hz, J(5-6a) = 9.2 Hz, J(5-6b) = 4.4 Hz, 1 H, 5-H], 3.79 (m 1 H, 3-H), 3.77 [ABX, J(5-6a) = 9.2 Hz, J(6a-6b) = 11.6 Hz, 1 H, 6-Ha], 3.68 [ABX, J(5-6b) = 4.4 Hz, J(6a-6b) = 11.6 Hz, 1 H, 6-Hb], 3.21 (q, J = 7.3 Hz, CH_2, NEt_3), 2.25 [ABXX′, J(1-1′a) = 10.8 Hz, J(1′a-P) = 15.7 Hz, J(1′a-1′b) = 15.7 Hz, 1 H, 1′-Ha], 2.13 [ABXX′, J(1-1′b) = 4.0 Hz, J(1′b-P) = 20.1 Hz, J(1′a-1′b) = 15.7 Hz, 1 H, 1′-Hb], 1.29 (t, J = 7.3 Hz, CH_3, NEt_3) ppm. ^{31}P NMR (101 MHz, D_2O): δ = 15.35 [d, J(Pα-Pβ) = 26.3 Hz, Pα] and –11.15 [d, J(Pα-Pβ) = 26.3 Hz, Pβ] ppm. MS (ESI–): m/z (%) = 563 (100) [M – H]$^-$. HRMS: calcd. for $C_{16}H_{25}N_2O_{16}P_2$ 563.0679; found 563.0656.

Uridine Diphosphate-*C*-β-D-Galactopyranose (6): A suspension of UMP (triethylammonium salt, 78.7 mg, 0.185 mmol) in a mixture of freshly distilled MeCN (950 μL), *N*,*N*-dimethylaniline (93 μL, 0.74 mmol), and Et_3N (51 μL, 0.37 mmol) was stirred under an argon atmosphere at 0 °C. Trifluoroacetic anhydride (154 μL, 1.11 mmol) was slowly added dropwise. The reaction was stirred for a few minutes at room temperature, after which time a red-brown coloration was observed. Excess trifluoroacetic anhydride and trifluoroacetic acid were removed from the reaction mixture under vacuum. In a separate flask, a mixture of *N*-Me-imidazole (74 μL, 0.92 mmol) and Et_3N (156 μL, 1.11 mmol) in anhydrous MeCN (150 μL) was cooled to 0 °C, then added to the flask containing the mixed phosphoryl anhydride. The reaction was stirred for 10 min at 0 °C, after which time a bright yellow solution was obtained (Solution A). In the meantime, a solution containing **17** (tributylammonium salt, 71.6 mg, 0.153 mmol) and 4 Å molecular sieves in MeCN (800 μL) was stirred for 30 min at 0 °C (Solution B). The solution of UMP-*N*-methylimidazolium (Solution A) was then added dropwise to the solution containing **17** (Solution B). The resulting mixture was stirred at 0 °C under an argon atmosphere for 15 h and then quenched with cold aqueous ammonium formate (3 mL, 250 mM, pH 7). After filtration through a Celite pad, the amines were extracted from the aqueous phase with CH_2Cl_2 (3 mL). The organic phase was washed with cold aqueous ammonium formate (2 mL, 250 mM, pH 7), and the combined aqueous phases were pooled and freeze-dried. The residue was purified by size-exclusion chromatography (Sephadex G15) eluted with a 50 mM triethylammonium acetate buffer (pH 6.8). The ap-

propriate fractions were pooled and freeze-dried. Compound **1** was further purified by reverse-phase (C18) HPLC with 1% MeCN in 50 mM triethylammonium acetate buffer pH 6.8 as eluent and a flow rate of 1 mL min^{-1}. This protocol afforded compound **1** as a white solid (55 mg, triethylammonium salt) in 54% yield. ^{1}H NMR (400 MHz, D_2O): δ = 7.94 [d, J(5′′-6′′) = 8.1 Hz, 1 H, 6′′-H], 6.00 [d, J(1′-2′) = 4.1 Hz, 1 H, 1′-H], 5.99 [d, J(5′′-6′′) = 8.1 Hz, 1 H, 5′′-H], 4.40–4.37 (m, 2 H, 2′-H, 3′-H), 4.29 (m, 1 H, 4′-H), 4.26 [ABXX′, J(4′-5′a) = 2.6 Hz, J(5′a-5′b) = 11.7 Hz, J(5′a-P) = 4.6 Hz, 1 H, 5′-Ha], 4.19 [ABXX′, J(4′-5′b) = 2.8 Hz, J(5′a-5′b) = 11.7 Hz, J(5′b-P) = 5.7 Hz, 1 H, 5′-Hb], 3.93 [d, J(3-4) = 3.4 Hz, 1 H, 4-H], 3.82 [ABX, J(5-6a) = 8.9 Hz, J(6a-6b) = 12.7 Hz, 1 H, 6a-H], 3.67–3.63 (m, 2 H, 5-H et 6-Hb), 3.63 [dd, J(2-3) = 9.5 Hz, J(3-4) = 3.4 Hz, 1 H, 3-H], 3.57 [qd, J(1-2) = J(1-P) = J(1-1′b) = 9.5 Hz, J(1-1′a) = 2.5 Hz, 1 H, 1-H], 3.45 [t, J(1-2) = J(2-3) = 9.5 Hz, 1 H, 2-H], 3.21 (q, J = 7.3 Hz, CH_2, Et_3N), 2.34 [ABXX′, J(1-1′a) = 2.5 Hz, J(1′a-1′b) = 15.4 Hz, J(1′a-P) = 19.5 Hz, 1 H, CH_2P], 2.06 [ABXX′, J(1-1′b) = 9.5 Hz, J(1′a-1′b) = 15.4 Hz, J(1′b-P) = 22.0 Hz, 1 H, CH_2P], 1.23 (t, J = 7.3 Hz, CH_3, Et_3N) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 166.57 (C-4′′), 152.22 (C-2′′), 141.99 (C-6′′), 103.06 (C-5′′), 88.89 (C-1′), 83.58 [d, J(4′-P) = 9.1 Hz, C-4′], 79.12 (C-5), 76.47 [d, J(1-P) = 5.4 Hz, C-1], 74.21 (C-3), 74.15 (C-3′), 72.10 [d, J(2-P) = 13.9 Hz, C-2], 70.00 (C-2′), 69.84 (C-4), 65.09 [d, J(5′-P) = 3.4 Hz, C-5′], 62.14 (C-6), 47.08 (CH_2, Et_3N), 31.29 [d, J(CH_2-P) = 140.0 Hz, CH_2P], 8.62 (CH_3, Et_3N) ppm. ^{31}P NMR (101 MHz, D_2O): δ = 15.08 [d, J(Pα-Pβ) = 25.3 Hz, Pα], –11.35 [d, J(Pα-Pβ) = 25.3 Hz, Pβ] ppm. MS (ESI–): m/z (%) = 563 (100) [M – H]$^-$. HRMS: calcd. for $C_{16}H_{25}N_2O_{16}P_2$ 563.0679; found 563.0689.

UDP-[1(1′)*Z*]-*exo*-Glycal-D-Galactopyranose (7): The procedure for the preparation of **5** and **6** was followed. The reaction time between **19** (30 mg, 0.043 mmol) and activated UMP (0.056 mmol) was 15 h at room temperature. The final *exo*-glycal was first purified by size-exclusion chromatography [Sephadex G15, eluent: 50 mM triethylammonium acetate buffer (pH 6.8)] and then by reverse phase C18 HPLC (eluent: 1% MeCN in 50 mM triethylammonium acetate buffer pH 6.8; flow rate: 1 mL min^{-1}). This protocol afforded nucleotide-sugar **7** as a viscous solid (19 mg, triethylammonium salt) in 67% yield. ^{1}H, ^{13}C, ^{31}P NMR, and mass spectra were in agreement with those published.[20] ^{1}H NMR (400 MHz, D_2O): δ = 7.96 [d, J(5′′-6′′) = 8.1 Hz, 1 H, 6′′-H], 5.97 [d, J(1′-2′) = 4.0 Hz, 1 H, 1′-H], 5.96 [d, J(5′′-6′′) = 8.1 Hz, 1 H, 5′′-H], 5.52 [d, J(1*exo*-P) = 10.5 Hz, J(1*exo*-2) = 1.6 Hz, 1 H, 1-H*exo*], 4.36 (m, 2 H, 2′-H, 3′-H), 4.27–4.18 (m, 4 H, 4′-H, 5′-Ha, 5′-Hb, 2-H), 4.09 [d, J(3-4) = 3.1 Hz, 1 H, 4-H], 3.92 (m, 2 H, 5-H, 6-Ha), 3.76 [t, J(5-6b) = J(6a-6b) = 7.8 Hz, 1 H, 6-Hb], 3.71 [dd, J(2-3) = 10.1 Hz, J(3-4) = 3.1 Hz, 1 H, 3-H], 3.19 (q, J = 7.3 Hz, CH_2, Et_3N), 1.27 (t, J = 7.3 Hz, CH_3, Et_3N) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 166.62 (C-4′′), 165.63 [d, J(1-P) = 1.7 Hz, C-1], 152.20 (C-2′′), 142.05 (C-6′′), 103.01 (C-5′′), 100.32 [d, J(1*exo*-P) = 186.3 Hz, C-1*exo*], 88.74 (C-1′), 83.66 [d, J(4′-P) = 9.0 Hz, C-4′], 80.55 (C-5), 74.15 (C-3′), 73.35 (C-3), 69.98 (C-2′), 69.37 (C-4), 68.80 [d, J(2-P) = 12.3 Hz, C-2], 65.01 [d, J(5′-P) = 5.3 Hz, C-5′], 61.63 (C-6), 47.03 (CH_2, Et_3N), 8.59 (CH_3, Et_3N) ppm. ^{31}P NMR (101 MHz, D_2O): δ = 3.04 [d, J(Pα-Pβ) = 24.3 Hz, Pα], –11.56 [d, J(Pα-Pβ) = 24.3 Hz, Pβ] ppm. MS (FAB+): m/z (%) = 585 (50) [M + Na]$^+$, 601 (100) [M +K]$^+$, 607 (50) [M – H + 2Na]$^+$. HRMS: calcd. for $C_{16}H_{24}O_{16}N_2P_2Na$ 585.0499; found 585.0495.

2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-1-(dimethoxyphosphoryl)-methyl-α-D-galactopyranose (12a): To a cooled (–78 °C) solution of freshly distilled dimethyl methylphosphonate (291 μL, 2.67 mmol) in anhydrous THF (10 mL) was added butyllithium (1.0 mL, 2.49 mmol, 2.5 M in hexane). After 20 min, a solution of 2,3,4,6-tetra-*O*-*tert*-butyldimethylsilyl-D-galactono-1,5-lactone **10**[17] (1.13 g, 1.78 mmol) in anhydrous THF (6 mL) was added. The temperature was maintained at –78 °C for 30 min after which the mixture was diluted with 1 M phosphate buffer at pH 7 (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 9:1→8.5:1.5) to furnish pyranose **12a** (855 mg, 63% yield) and furanose **12b** (230 mg, 17% yield) as colorless oils. $[\alpha]_D^{22}$ = +4.3 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (br., 1 H, OH-1), 4.21 (s, 1 H, 4-H), 4.14 [dd, J(2-3) = 9.4 Hz, J(3-4) = 1.8 Hz, 1 H, 3-H], 3.96 [d, J(2-3) = 9.4 Hz, 1 H, 2-H], 3.87 [dd, J(5-6b) = 5.5 Hz, 1 H, 5-H], 3.79 [d, J(H-P) = 11.1 Hz, 3 H, O CH_3], 3.72 [d, J(H-P) = 10.9 Hz, 3 H, O CH_3], 3.65 [t, J(5-6a) = J(6a-6b) = 9.5 Hz, 1 H, 6-Ha], 3.54 [ABX, J(5-6b) = 5.5 Hz, J(6a-6b) = 9.5 Hz, 1 H, 6-Hb], 2.57 [ABX, J(1′a-1′b) = 14.9 Hz, J(1′a-P) = 18.0 Hz, 1 H, 1′-Ha], 1.95 [ABX, J(1′a-1′b) = 14.9 Hz, J(1′b-P) = 18.6 Hz, 1 H, 1′-Hb], 0.98 (s, 18 H, 2 Si-*t*Bu), 0.95 (s, 9 H, Si-*t*Bu), 0.90 (s, 9 H, Si-*t*Bu), 0.20 (s, 3 H, Si-Me), 0.19 (s, 3 H, Si-Me), 0.17 (s, 6 H, 2 Si-Me), 0.12 (s, 3 H, Si-Me), 0.09 (s, 3 H, Si-Me), 0.07 (s, 3 H, Si-Me), 0.06 (s, 3 H, Si-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.00 [d, J(1-P) = 8.7 Hz, C-1], 73.90 [d, J(2-P) = 13.4 Hz, C-2], 72.61 (C-5), 72.43 (C-4), 72.16 [d, J(3-P) = 4.4 Hz, C-3], 60.39 (C-6), 53.45 [d, J(C-P) = 5.4 Hz, OMe], 51.57 [d, J(C-P) = 6.1 Hz, OMe], 34.17 [d, J(1′-P) = 133.9 Hz, C-1′], 26.99 [Si-C(CH_3)$_3$], 26.33 [Si-C(CH_3)$_3$], 26.07 [Si-C(CH_3)$_3$], 25.75 [Si-C(CH_3)$_3$], 19.36 [Si-C(CH_3)$_3$], 18.65 [Si-C(CH_3)$_3$], 18.25 [Si-C(CH_3)$_3$], 18.00 [Si-C(CH_3)$_3$], –2.13 (Si-Me), –3.22 (Si-Me), –3.69 (Si-Me), –4.55 (Si-Me), –4.38 (Si-Me), –4.69 (Si-Me), –5.33 (Si-Me), –5.37 (Si-Me) ppm. ^{31}P NMR (101 MHz, $CDCl_3$): δ = 32.09 ppm. MS (DCI-NH_3): m/z (%) = 759 (45) [M + H]$^+$, 776 (30) [M + NH4]$^+$, 741 (100) [M – H_2O + H]$^+$. HRMS: calcd. for $C_{33}H_{79}O_9NSi_4P$ 776.4570; found 776.4560.

[1(1′)*Z*]-2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-1-deoxy-1-(dimethoxyphosphoryl)methylidene-D-galactopyranose (14): To a solution of compound **12a** (784 mg, 1.03 mmol) in anhydrous THF (10.5 mL) at 0 °C was successively added pyridine (836 μL, 10.3 mmol) and trifluoroacetic anhydride (719 μL, 5.17 mmol). The resulting solution was stirred at 0 °C for 1 h. A saturated aqueous solution of $NaHCO_3$ was then added and extracted with EtOAc (100 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel chromatography (cyclohexane/EtOAc, 8:2) afforded *exo*-glycal **14** (536 mg, 70% yield) as a colorless syrup. $[\alpha]_D^{22}$ = +54.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22 [dd, J(1′-2) = 0.8 Hz, J(1′-P) = 13.5 Hz, 1 H, 1′-H], 4.39 [d, J(2-3) = 8.2 Hz, 1 H, 2-H], 4.33 [t, J(3-4) = J(4-5) = 2.0 Hz, 1 H, 4-H], 3.89 [t, J(5-6a) = J(6a-6b) = 6.5 Hz, 1 H, 6-Ha], 3.85 [ddd, J(4-5) = 2.0 Hz, J(5-6a) = 6.5 Hz, J(5-6b) = 8.1 Hz, 1 H, 5-H], 3.79 [AX, J(5-6b) = 8.1 Hz, 1 H, 6-Hb], 3.75 [d, J(H-P) = 11.3 Hz, 3 H, OMe], 3.74 [d, J(H-P) = 11.3 Hz, 3 H, OMe], 3.71 [dd, J(2-3) = 8.2 Hz, J(3-4) = 2.0 Hz, 1 H, 3-H], 0.96 (s, 9 H, Si-*t*Bu), 0.95 (s, 9 H, Si-*t*Bu), 0.94 (s, 9 H, Si-*t*Bu), 0.91 (s, 9 H, Si-*t*Bu), 0.19 (s, 3 H, Si-Me), 0.15 (2 s, 6 H, 2 Si-Me), 0.14 (2 s, 6 H, 2 Si-Me), 0.11 (s, 3 H, Si-Me), 0.09 (s, 3 H, Si-Me), 0.08 (s, 3 H, Si-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.44 [d, J(1-P) = 1.3 Hz, C-1], 94.50 [d, J(1′-P) = 191.3 Hz, C-1′], 82.12 (C-5), 75.43 (C-3), 71.39 [d, J(2-P) = 13.4 Hz, C-2], 69.75 (C-4), 60.72 (C-6), 52.41 [d, J(C-P) = 5.4 Hz, OMe], 51.93 [d, J(C-P) = 5.7 Hz, OMe], 26.28 [Si-C(CH_3)$_3$], 26.07 [Si-C(CH_3)$_3$], 26.02 [Si-C(CH_3)$_3$], 25.76 [Si-C(CH_3)$_3$], 18.64 [Si-C(CH_3)$_3$], 18.47 [Si-C(CH_3)$_3$], 18.17 [Si-C(CH_3)$_3$], 18.06 [Si-C(CH_3)$_3$], –3.93 (Si-Me), –4.20 (Si-Me), –4.36 (Si-Me), –4.47 (Si-Me), –4.77 (Si-Me), –4.92 (Si-Me), –5.35 (Si-Me), –5.42 (Si-Me) ppm. ^{31}P NMR

(101 MHz, $CDCl_3$): δ = 21.11 ppm. MS (DCI-NH_3): *m*/*z* (%) = 741 (100) $[M + H]^+$. HRMS: calcd. for $C_{33}H_{74}O_8Si_4P$ 741.4198; found 741.4196.

[1(1′)*Z*]-2,3,4,6-Tetra-*O*-benzyl-1-deoxy-1-(dibenzyloxyphosphoryl)-methylidene-D-galactopyranose (15): To a cooled (–78 °C) solution of freshly distilled dibenzyl methylphosphonate (481 mg, 1.74 mmol) in anhydrous THF (8 mL) was added butyllithium (704 μL, 1.74 mmol, 2.5 M in hexanes). After 20 min, a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactono-1,4-lactone **11** (469 mg, 0.87 mmol) in anhydrous THF (1.2 mL) was added. The temperature was maintained at –78 °C for 10 min after which the mixture was allowed to reach –40 °C over a period of 1 h. The solution was then diluted with 1 M phosphate buffer at pH 7 (15 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated. To a solution of this crude residue containing intermediate **13** in anhydrous THF (10 mL) was added pyridine (703 μL, 8.7 mmol) and trifluoroacetic anhydride (604 μL, 4.35 mmol) at 0 °C. The resulting solution was allowed to reach room temperature over a period of 1 h. Solvents were then evaporated under vacuum, and the crude was diluted with CH_2Cl_2 (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel chromatography (cyclohexane/EtOAc, 1:1) afforded *exo*-glycal **15** (582 mg, 83% yield) as a colorless oil.$[\alpha]_D^{22}$ = +66.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 30 H, H arom.), 5.51 [dd, *J*(1′-2) = 1.5 Hz, *J*(1′-P) = 13.7 Hz, 1 H, 1′-H], 5.07 [AX, *J*(H-P) = 8.2 Hz, 4 H, 2CH_2Ph phosphonate], 5.01 [AB, *J*(H-H) = 11.2 Hz, 1 H, CH_2Ph], 4.84 [AB, *J*(H-H) = 11.2 Hz, 1 H, CH_2Ph], 4.80 [AB, *J*(H-H) = 11.9 Hz, 1 H, CH_2Ph], 4.76 [AB, *J*(H-H) = 11.9 Hz, 1 H, CH_2Ph], 4.75 [AB, *J*(H-H) = 11.2 Hz, 1 H, CH_2Ph], 4.65 [AB, *J*(H-H) = 11.2 Hz, 1 H, CH_2Ph], 4.51 [ddd, *J*(1′-2) = 1.5 Hz, *J*(2-3) = 9.7 Hz, *J*(2-P) = 3.5 Hz, 1 H, 2-H], 4.47 [AB, *J*(H-H) = 11.7 Hz, 1 H, CH_2Ph], 4.42 [AB, *J*(H-H) = 11.7 Hz, 1 H, CH_2Ph], 4.14 [d, *J*(4-5) = 0.8 Hz, 1 H, 4-H], 3.88 [td, *J*(4-5) = 1.2 Hz, *J*(5-6a,b) = 6.5 Hz, 1 H, 5-H], 3.75 [t, *J*(5-6a) = *J*(6a-6b) = 8.9 Hz, 1 H, 6-Ha], 3.72 [dd, *J*(2-3) = 9.7 Hz, *J*(3-4) = 2.7 Hz, 1 H, 3-H], 3.63 [ABX, *J*(5-6b) = 5.3 Hz, *J*(6a-6b) = 8.9 Hz, 1 H, 6-Hb] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.32 [d, *J*(1-P) = 1.4 Hz, C-1], 138.21, 137.85, 137.57, 137.44 (4 Cq arom.), 136.67 [d, *J*(C-P) = 7.2 Hz, Cq arom.], 136.64 [d, *J*(C-P) = 7.2 Hz, Cq arom.], 128.37–127.44 (30 CH arom.), 94.42 [d, *J*(1′-P) = 191.7 Hz, C-1′], 81.61 (C-3), 78.30 (C-5), 76.44 [d, *J*(2-P) = 12.8 Hz, C-2], 74.78 (*C*H_2Ph), 74.50 (*C*H_2Ph), 73.72 (C-4), 73.38 (*C*H_2Ph), 72.54 (*C*H_2Ph), 67.64 (C-6), 67.04 [d, *J*(C-P) = 5.6 Hz, *C*H_2Ph], 66.70 [d, *J*(C-P) = 5.7 Hz, *C*H_2Ph] ppm. ^{31}P NMR (101 MHz, $CDCl_3$): δ = 18.88 ppm. MS (DCI-NH_3): *m*/*z* (%) = 797 (70) $[M + H]^+$, 814 (100) $[M + NH_4]^+$. HRMS: calcd. for $C_{49}H_{50}O_8P$ 797.3243; found 797.3239.

Dimethyl *C*-(2,3,4,6-tetra-*O*-*tert*-butyldimethylsilyl-β-D-galactopyranosyl)methanephosphonate (16): Compound **14** (200 mg, 0.27 mmol) was dissolved in ethyl acetate (20 mL) and vigorously stirred at room temperature under a H_2 atmosphere (1.5 bar) in the presence of $Pd(OH)_2$ (92 mg, 20% Pd on carbon, wet). After 8 h, the catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 7:3→5:5) to give compound **16** (172 mg, 90% yield) as a white solid. $[\alpha]_D^{24}$ = –11.0 (*c* = 0.8, $CHCl_3$). M.p. 64–65 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 1 H, 4-H), 3.79 [t, *J*(1-2) = *J*(2-3) = 8.7 Hz, 1 H, 2-H], 3.74 [d, *J*(H-P) = 10.9 Hz, 3 H, OMe], 3.72 [d, *J*(H-P) = 11.0 Hz, 3 H, OMe], 3.66 [t, *J*(5-6a) = *J*(6a-6b) = 8.7 Hz, 1 H, 6-Ha], 3.62 [d, *J*(2-3) = 8.7 Hz, 1 H, 3-H], 3.62–3.55 (m, 2 H, 1-H, 6-Hb), 3.45 [dd, *J*(5-6a) = 8.7 Hz, *J*(5-6b) = 5.4 Hz, 1 H, 5-H], 2.39 [ABXX′, *J*(1-1′a) = 1.6 Hz, *J*(1′a-1′b) = 15.4 Hz, *J*(1′a-P) = 20.5 Hz, 1 H, 1′-Ha], 1.82 [ABXX′, *J*(1-1′b) = 11.1 Hz, *J*(1′a-1′b) = 15.4 Hz, *J*(1′b-P) = 29.7 Hz, 1 H, 1′-Hb], 0.96 (s, 9 H, Si-*t*Bu), 0.94 (s, 9 H, Si-*t*Bu), 0.93 (s, 9 H, Si-*t*Bu), 0.89 (s, 9 H, Si-*t*Bu), 0.18 (s, 3 H, Si-Me), 0.16 (s, 3 H, Si-Me), 0.15 (s, 3 H, Si-Me), 0.14 (s, 3 H, Si-Me), 0.11 (s, 3 H, Si-Me), 0.08 (s, 3 H, Si-Me), 0.05 (s, 3 H, Si-Me), 0.04 (s, 3 H, Si-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.95 (C-5), 77.58 [d, *J*(3-P) = 3.1 Hz, C-3], 76.55 [d, *J*(1-P) = 6.3 Hz, C-1], 72.30 [d, *J*(2-P) = 15.8 Hz, C-2], 71.89 (C-4), 60.61 (C-6), 52.70 [d, *J*(C-P) = 6.0 Hz, OMe], 51.80 [d, *J*(C-P) = 6.2 Hz, OMe], 28.85 [d, *J*(1′-P) = 141.1 Hz, C-1′], 26.92 (Si-*t*Bu), 26.30 (Si-*t*Bu), 26.02 (Si-*t*Bu), 25.75 (Si-*t*Bu), 19.30 (Si-*t*Bu), 18.60 (Si-*t*Bu), 18.12 (Si-*t*Bu), 18.01 (Si-*t*Bu), –2.26 (Si-Me), –3.31 (Si-Me), –3.77 (Si-Me), –4.13 (2 Si-Me), –4.20 (Si-Me), –4.63 (Si-Me), –5.40 (Si-Me) ppm. ^{31}P NMR (101 MHz, $CDCl_3$): δ = 33.00 ppm. MS (DCI-NH_3): *m*/*z* (%) = 743 (100) $[M + H]^+$, 760 (20) $[M + NH_4]^+$. HRMS: calcd. for $C_{33}H_{76}O_8Si_4P$ 743.4355; found 743.4357.

***C*-(1-Deoxy-β-D-galactopyranosyl)methyl Phosphonic Acid (17):** Compound **15** (240 mg, 0.30 mmol) was dissolved in a mixture of EtOAc/MeOH (1:1.8 mL) and vigorously stirred at room temperature under a H_2 atmosphere (1.5 bar) with palladium hydroxide (240 mg, 20% Pd on carbon, wet) and Bu_3N (108 μL, 0.60 mmol). After 24 h, the catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated. Compound **17** (189 mg, tributylammonium salt) was obtained quantitatively as a white hygroscopic solid. $[\alpha]_D^{22}$ = +7.8 (*c* = 0.53, H_2O, 0.85 equiv. Bu_3N). ^1H NMR (400 MHz, D_2O): δ = 3.92 [d, *J*(3-4) = 3.4 Hz, 1 H, 4-H], 3.74 [ABX, *J*(5-6a) = 3.6 Hz, *J*(6a-6b) = 10.2 Hz, 1 H, 6-Ha], 3.67–3.62 (m, 2 H, 5-H, 6-Hb), 3.60 [dd, *J*(2-3) = 9.4 Hz, *J*(3-4) = 3.4 Hz, 1 H, 3-H], 3.50 [qd, *J*(1-2) = *J*(1-P) = *J*(1-1′b) = 9.4 Hz, *J*(1-1′a) = 2.8 Hz, 1 H, 1-H], 3.40 [t, *J*(1-2) = *J*(2-3) = 9.4 Hz, 1 H, 2-H], 3.11 [m, CH_2 (d), Bu_3N], 2.17 [ABXX′, *J*(1-1′a) = 2.8 Hz, *J*(1′a-1′a) = 15.4 Hz, *J*(1′a-P) = 19.0 Hz, 1 H, 1′-Ha], 1.82 [ABXX′, *J*(1-1′b) = 9.4 Hz, *J*(1′a-1′a) = 15.4 Hz, *J*(1′b-P) = 21.9 Hz, 1 H, 1′-Hb], 1.65 [m, CH_2 (c), Bu_3N], 1.35 [sex, *J*(H-H) = 7.3 Hz, CH_2 (b), Bu_3N], 0.91 [t, *J*(H-H) = 7.3 Hz, CH_3 (a), Bu_3N] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 78.92 (C-5), 76.75 (C-1), 74.10 (C-3), 72.20 [d, *J*(2-P) = 10.9 Hz, C-2], 69.63 (C-4), 61.96 (C-6), 52.97 [CH_2 (d)], 31.68 [d, *J*(1′-P) = 131.4 Hz, C-1′], 25.51 [CH_2 (c)], 19.61 [CH_2 (b)], 13.13 [CH_3(a)] ppm. ^{31}P NMR (101 MHz, D_2O): δ = 21.77 ppm. MS (FAB–): *m*/*z* (%) = 257 (100) $[M - H]^-$. HRMS: calcd. for $C_7H_{14}O_8P$ 257.0426; found 257.0433.

[1(1′)*Z*]-1-Deoxy-1-(dibenzyloxyphosphoryl)methylidene-2,3,4,6-tetra-*O*-*tert*-butyldimethylsilyl-D-galactopyranose (18): To a cooled (–78 °C) solution of freshly distilled dibenzyl methylphosphonate (1.74 g, 63.10 mmol) in anhydrous THF (250 mL) was added butyllithium (25.3 mL, 63.10 mmol, 2.5 M in hexanes). After 20 min, was added a solution of 2,3,4,6-tetra-*O*-*tert*-butyldimethylsilyl-D-galactono-1,5-lactone **10**[17] (2 g, 3.15 mmol) in anhydrous THF (12 mL). After 30 min at –78 °C the mixture was diluted with 1 M phosphate buffer at pH 7 (100 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 9:1) to yield the lactol intermediate (1.58 g, 55% yield) as a colorless oil. To a solution of this lactol (702 mg, 0.77 mmol) in anhydrous THF (7.7 mL) at 0 °C was successively added pyridine (624 μL, 7.72 mmol) and trifluoroacetic anhydride (537 μL, 3.86 mmol). The resulting solution was stirred at 0 °C for 2 h, stopped by adding an aqueous saturated solution of $NaHCO_3$ and extracted with EtOAc (100 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel

chromatography (cyclohexane/EtOAc, 8.5:1.5) afforded **18** (626 mg, 91% yield) as a colorless oil. $[\alpha]_D^{22}$ = +63.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 10 H, H arom.), 5.40 [dd, *J*(1′-2) = 1.4 Hz, *J*(1′-P) = 13.7 Hz, 1 H, 1′-H], 5.10 [ABX, *J*(H-P) = 8.2 Hz, *J*(H-H) = 12.2 Hz, 1 H, CH_2Ph], 5.08 [AX, *J*(H-P) = 8.1 Hz, 2 H, CH_2Ph], 5.05 [ABX, *J*(H-P) = 7.9 Hz, *J*(H-H) = 12.2 Hz, 1 H, CH_2Ph], 4.49 [ddd, *J*(1′-2) = 1.4 Hz, *J*(2-3) = 9.1 Hz, *J*(2-P) = 2.7 Hz, 1 H, 2-H], 4.28 [d, *J*(3-4) = 1.8 Hz, 1 H, 4-H], 3.81 (m, 1 H, 6-Ha), 3.72 (m, 2 H, 5-H, 6-Hb), 3.69 [dd, *J*(2-3) = 9.1 Hz, *J*(3-4) = 1.8 Hz, 1 H, 3-H], 0.97 (s, 9 H, Si-*t*Bu), 0.96 (2 s, 18 H, 2 Si-*t*Bu), 0.89 (s, 9 H, Si-*t*Bu), 0.21 (s, 3 H, Si-Me), 0.17 (s, 3 H, Si-Me), 0.16 (s, 6 H, 2 Si-Me), 0.15 (s, 3 H, Si-Me), 0.09 (s, 3 H, Si-Me), 0.05 (s, 3 H, Si-Me), 0.02 (s, 3 H, Si-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.32 (C-1), 136.88 [d, *J*(C-P) = 6.6 Hz, Cq arom.], 136.85 [d, *J*(C-P) = 7.1 Hz, Cq arom.], 128.33–127.45 (10 CH arom.), 94.63 [d, *J*(1′-P) = 192.2 Hz, C-1′], 81.23 (C-5), 75.55 (C-3), 70.63 [d, *J*(2-P) = 13.0 Hz, C-2], 70.49 (C-4), 67.01 [d, *J*(C-P) = 5.2 Hz, CH_2Ph], 66.52 [d, *J*(C-P) = 5.3 Hz, CH_2Ph], 60.03 (C-6), 26.41 [Si-*C*$(CH_3)_3$], 26.16 [Si-*C*$(CH_3)_3$], 26.02 [Si-*C*$(CH_3)_3$], 25.72 [Si-*C*$(CH_3)_3$], 18.78 [Si-*C*$(CH_3)_3$], 18.51 [Si-*C*$(CH_3)_3$], 18.18 [Si-*C*$(CH_3)_3$], 17.96 [Si-*C*$(CH_3)_3$], –3.74 (Si-Me), –3.93 (Si-Me), –4.22 (Si-Me), –4.47 (Si-Me), –4.80 (Si-Me), –5.02 (Si-Me), –5.41 (Si-Me), –5.42 (Si-Me) ppm. ^{31}P NMR (101 MHz, $CDCl_3$): δ = 19.59 ppm. MS (DCI-NH_3): *m*/*z* (%) = 893 (100) $[M + H]^+$. HRMS: calcd. for $C_{45}H_{82}O_8Si_4P$ 893.4824; found 893.4820.

{[1(1′)*Z*]-1-Deoxy-1-methylidene-D-galactopyranosyl}phosphonic Acid (19): A solution of phosphonate **18** (578 mg, 0.65 mmol) dissolved in anhydrous CH_2Cl_2 (30 mL) with Et_3N (182 μL, 1.30 mmol) and 10% activated Pd/C as catalyst (65 mg) was vigorously stirred for 1.5 h at room temperature under a H_2 atmosphere (1 bar). The suspension was then filtered through a pad of Celite, and the filtrate was concentrated to give a viscous oil. Tetrabutylammonium fluoride (850 mg, 2.73 mmol) was added at 0 °C to a solution of this compound dissolved in distilled THF (30 mL). After 4 h at room temperature, the reaction mixture was concentrated under reduced pressure, dissolved in a minimum amount of water, filtered through paper, and the aqueous layer was freeze-dried. The residue was dissolved in a minimum amount of water and applied to Dowex 50WX8–200 (Na^+ form) column (eluent: H_2O). The appropriate fractions (TLC conditions EtOH/NH_4OH/H_2O, 5:3:1) were pooled and freeze-dried. The compound was then purified by size-exclusion chromatography (Sephadex G15, eluent: H_2O) and then applied to a Dowex 50WX8–200 (Bu_3NH+ form) column. The desired fractions were combined and freeze-dried to give compound **19** (317 mg, 78% yield, bistributylammonium salt) as a white hygroscopic solid. $[\alpha]_D^{21}$ = +36.4 (*c* = 0.52, H_2O, 2 equiv. Bu_3N). ^1H NMR (400 MHz, D_2O): δ = 5.41 [dd, *J*(1′-2) = 1.8 Hz, *J*(1′-P) = 10.8 Hz, 1 H, 1′-H], 4.21 [ddd, *J*(1′-P) = 1.8 Hz, *J*(2-3) = 10.1 Hz, *J*(2-P) = 3.3 Hz, 1 H, 2-H], 4.08 [d, *J*(3-4) = 3.2 Hz, 1 H, 4-H], 3.91 [ABX, *J*(5-6a) = 7.8 Hz, *J*(6a-6b) = 11.1 Hz, 1 H, 6a-H], 3.85 (dd, 1 H, 5-H), 3.75 [ABX, *J*(5-6b) = 2.9 Hz, *J*(6a-6b) = 11.1 Hz, 1 H, 6-Hb], 3.68 [dd, *J*(2-3) = 10.1 Hz, *J*(3-4) = 3.2 Hz, 1 H, 3-H], 3.12 [m, CH_2(d), Bu_3N], 1.66 [m, CH_2(c), Bu_3N], 1.36 [sex, *J*(H-H) = 7.4 Hz, CH_2(b), Bu_3N], 0.92 [t, *J*(H-H) = 7.4 Hz, CH_3(a), Bu_3N] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 164.44 (C-1), 101.54 [d, *J*(1′-P) = 176.6 Hz, C-1′], 80.66 (C-5), 73.55 (C-3), 69.33 (C-4), 68.77 [d, *J*(2-P) = 11.3 Hz, C-2], 61.63 (C-6), 53.01 [CH_2(d), Bu_3N], 25.55 [CH_2(c), Bu_3N], 19.63 [CH_2(b), Bu_3N], 13.12 [CH_3(a), Bu_3N] ppm. ^{31}P NMR (101 MHz, D_2O): δ = 10.91 ppm. MS (FAB–): *m*/*z* (%) = 255 (100) $[M - H]^-$. HRMS: calcd. for $C_7H_{12}O_8P$ 255.0270; found 255.0265.

3,4,5,7-Tetra-*O*-benzyl-D-galactohept-1-enitol (21): To a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactose **20**[29] (2 g, 3.71 mmol) in anhydrous THF (20 mL) at –30 °C under an argon atmosphere was added very slowly *n*-butyllithium (1.5 mL, 3.71 mmol, 2.5 M in hexane), and the solution was stirred for 30 min at 0 °C. In a separate flask, a solution of methylenetriphenylphosphosphorane in dry THF (40 mL) prepared at 0 °C from methylenetriphenylphosphonium bromide (2.65 g, 7.42 mmol) and a solution of *n*-butyllithium (2.8 mL, 7.0 mmol, 2.5 M in hexane) was added at 0 °C. The mixture was stirred 8 h at room temperature and then cooled to 0 °C. A saturated aqueous solution of NH_4Cl (50 mL) was added, and the mixture was warmed to room temperature and diluted with CH_2Cl_2. The organic layer was separated and washed with water (5 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel chromatography (cyclohexane/EtOAc, 9:1→8:2) to yield **21** (1.4 g, 72% yield) as a colorless oil. $[\alpha]_D^{22}$ = –7.6 (*c* = 1.01, $CHCl_3$); ref.[30] $[\alpha]_D^{18}$ = –10.8 (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.26 (m, 20 H, H arom.), 5.98 [ddd, *J*(2-3) = 7.9 Hz, *J*(2-1*trans*) = 17.7 Hz, *J*(2-1*cis*) = 10.3 Hz, 1 H, 2-H], 5.44 [dd, *J*(1*trans*-1*cis*) = 1.2 Hz, *J*(2-1*trans*) = 17.7 Hz, 1 H, 1-H*trans*], 5.40 [dd, *J*(1*trans*-1*cis*) = 1.2 Hz, *J*(2-1*cis*) = 17.7 Hz, 1 H, 1-H*cis*], 4.86 (s, 2 H, CH_2Ph), 4.75 [AB, *J*(H-H) = 11.8 Hz, 1 H, CH_2Ph], 4.58 [AB, *J*(H-H) = 12.0 Hz, 1 H, CH_2Ph], 4.52 [AB, *J*(H-H) = 11.5 Hz, 1 H, CH_2Ph], 4.50 [AB, *J*(H-H) = 12.0 Hz, 1 H, CH_2Ph], 4.46 [AB, *J*(H-H) = 11.5 Hz, 1 H, CH_2Ph], 4.45 [AB, *J*(H-H) = 11.8 Hz, 1 H, CH_2Ph], 4.23 (m, 1 H, 6-H), 4.18 [dd, *J*(2-3) = 7.9 Hz, *J*(3-4) = 3.9 Hz, 1 H, 3-H], 3.93–3.89 (m, 2 H, 4-H, 5-H), 3.63 [ABX, *J*(6-7a) = 6.2 Hz, *J*(7a-7b) = 9.4 Hz, 1 H, 7-Ha], 3.58 [ABX, *J*(6-7a) = 6.5 Hz, *J*(7a-7b) = 9.4 Hz, 1 H, 7-Hb], 3.14 [d, *J*(6-OH) = 5.0 Hz, 1 H, OH-6] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.17, 138.11, 138.07, 137.94 (4 Cq arom.), 135.66 (C-2), 128.25–127.49 (20 CH arom.), 119.10 (C-1), 82.00 (C-4), 80.65 (C-3), 76.49 (C-5), 75.14 (CH_2Ph), 73.05 (CH_2Ph), 73.01 (CH_2Ph), 71.11 (C-7), 70.21 (CH_2Ph), 69.58 (C-6) ppm. MS (DCI-NH_3): *m*/*z* (%) = 556 (100) $[M + NH_4]^+$.

***C*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)iodomethane (22):** To a solution of compound **21** (1.14 g, 2.12 mmol) in dry THF (24 mL) under an argon atmosphere was added mercuric diacetate (1.35 g, 4.24 mmol). The reaction mixture was stirred at room temperature for 20 h. Et_3N was then added (3 drops) followed by KCl (316 mg, 4.24 mmol) solubilized in a minimum amount of water. After 1 h at room temperature, the reaction mixture was diluted with diethyl ether (100 mL), and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layer was dried with $MgSO_4$ and the solvents evaporated. The crude mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2) to yield intermediate mercurio adduct (1.52 g, 96% yield) as a colorless oil. To a stirred solution of this mercurio derivative (1.35 g, 3.0 mmol) in anhydrous CH_2Cl2 (10 mL) was added I_2 in dry CH_2Cl_2 (15 mL, *C* = 0.5 M, 7.6 mmol) dropwise under an argon atmosphere. After 6 h at room temperature, the reaction mixture was quenched with an aqueous solution of $Na_2S_2O_3$, with saturated NaCl, and then with water. The combined organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 9:1) to yield **22** (1.16 g, 90% yield) as a pale yellow oil. $[\alpha]_D^{22}$ = +16.1 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 20 H, H arom.), 4.75 [AB, *J*(H-H) = 12.0 Hz, 1 H, CH_2Ph], 4.74 [AB, *J*(H-H) = 11.8 Hz, 1 H, CH_2Ph], 4.68 [AB, *J*(H-H) = 10.0 Hz, 1 H, CH_2Ph], 4.65 [AB, *J*(H-H) = 10.2 Hz, 1 H, CH_2Ph], 4.64 [AB, *J*(H-H) = 12.7 Hz, 1 H, CH_2Ph], 4.63 [AB, *J*(H-H) = 12.7 Hz, 1 H, CH_2Ph], 4.61 [AB, *J*(H-H) = 11.8 Hz, 1 H, CH_2Ph], 4.59 [AB, *J*(H-H) = 12.0 Hz, 1 H, CH_2Ph], 4.17 [ddd, *J*(1-2) = 3.6 Hz, *J*(1-1′a) = 6.3 Hz, *J*(1-1′b) = 8.6 Hz, 1 H, 1-H], 4.11 (m, 1 H, 5-H), 4.08 [d, *J*(3-4) = 2.7 Hz, 1 H, 4-H], 4.01 [dd, *J*(1-2)

= 3.6 Hz, *J*(2-3) = 6.6 Hz, 1 H, 2-H], 3.97 [ABX, *J*(5-6a) = 7.2 Hz, *J*(6a-6b) = 10.7 Hz, 1 H, 6-Ha], 3.79 [ABX, *J*(5-6b) = 4.4 Hz, *J*(6a-6b) = 10.7 Hz, 1 H, 6-Hb], 3.76 [dd, *J*(2-3) = 6.6 Hz, *J*(3-4) = 2.7 Hz, 1 H, 3-H], 3.46 [ABX, *J*(1-1′a) = 6.3 Hz, *J*(1′a-1′b) = 10.4 Hz, 1 H, 1′-Ha, CH_2-I], 3.36 [ABX, *J*(1-1′b) = 8.6 Hz, *J*(1′a-1′b) = 10.4 Hz, 1 H, 1′-Hb, CH_2-I] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.28, 138.24, 138.20, 137.80 (4 Cq arom.), 128.41–127.46 (20 CH arom.), 75.79 (C-3), 75.71 (C-2), 73.65 (C-4), 73.45 (CH_2Ph), 73.23 (CH_2Ph), 73.08 (C-5), 72.91 (CH_2Ph), 72.88 (CH_2Ph), 71.59 (C-1), 66.78 (C-6), 2.73 (C-1′, CH_2-I) ppm. MS (DCI-NH_3): *m*/*z* (%) = 665 (50) $[M + H]^+$, 682 (100) $[M + NH_4]^+$. HRMS: calcd. for $C_{35}H_{38}O_5I$ 665.1754; found 665.1759. $C_{35}H_{37}IO_5$ (664.59): calcd. C 63.26 H 5.61; found C 63.66 H 5.75.

Diethyl *C*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)methanephosphonate (23): A solution of iodide **22** (1 g, 1.5 mmol) in triethyl phosphite (10.3 mL, 60.2 mmol) was heated at reflux (160 °C) for 12 h under an argon atmosphere. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 5:5) to afford compound **23** (0.94 g, 93% yield) as a colorless oil. $[\alpha]_D^{22}$ = +32.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 20 H, H arom.), 4.78–4.52 (m, 8 H, 4CH_2Ph), 4.52 (m, 1 H, 1-H), 4.14 [qd, *J*(H-H) = 7.0 Hz, *J*(H-P) = 2.7 Hz, 2 H, O$CH_2$$CH_3$], 4.12 [qd, *J*(H-H) = 7.0 Hz, *J*(H-P) = 2.7 Hz, 2 H, O*C*$H_2$$CH_3$], 4.12 (m, 1 H, 5-H), 4.09 [dd, *J*(3-4) = 2.7 Hz, *J*(4-5) = 3.2 Hz, 1 H, 4-H], 3.96 [dd, *J*(1-2) = 4.0 Hz, *J*(2-3) = 7.1 Hz, 1 H, 2-H], 3.91 [ABX, *J*(5-6a) = 6.6 Hz, *J*(6a-6b) = 10.1 Hz, 1 H, 6-Ha], 3.79 [ABX, *J*(5-6b) = 5.2 Hz, *J*(6a-6b) = 10.1 Hz, 1 H, 6-Hb], 3.71 [dd, *J*(2-3) = 7.1 Hz, *J*(3-4) = 2.7 Hz, 1 H, 3-H], 2.22 [AXX′, *J*(1-1′a) = 3.1 Hz, *J*(1′a-P) = 18.8 Hz, 1 H, 1′-Ha], 2.20 [AX, *J*(1′b-P) = 18.2 Hz, 1 H, 1′-Hb], 1.34 [t, *J*(H-H) = 7.0 Hz, 3 H, OCH_2CH_3], 1.30 [t, *J*(H-H) = 7.0 Hz, 3 H, OCH_2CH_3] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.32, 138.24, 138.17, 137.96 (4 Cq arom.), 128.25–127.36 (20 CH arom.), 76.18 (C-2), 76.07 (C-3), 73.57 (C-4, C-5), 73.18 (*C*H_2Ph), 73.11 (*C*H_2Ph), 73.01 (*C*H_2Ph), 72.64 (*C*H_2Ph), 67.04 (C-5), 68.94 (C-6), 61.58 [d, *J*(C-P) = 6.4 Hz, O*C*$H_2$$CH_3$], 61.48 [d, *J*(C-P) = 6.3 Hz, O*C*$H_2$$CH_3$], 24.72 [d, *J*(1′-P) = 140.0 Hz, C-1′], 16.32 (OCH_2CH_3), 16.26 (OCH_2CH_3) ppm. ^{31}P NMR (101 MHz, $CDCl_3$): δ = 29.50 ppm. MS (DCI-NH_3): *m*/*z* (%) = 675 (100) $[M + H]^+$, 692 (20) $[M + NH_4]^+$. HRMS: calcd. for $C_{39}H_{48}O_8P$ 675.3087; found 675.3092.

***C*-(1-Deoxy-α-D-galactopyranosyl)methyl Phosphonic Acid (24):** To a solution of **23** (510 mg, 0.76 mmol) in anhydrous carbon tetrachloride (20 mL) was added trimethylsilyl iodide (2.2 mL, 15.2 mmol) at 0 °C. The solution was stirred for 4 h at 0 °C and then allowed to reach room temperature over a period of 1 h. Water (10 mL) was then added, and the solvents were evaporated. The residue was washed several times with ether, and the combined aqueous phases were pooled and freeze-dried. The resulting product was dissolved in a minimum amount of water and purified by chromatography on Sephadex G15 (eluent: H_2O). The appropriate fractions (detected by TLC: EtOH/NH_4OH/H_2O, 5:3:1) were pooled and freeze-dried to give compound **24** as a white hygroscopic solid (164 mg, 84% yield). $[\alpha]_D^{21}$ = +32.3 (*c* = 0.52, H_2O, 0.7 equiv. Bu_3N). ^{1}H NMR (400 MHz, D_2O): δ = 4.39 [tdd, *J*(1-2) = 1.0 Hz, *J*(1-P) = 14.7 Hz, *J*(1-1′a) = 10.7 Hz, *J*(1-1′b) = 4.0 Hz, 1 H, 1-H], 3.99 [dd, *J*(1-2) = 1.0 Hz, *J*(2-3) = 5.8 Hz, 1 H, 2-H], 3.97 [dd, *J*(3-4) = 3.3 Hz, *J*(4-5) = 1.6 Hz, 1 H, 4-H], 3.89 (ddd, 1 H, 5-H), 3.79–3.74 (m, 2 H, 3-H, 6-Ha), 3.66 [ABX, *J*(5-6b) = 4.2 Hz, *J*(6a-6b) = 11.4 Hz, 1 H, 6-Hb], 3.12 [m, CH_2(d), Bu_3N], 2.06 [ABXX′, *J*(1-1′a) = 10.7 Hz, *J*(1′a-P) = 26.5 Hz, *J*(1′a-1′b) = 15.6 Hz, 1 H, 1′-Ha], 1.93 [ABXX′, *J*(1-1′b) = 4.0 Hz, *J*(1′b-P) = 19.6 Hz, *J*(1′a-1′b) = 15.6 Hz, 1 H, 1′-Hb], 1.66 [m, CH_2(c), Bu_3N], 1.36 [sex, *J*(H-H) = 7.4 Hz, CH_2(b), Bu_3N], 0.92 [t, *J*(H-H) = 7.4 Hz, CH_3(a), Bu_3N] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 72.20 (C-5), 72.11 [d, *J*(1-P) = 2.4 Hz, C-1], 69.98 (C-3), 69.16 (C-4), 68.57 [d, *J*(2-P) = 10.9 Hz, C-2], 61.16 (C-6), 53.01 [CH_2(d)], 24.72 [d, *J*(1′-P) = 140.0 Hz, C-1′], 25.55 [CH_2(c)], 19.63 [CH_2(b)], 13.12 [CH_3(a)] ppm. ^{31}P NMR (101 MHz, D_2O): δ = 21.99 ppm. MS (FAB–): *m*/*z* (%) = 257 (100) $[M - H]^-$. HRMS: calcd. for $C_7H_{14}O_8P$ 257.0426; found 257.0423.

***C*-α-D-Galactopyranose-1,2-cyclophosphonate (25):** ^{1}H NMR (400 MHz, D_2O): δ = 4.83 [tdd, *J*(1-P) = 3.3 Hz, *J*(1-1′a) = 11.1 Hz, *J*(1-2) = *J*(1-1′b) = 7.8 Hz, 1 H, 1-H], 4.34 [dd, *J*(1-2) = 7.8 Hz, *J*(2-3) = 8.9 Hz, 1 H, 2-H], 3.96 [dd, *J*(3-4) = 3.1 Hz, *J*(4-5) = 1.3 Hz, 1 H, 4-H], 3.90 (m, 1 H, 5-H), 3.87 [dd, *J*(2-3) = 8.9 Hz, *J*(3-4) = 3.1 Hz, 1 H, 3-H], 3.76 [ABX, *J*(5-6a) = 7.3 Hz, *J*(6a-6b) = 11.7 Hz, 1 H, 6-Ha], 3.71 [ABX, *J*(5-6b) = 4.8 Hz, *J*(6a-6b) = 11.7 Hz, 1 H, 6-Hb], 2.07 [ABXX′, *J*(1-1′a) = 11.1 Hz, *J*(1′a-P) = 17.8 Hz, *J*(1′a-1′b) = 14.1 Hz, 1 H, 1′-Ha], 1.96 [ABXX′, *J*(1-1′b) = 7.8 Hz, *J*(1′b-P) = 11.2 Hz, *J*(1′a-1′b) = 14.1 Hz, 1 H, 1′-Hb] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 76.68 [d, *J*(2-P) = 2.0 Hz, C-2], 72.90 [d, *J*(1-P) = 13.6 Hz, C-1], 72.75 (C-5), 71.08 [d, *J*(3-P) = 1.4 Hz, C-3], 68.92 (C-4), 61.32 (C-6), 22.00 [d, *J*(1′-P) = 115.5 Hz, C-1′] ppm. ^{31}P NMR (101 MHz, D_2O): δ = 36.44 ppm. MS (FAB–): *m*/*z* (%) = 239 (100) $[M - H]^-$. HRMS: calcd. for $C_7H_{12}O_7P$ 239.0321; found 239.0331.

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