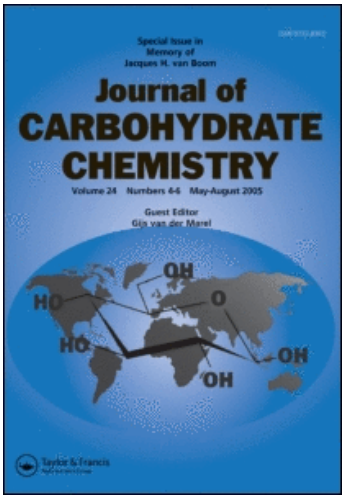

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Galactose-Phosphonates as Mimetics of the Sialyltransfer by Trypanosomal Sialidases

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Galactose-Phosphonates as Mimetics of the Sialyltransfer by Trypanosomal Sialidases

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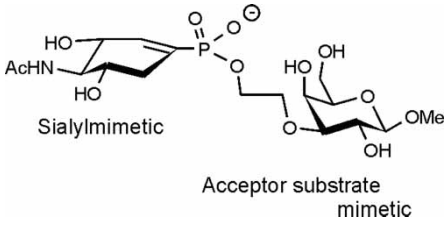
In an attempt to find competitive inhibitors of the trans-sialidase of the pathogen *Trypanosoma cruzi*, we have synthesized conjugates of carbocyclic sialylmimetics (e.g., cyclohexenephosphonates) and galactose derivatives. A trans-sialidase inhibition assay revealed an interesting preference for ethylidene-spacered conjugates involving the 3-position of the sugar.



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Keywords Sialidase, Trans-sialidase, Sialylmimetic, Carbasugars, *N*-acetylneuraminic acid, Phosphonates

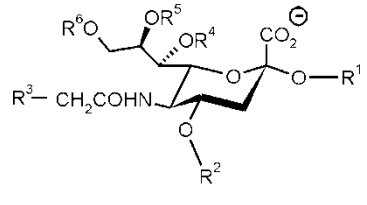
INTRODUCTION

The sialic acids, derivatives of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acids, are of great significance for recognition processes in higher organisms (Fig. 1).[1] The cell wall glycoconjugates of the latter contain sialic acids at exposed, often terminal, positions, linked to the respective glycan chain via a 2,3-, 2,6-, or a 2,8-glycosidic linkage. At this crucial position, sialic acids serve as receptors for endogenous or exogenous recognition events such as leucocyte targeting or microbial adhesion.[2,3] Often, microbial infection processes involve chemical modification, such as acetylation and deacetylation of the host cell sialic acids and, as a classical example, desialylation. In this case, the glycosidic bond between the sialic acid and the subterminal sugar is hydrolyzed through the action of microbial sialidases, a class of enzymes that as a result have been identified as possible targets to interfere with the respective infection processes.[4,5]

Synthetic organic chemists have therefore been seeking to mimic sialosides effectively while at the same time overcoming their metabolic instability, for instance, by replacing either the glycosidic or the ring oxygen by other atoms such as carbon or sulfur.[5,6] A prominent example for this strategy is the carbocyclic sialylmimetic, the influenza sialidase inhibitor anti-influenza drug oseltamivir.[7]

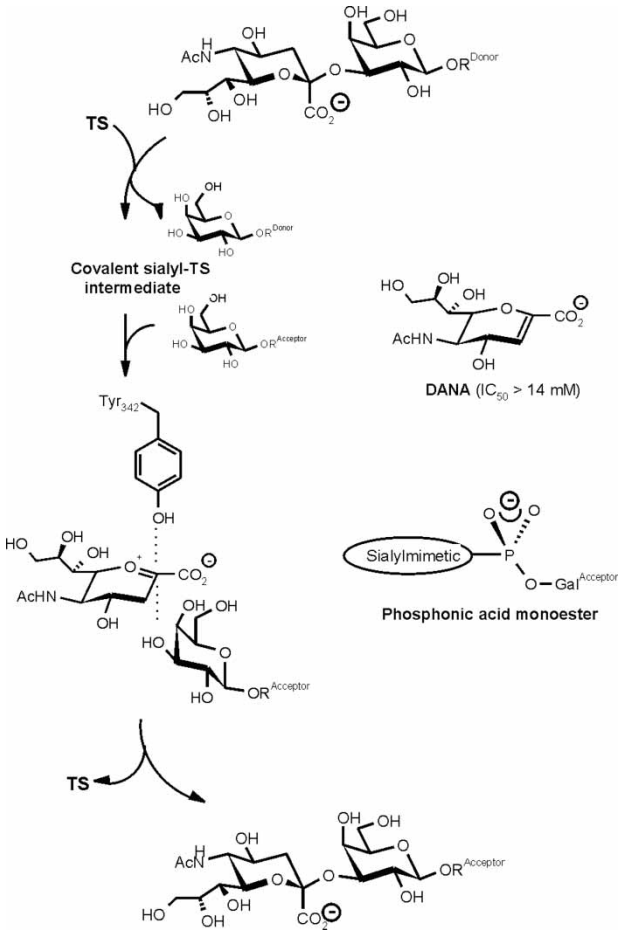
In many cases, however, mimetics of the sialic acid alone might not be sufficient to achieve effective inhibition. In Scheme 1, the example of the trans-sialidase of the parasite *Trypanosoma cruzi* is given to illustrate such a case.[8–11]

Although carrying glycoconjugates on its surface, the parasite *T. cruzi* cannot synthesize sialic acid de novo. Instead, it expresses a trans-sialidase (TcTS), which transfers a sialyl moiety to its own glycans rather than releasing it to the aqueous environment like "normal" sialidases. This sialyltransfer proceeds as a two-step reaction via a covalent enzyme-sialic acid intermediate



Sialic Acids

Figure 1: *N*-Acetylneuraminic acid (Neu5Ac, R^1-R^6 = H), the most prominent member of the family of sialic acids (R^1–R^6 = various modifications).



Scheme 1: Sialyltransfer by *T. cruzi* trans-sialidase.

involving Tyr 342 (Sch. 1). Detailed investigations have shown that, for efficient transfer to occur, the acceptor substrate must be bound simultaneously to the donor substrate. This is supported by the findings that in the absence of an acceptor substrate, sialoside hydrolysis is slow and the classical sialidase inhibitor and transition-state analog DANA is only a very weak inhibitor of TcTS.[12,13]

We have therefore concluded that carbocyclic sialylmimetics containing a phosphonate would allow attachment of an acceptor mimetic as a monoester while at the same time retaining a negative charge under physiologic conditions known to be important for recognition by all sialidases.[14]

Simple cyclohexenephosphonate monoesters developed by us such as **1** and **2** (Fig. 2) exhibited moderate, but encouraging, inhibition of TcTS, and we have recently succeeded in the synthesis of pseudo-sialosides involving sugars such as **3**.[15,16]

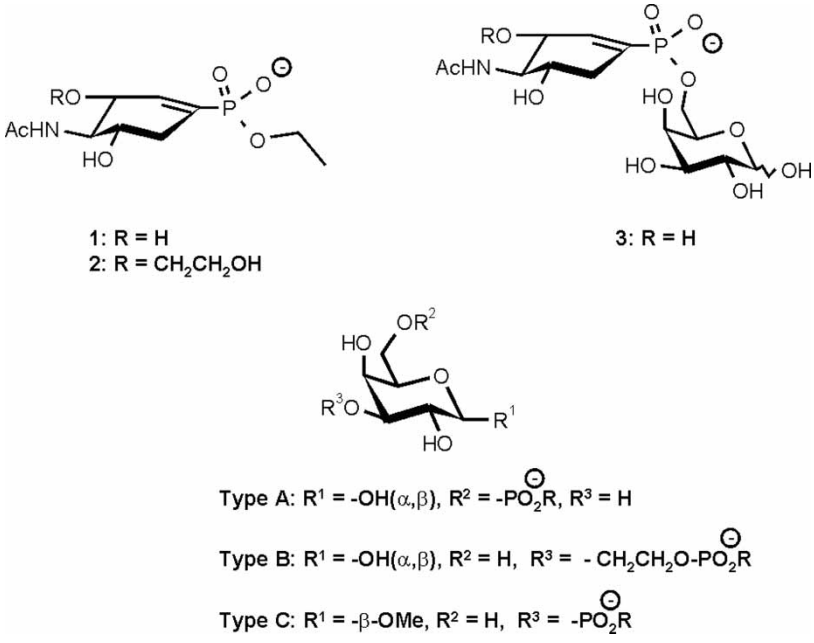


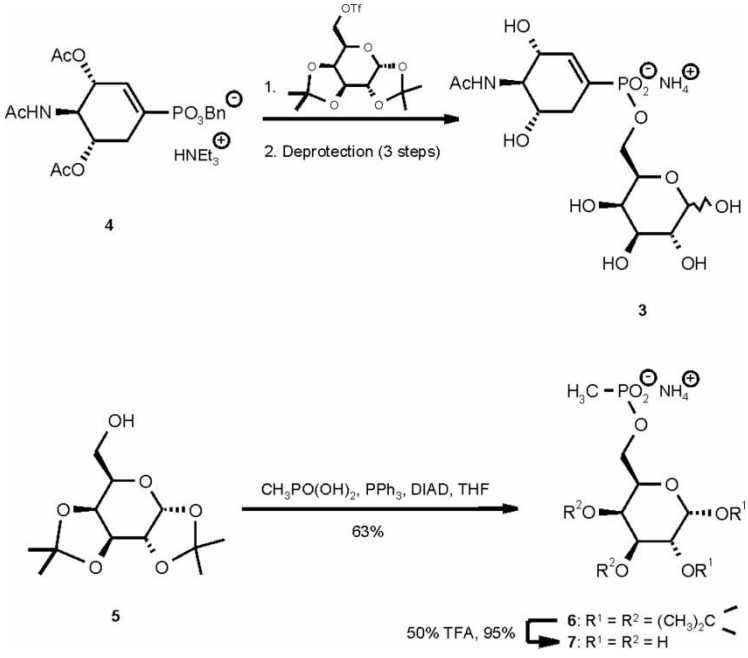
Figure 2: Previously investigated cyclohexenephosphonate monoesters and types of compounds included in this study.

Our phosphonates of type A (Fig. 2), including **3** itself, do not inhibit TcTS, so it became clear that a more systematic approach to simulate the TcTS sialyltransfer to the acceptor substrate is required. In this contribution, we report on methodologies to synthesize mimetics involving phosphonate monoesters and the 3-OH of galactose as the natural acceptor of the sialyl moiety when transferred by TcTS. Phosphonates of type B include a spacer between the galactose and the phosphonate, while the even more demanding phosphonates of type C are linked directly to the sugar hydroxyl group (Fig. 2).

RESULTS AND DISCUSSION

Type A

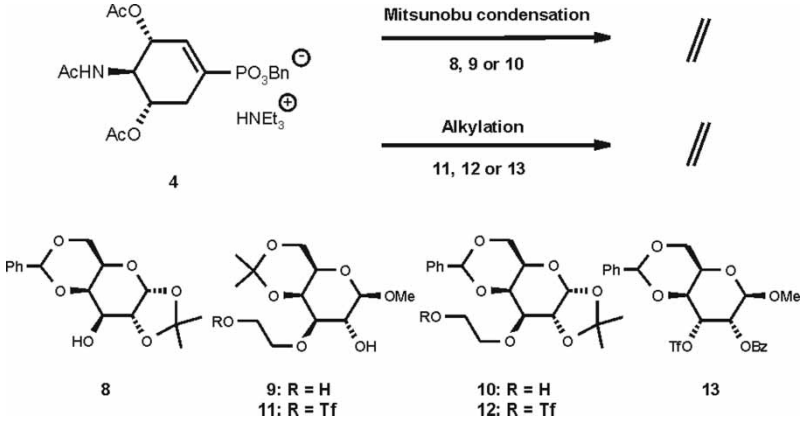
We have synthesized pseudo-sialoside **3** by alkylation of the protected L-xylo cyclohexenephosphonate monobenzyl ester **4** with the sugar triflate followed by deprotection (Sch. 2).[16] Esterification of methylphosphonic acid and galactose **5** under Mitsunobu conditions was straightforward, so we attempted to apply both strategies with suitable galactose derivatives, that is, Mitsunobu condensation of **4** with galactoses **8**, **9**, and **10** as well as alkylation of **3** with galactose triflates **11**, **12**, and **13** (Sch. 3). Much to our



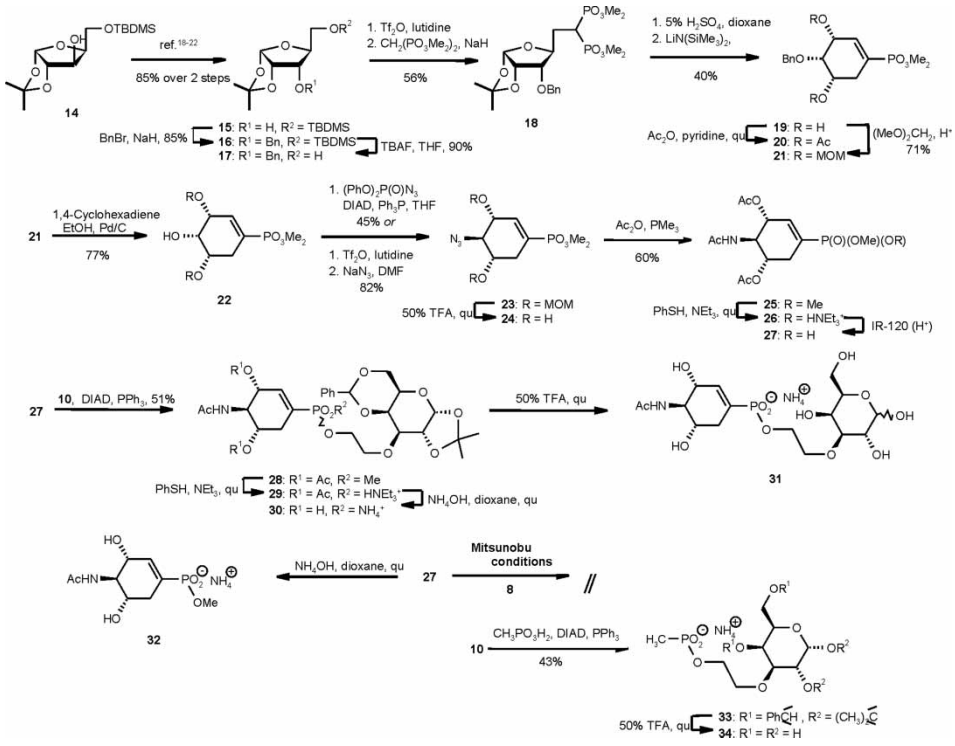
Scheme 2: Synthesis of type A conjugates.

disappointment, the monobenzyl esters seemed to not be suitable for a general approach with, for instance, triflate elimination being always faster than the corresponding alkylation reaction.[17]

Cyclohexenephosphonate-monomethylesters, however, did show a more promising behavior in Mitsunobu esterification.[16,17] We therefore applied



Scheme 3: Attempted synthesis of type B and C mimetics via the monobenzyl phosphonate.



Scheme 4: Synthesis of type B conjugates via the monomethyl phosphonate.

our established general methodology for the synthesis of *xylo*-configured cyclohexenephosphonates[18] to generate a suitable monomethylester (Sch. 4).

Type B

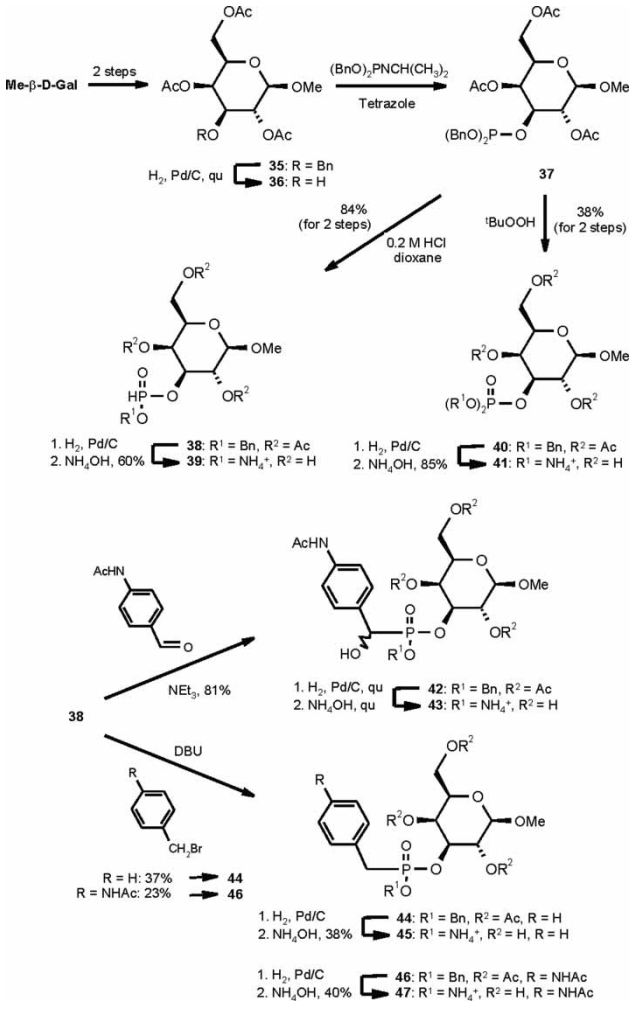
Starting from 5-silylated 1,2-*O*-isopropylidene-α-L-xylofuranose **14**, we inverted the absolute configuration at C-3 and benzylated ribose **15** to give **16** according to well-known procedures (Sch. 4).[18–22] In previous syntheses of ethyl[15,18,19] and benzyl esters,[16,17] we introduced azide as an acetamide precursor at this stage. In this case, however, the azide was not compatible with the conditions of methylenediphosphonate introduction. Desilylation of **16** to give 5-deprotected ribose **17** allowed activation as the triflate, which was readily substituted with the tetramethyl methylenediphosphonate anion to give 6-carbon sugar **18**. Removal of the isopropylidene group under acidic conditions liberated the aldehyde/hemiacetal, which was cyclized by treatment with strong base to furnish L-*xylo*-configured cyclohexenephosphonate **19** in 40% yield. Acetylation of **19** to give **20** was carried out under standard conditions to facilitate characterization, but unfortunately the acetyl groups tended to migrate under debenzylation conditions. To avoid this, we introduced

methoxymethyl groups at hydroxy groups 3 and 5 of **19** to give **21** and subsequently removed the benzyl group by transfer hydrogenation with 1,4-cyclohexadiene and palladium on charcoal, which gave **22** in good yield. Initially, we introduced the azide via a Mitsunobu procedure in only moderate yield of 45%, which we were able to significantly improve employing the two-step procedure via the triflate giving azide **23** in 82% yield. Treatment of 23 with 50% trifluoroacetic acid removed the methoxymethyl groups quantitatively to yield **24**, which was treated with trimethylphosphine and acetic anhydride to simultaneously achieve azide conversion into the acetamide and O-acetylation to give **25**. Quantitative cleavage of one methyl ester group with the thiophenol/triethylamine system resulted in the corresponding monoester salt **26**, which could be converted into the free acid **27** with acidic ion exchange resin.

Much to our delight, monomethylester **27** readily underwent Mitsunobu condensation with protected galactose-spacer conjugate **10** to give protected pseudo-sialoside **28** as a mixture of both diastereomeric diesters. Selective cleavage of the methyl ester with thiophenol/triethylamine resulted in quantitative formation of monoester **29**, which was readily deacetylated to give **30**. Finally, removal of the isopropylidene group resulted in type B target molecule **31**, which had previously been inaccessible employing benzyl esters. For comparison, we synthesized both the monomethyl ester **32** by saponification of diester **27** and the methylphosphonic acid conjugate **33** by Mitsunobu condensation with galactose **10**. The latter was finally deacetylated to give **34**, the second target molecule of type B (Sch. 4).

Type C

As mentioned above, esterification or alkylation of our modified phosphonates, to obtain the corresponding 3-phosphono-galactoses of type C, failed.[17] Consequently, we decided to introduce the phosphonate via the phosphite triester followed by partial hydrolysis and alkylation. To achieve this, a protected methyl β-galactopyranoside with a free hydroxyl group in the 3-position was required. We chose the stannylidene acetal-supported selective alkylation of the 3-OH group of methyl β-galactopyranoside with benzyl bromide followed by acetylation to give **35**, which was readily debenzylated to afford 3-OH free galactose **36** (Sch. 5). The labile triester **37** was not isolated but directly subjected to mild acid hydrolysis with silica gel to give phosphonate **38**, ready for alkylation. To investigate its behavior toward TcTS, we deprotected **38** to obtain type C target **39**. With the phosphonic acid triester at hand, synthesis of the corresponding phosphate was straightforward enough to include it in our study. Peroxide treatment of **37** gave the stable trialkyl phosphate **40**, which could be deprotected in two steps to give the 3-phosphate galactopyranoside **41** in high yield.



Scheme 5: Synthesis of type C conjugates via alkylation of H-phosphonates.

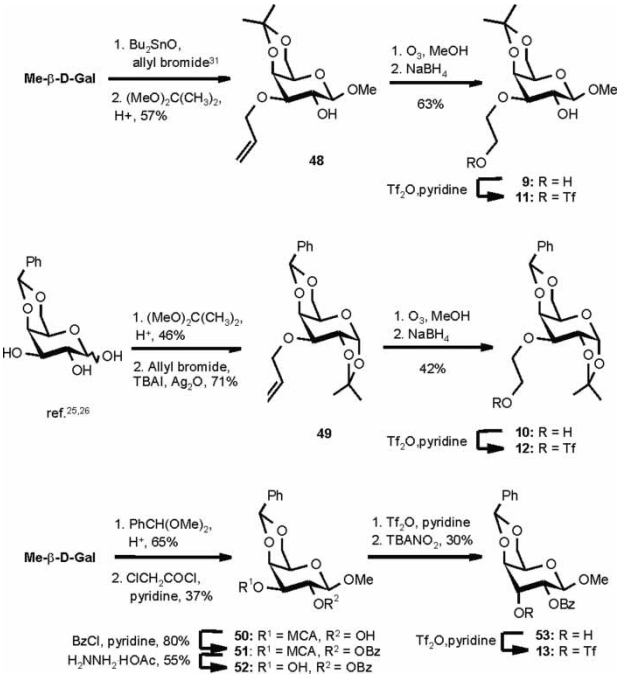
Phosphonic acid **38** proved to be the ideal starting material for the introduction of alkyl and aryl residues by various methods, two of which we included in this investigation so far. Firstly, aldehydes such as acetamido benzaldehyde as simple sialylmimetics react readily with phosphonates under basic conditions to form the respective substituted hydroxymethyl phosphonates, here **42**. This methodology has been extensively applied to the synthesis of sialyltransferase inhibitors by others.[23] We did not separate the resulting diasteromers, but it is clear that the new hydroxylated stereocenter opens the way to a wealth of straightforward further modifications. We deprotected **42** to give the next type C molecule as the diasteromeric mixture **43**, which was tested as such.

Alkylation of the phosphonate with alkyl halides does not come with stereocenter formation. To validate this approach, we alkylated phosphonate **38** with benzyl bromide and *p*-acetamido benzyl bromide to give **44** and **46**, respectively. Both molecules were deprotected to the type C targets under standard debenzylation and deacetylation conditions to yield **45** and **47** (Sch. 5).

This approach via 3-phosphono galactoses provides many options for library synthesis of potential TcTS inhibitors, some of which are currently being developed in our laboratory.

Synthesis of Galactose Derivatives

Generally, standard protecting group methodologies[24] were applied to the synthesis of galactose derivatives **9–13**, which were used in successful and attempted syntheses of pseudo-disaccharides (Sch. 6). In brief, methyl β-D-galactopyranoside was selectively allylated at the 3-hydroxy group via the stannylidene acetal and then isopropylidenated to give **48**. Conversion of the allyl group into the hydroxyethyl spacer via ozonolysis and reduction furnished the protected acceptor **9**, which, for alkylation attempts, could be activated as the triflate (**11**). To obtain a fully protected galactose-spacer conjugate, benzylidene galactose[25,26] was isopropylidenated and then allylated to give **49**.



Scheme 6: Synthesis of galactose derivatives.

Conversion of the allyl group was carried out as described above to form **10**, which, if required, was triflated (**12**).

The galactose derivatives lacking a spacer were synthesized from methyl β-D-galactopyranoside by first introducing the 4,6-benzylidene acetal and selectively acylating the 3-position with monochloroacetyl chloride to give **50**. Benzoylation to yield **51**, followed by deacetylation with hydrazinium acetate, furnished 3-OH-unprotected galactose **52** for use in Mitsunobu esterifications. Inversion of configuration for alkylation was achieved by activation as the triflate followed by substitution with nitrite and hydrolysis of the nitrous acid ester to give gulose **53**, the triflate of which (**13**) was readily formed with triflic anhydride and pyridine (Sch. 6).

Trans-sialidase Assay

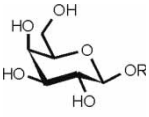
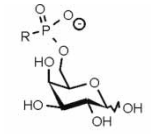
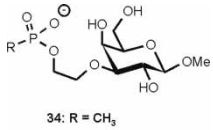
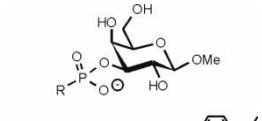
To assess the inhibitory activity of our compounds against TcTS, we used a trans-sialidase assay introduced by Schrader et al.[27] In brief, the reaction to be inhibited is the transfer of a sialic acid by TcTS from the commercially available donor 3′-sialyllactose to the 3-OH of the acceptor 4-methylumbelliferyl β-D-galactopyranoside. Sialylated derivatives are separated from uncharged acceptor by serial ion exchange chromatography and the product formed is quantified by total hydrolysis and measurement of 4-methylumbelliferone-fluorescence under basic conditions.

Methyl β-D-galactopyranoside, as an example for the minimal structural requirements an acceptor has to fulfill, and lactitol, as an example for a rather active substrate-analogous inhibitor,[28] were included in the assay. While results with the former have to be viewed with caution as sialylated methyl β-D-galactopyranoside can compete with the donor in the assay, sialylated lactitol, in contrast, has been shown to not act as a donor.[28]

The results obtained are summarized in Table 1. The weak binding of type A compound **7** did not come as a surprise as we had previously found pseudosialoside **3** to not inhibit,[16] thus indicating that a negatively charged group linked to the 6-OH of a galactose does not lead to a substantial increase in binding (e.g., by electrostatic interaction with the enzyme's arginine triade).

Linking a phosphonate to the 3-position of methyl β-D-galactopyranosidevia an ethylene spacer, however, enhances binding compared to the reference methyl galactoside. The effect obtained with type B inhibitors **31** and **34**, respectively, is not as pronounced as we had expected, but it is strong enough to shed light on how to proceed. We had previously published weak inhibition by L-*xylo* cyclohexenephosphonate monoethylesters[15] (i.e., **31** without the galactose), indicating also a positive effect of an ethyl group. These data taken together enable us now to establish, albeit still with caution, a first structure activity relationship based on an ethylidene linkage between a phosphonate-containing sialylmimetic and a methyl β-D-galactopyranoside.

Table 1: Inhibitory activity of the sialoside mimetics synthesized toward *T. cruzi* trans-sialidase (IC_{50} values, rounded to $\pm$ 0.5 mM based on three experiments).

β-Galactosides	Type A	Type B	Type C
 A: R = CH_3 B: R = 3-glucitol	 7: R = CH_3 3: R =	 34: R = CH_3 31: R =	 39: R = H 41: R = OH 43: R = 47: R = 45: R =

A: 5 mM; 7: >8 mM; 34: ~3 mM; 39: >8 mM; 47: >8 mM; B: 0.57 mM[23]; 3: n.i.; 31: ~1.5 mM; 41: >8 mM; 45: ~6 mM; 43: ~8 mM.

With regard to type C compounds, the introduction of a phosphonate, selected alkylphosphonates, and a phosphate at the 3-position of methyl β-D-galactopyranoside without linker did not lead to any improvement, rather the contrary, compared to galactose alone. It is, however, too early to abandon this type of structure as the "sialylmimetics" we used to establish the alkylation chemistry were rather basic. More examples of these readily accessible structures are definitely required.

CONCLUSIONS

As part of our program to find novel inhibitors of sialoside-processing enzymes, in particular trans-sialidases, we have established methodologies to synthesize pseudo-sialosides consisting of carbocyclic sialylmimetics containing a phosphonate linking them to galactoses. We have extended our established synthetic approach toward *xylo*-configured cyclohexenephosphonates to the L-*xylo* cyclohexenephosphonate monomethylester, which allows galactose attachment via Mitsunobu condensation and alkylation. In order to gain access to the otherwise elusive phosphonate linkage to the 3-position of galactose, we have investigated alkylation of the previously introduced phosphonate with simple sialylmimetics. This gives us straightforward access to libraries of potential inhibitors and is the subject of ongoing projects in our laboratory.

A number of pseudo-sialosides containing phosphonate-galactose linkages via the 6-position (type A), the spacered 3-position (type B), and the 3-position (type C) have been deprotected and subjected to a trans-sialidase inhibition assay. While type A and type C compounds displayed negligible inhibition, we found an interesting positive, albeit still moderate, effect of type B compounds with ethylidene spacer. This corresponds well with our previous data of cyclohexenephosphonate monoethylesters and indicates that sialylmimetic-ethylene spacer-galactose conjugates might be a common

denominator for more potent bisubstrate-type inhibitors of TcTS. Although these compounds still track lactitol or benzyl β-N-acetyllactosamine[29] regarding potency, they offer a wealth of possible modifications, some of which are being pursued by us.

EXPERIMENTAL

Reaction solvents were purchased anhydrous and used as received. Solvents for chromatography were distilled before use. Reactions were monitored by TLC using precoated silica gel 60 F_{254} plates. Compounds were detected by UV absorption and/or by staining with a molybdenum phosphate reagent (20 g ammonium molybdate and 0.4 g cerium(IV) sulfate in 400 mL of 10% aq. sulfuric acid) and subsequent heating at 120°C for 5 min. Silica gel 60 M (particle size 40–63 μm) from Macherey-Nagel, Düren, Germany, and 60 A Davisil (particle size 35–70 μm) from Fisher Scientific, UK, was used for flash chromatography. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Bruker DRX 600 spectrometer (at 600 MHz, 150.9 MHz, and 242.9 MHz, respectively) and a Bruker DPX-300 (at 300 MHz, 75.4 MHz, and 121.4 MHz, respectively). Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra were referenced to the residual proton resonance of the respective deuterated solvent, $CDCl_3$ (7.24 ppm), D_2O (4.63 ppm), and D_2O in CD_3OD (4.88 ppm). For ^{31}P NMR spectra H_3PO_4 was used as external standard (0 ppm). In some cases, ^{13}C chemical shifts were deduced from heteronuclear multiple quantum correlation (HMQC) spectra. In pseudo-disaccharidic systems, the cyclohexene ring is indicated by the suffix “a”, the sugar by the suffix “b”. Diastereomeric mixtures of mixed diesters are indicated by the suffix “h”(higher moving) and “l”(lower moving), but no attempts of separation were made. HR-ESI MS spectra were recorded on a Bruker Daltonics Apex III in positive mode with $MeOH/H_2O$ as solvent. MALDI MS spectra were recorded on a Bruker Biflex III spectrometer in positive, linear mode with a delayed extraction MALDI source or on a Kratos Analytic Kompact Maldi 2 using 3,5-dihydroxybenzoic acid (DHB), α-hydroxy-α-cyano-cinnamic acid (HCCA), or azidothymidine (ATT) as matrix.

Silica-based MPLC chromatography was carried out on the Büchi Sepacore system equipped with glass columns packed with LiChroprep Si 60 (15–25 μm) from Merck, Darmstadt, Germany.

Gel permeation chromatography was carried out in the 1- to 5-mg scale on a XK 16/70 column (bed volume 130 mL), from Amersham packed with Bio-Gel P2 Fine (particle size 45–90 μm) and 0.1 M NH_4HCO_3 as buffer. Detection was achieved with a differential refractometer from Knauer, Berlin, Germany.

The synthesis of compounds **1**–**4** has been described by us previously,[15,16,18,19] and compound **5** was synthesized according to the literature.[30]

Fine chemicals were purchased from Aldrich-, Sigma-, or Acros-Chemicals and were of the highest purity available.

Abbreviations: THF (tetrahydrofurane), Ph_3P (triphenyl phosphine), DIAD (diisopropyl azodicarboxylate), EtOAc (ethyl acetate), Tol (toluene), CHCA (α-cyano-α-hydroxycinnamic acid), TFA (trifluoroacetic acid), DCM (dichloromethane), TBAF (tetrabutylammonium fluoride), DHB (dihydroxy benzotriazole), TBAI (tetrabutylammonium iodide), DBU (diazabicycloundec-7-ene), BnBr (benzyl bromide).

Triethylammonium *O*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) methylphosphonate (6)

Methanephosphonic acid (21 mg, 0.21 mmol) was dissolved in 2 mL of dry THF, and galactose **5** (100 mg, 0.38 mmol) and Ph_3P (110 mg, 0.38 mmol) were added under argon. DIAD (75 μL, 0.38 mmol) was added and the mixture was stirred at 60°C for 2 days. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc:Tol 10:1 → EtOAc:MeOH 4:1, 1% NEt_3) to afford **6** (45 mg, 52%) as a colorless triethylammonium salt. TLC (EtOAc:MeOH 5:1): $R_f = 0.07$; $[\alpha]_D^{20} = -40.2$ (c = 1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 5.48 (d, 1H, $J_{1-2} = 4.8$ Hz, H-1), 4.63 (dd, 1H, $J_{2-3} = 2.4$, $J_{3-4} = 7.8$ Hz, H-3), 4.36 (dd, 1H, H-2), 4.30 (dd, 1H, $J_{4-5} = 1.2$ Hz, H-4), 4.04–3.91 (m, 3H, H-5, H-6, H-6′), 3.18 (q, 6H, $N(CH_2CH_3)_3$), 1.50 (s, 6H, $C(CH_3)_2$), 1.39 (s, 6H, $C(CH_3)_2$), 1.36–1.29 (m, 15H, P-CH_3 and $N(CH_2CH_3)_3$); ^{13}C NMR (151 MHz, CD_3OD) δ 109.8 ($C(CH_3)_2$), 97.9 (C-1), 72.2 (C-3), 72.1 (C-4), 71.9 (C-2), 68.8 (C-5), 64.7 (C-6), 47.5 ($N(CH_2CH_3)_3$), 26.5, 26.4 (each CH_3 of $C(CH_3)_2$), 12.5 ($N(CH_2CH_3)_3$), 11.6 (PCH_3); ^{31}P NMR (162 MHz, CD_3OD) δ 27.8 (s, PCH_3). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{13}H_{23}O_8P + Na)^+$ 361.1. Found 360.4.

Ammonium *O*-(α,β-D-galactopyranoside-6-yl-) methylphosphonate (7)

7 (10 mg, 0.023 mmol) was dissolved in 2 mL of 50% TFA and stirred at rt overnight. The mixture was lyophilized, dissolved in 1M $NH_4HCO_3^-$ buffer, and lyophilized again to afford **7** (6 mg, 95%) as a white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 5.15 (d, 1H, $J_{1-2} = 4.2$ Hz, H-1α), 4.49 (d, 2H, $J_{1-2} = 8.4$ Hz, H-1β), 4.02–3.70 (m, 14H, H-4, H-5, H-6, H-6′ both anomers and H-2α, H-3α), 3.55 (dd, 2H, $J_{2-3} = 3.6$, $J_{3-4} = 9.0$ Hz, H-3β), 3.38 (dd, 2H, H-2β),

1.21 (d, 6H, PCH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 96.4 (C-1 β), 92.3 (C-1α), 72.5 (C-3), 71.7 (C-2), 10.6 (PCH_3) ppm, C4-C6 not resolved; ^{31}P NMR (162 MHz, CD_3OD) δ 28.6 (s, PCH_3). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_7H_{15}O_8P + Na)^+$ 281.1. Found 281.1.

4,6-*O*-Benzylidene-1,2-*O*-isopropylidene-α-D-galactopyranoside (8)

Benzylidene galactose[21] (6.0 g, 0.022 mmol) was suspended in dry acetone (300 mL), and dimethoxypropane (3.57 mL, 0.0290 mmol) and *p*-TsOH (100 mg) were added and the reaction was stirred at rt overnight. The reaction mixture was neutralized with saturated $NaHCO_3^-$ solution, washed with DCM, and dried over $MgSO_4$. Flash chromatography (EtOAc:Tol 1:2) afforded **8** (3.1 g, 46%) as a colorless syrup. TLC (EtOAc:Tol 1:2): $R_f = 0.4$; $[\alpha]_D^{20} = -38.4$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52–7.36 (m, 5H, C_6H_5), 5.73 (s, 1H, C*H*Ph), 5.67 (d, 1H, $J_{1-2} = 5.4$ Hz, H-1), 4.65 (dd, 1H, $J_{2-3} = 2.4$, $J_{3-4} = 8.4$ Hz, H-3), 4.45 (dd, 1H, H-2), 4.33 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4), 3.99 (ddd, 1H, $J_{5-6'} = 4.8$, $J_{5-6} = 6.6$ Hz, H-5), 3.89 (dd, 1H, $J_{6-6'} = 11.4$ Hz, H-6), 3.78 (dd, 1H, H-6′),1.56, 1.34 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.8 (*C*-Ph), 129.3–127.4 (C_6H_5), 105.1 (*C*(CH_3)$_2$), 104.1 (*C*HPh), 96.6 (C-1), 72.1 (C-3), 71.9 (C-4), 70.2 (C-2), 68.2 (C-5), 62.2 (C-6), 26.1, 25.3 (C(*C*H_3)$_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{16}H_{20}O_6 + Na)^+$ 331.1. Found 331.1. Calcd for $(C_{16}H_{20}O_6 + K)^+$ 347.1. Found 347.1.

Methyl 3-*O*-hydroxyethyl-4,6-*O*-isopropylidene-β-D-galactopyranoside (9)

48 (300 mg, 1.1 mmol) was dissolved in MeOH (10 mL) and one spatula of solid $NaHCO_3$ was added as buffer. The mixture was cooled to −78°C and a constant stream of ozone was discharged until the solution turned blue. The reaction was allowed to warm up to rt and $NaBH_4$ (248 mg, 6.5 mmol) was added. After 2 h the reaction was complete, the solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc:MeOH 5:1) to afford **9** (240 mg, 78%) as a colorless syrup. TLC (EtOAc:MeOH 5:1): $R_f = 0.27$; $[\alpha]_D^{20} = +25.8$ (c = 1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 4.38 (pd, 1H, $J_{3-4} = 3.0$ Hz, H-4), 4.18 (d, 1H, $J_{1-2} = 7.2$ Hz, H-1), 4.14 (dd, 1H, $J_{5-6} = 1.8$, $J_{6-6'} = 12.6$ Hz, H-6), 3.83 (dd, 1H, H6′), 3.72–3.65 (m, 4H, HOCH_2CH_2O), 3.62 (dd, 1H, $J_{2-3} = 9.6$ Hz, H-2), 3.51 (s, 3H, OCH_3), 3.38 (m, 2H, H-3, H-5), 1.46, 1.36 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (151 MHz, CD_3OD) δ 105.3 (C-1), 100.3 (*C*(CH_3)$_2$), 81.8 (C-3), 71.6 (C-a), 70.9 (C-2), 67.7 (C-5), 66.7 (C-4), 63.9

(C-6), 62.4 (C-b), 57.3 (OCH_3), 29.5 ($C(CH_3)_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{12}H_{22}O_7 + Na)^+$ 301.1. Found 301.3. Calcd for $(C_{12}H_{22}O_7 + K)^+$ 317.1. Found 317.3.

4,6-*O*-Benzylidene-3-*O*-hydroxyethyl-1,2-*O*-isopropylidene-α-D-galactopyranoside (10)

49 (200 mg, 0.570 mmol) was dissolved in MeOH (12 mL) and the reaction was carried out as described for **9**. Following addition of $NaBH_4$ (88 mg, 2.9 mmol), the reaction was stirred until TLC indicated complete reduction. The mixture was evaporated in vacuo and the crude product was purified by flash chromatography (EtOAc:Tol 1:2 → 10:1) to yield **10** (110 mg, 55%) as a colorless syrup. TLC (EtOAc:Tol 10:1): $R_f = 0.57$; $[\alpha]_D^{20} = -42.1$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52–7.25 (m, 5H, C_6H_5), 5.75 (s, 1H, *H*Ph), 5.64 (d, 1H, $J_{1-2} = 4.8$ Hz, H-1), 4.66 (dd, 1H, $J_{2-3} = 2.4$, $J_{3-4} = 8.4$ Hz, H-3), 4.45 (dd, 1H, H-2), 4.35 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4), 4.10 (pt, 1H, H-5), 3.75–3.58 (m, 6H, CH_2CH_20; H6, H6′), 1.57, 1.35 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.0 (*C*-Ph), 130.0–126.3 (C_6H_5), 108.9 ($C(CH_3)_2$), 103.7 (*C*HPh), 96.3 (C-1), 72.5 (C-a), 72.0 (C-3), 71.5 (C-4), 70.0 (C-2), 69.5 (C-6), 66.6 (C-5), 61.5 (C-b), 26.0, 24.9 ($C(CH_3)_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{18}H_{24}O_7 + Na)^+$ 375.1. Found 375.0. Calcd for $(C_{18}H_{24}O_7 + K)^+$ 391.1. Found 391.0.

Methyl 4,6-*O*-isopropylidene-3-*O*-(2′-trifluoromethanesulfonyloxyethyl)-β-D-galacto-pyranoside (11)

9 (50 mg, 0.18 mmol) was dissolved in dry DCM (2 mL) and dry pyridine (29 μL, 0.36 mmol) was added. The solution was cooled to −30°C and triflic anhydride (39 μL, 0.23 mmol, in 500 μL of dry DCM) was added dropwise under argon. The reaction was complete after 1 h. The organic phase was washed with saturated $NaHCO_3^-$ solution, 1 M $KH_2PO_4^-$ solution, and $NaCl^-$ solution and dried over $MgSO_4$. The solvents were evaporated and the yellow syrup (30 mg, 43%) was used in the next step without further purification. TLC (EA:MeOH 5:1): $R_f = 0.6$.

4,6-*O*-Benzylidene-1,2-*O*-isopropylidene-3-*O*-(2′-trifluoromethanesulfonyloxyethyl)-α-D-galactopyranoside (12)

To a solution of **10** (40 mg, 0.11 mmol) in dry DCM (3 mL) was added dry 2,6-lutidine (18 μL, 0.22 mmol). The solution was cooled to −30°C and triflic

anhydride (24 μL, 0.12 mmol in 500 μL of dry DCM) was added dropwise under argon. The reaction was complete after 30 min. The organic phase was washed with saturated $NaHCO_3^-$ solution, 1M $KH_2PO_4^-$ solution, and $NaCl^-$ solution and dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was coevaporated three times with dry toluene. The orange residue (30 mg, 62%) was used in the next step without further purification. TLC (EtOAc:Tol 5:1): $R_f = 0.83$.

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-trifluoromethanesulfonyl-β-D-gulopyranoside (13)

Gulose **50** (50 mg, 0.13 mmol) was dissolved in dry DCM (1 mL), and dry pyridine (83 μL, 1.0 mmol) was added. The reaction mixture was cooled to 0°C and triflic anhydride (43 μL, 0.26 mmol) was added dropwise via canula. The reaction was allowed to warm up to rt and stirred for further 6 h. The reaction mixture was washed with sat. $NaHCO_3^-$ solution and 1 M $KH_2PO_4^-$ solution, the organic phase was dried over $MgSO_4$, and the solvents were evaporated. The crude product was purified by filtration over a short column with DCM as eluent to give **13** (70 mg, qu) as a yellow syrup. TLC (EtOAc:Tol 1:2): $R_f = 0.75$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10–7.00 (m, 10H, C_6H_5), 5.6 (s, 1H, C*H*Ph), 5.52 (m, 1H, H-3), 5.42 (pt, 1H, H-2), 4.97 (d, 1H, $J_{1-2} = 8.4$ Hz, H-1), 4.45 (dd, 1H, $J_{5-6} = 1.3$, $J_{6-6'} = 12.6$ Hz, H-6), 4.28 (bs, 1H, H-4), 4.15 (dd, 1H, $J_{5-6'} = 1.7$ Hz, H6′), 3.90 (bs, 1H, H-5), 3.53 (s, 3H, OMe).

1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-L-xylofuranose (14) and 1,2-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-L-ribofuranose (15)

Compounds **14** and **15** were synthesized as described by others (for D-xylose) and us previously.[18–22]

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-L-ribofuranose (16)

L-Ribose **15** (15.0 g, 49.3 mmol) and BnBr (8.8 mL, 74 mmol) were dissolved in dry DMF (280 mL). The solution was cooled to 0°C, NaH (1.77 g, 73.9 mmol) was added in portions under argon, and the temperature was allowed to rise to rt overnight under stirring. The reaction was quenched with MeOH (5 mL), the solvent was removed in vacuo, and the residue was dissolved in EtOAc, washed with water, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography (Tol:EtOAc 20:1) to yield **16** (16.5 g, 85%) as a colorless syrup. TLC (EtOAc:Tol 1:10): $R_f = 0.5$; $[\alpha]_D^{20} = -55.7$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H, C_6H_5), 5.68 (d, 1H, J_{1-}

$_2$ = 3.6 Hz, H-1), 4.74, 4.60 (d, 2H, J = 12.6 Hz, CH_2Ph), 4.53 (pt, 1H, H-2), 4.06 (m, 1H, H-4), 3.89–3.87 (m, 2H, H-3, H-5), 3.72 (dd, 1H, $J_{4-5'}$ = 3.0, $J_{5-5'}$ = 12 Hz, H-5′), 1.57, 1.32 (2s, 6H, C(CH_3)$_2$), 0.88 (s, 9H, C(CH_3)$_3$), 0.04 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.8 (*C*-Ph), 128.5–127.5 (C_6H_5), 112.8 (*C*(CH$_3$)$_2$), 103.9 (C-1), 79.4 (C-4), 77.7 (C-2), 76.4 (C-3), 72.5 (*C*H$_2$Ph), 61.1 (C-5), 26.9, 26.6 ((*CH*$_3$)$_2$), 25.9 (C(*CH*$_3$)$_3$), 18.3 (*C*(CH$_3$)$_3$), −5.0 (Si(*CH*$_3$)$_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{21}H_{34}O_5Si + Na)^+$ 417.2. Found 417.8. Calcd for $(C_{21}H_{34}O_5Si + K)^+$ 433.2. Found 433.7.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-L-ribofuranose (17)

16 (16.5 g, 42.0 mmol) was dissolved in dry THF (150 mL), the solution was cooled to 0°C, and TBAF-solution (1M, 46.5 mL in dry THF) was added. The reaction was stirred at rt for 2 h, the solvent was removed in vacuo, and the residue was purified by flash chromatography (Tol:EtOAc 2:1) to afford **17** (10.0 g, 85%) as a colorless syrup. TLC (EtOAc:Tol 1:10): R_f = 0.25; $[\alpha]_D^{20} = -82.7$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H, C_6H_5), 5.73 (d, 1H, J_{1-2} = 3.6 Hz, H-1), 4.75 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.59 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.57 (dd, 1H, J_{2-3} = 8.4 Hz, H-2), 4.12 (ddd, 1H, J_{3-4} = 4.2, J_{4-5} = 2.4 Hz, $J_{4-5'}$ = 9.0 Hz, H-4), 3.92 (dd, 1H, J_{4-5} = 2.4 Hz, $J_{5-5'}$ = 12.0 Hz, H-5), 3.84 (dd, 1H, H-3), 3.63 (dd, 1H, H-5′), 1.59, 1.34 (2s, 6H, C(CH_3)$_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.5 (*C*-Ph), 128.5–127.9 (C_6H_5), 113.1 (*C*(CH$_3$)$_2$), 104.0 (C-1), 78.8 (C-4), 77.7 (C-2), 76.5 (C-3), 72.3 (*C*H$_2$Ph), 60.6 (C-5), 26.8, 26.5 ((*CH*$_3$)$_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{15}H_{20}O_5 + Na)^+$ 303.1. Found 303.2. Calcd for $(C_{15}H_{20}O_5 + K)^+$ 319.1. Found 319.2.

Tetramethyl (3-*O*-benzyl-1,2-*O*-isopropylidene-3,5,6-trideoxy-α-L-ribofuranos-6,6′-diyl) bisphosphonate (18)

17 (2.00 g, 7.14 mmol) was dissolved in dry DCM (24 mL), dry 2,6-lutidine (1.65 mL, 14.2 mmol) was added, and the solution was cooled to −30°C. Triflic anhydride (1.44 mL, 8.56 mmol) in dry DCM (12 mL) was added via canula and the mixture was stirred at this temperature for 2 h. The mixture was extracted with saturated $NaHCO_3^-$ solution and $KH_2PO_4^-$ solution and dried over $MgSO_4$. The organic phases were evaporated in vacuo and the triflate was purified by column filtration with DCM. This afforded the corresponding triflate as an orange syrup (2.8 g, 95%). Tetramethyl methylenediphosphonate[32] (1.62 mL, 86.9 mmol) was dissolved in 50 mL of dry DMF under argon, and NaH (163 mg, 6.79 mmol) and 125 μL crown ether (15-crown-5) were added at 0°C.

After stirring for 30 min the freshly prepared triflate of 17 (1.80 g, 4.36 mmol) in dry DMF (50 mL) was added to the solution via a syringe. The mixture was stirred in the melting ice bath for 4 h and the reaction was quenched by addition of solid NH_4Cl. Following removal of DMF in vacuo, the residue was dissolved in DCM and washed several times with water. The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc:Tol 10:1 → MeOH:EtOAc 1:20) to give **18** (1.20 g, 56%) as a colorless syrup. TLC (EtOAc:Tol 10:1): $R_f = 0.3$; $[\alpha]_D^{20} = -24.3$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H, C_6H_5), 5.68 (d, 1H, $J_{1-2} = 3.7$ Hz, H-1), 4.75 (d, 2H, $J = 11.94$ Hz, CH_2Ph), 4.53 (dd, 1H, $J_{2-3} = 8.8$ Hz, H-2), 4.29 (ddd, 1H, $J_{3-4} = 4.2$, $J_{4-5} = 9.2$, $J_{4-5'} = 12.9$ Hz, H-4), 3.79 (12H, 4 OCH_3), 3.40 (dd, 1H, H-3), 2.83 (dd, 1H, $J_{5'-6} = 3.8$, $J_{5-6} = 8.8$ Hz, H-6), 2.29 (ddd, 1H, $J_{5-5'} = 14.3$ Hz, H-5), 2.03 (m, 1H, H-5′), 1.57, 1.36 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3 (*C*-Ph), 128.5–127.9 (C_6H_5), 103.7 (C-1), 82.6 (C-3), 78.0 (C-2), 75.4 (C-4), 72.1 (CH_2Ph), 53.4 ($POOCH_3$), 31.7 (C-6), 28.6 (C-5), 26.6 ($C(CH_3)_2$); ^{31}P NMR (151 MHz, $CDCl_3$) δ 27.86, 27.51 (2s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{20}H_{32}O_{10}P_2 + Na)^+$ 517.2. Found 516.8. Calcd for $(C_{20}H_{32}O_{10}P_2 + K)^+$ 533.2. Found 532.8.

Tetramethyl (3-*O*-benzyl-3,5,6-trideoxy-α,β-L-ribofuranos-6,6′-diyl) bisphosphonate and Dimethyl (3R, 4S, 5S)-4-benzyloxy-3,5-dihydroxy-1-cyclohexenephosphonate (19)

Synthesis and Characterization of the Hemiacetal Intermediate

18 (530 mg, 1.07 mmol) was dissolved in 30 mL dioxane/5% $H_2SO_4^-$ solution (1:1, 30 mL) and the mixture was stirred at 80°C until monitoring by TLC indicated the absence of starting material. After neutralization with saturated $NaHCO_3^-$ solution, the mixture was extracted several times with DCM. The organic phases were combined, dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography (EtOAc:MeOH 10:1) to yield the hemiacetal (315 mg, 65%) as a colorless syrup. TLC (EtOAc:MeOH 3:1): $R_f = 0.4$; ^{1}H NMR (600 MHz, $CDCl_3$, major anomer) δ 7.37–7.33 (m, 5H, C_6H_5), 5.23 (d, 1H, $J_{1-2} = 3.4$ Hz, H-1), 4.65 (d, 2H, $J = 14.1$ Hz, CH_2Ph), 4.35 (m, 1H, H-4), 4.02 (m, 1H, H-2), 3.80 (m, 12H, $POOCH_3$), 3.65 (m, 1H, H-3), 2.61 (m, 1H, H-6), 2.14 (m, 1H, H-5), 1.96 (m, 1H, H-5′); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.7 (*C*-Ph), 128.7–127.9 (C_6H_5), 96.7 (C-1), 82.9 (C-2), 81.0 (C-3), 77.2 (C-4), 72.8 (CH_2Ph), 53.2 ($POOCH_3$), 32.3 (C-6), 31.6 (C-5); ^{31}P NMR (151 MHz, $CDCl_3$) δ 28.9, 28.17, 27.69, 27.56 (4s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode)

Calcd for $(C_{17}H_{28}O_{10}P_2 + Na)^+$ 477.1. Found 477.0. Calcd for $(C_{17}H_{28}O_{10}P_2 + K)^+$ 493.1. Found 493.0.

Cyclization of the Hemiacetal

To a solution of the hemiacetal (500 mg, 1.10 mmol) in dry dioxane (20 mL) was added lithium bis(trimethylsilyl)amide (1M in dry THF, 1.65 mL, 1.65 mmol) at 0°C. The mixture was stirred for 4 h and then allowed to warm up to rt. The reaction mixture was neutralized with Dowex 50- H^+, filtered, and evaporated in vacuo. Purification by flash chromatography (EtOAc:MeOH 10:1) furnished **19** (207 mg, 62% from the hemiacetal) as a colorless syrup. TLC (EtOAc:MeOH 3:1): $R_f = 0.6$; $[\alpha]_D^{20} = -77.0$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.32 (m, 5H, C_6H_5), 6.67 (d, 1H, $J_{2\text{-P}} = 21.4$ Hz, H-2), 4.80 (d, 2H, $J = 11.9$ Hz, CH_2-Ph), 4.34 (bs, 1H, H-3), 4.13 (bs, 1H, H-5), 3.73–3.71 (m, 7H, H-4, POOCH_3), 2.50 (m, 1H, H-6), 2.40 (m, 1H, H-6′); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.8 (C-2), 128.6–128.1 (C_6H_5), 76.9 (C-4), 72.6 (CH_2Ph), 68.5 (C-5), 66.4 (C-3), 52.6 (POOCH_3), 31.3 (C-6); ^{31}P NMR (151 MHz, $CDCl_3$) δ 22.26 (s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{15}H_{21}O_6P + Na)^+$ 351.1. Found 351.5. Calcd for $(C_{15}H_{21}O_6P + K)^+$ 367.1. Found 367.6.

Dimethyl (3R,4S,5S)-4-benzyloxy-3,5-diacetoxy-1-cyclohexenephosphonate (20)

19 (45 mg, 0.14 mmol) was dissolved in Ac_2O/pyridine (1:9, 8 mL) and stirred at rt overnight. The solvents were evaporated and the syrup was purified by flash chromatography (Tol:EtOAc 1:10) to give **20** (48 mg, 90%). TLC (Tol:EtOAc 1:10): $R_f = 0.5$; $[\alpha]_D$ $^{20} = -32.0$ (c = 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.27 (m, 5H, C_6H_5), 6.46 (d,1H, $J_{2\text{-P}} = 21.0$ Hz, H-2), 5.52 (bs, 1H, H-3), 5.05 (bdd, 1H, $J = 7.8$ Hz, H-5), 4.71 (d, 2H, $J = 12.0$ Hz, CH_2-Ph), 4.10 (bs, 1H, H-4), 3.73–3.69 (m, 6H, POOCH_3), 2.65 (m, 2H, H-6, H-6′), 2.07, 2.00 (2s, 6H, OAc); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0 ($COCH_3$), 138.8 (C-2), 128.3-127.0 (C_6H_5), 74.1 (CH_2Ph), 73.8 (C-4), 70.5 (C-3), 69.8 (C-5), 52.6 (POOCH_3), 26.7 (C-6), 20.9 ($COCH_3$); ^{31}P NMR (151 MHz, $CDCl_3$) δ 20.95 (s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{19}H_{25}O_8P + Na)^+$ 435.1. Found 435.5. Calcd for $(C_{19}H_{25}O_8P + K)^+$ 451.1. Found 451.5.

Dimethyl (3R,4S,5S)-4-benzyloxy-3,5-di(methoxymethyloxy)-1-cyclohexenephosphonate (21)

19 (60 mg, 0.18 mmol) was dissolved in 40 mL of a mixture of DCM/dimethoxymethane (1:1) and 30 μL of triflic acid were added under argon.

The mixture was stirred at rt for 4 h. The reaction was then washed with saturated $NaHCO_3^-$ solution, and the organic phase was dried over $MgSO_4$ and evaporated in vacuo. Purification by MPLC (EtOAc:MeOH 29:1) resulted in **21** as a colorless syrup (55 mg, 71%). TLC (EtOAc: MeOH 10:1): $R_f = 0.48$; $[\alpha]_D^{20} = -32.5$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H, C_6H_5), 6.53 (d, 1H, $J_{2\text{-P}} = 21.6$ Hz, H-2), 4.85 (d, 2H, CH_2Ph), 4.65 (dd, 4H, $2CH_2O$), 4.34 (bs, 1H, H-3), 4.04 (bs, 1H, H-4), 3.82 (pt, 1H, $J = 7.8$ Hz, H-5), 3.68 (2d, 6H, $J_{\text{P-OMe}} = 10.8$ Hz, POOCH_3), 3.35 (2s, 6H, CH_2OCH_3), 2.49 (m, 2H, H-6, H-6′); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142 (C-2), 128.6–127.0 (C_6H_5), 95.5 (CH_2OCH_3), 74.5 (C-4), 73.9 (C-5, C-3), 73.4 (CH_2Ph), 55.8 (CH_3OCH_2), 52.7 (POOCH_3), 27.9 (C-6); ^{31}P NMR (151 MHz, $CDCl_3$) δ 21.7 (s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{19}H_{29}O_8P + Na)^+$ 439.2. Found 439.7. Calcd for $(C_{19}H_{29}O_8P + K)^+$ 455.2. Found 455.8.

Dimethyl (3R,4S,5S)-4-hydroxy-3,5-di(methoxymethyloxy)-1-cyclohexenephosphonate (22)

To **21** (65 mg, 0.16 mmol) in EtOH (5 mL) was added Pearlman's catalyst (60 mg) and 1,4-cyclohexadiene (3 mL) and the mixture was stirred at 50°C for 4 days. The catalyst was removed by filtration and the solvent was evaporated. Purification by column chromatography (EtOAc:MeOH 10:1) afforded **22** (33 mg, 65%) as a colorless syrup. TLC (EA:MeOH 10:1): $R_f = 0.26$; $[\alpha]_D^{20} = -10.6$ (c = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.50 (d, 1H, $J_{2\text{-P}} = 21.6$ Hz, H-2), 4.78, 4.73 (dd, 4H, $J_{\text{a-b}} = 10.2$ Hz, CH_2O), 4.32 (m, 1H, H-3), 4.23 (m, 1H, H-4), 3.82 (bt, 1H, H-5), 3.72 (2d, 6H, $J_{\text{P-OMe}} = 10.8$ Hz, POOCH_3), 3.44, 3.40 (2s, 6H, CH_2OCH_3), 2.47 (m, 2H, H-6, H-6′); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.0 (C-2), 95.3, 94.8 (CH_2OCH_3), 73.4 (C-3), 72.9 (C-5), 67.6 (C-4), 55.8, 55.4 (CH_3OCH_2), 52.2 (POOCH_3), 26.4 (C-6); ^{31}P NMR (151 MHz, $CDCl_3$) δ 20.7 (s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{12}H_{23}O_8P + Na)^+$ 349.1. Found 349.9. Calcd for $(C_{12}H_{23}O_8P + K)^+$ 365.1. Found 365.8.

Dimethyl (3R,4R,5S)-4-azido-3,5-di(methoxymethyloxy)-1-cyclohexenephosphonate (23)

22 (30 mg, 0.092 mmol) was dissolved in dry DCM (500 μL), dry pyridine (34 μL, 0.42 mmol) was added, and the solution was cooled to −30°C. Triflic anhydride (30 μL, 0.18 mmol) in dry DCM (300 μL) was added and the mixture was stirred at −10°C for 2 h. The mixture was washed with saturated $NaHCO_3^-$ solution and $KH_2PO_4^-$ solution and dried over $MgSO_4$. The organic phases were dried in vacuo and the triflate was obtained as an orange syrup

(40 mg, 95%), which was used without further purification. The triflate (30 mg, 0.066 mmol) was dissolved in dry DMF (2 mL), NaN_3 (22 mg, 0.33 mmol) and $^tBuNH_4Cl$ (3 mg) were added, and the mixture was stirred at 50°C overnight. DMF was removed in vacuo and the resulting oil was purified by flash chromatography (EtOAc), which afforded **23** (20 mg, 86%) of as a colorless syrup. TLC (EtOAc): $R_f = 0.3$; $[\alpha]_D^{20} = -38.6$ (c = 1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.52 (d, 1H, $J_{2\text{-P}} = 21.6$ Hz, H-2), 4.78, 4.76 (dd, 4H, CH_2O), 4.08 (bd, 1H, H-3), 3.71 (2d, 6H, $J_{\text{P-OMe}} = 10.8$ Hz, POOCH_3), 3.70 (1H, H-5 hidden under MOM), 3.56 (1H, H-4), 3.42, 3.40 (2s, 6H, CH_2OCH_3), 2.74 (m, 1H, H-6), 2.22 (m, 1H, H-6′); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.8 (C-2), 96.3, 95.9 (CH_2OCH_3), 76.1 (C-3), 74.2 (C-5), 66.9 (C-4), 55.7 (CH_3OCH_2), 52.7 (POOCH_3), 31.2 (C-6); ^{31}P NMR (151 MHz, $CDCl_3$) δ 19.9 (s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{12}H_{22}N_3O_7P + Na)^+$ 374.1. Found 374.1. Calcd for $(C_{12}H_{22}N_3O_7P + K)^+$ 390.1. Found 390.1.

Dimethyl (3R,4R,5S)-4-azido-3,5-dihydroxy-1-cyclohexenephosphonate (24)

23 (36 mg, 0.10 mmol) was dissolved in TFA (5 mL, 50%) and stirred at rt overnight. The solution was lyophilized and purified by flash chromatography (EtOAc:MeOH 7:1) to afford **24** (30 mg, qu) as a colorless syrup. TLC (EtOAc:MeOH 5:1): $R_f = 0.45$; $[\alpha]_D^{20} = -14.6$ (c = 1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.36 (d, 1H, $J_{2\text{-P}} = 22.2$ Hz, H-2), 4.16 (m, 1H, H-3), 3.76 (ddd, 1H, $J_{5-6} = 5.4$, $J_{4-5} = 10.2$ Hz, $J_{5-6'} = 15.2$ Hz, H-5), 3.64–3.60 (2d, 6H, $J_{\text{P-OMe}} = 11.4$ Hz, POOCH_3), 3.35 (dd, 1H, $J_{3-4} = 9.0$ Hz, H-4), 2.57 (m, 1H, H-6), 2.16 (m, 1H, H-6′); ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.0 (C-2), 70.6 (C-3), 69.1 (C-4), 68.1 (C-5), 53.1 (POOCH_3), 32.2 (C-6); ^{31}P NMR (151 MHz, $CDCl_3$) δ 22.7 (s, PO_3Me_2). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_8H_{14}N_3O_5P + Na)^+$ 286.1. Found 285.7.

Dimethyl (3R,4R,5S)-4-acetamido-3,5-diacetoxy-1-cyclohexenephosphonate (25)

24 (30 mg, 0.11 mmol) was dissolved in dry THF (1 mL) and added to a solution of Ac_2O (43 μL, 0.46 mmol) of PMe_3 in THF (1M, 680 μL, 0.68 mmol) under argon. The mixture was stirred at rt overnight. The solution was dried in vacuo and purified by flash chromatography (EtOAc:Tol 10:1 → EtOAc:MeOH 5:1) to yield **25** (21 mg, 58%) as a yellow syrup. TLC (EtOAc:MeOH 10:1): $R_f = 0.26$; $[\alpha]_D^{20} = -44.8$ (c = 1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.47 (d, 1H, $J_{2\text{-P}} = 19.2$ Hz, H-2), 5.55 (m, 1H, H-3), 5.10 (ddd, 1H, $J_{4-5} = 9.0$, $J_{5-6} = 5.4$, $J_{5-6'} = 10.8$ Hz, H-5), 4.25 (dd, 1H,

$J_{3-4} = 10.8$ Hz, H-4), 3.76 (2d, 6H, $J_{\text{P-OMe}} = 11.4$ Hz, POOCH_3), 2.75 (m, 1H, H-6), 2.34 (m, 1H, H-6′), 2.05, 2.03 (2s, 6H, OAc), 1.91 (s, 3H, NHAc); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0 (NHCOCH$_3$), 171.8 (COCH$_3$), 141.0 (C-2), 72.4 (C-3), 69.6 (C-5), 53.6 (C-4), 53.5 (POOCH_3), 30.8 (C-6), 22.7 (NHCOCH$_3$), 20.7, 20.6 (COCH$_3$); ^{31}P NMR (151 MHz, $CDCl_3$) δ 19.76 (s, PO$_3$Me$_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{14}H_{22}NO_8P + Na)^+$ 386.1. Found 385.6. Calcd for $(C_{14}H_{22}NO_8P + K)^+$ 402.1. Found 401.6.

Triethylammonium (methyl (3R,4R,5S)-4-acetamido-3,5-diacetoxy-1-cyclohexenephosphonate) (26)

25 (24 mg, 0.066 mmol) was dissolved in dry THF (750 μL), NEt$_3$ (129 μL, 0.93 mmol) and thiophenol (47 μL, 0.46 mmol) were added, and the mixture was stirred at rt for 48 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography (EtOAc:MEOH 10:1 → 4:1+ 1% NEt$_3$) to give triethylammonium salt **26** (29 mg, qu) in quantitative yield. TLC (EtOAc:MeOH 5:1): $R_f = 0.1$; $[\alpha]_D^{20} = -3.2$ (c = 0.5, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 6.21 (d, 1H, $J_{2\text{-P}} = 18.6$ Hz, H-2), 5.53 (pd, 1H, H-3), 5.08 (ddd, 1H, $J_{4-5} = 9.0$, $J_{5-6} = 5.4$ Hz, H-5), 4.21 (dd, 1H $J_{3-4} = 10.8$ Hz, H-4), 3.48 (1d, 3H, $J_{\text{P-OMe}} = 10.8$ Hz; POOCH_3), 3.18 (q, 6H, CH_2CH$_3$), 2.75 (m, 1H, H-6), 2.36 (m, 1H, H-6′), 2.04, 2.02 (2s, 6H, OAc), 1.90 (s, 3H, NHAc), 1.29 (t, 9H, CH$_2$CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 173, 173.6 (NHCOCH$_3$), 172.0 (COCH$_3$), 171.9 (COCH$_3$), 133.0 (C-2), 72.1 (C-3), 69.4 (C-5), 52.7 (C-4), 50.6 (POOCH_3), 46.1 (N(CH$_2$CH$_3$)$_3$), 30.6 (C-6), 22.7–20.7 (COCH$_3$), 9.2 (N(CH$_2$$CH_3$)$_3$); ^{31}P NMR (151 MHz, CD_3OD) δ 13.2 (s, PO$_3$Me$^-$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{13}H_{20}NO_8P + Na)^+$ 372.1. Found 372.3. Calcd for $(C_{13}H_{20}NO_8P + K)^+$ 388.3. Found 388.3.

Methyl ((3R,4R,5S)-4-acetamido-3,5-diacetoxy-1-cyclohexene) phosphonic acid (27)

26 (15 mg, 0.033 mmol) was dissolved in dioxane/water (1:1, 2 mL). Amberlite-IR-120 (H$^+$) was added until pH 2, the resin was removed by filtration, and the product was lyophilized from dioxane to give **27** (12 mg, qu). $[\alpha]_D^{20} = -8.34$ (c = 0.5, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 6.38 (d, 1H, $J_{2\text{-P}} = 49.8$ Hz, H-2), 5.52 (m, 1H, H-3), 5.08 (m, 1H, H-5), 4.23 (m, 1H, H-4), 3.65 (m, 3H; POOCH_3), 2.78 (m, 1H, H-6), 2.35 (m, 1H, H-6′), 2.05, 2.02 (2s, 6H, OAc), 1.92 (s, 3H, NHAc).

O-Methyl-*O*-(4,6-*O*-benzylidene-3-*O*-(1′-ethyl)-1,2-*O*-isopropylidene-α-D-galactopyranoside-2′-ýl)(3R,4R,5S)-4-acetamido-3,5-diacetoxy-1-cyclohexene-phosphonate (28) (h,l)

To a solution of acid **27** (15 mg, 0.043 mmol) in dry THF (1 mL) was added galactose derivative **10** (30 mg, 0.086 mmol), Ph_3P (23 mg, 0.086 mmol), and DIAD (17 μL, 0.086 mmol). The reaction was stirred at 60°C for 48 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (EtOAc:Tol 10:1 → EtOAc:MeOH 10:1) to afford a mixture of diastereomers **28 (h,l)** (15 mg, 51%) as a colorless syrup. No attempt to separate them was made. TLC (EtOAc:MeOH 10:1): $R_f = 0.30–0.35$; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51–7.25 (m, 5H, C_6H_5), 6.44 (m, 1H, H-2a), 5.74 (s, 1H, C*H*Ph), 5.61 (d, 1H, $J_{1-2} = 5.4$ Hz, H-1b), 5.50 (m, 1H, H-3a), 5.05 (m, 1H, H-5a), 4.63 (dd, 1H, $J_{2-3} = 2.4$ Hz, $J_{3-4} = 8.4$ Hz, H-3b), 4.41 (dd, 1H, H-2b), 4.36 (dd, 1H, $J_{3-4} = 9.0$ Hz, H-4a), 4.31 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4b), 4.20–4.06 (m, 4H, H-5b, 3H from ethyleneglycol), 3.74–3.60 (m, 6 H, POOMe, H-6′b, H-6b, 1H from ethyleneglycol), 2.70 (m, 1H, H-6a), 2.43 (m, 1H, H-6a′), 2.04, 2.02 (2s, 6H, OAc), 1.90 (s, 3H, NHAc), 1.55, 1.33 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1 ($NHCOCH_3$), 171.0 ($COCH_3$), 170.1 ($COCH_3$), 139.1 (C-2a), 136.2 (*C*-Ph), 128.8–126.3 (C_6H_5), 110.0 ($C(CH_3)_2$), 103.7 (*C*HPh), 96.3 (C-1b), 71.8 (C-3b), 71.5 (C-4b, C-3a), 70.0 (C-6b), 69.9 (C-2b), 68.6 (C-5a), 66.8 (C-5b), 65.3 (CH_2O), 53.0 (C-4a), 52.5 ($POOCH_3$), 30.4 (C-6a), 26.0, 24.9 ($C(CH_3)_2$), 23.3–20.8 ($COCH_3$); ^{31}P NMR (151 MHz, $CDCl_3$) δ 18.3, 18.0 (2s, PO_3Me_2). MALDI-MS (DHB, THF, pos. mode) Calcd for $(C_{31}H_{42}NO_{14}P + Na)^+$ 706.2. Found 706.4. Calcd for $(C_{31}H_{42}NO_{14}P + K)^+$ 722.2. Found 722.5.

Triethylammonium (4,6-*O*-benzylidene-3-*O*-(1′-ethyl)-1,2-*O*-isopropylidene-α-D-galactopyranoside-2′-yl) (3R,4R,5S)-4-acetamido-3,5-diacetoxy-1-cyclohexene-phosphonate (29)

28 (h,l) (15 mg, 0.022 mmol) was dissolved in dry THF (500 μL). NEt_3 (42 μL, 0.31 mmol) and thiophenol (16 μL, 0.15 mmol) were added and the reaction was stirred at rt for 2 days. The solvent was removed and the following flash chromatography (EtOAc:MeOH 10:1 → 5:1, 1% NEt_3) yielded **29** (9 mg, 60%) as a colorless solid. Tlc (EtOAc:MeOH 5:1): $R_f = 0.1$; ^{1}H NMR (600 MHz, CD_3OD) δ 7.51–7.35 (m, 5H, C_6H_5), 6.22 (d, 1H, $J_{2\text{-}P} = 18.6$ Hz, H-2a), 5.74 (s,1H, C*H*Ph), 5.57 (d, 1H, $J_{1-2} = 5.4$ Hz, H-1b), 5.49 (pd, 1H, $J_{3-4} = 8.4$ Hz, H-3a), 5.06 (dd, 1H, $J_{4-5} = 9.6$, $J_{5-6} = 5.4$ Hz, H-5a), 4.65 (dd, 1H, $J_{2-3} = 2.4$, $J_{3-4} = 8.4$ Hz, H-3b), 4.45 (dd, 1H, H-2b), 4.33 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4b), 4.22 (dd, 1H, $J_{3-4} = 8.4$ Hz, H-4a), 4.08–4.06 (m, 1H,

H-5b), 3.90–3.80 (m, 2H, from chain), 3.75–3.60 (m, 4H, 2H from chain, H-6b, H-6b′), 3.15 (q, 6H, CH_2CH$_3$), 2.83 (m, 1H, H-6a), 2.42 (m, 1H, H-6a′), 2.08, 2.00 (2s, 6H, OAc), 1.89 (s, 3H, NHAc), 1.53, 1.34 (2s, 6H, C(CH_3)$_2$), 1.29 (t, 9H, CH$_2$CH_3); ^{13}C NMR (151 MHz, CD$_3$OD) δ 170.6 (NH*C*OCH$_3$), 170.5 (*C*OCH$_3$), 170.5 (*C*OCH$_3$), 136.8 (C-2a), 133.1 (*C*-Ph), 129.3–127.5 (C_6H$_5$), 109.0 (*C*(CH$_3$)$_2$), 104.7 (*C*HPh), 97.6 (C-1b), 73.0 (C-3a, C-3b), 72.8 (C-4b), 72.1 (C-6b), 71.5 (C-2b), 70.7 (C-5a), 68.0 (C-5b), 64.6 (*C*H$_2$O), 53.9 (C-4a), 47.1 (N(*C*H$_2$CH$_3$)$_3$), 32.0 (C-6a), 25.0, 23.7 (C(*C*H$_3$)$_2$), 21.3-19.5 (CO*C*H$_3$), 19.4 (N(CH$_2$*C*H$_3$)$_3$); ^{31}P NMR (151 MHz, CD$_3$OD) δ 11.9 (s, *P*O$_3$R$^-$). MALDI-MS (CHCA, THF, pos. mode) Calcd for (C$_{30}$H$_{40}$NO$_{14}$P + Na)$^+$ 692.2. Found 692.5. Calcd for (C$_{30}$H$_{40}$NO$_{14}$P + K)$^+$ 708.2. Found 708.5.

Ammonium (4,6-*O*-benzylidene-3-*O*-(1′-ethyl)-1,2-*O*-isopropylidene-α-D-galactopyranoside-2′-yl) (3R,4R,5S)-4-acetamido-3,5-dihydroxy-1-cyclohexenephosphonate (30)

29 (8 mg, 0.01 mmol) was dissolved in water/dioxane (1:1, 1 mL) and 8 drops of 25% NH$_3$ aq solution were added. The reaction was stirred at rt for 4 days. The solvents were evaporated and the crude product was lyophilized from water to afford **30** (6 mg, qu) as a colorless solid. ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.51–7.35 (m, 5H, C_6H_5), 6.28 (d, 1H, $J_{2\text{-P}} = 13.2$ Hz, H-2a), 5.73 (s, 1H, C*H*Ph), 5.59 (d, 1H, $J_{1-2} = 4.8$ Hz, H-1b), 4.65 (dd, 1H, $J_{2-3} = 2.4$, $J_{3-4} = 8.4$ Hz, H-3b), 4.45 (dd, 1H, H-2b), 4.34 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4b), 4.10–4.00 (m, 2H, H-5b, H-3a), 3.90–3.85 (m, 2H from chain), 3.78–3.60 (m, 6H, 2H from chain, H-4a, H-5a, H-6b, H-6b′), 2.72 (m, 1H, H-6a), 2.25 (m, 1H, H-6a′), 2.08 (1s, 3H, NHAc), 1.53, 1.34 (2s, 6H, C(CH_3)$_2$); ^{13}C NMR (151 MHz, CD$_3$OD) δ 174.5 (NH*C*OCH$_3$), 138.2 (C-2a), 130.7–127.5 (C_6H$_5$), 110.0 (*C*(CH$_3$)$_2$), 104.5 (*C*HPh), 97.4 (C-1b), 72.9 (C-3b), 72.5 (C-4b), 72.4 (C-6b), 71.9 (*C*H$_2$O), 71.2 (C-2b), 70.8 (C-5b), 69.4 (C-5a), 67.8 (C-3a), 64.3 (*C*H$_2$O), 59.9 (C-4a), 35.1 (C-6a), 26.3-25.1 (C(*C*H$_3$)$_2$), 23.2 (CO*C*H$_3$); ^{31}P NMR (151 MHz, CD$_3$OD) δ 13.9 (s, *P*O$_3$R$^-$). MALDI-MS (CHCA, THF, pos. mode) Calcd for (C$_{26}$H$_{36}$NO$_{12}$P + Na)$^+$ 608.2. Found 608.3. Calcd for (C$_{26}$H$_{36}$NO$_{12}$P + K)$^+$ 624.2. Found 624.4.

Ammonium (3-*O*-(1′-ethyl)-α,β -D-galactopyranoside-2′-yl)(3R,4R,5S)-4-acetamido-3,5-dihydroxy-1-cyclohexenephosphonate (31)

30 (5 mg, 9 μmol) was dissolved in TFA (50%, 1 mL) and stirred overnight. The solvent was evaporated and the residue was lyophilized from water to afford **31** (3 mg, qu) as a colorless solid. ^{1}H NMR (600 MHz, D$_2$O) δ 6.16

(d, 2H, $J_{2\text{-P}} = 19.8$ Hz, H-2a), 5.14 (d, 0.8H, $J_{1-2} = 4.2$ Hz, H-1bα), 4.47 (dd, 1.3 H, $J_{1-2} = 7.8$ Hz, H-1bβ), 4.20–4.10 (m, 3H, H-3a both anomers), 3.86–3.59 (m, 25 H, H-4a, H-5a, H-6b, H-6b′ both anomers, CH_2CH_2O, H-3bα, H-2bα, H-5b, H-4b both anomers), 3.53 (dd, 1.3 H, $J_{2-3} = 9.6$ Hz, $J_{3-4} = 3.6$ Hz, H-3bβ), 3.37 (dd, 1.3 H, H-2bβ), 2.57 (m, 2H, H-6a), 2.14 (m, 2H, H-6a′), 1.95 (1s, 6H, NHAc); ^{13}C NMR (151 MHz, D_2O, selected data) δ 174.5 (NH*C*OCH$_3$), 138.1 (C-2a), 96.2 (C-1bβ), 92.1 (C-1bα), 72.5 (C-3bβ), 71.6 (C-2bβ), 33.2 (C-6a), 22.2 (CO*C*H$_3$); ^{31}P NMR (162 MHz, D_2O) δ 15.6 (s, *P*O$_3$R$^-$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{16}H_{28}NO_{12}P + Na)^+$ 480.1. Found 480.2. Calcd for $(C_{16}H_{28}NO_{12}P + K)^+$ 496.1. Found 496.2. [HR-ESI-MS] Calcd for $[M + 2Na\text{-}H]^+$ 502.1072. Found 502.1060.

Ammonium (methyl (3R,4R,5S)-4-acetamido-3,5-dihydroxy-1-cyclohexenephosphonate) (32)

27 (7 mg, 0.02 mmol) was dissolved in dioxane/water (1:1, 1 mL), 12 drops of 25% NH_3 aq solution were added, and the reaction was stirred at rt for 4 days. The solvents were removed in vacuo and the product was lyophilized from water to afford **32** (4 mg, qu) as a white lyophylisate. $[\alpha]_D^{20} = -5.4$ (c = 0.5, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 6.13 (d, 1H, $J_{2\text{-P}} = 19.8$ Hz, H-2), 4.15 (bs, 1H, H-3), 3.71 (m, 2H, H-5, H-4), 3.49 (1d, 3H, POO*C*H$_3$), 2.56 (m, 1H, H-6), 2.16 (m, 1H, H-6′), 1.95 (s, 3H, NHAc); ^{13}C NMR (151 MHz, D_2O) δ 175.0 (NH*C*OCH$_3$), 137.5 (C-2), 70.8 (C-3), 67.6 (C-5), 58.0 (C-4), 51.4 (POO*C*H$_3$), 33.3 (C-6), 22.0 (CO*C*H$_3$); ^{31}P NMR (162 MHz, D_2O) δ 16.2 (s, *P*O$_3$Me$^-$). MALDI-MS (DHB, THF, pos. mode) Calcd for $(C_9H_{16}NO_6P + Na)^+$ 288.1. Found 288.2. Calcd for $(C_9H_{16}NO_6P + K)^+$ 304.1. Found 304.3.

Triethylammonium *O*-(4,6-*O*-benzylidene-3-*O*-(1′-ethyl)-1,2-*O*-isopropylidene-α-D-galactopyranoside-2′-yl) methylphosphonate (33)

Methanephosphonic acid (15 mg, 0.16 mmol) was dissolved in dry THF (2 mL), and galactose **10** (82 mg, 0.23 mmol), Ph_3P (61 mg, 0.23 mmol), and finally DIAD (46 μL, 0.23 mmol) were added under an argon atmosphere. The mixture was stirred at 60°C for 2 days. The solvent was removed in vacuo and the crude product was purified by flash chromatography (EtOAc:Tol 10:1 → EtOAc:MeOH 10:1 → 4:1, 1% NEt_3) to afford **33** (37 mg, 42%) as a colorless syrup. TLC (EtOAc:Tol 10:1): $R_f = 0.1$; $[\alpha]_D^{20} = -40.3$ (c = 1, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD) δ 7.51–7.35 (m, 5H, C_6H_5), 5.72 (s, 1H, *H*Ph;), 5.57 (d, 1H, $J_{1-2} = 4.8$ Hz, H-1), 4.66 (dd, 1H, $J_{2-3} = 2.4$, $J_{3-4} = 8.4$ Hz, H-3), 4.46 (dd, 1H, H-2), 4.31 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4), 4.08 (m, 1H, H-5), 4.02–3.98 (m, 2H, CH_2CH_2O), 3.73 (dd, 1H, $J_{5-6} = 5.4$,

$J_{6-6'} = 10.2$ Hz, H-6), 3.65–3.60 (m, 3H, H-6′, CH_2CH_2O), 3.15 (q, 6H, CH_2CH_3), 1.51 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.32′1.25 (m, 12H, P-CH_3 and CH_2CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 138.2 (*C*-Ph), 130.7–127.5 (C_6H_5), 110.1 ($C(CH_3)_2$), 104.5 (*C*HPh), 97.5 (C-1), 72.9 (C-2), 72.5 (C-4), 71.7 (C-a), 71.1 (C-3), 70.8 (C-6), 67.8 (C-5), 64.4 (C-b), 47.2 ($N(CH_2CH_3)$, 26.3, 25.1 ($C(CH_3)_2$), 12.6 ($N(CH_2CH_3)_3$), 11.7 (PCH_3); ^{31}P NMR (151 MHz, CD_3OD) δ 27.3 (s, PCH_3). MALDI-MS (CHCA, THF, pos. mode) Calcd for ($C_{20}H_{29}O_9P + Na + H)^+$ 468.2. Found 468.8.

Ammonium *O*-(3-*O*-(1′-ethyl)-α,β-D-galactopyranoside-2′-yl) methylphosphonate (34)

33 (10 mg, 0.018 mmol) was dissolved in TFA (50%, 2 mL) and stirred at rt overnight. The reaction product was lyophilized, dissolved in 1M $NH_4HCO_3^-$ buffer, and lyophilized again to afford **34** (7 mg, 93%) as a colorless solid. ^{1}H NMR (600 MHz, D_2O) δ 5.14 (d, 1H, $J_{1-2} = 3.6$ Hz, H-1α), 4.45 (d, 2H, $J_{1-2} = 7.8$ Hz, H-1β), 3.97–3.60 (m, 25 H, H-4, H-5,H-6, H-6′, CH_2CH_2O both anomers and H-2 α, H-3 α), 3.51 (dd, 2H, $J_{2-3} = 3.6$ Hz, $J_{3-4} = 9.0$ Hz, H-3β), 3.35 (dd, 2H, H-2β), 3.05 (q, 6H, $N(CH_2CH_3)_3$), 1.32–1.28 (2s, 6H, PCH_3), 1.12 (t, 9H, $N(CH_2CH_3)_3$); ^{13}C NMR (151 MHz, D_2O) δ 96.5 (C-1 β), 92.2 (C-1 α), 72.7 (C-3), 71.8 (C-2), 46.8 ($N(CH_2CH_3)_3$), 11.9 (PMe), 11.5 ($N(CH_2CH_3)_3$) ppm, 4C unresolved; ^{31}P NMR (162 MHz, D_2O) δ 27.9 (s, PCH_3). [HR-ESI-MS] Calcd for $[M + 2Na\text{-}H]^+$ 347.0459. Found 347.0478.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-galactopyranoside (35)

Dibutyltin oxide (1.28 g, 5.1 mmol) was added to a solution of methyl β-D-galactopyranoside (995 mg, 5.1 mmol) in dry methanol (20 mL). The solution was stirred under reflux for 2 h and the methanol was removed by evaporation in vacuo by repeated coevaporation with toluene. The residue was taken up in dry toluene (40 mL), TBAI (2.28 g, 6.2 mmol) and benzyl bromide (1.2 mL, 10.3 mmol) were added, and the solution was stirred under reflux for 2 h. Excess benzyl bromide was destroyed by addition of sodium methoxide. The solution was evaporated and acetic anhydride (5 mL) and pyridine (1:2, 10 mL) was added to the residue and the mixture was stirred overnight at rt. The solvents were evaporated in vacuo and the residue was purified by medium performance liquid chromatography (MPLC) (Tol:EtOAc 3:1) to give **35** (1.35 g, 64%). TLC (EtOAc:Tol 1:3): $R_f = 0.3$. Physical data correspond to those reported.[32]

Methyl 2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (36)

35 (486 mg, 1.18 mmol) was dissolved in dry methanol (20 mL), Pd/C (20 mg) was added, and the mixture was stirred under an atmosphere of hydrogen for 2 h. Following filtration through celite the solvent was evaporated and the residue was purified by flash chromatography (Tol:EtOAc 1:3) to give compound **36** (368 mg, 97%). TLC (EtOAc:Tol 3:1): $R_f = 0.5$. Physical data correspond to those reported.[32]

O,O-Dibenzyl *O*-(methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) phosphonate (37)

36 (198 mg, 0.64 mmol) and tetrazole (118 mg, 1.66 mmol, 2.6 Eq) were mixed and dried thoroughly under vacuum. Dry DCM (10 mL) was added to the mixture under a nitrogen atmosphere and the mixture was stirred at rt until a clear solution was obtained. Dibenzyl diisopropylphosphoramidite (424 μL, 1.28 mmol) was added and the solution was stirred until no starting material was detectable. The triester **37** was not isolated but directly converted into the H-phosphonate **38** or the phosphate **40**.

O-Benzyl *O*-(methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) phosphonic acid (38)

HCl solution (0.2 M, 8 mL) and 1,4-dioxane (4 mL) were added to the triester solution obtained from 0.64 mmol of **36** followed by stirring for further 4 h. The organic phase was washed with water, dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography (Tol:EtOAc 1:2) to give **38** as a mixture of both diastereomeric H-phosphonates (240 mg, 84%). TLC (EtOAc:Tol 2:1): $R_f = 0.35$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.36 (m, 5H, -C_6H_5), 6.88 (d, 0.5H, $J_{P\text{-}H} = 724$ Hz, PH (1st diastereomer)), 6.80 (d, 0.5H, $J_{P\text{-}H} = 727$ Hz, PH (2nd diastereomer)), 5.46 (br s, 1H, H-4), 5.24–4.98 (m, 3H, H-2, C*H*$_2$Ph), 4.75–4.64 (m, 1H, H-3), 4.37, 4.33 (2d, 1H, H-1), 4.23–4.08 (m, 2H, H-6,H-6′), 3.87–3.79 (m, 1H, H-5), 3.51 (s, 3H, OCH_3), 2.18–2.06 (m, 9H, 3 OAc). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 8.45, 7.95 (2s, 1H, *P*H). [HR-ESI-MS] Calcd for $[C_{20}H_{27}O_{11}PNa]^+$ 497.1183. Found 497.1196.

Ammonium *O*-(methyl β-D-galactopyranoside-3-yl) phosphonate (39)

38 was debenzylated as described for **36**. The debenzylated compound was then treated with a mixture of 1,4-dioxane/25% NH_4OH solution (1:1, 4 mL) overnight at rt. The reaction mixture was lyophilized and **39** was purified by gel permeation chromatography (Biogel P4, 0.1 M NH_4HCO_3 buffer). ^{1}H NMR (300 MHz, D_2O) δ 6.66 (d, 0.7H, $J_{P\text{-}H} = 647$ Hz, P*H* (1st

diastereoisomer)), 6.46 (d, 0.3H, $J_{P\text{-}H} = 634$ Hz, P*H* (2nd diastereoisomer)), 4.22 (d, 1H, $J_{1-2} = 8.1$ Hz, H-1), 3.94–3.87 (m, 2H, H-3, H-4), 3.63–3.54 (m, 3H, H-5, H-6, H-6′), 3.46 (dd, H-2), 3.41 (s, 3H, OCH_3). ^{31}P NMR (121.4 MHz, D_2O) δ 9.14, 6.72 (2s, 1H, *P*H). [HR-ESI-MS] Calcd for $[C_7H_{15}O_8PNa]^+$ 281.0395. Found 281.0396.

Dibenzyl *O*-(methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) phosphate (40)

A solution of phosphite **37** (from 50 mg, 0.32 mmol of **36**), prepared from **36** as described above, was diluted with DCM (5 mL) and extracted with saturated NH_4Cl^- solution (5 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude phosphite was taken up in dry DCM (5 mL) and treated with tertbutyl hydroperoxyde (0.1 mL, 6M in decane) for 30 min at rt. Sodium bisulfite solution was added (0.5 M, 5 mL), the mixture was stirred for 15 min, and the organic phases were washed with NH_4Cl^- solution, dried, and evaporated. Flash chromatography (Tol:EtOAc 1:1) gave **40** as a colorless oil (70 mg, 75%). TLC (EtOAc: Tol 1:1): $R_f = 0.33$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.10 (m, 10H, 2 C_6H_5), 5.45 (d, 1H, $J = 3.3$ Hz, H-4), 5.14 (dd, 1H, $J_{2-3} = 9.7$, $J_{1-2} = 8.0$ Hz, H-2), 4.99–4.85 (m, 4H, 2 OCH_2Ph), 4.53 (ddd, 1H, $J_{3\text{-}P} = \sim 10$Hz, H-3), 4.27 (d, 1H, H-1), 4.10–4.02 (m, 2H, H-6, H-6′), 3.74 (dd, $J_{5-6} = J_{5-6'} = 6.6$ Hz, H-5), 3.43 (s, 3H, OCH_3), 2.02, 1.99, 1.78 (3s, 9H, 3 OAc); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ −0.75 (1P, *P*O(OR)$_3$). [HR-ESI-MS] Calcd for $[C_{27}H_{33}O_{12}PNa]^+$ 603.1607760. Found 603.1601841.

Ammonium *O*-(methyl 2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) phosphate (41)

40 was debenzylated and deacetylated as described for **36** and **38**. The crude product was purified by gel permeation chromatography (Biogel P4, 0.1 M NH_4HCO_3 buffer) and lyophilized. ^1H NMR (300 MHz, D_2O) δ 4.21 (d, 1H, $J_{1-2} = 8.1$ Hz, H-1), 3.89–3.82 (m, 2H, H-3, H-4), 3.64–3.55 (m, 3H, H-5, H-6, H-6′), 3.48 (dd, 1H, $J = 7.9$, 9.0 Hz, H-2), 3.41 (s, 3H, OCH_3). ^{31}P NMR (121.4 MHz, D_2O) δ −1.42 (s, 1P, O*P*O$_3^{2-}$). [HR-ESI-MS] Calcd for $[C_7H_{15}O_9PNa]^+$ 297.0355. Found 297.0345.

O-Benzyl *O*-(methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) (1-(4-acetamido)phenyl-hydroxymethyl)) phosphonate (42)

Compound **38** (50 mg, 0.10 mmol) was dissolved in dry DCM (2 mL). Para-acetamido benzaldehyde (21 mg, 0.12 mmol) and Et_3N (30 μL, 0.22 mmol) were added to the solution and the mixture was stirred for 3 h at rt. After removing

the solvent in vacuo, the compound was purified by flash chromatography (EtOAc: MeOH = 10:0.4) to afford compound **42** (54.6 mg, 81%) as a mixture of the four possible diastereomers. TLC (EtOAc: MeOH 10:0.4): $R_f = 0.20$; ^{1}H NMR (300 MHz, $CDCl_3$, complex, only selected signals given) δ 3.49, 3.50 (2s, 3H, OCH_3), 2.24–2.05 (m, 12 H, OAc, NHAc). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 23.76, 23.08, 22.28, 22.19 (4s, 4 R*P*O(OR)$_2$. [HR-ESI-MS] Calcd for $[C_{29}H_{36}NO_{13}PNa]^+$ 660.1816. Found 660.1777.

Ammonium *O*-(methyl β-D-galactopyranoside-3-yl) (1-(4-acetamido)phenyl-hydroxymethyl)) phosphonate (43)

Compound **42** was debenzylated and deacetylated as described for **36**, **38**, and **40** (yield 81%), purified by gel permeation chromatography (Biogel P4, 0.1 M NH_4HCO_3 buffer), and lyophilized.^{1}H NMR (300 MHz, D_2O) δ 7.24–7.44 (m, 4H, C_6H_4), 4.88–4.40 (1H, C*H*OH, below water signal), 4.28, 4.26 (2d, 1H, $J = 7.9$ Hz, H-1), 4.15–4.10 (m, 1H, H-3), 3.90, 3.82 (2d, 1H, H-4), 3.72–3.51 (m, 4H, H-2, H-5, H-6, H-6′), 3.47 (s, 3H, OCH_3), 2.05 (s, 3H, NHAc). ^{31}P NMR (121.4 MHz, D_2O) δ 19.0–18.5 (br s, R*P*O_2^-(OR)). [HR-ESI-MS] Calcd for $[C_{16}H_{24}NO_{10}PNa]^+$ 444.1041. Found 444.1030.

O-Benzyl *O*-(methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) (phenylmethyl) phosphonate (44)

38 (30 mg, 0.06 mmol) was dissolved in dry DCM (1 mL). DBU (9.6 μL, 0.06 mmol) and BnBr (7.5 μL, 0.06 mmol) were added and the mixture was stirred for 1 day under nitrogen atmosphere at rt. The reaction mixture was diluted with DCM (10 mL), washed with presaturated ammonium chloride solution (2 × 5 mL), dried with $MgSO_4$, filtered, and evaporated. Purification by flash chromatography (Tol:EtOAc = 1:1) yielded diastereomeric phosphonates **44** (13.3 mg, 37%, mixture). TLC (EtOAc:Tol 2:1): $R_f = 0.42$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.23 (m, 10H, C_6H_5), 5.43–5.39 (m, 1H, H-4), 5.20–5.14 (m, 1H, H-2), 4.96–4.79 (m, 4H, 2OCH_2Ph), 4.60–4.45 (m, 1H, H-3), 4.33–4.28 (m, 1H, H-1), 4.18–4.07 (m, 2H, H-6, H-6′), 3.86–3.74 (m, 1H, H-5), 3.50, 3.49 (2s, 3H, 2 OCH_3), 3.21–3.00 (2dd, 2H, 2 CH_2P), 2.09–1.80 (m, 9H, 3 OAc). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 28.86, 28.72 (2s, 1P, R*P*O(OR)$_2$). [EI-MS] Calcd for $[C_{27}H_{33}O_{11}PNa]^+$ 587.51. Found 587.34.

Ammonium *O*-(methyl β-D-galactopyranoside-3-yl) (phenylmethyl) phosphonate (45)

44 was debenzylated and deacetylated under the standard conditions described above. Purification by gel permeation chromatography (Biogel P4,

0.1 M NH_4HCO_3 buffer) yielded **45** (38%). ^{1}H NMR (300 MHz, D_2O) δ 7.25–7.23 (m, 5H, C_6H_5), 4.23 (d, 1H, $J_{1-2} = 7.9$ Hz, Hz, H-1), 3.95 (ddd, 1H, H-3), 3.72 (d, 1H, $J = 3.0$ Hz, H-4), 3.66–3.47 (m, 4H, H-2, H-5, H-6, H-6′), 3.45 (s, 3H, OCH_3), 2.99–2.85 (m, 2H, 2 CH_2P); ^{31}P NMR (121.4 MHz, D_2O) δ 24.16 (s, RPO_2^-(OR)). [HR-ESI-MS] Calcd for $[C_{14}H_{21}O_8PNa]^+$ 371.0866. Found 371.0866.

O-Benzyl *O*-(methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside-3-yl) (1-(4-acetamidophenyl)methyl) phosphonate (46)

46 was synthesized by benzylation of phosphonate **38** with one equivalent of p-acetamidobenzyl bromide as described for **44.** Following flash chromatography (EtOAc:Tol 2:1), **46** was obtained as a mixture of diastereomers in 23% yield. TLC (EtOAc:Tol 2:1): $R_f = 0.11$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.19 (m, 9H, C_6H_5, C_6H_4), 5.40, 5.26 (2d, 1H, H-4), 5.15 (dd, 1H, H-2), 4.97–4.78 (m, 2H, OCH_2Ph), 4.57–4.42 (m, 1H, H-3), 4.31, 4.27 (2d, 1H, H-1), 4.09–3.91 (m, 2H, H-6, H-6′), 4.31, 4.27 (2m, 1H, H-5), 3.48 (s, 3H, OCH_3), 3.16–2.97 (2dd, 2H, 2CH_2P), 2.17–2.04 (m, 12H, 3 OAc, NHAc). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 28.82 (br.s, 1P, R$PO(OR)_2$). [EI-MS] Calcd for $[C_{29}H_{36}NO_{12}PNa]^+$ 644.56. Found 644.36.

Ammonium *O*-(methyl β-D-galactopyranoside-3-yl) (1-(4-acetamidophenyl)methyl) phosphonate (47)

46 was debenzylated and deacetylated under the standard conditions described above. Purification by gel permeation chromatography (Biogel P4, 0.1 M NH_4HCO_3 buffer) yielded **47** (40%). ^{1}H NMR (300 MHz, D_2O) δ 7.25–7.20 (m, 4H, C_6H_4), 4.24 (d, 1H, $J_{1-2} = 7.9$ Hz, H-1), 3.96 (ddd, 1H, H-3), 3.71 (d, 1H, H-4), 3.66–3.48 (m, 4H, H-2, H-5, H-6, H-6′), 3.45 (s, 3H, OCH_3), 2.99–2.79 (2dd, 2H, 2 CH_2P); ^{31}P NMR (121.4 MHz, D_2O) δ 24.04, 23.20 (2 br. s, RPO_2^-(OR)). [HR-ESI-MS] Calcd for $[C_{16}H_{24}NO_9PNa]^+$ 428.1091. Found 428.1080.

Methyl 3-*O*-allyl-4,6-*O*-isopropylidene-β-D-galactopyranoside (48)

Methyl β-D-galactopyranoside (5.0 g, 26 mmol) and dibutyltin oxide (6.4 g) were dissolved in dry toluene (200 mL). The mixture was refluxed at 60°C for 24 h with a Dean-Starck apparatus. The solution was cooled to rt and the solvent was evaporated. The crude mixture was dissolved in dry toluene (100 mL), TBAI (9.5 g, 26 mmol) and allyl bromide (2.23 mL, 25.7 mmol) were added, and the mixture was heated to 70°C and stirred for further 5 h. The

solvent was evaporated in vacuo, the crude mixture was taken up in ethyl acetate, and the salts were removed by filtration. The organic layer was evaporated in vacuo and purified by flash chromatography (EtOAc:MeOH 5:1) to give the 3-O-allyl derivative (4.40 g, 73%) as a yellow syrup. The analytical data correspond to those reported.[33] Five hundred milligrams (2.13 mmol) of the 3-O-allyl derivative were dissolved in 2,2-dimethoxypropane (3 mL) and *p*-TsOH (50 mg) was added. The reaction was stirred at rt overnight and then quenched with saturated $NaHCO_3^-$ solution. The mixture was washed with DCM and water and the organic phases were dried over $MgSO_4$. The syrup was purified by flash chromatography (EtOAc:Tol 10:1) and afforded **48** (330 mg, 57%). TLC (EtOAc:Tol 10:1): $R_f = 0.3$; $[\alpha]_D^{20} = +39.7^\circ$ (c = 1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.95 (m, 1H, Hb), 5.29 (dd, 2H, $J_{c\text{-}c'} = 17.2$ Hz, Hc, c′), 4.23–4.08 (m, 4H, H-a, H-a′, H-4, H-1), 3.97 (m, 2H, $J_{5-6} = 6.4$, $J_{6-6'} = 11.6$ Hz, H-6), 3.86 (dd, 1H, $J_{5-6'} = 4.8$, $J_{6-6'} = 11.6$ Hz, H-6′), 3.72 (m, 1H, H-2), 3.56 (s, 3H, OMe), 3.52 (m, 1H, H-5), 3.37 (dd, 1H, $J_{2-3} = 9.6$, $J_{3-4} = 3.0$ Hz, H-3), 1.47, 1.46 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.1 (C-b), 117.8 (C-c), 108.3 ($C(CH_3)_2$), 103.7 (C-1), 80.0 (C-3), 71.1 (C-a), 70.9 (C-2), 69.7 (C-5), 67.0 (C-4), 62.8 (C-6), 57.3 (OCH_3), 30.9, 29.1 ($C(CH_3)_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{13}H_{22}O_6 + K)^+$ 313.1. Found 312.8.

3-*O*-Allyl-4,6-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-galactopyranoside (49)

Benzylidene galactose[25,26] was converted into **8** as described above. Compound **8** (200 mg, 0.649 mmol) was dissolved in DCM (12 mL). Allyl bromide (82 μL, 0.97 mmol) and silver oxide (1.1 g, 4.9 mmol) were added and the suspension was cooled to 0°C. TBAI (177 mg, 0.480 mmol) was added and the mixture was stirred in the dark for 24 gdh. The reaction was quenched by addition of 5 mL EtOH and filtered. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (EtOAc:Tol 1:2) to give **49** (160 mg, 71%) as a colorless syrup. TLC (EtOAc:Tol 1:2): $R_f = 0.71$, $[\alpha]_D^{20} = -6.6$ (c = 1, $CDCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.53–7.37 (m, 5H, C_6H_5), 5.90 (m, 1H, Hb), 5.76 (s, 1H, C*H*Ph), 5.63 (d, 1H, $J_{1-2} = 4.8$ Hz, H-1), 5.26 (dd, 1H, $J_{c\text{-}c'} = 16.8$ Hz, H-c), 5.15 (dd, 1H, H-c′), 4.64 (dd, 1H, $J_{3-4} = 8.4$, $J_{2-3} = 2.4$ Hz, H-3), 4.42 (dd, 1H, H-2), 4.35 (dd, 1H, $J_{4-5} = 1.8$ Hz, H-4), 4.09 (m, 1H, H-5), 4.03 (m, 2H, Ha,a′), 3.70–3.66 (m, 2H, H-6,6′), 1.57, 1.35 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.3 (C-b), 134.6 (*C*-Ph), 129.9–126.4 (C_6H_5), 117.2 (C-c), 108.1 ($C(CH_3)_2$), 103.8 (*C*HPh), 96.4 (C-1), 72.3 (C-a), 71.8 (C-3), 71.5 (C-4), 70.0 (C-2), 68.7 (C-6), 66.7 (C-5), 26.04, 24.9 ($C(CH_3)_2$). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{19}H_{24}O_6 + Na)^+$ 371.1. Found 371.6. Calcd for $(C_{19}H_{24}O_6 + K)^+$ 387.1. Found 387.5.

Methyl 3-*O*-chloroacetyl-4,6-*O*-benzylidene-β-D-galactopyranoside (50)

Methyl 4,6-O-benzylidene-β-D-galactose (4.76 g, 16.0 mmol), synthesized according to published procedures,[34] was dissolved in 200 mL of dry acetonitrile (200 mL). The solution was cooled to -15°C under an atmosphere of dry argon, and pyridine (1.49 mL, 18 mmol) and chloroacetyl chloride (1.39 mL, 18 mmol) were added with stirring. The solution was allowed to warm to rt overnight and the solvent was evaporated in vacuo. Flash chromatography of the crude product (EtOAc:Tol 5:1 $\rightarrow$ 10:1) yielded **50** (2.1 g, 37%) as a colorless powder. TLC (EtOAc:Tol 5:1): $R_f = 0.50$; $[\alpha]_D^{20} = +56.3$ (c = 1, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49–7.26 (m, 5H, C_6H_5), 5.51 (s, 1H, C*H*Ph), 4.93 (dd, 1H, $J_{2-3} = 10.2$, $J_{3-4} = 3.7$ Hz, H-3), 4.44 (d, 1H, H-4), 4.36 (bd, 1H, $J_{6-6'} = 12.5$ Hz, H-6), 4.29 (d, 1H, $J_{1-2} = 7.8$ Hz, H-1), 4.15 (2d, 2H, $J = 15.3$ Hz, CH_2Cl), 4.09 (dd, 1H, $J_{5-6'} = 1.8$ Hz, H-6′), 4.03 (dd, 1H, H-2), 3.59 (s, 3H, OMe), 3.53 (bs, 1H, H-5); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.3 (O*C*H$_2$Cl), 137.4 (*C*-Ph), 129.0–126.2 (C_6H_5), 103.9 (C-1), 101.0 (*C*HPh), 75.3 (C-3), 73.1 (C-4), 68.9 (C-6), 68.4 (C-2), 67.0 (*C*H$_2$Cl), 66.3 (C-5), 57.2 (OMe). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{16}H_{19}ClO_7 + Na)^+$ 381.1. Found 381.1.

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranoside (51)

50 (1.96 g, 5.47 mmol) was dissolved in dry DCM (20 mL) and pyridine (12 mL) and benzoyl chloride (0.99 mL, 11 mmol) were added at 0°C. After 1 h the reaction was complete and was quenched with saturated $NaHCO_3^-$ solution. The organic phase was separated and washed with water, dried over $MgSO_4$, and evaporated. Purification by flash chromatography (Tol:EtOAc 5:1) afforded **52** (2.03 g, 80%) as a colorless foam. TLC (EtOAc:Tol 1:5): $R_f = 0.61$; $[\alpha]_D^{20} = +26.0$ (c = 1, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01–7.42 (m, 10H, 2 C_6H_5), 5.68 (dd, 1H, $J_{1-2} = 7.8$ Hz, $J_{2-3} = 10.5$ Hz, H-2), 5.54 (s, 1H, C*H*Ph), 5.23 (dd, 1H, $J_{3-4} = 3.8$ Hz, H-3), 4.62 (d, 1H, H-1), 4.48 (bd, 1H, H-4), 4.41 (bd, 1H, $J_{6-6'} = 12.4$ Hz, H-6), 4.13 (bd, 1H, H-6′), 4.03 (d, 1H, $J = 15.3$ Hz, CH_2Cl), 3.96 (d, 1H, $J = 15.3$ Hz, CH_2Cl), 3.63 (bs, 1H, H-5), 3.53 (s, 3H, OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.3 (O*C*H$_2$Cl), 133.2–126.4 (C_6H_5), 101.9 (C-1), 101.1 (*C*HPh), 73.7 (C-3), 73.1 (C-4), 68.8 (C-6), 68.7 (C-2), 66.3 (C-5), 56.4 (OMe), 40.5 (*C*H$_2$Cl). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{23}H_{28}ClO_8 + Na)^+$ 485.1. Found 485.1. Calcd for $(C_{23}H_{28}ClO_8 + K)^+$ 501.1. Found 501.1.

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside (52)

51 (2.0 g, 4.3 mmol) was dissolved in dry DMF (100 mL) and hydrazinium acetate (580 mg, 6.48 mmol) was added. After 3 h the reaction was complete,

EtOAc was added, and the organic phase was washed with water and saturated $NaCl^-$ solution. The organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (Tol:EtOAc 2:1) gave **51** (900 mg, 55%) as a colorless powder. TLC (EtOAc:Tol 1:2): $R_f = 0.26$; $[\alpha]_D^{20} = +9.8$ (c = 1, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01–7.38 (m, 10H, C_6H_5), 5.57 (s, 1H, C*H*Ph), 5.35 (bt, 1H, $J_{1-2} = 8.4$ Hz, H-2), 4.53 (d, 1H, H-1), 4.39 (bd, 1H, $J_{6-6'} = 12.0$ Hz, H-6), 4.26 (dd, 1H, $J_{3-4} = 3.8$, $J_{4-5} = 1.1$ Hz, H-4), 4.11 (bd, 1H, H-6′), 3.89 (bd, 1H, $J_{2-3} = 9.7$ Hz, H-3), 3.56 (bs, 1H, H-5), 3.52 (s, 3H, OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3 (COC_6H_5), 129.9–126.5 (C_6H_5), 101.8 (C-1), 101.7 (*C*HPh), 75.9 (C-4), 72.8 (C-2), 72.1 (C-3), 69.1 (C-6), 66.7 (C-5), 56.8 (OMe). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{21}H_{22}O_7 + Na)^+$ 409.1. Found 409.5. Calcd for $(C_{21}H_{22}O_7 + K)^+$ 425.5. Found 425.5.

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-gulopyranoside (53)

52 (850 mg, 2.20 mmol) was dissolved in dry DCM (15 mL), and dry pyridine (0.31 mL, 3.8 mmol) and triflic anhydride (0.58 mL, 3.5 mmol) were added dropwise via canula at -20°C. After 2 h the reaction was complete, dry DCM (40 mL) was added, the reaction was quenched with saturated $NaHCO_3^-$ solution, and dried over $MgSO_4$. The solvent was evaporated and the crude product was dissolved in dry acetonitrile (15 mL) without further purification.

Tetrabutylammonium nitrite (1.7 g, 5.9 mmol) was added and the reaction was stirred at rt overnight. The solvent was removed in vacuo and the crude product was extracted with H_2O/EtOAc. The organic phases were dried over $MgSO_4$, the solvent was evaporated, and the product was purified via flash chromatography (EtOAc:Tol 1:1) to give **53** (254 mg, 30%) as a yellow foam. TLC (EtOAc:Tol 1:1): $R_f = 0.71$; $[\alpha]_D^{20} = -1.2$ (c = 1, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01–7.34 (m, 10H, C_6H_5), 5.57 (s, 1H, C*H*Ph), 5.37 (dd, 1H, $J_{1-2} = 8.4$, $J_{2-3} = 3.2$ Hz, H-2), 4.97 (d, 1H, H-1), 4.38 (m, 2H, H-3, H-6 hidden under H-3), 4.12 (m, 2H, H6′, H-4), 3.90 (bs, 1H, H-5), 3.53 (s, 3H, OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.6 (COC_6H_5), 133.3–126.4 (C_6H_5), 101.4 (*C*HPh), 98.9 (C-1), 76.3 (C-4), 71.0 (C-2), 69.4 (C-3), 69.2 (C-6), 65.6 (C-5), 56.5 (OMe). MALDI-MS (CHCA, THF, pos. mode) Calcd for $(C_{21}H_{22}O_7 + Na)^+$ 409.1. Found 409.4. Calcd for $(C_{21}H_{22}O_7 + K)^+$ 425.5. Found 425.4.

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