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Novel UDP-Glycal Derivatives as Transition State Analogue Inhibitors of UDP-GlcNAc 2-Epimerase

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Received September 4, 2003

The "epimerisation" of UDP-GlcNAc to ManNAc, the first step in the biosynthesis of sialic acids, is catalyzed by UDP-GlcNAc 2-epimerase. In this paper we report the synthesis of transition state based inhibitors of this enzyme. To mimic the assumed first transition state of this reaction (**TS 1**), we designed and synthesized the novel UDP-*exo*-glycal derivatives **1**−**4**. We also report herein the synthesis of **5** and **6**, the first *C*-glycosidic derivatives of 2-acetamidoglucal, and the synthesis of the ketosides **7** and **8**, which were designed as bis-substrate analogue and bis- product analogue, respectively, to mimic the second step of the reaction via the assumed second transition state **TS 2**.

Introduction

Sialic acids are located at the nonreducing end of oligosaccharide chains in vertebrate glycoconjugates. The most common sialic acid and the biosynthetic precursor for this family of 3-deoxy-2-keto-acids is *N*-acetyl neuraminic acid (Neu5Ac). Due to their terminal position in oligosaccharide chains, sialic acids play a key role in a wide range of biological functions, such as cell−cell recognition, cellular adhesion processes, virus−host recognition (for example, the recognition of influenza viruses), or protection of cells from pathogen attachment and degration. In addition, cancer cells are known to show an increased sialylation level on their glycocalix, and the metastatic potential of tumor cells has been correlated to the extent of their surface sialylation.[1−3]

The mammalian biosynthesis of neuraminic acid starts with the conversion of UDP-*N*-acetylglucosamine (UDP-GlcNAc) into *N*-acetylmannosamine (ManNAc), followed by a phosphorylation of the hydroxy group in the C-6-position. These two steps are catalyzed by the bifunctional enzyme UDP-GlcNAc 2-epimerase/ManNAc kinase.[4,5] This enzyme has been found to catalyze the rate-limiting step in this biosynthetic pathway and therefore serves as the key regulator of cell surface sialylation.[6] Point mutations of this enzyme result in the "human diseases hereditary inclusion body myopathy" (HIBM)[7] or sialuria, an inborn error of feedback inhibition.[8]

A recent mechanistic study by Tanner et al.[9] on UDP-GlcNAc 2-epimerase supports a reaction mechanism involving an *anti*-elimination of UDP to form the 2-acetamidoglucal, followed by the *syn*-addition of water (see Figure 1). Tanner et al. reported that the cleavage of the C−H bond at the C-2 position of UDP-GlcNAc is not a rate-determining step in the reaction mechanism. Furthermore, they could not observe any positional isotope exchange (PIX) using ^{18}O-labeled UDP-GlcNAc. This suggests that the elimination of UDP proceeds in a stepwise E1 mechanism with deprotonation of the formed oxocarbenium species (**TS 1**) in a fast second step to form the 2-acetamidoglucal. They could also demonstrate that the 2-acetamidoglucal serves as an alternative substrate and is converted to ManNAc by the UDP-GlcNAc 2-epimerase in a slow rate. If the reaction is run in the presence of UDP, an increased amount of ManNAc was observed. This implies that the hydration occurs while UDP is still bound to the active site of the enzyme.

Until now only some irreversible inhibitors of the UDP-GlcNAc 2-epimerase are known.[10] Ready access to efficient reversible inhibitors of this enzyme will facilitate a better understanding of the proposed mechanism and could lead to new interesting tools for studies on the influence of sialyl residues in biological systems. Potent inhibitors of the UDP-GlcNAc 2-epimerase could also serve as new lead structures for the design of inhibitors for related enzymes[11] such as glycosyltransferases.

As part of our ongoing program on the synthesis of potent transition state based glycosyltransferase in-

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10.1021/jo0353029 CCC: $27.50
Published on Web 01/10/2004

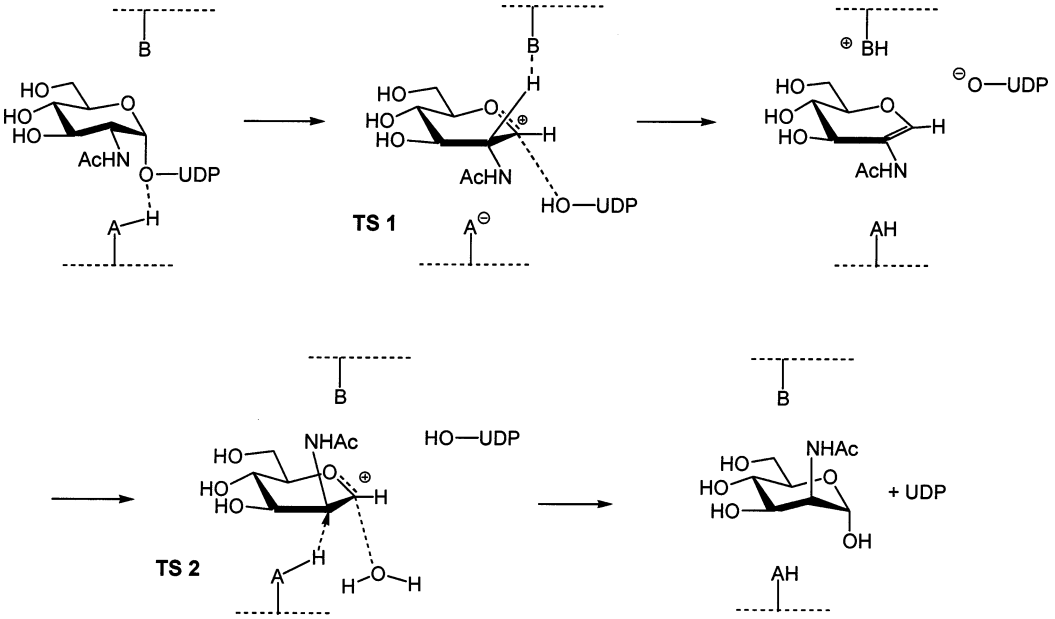
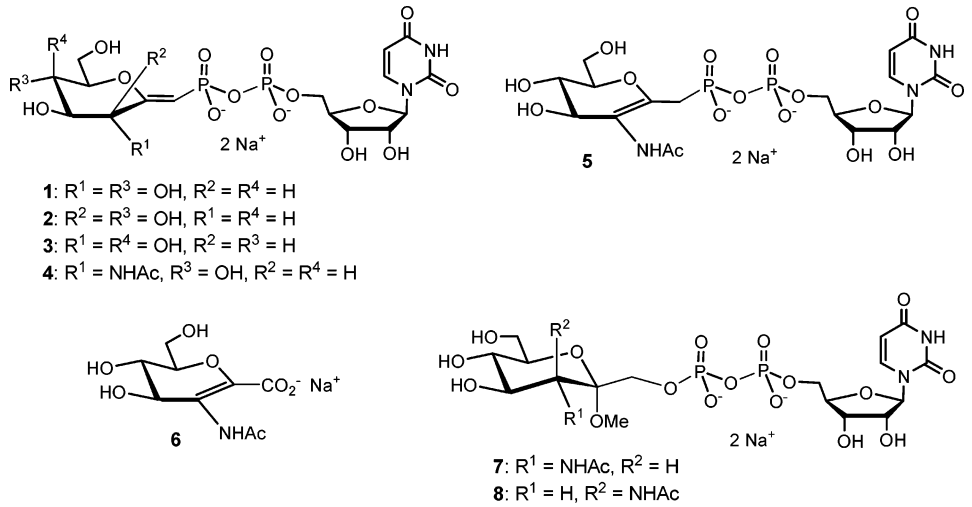


FIGURE 1. Proposed mechanism of the "epimerisation" from UDP-GlcNAc to ManNAc.

SCHEME 1. Synthesized Inhibitors 1−8



hibitors,[12−14] we designed and synthesized the *C*-glycosides **1**−**8** (see Scheme 1) as potential competitive inhibitors of the UDP-GlcNAc 2-epimerase.

Compounds **1**−**6** are designed to mimic the first transition state (**TS 1**), where the formed 2-acetamidoglucal is still close to the cleaved UDP-moiety (see Figure 1). Tanner et al.[9] reported that UDP-ManNAc was also recognized by the UDP-GlcNAc 2-epimerase as an alternative substrate. Therefore, comparison of the inhibition activity of compounds **1**−**4** could lead to further information concerning the recognition selectivity of the enzyme toward the carbohydrate moiety of the substrate, especially toward the recognition of the different sugar configurations. Compound **7** was designed as a bis-substrate analogue and compound **8** as a bis-product analogue, where the water molecule is close to or connected to the sugar molecule and the UDP moiety is still bound to the active site of the enzyme, thus potentially inhibiting the second step of the reaction via **TS 2**. The distance between the anomeric center and the UDP-part is increased in **7** and **8** by an additional methylene group. In all compounds, a *C*-glycosidic linkage replaces the labile natural glycosyl phosphate bond in order to increase the resistance to chemical and enzymatic hydrolysis.

Results and Discussion

In recent years, several preparations of substituted *exo*-glycals were reported. These methods include Ramberg−Bäcklund rearrangement of *S*-glycosides,[15,16] Wittig olefination of sugar lactones,[17] Keck reaction of glycosyl dihalides,[18] [2,3]-Wittig sigmatropic rearrangement,[19] or

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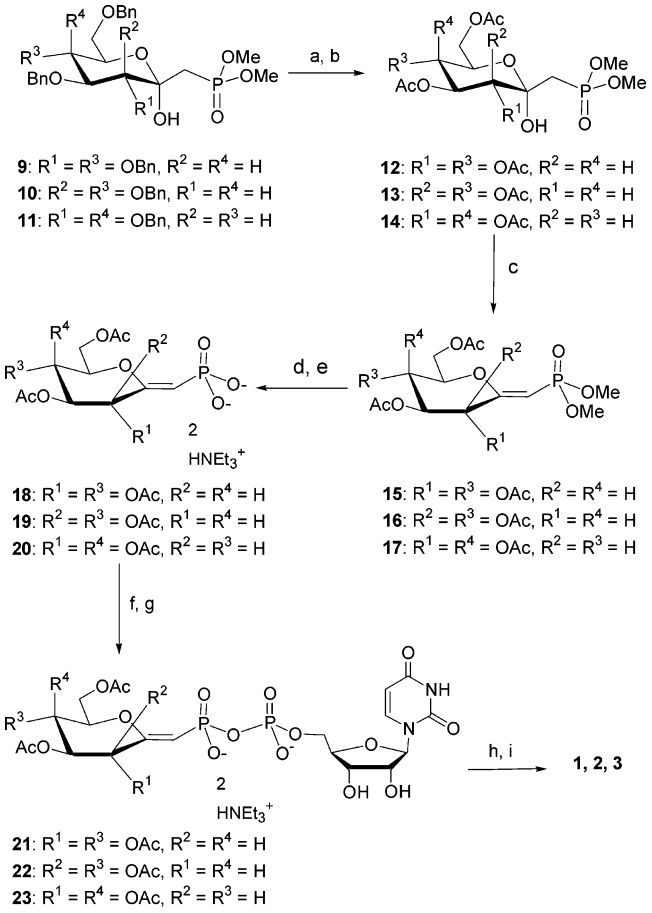
SCHEME 2[a]



[a] Reaction conditions: (a) H_2, Pd/C, MeOH; (b) Ac_2O, py, 0 °C−rt, 3 h; yield 86% (**12**), 56% (**13**), 22% (**14**); (c) $(CF_3CO)_2O$, py; yield 77% (**15**), 72% (**16**), 80% (**17**); (d) TMSBr, 2,6-lutidine, CH_2Cl_2; (e) MeOH, Et_3N; quantitative; (f) UMP-morpholidate, py, tetrazole; (g) RP18 HPLC; yield 22% (**21**), 20% (**22**), 30% (**23**); (h) MeOH/H_2O/Et_3N; (i) ion exchange (Na); yield 82% (**1**), 63% (**2**), 67% (**3**).

addition reactions to sugar lactones followed by elimination.[20−22] For the synthesis of the *exo*-glycals **1**−**3**, we used the recent method of Yang et al.[21,22] including such an addition to lactones followed by elimination (see Scheme 2). We started our synthesis with the known ketol phosphonates **9**−**11**, which were prepared by the addition of lithium dimethyl methylphosphonate to the sugar *δ*-lactones as reported by Dondoni and co-workers.[20] To avoid the problem of reduction of the generated double bond during hydrogenolysis of the benzyl protecting groups, we changed to acetyl protecting groups prior to the elimination step. Thus, the benzyl protecting groups of ketoses **9**−**11** were cleaved by hydrogenolysis followed by acetylation at reduced temperature to afford compounds **12**−**14** in good to moderate yields. Under these conditions, no acetylation of the C-2 hydroxy group was observed. For the elimination to the *exo*-glycal structures **15**−**17**, the ketoses **12**−**14** were treated with trifluoroacetic anhydride and pyridine to yield the desired *exo*-glycals **15**−**17** as single (*Z*)-isomers. This configuration is supported by the $^3J_{C,P}$-coupling constants ranging from 13.1 to 15.7 Hz, which is in good agreement with a reported $^3J_{C,P}$ *trans*-coupling of 14 Hz.[23] For the $^3J_{C,P}$ *cis*-coupling, constants of 7 Hz were reported.[24,25]

The deprotection of the methyl esters of the acid sensitive *exo*-glycal structures **15**−**17** was performed by transesterification with bromotrimethylsilane in the presence of 2,6-lutidine.[26] The resulting silyl esters were hydrolyzed in the presence of triethylamine to afford the mixed lutidinium/ triethylammonium salts **18**−**20** in quantitative yield, which could be used for the morpholidate coupling reaction without purification. The coupling reaction[27,28] was performed with the acetyl protected sugars, as recently suggested by Kosma et al.[29] After isolation by RP-18-HPLC, the protected target molecules **21**−**23** were obtained in moderate yields, which is quite usual for this procedure.[13,30,31] Deprotection with methanol/water/triethylamine (7:3:1) and ion exchange to the sodium form afforded the target compounds **1**−**3**.

For the synthesis of the 3-acetamido derivative **4**, we investigated a similar approach (see Scheme 3). Although the addition of organolithium reagents or Grignard reagents to 2-acetamidolactones is reported to be problematic,[32] the addition of lithium dimethyl methylphosphonate to the known 2-acetamidolactone **24**[33] under inverse conditions afforded the desired monoadduct **25** in acceptable yield. Hydrogenolysis followed by acetylation led to compound **26** in 75% yield. When we applied the elimination conditions according to Yang et al.[21,22] to the electron-rich benzyl protected ketose **25**, the desired *exo*-glycal **27** was formed as a single (*Z*)-isomer in 60% yield.

However, when we applied the same conditions to the elimination reaction starting from the electron poor acetylated ketose **26**, instead of the expected *exo*-glycal **29**, the very interesting *endo*-glycal **28** could be isolated after elongated reaction time in 42% yield. It has to be noted that, until now, no *C*-glycoside of an acetamidoglycal could be synthesized.

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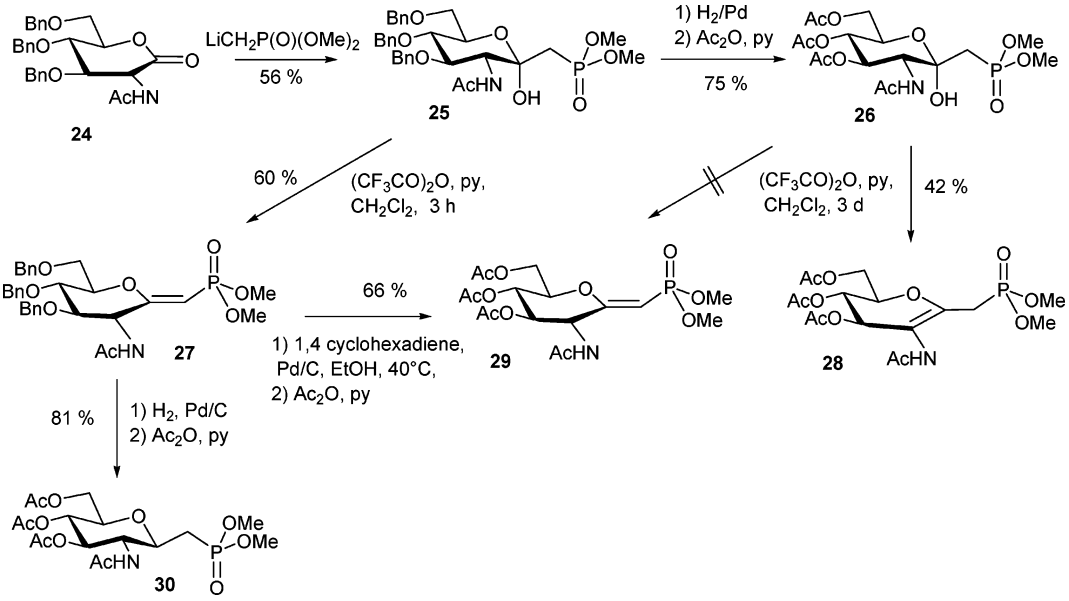
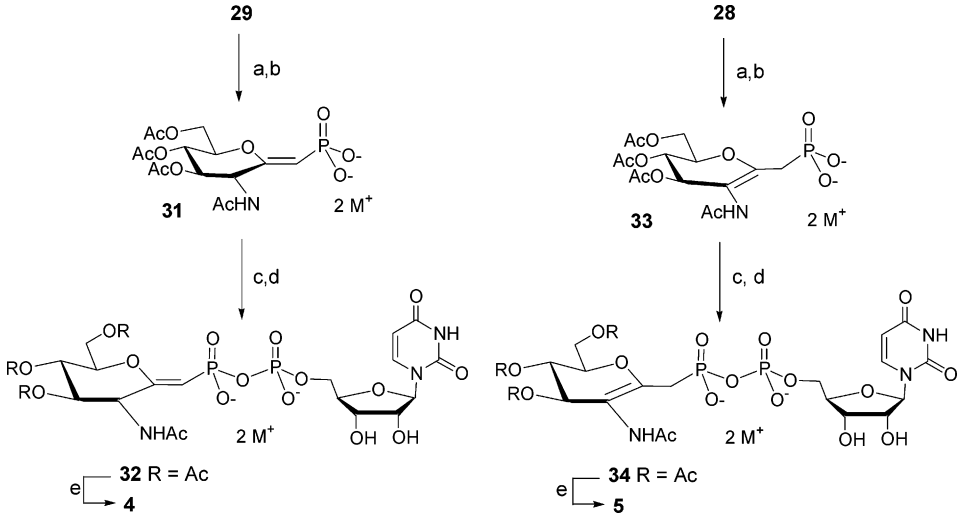
SCHEME 3. Synthesis of Glycals 28 and 29



SCHEME 4[a]



[a] Reaction conditions: (a) TMSBr, 2,6-lutidine, CH_2Cl_2; (b) MeOH, Et_3N, (quantitative); (c) UMP-morpholidate, tetrazole, py; (d) RP18 HPLC; yield 18% (**32**), 18% (**34**); (e) MeOH/H_2O/Et_3N (7:3:1); yield 50% (**4**), 39% (**5**).

To reach target compound **4**, it was now necessary to remove the benzyl protecting groups in the presence of the double bond. The use of standard hydrogenolysis conditions (Pd/C, H_2) resulted in a complete reduction of the double bond and after acetylation afforded the heptitol **30** in good yield. Starting from the *exo*-glycal **27** we succeeded in removing the benzyl protecting groups without reduction of the double bond by using hydrogen transfer conditions[34] with 1,4-cyclohexadiene as hydrogen donor. After acetylation the desired acetyl protected *exo*-glycal **29** was obtained in 66% yield.

Compounds **29** and **28** were now transformed to the final products **4** and **5** by the standard procedure (see Scheme 4). Transesterification and hydrolysis led to the phosphonates **31** and **33**, which were coupled with UMP-morpholidate to afford the protected compounds **32** and **34**, respectively. After purification, deprotection, and ion exchange, the target molecules **4** and **5** were isolated in 40−50% yield.

For access to analogues **7** and **8** of the second transition state, the ketosides **48** and **45** had to be synthesized first. The synthesis of the mannosamine derivative **45** starts with our recently published method;[35] C-2 elongation of the commercially available 2,3,5-tri-*O*-benzyl-arabinose leads to the heptulosonic acid derivative **35** (see Scheme 5).

The 3-azido-3-deoxy-2-*O*-methyl derivative **43** was prepared by either one of two procedures: (1) After ring closure of **35** to the *S*-ethyl glycoside **36**, the azide function was introduced in the 3-position to afford compound **38**. After oxidation to the sulfoxide **39** (diastereomer ratio R:S, 1:4; determination of the absolute con-

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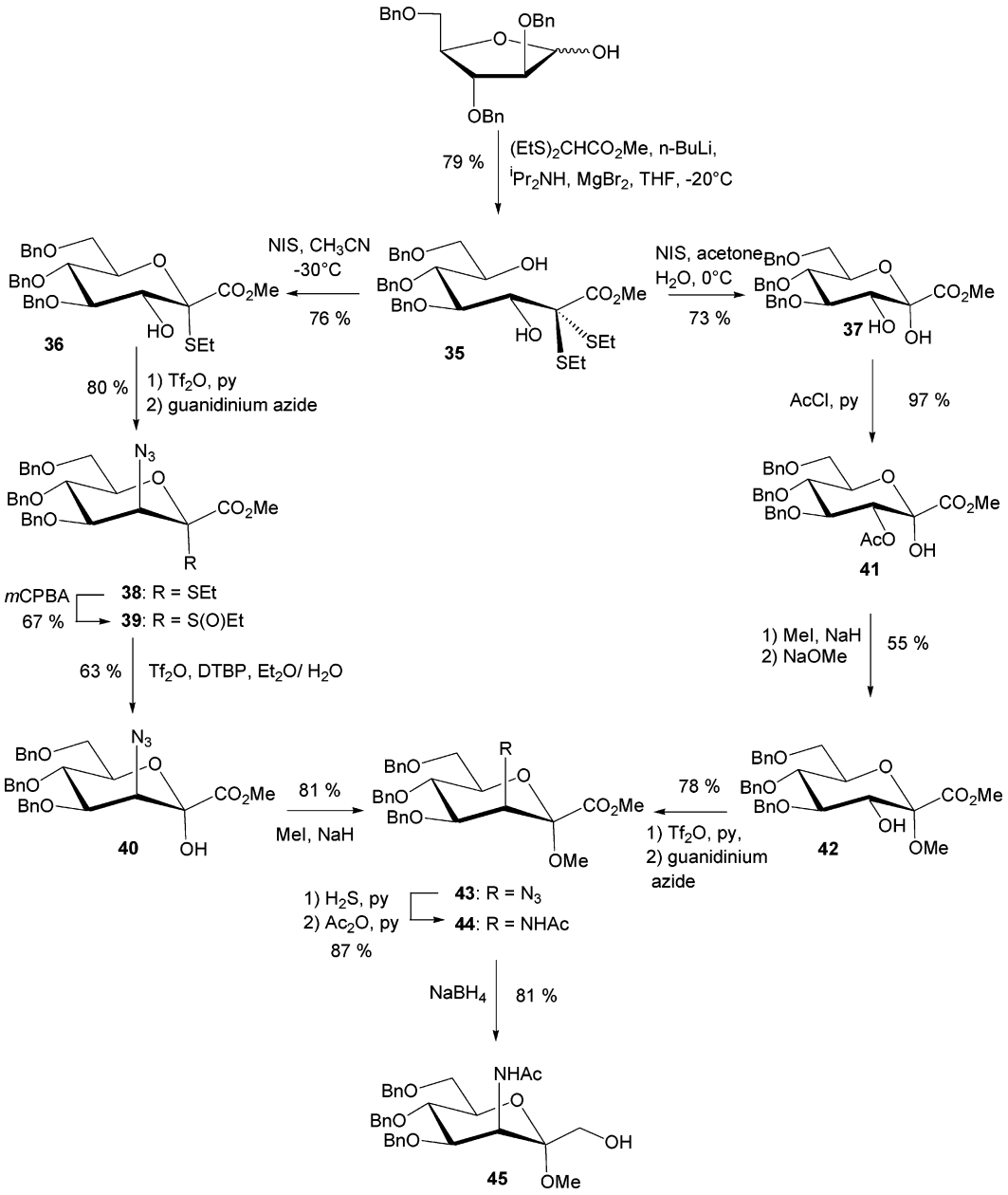
SCHEME 5. Synthesis of Ketoside 45



figuration by a method of Khiar[36]), the compound could be easily hydrolyzed with trifluoromethansulfonic anhydride and di-*tert*-butyl pyridine (DTBP) in the presence of water to yield the methyl heptulosonate **40**, which was methylated to afford compound **43** in 81% yield. (2) Ring closure and cleavage of the second *S*-ethyl group in **35** led to the methyl heptulosonate acid **37**, which could be acetylated selectively in the 3-position to afford compound **41**.[35] After methylation of the 2-hydroxy group and cleavage of the acetyl protecting group, the azide function was introduced in the 3-position to yield the desired compound **43**.

Transformation of the azide function to the acetamido group (→**44**), followed by reduction of the methyl ester to the alcohol, led to the desired target molecule **45**. The configuration of C-2 was confirmed by observing an NOE correlation between OMe and 4-H.

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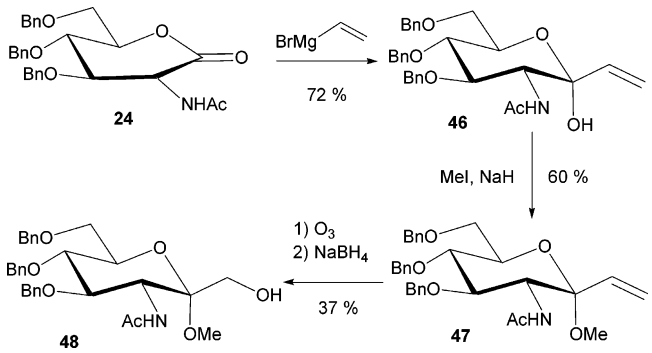
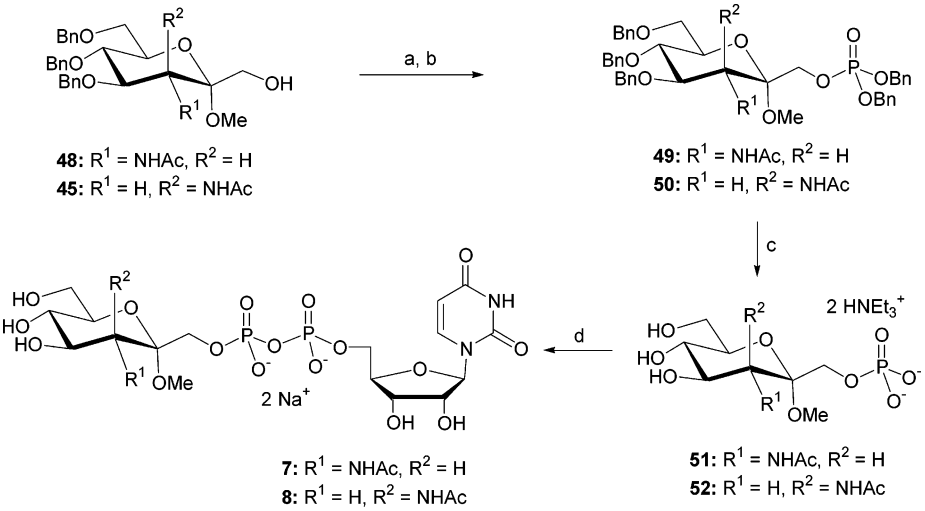
SCHEME 6. Synthesis of Ketoside 48



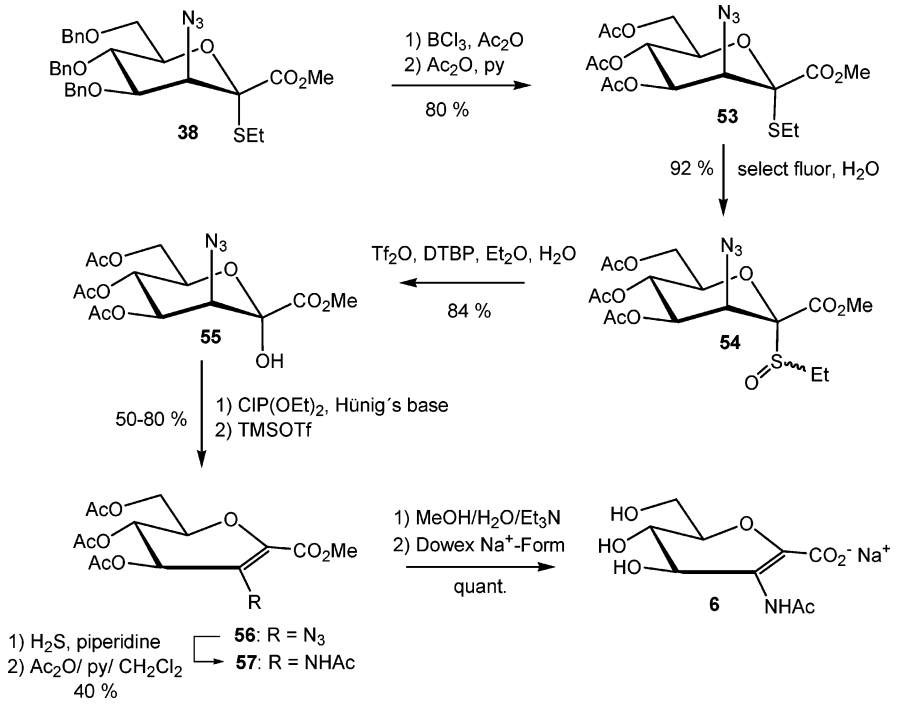
The glucosamine derivative **48** was obtained by a different approach (see Scheme 6). Vinyl Grignard addition to the lactone **24** led to the ketose **46** in 72% yield. After methylation of the 3-hydroxy group, oxidative

SCHEME 7[a]



[a] Reaction conditions: (a) $^{i}Pr_2NP(OBn)_2$, tetrazole; (b) $^{t}BuOOH$; yield 41% (**49**), 74% (**50**); (c) H_2, Pd/C, MeOH; Et_3N; quantitative; (d) UMP-morpholidate, tetrazole, py, 3 d; RP18 HPLC; ion exchange Na^+-form; yield 14% (**7**), 13% (**8**).

SCHEME 8. Synthesis of Acetamidoglucal Derivative 6



cleavage of the double bound by ozonolysis and reduction of the generated aldehyde the desired ketoside **48** was obtained in moderate yield.

The free hydroxy groups in **48** and **45** were phosphorylated, using the phosphitamide method,[37] to yield the dibenzyl phosphates **49** and **50**, respectively (see Scheme 7). After hydrogenolysis, the resulting free phosphates **51** and **52** were coupled with UMP-morpholidate to afford the target molecules **7** and **8**. The configuration at C-2 in compound **7** was confirmed by observing an NOE correlation between OMe and 6-H. (The C-2 configuration in compound **8** was confirmed on its precursor **45**.)

Encouraged by the successful synthesis of the first acetamidoglucal *C*-glycoside **28**, we also wanted to synthesize the related derivative **6**, which should be accessible from the ketose **38** (see Scheme 8).

Cleavage of the benzyl protecting groups with BCl_3 followed by acetylation led to compound **53** in good yield. Because this *S*-ethyl glycoside **53** is a poor donor, it was oxidized to the sulfoxide **54** (diastereomer ratio R:S, 2:3), which could be easily hydrolyzed by trifluoromethansulfonic anhydride and DTBP in the presence of water to afford the heptulosonic acid **55** in 80% yield. For the elimination to the glycal **56**, ketose **55** was treated with diethyl chlorophosphite and Hünig's base to get a phosphite as a glycosyl donor,[38] which on treatment with catalytic amounts of TMSOTf in the absence of an acceptor afforded the desired elimination product **56**. Attempts failed to generate glycal **56** directly from

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sulfoxide **54** by heating in benzene to induce sulfenic acid elimination.[39] The azide function in **56** was converted into the acetamido group and the produced glycal **57** was deprotected with methanol/water/triethylamine (7:3:1) to yield the final compound **6**.

All synthesized target molecules **1**−**8** were tested as inhibitors of the UDP-GlcNAc 2-epimerase. Under the employed conditions,[40] compounds **1**, **2** and **4**−**7** showed inhibition in the range from 40 to 60%, which indicates that these molecules have an affinity similar to the enzyme as that of the natural substrate [K_M(UDP-GlcNAc) = 11 μM],[4] under the assumption of a competitive mechanism, whereas compounds **3** and **8** only showed inhibition around 20%. The details of the biological evaluations will be published elsewhere.

Experimental Section

Solvents were purified according to standard procedures. NMR measurements were recorded at 22 °C on a Bruker AC 250 Cryospec, Joel JNM-GX 400, or Bruker DRX 600 spectrometer. Tetramethylsilane (TMS) or the resonance of the deuterated solvent was used as an internal standard; solvents: $CDCl_3$, δ = 7.24; D_2O, δ = 4.63; d_6-DMSO, δ = 2.49. For ^{31}P NMR, phosphoric acid was used as an external standard; ^{31}P NMR spectra were broadband ^{1}H-decoupled. MALDI-mass spectra were recorded on a Kratos Kompact Maldi 2, and 2,5-dihydroxybenzoic acid (DHB) or 6-aza-2-thiothymine (ATT) was used as the matrix. FAB mass spectra were measured on a Finnigan MAT312/AMD 5000 spectrometer. Thin-layer chromatography was performed on Merck silica gel plastic plates 60 F_{254} or Merck glass plates RP-18; compounds were visualized by treatment with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL). Flash chromatography was performed on J. T. Baker silica gel 60 (40−63 μm) at a pressure of 0.3 bar. Preparative HPLC separations were performed on an Autochrom System with a Shimadzu LC8A preparative pump and a Rainin Dynamax UV 1 Detector at 260 nm. The column used was a Lichrosorb RP-18, 7 μm, 250 × 16 mm^2 (Knauer, Germany).

General Procedure for the Morpholidate Coupling Method (GP1). The triethylammonium salt of the phosphate/phosphonate (ca. 30−100 mg) was coevaporated several times with dry pyridine. 4-Morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphomorpholidate (1.1−1.7 equiv) was added, and the mixture was again coevaporated twice with dry pyridine. The resulting residue was taken up in dry pyridine (1−2 mL), dry 1-*H*-tetrazole (1.5−3 equiv) was added, and the solution was stirred under argon for 3 days at room temperature. The reaction mixture was diluted with water (5 mL), and Hünigs base (0.1 mL) was added. The solution was concentrated under reduced pressure and coevaporated several times with water/Hünigs base (5 mL/ 0.1 mL). The resulting residue was purified by HPLC (mobile phase: 0.05 M triethylammonium bicarbonate (TEAB) + 0.5−10% CH_3CN).

The resulting triethylammonium salt was transformed into the sodium salt by ion exchange chromatography (Amberlite IR-120 Na^+-form or Dowex 50WXZ Na^+-form). The crude sodium salt was dissolved in a few drops of water, and ethanol (10 mL) was added to precipitate the product as a white powder.

Disodium Uridine 5′-[(*Z*)-2,6-Anhydro-1-deoxy-D-*gluco*-hept-1-enitol-1-yl phosphono] Phosphate (1). A solution of **21** (20 mg, 21 μmol) in a mixture of MeOH/H_2O/Et_3N (7:3:1, 2 mL) was stirred at room temperature for 2 h (TLC monitoring: $CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N, R_f = 0.25). After concentration under reduced pressure, lyophilization from water gave the Et_3NH-salt of **1** (16 mg, 21 μmol, quantitative) as a white solid. After ion exchange (Amberlite IR-120 Na^+-form), the resulting crude sodium salt was dissolved in water (1 drop) and the addition of ethanol (10 mL) caused **1** (10.5 mg, 17 μmol, 82%) to precipitate as a white powder. Et_3NH-salt: ^{1}H NMR (600 MHz, D_2O) δ = 1.15 (t, 18 H, NCH_2CH_3), 3.08 (q, 12 H, NCH_2CH_3), 3.40 (m, 1 H, 4″-H), 3.52 (m, 2 H, 5″-H, 6″-H), 3.68 (m, 1 H, 7a″-H), 3.85 (m, 2 H, 7b″-H, 3″-H), 4.08 (m, 2-H, 5a,b′-H), 4.15 (m, 1 H, 4′-H), 4.25 (m, 2 H, 2′-H, 3′-H), 5.38 (d, $J_{1'',P}$ = 11.2 Hz, 1 H, 1″-H), 5.85 (m, 2 H, 5-H, 1′-H), 7.85 (d, $J_{6,5}$ = 8.0 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O) δ = 7.7 (6 C, NCH_2CH_3), 46.1 (6 C, NCH_2CH_3), 59.6 (1 C, 7″-C), 64.0 (1 C, 5′-C), 67.9 (1 C, 5″-C), 69.0, 73.5 (2 C, 2′-C, 3′-C), 70.4 (d, $J_{C,P}$ = 13 Hz, 1 C, 3″-C), 75.3 (1 C, 4″-C), 80.0 (1 C, 6″-C), 82.7 (1 C, 4′-C), 87.8 (1 C, 1′-C), 99.3 (d, $J_{C,P}$ = 180 Hz, 1 C, 1″-C), 102.1 (1 C, 5-C), 141.1 (1 C, 6-C), 151.2 (1 C, 2″-C), 163.9, 165.7 (2 C, 2-C, 4-C); ^{31}P NMR (243 MHz, D_2O) δ = −13.0 (bd, 1 P, PO_4), 1.3 (bd, 1 P, PO_3); MALDI-MS (negative mode, ATT) m/z = 561.0 [M − 2 $HNEt_3^+$ + H^+]$^-$; $C_{16}H_{22}O_{16}N_2P_2$ × 2 $C_6H_{16}N$ (764.7). Na-salt: ^{1}H NMR (250 MHz, D_2O) δ = 3.35 (m, 1 H, 4″-H), 3.48 (m, 2 H, 5″-H, 6″-H), 3.65 (dd, $J_{7a,b''}$ = 12.5 Hz, $J_{7a'',6}$ = 3.0 Hz, 1 H, 7a″-H), 3.81 (m, 2 H, 7b″-H, 3″-H), 4.03 (m, 2-H, 5a,b′-H), 4.09 (m, 1 H, 4′-H), 4.20 (m, 2 H, 2′-H, 3′-H), 5.33 (dd, $J_{1'',P}$ = 11.2 Hz, $J_{1'',3''}$ = 1.8 Hz,1 H, 1″-H), 5.79 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 5-H), 5.81 (m, 1 H, 1′-H), 7.78 (d, $J_{6,5}$ = 8.1 Hz, 1 H, 6-H); $C_{16}H_{22}N_2O_{16}P_2Na_2$ (606.3).

Disodium Uridine 5′-[(*Z*)-2,6-Anhydro-1-deoxy-D-*manno*-hept-1-enitol-1-yl phosphono] Phosphate (2). A solution of **22** (29 mg, 31 μmol) in a mixture of MeOH/H_2O/Et_3N (7:3:1, 2 mL) was stirred at room temperature for 2 h (TLC monitoring: $CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N, R_f = 0.3). After concentration under reduced pressure and after ion exchange (Amberlite IR-120 Na-form), the resulting crude sodium salt was dissolved in water (1 drop) and the addition of ethanol (10 mL) caused **2** (11.8 mg, 19 μmol, 63%) to precipitate as a white powder: ^{1}H NMR (600 MHz, D_2O) δ = 3.71−3.77 (m, 5 H, 4″-H, 5″-H, 6″-H, 7a,b″-H), 4.09 (m, 2 H, 5a,b′-H), 4.17 (m, 1 H, 4′-H), 4.27 (m, 2 H, 2′-H, 3′-H), 4.31 (m, 1 H, 3″-H), 5.23 (d, $J_{1'',P}$ = 11.6 Hz, 1 H, 1″-H), 5.88 (m, 2 H, 5-H, 1′-H), 7.87 (d, $J_{6,5}$ = 8.0 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O) δ = 60.2 (1 C, 7″-C), 64.1 (1 C, 5′-C), 66.5 (1 C, 5″-C), 68.9 (d, $J_{C,P}$ = 14.5 Hz, 1 C, 3″-C), 69.0, 73.3 (2 C, 2'-C, 3′-C), 72.0 (1 C, 4″-C), 80.3 (1 C, 6″-C), 82.8 (1 C, 4′-C), 87.8 (1 C, 1′-C), 100.7 (d, $J_{C,P}$ = 185 Hz, 1 C, 1″-C), 102.1 (1 C, 5-C), 141.1 (1 C, 6-C), 151.5 (1 C, 2″-C), 162.4, 166.2 (2 C, 2-C, 4-C); ^{31}P NMR (162 MHz, D_2O) δ = −11.0 (d, J = 24.3 Hz, 1 P, PO_4), 2.9 (d, J = 24.3 Hz,1 P, PO_3). MALDI-MS (negative mode, ATT) m/z = 561.8 [M − 2 Na^+ + H^+]$^-$; $C_{16}H_{22}N_2O_{16}P_2Na_2$ (606.4).

Disodium Uridine 5'-[(*Z*)- 2,6-Anhydro-1-deoxy-D-*galacto*-hept-1-enitol-1-yl phosphono] Phosphate (3). A solution of **23** (37 mg, 40 μmol) in a mixture of MeOH/H_2O/Et_3N (7:3:1, 11 mL) was stirred at room temperature for 2 h (TLC monitoring: $CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N, R_f = 0.3). After concentration under reduced pressure and after ion exchange (Amberlite IR-120 Na-form), the resulting crude sodium salt was dissolved in water (1 drop) and the addition of ethanol (10 mL) caused **3** (16 mg, 26 μmol, 67%) to precipitate as a white powder: ^{1}H NMR (600 MHz, D_2O) δ = 3.61 (m, 2 H, 4″-H, 7a″-H), 3.80 (m, 2 H, 6″-H, 7b″-H), 3.98 (m 1 H, 5″-H), 4.10 (m, 3 H, 5a,b′-H, 3″-H), 4.16 (m, 1 H, 4′-H), 4.25 (m, 2 H, 2′-H, 3′-H), 5.40 (d, $J_{1'',P}$ = 11.6 Hz, 1 H, 1″-H), 5.84 (d, $J_{5,6}$= 8.0 Hz, 1 H, 5-H), 5.86 (d, $J_{1',2'}$ = 3 Hz, 1 H, 1′-H), 7.85 (d, $J_{6,5}$ = 8.1 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O) δ = 60.7 (1 C, 7″-C), 64.2 (1 C, 5′-C), 67.9 (d, $J_{C,P}$ = 12.2 Hz, 1 C, 3″-C), 68.5 (1 C, 5″-C), 69.1, 73.2 (2 C, 2′-C, 3′-C),

(38) Schmidt, R. R.; Martin, T. J. *Tetrahedron Lett.* **1992**, *33*, 6123−6126.
(39) Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754−6755.
(40) Employed conditions for the inhibition test: substrate and inhibitor were used in the same concentration *c*(UDP-GlcNAc) = *c*(inhibitor) = 1.25 mM. For details of the procedure see ref 10.

72.4 (1 C, 4″-C), 79.6 (1 C, 6″-C), 82.8 (1 C, 4′-C), 87.8 (1 C, 1′-C), 99.4 (d, $J_{C,P}$ = 187 Hz, 1 C, 1″-C), 102.1 (1 C, 5-C), 141.1 (1 C, 6-C), 151.6 (1 C, 2″-C), 164.7, 166.1 (2 C, 2-C, 4-C); ^{31}P NMR (162 MHz, D_2O) δ = −11.1 (d, J = 24 Hz, 1 P, PO_4), 3.6 (d, J = 24 Hz,1 P, PO_3); MALDI-MS (negative mode, ATT) m/z = 561.2 [M − 2 Na^+ + H^+]$^-$; $C_{16}H_{22}N_2O_{16}P_2Na_2$ (606.4).

Disodium Uridine 5′-[(*Z*)-3-Acetamido-2,6-anhydro-1,3-dideoxy-D-*gluco*-hept-1-enitol-1-yl phosphono] Phosphate (4). A solution of **32** (8 mg, 8.6 μmol) in a mixture of MeOH/H_2O/Et_3N (7:3:1, 2 mL) was stirred at room temperature for 2.5 h (TLC monitoring: $CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N, R_f = 0.25). After concentration under reduced pressure and after ion exchange (Amberlite IR-120 Na^+-form), the resulting crude sodium salt was dissolved in water (1 drop) and the addition of ethanol (10 mL) caused **4** (2.8 mg, 4.3 μmol, 50%) to precipitate as a white powder: ^{1}H NMR (250 MHz, D_2O) δ = 1.92 (s, 3 H, Ac), 3.40 (dd, $J_{4'',3''} = J_{4'',5''}$ = 9.8 Hz, 1 H, 4″-H), 3.55 (m, 2 H, 5″-H, 6″-H), 3.69 (dd, $J_{7a,b''}$ = 12.7 Hz, $J_{7a'',6''}$ = 3.9 Hz, 1 H, 7a″-H), 3.84 (dd, $J_{7b,a''}$ = 12.7 Hz, $J_{7b'',6''}$ = 2 Hz, 1 H, 7b″-H), 4.04−4.10 (m, 3 H, 4′-H, 5a,b′-H), 4.16−4.23 (m, 3 H, 2′-H, 3′-H, 3″-H), 5.14 (dd, $J_1''_{,P}$ = 10.8 Hz, $J_{1'',3''}$ = 1.8 Hz, 1 H, 1″-H), 5.77 (d, $J_{5,6}$ = 7.8 Hz, 1 H, 5-H), 5.81 (d, $J_{1',2'}$ = 3.5 Hz, 1 H, 1'-H), 7.76 (d, $J_{6,5}$ = 7.8 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O, HMQC) δ = 54.0 (1 C, 3″-C), 60.5 (1 C, 7″-C), 65.0 (1 C, 5′-C), 69.0 (1 C, 5″-C), 69.8, 74.1 (2 C, 2′-C, 3′-C), 74.2 (1 C, 4″-C), 80.9 (1 C, 6″-C), 83.5 (1 C, 4′-C), 88.7 (1 C, 1′-C), 101.0 (d, $J_{C,P}$ = 180 Hz, 1 C, 1″-C), 103.1 (1 C, 5-C), 142.0 (1 C, 6-C); ^{31}P NMR (243 MHz, D_2O) δ = −13.1 (d, J = 25 Hz, 1 P, PO_4), 0.62 (d, J = 25 Hz,1 P, PO_3); MALDI-MS (negative mode, ATT) m/z = 602.1 [M − 2 Na^+ + H^+]$^-$; (positive mode, ATT) m/z = 648.2 [M + H]$^+$, 670.2 [M + Na]$^+$; $C_{18}H_{25}N_3O_{16}P_2Na_2$ (647.4).

Disodium Uridine 5′-(3-Acetamido-2,6-anhydro-1,3-dideoxy-d-arabino-hept-2-enitol-1-yl phosphono) Phosphate (5). A solution of **34** (19 mg, 20 μmol) in a mixture of MeOH/H2O/Et_3N (7:3:1, 2 mL) was stirred at room temperature for 2 h (TLC monitoring: $CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N, R_f = 0.25). After concentration under reduced pressure, the crude product was purified by HPLC (RP-18, 0.05 M TEAB-buffer, 0.2%-1% CH_3CN; t_R = 12.5 min). After ion exchange (Amberlite IR-120 Na-form), the resulting crude sodium salt was dissolved in water (1 drop) and the addition of ethanol (10 mL) caused **5** (5 mg, 7.7 μmol, 39%) to precipitate as a white powder: ^{1}H NMR (600 MHz, D_2O) δ = 1.98 (s, 3 H, Ac), 2.46 (dd, $J_{1a'',P}$ = 20.7 Hz, $J_{1a,b''}$ = 15 Hz, 1 H, 1a″-H), 2.78 (dd, $J_{1b'',P}$ = 21 Hz, $J_{1b,a''}$ = 15 Hz, 1 H, 1b″-H), 3.67 (dd, $J_{5'',6''}$ = 9.1 Hz, $J_{5'',4''}$ = 6.9 Hz, 1 H, 5″-H) 3.76 (m, 2 H, 7a,b″-H), 3.88 (m, 1 H, 6″-H), 4.07 (m, 2 H, 5a,b′-H), 4.16 (m, 2 H, 4′-H, 4″-H), 4.25 (m, 2 H, 2′-H, 3′-H), 5.83 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 5-H), 5.86 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, 1′-H), 7.82 (d, $J_{6,5}$ = 8.1 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O, HMQC) δ = 31.0 (d, J = 190 Hz, 1 C, 1″-C), 59.9 (1 C, 7″-C), 65.0 (1 C, 5′-C), 68.8 (1 C, 5″-C), 69.6 (1 C, 4″-C), 69.9, 74.1 (2 C, 2′-C, 3′-C), 78.9 (1 C, 6″-C), 83.4 (1 C, 4′-C), 88.6 (1 C, 1′-C), 103.1 (1 C, 5-C), 142.0 (1 C, 6-C); ^{31}P NMR (162 MHz, D_2O) δ = −10.6 (d, J = 26.5 Hz, 1 P, PO_4), +10.4 (d, J = 26.5 Hz,1 P, PO_3); MALDI-MS (negative mode, ATT) m/z = 602.7 [M − 2 Na+ + H^+]$^-$; $C_{18}H_{25}N_3O_{16}P_2Na_2$ (647.4).

Sodium 3-Acetamido-2,6-anhydro-3-deoxy-d-*arabino*-hept-2-enopyranosonate (6). A solution of **57** (10 mg, 26 μmol) in MeOH/H_2O/Et_3N (7:3:1, 5 mL) was stirred at room temperature for 16 h. The solution was concentrated under reduced pressure and lyophilisized from water. The produced triethylammonium salt was transformed to the sodium salt by ion exchange chromatography (Dowex, Na^+-form). The sodium salt was purified by precipitation from water (1 drop) with EtOH (10 mL) to yield **6** (4.5 mg, 13 μmol, 50%) as a white powder: ^{1}H NMR (600 MHz, D_2O) δ = 1.98 (s, 3 H, Ac), 3.63 (dd, $J_{5,6}$ = 9.2 Hz, $J_{5,4}$ = 7.0 Hz, 1 H, 5 H), 3.75 (dd, $J_{7a,b}$ = 12.6 Hz, $J_{7a,6}$ = 5.8 Hz, 1 H, 7a−H), 3.83 (m, 2 H, 6-H, 7b−H), 4.57 (d, $J_{4,5}$ = 7.0 Hz, 1 H, 4-H); ^{13}C NMR (151 MHz, D_2O) δ = 22.3 (1 C, Ac), 59.6 (1 C, 7-C), 67.6 (1 C, 5-C), 68.7 (1 C, 4-C), 77.9 (1 C, 6-C), 117.8 (1 C, 3-C), 139.3 (1 C, 2-C), 168.1 (1 C, Ac), 172.2 (1 C, 1-C); MALDI-MS (negative mode, ATT) 246.0 [M − Na]$^-$; $C_9H_{12}NO_7Na$ (269.2).

Disodium Uridine 5′-(3-Acetamido-3-deoxy-2-*O*-methyl-α-D-*gluco*-hept-2-ulopyranos-1-yl Diphosphate) (7). The crude salt **51** (30 mg, 55 μmol) was treated for 3 days with 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphomorpholidate (54 mg, 80 μmol) and 1-*H*-tetrazole (12 mg, 0.17 mmol) in dry pyridine (2 mL), following the general procedure GP1. After HPLC (RP18, 0.05 M TEAB-buffer, 0.5% CH_3CN; flow rate: 12 mL/min, t_R = 15 min), ion exchange (Amberlite IR 120, Na^+-form), and precipitation from H_2O/EtOH, compound **7** (5.0 mg, 7.2 μmol, 13%) was obtained as a white solid: ^{1}H NMR (600 MHz, D_2O) δ = 1.90 (s, 3 H, Ac), 3.17 (s, 3 H, OMe), 3.36 (dd, $J_{5'',6''} = J_{5'',4''}$ = 9.6 Hz, 1 H, 5″-H), 3.44 (m, 1 H, 6″-H), 3.54 (dd, $J_{4'',5''} = J_{4'',3''}$ = 9.5 Hz, 1 H, 4″-H), 3.63 (dd, $J_{7a'',7b''}$ = 12.4 Hz, $J_{7a'',6''}$ = 5.8 Hz, 1 H, 7a″-H), 3.76 (dd, $J_{7b'',7a''}$ = 12.4 Hz, $J_{7b'',6''}$ = 1.8 Hz, 1 H, 7b″-H), 3.81 (dd, $J_{1a'',1b''}$ = 10.9 Hz, $J_{1a'',P}$ = 5.5 Hz, 1 H, 1a″-H), 3.93 (m, 2 H, 1b″-H, 3″-H), 4.02−4.11 (m, 3 H, 5a,b′-H, 4′-H), 4.20 (dd, $J_{2',1'} = J_{2',3'}$ = 5.2 Hz, 1 H, 2′-H), 4.23 (dd, $J_{3',2'} = J_{3',4'}$ = 5.2 Hz, 1 H, 3′-H), 5.76 (d, $J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 5.91 (d, $J_{1',2'}$ = 5.2 Hz, 1 H, 1'-H), 7.69 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O, HMQC) δ = 20.2 (1 C, Ac), 49.0 (1 C, OMe), 54.8 (1 C, 3″-C), 61.1 (1 C, 7″-C), 65.4 (1 C, 5′-C) 65.5 (1 C, 1″-C), 69.9 (1 C, 5″-C), 70.2 (1 C, 3′-C), 73.1 (1 C, 4″-C), 73.5 (1 C, 6″-C), 74.2 (1 C, 2′-C), 83.2 (1 C, 4′-C), 88.9 (1 C, 1′-C), 103.6 (1 C, 5-C), 141.6 (1 C, 6-C), 174.4 (1 C, Ac); ^{31}P NMR (243 MHz, D_2O) δ = −10.2, −9.7 (2 d, J = 20.2 Hz, 2 P); MALDI-MS (negative mode, ATT) m/z 650.8 [M − 2 Na^+ + H^+]$^-$, 672.7 [M − Na^+]$^-$; $C_{19}H_{29}N_3O_{18}P_2$ Na_2 (695.4).

Disodium Uridine 5′-(3-Acetamido-3-deoxy-2-*O*-methyl-α-D-*manno*-hept-2-ulopyranos-1-yl Diphosphate) (8). The crude salt 52 (50 mg, 90 μmol) was treated for 3 days with 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphomorpholidate (75 mg, 0.11 mmol) and 1-*H*-tetrazole (19 mg, 0.27 mmol) in dry pyridine (2 mL), following the general procedure GP1. After HPLC (RP18, 0.05 M TEAB-buffer, 0.5% CH_3CN; flow rate, 10 mL/min, t_R = 27 min), ion exchange (Amberlite IR 120, Na^+-form) and precipitation from H_2O/EtOH compound **8** (8.1 mg, 12 μmol, 13%) was obtained as a white solid: ^{1}H NMR (600 MHz, D_2O) δ = 1.96 (s, 3 H, Ac), 3.23 (s, 3 H, OMe), 3.43 (m, 2 H, 5″-H, 6″-H), 3.72 (m, 3 H, 1a″-H, 7a,b″-H), 3.95 (m, 2 H, 1b″-H, 4″-H), 4.08 (m, 2 H, 5a,b′-H), 4.16 (m, 1 H, 4′-H), 4.26 (m, 2 H, 2′-H, 3′-H), 4.35 (d, $J_{3'',4''}$ = 4.5 Hz, 1 H, 3″-H), 5.85 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 5-H), 5.88 (d, $J_{1',2'}$ = 3.5 Hz, 1 H, 1'-H), 7.84 (d, $J_{6,5}$ = 8.1 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, D_2O) δ = 22.0 (1 C, Ac), 48.3 (1 C, OMe), 52.0 (1 C, 3″-C), 60.3 (1 C, 7″-C), 61.1 (1 C, 1″-C), 64.8 (1 C, 5′ C), 66.4 (1 C, 5″-C), 69.6, 73.7 (2 C, 2'-C, 3′-C), 69.9 (1 C, 4″-C), 73.5 (1 C, 6″-C), 83.2 (1 C, 4′-C), 88.2 (1 C, 1′-C), 102.7 (1 C, 5-C), 141.5 (1 C, 6-C), 174.6 (1 C, Ac); ^{31}P NMR (243 MHz, D_2O) δ = −10.4, −9.8 (2 d, J = 19.5 Hz, 2 P); MALDI-MS (negative mode, ATT) m/z 650.6 [M − 2Na^+ + H^+]$^-$; $C_{19}H_{29}N_3O_{18}P_2$ Na_2 (695.4).

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*gluco*-2-heptulopyranose (9), 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*manno*-2-heptulopyranose (10), 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*galacto*-2-heptulopyranose (11). Compounds **9**, **10**, and **11** were prepared following a procedure by Dondoni et al.[20]

3,4,5,7-Tetra-*O*-acetyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*gluco*-2-heptuloPyranose (12). To a solution of **9** (4.9 g, 7.4 mmol) in methanol/ethyl acetate (3:1, 120 mL) Pd/C (10%, 60 mg) was added. The suspension was stirred at room temperature for 2 days under a positive pressure of hydrogen, then filtered, (Sartorius, 0.45 μm) and concentrated under reduced pressure. The residue was dissolved in pyridine (50 mL), Ac_2O (40 mL) was added at 0 °C, and the solution was stirred at 0 °C → room temperature for 3 h. Then the solution

was cooled to 0 °C and quenched with methanol (30 mL). After 5 min, the solution was concentrated under reduced pressure and coevaporated with toluene. Purification by flash chromatography (toluene/acetone 2:1) afforded **12** (3.0 g, 6.4 mmol, 86%) as a colorless solid: TLC (toluene/acetpme = 2:1), R_f = 0.27; $[\alpha]_D$ (*c* = 1, acetone) +22.4; mp 152 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.96, 2.01, 2.05, 2.09 (4 s, 12 H, Ac), 2.13 (d, $J_{H,P}$ = 18.5 Hz, 2 H, 1a,b-H), 3.70, 3.72 (2 d, $J_{H,P}$ = 11.3 Hz, 6 H, OMe), 4.11 (dd, $J_{7a,b}$ = 12.4 Hz, $J_{7a,6}$ = 2.4 Hz, 1 H, 7a-H), 4.20 (dd, $J_{7a,b}$ = 12.4 Hz, $J_{7b,6}$ = 4.4 Hz, 1 H, 7b-H), 4.29 (ddd, $J_{6,5}$ = 10.1 Hz, $J_{6,7b}$ = 4.4 Hz, $J_{6,7a}$ = 2.4 Hz, 1 H, 6-H), 4.87 (dd, $J_{3,4}$ = 10.0 Hz, $J_{3,OH}$ = 1 Hz, 1 H, 3-H), 5.06 (dd, $J_{5,6} = J_{5,4}$ = 10 Hz, 1 H, 5-H), 5.49 (dd, $J_{4,5} = J_{4,3}$ = 10 Hz, 1 H, 4-H), 6.22 (bs, 1 H, OH); MALDI-MS (positive mode, DHB) *m*/*z* = 493.9 $[M + Na]^+$. $C_{17}H_{27}O_{13}P$ (470.37), calcd: C, 43.41; H, 5.79. Found: C, 43.72; H, 5.57.

3,4,5,7-Tetra-*O*-acetyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*manno*-2-heptulopyranose (13). The procedure described for the synthesis of **12** was followed using **10** (600 mg, 0.91 mmol) to afford **13** (240 mg, 0.51 mmol, 56%) as a colorless syrup: TLC (toluene/acetone = 3:2), R_f = 0.55; $[\alpha]_D$ (*c* = 1, acetone) +1.8; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.93, 2.01, 2.03, 2.15 (4 s, 12 H, Ac), 1.95 (m, 1 H, 1a-H), 2.25 (dd, $J_{H,P}$ = 19 Hz, $J_{1a,b}$ = 15.2 Hz, 1 H, 1b-H), 3.72, 3.78 (2 d, $J_{H,P}$ = 11.2 Hz, 6 H, OMe), 4.08−4.28 (m, 3 H, 6-H, 7a,b-H), 5.17 (dd, $J_{5,6} = J_{5,4}$ = 9.9 Hz, 1 H, 5-H), 5.23 (d, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 5.46 (dd, $J_{4,5}$ = 9.9 Hz, $J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 6.34 (s, 1 H, OH); MALDI-MS (positive mode, DHB, dioxane) *m*/*z* = 493.0 $[M + Na]^+$, 509.0 $[M + K]^+$. $C_{17}H_{27}O_{13}P$ (470.37), calcd: C, 43.41; H, 5.79; Found: C, 43.13; H, 5.84.

3,4,5,7-Tetra-*O*-acetyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*galacto*-2-heptulopyranose (14). The procedure described for the synthesis of **12** was followed using **11** (1.8 g, 2.7 mmol) to afford **14** (280 mg, 0.6 mmol, 22%) as a colorless syrup: TLC (toluene/acetone = 3:2), R_f = 0.35; $[\alpha]_D$ (*c* = 0.5, dioxane) + 58.8; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.93, 2.00, 2.09, 2.12 (4 s, 12 H, 4Ac), 1.91−2−22 (m, 2 H, 1a,b-H), 3.70, 3.77 (2 d, $J_{H,P}$ = 11.2 Hz, 6 H, OMe), 4.09 (m, 2 H, 7a,b-H), 4.50 (ddd, $J_{6,7a} = J_{6,7b}$ = 6.7 Hz, $J_{6,5}$ = 1 Hz, 1 H, 6-H), 5.11 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,OH}$ = 1.6 Hz, 1 H, 3-H), 5.36 (d, $J_{4,3}$ = 10.5 Hz, $J_{4,5}$ = 3.3 Hz, 1 H, 4-H), 5.46 (dd, $J_{5,4}$ = 3.3 Hz, $J_{5,6}$ = 1.3 Hz, 1 H, 5-H), 6.19 (bs, 1 H, OH); MALDI-MS (positive mode, DHB, dioxane) *m*/*z* = 493.1 $[M + Na]^+$, 509.1 $[M + K]^+$; $C_{17}H_{27}O_{13}P$ (470.37), calcd: C, 43.41; H, 5.79. Found: C, 43.41; H, 5.51.

***(Z)*-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-dimethoxyphosphoryl-D-*gluco*-hept-1-enitol (15).** To a solution of **12** (1.3 g, 2.7 mmol) in abs dichloromethane (50 mL) were added pyridine (5 mL) and trifluoroacetic anhydride (3.5 mL, 24 mmol) at 0 °C. The solution was stirred at room temperature for 16 h. The reaction was stopped by adding a solution of $NaHCO_3$, and the water phase was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 2:1) afforded **15** (940 mg, 2.1 mmol, 77%) as a colorless oil: TLC (toluene/acetone = 4:3), R_f = 0.18; $[\alpha]_D$ (*c* = 2, acetone) +55.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.02, 2.04, 2.10, 2.12 (4 s, 12 H, Ac), 3.71 (2 d, $J_{H,P}$ = 11.3 Hz, 6 H, OMe), 4.07 (ddd, $J_{6,5}$ = 8.2 Hz, $J_{6,7a}$ = 4 Hz, $J_{6,7b}$ = 1 Hz 1 H, 6-H), 4.25 (dd, $J_{7a,b}$ = 12.6 Hz, $J_{7a,6}$ = 1 Hz, 1 H, 7a-H), 4.35 (dd, $J_{7b,a}$ = 12.6 Hz, $J_{7b,6}$ = 4.3 Hz, 1 H, 7b-H), 5.13 (d, $J_{1,P}$ = 10.2 Hz, 1 H, 1-H), 5.17 (dd, $J_{4,3} = J_{4,5}$ = 8.2 Hz, 1 H, 4-H), 5.24 (dd, $J_{5,4} = J_{5,6}$ = 8.4 Hz, 1 H, 5-H), 5.47 (d, $J_{3,4}$ = 8.1 Hz, 1 H, 3-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 20.49, 20.52, 20.6, 20.7 (4 C, Ac), 52.2, 52,7 (2 d, $J_{C,P}$ = 5.8 Hz, 2 C, OMe), 61.3 (1 C, 7-C), 67.3 (1 C, 5-C), 69.1 (d, $J_{C,P}$ = 13.9 Hz, 1 C, 3-C), 72.5 (1 C, 4-C), 76.4 (1 C, 6-C), 97.5 (d, $J_{C,P}$ = 192.5 Hz, 1 C, 1-C), 161.6 (1 C, 2-C), 168.8, 169.2, 169,7, 170.5 (4 C, Ac); ^{31}P NMR (243 MHz, $CDCl_3$) δ = 20.4 (1 P); MALDI-MS (positive mode, DHB, THF) *m*/*z* = 453.1 $[M + H]^+$, 475.2 $[M + Na]^+$, 491.2 $[M + K]^+$; $C_{17}H_{25}O_{12}P$ (452.36), calcd: C, 45.14; H, 5.57. Found: C, 45.09; H, 5.45.

***(Z)*-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-dimethoxyphosphoryl-D-*manno*-hept-1-enitol (16).** The procedure described for the synthesis of **15** was followed using **13** (218 mg, 0.46 mmol) to afford **16** (154 mg, 0.33 mmol, 72%) as a colorless oil: TLC (toluene/acetone = 4:3), R_f = 0.19; $[\alpha]_D$ (*c* = 1, acetone), +7.5; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.06, 2.07, 2.08, 2.10 (4 s, 12 H, Ac), 3.70 (2 d, $J_{H,P}$ = 11.5 Hz, 6 H, OMe), 4.18 (m, 1 H, 6-H), 4.30 (m, 2 H, 7a,b-H), 5.13 (d, $J_{1,P}$ = 10.3 Hz, 1 H, 1-H), 5.21 (m, 2 H, 4-H, 5-H), 5.67 (d, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 18.2, 18.3, 18.6, 18.6 (4 C, 4 Ac), 50.4 (2d, $J_{C,P}$ = 6 Hz, 2 C, OMe), 60.1 (1 C, 7-C), 64.7 (1 C, 5-C), 65.6 (d, $J_{C,P}$ = 15.7 Hz, 1 C, 3-C), 67.5 (1 C, 4-C), 74.5 (1 C, 6-C), 95.5 (d, $J_{C,P}$ = 191 Hz, 1 C, 1-C), 158.4 (1 C, 2-C), 167.2, 167.2, 167,5, 168.4 (4 C, 4 Ac); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 18.4 (1P); MALDI-MS (positive mode, DHB, THF) *m*/*z* = 453 $[M + H]^+$, 475 $[M + Na]^+$, 491 $[M + K]^+$. $C_{17}H_{25}O_{12}P$ (452.36), calcd: C, 45.14; H, 5.57. Found: C, 44.79; H, 5.18.

***(Z)*-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-dimethoxyphosphoryl-D-*galacto*-hept-1-enitol (17).** The procedure described for the synthesis of **15** was followed using **14** (200 mg, 0.43 mmol) to afford **17** (156 mg, 0.34 mmol, 80%) as a colorless oil: TLC (toluene/acetone = 1:1), R_f = 0.25; $[\alpha]_D$ (*c* = 1, acetone), +86.7; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.98, 2.06, 2.13, 2.16 (4 s, 12 H, 4 Ac), 3.72 (2 d, $J_{H,P}$ = 11.5 Hz, 6 H, OMe), 4.14−4.29 (m, 3 H, 6-H, 7a,b-H), 5.05−5.13 (m, 2 H, 1-H, 4-H), 5.54 (d, *J* = 3 Hz, 1 H, 5-H), 5.73 (ddd, $J_{3,4}$ = 10.6 Hz, $J_{3,P}$ = 3.7 Hz, $J_{3,1}$ = 1.8 Hz, 1 H, 3-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 20.5, 20.6, 20.7, 20.7 (4 C, 4 Ac), 52.0 (2 d, $J_{C,P}$ = 6 Hz, 2 C, OMe), 61.0(1 C, 7-C), 66.6 (d, $J_{C,P}$ = 13.1 Hz, 1 C, 3-C), 67.0 (1 C, 5-C), 70.7, 76.3 (2 C, 4-C, 6-C), 97.5 (d, $J_{C,P}$ = 190 Hz, 1 C, 1-C), 163.2 (1 C, 2-C), 169.7−170.5 (4 C, 4 Ac); MALDI-MS (positive mode, DHB, THF) *m*/*z* = 475.4 $[M + Na]^+$, 491.5 $[M + K]^+$. $C_{17}H_{25}O_{12}P$ (452.36), calcd: C, 45.14; H, 5.57. Found: C, 44.94; H, 5.48.

Bis-2,6-lutidinium *(Z)*-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*gluco*-hept-1-enitol-1-yl Phosphonate (18). To a solution of **15** (70 mg, 0.15 mmol) in abs acetonitrile (4 mL) and 2,6-lutidine (99 μL, 0.85 mmol) was added dropwise TMSBr (84 μL, 0.77 mmol) at 0 °C and under argon. After stirring at 0 °C to room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. After coevaporation with abs acetonitrile (twice) and then with dry methanol, the residue was again dissolved in methanol and Et_3N (0.1 mL) was added. Concentration under reduced pressure gave the 2,6-lutidinium salt **18** in quantitative yield.

Compound **18** was used for the next step without purification: ^{1}H NMR (250 MHz, MeOH-d_4) δ = 2.02, 2.03, 2.05, 2.12 (4 s, 12 H, Ac), 2.78 (s, 12 H, lutidine), 4.08 (ddd, $J_{6,5}$ = 9.5 Hz, $J_{6,7b}$ = 4.6 Hz, $J_{6,7a}$ = 2.4 Hz, 1 H, 6-H), 4.26 (dd, $J_{7a,b}$ = 13.4 Hz, $J_{7a,6}$ = 2.4 Hz, 1 H, 7a-H), 4.39 (dd, $J_{7b,a}$ = 13.4 Hz, $J_{7b,6}$ = 4.6 Hz, 1 H, 7b-H), 5.17 (dd, $J_{4,5} = J_{5,6}$ = 9.5 Hz, 1 H, 4-H), 5.22 (dd, $J_{5,4} = J_{5,6}$ = 9.5 Hz, 1 H, 5-H), 5.32 (dd, $J_{1,P}$ = 10.8 Hz, $J_{1,3}$ = 1.8 Hz, 1 H, 1-H), 5.42 (ddd, $J_{3,4}$ = 9.5 Hz, $J_{3,P}$ = 3.0 Hz, $J_{3,1}$ = 1.8 Hz, 1 H, 3-H), 7.57 (d, 4 H, lutidine), 8.18 (dd, 2 H, lutidine); MALDI-MS (negative mode, ATT) *m*/*z* = 423.8 $[M - 2\ Lut^+ + H^+]^-$; $C_{15}H_{19}O_{12}P \times 2\ C_7H_{10}N$ (638.6).

2,6-Lutidinium/Triethylammonium (*Z*)-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*manno*-hept-1-enitol-1-yl Phosphonate (19). Following the procedure described for the synthesis of **18**, compound **16** (95 mg, 0.21 mmol) was deprotected to afford **19** as a mixture of the triethylammonium and the lutidinium salts in quantitative yield. Compound **19** was used for the next step without purification: TLC ($CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N), R_f = 0.6; ^{1}H NMR (250 MHz, MeOH-d_4) δ = 1.29 (t, 7 H, Et_3NH), 1.96, 2.01, 2.02, 2.06 (4s, 12 H, Ac), 2.71 (s, 7 H, lutidine) 3.17 (q, 4.8 H, Et_3NH), 4.06 (m, 1 H, 6-H), 4.30 (dd, $J_{7a,b}$ = 12.6 Hz, $J_{7a,6}$ = 2.8 Hz, 1 H, 7a-H), 4.32 (dd, $J_{7b,a}$ = 12.6 Hz, $J_{7b,6}$ = 4.0 Hz, 1 H, 7b-H), 5.12 (dd, $J_{4,5}$ = 9.1 Hz, $J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 5.40 (m, 2 H, 1-H, 5-H), 5.60 (d, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 7.57 (d, 2.4 H, lutidine), 8.18 (dd, 1.2 H, lutidine); MALDI-MS (positive mode,

DHB) m/z = 447.0 [M − $HNEt_3^+$ − Lut^+ + 2 H^+ + Na^+]$^+$, 463.0 [M − $HNEt_3^+$ − Lut^+ + 2 H^+ + K^+]$^+$, 469.0 [M − $HNEt_3^+$ − Lut^+ + H^+ + 2 Na^+]$^+$, 485.0 [M − $HNEt_3^+$ − Lut^+ + H^+ + Na^+ + K^+]$^+$; $C_{15}H_{19}O_{12}P$ × 0.8 $HNEt_3$ × 1.2 $C_7H_{10}N$ (422.3 + 81.6 + 129.8 = 633.7).

2,6-Lutidinium/Triethylammonium (*Z*)-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*galacto*-hept-1-enitol-1-yl Phosphonate (20). Following the procedure described for the synthesis of **18**, compound **17** (150 mg, 0.33 mmol) was deprotected to afford **20** as a mixture of the triethylammonium and the 2,6-lutidinium salts in quantitative yield. Compound **20** was used for the next step without purification: ^{1}H NMR (250 MHz, MeOH-d_4) δ = 1.33 (t, 11 H, Et_3NH), 1.98, 2.04, 2.13, 2.15 (4 s, 12 H, Ac), 2.56 (s, 5 H, lutidine), 3.22 (q, 7 H, Et_3NH), 4.18−4.33 (m, 3 H, 6-H, 7a,b−H), 5.15 (dd, $J_{4,3}$ = 10.7 Hz, $J_{4,5}$ = 3.6 Hz, 1 H, 4-H), 5.28 (bd, $J_{1,P}$ = 9 Hz, 1 H, 1-H), 5.53 (d, J = 3.6 Hz, 1 H, 5-H), 5.63 (bd, $J_{3,4}$ = 10.7 Hz, 1 H, 3-H); $C_{15}H_{19}O_{12}P$ × 1.2 $HNEt_3$ × 0.8 $C_7H_{10}N$ (422.3 + 122.6 + 86.5 = 631.4).

Bis-triethylammonium Uridine 5'-[(*Z*)-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*gluco*-hept-1-enitol-1-yl-phosphono] Phosphate (21). The crude salt **18** (0.13 mmol) was dissolved in methanol (8 mL), and Et_3N (0.1 mL) was added. The solution was concentrated under reduced pressure to give the triethylammonium salt of **18**, which was treated for 3 d with UMP-morpholidate (100 mg, 0.15 mmol) and tetrazole (14 mg, 0.2 mmol) in pyridine (2 mL), following the general procedure GP1. (RP18-HPLC, 0.05 M TEAB-buffer; gradient, 10−15% CH_3CN over 30 min; flow rate, 11 mL/min, t_R = 8.5 min). Compound **21** (26 mg, 28 μmol, 22%) was obtained as a colorless solid: ^{1}H NMR (250 MHz, D_2O) δ = 1.12 (t, 18 H, NCH_2CH_3), 1.91, 1.93, 1.97, 1.99 (4 s, 12 H, Ac), 3.04 (q, 12 H, NCH_2CH_3), 3.99−4.20 (m, 7 H, 2′-H, 3′-H, 4′-H, 5a,b′-H, 6″-H, 7a″-H), 4.34 (dd, J = 12.2 Hz, J = 2.4 Hz, 1 H, 7b″-H), 5.11 (m, 2 H, 4″-H, 5″-H), 5.31 (m, 2 H, 1″-H, 3″-H), 5.79 (m, 2 H, 5-H, 1′-H), 7.78 (d, $J_{6,5}$ = 8.0 Hz, 1 H, 6-H); MALDI-MS (positive mode, DHB) m/z = 753.1 [M − 2 $HNEt_3^+$ + 2 H^+ + Na^+]$^+$, 769.2 [M − 2 $HNEt_3^+$ + 2 H^+ + K^+]$^+$; $C_{24}H_{30}N_2O_{20}P_2$ × 2 $C_6H_{16}N$ (932.8).

Bis-triethylammonium Uridine 5'-[(*Z*)-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*manno*-hept-1-enitol-1-yl phosphono] Phosphate (22). The crude salt **19** (0.16 mmol) was treated for 3 days with UMP-morpholidate (137 mg, 0.2 mmol) and tetrazole (22 mg, 0.32 mmol) in pyridine (4 mL), following the general procedure GP1. After HPLC (RP18, 0.05 M TEAB-buffer; gradient, 9−15% CH_3CN over 30 min; flow rate, 11 mL/min, t_R = 12.5 min), compound **22** (30 mg, 32 μmol, 20%) was obtained as a colorless solid: ^{1}H NMR (250 MHz, D_2O) δ = 1.04 (t, J = 7.2 Hz, 18 H, NCH_2CH_3), 1.83, 1.88, 1.92, 1.97 (4 s, 12 H, Ac), 2.95 (q, 12 H, NCH_2CH_3), 3.98−4.14 (m, 7 H, 2′-H, 3′-H, 4′-H, 5a,b′-H, 6″-H, 7a″-H), 4.28 (dd, J = 12.5 Hz, J = 2.5 Hz, 1 H, 7b″-H), 5.08 (dd, $J_{4'',5''}$ = 9.3 Hz, $J_{4'',3''}$ = 3.3 Hz, 1 H, 4″-H), 5.18 (dd, $J_{5'',4''}$ = $J_{5'',6''}$ = 9.3 Hz, 1 H, 5″-H), 5.36 (d, $J_{1'',P}$ = 10.3 Hz, 1 H, 1″-H), 5.49 (d, $J_{3'',4''}$ = 3.3 Hz, 1 H, 3″-H), 5.69 (d, $J_{5,6}$ = 7.9 Hz, 1 H, 5-H), 5.77 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H), 7.66 (d, $J_{6,5}$ = 7.9 Hz, 1 H, 6-H); MALDI-MS (negative mode, ATT) m/z = 729.3 [M − 2 $HNEt_3^+$ + H^+]$^-$; $C_{24}H_{30}N_2O_{20}P_2$ × 2 $C_6H_{16}N$ (932.8).

Bis-triethylammonium Uridine 5'-[(*Z*)-3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*galacto*-hept-1-enitol-1-yl phosphono] Phosphate (23). The crude salt **20** (0.3 mmol) was treated for 3 d with UMP-morpholidate (220 mg, 0.32 mmol) and tetrazole (42 mg, 0.6 mmol) in pyridine (10 mL), following the general procedure GP1. After HPLC (RP18, 0.05 M TEAB-buffer; gradient, 8−15% CH_3CN over 30 min; flow rate, 11 mL/min, t_R = 11.5 min) compound **23** (89 mg, 95 μmol, 30%) was obtained as a colorless solid: ^{1}H NMR (250 MHz, D_2O): δ = 1.05 (t, J = 7.3 Hz, 18 H, NCH_2CH_3), 1.79, 1.87, 1.94, 1.99 (4 s, 12 H, Ac), 2.96 (q, 12 H, NCH_2CH_3), 3.96−4.20 (m, 8 H, 2′-H, 3′-H, 4′-H, 5a,b′-H, 6″-H, 7a,b″-H), 5.01 (dd, $J_{4'',3''}$ = 10.3 Hz, $J_{4'',5''}$ = 3.2 Hz, 1 H, 4″-H), 5.25 (dd, $J_{1'',P}$ = 9.6 Hz, $J_{1'',3''}$ = 1 Hz, 1 H, 1″-H), 5.37 (bd, J = 3 Hz, 1 H, 5″-H), 5.48 (dd, $J_{3'',4''}$ = 10.3, Hz, $J_{3'',1''}$ = 1 Hz, 1 H, 3″-H), 5.72 (m, 2 H, 5-H, 1′-H), 7.75 (d, $J_{6,5}$ = 8.0 Hz, 1 H, 6-H); MALDI-MS (negative mode, ATT) m/z = 729.1 [M − 2 $HNEt_3^+$ + H^+]$^-$; $C_{24}H_{30}N_2O_{20}P_2$ × 2 $C_6H_{16}N$ (932.8).

2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-*glucono*-δ-lactone (24). This compound was synthesized following a procedure by Vasella et al.[33]

3-Acetamido-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1-dimethoxyphosphoryl-α-D-*gluco*-2-heptulopyranose (25). To a cooled (−80 °C) solution of dimethyl methylphosphonate (672 μL, 6.2 mmol) in dry THF (30 mL) was added dropwise a solution of *n*-BuLi (1.6 M in hexane, 3.9 mL, 6.2 mmol). After stirring at −80 °C for 15 min, a solution of **24** (1.5 g, 3.1 mmol) in dry THF (12 mL) was added dropwise to the reaction mixture. After stirring for 50 min at −80 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4-Cl (50 mL). The water layer was extracted with EtOAc; the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 4:1) afforded **25** (1.05 g, 1.7 mmol, 56%) as a colorless solid: TLC (toluene/acetone = 2:1), R_f = 0.41;[α]$_D$ (c = 1, acetone), +29.1; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.85 (s, 3 H, Ac), 2.19, 2.20 (2 d, $J_{H,P}$ = 18. Hz, 2 H, 1a,b-H), 3.62 (m 1 H, 7a-H), 3.66, 3.67 (2 d, $J_{H,P}$ = 11.2 Hz, 6 H, 2 OMe), 3.73 (m, 3 H, 4-H, 5-H, 7b-H), 4.03 (m, 2 H, 3-H, 6-H), 4.49 (s, 2 H, CH_2Ph), 4.58, 4.64 (2 d, J = 11.6 Hz, 2 H, CH_2Ph), 4.82, 4.83 (2 d, J = 11.1 Hz, 2 H, CH_2Ph), 5.54 (d, J = 10.1 Hz, 1 H, NH), 5.95 (bs, 1 H, OH), 7.21−7.34 (m, 15 H, Ph); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 23.4 (1 C, Ac), 32.9 (d, $J_{C,P}$ = 135.8 Hz, 1 C, 1-C), 51.8 (d, $J_{C,P}$ = 6.8 Hz, 1 C, OMe), 53.7 (d, $J_{C,P}$ = 5.6 Hz, 1 C, OMe), 56.8 (d, $J_{C,P}$ = 14.6 Hz, 1 C, 3-C), 68.5 (1 C, 7-C), 71.3 (1 C, 6-C), 73.2, 74.8, 74.9 (3 C, CH_2Ph), 78.4, 80.6 (2 C, 4-C, 5-C), 96.8 (d, J = 7.9 Hz, 1 C, 2-C), 127.7−138.4 (18 C, Ph), 170.1 (1 C, Ac); ^{31}P NMR (243 MHz, $CDCl_3$) δ = 29.7 (s, 1P); MALDI-MS (positive mode, DHB) m/z = 636.2 [M + Na]$^+$, 652.2 [M + K]$^+$. $C_{32}H_{40}NO_9P$ (613.6), calcd: C, 62.63; H, 6.57; N, 2.28. Found: C, 62.64; H, 6.72; N, 2.33.

3-Acetamido-4,5,7-tri-*O*-acetyl-1,3-dideoxy-1-dimethoxyphosphoryl-α-D-*gluco*-2-heptulopyranose (26). Following the procedure described for the synthesis of **12**, compound **25** (2.4 g, 3.9 mmol) to afford **26** (1.5 g, 3.2 mmol, 82%) as a colorless solid: TLC (toluene/acetone = 2:1), R_f = 0.27; [α]$_D$ (c = 1, acetone), +32.2; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.98, 1.99, 2.02, 2.04 (4 s, 12 H, Ac), 2.20 (2 d, J = 9.8 Hz, 2 H, 1a,b-H), 3.75 (2 d, $J_{H,P}$ = 5.5 Hz, 6 H, OMe), 4.18 (m, 4 H, 3-H, 6-H, 7a,b-H), 5.11 (dd, $J_{5,4}$ = $J_{5,6}$ = 5.1 Hz, 1 H, 5-H), 5.29 (dd, $J_{4,3}$ = $J_{4,5}$ = 5.1 Hz, 1 H, 4-H), 5.76 (bd, J = 5.3 Hz, 1 H, NH), 6.32 (bs, 1 H, OH); MALDI-MS (positive mode, DHB) m/z = 492.1 [M + Na]$^+$, 508.1 [M + K]$^+$. $C_{17}H_{28}NO_{12}P$ (469.4), calcd: C, 43.50; H, 6.01; N, 2.98. Found: C, 43.30; H, 6.09; N, 3.11.

(*Z*)-3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1-dimethoxyphosphoryl-D-*gluco*-hept-1-enitol (27). To a solution of **25** (200 mg, 0.32 mmol) in abs dichloromethane (10 mL) were added pyridine (1 mL) and trifluoroacetic anhydride (187 μL, 1.3 mmol) at 0 °C. The solution was stirred at 0 °C → room temperature for 3 h. The reaction mixture was poured into a solution of $NaHCO_3$, and the water phase was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 1:1) afforded **27** (106 mg, 0.18 mmol, 56%) as a colorless solid: TLC (toluene/acetone = 1:1), R_f = 0.19; [α]$_D$ (c = 1, acetone), +56.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.96 (s, 3 H, Ac), 3.63 (m, 6 H, 2 OMe), 3.72 (m, 1 H, 4-H), 3.75 (m, 2 H, 7a,b-H), 3.92 (m, 2 H, 5-H, 6-H), 4.56 (m, 3 H, CH_2Ph), 4.75 (m, 4 H, 3-H, CH_2Ph), 5.02 (d, $J_{1,P}$ = 11.6 Hz, 1 H, 1-H), 7.19−7.30 (m, 15 H, Ph), 7.59 (bs, 1 H, NH); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 22.9 (1 C, Ac), 52.1, 52.8 (2 d, $J_{C,P}$ = 5.5 Hz, 2 C, OMe), 52.6 (d, $J_{C,P}$ = 13.5 Hz, 1 C, 3-C), 68.1 (1 C, 7-C), 73.2, 74.3, 74.4 (3 C, CH_2Ph), 76.3, 79.6 (2 C, 5-C, 6-C), 80.9 (1 C, 4-C), 92.2 (d, $J_{C,P}$ = 192 Hz, 1 C, 1-C), 127.7−137.8 (18 C, Ph), 167.7 (1 C, 2-C), 170.4

(1 C, Ac); ^{31}P NMR (243 MHz, $CDCl_3$) $\delta = 18.8$ (s, 1P); MALDI-MS (positive mode, DHB) $m/z = 618.1$ $[M + Na]^+$, 634.1 $[M + K]^+$; $C_{32}H_{38}NO_8P$ (595.6), calcd: C, 64.53; H, 6.43; N, 2.35. Found: C, 64.73; H, 6.49; N, 2.42.

3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-1-dimethoxyphosphoryl-D-*arabino*-hept-2-enitol (28). To a solution of **26** (180 mg, 0.38 mmol) in abs dichloromethane (8 mL) were added pyridine (1 mL) and trifluoroacetic anhydride (260 μL, 1.8 mmol) at 0 °C. The solution was stirred at room temperature for 3 days. The reaction mixture was poured into a solution of $NaHCO_3$, and the water phase was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 2:3) afforded **28** (70 mg, 0.16 mmol, 42%) as a colorless solid: TLC (toluene/acetone = 1:2), $R_f = 0.15$; $[\alpha]_D$ ($c = 1$, acetone), − 63.8; ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 2.00$, 2.02, 2.03, 2.04 (4 s, 12 H, Ac), 2.26 (dd, $J_{1a,P} = 20.4$ Hz, $J_{1a,b} = 15.2$ Hz, 1 H, 1a-H), 2.94 (dd, $J_{1b,P} = 21.8$ Hz, $J_{1b,a} = 15.2$ Hz, 1 H, 1b-H), 3.78 (2 d, $J_{H,P} = 11.2$ Hz, 6 H, OMe), 4.22 (dd, $J_{7a,b} = 11.7$ Hz, $J_{7a,6} = 2.8$ Hz, 1 H, 7a-H), 4.36 (m, 2 H, 6-H, 7b-H), 5.20 (dd, $J_{5,4} = J_{5,6} = 5.5$ Hz, 1H, 5-H), 5.80 (m, 1H, 4-H), 7.67 (s, 1 H, NH); ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 20.6$, 20.7, 20.7, 22.9 (4 C, Ac), 28.0 (d, $J_{C,P} = 140$ Hz, 1 C, 1-C), 53.2 (2 d, $J_{C,P} = 10$ Hz, 2 C, OMe), 61.1 (1 C, 7-C), 67.0, 67.2 (2 C, 4-C, 5-C), 74.4 (1 C, 6-C), 109.8 (d, $J_{C,P} = 9.7$ Hz, 1 C, 3-C), 144.2 (d, $J_{C,P} = 10$ Hz, 1 C, 2-C), 169.6, 169.6, 170.0, 170.4 (4 C, Ac); ^{31}P NMR (243 MHz, $CDCl_3$) $\delta = 26.0$ (s, 1 P); MALDI-MS (positive mode, DHB) $m/z = 474.3$ $[M + Na]^+$, 490.4 $[M + K]^+$. $C_{17}H_{26}NO_{11}P$ (451.4), calcd: C, 45.24; H, 5.81; N, 3.10. Found: C, 45.71; H, 5.78; N, 3.10.

(*Z*)-3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-1-dimethoxyphosphoryl-D-*gluco*-hept-1-enitol (29). To a solution of **27** (60 mg, 100 μmol) in ethanol (3 mL) were added 1,4-cyclohexadien (2 mL) and Pd/C (10%, 50 mg). The suspension was stirred at 40 °C for 3 days. After complete conversion (monitoring with MALDI-MS and TLC: $CHCl_3$/MeOH/H_2O 6:4:1 + 1% Et_3N, $R_f = 0.2$), the suspension was filtered (Sartorius 0.45 μm) and concentrated under reduced pressure. The residue was dissolved in pyridine (1 mL), Ac_2O (0.5 mL) was added, and the solution was stirred at room temperature for 2 h. Then the solution was cooled to 0 °C and quenched with methanol (2 mL). After 5 min, the solution was concentrated under reduced pressure and coevaporated with toluene. Purification by flash chromatography (toluene/acetone 1:1) afforded **29** (30 mg, 60 μmol, 66%) as a colorless oil: TLC (toluene/acetone 1:2), $R_f = 0.16$; $[\alpha]_D$ ($c = 1$, acetone), +73.0; ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 2.00$, 2.03, 2.04, 2.10 (4 s, 12 H, Ac), 3.69, 3.72 (2 d, $J_{H,P} = 11.3$ Hz, 6 H, OMe), 3.96 (ddd, $J_{6,5} = 9.7$ Hz, $J_{6,7a} = 2.4$ Hz, $J_{6,7b} = 4.1$ Hz, 1H, 6-H), 4.24 (dd, $J_{7a,b} = 12.7$ Hz, $J_{7a,6} = 2.4$ Hz, 1 H, 7a-H), 4.36 (dd, $J_{7b,a} = 12.7$ Hz, $J_{7b,6} = 4.1$ Hz, 1 H, 7b-H), 4.84 (dddd, $J_{3,4} = 10.8$ Hz, $J_{3,NH} = 8.8$ Hz, $J_{3,P} = 3.8$ Hz, $J_{3,1} = 1.8$ Hz, 1 H, 3-H), 5.00 (dd, $J_{4,3} = 10.8$ Hz, $J_{4,5} = 9.4$ Hz, 1 H, 4-H), 5.18 (dd, $J_{1,P} = 10.6$ Hz, $J_{1,3} = 1.8$ Hz, 1 H, 1-H), 5.31 (dd, $J_{5,6} = J_{5,4} = 9.5$ Hz, 1 H, 5-H), 5.99 (d, $J_{NH,3} = 8.8$ Hz, 1 H, NH); MALDI-MS (positive mode, DHB) $m/z = 474.1$ $[M + Na]^+$, 490.1 $[M + K]^+$. $C_{17}H_{26}NO_{11}P$ (451.4), calcd: C, 45.24; H, 5.81; N, 3.10. Found: C, 45.28; H, 6.25; N, 2.77.

3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-1-dimethoxyphosphoryl-D-*glycero*-D-*gulo*-heptitol (30). To a solution of **27** (50 mg, 84 μmol) in methanol (10 mL) was added Pd/C (10%, 10 mg), and the suspension was stirred at room temperature under a slightly positive pressure of hydrogen for 16 h, then filtered (Sartorius, 0.45 μm), and concentrated under reduced pressure. The residue was dissolved in pyridine (2 mL), Ac_2O (1 mL) was added at 0 °C, and the solution was stirred at room temperature for 16 h. The solution was concentrated under reduced pressure and coevaporated with toluene. Purification by flash chromatography (toluene/acetone 1:2 → acetone) afforded **30** (31 mg, 68 μmol, 81%) as a colorless solid: TLC (toluene/acetone = 1:2), $R_f = 0.12$; $[\alpha]_D$ ($c = 1$, acetone), +3.2; ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.94$, 2.01, 2.01, 2.08 (4 s, 12 H, Ac), 2.02−2.11 (m, 2 H, 1a,b−H), 3.67−3.78 (m, 7 H, 6-H, OMe), 3.81 (m, 1 H, 2-H), 4.05 (ddd, $J_{3,4} = J_{3,2} = J_{3,NH} = 9.8$ Hz, 1 H, 3-H), 4.12 (dd, $J_{7a,b} = 12.4$ Hz, $J_{7a,6} = 2.3$ Hz, 1 H, 7a-H), 4.18 (dd, $J_{7b,a} = 12.4$ Hz, $J_{7b,6} = 5.2$ Hz, 1 H, 7b-H), 5.03 (dd, $J_{5,4} = J_{5,6} = 9.5$ Hz, 1 H, 5-H), 5.06 (dd, $J_{4,5} = J_{4,3} = 9.5$ Hz, 1 H, 4-H), 6.41 (d, $J = 9.8$ Hz, 1 H, NH); ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 20.6$, 20.6, 20.7, 23.1 (4 C, Ac), 27.8 (d, $J_{1,P} = 142$ Hz, 1 C, 1-C), 52.0, 53.0 (2 d, 2 C, OMe), 54.1 (d, $J_{3,P} = 15.6$ Hz, 1 C, 3-C), 62.3 (1 C, 7-C), 68.4 (1 C, 5-C), 74.0 (1 C, 4-C), 74.5 (1 C, 2-C), 75.8 (1 C, 6-C), 169.3, 170.6, 170.6, 171.2 (4 C, Ac); MALDI-MS (positive mode, DHB) $m/z = 454.6$ $[M + H]^+$, 476.7 $[M + Na]^+$, 492.7 $[M + K]^+$; $C_{17}H_{28}NO_{11}P$ (453.4).

2,6-Lutidinium/Triethylammonium (*Z*)-3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-D-*gluco*-hept-1-enitol-1-yl Phosphonate (31). Following the procedure described for the synthesis of **18**, compound **29** (28 mg, 62 μmol) was deprotected to afford **31** as a mixture of the triethylammonium and the lutidinium salts in quantitative yield. Compound **31** was used for the next step without purification: ^{1}H NMR (250 MHz, D_2O) $\delta = 1.33$ (t, $J = 7.3$ Hz, 9 H, NCH_2CH_3), 1.99, 1.99, 2.01, 2.06 (4 s, 12 H, Ac), 2.69 (s, 6 H, lutidine), 3.22 (q, 6 H, NCH_2CH_3), 3.98 (ddd, $J_{6,5} = 10.2$ Hz, $J_{6,7b} = 3$ Hz, $J_{6,7a} = 1.5$ Hz, 1 H, 6-H), 4.28 (dd, $J_{7a,b} = 12.5$ Hz, $J_{7a,6} = 1.5$ Hz, 1 H, 7a-H), 4.42 (dd, $J_{7b,a} = 12.5$ Hz, $J_{7b,6} = 3$ Hz, 1 H, 7b-H), 4.67 (m, 1 H, 3-H), 5.09 (dd, $J_{5,6} = J_{5,4} = 10.2$ Hz, 1 H, 5-H), 5.24 (dd, $J_{4,5} = J_{4,3} = 10.2$ Hz, 1 H, 4-H), 5.22 (dd, $J_{1,P} = 8.8$ Hz, $J_{1,3} = 1.5$ Hz, 1 H, 1-H). MALDI-MS (positive mode, DHB) 446.3 $[M - HNEt_3^+ - Lut^+ + 2\ H^+ + Na^+]^+$, 462.2 $[M - HNEt_3^+ - Lut^+ + 2\ H^+ + K^+]^+$, 468.3 $[M - HNEt_3^+ - Lut^+ + H^+ + 2\ Na^+]^+$, 484.2 $[M - HNEt_3^+ - Lut^+ + H^+ + 2\ K^+]^+$; $C_{15}H_{20}NO_{11}P \times 1.0\ HNEt_3 \times 1.0\ C_7H_{10}N$ (421.3 + 102.2 + 108.1 = 631.6).

Bis-triethylammonium Uridine 5′-[(*Z*)-3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-D-*gluco*-hept-1-enitol-1-yl phosphono] Phosphate (32). The crude salt **31** (60 μmol) was treated for 3 d with UMP-morpholidate (62 mg, 90 μmol) and tetrazole (7 mg, 0.1 mmol) in dry pyridine (2 mL), following the general procedure GP1. After HPLC (RP18, 0.05 M TEAB-buffer; gradient, 7−14% CH_3CN over 30 min; flow rate, 11 mL/min, $t_R = 12.5$ min), compound **32** (10 mg, 11 μmol, 18%) was obtained as a colorless solid: ^{1}H NMR (250 MHz, D_2O) $\delta = 1.06$ (t, $J = 7.2$ Hz, 18 H, NCH_2CH_3), 1.82, 1.85, 1.87, 1.92 (4 s, 12 H, Ac), 3.00 (q, $J = 7.2$ Hz, 12 H, NCH_2CH_3), 3.95−4.13 (m, 8 H, 2′-H, 3′-H, 4′-H, 5a,b′-H, 6″-H, 3″-H, 7a″-H), 4.32 (dd, $J_{7a,b''} = 12.4$ Hz, $J_{7b'',6''} = 2.3$ Hz, 1 H, 7b″-H), 4.99 (dd, $J_{5'',4''} = J_{5'',6''} = 9.6$ Hz, 1 H, 5″-H), 5.10 (dd, $J_{4'',5''} = J_{4'',3''} = 9.6$ Hz, 1 H, 4″-H), 5.23 (d, $J_{1'',P} = 9.7$ Hz, 1 H, 1″-H), 5.73 (d, $J_{5,6} = 7.9$ Hz, 1 H, 5-H), 5.77 (d, $J_{1',2'} = 3.2$ Hz, 1 H, 1′-H), 7.74 (d, $J_{6,5} = 7.9$ Hz, 1 H, 6-H); MALDI-MS (negative mode, ATT) $m/z = 728.6$ $[M - 2\ HNEt_3^+ + H^+]^-$, 750.6 $[M - 2\ HNEt_3^+ + Na^+]^-$; $C_{24}H_{31}N_3O_{19}P_2 \times 2\ C_6H_{16}N$ (931.8).

Bis-2,6-lutidinium 3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-D-*arabino*-hept-2-enitol-1-yl Phosphonate (33). Following the procedure described for the synthesis of **18**, compound **28** (54 mg, 0.12 mmol) was deprotected to afford the 2,6-lutidinium salt **33** in quantitative yield. Compound **33** was used for the next step without purification: ^{1}H NMR (250 MHz, D_2O) $\delta = 2.00$, 2.02, 2.04, 2.05 (4 s, 12 H, Ac), 2.52−2.74 (m, 2 H, 1a,b-H), 2.78 (s, 12 H, lutidine), 4.25 (dd, $J_{7a,b} = 14.2$ Hz, $J_{7a,6} = 6.0$ Hz, 1 H, 7a-H), 4.44 (m, 2 H, 6-H, 7b−H), 5.19 (dd, $J_{5,6} = 6.2$ Hz, $J_{5,4} = 5.1$ Hz, 1 H, 5-H), 5.73 (dd, $J_{4,5} = J_{4,P} = 5$ Hz, 1 H, 4-H), 7.72 (d, 4 H, lutidine), 8.34 (t, 2 H, lutidine); MALDI-MS (positive mode, DHB) $m/z = 446.2$ $[M - 2\ Lut^+ + 2\ H^+ + Na^+]^+$; (negative mode, ATT) $m/z = 422.0$ $[M - 2\ Lut^+ + H^+]^-$; $C_{15}H_{20}NO_{11}P \times 2\ C_7H_{10}N$ (637.6).

Bis-triethylammonium Uridine 5′-(3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-1,3-dideoxy-d-*arabino*-hept-2-enitol-1-yl phosphono) Phosphate (34). The crude salt **33** (0.11 mmol) was dissolved in methanol (10 mL), and Et_3N (0.1

mL) was added. The solution was concentrated under reduced pressure to give the triethylammonium salt of **33**, which was treated for 3 days with UMP-morpholidate (150 mg, 0.22 mmol) and tetrazole (23 mg, 0.33 mmol) in pyridine (2 mL), following the general procedure GP1. (RP18-HPLC, 0.05 M TEAB-buffer; gradient, 7−14% CH_3CN over 30 min; flow rate, 11 mL/min, t_R = 10.5 min). Compound **34** (19 mg, 20 μmol, 18%) was obtained as a colorless solid: ^{1}H NMR (250 MHz, D_2O) δ = 1.08 (t, J = 7.2 Hz, 18 H, NCH_2CH_3), 1.84, 1.88, 1.91, 1.92 (4 s, 12 H, Ac), 2.42−2.80 (m, 2 H, 1a,b″-H), 2.90 (q, J = 7.2 Hz, 12 H, NCH_2CH_3), 3.97−4.36 (m, 8 H, 2′-H, 3′-H, 4′-H, 5a,b′-H, 6″-H, 7a,b″-H), 5.06 (dd, $J_{5'',4''} = J_{5'',6''}$ = 5.1 Hz, 1 H, 5″-H), 5.46 (dd, $J_{4'',5''} = J_{4'',P}$ = 4.8 Hz, 1 H, 4″-H), 5.66 (d, $J_{5,6}$ = 8.0 Hz, 1 H, 5-H), 5.79 (d, $J_{1',2'}$ = 4.8 Hz, 1 H, 1′-H), 7.62 (d, $J_{6,5}$ = 8.0 Hz, 1 H, 6-H); MALDI-MS (negative mode, ATT) m/z = 728.7 [M − 2 $HNEt_3^+ + H^+]^-$; $C_{24}H_{31}N_3O_{19}P_2 \times 2\ C_6H_{16}N$ (931.8).

Methyl 4,5,7-Tri-*O*-benzyl-2-deoxy-D-*gluco*-heptulosonate Diethyldithioacetal (35). This compound was synthesized according to our published procedure.[35]

Methyl 4,5,7-Tri-*O*-benzyl-2-deoxy-2-ethylthio-α-D-*gluco*-hept-2-ulopyranosonate (36). To a cooled (−30 °C) solution of **35** (1.0 g, 1.63 mmol) in dry CH_3CN (30 mL) was added NIS (385 mg, 1.71 mmol). After stirring for 30 min at −30 °C, the reaction was quenched by the addition of Et_3N (2 mL), and aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ were added. After extraction with EtOAc, the pooled organic phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (toluene/ethyl acetate 10:1) afforded **36** (680 mg, 1.24 mmol, 76%) as a colorless oil: TLC (toluene/ethyl acetate = 6:1), R_f = 0.32; $[\alpha]_D$ (c = 1, $CHCl_3$), +76.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.21 (t, 3 H, SCH_2CH_3), 2.37−2.63 (m, 2 H, SCH_2CH_3), 3.60−3.61 (m, 2 H, 5-H, OH), 3.76 (m, 2 H, 7a,b-H), 3.86 (s, 3 H, CO_2CH_3), 4.00 (dd, $J_{4,3} = J_{4,5}$ = 9.1 Hz, 1 H, 4-H), 4.12−4.14 (m, 2 H, 3-H, 6-H), 4.53−5.06 (m, 6 H, CH_2Ph), 7.16−7.33 (m, 15 H, Ph); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 13.9 (1 C, SCH_2CH_3), 20.9 (1 C, SCH_2CH_3), 52,9 (1 C, CO_2CH_3), 68.4 (1 C, 7-C), 72.6 (1 C, 6-C), 73.3−75.7 (4 C, 3-C, CH_2Ph), 76.6 (1 C, 5-C), 82.5 (1 C, 4-C), 88.0 (1 C, 2-C), 127.6−138.8 (18 C, Ph), 170.9 (1 C, 1-C); $C_{31}H_{36}O_7S$ (552.68), calcd: C, 64.45; H, 6.11; N, 7.27. Found: C, 64.58; H, 6.00; N, 7.33.

Methyl 4,5,7-Tri-*O*-benzyl-α-D-*gluco*-hept-2-ulopyranosonate (37). This compound was synthesized according to our published procedure.[35]

Methyl 3-Azido-4,5,7-tri-*O*-benzyl-2,3-dideoxy-2-ethylthio-α-D-*manno*-hept-2-ulopyranosonate (38). To a cooled (0 °C) solution of **36** (4.0 g, 7.2 mmol) in dry CH_2Cl_2 (100 mL) were added pyridine (1.9 mL, 28 mmol) and trifluoromethansulfonic anhydride (2.3 mL, 14 mmol). After stirring at 0 °C for 1 h, the reaction was quenched by the addition of water. After extraction with EtOAc, the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was dissolved in DMF (100 mL), and tetramethylguanidinium azide (6.3 g, 40 mmol) was added to the solution. After stirring at room temperature for 16 h, the solution was diluted with water. After extraction with EtOAc, the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/ethyl acetate 15:1) afforded **38** (3.3 g, 5.7 mmol, 79%) as a colorless syrup: TLC (toluene/ethyl acetate = 6:1), R_f = 0.60; $[\alpha]_D$ (c = 1, acetone), +57.0; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.17 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 2.53 (q, J = 7.5 Hz, 2 H, SCH_2CH_3), 3.76 (dd, $J_{7a,b}$ = 11.3 Hz, $J_{7a,6}$ = 1.8 Hz, 1 H, 7a-H), 3.78 (dd, $J_{7b,6}$ = 4.8 Hz, $J_{7b,a}$ = 11.3 Hz, 1 H, 7b-H), 3.85−3.88 (m, 4 H, 5-H, CO_2CH_3), 4.06 (ddd, $J_{6,5}$ = 9.9 Hz, $J_{6,7b}$ = 4.8 Hz, $J_{6,7a}$ = 1.8 Hz, 1 H, 6-H), 4.20 (d, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.24 (dd, $J_{4,5}$ = 9.2 Hz, $J_{4,3}$ = 3.5 Hz, 1 H, 4-H), 4.53−4.85 (m, 6 H, CH_2Ph), 7.19−7.40 (m, 15 H, Ph); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 14.0 (1 C, SCH_2CH_3), 22.9 (1 C, SCH_2CH_3), 52.9 (1 C, CO_2CH_3), 64.3 (1 C, 3-C), 68.3 (1 C, 7-C), 72.8−75.3 (5 C, CH_2Ph, 5-C, 6-C), 79.8 (1 C, 4-C), 86.8 (1 C, 2-C), 127.5−138.4 (18 C, Ph), 167.9 (1 C, 1-C); MALDI-MS (positive mode, DHB, dioxane) 617 $[M + K]^+$, 601 $[M + Na]^+$; $C_{31}H_{35}N_3O_6S$ (577.69), calcd: C, 64.45; H, 6.11; N, 7.27. Found: C, 64.58; H, 6.00; N, 7.33.

(Methyl 3-Azido-4,5,7-tri-*O*-benzyl-2,3-dideoxy-α-D-*manno*-hept-2-ulopyranoson-2-yl)ethyl Sulfoxide (39). To a cooled (−78 °C) solution of **38** (500 mg, 0.87 mmol) in dry CH_2Cl_2 (10 mL) was added *meta*-chloroperbenzoic acid (150 mg, 0.87 mmol). After stirring the reaction mixture at −78 °C → 0 °C for 2 h, it was poured into a mixture of a saturated aqueous solution of $NaHCO_3$ and $NaHSO_3$. After extraction of the water layer with CH_2Cl_2, the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 10:1) afforded the colorless oil **39** (343 mg, 0.58 mmol, 67%) as a diastereomeric mixture (R:S = 1:4): TLC (toluene/acetone = 9:1), (R) R_f = 0.31, (S) R_f = 0.28; $[\alpha]_D$ (c = 1, acetone), (S) +40.4; ^{1}H NMR (250 MHz, $CDCl_3$) (R) δ = 1.31 (m, 3 H, SCH_2CH_3), 2.40, 3.12 (2m, 2 H, SCH_2CH_3), 3.65 (dd, $J_{7a,b}$ = 10.1 Hz, $J_{7a,6}$ = 4.4 Hz, 1 H, 7a−H), 3.73−3.82 (m, 4 H, 7b−H, CO_2CH_3), 3.92 (dd, $J_{5,4} = J_{5,6}$ = 9.5 Hz, 1 H, 5-H), 4.52−4.84 (m, 9 H, CH_2Ph, 3-H, 4-H, 6-H), 7.15−7.32 (m, 15 H, Ph); (S) δ = 1.34 (m, 3 H, SCH_2CH_3), 2.54, 2.82 (2m, 2 H, SCH_2CH_3), 3.66 (m, 2 H, 7a,b-H), 3.86−4.02 (m, 4 H, 5-H, CO_2CH_3), 4.31 (m, 1 H, 6-H), 4.50−4.92 (m, 8 H, CH_2Ph, 3-H, 4-H), 7.14−7.37 (m, 15 H, Ph); MALDI-MS (positive mode, DHB, dioxane): 617.0 $[M + Na]^+$, 633.1 $[M + K]^+$, 497.7 $[M - S(O)Et - N_3 + Na]^+$, 513.8 $[M - S(O)Et - N_3 + K]^+$. $C_{31}H_{35}N_3O_7S$ (593.68), calcd: C, 62.72; H, 5.94; N, 7.07. Found: C, 62.75; H, 5.94; N, 7.05.

Methyl 3-Azido-4,5,7-tri-O-benzyl-3-deoxy-α-D-*manno*-hept-2-ulopyranosonate (40). To a cooled (−78 °C) solution of **39** (37 mg, 62 μmol) in dry Et_2O (5 mL) were added 2,6-di-*tert*-butyl pyridine (14 μL, 62 μmol) and Tf_2O (11 μL, 62 μmol). After stirring at −78 °C for 10 min, water (0.1 mL in 5 mL Et_2O) was added to the solution. After the reaction mixture was stirred at −78 °C → 0 °C for 1 h, it was poured into a saturated aqueous solution of $NaHCO_3$. After extraction with CH_2Cl_2, the pooled organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 20:1) afforded **40** (21 mg, 39 μmol, 63%) as a colorless oil: TLC (toluene/acetone = 9:1), R_f = 0.24; $[\alpha]_D$ (c = 0.33, dioxane), +6.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.65−3.70 (m, 2 H, 7a,b-H), 3.81 (dd, $J_{5,6}$ = 9.7 Hz, $J_{5,4}$ = 9.2 Hz, 1 H, 5-H), 3.86 (s, 3 H, CO_2CH_3), 3.96 (ddd, $J_{6,5}$ = 9.7 Hz, $J_{6,7a}$ = 4.6 Hz, $J_{6,7a}$ = 2.4 Hz, 1 H, 6-H), 4.12 (d, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.18 (dd, $J_{4,5}$ = 9.2 Hz, $J_{4,3}$ = 3.5 Hz, 1 H, 4-H), 4.50−4.85 (m, 6 H, CH_2Ph), 7.15−7.30 (m, 15 H, Ph); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 53.5 (1 C, CO_2CH_3), 62.7 (1 C, 3-C), 68.7 (1 C, 7-C), 72.7−75.2 (5 C, CH_2Ph, 5-C, 6-C), 79.5 (1 C, 4-C), 95.1 (1 C, 2-C), 127.6−138.1 (18 C, Ph), 168.9 (1 C, 1-C); MALDI-MS (positive mode, DHB, dioxane) 556.6 $[M + Na]^+$, 572.6 $[M + K]^+$; $C_{29}H_{31}N_3O_7 \times 0.5\ H_2O$ (542.59), calcd: C, 64.20; H, 5.94; N, 7.74. Found: C, 64.26; H, 5.60; N, 7.56.

Methyl 3-*O*-Acetyl-4,5,7-tri-*O*-benzyl-α-D-*gluco*-hept-2-ulopyranosonate (41). This compound was synthesized according to our published procedure.[35]

Methyl 4,5,7-Tri-*O*-benzyl-2-*O*-methyl-α-D-*gluco*-hept-2-ulopyranosonate (42). To a solution of **41** (210 mg, 0.38 mmol) in dry DMF (4 mL) were added NaH (10 mg, 0.40 mmol) and methyl iodide (36 μL, 0.57 mmol), and the solution was stirred for 2 h at room temperature. After complete conversion (TLC monitoring, toluene/acetone = 6:1, R_f = 0.70), dry methanol (4 mL) and NaOMe (20 mg) were added and the reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of acidic ion exchange resin. After 2 min, the reaction mixture was filtered, and the solution was poured into an aqueous solution of NH_4Cl. After extraction of the water layer, the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/

acetone 10:1) afforded **42** (110 mg, 0.21 mmol, 55%) as a colorless oil: TLC (toluene/acetone = 6:1), $R_f = 0.39$; $[\alpha]_D$ (c = 1, acetone), +51.0; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.42 (bd, 1 H, OH), 3.41 (s, 3 H, OMe), 3.62−3.88 (m, 9 H, 3-H, 4-H, 5-H, 6-H, 7a,b-H, CO_2Me), 4.52−4.93 (m, 6 H, CH_2Ph), 7.14−7.38 (m, 15 H, Ph); MALDI-MS (positive mode, DHB, dioxane) m/z 545.2 $[MNa]^+$, 561.2 $[MK]^+$; $C_{30}H_{34}O_8 \times 0.5\ H_2O$ (531.6), calcd: C, 67.78; H, 6.63. Found: C, 67.77; H, 6.40.

Methyl 3-Azido-4,5,7-tri-*O*-benzyl-3-deoxy-2-*O*-methyl-α-D-*manno*-hept-2-ulopyranosonate (43). Method A (from 42). To a cooled (0 °C) solution of **42** (110 mg, 0.21 mmol) in dry CH_2Cl_2 (10 mL) were added pyridine (70 μL, 0.84 mmol) and trifluoromethansulfonic anhydride (70 μL, 0.42 mmol), and the reaction mixture was stirred at 0 °C → 15 °C for 2 h. The reaction was quenched by the addition of water, and the water phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (10 mL), and tetramethylguanidinium azide (200 mg, 0.6 mmol) was added. After stirring at 60 °C for 2 days, water (40 mL) was added to the solution. The water phase was extracted with CH_2Cl_2, the pooled organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 15:1) afforded **43** (90 mg, 0.16 mmol, 78%) as a colorless syrup. **Method B (from 40).** To a solution of **40** (80 mg, 0.15 mmol) in dry DMF (3 mL) were added NaH (4 mg, 0.16 mmol) and methyl iodide (14 μL, 0.22 mmol), and the solution was stirred for 2 h at room temperature. After complete conversion (TLC monitoring, toluene/acetone = 6:1, $R_f = 0.68$), dry methanol (1 mL) was added, and the solution was concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 12:1) afforded **43** (70 mg, 0.13 mmol, 87%) as a colorless syrup: TLC (toluene/acetone = 6:1), $R_f = 0.68$; $[\alpha]_D$ (c = 1, acetone), + 19.9; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.21 (s, 3 H, OMe), 3.68 (m, 1 H, 6-H), 3.76 (m, 2 H, 7a,b H), 3.85−3.93 (m, 4 H, 5-H, CO_2Me), 4.16 (dd, $J_{4,5}$ = 9.1 Hz, $J_{4,3}$ = 3.5 Hz, 1 H, 4-H), 4.27 (d, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.50−4.87 (m, 6 H, CH_2Ph), 7.14−7.39 (m, 15 H, Ph); MALDI-MS (positive mode, DHB, dioxane): m/z 570.4 $[M + Na]^+$. $C_{30}H_{33}N_3O_7$ (547.6), calcd: C, 65.80; H, 6.07; N, 7.67. Found: C, 65.63; H, 6.16; N, 7.38.

Methyl 3-Acetamido-4,5,7-tri-*O*-benzyl-3-deoxy-2-*O*-methyl-α-D-*manno*-hept-2-ulopyranosonate (44). A solution of **43** (420 mg, 0.77 mmol) in pyridine/water (2:1, 9 mL) was treated with H_2S for 5 min. After stirring for 16 h at room temperature, the solution was concentrated under reduced pressure and coevaporated with pyridine. The residue was dissolved in pyridine (8 mL), and Ac_2O (4 mL) was added. After stirring at room temperature for 20 h, the solution was concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 6:1) afforded **44** (350 mg, 0.62 mmol, 81%) as a colorless foam: TLC (toluene/acetone = 4:1), $R_f = 0.27$; $[\alpha]_D$ (c = 0.5, acetone), −14.2; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.93 (s, 3 H, Ac), 3.23 (s, 3 H, OMe), 3.69−3.88 (m, 7 H, 4-H, 5-H, 7a,b-H, CO_2Me), 4.14 (m, 1 H, 6-H), 4.46−4.92 (m, 6 H, CH_2Ph), 5.07 (dd, $J_{3,NH}$ = 9.9 Hz, $J_{3,4}$ = 4.3 Hz, 1 H, 3-H), 5.68 (d, J = 9.9 Hz, 1 H, NH), 7.14−7.39 (m, 15 H, Ph); MALDI-MS (positive mode, DHB) m/z 587.1 $[M + Na]^+$, 603.2 $[M + K]^+$. $C_{32}H_{37}NO_8 \times 0.25\ H_2O$ (568.1), calcd: C, 67.65; H, 6.65; N, 2.46. Found: C, 67.67; H, 6.75; N, 2.58.

3-Acetamido-4,5,7-tri-*O*-benzyl-3-deoxy-2-*O*-methyl-α-D-*manno*-hept-2-ulopyranose (45). To a cooled (0 °C) solution of **44** (300 mg, 0.53 mmol) in THF/EtOH (7:5, 12 mL) was added sodium borohydride (80 mg, 2.1 mmol), and the reaction mixture was stirred at room temperature for 20 h. After complete conversion (TLC monitoring toluene/acetone 1:1; R_f = 0.44), the solution was concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 3:1) afforded **45** (230 mg, 0.43 mmol, 81%) as a colorless oil. TLC (toluene/acetone = 1:1), $R_f = 0.44$; $[\alpha]_D$ (c = 1, acetone), + 5.1; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.06 (s, 3 H, Ac), 3.28 (s, 3 H, OMe), 3.40 (dd, $J_{1a,b}$ = 12.5 Hz, $J_{1a,OH}$ = 4.6 Hz, 1 H, 1a-H), 3.58−3.72 (m, 4 H, 1b-H, 5-H, 7a,b-H), 3.78 (m, 1 H, 6-H), 4.18 (dd, J = 10 Hz, J = 4.6 Hz, 1 H, OH), 4.29 (m, 1 H, 4-H), 4.43−4.65 (m, 6 H, 3-H, CH_2Ph), 4.87 (d, J = 11.1 Hz, 1 H, CH_2Ph), 5.86 (d, J = 9.9 Hz, 1 H, NH), 7.16−7.37 (m, 15 H, Ph); MALDI-MS (positive mode, DHB) m/z 558.5 $[M + Na]^+$. $C_{31}H_{37}NO_7$ (535.6), calcd: C, 69.51; H, 6.96; N, 2.61. Found: C, 69.48; H, 7.25; N, 2.38.

5-Acetamido-1,3,4-tri-*O*-benzyl-5,7,8-trideoxy-α-L-*gulo*-oct-7-en-6-ulopyranose (46). To a cooled (−85 °C) solution of **24** (2.4 g, 4.9 mmol) in dry THF (30 mL) was added dropwise a 1 M solution of vinylmagnesium bromide (8 mL, 8 mmol) in THF. After stirring for 1 h at −85 °C, the reaction was quenched with methanol (10 mL), and the reaction mixture was warmed to room temperature. The reaction mixture was poured into a diluted aqueous solution of NH_4Cl, and the water phase was extracted with Et_2O. The pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 4:1) afforded **46** (1.8 g, 3.5 mmol, 71%) as a colorless oil: TLC (toluene/acetone = 2:1), $R_f = 0.35$; $[\alpha]_D$ (c = 1, $CHCl_3$), +57.3; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.80 (s, 3 H, Ac), 3.25 (bs, 1 H, OH), 3.67−3.85 (m, 4 H, 1a,b−H, 3-H, 4-H), 4.02−4.13 (m, 2 H, 2-H, 5-H), 4.51−4.83 (m, 6 H, CH_2Ph), 5.19 (d, $J_{8a,7}$ = 10.7 Hz, 1 H, 8a-H), 5.39 (d, $J_{8b,7}$ = 17.3 Hz, 1 H, 8b-H), 5.48 (d, J = 8.5 Hz, 1 H, NH), 5.92 (dd, $J_{7,8b}$ = 17.3 Hz, $J_{7,8a}$ = 10.7 Hz, 1 H, 7-H), 7.16−7.31 (m, 15 H, Ph); MALDI-MS (positive mode, DHB) m/z 540.6 $[M + Na]^+$. $C_{31}H_{35}NO_6$ (517.6), calcd: C, 70.71; H, 6.89; N, 2.66. Found: C, 70.83; H, 6.56; N, 2.17.

5-Acetamido-1,3,4-tri-*O*-benzyl-6-*O*-methyl-5,7,8-trideoxy-α-L-*gulo*-oct-7-en-6-ulopyranose (47). To a solution of **46** (270 mg, 0.52 mmol) in dry DMF (10 mL) were added methyl iodide (39 μL, 0.63 mmol) and NaH (15 mg, 0.63 mmol), and the solution was stirred for 2 h at room temperature. After complete conversion (TLC monitoring, toluene/acetone = 4:1, $R_f = 0.51$), dry methanol (5 mL) was added, and the solution was concentrated under reduced pressure. Purification by flash chromatography (toluene/ acetone 6:1) afforded **47** (220 mg, 0.40 mmol, 77%) as a colorless oil: TLC (toluene/acetone = 4:1): $R_f = 0.51$; $[\alpha]_D$ (c = 0.5, acetone) = + 35.9; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86 (s, 3 H, Ac), 3.12 (s, 3 H, OMe), 3.64−3.78 (m, 5 H, 1a,b-H, 2-H, 3-H, 4-H), 4.16 (m, 1 H, 5-H), 4.55−4.87 (m, 6 H, CH_2Ph), 5.34 (dd, $J_{8a,7}$ = 10.7 Hz, $J_{8a,b}$ = 2.5 Hz, 1 H, 8a-H), 5.46 (m, 2 H, 8b-H, NH), 5.66 (dd, $J_{7,8b}$ = 17.5 Hz, $J_{7,8a}$ = 10.7 Hz, 1 H, 7-H), 7.19−7.36 (m, 15 H, Ph); MALDI-MS (positive mode, DHB) m/z 554.3 $[M + Na]^+$, 570.3 $[M + K]^+$. $C_{32}H_{37}NO_6$ (531.6), calcd: C, 72.29; H, 7.01; N, 2.63. Found: C, 71.85; H, 6.89; N, 2.67.

3-Acetamido-4,5,7-tri-*O*-benzyl-3-deoxy-2-*O*-methyl-α-D-*gluco*-hept-2-ulopyranose (48). Into a cooled (−85 °C) solution of **47** (50 mg, 0.11 mmol) in dry CH_2Cl_2 (10 mL) was bubbled ozone for 5 min until the color of the solution turned to blue. Then O_2 was bubbled into the solution for 5 min until the solution was colorless again. Polymer bound triphenylphosphine (67 mg, 0.2 mmol) was added, and the reaction mixture was stirred for 30 min at room temperature. The resin was filtered off, and the solution was concentrated under reduced pressure. The residue was dissolved in dry methanol (10 mL), and sodium borohydride (10 mg, 0.25 mmol) was added. After stirring for 1 h at room temperature, the solution was concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 4:1) afforded **48** (22 mg, 41 μmol, 37%) as a colorless solid: TLC (toluene/acetone = 2:1), $R_f = 0.32$; $[\alpha]_D$ (c = 1, $CHCl_3$), + 85.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.82 (s, 3 H, Ac), 3.20 (s, 3 H, OMe), 3.40 (d, J = 12.1 Hz, 1 H, 7a-H), 3.64−3.75 (m, 7 H, 1a,b-H, 4-H, 5-H, 6-H, 7b-H, OH), 4.22 (dd, $J_{3,NH}$ = $J_{3,4}$ = 9.9 Hz, 1 H, 3-H), 4.57−4.64 (m, 4 H, CH_2Ph), 4.81, 4.86 (2 d, J = 11.9 Hz, 2 H, CH_2Ph), 5.17 (d, J = 9.4 Hz, 1 H, NH), 7.21−7.36 (m, 15 H, Ph); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 23.1 (1 C, Ac), 48.4 (1 C, OMe), 52.6 (1 C, 3-C), 62.6 (1 C, 7-C), 68.8 (1 C, 1-C), 72.3 (1

C, 6-C), 73.5, 74.6, 75.0 (3 C, CH_2Ph), 78.8 (1 C, 5-C), 79.8 (1 C, 4-C), 100.5 (1 C, 2-C), 127.6−138.4 (18 C, Ph), 171.5 (1 C, Ac); MALDI-MS (positive mode, DHB) *m/z* 557.9 $[M + Na]^+$, 574.0 $[M + K]^+$. $C_{31}H_{37}NO_7$ (535.6), calcd: C, 69.51; H, 6.96; N, 2.61. Found: C, 69.65; H, 7.08; N, 2.43.

(3-Acetamido-4,5,7-tri-*O*-benzyl-3-deoxy-2-*O*-methyl-α-D-*gluco*-hept-2-ulopyranos-1-yl)di-*O*-benzyl Phosphate (49). Following the procedure described for the synthesis of **50**, compound **48** (140 mg, 0.26 mmol) was converted to afford **49** (70 mg, 88 μmol, 34%) as a colorless oil: TLC (toluene/acetone = 2:1), $R_f = 0.41$; $[\alpha]_D$ ($c = 0.5$, Diox), +18.2; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.81$ (s, 3 H, Ac), 3.22 (s, 3 H, OMe), 3.59−3.62 (m, 5 H, 4-H, 5-H, 6-H, 7a,b-H), 4.03 (m, 2 H, 1a,b-H), 4.39−4.57 (m, 5 H, CH_2Ph, 3-H), 4.79, 4.81 (2 d, $J = 12$ Hz, 2 H, CH_2Ph), 4.98−5.09 (m, 4 H, $POCH_2$Ph), 5.47 (d, $J = 10.0$ Hz, 1 H, NH), 7.15−7.37 (m, 25 H, Ph); MALDI-MS (positive mode, DHB) *m/z* 818.6 $[M + Na]^+$, 834.8 $[M + K]^+$. $C_{45}H_{50}NO_{10}P \times 1.5\ H_2O$ (822.9), calcd: C, 65.68; H, 6.49; N, 1.70. Found: C, 65.31; H, 6.22; N, 1.66.

(3-Acetamido-4,5,7-tri-*O*-benzyl-3-deoxy-2-*O*-methyl-α-D-*manno*-hept-2-ulopyranos-1-yl)di-*O*-benzyl Phosphate (50). To a solution of **45** (190 mg, 0.35 mmol) in abs CH_2Cl_2 (8 mL) were added 1*H*-tetrazole (55 mg, 0.78 mmol) and dropwise bis(benzyloxy)(diisopropylamino)phosphine (184 μL, 0.56 mmol). After stirring for 5 h, the solution was cooled to 0 °C, and a 5.5 M solution of *tert*-butyl hydroperoxide (110 μL, 0.6 mmol) in decane was added dropwise. After stirring for 1 h at room temperature, the reaction mixture was poured into an aqueous solution of $Na_2S_2O_3$. The organic phase was washed with brine, an aqueous solution of $NaHCO_3$, and again with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 4:1) afforded **50** (205 mg, 0.26 mmol, 74%) as a colorless oil: TLC (toluene/acetone 3:2), $R_f = 0.70$; $[\alpha]_D$ ($c = 0.7$, dioxane), + 14.4; ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.91$ (s, 3 H, Ac), 3.21 (s, 3 H, OMe), 3.56−3.77 (m, 4 H, 6-H, 5-H, 7a,b−H), 3.94 (dd, $J_{1a,P} = 10.9$ Hz, $J_{1a,b} = 5.4$ Hz, 1 H, 1a-H), 4.15 (m, 2 H, 1b−H, 4-H), 4.39−4.58 (m, 4 H, CH_2Ph), 4.78−4.95 (m, 3 H, 3-H, CH_2Ph), 5.08 (m, 4 H, $POCH_2$Ph), 5.73 (d, $J = 10.2$ Hz, 1 H, NH), 7.16−7.38 (m, 25 H, Ph); MALDI-MS (positive mode, DHB) *m/z* 818.6 $[M + Na]^+$. $C_{45}H_{50}NO_{10}P \times H_2O$ (813.9), calcd: C, 66.41; H, 6.43; N, 1.72. Found: C, 66.01; H, 5.96; N, 1.78.

Bis-triethylammonium (3-Acetamido-3-deoxy-2-*O*-methyl-α-D-*gluco*-hept-2-ulopyranos-1-yl)phosphate (51). Following the procedure described for the synthesis of **52**, compound **49** (70 mg, 88 μmol) was deprotected to afford the triethylammonium salt **51** in quantitative yield, which could be used without purification for the next step: ^{1}H NMR (250 MHz, D_2O) $\delta = 1.15$ (q, 18 H, Et_3N), 1.93 (s, 3 H, Ac), 3.07 (q, 12 H, Et_3N), 3.21 (s 3 H, OMe), 3.36−3.45 (m, 2 H, 5-H, 6-H), 3.47−3.62 (m, 2 H, 4-H, 7a−H), 3.64−3.87 (m, 3 H, 1a,b-H, 7b-H), 3.94 (m, 1 H, 3-H); MALDI-MS (negative mode, ATT) *m/z* 344.9 $[M - 2\ HNEt_3^+ + H^+]^-$; $C_{22}H_{50}N_3O_{10}P$ (547.5).

Bis-triethylammonium (3-Acetamido-3-deoxy-2-*O*-methyl-α-D-*manno*-hept-2-ulopyranos-1-yl)phosphate (52). To a solution of **50** (80 mg, 0.1 mmol) in methanol (8 mL) was added Pd/C (10%, 20 mg). The suspension was stirred at room temperature for 20 h under a positive pressure of hydrogen. After filtration (Sartorius, 0.45 μm), Et_3N (0.1 mL) was added to the filtrate. The solution was concentrated under reduced pressure to afford the triethylammonium salt **52** in quantitative yield. Compound **52** could be used without purification for the next step: ^{1}H NMR (250 MHz, D_2O): $\delta = 1.14$ (q, 18 H, Et_3N), 1.92 (s, 3 H, Ac), 3.05 (q, 12 H, Et_3N), 3.19 (s 3 H, OMe), 3.40 (m, 2 H, 5-H, 6-H), 3.59 (dd, $J_{1a,P} = 11.0$ Hz, $J_{1a,b} = 4.3$ Hz, 1 H, 1a-H), 3.70 (m, 2 H, 7a,b-H), 3.84 (dd, $J_{1b,P} = 11.7$ Hz, $J_{1b,a} = 4.3$ Hz, 1 H, 1b-H), 3.92 (dd, $J_{4,5} = 9.7$ Hz, $J_{4,3} = 4.5$ Hz, 1 H, 4-H), 4.35 (d, $J_{3,4} = 4.5$ Hz, 1 H, 3-H); MALDI-MS (negative mode, ATT) *m/z* 344.7 $[M - 2\ HNEt_3^+ + H^+]^-$; $C_{22}H_{50}N_3O_{10}P$ (547.5).

Methyl 4,5,7-Tri-*O*-acetyl-3-azido-2,3-dideoxy-2-ethylthio-α-D-*manno*-hept-2-ulopyranosononate (53). A cooled (−20 °C) solution of **36** (250 mg, 0.44 mmol) in CH_2Cl_2/Ac_2O (20:1, 10 mL) was treated with a 1 M solution of BCl_3 in CH_2Cl_2 (9 mL). After stirring at −20 °C, the reaction was stopped by the addition of a saturated aqueous solution of $NaHCO_3$. After extraction of the water phase with EtOAc, the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was dissolved in pyridine/Ac_2O (2:1, 10 mL) and stirred for 16 h. The solution was concentrated under reduced pressure and coevaporated with toluene. Purification by flash chromatography (toluene/ethyl acetate 4:1) afforded **53** (110 mg, 0.25 mmol, 58%) as a colorless solid: TLC (toluene/ethyl acetate = 1:1), $R_f = 0.58$; $[\alpha]_D$ ($c = 0.2$, $CHCl_3$), + 44.0; ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.21$ (t, $J = 7.6$ Hz, 3 H, SCH_2CH_3), 2.04, 2.06, 2.09 (3 s, 9 H, Ac), 2.57 (q, $J = 7.6$ Hz, 2 H, SCH_2CH_3), 3.86 (s, 3 H, CO_2CH_3), 4.10−4.29 (m, 3 H, 6-H, 7a,b-H), 4.37 (d, $J_{3,4} = 3.7$ Hz, 1 H, 3-H), 5.28 (dd, $J_{5,4} = 9.8$ Hz, $J_{5,6} = 9.7$ Hz, 1 H, 5-H), 5.49 (dd, $J_{4,5} = 9.8$ Hz, $J_{4,3} = 3.7$ Hz, 1 H, 4-H). $C_{16}H_{23}N_3O_9S$ (433.43), calcd: C, 44.34; H, 5.35; N, 9.69. Found: C, 44.36; H, 5.44; N, 9.36.

(Methyl 4,5,7-Tri-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*manno*-hept-2-ulopyranosonon-2-yl)ethyl Sulfoxide (54). A solution of **53** (220 mg, 0.51 mmol) in acetonitrile/water (5:1, 6 mL) was treated with Select-Fluor (220 mg, 0.62 mmol) and stirred at room temperature for 30 min. Then the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, and the water layer was extracted with CH_2Cl_2. The pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 6:1) afforded the diasteriomeric mixture (R:S = 2:3) of **54** (210 mg, 0.47 mmol, 92%) as a colorless foam: TLC (toluene/acetone = 3:1), (S) $R_f = 0.32$, (R) $R_f = 0.41$; ^{1}H NMR (250 MHz, $CDCl_3$) (R) $\delta = 1.41$ (t, $J = 7.6$ Hz, 3 H, SCH_2CH_3), 2.02, 2.05, 2.10 (3 s, 9 H, Ac), 2.64, 2.84 (2 m, 2 H, SCH_2CH_3), 3.92 (s, 3 H, OMe), 4.08−4.24 (m, 3 H, 6-H, 7a,b-H), 4.86 (d, $J_{3,4} = 3.7$ Hz, 1 H, 3-H), 5.35 (dd, $J_{5,4} = J_{5,6} = 10.0$ Hz, 1 H, 5-H), 5.67 (dd, $J_{4,5} = 10.0$ Hz, $J_{4,3} = 3.7$ Hz, 1 H, 4-H); S: $\delta = 1.39$ (t, $J = 7.6$ Hz, 3 H, SCH_2CH_3), 2.02, 2.07, 2.10 (3 s, 9 H, Ac), 2.61, 3.13 (2 m, 2 H, SCH_2CH_3), 3.83 (s, 3 H, OMe), 4.10−4.24 (m, 2 H, 7a,b-H), 4.96 (d, $J_{3,4} = 3.9$ Hz, 1 H, 3-H), 5.05 (ddd, $J_{6,5} = 10.2$ Hz, $J_{6,7a} = 4.6$ Hz, $J_{6,7b} = 2.8$ Hz, 1 H, 6-H), 5.41 (dd, $J_{5,4} = J_{5,6} = 10.2$ Hz, 1 H, 5-H), 5.91 (dd, $J_{4,5} = 10.2$ Hz, $J_{4,3} = 3.9$ Hz, 1 H, 4-H); MALDI-MS (positive mode, DHB, dioxane) 472.2 $[M + Na]^+$, 488.3 $[M + K]^+$, 353.2 $[M - S(O)Et - N_3 + Na]^+$, 369.3 $[M - S(O)Et - N_3 + K]^+$; $C_{16}H_{23}N_3O_{10}S$ (449.4).

Methyl 4,5,7-Tri-*O*-acetyl-3-azido-3-deoxy-α,β-D-*manno*-hept-2-ulopyranosonate (55). To a cooled (−70 °C) solution of **54** (945 mg, 2.1 mmol) in dry Et_2O/CH_2Cl_2 (1:1, 40 mL) were added 2,6-di-*tert*-butyl pyridine (540 μL, 2.4 mmol) and Tf_2O (406 μL, 2.4 mmol). After stirring for 5 min at −70 °C, water (1 mL + 4 mL Et_2O) was added to the solution. After the reaction mixture was stirred at −70 °C → −30 °C for 1 h, the solution was poured into a saturated aqueous solution of $NaHCO_3$. After extraction of the water phase with EtOAc, the pooled organic phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 4:1) afforded **55** (712 mg, 1.8 mmol, 88%) as a colorless oil: TLC (toluene/ethyl acetate = 1:1), $R_f = 0.30$; ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 2.03$, 2.08, 2.09 (3 s, 9 H, Ac), 3.88 (s, 3 H, CO_2CH_3), 4.05−4.32 (m, 4 H, 3-H, 6-H, 7a,b-H), 5.34 (dd, $J_{5,4} = 9.9$ Hz, $J_{5,6} = 9.8$ Hz, 1 H, 5-H), 5.48 (dd, $J_{4,5} = 9.9$ Hz, $J_{4,3} = 3.6$ Hz, 1 H, 4-H); FAB-MS (positive mode, NBA, NaI) *m/z* = 412 $[M + Na]^+$, 390 $[M + H]^+$; $C_{14}H_{19}N_3O_{10}$ (389.32).

Methyl 4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-azido-3-deoxy-D-*arabino*-hept-2-enopyranosonate (56). To a solution of **55** (40 mg, 103 μmol) in dry acetonitrile (5 mL) were added Hünigs base (36 μL, 206 μmol) and diethyl chlorophosphit (22 μL, 155 μmol). After stirring at room temperature for 15 min, Et_3N (1 mL) was added and the solution was concentrated under reduced pressure to a volume of 1 mL ($T < 30$ °C). This

solution was filtered by short flash chromatography (toluene/Et_3N 20:1). The crude material was dissolved in dry CH_2Cl_2 (20 mL) and treated with TMSOTf (8 μL, 40 μmol). After stirring at room temperature for 5 min, the solution was poured into a saturated aqueous solution of $NaHCO_3$. After extraction of the water phase with EtOAc, the pooled organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (toluene/ethyl acetate 4:1) afforded **56** (32 mg, 86 μmol, 81%) as a colorless oil: TLC (toluene/ethyl acetate = 1:1), $R_f = 0.54$; $[\alpha]_D$ ($c = 0.5$, $CHCl_3$), +5.5; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.07, 2.07, 2.12 (3 s, 9 H, Ac), 3.87 (s, 3 H, CO_2CH_3), 4.19 (dd, $J_{7a,b} = 12.2$ Hz, $J_{7a,6} = 3.7$ Hz, 1 H, 7a-H), 4.39 (dddd, $J_{6,5} = 6.3$ Hz, $J_{6,7b} = 6.1$ Hz, $J_{6,7a} = 3.7$ Hz, $^4J_{6,4} < 1$ Hz, 1 H, 6-H), 4.49 (dd, $J_{7b,a} = 12.2$ Hz, $J_{7b,6} = 6.1$ Hz, 1 H, 7b-H), 5.23 (dd, $J_{5,6} = 6.3$ Hz, $J_{5,4} = 4.4$ Hz, 1 H, 5-H), 5.66 (dd, $J_{4,5} = 4.2$ Hz, $^4J_{4,6} < 1$ Hz, 1 H, 4-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.1 (3 C, Ac), 53.2 (1 C, OMe), 60.7 (1 C, 7-C), 67.8, 68.0 (2 C, 4-C, 5-C), 75.0 (1 C, 6-C), 121.6 (1 C, 3-C), 136.2 (1 C, 2-C), 161.4 (1 C, 1-C), 169.8, 170.2, 170.9 (3 C, Ac); FAB-MS (positive mode, NBA, NaI) m/z = 394 $[M + Na]^+$, 366 $[M - N_2 + Na]^+$; $C_{14}H_{17}N_3O_9$ (371.30).

Methyl 3-Acetamido-4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*arabino*-hept-2-enopyranosonate (57). To a solution of **56** (72 mg, 0.19 mmol) in MeOH (10 mL) was added piperidine (100 μL), and H_2S was bubbled into the solution for 5 min. After stirring for 15 min at room temperature, the solution was concentrated under reduced pressure. The crude material (626) was dissolved in CH_2Cl_2 (15 mL) and treated with Ac_2O (1 mL). After stirring at room temperature for 5 h, pyridine (0.5 mL) was added, and the solution was stirred at room temperature for 16 h. After concentration under reduced pressure, the compound was purified by flash chromatography (toluene/ethyl acetate 4:1) to afford **57** (30 mg, 78 μmol, 41%) as a colorless oil: TLC (toluene/acetone = 2:1), $R_f = 0.46$; $[\alpha]_D$ ($c = 0.8$, dioxane), −39.4; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.02, 2.07, 2.08, 2.10 (4 s, 12 H, Ac), 3.86 (s, 3 H, CO_2CH_3), 4.11 (dd, $J_{7a,b} = 12.3$ Hz, $J_{7a,6} = 3.4$ Hz, 1 H, 7a-H), 4.37 (m, 1 H, 6-H), 4.55 (dd, $J_{7b,a} = 12.3$ Hz, $J_{7b,6} = 6.6$ Hz, 1 H, 7b-H), 5.19 (dd, $J_{5,6} = 4.5$ Hz, $J_{5,4} = 4.2$ Hz, 1 H, 5-H), 6.38 (d, $J_{4,5} = 4.2$ Hz, 1 H, 4-H), 9.94 (bs, 1 H, NH); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 20.6, 20.7, 20.8, 24.8 (4 C, 4 Ac), 52.7 (1 C, CO_2CH_3), 60.4 (1 C, 7-C), 66.0 (1 C, 4-C), 66.8 (1 C, 5-C), 73.8 (1 C, 6-C), 126.2 (1 C, 3-C), 129.0 (1 C, 2-C), 164.8, 168.1, 169.4, 169.5, 170.5 (5 C, Ac, 1-C); MALDI-MS (positive mode, DHB) 410.3 $[M + Na]^+$, 426.3 $[M + K]^+$. $C_{16}H_{21}NO_{10}$ (387.3), calcd: C, 49.61; H, 5.46; N, 3.61. Found: C, 49.55; H, 5.76; N, 3.54.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Supporting Information Available: Supporting Information Available. NMR Spectra of compounds **1**−**8**, **12**−**23**, **25**−**34**, **36**, **38**−**40**, and **42**−**57**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0353029