Synthesis of Novel Donor Mimetics of UDP-Gal, UDP-GlcNAc, and UDP-GalNAc as Potential Transferase Inhibitors†

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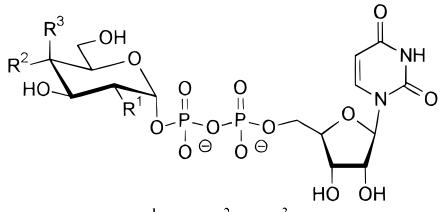
For the enzymatic transfer of galactose, *N*-acetylglucosamine, and *N*-acetylgalactosamine, UDP-Gal (**1**), UDP-GlcNAc (**2**), and UDP-GalNAc (**3**) are employed, and UDP serves as a feedback inhibitor. In this paper the synthesis of the novel UDP-sugar analogues **4**, **5**, and **6** as potential transferase inhibitors is described. Compounds **4**−**6** feature C-glycosidic hydroxymethylene linkages between the sugar and nucleoside moieties in contrast to the anomeric oxygens in the natural derivatives **1**−**3**.

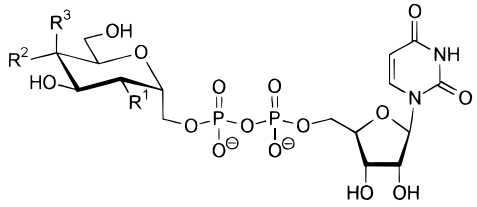
Introduction

In recent years much progress has been made toward a broader understanding of the functions of complex oligosaccharide structures. It is now well accepted that carbohydrates, in addition to their well-known role as molecules for energy storage, are of crucial importance in various biological processes such as cell−cell recognition, tumor cell metastasis, and leukocyte adhesion during inflammation.[1,2] Despite the rapidly growing knowledge in this field, the molecular basis of many processes is often still uncertain. The glycosyl transferases of the Leloir pathway are key catalysts for synthesis of oligosaccharides and glycoconjugates in vivo.[3−5] These enzymes transfer activated monosaccharide units in the form of their nucleotide diphosphate derivatives to a specific free hydroxy group of the acceptor molecule. Modulation or inhibition of this transfer reaction provides an excellent opportunity for intervention of the oligosaccharide biosynthesis and to obtain a more complete understanding of the structure−function relation of oligosaccharides on a molecular basis.[6]

Because UDP-Gal (**1**), UDP-GlcNAc (**2**), and UDP-GalNAc (**3**) are donor substrates of the various Gal-, GlcNAc-, and GalNAc-transferases, we present herein new donor mimetics **4**−**6** as potential inhibitors of the corresponding transferases. Inhibition of these enzymes is of particular interest, as they are involved in many important biological processes. For example, UDP-Gal (**1**) and UDP-GalNAc (**3**) are key intermediates in the biosynthesis of O-glycoproteins, a process which is still under investigation.[7] UDP-Gal (**1**) and UDP-GlcNAc (**2**) are intermediates in the biosynthesis of cell surface ligands which mediate various cell−cell recognition phenomena.[1] UDP-GlcNAc (**2**) plays an important role in the biosynthesis of N-glycoproteins in general and is involved in the recently described dynamic O-GlcNAcylation of specific proteins.[8,9] Inhibitors for these metabolic pathways should be appreciated and enhance the understanding of such processes.[10]



1 R^1= OH, R^2= H, R^3= OH
2 R^1= NHAc, R^2= OH, R^3= H
3 R^1= NHAc, R^2= H, R^3= OH



4 R^1= OH, R^2= H, R^3= OH
5 R^1= NHAc, R^2= OH, R^3= H
6 R^1= NHAc, R^2= H, R^3= OH

A common approach for the synthesis of natural saccharide phosphate mimetics is the substitution of a phosphoester oxygen atom by a carbon atom, resulting in the formation of isosteric C-glycosidic phosphonates.[11−14] However, phosphonates have the inherent disadvantage of being markedly different in charge and shape under physiological conditions.[15] In addition such ground-state analogues are expected to show only modest inhibition rates. For this reason we have decided to substitute the

† Dedicated to Professor Pierre Sinaÿ on the occasion of his 62nd birthday.

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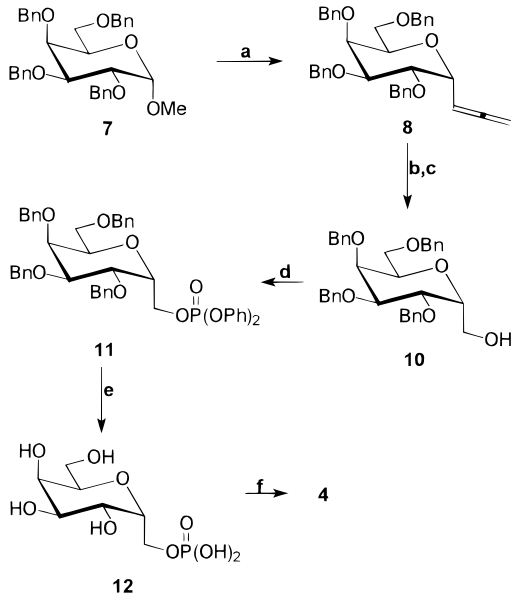
Scheme 1[a]



[a] Key: (a) Propargyl-TMS, CH_3CN, $BF_3{\cdot}Et_2O$. (b) O_3, CH_2Cl_2. (c) $NaBH_4$, EtOH. (d) $PO(OPh)_2Cl$, Py, DMAP. (e) (1) Pd/C, MeOH. (2) PtO_2, MeOH, uridine 5′-monophosphomorpholidate, 1*H*-tetrazole, Py.

anomeric hydroxy group of Gal, GlcNAc, and GalNAc with a hydroxymethylene group to give the homologous C-glycosidic UDP-sugars **4**−**6** after phosphorylation and coupling with UMP. Compounds **4**−**6** are distinguished by phosphoester bonds between the sugars and the nucleotides. The labile glycosidic phosphoester bonds of the natural donors **1**−**3** are replaced by C-glycosidic linkages to give **4**−**6** a high resistance to chemical and enzymatic hydrolysis. The distances between the anomeric centers and the nucleotides are somewhat increased. This may lead to stronger binding since the compounds will more closely resemble the transition state formed during the enzymatic reaction.[16] Therefore, the mimetics **4**−**6** may be considered to be suitable transferase inhibitors.

Results and Discussion

For the synthesis of the UDP-sugar mimetics **4**−**6** the appropriate phosphates **11**, **22**, and **25** had to be synthesized first. Starting from benzyl-protected methyl galactoside **7**, conversion under Lewis acid catalysis ($BF_3{\cdot}Et_2O$) gave the C-glycosidic α-allene derivative **8**.[17] Only a minor amount of the *β*-anomer was formed, which could easily be separated by column chromatography. Oxidative cleavage of **8** by ozonolysis led to the appropriate aldehyde, which was subjected to $NaBH_4$ reduction to give the C-glycosidic 1-hydroxymethylene derivative **9**. The subsequent phosphorylation was performed by treatment of the alcohol **9** with diphenylchlorophosphate to give the phosphate **10**. Hydrogenolysis of the protective groups using subsequently Pd/C and PtO_2 afforded the deprotected 1-*C*-α-hydroxymethylene galactose phosphate (**12**) (Scheme 1).

For access to the 1-*C*-α-hydroxymethylene-GlcNAc and 1-*C*-α-hydroxymethylene-GalNAc phosphates (**22**, **25**) C-glycosidic linkages at the anomeric centers of GlcNAc and GalNAc had to be established. In the area of C-glycoside chemistry, only a limited number of procedures are known for the demanding task to introduce a C-glycosidic bond into 2-amino-sugars.[18−21] We chose the method recently published by Kessler et al. using a dianion strategy.[22−24] The benzylated, anomerically unblocked GlcNAc and GalNAc derivatives **12** and **13** were converted to the anomeric chlorides according to the literature.[23] These were converted into their dilithium intermediates, and by treatment with carbon dioxide the 1-*C*-α-carboxylic acids **14** and **15** were obtained. Subsequent methylation led to the methyl esters **16** and **17**, which were reductively converted to the 1-*C*-α-hydroxymethylene-GlcNAc and -GalNAc derivatives **18** and **19**.

Attempts to form the 1-*C*-α-hydroxymethylene derivatives directly by reaction of the dianion intermediates with paraformaldehyde or formaldehyde gave no results or only very low yields of the desired products. Phosphorylation of the benzylated 1-*C*-α-hydroxymethylene-GlcNAc **18** gave the diphenyl phosphate **20**, which could be deprotected by hydrogenolysis to give the free phosphate **22**, using the same procedure as described for the galactose phosphate **11**. To obtain the appropriate C-glycosidic GalNAc phosphate, a different approach had to be used, since all attempts to reductively cleave the phenyl phosphate ester group of **21** accordingly did not meet with success. Thus, starting with the alcohol **19**, the dibenzyl phosphite **23** was formed and oxidatively converted to the dibenzyl phosphate **24**. The following hydrogenolysis using Pd/C gave the desired completly deprotected phosphate **25** (Scheme 2).

The synthesis of the UDP-Gal (**4**) UDP-GlcNAc (**5**), and UDP-GalNAc (**6**) mimetics was performed following a recent procedure of Wittmann and Wong,[25] which is an improved variant of the Moffat−Khorana phosphomorpholidate coupling method.[26] The diphosphates could be isolated in 48−55% yield. The ^{1}H NMR and ^{13}C NMR spectra showed the expected signals; a nearly complete assignment could be performed by 2D NMR experiments. In the case of **6** signal broadening due to coalescence phenomena prevented a detailed signal identification in the ^{1}H NMR spectrum. The ^{31}P NMR spectra of **4**, **5**, and **6** show the two characteristic phosphorus atom signals with P−P geminal couplings. In the case of **6**, low-temperature spectra recorded at 253 K provided signals with the expected doublet structures.

In this paper we report on the synthesis of C-glycosidic UDP-Gal, UDP-GlcNAc, and UDP-GalNAc mimetics. This novel class of compounds is presumed to feature potent inhibition of glycosyltransferases because they are structurally related to the transition states of the ap-

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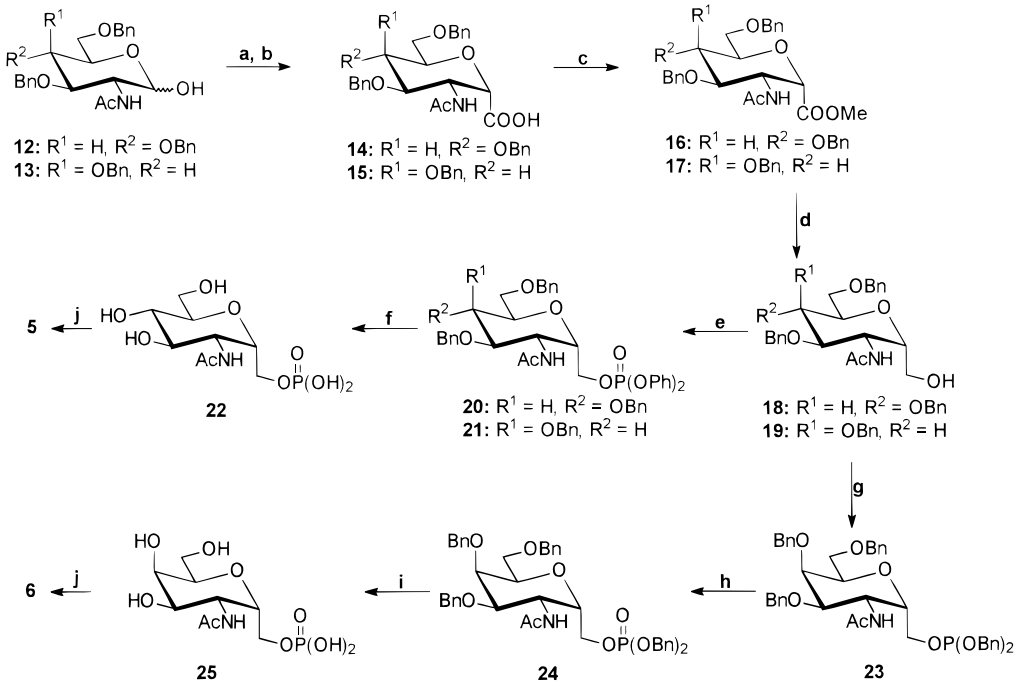
Scheme 2[a]



[a] Key: (a) $SOCl_2$, Tol. (b) (1) BuLi, THF. (2) LiNaph, THF. (3) CO_2. (c) MeI, DMF. (d) $NaBH_4$, EtOH. (e) $PO(OPh)_2Cl$, Py, DMAP. (f) (1) Pd/C, MeOH. (2) PtO_2, MeOH. (g) Di(benzyloxy)-*N*,*N*-diisopropylphosphoamidite, CH_2Cl_2, 1*H*-tetrazole. (h) MCPBA. (i) Pd/C, MeOH. (j) Uridine 5′-monophosphomorpholidate, 1*H*-tetrazole, Py.

propriate transfer reactions. Insight into various mechanisms of several metabolic processes is expected, biological evaluations are currently under investigation, and the results will be reported in due course.

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 400 or DMX 500. *J* values are given in hertz. 2D experiments were done for all novel compounds. Optical rotations were measured with a Perkin-Elmer 243 polarimeter. MALDI-TOF mass spectra were obtained on a Bruker Biflex III spectrometer. Merck silica gel 60 (partical size 40−63 μm) was employed for flash chromatography. For gel permeation chromatography Biogel P-2 was used.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-L-*gluco*-heptitol (9). A solution of allene **8**[17] (2.0 g, 3.55 mmol) in dry CH_2Cl_2 (80 mL) was stirred at −65 °C. Ozone was bubbled through for 2 h until the blue color indicated a saturated solution. Excess ozone was removed by purging with nitrogen. Dimethyl sulfide was added, and the solution was stirred overnight. Evaporation under reduced pressure gave the crude aldehyde, which was redissolved in dry ethanol (40 mL). The solution was cooled to 0 °C, and sodium borohydride (0.3 g, 7.9 mmol) was added and stirred for 4 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated and the residue chromatographically purified by flash chromatography over silica gel (petroleum ether (50−70)−EtOAc, 4:1) to give alcohol **9** as an oil (672 mg, 34%): $[\alpha]^{20}_D$ = +30.0 (*c* 1,CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.54 (dd, 1H, *J* = 4.5, 10.2, H-1), 3.61 (dd, 1H, *J* = 4.6, 11.7, H-7), 3.68 (dd, 1H, *J* = 3.1, 7.1, H-4), 3.75 (dd, 1H, *J* = 8.1, 11.7, H-7′), 3.77−3.81 (m, 2H, H-1′, H-3), 3.92 (dd, 1H, *J* = 3.1, 4.1, H-5), 3.97−4.03 (m, 2H, H-2, H-6), 4.36−4.65 (m, 8H, 4 × CH_2−Bn), 7.16−7.27 (m, 20H, Ar), ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 59.78 (1C, C-7), 66.39 (1C, C-1), 70.30, 72.10 (2C, C-2, C-6), 71.98, 72.13, 72.27, 72.31 (4 × 1C, 4 × CH_2−Bn), 73.00 (1C, C-5), 74.98 (1C, C-3), 75.55 (1C, C-4), 126.50, 126.64, 126.70, 126.75, 126.81, 126.89, 126.97, 127.00, 127.10, 127.33, 127.37, 127.48, 136.80, 137.15, 137.26, 137.31 (24C, Ar). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.58; H, 6.84.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-L-*gluco*-heptitol-1-yl) Di-*O*-phenyl Phosphate (10). Compound **9** (252 mg, 0.45 mmol) was dissolved in dry pyridine (3 mL) under argon atmosphere, diphenyl chlorophosphate (0.2 mL, 1.0 mmol) and a catalytic amount of DMAP were added, and the solution was stirred overnight. The solvent was evaporated under reduced pressure and the residue codistilled three times with toluene and purified by flash chromatography over silica gel (petroleum ether (50−70)−EtOAc, 4:1) to give 273 mg (77%) of the phosphate **10** as an oil: $[\alpha]^{20}_D$ = +16.3 (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.59 (dd, 1H, *J* = 4.6, 10.2, H-7), 3.60 (dd, 1H, *J* = 3.6, 6.6, H-4), 3.70 (dd, 1H, *J* = 7.1, 10.2, H-7′), 3.80 (dd, 1H, *J* = 4.1, 6.6, H-3), 3.93 (dd, 1H, *J* = 3.6, 3.1, H-5), 4.09 (ddd, 1H, *J* = 3.1, 4.6, 7.1, H-6), 4.17 (m, 1H, H-2), 4.31 (m, 1H, H-1), 4.60 (m, 9H, 4 × CH_2−Bn, H-1′), 7.25−7.06 (m, 30H, Ar); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 65.09 (d, 1C, *J* = 6.1, C-1), 65.78 (1C, C-7), 68.91 (1C, C-2), 71.83, 72.12, 72.18, 72,45 (4 × 1C, CH_2−Bn), 72.26 (1C, C-6), 72.75 (1C, C-5), 74.02 (1C, C-3), 75.49 (1C, C-4), 119.05, 119.10, 119.14, 124.31, 126.44, 126.60, 126.75, 126.81, 126.93, 127.30, 127.36, 127.41, 128.73, 128.76, 137.23, 137.30 (36 C, Ar); ^{31}P NMR ($CDCl_3$, 80 MHz) δ 1.0; MALDI-TOF (positive mode, DHB) *m*/*z* calcd for $C_{47}H_{47}O_9P$ 786, found 809 (M + Na)$^+$. Anal. Calcd for $C_{47}H_{47}O_9P$: C, 71.74; H, 6.02. Found: C, 71.28; H, 5.98.

(2,6-Anhydro-D-*glycero*-L-*gluco*-heptitol-1-yl) Phosphate (11). To a solution of di-*O*-phenyl phosphate **10** (263 mg, 0.33 mmol) in dry methanol (25 mL) was added Pd/C (10%, 100 mg), and the mixture was stirred for 72 h at 45 °C under hydrogen atmosphere (1 bar). The catalyst was filtered off, and the solvent was evaporated under reduced pressure. The oily residue was redissolved in dry methanol (15 mL), PtO_2 (50 mg) was added, and the mixture was stirred for another 72 h under hydrogen atmosphere. Filtration and evaporation afforded 82 mg (100%) of **11** as a white hygroscopic solid, which was used for the following conversion without further purification: $[\alpha]^{20}_D$ = +30.8 (*c* 0.5, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 3.53 (dd, 1H, *J* = 4.1, 11.7, H-7), 3.60 (dd, 1H, *J* = 7.6, 11.7, H-7′), 3.69 (dd, 1H, *J* = 3.6, 9.7, H-4), 3.81−3.83 (m, 2H, H-5, H-6), 3.88 (dd, 1H, *J* = 5.6, 9.7, H-3), 3.93 (dd, 1H, *J* = 6.1, 8.6, H-1), 4.05−

4.09 (m, 2H, H-1′, H-2); ^{13}C NMR (D_2O, 100.62 MHz) δ 61.23 (1C, C-7), 61.75 (d, 1C, J = 5.1, C-1), 67.86 (1C, C-3), 69.03 (1C, C-5), 70.34 (1C, C-4), 73.51 (1C, C-6), 74.57 (1C, C-2); ^{31}P NMR (D_2O, 80 MHz) δ 0.96; MALDI-TOF (positive mode, DHB) m/z calcd for $C_7H_{15}O_9P$ 274, found 297 $(M + Na)^+$ and 313 $(M + K)^+$.

Ammonium (2,6-Anhydro-D-*glycero*-L-*gluco*-heptitol-1-yl) (Uridine-5′-yl) Diphosphate (4). To a solution of phosphate **11** (80 mg, 0.29 mmol) in water (4 mL) were added pyridine (12 mL) and tri-*N*-octylamine (128 μL, 0.29 mmol). The solvent was removed under reduced pressure, and the oily residue was codistilled with dry pyridine (3 × 2 mL) and dried under vacuum for 2 h. Subsequently 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphomorpholidate (367 mg, 0.465 mmol) and 1*H*-tetrazole (65 mg, 0.92 mmol) were added under argon atmosphere, and the mixture was dissolved in dry pyridine (1.5 mL) and stirred at room temperature for 2 d. The solution was diluted with water (2 mL) and evaporated. The residue was suspended in 0.1 M aqueous NH_4HCO_3 and extracted with ether to give a clear solution. The solvent was evaporated under reduced pressure, redissolved in water, and lyophilized. The solid residue was purified on Biogel P-2 to yield (83 mg, 48%) **4** as a white solid: $[\alpha]^{20}_D$ = +27.0 (*c* 1, H_2O); R_f 0.25 (*i*-PrOH/1 M NH_4HCO_3); ^{1}H NMR (D_2O, 500 MHz) δ 3.53 (dd, 1H, J = 7.5, 11.8, H-7), 3.61 (dd, 1H, J = 4.4, 11.8, H-7′), 3.72 (dd, 1H, J = 3.4, 9.8, H-4), 3.87−3.84 (m, 1H, H-5, H-6), 3.88 (dd, 1H, J = 5.6, 9.8, H-3), 4.02 (dd, 1H, J = 5.5, 8.3, H-5-Rib), 4.04 (dd, 1H, J = 5.7, 9.1, H-1), 4.08−4.06 (m, 1H, H-5′-Rib), 4.10 (m, 1H, H-2), 4.14−4.12 (m, 2H, H-4-Rib, H-1′), 4.22−4.19 (m, 2H, H-2-Rib, H-3-Rib), 5.80 (d, 1H, J = 4.1, H-1-Rib), 5.82 (d, 1H, J = 8.1, H-5-U), 7.80 (d, 1H, J = 8.1, H-6-U);^{13}C NMR (D_2O, 125 MHz) δ 61.15 (1C, C-7), 62.60 (d, 1C, J = 5.0, C-1), 65.27 (d, 1C, J = 5.1, C-5-Rib), 67.95 (1C, C-3), 69.00 (1C, C-5), 70.37 (1C, C-2-Rib/C-3-Rib), 73.61 (1C, C-6), 73.72 (1C, C-4), 74.15 (1C, C-2-Rib/C-3-Rib), 74.50 (1C, C-2), 83.63 (d, 1C, J = 9.2, C-4-Rib), 88.69 (1C, C-1-Rib), 103.03 (1C, C-6-U), 142.02 (1C, C-5-U), 152.15 (1C, C-4-U), 166.63 (1C, C-2-U); ^{31}P NMR (D_2O, 80 MHz) δ −10.54 (d, 1P, J = 20), −10.92 (d, 1P, J = 20); MALDI-TOF (negative mode, DHB) m/z calcd for $C_{16}H_{32}N_4O_{17}P_2$ 614, found 579 $(M - 2\ NH_4^+ + H^+)^-$.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-D-*ido*-heptonic Acid (14). To a suspension of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose (**12**)[23] (5.0 g, 10.2 mmol) under argon atmosphere in dry toluene (30 mL) and dry chloroform (30 mL) was added thionyl chloride (30 mL), and the resulting solution was stirred for 0.5 h. Subsequently the solution was evaporated, and the solid residue was codistilled with toluene (2 × 30 mL) and dried under vacuum. The chloride was dissolved in dry THF (80 mL) and cooled to −95 °C. Butyllithium (8 mL, 1.6 M in hexane, 12.8 mmol) was added (0.5 min) followed by a freshly prepared 1 M lithium naphthalenide solution (24 mL, 24 mmol) in THF (0.5 min). Carbon dioxide was bubbled through for 1 h at −78 °C, and then the solution was warmed to room temperature and diluted with saturated aqueous NH_4HCO_3 solution (30 mL) and EtOAc (50 mL). The organic phase was separated and the aqueous phase acidified with 5 M aqueous HCl to pH 5 and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated under vacuum, and chromatographically purified over silica gel (petroleum ether (50−70)−EtOAc, 2:1 to 1:3, and then EtOAc−MeOH−AcOH, 20:2:1 to 2:2:1) to afford **14** (3.48 g, 66%) as a yellow foam: $[\alpha]^{20}_D$ = +28.3 (*c* 1.02, acetone); R_f 0.41 (CH_2Cl_2/MeOH/TFA, 3:1:0.05); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.79 (s, 3H, CH_3), 3.38 (dd, 1H, J = 8.7, 7.6, H-5), 3.50 (d, 1H, J = 2.9, 11.2, H-7), 3.53 (dd, 1H, J = 5.3, 11.2, H-7′), 3.78 (dd, 1H, J = 7.6, 9.7, H-4), 3.88 (ddd, 1H, J = 2.9, 5.3, 8.7, H-6), 3.97 (ddd, 1H, 5.8, 8.7, 9.3, H-3), 4.20 (d, 1H, J = 5.8, H-2), 4.38−4.67 (m, 6H, 3 × CH_2−Bn), 7.08−7.24 (15H, Ar), 7.80 (d, 1H, J = 8.7, NH); ^{13}C NMR (DMSO-d_6, 100.62 MHz) δ 22.91 (1C, CH_3), 50.59 (1C, C-3), 68.94 (1C, C-7), 72.57 (1C, CH_2−Bn), 72.74 (1C, C-2), 73.83 (1C, CH_2−Bn), 74.00 (1C, CH_2−Bn), 74.92 (1C, C-6), 77.85 (1C, C-5), 79.12 (1C, C-4), 127.81, 127.94, 128.00, 128.06, 128.56, 128.63, 138.50, 138.56, 138.97 (15C, Ar), 169.94, 171.35 (2 × 1C, CONH, COOH); MALDI-TOF (positive mode, DHB) m/z calcd for $C_{30}H_{33}NO_7$ 519, found 542 $(M + Na)^+$ and 558 $(M + K)^+$. Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.33; H, 6.48; N, 2.68.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-D-*ido*-heptonic Acid Methyl Ester (16). To a solution of acid **14** (3.45 g, 6.64 mmol) in DMF (40 mL) were added $CsCO_3$ (2.6 g) and methyl iodide (0.5 mL, 8.0 mmol), and the mixture was stirred for 14 h. The solvent was removed under reduced pressure and the residue dissolved in EtOAc−water. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and filtered. The solvent was evaporated under vacuum to give **16** (3.0 g, 85%; mp 120 °C) as a white solid: $[\alpha]^{20}_D$ = +41.4 (*c* 0.37, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H, CH_3), 3.58 (dd, 1H, J = 9.7, 4.6, H-6), 3.65 (s, 3H, $COOCH_3$), 3.67−3.73 (m, 3H, H-4, H-7, H-7′), 4.08 (dd, 1H, J = 5.6, 9.7, H-5), 4.42−4.52 (m, 6H, H-2, H-3, 2 x CH_2−Bn), 4.54−4.60 (m, 2H, CH_2−Bn), 6.34 (d, 1H, J = 9.2, NH), 7.14−7.29 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 22.22 (1C, CH_3), 46.98 (1C, C-3) 51.28 (1C, COO−CH_3), 66.44 (1C, C-7), 69.01 (1C, C-2), 71.77, 72.02, 72.25 (3 × 1C, 3 × CH_2−Bn), 73.19 (1C, C-6), 74.48, 74.66 (2 × 1C, C-4, C-5), 126.71, 126.82, 126.97, 127.15, 127.38, 127.50, 127.53, 136.33, 136.55, 136.91 (15C, Ar), 168.73, 169.34 (2 × 1C, CONH, $COOCH_3$); MALDI-TOF (DHB, positive mode) m/z calcd for $C_{31}H_{35}NO_7$ 533, found 534 $(M + H)^+$. Anal. Calcd for $C_{31}H_{35}NO_7$: C, 69.78; H, 6.61; N, 2.62. Found: C, 69.65; H, 6.57; N, 2.59.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-1-hydroxy-D-*glycero*-D-*ido*-heptitol (18). To a solution of **16** (3.0 g 5.62 mmol) in dry ethanol/THF (2.5:1, 10 mL) at 0 °C was added sodium borohydride (638 mg, 10.87 mmol), and the mixture was stirred for 0.5 h at this temperature and then 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was diluted with saturated aqueous NH_4HCO_3 solution and CH_2Cl_2. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with saturated aqueous NH_4HCO_3 solution and brine, dried ($MgSO_4$), filtered, and evaporated under vacuum. Purification of the crude product by flash chromatography over silica gel yielded the alcohol **18** (1.82 g, 64%; mp 89−91 °C) as a white solid: $[\alpha]^{20}_D$ = +20.1 (*c* 1.22, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (s, 3H, CH_3), 3.25 (dd, 1H, J = 6.1,11.7, H-1), 3.52 (dd, 1H, J = 9.1, 11.7, H-1′), 3.56 (d, 1H, J = 3.0, H-4), 3.64 (d, 1H, J = 3.0, H-5), 3.66 (dd, 1H, J = 7.1, 10.2, H-7), 3.78 (dd, 1H, J = 7.6, 10.2, H-7′), 3.96 (ddd, 1H, J = 6.1, 8.7, 9.1, H-2), 4.15−4.22 (m, 2H, H-3, H-6), 4.37 (dd, 2H, CH_2−Bn), 4.44 (dd, 2H, CH_2−Bn), 4.56 (dd, 2H, CH_2−Bn), 7.13−7.30 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 22.08 (1C, CH_3), 44.54 (1C, C-3) 59.83 (1C, C-1), 66.43 (1C, C-7), 66.66 (1C, C-2), 70.87, 70.92 (2 × 1C, 2 × CH_2−Bn), 72.20 (1C, C-4), 72.33 (1C, CH_2−Bn), 72.36 (1C, C-5), 73.56 (1C, C-6), 126.49, 126.68, 126.75, 126.85, 126.99, 127.29, 127.53, 127.67, 136.01, 136.18, 136.99 (15C, Ar), 170.50 (1C, CONH); MALDI-TOF (positive mode, DHB) m/z calcd for $C_{30}H_{35}NO_6$ 505, found 506 $(M + H)^+$ and 528 $(M + Na)^+$. Anal. Calcd for $C_{30}H_{35}NO_6$: C, 71.27; H, 6.98; N, 2.77. Found: C, 71.34; H, 7.01; N, 2.74.

(3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-D-*ido*-heptitol-1-yl) Di-*O*-phenyl Phosphate (20). The procedure described for the synthesis of **10** was followed with the alcohol **18** (240 mg, 0.48 mmol). Purification by flash chromatography over silica gel (petroleum ether−EtOAc, 1:2) afforded 303 mg of the phosphate **20** (86%) as a yellow oil: $[\alpha]^{20}_D$ = −0.8 (*c* 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H, CH_3), 3.57−3.60 (m, 2H), 3.60 (dd, 1H, J = 6.6, 9.7, H-7), 3.68 (dd, 1H, J = 7.4, 9.7, H-7′), 4.11−4.25 (m, 5H), 4.34−4.41 (m, 4H, 2 × CH_2−Bn), 4.50 (dd, 2H, CH_2−Bn), 6.58 (d, 1H, J = 9.67, NH), 7.04−7.26 (m, 25H, Ar); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 22.13 (1C, CH_3), 44.99 (1C, C-3), 68.31 (d, 1C, J = 4.1, C-1), 70.98, 71.18, 72.30 (3 × 1C, 3 × CH_2−Bn), 66.94, 72.04, 73.23, 73.99, 119.07, 119.12, 119.30, 123.36, 124.31, 126.57,126.59, 126.66, 126.76, 126.94, 127.12, 127.38, 127.51, 127.56, 128.36, 128.72, 136.23, 136.33 (30C, Ar), 169.12 (1C, CONH); MALDI-TOF (positive mode, DHB) m/z calcd for

$C_{42}H_{44}NO_9P$ 737, found 738 $(M + H)^+$. Anal. Calcd for $C_{42}H_{44}NO_9P$: C, 68.38; H, 6.01; N, 1.90. Found: C, 68.98; H, 5.81; N, 1.91.

(3-Acetamido-2,6-anhydro-3-deoxy-D-*glycero*-D-*ido*-heptitol-1-yl) Phosphate (22). The procedure described for the synthesis of **11** was followed using the phosphate **20** (293 mg, 0.4 mmol) to provide 111 mg of **22** (93%) as a hygroscopic white solid, which was used for the following conversion without further purification: $[\alpha]^{20}_D = +29$ (*c* 0.5, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.88 (s, 3H, CH_3), 3.27 (dd, 1H, $J = 3.5, 9.2$, H-5), 3.59 (dd, 1H, $J = 4.3, 12.1$, H-7), 3.68 (dd, 1H, $J = 8.0, 12.1$, H-7′), 3.75 (dd, 1H, $J = 9.7, 3.5$, H-4), 3.87−3.91 (m, 2H, H-5, H-6), 3.95 (dd, 1H, $J = 5.7, 9.7$, H-3), 4.00 (dd, 1H, $J = 5.8, 8.3$, H-1), 4.10−4.16 (m, 2H, H-1′, H-2); ^{13}C NMR (D_2O, 100.62 MHz) δ 24.84 (1C, CH_3), 55.27 (1C, C-3), 63.99 (1C, C-7), 66.33 (d, 1C, $J = 5.1$, C-1), 73.53 (1C, C-5), 74.21 (1C, C-4), 75.60 (1C, C-2), 77.69 (1C, C-6), 170.32 (1C, CONH); ^{31}P NMR (D_2O, 80 MHz) δ 0.57.

Ammonium (3-Acetamido-2,6-anhydro-3-deoxy-D-*glycero*-D-*ido*-heptitol-1-yl) (Uridine-5′-yl) Diphosphate (5). The procedure described for the synthesis of **4** was followed using **22** (100 mg, 0.32 mmol) to give 107 mg of **5** (53%) as a white solid: $[\alpha]^{20}_D = +30.6$ (*c* 1, H_2O); R_f 0.24 (*i*-PrOH/1 M NH_4HCO_3) ^1H NMR (D_2O, 500 MHz) δ 1.89 (s, 3H, CH_3), 3.29 (dd, 1H, $J = 8.2, 9.9$, H-5), 3.59 (dd, 1H, $J = 5.2, 12.3$, H-7), 3.76 (dd, 1H, $J = 2.3, 12.3$, H-7′), 3.80 (ddd, 1H, $J = 2.3, 5.2, 9.9$, H-6), 3.90 (dd, 1H, $J = 8.2, 10.6$, H-4), 3.95 (dd, 1H, $J = 6.0, 10.6$, H-3), 4.03−4.09 (m, 3H, H-1, H-2, H-5′-Rib), 4.12 (dd, 1H, $J = 4.5, 11.8$, H-5-Rib), 4.15−4.19 (m, 2H, H-1, H-4-Rib), 4.23−4.26 (m, 2H, H-2-Rib, H-3-Rib), 5.85 (d, 1H, $J = 4.1$, H-1-Rib), 5.86 (d, 1H, $J = 8.2$, H-5-U), 7.83 (d, 1H, $J = 8.2$, H-6-U); ^{13}C NMR (D_2O, 125 MHz) δ 22.32 (1C, CH_3), 52.73 (1C, C-3), 61.47 (1C, C-7), 65.12 (d, 1C, $J = 6.1$, C-5-Rib), 65.30 (d, 1C, $J = 5.1$, C-1), 70.05, 71.03 (1C, C-5), 72.91 (d, 1C, $J = 9.2$, C-2), 71.73 (1C, C-4), 74.15, 75.42 (1C, C-6), 83.58 (1C, C-4-Rib), 88.76 (1C, C-1-Rib), 103.02 (1C, C-6-U), 141.99 (1C, C-5-U), 152.20 (1C, C-4-U), 166.61 (1C, C-2-U), 175.19 (1C, CONH); ^{31}P NMR (D_2O, 80 MHz) δ −10.84 (d, 1P, $J = 20.9$), −11.24 (d, 1P, $J = 20.9$); MALDI-TOF (negative mode, DHB) *m*/*z* calcd for $C_{18}H_{35}N_5O_{17}P_2$ 655, found 620 $(M - 2NH_4^+ + H)^-$.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-L-*gluco*-heptonic Acid (15).[27] Following the procedure described for the synthesis of **14**, compound **13** (2.24 g, 4.6 mmol)[24] was converted to afford of **15** (1.24 g, 53%) as a yellow foam: $[\alpha]^{20}_D = +12.5$ (*c* 0.5, $CHCl_3$); R_f 0.40 (CH_2Cl_2/MeOH/TFA, 3:1:0.05); ^1H NMR (DMSO-d_6, 400 MHz) δ 1.85 (s, 3H, CH_3), 3.60 (dd, 1H, $J = 4.5, 10.6$, H-7), 3.73 (m, 1H, H-7′), 3.91 (dd, 1H, $J = 3.1, 7.6$, H-4), 4.07 (dd, 1H, $J = 3.1, 3.1$, H-5), 4.30 (m, 1H, H-6), 4.41−4.59 (m, 8H, H-2, H-3, 3 × CH_2−Bn), 7.19−7.39 (m, 15H, Ar), 8.07 (d, 1H, $J = 7.6$, NH); ^{13}C NMR (DMSO-d_6, 100.62 MHz) δ 22.88 (1C, CH_3), 47.88 (1C, C-3), 67.61 (1C, C-7), 71.74 (1C, C-2), 72.41 (2 × 1C, 2 × CH_2−Bn), 73.18 (1C, C-5), 74.08, 74.16 (2 × 1C, CH_2−Bn, C-6), 76.03 (1C, C-4), 127.76, 127.84, 128.01, 128.47, 128.54, 128.56, 128.59, 138.67, 138.84, 138.86 (15C, Ar), 169.94, 171.32 (2 × 1C, CONH, COOH); MALDI-TOF (positive mode, DHB) *m*/*z* calcd for $C_{30}H_{33}NO_7$ 519, found 520 $(M + H)^+$ and 542 $(M + Na)^+$. Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 68.89; H, 6.31; N, 2.58.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-L-*gluco*-heptonic Acid Methyl Ester (17). The procedure described for the synthesis of **16** was followed using **15** (1.0 g, 1.93 mmol) to give 1.24 g of **17** (97%; mp 133 °C) as a yellow solid: $[\alpha]^{20}_D = +10.4$ (*c* 0.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81 (s, 3H, CH_3), 3.63−3.69 (m, 4H, CH_3, H-6), 3.75−3.83 (m, 3H, H-4, H-7, H-7′), 4.02−4.07 (m, 1H, H-5), 4.39−4.66 (m, 6H, H-2, H-3, 3 × CH_2−Bn), 6.68 (d, 1H, $J = 7.6$, NH), 7.19−7.28 (m, 15H, Ar); ^{13}C NMR (100.62 MHz, DMSO-d_6, 363 K): δ 23.27 (1C, CH_3), 48.68 (1C, C-3) 52.35 (1C, COO−CH_3), 68.65 (1C, C-7), 72.26 (1C, C-2), 72.56, 73.20, 73.83 (3 × 1C, 3 × CH_2−Bn), 74.21 (1C, C-6), 74.97 (1C, C-5), 77.10 (1C, C-4), 128.19, 128.26, 128.33, 128,39, 128.95, 128.99, 129.24, 139.36, 139.48, 139.52 (15C, Ar), 170.43, 170.82 (2 × 1C, CONH, $COOCH_3$); MALDI-TOF (positive mode, DHB) *m*/*z* calcd for $C_{31}H_{35}NO_7$ 533, found 534 $(M + H)^+$ and 556 $(M + Na)^+$. Anal. Calcd for $C_{31}H_{35}NO_7$: C, 69.78; H, 6.61; N, 2.62. Found: C, 69.52; H, 6.45; N, 2.60.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-1-hydroxy-D-*glycero*-L-*gluco*-heptitol (19). The procedure described for the synthesis of **18** was followed using the ester **17** (1.2 g, 2.25 mmol) to afford 808 mg of **19** (71%; mp 139 °C) as a white solid: $[\alpha]^{20}_D = +31.6$ (*c* 1, H_2O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.90 (s, 3H, CH_3), 3.49−3.56 (m, 2H, CH_2-1), 3.65−3.70 (m, 2H, H-5, H-7), 3.86 (dd, 1H, $J = 3.0, 4.5$, H-4), 4.02 (m, 1H, H-2), 4.08 (dd, 1H, $J = 9.0, 11.7$, H-7′), 4.14 (ddd, 1H, $J = 4.5, 4.5, 7.8$, H-3), 4.24 (ddd, 1H, $J = 2.8, 6.0, 9.0$, H-6), 4.37−4.64 (m, 6H, 3 × CH_2−Bn), 7.16−7.24 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 22.33 (1C, CH_3), 48.96 (1C, C-3) 61.18 (1C, C-1), 64.61 (1C, C-7), 65.57 (1C, C-2), 70.20 (1C, CH_2−Bn), 71.60 (1C, C-5), 71.68 (1C, CH_2−Bn), 72.28 (1C, CH_2−Bn), 73.04 (1C, C-4), 74.04 (1C, C-6), 126.53, 126.59, 126.62, 126.68, 126.82, 126.88, 127.32, 127.41, 136.68, 137.13, 137.22 (15C, Ar), 169.57 (1C, CONH); MALDI-TOF (positive mode, DHB) *m*/*z* calcd for $C_{30}H_{35}NO_6$ 505, found 506 $(M + H)^+$ and 528 $(M + Na)^+$. Anal. Calcd for $C_{30}H_{35}NO_6$: C, 71.27; H, 6.98; N, 2.77. Found: C, 70.98; H, 6.91; N, 2.72.

(3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-L-*gluco*-heptitol-1-yl) Di-*O*-benzyl Phosphate (24). To a stirred suspension of 1*H*-tetrazole (167 mg, 2.38 mmol) in dry CH_2Cl_2 (1.5 mL) was added dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.39 mL, 1.19 mmol), and the mixture was stirred for 15 min under argon atmosphere. The alcohol **19** (240 mg, 0.48 mmol), dissolved in dry CH_2Cl_2 (1.5 mL), was added, and the mixture was stirred at room temperature for 4 h. Subsequently the reaction mixture was cooled to 0 °C, MCPBA (70%, 330 mg, 1.37 mmol) was added, and stirring was continued for 45 min. The solvent was removed under reduced pressure (bath temperature <40 °C), and the residue was purified by flash chromatography over silica gel (petroleum ether (50−70)−EtOAc, 1:1 to 1:2) to afford 265 mg of the phosphate **24** (74%) as an oil: $[\alpha]^{20}_D = +4.6$ (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.82 (s, 3H, CH_3), 3.62 (dd, 1H, $J = 3.5, 11.4$, H-7), 3.67 (dd, 1H, $J = 2.8, 5.5$, H-5), 3.74 (dd, 1H, $J = 3.0, 5.5$, H-4), 3.86−3.92 (m, 2H, H-1, H-7′), 4.04 (dd, 1H, $J = 7.2, 11.8$, H-1′), 4.13 (dd, 1H, $J = 2.8, 3.5$, H-6), 4.18 (dd, 1H, $J = 5.7, 7.2$, H-2), 4.26 (m, 1H, H-3), 4.36−4.60 (m, 6H, 3 × CH_2−Bn), 4.88−4.96 (m, 4H, 2 × CH_2−Bn-PO_4), 5.95 (d, 1H, $J = 8.3$, NH), 7.15−7.23 (m, 25H, Ar); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 22.14 (1C, CH_3), 47.66 (1C, C-3), 66.17 (d, 1C, $J = 6.1$, C-1), 68.53, 68.61 (2C, 2 × CH_2−Bn−PO_4), 68.66 (1C, C-7), 70.89 (1C, CH_2−Bn), 71.42 (1C, C-5), 71.56, 72.22 (2 × 1C, 2 × CH_2−Bn), 73.76 (1C, C-4), 74.07, 74.10 (2 × 1C, C-2, C-6) 126.64, 126.67, 126.79, 126.91, 126.99, 127.36, 127.38, 127.56, 127.61, 127.67, 134.68, 136.74, 137.06, 137.19 (30C, Ar), 169.25 (1C, CONH); ^{31}P NMR ($CDCl_3$, 80 MHz,) δ −0.04; MALDI-TOF (positive mode, DHB) *m*/*z* calcd for $C_{44}H_{48}NO_9P$ 765, found 766 $(M + H)^+$ and 788 $(M + Na)^+$. Anal. Calcd for $C_{44}H_{48}NO_9P$: C, 69.01; H, 6.32; N, 1.83. Found: C, 68.83; H, 6.42; N, 1.78.

(3-Acetamido-2,6-anhydro-3-deoxy-D-*glycero*-L-*gluco*-heptitol-1-yl) Phosphate (25). To a solution of **24** (250 mg, 0.33 mmol) in dry methanol (25 mL) was added Pd/C (10%, 125 mg), and the suspension was stirred under hydrogen atmosphere at 50 bar for 10 h. The catalyst was filtered off, and the solvent was removed under reduced pressure to afford 95 mg of **25** (91%) as a white hygroscopic solid, which was used for the next conversion without further purification: $[\alpha]^{20}_D = +31.8$ (*c* 1, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.92 (s, 3H, CH_3), 3.57 (dd, 1H, $J = 4.4, 11.8$, H-7), 3.62 (dd, 1H, $J = 7.8, 11.8$, H-7′), 3.87 (dd, 1H, $J = 1.5, 3.3$, H-5), 3.91−3.96 (m, 3H, H-1,H-4, H-6), 4.07 (dd, 1H, $J = 11.8$, H-1), 4.11 (dd, 1H, $J = 5.8, 6.5$, H-2), 4.18 (dd, 1H, $J = 6.5, 10.9$, H-3); ^{13}C NMR (D_2O, 100.62) δ 22.32 (1C, CH_3), 48.99 (1C, C-3), 61.81 (1C, C-7), 63.82 (d, 1C, $J = 5.1$, C-1), 68.31, 68.64 (1C, C-5), 72.98 (d, 1C, $J = 10.2$, C-2), 74.20, 162.52 (1C, CONH); ^{31}P NMR (D_2O, 80 MHz) δ 1.02.

(27) **15** is described in ref 24, but no analytical data were given.

Ammonium (3-Acetamido-2,6-anhydro-3-deoxy-D-*glycero*-L-*gluco*-heptitol-1-yl) (Uridine-5′-yl) Diphosphate (6). The procedure described for the synthesis of **4** was followed using **25** (90 mg, 0.29 mmol) to give 112 mg of **6** (55%) as a white solid: $[\alpha]^{20}_D = +45.2$ (*c* 1, H_2O); R_f 0.24 (*i*-PrOH/1 M NH_4HCO_3); ^{1}H NMR (D_2O, 500 MHz) δ 1.89 (2, 3H, CH_3), 3.46−3.58 (m, 2H, CH_2-7), 3.82 (m, 1H, H-5), 3.95−4.20 (m, 11H), 5.79−5.82 (m, 2H, H-1-Rib, H-5-U), 7.79 (d, 1H, $J = 7.9$, H-6-U); ^{13}C NMR (D_2O, 125 MHz) δ 22.38 (1C, CH_3), 48.92 (1C, C-3), 61.90 (1C, C-7), 65.28 (d, 1C, $J = 7.12$, C-5-Rib), 65.35, 68.29, 68.67, 70.03 (1C, C-2), 74.16, 74.45, 83.60 (d, 1C, C-4-Rib), 88.78 (1C, C-1-Rib), 103.00 (1C, C-6-U), 142.00 (1C, C-4-U), 152.20 (1C, C-4-U), 164.62 (1C, C-2-U), 175.73 (1C, CONH); ^{31}P NMR (D_2O−MeOH, 2:1; 80 MHz, 253 K) δ −8.99 (d, 1P, $J = 20.0$), −8.73 (d, 1P, $J = 20.0$); MALDI-TOF (negative mode, DHB) *m*/*z* calcd for $C_{18}H_{35}N_5O_{17}P_2$ 655, found 620 $(M - 2\ NH_4^+ + H)^-$.

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Supporting Information Available: ^{13}C NMR spectra for **4**−**6**, **11**, **22**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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