Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 343 (2008) 1012–1022
Carbohydrate RESEARCH

Synthesis of UDP-glucose derivatives modified at the 3-OH as potential chain terminators of β-glucan biosynthesis

Ramona Danac,[a] Lucy Ball,[b] Sarah J. Gurr[b] and Antony J. Fairbanks[a,*]

[a]*Chemistry Research Laboratory, Oxford University, Mansfield Road, Oxford OX1 3TA, UK*
[b]*Department of Plant Sciences, Oxford University, South Parks Road, Oxford OX1 3RB, UK*

Received 13 December 2007; received in revised form 17 January 2008; accepted 22 January 2008
Available online 2 February 2008

Abstract—A series of UDP-D-glucose derivatives and precursors that have been modified at C-3 were synthesised from D-glucose as potential chain terminators of β-glucan biosynthesis. None of the UDP-derivatives or the precursors tested displayed significant anti-fungal activity in a series of germination assays on the dermatophyte *Trichophyton rubrum*.

Keywords: Anti-fungal agents; β-Glucan; Biosynthesis; Oligosaccharides; Chain termination

1. Introduction

Oligomeric carbohydrate structures that are specific to pathogenic organisms, and which are vital for their survival, represent particularly attractive targets for therapeutic intervention.[1] Over recent years, substantial effort has been expended in the search for potent inhibitors of glycosyl transferases, both as a means of treating human disease and, more relevantly, to disrupt pathogen-specific biosynthetic pathways.[2] However, the design of such inhibitors can be problematic, since in many cases little is known about the precise enzymes involved. Moreover, such inhibitors in general have to mimic a reaction transition state which effectively involves three distinct species—the glycosyl acceptor, the nucleoside di-phosphate, and the glycosyl donor. The net result is that specifically designed glycosyl transferase inhibitors have yet to find clinical application.[3]

This lack of success invokes the need for alternative approaches to be considered. In particular, where the targeted oligosaccharide consists of multiple monosaccharide repeat units, an alternative strategy to enzymatic inhibition may prove useful. Such an approach would be to invoke chain termination of oligosaccharide biosynthesis by the synthesis and use of carbohydrate derivatives that have been modified at the hydroxyl group at which subsequent units would be added after their incorporation into the growing oligosaccharide chain.

Chain-termination processes involving modified monosaccharide derivatives have previously been implicated in the biological effects of some monosaccharide derivatives on mammalian glycoconjugate[4] and glycosoaminoglycan biosynthesis.[5] However, a chain-termination approach has not yet been more widely investigated, particularly as a strategy for the development of new classes of inhibitors of the biosynthesis of pathogenic oligosaccharides. This 'oligosaccharide' situation contrasts with the widespread use of chain termination of oligonucleotide synthesis, ranging from its original development by Sanger et al.[6] as a means of DNA sequencing, to several anti-viral therapies currently in clinical use, perhaps most pre-eminently in the case of AZT.[7] Moreover, the growing body of data demonstrating that many glycosyl transferases do process activated donor substrates that have been modified in a minimal way at a single hydroxyl group[8,9] augurs well for a chain-termination approach.

As part of a program[10] aimed at investigating the potential opportunities that chain termination of oligosaccharide biosynthesis offers to disease control, we became

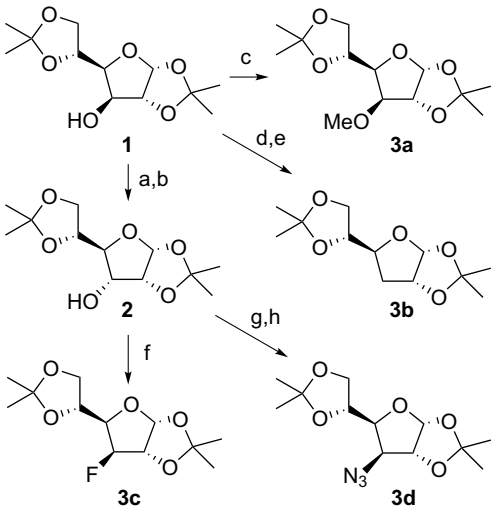
* Corresponding author. E-mail: antony.fairbanks@chem.ox.ac.uk

0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.01.031

interested in the rational design of novel anti-fungal agents. Fungal infections represent a serious hazard to human and animal health,[11] and, just as for bacterial infection, drug resistance to current therapies is increasing.[12] The fungal cell wall consists of large sections of oligosaccharide materials including chitin, and β-glucan. The biosynthesis of these non-mammalian oligosaccharides could be potentially targeted[13] using a chain-termination approach. The synthesis and anti-fungal activity of a variety of *N*-acetylglucosamine derivatives, which were rationally designed as potential chain terminators of chitin biosynthesis, have already been reported.[10a,b] The other potential target, β-glucan, is assembled stepwise by the β-(1→3) glucan synthases,[14] which transfer single glucose residues to a growing oligomeric chain; the donor substrate for these enzymes being UDP-D-glucose. Potential chain terminators of this process are, therefore, D-glucose residues in which the 3-OH has been modified. If such materials are processed by a β-(1→3) glucan synthase, then their transfer to the terminus of a growing glucan chain will result in a chain-termination step since the required 3-OH at which subsequent units would be added will now be lacking. The most obvious approach was that of synthesising and testing the modified UDP-glucose donors themselves, since these are the actual substrates processed by β-(1→3) glucan synthases, although previous work implied that the high polarity of such compounds may compromise their ability to penetrate intracellularly and thus produce any anti-fungal effects.[10b] Alternatively, potential pro-drug molecules could be synthesised, which may then be converted to the active UDP-donors once inside the fungal cell. Following on from the previous work,[10a,b] which had identified GlcNAc derivatives that displayed anti-fungal activity, isosteric replacement of the 3-OH of glucose was envisaged by replacement of the OH group by –H, –OMe, –F, –NHAc and N_3.

2. Results and discussion

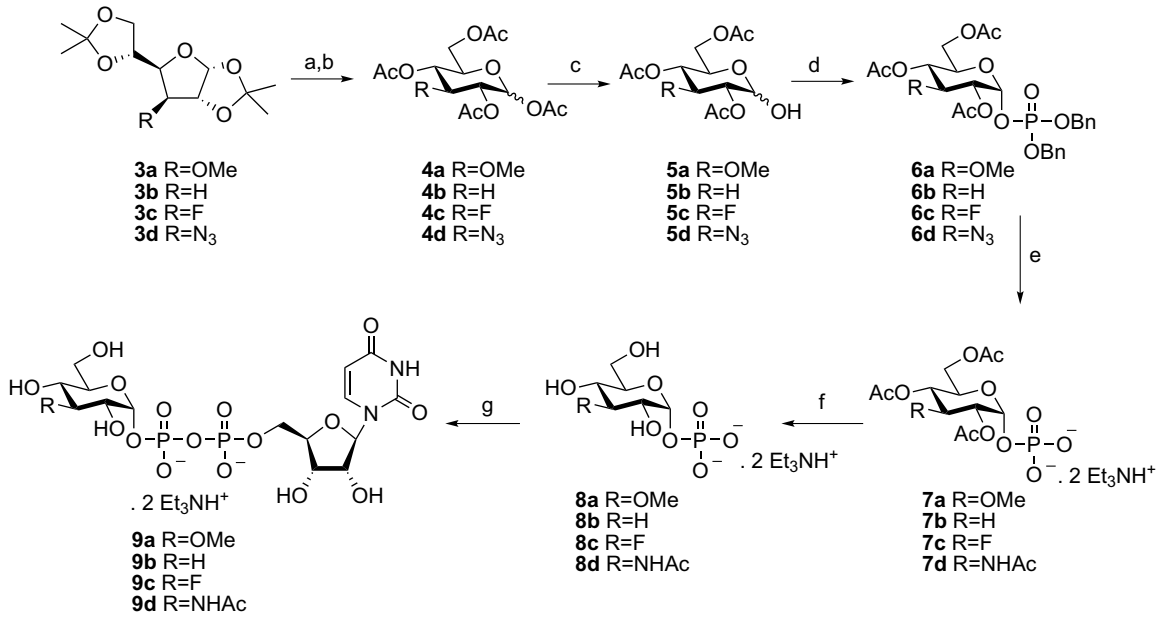
Selective access to the 3-OH for modification was achieved using diacetone glucose **1** as the starting material. A variety of standard synthetic procedures were undertaken to achieve the desired functional group inter-conversions (Scheme 1). Methylation by treatment of **1** with potassium hydroxide and methyl iodide in acetone in the presence of tetrabutylammonium bromide as a phase transfer catalyst[15] produced methyl ether **3a**, whilst conversion to an intermediate xanthate ester by sequential treatment of **1** with sodium hydride, carbon disulfide and methyl iodide in THF, followed by tributyl tin hydride mediated free radical reduction led to deoxy compound **3b**. Introduction of either nitrogen or fluorine at C-3 of glucose required a double inversion



Scheme 1. Reagents and conditions: (a) PCC, CH_2Cl_2, 4Å molecular sieves; (b) $NaBH_4$, EtOH, H_2O, 68% over two steps; (c) KOH, MeI, Bu_4NBr, acetone, 0 °C to rt; 86%; (d) NaH, THF, imidazole, then CS_2, then MeI; (e) $BuSn_3H$, toluene, reflux, 62% over two steps; (f) DAST, 2,4,6-collidine, CH_2Cl_2, −20 °C to rt, 61%; (g) Tf_2O, pyridine, CH_2Cl_2, −20 °C; (h) NaN_3, DMF, 50 °C, 93% over two steps.

of configuration. Thus, the usual oxidation/reduction sequence led readily to diacetone allose **2**, which was then converted to fluoride **3c** by treatment with diethylamino sulfur trifluoride (DAST) and collidine in dichloromethane, and to azide **3d** by a triflation/azide displacement sequence (Scheme 1).

Attention then turned to conversion of these furanose derivatives into the corresponding pyranose peracetates, glycosyl phosphates and UDP-derivatives (Scheme 2). A parallel series of transformations ultimately allowed access to the UDP-derivatives **9a**–**d**, and in addition provided potential pro-drug intermediates, which were also tested for anti-fungal activity. Treatment of furanose diacetonides **3a**–**d** with aqueous trifluoroacetic acid followed by complete acetylation of the crude products by treatment with acetic anhydride and pyridine produced the pyranose acetates **4a**–**d** as mixtures of anomers. It was notable that the yield of 3-deoxy acetate **4b** was considerably lowered by the formation of furanose by-products.[16] Selective removal of the anomeric acetate of **4a**–**d** was achieved using a mixture of ethylene diamine and acetic acid in THF, leading to hemiacetals **5a**–**d**. Phosphorylation with tetrabenzyl pyrophosphate[17] gave the benzyl protected anomeric phosphates **6a**–**d** as anomeric mixtures in which the desired α-anomers were predominant (α:β ratios ~5:1), and which in all the cases were readily separated by silica gel flash chromatography. Removal of the benzyl protecting groups was achieved by catalytic hydrogenation in methanol in the presence of palladium hydroxide providing phosphates **7a**–**c**, which were converted to the corresponding triethylammonium salts by the addition of triethylamine, and which were then used in the

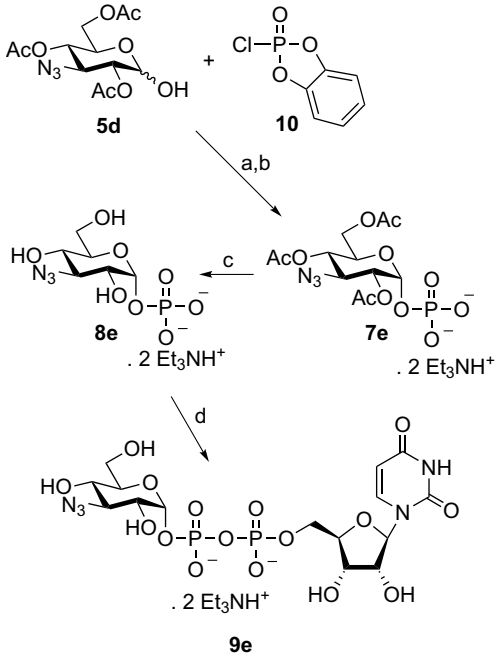


Scheme 2. Reagents and conditions: (a) CF_3CO_2H, H_2O, AcOH, rt; (b) Ac_2O, pyridine; **4a**, 86%; **4b** 20%; **4c** 61%; **4d** 80%; (c) $(CH_2NH_2)_2$, AcOH, THF, rt; **5a**, 70%; **5b** 70%; **5c** 65%; **5d** 67%; (d) LDA, $[(BnO)_2P(O)]_2O$, THF, −78 to 0 °C; **6aα**, 68%; **6bα**, 52%; **6cα**, 74%; **6dα**, 73%; (e) H_2, $Pd(OH)_2$, MeOH, (and Ac_2O for **7d**); (f) Et_3N, MeOH, H_2O, rt; **8a**, 89%; **8b**, 92%; **8c**, 90%; **8d**, 93%; (g) UMP-morpholidate, tetrazole, pyridine, rt; **9a**, 51%; **9b**, 52%; **9c**, 51%; **9d**, 54%.

next step without further purification or characterisation. In the case of phosphate **6d**, it was envisaged that hydrogenation would cause concomitant reduction of the azide group and acetic anhydride was added to the reaction mixture before hydrogenation, which resulted in the formation of acetamide **7d**. Deacetylation of the crude glycosyl phosphate triacetates **7a–d** was achieved by treatment with a mixture of triethylamine, MeOH and water to produce the deprotected glycosyl phosphates **8a–d** as their triethylammonium salts. Finally coupling of **8a–d** with UMP-morpholidate provided the corresponding UDP-derivatives **9a–d** (Scheme 2).

Due to the simultaneous reduction of the azide functionality during the removal of the benzyl protecting groups observed above, a different reaction sequence was undertaken to access the 3-azido UDP-derivative **9e** (Scheme 3). Phosphorylation[18] of hemiacetals **5d** with *o*-phenylene phosphorochloridate **10**, followed by the removal of the *o*-phenylene protecting group using lead tetraacetate in dioxane, gave the azido glycosyl phosphate **7e**. Acetate deprotection, again by treatment with a mixture of triethylamine, MeOH and water, produced the deprotected azido glycosyl phosphate **8e**. Finally, coupling with UMP-morpholidate provided the corresponding UDP-derivative **9e** (Scheme 3).

Potential anti-fungal action of the putative chain-termination compounds was assessed using an assay which measured the effect of compounds on germination of fungal spores/germlings of the dermatophyte[19] *Trichophyton rubrum*, a fungal pathogen that causes superficial skin diseases in humans and animals. Of the compounds that were tested **4a–d**, **5a–d** **6a–d**, **8a–e** and **9a–e**, only compound **6a** (~40% inhibition of germination at a 1 mM concentration) displayed significant biological activity in the 1–1000 μM range that was examined. These results contrast somewhat with biological test data previously obtained[10a,b] for a series of



Scheme 3. Reagents and conditions: (a) collidine, **10**, THF, 0 °C to rt; (b) $Pb(OAc)_4$, dioxane, 12 °C to rt; (c) Et_3N, MeOH, H_2O, rt, 46% over three steps; (d) UMP-morpholidate, pyridine, rt, 55%.

protected GlcNAc derivatives, which had been modified at C-4 as potential chain terminators of chitin biosynthesis. Based on previous experience, the lack of in vivo bioactivity of the UDP-derivatives **9a**–**e** and glycosyl phosphates **8a**–**e** was unsurprising; poor cellular penetration of these highly polar compounds probably limited their availability to interfere with β-glucan biosynthesis. However, the lack of activity of acetates **4a**–**d**/**5a**–**d**, which may have been expected to act as potential pro-drugs,[20] was more thought provoking. Whilst it is perhaps unreasonable to speculate too deeply since the mode of action of the anti-fungal GlcNAc compounds has not been thoroughly investigated, it is possible to imagine that perhaps the intracellular machinery of β-glucan biosynthesis is less tolerant than that of chitin biosynthesis, and potential chain terminators may not be processed through the required biosynthetic steps. Alternatively pro-drug protecting group identity may also play an important role in producing bioactivity.[21]

3. Conclusions

A series of D-glucose acetates, glycosyl phosphates and UDP-derivatives that have been modified at C-3 have been synthesised as potential inhibitors of β-(1→3)-glucan biosynthesis. Compounds were tested for anti-fungal activity in a spore germination assay on the fungus *T. rubrum*. Although one of the test compounds did show moderate anti-fungal activity at a concentration of 1 mM, the general conclusion reached was that this series of compounds did not display significant anti-fungal activity. Further investigations into the potential uses of carbohydrate chain terminators as the basis for novel strategies against a variety of other infective agents are in progress, and the results will be reported in due course.

4. Experimental

4.1. General

Melting points were recorded on a Kofler hot block and are uncorrected. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on Bruker DPX 250 (250 MHz), Bruker DPX 400 (400 MHz), Bruker DQX 400 (400 MHz), Bruker AVC 500 (500 MHz) or Bruker AMX 500 (500 MHz) spectrometers. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. Low resolution mass spectra were recorded on a Micromass Platform 1 spectrometer using electrospray ionisation in either positive or negative polarity (ES^+ or ES^-), or using a VG Micromass spectrometer. High resolution mass spectra were recorded on a Walters 2790-Micromass LCT electrospray ionisation mass spectrometer, using either electrospray ionisation (NH_3, Cl) techniques as stated. *m*/*z* Values are reported in Daltons and are followed by their percentage abundance in parentheses. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. Microanalyses were performed by the Inorganic Chemistry Laboratory Elemental Analysis service, Oxford University, UK. Thin layer chromatography (TLC) was carried out on Merck Kieselgel $60F_{254}$ pre-coated glass-backed plates. Visualisation of the plates was achieved using a UV lamp ($\lambda_{max} = 254$ or 365 nm), and/or ammonium molybdate (5% in 2 M sulfuric acid), or sulfuric acid (5% in ethanol). Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Dichloromethane was distilled from calcium hydride, or dried on an alumina column. Anhydrous THF, DMF, pyridine, MeOH and toluene were purchased from Fluka over molecular sieves. 'Petrol' refers to the fraction of light petrol ether boiling in the range of 40–60 °C. CMAW (chloroform/MeOH/acetic acid/water) used as eluant was prepared in the following ratio ($CHCl_3$/MeOH/AcOH/H_2O, 60:30:3:5). Purification of the UDP-derivatives was performed as previously described.[10b] Compounds **2**,[22,23] **3a**,[15] **3b**,[24] **3c**,[25] **3d**,[22a] **4a**,[26] **4b**,[27] **4c**,[28] **4d**,[29] **5a**[30] and **5c**[18] were prepared using the routes shown in Schemes 1 and 2, and exhibited spectroscopic data in agreement with those reported previously.

4.2. 2,4,6-Tri-*O*-acetyl-3-deoxy-D-ribo-hexopyranose (5b)

Glacial acid acetic (0.50 g, 8.42 mmol, 1.4 equiv) was added drop-wise to a stirred solution of ethylenediamine (3.10 g, 0.051 mol, 1.2 equiv) in THF (50 mL). Tetraacetate **4b** (2 g, 6.0 mmol, 1 equiv) was added, and the resulting mixture was then stirred for 48 h at rt. After this time water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with aqueous HCl (2.0 M, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and then concentrated in vacuo. Purification by flash chromatography (petrol/ethyl acetate 1:1) yielded triacetate **5b** (1.22 g, 70%) as a colourless oil as a mixture of anomers (α:β ratio approximately 2:1 by integration over selected parts of the ^1H NMR spectrum); ν_{max} (thin film) 3362 (br, OH), 1750 (br s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.63 (1H, aq, *J* 11.2 Hz, H-3aβ), 1.99 (1H, aq, *J* 11.2 Hz, H-3aα), 2.03, 2.04, 2.07 (6 × H, 3 × s, 6 × OCC*H*$_3$), 2.27 (1H, adt, *J* 4.8 Hz, *J* 11.3 Hz, H-3eα), 2.51 (1H, adt, *J* 4.8 Hz, *J* 11.9 Hz, H-3′β), 3.71 (1H, adt, *J* 4.1 Hz, *J* 9.5 Hz, H-5β), 4.12–4.19 (5H, m, H-5α, H-6, H-6′), 4.67 (1H, d, $J_{1,2}$ 7.8 Hz, H-1β), 4.70–4.87 (4H, m, H-4, H-2), 5.32 (1H, d, $J_{1,2}$ 3.1 Hz, H-1α); δ_c (100.6 MHz, $CDCl_3$) 20.7, 20.8, 20.9, 21.0

(6 × C=O*C*H$_3$), 28.3 (C-3α), 32.9 (C-3β), 62.5 (C-6α), 62.6 (C-6β), 65.8 (C-4β), 65.9 (C-4α), 67.6 (C-5α), 68.2 (C-2α), 70.2 (C-2β), 75.2 (C-5β), 89.3 (C-1α), 96.9 (C-1β), 169.6, 169.7, 170.5, 170.8, 171.0, (6 × CH$_3$*C*=O); *m*/*z* (ES$^+$) 272 (M−H$_2$O+H$^+$, 100%), 313 (M+Na$^+$, 49%); HRMS (ES$^+$) calcd for $C_{12}H_{18}O_8Na$ (MNa$^+$) 313.0826; found 313.0888. (Found: C, 49.63; H, 6.20. $C_{12}H_{18}O_8$ requires C, 49.65; H, 6.25).

4.3. 2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-D-glucopyranose (5d)

Glacial acid acetic (3.98 g, 0.066 mol, 1.4 equiv) was added drop-wise to a stirred solution of ethylenediamine (3.42 g, 0.057 mol, 1.2 equiv) in THF (300 mL). Tetra-acetate **4d** (17.7 g, 0.047 mol, 1 equiv) was added, and the resulting mixture was then stirred for 48 h at rt. After this time water (300 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with aqueous HCl (2.0 M, 400 mL), saturated aqueous $NaHCO_3$ (400 mL) and then concentrated in vacuo. Purification by flash chromatography (petrol/ethyl acetate, 1:1) yielded tri-acetate **5d** (10.5 g, 67%) as a colourless oil as a mixture of anomers (α:β ratio approximately 4:1 by integration over selected parts of the ^{1}H NMR spectrum); ν_{max} (thin film) 3441 (br, w, OH), 2111 (s, N_3), 1747 (br s, C=O), δ_H (400 MHz, $CDCl_3$) 2.06, 2.11, 2.14 (3 × 6H, 3 × s, 6 × OCC*H*$_3$), 3.66 (1H, at, *J* 10.1 Hz, H-3β), 3.71 (1H, m, H-5β), 4.03 (1H, at, *J* 10.4 Hz, H-3α), 4.06 (1H, dd, $J_{6,5}$ 3.8 Hz, $J_{6,6'}$ 9.9 Hz, H-6α), 4.14–4.20 (4H, m, H-6′α, H-5α, H-6β, H-6′β), 4.66 (1H, d, $J_{1,2}$ 7.8 Hz, H-1β), 4.72 (1H, dd, $J_{2,1}$ 3.5 Hz, $J_{2,3}$ 10.6 Hz, H-2α), 4.77 (1H, at, *J* 8.1 Hz, H-2β), 4.92 (2H, m, H-4α, H-4β), 5.39 (1H, d, $J_{1,2}$ 3.3 Hz, H-1α); δ_c (100.6 MHz, $CDCl_3$) 20.6, 20.7, 20.9 (6 × C=O*C*H$_3$), 60.6 (C-3α), 62.1 (C-6), 63.8 (C-3β), 67.1 (C-5α), 68.4 (C-4), 71.9 (C-2α), 72.6 (C-5β), 73.2 (C-2β), 89.5 (C-1α), 95.6 (C-1β), 169.4, 169.5, 170.1, 170.5, 170.9, 171.1 (6 × CH$_3$*C*=O); *m*/*z* (ES$^+$) 349 (M+NH$_4^+$, 100%), 314 (M−H$_2$O+H$^+$, 60%), 354 (M+Na$^+$, 42%); HRMS (ES$^+$) calcd for $C_{12}H_{17}O_8N_3Na$ (MNa$^+$) 354.0913; found 354.0908. (Found: C, 43.45; H, 5.73; N, 12.61. $C_{12}H_{17}O_8N_3$ requires C, 43.51; H, 5.71; N, 12.68).

4.4. Dibenzylphosphate-2,4,6-tri-*O*-acetyl-3-*O*-methyl-D-glucopyranoside (6a)

LDA (1.7 mL of a 2.0 M solution in THF/heptane/ethylbenzene, 3.4 mmol, 1.1 equiv) was added slowly to a stirred solution of triacetate **5a** (1 g, 3.1 mmol, 1 equiv) in THF (40 mL) at −78 °C under argon. After 15 min, a solution of tetrabenzyl pyrophosphate (2.18 g, 4.03 mmol, 1.3 equiv) in THF (10 mL) was added, and the reaction mixture was allowed to warm to 0 °C. After 5 h at 0 °C a saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/petrol, 6:4) to afford the two anomers of dibenzylphosphate **6a** (1.22 g of the α-anomer **6aα**, 68% and 0.38 g of the β-anomer **6aβ**, 21%) as pale yellow oils. **6aα**: $[\alpha]_D^{20}$ +74 (*c* 1.0, $CHCl_3$); ν_{max} (thin film) 1749 (br s, C=O); δ_H (400 MHz, $CDCl_3$) 1.92, 1.98, 2.10 (3 × 3H, 3 × s, 3 × COC*H*$_3$), 3.67 (1H, at, *J* 9.7 Hz, H-3), 3.94 (1H, dd, $J_{6,5}$ 2.3 Hz, $J_{6,6}$ 12.4 Hz, H-6), 4.01 (1H, ddd, $J_{5,6}$ 2.3 Hz, $J_{5,6'}$ 4.5 Hz, $J_{5,4}$ 10.1 Hz, H-5), 4.13 (1H, dd, $J_{6',5}$ 4.5 Hz, $J_{6',6}$ 12.4 Hz, H-6′), 4.85 (1H, adt, *J* 3.3 Hz, *J* 9.6 Hz, H-2), 5.03 (1H, at, *J* 10.1 Hz, H-4), 5.05–5.11 (4H, m, 2 × PhC*H*$_2$), 5.86 (1H, dd, $J_{1,P}$ 5.9 Hz, $J_{1,2}$ 3.3 Hz, H-1), 7.35–7.38 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.5, 20.6, 20.7 (3 × CO*C*H$_3$), 60.4 (O*C*H$_3$), 61.6 (C-6), 68.7 (C-4), 69.6 (d, $J_{C,P}$ 6.0 Hz, 2 × Ph*C*H$_2$), 69.7 (C-5), 71.7 (d, $J_{C-2,P}$ 7.0 Hz, C-2), 77.6 (d, C-3), 94.2 (d, $J_{C-1,P}$ 6.0 Hz, C-1), 128.0, 128.7, 128.8, 135.3, 135.3, 135.4 (12 × Ar-C), 169.3, 169.8, 170.6 (3 × CH$_3$CO); δ_P (162 MHz, $CDCl_3$) −2.51 (^{1}H decoupled); *m*/*z* (ES$^+$) 602 (M+Na$^+$, 100%); HRMS (ES$^+$) calcd for $C_{27}H_{33}O_{12}PNa$ (MNa$^+$) 603.1607; found 603.1602. (Found: C, 55.79; H, 5.67; P, 5.25. $C_{27}H_{33}O_{12}P$ requires C, 55.86; H, 5.73; P, 5.34). **6aβ**: δ_H (400 MHz, $CDCl_3$) 1.98, 1.99, 2.11 (3 × 3H, 3 × s, 3 × COC*H*$_3$), 3.43 (3H, s, OC*H*$_3$), 3.51 (1H, at, *J* 9.6 Hz, H-3), 3.72 (1H, ddd, $J_{5,6}$ 2.5 Hz, $J_{5,6'}$ 5.0 Hz, $J_{5,4}$ 9.9 Hz, H-5), 4.10 (1H, dd, $J_{6,5}$ 2.5 Hz, $J_{6,6'}$ 12.4 Hz, H-6), 4.20 (1H, dd, $J_{6',5}$ 5.0 Hz, $J_{6',6}$ 12.4 Hz, H-6′), 5.01–5.14 (6H, m, H-4, 2 × PhC*H*$_2$, H-2), 5.30 (1H, at, *J* 7.8 Hz, H-1), 7.33–7.37 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.6, 20.7, 20.8 (3 × CO*C*H$_3$), 59.3 (O*C*H$_3$), 61.8 (C-6), 68.5 (C-4), 69.6, 69.7 (2 × d, $J_{C,P}$ 6.0 Hz, 2 × Ph*C*H$_2$), 71.9 (d, $J_{C-2,P}$ 8.0 Hz, C-2), 72.8 (C-5), 80.9 (C-3), 96.5 (d, $J_{C-1,P}$ 4.0 Hz, C-1), 127.8, 127.9, 128.4, 128.5, 128.6, 135.1, 135.2, 135.3 (12 × Ar-C), 169.2, 169.3, 170.6 (3 × CH$_3$CO); δ_P (162 MHz, $CDCl_3$) −3.16 (^{1}H decoupled).

4.5. Dibenzylphosphate-2,4,6-tri-*O*-acetyl-3-deoxy-D-ribo-hexopyranoside (6b)

LDA (0.73 mL of a 2.0 M solution in THF/heptane/ethylbenzene, 1.4 mmol, 1.1 equiv) was added slowly to a stirred solution of triacetate **5b** (0.4 g, 1.3 mmol, 1 equiv) in THF (20 mL) at −78 °C under argon. After 15 min, a solution of tetrabenzyl pyrophosphate (0.96 g, 1.8 mmol, 1.3 equiv) in THF (10 mL) was added, and the reaction mixture was allowed to warm to 0 °C. After 5 h at 0 °C a saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined

organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/petrol, 6:4) to afford the two anomers of dibenzylphosphate **6b** (0.4 g of the α-anomer **6bα**, 52% and 0.18 g of the β-anomer **6bβ**, 24%) as colourless oils. **6bα**: $[\alpha]_D^{20}$ +84 (*c* 1.0, $CHCl_3$); ν_{max} (thin film) 1748 (br s, C=O); δ_H (400 MHz, $CDCl_3$) 1.90, 1.98 (2 × 3H, 2 × s, 2 × C=OCH_3), 2.01–2.05 (1H, m, H-3a), 2.06 (3H, s, C=OCH_3), 2.32 (1H, adt, *J* 4.8 Hz, *J* 11.4 Hz, H-3e), 3.98–4.02 (2H, m, H-5, H-6), 4.16 (1H, dd, $J_{6',5}$ 5.0 Hz, $J_{6',6}$ 12.9 Hz, H-6′), 4.82–4.94 (2H, m, H-2, H-4), 5.07–5.12 (4H, m, 2 × PhCH_2), 5.81 (1H, dd, $J_{1,2}$ 3.0 Hz, $J_{1,P}$ 6.3 Hz, H-1), 7.34–7.38 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.5, 20.6, 20.8 (3 × C=O*C*H_3), 28.4 (C-3), 61.8 (C-6), 65.0 (C-4), 67.0 (d, $J_{C-2,P}$ 7.0 Hz, C-2), 69.4 (d, $J_{C,P}$ 5.0 Hz, 2 × Ph*C*H_2), 69.6 (C-5), 93.4 (d, $J_{C-1,P}$ 6.0 Hz, C-1), 127.9, 128.6, 128.7, 135.4, 133.5 (12 × Ar-C), 169.4, 169.7, 170.6 (3 × CH_3C=O); δ_P (162 MHz, $CDCl_3$) −2.07 (^{1}H decoupled); *m*/*z* (ES^+) 609 (M+MeCN/NH_4^+, 100%), 573 (M+Na^+, 55%), 568 (M+NH_4^+, 20%), 551 (M+H^+, 15%); HRMS (ES^+) calcd for $C_{26}H_{31}O_{11}PNa$ (MNa^+) 573.1501; found 573.1496. (Found: C, 56.70; H, 5.67; P, 5.52. $C_{26}H_{31}O_{11}P$ requires C, 56.73; H, 5.68; P, 5.63). **6bβ**: δ_H (400 MHz, $CDCl_3$) 1.63 (1H, aq, *J* 11.8 Hz, H-3a), 1.89, 1.94, 2.02 (3 × 3H, 3 × s, 3 × C=OCH_3), 2.57 (1H, adt, *J* 5.0 Hz, *J* 12.3 Hz, H-3e), 3.80 (1H, m, H-5), 4.16 (2H, m, H-6, H-6′), 4.80–4.90 (2H, m, H-2, H-4), 5.00–5.08 (4H, m, 2 × PhCH_2), 5.32 (1H, at, *J* 6.8 Hz, H-1), 7.29–7.32 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.6, 20.7, 20.8 (3 × C=O*C*H_3), 32.4 (C-3), 62.1 (C-6), 65.0 (C-4), 68.4 (d, $J_{C-2,P}$ 9.0 Hz, C-2), 69.5 (d, $J_{C,P}$ 7.0 Hz, 2 × Ph*C*H_2), 75.8 (C-5), 97.7 (d, $J_{C-1,P}$ 5.0 Hz, C-1), 127.7, 127.9, 128.0, 128.3, 128.5, 128.6, 128.7 (12 × Ar-C), 169.3, 169.4, 170.5 (3 × CH_3C=O); δ_P (162 MHz, $CDCl_3$) −3.20 (^{1}H decoupled).

4.6. Dibenzylphosphate-2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-D-glucopyranoside (6c)

LDA (1.8 mL of a 2.0 M solution in THF/heptane/ethylbenzene, 3.6 mmol, 1.1 equiv) was added slowly to a stirred solution of triacetate **5c** (1 g, 3.24 mmol, 1 equiv) in THF (40 mL) at −78 °C under argon. After 15 min, a solution of tetrabenzyl pyrophosphate (2.27 g, 4.22 mmol, 1.3 equiv) in THF (10 mL) was added, and the reaction mixture was allowed to warm to 0 °C. After 5 h at 0 °C a saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/petrol, 1:1) to afford the two anomers of dibenzylphosphate **6c** (1.27 g of the α-anomer **6cα**, 74% and 0.34 g of the β-anomer **6cβ**, 18%) as colourless oils. **6cα**: $[\alpha]_D^{20}$ +69 (*c* 1.0, $CHCl_3$); ν_{max} (thin film) 1748 (br s, C=O); δ_H (400 MHz, $CDCl_3$) 1.96, 2.01, 2.11 (3 × 3H, 3 × s, 3 × C=OCH_3), 3.92–3.99 (2H, m, H-5, H-6), 4.16 (1H, dd, $J_{6',5}$ 4.5 Hz, $J_{6',6}$ 12.6 Hz, H-6′), 4.72 (1H, adt, $J_{3,F}$ 53.0 Hz, *J* 9.3 Hz, H-3), 4.99–5.11 (5H, m, H-2, 2 × PhCH_2), 5.19–5.27 (1H, m, *J* 12.9 Hz, *J* 10.4 Hz, *J* 9.11 Hz, H-4), 5.89 (1H, adt, $J_{1,P}$ 6.8 Hz, *J* 3.5 Hz, H-1), 7.34–7.39 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.5, 20.6 (3 × C=O*C*H_3), 61.0 (C-6), 68.0 (d, $J_{C-4,F}$ 18.0 Hz, C-4), 69.0 (d, $J_{C-5,F}$ 7.0 Hz, C-5), 69.4 (d, $J_{C,P}$ 5.0 Hz, 2 × Ph*C*H_2), 67.0 (dd, $J_{C-2,F}$ 17.0 Hz, $J_{C-2,P}$ 7.0 Hz, C-2), 88.5 (d, $J_{C-3,F}$ 188 Hz, C-3), 94.0 (dd, $J_{C-1,F}$ 9.0 Hz, $J_{C-1,P}$ 5.0 Hz, C-1), 128.0, 128.6, 128.7, 128.8 (12 × Ar-C), 169.1, 169.7, 170.5 (3 × CH_3C=O); δ_P (162 MHz, $CDCl_3$) −2.62 (^{1}H decoupled); δ_F (376 MHz, $CDCl_3$) −200.9 (^{1}H decoupled); *m*/*z* (ES^+) 627 (M+MeCN/NH_4^+, 100%), 586 (M+NH_4^+, 40%), 569 (M+H^+, 15%); HRMS (ES^+) calcd for $C_{26}H_{30}O_{11}FPNa$ (MNa^+) 591.1408; found 591.1402. (Found: C, 54.91; H, 5.33; P, 5.29. $C_{26}H_{30}O_{11}F$ P requires C, 54.93; H, 5.32; P, 5.45). **6cβ**: δ_H (400 MHz, $CDCl_3$) 1.98, 2.02, 2.12 (3 × 3H, 3 × s, 3 × C=OCH_3), 3.74 (1H, m, H-6), 4.12 (1H, dd, $J_{6,5}$ 2.0 Hz, $J_{6,6'}$ 12.4 Hz, H-6′), 4.24 (1H, dd, $J_{6',5}$ 4.8 Hz, $J_{6',6}$ 12.4 Hz, H-6′), 4.59 (1H, adt, $J_{3,F}$ 51.8 Hz, *J* 9.1 Hz, H-3), 5.01–5.10 (4H, m, 2 × PhCH_2), 5.25–5.31 (3H, m, H-4, H-2, H-1), 7.31–7.36 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.6 (3 × C=O*C*H_3), 61.1 (C-6), 67.6 (d, $J_{C-4,F}$ 19.0 Hz, C-4), 69.7 (d, $J_{C,P}$ 6.0 Hz, 2 × Ph*C*H_2), 71.2 (dd, $J_{C-2,F}$ 19.0 Hz, $J_{C-2,P}$ 9.0 Hz, C-2), 71.7 (d, $J_{C-5,F}$ 8.0 Hz, C-5), 90.6 (d, $J_{C-3,F}$ 193 Hz, C-3), 95.7 (dd, $J_{C-1,F}$ 12.0 Hz, $J_{C-1,P}$ 5.0 Hz, C-1), 127.8, 127.9, 128.0, 128.4, 128.5, 128.7, 128.9 (12 × Ar-C), 169.0, 169.1, 170.5 (3 × CH_3C=O); δ_P (162 MHz, $CDCl_3$) −3.17 (^{1}H decoupled); δ_F (376 MHz, $CDCl_3$) −196.4 (^{1}H decoupled).

4.7. Dibenzylphosphate-2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-D-glucopyranoside (6d)

LDA (1.7 mL of a 2.0 M solution in THF/heptane/ethylbenzene, 3.3 mmol, 1.1 equiv) was added slowly to a stirred solution of triacetate **5d** (1 g, 3.02 mmol, 1 equiv) in THF (40 mL) at −78 °C under argon. After 15 min, a solution of tetrabenzyl pyrophosphate (2.11 g, 3.91 mmol, 1.3 equiv) in THF (10 mL) was added, and the reaction mixture was allowed to warm to 0 °C. After 5 h at 0 °C a saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/petrol, 1:1) to afford the two anomers of dibenzylphosphate **6d** (1.29 g of the α-anomer **6dα**, 73% and 0.31 g of the β-anomer

6dβ, 17.5%) as pale yellow oils. **6dα**: $[\alpha]_D^{20}$ +84 (*c* 1.0, $CHCl_3$); ν_{max} (thin film) 2110 (br s, N_3), 1750 (br s, C=O); δ_H (400 MHz, $CDCl_3$) 1.96, 2.00, 2.12 (3 × 3H, 3 × s, 3 × C=OCH_3), 4.80 (1H, at, *J* 10.1 Hz, H-3), 3.92 (1H, dd, $J_{6,5}$ 2.3 Hz, $J_{6,6}$ 12.4 Hz, H-6), 3.97 (1H, ddd, $J_{5,6}$ 2.3 Hz, $J_{5,6'}$ 4.0 Hz, $J_{5,4}$ 10.1 Hz, H-5), 4.12 (1H, dd, $J_{6',5}$ 4.0 Hz, $J_{6',6}$ 12.4 Hz, H-6′), 4.78 (1H, ddd, $J_{2,3}$ 10.1 Hz, $J_{2,P}$ 2.8 Hz, $J_{2,1}$ 3.3 Hz, H-2), 4.95 (1H, at, *J* 10.1 Hz, H-4), 5.05–5.15 (4H, m, 2 × PhCH_2), 5.85 (1H, dd, $J_{1,P}$ 6.8 Hz, $J_{1,2}$ 3.3 Hz, H-1), 7.36–7.39 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.6 (3 × C=O*C*H_3), 60.1 (C-3), 61.3 (C-6), 67.4 (C-4), 69.7 (C-5), 69.7, 69.8 (d, $J_{C,P}$ 6.0 Hz, 2 × Ph*C*H_2), 70.6 (d, $J_{C-2,P}$ 7.0 Hz, C-2), 93.3 (d, $J_{C-1,P}$ 5.0 Hz, C-1), 128.0, 128.5, 128.7, 128.8, 128.9 (12 × Ar-C), 169.1, 169.6, 170.5 (3 × CH_3C=O); δ_P (162 MHz, $CDCl_3$) −2.50 (^{1}H decoupled); *m*/*z* (ES^+) 614 ($M+Na^+$, 100%), 650 ($M+MeCN/NH_4^+$, 18%); HRMS (ES^+) calcd for $C_{26}H_{30}O_{11}N_3PNa$ (MNa^+) 614.1515; found 614.1510. (Found: C, 52.59; H, 5.08; N, 7.03; P, 5.15. $C_{26}H_{30}O_{11}N_3P$ requires C, 52.79; H, 5.11; N, 7.10; P, 5.24). **6dβ**: δ_H (400 MHz, $CDCl_3$) 1.99, 2.01, 2.14 (3 × 3H, 3 × s, 3 × C=OCH_3), 3.67 (1H, at, *J* 10.1 Hz, H-3), 3.78 (1H, m, H-5), 4.10 (1H, dd, $J_{6,5}$ 2.5 Hz, $J_{6,6'}$ 12.6 Hz, H-6), 4.21 (1H, dd, $J_{6',5}$ 5.0 Hz, $J_{6',6}$ 12.6 Hz, H-6′), 5.05–5.09 (6H, m, H-4, H-2, 2 × PhCH_2), 5.33 (1H, at, *J* 7.6 Hz, H-1), 7.30–7.37 (10H, m, 10 × Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.6 (3 × C=O*C*H_3), 61.5 (C-6), 63.7 (C-3), 67.8 (C-4), 69.7, 69.8 (2 × d, $J_{C,P}$ 6.0 Hz, 2 × Ph*C*H_2), 70.9 (d, $J_{C-2,P}$ 9.0 Hz, C-2), 73.5 (C-5), 96.4 (d, $J_{C-1,P}$ 4.0 Hz, C-1), 127.8, 127.9, 128.0, 128.4, 128.5, 128.6 (12 × Ar-C), 169.0, 169.1, 170.5 (3 × CH_3C=O); δ_P (162 MHz, $CDCl_3$) −3.21 (^{1}H decoupled).

4.8. Phosphate-2,4,6-tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranoside, ditriethylammonium salt (7a)

$Pd(OH)_2$ (0.08 g, 20% w/w) was added to a solution of compound **6a** (0.4 g, 0.69 mmol, 1 equiv) in dry MeOH (10 mL), and the resulting solution was stirred under an atmosphere of hydrogen at rt. After 12 h, the solution was filtered through Celite®. Et_3N (0.20 mL, 1.44 mmol, 2.1 equiv) was then added and the resulting mixture was concentrated in vacuo to afford triethylammonium salt **7a** (0.39 g, 94%) as a colourless oil, which was used in the next step without further purification.

4.9. Phosphate-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-ribo-hexopyranoside, ditriethylammonium salt (7b)

$Pd(OH)_2$ (0.06 g, 20% w/w) was added to a solution of compound **6b** (0.3 g, 0.54 mmol, 1 equiv) in dry MeOH (10 mL), and the resulting solution was stirred under an atmosphere of hydrogen at rt. After 12 h, the solution was filtered through Celite®. Et_3N (0.16 mL, 1.14 mmol, 2.1 equiv) was then added and the resulting mixture was concentrated in vacuo to afford triethylammonium salt **7b** (0.27 g, 88%) as a colourless oil, which was used in the next step without further purification.

4.10. Phosphate-2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-α-D-glucopyranoside, ditriethylammonium salt (7c)

$Pd(OH)_2$ (0.08 g, 20% w/w) was added to a solution of compound **6c** (0.4 g, 0.70 mmol, 1 equiv) in dry MeOH (10 mL), and the resulting solution was stirred under an atmosphere of hydrogen at rt. After 12 h, the solution was filtered through Celite®. Et_3N (0.20 mL, 1.48 mmol, 2.1 equiv) was then added and the resulting mixture was concentrated in vacuo to afford triethylammonium salt **7c** (0.42 g, 90%) as a colourless oil, which was used in the next step without further purification.

4.11. Phosphate-2,4,6-tri-*O*-acetyl-3-acetamido-3-deoxy-α-D-glucopyranoside, ditriethylammonium salt (7d)

$Pd(OH)_2$ (0.08 g, 20% w/w) and Ac_2O (0.13 mL, 1.34 mmol, 1.5 equiv) were added to a solution of compound **6d** (0.4 g, 0.67 mmol, 1 equiv) in dry MeOH (10 mL), and the resulting solution was stirred under an atmosphere of hydrogen at rt. After 12 h, the solution was filtered through Celite®. Et_3N (0.20 mL, 1.41 mmol, 2.1 equiv) was then added and the resulting mixture was concentrated in vacuo to afford triethylammonium salt **7d** (0.37 g, 86%) as a colourless oil, which was used in the next step without further purification.

4.12. Phosphate-3-*O*-methyl-α-D-glucopyranoside, ditriethylammonium salt (8a)

Compound **7a** (0.39 g, 0.64 mmol, 1 equiv) was dissolved in a mixture of MeOH (5 mL), H_2O (2 mL) and Et_3N (1 mL) and the resulting solution was stirred under argon at room temperature for 6 days. The mixture was then concentrated in vacuo, and the residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.2–0.35 M) to afford triethylammonium salt **8a** (0.27 g, 89%) as a white solid; δ_H (400 MHz, D_2O) 1.15 (18H, t, *J* 7.3 Hz, NCH_2CH_3), 3.07 (12H, q, NCH_2), 3.35–3.47 (3H, m, H-4, H-3, H-2), 3.50 (3H, s, OCH_3), 3.63 (1H, dd, $J_{6,6'}$ 12.4 Hz, $J_{6,5}$ 4.8 Hz, H-6), 3.72 (1H, dd, $J_{6',6}$ 12.4 Hz, $J_{6',5}$ 1.5 Hz, H-6′), 3.75 (1H, m, H-5), 5.33 (1H, dd, $J_{1,P}$ 7.1 Hz, $J_{1,2}$ 3.2 Hz, H-1); δ_C (100.6 MHz, D_2O) 8.6 (NCH_2CH_3), 46.9 (NCH_2CH_3), 60.4 (OCH_3), 60.6 (C-6), 69.2 (C-4), 71.6 (d, $J_{C-2,P}$ 8.0 Hz, C-2), 72.7 (C-5), 83.0 (C-3), 94.8 (d, $J_{C-1,P}$ 6.0 Hz, C-1); δ_P (162 MHz, D_2O) −0.21 (^{1}H decoupled); *m*/*z* (ES^-) 273 ($M-H^+$, 100%); HRMS (ES^-) calcd for $C_7H_{14}O_9P$ ($M-H^+$) 273.0380; found 273.0370.

4.13. Phosphate-3-deoxy-α-D-ribo-hexopyranoside, ditriethylammonium salt (8b)

Compound **7b** (0.27 g, 0.47 mmol, 1 equiv) was dissolved in a mixture of MeOH (5 mL), H_2O (2 mL) and Et_3N (1 mL), and the resulting solution was stirred under argon at room temperature for 6 days. The mixture was then concentrated in vacuo, and the residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.2–0.35 M) to afford triethylammonium salt **8b** (0.19 g, 92%) as a white solid; δ_H (400 MHz, D_2O) 1.15 (18H, t, J 7.3 Hz, NCH_2CH_3), 1.70 (1H, aq, J 11.6 Hz, H-3a), 2.04 (1H, m, H-3e), 3.07 (12H, q, J 7.3 Hz, NCH_2), 3.50 (1H, m, H-4), 3.56–3.72 (4H, m, H-5, H-2, H-6, H-6′), 5.26 (1H, dd, $J_{1,P}$ 5.3 Hz, $J_{1,2}$ 3.3 Hz, H-1); δ_C (100.6 MHz, D_2O) 8.6 (NCH_2CH_3), 34.3 (C-3), 47.0 (NCH_2CH_3), 60.9 (C-6), 64.4 (C-4), 67.2 (d, $J_{C-2,P}$ 8.0 Hz, C-2), 73.2 (C-5), 93.4 (d, $J_{C-1,P}$ 5.0 Hz, C-1); δ_P (162 MHz, D_2O) 0.54 (^{1}H decoupled); m/z (ES^-) 243 ($M-H^+$, 100%), 487 ($2M-H^+$, 50%), 731 ($3M-H^+$, 25%); HRMS (ES^-) calcd for $C_6H_{12}O_8P$ ($M-H^+$) 243.0275; found 243.0267.

4.14. Phosphate-3-deoxy-3-fluoro-α-D-glucopyranoside, ditriethylammonium salt (8c)

Compound **7c** (0.42 g, 0.71 mmol, 1 equiv) was dissolved in a mixture of MeOH (5 mL), H_2O (2 mL) and Et_3N (1 mL), and the resulting solution was stirred under argon at room temperature for 6 days. The mixture was then concentrated in vacuo, and the residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.2–0.35 M) to afford triethylammonium salt **8c** (0.29 g, 90%) as a white solid; δ_H (400 MHz, D_2O) 1.15 (18H, t, J 7.3 Hz, NCH_2CH_3), 3.08 (12H, q, J 7.3 Hz, NCH_2), 3.59– 3.76 (4H, m, H-4, H-2, H-6, H-6′), 3.78 (1H, m, H-5), 4.53 (1H, adt, $J_{3,F}$ 54.6 Hz, J 9.1 Hz, H-3), 5.39 (1H, m, H-1); δ_C (100.6 MHz, D_2O) 8.6 (NCH_2CH_3), 46.9 (NCH_2CH_3), 60.3 (C-6), 68.0 (d, $J_{C-4,F}$ 18.0 Hz, C-4), 70.5 (dd, $J_{C-2,F}$ 17.0 Hz, $J_{C-2,P}$ 8.0 Hz, C-2), 72.1 (d, $J_{C-5,F}$ 7.0 Hz, C-5), 95.2 (d, $J_{C-3,F}$ 178.0 Hz, C-3), 94.7 (dd, $J_{C-1,F}$ 10.0 Hz, $J_{C-1,P}$ 5.0 Hz, C-1); δ_P (162 MHz, D_2O) −0.08 (^{1}H decoupled); δ_F (376 MHz, $CDCl_3$) −200.5 (^{1}H decoupled); m/z (ES^-) 261 ($M-H^+$, 100%), 523 ($2M-H^+$, 37%), 1046 ($3M-H^+$, 10%); HRMS (ES^-) calcd for $C_6H_{11}FO_8P$ ($M-H^+$) 261.0180; found 261.0170.

4.15. Phosphate-3-acetamido-3-deoxy-α-D-glucopyranoside, ditriethylammonium salt (8d)

Compound **7d** (0.37 g, 0.59 mmol, 1 equiv) was dissolved in a mixture of MeOH (5 mL), H_2O (2 mL) and Et_3N (1 mL), and the resulting solution was stirred under argon at room temperature for 6 days. The mixture was then concentrated in vacuo, and the residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.2–0.35 M) to afford triethylammonium salt **8d** (0.27 g, 93%) as a white solid; δ_H (400 MHz, D_2O) 1.15 (18H, t, J 7.3 Hz, NCH_2CH_3), 1.93 (3H, s, $NHCOCH_3$), 3.08 (12H, q, J 7.3 Hz, NCH_2), 3.36 (1H, at, J 9.9 Hz, H-4), 3.48 (1H, adt, J 10.6 Hz, J 2.8 Hz, H-2), 3.65 (1H, dd, $J_{6,6'}$ 12.4 Hz, $J_{6,5}$ 4.3 Hz, H-6), 3.71 (1H, dd, $J_{6',6}$ 12.4 Hz, $J_{6',5}$ 2.3 Hz, H-6′), 3.79 (1H, m, H-5), 3.99 (1H, at, J 10.4 Hz, H-3), 5.38 (1H, dd, $J_{1,P}$ 7.1 Hz, $J_{1,2}$ 3.5 Hz, H-1); δ_C (100.6 MHz, D_2O) 8.6 (NCH_2CH_3), 22.6 ($NHCOCH_3$), 47.0 (NCH_2CH_3), 54.2 (C-3), 60.6 (C-6), 67.9 (C-4), 71.6 (d, $J_{C-2,P}$ 9.0 Hz, C-2), 73.1 (C-5), 94.6 (d, $J_{C-1,P}$ 5.0 Hz, C-1); 172.9 ($NHCOCH_3$); δ_P (162 MHz, D_2O) −1.05 (^{1}H decoupled); m/z (ES^-) 300 ($M-H^+$, 100%), 601 ($2M-H^+$, 30%); HRMS (ES^-) calcd for $C_8H_{15}NO_9P$ ($M-H^+$) 300.0489; found 300.0479.

4.16. Phosphate-3-azido-3-deoxy-α-D-glucopyranoside, ditriethylammonium salt (8e)

A solution of azide **5d** (1.0 g, 3.02 mmol, 1 equiv) in dry THF (25 mL) was added to a stirred solution of *o*-phenylene phosphorochloridate **10** (1.72 g, 9.06 mmol, 3 equiv) and *sym*-collidine (1.28 g, 10.0 mmol, 3.5 equiv) in THF (25 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then filtered to remove the precipitate. Water (0.4 mL) and *sym*-collidine (1.28 g) were added to the filtrate and the reaction mixture was stirred for a further 30 min at room temperature. The solution was then cooled to 0 °C and re-filtered before the solvent was removed in vacuo. The product was then dried thoroughly under vacuum. The residue was dissolved in a minimal amount of dioxane (~5 mL), cooled to 12 °C, lead tetraacetate (2.67 g, 6.02 mmol, 2 equiv) was added and the reaction mixture was then stirred for 3 h at room temperature. The solvent was then removed and the residue of crude **7e** was dissolved in a mixture of MeOH (10 mL), Et_3N (2 mL) and water (4 mL). The resulting mixture was stirred under argon at room temperature for 6 days. The reaction mixture was then concentrated in vacuo, and the residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.2–0.35 M) to afford triethylammonium salt **8e** (0.67 g, 46%) as a white solid; δ_H (400 MHz, D_2O) 1.16 (18H, t, J 7.2 Hz, NCH_2CH_3), 3.08 (12H, q, J 7.2 Hz, NCH_2), 3.38 (1H, at, J 10.2 Hz, H-4), 3.47 (1H, adt, J 10.2 Hz, J 2.7 Hz, H-2), 3.59–3.67 (2H, m, H-3, H-6), 3.72 (1H, dd, $J_{6',6}$ 12.6 Hz, $J_{6',5}$ 1.7 Hz, H-6′), 3.77 (1H, m, H-5), 5.35 (1H, dd, $J_{1,P}$ 6.8 Hz, $J_{1,2}$ 3.4 Hz, H-1); δ_C (100.6 MHz, D_2O) 8.6 (NCH_2CH_3), 47.0 (NCH_2CH_3), 60.4 (C-6), 66.0 (C-3), 68.4 (C-4), 70.7

(d, $J_{C-2,P}$ 9.6 Hz, C-2), 72.7 (C-5), 94.5 (d, $J_{C-1,P}$ 6.4 Hz, C-1); δ_P (162 MHz, D_2O) −1.39 (^{1}H decoupled); *m*/*z* (ES^-) 284 ($M-H^+$, 30%), 569 ($2M-H^+$, 100%), 854 ($3M-H^+$, 80%), 1138 ($4M-H^+$, 35%); HRMS (ES^-) calcd for $C_6H_{12}N_3O_8P$ ($M-H^+$) 284.0289; found 284.0281.

4.17. Uridinediphosphoryl-3-*O*-methyl-α-D-glucopyranoside, ditriethylammonium salt (9a)

4-Morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphormorpholidate (0.43 g, 0.63 mmol, 2 equiv) and tetrazole (0.066 g, 0.94 mmol, 3 equiv) were added to a solution of compound **8a** (0.15 g, 0.31 mmol, 1 equiv) in dry pyridine (10 mL), and the resulting solution was stirred at room temperature. After 6 days the solution was concentrated in vacuo. The residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.35–0.5 M) to afford UDP-derivative **9a** (0.13 g, 51%) as a white solid, $[\alpha]_D^{22}$ +20 (*c* 1.25, MeOH); δ_H (400 MHz, D_2O) 1.11 (18H, t, *J* 7.3 Hz, NCH_2CH_3), 3.03 (12H, q, *J* 7.3 Hz, NCH_2CH_3), 3.35–3.47 (3H, m, glu: H-4, H-3, H-2), 3.48 (3H, s, OCH_3), 3.62 (1H, dd, $J_{6,5}$ 4.5 Hz, $J_{6,6'}$ 12.4 Hz, glu: H-6), 3.70 (1H, dd, $J_{6',5}$ 2.3 Hz, $J_{6',6}$ 12.4 Hz, glu: H-6′), 3.77 (1H, m, glu: H-5), 3.91–4.24 (5H, m, rib: H-5, H-5′, H-4, H-3, H-2), 5.45 (1H, dd, $J_{1,P}$ 7.1 Hz, $J_{1,2}$ 3.0 Hz, glu: H-1), 5.80 (2H, m, rib: H-1, U: H-5), 7.82 (1H, d, *J* 8.1 Hz, U: H-6); δ_C (100.6 MHz, D_2O) 8.5 (NCH_2CH_3), 46.9 (NCH_2CH_3), 60.4 (glu: C-6), 60.5 (OCH_3), 65.3 (d, $J_{C-5,P}$ 5.0 Hz, rib: C-5), 68.9 (glu: C-4), 70.0 (rib: C-3), 71.6 (d, $J_{C-2,P}$ 9.0 Hz, glu: C-2), 73.1 (glu: C-5), 74.1 (rib: C-2), 83.1 (glu: C-3), 83.6 (d, $J_{C-4,P}$ 10.0 Hz, rib: C-4), 88.7 (rib: C-1), 96.0 (d, $J_{C-1,P}$ 7.0 Hz, glu: C-1), 102.9 (U: C-5), 141.9 (U: C-6), 152.1 (U: C-4), 167.5 (U: C-2); δ_P (162 MHz, D_2O) −11.1, −12.9 (^{1}H decoupled); *m*/*z* (ES^-) 579 ($M-H^+$, 100%); HRMS (ES^-) calcd for $C_{16}H_{25}N_2O_{17}P_2$ ($M-H^+$) 579.0628; found 579.0629.

4.18. Uridinediphosphoryl-3-deoxy-α-D-ribo-hexopyranoside, ditriethylammonium salt (9b)

4-Morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphormorpholidate (0.30 g, 0.44 mmol, 2 equiv) and tetrazole (0.047 g, 0.67 mmol, 3 equiv) were added to a solution of compound **8b** (0.10 g, 0.22 mmol, 1 equiv) in dry pyridine (8 mL) and the resulting solution was stirred at room temperature. After 6 days, the solution was concentrated in vacuo. The residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.35–0.5 M) to afford UDP-derivative **9b** (0.09 g, 52%) as a white solid, $[\alpha]_D^{22}$ +19 (*c* 0.5, MeOH); δ_H (400 MHz, D_2O) 1.11 (18H, t, *J* 7.3 Hz, NCH_2CH_3), 1.67 (1H, aq, *J* 11.6 Hz, glu: H-3_{ax}), 2.05 (1H, adt, *J* 11.4 Hz, *J* 4.5 Hz, glu: H-3_{eq}), 3.02 (16H, q, *J* 7.3 Hz, NCH_2), 3.47–3.72 (5H, m, glu: H-4, H-2, H-5, H-6, H-6′), 3.90–4.25 (5H, m, rib: H-5, H-5′, H-4, H-3, H-2), 5.39 (1H, dd, $J_{1,2}$ 3.3 Hz, $J_{1,P}$ 7.1 Hz, glu: H-1), 5.82 (2H, m, rib: H-1, U: H-5), 7.84 (1H, d, $J_{5,6}$ 8.1 Hz, U: H-6); δ_C (100.6 MHz, D_2O) 8.55 (NCH_2CH_3), 34.5 (glu: C-3), 46.9 (NCH_2CH_3), 60.7 (glu: C-6), 64.1 (glu: C-4), 65.2 (d, $J_{C-5,P}$ 6.0 Hz, rib: C-5), 67.0 (d, $J_{C-2,P}$ 8.0 Hz, glu: C-2), 69.9 (rib: C-3), 73.7 (glu: C-5), 74.1 (rib: C-2), 83.6 (d, $J_{C-4,P}$ 10.0 Hz, rib: C-4), 88.8 (rib: C-1), 94.8 (d, $J_{C-1,P}$ 7.0 Hz, glu: C-1), 102.9 (U: C-5), 142.0 (U: C-6), 151.1 (U: C-4), 166.5 (U: C-2); δ_P (162 MHz, D_2O) −11.2, −12.5 (^{1}H decoupled); *m*/*z* (ES^-) 549 ($M-H^+$, 100%); HRMS (ES^-) calcd for $C_{15}H_{23}N_2O_{16}P_2$ ($M-H^+$) 549.0522; found 549.0524.

4.19. Uridinediphosphoryl-3-deoxy-3-fluoro-α-D-glucopyranoside, ditriethylammonium salt (9c)

4-Morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphormorpholidate (0.44 g, 0.64 mmol, 2 equiv) and tetrazole (0.068 g, 0.97 mmol, 3 equiv) were added to solution of compound **8c** (0.15 g, 0.32 mmol, 1 equiv) in dry pyridine (10 mL) and the resulting solution was stirred at room temperature. After 6 days, the solution was concentrated in vacuo. The residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.35–0.5 M) to afford UDP-derivative **9c** (0.12 g, 51%) as a white solid, $[\alpha]_D^{22}$ +9.1 (*c* 1.0, MeOH); δ_H (400 MHz, D_2O) 1.13 (18H, t, *J* 7.5 Hz, NCH_2CH_3), 3.04 (12H, q, *J* 7.5 Hz, NCH_2), 3.61–3.83 (5H, m, glu: H-5, H-6, H-6′, H-4, H-2), 3.92–4.27 (5H, m, rib: H-5, H-5′, H-4, H-3, H-2), 4.50 (1H, adt, $J_{3,F}$ 54.3 Hz, *J* 9.2 Hz, glu: H-3), 5.52 (1H, m, glu: H-1), 5.80–5.85 (2H, m, rib: H-1, U: H-5), 7.85 (1H, d, *J* 7.8 Hz, U: H-6); δ_C (100.6 MHz, D_2O) 8.6 (NCH_2CH_3), 46.9 (NCH_2CH_3), 60.1 (glu: C-6), 64.1 (d, $J_{C-5,P}$ 5.0 Hz, rib: C-5), 66.2 (d, $J_{C-4,F}$ 17.0 Hz, glu: C-4), 69.7 (dd, $J_{C-2,F}$ 19.0 Hz, $J_{C-2,P}$ 6.0 Hz, glu: C-2), 70.2 (rib: C-3), 72.9 (d, $J_{C-5,F}$ 6 Hz, glu: C-5), 74.2 (rib: C-2), 84.1 (d, $J_{C-4,P}$ 8.0 Hz, rib: C-4), 88.7 (rib: C-1), 94.1 (dd, $J_{C-1,P}$ 5.0 Hz, $J_{C-1,F}$ 9.0 Hz, glu: C-1), 95.0 (d, $J_{C-3,F}$ 184 Hz, glu: C-3), 102.9 (U: C-5), 142.2 (U: C-6), 152.2 (U: C-4), 166.6 (U: C-2); δ_P (162 MHz, D_2O) −11.2, −13.1 (^{1}H decoupled); δ_F (376.6 MHz, D_2O) −200.4 (^{1}H decoupled); *m*/*z* (ES^-) 567 ($M-H^+$, 100%); HRMS (ES^-) calcd for $C_{15}H_{22}FN_2O_{16}P_2$ ($M-H^+$) 567.0428; found 567.0431.

4.20. Uridinediphosphoryl-3-acetamido-3-deoxy-α-D-glucopyranoside, ditriethylammonium salt (9d)

4-Morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphormorpholidate (0.41 g, 0.59 mmol,

2 equiv) and tetrazole (0.062 g, 0.88 mmol, 3 equiv) were added to a solution of compound **8d** (0.15 g, 0.30 mmol, 1 equiv) in dry pyridine (10 mL) and the resulting solution was stirred at room temperature. After 6 days, the solution was concentrated in vacuo. The residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.35–0.5 M) to afford UDP-derivative **9d** (0.13 g, 54%) as a white solid, $[\alpha]_D^{22}$ +13 (*c* 0.75, MeOH); δ_H (400 MHz, D_2O) 1.09 (18H, t, *J* 7.3 Hz, NCH_2CH_3), 1.88 (3H, s, C=OCH_3), 3.00 (12H, q, *J* 7.3 Hz, NCH_2CH_3), 3.34 (1H, at, *J* 10.1 Hz, glu: H-4), 3.46 (1H, m, glu: H-2), 3.63 (1H, dd, $J_{6,5}$ 4.5 Hz, $J_{6,6'}$ 12.4 Hz, glu: H-6), 3.69 (1H, dd, $J_{6',5}$ 2.0 Hz, $J_{6',6}$ 12.4 Hz, glu: H-6′), 3.80 (1H, m, glu: H-5), 3.93–4.24 (6H, m, glu: H-3, rib: H-2, H-3, H-4, H-5, H-5′), 5.49 (1H, dd, $J_{1,P}$ 7.3 Hz, $J_{1,2}$ 3.5 Hz, glu: H-1), 5.79 (2H, m, rib: H-1, U: H-5), 7.79 (1H, d, *J* 8.1 Hz, U: H-6); δ_C (100.6 MHz, D_2O) 8.5 (NCH_2CH_3), 22.2 (C=OCH_3), 46.9 (NCH_2CH_3), 54.4 (glu: C-3), 60.6 (glu: C-6), 65.3 (d, $J_{C-5,P}$ 5.0 Hz, rib: C-5), 67.9 (glu: C-4), 70.0 (rib: C-3), 71.8 (d, $J_{C-2,P}$ 7.0 Hz, glu: C-2), 73.3 (glu: C-5), 74.2 (rib: C-2), 83.6 (d, $J_{C-4,P}$ 9.0 Hz, rib: C-4), 88.8 (rib: C-1), 95.3 (d, $J_{C-1,P}$ 4.0 Hz, glu: C-1), 102.7 (U: C-5), 141.9 (U: C-6), 151.5 (U: C-4), 169.6 (U: C-2), 178.2 (CH_3C=O); δ_P (162 MHz, D_2O) −11.2, −12.8 (^{1}H decoupled); *m*/*z* (ES^-) 606 ($M-H^+$, 100%); HRMS (ES^-) calcd for $C_{17}H_{26}N_3O_{17}P_2$ ($M-H^+$) 606.0737; found 606.0729.

4.21. Uridinediphosphoryl-3-azido-3-deoxy-α-D-glucopyranoside, ditriethylammonium salt (9e)

4-Morpholine-*N*,*N*′-dicyclohexylcarboxamidinium uridine 5′-monophosphormorpholidate (0.26 g, 0.37 mmol, 1.1 equiv) was added to a solution of compound **8e** (0.16 g, 0.34 mmol, 1 equiv) in dry pyridine (3 mL) and the resulting solution was stirred at room temperature. After 10 days, the solution was concentrated in vacuo. The residue was applied to a DEAE Sephadex A25 anion exchange column using a triethylammonium bicarbonate buffer gradient (0.35–0.5 M) to afford uridinediphosphoryl-3-azido-3-deoxy-α-D-glucopyranoside, ditriethylammonium salt **9e** (0.15 g, 55%) as a white solid, $[\alpha]_D^{22}$ +29 (*c* 0.5, MeOH); δ_H (400 MHz, CD_3OD) 1.32 (18H, t, *J* 7.3 Hz, NCH_2CH_3), 3.19 (12H, q, *J* 7.3 Hz, NCH_2CH_3), 3.33 (1H, at, *J* 7.8 Hz, glu: H-4), 3.40 (1H, adt, *J* 9.8 Hz, *J* 2.8 Hz, glu: H-2), 3.64–3.71 (2H, m, glu: H-3, H-6), 3.79–3.82 (1H, dd, $J_{6',5}$ 2.0 Hz, $J_{6',6}$ 11.9 Hz, glu: H-6′), 3.90 (1H, m, glu: H-5), 4.14 (1H, m, rib: H-4), 4.24–4.30 (3H, m, rib: H-2, H-5, H-5′), 4.37 (1H, at, *J* 4.8 Hz, rib: H-3), 5.68 (1H, dd, $J_{1,P}$ 7.8 Hz, $J_{1,2}$ 3.5 Hz, glu: H-1), 5.86 (1H, d, *J* 8.1 Hz, U: H-5), 5.98 (1H, d, *J* 4.8 Hz, rib: H-1), 8.07 (1H, d, *J* 8.1 Hz, U: H-6); δ_C (100.6 MHz, CD_3OD) 8.2 (NCH_2CH_3), 46.5 (NCH_2CH_3), 61.3 (glu: C-6), 65.1 (d, $J_{C-5,P}$ 6.0 Hz, rib: C-5), 67.6 (glu: C-3), 68.9 (glu: C-4), 70.2 (rib: C-3), 71.9 (d, $J_{C-2,P}$ 8.0 Hz, glu: C-2), 73.6 (glu: C-5), 74.7 (rib: C-2), 84.1 (d, $J_{C-4,P}$ 6.5 Hz, rib: C-4), 88.8 (rib: C-1), 95.7 (d, $J_{C-1,P}$ 4.0 Hz, glu: C-1), 102.3 (U: C-5), 141.7 (U: C-6), 159.7 (U: C-4), 165.2 (U: C-2); δ_P (162 MHz, CD_3OD) −11.3, −13.1 (^{1}H decoupled); *m*/*z* (ES^-) 590 ($M-H^+$, 100%); HRMS (ES^-) calcd for $C_{17}H_{22}N_5O_{16}P_2$ ($M-H^+$) 590.0542; found 590.0542.

4.22. Germination assays

The effect of compounds **4a**–**d**, **5a**–**d**, **6a**–**d**, **8a**–**e** and **9a**–**e** was assessed on the germination of *T. rubrum* microconidia as follows. *T. rubrum* conidia were harvested, and the spore suspensions were adjusted to the appropriate density. Test compounds were made up into solution and added to the spore suspension to obtain final concentrations of 0 μM (control), 1 μM, 10 μM, 100 μM and 1mM of each test compound. The resulting suspensions were pipetted with the appropriate number of replicates onto 0.1% keratin agar and incubated for 24 h at 30 °C. After incubation, the images of the germinated spores were taken to allow assessment of germ tube formation. A sample of 30 sets of 10 spores was counted to quantify germ tube initiation. The number of spores out of 300 counted per treatment was recorded as a proportion and plotted. Error bars were estimated as the standard deviation within treatments. Compound **6a** showed 40% inhibition of germ tube formation with respect to the relevant control at a concentration of 1mM. No other compounds showed significant inhibition of germination at any of the concentrations tested.

Acknowledgement

The authors gratefully acknowledge the European Union (Marie Curie Intra-EU Fellowship to R.D.).

References

1. (a) Asano, N. *Glycobiology* **2003**, *13*, 93R–104R; (b) Sears, P.; Wong, C.-H. *Angew. Chem.* **1999**, *111*, 2446–2471; *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324.
2. Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364.
3. Glycosyltransferase inhibitors currently in clinical use tend either to be naturally occurring antibiotics, or compounds that were originally synthesised for other purposes. In the carbohydrate field the most prominent of these is *N*-butyldeoxynojirimycin, long promulgated as a glycosidase inhibitor, which has in fact found clinical use as an inhibitor of a ceramide-specific glucosyltransferase for the treatment of Gaucher's disease. See: Cox, T.; Lachmann, R.; Hollak, C.; Aerts, J.; van Weely, S.; Hrebícek, M.;

Platt, F.; Butters, T.; Dwek, R.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A. *Lancet* **2000**, *355*, 1481–1485.
4. (a) Dimitroff, C. J.; Bernacki, R. J.; Sackstein, R. *Blood* **2003**, *101*, 602–610; (b) Woynarowska, B.; Dimitroff, C. J.; Sharma, M.; Matta, K. L.; Bernacki, R. J. *Glycoconj. J.* **1996**, *13*, 663–674; (c) Woynarowska, B.; Skrincosky, D. M.; Haag, A.; Sharma, M.; Matta, K. L.; Bernacki, R. J. *J. Biol. Chem.* **1994**, *269*, 22797–22803; (d) Bernacki, R. J., Korytnyk, W. In *The Glycoconjugates*; Academic Press: New York, 1982; Vol 4, pp 245–263.
5. (a) Berkin, A.; Szarek, W. A.; Kisilevsky, R. *Glycoconj. J.* **2005**, *22*, 443–451; (b) Kisilevsky, R.; Szarek, W. A.; Ancsin, J. B.; Elimova, E.; Marone, S.; Bhat, S.; Berkin, A. *Am. J. Pathol.* **2004**, *164*, 2127–2137; (c) Berkin, A.; Szarek, W. A.; Kisilevsky, R. *Carbohydr. Res.* **2002**, *337*, 37–44; (d) Thomas, S. S.; Plenkiewicz, J.; Ison, E. R.; Bols, M.; Zou, W.; Szarek, W. A.; Kisilevsky, R. *Biochim. Biophys. Acta* **1995**, *1272*, 37–48.
6. Sanger, F.; Nicklen, S.; Coulson, A. R. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5463–5467.
7. Goody, R. S.; Müller, B.; Restle, T. *FEBS Lett.* **1991**, *291*, 1–5.
8. See for example: (a) Sujino, K.; Uchiyama, T.; Hindsgaul, O.; Seto, N. O. L.; Wakarchuk, W. W.; Palcic, M. M. *J. Am. Chem. Soc.* **2000**, *122*, 1261–1269; (b) Kajihara, Y.; Endo, T.; Ogasawara, H.; Kodama, H.; Hashimoto, H. *Carbohydr. Res.* **1995**, *269*, 273–294; (c) Srivastava, G.; Hindsgaul, O.; Palcic, M. M. *Carbohydr. Res.* **1993**, *245*, 137–144.
9. There are more than 50 examples of modified donors acting as substrates for glycosyl transferases. For a review see: Qian, X.; Sujino, K.; Palcic, M. M. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley VCH, 2000; Vol. 2, pp 685–703.
10. (a) Danac, R.; Ball, L.; Gurr, S. J.; Muller, T.; Fairbanks, A. J. *ChemBioChem* **2007**, *8*, 1241–1245; (b) Muller, T.; Danac, R.; Ball, L.; Gurr, S. J.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2007**, *18*, 1299–1307; (c) Smellie, I. A.; Bhakta, S.; Sim, E.; Fairbanks, A. J. *Org. Biomol. Chem.* **2007**, *5*, 2257–2266.
11. Nucci, M.; Marr, K. A. *Emerg. Infect.* **2005**, *41*, 521–526.
12. Vanden Bossche, H.; Marichal, P.; Odds, F. C. *Trends Microbiol.* **1994**, *2*, 393–400.
13. Georgopapadadakou, N. H.; Tkacz, J. S. *Trends Microbiol.* **1995**, *3*, 98–104.
14. Bowman, S. M.; Free, S. J. *BioEssays* **2006**, *28*, 799–808.
15. Yan, S.; Klemm, D. *Tetrahedron* **2002**, *58*, 10065–10071.
16. Withers, S. G.; Percival, M. D.; Street, I. P. *Carbohydr. Res.* **1989**, *187*, 43–66.
17. Elhalabi, J.; Rice, K. G. *Carbohydr. Res.* **2002**, *337*, 1935–1940.
18. Weigel, T. M.; Liu, L.; Liu, H. *Biochemistry* **1992**, *31*, 2129–2139.
19. Weitzman, I.; Summerbell, R. C. *Clin. Microbiol. Rev.* **1995**, *8*, 240–259.
20. One referee doubted the ability of acetates such as **4/5** to act as pro-drugs of **9** since they would be required to pass through several intermediate biosynthetic steps. However our previous work (Ref. 10a) had indicated that esters similar to **4/5** were in fact the most bioactive compounds. Whilst the mode of action of those compounds has yet to be proven, extensive previous work on mammalian glycoconjugate and glycosoaminoglycan biosynthesis (see Ref. 4 and 5) has already demonstrated that simple carbohydrate esters can act as pro-drugs and can be converted into the corresponding UDP-donors intracellularly.
21. It is notable that the anti-fungal GlcNAc derivatives described in Ref. 10a were benzoate esters, in contrast with the acetate esters tested in this study. Whilst the anti-fungal activity of benzoate salts themselves is well known, it is also notable that the bioactivity observed in Ref. 10a is an order of magnitude more potent than could possibly arise from benzoate alone.
22. (a) Austin, G. N.; Baird, P. B.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095–3108; (b) Collins, P. M. *Tetrahedron* **1965**, *21*, 1809–1815.
23. Jiang, J.; Biggins, J. B.; Thorson, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 6803–6809.
24. Iacono, S.; Rasmussen, J. R. *Org. Synth.* **1990**, *7*, 139.
25. Doboszewski, B.; Hay, G. W.; Szarek, W. A. *Can. J. Chem.* **1987**, *65*, 412–419.
26. Barker, S. A.; Homer, J.; Keith, M. C.; Thomas, L. F. *J. Chem. Soc.* **1963**, 1538–1543.
27. (a) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522–4530; (b) Ferrier, R. J.; Overend, W. G.; Sankey, G. H. *J. Chem. Soc* **1965**, 2830–2836.
28. Withers, S. G.; MacLennan, D. J.; Street, I. P. *Carbohydr. Res.* **1986**, *154*, 127–144.
29. Suhara, Y.; Yamaguchi, Y.; Collins, B.; Schnaar, R. L.; Yanagishita, M.; Hildreth, J. E. K.; Shimida, I.; Ichikawa, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1999–2013.
30. Han, X. B.; Jiang, Z. H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1993**, 853–858.