SYNTHESIS OF PEPTIDOGLYCAN UNITS WITH UDP AT THE ANOMERIC POSITION

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A series of UDP-disaccharide peptide compounds were synthesized as synthetic substrate analogues or potential inhibitors of glycosyl transferase. Fluorescent compounds have been prepared with the aim of developing a screening method for selecting transglycosylase inhibitors.

Keywords: Peptidoglycans; UDP-disaccharide; Dansyl; Dipeptides; Oligosaccharides; Glycopeptides; Amino sugars; Carbohydrates; Glycosidations; Glycosyl transferases.

The recent increase in bacterial resistance to active agents, like glycopeptide antibiotics (vancomycin) and β-lactam antibiotics (penicillin) which inhibit the growth of peptidoglycan, by specific inhibition of penicillin-binding-proteins (PBPs), has reached an alarming level and has begun to erode their once reliable clinical efficacy[1].

The peptidoglycan (PG), which forms a sacculus around the bacterial cell, is an essential cell wall polymer protecting bacteria from lyses under high osmotic pressures[2]. Many of the safe and potent antibiotics function by inhibiting peptidoglycan synthesis and a lot of research has been devoted to isolate and characterize enzymes involved in the synthesis of peptidoglycan. All these proteins are potential targets for designing new antibiotics.

Peptidoglycan is present in prokaryotes and has never been identified in eukaryote cells. In Gram-positive bacteria as much as 90% of the cell wall consists of peptidoglycan whereas in Gram-negative bacteria this figure is only 5–20% [3]. Structurally the peptidoglycan layer is composed of linear polysaccharide chains of alterning *N*-acetylglucosamine and *N*-acetylmuramic acid units, cross-linked via short peptides appended to muramic

acid[4]. The peptidoglycan biosynthesis takes place in three distinct stages[5]. The first occurs in the cytosol in which UDP-*N*-acetylglucosamine is converted in two steps into UDP-*N*-acetylmuramic acid by MurA and MurB enzymes. Then, MurC, MurD, MurE and MurF ATP-dependent ligases catalyse the formation of the UDP-*N*-acetylmuramoyl-pentapeptide by sequential addition of L-alanine, D-glutamic acid, L-lysine (in the case of Gram-positive bacteria) or *meso*-diaminopimelic acid (in the case of Gram-negative bacteria) and the preformed D-alanyl-D-alanine dipeptide. The second step occurs at the cytoplasmic surface of bacteria membrane in which MraY catalyzes a pyrophosphate exchange reaction in which the UDP-MurNAc-pentapeptide is coupled to a transmembrane carrier, the C_{55}-isoprenoid alcohol phosphate. The product of this reaction provides the lipid I intermediate. Then MurG catalyses the transfer of GlcNAc from UDP-GlcNAc to the C(4)-hydroxyl group of lipid I. The product of this reaction provides in turn the ultimate monomeric intermediate of bacterial cell wall: the lipid II. The third stage occurs in the bacterial cell wall after the translocation of lipid II to the extracellular site of the cell membrane. The assembly of the lipid II units into the peptidoglycan is carried out by specialized transferases, i.e. glycosyl transferase, which catalyses glycan chain elongation (transglycosylation) by displacing the pyrophosphate linked to C(1) of *N*-acetylmuramic acid of one disaccharide unit by the C(4) hydroxyl group of *N*-acetylglucosamine of another disaccharide unit. Then an acyl serine transferase working as transpeptidase catalyses peptide cross-linking between glycan strands. The rupture of the D-alanyl-D-alanine bond at the carboxy end of a pentapeptide unit and the attack of the penultimate D-alanyl by the amino group of a *meso*-diaminopimelic acid or lysine residue of another peptide proceeds via the formation of a peptidyl enzyme in which the D-alanyl moiety is linked as an ester to a serine residue at the enzyme active site.

The pathway to peptidoglycan is one of the most highly conserved metabolic pathways in bacteria and is a major target for antibiotics. Understanding how peptidoglycan is made is essential for understanding how bacteria build up their cell wall and it is important information for designing new antibiotics. In a recent contribution, Kahne and co-workers suggest that the antibacterial effects of some glycopeptide derivatives are not necessarily based on strong peptide binding but rather on interactions with proteins involved in the transglycosylation steps of the cell wall biosynthesis[6]. Here we have developed chemical tools, synthetic substrate analogues and potential inhibitors that enable the study of enzymes involved in the final steps of peptidoglycan biosynthesis and especially the glycosyl transferase step for which the mechanism of action is not yet known. We have synthe-

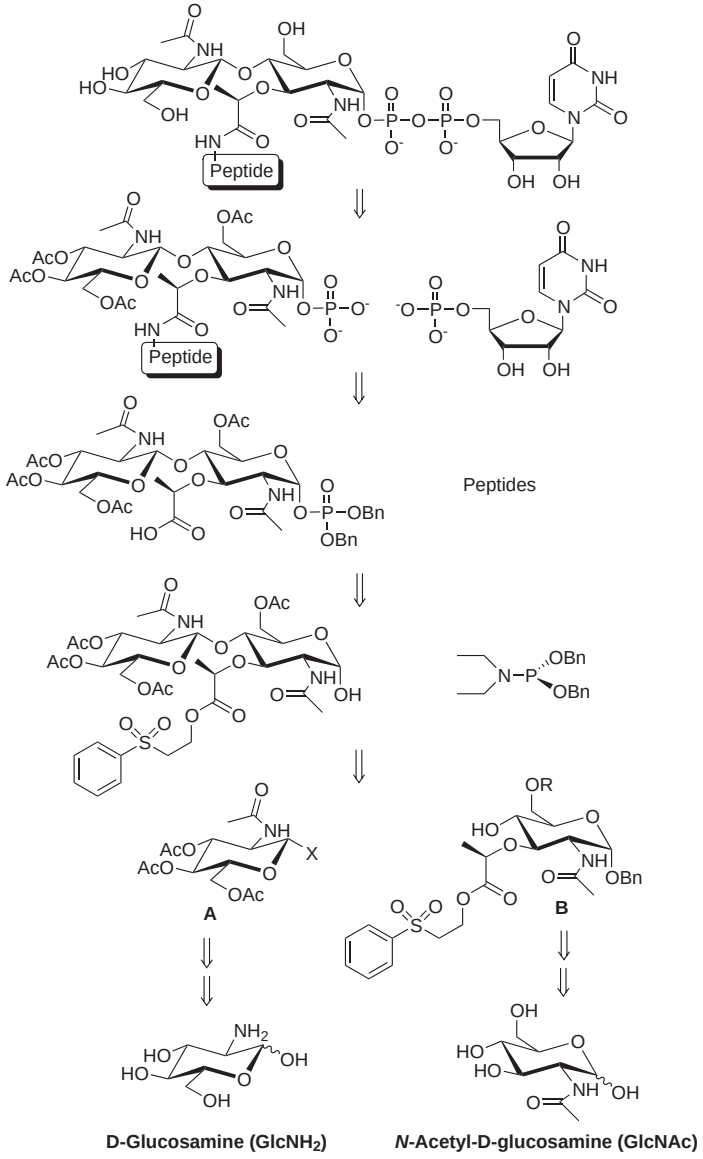
sized peptidoglycan monomer with modification in the peptide moiety and with a uridine diphosphate at the anomeric position. We selected the uridine moiety (instead of a lipid moiety) because previous studies have demonstrated that UDP-disaccharide-pentapeptide inhibits the glycosyl transferase reaction[7]. Fluorescent as well as non-fluorescent probes have been obtained. The fluorescent compound has been synthesized with the aim of developing a screening method for selecting transglycosylase inhibitors.

CHEMISTRY AND DISCUSSION

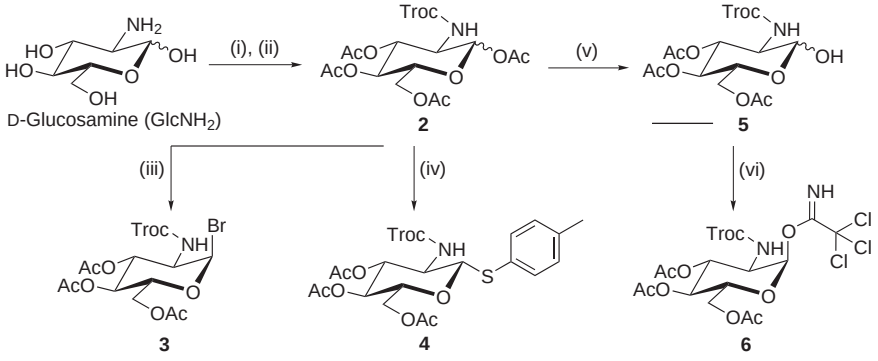
Recently, three synthetic schemes[8–10] to obtain natural lipid II have been published. The first describes the conversion of lipid I to lipid II using purified *E. coli* MurG [8]. In the second and the third one, the compounds were obtained by total syntheses[9,10]. These last one[10] has been used as a guide for the preparation of lipid II analogues described in this article.

To introduce the desired modifications, we first synthesized the core disaccharide of the peptidoglycan unit. The key starting material consists of the fully protected *N*-acetyl-D-glucosamine and *N*-acetylmuramic acid. The disconnection in the retrosynthetic scheme of this disaccharide leads to two structurally related glycoside derivatives **A** (donor) and **B** (acceptor) which could be obtained, respectively, from D-glucosamine ($GlcNH_2$) and *N*-acetyl-D-glucosamine (GlcNAc) for the glycosylation step[11] (Scheme 1).

For the large-scale synthesis of the core of the glycan, we investigated the best choice of the leaving group at the anomeric position of the glycosyl donor **A**, the best way to liberate the 4-hydroxyl group of the acceptor fragment **B**, and finally the activating agent which is most appropriate for the coupling reaction. To obtain donor fragments with different reactivity at the anomeric center we have prepared various examples of *N*-[(2,2,2-trichloroethoxy)carbonyl] (*N*-Troc) acetylated donor **A** (Scheme 2). Our investigations cover three basic methods for oxazoline intermediate formation i.e. the Koenigs–Knorr glycosylation method with an α-bromo glycoside[12], a thioglycoside activation[13] and Schimdt's trichloroacetimidate method[14]. Glycoside bond formation with donors derived from GlcNAc occurs generally via neighboring group participation. *N*-Phthaloyl (*N*-Phth) protected donor usually gives the desired β-glycoside in high yield and stereoselectivity, but recently, the *N*-Troc protecting group has resulted in a 40-fold more reactive building block than the phthaloyl protecting congeners[13]. Therefore we decided to use the Troc group for protection of the 2-amino substituent of glucosamine. Protection of the amino group with



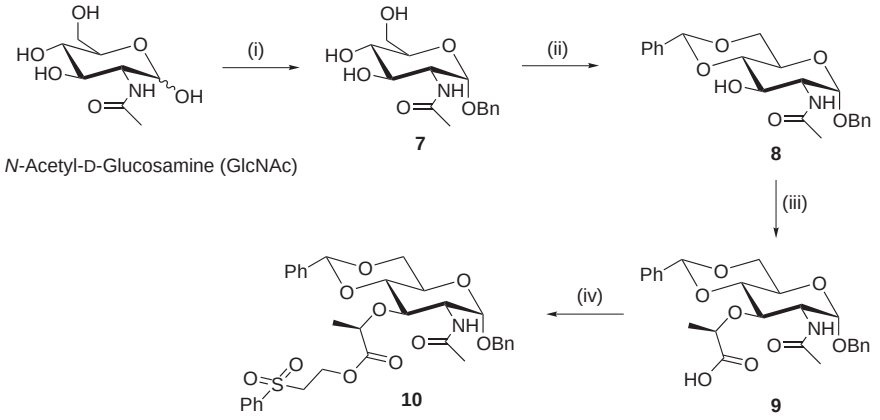
SCHEME 1
Retrosynthetic analysis



(i) TrocCl, $NaHCO_3$, H_2O; (ii) Ac_2O, pyridine, 98%; (iii) HBr, 33% in $AcOH/CH_2Cl_2$, 97%; (iv) 4-methylbenzenethiol, $BF_3{\cdot}(Et_2O)_2$, CH_2Cl_2. 85%; (v) NH_2NH_2, CH_3COOH; (vi) Cl_3CCN, DBU, CH_2Cl_2, 79%

SCHEME 2
Donor fragment synthesis

(2,2,2-trichloroethoxy)carbonyl chloride in the presence of aqueous sodium hydrogencarbonate is followed by per-*O*-acetylation to give **2** (as α, β mixture) in almost quantitative yield[12]. Then compound **2** was brominated using 33% HBr in AcOH in dichloromethane to give the first donor **3** in high yield[12]. In the second example compound **2** was treated with *p*-thiocresol in presence of boron trifluoride diethyl etherate as catalyst to provide compound **4** in 85% yield[13]. Regioselective hydrazinolysis of the anomeric *O*-acetyl group of **2** followed by activation of the anomeric position for nucleophilic attack has been carried out by treatment of **5** with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base to give compound **6** in 79% yield[14] (Scheme 2). In parallel, we have prepared the muramic acid acceptors **B** from commercially available GlcNAc (Scheme 3). Starting from the benzyl α-D-glycoside **7**, which was obtained according to the Fischer method[15,16], the 4,6-benzylidene derivative **8** was obtained in 95% yield. Therefore, **7** was treated with benzaldehyde and triethyl orthoformate in presence of *p*-toluenesulfonic acid in a mixture of DMF and dioxane[17]. Compound **9** was obtained by *O*-alkylation of the sodium salt of benzyl 2-acetamido-4,6-benzylidene-2-deoxy-α-D-glucopyranoside (generated from **8** with sodium hydride in dioxane) using L-2-chloropropionic acid in 80% yield[18,19]. The carboxylic function of **9** was protected as 2-(phenylsulfonyl)ethyl ester **10** [20]. Starting from this derivative **10**, we have studied the possibilities to remove the protective group at the 4-hydroxyl group for the glycosylation step. The first

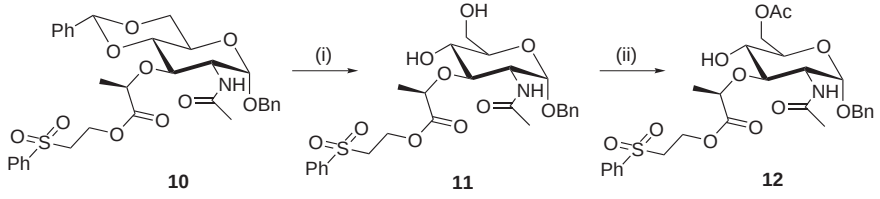


N-Acetyl-D-Glucosamine (GlcNAc)

(i) $PhCH_2OH/AcCl$, 70 °C, 65%; (ii) PhCHO, $(EtO)_3CH$, TsOH, dioxane/DMF, 95%; (iii) NaH, L-2-chloro-propionic acid, dioxane, 65 °C, 80%; (iv) $PhSO_2EtOH$, EDCl, DMAP, CH_2Cl_2, 98%

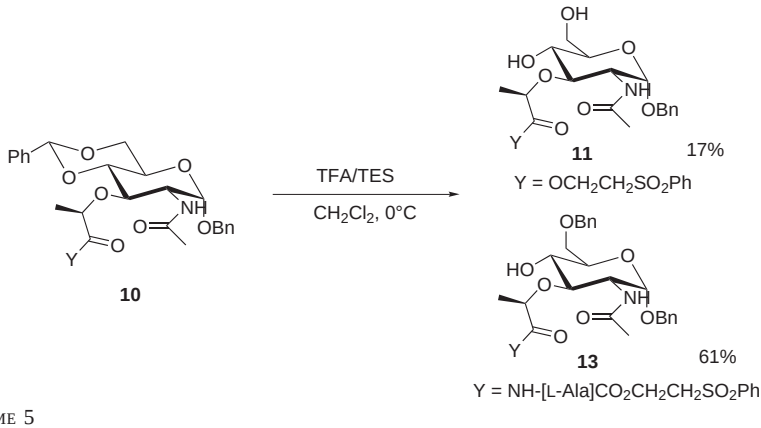
SCHEME 3
Acceptor fragment synthesis

possibility is to remove the benzylidene group in acid media and selectively monoacetylate the 6-hydroxyl group to generate the glycosyl acceptor **12** [9,21] (Scheme 4). An alternative way is to obtain the *O*-6 benzyl-protected intermediate by reductive opening of the benzylidene group of compound **10**. Saha and co-workers[11] have described the possibility to convert the 4,6-*O*-benzylidene-protected muramic acid derivatives in the corresponding 6-*O*-benzyl-4-hydroxy derivatives **13** using triethylsilane (TES) and trifluoroacetic acid (TFA) in dichloromethane (Scheme 5). However, under the reported conditions only 17% of the dideprotected compound **11** and 83%



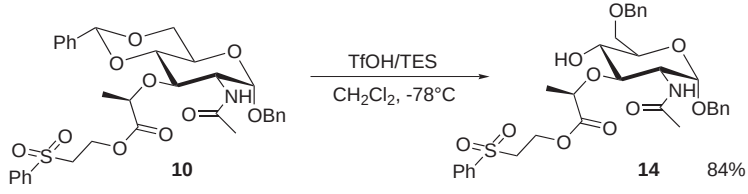
(i) CH_3COOH 80%, 60 °C, 95%; (ii) AcCl, pyridine, CH_2Cl_2, –30 °C, 87%

SCHEME 4
Acceptor fragment synthesis



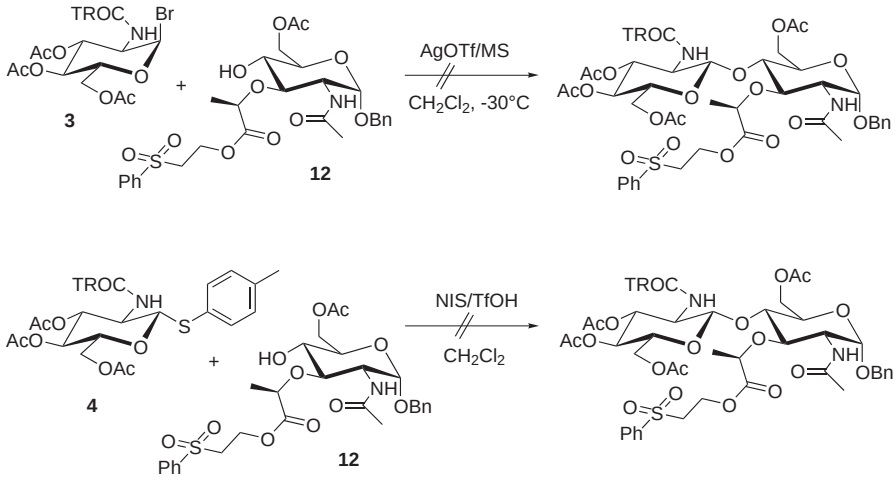
SCHEME 5

of the starting material was observed after 16 h reaction (Scheme 5). A more recent work described the reductive ring opening of 4,6-*O*-benzylidene acetal in carbohydrates using triflic acid and triethylsilane as reductive agents in dichloromethane at –78 °C [22]. By changing the acid from TFA to TfOH the reaction took place smoothly and with excellent selectivity to give the desired product **14** in a yield of 84% (Scheme 6). When we reacted the

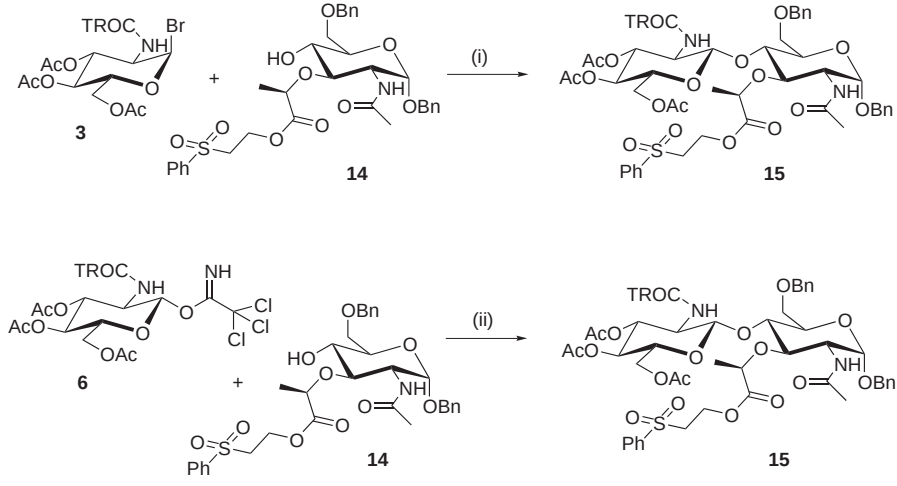


SCHEME 6

glycosyl acceptor **12** with the glycosyl bromide **3** utilizing AgOTf as promoter under the same conditions as described by Schwartz et al.[9] in the first chemical total synthesis of lipid II, we have not observed the formation of the aimed disaccharide (Scheme 7). We have obtained the same negative result when we combined the thioglycoside donor **4** with the acceptor **12** in presence of a mixture of *N*-iodosuccinimide and triflic acid as described in the synthesis of lipid II analogues by Sadamoto et al.[21] These results demonstrates the difficulty of this reaction which could be explained in part by the poor nucleophilicity of the 4-hydroxyl group of the muramic acid residue. However, when the glycoside acceptor **14** with benzyl protective group at the 6 position of the muramic acid residue was reacted with the glycosyl bromide **3** under Koenigs–Knorr conditions (Scheme 8), the desired disaccharide was obtained in 55% yield (74% reported in the literature[11]).



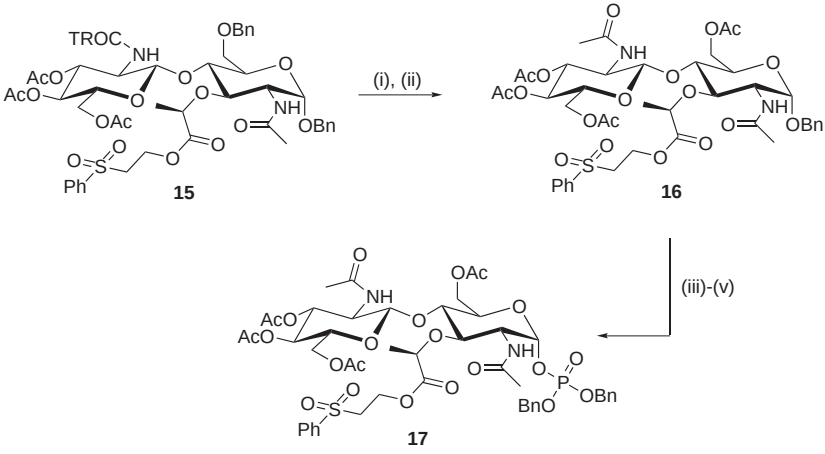
SCHEME 7



(i) AgOTf, MS 4Å, CH_2Cl_2, 55%; (ii) TMSOTf, MS 4Å, CH_2Cl_2, 76%

SCHEME 8

The best way to obtain the desired β-linked disaccharide **15** is using the trichloroacetimidate donor **6** and the acceptor **14** in mild conditions utilizing only 0.2 equivalent of TMSOTf under rigorously anhydrous conditions[23] (yield 76%). The 6-*O*-benzyl group of **15** was removed (Scheme 9) using a mixture of acetic anhydride, acetic acid (3:1) and anhydrous zinc chloride and the free alcohol generated in situ was acetylated[11]. Zinc dust

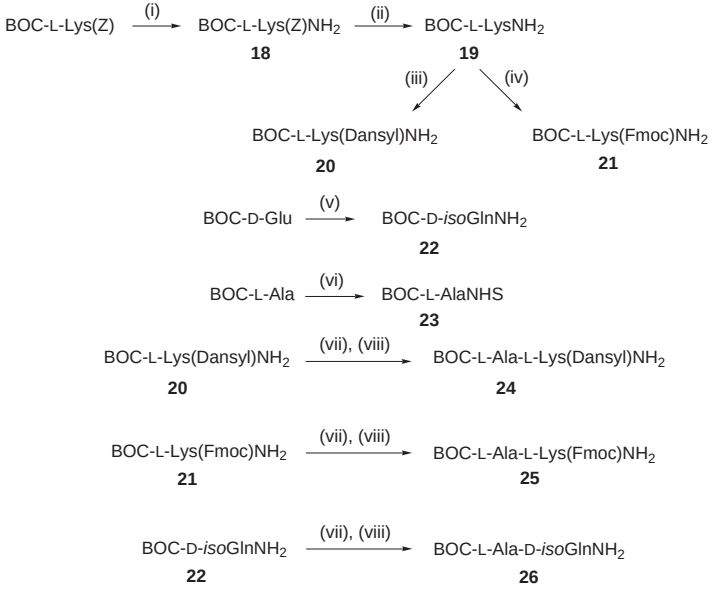


(i) $ZnCl_2$, $AcOH/Ac_2O$ (1/3); (ii) Zn dust, $THF/Ac_2O/AcOH$ (3/2/1), 84%; (iii) H_2, Pd/C, MeOH; (iv) dibenzyl-*N*,*N*-diethylphosphoramidite/tetrazole, CH_3CN; (v) H_2O_2 45%, THF, –78 °C, 75% (3 steps)

SCHEME 9

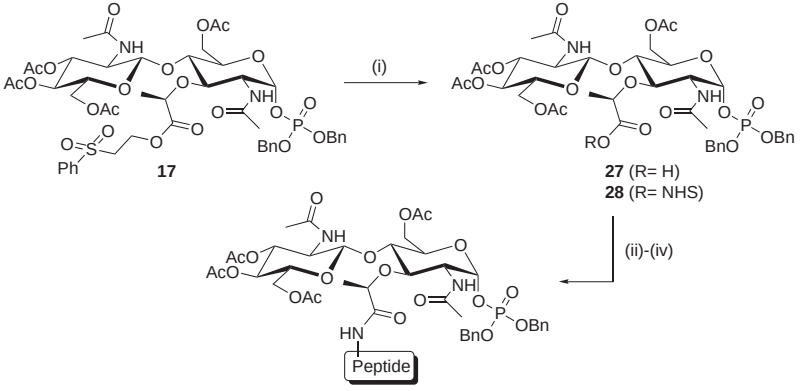
was added to the reaction mixture to remove the Troc group from the glucosamine moiety, liberating the amine function which is acetylated to afford compound **16** in 84% yield[11,23]. Hydrogenolytic cleavage of the benzyl protecting group followed by treatment with dibenzyl *N*,*N*-diethylphosphoramidite and tetrazole in dichloromethane and oxidation with hydrogen peroxide afforded the desired α-phosphate product **17** in 75% yield[10]. In parallel we have prepared via standard peptide synthesis protocols several peptide side chains that may be connected to the carboxylic acid function of the muramic acid moiety. We have chosen to synthesize short peptides (Scheme 10) in order to find out the minimal requirement for recognition by enzymes involved in the peptidoglycan synthesis. From peptides **24**, **25**, and **26** we have prepared compounds **29**, **30**, and **31** (Scheme 11). Removal of the 2-(phenylsulfonyl)ethyl ester was achieved by treatment of **17** with DBU. The intermediate carboxylic acid **27** was activated through conversion to the corresponding NHS-ester **28** and added to a solution of the peptides (**24**, **25** or **26**) (which were first deblocked using TFA in dichloromethane) in DMF with iPr_2NEt providing compounds **29**, **30**, and **31**.

The exact mechanism of the glycosyl transferase is not yet known[24]. The linear assembly of the glycan chain proceeds by repetitive addition either of the disaccharide peptide units on the preformed peptidoglycan or by addition of growing peptidoglycan on the disaccharide peptide unit. In the first



(i) isobutyl chloroformate/Et_3N, THF, NH_4OH (28%); (ii) H_2, Pd/C, MeOH; (iii) DansylCl/Et_3N, CH_2Cl_2; (iv) FmocCl, $NaHCO_3/H_2O$; (v) 4-nitrophenol/DCC, THF and NH_4OH (28%); (vi) NHS/EDCI, DMF; (vii) CH_2Cl_2/TFA; (viii) **23**, DIEA, DMF

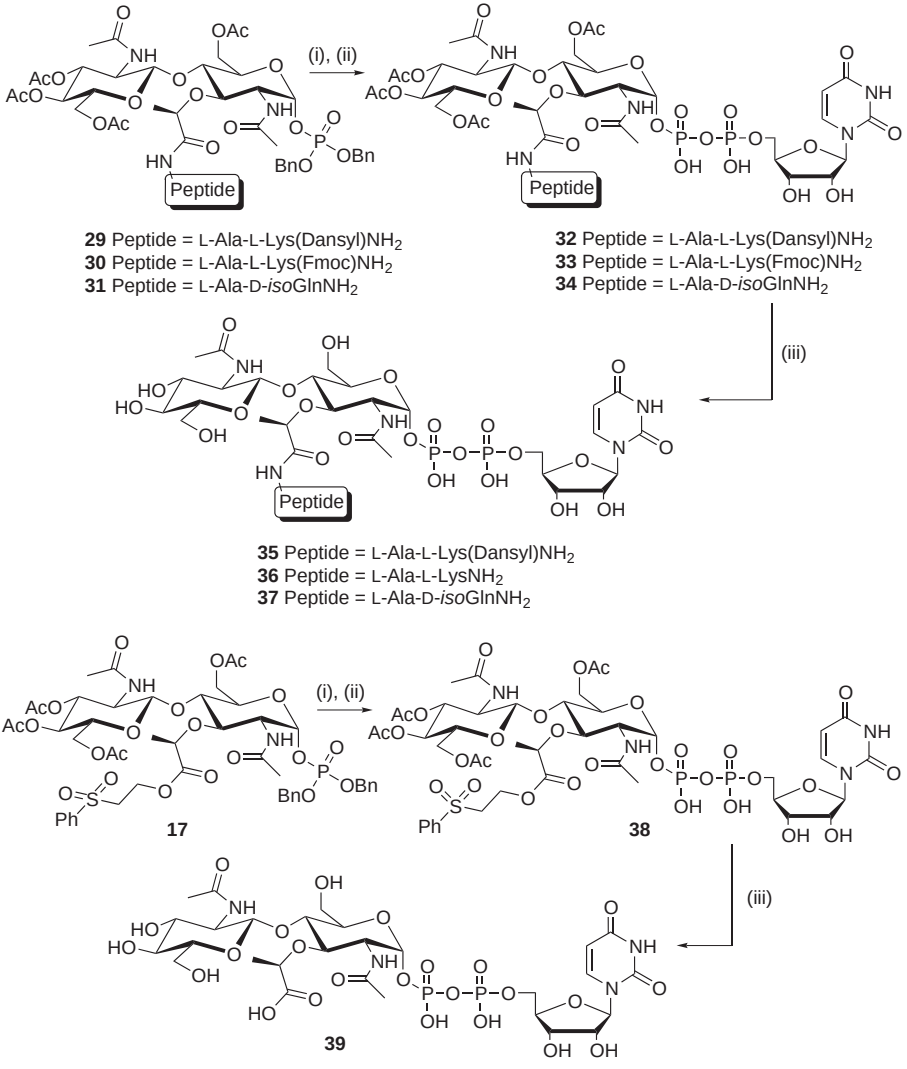
SCHEME 10



29 Peptide = L-Ala-L-Lys(Dansyl)NH_2
30 Peptide = L-Ala-L-Lys(Fmoc)NH_2
31 Peptide = L-Ala-D-*iso*GlnNH_2

(i) DBU, CH_2Cl_2; (ii) NHS/EDCI in DMF; (iii) **24, 25, 26**, CH_2Cl_2/TFA (2/1); (iv) unprotected peptides/ DIEA in DMS

SCHEME 11
Synthesis of peptide conjugated disaccharide



29 Peptide = L-Ala-L-Lys(Dansyl)NH_2
30 Peptide = L-Ala-L-Lys(Fmoc)NH_2
31 Peptide = L-Ala-D-*iso*GlnNH_2

32 Peptide = L-Ala-L-Lys(Dansyl)NH_2
33 Peptide = L-Ala-L-Lys(Fmoc)NH_2
34 Peptide = L-Ala-D-*iso*GlnNH_2

35 Peptide = L-Ala-L-Lys(Dansyl)NH_2
36 Peptide = L-Ala-L-LysNH_2
37 Peptide = L-Ala-D-*iso*GlnNH_2

(i) H_2, Pd/C, MeOH; (ii) Uridine 5'-phosphomorpholidate/tetrazole, CH_3CN; (iii) 1M NaOH, DMF

SCHEME 12
UDP coupling and total deprotection

case, lipid II is considered as the glycosyl donor substrate and in the second case lipid II is functioning as the acceptor and the growing chain is transferred to the 4-OH group of the GlcNAc of lipid II. That means that, when the lipid II monomer is an acceptor, it is not necessarily bound to undecaprenyl pyrophosphate[7]. Therefore, we chose to couple the disaccharide unit to uridine monophosphate instead of a lipid chain. After hydrogenolytic cleavage of the phosphodiester protecting groups and treatment with uridine 5-monophosphomorpholidate under anhydrous conditions[20] in presence of tetrazole in DMF, the corresponding protected UDP-disaccharide peptide compounds **32**, **33**, and **34** are obtained (Scheme 12). Rapid deprotection with aqueous sodium hydroxide and chromatographic purification by reverse phase HPLC finally afforded pure UDP-compounds **35**, **36**, and **37** in average 17% yield based on **17**.

We have also prepared the analogue lacking a peptide side chain. The compound **39** was obtained in one pot from the compound **17** (16% yield).

These compounds were tested for their potential to inhibit the glycosyl transferase activity of *E. coli* penicillin-binding protein type 1b (PBP 1b). However, we did not find inhibitory activity of the glycosyl transferase activity at 100 μmol l^{-1}. This activity was measured in the presence of [^{14}C]lipid II (1.5 μmol l^{-1}) and PBP 1b (18 nmol l^{-1}) at 30 °C during 15 min. The full biological testing of all the synthesized compounds will be the subject of a separate publication[7].

EXPERIMENTAL

General

All reactions using air- or moisture-sensitive reagents were conducted in an inert nitrogen atmosphere. Solvents were dried and distilled under argon prior to use or purchased in anhydrous form from commercial sources. Brine refers to a saturated aqueous solution of NaCl. TLC was performed using silica gel F254 precoated aluminum sheets and visualized by ultraviolet light or by anisaldehyde, 25% H_2SO_4 in ethanol, followed by heating. Column chromatography was performed using silica gel 60, 230–400 mesh. HPLC analyses and purifications were performed using Alltech® HS Hyper Prep 100 BDS column C-18 8μ (length 250 mm) with specified solvent and flow rate. NMR spectra were acquired on a Varian Unity 500 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, in $CDCl_3$ or DMSO-d_6 unless otherwise noted. Chemical shifts are given in ppm (δ-scale) with the residual solvent peak (^{1}H $CHCl_3$, 7.26; ^{13}C $CDCl_3$, 77) as internal standard. Coupling constants (*J*) are reported in Hz. Exact mass spectra were acquired on a quadrupole time-of-flight mass spectrometer (Q-Tof-2, Micromass, Manchester, U.K.) equipped with a standard electrospray-ionization (ESI) interface, samples were infused in iPrOH/H_2O (1:1) at 3 μl min^{-1}.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-(α,β)-D-glucopyranoside (**2**)

(Trichloroethoxy)carbonyl chloride (46 ml, 347.7 mmol) was added dropwise at room temperature to a vigorously stirred solution of D-glucosamine hydrochloride (50 g, 231.8 mmol) and $NaHCO_3$ (39 g, 463.7 mmol) in water (300 ml). The mixture was stirred overnight. The precipitate was filtered off and washed with water until the unreacted chloride was removed. The white solid product was recrystallized from EtOH to yield 73.2 g (89%) of waxy material **1** (ESI-MS for $C_9H_{14}Cl_3NNaO_7$ calculated $[M + Na]^+$: 375.9734; found: 375.9734). The Troc-aminoglucosamine **1** (72 g, 203.4 mmol) was dissolved in dry pyridine (200 ml), Ac_2O (105.7 ml, 1118.7 mmol) was added, and the mixture was stirred at room temperature for 12 h. The product was concentrated and coevaporated with toluene. The residue was dissolved in CH_2Cl_2 (500 ml) and the organic layer was washed with 1 M HCl, H_2O and brine, and dried with Na_2SO_4. The solvent was removed to obtain a white foam of the Troc-aminoperacetylglucosamine **2** which was dried in vacuo (104 g, 98%). ^{1}H NMR ($CDCl_3$): 6.23 (d, J = 3.66, 1 H, H_1), 5.27 (t, J = 9.52, 1 H, H_3), 5.19 (t, J = 10.1, 1 H, H_4), 4.82 and 4.63 (AX, J = 11.96, CH_2), 4.24 (m, 2 H, H_2, H_6), 4.05 (m, 2 H, H_5, $H_{6'}$), 2.20 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 171.14, 170.55, 169.09, 168.53 (4 × C=O), 154.01 (C=O), 95.18 (CCl_3), 90.36 (C_1), 74.58 (CH_2), 70.32 (C_3), 69.66 (C_5), 67.54 (C_4), 61.44 (C_6), 53.15 (C_2), 20.79, 20.58, 20.55, 20.46 (4 × CH_3). ESI-MS for $C_{17}H_{22}Cl_3NNaO_{11}$ calculated $[M + Na]^+$: 544.0156; found: 544.0156 (ref.[2]).

3,4,6-Tri-*O*-acetyl-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-α-D-glucopyranosyl Bromide (**3**)

The *N*-Troc-peracetylglucosamine **2** (8.28 g, 15 mmol) was dissolved in CH_2Cl_2 (200 ml) and HBr (20.0 ml, 33% in AcOH) was added at 0 °C and kept at 0 °C for 1 h. The reaction was allowed to warm up to room temperature during 1 h. After 2 h the reaction was complete by TLC and was worked up. The solution was diluted with CH_2Cl_2 (200 ml) and washed with ice water, 1% $NaHCO_3$, saturated $NaHCO_3$, brine and dried over Na_2SO_4. The sample was filtered and concentrated to a colorless oil and recrystallized from Et_2O/hexanes to yield compound **3** (7.83 g, 96%), m.p. 97–98 °C.

p-Tolyl 3,4,6-Tri-*O*-acetyl-2-deoxy-l-thio-2-[(2,2,2-trichloroethoxy)carbonylamino]-β-D-glucopyranoside (**4**)

To a mixture of compound **2** (6.69 g, 12.8 mmol) and 4-methylthiophenol (2.18 g, 15.3 mmol) in CH_2Cl_2 (30 ml) was added boron trifluoride diethyl etherate (48%; 4.87 ml, 38.4 mmol), and the mixture was stirred overnight. Then the reaction was diluted with CH_2Cl_2 (100 ml) and washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography with hexane/EtOAc (3:1) as eluent to give **4** (6.15 g, 82%). ^{1}H NMR ($CDCl_3$): 7.41 (d, J = 8.06, 2 H, H_{arom}), 7.11 (d, J = 7.81, 2 H, H_{arom}), 5.40 (d, J = 9.03, 1 H, NH), 5.28 (t, J = 9.76, 1 H, H_3), 5.00 (t, J = 9.77, 1 H, H_4), 4.81–4.67 (m, 3 H, CH_2, H_1), 4.15–4.24 (m, 2 H, H_6, $H_{6'}$), 3.72 (m, 1 H, H_5), 3.67 (m, 1 H, H_2), 2.34 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 170.05, 170.00, 169.41 (3 × C=O), 153.87 (C=O), 138.64 (C_{arom}), 133.59, 129.68 (4 × CH_{arom}), 127.93 (C_{arom}), 95.39 (CCl_3), 86.66 (C_1), 75.70 (C_3), 74.49 (CH_2), 73.23 (C_5), 68.57 (C_4), 62.29 (C_6), 54.95 (C_2),

21.11 (CH_3), 20.67, 20.56, 20.50 (3 × CH_3). ESI-MS for $C_{22}H_{26}Cl_3NNaO_9$ calculated $[M + Na]^+$: 608.0291; found: 608.0312.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-α-D-glucopyranosyl Trichoroacetimidate (**6**)

A solution of **2** (35.0 g, 67.0 mmol) and hydrazinium acetate (7.4 g, 80.0 mmol) in DMF (250 ml) was stirred at room temperature for 20 min, then diluted with EtOAc (250 ml), washed with water, then with saturated aqueous $NaHCO_3$, and again with water, dried with Na_2SO_4 and concentrated. The compound **5** obtained was dissolved in CH_2Cl_2 (250 ml), trichloroacetonitrile (66.0 ml, 670 mmol) and DBU (2.0 ml, 13.4 mmol) were added and the mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel using hexane/EtOAc (2:1) containing 0.1% of triethylamine as eluent to afford compound **6** as a white foam (35 g, 83%). ^{1}H NMR ($CDCl_3$): 8.82 (s, 1 H, NH), 6.43 (d, J = 3.4, 1 H, H_1), 5.35 (t, J = 10.1, 1 H, H_3), 5.25 (t, J = 10.1, 1 H, H_4), 4.73 and 4.71 (AX, J = 12.2, 2 H, CH_2), 4.20–4.32 (m, 2 H, H_2, H_6), 4.09–4.16 (m, 2 H, H_5, $H_{6'}$), 2.08 (s, 3 H, CH_3), 2.06 (s, 6 H, 2 × CH_3). ^{13}C NMR ($CDCl_3$): 171.08, 170.52, 169.21 (3 × COO), 160.34 (OCN)) 154.10 (OCON), 94.48 (C_1), 95.17, 91.70 (2 × CCl_3), 74.60 (CH_2), 70.21 (C_3, C_5), 67.36 (C_4), 61.34 (C_6), 53.83 (C_2), 20.60 (2 × CH_3), 20.50 (CH_3). ESI-MS for $C_{17}H_{21}Cl_6N_2NaO_{10}$ calculated $[M + Na]^+$: 645.9; found: 645.6.

Benzyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (**7**)

Acetyl chloride (11 ml, 154.7 mmol) was added to a suspension of finely powdered *N*-acetyl-D-glucosamine (25.7 g, 116.4 mmol) in benzyl alcohol (150 ml). The mixture was stirred at 75 °C for 4 h. Then, the excess of benzyl alcohol was removed in vacuo, the resulting syrup was suspended in diisopropyl ether (500 ml) and was kept at 4 °C overnight. The precipitate was filtered off and washed with cold diisopropyl ether and diethyl ether to yield 30.0 g (70%) of compound **7**. ^{1}H NMR (DMSO-d_6): 7.81 (d, J = 8.0, AcN**H**, 1 H), 7.38–7.24 (m, Ar-**H**$_{o,m}$, 4 H), 7.27 (m, 1 H, Ar-H_p), 5.02 (d, J = 5.6, 1 H, 4-OH), 4.77 (d, J = 5.6, 1 H, 3-OH), 4.73 (d, J = 3.6, 1 H, H_1), 4.67 and 4.18 (AX, J = 12.5, 1 H, CH_2), 4.53 (t, J = 6.0, 1 H, 6-OH), 3.69 (ddd, J = 10.7, 8.0, 3.4, 1 H, H_2), 3.66 (ddd, J = 11.4, 5.6, 1.8, 1 H, H_6), 3.56 (ddd, J = 10.7, 8.5, 5.4, 1 H, H_3), 3.51 (dt, J = 11.4, 5.8, 5.8, 1 H, $H_{6'}$), 3.47 (ddd, J = 10.0, 5.6, 1.9, 1 H, H_5), 3.18 (ddd, J = 9.9, 8.5, 5.6, 1 H, H_4), 1.84 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 169.55 (C=O), 138.01 (C_{arom}), 128.21, 127.58 (CH_{arom}), 127.45 (CH_{arom}), 96.01 (C_1), 73.16 (C_5), 70.96 (C_4), 70.63 (C_3), 67.84 (CH_2), 60.95 (C_6), 53.87 (C_2), 22.62 (CH_3). ESI-MS for $C_{15}H_{22}NO_6$ calculated $[M + H]^+$: 312.1447; found: 312.1446.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**8**)

Compound **7** was dried by coevaporation with anhydrous ethanol and toluene in vacuo. To the dry compound **7** (18.5 g, 59.4 mmol) was added anhydrous DMF (150 ml) and anhydrous dioxane (150 ml), triethyl orthoformate (30 ml, 180.4 mmol), benzaldehyde (24 ml, 236.3 mmol) and *p*-toluenesulfonic acid (5.7 g). The mixture was stirred at room temperature for 20 h. Absolute diethyl ether was added and the mixture was stirred at 0 °C for 1 h and the precipitate was filtered off. After washing with diethyl ether the filtrate was dried in vacuo to give **8** (22.5 g, 95%). ^{1}H NMR (DMSO-d_6): 7.99 (d, J = 8.0, 1 H, AcNH), 7.45 (m, 2 H, H_{arom}), 7.42–7.34 (m, 7 H, H_{arom}), 7.30 (m, 1 H, H_{arom}), 5.62 (s, 1 H, CH), 5.19 (d, J = 5.8,

1 H, 3-OH), 4.81 (d, J = 3.6, 1 H, H_1), 4.70 and 4.49 (AX, J = 12.5, 2 H, CH_2), 4.14 (dd, J = 8.5, 3.7, 1 H, H_6), 3.85 (ddd, J = 3.6, 8.0, 10.3, 1 H, H_2), 3.75 (m, 2 H, H_3, $H_{6'}$), 3.70 (dt, J = 4.4, 10.2, 1 H, H_5), 3.52 (t, J = 10.0, 1 H, H_4), 1.85 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 169.56 (C=O), 137.80 (C_{arom}), 128.91, 128.29, 128.07, 127.69, 127.62, 126.45 (CH_{arom}), 100.94 ($CH_{benzylidene}$), 97.02 (C_1), 82.13 (C_4), 68.68 (CH_2), 68.09 (C_6), 67.29 (C_3), 62.93 (C_5), 54.35 (C_2), 22.59 (CH_3). ESI-MS for $C_{22}H_{26}NO_6$ calculated $[M + H]^+$: 400.1760; found: 400.1758.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(D-1-carboxyethyl)-α-D-glucopyranoside (**9**)

Compound **8** (11.36 g, 28.5 mmol) was dissolved in anhydrous dioxane (250 ml). The suspension was treated with NaH (18.3 g of a 60% suspension in mineral oil, 457.5 mmol) in small portions. The mixture was stirred at 95 °C for 2 h and cooled down to 65 °C. (*S*)-2-Chloropropionic acid (4 ml, 46.4 mmol) in anhydrous dioxane (75 ml) was slowly added and the mixture was stirred at 60 °C for 3 h. The reaction was cooled to 10 °C and diluted with a small portion of methanol and water. The solution was concentrated in vacuo, and the residue, after dissolution in diethyl ether was vigorously stirred with a saturated aqueous solution of NaCl. The ether layer was concentrated in vacuo to 100 ml, and to this solution a 6 M HCl solution was slowly added. The precipitate was filtered off, washed with diethyl ether and recrystallized from $CHCl_3$/MeOH (95:5) to obtain **9** (10.79 g, 80%). m.p. 269–270 °C (lit.[16] 264–265 °C). ^{1}H NMR (DMSO-d_6): 7.96 (d, J = 6.1, 1 H, NH), 7.45–7.28 (m, 10 H, H_{arom}), 5.69 (s, 1 H, CH), 5.04 (d, J = 3.4, 1 H, H_1), 4.69 and 4.49 (AX, J = 12.4, 2 H, CH_2), 4.29 (q, J = 6.8, 1 H, CH), 4.27 (m, 1 H, H_3), 4.15 (dd, J = 9.8, 4.2, 1 H, H_6), 3.84–3.70 (m, 5 H, H_2, H_3, H_4, H_5, $H_{6'}$), 1.86 (s, 3 H, CH_3), 1.28 (d, J = 6.8, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 175.39 ($C{=}O_{acid}$), 169.64 ($C{=}O_{amide}$), 137.72 (C_{arom}), 128.95, 128.41, 128.29, 127.79, 125.97 (CH_{arom}), 100.42 ($CH_{benzylidene}$), 96.94 (C_1), 81.67 (C_4), 75.21 (C_3, CH), 69.14 (CH_2), 68.00 (C_6), 63.02 (C_5), 53.63 (C_2), 22.71 (CH_3), 18.78 (CH_3). ESI-MS for $C_{25}H_{30}NO_8$ calculated $[M + H]^+$: 472.1971; found: 472.1974.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)ethoxy]-carbonyl}ethyl)-α-D-glucopyranoside (**10**)

To a suspension of **9** (10.13 g, 21.5 mmol) in anhydrous CH_2Cl_2 (150 ml) was added DMAP (131 mg, 1.75 mmol) and 2-(phenylsulfonyl)ethanol (4.39 g, 23.6 mmol). The mixture was diluted with CH_2Cl_2 and was washed with a 0.5 M HCl. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified on silica gel with $CHCl_3$ as eluent to obtain pure compound **10** (11.55 g, 84%). ^{1}H NMR ($CDCl_3$): 7.83 (br d, 2 H, H_{arom}), 7.48–7.24 (m, 14 H, H_{arom}, NH), 5.55 (s, 1 H, CH), 5.35 (d, J = 3.6, 1 H, H_1), 4.68 and 4.53 (AX, J = 12.0, 2 H, CH_2), 4.47 (m, 2 H, CH_2), 4.22 (dd, J = 10.3, 4.6, 1 H, H_6), 4.17 (q, J = 7.1, 1 H, CH), 3.92 (ddd, J = 9.0, 5.1, 3.6, 1 H, H_2), 3.84 (ddd, J = 10.1, 9.2, 4.6, 1 H, H_5), 3.74 (t, J = 10.3, 1 H, $H_{6'}$), 3.70 (t, J = 9.0, 1 H, H_3), 3.65 (t, J = 9.0, 1 H, H_4), 3.44 (m, 2 H, CH_2), 2.01 (s, 3 H, CH_3), 1.18 (d, J = 7.0, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 174.28 ($C{=}O_{acid}$), 170.69 ($C{=}O_{amide}$), 139.11, 137.38, 137.31 (C_{arom}), 134.17, 129.27, 129.05, 128.37, 128.29, 127.92, 127.88, 127.84, 125.90 (CH_{arom}), 101.33 ($CH_{benzylidene}$), 97.29 (C_1), 83.27 (C_4), 74.89 (C_3), 74.84 (CH), 70.35 (CH_2), 68.93 (C_6), 62.87 (C_5), 58.31 (CH_2), 54.91 (CH_2), 54.06 (C_2), 23.07 (CH_3), 18.33 (CH_3). ESI-MS for $C_{33}H_{38}NO_{10}S$ calculated $[M + H]^+$: 640.2216; found: 640.2220.

Benzyl 2-Acetamido-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)ethoxy]carbonyl}ethyl)-α-D-glucopyranoside (**11**)

A suspension of compound **10** (6.07 g, 9.5 mmol) in 80% acetic acid was stirred at 60 °C until after 90 min the starting material disappeared as shown by TLC analysis (EtOAc). The solvent was removed and the resulting oil was coevaporated with toluene and then purified by silica gel chromatography with $CHCl_3$/MeOH (95:5) as eluent to yield a white foam (4.92 g, 94%). ^{1}H NMR ($CDCl_3$): 7.89 (dt, *J* = 8.30, 1.95, 2 H, H_{arom}), 7.65 (tt, *J* = 7.56, 1.23, 1 H, H_{arom}), 7.54 (t, *J* = 8.3, 2 H, H_{arom}), 7.40 (d, *J* = 5.61, 1 H, NH), 7.30 (m, 5 H, H_{arom}), 5.23 (d, *J* = 3.17, 1 H, H_1), 4.66–4.42 (m, 5 H, CH_2Bn, CH_2, CH), 3.79 (m, 2 H, H_2, H_6), 3.72 (m, 2 H, H_4, H-6′), 3.60 (m, 2 H, H_3, H-5), 3.46 (td, *J* = 6.11, 1.71, 2 H, CH_2-5), 1.99 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 175.06, 171.16 (2 × C=O), 138.91, 137.52 (C_{arom}), 134.19, 129.44, 128.32, 127.97, 127.73, 127.68 (CH_{arom}), 96.44 (C_1), 77.00 (C_3), 74.57 (CH), 71.96 (C_5), 71.90 (C_4), 69.85 (CH_2), 61.68 (C_6), 58.01 (CH_2), 54.83 (CH_2), 53.43 (C_2), 23.01 (CH_3), 18.60 (CH_3). ESI-MS for $C_{26}H_{34}NO_{10}S$ calculated $[M + H]^+$: 552.1903; found: 552.1904.

Benzyl 2-Acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)ethoxy]carbonyl}-ethyl)-α-D-glucopyranoside (**12**)

Compound **11** (1.49 g, 2.7 mmol) was dissolved in CH_2Cl_2 (20 ml), the solution was cooled to –30 °C, and pyridine (0.45 ml, 5.4 mmol) was added to the solution. A solution of acetyl chloride (0.25 ml, 3.5 mmol) in CH_2Cl_2 was added dropwise at –30 °C over a period of 45 min. The solution was warmed slowly to 0 °C and was diluted with CH_2Cl_2 (50 ml). This solution was washed with 0.01 M HCl (50 ml) and with brine (50 ml). The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography with $CHCl_3$ as eluent to obtain a foamy solid **12** (1.41 g, 87%). ^{1}H NMR ($CDCl_3$): 7.94 (d, *J* = 8.30, 2 H, H_{arom}), 7.68 (t, *J* = 7.45, 1 H, H_{arom}), 7.60 (t, *J* = 8.41, 2 H, H_{arom}), 7.40 (d, *J* = 5.63, 1 H, NH), 7.30 (m, 5 H, H_{arom}), 5.30 (d, *J* = 3.41, 1 H, H_1), 4.65–4.49 (m, 5 H, CH_2Bn, CH_2, CH), 3.98 (m, 2 H, H_2, H_6), 3.83 (m, 2 H, H_4, $H_{6'}$), 3.68 (m, 2 H, H_3, H_5), 3.36 (d, *J* = 5.62, 2 H, CH_2-5), 2.12 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 177.04, 174.93, 171.46 (3 × C=O), 138.98, 137.20 (C_{arom}), 133.97, 129.38, 128.22, 127.91, 127.88, 127.78 (CH_{arom}), 96.59 (C_1), 76.88 (C_3), 74.87 (CH), 71.62 (C_4), 71.09 (C_5), 70.62 (CH_2), 62.97 (C_6), 58.17 (CH_2), 56.16 (CH_2), 54.84 (C_2), 22.83 (CH_3), 22.75 (CH_3), 18.50 (CH_3). ESI-MS for $C_{28}H_{36}NO_{11}S$ calculated $[M + H]^+$: 594.2009; found: 594.2009.

Benzyl 2-Acetamido-6-*O*-benzyl-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)ethoxy]carbonyl}-ethyl)-α-D-glucopyranoside **14**

A solution of **10** (3.9 g, 6.1 mmol) in dichloromethane (50 ml) in presence of molecular sieves (2.3 g) was stirred at room temperature for 30 min and then was cooled to –78 °C. Triethylsilane (2.95 ml, 18.1 mmol) and triflic acid (1.1 ml, 12.2 mmol) were added successively. After stirring for 1 h, $NaHCO_3$ and MeOH were added. The mixture was warmed up to room temperature, diluted with CH_2Cl_2 and washed with saturated solution of $NaHCO_3$, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo; the residue was purified on silica gel column with $CHCl_3$/MeOH (0–5%) as eluent giving pure compound **14** (3.55 g, 91%). ^{1}H NMR ($CDCl_3$): 7.9 (m, 2 H, H_{arom}), 7.5 (m, 3 H,

H_{arom}), 7.3 (m, 10 H, H_{arom}), 7.2 (d, J = 5.4, 1 H, NH), 5.3 (d, J = 3.2, 1 H, H_1), 4.65 and 4.49 (AB system, J = 12.0, 2 H, CH_2), 4.59 and 4.52 (AB system, J = 12.0, 2 H, CH_2), 4.50–4.42 (m, 3 H, CH_2, CH), 3.80 (ddd, J = 10.9, 5.4, 3.2, 1 H, H_2), 3.75–3.70 (m, 2 H, H_5, H_6), 3.68 (dt, J = 2.3, 9.8, 1 H, H_4), 3.60 (m, 2 H, H_3, $H_{6'}$), 3.4 (m, 2 H, CH_2), 3.3 (d, J = 2.4, 1 H, 4-OH), 1.9 (s, 3 H, CH_3), 1.2 (d, J = 7.0, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 175.02 ($C{=}O_{ester}$), 169.61 ($C{=}O_{amide}$), 139.09, 137.63 (C_{arom}), 134.15, 129.43, 128.50, 128.33, 128.20, 128.02, 127.94, 127.74 (CH_{arom}), 96.62 (C_1), 77.33 (C_3), 75.09 (C_4), 74.33 (CH), 73.82 (CH_2Bn), 71.33 (C_6), 70.11 (CH_2Bn), 69.24 (C_5), 58.09 (CH_2), 54.94 (CH_2S), 53.03 (C_2), 23.10 (CH_3), 18.65 (CH_3). ESI-MS for $C_{33}H_{40}NO_{10}S$ calculated $[M + H]^+$: 642.2372; found: 642.2371.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-benzyl-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)-ethoxy]carbonyl}ethyl)-α-D-glucopyranoside (**15**)

To a solution of **14** (4.0 g, 6.2 mmol) in CH_2Cl_2 (10 ml) were added 4Å molecular sieves (7 g) and TMSOTf (0.11 ml, 1.2 mmol). To this mixture was added dropwise a solution of compound **6** (11.7 g, 18.7 mmol) in CH_2Cl_2 (10 ml). Then the solution was stirred for 24 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ solution, water and brine, then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel utilizing a gradient of MeOH in CH_2Cl_2 (0–5%) as eluent and yielding the disaccharide **15** as a white foam (4.9 g, 72%). ^{1}H NMR ($CDCl_3$): 7.93 (br d, 2 H, H_{arom}), 7.70 (br t, 1 H, H_{arom}), 7.25–7.62 (overlapped m, 14 H, 12 H_{arom}, 2 NH), 5.36 (d, J = 3.4, 1 H, H_{1m}), 4.95 (t, J = 9.7, 1 H, H_{4g}), 4.88 and 4.34 (d, J = 12.0, 2 H, CH_2Bn), 4.76 (t, J = 10.0, 1 H, H_{3g}), 4.72 and 4.62 (d, J = 12.0, 2 H, CH_{2Troc}), 4.58 and 4.49 (d, J = 12.0, 2 H, CH_2Bn), 4.50 and 4.42 (m, 2 H, CH_2), 4.38 (m, 1 H, CHO), 4.34 (overlapped m, H_{6g}), 4.22 (d, J = 8.3, 1 H, H_{1g}), 3.99 (d, J = 12.0, 1 H, $H_{6'g}$), 3.91 (t, J = 9.3, 1 H, H_{3m}), 3.78 (m, 1 H, H_{2m}), 3.64 (d, J = 10.8, 1 H, H_{6m}), 3.56 (d, J = 10.0, H_{5m}), 3.51 (t, J = 9.3, 1 H, H_{4m}), 3.48 (m, 1 H, H_{2g}), 3.45 (m, 2 H, CH_2S), 3.41 (m, 1 H, H_{5g}), 3.39 (d, J = 10.8, 1 H, $H_{6'm}$), 2.05 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3), 1.18 (d, J = 6.8, CH_3). ^{13}C NMR ($CDCl_3$): 174.60 (COO), 170.58, 170.36, 170.15 (3 × Ac), 169.53 (CON), 153.89 (OCON), 139.11, 137.20 (C_{arom}), 134.14 (CH_{arom}) 129.47 (4 × CH_{arom}), 129.14 (2 × CH_{arom}), 129.17 (CH_{arom}), 128.34, 128.09 (4 × CH_{arom}), 127.75 (2 × CH_{arom}) 127.79 (CH_{arom}), 100.12 (C_{1g}), 96.59 (C_{1m}), 92 (CCl_3), 77.48 (C_{3m}), 75.25 (C_{4m}), 74.63 (CHO), 74.42 (CH_{2Troc}), 73.81 (CH_2Bn), 72.51 (C_{3g}), 71.32 (C_{5g}), 70.39 (CH_2Bn), 69.90 (C_{5m}), 68.33 (C_{4g}), 67.06 (C_{6m}), 61.49 (C_{6g}), 58.14 (CH_2O), 56.19 (C_{2g}), 54.88 (CH_2S), 54.15 (C_{2m}), 23.01, 20.58 (4 × CH_3), 18.05 (CH_3). ESI-MS for $C_{48}H_{58}Cl_3N_2O_{19}S$ calculated $[M + H]^+$: 1103.2421; found: 1103.2411.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)ethoxy]carbonyl}ethyl)-α-D-glucopyranoside (**16**)

To a solution of **15** (3 g, 2.7 mmol) in Ac_2O/AcOH (2:1, 30 ml) was added $ZnCl_2$ (3.7 g, 27.2 mmol). The mixture was stirred overnight. Then the solvent was removed and the residual oil was dissolved in a mixture of THF/Ac_2O/AcOH (3:2:1, 30 ml). Zn dust (7.0 g, 108.8 mmol) was added and the mixture was stirred overnight. The reaction mixture was filtered through Celite, washed with CH_2Cl_2 and then concentrated under reduced pressure. The res-

idue was coevaporated with toluene three times and then dissolved in CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on a column of silica gel and eluted with 2% MeOH in CH_2Cl_2 affording the desired compound **16** (2.1 g, 85%). ^{1}H NMR ($CDCl_3$): 7.95 (d, J = 7.3, 2 H, H_{arom}), 7.73 (t, J = 7.4, 1 H, H_{arom}), 7.63 (t, J = 7.3, 2 H, H_{arom}), 7.63 (obs, 1 H, NH_m), 7.35–7.27 (m, 5 H, H_{arom}), 6.17 (d, J = 9.0, 1 H, NH_g), 5.28 (d, J = 3.4, 1 H, H_{1m}), 5.11 (t, J = 9.5, 1 H, H_{3g}), 5.09 (t, J = 9.3, 1 H, H_{4g}), 4.61 and 4.51 (AX, J = 12.2, 2 H, CH_2Bn), 4.57–4.43 (overlapped m, 2 H, CH_2O), 4.50 (q, J = 6.9, 1 H, CH), 4.39 (d, J = 8.6, 1 H, H_{1g}), 4.37 (dd, J = 12.4, 4.6, 1 H, H_{6g}), 4.24 (dd, J = 12.0, 2.2, 1 H, H_{6m}), 4.19 (d, J = 11.8, 1 H, $H_{6'm}$), 4.05 (dd, J = 12.4, 2.0, 1 H, $H_{6'g}$), 4.05 (overlapped m, 1 H, H_{2g}), 3.78 (m, 1 H, H_{2m}), 3.73–3.66 (m, 2 H, H_{3m}, H_{5m}), 3.65–3.57 (overlapped m, 2 H, H_{5g}, H_{4m}), 3.57–3.47 (m, 2 H, CH_2S), 2.13 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 1.21 (d, J = 6.8, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 175.28 (COO), 171.16 (Ac), 170.70 (2 Ac), 170.69 (Ac), 170.32 (Ac, CON), 169.32 (CON), 139.04 (C_{arom}), 137.36 (C_{arom}), 134.16 (CH_{arom}), 129.50 (2 × CH_{arom}), 128.30 (2 × CH_{arom}), 128.06 (2 × CH_{arom}), 127.78 (CH_{arom}), 127.67 (2 × CH_{arom}), 101.06 (C_{1g}), 96.31 (C_{1m}), 78.17 (C_{3m}), 74.86 (C_{4m}), 74.68 (CH), 72.87 (C_{3g}), 71.89 (C_{5g}), 70.32 (CH_2Bn), 69.37 (C_{5m}), 68.07 (C_{4g}), 61.92 (C_{6m}), 61.59 (C_{6g}), 58.17 (CH_2O), 54.79 (CH_2S), 54.27 (C_{2g}), 53.89 (C_{2m}), 23.01, (CH_3), 22.97 (CH_3), 20.51 (4 × CH_3), 18.05 (CH_3). ESI-MS for $C_{42}H_{55}N_2O_{19}S$ calculated $[M + H]^+$: 923.3120; found: 923.3114.

Dibenzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(D-1-{[2-(phenylsulfonyl)ethoxy]carbonyl}ethyl)-α-D-glucopyranosyl Phosphate (**17**)

Compound **16** (1.8 g, 2.0 mmol) was dissolved in THF/MeOH (4:1, 20 ml), then 10% Pd/C (500 mg) was added and the suspension was stirred and cooled in ice-bath. The suspension was warmed to room temperature and hydrogenated at room temperature for 2 h. The catalyst was collected by filtration on Celite and the filtrate was concentrated in vacuo to afford a white solid which was triturated with diethyl ether/hexane. The resulting solid (1.5 g, 92%) was collected and dried under high vacuum for 16 h (ESI-MS for $C_{35}H_{49}N_2O_{19}S$ calculated $[M + H]^+$: 833.2650; found 833.2653). The white powder (1.5 g, 1.83 mmol) was dissolved in 0.5 M solution of tetrazole in acetonitrile (20 ml, 9.2 mmol) and dibenzyl *N*,*N*-diethylphosphoramidite (1.6 ml, 5.5 mmol). The mixture was stirred at room temperature for 4 h. Then the mixture was diluted with dichloromethane (20 ml) and washed with saturated aqueous solution of $NaHCO_3$, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo. The residue obtained was dried overnight over P_2O_5 in high vacuum. The oil was dissolved in THF (30 ml), cooled to –80 °C, and then hydrogen peroxide (45%, 3.5 ml) was added dropwise. The mixture was allowed to warm to room temperature over 2 h. The solution was cooled in an ice-bath, and diluted with ethyl acetate followed by a saturated solution of $Na_2S_2O_3$ (10 ml), with stirring for a few minutes. The organic layer was washed with water and brine and dried with Na_2SO_4, filtered and concentrated in vacuo to provide a colorless oil, which was triturated with Et_2O/hexane. The solid was filtered and dried over P_2O_5 in high vacuum to give compound **17** (1.5 g, 77%). ^{1}H NMR ($CDCl_3$): 7.96 (d, J = 7.3, 2 H, H_{arom}), 7.74 (m, 1 H, 2 H, H_{arom} and NH_m), 7.65 (t, J = 7.7, 2 H, H_{arom}), 7.38–7.27 (overlapped m, 10 H, 2 × Bn), 6.21 (m, 1 H, NH_g), 6.05 (dd, $J_{H/H}$ = 3.2, $J_{H/P}$ = 5.6, 1 H, H_{1m}), 5.13 (t, J = 9.5, 1 H, H_{3g}), 5.09 (t, J = 9.5, 1 H, H_{4g}), 5.05 and 5.00

(2 × d, $J_{H/P}$ = 7.5, 7.8, 2 × 2 H, 2 × CH_2Bn), 4.57 (m, 1 H, O-CH_{2A}), 4.52 (q, *J* = 6.8, O-CH), 4.43 (m, 1 H, O-CH_{2B}), 4.43 (d, *J* = 9.7, 1 H, H_{1g}), 4.38 (dd, *J* = 12.5, 4.5, 1 H, H_{6g}), 4.22–4.16 (m, 2 H, H_{6m} and $H_{6'm}$), 4.08–4.01 (m, 2 H, $H_{6'g}$ and H_{2g}), 3.88 (dm, *J* = 9.7, 1 H, H_{5m}), 3.82 (m, 1 H, H_{2m}), 3.77 (t, *J* = 9.8, 1 H, H_{3m}), 3.64 (m, 1 H, H_{5g}), 3.56 (t, *J* = 9.8, H_{4m}), 3.58–3.46 (m, 2 H, CH_2S), 2.05 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3), 1.23 (d, *J* = 6.8, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 175.32 (COO), 171.08 (Ac), 170.95 (Ac), 170.63 (Ac), 170.35 (Ac), 170.32 (CON), 169.33 (CON), 139.08 (C_{arom}), 135.50 (d, $J_{C/P}$ = 6.8, 2 × C_{arom}), 134.19 (CH_{arom}), 129.55 (2 × CH_{arom}), 128.55 (6 × CH_{arom}), 128.06 (2 × CH_{arom}), 127.87 (2 × CH_{arom}), 127.83 (2 × CH_{arom}), 100.89 (C_{1g}), 95.25 (C_{1m}), 77.13 (C_{3m}), 74.89 (CH), 74.04 (C_{4m}), 72.77 (C_{3g}), 71.94 (C_{5g}), 71.05 (C_{5m}), 69.46 (d, $J_{C/P}$ = 6.0, CH_2Bn), 69.38 (d, $J_{C/P}$ = 6.0, CH_2Bn), 68.08 (C_{4g}), 61.59 (C_{6m}), 61.45 (C_{6g}), 58.28 (CH_2O), 54.77 (CH_2S), 54.31 (C_{2g}), 53.82 (d, $J_{C/P}$ = 8.0, C_{2m}), 23.03 (CH_3, Ac), 22.72 (CH_3, Ac), 20.76 (CH_3, Ac), 20.53 (CH_3, Ac), 20.52 (2 × CH_3, Ac), 17.99 (CH_3). ^{31}P NMR ($CDCl_3$, 202 MHz): –2.553. ESI-MS for $C_{49}H_{61}N_2NaO_{22}PS$ calculated $[M + Na]^+$: 1115.3071; found: 1115.3105.

N$^{\varepsilon}$-(Benzyloxycarbonyl)-*N*$^{\alpha}$-(*tert*-butoxycarbonyl)-L-lysinamide (**18**)

Boc-Lys(CBz) (4.75 g, 12.5 mmol) was dissolved in dry THF (25 ml) and cooled to –10 °C. Then triethylamine (2.15 ml, 15 mmol) and isobutyl chloroformate (2 ml, 15 mmol) were added. The mixture was stirred in inert atmosphere at –10 °C for 2 h. Then aqueous ammonia solution (25%, 40 ml) was added, the solution was stirred at –10 °C for 30 min and was allowed to warm to room temperature overnight. Then the solvents were removed in vacuo and the residue was redissolved in dichloromethane and washed with 1 M $NaHCO_3$ and water. The organic layer was dried with Na_2SO_4, filtered and concentrated. The crude material obtained was recrystallized from CH_2Cl_2/MeOH to provide compound **18** (4.14 g, 87%), m.p. 148–149 °C (lit.[24] 142 °C). ^{1}H NMR (DMSO-d_6): 7.38–7.28 (m, 5 H, H_{arom}), 7.20 (br, 2 H, 2 NH), 6.91 (br, 1 H, NH), 6.66 (d, *J* = 8.0, NH), 5.00 (s, 2 H, CH_2O), 3.81 (m, 1 H, CH), 2.97 (q, *J* = 6.2, 2 H, $CH_2\varepsilon$), 1.56 and 1.47 (m, 2 H, $CH_2\beta$), 1.38 (m, 2 H, CH_2S), 1.37 (s, 9 H, *t*-Bu), 1.25 (m, 2 H, $CH_2\gamma$). ^{13}C NMR (DMSO-d_6): 174.35 (C=O_{amide}), 156.16 (COO_{CBz}), 155.40 (COO_{Boc}), 137.36 (C_{arom}), 128.47 (CH_m), 127.78 (CH_{o+p}), 77.96 (C-O), 65.18 (CH_2), 54.19 (CHα), 40.19 ($CH_2\varepsilon$), 31.73 ($CH_2\beta$), 29.19 ($CH_2\delta$), 28.27 (CH_{3Boc}), 22.87 ($CH_2\gamma$). ESI-MS for $C_{19}H_{29}N_3NaO_5$ calculated $[M + Na]^+$: 402.2005; found: 402.1994.

N$^{\alpha}$-(*tert*-Butoxycarbonyl)-*N*$^{\varepsilon}$-dansyl-L-lysinamide (**20**)

Amino acid **18** (930 mg, 2.1 mmol) was added to a suspension of 10% palladium on carbon (100 mg) in methanol (15 ml). The mixture was cooled and degassed, warmed to room temperature and hydrogenated at atmospheric pressure for 1.5 h. The catalyst was collected by filtration on Celite and the filtrate was concentrated in vacuo to an off-white solid which was dried over P_2O_5 in high vacuum overnight to obtain 650 mg of crude compound **19** ($[M + H]^+$: 317.1). The off-white solid (500 mg, 2.0 mmol) was dissolved in dry dichloromethane, and dansyl chloride (604 mg, 2.2 mmol) and triethylamine (0.57 ml, 4.1 mmol) were added. The mixture was stirred at room temperature for 3 h, then diluted with dichloromethane and washed with 0.5 M HCl, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was eluted from a column of silica gel with CH_2Cl_2/MeOH (9:1) to give compound **20** (780 mg, 80%). ^{1}H NMR (DMSO-d_6): 8.45 (d,

J = 8.5, 1 H, CH_{arom}), 8.31 (d, *J* = 8.6, 1 H, CH), 8.09 (d, *J* = 7.3, 1 H, CH), 7.85 (t, *J* = 5.7, NH), 7.61 (dd, *J* = 7.3, 8.3, 1 H, CH), 7.58 (dd, *J* = 7.6, 8.5, 1 H, CH), 7.25 (d, *J* = 7.5, 1 H, CH), 7.15 and 6.88 (s, 2 × 1 H, NH_2), 6.60 (d, *J* = 8.0, 1 H, NH), 3.74 (m, 1 H, CH), 2.83 (s, 6 H, $N(CH_3)_2$), 2.74 (q, *J* = 6.6, 2 H, $CH_2\varepsilon$), 1.44 and 1.35 (m, 2 H, $CH_2\beta$), 1.36 (s, 9 H, *t*-Bu), 1.34 (m, 2 H, $CH_2\delta$), 1.23–1.12 (m, 2 H, $CH_2\gamma$). ^{13}C NMR (DMSO-d_6): 174.23 ($C{=}O_{amide}$), 155.33 ($C{=}O_{Boc}$), 151.25, 136.24 (C_{arom}), 129.30 (CH_{arom}), 129.17, 129.09 (C_{arom}), 128.20, 127.81, 123.65, 119.32, 115.22 (CH_{arom}), 77.95 (C-O), 54.06 (CHα), 45.14 (2 × NCH_3), 42.38 ($CH_2\varepsilon$), 31.49 ($CH_2\beta$), 29.03 ($CH_2\delta$), 28.24 (CH_{3Boc}), 22.65 ($CH_2\gamma$). ESI-MS for $C_{23}H_{35}N_4O_5S$ calculated $[M + H]^+$: 479.2328; found: 479.2329.

N$^{\alpha}$-(*tert*-Butoxycarbonyl)-*N*$^{\varepsilon}$-[(fluoren-9-ylmethoxy)carbonyl]-L-lysinamide (**21**)

In the same manner as for compound **20**, the crude compound **19** was obtained by hydrogenation of compound **18**. The off-white solid (500 mg, 2.0 mmol) was dissolved in saturated aqueous solution of $NaHCO_3$ and Fmoc chloride (633 mg, 2.4 mmol) was added. A precipitate appeared and stirring was kept overnight. Then the suspension was diluted with dichloromethane and washed with water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was eluted from a column of silica gel with CH_2Cl_2/MeOH (9:1) to give compound **21** (744 mg, 81%). ^{1}H NMR (DMSO-d_6): 7.88 (d, *J* = 7.3, 2 H, H_{arom}), 7.68 (d, *J* = 7.4, 2 H, H_{arom}), 7.41 (t, *J* = 7.4, 2 H, H_{arom}), 7.33 (t, *J* = 7.4, 2 H, H_{arom}), 7.25 (t, *J* = 5.5, 1 H, NH), 7.21 and 6.91 (s, 2 × 1 H, NH_2), 6.66 (d, *J* = 8.1, 1 H, NH), 4.29 (d, *J* = 6.8, 2 H, CH_2), 4.20 (t, *J* = 6.8, 1 H, CH), 3.83 (m, 1 H, CHα), 2.96 (q, *J* = 6.4, 2 H, $CH_2\varepsilon$), 1.57 and 1.48 (m, 2 H, $CH_2\beta$), 1.37 (s, 9 H, *t*-Bu), 1.36 (m, 2 H, CH_2S), 1.26 (m, 2 H, $CH_2\gamma$). ^{13}C NMR (DMSO-d_6): 174.34 ($C{=}O_{amide}$), 156.14 ($C{=}O_{Fmoc}$), 155.39 (COO_{Boc}), 144.01, 140.80 (C_{arom}), 127.64, 127.10, 125.20, 120.15 (CH_{arom}), 77.95 (C-O), 65.26 (CH_2-O), 54.20 (CHα), 46.85 (CH), 40.13 ($CH_2\varepsilon$), 31.74 ($CH_2\beta$), 29.16 ($CH_2\delta$), 28.25 (CH_{3Boc}), 22.86 ($CH_2\gamma$). ESI-MS for $C_{26}H_{33}N_3NaO_5$ calculated $[M + Na]^+$: 490.2318; found: 490.2330.

N-(*tert*-Butoxycarbonyl)-D-glutamic Diamide (**22**)

Commercial Boc-D-Glu (2.5 g, 10.1 mmol) and 4–nitrophenol (2.8 g, 20.2 mmol) were dissolved in THF (40 ml). DCC (4.4 g, 21.2 mmol) was added at 0 °C and the solution was stirred at room temperature overnight. The resulting *N*,*N*′-dicyclohexylurea was filtered off and NH_4OH (25%, 20 ml) was added to the filtrate. The solution was stirred at room temperature for 18 h. Then the solution was concentrated in vacuo and the residue was dissolved in H_2O (50 ml). The solution was neutralized with 10% aqueous formic acid, the aqueous solution was extracted with ethyl acetate (3 × 50 ml) and lyophilized. The residue was recrystallized from EtOH to give compound **22** (1.5 g, 62%), m.p. 125–126 °C (lit.[26] 132–133 °C). ^{1}H NMR (DMSO-d_6): 7.30 (br, 2 H, NH_2), 6.96 (s, 1 H, NH), 6.73 (s, 2 H, NH), 3.81 (m, 1 H, CH), 2.08 (m, 2 H, $CH_2\gamma$), 1.81 and 1.68 (m, 2 H, $CH_2\beta$), 1.36 (s, 9 H, *t*-Bu). ^{13}C NMR (DMSO-d_6): 174.07 ($C{=}O_{amide}$), 173.95 (C=O), 155.34 ($C{=}O_{Boc}$), 78.06 (C-O), 54.04 (CHα), 31.08 ($CH_2\gamma$), 28.28 (CH_{3Boc}), 27.94 ($CH_2\beta$). ESI-MS for $C_{10}H_{19}N_3NaO_4$ calculated $[M + Na]^+$: 268.1273; found: 268.1270.

N-(*tert*-Butoxycarbonyl)-L-alanyl *N*-Hydroxysuccinimidyl Ester (**23**)

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5.6 g, 29.2 mmol) and *N*-hydroxysuccinimide (3.1 g, 26.9 mmol) were added to a solution of Boc-L-Ala (5.08 g, 26.8

mmol) in anhydrous dioxane (20 ml). The mixture was stirred at room temperature overnight. Then the solution was concentrated in vacuo and redissolved in ethyl acetate (50 ml) and washed with water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated to provide a foam which was recrystallized from EtOH to provide compound **23** (6.9 g, 89%), m.p. 154–155 °C. ^{1}H NMR (DMSO-d_6): 7.61 (d, J = 7, 1 H, NH), 4.41 (m, 1 H, CH), 2.80 (s, 4 H, 2 × CH_2), 1.41 (d, J = 7.3, CH_3), 1.39 (s, 9 H, *t*-Bu). ^{13}C NMR (DMSO-d_6): 170.01 ($C{=}O_{succinimide}$), 169.49 ($C{=}O_{acid}$), 155.11 ($C{=}O_{Boc}$), 78.75 (C-O), 47.47 (CH), 28.18 (CH_{3Boc}), 25.53 (2 × CH_2), 17.01 (CH_3). ESI-MS for $C_{12}H_{18}N_2NaO_6$ calculated $[M + Na]^+$: 309.1062; found: 309.1049.

N-(*tert*-Butoxycarbonyl)-L-alanyl-N^{ε}-dansyl-L-lysinamide (**24**)

Trifluoroacetic acid (5 ml) was added to a solution of compound **20** (932 mg, 1.9 mmol) in dichloromethane (5 ml) and the mixture was stirred at room temperature for 2 h. The solution was concentrated in vacuo and dried under high vacuum to provide the trifluoroacetate salt as an oil. The salt thus obtained was added to a solution of **23** (588 mg, 1.95 mmol) in anhydrous DMF (10 ml) and *N*,*N*-diisopropylethylamine (0.61 ml, 5.9 mmol) was added. The mixture was stirred at room temperature overnight. Then the solvent was removed and the residue was redissolved in dichloromethane (20 ml) and was washed with 0.5 M HCl, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was purified on silica gel with CH_2Cl_2/MeOH (9.5:0.5) to give compound **24** (749 mg, 70%). ^{1}H NMR (DMSO-d_6): 8.45 (d, J = 8.3, 1 H, H_{dansyl}), 8.31 (d, J = 8.6, 1 H, H_{dansyl}), 8.09 (d, J = 7.3, 1 H, H_{dansyl}), 7.84 (t, J = 5.7, 1 H, NH), 7.61 (dd, J = 8.6, 7.1, 1 H, H_{dansyl}), 7.59 (d, J = 8.3, NH), 7.58 (dd, J = 8.5, 7.5, 1 H, H_{dansyl}), 7.23 (d, J = 7.3, 1 H, H_{dansyl}), 7.26 and 7.00 (brs, 2 H, NH_2), 6.97 (d, J = 7.0, 1 H, NH), 4.12 (m, 1 H, CH_{Lys}), 3.92 (m, 1 H, CH_{Ala}), 2.81 (s, 6 H, $(CH_3)_2$), 2.73 (q, J = 6.6, 2 H, $CH_2\varepsilon$), 1.53 and 1.40 (m, 2 H, $CH_2\beta$), 1.33 (m, 2 H, $CH_2\delta$), 1.33 (s, 9 H, *t*-Bu), 1.18 (m, 2 H, $CH_2\gamma$), 1.15 (d, J = 7.0, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 173.50 ($C{=}O_{amide}$), 172.50 (C=O), 155.25 ($C{=}O_{Boc}$), 151.41, 136.18 (C_{arom}), 129.38 (CH_{arom}), 129.22, 129.17 (C_{arom}), 128.26, 127.85, 123.63, 119.25, 115.17 (CH_{arom}), 78.23 (C-O), 51.95 (CH_{Lys}), 50.07 (CH_{Ala}), 45.13 (NMe_2), 42.47 ($CH_2\varepsilon$), 31.73 ($CH_2\beta$), 29.08 ($CH_2\delta$), 28.22 (CH_{3Boc}), 22.28 ($CH_2\gamma$), 17.90 (CH_3). ESI-MS for $C_{26}H_{40}N_5O_6S$ calculated $[M + H]^+$: 550.2699; found: 550.2673.

N-(*tert*-Butoxycarbonyl)-L-alanyl-N^{ε}-[(fluoren-9-ylmethoxy)carbonyl]-L-lysinamide (**25**)

Trifluoroacetic acid (5 ml) was added to a solution of compound **21** (500 mg, 1.1 mmol) in dichloromethane (5 ml) and the mixture was stirred at room temperature for 2 h. The solution was concentrated in vacuo and dried under high vacuum to provide the trifluoroacetate salt as an oil. The salt thus obtained was added to a solution of **23** (315 mg, 1.1 mmol) in anhydrous DMF (10 ml) and *N*,*N*-diisopropylethylamine (0.57 ml, 3.3 mmol) was added. The mixture was stirred at room temperature overnight. Then the solvent was removed and the residue was redissolved in dichloromethane (20 ml) and washed with 0.5 M HCl, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was eluted from silica gel with CH_2Cl_2/MeOH (9:1) to give compound **25** (455 mg, 77%). ^{1}H NMR (DMSO-d_6): 7.88 (d, J = 7.6, 2 H, H_{arom}), 7.68 (d, J = 7.1, 2 H, H_{arom}), 7.65 (d, J = 8.1, 1 H, NH), 7.41 (t, J = 7.7, 2 H, H_{arom}), 7.33 (t, J = 8.5, 2 H, H_{arom}), 7.31 and 7.02 (br, 2 H, NH_2), 7.24 (t, J = 5.3, 1 H, NH), 7.01 (d, J = 6.3, NH), 4.28 (d, J = 6.8, 2 H, CH_2O), 4.20 (m,

1 H, CH_{Lys}), 4.20 (m, 1 H, CH), 3.95 (m, 1 H, CH_{Ala}), 2.96 (q, *J* = 6.2, 2 H, $CH_2\varepsilon$), 1.66 and 1.52 (m, 2 H, $CH_2\beta$), 1.38 (m, 2 H, $CH_2\delta$), 1.37 (s, 9 H, *t*-Bu), 1.24 (m, 2 H, $CH_2\gamma$), 1.18 (d, *J* = 7.1, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 173.57 ($C{=}O_{amide}$), 172.52 (C=O), 156.13 ($C{=}O_{Fmoc}$), 155.26 ($C{=}O_{Boc}$), 144.01, 140.75 (C_{arom}), 127.15, 127.11, 125.29, 120.16 (CH_{arom}), 78.26 (C-O), 65.28 (CH_2-O), 52.09 (CH_{Lys}), 50.17 (CH_{Ala}), 46.85 (CH), 40.23 ($CH_2\varepsilon$), 31.95 ($CH_2\beta$), 29.19 ($CH_2\delta$), 28.23 (CH_{3Boc}), 22.47 ($CH_2\gamma$), 17.97 (CH_3). ESI-MS for $C_{29}H_{39}N_4O_6$ calculated $[M + H]^+$: 539.2870; found: 539.2869.

[*N*-(*tert*-Butoxycarbonyl)-L-alanyl]glutamic Diamide (**26**)

Trifluoroacetic acid (5 ml) was added to a solution of compound **22** (1.1 g, 4.6 mmol) in dichloromethane (5 ml) and the mixture was stirred at room temperature for 2 h. The solution was concentrated in vacuo and dried under high vacuum to provide the trifluoroacetate salt as an oil. The salt thus obtained was added to a solution of **23** (1.3 mg, 4.6 mmol) in anhydrous DMF (15 ml) and *N*,*N*-diisopropylethylamine (1 ml, 9.3 mmol) was added. The mixture was stirred at room temperature overnight. Then the solvent was removed and the residue was redissolved in dichloromethane (40 ml), and washed with 0.5 M HCl, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was eluted from silica gel with CH_2Cl_2/MeOH (8:2) to give compound **26** (843 mg, 58%). ^{1}H NMR (DMSO-d_6): 7.87 (d, *J* = 7.6, 1 H, NH), 7.30 and 6.93 (s, 2 H, NH_2), 7.27 and 7.10 (s, 2 H, NH_2), 7.04 (d, *J* = 6.1, 1 H, NH), 4.12 (m, 1 H, CH_{Glu}), 3.95 (m, 1 H, CH_{Ala}), 2.135 (t, *J* = 7.8, 2 H, $CH_2\gamma$), 1.97 and 1.70 (m, 2 H, $CH_2\beta$), 1.37 (s, 9 H, *t*-Bu), 1.18 (d, *J* = 7.1, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 173.90 ($C{=}O_{amide}$), 173.40 ($C{=}O_{amide}$), 171.64 (C=O), 155.44 ($C{=}O_{Boc}$), 78.33 (C-O), 52.66 (CH_{Glu}), 50.07 (CH_{Ala}), 31.79 ($CH_2\gamma$), 28.27 (CH_{3Boc}), 27.97 ($CH_2\beta$), 17.82 (CH_3). ESI-MS for $C_{13}H_{24}N_4NaO_5$ calculated $[M + Na]^+$: 339.1644; found: 339.1648.

Dibenzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-{D-1-[(*N*-hydroxysuccinimidyloxy)carbonyl]ethyl}-α-D-glucopyranosyl Phosphate (**28**)

To a solution of compound **17** (1.2 g, 1.1 mmol) in dichloromethane (20 ml) was added dropwise at 0 °C DBU (0.175 ml, 1.1 mmol). After 30 min the solution was diluted with dichloromethane and washed with 1 M HCl, water and brine. The organic layer was dried with Na_2SO_4, filtered, concentrated and triturated with Et_2O. After filtration, the crude compound **27** was dried over P_2O_5 in high vacuum. The acid (1 g, 1.1 mmol) was dissolved in anhydrous DMF (20 ml) and *N*-hydroxysuccinimide (187 mg, 1.6 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (311 mg, 1.62 mmol) were added. The mixture was stirred at room temperature overnight. Then the solution was concentrated in vacuo, the residue was redissolved in ethyl acetate (30 ml) and washed with water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated to provide a colorless foam which was triturated with Et_2O to give the NHS-ester **28** (977 mg, 87%). ESI-MS for $C_{45}H_{56}N_3NaO_{22}P$ calculated $[M + Na]^+$: 1044.2991; found: 1044.2988.

Dibenzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(D-2-propionyl-L-alanyl-N^{ε}-dansyl-L-lysinamide)-α-D-glucopyranosyl Phosphate (**29**)

The dipeptide **24** (364.0 mg, 0.66 mmol) was treated with trifluoroacetic acid (5 ml) in dichloromethane (5 ml) for 2 h, then the solvent was removed in vacuo and the residue was coevaporated with toluene to provide the trifluoroacetate salt as an oil. The salt thus obtained was added to a solution of the NHS-ester **28** (517 mg, 0.51 mmol) and *N*,*N*-diisopropylethylamine (0.283 ml, 1.6 mmol) in DMF (3 ml), and stirred at room temperature under inert atmosphere for 24 h. Then the solvent was removed under reduce pressure and the residue was redissolved in dichloromethane, washed with 0.5 M HCl solution, water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was triturated with diethyl ether to provide the compound **29** (634 mg, 92%). ^{1}H NMR ($CDCl_3$): 8.52 (d, J = 8.5, 1 H, H_{dansyl}), 8.34 (d, J = 8.8, 1 H, H_{dansyl}), 8.18 (d, J = 7.2, 1 H, H_{dansyl}), 8.03 (m, 1 H, NH_m), 7.52 (d, J = 8.7, 1 H, H_{dansyl}), 7.50 (d, J = 7.6, 1 H, H_{dansyl}), 7.16 (d, J = 7.6, 1 H, H_{dansyl}), 7.46 (m, 1 H, $NH\alpha_{Ala}$), 7.19 (m, 1 H, $NH\alpha_{Lys}$), 6.84 (m, 1 H, NH_g), 6.63 (brs, 1 H, $NH_{2/A}$), 6.37 (m, 1 H, $NH\varepsilon_{Lys}$), 6.33 (brs, 1 H, $NH_{2/B}$), 5.99 (dd, J = 3.2, 5.8, 1 H, H_{1m}), 5.26 (t, J = 10.1, 1 H, H_{3g}), 5.08 (t, J = 9.8, 1 H, H_{4g}), 5.08–5.02 (dAB, $J_{H/P}$ = 7.3, 2 H, CH_2Bn), 5.01–4.93 (dAB, $J_{H/P}$ = 6.4, 2 H, CH_2Bn), 4.72 (q, J = 6.6, 1 H, CHO), 4.67 (d, J = 8.3, 1 H, H_{1g}), 4.45 (p, J = 7.1, 1 H, CH_{Ala}), 4.40–4.37 (m, 2 H, CH_{Lys}, H_{6g}), 4.31 (d, J = 12.3, H_{6m}), 4.16 (dd, J = 3.4, 12.2, 1 H, $H_{6'm}$), 4.08 (d, J = 10.5, 1 H, $H_{6'g}$), 4.03 (m, 2 H, H_{5m}, H_{2g}), 3.90 (m, 2 H, H_{2m}, H_{4m}), 3.68 (brd, J = 8.3, 1 H, H_{5g}), 3.61 (t, J = 9.9, 1 H, H_{3m}), 2.86 (s, 6 H, $N(CH_3)_2$), 2.84 (m, 2 H, $CH_2\varepsilon$), 2.03 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 1.73 and 1.63 (br, 2 H, $CH_2\beta$), 1.50 and 1.40 (obs, 4 H, $CH_2\gamma$, $CH_2\delta$), 1.47 (d, J = 7.1, CH_{3Ala}), 1.43 (d, J = 6.6, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 175.28 (CONH), 174.08 (CO_{amide}), 172.60 (CONH), 171.41, 171.34, 170.83, 170.68 (4 × OAc), 170.57 (NHAc), 169.46 (NHAc), 151.78 (C_{dansyl}), 135.39 (d, $J_{C/P}$ = 7.5, C, Bn), 135.29 (d, $J_{C/P}$ = 7.5, C, Bn), 134.98 (C_{dansyl}), 130.20 (CH_{dansyl}), 129.82, 129.60 (C_{dansyl}), 129.15 (CH_{dansyl}), 128.57 (6 × CH_{arom}), 128.16 (CH_{dansyl}), 127.94 (4 × CH_{arom}), 123.16 (CH_{dansyl}), 118.93 (CH_{dansyl}), 115.17 (CH_{dansyl}), 99.59 (C_{1g}), 95.80 (d, J = 7.0, C_{1m}), 76.64 (C_{3m}), 75.15 (CHO), 74.64 (C_{4m}), 72.30 (C_{3g}), 71.97 (C_{5g}), 70.97 (C_{5m}), 69.68 (d, J = 5.6, CH_2Bn), 69.61 (d, J = 5.6, CH_2Bn), 68.63 (C_{4g}), 62.05 (C_{6m}), 61.82 (C_{6g}), 54.80 (C_{2g}), 53.97 (C_{2m}), 52.36 (CH_α, Lys), 49.99 (CH_α, Ala), 45.32 (2 × N-CH_3), 42.34 ($CH_{2\varepsilon}$, Lys), 31.13 ($CH_{2\beta}$, Lys), 28.25 ($CH_{2\delta}$, Lys), 23.18 (CH_3, NHAc), 22.70 (CH_3, NHAc), 21.45 ($CH_{2\gamma}$, Lys), 20.74 (CH_3, OAc), 20.63 (CH_3, OAc), 20.54 (2 × CH_3, OAc), 19.24 (CH_3Ala), 17.42 (CH_3Ala).^{31}P NMR ($CDCl_3$, 202 MHz): –3.085. ESI-MS for $C_{62}H_{83}N_7O_{23}PS$ calculated $[M + H]^+$: 1356.4998; found: 1356.4943.

Dibenzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-{D-2-propionyl-L-alanyl-N^{ε}-(fluoren-9-ylmethoxy)carbonyl-L-lysinamide}-α-D-glucopyranosyl Phosphate (**30**)

Compound **30** was prepared from compound **28** (200.0 mg, 0.196 mmol) and the deprotected dipeptide **25** (161.0 mg, 0.300 mmol) as described for the preparation of compound **29**, yielding 160.68 mg (61%). ^{31}P NMR (DMSO-d_6, 202 MHz): –2.048. ESI-MS for $C_{65}H_{82}N_6O_{23}P$ calculated $[M + H]^+$: 1345.5168; found: 1345.5248.

Dibenzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→4)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(D-2-propionyl-L-alanyl-D-glutamic diamide)-α-D-glucopyranosyl Phosphate (**31**)

Compound **31** was prepared from compound **28** (200.0 mg, 0.196 mmol) and the deprotected dipeptide **26** (100 mg, 0.294 mmol) as described for the preparation of compound **29**, yielding 120.95 mg (55%). ^{31}P NMR (DMSO-d_6, 202 MHz): –1.951. ESI-MS for $C_{49}H_{68}N_6O_{22}P$ calculated $[M + H]^+$: 1123.4125; found: 1123.4156.

P^1-Uridin-5′-yl P^2-[(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-2-deoxy-3-*O*-(D-2-propionyl-L-alanyl-N^ε-dansyl-L-lysinamide)-α-D-glucopyranosyl] Diphosphate (**35**)

The disaccharidyl dipeptide **29** (118.30 mg, 0.09 mmol) was dissolved in methanol (4 ml) and 10% palladium on carbon (100 mg) was added. The suspension was cooled to 0 °C and the reaction mixture was degassed. Then the mixture was warmed to room temperature and hydrogenated at atmospheric pressure for 2 h. The catalyst was collected by filtration on Celite and the filtrate was treated with pyridine (0.5 ml) and concentrated in vacuo to afford a white solid which was triturated with diethyl ether. The resulting solid (99.6 mg, 95%) was collected and dried under high vacuum for 16 h. Then the dried solid was reacted with uridine 5′-monophosphomorpholidate 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidine salt (92.7 mg, 0.135 mmol) and 0.5 M tetrazole in acetonitrile (0.6 ml) in pyridine (1 ml). The mixture was stirred at room temperature for 2 days. The mixture was then concentrated in vacuo and dissolved in dioxane (1 ml) followed by 1 M NaOH (0.5 ml). The mixture was stirred at room temperature for 1 h. The solution was concentrated in vacuo at 30 °C and the residue was dissolved in water (1 ml), and the solution was filtered and purified by reverse phase HPLC on a Alltech® HS Hyper Prep 100 BDS column C-18 8μ (length 250 mm) employing a gradient elution of A/B (100:0) to A/B (80:20) over 15 min at a flow rate of 3 ml min^{-1} where A = 0.05 M aqueous $HCOONH_4$ and B = MeCN. Lyophilisation of the column fractions afforded pure **35** (21.2 mg, 18%) as a yellow powder. ^{1}H NMR (DMSO-d_6): 8.44 (d, J = 8.3, H_{dansyl}), 8.30 (d, J = 8.6, H_{dansyl}), 8.09 (d, J = 7.3, H_{dansyl}), 7.89 (d, J = 8.1, 1 H, H_{6u}), 7.61 (dd, J = 7.3, 8.6, H_{dansyl}), 7.58 (dd, J = 7.3, 8.6, H_{dansyl}), 7.23 (d, J = 7.3, H_{dansyl}), 5.80 (d, J = 5.1, $H_{1'u}$), 5.64 (d, J = 8.1, H_{5u}), 5.36 (d, J = 5.4, H_{1m}), 4.21 (m, 1 H, CHO), 4.15 (m, 1 H, CH_αAla), 4.06 (m, 3 H, $H_{2'u}$, H_{5m}, CH_αLys), 3.93 (m, 1 H, $H_{4'u}$), 3.90 (m, 3 H, $H_{5'u}$, $H_{5''u}$), 3.88 (m, 1 H, H_{2g}), 3.68 (m, 2 H, H_{3g}, H_{5g}), 3.68 and 3.40 (m, 2 H, H_{6g}, $H_{6'g}$), 3.66 and 3.58 (m, 2 H, H_{6m}, $H_{6'm}$), 3.40 (m, 3 H, H_{2m}, H_{4m}, H_{4g}), 3.05 (m, 1 H, H_{3m}), 3.01 (m, 1 H, $H_{3'u}$), 2.83 (m, 6 H, NMe_2), 2.72 (m, 2 H, $CH_{2\varepsilon}$ Lys), 2.80 (m, 2 H, $CH_{2\beta}$ Lys), 1.81 (s, 6 H, 2 × Ac), 1.34 (m, 4 H, $CH_{2\delta}$, $CH_{2\gamma}$ Lys), 1.24 (s, 6 H, 2 × CH_3). ^{13}C NMR (DMSO-d_6): 173.69, 173.63, 172.33, 170.29, 169.42, 163.36, 150.99, 140.98, 102.07, 100.58, 93.79, 87.58, 83.59, 76.55, 76.46, 76.30, 75.14, 74.00, 73.44, 72.58, 71.39, 70.02, 64.61, 61.77, 59.60, 55.90, 53.38, 52.40, 48.86, 45.14, 42.30, 29.51, 29.00, 23.07, 22.67, 21.87, 18.79, 17.87. ^{31}P NMR (DMSO-d_6, 202 MHz): –9.540 (d, J = 19.5), –12.56 (d, J = 19.8). ESI-MS for $C_{48}H_{71}N_9O_{27}P_2S$ calculated $[M + H]^+$: 1299.3655; found: 1299.3656.

P^1-Uridin-5′-yl P^2-[(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-2-deoxy-3-*O*-(D-2-propionyl-L-alanyl-L-lysinamide)-α-D-glucopyranosyl] Diphosphate (**36**)

The disaccharidyl dipeptide **30** (145 mg, 0.108 mmol) was dissolved in methanol (6 ml) and 10% palladium on carbon (150 mg) was added. The suspension was cooled to 0 °C and the

reaction mixture was degassed. Then the mixture was warmed to room temperature and hydrogenated at atmospheric pressure for 2 h. The catalyst was collected by filtration on Celite and the filtrate was treated with pyridine (0.5 ml) and concentrated in vacuo to afford a white solid which was triturated with diethyl ether. The resulting solid (100 mg, 79%) was collected and dried under high vacuum for 16 h. Then the dried solid was reacted with uridine 5′-monophosphomorpholidate 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidine salt (88.5 mg, 0.129 mmol) and 0.5 M tetrazole in acetonitrile (1.72 ml, 0.86 mmol). The mixture was stirred at room temperature for 2 days. The mixture was then concentrated in vacuo and dissolved in dioxane (1 ml) followed by 1 M NaOH (0.5 ml). The mixture was stirred at room temperature for 1 h. The compound **36** was purified as described for **35**, yielding 12.3 mg (13%). ^{31}P NMR (DMSO-d_6, 202 MHz): –10.930 (d, J = 20.7), –12.710 (d, J = 21.4). ESI-MS for $C_{37}H_{63}N_8O_{25}P_2$ calculated $[M + H]^+$: 1081.3379; found: 1081.3412.

P^1-Uridin-5′-yl *P*^{2}-[(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-2-deoxy-3-*O*-(D-2-propionyl-L-alanyl-D-glutamic diamide)-α-D-glucopyranosyl] Diphosphate (**37**)

The disaccharidyl dipeptide **31** (100 mg, 0.089 mmol) was dissolved in methanol (3 ml) and 10% palladium on carbon (80 mg) was added. The suspension was cooled to 0 °C and the reaction mixture was degassed. Then the mixture was warmed to room temperature and hydrogenated at atmospheric pressure for 2 h. The catalyst was collected by filtration on Celite and the filtrate was treated with pyridine (0.5 ml) and concentrated in vacuo to afford a white solid which was triturated with diethyl ether. The resulting solid (60.48 mg, 72%) was collected and dried under high vacuum for 16 h. Then the dried solid was reacted with uridine 5′-monophosphomorpholidate 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidine salt (66.13 mg, 0.09 mmol) and 0.5 M tetrazole in acetonitrile (1.28 ml, 0.64 mmol). The mixture was stirred at room temperature for 2 days. The mixture was then concentrated in vacuo and dissolved in dioxane (1 ml) followed by 1 M NaOH (0.5 ml). The mixture was stirred at room temperature for 1 h. The compound **37** was purified as described for **35**, yielding 13.8 mg (20%). ^{31}P NMR (DMSO-d_6, 202 MHz): –11.45 (d, $J_{P,P}$ = 20.8), –13.63 (d, $J_{P,P}$ = 22.6). ESI-MS for $C_{36}H_{59}N_8O_{26}P_2$ calculated $[M + H]^+$: 1081.3015; found: 1081.3020.

P^1-Uridin-5′-yl *P*^{2}-[(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-2-deoxy-3-*O*-(D-1-carboxyethyl)-α-D-glucopyranosyl] Diphosphate (**39**)

The disaccharide **17** (150 mg, 0.137 mmol) was dissolved in methanol (3 ml) and 10% palladium on carbon (150 mg) was added. The suspension was cooled to 0 °C to aid in degassing the reaction mixture. Then, the mixture was warmed to room temperature and hydrogenated at atmospheric pressure for 2 h. The catalyst was collected by filtration on Celite and the filtrate was treated with pyridine (0.5 ml) and concentrated in vacuo to afford a white solid which was triturated with diethyl ether. The resulting solid (90 mg, 72%) was collected and dried under high vacuum for 16 h. Then the dried solid was combined with uridine 5′-monophosphomorpholidate 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidine salt (100 mg, 0.147 mmol) and 0.5 M tetrazole in acetonitrile (2 ml, 0.986 mmol). The mixture was stirred at room temperature for 2 days. The mixture was then concentrated in vacuo and dissolved in dioxane (1 ml) followed by 1 M NaOH (0.5 ml). The mixture was stirred at room temperature for 1 h. The compound **39** was purified as described for **35**, yielding 19.10 mg (16%). ^{31}P NMR (DMSO-d_6, 202 MHz): –10.297 (d, $J_{P,P}$ = 14.0), –11.576 (d, $J_{P,P}$ = 13.9). ESI-MS for $C_{28}H_{43}N_4Na_2O_{24}P_2$ calculated $[(M - H) + 2\ Na]^+$: 927.1537; found: 927.1539.

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