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A simple iterative method for the synthesis of β-(1→6)-glucosamine oligosaccharides

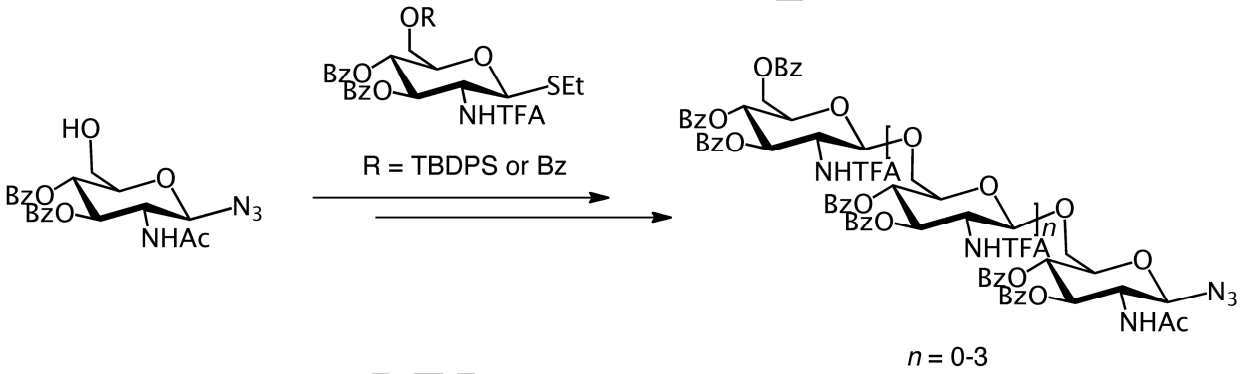
Lucy G. Weaver[†], Yogendra Singh[†], Joanne T. Blanchfield[†*], Paul L. Burn[‡*]

[†] The School of Chemistry and Molecular Biosciences, University of Queensland, St Lucia, QLD 4072, Australia

[‡]Centre for Organic Photonics & Electronics, University of Queensland, St Lucia, QLD 4072, Australia

Corresponding Authors. Email: j.blanchfield@uq.edu.au, p.burn2@uq.edu.au.

Graphical Abstract



Abstract

Poly-*N*-acetylglucosamine (PNAG) saccharides are an important constituent of bacterial biofilms, such as those produced by *Staphylococcus aureus*. We have developed a simple two-step iterative method for the synthesis of β-(1→6)-glucosamine oligosaccharides that are structurally similar to PNAG. We illustrate the method with the formation of a pentasaccharide. The key building block is an orthogonally protected *N*-trifluoroacetamido thioglycoside donor that was added in succession to a glycosyl acceptor, enabling efficient glycosylation of the growing chain. In the second step of the iterative cycle, this building block is quantitatively

deprotected at the C-6-hydroxyl position, ready for the next saccharide addition. Building from an azido-functionalized GlcNAc monosaccharide acceptor, the pentasaccharide was synthesised in seven steps in an overall yield of 25%.

Keywords

N-Acetyl-D-glucosamine (GlcNAc); β-(1→6)-Glucosamine oligosaccharides; *Staphylococcus aureus*; Poly-*N*-acetylglucosamine (PNAG); Biofilm, Polysaccharide Intercellular Adhesin (PIA).

1. Introduction

Glucosamine units are often incorporated into or form a major constituent of polysaccharides that play a critical role in a variety of biological systems and processes.[1, 2] Of particular clinical significance is the role β-(1→6)-poly-*N*-acetyl-D-glucosamine (PNAG) plays in the virulence of bacterial biofilms produced by coagulase negative strains such as *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidimeridis*.[3-5] *S. aureus* in particular has manifested itself as a world-wide health problem, primarily due to the emergence of antibiotic resistant bacterial strains (e.g. MRSA), and this has sparked global interest in developing alternative therapies to antibiotics, such as a vaccine.[6-11] Approaches utilizing β-(1→6)-glucosamine polysaccharides conjugated with a carrier protein have successfully elicited protective anti-PNAG antibodies during *in vivo* studies.[12-14] This was demonstrated most recently by Maira-Litrán et al. who showed that the deactylated form of a PNAG analogue bound to another *S. aureus* antigen, clumping factor A, produced a bivalent vaccine that elicited protective antibodies in mice.[13]

In order to reproducibly generate such constructs it would be advantageous to have a reliable synthetic methodology for the preparation of oligosaccharides, rather than having to isolate and purify the complex carbohydrates from the bacterial specimen itself.[3, 15, 16] Despite over 50 years of research in this field, there are only a handful of reliable synthetic methodologies developed for the synthesis of β-(1→6)-glucosamine polysaccharides.[1, 12, 16-27] Perhaps the simplest method for generating such oligosaccharides is the technique of acid reversion, that has been reported for the synthesis of oligomers between two and six monosaccharide units in length.[17, 18] Despite the simplicity of using an unprotected sugar to rapidly generate the oligosaccharides, the method is inherently inefficient as it produces an uncontrolled mixture of short chain carbohydrates with consequent problems of separation and purification.

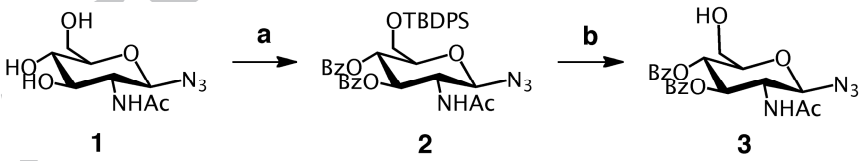
The alternative methods all require protecting group strategies for the production of β-(1→6)-glucosamine polysaccharides. Of these methodologies, most involve the use of activated glycosyl donors possessing the phthalimido (Phth) protecting group at the 2-amino-2-deoxy position.[16, 19-27] This was most recently demonstrated by Yudina et al. who successfully synthesised, via a convergent blockwise process, a nonasaccharide that had varying degrees of *N*-acetylation at the 2-amino-2-deoxy position of the final saccharides.[20] Although *N*-trifluoroacetyl glucosamine derivative have been used previously in other areas of carbohydrate synthesis,[1] no PNAG-derived oligosaccharide synthesis of this nature utilises solely this protecting group throughout its methodology. We selected this group for blocking the 2-amino-2-deoxy position during our synthesis because of its ease of attachment and subsequent deprotection (if required), as well as its ability to generate β-selective glycosidic linkages. In the interest of simplifying the synthetic methodology for the preparation of β-(1→6)-glucosamine

polysaccharides, we herein report a two-step iterative approach to a β-(1→6)-glucosamine pentasaccharide, using a selectively protected thioglycoside donor as the key building block.

2. Results and Discussion

The β-(1→6)-glucosamine oligosaccharides were built from the starting glycosyl acceptor **3**, which was an azido-functionalized GlcNAc monosaccharide acceptor, protected with benzoyl groups at the C-3 and C-4 hydroxyl positions. The azide group was placed at the reducing end of **3** to enable conjugation of the oligosaccharides to other structures if required. This could be achieved using cycloaddition chemistry to an alkyne moiety or via reduction of the azide followed by further conjugation of the resultant amine.

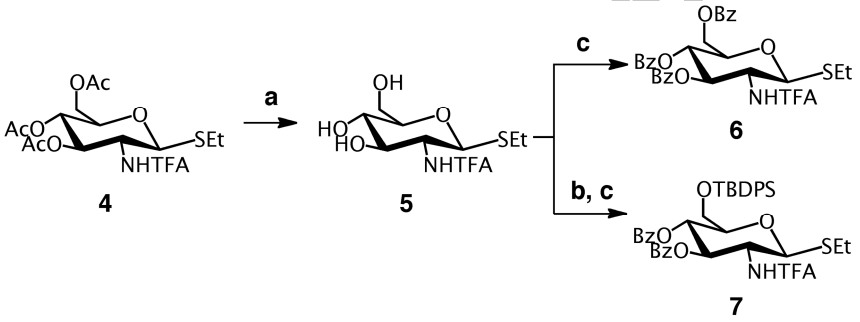
Surprisingly, although the existence of compound **3** was reported in 2001,[28] there is no experimental or characterisation data relating to its identity and purity. For this reason, we have included a synthetic route to compound **3**, which was achieved in two steps from the starting material 2-acetamido-2-deoxy-β-D-glucopyranosyl azide **1** (Figure 1).[29] The C-6 hydroxyl position of this glycosyl azide was selectively protected with the *tert*-butyldiphenylsilyl (TBDPS) protecting group, before benzoylation with benzoyl chloride to give **2** in 84% yield for the two-step process.



Scheme 1. Synthesis of the glycosyl acceptor **3**. (a) TBDPSCl, DMAP, pyridine; BzCl, DMAP, pyridine, CH_2Cl_2; (b) TBAF (1.0 M in THF), HOAc, THF.

Deprotection of intermediate **2** to give acceptor **3** was achieved quantitatively by treatment of the silyl-protected monosaccharide with tetra-*n*-butylammonium fluoride in the presence of acetic acid. Use of acetic acid in this reaction, giving a slightly acidic reaction medium, prevented formation of unwanted side products arising from migration of the neighbouring acyl groups.

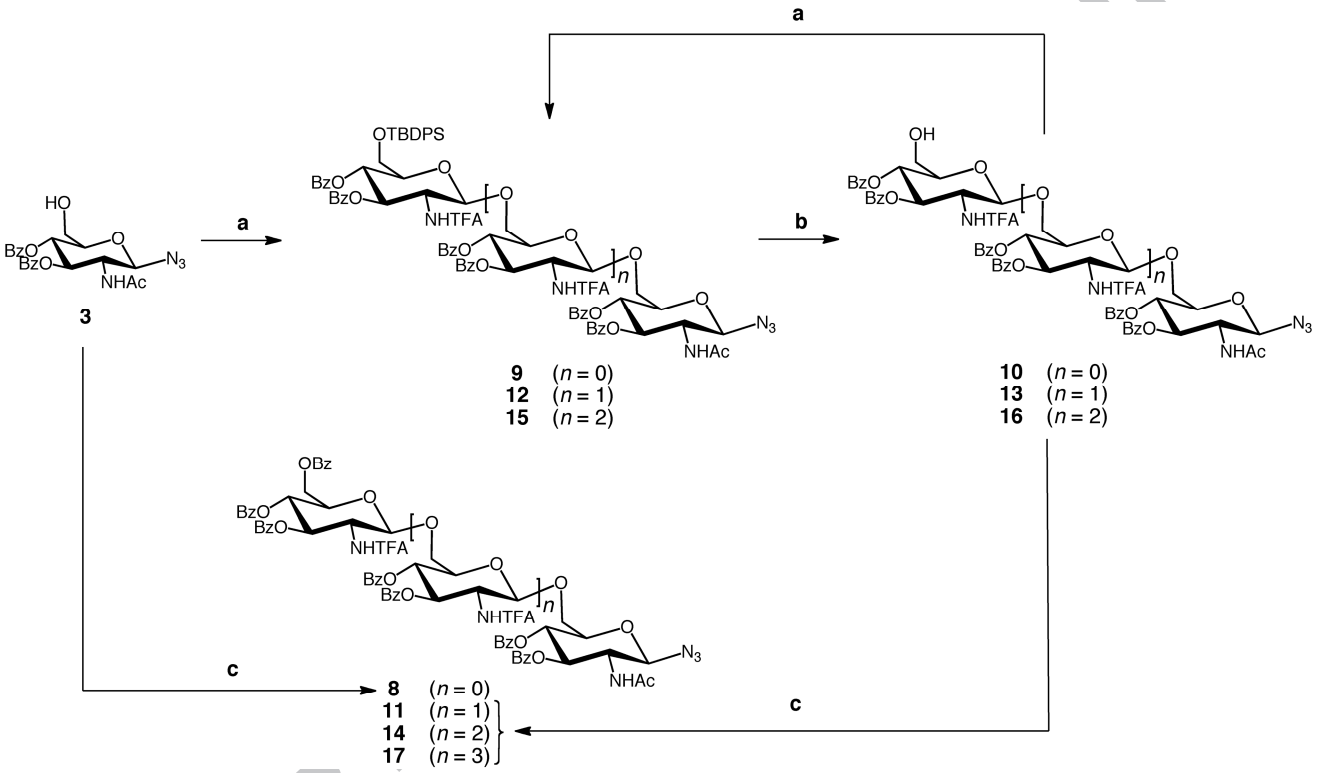
The syntheses of the glycosyl capping donor **6** and key building block **7** were completed in three steps from ethyl 2-trifluoroacetamido-3,4,6-tri-*O*-acetyl-1-thio-2-deoxy-β-D-glucopyranoside **4**.[30] Acetylated thioglycoside **4** was deprotected following the Zémplen de-*O*-acetylation procedure[31] to generate intermediate **5**. Treatment with benzoyl chloride furnished the per-benzoylated glycosyl donor **6** in 92% yield, whilst an alternate treatment with TBDPSCl followed by benzoyl chloride, resulted in the synthesis of the glycosyl donor **7** (87%).



Scheme 2. Preparation of glycosyl donors **6** and **7**. (a) NaOMe, MeOH; (b) TBDPSCl, DMAP, pyridine; (c) BzCl, DMAP, pyridine, CH_2Cl_2.

To illustrate the iterative glycosylation process, donor **7** was used for chain extension and donor **6** for capping the growing oligosaccharide built from acceptor **3**. The reason for terminating each oligosaccharide with donor **6** rather than the orthogonally protected donor **7** was to ensure that the number of different protecting groups on the final oligosaccharide was kept to an absolute minimum, as well as the number of synthetic steps required for protecting group

removal (if pertinent). The glycosylation process is depicted in Scheme 3 and a summary of the yields is given in Table 1. The disaccharide **8** was formed by reacting glycosyl acceptor **3** with donor **6**, in the presence of *N*-iodosuccinimide (NIS) and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf).

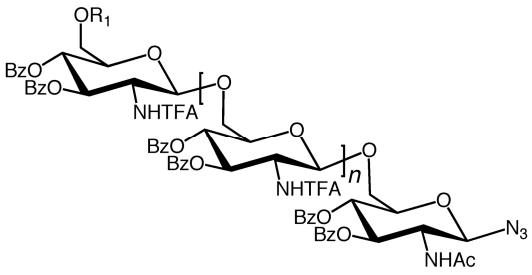


Scheme 3. Illustration of the two-step iterative cycle for the synthesis of β-(1→6)-glucosamine oligosaccharides. (a) **7**, NIS, TMSOTf, CH_2Cl_2; (b) TBAF, HOAc, THF; (c) **6**, NIS, TMSOTf, CH_2Cl_2.

To build the trisaccharide **11**, acceptor **3** was reacted with donor **7** under the same coupling conditions to give **9**. The TBDPS protecting group on **9** was then removed with tetra-*n*-butylammonium fluoride under acidic conditions to form **10**, which was then capped with donor **6**. It is important to note that at each stage of oligosaccharide growth, the deprotection step

occurred in a quantitative yield. Trisaccharide **11** was thus formed in a 71% yield over the three steps. To form the tetra- and pentasaccharides there were one and two deprotection/coupling cycles with **7** respectively, before capping with **6**. Importantly, the yields of the glycosylation reactions were all in the range of 65%-95%, which in some cases is significantly higher than those previously reported (Table 1).

Table 1.[a] Yields corresponding to the relevant β-(1→6)-glucosamine oligosaccharides.



Donor	Acceptor	Glycoside	R_1	*n*	Yield (%)[b]
7	**3**	**9**	TBDPS	0	83
7	**10**	**12**	TBDPS	1	65
7	**13**	**15**	TBDPS	2	70
6	**3**	**8**	Bz	0	86
6	**10**	**11**	Bz	1	95
6	**13**	**14**	Bz	2	77
6	**16**	**17**	Bz	3	68

[a] *n* = 0, disaccharide; *n* = 1, trisaccharide; *n* = 2, tetrasaccharide; *n* = 3, pentasaccharide. [b] yield of coupling reaction only.

The overall yield of 25% for the pentasaccharide was achieved in seven simple steps from the starting building units. While the overall yield is not significantly higher than some of the best previously published procedures,[19, 20] our method has the advantage that the synthesis of each of the starting monosaccharides is straightforward and short, being prepared in only 1-3 steps from the unprotected monosaccharides **1** and **5**, respectively. Although it was not necessary for our

research purposes to deprotect these oligosaccharides, this could be achieved by using basic conditions such as 0.1 M aqueous sodium hydroxide in acetone, which removes both the *O*-benzoyl and *N*-trifluoroacetyl protecting groups in the one pot.[1] This again emphasises the simplicity of the protecting group strategy employed in this synthetic methodology.

In summary, we have reported an efficient two-step iterative route for preparing β-(1→6)-glucosamine oligosaccharides using *N*-trifluoroacetamido protected thioglycoside donors. The utilization of the *N*-trifluoroacetyl substituted donor in this case provides a simple, much-needed alternative to the *N*-phthalimido-protected donors utilised in many methodologies to date.

3. Experimental Section

3.1 General Methods

Materials obtained commercially were reagent grade unless otherwise stated. Anhydrous solvents were distilled under nitrogen or argon prior to use, according to the established procedures.[32] Thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} plates (Merck, aluminium backed) and compounds were visualised either by treatment with anisidine phthalate dip followed by heating, or under a UV lamp. Melting points were measured on a Büchi Melting Point apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba NA 1500 Elemental Analyser. Optical rotations were measured at the sodium D line (589 nm) at the ambient temperature using a 1 mL quartz cell with a 10 cm path length, using a Jasco P-2000 polarimeter. UV-Visible absorption measurements were recorded on a Perkin Elmer Lambda 35 Spectrometer. NMR spectra were recorded on either a Bruker Avance 400 or 500 MHz spectrometer equipped with Topspin software. Proton (^{1}H) and carbon (^{13}C) assignments were made using DEPT, COSY, TOCSY (100 ms mixing time), HSQC and HMBC

experiments. Spectra of compounds run in deuterated chloroform ($CDCl_3$) or a mixture of $CDCl_3$ and deuterated methanol (CD_3OD) were referenced to residual chloroform at δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR. All reported coupling constants (*J* values) are three bond H-H couplings (^3J) unless otherwise stated. High-resolution mass spectrometry (HRMS) was performed on a Bruker microTOF-Q (quadrupole – Time of Flight) mass spectrometer with a Bruker ESI source, in positive electrospray ionization mode. Agilent ESI Tunemix was used as an external calibration for accurate mass measurements. Infrared spectra of neat samples were recorded on a Perkin-Elmer Spectrum 100 FT-IR Spectrometer with a diamond/ZnSe universal ATR attachment.

3.2 2-Acetamido-6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (**2**)

A solution of 2-acetamido-2-deoxy-β-D-glucopyranosyl azide **1**[29] (0.38 g, 1.55 mmol), TBDPSCl (0.44 mL, 1.70 mmol), DMAP (9.50 mg, 77.4 μmol), and anhydrous pyridine (10 mL) was stirred under nitrogen at room temperature for 3 d. The reaction mixture was cooled in an ice-water bath and then BzCl (0.54 mL, 4.65 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to the stirred solution. The reaction mixture was allowed to warm to room temperature before being stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (80 mL) followed by satd $NaHCO_3$ (80 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (60%) that included 0.25% Et_3N as the eluent. The main fraction was collected and the solvent removed to give **2** as a white solid: 0.90 g, 84 %; mp 83-85 °C; $[\alpha]_D^{23}$-74.6° (*c* 0.59, CH_2Cl_2); R_f 0.23 (100% Et_2O); λ_{abs} [CH_2Cl_2]/nm : 228 (log ε/$M^{-1}cm^{-1}$, 4.58), 264 (3.52), 271 (3.54), 283 (3.40); IR (neat); *ν*

3284 (NH), 2114 (N_3), 1727 and 1265 (ester), 1067 and 690 (C-O, C-F), 1025 (Si-O), 701 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 400 MHz) δ 7.96-7.94 (m, 2H, Ar-H), 7.87-7.85 (m, 2H, Ar-H), 7.72-7.70 (m, 2H, Ar-H), 7.58-7.49 (m, 4H, Ar-H), 7.42-7.28 (m, 8H, Ar-H), 7.20-7.17 (m, 2H, Ar-H), 5.83 (d, 1H, $J_{NH,2}$ 9.2 Hz, N**H**COCH$_3$), 5.75 (t, 1H, $J_{4,3}$ 9.6, $J_{4,5}$ 9.2 Hz, H-4), 5.61 (t, 1H, $J_{3,2}$ 10.4, $J_{3,4}$ 9.6 Hz, H-3), 4.77 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1), 4.25 (q, 1H, $J_{2,3}$ 10.4, $J_{2,1}$ 9.2, $J_{2,NH}$ 9.2 Hz, H-2), 3.89-3.80 (m, 3H, H-5, H-6), 1.90 (s, 3H, NHCOC**H$_3$**), 1.04 (s, 9H, C(C**H$_3$**)$_3$); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 170.5 (NH**C**OCH$_3$), 167.1 (O**C**OAr), 164.8 (O**C**OAr), 135.6 (Ar-CH), 135.5 (Ar-CH), 133.6 (Ar-CH), 133.3 (Ar-CH), 132.9 (Ar-C-), 132.8 (Ar-C-), 129.9 (Ar-CH), 129.69 (Ar-CH), 129.66 (Ar-CH), 129.6 (Ar-CH), 129.1 (Ar-C-), 128.6 (Ar-C-), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.7 (Ar-CH), 127.6 (Ar-CH), 88.6 (C-1), 77.0 (C-5), 73.2 (C-3), 68.4 (C-4), 62.2 (C-6), 54.5 (C-2), 26.6 (C(**C**H$_3$)$_3$), 23.2 (NHCO**C**H$_3$), 19.2 (**C**(CH$_3$)$_3$); Anal. Calcd for $C_{38}H_{40}N_4O_7Si$: C, 65.88; H, 5.82; N, 8.09. Found: C, 66.03; H, 5.87; N, 8.11.

3.3 2-Acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (**3**)

A solution of compound **2** (1.06 g, 1.53 mmol) in anhydrous THF (20 mL), HOAc (0.87 mL, 15.3 mmol) and TBAF (1.0 M in THF; 7.63 mL, 7.63 mmol) was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (200 mL) and washed with satd NH_4Cl solution (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography over silica gel using Et_2O (100%) as the eluent. The main fraction was collected and the solvent removed to give **3** as a white solid: 0.69 g, quant.; mp 72-74 °C; $[\alpha]_D^{21}$-124.3° (*c* 0.09, CH_2Cl_2); R_f 0.23 (100% Et_2O); λ_{abs} [CH_2Cl_2]/nm : 233 (log ε/$M^{-1}cm^{-1}$, 4.51), 275 (3.57), 283 (3.48), 315 (3.33); IR (neat); *v* 3281 (NH), 2115 (N_3), 1722 and 1248 (ester), 1068 and 690 (C-O, C-F), 707 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz) δ 7.93-7.90 (AA'BB'C, 4H, Ar-H), 7.52-7.48 (AA'BB'C, 2H, Ar-H), 7.37-

7.33 (AA'BB'C, 4H, Ar-H), 6.01 (d, 1H, $J_{NH,2}$ 8.9 Hz, N**H**COCH$_3$), 5.80 (t, 1H, $J_{3,2}$ 10.7, $J_{3,4}$ 9.5 Hz, H-3), 5.51 (t, 1H, $J_{4,5}$ 9.8, $J_{4,3}$ 9.7 Hz, H-4), 4.98 (d, 1H, $J_{1,2}$ 9.3 Hz, H-1), 4.18 (q, 1H, $J_{2,3}$ 10.6, $J_{2,1}$ 9.1, $J_{2,NH}$ 9.1 Hz, H-2), 3.90-3.85 (m, 2H, H-5, H-6$_a$), 3.74 (dd, 1H, $^2J_{6b,6a}$ 12.9, $J_{6b,5}$ 4.5 Hz, H-6$_b$), 1.89 (s, 3H, NHCOC**H$_3$**); ^{13}C NMR (CDCl$_3$; 125 MHz) δ 170.6 (NH**C**OCH$_3$), 166.7 (O**C**OAr), 165.9 (O**C**OAr), 133.73 (Ar-CH), 133.66 (Ar-CH), 129.8 (Ar-CH), 128.5 (Ar-CH, Ar-C-), 128.4 (Ar-C-), 88.7 (C-1), 76.6 (C-5), 72.4 (C-3), 69.0 (C-4), 61.2 (C-6), 54.5 (C-2), 23.2 (NHCO**C**H$_3$). HRMS: Calcd for $C_{22}H_{22}N_4NaO_7^+$ [M+ Na]$^+$ *m/z* = 477.1381. Found: 477.1373.

3.4 Ethyl 2-trifluoroacetamido-1-thio-2-deoxy-β-D-glucopyranoside (5)

A solution of ethyl 2-trifluoroacetamido-3,4,6-tri-*O*-acetyl-1-thio-2-deoxy-β-D-glucopyranoside **4**[30] (0.11 g, 0.26 mmol) in MeOH (2 mL) was treated with NaOMe (cat.; 2.0 mg of Na° in 1 mL of MeOH) and stirred at room temperature for 2 h. Amberlyst strong cation exchange resin [IR120 (H^+)] was added and stirring was continued for an additional 5 min. The reaction mixture was filtered, the solvent removed and the residue dried further under high vacuum to give **5** a yellow solid: 82.0 mg, quant.; IR (neat); *v* 3526 (OH), 3262 (NH), 1700 and 1161 cm^{-1} (ester); ^{1}H NMR (CD$_3$OD; 500 MHz): *δ* 4.32 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 3.85 (dd, 1H, $^2J_{6a,6b}$ 12.1, $J_{6a,5}$ 2.1 Hz, H-6$_a$), 3.67 (dd, 1H, $^2J_{6b,6a}$ 12.1, $J_{6b,5}$ 5.4 Hz, H-6$_a$), 3.30-3.23 (m, 3H, H-3, H-4, H-5), 2.81-2.69 (m, 2H, *J* 9.9 Hz, S-C**H$_2$**-CH$_3$), 2.61 (t, 1H, $J_{2,1}$ 9.9, $J_{2,3}$ 9.0 Hz, H-2), 1.29 (t, 3H, *J* 7.5 Hz, S-CH$_2$-C**H$_3$**); ^{13}C NMR (CD$_3$OD; 100 MHz): *δ* 160.2, 159.8 (NH**C**OCF$_3$), 119.7, 116.8 (NHCO**C**F$_3$), 87.5 (C-1), 82.2 (C-5), 79.4 (C-3), 71.8 (C-4), 63.0 (C-6), 57.7 (C-2), 25.1 (S-**C**H$_2$-CH$_3$), 15.5 (S-CH$_2$-**C**H$_3$); HRMS: Calcd for $C_{10}H_{16}F_3NNaO_5S^+$ [M+Na]$^+$ *m/z* = 342.0593. Found: 342.0607.

3.5 Ethyl 2-trifluoroacetamido-3,4,6-tri-*O*-benzoyl-1-thio-2-deoxy-β-D-glucopyranoside (6)

A solution of compound **5** (0.63g, 1.98 mmol), BzCl (1.04 mL, 3.00 mmol), DMAP (12.2 mg, 0.100 mmol), anhydrous pyridine (20 mL) and anhydrous CH_2Cl_2 (10 mL) was stirred under nitrogen at room temperature for 2 d. The reaction mixture was diluted with EtOAc (400 mL) and washed with water (100 mL) followed by satd $NaHCO_3$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel using a Et_2O:light petroleum mixture (40%) as the eluent. The main fraction was collected and the solvent removed to give **6** as a white solid: 1.17 g, 92%; mp 176-177 °C; $[\alpha]_D^{23}$-42.2° (*c* 0.36, CH_2Cl_2); R_f 0.31 (50% Et_2O/pet. spirit); λ_{abs} (CH_2Cl_2)/nm : 233 (log ε/$M^{-1}cm^{-1}$, 4.27), 275 (3.24), 284 (3.10); IR (neat); *v* 3255 (NH), 1734 and 1267 (ester), 706 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 8.00-7.98 (AA'BB'C, 2H, Ar-H), 7.92-7.90 (AA'BB'C, 2H, Ar-H), 7.86-7.84 (AA'BB'C, 2H, Ar-H), 7.55-7.50 (AA'BB'C, 2H, Ar-H), 7.45-7.41 (AA'BB'C, 1H, Ar-H), 7.39-7.34 (AA'BB'C, 4H, Ar-H), 7.29-7.26 (AA'BB'C, 2H, Ar-H), 7.20 (d, 1H, $J_{NH,2}$ 9.5 Hz, N**H**$COCF_3$), 5.87 (t, 1H, $J_{3,2}$ 10.2, $J_{3,4}$ 9.7 Hz, H-3), 5.68 (t, 1H, $J_{4,5}$ 9.8 Hz, $J_{4,3}$ 9.7 Hz, H-4), 4.90 (d, 1H, $J_{1,2}$ 10.3 Hz, H-1), 4.64 (dd, 1H, $^2J_{6a,6b}$ 12.3 $J_{6a,5}$ 3.0 Hz, H-6_a), 4.52-4.46 (m, 2H, H-2, H-6_b), 4.25 (ddd, 1H, $J_{5,4}$ 9.9, $J_{5,6b}$ 5.3, $J_{5,6a}$ 3.0 Hz, H-5), 2.76-2.65 (m, 2H, S-C**H$_2$**-CH_3), 1.21 (t, 3H, *J* 7.5, *J* 7.4 Hz, S-CH_2-C**H$_3$**); ^{13}C NMR ($CDCl_3$; 125 MHz): δ 167.3 (O**C**OAr), 166.1 (O**C**OAr), 165.1 (O**C**OAr), 157.6, 157.3 (NH**C**OCF_3), 134.0 (Ar-CH), 133.6 (Ar-CH), 133.2 (Ar-CH), 129.9 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 129.4 (Ar-C-), 128.60 (Ar-C-), 128.57 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-C-), 116.6, 114.3 (NHCO**C**F_3), 83.8 (C-1), 76.2 (C-5), 73.9 (C-3), 69.4 (C-4), 63.3 (C-6), 53.9 (C-2), 24.3 (S-**C**H_2-CH_3), 14.8 (S-CH_2-**C**H_3); Anal. Calcd for $C_{31}H_{28}F_3NO_8S$: C, 58.95; H, 4.47; N, 2.22; S, 5.08. Found: C, 58.83; H, 4.43; N, 2.21; S, 4.93.

3.6 Ethyl 2-trifluoroacetamido-6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzoyl-1-thio-2-deoxy-β-D-glucopyranoside (7)

A solution of compound **5** (3.49 g, 11.2 mmol), TBDPSCl (5.82 mL, 22.4 mmol), DMAP (68.4 mg, 0.560 mmol), and anhydrous pyridine (100 mL) was stirred under nitrogen at room temperature for 2 d. The reaction mixture was cooled in an ice-water bath and then BzCl (7.80 mL, 67.2 mmol) in anhydrous CH_2Cl_2 (100 mL) was added to the stirred solution. The reaction mixture was allowed to warm to room temperature before being stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (400 mL) and washed with water (100 mL) followed by satd $NaHCO_3$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography over silica gel using a Et_2O:light petroleum mixture (30%) that included 0.25% Et_3N as the eluent. The main fraction was collected and the solvent removed to give **7** as a white solid: 7.47 g, 87%; mp 77-79 °C; $[\alpha]_D^{23}$-63.8° (*c* 0.41, CH_2Cl_2); R_f 0.62 (50% Et_2O/pet. spirit); λ_{abs} (CH_2Cl_2)/nm : 230 (log ε/$M^{-1}cm^{-1}$, 4.50), 266 (3.42), 272 (3.42), 283 (3.23); IR (neat); *ν* 3307 (NH), 1723 and 1266 (ester), 1068 and 693 (C-O, C-F), 1027 (Si-O), 702 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): *δ* 7.94-7.92 (AA'BB'C, 2H, Ar-H), 7.84-7.82 (AA'BB'C, 2H, Ar-H), 7.74-7.72 (AA'BB'C, 2H, Ar-H), 7.59-7.57 (AA'BB'C, 2H, Ar-H), 7.54-7.51 (AA'BB'C, 1H, Ar-H), 7.48-7.44 (AA'BB'C, 1H, Ar-H), 7.42-7.27 (AA'BB'C, 8H, Ar-H), 7.22 (d, 1H, $J_{NH,2}$ 9.5 Hz, N**H**$COCF_3$), 7.19-7.16 (AA'BB'C, 2H, Ar-H), 5.82 (t, 1H, $J_{3,4}$ 10.0, $J_{3,2}$ 10.0 Hz, H-3), 5.74 (t, 1H, $J_{4,3}$ 9.5, $J_{4,5}$ 9.5 Hz, H-4), 4.80 (d, 1H, $J_{1,2}$ 10.0 Hz, H-1), 4.49 (q, 1H, $J_{2,1}$ 10.0, $J_{2,3}$ 10.0, $J_{2,NH}$ 9.5 Hz, H-2), 3.93 (dq, 1H, $J_{5,4}$ 9.5, $J_{5,6a}$ 3.5, $J_{5,6b}$ 2.0 Hz, H-5), 3.89-3.83 (m, 2H, H-6), 2.83-2.71 (m, 2H, S-C**H$_2$**-CH_3), 1.25 (t, 3H, S-CH_2-C**H$_3$**), 1.05 (s, 9H, C(C**H$_3$**)$_3$); ^{13}C NMR ($CDCl_3$; 100 MHz): *δ* 167.5 (O**C**OAr), 164.8 (O**C**OAr), 157.6, 157.2 (NH**C**$COCF_3$), 135.6

(Ar-CH), 135.5 (Ar-CH), 133.9 (Ar-CH), 133.4 (Ar-CH), 132.9 (Ar-CH), 132.8 (Ar-C-), 129.9 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 129.5 (Ar-CH), 129.1 (Ar-C-), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-C-), 127.63 (Ar-CH, Ar-C-), 127.57 (Ar-CH), 116.9, 114.1 (NHCO**C**F_3), 83.4 (C-1), 79.1 (C-5), 74.5 (C-3), 68.8 (C-4), 62.5 (C-6), 53.8 (C-2), 26.5 (C(**C**H_3)$_3$), 23.7 (S-**C**H_2-CH_3), 19.1 (**C**$(CH_3)_3$), 14.9 (S-CH_2-**C**H_3); Anal. Calcd for $C_{40}H_{42}F_3NO_7SSi$: C, 62.73; H, 5.53; N, 1.83; S, 4.19. Found: C, 62.71; H, 5.57; N, 1.81; S, 3.78.

3.7 6-*O*-(2-Trifluoroacetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (**8**)

A solution of glycosyl acceptor **3** (23.6 mg, 51.9 µmol), glycosyl donor **6** (32.8 mg, 51.9 µmol), NIS (17.5 mg, 77.9 µmol) and anhydrous CH_2Cl_2 (5 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (0.9 µL, 4.97 µmol) was added to the reaction mixture and stirring was continued for 24 h. Et_3N (4.0 µL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using a Et_2O:light petroleum mixture (90%) as the eluent. The main fraction was collected and the solvent removed to give **8** as a white solid: 29.7 mg, 86%; mp 141-143 °C (dec.); $[\alpha]_D^{24}$-36.1° (*c* 0.38, CH_2Cl_2); R_f 0.61 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 233 (log ε/$M^{-1}cm^{-1}$, 5.33), 275 (4.24), 283 (4.16); IR (neat); *v* 3337 (NH), 2117 (N_3), 1722 and 1264 (ester), 1067 and 690 (C-O, C-F), 706 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 7.95-7.90 (AA'BB'C, 6H, Ar-H), 7.85-7.82 (AA'BB'C, 4H, Ar-H), 7.73 (d, 1H, $J_{NH,2}$ 9.0 Hz, N**H**$COCF_3^{II}$), 7.50-7.42 (AA'BB'C, 4H, Ar-H), 7.40-7.26 (AA'BB'C, 9H, Ar-H), 7.25-7.20 (AA'BB'C, 2H, Ar-H), 6.10 (d, 1H, $J_{NH,2}$ 8.6 Hz, N**H**$COCH_3^{I}$), 5.93 (t, 1H, $J_{3,2}$ 10.4, $J_{3,4}$ 9.6 Hz, H-3^{I}), 5.76-5.71 (m, 2H, H-3^{II}, H-4^{II}), 5.46 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.7 Hz, H-4^{I}), 5.11 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1^{I}), 4.81 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{II}), 4.61 (q, 1H, $J_{2,3}$ 10.1, $J_{2,1}$ 8.7, $J_{2,NH}$ 8.7 Hz, H-2^{II}), 4.56 (dd, 1H, $J_{6a,6b}$ 12.3, $J_{6a,5}$ 3.1 Hz,

H-6_a^{II}), 4.42 (dd, 1H, $^2J_{6b,6a}$ 12.3, $J_{6b,5}$ 4.9 Hz, H-6_b^{II}), 4.24 (dd, 1H, $J_{6a,6b}$ 11.8, $J_{6a,5}$ 1.5 Hz, H-6_a^{I}), 4.10-4.07 (br m, 1H, H-5^{II}), 4.01 (dq, 1H, $J_{5,4}$ 10.0, $J_{5,6b}$ 5.0, $J_{5,6a}$ 1.7 Hz, H-5^{I}), 3.97 (q, 1H, $J_{2,3}$ 10.3, $J_{2,1}$ 9.4, $J_{2,NH}$ 9.1 Hz, H-2^{I}), 3.63 (dd, 1H, $^2J_{6b,6a}$ 11.9, $J_{6b,5}$ 5.2 Hz, H-6_b^{I}), 1.82 (s, 3H, NHCOC$\mathbf{H_3^I}$); ^{13}C NMR ($CDCl_3$; 125 MHz): δ 170.8 (NH**C**OCH_3^I) 166.5 (O**C**OAr), 166.3 (O**C**OAr), 166.1 (O**C**OAr), 165.7 (O**C**OAr), 165.0 (O**C**OAr), 157.9, 157.6 (NH**C**OCF_3^{II}), 133.8 (Ar-CH), 133.6 (Ar-CH), 133.5 (Ar-CH), 133.4 (Ar-CH), 133.1 (Ar-CH), 129.85 (Ar-CH), 129.83 (Ar-CH), 129.80 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 129.3 (Ar-C-), 128.7 (Ar-C-), 128.51 (Ar-C-), 128.48 (Ar-CH), 128.44 (Ar-C-), 128.42 (Ar-CH), 128.40 (Ar-CH), 128.34 (Ar-CH), 128.27 (Ar-CH), 128.1 (Ar-C-), 116.9, 114.6 (NHCO**C**F_3^{II}), 101.6 (C-1^{II}), 88.3 (C-1^{I}), 75.4 (C-5^{I}), 72.8 (C-3^{II}), 72.3 (C-5^{II}), 72.1 (C-3^{I}), 69.2 (C-4^{II}), 69.1 (C-4^{I}), 68.4 (C-6^{I}), 62.8 (C-6^{II}), 54.9 (C-2^{I}), 54.8 (C-2^{II}), 23.1 (NHCO**C**H_3^I); Anal. Calcd for $C_{51}H_{44}F_3N_5O_{15}Si$: C, 59.82; H, 4.33; N, 6.84. Found: C, 59.85; H, 4.42; N, 6.75.

3.8 6-*O*-(2-Trifluoroacetamido-6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (**9**)

A solution of glycosyl acceptor **3** (1.16 g, 2.56 mmol), glycosyl donor **7** (2.35 g, 3.07 mmol), NIS (0.83 g, 0.31 mmol) and anhydrous CH_2Cl_2 (20 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (46.2 µL, 0.260 mmol) was added to the reaction mixture and stirring was continued for 25 h. Et_3N (17.0 µL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (50%) that included 0.25% Et_3N as the eluent. The main fraction was collected and the solvent removed to give **9** as a white solid: 2.46 g, 83%; mp 94-96 °C; $[\alpha]_D^{24}$-44.1° (*c* 0.24, CH_2Cl_2); R_f 0.77 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 232 (log ε/$M^{-1}cm^{-1}$, 4.80), 272 (3.95), 283 (3.86); IR (neat); *v* 3332 (NH), 2118 (N_3), 1724 and 1268 (ester), 1068

and 690 (C-O, C-F), 1025 (Si-O), 705 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 7.97-7.92 (AA'BB'C, 4H, Ar-H), 7.90-7.84 (AA'BB'C, 4H, Ar-H), 7.66-7.64 (AA'BB'C, 2H, Ar-H), 7.57-7.49 (AA'BB'C, 6H, Ar-H), 7.42-7.34 (m, 10H, N**H**$COCF_3^{II}$, Ar-H), 7.30-7.25 (AA'BB'C, 3H, Ar-H), 7.18-7.15 (AA'BB'C, 2H, Ar-H), 5.85 (t, 1H, $J_{3,4}$ 9.5, $J_{3,2}$ 9.4 Hz, H-3^I), 5.68 (d, 1H, $J_{NH,2}$ 8.3 Hz, N**H**$COCH_3^I$), 5.62 (t, 1H, $J_{4,3}$ 9.6, $J_{4,5}$ 9.6 Hz, H-4^{II}), 5.55 (t, 1H, $J_{3,2}$ 10.4, $J_{3,4}$ 9.6 Hz, H-3^{II}), 5.48 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.6 Hz, H-4^I), 5.12 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1^I), 4.60 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{II}), 4.41 (q, 1H, $J_{2,3}$ 10.4, $J_{2,NH}$ 8.7, $J_{2,1}$ 8.7 Hz, H-2^{II}), 4.20 (dd, 1H, $^2J_{6a,6b}$ 12.0, $J_{6a,5}$ 1.9 Hz, H-6_a^I), 3.94 (dq, 1H, $J_{5,4}$ 10.0, $J_{5\,6b}$ 4.5, $J_{5,6a}$ 1.9 Hz, H-5^I), 3.85 (q, 1H, $J_{2,3}$ 10.7, $J_{2,1}$ 8.9, $J_{2,NH}$ 8.6 Hz, H-2^I), 3.82-3.77 (m, 2H, H-6^{II}), 3.72 (dq, 1H, $J_{5,4}$ 9.6, $J_{5,6b}$ 4.6, $J_{5,6a}$ 2.4 Hz, H-5^{II}), 3.49 (dd, 1H, $^2J_{6b,6a}$ 12.1, $J_{6b,5}$ 4.6 Hz, H-6_b^I), 1.92 (s, 3H, NHCOC$\mathbf{H_3^I}$), 0.99 (s, 9H, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 170.9 (NH**C**OCH_3^I), 166.8 (O**C**OAr), 166.4 (O**C**OAr), 165.7 (O**C**OAr), 164.9 (O**C**OAr), 157.7, 157.3 (NH**C**OCF_3^I), 135.6 (Ar-CH), 135.4 (Ar-CH), 133.9 (Ar-CH), 133.6 (Ar-CH), 133.5 (Ar-CH), 133.3 (Ar-CH), 133.0 (Ar-CH), 132.8 (Ar-CH), 129.9 (Ar-CH), 129.74 (Ar-CH), 129.65 (Ar-CH), 129.55 (Ar-CH), 129.0 (Ar-C-), 128.53 (Ar-CH, Ar-C-), 128.48 (Ar-CH, Ar-C-), 128.45 (Ar-CH), 128.40 (Ar-CH), 128.32 (Ar-CH), 128.24 (Ar-C-), 127.56 (Ar-CH), 127.53 (Ar-CH), 117.2, 114.3 (NHCO**C**F_3^{II}), 101.5 (C-1^{II}), 88.2 (C-1^I), 75.4 (C-5^{II}), 75.3 (C-5^I), 73.3 (C-3^{II}), 72.2 (C-3^I), 69.1 (C-4^I), 68.8 (C-4^{II}), 67.9 (C-6^I), 62.6 (C-6^{II}), 55.0 (C-2^I), 54.9 (C-2^{II}), 26.6 (C(**C**$H_3)_3$), 23.1 (NHCO**C**H_3^I), 19.1 (**C**$(CH_3)_3$); HRMS: Calcd for $C_{60}H_{58}F_3N_5NaO_{14}Si^+$ $[M+Na]^+$ *m/z* = 1180.3594. Found: 1180.3551.

3.9 6-*O*-(2-Trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (10)

A solution of disaccharide **9** (0.43 g, 0.37 mmol) in anhydrous THF (5 mL), HOAc (0.430 mL, 7.45 mmol) and TBAF (3.60 mL, 3.60 mmol) was stirred at room temperature for 19 h. The reaction mixture was diluted with Et_2O (300 mL) and washed with satd NH_4Cl solution (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography over silica gel using Et_2O (100%) as the eluent. The main fraction was collected and the solvent removed to give **10** as a white solid: 0.34 g, quant.; mp 136-138 °C; $[\alpha]_D^{24}$+1.2° (*c* 0.59, CH_2Cl_2); R_f 0.19 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 234 (log ε/$M^{-1}cm^{-1}$, 4.70), 276 (3.68), 283 (3.61), 324 (3.22); IR (neat); *v* 3336 (NH), 2117 (N_3), 1721 and 1261 (ester), 1068 and 690 (C-O, C-F), 707 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 7.95-7.88 (AA'BB'C, 8H, Ar-H), 7.56-7.46 (m, 5H, N**H**$COCF_3^{II}$, Ar-H), 7.40-7.33 (AA'BB'C, 8H, Ar-H), 5.92 (d, 1H, $J_{NH,2}$ 8.5 Hz, N**H**$COCH_3^{I}$), 5.84 (t, 1H, $J_{3,2}$ 9.5, $J_{3,4}$ 9.5 Hz, H-3^{I}), 5.70 (t, 1H, $J_{3,2}$ 9.7, $J_{3,4}$ 9.6 Hz, H-3^{II}), 5.51 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.6 Hz, H-4^{I}), 5.41 (t, 1H, $J_{4,5}$ 9.6, $J_{4,3}$ 9.6 Hz, H-4^{II}), 5.08 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1^{I}), 4.75 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{II}), 4.36 (q, 1H, $J_{2,NH}$ 10.8, $J_{2,3}$ 8.7, $J_{2,1}$ 8.6 Hz, H-2^{II}), 4.25 (dd, 1H, $^2J_{6a,6b}$ 11.5, $J_{6a,5}$ 2.3 Hz, H-6_a^{I}), 4.02-3.92 (m, 2H, H-2^{I}, H-5^{I}), 3.78 (dd, 1H, $^2J_{6a,6b}$ 12.6, $J_{6a,5}$ 1.8 Hz, H-6_a^{II}), 3.72-3.62 (m, 3H, H-5^{II}, H-6_b^{I}, H-6_b^{II}), 1.89 (s, 3H, NHCOC$\mathbf{H_3^I}$); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 170.7 (NH**C**OCH_3), 166.6 (O**C**OAr), 166.4 (O**C**OAr), 166.0 (O**C**OAr), 165.8 (O**C**OAr), 157.7, 157.3 (NH**C**OCF_3), 134.0 (Ar-CH), 133.73 (Ar-CH), 133.69 (Ar-CH), 133.62 (Ar-CH), 130.0 (Ar-CH), 129.89 (Ar-CH), 129.86 (Ar-CH), 129.79 (Ar-CH), 128.7 (Ar-CH), 128.51 (Ar-CH, Ar-C-), 128.48 (Ar-CH, Ar-C-), 128.44 (Ar-CH), 128.3 (Ar-C-), 117.1, 114.3 (NHCO**C**F_3), 101.2 (C-1^{II}), 88.3 (C-1^{I}), 75.1 (C-5^{I}), 74.8 (C-5^{II}), 72.6 (C-3^{II}), 72.0 (C-3^{I}), 69.2 (C-4^{I}), 69.0 (C-4^{II}), 67.9 (C-6^{I}), 61.1 (C-6^{II}), 55.0 (C-2^{I}), 54.7 (C-2^{II}), 23.3 (NHCO**C**H_3); HRMS: Calcd for $C_{44}H_{40}F_3N_5NaO_{14}^+$ $[M + Na]^+$ *m/z* = 942.2416. Found: 942.2386.

3.10 6-*O*-[6-*O*-(2-Trifluoroacetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (11)

A solution of glycosyl acceptor **10** (0.63 g, 0.68 mmol), glycosyl donor **6** (0.48 g, 0.75 mmol), NIS (0.250 g, 1.13 mmol) and anhydrous CH_2Cl_2 (10 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (12.4 µL, 0.068 mmol) was added to the reaction mixture and stirring was continued for 19 h. Et_3N (70.0 µL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (80%) as the eluent. The main fraction was collected and the solvent removed to give **11** as a white solid: 0.76 g, 95%; mp 150-152 °C (dec.); $[\alpha]_D^{24}$+39.7° (*c* 0.46, CH_2Cl_2); R_f 0.31 (80% Et_2O/pet. spirit); λ_{abs} (CH_2Cl_2)/nm : 234 (log ε/$M^{-1}cm^{-1}$, 4.93), 275 (3.88), 284 (3.78); IR (neat); *ν* 3323 (NH), 2118 (N_3), 1720 and 1268 (ester), 1065 and 690 (C-O, C-F), 707 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): *δ* 7.94-7.83 (m, 15H, N**H**$COCF_3^{II}$, Ar-H), 7.52-7.43 (AA'BB'C, 7H, Ar-H), 7.36-7.26 (m, 15H, N**H**$COCF_3^{II}$, Ar-H), 6.09 (d, 1H, $J_{NH,2}$ 8.7, N**H**$COCH_3^{I}$), 5.88 (t, 1H, $J_{3,2}$ 10.3, $J_{3,4}$ 9.8 Hz, H-3^{I}), 5.78 (t, 1H, $J_{3,4}$ 10.4, $J_{3,2}$ 9.5 Hz, H-3^{III}), 5.73-5.69 (m, 2H, H-3^{II}, H-4^{III}), 5.46 (t, 1H, $J_{4,3}$ 9.7, $J_{4,5}$ 9.7 Hz, H-4^{I}), 5.38 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.6 Hz, H-4^{II}), 5.08 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1^{I}), 4.80 (d, 1H, $J_{1,2}$ 8.3 Hz, H-1^{III}), 4.74 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{II}), 4.56-4.51 (m, 2H, H-2^{III}, H-6_a^{III}), 4.42 (dd, 1H, $^2J_{6b,6a}$ 12.3, $J_{6b,5}$ 5.3 Hz, H-6_a^{III}), 4.26 (q, 1H, $J_{2,3}$ 10.6, $J_{2,NH}$ 8.9, $J_{2,1}$ 8.6 Hz, H-2^{II}), 4.14-4.04 (m, 4H, H-5^{I}, H-5^{III}, H-6_a^{I}, H-6_a^{II}), 4.02 (q, 1H, $J_{2,3}$ 10.3, $J_{2,1}$ 9.2, $J_{2,NH}$ 9.1 Hz, H-2^{I}), 3.89 (ddd, 1H, $J_{5,4}$ 9.9, $J_{5,6b}$ 5.8, $J_{5,6a}$ 1.7 Hz, H-5^{II}), 3.72 (dd, 1H, $^2J_{6b,6a}$ 12.2, $J_{6b,5}$ 5.4 Hz, H-6_b^{I}), 3.65 (dd, 1H, $^2J_{6b,6a}$ 11.9, $J_{6b,5}$ 5.8 Hz, H-6_b^{II}), 1.84 (s, 3H, NHCOC**H$_3^{I}$**); ^{13}C NMR ($CDCl_3$; 125 MHz): *δ* 170.9 (NH**C**OCH_3), 166.6 (O**C**OAr), 166.4 (O**C**OAr), 166.3 (O**C**OAr), 166.1 (O**C**OAr), 166.0 (O**C**OAr), 165.6 (O**C**OAr),

165.1 (O**C**OAr), 157.88, 157.64, 157.59, 157.34, (NH**C**OCF$_3^{II}$, NH**C**OCF$_3^{III}$), 133.85 (Ar-CH), 133.77 (Ar-CH), 133.57 (Ar-CH), 133.55 (Ar-CH), 133.53 (Ar-CH), 133.46 (Ar-CH), 133.21 (Ar-CH), 129.91 (Ar-CH), 129.85 (Ar-CH), 129.81 (Ar-CH), 129.73 (Ar-CH), 129.67 (Ar-CH), 129.3 (Ar-C-), 128.68 (Ar-C-), 128.56 (Ar-CH, Ar-C-), 128.49 (Ar-CH, Ar-C-), 128.47 (Ar-CH), 128.42 (Ar-CH, Ar-C-), 128.37 (Ar-CH), 128.2 (Ar-C-), 116.84, 116.78, 114.55, 114.49, (NHCO**C**F$_3^{II}$, NHCO**C**F$_3^{III}$), 101.6 (C-1^{III}), 101.2 (C-1^{II}), 88.3 (C-1^{I}), 75.2 (C-5^{I}), 73.5 (C-5^{II}), 72.7 (C-3^{III}), 72.42 (C-3^{II}), 72.37 (C-5^{III}), 72.2 (C-3^{I}), 69.6 (C-4^{I}), 69.4 (C-4^{III}), 69.3 (C-4^{II}), 69.0 (C-6^{II}), 68.8 (C-6^{I}), 63.0 (C-6^{III}), 55.0 (C-2^{II}, C-2^{III}), 54.8 (C-2^{I}), 23.1 (NHCO**C**H$_3$); Anal. Calcd for $C_{73}H_{62}F_6N_6O_{22}$: C, 58.87; H, 4.20; N, 5.64. Found: C, 58.66; H, 4.32; N, 5.46.

3.11 6-*O*-[6-*O*-(2-Trifluoroacetamido-6-*O*-*tert*-butyldiphenylsilyl 3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (12)

A solution of glycosyl acceptor **10** (1.02 g, 1.11 mmol), glycosyl donor **7** (1.02 g, 1.33 mmol), NIS (0.45 g, 2.0 mmol) and anhydrous CH_2Cl_2 (15 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (20.0 μL, 0.11 mmol) was added to the reaction mixture and stirring was continued for 19 h. Et_3N (0.11 mL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (75%) that included 0.25% Et_3N as the eluent. The main fraction was collected and the solvent removed to give **12** as a white solid: 1.16 g, 65%; mp 138-140 °C (dec.); $[\alpha]_D^{24}$+26.7° (*c* 0.49, CH_2Cl_2); R_f 0.89 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 234 (log ε/$M^{-1}cm^{-1}$, 4.87), 274 (3.85), 283 (3.76); IR (neat); *v* 3330 (NH), 2118 (N_3), 1724 and 1270 (ester), 1067 and 690 (C-O, C-F), 1025 (Si-O), 706 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 7.95-7.87 (AA'BB'C, 10H, Ar-H), 7.84-7.82 (AA'BB'C, 2H, Ar-H), 7.59-5.57 (AA'BB'C, 2H,

Ar-H), 7.55-7.46 (m, 9H, N**H**COCF$_3^{III}$, Ar-H), 7.39-7.31 (AA'BB'C, 12H, Ar-H), 7.29 (d, 1H, $J_{NH,2}$ 9.0 Hz, N**H**COCF$_3^{II}$), 7.26-7.18 (AA'BB'C, 4H, Ar-H), 7.14-7.11 (AA'BB'C, 2H, Ar-H), 5.90-5.84 (m, 2H, N**H**COCH$_3^{I}$, H-3^{I}), 5.69 (t, 1H, $J_{3,2}$ 9.5, $J_{3,4}$ 9.5 Hz, H-3^{II}), 5.64-5.58 (m, 2H, H-3^{III}, H-4^{III}), 5.48 (t, 1H, $J_{4,5}$ 10.0, $J_{4,3}$ 9.5 Hz, H-4^{I}), 5.43 (t, 1H, $J_{4,5}$ 9.5, $J_{4,3}$ 9.5 Hz, H-4^{II}), 5.10 (d, 1H, $J_{1,2}$ 9.0 Hz, H-1^{I}), 4.72 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1^{II}), 4.64 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{III}), 4.40 (q, 1H, $J_{2,3}$ 9.5, $J_{2,NH}$ 9.0, $J_{2,1}$ 9.0 Hz, H-2^{III}), 4.28 (q, 1H, $J_{2,3}$ 11.0, $J_{2,NH}$ 8.5, $J_{2,1}$ 8.5 Hz, H-2^{II}), 4.21 (dd, 1H, $J_{6b,6a}$ 11.5, $J_{6b,5}$ 1.5 Hz, H-6$_b^{I}$), 4.12 (dd, 1H, $J_{6b,6a}$ 11.5, $J_{6b,5}$ 1.5 Hz, H-6$_b^{II}$), 4.04 (ddd, 1H, $J_{5,4}$ 10.0, $J_{5,6a}$ 4.5, $J_{5,6b}$ 2.0 Hz, H-5^{I}), 3.95 (q, 1H, $J_{2,NH}$ 9.5, $J_{2,1}$ 9.0, $J_{2,3}$ 9.0 Hz, H-2^{I}), 3.88 (ddd, 1H, $J_{5,4}$ 10.0, $J_{5,6a}$ 5.5, $J_{5,6b}$ 1.5 Hz, H-5^{II}), 3.80-3.77 (m, 1H, H-6^{III}), 3.75-3.70 (m, 1H, H-5^{III}), 3.66 (dd, 1H, $^2J_{6a,6b}$ 12.0, $J_{6a,5}$ 4.5 Hz, H-6$_a^{I}$), 3.54 (dd, 1H, $^2J_{6a,6b}$ 11.5, $J_{6a,5}$ 5.5 Hz, H-6$_a^{II}$), 1.88 (s, 3H, NHCOC**H$_3^{I}$**), 0.95 (s, 9H, C(C**H$_3$**)$_3$); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 170.8 (NH**C**OCH$_3^{I}$), 166.8 (O**C**OAr), 166.4 (2 x O**C**OAr), 166.0 (O**C**OAr), 165.7 (O**C**OAr), 164.9 (O**C**OAr), 157.7, 157.6, 157.30, 157.26 (NH**C**OCF$_3^{II}$, NH**C**OCF$_3^{III}$), 135.5 (Ar-CH), 135.4 (Ar-CH), 133.92 (Ar-CH), 133.89 (Ar-CH), 133.60 (Ar-CH), 133.56 (Ar-CH), 133.51 (Ar-CH), 133.3 (Ar-CH), 132.9 (Ar-CH), 132.8 (Ar-CH), 130.0 (Ar-CH), 129.81 (Ar-C-), 129.79 (Ar-CH), 129.68 (Ar-CH, Ar-C-), 129.63 (Ar-CH), 129.57 (Ar-CH), 129.0 (Ar-CH), 128.6 (Ar-CH, Ar-C-), 128.53 (Ar-CH), 128.48 (Ar-CH), 128.4 (Ar-CH, Ar-C-), 128.36 (Ar-CH), 128.34 (Ar-CH), 128.30 (Ar-C-), 128.26 (Ar-C-), 127.5 (Ar-CH), 117.2, 117.1, 114.30, 114.26 (NHCO**C**F$_3^{II}$, NHCO**C**F$_3^{III}$), 101.5 (C-1^{III}), 101.2 (C-1^{II}), 88.3 (C-1^{I}), 75.33 (C-5^{III}), 75.25 (C-5^{I}), 73.5 (C-5^{II}), 73.2 (C-3^{III}), 72.6 (C-3^{II}), 72.1 (C-3^{I}), 69.3 (C-4^{I}), 69.2 (C-4^{II}), 68.8 (C-4^{III}), 68.3 (C-6^{I}, C-6^{II}), 62.7 (C-6^{III}), 55.0 (C-2^{III}), 54.94 (C-2^{I}), 54.87 (C-2^{II}), 26.5 (C(**C**H$_3$)$_3$), 23.2 (NHCO**C**H$_3^{I}$), 19.1 (**C**(CH$_3$)$_3$); Anal. Calcd for $C_{82}H_{76}F_6N_6O_{21}Si$: C, 60.66; H, 4.72; N, 5.18. Found: C, 60.96; H, 5.14; N, 4.89.

3.12 6-*O*-[6-*O*-(2-Trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (13)

A solution of trisaccharide **12** (93.2 mg, 0.060 mmol) in anhydrous THF (3 mL), HOAc (65.7 μL, 1.15 mmol) and TBAF (0.57 mL, 0.57 mmol) was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (200 mL) and washed with satd NH_4Cl solution (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (90%) as the eluent. The main fraction was collected and the solvent removed to give **13** as a white solid: 79.5 mg, quant.; mp 151-153 °C (dec.); $[\alpha]_D^{23}$-5.7° (*c* 0.69, CH_2Cl_2); R_f 0.42 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 234 (log ε/$M^{-1}cm^{-1}$, 4.97), 276 (3.91), 284 (3.81); IR (neat); *v* 3336 (NH), 2118 (N_3), 1724 and 1272 (ester), 1068 and 690 (C-O, C-F), 708 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): *δ* 7.94-7.88 (AA'BB'C, 12H, Ar-H), 7.84 (br d, 1H, N**H**$COCF_3^{III}$), 7.54-7.46 (AA'BB'C, 7H, Ar-H), 7.38-7.30 (m, 12H, N**H**$COCF_3^{II}$, Ar-H), 6.31 (br d, 1H, N**H**$COCH_3^{I}$), 5.86-5.82 (m, 2H, H-3^{I}, H-3^{II}), 5.77 (t, 1H, $J_{3,4}$ 9.5, $J_{3,2}$ 9.5 Hz, H-3^{III}), 5.49 (br t, 2H, H-4^{I}, H-4^{II}), 5.34 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.6 Hz, H-4^{III}), 5.07 (d, 1H, $J_{1,2}$ 9.1 Hz, H-1^{I}), 4.87 (d, 1H, $J_{1,2}$ 8.3 Hz, H-1^{II}), 4.75 (d, 1H, $J_{1,2}$ 8.3 Hz, H-1^{III}), 4.33 (q, 1H, $J_{2,3}$ 10.5, $J_{2,NH}$ 8.7, $J_{2,1}$ 8.6 Hz, H-2^{III}), 4.22-4.05 (m, 5H, H-2^{I}, H-2^{II}, H-5^{I}, H-6_a^{I}, H-6_a^{II}), 3.89-3.86 (br m, 1H, H-5^{II}), 3.79 (br d, 1H, $J_{6a,6b}$ 12.5 Hz, H-6_a^{III}), 3.75-3.68 (m, 2H, H-5^{III}, H-6_b^{I}), 3.65 (dd, 1H, $^2J_{6b,6a}$ 11.5, $J_{6b,5}$ 3.5 Hz, H-6_b^{II}), 3.60 (dd, 1H, $^2J_{6b,6a}$ 12.5, $J_{6b,5}$ 4.5 Hz, H-6_b^{III}), 1.86 (s, 3H, NHCOC**H$_3^{I}$**); ^{13}C NMR ($CDCl_3$; 125 MHz): *δ* 171.1 (NH**C**OCH_3^{I}), 166.52 (O**C**OAr), 166.45 (O**C**OAr), 166.3 (O**C**OAr), 166.0 (2 x O**C**OAr), 165.8 (O**C**OAr), 157.9, 157.7, 157.6, 157.4 (NH**C**OCF_3^{II}, NH**C**OCF_3^{III}), 133.9 (Ar-CH), 133.8 (Ar-CH), 133.7 (Ar-CH), 133.6 (Ar-CH), 133.5 (Ar-CH),

129.94 (Ar-CH), 129.86 (Ar-CH, Ar-C-), 129.83 (Ar-CH), 129.79 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH, Ar-C-), 128.42 (Ar-CH), 128.37 (Ar-C-), 116.82, 116.78, 114.53, 114.49 (NHCO**C**F_3^{II}, NHCO**C**F_3^{III}), 101.09 (C-1^{III}), 101.02 (C-1^{II}), 88.3 (C-1^{I}), 75.4 (C-5^{I}), 74.8 (C-5^{III}), 73.0 (C-5^{II}), 72.6 (C-3^{III}), 72.4 (C-3^{I}), 72.1 (C-3^{II}), 69.6 (C-4^{I}), 69.4 (C-4^{II}), 69.3 (C-4^{III}), 68.9 (C-6^{I}), 68.3 (C-6^{II}), 61.1 (C-6^{III}), 55.4 (C-2^{II}), 54.8 C-2^{III}), 54.7 (C-2^{I}), 23.0 (NHCO**C**H_3^{I}); HRMS: Calcd for $C_{66}H_{58}F_6N_6NaO_{21}^+$ $[M + Na]^+$ *m/z* = 1407.3451. Found: 1407.3448.

3.13 6-*O*-[6-*O*-(6-*O*-[2-Trifluoroacetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (14)

A solution of glycosyl acceptor **13** (0.56 g, 0.40 mmol), glycosyl donor **6** (0.28 g, 0.44 mmol), NIS (0.15 g, 0.66 mmol) and anhydrous CH_2Cl_2 (10 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (8.0 µL, 0.04 mmol) was added to the reaction mixture and stirring was continued for 23 h. Et_3N (37.0 µL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (85%). The main fraction was collected and the solvent removed to give **14** as a white solid: 0.60 g, 77%; mp 160-162 °C; $[\alpha]_D^{24}$-43.2° (*c* 1.03, CH_2Cl_2); R_f 0.34 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 233 (log ε/$M^{-1}cm^{-1}$, 5.09), 275 (4.04), 284 (3.96); IR (neat); *ν* 3329 (NH), 2118 (N_3), 1720 and 1269 (ester), 1067 and 690 (C-O, C-F), 708 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): *δ* 8.18 (d, 1H, $J_{NH,2}$ 8.5 Hz, N**H**COCF_3^{II}), 8.11-8.01 (AA'BB'C, 12H, Ar-H), 7.98 (d, 1H, $J_{NH,2}$ 9.0 Hz, N**H**COCF_3^{IV}), 7.95-7.94 (AA'BB'C, 2H, Ar-H), 7.91-7.89 (AA'BB'C, 2H, Ar-H), 7.67-7.65 (AA'BB'C, 2H, Ar-H), 7.63-7.60 (AA'BB'C, 1H, Ar-H), 7.56-7.53 (AA'BB'C, 2H, Ar-H), 7.50-7.40 (AA'BB'C, 10H, Ar-H), 7.38-7.36 (AA'BB'C, 2H, Ar-H),

7.32-7.28 (AA'BB'C, 8H, Ar-H), 7.25-7.22 (AA'BB'C, 2H, Ar-H), 7.19 (d, 1H, $J_{NH,2}$ 9.5 Hz, N**H**COCH$_3^{I}$), 7.10-7.06 (m, 3H, N**H**COCF$_3^{III}$, Ar-H), 6.05-5.97 (m, 2H, H-3^{II}, H-4^{IV}), 5.88-5.82 (m, 2H, H-3^{I}, H-3^{IV}), 5.71 (t, 1H, $J_{4,3}$ 9.5, $J_{4,5}$ 9.5 Hz, H-4^{III}), 5.43 (t, 1H, $J_{4,3}$ 9.7, $J_{4,5}$ 9.7 Hz, H-4^{I}), 5.28-5.21 (m, 2H, H-3^{III}, H-4^{II}), 5.05 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1^{I}), 4.90 (d, 1H, $J_{1,2}$ 8.3 Hz, H-1^{II}), 4.81 (br dd, 1H, $J_{6a,6b}$ 12.1, $J_{6a,5}$ 4.4 Hz, H-6$_a^{IV}$), 4.76-4.56 (m, 8H, H-1^{III}, H-1^{IV}, H-2^{I}, H-2^{II}, H-2^{III}, H-2^{IV}, H-5^{I}, H-5^{II}), 4.22 (t, 1H, $J_{6a,6b}$ 11.7 Hz, H-6$_a^{II}$), 4.20-4.11 (m, 4H, H-5^{III}, H-5^{IV}, H-6$_a^{I}$, H-6$_b^{IV}$), 3.97 (d, 1H, $^2J_{6b,6a}$ 11.6 Hz, H-6$_b^{II}$), 3.90-3.85 (m, 1H, H-6$_a^{III}$), 3.65-3.59 (m, 1H, H-6$_b^{I}$), 3.40 (d, 1H, $^2J_{6b,6a}$ 11.9 Hz, H-6$_b^{III}$), 1.61 (s, 3H, NHCOC**H$_3^{I}$**); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 171.4 (NH**C**OCH$_3^{I}$), 166.6 (O**C**OAr), 166.5 (O**C**OAr), 166.42 (O**C**OAr), 166.36 (O**C**OAr), 166.2 (O**C**OAr), 165.6 (O**C**OAr), 165.2 (O**C**OAr), 164.9 (O**C**OAr), 158.6, 158.21, 158.18, 158.1, 157.83, 157.76 (NH**C**OCF$_3^{II}$, NH**C**OCF$_3^{III}$, NH**C**OCF$_3^{IV}$), 134.1 (Ar-CH), 133.78 (Ar-CH), 133.76 (Ar-CH), 133.73 (Ar-CH), 133.66 (Ar-CH), 133.5 (Ar-CH), 133.3 (Ar-CH), 133.2 (Ar-CH), 130.2 (Ar-CH), 130.14 (Ar-CH, Ar-C-), 130.07 (Ar-CH), 130.06 (Ar-CH), 129.9 (Ar-CH), 129.84 (Ar-CH), 129.77 (Ar-CH), 129.7 (Ar-CH), 129.5 (Ar-C-), 129.3 (Ar-C-), 129.1 (Ar-C-), 128.98 (Ar-C-), 128.89 (Ar-CH), 128.76 (Ar-CH), 128.68 (Ar-C-), 128.64 (Ar-CH), 128.57 (Ar-CH), 128.52 (Ar-CH), 128.45 (Ar-CH), 128.43 (Ar-C-), 128.35 (Ar-CH), 128.32 (Ar-C-), 128.25 (Ar-CH), 117.0, 116.9, 116.6, 114.2, 114.1, 113.7, (NHCO**C**F$_3^{II}$, NHCO**C**F$_3^{III}$, NHCO**C**F$_3^{IV}$), 104.0 (C-1^{IV}), 103.1 (C-1^{III}), 101.7 (C-1^{II}), 89.2 (C-1^{I}), 74.6 (C-5^{I}), 73.8 (C-5^{III}, C-5^{IV}), 73.6 (C-6^{II}), 73.4 (C-5^{II}), 73.2 (C-6^{III}), 72.8 (C-3^{I}), 72.62 (C-3^{III}), 72.55 (C-3^{II}), 71.8 (C-6^{I}), 71.30 (C-3^{IV}), 71.25 (C-4^{I}), 71.1 (C-4^{II}), 69.6 (C-4^{IV}), 69.4 (C-4^{III}), 63.6 (C-6^{IV}), 55.4 (C-2^{III}), 55.2 (C-2^{IV}), 54.4 (C-2^{II}), 53.4 (C-2^{I}), 22.6 (NHCO**C**H$_3^{I}$); Anal. Calcd for $C_{95}H_{80}F_9N_7O_{29}$: C, 58.37; H, 4.13; N, 5.02. Found: C, 58.08; H, 4.24; N, 4.97.

3.14 6-*O*-[6-*O*-(6-*O*-[2-Trifluoroacetamido-6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)]-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (15)

A solution of glycosyl acceptor **13** (31.3 mg, 0.020 mmol), glycosyl donor **7** (19.0 mg, 0.020 mmol), NIS (8.4 mg, 0.04 mmol) and anhydrous CH_2Cl_2 (13 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (0.5 µL, 2.76 µmol) was added to the reaction mixture and stirring was continued for 23 h. Et_3N (1.0 µL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (75%). The main fraction was collected and the solvent removed to give **15** as a white solid: 33.1 mg, 70%; mp 118 °C (dec.); $[\alpha]_D^{24}$-76.3° (*c* 0.12, CH_2Cl_2); R_f 0.66 (100% Et_2O); λ_{abs} (CH_2Cl_2)/nm : 233 (log ε/$M^{-1}cm^{-1}$, 5.14), 274 (4.11), 284 (4.00); IR (neat); *v* 3324 (NH), 2116 (N_3), 1721 and 1271 (ester), 1067 and 690 (C-O, C-F), 1025 (Si-O), 708 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 8.12-8.08 (m, 3H, N**H**$COCF_3^{II}$, Ar-H), 8.03-7.91 (m, 14H, N**H**$COCF_3^{IV}$, Ar-H), 7.60 (AA'BB'C, 2H, Ar-H), 7.52-7.41 (AA'BB'C, 8H, Ar-H), 7.40-7.28 (AA'BB'C, 13H, Ar-H), 7.23-7.16 (AA'BB'C, 5H, Ar-H), 7.13-7.10 (AA'BB'C, 5H, Ar-H), 7.05 (d, 1H, $J_{NH,2}$ 9.1 Hz, N**H**$COCH_3^I$), 6.98-6.93 (m, 3H, N**H**$COCF_3^{III}$, Ar-H), 5.90 (t, 1H, $J_{3,4}$ 10.5, $J_{3,2}$ 10.5 Hz, H-3^{II}), 5.87-5.80 (m, 2H, H-3^I, H-4^{IV}), 5.77 (t, 1H, $J_{3,4}$ 10.0, $J_{3,2}$ 9.5 Hz, H-3^{IV}), 5.76 (t, 1H, $J_{4,3}$ 10.0, $J_{4,5}$ 9.5 Hz, H-4^{III}), 5.42 (t, 1H, $J_{4,3}$ 10.0, $J_{4,5}$ 9.5 Hz, H-4^I), 5.36 (t, 1H, $J_{3,4}$ 10.0, $J_{3,2}$ 10.0 Hz, H-3^{III}), 5.29 (t, 1H, $J_{4,3}$ 10.0, $J_{4,5}$ 9.5 Hz, H-4^{II}), 5.01 (d, 1H, $J_{1,2}$ 9.0 Hz, H-1^I), 4.92 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{II}), 4.66-4.56 (m, 6H, H-1^{IV}, H-2^I, H-2^{II}, H-2^{III}, H-2^{IV}, H-5^I), 4.47 (t, 1H, $J_{5,4}$ 9.5 Hz, H-5^{II}), 4.26 (t, 1H, $J_{5,4}$ 10.0 Hz, H-5^{III}), 4.22 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1^{III}), 4.18-4.10 (m, 2H, H-6_a^I, H-6_a^{II}), 3.90-3.84 (m, 2H, H-5^{IV}, H-6_a^{III}),

3.80-3.71 (m, 3H, H-6_b^{II}, H-6^{IV}), 3.68 (d, 1H, $^2J_{6b,6a}$ 12.0 Hz, H-6_b^{I}), 3.56 (d, 1H, $^2J_{6b,6a}$ 12.0 Hz, H-6_b^{III}), 1.67 (s, 3H, NHCOC$\mathbf{H_3}^{I}$), 1.04 (s, 9H, C(C$\mathbf{H_3})_3$); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 171.1 (NH**C**OCH_3^{I}), 166.8 (O**C**OAr), 166.6 (O**C**OAr), 166.5 (O**C**OAr), 166.3 (O**C**OAr), 166.2 (O**C**OAr), 165.04 (O**C**OAr), 164.96 (O**C**OAr), 164.89 (O**C**OAr), 158.4, 158.1, 157.7 (NH**C**OCF_3^{II}, NH**C**OCF_3^{III}, NH**C**OCF_3^{IV}), 135.5 (Ar-CH), 135.3 (Ar-CH), 133.9 (Ar-CH), 133.8 (Ar-CH), 133.7 (Ar-CH), 133.6 (Ar-CH, Ar-C-), 133.5 (Ar-CH), 133.3 (Ar-CH), 131.5 (Ar-C-), 130.2 (Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-CH), 129.9 (Ar-CH), 129.81 (Ar-CH), 129.77 (Ar-CH), 129.7 (Ar-CH), 129.1 (Ar-C-), 128.9 (Ar-C-), 128.71 (Ar-C-), 128.67 (Ar-C-), 128.61 (Ar-CH), 128.57 (Ar-CH, Ar-C-), 128.51 (Ar-CH), 128.47 (Ar-CH), 128.4 (Ar-CH, Ar-C-), 128.3 (Ar-CH), 128.23 (Ar-CH), 128.15 (Ar-C-), 127.55 (Ar-CH), 127.47 (Ar-CH), 117.0, 116.9, 116.7, 114.2, 114.1, 113.8 (NHCO**C**F_3^{II}, NHCO**C**F_3^{III}, NHCO**C**F_3^{IV}), 103.8 (C-1^{IV}), 103.1 (C-1^{III}), 101.5 (C-1^{II}), 89.1 (C-1^{I}), 77.1 (C-5^{IV}), 74.8 (C-5^{I}), 73.8 (C-5^{III}), 73.1 (C-5^{II}), 72.9 (C-6^{II}), 72.8 (C-3^{I}), 72.49 (C-3^{II}), 72.43 (C-6^{III}), 72.37 (C-3^{III}), 71.7 (C-3^{IV}), 71.5 (C-6^{I}), 71.0 (C-4^{I}), 70.7 (C-4^{II}), 69.5 (C-4^{III}), 69.0 (C-4^{IV}), 64.3 (C-6^{IV}), 55.2 (C-2^{IV}), 55.1 (C-2^{III}), 54.5 (C-2^{II}), 53.5 (C-2^{I}), 26.7 (C(**C**$H_3)_3$), 22.6 (NHCO**C**H_3^{I}), 18.9 (**C**$(CH_3)_3$); HRMS: Calcd for $C_{104}H_{94}F_9N_7NaO_{28}Si^+$ $[M + Na]^+$ *m/z* = 2110.5665. Found: 2110.5629.

3.15 6-*O*-[6-*O*-(6-*O*-[2-Trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (16)

A solution of tetrasaccharide **15** (30.2 mg, 0.020 mmol) in anhydrous THF (5 mL), HOAc (16.6 µL, 0.290 mmol) and TBAF (0.15 mL, 0.15 mmol) was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with satd NH_4Cl solution

(10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography over silica gel using an Et_2O:light petroleum mixture (90%) as the eluent. The main fraction was collected and the solvent removed to give **16** as a white solid: 26.8 mg, quant.; mp 163-165 °C (dec.); $[\alpha]_D^{24}$-58.4° (*c* 0.17, CH_2Cl_2); R_f 0.22 (100% Et_2O); λ_{abs} ($CH2Cl_2$)/nm : 234 (log ε/$M^{-1}cm^{-1}$, 5.00), 276 (3.93), 284 (3.84); IR (neat); *v* 3323 (NH), 2118 (N_3), 1720 and 1271 (ester), 1066 and 690 (C-O, C-F), 707 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$; 500 MHz): δ 7.99-7.97 (AA'BB'C, 4H, Ar-H), 7.96-7.87 (AA'BB'C, 12H, Ar-H), 7.55-7.50 (AA'BB'C, 3H, Ar-H), 7.47-7.42 (AA'BB'C, 7H, Ar-H), 7.41-7.35 (AA'BB'C, 7H, Ar-H), 7.32-7.24 (AA'BB'C, 5H, Ar-H), 7.19-7.16 (AA'BB'C, 2H, Ar-H), 5.85 (t, 1H, $J_{3,2}$ 10.5, $J_{3,4}$ 9.9 Hz, H-3^{II}), 5.79 (t, 1H, $J_{3,2}$ 10.3, $J_{3,4}$ 10.0 Hz, H-3^{I}), 5.72-5.66 (m, 2H, H-3^{III}, H-3^{IV}), 5.57 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.5 Hz, H-4^{III}), 5.42 (t, 1H, $J_{4,3}$ 9.5, $J_{4,5}$ 9.5 Hz, H-4^{IV}), 5.32 (t, 1H, $J_{4,3}$ 9.8, $J_{4,5}$ 9.8 Hz, H-4^{I}), 5.25 (t, 1H, $J_{4,3}$ 9.8, $J_{4,5}$ 9.7 Hz, H-4^{II}), 4.97 (d, 1H, $J_{1,2}$ 9.4 Hz, H-1^{I}), 4.83 (d, 1H, $J_{1,2}$ 8.3 Hz, H-1^{II}), 4.75 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{III}), 4.62 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{IV}), 4.47 (br t, 2H, H-2^{III}, H-5^{I}), 4.40-4.30 (m, 4H, H-2^{I}, H-2^{II}, H-2^{IV}, H-5^{II}), 4.17 (br td, 1H, $J_{5,4}$ 10.0, $J_{5,6a}$ 2.5, $J_{5,6b}$ 2.0 Hz, H-5^{III}), 4.03-3.99 (m, 2H, H-6$_a^{I}$, H-6$_a^{II}$), 3.89-3.84 (m, 2H, H-6$_b^{II}$, H-6$_a^{III}$), 3.77 (br dd, 1H, $^2J_{6b,6a}$ 12.0, $J_{6b,5}$ 1.5 Hz, H-6$_b^{I}$), 3.71-3.65 (m, 3H, H-5^{IV}, H-6$_b^{III}$, H-6$_a^{IV}$), 3.56 (br d, 1H, H-6$_b^{IV}$), 1.80 (s, 3H, NHCOC**H**$_3^{\mathbf{I}}$); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 171.4 (NH**C**OCH$_3^{I}$), 166.5 (O**C**OAr), 166.44 (O**C**OAr), 166.37 (O**C**OAr), 166.2 (O**C**OAr), 166.1 (O**C**OAr), 166.03 (O**C**OAr), 165.96 (O**C**OAr), 165.5 (O**C**OAr), 158.3, 158.1, 157.9, 157.7 (NH**C**OCF$_3^{II}$, NH**C**OCF$_3^{III}$, NH**C**OCF$_3^{IV}$), 133.8 (Ar-CH), 133.7 (Ar-CH), 133.6 (Ar-CH), 133.5 (Ar-CH), 133.4 (Ar-CH), 133.3 (Ar-CH), 129.94 (Ar-CH), 129.92 (Ar-CH), 129.86 (Ar-CH), 129.85 (Ar-CH), 129.78 (Ar-CH), 129.76 (Ar-CH), 128.9 (Ar-C-), 128.71 (Ar-C-), 128.65 (Ar-CH), 128.6 (Ar-C-), 128.55 (Ar-CH), 128.52 (Ar-CH, Ar-C-), 128.50

(Ar-CH), 128.43 (Ar-C-), 128.40 (Ar-CH), 128.34 (Ar-CH), 128.30 (Ar-CH), 128.28 (Ar-CH, Ar-C-), 117.0, 114.2 (NHCO**C**F_3^{II}, NHCO**C**F_3^{III}, NHCO**C**F_3^{IV}), 102.4 (C-1^{III}), 102.3 (C-1^{IV}), 101.3 (C-1^{II}), 88.8 (C-1^{I}), 74.8 (C-5^{IV}), 74.7 (C-5^{I}), 73.7 (C-5^{III}), 73.1 (C-5^{II}), 72.8 (C-3^{I}), 72.3 (C-3^{II}, C-3^{III}), 71.9 (C-6^{II}), 71.7 (C-3^{IV}), 70.9 (C-6^{III}), 70.6 (C-4^{I}, C-4^{II}, C-6^{I}), 70.3 (C-4^{III}), 69.6 (C-4^{IV}), 61.1 (C-6^{IV}), 54.7 (C-2^{III}), 54.6 (C-2^{IV}), 54.4 (C-2^{II}), 53.5 (C-2^{I}), 22.5 (NHCOCH_3^{I}); HRMS: Calcd for $C_{88}H_{76}F_9N_7NaO_{28}^+$ $[M+Na]^+$ *m/z* = 1872.4487. Found: 1872.4494.

3.16 6-*O*-[6-*O*-(6-*O*-[6-*O*-(2-Trifluoroacetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl)-2-trifluoroacetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl]-2-acetamido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl azide (**17**)

A solution of glycosyl acceptor **16** (18.7 mg, 0.010 mmol), glycosyl donor **6** (14.8 mg, 0.020 mmol), NIS (5.8 mg, 0.03 mmol) and anhydrous CH_2Cl_2 (2 mL) was stirred under nitrogen at room temperature for 30 min. TMSOTf (0.400 µL, 2.34 µmol) was added to the reaction mixture and stirring was continued for 21 h. Et_3N (20.0 µL) was added to quench the reaction and the solvent was removed. The residue was purified by column chromatography over silica gel using an EtOAc:light petroleum mixture (50%). The main fraction was collected and the solvent removed to give **17** as a white solid: 16.6 mg, 68%; mp 161-163 °C (dec.); $[\alpha]_D^{23}$-104.2° [*c* 1.41, CH_2Cl_2/MeOH (1:1)]; R_f 0.51 (60% EtOAc/light petroleum); λ_{abs} [CH_2Cl_2/MeOH (1:1)]/nm : 238 (log ε/$M^{-1}cm^{-1}$, 5.63), 275 (4.79), 284 (4.69); IR (neat); *v* 3323 (NH), 2118 (N_3), 1720 and 1268 (ester), 1065 and 690 (C-O, C-F), 707 cm^{-1} (Ar); ^{1}H NMR ($CDCl_3$/CD_3OD; 500 MHz): δ 8.10-8.09 (AA'BB'C, 2H, Ar-H), 7.98-7.96 (AA'BB'C, 6H, Ar-H), 7.95-7.93 (AA'BB'C, 4H, Ar-H), 7.89-7.88 (AA'BB'C, 6H, Ar-H), 7.54-7.47 (AA'BB'C, 3H, Ar-H),

7.45-7.28 (AA'BB'C, 24H, Ar-H), 7.25-7.22 (AA'BB'C, 4H, Ar-H), 7.16-7.12 (AA'BB'C, 4H, Ar-H), 7.08-7.05 (AA'BB'C, 2H, Ar-H), 6.08 (t, 1H, $J_{3,2}$ 9.8, $J_{3,4}$ 9.7 Hz, H-3^{III}), 5.84 (t, 1H, $J_{3,2}$ 10.4, $J_{3,4}$ 10.3 Hz, H-3^{II}), 5.82 (t, 1H, $J_{3,4}$ 10.2, $J_{3,2}$ 10.2 Hz, H-3^{I}), 5.68 (t, 1H, $J_{4,5}$ 9.8, $J_{4,3}$ 9.7 Hz, H-4^{III}), 5.62 (t, 1H, $J_{4,5}$ 9.7, $J_{4,3}$ 9.2 Hz, H-4^{IV}), 5.59 (t, 1H, $J_{4,5}$ 9.8, $J_{4,3}$ 9.4 Hz, H-4^{V}), 5.53 (t, 1H, $J_{3,2}$ 10.5, $J_{3,4}$ 9.1 Hz, H-3^{IV}), 5.48 (t, 1H, $J_{3,2}$ 10.7, $J_{3,4}$ 9.2 Hz, H-3^{V}), 5.23 (t, 1H, $J_{4,5}$ 9.8, $J_{4,3}$ 9.8 Hz, H-4^{I}), 5.09 (t, 1H, $J_{4,3}$ 9.9, $J_{4,5}$ 9.8 Hz, H-4^{II}), 5.04 (d, 1H, $J_{1,2}$ 9.3 Hz, H-1^{I}), 4.90 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{II}), 4.74 (td, 1H, $J_{5,4}$ 10.3, $J_{5,6a}$ 2.4 Hz, H-5^{I}), 4.71-4.65 (m, 2H, H-1^{III}, H-2^{III}), 4.59-4.54 (m, 4H, H-1^{IV}, H-2^{V}, H-5^{II}, H-5^{III}), 4.51-4.44 (m, 4H, H-2^{I}, H-2^{II}, H-2^{IV}, H-$6_a{}^{V}$), 4.36 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{V}), 4.16-4.06 (m, 4H, H-$6_b{}^{V}$, H-$6_a{}^{I}$, H-$6_a{}^{II}$, H-$6_a{}^{III}$), 4.03 (td, $J_{5,4}$ 10.0, $J_{5,6b}$ 1.9 Hz, H-5^{IV}), 3.96 (ddd, $J_{5,4}$ 10.0, $J_{5,6a}$ 4.9, $J_{5,6b}$ 2.4 Hz, H-5^{V}), 3.90 (dd, 1H, $^{2}J_{6a,6b}$ 12.6, $J_{6a,5}$ 2.5 Hz, H-$6_a{}^{IV}$), 3.58 (br dd, 2H, H-$6_b{}^{I}$, H-$6_b{}^{III}$), 3.50 (br dd, 1H, H-$6_b{}^{II}$), 3.24 (dd, 1H, $^{2}J_{6b,6a}$ 12.6, $J_{6b,5}$ 1.7 Hz, H-$6_b{}^{IV}$), 1.83 (s, 3H, NHCOC$\mathbf{H_3}^{I}$); ^{13}C NMR ($CDCl_3/CD_3OD$; 100 MHz): δ 172.0 (NH**C**O$CH_3{}^{I}$), 166.54 (O**C**OAr), 166.43 (O**C**OAr), 166.33 (O**C**OAr), 166.29 (O**C**OAr), 166.27 (O**C**OAr), 166.1 (O**C**OAr), 165.87 (O**C**OAr), 165.77 (O**C**OAr), 165.1 (O**C**OAr), 164.8 (O**C**OAr), 158.8, 158.6, 158.4, 158.2, 157.8 (NH**C**O$CF_3{}^{II}$, NH**C**O$CF_3{}^{III}$, NH**C**O$CF_3{}^{IV}$, NH**C**O$CF_3{}^{V}$), 133.7 (Ar-CH), 133.6 (Ar-CH), 133.5 (Ar-CH), 133.4 (Ar-CH), 133.3 (Ar-CH), 133.2 (Ar-CH), 133.14 (Ar-CH), 133.08 (Ar-CH), 130.0 (Ar-CH), 129.8 (Ar-CH), 129.7 (Ar-CH), 129.66 (Ar-CH), 129.61 (Ar-CH), 129.58 (Ar-CH), 129.4 (Ar-CH), 129.02 (Ar-C-), 128.98 (Ar-C-), 128.88 (Ar-C-), 128.82 (Ar-C-), 128.78 (Ar-CH, Ar-C-), 128.75 (Ar-CH), 128.58 (Ar-C-), 128.46 (Ar-CH, Ar-C-), 128.41 (Ar-CH), 128.37 (Ar-C-), 128.31 (Ar-CH), 128.22 (Ar-CH), 128.19 (Ar-CH, Ar-C-), 128.09 (Ar-CH), 128.0 (Ar-C-), 116.87, 116.85, 116.6, 114.0, 113.73, 113.71, 113.2 (NHCO**C**$F_3{}^{II}$, NHCO**C**$F_3{}^{III}$, NHCO**C**$F_3{}^{IV}$, NHCO**C**$F_3{}^{V}$), 103.4 (C-1^{IV}), 103.1 (C-1^{V}), 102.7 (C-1^{III}), 100.8 (C-1^{II}), 88.9 (C-1^{I}), 74.03 (C-5^{I}),

73.97 (C-5^{IV}), 73.8 (C-6^{III}), 73.6 (C-5^{III}), 73.4 (C-6^{IV}), 73.1 (C-5^{V}, C-6^{II}), 72.9 (C-3^{I}), 72.4 (C-5^{II}), 72.3 (C-3^{II}), 71.8 (C-3^{III}), 71.5 (C-3^{V}), 71.4 (C-3^{IV}, C-6^{I}), 71.3 (C-4^{II}, C-4^{III}), 71.1 (C-4^{I}), 70.3 (C-4^{IV}), 70.0 (C-4^{V}), 63.5 (C-6^{V}), 54.8 (C-2^{IV}), 54.5 (C-2^{III}), 54.3 (C-2^{II}, C-2^{V}), 53.3 (C-2^{I}), 22.1 (NHCO**C**H_3^{I}); Anal. Calcd for $C_{117}H_{98}F_{12}N_8O_{36}$: C, 58.07; H, 4.08; N, 4.63. Found: C, 57.94; H, 4.31; N, 4.40.

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Supporting Information Available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Highlights from: A simple iterative method for the synthesis of β-(1→6)-glucosamine oligosaccharides

- Efficient, scalable, and high yielding synthesis of β-(1→6)-glucosamine oligosaccharide.
- Use of *N*-trifluoroacetyl substituted donors provides a simple and much-needed alternative to the *N*-phthalimido-protected donors utilised in many methodologies to date.
- A two-step, iterative process applied to generate the protected pentasaccharide in an overall yield of 25%.
- Fully characterised oligomers may be useful in preparation of vaccines targeting bacterial biofilms.