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Synthesis of oligosaccharide libraries from GBS capsular polysaccharides for structure-based selection of vaccine candidates

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Chapter 3

Regioselective Strategies to GlcNAcβ1-3Gal Disaccharide Synthons

Novel intermediates for preparation of Group B Streptococcus polysaccharide antigens, Adamo, R.; Del Bino, L. *PCT Int. Appl.*, **2019**, Patent n° WO 2019012476 A1 20190117

Introduction

Despite the enormous possible variation in carbohydrate structures, some motifs are recurrently expressed both by prokaryotic and eukaryotic cell. One example is the disaccharide GlcNAc-β-(1→3)Galβ, which is present in several bacterial carbohydrates, including the Group B *Streptococcus* (GBS) type Ia, Ib and III capsular polysaccharides, *Streptococcus pneumoniae* type 14 (Pn14), and *Neisseria meningitidis* lipooligosaccharide (Figure 1). This motif is also a component of mammalian glycans, such as the milk oligosaccharide lacto-*N*-tetraose.

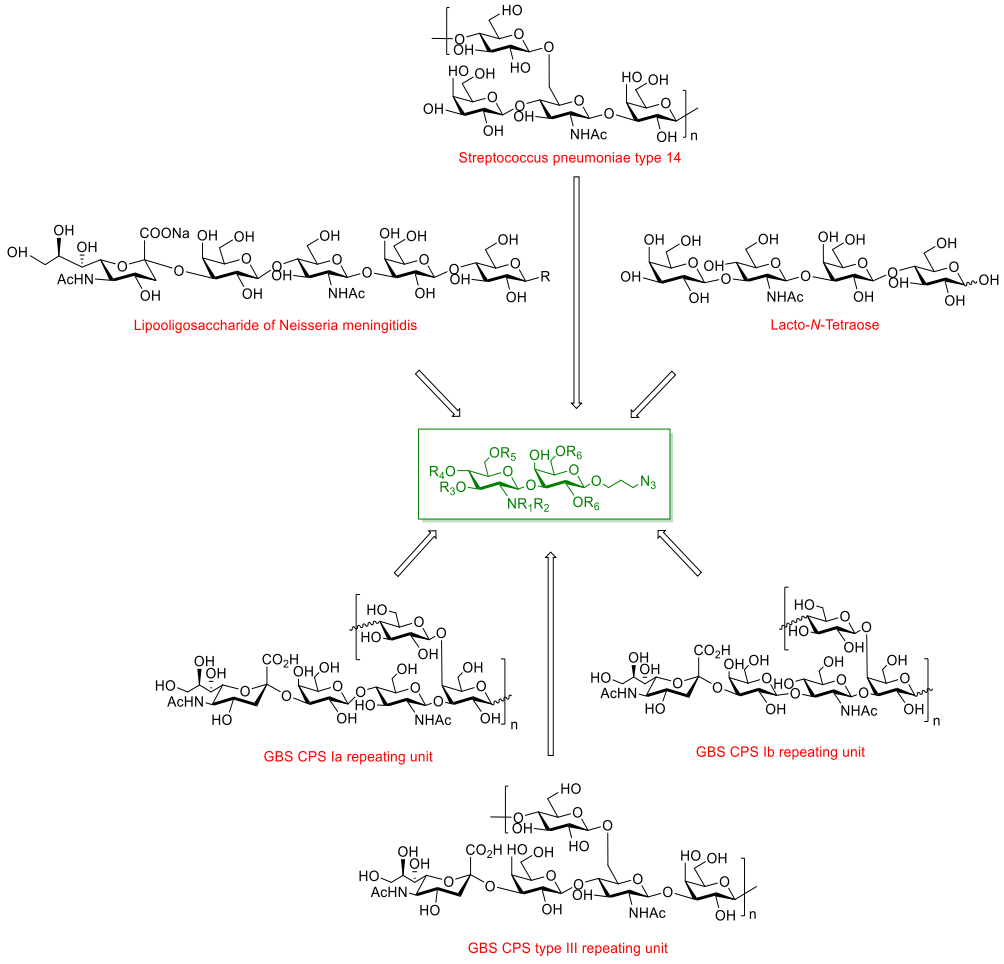


Figure 1. Example of bacterial and mammalian structures containing the GlcNAc-β-(1→3)Galβ disaccharide moiety

Interest towards the synthesis of CPS Ia and Ib oligosaccharide fragments is based on the willingness to investigate the structural features regulating the interactions with serotype specific mAbs and start delineating potential oligosaccharide epitopes. While approaching the synthesis,

the formation of the disaccharide GlcNAcβ1-3Gal motif was envisaged as a key step to enable convergent syntheses of a variety of structures depicted in Figure 1. Typically, installation of the GlcNAcβ1-3Gal disaccharide within more complex glycans has been achieved with the 4-hydroxyl group of the Gal acceptor either protected or already engaged in a glycosidic linkage. For instance, Craft et al.[1] recently observed that a 4-*O*-acetyl group was needed in the Gal acceptor to achieve glycosylation at position 3 with an *N*-Trichloroethoxycarbonyl protected glucosamine donor. This finding was in line with previous reports[2, 3] where the position 3 of a 4-*O*-acetyl Gal acceptor was glycosylated with a *N*-phthalimido protected glucosamine thioglycoside donor during the synthesis of GBS PSIII fragments. Demchenko et al[4] synthesized a heptasaccharide fragment of GBS PSIII via a [5+2] block coupling in which 3-OH of a lactose acceptor was glycosylated regioselectively in the presence of a 4-OH. The regioselective glycosylation of the 3-OH of Gal in the presence of 4-OH has also been described in the synthesis of fragments from *Streptococcus pneumoniae* type 14, although by the use of a 3,4,6-tri-*O*-acetylated GlcNAc donor further chemical elongation of this residue was not foreseen. A similar approach was used for the preparation of a pentasaccharide from *N. meningitidis* LOS, where the sialic acid was inserted by enzymatic reaction with the deprotected Pn14-like fragment[5].

Finally, in the recently described preparation of a CPS Ia repeating unit[6], a 4,6-*O*-benzylidene protected Gal acceptor was used for glycosylation with a glucosamine trichloroacetimidate donor, subsequent regioselective ring opening preceded the glycosylation of position 4, thereby resulting in the construction of the trisaccharide GlcNAcβ1-3[Glcβ1-4)]Gal.

There is a growing demand of expeditious procedures for the construction of complex glycans, and regio- and stereoselective reactions distinguishing among diverse deprotected hydroxyls are highly desirable to simplify the oligosaccharide assembly[7-9].

It was therefore reasoned that regioselective glycosylation of Gal 3-OH would be key for accelerating the synthesis of the GlcNAcβ1-3Gal disaccharide and rendering the 4-OH available for further glycosylation without the need of tedious protection/deprotection sequences[10].

In this chapter, tactics to achieve regioselective syntheses of protected GlcNAcβ1-3Gal building blocks are described. These key synthons can be used then in convergent routes towards a series of fragments from CPS Ia and Ib capsular polysaccharides with a built-in aminopropyl linker amenable for future conjugation to carrier proteins.

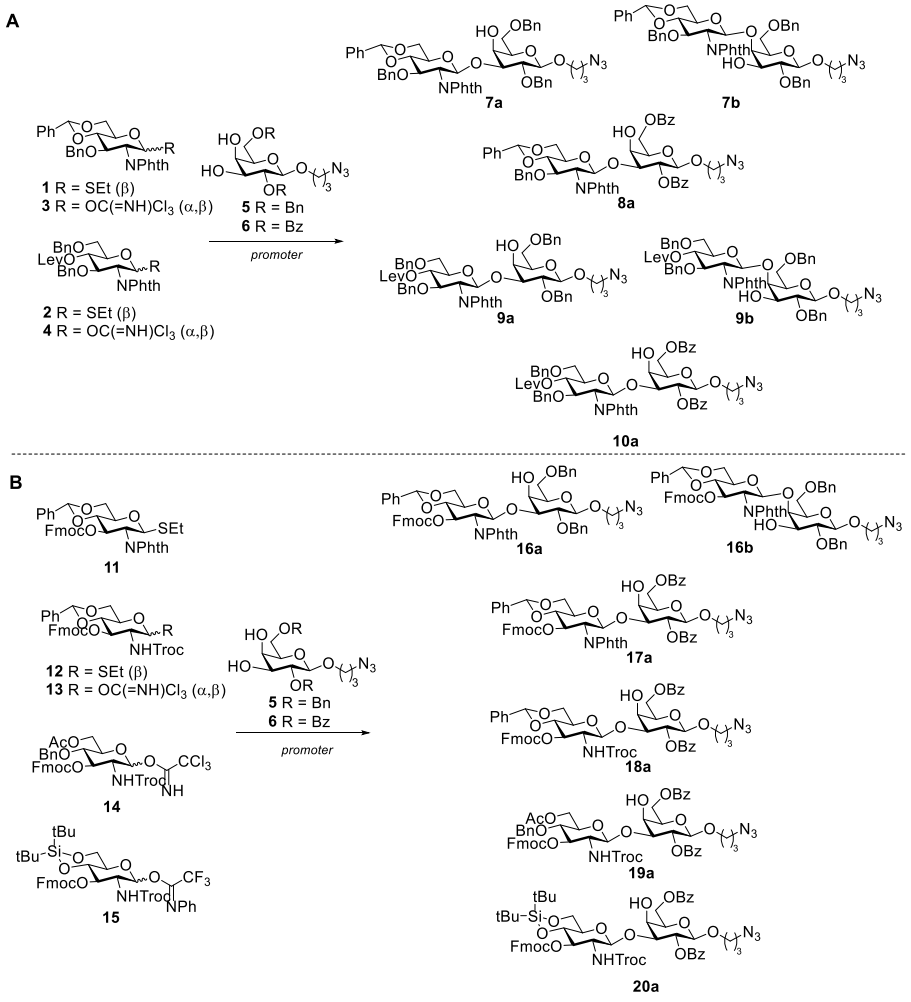
Results and Discussion

Protecting groups play a key role in oligosaccharides assembly[11-13]. They are employed to mask specific hydroxyl and amino groups to differentiate their reactivity and allow for selective modification, but they also have a large impact on the regio- and stereoselective control of the glycosylation. For example, the nature of the protective group installed at the C-2 position of the donor has a major impact on the stereoselectivity of glycosylation. When a participating protective group is installed at the C-2 position of a glycosyl donor, the glycosylation proceeds through an

acyloxonium intermediate, by which the nucleophilic attack takes place preferentially from the opposite face of the sugar ring, leading to the stereoselective formation of the 1,2-*trans* glycosidic linkage[14]. In additon, the reactivity of glycosyl donors and acceptors can be tuned by the employment of electron-withdrawing (disarming) or electron-donating (arming) protecting groups, such as benzoyl or benzyl groups, respectively[12, 15].

To achieve a regioselective synthesis of the key target GlcNAcβ1-3Gal disaccharides, the effect of arming benzyl and disarming benzoyl groups[15-17] at position 2 and 6 of the Gal acceptors on the reactivity of the 3- and 4-OH, was investigated, in combination with various protecting and leaving groups in the GlcN donors. Accordingly, a series of glucosamine thioglycoside and trichloroacetimidate donors in which the amine was protected by either the phthalimido (Phth) or trichloroethyl carbamate (Troc) participating groups was synthesized. The levulinoyl (Lev) and fluorenylmethyloxycarbonyl (Fmoc) were selected for temporary protection of either position 3 or 4. Alternatively, a 4,6-*O*-benzylidene was used to lock the 4 and 6 hydroxyls in GlcN to be subjected to regioselective ring opening delivering the 4-OH at a later stage of the synthesis. The glucosamine and galactose building blocks necessary for evaluating the glycosylation conditions were all prepared from commercially available starting materials and all intermediates were fully characterized when not already described in the literature (See Experimental section for details).

The prepared donors and acceptors were coupled under several glycosylation conditions to optimize the synthesis of the GlcNAcβ1-3Gal building block. In Table 1 and Scheme 1 the conditions for the preparation of a GlcNAcβ1-3Gal synthon with a temporary group at its C4'-OH, to allow the ensuing assembly of GBS CPSIa fragments are described.



Scheme 1. A) Preparation of disaccharide intermediates **7-10** for the synthesis of the GBS CPS Ia repeating unit. Promoters and conditions are described in Table 1. B) Preparation of disaccharide intermediates **16-20** for the synthesis of the GBS PSIb repeating unit. Promoters and conditions are described in Table 2.

When the ethylthioglycoside **1** was coupled with acceptors **5** and **6** using NIS/TfOH as promoters at -30°C, no product formation was observed (Entry 1 and 6, Table 1) due to donor decomposition. In the presence of the milder Lewis acid AgOTf at -30°C, NIS promoted condensation of **1** or **2** with **5** afforded along with the desired product **7a** and **8a**, respectively, the 4-*O*-glycosylated regioisomers (Entry 2-3, Table 1). The formation of the β-(1→4) linkage in disaccharide **8b** was confirmed by acetylation and NMR analysis of the acetylated product. In the ^{1}H NMR spectrum a shift from 3.32 to 4.69 ppm of the H-3 signal of Gal, appearing as a doublet of doublets with $J_{2,3}$ = 10.3 Hz and $J_{3,4}$ = 2.5 Hz was observed, confirming occurrence of glycosylation at position 4.

Table 1. Reactions of GlcN donors **1-4** with Gal acceptors **5-6**

Entry	Donor	Acceptor	Product	Yield
1	**1**	**5**	NIS/TfOH, - 30 °C	nd[a]
2	**1**	**5**	NIS/Ag(OTf), 30°C	**7a** (43%), **7b** (26%)
3	**2**	**5**	NIS/Ag(OTf), - 30°C	**8a** (40%), **8b** (28%)
4	**3**	**5**	TMSOTf, - 10°C	**7a** (31%)
5	**4**	**5**	TMSOTf, -10°C	**8a** (45%)
6	**1**	**6**	NIS/TfOH, - 30°C	nd[a]
7	**1**	**6**	NIS/Ag(OTf), - 30°C	**9a** (53%)
8	**2**	**6**	NIS/Ag(OTf), - 30°C	**10a** (65%)
9	**4**	**6**	TMSOTf, -10°C	**10a** (33%)
10	**3**	**6**	TMSOTf, - 10°C	**9a** (77%)

a. DCM was the solvent in all tested conditions. b. nd = not determined, product could not be detected.

Reaction of the 4,6-*O*-benzylidene glucosamine trichloroacetimidate **3** with **5** in presence of TMSOTf at -10°C (Entry 4, Table 1) provided the desired product **7a** in 31% yield, due to concomitant conversion of the donor into the anomeric acetamide byproduct. On the other hand, the imidate **4** and acceptor **5** exclusively gave **8a** with a higher yield (45%, Entry 5, Table 1), showing that the combination of 4,6-*O*-benzylidene protection and trichloroacetoimidoyl leaving group resulted in improved regioselectivity, but still moderate yield.

When the di-*O*-benzoyl acceptor **6** was exploited, reaction with both donor **1** and **2** under NIS/AgOTf activation regioselectively afforded compound **9a** (53%) and **10a** (65%), respectively (Entry 7-8, Table 1). The imidate **4** (Entry 9, Table 1) also solely gave compound **10a**, but in a lower yield (33%). Finally, combination of the 4,6-*O*-benzylidene **3** (Entry 10, Table 1) and acceptor **6** enabled to attain **9a** in satisfactory 77% yield.

To summarize, these findings indicated that 2,6-di-*O*-Bz Gal acceptor (**6**) generally lead to higher regioselectivity and yields compared to the 2,6-di-*O*-benzyl derivative (**5**). Trichloroacetimidate donors **3** and **4** showed higher regioselectivity with both the 2,6-di-*O*-Bz and 2,6-di-*O*-Bn Gal acceptors, but with variable yields. The most efficient routes to GlcNAc-β-(1→3)Gal were achieved by combination of the 2,6-di-*O*-Bz acceptor **6** with either 4-*O*-levulinoyl ethylthiol **2** under NIS/AgOTf mediated activation or the 4,6-*O*-benzylidene GlcN imidate **3** in presence of TMSOTf, which led to disaccharides **10a** and **9a**, respectively. Furthermore, the 3,6-di-*O*-benzyl ether **2** with NIS/AgOTf activation performed better than the trichloroacetimidate counterpart **4**.

On the basis of these results, the same strategy to attain regioselectivity was transferred to glucosamine donors with an orthogonal protection at C3'-OH, in order to obtain a disaccharide synthon, following the preparation of the repeating unit of the GBS PS Ib. Fmoc was chosen as temporary protecting group, and the corresponding glucosamine donors protected as *N*-phthalimido or *N*-trichloroethoxycarbamoyl derivatives were tested. In order to evaluate the effect of the torsional constrain of the donor on the glycosylation outcome, glucosamine trichloroacetimidate **14** presenting the 4-OBn, 6-OAc protecting group pattern was tested, as well as the trifluoroacetimidate donor **15** where the 4,6 hydroxyls are locked in a silylidene ring[18].

Table 2. Reaction of GlcN donors **11-15** with Gal acceptors **5-6**

Entry	Donor	Acceptor	Product	Yield
1	**11**	**5**	NIS/TfOH, - 30°C	**16a** (30%), **16b** (<5%)
2	**11**	**5**	NIS/AgOTf, - 30°C	**16a** (38%), **16b** (26%)
3	**11**	**6**	NIS/TfOH, - 30°C	**17a** (40%)
4	**11**	**6**	NIS/AgOTf, - 30°C	**17a** (68%)
5	**12**	**6**	NIS/TfOH, - 30°C	nd[a]
6	**12**	**6**	NIS/AgOTf, - 30°C	**18a** (65%)
7	**13**	**6**	TMSOTf, - 10°C	**18a** (70%)
8	**14**	**11**	TMSOTf, - 10°C	**19a** (50%)
9	**15**	**11**	TMSOTf, - 10°C	**20a** (62%)

a. DCM was the solvent in all tested conditions. b. nd = not determined, product could not be detected.

Table 2 summarizes the results obtained with these donors and acceptors.

The glycosylation of di-*O*-benzyl acceptor **11** with donor **5** using NIS with either TfOH or AgOTf as co-promoters gave variable mixtures of the β-(1→3) **16a** and β-(1→4) **16b** disaccharides (Entry 1-2, Table 2). Switching to the use of di-*O*-benzoyl acceptor **6** in combination with donor **11** in the presence of NIS/TfOH allowed the attainment of the desired product **17a** (40%, Entry 3, Table 2), although it was obtained as a mixture with a non-identified byproduct. The use of NIS/AgOTf activation at -30°C further improved the yield up to 68% (Entry 4, Table 2), confirming the better capacity of benzoyl protection to control the regioselectivity of the reaction. These conditions were proven to be also efficient for the GlcNTroc donor **12** which gave **18a** in 65% yield (Entry 6, Table 2). When the corresponding trichloroacetimidate **13** was exploited, the yield was increased up to 70% (Entry 7, Table 2), corroborating the potential of this type of donors for the regioselective control of the reaction. On the other hand, the yield dropped to 50% when the imidate glucosamine **14** was used to glycosylate the 2,6-di-*O*-benzoylated Gal **6** (Entry 8, Table 2). Finally, trifluoroacetimidate glucosamine **15** bearing a 4,6-*O*-silylidene protection in presence of TMSOTf as promoter afforded the target disaccharide **20a** with a yield (62%, Entry 9, Table 2) slightly lower compared to the benzylidene-protected counterpart **13**, suggesting that the glycosylation reaction might benefit from torsional disarming effect in the donor[19]. Trichloroacetimidate donor **13** and the 2,6-di-*O*-benzoylated acceptor **6** proved to be the best coupling partners to obtain the target GlcNAc-β-(1→3)-Gal motif for further elongation in position 3 of glucosamine.

Overall, these results can be rationalized as the regioselectivity of the glycosylation benefits from the more pronounced electron withdrawing effect of the 2,6- di-*O*-benzoyl in comparison with the 2,6-di-*O*-benzyl substituents in the Gal acceptor. Indeed, the benzoyl groups further decrease the intrinsically lower nucleophilicity of the axial 4-hyodroxyl with respect to the 3-hydroxyl group. In addition, mild activation conditions (NIS/AgOTf) for the thioglycoside donor or the torsional

disarming effect of the benzylidene group for the trichloroacetimidate donor appear to favour the glycosylation reaction over side product formation.

Conclusion

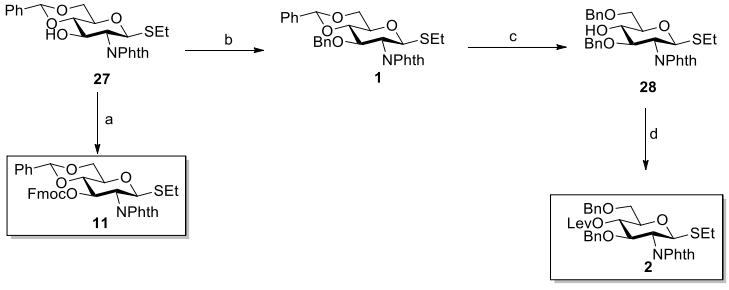
This chapter has introduced the concept of regioselective β(1→3) glycosylation of galactose by using a number of glucosamine donors with a different pattern of protecting groups; the aim of this methodological work was to identify the best combinations of donor and acceptor to prepare the biologically relevant GlcNAc-β-(1→3)Galβ disaccharide with high yield and complete regioselectivity. It was demonstrated that not only the leaving group and the protective groups on the glycosyl donor are important factors in determining the outcome of the glycosylation reaction, but also the stereoelectronic effect of the protecting groups on the glycosyl acceptor plays a crucial role. The use of the electron-withdrawing benzoyl protecting group on the galactose C2 and C6 hydroxyls instead of electron-neutral benzyl groups, resulted in effective deactivation of the galactose C4-OH towards the glycosylation. Therefore, only the β(1→3) linkage was formed during the glycosylation with the selected glucosamine building blocks.
Thus, conditions for an efficient and completely regioselective β-(1→3)-glycosylation of galactose were identified employing glucosamine donors with orthogonal protective groups both at 4-OH or 3-OH. This gave access to key disaccharide synthons which are intermediates to the synthesis of linear and branched oligosaccharide fragments from several bacterial carbohydrates.
The elongation of selected disaccharides at the galactose C4-OH and at glucosamine C3 or C4-OH can give access to biologically relevant oligosaccharide fragments from GBS serotype Ia, Ib and III capsular polysaccharide, to be used for determining the structure-immunogenicity relationship of the corresponding glycoconjugate vaccines, as will be described in following chapters of this thesis.

Experimental

General Methods and procedures. Reactions were monitored by thin-layer chromatography (TLC) on Silica Gel 60 F254 (Sigma Aldrich); after exam under UV light, compounds were visualized by heating with 10% (v/v) ethanolic H_2SO_4. In the work up procedures, organic solutions were washed with the amounts of the indicated aqueous solutions, then dried with anhydrous Na_2SO_4, and concentrated under reduced pressure at 30–50ºC on a water bath. Column chromatography was performed on Silica Gel 60 (Sigma Aldrich, 0.040–0.063 nm) or using pre-packed silica cartridges RediSep (Teledyne-Isco, 0.040–0.063 nm) or Biotage SNAP Ultra (Biotage, silica 0.050 nm). Unless otherwise specified, a gradient 0-100% of the elution mixture was applied in a Combiflash Rf (Teledyne-Isco) or Biotage Isolera instrument. Solvent mixtures less polar than those used for TLC were used at the onset of separation. ^{1}H NMR spectra were measured at 400 MHz and 298 K with a Bruker AvanceIII 400 spectrometer; ^{1}H values are reported in ppm, relative to internal Me_4Si (^{1}H = 0.00, $CDCl_3$); solvent peak for D_2O was calibrated at 4.79 ppm. ^{13}C NMR spectra were measured at 100 MHz and 298 K with a Bruker AvanceIII 400 spectrometer; ^{13}C values are reported in ppm relative to the signal of $CDCl_3$ (^{13}C = 77.0, $CDCl_3$). Assignments of NMR signals were made by homonuclear and heteronuclear 2-dimensional correlation spectroscopy, run with the software supplied with the spectrometer. Assignment of ^{13}C NMR spectra of some compounds was aided by comparison with spectra of related substances reported previously from this laboratory or elsewhere. When reporting assignments of NMR signals, sugar residues in oligosaccharides are indicated with capital letters. Exact masses were measured by electron spray ionization cut-off spectroscopy, using a Q-Tof micro Macromass (Waters) instrument. Structures of these compounds follow unequivocally from the mode of synthesis, NMR data and *m/z* values found in their mass spectra.

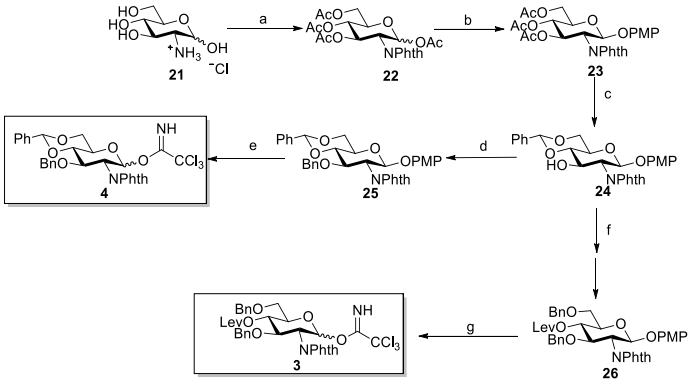
Synthetic schemes

Syntheses of the thioglycoside donors **1**, **2** and **11**[20]



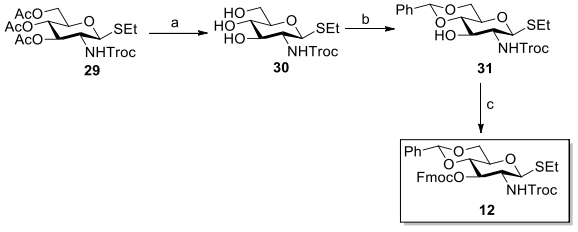
Scheme 2. *Reagents and conditions:* a) Fmoc-Cl, Py, DCM, 64%; b) BnBr, NaH, TBAI, DMF, 0°C, 82%; c) $Me_3N{\cdot}BH_3$, $BF_3{\cdot}Et_2O$, ACN, 0°C; 78% d) Levulinic acid, DCC, DMAP, dry DCM, 77%.

Syntheses of the trichloroacetimidate donors **3** and **4**



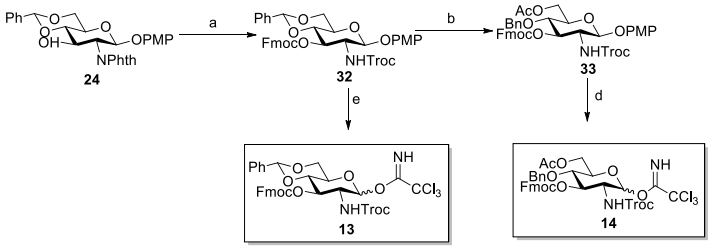
Scheme 3. *Reagents and conditions:* a) $(Phth)_2O$, TEA, MeOH; Ac_2O, Py, DMAP; 75% over two steps; b) *p*-methoxyphenol, $BF_3{\cdot}Et_2O$, DCM dry, 0°C, 89%; c) NaOMe, MeOH; $PhCH(OMe)_2$, PTSA, CH_3CN, 84% over two steps; d) BnBr, NaH, TBAI, DMF, 0°C, 82%; e) CAN, CH_3CN/H_2O, 0°C; CCl_3CN, DBU, DCM dry, 70% over two steps; f) $Me_3N{\cdot}BH_3$, $BF_3{\cdot}Et_2O$, ACN, 0°C; Levulinic acid, DCC, DMAP, dry DCM, 70% over two steps; g) CAN, CH_3CN/H_2O, 0°C; CCl_3CN, DBU, DCM dry, 70% over two steps.

Synthesis of the thioglycoside donor **12**[21]



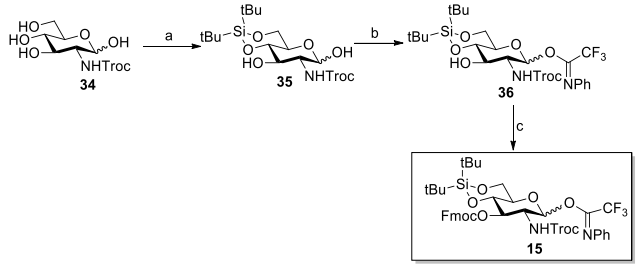
Scheme 4. *Reagents and conditions:* a) MeONa, MeOH, quantitative; b) $PhCH(OMe)_2$, PTSA, CH_3CN, 84%; c) Fmoc-Cl, Py, DCM, 94%.

Syntheses of the trichloroacetimidate **13** and **14**



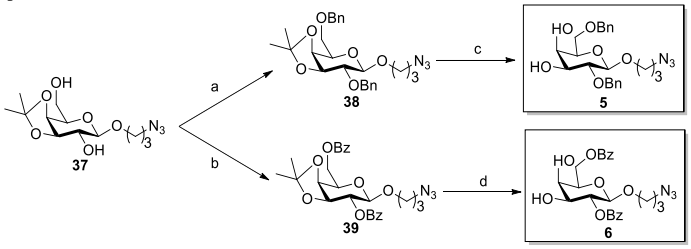
Scheme 5. *Reagents and Conditions*: a) $H_2NCH_2CH_2NH_2$, EtOH, 70° C; $NaHCO_3$, Troc-Cl, H_2O/Et_2O; Fmoc-Cl, DCM/Py 10:1, 60% yield over three steps; b) $PhBCl_2$, Et_3SiH, DCM dry, -78°C; Ac_2O/Py, 0° to rt, 50% yield over two steps; c) CAN, CH_3CN/H_2O, 0°C; CCl_3CN, DBU, DCM dry, 50% over two steps; d) CAN, CH_3CN/H_2O, 0°C; CCl_3CN, DBU, DCM dry, 41% over two steps.

Synthesis of the trifluoroacetimidate **15**[22]



Scheme 6. *Reagents and conditions:* a) $(tBu)_2Si(OTf)_2$, DMF, -30°C, 90% b) 2,2,2-Trifluoro-N-phenylacetimidoyl chloride, Cs_2CO_3, DCM dry, 85% c) Fmoc-Cl, Py, DCM, 94%.

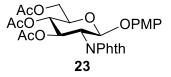
Syntheses of acceptors **5** and **6**[23]



Scheme 7. *Reagent and conditions*: a) BnBr, NaH, DMF, 0°C to rt, 90%; b) BzCl, Py, 0° to rt, 95%; c) $AcOH/H_2O$, 70°C, 92%; d) $AcOH/H_2O$, 70°C, 92%.

Synthesis of building blocks

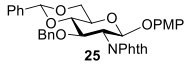
***p*-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside 23.** Compound **22** (17 g, 35.6 mmol) was dissolved in dry DCM (60.0 mL) at 0°C with 4Å activated molecular sieves (40 g) and stirred for 10 min under nitrogen. *p*-Methoxyphenol (25 g, 201.4 mmol) and boron trifluoride etherate (24 mL, 194.5 mmol) were added at 0°C. After 1 h the mixture was allowed to warm up to rt. Stirring was continued for further 24 h, when TLC showed complete reaction (7:3 cyclohexane:EtOAc). TEA was added, solid was filtered off and the solvent removed at reduced pressure. The crude was purified by flash chromatography (cyclohexane:EtOAc) giving **23** (18 g, 89%) as a brown oil. $[\alpha]_D^{25}$ = +63.04° (c 1.3, $CHCl_3$). ESI HR-MS ($C_{27}H_{27}NO_{11}$) *m/z* $[M+Na]^+$ found 564.1473; calcd 564.1482.



^{1}H NMR (400 MHz, CDCl3) δ 7.80-6.66 (m, 8H, H-Ar), 5.81 (m, 2H, H-1, H-3) , 5.19 (t, *J* = 9.7, 1H, H-4), 4.50 (dd, $J_{1,2}$ = 8.6 Hz, $J_{2,3}$ = 10.6 Hz, 1H, H-2), 4.29 (dd, $J_{5,6a}$ = 5.3 Hz, $J_{6a,6b}$ = 12.3 Hz, 1H, H-6a) , 4.16 (dd, $J_{5,6b}$ = 1.9, 1H, H-6b), 3.90-3.86 (m, 1H, H-5), 3.66 (s, 3H, O*CH*$_3$) , 2.04, 1.98, 1.82 (3 x s, 3H each, 3 x C*H*$_3$CO).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.2, 169.5 (3 x CO), 134.4-114.4 (C-Ar), 97.5 (C-1), 72.0 (C-5), 70.7 (C-3), 68.9 (C-4), 62.0 (C-6), 55.6 (O*C*H$_3$), 54.5 (C-2), 20.8, 20.7, 20.5 (3 x CO*C*H$_3$).

***p*-Methoxyphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside 25.**



Sodium methoxide was added to a stirred mixture of compound **23** (18.0 g, 35.6 mmol) in methanol (40 mL) until pH 9. After 20 h the reaction was quenched with Dowex 50WX2. After the filtration of the resin, the filtrate was evaporated under reduced pressure.

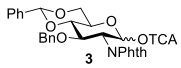
To the crude material acetonitrile (30 mL), benzaldehyde dimethyl acetal (6.9 mL, 68 mmol) and *p*-toluenesulfonic acid (0.470 g, 2.73 mmol) were added. After 3 h the reaction was quenched with triethylamine (4.7 mL), and the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (cyclohexane: EtOAc) to afford **24** (6.3 g, 84 % yield) as a yellow solid.

Sodium hydride (0.148 g, 3.7 mmol) was added to a stirred solution of compound **24** (0.930 g, 1.85 mmol) in N,N-dimethylformamide (7.0 mL) at 0°C under nitrogen. After 15 min benzyl bromide (0.66 mL, 5.55 mmol) was added, and the mixture was allowed warming to rt. After 2 h methanol (10 mL) was added, and the mixture was evaporated under reduced pressure. The product was dissolved in EtOAc and washed with $NaHCO_3$ (x2), dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by flash chromatography (cyclohexane: EtOAc) to afford **25** (0.900 g, 82% yield) as a yellow solid. $[\alpha]_D^{25} = +65.17^\circ$ (c 1.1, $CHCl_3$). ESI-HR MS ($C_{35}H_{31}NO_8$) m/z $[M+Na]^+$ found 616.1866; calcd 616.1947.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78- 6.74 (m, 18H, H-Ar), 5.77 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 5.68 (s, 1H, C*H*Ph), 4.86 (d, ^2J=12.4 Hz, 1H, C*H*HPh), 4.57 (d, ^2J = 12.4 Hz, 1H, CH*H*Ph), 4.53-4.48 (m, 2H, H-3, H-2), 4.45 (dd, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 10.4 Hz, 1H, H-6a), 3.98-3.88 (m, 2H, H-4, H-6b), 3.80-3.74 (m, 1H, H-5), 3.73 (s, 3H, OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.00-114.53 (C-Ar), 101.40 (*C*HPh), 98.00 (C-1), 83.00 (C-4), 74.20 (*C*H_2Ph), 74.51 (C-3), 68.74 (C-6), 55.74 (C-2), 66.30 (C-5), 55.60 (O*C*H_3).

3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-*α,β*-D-glucopyranosyl trichloroacetimidate 3.

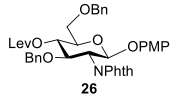


3

Cerium ammonium nitrate (5.110 g, 9.32 mmol) was added to a stirred solution of compound **25** (3 g, 4.66 mmol) in 4:1 acetonitrile: water (50 mL) at 0°C. After 3 h, TLC (7:3 cyclohexane:EtOAc) showed the disappearance of the starting material and the formation of one major spot. The reaction was washed with a solution of $NaHCO_3$ (x 2) and the combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The crude (1.681 g, 3.45 mmol) was dissolved in DCM (10 mL) dry under nitrogen and trichloroacetonitrile (1.730 mL, 17.25 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (0.152 mL, 1.03 mmol) were added. After stirring for 2h at rt, TLC (7:3 cyclohexane:EtOAc) showed complete reaction. The solvent was removed at reduced pressure and the crude was purified by flash chromatography (cyclohexane:EtOAc) to afford **3** (1.524 g) in 70% yield in 2:1 α/β ratio. $[\alpha]_D^{25} = +64.25^\circ$ (c 4.15, $CHCl_3$). ESI MS ($C_{30}H_{25}Cl_3N_2O_7$) *m/z* $[M+H]^+$ found 632.06; calcd 631.89.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (s, 1H, NH), 7.62-6.80 (m, 14H, H-Ar), 6.42 (d, $J_{1,2}$ = 8.4 Hz, H-1_β), 6.30 (d, $J_{1,2}$ = 3.8 Hz, H-1_α), 5.60 (s, 1H, C*H*Ph$_\alpha$), 5.57 (s, 1H, C*H*Ph$_\beta$), 5.46 (t, J = 9.0 Hz, H-3_α), 4.95 (d, ^2J= 11.1 Hz, 1H, C*H*HPh$_\alpha$), 4.75 (d, ^2J = 12.4 Hz, 1H, C*H*HPh$_\beta$), 4.62 (d, ^2J = 11.1 Hz, 1H, CH*H*Ph$_\alpha$), 4.58-4-52 (m, H-2_α) , 4.94-4.36 (m, H-2_β, H-3_β, CH*H*Ph$_\beta$, H-$6a_\beta$), 4.33-4.31 (m, H-$6a_\alpha$), 4.18-4.12 (m, H-5_α), 3.86-3.76 (m, H-4_α, H-$6b_\alpha$, H-4_β, H-5_β, H-$6b_\beta$)

***p*-Methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-levulinoyl-2-phthalimido-*β*-D-glucopyranoside 26.**



26

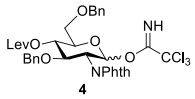
A solution of **24** (0.500 g, 0.9 mmol) in ACN (5 mL) was cooled at 0°C. $Me_3N{\cdot}BH_3$ (274 mg, 3.76 mmol) and $BF_3{\cdot}O(Et)_2$ (0.464 mL, 3.76 mmol) were added, and the reaction was stirred for 2 h under nitrogen. TLC (7:3 cyclohexane:EtOAc) showed complete reaction. TEA was added until neutral pH, followed by MeOH. The solvent was removed at reduced pressure and the crude was purified by flash chromatography (cyclohexane:EtOAc).

To the obtained product (0.400 g, 0.67 mmol) dissolved in DCM (5 mL), N-N-ethylcarbodiimide hydrochloride (0.206 g, 1.0 mmol), 4-dimethylaminopyridine (0.122 g, 1.0 mmol) and levulinic acid (0.156 g, 1.34 mmol) were added. The mixture was stirred overnight at rt. The solvent was removed by rotary evaporation, and the resulting crude material was purified by flash chromatography (cyclohexane:EtOAc) to give the compound **26** (325 mg) in 70% yield. $[\alpha]_D^{25} = +78.37^\circ$ (c 3.25, $CHCl_3$). ESI HR-MS ($C_{40}H_{39}NO_{10}$) *m/z* $[M+Na]^+$ found 716.2447; calcd 716.2472.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-6.58 (m, 18H, H-Ar), 5.57 (d, $J_{1,2}$ =8.8 Hz, H-1), 5.14 (t, J = 8.9 Hz, 1H, H-4), 4.62 (d, ^2J = 11.9 Hz, 1H, C*H*Ph), 4.46 -4.42 (m, 3H, CH_2PH, H-3, H-2), 4.28 (d, ^2J = 11.9 Hz, 1H, C*H*HPh), 3.82-3.67 (m, 1H, H-5), 3.61 (s, 3H, OCH_3), 3.58-3.54 (m, 2H, H-6), 2.59 (t, J = 6.4 Hz, 2H, CH_2CO), 2.41 (t, J = 6.4Hz, 2H, CH_2COO), 2.07 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 171.5, 160.8 (3 x CO), 137.0-114.0 (C-Ar), 97.4 (C-1), 72.9 (C-4), 74.2 (CH_2Ph), 73.59 (CH_2Ph), 77.24 (C-3), 55.41 (C-2), 73.8 (C-5), 69.56 (C-6), 55.55 (OCH_3), 37.77 (CH_2CO), 29.83 (CH_3), 27.94 (CH_2COO).

3.6-Di-*O*-benzyl-2-deoxy-4-*O*-levulinoyl-2-phthalimido-*β*-D-glucopyranosyl trichloroacetimidate 4.



4

Cerium ammonium nitrate (515 mg, 0.94 mmol) was added to a stirred solution of compound **26** (325 mg, 0.47 mmol) in 4:1 acetonitrile:water (25 mL) at 0°C. After 3 h, a TLC (cyclohexane: EtOAc 1:1) showed the disappearance of the starting material and the formation of one major spot. The reaction was washed two times with a solution of $NaHCO_3$ and the organic phase was dried with Na_2SO_4 and evaporated under reduced pressure.

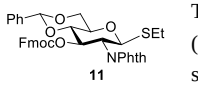
The crude was dissolved in DCM dry (10 mL) under nitrogen and trichloroacetonitrile (0.368 g, 2.55 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (0.023 g, 0.153 mmol) were respectively added. After stirring for 2h at rt, TLC showed complete reaction (1:1 cyclohexane:EtOAc). The solvent was removed at reduced pressure and the crude was purified by flash chromatography (cyclohexane:EtOAc) to afford **4** (261 mg, yield 70%). $[\alpha]_D^{25}$ = +68.49° (c 0.55, $CHCl_3$). ESI HR-MS ($C_{35}H_{33}Cl_3N_2O_9$) *m/z* $[M+Na]^+$ found 732.0040; calcd 732.0035.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-6.85 (m, 14H, H-Ar), 6.36 (d, $J_{1,2}$ = 7.6 Hz, H-1$_\beta$), 5.22 (t, J = 9.0 Hz, 1H, H-4), 4.62 (d, ^2J = 12.3 Hz, 1H, C*H*HPh$_b$), 4.53-4.39 (m, 4H, H-2, H-3, C*H*HPh$_a$, CH*H*Ph$_a$), 4.30 (d, ^2J = 12.3 Hz, 1H, CH*H*Ph$_b$), 3.92-3.85 (m, 1H, H-5), 3.66-3.53 (m, 2H, H-6), 2.65-2.48 (m, 2H, CH_2CO), 2.47-2.29 (m, 2H, CH_2COO), 2.06 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 171.6, 160.8 (3 x CO), 133.9-123.3 (C-Ar), 93.9 (C-1), 76.7 (C-3), 74.44 (C-5), 74.11, 73.48, 72.17 (C-4), 68.89 (C-6), 54.46 (C-2), 37.69 (*C*H_2CO), 33.96, 29.79 (CH_3), 27.91 (*C*H_2COO), 25.62, 24.95.

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0-123.4 (C-Ar), 101.4 (*C*HPh$_\beta$), 101.3 (*C*HPh$_\alpha$), 95.4 (C-1$_\alpha$), 94.3 (C-1$_\beta$), 83.4, 82.5 (C-4), 74.7, 74.3, 74.2 (C-3$_\beta$), 72.4 (C-3$_\alpha$), 68.5, 66.9 (C-5$_\beta$), 65.4 (C-5$_\alpha$), 54.7 (C-2).

Ethylthio 4,6-*O*-benzylidene-2-deoxy-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-phthalimido-*β*-D-glucopyranoside 11.

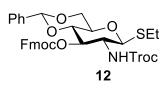


11

The known compound **27** (200 mg, 0.45 mmol) was dissolved in dry DCM (10 mL). Fmoc-Cl (351 mg, 1.36 mmol) and pyridine (0.182 mL, 2.25 mmol) were added at 0°C, and the reaction stirred at rt for 1 h. TLC (4:1 cyclohexane:EtOAc) showed complete reaction, the solvent was removed under reduced pressure and the crude was purified by flash chromatography (8:2 cyclohexane:EtOAc) to afford **11** (202 mg) in 64% yield as pale yellow oil. $[\alpha]_D^{25}$= +13.53° (c 2.5, $CHCl_3$). ESI HR-MS ($C_{38}H_{33}NO_8S$) *m/z* $[M+Na]^+$ found 686.1807; calcd 686.1825.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.95 (m, 17H, H-Ar), 5.88 (t, J= 9.5 Hz, 1H, H-3), 5.59-5.65 (m, 2H, C*H*Ph, H-1), 4.58 (t, J= 10.3 Hz, 1H, H-2), 4.47-4.52 (m, 1H, CH_{2a}^{Fmoc}), 4.09-4.17 (m, 2H, H-6), 3.92-4.00 (m, 2H, CH^{Fmoc}, H-4), 3.84-3.92 (m, 2H, CH_{2b}^{Fmoc}, H-5), 2.65-2.85 (m, 2H, SCH_2), 1.25 (t, J = 7.3 Hz, 3H, SCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.2, 154.5 (3 x CO), 143.1-119.9 (C-Ar), 101.8 (*C*HPh), 81.9 (C-1), 79.2 (C-4), 74.4 (C-3), 70.5 (C-5), 70.3, 68.6 (C-6), 55.4, 54.1 (C-2), 46.3, 26.9, 24.4 (S*C*H_2), 14.9 (SCH_2CH_3).

Ethylthio 4,6-*O*-benzylidene-2-deoxy-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-glucopyranoside 12.



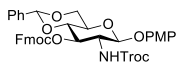
12

Compound **31** (219 mg, 0.45 mmol) was dissolved in 5.0 mL of dry DCM and the resulting solution was cooled down to 0°C. Pyridine (0.250 mL) was added, followed by Fmoc-Cl (0.310 mL, 1.125 mmol). The reaction mixture was stirred for 30 min. The crude was purified by column chromatography (7:3 cyclohexane:EtOAc) to afford **12** (300 mg, 94% yield) as a white solid. $[\alpha]_D^{25}$= -14.18° (c 0.025, $CHCl_3$). ESI HR-MS ($C_{33}H_{32}Cl_3NO_8S$) *m/z* $[M+Na]^+$ found 730.0852; calcd 730.0812.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.19 (m, 13H, Ar-H), 5.59 (s, 1H, C*H*Ph), 5.31 (d, $J_{N,H}$ = 9.2 Hz, 1H, NH), 5.20 (t, *J* = 9.8 Hz, 1H, H-3), 4.7 (d, $J_{1,2}$ = 10.2 Hz, 1H, H-1), 4.65 (d, ^2J = 2.54 Hz, 2H, Cl_3CCH_2), 4.45-4.35 (m, 3H, H-6, CH_2^{Fmoc}), 4.26 (t, *J* = 7.5 Hz, 1H, CH^{Fmoc}), 3.92 (t, *J* = 9.9 Hz, 1 H, H-2), 3.88-3.80 (m, 2H, H-6', H-4), 3.65-3.57 (m, 1H, H-5), 2.70-2.78 (m, 2H, CH_2SEt), 1.28 (t, 3H, *J* = 7.4 Hz, CH_3SEt).

^{13}C NMR (101 MHz, $CDCl_3$) δ 129.3-120.2 (C-Ar), 101.8 (*C*HPh), 85.5 (C-1), 78.7 (C-4), 76.5 (C-3), 74.8 (Cl_3CCH_2), 71.0 (CH_2^{Fmoc}), 70.7 (C-6), 68.7 (C-5), 56.1 (C-2), 46.7 (CH^{Fmoc}), 24.6 (CH_2 SEt), 14.9 (CH_3SEt).

***p*-Methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-glucopyranoside 32.**



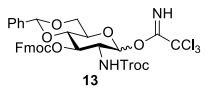
32

Compound **24** (2.014 g, 3.64 mmol) was dissolved in 20.0 mL of ethanol and ethylenediamine (1.2 mL, 18.22 mmol) was added. The resulting reaction mixture was stirred at 70°C for 6 h. After 6 h TLC (cyclohexane:EtOAc 1:1) showed full conversion of the starting material and formation of a new spot on the baseline. The reaction mixture was evaporated under reduced pressure affording a white solid. The crude was resuspended in methanol and filtered under vacuum. The filtrate was evaporated to dryness affording a yellow syrup, which was redissolved in 20.0 mL of a 1:1 Et_2O/H_2O mixture. The resulting solution was cooled down to 0°C and $NaHCO_3$ (3.06 mg, 36.4 mmol) was added, followed by Troc-Cl (2.5 mL, 18.2 mmol). The resulting reaction mixture was stirred at 0°C for 45 min, then checked by TLC (7:3 cyclohexane/EtOAc), which showed complete consumption of the starting material. The reaction mixture was quenched by addition of aqueous $NaHCO_3$, then extracted with DCM (3 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure affording a pale solid as a crude. The crude was purified by flash column chromatography using a gradient from 0 to 100% of EtOAc in cyclohexane. Clean fractions were collected and evaporated under reduced pressure affording the product as a white solid (1.419 g, 66% yield). The compound (1.2 g, 2.03 mmol) was dissolved in 10.0 mL of dry DCM. The resulting solution was cooled down to 0°C in an ice-water bath, then Fmoc-Cl (1.3 g, 5.078 mmol) and pyridine (0.5 mL) were added. The reaction mixture was stirred for 1 h at rt, then checked by TLC (cyclohexane/EtOAc), which showed full conversion of starting material. The crude was evaporated under reduced pressure and purified by flash column chromatography. Pure fractions were collected and evaporated to dryness affording compound **32** (1.3 g, 60% yield over three steps). $[\alpha]_D^{25}$ = -1.19˚ (c 1.1, $CHCl_3$). ESI HR-MS ($C_{38}H_{34}Cl_3NO_{10}$) *m/z* $[M+NH_4]^+$ found 787.1596; calcd 787.1587.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-2.22 (m, Ar-H), 5.58 (s, 1H, C*H*Ph), 5.48 (d, $J_{N,H}$ = 8.7 Hz, 1H, NH), 5.33 (t, *J* = 10.0 Hz, 1H, H-3), 5.15 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 4.70 (d, ^2J = 11.8 Hz, 1H, C*H*HCCl$_3$), 4.63 (d, 1H, CH*H*CCl$_3$), 4.47-4.33 (m, C*H*H^{Fmoc}, 3H, H-6), 4.25 (t, *J* = 7.2 Hz, 1H, CH^{Fmoc}), 3.97 (t, *J* = 8.9 Hz, 1H, H-2), 3.90-3.82 (m, 2H, C*H*H^{Fmoc}, H-4), 3.77 (s, 3H, OCH_3), 3.64-3.56 (m, 1H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 155.1 (2 x CO), 154.2 (C_q), 151.0 (C_q), 144.3-114.6 (C-Ar), 101.6 (*C*HPh), 100.9 (C-1), 78.5 (C-4), 74.9 (C-3), 74.5 (CH_2CCl_3), 70.5 (C-6), 68.5 (CH_2^{Fmoc}), 66.3 (C-5), 57.1 (C-2), 55.7 (OCH_3), 46.5 (CH^{Fmoc}).

4,6-*O*-benzylidene-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-*α,β*-D-glucopyranosyl trichloroacetimidate 13.



13

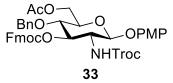
Compound **32** (1.550 g, 2.06 mmol) was dissolved in 15 mL of a 4:1 ACN/H_2O mixture and the resulting suspension was cooled down to 0°C. Cerium ammonium nitrate (2.16 g, 4.12 mmol) was added and the reaction was stirred for 2 h at 0°C. After 2 h, TLC (6:4 cycloexane:EtOAc) showed disappearance of the starting material. The reaction mixture was diluted with DCM and washed twice with iced aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography (cyclohexane/EtOAc). Pure fractions were collected and evaporated affording the target 1-OH intermediate (1.1 g, 80% yield) as colorless oil.

The 1-OH intermediate (0.212 g, 0.319 mmol) was dissolved in a 1:1 DCM/CCl_3CN mixture under nitrogen atmosphere and cooled down to 0°C. NaH (1.28 mg, 0.032 mmol) was added and the resulting solution was stirred for 3 h and let slowly to go to rt. After 3 h TLC (6:4 cyclohexane/EtOAc) showed full conversion of the starting material; the reaction mixture was evaporated under reduced pressure and the crude was purified on column chromatography with a gradient from 0 to 100% of EtOAc in hexane (containing 3% of TEA). Pure fractions were collected and evaporated under reduced pressure affording the glucosamine imidate **13** as a colorless oil (0.125 g, 50% yield,) primarily as α anomer. $[\alpha]_D^{25} = +31.33^\circ$ (c 0.2, $CHCl_3$). ESI HR-MS ($C_{33}H_{28}Cl_6N_2O_9$) *m/z* $[M+H]^+$ found 806.0878; calcd 806.9926.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, C=NH); 7.54-7.14 (m, 13H, Ar-H); 6.39 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1); 5.57 8s, 1H, C*H*Ph); 5.38 (d, $J_{N,H}$ = 9.7 Hz, 1H, NH), 5.28 (t, J = 10.1 Hz, 1H, H-3), 4.67 (d, ^2J = 12.0 Hz, 1H, C*H*HCCl$_3$), 4.48 (d, 1H, CH*H*CCl$_3$), 4.41-4.30 (m, 3H, incl. H-2, H-6); 4.25-4.19 (m, 1H, C*H*^{Fmoc}), 4.09-4.02 (m, 1H, H-5), 3.91 (t, 1H, J = 9.7 Hz, H-4), 3.79 (t, J = 10.4 Hz, 1H, H-6b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7 (CO), 143.1, 143.0, 129.6-120.0 (C-Ar), 101.7 (*C*HPh), 95.1 (C-1), 78.3 (C-4), 77.2, 74.7 (*C*H$_2$CCl$_3$), 73.4 (C-3), 70.7 (*C*H$_2^{Fmoc}$), 70.1 (*C*H$_2$Ph), 68.5 (C-6), 65.4 (C-5), 65.2, 54.6 (C-2), 50.4, 46.4 (*C*H^{Fmoc}).

***p*-Methoxyphenyl 6-*O*-acetyl-4-*O*-benzyl-2-deoxy-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-glucopyranoside 33.**



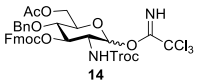
33

Compound **32** (370 mg, 0.49 mmol) was dissolved in 5.0 mL of dry DCM under nitrogen atmosphere in presence of 4 Å activated molecular sieves. The resulting suspension was cooled down to -78°C, when dichlorophenylborane (0.229 mL, 1.764 mmol) and Et_3SiH (0.549 mL, 3.43 mmol) were added. The resulting reaction mixture was stirred and allowed to slowly reach rt. TLC (6:4 cylcohexane:EtOAc) showed consumption of the starting material, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was dissolved in a 1:1 solution of Ac_2O/pyridine. The resulting reaction mixture was stirred at rt. After 16 h TLC (6:4 cyclohexane/EtOAc) showed complete reaction, then the crude mixture was coevaporated with toluene and the residue was purified by column chromatography (cyclohexane/EtOAc). Pure fractions were collected and evaporated to dryness affording glucosamine **33** (185 mg, 50% yield over two steps). $[\alpha]_D^{25} = -11.07^\circ$ (c 0.025, $CHCl_3$). ESI HR-MS ($C_{41}H_{40}Cl_3NO_{10}$) *m/z* $[M+Na]^+$ found 834.1625; calcd 834.1615.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-6.76 (m, 22H, Ar-H); 5.36 (d, $J_{N,H}$ = 9.0 Hz, 1H, NH), 5.18 (dd, $J_{3,4}$ = 10.5 Hz, $J_{2,3}$ = 8.8 Hz, 1H, H-3), 4.99 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 4.72-4.62 (m, 3H, C*H*$_2$CCl$_3$, C*H*HPh), 4.54 (d, ^2J = 11.5 Hz, 1H, CH*H*Ph), 4.51-4.44 (m, 1H, C*H*H^{Fmoc}), 4.41-4.32 (m, 2H, H-6a, CH*H*^{Fmoc}), 4.27-4-20 (m, 2H, CH^{Fmoc}, H-6b), 3.94 (t, 1H, J = 8.9 Hz, H-2), 3.79-3.65 (m, 2H, H-4, H-5), 3.76 (s, 3H, OC*H*$_3$), 2.04 (s, 3H, CH$_3$CO).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 155.8, 155.3 (3 x CO), 154.2-114.5 (C-Ar), 100.4 (C-1), 78.7 (C-3), 75.3 (C-5), 74.8 (*C*H$_2$CCl$_3$), 72.8 (C-4), 70.5 (*C*H$_2^{Fmoc}$), 62.6 (C-6), 56.5 (C-2), 55.7 (O*C*H$_3$), 46.7 (CH^{Fmoc}), 20.8 (*C*H$_3$CO).

6-*O*-Acetyl-4-*O*-benzyl-2-deoxy-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*α,β*-D-glucopyranosyl trichloroacetimidate 14.



14

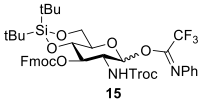
Compound **33** (185 mg, 0.227 mmol) was dissolved in 10 mL of a 4:1 acetonitrile/water mixture and the resulting solution was cooled down to 0°C using a water/ice bath. Cerium ammonium nitrate (373 mg, 0.680 mmol) was added and the resulting reaction mixture was stirred at 0°C. After 2 h TLC (3:2 cycloexane:EtOAc) showed full consumption of the starting material. The reaction mixture was poured into iced $NaHCO_3$ and extracted with DCM (3x20 mL). The organic phases were dried over Na_2SO_4 and evaporated under reduced pressure affording a crude product which was directly dissolved in 2.0 mL of a 1:1 CCl_3CN/DCM mixture. The resulting solution was cooled down to 0°C, NaH (60% dispersion in mineral oil, 1.0 mg, 0.0212 mmol) and trichloroacetonitrile (2 mL) were added and the resulting reaction mixture was stirred for 2 h, letting slowly reach rt.

After 2 h, TLC (6:4 cyclohexane:EtOAc) showed full conversion of the starting material, so the reaction was quenched by addition of Et_3N and the reaction mixture was evaporated to dryness. The crude was purified by column chromatography with a gradient of EtOAc in cyclohexane (containing 1% of TEA). Pure fractions were collected and evaporated to dryness affording the target compound **14** as a clear oil (0.085 g, 41% yield over two steps, only α). $[\alpha]_D^{25} = +9.63^\circ$ (c 0.85, $CHCl_3$). ESI HR-MS ($C_{36}H_{34}Cl_6N_2O_9$) *m/z* $[M+Na]^+$ found 871.0300; calcd 871.0293.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, $NHCCl_3$); 7.84-7.24 (m, 13H, Ar-H); 6.42 (d, $J_{1,2}$ = 3.4 Hz, 1H, H-1), 5.37 (d, $J_{N,H}$ = 9.2 Hz, 1H, NH), 5.30 (dd, $J_{3,4}$ = 11.4 Hz, $J_{2,3}$ = 9.6. 1H, H-3); 4.78 (d, ^2J = 11.0 Hz, 1H, C*H*HPh), 4.71-4.50 (m, 4H, CH_2CCl_3, CH*H*Ph, CH^{Fmoc}), 4.56-4.24 (m, 5H, H-2, H-6, CH_2^{Fmoc}), 4.09 (dt, 1H, $J_{4,5}$ =9.9 Hz, $J_{5,6}$ = 2.9 Hz, H-5); 3.99 (t, 1H, *J* = 9.5 Hz, H-4), 2.06 (s, 3H, CH_3CO).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (CNH), 163.7, 160.6, 155.6 (CO), 143.2-120.1 (C-Ar), 100.0 (Cq), 94.8 (C-1), 77.2 (C-3), 75.1 (*C*H_2Ph), 74.6 (*C*H_2CCl_3), 74.1 (C-4), 71.4 (C-5), 70.7 (*C*H_2^{Fmoc}), 62.0 (C-6), 54.2 (C-2), 46.5 (*C*H^{Fmoc}), 20.8 (*C*H_3CO).

4,6-*O*-di-*tert*-butylsilylidene-2-deoxy-3-*O*-(9*H*-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*α,β*-D-glucopyranosyl *N*-phenyl-trifluoroacetimidate 15.



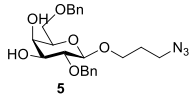
15

Compound **36** (2.278 g, 3.42 mmol) was dissolved in 10.0 mL of dry DCM and the resulting solution was cooled down to 0°C. Pyridine (1.0 mL) was added, followed by Fmoc-Cl (2.2 g, 8.55 mmol). The reaction mixture was stirred for 1 hour at rt. The crude was purified by column chromatography (9:1 cyclohexane:EtOAc) to afford **15** (2.0 g, 70% yield) as a white solid. $[\alpha]_D^{25} = +27.87^\circ$ (c 0.05, $CHCl_3$). ESI HR-MS ($C_{40}H_{44}Cl_3F_3N_2O_9Si$) *m/z* $[M+Na\text{-}CNPhCF_3]^+$ found 737.3012; calcd 738.1430.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-6.78 (m, 13H, Ar-H); 5.99 (bs, 1H, H-1), 5.26 (d, $J_{N,H}$ = 8.9 Hz, 1H, NH), 5.10-5.01 (m, 1H, H-3), 4.73 (d, ^2J = 12.1 Hz, 1H, C*H*$HCCl_3$), 4.62 (d, 1H, CH*H*CCl_3); 4.47 (dd, *J* = 9.9, 7.9 Hz, 1H, C*H*H^{Fmoc}), 4.40-4.33 (m, 1H, CH*H*^{Fmoc}), 4.31-4.15 (m, 3H, H-2, CH^{Fmoc}, H-6a); 4.10-3.91 (m, 3H, H-6b, H-4, H-5), 1.05 (s, 9H, tBu), 0.95 (s, 9H, tBu).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 154.0 (CO), 143.2 (C_q), 141.3 (C_q), 129.4-119.2 (C-Ar), 94.9 (CCl_3), 93.6 (C-1), 77.6 (C-3), 74.6 (C-4, C-5), 75.4 (*C*H_2CCl_3), 71.4 (C_q), 70.6 (*C*H_2^{Fmoc}), 65.9 (C-6), 55.6 (C-2), 46.5 (*C*H^{Fmoc}), 27.3 (tBu), 26.8 (tBu), 22.7 (*C*$(CH_3)_3$), 20.0 (*C*$(CH_3)_3$).

3-Azidopropyl 2,6-di-*O*-benzyl-*β*-D-galactopyranoside 5.

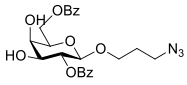


5

A suspension of compound **38**[23] (3.0 g, 5.7 mmol) in 80% aqueous AcOH (20 mL) was stirred at 70°C for 2 h when TLC (7: 3 cyclohexane:EtOAc) showed complete conversion of the starting material to a slower moving spot. Solvents were evaporated in vacuo, coevaporated with toluene to remove traces of AcOH. The residue was purified by flash chromatography using cyclohexane:EtOAc as eluent to give the pure product **10** (2.5 g, 92%) as yellow oil. $[\alpha]_D^{25} = +12.78^\circ$ (c 1.05, $CHCl_3$). ESI HR-MS ($C_{23}H_{29}N_3O_6$) *m/z* $[M+Na]^+$ found 466.2023; calcd 466.1954.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.25 (m, 10H, H-Ar), 4.95 (d, ^{2}J= 11.6 Hz, 1H, C*H*HPh), 4.69 (d, ^{2}J = 11.6 Hz, 1H, CH*H*Ph), 4.62 (s, 2H, CH_2Ph), 4.38 (d, $J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.07-4.00 (m, 2H, OCH_{2b}, H-4), 3.83-3.73 (m, 2H, H-6), 3.69-3.58 (m, 3H, OCH_{2a}, H-3, H-2), 3.55-3.49 (m, 1H, H-5), 3.44 (t, J = 5.4 Hz, 2H, CH_2N_3), 1.93 (m, 2H, C$H_2CH_2N_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 128.6-127.7 (C-Ar), 103.6 (C-1), 79.16 (C-5), 74.73 (*C*H_2Ph), 73.72 (*C*H_2Ph), 73.28 (C-2), 73.13 (C-3), 69.34 (C-6), 68.94 (C-4), 66.54 (O*C*H_2), 48.37 (*C*H_2N_3), 29.27 (*C*$H_2CH_2N_3$).

3-Azidopropyl 2,6-di-*O*-benzoyl-*β*-D-galactopyranoside 6.



6

A suspension of compound **39**[23] (3.0 g, 5.7 mmol) in 80% aqueous AcOH (20 mL) was stirred at 70°C for 2 h when TLC (7:3 cyclohexane: EtOAc) showed complete conversion of the starting material to a slower moving spot. Solvents were evaporated in vacuo, coevaporated with toluene to remove traces of AcOH. The residue was purified by flash chromatography using cyclohexane:EtOAc as eluent to give the pure product **6** (2.5 g, 92%). $[\alpha]_D^{25}$ = -3.94° (c 0.45, $CHCl_3$). ESI HR-MS ($C_{23}H_{25}N_3O_8$) *m/z* $[M+Na]^+$ found 494.1591; calcd 494.1539.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.38 (m, 10H, H-Ar), 5.14 (t, J = 8.9 Hz, 1H, H-2), 4.69-4.64 (m, 1H, H-6a), 4.56-4.50 (m, 2H, H-1, H-6b), 3.98 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-4), 3.97-3.88 (m, 1H, OCH_{2a}), 3.86-3.83 (m, 1H, H-5), 3.81-3.78 (m, 1H, H-3), 3.59-3.53 (m, 1H, OCH_{2b}), 3.21 (t, J = 6.5 Hz, 2H, CH_2N_3), 1.82-1.65 (m, 2H, C$H_2CH_2N_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.29, 166.62 (2 x CO), 133.7-128.4 (C-Ar), 101.09 (C-1), 99.9, 74.31 (C-2), 72.78 (C-3), 72.21 (C-5), 68.59 (C-4), 66.38 (O*C*H_2), 62.77 (C-6), 47.95 (*C*H_2N_3), 29.03 (*C*$H_2CH_2N_3$).

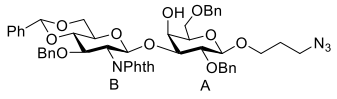
Preparations of disaccharides

Procedure A for glycosylation with thioglycoside donors with NIS/TfOH.
Donor (0.11 mmol) and acceptor (0.1 mmol) with activated 4 Å molecular sieves (0.1 g) were added at the solution of dry DCM (5 mL) and stirred for 20 min under nitrogen. NIS (0.2 mmol) and TfOH (0.02 mmol) were added at –30°C. The reaction was stirred for 2 and then allowed to warm up to rt. Stirring was continued for 12 h, monitoring by TLC (Tol:EtOAc or cyclohexane:EtOAc). The reaction was stirred for 12 h monitoring by (Tol:EtOAc or cyclohexane:EtOAc). the reaction was quenched with TEA, the solid filtered off and the solvent removed at reduced pressure. The crude was purified by flash chromatography (cyclohexane:EtOAc) to give the purified products.

Procedure B for glycosylation with thioglycoside donors with NIS/AgOTf.
A solution of donor (0.11 mmol) and acceptor (0.1 mmol) with activated 4 Å molecular sieves (0.1 g) in dry DCM (5 mL) was stirred for 20 min under nitrogen. NIS (0.2 mmol) and AgOTf (0.02 mmol) were added at –30°C. The reaction was stirred in the dark allowing to warm up to rt. After TLC (Tol:EtOAc or cyclohexane:EtOAc) showed complete reaction, the mixture was quenched with TEA, the solid filtered off and the solvent removed at reduced pressure. The crude was purified by flash chromatography (cyclohexane:EtOAc) to give the purified products.

Procedure C for glycosylation with trichloroacetimidate/trifluoroacetimidate donors
A solution of donor (0.11 mmol) and acceptor (0.1 mmol) with activated 4 Å molecular sieves (0.1 g) in dry DCM (5 mL) was stirred for 20 min under nitrogen. TMSOTf (0.02 mmol) was added at –10°C. After 4 h (TLC; Tol:EtOAc or cyclohexane:EtOAc) the reaction was quenched with TEA, the solid filtered off and the solvent removed at reduced pressure. The crude was purified by flash chromatography (Tol:EtOAc or cyclohexane:EtOAc) to afford the purified products.

3-Azidopropyl 4,6-*O*-benzilidene-3-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzyl-*β*-D-galactopyranoside 7a.



7a

Protocol A: **7a** not detected

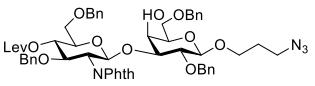
Protocol B. After flash chromatography (cyclohexane:EtOAc) a 3:2 mixture (61% yield) of disaccharide **7a** and the β-(1→4) product, which could not be isolated as a clean compound, was obtained.

Protocol C **7a**, 31% yield. $[\alpha]_D^{25}$ = +14.39° (c 0.25, $CHCl_3$). ESI HR-MS ($C_{51}H_{52}N_4O_{12}$) *m/z* [*M*+ Na]$^+$ found 935.3396; calcd 935.3479.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-6.87 (m, 24H, 24H-Ar) 5.65 (s, 1H, C*H*Ph), 5.48 (d, $J_{1,2}$ = 10.2 Hz, 1H, H-1^B), 4.81 (d, ^2J = 12.2 Hz, 1H, C*H*HPh), 4.59 (s, 2H, C*HH*Ph), 4.50 (d, ^2J = 12.2 Hz, 1H, CH*H*Ph), 4.45-4.43 (m, 1H, C*H*HPh), 4.34-4.32 (m, 2H, H-6a^B, H-2^B), 4.23-4.20 (m, 2H, CH*H*Ph, H-1^A), 4.05 (d, $J_{3,4}$ = 2.8 Hz, 1H, H-4^A), 3.89-3.78 (m, 4H, H-6b^B,OCH_{2a}, H-6a^A, H-5^B), 3.74-3.67 (m, 2H, H-6b^A, H-3^B), 3.60-3.57 (m, 3H, H-4^B, H-3^A, H-5^A), 3.48-3.40 (m, 2H, OCH$_{2b}$, H-2^A), 3.16 (dt, *J* = 3.2, 6.5 Hz, 2H, CH_2N$_3$), 1.70 (dt, *J* = 6.6, 13.3 Hz, 2H, CH_2CH$_2$N$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 129.13-123.28 (C-Ar), 103.34 (C-1^A), 101.40 (*C*HPh), 99.68 (C-1^B), 82.86, 82.79 (C-5^B), 77.59 (C-2^A), 74.44, 74.30 (*C*H$_2$Ph), 74.16 (*C*H$_2$Ph), 73.67 (*C*H$_2$Ph), 69.07 (C-6^A), 68.67 (C-6^B), 68.19 (C-4^A), 66.42 (O*C*H$_2$), 66.22 (C-3^B), 55.87 (C-2^B), 48.12 (*C*H$_2$N$_3$), 29.07 (*C*H$_2$CH$_2$N$_3$).

3-Azidopropyl 3,6-*O*-benzyl-2-deoxy-4-*O*-levulinoyl-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzyl-*β*-D-galactopyranoside 9a.



9a

Protocol A. No reaction observed.

Protocol B. **9a** and **9b** were obtained in 40% and 28% yield, respectively.

Protocol C. **9a** was purified in 31% yield.

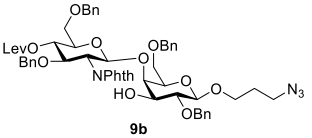
$[\alpha]_D^{25}$ = + 43.28° (c 0.65, $CHCl_3$). ESI HR-MS ($C_{56}H_{60}N_4O_{14}$) *m/z* [*M*+ Na]$^+$ found 1035.3871; calcd 1035.7878.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-6. 85 (m, 24H, H-Ar), 5.41 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1^B), 5.12 (t, *J* = 9.3 Hz, 1H, H-4^B), 4.66 (d, J= 12.4 Hz, 1H, C*H*HPh$_a$), 4.59-4.36 (m, 7H, 5 x C*H*Ph, H-3^B, H-2^B), 4.33 (d, ^2J = 12.4 Hz, 1H, CH*H*Ph), 4.23 (d, ^2J = 11.1 Hz, 1H, C*H*HPh), 4.20 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1^A), 4.08 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4^A), 3.90-3.80 (m, 1H, OCH$_{2a}$),3.73-3.42 (m, 9H, H-5^B, H-6a,b^B, H-6a,b^A, H-2,5,3^A, OCH$_{2b}$) 3.18 (t, *J* = 6.9 Hz, CH_2N$_3$), 2.71-2.68 (m, 2H, CH$_2^{Lev}$), 2.59-2.43 (m, 2H, CH$_2^{Lev}$), 2.18 (s, 3H, CH$_3^{Lev}$), 1.76-1.67 (m, 2H, CH_2CH$_2$N$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 171.6, 128.42-123.29 (C-Ar), 103.15 (C-1^A), 98.59 (C-1^B), 83.55 (C-3^A), 77.5 (C-5^A), 76.9 (C-3^B), 74.47 (CH$_2$Ph), 74.10 (CH$_2$Ph), 74.16 (CH$_2$Ph), 73.57 (CH$_2$Ph), 73.45 (C-5^B), 73.18 (C-2^A), 72.45 (C-4^B), 69.66 (C-6^B), 69.46 (C-6^A), 67.84 (C-4^A), 66.32 (O*C*H$_2$), 55.42(C-2^B) , 48.17 (*C*H$_2$N$_3$), 37.70 (*C*H$_2^{Lev}$), 29.79 (*C*H$_3^{Lev}$), 29.10 (*C*H$_2$CH$_2$N$_3$), 27.88 (*C*H$_2^{Lev}$).

Azidopropyl 3,6-*O*-benzyl-2-deoxy-4-*O*-levulinoyl-2-phthalimido-*β*-D-glucopyranosyl-(1→4)-2,6-di-*O*-benzyl-*β*-D-galactopyranoside 9b

$[\alpha]_D^{25}$ = + 18.87° (c 1.9, $CHCl_3$). ESI HR-MS ($C_{56}H_{60}N_4O_{14}$) *m/z* [*M*+ Na]$^+$ found 1035.3914; calcd 1035.3878.



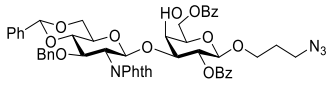
9b

^{1}H NMR (400 MHz, $CDCl_3$) δ) δ 7.23-6.83 (m, 24H, H-Ar), 5.23 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1^B), 5.09 (t, *J* = 9.7 Hz, 1H, H-4^B), 4.59 (d, *J* = 9.5 Hz, 1H, C*H*HPh), 4.54-4.22 (m, 9H, 7 x each C*H*HPh, H-3^B, H-2^B), 4.07 (d, $J_{1,2}$ = 7.7 Hz,1H, H-1^A), 3.84 (d, $J_{3,4}$ = 2.7 Hz,1H, H-4^A), 3.80-3.42 (m, 8H, OCH$_2$, H-6a,b^A, H-6a,b^B, H-5^A, H-5^B), 3.32 (dd, $J_{2,3}$ = 9.7 Hz, 1H, H-3^A), 3.24 (t, *J* = 6.8 Hz, 2H, CH_2N$_3$), 2.87 (t, *J* = 8.6 Hz, 1H, H-2^A), 2.54-2.35 (m, 4 H, CH$_2$CH$_2^{Lev}$), 2.08 (s, 1H, CH$_3^{Lev}$), 1.80-1.67 (m, 2H, CH_2CH$_2$N$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6-122.9 (C-Ar), 103.08 (C-1^A), 99.70(C-1^B), 79.89 (C-2^A), 76.8 (C-3^B), 76.6 (C-4^A), 73.79 (C-5^A), 73.46 (*C*H$_2$Ph) ,73.34 (2 x *C*H$_2$Ph), 72.86 (*C*H$_2$Ph), 72.70 (C-3^A), 72.64 (C-5^B), 69.84 (C-6$^{A/B}$),

69.71 (C-6$^{A/B}$), 66.02 (O*C*H$_2$), 55.68 (C-2^B), 48.35 (*C*H$_2$N$_3$), 37.74 (*C*H$_2^{Lev}$), 29.80 (*C*H$_2^{Lev}$), 29.17 (*C*H$_2$CH$_2$N$_3$), 27.95 (*C*H$_3^{Lev}$).

3-Azidopropyl 4,6-*O*-benzilidene-3-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside 8a



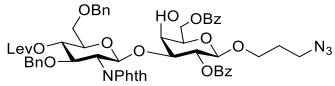
8a

Protocol B. **8a,** 53% yield.
Protocol C. **8a**, 77% yield.
[α]$_D^{25}$ = + 44.98° (c 0.4, CHCl$_3$). ESI HR-MS (C$_{51}$H$_{48}$N$_4$O$_{14}$): *m/z* = [*M*+Na]$^+$ found 963.3200; calcd 963.3065.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08-6.64 (m, 24H, H-Ar), 5.53 (s, 1H, C*H*Ph), 5.32 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1^B), 5.22 (t, *J* = 8.9 Hz,1H, H-2^A), 4.67-4.49 (m, 3H, H-6^A, C*H*HPh), 4.37-4.29 (m, 2H, CH*H*Ph, H-1^A), 4.29-4.22 (m, 2H, H-6a^B, H-3^B), 4.18 (dd, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 10.1 Hz, 1H, H-2^B), 4.11 (dd, 1H, $J_{3,4}$ = 2.8 Hz, H-4^A), 3.83-3.68 (m, 5H, H-5^A, H-3^A, H-4^B, H-6b^B, OCH$_{2a}$), 3.62-3.53 (m, 1H, H-5^B), 3.31 (dt, *J* = 4.3, 8.6 Hz, 1H, OCH$_{2b}$), 3.01-2.85 (m, 2H, C*H*$_2$N$_3$), 1.66-1.42 (m, 2H, C*H*$_2$CH$_2$N$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 166.4-164.5 (2 x C=O), 137.7-122.7 (C-Ar), 101.4 (*C*HPh), 101.2 (C-1^A), 99.9 (C-1^B), 82.7 (C-4^B), 80.8 (C-3^A), 74.2 (C-3^B), 74.0 (*C*H$_2$Ph), 71.9 (C-5^A), 70.5 (C-2^A), 68.6 (C-6^B), 68.5 (C-4^A), 66.3 (C-5^B), 65.9 (O*C*H$_2$), 63.5 (C-6^A), 55.5 (C-2^B), 47.8 (*C*H$_2$N$_3$), 28.9 (*C*H$_2$CH$_2$N$_3$).

3-Azidopropyl 3,6-*O*-benzyl-2-deoxy-4-*O*-levulinoyl-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside 10a.



10a

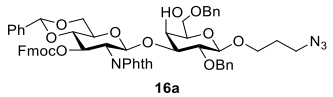
Protocol A. No product formation.
Protocol B. **10a,** 65% yield.
Protocol C. **10a**, 33% yield.
[α]$_D^{25}$ = + 62.78° (c 1.4, CHCl$_3$). ESI HR-MS (C$_{56}$H$_{56}$N$_4$O$_{16}$) *m/z* [*M*+Na]$^+$ found 1063.3577; calcd 1063.3589.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05-6.84 (m, 24H, H-Ar), 5.36 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1^B), 5.31 (d, *J* = 8.9 Hz, 1H, H-4^B), 5.08 (t, *J* = 9.1 Hz, 1H, H-2^A), 4.61-4.44 (m, 5H, H-6^A, 3 x C*H*HPh), 4.39 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^A), 4.36-4.34 (m, 1H, H-3^B), 4.31-4.29 (m, 1H, H-2^B), 4.27-4.24 (m, 2H, H-4^A, CH*H*Ph), 3.86-3.79 (m, 4H, OCH$_{2a}$, H-3,5^A, H-5^B), 3.60-3.58 (m, 2H, H-6^B), 3.41 (dt, *J* = 4.5, 9.2 Hz, 1H, OCH$_{2b}$), 3.20 (t, *J* = 6.5 Hz, 2H, C*H*$_2$N$_3$), 3.10-2.65 (m, 4H, *CH*$_2$*CH*$_2^{Lev}$), 2.16 (s, 3H, CH$_3^{Lev}$), 1.64-1.56 (m, 2H, C*H*$_2$CH$_2$N$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 166.8, 164.0 (C=O), 133.1-127.3 (C-Ar), 101.13 (C-1^A), 101.40, 98.82 (C-1^B), 81.05, 73.91, 73.49, 72.33, 72.04 (C-2^A), 70.49 (C-4^B), 69.52, 68.07, 65.84 (O*C*H$_2$), 63.73, 55.10 (C-2^B), 47.79 (*C*H$_2$N$_3$, *C*H$_2^{Lev}$), 37.68 (*C*H$_2^{Lev}$), 29.78 (*C*H$_3^{Lev}$), 28.86 (*C*H$_2$CH$_2$N$_3$), 27.84 (*C*H$_2^{Lev}$).

3-Azidopropyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(9-fluorenylmethyloxycarbonyl)-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzyl-*β*-D-galactopyranoside 16a.

Protocol A. After flash chromatography (Tol:EtOAc) **16a** and **16b** were purified in 30% and <5% yield, respectively.



16a

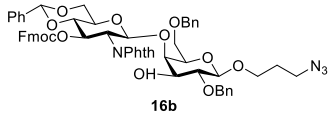
Protocol B. **16a**, 38% yield; **16b**, 26% yield.
[α]$_D^{25}$ = +10.37° (c 0.9, CHCl$_3$). ESI HR-MS (C$_{59}$H$_{56}$N$_4$O$_{14}$) *m/z* [*M*+Na]$^+$ found 1067.3629; calcd 1067.3691.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63-6.85 (m, 27 H, H-Ar), 5.71 (t, *J* = 10.1 Hz, 1H, H-3^B), 5.62 (d, $J_{1,2}$ = 8.7 Hz, 1H, H-1^B), 5.51 (s, 1H, C*H*Ph), 4.51, 4.48 (2 d, ^2J = 12.3 Hz, 2H, 2 x C*HH*Ph), 4.47 (dd, $J_{2,3}$ = 10.4 Hz, 1H, H-2^B), 4.38 (d, ^2J = 11.7 Hz, 1H, C*H*HPh), 4.31 (dd, $J_{5a,6a}$ = 4.6 Hz, $J_{6a,6b}$ = 10.2 Hz, 1H, H-6^A), 4.17-4.13 (m, 2H, H-1^A, CH*H*Ph), 4.01-3.99 (m, 2H, H-4^A, CH$_2^{Fmoc}$), 3.87-3.81 (m, 2H, H-4^B, CH^{Fmoc}), 3.79-3.61 (m, 5H, H-6$^B_{a,b}$, H-6b^A, OCH$_{2a}$, H-5^B), 3.57 (dd, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 9.5 Hz, 1H, H-3^A), 3.51 (t, *J* = 6.0 Hz,

1H, H-2^{A}), 3.39 (dd, $J_{4,5}$ = 7.7 Hz, $J_{5,6a}$ = 9.2 Hz, 1H, H-5^{A}), 3.36-3.33 (m, 1H, OCH$_{2b}$), 3.06 (dt, *J* = 3.5, 6.8 Hz, 2H, C*H*$_2$N$_3$), 1.64-1.57 (m, 2H, C*H*$_2$CH$_2$N$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 134.04-119.88 (C-Ar), 103.42 (C-1^{A}), 101.83 (*C*HPh), 99.45 (C-1^{B}), 83.06 (C-3^{A}), 78.91 (C-4^{B}), 77.55 (C-5^{A}), 74.27 (*C*H$_2$Ph), 73.69 (C-3^{B}), 73.49 (*C*H$_2$Ph), 73.38, 72.73 (C-2^{A}), 70.36, 69.02 (C-6^{B}), 68.57 (C-6^{A}), 68.20 (C-4^{A}), 66.48 (O*C*H$_2$), 66.29 (C-5^{B}), 60.42, 55.25 (C-2^{B}), 48.36, 48.12 (C*H*$_2$N$_3$), 46.32 (*C*H^{Fmoc}), 29.08 (C*H*$_2$CH$_2$N$_3$), 28.25, 21.07, 14.21.

3-Azidopropyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(9-fluorenylmethyloxycarbonyl)-2-phthalimido-*β*-D-glucopyranosyl-(1→4)-2,6-di-*O*-benzyl-*β*-D-galactopyranoside 16b.



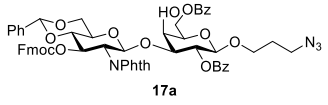
16b

[α]$_D^{25}$ = -8.99° (c 0.85, CHCl$_3$). ESI HR-MS (C$_{59}$H$_{56}$N$_4$O$_{14}$) *m/z* [*M*+Na]$^+$ found 1067.3680; calcd 1067.3691.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70-6.94 (m, 27 H, H-Ar), 5.89 (t, *J* = 9.3Hz, 1H, H-3^{B}), 5.51 (s, 1H, C*H*Ph), 5.47 (d, $J_{1,2}$ = 7.8 Hz,1H, H-1^{B}), 4.55-4.48 (m, 3H, 2 CH*H*Ph, H-2^{B}), 4.16-4.08 (m, 3H, 2 CH*H*Ph, includ. d, 4.12, $J_{1,2}$ = 7.7 Hz, H-1^{A}), 3.95 (m, 2H, CH^{Fmoc}, H-4^{A}), 3.89-3.62 (m, 7H, includ. H-4,5,6^{B}, H-6^{A}, OCH$_{2a}$), 3.58 (m, 1H, OCH$_{2b}$), 3.47 (m, 1H, H-5^{A}), 3.36 (dd, $J_{3,4}$ = 2.9, $J_{2,3}$ = 7.2 Hz, 1H, H-3^{A}), 3.30 (m, 2H, CH$_2$N$_3$), 3.00 (dd, $J_{1,2}$ = 7.7 Hz, $J_{2,3}$ = 9.8 Hz, 1H, H-2^{A}), 1.80 (m, 2H, C*H*$_2$CH$_2$N$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 134.0-119.9 (C-Ar), 103.27 (C-1^{A}), 101.7 (C*H*Ph), 100.4 (C-1^{B}), 79.9 (C-2^{A}), 79.1 (C-4^{B}), 77.2 (C-4^{A}), 74.9 (*C*H$_2$Ph), 73.6 (C-3^{B}), 73.4 (*C*H$_2$Ph), 72.8 (C-3^{A}), 70.2 (C-5$^{A/B}$), 68.8, 68.6 (C-6^{A,B}), 66.2 (O*C*H$_2$), 65.4 (C-5$^{A/B}$), 55.3 (C-2^{B}), 48.4 (*C*H$_2$N$_3$), 46.4 (*C*H^{Fmoc}), 29.2 (*C*H$_2$CH$_2$N$_3$).

3-Azidopropyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-3-*O*-(9-fluorenylmethyloxycarbonyl)-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside 17a.



17a

Protocol A. **17a**, 40% yield.

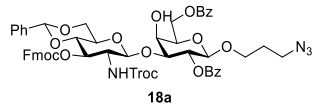
Protocol B. **17a**, 68% yield.

[α]$_D^{25}$ = + 36.44° (c 0.65, CHCl$_3$). ESI HR-MS (C$_{59}$H$_{52}$N$_4$O$_{16}$) *m/z* ([*M*+Na]$^+$ found 1095.3247; calcd 1095.3276.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01-7.07 (m, 27 H, H-Ar), 5.62-5.57 (m, 1H, H-3^{B}), 5.56 (d, $J_{1,2}$ = 8.5 Hz, 1H, H-1^{B}), 5.50 (s, 1H, C*H*Ph), 5.27 (t, *J* = 9.1 Hz, 1H, H-2^{A}), 4.63 (dd, $J_{5,6a}$ = 11.0 Hz, $J_{6a,6b}$ = 5.0 Hz, 1H, H-6a^{A}), 4.55 (dd, $J_{5,6a}$ = 11.0 Hz, $J_{6a,6b}$ = 4.9 Hz, 1H, H-6b^{A}), 4.41 (t, *J* = 9.4 Hz, 1H, H-2^{B}), 4.34 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^{A}), 4.31-4.27 (d, $J_{6a,6b}$ = 12.0 Hz, 1H, H-6a^{B}), 4.15 (d, $J_{3,4}$ = 3.2 Hz, 1H, H-4^{A}), 3.93 (d, *J* = 7.8 Hz, 2H, CH$_2^{Fmoc}$), 3.85-3.59 (m, 7H, H-3,5^{A}, H-4,5^{B}, H-6b^{B}, CH^{Fmoc}, OCH$_{2a}$), 3.36-3.30 (m, 1H, OCH$_{2b}$), 3.01-2.87 (m, 2H, C*H*$_2$N$_3$), 1.63-1.43 (m, 2H, C*H*$_2$CH$_2$N$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 166.4, 164.6, 154.3 (3 x C=O), 133.78-119.84 (C-Ar), 101.84 (*C*H$_2$Ph), 101.24 (C-1^{A}), 99.67 (C-1^{B}), 81.09 (C-4^{B}), 78.77 (C-3^{A}), 73.23, 71.88 (C-5^{A}), 70.48 (*C*H$_2^{Fmoc}$), 70.33 (C-2^{B}), 68.52 (C-4^{A}), 68.47 (C-6^{B}), 66.34 (C-5^{B}), 65.99 (O*C*H$_2$), 63.38 (C-6^{A}), 54.90 (C-2^{B}), 47.76 (*C*H$_2$N$_3$), 46.25 (*C*H^{Fmoc}), 28.86 (*C*H$_2$CH$_2$N$_3$).

3-Azidopropyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(9H-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside 18a.



18a

Protocol B. **18a,** 65% yield.

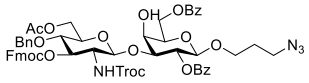
*Protocol C.***18a**, 70% yield.

[α]$_D^{25}$ = -10.29° (c 0.55, CHCl$_3$). ESI HR-MS (C$_{54}$H$_{51}$Cl$_3$N$_4$O$_{16}$) *m/z* ([*M*+ Na]$^+$ found 1134.2173; calcd (1134.2138).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.17-7.10 (m, 23H, Ar-H), 5.56-5.48 (m, 2H, C*H*Ph, H-2^{A}), 5.24 (t, *J* = 10.0 Hz, 1H, H-3^{B}), 5.09 (d, $J_{N,H}$ = 8.3 Hz, 1H, NH), 4.99 (d, $J_{1,2}$ = 7.8 Hz, 1H, H-1^{B}), 4.73 (dd, *J* = 4.9, 11.4 Hz, 1H, C*H*HCCl$_3$),

4.65 (dd, 1H, CH*H*CCl$_3$), 4.55 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^A), 4.37-4.25 (m, 4H, CH$_2^{Fmoc}$, H-6a^A, H-6a^B), 4.25-4.15 (m, 2H, CH^{Fmoc}, H-5^B), 4.09 (d, $J_{6a,6b}$ = 12.0 Hz, 1H, H-6b^A), 4.03-3.91 (m, 3H, incl. OCH$_{2a}$, H-3^A, H-4^A), 3.86-3.70 (m, 3H, H-2^B, H-6b^B, H-4^B), 3.69-3.48 (m, 2H, H-5^A ,OCH$_{2b}$), 3.26-3.13 (m, 2H, CH$_2$N$_3$), 2.05-1.51 (m, 2H, C*H*$_2$CH$_2$N$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.3, 155.0 (2 x CO), 143.0-120.1 (C-Ar), 101.6 (*C*HPh), 101.6 (C-1^A), 101.3 (C-1^B), 80.6 (C-4^A), 78.3 (C-4^B), 74.1 (C-3^B), 73.9 (C-6^A), 72.1 (C-3^A), 70.9 (C-2^A), 70.4 (*C*H$_2^{Fmoc}$), 68.7 (C-5^B), 68.4 (C-6^B), 66.4 (O*C*H$_2$), 63.4 (*C*H$_2$CCl$_3$), 57.2 (C-5^A), 47.9 (*C*H$_2$N$_3$), 46.5 (*C*H^{Fmoc}), 29.6 (*C*H$_2$CH$_2$N$_3$).

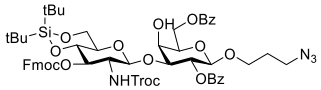
3-Azidopropyl 6-*O*-acetyl-4-*O*-benzyl-2-deoxy-3-*O*-(9H-fluoren-9-ylmethyl carbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-glucopyranosyl-(1→3)-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside 19a.



19a

Protocol C: **19a**, 50% yield.
[α]$_D^{25}$ = +2.96° (c 0.6, CHCl$_3$). ESI HR-MS (C$_{56}$H$_{55}$Cl$_3$N$_4$O$_{17}$) *m/z* ([*M*+ K]$^+$ found 1199.2210; calcd 1199.2259.
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14-7.31 (m, 23H, Ar-H), 5.52 (dd, $J_{2,3}$ = 9.4 Hz, $J_{3,4}$ = 8.0 Hz, 1H, H-2^A), 5.19-5.08 (m, 2H, NH, H-3^B), 4.86 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1^B), 4.76-4.63 (m, 4H, C*H*$_2$Ph, C*H*HCl$_3$), 4.56 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1^A), 4.51 (d, *J* = 11.3 Hz, 1H, C*H*HCl$_3$), 4.44-4.30 (m, 4H), 4.24 (d, $J_{3,4}$ = 2.6 Hz, 1H, H-4^A), 4.18-4.12 (m, 2H), 4.04 (d, $J_{6a,6b}$ = 12.3 Hz, 1H, H-6), 4.00-3.90 (m, 3H), 3.66-3.51 (m, 4H), 3.25-3.17 (m, 2H, CH$_2$N$_3$), 2.06 (s, 3H, CH$_3$CO), 1.83-1.66 (m, 2H, C*H*$_2$CH$_2$N$_3$).
^{13}C NMR (101 MHz, CDCl$_3$) δ 133.4-120.2 (C-Ar), 101.1 (C-1^A), 100.6 (C-1 ^{B}), 81.4, 78.6 (C-2^A), 74.7, 73.9, 72.3, 70.8 (C-3^B), 70.3, 68.3 (C-4^A), 66.2, 63.5, 62.5, 62.0, 48.1 (OCH$_2$), 46.7 (CH^{Fmoc}), 29.2 (*C*H$_2$CH$_2$N$_3$), 21.6 (COCH$_3$).

3-Azidopropyl 4,6-*O*-di-*tert*-butylsilylidene-2-deoxy-3-*O*-(9H-fluoren-9-ylmethylcarbonate)-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-glucopyranosyl-(1→3)-2,6-di-O-benzoyl-*β*-D-galactopyranoside 20a.



20a

A solution of donor **20** (0.330 g, 0.38 mmol) and acceptor **11** (150 mg, 0.316 mmol) with activated 4 Å molecular sieves (0.2 g) in dry DCM (5 mL) was stirred for 20 min under nitrogen. TMSOTf (11.4 µL, 0.063 mmol) was added at 0°C. After 4 h (TLC; Tol:EtOAc 8:2) the reaction was quenched with TEA, the solid filtered off and the solvent removed at reduced pressure. The crude was purified by flash chromatography (Tol:EtOAc 8:2) to afford disaccharide **20a** (220 mg, 62% yield) as a pale solid.
[α]$_D^{25}$ = -33.62° (c 0.2, CHCl$_3$). ESI HR-MS (C$_{55}$H$_{63}$Cl$_3$N$_4$O$_{16}$Si) *m/z* [*M*+ Na]$^+$ found 1191.2927; calcd 1191.2966. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12-7.28 (m, 18H, Ar-H), 5.49 (dd, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 8.1 Hz, 1H, H-2^A), 5.09-5.00 (m, 2H, H-3^B, NH), 4.99-4.81 (m, 2H, incl. H-1^B, C*H*HCCl$_3$), 4.73-4.56 (m, 3H, incl. CH$_2^{Fmoc}$ CH*H*CCl$_3$), 4.53 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1^A), 4.41-4.19 (m, 4H, incl. CH^{Fmoc}, H-6a^B, H-6b^B), 4.17 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4^A), 4.13 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6), 4.06-3.81 (m, 5H, incl. H-3^A, CH$_{2a}$), 3.66-3.41 (m, 3H, incl. H-2^B, CH$_{2b}$), 3.31-3.15 (m, 2H, CH$_2$N$_3$), 1.86-1.62 (m, 2H, C*H*$_2$CH$_2$N$_3$), 1.03 (s, 9H, tBu), 0.92 (s, 9H, tBu).
^{13}C NMR (101 MHz, CDCl$_3$) δ 166.4, 165.2, 155.1, 154.6 (4 x CO), 143.4-120.1 (C-Ar), 101.3 (C-1^A), 101.1 (C-1^B), 100.0 (C$_q$), 80.3, 77.9, 77.2, 75.5, 75.1, 74.9, 73.8, 73.7, 72.0, 71.9, 70.6, 70.4, 68.6, 66.4, 66.2, 66.0, 63.4, 56.6 (C-2^B), 47.9 (O*C*H$_2$), 46.5 (*C*H^{Fmoc}), 29.0 (*C*H$_2$CH$_2$N$_3$), 27.3 (tBu), 26.8 (tBu), 22.7 (*C*(CH$_3$)$_3$), 19.9 (*C*(CH$_3$)$_3$).

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