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Structure-reactivity relationships in glycosylation chemistry

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Chapter 6: Mapping the reactivity of 2,3-di-N-acetyl glucuronic acid and 2,4-di-N-acetyl bacillosamine building blocks in the synthesis of a highly N-acetylated Acinetobacter Baumannii LUH5554 tetrasaccharide

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Introduction

The bacterial glycome presents an immensely diverse collection of polysaccharide structures and while the mammalian glycans are built up using a relatively small palette of monosaccharides with little structural variation, bacterial glycans are built up form hundreds of different monosaccharides having an enormous structural variety. Because of their unique structures, bacterial exopolysaccharides and capsular polysaccharides represent attractive targets for our immune system and these structures have been very successfully exploited in the development of vaccines to prevent bacterial infections.

Acinetobacter Baumannii is a Gram-negative bacterium and an opportunistic pathogen, primarily infecting people with a weakened immune system.[1] It is the "A" in the ESKAPE pathogens, six bacteria that have been identified by the World Health Organisation (WHO) as high risk pathogens because of their high rate of antibiotic resistance and (hospital-derived) infections.[2,3] Because of the threat they present to global health, alternative strategies to combat the ESKAPE pathogens are direly needed and the development of active or passive immunisation strategies present attractive options. *A. baumannii* strains express a polysaccharide capsule, shielding the bacterial cell from its surrounding and environmental influences,[4] and these carbohydrates may be attractive targets for vaccine development.[5, 6] Synthetic fragments of these capsular polysaccharides can serve as well-defined antigens and be used for epitope mapping studies. They also allow for structural and interaction studies with binding partners, such as antibodies and immune cell receptors, at the atomic level.[7-9]

The capsular polysaccharide of *A. baumannii* LUH 5554 is built up of two rare monosaccharides, 2,4-di-*N*-acetyl-α-D-quinovose (2,4-di-*N*-acetyl bacillosamine, QuiNAc4NAc) and 2,3-di-*N*-acetyl-β-D-glucuronic acid (GlcNAc3NAcA) that form tetrasaccharide repeating units, with the structure [→4)-β-D-Glc*p*NAc3NAcA-(1→3)-α-D-Qui*p*NAc4NAc-(1→3)-α-D-Qui*p*NAc4NAc-(1→4)-β-D-Glc*p*NAc3NAcA-(1→] (***Figure 1***).[10] Strikingly, the repeating unit does not contain a single alcohol functionality but only features deoxy centres, carboxylates and acetamide groups! This Chapter describes the assembly of the *A. baumannii* LUH 5554 tetrasaccharide repeating unit. It presents effective multi-Gram scale routes of synthesis towards the monosaccharide building blocks and maps their reactivity in model glycosylation reactions. These studies have allowed the stereoselective assembly of the tetrasaccharide and will be of benefit in synthesis campaigns directed at the assembly of other bacterial glycans. For example, the rare GlcNAc3NAcA and QuiNAc4NAc constituents can also be found in other bacteria such as *Fusobacterium nucleatum*, an anaerobic bacterium that lives in the human mouth where it causes periodontitis, furthermore the bacterium has been linked to colorectal cancer and pregnancy complications,[11] *Neisseria meningitidis*, which causes meningitis and other meningococcal diseases,[12] the halophilic bacterium *Haloferax denitrificans,*[13] *Psychrobacter cryohalolentis*, a bacterium

that lives in cold briny environments,[14] *Plesiomonas shigelloides*, which is responsible for severe cases of travellers' diarrhoea,[15] and the marine bacterium *Pseudoalteromonas*.[16]

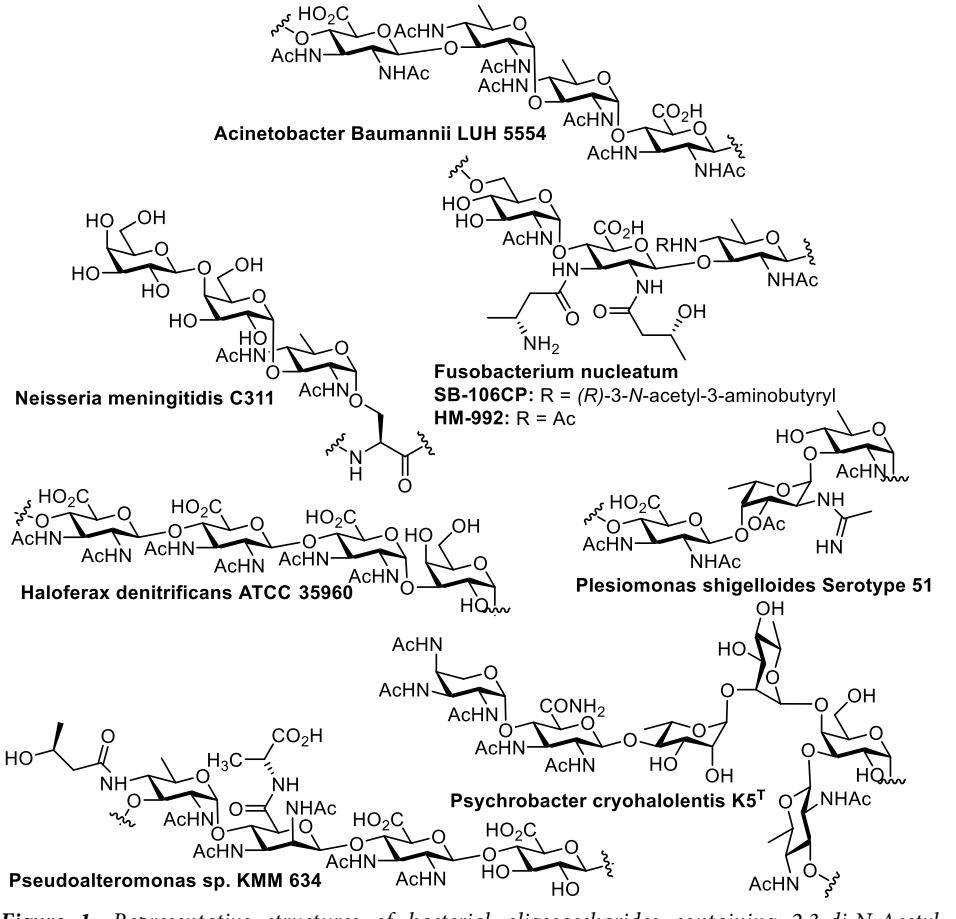


Figure 1: *Representative structures of bacterial oligosaccharides containing 2,3-di-N-Acetyl glucuronic acid and/or 2,4-di-N-acylated bacillosamine.*

Results and discussion

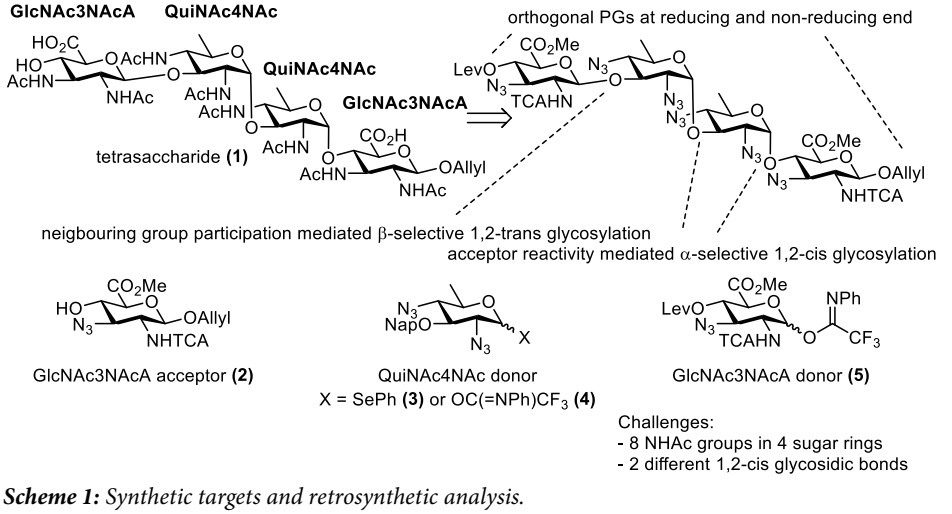
Retrosynthetic analysis

The retrosynthetic strategy towards the target *A. Baumannii* repeating tetrasaccharide is depicted in ***Scheme 1***. It contains an *O*-allyl group on the reducing end which can be used for future conjugation or immobilisation purposes, but can also serve as a

temporary protecting group to create a donor synthon to generate longer oligosaccharide fragments.

The hydroxyl at the non-reducing end is protected with a levulinoyl (Lev) ester, that can be removed orthogonally to all other used protecting groups. The designed protecting group strategy should thus allow for the generation of a tetrasaccharide donor and tetrasaccharide acceptor building block that can be exploited in the [4n+4] assembly of larger oligomers.

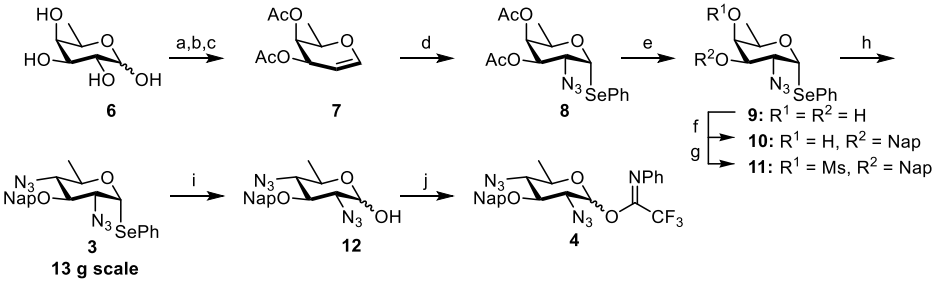
The GlcNAc3NAcA units in the *A. baumannii* tetrasaccharide are liked in a 1,2-*trans* fashion, so a stereoselective glycosylation can be accomplished using neighbouring group participation. Previously, 2,3-di-*N*-troc protected GlcNAc3NAcA building blocks[17] as well as a building block with a C-3-acetamide[18] have been unsuccessful and therefore it was decided to use an *N*-trichloroacetyl protected building block (**5**). The bacillosamine units in the tetrasaccharide are linked in a 1,2-*cis* fashion and relatively little is known about the stereoselectivity of glycosylations of bacillosamine donors carrying non-participating groups.[19] Approaches have been reported based on the use of '*in situ* anomerisation' strategy,[20] and indirect methods, based on glycosylations with a galactose- or fucose donor followed by C-4 inversion have also been used.[21, 22] Thus, here three building blocks were identified for the synthesis of the protected tetrasaccharide: a GlcNAc3NAcA acceptor for the reducing end with the anomeric allyl linker (**2**), a bacillosamine (QuiNAc4NAc) donor, which can be either a selenophenyl or *N*-phenyl trifluoroacetimidate (PTFAI) donor (**3** or **4**, respectively) and which has a C-2-azide as a non-participating masked amino functionality, and GlcNAc3NAcA donor **5** for the non-reducing end.



Scheme 1: *Synthetic targets and retrosynthetic analysis.*

Synthesis of 2,4-di-*N*-acetyl bacillosamine and 2,3-di-*N*-acetyl glucuronic acid building blocks

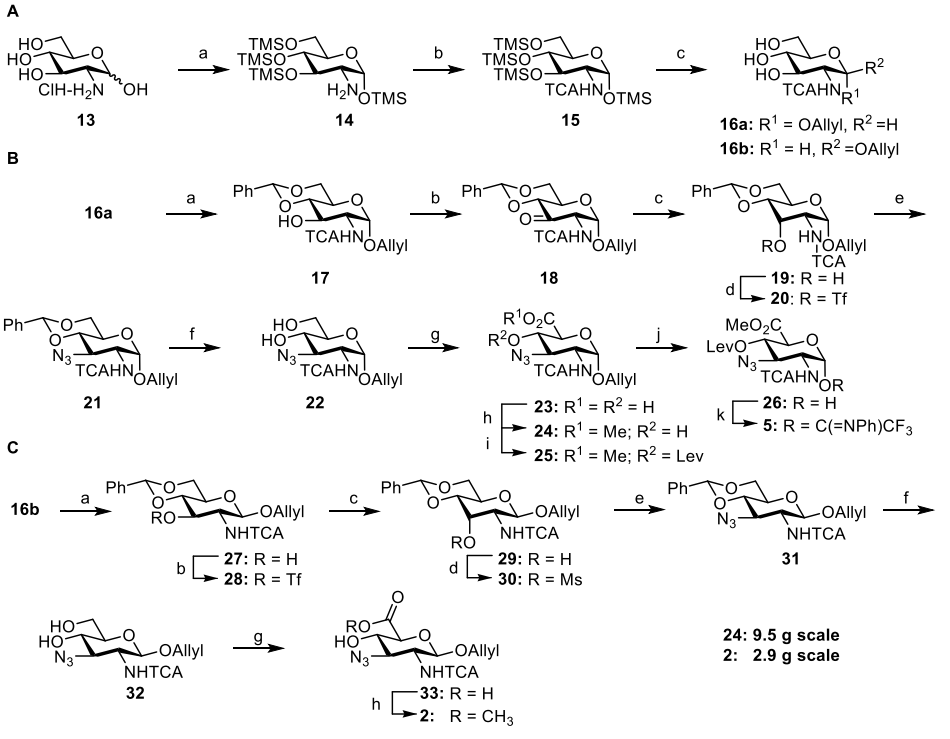
The synthesis of the bacillosamine building block (***Scheme 2***) starts from D-fucose (**6**), which is transformed into 3,4-di-*O*-acetyl-D-fucal (**7**) in high yield over 3 steps. In the next step, the anomeric selenophenol and the C-2-azide were simultaneously installed.[23, 24] After deacetylation under Zemplén conditions, a 2-naphthylmethyl (NAP) ether was regioselectively introduced *via* the intermediate dibutyltin ketal. The installation of the axial C-4-azide was first attempted using the C-4-triflate, but this proved unsuccessful because the triflate could not be isolated due to decomposition. The reaction between the C-4-mesylate and NaN_3 showed no conversion of the starting material but when the mesylate was treated with NaN_3 and TBABr at 70 °C,[19,24] the desired di-azide was obtained in 71%. This synthesis could be performed on large scale and selenophenyl donor **3** was generated on a 26 mmol scale. Compound **3** can be used directly as donor or converted to PTFAI-donor **4** by NIS mediated hydrolysis followed by conversion into the imidate.



Scheme 2: *Synthesis of the bacillosamine building blocks. Reagents and conditions: a) Ac_2O, pyridine; b) HBr/HOAc, DCM; c) Zn, NH_4Cl, EtOAc, 70 °C, 90% over 3 steps; d) Ph_2Se, BAIB, $TMSN_3$, DCM, -30 °C to -10 °C, 77%; e) NaOMe, MeOH, 82%; f) i: DBTO, toluene, 130 °C, ii: NapBr, TBAI, toluene, 100 °C, 81 %; g) MsCl, pyridine, 80%; h) NaN_3, TBABr, DMF, 70 °C, 71%; i) NIS, THF/H_2O, 99%; j) PTFAI-Cl, NaH, DCM, 64%.*

The design of the α-*O*-allyl-2,3-diamino glucuronic acid building block was inspired by the work of Yin and Seeberger and coworkers, who reported the preparation of allyl 2-deoxy-2-*N*-trichloroacetyl-α-D-glucopyranoside (**16a**, ***Scheme 3A***) from glucosamine in 37% over 6 steps.[18] Here, a more efficient route is presented, based on the work of Lin and Wang and coworkers.[25] First, glucosamine hydrochloride was selectively *O*-silylated using HMDS in acetonitrile. Next, the trichloroacetyl protecting group was installed in excellent yield. In one pot, the silyl ethers were cleaved and the anomeric allyl group was installed through a Fischer glycosylation. This method yielded

compound **16a** in 53% over 3 steps. In addition, 32% of β-anomer **16b** was obtained (***Scheme 3A***). The anomers were separated and both converted to the two corresponding glucuronic acid building blocks. The synthesis of glucuronic acid building blocks from the α-anomer (***Scheme 3B***) starts with protection of the C-4- and C-6-alcohols with a benzylidene acetal. Subsequently the C-3 alcohol was inverted by oxidation with Dess-Martin periodinane followed by reduction with $NaBH_4$ to form *allo*-configured building block **19**. The C-3-azide was installed by triflation of the axial alcohol, followed by substitution with NaN_3. The benzylidene was then removed using PTSA in methanol, yielding building block **22**. The regioselective oxidation of the primary alcohol was effected with TEMPO/BAIB to give, after methylation, acceptor **24**. The latter building block was assembled on 24 mmol scale and can be used as an acceptor, or turned into PTFAI-donor **5** by protection of the C-4-OH in a Steglich esterification with levulinic acid, deprotection of the anomeric allyl group using $PdCl_2$ and installation of the imidate. Acceptor **2** was synthesized in a similar fashion starting from β-anomer **16b** (***Scheme 3C***). The inversion of C-3-alcohol however, was achieved using a different strategy, because the oxidation-reduction sequence led to the formation of *gluco*-epimer alongside decomposition products. Thus, inversion of the C-3-alcohol in **27** was achieved by a Latrell-Dax epimerisation, through triflation of the alcohol followed by a substitution with $NaNO_2$. Next triflation of the *allose*-configured compound **29** was attempted. This reaction was significantly slower than the reaction on the corresponding α-anomer and the generated triflate decomposed with extended reaction times. Therefore, a mesylate was installed instead, which was subsequently substituted using tetrabutylammonium azide at 70 °C.



Scheme 3: *Synthesis of 2,3-di-N-acetyl glucuronic acid building blocks* ***A:*** *synthesis of 1-allyl-2-trichloroacetamide glucosamine. Reagents and conditions: a) HMDS, ACN; b) TCACl, DCM/pyr 7:3, 0°C to RT, 99% over 2 steps; c) AcCl, allyl-OH, 0 to 80 °C, 53% of* ***16a*** *and 32% of* ***16b; B:*** *synthesis of α-O-allyl acceptor* ***24*** *and α-PTFAI donor* ***5****. Reagents and conditions: a) $PhCH(OMe)_2$, PTSA, ACN, 60 °C, 300 mbar 86%; b) Dess-Martin periodinane, DCM; c) $NaBH_4$, MeOH, -10 °C to RT, 70% over 2 steps; d) Tf_2O, DMAP, DCM, 0 °C; e) NaN_3, DMF, 94% over 2 steps; f) PTSA, MeOH, reflux, 76%; g) TEMPO, BAIB, DCM/H_2O 2:1; h) MeI, $NaHCO_3$, DMF, 60% over 2 steps; i) LevOH, EDCI-HCl, DMAP, DCM, 100%; j) $PdCl_2$, MeOH/DCM, 3:2, 92% k) PTFAI-Cl, K_2CO_3, DCM/H_2O, 10:1, 70%;* ***C:*** *Synthesis of β-O-allyl acceptor* ***2****. Reagents and conditions: a) $PhCH(OMe)_2$, PTSA, ACN, 60 °C, 300 mbar 94%; b) Tf_2O, pyridine, DCM, - 10 °C; c) $NaNO_2$, DMF, 54% over 2 steps; d) MsCl, pyridine; e: Bu_4NN_3, acetonitrile, 70 °C, 65% over 2 steps; f) PTSA, methanol, 60 °C, 97%; g) TEMPO, BAIB, DCM/H_2O 2:1; h) MeI, $NaHCO_3$, DMF, 52% over 2 steps.*

Bacillosamine glycosylations

To study the glycosylating properties of the bacillosamine donors **3** and **4** their activation and the formation of reactive intermediates was studied by VT-NMR (***Figure 2***). When a mixture of donor **3** and Ph_2SO in CD_2Cl_2 was treated with Tf_2O at -80 °C, three new species were formed, which were identified as the α-triflate (**A**, H-1: 6.10 (d, *J* = 3.0 Hz)), the α-oxosulfonium triflate (**B**, H-1: 6.31 (d, *J* = 3.5 Hz)) and the β-oxosulfonium triflate (**C**, H-1: 5.61 (d, *J* = 8.3 Hz)). When the NMR probe was slowly warmed with 10 °C increments, the β-oxosulfoxonium triflate proved to be the least stable of the three intermediates and it almost fully disappeared at -40 °C, while decomposition of the other species started around -30 °C. When imidate donor **4** was treated with triflic acid at -80 °C, clean formation of the α-triflate was observed.

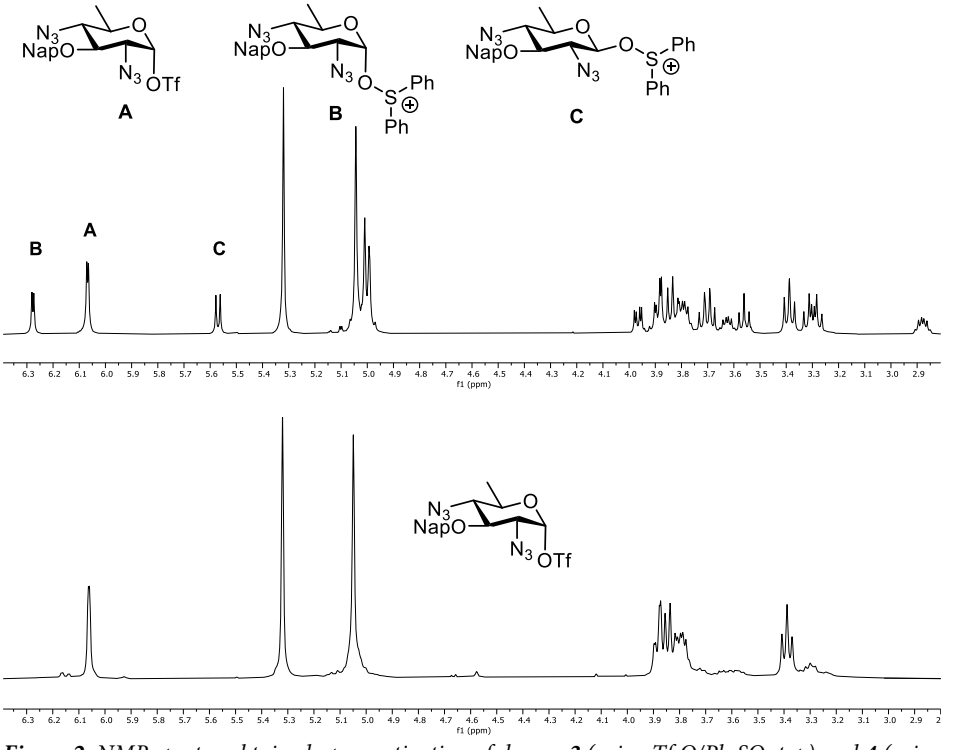
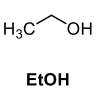


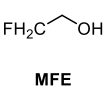
***Figure 2**: NMR spectra obtained upon activation of donors **3** (using Tf_2O/Ph_2SO, top) and **4** (using TfOH, bottom) at -50 °C in CD_2Cl_2.*

Next, the glycosylations of bacillosamine donor **3** were investigated in a series of Ph_2SO/Tf_2O mediated glycosylations (***Table 1***) with model acceptors of gradually varying nucleophilicity (EtOH-TFE).[23, 26-28] These glycosylation showed that the stereochemical outcome of glycosylations with donor **3** is highly dependent on the nucleophilicity of the acceptor, with the glycosylation of ethanol giving nearly complete β-selectivity, while glycosylation of trifluoroethanol provided primarily the α-product. Next 2,3-di-*N*-acetyl glucuronic acid acceptor **24** and bacillosamine acceptor **34,** obtained by treatment of glycosylation product **3D** with DDQ, were glycosylated with **3**. Based on previous studies both the CO_2Me group[29] as well as the azide (*this thesis,* chapter 5) were expected to have a strong disarming effect on the neighbouring alcohol, lowering its nucleophilicity and thus rendering the glycosylations with the acceptor α-selective. Indeed, the glycosylations of **3** with acceptor **24** and acceptor **34** provided the desired α-product with good selectivity. The yield of the reaction with the diaminoglucuronic acid acceptor **24** was moderate.

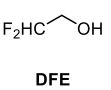
***Table 1**: Stereoselectivity of bacillosamine donor **3**, α:β ratios, yield in parentheses.*



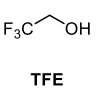
EtOH



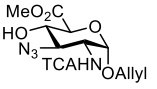
MFE



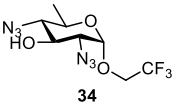
DFE



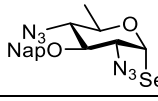
TFE



24



34

Donor	**EtOH**	**MFE**	**DFE**	**TFE**	**24**	**34**
	**3A** **1:8** (84%)	**3B** **1:2** (75%)	**3C** **2.9:1** (66%)	**3D** **22:1** (94%)	**3E** **12:1** (42%)	**3F** **6.6:1** (75%)

Conditions for pre-activation: 0.05 M donor in DCM, 1.3 eq Ph_2SO, 1.3 eq Tf_2O, 2.5 eq TTBP, 2 eq acceptor. Activation from -80 °C to -60 °C, glycosylation from -80 °C to -60 °C.

A potential mechanistic explanation for the stereochemical outcome of the glycosylations of donor **3** is given in ***Figure 3***. Upon activation of donor **3** with Ph_2SO and Tf_2O, three reactive species are formed, the α-triflate, the α-oxosulfonium triflate and the β-oxosulfonium triflate, with the latter being the least stable. Strong nucleophiles can react with one of the (more stable) α-species in an S_N2-type reaction to form the β-product, while less reactive nucleophiles require a stronger electrophile, such as the more reactive β-oxosulfonium triflate to form the α-product. The least reactive nucleophiles react likely react with an oxocarbenium ion intermediate in an S_N1-like reaction to form the α-product.

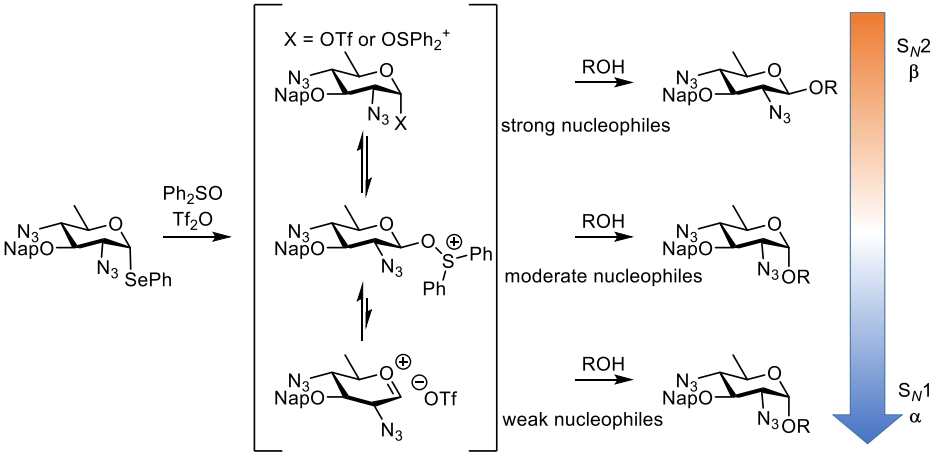
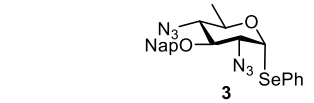


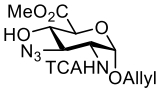
Figure 3: *Mechanistic rationale for the observed stereoselectivity of donor* ***3****.*

Synthesis of the tetrasaccharide

Next, the assembly of the target tetrasaccharide was undertaken, starting with optimization of the glycosylation between the bacillosamine donor and diaminoglucuronic acid acceptor (***Table 2***). Although the glycosylation of donor **3** and acceptor **24** under pre-activation conditions proceeded with high α-selectivity, the yield was relatively poor (Table 2, entries **1** and **2**). When imidate donor **4** was reacted with the same acceptor using in-situ activation conditions, the desired product was obtained in high yield, but with no stereoselectivity (entry **3**). When Ph_2SO was added to this activation procedure the α-selectivity was significantly improved, at the expense of a lower yield (entry **4**). The increased stereoselectivity in the latter glycosylation suggests that the oxosulfonium triflates play an important role in determining the stereoselective outcome of the glycosylation reaction, with the most reactive covalent species **C** (Figure 2), providing the desired α-product. The yield of the pre-activation glycosylation could be further improved by decreasing the amount of Ph_2SO and Tf_2O and raising the temperature of the glycosylation reaction (entries **5**-**7**). It has previously been shown that selenoglycosides can be completely activated using half an equivalent of Ph_2SO and Tf_2O.[23] The excess of diphenylsulfonium bistriflate, generated in the glycosylations described in entries 1 and 2, that is not used for the activation of the selenoglycoside may react with the acceptor alcohol, preventing it from being glycosylated.[30, 31] Indeed, the use of a bit more than half an equivalent of the activator led to complete activation of the bacillosamine donor and the desired increase in yield. The glycosylation with β-*O*-allyl acceptor **2** proceeded best and delivered the target disaccharide with the highest yield (entry **7**).

Table 2: *Optimisation of the glycosylations of the bacillosamine donors.*





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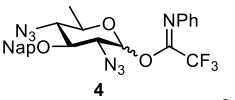
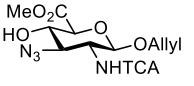
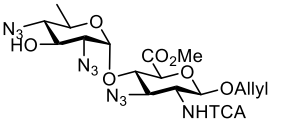




2



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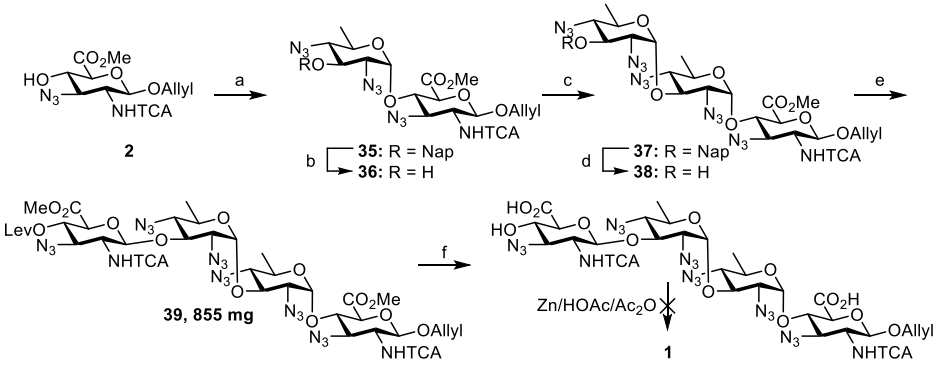
Entry	Donor (eq)	Acceptor (eq)	Activator (eq)	Additive (eq)	Solvent Temp [°C]	Product (yield)	α:β
1	**3** (1)	**24** (2)	Ph_2SO/Tf_2O (1.3/1.3)	TTBP (2.5)	DCM -80 → -60	**3E** (42%)	**12:1**
2	**3** (1.3)	**24** (1)	Ph_2SO/Tf_2O (1.3/1.3)	TTBP (2.5)	DCM -80 → -60	**3E** (31%)	**10:1**
3	**4** (1.3)	**24** (1)	TMSOTf (0.2)	-	DCM -80 → 0	**3E** (83%)	**1:1**
4	**4** (1.3)	**24** (1)	TMSOTf (0.2)	Ph_2SO (1.5)	DCM -80 → 0	**3E** (38%)	**9:1**
5	**3** (1.3)	**24** (1)	Ph_2SO/Tf_2O (1.3/0.65)	TTBP (2.5)	DCM -80 → 0	**3E** (55%)	**13:1**
6	**3** (1.3)	**24** (1)	Ph_2SO/Tf_2O (0.65/0.65)	TTBP (2.5)	DCM -80 → 0	**3E** (65%)	**13:1**
7	**3** (1.3)	**2** (1)	Ph_2SO/Tf_2O (0.65/0.65)	TTBP (2.5)	DCM -80 → 0	**35** (74%)[a]	**10:1**
8	**3** (1.3)	**36** (1)	Ph_2SO/Tf_2O (0.65/0.65)	TTBP (2.5)	DCM -80 → 0	**37** (38%)	**4.5:1**
9	**3** (1.3)	**36** (1)	Ph_2SO/Tf_2O (0.65/0.65)	TTBP (2.5)	1:1 Et_2O/DCM -80 → 0	**37** (81%)	**10:1**

Reactions with 3 A molecular sieves (rods, 3/16"). Entries 1-7 were performed with a donor concentration of 0.05 M. in entries 8 and 9, the concentration of the donor was 0.025 M due to lower solubility of acceptor ***36.*** *a: yield based on 0.1 mmol scale. On 4 mmol scale, the yield was 81%*

With disaccharide **35** the assembly of the target tetrasaccharide was continued (***scheme 4***). Thus, product **35** was treated with DDQ to obtain disaccharide acceptor **36**. It was observed that this disaccharide had a relatively low solubility and therefore it was used in the ensuing glycosylation reaction at a lower concentration (0.025 M *vs* 0.05M used for the condensation before). This led to formation of the trisaccharide in moderate

yield and with moderate α-selectivity (table 2, entry **8**). [§] Switching the solvent from DCM to a 1:1 mixture of DCM and diethyl ether increased both the α-selectivity and the yield (table 2, entry **9**). Likely the decreased solvent polarity promotes the S_N2 reaction of the β-oxosulfonium triflate while leveraging its high reactivity. Unmasking the Nap ether with DDQ the delivered trisaccharide acceptor **38**, which was reacted with donor **5** under in-situ activation conditions, to yield tetrasaccharide **39** in 59% yield on 670 μmol scale. Deprotection of the tetrasaccharide started with removal of the methyl and levulinoyl esters, When the tetrasaccharide was treated with sodium hydroxide for 2 hr at RT, the esters were selectively removed leaving the trichloroacetamides unscathed. Unfortunately, the subsequent Zn/AcOH reduction and subsequent acetylation to transform both the azides and trichloroactyl groups into the corresponding acetamides was unsuccessful. Investigations towards a full deprotection and acetylation sequence to successfully transform tetrasaccharide **39** into the target tetrasaccharide **1** are currently in progress.



Scheme 4: *assembly of tetrasaccharide **39** Reagents and conditions: a) first donor **3**, Ph_2SO, TTBP, Tf_2O, DCM, -80 °C → -60 °C → -80 °C, then acceptor **2**, -80 °C → 0 °C, 81%, α:β = 10:1; b) DDQ, 9:1 DCM/H_2O, 89%; c) first donor **3**, Ph_2SO, TTBP, Tf_2O, 1:1 Et_2O/DCM, -80 °C → -60 °C → -80 °C, then acceptor **36**, -80 °C → 0 °C, 81%, α:β = 10:1; d) DDQ, 9:1 DCM/H_2O, 62%; e) first donor **5** and acceptor **38**, DCM, 0 °C, then TMSOTf, 59%, α:β <1:20; f) 1:1 THF/1M aq. NaOH, 2 hr at RT*

[§] An attempt was made to increase the α-selectivity by using *N,N*-methylphenylformamide as additive, but this yielded only a trace amount of trisaccharide, with 1,1'-linked donor and unreacted acceptor as the main products

Conclusions

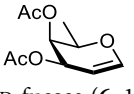
The synthesis of a highly *N*-acetylated oligosaccharide from the capsule of *Acinetobacter Baumannii,* consisting of 2,4-di-*N*-acetyl bacillosamine and 2,3-di-*N*-acetyl glucuronic acid, was accomplished. To this end, scalable routes towards the rare monosaccharide building blocks were developed. Bacillosamine building block **3** was prepared on 26 mmol scale and 2,3-di-*N*-acetyl glucuronic acid building block **24** on a 23 mmol scale. Next, the glycosylating properties of the bacillosamine donors were investigated by low temperature NMR characterisation of reactive species that were formed upon activation and a series of glycosylation reactions with a set of model acceptors, of gradually decreasing nucleophilicity. Activation of the bacillosamine selenophenyl donor **3** with Ph_2SO and Tf_2O led to the formation of three reactive species upon reaction, the anomeric α-triflate, α-oxosulfonium triflate and the β-oxosulfonium triflate. The latter β-oxosulfonium triflate proved to be the least stable of the three intermediates. PTFAI donor **4** generated only the α-triflate upon reaction with TfOH. It was found that the stereoselectivity of glycosylations of donor **3** under pre-activation conditions strongly depends on the nucleophilicity of the acceptor, as the stereoselectivity gradually changed from nearly completely β-selective for the most nucleophilic acceptor (ethanol) to completely α-selective for the weakest nucleophile (trifluoroethanol). The carbohydrate acceptors that were studied in the context of the assembly of the target *A. baumannii* tetrasaccharide provided α-selective glycosylations, which can be accounted for by the presence of the flanking de-activating groups in these acceptors (*i.e.* the neighboring methyl ester and azides). It was found that Ph_2SO played an important role in shaping the stereoselectivity of the glycosylations, pointing to the reactive β-oxosulfonium triflate as an important intermediate for the α-selective bacillosaminylation reactions. In these glycosylations, Ph_2SO thus functions as a nucleophilic additive to modulate the reactivity of the glycosylating species, similar to the formamide additives that have recently gained significant attention in the development of stereoselective glycosylation reactions. The developed protecting group scheme not only allowed to generate the target tetrasaccharide, it will also enable the generation of tetrasaccharide building blocks to assemble larger fragments of the *A. baumannii* polysaccharide in a [4n+4] glycosylation approach. These can be used to study the structural properties of these fascinating highly *N*-acetylated oligosaccharide structures and their interaction with components of the host immune system.

Experimental

General experimental procedures

General experimental procedures: All chemicals were of commercial grade and used as received unless stated otherwise. Dichloromethane (DCM) was stored over activated 4 Å molecular sieves for at least 24 h before use. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over P_2O_5 and stored at -20°C under a nitrogen atmosphere. Overnight temperature control was achieved by a FT902 Immersion Cooler (Julabo). Flash column chromatography was performed on silica gel 60 Å (0.04 – 0.063 mm, Screening Devices B.V.). Size-exclusion chromatography was performed on Sephadex (LH-20, GE Healthcare Life Sciences) by isocratic elution with DCM/MeOH (1/1, v/v). Thin-layer chromatography (TLC) analysis was conducted on TLC silica gel 60 plates (Kieselgel 60 F254, Merck) with UV detection by (254 nm) and by spraying with 20% sulfuric acid in ethanol or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g/L) and $(NH_4)_4Ce(SO4)_4{\cdot}2H_2O$ (10 g/L) in 10% aq. sulfuric acid followed by charring at ±250 °C. High-resolution mass spectrometry (HRMS) was performed on a Thermo Finnigan LTQ Orbitrap mass spectrometer equipped with an electrospray ion source in positive-ion mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275 °C) with resolution R = 60.000 at m/z 400 (mass range of 150-4000) and dioctylphtalate (m/z=391.28428) as lock mass, or on a Waters Synapt G2-Si (TOF) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV) and LeuEnk (m/z = 556.2771). as internal lock mass. 1H and 13C NMR spectra were recorded on Bruker AV-400, Bruker DMX-400, and Bruker AV-500 NMR instruments. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as an internal standard or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hertz (Hz). All presented 13C-APT spectra are proton-decoupled. NMR peak assignments were made using COSY and HSQC. When necessary, additional NOESY, HMBC and HMBC-GATED experiments were used to further elucidate the structure. The anomeric product ratios were based on careful analysis of the crude reaction mixture and the purified reaction product by integration of representative 1H NMR signals. IR spectra were recorded on a Shimadzu FTIR-8300 IR spectrometer and are reported in cm-1. Specific rotations were measured on a Propol automatic polarimeter or an Anton-Paar MCP-100 modular circular polarimeter at 589 nm unless otherwise stated.

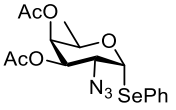
3,4-di-*O*-acetyl-D-fucal (7)



D-fucose (**6**, 10 g, 60.9 mmol) was dissolved in pyridine (0.2 M), after which Ac_2O (29 mL, 305 mmol, 5 eq) was added. The reaction mixture was stirred overnight and concentrated. The residue was dissolved in ethyl acetate and washed with 1M HCl and sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to obtain the crude per-acetylated fucose, which was used without further purification. Per-acetylated fucose was dissolved in DCM (0.25 M) and cooled to 0 °C. HBr (33% in HOAc, 77 mL, 425 mmol, 7.5 eq) was added dropwise and the reaction was allowed to warm to RT. After 2 hr, the reaction

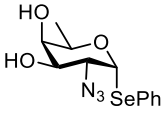
mixture was concentrated and azeotroped with toluene at 30 °C, yielding the anomeric bromide. The residue was dissolved in EtOAc (0.25 M) and washed with sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$, after which NH_4Cl (22.8 g, 425 mmol, 7.5 eq) and freshly activated zinc (27.8 g, 425 mmol, 7.5 eq) were added. The reaction mixture was heated to a reflux overnight, filtered and concentrated. The residue was purified over silica (5% Et_2O in pentane with 1% Et_3N) yielding the title compound as white solid. Yield: 10.9 g, 51 mmol, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 6.3, 2.0 Hz, 1H, H-1), 5.58 (dtd, *J* = 4.9, 2.0, 1.1 Hz, 1H, H-3), 5.29 (dt, *J* = 4.9, 1.6 Hz, 1H, H-4), 4.64 (dt, *J* = 6.3, 1.9 Hz, 1H, H-2), 4.23 (qq, *J* = 6.5, 1.0 Hz, 1H, H-5), 2.16 (s, 3H, CH_3 Ac), 2.02 (s, 3H, CH_3 Ac), 1.28 (d, *J* = 6.6 Hz, 3H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.5 (C=O), 146.2 (C-1), 98.4 (C-2), 71.6 (C-5), 66.3 (C-4), 65.1 (C-4), 20.9, 20.8 (CH_3 Ac), 16.6 (C-6). Spectra in agreement with literature.[32]

Phenyl 2-deoxy-2-azido-3,4,-di-*O*-acetyl-1-seleno-α-D-fucopyranoside (8)



Compound **7** (19.38 g, 90.47 mmol) and diphenyl diselenide (28.24 g, 90.47 mmol, 1 eq) were dissolved in DCM (0.2M) and degassed with N_2 in an ultrasonic bath. After this, the solution was cooled to -30 °C and BIAB (29.14 g, 90.47 mmol, 1 eq) and $TMSN_3$ (23.69 mL, 180.9 mmol, 2 eq) were added. The reaction mixture was allowed to warm to -10 °C and kept at that temperature overnight. Excess reagents were quenched by the addition of 20 mL cyclohexene, after which the reaction mixture was allowed to warm to RT and concentrated under reduced pressure. Silica chromatography (2% acetone in pentane) yields the title compound as yellow oil. Yield: 28.70 g, 69.61 mmol, 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 2H, CH_{arom}), 7.34 – 7.27 (m, 3H, CH_{arom}), 5.95 (d, *J* = 5.4 Hz, 1H, H-1), 5.32 (dd, *J* = 3.3, 1.2 Hz, 1H, H-4), 5.13 (dd, *J* = 10.8, 3.2 Hz, 1H, H-3), 4.50 (dd, *J* = 6.4 Hz, 1.2 Hz, 1H, H-5), 4.23 (dd, *J* = 10.8, 5.4 Hz, 1H, H-2), 2.17 (s, 3H, CH_3 Ac), 2.07 (s, 3H, CH_3 Ac), 1.09 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 169.9 (C=O), 134.9, 129.4 (CH_{arom}), 128.3 (C_q), 128.2 (CH_{arom}), 84.6 (C-1), 71.8 (C-3), 70.3 (C-4), 67.7 (C-5), 59.0 (C-2), 20.9, 20.8 (CH_3 Ac), 16.0 (C-6). Spectra in agreement with literature.

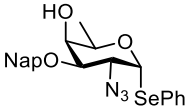
Phenyl 2-deoxy-2-azido-1-seleno-α-D-fucopyranoside (9)



Product **7** (28.70 g, 69.61 mmol) was dissolved in MeOH (0.5 M) and NaOMe (1.88 g, 34.80 mmol, 0.5 eq) was added. The mixture was stirred for 17 h after which the reaction was neutralized with Amberlite-H^+, filtered and concentrated under reduced pressure. The product was recrystallized using EtOAc/pentane and concentrated mother liquor was purified via silica chromatography (15% acetone in pentane), yielding product **18** as a white solid. Total yield: 18.80 g, 57.28 mmol, 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.52 (m, 2H, CH_{arom}), 7.37 – 7.22 (m, 3H, CH_{arom}), 5.91 (d, *J* = 5.3 Hz, 1H, H-1), 4.38 (q, *J* = 6.6 Hz, 1H, H-5), 4.06 (dd, *J* = 9.9, 5.3 Hz, 1H, H-2), 3.88 – 3.75 (m, 2H, H-3, H-4), 2.67 (s, 2H, 3-OH, 4-OH), 1.26 (d, *J* = 6.6 Hz, 3H,

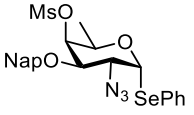
H-6); ^{13}C NMR (75 MHz, $CDCl_3$) 134.7, 129.4 (CH_{arom}), 128.7 (C_q), 128.1 (CH_{arom}), 85.2 (C-1), 71.7, 71.5 (C-3, C-4), 68.9 (C-5), 62.1 (C-2), 16.2 (C-6). Spectra in agreement with literature.[33]

Phenyl 2-deoxy-2-azido-3-*O*-(2-naphthyl)methyl-1-seleno-α-D-fucopyranoside (10)



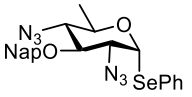
Compound **9** (18.8 g, 57.3 mmol) and Bu_2SnO (14.5 g, 58.4 mmol, 1.02 eq) were dissolved in toluene in a flask equipped with a Dean-Stark apparatus. The reaction mixture was heated to a vigorous reflux for under removal of water for 2 hr, after which NapBr (13.3 g, 60.1 mmol, 1.05 eq) and TBABr (19.4 g, 60.1 mmol, 1.05 eq) were added at 60 °C. The reaction mixture was then heated to a reflux for 1 hr, after which it was cooled to RT and quenched with 10% aq. KF solution. The phases were separated and the aqueous phase was extracted with ethyl acetate. Combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified over silica (5% acetone in pentane) to yield the title compound as yellow solid. Yield: 21.7 g, 46.3 mmol, 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 4H, CH_{arom}), 7.60 – 7.54 (m, 2H, CH_{arom}), 7.55 – 7.46 (m, 3H, CH_{arom}), 7.31 – 7.23 (m, 4H, CH_{arom}), 5.89 (d, *J* = 5.4 Hz, 1H, H-1), 4.91 (d, *J* = 11.2 Hz, 1H, C*H*H Nap), 4.85 (d, *J* = 11.5 Hz, 1H, CH*H* Nap), 4.28 (q, *J* = 6.6 Hz, 1H, H-5), 4.20 (dd, *J* = 10.2, 5.3 Hz, 1H, H-2), 3.89 (dt, *J* = 3.1, 1.5 Hz, 1H, H-4), 3.74 (dd, *J* = 10.2, 3.1 Hz, 1H, H-3), 2.42 (t, *J* = 1.6 Hz, 1H, 4-OH), 1.24 (d, *J* = 6.6 Hz, 3H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6 (CH_{arom}), 133.4, 133.3 (C_q), 129.2, 128.8 (CH_{arom}), 128.6 (C_q), 128.1, 128.0, 127.9, 127.9, 127.1, 126.5, 126.4, 125.8 (CH_{arom}), 85.3 (C-1), 79.4 (C-3), 72.4 (CH_2 Nap), 68.7, 68.7 (C-4, C-5), 60.4 (C-2), 16.2 (C-6). Spectra in agreement with literature.[24]

Phenyl 2-deoxy-2-azido-3-*O*-(2-naphthyl)methyl-4-*O*-methanesulfonyl-1-seleno-α-D-fucopyranoside (11)



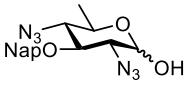
Compound **10** (21.7g, 46.3 mmol) was dissolved in pyridine (0.5 M), after which methanesulfonyl chloride (5.4 mL, 69.4 mmol, 1.5 eq) was added dropwise. After full conversion as indicated by TLC, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1M HCl and sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated. Silica chromatography (15% acetone in pentane) yields the title compound as yellow oil. Yield: 20.3 g, 37.1 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.80 (m, 4H, CH_{arom}), 7.59 – 7.54 (m, 3H, CH_{arom}), 7.54 – 7.48 (m, 2H, CH_{arom}), 7.33 – 7.26 (m, 3H, CH_{arom}), 5.93 (d, *J* = 5.4 Hz, 1H, H-1), 5.11 (dd, *J* = 3.0, 1.1 Hz, 1H, H-4), 4.99 (d, *J* = 10.6 Hz, 1H, C*H*H Nap), 4.88 (d, *J* = 10.6 Hz, 1H, CH*H* Nap), 4.49 – 4.39 (m, 1H, H-5), 4.14 (dd, *J* = 10.4, 5.3 Hz, 1H, H-2), 3.85 (dd, *J* = 10.4, 3.0 Hz, 1H, H-3), 2.99 (s, 3H, CH_3 Ms), 1.27 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8 (CH_{arom}), 133.8, 133.4, 133.3 (C_q), 129.4, 128.7, 128.2, 128.2 (CH_{arom}), 127.9 (C_q), 127.9, 127.8, 126.5, 126.5, 126.2 (CH_{arom}), 84.6 (C-1), 79.0 (C-4), 77.5 (C-3), 73.2 (CH_2 Nap), 67.9 (C-5), 60.6 (C-2), 39.3 (CH_3 Ms), 16.6 (C-6). Spectra in agreement with literature.[24]

Phenyl 2,4-dideoxy-2,4-diazido-3-*O*-(2-naphthyl)methyl-1-seleno-α-D-quinopyranoside (3)



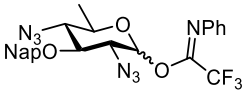
Compound **9** (20.3 g, 37.1 mmol) was dissolved in DMF with NaN_3 (24.1 g, 371 mmol, 10 eq) and TBABr (35.8 g, 111 mmol, 3 eq), after which the reaction mixture was heated to 70 °C. When TLC showed full conversion of the starting material, the mixture was cooled to RT, diluted with water and extracted with diethyl ether. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica (1% acetone in pentane) yielding the title compound as a yellow oil. Yield: 13.0 g, 26.4 mmol, 71%. $[\alpha]_D^{25}$ = 176.3° (c = 0.48, $CHCl_3$); IR (thin film): 741, 1084, 1269, 2105; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.79 (m, 4H, CH_{arom}), 7.61 – 7.53 (m, 3H, CH_{arom}), 7.51 – 7.44 (m, 2H, CH_{arom}), 7.33 – 7.25 (m, 3H, CH_{arom}), 5.81 (d, *J* = 5.3 Hz, 1H, H-1), 5.06 (d, *J* = 10.5 Hz, 1H, C*H*H Nap), 5.02 (d, *J* = 10.6 Hz, 1H, CH*H* Nap), 4.04 (dq, *J* = 10.1, 6.2 Hz, 1H, H-5), 3.87 (dd, *J* = 9.9, 5.3 Hz, 1H, H-2), 3.62 (t, *J* = 9.6 Hz, 1H, H-3), 3.20 (dd, *J* = 10.1, 9.3 Hz, 1H, H-4), 1.28 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7 (CH_{arom}), 134.5, 133.4, 133.3 (C_q), 129.3, 128.4 (CH_{arom}), 128.3 (C_q), 128.2, 128.2, 127.8, 127.7, 126.4, 126.3, 126.3 (CH_{arom}), 84.7 (C-1), 81.0 (C-3), 76.0 (CH_2 Nap), 69.6 (C-5), 68.3 (C-4), 65.0 (C-2), 18.2 (C-6); HRMS: $[M+H]^+$ calcd for $C_{23}H_{22}N_6O_2SeH$ 495.10428 , found 495.10387.

2,4-dideoxy-2,4-diazido-3-*O*-(2-naphthyl)methyl-α,β-D-quinopyranose (12)



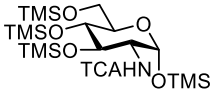
Compound **3** (1.80 g, 3.65 mmol) was dissolved in 0.25 M 1:1 and cooled to 0 °C. NIS (1.23 g, 5.47 mmol, 1.5 eq) was added and the reaction mixture was slowly allowed to warm to RT. After full conversion, excess NIS was quenched with sat. aq. $Na_2S_2O_3$. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in DCM and washed with water. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica (10% → 20% acetone) yielding the title compound as white solid. Yield: 1.28 g, 3.62 mmol, 99%, α:β = 1:1.1; data reported for a 1:1 mixture of anomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 8H, CH_{arom}), 7.56 (td, *J* = 8.5, 1.7 Hz, 2H, CH_{arom}), 7.51 – 7.43 (m, 4H, CH_{arom}), 5.26 (t, *J* = 3.3 Hz, 1H, H-1α), 5.05 (d, *J* = 10.8 Hz, 3H, C*H*H Nap, CH_2 Nap), 4.97 (d, *J* = 10.7 Hz, 1H, CH*H* Nap), 4.51 (dd, *J* = 7.9, 4.4 Hz, 1H, H-1β), 3.94 – 3.83 (m, 2H, H-3α, H-5α), 3.62 (d, *J* = 4.6 Hz, 1H, 1-OHβ), 3.44 (dd, *J* = 10.1, 2.8 Hz, 1H, H-2α), 3.37 (dd, *J* = 9.7, 7.8 Hz, 1H, H-2β), 3.29 (dd, *J* = 9.7, 8.8 Hz, 1H, H-3β), 3.23 (dq, *J* = 9.6, 5.9 Hz, 1H, H-5β), 3.16 (ddd, *J* = 10.2, 9.2, 2.2 Hz, 2H, H-4αβ), 3.04 (dd, *J* = 3.5, 1.3 Hz, 1H, 1-OHα), 1.34 (d, *J* = 5.9 Hz, 3H, H-6β), 1.31 (d, *J* = 6.2 Hz, 3H, H-6α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 134.7, 133.4, 133.4, 133.3 (C_q), 128.5, 128.2, 128.2, 127.8, 127.8, 127.6, 127.6, 126.4, 126.3, 126.3, 126.3, 126.2 (CH_{arom}), 96.1 (C-1β), 92.1 (C-1α), 81.3 (C-3β), 78.5 (C-3α), 75.7, 75.7 (CH_2 Nap), 71.1 (C-5β), 68.7 (C-4β), 67.7 (C-2β, C-4α), 66.8 (C-5α), 64.2 (C-2α), 18.52 (C-6αβ); HRMS: $[M+H-N_2]^+$ calcd for $C_{17}H_{18}N_4O_3H$ 327.14517, found 327.14486

_N_-phenyl-_O_-(2,4-dideoxy-2,4-diazido-3-_O_-(2-naphthyl)methyl-α,β-D-quinopyranosyl) trifluoroacetimidate (4)



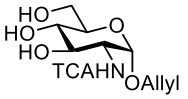
Compound **11** (1.28 g, 3.62 mmol) was dissolved in DCM, after which PTFAI-Cl (0.92 mL, 5.79 mmol, 1.6 eq) and NaH (60% dispersion in mineral oil, 220 mg, 5.43 mmol, 1.5 eq) were added. After 3 hr, an extra 0.5 eq of PTFAI-Cl and NaH were added. Upon full conversion, the reaction was quenched with water and extracted with DCM. The organic phase was dried with $MgSO_4$ and concentrated. The residue was purified over silica (98:1:1 pentane/Et_2O/Et_3N) to yield the title compound as a white solid. Yield: 1.21 g, 2.30 mmol, 64%, α:β = 1:3.5. Data reported for a 0.3:1 mixture. ^{1}H NMR (500 MHz, $CDCl_3$, 323 K) δ 7.84 (ddd, *J* = 13.2, 6.5, 4.2 Hz, 5.2H, CH_{arom}), 7.59 – 7.51 (m, 1.3H, CH_{arom}), 7.47 (p, *J* = 5.1 Hz, 2.6H, CH_{arom}), 7.30 (t, *J* = 7.7 Hz, 2.6H, CH_{arom}), 7.11 (td, *J* = 7.5, 1.2 Hz, 1.3H, CH_{arom}), 6.88 – 6.80 (m, 2.6H, CH_{arom}), 6.34 (s, 0.3H, H-1α), 5.44 (s, 1H, H-1β), 5.07 – 5.03 (m, 1.6H, C*H*H Napβ, CH_2 Napα), 5.00 (d, *J* = 10.9 Hz, 1H, CH*H* Napβ), 3.84 (t, *J* = 9.7 Hz, 0.3H, H-3α), 3.75 (dq, *J* = 12.2, 6.1 Hz, 0H, H-5α), 3.63 (t, *J* = 9.0 Hz, 1.3H, H-2αβ), 3.40 – 3.27 (m, 1H, H-3β), 3.25 – 3.08 (m, 2.3H, H-4αβ, H-5β), 1.38 – 1.33 (m, 3.9H, H-6αβ); ^{13}C NMR (126 MHz, $CDCl_3$, 323 K) δ 143.3, 134.8, 133.6, 133.5 (C_q), 129.0, 129.0, 128.5, 128.3, 128.2, 127.9, 127.9, 127.6, 127.5, 126.4, 126.3, 126.3, 126.3, 124.8, 119.6, 119.5, (CH_{arom}) 95.8 (C-1β), 93.9 (C-1α), 81.5 (C-3β), 78.8 (C-3α), 75.9 (CH_2 Napα), 75.8 (CH_2 Napβ), 72.1 (C-5β), 69.6 (C-5α), 68.3 (C-4α), 67.7 (C-4β), 65.9 (C-2β), 63.6 (C-2α), 18.5 (C-6α), 18.4 (C-6β); HRMS: $[M+H-N_2]^+$, calcd for $C_{25}H_{22}F_3N_5O_3H$ 498.17475, found 498.17448

2-Deoxy-2-trichloroacetamido-1,3,4,6-tetra-_O_-trimethylsilyl-α-D-glucopyranose (15)



D-glucosamine hydrochloride (**13**, 43.1 g, 200 mmol) and HMDS (105 mL, 500 mmol, 2.5 eq) were dissolved in 500 mL acetonitrile and stirred for 3 hr at RT, after which the solids were filtered off and the reaction mixture was concentrated under reduced pressure, yielding **14**. The residue was dissolved in 1L 7:3 DCM/pyridine and cooled to 0 °C. Trichloroacetyl chloride (24.7 mL) was added dropwise and the reaction mixture was allowed to warm to RT overnight after which solvents were removed under reduced pressure. The residue was dissolved in DCM and washed with water. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure, yielding the title compound as amber coloured oil, which was used without further purification. Yield: 121.7 g, 198 mmol, 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 9.6 Hz, 1H, NH), 5.12 (d, *J* = 3.4 Hz, 1H, H-1), 3.94 (td, *J* = 9.6, 3.4 Hz, 1H, H-2), 3.79 (dd, *J* = 9.5, 7.7 Hz, 1H, H-3), 3.76 – 3.69 (m, 2H, 2x H-6), 3.68 – 3.60 (m, 2H, H-4, H-5), 0.19 (s, 9H, CH_3 TMS), 0.17 (s, 9H, CH_3 TMS), 0.16 (s, 9H, CH_3 TMS), 0.11 (s, 9H, CH_3 TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (C=O), 91.9 (C-1), 73.5 (C-3), 73.1, 71.9 (C-4, C-5), 61.6 (C-6), 57.0 (C-2), 1.2 (CH_3 TMS), 0.9 (CH_3 TMS), 0.0 (CH_3 TMS), -0.2 (CH_3 TMS). Spectra in agreement with literature.[25]

Allyl 2-deoxy-2-trichloroacetamido-α-D-glucopyranoside (16a)

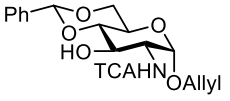


Compound **15** (117 g, 191 mmol) was dissolved in 500 mL allyl alcohol and cooled to 0 °C, after which acetyl chloride (13.6 mL, 191 mmol, 1 eq) was added. When TLC shows full removal of the TMS groups, the temperature was raised to 80 °C. When TLC shows disappearance of the starting material, the temperature is lowered to 0 °C and the reaction in quenched with $NaHCO_3$ (32.1 g, 382 mmol, 2 eq). Solids were filtered off and the solvent was removed under vacuum. The residue is purified with silica chromatography (5% methanol in DCM), yielding the title compound as off-white solid. Yield: 37.1 g, 102 mmol, 53%. ^{1}H NMR (400 MHz, MeOD) δ 5.92 (dddd, *J* = 17.1, 10.5, 6.2, 5.1 Hz, 1H, CH_2-C*H*=CH_2), 5.32 (dq, *J* = 17.3, 1.7 Hz, 1H, CH_2-CH=C*H*H), 5.21 – 5.15 (m, 1H, CH_2-CH=CH*H*), 4.95 (d, *J* = 2.8 Hz, 1H, H-1), 4.23 (ddt, *J* = 13.2, 5.1, 1.5 Hz, 1H, C*H*H-CH=CH_2), 4.03 (ddt, *J* = 13.2, 6.2, 1.3 Hz, 1H, CH*H*-CH=CH_2), 3.88 – 3.80 (m, 3H, H-2, H-3, H-6), 3.71 (dd, *J* = 11.8, 5.6 Hz, 1H, H-6), 3.63 (ddd, *J* = 9.7, 5.6, 2.2 Hz, 1H, H-5), 3.42 – 3.36 (m, 1H, H-4); ^{13}C NMR (101 MHz, MeOD) δ 164.2 (C=O), 135.2 (CH_2-*C*H=CH_2), 118.0 (CH_2-CH=*C*H_2), 96.9 (C-1), 74.1 (C-5), 72.2 (C-3, C-4), 69.3 (*C*H_2-CH=CH_2), 62.6 (C-6), 57.5 (C-2). Spectra in agreement with literature.[34] Further elution also yielded the β-anomer as orange solid. Yield: 22.0 g, 60.3 mmol, 32%, giving a total yield of 85%

Allyl 2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (16b)

^{1}H NMR (400 MHz, MeOD) δ 5.86 (ddt, *J* = 17.2, 10.7, 5.4 Hz, 1H, CH_2-C*H*=CH_2), 5.26 (dq, *J* = 17.3, 1.7 Hz, 1H, CH_2-CH=C*H*H), 5.10 (dq, *J* = 10.5, 1.5 Hz, 1H, CH_2-CH=CH*H*), 4.59 (d, *J* = 8.1 Hz, 1H, H-1), 4.33 (ddt, *J* = 13.2, 5.0, 1.6 Hz, 1H, C*H*H-CH=CH_2), 4.07 (ddt, *J* = 13.2, 5.7, 1.5 Hz, 1H, CH*H*-CH=CH_2), 3.88 (dd, *J* = 11.9, 2.1 Hz, 1H, H-6), 3.72 – 3.59 (m, 3H, H-2, , H-6), 3.35 – 3.24 (m, 2H); ^{13}C NMR (101 MHz, MeOD) δ 164.5, 135.4, 117.2, 101.3, 78.0, 75.0, 72.3, 71.0, 62.7, 59.2. spectra in agreement with literature.[35]

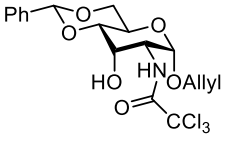
Allyl 2-deoxy-2-trichloroacetamido-4,6-*O*-benzylidene-α-D-glucopyranoside (17)



16a (37 g, 101 mmol), PTSA-H_2O (0.97 g, 5.1 mmol, 0.05 eq) and benzaldehyde dimethylacetal (16.8 mL, 112 mmol, 1.1 eq) were dissolved in 1L acetonitrile and heated to 60 °C at 300 mbar. After full conversion of the starting material, the reaction was quenched with 0.1 eq Et_3N and concentrated under reduced pressure. Crystallisation (DCM/pentane) yields the title compound as off-white solid. Yield: 39.7 g, 87 mmol, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H, CH_{arom}), 7.38 (qd, *J* = 3.7, 1.7 Hz, 3H, CH_{arom}), 6.96 (d, *J* = 8.7 Hz, 1H, NH), 5.88 (dddd, *J* = 16.9, 10.4, 6.4, 5.4 Hz, 1H, CH_2-C*H*=CH_2), 5.57 (s, 1H, C*H*Ph), 5.31 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H, CH_2-CH=CH*H*), 4.99 (d, *J* = 3.8 Hz, 1H, H-1), 4.29 (dd, *J* = 10.1, 4.7 Hz, 1H, H-6), 4.26 – 4.15 (m, 2H, H-2, C*H*H-CH=CH_2), 4.08 – 4.00 (m, 2H, H-3, CH*H*-CH=CH_2), 3.89 (td, *J* = 9.8, 4.7 Hz, 1H, H-5), 3.78 (t, *J* = 10.3 Hz, 1H, H-6), 3.61 (t, *J* =

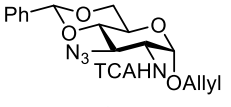
9.3 Hz, 1H, H-4), 2.63 (d, *J* = 3.2 Hz, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 (C=O), 137.0 (C_q), 133.0 (CH_2-*C*H=CH_2), 129.5, 128.5, 126.4 (CH_{arom}), 118.9 (CH_2-CH=*C*H_2), 102.1 (CHPh), 96.4 (C-1), 81.8 (C-4), 70.0 (C-3), 69.0, 68.8 (C-6, *C*H_2-CH=CH_2), 62.9 (C-5), 55.5 (C-2). Spectra in agreement with literature.[18]

Allyl 2-deoxy-2-trichloroacetamido-4,6-*O*-benzylidene-α-D-allopyranoside (19)



Compound **17** (39.1 g, 86 mmol) and Dess-Martin periodinane (47.6 g, 112 mmol, 1.3 eq) were dissolved in DCM and stirred until TLC showed full conversion. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ and extracted with DCM. The combined organic phases were dried and concentrated to yield the crude ketone **18** which was used immediately in the next reaction. The ketone was dissolved in methanol and cooled to -10 °C, after which $NaBH_4$ (13.1 g, 345 mmol, 4 eq) was added in small portions. After the final addition, the reaction mixture was allowed to warm to RT. After full conversion of the starting material, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic phase was dried with $MgSO_4$ and concentrated. Silica chromatography (20% Et_2O in pentane) yields the title compound as colourless oil that slowly solidifies. Yield: 27.4 g, 60.6 mmol, 70% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 6.6, 3.1 Hz, 2H, CH_{arom}), 7.44 (d, *J* = 8.8 Hz, 1H, NH), 7.40 – 7.35 (m, 3H, CH_{arom}), 5.87 (dddd, *J* = 17.0, 10.4, 6.5, 5.2 Hz, 1H, CH_2-C*H*=CH_2), 5.62 (s, 1H, C*H*Ph), 5.31 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.24 (dq, *J* = 10.4, 1.2 Hz, 1H, CH_2-CH=CH*H*), 4.99 (d, *J* = 4.2 Hz, 1H, H-1), 4.37 (dd, *J* = 10.3, 5.1 Hz, 1H, H-6), 4.30 – 4.23 (m, 2H, H-3, C*H*H-CH=CH_2), 4.23 – 4.17 (m, 2H, H-2, H-5), 4.05 (ddt, *J* = 13.0, 6.5, 1.2 Hz, 1H, CH*H*-CH=CH_2), 3.79 (t, *J* = 10.3 Hz, 1H, H-6), 3.65 (dd, *J* = 9.7, 2.8 Hz, 1H, H-4), 2.75 (d, *J* = 5.9 Hz, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (C=O), 137.0 (C_q), 133.0 (CH_2-*C*H=CH_2), 129.4, 128.5, 126.3 (CH_{arom}), 118.9 (CH_2-CH=*C*H_2), 102.0 (CHPh), 96.0 (C-1), 92.3 (CCl_3), 78.2 (C-4), 69.5 (*C*H_2-CH=CH_2), 69.1 (C-6), 67.3 (C-3), 57.7 (C-5), 51.2 (C-2). Spectra in agreement with literature.[18]

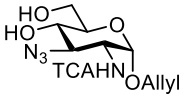
Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-4,6-*O*-benzylidene-α-D-glucopyranoside (21)



Compound **19** (27.4 g, 60.5 mmol) and DMAP (22.2 g, 182 mmol, 3 eq) were dissolved in DCM and cooled to -10 °C, after which triflic anhydride (20.3 mL, 121 mmol, 2 eq) was added dropwise, after which the reaction mixture was slowly allowed to warm to RT. After full of the starting material, the reaction mixture was acidified with 5 eq of acetic acid and washed with water. The organic phase was dried with $MgSO_4$ and concentrated at 25 °C, yielding triflate **20**. The crude triflate was dissolved in DMF with NaN_3 (19.7 g, 303 mmol, 5 eq) and stirred overnight, after which the reaction mixture was poured in 10x the volume of water under vigorous stirring. The precipitated solid was collected by filtration, washed with water, dissolved in DCM and washed with brine. Organic phase was dried with $MgSO_4$ and concentrated, yielding

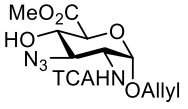
the slightly impure title compound as a white solid. Yield: 24.7 g, 51.6 mmol, 85% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H, CH_{arom}), 7.38 (dq, *J* = 8.5, 2.3 Hz, 3H, CH_{arom}), 6.90 (d, *J* = 9.5 Hz, 1H, NH), 5.87 (dddd, *J* = 17.0, 10.3, 6.5, 5.4 Hz, 1H, CH_2-C*H*=CH_2), 5.63 (s, 1H, C*H*Ph), 5.35 – 5.25 (m, 2H, CH_2-CH=C*H*$_2$), 4.91 (d, *J* = 3.7 Hz, 1H, H-1), 4.32 (dd, *J* = 10.3, 4.8 Hz, 1H, H-6), 4.24 (ddt, *J* = 12.7, 5.4, 1.3 Hz, 1H, C*H*H-CH=CH_2), 4.13 (ddd, *J* = 10.8, 9.6, 3.7 Hz, 1H, H-2), 4.04 (ddt, *J* = 12.7, 6.6, 1.2 Hz, 1H, CH*H*-CH=CH_2), 3.98 – 3.89 (m, 2H, H-3, H-5), 3.80 (t, *J* = 10.3 Hz, 1H, H-6), 3.70 (t, *J* = 9.6 Hz, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (C=O), 136.7 (C_q), 132.7 (CH_2-*C*H=CH_2), 129.3, 128.5, 126.0 (CH_{arom}), 119.3 (CH_2-CH=*C*H$_2$), 101.6 (CHPh), 96.0 (C-1), 80.4 (C-4), 69.0 (*C*H_2-CH=CH_2), 68.8 (C-6), 63.3 (C-5), 61.3 (C-3), 53.6 (C-2). Spectra in agreement with literature.[18]

Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-α-D-glucopyranoside (22)



Compound **21** (24 g, 50.2 mmol) and PTSA-H_2O (0.96 g, 5.02 mmol, 0.1 eq) were dissolved in methanol (0.3 M) and heated to a gentle reflux. After full conversion, the reaction was cooled to RT, neutralised with 0.2 eq Et_3N and concentrated under reduced pressure. The residue was purified over silica (25% acetone in pentane) to yield the title compound as white solid. Yield: 14.9 g, 38.2 mmol, 76%. ^{1}H NMR (400 MHz, Acetone) δ 8.22 (d, *J* = 8.3 Hz, 1H, NH), 5.92 (dddd, *J* = 17.2, 10.7, 5.9, 5.0 Hz, 1H, CH_2-C*H*=CH_2), 5.35 (dq, *J* = 17.3, 1.7 Hz, 1H, CH_2-CH-C*H*H), 5.16 (dq, *J* = 10.5, 1.4 Hz, 1H, CH_2-CH=CH*H*), 5.08 (d, *J* = 5.7 Hz, 1H, 4-OH), 4.92 (d, *J* = 3.6 Hz, 1H, H-1), 4.24 (ddt, *J* = 13.4, 5.0, 1.6 Hz, 1H, C*H*H-CH=CH_2), 4.08 – 4.01 (m, 2H, H-3, C*H*H-CH=CH_2), 3.86 – 3.71 (m, 4H, 6-OH, H-2, 2x H-6), 3.70 – 3.59 (m, 2H, H-4, H-5); ^{13}C NMR (101 MHz, Acetone) δ 162.6 (C=O), 134.9 (CH_2-*C*H=CH_2), 117.4 (CH_2-CH=*C*H$_2$), 96.0 (C-1), 73.6 (C-4), 71.1 (C-5), 68.7 (*C*H_2-CH=CH_2), 64.7 (C-3), 62.1 (C-6), 54.9 (C-2). Spectra in agreement with literature[18]

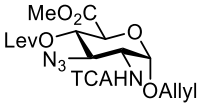
Methyl (Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-α-D-glucopyranosyl uronate) (24)



Compound **22** (14.8 g, 38.1 mmol) was dissolved in 300 mL 2:1 DCM/H_2O after which TEMPO (2.98 g, 19.1 mmol, 0.5 eq) and BAIB (30.7 g, 95 mmol, 2.5 eq) were added. After full conversion, the reaction mixture was concentrated under reduced pressure, yielding crude uronic acid **23**. The residue was coevaporated twice with toluene and dissolved in 200 mL DMF with $NaHCO_3$ (14.4 g, 171 mmol, 4.5 eq) and methyl iodide (17.8 mL, 286 mmol, 7.5 eq). After 18 hr, the reaction mixture was diluted with water and extracted twice with diethyl ether. Combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica (15% acetone in pentane) to yield the title compound as white solid. Yield: 9.5 g, 22.8 mmol, 60%. $[\alpha]_D^{25}$ = 70.5° (c = 0.63, $CHCl_3$); IR (thin film): 821, 1057, 1518, 1717, 2111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 9.4 Hz, 1H, NH), 5.88 (dddd, *J* = 17.0, 10.3, 6.6, 5.4 Hz, 1H, CH_2-C*H*-CH_2), 5.34 (dq, *J* = 17.2, 1.4 Hz, 1H, CH_2-CH=C*H*H), 5.29 (dq, *J* = 10.4, 1.1 Hz, 1H, CH_2-CH=CH*H*), 4.99 (d, *J* = 3.6 Hz, 1H, H-1), 4.29 (ddt, *J* = 12.5, 5.1, 1.2 Hz, 1H,

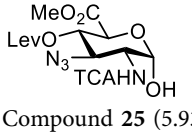
C*H*H-CH=CH_2), 4.24 (d, *J* = 9.7 Hz, 1H, H-5), 4.12 – 4.02 (m, 2, H-2, CH*H*-CH=CH_2), 3.92 (td, *J* = 9.6, 2.6 Hz, 1H, H-4), 3.87 (s, 3H, CH_3 CO_2Me), 3.77 (dd, *J* = 11.1, 9.3 Hz, 1H, H-3), 3.48 (d, *J* = 2.8 Hz, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C-6), 162.0 (C=O), 132.5 (CH_2-*C*H=CH_2), 119.6 (CH_2-CH=*C*H_2), 95.6 (C-1), 92.3 (CCl_3), 71.3 (C-4), 70.4 (C-5), 69.3 (*C*H_2-CH=CH_2), 63.5 (C-3), 53.2 (CH_3 CO_2Me), 52.7 (C-2); HRMS: $[M+Na]^+$ calcd for $C_{12}H_{15}Cl_3N_4O_6Na$ 438.99494, found 438.99469.

Methyl (Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-4-levulinoyl-α-D-glucopyranosyl uronate) (25)



24 (3.13 g, 7.50 mmol), levulinic acid (1.15 mL, 11.3 mmol, 1.5 eq) and DMAP (2.75 g, 22.5 mmol, 3 eq) were dissolved dichloromethane, after which EDC-HCl (2.16 g, 11.3 mmol, 1.5 eq) was added in portions. After full conversion of the starting material, the reaction mixture was diluted with DCM and washed with 1M aq. HCl and with sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to yield the pure title compound as white solid. Yield: 3.87 g, 7.50 mmol, 100%. $[\alpha]_D^{25}$ = 89.8° (c = 0.25, $CHCl_3$); IR (thin film): 756, 1057, 1152, 1251, 1518, 1717, 1759, 2111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 9.4 Hz, 1H, NH), 5.86 (dddd, *J* = 17.1, 10.3, 6.7, 5.4 Hz, 1H, CH_2-C*H*=CH_2), 5.37 – 5.26 (m, 2H, CH_2-CH=C*H*$_2$), 5.12 (t, *J* = 9.8 Hz, 1H, H-4), 5.03 (d, *J* = 3.6 Hz, 1H, H-1), 4.33 (d, *J* = 9.9 Hz, 1H, H-5), 4.28 (ddt, *J* = 12.7, 5.4, 1.3 Hz, 1H, C*H*H-CH=CH_2), 4.18 (ddd, *J* = 11.0, 9.4, 3.7 Hz, 1H, H-2), 4.08 (ddt, *J* = 12.8, 6.7, 1.1 Hz, 1H, CH*H*-CH=CH_2), 3.89 (dd, *J* = 11.0, 9.7 Hz, 1H, H-3), 3.77 (s, 3H, CH_3 CO_2Me), 2.89 – 2.78 (m, 1H, C*H*H Lev), 2.77 – 2.71 (m, 1H, CH*H* Lev), 2.71 – 2.65 (m, 1H, C*H*H Lev), 2.64 – 2.54 (m, 1H, CH*H* Lev), 2.20 (s, 3H, CH_3 Lev); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0 (C=O), 171.4, 167.8 (C-6, C=O), 161.9 (C=O), 132.3 (CH_2-*C*H=CH_2), 119.9 (CH_2-CH=*C*H_2), 95.3 (C-1), 70.4 (C-4), 69.5 (*C*H_2-CH=CH_2), 69.0 (C-5), 61.9 (C-3), 53.3 (CH_3 CO_2Me), 52.7 (C-2), 37.7 (CH_2 Lev), 29.9 (CH_3 Lev), 27.7 (CH_2 Lev); HRMS: $[M+NH_4]^+$ calcd for $C_{17}H_{21}Cl_3N_4O_8NH_4$ 532.07632, found 532.07594.

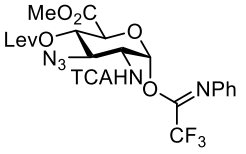
Methyl (2,3-dideoxy-2-trichloroacetamido-3-azido-4-levulinoyl-α-D-glucopyranosyl uronate) (26)



Compound **25** (5.93 g, 11.5 mmol) was dissolved in 100 mL 3:2 MeOH/DCM, and $PdCl_2$ (408 mg, 2.30 mmol, 0.2 eq) was added. After full conversion of the starting material the reaction mixture was filtered over celite and concentrated under reduced pressure. The residue was purified over silica (30% acetone in pentane) to yield the title compound as off-white foam. Yield: 5.01 g, 10.5 mmol, 92%. $[\alpha]_D^{25}$ = 131.3° (c = 0.08, $CHCl_3$); IR (thin film): 1063, 1150, 1713, 1753, 2111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 9.3 Hz, 1H, NH), 5.41 (s, 1H, H-1), 5.12 (t, *J* = 9.7 Hz, 1H, H-4), 4.55 (d, *J* = 9.9 Hz, 1H, H-5), 4.24 (s, 1H, OH), 4.17 (ddd, *J* = 10.9, 9.4, 3.5 Hz, 1H, H-2), 3.95 (dd, *J* = 10.8, 9.6 Hz, 1H, H-3), 3.76 (s, 3H, CH_3 CO_2Me), 2.90 – 2.80 (m, 1H, C*H*H Lev), 2.77 – 2.73 (m, 1H, CH*H* Lev), 2.71 – 2.67 (m, 1H, C*H*H Lev), 2.64 – 2.56 (m, 1H, CH*H*

Lev), 2.21 (s, 3H, CH_3 Lev); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 168.3 (C-6, C=O), 162.1 (C=O), 90.8 (C-1), 70.4 (C-4), 68.6 (C-5), 61.6 (C-3), 53.4 (CH_3 CO_2Me), 53.0 (C-2), 37.7 (CH_2 Lev), 30.0 (CH_3 Lev), 27.7 (CH_2 Lev); HRMS: $[M+NH_4]^+$ calcd for $C_{14}H_{17}Cl_3N_4O_8$ 492.04502, found 492.04478

<u>*N*-Phenyl-O-(Methyl (2,3-dideoxy-2-trichloroacetamido-3-azido-4-levulinoyl-α-D-glucopyranosyl uronate)) trifluoroacetimidate (5)</u>



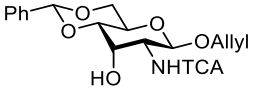
Compound **26** (4.99 g, 10.5 mmol) was dissolved in 100 mL DCM with 10 mL water, K_2CO_3 (4.35 g, 31.5 mmol, 3 eq) and PTFAI-Cl (5 mL, 31.5 mmol, 3 eq). The reaction mixture was stirred vigorously until TLC showed full conversion of the starting material,after which the reaction mixture was diluted with water and extracted twice with DCM. Combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from Et_2O to yield the title compound (pure α-anomer) as a white powder. The concentrated mother liquor was purified via silica chromatography (20%→30% acetone in pentane with 1% Et_3N) to obtain extra product (enriched in α-anomer) as an orange solid. Total yield: 4.78 g, 7.39 g, 70%. $[\alpha]_D^{25}$ = 80.2° (c = 0.27, $CHCl_3$); IR (thin film): 822, 1027, 1116, 1209, 1720, 1763, 2112; data for the α-anomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.9 Hz, 2H, CH_{arom}), 7.14 (t, *J* = 7.5 Hz, 1H, CH_{arom}), 6.84 – 6.74 (m, 3H, NH, CH_{arom}), 6.55 (s, 1H, H-1), 5.25 (t, *J* = 9.6 Hz, 1H, H-4), 4.40 (d, *J* = 9.7 Hz, 1H, H-5), 4.37 – 4.30 (m, 1H, H-2), 4.10 – 3.99 (m, 1H, H-3), 3.79 (s, 3H, CH_3 OMe), 2.90 – 2.59 (m, 4H, 2x CH_2 Lev), 2.21 (s, 3H, CH_3 Lev); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 166.9 (C-6, C=O), 129.0, 125.1, 119.3 (CH_{arom}), 70.9 (C-5), 70.0 (C-4), 60.7 (C-3), 53.5 (CH_3 CO_2Me), 52.1 (C-2), 37.7 (CH_2 Lev), 29.9 (CH_3 Lev), 27.7 (CH_2 Lev); HRMS: $[M+Na]^+$ calcd for $C_{22}H_{21}Cl_3F_3N_5O_8Na$ 668.0300, found 668.02966

<u>Allyl 2-deoxy-2-trichloroacetamido-4,6-*O*-benzylidene-β-D-glucopyranoside (27)</u>

16b (21.9 g, 60 mmol), PTSA-H_2O (571 mg, 3 mmol, 0.05 eq) and benzaldehyde dimethylacetal (9.95 mL, 66 mmol, 1.1 eq) were dissolved in 1L acetonitrile and heated to 60 °C. After full conversion of the starting material, 0.1 eq of triethylamine was added and the reaction mixture was concentrated under reduced pressure. The residue was recrystallized from DCM/pentane to yield the title compound as off-white solid. Yield: 25.4 g, 56.1 mmol, 94%. ^1H NMR (400 MHz, Acetone) δ 8.30 (d, *J* = 9.1 Hz, 1H, NH), 7.50 (dd, *J* = 6.6, 3.1 Hz, 2H, CH_{arom}), 7.42 – 7.31 (m, 3H, CH_{arom}), 5.88 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H, CH_2-C*H*=CH_2), 5.65 (s, 1H, C*H*Ph), 5.29 (dq, *J* = 17.3, 1.8 Hz, 1H, CH_2-CH=C*H*H), 5.11 (dq, *J* = 10.5, 1.5 Hz, 1H, CH_2-CH=CH*H*), 4.90 (d, *J* = 5.0 Hz, 1H, OH), 4.85 (d, *J* = 8.4 Hz, 1H, H-1), 4.35 – 4.21 (m, 2H, H-6, C*H*H-CH=CH_2), 4.16 – 4.05 (m, 2H, H-3, CH*H*-CH=CH_2), 3.88 (dt, *J* = 10.0, 9.1 Hz, 1H, H-2), 3.81 (t, *J* = 10.2 Hz, 1H, H-6), 3.59 (t, *J* = 9.2 Hz, 1H, H-4), 3.43 (td, *J* = 9.8, 5.0 Hz, 1H, H-5); ^{13}C NMR (101 MHz, Acetone) δ 162.6 (C=O), 139.1 (C_q), 135.2 (CH_2-*C*H=CH_2), 129.6, 128.8, 127.3 (CH_{arom}), 116.9 (CH_2-

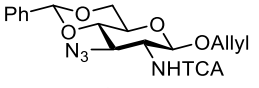
CH=CH_2), 102.1 (CHPh), 101.6 (C-1), 82.8 (C-4), 71.4 (C-3), 70.6 (*C*H_2-CH=CH_2), 69.1 (C-6), 67.3 (C-5), 59.5 (C-2). Spectra in agreement with literature.[35]

Allyl 2-deoxy-2-trichloroacetamido-4,6-*O*-benzylidene-β-D-allopyranoside (29)



Compound **27** (20.5 g, 45.3 mmol) and pyridine (9.1 mL, 113 mmol, 2.5 eq) were dissolved in 250 mL DCM and cooled to -10 °C, after which triflic anhydride (11.4 mL, 67.9 mmol, 1.5 eq) was added dropwise. After full conversion, the reaction mixture was washed twice with 1M aq. $CuSO_4$. The organic phase was dried with $MgSO_4$ and concentrated at 30 °C, yielding the crude triflate **28** which was used without further purification. The triflate was dissolved in 50 mL DMF with $NaNO_2$ (31.2 g, 453 mmol, 10 eq) and stirred for 48 hr, after which the reaction mixture was diluted with water and extracted twice with diethyl ether. Organic phases were combined, dried with $MgSO_4$ and concentrated under reduced pressure. Silica chromatography (20% acetone in pentane) yields the title compound as a white foam. Yield: 11.1 g, 24.4 mmol, 54%. $[\alpha]_D^{25}$ = -37.2° (c = 0.12, $CHCl_3$); IR (thin film): 757, 1089, 1513, 1717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 6.6, 3.2 Hz, 2H, CH_{arom}), 7.42 – 7.36 (m, 3H, CH_{arom}), 7.23 (d, *J* = 9.3 Hz, 1H, NH), 5.85 (dddd, *J* = 16.8, 10.7, 6.1, 4.9 Hz, 1H, CH_2-C*H*=CH_2), 5.62 (s, 1H, C*H*Ph), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H, CH_2-CH=C*H*H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H, CH_2-CH=CH*H*), 4.79 (d, *J* = 8.4 Hz, 1H, H-1), 4.43 – 4.34 (m, 2H, H-6, C*H*H-CH=CH_2), 4.32 (s, 1H, H-3), 4.15 (td, *J* = 8.4, 2.6 Hz, 1H), 4.08 (ddt, *J* = 13.1, 6.1, 1.4 Hz, 1H, CH*H*-CH=CH_2), 4.00 (td, *J* = 9.9, 5.0 Hz, 1H, H-2), 3.82 (t, *J* = 10.3 Hz, 1H, H-6), 3.68 (dd, *J* = 9.4, 2.5 Hz, 1H, H-4), 2.60 (s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (C=O), 136.9 (C_q), 133.5 (CH_2-*C*H=CH_2), 129.5, 128.6, 126.2 (CH_{arom}), 117.9 (CH_2-CH-*C*H_2), 101.9 (CHPh), 99.3 (C-1), 78.6 (C-4), 70.5 (*C*H_2-CH=CH_2), 69.1 (C-6), 68.4 (C-3), 63.5 (C-5), 53.8 (C-2); HRMS: $[M+Na]^+$ calcd for $C_{18}H_{20}Cl_3NO_6Na$ 474.02484, found 474.02447

Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-4,6-*O*-benzylidene-β-D-glucopyranoside (31)



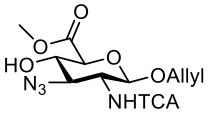
Compound **29** (10.5 g, 23.1 mmol) was dissolved in 25 mL pyridine, and mesyl chloride (3.59 mL, 46.4 mmol 2 eq) was added dropwise. After full conversion, the reaction mixture was diluted with ethyl acetate and washed twice with 1M aq. $CuSO_4$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure, yielding the mesylate **30** as off-white foam, which was used directly without further purification. The crude mesylate was dissolved in 100 mL acetonitrile with freshly prepared tetrabutylammonium azide[36] (16.4 g, 57.5 mmol, 2.5 eq). The reaction mixture was heated to 70 °C until full conversion of the starting material. After which the reaction mixture was cooled to RT and poured in approx. 5 times the volume of water under vigorous stirring. The precipitate was collected by filtration, washed with water, dried and purified over silica (10%→20% acetone in pentane) yielding the impure title compound as white solid. Yield: 7.13 g, 14.9 mmol, 65%. $[\alpha]_D^{25}$ = -21.4° (c = 0.21, $CHCl_3$); IR (thin film): 750, 1088, 1368, 1694, 2108; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H, CH_{arom}), 7.43 – 7.33 (m, 3H, CH_{arom}), 7.00 (d, *J* = 7.6 Hz, 1H, H-1), 5.85 (dddd, *J* = 16.9, 10.4, 6.4, 5.4 Hz, 1H, CH_2-C*H*-CH_2), 5.59 (s, 1H, C*H*Ph), 5.29 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.22 (dq, *J* = 10.3, 1.2 Hz, 1H,

CH_2-CH=CH*H*), 5.04 (d, *J* = 8.3 Hz, 1H, H-1), 4.46 – 4.30 (m, 3H, H-3, H-6, C*H*H-CH=CH_2), 4.10 (ddt, *J* = 12.7, 6.4, 1.3 Hz, 1H, CH*H*-CH=CH_2), 3.85 – 3.77 (m, 1H, H-6), 3.64 – 3.56 (m, 2H, H-4, H-6), 3.35 (dt, *J* = 10.9, 8.0 Hz, 1H, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (C=O), 136.7 (C_q), 133.1 (C_q), 129.3 (CH_2-*C*H=CH_2), 128.5, 126.2, 126.1 (CH_{arom}), 118.8 (CH_2-CH=*C*H_2), 101.6 (CHPh), 98.7 (C-1), 80.7 (C-4), 70.9 (*C*H_2-CH=CH_2), 68.7 (C-6), 67.2 (C-5), 60.7 (C-3), 58.1 (C-2); HRMS: $[M+Na]^+$ calcd for $C_{18}H_{19}Cl_3N_4O_5Na$ 499.03132 found 499.06137

Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-β-D-glucopyranoside (32)

Compound **31** (6.62 g, 13.8 mmol) and PTSA-H_2O (263 mg, 1.38 mmol, 0.1 eq) were dissolved in MeOH (0.25M) and heated to 60 °C. After full conversion, the reaction mixture was neutralised with triethylamine and concentrated under reduced pressure. The residue was precipitated using DCM/pentane, yielding the impure title compound as white solid. Yield: 5.20 g, 13.4 mmol, 97%. $[\alpha]_D^{25}$ = -164.8° (c = 0.19, $CHCl_3$); IR (thin film): 668, 1047, 1075, 1527, 1697, 2106; ^{1}H NMR (400 MHz, Acetone) δ 8.44 (d, *J* = 9.1 Hz, 1H, NH), 5.86 (dddd, *J* = 17.2, 10.6, 5.6, 5.0 Hz, 1H, CH_2-C*H*=CH_2), 5.26 (dq, *J* = 17.3, 1.8 Hz, 1H, CH_2-CH=C*H*H), 5.12 – 5.05 (m, 2H, OH, CH_2-CH=CH*H*), 4.76 (d, *J* = 8.3 Hz, 1H, H-1), 4.29 (ddt, *J* = 13.4, 4.9, 1.6 Hz, 1H, C*H*H-CH=CH_2), 4.08 (ddt, *J* = 13.4, 5.7, 1.6 Hz, 1H, CH*H*-CH=CH_2), 3.91 – 3.82 (m, 2H, H-3, H-6), 3.75 – 3.67 (m, 2H, H-2, H-6), 3.57 (td, *J* = 9.4, 5.8 Hz, 1H, H-4), 3.38 (ddd, *J* = 9.7, 5.2, 2.2 Hz, 1H, H-5); ^{13}C NMR (101 MHz, Acetone) δ 162.6 (C=O), 135.2 (CH_2-*C*H=CH_2), 116.9 (CH_2-CH=*C*H_2), 100.7 (C-1), 78.3 (C-5), 70.9 (C-4), 70.2 (*C*H_2-CH=CH_2), 67.8 (C-6), 62.3 (C-5), 56.7 (C-2); HRMS: $[M+Na]^+$ calcd for $C_{11}H_{15}Cl_3N_4O_5Na$ 411.00002, found 411.00021.

Methyl (Allyl 2,3-dideoxy-2-trichloroacetamido-3-azido-β-D-glucopyranosyl uronate) (2)



Compound **32** (5.20 g, 13.4 mmol) was suspended in 90 mL 2:1 DCM/H_2O and TEMPO (1.04 g, 6.67 mmol, 0.5 eq) and BAIB (10.8 g, 33.4 mmol, 2.5 eq) were added under vigorous stirring. After full conversion, the reaction mixture was concentrated under reduced pressure, yielding crude acid **33**. The residue was coevaporated 3x with toluene and dissolved in DMF. K_2CO_3 (5.05 g, 60.1 mmol, 4.5 eq) and methyl iodide (6.23 mL, 100 mmol, 7.5 eq) were added and the reaction mixture was stirred for 18 hr, after which it was diluted with water and extracted twice with diethyl ether. Organic phases were combined, dried with $MgSO_4$ and concentrated under reduced pressure. Silica chromatography (20% acetone in pentane) yields the title compound as a white solid. Yield: 2.87 g, 6.87 mmol, 52%. $[\alpha]_D^{25}$ = -18.1° (c = 0.28, $CHCl_3$); IR (thin film): 823, 1040, 1087, 1258, 1530, 1697, 1734, 2108; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.4 Hz, 1H, NH), 5.85 (dddd, *J* = 17.0, 10.4, 6.4, 5.3 Hz, 1H, CH_2-C*H*=CH_2), 5.29 (dq, *J* = 17.2, 1.4 Hz, 1H, CH_2-CH=C*H*H), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H, CH_2-CH=CH*H*), 5.07 (d, *J* = 8.2 Hz, 1H, H-1), 4.38 (ddt, *J* = 12.7, 5.3, 1.3 Hz, 1H, C*H*H-CH=CH_2), 4.25 (dd, *J* = 11.1, 9.2 Hz, 1H, H-3), 4.12 (ddt, *J* = 12.7, 6.5, 1.3 Hz, 1H, CH*H*-CH=CH_2), 3.99 (d, *J* = 9.7 Hz, 1H, H-5), 3.86 (s, 4H, H-4, CH_3 CO_2Me), 3.42 (s, 1H, OH), 3.26 (dt, *J* = 11.1, 7.8 Hz, 1H, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ

169.6 (C-6), 162.3 (C=O), 133.0 (CH_2-*C*H=CH_2), 118.9 (CH_2-CH=*C*H_2), 98.3 (C-1), 74.5 (C-5), 72.0 (C-4), 70.9 (*C*H_2-CH=CH_2), 62.9 (C-3), 57.3 (C-2), 53.2 (CH_3 CO_2Me); HRMS: $[M+Na]^+$ calcd for $C_{12}H_{15}Cl_3N_4O_6$ 438.99494, found 438.994455.

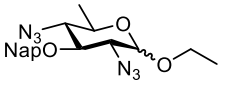
Procedure for VT-NMR experiments of bacillosamine donors

Donor **4** (30 μmol) or a mixture of donor **3** (30 μmol) and Ph_2SO (39 μmol) was coevaporated with toluene, dissolved in 0.6 mL of CD_2Cl_2 under nitrogen atmosphere and transferred to an oven-dried NMR tube flushed with nitrogen gas and sealed with an NMR tube septum. The magnet was cooled to -80 °C, locked, and shimmed and the sample was measured prior to activation. In a separate cold bath (-80 °C) the sample was treated with Tf_2O (donor **3**, 39 μmol) or TfOH (donor **4**, 39 μmol) and shaken and recooled 3x. Thecold sample was wiped dry and quickly inserted back in the cold magnet. The first ^{1}H NMR spectrum was immediately recorded. The sample was then reshimmed, and spectra were recorded in 10 °C intervals with at least 5 min of equilibration time for every temperature.

General procedure for model glycosylations

Donor (0.1 mmol, 1 eq), Ph_2SO (0.13 mmol, 1.3 eq) and TTBP (0.25 mmol, 2.5 eq) were coevaporated twice with toluene, dissolved in 2 mL DCM and stirred for 30 min at RT with 3 Å molecular sieves. The solution was cooled to -80 ^{0}C and Tf_2O (22 μL, 0.13 mmol, 2 eq) was added. The reaction mixture was allowed to warm to −60 ^{0}C and then recooled to −78 ^{0}C, after which the acceptor (0.2 mmol, 2 eq) in DCM (0.4 mL, 0.5 M) was added. The reaction mixture was allowed to warm to −60 ^{0}C for and stirred for 2 hr at that temperature. The reaction was quenched with 2 mL sat aq $NaHCO_3$, and the mixture was diluted with DCM. The solution was transferred to a separatory funnel, water was added, the layers were separated, and the water phase was extracted once more with DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography and/or sephadex LH-20 size-exclusion chromatography yielded the glycosylation product as a mixture of anomers.

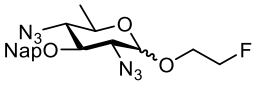
Ethyl 2,4-dideoxy-2,4-diazido-3-*O*-(2-naphthyl)methyl-α,β-D-quinopyranoside (3A)



The title comound was synthesised from donor **3** and ethanol according to the genereral procedure for model glycosylations as colourless oil. Yield: 32 mg, 84 μmol, 84%, α:β = 1:8. Data for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 4H, CH_{arom}), 7.55 (dd, *J* = 8.6, 1.6 Hz, 1H, CH_{arom}), 7.50 – 7.44 (m, 2H, CH_{arom}), 5.06 (d, *J* = 10.8 Hz, 1H, C*H*H Nap), 4.96 (d, *J* = 10.8 Hz, 1H, CH*H* Nap), 4.25 (d, *J* = 8.0 Hz, 1H, H-1), 3.95 (dq, *J* = 9.4, 7.1 Hz, 1H, C*H*H Et), 3.62 (dq, *J* = 9.4, 7.1 Hz, 1H, CH*H* Et), 3.43 (dd, *J* = 9.7, 8.1 Hz, 1H, H-2), 3.28 (t, *J* = 9.3 Hz, 1H, H-3), 3.23 – 3.11 (m, 2H, H-4, H-5), 1.35 (d, *J* = 5.8 Hz, 3H, H-6), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9, 133.4, 133.3 (C_q), 128.4, 128.2, 128.2, 127.8, 127.8, 127.5, 127.5, 126.3, 126.3, 126.2, 126.2, 126.2, 126.2 (CH_{arom}), 101.8 (C-1), 81.3 (C-3), 75.5 (CH_2 Nap), 70.8 (C-5), 67.8 (C-4), 66.3 (C-2), 66.0 (CH_2 Et), 18.5 (C-6), 15.2 (CH_2 Et); diagnostic peaks for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (d, *J* = 3.5 Hz, 1H, H-1), 3.89 (dd, *J* = 10.1, 9.2 Hz, 1H), 3.74 (dq, *J* = 9.8, 7.1 Hz, 1H, C*H*H Et), 3.34 (dd, *J* = 10.1, 3.5 Hz, 1H, H-2); ^{13}C NMR

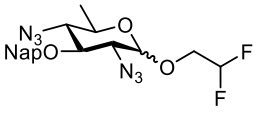
(101 MHz, $CDCl_3$) δ 97.5 (C-1), 78.7, 68.8, 66.5, 64.0, 63.6, 18.5, 15.1; HRMS: $[M+NH_4]^+$ calcd for $C_{19}H_{22}N_6O_3NH_4$ 400.20916, found 400.20904.

2-Fluoroethyl 2,4-dideoxy-2,4-diazido-3-*O*-(2-naphthyl)methyl-α,β-D-quinopyranoside (3B)



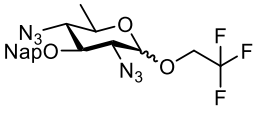
The title comound was synthesised from donor **3** and 2-fluoroethanol according to the genereral procedure for model glycosylations as colourless oil. Yield: 30 mg, 75 µmol, 75%, α:β = 1:2. Data reported for a 1:2 mixture of anomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dddt, *J* = 9.6, 7.7, 5.3, 2.4 Hz, 12H, CH_{arom}), 7.56 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 3H, CH_{arom}), 7.51 – 7.43 (m, 6H, CH_{arom}), 5.08 – 5.02 (m, 4H, C*H*H Napα, CH*H* Napα), 4.96 (d, *J* = 10.8 Hz, 2H, CH*H* Napβ), 4.92 (d, *J* = 3.5 Hz, 1H, H-1α), 4.72 – 4.62 (m, 3H, CH_2-C*H*HFαβ), 4.60 – 4.49 (m, 3H, CH_2-CH*H*Fαβ), 4.31 (d, *J* = 8.1 Hz, 2H, H-1β), 4.13 – 3.98 (m, 2H, C*H*H-CH_2Fβ), 3.96 – 3.74 (m, 5H, H-5α, C*H*H-CH_2Fα, CH*H*-CH_2Fαβ), 3.74 – 3.66 (m, 1H, H-5α), 3.46 (dd, *J* = 9.7, 8.1 Hz, 2H, H-2β), 3.38 (dd, *J* = 10.1, 3.5 Hz, 1H, H-2α), 3.29 (t, *J* = 9.3 Hz, 2H, H-3β), 3.25 – 3.12 (m, 5H, H-4αβ, H-5β), 1.36 (d, *J* = 5.7 Hz, 6H, H-6β), 1.32 (d, *J* = 6.2 Hz, 3H, H-6α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 133.3, 133.3, 133.2 (C_q), 128.3, 128.1, 128.1, 127.7, 127.7, 127.4, 127.4, 126.3, 126.2, 126.2, 126.1, 126.1 (C_q), 102.1 (C-1β), 98.0 (C-1α) 82.7 (d, *J* = 170.1 Hz, CH_2-*C*H_2Fβ), 82.4 (d, *J* = 170.4 Hz, CH_2-*C*H_2Fα), 81.1 (C-3β), 78.4 (C-3α), 75.5, 75.5 (CH_2 Napαβ), 70.8 (C-5β), 68.9 (d, *J* = 20.2 Hz, *C*H_2-CH_2Fβ)) 68.6 (C-4α), 67.6 (C-4β), 67.3 (d, *J* = 20.1 Hz, *C*H_2-CH_2Fα), 66.7 (C-5α), 66.3 (C-2β), 63.5 (C-2α), 18.4 (C-6β), 18.4 (C-6α); HRMS: $[M+NH_4]^+$ calcd for $C_{19}H_{21}FN_6O_3NH_4$ 418.19974, found 418.19933.

2,2-Difluoroethyl 2,4-dideoxy-2,4-diazido-3-*O*-(2-naphthyl)methyl-α,β-D-quinopyranoside (3C)



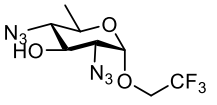
The title comound was synthesised from donor **3** and 2,2-difluoroethanol according to the genereral procedure for model glycosylations as colourless oil. Yield: 28 mg, 66 µmol, 66%, α:β = 2.9:1. Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 4H, CH_{arom}), 7.56 (dd, *J* = 8.4, 1.7 Hz, 1H, CH_{arom}), 7.50 – 7.44 (m, 2H, CH_{arom}), 6.11 – 5.75 (m, 1H, CH_2-C*H*F_2), 5.03 (d, *J* = 1.8 Hz, 2H, CH_2 Nap), 4.90 (d, *J* = 3.5 Hz, 1H, H-1), 3.88 – 3.73 (m, 3H, H-3, C*H*$_2$-CHF_2), 3.69 – 3.61 (m, 1H, H-5), 3.39 (dd, *J* = 10.2, 3.5 Hz, 1H, H-2), 3.17 (dd, *J* = 10.2, 9.3 Hz, 1H, H-4), 1.33 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 133.4, 133.3 (C_q), 128.4, 128.2, 127.8, 127.5, 126.3, 126.3, 126.2 (CH_{arom}), 113.8 (t, *J* = 241.0 Hz, CH_2-*C*HF_2), 98.5 (C-1), 78.3 (C-3), 75.7 (CH_2 Nap), 68.5 (C-4), 67.3 (t, *J* = 28.7 Hz, *C*H_2-CHF_2), 67.2 (C-5), 63.5 (C-2), 18.4 (C-6); diagnostic peaks for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, *J* = 10.7 Hz, 1H, C*H*H Nap), 4.97 (d, *J* = 10.7 Hz, 1H, CH*H* Nap), 4.29 (d, *J* = 8.0 Hz, 1H, H-1), 3.98 (dtd, *J* = 17.6, 12.0, 3.3 Hz, 1H, C*H*H-CHF_2), 3.45 (dd, *J* = 9.7, 8.0 Hz, 1H, H-2), 3.28 (t, *J* = 9.3 Hz, 1H, H-3), 1.36 (d, *J* = 5.8 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 102.3 (C-1), 81.1, 71.1, 67.6, 66.3, 18.4; HRMS: $[M+NH_4]^+$ calcd for $C_{19}H_{20}F_2N_6O_3NH_4$ 436.19032, found 436.19015

2,2,2-Trifluoroethyl 2,4-dideoxy-2,4-diazido-3-*O*-(2-naphthyl)methyl-α,β-D-quinopyranoside (3D)



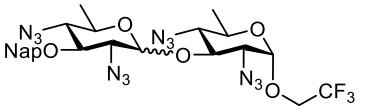
The title comound was synthesised from donor **3** and 2,2,2-trifluoroethanol according to the genereral procedure for model glycosylations as colourless oil. Yield: 41 mg, 94 µmol, 94%, α:β = 22:1. Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.80 (m, 4H, CH_{arom}), 7.56 (dd, *J* = 8.4, 1.7 Hz, 1H, CH_{arom}), 7.51 – 7.43 (m, 2H, CH_{arom}), 5.05 (d, *J* = 10.5 Hz, 1H, C*H*H Bn), 5.01 (d, *J* = 10.6 Hz, 1H, CH*H* Bn), 4.93 (d, *J* = 3.6 Hz, 1H, H-1), 3.95 (qd, *J* = 8.5, 1.7 Hz, 2H, C*H*$_2$-CF_3), 3.86 (dd, *J* = 10.2, 9.3 Hz, 1H, H-3), 3.64 (dq, *J* = 10.1, 6.2 Hz, 1H, H-5), 3.40 (dd, *J* = 10.1, 3.6 Hz, 1H, H-2), 3.17 (dd, *J* = 10.2, 9.3 Hz, 1H, H-4), 1.33 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6, 133.4, 133.3 (C_q), 128.5, 128.2, 127.8, 127.5, 126.3, 126.3, 126.2 (CH_{arom}), 123.5 (q, *J* = 278.5 Hz, CH_2-*C*F_3), 98.6 (C-1), 78.2 (C-3), 75.7 (CH_2 Nap), 68.4 (C-4), 67.5 (C-5), 65.1 (q, *J* = 35.3 Hz, *C*H_2-CF_3), 63.3 (C-2), 18.4 (C-6); diagnostic peaks for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (d, *J* = 8.0 Hz, 1H, H-1), 4.14 (dq, *J* = 12.6, 8.7 Hz, 1H), 4.10 (s, 1H), 3.46 (dd, *J* = 9.7, 8.0 Hz, 1H, H-2), 3.28 (t, *J* = 9.3 Hz, 1H), 1.35 (d, *J* = 5.7 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 101.8 (C-1), 81.0, 71.2, 66.3; HRMS: $[M+NH_4]^+$ calcd for $C_{19}H_{19}F_3N_6O_3NH_4$ 454.18090, found 454.18074

2,2,2-Trifluoroethyl 2,4-dideoxy-2,4-diazido-α-D-quinopyranoside (34)



3D (166 mg, 0.38 mmol) and DDQ (129 mg, 0.57 mmol, 1.5 eq) were dissolved in 9:1 DCM/H_2O (0.3M) after full conversion, the reaction mixture was diluted with DCM and washed twice with sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica (15% Et_2O in pentane) to yield the title product as colourless oil. Yield: 71 mg, 0.24 mmol, 63%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (d, *J* = 3.6 Hz, 1H, H-1), 4.06 – 3.89 (m, 3H, H-3, C*H*$_2$-CF_3), 3.66 (dqd, *J* = 10.1, 6.3, 0.7 Hz, 1H, H-5), 3.30 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 3.11 (dd, *J* = 10.1, 9.3 Hz, 1H, H-4), 2.92 (d, *J* = 4.1 Hz, 1H, OH), 1.34 (d, *J* = 6.3 Hz, 3H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.4 (C-1), 70.6 (C-3), 68.6 (C-4), 67.4 (C-5), 65.2 (q, *J* = 35.4 Hz, *C*H_2-CF_3) 63.1 (C-2), 18.3 (C-6)

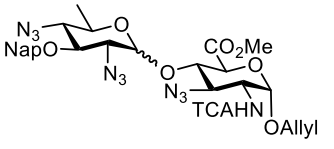
Disaccharide 3E



The title comound was synthesised from donor **3** and acceptor **34** according to the genereral procedure for model glycosylations as colourless oil. Yield: 48 mg, 75 µmol, 75%, α:β = 6.6:1. Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.82 (m, 4H, CH_{arom}), 7.58 (dd, *J* = 8.4, 1.7 Hz, 1H, CH_{arom}), 7.51 – 7.45 (m, 2H, CH_{arom}), 5.31 (d, *J* = 3.7 Hz, 1H, H-1'), 5.04 (s, 2H, CH_2 Nap), 5.00 (d, *J* = 3.7 Hz, 1H, H-1), 4.03 – 3.92 (m, 3H, H-5/H-5', C*H*$_2$-CF_3), 3.87 – 3.77 (m, 2H, H-3, H-3'), 3.73 (dq, *J* = 10.0, 6.2 Hz, 1H, H-5/H-5'), 3.48 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2'),

3.24 – 3.13 (m, 2H, H-4, H-4'), 3.04 (dd, *J* = 10.4, 3.6 Hz, 1H, H-2), 1.40 – 1.36 (m, 6H, H-6, H-6'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 133.4, 133.3 (C_q), 128.5, 128.2, 127.8, 127.6, 126.3, 126.3, 126.2 (CH_{arom}), 99.3, 99.2 (C-1, C-1'), 78.5 (C-3'), 75.7 (C-3), 75.5 (CH_2 Nap), 69.6, 68.8 (C-4, C-4'), 67.8, 67.8 (C-5, C-5'), 65.1 (q, *J* = 35.6 Hz, *C*H_2-CF_3) 63.9 (C-2'), 61.2 (C-2), 18.8, 18.2 (C-6, C-6'); diagnostic peaks for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (d, *J* = 7.9 Hz, 1H, H-1'), 4.09 (dd, *J* = 10.2, 9.2 Hz, 1H), 3.59 (dq, *J* = 10.2, 6.1 Hz, 1H), 3.41 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 3.34 (t, *J* = 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 101.4 (C-1'), 98.4 (C-1), 81.3, 75.9, 75.7, 71.0, 67.7, 67.0, 66.6, 66.3, 63.3, 18.4, 18.4

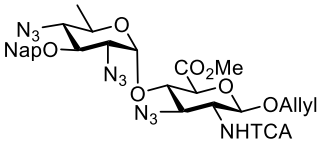
Disaccharide 3F



Pre-activation: Donor **3** (100-130 μmol, 1-1.3 eq), Ph_2SO (0.65-1.3 eq) and TTBP (2.5 eq) were coevaporated twice with toluene and dissolved in DCM (0.05 M donor). 3Å molecular sieves were added and the reaction mixture was stirred for 30-60 min at RT, before being cooled to -80 °C. Tf_2O (0.65-1.3 eq) was added and the reaction was allowed to warm to -60 °C and kept at that temperature for 1 min. before being recooled to -80 °C. Acceptor **24** (1-2 eq) was added dropwise over 30 s as a freshly prepared 0.5M solution in DCM. The reaction mixture was then allowed to warm to the specified temperature and quenched with 2 mL sat. aq. $NaHCO_3$ after 2 hr (-50 °C or - 60 °C) or 30 s (0 °C). The mixture was diluted with DCM. The solution was transferred to a separatory funnel, water was added, the layers were separated, and the water phase was extracted once more with DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography and/or sephadex LH-20 size-exclusion chromatography yielded the glycosylation product as a mixture of anomers. *In situ activation*: donor **4** (130 μmol, 1.3 eq), acceptor **24** (1 eq) and Ph_2SO (0 or 1.5 eq) twice with toluene and dissolved in DCM (0.05 M donor). 3Å molecular sieves were added and the reaction mixture was stirred for 30-60 min at RT, before being cooled to -80 °C. TMSOTf (0.2 eq) was added and the reaction mixture was slowly allowed to warm to 0 °C and quenched with 2 mL sat. aq. $NaHCO_3$. The mixture was diluted with DCM. The solution was transferred to a separatory funnel, water was added, the layers were separated, and the water phase was extracted once more with DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography and/or sephadex LH-20 size-exclusion chromatography yielded the glycosylation product as a mixture of anomers. Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.81 (m, 4H, CH_{arom}), 7.56 (dd, *J* = 8.4, 1.7 Hz, 1H, CH_{arom}), 7.51 – 7.43 (m, 3H, CH_{arom}), 6.83 (d, *J* = 9.7 Hz, 1H, NH), 5.88 (dddd, *J* = 17.1, 10.3, 6.8, 5.4 Hz, 1H, CH_2-C*H*-CH_2), 5.38 – 5.28 (m, 3H, H-1', CH_2-CH=C*H*$_2$), 5.03 (d, *J* = 10.5 Hz, 1H, C*H*H Nap), 5.00 (d, *J* = 10.5 Hz, 1H, CH*H* Nap), 4.94 (d, *J* = 3.6 Hz, 1H, H-1), 4.32 – 4.16 (m, 3H, H-2, H-5, C*H*H-CH=CH_2), 4.07 (ddt, *J* = 12.8, 6.8, 1.1 Hz, 1H, CH*H*-CH=CH_2), 3.92 (t, *J* = 9.5 Hz, 1H, H-4), 3.85 – 3.78 (m, 4H, H-3, CH_3 CO_2Me), 3.77 – 3.69 (m, 1H, H-3'), 3.54 – 3.36 (m, 2H, H-2', H-5'), 3.12 (dd, *J* = 10.1, 9.4 Hz, 1H, H-4'), 1.28 (d, *J* = 6.2 Hz, 3H, H-6'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C-6), 162.1 (C=O), 134.6, 133.4, 133.3 (C_q), 132.3 (CH_2-*C*H=CH_2), 128.4, 128.2, 127.8, 127.6, 126.3, 126.3, 120.0 (CH_{arom}), 98.6 (C-1'), 95.4 (C-1), 78.5 (C-

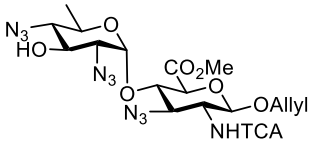
3'), 76.3 (C-4), 75.7 (CH_2 Nap), 70.9 (C-5), 69.3 (CH_2-CH=CH_2), 68.4 (C-4'), 67.7 (C-5'), 64.6 (C-3), 64.0 (C-2'), 53.4 (C-2), 53.0 (CH_3 CO_2Me), 18.3 (C-6); Diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 3.4 Hz, 1H, H-1), 4.39 (d, *J* = 8.0 Hz, 1H, H-1'), 3.37 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2'), 1.39 (d, *J* = 6.0 Hz, 3H, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.6 (C-1'); HRMS: $[M+NH_4]^+$ calcd for $C_{29}H_{31}Cl_3N_{10}O_8NH_4$ 770.17302, found 770.17275

Disaccharide 35



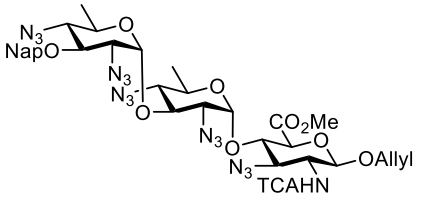
Donor **3** (2.61 g, 5.29 mmol, 1.3 eq), Ph_2SO (535 mg, 2.65 mmol, 0.65 eq) and TTBP (2.53 g, 10.2 mmol, 2.5 eq) were coevaporated twice with toluene and dissolved in 100 mL anhydrous DCM. 3Å molecular sieves were added and the reaction mixture was stirred for 30-60 min at RT, before being cooled to -80 °C. Tf_2O (0.44 mL, 2.65 mmol, 0.65 eq) was added and the reaction was allowed to warm to -60 °C and kept at that temperature for 1 min. before being recooled to -80 °C. Acceptor **35** (1.70 g, 4.07 mmol, 1 eq.) was added dropwise over 30 s as a freshly prepared 0.5M solution in DCM. The reaction mixture was then slowly allowed to warm to 0 °C and quenched with 200 mL sat. aq. $NaHCO_3$. The mixture was diluted with DCM. The solution was transferred to a separatory funnel, water was added, the layers were separated, and the water phase was extracted once more with DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography (15% acetone in pentane) yields the title compound as white foam. Yield: 2.48 g, 3.29 mmol, 81%, α:β = 10:1. $[\alpha]_D^{25}$ = 61.0° (c = 0.50, $CHCl_3$); IR (thin film): 757, 1033, 1073, 1563, 1696, 1753, 2109; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.80 (m, 4H, CH_{arom}), 7.57 (dd, *J* = 8.4, 1.6 Hz, 1H, CH_{arom}), 7.50 – 7.45 (m, 2H, CH_{arom}), 7.10 (d, *J* = 7.3 Hz, 1H, NH), 5.83 (dddd, *J* = 17.0, 10.4, 6.4, 5.3 Hz, 1H, CH_2-C*H*=CH_2), 5.28 (dq, *J* = 17.1, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.25 (d, *J* = 3.6 Hz, 1H, H-1'), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H, CH_2-CH=CH*H*), 5.07 (d, *J* = 8.0 Hz, 1H, H-1), 5.02 (d, *J* = 3.5 Hz, 2H, CH_2 Nap), 4.39 (dd, *J* = 10.8, 9.0 Hz, 1H, H-3), 4.34 (ddt, *J* = 12.8, 5.2, 1.4 Hz, 1H, C*H*H-CH=CH_2), 4.07 (ddt, *J* = 12.6, 6.4, 1.2 Hz, 1H, CH*H*-CH=CH_2), 4.03 (d, *J* = 9.4 Hz, 1H, H-5), 3.88 (t, *J* = 9.2 Hz, 1H, H-4), 3.79 (s, 3H, CH_3 CO_2 Me), 3.73 (t, *J* = 9.8 Hz, 1H, H-3'), 3.50 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2'), 3.45 (dq, *J* = 10.2, 6.2 Hz, 1H, H-5'), 3.35 (dt, *J* = 10.8, 7.7 Hz, 1H, H-2), 3.12 (t, *J* = 9.9 Hz, 1H, H-4'), 1.28 (d, *J* = 6.2 Hz, 3H, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8 (C-6), 162.5 (C=O), 134.6, 133.4, 133.3 (C_q), 133.0 (CH_2-*C*H=CH_2), 128.4, 128.2, 127.8, 127.7, 126.4, 126.2 (CH_{arom}), 118.9 (CH_2-CH=*C*H_2), 98.6 (C-1'), 97.9 (C-1), 92.1 (CCl_3) 78.7 (C-3'), 77.4 (C-4), 75.8 (CH_2 Nap), 75.4 (C-5), 70.8 (*C*H_2-CH=CH_2), 68.4 (C-4'), 67.8 (C-5'), 64.1 (C-2'), 63.3 (C-3), 58.1 (C-2), 53.0 (CH_3 CO_2 Me), 18.3 (C-6); HRMS: $[M+X]^+$ calcd for $C_{29}H_{31}Cl_3N_{10}O_8NH_4$ 770.17302, found 770.17284. The β-anomer was removed by silica chromatography in the next step.

Disaccharide 36



Disaccharide **35** (2.45 g, 3.25 mmol) and DDQ (1.48 g, 6.50 mmol, 2 eq) were dissolved in 100 mL 9:1 DCM/H_2O and stirred at room temperature until TLC indicated full conversion of the starting material. After which the reaction mixture was transferred to a separatory funnel and washed twice with sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica (20% acetone) to provide the title compound as white solid. Yield: 1.77 g, 2.88 mmol, 89%. $[\alpha]_D^{25}$ = 57.2° (c = 1.28, $CHCl_3$); IR (thin film): 1036, 1070, 1530, 1694, 1750, 2109; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.6 Hz, 1H, NH), 5.82 (dddd, *J* = 17.0, 10.4, 6.4, 5.3 Hz, 1H, CH_2-C*H*=CH_2), 5.30 – 5.25 (m, 2H, H-1', CH_2-CH=C*H*H), 5.21 (dd, *J* = 10.4, 1.4 Hz, 1H, CH_2-CH=CH*H*), 5.01 (d, *J* = 8.0 Hz, 1H, H-1), 4.38 – 4.30 (m, 2H, H-3, C*H*H-CH=CH_2), 4.12 – 4.00 (m, 2H, H-5, CH*H*-CH=CH_2), 3.91 – 3.84 (m, 2H, H-3', H-4), 3.81 (s, 3H, CH_3 CO_2Me), 3.48 – 3.37 (m, 3H, H-2, H-2', H-5'), 3.12 (d, *J* = 4.2 Hz, 1H, OH), 3.06 (t, *J* = 9.8 Hz, 1H, H-4'), 1.28 (d, *J* = 6.2 Hz, 3H, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1 (C-6), 162.6 (C=O), 133.0 (CH_2-*C*H=CH_2), 118.9 (CH_2-CH=*C*H_2), 98.4 (C-1'), 98.1 (C-1), 77.0 (C-4), 75.3 (C-5), 71.3 (C-3'), 70.8 (*C*H_2-CH=CH_2), 68.5 (C-4), 67.5 (C-5'), 63.9 (C-2'), 63.6 (C-3), 58.0 (C-2), 53.1 (CH_3 CO_2 Me), 18.2 (C-6'); HRMS: $[M+NH_4]^+$ calcd for $C_{16}H_{23}Cl_3N_{10}O_8NH_4$ 630.11042, found 630.11019

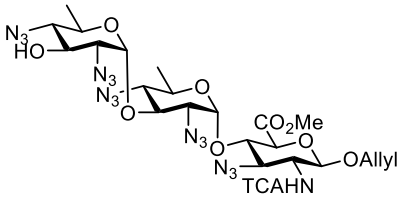
Trisaccharide 37



Donor **3** (64 mg, 0.13 mmol, 1.3 eq), Ph_2SO (13 mg, 0.065 mmol, 0.65 eq) and TTBP (62 mg, 0.25 mmol, 2.5 eq) were coevaporated twice with toluene and dissolved in 2.6 mL 1:1 Et_2O/DCM. 3Å molecular sieves were added and the reaction mixture was stirred for 60 min at RT, before being cooled to -80 °C. Tf_2O (130 µL of a freshly prepared 0.5M sln. in 1:1 Et_2O/DCM, 0.065 mmol, 0.65 eq) was added and the reaction was allowed to warm to -60 °C and kept at that temperature for 1 min. before being recooled to -80 °C. Acceptor **36** (1.70 g, 4.07 mmol, 1 eq.) was added dropwise over 30 s as a freshly prepared 0.05M solution in 1:1 DCM/Et_2O. The reaction mixture was then slowly allowed to warm to 0 °C and quenched with 2 mL sat. aq. $NaHCO_3$. The mixture was diluted with DCM. The solution was transferred to a separatory funnel, water was added, the layers were separated, and the water phase was extracted once more with DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography (15% acetone in pentane) yields the title compound as white foam. Yield: 77 mg, 81 µmol, 81%, α:β = 10:1. $[\alpha]_D^{25}$ = 103.0° (c = 0.52, $CHCl_3$); IR (thin film): 756, 821, 1070, 1527, 1696, 1753, 2109; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.81 (m, 4H, CH_{arom}), 7.58 (dd, *J* = 8.5, 1.7 Hz, 1H, CH_{arom}), 7.51 – 7.43 (m, 2H, CH_{arom}), 7.10 (d, *J* = 7.4 Hz, 1H, NH),

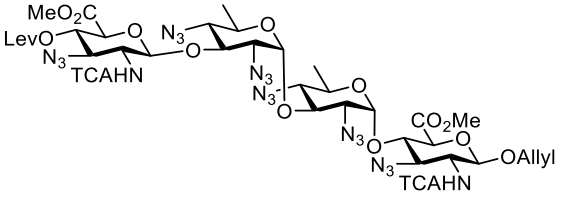
5.82 (dddd, *J* = 17.0, 10.4, 6.5, 5.3 Hz, 1H, CH_2-C*H*=CH_2), 5.40 (d, *J* = 3.7 Hz, 1H, H-1'), 5.37 (d, *J* = 3.7 Hz, 1H, H-1''), 5.27 (dq, *J* = 17.3, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.22 (dq, *J* = 10.3, 1.3 Hz, 1H, CH_2-CH=CH*H*), 5.04 (s, 2H, CH_2 Nap), 5.03 (d, *J* = 8.1 Hz, 1H, H-1), 4.39 (dd, *J* = 10.8, 9.1 Hz, 1H, H-3), 4.33 (ddt, *J* = 12.7, 5.3, 1.4 Hz, 1H, C*H*H-CH=CH_2), 4.10 – 4.05 (m, 1H, CH*H*-CH=CH_2), 4.03 (d, *J* = 9.4 Hz, 1H, H-5), 3.96 – 3.86 (m, 2H, H-4, H-5'), 3.85 – 3.77 (m, 4H, H-3'', CH_3 CO_2Me), 3.70 (dd, *J* = 10.4, 9.3 Hz, 1H, H-3'), 3.52 – 3.46 (m, 2H, H-2'', H-5''), 3.42 (dt, *J* = 10.9, 7.8 Hz, 1H, H-2), 3.22 – 3.11 (m, 3H, H-2', H-4', H-4''), 1.37 (d, *J* = 6.2 Hz, 3H, H-6'), 1.33 (d, *J* = 6.2 Hz, 3H, H-6''); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9 (C-6), 162.5 (C=O), 134.7, 133.4, 133.3 (C_q), 132.9 (CH_2-*C*H=CH_2), 129.3, 128.4, 128.2, 127.8, 127.6, 126.3, 126.2 (CH_{arom}), 119.0 (CH_2-CH=*C*H_2), 98.8, 98.8 (C-1', C-1''), 97.9 (C-1), 92.0 (CCl_3), 78.5 (C-3''), 76.7 (C-4), 75.7 (CH_2 Nap), 75.2, 75.1 (C-3', C-5), 70.8 (*C*H_2-CH=CH_2), 69.3, 68.8 (C-4', C-4''), 67.9, 67.8 (C-5', C-5''), 63.9 (C-2''), 63.4 (C-3), 62.4 (C-2'), 58.2 (C-2), 53.0 (CH_3 CO_2Me), 18.7 (C-6'), 18.0 (C-6''); HRMS: $[M+NH_4]^+$ calcd for $C_{35}H_{39}Cl_3N_{16}O_{10}NH_4$ 966.24389, found 966.24377. The β-anomer was removed by silica chromatography in the next step.

Trisaccharide 38



Trisaccharide **37** (1.90 g, 2.00 mmol) and DDQ (0.91 g, 4.00 mmol, 2 eq) were dissolved in 50 mL 9:1 DCM/H_2O and stirred at room temperature until TLC indicated full conversion of the starting material. After which the reaction mixture was transferred to a separatory funnel and washed twice with sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica (20% acetone) to provide the title compound as white solid. Yield: 996 mg, 1.23 mmol, 62%. $[\alpha]_D^{25}$ = 102.1° (c = 0.32, $CHCl_3$); IR (thin film): 757, 1069, 1257, 1527, 1696, 1751, 2109; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.4 Hz, 1H, NH), 5.82 (dddd, *J* = 17.0, 10.4, 6.5, 5.3 Hz, 1H, CH_2-C*H*=CH_2), 5.39 (d, *J* = 3.8 Hz, 1H, H-1'), 5.36 (d, *J* = 3.7 Hz, 1H, H-1''), 5.28 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.22 (dq, *J* = 10.3, 1.3 Hz, 1H, CH_2-CH=CH*H*), 5.04 (d, *J* = 8.0 Hz, 1H, H-1), 4.40 (dd, *J* = 10.8, 9.1 Hz, 1H, H-3), 4.33 (ddt, *J* = 12.7, 5.3, 1.4 Hz, 1H, C*H*H-CH=CH_2), 4.07 (ddt, *J* = 12.7, 6.4, 1.3 Hz, 1H, CH*H*-CH=CH_2), 4.03 (d, *J* = 9.4 Hz, 1H, H-5), 4.00 – 3.88 (m, 3H, H-3'', H-4, H-5''), 3.82 (s, 3H, CH_3 CO_2Me), 3.71 – 3.66 (m, 1H, H-3'), 3.50 (dq, *J* = 12.4, 6.2 Hz, 1H, H-5'), 3.41 (dt, *J* = 10.2, 7.4 Hz, 1H, H-2), 3.37 (dd, *J* = 10.3, 3.8 Hz, 1H, H-2''), 3.18 (dd, *J* = 10.4, 3.7 Hz, 1H, H-2'), 3.15 – 3.07 (m, 2H, H-4', H-4''), 2.86 (d, *J* = 3.7 Hz, 1H, OH), 1.37 (d, *J* = 6.2 Hz, 3H, H-6''), 1.33 (d, *J* = 6.2 Hz, 3H, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9 (C-6), 162.5 (C=O), 132.9 (CH_2-*C*H=CH_2), 119.0 (CH_2-CH=*C*H_2), 98.8, 98.7 (C-1', C-1''), 97.9 (C-1), 92.0 (CCl_3) 76.7 (C-4), 75.2, 75.2 (C-3', C-5), 70.9 (C-3''), 70.8 (*C*H_2-CH=CH_2), 69.4, 69.0 (C-4', C-4''), 67.9 (C-5'), 67.6 (C-5''), 63.7 (C-2''), 63.4 (C-3), 62.3 (C-2'), 58.2 (C-2), 53.1 (CH_3 CO_2Me), 18.6 (C-6''), 18.0 (C-6'); HRMS: $[M+NH_4]^+$ calcd for $C_{24}H_{31}Cl_3N_{16}O_{10}NH_4$ 826.18129, found 826.18079

Tetrasaccharide 39



Donor **5** (960 mg, 1.49 mmol, 1.3 eq) and acceptor **38** (925 mg, 1.14 mmol, 1 eq) were coevaporated twice with toluene and dissolved in 30 mL DCM. 3Å molecular sieves were added and the reaction mixture was stirred for 30 min at RT, before being cooled to 0 °C. TMSOTf (2,28 mL of a freshly prepared 0.1 M solution in DCM, 0.228 mmol, 0.2 eq) was added. After TLC shows complete disappearance of acceptor **39**, the reaction mixture was quenched with 0.2 mL triethylamine, filtered over a small plug of celite and concentrated under reduced pressure. The residue was purified over silica (20%→40% acetone in pentane) to yield the title compound as pinkish foam. Yield: 855 mg, 0.67 mmol, 59%. $[\alpha]_D^{25}$ = 32.0° (c = 0.70, $CHCl_3$); IR (thin film): 757, 821, 1039, 1259, 1527, 1700, 1717, 1754, 2106; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.4 Hz, 1H, NH), 7.15 (d, *J* = 7.4 Hz, 1H, NH), 5.82 (dddd, *J* = 17.0, 10.4, 6.4, 5.3 Hz, 1H, CH_2-C*H*-CH_2), 5.38 (d, *J* = 3.8 Hz, 1H, H-1'), 5.37 – 5.34 (m, 2H, H-1'', H-1'''), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2-CH=C*H*H), 5.21 (dq, *J* = 10.4, 1.3 Hz, 1H, CH_2-CH=CH*H*), 5.10 (t, *J* = 9.7 Hz, 1H, H-4'''), 5.03 (d, *J* = 8.0 Hz, 1H, H-1), 4.49 (dd, *J* = 11.0, 9.7 Hz, 1H, H-3'''), 4.39 (dd, *J* = 10.8, 9.1 Hz, 1H, H-3), 4.33 (ddt, *J* = 12.8, 5.3, 1.4 Hz, 1H, C*H*H-CH=CH_2), 4.14 (d, *J* = 9.9 Hz, 1H, H-5'''), 4.07 (ddt, *J* = 12.8, 6.5, 1.2 Hz, 1H, CH*H*-CH=CH_2), 4.03 (d, *J* = 9.4 Hz, 1H, H-5), 3.98 (dd, *J* = 10.2, 9.3 Hz, 1H, H-3''), 3.93 – 3.85 (m, 2H, H-4, H-5''), 3.81 (s, 3H, CH_3 CO_2Me), 3.74 (s, 3H, CH_3 CO_2Me), 3.69 – 3.61 (m, 1H, H-3'), 3.53 – 3.36 (m, 4H, H-2, H-2'', H-2''', H-5'), 3.17 (dd, *J* = 10.4, 3.8 Hz, 1H, H-2'), 3.13 – 3.06 (m, 2H, H-4', H-4''), 2.85 – 2.71 (m, 2H, CH_2 Lev), 2.71 – 2.57 (m, 2H, CH_2 Lev), 2.20 (s, 3H, CH_3 Lev), 1.35 (d, *J* = 6.2 Hz, 3H, H-6''), 1.32 (d, *J* = 6.2 Hz, 3H, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.1, 171.5 (C=O), 167.9, 167.0 (C-6, C-6'''), 162.6, 162.5 (C=O), 132.9 (CH_2-*C*H=CH_2), 118.9 (CH_2-CH=*C*H_2), 98.8, 98.7, 98.5 (C-1', C-1'', C-1'''), 98.0 (C-1), 77.6 (C-3''), 76.9 (C-4), 75.6 (C-3'), 75.2 (C-5), 73.3 (C-5'''), 71.1 (C-4'''), 70.8 (*C*H_2-CH=CH_2), 69.0 (C-4'), 67.8 (C-5'), 67.6 (C-5''), 67.1 (C-4''), 63.3 (C-3), 63.1 (C-2''), 62.4 (C-2'), 61.1 (C-3'''), 58.1, 57.6 (CH_3 CO_2Me), 53.2, 53.0 (C-2, C-2'''), 37.8 (CH_2 Lev), 29.9 (CH_3 Lev), 27.8 (CH_2 Lev), 18.6 (C-6''), 18.0 (C-6'); HRMS: $[M+NH_4]^+$ calcd for $C_{38}H_{46}Cl_6N_{20}O_{17}NH_4$ 1284.17955, found 1248.1789

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