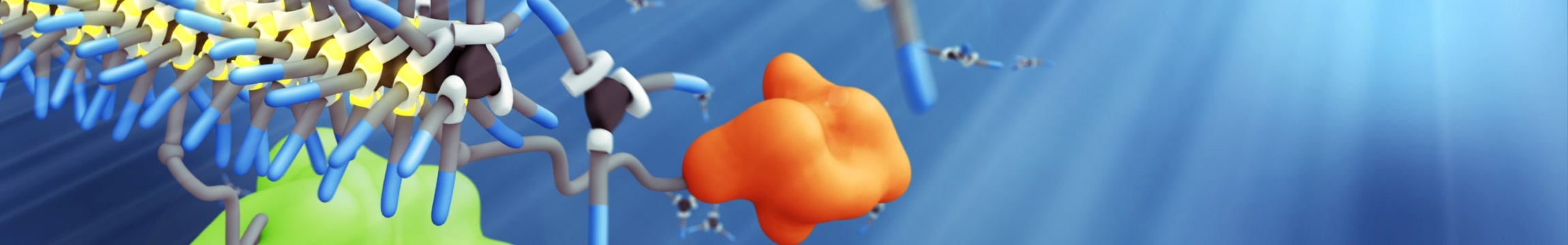
Synthesis of water-soluble supramolecular fiber components





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6-8-2018

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Graduation thesis





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# Samenvatting

Koolhydraten zijn biomoleculen en spelen een belangrijke rol in diverse biologische processen, zoals immuunafweer, celgroei en structurele ondersteuning.

Biomaterialen zoals hydrogellen zijn zeer aantrekkelijk als supramoleculaire vezelcomponenten, omdat hun waterige omgeving kunnen de extracellulaire matrix nabootsen.

Een van de huidige hydrogelontwerpen voor weefselkweek zijn gebaseerd op tetraethyleen glycol gekoppeld aan een benzeen-1,3,5-tricarboxamide-kern. Deze niet-biologische motieven staan bekend om het veroorzaken van een ongewenste immuunreactie. Door de poly(ethyleen)glycol eenheid te vervangen voor natuurlijke stoffen, zoals mono- of disachariden, kunnen deze ongewenste immuunreacties mogelijk worden voorkomen. Daarnaast zouden potentiële veranderingen in auto-montage van deze supramoleculaire vezelcomponenten in water verbeterd kunnen worden door verschillende supramoleculaire interacties, zoals waterstofbruggen, π-π interacties en hydrofobe effect.

Om functionaliteiten in deze vezelcomponenten te kunnen introduceren, zou een azide in de glycosyldonoren geïntroduceerd kunnen worden. Dit azide kan vervolgens worden gebruikt als een handvat om andere functionaliteiten aan te klikken, bijvoorbeeld fluoroforen of groeifactoren.

Om deze supramoleculaire vezelcomponenten te synthetiseren worden twee imidaat-donoren gesynthetiseerd. In een van deze donoren wordt een azide geïntroduceerd om andere functionaliteiten aan te klikken. Deze glycosyldonoren worden dan aan de acceptor gekoppeld door glycosyleering tot het supramoleculaire vezelcomponent. Zowel de niet-gefunctionaliseerde glycosyldonor als de azide-gefunctionaliseerde glycosyldonor werden in 27% en 3% totale opbrengst gesynthetiseerd. De acceptor werd met de niet-gefunctionaliseerde glycosyldonor tot de surpamoleculaire vezelcomponent gekoppeld in een opbrengst van 56%. De acceptor werd ook met beide donoren in verschillende synthese routes tot het supramoleculaire vezelcomponent gekoppeld, via een intermediair product. Na optimalisatie van de reactie en beginnend met de azide-gefunctionaliseerde donor, werd het intermediair product in 16% opbrengst gesynthetiseerd. Het eindproduct zou nog gesynthetiseerd en ontschermd moeten worden voordat ze hydrogellen kunnen vormen.

# List of abbreviations

Ac acetyl

aq. aqueous

BTA benzene-1,3,5-tricarboxamide

BTC benzene-1,3,5-tricarbonyl trichloride

Bz benzoyl

COSY correlation spectroscopy

δ chemical shift (ppm)

d doublet

dd double doublet

DCM dichloromethane

DMAP 4-dimethylaminopyridine

DMF dimethylformamide

ECM extracellular matrix

EtOAc ethyl acetate

Equiv. molar equivalents

FBR Foreign Body Response

HSQC Heteronuclear Single Quantum Coherence

h hour

Hz Hertz

HFIP hexafluorisopropanol

IR infrared

*J* coupling constant

m multiplet

M molar

MHz mega hertz

min minutes

MS molecular sieves

NIS *N*-iodosuccinimide

NMR Nuclear Magnetic Resonance

PE pentane

Ph phenyl

ppm parts per million

q quartet

rt room temperature

R*f* retention factor

s singlet

sat. saturated

t triplet

TFA trifluoracetic acid

TfOH triflic acid

TLC Thin Layer Chromatography

TMS trimethylsilane

TMSOTf [trimethylsilyl trifluoromethanesulfonate](https://www.sigmaaldrich.com/catalog/product/aldrich/225649?lang=en&region=US)

Ts tosyl

# Introduction

## **Biological background**

Carbohydrates are biomolecules that have an important role in biological processes, such as immune defense, cell growth, and structural support.1 These biomaterials are excellent for tissue engineering.2 Carbohydrates are widely used in biomedicine and cells have the ability to feel other carbohydrates by cell surface lectin found in mammals.3

Biomaterials such as hydrogels are very attractive as supramolecular polymers since their aqueous environment can mimic the ECM, absorbing up to 99% of water of its environment by the hydrophilic part of the polymer. This allows the encapsulation of cells under physiological conditions.Also, nutrient diffusion is possible due to water molecules filling up the space in the network.4 This produces a 3D environment where the hydrogel can remodel the *in vivo* situation. In the biomedical field, organoids are becoming very important since they closely recapitulate the *in vivo* organs and this could regenerate diseased tissue in the near future. Organoids are *in vitro* cultured multi-cellular structures from adult stem cells.5,6 Inspired by the ECM (Figure 1), many natural and synthetic systems have been developed as hydrogels for the culture of various cells *in vitro*. Synthetic systems for mimicking the ECM are based more specifically on a multi-component supramolecular biomaterial.7

**Figure 1.** A schematic scheme of the ECM as a target for an artificial ECM mimic. Cell surface receptors (e.g. integrins; in green) bind to ECM proteins, there by anchoring the cell to the ECM.8



Amphiphiles, which are molecules containing both hydrophilic and hydrophobic parts, based on carbohydrates have the ability to recognize other carbohydrates, are biocompatible and have excellent water-solubility. In previous work by Leenders, C. M. A., *et al*. water-soluble tetraethylene glycol units connected to BTA derivates through a C12-alipatic spacer can form supramolecular polymers in water above a critical concentration. Interestingly, by introducing different monosaccharide, the self-assembly behavior of BTAs in water can still be achieved (Figure 2).9

**Figure 2.** Glucose-functionalized BTA.



Some of the main driving forces for self-assembly are hydrogen bonding and π-π stacking. In addition, the hydrophobic effect can also play an important role driving self-assembly process in water. BTA derivatives with an aliphatic spacer creates a hydrophobic pocket, and tetraethylene glycol or saccharides motifs on the edge of the molecule with alcohol end groups provide water solubility by making hydrogen bonds.10 Poly(ethylene)glycol-based hydrogel are the future for tissue engineering. But, when used *in vivo*, they are known to trigger a foreign body response (FBR). This happens when the scaffold injures the surrounding tissue during the process of surgically implanting the scaffold and will lead to an acute inflammatory response. The FBR happens mostly to all non-biological scaffolds, like poly(ethylene)glycol hydrogels.11 By replacing this poly(ethylene)glycol unit with natural substances, e.g. mono- or disaccharide, the FBR could possibly be prevented. Furthermore, potential additions in auto-assembling would be improved due to several supramolecular interactions, such as directional hydrogen bonds, π-π interactions and hydrophobic effects.12

## **Water-soluble supramolecular fiber component**

In collaboration with Eindhoven University of Technology, the goal is to synthesize water-soluble supramolecular fiber components (hydrogels) based on the BTA for mimicking the ECM. Is these BTA components the tetraethylene glycol units would be replaced by mono- or disaccharides, e.g. glucose or cellobiose (

Figure **3**). In order to be able to introduce functionalities in these fiber components, we would like to introduce an azide into the glycosyl donors. This azide can then be used as a handle to introduce other functionalities, e.g. fluorophore, growth factors or antibiotics for the organoids. Furthermore, kinetic studies could be done with these fibers when they are conjugated to fluorophores.

**Figure 3.** Polyethylene glycol based BTA (left) vs. saccharide-based BTA (right) for mimicking the ECM.



The retro synthesis of the water-soluble supramolecular fiber component is shown in Scheme 1. This supramolecular fiber component is made up of building blocks **3, 4** and **5** and were prepared according to known procedures. In order to synthesize the water-soluble supramolecular fiber components, the building blocks would be coupled together via glycosylation reaction. This is a complex chemical reaction because there are several ways for making these fibers. As depicted in Scheme 1, on the acceptor we have three free hydroxyl to couple our glycosyl donors to synthesize the water-soluble supramolecular fiber component. First of all, the non-functionalized donor **3** could be coupled three times on the BTA-core (main batch). Second of all, as the main goal is to introduce functionalities in these fiber components, the glycosyl donor **3** could be first coupled twice on the BTA-core, having then one hydroxyl left for coupling the functionalized glycosyl donor **4**. Third of all, the coupling could also be done the other way around by first coupling the glycosyl donor **4** once and then the glycosyl donor **3** twice. The challenge here is that this is a two-step reaction and the formed products could be the BTA-core with 3x coupled donor, 2x coupled donor and a free hydroxyl, and 1x coupled donor and two free hydroxyl. Having a distribution of these products the yield of the desired product could not be so greatly. Finally, the glycosyl donor (protected as well as non-protected) could also be coupled to the amine linker first and then making a peptide bond forming the BTA-core (or the final product). Previous work showed these amide formation reactions as low yielding and poorly scalable (data not shown).

**Scheme 1.** Retro synthesis of the water-soluble supramolecular fiber component.



To make these glycosyl donors reactive for glycosylation, introduction of an imidate on the anomeric position was chosen. This imidate can easily be activated with triflic acid. The protecting groups of the building blocks were carefully chosen as neighboring group participation for stereoselectivity and so they could be easily removed under basic conditions.

Starting with D-glucose, benzoylation13 of the free hydroxyl groups and then selective deprotection of the anomeric center14 was done in order to introduce the reactive imidate15 on building block **3** for glycosylation.

By acetylating D-glucose16, protection of the anomeric center with a thio-functionality17 was possible. This anomeric protecting group is orthogonal with the other protecting groups and this orthogonality allows the selective deprotection of the anomeric center with no decomposition of other protecting groups.18 Deacetylation under basic condition17 would make the hydroxyl groups ‘free’ again. To introduce the azide functionality on the 6th position, the primary alcohol needs to be substituted by a good leaving group, such as a tosyl group.19 Tosylation works best with primary alcohols making it easier to introduce the azide on the 6th position as there is only one primary alcohol. To do this on secondary alcohols an extra step would be needed and this can lead to problems like rearrangement of the molecule. The next two steps before introducing the imidate can be done in two ways. Both benzoylation13 and then azide introduction19 or vice versa is possible. Selective deprotection of the anomeric center20 is done in order to introduce the imidate15.

Compound **7** was previously synthesized and was used as a starting material for making compound **5**. An alkyl halide was converted into a primary amine using phthalimide followed by cleavage of the phthalimide with hydrazine resulting in the amine linker **6** and phthalhydrazide byproduct.21 This linker is then attached to compound **8** forming acceptor **5**22(BTA-core) with three free hydroxyls that would be the nucleophile in the glycosylation reaction for making the supramolecular fiber component. After deprotection under basic condition, these saccharide-based BTAs could form hydrogels.

## **Glycosylation reaction**

One of the main challenges in carbohydrate chemistry is the formation of *O*-glycosidic bonds with a specific stereoselectivity. In a chemical glycosylation reaction the leaving group of the glycosyl donor is activated by a strong Lewis acid, such as triflic acid. The nucleophilic hydroxyl acceptor attacks the glycosyl donor forming this glycosidic linkage.23 The resulting product in this coupling reaction can either be α- or β-configuration products. Currently there are different manipulations for controlling the stereochemistry of the desired product.24 Here is where neighboring groups participation comes in action. Even though the main function of protecting groups is to protect a functional group in the glycosyl donor from reacting in a glycosylation reaction, they surely can control the stereochemical outcome. They also play an important role in the reactivity of the glycosyl donor.25 An ester protecting group on the C-2 hydroxyl leads the formation of trans-glycosidic linkage due to the cyclic oxonium ion intermediate24,26 (Figure 4).

**Figure 4.** Neighboring group participation for the preparation of 1,2-trans-glycoside or β-glycoside.



During glycosylation, water present in the reaction mixture, either from moisture present in the solvent or atmosphere or from water generated during the reaction, can result in hydrolysis products27 (by water reacting as a competitive nucleophile). Such reactions must be performed under completely anhydrous conditions. Nowadays, molecular sieves, both powdered and non-powdered and both 3 Å and 4 Å are frequently added to reaction mixtures in order to scavenge water. Furthermore, drying out the donor/acceptor mixture before the activation process through several co-evaporations with toluene will remove traces of water. In addition, performing the glycosylation reaction under nitrogen atmosphere and with an excess of glycosyl donor gives good results.27

# Results and discussion

The synthesis of the water-soluble supramolecular fiber component building blocks are described in this chapter. Firstly, the synthesis of the non-functionalized as well as the azide-functionalized glycosyl donor and the acceptor will be discussed. Secondly, the glycosylation reaction for making the water-soluble supramolecular fiber component will be discussed. Reaction mechanisms can be found in the supplementary data on page 30.

## **Synthesis of the glycosyl donors and acceptor**

Synthesis of the non-functionalized glycosyl donor **3** is shown in Scheme 2. Compound **9** was afforded as an anomeric mixture (α/β: 3/1). Some benzoic acid was still present with the product even after purification. Selective deprotection of the anomeric center afforded hemiacetal **10** as an anomeric mixture (α/β: 4/1). Treatment of hemiacetal **10** with trichloroacetonitrile and K2CO3 afforded glycosyl donor **3** (α-product) in 46% yield. This building block was stored at -30 °C when unused. The overall yield for this building block was 27% over 3 steps.

**Scheme 2.** Synthetic scheme of glycosyl donor **3.**



Reagents and conditions: (a) BzCl, pyridine, 0 °C to rt, qnt; (b) (NH2)2.HOAc, DMF, 0 °C to rt, 59%; (c) CCl3CN, K2CO3, DCM, 0 °C to rt, 46%.

Synthesis of the azide-functionalized glycosyl donor **4** is shown in

Scheme **3**. Starting again with D-glucose, protection of the free hydroxyl groups with acetic acid anhydride under basic conditions afforded compound **11** as an anomeric mixture (α/β: 10/1). Anomeric protection with thiophenol and boron trifluoride etherate and separation of the anomeric mixture by crystallization with ethanol afforded compound **12** (β-product) in only 54% yield. The other 46% could have been the α-product or non-reacted starting material. Maybe by performing the reaction in a higher concentration than 0.5 M DCM, the reaction time could have been shorter. Deprotection of the hydroxyl groups with sodium methoxide afforded compound **13**.Treatment of compound **13** with *p*-tosyl chloride afforded compound **14** in poor yield. In this reaction DMAP was used to improve the yield because there were no development seen on TLC. The addition of an extra 2 equivalents of *p*-tosyl chloride and stirring overnight did not improve the yield either. Instead, the starting material was completely gone forming two by products; one of them a 2nd tosyl group on of the secondary hydroxyl groups. This was confirmed with 1H NMR spectra.

Before the introduction of the azide functionality on the 6th position, two different synthesis routes were performed on a small scale to afford compound **16** with the highest yield. Firstly, introduction of the azide functionality with sodium azide yielded compound **15b**. Next, benzoylation with benzoyl chloride afforded compound **16** in 11% yield over 2 steps. Lastly, benzoylation of **14** afforded compound **15a** and introduction of the azide afforded compound **16** in 68% yield over 2 steps. The latter was achieved in a higher yield so this route was used to make thio-donor **16**. This thio-donor was not fully converted into glycosyl donor **4** as this donor could also be used for glycosylation in an alternative route. Thio-donor **16** was half converted into imidate-donor **4** by NIS hydrolysis and imidate introduction. Azide-functionalized glycosyl donor **4** (α-product)in was made in 40% yield. The other 60% was a mixture of the β-product and starting material. The overall yield was only 3% over 8 steps. This building block was also stored at -30 °C when unused.

**Scheme 3.** Synthetic scheme of glycosyl donor **4.**



Reagents and conditions: (d) Ac2O, pyridine, 0 °C to rt, overnight, 96%; (e) PhSH, BF3.Et2O, DCM, rt, 10 days, 54%; (f) NaOMe, MeOH, rt, 15 min., qnt; (g) p-TsCl, pyridine, 0 °C to rt, 52 h, 37%; (h) BzCl, pyridine, 0 °C to rt, overnight, 86%; (i) NaN3, DMF, 120 °C, overnight, 79%; (i) NaN3, DMF, 110 °C, overnight, 21%; (k) BzC, DMAP, Et3N, DCM, 0 °C to rt, overnight, 55%; (l) NIS, TFA, DCM, 0 °C, 1.5 h, 66%; (m) CCl3CN, K2CO3, DCM, 0 °C to rt, overnight, 40%.

Synthesis of acceptor **5** is shown in Scheme 4. Starting with compound **7**, the phthalimide was cleaved with hydrazine hydrate to afford compound **6** in only 46% yield. The synthesis of acceptor **5** was done several times and achieved in different yields (52 – 88%). Starting with commercially available 12-amino-1-dodecanol **6** and benzene-1,3,5-tricarbonyl trichloride (BTC) **8** and stirring overnight, acceptor **4** was afforded in 88% yield. Starting with self-synthesized 12-amino-1-dodecanol, commercially available BTC and stirring over the weekend, acceptor **5** was made in 71% yield, but with the highest purity (determined with NMR spectra). The overall yield for making acceptor **5** was 33% over 2 steps.

**Scheme 4.** Synthetic scheme of acceptor **5.**



Reagents and conditions: (a) (NH2)2.H2O, EtOH, 80 °C, 2.5 h, 46%; (b) Et3N, DCM, rt, 60 h, 71%.

## Glycosylation reaction

Glycosyl donor **3** was coupled three times onto acceptor **5** affording compound **1** as the main batch (Scheme 5 & Table 1; entry 1). These reactions were performed in a mixture of DCM/HFIP (4/1, v/v, 0.023 M) in order to dissolve the acceptor because this is insoluble in DCM.

**Scheme 5.** Glycosylation reaction.



Reagents and conditions. (a) DCM/HFIP, MS, TfOH, 0 °C, 3.5 h, 56%.

Acceptor **5** was also glycosylated with glycosyl donors **3** and **4** in two differentroutes to synthesize compound **2** via intermediate **19** and **21** respectively (Scheme 6). Thio-donor **16** was also tested in another route to make intermediate **19** to see if thio-glycosylation works better than imidate-glycosylation (

Scheme ***7***).

As depicted in Scheme 6 (top), glycosyl donor **3** would be coupled twice on the acceptor to form the intermediate **19**. Next, azide-functionalized donor **4** would be coupled once on the intermediate product to make the final compound **2**. Glycosyl donor **3** (Table 1; entry 2) was previously glycosylated using 0.4 equivalents of the activator and this afforded intermediate **19** and by product **20** (Figure 5). The migrated benzoyl ester was identified with NMR spectra as a triplet at 4.3 ppm. A new attempt was carried out with 0.2 equivalents of the activator (Table 1; entry 3) in order to see if benzoyl ester migration could be avoided. In this case the intermediate was formed as a mixture of compound **18** (ortho ester), compound **19** (intermediate product), and compound **20** (migrated benzoyl ester) (Figure 5) in poor yields. This ortho ester was observed and isolated as a mixture and could not be separated from the desired product. Stirring the reaction overnight (Table 1; entry 7) did not open/break the ortho ester formed either. During the reaction a very stable dioxolenium ion28 is formed causing the formation of compound **18**.

The other synthesis route depicted in Scheme 6 (bottom) was carried out to afford final compound **2**. Firstly, azide-functionalized glycosyl donor **4** was glycosylated with acceptor **5** to afford the intermediate product **21**. By using 0.4 equivalents of the activator (Table 1; entry 8) the same ortho ester mixture was formed. However, by using 0.5 equivalents of the activator instead of 0.4 equivalents (Table 1; entry 9), the desired intermediate **21** was formed with no side products, but in a very poor yield. The reaction was followed by TLC but it was quenched earlier than it should have been. There was still starting material present and the yield would have been improved with a longer reaction time.

**Scheme 6.** Synthetic routes for making the water-soluble supramolecular fiber component.



Reagents and conditions. (a) DCM/HFIP, MS, TfOH, 0 °C, 1 h, 29%; (b) TMSOTf, DCM, 0 °C, 1 h, 7%; (c) Donor **4**, DCM, MS, TfOH, 0 °C; (d) DCM/HFIP, MS, TfOH, 3 h, 0 °C, 16%; (e) Donor **3**, DCM, MS, TfOH, 0 °C.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1.** Optimization of the glycosylation reaction of intermediate **19** and **21.** | | | | | | | | |
| **Entry** | **Scale acceptor**  **(mmol)** | **Donor** | **Eq.**  **donor** | **Eq. activator** | **T (°C)** | **t**  **(h)** | **Product**  **(mixture ratio)** | **Yield**  **(%)** |
| 1 | 0.10 | **3** | 5.0 | 1.0 a | 0 | 3.5 | **1** | 56 |
| 2 | 0.25 | **3** | 2.2 | 0.4 a | 0 | 2.5 | **19/20** (1.7:0.2) | 31 |
| 3 | 0.88 | **3** | 2.2 | 0.2 a | 0 | 2.5 | **18/19/20** (0.9:0.8:0.1) | 22 |
| 4 | 0.10 | **3** | 2.2 | 0.3 a | 0 | 1 | **18/19/20** (1.1:0.7:0.1) | 65 |
| 5 | 0.10 | **3** | 2.2 | 0.4 a | 0 | 1 | **18/19/20** (0.6:0.8:0.1) c | 29 |
| 6 | 0.10 | **3** | 2.2 | 0.4 a | 0 | 2 | **18/19/20** (0.2:0.5:0.1) | 19 |
| 7 | 0.10 | **3** | 2.2 | 0.4 a | +4 | 18 | **18/19/20** (0.3:1.5:0.2) | 18 |
| 8 | 0.10 | **4** | 1.0 | 0.4 a | 0 | 2.5 | **18/19/20** (0.2:0.7:0.01) | 27 |
| 9 | 0.20 | **4** | 1.5 | 0.5 a | 0 | 3 | **21** | 16 |
| 10 | 0.10 | **16** | 2.5 | 0.5 b | +4 | 36 | **22** |  |

a TfOH

b NIS, TfOH

c Treated with TMSOTf

**Figure 5.** Formed side products with the intermediate during the glycosylation reaction.

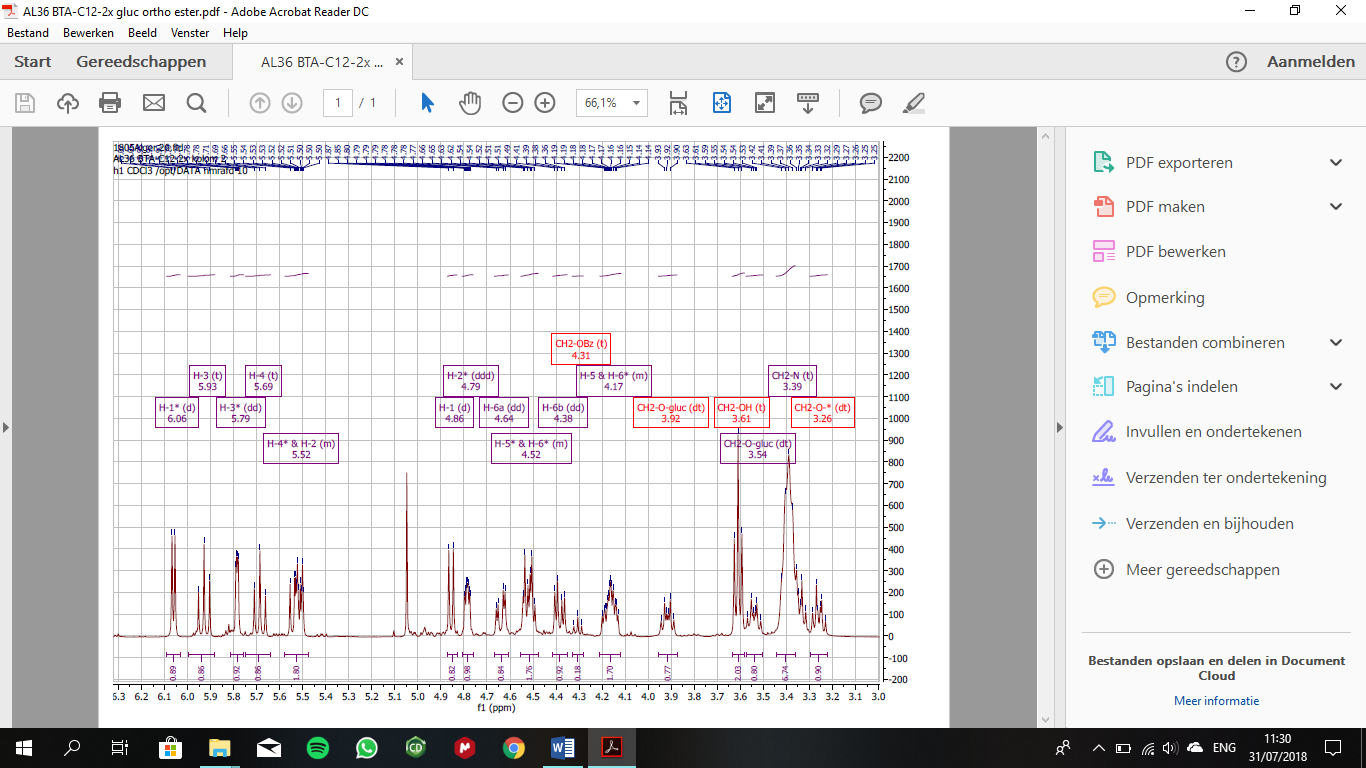


The ratio of the mixture of compounds (Table 1) was determined by comparing the integrals of the peak from the CH2 next to the oxygen with the CH2 next to the hydroxyl shown in Figure 6 and 7.

**Figure 6.** Formed side products with the intermediate during the glycosylation reaction. The integrals for determining the ratio are shown with arrows.



**Figure 7.** 1H-NMR spectrum of a mixture of compounds **18**, **19**, and **20** (table 1; entry 3). The integrals for determining the ratio are shown with arrows.



Next a final synthesis route shown in

Scheme ***7*** was carried out to afford intermediate **21**. Thio-donor **16** (Table 1; entry 10) was glycosylated with acceptor **5** and, interestingly, only ortho ester product was formed and no intermediate at all.

***Scheme 7.*** *Thio-glycosylation for making compound* ***2.***



Reagents and conditions. (a) DCM/HFIP, MS, NIS, TfOH, 0 °C, 36 h, 16%. (b) Donor **4**, DCM, MS, TfOH, 0 °C.

A new reaction was carried out in order to open/break the ortho ester to afford intermediate **19** (Scheme 8). Treatment of compound **18** with TMSOTf opened the dioxolenium ion allowing nucleophilic attack on the anomeric center affording a mixture of compound **19** and **20** in 33% yield. Purification by size-exclusion chromatography isolated intermediate **19** in 7% yield.

**Scheme 8.** Ortho ester opening reaction.



Reagents and conditions. (a) DCM, TMSOTf, 0 °C, 1 h, 7%.

Before performing the alternative route for making intermediate **21**, azide-functionalized glycosyl donor **4** was glycosylated with one of the batches of mixture of compounds **18, 19** and **20** in order to afford the final compound **2** (Scheme 9). Unfortunately, the ortho ester product as well as the migrated benzoyl ester were still present. NMR-spectroscopy showed the disappearance of the free hydroxyl group thus indicating the coupling of the glycosyl donor. Also, IR-spectroscopy showed an azide functionality at 2200 cm-1 indicating the presence of the azide-functionalized donor **4**.

**Scheme 9.** Glycosylation reaction.



Reagents and conditions: (a) Donor **3**, DCM, MS, 0 °C, 3 h.

# Conclusion

Glycosyl donor **3** was synthesized in an overall yield of 27% over 3 steps and azide-functionalized glycosyl donor **4** was synthesized in an overall yield of 3% over 8 steps. Starting from self-synthesized 12-amino-1-dodecanol, acceptor **5** was synthesized in 33% over 2 steps.

Acceptor **5** was glycosylated with donors **3, 4** and **16** in different synthetic routes to afford the water-soluble supramolecular fiber component **1** and **2**. Final compound **1** (main batch) was synthesized in 56% yield. Intermediate product **19** was further purified by size-exclusion chromatography and was isolated in 7% yield. After optimization of the reaction conditions and starting with azide-functionalized donor **4,**  the intermediate product **21** was synthesized in 16% yield. This is the first step towards the final compound **2**.

# Future prospects

Future research plan consists of:

1. Optimization of glycosylation reaction with donor **3**;
2. Glycosylation with a different Lewis acid;
3. Synthesis of cellobiose-donor(s) and glycosylation.

**Optimization with donor 3.**

As described before, acceptor **5** was glycosylated with donor **3** forming a mixture of the intermediate product together with two by products. It is known that using 0.4 equivalents or more of TfOH, benzoyl migration is achieved. Using less equivalents of TfOH, ortho ester formation is also achieved. By using 0.2 equivalents of TfOH with a longer reaction time, e.g. by stirring overnight, formation of the two by products could possibly be prevented.

**Glycosylation with a different Lewis acid.**

Another glycosylation reaction could be performed using BF3.OEt2 as the activator and starting with donor **4** to synthesize intermediate **19**. Using BF3.OEt2 as a milder activator could possibly prevent benzoyl ester migration and/or ortho ester.

**Synthesis of cellobiose-donor and glycosylation.**

A cellobiose-functionalized BTA could also be synthesized with a cellobiose donor (Scheme 10). Introduction of the azide could also be introduced into this donor. This azide can then be used as a handle to introduce other functionalities, e.g. fluorophore, growth factors, antibiotics for the organoids or for kinetic studies.

**Scheme 10.** Synthetic scheme of cellobiose donor.



Reagents and conditions: (a) BzCl, pyridine, 0 °C to rt; (b) (NH2)2.HOAc, 0 °C to rt; (c) K2CO3, CCl3CN, DCM, 0 °C to rt; (d) Ac2O, pyridine, 0 °C to rt; (e) PhSH, BF3.Et2O, DCM, rt; (f) NaOMe, MeOH, rt; (g) TsOH, PhCH(OMe)2, DCM; (h) BzCl, pyridine, 0 °C to rt; (i) MeOH, TsOH; (j) p-TsCl, pyridine, 0 °C to rt; (k) NaN3, DMF, 110 °C; (l) BzCl, pyridine, 0 °C to rt.

# Experimental section

**General experimental procedures and materials**

All reactions were carried out in oven-dried glassware and all chemicals were used as received unless stated otherwise. All moisture sensitive reactants were co-evaporated with anhydrous toluene and reactions were performed under a nitrogen atmosphere. Molecular sieves (3Å) were flame dried before use. Column chromatography was performed using forced flow of the indicated solvent systems on Screening Devices Silica gel 60 (40 – 63 µm mesh). Analytical TLC was performed on aluminum sheets, pre-coated with silica gel (Merck, silica gel 60, F254). Compounds were visualized with UV-absorptions (254 nm), by spraying either 20% H2SO4 in EtOH or a solution of (NH4)6Mo7O24.H2O (25 g/L) followed by charring at ~150 °C. 1H and 13C NMR spectra were recorded on a Bruker AV-400liq or AV-400imaging (400/100 MHz) spectrometer at ambient temperature. Chemical shifts are reported as δ values (ppm) and directly referenced to TMS (0.00 ppm) in CDCl3 or via a solvent residual peak. Coupling constants (*J*) are given in Hz and all 13C spectra are proton coupled. NMR assignments were made using COSY and HSQC unless stated otherwise. TLC-MS analysis was performed on a Camag TLC-MS Interface combined with an API165 (SCIEX) mass spectrometer (eluted with *tert*-butylmethylether/EtOAc/MeOH, 5/4/1, v/v/v + 0.1% formic acid, flow rate 0.1 mL/min). High resolution mass spectra were recorded on a Thermo Finnigan LTQ Orbitrap equipped with an electronspray ion source in positive 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 = 150 – 4000) and dioctylphtalate (m/z = 391.28428) as “lock mass”. IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm-1. Optical rotation was measured on an Anton Paar MCP 100 Modular Circular polarimeter at 20 °C, concentration = 10 mg/mL and cell length = 10 cm.

**1,2,3,4,6-Penta-*O*-benzoyl-α,β-D-glucopyranoside (9).**D-glucose (1.95 g, 10.8 mmol) was dissolved in pyridine (25 mL, 0.4 M), and upon cooling to 0 ˚C, benzoyl chloride (11.2 mL, 96.4 mmol; 9.6 equiv) was added dropwise. After being stirred for 4 h, the mixture was diluted with Et2O, and upon cooling, the reaction was quenched with water, washed with HCl (aq., 1 M, 3x), KOH (aq., 1 M, 1x) and NaHCO3 (sat. aq., 1x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure to yield the crude compound **9** (7.57 g, 10.8 mmol, 100%), which was used without further purification (α/β ratio = 3/1). TLC *Rf* 0.42 (EtOAc/PE, 1/3, v/v). All NMR spectra were in full accordance with those previously published.13; 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC, α-product) δ 8.19 – 8.15 (m, 8H, CHarom), 8.05 – 8.01 (m, 3H, CHarom), 7.97 – 7.85 (m, 8H, CHarom), 7.71 – 7.64 (m, 4H, CHarom), 7.58 – 7.27 (m, 25H, CHarom), 6.86 (d, *J* = 3.7 Hz, 1H, H-1), 6.32 (t, 1H, H-3), 5.87 (t, 1H, H-4), 5.69 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2), 4.69 – 4.60 (m, 2H, H-5 & H-6a), 4.54 – 4.46 (m, 1H, H-6b); 13C NMR (101 MHz, CDCl3, HSQC) δ 166.2, 166.0, 165.5, 165.2, 164.5, 162.5 (C=O), 134.7, 134.1, 133.7, 133.6, 133.5, 133.3, 130.7, 130.3, 130.2, 130.0, 130.0, 130.0, 129.9, 129.9, 129.6, 129.1, 129.0, 129.0, 128.9, 128.8, 128.6, 128.6, 128.5, 128.5 (CHarom), 90.1 (C-1), 70.9 (C-3), 70.6 (C-2), 70.6 (C-5), 68.9 (C-4), 62.6 (C-6), 21.2, 14.3 (C=O); IR (neat): 2959, 1720, 1601, 1450, 1250, 1176, 1090, 1067, 1020 cm-1.

**2,3,4,6-Tetra-*O*-benzoyl-α,β-D-glucopyranose (10).** Compound **9** (7.57 g, 10.8 mmol) was dissolved in DMF (50 mL, 0.2 M), and upon cooling to 0 ˚C, hydrazine acetate (2.44 g, 26.5 mmol; 2.5 equiv) was added. After being stirred for 5 h, the mixture was diluted with EtOAc and washed with HCl (aq., 1 M, 3x), brine (1x) and NaHCO3 (sat. aq., 2x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/PE, 1/4, v/v) yielded compound **10** (4.36 g, 7.30 mmol, 59%) as a colorless oil (α/β ratio = 4/1). TLC *Rf* 0.76 (EtOAc/PE, 5/5, v/v).

1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC, α-product) δ 8.08 – 7.83 (m, 11H, CHarom), 7.57 – 7.26 (m, 16H, CHarom), 6.26 (t, *J* = 9.9 Hz, 1H, H-3), 5.77 (d, *J* = 3.8 Hz, 1H, H-1), 5.76 – 5.71 (m, 1H, H-4), 5.32 (dd, *J* = 10.2, 3.5 Hz, 1H, H-2), 4.71 – 4.65 (m, 1H, H-5), 4.68 – 4.63 (m, 1H, H-6a), 4.43 (dd, *J* = 12.5, 4.5 Hz, 1H, H-6b), 3.63 (br s, 1H, OH); 13C NMR (101 MHz, CDCl3, HSQC) δ 166.0, 165.4 (C=O), 133.6, 133.6, 133.3, 130.1, 130.0, 129.9, 129.8, 129.7, 129.2, 129.0, 129.0, 128.6, 128.6, 128.5, 128.4 (CHarom), 90.6 (C-1), 72.4 (C-2), 70.2 (C-4), 69.5 (C-3), 67.9 (C-5), 62.9 (C-6); IR (neat): 3448, 2960, 1724, 1601, 1450, 1263, 1093, 1068, 1025 cm-1.

**2,3,4,6-Tetra-α-D-glucopyranosyl trichloroacetimidate (3).**Hemiacetal **10** (4.36 g, 7.30 mmol) was dissolved in DCM (40 mL, 0.2 M), and upon cooling to 0 ˚C, trichloroacetonitrile (1.10 mL, 10.9 mmol; 1.5 equiv) was added and K2CO3 (2.39 g, 17.3 mmol; 2.4 equiv) was added in scoops. After being stirred overnight, the mixture was filtered over Celite and washed with brine (2x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (Et2O/PE, 1/3, v/v) yielded compound **3** (2.47 g, 3.33 mmol, 46%) as a white foam. TLC *Rf* 0.65 (Et2O/PE, 5/5, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 8.63 (s, 1H, NH), 8.07 – 8.00 (m, 2H, CHarom), 8.00 – 7.92 (m, 4H, CHarom), 7.91 – 7.84 (m, 2H, CHarom), 7.61 – 7.52 (m, 1H, CHarom), 7.52 (tt, *J* = 7.9, 1.3 Hz, 2H, CHarom), 7.48 – 7.26 (m, 10H, CHarom), 6.84 (d, *J* = 3.7 Hz, 1H, H-1), 6.28 (t, *J* = 9.9 Hz, 1H, H-3), 5.82 (t, *J* = 9.9 Hz, 1H, H-4), 5.62 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2), 4.69 – 4.60 (m, 2H, H-5 & H-6a), 4.49 (dd, *J* = 13.0, 5.5 Hz, 1H, H-6b); 13C NMR (101 MHz, CDCl3, HSQC) δ 160.7 (C=O), 133.7, 133.5, 133.3, 130.1, 129.9, 129.9, 128.6, 128.5, 128.5 (CHarom), 93.3 (C-1), 70.8 (C-3 / C-5), 70.3 (C-2), 68.8 (C-4), 62.6 (C-6); [α]D20 = - 122.2 ° (c. 0.006, DCM); IR (neat): 3441, 2926, 1724, 160.1, 1452, 1266, 1093, 1068, 1029 cm-1.

**1,2,3,4,6-Penta-*O*-acetyl-α,β-D-glucopyranose (11).**D-glucose (18.4 g, 102 mmol) was dissolved in pyridine (250 mL, 0.4 M), and upon cooling to 0 ˚C, acetic acid anhydride (71.0 mL, 750 mmol; 7.5 equiv) was added dropwise. After being stirred overnight, the reaction mixture was quenched with MeOH at 0 ˚C, diluted with EtOAc, washed with HCl (aq., 1M, 3x) and brine (1x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure to yield compound **11** (37.5 g, 96.1 mmol, 96%) as a white solid (α/β ratio = 10/1) and was used in the next reaction without further purification. TLC *Rf* 0.94 (EtOAc/PE, 7/3, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC, α-product) δ 6.34 (d, *J* = 3.7 Hz, 1H, H-1), 5.48 (t, *J* = 10.4, 9.4 Hz, 1H, H-3), 5.19 – 5.08 (m, 2H, H-4 & H-2), 4.30 – 4.24 (m, 1H, H-6a), 4.16 – 4.07 (m, 2H, H-5 & H-6b), 2.19 (s, 3H, CH3), 2.13 – 2.08 (m, 3H, CH3), 2.07 – 2.00 (m, 9H, CH3 (3x)); 13C NMR (101 MHz, CDCl3, HSQC) δ 170.7, 170.3, 169.7, 169.4, 168.8 (C=O), 89.1 (C-1), 69.8 (C-3 / C-5), 69.2 (C-2), 67.9 (C-4), 61.4 (C-6), 20.9, 20.7, 20.7, 20.6, 20.5 (CH3); IR (neat): 2949, 1738, 1481, 1366, 1086, 1027 cm-1.

**Phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (12).**Compound **11** (37.5 g, 96.1 mmol) was dissolved in dried DCM(192 mL, 0.5 M) and thiophenol (12.0 mL, 118 mmol; 1.2 equiv) and BF3.Et2O (36.0 mL, 292 mmol; 3 equiv) were added under N2 atmosphere. After being stirred at room temperature for 10 days, the reaction mixture was quenched with Et3N and NaHCO3 (sat. aq.) at 0 ˚C, diluted in EtOAc and washed with NaOH (aq., 1 M, 5x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. The solid (anomeric mixture) was dissolved in boiling EtOH and after 10 min. the mixture was cooled to rt. The formed crystals were filtered off and collected yielding compound **12** (22.8 g, 51.8 mmol, 54%) as white crystals. TLC *Rf* 0.60 (EtOAc/PE, 5/5, v/v).

1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 7.52 – 7.48 (m, 2H, CHarom), 7.35 – 7.29 (m, 3H, CHarom), 5.23 (t, *J* = 9.4 Hz, 1H, H-3), 5.05 (t, *J* = 10.1, 9.5 Hz, 1H, H-2), 4.98 (t, *J* = 10.1, 9.3 Hz, 1H, H-4), 4.71 (d, *J* = 10.1 Hz, 1H, H-1), 4.26 – 4.16 (m, 2H, H-6), 3.76 – 3.70 (m, 1H, H-5), 2.09 (d, *J* = 2.9 Hz, 6H, CH3 (2x)), 2.01 (d, *J* = 11.5 Hz, 6H, CH3 (2x)); 13C NMR (101 MHz, CDCl3, HSQC) δ 170.7, 170.3, 169.5, 169.4 (C=O), 133.2, 131.8, 129.1, 128.6 (CHarom), 85.9 (C-1), 75.9 (C-3), 74.1 (C-2), 70.0 (C-4), 68.3 (C-5), 62.3 (C-6), 20.9, 20.9, 20.8, 20.7 (C=O); [α]D20 = - 17.7 ° (c. 0.007, DCM); IR (neat): 2949, 1740, 1481, 1439, 1366, 1300, 1213, 1027 cm-1.

**Phenyl-1-thio-β-D-glucopyranoside (13).** Compound **12** (19.2 g, 43.6 mmol) was suspended in basic solution of MeOH (90 mL, 0.5 M) and NaOMe (0.948 g, 17.5 mmol; 0.4 equiv) and the mixture was stirred at room temperature overnight. This solution was then treated with Amberlite ion-exchange resin (H+) until pH = 4. The resin was immediately filtered off, and the solvent was removed under reduced pressure to quantitatively yield compound **13** (11.9 g, 43.6 mmol) as a white solid and was used in the next reaction without further purification. TLC *Rf* 0 (EtOAc/PE, 5/5, v/v); 1H NMR (400 MHz, Methanol-*d*4) δ 7.60 – 7.52 (m, 2H, CHarom), 7.35 – 7.22 (m, 3H, CHarom), 4.94 – 4.88 (m, 10H, CHarom), 4.60 (d, *J* = 9.7, 1.7 Hz, 1H, H-1), 3.87 (dd, *J* = 12.1, 1.8 Hz, 1H, H-6a), 3.71 – 3.62 (m, 1H, H-6b), 3.39 – 3.17 (m, 4H, H-2 / H-3 / H-4 / H-5); 13C NMR (101 MHz, MeOD) δ 132.7, 129.9, 128.3 (CHarom), 89.4 (C-1), 82.0 (C-3), 79.7 (C-4), 73.8 (C-2), 71.3 (C-5), 62.9 (C-6); [α]D20 = - 24.9 ° (c. 0.007, MeOH); IR (neat): 3332, 2946, 2834, 1644, 1418, 1020 cm-1.

**Phenyl-6-*O*-*p*-toluenesulfonyl-1-thio-β-D-glucopyranoside (14).** Thioglycoside **13** (11.9 g, 43.6 mmol) was dissolved in pyridine (130 mL, 0.57 M) and *p*-toluenesulfonyl chloride (16.6 g, 86.6 mmol; 2 equiv) was added to this solution at 0 °C. After 4 h at 0 °C, the reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 16 h. DMAP (1.07 g, 8.66 mmol; 0.2 equiv) was added and the reaction was stirred overnight. *p*-Toluenesulfonyl chloride (16.7 g, 86.6 mmol; 2 equiv) was added and, after 4 h at 0 °C, the reaction mixture was stirred at room temperature overnight. The reaction was then quenched by addition of MeOH (20 mL), diluted in EtOAc, washed with HCl (aq., 1 M, 2x), NaHCO3 (sat. aq., 1x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/Et2O, 5/5, v/v) yielded compound **14** (6.90 g, 16.2 mmol, 37%) as a white solid. TLC *Rf* 0.49 (MeOH/EtOAc, 0.1/9.9, v/v); All NMR spectra were in full accordance with those previously published.17; 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 7.81 (t, *J* = 1.9 Hz, 1H, CHarom), 7.79 (t, *J* = 1.9 Hz, 1H, CHarom), 7.46 – 7.42 (m, 2H, CHarom), 7.33 – 7.29 (m, 2H, CHarom), 7.27 – 7.21 (m, 3H, CHarom), 4.47 (d, *J* = 9.7 Hz, 1H, H-1), 4.32 – 4.25 (m, 2H, H-6), 3.56 – 3.50 (m, 1H, H-3), 3.50 – 3.44 (m, 2H, H-4 & H-5), 3.28 (dd, *J* = 9.7, 8.5 Hz, 1H, H-2), 3.15 (br s, 3H, OH (3x)), 2.40 (s, 3H, CH3); 13C NMR (101 MHz, CDCl3, HSQC) δ 145.2, 132.8, 132.7, 131.8, 130.1, 129.2, 128.2 (CHarom), 87.8 (C-1), 77.6 (C-3 or C-4 or C-5), 71.8 (C-2), 69.2 (C-3 or C-4 or C-5), 68.9 (C-6), 21.8 (CH3); [α]D20 = + 2.4 ° (c. 0.005, DCM); IR (neat): 3351, 2921, 2359, 1598, 1481, 1439, 1357, 1173, 1008 cm-1.

**Phenyl-2,3,4-tri-*O*-benzoyl-6-*O*-*p*-toluenesulfonyl-1-thio-β-D-glucopyranoside (15).**Compound **14** (6.90 g, 16.2 mmol) was dissolved in pyridine (41 mL, 0.4 M), and upon cooling to 0 ˚C, benzoyl chloride (8.50 mL, x mmol; 4.5 equiv) was added dropwise. After being stirred overnight, the mixture was diluted with Et2O, and upon cooling, the reaction was quenched with water, washed with HCl (aq., 1 M, 3x), KOH (aq., 1 M, 2x) and NaHCO3 (sat. aq., 1x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (1/9 → 2/8 → 5/5, v/v, EtOAc/PE) yielded compound **15** (10.2 g, 13.8 mmol, 86%) as a colorless oil. TLC *Rf* 0.65 (EtOAc/PE, 3/7, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 7.98 – 7.91 (m, 2H, CHarom), 7.89 – 7.82 (m, 2H, CHarom), 7.80 – 7.71 (m, 4H, CHarom), 7.57 – 7.47 (m, 2H, CHarom), 7.50 – 7.20 (m, 15H, CHarom), 5.83 (t, *J* = 9.5 Hz, 1H, H-3), 5.39 (t, *J* = 9.2 Hz, 1H, H-2), 5.34 (t, 1H, H-4), 4.97 (d, *J* = 10.0 Hz, 1H, H-1), 4.26 (dd, *J* = 11.1, 2.4 Hz, 1H, H-6a), 4.20 – 4.11 (m, 1H, H-6b), 4.11 – 4.05 (m, 1H, H-5), 2.36 (s, 3H, CH3); 13C NMR (101 MHz, CDCl3, HSQC) δ 165.8, 165.3, 165.1 (C=O), 145.2, 133.8, 133.5, 133.4, 133.1, 131.7, 130.0, 130.0, 129.8, 129.2, 128.7 (Cq), 128.6, 128.6, 128.6, 128.5, 128.4, 128.2 (CHarom), 86.2 (C-1), 77.5 (C-3), 74.0 (C-2), 70.3 (C-4), 69.1 (C-5), 68.2 (C-6); [α]D20 = + 25.7 ° (c. 0.009, DCM); IR (neat): 2953, 1731, 1601, 1450, 1366, 1259, 1177, 1091, 1068, 1025 cm-1.

**Phenyl-6-azido-2,3,4-tri-*O*-benzoyl-6-deoxy-1-thio-β-D-glucopyranoside (16).** Thioglycoside **15** (10.2 g, 13.8 mmol) was dissolved in DMF (140 mL, 0.1 M) and sodium azide (4.49 g, 69.0 mmol; 5 equiv) was added successively. This suspension was heated to 120 °C overnight. The reaction mixture was cooled to room temperature and diluted in EtOAc, washed with NaHCO3 (sat. aq.) (1x) and brine (1x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (Et2O/PE, 3/7, v/v) yielded compound **16** (6.68 g, 11.0 mmol, 79%) as a yellow oil. TLC *Rf* 0.68 (EtOAc/PE, 3/7, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 7.97 (d, 2H, CHarom), 7.90 (d, 2H, CHarom), 7.79 (d, 2H, CHarom), 7.59 – 7.45 (m, 4H, CHarom), 7.45 – 7.28 (m, 9H, CHarom), 7.24 (d, *J* = 15.4 Hz, 1H), 5.90 (t, 1H, H-3), 5.49 (dd, 1H, H-2), 5.45 (t, 1H, H-4), 5.06 (d, 1H, H-1), 4.02 – 3.93 (m, 1H, H-5), 3.51 (dd, *J* = 13.5, 6.8 Hz, 1H, H-6a), 3.43 (dd, *J* = 13.5, 2.8 Hz, 1H, H-6b); 13C NMR (101 MHz, CDCl3, HSQC) δ 165.8, 165.3, 165.1 (C=O), 133.9, 133.7, 133.6, 133.4, 133.3, 131.1, 129.9, 129.9, 129.8, 129.6, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 127.1 (CHarom), 86.3 (C-1), 77.7 (C-5), 74.1 (C-3), 70.5 (C-2), 70.0 (C-4), 51.6 (C-6); [α]D20 = + 26.7 ° (c. 0.019, DCM); IR (neat): 2920, 2102, 1727, 1601, 1584, 1450, 1274, 1254, 1067, 1025 cm-1.

**6-Azido-2,3,4-tri-*O*-benzoyl-6-deoxy-α,β-D-glucopyranose (17).** Thioglycoside **16** (3.34 g, 5.50 mmol) was co-evaporated with toluene (2x) under N2 atmosphere, dissolved in dried DCM (55 mL, 0.1 M) and cooled to 0 ˚C. NIS (1.37 g, 6.05 mmol, 1.1 equiv) and TFA (0.50 mL, 6.05 mmol, 1.1 equiv) were added successively. After 1.5 h, the reaction mixture was quenched with Na2S2O3 (sat. aq.) (40 mL) and NaHCO3 (sat. aq.) (40 mL) and stirred for an extra hour. The mixture was diluted in EtOAc and washed with NaHCO3 (sat. aq., 3x). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography (3/7 → 4/6, v/v, Et2O/PE) yielded hemiacetal **17** (1.87 g, 3.61 mmol, 66%) as a colorless oil (α/β ratio = 4/1). TLC *Rf* 0.29 (EtOAc/PE, 2/8, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC, α-product) δ 8.01 – 7.81 (m, 9H, CHarom), 7.56 – 7.23 (m, 13H, CHarom), 6.23 (t, *J* = 9.9 Hz, 1H, H-3), 5.79 (d, *J* = 3.6 Hz, 1H, H-1), 5.55 (t, *J* = 9.8, 1.6 Hz, 1H, H-4), 5.31 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 4.54 – 4.47 (m, 1H, H-5), 3.53 – 3.40 (m, 2H, H-6). 13C NMR (101 MHz, CDCl3) δ 166.7, 165.9, 165.9, 165.9, 165.5, 165.4 (C=O), 134.0, 133.8, 133.7, 133.7, 133.5, 133.5, 133.3, 130.0, 129.9, 129.9, 129.9, 129.8, 129.7, 129.4, 129.1, 128.9, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 124.9 (CHarom), 90.4 (C-1), 72.2 (C-2), 70.1 (C-3), 70.0 (C-4), 69.9 (C-5), 51.2 (C-6); IR (neat): 3019, 2106, 1728, 1602, 1452, 1263, 1214 cm-1.

**6-Azido-2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-glucopyranosyl trichloroacetimidate (4).**Hemiacetal **17** (1.87 g, 3.61 mmol) was dissolved in DCM (18 mL, 0.2 M), and upon cooling to 0 ˚C, trichloroacetonitrile (1.10 mL, 10.8 mmol; 3 equiv) was added and K2CO3 (2.09 g, 14.5 mmol; 4 equiv) was added in scoops. After being stirred overnight, the mixture was filtered over Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel (2/8 → 4/6, v/v, Et2O/PE,) yielded compound **4** (955 mg, 1.44 mmol, 40%) as an yellow oil. TLC *Rf* 0.73 (EtOAc/PE, 2/8, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 8.72 (s, 1H, NH), 8.00 – 7.94 (m, 4H, CHarom), 7.89 – 7.85 (m, 2H, CHarom), 7.54 – 7.42 (m, 2H, CHarom), 7.42 – 7.29 (m, 6H, CHarom), 7.25 (t, *J* = 7.8 Hz, 2H, CHarom), 6.89 (d, *J* = 3.6 Hz, 1H, H-1), 6.28 (t, *J* = 9.9 Hz, 1H, H-3), 5.72 (t, *J* = 9.9 Hz, 1H, H-4), 5.64 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2), 4.50 (ddd, *J* = 10.2, 5.3, 3.0 Hz, 1H, H-5), 3.56 – 3.46 (m, 2H, H-6); 13C NMR (101 MHz, CDCl3, HSQC) δ 165.6, 165.3, 165.2, 164.7 (C=O), 160.7 (C=NH), 133.7, 133.6, 133.3 , 129.9, 129.9, 129.9 (CHarom), 129.7, 128.8, 128.5 (Cq), 128.5, 128.4, 128.4, 128.3 (CHarom), 92.9 (C-1), 71.9 (C-2), 70.6 (C-5), 69.9 (C-3), 69.2 (C-4), 50.7 (C-6); [α]D20 = + 38.0 ° (c. 0.067, DCM); IR (neat): 3345, 3019, 2106, 1731, 1677, 1602, 1452, 1262, 1091, 1068 cm-1.

**12-amino-1-dodecanol (6).** 2-(12-hydroxydodecyl)isoindoline-1,3-dione **7** (5.11 g, 15.4 mmol) was diluted in EtOH (154 mL, 0.1 M), hydrazine hydrate (3.30 mL, 67.8 mmol, 4.4 equiv) was added dropwise and the reaction mixture was refluxed at 80 ˚C for 2.5 h, resulting in the formation of a white precipitate. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The solid was diluted in DCM and extracted with 1.0 M HCl (aq., 3x). NaHCO3 was added to the water layer until the pH was raised to 7. The water layer was treated with 1.0 M NaOH (aq.) until pH = 10 and extracted with DCM (3x). The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure to yield compound **6** (1.46 g, 7.23 mmol, 47%) as a white solid. TLC *Rf* 0 (EtOAc/PE, 7/3, v/v); 1H-NMR spectra was in full accordance with those previously published.21; 1H NMR (400 MHz, Chloroform-*d*) δ 3.62 (t, *J* = 6.6 Hz, 2H, CH2-*O*), 2.71 – 2.64 (m, 2H, CH2-*N*), 1.55 (dt, *J* = 8.0, 6.4 Hz, 2H, CH2), 1.43 (t, *J* = 7.1 Hz, 2H, CH2), 1.42 – 1.25 (m, 18H, CH2 (9x)); IR (neat): 3359, 2919, 2849, 1612, 1559, 1460, 1347, 1332, 1060, 1037 cm-1.

 **(Dodeca-12-ol)-1,3,5-amidebenzyl (5).** To a co-evaporated solution of benzene-1,3,5-tricarbonyl trichloride **8** (0.535 g, 2.04 mmol, 1 equiv) in DCM (20 mL, 0.1 M) was added dropwise a co-evaporated solution of 12-amino-1-dodecanol **6** (1.32 g, 6.56 mmol, 3.3 equiv) and Et3N (0.5 mL) in DCM (33 mL, 0.2 M) at 0 ˚C under N2 atmosphere. After being stirred over the weekend, the reaction mixture was filtered and rinsed with DCM (300 mL), dissolved in MeOH, absorbed on silica and concentrated under reduced pressure. Purification by flash chromatography on silica gel (MeOH/CHCl3, 5/95, v/v) yielded compound **5** (1.09 g, 1.44 mmol, 71%) as a white solid. TLC *Rf* 0.47 (MeOH/CHCl3, 1/9, v/v); 1H NMR (400 MHz, Methanol-*d*4, HH-COSY, HSQC) δ 8.37 (s, 3H, CHarom), 3.53 (t, *J* = 6.6 Hz, 6H, CH2-*OH* (3x)), 3.40 (t, *J* = 7.1 Hz, 6H, CH2-*N* (3x)), 1.64 (p, *J* = 7.3 Hz, 7H, CH2), 1.51 (q, *J* = 6.9 Hz, 6H, CH2 (3x)), 1.40 – 1.29 (m, 42H, CH2 (21x)); 13C NMR (101 MHz, MeOD, HSQC) δ 168.7 (C=O), 136.9, 129.7 (CHarom), 63.0 (CH2-*OH)*, 49.6, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 41.2 (CH2-*N*), 33.7, 30.8, 30.7, 30.6, 30.5, 28.1, 27.0 (CH2); IR (neat): 3266, 2916, 1629, 1541, 1466, 1293, 1056 cm-1.

**Dodeca-1,3,5-amidebenzyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (1).** Acceptor **5** (78.4 mg, 0.103 mmol, 1 equiv) and donor **3** (382 mg, 0.516 mmol, 5 equiv) were combined and co-evaporated (3x) with toluene under N2 atmosphere. The reaction mixture was dissolved in DCM/HFIP (6.25 mL, 0.023 M, 4/1, v/v) and flame dried molecular sieves (3Å) were added. The mixture was stirred for 30 min at rt, and upon cooling to 0 ˚C, TfOH (12 µL, 0.136 mmol, 1.3 equiv) was added dropwise. After being stirred at 0 °C for 4 h, the reaction mixture was quenched with Et3N (0.1 mL), diluted in DCM and washed with NaOH (1 M, aq., 1x), HCl (1 M, sat. aq., 1x) and NaHCO3 (sat. aq., 1x). The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (3/7 → 5/5 → 7/3, v/v, EtOAc/PE) yielded compound **1** (140 mg, 0.0560 mmol, 56%) as a colorless solid. TLC *Rf* 0.65 (EtOAc/PE, 6/4, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 8.39 (s, 3H, CHarom), 8.03 – 8.00 (m, 6H, CHarom), 7.98 – 7.94 (m, 6H, CHarom), 7.92 – 7.88 (m, 6H, CHarom), 7.85 – 7.81 (m, 6H, CHarom), 7.56 – 7.23 (m, 32H, CHarom), 6.74 (q, *J* = 5.8 Hz, 3H, NH), 5.92 (t, *J* = 9.7 Hz, 3H, H-3), 5.68 (t, *J* = 9.7 Hz, 3H, H-4), 5.53 (dd, *J* = 9.8, 7.8 Hz, 3H, H-2), 4.85 (d, *J* = 7.8 Hz, 3H, H-1), 4.64 (dd, *J* = 12.1, 3.3 Hz, 3H, H-6a), 4.51 (dd, *J* = 12.1, 5.2 Hz, 3H, H-6b), 4.20 – 4.14 (m, 3H, H-5), 3.91 (dt, *J* = 9.7, 6.2 Hz, 3H, C*H*H-*O*), 3.54 (dt, *J* = 9.8, 6.7 Hz, 3H, CH*H-O*), 3.43 (q, *J* = 6.8 Hz, 6H, CH2-*N*), 1.63 – 0.98 (m, 42H, CH2 (21x)); 13C NMR (101 MHz, CDCl3, HSQC) δ 166.3, 165.9, 165.9, 165.3, 165.2 (C=O), 135.3 (Cq), 133.5, 133.3, 133.3, 133.2, 132.9, 129.9, 129.8, 129.8 (CHarom), 129.7 (Cq), 129.6 (CHarom), 129.5, 128.9, 128.9 (Cq), 128.5, 128.4, 128.4, 128.4, 128.2 (CHarom), 101.4 (C-1), 73.0 (C-3), 72.2 (C-5), 72.0 (C-2), 70.5 (CH2-*O*), 70.0 (C-4), 63.3 (C-6), 40.5 (CH2-*N*), 33.9, 32.0, 29.8, 29.7, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.4, 29.3, 29.3, 29.0, 28.8, 27.1, 26.1, 25.8 (CH2); [α]D20 = + 11.9 ° (c. 0.010, DCM); IR (neat): 2924, 2853, 1724, 1642, 1602, 1555, 1450, 1262, 1091, 1068, 1025 cm-1.

**Dodeca-1,3,5-amidebenzyl-3,4,6-tri-*O*-benzoyl-1,2-*O*-[1-exo-benzylidene]-D-glucopyranoside (18).** Acceptor **5** (0.670 g, 0.881 mmol, 1 equiv) and donor **3** (1.46 g, 1.94 mmol, 2.2 equiv) were combined and co-evaporated (3x) with toluene under N2 atmosphere. The reaction mixture was dissolved in DCM/HFIP (38 mL, 0.023 M, 4/1, v/v) and flame dried molecular sieves (3Å) were added. The mixture was stirred for 30 min at rt, and upon cooling to 0 ˚C, TfOH (15.6 µL, 0.176 mmol, 0.2 equiv) was added dropwise (variations are shown in Table 1). After being stirred at 0 °C for 2.5 h, the reaction mixture was quenched with Et3N (0.1 mL), diluted in DCM and washed with NaOH (1 M, aq., 1x). The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (0/10 → 1/9, v/v, EtOAc/Et2O) yielded a mixture of compounds **18, 19** and **20** (0.369 g, 0.192 mmol, 22%) as a colorless oil. TLC *Rf* 0.58 (100% Et2O). 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 8.35 (s, 3H, CHarom), 8.11 – 8.06 (m, 2H, CHarom), 8.06 – 7.99 (m, 3H, CHarom), 7.99 – 7.86 (m, 8H, CHarom), 7.86 – 7.81 (m, 2H, CHarom), 7.81 – 7.76 (m, 2H, CHarom), 7.63 – 7.21 (m, 22H, CHarom), 7.10 – 6.98 (m, 3H, CHarom), 6.06 (d, *J* = 5.2 Hz, 1H, H-1), 5.79 (dd, *J* = 3.2, 1.4 Hz, 1H, H-3), 5.58 – 5.48 (m, 2H, H-4), 4.79 (ddd, *J* = 5.3, 3.1, 1.2 Hz, 1H, H-2), 4.55 – 4.48 (m, 2H, H-6a), 4.31 (t, *J* = 6.7 Hz, 0H, CH2-*O*Bz), 4.21 – 4.12 (m, 2H, H-6b), (t, *J* = 6.6 Hz, 2H, CH2-*O*H), 3.38 (dq, *J* = 16.1, 9.4, 7.8 Hz, 8H, CH2-*N*), 3.26 (dt, *J* = 9.1, 6.6 Hz, 1H, CH2-*O*), 1.65 – 0.96 (m, 69H, CH2); 13C NMR (101 MHz, CDCl3, HSQC) δ 166.2, 166.1, 165.9, 165.3, 165.2, 164.7 (C=O), 135.3 (Cq), 133.7, 133.6, 133.5, 133.3, 133.2, 133.2, 133.1, 132.9, 130.1, 130.0, 129.9, 129.9, 129.8, 129.8 (CHarom), 129.7 (Cq), 129.6 (CHarom), 129.5 (Cq), 129.4, 129.2, 129.0, 128.9, 128.9, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 126.4, 125.6, 121.4 (CHarom), 97.6 (C-1), 72.1 (C-2), 69.3 (C-3), 68.6 (C-4), 67.5 (C-5), 64.3 (C-6), 64.1 (CH2-*O*), 63.3 (CH2-*O*Bz), 62.9 (CH2-*O*H), 40.5 (CH2-*N*), 40.4, 34.3, 32.8, 30.4, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 27.1, 26.9, 26.1, 25.8, 25.7, 21.3, 14.2 (CH2).

**Dodeca-1,3,5-amidebenzyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (2x) (19).**Compound **18** (55.3 mg, 0.0288 mmol) was co-evaporated (3x) with toluene under N2 atmosphere and dissolved in dried DCM (0.3 mL, 0.2 M). Upon cooling to 0 °C, a solution of TMSOTf in DCM (0.174 mL, 0.0115 mmol, 0.4 equiv) was added dropwise. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with Et3N (0.1 mL), diluted in Et2O and washed with brine. The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (9/1 → 10/0, v/v, Et2O/PE to EtOAc /Et2O, 2/8, v/v) yielded a mixture of compound **19** and **20** (18.2 mg, 949 µmol, 33%) as a yellow oil. TLC *Rf* 0.47 (EtOAc/Et2O, 2/8, v/v). Further purification by size-exclusion chromatography (MeOH/DCM, 1/1, v/v) isolated compound **19** (4.10 mg, 2.13 µmol, 7%) as a colorless oil. 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 8.35 (s, 3H, CHarom), 8.05 – 7.98 (m, 5H, CHarom), 7.98 – 7.93 (m, 5H, CHarom), 7.93 – 7.86 (m, 5H, CHarom), 7.86 – 7.80 (m, 5H, CHarom), 7.52 (dd, *J* = 19.0, 7.5 Hz, 4H, CHarom), 7.39 (d, *J* = 7.4 Hz, 6H, CHarom), 6.53 (s, 3H, NH), 5.90 (t, *J* = 9.7 Hz, 2H, H-3), 5.67 (t, *J* = 9.7 Hz, 2H, H-4), 5.52 (dd, *J* = 9.8, 7.9 Hz, 2H, H-2), 4.83 (d, *J* = 7.9 Hz, 2H, H-1), 4.63 (dd, *J* = 12.1, 3.2 Hz, 2H, H-6a), 4.50 (dd, *J* = 12.1, 5.2 Hz, 2H, H-6b), 4.15 (dt, *J* = 8.8, 4.5 Hz, 2H, H-5), 3.96 – 3.86 (m, 3H, C*H*H-*O*), 3.63 (t, *J* = 6.6 Hz, 2H, CH2-*O*H), 3.58 – 3.50 (m, 1H, CH*H-O*), 3.46 (d, *J* = 6.8 Hz, 7H, CH2-*N*), 1.25 (t, *J* = 7.0 Hz, 58H, CH2 (29x)); [α]D20 = + 9.0 ° (c. 0.002, DCM); IR (neat): 3325, 2921, 2851, 2359, 1728, 1647, 1541, 1452, 1263, 1093, 1068 cm-1.

**Dodeca-1,3,5-amidebenzyl-6-azido-2,3,4-tri-*O*-benzoyl-6-deoxy-β-D-glucopyranoside (1x) (21).**Acceptor **5** (0.154 g, 0.203 mmol, 1 equiv) and donor **4** (0.183 g, 0.276 mmol, 1.4 equiv) were combined and co-evaporated (3x) with toluene under N2 atmosphere. The reaction mixture was dissolved in DCM/HFIP (8.70 mL, 0.023 M, 4/1, v/v) and flame dried molecular sieves (3Å) were added. The mixture was stirred for 30 min at rt, and upon cooling to 0 ˚C, TfOH (8.85 µL, 0.100 mmol, 0.5 equiv) was added dropwise. After being stirred at 0 °C for 3 h, the reaction mixture was quenched with Et3N (0.1 mL), diluted in DCM and washed with NaOH (1 M, aq., 1x), HCl (1 M, sat. aq., 1x) and NaHCO3 (sat. aq., 1x). The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. The solid was dissolved in MeOH, absorbed on silica and concentrated under reduced pressure. Purification by flash chromatography on silica gel (4/96 → 1/9 → 5/5, v/v, EtOAc/Et2O) yielded compound **21** (41.2 mg, 0.0327 mmol, 16%) as a yellow oil. TLC *Rf* 0.26 (EtOAc/Et2O, 2/8, v/v); 1H NMR (400 MHz, Chloroform-*d,* HH-COSY, HSQC) δ 8.38 (s, 3H, CHarom), 7.98 – 7.88 (m, 4H, Harom), 7.85 – 7.78 (m, 2H, Harom), 7.57 – 7.48 (m, 2H, Harom), 7.48 – 7.32 (m, 6H, Harom), 7.28 (t, *J* = 7.8 Hz, 3H, Harom), 7.01 (t, *J* = 14.7, 10.2, 5.7 Hz, 3H, NH), 5.88 (t, *J* = 9.7 Hz, 1H, H-3), 5.50 (dd, *J* = 9.9, 7.9 Hz, 1H, H-2), 5.44 (t, *J* = 9.7 Hz, 1H, H-4), 4.84 (d, *J* = 7.9 Hz, 1H, H-1), 4.02 – 3.97 (m, 1H, H-5), 3.97 – 3.92 (m, 1H, C*H*H-*O*), 3.62 (t, *J* = 6.6 Hz, 4H, CH2-*O*H), 3.58 (dd, *J* = 6.1, 3.3 Hz, 1H, CH*H*-*O*), 3.56 – 3.52 (m, 1H, H-6a), 3.41 (q, *J* = 6.8 Hz, 6H, CH2-*N*), 3.30 (dd, *J* = 13.4, 2.4 Hz, 1H, H-6b), 1.65 – 1.48 (m, 12H, CH2 (6x)), 1.39 – 0.99 (m, 64H, CH2 (32x)); 13C NMR (101 MHz, CDCl3, HSQC) δ 166.1, 165.9, 165.5, 165.2 (C=O), 135.3, 133.8, 133.4, 133.3, 130.0, 129.9, 129.9, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3 (CHarom), 101.2 (C-1), 74.3 (C-5), 72.8 (C-3), 71.9 (C-2), 70.6 (C-4), 70.4 (CH2-*O*), 63.0 (CH2-*O*H), 51.5 (C-6), 40.6 (CH2-*N*), 32.9, 30.4, 29.8, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 27.2, 27.0, 25.9, 25.8 (CH2); IR (neat): 3275, 2924, 2359, 2100, 1731, 1645, 1450, 1315, 1262, 1068 cm-1.

**Dodeca-1,3,5-amidebenzyl-6-azido-3,4-di-*O*-benzoyl-1,2-*O*-[1-exo-benzylidene]-β-D-glucopyranoside (22).** Acceptor **5** (78.0 mg, 0.103 mmol, 1 equiv) and thio-donor **16** (63.3 mg, 0.104 mmol, 1 equiv) were combined and co-evaporated (3x) with toluene under N2 atmosphere. The reaction mixture was dissolved in DCM/HFIP (4.40 mL, 0.023 M, 4/1, v/v) and flame dried molecular sieves (3Å) were added. The mixture was stirred for 30 min at rt, and upon cooling to 0 ˚C, NIS (31.8 mg, 0.136 mmol, 1.3 equiv) and TfOH (1.80 µL, 0.0206 mmol, 0.2 equiv) were added successively. The reaction was followed by TLC and after being stirred at 0 °C for 36 h, the reaction mixture was quenched with NaHCO3 (sat. aq.) (2 mL) followed by Na2S2O3 (sat. aq.) (2 mL) and extracted (3x) with DCM. The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/Et2O, 2/8, v/v) yielded compound **22** (8.20 mg, 6.51 µmol, 7%) as a colorless oil. TLC *Rf* 0.48 (100% Et2O).

**Dodeca-1,3,5-amidebenzyl-(6-azido)-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (2).** Compound **21** (29.4 mg, 0.0234 mmol) and donor **3** (40.5 mg, 0.0547 mmol, 2.3 equiv) were combined and co-evaporated (3x) with toluene under N2 atmosphere. The reaction mixture was dissolved in DCM (1 mL, 0.023 M) and flame dried molecular sieves (3Å) were added. The mixture was stirred for 30 min at rt, and upon cooling to 0 ˚C, TfOH (2 µL, 0.0234 mmol, 1 equiv) was added dropwise. After being stirred at 0 °C for 5 h, the reaction mixture was quenched with Et3N (0.1 mL) and concentrated under reduced pressure. Purification by size-exclusion chromatography (MeOH/DCM, 1/1, v/v) yielded no product.

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# Attachment 1. Reaction mechanisms

**Scheme 11.** Benzoylation with benzoyl chloride under basic conditions.



**Scheme 12.** Selective deprotection of the anomeric center with hydrazine acetate.



**Scheme 13.** Imidate introduction.



**Scheme 14.** Acetylation with acetic acid anhydride under basic conditions.



**Scheme 15.** Anomeric protection with thiophenol.



**Scheme 16.** Deacetylation under basic conditions.



**Scheme 17.** Tosylation of the primary alcohol.



**Scheme 18**. Benzoylation with benzoyl chloride under basic conditions.



**Scheme 19.** Introduction of the azide by substitution of the tosyl.



**Scheme 20.** Selective deprotection of the anomeric center with NIS and TFA.



**Scheme 21**. Imidate introduction.



**Scheme 22.** Glycosylation reaction.



**Scheme 23**. Synthesis of the acceptor.



**Scheme 24.** Gabriel synthesis of amines.