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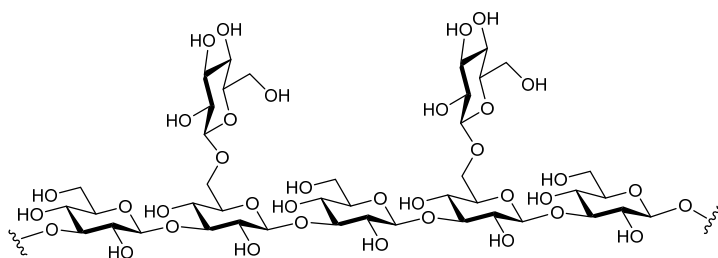
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Chapter 5

Synthesis of β -1,3-glucan fragments

Introduction

β -(1,3)-glucans are naturally occurring polysaccharides and were originally identified as essential constituents of the cell wall in fungi and as major storage source in brown seaweed. These glucans are also found on several pathogenic bacteria.¹ The healing and immunostimulating role of these polysaccharides has long been known and β -1,3-glucans have nowadays been identified as Dectin-1 ligands.² From a structural point of view these glucans have a linear β -1,3-linked backbone can be substituted in a random fashion with β -1,6-glucosyl branches. A well-known example is Lentinan (Figure 1),³ which is isolated from Shiitake and Maitake mushrooms and probed as anti-cancer drug. Research towards the elucidation of the immunostimulating properties of these polysaccharides requires sufficient amounts of pure, well-defined oligomers. The availability of a row of β -(1,3)-glucans of variable length can be very valuable to elucidate structure-activity relationships of these polysaccharides.

Figure 1. Lentinan, a glucan with β -(1,3)-linkages, known as antitumor agent.

Several syntheses of β -(1,3)-glucans, both branched and linear, have been reported.^{4,5} To allow access to a library of β -(1,3)-glucans it is desirable to prepare these (functionalized) fragments of oligosaccharides in a more convenient, and possibly automated fashion.⁶ In this Chapter, the solution phase synthesis of a β -1,3-glucan trisaccharide is explored and initial experiments to bring the synthesis to a solid phase synthesis platform are described.

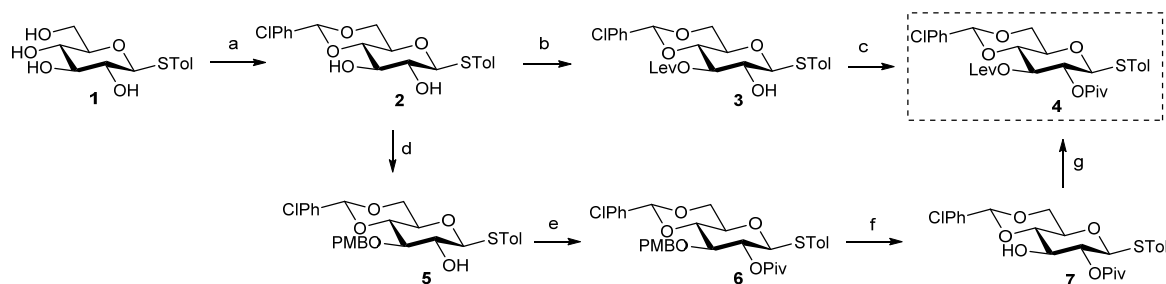
Results & Discussion

Solution phase synthesis of a β -1,3-glucan trisaccharide.

For the synthesis of β -(1,3)-glucan fragments, thioglucoside **4** (Scheme 1) was selected as precursor for the synthesis of the corresponding trifluoro-*N*-phenylimidate donor (Scheme 2, **9**).⁷ The thio-functionality in **4** acts as a temporary masking group for the anomeric hydroxyl group, which in turn can be converted to the trifluoro-*N*-phenylimidate functionality in **9**. For the introduction of β -glycosidic linkages, the participating and sterically demanding C-2-*O*-pivaloyl (Piv) group was chosen instead of the commonly used benzoyl group. Due to steric bias of the *tert*-butyl group, possible orthoester formation during the glycosylation is minimized. The use of the benzoyl protective group for the introduction of *trans* glycosidic linkages can lead to *cis*-fused product and orthoester formation.^{5b} The 4,6-*O*-*p*-chlorobenzylidene diol protective group was described to be more stable than the unsubstituted benzylidene acetal as the electron-withdrawing *p*-chloro substituent limits susceptibility towards acidic conditions.⁸ The extra stability is desirable in a solid phase synthesis, in which a relatively large amount of strong acid is repetitively used during the glycosylation step. The levulinoyl group serves as a temporary protecting group for the C-3 hydroxyl, which is to be elongated. The synthesis of target thioglucoside started with the introduction of the 4,6-*O*-chlorobenzylidene acetal. Condensation of glycoside **1** with *p*-chlorobenzaldehyde and a catalytic amount of *p*-TsOH in DMF proved to be ineffective under atmospheric pressure at elevated temperatures. Performing the reaction under reduced pressure (30 mbar) at 50 °C gave glucoside **2** in 90% yield. Glucoside **2** was converted to a tin acetal by treatment with Bu₂SnO in refluxing toluene. After cooling down to room temperature, levulinic anhydride was added to the reaction mixture. This resulted in the regioselective introduction of the levulinoyl ester at the C-3 position. According to the conditions described by Ishihara *et al.*,⁹ the pivaloyl group was installed with pivalic anhydride and a catalytic amount of Sc(O^tPr)₃ to give the fully protected glucoside **4** in 81% yield. Unfortunately, this route gave difficulties in scaling up. In particular, the regioselective introduction of the levulinoyl group at the C-3 position could not be achieved on a larger

scale. Therefore, a more robust route in which the *para*-methoxybenzyl (PMB) group was used for interim protection of the C-3 hydroxyl was employed. First, the free hydroxyl groups in diol **1** were silylated by treatment with TMSCl in pyridine. Then, the C-3 position was regioselectively *p*-methoxybenzylated using *p*-anisaldehyde and triethylsilane (TES) in the presence of a catalytic amount of TMSOTf at $-86\text{ }^{\circ}\text{C}$.¹⁰ Finally, addition of TBAF resulted in desilylation of the intermediate and glucoside **5** was isolated in 73% yield. The introduction of the PMB group was successfully accomplished on 51 mmol scale, which shows the robustness of this reaction on big scale. The pivaloyl group was introduced at the C-2 position utilizing pivaloyl chloride and DMAP in refluxing pyridine to give fully protected **6** in 82% yield. The high temperature was required for the installation of the pivaloyl ester, because no conversion was attained at room temperature. The *para*-methoxybenzyl ether in **6** was cleaved with DDQ in a mixture of DCM and H_2O , resulting in glucoside **7**. The hydroxyl at the C-3 position was protected with a levulinoyl group using LevOH and DIC in the presence of DMAP, yielding central building block **4**.

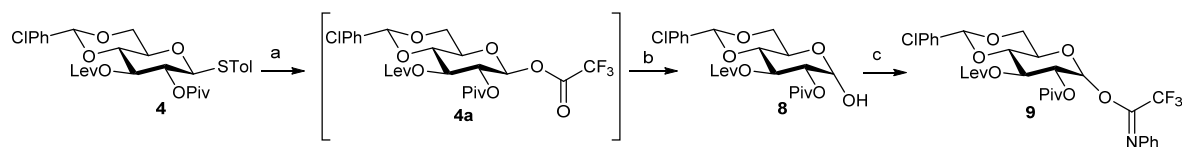
Scheme 1. Synthesis of glucoside building block **4**.



Reagents and conditions: (a) *p*-chlorobenzaldehyde, *p*-TsOH, DMF, $50\text{ }^{\circ}\text{C}$, 30 mbar, 90%; (b) Bu_2SnO , toluene, reflux, then 2.5M Lev₂O in THF, 86%/2 steps; (c) Piv_2O , $\text{Sc}(\text{OTf})_3$, MeCN, 81%; (d) (i) TMSCl, pyridine, $0\text{ }^{\circ}\text{C}$, (ii) *p*-anisaldehyde, TES, TMSOTf, DCM, $-86\text{ }^{\circ}\text{C}$, then TBAF, 73%/2 steps; (e) PivCl , DMAP, pyridine, reflux, 82%; (f) DDQ, DCM/ H_2O , 78%; (g) LevOH, DIC, DMAP, DCM, 90%.

Having thioglucoside **4** in hand, the corresponding trifluoro-*N*-phenyl imidate donor **9** was prepared (Scheme 2). Donor **9** can be directly activated with triflic acid (TfOH) making this a convenient donor in an automated synthesis. To prepare donor **9** from thioglucoside **4** the anomeric thiotoluyll group is to be hydrolyzed. The presence of the acid-labile chlorobenzylidene protective group in donor **4** required an anhydrous method. Therefore, glucoside **4** was treated with a combination of NIS and TFA¹¹ to provide the intermediate anomeric trifluoroacetate **4a**.

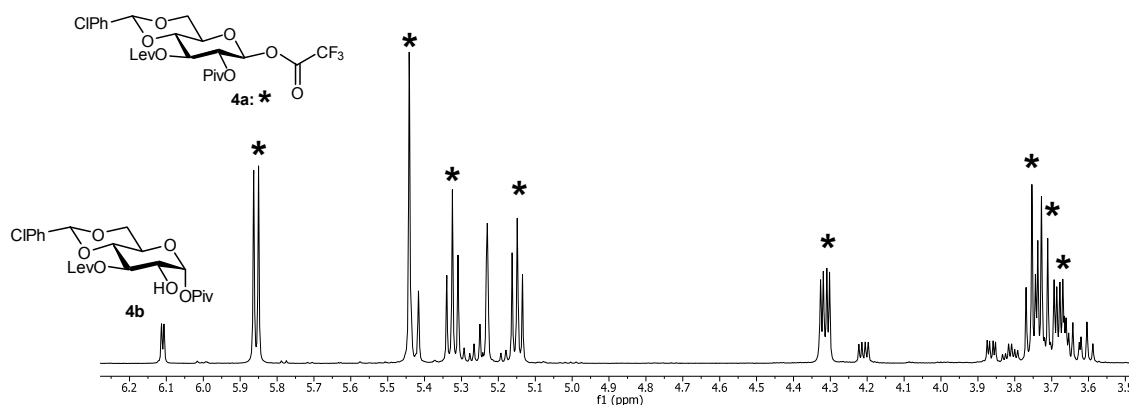
Scheme 2. Synthesis of glucoside donor **9**.



Reagents and conditions: (a) NIS, TFA, DCM, $0\text{ }^{\circ}\text{C}$; (b) piperidine, 85%; (c) $\text{ClC}(\text{=NPh})\text{CF}_3$, DBU, acetone, $0\text{ }^{\circ}\text{C}$, 94%.

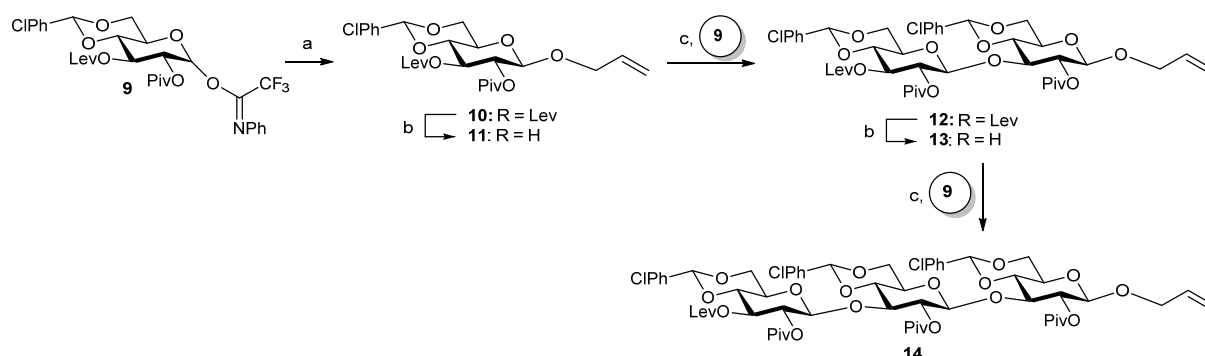
NMR spectroscopy revealed the anomeric trifluoroacetate to be the β anomer only ($J_{1,2} = 7.8$ Hz). In the ^1H NMR spectrum of **4a** a smaller set of signals was also observed, corresponding to pivaloyl-migration product **4b** (Figure 2, $J_{1,2} = 3.6$ Hz, $\sim 15\%$).¹² Cleavage of the anomeric trifluoroacetate group with piperidine led to hemiacetal **8**. The corresponding trifluoro-*N*-phenyl imidate donor **9** was obtained by treatment of **8** with *N*-phenyl trifluoroacetimidoyl chloride¹³ and DBU in acetone.

Figure 2. Part of the ^1H NMR spectrum of glucoside **4** after treatment with NIS/TFA in $\text{DCM-}d_2$ at 0°C .



With glucosyl donor **9** in hand, its glycosylating properties were studied by the solution phase synthesis of a trimeric β -1,3-glucan fragment (Scheme 3). Allyl alcohol was selected as the first acceptor to obtain the same allyl glucoside product as produced by executing an automated synthesis using the 1,4-butanediol linker. Glucosyl donor **9** was reacted with allyl alcohol and TfOH (cat.) yielding allyl glucoside **10** in 70% yield. The temporary levulinoyl group was removed with hydrazine hydrate in a mixture of pyridine and acetic acid giving glucosyl acceptor **11** in 96%. Next, donor **9** and acceptor **11** were coupled with a catalytic amount of TfOH in DCM, which led to the isolation of disaccharide **12** in 99% yield. Subsequent delevulinoylation of the disaccharide afforded disaccharide acceptor **13**, which was glycosylated with donor **9** to give trisaccharide **14** in 80% yield.

Scheme 3. Synthesis of trisaccharide **14**.



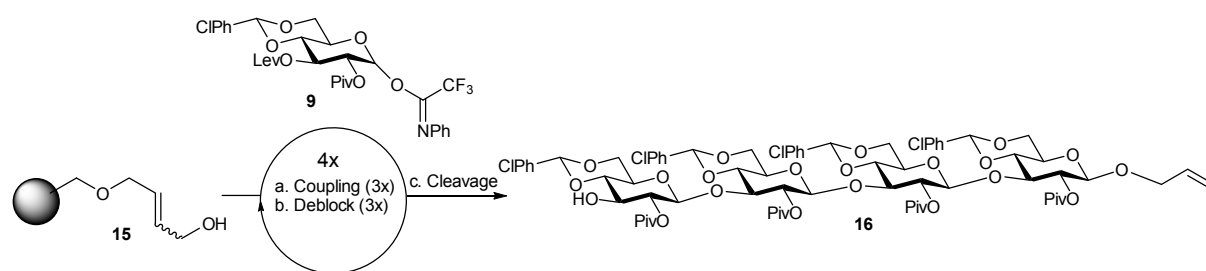
Reagents and conditions: (a) Allyl alcohol, TfOH, DCM, 0°C , 70%; (b) hydrazine hydrate, pyridine/AcOH, **11**: 96%, **13**: 94%; (c) TfOH, DCM, 0°C , **12**: 99%, **14**: 80%.

NMR analysis of the trisaccharide revealed several remarkable features. First, the anomeric proton of the middle glucoside showed a very small coupling constant ($J_{1,2} = 2.1$ Hz), which is unexpected for a β -glucosyl linkage in a 4C_1 conformation. This small coupling was not observed in the NMR analysis of the disaccharide precursor. Also, the H-2' signal of the middle residue was not split into the expected triplet. Instead, a broad singlet was observed. H-H COSY NMR showed only a weak correlation between H-2' and H-3'. Furthermore, TOCSY NMR analysis showed two distinct spin systems in the middle glucoside: a spin system between H-1' and H-2' and a spin system of H-3' through H-6', indicating that the middle glucoside does not adopt the expected 4C_1 chair conformation. Another noteworthy observation is the shift of the benzylidene proton of the middle glucoside. This proton is about 1 ppm upfield compared to the other two benzylidene signals, which suggests a high degree of electron shielding. These results are in line with structural effects reported for 4,6-*O*-benzylidinated β -1,3-glucans. Vetricka and coworkers¹⁴ performed a series of NOESY NMR experiments, which suggest that the affected glucosides uptake a pseudorotational itinerary between the 4C_1 and 1,4B or $B_{2,5}$ conformation rather than the 4C_1 chair which is the unaffected glucoside residue. The crystal structure of a 4,6-*O*-benzylidene protected hexasaccharide reported by Ensley *et al.*⁴ confirmed that glucoside residues in between (third and fifth) adopt a twist boat conformation whereas all other units were found in a 4C_1 conformation.

Taken together, the above described results show that the trifluoro-*N*-phenyl imidate donor **9** is a suitable donor for the construction of the β -1,3-glycosidic linkages. The 4,6-*O*-chlorobenzylidene functionality remains intact during the glycosylations and the C-2-pivaloyl ester ensures stereoselective couplings. Encouraged by the successful solution phase synthesis of trisaccharide **14**, the solution phase chemistry was translated to an automated solid phase format.

Automated synthesis of β -1,3-glucan fragments.

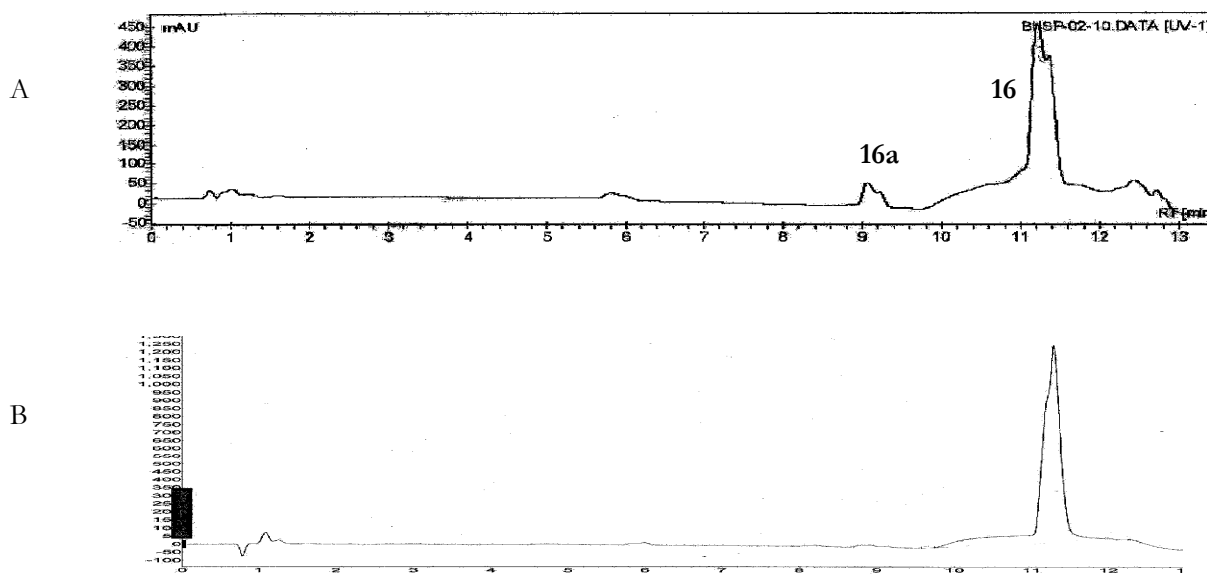
The automated synthesis of a tetrameric β -glucan fragment¹⁵ was explored using the above described donor **9** and 1,4-butene-diol linker **15** (Scheme 4).¹⁶ This linker is stable towards the reaction conditions applied and the product can be cleaved via a cross metathesis reaction with ethene and Grubbs first-generation catalyst at the end of the synthesis.¹⁷ Donor **9** was used in excess (3 eq. per coupling cycle) and since the glycosylation proceeded fast in solution phase, a short coupling time (3x 15 minutes) was employed. The amount of triflic acid (0 °C and 0.1 eq. per donor, respectively) and the temperature were not changed with respect to the solution phase synthesis. The temporary levulinoyl group was cleaved at 40 °C to ensure rapid and complete unmasking of the C-3-hydroxyl.

Scheme 4. Automated synthesis of tetrasaccharide **16**.

Reagents and conditions: (a) Donor **9** (3 eq.), TfOH (0.3 eq.), 0 °C, 15 min.; (b) hydrazine acetate (10 eq.), pyridine/AcOH, 40 °C, 10 min.; (c) Grubbs first-generation catalyst, ethene, DCM, overnight, 44%.

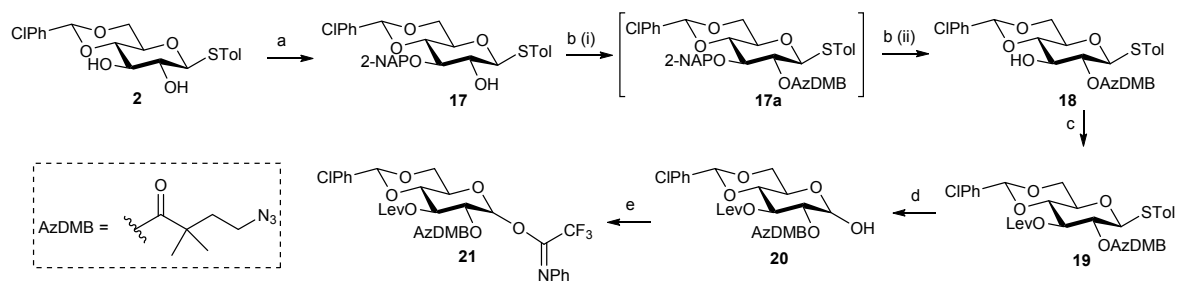
After cleavage from the resin and filtration over a plug of silica, LC-MS analysis showed the predominant formation of tetrasaccharide **16**, along with presence of a minor amount trisaccharide **16a** (tetramer: trimer, ~26:1) and trace amounts of disaccharide (Figure 3). Preparative HPLC was employed to isolate tetrasaccharide **16** in 44% yield (~91% yield/step). In an attempt to further improve the efficiency of the synthesis of tetrasaccharide **16**, the couplings were performed at 20 °C. LC-MS analysis of the so-obtained product however revealed a higher proportion of trisaccharide relative to the tetrasaccharide. Therefore, the glycosylation temperature was set to 0 °C for further syntheses. Although the automated preparation of the tetrameric β -1,3-glucan fragment was successful, deprotection of the pivaloyl esters turned out to be troublesome. Treatment with bases such as ammonia and KOH did not result in deprotection of the C-2 position. Therefore, a pivaloyl-like group that can be cleaved in a milder and faster fashion was investigated.

Figure 3. LC-MS chromatograms of the crude tetrasaccharide after cleavage from the resin (A, C4 column, linear gradient 70 \rightarrow 90% B) and after HPLC purification (B).



Synthesis of β -1,3-glucan fragments with the AzDMB-protective group.

To circumvent the troublesome deprotection of the pivaloyl group the recently reported 4-azido-2,2-dimethyl-butanoyl (AzDMB) protective group (Scheme 5) was implemented.¹⁸ The appended azido functionality allows the cleavage of the ester by a Staudinger reduction reaction or hydrogenation. The synthesis of the glucosyl donor **21** starts with diol **2** which was regioselectively 2-methylnaphthylated at the C-3 position. This was achieved by first preparation of the tin ketal followed by treatment with 2-naphthylmethyl bromide and CsF in DMF to yield alcohol **17** in 69% yield. Subsequent treatment of **17** with freshly prepared AzDMBCl in pyridine gave fully protected glucoside **17a**. Because this product could not be separated from 4-azido-2,2-dimethyl-butanolic acid, the crude product was subjected to a mixture of DDQ in DCM/H₂O to give glucoside **18** in 78% yield over 2 steps. The free hydroxyl was protected with a levulinoyl group to give fully protected glucoside **19** in 90% yield. Thio-donor **19** was transformed into imidate **21** using the same sequence of reactions, as described for the synthesis of pivaloyl-donor **9** from hemiacetal **4**.

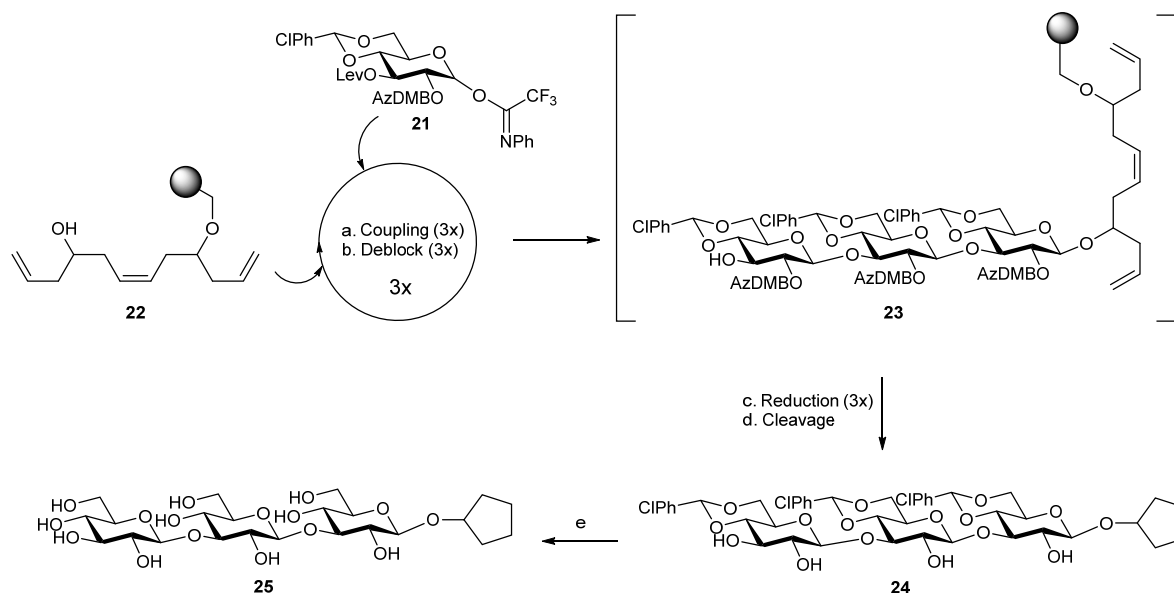
Scheme 5. Synthesis of AzDMB-donor **21**.

Reagents and conditions: (a) (i) Bu₂SnO, toluene, reflux, (ii) 2-NAP-Br, CsF, DMF, overnight, 69%/2 steps; (b) (i) AzDMBCl, pyridine, 110 °C, (ii) DDQ, DCM/H₂O, 78%/2 steps; (c) LevOH, DIC, DMAP, DCM, 90%; (d) NIS, TFA, DCM, 0 °C, then piperidine, 86%; (e) ClC(=NPh)CF₃, Cs₂CO₃, acetone, 96%.

The AzDMB protected donor **21** was explored in the solid phase synthesis of trisaccharide **25** (Scheme 6). The tandem RCM cleavable linker **22**, described in Chapter 4, was applied. Since the coupling (3x 3 eq. of donor, 3x 0.1 eq. of TfOH) and deblocking conditions (3x 6.7 eq. of hydrazine hydrate) described above were shown to be effective, the same conditions were applied. Before cleaving the product from the resin the AzDMB groups were removed on-resin by Staudinger reduction of the azides¹⁹ with tributylphosphine in the presence of aqueous KOH. Some optimization was required because the hydrophobic polystyrene resin significantly shrinks in aqueous solutions, making the azides on the resin inaccessible for the reagents. Using a mixture of 0.5M aqueous KOH in dioxane (1/19, v/v) and 9 eq. of tributylphosphine at elevated temperature (50 °C) led to the desired triple deprotection and set the stage to release the trisaccharide from the resin by tandem RCM. The resin was treated with Grubbs second-generation catalyst for 2 hours, after which the trisaccharide was isolated. LC-MS analysis of the crude product showed that the whole synthetic procedure had proceeded uneventfully and no benzylidene cleavage products or diastereomers resulting from non-selective glycosylation reactions could be observed. After purification of the trisaccharide over a small plug of silica the target trisaccharide **24** was isolated in 36% yield (~88% per

step). Cleavage of the *p*-chlorobenzylidene functions was readily accomplished by hydrogenolysis in a THF/H₂O/*t*BuOH solvent mixture to provide β -glucan trisaccharide **25** in 91% yield.

Scheme 6. Solid phase synthesis of a trisaccharide β -1,3-glucan fragment.



Reagents and conditions: (a) Donor **21** (3 eq.), TfOH (0.3 eq.), DCM, 0 °C, 15 min.; (b) hydrazine hydrate (6.7 eq.), pyridine/AcOH, 40 °C, 10 min.; (c) Bu₃P (9 eq.), dioxane/0.5M KOH, 50 °C, 90 min.; (d) Grubbs second-generation catalyst (0.12 eq.), DCM, 2 h., 36%/8 steps; (e) H₂, Pd/C, THF/H₂O/*tert*-BuOH, 2 h., 91%.

Conclusions

The successful solution phase synthesis of a β -(1,3)-glucan trisaccharide formed the basis for the automated solid synthesis of a partly protected tetrameric β -(1 \rightarrow 3)-glucan fragment. However, cleavage of the pivaloyl esters in this tetrasaccharide turned out to be troublesome and did not give the fully unprotected targets. Replacement of the pivaloyl by the mildly cleavable AzDMB protective group led to the first successful solid phase synthesis of a β -(1,3)-glucan trisaccharide fragment. Having established the glycosylation properties and deprotection conditions, the (automated) solid phase synthesis of larger β -(1,3)-glucan fragments can now be explored.

Experimental section

General experimental procedures. Chemical shifts (δ) are given in ppm relative to TMS as internal standard. All ¹³C APT NMR spectra are proton decoupled. Reactions were performed at rT unless stated otherwise and were followed by TLC analysis with detection by UV-absorption (254 nm) where applicable and by spraying with 20% sulphuric acid in EtOH or with a solution of (NH₄)₆Mo₇O₂₄·H₂O (25 g L⁻¹), followed by charring at 150 °C. Flash column chromatography was performed on silica gel (0.04-0.063 nm) and size exclusion chromatography (SEC) was performed on Sephadex™ LH-20. Experiments that required an inert atmosphere were carried out under dry argon. Dichloromethane

(p.a.) was distilled over P_2O_5 prior to use. Molecular sieves (3Å) were flame-dried before use. LC-MS analysis was performed using a C4 column with the following solvent systems: A = 100% water, B = 100% acetonitrile, C = 1% TFA.

General experimental procedures for (automated) solid phase synthesis. The synthesizer used was supplied by Ancora Pharmaceuticals. The synthesizer's solvent bottles are filled with commercially acquired solvents, which are pre-dried 24 h. before use on 4Å molecular sieves. The solutions containing building block, activator and deblocking reagents are freshly prepared directly before use with pre-dried solvents. During the synthesis of trisaccharide **24**, the coupling, deblocking, and reduction reagents were added manually.

Reagent solutions:

Building block: Donor **9** or **21** in DCM (0.09M)

Activator: Trifluoromethanesulfonic acid in DCM (0.09M)

Deblocking: Synthesis of tetramer **16**: Hydrazine acetate in pyridine/AcOH (4/1, v/v, 0.12M)

Synthesis of trisaccharide **24**: Hydrazine hydrate in pyridine/AcOH (4/1, v/v, 0.12M)

Reduction Bu_3P in THF dioxane/0.5M KOH (19/1, v/v, 0.25M)

Protocol A: Agitation of the resin during washing. After addition of the appropriate solvent (2-4 mL), a gas-flow is applied from the bottom of the reaction vessel (RV) for 15 seconds to agitate the resin suspension. Then the RV is emptied.

Protocol B: Agitation of the resin during reaction. After addition of the appropriate solvent (2-4 mL), a gas-flow is applied from the bottom of the RV for 10 seconds to agitate the resin suspension. Then the purging is halted and the suspension is allowed to settle for 20 sec.

Protocol C: Swelling of new resin. The RV is charged with dry resin. The resin is washed with DCM (3x), alternating THF and hexane (3x), THF (1x) and DCM (3x). Every wash step involves protocol A.

Protocol D: Washing of the resin before or after the reaction. If applicable, the chiller temperature is set to ambient. The pre-swollen resin is washed with alternating THF and hexane (3x), followed by THF (1x) and DCM (3x). Every wash step involves protocol A.

Protocol E: Coupling cycle. The resin is washed with DCM (3x) before the building block solution (1.5 mL, 0.09M) is added. Then, the temperature is set to -5 °C to ensure an actual temperature of 0 °C in the RV. Simultaneously a pause of 10 min is started. When the temperature of the chiller has reached its target point, the activator solution (300 μ L for the synthesis of tetrasaccharide **15**, 150 μ L for the synthesis of trisaccharide **24**) is added. Protocol B is applied for 15 min. Then the RV is emptied and the solution is collected in a mixture of DCM/H₂O/triethylamine (50/5/1, v/v/v). The resin is washed with DCM (3x) and the solutes are similarly collected.

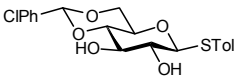
Protocol F: Deblocking. The resin is washed with DMF (3x) before the deblock solution (2.5 mL, 0.12M) is added. The temperature was raised to 40 °C and the resin was agitated using protocol B for 10 min. Then the RV is emptied and the resin is washed with DMF (3x).

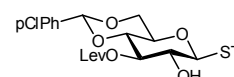
Protocol G: Washing of the resin after deblocking. The temperature of the chiller is set to ambient. The resin is successively washed with DMF (3x), DCM (3x), alternating THF and hexane (6x), 0.01M AcOH in THF (6x) and THF (3x). Every wash step involves protocol A.

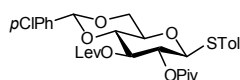
Protocol H: Reduction. The resin is washed with THF (3x) before the reduction solution is added (2.13 mL) and the resin is agitated using protocol B for 90 min. while the temperature is raised to 50 °C. Then the RV is emptied and the resin is washed with DMF (6x) and THF (6x).

Protocol I: Washing of the resin after reduction. The temperature of the chiller is set to ambient. The resin is successively washed with DMF (6x), DCM (3x), alternating THF and hexane (6x), 0.01M AcOH in THF (6x) and THF (3x). Every wash step involves protocol A.

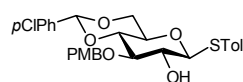
Protocol J: Suspending of the resin for isolation. The resin is washed with alternating DCM and MeOH (2x), followed by a mixture of DCM/MeOH (7/1, v/v, 2x), both employing protocol A. Then a mixture of DCM/MeOH (7/1, v/v) is added, the resin is agitated for 15 sec. after which time the gas-flow was halted and the program was paused. The suspended resin is isolated and this last procedure is repeated two times.

 ***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-1-thio- β -D-glucopyranoside (2):** To a solution of thioglucoside **1** (20 g, 69.8 mmol) in DMF (0.6 M, 120 mL) was added *p*-chlorobenzaldehyde (210 mmol, 29.4 g, 3 eq.) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred on a rotary evaporator (50 °C, 30 mbar) for 3.5 hours. The reaction was quenched with TEA until pH ~7. The mixture was concentrated in vacuo, co-evaporated with toluene and crystallized from EtOAc/PE to give the title compound in 90% yield (62.9 mmol, 25.7 g). Melting point: 188 °C. $[\alpha]_D^{25}$: -44.4 (c = 1, MeCN). IR (neat, cm^{-1}): 3362, 2914, 2870, 2852, 1668, 1653, 1601, 1493, 1449, 1402, 1371, 1350, 1296, 1281, 1269, 1240, 1215, 1167, 1140, 1107, 1086, 1072, 1040, 4013, 988, 976, 947, 930, 908, 893, 872, 833, 808. ^1H NMR (400 MHz, DMSO- d_6 , HH-COSY, HSQC): 7.45 (s, 4H, H_{arom}), 7.35 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.16 (d, 2H, $J = 8.0$ Hz, H_{arom}), 5.59-5.58 (m, 2H, CH benzylidene, C-2-OH), 4.46 (d, 1H, $J = 5.2$ Hz, C-3-OH), 4.74 (d, 1H, $J = 9.6$ Hz, H-1), 4.18 (dd, 1H, $J = 10.0$ Hz, $J = 4.8$ Hz, H-6a), 3.66 (t, 1H, $J = 10.0$ Hz, H-6b), 3.49 (m, 2H, H-3, H-5), 3.14 (m, 2H, H-2, H-4), 2.29 (s, 3H, CH_3 STol). ^{13}C APT NMR (100 MHz, DMSO- d_6); HH-COSY, HSQC): 136.7 (C_q C_{arom}), 133.4 (C_q C_{arom}), 131.4-128.2 (CH_{arom}), 99.7 (CH benzylidene), 87.6 (C-1), 80.3 (C-3), 74.2 (C-2 or C-4), 72.9 (C-2 or C-4), 69.6 (C-5), 67.8 (C-6), 20.9 (CH_3 STol). HRMS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{21}\text{ClO}_5\text{SNa}$: 431.06904, found 431.06893.

 ***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-levulinoyl-1-thio- β -D-glucopyranoside (3):** To a solution of glucoside **2** (5.0 g, 12.2 mmol) in toluene (0.3 M, 40 mL) was added Bu_2SnO (3.2 g, 12.8 mmol, 1.1 eq.). The mixture was refluxed for 18 hours, after which it was cooled to room temperature. Next levulinic anhydride (26.8 mmol, 10.8 mL of a 2.5M solution in THF) was added. After TLC analysis (DCM/acetone, 19/1, v/v) confirmed formation of a higher running compound, the mixture was quenched with MeOH, washed with H_2O and brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. Crystallization from PE/EtOAc gave the product in 86% yield, (5.3 g, 10.5 mmol). Melting point: 141 °C. $[\alpha]_D^{25}$: -44.4 (c = 1, DCM). IR (neat, cm^{-1}): 3397, 2982, 2878, 1742, 1709, 1601, 1493, 1456, 1418, 1402, 1360, 1304, 1267, 1186, 1155, 1105, 1070, 1030, 1015, 991, 972, 937, 908, 883, 810. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.44 (d, 2H, $J = 8.0$ Hz, CH arom), 7.34 (m, 4H, H_{arom}), 7.15 (d, 2H, $J = 8.0$ Hz, H_{arom}), 5.44 (s, 1H, CH benzylidene), 5.23 (t, 1H, $J = 9.2$ Hz, H-3), 4.63 (d, 1H, $J = 9.6$ Hz, H-1), 4.36 (dd, 1H, $J = 10.4$ Hz, $J = 4.8$ Hz, H-6a), 3.75 (t, 1H, $J = 10.0$ Hz, H-6b), 3.54 (m, 3H, H-2, H-4, H-5), 3.05 (d, 1H, $J = 2.8$ Hz, C-2-OH), 2.78 (m, 2H, CH_2 Lev), 2.60 (m, 2H, CH_2 Lev), 2.36 (s, 3H, CH_3 Lev), 2.15 (s, 3H, CH_3 STol). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 207.1 (C=O Lev ketone), 172.7 (C=O Lev), 139.0 (C_q C_{arom}), 135.5 (C_q C_{arom}), 135.0 (C_q C_{arom}), 134.0 (CH_{arom}), 130.0 (CH_{arom}), 128.5 (CH_{arom}), 127.6 (CH_{arom}), 127.4 (C_q C_{arom}), 100.7 (CH benzylidene), 89.2 (C-1), 78.2 (C-2), 75.2 (C-3), 71.5 (C-4 or C-5), 70.7 (C-4 or C-5), 68.6 (C-6), 38.3 (CH_2 Lev), 29.9 (CH_3 Lev), 28.2 (CH_2 Lev), 21.3 (CH_3 STol). HRMS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{29}\text{ClO}_6\text{SNa}$: 529.10582, found 529.10553.

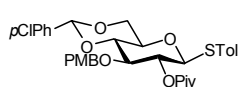


***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-levulinoyl-2-*O*-pivaloyl-1-thio- β -D-glucopyranoside (4):** *Method A:* To a solution of glucoside **3** (0.9 g, 1.8 mmol) in MeCN (9 mL, 0.2 M) was added Piv₂O (1.7 mL, 8.9 mmol, 5 eq.) and Sc(OTf)₃ (1.5 mL of a 60mM solution in MeCN, 0.09 mmol, 0.08 eq.). After 60 minutes, TLC analysis (DCM/acetone, 19/1, v/v) confirmed complete consumption of the starting material, and the mixture was quenched with sat. aq. NaHCO₃ and diluted in Et₂O. The organic layer was washed three times with sat. aq. NaHCO₃ and once with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Crystallization from MeOH gave the title compound in 81% yield (0.85 g, 1.44 mmol). *Method B:* To an ice-cooled solution of glucoside **7** (2.85 g, 5.8 mmol) in DCM (20 mL, 0.3M) was added LevOH (1.6 mL, 15.1 mmol, 2.6 eq.), DIC (1.2 mL, 7.5 mmol, 1.3 eq.) and DMAP (0.07 g, 0.6 mmol, 0.1 eq.). The mixture was allowed to warm to room temperature. After TLC analysis (DCM/acetone, 19/1, v/v) indicated complete conversion, the reaction was quenched with MeOH. The organic phase was washed with sat. aq. NaHCO₃ (3x), water and brine. The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. After column chromatography (PE/EtOAc: 9/1 \rightarrow 7/3), the product was obtained in 90% yield (5.2 mmol, 3.09 g). Melting point: 146 °C. $[\alpha]_D$: -4.6 (c = 1, CHCl₃). IR (neat, cm⁻¹): 2974, 2916, 2862, 1749, 1740, 1719, 1441, 1479, 1422, 1375, 1364, 1354, 1281, 1273, 1209, 1180, 1157, 1148, 1125, 1092, 1067, 1016, 978, 949, 941, 879, 841, 826, 806, 797, 770. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.37-7.31 (m, 6H, H_{arom}), 7.14 (d, 2H, *J* = 8.0 Hz, H_{arom}), 5.46 (s, 1H, CH benzylidene), 5.35 (t, *J* = 9.4 Hz, H-3), 4.99 (t, 1H, *J* = 9.6 Hz, H-2); 4.73 (d, 1H, *J* = 10 Hz, H-1); 4.37 (dd, 1H, *J* = 10.4 Hz, *J* = 4.8 Hz, H-6a), 3.78 (t, 1H, *J* = 9.8 Hz, H-6b), 3.65 (t, 1H, *J* = 9.6 Hz, H-4), 3.54 (dt, 1H, *J* = 9.6 Hz, *J* = 4.8 Hz, H-5), 2.69-2.66 (m, 2H, CH₂ Lev), 2.57-2.52 (m, 2H, CH₂ Lev), 2.35 (s, 3H, CH₃ STol), 2.14 (s, 3H, CH₃ Lev), 1.26 (s, 9H, 3x CH₃ Piv). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 205.9 (C=O Lev ketone), 176.8 (C=O Piv), 171.7 (C=O Lev), 138.9-135.1 (C_q C_{arom}), 133.6-128.5 (CH_{arom}), 128.3 (C_q C_{arom}), 127.8 (CH_{arom}), 100.7 (CH benzylidene), 87.5 (C-1), 78.4 (C-4), 73.0 (C-3), 70.6 (C-5), 70.0 (C-2), 68.6 (C-6), 38.9 (C_q Piv), 37.9 (CH₂ Lev), 29.9 (CH₃ Lev), 28.0 (CH₂ Lev), 27.2 (CH₃ Piv), 21.3 (CH₃ STol). HRMS: [M+Na]⁺ calcd for C₃₀H₃₅ClO₈SNa: 613.16389, found 613.16375.



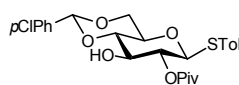
***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-(*p*-methoxybenzyl)-1-thio- β -D-glucopyranoside (5)** To a stirred solution of glucoside **2** (25.0 g, 51.5 mmol) in pyridine (100 mL, 0.5M) was added TMSCl (19.5 mL, 153.5 mmol, 3.0 eq.) at 0 °C. The mixture was gradually warmed to room temperature, and after TLC analysis (DCM/acetone, 19/1, v/v) indicated complete conversion of the starting material, the mixture was diluted in EtOAc and washed with H₂O (2x). The combined aqueous phases were extracted with EtOAc (2x). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was coevaporated with toluene. The silyl ether was dissolved in DCM (350 mL, 0.15M), *p*-anisaldehyde (7.0 mL, 11.3 mmol, 1.1 eq.) was added and the mixture was cooled to -86 °C. Added was Et₃SiH (1.8 mL, 56.5 mmol, 1.1 eq.) and TMSOTf (0.8 mL, 4.5 mmol, 0.09 eq.) and the mixture was stirred at -86 °C overnight, after which TLC analysis (PE/EtOAc, 3/1, v/v) indicated complete conversion of the starting material. The mixture was quenched with MeOH and NaOMe (up to pH ~ 9) and the mixture was warmed to room temperature. The mixture was diluted with DCM, washed with sat. aq. NaHCO₃. The aqueous phase was extracted with DCM (2x). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude compound was treated with TBAF (1M solution in THF, 55 mL, 55 mmol, 1.07 eq.) and stirred at room temperature until TLC analysis (PE/EtOAc, 3/1, v/v) indicated complete conversion. The reaction mixture was diluted with DCM and washed with sat. aq. NaHCO₃. The aqueous phase was extracted with DCM (2x). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. Crystallization from hot EtOH gave the product as a white solid in 73% yield (23.8 g, 37.6 mmol). Melting point: 163 °C. $[\alpha]_D$: -46.6 (c = 1, DCM). IR (neat, cm⁻¹): 3487, 2953, 2920, 2882, 2862, 1614, 1603, 1514, 1491, 1466, 1400, 1379, 1348, 1304, 1250, 1227, 1171,

1130, 1148, 1084, 1070, 1013, 982, 972, 943, 883, 856, 810. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.43-7.34 (m, 6H, H_{arom}), 7.26 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.12 (d, 2H, $J = 8.0$ Hz, H_{arom}), 6.84 (d, 2H, $J = 8.4$ Hz, H_{arom}), 5.51 (s, 1H, CH benzyldiene), 4.83 (d, 1H, $J = 11.2$ Hz, CHH PMB), 4.71 (d, 1H, $J = 11.2$ Hz, CHH PMB), 4.54 (d, 1H, $J = 9.6$ Hz, H-1), 4.36 (dd, 1H, $J = 10.8$ Hz, $J = 4.8$ Hz, H-6a), 3.81-3.73 (m, 4H, H-6b, CH_3 PMB), 3.66-3.56 (m, 2H, H-3, H-4), 3.49-3.43 (m, 2H, H-2, H-5), 2.52 (d, 1H, $J = 2.0$ Hz, C-2-OH), 2.34 (s, 3H, CH_3 STol). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 159.5 (C_q C_{arom}), 138.9, 135.9, 135.0 (C_q C_{arom}), 134.0 (CH_{arom}), 130.3 (C_q C_{arom}), 130.0 (CH_{arom}), 129.9 (CH_{arom}), 128.6 (CH_{arom}), 127.6 (CH_{arom}), 127.3 (C_q C_{arom}), 114.0 (CH_{arom}), 100.6 (CH benzyldiene), 88.7 (C-1), 81.3 (C-3 or C-4), 81.2 (C-3 or C-4), 74.6 (CH_2 PMB), 72.2 (C-2 or C-5), 70.8 (C-2 or C-5), 68.7 (C-6), 55.4 (CH_3 PMB), 21.3 (CH_3 STol). HRMS: $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{28}\text{H}_{33}\text{ClO}_6\text{SN}$: 546.17116, found 546.19636.



***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-(*p*-methoxybenzyl)-2-*O*-pivaloyl-1-thio- β -D-glucopyranoside (6)** To a solution of glucoside **5** (15.9 g, 30.0 mmol) in pyridine (75 mL, 0.4M) was added PivCl (7.20 mL, 60.0 mmol, 2

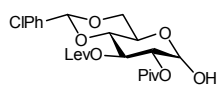
eq.) and a catalytic amount of DMAP (0.37 g, 3.0 mmol, 0.1 eq.). The mixture was heated to reflux and stirred until TLC (PE/EtOAc, 4/1, v/v) showed complete consumption of the starting material. The mixture was cooled to room temperature, diluted with EtOAc and washed with aqueous 1M HCl solution (3x), water (1x) and brine. The organic phase was dried over MgSO_4 , filtered and concentrated *in vacuo*. After crystallization from hot EtOH, the title compound was obtained in 82% yield (15.1 g, 24.6 mmol). Melting point: 143 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{25}$: -29.4 ($c = 1$, DCM). IR (neat, cm^{-1}): 2974, 2959, 2932, 2905, 2872, 2832, 1724, 1614, 1512, 1493, 1477, 1468, 1425, 1398, 1371, 1329, 1302, 1279, 1244, 1213, 1173, 1150, 1082, 1067, 1051, 1042, 1003, 982, 962, 943, 928, 889, 880, 824, 812, 802. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.37-7.33 (m, 6H, H_{arom}), 7.17-7.11 (m, 4H, H_{arom}), 6.81 (d, 2H, $J = 8.8$ Hz, H_{arom}), 5.51 (s, 1H, CH benzyldiene), 5.03 (dd, 1H, $J = 10.0$ Hz, $J = 8.4$ Hz, H-2), 4.72 (d, 1H, $J = 11.2$ Hz, CHH PMB), 4.67 (d, 1H, $J = 10.0$ Hz, H-1), 4.58 (d, 1H, $J = 11.2$ Hz, CHH PMB), 4.37 (dd, 1H, $J = 10.8$ Hz, $J = 4.8$ Hz, H-6a), 3.81-3.78 (m, 5H, H-3, H-6b, OCH_3 PMB), 3.70 (t, 1H, $J = 9.2$ Hz, H-4), 3.47 (dt, 1H, $J = 9.6$ Hz, $J = 4.8$ Hz, H-5), 2.34 (s, 3H, CH_3 STol), 1.24 (s, 9H, CH_3 Piv). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 176.6 (C=O Piv), 159.3 (C_q C_{arom}), 138.6-135.0 (C_q C_{arom}), 133.4 (CH_{arom}), 130.2 (C_q C_{arom}), 129.9-129.3 (CH_{arom}), 128.7 (C_q C_{arom}), 128.6-113.8 (CH_{arom}), 100.6 (CH benzyldiene), 87.7 (C-1), 81.2 (C-4), 80.1 (C-3), 74.4 (CH_2 PMB), 71.2 (C-2), 70.5 (C-5), 68.7 (C-6), 55.4 (CH_3 PMB), 38.9 (C_q Piv), 27.3 (CH_3 Piv), 21.3 (CH_3 STol). HRMS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{33}\text{H}_{37}\text{ClO}_7\text{SNa}$: 635.18407, found 635.18401.



***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-pivaloyl-1-thio- β -D-glucopyranoside (7)**: To a solution of thioglucoside **6** (9.19 g, 15 mmol) in DCM/ H_2O (9/1, v/v, 150 mL, 0.1M) was added DDQ (4.09 g, 18 mmol, 1.2

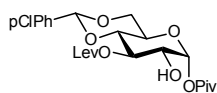
eq.), and the resulting dark mixture was stirred vigorously at room temperature. After TLC analysis (toluene/EtOAc, 9/1, v/v) indicated complete conversion of the starting material, the reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution, diluted with EtOAc and washed with sat. aq. NaHCO_3 solution, water and brine. The organic phase was dried over MgSO_4 , filtered and concentrated *in vacuo*. The title compound was obtained after crystallization from hot EtOH in 78% yield. (5.75 g, 11.7 mmol). Melting point: 144 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{25}$: -46 ($c = 1.5$, DCM). IR (neat, cm^{-1}): 2957, 2878, 2855, 1726, 1647, 1601, 1491, 1479, 1458, 1423, 1396, 1371, 1325, 1279, 1254, 1213, 1165, 1150, 1045, 1013, 995, 984, 964, 941, 928, 916, 878, 864, 835, 822, 810. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.37-7.32 (m, 6H, CH arom), 7.14 (d, 2H, $J = 8.0$ Hz, CH arom), 5.50 (s, 1H, CH benzyldiene), 4.88 (dd, 1H, $J = 10.0$ Hz, $J = 8.8$ Hz, H-2), 4.70 (d, 1H, $J = 10.0$ Hz, H-1), 4.37 (dd, 1H, $J = 10.4$ Hz, $J = 4.8$ Hz, H-6a), 3.91 (dt, 1H, $J = 8.8$ Hz, $J = 3.2$ Hz, H-3), 3.78 (t, 1H, $J = 10.2$ Hz, H-6b), 3.56 (t, 1H, $J = 9.2$ Hz, H-4), 3.47 (dt, 1H, $J = 10.0$ Hz, $J = 4.8$ Hz, H-5), 2.57 (d, 1H, $J = 3.2$ Hz, OH), 2.35 (s, 3H,

CH₃ STol), 1.26 (s, 9H, 3x CH₃ Piv). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 177.8 (C=O Piv), 138.8, 135.5, 135.2 (C_q C_{arom}), 133.5 (CH_{arom}), 129.9 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (C_q C_{arom}), 127.9 (CH_{arom}), 101.1 (CH benzylidene), 87.2 (C-1), 80.7 (C-4), 73.9 (C-3), 72.4 (C-2), 70.3 (C-5), 68.6 (C-6), 39.0 (C_q Piv), 27.3 (CH₃ Piv), 21.3 (CH₃ STol). HRMS: [M+Na]⁺ calcd for C₂₅H₂₉ClO₆Na: 515.12656, found 515.12628.



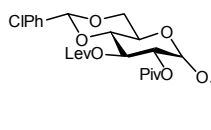
4,6-O-(*p*-chlorobenzylidene)-3-O-levulinoyl-2-O-pivaloyl-D-glucopyranose

(8): To a solution of glucoside **4** (296 mg, 0.5 mmol) in DCM (5.0 mL, 0.1M) was added NIS (124 mg, 0.55 mmol, 1.1 eq.) and TFA (0.42 mL, 0.55 mmol, 1.1 eq.) at 0 °C. After TLC analysis (toluene/EtOAc, 4/1, v/v) showed total conversion of the starting material, piperidine (0.15 mL, 1.5 mmol, 3.0 eq.) was slowly added. After TLC analysis (PE/EtOAc, 7/3, v/v) indicated total consumption of the trifluoroacetyl glucoside, the reaction was quenched with Na₂S₂O₃ (aq., sat.), diluted in DCM and washed with 1M HCl solution, water and brine. The organic phase was dried with MgSO₄, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 1:0 → 7:3) gave the title compound as a mixture of α - and β -isomers (1.7/1), in 85% yield. IR (neat, cm⁻¹): 3300, 2979, 2870, 1746, 1722, 1703, 1601, 1479, 1368, 1323, 1306, 1281, 1219, 1184, 1152, 1090, 1053, 1013, 986, 968, 943, 837, 820, 77. α isomer: ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.39 (d, 2H, *J* = 8.4 Hz, H_{arom}), 7.32 (d, 2H, *J* = 8.4 Hz, CH_{arom}), 5.65 (t, 1H, *J* = 10.0 Hz, H-3), 5.48 (s, 1H, CH benzylidene), 5.44 (t, 1H, *J* = 3.2 Hz, H-1), 5.84 (dd, 1H, *J* = 9.8 Hz, *J* = 9.8 Hz, H-2), 4.27 (dd, *J* = 10.2 Hz, *J* = 4.8 Hz, H-6a), 4.14 (dt, 1H, *J* = 9.8 Hz, *J* = 4.8 Hz, H-5), 3.73 (t, 1H, *J* = 10.0 Hz, H-6b), 3.65 (t, *J* = 9.8 Hz, H-4), 3.24 (d, *J* = 3.2 Hz, C-1-OH), 2.73-2.69 (m, 2H, CH₂ Lev), 2.61-2.54 (m, 2H, CH₂ Lev), 2.15 (s, 3H, CH₃ Lev), 1.20 (s, 9H, 3x CH₃ Piv). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 206.3 (C=O Lev ketone), 178.0 (C=O Piv), 171.7 (C=O Lev), 135.4-135.0 (C_q C_{arom}), 128.5 (CH_{arom}), 127.8 (CH_{arom}), 100.8 (CH benzylidene), 91.1 (C-1), 79.3 (C-4), 71.7 (C-2), 69.0 (C-3), 68.9 (C-6), 62.5 (C-5), 38.9 (C_q Piv), 37.9 (CH₂ Lev), 30.0 (CH₃ Lev), 28.0 (CH₂ Lev), 27.0 (CH₃ Piv). HRMS: [M+Na]⁺ calcd for C₂₃H₂₉ClO₉Na: 507.13978, found 507.13923.



Pivaloyl 4,6-O-(*p*-chlorobenzylidene)-3-O-levulinoyl- α -D-glucopyranoside

(4b) The title compound was isolated as a side-product in thioglycoside hydrolysis, in varying amounts. [α]_D: +50 (c = 1, DCM). IR (neat, cm⁻¹): 3495, 2972, 2932, 2914, 2870, 1751, 1713, 1601, 1493, 1477, 1458, 1414, 1398, 1366, 1319, 1287, 1234, 1204, 1179, 1152, 1136, 1101, 1080, 1024, 1016, 988, 966, 943, 908, 893, 810. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.42 (d, 2H, *J* = 8.4 Hz, CH_{arom}), 7.34 (d, 2H, *J* = 8.4 Hz, CH_{arom}), 6.22 (d, 1H, *J* = 4.0 Hz, H-1), 5.50 (s, 1H, CH benzylidene), 5.35 (t, 1H, *J* = 9.6 Hz, H-3), 4.32 (dd, 1H, *J* = 10.4 Hz, *J* = 4.8 Hz, H-6a), 3.93 (dd, 1H, *J* = 9.6 Hz, *J* = 4.0 Hz, H-2), 3.88 (dt, 1H, *J* = 9.8 Hz, *J* = 4.8 Hz, H-5), 3.73 (t, 1H, *J* = 10.0 Hz, H-6b), 3.68 (t, 1H, *J* = 9.6 Hz, H-4), 2.81 (m, 2H, CH₂ Lev), 2.65 (m, 2H, CH₂ Lev), 2.17 (s, 3H, CH₃ Lev), 1.28 (s, 9H, 3x CH₃ Piv). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 207.2 (C=O Lev ketone), 176.9 (C=O Piv), 173.5 (C=O Lev), 135.4 (C_q C_{arom}), 135.1 (C_q C_{arom}), 128.6 (CH_{arom}), 127.8 (C_q C_{arom}), 100.8 (CH benzylidene), 91.7 (C-1), 78.2 (C-4), 72.8 (C-3), 71.1 (C-2), 68.8 (C-6), 65.0 (C-5), 39.4 (C_q Piv), 38.3 (CH₂ Lev), 30.0 (CH₃ Lev), 28.2 (CH₂ Lev), 27.2 (CH₃ Piv). HRMS: [M + Na]⁺ calcd for C₂₃H₂₉ClO₉Na 507.13978, found 507.13953.

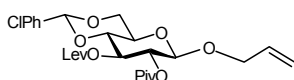


4,6-O-(*p*-chlorobenzylidene)-3-O-levulinoyl-1-O-(*N*-phenyl

trifluoroacetimidoyl)-2-O-pivaloyl- α / β -D-glucopyranoside (9):

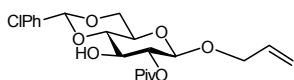
To an ice-cooled solution of hemiacetal **8** (1.6 g, 3.3 mmol) in acetone (17 mL, 0.2M) was added *N*-phenyl trifluoroacetimidoyl chloride (0.61 mL, 4.0 mmol, 1.2 eq.) and DBU (0.64 mL, 3.3 mmol, 1 eq.). After 2.5 hours at 0 °C, TLC (toluene/EtOAc, 4/1, v/v) indicated complete conversion of the starting material. The mixture was diluted with H₂O and extracted with EtOAc (3x). The combined organics were washed with H₂O, brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc/TEA 100/0/1 →

85/15/1) afforded the glucosyl imidate in 94% yield (2.0 g, 3.1 mmol, α/β : 1/2). IR (neat, cm^{-1}): 2972, 2936, 2914, 2864, 2847, 2826, 1746, 1715, 1599, 1491, 1481, 1398, 1368, 1325, 1310, 1279, 1250, 1204, 1177, 1153, 1125, 1101, 1084, 1061, 1016, 974, 941, 904, 895, 881, 835, 810. β -isomer: ^1H NMR (400 MHz, CDCl_3 , 323 K, HH-COSY, HSQC): 7.41-7.25 (m, 6H, H_{arom}), 7.14-7.08 (m, 1H, H_{arom}), 6.82-6.76 (m, 2H, H_{arom}), 5.86 (bs, 1H, H-1), 5.46 (s, 1H, CH benzyldiene), 5.33 (t, 1H, $J = 8.8$ Hz, H-3), 5.23 (t, 1H, $J = 8.4$ Hz, H-2), 4.34-4.31 (m, 1H, H-6a), 3.79-3.71 (m, 2H, H-4, H-6b), 3.50 (bs, 1H, H-5), 2.69-2.66 (m, 2H, CH_2 Lev), 2.61-2.56 (m, 2H, CH_2 Lev), 2.12 (s, 3H, CH_3 Lev), 1.20 (s, 9H, 3x CH_3 Piv). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 205.5 (C=O Lev ketone), 177.5 (C=O Piv), 171.6 (C=O Lev), 143.1 (C=N), 135.5-135.2 (C_q C_{arom}), 129.0-119.4 (CH_{arom}), 101.1 (CH benzyldiene), 92.6 (C-1), 78.8 (C-4), 70.1 (C-2), 69.2 (C-3), 68.6 (C-6), 65.2 (C-5), 39.0 (C_q C_{arom}), 37.9 (CH_2 Lev), 28.0 (CH_3 Lev), 27.0 (CH_2 Lev), 27.0 (CH_3 Piv). HRMS: $[\text{M}+\text{Na}]^+$ calcd $\text{C}_{23}\text{H}_{29}\text{ClO}_9\text{Na}$: 507.13978, found 507.13923.



Allyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-levulinoyl-2-*O*-pivaloyl- β -D-glucopyranoside (10) To a solution of glucosyl imidate **9** (0.13 g, 0.2 mmol) in DCM (4.0 mL, 50mM) were added flame-dried 3Å molecular

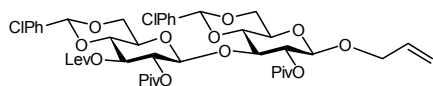
sieves and the mixture was cooled to 0 °C. Allyl alcohol (dried over K_2CO_3 , 0.04 mL, 0.6 mmol, 3 eq.) was added and the reaction was stirred for 30 minutes. TfOH (1.8 μL , 0.02 mmol, 0.1 eq.) was added and the reaction was gradually warmed to room temperature. After 120 minutes, the reaction was neutralized with TEA, washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc: 19/1 \rightarrow 4/1) afforded the title compound in 70% yield (73 mg, 0.14 mmol). $[\alpha]_D$: -63.2 ($c = 1.1$, DCM). IR (neat, cm^{-1}): 2972, 2955, 2924, 2909, 2893, 2874, 1740, 1715, 1603, 1495, 1479, 1468, 1425, 1396, 1362, 1319, 1304, 1277, 1209, 1177, 1150, 1125, 1086, 1061, 1030, 986, 976, 951, 937, 922, 908, 878, 829. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.39 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.33 (d, 2H, $J = 8.4$ Hz, H_{arom}), 5.83 (ddd, 1H, $J = 22.8$ Hz, $J = 11.2$ Hz, $J = 5.6$ Hz, CH allyl), 5.48 (s, 1H, CH benzyldiene), 5.34 (t, 1H, $J = 9.6$ Hz, H-3), 5.27 (dd, 1H, $J = 17.4$ Hz, $J = 1.4$ Hz, C=CHH allyl), 5.20 (dd, 1H, $J = 10.4$, $J = 1.4$ Hz, C=CHH allyl), 5.05 (dd, 1H, $J = 9.2$ Hz, $J = 8.0$ Hz, H-2), 4.62 (d, 1H, $J = 7.6$ Hz, H-1), 4.38-4.32 (m, 2H, H-6a, CHH allyl), 4.07 (dd, 1H, $J = 12.8$ Hz, $J = 6.4$ Hz, CHH allyl), 3.80 (t, 1H, $J = 10.4$ Hz, H-6b), 3.70 (t, 1H, $J = 9.6$ Hz, H-4), 3.51 (dt, 1H, $J = 9.6$ Hz, $J = 4.8$ Hz, H-5), 2.71-2.68 (m, 2H, CH_2 Lev), 2.59-2.54 (m, 2H, CH_2 Lev), 2.15 (s, 3H, CH_3 Lev), 1.18 (s, 9H, 3x CH_3 Piv). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 206.0 (C=O Lev ketone), 177.0 (C=O Piv), 171.2 (C=O Lev), 135.5 (C_q C_{arom}), 135.0 (C_q C_{arom}), 133.2 (CH allyl), 128.5-127.5 (CH_{arom}), 118.1 (C=CH₂ allyl), 100.7 (C-1, CH benzyldiene), 78.6 (C-4), 71.7 (C-2 or C-3), 71.6 (C-2 or C-3), 70.7 (CH_2 allyl), 68.7 (C-6), 66.4 (C-5), 38.9 (C_q Piv), 37.9 (CH_2 Lev), 29.9 (CH_3 Lev), 28.0 (CH_2 Lev), 27.1 (CH_3 Piv). HRMS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{33}\text{ClO}_9\text{Na}$: 547.17053, found 547.17029.



Allyl 4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-pivaloyl- β -D-glucopyranoside (11) To a stirred solution of allyl glucoside **10** (210 mg, 0.38 mmol) in argon-flushed pyridine/AcOH (4/1, 4 mL, 0.1M),

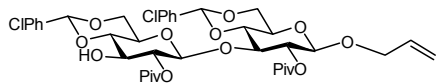
hydrazine hydrate (0.11 mL, 2.0 mmol, 5 eq.) was added and the mixture was stirred for 30 minutes at room temperature. The reaction was quenched with acetone, diluted with 1M HCl solution and extracted three times with DCM. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc: 9/1 \rightarrow 4/1) gave the product in 96% yield. $[\alpha]_D$: -68.6 ($c = 1$, DCM). IR (neat, cm^{-1}): 3470, 3368, 2974, 2963, 2932, 2874, 1746, 1722, 1493, 1477, 1458, 1398, 1371, 1352, 1281, 1267, 1229, 1182, 1171, 1152, 1130, 1088, 1074, 1047, 1013, 980, 926, 885, 812. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.42 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.32 (d, 2H, $J = 8.4$ Hz, H_{arom}), 5.84 (ddd, 1H, $J = 22.8$ Hz, $J = 11.2$ Hz, $J = 5.6$ Hz, CH allyl), 5.49 (s, 1H, CH benzyldiene), 5.27 (dd, 1H, $J = 17.2$ Hz, $J = 1.6$ Hz, C=CHH allyl), 5.19 (d, 1H,

$J = 10.4$ Hz, $J = 1.4$ Hz, C=CHH allyl), 4.91 (t, 1H, $J = 8.8$ Hz, H-2), 4.55 (d, 1H, $J = 7.6$ Hz, H-1), 4.33 (m, 2H, H-6a, CHH allyl), 4.06 (dd, $J = 13.0$ Hz, $J = 6.2$ Hz, CHH allyl), 3.85 (t, 1H, $J = 9.2$ Hz, H-3), 3.76 (t, 1H, $J = 10.2$ Hz, H-6b), 3.57 (t, 1H, $J = 9.4$ Hz, H-4), 3.40 (dt, 1H, $J = 9.6$ Hz, $J = 4.8$ Hz, H-5), 1.22 (s, 9H, 3x CH₃ Piv). ¹³C NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 178.2 (C=O Piv), 135.6-135.2 (C_q C_{arom}), 133.4 (CH allyl), 128.6-127.9 (CH_{arom}), 118.0 (CH=CH₂ allyl), 101.1 (CH benzylidene), 100.5 (C-1), 81.1 (C-4), 74.4 (C-2), 72.7 (C-3), 70.5 (CH₂ allyl), 68.7 (C-6), 66.2 (C-5), 39.1 (C_q Piv), 27.2 (CH₃ Piv). HRMS: [M+Na]⁺ calcd for C₂₁H₂₇ClO₇Na: 449.13375, found 449.13362.



Allyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-[4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-levulinoyl-2-*O*-pivaloyl- β -D-glucopyranosyl]-2-*O*-pivaloyl- β -D-glucopyranoside (12)

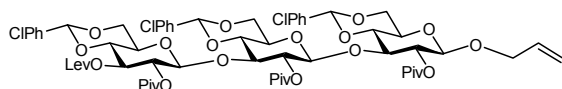
To a stirred solution of donor **9** (250 mg, 0.38 mmol, 1.2 eq.) and acceptor **11** (136 mg, 0.32 mmol) in DCM (10 mL, 0.03M) were added 3Å MS. After 30 minutes at 0 °C, TfOH (2.6 μ L, 0.03 mmol) was added and the mixture was gradually warmed to room temperature. After 4 hours TLC analysis (DCM/acetone: 49/1, v/v) indicated complete conversion of the starting material and the reaction was quenched with TEA (0.3 mL) and washed with brine. The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by size-exclusion chromatography (DCM/MeOH: 1/1) gave the product as a white solid in 99% yield (0.29 g, 0.32 mmol). [α]_D: -51.6 (c = 0.9, DCM). IR (neat, cm⁻¹): 2974, 2932, 2911, 2874, 1742, 1721, 1603, 1495, 1481, 1462, 1398, 1369, 1302, 1275, 1230, 1207, 1180, 1125, 1088, 1059, 1034, 1017, 1003, 941, 881, 818. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.45 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.35-7.31 (m, 6H, H_{arom}), 5.82 (ddd, 1H, $J = 22.0$ Hz, $J = 10.8$ Hz, $J = 6.0$ Hz, CH allyl), 5.53 (s, 1H, CH benzylidene), 5.28-5.12 (m, 3H, C=CH₂ allyl, H-3'), 5.10 (s, 1H, CH benzylidene'), 5.04 (t, 1H, $J = 7.8$ Hz, H-2), 4.96 (t, 1H, $J = 6.4$ Hz, H-2'), 4.87 (d, 1H, $J = 6.0$ Hz, H-1'), 4.52 (d, 1H, $J = 7.6$ Hz, H-1), 4.37-4.29 (m, 2H, H-6a, CHH allyl), 4.25 (dd, 1H, $J = 10.4$ Hz, $J = 4.8$ Hz, H-6a'), 4.14 (t, 1H, $J = 8.8$ Hz, H-3), 4.00 (dd, 1H, $J = 12.8$ Hz, $J = 6.0$ Hz, CHH allyl), 3.88 (t, 1H, $J = 9.4$ Hz, H-4'), 3.78 (t, 1H, $J = 10.4$ Hz, H-6b), 3.74 (t, 1H, $J = 9.6$ Hz, H-4), 3.64 (t, 1H, $J = 10.4$ Hz, H-6b'), 3.52-3.46 (m, 2H, H-5, H-5'), 2.73-2.55 (m, 4H, 2x CH₂ Lev), 2.16 (s, 3H, CH₃ Lev), 1.24-1.17 (m, 18H, 6x CH₃ Piv). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 206.1 (C=O Lev ketone), 177.0 (C=O Piv), 176.3 (C=O Piv, C=O Lev), 135.8 (C_q C_{arom}), 135.4 (C_q C_{arom}), 135.3 (C_q C_{arom}), 134.9 (C_q C_{arom}), 133.2 (CH allyl), 128.7 (CH_{arom}), 128.5 (CH_{arom}), 128.0 (CH_{arom}), 127.7 (CH_{arom}), 118.0 (C=CH₂ allyl), 101.1 (CH benzylidene), 100.5 (C-1), 100.3 (CH benzylidene'), 98.9 (C-1'), 78.8 (C-4), 77.9 (C-4'), 75.1 (C-3), 73.8 (C-2), 72.4 (C-2' or C-3'), 72.2 (C-2' or C-3'), 70.3 (CH₂ allyl), 68.9 (C-6 or C-6'), 68.7 (C-6 or C-6'), 66.5 (C-5 or C-5'), 66.0 (C-5 or C-5'), 38.9 (C_q Piv), 37.9 (CH₂ Lev), 30.0 (CH₃ Lev), 28.0 (CH₂ Lev), 27.2 (CH₃ Piv). HRMS: [M+Na]⁺ calcd for C₄₄H₅₄Cl₂O₁₅Na: 915.27320, found 915.27375.



1-*O*-allyl-4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-[4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-pivaloyl- β -D-glucopyranosyl]-2-*O*-pivaloyl- β -D-glucopyranoside (13)

To a solution of disaccharide **12** (0.19 g, 0.21 mmol) in argon-flushed pyridine/AcOH (4/1, v/v, 2 mL, 0.1M) was added argon-flushed hydrazine hydrate (0.057 mL, 1.0 mmol, 5 eq.). After TLC analysis (DCM/acetone: 19/1, v/v) indicated complete conversion of the starting product, the reaction mixture was quenched with acetone, diluted with EtOAc, washed with 1M HCl (3x) and brine. The organics were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 9/1 \rightarrow 7/3, v/v) afforded the title compound in 94% yield (0.15 g, 0.20 mmol). [α]_D: -30.8 (c = 0.5, DCM). IR (neat, cm⁻¹): 3447, 2974, 2934, 2907, 2874, 1738, 1603, 1495, 1479, 1462, 1398, 1369, 1302, 1277, 1229, 1209, 1171, 1132, 1090, 1059, 1034, 1016, 1003, 941, 930, 883, 816. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.44 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.33-7.27 (m, 6H, H_{arom}), 5.82 (ddd, 1H, $J = 22.0$ Hz, $J = 10.6$ Hz, $J = 5.6$ Hz, CH allyl), 5.51 (s, 1H, CH benzylidene), 5.26 (dd,

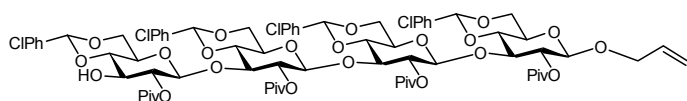
1H, $J = 17.2$ Hz, $J = 1.6$ Hz, CH=CHH allyl), 2.19 (dd, 1H, $J = 10.4$ Hz, $J = 1.2$ Hz, CH=CHH allyl), 5.10 (s, 1H, CH benzylidene), 5.06 (t, 1H, $J = 8.0$ Hz, H-2), 4.91 (d, 1H, $J = 5.6$ Hz, H-1'), 4.83 (t, 1H, $J = 5.6$ Hz, H-2''), 4.53 (d, 1H, $J = 7.2$ Hz, H-1), 4.37-4.29 (m, 2H, H-6a, CHH allyl), 4.23 (dd, 1H, $J = 10.2$ Hz, $J = 4.8$ Hz, H-6a'), 4.15 (t, 1H, $J = 8.8$ Hz, H-3), 4.01 (dd, 1H, $J = 12.8$ Hz, $J = 6.4$ Hz, CHH allyl), 3.85-3.71 (m, 4H, H-3', H-4, H-4', H-6b), 3.63 (t, 1H, $J = 10.4$ Hz, H-6b'), 3.53-3.46 (m, 2H, H-5, H-5'), 2.78 (bs, 1H, 3-OH'), 1.23-1.20 (m, 18H, 6x CH₃ Piv). ¹³C NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 178.3 (C=O Piv), 176.4 (C=O Piv), 135.8 (C_q C_{arom}), 135.5 (C_q C_{arom}), 135.3 (C_q C_{arom}), 135.1 (C_q C_{arom}), 133.2 (CH allyl), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 127.9 (CH_{arom}), 127.7 (CH_{arom}), 117.9 (C=CH₂ allyl), 101.1 (CH benzylidene), 100.5 (CH benzylidene), 100.4 (C-1), 98.7 (C-1'), 80.4 (C-4 or C-4'), 78.9 (C-4 or C-4'), 75.2, 75.1 (C-2', C-3), 73.9 (C-2), 73.0 (C-3'), 70.2 (CH₂ allyl), 68.8 (C-6 of C-6'), 68.7 (C-6 or C-6'), 66.4 (C-5 or C-5'), 65.8 (C-5 or C-5'), 38.9 (C_q Piv), 38.9 (C_q Piv), 27.1 (CH₃ Piv), 27.1 (CH₃ Piv). HRMS: [M+Na]⁺ calcd for C₃₉H₄₈Cl₂O₁₃Na: 817.23642, found 817.23677.



Allyl 4,6-O-(*p*-chlorobenzylidene)-3-O-[4,6-O-(*p*-chlorobenzylidene)-3-O-{4,6-O-(*p*-chlorobenzylidene)-3-O-levulinoyl-2-O-

pivaloyl-β-D-glucopyranosyl]-2-O-pivaloyl-β-D-glucopyranosyl]-2-O-pivaloyl-β-D-

glucopyranoside (14) To a stirred solution of donor **9** (131 mg, 0.20 mmol) and acceptor **13** (110 mg, 0.14 mmol) in DCM (4 mL, 50mM) were added 3Å MS at 0 °C. After 30 minutes, TfOH (2 μL, 0.02 mmol) was added and the mixture was warmed to room temperature. After two hours, TLC analysis (DCM/acetone: 19/1, v/v) indicated consumption of the starting material, and the reaction was stopped by addition of TEA (0.2 mL). The organic phase was washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by size-exclusion chromatography (DCM/MeOH, 1/1) gave the title trisaccharide in 80% yield (141 mg, 0.11 mmol). [α]_D: -104.4 (c = 1, DCM). IR (neat, cm⁻¹): 2972, 2932, 2911, 2872, 1738, 1603, 1495, 1479, 1462, 1398, 1369, 1319, 1302, 1275, 1207, 1180, 1123, 1088, 1051, 1032, 1015, 99, 941, 912, 880, 814. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.54 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.36-7.26 (m, 6H, H_{arom}), 7.23 (d, 2H, $J = 8.0$ Hz, H_{arom}), 7.18 (d, 2H, $J = 8.4$ Hz, H_{arom}), 5.82 (ddd, $J = 22.4$ Hz, $J = 10.8$ Hz, $J = 5.6$ Hz, CH allyl), 5.62 (s, 1H, CH benzylidene), 5.40 (s, 1H, CH benzylidene), 5.34 (t, 1H, $J = 9.0$ Hz, H-3''), 5.28-5.17 (m, 2H, C=CH₂ allyl), 5.05-4.98 (m, 3H, H-2, H-1'', H-2''), 4.92 (d, 1H, $J = 2.4$ Hz, H-1'), 4.79 (bs, 1H, H-2'), 4.50 (d, 1H, $J = 7.8$ Hz, H-1), 4.41 (s, 1H, CH benzylidene), 4.39-4.26 (m, 4H, H-6a, H-4', H-6a''), CHH allyl), 4.20 (t, 1H, $J = 9.2$ Hz, H-3), 4.10 (dd, 1H, $J = 9.8$ Hz, $J = 4.8$ Hz, H-6a'), 4.01 (dd, $J = 12.8$ Hz, $J = 6.4$ Hz, CHH allyl), 3.79 (t, 1H, $J = 10.4$ Hz, H-6b), 3.76-3.71 (m, 3H, H-3', H-4'', H-6b''), 3.67 (t, 1H, $J = 9.4$ Hz, H-4), 3.57-3.51 (m, 4H, H-5, H-5', H-5'', H-6b'), 2.71-2.68 (m, 2H, CH₂ Lev), 2.59-2.55 (m, 2H, CH₂), 2.14 (s, 3H, CH₃), 1.41-1.17 (m, 27H, 9x CH₃ Piv). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 206.0 (C=O Lev ketone), 177.1 (C=O Piv), 177.0 (C=O Piv), 176.2 (C=O Piv), 171.7 (C=O Lev), 135.8-134.7 (C_q C_{arom}), 133.2 (CH allyl), 128.7-127.5 (CH_{arom}), 118.1 (C=CH₂ allyl), 101.8 (CH benzylidene), 100.7 (C-1, CH benzylidene), 99.5 (CH benzylidene), 99.0 (C-1''), 96.7 (C-1'), 79.2 (C-4), 78.6 (C-4''), 77.2 (C-3'), 76.6 (C-4'), 74.3 (C-2''), 73.4 (C-2), 72.6 (C-3), 72.2 (C-3''), 71.7 (C-2), 70.5 (CH₂ allyl), 68.9-68.7 (C-6, C-6', C-6''), 66.8-65.0 (C-5, C-5', C-5''), 39.0-38.8 (C_q Piv), 37.9 (CH₂ Lev), 29.9 (CH₃ Lev), 28.0 (CH₂ Lev), 27.4-27.1 (CH₃ Piv). HRMS: [M+Na]⁺ calcd for C₆₂H₇₅Cl₃O₂₁Na: 1283.37746, found 1283.37586.

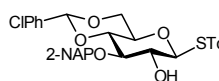


Allyl 4,6-O-(*p*-chlorobenzylidene)-3-O-[4,6-O-(*p*-chlorobenzylidene)-3-O-{4,6-O-(*p*-chlorobenzylidene)-3-

O-(4,6-O-(*p*-chlorobenzylidene)-2-O-pivaloyl-β-D-glucopyranosyl)-2-O-pivaloyl-β-D-

glucopyranosyl]-2-O-pivaloyl-β-D-glucopyranosyl]-2-O-pivaloyl-β-D-glucopyranoside (16): The RV was charged with functionalized Merrifield polystyrene **15** (100 mg, 45 μmol) and prepared for the

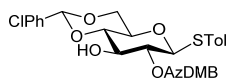
synthesis using protocol C. Then, the coupling/deprotection cycle was run to couple donor **9** four times. After the synthesis was complete, protocol J was used to isolate the resin. After cleavage with Grubbs first-generation catalyst and filtration over a plug of silica, preparative RP-HPLC yielded the pure tetrasaccharide in 44% yield (18 mg, 22.6 μ mol). $[\alpha]_D$: -20 ($c = 0.26$, DCM). IR (neat, cm^{-1}): 2972, 2934, 2909, 2872, 1740, 1603, 1495, 1479, 1462, 1398, 1371, 1300, 1275, 1261, 1207, 1173, 1123, 1126, 1088, 1051, 1034, 1016, 1001, 941, 912, 881, 816. ^1H NMR (400 MHz, CDCl_3 , HH-COSY, HSQC): 7.57 (d, 2H, $J = 8.4$ Hz, CH arom), 7.37-7.24 (m, 12H, H_{arom}), 7.19 (d, 2H, $J = 8.4$ Hz, H_{arom}), 5.83 (ddd, 1H, $J = 22.0$ Hz, $J = 10.8$ Hz, $J = 6.0$ Hz, CH allyl), 5.74 (s, 1H, CH benzyldiene), 5.29-5.17 (m, 3H, CH benzyldiene, C=CH₂ allyl), 5.03 (t, 1H, $J = 8.4$ Hz, H-2), 4.98 (d, 1H, $J = 4.8$ Hz, H-1'), 4.94-4.91 (m, 2H, H-1'', H-2''), 4.90 (d, 1H, $J = 3.2$ Hz, H-1'''), 4.86 (s, 1H, CH benzyldiene), 4.83-4.80 (m, 2H, H-2'', H-2'''), 4.62 (s, 1H, CH benzyldiene), 4.51 (d, 1H, $J = 7.6$ Hz, H-1), 4.38 (dd, 1H, $J = 10.4$ Hz, $J = 4.8$ Hz, H-6a), 4.35-4.20 (m, 4H, CHH allyl, H-3, 2x H-6), 4.16-4.14 (m, 2H, 2x H-6), 4.06-3.99 (m, 2H, CHH allyl, H-4'), 3.92 (dd, 1H, $J = 4.8$ Hz, $J = 8.6$ Hz, H-3'), 3.86-3.79 (m, 4H, H-3'', H-3''', H-4, 2x H-6), 3.68-3.44 (m, 7H, H-4'', H-4''', 4x H-5, H-6), 1.28-1.18 (m, 36H, 12x CH₃ Piv). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 178.4 (C=O Piv), 176.9 (C=O Piv), 176.7 (C=O Piv), 176.4 (C=O Piv), 136.0 (C_q C_{arom}), 135.8 (C_q C_{arom}), 135.7 (C_q C_{arom}), 135.6 (C_q C_{arom}), 135.2 (C_q C_{arom}), 135.1 (C_q C_{arom}), 135.0 (C_q C_{arom}), 133.3 (CH allyl), 128.7 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 128.4 (CH_{arom}), 127.9 (CH_{arom}), 127.8 (CH_{arom}), 127.8 (CH_{arom}), 118.1 (C=CH₂ allyl), 101.5 (CH benzyldiene), 100.9 (CH benzyldiene), 100.7 (CH benzyldiene), 100.5 (CH benzyldiene), 100.2 (C-1), 99.6 (C-1'' or C-1'''), 97.3 (C-1'), 97.0 (C-1'' or C-1'''), 80.7 (C-4'' or C-4'''), 79.0 (C-3'' or C-3''' or C-4), 77.9 (C-4'), 77.5 (C-3), 76.8 (C-4'' or C-4'''), 75.3 (C-3'' or C-3''' or C-4), 74.8 (C-2', C-2'' or C-2'''), 74.4 (C-2), 74.2, 74.0 (2x C-2' or C-2'' or C-2'''), 73.0 (C-3'' or C-3''' or C-4), 72.6 (C-3), 70.5 (CH₂ allyl), 68.9, 68.9, 68.8, 68.7 (4x C-6), 66.9, 65.8, 65.6, 65.5 (4x C-5), 39.0-38.9 (4x C_q Piv), 27.4, 27.4, 27.4, 27.1 (4x CH₃ Piv). HRMS: $[\text{M}+\text{NH}_4]^+$ calcd for C₇₅H₉₄Cl₄O₂₅N: 1548.48635, found 1548.48791.



***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-(naphthalen-2-methyl)-1-thio-**

β -D-glucopyranoside (17): Glucoside **2** (7.0 g, 25.7 mmol) was suspended in toluene (64 mL, 0.4M) followed by addition of Bu₂SnO (6.40 g, 25.7 mmol, 1

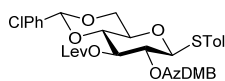
eq.). The reaction mixture was heated to reflux and stirred for 2 h. The reaction mixture was cooled to rT, concentrated, and co-concentrated with toluene. The obtained white solid was dissolved in DMF (86 mL, 0.3M) followed by addition of 2-(bromomethyl)naphthalene (6.85 g, 30.9 mmol, 1.2 eq.) and CsF (5.08 g, 33.4 mmol, 1.3 eq.). The reaction mixture was stirred overnight. A white suspension was obtained. The reaction mixture was diluted with EtOAc, washed with H₂O, brine, dried over MgSO₄, filtered, and concentrated. A white solid was obtained, which was recrystallized from EtOH. The title compound was obtained as a white powder in 69% yield over 2 steps (9.7 g, 17.63 mmol). Melting point: 172 °C. $[\alpha]_D$: -33 ($c = 1$, DCM). IR (neat, cm^{-1}): 3300, 2912, 1367, 1265, 1107, 1085, 1008, 810, 734, 705, 611. ^1H NMR (300 MHz, CDCl_3 , HH-COSY, HSQC): 7.92-7.63 (m, 4H, H_{arom}), 7.53-7.34 (m, 9H, H_{arom}), 7.12 (d, 2H, $J = 8.1$ Hz, H_{arom}), 5.52 (s, 1H, CH chlorobenzylidene), 5.03 (d, 1H, $J = 12.0$ Hz, CHH naphthylmethyl), 4.96 (d, 1H, $J = 12.0$ Hz, CHH naphthylmethyl), 4.55 (d, 1H, $J = 9.6$ Hz, H-1), 4.36 (dd, 1H, $J = 10.5$ Hz, $J = 4.8$ Hz, H-6a), 3.79-3.42 (m, 5H, H-6b, H-2, H-3, H-4, H-5), 2.57 (d, 1H, $J = 2.8$ Hz, C-2-OH), 2.34 (s, 3H, CH₃ STol). ^{13}C APT NMR (100 MHz, CDCl_3 , HH-COSY, HSQC): 135.7 (C_q C_{arom}), 133.8 (CH_{arom}), 129.8 (CH_{arom}), 128.4 (C_q C_{arom}), 128.2-125.9 (CH_{arom}), 100.6 (CH benzyldiene), 88.8 (C-1), 81.4 (C-3 or C-4), 80.9 (C-3 or C-4), 74.8 (CH₂ naphthylmethyl), 72.4 (C-2), 70.6 (C-5), 68.6 (C-6), 21.2 (CH₃ STol). HRMS: $[\text{M}+\text{H}]^+$ calcd for C₃₁H₃₀ClO₅S 549.14970, found 549.14958.



***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-(4-azido-2,2-dimethylbutanoyl)-**

1-thio- β -D-glucopyranoside (18): 4-Azido-2,2-dimethylbutanoic acid (1.90 g, 12.14 mmol, 2 eq. relative to glucoside) was dissolved in DCM (30.4 mL, 0.4M)

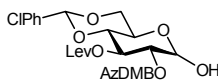
followed by addition of oxalyl chloride (2.60 mL, 30.4 mmol, 2.5 eq. relative to 4-Azido-2,2-dimethylbutanoic acid). The reaction mixture was heated to reflux and stirred for 1 h. The reaction mixture was concentrated and co-evaporated with toluene (2x) and chloroform (1x). The obtained acid chloride was dissolved in pyridine (30.4 mL, 0.2M) and cooled to 0 °C, followed by slow addition of glucoside **17** (3.25 g, 6.07 mmol). The reaction mixture was heated to 110 °C and the reaction mixture was stirred overnight. TLC analysis (hexane/ EtOAc: 3/1, v/v) showed total conversion into a higher running spot (hexane/EtOAc: 3/1, v/v, R_f 0.81) and the reaction mixture was cooled to rT, concentrated in vacuo and co-concentrated with toluene (2x). The obtained yellowish oil (crude **17a**) was dissolved in a DCM/H₂O mixture (9/1, 91.1 mL, 0.1M) and the resulting mixture was cooled to 0 °C. DDQ (3.10 g, 13.67 mmol, 1.5 eq.) was added and the reaction mixture was allowed to warm to rT. After 1 h., TLC analysis showed total conversion into a lower running spot (hexane/EtOAc: 3/1, R_f 0.75). The reaction mixture was quenched by addition of Na₂S₂O₃ (aq., sat.), diluted with DCM, followed by separation of the layers. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. A yellow oil was obtained. Column chromatography (pentane/EtOAc: 1/0 → 7/3) gave the title compound as a colorless oil, which crystallized on standing. Glucoside **18** was obtained in 78% yield over 2 steps (3.20 g, 4.75 mmol). $[\alpha]_D$: -34 (c = 1, DCM). IR (neat, cm⁻¹): 2926, 2096, 1737, 1263, 1089, 813, 731, 702, 665. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.40-7.24 (m, 6H, H_{arom}), 7.13-7.11 (m, 2H, H_{arom}), 5.49 (s, 1H, CHPh chlorobenzylidene), 4.92 (t, 1H, J = 10.0 Hz, H-2), 4.767 (d, 1H, J = 10.0 Hz, H-1), 4.32 (dd, 1H, J = 10.8 Hz, J = 5.2 Hz, H-6a), 3.89 (t, 1H, J = 9.6 Hz, H-3), 3.73 (t, 1H, J = 10.4 Hz, H-6b), 3.51 (t, 1H, J = 9.6 Hz, H-4), 3.45-3.36 (m, 3H, H-5, CH₂ AzDMB), 3.14 (bs, 1H, OH), 2.33 (s, 3H, CH₃ STol), 2.00-1.80 (m, 2H, CH₂ AzDMB), 1.27 (s, 3H, CH₃ AzDMB), 1.23 (s, 3H, CH₃ AzDMB). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 175.6 (C=O), 138.4 (C_q C_{arom}), 135.3-134.8 (C_q C_{arom}), 133.0 (CH_{arom}), 129.7-128.3 (CH_{arom}), 128.2 (C_q C_{arom}), 128.2-127.7 (CH_{arom}), 100.8 (CHPh chlorobenzylidene), 86.8 (C-1), 80.2 (C-4), 73.3 (C-3), 72.2 (C-2), 70.1 (C-5), 68.2 (C-6), 47.8 (CH₂ AzDMB), 40.9 (C_q AzDMB), 38.7 (CH₂ AzDMB), 25.6 (CH₃ AzDMB), 24.6 (CH₃ AzDMB), 21.0 (CH₃ STol). HRMS: [M+H]⁺ calcd for C₂₆H₃₁ClN₃O₆S: 548.16166, found 548.16149.



***p*-Tolyl 4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-(4-azido-2,2-dimethylbutanoyl)-**

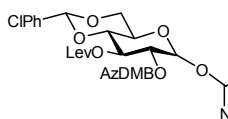
3-*O*-levulinyl-1-thio-β-D-glucopyranoside (19): Glucoside **18** (2.34 g, 6.25 mmol) was dissolved in DCM (31 mL, 0.2M) followed by addition of LevOH

(823 μL, 8.13 mmol, 1.3 eq.), DIC (950 μL, 8.13 mmol, 1.3 eq.) and DMAP (cat.). The reaction mixture was stirred for 15 min, after which TLC analysis showed total conversion into a slightly lower running spot (PE/EtOAc: 3/1, v/v, R_f 0.63). The reaction mixture was filtered, diluted with DCM, washed with H₂O, brine, dried over MgSO₄, filtered, and concentrated. A white solid was obtained. Column chromatography (hexane/EtOAc: 1/0 → 7/3) gave the title compound as a white solid in 90% yield (3.48 g, 5.63 mmol). $[\alpha]_D$: -112 (c = 2). IR (neat, cm⁻¹): 2098, 1745, 1718, 1421, 1367, 1265, 1089, 1014, 731, 702, 663. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.36-7.26 (m, 6H, H_{arom}), 7.15-7.13 (m, 2H, H_{arom}), 5.45 (s, 1H, CH benzylidene), 5.35 (t, 1H, J = 9.2 Hz, H-3), 5.02 (t, 1H, J = 9.6 Hz, H-2), 4.74 (d, 1H, J = 10.0 Hz, H-1), 4.36 (dd, 1H, J = 10.8 Hz, J = 5.2 Hz, H-6a), 3.77 (t, 1H, J = 10.4 Hz, H-6b), 3.64 (t, 1H, J = 9.6 Hz, H-4), 3.56-3.50 (m, 1H, H-5), 3.39-3.33 (m, 2H, CH₂ AzDMB), 2.93-2.66 (m, 2H, CH₂ Lev), 2.59-2.50 (m, 2H, CH₂ Lev), 2.35 (s, 3H, CH₃, STol), 2.13 (s, 3H, CH₃ Lev), 1.94-1.86 (m, 6H, 2x CH₃ AzDMB). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 205.7 (C=O Lev ketone), 175.2 (C=O AzDMB), 171.6 (C=O Lev), 137.8 (C_q C_{arom}), 135.2 (C_q C_{arom}), 134.8 (C_q C_{arom}), 133.3 (CH_{arom}), 128.3 (CH_{arom}), 127.8 (C_q C_{arom}), 127.6 (CH_{arom}), 100.5 (CH benzylidene), 87.0 (C-1), 78.2 (C-4), 72.8 (C-3), 70.3 (C-5), 70.2 (C-2), 68.3 (C-6), 47.6 (CH₂ AzDMB), 41.1 (C_q AzDMB), 38.3 (CH₂ AzDMB), 37.5 (CH₂ Lev), 29.7 (CH₃ Lev), 27.7 (CH₂ Lev), 25.3 (CH₃ AzDMB), 25.0 (CH₃ AzDMB), 21.1 (CH₃ STol). HRMS: [M+K]⁺ calcd for C₃₁H₃₆ClN₃O₈SK: 684.15405, found 684.15432.



4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-(4-azido-2,2-dimethylbutanoyl)-3-*O*-levulinyl- α/β -D-glucopyranose (20**):**

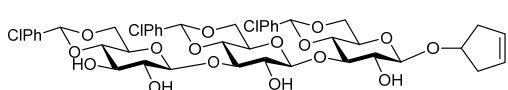
Glucoside **19** (372 mg, 0.60 mmol) was dissolved in freshly distilled DCM (3 mL, 0.2M) and the reaction mixture was stirred under argon and cooled to 0 °C. NIS (148 mg, 0.66 mmol, 1.1 eq.) and TFA (51 μ L, 0.66 mmol, 1.1. eq.) were added. TLC analysis (PE/EtOAc: 12/8, v/v) did not show any R_f difference but an UV positive spot (indicating *p*-thiocresol being formed) was observed. After 1 h., the reaction mixture was cooled to 0 °C, followed by piperidine (178 μ L, 1.80 mmol, 3 eq.). After 30 min., TLC analysis showed total conversion of the anomeric trifluoroacetate into a lower running spot (PE/EtOAc: 12/8, v/v, R_f 0.41). The reaction mixture was quenched by subsequent addition of triethylamine (reaction mixture turned from dark purple to yellow) and Na₂S₂O₃ (aq., sat.) (yellow reaction mixture turned colorless). The reaction mixture was diluted with DCM, washed with H₂O, dried over MgSO₄, filtered, and concentrated. Column chromatography (PE/EtOAc: 1/0 \rightarrow 4/6) gave hemiacetal **20** as an anomeric mixture (α/β : 1/0.6) and a colourless oil in 86% yield (278 mg, 0.51 mmol). IR (neat, cm⁻¹): 2096, 1720, 1419, 1365, 1265, 1089, 1014, 815, 732, 702. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.40-7.36 (m, 3.2H, H_{arom}), 7.33-7.28 (m, 3.2H, H_{arom}), 5.64 (t, 1H, J = 9.6 Hz, H-3 α), 5.48 (s, 0.6H, CH benzyldiene β), 5.45 (s, 1H, CH benzyldiene α), 5.36 (t, 0.6H, J = 9.6 Hz, H-2 β), 4.91 (t, 0.6H, J = 0.6H, H-3 β), 4.82-4.79 (m, 1.6H, H-1 β , H-2 α), 4.34 (dd, 0.6H, J = 10.4 Hz, J = 4.8 Hz, H-6a β), 4.27 (dd, 1H, J = 10.4 Hz, J = 4.8 Hz, H-6a α), 4.16-4.10 (m, 1H, H-5 α), 3.79-3.67 (m, 1.6H, H-6a α , H-6b β), 3.67-3.62 (m, 1.6H, H-4 α , H-4 β), 3.56-3.52 (m, 0.6H, H-5 β), 3.34-3.26 (m, 3.2H, CH₂ AzDMB α , CH₂ AzDMB β), 2.76-2.69 (m, 3.2H, CH₂ Lev α , CH₂ Lev β), 2.60-2.55 (m, 3.2H, CH₂ Lev α , CH₂ Lev β), 2.15 (s, 4.8H, CH₃ Lev α , CH₃ Lev β), 2.04-1.88 (m, 1.6H, CHH AzDMB α , CHH AzDMB β), 1.86-1.76 (m, 1.6H, CHH AzDMB α , CHH AzDMB β), 1.21 (9.6 H, 2x CH₃ AzDMB α , 2x CH₃ AzDMB β). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 206.3 (C=O Lev ketone α), 206.1 (C=O Lev ketone β), 176.7 (C=O AzDMB β), 176.4 (C=O AzDMB α), 171.6 (C=O Lev α , C=O Lev β), 135.4-134.7 (CH_{arom}), 128.3-127.5 (CH_{arom}), 100.5 (CH benzyldiene α), 100.5 (CH benzyldiene β), 96.0 (C-1 β), 90.5 (C-1 α), 78.9 (C-4 α), 78.4 (C-4 β), 73.8 (C-2 β), 72.1 (C-2 α), 71.7 (C-3 β), 68.7 (C-3 α), 68.6 (C-6 α), 68.2 (C=6 β), 66.4 (C-5 β), 62.2 (C-5 α), 47.8 (CH₂ AzDMB α), 47.6 (CH₂ AzDMB β), 41.1 (C_q AzDMB β), 40.8 (C_q AzDMB α), 38.4 (CH₂ AzDMB α , CH₂ AzDMB β), 37.6 (CH₂ Lev α), 37.5 (CH₂ Lev β), 29.7 (CH₃ Lev α), 29.7 (CH₃ Lev β), 27.7 (CH₂ Lev), 27.6 (CH₂ Lev), 25.3 (CH₃ AzDMB α), 24.4 (CH₃ AzDMB β). HRMS: [M+H]⁺ calcd for C₂₄H₃₁ClN₃O₉: 540.17433, found 540.17418.



4,6-*O*-(*p*-chlorobenzylidene)-2-*O*-(4-azido-2,2-dimethylbutanoyl)-3-*O*-levulinyl-1-*O*-(*N*-[phenyl]-trifluoroacetimidoyl)- α/β -D-glucopyranoside (21**):**

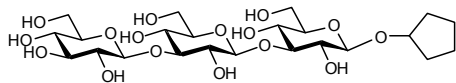
Hemiacetal **20** (1.71 g, 3.17 mmol) was dissolved in acetone (21.1 mL, 0.15M), and the reaction mixture was cooled to 0 °C. *N*-phenyl-trifluoroacetimidoyl chloride (0.66 mL, 4.78 mmol, 1.5 eq.) and Cs₂CO₃ (1.03 g, 3.17 mmol, 1 eq.) were added. The reaction mixture was allowed to warm to rT. After 1 h., TLC analysis showed total conversion into a higher running spot (hexane/EtOAc: 3/1, v/v, R_f 0.41). The reaction mixture was filtered over celite and concentrated. Column chromatography (hexane/EtOAc + 1% TEA: 1/0 \rightarrow 7/3) gave the title compound as an anomeric mixture (α/β : 1/2) and as a transparent oil in 96% yield (1.99 g, 3.03 mmol). IR (neat, cm⁻¹): 2096, 1745, 1716, 1367, 1321, 1267, 1207, 1153, 1116, 1087, 1014, 906, 815, 777, 734, 694, 665. ¹H NMR (400 MHz, 50 °C, CDCl₃, HH-COSY, HSQC): 7.41-7.24 (m, 9H, H_{arom}), 7.14-7.10 (m, 1.5H, H_{arom}), 6.83-6.77 (m, 3H, H_{arom}), 6.51 (s, 0.5H, H-1 α), 5.86 (s, 1H, H-1 β), 5.67 (t, 0.5H, J = 10.0 Hz, H-3 α), 5.49 (s, 0.5H, CH benzyldiene α), 5.46 (s, 1H, CH *p*-chlorobenzylidene β), 5.33 (t, 1H, J = 9.2 Hz, H-3 β), 5.24 (t, 1H, J = 8.0 Hz, H-2 β), 5.10 (dd, 0.5H, J = 10.0 Hz, J = 4.0 Hz, H-2 α), 4.37-4.31 (m, 1.5 H, H-6a α , H-6a β), 4.04-3.95 (m, 0.5H, H-5 α), 3.80-3.72 (m, 3H, H-4 α , H-4 β , H-6b α , H-6b β), 3.50 (m, 1H, H-5 β), 3.31-.26 (m, 3H, CH₂ AzDMB α , CH₂ AzDMB β), 2.71-2.66 (m, 3H, CH₂ Lev α , CH₂ Lev β), 2.61-2.56 (m, 2H, CH₂ Lev α , CH₂ Lev β),

2.18 (s, 4.5H, CH₃ Lev α, CH₃ Lev β). ¹³C APT NMR (100 MHz, 50 °C, CDCl₃, HH-COSY, HSQC): 205.3 (C=O Lev ketone α, C=O Lev ketone β), 175.0 (C=O AzDMB α, C=O AzDMB β), 171.5 (C=O Lev α), 171.4 (C=O Lev ketone β), 142.8 (C_q C_{arom}), 135.3-135.0 (C_q C_{arom}), 128.8 (CH_{arom}), 128.3 (CH_{arom}), 127.7 (CH_{arom}), 127.6 (CH_{arom}), 124.8 (CH_{arom}), 124.6 (CH_{arom}), 119.3 (CH_{arom}), 119.1 (CH_{arom}), 100.9 (CH *p*-chlorobenzylidene α), 100.8 (CH *p*-chlorobenzylidene β), 94.7 (C-1 β), 92.3 (C-1 α), 78.5 (H-4 α), 78.0 (C-4 β), 71.6 (C-3 β), 71.1 (C-2 β), 70.2 (C-2 α), 68.9 (C-3 α), 68.3 (C-6 α), 68.2 (C-6 β), 66.9 (C-5 β), 64.8 (C-5 α), 47.7 (CH₂ AzDMB α), 47.6 (CH₂ AzDMB β), 41.3 (C_q AzDMB α, C_q AzDMB β), 38.4 (CH₂ AzDMB α), 38.2 (CH₂ AzDMB β), 37.6 (CH₂ Lev α, CH₂ Lev β), 29.6 (CH₃ Lev α), 29.5 (CH₃ Lev β), 29.8 (CH₂ Lev α, CH₂ Lev β), 25.0 (CH₃ AzDMB β), 24.8 (CH₃ AzDMB α). HRMS: [M+Na]⁺ calcd for C₃₂H₃₄ClF₃N₄O₉Na: 733.18586, found 733.18592



Cyclopentenyl 4,6-*O*-(*p*-chlorobenzylidene)-3-*O*-[(4,6-*O*-(*p*-chlorobenzylidene)-(3-*O*-(4,6-*O*-(*p*-chlorobenzylidene)-β-D-glucopyranosyl)]-(β-D-glucopyranosyl)-β-D-glucopyranoside (24):

The resin was washed with dry DCM (8x), suspended in DCM (4.5 mL, 0.01M) and purged with argon. Grubbs second-generation catalyst (~3 mg) was added and the resulting brown suspension was allowed to stand at rT for 2 h. The solution was filtered off and the resin was washed with DCM and MeOH. The filtrates were concentrated and the obtained residue was filtered over a plug of silica (DCM/MeOH, 99/1, v/v) and concentrated. The title compound was isolated as a white solid in 36% yield over 8 steps (15 mg, 16 μmol). [α]_D: -6.0 (c = 0.1, ACN). IR (neat, cm⁻¹): 2924, 2854, 1421, 1379, 1265, 1172, 1074, 1014, 915, 732, 702, 621. ¹H NMR (400 MHz, CDCl₃, HH-COSY, HSQC): 7.43 (d, 6H, *J* = 8.0 Hz, H_{arom}), 7.34 (d, 6H, *J* = 8.4 Hz, H_{arom}), 5.71-5.69 (m, 1H, H-3 cyclopentenyl), 5.53 (s, 2H, 2x *CHPh* chlorobenzylidene), 5.50 (s, 1H, *CHPh* chlorobenzylidene), 4.65-4.57 (m, 3H, H-1 cyclopentenyl, 2x H-1), 4.50 (d, 1H, *J* = 8.0 Hz, H-1), 3.35 (dd, 1H, *J* = 10.8 Hz, *J* = 6.0 Hz, H-6a), 4.29-4.24 (m, 2H, 2x H-6a), 3.81-3.75 (m, 7H, 3x H-6b, 3x H-3, H-2), 3.69-3.54 (m, 5H, 2x H-2, 3x H-4), 3.49-3.38 (m, 3H, 3x H-5), 2.70-2.58 (m, 2H, 2x H-2 cyclopentenyl), 2.55-2.47 (m, 2H, 2x H-2 cyclopentenyl). ¹³C APT NMR (100 MHz, CDCl₃, HH-COSY, HSQC): 135.5-135.0 (C_q C_{arom}), 130.9-127.4 (CH_{arom}, C-3 cyclopentenyl), 105.6 (C-1), 105.5 (C-1), 101.8 (C-1), 101.1 (*CHPh* chlorobenzylidene), 100.3 (*CHPh* chlorobenzylidene), 100.2 (*CHPh* chlorobenzylidene), 84.5, 83.5, 80.1, 78.7, 78.6, 75.2, 74.5, 73.9, 73.2 (3x C-2, 3x C-3, 3x C-4), 79.0 (C-1 cyclopentenyl), 68.5 (2x C-6), 68.3 (C-6), 66.9 (C-5), 66.8 (C-5), 66.6 (C-5), 40.2 (C-2 cyclopentenyl), 39.4 (C-2 cyclopentenyl). HRMS: [M+Na]⁺ calcd for C₄₅H₅₁Cl₃O₁₅Na: 959.18219, found 959.18249.



Cyclopentanyl 3-*O*-[(3-*O*-β-D-glucopyranosyl)]-β-D-glucopyranosyl)-β-D-glucopyranoside (25):

Trisaccharide **24** (9 mg, 9.59 μmol) was dissolved in a mixture of THF/H₂O/*tert*-BuOH (2/1/1, v/v/v, 1 mL, 0.01M). The reaction mixture was purged with argon followed by addition of Pd/C (cat.). After stirring under argon for 15 min., the reaction mixture was purged with H₂ (g) and stirred for 2 h. TLC analysis showed total conversion into a single lower running spot (DCM/MeOH, 3/1, v/v, R_f 0.2). The reaction mixture was filtered over a Whatmann filter, washed with H₂O, neutralized with ammonia,²⁰ and concentrated. The obtained residue was subjected to gel filtration (HW-40, 0.15M NH₄OAc in H₂O) and subsequent lyophilization. The deprotected trimer was obtained as a fine white powder in 91% yield (5.0 mg, 8.7 μmol). ¹H NMR (600 MHz, 284 K, D₂O, HH-COSY, HSQC): 4.74 (d, 1H, *J* = 8.4 Hz, H-1), 4.72 (d, 1H, *J* = 7.8 Hz, H-1), 4.50 (d, 1H, *J* = 8.4 Hz, H-1), 4.42-4.40 (m, 1H, H-1 cyclopentanyl), 3.90-3.87 (m, 2H, 2x H-6a), 3.75-3.66 (m, 5H, 3x H-6b, H-3, H-4), 3.52-3.38 (m, 9H, 2x H-2, 2x H-4, 2x H-3, 3x H-5), 3.31 (t, 1H, *J* = 7.8 Hz, H-2), 1.86-1.52 (m, 8H, 4x H-2 cyclopentanyl, 2x H-3 cyclopentanyl). ¹³C NMR (150 MHz, 284 K, D₂O, HH-COSY, HSQC): 103.8 (C-1), 103.5 (C-1), 101.6 (C-1), 85.0 (C-3 or C-4), 84.9 (C-3 or C-4), 83.4 (C-1 cyclopentanyl), 77.0, 76.6, 76.5, 76.5, 74.4, 70.5, 69.1, 69.1 (C-2, 2x C-3, 3x C-4, 3x C-5),

74.3 (C-2), 74.0 (C-2), 61.7 (C-6), 61.7 (C-6), 61.6 (C-6), 33.4 , 32.6 (C-2, C-3 cyclopentanyl). HRMS: [M+Na]⁺ calcd for C₂₃H₄₀O₁₆Na: 595.22086, found 595.22052

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