Tetrahedron 66 (2010) 8036–8046

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of glycosaminoglycan oligosaccharides. Part 5: Synthesis of a putative heparan sulfate tetrasaccharide antigen involved in prion diseases☆

Katalin Daragics, Péter Fügedi *

Department of Carbohydrate Chemistry, Chemical Research Center, Hungarian Academy of Sciences, Pusztaszeri út 59-67, H-1025 Budapest, Hungary

ARTICLE INFO

Article history:
Received 16 April 2010
Received in revised form 12 July 2010
Accepted 3 August 2010
Available online 7 August 2010

Keywords:
Heparan sulfate
Prion diseases
Oligosaccharide synthesis
N-Acetyl-D-glucosamine
Glycosylation
Thioglycosides

ABSTRACT

The synthesis of the putative prion-associated heparan sulfate tetrasaccharide containing two D-glucuronic acid units is reported. Key to the synthesis were the differentiation of the *N*-acetylated and *N*-unsubstituted glucosamine units, the high-yielding glucosylation at O-4 of an *N*-acetyl-D-glucosamine derivative and the α-selective glycosylation of the 4′-OH group of a β-D-Glc*p*A-(1→4)-D-Glc*p*NAc disaccharide building block with a disaccharide thioglycoside donor.

1. Introduction

Heparin (H) and heparan sulfate (HS), members of the glycosaminoglycan (GAG) family, are built up of linear chains of alternating D-glucosamine and hexuronic acid units.[1] They are the most heterogeneous polysaccharides since various epimerization and sulfation patterns may occur along the linear carbohydrate backbone. The uronic acid may be either D-glucuronic acid (GlcA) or L-iduronic acid (IdoA), while *O*-sulfation may occur at the O-2 position of the uronic acids and at the O-3 and/or O-6-positions of the aminosugar. Additionally, the amino group of the D-glucosamine unit can be *N*-sulfated, *N*-acetylated or remain unsubstituted. Heparan sulfate is more heterogeneous than heparin, and it contains more *N*-acetyl-D-glucosamine and D-glucuronic acid units, and less *O*- and *N*-sulfates.

Heparin and heparan sulfate interact and regulate the activity of a large number of proteins, such as coagulation and growth factors, cytokines, chemokines, viral proteins, and others.[2] Though the binding of heparin and heparan sulfate to some proteins are non-specific, many of the biologically relevant interactions of H/HS show a great deal of specificity. It is commonly assumed that specific oligosaccharide structures within the heterogeneous polysaccharide chains are responsible for the binding to individual proteins.[2a]

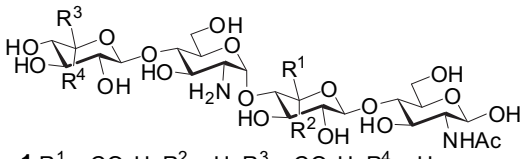
Evidence has been forthcoming for the possible involvement of specific carbohydrate sequences of heparan sulfate in neurodegenerative pathologies, such as Alzheimer's disease and transmissible spongiform encephalopathies (TSEs).[3] TSEs are characterized by the accumulation of scrapie prion protein (PrP^{Sc}),[4] a misfolded, abnormally protease-resistant isoform of the normally existing cellular prion protein (PrP^{C}).[5] In particular, heparan sulfate may play a role in the conversion of PrP^{C} to PrP^{Sc}.[3d,e] This has arisen as a result of the finding that amyloid plaques are rich in heparan sulfate proteoglycans.[3a,c,6] Recently, it has been shown that a heparan sulfate antigen recognized by the monoclonal antibody 10E4 is uniquely codistributed with the abnormal prion protein (PrP^{Sc}) in scrapie infected mice.[7] The antigen-active fragment from heparan sulfate was isolated after partial depolymerization with heparin lyase III, and its structure was determined to be a non-sulfated tetrasaccharide with an inner *N*-unsubstituted D-glucosamine and an *N*-acetyl-D-glucosamine unit at the reducing end (UA-GlcN-UA-GlcNAc).[7] The identity of the uronic acid units was not firmly established, the four possible isomeric structures are shown in Figure 1. There was some evidence that the uronic acid at the non-reducing terminal is D-glucuronic acid and not L-iduronic acid.[7]

In our ongoing program on the preparation of libraries of glycosaminoglycan oligosaccharides,[8] we thought that tetrasaccharide **1** (Fig. 1) could be an interesting synthetic target molecule in

☆ For Part 4, see Ref. 8d.

* Corresponding author. Tel.: +36 1 438 1100; fax: +36 1 438 1145; e-mail address: pfugedi@chemres.hu (P. Fügedi).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.08.004



1 $R^1 = CO_2H$, $R^2 = H$, $R^3 = CO_2H$, $R^4 = H$
2 $R^1 = H$, $R^2 = CO_2H$, $R^3 = CO_2H$, $R^4 = H$
3 $R^1 = CO_2H$, $R^2 = H$, $R^3 = H$, $R^4 = CO_2H$
4 $R^1 = H$, $R^2 = CO_2H$, $R^3 = H$, $R^4 = CO_2H$

Figure 1.

relation to prion-diseases and other neurodegenerative pathologies as, e.g., Alzheimer's disease. Parallel to our work[9] the synthesis of the free tetrasaccharides **1** and **2** has been reported.[10] Additionally, the synthesis of the (2-aminoethylsulfonyl)pentyl α-glycoside of the alternative structure **3** has also been described.[11] Compounds **1** and **2** have been tested using a neoglycolipid technology, and the antibody 10E4 was found to bind neither **1** nor **2**.[10] It should be noted that compounds **1** and **2** were synthesized as free oligosaccharides and tested as anomeric mixtures. Oligosaccharides with free reducing ends are not well suited for biological testing due to their aldehyde-like reactivity. In addition, reaction of the reducing end with the free amino group of the oligosaccharide might occur. This reaction has actually been observed in the synthesis of heparin oligosaccharides and necessitated the resynthesis of the antithrombin III-binding pentasaccharide in the form of its glycoside.[12] We now report on the synthesis of the methyl α-glycoside of compound **1**, in which the reducing end is blocked and its configuration is fixed as the naturally occurring one.

2. Results and discussion

2.1. Synthetic considerations

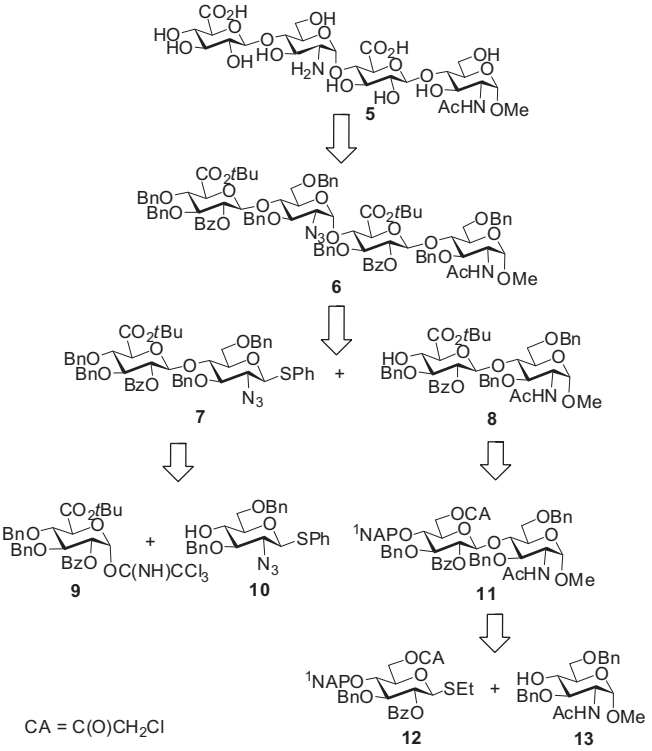
One of the chemical challenges in the synthesis of tetrasaccharides **1**–**4** is the differentiation of the two amino groups of the two D-glucosamine units. Although the chemical syntheses of some HS oligosaccharides containing both *N*-acetylated and *N*-sulfated units have already been described,[13] the type of differentiation needed for target molecule **1** still remains a challenge.[14] Apparently, the most obvious strategy would be to use *N*-acetylated D-glucosamine units for the reducing end. Derivatives of *N*-acetyl-D-glucosamine, however, are known to be poor nucleophiles in glycosylation reactions.[15] The 4-OH group of *N*-acetyl-D-glucosamine is generally considered to have particularly low reactivity: according to competition experiments the 4-OH of a 2-deoxy-2-azido-glucose derivative was ten times more reactive than that of the corresponding *N*-acetyl acceptor.[15b] Furthermore, the oxygen of the acetamido group may act as a competitive nucleophile, leading to the formation of unstable glycosyl imidate side-products.[16] The difficulties caused by the *N*-acetyl group do not seem to be restricted to the glycosylation of the *N*-acetyl-D-glucosamine unit itself. Thus, in an attempted synthesis of the tetrasaccharide **1**, a complete inhibitory effect of a remote *N*-acetyl group upon glycosylations with trichloroacetimidate donors has been observed, even when not the GlcNAc unit itself was glycosylated, but it was present at the reducing end of a disaccharide.[17]

The reactivity problems associated with the *N*-acetyl-D-glucosamine unit are further aggravated by the fact that, compared to other monosaccharides, D-glucuronic acid derivatives are known to be unreactive glycosyl donors.[18] Glycosylations with different types of D-glucuronosyl donors often fail completely or give the desired glycoside in low yields accompanied by side-products, such as orthoesters, acylated acceptors and other types of by-products.[19] The reactivity problems associated with both the glycosyl donor and the acceptor make the direct synthesis of the β-D-Glc*p*A-(1→4)-D-Glc*p*NAc linkage very challenging.[19c] To the best of our knowledge there is only one example of successful direct creation of this bond.[20]

Due to these problems, the syntheses of tetrasaccharides (**1**–**3**) could only be accomplished by indirect ways. One of the indirect routes used an O-1 to N-2 acetyl transfer for the regioselective differentiation of the azide moiety at C-2 of the reducing end.[10] By this method, only the reducing sugars are accessible, in which the anomeric configuration at the reducing end is not fixed. In the other approach, the D-glucosamine units were differentiated by employing an *N*,*N*-diacetyl moiety in the reducing-end unit.[11] The use of this group was also intended to alleviate the reactivity problems associated with the *N*-acetyl group; nevertheless, the yields in the glycosylations were moderate. In addition, the *N*,*N*-diacetyl derivatives proved to be labile not only to basic, but also to acidic conditions, thereby lowering the yields of the total synthesis of the derivative of **3**.

A further challenge in the synthesis is the stereoselective formation of the α-D-Glc*p*N-(1→4)-D-Glc*p*A linkage. It has previously been suggested that this requires the D-glucuronic acid locked in the unusual $^1C_4$ conformation.[21] As conformationally constrained compounds, 1,2-*O*-acetals are proposed. The formation of this type of derivative, however, is possible only for glycosyl acceptors, which are at the reducing end; they cannot be prepared in oligosaccharides in which the anomeric center of the D-glucuronic acid unit is already involved in a glycosidic linkage.

We have developed a synthesis of compound **5** (Scheme 1), the methyl α-glycoside of tetrasaccharide **1**, in which an *N*-acetyl-D-glucosamine unit is used directly at the reducing end and stereoselective formation of the α-D-Glc*p*N-(1→4)-D-Glc*p*A linkage is achieved by using a glycosyl acceptor having the D-glucuronic acid unit in its natural $^4C_1$ conformation.



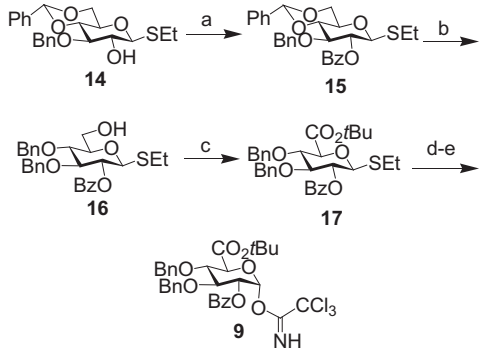
CA = $C(O)CH_2Cl$

Scheme 1. Retrosynthesis of tetrasaccharide **5**.

The synthesis of the tetrasaccharide **5** was envisioned by a convergent 2+2 block synthesis approach to afford the fully protected tetrasaccharide precursor **6** from the disaccharide building blocks **7** and **8** using thioglycoside glycosyl donors in the key glycosylation steps (Scheme 1). The two, differently *N*-substituted, D-glucosamine units were distinguished by using the *N*-acetyl group itself for the reducing-end unit, and masking the free amino group of the interchain D-glucosamine as an azide. To assure 1,2-*trans* selectivity in glycosylations, the benzoyl group, which is known to give cleaner reactions and be less prone to orthoester formation than the commonly used acetyl group,[22] was selected for the protection of O-2 of the D-glucuronic acid units, whereas benzyl groups were used for permanent protection at other positions. The non-reducing end disaccharide building block (**7**) was planned to be prepared by reaction of the D-glucuronic acid trichloroacetimidate **9** with the 2-azido-2-deoxy-D-glucose thioglycoside acceptor (**10**). As discussed above, the synthesis of the reducing-end unit **8** was expected to present difficulties. Therefore, the synthesis was planned so that the critical glycosylations could be performed both on the D-glucose and on the D-glucuronic acid level. Thus, preparation of disaccharide **8** was designed by oxidation from **11**, which should be accessible from the D-glucose thioglycoside donor **12** and the *N*-acetyl-D-glucosamine acceptor **13**. The selection of a pair of orthogonal protecting groups, (1-naphthyl)methyl (^{1}NAP) and chloroacetyl (CA) for O-4 and O-6, respectively, in **12** assured that the coupling leading to the tetrasaccharide, can be performed both on D-glucose and D-glucuronic acid acceptors prepared from the same intermediates.

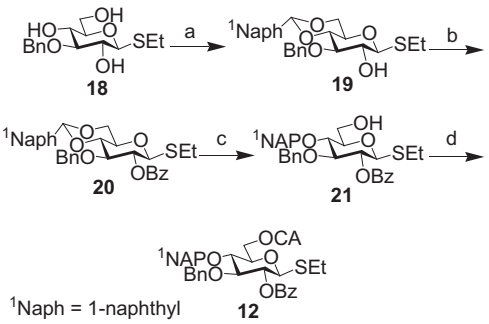
2.2. Synthesis of monosaccharide building blocks

For the synthesis of compound **9**, the known thioglycoside **14**[23] was first benzoylated to give **15** (Scheme 2). Reductive ring-opening of the benzylidene acetal using BH_3·THF–TMSOTf[24] afforded the 4-*O*-benzyl ether **16** in 89% yield. Oxidation of **16** with pyridinium dichromate (PDC) in the presence of acetic anhydride and *tert*-butanol[25] gave the *tert*-butyl D-glucuronate (**17**), which was converted to the corresponding trichloroacetimidate donor (**9**) in two steps in 64% yield.



Scheme 2. Reagents and conditions: (a) BzCl, CH_2Cl_2, pyridine, 91%; (b) BH_3·THF, TMSOTf, CH_2Cl_2, 89%; (c) PDC, Ac_2O, *t*-BuOH, CH_2Cl_2, 74%; (d) NBS, CH_3CN–H_2O 9:1, 65%; (e) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 98%.

For the synthesis of the D-glucose donor **12**, the known triol **18**[23b,26] was reacted with 1-naphthaldehyde dimethyl acetal in the presence of camphorsulfonic acid (CSA) to afford **19** (Scheme 3). After benzoylation of the free hydroxyl group, regioselective reductive opening of the (1-naphthyl)methylene acetal of **20** with BH_3·THF–TMSOTf gave the corresponding 4-*O*-(1-naphthyl) methyl derivative **21** in 90% yield. Chloroacetylation of **21** afforded the D-glucose thioglycoside donor **12** in 87% yield.

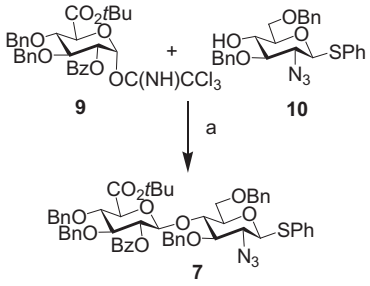


Scheme 3. Reagents and conditions: (a) ^{1}NaphCH(OMe)$_2$, CSA, DMF, 84%; (b) BzCl, pyridine, 94%; (c) BH_3·THF, TMSOTf, CH_2Cl_2, 90%; (d) $(ClCH_2CO)_2O$, Et_3N, CH_2Cl_2, -30 °C, 87%.

The *N*-acetyl-D-glucosamine acceptor **13**[27] and the 2-azido-2-deoxy-D-glucose acceptor **10**[28] were prepared by literature methods.

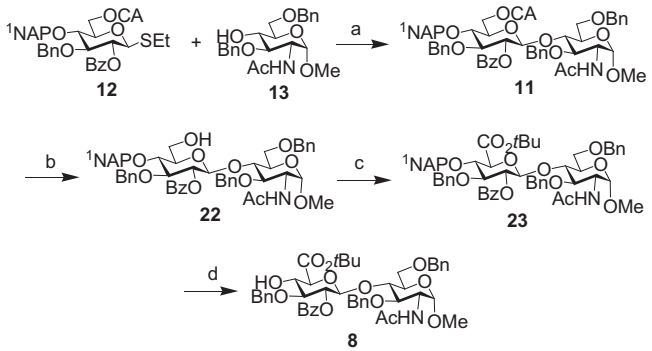
2.3. Synthesis of disaccharide building blocks

The synthesis of the non-reducing end disaccharide building block **7** was smoothly accomplished by TMSOTf-catalyzed reaction of the 2-*O*-benzoyl-protected D-glucuronic acid imidate **9** with the azido acceptor **10**, the reaction provided the desired disaccharide donor **7** in 89% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) TMSOTf, toluene, −30 °C, 89%.

For the synthesis of the disaccharide glycosyl acceptor **8** (Scheme 5), the glycosylation of the *N*-acetyl-D-glucosamine acceptor **13** with the D-glucose donor **12** was studied using different promoters (Table 1). Reactions promoted by dimethyl(methylthio) sulfonium triflate (DMTST),[22] and dimethyl disulfide-triflic anhydride[29] gave **11** in 64% and 50% yield, respectively. The best yield was obtained by using methyl triflate,[30] in this reaction **11** was obtained in 81% yield.



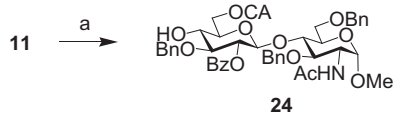
Scheme 5. Reagents and conditions: (a) see Table 1; (b) HDTC, DMF, 77%; (c) PDC, Ac_2O, *t*-BuOH, CH_2Cl_2, 73%; (d) CAN, MeCN-H_2O 9:1, 77%.

Table 1
Reaction of donor **12** and acceptor **13** using different promoters

Entry	Promoter	Equiv of promoter (equiv)	Reaction temperature	Reaction time (h)	Isolated yield of **11** (%)
1	DMTST	4	0 °C→rt	4	64
2	Me_2S_2–Tf_2O	1.5	0 °C	2	50
3	MeOTf	4	0 °C→rt	4	81

Removal of the temporary chloroacetyl protecting group by hydrazinedithiocarbonate (HDTC)[31] afforded the alcohol **22**. Oxidative esterification of **22** using PDC in the presence of acetic anhydride and *tert*-butanol afforded the *tert*-butyl uronate **23**. The D-glucuronic acid glycosyl acceptor **8** was obtained by oxidative removal of the (1-naphthyl)methyl group with ceric ammonium nitrate (CAN)[8b] in 77% yield.

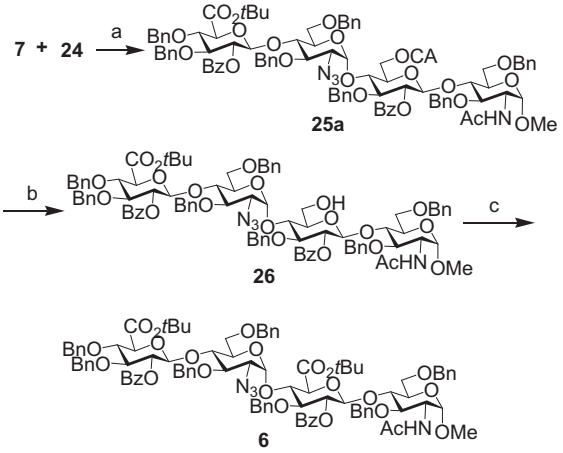
Another disaccharide acceptor containing a free hydroxyl group at O-4 on a D-glucose unit was synthesized by removing the temporary (1-naphthyl)methyl group of **11** by CAN to give **24** (Scheme 6).



Scheme 6. Reagents and conditions: (a) CAN, MeCN–H_2O 9:1, 71%.

2.4. Synthesis of the protected tetrasaccharide

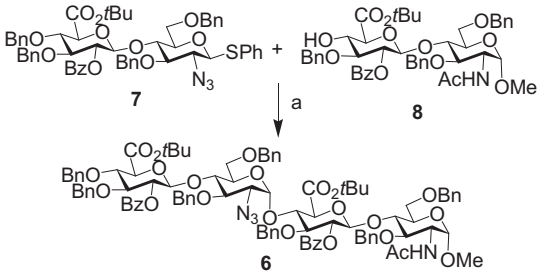
DMTST-promoted glycosylation of the D-glucose-containing disaccharide acceptor **24** with the disaccharide thioglycoside **7** afforded the α-linked tetrasaccharide **25α** as the major product, isolated in 40% yield (Scheme 7). The β-linked tetrasaccharide **25β** was also obtained in 14% yield. The anomeric configuration of **25α** is supported by the $^3J_{1c,2c}$ and $^1J_{C\text{-}1c,H\text{-}1c}$ coupling constants being 4.0 Hz and 176.5 Hz, respectively, whereas the corresponding values for **25β** were 9.5 Hz and 165.0 Hz.[32]



Scheme 7. Reagents and conditions: (a) DMTST, Et_2O, CH_2Cl_2, 40%; (b) HDTC, DMF, 55%; (c) PDC, Ac_2O, *t*-BuOH, CH_2Cl_2, 53%.

Removal of the temporary chloroacetyl protecting group from **25α** by HDTC then afforded the alcohol **26**, which was oxidized to the desired tetrasaccharide **6**.

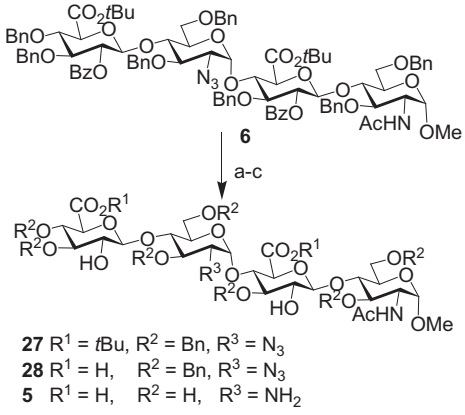
The direct route to **6** involved the glycosylation of the D-glucuronic acid-containing disaccharide acceptor **8** with the disaccharide thioglycoside donor **7**. Interestingly, methyl triflate-promoted glycosylation, which afforded the best results in the preparation of disaccharide **11** (Table 1), gave none of the desired tetrasaccharide **6**. On the other hand, glycosylation of the disaccharide acceptor **8** with the thioglycoside **7** using DMTST as promoter resulted stereoselectively in the α-linked tetrasaccharide **6**, isolated in 56% yield (Scheme 8). In contrast to the glycosylation of the acceptor **23** with the same donor, no β-linked tetrasaccharide could be isolated from this reaction. The successful glycosylation of the *N*-acetyl-D-glucosamine-containing acceptor also suggests that the previously reported inhibitory effect of the remote *N*-acetyl group might be overcome by the appropriate choice of the donor and the promoter.



Scheme 8. Reagents and conditions: (a) DMTST, Et_2O, CH_2Cl_2, 56%.

2.5. Preparation of the unprotected heparan sulfate tetrasaccharide

For the conversion of the protected tetrasaccharide **6** to the target compound **5**, **6** was first debenzoylated using sodium hydroxide in tetrahydrofuran–methanol (Scheme 9). Under the conditions employed possible β-elimination in the D-glucuronic acid units was avoided. The *tert*-butyl uronates of **27** were hydrolyzed next with 20% trifluoroacetic acid in dichloromethane, and then catalytic hydrogenation of **28** with palladium on carbon removed the benzyl groups and reduced the azido group, to afford the methyl α-glycoside of the heparan sulfate tetrasaccharide **5**.



Scheme 9. Reagents and conditions: (a) NaOH, THF, MeOH, 64%; (b) TFA, CH_2Cl_2, 91%; (c) Pd–C, MeOH, 70%.

3. Conclusion

The synthesis of the methyl α-glycoside (**5**) of the putative prion-associated tetrasaccharide **1** was accomplished in a highly stereoselective manner without masking the *N*-acetyl group at the reducing end. Glycosylations, which are considered problematic in the literature were successfully accomplished. Thus, high-yielding glycosylation of the unreactive 4-OH group of an *N*-acetyl-D-glucosamine

acceptor and α-selective glycosylation of the 4′-OH group of a β-D-Glc*p*A-(1→4)-D-Glc*p*NAc disaccharide building block were achieved by using thioglycoside glycosyl donors.

4. Experimental

4.1. General methods

Evaporations were performed under reduced pressure on rotary evaporators with bath temperatures not exceeding 40 °C. All reactions sensitive to air or moisture were carried out under argon atmosphere with anhydrous solvents. Air- and moisture-sensitive liquids and solutions were transferred via a syringe. Molecular sieves (4 Å) were flame dried before use. Dichloromethane was distilled from CaH_2, and stored over 4 Å molecular sieves. Solvents used for column chromatography were of technical grade and distilled before use. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (E. Merck, Darmstadt), the compounds were detected under UV light and by spraying the plates with a 0.02 M solution of resorcinol in 20% methanolic H_2SO_4 followed by heating. For column chromatography silica gel 60 (0.040–0.063 mm) (E. Merck) was employed. Melting points were determined in capillary tubes on a Griffin melting point apparatus and are uncorrected. Optical rotations were measured at rt with an Optical Activity P-2000 (Jasco) polarimeter. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. The NMR spectra were recorded on Varian Unity Inova 5000 (^{1}H: 500 MHz, ^{13}C: 125 MHz), Varian Unity Inova 3000 (^{1}H: 300 MHz; ^{13}C: 75 MHz), and Varian Unity Inova 2000 (^{1}H: 200 MHz; ^{13}C: 50 MHz) spectrometers at ambient temperature in $CDCl_3$, and assigned using 2D-methods (COSY, HSQC). The chemical shifts were referenced to TMS (0.00 ppm for ^{1}H) and to the central line of $CDCl_3$ (77.0 ppm for ^{13}C), and to the methyl signal of acetone (2.22 ppm for ^{1}H, 30.89 ppm for ^{13}C) for solutions in D_2O, as internal standards. Elemental analyses were performed with an Elementar Vario EL III instrument at the Analytical Department of the Chemical Research Center, Hungarian Academy of Sciences.

4.2. Ethyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (15)

Benzoyl chloride (2.8 mL, 24 mmol, 2 equiv) was added dropwise to a solution of **14**[23] (4.83 g, 12 mmol) in a mixture of dry CH_2Cl_2 (25 mL) and dry pyridine (20 mL) at 0 °C. The reaction mixture was stirred at rt overnight, after which the reaction was quenched with water (5 mL). The mixture was diluted with CH_2Cl_2 (500 mL), was washed with 2 M aq HCl (200 mL), saturated aq $NaHCO_3$ (200 mL) and water (200 mL), dried, and concentrated. Purification by column chromatography (toluene–acetone, 95:5→9:1) afforded **15** as white crystals (5.52 g, 91%); R_f (toluene–acetone, 9:1) 0.84; mp 124–125 °C (from EtOAc–hexanes); lit.[23b] 127 °C; $[\alpha]_D$ +26 (*c* 0.63, $CHCl_3$); lit.[23b] $[\alpha]_D$ −50 (*c* 0.10, $CHCl_3$); lit.[33] $[\alpha]_D$ +25.5 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00–7.08 (m, 15H, aromatic), 5.62 (s, 1H, PhCH), 5.34 (dd, 1H, $J_{1,2}$ 10.1 Hz, $J_{2,3}$ 8.8 Hz, H-2), 4.83 (d, 1H, *J* 11.9 Hz, ½PhCH_2), 4.68 (d, 1H, *J* 11.9 Hz, ½PhCH_2), 4.62 (d, 1H, $J_{1,2}$ 10.1 Hz, H-1), 4.41 (dd, 1H, $J_{5,6a}$ 4.8 Hz, $J_{6a,6b}$ 10.4 Hz, H-6a), 3.95–3.78 (m, 3H, H-3,4,6b), 3.56 (ddd, 1H, $J_{4,5}$ 2.8 Hz, $J_{5,6a}$ 4.8 Hz, $J_{5,6b}$ 9.4 Hz, H-5), 2.72 (q, 2H, SCH_2CH$_3$), 1.22 (t, 3H, *J* 7.4 Hz, SCH$_2$CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3 (C(O)Ph), 137.9, 137.3, 133.3, 130.0, 129.9, 129.2, 128.5, 128.4, 128.3, 128.2, 127.7, 126.1 (aromatic), 101.4 (PhCH), 84.4 (C-1), 81.8 and 79.3 (C-3, C-4), 74.3 (PhCH_2), 72.5 (C-2), 70.8 (C-5), 68.6 (C-6), 24.1 (SCH_2CH$_3$), 14.9 (SCH$_2$CH_3). Anal. Calcd for $C_{29}H_{30}O_6S$: C, 68.75; H, 5.97; S, 6.33. Found: C, 68.57; H, 5.98; S, 6.35.

4.3. Ethyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside (16)

To a solution of **15** (5.06 g, 10 mmol) in dry CH_2Cl_2 (80 mL), a 1 M solution of borane in THF (20 mL, 20 mmol, 2 equiv) was added followed by TMSOTf (0.27 mL, 1.5 mmol, 0.15 equiv) and the mixture was stirred under argon at rt. After 3 h, TLC (toluene–acetone, 9:1) indicated the disappearance of the starting material. Et_3N (5 mL) was added, followed by careful addition of MeOH (10 mL) until the evolution of H_2 ceased. The mixture was concentrated, and the residue was co-evaporated with MeOH (35 mL) three times. Purification of the residue by silica gel column chromatography (toluene–acetone, 95:5→9:1) afforded **16** as white crystals (4.52 g, 89%); R_f (toluene–acetone, 9:1) 0.46; mp 91–92 °C (from EtOAc–hexanes); $[\alpha]_D$ +33.5 (*c* 0.26, $CHCl_3$); IR ν_{max} (film): 2961, 1722, 1266, 1093, 1028, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04–7.10 (m, 15H, aromatic), 5.28 (dd, 1H, $J_{1,2}$ 10.0 Hz, $J_{2,3}$ 9.0 Hz, H-2), 4.86 (d, 1H, *J* 10.7 Hz, ½PhCH_2), 4.82–4.71 (m, 2H, PhCH_2), 4.68 (d, 1H, *J* 11.0 Hz, ½PhCH_2), 4.57 (d, 1H, $J_{1,2}$ 10 Hz, H-1), 3.94–3.66 (m, 4H, H-3,4,6a,6b), 3.58 (ddd, 1H, $J_{4,5}$ 9.4 Hz, $J_{5,6a}$ 4.8 Hz, $J_{5,6b}$ 2.8 Hz, H-5), 2.70 (q, 2H, SCH_2CH$_3$), 2.02 (s, 1H, OH), 1.22 (t, 3H, *J* 7.5 Hz, SCH$_2$CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3 (C(O)Ph), 137.8, 137.7, 133.2, 129.8, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7 (aromatic), 84.1 (C-1), 83.8 (C-3), 79.8 and 77.7 (C-4, C-5), 75.3 and 75.2 (2 PhCH_2), 72.5 (C-2), 62.1 (C-6), 24.1 (SCH_2CH$_3$), 14.9 (SCH$_2$CH_3). Anal. Calcd for $C_{29}H_{32}O_6S$: C, 68.48; H, 6.34; S, 6.30. Found: C, 68.30; H, 6.36; S, 6.32.

4.4. *tert*-Butyl (ethyl 3,4-di-*O*-benzyl-2-*O*-benzoyl-1-thio-β-D-glucopyranoside)uronate (17)

To a solution of **16** (4.07 g, 8 mmol) in dry CH_2Cl_2 (60 mL), PDC (6.02 g, 16 mmol, 2 equiv), Ac_2O (7.6 mL, 80 mmol, 10 equiv), and *tert*-butyl alcohol (15.3 mL, 160 mmol, 20 equiv) were added. The mixture was stirred for 3 h at rt, and it was then applied on the top of a silica gel column having a layer of EtOAc. The chromium compounds were allowed to precipitate in the presence of EtOAc and after 30 min the product was eluted with EtOAc. After evaporating the solvent, the residue was purified by column chromatography (toluene–acetone, 98:2→95:5) to give **17** as white crystals (3.42 g, 74%); R_f (toluene–acetone, 95:5) 0.71; mp 109–110 °C (from EtOAc–hexanes); $[\alpha]_D$ +6.3 (*c* 0.41, $CHCl_3$); IR ν_{max} (film): 2977, 1732, 1453, 1368, 1265, 1154, 1070, 1026, 750, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04–7.10 (m, 15H, aromatic), 5.34 (dd, 1H, $J_{1,2}$ 9.9 Hz, $J_{2,3}$ 8.6 Hz, H-2), 4.83 (d, 1H, *J* 10.7 Hz, ½PhCH_2), 4.77–4.69 (m, 2H, PhCH_2), 4.64 (d, 1H, *J* 11.0 Hz, ½PhCH_2), 4.56 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 4.03–3.85 (m, 2H, H-4,5), 3.83 (dd, 1H, $J_{2,3}$ 8.6 Hz, $J_{3,4}$ 9.0 Hz, H-3), 2.73 (m, 2H, SCH_2CH$_3$), 1.49 (s, 9H, C(CH_3)$_3$), 1.23 (t, 3H, *J* 7.5 Hz, SCH$_2$CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.1 (C-6), 165.2 (C(O)Ph), 137.9, 137.6, 133.2, 129.8, 128.4, 128.3, 128.2, 128.0, 127.8, 127.71, 127.67 (aromatic), 84.0 and 83.4 (C-1, C-3), 82.4 (*C*(CH$_3$)$_3$), 79.5 (2C, C-4, C-5), 75.2 and 75.1 (2 PhCH_2), 72.0 (C-2), 27.9 (C(*C*H$_3$)$_3$), 23.9 (SCH_2CH$_3$), 14.9 (SCH$_2$CH_3). Anal. Calcd for $C_{33}H_{38}O_7S$: C, 68.49; H, 6.62; S, 5.54. Found: C, 68.31; H, 6.64; S, 5.55.

4.5. *tert*-Butyl (2-*O*-benzoyl-3,4-di-*O*-benzyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranose)uronate (9)

To a solution of **17** (2.72 g, 4.7 mmol) in 95% aq MeCN (30 mL), *N*-bromosuccinimide (0.962 g, 5.4 mmol, 1.15 equiv) was added at 0 °C. After stirring for 30 min at rt, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ solution, diluted and extracted with CH_2Cl_2, washed with water, dried, and concentrated. Purification by column chromatography (toluene–acetone, 95:5→9:1) afforded the crude hemiacetal as white crystals (1.64 g,

65%); mp 139–140 °C (from EtOAc–hexanes); $[\alpha]_D$ +77 (*c* 0.52, $CHCl_3$). The hemiacetal was then dissolved in dry CH_2Cl_2 (20 mL) at 0 °C under argon, followed by addition of CCl_3CN (3.0 mL, 30 mmol, 10 equiv) and DBU (0.114 mL, 0.76 mmol, 0.25 equiv). After stirring for 1 h at 0 °C, TLC showed completion of reaction and the product was purified by flash chromatography over a short silica gel column (hexanes–EtOAc 4:1, +1% Et_3N) to yield **9** (2.04 g, 98%) as a colorless syrup (pure α-product); R_f (hexanes–EtOAc 4:1, +0.5% Et_3N) 0.41; $[\alpha]_D$ +78 (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.53 (s, 1H, NH), 7.96–7.92 (dd, 2H, aromatic), 7.56–7.16 (m, 13H, aromatic), 6.66 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.40 (dd, 1H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2), 4.88 (d, 1H, *J* 10.5 Hz, ½$PhCH_2$), 4.79 (2d, 2H, *J* 11.0 Hz, $PhCH_2$), 4.71 (d, 1H, *J* 10.5 Hz, ½$PhCH_2$), 4.42–4.21 (m, 2H, H-4,5), 4.02 (dd, 1H, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 9.4 Hz, H-3), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.4 (C-6), 165.5 (C(O)Ph), 160.5 (CNH), 137.8, 133.4, 129.9, 129.3, 128.5 (2C), 128.4, 128.1, 128.0, 127.9 and 127.8 (aromatic), 93.9 (C-1), 82.8 ($C(CH_3)_3$), 79.4 and 78.7 (C-3, C-4), 75.60 and 75.55 (2 $PhCH_2$), 74.1 (C-5), 72.4 (C-2), 28.0 ($C(CH_3)_3$); MS-ESI: $[M+Na]^+$ 700.3. Anal. Calcd for $C_{33}H_{34}Cl_3NO_8$: C, 58.38; H, 5.05; N, 2.06. Found: C, 58.19; H, 5.08; N, 2.07.

4.6. Ethyl 3-*O*-benzyl-4,6-*O*-(1-naphthyl)methylene-1-thio-β-D-glucopyranoside (19)

To a solution of **18**[23b,26] (3.77 g, 12 mmol) in dry DMF (25 mL), 1-naphthaldehyde dimethyl acetal (3.8 mL, 18 mmol, 1.5 equiv), and CSA (0.28 g, 1.2 mmol) were added. The mixture was stirred at 50 °C under reduced pressure (30 mbar) for 4 h, neutralized with saturated aq $NaHCO_3$ (10 mL), and concentrated. To the residue, hexanes (100 mL) and water (100 mL) were added, and the mixture was stirred overnight. The precipitated crystalline material was filtered off and crystallized from EtOAc–hexanes to afford **19** as white crystals (4.57 g, 84%); R_f (toluene–acetone, 9:1) 0.48; mp 170–171 °C; $[\alpha]_D$ −12 (*c* 0.23, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18–8.12 (dd, 1H, aromatic), 7.90–7.75 (m, 3H, aromatic), 7.54–7.24 (m, 8H, aromatic), 6.12 (s, 1H, ^{1}NaphCH), 4.88 (d, 1H, *J* 11.5 Hz, ½$PhCH_2$), 4.72 (d, 1H, *J* 11.5 Hz, ½$PhCH_2$), 4.52 (d, 1H, $J_{1,2}$ 9.7 Hz, H-1), 4.46 (dd, 1H, $J_{5,6a}$ 4.8 Hz, $J_{6a,6b}$ 10.4 Hz, H-6a), 3.96–3.83 (m, 2H, H-4,6b), 3.74–3.62 (m, 3H, H-2,3,5), 2.75 (q, 2H, *J* 7.5 Hz, S$CH_2$$CH_3$), 2.56 (d, 1H, $J_{2,OH}$ 1.8 Hz, OH), 1.32 (t, 3H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 133.9, 132.5, 130.6, 129.9, 128.7, 128.5, 128.2, 127.9, 126.4, 125.8, 125.1, 124.2, 124.0 (aromatic), 100.4 (^{1}NaphCH), 86.8 (C-1), 81.8 and 81.6 (C-3, C-4), 74.8 ($PhCH_2$), 73.2 (C-2), 70.9 (C-5), 69.0 (C-6), 24.6 (SCH_2CH_3), 15.3 (SCH_2CH_3). Anal. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24; S, 7.08. Found: C, 68.82; H, 6.26; S, 7.10.

4.7. Ethyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-(1-naphthyl) methylene-1-thio-β-D-glucopyranoside (20)

Benzoyl chloride (0.87 mL, 7.5 mmol, 1.5 equiv) was added dropwise to a solution of **19** (2.26 g, 5 mmol) in a mixture of dry CH_2Cl_2 (10 mL) and dry pyridine (10 mL) at 0 °C. The mixture was stirred at rt overnight, after which the reaction was quenched with water (5 mL). The mixture was diluted with CH_2Cl_2 (300 mL), washed with 2 M aq HCl (150 mL), saturated aq $NaHCO_3$ (150 mL) and water (150 mL), dried, and concentrated. The residue was purified by column chromatography (toluene–acetone, 95:5→9:1) to give **20** as white crystals (2.62 g, 94%); R_f (toluene–acetone, 9:1) 0.80; mp 145–147 °C (from EtOAc–hexanes), $[\alpha]_D$ +45 (*c* 0.95, $CHCl_3$); IR ν_{max} (film): 2871, 1727, 1453, 1268, 1105, 1070, 1026, 755, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20–8.14 (dd, 1H, aromatic), 8.05–7.99 (dd, 1H, aromatic), 7.92–7.78 (m, 3H, aromatic), 7.62–7.42 (m, 7H, aromatic), 7.12–6.99 (m, 5H, aromatic), 6.14 (s, 1H, ^{1}NaphCH), 5.39 (dd, 1H, $J_{1,2}$ 10.0 Hz, $J_{2,3}$ 8.4 Hz, H-2), 4.75 (d, 1H, *J* 11.8 Hz, ½$PhCH_2$), 4.66 (d, 1H, $J_{1,2}$ 10.0 Hz, H-1), 4.58 (d, 1H, *J* 11.8 Hz, ½$PhCH_2$), 4.51 (dd, 1H, $J_{5,6a}$ 4.9 Hz, $J_{6a,6b}$ 10.4 Hz, H-6a), 4.04–3.86 (m, 3H, H-3,4,6b), 3.69 (ddd, 1H, $J_{4,5}$ 9.5 Hz, $J_{5,6a}$ 4.9 Hz, $J_{5,6b}$ 9.6 Hz, H-5), 2.76 (dq, 2H, *J* 7.5 Hz, S$CH_2$$CH_3$), 1.24 (t, 3H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.2 (C(O)Ph), 137.8, 133.9, 133.2, 132.4, 130.0, 129.9, 128.7, 128.4, 128.1, 127.6, 126.4, 125.8, 125.1, 124.2, 124.0 (aromatic), 100.5 (^{1}NaphCH), 84.5 (C-1), 82.2 and 79.4 (C-3, C-4), 74.4 ($PhCH_2$), 72.1 (C-2), 70.9 (C-5), 69.0 (C-6), 24.1 (SCH_2CH_3), 14.9 (SCH_2CH_3). Anal. Calcd for $C_{33}H_{32}O_6S$: C, 71.20; H, 5.79; S, 5.76. Found: C, 71.01; H, 5.81; S, 5.77.

4.8. Ethyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl)methyl-1-thio-β-D-glucopyranoside (21)

To a solution of **20** (2.50 g, 4.5 mmol) in dry CH_2Cl_2 (20 mL), a 1 M solution of borane in THF (9 mL, 9 mmol, 2 equiv) was added followed by TMSOTf (0.12 mL, 0.67 mmol, 0.15 equiv) and the mixture was stirred under argon at rt. After 3 h, TLC (toluene–acetone, 9:1) indicated the disappearance of the starting material. Et_3N (2 mL) was added, followed by careful addition of MeOH (5 mL) until the evolution of H_2 ceased. The mixture was concentrated and the residue was co-evaporated with MeOH (25 mL) three times. Purification of the residue by silica gel column chromatography (toluene–acetone, 95:5→9:1) afforded **21** as white crystals (2.26 g, 90%); R_f (toluene–acetone, 9:1) 0.35; mp 122–123 °C (from EtOAc–hexanes); lit.[24] mp 119–120 °C; $[\alpha]_D$ +56 (*c* 0.50, $CHCl_3$); lit.[24] $[\alpha]_D$ +54 (*c* 0.47, $CHCl_3$); IR ν_{max} (film): 2959, 1726, 1267, 1070, 775, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08–7.96 (m, 3H, aromatic), 7.90–7.78 (m, 2H, aromatic), 7.60–7.38 (m, 7H, aromatic), 7.16–7.10 (m, 5H, aromatic), 5.41 (d, 1H, *J* 11.7 Hz, ½$NaphCH_2$), 5.33 (dd, 1H, $J_{2,3}$ 8.8 Hz, H-2), 5.12 (d, 1H, *J* 11.7 Hz, ½$NaphCH_2$), 4.74 (2d, 2H, *J* 11.0 Hz, $PhCH_2$), 4.58 (d, 1H, $J_{1,2}$ 10.2 Hz, H-1), 3.93 (dd, 1H, $J_{3,4}$ 9.2 Hz, H-3), 3.83 (dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 3.77 (m, 1H, H-6a), 3.62 (dd, 1H, *J* 2.6 Hz, *J* 7.3 Hz, H-6b), 3.48 (m, 1H, H-5), 2.72 (q, 2H, *J* 7.4 Hz, S$CH_2$$CH_3$), 1.88 (t, 1H, *J* 6.6 Hz, OH), 1.25 (t, 3H, *J* 7.4 Hz, SCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.4 (C(O)Ph), 137.9 133.9, 133.8, 133.3, 131.6, 129.9, 129.0, 128.8, 128.6, 128.4, 128.0, 127.8, 126.8, 126.5, 126.0, 125.4, 123.8 (aromatic), 84.6 (C-1), 83.9 (C-3), 79.9 and 77.6 (C-4, C-5), 75.3 ($PhCH_2$), 73.0 ($PhCH_2$), 72.8 (C-2), 62.2 (C-6), 24.2 (SCH_2CH_3), 15.0 (SCH_2CH_3). Anal. Calcd for $C_{33}H_{34}O_6S$: C, 70.94; H, 6.13; S, 5.74. Found: C, 70.79; H, 6.15; S, 5.76.

4.9. Ethyl 2-*O*-benzoyl-3-*O*-benzyl-6-*O*-chloroacetyl-4-*O*-(1-naphthyl)methyl-1-thio-β-D-glucopyranoside (12)

To a stirred solution of **21** (1.90 g, 3.4 mmol) in dry CH_2Cl_2 (20 mL), Et_3N (0.94 mL, 6.8 mmol, 2 equiv) was added, then a solution of 90% chloroacetic anhydride (0.70 g, 3.7 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at −30 °C. The mixture was stirred for 30 min at −30 °C under argon, after which the reaction was quenched with water (5 mL), diluted with CH_2Cl_2 (400 mL), washed with 2 M aq HCl (150 mL), saturated aq $NaHCO_3$ (150 mL) and water (150 mL), dried, and concentrated. The residue was purified by column chromatography (toluene–acetone, 95:5→9:1) to give **12** as white crystals (1.88 g, 87%); R_f (toluene–acetone, 9:1) 0.58; mp 89–90 °C (from EtOAc–hexanes); $[\alpha]_D$ +85 (*c* 0.28, $CHCl_3$); IR ν_{max} (film): 2349, 1724, 1632, 1451, 1267, 1167, 1089, 1026, 773, 710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06–8.02 (dd, 2H, aromatic), 7.99–7.96 (dd, 1H, aromatic), 7.88–7.81 (m, 2H, aromatic), 7.59–7.38 (m, 7H, aromatic), 7.18–7.13 (m, 5H, aromatic), 5.40 (d, 1H, *J* 11.8 Hz, ½$NaphCH_2$), 5.34 (dd, 1H, $J_{1,2}$ 9.9 Hz, $J_{2,3}$ 8.8 Hz, H-2), 5.07 (d, 1H, *J* 11.8 Hz, ½$NaphCH_2$), 4.76 (2d, 2H, *J* 11.9 Hz, $PhCH_2$), 4.54 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 4.31 (dd, 1H, $J_{5,6a}$ 2.0 Hz, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.99 (dd, 1H, $J_{5,6b}$ 4.4 Hz, H-6b), 3.94 (dd, 1H, $J_{3,4}$ 8.8 Hz, H-3), 3.87 (d, 1H, *J* 14.9 Hz, CH_2Cl), 3.79 (dd, 1H, $J_{3,4}$ 8.8 Hz, $J_{4,5}$ 9.9 Hz, H-4), 3.76 (d, 1H, *J* 14.9 Hz, CH_2Cl), 3.60 (m, 1H, H-5), 2.66

(m, 2H, SCH_2CH_3), 1.19 (t, 3H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5 ($C(O)CH_2Cl$), 165.2 (C(O)Ph), 137.4, 133.6, 133.2, 133.1, 131.5, 129.8, 129.7, 129.0, 128.7, 128.4, 128.3, 127.9, 127.7, 127.1, 126.5, 125.9, 125.2, 123.5 (aromatic), 84.7 (C-3), 83.5 (C-1), 76.7 (C-5), 76.0 (C-4), 75.3 (CH_2Ph), 72.5 ($NaphCH_2$), 72.3 (C-2), 64.3 (C-6), 40.5 (CH_2Cl), 24.0 (SCH_2CH_3), 14.9 (SCH_2CH_3). Anal. Calcd for $C_{35}H_{35}ClO_7S$: C, 66.18; H, 5.55; S, 5.05. Found: C, 66.01; H, 5.57; S, 5.06.

4.10. Phenyl [*tert*-butyl (2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside) (7)

A mixture of **9** (2.04 g, 3 mmol, 1.36 equiv), **10** (1.05 g, 2.2 mmol), and freshly activated 4 Å molecular sieves (2 g) in dry toluene (30 mL) was stirred at −30 °C under argon for 30 min. Then TMSOTf (0.136 mL, 0.75 mmol, 0.25 equiv) was added dropwise. After stirring at −30 °C for 1 h, the reaction was quenched by the addition of Et_3N (2 mL). The mixture was filtered through a pad of Celite, the filtrate was diluted with CH_2Cl_2 (400 mL) and washed with 2 M aq HCl (150 mL), saturated aq $NaHCO_3$ (150 mL), and water (150 mL); it was dried and concentrated. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 9:1→4:1) to provide disaccharide **6** (1.94 g, 89%) as a colorless syrup; R_f (hexanes–EtOAc, 4:1) 0.46; $[\alpha]_D$ −18.5 (*c* 0.38, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.90–7.87 (dd, 2H, aromatic), 7.55–7.05 (m, 28H, aromatic), 5.31 (dd, 1H, $J_{2d,3d}$ 9.1 Hz, $J_{2d,1d}$ 8.3 Hz, H-2d), 5.11 (d, 1H, *J* 11.1 Hz, ½$PhCH_2$), 4.82 (d, 1H, $J_{1d,2d}$ 8.3 Hz, H-1d), 4.80 (d, 1H, *J* 10.3 Hz, ½$PhCH_2$), 4.74–4.62 (m, 4H, 2 $PhCH_2$), 4.58 (d, 1H, *J* 11.2 Hz, ½$PhCH_2$), 4.37 (d, 1H, *J* 12.1 Hz, ½$PhCH_2$), 4.22 (d, 1H, $J_{1c,2c}$ 10.2 Hz, H-1c), 4.01 (dd, 1H, $J_{4d,3d}$ 9.0 Hz, $J_{4d,5d}$ 9.1 Hz, H-4d), 3.97 (dd, 1H, $J_{4c,3c}$ 9.0 Hz, $J_{4c,5c}$ 9.4 Hz, H-4c), 3.82 (d, 1H, $J_{4d,5d}$ 9.1 Hz, H-5d), 3.69 (dd, 1H, $J_{3d,2d}$ 9.1 Hz, $J_{3d,4d}$ 9.0 Hz, H-3d), 3.66 (dd, 1H, $J_{5c,6c}$ 3.3 Hz, $J_{6c,6c'}$ 11.2 Hz, H-6c), 3.49 (dd, 1H, $J_{5c,6c'}$ 1.4 Hz, H-6c′), 3.39 (dd, 1H, $J_{3c,2c}$ 9.5 Hz, $J_{3c,4c}$ 9.0 Hz, H-3c), 3.27 (dd, 1H, $J_{2c,3c}$ 9.5 Hz, $J_{2c,1c}$ 10.2 Hz, H-2c), 3.09 (m, 1H, H-5c), 1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0 (C-6d), 164.6 (C(O)Ph), 138.1, 137.9, 137.8, 137.4, 133.3, 133.2, 131.1, 129.5, 129.3, 128.9, 128.8, 128.48, 128.45, 128.40, 128.2, 128.12, 128.10, 128.08, 127.81, 127.77, 127.6, 127.5, 127.4, 125.2 (aromatic), 100.3 (C-1d), 86.0 (C-1c), 82.4 ($C(CH_3)_3$), 82.3 (C-3c), 81.6 (C-3d), 79.6 (C-4d), 78.6 (C-5c), 76.0 (C-4c), 75.6 (C-5d), 75.3, 74.8, and 74.7 ($3CH_2Ph$), 73.6 (C-2d), 73.4 (CH_2Ph), 67.5 (C-6c), 64.6 (C-2c), 27.8 ($C(CH_3)_3$). Anal. Calcd for $C_{57}H_{59}N_3O_{11}S$: C, 68.86; H, 5.98; N, 4.23; S, 3.23. Found: C, 68.70; H, 6.00; N, 4.22; S, 3.24.

4.11. Methyl [2-*O*-benzoyl-3-*O*-benzyl-6-*O*-chloroacetyl-4-*O*-(1-naphthyl)methyl-β-D-glucopyranosyl]-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (11)

4.11.1. Using DMTST as promoter (Table 1, entry 1). A mixture of **12** (0.83 g, 1.3 mmol, 1.3 equiv), **13**[27] (0.42 g, 1 mmol), and activated 4 Å molecular sieves (1 g) was stirred in dry CH_2Cl_2 (10 mL) at 0 °C under argon for 30 min, then DMTST (1.34 g, 5.2 mmol, 4 equiv) was added and the reaction temperature was allowed to reach rt. After 4 h, the reaction was quenched with Et_3N (1 mL). The mixture was filtered through a pad of Celite, the filtrate was diluted with CH_2Cl_2 (300 mL) and washed with 2 M aq HCl (125 mL), saturated aq $NaHCO_3$ (125 mL) and water (125 mL), dried, and concentrated. The residue was purified by column chromatography (toluene–acetone, 9:1→3:1) to give **11** as white crystals (0.63 g, 64%).

4.11.2. Using Me_2S_2–Tf_2O as promoter (Table 1, entry 2). A 1 M solution of Me_2S_2–Tf_2O (1.9 mL, 1.9 mmol, 1.5 equiv) in dry CH_2Cl_2 was added to a mixture containing **12** (0.80 g, 1.26 mmol, 1.26 equiv), **13** (0.42 g, 1 mmol), and activated 4 Å molecular sieves (1 g) in dry CH_2Cl_2 (10 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C, after 2 h the reaction was quenched with Et_3N (1 mL). Processing the mixture as above afforded **11** (0.49 g, 50%) as white crystals.

4.11.3. Using MeOTf as promoter (Table 1, entry 3). A mixture of **12** (0.62 g, 0.98 mmol, 1.3 equiv), **13** (0.31 g, 0.75 mmol), and activated 4 Å molecular sieves (1 g) was stirred in dry CH_2Cl_2 (10 mL) at 0 °C under argon for 30 min, then MeOTf (0.43 mL, 3.9 mmol, 4 equiv) was added and the reaction mixture was allowed to come to rt. After 4 h, the reaction was quenched with Et_3N (1 mL). Processing the mixture as above gave **11** (0.60 g, 81%) as white crystals.

R_f (toluene–acetone, 3:1) 0.39; mp 166–167 °C (from EtOAc–hexanes); $[\alpha]_D$ +93 (*c* 0.29, $CHCl_3$); IR ν_{max} (film): 2896, 2349, 1731, 1655, 1509, 1452, 1364, 1266, 1071, 1026, 753, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02–7.92 (m, 4H, aromatic), 7.64–7.08 (m, 23H, aromatic), 5.35 (d, 1H, *J* 11.9 Hz, ½$NaphCH_2$), 5.29 (dd, 1H, $J_{2b,1b}$ 9.2 Hz, $J_{2b,3b}$ 8.3 Hz, H-2b), 5.16 (d, 1H, $J_{NH,2a}$ 8.8 Hz, NH), 5.02 (d, 1H, *J* 11.9 Hz, ½$NaphCH_2$), 4.86 (d, 1H, *J* 12.4 Hz, ½$PhCH_2$), 4.77 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.74 (d, 1H, *J* 10.9 Hz, ½$PhCH_2$), 4.68–4.61 (m, 2H, H-1b, ½$PhCH_2$), 4.59 (d, 1H, $J_{1a,2a}$ 3.5 Hz, H-1a), 4.51 (d, 1H, *J* 12.4 Hz, ½$PhCH_2$), 4.35 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.14 (ddd, 1H, $J_{2a,1a}$ 3.5 Hz, $J_{2a,3a}$ 10.2 Hz, $J_{NH,2a}$ 8.8 Hz, H-2a), 4.12–3.93 (m, 2H, H-6b,6b′), 3.98 (dd, 1H, $J_{4a,3a}$ 9.0 Hz, $J_{4a,5a}$ 9.6 Hz, H-4a), 3.76–3.66 (m, 3H, H-3b,4b,5b), 3.58 (2d, 2H, *J* 14.9 Hz, CH_2Cl), 3.54–3.36 (m, 4H, H-3a,5a,6a,6a′), 3.18 (s, 3H, OCH_3), 1.71 (s, 3H, $CH_3C(O)NH$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 ($NHC(O)CH_3$), 166.5 ($C(O)CH_2Cl$), 164.8 (C(O)Ph), 139.3, 138.2, 137.5, 133.7, 133.4, 133.2, 131.5, 129.7, 129.6, 128.9, 128.7, 128.63, 128.56, 128.3, 128.1, 128.06, 127.99, 127.9, 127.8, 127.6, 127.4, 126.9, 126.5, 125.9, 125.2, 123.6 (aromatic), 100.2 (C-1b), 98.3 (C-1a), 83.3 (C-3b), 77.3 and 77.1 (C-3a, C-4b), 76.7 (C-5b), 75.2 ($PhCH_2$), 74.1 (C-4a), 73.9 and 73.6 (2 $PhCH_2$), 72.40 ($NaphCH_2$), 72.37 (C-2b), 70.2 (C-5a), 67.6 (C-6a), 64.1 (C-6b), 55.0 (OCH_3), 52.2 (C-2a), 40.4 (CH_2Cl), 23.2 ($CH_3C(O)NH$). Anal. Calcd for $C_{56}H_{58}ClNO_{13}$: C, 68.04; H, 5.91; N, 1.42. Found: C, 67.90; H, 5.93; N, 1.41.

4.12. Methyl [2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl) methyl-β-D-glucopyranosyl]-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (22)

To a solution of **11** (0.69 g, 0.7 mmol) in dry DMF (10 mL), a 0.417 M solution of HDTC[31] (5.0 mL, 2.1 mmol, 3 equiv) in ethanol–water–dioxane (4:2:1) was added. The mixture was stirred at rt for 30 min, diluted with CH_2Cl_2 (300 mL), washed with 2 M aq HCl (100 mL), saturated aq $NaHCO_3$ (100 mL), and water (100 mL); it was dried, and concentrated. The residue was purified by column chromatography (toluene–acetone, 4:1) to give **22** as white crystals (0.49 g, 77%); R_f (toluene–acetone, 2:1) 0.27; mp 158 °C (from EtOAc–hexanes); $[\alpha]_D$ +69 (*c* 0.35, $CHCl_3$); IR ν_{max} (film): 2349, 1729, 1654, 1541, 1453, 1364, 1267, 1071, 1047, 772, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98–7.77 (m, 4H, aromatic), 7.61–7.02 (m, 23H, aromatic), 5.29 (d, 1H, *J* 11.6 Hz, ½$NaphCH_2$), 5.27–5.22 (m, 2H, NH, ½$NaphCH_2$), 5.19 (dd, 1H, $J_{2b,3b}$ 9.2 Hz, $J_{2b,1b}$ 8.4 Hz, H-2b), 5.02 (d, 1H, *J* 11.7 Hz, ½$PhCH_2$), 4.84 (d, 1H, *J* 12.0 Hz, ½$PhCH_2$), 4.69 (d, 1H, $J_{1b,2b}$ 8.4 Hz, H-1b), 4.64 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.57 (d, 1H, $J_{1a,2a}$ 3.6 Hz, H-1a), 4.54–4.44 (m, 2H, $PhCH_2$), 4.28 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.10 (ddd, 1H, $J_{2a,1a}$ 3.6 Hz, $J_{2a,3a}$ 10.4 Hz, $J_{NH,2a}$ 8.7 Hz, H-2a), 3.92 (dd, 1H, $J_{4a,3a}$ 9.2 Hz, $J_{4a,5a}$ 9.2 Hz, H-4a), 3.63–3.50 (m, 4H, H-3b,5b,6a,6b), 3.45 (dd, 1H, $J_{3a,4a}$ 9.2 Hz, $J_{3a,2a}$ 10.4 Hz, H-3a), 3.38–3.29 (m, 2H, H-4b,5a), 3.26–3.17 (m, 2H, H-6a′,6b′), 3.15 (s, 3H, OCH_3), 1.76 (s, 3H, $CH_3C(O)NH$), 1.71 (br s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 ($NHC(O)CH_3$), 165.0 (C(O)Ph), 138.7, 137.9, 137.6, 133.6, 133.5, 133.2, 131.3, 129.7, 129.5, 128.8, 128.7, 128.6, 128.57, 128.46, 128.4, 128.2, 128.1, 128.0, 127.7, 127.63, 127.58, 126.4, 126.3, 125.8, 125.6, 125.2, 123.6 (aromatic), 100.2

(C-1b), 98.5 (C-1a), 82.9 (C-3b), 78.0 and 77.6 (C-3a, C-4b), 76.8 and 75.4 (C-4a, C-5b), 75.0, 74.5, and 74.3 (3 $PhCH_2$), 73.6 (C-2b), 72.7 ($NaphCH_2$), 70.3 (C-5a), 67.5 (C-6a), 61.8 (C-6b), 55.1 (OCH_3), 52.2 (C-2a), 23.3 ($CH_3C(O)NH$). Anal. Calcd for $C_{54}H_{57}NO_{12}$: C, 71.11; H, 6.30; N, 1.54. Found: C, 70.96; H, 6.32; N, 1.55.

4.13. Methyl {*tert*-butyl [2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl)methyl-β-D-glucopyranosyl]uronate}-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (23)

To a solution of **22** (0.46 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL), PDC (0.38 g, 1 mmol, 2 equiv), Ac_2O (0.47 mL, 5 mmol, 10 equiv), and *tert*-butyl alcohol (0.96 mL, 10 mmol, 20 equiv) were added. The mixture was stirred at rt for 6 h, and it was then applied on the top of a silica gel column in EtOAc with a 10 cm layer of EtOAc on top of the gel. The chromium compounds were allowed to precipitate in the presence of EtOAc and, after 30 min, the product was eluted with EtOAc. After evaporating the solvent, the residue was purified by column chromatography (toluene–acetone, 4:1→3:1) to give **23** as white crystals (0.36 g, 73%); R_f (toluene–acetone, 2:1) 0.32; mp 84–85 °C (from EtOAc–hexanes); $[\alpha]_D$ +42 (*c* 0.52, $CHCl_3$); IR ν_{max} (film): 2926, 2361, 1737, 1666, 1539, 1453, 1368, 1266, 1153, 1094, 1070, 1049, 793, 749, 711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98–7.76 (m, 5H, aromatic), 7.60–6.98 (m, 22H, aromatic), 5.35 (dd, 1H, $J_{2b,3b}$ 8.8 Hz, $J_{2b,1b}$ 8.2 Hz, H-2b), 5.21 (s, 2H, $NaphCH_2$), 5.04 (d, 1H, $J_{NH,2a}$ 8.7 Hz, NH), 4.98 (d, 1H, *J* 12.6 Hz, ½$PhCH_2$), 4.72 (d, 1H, *J* 12.3 Hz, ½$PhCH_2$), 4.70 (d, 1H, $J_{1b,2b}$ 8.2 Hz, H-1b), 4.66 (d, 1H, $J_{1a,2a}$ 3.5 Hz, H-1a), 4.61 (d, 1H, *J* 11.2 Hz, ½$PhCH_2$), 4.58 (d, 1H, *J* 12.6 Hz, ½$PhCH_2$), 4.53 (d, 1H, *J* 11.2 Hz, ½$PhCH_2$), 4.34 (d, 1H, *J* 12.3 Hz, ½$PhCH_2$), 4.14 (dd, 1H, $J_{4b,3b}$ 9.3 Hz, $J_{4b,5b}$ 9.0 Hz, H-4b), 4.10 (ddd, 1H, $J_{2a,1a}$ 3.5 Hz, $J_{2a,3a}$ 8.8 Hz, $J_{NH,2a}$ 8.7 Hz, H-2a), 4.06 (dd, 1H, $J_{4a,3a}$ 8.9 Hz, $J_{4a,5a}$ 9.5 Hz, H-4a), 3.86 (d, 1H, $J_{4b,5b}$ 9.0 Hz, H-5b), 3.70–3.62 (m, 2H, H-3b,6a), 3.52 (dd, 1H, $J_{3a,4a}$ 8.9 Hz, $J_{3a,2a}$ 8.8 Hz, H-3a), 3.41 (m, 1H, H-5a), 3.38 (dd, 1H, $J_{5a,6a'}$ 1.5 Hz, $J_{6a,6a'}$ 10.2 Hz, H-6a′), 3.16 (s, 3H, OCH_3), 1.71 (s, 3H, $CH_3C(O)NH$), 1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8 ($NHC(O)CH_3$), 167.2 (C-6b), 164.8 (C(O)Ph), 139.2, 138.0, 137.5, 133.6, 133.5, 133.2, 131.1, 129.6, 129.4, 128.9, 128.5, 128.4, 128.32, 128.30, 128.27, 128.22, 128.18, 128.16, 128.12, 128.08, 128.06, 128.02, 127.99, 127.91, 127.79, 127.67, 127.61, 127.56, 127.4, 127.3, 126.0, 125.8, 125.6, 125.2, 123.6 (aromatic), 100.5 (C-1b), 98.2 (C-1a), 82.4 ($C(CH_3)_3$), 81.7 (C-3b), 79.7 (C-4b), 77.4 (2C, C-3a, C-4a), 75.6 (C-5b), 74.7, 74.2, and 73.7 (3 $PhCH_2$), 73.5 (C-2b), 72.6 ($NaphCH_2$), 70.0 (C-5a), 67.4 (C-6a), 54.9 (OCH_3), 52.2 (C-2a), 27.7 ($C(CH_3)_3$), 23.1 ($CH_3C(O)NH$). Anal. Calcd for $C_{58}H_{63}NO_{13}$: C, 70.93; H, 6.47; N, 1.43. Found: C, 70.76; H, 6.49; N, 1.44.

4.14. Methyl [*tert*-butyl (2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (8)

To a solution of **23** (0.35 g, 0.36 mmol) in MeCN–water (10 mL, 9:1), CAN (0.59 g, 1 mmol, 3 equiv) was added. The mixture was stirred at rt for 3 h, then it was diluted with CH_2Cl_2 (200 mL), washed with saturated aq $NaHCO_3$ (75 mL), brine (75 mL), and water (75 mL); it was dried and concentrated. The residue was purified by column chromatography (toluene–acetone, 9:1→3:1) to give **8** (0.23 g, 77%) as a syrup; R_f (toluene–acetone, 3:2) 0.40; $[\alpha]_D$ +56 (*c* 0.37, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.92–7.87 (dd, 2H, aromatic), 7.60–7.12 (m, 18H, aromatic), 5.35 (dd, 1H, $J_{2b,3b}$ 8.1 Hz, $J_{2b,1b}$ 8.2 Hz, H-2b), 5.11 (d, 1H, $J_{NH,2a}$ 8.6 Hz, NH), 4.96 (d, 1H, *J* 12.8 Hz, ½$PhCH_2$), 4.75 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.70–4.64 (m, 3H, H-1b, $PhCH_2$), 4.62 (d, 1H, $J_{1a,2a}$ 3.6 Hz, H-1a), 4.57 (d, 1H, *J* 12.8 Hz, ½$PhCH_2$), 4.32 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.10 (ddd, 1H, $J_{2a,1a}$ 3.6 Hz, $J_{2a,3a}$ 9.2 Hz, $J_{NH,2a}$ 8.6 Hz, H-2a), 4.03 (dd, 1H, $J_{4a,3a}$ 8.9 Hz, $J_{4a,5a}$ 9.6 Hz, H-4a), 3.95 (dd, 1H, $J_{4b,3b}$ 9.2 Hz, $J_{4b,5b}$ 9.4 Hz, H-4b), 3.64 (dd, 1H, $J_{5a,6a}$ 3.0 Hz, $J_{6a,6a'}$ 10.9 Hz, H-6a), 3.61 (d, 1H, $J_{4b,5b}$ 9.4 Hz, H-5b), 3.50 (dd, 1H, $J_{3a,4a}$ 8.9 Hz, $J_{3a,2a}$ 9.2 Hz, H-3a), 3.48 (dd, 1H, $J_{3b,4b}$ 9.2 Hz, $J_{3b,2b}$ 8.1 Hz, H-3b), 3.42 (m, 1H, H-5a), 3.36 (dd, 1H, $J_{5a,6a'}$ 1.8 Hz, $J_{6a,6a'}$ 10.9 Hz, H-6a′), 3.17 (s, 3H, OCH_3), 1.72 (s, 3H, $CH_3C(O)NH$), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 ($NHC(O)CH_3$), 168.2 (C-6b), 164.8 (C(O)Ph), 139.3, 138.0, 137.9, 133.2, 129.7, 129.5, 129.0, 128.6, 128.5, 128.41, 128.36, 128.3, 128.24, 128.16, 128.1, 128.02, 128.01, 127.9, 127.8, 127.74, 127.68, 127.6, 127.5, 127.4, 125.2 (aromatic), 100.4 (C-1b), 98.2 (C-1a), 83.3 ($C(CH_3)_3$), 81.0 (C-3b), 77.4 (C-3a), 77.2 (C-4a), 74.5 (C-5b), 74.3, 74.0, and 73.5 ($3CH_2Ph$), 73.1 (C-2b), 72.6 (C-4b), 70.0 (C-5a), 67.5 (C-6a), 55.0 (OCH_3), 52.2 (C-2a), 27.8 ($C(CH_3)_3$), 23.2 ($CH_3C(O)NH$). Anal. Calcd for $C_{47}H_{55}NO_{13}$: C, 67.05; H, 6.58; N, 1.66. Found: C, 66.91; H, 6.60; N, 1.66.

4.15. Methyl (2-*O*-benzoyl-3-*O*-benzyl-6-*O*-chloroacetyl-β-D-glucopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (24)

To a solution of **11** (0.49 g, 0.5 mmol) in MeCN–water (10 mL, 9:1), CAN (0.82 g, 1.5 mmol, 3 equiv) was added. The mixture was stirred at rt for 1 h, then it was diluted with CH_2Cl_2 (200 mL), washed with saturated aq $NaHCO_3$ (75 mL), brine (75 mL), and water (75 mL); it was dried and concentrated. The residue was purified by column chromatography (toluene–acetone, 4:1) to give **24** as white crystals (0.30 g, 71%); R_f (toluene–acetone, 2:1) 0.28; mp 168–169 °C (from EtOAc–hexanes); $[\alpha]_D$ +38 (*c* 0.47, $CHCl_3$); IR ν_{max} (film): 2904, 1713, 1656, 1548, 1496, 1453, 1370, 1316, 1270, 1088, 1071, 1049, 1028, 751, 711, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.95–7.06 (m, 20H, aromatic), 5.40 (d, 1H, $J_{NH,2a}$ 8.7 Hz, NH), 5.21 (dd, 1H, $J_{2b,3b}$ 9.2 Hz, $J_{2b,1b}$ 8.4 Hz, H-2b), 4.90 (d, 1H, *J* 12.4 Hz, ½$PhCH_2$), 4.75 (d, 1H, *J* 11.3 Hz, ½$PhCH_2$), 4.72–4.67 (m, 3H, H-1b, $PhCH_2$), 4.65 (d, 1H, $J_{1a,2a}$ 3.6 Hz, H-1a), 4.52 (d, 1H, *J* 12.4 Hz, ½$PhCH_2$), 4.40 (dd, 1H, $J_{5b,6b}$ 4.2 Hz, $J_{6b,6b'}$ 11.7 Hz, H-6b), 4.35–4.25 (m, 2H, H-6b′, ½$PhCH_2$), 4.11 (ddd, 1H, $J_{2a,1a}$ 3.6 Hz, $J_{2a,3a}$ 8.8 Hz, $J_{NH,2a}$ 8.7 Hz, H-2a), 4.01 (dd, 1H, $J_{4a,3a}$ 9.9 Hz, $J_{4a,5a}$ 9.2 Hz, H-4a), 3.94–3.82 (m, 4H, H-4b,5b, CH_2Cl), 3.64 (dd, 1H, $J_{3b,2b}$ 9.2 Hz, $J_{3b,4b}$ 9.3 Hz, H-3b), 3.62 (dd, 1H, $J_{5a,6a}$ 3.3 Hz, $J_{6a,6a'}$ 11.6 Hz, H-6a), 3.49 (dd, 1H, $J_{3a,4a}$ 9.9 Hz, $J_{3a,2a}$ 8.8 Hz, H-3a), 3.44–3.30 (m, 2H, H-5a,6a′), 3.18 (s, 3H, OCH_3), 1.71 (s, 3H, $CH_3C(O)NH$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0 ($NHC(O)CH_3$), 167.6 ($C(O)CH_2Cl$). 164.9 (C(O)Ph), 139.2, 138.0, 137.9, 133.3, 129.6, 129.5, 128.5, 128.4, 128.32, 128.30, 128.2, 128.1, 128.0, 127.95, 127.91, 127.88, 127.79, 127.6, 127.3 (aromatic), 100.4 (C-1b), 98.3 (C-1a), 82.1 (C-3b), 77.3 (C-3a), 77.0 (C-5b), 74.6 and 73.8 (2 $PhCH_2$), 73.7 (C-4a), 73.5 (CH_2Ph), 73.3 (C-2b), 70.5 and 70.1 (C-4b, C-5a), 67.5 (C-6a), 64.5 (C-6b), 55.0 (OCH_3), 52.2 (C-2a), 40.6 (CH_2Cl), 23.2 ($CH_3C(O)NH$). Anal. Calcd for $C_{45}H_{50}ClNO_{13}$: C, 63.71; H, 5.94; N, 1.65. Found: C, 63.55; H, 5.96; N, 1.66.

4.16. Methyl [*tert*-butyl(2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(2-*O*-benzoyl-3-*O*-benzyl-6-*O*-chloroacetyl-β-D-glucopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (25α)

A mixture of **7** (0.50 g, 0.5 mmol, 1.25 equiv), **24** (0.34 g, 0.4 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.08 g, 0.4 mmol, 1 equiv), and activated 4 Å molecular sieves (1 g) was stirred in a mixture of dry CH_2Cl_2 (4 mL) and dry Et_2O (12 mL) at 0 °C under argon for 30 min, then DMTST (0.52 g, 2 mmol, 4 equiv) was added. After stirring for 6 h at rt, the reaction was quenched with Et_3N (1 mL). The mixture was filtered through a pad of Celite, the filtrate was diluted with CH_2Cl_2 (250 mL), and washed with 2 M aq HCl (100 mL), saturated aq $NaHCO_3$ (100 mL), and water (100 mL); it was dried and concentrated. The residue was purified by column chromatography (toluene–acetone, 9:1→4:1) to give first the

β-anomer (**25β**) as a syrup (0.10 g, 14%); R_f (toluene–acetone, 4:1) 0.34; $[\alpha]_D$ +29 (*c* 0.56, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.14–8.10 (d, 1H, aromatic), 7.95–7.90 (d, 2H, aromatic), 7.58–7.02 (m, 42H, aromatic), 5.36 (dd, 1H, $J_{2d,3d}$ 8.2 Hz, $J_{2d,1d}$ 8.8 Hz, H-2d), 5.28 (dd, 1H, $J_{2b,1b}$ 8.6 Hz, $J_{2b,3b}$ 9.0 Hz, H-2b), 5.06 (d, 1H, $J_{NH,2a}$ 7.8 Hz, NH), 4.97–4.92 (m, 2H, $PhCH_2$), 4.86 (d, 1H, *J* 11.0 Hz, ½$PhCH_2$), 4.83 (d, 1H, *J* 10.9 Hz, ½$PhCH_2$), 4.80 (d, 1H, *J* 12.4 Hz, ½$PhCH_2$), 4.77 (d, 1H, *J* 12.7 Hz, ½$PhCH_2$), 4.75–4. 58 (m, 8H, 3 $PhCH_2$, H-1c, H-1d), 4.57 (d, 1H, $J_{1b,2b}$ 8.6 Hz, H-1b), 4.55–4.45 (m, 3H, $PhCH_2$, H-1a), 4.36 (d, 1H, $J_{6b,6b'}$ 12.1 Hz, H-6b), 4.13 (s, 2H, CH_2Cl), 4.05 (ddd, 1H, $J_{2a,1a}$ 3.4 Hz, $J_{2a,3a}$ 10.3 Hz, $J_{NH,2a}$ 7.8 Hz, H-2a), 4.02–3.95 (m, 3H, H-4a,4c,4d), 3.94–3.87 (m, 2H, H-5d,6b′), 3.82 (dd, 1H, $J_{3b,4b}$ 8.9 Hz, $J_{4b,5b}$ 9.2 Hz, H-4b), 3.78–3.67 (m, 4H, H-3a,3b,3d,5b), 3.67 (dd, 1H, $J_{5c,6c}$ 3.0 Hz, $J_{6c,6c'}$ 11.1 Hz, H-6c), 3.62 (dd, 1H, $J_{5,6a}$ 2.0 Hz, $J_{6a,6a'}$ 11.6 Hz, H-6a), 3.46 (dd, 1H, $J_{2c,1c}$ 9.5 Hz, $J_{2c,3c}$ 9.8 Hz, H-2c), 3.43–3.34 (m, 4H, H-3c,5a,6a′,6c′), 3.19 (m, 1H, H-5c), 3.16 (s, 3H, OCH_3), 1.70 (s, 3H, $CH_3C(O)NH$), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 ($NHC(O)CH_3$), 167.2 ($C(O)CH_2Cl$), 166.4 (C-6d), 165.2 and 164.7 (2C(O)Ph), 139.0, 138.1, 137.8, 137.7, 137.6, 137.4, 137.3, 137.1, 133.3, 133.2, 129.6, 129.4, 129.3, 129.0, 128.99, 128.8, 128.7, 128.5, 128.44, 128.40, 128.3, 128.2, 128.1, 128.05, 128.03, 127.98, 127.9, 127.8, 127.74, 127.70, 127.65, 127.58, 127.51, 127.43, 127.40, 127.3, 127.18, 127.16, 126.9, 125.1 (aromatic), 100.2 (C-1d, $J_{C\text{-}1d,H\text{-}1d}$ 165.4 Hz), 98.6 (C-1b, $J_{C\text{-}1b,H\text{-}1b}$ 163.6 Hz), 98.3 (C-1c, $J_{C\text{-}1c,H\text{-}1c}$ 165.0 Hz), 98.0 (C-1a, $J_{C\text{-}1a,H\text{-}1a}$ 172.5 Hz), 83.3 (C-3b), 82.4 (2C, C-3c, $C(CH_3)_3$), 81.4 (C-3d), 79.1 (C-4d), 77.5 (C-4b), 76.4 and 75.5 (C-5c, C-5d), 75.4 and 75.2 (C-3a, C-4a), 74.81 ($PhCH_2$), 74.76 (2C, C-4c, C-5b), 74.6, 74.3, 74.1, 73.8, 73.6, and 72.9 (6 $PhCH_2$), 72.6 and 72.3 (C-2b, C-2d), 70.1 (C-5a), 67.9 (C-6c), 67.2 (C-6a), 65.35 and 65.32 (C-2c, C-6b), 55.0 (OCH_3), 52.1 (C-2a), 41.1 (CH_2Cl), 27.8 ($C(CH_3)_3$), 23.1 ($CH_3C(O)NH$). Anal. Calcd for $C_{96}H_{103}ClN_4O_{24}$: C, 66.56; H, 5.99; N, 3.23. Found: C, 66.41; H, 6.01; N, 3.24.

Eluted second was the α-anomer (**25α**) (0.28 g, 40%) as a syrup; R_f (toluene–acetone, 4:1) 0.31; $[\alpha]_D$ +34 (*c* 0.62, $CHCl_3$); IR ν_{max} (film): 2924, 2110, 1732, 1636, 1453, 1368, 1265, 1070, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.94–7.90 (dd, 2H, aromatic), 7.86–7.83 (d, 2H, aromatic), 7.60–7.04 (m, 41H, aromatic), 5.48 (d, 1H, $J_{1c,2c}$ 4.0 Hz, H-1c), 5.27 (dd, 1H, $J_{2d,3d}$ 8.1 Hz, $J_{2d,1d}$ 8.4 Hz, H-2d), 5.23 (dd, 1H, $J_{2b,3b}$ 9.3 Hz, $J_{2b,1b}$ 8.2 Hz, H-2b), 5.20–5.16 (m, 2H, NH, ½$PhCH_2$), 4.83 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.80 (d, 1H, *J* 10.9 Hz, ½$PhCH_2$), 4.74 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.72–4.63 (m, 6H, 2 $PhCH_2$, H-1b,1d), 4.61 (d, 1H, $J_{1a,2a}$ 3.6 Hz, H-1a), 4.59 (d, 1H, *J* 11.8 Hz, ½$PhCH_2$), 4.57–4. 53 (m, 3H, 1½$PhCH_2$), 4.50–4.47 (m, 2H, $PhCH_2$), 4.36 (m, 1H, H-6b), 4.18 (s, 2H, CH_2Cl), 4.06 (ddd, 1H, $J_{2a,1a}$ 3.6 Hz, $J_{2a,3a}$ 9.6 Hz, $J_{NH,2a}$ 8.7 Hz, H-2a), 4.02 (dd, 1H, $J_{4d,3d}$ 9.3 Hz, $J_{4d,5d}$ 9.0 Hz, H-4d), 4.00–3.94 (m, 3H, H-4a,4b,4c), 3.81–3.72 (m, 3H, H-5b,5d,6b′), 3.68–3.59 (m, 4H, H-3a,3d,6a,6c), 3.45 (dd, 1H, $J_{3b,4b}$ 8.2 Hz, $J_{3b,2b}$ 9.0 Hz, H-3b), 3.42–3.32 (m, 4H, H-3c,5a,6a′,6c′), 3.24 (dd, 1H, $J_{2c,1c}$ 4.0 Hz, $J_{3c,2c}$ 11.0 Hz, H-2c), 3.19 (s, 3H, OCH_3), 3.14 (m, 1H, H-5c), 1.72 (s, 3H, $CH_3C(O)NH$), 1.41 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 ($NHC(O)CH_3$), 167.0 ($C(O)CH_2Cl$), 166.4 (C-6d), 164.9, 164.7 (2C(O)Ph), 139.1, 138.1, 137.9, 137.8, 137.6, 137.5, 137.3, 137.2, 133.2, 133.0, 129.5, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.51, 128.46, 128.4, 128.3, 128.2, 128.1, 128.05, 128.03, 127.98, 127.9, 127.8, 127.74, 127.70, 127.65, 127.58, 127.51, 127.43, 127.40, 127.3, 127.18, 127.16, 126.9, 125.1 (aromatic), 100.3 (C-1d, $J_{C\text{-}1d,H\text{-}1d}$ 165.0 Hz), 99.7 (C-1b, $J_{C\text{-}1b,H\text{-}1b}$ 163.7 Hz), 98.4 (C-1a, $J_{C\text{-}1a,H\text{-}1a}$ 172.8 Hz), 98.2 (C-1c, $J_{C\text{-}1c,H\text{-}1c}$ 176.5 Hz), 83.0 (C-3b), 82.3 (2C, $C(CH_3)_3$, C-3c), 81.8 (C-3d), 79.7 (C-4d), 77.3 (C-4b), 76.9 and 75.7 (C-5c, C-5d), 75.6 and 75.3 (C-3a, C-4a), 74.9 ($PhCH_2$), 74.8 and 74.7 (C-4c, C-5b), 74.6, 74.3, 74.0, 73.7, 73.5, and 73.2 (6 $PhCH_2$), 72.3 and 71.7 (C-2b, C-2d), 70.1 (C-5a), 67.4 (C-6c), 66.9 (C-6a), 63.9 (C-6b), 62.5 (C-2c), 55.0 (OCH_3), 52.2 (C-2a), 40.6 (CH_2Cl), 27.8 ($C(CH_3)_3$), 23.2 ($CH_3C(O)NH$). Anal. Calcd for $C_{96}H_{103}ClN_4O_{24}$: C, 66.56; H, 5.99; N, 3.23. Found: C, 66.40; H, 6.01; N, 3.24.

4.17. Methyl [*tert*-butyl(2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-[*tert*-butyl (2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (26)

To a solution of **25α** (0.42 g, 0.24 mmol) in dry DMF (8 mL), a 0.417 M solution of HDTC[31] (1.73 mL, 0.72 mmol, 3 equiv) in ethanol–water–dioxane (4:2:1) was added. The mixture was stirred at rt for 2 h, diluted with CH_2Cl_2 (200 mL), washed with 2 M aq HCl (75 mL), saturated aq $NaHCO_3$ (75 mL), and water (75 mL); then it was dried and concentrated. The residue was purified by column chromatography (toluene–acetone, 4:1) to give **26** as a syrup (0.22 g, 55%); R_f (toluene–acetone, 3:1) 0.30; $[\alpha]_D$ +37 (*c* 0.22, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.94–7.90 (dd, 2H, aromatic), 7.86–7.83 (d, 2H, aromatic), 7.60–7.04 (m, 41H, aromatic), 5.48 (d, 1H, $J_{1c,2c}$ 4.0 Hz, H-1c), 5.28 (dd, 1H, $J_{2d,3d}$ 8.1 Hz, $J_{2d,1d}$ 8.4 Hz, H-2d), 5.23 (dd, 1H, $J_{2b,3b}$ 9.3 Hz, $J_{2b,1b}$ 8.2 Hz, H-2b), 5.20–5.16 (m, 2H, NH, ½$PhCH_2$), 4.84 (d, 1H, *J* 12.3 Hz, ½$PhCH_2$), 4.81 (d, 1H, *J* 10.9 Hz, ½$PhCH_2$), 4.80 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.74 (d, 1H, *J* 12.3 Hz, ½$PhCH_2$), 4.71 (d, 1H, *J* 11.1 Hz, ½$PhCH_2$), 4.69–4.64 (m, 4H, $PhCH_2$, H-1b, H-1d), 4.62 (d, 1H, $J_{1a,2a}$ 3.6 Hz, H-1a), 4.59 (d, 1H, *J* 11.8 Hz, ½$PhCH_2$), 4.56–4.47 (m, 3H, 1½$PhCH_2$), 4.36 (2d, 2H, *J* 10.4 Hz, $PhCH_2$), 4.15 (ddd, 1H, $J_{2a,1a}$ 3.6 Hz, $J_{2a,3a}$ 9.6 Hz, $J_{NH,2a}$ 8.7 Hz, H-2a), 4.02 (dd, 1H, $J_{4d,3d}$ 9.3 Hz, $J_{4d,5d}$ 9.0 Hz, H-4d), 4.00–3.94 (m, 3H, H-4a,4b,4c), 3.81–3.73 (m, 2H, H-5b,5d), 3.69–3.58 (m, 5H, H-3a,3d,6a,6b,6c), 3.46 (dd, 1H, $J_{3b,4b}$ 8.2 Hz, $J_{3b,2b}$ 9.0 Hz, H-3b), 3.42–3.33 (m, 4H, H-3c,5a,6a′,6c′), 3.31 (dd, 1H, $J_{5b,6b'}$ 1.6 Hz, $J_{6b,6b'}$ 10.1 Hz, H-6b′), 3.19 (s, 3H, OCH_3), 3.14 (m, 1H, H-5c), 3.04 (dd, 1H, $J_{2c,1c}$ 4.1 Hz, $J_{3c,2c}$ 11.0 Hz, H-2c), 1.82 (s, 3H, $CH_3C(O)NH$), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 ($NHC(O)CH_3$), 167.0 (C-6d), 164.9 and 164.7 (2C(O)Ph), 138.9, 138.3, 138.0, 137.9, 137.62, 137.58, 137.2, 133.40, 133.36, 129.6, 129.5, 129.3, 129.2, 128.99, 128.8, 128.6, 128.5, 128.44, 128.40, 128.3, 128.2, 128.1, 128.05, 128.03, 127.98, 127.9, 127.7, 127.63, 127.59, 127.5, 127.4, 127.3, 127.1 (aromatic), 100.3 (C-1d, $J_{C\text{-}1d,H\text{-}1d}$ 162.6 Hz), 99.7 (C-1b, $J_{C\text{-}1b,H\text{-}1b}$ 156.7 Hz), 98.4 (C-1a, $J_{C\text{-}1a,H\text{-}1a}$ 167.5 Hz), 97.6 (C-1c, $J_{C\text{-}1c,H\text{-}1c}$ 176.4 Hz), 83.4 (C-3b), 82.3 (2C, C-3c, $C(CH_3)_3$), 81.6 (C-3d), 79.6 (C-4d), 77.6 (C-4b), 76.3 (C-5c), 75.6 (C-5d), 75.2 and 74.9 (C-3a, C-4a), 74.85 ($PhCH_2$), 74.81 (C-4c), 74.6, 74.3, 74.0, 73.9 73.7, 73.5 (6 $PhCH_2$), 73.6 and 72.7 (C-2b, C-2d), 70.7 and 70.1 (C-5a, C-5b), 67.2 (C-6c), 67.0 (C-6a), 62.3 (C-2c), 61.1 (C-6b), 55.0 (OCH_3), 52.1 (C-2a), 27.8 ($C(CH_3)_3$), 23.3 ($CH_3C(O)NH$). Anal. Calcd for $C_{94}H_{102}N_4O_{23}$: C, 68.18; H, 6.21; N, 3.38. Found: C, 68.01; H, 6.23; N, 3.39.

4.18. Methyl [*tert*-butyl(2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-[*tert*-butyl (2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside) (6)

*4.18.1. By oxidation of **26** (Scheme 7).* To a solution of **26** (0.12 g, 0.072 mmol) in dry CH_2Cl_2 (6 mL), PDC (0.054 g, 0.14 mmol, 2 equiv), Ac_2O (0.07 mL, 0.72 mmol, 10 equiv), and *tert*-butyl alcohol (0.14 mL, 1.45 mmol, 20 equiv) were added. The mixture was stirred overnight at rt, and it was then applied on the top of a silica gel column in EtOAc with a 10 cm layer of EtOAc on top of the gel. The chromium compounds were allowed to precipitate in the presence of EtOAc and, after 30 min, the product was eluted with EtOAc. After evaporating the solvent, the residue was purified by column chromatography (toluene–acetone, 4:1→3:1) to give **6** as a syrup (0.066 g, 53%).

*4.18.2. By glycosylation of **8** (Scheme 8).* A mixture of **8** (0.22 g, 0.26 mmol), **7** (0.32 g, 0.32 mmol, 1.24 equiv), and 4 Å molecular sieves (1 g) was stirred in a mixture of dry CH_2Cl_2 (3 mL) and dry

Et_2O (9 mL) at 0 °C under argon for 30 min, then DMTST (0.41 g, 1.6 mmol, 5 equiv) was added. After 2 days, the reaction was quenched with Et_3N (1 mL). The mixture was filtered through a pad of Celite, the filtrate was diluted with CH_2Cl_2 (200 mL), and washed with 2 M aq HCl (75 mL), saturated aq $NaHCO_3$ (75 mL), and water (75 mL); then it was dried and concentrated. The residue was purified by column chromatography (toluene–acetone, 4:1→3:1) to give **6** (0.25 g, 56%) as a syrup; R_f (toluene–acetone, 3:1) 0.34; $[\alpha]_D$ +37 (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.90 (dd, 2H, aromatic), 7.82–7.79 (d, 2H, aromatic), 7.60–7.02 (m, 41H, aromatic), 5.48 (d, 1H, $J_{1c,2c}$ 4.0 Hz, H-1c), 5.28 (dd, 1H, $J_{2d,3d}$ 9.4 Hz, $J_{2d,1d}$ 8.4 Hz, H-2d), 5.24 (dd, 1H, $J_{2b,3b}$ 9.4 Hz, $J_{2b,1b}$ 8.2 Hz, H-2b), 5.12 (d, 1H, *J* 11.1 Hz, ½$PhCH_2$), 4.90 (d, 1H, $J_{NH,2}$ 8.6 Hz, NH), 4.83 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.80 (d, 1H, *J* 10.9 Hz, ½$PhCH_2$), 4.78 (d, 1H, *J* 12.2 Hz, ½$PhCH_2$), 4.74 (d, 1H, *J* 12.3 Hz, ½$PhCH_2$), 4.71 (d, 1H, *J* 11.1 Hz, ½$PhCH_2$), 4.69–4.64 (m, 4H, $PhCH_2$, H-1b,1d), 4.62 (d, 1H, $J_{1a,2a}$ 3.6 Hz, H-1a), 4.59 (d, 1H, *J* 11.8 Hz, ½$PhCH_2$), 4.56–4.47 (m, 3H, 1½$PhCH_2$), 4.37 (2d, 2H, *J* 12.2 Hz, $PhCH_2$), 4.15 (ddd, 1H, $J_{2a,1a}$ 3.6 Hz, $J_{2a,3a}$ 9.6 Hz, $J_{NH,2a}$ 8.7 Hz, H-2a), 4.02 (dd, 1H, $J_{4d,3d}$ 9.3 Hz, $J_{4d,5d}$ 9.0 Hz, H-4d), 4.00–3.94 (m, 3H, H-4a,4b,4c), 3.81–3.73 (m, 2H, H-5b,5d), 3.68–3.59 (m, 5H, H-3a,3b,3d,6a,6c), 3.42–3.33 (m, 5H, H-3c,5a,5c,6a′,6c′), 3.24 (dd, 1H, $J_{2c,1c}$ 4.0 Hz, $J_{3c,2c}$ 11.0 Hz, H-2c), 3.18 (s, 3H, OCH_3), 1.74 (s, 3H, CH_3C(O)NH), 1.42 (2s, 18H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 ($NHC(O)CH_3$), 167.0 (C-6d), 166.3 (C-6b), 164.7 and 164.6 (2C(O)Ph), 139.2, 138.2, 138.1, 137.9, 137.8, 137.5, 137.4, 137.2, 133.4, 133.3, 129.73, 129.67, 129.5, 129.3, 128.79, 128.77, 128.71, 128.6, 128.5, 128.4, 128.33, 128.27, 128.25, 128.22, 128.20, 127.9, 127.8, 127.70, 127.64, 127.59, 127.5, 127.4, 127.3, 127.1 (aromatic), 100.5 (C-1d), 99.9 (C-1b), 98.2 (C-1a), 97.3 (C-1c), 82.5 (C-3b), 82.3 (3C, C-3c, $2C(CH_3)_3$), 82.1 (C-3d), 79.7 (C-4d), 77.3 (C-4b), 76.0 (C-5c), 75.6 (C-5d), 75.1 (2C, C-3a, C-4a), 75.0 ($PhCH_2$), 74.8 (C-4c), 74.6, 74.3, 74.1, 73.8, 73.7, and 73.54 (6 $PhCH_2$), 73.51 and 73.4 (C-2b, C-2d), 70.7 and 69.9 (C-5a, C-5b), 67.2 (C-6c), 66.9 (C-6a), 62.8 (C-2c), 55.1 (OCH_3), 52.2 (C-2a), 27.9 ($C(CH_3)_3$), 27.6 ($C(CH_3)_3$), 23.2 (CH_3C(O)NH). Anal. Calcd for $C_{98}H_{108}N_4O_{24}$: C, 68.20; H, 6.31; N, 3.25. Found: C, 68.03; H, 6.33; N, 3.26; MS-ESI: $[M+H]^+$ 1725.4; HRMS (ES^+) calcd for $C_{49}H_{56}N_2O_{12}^+$ $[M+2H]^{2+}$ 864.3799. Found: 864.3833.

4.19. Methyl [(β-D-glucopyranosyl)uronic acid]-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-(1→4)-[(β-D-glucopyranosyl)uronic acid]-(1→4)-(2-acetamido-2-deoxy-α-D-glucopyranoside) (5)

To a solution of compound **6** (0.114 g, 0.066 mmol) in THF–MeOH (5 mL, 2:1), 1 M aq NaOH solution (40 μL) was added. The reaction mixture was stirred for 3 days at rt, neutralized with Amberlite IR120 (H^+) resin, filtered, and concentrated. The residue was purified by column chromatography (toluene–methanol, 9:1) to give **27** as a syrup (0.064 g, 64%); R_f (toluene–methanol, 9:1) 0.29; $[\alpha]_D$ +39 (*c* 0.69, $CHCl_3$); MS-ESI: $[M+H]^+$ 1517.2; HRMS (ES^+) calcd for $C_{42}H_{52}N_2O_{11}^+$ $[M+2H]^{2+}$ 760.3585. Found: 760.3571.

A solution of **27** (0.062 g, 0.041 mmol) in a 20% solution of TFA in CH_2Cl_2 (6 mL) was stirred for 1 h, the mixture was concentrated, and the residue was co-evaporated with toluene to give crude **28** (0.052 g, 91%) as a syrup. R_f (toluene–methanol, 9:1) 0.21; MS-ESI: $[M+H]^+$ 1405.3.

A solution of **28** (0.051 g, 0.036 mmol) in MeOH (5 mL) was hydrogenated with 10% Pd–C (0.050 g) under atmospheric pressure at rt. After 2 days, the mixture was filtered through a pad of Celite and concentrated. The residue was purified by column chromatography (EtOAc–MeOH–H_2O, 3:2:1), after which it was eluted from a column of Sephadex G-25 using water as eluent and lyophilized to afford **5** (0.019 g, 70%) as a foam; R_f (EtOAc–MeOH–H_2O, 2:2:1) 0.24; $[\alpha]_D$ +26 (*c* 0.30, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 5.52 (d, 1H, $J_{1c,2c}$ 3.6 Hz, H-1c), 4.74 (d, 1H, $J_{1a,2a}$ 3.5 Hz, H-1a), 4.42 (d, 1H, $J_{1b,2b}$ 7.9 Hz, H-1b), 4.38 (d, 1H, $J_{1d,2d}$ 8.0 Hz, H-1d), 3.87–3.81 (m, 2H, H-3a,3c), 3.80–3.70 (m, 8H, H-2a,5a,5b,5c,6a,6a′,6c,6c′), 3.70–3.60 (m, 3H, H-3b,4b,5d), 3.60–3.51 (m, 2H, H-4a,4c), 3.43–3.35 (m, 3H, H-3d,4d,5a), 3.28 (m, 1H, H-2b), 3.25 (s, 3H, OCH_3), 3.22 (m, 1H, H-2d), 3.18 (dd, 1H, $J_{2c,3c}$ 10.3 Hz, $J_{2c,1c}$ 3.6 Hz, H-2c), 1.89 (s, 3H, CH_3C(O)NH); ^{13}C NMR (75 MHz, D_2O): δ 175.0 and 174.8 (2C) ($NHC(O)CH_3$, C-6b, C-6d), 102.6 (C-1d), 102.5 (C-1b), 98.1 (C-1a), 95.6 (C-1c), 79.5 (C-4a), 78.0 (C-4c), 76.4 (2C), 76.3 and 76.2 (C-3b, C-4b, C-5b, C-5d), 75.4, 73.4 (2C) and 72.2 (C-3d, C-4d, C-2b, C-2d), 70.7 (C-5c), 70.0 (C-3c), 69.9 (C-5a), 68.7 (C-3a), 60.3 (2C, C-6a, C-6c), 55.6 (OCH_3), 54.4 (C-2c), 53.7 (C-2a), 22.3 (CH_3C(O)NH); MS-ESI: $[M+H]^+$ 749.1; HRMS (ES^+) calcd for $C_{27}H_{44}N_2NaO_{22}^+$ $[M+H+Na]^+$ 771.2283; Found: 771.2271.

Acknowledgements

We are grateful to Dr. Tibor Bakó (Egis Pharmaceuticals Ltd.) for the assistance in recording the NMR spectra and for helpful discussions. We also thank Dr. Pál Szabó (Chemical Research Center, Hungarian Academy of Sciences) and Zsuzsánna Csíki (Chemical Research Center, Hungarian Academy of Sciences) for the assistance in recording the MS and IR spectra, respectively.

Supplementary data

Supplementary data (copies of NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.08.004.

References and notes

1. (a) Lane, D. A.; Lindahl, U. *Heparin. Chemical and Biological Properties, Clinical Applications*; CRC: Boca Raton, Florida, USA, 1989; (b) Kjellén, L.; Lindahl, U. *Annu. Rev. Biochem.* **1991**, *60*, 443–475; (c) Casu, B.; Lindahl, U. *Adv. Carbohydr. Chem. Biochem.* **2001**, *57*, 159–206; (d) Garg, H. G.; Linhardt, R. J.; Hales, C. A. *Chemistry and Biology of Heparin and Heparan Sulfate*; Elsevier: Amsterdam, The Netherlands, 2005.
2. (a) Conrad, E. H. *Heparin-Binding Proteins*; Academic: San Diego, CA, USA, 1998; (b) Capila, I.; Linhardt, R. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 390–412; (c) Fügedi, P. *Mini-Rev. Med. Chem.* **2003**, *3*, 659–667.
3. (a) Snow, A. D.; Wight, T. N. *Neurobiol. Aging* **1989**, *10*, 481–497; (b) Snow, A. D.; Castillo, G. M. *Amyloid-Int. J. Exp. Clin. Investig.* **1997**, *4*, 135–141; (c) Diaz-Nido, J.; Wandosell, F.; Avila, J. *Peptides* **2002**, *23*, 1323–1332; (d) Mayer-Sonnenfeld, T.; Zeigler, M.; Halimi, M.; Dayan, Y.; Herzog, C.; Lasmezas, C. I.; Gabizon, R. *Neurobiol. Dis.* **2005**, *20*, 738–743; (e) Hijazi, N.; Kariv-Inbal, Z.; Gasset, M.; Gabizon, R. *J. Biol. Chem.* **2005**, *280*, 17057–17061.
4. Prusiner, S. B. *Science* **1982**, *216*, 136–144.
5. Mehrpour, M.; Codogno, P. *Cancer Lett.* **2010**, *290*, 1–23.
6. Su, J. H.; Cummings, B. J.; Cotman, C. W. *Neuroscience* **1992**, *51*, 801–813.
7. Leteux, C.; Chai, W.; Nagai, K.; Herbert, C. G.; Lawson, A. M.; Feizi, T. *J. Biol. Chem.* **2001**, *276*, 12539–12545.
8. (a) Tatai, J.; Osztrovszky, G.; Kajtár-Peredy, M.; Fügedi, P. *Carbohydr. Res.* **2008**, *343*, 596–606; (b) Tatai, J.; Fügedi, P. *Tetrahedron* **2008**, *64*, 9865–9873; (c) Csíki, Z.; Fügedi, P. *Tetrahedron Lett.* **2010**, *51*, 391–395; (d) Csíki, Z.; Fügedi, P. *Tetrahedron* **2010**, *66*, 7821–7837.
9. Daragics, K.; Fügedi, P. 14th European Carbohydrate Symposium, Lübeck, Germany, 2007, Abstract PO-050.
10. Hamza, D.; Lucas, R.; Feizi, T.; Chai, W.; Bonnaffé, D.; Lubineau, A. *ChemBioChem* **2006**, *7*, 1856–1858.
11. Bindschädler, P.; Noti, C.; Castagnetti, E.; Seeberger, P. H. *Helv. Chim. Acta* **2006**, *89*, 2591–2610.
12. Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Jacquinet, J.-C.; Sinaÿ, P.; Torri, G. *Carbohydr. Res.* **1987**, *167*, 67–75.
13. (a) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1671–1690; (b) de Paz, J.-L.; Ojeda, R.; Reichardt, N.; Martin-Lomas, M. *Eur. J. Org. Chem.* **2003**, 3308–3324; (c) de Paz, J. L.; Martin-Lomas, M. *Eur. J. Org. Chem.* **2005**, 1849–1858; (d) Lohman, G. J. S.; Seeberger, P. H. *J. Org. Chem.* **2004**, *69*, 4081–4093.
14. For a recent paper attempting to find a solution to this problem, see: Bindschädler, P.; Dialer, L. O.; Seeberger, P. H. *J. Carbohydr. Chem.* **2009**, *28*, 395–420.
15. (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173; (b) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825.
16. (a) Liao, L.; Auzanneau, F.-I. *Org. Lett.* **2003**, *5*, 2607–2610; (b) Liao, L.; Auzanneau, F.-I. *J. Org. Chem.* **2005**, *70*, 6265–6273; (c) Hendel, J. L.; Cheng, A.; Auzanneau, F.-I. *Carbohydr. Res.* **2008**, *343*, 2914–2923; (d) Tamura, J.; Nakada, Y.; Taniguchi, K.; Yamane, M. *Carbohydr. Res.* **2008**, *343*, 39–47.

17. Lucas, R.; Hamza, D.; Lubineau, A.; Bonnaffé, D. *Eur. J. Org. Chem.* **2004**, 2107–2117.
18. (a) Garegg, P. J.; Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200–2204; (b) Krog-Jensen, C.; Oscarson, S. *Carbohydr. Res.* **1998**, *308*, 287–296; (c) Stachulski, A. V.; Jenkins, G. N. *Nat. Prod. Rep.* **1998**, *15*, 173–186.
19. For some recent examples of problematic glycosylations with D-glucuronic acid donors, see: (i) Failure of glycoside formation: (a) Madaj, J.; Trynda, A.; Jankowska, M.; Wisniewski, A. *Carbohydr. Res.* **2002**, *337*, 1495–1498; (b) Zhao, W.; Kong, F. *Carbohydr. Res.* **2004**, *339*, 1779–1786; (c) Rele, S. M.; Iyer, S. S.; Baskaran, S.; Chaikof, E. L. *J. Org. Chem.* **2004**, *69*, 9159–9170; (d) O'Brien, A.; Lynch, C.; O'Boyle, K. M.; Murphy, P. V. *Carbohydr. Res.* **2004**, *339*, 2343–2354; (e) Zhao, W.; Kong, F. *Carbohydr. Res.* **2005**, *340*, 1673–1681; (ii) Orthoester formation: Ref. 19e: (f) Tamura, J.; Neumann, K. W.; Ogawa, T. *Liebigs Ann.* **1996**, 1239–1257; (g) Kaji, E.; Harita, N. *Tetrahedron Lett.* **2000**, *41*, 53–56; (h) Lu, X.-A.; Chou, C.-H.; Wang, C.-C.; Hung, S.-C. *Synlett* **2003**, 1364–1366; (iii) Formation of acylated acceptor: Ref. 19a,b.; (i) Stachulski, A. V. *Tetrahedron Lett.* **2001**, *42*, 6611–6613; (iv) Formation of other types of products: (j) Pearson, A. G.; Kiefel, M. J.; Ferro, V.; von Itzstein, M. *Carbohydr. Res.* **2005**, *340*, 2077–2085.
20. Ochiai, H.; Ohmae, M.; Kobayashi, S. *Carbohydr. Res.* **2004**, *339*, 2769–2788.
21. (a) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2128–2131; (b) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem.—Eur. J.* **2003**, *9*, 140–169.
22. Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9–C12.
23. (a) Garegg, P. J.; Kvarnström, I.; Niklasson, A.; Niklasson, G.; Svensson, S. C. *J. Carbohydr. Chem.* **1993**, *12*, 933–953; (b) Ziegler, T.; Eckhardt, E.; Birault, V. *J. Org. Chem.* **1993**, *58*, 1090–1099.
24. Daragics, K.; Fügedi, P. *Tetrahedron Lett.* **2009**, *50*, 2914–2916.
25. Corey, E. J.; Samuelsson, B. *J. Org. Chem.* **1984**, *49*, 4735–4735.
26. Nilsson, M.; Svahn, C.-M.; Westman, J. *Carbohydr. Res.* **1993**, *246*, 161–172.
27. Rana, S. S.; Barlow, J. J.; Matta, K. L. *Carbohydr. Res.* **1983**, *113*, 257–271.
28. Martin-Lomas, M.; Flores-Mosquera, M.; Chiara, J. L. *Eur. J. Org. Chem.* **2000**, 1547–1562.
29. Tatai, J.; Fügedi, P. *Org. Lett.* **2007**, *9*, 4647–4650.
30. Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105–113.
31. van Boeckel, C. A. A.; Beetz, T. *Tetrahedron Lett.* **1983**, *24*, 3775–3778.
32. Monosaccharide units of the tetrasaccharide are denoted by the letters a–d, starting from the reducing end.
33. Zegelaar-Jaarsveld, K.; Smits, S. A. W.; van der Marel, G. A.; van Boom, J. H. *Bioorg. Med. Chem.* **1996**, *4*, 1819–1832.