Chapter 4

A Synthetic Approach for Elucidating the Structure-Function Relationships of Chondroitin Sulfate in Neurobiology

Portions of this chapter were taken from a manuscript co-authored with Sarah E. Tully, Ross Mabon, Cristal I. Gama, Xuewei Liu, and Linda C. Hsieh-Wilson.

NMR characterization of the trisaccharide and hexasaccharide was performed with Dr. Scott Ross.

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Abstract

Chondroitin sulfate (CS) glycosaminoglycans are linear, sulfated oligosaccharides that play crucial roles in neuronal development, including the regulation of neurite outgrowth, axonal guidance, neurogenesis, and neuronal migration. In order to understand the relationship between CS structure and function in neurobiology, the synthesis of CS oligosaccharides of defined length and sulfation motifs is necessary. Herein we present a modular synthesis of CS molecules capable of providing access to a variety of CS sulfation patterns of defined lengths. Using this convergent approach, a focused library of the CS-E sulfation pattern was synthesized and a tetrasaccharide was determined to be the minimal length required for neuronal activity.

Introduction

Chondroitin sulfate (CS) glycosaminoglycans are linear, sulfated oligosaccharides that are ubiquitously expressed and play crucial roles in cell growth, differentiation, and migration (1). Made of repeating disaccharide subunits composed of D-glucuronic acid (GlcA) and 2-acetamido-2-deoxy-D-galactose (GalNAc), the CS oligosaccharide backbone can be sulfated at various positions, leading to the enormous amount of structural diversity that is believed to regulate the ability of CS to interact with specific proteins (Figure 4.1) (2). For example, a simple CS hexasaccharide can have 4,096 unique structures which differ only by their sulfation motifs. Yet, *in vivo*, CS oligosaccharides are known to be as long as 100 disaccharide units, highlighting their potential to store vast amounts of biological information.

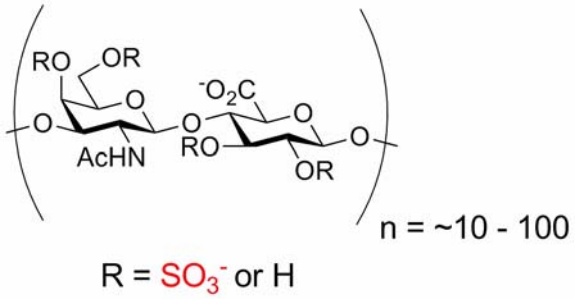


Figure 4.1. Structure of chondroitin sulfate glycosaminoglycans. Potential sites of sulfation are indicated.

In the body, CSs are found covalently attached to core proteins called chondroitin sulfate proteoglycans (CSPGs) (3,4). These proteoglycans are either secreted into the extracellular matrix or located at cell surfaces. By binding protein ligands, CSs mediate proteoglycan function. CSPGs can act by recruiting protein ligands, such as growth factors, to their cognate receptors on the cell surface, thereby initiating signal

transduction cascades (Figure 4.2) (5). Studies have shown that CSPGs play key roles in brain development through regulation of functions such as neurite outgrowth and axonal guidance (3,4).

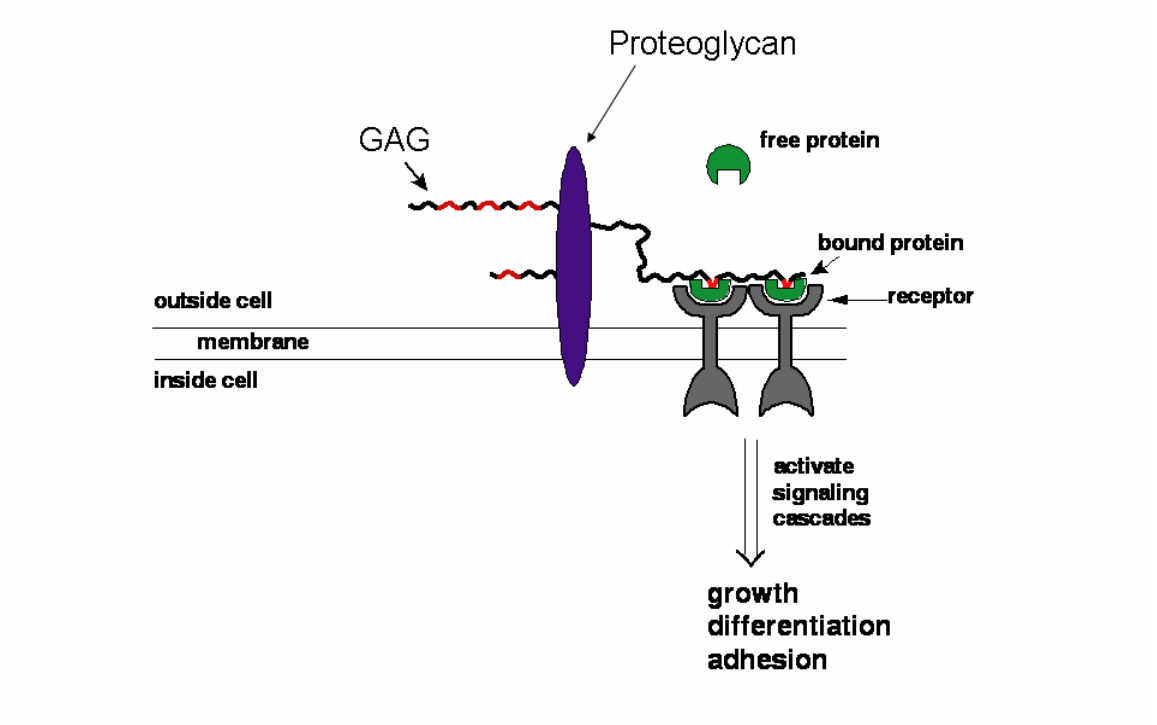


Figure 4.2. Model of proteoglycan function at the cell surface

Several lines of evidence indicate that the specific CS sulfation patterns on CSPGs dictate protein binding and, therefore, proteoglycan function (6). Distinct CS sulfation patterns and the expression of sulfotransferases, the enzymes that sulfate CSs, are precisely co-regulated in a spatiotemporal manner during brain development (7–9). In addition, a number of studies using CS preparations enriched in particular sulfation patterns have demonstrated how precisely CS structure determines its function. For example, preparations enriched in CS-E (CS molecules sulfated at the 4- and 6-positions of GalNAc) inhibit the nerve cell adhesion normally mediated by the neurotrophic factor midkine, while preparations of other CS sulfation sequences do not inhibit this adhesion

(10). Based on investigations using a monoclonal antibody, a sulfation-dependent CS epitope on the CSPG DSD-1 was found to be sufficient to promote neurite outgrowth. This led to the structural determination of two unique, sulfated hexasaccharides that give DSD-1 its neurite-promoting function (11,12).

Current CS isolation methods are limited. The CS preparations previously described were obtained by first isolating CS from the cartilage of various organisms, followed by enzymatic digestion with chondroitinases and purification by HPLC or gel filtration chromatography. These "purified" CS preparations continue to display considerable structural microheterogeneity, a fact illustrated by the observation that only 21.2% of the disaccharides in "pure" CS-D preparations (CSs sulfated at the 2-position of GlcA and the 6-position of GalNAc) are truly CS-D units (8,11).

Thus, CSs of a defined length and sulfation sequence cannot be purified and studied, hampering efforts to understand their precise biological roles. For instance, CS has been shown to prevent the growth of axons; yet it is also found in developing, growth-permissive regions (13,14). In addition, CSs have been shown both to stimulate and to attenuate the growth of cultured neurons (11,15,16). Notably, the molecules used in these studies were ~200 saccharides in length, poorly defined, and heterogeneously sulfated — features that might account for the contradictory observations. Synthetic access to CS molecules of defined length and sulfation pattern, in combination with biological studies, should enable a systematic examination of structure-activity relationships. While a number of reports of the chemical synthesis of CS molecules of various sulfation patterns exist, the biological activities of these molecules have not been reported (17).

We therefore sought to develop a modular synthesis of CS oligosaccharides that would provide synthetic access to a variety of CS sulfation patterns for biological study. As a first step, we chose to synthesize a focused library of CS-E oligosaccharides in order to determine the minimal length required for neuronal activity, since the CS-E sulfation motif has been implicated in the modulation of cell growth (Figure 4.3).

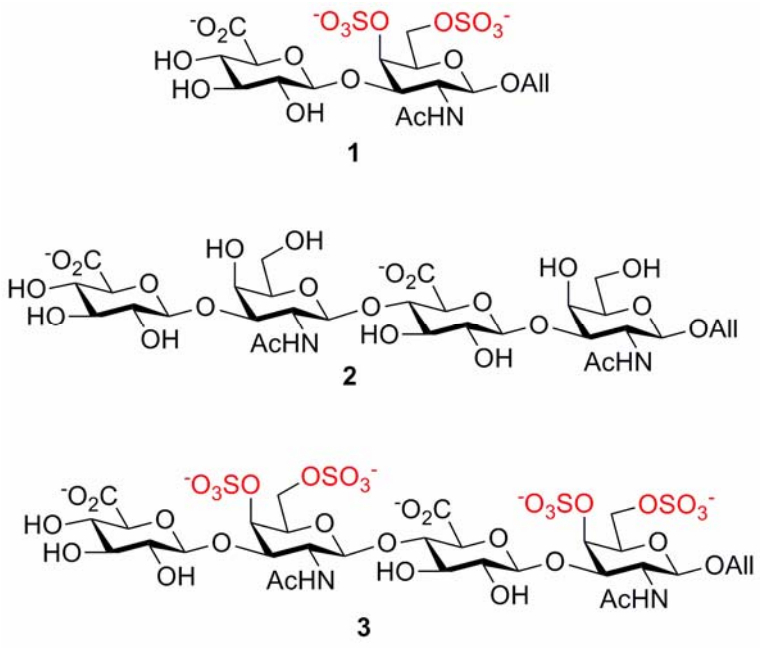


Figure 4.3. Structure of the initial target chondroitin sulfate library: CS-E disaccharide **1**; unsulfated tetrasaccharide **2**; CS-E tetrasaccharide **3**. All = allyl; Ac = acetyl

Results and Discussion

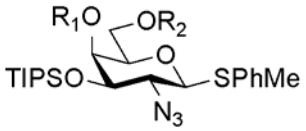
Preliminary Synthetic Design

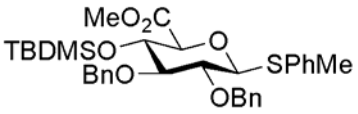
In considering the synthetic design, an orthogonal protecting group strategy was used to allow us to control the sulfation pattern and formation of β-glycosidic linkages in the final library. Previous studies have shown that protecting groups can greatly impact

both the yield and stereoselectivity of a glycosidic coupling reaction. For example, electron-withdrawing groups such as esters tend to deactivate the donor molecule by increasing the activation energy required to form the oxonium ion transition state of the glycosylation reaction (18).

Stereoselectivity of the coupling reaction is largely determined by the protecting group on the C-2 position of the donating species. Donors with a carbonyl functionality at the C-2 position exhibit neighboring-group participation, leading to formation of the less thermodynamically favored β linkages. Although the natural acetylated amine in the C-2 position of CS should act as a participating group, it cannot be used, as it deactivates glycosyl donors by forming a stable oxazoline species (19). The stereoselectivity for donors lacking a C-2 participating group is more unpredictable and generally must be experimentally determined (18).

With these issues in mind, we designed molecules **4**–**8** as target monomers for the synthesis of CS molecules capable of sulfation at the 4- and 6-positions of GalNAc (Figure 4.4). Monomers **4**–**8** utilize the acetyl, benzyl, silyl, and azido functionalities. Benzyl ethers were chosen to protect positions that would be free hydroxyl groups in the final product because they are stable, tend not to decrease the coupling reactivities of the sugars, and can be readily removed in the last step of the synthesis using H_2 with Pd/C. Acetate groups were chosen to protect positions that would be sulfated in the final product. They are easily cleaved under basic conditions. Silyl groups were chosen to protect positions where glycosidic linkages would be formed as they can be removed selectively with tetrabutylammonium fluoride in the presence of acetate and benzyl groups.





4: R_1 = Bn; R_2 = Bn
5: R_1 = Bn; R_2 = Ac
6: R_1 = Ac; R_2 = Bn
7: R_1 = Ac; R_2 = Ac

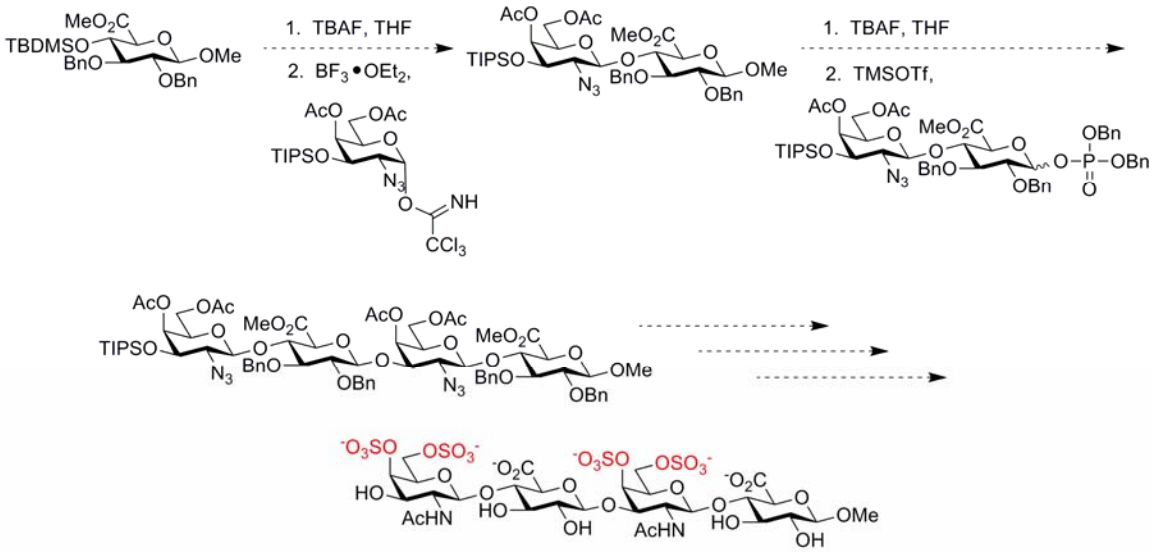
8

Figure 4.4. Monomers **4**–**8** for the synthesis of CS oligosaccharides by the synthetic route illustrated in Scheme 4.1. Acetyl groups protect positions that are sulfated in the final product. Benzyl groups protect positions that are free hydroxyl groups in the final product. Bn = benzyl; TIPS = triisopropylsilyl; TBDMS = *tert*-butyldimethylsilyl; Me = methyl

The amine was masked as an azide because the azide functionality is readily installed (20), very stable, and can be reduced and acetylated in a single step to give the desired acetylated amine (21). Azides also offer flexibility because they can be readily reduced and protected with trichloroacetyl, pthalamido, or other protecting groups (22).

The C-1 position of the monomers was protected with the *p*-toluenethiol group because the group is stable, readily synthesized, and UV-active. Thioglycosides also offer synthetic flexibility as they can be readily converted into glycosyl phosphates, imidates, halides, or other activated glycosyl donors (18,19).

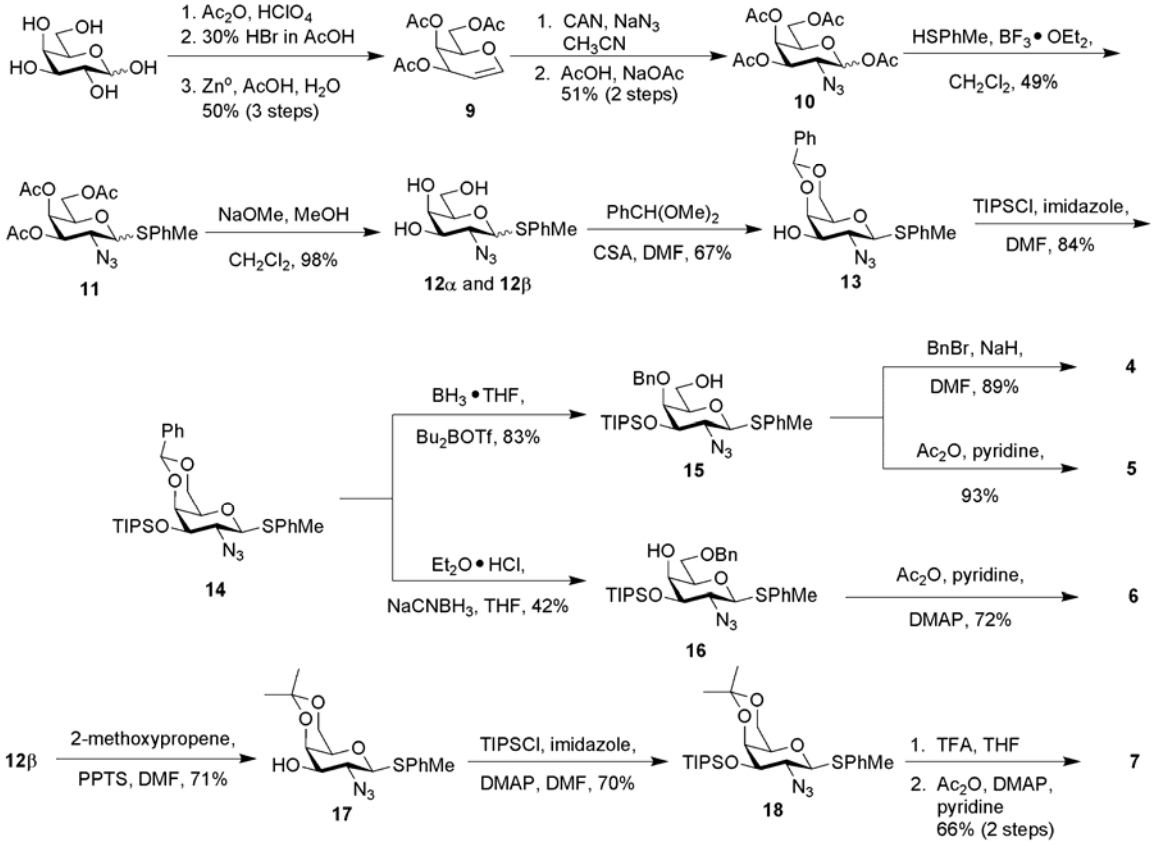
Thus, monomers **7** and **8** would be used to generate target molecules **1** and **3** (Scheme 4.1), and monomers **4** and **8** would be used to generate target molecule **2**. The synthetic strategy relies on efficient coupling of the monomers to form β(1,4) and β(1,3) linkages. Previous studies have shown that glycosyl imidates with azido groups in the C-2 position can be used to afford β(1,4) linkages (23–25). Moreover, glycosyl phosphate donors with non-participating benzyl groups at the C-2 position have been demonstrated to give β(1,3) disaccharide products (26–28).



Scheme 4.1. Proposed synthetic route for the CS library. TBAF = tetrabutylammonium fluoride; THF = tetrahydrofuran; TMSOTf = trimethylsilyl trifluoromethanesulfonate

Synthesis of the Preliminary GalNAc Monomers

A synthetic route on a multigram scale was developed for galactosamine monomers **4–7** starting from D-galactose (Scheme 4.2). Galactose was converted to the tri-*O*-acetylgalactal **9** in a three-step, one-pot reaction in 50% overall yield. Azidonitration of **9**, followed by reaction with sodium acetate in acetic acid afforded azide **10** as a mixture of α- and β-anomers in 51% yield. **10** was converted to the thioglycoside **11** in 49% yield by reaction with *p*-toluenethiol and boron trifluoride diethyl etherate. Deacetylation of thioglycoside **11** with sodium methoxide in methanol yielded triols **12α** and **12β**. The α- and β-anomers were separated at this stage to facilitate characterization by NMR of **12** and subsequent products. In addition, we wanted to isolate the β-thioglycoside monomer as β-thioglycosides have previously been used as glycosyl donors to obtain β selectivity in glycosidic bond coupling reactions (29–31). The α-anomer, however, is also valuable as it can be readily converted to the corresponding glycosyl imidate or phosphate.



Scheme 4.2. Synthesis of galactosamine monomers **4**–**7**. CAN = cerium ammonium nitrate; CSA = 10-camphorsulfonic acid; DMAP = 4-(dimethylamino)pyridine; PPTS = pyridinium *p*-toluenesulfonate; DMF = *N*,*N*-dimethylformamide; TFA = trifluoroacetic acid

Benzylidene protection of **12β** was achieved with benzaldehyde dimethyl acetal using 10-camphorsulfonic acid as catalyst to give **13** in 67% yield. Reaction of **13** with triisopropylsilyl chloride (TIPS-Cl) and imidazole afforded silyl-protected **14** in 84% yield. The benzylidene ring of **14** could be regioselectively opened with borane in tetrahydrofuran and dibutylboron triflate to give exclusively the 4-benzylated alcohol **15** in 83% yield. Benzylation of **15** using benzylbromide with sodium hydride proceeded smoothly to give the desired monomer **4** in 89% yield. Alternatively, **15** could be converted to monomer **5** in 93% yield using acetic anhydride in pyridine. Monomer **6**

was readily produced from **14** using sodium cyanoborohydride and diethyl ether in hydrogen chloride to give **16**, followed by acetylation.

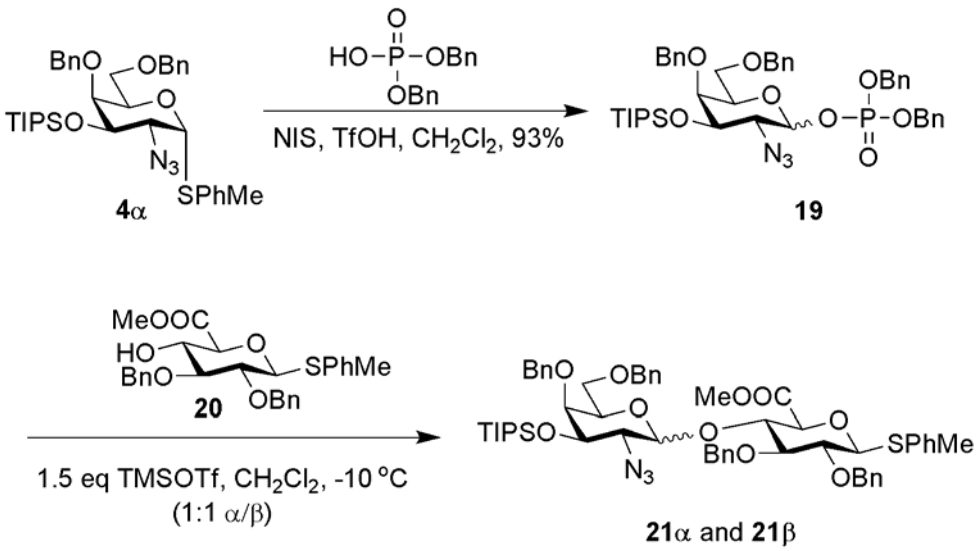
Monomer **7** was synthesized from **12β** in four steps. Protection of **12β** with 2-methoxypropene and a catalytic amount of pyridinium *p*-toluenesulfonate gave acetonide **17** in 71% yield. Protection of acetonide **17** using TIPS-Cl, imidazole, and catalytic 4-(dimethylamino)pyridine (DMAP) produced silyl ether **18** in 70% yield. **18** was readily converted to monomer **7** in 66% yield over two steps by deprotection of the acetonide ring with trifluoroacetic acid followed by reaction with acetic anhydride, pyridine, and DMAP. Concurrently, Sarah E. Tully developed the synthesis of GlcA monomer **8**.

Preliminary Exploration of the β(1,4) Glycosidic Bond Coupling Reaction

With the monomers in hand, we investigated the glycosidic bond coupling reactions. Our initial studies utilized the GalNAc donor **4** because it lacks deactivating ester groups. We explored the effect of the glycosyl donor on product selectivity by investigating two activating groups: dibenzylphosphates and α-trichloroacetimidates.

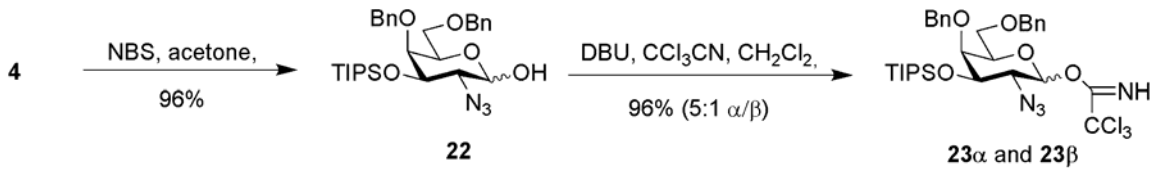
Glycosyl phosphates have previously been shown to give β-selectivity with non-participating groups at C-2 (26–28). Moreover, Sarah E. Tully found that using phosphate donors containing benzyl groups in the C-2 position of **8** afforded complete β-selectivity for the formation of β(1,3) CS linkages. The glycosyl phosphate donor **19** was formed in 93% yield by reacting monomer **4α** with dibenzyl phosphate, *N*-iodosuccinimide (NIS), and triflic acid (Scheme 4.3). Unfortunately, coupling of **19** to acceptor **20** (synthesized by Sarah E. Tully) using trimethylsilyl

trifluoromethanesulfonate (TMSOTf) as catalyst at -10 ^{o}C did not result in β-selectivity for the β(1,4) linkage.



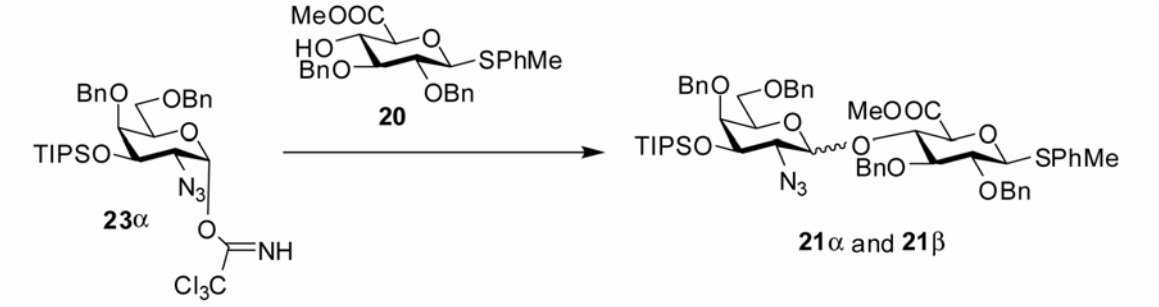
Scheme 4.3. Activation of a galactosamine monomer by dibenzyl phosphate and subsequent coupling. NIS = *N*-iodosuccinimide

α-Trichloroacetimidates are also precedented to afford β-selectivity with non-participating groups, such as azides, in the C-2 position (23,25,32). Glycosyl imidates **23α** and **23β** were synthesized from monomer **4** by hydrolysis with *N*-bromosuccinimide (NBS) in 96% yield, followed by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and trichloroacetonitrile to form the imidate as a 5:1 α:β mixture in 96% yield (Scheme 4.4). As only α-imidates have previously been shown to yield β-disaccharides (23,25,32), we sought reaction conditions that would favor the α-imidate product. Precedence indicated that use of a strong base would result in α-selectivity (33). While sodium hydride produced a 2:1 α:β mixture in 66% total yield, DBU afforded the desired α-anomer with greater selectivity.



Scheme 4.4. Activation of galactosamine monomer **4**. NBS = *N*-bromosuccinimide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

The coupling of **23α** to acceptor **20** to form disaccharide **21** was explored under a variety of solvent, Lewis acid, and temperature conditions (Scheme 4.5). The α:β selectivity for each reaction was determined by HPLC. The optimized reaction conditions resulted in an excellent yield of 94% with good β-selectivity of 82β:18α.



Reaction No.	Solvent	Temp. (°C)	Catalyst	Equiv. of Catalyst	Product Selectivity	Total Yield
1	CH_3CN	-20	$BF_3 \bullet OEt_2$	0.4	57β:43α	21%
2	CH_3CN	-10	$BF_3 \bullet OEt_2$	0.4	37β:63α	30%
3	CH_3CN	-40	TMSOTf	0.18	56β:44α	27%
4	CH_3CN	-20	TMSOTf	0.05	47β:53α	-
5*	CH_2Cl_2:C_6H_{12}	-25	$BF_3 \bullet OEt_2$	0.4	67β:33α	-
6*	toluene	-20	$BF_3 \bullet OEt_2$	0.4	60β:40α	-
7*	toluene	-20	TMSOTf	0.1	63β:37α	-
8*	toluene	+ 4	$BF_3 \bullet OEt_2$	0.1	79β:21α	-
9*	**toluene**	**-20**	**$BF_3 \bullet OEt_2$**	**0.1**	**82β:18α**	**-**
10*	**toluene**	**-10**	**$BF_3 \bullet OEt_2$**	**0.1**	**82β:18α**	**94%**

*Catalyst added periodically over the reaction time.

Scheme 4.5. Summary of key reactions for the optimization of the β(1,4) model coupling reaction

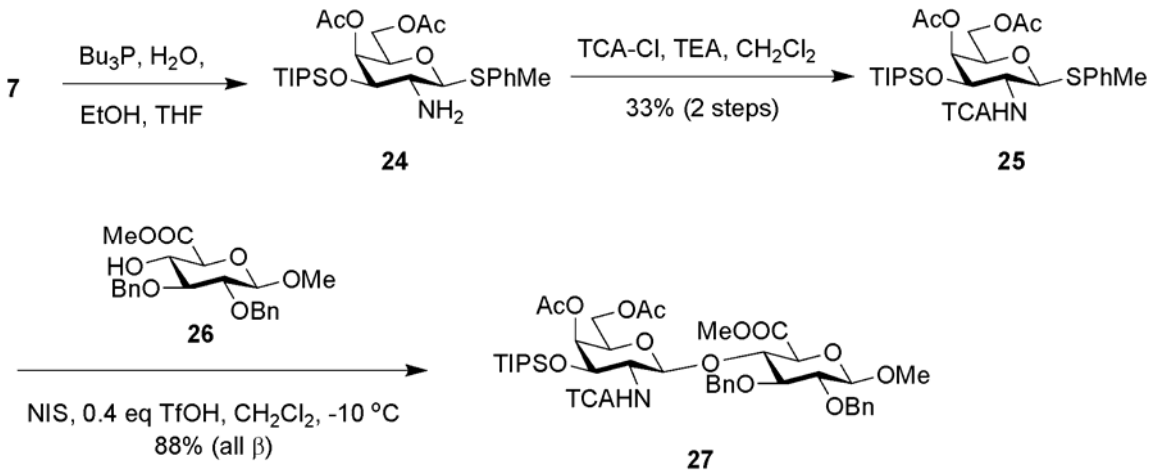
Installation and Exploration of the TCA Protecting Group

When extending our synthetic methodology to solid-phase, β selectivity will become particularly important. Thus, while good selectivity in high yield was obtained for the β(1,4) glycosidation, we desired greater selectivity. We therefore investigated the use of a trichloroacetyl (TCA) group at the C-2 position of the GalNAc monomer.

The TCA functionality offers a number of advantages. The high electronegativity of the chlorine atoms decreases the nucleophilicity of the carbonyl oxygen of the TCA group relative to the acetyl group. For the glycosidic bond coupling reaction, this translates to an oxazoline transition state that is less stable than that of the corresponding acetyl-protected amine (18,20). Thus, while the acetylated amine does not undergo efficient glycosidation, the TCA group has previously been demonstrated to yield excellent β selectivity with both β-thioglycoside and α-imidate donors (18,29,34,35). In addition, the TCA group is easily installed, yet readily removed and acetylated in a single step using tributylstannane and azoisobutyronitrile (35).

Installation of the TCA group to yield thioglycoside **25** proved to be challenging (Scheme 4.6). A number of conditions were investigated for reduction of azide **7** to the free amine **24**. These conditions included the use of various phosphine reducing agents (triphenylphosphine, tributylphosphine, trimethylphosphine), sodium borohydride with nickel (II) chloride and boric acid, and catalytic hydrogenation with 10% palladium on carbon. However, all conditions resulted in less than 40% yield. Isolation of side products suggested that acyl migration was occurring before TCA protection could be performed. The optimal conditions utilized tributylphosphine and water in ethanol and

tetrahydrofuran. The TCA-protected thioglycoside **25** was obtained following reaction with trichloroacetyl chloride and triethylamine in 33% yield over both steps.

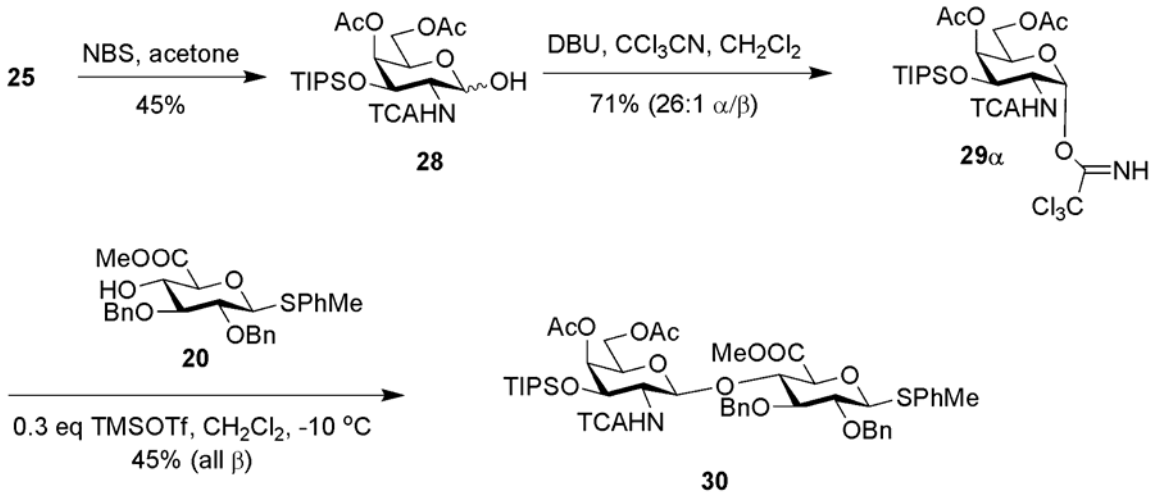


Scheme 4.6. Installation of the TCA group and preliminary investigations of the TCA-mediated β(1,4) coupling reaction via a thioglycoside-activated monomer. TEA = triethylamine; TCA = trichloroacetyl

With thioglycoside **25** in hand, its coupling to acceptor **26** was next investigated**.** Initial studies based on literature precedence using NIS and TMSOTf resulted in very low yields. Previous reports indicated that the use of triflic acid rather than TMSOTf could increase product formation (36). However, when NIS and triflic acid (0.7 equivalents) were used as activators, the disaccharide lacking the TIPS group was obtained in 29% yield, as well as the desired disaccharide product **27** in 36% yield. Using less triflic acid (0.4 equivalents) prevented removal of the acid-sensitive silyl group and resulted in a significant increase in product formation, with the desired disaccharide product **27** being obtained in 88% yield. Formation of the α-disaccharide was not detected by NMR.

To compare the relative reactivities and selectivities of α-imidates and β-thioglycosides, the coupling of α-trichloroacetimidate **29α** to acceptor **20** was examined

(Scheme 4.7). TCA-protected trichloroacetimidate **29α** was synthesized following the methods used for the formation of the dibenzylated imidate **23α**. Briefly, thioglycoside **25** was hydrolyzed with NBS in 45% yield, and **29α** was formed from the hydrolyzed product **28** using DBU and trichloroacetonitrile in 71% yield with excellent α-selectivity (26:1 α/β). Coupling of imidate **29α** to thioglycoside **20** using TMSOTf yielded the desired product **30** in 45% yield without any appreciable observation of the α-disaccharide. The difference in selectivities (100% β for **29α** versus 82% β for **23α**) illustrates the effectiveness of the TCA group in directing the stereoselectivity of the glycosylation reaction.



Scheme 4.7. Exploration of the TCA-mediated β(1,4) coupling reaction via a trichloroacetimidate-activated monomer

Exploration of the β(1,4) Coupling Reaction with the Modified GalNAc Monomer

Concurrent preliminary investigations by Sarah E. Tully indicated that sulfation of our oligosaccharides may be challenging due to the high charge density and steric hindrance of the resulting sulfated product (22,37). Ross Mabon therefore investigated

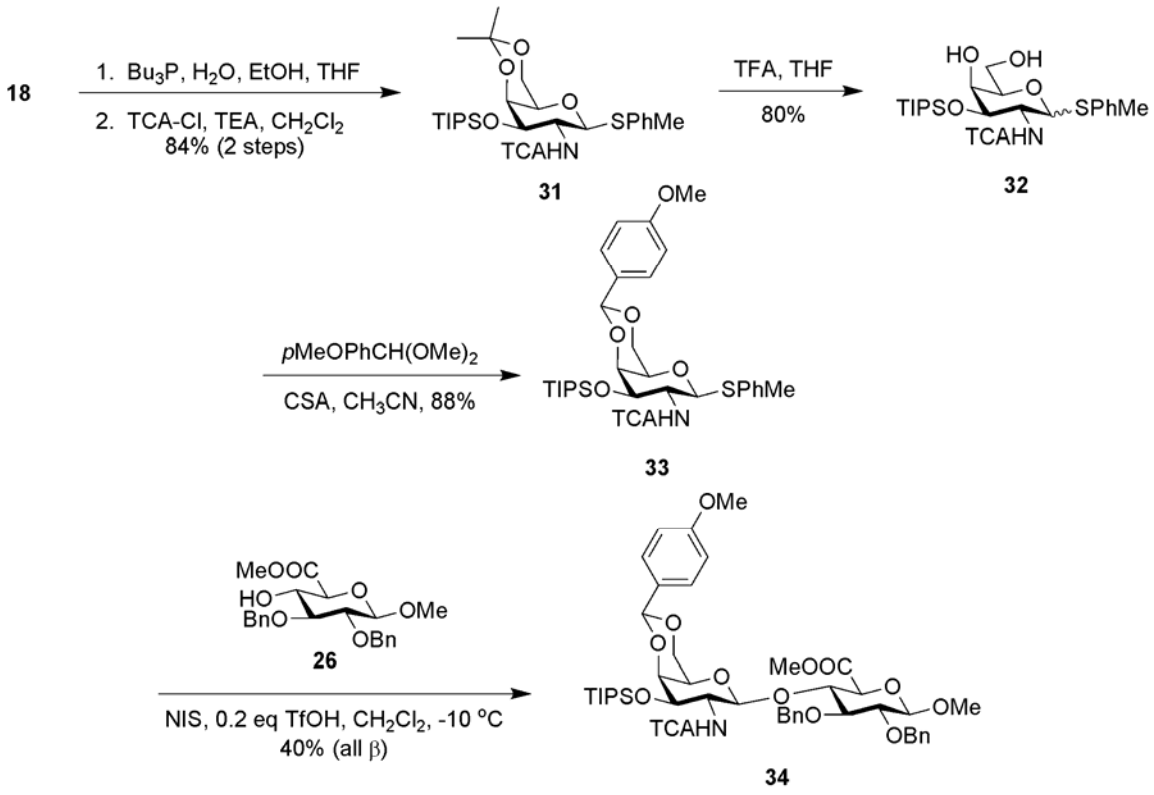
the exchange of the acetyl protecting groups for the *p*-methoxybenzylidene ring. In particular, the TCA group can be converted readily to the desired acetate using tributylstannane and azoisobutyronitrile in the presence of the *p*-methoxybenzylidene ring. In addition, the benzylidene ring can be regioselectively opened to afford either the 4-hydroxyl or 6-hydroxyl product using the previously-developed conditions. This approach may allow for controlled sulfation of the more difficult C-4 position, followed by deprotection of the *p*-methoxybenzyl (PMB) group and sulfation of the C-6 position. This new strategy would be an elegant route to 4-monosulfated, 6-monosulfated, or 4,6-disulfated CSs originating from a single GalNAc monomer and a single GlcA monomer.

To confirm the use of the *p*-methoxybenzylidene ring, the coupling of thioglycoside **33** to acceptor **26** was next investigated. For these preliminary investigations, thioglycoside donor **33** was synthesized from the acetonide-protected thioglycoside **18** in 4 steps (Scheme 4.8). Reduction of the azide with tributylphosphine and water, followed by TCA protection gave **31** in 84% yield. Hydrolysis of the acetonide ring with trifluoroacetic acid gave diol **32** in 80% yield. Donor **33** was then readily obtained in 88% yield using *p*-anisaldehyde dimethyl acetal and 10-camphorsulfonic acid as catalyst to form the *p*-methoxybenzylidene ring. Glycosylation studies using NIS and triflic acid to couple thioglycoside **33** to acceptor **26** yielded the desired β-disaccharide **34** in 40% yield. Importantly, no α-disaccharide was observed.

Exploration of the Benzoyl Protecting Group

Based on the β-stereoselectivity observed with the use of the TCA protecting group, we decided to explore the substitution of the benzyl groups in GlcA monomer **8**

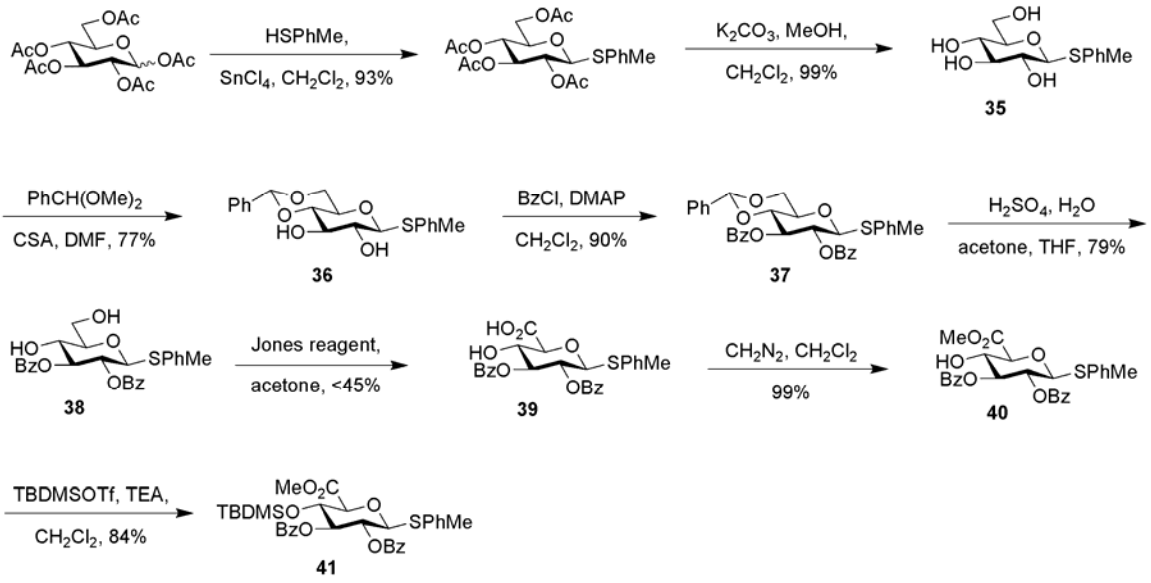
with benzoyl (Bz) protecting groups, which would be capable of serving as participating groups in the C-2 position and are precedented to do so (38). Preliminary investigations for the installation of the benzoyl groups were based on the route developed by Sarah E. Tully for the synthesis of monomer **8**.



Scheme 4.8. Exploration of the TCA-mediated β(1,4) coupling reaction with monomers utilizing the *p*-methoxybenzyl protecting group

Commercially available β-D-glucose pentaacetate was converted to the thioglycoside in 93% yield, followed by deacetylation with potassium carbonate and methanol to form **35** in 99% yield (Scheme 4.9). Protection of tetraol **35** to form **36** with benzaldehyde dimethyl acetal and catalytic 10-camphorsulfonic acid proceeded in 77% yield. Rather than dibenzylation of **36**, dibenzoylation with benzoyl chloride and DMAP was performed to give **37** in 90% yield. Removal of the benzylidene ring with sulfuric

acid and water yielded diol **38**. The previously developed route had next utilized a selective acetylation at the C-6 hydroxyl. To decrease reaction steps, selective oxidation at the C-6 position of **38** was explored. Oxidation with pyridinium dichromate led to product degradation, but utilization of Jones reagent successfully generated **39**, though in relatively low yields (~40%) (39). Esterification of the acid with diazomethane followed by silyl protection at the C-4 hydroxyl yielded the GlcA monomer **41**. Preliminary coupling reactions utilizing monomer **41** performed by Sarah E. Tully and Ross Mabon indicated that the benzoyl protecting groups would provide the desired β-stereoselectivity in good yield.

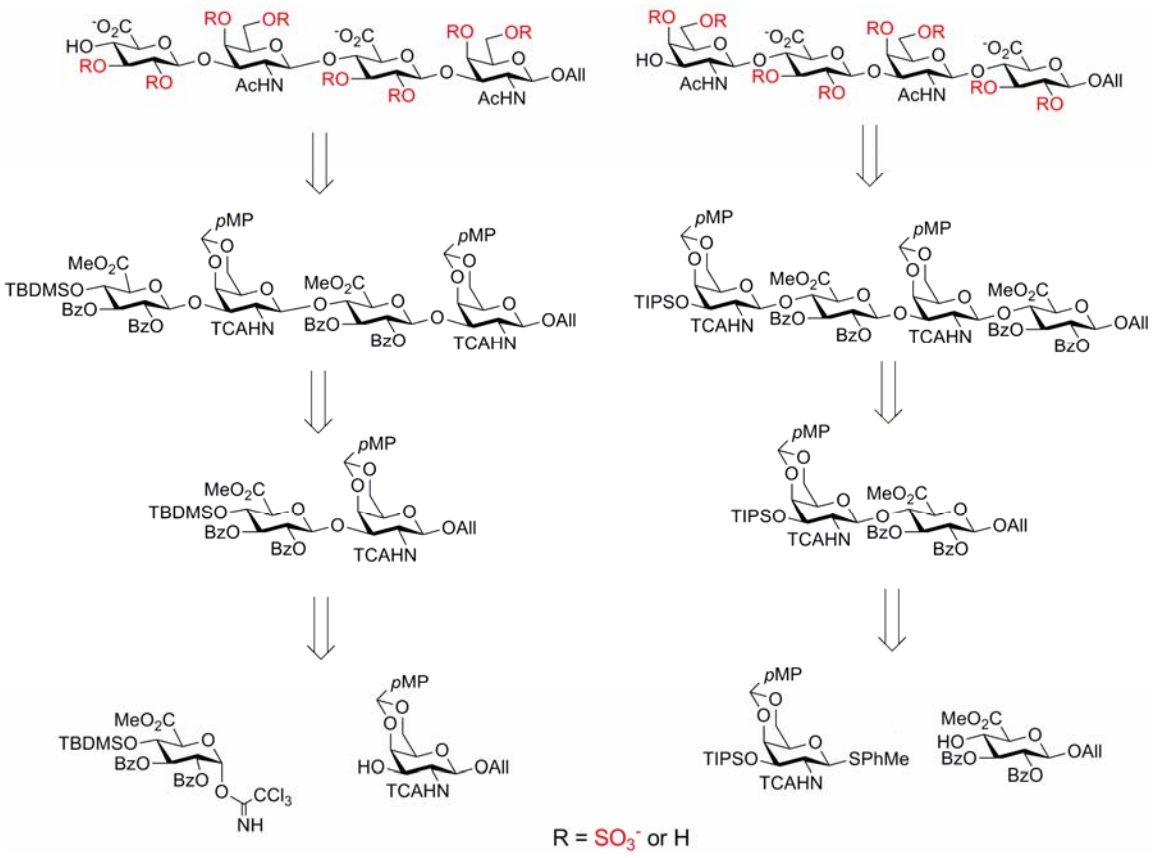


Scheme 4.9. Exploration of the glucuronic acid monomer utilizing the Bz protecting group. Bz = benzoyl

Revised Synthetic Design

Based on these preliminary investigations, we refined our orthogonal protecting group strategy. The acetyl and benzyl groups were replaced on the galactosamine

monomer with the readily cleavable *p*-methoxybenzylidene ring. TCA and benzoyl groups were placed at the C-2 positions of the GalNAc and GlcA monomers, respectively, to direct the stereochemistries of the β(1,3) and β(1,4) glycosidic bond coupling reactions. In addition, we decided to place an allyl group at the reducing end of the oligosaccharides, which we anticipated to offer a convenient means to conjugate our molecules to proteins, surfaces, and small molecules.



Scheme 4.10. Revised retrosynthetic analysis 1 (left) and retrosynthetic analysis 2 (right) of the CS-E tetrasaccharides utilizing the Bz, TCA, and PMB protecting groups. *p*MP = *p*-methoxyphenyl

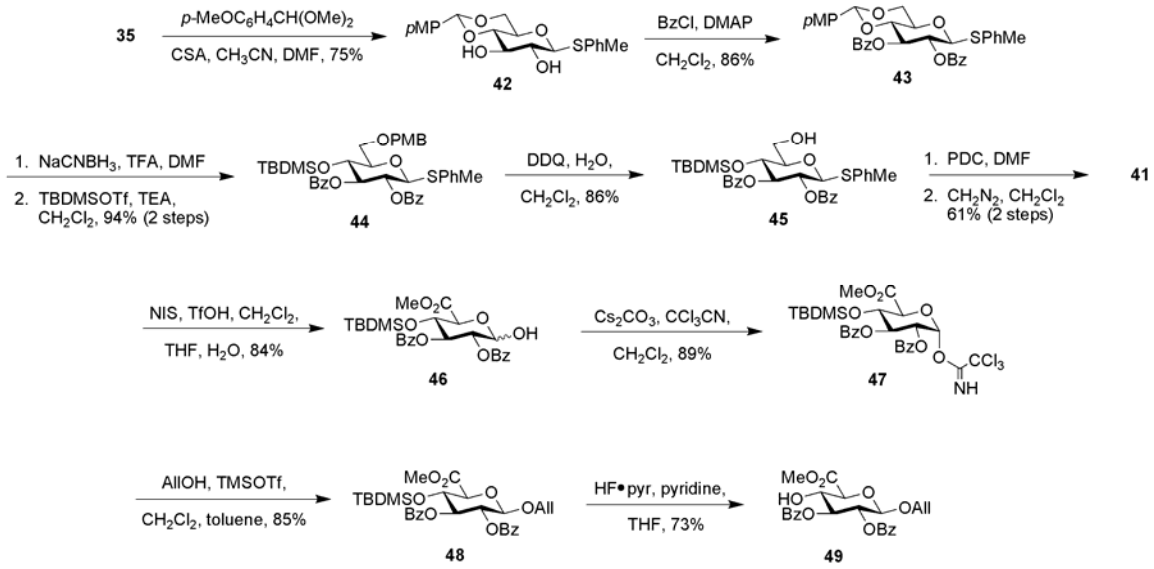
Based on this new strategy, a new retrosynthetic analysis of the CS-E tetrasaccharide was performed (Scheme 4.10). Two possible routes were recognized, both of which can be followed from common GlcA and GalNAc monomer syntheses. In

retrosynthesis 1, the less-hindered β(1,3) coupling reaction is performed first to form the disaccharide, while in retrosynthesis 2, the more-hindered β(1,4) coupling reaction is performed earlier. We decided to explore both synthetic routes to determine which would give the highest yields with the greatest stereoselectivity.

Optimized Synthesis of the Revised GlcA Monomers

An optimized synthesis for the refined GlcA monomers was developed that avoided the low-yielding Jones oxidation and cumbersome benzylidene deprotection/C-6 hydroxyl re-protection (Scheme 4.11). Protection of tetraol **35** using *p*-methoxybenzylidene dimethyl acetal and catalytic 10-camphorsulfonic acid yielded diol **42** in 70% yield, from which **43** was produced in 86% yield with benzoyl chloride and DMAP. Regioselective ring opening of **43** performed with sodium cyanoborohydride and trifluoroacetic acid yielded the PMB group exclusively at the C-6 position. The C-4 hydroxyl could then be protected with a silyl group to give **44** in 94% yield over both steps. Oxidative cleavage of the PMB group with DDQ was then performed to afford **45** in 86% yield. Oxidation of the C-6 hydroxyl was achieved with pyridinium dichromate, and the methyl ester **41** was produced by reaction of the acid with diazomethane. The thioglycoside was next hydrolyzed with NIS and triflic acid to give **46**, which was reacted with cesium carbonate and trichloroacetonitrile to afford imidate **47**, the key GlcA monomer in retrosynthesis 1. Finally, imidate **47** was coupled to allyl alcohol to form **48**, followed by silyl deprotection with HF•pyridine to produce acceptor **49**, the key GlcA monomer of retrosynthesis 2. Reaction of **48** with TBAF resulted in β-elimination

of the C-4 hydroxyl. Importantly, synthesis of the two GlcA monomers was achieved on a multigram scale.



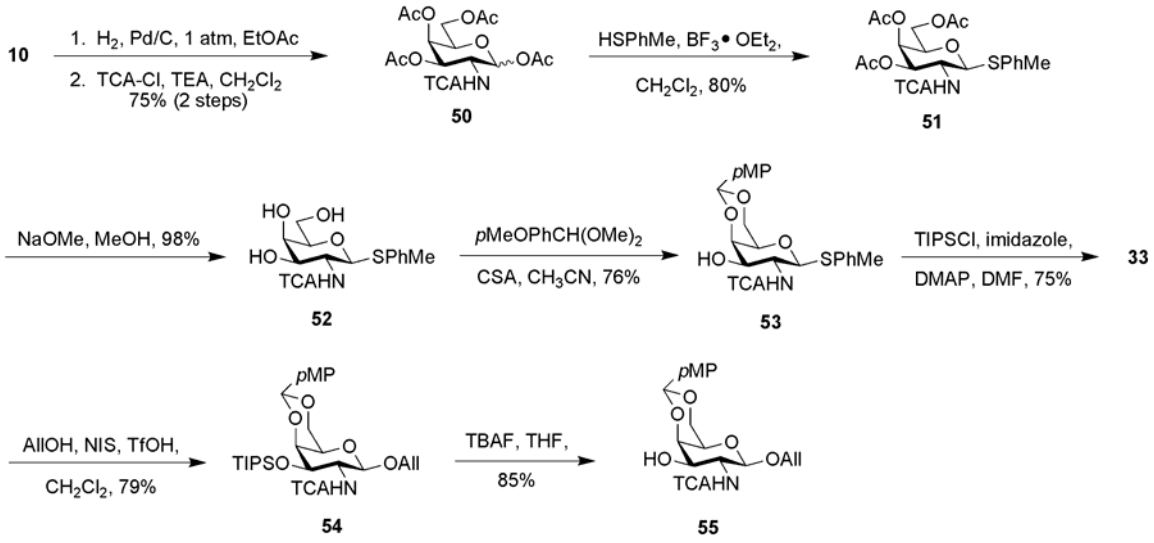
Scheme 4.11. Final synthetic route for the glucuronic acid monomer. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; PDC = pyridinium dichromate; pyr = pyridine

Optimized Synthesis of the Revised GalNAc Monomers

An optimized synthetic route for the refined GalNAc monomers was developed by Ross Mabon that circumvented the low-yielding azide reduction with tributylphosphine, as well as affording exclusively the more desirable β-thioglycoside (Scheme 4.12). Reduction of the peracetylated azide **10** was achieved via hydrogen and Pd/C, and was followed by TCA protection to give **50** in 75% yield. The thioglycoside was prepared using boron trifluoride diethyl etherate and *p*-toluenethiol to give the β-glycoside **51** due to the presence of the TCA participating group. Deacetylation was followed by *p*-methoxybenzylidene ring protection to afford **53**. Silyl protection at the C-

3 hydroxyl of **53** yielded **33**, the key GalNAc monomer of retrosynthesis 2. Initial couplings by Ross Mabon of GlcA imidate **47** to thioglycoside acceptor **53** had found that a significant by-product of the reaction was thioglycoside **41**, presumably via an intermolecular aglycon transfer reaction. Thus, to prevent this transfer, thioglycoside **33** was coupled to allyl alcohol to form **54**, followed by silyl deprotection with TBAF to yield allyl acceptor **55**, the key GalNAc monomer of retrosynthesis 1. The synthesis of both GalNAc monomers was accomplished on a multigram scale.

To shorten the synthetic route to monomer **55**, allylation of molecule **50** was explored. However, activation with triflic acid and NIS resulted in low yields (<25%), with the major product being the recovery of starting material.

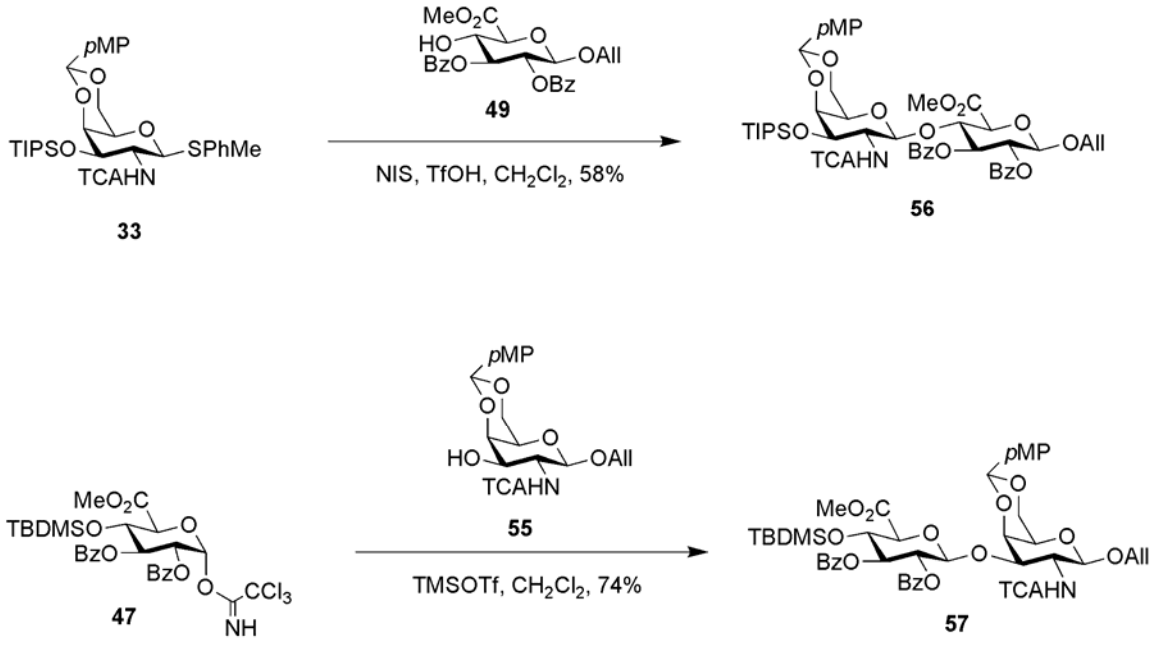


Scheme 4.12. Final synthetic route for the galactosamine monomer

Exploration of the Glycosidic Bond Coupling Reactions with the Refined Monomers

With the monomers in hand, we proceeded to investigate the coupling reactions to form the key disaccharide intermediates. Since the preliminary investigations of the

β(1,4) coupling reactions had indicated use of the GalNAc thioglycoside donor gave higher yields than reaction with GalNAc imidate donors, and since synthesis of the imidate donor requires an additional two reactions, optimization of the β(1,4) coupling reaction with the refined monomers was focused on the use of the thioglycoside donor. Thioglycoside **33** was coupled to allyl glycoside acceptor **49** using NIS and the dropwise addition of triflic acid in dichloromethane at -15 ^{o}C to yield the desired β-linked disaccharide **56** (Scheme 4.13). However, the corresponding α-linked disaccharide was also obtained in ~32% yield, which could be separated from the β-linked disaccharide by standard flash chromatography.

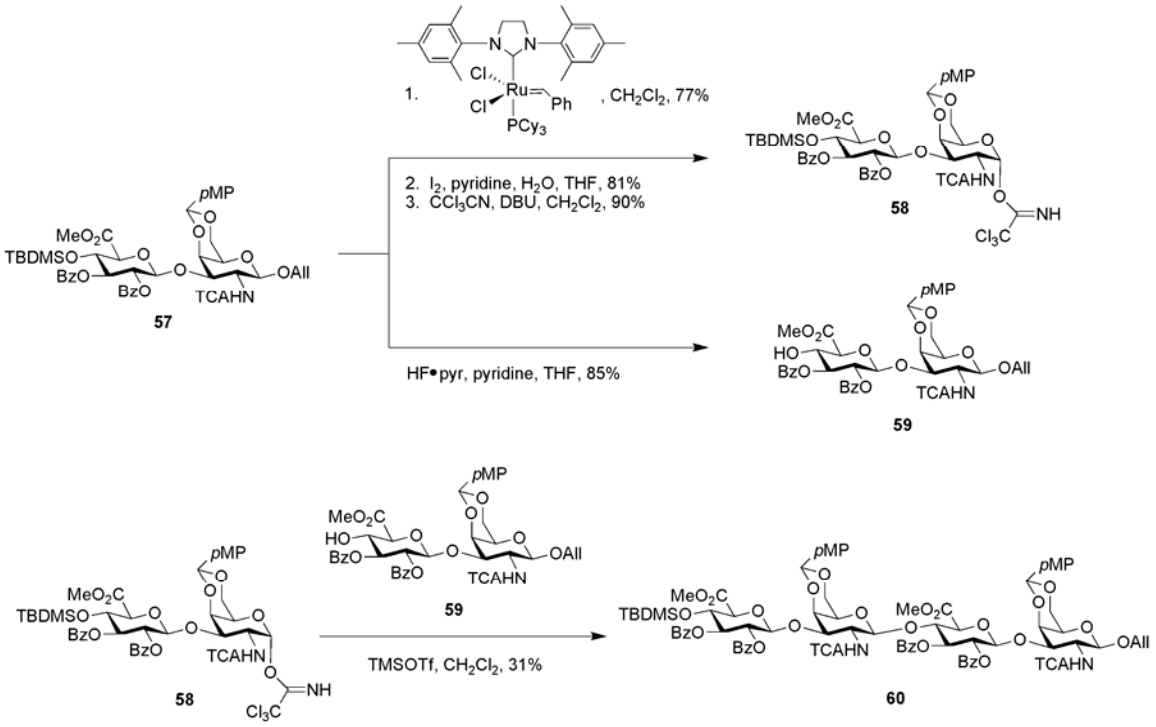


Scheme 4.13. Exploration of the glycosidic bond coupling reactions utilizing the optimized protecting group strategy

Ross Mabon and Sarah E. Tully concurrently investigated the formation of the β(1,3) coupling reaction with the refined monomers from retrosynthesis 1. In contrast to the β(1,4) coupling reaction, reaction of imidate donor **47** to acceptor **55** with TMSOTf in

dichloromethane at -40 ^{o}C yielded exclusively the desired β-linked disaccharide **57** in 74% yield. With the higher yield and greater stereoselectivity of the coupling reaction, disaccharide **57** would be easier to synthesize on a multigram scale. Thus, we decided to proceed with the synthesis of our target molecules using retrosynthesis 1 and molecule **57** as the key disaccharide unit.

Synthesis of the Fully-Protected Tetrasaccharide



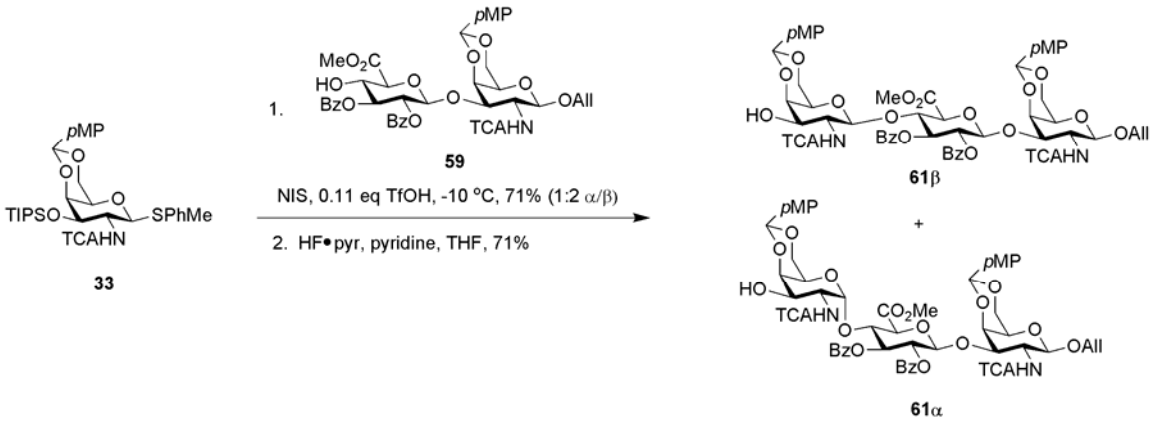
Scheme 4.14. Synthesis of the fully-protected tetrasaccharide

Ross Mabon investigated the formation of the fully-protected tetrasaccharide from the key disaccharide building block **57**, which could be converted to both the imidate donor and the allyl glycoside acceptor for the formation of the tetrasaccharide (Scheme

4.14). Conversion of the C-1 allyl group to the imidate was achieved by treatment with Grubbs' second-generation catalyst in the presence of H_2 (40), followed by hydrolysis of the enol ether and conversion to trichloroacetimidate **58** under standard conditions (41,42). The disaccharide acceptor **59** was readily obtained by silyl deprotection of **57** with HF•pyridine. Coupling of imidate **58** to acceptor **59** was achieved by activation with TMSOTf at -15 ^{o}C to yield the desired tetrasaccharide **60**. Importantly, this synthetic route enabled us to generate gram quantities of the desired tetrasaccharide.

Synthesis and NMR Characterization of a Trisaccharide and Hexasaccharide

We also explored the formation of trisaccharides using thioglycoside **33** and disaccharide acceptor **59** (Scheme 4.15). Synthesis of trisaccharides would provide access to CS molecules with an odd number of monosaccharide units. They could also be coupled to form hexasaccharides, as CS molecules longer than tetrasaccharides are also desirable. In addition, the use of **33** served as a model for the coupling of a galactosamine thioglycoside to the disaccharide acceptor.



Scheme 4.15. Synthesis of a trisaccharide

The coupling reaction was found to give two major trisaccharide products. The stereochemistry of these molecules was determined by 2-D NMR experiments on the desilylated products **61β** and **61α**. Despite optimization for production of the β-anomer, the reaction gave poor stereoselectivity, with only a 1:2 ratio of the α- versus β-anomers.

NMR characterization was performed on desilylated **61β** and **61α** because it was found that the presence of the C-3 hydroxyl on the terminal GalNAc monomer in these compounds greatly eased NMR characterization. The proton on the C-3 hydroxyl group is readily identified in the NMR spectrum by its low chemical shift, allowing for the identification of the anomeric proton of the terminal GalNAc unit (Figures 4.5–6).

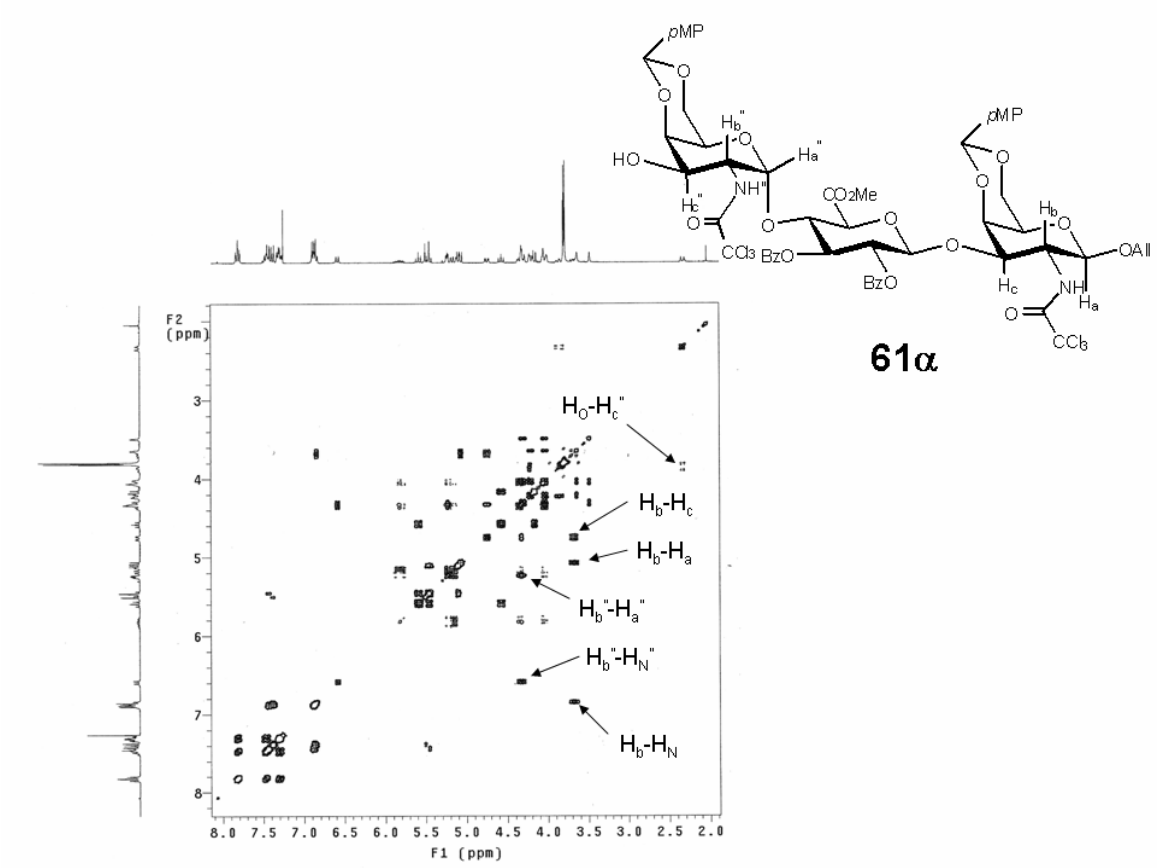


Figure 4.5. Spectrum from a gCOSY (correlation spectroscopy) experiment of trisaccharide **61α**, obtained on a 300 MHz spectrometer in $CDCl_3$. For H_a", δ was found to be 5.23 ppm, and J = 3.3 Hz. Proton assignments were verified with additional NMR experiments. For clarity, only protons highlighted in the spectrum are indicated in the chemical structure shown.

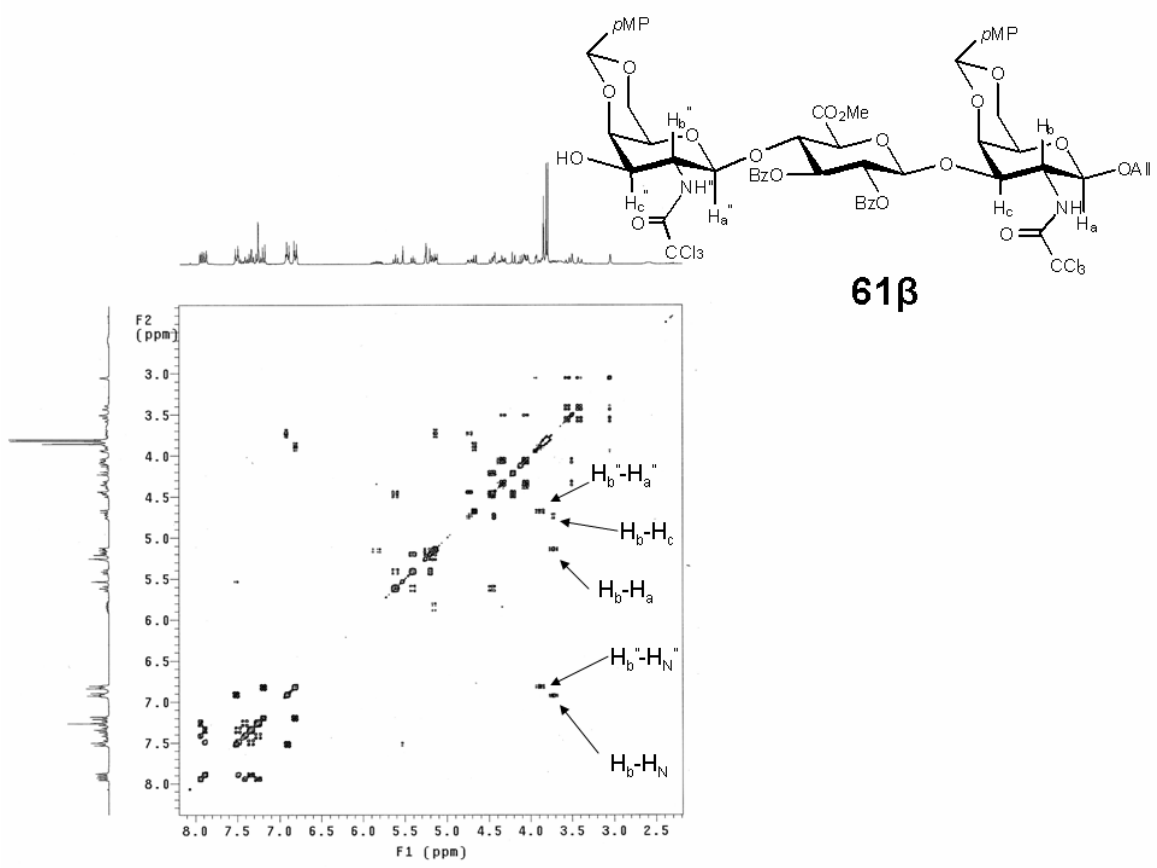
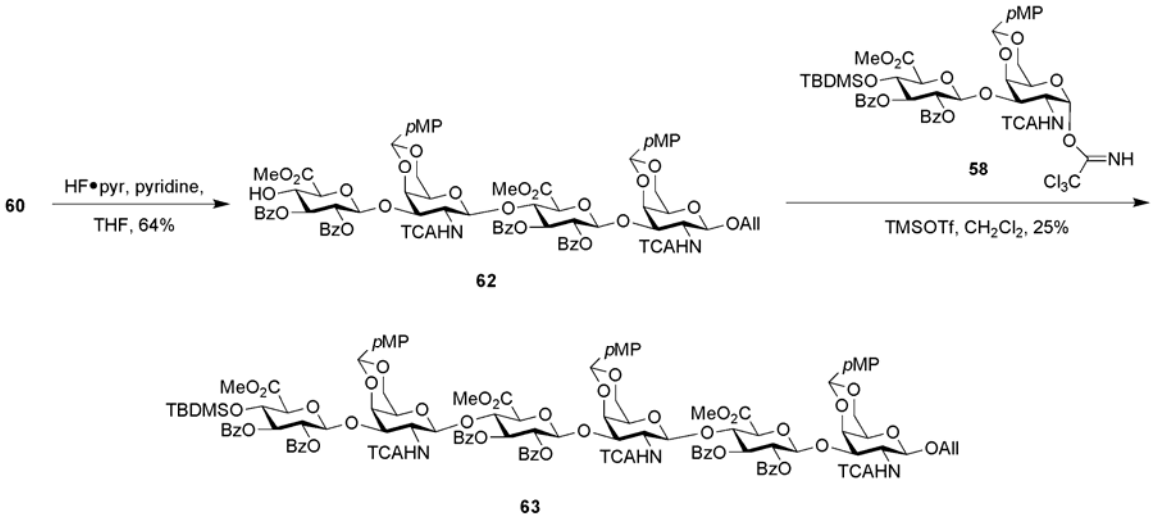


Figure 4.6. Spectrum from a gCOSY (correlation spectroscopy) experiment of trisaccharide **61β**, obtained on a 300 MHz spectrometer in $CDCl_3$. For H_a", δ was found to be 4.67 ppm, and J = 8.1 Hz. Proton assignments were verified with additional NMR experiments. For clarity, only protons highlighted in the spectrum are indicated in the chemical structure shown.

Sarah E. Tully investigated the synthesis of the fully-protected hexasaccharide (Scheme 4.16). Tetrasaccharide **60** was desilylated to give acceptor **62**, which was then coupled to imidate **58** with TMSOTf in an unoptimized yield of 25% to give fully-protected hexasaccharide **63**.

The β-stereochemistries of the glycosidic bond linkages of **63** were also verified by 2-D NMR experiments. In particular, elucidation of the stereochemistry of the 1,4-linkages was required since the β(1,3) linkages were already verified in the simpler disaccharide subunits. The N-H protons (H_N) of the GalNAc units are easily identified by their distinctive chemical shifts. Variation in the peak heights of the TOCSY spectra then allow for the identification of the anomeric protons on each GalNAc residue (Figure 4.7).



Scheme 4.16. Synthesis of a hexasaccharide

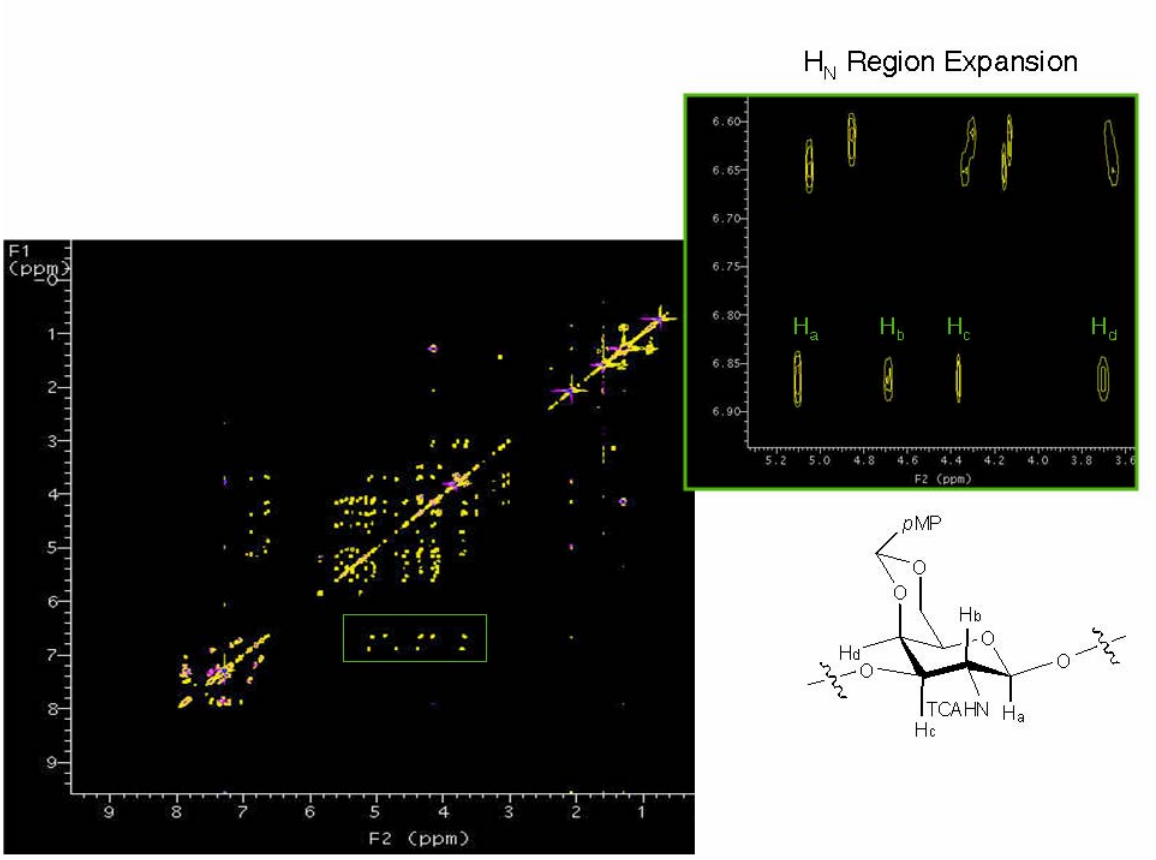
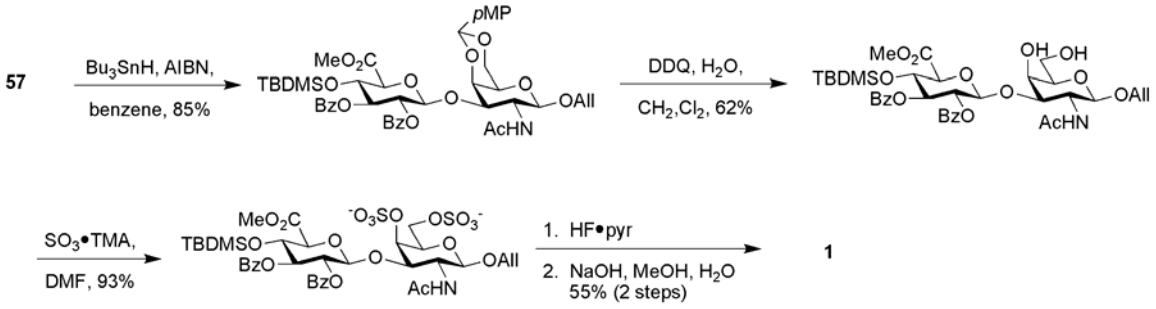


Figure 4.7. Spectrum from a TOCSY (Total Correlation Spectroscopy) experiment of hexasaccharide **63**, obtained with a 150 ms mixing time on a 600 MHz spectrometer in $CDCl_3$. The H_N region of the spectrum, which is highlighted with a green box, is expanded. Proton identification for a GalNAc unit is indicated.

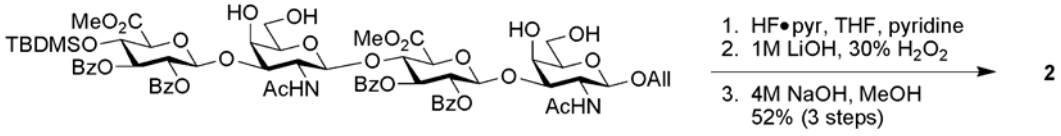
Conclusion

We have developed a modular synthesis of CS oligosaccharides of defined lengths and a variety of sulfation patterns. This convergent approach was successfully used to synthesize a focused library of defined lengths of the CS-E sulfation pattern (molecules **1**–**3**; Schemes 4.17–19). This initial library of molecules was used to show that a CS-E tetrasaccharide was the minimal motif needed for stimulation of neuronal growth and differentiation, the first direct investigations into the structure-activity relationships of CS using homogenous, synthetic molecules. In addition, this synthetic route is capable of accessing a variety of CS sulfation patterns (Scheme 4.20) (43).

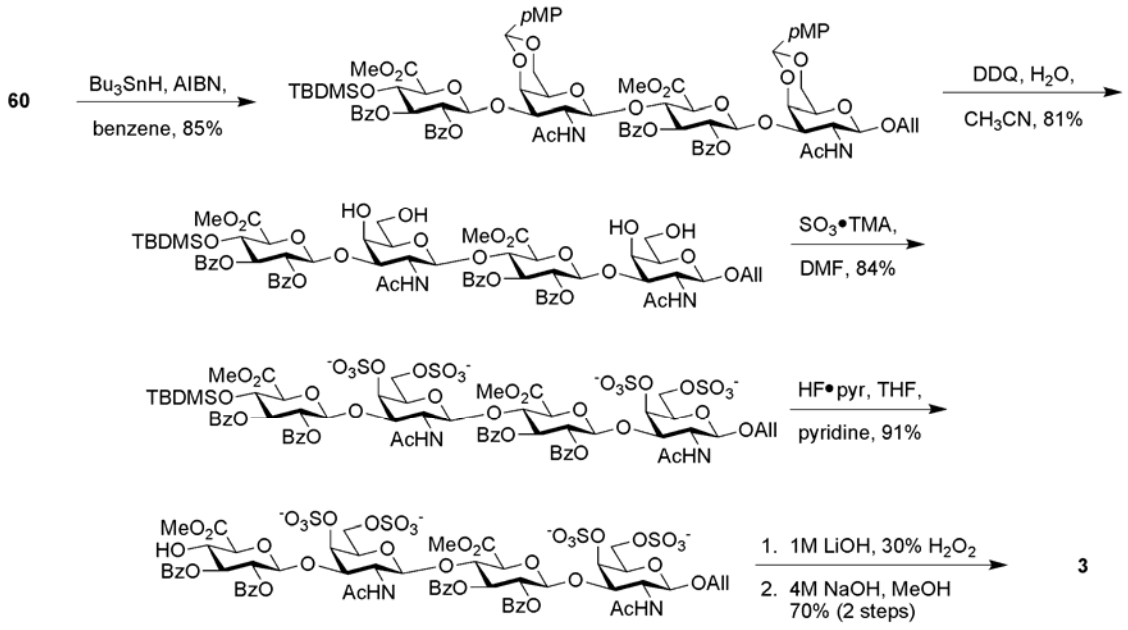
Access to these CS molecules should provide new chemical approaches to understand and manipulate neuronal growth and regeneration.



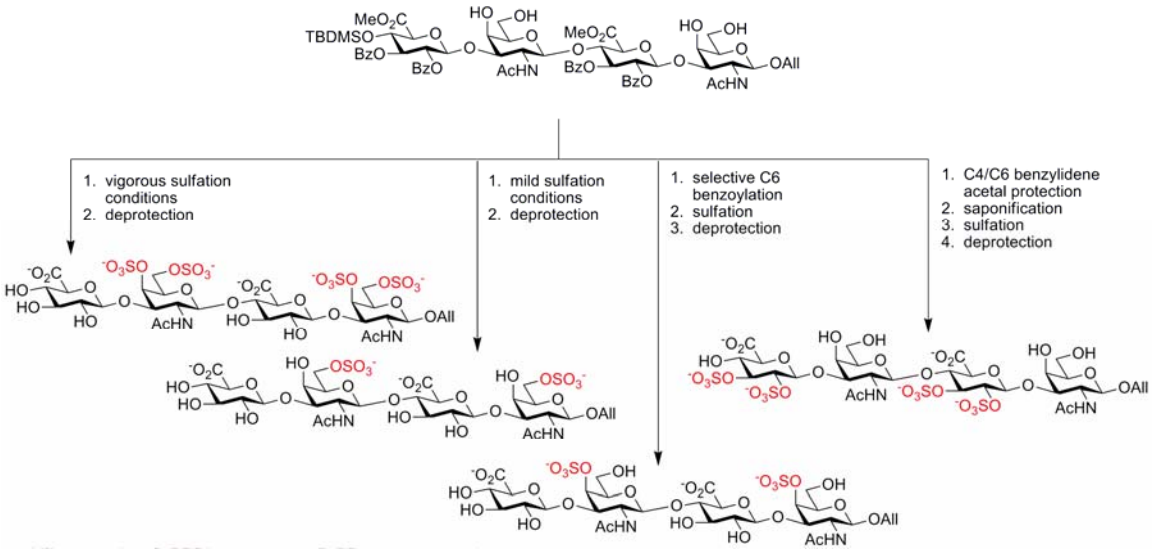
Scheme 4.17. Completion of the synthesis of the CS-E disaccharide. Bu = butyl; AIBN = 2,2'-azobis(2-methylpropionitrile); TMA = trimethylamine



Scheme 4.18. Completion of the synthesis of an unsulfated CS tetrasaccharide.



Scheme 4.19. Completion of the synthesis of the CS-E tetrasaccharide



Scheme 4.20. Accessing different sulfation patterns from the common tetrasaccharide

Materials and Methods

General

Reactions were performed in flame-dried glassware under an argon atmosphere using freshly distilled solvents, and all other chemicals and reagents were used without further purification unless otherwise noted. Thin layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 precoated plates (0.25 mm), and spots were visualized using fluorescence quenching, cerium ammonium molybdate stain, and/or ninhydrin stain. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Preparatory TLC purifications were performed on E. Merck silica gel 60 F254 precoated plates. ^{1}H NMR spectra were obtained using a Varian Mercury 300 (300 MHz) or Varian Mercury 600 (600 MHz) spectrometer and are reported in parts per million (δ) relative to tetramethylsilane (0.0 ppm). Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m =

multiplet), coupling constant in Hz, and integration. ^{13}C NMR spectra were obtained on a Varian Mercury 300 (75 MHz) spectrometer and are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotation was measured with a JASCO P-1010 instrument. Mass spectra were obtained by the Protein/Peptide MicroAnalytical Laboratory and the Mass Spectrometry Facility at the California Institute of Technology.

Tri-*O*-acetylgalactal (9). The procedure for the preparation of **9** was adapted from Kozikowski et al. (20). A stirred suspension of D-galactose (0.142 g, 0.788 mmol) in acetic anhydride (80 mL) was treated dropwise with 70% perchloric acid (0.5 mL). Additional D-galactose (19.858 g, 110.2 mmol) was added in small portions over a period of 45 min. The reaction mixture was maintained at 40 ^{o}C during the addition by periodic cooling in an ice bath. When the addition of D-galactose was complete, the solution was cooled to room temperature and 30% HBr in acetic acid (88 mL) was added. The reaction was stirred at room temperature for 1.5 h. The reaction mixture was then diluted with CH_2Cl_2 (186 mL), washed with cold water (2 x 54 mL), and washed with 5% aqueous $NaHCO_3$ (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. This syrup was added over a period of 2 h to Zn^{o} (50.4 g, 767 mmol) in 50% aqueous acetic acid (320 mL) with mechanical stirring while maintaining the reaction temperature at –20 ^{o}C. After the addition was complete, the reaction was stirred at 0 ^{o}C for 1.5 h. The reaction mixture was then filtered through Celite and diluted with CH_2Cl_2 (200 mL). This was then washed with ice water (3 x 70 mL), and the organic layers washed with cold saturated aqueous $NaHCO_3$ (2 x 60 mL)

and brine (60 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (30% EtOAc:hexanes) to afford tri-*O*-acetylgalactal **9** (15.02 g, 50%) as a clear, colorless syrup. The spectral data agreed with published data. R_f 0.60 (50% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 6.45 (dd, *J* = 6.3, 1.8 Hz, 1H), 5.54–5.55 (m, 1H), 5.41–5.43 (m, 1H), 4.72 (dq, *J* = 2.1, 1.5 Hz, 1H), 4.21–4.29 (m, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H). ESI/MS (M + Na) calculated for $C_{12}H_{16}O_7$: 295.24; found: 295.2.

Acetyl 2-Deoxy-2-azido-3,4,6-tri-*O*-acetyl-α,β-D-galactopyranoside (10). The procedure for the preparation of **9** was adapted from Lemieux et al. (44). Galactal **9** (21.9 g, 80.4 mmol) was dissolved in CH_3CN (292 mL) and cooled to –15 ^oC under Ar. A dry mixture of NaN_3 (7.8 g, 121 mmol) and cerium ammonium nitrate (132 g, 241 mmol) was added. The reaction was stirred at –15 ^oC for 20.5 h. Cold diethyl ether and water were added. The organic layer was separated and washed with ice-cold water (3 x), dried (Na_2SO_4), filtered, and concentrated to afford a white-yellow paste. This syrup was dissolved in glacial acetic acid (190 mL), and anhydrous sodium acetate (13.2 g) was added. The reaction was heated to 114 ^oC and stirred for 4.5 h. The reaction was allowed to cool to room temperature and then diluted with CH_2Cl_2. The organic layer was washed with ice water, saturated aqueous $NaHCO_3$ (2 x), water, and brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated to afford a yellow-white solid. The product was purified by flash chromatography (25% EtOAc:hexanes) to afford **10** (15.5 g, 51%) as a white, crystalline solid. The spectral data agreed with published data. R_f 0.61 (50% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 6.32 (d,

J = 3.9 Hz, 1H, α-isomer), 5.54 (d, *J* = 8.7 Hz, 1H, β-isomer), 5.47 (dd, *J* = 3.0, 1.2 Hz, 1H, α-isomer), 5.40 (dd, *J* = 3.45, 1.2 Hz, 1H, β-isomer), 5.31 (dd, *J* = 10.8, 3.3 Hz, 1H, α-isomer), 4.89 (dd, *J* = 10.8, 3.3 Hz, 1H, β-isomer), 4.04–4.15 (m, 3H, α-isomer), 4.04–4.15 (m, 3H, β-isomer), 3.93 (q, *J* = 11.1, 3.6 Hz, 1H, α-isomer), 3.84 (q, *J* = 11.1, 3.6 Hz, 1H, α-isomer), 3.84 (q, *J* = 9.75, 8.7 Hz, 1H, β-isomer), 2.20 (s, 3H, α-isomer), 2.17 (s, 3H, β-isomer), 2.16 (s, 3H, β-isomer), 2.09 (s, 3H, α-isomer), 2.07 (s, 3H, β-isomer), 2.06 (s, 3H, α-isomer), 2.04 (s, 3H, α-isomer), 2.03 (s, 3H, β-isomer). ESI/MS (M + Na) calculated for $C_{14}H_{19}N_3O_9$: 396.31; found 396.0.

***p*-Methylphenyl 2-deoxy-2-azido-3,4,6-tri-*O*-acetyl-1-thio-α,β-D-galactopyranoside (11).** **10** (7.2 g, 19.3 mmol) and *p*-toluenethiol (3.6 g, 28.9 mmol) were dissolved in CH_2Cl_2 (122 mL). The solution was cooled to 0 ^oC, and boron trifluoride diethyl etherate (3.26 mL, 25.1 mmol) was added. The reaction was allowed to stir at r.t. for 46 h. The reaction was then diluted with CH_2Cl_2 and washed with a 1:1 solution of saturated aqueous $NaHCO_3$: H_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x) and water. The organic layer was then dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (25% EtOAc:hexanes) to afford **11** (4.15 g, 49%) as a pale yellow syrup and recovery of starting material **10** (3.42 g, 48%). R_f 0.54 (40% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.12–7.17 (m, 4H), 5.61 (d, *J* = 5.4 Hz, 1H, H-1 of α-isomer), 5.48 (dd, *J* = 3.2, 1.2 Hz, 1H), 5.34 (dd, *J* = 2.6, 1.2 Hz, 1H), 5.17 (dd, *J* = 11.1, 3.3 Hz, 1H), 4.85 (dd, *J* = 10.4, 3.3 Hz, 1H), 4.77 (t, *J* = 6.6 Hz, 1H), 4.46 (d, *J* = 9.9 Hz, 1H, H-1 of β-isomer), 4.29 (dd, *J* = 11.0, 5.4 Hz, 1H), 4.07–

4.20 (m, 4H), 3.86 (dt, *J* = 6.5, 1.2 Hz, 1H), 3.63 (t, *J* = 10.2 Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). ESI/MS (M + Na) calculated for $C_{19}H_{23}N_3O_7S$: 460.46; found 460.2.

***p*-Methylphenyl 2-deoxy-2-azido-1-thio-α,β-D-galactopyranoside (12α, 12β).** Method A: **11** (1.0 g, 2.3 mmol) was dissolved in CH_2Cl_2 (4.5 mL). Methanol (9 mL) and potassium carbonate (0.32 g, 2.3 mmol) were added. The reaction was allowed to stir at r.t. for 35 min. The reaction was quenched with saturated aqueous ammonium chloride (15 mL). The organic layer was diluted with EtOAc, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x). The combined organic layers were washed with brine and water, dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (75% EtOAc:hexanes) to afford **12α** (0.37 g, 52%) as a white crystalline solid. R_f 0.26 (75% EtOAc:hexanes). ^{1}HNMR (300 MHz, CD_3OD): δ = 7.42 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 4.34 (dt, *J* = 6.2, 0.9 Hz, 1H), 4.07 (dd, *J* = 11.3, 5.7 Hz, 1H), 3.95 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.62–3.77 (m, 4H), 2.31 (s, 3H). Next eluted was **12β** (0.29 g, 41%) as a white crystalline solid. R_f 0.19 (75% EtOAc:hexanes). ^{1}HNMR (300MHz, CD_3OD): δ = 7.49 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.43 (d, *J* = 9.0 Hz, 1H), 3.83 (dd, *J* = 3.0, 0.9 Hz, 1H), 3.66–3.77 (m, 3H), 3.46–3.52 (m, 3H), 2.32 (s, 3H). ESI/MS (M + Na) calculated for $C_{13}H_{17}N_3O_4S$: 334.35; found 334.0.

Method B: **11** (3.0 g, 6.9 mmol) was dissolved in CH_2Cl_2 (5 mL). MeOH was added and the mixture stirred at r.t. for 20 min. 25% NaOMe in MeOH (47 μL, 0.2 mmol) was added and the reaction stirred at r.t. for 16 h. The reaction was neutralized

with Dowex 50X8-200 ion-exchange resin, filtered, and concentrated. The crude was used without further purification. Crude Mass: 2.1 g, 98%.

***p*-Methylphenyl 4,6-*O*-benzylidene-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (13). 12β** (0.12 g, 0.39 mmol) was dissolved in DMF (2.6 mL). Acetonitrile (1.3 mL) was added, and the reaction was stirred at r.t. Benzaldehyde dimethyl acetal (0.32 g, 2.3 mmol) and 10-camphorsulfonic acid (0.004 g, 0.02 mmol) were added. The reaction was allowed to stir at r.t. for 19.5 h. The reaction was quenched with TEA (1 mL) and concentrated. The product was purified by flash chromatography (25% EtOAc:hexanes) to afford **13** (0.1 g, 67%) as a white solid. R_f 0.30 (50% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.1 Hz, 2H), 7.39–7.43 (m, 5H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.53 (s, 1H), 4.41 (dd, *J* = 12.5, 1.5 Hz, 1H), 4.37 (d, *J* = 9.9 Hz, 1H), 4.18 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.03 (dd, *J* = 1.5, 12.6 Hz, 1H), 3.65 (dd, *J* = 9.8, 3.3 Hz, 1H), 3.45–3.52 (m, 2H), 2.37 (s, 3H). ESI/MS (M + Na) calculated for $C_{20}H_{21}N_3O_4S$: 422.45; found 422.0.

***p*-Methylphenyl 4,6-*O*-benzylidene-3-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (14). 13** (0.71 g, 1.8 mmol) was dissolved in DMF (3.3 mL). Imidazole (0.36 g, 5.33 mmol) and then triisopropylsilyl chloride (0.76 mL, 3.55 mmol) were added. The reaction was allowed to stir at r.t. for 14 h. An additional 0.5 eq of TIPS-Cl (0.2 mL) was added, and the reaction continued to stir at r.t. for 25 h. The reaction was diluted with EtOAc and quenched with H_2O and sat. aq. $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (3 x). The combined organic

layers were washed with brine, dried ($NaSO_4$), filtered, and concentrated. The product was purified by flash chromatography (8% →12% EtOAc:hexanes) to afford **14** (0.83 g, 84%) as a white crystalline solid. R_f 0.51 (25% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.1 Hz, 2H), 7.42–7.46 (m, 2H), 7.36-7.40 (m, 3H), 7.00 (d, *J* = 7.8 Hz, 2H), 7.49 (s, 1H), 4.36–4.41 (m, 2H), 4.05 (dd, *J* = 3.0, 0.9 Hz, 1H), 4.01 (dd, *J* = 12.3, 1.5 Hz, 1H), 3.74 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.64 (t, *J* = 9.6 Hz, 1H), 3.44 (d, *J* = 0.9 Hz, 1H), 2.31 (s, 3H), 1.00–1.10 (m, 21H). ESI/MS (M + Na) calculated for $C_{29}H_{41}N_3O_4SSi$: 578.8; found 578.2.

***p*-Methylphenyl 4-*O*-benzyl-3-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (15).** **14** (0.6 g, 1.1 mmol) was treated with a 1 M solution of BH_3 in THF (11 mL) at 0 ^oC. The solution was stirred for 5 min. A 1 M solution of dibutylboron triflate (1.1 mL) was then added. The reaction was allowed to stir at 0 ^oC for 9 h. TEA (0.6 mL) was added to quench the reaction. MeOH was then added dropwise until H_2 production was no longer observed. The reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The organic layer was washed with brine, dried ($NaSO_4$), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (20% EtOAc:hexanes) to afford **15** (0.50 g, 83%) as a yellow syrup. R_f 0.54 (25% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.8 Hz, 2H), 7.26–7.36 (m, 5H), 7.01 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.41 (dd, *J* = 8.7, 0.9 Hz, 1H), 3.90 (dd, *J* = 11.4, 7.2 Hz, 1H), 3.72-3.79 (m, 3H), 3.65 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.50 (dd, *J* = 4.8, 6.8 Hz, 1H), 2.31 (s,

3H), 1.11–1.15 (m, 21H). ESI/MS (M + Na) calculated for $C_{29}H_{43}N_3O_4SSi$: 580.81; found 580.2.

***p*-Methylphenyl di-4,6-*O*-benzyl-*3*-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (4).** **15** (0.12 g, 0.22 mmol) was dissolved in DMF (1.5 mL) and cooled to 0 ^oC. Sodium hydride (0.01 g, 0.43 mmol) was added, and the solution was allowed to stir at 0 ^oC for 15 min. Benzyl bromide (0.05 mL, 0.43 mmol) was then added. The reaction was allowed to stir at at 0 ^oC for 5 min and then warmed to r.t. The reaction stirred at r.t. for 3 h. Additional benzyl bromide and sodium hydride were added, and the reaction continued to stir for 45 min. The reaction was then quenched with MeOH (0.8 mL) and H_2O (0.8 mL). EtOAc was added, and the aqueous layer extracted with EtOAc (3 x). The combined organic layers was washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (6% EtOAc:hexanes) to afford **4** (0.1243 g, 89%) as a yellow syrup. R_f 0.68 (25% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.8 Hz, 2H), 7.22–7.34 (m, 10H), 6.97 (d, *J* = 8.1 Hz, 2H), 4.98 (d, *J* = 11.1 Hz, 1H), 4.38–4.55 (m, 4H), 3.85 (d, *J* = 1.5 Hz, 1H), 3.60–3.77 (m, 5H), 2.30 (s, 3H), 1.06–1.16 (m, 21H). ESI/MS (M + Na) calculated for $C_{36}H_{49}N_3O_4SSi$: 670.93; found 670.4.

***p*-Methylphenyl 6-*O*-acetyl-4-*O*-benzyl-*3*-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (5).** **15** (0.28 g, 0.50 mmol) was dissolved in pyridine (2.5 mL). Acetic anhydride (0.48 mL, 5.0 mmol) was added. The reaction was stirred at r.t. for 10 h. The reaction was then concentrated to afford a yellow syrup. The product was

purified by flash chromatography (10% EtOAc:hexanes) to afford **5** (0.2777 g, 93%). R_f 0.26 (10% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.4 Hz, 2H), 7.27–7.36 (m, 5H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.04 (d, *J* = 11.1 Hz, 1H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.40 (dd, *J* = 1.5, 8.0 Hz, 1H), 4.19–4.34 (m, 2H), 3.61–3.73 (m, 4H), 2.30 (s, 3H), 2.05 (s, 3H), 1.05–1.25 (m, 21H). ESI/MS (M + Na) calculated for $C_{31}H_{45}N_3O_5SSi$: 622.85; found 622.2.

***p*-Methylphenyl 6-*O*-benzyl-3-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (16).** To a mixture of **14** (0.074 g, 0.13 mmol) and 3 Å activated molecular sieves was added THF (2 mL). The solution was stirred for 35 min at r.t. Sodium cyanoborohydride (0.12 g, 2.0 mmol) was added to the reaction in a minimum volume of THF (4 mL). A 1 M solution of HCl in diethyl ether (2 mL) was then added dropwise until gas evolution ceased. The reaction was allowed to stir at r.t. for 4 h. The reaction was quenched by dropwise addition of sat. aq. $NaHCO_3$ (3 mL). The reaction mixture was then diluted with CH_2Cl_2 and filtered through Celite. The Celite pad was rinsed with additional CH_2Cl_2 and H_2O. The filtrate was washed with water (1 x). The organic layer was dried ($NaSO_4$), filtered, and concentrated to afford a yellow syrup. The product was purified by preparatory TLC (10% EtOAc:hexanes, 1 mm SiO_2 plate) to afford **16** (0.031 g, 42%). R_f 0.61 (25% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.4 Hz, 2H), 7.31–7.36 (m, 5H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.59 (s, 2H), 4.40 (d, *J* = 10.2 Hz, 1H), 3.88 (dd, *J* = 0.6, 3.3 Hz, 1H), 3.80 (d, *J* = 5.7 Hz, 2H), 3.65 (dd, *J* = 9.0, 3.3 Hz, 1H), 3.60 (dt, *J* = 5.4, 0.9 Hz, 1H), 3.51 (dd, *J* = 9.9, 9.3 Hz, 1H), 2.34 (s,

3H), 1.09–1.12 (m, 21H). ESI/MS (M + Na) calculated for $C_{29}H_{43}N_3O_4SSi$: 580.81; found 580.2.

***p*-Methylphenyl 6-*O*-benzyl-4-*O*-acetyl-*3*-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (6). 16** (0.05 g, 0.09 mmol) was dissolved in pyridine (0.8 mL). Acetic anhydride (0.08 mL, 0.9 mmol) was added. The reaction was stirred at r.t. for 25.5 h. 4-(dimethylamino)pyridine (2 mg, 0.018 mmol) was added, and the reaction was stirred for an additional 4 h. The reaction was then concentrated to afford a yellow syrup. The product was purified by preparatory TLC (10% EtOAc:hexanes) to afford **6** (0.0362 g, 72%). R_f 0.59 (10% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.1 Hz, 2H), 7.29–7.34 (m, 5H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.30 (d, *J* = 3.0 Hz, 1H), 4.44–4.54 (m, 3H), 3.66–3.75 (m, 2H), 3.49–3.59 (m, 3H), 2.33 (s, 3H), 2.04 (s, 3H), 1.04–1.10 (m, 21H). ESI/MS (M + Na) calculated for $C_{31}H_{45}N_3O_5SSi$: 622.85; found 622.2.

***p*-Methylphenyl 4,6-*O*-acetonide-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (17). 12β** (0.1 g, 0.321 mmol) and 2-methoxypropene (62 μL, 0.642 mmol) were dissolved in DMF (1.5 mL). Pyridinium *p*-toluene sulfonate (32.3 mg, 0.128 mmol) was added, and the reaction was allowed to stir at r.t. for 6 h. The reaction was diluted with EtOAc and quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (30% EtOAc:hexanes) to afford **17** (0.080 g, 71%) as a white solid. R_f 0.17 (30% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.4 Hz, 2H),

7.14 (d, *J* = 8.4 Hz, 2H), 4.31 (d, *J* = 9.6 Hz, 1H), 4.12 (dd, *J* = 3.9, 1.2 Hz, 1H), 4.01–4.02 (m, 2H), 3.53–3.56 (m, 1H), 3.48 (q, *J* = 14.1, 9.3 Hz, 1H), 3.37 (m, 1H), 2.30 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H). ESI/MS (M + Na) calculated for $C_{16}H_{21}N_3O_4S$: 374.12; found 374.2.

***p*-Methylphenyl 4,6-*O*-acetonide-3-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (18).** **17** (0.7051 g, 2.01 mmol) was dissolved in DMF (9 mL). Imidazole (0.273 g, 4.01 mmol), 4-(dimethylamino)pyridine (49 mg, 0.401 mmol), and triisopropylsilyl chloride (0.644 mL, 3.01 mmol) were added, and the reaction was allowed to stir at r.t. for 15 h. The reaction was diluted with EtOAc and quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (30% EtOAc:hexanes) to afford **18** (0.713 g, 70%) as a white solid. R_f 0.81 (30% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 4.23–4.35 (m, 1H), 4.01 (dd, *J* = 8.1, 1.8 Hz, 3H), 3.57–3.63 (m, 2H), 3.28 (d, *J* = 3.0 Hz, 1H), 2.34 (s, 3H), 1.40 (s, 6H), 1.05 (s, 21H). ESI/MS (M + Na) calculated for $C_{25}H_{41}N_3O_4SSi$: 530.25; found 530.2.

***p*-Methylphenyl di-4,6-*O*-acetyl-*3*-*O*-triisopropylsilyl-2-deoxy-2-azido-1-thio-β-D-galactopyranoside (7).** **18** (0.8152 g, 1.61 mmol) was dissolved in THF (8 mL), cooled to 0 ^oC, and stirred for 15 min. Trifluoroacetic acid (8 mL) was added, and the reaction was allowed to stir at 0 ^oC for 1 h and closely monitored by TLC. The reaction was then

poured over ice water and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x), brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellow syrup. This crude reaction mixture was dissolved in pyridine (2 mL). Acetic anhydride (1.31 mL, 13.89 mmol) and 4-(dimethylamino)pyridine (34 mg, 0.28 mmol) were added. The reaction was stirred at r.t. for 2 h. The reaction was then concentrated to afford a yellow syrup. The product was purified by flash chromatography (20% EtOAc:hexanes) to afford **7** (0.5089 g, 66%) as a yellow syrup. R_f 0.74 (30% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 5.23 (d, *J* = 2.4 Hz, 1H), 4.42 (d, *J* = 9.0 Hz, 1H), 4.03–4.17 (m, 2H), 3.71–3.77 (m, 2H), 3.52 (t, *J* = 9.9 Hz, 1H), 2.35 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.02–1.09 (m, 21H). ESI/MS (M + Na) calculated for $C_{26}H_{41}N_3O_6SSi$: 574.76; found 574.2.

Dibenzyl di-4,6-*O*-benzyl-3-*O*-triisopropylsilyl-2-deoxy-2-azido-α,β-D-galactopyranoside phosphate (19). **4α** (68 mg, 0.10 mmol) was added to dibenzyl phosphate (50 mg, 0.18 mmol). These were azeotropically dried with toluene (2 x) and left under vacuum overnight. This was dissolved in THF (0.64 mL), and 3 Å powdered molecular sieves were added. The reaction mixture was stirred at r.t. for 3 h. *N*-iodosuccinimide was added, and the reaction was cooled to -30 ^oC. Triflouoromethane sulfonic (triflic) acid was added, and the reaction mixture was stirred at -30 ^oC for 1 h. The reaction was warmed to r.t. and stirred an additional 1.25 h. The reaction was then quenched with 1 M NaS_2O_3 and diluted with EtOAc. This was filtered through filter paper. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers

were washed with brine, dried (Mg_2SO_4), filtered through Celite, and concentrated. The product was purified by flash chromatography (20% EtOAc:hexanes) to afford **19** (77.8 mg, 93%). R_f 0.22 (20% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.26–7.35 (m, 40H), 5.88 (dd, *J* = 6.0, 3.3 Hz, 2H), 5.01–5.14 (m, 12H), 4.35–4.57 (m, 6H), 4.23 (dd, *J* = 10.4, 2.4 Hz, 2H), 4.05–4.17 (m, 4H), 3.96 (d, *J* = 1.2 Hz, 2H), 3.41–3.90 (m, 6H), 1.13–1.19 (m, 42H). ESI/MS (M + Na) calculated for $C_{43}H_{56}N_3O_8PSi$: 824.97; found 824.4.

Disaccharides (21α, 21β). Method A: **23α** (10 mg, 0.0146 mmol) was combined with **20** (11 mg, 0.022 mmol) and azeotropically dried with toluene (2 x). This was left under vacuum overnight. This was dissolved in toluene (0.23 mL), and 4 Å powdered molecular sieves were added. The reaction mixture was stirred at r.t. for 2 h. The reaction was cooled to -10 ^{o}C. A 0.25 M solution of $BF_3 \bullet OEt_2$ (3 μL) was added to the reaction. An additional aliquot of $BF_3 \bullet OEt_2$ solution (1.3 μL) was added after 1 hour, and again after 2.5 hrs of stirring. After a total of 3h 40 m of stirring with acid, the reaction was quenched with TEA, filtered, and concentrated. The product was purified by flash chromatography (3% EtOAc:hexanes) to afford **21α** and **21β** (13.9 mg, 94%, 18:82 α/β). R_f 0.62 (20% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): For **21α:** δ = 7.43 (d, *J* = 8.1 Hz, 2H), 7.24–7.34 (m, 20H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.49 (d, *J* = 3.6 Hz, 1H, H-1 of galactose), 4.87–4.96 (m, 4H), 4.64 (d, *J* = 10.2 Hz, 1H), 4.62 (d, *J* = 9.9 Hz, 1H, H-1 of GlcA), 4.43–4.54 (m, 3H), 4.20 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.08 (t, *J* = 9.3 Hz, 1H), 3.86–3.93 (m, 2H), 3.43–3.79 (m, 9H), 2.34 (s, 3H), 1.10–1.20 (m, 21H). ESI/MS (M + Na) calculated for $C_{57}H_{71}N_3O_{10}SSi$: 1041.33; found 1040.4. For **21β:** δ =

7.42 (d, *J* = 8.4 Hz, 2H), 7.07–7.37 (m, 22H), 4.99–5.05 (m, 2H), 4.73–4.81 (m, 2H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 9.9 Hz, 1H, H-1 of GlcA), 4.48 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.27 (d, *J* = 7.8 Hz, 1H, H-1 of galactose), 4.24 (d, *J* = 12.0 Hz, 1H), 4.09 (t, *J* = 9.9 Hz, 1H), 3.94 (d, *J* = 9.9 Hz, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 2.1 Hz, 1H), 3.26–3.69 (m, 7H), 2.33 (s, 3H), 1.07–1.14 (m, 21H). ESI/MS (M + Na) calculated for $C_{57}H_{71}N_3O_{10}SSi$: 1041.33; found 1040.4.

Method B: **19** (61 mg, 0.076 mmol) was combined with **20** (19 mg, 0.038 mmol) and azeotropically dried with toluene (2 x). This was dried overnight under vacuum. The reactants were dissolved in dichloromethane (0.33 mL), and 4 Å powdered molecular sieves were added. The reaction was stirred at r.t. for 3 h. The reaction was then cooled to -10 ^{o}C for 30 min. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (10 μL, 0.057 mmol) was added. The reaction continued to stir for 1 h. The reaction was then quenched with TEA, diluted with EtOAc, filtered, and concentrated to afford a yellow-brown syrup.

Di-4,6-*O*-benzyl-3-*O*-triisopropylsilyl-2-deoxy-2-azido-α,β-D-galactopyranoside (22). **4** (0.12 g, 0.19 mmol) was dissolved in acetone (4 mL) and cooled to -15 ^{o}C. The reaction flask was covered in Al foil. *N*-bromosuccinimide (0.05 g, 0.28 mmol) was added to the reaction. The reaction was stirred at -15 ^{o}C for 3 h 20 m. Sat. aq. $NaHCO_3$ (3 mL) was added to quench the reaction. Additional water was added, and the reaction was diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried ($NaSO_4$), filtered, and concentrated to afford a yellow syrup. The product was purified by flash

chromatography (20% EtOAc:hexanes) to afford **22** (0.096 g, 96%) as a pale yellow syrup. R_f 0.76 (20% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.29–7.33 (m, 20H), 5.05 (d, *J* = 10.8 Hz, 2H), 5.39 (d, *J* = 3.3 Hz, 1H), 4.20 (t, *J* = 6.0 Hz, 1H), 3.29 (dd, *J* = 10.4, 3.0 Hz, 1H), 4.41–4.57 (m, 7H), 3.53–3.67 (m, 7H), 3.77 (s, 1H), 3.88 (d, *J* = 1.8 Hz, 1H), 3.92 (dd, *J* = 10.1, 3.3 Hz, 1H), 1.12–1.18 (m, 42H). ESI/MS (M + Na) calculated for $C_{29}H_{43}N_3O_5Si$: 564.74; found 564.4.

Trichloroacetyl di-4,6-*O*-benzyl-3-*O*-triisopropylsilyl-2-deoxy-2-azido-α,β-D-galactopyranoside imidate (23α, 23β). **22** (65 mg, 0.12 mmol) was dissolved in dichloromethane (1.1 mL). Trichloroacetonitrile (0.12 mL, 1.2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (9 μL, 0.06 mmol) were added to the reaction. The reaction was stirred at r.t. for 5.5 h. It was then concentrated to afford a brown syrup. The product was purified by flash chromatography (2% EtOAc:hexanes + 2.5% TEA) to afford **23α** (0.0665 g, 81%). R_f 0.51 (20% EtOAc:hexanes + 2% TEA). ^{1}HNMR (300MHz, $CDCl_3$): δ = 8.62 (s, 1H), 7.26–7.34 (m, 10H), 6.44 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.48 (d, *J* = 6.9 Hz, 2H), 4.38 (dd, *J* = 10.5, 2.4 Hz, 1H), 4.21 (dd, *J* = 10.5, 3.3 Hz, 1H), 4.15 (dd, *J* = 6.3, 6.8 Hz, 1H), 4.01 (d, *J* = 1.2 Hz, 1H), 3.68 (dd, *J* = 8.1, 9.3 Hz, 1H), 3.56 (dd, *J* = 9.3, 5.4 Hz, 1H), 1.13–1.21 (m, 21H). ESI/MS (M + Cl) calculated for $C_{31}H_{43}Cl_3N_4O_5Si$: 721.59; found 721.4. Next eluted was **23β** (0.012 g, 15%). R_f 0.44 (20% EtOAc:hexanes + 2% TEA).

***p*-Methylphenyl di-4,6-*O*-acetyl-*3*-*O*-triisopropylsilyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-galactopyranoside (25).** **7** (72 mg, 0.13 mmol) was dissolved in THF (68

μL), EtOH (0.27 mL), and water (68 μL). A 1 M solution of tributylphosphine in THF (0.21 mL) was added and the reaction stirred for 25 min at r.t. The reaction mixture was then concentrated without heating. The crude **24** was azeotropically dried with toluene (2 x) and dried under vacuum for 15 min. This crude was dissolved in dichloromethane and cooled to 0 ^{o}C. TEA (54 μL) was added, and then trichloroacetyl chloride (23 μL) was added. The reaction was stirred for 22 min. The reaction was then quenched with sat aq $NaHCO_3$ and diluted with dichloromethane. The aqueous layer was extracted with dichloromethane (3 x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. This crude was purified by preparatory TLC (18% EtOAc:hexanes, run up 2 x) to afford **25** (0.0289 g, 33%). R_f 0.69 (40% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.32 (d, *J* = 3.3 Hz, 1H), 5.14 (d, *J* = 11.1 Hz, 1H), 4.49 (d, *J* = 9.9 Hz, 1H), 4.04–4.19 (m, 2H), 3.76–3.87 (m, 2H), 2.33 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 0.99-1.06 (m, 21H). ESI/MS (M + Cl) calculated for $C_{28}H_{42}Cl_3NO_7SSi$: 706.60; found 706.4.

Disaccharide (27). 25 (17.6 mg, 0.026 mmol) was combined with **26** (8 mg, 0.02 mmol) and azeotropically dried with toluene (2 x). This was dried overnight under vacuum. The reactants were dissolved in dichloromethane (0.24 mL). 4 Å powdered molecular sieves and *N*-iodosuccinimide (6.3 mg, 0.03 mmol) were added. The reaction was stirred at r.t. for 1 h. The reaction was then cooled to -10 ^{o}C. A 1 M solution of triflic acid (5 μL) was added. The reaction was allowed to stir for 20 min. An additional aliquot of triflic acid solution (3 μL) was added. The reaction continued to stir for an additional 40 min. The reaction was then quenched with TEA, diluted with EtOAc, washed with 1 M

$Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (5%→10→15%→20% EtOAc:hexanes) to afford **27** (16.8 mg, 88%). R_f 0.61 (40% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.25–7.37 (m, 10H), 6.91 (d, *J* = 9.0 Hz, 1H), 5.28 (d, *J* = 2.7 Hz, 1H), 5.00 (d, *J* = 11.1 Hz, 1H), 4.89 (d, *J* = 8.4 Hz, 1H, H-1 of galactose), 4.65–4.82 (m, 3H), 4.34 (d, *J* = 7.2 Hz, 1H, H-1 of GlcA), 3.98–4.18 (m, 4H), 3.72–3.89 (m, 6H), 3.53–3.61 (m, 4H), 3.39 (dd, *J* = 7.2, 8.3 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.03 (s, 21H). ESI/MS (M + Na) calculated for $C_{43}H_{60}Cl_3NO_{14}Si$: 972.37; found 972.4.

Di-4,6-*O*-acetyl-3-*O*-triisopropylsilyl-2-deoxy-2-trichloroacetamido-α,β-D-galactopyranoside (28). **25** (26 mg, 0.039 mmol) was dissolved in acetone (0.96 mL) and cooled to -15 ^{o}C. The reaction flask was covered in Al foil. *N*-bromosuccinimide (10.3 mg, 0.58 mmol) was added to the reaction. The reaction was stirred at -15 ^{o}C for 3 h 35 min. Sat. aq. $NaHCO_3$ was added to quench the reaction. Additional water was added, and the reaction was diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography (10%→15%→20% EtOAc:hexanes) to afford **28** (9.8 mg, 45%) as a pale yellow syrup. R_f 0.54 (40% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 6.92 (d, *J* = 9.6 Hz, 2H), 5.32–5.39 (m, 4H), 4.28–4.48 (m, 6H), 4.17–4.24 (m, 2H), 3.84–4.06 (m, 2H), 2.16

(s, 6H), 2.07 (s, 6H), 0.98–1.10 (m, 42H). ESI/MS (M + Cl) calculated for $C_{21}H_{36}Cl_3NO_8Si$: 600.41; found 600.2.

Trichloroacetyl di-4,6-*O*-acetyl-3-*O*-triisopropylsilyl-2-deoxy-2-trichloroacetamido-α,β-D-galactopyranoside imidate (29α, 29β). **28** (48 mg, 0.085 mmol) was dissolved in dichloromethane (0.78 mL). Trichloroacetonitrile (85 μL, 0.85 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.4 μL, 0.042 mmol) was added to the reaction. The reaction was stirred at r.t. for 95 m. The reaction mixture was then concentrated to afford a brown syrup. The product was purified by flash chromatography (10% EtOAc:hexanes + 3% TEA) to afford **29β** and **29α** (41 mg, 71%, 26:1 α/β) as a white solid. For **29β**: R_f 0.75 (40% EtOAc:hexanes + TEA). For **29α**: R_f 0.69 (40% EtOAc:hexanes + TEA). ^{1}HNMR (300MHz, $CDCl_3$): δ = 8.77 (s, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.46 (d, *J* = 3.3 Hz, 1H), 5.44 (d, *J* = 3.3 Hz, 1H), 4.61-4.69 (m, 1H), 4.48 (dd, *J* = 3.3, 10.8 Hz, 1H), 4.20–4.31 (m, 2H), 3.97 (dd, *J* = 6.6, 11.4 Hz, 1H), 2.16 (s, 3H), 2.02 (s, 3H), 0.98–1.10 (m, 21H). ESI/MS (M + Na) calculated for $C_{23}H_{36}Cl_6N_2O_8Si$: 732.33; found 731.0.

Disaccharide (30). **29α** (21.7 mg, 0.031 mmol) was combined with **20** (9.9 mg, 0.02 mmol) and azeotropically dried with toluene (3 x). 4 Å powdered molecular sieves were added, and this was left under vacuum overnight. This was dissolved in dichloromethane (0.7 mL). The reaction mixture was stirred at r.t. for 1 h. The reaction was cooled to -10 ^oC. A 0.25 M solution of TMSOTf (8 μL) was added to the reaction. An additional aliquot of TMSOTf solution (4 μL) was added 15 min, 38 min, 1 h 53 min, and 2 h 30

min after initial TMSOTf addition. After a total of 2 h 45 min of stirring with acid, the reaction was quenched with TEA, filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (5%→10%→15%→20% EtOAc:hexanes) to afford **30** (9.3 mg, 45%). R_f 0.22 (20% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.5 Hz, 2H), 7.26–7.37 (m, 10H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 1H), 5.29 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.89 (d, *J* = 8.1 Hz, 1H, H-1 of galactose), 4.67–4.78 (m, 3H), 4.60 (d, *J* = 9.3 Hz, 1H, H-1 of GlcA), 3.97–4.17 (m, 4H), 3.73–3.89 (m, 6H), 3.63 (t, *J* = 8.7 Hz, 1H), 3.41 (dd, *J* = 7.1, 9.0 Hz, 1H), 2.33 (s, 3H), 2.024 (s, 3H), 2.016 (s, 3H), 1.03 (s, 21H). ESI/MS (M + Na) calculated for $C_{49}H_{64}Cl_3NO_{13}SSi$: 1064.53; found 1064.2.

***p*-Methylphenyl 4,6-*O*-acetonide-3-*O*-triisopropylsilyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-galactopyranoside (31).** **18** (73.5 mg, 0.14 mmol) was dissolved in THF (0.12 mL), EtOH (0.30 mL), and water (74 μL). A 1 M solution of tributylphosphine in THF (0.23 mL) was added and the reaction stirred for 20 min at r.t. The reaction mixture was then concentrated without heating. The crude was azeotropically dried with toluene (1 x) and dried under vacuum for 40 min. This crude was dissolved in dichloromethane (1.4 mL) and cooled to 0 ^oC. TEA (59 μL) was added, and then trichloroacetyl chloride (26 μL) was added. The reaction was stirred for 23 min. The reaction was then quenched with sat. aq. $NaHCO_3$ and diluted with dichloromethane. The aqueous layer was extracted with dichloromethane (3 x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. The product was purified by flash chromatography (5%→10% EtOAc:hexanes) to afford **31**

(76.1 mg, 84%) as a crystalline white solid. R_f 0.29 (20% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 6.9 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 4.53 (dd, *J* = 3.3, 9.9 Hz, 1H), 4.10–4.15 (m, 1H), 4.01 (d, *J* = 1.5 Hz, 1H), 3.65–3.76 (m, 1H), 3.39 (s, 1H), 2.34 (s, 3H), 1.43 (s, 6H), 1.04 (s, 21H). ESI/MS (M + Na) calculated for $C_{27}H_{42}Cl_3NO_5SSi$: 650.13; found 650.2.

***p*-Methylphenyl *3-O*-triisopropylsilyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-galactopyranoside (32).** **31** (52 mg, 0.084 mmol) was dissolved in THF (0.4 mL), cooled to 0 ^oC, and stirred for 15 min. Trifluoroacetic acid (0.4 mL) was added, and the reaction was allowed to stir at 0 ^oC for 65 min. The reaction was then poured over ice water and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x) and brine, dried (Na_2SO_4), filtered, and concentrated to afford a yellow syrup. The product was purified by prepatory TLC (20% EtOAc:hexanes, run up 2 x) to afford **32** (39.1 mg, 80%) as a white solid. R_f 0.25 (30% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.39 (dd, *J* = 3.3, 9.9 Hz, 1H), 3.93–4.04 (m, 2H), 3.68–3.84 (m, 2H), 3.58–3.63 (m, 1H), 2.33 (s, 3H), 1.06 (s, 21H). ESI/MS (M + Na) calculated for $C_{24}H_{38}Cl_3NO_5SSi$: 610.06; found 610.0.

***p*-Methylphenyl 4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-1-thio-β-D-galactopyranoside (33).** Method A: **32** (39 mg, 0.066 mmol) was dissolved in acetonitrile (0.6 mL). *p*-anisaldehyde dimethyl acetal (26 μL, 0.13 mmol) and 10-

camphorsulfonic acid (0.3 mg, 0.001 mmol) were added. The reaction was allowed to stir at r.t. for 19 min. The reaction was quenched with TEA and concentrated to afford a peach solid. The product was purified by preparatory TLC (12% EtOAc:hexanes) to afford **31** (41.2 mg, 88%) as a white solid. R_f 0.23 (16% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.84–6.90 (m, 3H), 5.45 (s, 1H), 5.39 (d, *J* = 9.9 Hz, 1H), 4.62 (dd, *J* = 3.3, 9.9 Hz, 1H), 4.37 (dd, *J* = 1.2, 12.3 Hz, 1H), 4.08–4.15 (m, 1H), 4.00 (dd, *J* = 1.5, 12.6 Hz, 1H), 3.83 (s, 3H), 3.66–3.76 (m, 1H), 3.55 (s, 1H), 2.34 (s, 3H), 1.01 (s, 21H). ESI/MS (M + Na) calculated for $C_{32}H_{44}Cl_3NO_6SSi$: 728.19; found 728.2.

Method B: To a solution of **53** (5.6 g, 0.010 mol) in dry DMF (50 mL) at r.t. was added triisopropylsilyl chloride (6.3 g, 0.033 mol, 7.0 mL), imidazole (2.7 g, 0.040 mol) and 4-(dimethylamino)pyridine (0.49 g, 40 mol%). The reaction mixture was stirred for 4 h whereupon further triisopropylsilyl chloride (3.2 g, 3.5 mL, 0.016 mol), imidazole (1.4 g, 0.020 mol), and 4-(dimethylamino)pyridine (0.25 g, 20 mol%) were added. The reaction mixture was stirred for 12 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organics washed with brine and dried over $MgSO_4$ to afford a pale yellow oil. Purification of this oil by flash chromatography (10% $\rightarrow$ 15% EtOAc:hexanes) afforded **33** (5.3 g, 75%) as a white solid.

Disaccharide (34). **33** (43 mg, 0.061 mmol) was combined with **26** (18.8 mg, 0.047 mmol) and azeotropically dried with toluene (2x). This was dried under vacuum overnight. The reactants were dissolved in dichloromethane (0.55 mL). 4 Å powdered molecular sieves were added. This was stirred at r.t. for 1 h 25 min. *N*-iodosuccinimide

(15 mg, 0.065 mmol) was added, and the reaction was cooled to -10 ^{o}C. A 1 M solution of triflic acid (5 μL) was added. The reaction was allowed to stir for 25 min, and an additional aliquot of triflic acid (3 μL) was added. The reaction was stirred an additional 1 h 15 min. The reaction was then quenched with TEA, filtered, diluted with EtOAc, and washed with 1 M $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography (10 → 20% EtOAc:hexanes) to afford disaccharide **34** (19.4 mg, 40%). R_f 0.53 (40% EtOAc:hexanes). ^{1}HNMR (300MHz, $CDCl_3$): δ = 7.38–7.41 (m, 4H), 7.26–7.29 (m, 5H), 7.15–7.17 (m, 3H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.46 (s, 1H), 5.16 (d, *J* = 11.1 Hz, 1H), 5.02 (d, *J* = 8.1 Hz, 1H, H-1 of galactose), 4.80 (d, *J* = 11.1 Hz, 1H), 4.66–4.72 (m, 2H), 4.35 (d, *J* = 7.2 Hz, 1H, H-1 of GlcA), 3.77–4.29 (m, 7H), 3.83 (s, 3H), 3.77 (s, 3H), 3.65 (t, *J* = 8.7 Hz, 1H), 3.54 (s, 3H), 3.37–3.43 (m, 2H), 0.98–1.04 (m, 21H). ESI/MS (M + Na) calculated for $C_{47}H_{62}Cl_3NO_{13}Si$: 1006.43; found 1006.4.

***p*-Methylphenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-*β*-D-glucopyranoside (42).** The procedure for the preparation of **42** was adapted from Ye et al. (45). **35** (46) (36.7 g, 128.2 mmol) was dissolved in DMF (30 mL) and CH_3CN (300 mL). *p*-Anisaldehyde dimethyl acetal (44 mL, 256.3 mmol) and 10-camphorsulfonic acid (6 g, 25.6 mmol) were added. The reaction was stirred at r.t. for 12 h. The reaction was quenched with triethylamine and concentrated to afford an orange syrup. The product was purified by flash chromatography (50% → 70% EtOAc:hexanes) to afford **42** (36.3 g, 70%) as a white crystalline solid. R_f 0.26 (50% EtOAc:hexanes). $[\alpha]_D^{21}$ = -38 (*c* = 1.0, CH_2Cl_2); IR

(thin film on NaCl): υ = 3447, 2869, 1614, 1518, 1250, 1104, 1084, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.1 Hz, 2H, Ph), 7.39 (d, *J* = 9.0 Hz, 2H, Ph), 7.15 (d, *J* = 7.5 Hz, 2H, Ph), 6.88 (d, *J* = 9.0 Hz, 2H, Ph), 5.48 (s, 1H, 6.82, MeOPhC*H*), 4.56 (d, *J* = 9.9 Hz, 1H, H-1), 4.35 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.85–3.72 (m, 5H), 3.50–3.39 (m, 3H), 2.80 (br s, 1H, OH), 2.67 (br s, 1H, OH), 2.36 (s, 3H, SPhCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 138.2, 133.6, 132.1, 129.9, 129.4, 127.7, 113.7, 101.8, 88.7, 80.2, 74.5, 72.5, 70.5, 68.6, 55.3, 21.2; FAB MS: *m/z*: calculated for $C_{21}H_{25}O_6S$: 405.1372; found: 405.1359 $[M + H]^+$.

***p*-Methylphenyl 2,3-di-*O*-benzoyl-4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside (43).** **42** (23.7 g, 58.6 mmol) was dissolved in CH_2Cl_2 (670 mL). In a separate flask, benzoyl chloride (17 mL, 146 mmol) was added dropwise to a solution of DMAP (25.05 g, 205 mmol) in CH_2Cl_2 (225 mL). The benzoyl chloride/DMAP solution was then slowly added to the solution of *p*-methylphenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside. An additional volume of CH_2Cl_2 (19 mL) was used to complete the transfer of solution. The reaction was allowed to stir at r.t. for 25 min and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield a pale yellow solid. This crude material was washed with MeOH. Crystallization from EtOAc afforded **43** as a white solid (30.8 g, 86%). R_f 0.43 (30% EtOAc:hexanes). $[\alpha]_D^{22}$ = +25 (*c* = 0.42, CH_2Cl_2); IR (thin film on NaCl): υ = 2934, 1740, 1735, 1730, 1715, 1700, 1617, 1614, 1517, 1272, 1251, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.90 (m, 4H, Ph), 7.56–7.30 (m, 10H, Ph), 7.12 (d, *J*

= 8.1 Hz, 2H, Ph), 6.82 (d, *J* = 8.7 Hz, 2H, Ph), 5.76 (dd, *J* = 9.3, 9.3, 1H, H-3), 5.49 (s, 1H, MeOPhC*H*), 5.43 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 4.95 (d, *J* = 10.5 Hz, 1H, H-1), 4.43 (dd, *J* = 4.5, 10.8 Hz, 1H), 3.90–3.82 (m, 2H), 3.76–3.67 (m, 4H), 2.35 (s, 3H, SPhCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 165.2, 160.1, 138.8, 133.8, 133.3, 133.1, 129.9, 129.8, 129.8, 129.4, 129.3, 129.2, 128.4, 128.3, 127.9, 127.5, 113.6, 101.5, 87.3, 78.5, 73.4, 71.1, 71.0, 68.5, 55.3, 21.3; FAB MS: *m/z*: calculated for $C_{35}H_{33}O_8S$: 613.1896; found: 613.1879 $[M + H]^+$.

***p*-Methylphenyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (44).** The procedure for the regioselective ring opening of **43** was adapted from Johansson et al. (47). **43** (12.0 g, 19.6 mmol) was combined with sodium cyanoborohydride (6.15 g, 97.9 mmol), activated 3Å powdered molecular sieves (20 mL), and dissolved in DMF (261 mL). The reaction was cooled to 0 ^oC. Trifluoroacetic acid (15.3 mL, 196 mmol) was added dropwise to the reaction. The reaction was stirred at 0 ^oC for 1 h, and then allowed to warm to r.t. The reaction stirred at r.t. for 1 d. It was then filtered, diluted with CH_2Cl_2, and quenched with cold saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (2x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1x) and brine (1x), dried over Na_2SO_4, filtered, and concentrated. To remove the remaining sodium cyanoborohydride, the crude material was re-dissolved in CH_2Cl_2 (250 mL) and washed with brine (3x). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford a white solid containing the desired alcohol. R_f 0.23 (30% EtOAc:hexanes).

The crude alcohol was dissolved in CH_2Cl_2 (476 mL), triethylamine (8.2 mL, 58.6 mmol) was added, and the reaction cooled to 0 ^oC. *tert*-Butyldimethylsilyl trifluoromethansulfonate (11.2 mL, 48.8 mmol) was added dropwise to the reaction. The reaction was allowed to warm to r.t. and stirred for 3 h. It was then quenched with saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford an orange syrup. The product was purified by flash chromatography (10% → 12% EtOAc:hexanes) to afford **44** (13.24 g, 94%) as a white foam. R_f 0.64 (30% EtOAc:hexanes). $[\alpha]_D^{22}$ = +36 (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 2953, 2928, 2856, 1734, 1612, 1602, 1513, 1451, 1272, 1251, 1106, 1089, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.87 (m, 4H, Ph), 7.51–7.27 (m, 10H, Ph), 7.03 (d, *J* = 7.8 Hz, 2H, Ph), 6.94–6.91 (m, 2H, Ph), 5.59 (dd, *J* = 9.2, 9.2 Hz, 1H, H-3), 5.30 (dd, *J* = 9.6, 9.6 Hz, 1H, H-2), 4.88 (d, *J* = 9.6 Hz, 1H, H-1), 4.60 (d, *J* = 11.4 Hz, 1H, C*H*$_2$PhOMe), 4.51 (d, *J* = 11.7 Hz, 1H, C*H*$_2$PhOMe), 4.01 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4), 3.84–3.64 (m, 6H, H-5, H-6a, H-6b, PhOC*H*$_3$), 2.32 (s, 3H, SPhC*H*$_3$), 0.74 [s, 9H, (C*H*$_3$)$_3$CSi], 0.02 (s, 3H, C*H*$_3$Si), -0.22 (s, 3H, C*H*$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 165.3, 159.2, 138.2, 133.4, 133.1, 133.0, 130.5, 129.9, 129.9, 129.8, 129.7, 129.5, 129.3, 128.6, 128.4, 128.3, 113.9, 86.1, 81.0, 77.5, 73.3, 71.3, 69.4, 68.7, 55.5, 25.9, 21.5, 18.1, -3.9, -4.4; FAB MS: *m/z*: calculated for $C_{41}H_{47}O_8SSi$: 727.2785; found: 727.2761 $[M]^+$.

***p*-Methylphenyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-1-thio-*β*-D-glucopyranoside (45).** The procedure for the preparation of **45** was adapted from Zhang

et al. (48). In a flask covered with aluminum foil, **44** (13.2 g, 18.1 mmol) was dissolved in CH_2Cl_2 (440 mL). Water (23 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.93 g, 21.7 mmol) were added. The reaction was stirred at r.t. for 13 h. The reaction was then quenched with aqueous $NaHCO_3$, and water was added to dissolve all solids. The aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield a peach solid. The product was purified by flash chromatography (40% CH_2Cl_2:hexanes → 100% CH_2Cl_2 → 10% EtOAc: CH_2Cl_2) to afford **45** (9.42 g, 86%) as a white foam. R_f 0.41 (20% EtOAc:hexanes). $[\alpha]_D^{22} = +62$ (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3442, 2951, 2928, 2856, 1733, 1602, 1493, 1451, 1273, 1088, 1070, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.88 (m, 4H, Ph), 7.52–7.45 (m, 2H, Ph), 7.38–7.32 (m, 6H, Ph), 7.12 (d, *J* = 8.1 Hz, 2H, Ph), 5.62 (dd, *J* = 9.3, 9.3 Hz, 1H, H-3), 5.29 (dd, *J* = 9.6, 9.6 Hz, 1H, H-2), 4.93 (d, *J* = 9.9 Hz, 1H, H-1), 4.02–3.92 (m, 2H), 3.81–3.73 (m, 1H), 3.60–3.55 (d, *J* = 11.4 Hz, 1H), 2.35 (s, 3H, SPhC*H*$_3$), 1.95 (br s, 1H, OH), 0.76 [s, 9H, (C*H*$_3$)$_3$CSi], 0.07 (s, 3H, C*H*$_3$Si), -0.20 (s, 3H, C*H*$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 165.4, 138.7, 133.5, 133.3, 133.2, 130.0, 130.0, 129.9, 129.8, 129.4, 128.5, 128.5, 128.4, 86.4, 81.1, 77.2, 71.3, 69.0, 62.0, 25.9, 21.6, 18.2, -3.9, -4.3; FAB MS: *m/z*: calculated for $C_{33}H_{41}O_7SSi$: 609.2342; found: 609.2321 $[M + H]^+$.

***p*-Methylphenyl (methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranosyluronate (41).** **45** (9.42 g, 15.5 mmol) was dissolved in DMF (115 mL). Pyridinium dichromate (34.9 g, 92.8 mmol) was added, and the reaction was stirred at r.t. for 3 d. To precipitate and remove the chromium salts, EtOAc was added, and the

reaction was filtered and concentrated (3x). The remaining salts were removed by flash chromatography (100% EtOAc) to yield a white foam containing the desired carboxylic acid. R_f 0.17 (30% EtOAc:hexanes).

The crude acid was dissolved in CH_2Cl_2 (187 mL) and cooled to 0 ^oC. Diazomethane (93 mL, 0.2 M in diethyl ether, 18.6 mmol) was slowly added. The reaction stirred at 0 ^oC for 1 h. Glacial acetic acid was added to quench the reaction. It was then concentrated and purified by flash chromatography (10% → 15% EtOAc:hexanes) to yield **41** (6.04 g, 61%) as a white solid. R_f 0.67 (30% EtOAc:hexanes). $[\alpha]_D^{22}$ = +54 (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3443, 2953, 2928, 2857, 1732, 1601, 1493, 1451, 1437, 1269, 1085, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.86 (m, 4H, Ph), 7.52–7.46 (m, 2H, Ph), 7.38–7.31 (m, 6H, Ph), 7.10 (d, *J* = 8.1 Hz, 2H, Ph), 5.59 (dd, *J* = 9.3, 9.3 Hz, 1H, H-3), 5.30 (dd, *J* = 9.6, 9.6 Hz, 1H, H-2), 4.90 (d, *J* = 9.9 Hz, 1H, H-1), 4.26 (dd, *J* = 9.2, 9.2 Hz, 1H, H-4), 4.08 (d, *J* = 8.7 Hz, 1H, H-5), 3.82 (s, 3H, $COOCH_3$), 2.33 (s, 3H, $SPhCH_3$), 0.71 [s, 9H, $(CH_3)_3CSi$], -0.05 (s, 3H, CH_3Si), -0.22 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 168.3, 165.9, 165.3, 138.8, 133.7, 133.4, 133.4, 130.0, 130.0, 130.0, 129.7, 129.5, 128.5, 128.2, 87.2, 80.4, 76.6, 70.9, 70.7, 52.8, 25.6, 21.4, 18.0, -4.2, -4.9; FAB MS: *m/z*: calculated for $C_{34}H_{41}O_8SSi$: 637.2291; found: 637.2284 $[M + H]^+$.

Methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-α/β-D-glucopyranosyluronate (46). **41** (6.09 g, 9.56 mmol) was dissolved in CH_2Cl_2 (67 mL) and water (0.7 mL) was added. A solution was prepared containing 2.93 g *N*-iodosuccinimide, 127 mL CH_2Cl_2, 3.1 mL THF, and 78 μL triflic acid. 130 mL of this solution was added to the reaction

mixture. The reaction stirred at r.t. for 5.5 h. It was then quenched with 1 M $Na_2S_2O_3$ and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography (15% →30% EtOAc:hexanes) to afford **46** (4.27 g, 84%, 6.2β:1α) as a white foam. R_f 0.30, 0.36 (30% EtOAc:hexanes). $[\alpha]_D^{22}$ = +99 (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3455, 2954, 2930, 2857, 1732, 1602, 1451, 1275, 1110, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18–8.07 (m, 4H, Ph), 7.99–7.90 (m, 4H, Ph), 7.69–7.31 (m, 12H, Ph), 6.55 (d, *J* = 3.3 Hz, 1H, H-1, α), 5.94 (dd, *J* = 9.0, 9.9 Hz, 1H), 5.72–5.58 (m, 3H), 5.22–5.14 (m, 2H), 4.62 (d, *J* = 9.3 Hz, 1H, H-1, β), 4.40–4.27 (m, 2H), 4.13 (d, *J* = 9.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.46 (d, *J* = 3.6 Hz, 1H), 0.76 (s, 9H), 0.75 (s, 9H), -0.01 (s, 6H), -0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 169.0, 168.7, 167.4, 167.3, 166.1, 165.9, 165.0, 134.2, 133.9, 133.8, 133.6, 133.4, 130.3, 130.2, 130.1, 129.9, 129.1, 129.0, 128.8, 128.6, 128.6, 92.2, 90.9, 75.8, 74.8, 74.6, 74.6, 72.5, 72.4, 72.3, 71.1, 70.5, 70.2, 52.9, 25.7, 25.6, 18.0, -4.2, -4.9; FAB MS: *m/z*: calculated for $C_{27}H_{35}O_9Si$: 531.2050; found: 531.2041 $[M + H]^+$.

Methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*α*-D-glucopyranosyluronate trichloroacetimidate (47). The procedure for the preparation of **47** was adapted from Driguez et al. (41). **46** (3.32 g, 6.26 mmol) was coevaporated with toluene (2 x 20 mL) and dried under vacuum overnight. It was then dissolved in CH_2Cl_2 (49 mL). Trichloroacetonitrile (3.8 mL, 37.5 mmol) and Cs_2CO_3 (0.82 g, 2.5 mmol) were added. After stirring at r.t. for 4 h, additional trichloroacetonitrile (0.95 mL, 9.5 mmol) and

Cs_2CO_3 (0.20 g, 0.6 mmol) were added. The reaction was allowed to stir an additional 4 h and then concentrated. The product was purified by flash chromatography (10% EtOAc:hexanes + 0.1% TEA) to afford **47** (3.77 g, 89%), with a trace amount of the β anomer, as a white foam. R_f 0.57 (30% EtOAc:hexanes). $[\alpha]_D^{22} = +99$ (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3343, 2954, 2930, 2858, 1757, 1735, 1676, 1602, 1451, 1315, 1267, 1111, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (s, 1H, NH), 7.96–7.87 (m, 4H, Ph), 7.53–7.29 (m, 6H, Ph), 6.74 (d, *J* = 3.9 Hz, 1H, H-1), 5.99 (dd, *J* = 9.0, 10.2 Hz, 1H, H-3), 5.43 (dd, *J* = 3.9, 10.5 Hz, 1H, H-2), 4.51 (d, *J* = 9.3 Hz, 1H, H-5), 4.38 (dd, *J* = 9.3, 9.3 Hz, 1H, H-4), 3.81 (s, 3H, COOCH_3), 0.74 [s, 9H, (CH_3)$_3$CSi], -0.01 (s, 3H, CH_3Si), -0.15 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 165.7, 165.7, 160.8, 133.7, 133.5, 130.1, 129.9, 129.7, 128.7, 128.6, 128.6, 93.4, 74.6, 72.5, 70.9, 70.8, 53.0, 53.0, 25.7, 18.0, -4.1, -4.9; ESI MS: *m/z*: calculated for $C_{29}H_{34}Cl_3NNaO_9Si$: 696.1; found: 696.2 $[M+Na]^+$.

1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-α/β-D-galactopyranoside (50). To **10** (0.10g, 0.268mmol) in THF (5ml) was added *p*-tosic acid monohydrate (0.051g, 0.268mmol) followed by Pd/C (0.017g, 6mol%). The reaction was then placed under an atmosphere of hydrogen and stirred at ambient temperature for 18 hours. The Pd/C was removed by filtration through Celite and the solvent removed *in vacuo* to afford an anomeric mixture of crude amines as a pale yellow foam. The crude mixture was used for the next step without purification. To a solution of crude amines in THF (5ml), cooled to 0˚C was added TCACl (0.22g, 1.21mmol, 0.13ml) followed by Et_3N (0.18g, 1.79mmol, 0.25ml). The reaction mixture was stirred at 0˚C for 15 minutes and then quenched with

sat. $NaHCO_3$ (aq). The water layer was separated and extracted with CH_2Cl_2 (2x) and the combined organics dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a yellow oil. Purification of this oil by flash chromatography (30% → 40% EtOAc/hexanes) afforded **50** (0.099g, 0.20mmol, 75%) as a colourless solid. R_f 0.61 and 0.53 (60% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 9.0 Hz, 2H, N*H*TCA), 6.30 (d, *J* = 3.9 Hz, 1H, H-1, α), 5.45 (d, *J* = 3.3 Hz, 3H), 5.32 (dd, *J* = 3.5 Hz and 11.3 Hz, 2H), 4.58 (m, 2H), 4.26 (dd, *J* = 6.6 Hz, 6.6 Hz, 2H), 4.20–4.03 (m, 4H), 2.17 (s, 6H, OC(O)C*H*$_3$), 2.15 (s, 6H, OC(O)C*H*$_3$), 2.02 (s, 6H, OC(O)C*H*$_3$), 2.00 (s, 6H, OC(O)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 170.5, 170.2, 168.7, 162.2, 90.5, 69.0, 67.8, 66.8, 61.5, 49.6, 21.2, 21.0; HR-FAB MS: *m/z*: calculated for $C_{16}H_{19}Cl_3NO_{10}$: 490.0075; found: 490.0073 [*M* - H]$^-$.

***p*-Methylphenyl 2-deoxy-2-trichloroacetamido-3,4,6-tri-*O*-acetyl-1-thio-β-D-galactopyranoside (51).** To a solution of **50** (0.050 g, 0.10 mmol) in dry CH_2Cl_2 (0.35 mL) was added *p*-toluenethiol (0.042 g, 0.34 mmol) followed by BF_3•OEt_2 (0.043 g, 38 μL, 0.30 mmol), and the reaction mixture stirred at r.t. After 2 h, a further addition of *p*-toluenethiol (0.012 g, 0.10 mmol) and BF_3•OEt_2 (0.014 g, 13 μL, 0.10 mmol) was made followed by stirring at r.t. for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the organic phase washed twice with saturated aqueous $NaHCO_3$ and water. The aqueous layers were back extracted with CH_2Cl_2 (3x) and the combined organics washed with brine and dried over Na_2SO_4 to afford an amber oil. Purification of this oil by flash chromatography (20% → 25% EtOAc:hexanes) afforded **51** (0.044 g, 80%) as a white solid. R_f 0.51 (50% EtOAc:hexanes). $[\alpha]_D^{23}$ = -2.4 (*c* = 0.5,

CH_2Cl_2); IR (thin film on NaCl): υ = 3450, 1752, 1655, 1529, 1493, 1370, 1230, 1082, 1045 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.3 Hz, 2H, SC_6H_4Me), 7.12 (d, *J* = 8.3 Hz, 2H, SC_6H_4Me), 6.77 (d, *J* = 8.7 Hz, 1H, N*H*TCA), 5.39 (d, *J* = 3.3 Hz, 1H, H-4), 5.29 (dd, *J* = 3.3, 11.1 Hz, 1H, H-3), 4.89 (d, *J* = 10.5 Hz, 1H, H-1), 4.22–4.09 (m, 3H, H-2, H-6), 3.94 (dd, *J* = 6.6, 6.6 Hz, 1H, H-5), 2.34 (s, 3H, SPhCH_3), 2.13 (s, 3H, OC(O)CH_3), 2.04 (s, 3H, OC(O)CH_3), 1.97 (s, 3H, OC(O)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.5, 170.2, 161.9, 138.8, 133.5, 129.9, 128.5, 92.5, 87.2, 74.9, 70.9, 67.1, 62.0, 51.7, 21.6, 21.1, 21.0, 20.9; HR-FAB MS: *m/z*: calculated for $C_{21}H_{25}Cl_3NO_8S$: 556.0367; found: 556.0369 $[M + H]^+$.

***p*-Methylphenyl 2-deoxy-2-trichloroacetamido-3-*O*-triisopropylsilyl-4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-galactopyranoside (52).** A solution of **51** (17.9 g, 0.0320 mol) in dry CH_2Cl_2 (85 mL) and MeOH (435 mL) was stirred at r.t. for 30 min and NaOMe (25 wt% solution in MeOH, 0.52 g, 2.1 mL, 9.6 mmol) was then added. After stirring for 2 h, DOWEX 50X8-200 added and stirring continued for an additional 30 min. The DOWEX beads were removed by filtration and the solvent removed *in vacuo* to afford **52** (13.5 g, 98%) as a yellow solid. This compound was suitable for the next step without purification.

***p*-Methylphenyl 2-deoxy-2-trichloroacetamido-4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-galactopyranoside (53).** To a solution of **52** (13.5 g, 0.0310 mol) in acetonitrile (800 mL, minimum amount) was added *p*-anisaldehyde dimethyl acetal (11 g, 12 mL, 0.063 mol) and DL-10-camphorsulfonic acid (10 mol%) and the mixture stirred at r.t. for 12 h.

The reaction mixture was quenched with TEA and the solvent concentrated to afford a yellow solid. Purification of this solid by flash chromatography (40% → 80% EtOAc:hexanes) afforded **53** (13 g, 76%) as a white solid. R_f 0.25 (50% EtOAc:hexanes). $[\alpha]_D^{24}$ = -14.6 (*c* = 0.5, CH_2Cl_2); IR (thin film on NaCl): υ = 3333, 1687, 1615, 1519, 1492, 1403, 1364, 1301, 1248, 1167, 1095, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.4 Hz, 2H, SC_6H_4Me), 7.34 (d, *J* = 8.7 Hz, 2H, C_6H_4OMe), 7.12 (d, *J* = 8.4 Hz, 2H, SC_6H_4Me), 6.88 (d, *J* = 8.7 Hz, 2H, C_6H_4OMe), 6.81 (d, *J* = 7.5 Hz, 1H, N*H*TCA), 5.48 (s, 1H, MeOPhC*H*), 5.03 (d, *J* = 9.9 Hz, 1H, H-1), 4.37 (dd, *J* = 1.5, 12.6 Hz, 1H, H-6), 4.20–4.10 (m, 2H, H-3, H-4), 4.01 (dd, *J* = 1.5, 12.6 Hz, 1H, H-6), 3.83 (s, 3H, PhOCH_3), 3.69 (m, 1H, H-2), 3.57 (s, 1H, H-5), 2.58 (d, *J* = 10.5 Hz, 1H, O*H*), 2.37 (s, 3H, SPhCH_3); ^{13}C NMR, (75 MHz, $CDCl_3$): δ = 162.1, 160.5, 139.0, 134.7, 130.2, 130.0, 128.1, 126.9, 113.8, 101.4, 84.0, 75.2, 70.7, 70.3, 69.5, 55.7, 54.4, 21.7; HR-FAB MS: *m/z*: calculated for $C_{23}H_{25}Cl_3NO_6S$: 548.0469; found: 548.0448 $[M + H]^+$.

Allyl 2-deoxy-2-trichloroacetamido-3-*O*-triisopropylsilyl-4,6-*O*-*p*-methoxybenzylidene-β-D-galactopyranoside (54). To a solution of **33** (11 g, 0.016 mol) in dry CH_2Cl_2 (675 mL) was added 4Å powdered molecular sieves. After stirring for 1 h at r.t., allyl alcohol (9.3 g, 11 mL, 0.16 mol) and *N*-iodosuccinimide (5.3 g, 0.023 mol) were added, and the mixture was cooled to 0 °C. Triflic acid (0.5 *N* solution in CH_2Cl_2, 1.44 g, 9.60 mmol, 19.2 mL) was added and the reaction stirred at 0 °C for 10 min. The mixture was quenched with TEA, washed with brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow oil. Purification of this oil by flash chromatography (5% → 15% EtOAc:hexanes) afforded **54** (8.1 g, 79%) as a white solid.

R_f 0.41 (30% EtOAc:hexanes). $[\alpha]_D^{24}$ = +38.1 (*c* = 0.5, CH_2Cl_2); IR (thin film on NaCl): υ = 3445, 1644, 1520, 1463, 1368, 1249, 1171, 1123, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.9 Hz, 2H, C_6H_4OMe), 6.97 (d, *J* = 7.2 Hz, 1H, N*H*TCA), 6.87 (d, *J* = 8.9 Hz, 2H, C_6H_4OMe), 5.96–5.83 (m, 1H, $OCH_2CH=CH_2$), 5.49 (s, 1H, MeOPhC*H*), 5.26 (dd, *J* = 1.4, 17.3 Hz, 1H, $OCH_2CH=CH_2$), 5.17 (dd, *J* = 1.4, 10.5 Hz, 1H, $OCH_2CH=CH_2$), 5.16 (d, *J* = 8.1 Hz, 1H, H-1), 4.65 (dd, *J* = 3.3, 10.5 Hz, 1H, H-3), 4.37 (m, 2H, $OCH_2CH=CH_2$, H-6), 4.13–4.05 (m, 3H, $OCH_2CH=CH_2$, H-4, H-6), 3.81 (s, 3H, $PhOCH_3$), 3.75 (m, 1H, H-2), 3.48 (s, 1H, H-5), 1.05 (s, 21H, $[(CH_3)_2CH]_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 160.1, 134.0, 130.5, 127.8, 118.2, 113.6, 101.2, 97.8, 76.6, 70.6, 69.9, 69.5, 66.7, 64.2, 57.6, 55.6, 18.5, 18.4, 13.1; HR-FAB MS: *m/z*: calculated for $C_{25}H_{37}Cl_3NO_6Si$: 580.1456; found: 580.1474 [M^+ - OAll].

Allyl 2-deoxy-2-trichloroacetamido-4,6-*O*-*p*-methoxybenzylidene-β-D-galactopyranoside (55). To a solution of **54** (8.00 g, 12.5 mmol) in THF (290 mL) was added tetrabutylammonium fluoride (1 *N* solution in THF, 4.91 g, 18.8 mL, 18.8 mmol) and the mixture stirred at r.t. for 8 h. At this time a second addition of tetrabutylammonium fluoride (2.5 g, 9.4 mmol, 9.4 mL) was made and the reaction stirred for an additional 12 h. The solvent was removed *in vacuo* to afford a yellow oil. Purification of this oil by flash chromatography (40% → 80% EtOAc:hexanes) yielded **55** (5.14 g, 85%) as a white solid. R_f 0.17 (50% EtOAc:hexanes). $[\alpha]_D^{24}$ = +0.62 (*c* = 0.5, CH_2Cl_2); IR (thin film on NaCl): υ = 3423, 1686, 1616, 1531, 1402, 1366, 1303, 1249, 1170, 1097, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.7 Hz, 2H, C_6H_4OMe), 6.89 (d, *J* = 8.7 Hz, 2H, C_6H_4OMe), 6.87 (m, 1H, N*H*TCA), 5.95–5.82 (m,

1H, $OCH_2CH{=}CH_2$), 5.54 (s, 1H, MeOPhC*H*), 5.29 (dd, *J* = 1.4, 17.7 Hz, 1H, $OCH_2CH{=}CH_2$), 5.19 (dd, *J* = 1.4, 10.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.84 (d, *J* = 8.4 Hz, 1H, H-1), 4.44–4.32 (m, 2H, H-3, H-6), 4.26–4.07 (m, 4H, $OCH_2CH{=}CH_2$, H-4, H-6), 3.81 (m, 1H, H-2), 3.81 (s, 3H, $PhOCH_3$), 3.53 (s, 1H, H-5), 2.71 (d, *J* = 9.9 Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 160.4, 153.6, 133.7, 130.0, 127.9, 118.3, 113.8, 101.6, 98.7, 75.2, 70.4, 69.4, 69.3, 67.0, 57.2, 55.7; HR-FAB MS: *m/z*: calculated for $C_{19}H_{23}Cl_3NO_7$: 482.0540; found: 482.0531 $[M + H]^+$.

Allyl (4,6-*O*-*p*-methoxybenzylidene-3-*O*-triisopropylsilyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1 → 4)-methyl 2,3-di-*O*-benzoyl-β-D-glucopyranosyluronate (56). **33** (0.044 g, 0.063 mmol) and **49** (0.016 g, 0.035 mmol) were combined, azeotropically dried with toluene (2x) and dried under vacuum overnight. The mixture was dissolved in CH_2Cl_2 (0.5 mL) and 4Å powdered molecular sieves were added. The mixture was stirred for 1 h at r.t. *N*-iodosuccinimide (16 mg, 0.07 mmol), and then the reaction was cooled to –15 ˚C and stirred for 20 min. Triflic acid (0.25 *N* solution in CH_2Cl_2, 15 μL, 0.004 mmol) was added dropwise, and the reaction was stirred at –15 ˚C for 30 min, then quenched with TEA. The mixture was diluted with EtOAc and filtered. The filtrate was washed with sat. aq. $NaHCO_3$ and 1M $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc (3x), and the combined organic layers were dried ($NaSO_4$), filtered, and concentrated. Purification of the crude reaction mixture was achieved by preparative thin layer chromatography (25% EtOAc:hexanes), affording **56** (21 mg, 58%) as a white solid. The α-linked product was observed in ~32% yield. R_f 0.50 (30% EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.93 (m, 4H, Ar*H*), 7.53–

7.48 (m, 1H, Ar*H*), 7.39–7.31 (m, 3H, Ar*H*), 7.23–7.18 (m, 2H, Ar*H*), 7.07 (d, *J* = 9.0 Hz, 2H, C_6H_4OMe), 6.82 (d, *J* = 7.8 Hz, 1H, N*H*TCA), 6.74 (d, *J* = 8.1 Hz, 2H, C_6H_4OMe), 5.84–5.71 (m, 1H, $OCH_2CH{=}CH_2$), 5.71 (dd, *J* = 8.7, 9.0 Hz, 1H, H-2 GlcA), 5.38 (dd, *J* = 8.7, 9.3 Hz, 1H, H-3 GlcA), 5.28–5.20 (m, 3H, H-1 GalNAc, MeOPhC*H*, $OCH_2CH{=}CH_2$), 5.14 (dd, *J* = 1.5, 11.2 Hz, 1H, $OCH_2CH{=}CH_2$), 4.83 (d, *J* = 7.2 Hz, 1H, H-1 GlcA), 4.60 (dd, *J* = 8.7, 8.7 Hz, 1H, H-4 GlcA), 4.38–4.32 (m, 2H, H-3 GalNAc, $OCH_2CH{=}CH_2$), 4.18–4.09 (m, 2H, H-5 GlcA, $OCH_2CH{=}CH_2$), 3.96–3.67 (m, 4H, H-6 GalNAc, H-6 GalNAc, H-2 GalNAc, H-4 GalNAc) 3.86 (s, 3H, CO_2CH_3), 3.80 (s, 3H, PhOCH_3), 3.31 (s, 1H, H-5 GalNAc), 0.99 (s, 21H, $[(CH_3)_2CH]_3$); ESI MS: *m/z*: calculated for $C_{49}H_{61}Cl_3NO_{15}Si$: 1038.4; found 1038.5 $[M + H]^+$.

Allyl (methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranoside (57). A mixture of donor **47** (0.500 g, 0.741 mmol) and acceptor **55** (0.300 g, 0.62 mmol) was coevaporated with toluene (3 x 3 mL) and dried under vacuum overnight. The mixture was dissolved in CH_2Cl_2 (16 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at r.t. for 1.5 h. The reaction was then cooled to -40 °C and stirred for an additional 30 min. Trimethylsilyl trifluoromethanesulfonate (1 M in CH_2Cl_2, 125 μL, 0.123 mmol) at -40 °C was added to the reaction dropwise. The reaction was allowed to stir an additional 30 min. It was then warmed to -10 °C over a period of 30 min, quenched with triethylamine, and allowed to warm to r.t. The reaction was filtered and concentrated to afford a yellow syrup. The product was purified by flash chromatography (30% EtOAc:hexanes) to

afford **57** (0.456 g, 74%) as a white solid. R_f 0.12 (30% EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.82 (m, 4H, Ph), 7.48–7.39 (m, 4H, Ph), 7.35–7.26 (m, 4H, Ph), 6.86 (d, *J* = 8.7 Hz, 2H, Ph), 6.82 (d, *J* = 7.2 Hz, 1H, NH), 5.89–5.76 (m, 1H, OCH_2CH=CH_2), 5.45 (s, 1H, MeOPhC*H*), 5.52–5.39 (m, 2H, GlcA H-2, H-3), 5.22 (dd, *J* = 1.6, 17.6 Hz, 1H, OCH_2CH=CH_2), 5.13 (dd, *J* = 1.0, 10.4 Hz, 1H, OCH_2CH=CH_2), 5.08 (d, *J* = 7.5 Hz, 1H, GlcA H-1), 5.05 (d, *J* = 8.1 Hz, 1H, GalN H-1), 4.67 (dd, *J* = 3.3, 10.8 Hz, 1H, GalN H-3), 4.36–4.27 (m, 4H, GalN H-4, GalN H-6a, GlcA H-4, OCH_2CH=CH_2), 4.10 (d, *J* = 9.3 Hz, 1H, GlcA H-5), 4.07–4.01 (m, 2H, GalN H-6b, OCH_2CH=CH_2), 3.79 (s, 6H, COOCH_3, PhOCH_3), 3.77–3.68 (m, 1H, GalN H-2), 3.48 (s, 1H, GalN H-5), 0.72 [s, 9H, (CH_3)$_3$CSi], -0.08 (s, 3H, CH_3Si), -0.23 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 165.7, 165.2, 162.3, 160.0, 133.8, 133.4, 133.4, 130.5, 130.0, 129.9, 129.5, 129.2, 128.5, 127.7, 118.2, 113.6, 100.7, 100.6, 97.8, 92.3, 76.4, 75.8, 75.6, 73.6, 72.0, 70.9, 70.6, 69.2, 66.8, 55.6, 55.4, 52.9, 25.7, 18.1, -4.0, -4.7; FAB MS: *m/z*: calculated for $C_{46}H_{53}Cl_3NO_{15}Si$: 992.2250; found: 992.2255 $[M]^+$.

Methyl (2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-α-D-galactopyranoside trichloroacetimidate (58). To a solution of **57** (2.5 g, 2.5 mmol) in dry CH_2Cl_2 (40 mL) was added Grubbs' second-generation catalyst (0.43 g, 20 mol%), and the mixture stirred at r.t. for 2 h. The solvent was removed *in vacuo* to afford a brown oil. Purification of this oil by flash chromatography (15% → 20% EtOAc:hexanes) afforded *E/Z*-prop-2-enyl (methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-

trichloroacetamido-*β*-D-galactopyranoside (1.92 g, 77%) as a white solid. R_f (E and Z) 0.68 (60% EtOAc:hexanes). $[\alpha]_D^{25}$ = +29.1 (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3308, 2954, 2858, 1755, 1734, 1717, 1694, 1617, 1602, 1540, 1520, 1452, 1371, 1268, 1221, 1176, 1147, 1089, 1069, 1040, 1026, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 3H, Ar*H*), 7.48–7.28 (m, 10H, Ar*H*, OC*H*=CHCH$_3$), 6.87 (d, *J* = 8.7 Hz, 2H, C_6H_4OMe), 6.82 (d, *J* = 6.6 Hz, 1H, N*H*TCA), 6.17 (m, 1H, CH=C*H*CH$_3$), 5.52–5.40 (m, 3H, MeOPhC*H*, H-2 GlcA, H-3 GlcA), 5.19 (d, *J* = 8.1 Hz, 1H, H-1 GalNAc), 5.08 (d, *J* = 7.2 Hz, 1H, H-1 GlcA), 4.68 (dd, *J* = 3.8, 11.0 Hz, 1H, H-3 GalNAc), 4.39–4.28 (m, 3H, H-4 GalNAc, H-4 GlcA, H-6 GalNAc), 4.16–4.02 (m, 2H, H-5 GlcA, H-6 GalNAc), 3.87 (m, 1H, H-2 GalNAc), 3.81 (s, 3H, PhOC*H*$_3$), 3.80 (s, 3H, CO_2C*H*$_3$), 3.54 (s, 1H, H-5), 1.51 (m, 3H, OCH=CHC*H*$_3$), 0.72 (s, 9H, (C*H*$_3$)$_3$CSi), -0.07 (s, 3H, C*H*$_3$Si), -0.22 (s, 3H, C*H*$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 165.7, 165.3, 162.4, 162.3, 160.0, 143.5, 142.1, 133.5, 133.4, 130.4, 130.1, 129.9, 129.5, 129.1, 128.5, 127.7, 113.6, 105.7, 104.8, 100.8, 100.6, 100.5, 98.4, 98.0, 76.5, 75.6, 75.5, 73.5, 73.4, 72.0, 70.9, 69.0, 67.2, 67.1, 55.6, 55.1, 55.0, 52.9, 25.7, 18.1, 12.6, 9.7, -4.0, -4.7.

To a solution of *E/Z*-prop-2-enyl (methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranoside (6.2 g, 6.3 mmol) in dry THF (118 mL), water (24 mL) and pyridine (1.9 mL) was added iodine (3.1 g) and the mixture stirred at ambient temperature for 30 min. The solvent was removed *in vacuo* to afford a yellow oil. The oil was taken up in EtOAc and washed with 5% aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo*

to afford a pale yellow oil. Purification of this oil by flash chromatography (40% → 60% EtOAc:hexanes) afforded an anomeric mixture of methyl (2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*α*/*β*-D-galactopyranoside (4.8 g, 81%) as a pale yellow solid. R_f 0.28 and 0.18 (50% EtOAc:hexanes). $[\alpha]_D^{25}$ = +79.0 (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3521, 2930, 1738, 1682, 1615, 1519, 1452, 1394, 1251, 1172, 1093, 1069, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 7.92–7.85 (m, 3H, Ar*H*), 7.54–7.45 (m, 3H, Ar*H*), 7.40–7.27 (m, 4H, Ar*H*), 7.12 (d, *J* = 9.0 Hz, 2H, C_6H_4OMe), 6.96 (d, *J* = 6.3Hz, 1H, N*H*TCA), 6.72 (d, *J* = 9.0 Hz, 2H, C_6H_4OMe), 5.60 (m, 1H, H-1 GalNAc), 5.50 (dd, *J* = 8.2, 8.2 Hz, 1H, H-3 GlcA), 5.42 (dd, *J* = 8.2, 8.2 Hz, 1H, H-2 GlcA), 5.24 (s, 1H, MeOPhC*H*), 5.21 (d, *J* = 7.5 Hz, 1H, H-1 GlcA), 4.39–4.35 (m, 4H, H-3 GalNAc, H-4 GalNAc, H-4 GlcA), 4.23–4.02 (m, 3H, H-2 GalNAc, H-5 GlcA, H-6 GalNAc), 3.96 (s, 1H, H-5 GalNAc), 3.79 (s, 3H, $PhOCH_3$), 3.75 (s, 3H, CO_2CH_3), 3.03 (d, *J* = 3.3 Hz, 1H, O*H*), 0.73 (s, 9H, $(CH_3)_3CSi$), -0.08 (s, 3H, CH_3Si), -0.22 (s, 3H, CH_3Si); ESI MS: *m/z*: calculated for $C_{43}H_{50}Cl_3NO_{15}Si$: 954.2914; found: 954.2910 $[M - H]^-$.

To a solution of methyl (2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*α*/*β*-D-galactopyranoside (4.6 g, 4.8 mmol) in dry CH_2Cl_2 (190 mL) cooled to 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.29 g, 0.29 mL, 1.9 mmol) and trichloroacetonitrile (10 g, 7.2 mL, 71 mmol). After stirring for 15 min, the mixture was quenched with TEA and concentrated *in vacuo* to afford a yellow oil. Purification of this oil by flash chromatography (35% EtOAc:hexanes, + 2% TEA)

afforded **58** (4.7 g, 90%) as a pale yellow foam. R_f 0.74, (50% EtOAc:hexanes). $[\alpha]_D^{24}$ = +12.0 (*c* = 0.5, CH_2Cl_2); IR (thin film on NaCl): υ = 3422, 2956, 2991, 2361, 1731, 1676, 1616, 1519, 1452, 1373, 1271, 1177, 1147, 1094, 1070, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.69 (s, 1H, C=N*H*), 7.90 (m, 4H, Ar*H*), 7.51 (m, 2H, Ar*H*), 7.42–7.26 (m, 4H, Ar*H*), 7.00 (d, *J* = 8.9 Hz, 2H, C_6H_4OMe), 6.93 (d, *J* = 5.4 Hz, 1H, N*H*TCA), 6.77 (d, *J* = 2.1 Hz, 1H, H-1 GalNAc), 6.68 (d, *J* = 8.9 Hz, 2H, C_6H_4OMe), 5.52 (dd, *J* = 8.7, 8.7 Hz, 1H, H-3 GlcA), 5.45 (dd, *J* = 8.7, 8.7 Hz, 1H, H-2 GlcA), 5.27 (d, *J* = 7.8 Hz, 1H, H-1 GalNAc), 5.17 (s, 1H, MeOPhC*H*), 4.62 (m, 2H, H-4 GalNAc, H-4 GlcA), 4.49 (m, 1H, H-3 GalNAc), 4.31 (m, 2H, H-2 GalNAc, H-6 GalNAc), 4.18 (d, *J* = 9.0 Hz, 1H, H-5 GlcA), 4.00 (d, *J* = 12.6 Hz, 1H, H-6 GalNAc), 3.94 (s, 1H, H-5 GalNAc), 3.75 (s, 3H, PhOCH_3), 3.74 (s, 3H, CO_2CH_3), 0.73 (s, 9H, $(CH_3)_3$CSi), -0.06 (s, 3H, CH_3Si), -0.19 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 165.9, 165.6, 162.0, 160.4, 133.9, 133.6, 130.1, 129.9, 129.4, 128.7, 128.6, 127.6, 113.6, 101.1, 98.4, 95.3, 77.2, 75.5, 74.4, 71.2, 70.9, 69.2, 69.0, 65.5, 55.6, 53.0, 50.5, 46.5, 25.7, -4.0, -4.8.

Allyl (methyl 2,3-di-*O*-benzoyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranoside (59). To a solution of **57** (2.5 g, 2.5 mmol) in dry THF (40 mL) and pyridine (40 mL) cooled to 0 °C was added HF•pyridine (13 mL, 715 mmol). The reaction mixture was warmed to r.t. and stirred for 18 h. The mixture was then diluted with EtOAc and washed with 10% aqueous $CuSO_4$. The aqueous phase was extracted with EtOAc (3x) and the combined organics washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow oil. Purification of this oil by flash chromatography

(30 → 60% EtOAc:hexanes) afforded **59** (1.9 g, 85%) as a white solid. R_f 0.35 (60% EtOAc:hexanes). $[\alpha]_D^{25}$ = +32.8 (*c* = 1.0, CH_2Cl_2); IR (thin film on NaCl): υ = 3422, 1731, 1616, 1519, 1452, 1369, 1251, 1173, 1093, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.87 (m, 4H, Ar*H*), 7.50–7.42 (m, 4H, Ar*H*, C_6H_4OMe), 7.36–7.26 (m, 4H, ArH), 7.01 (d, *J* = 6.6 Hz, 1H, N*H*TCA), 6.89 (d, *J* = 8.7 Hz, 2H, C_6H_4OMe), 5.89–5.77 (m, 1H, $OCH_2CH{=}CH_2$), 5.47 (m, 3H, MeOPhC*H*, H-2 GlcA, H-3 GlcA), 5.26–5.12 (m, 4H, $OCH_2CH{=}CH_2$, H-1 GalNAc, H-1 GlcA), 4.73 (dd, *J* = 3.6, 11.4 Hz, 1H, H-3 GalNAc), 4.41–4.28 (m, 3H, $OCH_2CH{=}CH_2$, H-4 GalNAc, H-6 GalNAc), 4.19 (m, 1H, H-4 GlcA), 4.12–4.02 (m, 3H, $OCH_2CH{=}CH_2$, H-5 GlcA, H-6 GalNAc), 3.83 (s, 3H, $PhOCH_3$), 3.81 (s, 3H, CO_2CH_3), 3.72 (m, 1H, H-2 GalNAc), 3.48 (s, 1H, H-5 GalNAc), 3.45 (d, *J* = 3.3 Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 166.6, 165.2, 162.3, 160.1, 133.8, 133.6, 133.5, 130.4, 130.1, 130.0, 129.2, 129.1, 128.7, 128.6, 127.5, 118.2, 113.7, 100.8, 100.7, 97.7, 76.1, 75.4, 74.3, 74.1, 71.4, 70.7, 69.3, 66.8, 55.7, 53.4; ESI MS: *m/z*: calculated for $C_{40}H_{39}Cl_3NO_{15}$; 880.1; found: 880.2 $[M - H]^-$.

Allyl (methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyluronate)-(1 → 3)-(4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1 → 4)-(methyl 2,3-di-*O*-benzoyl-β-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (60). **58** (0.20 g, 0.182 mmol) and **59** (0.13 g, 0.15 mmol) were combined and co-evaporated with toluene (3x) and put under high vacuum overnight to dry. The mixture was dissolved in CH_2Cl_2 (3 mL) and activated 4 Å powdered molecular sieves were added. The mixture was stirred for 1 h at r.t. and then

cooled to -15°C. Trimethylsilyl trifluoromethanesulfonate (0.5 *N* solution in CH_2Cl_2, 0.0068 g, 0.031 mmol, 61 μL) was added and the reaction was stirred at -15°C for 30 min and then quenched with TEA. The mixture was filtered and concentrated to afford a yellow oil. Purification of this oil by flash chromatography (30 → 40% EtOAc:hexanes containing 0.1% TEA) afforded **60** (85 mg, 31%) as a white solid. R_f 0.43 (60% EtOAc:hexanes). $[\alpha]_D^{25}$ = +13.4 (*c* = 0.5, CH_2Cl_2); IR (thin film on NaCl): υ = 3424, 2956, 2361, 1732, 1638, 1519, 1452, 1368, 1251, 1173, 1093, 1173, 1093, 1070, 1028; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88–7.80 (m, 8H, Ar*H*), 7.49–7.45 (m, 4H, Ar*H*), 7.38–7.28 (m, 8H, Ar*H*), 7.22–7.20 (m, 2H, Ar*H*), 7.06 (d, *J* = 8.4 Hz, 2H, C_6H_4OMe), 6.93 (d, *J* = 8.4 Hz, 2H, C_6H_4OMe), 6.85 (d, *J* = 6.6 Hz, 1H, N*H*TCA), 6.74 (d, *J* = 8.4 Hz, 2H, C_6H_4OMe), 6.66 (d, *J* = 7.2 Hz, 1H, N*H*TCA), 5.87–5.81 (m, 1H, OCH_2CH=CH_2), 5.58 (dd, *J* = 7.8, 7.8 Hz, 1H, H-3 GlcA), 5.49 (s, 1H, MeOPhC*H*), 5.44 (dd, *J* = 8.7, 8.7 Hz, 1H, H-3 GlcA), 5.35 (m, 2H, H-2 GlcA, H-2 GlcA), 5.23 (d, *J* = 18.0 Hz, 1H, OCH_2CH=CH_2), 5.20 (s, 1H, MeOPhC*H*), 5.15–5.12 (m, 2H, OCH_2CH=CH_2, H-1 GlcA), 5.11 (d, *J* = 7.8 Hz, 1H, H-1 GalNAc), 5.03 (d, *J* = 7.2 Hz, 1H, H-1 GlcA), 5.00 (d, *J* = 8.4 Hz, 1H, H-1 GalNAc), 4.68 (dd, *J* = 3.6, 10.8 Hz, 1H, H-3 GalNAc), 4.58 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4 GlcA), 4.39–4.30 (m, 5H, OCH_2CH=CH_2, H-3 GalNAc, H-4 GalNAc, H-4 GlcA, H-6 GalNAc), 4.14 (m, 2H, H-4 GalNAc, H-5 GlcA), 4.06–3.91 (m, 3H, OCH_2CH=CH_2, H-5 GlcA, H-6 GalNAc), 3.83 (s, 3H, PhOCH_3), 3.81–3.68 (m, 4H, H-2 GalNAc, H-2 GalNAc, H-6 GalNAc, H-6 GalNAc), 3.80 (s, 3H, PhOCH_3), 3.80 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CO_2CH_3), 3.48 (s, 1H, H-5 GalNAc), 3.10 (s, 1H, H-5 GalNAc), 0.72 (s, 9H, $(CH_3)_3$CSi), -0.09 (s, 3H, CH_3Si), -0.24 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 168.4, 165.7, 165.4, 165.2, 165.1, 162.2, 161.9, 160.0,

159.8, 133.8, 133.4, 133.3, 133.1, 130.5, 130.4, 130.2, 130.1, 130.0, 129.9, 129.6, 129.5, 129.2, 129.1, 128.6, 128.5, 128.4, 127.9, 127.8, 118.2, 113.7, 113.4, 100.8, 100.5, 100.4, 100.2, 98.6, 97.7, 77.4, 76.4, 75.9, 75.8, 75.3, 75.0, 74.2, 74.1, 73.5, 73.4, 72.1, 71.9, 70.8, 70.6, 69.3, 68.4, 66.9, 55.7, 55.6, 54.8, 53.5, 52.8, 25.7, 18.1, -4.1, -4.8. ESI MS: *m/z*: calculated for $C_{83}H_{89}Cl_6N_2O_{29}Si$: 1819.4; found 1820.4 $[M + H]^+$.

Allyl (4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranosyl)-(1 → 4)-(methyl 2,3-di-*O*-benzoyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranoside (61α, 61β). **33** (65.6 mg, 0.0931 mmol) was combined with **59** (41 mg, 0.0465 mmol) and azeotropically dried with toluene (2x). This was dried under high vacuum overnight. The reactants were dissolved in dichloromethane (0.53 mL). Activated 4 Å powdered molecular sieves were added. This was stirred at r.t. for 1 h 40 min. *N*-iodosuccinimide (23 mg, 0.102 mmol) was added, and the reaction was cooled to -12 ^oC. A cooled 0.1 M solution of triflic acid in dichloromethane (49 μL) was added. The reaction was allowed to stir for 1 hr 10 min. The reaction was then quenched with TEA, filtered, diluted with EtOAc, and washed with 1 M $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by preparatory TLC (38% EtOAc:hexanes) to afford the α-anomer (17.6 mg, 26%) and the β-anomer (30.8 mg, 45%).

The α-anomer (23 mg, 0.0157 mmol) was dissolved in dry THF (0.24 mL) and pyridine (0.24 mL). The mixture was cooled to 0 °C and HF•pyridine (0.08 mL) was

added. The reaction was slowly allowed to warm to 10°C with stirring over a 19 h period. The mixture was then allowed to warm to r.t. and stirred an addition 8 h. The reaction was then diluted with EtOAc and washed with 10% aqueous $CuSO_4$. The aqueous phase was extracted with EtOAc (4x) and the combined organics washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The crude mixture was purified by preparatory TLC (30% EtOAc:CH_2Cl_2) to afford **61α** (11.4 mg, 56%) as a white solid.

The β-anomer (17.1 mg, 0.117 mmol) was dissolved in dry THF (0.18 mL) and pyridine (0.18 mL). The mixture was cooled to 0 °C and HF•pyridine (0.06 mL) was added. The reaction was stirred for 42 h at 0 °C. The reaction was then diluted with EtOAc and washed with 10% aqueous $CuSO_4$. The aqueous phase was extracted with EtOAc (4x) and the combined organics washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The crude mixture was purified by preparatory TLC (70% EtOAc:hexanes) to afford **61β** (10.8 mg, 71%) as a white solid.

Allyl (methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1 → 3)-(4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranosyl)-(1 → 4)-methyl 2,3-di-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1 → 3)-(4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranosyl)-(1 → 4)-(methyl 2,3-di-*O*-benzoyl-*β*-D-glucopyranosyluronate)-(1 → 3)-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranoside (63). 58 (0.073 g, 0.066 mmol) and **62** (0.094 g, 0.055 mmol) were combined, azeotroped by co-

evaporation with toluene (3x), and placed under high vacuum overnight to dry. The mixture was dissolved in CH_2Cl_2 (1.2 mL) and 4Å powdered molecular sieves added. After stirring for 1 h at r.t., the reaction mixture was cooled to –15 ˚C. Trimethylsilyl trifluoromethanesulfonate (0.25 *N* in CH_2Cl_2, 60 μL, 0.011 mmol) was added, and the reaction was stirred at –15 ˚C for 30 min and quenched with TEA. The mixture was filtered and the solvent removed *in vacuo* to afford a yellow oil. Purification of this oil by flash chromatography (35 → 50% EtOAc:hexanes) afforded **63** (32 mg, 25%) as a white solid. R_f 0.56 (60% EtOAc:hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 8H, Ar*H*), 7.81 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.48–7.26 (m, 18H, Ar*H*), 7.22–7.17 (m, 6H, Ar*H*), 7.05 (d, *J* = 8.4 Hz, 2H, C_6H_4OMe), 6.90 (d, *J* = 9.0 Hz, 2H, C_6H_4OMe), 6.86 (d, *J* = 7.2 Hz, 1H, N*H*TCA), 6.81 (d, *J* = 8.4 Hz, 2H, C_6H_4OMe), 6.72 (d, *J* = 8.4 Hz, 2H, C_6H_4OMe), 6.63 (d, *J* = 7.2 Hz, 1H, N*H*TCA), 6.60 (d, *J* = 7.2 Hz, 1H, N*H*TCA), 5.84 (m, 1H, OCH_2CH=CH_2), 5.59 (dd, *J* = 8.1, 8.1 Hz, 1H H-3 GlcA), 5.52 (dd, *J* = 7.5, 7.5 Hz, 1H, H-3 GlcA), 5.49 (s, 1H, MeOPhC*H*), 5.44 (dd, *J* = 8.4, 8.4 Hz, 1H H-3 GlcA), 5.36 (m, 2H, H-2 GlcA, H-2 Glc-A), 5.27 (dd, *J* = 6.9, 6.9 Hz, 1H, H-2 GlcA), 5.24 (s, 1H, MeOPhC*H*), 5.22 (s, 1H, OCH_2CH=CH_2), 5.15 (m, 3H, OCH_2CH=CH_2, H-1 GlcA, MeOPhC*H*), 5.11 (d, *J* = 7.8 Hz, 1H, H-1 GalNAc), 5.05 (m, 2H, H-1 GalNAc, H-1 GlcA), 5.02 (d, *J* = 7.2 Hz, 1H, H-1 GlcA), 4.86 (d, *J* = 7.8 Hz, 1H, H-1 GalNAc), 4.69 (dd, *J* = 3.3, 11.1 Hz, 1H, H-1 GlcA), 4.59 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4 GlcA), 4.54 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4 GlcA), 4.37–4.30 (m, 6H, H-4 GlcA, H-5 GalNAc, H-3 GalNAc, OCH_2CH=CH_2, H-6 GalNAc, H-4 GalNAc), 4.16–4.03 (m, 7H, OCH_2CH=CH_2, H-6 GalNAc, H-5 GlcA, H-5 GlcA, H-4 GalNAc, H-5 GlcA, H-4 GalNAc), 3.81–3.76 (m, 2H, H-6 GalNAc, H-6 GalNAc), 3.80–3.77 (6s, 18H, CO_2CH_3,

PhOCH_3), 3.73–3.61 (m, 5H, H-6 GalNAc, H-6 GalNAc, H-2 GalNAc, H-2 GalNAc, H-2 GalNAc), 3.48 (s, 1H, H-5 GalNAc), 3.08 (s, 1H, H-5 GalNAc), 3.00 (s, 1H, H-5 GalNAc), 0.72 (s, 9H, (CH_3)$_3$CSi), -0.10 (s, 3H, CH_3Si), -0.25 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 168.5, 168.4, 165.7, 165.5, 165.4, 165.3, 165.1, 165.0, 162.3, 161.9, 161.8, 160.0, 159.9, 159.8, 133.7, 133.4, 133.3, 133.1, 130.7, 130.5, 130.4, 130.2, 130.1, 130.0, 129.9, 129.5, 129.4, 129.2, 129.1, 128.6, 128.5, 128.4, 128.0, 127.8, 127.7, 118.2, 113.7, 113.4, 113.3, 102.9, 100.7, 100.6, 100.5, 100.1, 98.8, 98.4, 97.7, 97.6, 92.5, 92.4, 92.3, 77.5, 76.4, 75.8, 75.7, 75.3, 75.2, 75.0, 74.3, 74.2, 74.1, 73.8, 73.6, 73.5, 73.4, 72.1, 71.9, 70.8, 70.6, 69.3, 68.6, 66.8, 55.6, 55.5, 54.9, 54.7, 53.5, 53.4, 52.8, 30.1, 25.7, 18.1, -4.1, -4.8. ESI MS: *m/z*: calculated for $C_{120}H_{123}Cl_9N_3O_{43}Si$: 2637.4; found 2637.5 $[M + H]^+$.

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