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Stannylene-Mediated Regioselective 6-*O*-Glycosylation of Unprotected Phenyl 1-Thioglycopyranosides

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A straightforward procedure is described for the synthesis of (1→6)-linked saccharides by regioselective glycosylation of unprotected glycosyl acceptors. Phenyl 1-thioglycopyranosides derived from D-glucose, D-galactose and D-mannose were treated with dibutyltin oxide to introduce a stannylene acetal, and then subjected to selective glycosylation at the 6-position with the Koenigs–Knorr protocol. Peracylated glycosyl bromides of D-glucose, D-galactose, D-mannose and D-glucosamine were employed as the donors to give the corresponding (1→6)-linked disaccharides in moderate to good yields. The best results were obtained with glycosyl donors and acceptors derived from D-glucose and D-galactose. Fully acylated disaccharide thioglycosides could also serve as glycosyl donors for the regioselective coupling. Brominolysis and subsequent Koenigs–Knorr coupling with the stannylene acetal of phenyl 1-thio-β-D-glucopyranoside gave rise to the corresponding (1→6)-linked trisaccharides in moderate yields.

Introduction

Complex carbohydrates constitute a major class of cell-surface molecules, and play a crucial role in numerous biological processes such as cell recognition events, cellular adhesion and communication, as well as protein structure and function.[1] The growing interest towards a better understanding of these processes has stimulated a large number of studies in the field of glycobiology and has increased the demand for structurally defined oligosaccharides.[2]

Chemical synthesis is the most widespread and versatile protocol to access pure and well-defined oligosaccharides, and a vast array of glycosylation methods are available.[3] In addition, contemporary glycosylation strategies such as solid-phase,[4,5] one-pot[5,6] and armed/disarmed[7] approaches continue to be further developed. As a result, the synthesis of almost any oligosaccharide is possible, although certain glycosidic linkages may still pose a challenging task. However, regardless of the glycosylation strategy, modern oligosaccharide synthesis continues to employ multiple protecting groups to mask hydroxy groups that are not involved in the glycosylations.[8] This causes the synthesis of a target oligosaccharide to be a rather time-consuming process, since a majority of the reactions are used for protection and deprotection of the hydroxy groups. An obvious solution to this problem would be to develop regioselective glycosylations with unprotected carbohydrates.

During the past two decades, there have been several studies on the glycosylation of unprotected glycosyl acceptors. These investigations have been carried out both in the absence[9–11] and in the presence[12–18] of special additives in order to control the regioselectivity. In the absence of any additional reagents, the direct Koenigs–Knorr glycosylation of unprotected 2-(trimethylsilyl)ethyl β-D-galactopyranoside with several glycosyl bromides gave the 6-linked saccharides in 75–90% yield.[9] Similar regioselectivity, however, could not be achieved with unprotected gluco- and mannopyranosides. Glycosylation of unprotected β-pyranosides of glucose and *N*-acetylglucosamine gave near statistical mixtures of all possible glycosylation products.[10] Glycosylation of unprotected α-mannopyranosides gave mainly the 6-linked disaccharides and the 3,6-linked trisaccharides, but the isolated yields were modest.[11]

Several additives based on tin and boron have been examined in an attempt to further direct the glycosylations. Dibutyltin oxide-mediated coupling of unprotected methyl β-D-galactopyranoside with different donors gave the 6-linked disaccharides in good yields.[12,13] A notable shift in regioselectivity to the 3-linked disaccharide could be achieved in the presence of fluoride, although the isolated yield was modest.[14] On the other hand, treatment of methyl β-D-glucopyranoside with dibutyltin oxide, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide and tetrabutylammonium iodide furnished the 6-linked disaccharide in a mere 44% yield.[12] Under similar conditions, unprotected methyl β-lactoside gave a 58% yield of the 6′-linked trisaccharide in a reaction with bis(tributyltin) oxide and 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide.[15]

With a special diarylborinic acid as the additive, Koenigs–Knorr glycosylation of methyl α-D-galactopyran-

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oside and α-D-mannopyranoside proceeded selectively at the 3- and the 6-positions to afford the corresponding trisaccharides in good yields.[16] Very recently, another diaryl borinic acid was used to catalyze the regioselective Koenigs–Knorr glycosylation of unprotected acceptors, although no acceptor with a free primary hydroxy group was investigated.[17] With *p*-methoxyphenylboronic acid as the additive, an in-situ masking of the 4- and the 6-hydroxy groups took place, and Koenigs–Knorr glycosylations on methyl β-D-galactopyranoside could be directed to the 3-position in good yield.[18] With methyl β-D-glucopyranoside, however, poor regioselectivity was observed under the same conditions.[18]

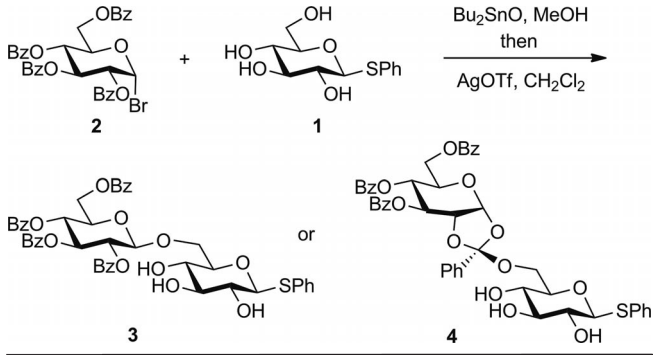
In all, the chemical glycosylation of unprotected carbohydrates is still in its infancy and there is room for much development in this area. Most of the studies so far have briefly investigated different methods for controlling the regioselectivity, but more comprehensive studies are needed to fully understand the scope and limitations. We decided to compare the regioselective glycosylation of several unprotected phenyl 1-thioglycopyranosides, since this would provide an easy route to a number of thioglycoside building blocks that could be useful glycosyl donors. Dibutyltin oxide was selected for directing the glycosylations because stannylene acetals have been widely applied in carbohydrate chemistry for controlling regioselective esterifications and alkylations of diols and polyols.[19]

Results and Discussion

Phenyl thioglycosides are easily prepared from the corresponding peracetylated monosaccharides by reaction with thiophenol and boron trifluoride etherate.[20] In addition, the unprotected phenyl thioglycosides of glucose, galactose and mannose are all crystalline and therefore easily available on a large scale. Phenyl 1-thio-β-D-glucopyranoside (**1**) was selected as the test substrate for optimizing the glycosylation, because regioselective couplings to glucose have proven notoriously difficult. The Koenigs–Knorr procedure was chosen as the coupling method due to the high reactivity of glycosyl halides, and to avoid any simultaneous activation of the thiophenyl group in the acceptor. Therefore, 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**2**) was selected as the donor for the optimization.

First, the stannylene acetal was installed by refluxing acceptor **1** with dibutyltin oxide in methanol until a clear solution was obtained. The solvent was removed and replaced with dichloromethane. Notably, acceptor **1** was soluble in dichloromethane after attachment of the stannylene acetal. The Koenigs–Knorr coupling was then investigated under different conditions (Table 1). Soluble silver triflate was chosen as the promoter because silver carbonate gave essentially no conversion. In the absence of any other additives, the glycosylation produced the β(1→6)-linked disaccharide **3** as the sole product in 42% yield after 3 h (Entry 1). No improvement was observed by increasing the reaction time to 6 h, and different additives were therefore investigated. Addition of 2,4,6-collidine to the reaction gave 58% yield, but the product turned out to be orthoester **4** (Entry 2). It is well known that a base can cause orthoester formation in the silver triflate-promoted glycosylation with 2-*O*-acyl glycosyl bromides.[21] The orthoester may constitute the kinetic product, and the base may prevent the subsequent rearrangement into the 1,2-*trans* glycoside. The weaker base 1,1,3,3-tetramethylurea (TMU) has shown promising results for generating the 1,2-*trans* glycoside exclusively,[22] but in our case the coupling led to a mixture of several products which were not further identified (Entry 3). Molecular sieves were then investigated in order to remove traces of water and methanol which may still have been present after the stannylene acetal formation. Gratifyingly, the yield of the β(1→6)-linked disaccharide increased to 56%, and the reaction was allowed to proceed for 6 h where no further conversion was observed (Entry 4). An additional improvement was achieved by using a slightly larger excess of the donor, which produced disaccharide **3** as the sole product in 85% yield (Entry 5). This is a remarkable result given the previous difficulties with regioselective glycosylations on glucopyranosides.

Table 1. Optimization of the regioselective glycosylation.[a]



Entry	Additive	Time	Product	Yield[b]
1	–	3 h[c]	**3**	42%
2	collidine	3 h	**4**	58%
3	TMU	3 h	–	–
4	MS (4 Å)	6 h	**3**	56%
5[d]	MS (4 Å)	6 h	**3**	85%
6[e]	MS (4 Å)	6 h	**3**	32%

[a] Reaction conditions: Bu_2SnO (0.75 mmol), acceptor **1** (0.5 mmol), MeOH, reflux, 3 h, then donor **2** (0.75 mmol), AgOTf (1.1 mmol), additive, CH_2Cl_2, –30 °C to 10 °C, time. [b] Isolated yield. [c] No improvement in yield with 6 h reaction time. [d] With 0.9 mmol of **2** and AgOTf. [e] In the absence of Bu_2SnO and with dioxane instead of CH_2Cl_2.

The importance of the stannylene acetal was verified by attempting the direct Koenigs–Knorr coupling between **1** and **2** in the absence of the acetal. This only led to decomposition of the donor and no reaction occurred with the acceptor. The poor solubility of acceptor **1** in dichloromethane, however, could account for this result, and the coupling between **1** and **2** was therefore repeated in dioxane where **1** was completely soluble. In this case, however, only 32% of disaccharide **3** was isolated (Entry 6), which was lower than the other yields in Table 1. As a result, the opti-

mized conditions for the glycosylation employed 1.8 equiv. of the donor in the presence of molecular sieves. With this protocol in hand, our attention then turned to other donors and acceptors in order to explore the scope and limitations of the reaction.

Perbenzoylated galactopyranosyl and mannopyranosyl bromides **5** and **6** and peracetylated trichloroacetamido glucopyranosyl bromide **7** were selected as additional donors (Figure 1). When these were treated with acceptor **1**, the (1→6)-linked disaccharides were obtained in 71%, 33% and 52% yields, respectively (Table 2, Entries 1–3). A longer reaction time was required for glucosamine donor **7** because TLC analysis of the reaction showed simultaneous formation of a minor second product which was only slowly converted into the desired disaccharide. This second product was not isolated, but TLC comparison with an authentic sample[23] showed it to be the corresponding oxazoline of **7** which is a known intermediate in glycosylations with 2-trichloroacetamido glycosyl donors.[23]

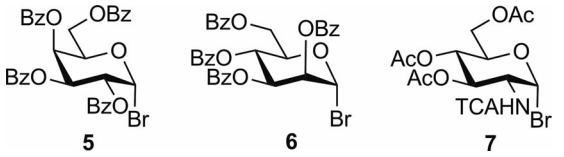


Figure 1. Glycosyl donors **5**–**7**.

Next, the four glycosyl donors were treated with phenyl 1-thio-β-D-galactopyranoside (**11**) and -α-D-mannopyranoside (**12**) as the acceptors (Figure 2). With the former, good yields were obtained of the (1→6)-linked disaccharides when **2**, **5** and **7** were employed as the donors, while mannosyl bromide **6** gave a low yield (Table 2, Entries 4–7). With **12** as the acceptor, moderate yields of the (1→6)-linked disaccharides were achieved in the glycosylations with **2**, **5** and **7** (Entries 8–10). The reaction between **2** and **12** was repeated in the presence of 2.5 equiv. of dibutyltin oxide and 3.5 equiv. of **2**, but these conditions only led to a slightly lower yield of the disaccharide. The coupling between mannose donor **6** and acceptor **12** was also studied, but in this case a complex mixture of products was obtained which was not further investigated (result not shown). Except for this case, the reactions in Table 2 did not show any other coupling products than the desired disaccharides together with unreacted acceptor and decomposed donor. Thorough drying of the acceptor stannylene acetal and the use of molecular sieves ensured that methanol was completely removed, and the reactions were not accompanied by methyl glycoside formation.

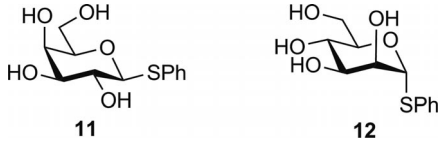
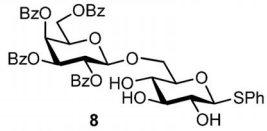
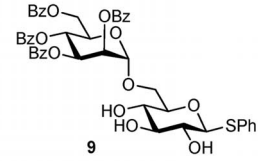
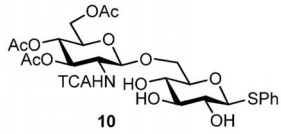
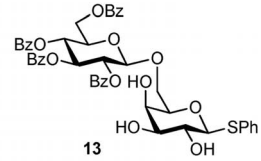
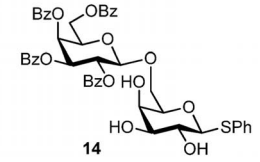
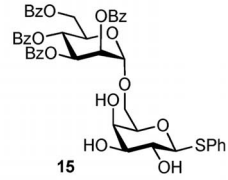
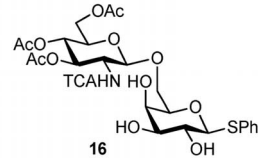
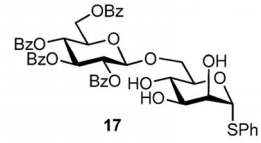
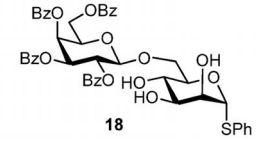
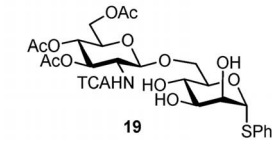


Figure 2. Glycosyl acceptors **11** and **12**.

Table 2. Koenigs–Knorr glycosylation of unprotected phenyl 1-thioglycopyranosides.[a]

Entry	Donor	Acceptor	Product	Yield[b]
1	**5**	**1**	 **8**	71%
2	**6**	**1**	 **9**	33%
3[c]	**7**	**1**	 **10**	52%
4	**2**	**11**	 **13**	76%
5	**5**	**11**	 **14**	62%
6	**6**	**11**	 **15**	23%
7[c]	**7**	**11**	 **16**	66%
8	**2**	**12**	 **17**	49%
9	**5**	**12**	 **18**	38%
10[c]	**7**	**12**	 **19**	48%

[a] Reaction conditions: Bu_2SnO (0.75 mmol), acceptor (0.5 mmol), MeOH, reflux, 3 h, then donor (0.9 mmol), AgOTf (0.9 mmol), 4 Å MS, CH_2Cl_2, –30 °C to 10 °C, 6 h. [b] Isolated yield. [c] Reaction time 22 h.

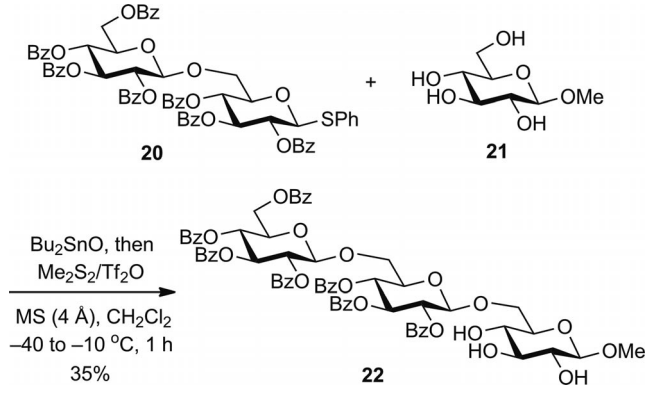
The structures of the disaccharides were unequivocally elucidated by NMR spectroscopy and mass spectrometry. The position of the interglycosidic linkages were verified from the deshielding of the ^{13}C NMR signal due to the additional substituent.[14] In fact, for all disaccharides, the C-6 carbon atoms resonate at a considerably lower magnetic field (69.2–68.6 ppm) as compared to those of the unprotected acceptors (62.7–61.2 ppm). A further confirmation was obtained by HMBC analysis, which showed correlations between the anomeric H-1′ and the two H-6 protons in the disaccharides. When glucose, galactose and glucosamine were used as the donors, the β-linkages in the disaccharides were established from the $J_{H\text{-}1',H\text{-}2'}$ coupling constants. With mannose as the donor the α-linkages were verified from the $J_{C\text{-}1',H\text{-}1'}$ coupling constants which were around 175 Hz.[24]

The best results in Table 2 were obtained with glucose and galactose substrates as the donor and the acceptor, while mannose substrates gave lower yields. It is not clear why mannose gives inferior results both as a donor and as an acceptor. Previously, glycosylation of the 6-position in unprotected hexopyranosides had only been achieved in good yield with β-D-galactopyranosides.[9,12,13] This is also observed with acceptor **11** in Table 2, entries 4, 5 and 7. Good-yielding glycosylation of the 6-position in unprotected gluco- and mannopyranosides has never been described. The results in Tables 1 and 2 show that a β-D-glucopyranoside can now be selectively glycosylated in good yield with certain donors, while an α-D-mannopyranoside is still a problematic acceptor.

All the couplings are believed to proceed by formation of the 4,6-stannylene acetal of the acceptor which is then glycosylated at the most reactive 6-position. With galactose and mannose acceptors, stannylene acetals can also be formed at the 3,4- and the 2,3-positions, respectively. In fact, benzylation and benzoylation of methyl β-D-galactopyranoside and α-D-mannopyranoside in the presence of dibutyltin oxide takes place predominately at the 3-position.[25] However, benzyl bromide and benzoyl chloride are sterically less encumbered than a glycosyl bromide. In addition, equilibriums are known to exist between the different stannylene acetals,[19] and together with the steric demand of the donor, this is believed to explain the exclusive glycosylation of the primary position in the acceptors.[14] A similar regioselectivity dependence on the size of the electrophile has been observed when unprotected lactosides are reacted in the presence of dibutyltin oxide. Allylation with allyl bromide gives the 3′-*O*-allylated product, while silylation with the more bulky *tert*-butyldimethylsilyl chloride affords exclusively the 6′-*O*-silylated compound.[26]

With the successful preparation of several disaccharides we decided to extend the investigations to the synthesis of trisaccharides. A disaccharide would then be employed either as the donor or as the unprotected acceptor. The latter approach was examined first with benzyl β-lactoside as the acceptor. The stannylene acetal was introduced as described in Table 1, and the resulting complex was found to be soluble in dichloromethane. However, the subsequent Koenigs–Knorr glycosylation with bromide **2** in the presence of molecular sieves produced a mixture of several coupling products, and no attempts were made to further improve this result. Instead, it was decided to use a disaccharide as the donor and to study the glycosylation of unprotected monosaccharide acceptors.

For these studies a thioglycoside disaccharide was selected as the donor because it may then be possible to use the products from Tables 1 and 2 for an additional glycosylation with an unprotected acceptor. Therefore, disaccharide **3** was converted into the corresponding perbenzoylated derivative **20**, which was investigated in two different glycosylation reactions. In the first approach, disaccharide **20** was directly activated with dimethyl disulfide and triflic anhydride[27] and coupled with the stannylene acetal of methyl β-D-glucopyranoside (**21**) (Scheme 1). Initially, the coupling was carried out by activating the donor at –40 °C in the presence of the stannylene acetal of the acceptor. However, this only afforded trisaccharide **22** in 5% yield, which was probably due to tin acetal decomposition, because a considerable amount of unreacted acceptor was detected by TLC. As a result, the conditions were altered by premixing donor **20** with dimethyl disulfide and triflic anhydride for 10 min before adding the stannylene acetal of the acceptor. This now led to complete consumption of acceptor **21**, and trisaccharide **22** was isolated as the sole product in 35% yield. Although this was a considerable improvement, it was still not a completely satisfactory result. Unfortunately, attempts to further optimize the coupling by prolonging the reaction time or the time for pre-activating the donor only led to similar yields. Changing the promoter to *N*-iodosuccinimide and triethylsilyl triflate gave no coupling, but instead silylation of the acceptor was observed.

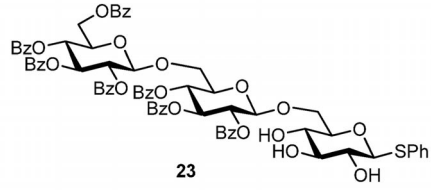
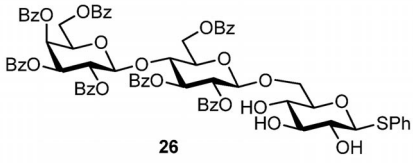
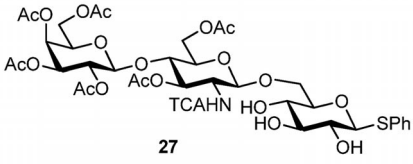


Scheme 1. Glycosylation of methyl β-D-glucopyranoside.

Therefore, a second glycosylation approach was investigated where thioglycoside **20** was first converted into the corresponding glycosyl bromide and then coupled under Koenigs–Knorr conditions. The advantage of this strategy is that a thioglycoside could now be used as the acceptor, and for this reason thioglucoside **1** was selected as the other coupling partner. Accordingly, donor **20** was treated with 0.5 equiv. of bromine followed by addition of silver triflate and the stannylene acetal of glucoside **1**. With a donor:ac-

ceptor ratio of 2:1, this gave rise to trisaccharide **23** in 40% yield (Table 3, Entry 1). The same glycosylation was also performed with disaccharides **24** and **25** as donors (Figure 3) to afford trisaccharides **26** and **27** in 46% and 57% yield, respectively (Table 3, Entries 2 and 3). In all three cases, small amounts of byproducts were observed by TLC, but were not further characterized. These experiments illustrate that the strategy can be extended to disaccharide donors, although at the expense of a slightly lower coupling yield.

Table 3. Koenigs–Knorr glycosylation of phenyl 1-thio-β-D-glucopyranoside (**1**).[a]

Entry	Donor	Product	Yield[b]
1	**20**	 **23**	40%
2	**24**	 **26**	46%
3	**25**	 **27**	57%

[a] Reaction conditions: (i) Bu_2SnO (0.37 mmol), **1** (0.25 mmol), MeOH, reflux, 3 h; (ii) donor (0.5 mmol), Br_2 (0.25 mmol), CH_2Cl_2, room temp., then activated **1**, AgOTf (0.5 mmol), 4 Å MS, CH_2Cl_2, –40 °C to 10 °C, 6 h. [b] Isolated yield.

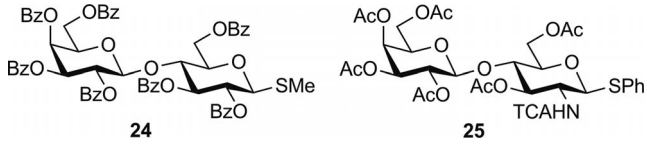


Figure 3. Glycosyl donors **24** and **25**.

Conclusions

In summary, we have further developed the stannylene-mediated regioselective glycosylation of unprotected glycosyl acceptors. The best results were achieved with glycosyl donors and acceptors derived from glucose and galactose, while mannose substrates gave lower yields. With phenyl 1-thiohexopyranosides as the acceptors, the approach gives easy access to several (1→6)-linked disaccharide thioglycosides which are useful building blocks in oligosaccharide synthesis.

Experimental Section

General: All reactions were performed under an argon atmosphere. Molecular sieves (MS) were flame dried before use. Dichloromethane was dried with 3 Å MS. Methanol was distilled from sodium and then dried with 3 Å MS. Phenyl 1-thio-β-D-glucopyranoside (**1**),[20] phenyl 1-thio-β-D-galactopyranoside (**11**),[28] phenyl 1-thio-α-D-mannopyranoside (**12**),[29] methyl 1-thiolactoside,[30] 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**2**),[31] 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**5**),[32] 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**6**),[33] 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl bromide (**7**)[23] and phenyl 1-thio-*N*-trichloroacetyllactosamine hexaacetate (**25**)[34] were synthesized according to literature procedures. TLC was performed on aluminum plates coated with silica gel 60. Visualization was carried out by UV and by dipping in 20% solution of sulfuric acid in ethanol followed by heating. Flash column chromatography was performed with silica gel 60 (40–63 μm). NMR spectra were recorded with a Varian Mercury 300 or a Varian Unity Inova 500 instrument. Chemical shifts are measured relative to the residual solvent signal in $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.0 ppm) or TMS. Assignment of ^1H and ^{13}C resonances were based on COSY, HSQC and HMBC experiments. HRMS analyses were performed with an Agilent 1100 LC system with a diode array detector and equipped with a Luna C_{18} column (3 μm, 50 mm × 2 mm). The LC was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe and operating in positive electrospray mode. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Melting points were measured with a Stuart SMP30 apparatus.

Tin-Mediated Glycosylation with Peracylated Glycosyl Bromide (Method A): A suspension of the unprotected phenyl 1-thiohexopyranoside (0.5 mmol) and Bu_2SnO (0.75 mmol) in MeOH (3.0 mL) was refluxed until a clear solution was obtained (3 h). The solvent was evaporated in vacuo followed by drying at high vacuum for 2 h to give the stannylene derivative as a colorless foam. The bromide donor (0.9 mmol) and 4 Å MS (500 mg) were added to a solution of the stannylene derivative in CH_2Cl_2 (5 mL). The suspension was stirred at –30 °C for 30 min. AgOTf (0.9 mmol) was then added, and the mixture was stirred in the dark while the temperature was allowed to reach 10 °C. After 6 h the mixture was filtered, diluted with CH_2Cl_2, washed once with 2 M aqueous HCl, once with saturated aqueous $NaHCO_3$ and once with water. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (toluene/acetone, 8:2→6:4) to afford the pure disaccharide.

Tin-Mediated Glycosylation with Peracylated Thioglycoside in the Presence of Bromine (Method B): The thioglycoside donor (0.5 mmol) was dissolved in CH_2Cl_2 (2 mL), and a 1 M solution of Br_2 in CH_2Cl_2 (0.25 mL, 0.25 mmol) was added at room temperature. The orange solution was stirred at room temperature until it turned yellow (from 1 h to 16 h). The solution was then added via syringe at –40 °C to a suspension of the stannylene derivative of the acceptor (0.25 mmol, prepared as reported in method A), AgOTf (0.75 mmol) and 4 Å MS (250 mg) in CH_2Cl_2 (3 mL). The mixture was stirred for 6 h in the dark while the temperature was allowed to reach 10 °C. Then solids were filtered off, and the filtrate was diluted with CH_2Cl_2 and successively washed with 2 M aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel column chromatography (toluene/acetone, 8:2→6:4) to afford the pure trisaccharide.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (3): The coupling between **1** and **2** was performed according to method A to afford disaccharide **3** as a colorless foam (362 mg, 85%). $[\alpha]_D^{25}$ = +9.5 (*c* = 0.8, $CHCl_3$). R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.15 (m, 25 H, Ar), 5.79 (t, *J* = 9.6 Hz, 1 H, 3′-H), 5.61 (t, *J* = 9.6 Hz, 1 H, 4′-H), 5.44 (t, *J* = 9.6 Hz, 1 H, 2′-H), 4.87 (d, *J* = 7.9 Hz, 1 H, 1′-H), 4.61 (dd, *J* = 3.0, 12.3 Hz, 1 H, 6′-H_a), 4.35 (m, 2 H, 1-H, 6′-H_b), 4.00 (m, 2 H, 5′-H, 6-H_a), 3.79 (dd, *J* = 3.0, 11.5 Hz, 1 H, 6-H_b), 3.35 (m, 3 H, 2-H, 3-H, 4-H), 3.19 (br. t, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 165.7, 165.5, 165.1 (4 × C=O), 133–127 (Ar), 101.2 (C-1′), 87.6 (C-1), 78.8 (C-5), 77.6 (C-4), 72.7 (C-3′), 72.1, 71.9 (C-2, C-3), 71.8 (C-5′), 70.3 (C-2′), 69.5 (C-6), 69.2 (C-4′), 62.7 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2177.

3,4,6-Tri-*O*-benzoyl-1,2-*O*-(phenyl 1-thio-β-D-glucopyranosid-6-yloxy-1-benzylidene)-α-D-glucopyranose (4): The coupling between **1** and **2** was performed according to method A in the presence of 2,4,6-collidine (1.12 mmol), and the reaction was stopped after 3 h to afford a mixture (280 mg) containing 90% of orthoester **4** and 10% of 2,4,6-collidine. R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90–6.99 (m, 25 H, Ar), 5.91 (d, *J* = 4.5 Hz, 1 H, 1′-H), 5.67 (br. s, 1 H, 3′-H), 5.39 (d, *J* = 9.0 Hz, 1 H, 4′-H), 4.73 (br. s, 1 H, 2′-H), 4.45–4.24 (m, 3 H, 1-H, 6′-H_a, 6′-H_b), 4.06–4.00 (m, 1 H, 5-H), 3.80–3.16 (m, 10 H, 2-H, 3-H, 4-H, 5-H, 6-H_a, 6-H_b) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 165.1, 164.4 (3 × C=O), 134.6–120.9 (Ar, C-7), 97.6 (C-1′), 87.4 (C-1), 77.8, 77.7, 77.5, 71.8, 71.5 (C-2′), 70.2, 68.8 (C-3′), 68.3 (C-4′), 67.3 (C-5′), 63.9 ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2198.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (8): The coupling between **1** and **5** was performed according to method A to afford disaccharide **8** as a glassy solid (303 mg, 71%). $[\alpha]_D^{25}$ = +37.8 (*c* = 1, $CHCl_3$). R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.12 (m, 25 H, Ar), 5.92 (br. s, 1 H, 4′-H), 5.72 (m, 1 H, 2′-H), 5.52 (dd, *J* = 3.0, 10.0 Hz, 1 H, 3′-H), 4.86 (d, *J* = 7.8 Hz, 1 H, 1′-H), 4.58 (dd, *J* = 6.6, 11.4 Hz, 1 H, 6′-H_a), 4.37–4.31 (m, 2 H, 6′-H_b, 1-H), 4.22–4.10 (m, 2 H, 6-H_a, 5′-H), 3.84 (dd, *J* = 6.0, 11.0 Hz, 1 H, 6-H_b), 3.39–3.30 (m, 3 H, 2-H, 3-H, 4-H), 3.17 (br. t, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.5, 165.4, 165.4 (4 × C=O), 133–128 (Ar), 101.6 (C-1′), 87.8 (C-1), 78.5 (C-5), 77.5 (C-4), 71.6 (C-5′), 71.5, 70.4, 71.4 (C-3′), 69.7 (C-2′), 69.3 (C-6), 68.0 (C-4′), 61.9 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2184.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (9): The coupling between **1** and **6** was performed according to method A to afford disaccharide **9** as a colorless foam (140 mg, 33%). $[\alpha]_D^{25}$ = –35.9 (*c* = 1, $CHCl_3$). R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.00 (m, 25 H, Ar), 6.06 (t, *J* = 10.2 Hz, 1 H, 4′-H), 5.85 (dd, *J* = 2.7, 9.6 Hz, 1 H, 3′-H), 5.71 (br. s, 1 H, 2′-H), 5.05 (s, 1 H, 1′-H), 4.64–4.49 (m, 3 H, 1-H, 5′-H, 6′-H_a), 4.34 (dd, *J* = 3.6, 12.6 Hz, 1 H, 6′-H_b), 3.91 (br. s, 2 H, 6-H_a, 6-H_b), 3.64–3.58 (m, 2 H, 3-H, 5-H), 3.54–3.48 (br. d, 1 H, 4-H), 3.45–3.37 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 165.7, 166.4, 166.3 (4 × C=O), 133.4–128.3 (Ar), 97.4 ($J_{C,H}$ = 173.5 Hz, C-1′), 88.2 ($J_{C,H}$ = 156.0 Hz, C-1), 78.4 (C-5), 78.1 (C-3), 72.1 (C-2), 70.4 (C-3′), 70.2 (C-4), 70.1 (C-2′), 68.7 (C-5′), 67.2 (C-6), 66.5 (C-4′), 62.6 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2202.

Phenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (10): The coupling between **1** and **7** was performed according to method A and stopped after 22 h to afford disaccharide **10** as a colorless solid (183 mg, 52%). $[\alpha]_D^{25}$ = –29.3 (*c* = 0.9, $CHCl_3$). R_f = 0.3 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 2 H, Ar), 7.34–7.32 (m, 3 H, Ar), 7.07 (d, *J* = 9.3 Hz, 1 H, NH), 5.28 (t, *J* = 10.2 Hz, 1 H, 3′-H), 5.11 (t, *J* = 9.9 Hz, 1 H, 4′-H), 4.77 (d, *J* = 8.4 Hz, 1 H, 1′-H), 4.50 (d, *J* = 9.6 Hz, 1 H, 1-H), 4.27–4.15 (m, 2 H, 6′-H_a, 6′-H_b), 4.10–4.06 (m, 1 H, 6-H_a), 4.03–3.97 (m, 1 H, 2′-H), 3.82 (dd, *J* = 5.4, 12.0 Hz, 1 H, 6-H_b), 3.74–3.67 (m, 1 H, 5′-H), 3.57–3.45 (m, 3 H, 3-H, 5-H, 4-H), 3.31 (t, *J* = 9.9 Hz, 1 H, 2-H), 2.08, 2.05, 2.03 (s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.8, 169.5 (3 × C=O), 162.0 (NH-C=O), 132.7–128.3 (Ar), 100.7 (C-1′), 92.1 (CCl_3), 87.8 (C-1), 78.7, 77.6, 71.9 (C-5′), 71.7 (C-3′), 71.6 (C-2), 69.8, 68.9 (C-6), 68.3 (C-4′), 61.8 (C-6′), 55.8 (C-2′), 20.8, 20.6, 20.5 (3 × CH_3) ppm. HRMS: calcd. for $C_{26}H_{32}Cl_3NO_{13}S$ [M + Na]$^+$ 726.0552; found 726.0556.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (13): The coupling between **11** and **2** was performed according to method A to afford disaccharide **13** as a colorless foam (326 mg, 76%). $[\alpha]_D^{25}$ = +5.1 (*c* = 0.7, $CHCl_3$). R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.19 (m, 25 H, Ar), 5.80 (t, *J* = 9.6 Hz, 1 H, 3′-H), 5.61 (t, *J* = 9.6 Hz, 1 H, 4′-H), 5.41 (dd, *J* = 8.1, 9.6 Hz, 1 H, 2′-H), 4.86 (d, *J* = 8.1 Hz, 1 H, 1′-H), 4.72 (dd, *J* = 3.3, 12.3 Hz, 1 H, 6′-H_a), 4.37–4.29 (m, 2 H, 6′-H_b, 1-H), 4.07–4.01 (m, 1 H, 5′-H), 3.98–3.92 (m, 1 H, 6-H_a), 3.91–3.85 (m, 2 H, 4-H, 3-H), 3.60–3.50 (m, 2 H, 5-H, 2-H), 3.40 (dd, *J* = 3.6, 9.0 Hz, 1 H, 6-H_b) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 165.7, 165.2, 165.1 (4 × C=O), 133.5–128.2 (Ar), 101.1 (C-1′), 88.5 (C-1), 77.1 (C-5), 74.3 (C-3), 72.7 (C-5′), 72.4 (C-3′), 71.6 (C-2′), 69.9 (C-4′), 69.2 (C-2), 68.0 (C-4), 67.8 (C-6), 62.4 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2185.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (14): The coupling between **11** and **5** was performed according to method A to afford disaccharide **14** as a glassy solid (266 mg, 62%). $[\alpha]_D^{25}$ = +54.2 (*c* = 0.9, $CHCl_3$). R_f = 0.5 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.13 (m, 25 H, Ar), 5.91 (d, *J* = 3.3 Hz, 1 H, 4′-H), 5.73–5.67 (m, 1 H, 2′-H), 5.50 (dd, *J* = 3.3, 10.0 Hz, 1 H, 3′-H), 4.86 (d, *J* = 8.1 Hz, 1 H, 1′-H), 4.56 (dd, *J* = 6.6, 11.4 Hz, 1 H, 6′-H_a), 4.41–4.33 (m, 2 H, 6′-H_b, 1-H), 4.22 (t, *J* = 6.6 Hz, 1 H, 5′-H), 4.03–3.92 (m, 1 H, 6-H_a), 3.88 (br. s, 1 H, 6-H_b), 3.56 (m, 2 H, 5-H, 4-H), 3.42–3.05 (m, 2 H, 3-H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.5, 165.4, 165.3 (4 × C=O), 133.6–127.9 (Ar), 101.5 (C-1′), 88.5 (C-1), 74.2 (C-2), 74.2 (C-3), 71.5 (C-3′), 71.5 (C-5′), 69.8 (C-5), 69.6 (C-2′), 68.5 (C-6), 68.2 (C-4), 68.1 (C-4′), 61.9 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2187.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (15): The coupling between **11** and **6** was performed according to method A to afford disaccharide **15** as a colorless foam (97 mg, 23%). $[\alpha]_D^{25}$ = –26.5 (*c* = 0.9, $CHCl_3$). R_f = 0.3 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12–7.15 (m, 25 H, Ar), 6.06 (t, *J* = 9.9 Hz, 1 H, 3′-H), 5.85 (dd, *J* = 3.0, 10.0 Hz, 1 H), 5.68 (br. s, 1 H), 5.08 (s, 1 H, 1′-H), 4.64–4.52 (m, 3 H, 1-H, 6′-H_a, 6-H_a), 4.30 (dd, *J* = 4.5, 12.0 Hz, 1 H, 6′-H_b), 4.18–4.15 (m, 1 H), 4.01 (br. s, 1 H, 6-H_b), 3.89–3.85 (m, 1 H), 3.78 (dd, *J* = 5.0, 10.5 Hz, 1 H), 3.69–3.63 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 165.6, 165.4, 165.3 (4 × C=O), 133.8–128.3 (Ar), 97.4 ($J_{C,H}$ = 176.7 Hz, C-1′), 89.4 ($J_{C,H}$ = 154.5 Hz, C-1), 76.8, 74.7, 70.3, 70.2, 69.8, 68.9 (C-6), 68.7, 67.3, 66.4, 62.6 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2192.

Phenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (16): The coupling between **11** and **7** was performed according to method A and stopped after 22 h to afford disaccharide **16** as a colorless solid (230 mg, 66%). $[\alpha]_D^{25}$ = –21.8 (*c* = 1, $CHCl_3$). R_f = 0.3 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 2 H, Ar), 7.34–7.29 (m, 3 H, Ar), 6.95 (d, *J* = 9.3 Hz, 1 H, NH), 5.24 (t, *J* = 10.5 Hz, 1 H, 3′-H), 5.08 (t, *J* = 9.9 Hz, 1 H, 4′-H), 4.74 (d, *J* = 7.8 Hz, 1 H, 1′-H), 4.52 (d, *J* = 9.9 Hz, 1 H, 1-H), 4.26–4.15 (br. m, 2 H, 6′-H_a, 6′-H_b), 4.00–3.94 (br. m, 3 H, 2′-H), 3.90–3.85 (br. m, 1 H, 6-H), 3.75–3.59 (br. m, 7 H, 5′-H, 2-H), 2.07, 2.04, 2.01 (s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.8, 169.5 (3 × C=O), 162.3 (HN-C=O), 132.7, 132.0, 129.2, 128.1 (Ar), 100.6 (C-1′), 92.1 (CCl_3), 88.8 (C-1), 77.5, 74.4, 71.9, 71.6 (C-3′), 69.8 (C-5′), 68.7, 68.4 (C-6), 68.3 (C-4′), 61.8 (C-6′), 55.7 (C-2′), 20.8, 20.6, 20.5 (3 × CH_3) ppm. HRMS: calcd. for $C_{26}H_{32}Cl_3NO_{13}S$ [M + Na]$^+$ 726.0552; found 726.0540.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (17): The coupling between **12** and **2** was performed according to method A to afford disaccharide **17** as an amorphous solid (209 mg, 49%). $[\alpha]_D^{25}$ = +104 (*c* = 0.5, $CHCl_3$). R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.24 (m, 25 H, Ar), 5.82 (t, *J* = 9.0 Hz, 1 H, 3′-H), 5.60 (t, *J* = 9.0 Hz, 1 H, 4′-H), 5.48 (br. d, 1 H, 2′-H), 5.42 (br. s, 1 H, 1-H), 4.85 (d, *J* = 8.0 Hz, 1 H, 1′-H), 4.58 (dd, *J* = 4.0, 12.0 Hz, 1 H, 6′-H_a), 4.36 (dd, *J* = 6.0, 12.0 Hz, 1 H, 6′-H_b), 4.11–4.03 (br. m, 4 H), 3.89 (dd, *J* = 5.0, 11.1 Hz, 1 H, 6-H_b), 3.69–3.63 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 165.7, 165.4, 165.1 (4 × C=O), 133–127 (Ar), 101.0 (C-1′), 87.7 (C-1), 72.6 (C-3′), 72.2 (C-2′), 72.0, 71.9 (3 × C), 69.4 (C-5′), 69.0 (C-6), 68.3 (C-5), 62.8 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2197.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (18): The coupling between **12** and **5** was performed according to method A (reaction temperature –70 °C to 10°) to afford disaccharide **18** as a glassy solid (162 mg, 38%). $[\alpha]_D^{25}$ = +120.4 (*c* = 1, $CHCl_3$). R_f = 0.5 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.13 (m, 25 H, Ar), 5.91 (d, *J* = 3.3 Hz, 1 H, 4′-H), 5.73 (m, 1 H, 2′-H), 5.56 (dd, *J* = 3.6, 10.8 Hz, 1 H, 3′-H), 5.45 (d, *J* = 1.2 Hz, 1 H, 1-H), 4.83 (d, *J* = 7.2 Hz, 1 H, 1′-H), 4.59 (dd, *J* = 6.3, 11.4 Hz, 1 H, 6′-H_a), 4.33 (dd, *J* = 5.7, 11.4 Hz, 1 H, 6′-H_b), 4.26–4.20 (br. t, 1 H, 5′-H), 4.15–4.02 (m, 3 H), 3.92 (dd, *J* = 4.2, 12.0 Hz, 1 H, 6-H), 3.66–3.56 (m, 2 H), 2.63 (br. s, 3 H, 3 × OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.6, 165.5, 165.4 (4 × C=O), 133.7–127.4 (Ar), 102.2 (C-1′), 87.8 (C-1), 72.0 (C-3), 71.9, 71.7 (C-5′), 71.5, 71.2 (C-3′), 69.9 (C-2′), 69.4 (C-6), 68.3, 68.0 (C-4′), 61.9 (C-6′) ppm. HRMS: calcd. for $C_{46}H_{42}O_{14}S$ [M + Na]$^+$ 873.2187; found 873.2191.

Phenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (19): The coupling between **12** and **7** was performed according to method A and stopped after 22 h to afford disaccharide **19** as a white solid (170 mg, 48%). $[\alpha]_D^{25}$ = +63.2 (*c* = 0.9, $CHCl_3$). R_f = 0.3 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 2 H, Ar), 7.26–7.19 (m, 4 H, Ar, NH), 5.49 (s, 1 H, 1-H), 5.23 (t, *J* = 9.3 Hz, 1 H, 3′-H), 5.04 (t, *J* = 9.6 Hz, 1 H, 4′-H), 4.74 (d, *J* = 9.0 Hz, 1 H, 1′-H), 4.21–4.07 (m, 4 H, 6′-H_a, 6′-H_b, 4-H, OH), 4.01–3.82 (m, 3 H, 2′-H, 6-H_a, 6-H_b), 3.80–3.65 (br. m, 2 H, 5′-H, OH), 3.63–3.40 (m, 3 H, 5-H, 3-H, OH), 2.00, 1.97, 1.95 (s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 170.8, 169.4 (3 × C=O), 162.5 (NH-C=O), 133.7, 131.0, 129.2, 127.5 (Ar), 100.8 (C-1′), 92.2 (CCl_3), 87.8 (C-1), 72.0 (C-5′), 71.9 (C-5), 71.9, 71.5, 71.5 (C-3′), 68.8 (C-6), 68.3 (C-4′), 68.0, 61.8 (C-6′), 55.8 (C-2′), 21.0, 20.9, 20.8 (3 × CH_3) ppm. HRMS: calcd. for $C_{26}H_{32}Cl_3NO_{13}S$ [M + Na]$^+$ 726.0552; found 726.0554.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (20): Disaccharide **3** (1.8 g, 2.1 mmol) was dissolved in pyridine (4.2 mL), and benzoyl chloride (2.5 mL, 21 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight. CH_2Cl_2 was added, followed by water. After separation, the organic phase was washed twice with saturated aqueous $NaHCO_3$ and twice with water. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to leave an amorphous solid which was crystallized from toluene/pentane to give the title compound as a white crystalline solid (1.929 g, 80%). $[\alpha]_D^{25}$ = +63.2 (*c* = 0.9, $CHCl_3$). R_f = 0.7 (toluene/acetone, 9:1). M.p. 193–197 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05–7.15 (m, 40 H, Ar), 5.79–5.69 (m, 2 H, 3′-H, 3-H), 5.52 (t, *J* = 9.5 Hz, 1 H, 4′-H), 5.42 (t, *J* = 9.0 Hz, 1 H, 2′-H), 5.28 (t, *J* = 9.9 Hz, 1 H, 2-H), 5.18 (t, *J* = 9.6 Hz, 1 H, 4-H), 4.88 (d, *J* = 8.4 Hz, 1 H, 1′-H), 4.84 (d, *J* = 10.2 Hz, 1 H, 1-H), 4.52 (dd, *J* = 3.0, 12.6 Hz, 1 H, 6′-H_a), 4.33 (dd, *J* = 4.8, 12.6 Hz, 1 H, 6′-H_b), 3.99–3.92 (m, 2 H, 5′-H, 5-H), 3.89 (br. s, 2 H, 6-H_a, 6-H_b) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 165.8, 165.6, 165.3, 165.2, 165.1, 164.9 (7 × C=O), 134.5–128.4 (Ar), 100.9 (C-1′), 85.9 (C-1), 78.4 (C-5), 74.0 (C-3), 72.9 (C-3′), 72.2 (C-5′), 71.8 (C-2′), 70.5 (C-2), 69.6 (C-4), 69.5 (C-4′), 68.2 (C-6), 62.8 (C-6′) ppm. HRMS: calcd. for $C_{67}H_{54}O_{17}S$ [M + Na]$^+$ 1185.2974; found 1185.3017.

Methyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (22): A solution of Me_2S_2–Tf_2O (1 M, 1.12 mL, 1.12 mmol, prepared following a reported procedure[27]) in CH_2Cl_2 was added to a suspension of donor **20** (0.75 mmol) and 4 Å MS (1.0 g) in CH_2Cl (2 mL). The mixture was stirred for 10 min at –40 °C. At this point, the stannylene derivative of acceptor **21** (0.5 mmol, prepared as reported in method A) was dissolved in CH_2Cl_2 (3 mL) and added via syringe to the activated donor at –40 °C. The reaction mixture was stirred for one hour, allowing the temperature to reach –10 °C, and quenched by addition of excess Et_3N (9 mmol), diluted with CH_2Cl_2, filtered and successively washed with 2 M aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was subjected to silica gel column chromatography (toluene/acetone, 8:2→6:4) to afford the pure trisaccharide **22** as a colorless foam (224.5 mg, 35%). $[\alpha]_D^{25}$ = –10.2 (*c* = 1, $CHCl_3$). R_f = 0.5 (toluene/acetone, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.15 (m, 35 H, Ar), 5.84 (t, *J* = 9.3 Hz, 1 H, 3′′-H), 5.73 (t, *J* = 9.9 Hz, 1 H, 3′-H), 5.61 (t, *J* = 10.2 Hz, 1 H, 4′′-H), 5.47 (t, *J* = 9.0 Hz, 1 H, 2′′-H), 5.35 (t, *J* = 9.0 Hz, 1 H, 2′-H), 5.23 (t, *J* = 9.3 Hz, 1 H, 4′-H), 5.03 (d, *J* = 7.8 Hz, 1 H, 1′′-H), 4.69 (d, *J* = 7.5 Hz, 1 H, 1′-H), 4.58 (dd, *J* = 3.3, 12.6 Hz, 1 H, 6′′-H_a), 4.41 (dd, *J* = 4.8, 12.6 Hz, 1 H, 6′′-H_b), 4.11–4.07 (m, 2 H, 5′′-H, 6-H_a), 4.04 (d, *J* = 7.8 Hz, 1-H), 3.95–3.84 (m, 3 H, 6′-H_a, 6′-H_b, 5′-H), 3.68–3.63 (m, 1 H, 6-H_b), 3.50–3.43 (m, 1 H, 3-H), 3.41–3.37 (m, 2 H, 5-H, 4-H), 3.29–3.24 (m, 1 H, 2-H), 3.19 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 166.1, 165.6, 165.3, 165.2, 165.1, 165.0 (7 × C=O), 133.4–128.2 (Ar), 103.2 (C-1), 101.3 (C-1′′), 100.7 (C-1′), 76.4 (C-3), 74.8 (C-5), 74.4 (C-5′), 73.6 (C-2), 72.8 (C-3′′), 72.5 (C-3′), 72.3 (C-5′′), 71.8 (C-2′′), 71.3 (C-2′), 70.7 (C-4), 69.5 (C-4′), 69.4 (C-4′′), 68.4 (C-6), 68.1 (C-6′), 62.8 (C-6′′), 56.7 (OCH_3) ppm. HRMS: calcd. for $C_{68}H_{62}O_{23}$ [M + Na]$^+$ 1269.3574; found 1269.3647.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (23): The coupling between **1** and **20** was performed according to

method B to afford trisaccharide **23** as a glassy solid (133 mg, 40%). $[\alpha]_D^{25}$ = –13.7 (*c* = 1, $CHCl_3$). R_f = 0.6 (toluene/acetone, 6:4). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.13 (m, 40 H, Ar), 5.87 (t, *J* = 10.5 Hz, 1 H, 3′-H), 5.71 (t, *J* = 9.6 Hz, 1 H, 3′′-H), 5.59 (t, *J* = 10.2 Hz, 1 H, 4′-H), 5.47 (dd, *J* = 8.1, 10.5 Hz, 1 H, 2′-H), 5.35 (dd, *J* = 8.1, 9.6 Hz, 1 H, 2′′-H), 5.26–5.18 (m, 1 H, 4′′-H), 5.00 (d, *J* = 8.1 Hz, 1 H, 1′-H), 4.67 (d, *J* = 8.1 Hz, 1 H, 1′′-H), 4.54 (dd, *J* = 3.0, 12.3 Hz, 1 H, 6′-H_a), 4.45 (d, *J* = 9.9 Hz, 1 H, 1-H), 4.38 (dd, *J* = 4.8, 12.3 Hz, 1 H, 6′-H_b), 4.11–3.78 (br. m, 6 H, 5′′-H, 5′-H, 6′′-H_a, 6′′-H_b, 6-H_a, 6-H_b), 3.71–3.66 (m, 1 H, 5-H), 3.55–3.41 (br. m, 3 H, 3-H, 4-H, OH), 3.28 (t, *J* = 9.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 166.0, 165.6, 165.4, 165.2, 165.1, 165.0 (7×C=O), 133.5–127.8 (Ar), 101.4 (C-1′), 100.7 (C-1′′), 88.2 (C-1), 78.6, 77.8, 74.3, 72.7 (C-3′), 72.6 (C-3′′), 72.2 (C-2′), 71.9 (C-2′′), 71.8 (C-2), 71.5, 70.3 (C-4′), 69.6 (C-4′′), 69.4, 68.6 (C-6′, C-6), 68.3, 62.8 (C-6′′) ppm. HRMS: calcd. for $C_{73}H_{64}O_{22}S$ $[M + Na]^+$ 1347.3502; found 1347.3566.

Methyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (24): Methyl 1-thiolactoside (2 g, 5.4 mmol) was dissolved in pyridine (5 mL), and benzoyl chloride (6.3 mL, 54 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight and worked up as described above. The residue was purified by silica gel column chromatography (toluene/acetone, 10:0→9:1) to afford the title compound as a colorless foam (5.3 g, 89%). $[\alpha]_D^{25}$ = +52.2 (*c* = 1.1, $CHCl_3$). R_f = 0.8 (toluene/acetone, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.05 (m, 35 H, Ar), 5.76 (t, *J* = 9.6 Hz, 1 H, 3-H), 5.67–5.62 (m, 2 H, 2′-H, 4′-H), 5.43 (t, *J* = 8.7 Hz, 1 H, 2-H), 5.30 (dd, *J* = 3.9, 10.2 Hz, 1 H, 3′-H), 4.80 (d, *J* = 7.5 Hz, 1 H, 1′-H), 4.54 (d, *J* = 9.9 Hz, 1 H, 1-H), 4.51–4.39 (m, 2 H, 6-H_a, 6-H_b), 4.17 (t, *J* = 9.9 Hz, 1 H, 4-H), 3.85–3.59 (m, 4 H, 6′-H_a, 6′-H_b, 5′-H, 5-H), 2.09 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 165.7, 165.4, 165.3, 165.3, 165.2, 164.7 (7×C=O), 133.6–128.2 (Ar), 100.9 (C-1′), 83.2 (C-1), 75.8 (C-4), 73.9 (C-3), 71.7 (C-3′), 71.3, 69.8, 69.8 67.4 (C-5, C-5′, C-4′, C-2′, C-2), 62.5 (C-6), 60.9 (C-6′), 11.6 (CH_3) ppm. HRMS: calculated for $C_{62}H_{52}O_{17}S$ $[M + Na]^+$ 1123.2817; found 1123.2835.

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (26): The coupling between **1** and **24** was performed according to method B to afford trisaccharide **26** as a glassy solid (152 mg, 46%). $[\alpha]_D^{25}$ = +23.5 (*c* = 1, $CHCl_3$). R_f = 0.7 (toluene/acetone, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.05 (m, 40 H, Ar), 5.72–5.63 (m, 3 H, 2′′-H, 3′-H, 4′′-H), 5.38–5.30 (m, 2 H, 2′-H, 3′′-H), 4.82 (d, *J* = 8.1 Hz, 1 H, 1′′-H), 4.70 (d, *J* = 8.1 Hz, 1 H, 1′-H), 4.58–4.52 (br. d, 1 H, 6′-H_a), 4.38 (dd, *J* = 4.2, 12.9 Hz, 1 H, 6′-H_b), 4.33 (d, *J* = 9.3 Hz, 1 H, 1-H), 4.17 (t, *J* = 9.6 Hz, 1 H, 4′-H), 3.95 (br. d, 1 H, 6-H_a), 3.84 (t, *J* = 6.0 Hz, 1 H, 5-H), 3.76–3.70 (br. d, 1 H, 6-H_b), 3.69–3.63 (m, 3 H, 5′-H, 6′′-H_a, 6′′-H_b), 3.40–3.29 (m, 3 H, 3-H, 4-H, 5′′-H), 3.14 (t, *J* = 9.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 165.6, 165.4, 165.3, 165.3, 165.2, 164.8 (7×C=O), 133.5–128.2 (Ar), 101.0 (C-1′′), 100.9 (C-1′), 87.8 (C-1), 78.6, 77.6, 75.8 (C-4′), 73.1 (C-5′), 72.7, 71.8, 71.7 (C-2), 71.7, 71.3 (C-5′), 70.5, 69.9, 69.0 (C-6), 67.5, 62.0 (C-6′), 60.9 (C-6′′) ppm. HRMS: calcd. for $C_{73}H_{64}O_{22}S$ $[M + Na]^+$ 1347.3502; found 1347.3559.

Phenyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (27): The coupling between **1** and **25** was performed according to method B to afford trisaccharide **27** as a glassy solid (141 mg, 57%). $[\alpha]_D^{25}$ = –14.4 (*c* = 1, $CHCl_3$). R_f = 0.5 (toluene/acetone, 4:6). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.14 (m, 6 H, Ar, NH), 5.34 (d, *J* = 3.6 Hz, 1 H), 5.19–5.07 (m, 2 H, 3′-H), 4.96 (dd, *J* = 3.6, 11.1 Hz, 1 H), 4.63 (d, *J* = 8.1 Hz, 1 H, 1′-H), 4.57–4.49 (m, 3 H, 1′′-H, 1-H), 4.12–3.76 (m, 10 H), 3.62–3.38 (m, 5 H), 3.36–3.28 (br. t, 1 H, 2-H), 2.14, 2.10, 2.05, 2.04, 1.96 (s, 18 H, 6×CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 170.6, 170.4, 170.1, 170.0, 169.3 (6×C=O), 162.3 (HN-C=O), 132.6–128.3 (Ar), 101.2 (C-1′), 100.8 (C-1′′), 92.2 (CCl_3), 87.8 (C-1), 78.9, 77.7, 75.9, 72.8, 71.9, 71.8, 70.7, 70.6, 69.8, 69.1, 68.6, 66.6, 61.8, 60.6, 55.4, 20.9, 20.7, 20.6, 20.5 (6×CH_3) ppm. HRMS: calcd. for $C_{38}H_{48}Cl_3NO_{21}S$ $[M + Na]^+$ 1014.1397; found 1014.1431.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all products.

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