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Glycosyl thioimidates in a highly convergent one-pot strategy for oligosaccharide synthesis

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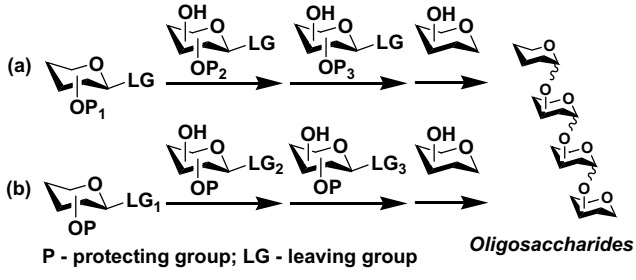
Abstract—Application of two classes of thioimidoyl derivatives, *S*-benzoxazolyl (SBox) and *S*-thiazolyl (STaz) glycosides to selective activation over thioglycosides is described. These results allowed us to synthesize a tetrasaccharide derivative using a leaving group differentiated one-pot strategy in 73% yield over three sequential glycosylation steps.

1. Introduction

Recent understanding of the involvement of carbohydrate molecules and conjugates in many vital biological processes[1] and, consequently, the appreciation of their tremendous therapeutic potential[2] has stimulated the development of new methods for the synthesis of this class of compounds. The main efforts in the field of synthetic carbohydrate chemistry have been focused on the development of new glycosylation methodologies and convergent strategies for oligosaccharide synthesis, in which the number of synthetic and purification steps is reduced. As a result, many efficient approaches have been developed both on the solid phase[3] and in solution.[4] The most efficient solution-based techniques include armed–disarmed,[5] active–latent,[6] orthogonal/semi-orthogonal,[7,8] and one-pot strategies.[9,10] Amongst these, one-pot strategies perhaps offer the shortest pathway to oligosaccharides, as the sequential glycosylation reactions are performed in a single flask (pot) and do not require isolation and purification of the intermediates. Although many variations of the one-pot strategy have been developed,[11] there are two major concepts these protocols are based upon.

The first approach is relying on the chemoselectivity principle, according to which the reactivity difference between the glycosyl donor and the glycosyl acceptor is achieved by varying the electronic properties of protecting groups in either or in both of the reaction components.[9,10,12] It is now well known that electron-withdrawing groups deactivate (disarm) the leaving group while electron-donating moieties activate (arm) the leaving group.[13] As illustrated in Scheme 1a, this approach in its conventional mode requires a set of building blocks with the same type of a leaving group, the reactivity of which is differentiated by the protecting group pattern. In this context, the reactivity difference between similarly protected sugars of different series has to be also taken into consideration. For example, the reactivity ratio between per-benzylated *S*-(*p*-methylphenyl) glycosides of L-fuco, D-galacto, and D-gluco series was found to be 27.1/6.4/1, respectively.[10]

The second concept is based on selective activation of one leaving group over another (Scheme 1b).[14] Since this



Scheme 1. Two concepts for one-pot oligosaccharide assembly: (a) chemoselective activation (reactivity is differentiated by protecting groups) and (b) selective activation (reactivity is differentiated by leaving groups).

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is a leaving group-based concept, one should be flexible with the protecting groups. Unfortunately, the number of leaving groups suitable for multi-step sequential selective activation is limited to too few examples at this stage.

A common feature of both of these approaches is that they are reactivity based, regardless whether the difference in reactivity is achieved by the protecting groups or by the leaving group. Being more reactive under certain reaction conditions, the glycosyl donor unit is activated over the less reactive glycosyl acceptor. Subsequently, the saccharide obtained is then served as the glycosyl donor under adjusted reaction conditions. For this purpose, a promoter, suitable for its activation is added along with the glycosyl acceptor for the next step.

As a part of the program to develop new methods and strategies for convergent oligosaccharide synthesis, herein we report the application of glycosyl thioimidates to a convergent one-pot procedure. We have already reported the synthesis of two glycosyl donors of this class, *S*-benzoxazolyl (SBox)[15–17] and *S*-thiazolyl (STaz, 4,5-dihydrothiazol-2-yl)[18] glycosides, and their evaluation in stereoselective glycosylations. We demonstrated that the SBox and STaz derivatives can be glycosidated in high yields and with excellent stereoselectivity. Unique activation conditions allow the application of thioimidate derivatives in selective activation approaches. For example, either SBox or STaz derivatives can be selectively activated over *S*-ethyl or *O*-pentenyl glycosides in the presence of AgOTf. We have also demonstrated that STaz derivatives withstand NIS/TfOH, conventional conditions for *S*-alkyl/aryl activation.[18] The following describes our systematic studies of selective thioimidoyl activation and its application to convergent one-pot strategy.

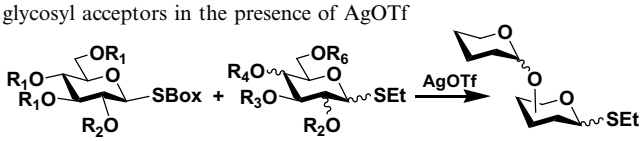
2. Results and discussion

2.1. Selective activation of SBox glycosyl donors over *S*-ethyl glycosyl acceptors

We have already reported that selective activation of the SBox glycosyl donors over SEt glycosyl acceptors is achieved in the presence of AgOTf.[16,17] To expand these studies we glycosylated SEt glycosyl acceptors **2a**,[19] **2b**,[20] and **2c**[21] with SBox glycosyl donors **1a**[17] and **1b**.[16] Complete stereoselectivity was achieved in 1,2-*trans*-glycosidations of per-benzoylated SBox glucoside **1a** with *S*-ethyl glycosyl acceptors **2a**–**c**. These experiments are summarized in Table 1 (entries 1–3). Thus, disaccharide derivatives **3**, **4**,[17] and **5**[17] (Fig. 1) were obtained in 95%, 99%, and 96% yield, respectively. Comparable glycosylation yields were achieved in glycosidations of **1b** with acceptors **2b** and **2c**.

Glycosyl donor **1b** bearing a nonparticipating benzyl ether group at C-2, is known to provide excellent stereocontrol even in methylene chloride, a solvent, which does not normally promote 1,2-*cis*-stereoselectivity.[16]

Table 1. Chemoselective activation of SBox glycosyl donors over SEt glycosyl acceptors in the presence of AgOTf



1a: R_1=R_2=Bz
1b: R_1=Ac, R_2=Bn

2a: β-D-Glc, R_2=R_3=R_4=Bz, R_6=H
2b: β-D-Gal, R_2=R_3=R_4=Bz, R_6=H
2c: α-D-Man, R_2=R_3=R_6=Bn, R_4=H

Disaccharides 3-7 (See Figure 1)

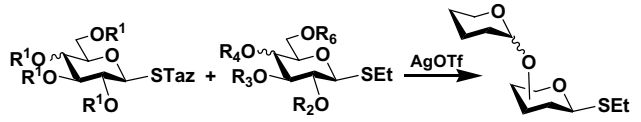
Entry	Donor	Acceptor	Product	Yield (%)	α/β Ratio
1	**1a**	**2a**	**3**	95	β Only
2	**1a**	**2b**	**4**	99	β Only
3	**1a**	**2c**	**5**	96	β Only
4	**1b**	**2b**	**6**	98	α Only
5	**1b**	**2c**	**7**	92	α Only

These reactions were no exception in this regard: 1,2-*cis*-linked disaccharides **6**[16] and **7** (Fig. 1) were obtained with complete stereoselectivity in 98% and 92% yield respectively (entries 4 and 5). It should be noted that high yields, no by-product formation, and complete stereoselectivity are welcomed traits of any chemical reaction that become increasingly important in one-pot procedures. In this respect, SBox glycosidations were regarded as very promising.

2.2. Selective activation of STaz glycosyl donors over *S*-ethyl glycosyl acceptors

Having completed preliminary evaluation of the SBox glycosides in selective activation processes, we turned our attention to the investigation of the STaz glycosides. Also in this case, AgOTf was found to be the promoter of choice. Per-benzoylated STaz derivatives of the D-gluco **8a**[18] and D-galacto **8b**[18] series were selected to probe 1,2-*trans*-glycosidation experiments with *S*-ethyl glycosyl acceptors **2a** and **2b**. These glycosylations proceeded smoothly and allowed us consistently good results. Thus, the disaccharide derivatives **3**, **4**, **9**,[22] and **10**[23] (Fig. 1) were obtained in 80–85% yield with complete 1,2-*trans*-selectivity (Table 2, entries 1–4).

Table 2. Chemoselective activation of STaz glycosyl donors over SEt glycosyl acceptors in the presence of AgOTf



8a: D-Glc, R^1=Bz
8b: D-Gal, R^1=Bz
8c: D-Glc, R^1=Bn
8d: D-Gal, R^1=Bn

2a: D-Glc, R_2=R_3=R_4=Bz, R_6=H
2b: D-Gal, R_2=R_3=R_4=Bz, R_6=H
2d: D-Glc, R_2=Bn,R_3=H, R_4,R_6= >CHPh

Disaccharides 3,4,9-15 (See Figure 1)

Entry	Donor	Acceptor	Product	Yield (%)	α/β Ratio
1	**8a**	**2a**	**3**	80	β Only
2	**8a**	**2b**	**4**	82	β Only
3	**8b**	**2a**	**9**	81	β Only
4	**8b**	**2b**	**10**	85	β Only
5	**8c**	**2a**	**11**	90	2.5:1
6	**8c**	**2b**	**12**	86	2:1
7	**8c**	**2d**	**13**	93	5.0:1
8	**8d**	**2a**	**14**	98	1.8:1
9	**8d**	**2b**	**15**	99	1.4:1

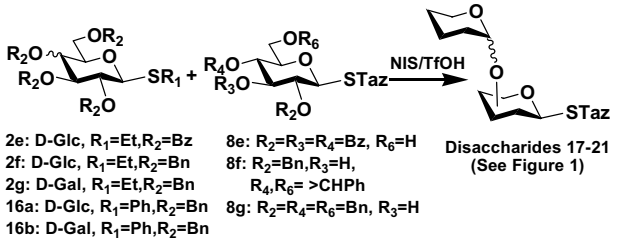
Per-benzylated STaz glycosides **8c**[18] and **8d**[18] were employed in 1,2-*cis*-glycosylations of the SEt moiety-containing glycosyl acceptors **2a**,**b**, and **2d**.[21] In all cases high yields were achieved, thus, disaccharides **11**,[19] **12**,[8] **13**,[18] **14**, and **15** (Fig. 1) were obtained as anomeric mixtures in 86–99% yield (Table 2, entries 5–9). Previously, we demonstrated that the selectivity of 1,2-*cis*-glycosidation of STaz glycosides can be significantly improved by the use of partially acetylated glycosyl donors[18] or by performing the reaction in a participating solvent system, such as toluene–dioxane.[18,24] It should be noted that the stereoselectivity achieved with the secondary glycosyl acceptor **2d** was significantly higher (α/β 5.0:1) than that achieved with primary glycosyl acceptors **2a** or **2b** (typically around 2:1).

2.3. Selective activation of *S*-ethyl and *S*-phenyl glycosyl donors over STaz glycosyl acceptors

Most commonly, SBox glycosides allow marginally better results in comparable glycosylation reactions, which is assumed to be due to their higher reactivity in comparison to that of STaz glycosides (see, for example, entries 1 and 2 in Tables 1 and 2). Thus, we have recently demonstrated that STaz glycosides are significantly more stable than SBox glycosides under a variety of reaction conditions, ranging from the use of strong acids to the use of strong inorganic bases.[18] Remarkably, the STaz glycosides are even more stable than similarly protected *S*-ethyl and *S*-phenyl glycosides. Comparative experiments were performed in the presence of acidic thiophilic reagents, for example, *N*-iodosuccinimide/catalytic TfOH, commonly used for thioglycoside hydrolysis.[25] It has been clearly demonstrated that the STaz moiety is entirely stable under these reaction conditions, while either SEt or SPh glycosides were hydrolyzed in the matter of minutes.[18]

Based on these observations, we anticipated that it might be possible to activate SEt or SPh glycosyl donors over STaz glycosides. To prove this, we synthesized a number of building blocks, *S*-alkyl/aryl glycosyl donors **2e**,[26] **2f**,[27] **2g**,[28] **16a**,[29] and **16b**[30] and STaz glycosyl acceptors **8e**,[31] **8f**,[18] and **8g**.[31] Reactions with conventional thioglycosides rarely proceed quantitatively due to a number of side processes commonly taking place along with glycosylation, the most important of which is hydrolysis.[32] To suppress those, the reactions were initiated at −20 °C and then were allowed to gradually warm up to room temperature. As a result of these precautions, glycosidations of the *S*-ethyl glycosyl donors of the D-gluco series **2e** and **2f** proceeded very well. While per-benzoylated donor **2e** allowed 1,2-*trans*-linked disaccharide **17**[31] (Fig. 1) with complete stereoselectivity in 81% yield (Table 3, entry 1), 1,2-*cis*-glycosidations of **2f** with acceptors **8e**–**g** were nonstereoselective. As a result, disaccharides **18**,[18] **19**,[31] and **20**[31] (Fig. 1) were obtained in 80–98% yield with α/β-stereoselectivity ranging from 1.2:1 to 2.1:1 (Table 3, entries 2–4). Unfortunately, we were not able to control the glycosidation of a more reactive D-galacto derivative **2g** at this temperature. Thus, reaction of **2g** with **8f** afforded **21** (Fig. 1) in only 40% yield. The major by-product in this case was the hemiacetal, a product of the competing hydrolysis. Quite possibly, this side reaction could be suppressed by varying the solvent or by using a milder promoter, such as iodonium(dicollidine)perchlorate and/or by lowering the reaction temperature. These results, along with aforementioned STaz activation over SEt glycosides imply a fully orthogonal character of the two classes of leaving groups. Very comparable results were achieved with SPh glycosyl donors **16a** and **16b**.

Table 3. Chemoselective activation of SEt and SPh glycosyl donors over STaz glycosyl acceptors in the presence of NIS/catalytic TfOH

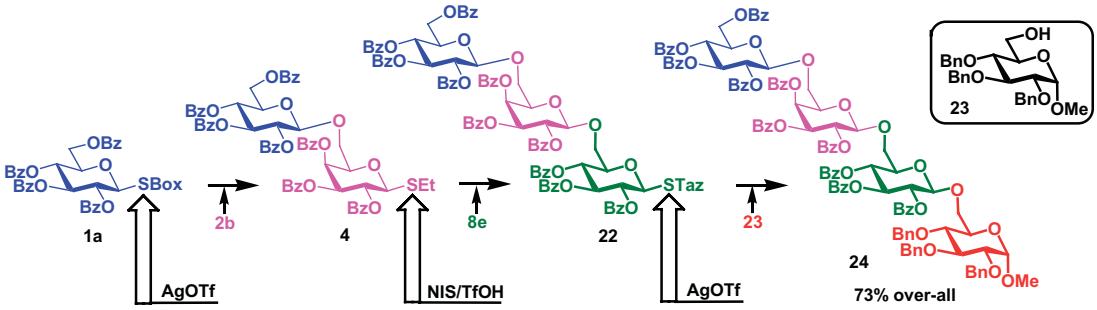


Entry	Donor	Acceptor	Product	Yield (%)	α/β Ratio
1	**2e**	**8e**	**17**	81	β Only
2	**2f**	**8f**	**18**	85	1.2:1
3	**2f**	**8g**	**19**	80	2.1:1
4	**2f**	**8e**	**20**	98	1.2:1
5	**2g**	**8f**	**21**	40	2.7:1
6	**16a**	**8e**	**20**	75	1.4:1
7	**16b**	**8f**	**21**	48	1.1:1

2.4. Thioimidate-based one-pot glycosylation strategy

Based on the results of selective activations, we assumed that it should be possible to perform the following activation sequence. Presumably, the most reactive SBox moiety has to be activated first over SEt, subsequently, SEt is then activated over STaz (SBox+SEt+STaz activation sequence). To execute this one-pot sequence along with the anticipated pathway, we chose the following building blocks: SBox glycosyl donor **1a** to be glycosidated at the first step with *S*-ethyl glycosyl acceptor **2b**. This should result in a disaccharide derivative **4**, the SEt moiety of which will be activated over the STaz moiety of the second step acceptor **8e** (Scheme 2). The resulting trisaccharide **22** could be then glycosidated with 6-OH glycosyl acceptor **23**[33] bearing a stable *O*-methyl moiety at the anomeric center to afford a linear tetrasaccharide **24**. The promoters of choice would be: AgOTf for the activation of the SBox, NIS/catalytic TfOH for the activation of *S*-ethyl, and, finally, more AgOTf should be added for the activation of STaz moiety of **22**.

Having selected the building blocks and the promoters suitable with their sequential glycosylations, we were set to perform the synthesis, which was executed as follows. A mixture of SBox glycoside **1a** (1.1 equiv), ethylthio glycoside **2b** (1.0 equiv) and molecular sieves 3 Å in 1,2-dichloroethane was treated with AgOTf (2.2 equiv) at room temperature. As anticipated, the reaction was complete in less than 10 min, at this stage only the product **4** could be seen by TLC. Subsequently, STaz



Scheme 2. One-pot synthesis of **24** from building blocks **1a**, **2b**, **8e**, and **23**.

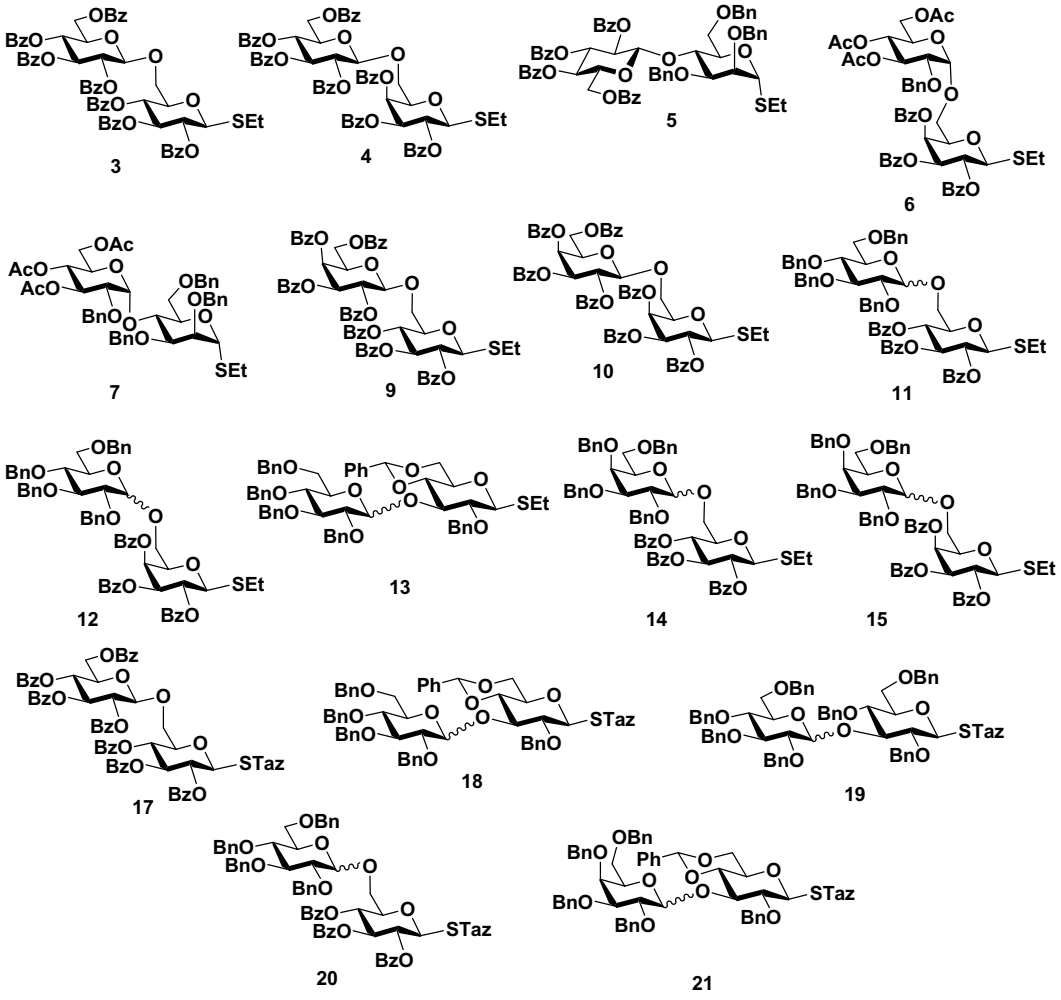


Figure 1. Structures of disaccharide derivatives **3**–**7**, **9**–**15**, **17**–**21**.

acceptor **8e** (0.9 equiv) and promoter NIS/TfOH (2.2/0.22 equiv) were added to the reaction mixture, which was left stirring for 30 min, when the TLC showed the disappearance of the starting material. Only one spot corresponding to **22** could be detected at this stage. To complete the sequence, acceptor **23** (1 equiv) along with another portion of AgOTf (2.2 equiv) was added to the reaction mixture. As a result, the desired tetrasaccharide **24** was obtained in 73% isolated yield over three steps.

A possible alternative to this strategy would be the use of a stoichiometric amount of TfOH in the last step, as it, together with NIS remaining from the second activation step, could serve as an activator for the STaz functionality. However, this activation approach has proven to be somewhat less efficient.

3. Conclusions

In conclusion, we investigated selective activation of two classes of thioimidoyl derivatives, *S*-benzoxazolyl (SBox) and *S*-thiazolyl (STaz) glycosides over *S*-ethyl glycosides. In addition, we demonstrated that *S*-ethyl

and *S*-phenyl glycosides can be selectively activated over STaz glycosides. These results clearly demonstrate the versatility of glycosyl thioimidates and their high potential in the glycoside and, consequently, oligosaccharide synthesis. The selective activation conditions were applied to the one-pot synthesis of a linear tetrasaccharide derivative in 73% yield over three sequential glycosylation steps. This was achieved by the stepwise activation of SBox over *S*-ethyl, *S*-ethyl over STaz, and, finally STaz over stable glycosyl acceptor (OMe). It is anticipated that the strategy outlined here can be applied in the syntheses of many oligosaccharides and glycoconjugates for subsequent biological studies and potential therapeutic applications.

4. Experimental

4.1. General

Column chromatography was performed on silica gel 60 (EM Science, 70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F254 (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at >40 °C. CH_2Cl_2 and $(ClCH_2)_2$ were distilled from CaH_2 directly prior to application. Molecular sieves (3 Å or 4 Å), used for reactions, were crushed and activated in vacuo at 390 °C during 8 h in the first instance and then for 2–3 h at 390 °C directly prior to application. AgOTf (Acros) was co-evaporated with toluene (3 × 10 mL) and dried in vacuo for 2–3 h directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). HRMS determinations were made with the use of JEOL MStation (JMS-700) mass spectrometer.

4.2. General AgOTf-promoted glycosylation procedure for selective activation of STaz and SBox glycosyl donors

A mixture of the glycosyl donor (0.05 mmol), glycosyl acceptor (0.045 mmol), and freshly activated molecular sieves (3 Å, 90 mg) in CH_2Cl_2 or $(ClCH_2)_2$ (0.5 mL) was stirred under argon for 1 h. AgOTf (0.10 mmol) was added. The reaction mixture was then stirred for 10–30 min at rt. Upon completion, the reaction mixture was diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $NaHCO_3$ (15 mL) and water (3 × 10 mL), the organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene gradient elution) to allow the corresponding disaccharide. Anomeric ratios (if applicable) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside 3 was obtained from **1a** and **2a** or **8a** and **2a** in 95% or 80% yield, respectively. Analytical data for **3**: R_f = 0.65 (ethyl acetate–hexane, 1/1, v/v); $[\alpha]_D^{27} = +17.0$ (*c* 0.9, $CHCl_3$); ^{1}H NMR data: δ 7.26–8.00 (m, 35H), 5.88 (dd, 1H, *J* = 9.6 Hz), 5.82 (dd, 1H, *J* = 9.5 Hz), 5.63 (dd, 1H, *J* = 9.7 Hz), 5.52 (dd, 1H, *J* = 7.8, *J* = 9.7 Hz), 5.40 (dd, 1H, *J* = 9.7 Hz), 5.33 (dd, 1H, *J* = 9.7 Hz), 5.00 (d, 1H, *J* = 7.8 Hz), 4.67 (d, 1H, *J* = 10.0 Hz), 4.62 (dd, 1H, *J* = 3.0, *J* = 12.1 Hz), 4.42 (dd, 1H, *J* = 5.0, *J* = 12.1 Hz), 3.80–4.16 (m, 4H), 2.55 (m, 2H), 1.10 (t, 3H) ppm; ^{13}C NMR data: δ, 166.27, 165.99, 165.89, 165.60, 165.37, 165.34, 165.32, 133.68, 133.64, 133.43, 133.36, 130.09, 130.05, 129.97, 129.90, 129.77, 129.48, 129.42, 129.08, 129.02, 128.99, 128.93, 128.64, 128.61, 128.54, 128.49, 128.45, 101.46, 83.65, 78.31, 74.26, 73.10, 72.51, 72.08, 70.80, 69.93, 69.77, 68.79, 63.12, 24.28, 14.96 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{63}H_{54}O_{17}SNa$ 1137.2979, found 1137.2985.

Ethyl 4-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-2,3,6-tri-O-benzyl-1-thio-α-D-mannopyranoside 7 was obtained from **1b** and **2c** in 92% yield. Analytical data for **7**: R_f = 0.55 (acetone–toluene, 1:4, v/v); $[\alpha]_D^{25} = +72.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR data: δ 7.03–7.33 (m, 20H), 5.68 (d, 1H, *J* = 3.7 Hz), 5.35 (d, 1H, *J* = 1.6 Hz), 5.26 (dd, 1H, *J* = 9.8 Hz), 4.81 (dd, 1H, *J* = 9.8 Hz), 4.29–4.65 (m, 8H), 4.14 (m, 2H), 4.03 (dd, 1H, *J* = 3.6 Hz, *J* = 12.3 Hz), 3.75–3.94 (m, 4H), 3.54–3.70 (m, 2H), 3.36 (dd, 1H, *J* = 3.7 Hz, *J* = 10.1 Hz), 2.65 (m, 2H), 1.99, 1.99, 1.93 (3s, 9H), 1.30 (t, 3H) ppm; ^{13}C NMR data: δ, 170.81, 170.33, 169.96, 138.57, 138.40, 138.23, 137.89, 128.63, 128.57, 128.50, 127.94, 127.91, 127.80, 127.72, 127.23, 97.80, 81.93, 80.78, 77.46, 76.08, 73.66, 72.39, 72.25, 71.81, 71.72, 70.91, 69.69, 68.63, 67.92, 61.99, 25.67, 15.24 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{48}H_{56}O_{13}SNa$ 895.3339, found 895.3354.

Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside 14 was obtained from **8d** and **2a** in 98% yield (α/β 1.8/1). Analytical data for α-**14**: R_f = 0.40 (ethyl acetate-hexane, 3/7, v/v); selected ^{1}H NMR data: δ 4.80 (d, 1H, *J* = 3.9 Hz), 4.73 (d, 1H, *J* = 10.1), 4.47 (d, 1H, *J* = 7.6 Hz) ppm; selected ^{13}C NMR data: δ, 104.11, 98.19, 83.78 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{63}H_{62}O_{13}SNa$ 1081.3809, found 1081.3820.

Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-1-thio-β-D-galactopyranoside 15 was obtained from **8d** and **2b** in 99% yield (α/β 1.4:1). Analytical data for α-**15**: R_f = 0.40 (ethyl acetate–hexane, 3/7, v/v); selected ^{1}H NMR data: δ 4.79 (d, 1H, *J* = 3.7 Hz), 4.72 (d, 1H, *J* = 9.6 Hz), 4.38 (d, 1H, *J* = 7.5 Hz) ppm; selected ^{13}C NMR data: δ, 104.12, 98.80, 84.14 ppm; HR-FAB MS $[M+Na]^+$ see data for compound **14**.

4.3. General NIS/TfOH-promoted glycosylation procedure for the selective activation of SEt and SPh glycosyl donors

A mixture the glycosyl donor (0.05 mmol), glycosyl acceptor (0.045 mmol), and freshly activated molecular

sieves (4 Å, 90 mg) in $(ClCH_2)_2$ (0.5 mL) was stirred for 1 h under argon. The reaction mixture was cooled to −20 °C, NIS (0.10 mmol) and TfOH (0.01 mmol) were added and the reaction mixture was stirred for 5 min to 16 h at −20 °C to rt. Upon completion, the solid was filtered-off and washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $Na_2S_2O_3$ (15 mL) water (3 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene gradient elution) to allow the corresponding disaccharide.

4,5-Dihydrothiazol-2-yl 2-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside 21 was obtained from **2g** and **8f** in 40% yield (α/β 2.7:1) or from **16b** and **8f** in 48% yield (α/β 1.1:1). Analytical data for α-**21**: $R_f = 0.65$ (ethyl acetate–hexane, 1:1, v/v); selected ^1H NMR data: 7.05–7.27 (m, 30H) 5.62 (d, 1H, $J = 3.5$ Hz), 5.36 (s, 1H), 5.28 (d, 1H, $J = 10.0$ Hz), 4.40–4.81 (m, 10H), 4.01–4.19 (m, 6H), 3.57–3.90 (m, 5H), 3.15–3.53 (m, 5H) ppm; selected ^{13}C NMR data: δ, 163.14, 139.12, 138.66, 138.54, 137.50, 128.60, 128.47, 128.43, 128.39, 128.34, 128.03, 127.76, 127.73, 127.67, 127.61, 127.53, 126.43, 101.94, 96.9, 85.43, 82.37, 79.73, 78.15, 77.44, 76.00, 75.59, 75.08, 73.29, 73.03, 72.15, 70.29, 69.14, 68.83, 64.55, 58.10, 35.37, 29.92 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{57}H_{60}O_{10}S_2$ 982.3659, found 982.3649.

4.4. One-pot glycosylation procedure for the synthesis of methyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside 24

A mixture of **1a** (0.0274 mmol), **2b** (0.0249 mmol), and freshly activated molecular sieves (3 Å, 60 mg) in $(ClCH_2)_2$ (0.5 mL) was stirred under argon for 1 h. AgOTf (0.0603 mmol) was added. The reaction mixture was then stirred for 10 min at rt. Upon completion, the reaction mixture was cooled to −20 °C, **8e** (0.0224 mmol) NIS (0.05 mmol), and TfOH (0.005 mmol) were added and the reaction mixture was stirred for 30 min. Upon completion, the reaction mixture was wormed up to room temperature and then **23** (0.0249 mmol) and AgOTf (0.05 mmol) were added. Upon completion (2 h), the solid was filtered-off and washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $Na_2S_2O_3$ (15 mL) water (3 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene gradient elution) to allow **24** in 73% yield. Analytical data for **24**: $R_f = 0.55$ (acetone–toluene, 1/9, v/v); $[\alpha]_D^{27} = +153.0$ (*c* 0.7, $CHCl_3$); ^1H NMR data: δ 7.00–8.15 (m, 65H), 6.01 (dd, 1H, $J = 9.7$ Hz), 5.84 (m, 2H), 5.79 (dd, 1H, $J = 9.6$ Hz), 5.64–5.71 (m, 2H), 5.45–5.56 (m, 3H), 5.40 (dd, 1H, $J = 9.5$ Hz), 4.97 (d, 1H, $J = 7.8$ Hz), 4.88 (d, 1H, $J = 11.0$ Hz), 4.74 (d, 1H, $J = 7.7$ Hz), 4.73 (d, 1H, $J = 11.8$ Hz), 4.67 (d, 1H, $J = 11.0$ Hz), 4.58 (d, 1H, $J = 11.8$ Hz), 4.56 (d, 1H, $J = 3.2$ Hz), 4.44–4.51 (m, 3H), 4.42 (d, 1H, $J = 11.4$ Hz), 4.29 (dd, 1H, $J = 4.4$, $J = 11.8$ Hz), 4.22 (d, 1H, $J = 11.4$ Hz), 3.97–4.11 (m, 5H), 3.75–3.90 (m, 4H), 3.44–3.56 (m, 2H), 3.30–3.38 (m, 5H) ppm; ^{13}C NMR data: δ, 166.20, 165.95, 165.57, 165.51, 165.33, 165.24, 165.05, 140.26, 139.12, 138.66, 138.39, 138.08, 133.60, 133.46, 133.33, 133.25, 130.11, 130.00, 129.92, 129.81, 129.24, 129.01, 128.73, 128.64, 128.55, 128.48, 128.43, 128.31, 128.08, 128.01, 127.47, 125.50, 125.07, 124.25, 119.08, 101.82, 101.12, 101.12, 98.27, 82.02, 80.02, 77.43, 75.59, 74.58, 74.31, 73.61, 73.61, 73.01, 73.01, 72.47, 72.14, 71.98, 71.59, 70.23, 70.13, 70.01, 69.63, 69.63, 68.68, 67.76, 67.59, 63.07 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{116}H_{102}O_{31}Na$ 2013.6303, found 2013.6287.

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