JOC Article

Application of Glycosyl Thioimidates in Solid-Phase Oligosaccharide Synthesis

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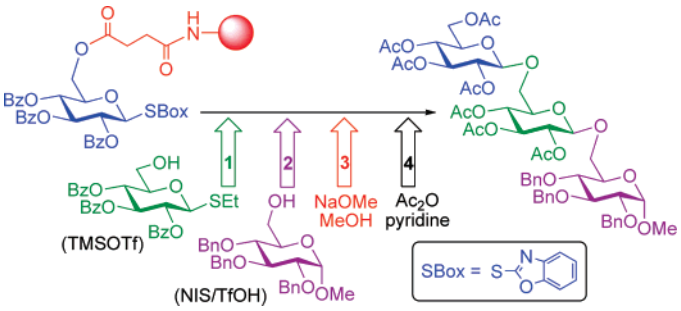

Two stable classes of thioimidoyl derivatives, *S*-benzoxazolyl (SBox) and *S*-thiazolinyl (STaz) glycosides, were investigated as glycosyl donors for solid-phase oligosaccharide synthesis. It was demonstrated that these derivatives are suitable for both glycosyl acceptor-bound and glycosyl donor-bound strategies, commonly employed in resin-supported oligosaccharide synthesis.

Introduction

One of the main drawbacks in studying the biological functions of glycoconjugates and oligosaccharides is their limited availability in pure form from natural sources. Therefore, there are expectations that efficient chemical or chemoenzymatic syntheses would make complex carbohydrates more accessible to general chemical, biochemical, and industrial audiences to keep in pace with the exploding area of glycobiology.[1] In spite of significant progress in the area of synthetic carbohydrate chemistry, complex glycostructures remain among the most challenging targets of modern synthetic chemistry.[2,3] The past decade has witnessed an expansion of methods and strategies used for both solution-phase[4−6] and solid-phase oligosaccharide synthesis.[7]

Oligosaccharide synthesis on the solid phase by using insoluble polymeric support is a very attractive technique that allows the following: rapid synthesis of oligosaccharide sequences without the necessity of purifying (and characterizing) the intermediates; ease of excess reagent removal; and performance in an automated fashion that has the potential to significantly reduce the labor associated with the whole process.[8−24] Nevertheless, there are some limitations: large

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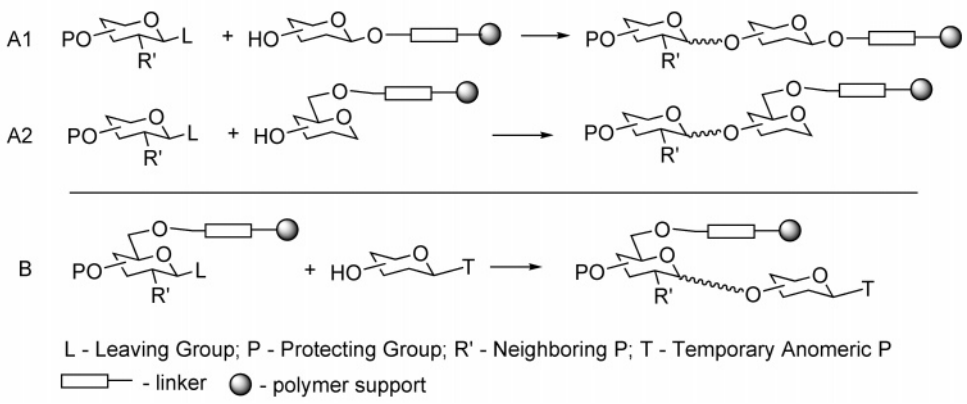
SCHEME 1



reagent excess, limited use of molecular sieves, large volume of waste solvent, cumbersome analysis of intermediates, lower stereoselectivity, loss and poisoning of resin, reagent trapping, etc. Some of these issues can be addressed by developing versatile glycosyl donors that would be both stable and highly reactive under certain reaction conditions. In spite of significant progress in recent years, none of the currently employed methods are capable of solving all of these challenges. Arguably, each complex synthetic target still requires careful retroanalysis, thorough preliminary studies, and cumbersome selection of the reaction components: resins, linkers, building blocks, promoters, solvents, etc.

Recently we demonstrated that two stable classes of thioimidoyl derivatives, *S*-benzoxazolyl (SBox)[25] and *S*-thiazolinyl (STaz)[26] glycosides, are capable of very rapid and stereoselective solution-phase glycosylations under mild reaction conditions.[27] These positive characteristics stimulated our interest in testing the glycosyl thioimidates in glycosylations on the solid phase. Herein we report our studies demonstrating that the SBox and STaz glycosides can serve as capable building blocks in a variety of synthetic applications on the solid phase.

Results and Discussion

There are two main strategies for solid-phase oligosaccharide synthesis differing in the type of attachment (Scheme 1). In strategy A, the glycosyl acceptor unit is bound to the solid support either through the anomeric carbon (A1) or via another position, e.g., at C-6 (A2). In this case, the glycosyl donor and promoter are in the solution and this offers an important advantage as the couplings tend to be more predictable and the results acquired in the solution-phase synthesis can be more easily translated to the solid phase. As a result, a vast variety of glycosyl donors have been investigated along this pathway.[7] Since the glycosyl donor is exposed to a large amount of the solution-phase activator, these reactions are often performed at low temperatures to extend its survivability in the prolonged experiments that are common for glycosylation on the solid support.

In approach B, the glycosyl donor linked to the solid support via a suitable hydroxyl group is reacted with the solution-phase glycosyl acceptor. In principle, this approach would allow rapid oligosaccharide synthesis by applying (chemo)selective activation strategies that would not require additional deprotection steps. A principal drawback of this strategy resides in the fact that most side reactions during glycosylation involve the glycosyl donor,[28] which in this application will result in the termination of the chain elongation. As a result, the number of glycosyl donors suitable for this approach pioneered by Danishefsky[29] and Ogawa[30] remains low.[7] Two-directional techniques combining approaches A and B are also known.[31,32]

Our intention was to evaluate the applicability of the thioimidate methodology to both glycosyl acceptor-bound and glycosyl donor-bound approaches to solid-phase oligosaccharide synthesis. This paper highlights the most important results acquired in our laboratory.

Acceptor-Bound Glycosylation Strategy. Having investigated a number of options for the study of the glycosyl acceptor-bound approach, we chose insoluble Merrifield and Tentagel terminal amine resins due to their general versatility, compatibility with a broad range of reaction conditions, relatively low cost, and high loading capacity, 0.9−1.2 and 0.4−0.6 mmol/g, respectively. The 3,6-diol building block **1**[33] was reacted with succinic anhydride in the presence of dimethylaminopyridine (DMAP) in pyridine to afford derivative **2** containing a carboxyl linker suitable for immobilization on the resin (Scheme 2). The immobilization through the formation of an amide linkage between the carboxyl of compound **2** and the amine group of the resin was accomplished in the presence of 1,3-dicyclohexylcarbodiimide (DCC). The loading capacity of the resulting glycopolymers **3a** and **3b** was nearly quantitative for the upper

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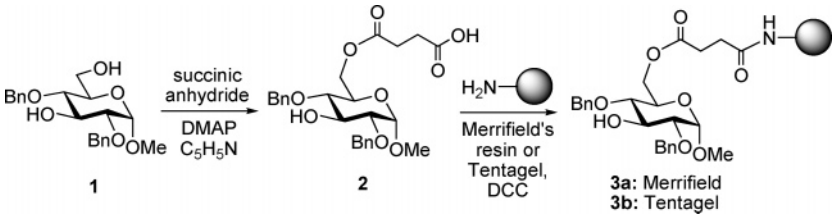
SCHEME 2



capacity range (1.2 and 0.6 mmol/g, respectively). This was determined by the treatment of the loaded beads with dilute NaOMe solution in methanol and recovering compound **2** from the conjugate **3a** and **3b** in 98% and 95% yield, respectively, based on the expected maximal loading.

Having obtained sugar-coated resins **3a** and **3b**, we turned our attention to the investigation of suitable reaction conditions for glycosylations. For this purpose we initially selected five glycosyl donors of the D-gluco series that have been developed in our laboratory: SBox glycosides **4**,[34] **7**,[35] and **10**,[25] as well as STaz glycosides **6** and **9**.[26,36] It should be noted that the selection of these building blocks was driven by the intention to investigate the synthesis of both 1,2-trans and 1,2-cis glycosides. Apparently, glycosyl donors bearing a nonparticipating group at C-2 (2-*O*-benzyl) **7**, **9**, and **10** are suitable precursors for the synthesis of 1,2-cis glycosides, whereas their 2-*O*-benzoylated counterparts **4** and **6** are suitable for 1,2-trans glycosylations.

All glycosyl donors under investigation provided very high yields and stereoselectivities in the solution-based di- and oligosaccharide syntheisis especially in the presence of silver(I) trifluormethanesulfonate (AgOTf) as promoter.[27] However, formation of the expected disaccharide **5** was not detected when perbenzoylated glycosyl donors **4** or **6** were glycosidated with **3a** in the presence of AgOTf (entries 1 and 2, Table 1). This result is seemingly in contradiction with our earlier observation for the solution-phase glycosylations that required very short reaction times and provided the requisite glycosides in nearly quantitative yields.[25,26] Herein though, the high reactivity of thioimidates in the presence of AgOTf in combination with the low reactivity of the resin-bound secondary alcohol creates an obvious mismatch. This reactivity difference results in rapid side reactions including hydrolysis and self-condensation of the solution-based glycosyl donor, rather than the anticipated glycosylation. Therefore, we assumed that the competing side reactions could be suppressed by using less reactive promoters known from our studies of activation of the thioimidoyl moieties in solution: $Cu(OTf)_2$, MeOTf, NIS/TfOH, NIS/TMSOTf, TfOH, and TMSOTf.[36,37]

The systematic screening resulted in the discovery of the activation conditions, suitable for efficient glycosylation of the Merrifield resin-bound acceptor **3a** with SBox glycosyl donor **4** and its STaz counterpart **6**. We determined that TMSOTf-promoted glycosidation of **4** and MeOTf-promoted glycosidation of **6** proceeded nearly quantitatively providing the disaccharide **5** in excellent yields of 95% and 98%, respectively (entries 3 and 4, Table 1). Interestingly, in spite of a structural parity of the SBox and STaz leaving groups, high donor−promoter specificities have been discovered. Thus, switching the donor−promoter combination resulted in significantly compromised results; i.e., glycosidation of **4** in the presence of MeOTf or glycosidation of **6** in the presence of TMSOTf afforded disaccharide **5** in only 20% and 10%, respectively.

Having established suitable reaction conditions for the synthesis of 1,2-trans-linked disaccharides, we turned our attention to investigating building blocks bearing a nonparticipating 2-*O*-benzyl substituent. It is well-known that per-benzylated compounds are significantly more reactive (armed) than their acylated counterparts (disarmed).[38] Therefore, we suspected that the increased reactivity of the building blocks **7** and **9**, in comparison to their per-benzoylated counterparts **4** and **6**, would be detrimental for glycosylations of the resin-bound acceptor. Indeed, when acceptor **3a** was reacted with **7** (TMSOTf) or **9** (MeOTf) the disaccharide **8** was isolated in significantly lower yields of 54% and 32%, respectively (entries 5 and 6, Table 1). These results prompted us to investigate glycosyl donor **10** bearing the 2-*O*-benzyl-3,4,6-tri-*O*-acetyl group pattern that was determined to be significantly less reactive than its per-benzylated analogue **7**.[35] Indeed, this glycosylation was significantly more successful and the requisite disaccharide **11** was formed in a good yield of 80% (entry 7, Table 1). In should be emphasized that the latter glycosylation was completely α-stereoselective, whereas the stereoselectivity achieved with per-benzylated glycosyl donors **7** and **9** was low.

Being encouraged by the preliminary results, we translated our findings to the synthesis of other targets, in particular, derivatives of the galacto and glucosamino series. For this purpose, STaz glycoside **12**[26] and SBox glycosides **14**,[25] **16**,[39] and **18**[39] were selected. The glycosylations of acceptor **3a** were uneventful, and the corresponding disaccharides **13**, **15**, **17**, and **19** were obtained in 51−82% yield (entries 8−11, Table 1).

On a similar note, Tentagel-bound acceptor **3b** was investigated. In this case, NIS/TMSOTf-promoted glycosidations of the SBox glycosides **4**, **7**, and **10** were the most advantageous. As a result, disaccharides **5**, **8**, and **11** were obtained in good yields of 78−98%; and in the case of glycosyl donors **4** and **10**, excellent β- and α-stereoselectivity was achieved, respectively. These results are summarized in Table 1, entries 12−14.

Donor-Bound Glycosylation Strategy. For the study of the glycosyl donor-bound approach, we chose differently protected 6-hydroxyl SBox building blocks **21a** and **21b**,[35] capable of 1,2-trans and 1,2-cis glycosylation, respectively. For the insoluble

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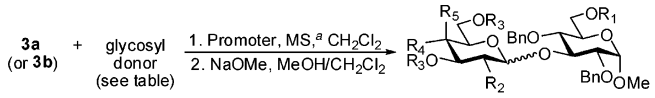
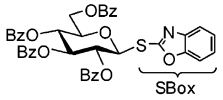
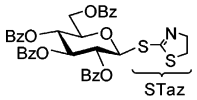
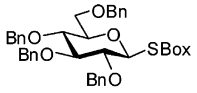
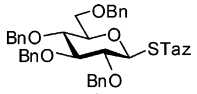
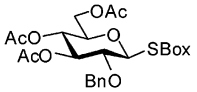
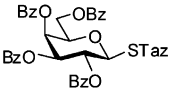
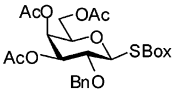
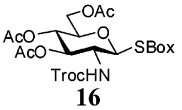
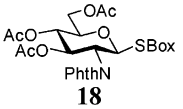
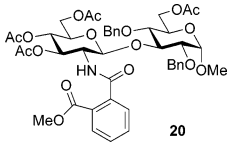
TABLE 1. Synthesis of Disaccharides by the Acceptor-Bound Approach



5: $R_1=R_3=R_5=H$, $R_2=R_4=OH$
8: $R_1=R_5=H$, $R_2=R_4=OBn$, $R_3=Bn$
11: $R_1=R_3=R_5=H$, $R_2=OBn$, $R_4=OH$
13: $R_1=R_3=R_4=H$, $R_2=R_5=OH$
15: $R_1=R_3=R_4=H$, $R_2=OBn$, $R_5=OH$
17: $R_1=R_3=Ac$, $R_2=NHCOOMe$, $R_4=OAc$, $R_5=H$
19: $R_1=R_3=Ac$, $R_2=NPhth$, $R_4=OAc$, $R_5=H$

Entry	Acceptor	Donor	Promoter	Product	Yield, %	α/β ratio
1	**3a**	 **4**	AgOTf	**5**	0	-
2	**3a**	 **6**	AgOTf	**5**	0	-
3	**3a**	**4**	TMSOTf	**5**	95	β only
4	**3a**	**6**	MeOTf	**5**	98	β only
5	**3a**	 **7**	TMSOTf	**8**	54	3/2
6	**3a**	 **9**	MeOTf	**8**	32	1/1
7	**3a**	 **10**	TMSOTf	**11**	80	α only
8	**3a**	 **12**	MeOTf	**13**	82	β only
9	**3a**	 **14**	TMSOTf	**15**	52	5/1
10	**3a**	 **16**	TMSOTf	**17**[b]	51	β only
11	**3a**	 **18**	TMSOTf	**19**[c]	75	β only
12	**3b**	**4**	NIS/TMSOTf	**5**	98	β only
13	**3b**	**7**	NIS/TMSOTf	**8**	78	1.2/1
14	**3b**	**10**	NIS/TMSOTf	**11**	89	5/1

[a] All glycosylations were performed in dichloromethane under argon at room temperature in the presence of molecular sieves (MS): 3 Å with AgOTf or MeOTf and 4 Å with TMSOTf or NIS/TMSOTf. [b] The product was *N,O*-acetylated (Ac_2O/pyridine) to simplify the purification. [c] The product after cleavage and acetylation was obtained as a separable mixture of **19** and **20** (1/2), the total disaccharide yield is given.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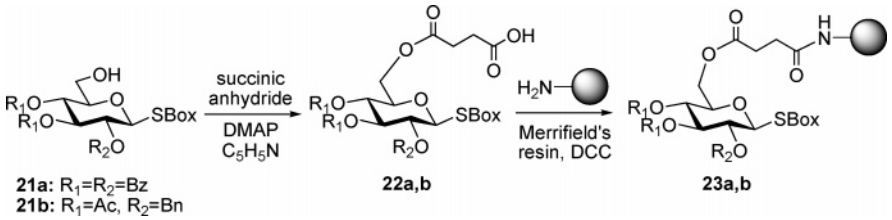
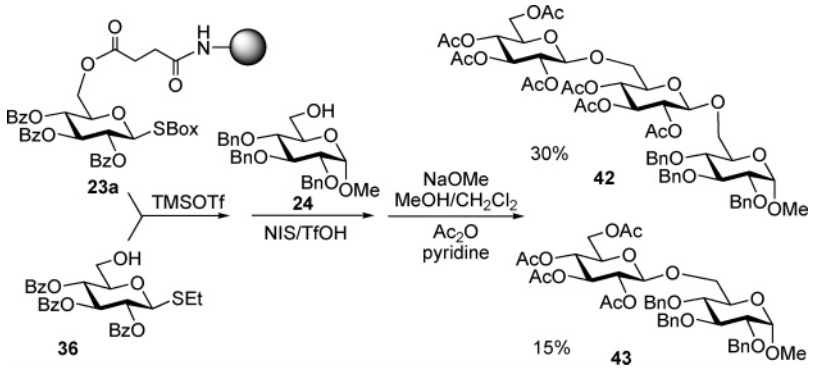
SCHEME 3



SCHEME 4



polymeric support we chose Merrifield terminal amine resin. The SBox glycosides **21a** and **21b** were reacted with succinic anhydride in the presence of DMAP in pyridine to afford the corresponding derivatives **22a** and **22b** bearing a carboxyl linker suitable for immobilization on the resin (Scheme 2). The immobilization through the formation of an amide linkage between the carboxyl of compounds **22a** or **22b** and the amine group of the resin was accomplished as described for the synthesis of **3a**. The loading capacity of the resulting glycopolymers **23a** and **23b** (Scheme 3) was nearly quantitative for the upper capacity range (1.2 mmol/g). This conclusion was based on the recovery of the corresponding methyl glycosides (~95%) resulting from the displacement of the SBox moiety during the prolonged deacylation/cleavage with MeOTf.

Having obtained glycosyl donor-coated resins **23a** and **23b**, we turned our attention to investigating suitable reaction conditions for their glycosidations. For this purpose, we initially selected a number of common glycosyl acceptors **24**,[33] **26**,[40] **28**,[41] **30**,[42] **32**, and **34**. It should be noted that the selection of these building blocks was driven by the intention to investigate the scope and limitation of the methodology toward the synthesis of various glycosidic linkages. Bearing in mind our experience with the acceptor-bound approach, we carefully approached the task of identifying suitable promoters. Upon screening a variety of conditions, we determined that in most part AgOTf or TMSOTf provide the highest yields. All glycosidations of 2-*O*-benzoylated donor **23a** were β-stereoselective. These studies are summarized in Table 2, entries 1−6.

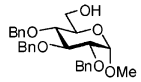
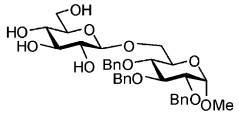
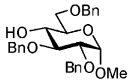
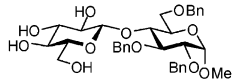
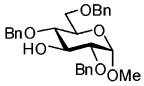
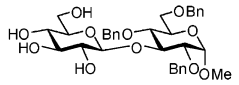
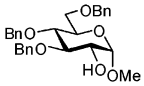
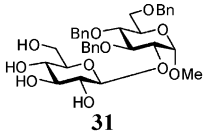
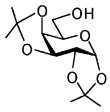
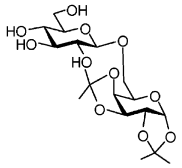
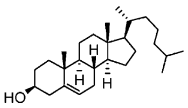
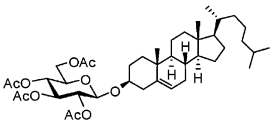
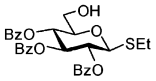
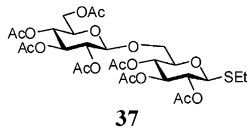
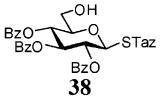
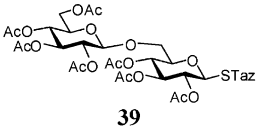
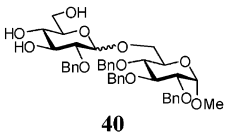
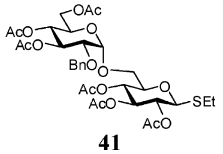
Along similar lines, we performed glycosylations of glycosyl acceptors bearing a temporary anomeric substituent, which under an appropriate set of reaction conditions can be turned into a potent leaving group. For these studies we chose partially protected *S*-ethyl glycoside **36**[43] and STaz glycoside **38**.[36] TMSOTf-promoted glycosylations provided the desired products **37** and **39** in moderate yields of 37% and 25%, respectively (entries 7 and 8, Table 2). The latter reaction was complicated by partial activation of the STaz moiety of the glycosyl acceptor due to apparent cross-reactivity of the SBox and STaz moieties under TMSOTf-promoted glycosylation conditions. If the reaction time was doubled, no disaccharide **39** could be detected due to the activation of the STaz moiety resulting in the formation of higher oligomers.

Glycosidation of 2-*O*-benzylated resin bound glycosyl donor **23b** was rather disappointing due to relatively low yields and poor stereoselectivity in a majority of test reactions attempted. A representative example of these studies is shown in Table 2, entry 9. Surprizingly, when *S*-ethyl glycosyl acceptor **36** was glycosylated, complete α-stereoselectivity was detected; unfortunately, the yield of this transformation was low (entry 10, Table 2). Very comparable results have been obtained with glycosyl donors **22a** and **22b** immobilized on Tentagel resin. These glycosylations were performed in the presence of NIS/TMSOTf or MeOTf as promoters and afforded the requisite disaccharide derivatives in 50−75% yield.

Application to Multistep Synthesis. The results of the selective activation of the resin-bound SBox glycosyl donor over the glycosyl acceptor bearing an *S*-ethyl anomeric moiety prompted us to investigate the multistep oligosaccharide synthesis. For this purpose, we performed coupling of glycosyl donor **23a** and glycosyl acceptor **36** and, without isolating the intermediate, the next glycosylation step was attempted. This involved reaction between the immobilized intermediate disaccharide donor with added glycosyl acceptor **24** in the presence of NIS/TfOH, common activation conditions for glycosidation of thioglycosides (Scheme 4).[44] The resulting glycopolymer was subjected to cleavage with MeONa and subsequent per-*O*-acetylation to afford the trisaccharide **42** in 30% yield overall.

(40) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10−C11.
(41) Koto, S.; Takebe, Y.; Zen, S. *Bull. Chem. Soc. J.* **1972**, *45*, 291−293.
(42) Sollogoub, M.; Das, S. K.; Mallet, J.-M.; Sinay, P. *C. R. Acad. Sci. Ser. 2* **1999**, *2*, 441−448.
(43) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275−278.
(44) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179−205.

TABLE 2. Synthesis of Disaccharides by the Donor-Bound Approach

Entry	Donor	Acceptor	Promoter	Product	Yield, %	α/β ratio
1	**23a**	 **24**	AgOTf	 **25**	87	β only
2	**23a**	 **26**	AgOTf	 **27**	56	β only
3	**23a**	 **28**	AgOTf	 **29**	98	β only
4	**23a**	 **30**	TMSOTf	 **31**	49	β only
5	**23a**	 **32**	AgOTf	 **33**	45	β only
6	**23a**	 **34**	AgOTf	 **35**	51[a]	β only
7	**23a**	 **36**	TMSOTf	 **37**	37[a]	β only
8	**23a**	 **38**	TMSOTf	 **39**	25[a]	β only
9	**23b**	**24**	AgOTf	 **40**	54	1/1
10	**23b**	**36**	TMSOTf	 **41**	35[a]	α only

[a] The disaccharide was *O*-acetylated (Ac_2O/pyridine) to simplify the purification.

In addition, disaccharide **43** was also formed (15% yield) as a result of coupling between glycosyl donor **23a**, remaining after the first glycosylation step, with added glycosyl acceptor **24**.

Conclusions

Many common glycosyl donors can be used in solid-phase oligosaccharide synthesis via acceptor-bound approaches, and the glycosyl thioimidates investigated herein are no exception. A variety of applications were proven to be highly efficient and stereoselective with both STaz and SBox glycosides. These compounds were sufficiently stable under reaction conditions that withstood prolonged glycosylation experiments at room temperature. These observations differ significantly from those made with other commonly employed glycosyl donors including sulfoxides (−78 °C),[45] phosphates (−50 °C),[46] or trichloroacetimidates (−40 °C).[22] The glycosyl donor-bound approach for

(45) Yan, L.; Taylor, C. M.; Goodnow, R.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6953−6954.

resin-supported oligosaccharide synthesis is by far more challenging overall, and this is reflected in the low number of reports dedicated to these studies. Only stable glycosyl donors such as glycals, thioglycosides, or fluorides that are less prone to having side reactions can be used along this strategy. We demonstrated that the SBox glycosides also fit in this rare category, and provide good yields throughout. One of the important characteristics of the thioimidoyl moiety is that it can be selectively activated over alkyl/aryl thioglycosides and this advantageous feature was explored herein by synthesizing a trisaccharide derivative via selective activation in two glycosylation steps.

Experimental Section

General Procedure for Introducing the Succinoyl Linker: Preparation of Building Blocks 2, 22a, and 22b. 4-(*N*,*N*-Dimethylamino)pyridine (0.169 mmol) and succinic anhydride (1.69 mmol) were added to a stirred solution of partially protected derivative (**1**, **21a**, or **21b**, 1.69 mmol) in dry pyridine (10 mL) at room temperature under argon. The reaction mixture was stirred for 16 h at room temperature under argon. Upon completion (~16 h), the reaction mixture was concentrated under reduced pressure, then the residue was dissolved in dichloromethane (60 mL) and washed with water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 1/1, v/v) to afford compounds **2**, **22a**, or **22b**, respectively.

Methyl 2,4-di-*O*-benzyl-6-*O*-(3-hydroxycarbonylpropanoyl)-α-D-glycopyranoside (2): The title compound was obtained from methyl 2,4-di-*O*-benzyl-α-D-glycopyranoside (**1**)[33] in 75% yield as a white amorphous solid. Analytical data for **2**: R_f 0.37 (methanol/dichloromethane, 1/9, v/v); $[\alpha]^{29}_D$ +59.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.51−2.53 (m, 4H), 3.23 (s, 3H), 3.25−3.35 (m, 2H), 3.70 (m, 1H), 4.02 (dd, 1H, J = 9.8 Hz), 4.16−4.28 (m, 2H), 4.52−4.67 (m, 4H), 4.81 (d, 1H, J = 11.1 Hz), 7.18−7.29 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$) δ 28.9, 29.0, 55.4, 63.6, 68.4, 73.3, 73.8, 74.7, 76.8, 79.8, 97.6, 128.1, 128.3 (×3), 128.4 (×3), 128.7 (×2), 128.8, 138.0, 138.3, 172.0, 177.5 ppm; HR-FAB MS calcd for $C_{25}H_{29}Na_2O_9$ $[M - H + 2Na]^+$ 519.1607, found 519.1586.

Benzoxazolyl 2,3,4-tri-*O*-benzoyl-6-*O*-(3-hydroxycarbonylpropanoyl)-β-D-glycopyranoside (22a): The title compound was obtained from benzoxazolyl 2,3,4-tri-*O*-benzoyl-β-D-glycopyranoside (**21a**)[35] in 80% yield as a white amorphous solid. Analytical data for **22a**: R_f 0.43 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]^{26}_D$ +83.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.47−2.57 (m, 4H), 4.19−4.32 (m, 3H), 5.59 (dd, 1H, J = 9.6 Hz), 5.67 (dd, 1H, J = 9.8 Hz), 5.91 (d, 1H, J = 7.7 Hz), 5.95 (dd, 1H, J = 9.4 Hz), 7.17−7.85 (19H) ppm; ^{13}C NMR ($CDCl_3$) δ, 27.9, 27.8, 61.6, 67.8, 69.4, 72.7, 75.6, 82.8, 109.2, 117.8, 123.6, 123.7, 127.3 (×2), 127.4 (×2), 127.5 (×2), 127.6 (×3), 128.7 (×2), 128.8 (×2), 128.9, 132.3, 132.5, 132.6, 140.2, 147.1, 150.8, 160.3, 164.2, 164.6 (×2), 170.7, 175.7 ppm; HR-FAB MS calcd for $C_{38}H_{30}NNa_2O_{12}S$ $[M - H + Na]^+$ 770.1284, found 770.1299.

Benzoxazolyl 3,4-di-*O*-acetyl-2-*O*-benzyl-6-*O*-(3-hydroxycarbonylpropanoyl)-β-D-glycopyranoside (22b): The title compound was obtained from benzoxazolyl 3,4-di-*O*-acetyl-2-*O*-benzyl-β-D-glycopyranoside (**21b**)[35] in 78% yield as a white amorphous solid. Analytical data for **22b**: R_f 0.30 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{26}_D$ +10.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.86, 1.96 (2s, 3H), 2.51−2.53 (m, 4H), 3.79 (dd, 1H, J = 9.0 Hz), 3.85 (m, 1H), 4.13−4.15 (m, 2H), 4.64 (dd, 2H, J = 11.2 Hz), 5.03 (dd, 1H, J = 9.8 Hz), 5.25 (dd, 1H, J = 9.5 Hz), 5.40 (d, 1H, J = 10.0 Hz), 7.16−7.25 (9H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.8, 20.9, 29.2, 29.3, 62.5, 68.4, 75.5, 75.8, 76.4, 77.6, 78.3, 84.9, 110.4, 119.2, 124.9 (×2), 128.3 (×2), 128.7 (×2), 137.2, 141.5, 151.9, 161.3, 170.0, 170.1, 171.9, 176.3 ppm; HR-FAB MS calcd for $C_{28}H_{30}NO_{11}S$ $[M + H]^+$ 588.1540, found 588.1561.

General Procedure for the Immobilization on the Resin: Preparation of Glycopolymer Conjugates 3a, 3b, 23a, and 23b. Aminomethyl polymer resin (50 mg, 0.04−0.06 mmol of NH_2 functional group) was swollen in dry dichloromethane (2 mL) for 30 min at room temperature. Then a mixture of succinoylated sugar **2**, **22a**, or **22b** (0.18 mmol) and 1,3-dicyclohexylcarbodiimide (48 mg, 0.18 mmol) in dry dichloromethane (2 mL) was added. The resulting reaction mixture was agitated for 72 h, then the resin was separated by sintered filter, washed successively with methanol (5 × 5 mL) and dichloromethane (5 × 5 mL), and dried in vacuo. The loading capacity of the resulting glycopolymer was determined by cleavage off the beads by the general procedures provided below.

General Procedures for Glycosylation on the Resin: Preparation of Disaccharides. Method A: AgOTf-Promoted Glycosylation. A mixture of resin-bound glycosyl acceptor (or donor, 0.06 mmol), glycosyl donor (or acceptor, 0.18 mmol), coevaporated with toluene (3 × 10 mL) and dried in vacuo for 2 h directly prior to application, and molecular sieves (3 Å, 200 mg) in dry dichloromethane (4 mL) was agitated for 12 h at room temperature. Then AgOTf (0.24 mmol) was added and the mixture was agitated for 48 h at room temperature under argon. After that, glycosyl donor (0.18 mmol) in dry dichloromethane (1 mL) and AgOTf (0.24 mmol) were added and the reaction mixture was agitated for an additional 48 h. The resin was separated by sintered filter, washed successively with methanol (5 × 5 mL) and dichloromethane (5 × 5 mL), and dried in vacuo. The residual resin was suspended in dry dichloromethane (2 mL) before adding 1 N sodium methoxide solution in methanol (2 mL). The reaction mixture was agitated at room temperature for 48 h; the pH was monitored and adjusted within pH ~8−9 range with 1 N sodium methoxide solution, if needed. The resin was separated by sintered filter, washed successively with methanol (3 × 5 mL) and dichloromethane (3 × 5 mL), and dried in vacuo. The combined filtrate was neutralized with Dowex (H^+), the resin was filtered off, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel (methanol/dichloromethane or ethyl acetate/hexane gradient elution) to provide the requisite disaccharide derivative.

Method B: TMSOTf-Promoted Glycosylation. A mixture of resin-bound glycosyl acceptor (or donor, 0.06 mmol), glycosyl donor (or acceptor, 0.18 mmol), coevaporated with toluene (3 × 10 mL) and dried in vacuo for 2 h directly prior to application, and molecular sieves (4 Å, 200 mg) in dry dichloromethane (4 mL) was agitated for 12 h at room temperature. Then TMSOTf (0.24 mmol) was added and the mixture was agitated for 48 h at room temperature under argon. After that, glycosyl donor (0.18 mmol) in dry dichloromethane (1 mL) and TMSOTf (0.24 mmol) were added and the reaction mixture was agitated for an additional 48 h. The resin was separated by sintered filter, washed successively with methanol (5 × 5 mL) and dichloromethane (5 × 5 mL), and dried in vacuo. The residual resin was subjected to NaOMe treatment and purification as described for Method A to afford the requisite disaccharide.

Method C: MeOTf-Promoted Glycosylation. A mixture of resin-bound glycosyl acceptor (0.06 mmol), glycosyl donor (0.18 mmol), coevaporated with toluene (3 × 10 mL) and dried in vacuo for 2 h directly prior to application, and molecular sieves (3 Å, 200 mg) in dry dichloromethane (4 mL) was agitated for 12 h at room temperature. Then MeOTf (0.24 mmol) was added and the mixture was agitated for 48 h at room temperature under argon. After that, glycosyl donor (0.18 mmol) in dry dichloromethane (1 mL) and MeOTf (0.24 mmol) were added and the reaction mixture was agitated for an additional 48 h. The resin was separated by sintered filter, washed successively with methanol (5 × 5 mL) and dichloromethane (5 × 5 mL), and dried in vacuo. The residual resin was subjected to NaOMe treatment and purification as described for Method A to afford the requisite disaccharide.

(46) Palmacci, E. R.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 595−606.

Method D: NIS/TMSOTf-Promoted Glycosylation. A mixture of resin-bound glycosyl acceptor **3b** (0.03 mmol), glycosyl donor (0.09 mmol), coevaporated with toluene (3 × 5 mL) and dried in vacuo for 2 h directly prior to application, and molecular sieves (4 Å, 200 mg) in dry dichloromethane (4 mL) was agitated for 12 h at room temperature. Then NIS (0.12 mmol) and TMSOTf (0.0012 mmol) were added and the mixture was agitated for 24 h at room temperature under argon. The resin was separated by sintered filter, washed successively with methanol (5 × 5 mL) and dichloromethane (5 × 5 mL), and then re-suspended in dichloromethane and agitated for several minutes to allow the resin swallow. The resin was collected by using a plastic pipet and so was separated from molecular sieves, and dried in vacuo for 24 h. The glycosylation−filtration cycle was repeated twice. The residual resin was swollen in methanol and subjected to NaOMe treatment and purification as described for Method A to afford the requisite disaccharide.

Methyl 2,4-di-*O*-benzyl-3-*O*-(β-D-glucopyranosyl)-α-D-glucopyranoside (5): The title compound was obtained from **3a** and **4**[34] by Method B in 95% yield, **3a** and **6**[36] by Method C in 98% yield, or **3b** and **4** by Method D in 98% yield as a white amorphous solid. Analytical data for **5**: R_f 0.34 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{26}_D$ +17.5 (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 3.22−3.36 (m, 6H), 3.37−3.83 (m, 8H), 4.27 (m, 1H), 4.59−4.68 (m, 3H), 4.79−4.84 (m, 2H), 5.08 (d, 1H, J = 10.2 Hz), 7.27−7.46 (m, 10H) ppm; ^{13}C NMR (CD_3OD) δ 50.0, 55.6, 62.2, 63.5, 72.5, 74.3, 76.2, 76.7, 77.9, 78.2, 78.6, 78.9, 81.9, 99.1, 104.2, 129.1, 129.2, 129.5 (×2), 129.6 (×2), 129.8 (×2), 130.1 (×2), 139.5, 139.8 ppm; HR-FAB MS calcd for $C_{27}H_{36}NaO_{11}$ $[M + Na]^+$ 559.2155, found 559.2168.

Methyl 2,4-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (8): The title compound was obtained from **3a** and **7**[35] by Method B in 54% yield (α/β = 3/2), **3a** and **9**[36] by Method C in 32% yield (α/β = 1/1), or **3b** and **7** by Method D in 78% yield (α/β = 1.2/1) as a white amorphous solid. Selected analytical data for **8**: R_f 0.34 (ethyl acetate/hexanes, 2/3, v/v); ^{1}H NMR ($CDCl_3$) δ, 5.72 (d, 1H, J = 7.0 Hz), 4.98 (d, 1H, J = 4.2 Hz), 5.72 (d, 1H, J = 3.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 97.6, 97.8, 98.0, 102.8 ppm; HR-FAB MS calcd for $C_{55}H_{60}NaO_{11}$ $[M + Na]^+$ 919.4033, found 919.4067.

Methyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (11): The title compound was obtained from **3a** and **10**[25] by Method B in 80% yield (α only) or **3b** and **10** by Method D in 89% yield (α/β = 5/1) as a white amorphous solid. Analytical data for α-**11**: R_f 0.24 (methanol/dichloromethane, 1/9, v/v); $[\alpha]^{29}_D$ +24.7 (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ, 3.29−3.34 (m, 4H), 3.46−3.79 (m, 8H), 3.96 (dd, 1H, J = 9.2 Hz), 4.13−4.17 (m, 1H), 4.28 (dd, 1H, J = 8.6 Hz), 4.44 (d, 1H, J = 11.9 Hz), 4.56−4.71 (m, 5H), 4.94 (d, 1H, J = 11.9 Hz), 5.56 (d, 1H, J = 3.4 Hz), 6.92−7.39 (m, 15H) ppm; ^{13}C NMR (CD_3OD) δ 55.4, 61.8, 62.5, 70.5, 70.6, 71.4, 73.4 (×2), 73.5, 73.7, 76.2, 78.6, 78.9, 79.2, 97.1, 97.8, 126.9 (×3), 127.7, 128.2 (×2), 128.4, 128.6 (×2), 128.7 (×2), 128.8, (×4), 137.8, 137.9, 138.4 ppm; HR-FAB MS calcd for $C_{34}H_{42}NaO_{11}$ $[M + Na]^+$ 649.2625, found 649.2603.

Methyl 2,4-di-*O*-benzyl-3-*O*-(β-D-galactopyranosyl)-α-D-glucopyranoside (13): The title compound was obtained from **3a** and **12**[26] by Method C in 82% yield as a white amorphous solid. Analytical data for **13**: R_f 0.27 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{27}_D$ +22.5 (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ, 3.31 (s, 3H), 3.32−3.84 (m, 11H), 4.25 (m, 1H), 4.55 (d, 1H, J = 10.9 Hz), 4.58 (d, 1H, J = 3.8 Hz), 4.63 (d, 1H, J = 11.6 Hz), 4.77−4.87 (m, 2H), 5.14 (d, 1H, J = 9.8 Hz), 7.25−7.53 (m, 10H) ppm; ^{13}C NMR (CD_3OD) δ 55.6, 62.2, 63.0, 70.6, 72.5, 73.5, 74.4, 75.1, 76.7, 77.3, 77.9, 79.2, 82.1, 99.2, 105.1, 129.1, 129.2, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.0, 130.5, 139.6, 139.9 ppm; HR-FAB MS calcd for $C_{27}H_{36}O_{11}Na$ $[M + Na]^+$ 559.2155, found 559.2147.

Methyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (15): The title compound was obtained from **3a** and **14**[25] by Method B in 52% (α/β = 5/1) yield as a white amorphous solid. Analytical data for α-**15**: R_f 0.25 (methanol/dichloromethane, 1/9, v/v); ^{1}H NMR (CD_3OD) δ 3.25−3.30 (m, 4H), 3.43−3.77 (m, 8H), 3.86−3.89 (m, 1H), 4.12−4.19 (m, 2H), 4.36−4.51 (m, 5H), 4.62 (d, 1H, J = 3.4 Hz), 4.78 (d, 1H, J = 11.8 Hz), 5.53 (d, 1H, J = 3.0 Hz), 7.07−7.25 (15H) ppm; ^{13}C NMR (CD_3OD) δ 55.3, 61.6, 63.4, 67.9 (×2), 70.6, 71.8, 73.1, 73.7, 73.7, 75.1, 76.3, 78.6, 79.1, 97.3, 97.5, 127.0 (×2), 127.7, 128.0, 128.1 (×2), 128.2 (×2), 128.5 (×2), 128.6 (×2), 128.7 (×2), 128.8, 137.6, 138.0, 138.2 ppm; HR-FAB MS calcd for $C_{34}H_{42}O_{11}$-Na $[M + Na]^+$ 649.2625, found 649.2637.

Methyl 3-*O*-(2-methoxycarbamoyl-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-*O*-acetyl-2,4-di-*O*-benzyl-α-D-glucopyranoside (17): The title compound was obtained from **3a** and **16**[39] by Method B followed by acetylation (see below) in 51% yield as a white amorphous solid. **General acetylation procedure:** The residue, recovered from the cleavage off the resin-bound disaccharide, was dissolved in dry pyridine (1 mL) and acetic anhydride (0.5 mL) was added at 0 °C. The reaction was allowed to gradually warm to room temperature and kept for an additional 12 h. The reaction was quenched by adding methanol (2 mL) then cooled to room temperature, and the volatiles were removed under reduced pressure. The residue was coevaporated with toluene (3 × 5 mL) and then purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the requisite per-acetylated compound. Analytical data for **17**: R_f 0.36 (ethyl acetate/hexanes, 3/2, v/v); $[\alpha]^{27}_D$ +21.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.97, 2.01, 2.02, 2.03 (4s, 12H), 3.30 (s, 3H), 3.44−3.58 (m, 2H), 3.58−3.63 (m, 1H), 3.74 (s, 3H), 3.77−3.79 (m, 2H), 4.02 (dd, 1H, J = 2.2 Hz, J = 12.2 Hz), 4.20−4.28 (m, 4H), 4.50 (d, 1H, J = 10.8 Hz), 4.57−4.68 (m, 3H), 4.83 (d, 1H, J = 8.5 Hz), 4.87 (dd, 1H, J = 10.2), 5.04−5.10 (m, 2H), 7.25−7.42 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.8, 20.9, 21.1, 29.6, 29.9, 52.7, 55.3, 63.2, 68.6 (×2), 71.8, 73.1, 73.4, 74.9, 75.3, 76.8, 80.0, 81.1, 97.2, 102.2, 128.0, 128.2, 128.5 (×3), 128.6 (×2), 128.7, 129.1 (×2), 137.8, 138.4, 156.9, 169.6, 170.9 (×3) ppm; HR-FAB MS calcd for $C_{37}H_{47}$-$NNaO_{16}$ $[M + Na]^+$ 784.2793, found 784.2829.

Methyl 6-*O*-acetyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,4-di-*O*-benzyl-α-D-glucopyranoside (19): The title compound was obtained from **3a** and **18**[39] by Method B and acetylated prior to isolation as described for the synthesis of **17** in 75% yield as a foam. Further analysis of the disaccharide fraction showed the presence of two compounds, **19** and methyl 6-*O*-acetyl-3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-(*o*-methoxycarbonyl)benzamido-β-D-glucopyranosyl]-2,4-di-*O*-benzyl-α-D-glucopyranoside (**20**), which were isolated by additional column chromatography on silica gel (ethyl acetate/hexane slow gradient elution) in 25% and 50%, respectively; both compounds were obtained as foams. Analytical data for **19**: R_f 0.22 (ethyl acetate/hexanes, 2/3 v/v); $[\alpha]^{26}_D$ +9.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.88, 1.94, 2.00, 2.00 (4s, 12H), 3.08 (s, 3H), 3.17 (dd, 1H, J = 3.5 Hz, J = 9.6 Hz), 3.30 (dd, 1H, J = 8.8 Hz, J = 9.9 Hz), 3.75 (m, 1H), 3.79 (d, 1H, J = 12.5 Hz), 3.86 (m, 1H), 4.04−4.14 (m, 4H), 4.28−4.38 (m, 2H), 4.40 (dd, 1H, J = 8.4 Hz, J = 10.7 Hz), 4.58 (d, 1H, J = 11.2 Hz), 4.66 (d, 1H, J = 12.5 Hz), 5.04 (d, 1H, J = 11.2 Hz), 5.20 (dd, 1H, J = 9.9 Hz), 5.82 (d, 1H, J = 8.4 Hz), 5.57−6.01 (dd, 1H, J = 10.7 Hz, J = 9.1 Hz), 7.12−8.00 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.7, 20.9 (×2), 21.0, 29.9, 55.0, 55.7, 62.1, 63.2, 68.2, 69.3, 70.8, 71.60, 74.1, 74.7, 75.4, 76.8, 78.4, 80.9, 97.7, 98.3, 123.9, 128.0, 128.3 (×6), 128.6 (×2), 128.7 (×3), 138.3 (×2), 138.4, 167.7 (×2), 169.9, 170.3, 170.8, 170.9 ppm; HR-FAB MS calcd for $C_{43}H_{47}NNaO_{16}$ $[M + Na]^+$ 856.2793, found 856.2769.

Analytical data for **20**: R_f 0.28 (ethyl acetate/hexanes, 3/2, v/v); $[\alpha]^{26}_D$ +0.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.93, 1.94, 1.97, 2.00 (4s, 12H), 3.22 (s, 3H), 3.45 (dd, 1H, J = 8.7 Hz), 3.54 (dd, 1H, J = 3.4 Hz, J = 9.5 Hz), 3.63 (m, 1H), 3.72 (m, 1H), 3.82 (s, 3H), 3.98−4.06 (m, 2H), 4.13−4.25 (m, 3H), 4.32−4.42 (m, 2H), 4.50 (d, 1H, J = 10.8 Hz), 4.58 (d, 1H, J = 3.3 Hz), 4.88−4.95 (m, 2H), 5.04 (d, 1H, J = 11.1 Hz), 5.12 (dd, 1H, J = 9.6 Hz),

5.40 (d, 1H, J = 9.5 Hz), 6.91−7.92 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.8 (×2), 21.0, 21.1, 52.6, 54.4, 55.3, 62.3, 63.2, 68.6, 68.7, 71.9, 72.0, 73.4, 75.0 (×2), 80.0, 81.2, 97.0, 102.0, 127.0 (×2), 127.5, 128.0, 128.3, 128.5 (×2), 128.7 (×2), 129.0 (×2), 129.8, 130.0, 130.1, 132.1, 137.6, 138.1, 138.4, 166.8, 169.0, 169.5, 170.8 (×2), 180.0 ppm; HR-FAB MS calcd for $C_{44}H_{51}NNaO_{17}$ [M + Na]$^+$ 888.3055, found 888.3066.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(β-D-glucopyranosyl)-α-D-glucopyranoside (25): The title compound was obtained from **23a** and **24**[33] by Method A in 87% yield as a white amorphous solid. Analytical data for **25**: R_f 0.30 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{29}_D$ +3.9 (*c* 1, MeOH); ^{1}H NMR (CD_3SOCD_3) δ 2.96−3.17 (m, 4H), 3.26−3.38 (m, 4H), 3.40−3.50 (m, 2H), 3.57−3.78 (m, 4H), 4.00 (d, 1H, J = 9.8 Hz), 4.15 (d, 1H, J = 7.7 Hz), 4.50 (dd, 1H, J = 5.8 Hz), 4.61−4.86 (m, 7H, J = 4.2 Hz), 4.90 (d, 1H, J = 4.2 Hz), 4.95 (d, 1H, J = 4.5 Hz), 5.15 (d, 1H, J = 4.9 Hz), 7.26−7.37 (m, 15H) ppm; ^{13}C NMR (CD_3SOCD_3) δ 54.6, 61.0, 67.4, 69.7, 70.0, 71.3, 73.4, 74.0, 74.4, 76.6, 76.9, 77.0, 79.4, 81.2, 96.9, 103.4, 127.4, 127.5, 127.6 (×6), 128.1 (×3), 128.2 (×2), 128.2 (×2), 138.5, 138.8, 138.8; HR-FAB MS calcd for $C_{34}H_{42}NaO_{11}$ [M + Na]$^+$ 649.2625, found 649.2640.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(β-D-glucopyranosyl)-α-D-glucopyranoside (27): The title compound was obtained from **23a** and **26**[40] by Method A in 56% yield as a white amorphous solid. Partial characterization data for compound **27** have been reported previously.[47] Spectral data for **27**: ^{1}H NMR (CD_3OD) δ 3.14−3.34 (m, 3H), 3.38 (s, 3H), 3.47−3.57 (m, 2H), 3.68−3.90 (m, 4H), 3.94−4.01 (m, 2H), 4.41 (d, 1H, J = 7.4 Hz), 4.51−4.75 (m, 6H), 4.77 (d, 1H, J = 3.7 Hz), 4.97 (d, 1H, J = 10.4 Hz), 6.61−7.43 (m, 15H) ppm; ^{13}C NMR (CD_3OD) δ 55.7, 63.4, 69.5, 71.8, 72.3, 74.3, 74.4, 75.9, 76.7, 77.4, 78.1, 78.9, 80.9, 81.8, 99.2, 103.7, 128.9, 129.0 (×2), 129.1 (×2), 129.3 (×2), 129.4 (×2), 129.6 (×4), 130.1 (×2), 139.7, 139.7 (×2) ppm; HR-FAB MS calcd for $C_{34}H_{42}NaO_{11}$ [M + Na]$^+$ 649.2625, found 649.2603.

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(β-D-glucopyranosyl)-α-D-glucopyranoside (29): The title compound was obtained from **23a** and **28**[41] by Method A in 98% yield as a white amorphous solid. Analytical data for **29**: R_f 0.33 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{26}_D$ +11.4 (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 3.10−3.28 (m, 6H), 3.42−3.71 (m, 8H), 4.13 (dd, 1H, J = 10.4 Hz), 4.36−4.58 (m, 5H), 4.68−4.77 (m, 2H), 4.87 (d, 1H, J = 11.4 Hz), 7.18−7.35 (m, 15H) ppm; ^{13}C NMR (CD_3OD) δ 55.7, 63.4, 70.0, 71.4, 72.5, 74.4, 74.6, 76.2, 76.7, 78.0, 78.1, 78.6, 78.9, 81.9, 99.2, 104.2, 129.0, 129.1, 129.2, 129.3 (×2), 129.5 (×2), 129.6 (×4), 129.8 (×2), 130.2 (×2), 139.3, 139.6, 139.8 ppm; HR-FAB MS calcd for $C_{34}H_{42}NaO_{11}$ [M + Na]$^+$ 649.2625, found 649.2655.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(β-D-glucopyranosyl)-α-D-glucopyranoside (31): The title compound was obtained from **23a** and **30**[42] by Method B in 49% yield as a white amorphous solid. Analytical data for **31**: R_f 0.29 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{27}_D$ +17.2 (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 3.11−3.32 (m, 6H), 3.44 (dd, 1H, J = 9.3 Hz), 3.53−3.84 (m, 8H), 4.36−4.64 (m, 5H), 4.64 (dd, 2H, J = 12.3 Hz), 4.82 (d, 1H, J = 3.5 Hz), 5.02 (d, 1H, J = 11.5 Hz), 7.04−7.29 (m, 15H) ppm; ^{13}C NMR (CD_3OD) δ 55.7, 62.9, 70.0, 71.6, 71.8, 74.5, 75.3, 76.2, 76.6, 78.2 (×2), 79.4, 81.0, 83.0, 101.3, 105.7, 128.7, 128.8, 128.9, 129.0 (×2), 129.2 (×2), 129.4 (×2), 129.5 (×2), 129.6 (×2), 129.7-(×2), 139.6, 139.8, 140.3; HR-FAB MS calcd for $C_{34}H_{42}NaO_{11}$ [M + Na]$^+$ 649.2625, found 649.2602.

6-*O*-(β-D-Glucopyranosyl)-1,2:3,4-*O*-isopropylidene-α-D-galactopyranose (33): The title compound was obtained from **23a** and commercial **32** by Method A in 45% yield as a white amorphous solid. Analytical data for **33**:[48] R_f 0.24 (methanol/dichloromethane, 1/6, v/v); $[\alpha]^{26}_D$ −50.8 (*c* 1, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.34, 1.35, 1.41, 1.53 (4s, 12H), 3.21 (dd, 1H, J = 7.8 Hz), 3.25−3.32 (m, 3H), 3.63−3.70 (m, 2H), 3.88 (dd, 1H, J = 11.3 Hz), 4.03−4.10 (m, 2H), 4.28−4.33 (m, 2H), 4.39 (dd, 1H, J = 2.4 Hz, J = 5.0 Hz), 4.64 (dd, 1H, J = 2.4 Hz, J = 7.9 Hz), 5.52 (d, 1H, J = 5.0 Hz) ppm; ^{13}C NMR (CD_3OD) δ 24.7, 25.3, 26.4, 62.9, 69.0, 70.0, 71.8, 72.1 (×2), 72.6, 75.2, 77.9, 78.1, 97.9, 104.9, 110.2, 110.6 ppm; HR-FAB MS calcd for $C_{18}H_{30}NaO_{11}$ [M + Na]$^+$ 445.1686, found 445.1688.

(3β)-Cholest-5-en-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (35): The title compound was obtained from **23a** and commercial **34** by Method A and acetylated prior to isolation as described for the synthesis of **17** in 51% yield as a white amorphous solid. Partial characterization data for compound **35** have been reported previously.[49] Spectral data for **35**: ^{1}H NMR ($CDCl_3$) δ 0.68−2.23 (m, 43H, cholestenyl), 3.49 (m, 1H, OCH cholestenyl), 3.69 (m, 1H, H-5), 4.12 (dd, 1H, $J_{5,6a}$ = 2.4 Hz, H-6$_a$), 4.27 (dd, 1H, $J_{5,6b}$ = 4.8 Hz, H-6$_b$), 4.60 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.93−4.99 (m, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 5.08 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.21 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3′), 5.36 (br d, 1H, =CH− cholestenyl) ppm; ^{13}C NMR ($CDCl_3$) δ 12.1, 18.9, 19.6 (×2), 20.8 (×2), 20.7, 20.9 (×2), 21.0 (×2), 22.8, 23.0 (×2), 24.0 (×2), 28.2, 29.7 (×2), 32.1, 36.0, 36.9, 39.7 (×2), 42.5, 50.4, 53.6, 56.4, 57.0, 68.8, 71.7, 71.9, 73.1, 76.8, 80.3, 99.9, 122.4, 140.6, 169.5, 169.6, 170.6, 170.9 ppm; HR-FAB MS calcd for $C_{41}H_{64}NaO_{10}$ [M + Na]$^+$ 739.4397, found 739.4365.

Ethyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (37): The title compound was obtained from **23a** and **36**[43] by Method B and acetylated prior to isolation as described for the synthesis of **17** in 37% yield as a white amorphous solid. The isolated sample was essentially the same as described previously.[50]

2-Thiazolinyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (39): The title compound was obtained from **23a** and **38**[36] by Method B and acetylated prior to isolation as described for the synthesis of **17** in 25% yield as a white amorphous solid. Analytical data for **39**: R_f 0.28 (ethyl acetate/hexanes, 3/2, v/v); $[\alpha]^{28}_D$ −10.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.00, 2.02, 2.04, 2.05, 2.06, 2.07, 2.10 (7s, 21H), 3.44 (m, 2H), 3.60−3.71 (m, 2H), 3.77−3.84 (m, 2H), 4.11−4.42 (m, 4H), 4.67 (d, 1H, J = 8.0 Hz), 4.90−4.99 (m, 2H), 5.04−5.20 (m, 3H), 5.26 (dd, 1H, J = 10.3 Hz), 5.47 (d, 1H, J = 10.4 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 20.8 (×4), 20.9 (×2), 21.0, 35.5, 61.9, 64.4, 67.8, 68.5, 68.9, 69.5, 71.3, 72.1, 73.1, 73.9, 76.8, 78.2, 83.0, 100.3, 169.6 (×2), 169.7, 169.8, 170.2, 170.5, 170.9 ppm; HR-FAB MS calcd for $C_{29}H_{39}NNaO_{17}S_2$ [M + Na]$^+$ 760.1557, found 760.1539.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-*O*-benzyl-β-D-glucopyranosyl)-D-glucopyranoside (40): The title compound was obtained from **23b** and **24**[33] by Method A in 54% yield (anomeric mixture α/β ≈ 1/1) as a white amorphous solid. Selected analytical data for **40**: R_f 0.25 (methanol/dichloromethane, 1/9, v/v); ^{1}H NMR (CD_3OD) δ 4.23 (d, 1H, J = 9.0 Hz), 4.56 (d, 1H, J = 3.6 Hz), 4.60 (d, 1H, J = 3.5 Hz), 4.95 (d, 1H, J = 3.4 Hz) ppm; ^{13}C NMR (CD_3OD) δ 98.6, 99.3, 99.3, 105.0 ppm; HR-FAB MS calcd for $C_{41}H_{48}NaO_{11}$ [M + Na]$^+$ 739.3094, found 739.3099.

Ethyl 2,3,4-tri-*O*-acetyl-6-*O*-(2-*O*-benzyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (41): The title compound was obtained from **23b** and **36**[43] by Method B and acetylated prior to isolation as described for the synthesis of **17** in 35% yield as a colorless foam. Analytical data for **41**: R_f 0.25 (ethyl acetate/hexanes, 2/3, v/v); $[\alpha]^{26}_D$ +39.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H), 1.93, 1.94, 1.97, 1.98, 1.99, 2.01 (6s, 18H), 2.63 (m, 2H), 3.41 (dd, 1H, J = 2.1 Hz, J = 10.3 Hz), 3.50 (dd,

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1H, J = 3.5 Hz, J = 10.0 Hz), 3.61−3.76 (m, 2H), 3.95 (dd, 1H, J = 1.9 Hz, J = 12.3 Hz), 4.07 (m, 1H), 4.21 (dd, 1H, J = 4.0 Hz, J = 12.4 Hz), 4.45 (d, 1H, J = 10.1 Hz), 4.55 (dd, 2H), 4.71 (d, 1H, J = 3.4 Hz), 4.83−4.93 (m, 3H), 5.17 (dd, 1H, J = 9.3 Hz), 5.36 (dd, 1H, J = 9.6 Hz), 7.21−7.28 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 15.1, 20.8 (×2), 20.9 (×2), 21.0, 24.7, 62.0, 67.4, 67.5 (×2), 68.6, 69.6, 70.2, 71.9, 73.3, 74.0, 76.8, 77.9, 83.6, 96.8, 128.0 (×2), 128.2, 128.7 (×2), 137.9, 169.6, 169.8, 169.9, 170.2, 170.3, 170.8 ppm; HR-FAB MS calcd for $C_{33}H_{44}NaO_{16}S$ $[M + Na]^+$ 751.2248, found 751.2263.

Methyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (42): Building blocks **23a** and **36** were reacted in accordance with Method B. Prior to cleaving off the solid support, the dried residue containing the immobilized intermediate disaccharide (0.06 mmol) was mixed with glycosyl acceptor **24** (0.18 mmol) and molecular sieves (4 Å, 200 mg), and the resulting mixture was agitated in dry dichloromethane (4 mL) for 12 h at room temperature. Then NIS (0.24 mmol) and TfOH (0.0024 mmol) were added and the reaction mixture was agitated for 72 h at room temperature under argon. The resin was separated by sintered filter, washed successively with methanol (5 × 5 mL) and dichloromethane (5 × 5 mL), and dried in vacuo. The residual resin was then subjected to treatment with NaOMe as described for Method A followed by acetylation as described for the synthesis of **17**. The crude residue was purified by column chromatography to afford the title trisaccharide **42** and methyl 6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**43**) as colorless foams in 30% and 15%, respectively. Analytical data for **42**: R_f 0.46 (ethyl acetate/hexanes, 1/1, v/v); $[\alpha]^{27}_D$ −0.62 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.81, 1.91, 191, 1.92, 1.94, 1.95, 2.00 (7s, 21H), 3.30 (s, 3H), 3.38−3.47 (m, 2H), 3.52−3.78 (m, 6H), 3.90 (dd, 1H, J = 9.3 Hz), 3.98−4.06 (m, 2H), 4.18 (dd, 1H, J = 4.8 Hz, J = 12.3 Hz), 4.44−4.54 (m, 4H), 4.57 (d, 1H, J = 13.5 Hz), 4.70−5.12 (m, 10H), 7.17−7.31 (m, 15H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.3, 20.8 (×6), 20.9 (×2), 29.9 (×2), 55.5 (×2), 62.0, 68.45, 69.2 (×2), 71.3, 71.6, 72.2, 72.9, 73.2, 73.7, 73.8, 75.9, 77.6, 82.1, 98.5, 100.9, 127.8, 127.9, 128.1 (×2), 128.2, 128.4, 128.6, 128.7, 128.8, 138.3 (×2), 138.4 (×2), 138.9 (×2), 169.2, 169.3, 169.6, 169.8, 170.2, 170.6, 170.1, 170.3, 170.5, 170.8 ppm; HR-FAB MS calcd for $C_{54}H_{66}NaO_{23}$ $[M + Na]^+$ 1105.3893, found 1105.3871.

Characterization data for **43** were essentially the same as those reported previously.[51]

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Supporting Information Available: Spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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