

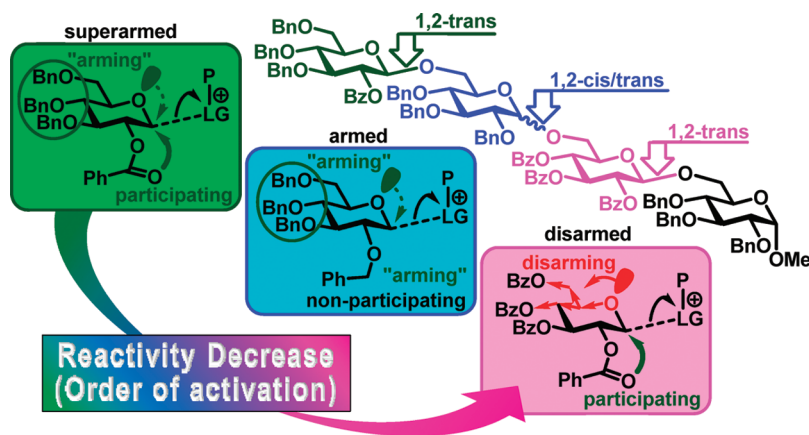
## Superarming Common Glycosyl Donors by Simple 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl Protection

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A complementary concept for superarming glycosyl donors through the use of common protecting groups was previously discovered with *S*-benzoxazolyl (SBox) glycosyl donors. As this strategy can be of benefit to existing oligosaccharide methodologies, it has now been expanded to encompass a wide array of common, stable glycosyl donors. The versatility of this developed technique has been further illustrated in application to a sequential chemoselective oligosaccharide synthesis, wherein a superarmed ethyl thioglycoside was incorporated into the conventional armed–disarmed strategy.

### Introduction

Only recently has the tremendous biological significance and therapeutic potential of carbohydrates and conjugates thereof (glycoproteins, glycolipids, proteoglycans, etc.) begun to emerge.<sup>1</sup> However, success in studying these fascinating biomolecules has proven to be directly correlated to the availability of the involved carbohydrates. With the low availability of pure natural isolates, the invention of efficient chemical and enzymatic methods for the synthesis of complex carbohydrates has become increasingly important. This need has led to the development of many excellent new methods for glycoside synthesis,<sup>2,3</sup> from which a variety of

expeditious strategies for oligosaccharide assembly have surfaced.<sup>4,5</sup> Among these, the armed–disarmed strategy is of particular interest.<sup>6,7</sup> As first introduced by Fraser-Reid and co-workers, this approach allows for the expeditious synthesis of oligosaccharides while necessitating only one type of anomeric leaving group. Thus, the reactivities of the building blocks involved in such chemoselective activations are differentiated by the electronic and/or torsional effects of the protecting groups.<sup>8–10</sup> Though initially discovered with

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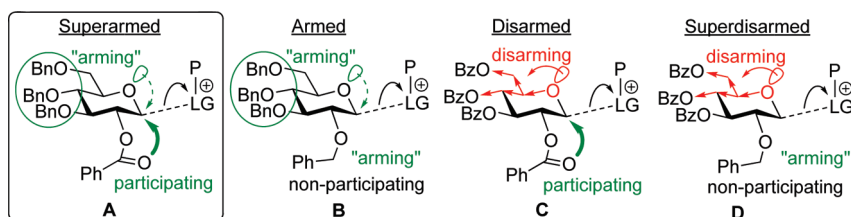


FIGURE 1. Cooperative arming and disarming effects.

*O*-pentenyl glycosides, the armed–disarmed concept has since been proven with many other classes of glycosyl donors.<sup>5</sup>

This strategy led to the commonly accepted belief that benzylated derivatives are *always* significantly more reactive than their benzoylated counterparts and that the overall glycosyl donor reactivity is in direct correlation with the total number of benzyl substituents.<sup>11</sup> However, this presumption was challenged with the discovery of the *O*-2/*O*-5 cooperative effect, wherein it was observed that glycosyl donors with mixed protecting group patterns showed unexpected reactivity trends.<sup>12</sup> This was the first indication that the reactivity of the glycosyl donor was *not limited* to the electron-withdrawing/-donating (or torsional) effects of its protecting groups. Therein, it was proposed that the reactivity of glycosyl donors was also influenced by how well the glycosyl cation, formed upon promoter (P)-assisted leaving group (LG) departure, could self-stabilize. As depicted in Figure 1, in the case of the armed, benzylated glycosyl donor (B), stabilization can be efficiently achieved via the oxacarbenium intermediate through resonance with the electronically “armed” lone pair electrons of *O*-5. However, in the case of the per-benzoylated derivative (C), this type of stabilization would be less likely due to the electron-withdrawing substituents at C-4 and C-6. Instead, the acyl substituent at C-2 allows for stabilization via the acyloxonium intermediate. Therefore, the combination of these two opposing effects results in the decreased reactivity of disarmed donor (C) relative to B.

It then follows that a glycosyl donor wherein there is no stabilization/participating group at C-2, and electron-withdrawing groups at the remaining positions, would be even further deactivated, as is the case for superdisarmed glycosyl donor (D).<sup>12</sup> Crich and Li additionally investigated this phenomenon for the *S*-benzoxazolyl (SBox) glycosyl donors of the *D*-gluco series, finding that in order for this C-2 stabilization to occur, a 1,2-*trans* anomeric configuration is necessary.<sup>13</sup> This suggests that the lone pair at C-2 must *also* have access to the developing positive charge as the leaving group departs implying that anchimeric assistance is in part, if not fully, responsible for the observed C-2 effect. Building upon this concept, we then determined that glycosyl donors possessing a participating moiety at C-2 and an electronically armed lone pair at *O*-5 (A) would have exceptionally high reactivity as the both stabilizing effects would be combined.<sup>14,15</sup>

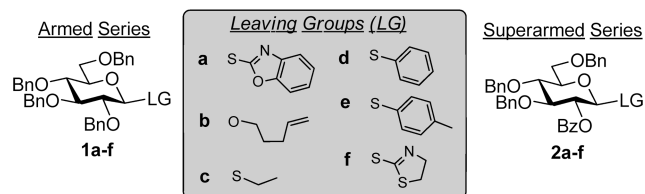


FIGURE 2. Glycosyl donors of the armed and superarmed series.

## Results and discussion

This concept of superarming was previously explored with benzoxazolyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio- $\beta$ -*D*-glucopyranosides (SBox glycosides) of the *D*-gluco, *D*-galacto, and *D*-manno series;<sup>14,15</sup> however, it remained unclear whether this principle could be applied to other classes of leaving groups. Previously, the term “superarmed” was coined by Bols and co-workers in their recent publications in reference to conformationally modified glycosyl donors.<sup>16–18</sup> Herein, we describe the investigation of stable glycosyl donors of the armed (1) and superarmed (2) series, bearing common leaving groups: *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl, and *S*-thiazolyl (STaz, Figure 2). All test glycosylations were performed with the standard glycosyl acceptor **3**<sup>19</sup> to afford disaccharides **4**<sup>20</sup> and **5**<sup>20</sup> from glycosyl donors of the armed and superarmed series, respectively (Table 1). Additionally, the obtained results were compared to the previously investigated SBox glycosides **1a**<sup>21</sup> and **2a**.<sup>14</sup>

It should be noted that the key feature of any chemoselective activation lies in choosing suitable reaction conditions that will allow for the reactivity levels of the building blocks to be differentiated. However, establishing a reactivity differentiation becomes increasingly difficult with the highly reactive superarmed and armed glycosyl donors. In our previous work, we described that the reactivity of armed and superarmed SBox glycosides, **1a** and **2a**, respectively, can be effectively separated in the presence of dimethyl(methylthio)sulfonium trifluoromethanesulfonate<sup>22</sup> (DMTST) as a promoter (Table 1, entries 1 and 2).<sup>14</sup> Herein, we also determined that an equally successful differentiation can be achieved in the presence of copper(II) trifluoromethanesulfonate

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**TABLE 1. Comparative Activation of Armed (1) and Superarmed (2) Glycosyl Donors**

Glycosyl Donor (D)		Glycosyl Acceptor		Coupling Product (CP)			
entry	D	P	temp (°C)	time	CP	yield (%)	α/β
1	<b>1a</b>	DMTST	0	2 h	<b>4</b>	92	2:1
2	<b>2a</b>	DMTST	0	5 min	<b>5</b>	86	β only
3	<b>1a</b>	Cu(OTf) <sub>2</sub>	0	2 h	<b>4</b>	99	2:1
4	<b>2a</b>	Cu(OTf) <sub>2</sub>	0	20 min	<b>5</b>	96	β only
5	<b>1b</b>	IDCP	-10	20 h	<b>4</b>	62	3:1
6	<b>2b</b>	IDCP	-10	3 h	<b>5</b>	53	β only
7	<b>1c</b>	IDCP	-10	96 h	<b>4</b>	82	2:1
8	<b>2c</b>	IDCP	-10	96 h	<b>5</b>	78	β only
9	<b>1c</b>	MeOTf	0	18 h	<b>4</b>	95	2:1
10	<b>2c</b>	MeOTf	0	6 h	<b>5</b>	96	β only
11	<b>1c</b>	DMTST	-20	1 h	<b>4</b>	90	2:1
12	<b>2c</b>	DMTST	-20	10 min	<b>5</b>	89	β only

(Table 1, entries 3 and 4). This result offers further significance, as Cu(OTf)<sub>2</sub> is a promoter unique to thioimidoyl leaving groups.

In order to differentiate between armed and superarmed *O*-pentenyl glycosides, **1b**<sup>23</sup> and **2b**,<sup>24</sup> respectively, we chose iodonium(di- $\gamma$ -collidine)perchlorate<sup>25</sup> (IDCP), as this mild promoter has proven effective for chemoselectively activating armed pentenyl glycosides over their disarmed counterparts at rt.<sup>6</sup> However, these reaction conditions were found to be too powerful, as both glycosyl donors **1b** and **2b** were activated in a matter of minutes at rt. Additionally, no significant difference in reactivity was observed when *O*-pentenyl glycosides were investigated in the presence of NIS (rt), NBS (45 °C), or NIS/TfOH (-20 °C), albeit in a majority of the comparative glycosylations, superarmed donor **1b** was slightly *more reactive* (the extended experimental results are available as a part of the Supporting Information). Ultimately, the application of IDCP at low temperature (-10 °C) was deemed the most successful in terms of the differential activation of *O*-pentenyl glycosides. Thus, 20 h was required for the glycosidation of **1b**, whereas the glycosidation of **2b** was complete in about 3 h (Table 1, entries 5 and 6). The yields obtained with both armed and superarmed pentenyl glycosides under these reaction conditions, however, remained modest (62% and 53%, respectively).

Consequently, we investigated *S*-ethyl glycosides **1c**<sup>26</sup> and **2c**<sup>27</sup> in the presence of relatively mild promoters, including IDCP, DMTST, and MeOTf at reduced temperatures (Table 1, entries 7–12). While reactions in the presence of IDCP showed an insufficient difference in reactivity (Table 1, entries 7 and 8), the best differentiation was achieved with

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**TABLE 2. Activation of Armed (1) and Superarmed (2) Glycosyl Donors in the Presence of Iodine (3 Molar Equiv)**

entry	donor	time (h)	product	yield (%)	ratio α/β
1	<b>1c</b>	10	<b>4</b>	89	1:4
2	<b>2c</b>	1	<b>5</b>	93	β only
3	<b>1d</b>	15	<b>4</b>	74	1:2
4	<b>2d</b>	8	<b>5</b>	78	β only
5	<b>1e</b>	15	<b>4</b>	63	1:2
6	<b>2e</b>	12	<b>5</b>	72	β only
7	<b>1f</b>	19	<b>4</b>	87	1:2
8	<b>2f</b>	19	<b>5</b>	85	β only
9	<b>1b</b>	17	<b>4</b>	82	1:2.8
10	<b>2b</b>	17	<b>5</b>	84	β only
11	<b>1a</b>	48	<b>4</b>	NR <sup>a</sup>	
12	<b>2a</b>	20	<b>5</b>	95	β only

<sup>a</sup>NR: no reaction, although glycosyl donor **1a** smoothly reacted at rt in 13 h affording disaccharide **4** in 95% (α:β = 1:2).

MeOTf at 0 °C or DMTST at -20 °C, wherein a 3- and 6-fold increase in reactivity was achieved, respectively (Table 1, entries 9–12). Additionally, the yields for both armed and superarmed glycosyl donors were good to excellent across the board. Upon investigating a variety of other known thioglycoside promoters,<sup>28–30</sup> we found results with molecular iodine, introduced by Field as a mild promoter for the activation of methyl thioglycosides,<sup>31</sup> at -25 °C to be the most impressive. Thus, while activation of the armed glycosyl donor **1c** required at least 10 h, the reaction of its superarmed counterpart **2c** completed in less than 1 h, displaying a 10-fold reactivity increase (Table 2, entries 1 and 2). Encouraged by these results, iodine was tested as the promoter in subsequent studies with *O*-pentenyl donors (**1b** and **2b**), as well as common classes of thioglycoside donors,<sup>28–30</sup> *S*-phenyl (**1d**<sup>32</sup> and **2d**<sup>33</sup>), *S*-tolyl (**1e**<sup>34</sup> and **2e**), and STaz glycosides (**1f**<sup>35</sup> and **2f**). Although we observed that the superarmed glycosyl donors of both the *S*-phenyl and *S*-tolyl series reacted faster (Table 2, entries 3–6), no significant differentiation was achieved under these reaction conditions.

Furthermore, no reactivity differentiation could be established in the presence of iodine between the armed and superarmed STaz glycosyl donors **1f** and **2f**, or between *O*-pentenyl glycosides **1b** and **2b**, respectively (Table 2, entries

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**TABLE 3. Competitive Activations of *S*-Ethyl Glycosyl Donors: **1c** (Armed) vs **2c** (Superarmed)**

entry	Glycosyl Donors		Glycosyl Acceptor	Coupling Products	
	<b>1c</b> (1.1 equiv)	<b>2c</b> (1.1 equiv)	<b>3</b> (1 equiv)	<b>4</b>	<b>5</b>
	temp (°C)	time (h)	ratio <b>4:5</b> <sup>a</sup>	yield of <b>4</b> <sup>b</sup> (%) ( $\alpha/\beta$ )	yield of <b>5</b> <sup>b</sup> (%) ( $\alpha/\beta$ )
1	rt	1	1:0.8	53 (1:1.7)	45 ( $\beta$ only)
2	-10	1	1:2.4	22 (1:4)	51 ( $\beta$ only)
3	-25	3	1:4	14 (1:4)	62 ( $\beta$ only)
4	-35	24	1:1.5	11 (1:5)	26 ( $\beta$ only)

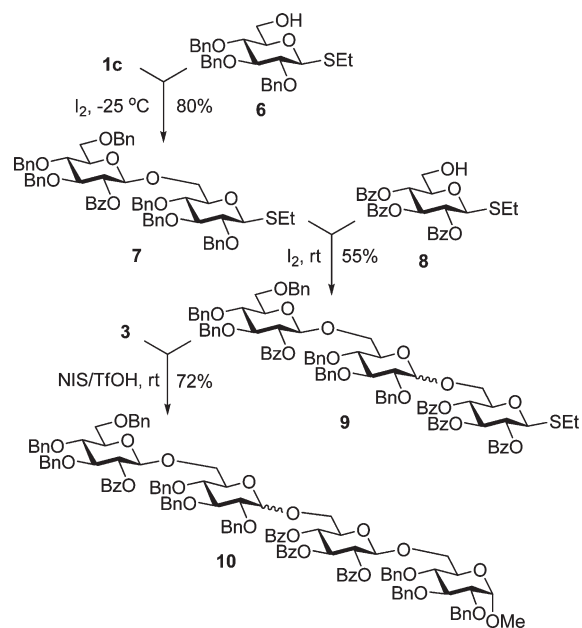
<sup>a</sup>Determined by comparing integral intensities of the corresponding signals in the NMR spectra recorded for the crude reaction mixtures.  
<sup>b</sup>Isolated yields.

7–10). Although both *O*-pentenyl and STaz glycosides easily react in accordance with the conventional armed–disarmed activation scheme,<sup>6,36</sup> we have found the differentiation between the more closely positioned superarmed and armed glycosides to be challenging. It is possible that the protecting group effect is decreased in cases of remote activation,<sup>37</sup> as is typical for both the *O*-pentenyl and STaz glycosides (alkene<sup>7</sup> and nitrogen atom of the thiazoline ring,<sup>38</sup> respectively) and is opposite in cases of direct activation<sup>21</sup> cases (anomeric sulfur atom of *S*-ethyl and SBox glycosyl donors).

Following this rationale, we additionally tested the armed and superarmed SBox donors (**1a** and **2a**, respectively) wherein we found that the reactivity difference between them in the presence of iodine at -25 °C was remarkable (Table 2, entries 11 and 12). While no reaction took place with the armed glycosyl donor **1a**, the superarmed glycosyl donor **2a** reacted very smoothly and afforded the corresponding disaccharide **5** in 20 h (95%). It should be noted that the armed SBox glycoside **1a** can also be activated with iodine, but this was only accomplished at rt. Interestingly, the fact that the SBox glycosides reacted much slower than their *S*-ethyl counterparts was rather unanticipated, as SBox glycosides are typically much more reactive and can be selectively activated in the presence of alkyl/aryl thioglycosides.<sup>21,39</sup>

As verification of the promising results obtained with *S*-ethyl glycosides in the presence of iodine, we set up direct competitive glycosylations. To optimize the reaction conditions for a chemoselective oligosaccharide assembly, the competitive glycosylations were investigated at a variety of reaction temperatures (Table 3). These reactions were carried out by placing equimolar amounts (1.1 equiv each) of the armed **1c** and superarmed **2c** glycosyl donors in the same reaction vessel with glycosyl acceptor **3** (1 equiv). Upon addition of iodine (3 equiv), both glycosyl donors competed for the same acceptor to form either disaccharide **4** or **5**. The highest product ratio in these competitive glycosylations was also obtained at -25 °C, wherein the 1,2-*trans*-linked dis-

**SCHEME 1. Sequential Activation of Differently Protected *S*-Ethyl Building Blocks: Synthesis of Tetrasaccharide **10****



accharide **5** (derived from superarmed glycosyl donor **2c**) was isolated in 62% yield (Table 3, entry 3). Conversely, the disaccharide **4** (derived from armed glycosyl donor **1c**) was isolated in only 14% yield ( $\alpha/\beta = 1:4$ ).

Having investigated the superarming and arming effects in direct competitive glycosylations with glycosyl donors of the *S*-ethyl series, we now turned our attention to a sequential tetrasaccharide synthesis. To begin, the chemoselective activation of the superarmed glycosyl donor **2c** over the “armed” glycosyl acceptor **6**<sup>40</sup> was successfully carried out in the presence of iodine at -25 °C (Scheme 1). Subsequently, the resulting armed disaccharide **7**, obtained in 80% yield, was coupled with “disarmed” glycosyl acceptor **8**.<sup>41</sup> This chemoselective activation was also performed in the presence of iodine, but this time at rt. The resulting trisaccharide **9**, obtained in 55% yield ( $\alpha/\beta = 1:2.6$ ), was then reacted with glycosyl acceptor **3** in the presence of NIS/TfOH, and the resulting tetrasaccharide **10** was isolated in 72% yield. Overall, this synthesis serves as ultimate proof of the utility of this superarmed approach in chemoselective oligosaccharide synthesis.

In conclusion, a promising new concept for superarming glycosyl donors through the use of common protecting groups has now been extended to encompass a range of common glycosyl donors. Although it was initially necessary to fine-tune the reaction conditions and carefully select an adequate (mild) promoter, once established, the reactivity of the superarmed glycosyl donors was able to be exploited. This approach ultimately provides an additional synthetic building block that can be integrated into the conventional chemoselective armed–disarmed strategy. Results obtained herein were both consistent and high yielding, thus, offering this is a general methodology for cases wherein a 1,2-*trans* linkage must be introduced prior to other linkages.

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Additionally, the superarmed glycosyl donors can be easily obtained by conventional synthetic methods. Currently, further application of this superarmed concept toward selective activation and orthogonal approaches to oligosaccharide synthesis is under pursuit in our laboratory.

## Experimental Section

**Preparation of Superarmed Glycosyl Donors 2e and 2f.** *p*-Methylphenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-1-thio- $\beta$ -D-glucopyranoside (**2e**). The title compound was obtained using a modified protocol similar to that previously reported.<sup>7,8,14</sup> CH<sub>2</sub>Cl<sub>2</sub> (9.0 mL) and *p*-toluenethiol (1.6 g, 13.03 mmol) were added to 3,4,6-tri-*O*-benzyl-1,2-*O*-(methylorthobenzoate)  $\alpha$ -D-glucopyranoside<sup>14</sup> (740 mg, 1.31 mmol) and molecular sieves (3 Å, 850 mg), and the resulting mixture was stirred under argon for 45 min. Trimethylsilyl trifluoromethanesulfonate (6  $\mu$ L, 0.328 mmol) was added, and the reaction mixture was stirred under argon for 16 h at rt. After that, the reaction mixture was neutralized by the addition of triethylamine (~0.1 mL) and diluted with CH<sub>2</sub>Cl<sub>2</sub>, and the solid was filtered off and rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (~30 mL) was washed with water (10 mL), 20% aq NaHCO<sub>3</sub> (10 mL), and water (3  $\times$  10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes gradient elution) to afford the title compound **2e** as a white solid in 70% yield. Analytical data for **2e**:  $R_f$  = 0.54 (ethyl acetate/hexanes, 3/7, v/v); mp 134–135 °C (diethyl ether/hexanes);  $[\alpha]_D^{22} + 32.5$  ( $c$  = 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR  $\delta$  2.18 (s, 3H, SPHCH<sub>3</sub>), 3.48 (m, 1H,  $J_{5,6a}$  = 1.9 Hz,  $J_{5,6b}$  = 3.6 Hz, H-5), 3.62 (dd, 1H,  $J_{4,5}$  = 9.5 Hz, H-4), 3.65–3.78 (m, 3H, H-3, 6a, 6b), 4.42–4.75 (m, 6H, 3  $\times$  CH<sub>2</sub>Ph), 4.61 (d, 1H,  $J_{1,2}$  = 10.0 Hz, H-1), 5.14 (dd, 1H,  $J_{2,3}$  = 9.0 Hz, H-2), 6.80–8.00 (m, 24H aromatic) ppm; <sup>13</sup>C NMR  $\delta$  21.3, 69.1, 72.7, 73.7, 75.2, 75.5, 76.8, 77.2, 77.4, 77.7, 78.0, 79.7, 84.5, 86.4, 127.7 ( $\times$ 3), 127.8 ( $\times$ 3), 127.8 ( $\times$ 3), 128.0, 128.1 ( $\times$ 2), 128.3, 128.4 ( $\times$ 2), 128.5 ( $\times$ 2), 128.7 ( $\times$ 2), 128.8 ( $\times$ 2), 128.9 ( $\times$ 2), 128.9 ( $\times$ 3), 129.1, 130.0 ( $\times$ 2), 130.3 ( $\times$ 2), 130.4, 133.6, 133.9 ( $\times$ 3), 138.1, 138.4, 138.5, 138.7, 165.3 ppm; HR-FAB MS  $[M + Na]^+$  calcd for C<sub>41</sub>H<sub>40</sub>O<sub>6</sub>Na<sup>+</sup> 683.2443, found 683.2624.

**Thiazoliny 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-1-thio- $\beta$ -D-glucopyranoside (**2f**).** The title compound was obtained using a modified protocol similar to that previously reported.<sup>42</sup> 3,4,6-Tri-*O*-benzyl-1,2-*O*-(methylorthobenzoate)  $\alpha$ -D-glucopyranoside<sup>14</sup> (200 mg, 0.35 mmol) was mixed with molecular sieves (3 Å, 1.2 g) and 2-mercaptothiazoline (420 mg, 3.52 mmol) and dried in vacuo for 15 min. Acetonitrile (2.6 mL) was added, and the resulting mixture was stirred under argon for 1 h. Mercuric bromide (13 mg, 0.035 mmol) was added, and the resulting reaction mixture was heated at reflux for 16 h. The volatiles were evaporated under reduced pressure, the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and the solid was filtered off and rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 1 N aq NaOH (10 mL) and water (3  $\times$  10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the title compound **2f** as a white solid in 70% yield. Analytical data for **2f**:  $R_f$  = 0.47 (ethyl acetate/hexane, 4/6, v/v); mp 141–143 °C (diethyl ether–hexanes);  $[\alpha]_D^{22} + 81.2$  ( $c$  = 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR  $\delta$  3.43 (m, 2H, NCH<sub>2</sub>), 3.82 (m, 1H, H-5), 3.88–3.98 (m, 2H, H-6a, 6b), 4.03 (dd, 1H,  $J_{4,5}$  = 9.1 Hz, H-4), 4.05 (dd, 1H,  $J_{3,4}$  = 8.8 Hz, H-3), 4.30 (m, 2H, CH<sub>2</sub>S), 4.75 (dd, 2H,  $J^2$  = 11.9 Hz, CH<sub>2</sub>Ph), 4.85 (dd, 2H,  $J^2$  = 10.9 Hz, CH<sub>2</sub>Ph), 4.87 (dd, 2H,  $J^2$  =

11.0 Hz, CH<sub>2</sub>Ph), 5.55 (dd, 1H,  $J_{2,3}$  = 8.5 Hz, H-2), 5.67 (d, 1H,  $J_{1,2}$  = 10.3 Hz, H-1), 7.22–8.20 (m, 20H, aromatic) ppm; <sup>13</sup>C NMR  $\delta$  35.6, 64.3, 68.8, 72.4, 73.6, 75.3, 75.5, 77.8, 80.0, 83.1, 84.3, 127.8, 127.9, 128.0, 128.1 ( $\times$ 2), 128.1 ( $\times$ 2), 128.2 ( $\times$ 2), 128.5 ( $\times$ 2), 128.6 ( $\times$ 3), 128.6 ( $\times$ 2), 129.7, 130.1 ( $\times$ 2), 133.5, 137.9, 138.2, 138.3, 163.7, 165.4 ppm; HR-FAB MS  $[M + Na]^+$  calcd for C<sub>37</sub>H<sub>37</sub>NO<sub>6</sub>S<sub>2</sub>Na<sup>+</sup> 678.1959, found 678.1977.

**Preparation of Di- And Oligosaccharides (4, 5, 7, 9, and 10).** **Method A: Typical DMTST-Promoted Glycosylation Procedure.** A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in 1,2-dichloroethane (DCE, 1.6 mL) was stirred under argon for 1 h. The mixture was chilled to 0 or –20 °C (see Table 1), DMTST<sup>22</sup> (0.33 mmol) was added, and the reaction mixture was stirred for 5 min to 2 h (see Table 1). Upon completion, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and the solid was filtered off and rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 20% aq NaHCO<sub>3</sub> (10 mL) and water (3  $\times$  10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution).

**Method B: Typical Cu(OTf)<sub>2</sub>-Promoted Glycosylation Procedure.** A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 1 h followed by the addition of freshly conditioned Cu(OTf)<sub>2</sub> (0.22 mmol). The reaction mixture was stirred for 20 min to 2 h at 0 °C (see Table 1) and then diluted with CH<sub>2</sub>Cl<sub>2</sub>, the solid was filtered off and rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 20% aq NaHCO<sub>3</sub> (10 mL) and water (3  $\times$  10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution).

**Method C: Typical IDCP-Promoted Glycosylation Procedure.** A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 1 h. The reaction mixture was then chilled to –10 °C, IDCP<sup>25</sup> (0.22 mmol) was added, and the reaction mixture was stirred for 3–96 h (see Table 1). Upon completion, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and the solid was filtered off and rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 20% NaHCO<sub>3</sub> (10 mL) and water (3  $\times$  10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution).

**Method D: Typical MeOTf-Promoted Glycosylation Procedure.** A mixture containing the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 1 h. The mixture was chilled to 0 °C, MeOTf (0.39 mmol) was added, and the reaction mixture was stirred for 6–18 h (see Table 1). The mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub>, the solid was filtered off, and the residue was rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 20% NaHCO<sub>3</sub> (10 mL) and water (3  $\times$  10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution).

**Method E: Typical Iodine-Promoted Glycosylation Procedure.** A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 16 h. The mixture was chilled to –25 °C (or as indicated in Table 3 or Scheme 1), iodine (0.33 mmol) was added, and the reaction mixture was stirred for 1–48 h (see Table 2). Upon completion,

(42) Beignet, J.; Tiernan, J.; Woo, C. H.; Benson, M. K.; Cox, L. R. *J. Org. Chem.* **2004**, *69*, 6341–6356.

the mixture was quenched with Et<sub>3</sub>N and diluted with CH<sub>2</sub>Cl<sub>2</sub>, the solid was filtered off, and the residue was rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and water (3 × 10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution).

**Method F: Typical NIS/TfOH-Promoted Glycosylation Procedure.** A mixture containing the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in DCE (1.6 mL) was stirred under argon for 16 h. NIS (0.22 mmol) and TfOH (0.022 mmol) were added, and the reaction mixture was stirred for 1 h. Upon completion, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, the solid was filtered off, and the residue was rinsed successively with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate (30 mL) was washed with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and water (3 × 10 mL). The organic phase was separated, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution).

**Methyl O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (4).** The spectroscopic and analytical data for the title compound were in good agreement with those reported previously.<sup>20</sup>

**Methyl O-(2-O-Benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (5).** The spectroscopic and analytical data for the title compound were in good agreement with those reported previously.<sup>20</sup>

**Ethyl O-(2-O-Benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside (7).** The title compound was obtained as a colorless syrup from **1c**<sup>26</sup> and **6**<sup>40</sup> by method E in 80% yield. Analytical data for **7**: *R*<sub>f</sub> = 0.4 (ethyl acetate/hexanes, 3/7, v/v); [α]<sub>D</sub><sup>23</sup> +18.4 (*c* = 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR δ 1.13 (t, 3H, *J* = 8.0 Hz, SCH<sub>2</sub>CH<sub>3</sub>), 2.51 (m, 2H, SCH<sub>2</sub>CH<sub>3</sub>), 3.31 (dd, 1H, *J*<sub>2,3</sub> = 9.0 Hz, H-2), 3.32–3.46 (m, 2H, H-4, 5), 3.48–3.65 (m, 3H, H-3, 5', 6a), 3.67–3.82 (m, 4H, H-3', 4', 6a', 6b'), 4.10 (d, 1H, *J*<sub>5,6b</sub> = *J*<sub>6a,6b</sub> = 10.5 Hz, H-6b), 4.32 (d, 1H, *J*<sub>1,2</sub> = 9.7 Hz, H-1), 4.40–4.87 (m, 13H, H-1', 6 × CH<sub>2</sub>Ph), 5.31 (br dd, 1H, H-2'), 7.05–8.00 (m, 35H, aromatic) ppm; <sup>13</sup>C NMR δ 15.2, 24.7, 29.9, 68.4, 69.2, 74.0, 75.4, 75.7, 75.8, 75.8, 76.0, 77.6, 78.4, 79.1, 82.0, 83.3, 84.9, 86.9, 101.4, 128.0 (×2), 128.1 (×4), 128.2 (×3), 128.2 (×4), 128.4 (×4), 128.4 (×4), 128.6 (×3), 128.8 (×6), 128.8 (×5), 128.8 (×5), 130.2 (×2), 138.2, 138.4 (×2), 138.5, 166.0 ppm; HR-FAB MS [*M* + Na]<sup>+</sup> calcd for C<sub>63</sub>H<sub>66</sub>O<sub>11</sub>SNa<sup>+</sup> 1053.4224, found 1053.4238.

**Ethyl O-(2-O-Benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1 → 6)-O-(2,3,4-tri-O-benzyl-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside (9).** The title compound was obtained as a pale yellow syrup from **7** and **8**<sup>41</sup> by

method E (rt) in 55% yield (α/β = 1:2.6). Analytical data for **9**: *R*<sub>f</sub> = 0.3 (ethyl acetate/hexane, 3/7, v/v); <sup>1</sup>H NMR (selected data for β-**9**) δ 1.13 (t, 3H, *J* = 8.0 Hz, SCH<sub>2</sub>CH<sub>3</sub>), 2.65 (m, 2H, SCH<sub>2</sub>CH<sub>3</sub>), 3.26 (dd, 1H, *J*<sub>2',3'</sub> = 8.9 Hz, H-2'), 3.30–3.58 (m, 4H, H-3', 4', 5', 6a), 3.62–4.20 (m, 9H, H-3'', 4'', 5, 5'', 6a', 6a'', 6b, 6b', 6b''), 4.35 (d, 1H, *J*<sub>1',2'</sub> = 7.7 Hz, H-1'), 4.35–4.95 (m, 14H, H-1, 1'', 12 × CH<sub>2</sub>Ph), 5.32 (dd, 1H, *J*<sub>2'',3''</sub> = 9.5 Hz, H-2''), 5.38 (dd, 1H, *J*<sub>4,5</sub> = 7.0 Hz, H-4), 5.49 (dd, 1H, *J*<sub>2,3</sub> = 9.7 Hz, H-2), 5.86 (dd, 1H, *J*<sub>3,4</sub> = 9.7 Hz, H-3), 7.05–8.15 (m, 50H aromatic) ppm; <sup>13</sup>C NMR δ 15.0 (×2), 24.4, 29.9, 69.0, 70.4, 70.9, 73.7 (×2), 74.1, 74.4, 74.9 (×2), 75.2, 75.2, 75.4, 75.6, 77.7, 78.1, 78.4 (×2), 82.3, 83.0, 83.9, 84.6, 101.4, 103.9, 127.6 (×2), 127.8 (×2), 127.8 (×2), 127.9, 128.0, 128.1 (×4), 128.2 (×2), 128.4, 128.4 (×4), 128.5 (×4), 128.6 (×5), 128.7, 129.0, 129.1, 129.5, 129.9 (×2), 130.0, 130.0 (×2), 130.1, 133.2, 133.4 (×2), 133.6 (×2), 138.1 (×2), 138.2 (×2), 138.3, 138.4 (×2), 138.8 (×4), 165.3 (×2), 165.4 (×2), 165.6 (×3), 166.0 (×2) ppm; HR-FAB MS [*M* + Na]<sup>+</sup> calcd for C<sub>90</sub>H<sub>88</sub>O<sub>19</sub>SNa<sup>+</sup> 1527.5538, found 1527.5558.

**Methyl O-(2-O-Benzoyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1 → 6)-O-(2,3,4-tri-O-benzyl-D-glucopyranosyl)-(1 → 6)-O-(2,3,4-tri-O-benzyl-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (10).** The title compound was obtained as a colorless syrup **3** and **9** by method F in 72% yield. Selected analytical data for β-**10**: *R*<sub>f</sub> = 0.66 (ethyl acetate/hexane, 2/3, v/v); <sup>1</sup>H NMR δ 4.24 (d, 1H, *J*<sub>1'',2''</sub> = 7.8 Hz, H-1''), 4.29 (d, 1H, *J*<sub>1,2</sub> = 3.3 Hz, H-1), 4.44 (d, 1H, H-1'), 4.47 (d, 1H, H-1''') ppm; <sup>13</sup>C NMR δ 55.7, 67.7, 68.4, 68.8, 69.8, 70.0, 72.2, 73.3, 73.9, 74.3, 74.8, 74.9, 75.0, 75.4, 75.6, 75.8, 77.6 (×2), 77.9, 78.2, 79.6 (×2), 80.1, 82.2, 83.1, 98.3, 98.5, 101.0, 101.6, 127.4 (×3), 127.8, 128.0 (×3), 128.2 (×6), 128.3 (×4), 128.3 (×4), 128.4, 128.5 (×3), 128.7 (×5), 128.7 (×6), 128.8 (×7), 128.8 (×7), 128.8 (×6), 129.0 (×5), 129.1, 129.2, 129.4 (×3), 129.4, 129.6, 130.0, 130.1 (×3), 130.3, 130.4, 133.5, 133.6, 133.9, 136.2, 138.1, 138.3, 138.4, 138.6, 138.8, 139.3, 165.2, 165.4, 165.8, 166.1 ppm; HR-FAB MS [*M* + Na]<sup>+</sup> calcd for C<sub>116</sub>H<sub>114</sub>O<sub>25</sub>Na<sup>+</sup> 1929.7547, found 1929.7583.

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**Supporting Information Available:** Extended experimental data, general experimental procedures, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.