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Glycosidation of Thioglycosides in the Presence of Bromine: Mechanism, Reactivity, and Stereoselectivity

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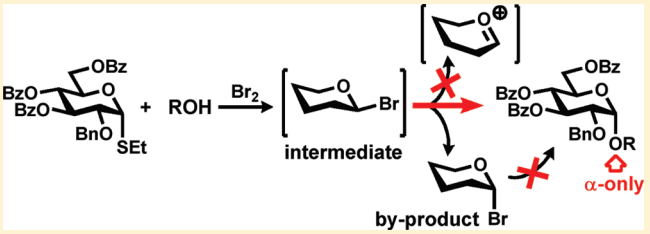
Supporting Information

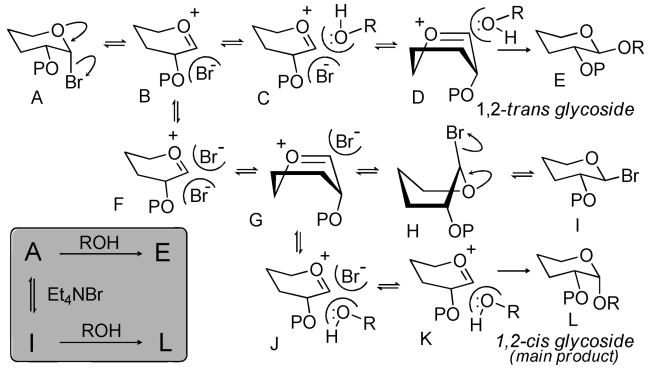
ABSTRACT: Elaborating on previous studies by Lemieux for highly reactive "armed" bromides, we discovered that β-bromide of the superdisarmed (2-*O*-benzyl-3,4,6-tri-*O*-benzoyl) series can be directly obtained from the thioglycoside precursor. When this bromide is glycosidated, α-glycosides form exclusively; however, the yields of such transformations may be low due to the competing anomerization into α-bromide that is totally unreactive under the established reaction conditions.



INTRODUCTION

Owing to many recent breakthroughs in the field, the formation of many glycosidic bonds can be readily achieved.[1−3] However, the ability to effectively control the stereoselectivity of glycosylation, a remarkably complex and multistep reaction that involves activation, dissociation, nucleophilic attack, and deprotonation,[4−6] is still limited. Building upon our earlier discoveries of the O-2/O-5 cooperative effect in glycosylation and the superdisarmed glycosyl donors bearing the 2-*O*-benzyl-3,4,6-*O*-triacyl protecting group pattern,[7] herein we present a study toward the development of a highly stereocontrolled glycosylation using glycosyl bromides as glycosyl donors generated *in situ*. Glycosyl bromides are the most studied glycosyl donors,[8] and their halide-ion-catalyzed glycosidation introduced by Lemieux et al. in 1975 is arguably the most significant application in synthesis.[9] Overall, Lemieux's approach is among the most stereoselective procedures for direct synthesis of 1,2-*cis*-glycosides developed to date.[10] Thus, it was found that a rapid equilibrium could be established between α-halide **A** and its more reactive β-counterpart **I** by adding tetraalkylammonium bromide (Scheme 1). At first, expulsion of the α-halide **A** leads to ion-pair **B**. Since no inverted 1,2-*trans*-glycoside **E** is formed, ion-pair triplet **F** leading to the anomerized β-linked bromide **I** was assumed to be a more energetically favorable pathway. The existence of alternate conformations for intermediates **G** and **H** *en route* to/from **I** was deemed necessary to form/activate the equatorial bond.[11] The highly reactive β-halide **I** rapidly dissociates back into ion-pair **G**, whereupon it quickly undergoes nucleophilic attack to form the 1,2-*cis* product **L**. As an end result, nucleophilic substitution of the β-bromide **I** occurs favorably, whereas the α-bromide **A** anomerizes before glycosylation can occur.

Scheme 1. Lemieux's *in Situ* Anomerization Concept



RESULTS AND DISCUSSION

Does the Lemieux concept offer a practical application to synthesis of glycosides and oligosaccharides? Yes, but it lacks generality, as it requires very reactive perbenzylated bromides or iodides[8,12−14] as glycosyl donors and provides satisfactory results mainly with the highly reactive series, fucose and galactose. In our hands, this procedure was found less effective, and thorough investigation of differently protected glucosyl bromides **1a**−**5a** in reactions with glycosyl acceptor **6**[15] showed that it is mainly applicable to glycosidation of perbenzylated bromide **1a**.[16] Even then, the reaction was extremely sluggish and proceeded only halfway in 120 h (entry 1, Table 1). The stereoselectivity obtained for disaccharide **7**[17] was good (α/β = 9/1) but far from being exclusive. In addition, the application of such uniformly protected building blocks to oligosaccharide synthesis is limited to the introduction of the terminal units only. Our consecutive attempt to diversify the protecting group

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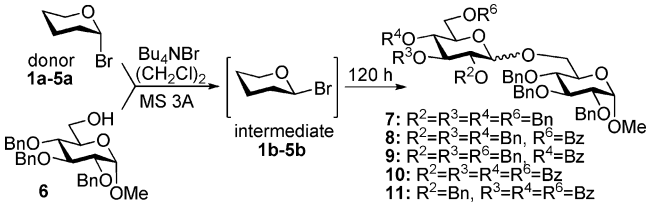
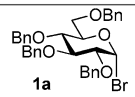
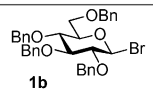
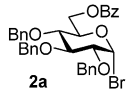
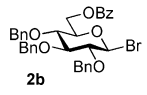
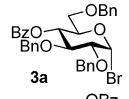
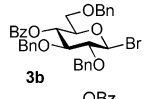
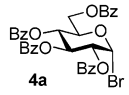
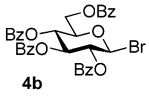
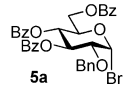
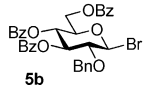
Table 1. Glycosidation of Differently Protected Glycosyl Bromides 1a–5a in the Presence of Bu_4NBr[a]



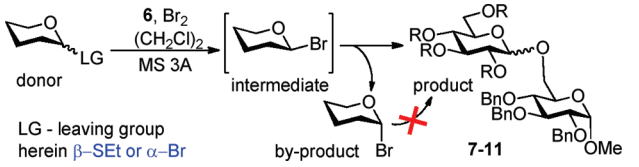
Entry	Glycosyl donor	Intermediate	Product (yield,[b] α/β ratio[c])
1			**7** (50%, 9.0/1)
2			**8** (43%, 24/1)
3			**9** (15%, 6.2/1)
4			**10** (no reaction)
5			**11** (no reaction)

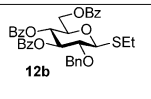
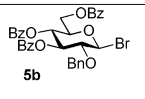
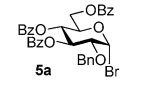
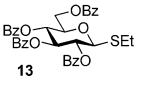
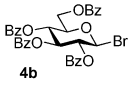
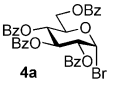
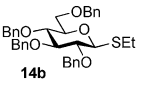
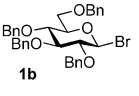
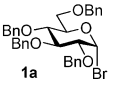
[a]Herein and throughout the article, α- and β-linked glycosyl donors or reactive intermediates are designated with letters **a** and **b** in the compound numbering, respectively. [b]Herein and below, whenever the reaction was balanced to estimate the amount of the unreacted glycosyl donor remaining, a combined yield for disaccharide and donor remaining was typically in the range of 87–97%. [c]Herein and below, the anomeric ratios were determined by comparison of the integral intensities of the corresponding signals in NMR spectra. Data for spectra wherein no opposite anomer could be detected or recorded ratios were above 25/1 are listed as a conservative estimate of >25/1.

pattern by adding a single benzoyl substituent led to the notable decrease in the rate of glycosylation and yields (entries 2 and 3). Stereoselectivity and yields observed with 6-*O*-benzoyl bromide **2a** and 4-*O*-benzoyl bromide **3a** differed drastically, indicating that the electron withdrawal is very position dependent.[18,19] Not surprisingly, our attempts to activate bromides **4a**[20] and **5a** bearing the disarming and superdisarming protecting group pattern, respectively, have failed completely under Lemieux's inversion conditions (entries 4 and 5).

Interestingly, β-ethylthioglycoside **12b**[21] reacted readily in the presence of bromine and provided disaccharide **11** as the α-linked diastereomer only (entry 1, Table 2). This result was rather unexpected, since we first believed that glycosyl bromide **5a** was the reactive intermediate in this reaction. We also noticed that no reaction would take place if acceptor **6** was added at the later stage when all thioglycoside **12b** has been consumed. We also observed that bromide **5a** cannot be glycosidated in the presence of bromine (entry 2). These observations led us to a working hypothesis that *thioglycoside **12b** is first converted into the corresponding β-bromide **5b*** that reacts readily with the glycosyl acceptor to give the α-linked glycoside. Literature precedent for this exists, and the formation of β-bromides from thioglycosides and selenium glycosides has been documented.[22,23] Along similar lines, β-chlorides have been also synthesized and used.[24–26] In a majority of previous

Table 2. Glycosidation of Thioglycosides 12b, 13, and 14b with Glycosyl Acceptor 6 via the Intermediacy of β-Bromides



Entry	Glycosyl donor	Anticipated intermediate	Time	Product (yield, α/β ratio)
1			16 h	**11** (28%, >25/1)
2		**5b** (not formed)	16 h	**11** (no reaction)
3			16 h	**10** (45%, >1/25)
4		**4b** (not formed)	16 h	**10** (no reaction)
5			10 min	**7** (71%, 2.2/1)
6		**1b**	10 min	**7** (67%, 1.5/1)

studies, however, the reaction of thioglycosides with bromine was used to generate the corresponding glycosyl bromide, which upon isolation is usually seen as the α-anomer only.[16,27]

It is possible that in the absence of the glycosyl acceptor the kinetic β-bromide rapidly equilibrates into the thermodynamically more stable α-anomer. Alternatively, if the glycosyl acceptor is present from the beginning, β-bromide can undergo direct nucleophilic displacement that arguably takes place via the concerted bimolecular (or close ion-pair) pathway, resulting in the formation of the inverted α-linked glycoside only. Since the disaccharide **11** was isolated in only 28% yield along with 63% of α-bromide **5a**, we hypothesized that *there is a competition between β-bromide glycosidation and anomerization* and that the latter is favored under these reaction conditions. With both glycosylation and anomerization reactions being irreversible under these reaction conditions, the resulting α-bromide **5a** is kinetically stable and cannot be glycosidated.

In a similar fashion, perbenzoylated thioglycoside **13**[28] was glycosidated in the presence of bromine to afford β-linked product disaccharide **10**[29] in 45% yield (entry 3). Since α-bromide **4a** did not undergo any glycosidation under these reaction conditions (entry 4), we conclude that the formation of **10** also takes place via the intermediacy of β-bromide **4b**. It should be noted that, in contrast to the previous example with **5b**, β-bromide **4b** is equipped with the participating group at C-2. Therefore, **4b** undergoes the sequential two-step displacement via the intermediacy of the bicyclic acyloxonium ion (*vide infra*, Scheme 3). Since no α-linked disaccharide formation was detected, this appears to be the only route leading to glycosylation, which agrees well with the well-understood

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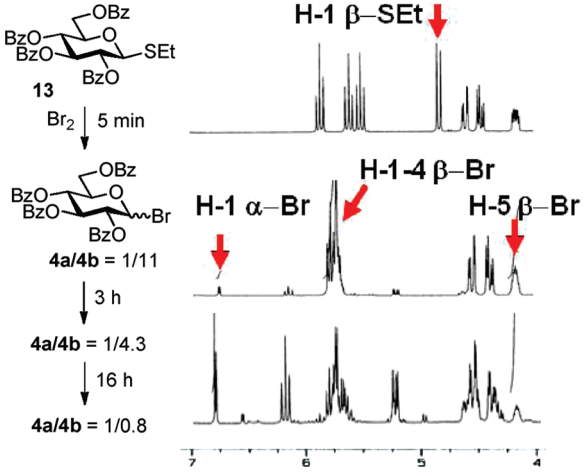
effect of neighboring participating groups.[30−33] When a similar glycosylation experiment was set up with perbenzylated thioglycoside **14b**,[34] disaccharide **7** was readily obtained in a good yield of 71%, but as a mixture of diastereomers (entry 5). Also perbenzylated α-bromide **1a** reacted readily under these reaction conditions (entry 6), providing an outcome similar to that obtained with thioglycoside **14b**. Perhaps this reaction proceeds via the classic S_N1 pathway, via the intermediacy of the flattened oxacarbenium ion (*vide infra*) that has a tendency to result in scrambled stereoselectivity,[4,35] even under carefully controlled reaction conditions.

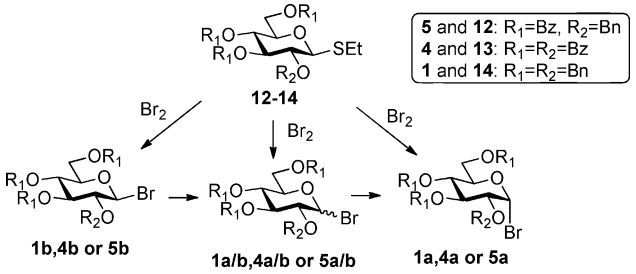
Therefore, we decided to investigate the reaction between superdisarmed thioglycoside **12b** and glycosyl acceptor **6** that in the presence of bromine leads to complete stereoselectivity. In order to understand why only a modest yield of 28% could be achieved, we needed to delineate between two possible reactions pathways by which the reaction may proceed. First, the rates of formation of the diastereomeric bromides **5a** and **5b** can be similar, but only the β-anomer **5b** then elaborates into glycoside **11**, while the α-bromide **5a** remains intact. Second, it is also possible that the kinetic β-bromide **5b** forms first and then anomerizes into its more stable α-counterpart **5a** concomitantly with glycosidation. Inspired by previous mechanistic studies,[17,36−39] we hoped that monitoring the reaction by NMR would help to differentiate between the two possible pathways. We initially investigated the reaction of perbenzoylated β-thioglycoside **13** with bromine in $CDCl_3$ that was performed in the standard 5 mm NMR tube directly. As depicted in Scheme 2, α- and β-bromides (**4a** and **4b**) form

Scheme 2. *In Situ* NMR Monitoring of the Reaction of Thioglycoside 13 with Bromine



rapidly (5 min), with a vast predominance of **4b** (α/β = 1/11). This was then followed by a relatively slow anomerization of the β-bromide **4b** into its α-counterpart **4a**, resulting in a nearly equal mixture of anomers with a slight predominance of **4a** after 16 h (see also entry 1 in Table 3). A very similar result was obtained from an analogous reaction performed in CD_2Cl_2. The predominant formation of the β-bromide **4b** in this case can be attributed to the assistance of the neighboring benzoyl substituent at C-2. Hence, it was important to establish how the β-thioglycosides of the armed and superdisarmed series **14b** and **12b**, respectively, both bearing a nonparticipating 2-*O*-benzyl substituent, react. The results of this study are summarized in Table 3.

Table 3. NMR Monitoring of Reactions of Thioglycosides 12−14 with Bromine Followed by the Anomerization of Glycosyl Bromides 1, 4, and 5



entry	reaction	temp	time recorded	ratio α/β
1	**13** → **4a/4b**	rt	5 min	1/10.7
			15 min	1/10.3
			30 min	1/9.0
			3 h	1/4.3
			16 h	1/0.8
2	**14b** → **1a/1b**	rt	5 min	>25/1
3	**14b** → **1a/1b**	low[a]	5 min	7.3/1
			10 min	8.9/1
			20 min	10.2/1
			1 h	12.7/1
4	**12b** → **5a/5b**	rt	5 min	2.1/1
			15 min	2.2/1
			1 h	2.4/1
5	**14a** → **1a/1b**	rt	5 min	>25/1
6	**14a** → **1a/1b**	low[a]	5 min	>1/25
			10 min	1/2.5
			15 min	1/0.9
			30 min	1/0.3
			1 h	>25/1
7	**12a** → **5a/5b**	rt	5 min	1/20
			15 min	1/17.3
			30 min	1/16.3
			3 h	1/11.5
			16 h	1/4.5

[a]See text and the Experimental Section

The reaction of perbenzylated thioglycoside **14b** was extremely fast at room temperature, and by the time the first ^1H NMR was acquired, about 5 min after the addition of bromine, α-bromide **1a** had formed exclusively (entry 2). Therefore, we attempted to perform the reaction monitoring at lower temperature as follows. Thioglycoside **14b** was dissolved in $CDCl_3$ and placed in the standard 5 mm NMR tube equipped with a septum, which was then placed into liquid nitrogen (−196 °C) for 10 min. Bromine (1.0 equiv) was added via syringe, the NMR tube was immediately inserted into the magnet, and the proton spectrum was recorded (approximately 5 min after Br_2 addition). This approach allowed us to detect a 7.3/1 α/β mixture of **1a**/**1b**, which was then observed to further equilibrate into the α-bromide **1a** (entry 3).

Next, the reaction of thioglycoside **12b** equipped with the superdisarming protecting group pattern (2-*O*-benzyl-3,4,6-tri-*O*-benzoyl) was investigated. Room-temperature experiment

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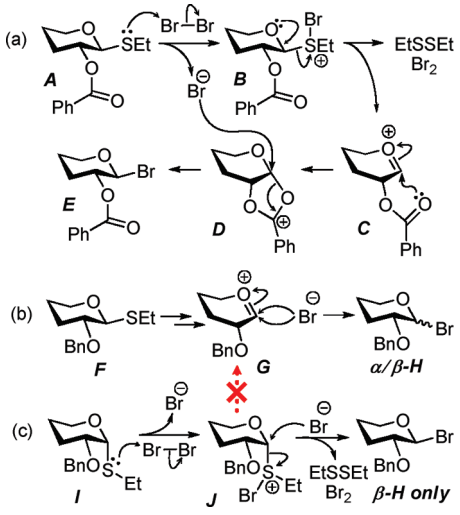
resulted in the formation of a 2.1/1 mixture with predominance of α-anomer **5a** (entry 4). This mixture then began equilibrating slowly, and further accumulation of α-anomer **5a** was monitored by NMR. The outcome of this experiment revealed that even though only β-anomer **5b** can be glycosidated under these reaction conditions, the predominant direct formation of α-anomer **5a** is a conceptual barrier for the possibility to improve the yield on this reaction. Indeed, if one assumes that the β-anomer in a 2.1/1 α/β-mixture was to react entirely, the theoretical yield of its glycosidation still could not exceed 32% based on the starting thioglycoside **12b**. This calculated yield correlates well with the observed yield of 28% (see Table 2, entry 1) and corresponds to about 88% of conversion β-bromide **5b** into disaccharide **11**, leaving about 12% as a result of the concomitant competing anomerization of **5b** into **5a**.

This result is significant as it demonstrates that the glycosidation of **12b** (at least with glycosyl acceptor **6**) is significantly faster than its competing anomerization into **5a**. Since no Lemieux-like equilibrium could be established with the unreactive bromides (*vide supra*), the only possibility to improve the yield of such glycosylation is to ensure that β-bromide is generated predominantly. The necessity to improve the reaction conditions stimulated us to look into possible mechanistic pathways by which this transformation may proceed. In the case of thioglycosides equipped with the neighboring participating group at C-2, such as **13**, or schematically represented as **A** in Scheme 3a, the β-thioglycoside undergoes a double displacement via the intermediacy of the bicyclic acyloxonium ion **D**. Thus, upon interaction of **A** with bromine, a reactive sulfonium intermediate **B** is generated.[21,40] The promoter-assisted leaving-group departure results in the formation of the oxacarbenium intermediate **C**. The leaving group first departs as an unstable BrSEt species that then disproportinates into ethyl disulfide (easily detectable by NMR) and bromine. Oxacarbenium ion **C** is then stabilized via anchimeric assistance of the neighboring benzoyl group, resulting in the formation of cyclic acyloxonium intermediate **D**. The formation of the latter can be used to explain the preferential formation of β-bromide **E**, as was detected for **4b** (entry 1, Table 3).

Scheme 3. Mechanistic Rationale for the Transformation of Thioglycosides A, F, and I into Bromides E and H in the Presence of Bromine



In the case of β-thioglycosides **12b** and **14b** bearing a nonparticipating 2-*O*-benzyl substituent, schematically shown as **F** in Scheme 3b, there is no direct route that would lead to the stereoselective formation of the corresponding β-bromides. Although arguably the β-bromide is the kinetic product from the oxacarbenium intermediate **G**, our results showed that the formation of the more stable α-bromide predominated in both cases, with the highest β-bromide content obtained in the case of the superdisarmed series (**5a**/**5b**, α/β = 2.1/1, see Table 3, entry 4). We conceptualized that the use of α-thioglycosides as an alternative starting material may offer a more direct route to obtain the corresponding β-bromides. Our working hypothesis is depicted in Scheme 3c. Thus, promoter-assisted activation of the leaving group in α-thioglycoside **I** with bromine will lead to the formation of α-sulfonium ion **J**. Two possible pathways by which **J** converts into bromides **H** that would be reasonable to assume are as follows. First, the formation of β-**H** takes place directly via the concerted nucleophilic (or close-ion-pair) displacement of the BrSEt leaving group, leading to complete inversion. Second, upon monomolecular departure of the activated leaving group in **J**, the reaction would then proceed via the intermediacy of the oxacarbenium ion **G**, which would likely result in the formation of the anomeric mixture of α/β-**H**. This mechanism implies that a stoichiometric amount of bromine is not required because it would be partially regenerated upon disproportionation of BrSEt intermediate (*vide infra*).

To delineate the most viable reaction pathway by which α-SEt glycosides elaborate into β-bromides, we first obtained perbenzylated derivative **14a**.[41] Disappointingly, the NMR experiment with **14a** performed at rt led to the formation of α-bromide **1a** (entry 5, Table 3). When essentially the same experiment as described for **14b** was performed at low temperature, β-bromide **1b** was formed predominantly (α/β > 1/25, entry 6), with a trace amount of unreacted α-thioglycoside still remaining. This was an ultimate proof of concept and a solid indication that we have begun advancing in the right direction. Subsequently, we observed that **1b** begins equilibrating very rapidly, with complete anomerization detected within 1 h after the addition of bromine (judged by the formation of **1a**). Assuming that the rate of this transformation would be difficult to control in a typical competing glycosylation experiment, we had hoped that thioglycoside **12a**,[21] bearing a superdisarming 2-benzyl-3,4,6-tribenzoyl protecting group pattern, would allow for reaction rates that are easier to comprehend, and hence allow us to achieve better control of its glycosidations. Figure 1 shows a series of NMR spectra that have been acquired at different time points of such reaction performed at rt (see also the summary in entry 7, Table 3).

After a spectrum of the starting material **12a** was recorded (Figure 1a), bromine (1 equiv) was injected into the NMR tube. A subsequent NMR spectrum recorded 5 min after the addition of Br_2 showed that bromides **5a**/**5b** are formed in a ratio of 1/20, favoring the β-anomer (Figure 1b). The ratios were measured by comparison of the integral intensities of the stand-alone signals corresponding to H-1 of α-bromide **5a** (6.48 ppm) and H-5 of β-bromide **5b** (4.20 ppm), which were clearly separable from the rest of the signals. At this time, about 24% of the starting material **12a** was still remaining, as judged by measuring the integral intensity of its H-3 signal (5.96 ppm). Subsequent NMR spectra recorded at 15 and 30 min time points after the addition of bromine showed that **12a** was

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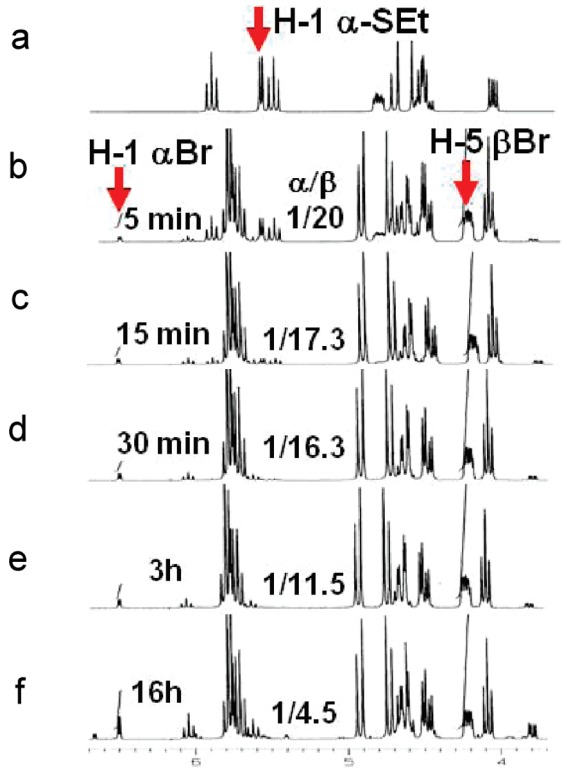
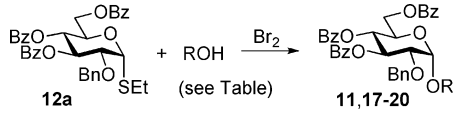


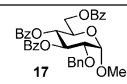
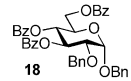
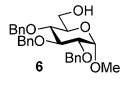
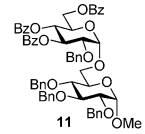
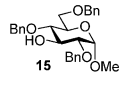
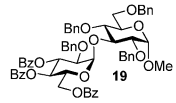
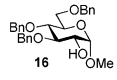
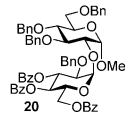
Figure 1. NMR monitoring of the conversion of thioglycoside **12a** into bromides **5a**/**5b** at rt.

completely consumed (by 30 min, Figure 1d), and β-bromide **5b** began a relatively slow anomerization into its more stable α-counterpart **5a**. Therefore, these results confirm the initial assumption that the anomerization of superdisarmed bromide **5b** is much slower than that of its armed, perbenzylated counterpart **1b**. Moreover, anomerization of **5b** is even slower than that of perbenzoylated disarmed bromide **4b**, as **5b** is still present as the major product after 16 h (Figure 1f), whereas **4b** was already surpassed by **4a** by the same time point (compare entries 1 and 7, Table 3). It should be noted that, by this time point, traces of the hydrolysis product (hemiacetal) have begun to appear, as evident from the new anomeric signal at ~6.7 ppm (Figure 1f).

Having established the most favorable reaction conditions for the formation of β-bromide **5b** at rt, we turned our attention to studying its glycosidation. For this purpose we obtained a number of glycosyl acceptors ranging from simple aliphatic alcohols to representative secondary hydroxyls of monosaccharide acceptors **15**[42] and **16**.[43] Since under the established reaction conditions only **5b** is able to react while **5a** remains inert (*vide supra*), all glycosylations summarized in Table 4 provided the respective products with complete α-stereoselectivity. All ratios of the final products are recorded as our conservative estimate α/β > 25/1, although in most cases no traces of the β-linked products were even detected. Although the issue of the stereoselectivity of this glycosylation has been resolved, it also has become apparent that the yield of these reactions ultimately depends on the rate with which the products are forming and the ability of the glycosylation to outperform the competing isomerization. For instance, relatively high yields could be achieved in all cases of glycosylations of highly reactive glycosyl acceptors: MeOH (78% of **17**,[21] entry 1), BnOH (75% of **18**, entry 2), and 6-OH

Table 4. Glycosidation of Thioglycoside 12a with Various Glycosyl Acceptors



Entry	*ROH*	*Time*	*Product*	*yield, α/β ratio*
1	MeOH	16 h	 **17**	78%, >25/1
2	BnOH	16 h	 **18**	75%, >25/1
3	 **6**	16 h	 **11**	67%, >25/1
4	 **15**	48 h	 **19**	35%, >25/1
5	 **16**	48 h	 **20**	27%, >25/1

acceptor **6** (67% of **11**, entry 3). Unfortunately, glycosylations of secondary acceptors **15** and **16** were below preparative value, and although also complete stereoselectivity was recorded herein, 1→3- and 1→2-linked disaccharides **19** and **20** were isolated in only 35% (entry 4) and 27% (entry 5) yields, respectively. As mentioned previously, the overall stoichiometry of this reaction implies that a stoichiometric amount of bromine is not required because it would be partially regenerating upon disproportionation of BrSEt intermediate (*vide infra*). At this stage, however, reactions in the presence of a substoichiometric amount of bromine appear to be much slower, and the yields obtained are below the preparative value. We do not yet currently have any data on the formation and roles of other side products, such as HBr, which might also be forming as a result of the deprotonation of glycoside products with bromonium ion.

Certainly, if an efficient equilibrium between unreactive bromide **5a** into its very reactive counterpart **5b** could be established, this would help us to regenerate **5b** and ultimately drive the glycosylation to completion, which would result in improved yields. Since our preliminary study (Table 1) clearly demonstrated that bromide **5a** cannot be anomerized in the presence of Bu_4NBr, we assumed that its anomerization might be possible with the assistance of heavy-metal-based promoters. As discovered in 1901 by Koenigs and Knorr[44] (and independently by Fischer and Armstrong),[45] glycosyl halides can be activated in the presence of Ag_2CO_3 or Ag_2O. The silver salt was used with the primary intention to scavenge the hydrogen halide byproduct, and it was not until the early 1930s that it was realized that the silver salt plays an active role by assisting in the leaving group's departure.[46,47] Additionally, as shown by Helferich et al.,[48−50] mercury(II) salts offer even more potent assistance for the leaving group's departure.

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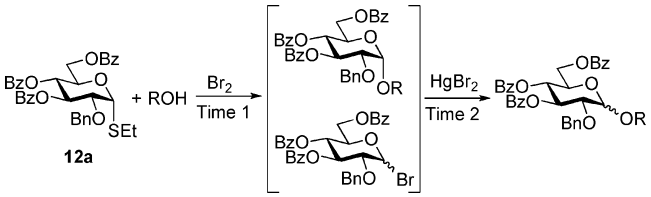
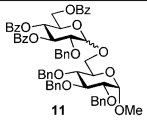
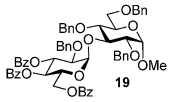
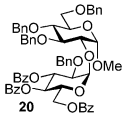
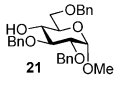
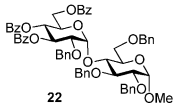
Therefore, the investigation of metal salt-based activators appealed to us as attractive for further study. In particular, we assumed that mercury(II) bromide would be capable of both assisting the leaving group's departure and providing bromide anion to effect the subsequent *in situ* anomerization of **5a** into **5b**. Helferich's study also demonstrated that faster reactions often result in a decreased stereoselectivity. Therefore, a delicate balance between the reactivity and stereoselectivity should be kept in place to ensure success of the metal-assisted activation.

To investigate the role that $HgBr_2$ may have on the outcome of glycosylation, we performed a series of experiments, summarized in Table 5. Glycosidation of **12a** with standard

Table 5. Glycosidation of Thioglycoside 12a in the Presence of Br_2 and $HgBr_2$ with Various Glycosyl Acceptors



Entry	ROH	Time 1 Time 2	Product	yield, α/β ratio
1	**6**	0 h 5 h	 **11**	86%, 8.0/1
2	**6**	0.25 h 5 h	**11**	83%, 8.4/1
3	**6**	4 h 8 h	**11**	79%, 8.1/1
4	**6**	16 h 21 h	**11**	72%, 10.5/1
5	**15**	0.25 h 16 h	 **19**	89%, >25/1
6	**16**	0.25 h 16 h	 **20**	87%, >25/1
7	 **21**	0.25 h 24 h	 **22**	82%, >25/1

6-OH acceptor **6** was initiated in the presence of Br_2 (1.3 equiv), and $HgBr_2$ (1.3 equiv) was subsequently added at different time points into the reaction mixture at rt. Since no activation of **12a** in the presence of $HgBr_2$ and in the absence of Br_2 took place, glycosyl bromide is indeed the reactive intermediate in this reaction. Along with the notable increase of the yield up to 86% (entries 1–4), the stereoselectivity remained very high, but in all cases the presence of β-linked disaccharide **11** could be detected. The reduced stereoselectivity obtained here can serve as an indication that **5a** reacted with glycosyl acceptor either directly or via the intermediacy of the oxacarbenium ion, but not via **5b**. Not surprisingly, higher stereoselectivity was detected with a longer time period (time 1) before the addition of $HgBr_2$ (entry 4).

Significantly improved yields have been also obtained with secondary glycosyl acceptors **15** and **16**. Thus, disaccharides **19** and **20** were obtained in 89% and 87% yield, respectively (entries 5 and 6). We conclude that the metal-assisted protocol is predominantly suitable for glycosylations of less reactive glycosyl acceptors, as in the absence of the metal promoter the anomerization easily outperforms glycosylation. Even glycosylation of the unreactive 4-OH glycosyl acceptor **21**[51] was possible under these reaction conditions. Thus, 1→4-linked disaccharide **22** was readily obtained in 82% yield, whereas Br_2-only activation of **12a** provided only a trace amount of **22** (data not shown).

CONCLUSIONS

The conceptual similarity between this approach and Lemieux's halide-assisted procedure introduced in 1975[9] is undeniable. However, because no equilibrium between superdisarmed bromides **5a** and **5b** could be established by the addition of tetraalkylammonium bromide, we believe that the method described herein offers a complementary approach. The fact that α-bromide **5a** was found totally unreactive in the presence of bromine *is a particularly significant result*, as it assures that its β-counterpart **5b** will be the key (and apparently the only) species *en route* to the glycosylation product under these reaction conditions.

Both simple aliphatic alcohols and the less reactive sugar acceptor **6** provided the corresponding glycosides with complete α-stereoselectivity. Glycosylation of secondary acceptors is slower, which gives a window for the β-bromide to anomerize, and this is ultimately reflected in lower yields of glycosylations in the presence of bromine only. The efficiency of glycosylation of secondary acceptors can be significantly improved by the addition of mercury(II) bromide copromoter. This modification allowed for very good yields and complete stereoselectivity. Although the yield of glycosylation of primary acceptor **6** can also be significantly improved by the addition of mercury(II) bromide copromoter, it also leads to decreased stereoselectivity.

EXPERIMENTAL SECTION

General. Column chromatography was performed on silica gel 60, and reactions were monitored by TLC on Kieselgel 60 F_{254}. Preparative layer chromatography was performed on PLC silica gel 60 glass plates, Kieselgel 60 F_{254}, 1 mm. 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. Mercury(II) bromide (99%+, reagent grade) and tetrabutylammonium bromide (99%+, reagent grade) were used as received. CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 directly prior to application. Pyridine was dried by refluxing with CaH_2 and then distilled and stored over molecular sieves (3 Å). Molecular sieves (3 Å) used for reactions were crushed and activated *in vacuo* at 390 °C for 8 h in the first instance and then for 2–3 h at 390 °C directly prior to application. Optical rotations are listed in deg dm^{-1} cm^3 g^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ at 300 and 500 MHz, and ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 and 125 MHz. HR-FAB-MS determinations were made with the use of a matrix of *m*-nitrobenzyl alcohol, with NaI as necessary.

Synthesis of Glycosyl Donors. *6-O-Benzoyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl Bromide (**2a**).* A solution of ethyl 6-*O*-benzoyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[52] (0.50 g, 0.83 mmol) and activated molecular sieves (3 Å, 0.40 g) in CH_2Cl_2 (12.5 mL) was stirred under argon for 1 h. A freshly prepared solution of Br_2 in CH_2Cl_2 (8 mL, 1/165, v/v) was then added, and the reaction mixture was kept for 15 min at rt. After that, the solid was filtered off,

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and the filtrate was concentrated *in vacuo* at rt. The residue was purified by silica gel flash column chromatography (ethyl acetate–toluene gradient elution) to obtain the title compound as a colorless syrup in 59% yield (0.31 g, 0.50 mmol). Analytical data for **2a**: R_f = 0.43 (ethyl acetate–hexane, 1/4, v/v); $[\alpha]_D^{24}$ +122.6 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.56 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 3.73 (dd, 1H, $J_{4,5}$ = 9.1 Hz, H-4), 4.11 (dd, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 4.27 (m, 1H, $J_{5,6a}$ = 3.0 Hz, H-5), 4.50–5.02 (m, 8H, 3×CH_2Ph, H-6a, 6b), 6.41 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 7.20–7.60 (m, 18H, aromatic), 7.90 (d, 2H, aromatic) ppm; ^{13}C NMR δ 62.6, 72.9, 73.9, 75.5, 76.1, 76.2, 80.0, 82.2, 91.1, 128.1, 128.2 (×3), 128.3 (×2), 128.4 (×3), 128.6 (×2), 128.7 (×4), 128.8 (×2), 129.8 (×3), 164.1 ppm; HR FAB-MS [M+Na]$^+$ calcd for $C_{34}H_{33}O_6BrNa$ 639.1358, found 639.1332.

*4-O-Benzoyl-2,3,6-tri-O-benzyl-α-D-glucopyranosyl Bromide (**3a**).* Benzoyl chloride (0.14 mL, 1.21 mmol) was added dropwise to a stirred solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[53] (0.50 g, 1.01 mmol) in pyridine (5.0 mL) at 0 °C. The resulting reaction mixture was kept for 1 h, methanol (2 mL) was added, and the mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with 1 N HCl (15 mL) and water (3 × 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to obtain ethyl 4-*O*-benzoyl-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**23**) as a white solid in 89% yield (0.54 g, 0.90 mmol). Analytical data for **23**: R_f = 0.52 (ethyl acetate–hexane, 3/7, v/v); $[\alpha]_D^{22}$ −49.8 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 1.42 (t, 3H, SCH$_2$CH_3), 2.86 (m, 2H, SCH_2CH$_3$), 3.60–3.90 (m, 5H, H-2, 3, 5, 6a, 6b), 4.53 (dd, 2H, ^2J = 12.3 Hz, CH_2Ph), 4.62 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.68–5.00 (m, 4H, 2×CH_2Ph), 5.35 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-4), 7.17–8.00 (m, 20H, aromatic) ppm; ^{13}C NMR δ 15.4, 25.3, 70.1, 71.7, 73.7, 75.5, 75.8, 78.0, 81.8, 83.8, 85.3, 127.7, 127.8 (×3), 128.1 (×3), 128.4 (×4), 128.6 (×5), 129.9 (×2), 133.4, 137.9, 138.0 (×2), 165.5 ppm; HR-FAB-MS [M+Na] calcd for $C_{36}H_{38}O_6SNa$ 621.2287, found 621.2299.

A solution of **23** (0.5 g, 1.59 mmol) and activated molecular sieves (3 Å, 0.40 g) in CH_2Cl_2 (12.5 mL) was stirred under argon for 1 h. A freshly prepared solution of Br_2 in CH_2Cl_2 (8 mL, 1/165, v/v) was then added, and the reaction mixture was kept for 15 min at rt. After that, the solid was filtered off, and the filtrate was concentrated *in vacuo* at rt. The residue was purified by silica gel flash column chromatography (ethyl acetate–toluene gradient elution) to obtain the title compound **3a** as a colorless syrup in 70% yield (0.36 g, 0.58 mmol). Analytical data for **3a**: R_f = 0.42 (ethyl acetate–hexane, 1/4, v/v); $[\alpha]_D^{24}$ +110.6 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.55–3.72 (m, 3H, H-2, 6a, 6b), 4.16 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.34 (m, 1H, $J_{5,6a}$ = 3.7 Hz, H-5), 4.51 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.77 (dd, 2H, ^2J = 12.7 Hz, CH_2Ph), 4.88 (d, 1H, ^2J = 11.2 Hz, $^1/_2$CH_2Ph), 5.56 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 6.47 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 7.13–7.50 (m, 17H, aromatic), 7.62 (m, 1H, aromatic), 8.00 (d, 2H, aromatic) ppm; ^{13}C NMR δ 67.9, 69.4, 73.1, 73.7, 74.1, 75.5, 79.3, 79.5, 91.4, 127.7, 127.8, 128.0 (×2), 128.2 (×3), 128.3 (×3), 128.3 (×4), 128.4 (×2), 128.5 (×2), 128.7 (×3), 129.6, 129.9 (×2), 133.4, 137.4, 137.5, 137.9, 165.2 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{34}H_{33}BrO_6Na$ 639.1358, found 639.1343.

*3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-glucopyranosyl Bromide (**5a**).* A solution of ethyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside[21] (1.0 g, 1.59 mmol) and activated molecular sieves (3 Å, 0.79 g) in CH_2Cl_2 (24 mL) was stirred under argon for 1 h. A freshly prepared solution of Br_2 in CH_2Cl_2 (15 mL, 1/165, v/v) was added, and the reaction mixture was kept for 15 min at rt. After that, the solid was filtered off, and the filtrate was concentrated *in vacuo* at rt. The residue was redissolved in CH_2Cl_2 and then washed with distilled water. The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo* at rt, and the residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to afford the title compound as a white solid in 71% yield (0.76 g, 1.18 mmol). Analytical data for **5a**: R_f = 0.52 (ethyl acetate–hexane, 2/3, v/v); $[\alpha]_D^{23}$ +65.2 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.78 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.45 (dd, 1H, $J_{5,6a}$ = 4.7 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.54–4.70 (m, 4H, H-5, 6b, CH_2Ph), 5.60 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 6.03 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 6.48 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 7.22–7.57 (m, 14H, aromatic), 7.93 (dd, 4H, aromatic), 8.03 (dd, 2H, aromatic) ppm; ^{13}C NMR δ 62.4, 68.4, 72.3, 72.8 (×2), 76.8, 89.3, 128.2 (×2), 128.4, 128.5 (×2), 128.5 (×2), 128.6 (×2), 128.7 (×2), 128.8, 129.5, 129.7, 129.9 (×4), 130.1 (×2), 133.3, 133.4, 133.7, 136.8, 165.4, 165.6, 166.3 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{34}H_{29}O_8BrNa$ 667.0943, found 667.0970.

*3,4,6-Tri-O-benzoyl-2-O-benzyl-β-D-glucopyranosyl Bromide (**5b**).* A solution of ethyl 2-*O*-benzyl-3,4,6-tri-*O*-benzoyl-1-thio-α-D-glucopyranoside[21] (0.03 mg, 0.04 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube was frozen in liquid nitrogen. After that, 98% bromine solution (2.4 μL, 0.04 mol) was added directly to the NMR tube. ^{1}H NMR was recorded immediately. Selected analytical data for **5b**: ^{1}H NMR δ 4.07 (dd, 1H, $J_{2,3}$ = 7.8 Hz, H-2), 4.20 (m, 1H, H-5), 4.46 (dd, 1H, $J_{5,6a}$ = 5.1 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.57 (dd, 1H, $J_{5,6b}$ = 3.1 Hz, H-6b), 4.72 (d, 1H, ^2J = 10.7 Hz, $^1/_2$CH_2Ph), 4.91 (d, 1H, ^2J = 10.8 Hz, $^1/_2$CH_2Ph), 5.67–5.81 (m, 3H, H-1, 3, 4), 7.19–8.05 (m, 20H, aromatic) ppm; ^{13}C NMR δ 63.0, 68.8, 74.8, 75.3, 76.4, 81.7, 82.6, 128.2, 128.4 (×2), 128.5 (×4), 128.6 (×4), 129.2, 129.6, 129.9 (×2), 130.0 (×3), 130.1 (×2), 133.3, 133.6, 133.7, 136.9, 165.3, 165.6, 166.2 ppm; FAB-MS [M+Na]$^+$ for $C_{34}H_{29}O_8BrNa$ 667.1.

Synthesis of Glycosides and Disaccharides. *Method A: General Bu_4NBr-Promoted Glycosylation Procedure.* A mixture of the glycosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred under argon for 1 h. Bu_4NBr (0.20 mmol) was added, and the reaction mixture was stirred 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 $NaHCO_3$ (10 mL) and water (3 × 15 mL), and the organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to give the corresponding disaccharide. Anomeric ratios (if applicable) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Method B: General Br_2-Promoted Glycosylation Procedure. A mixture of the glycosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred under argon for 1 h. Bromine (0.10–0.13 mmol) was added, and the resulting mixture was stirred 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 $NaHCO_3$ (10 mL) and water (3 × 15 mL), and the organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to give the corresponding disaccharide. Anomeric ratios (if applicable) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Method C: General Br_2/$HgBr_2$-Promoted Glycosylation Procedure. A mixture of the glycosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $(ClCH_2)_2$ (2 mL) was stirred under argon for 1 h. Bromine (0.13 mmol) was added, and the resulting mixture was stirred at rt and monitored with TLC. After time 1 listed in Table 5, mercury(II) bromide (0.13 mmol) was added, and the reaction mixture was stirred for time 2 (Table 5). 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 $NaHCO_3$ (10 mL) and water (3 × 15 mL), and the organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to give the corresponding disaccharide. Anomeric ratios (if applicable) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

*Methyl 6-O-(6-O-Benzoyl-2,3,4-tri-O-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**8**).* The title compound

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was obtained by method B from **2a** and **6** in 45% yield as a colorless syrup (α/β = 24/1). Analytical data for α-**8**: R_f = 0.41 (ethyl acetate−hexane, 3/7, v/v); ^{1}H NMR δ 3.32 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, H-2′), 3.46−3.54 (m, 3H, H-2, 4, 4′), 3.62 (m, 1H, $J_{6a,6b}$ = 10.1 Hz, H-6a), 3.72 (m, 2H, H-5, 6b), 3.90 (m, 3H, H-3, 3′, 5′), 4.31 (dd, 1H, $J_{5',6a'}$ = 4.4 Hz, $J_{6a',6b'}$ = 11.9 Hz, H-6a′), 4.43 (dd, 1H, $J_{5',6b'}$ = 2.0 Hz), 4.47−4.64 (m, 7H, $J_{1',2'}$ = 3.3 Hz, H-1′, 3×CH_2Ph), 4.70−4.75 (m, 2H, CH_2Ph), 4.81−4.93 (m, 5H, $J_{1,2}$ = 3.6 Hz, H-1, 3×CH_2Ph) ppm; ^{13}C NMR δ 55.4, 63.6, 66.2, 69.1, 70.6, 72.6, 73.5, 75.2 (×2), 75.9 (×2), 77.4, 78.0, 80.3, 80.4, 81.9, 82.3, 97.1, 98.1, 127.8 (×3), 127.9 (×7), 128.0 (×2), 128.1 (×2), 128.2 (×4), 128.4 (×3), 128.5 (×6), 128.6 (×4), 129.8 (×3), 130.2, 133.2, 138.2, 138.3, 138.5 (×2), 138.7, 139.0, 166.4 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{62}H_{64}O_{12}Na$ 1023.4295, found 1023.4277.

*Methyl 6-O-(4-O-Benzoyl-2,3,6-tri-O-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**9**).* The title compound was obtained by method B from **3a** and **6** in 15% yield as a colorless syrup (α/β = 6.2/1). Selected analytical data for α-**9**: R_f = 0.41 (ethyl acetate−hexane, 3/7, v/v); ^{1}H NMR δ 3.38 (s, OCH_3), 3.47 (m, 2H, H-2′, 4), 3.98−4.11 (m, 3H, H-3, 3′, 5), 4.59 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1′), 4.96 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1), 5.31 (dd, 1H, $J_{4',5'}$ = 9.5 Hz, H-4′) ppm; ^{13}C NMR δ 55.3, 69.1, 69.3, 70.6, 71.1, 72.7, 73.6, 73.7, 75.1, 75.2, 75.9, 77.4, 78.1, 78.4, 79.9, 80.3, 82.4, 97.5, 98.2, 127.5 (×2), 127.6 (×2), 127.8 (×5), 127.9 (×3), 128.1 (×2), 128.2 (×4), 128.3 (×3), 128.4, 128.5 (×3), 128.6 (×6), 129.9 (×2), 130.1 (×3), 133.2, 138.0, 138.3, 138.5, 138.7, 139.0, 165.5 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{62}H_{64}O_{12}Na$ 1023.4295, found 1023.4365.

*Methyl 6-O-(3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**11**).* The title compound was obtained by method B from **12a** and **5** in 67% yield as a colorless syrup (α/β > 25/1). Analytical data for α-**11**: R_f = 0.51 (ethyl acetate−toluene, 3/17, v/v); $[\alpha]_D^{23}$ +18.9 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.30 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 3.38 (s, 3H, OCH_3), 3.49 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.65 (dd, 1H, $J_{2',3'}$ = 10.0 Hz, H-2′), 3.69−3.81 (m, 3H, H-5, 6a, 6b), 3.93 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.20−4.34 (m, 2H, $J_{5,6a}$ = 5.5 Hz, H-5, 6a), 4.48 (dd, 2H, ^2J = 11.6 Hz, CH_2Ph), 4.39−4.55 (m, 3H, $J_{1,2}$ = 3.7 Hz, H-1, 5′, 6b′), 4.58 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.76 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.89 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 5.01 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 5.36 (dd, 1H, $J_{4',5'}$= 9.8 Hz, H-4′), 5.89 (dd, 1H, $J_{3',4'}$ = 9.7 Hz, H-3′), 6.90−8.95 (m, 35H, aromatic) ppm; ^{13}C NMR δ 55.4, 63.4, 66.3, 67.9, 70.0, 70.6, 72.0, 72.3, 73.5, 75.2, 75.9, 77.4, 78.0, 80.0, 82.3, 96.8, 98.1, 127.7, 127.8, 127.9 (×2), 128.0 (×3), 128.1 (×3), 128.2 (×2), 128.4 (×2), 128.5 (×9), 128.6 (×4), 129.2, 129.8 (×2), 129.9 (×3), 130.0 (×2), 133.2 (×2), 133.5, 137.8, 138.3, 138.6, 139.0, 165.7, 165.9, 166.3 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{62}H_{60}O_{14}Na$ 1051.3881, found 1051.3904.

*Benzyl 3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-glucopyranoside (**18**).* The title compound was obtained by method B from **12a** and benzyl alcohol as a clear film in 75% yield. Analytical data for **18**: R_f = 0.35 (ethyl acetate−toluene, 1/19, v/v); $[\alpha]_D^{25}$ +29.3 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.78 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 4.37−4.51 (m, 5H, CH_2Ph, H-5, 6a, 6b), 4.62 (d, 1H, ^2J = 12.3 Hz, $^1/_2$ CH_2Ph), 4.98 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.99 (d, 1H, ^2J = 12.0 Hz, $^1/_2$ CH_2Ph), 5.49 (dd, 1H, $J_{4,5}$ = 9.93 Hz, H-4), 6.03 (dd, 1H $J_{3,4}$ = 9.7 Hz, H-3), 7.14−8.02 (m, 25H, aromatic); ^{13}C NMR ($CDCl_3$) δ 31.4, 63.4, 68.1, 69.6, 70.1, 72.2, 77.4, 77.8, 95.5, 128.0 (×2), 128.1, 128.2, 128.4 (×2), 128.5 (×2), 128.6 (×5), 128.7 (×3), 128.8, 129.1, 129.9 (×3), 130.0 (×3), 130.1 (×2), 133.2, 133.3, 133.5, 136.9, 137.7, 165.7, 165.9, 166.4 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{41}H_{36}O_9Na$ 695.2257, found 695.2244.

*Methyl 3-O-(3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-glucopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside (**19**).* The title compound was obtained by method C from **12a** and **15** in 89% yield as a colorless syrup (α/β > 25/1). Selected analytical data for α-**19**: R_f = 0.54 (ethyl acetate−toluene, 3/17, v/v); $[\alpha]_D^{23}$ +88.9 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.31 (s, 3H, OCH_3), 3.60 (dd, 1H, $J_{5,6a}$ = 1.7 Hz, $J_{6a,6b}$ = 10.7 Hz, H-6a), 3.66 (dd, 1H, $J_{5,6b}$ = 3.4 Hz, H-6b), 3.69 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 3.71−3.78 (m, 2H, $J_{2',3'}$ = 9.8 Hz, H-2′, 5), 3.83 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 4.00 (dd, 1H, $J_{5',6a'}$ = 4.7 Hz, $J_{6a',6b'}$ = 12.3 Hz, H-6a′), 4.34 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.34 (dd, 1H, $J_{5',6b'}$ = 2.3 Hz, H-6b′), 4.38 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.49 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.65 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph),4.69 (dd, 2H, ^2J = 11.5 Hz, CH_2Ph), 4.73 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.94 (m, 1H, H-5′), 5.43 (dd, 1H, $J_{4',5'}$ = 10.0 Hz, H-4′), 5.68 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 6.08 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, H-3′), 6.80−8.10 (m, 35H, aromatic) ppm; ^{13}C NMR δ 55.3, 63.3, 67.7, 68.6, 69.9, 72.3, 72.7, 73.5 (×2), 73.7, 76.5, 77.2, 77.3, 78.4, 78.8, 97.1, 97.6, 126.7 (×2), 127.4, 127.8, 127.9, 128.0 (×2), 128.1 (×2), 128.2, 128.3 (×2), 128.4 (×11), 128.6 (×2), 128.7 (×2), 129.3, 129.9 (×2), 129.9 (×4), 130.1 (×2), 130.3, 132.9, 133.1, 133.3, 137.3, 137.9, 138.0, 138.6, 165.6, 166.0, 166.5 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{62}H_{60}O_{14}Na$ 1051.3881, found 1051.3897.

*Methyl 2-O-(3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-glucopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside (**20**).* The title compound was obtained by method C from **12a** and **16** in 87% yield as a colorless syrup (α/β > 25/1). Selected analytical data for α-**20**: R_f = 0.54 (ethyl acetate−toluene, 3/17, v/v); $[\alpha]_D^{23}$ +107.8 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.49 (s, 3H, OCH_3), 3.69 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.73 (dd, 1H, $J_{5,6a}$ = 1.8 Hz, $J_{6a,6b}$ = 10.7 Hz, H-6a), 3.81 (dd, 1H, $J_{5,6b}$ = 3.5 Hz, H-6b), 3.81−3.86 (m, 1H, H-5), 3.85 (dd, 1H, $J_{2',3'}$ = 10.0 Hz, H-2′), 4.01 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.13 (dd, 1H, $J_{5',6a'}$ = 5.3 Hz, $J_{6a',6b'}$ = 12.2 Hz, H-6a′), 4.18 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-3), 4.39 (dd, 1H, $J_{5',6b'}$ = 2.1 Hz, H-6b′), 4.62 (m, 1H, H-5′), 4.62 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.67 (s, 2H, CH_2Ph), 4.68 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.99 (d, 1H, H-1), 5.10 (dd, 2H, ^2J = 11.3 Hz, CH_2Ph), 5.14 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 5.45 (dd, 1H, $J_{4',5'}$ = 10.0 Hz, H-4′), 6.06 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, H-3′), 7.10−8.11 (m, 35H, aromatic) ppm; ^{13}C NMR δ 55.2, 63.0, 68.0, 68.7, 69.7, 70.5, 72.3, 72.7, 73.8, 75.3, 75.4, 75.9, 76.5, 78.4, 80.7, 94.2, 96.6, 127.5 (×2), 127.6, 127.9 (×2), 128.0 (×2), 128.1 (×2), 128.2, 128.5 (×9), 128.4 (×11), 128.6 (×7), 129.1, 129.9 (×2), 130.0 (×2), 130.1 (×2), 133.1, 133.2, 133.4, 137.8, 138.2, 138.3, 138.7, 165.6, 165.7, 166.2 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{62}H_{60}O_{14}Na$ 1051.3881, found 1051.3908.

*Methyl 4-O-(3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (**22**).* The title compound was obtained by method C from **12a** and **21** in 82% yield as a colorless syrup (α/β > 25/1). Selected analytical data for α-**22**: R_f = 0.51 (ethyl acetate−toluene, 3/17, v/v); $[\alpha]_D^{23}$ +42.3 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 3.37 (s, 3H, OCH_3), 3.56 (dd, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 3.62 (dd, 1H, $J_{2',3'}$ = 9.8 Hz, H-2′), 3.66 (dd, 1H, $J_{6a,6b}$ = 11.1 Hz, H-6a), 3.88 (m, 1H, H-5), 4.01 (dd, 1H, H-6b), 4.04−4.14 (m, 2H, H-3, 4), 4.18 (dd, 1H, $J_{5',6a'}$ = 5.1 Hz, $J_{6a',6b'}$ = 12.2 Hz, H-6a′), 4.28−4.39 (m, 2H, $J_{5',6b'}$ = 2.6 Hz, H-5′, 6b′), 4.31 (dd, 2H, ^2J = 12.4 Hz, CH_2Ph), 4.53 (s, 2H, CH_2Ph), 4.59 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 4.64 (dd, 2H, ^2J = 12.1 Hz, CH_2Ph), 4.93 (dd, 2H, ^2J = 11.6 Hz, CH_2Ph), 5.40 (dd, 1H, $J_{4',5'}$ = 9.8 Hz, H-4′), 5.64 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 5.94 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, H-3′), 6.59−8.01 (m, 35H, aromatic) ppm; ^{13}C NMR δ 55.4, 63.3, 68.5, 69.2, 69.8, 69.9, 71.8, 72.7, 73.6, 73.7, 74.4, 74.7, 77.4, 80.2, 81.7, 96.6, 98.0, 127.1 (×2), 127.2, 127.7 (×2), 127.8, 127.9, 128.0 (×2), 128.1, 128.3 (×3), 128.4 (×2), 128.5 (×7), 128.6 (×2), 128.7 (×2), 129.2 (×2), 129.8, 129.9 (×3), 130.0 (×3), 133.1, 133.2, 133.5, 137.4, 138.0, 138.2, 139.3, 165.6, 165.9, 166.2 ppm; HR-FAB-MS [M+Na]$^+$ calcd for $C_{62}H_{60}O_{14}Na$ 1051.3881, found 1051.3893.

Low-Temperature *in Situ* NMR Monitoring. A thioglycoside (10 mg) was dissolved in $CDCl_3$ (0.7 mL) and placed in the standard 5 mm NMR tube equipped with a septum, and the tube was then placed into a Dewar filled with liquid nitrogen (−196 °C) for 10 min. Bromine (1.0 equiv) was added via syringe, the NMR tube was removed from the Dewar (upon which the temperature was allowed to increase to ambient) and immediately inserted into the magnet, and the proton spectrum was recorded (approximately 5 min after Br_2 addition).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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DEDICATION

Dedicated to the memory of David Gin.

REFERENCES

(1) Galonic, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000−1007.
(2) *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008.
(3) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900−1934.
(4) Whitfield, D. M. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 83−159.
(5) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497−510.
(6) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144−1153.
(7) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215−3218.
(8) Kulkarni, S. S.; Gervay-Hague, J. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008, p 59−93.
(9) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062 and references therein..
(10) Demchenko, A. V. *Synlett* **2003**, 1225−1240.
(11) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8293−8298.
(12) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119−125.
(13) Meloncelli, P. J.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1110−1122.
(14) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2002**, *4*, 2039−2042.
(15) Liptak, A.; Jodal, I.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1−11.
(16) Weygand, F.; Ziemann, H. *Justus Liebigs Ann.Chem.* **1962**, *657*, 179−198.
(17) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.
(18) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem.—Eur. J.* **2002**, *8*, 1218−1226.
(19) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259−265.
(20) Lemieux, R. U. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolform, M. L., Eds.; Academic Press Inc.: New York/London, 1963; Vol. *2*, pp 226−228.
(21) Mydock, L. K.; Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2011**, *13*, 2928−2931.
(22) Crich, D.; Dai, Z.; Gastaldi, S. *J. Org. Chem.* **1999**, *64*, 5224−5229.
(23) Yamago, S.; Yamada, T.; Hara, O.; Ito, H.; Mino, Y.; Yoshida, J. *Org. Lett.* **2001**, *3*, 3867−3870.
(24) Chittenden, G. J. F. *Carbohydr. Res.* **1992**, *242*, 297−301.
(25) Ibatulin, F. M.; Selivanov, S. I. *Tetrahedron Lett.* **2002**, *43*, 9577−9580.
(26) Pozsgay, V.; Robbins, J. B. *Carbohydr. Res.* **1995**, *277*, 51−66.
(27) Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860−2863.
(28) Lonn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301−306.
(29) Codee, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057−1064.
(30) Goodman, L. *Adv. Carbohydr. Chem. Biochem.* **1967**, *22*, 109−175.
(31) Bérces, A.; Enright, G.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460−5464.
(32) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291−13295.
(33) Stalford, S. A.; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Org. Biomol. Chem.* **2009**, *7*, 4842−4852.
(34) Andersson, F.; Fugedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919−3922.
(35) Nukada, T.; Berces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.* **2005**, *340*, 841−852.
(36) Capon, B. *Chem. Rev.* **1969**, *69*, 407−496.
(37) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112−13119.
(38) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386−5389 and references therein.
(39) Boebel, T. A.; Gin, D. Y. *J. Org. Chem.* **2005**, *70*, 5818−5826.
(40) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J. *Org. Lett.* **2011**, *13*, 1544−1547.
(41) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.
(42) Zhang, Z.; Wong, C. H. *Tetrahedron* **2002**, *58*, 6513−6519.
(43) Sollogoub, M.; Das, S. K.; Mallet, J.-M.; Sinay, P. *C. R. Acad. Sci. Ser. 2* **1999**, *2*, 441−448.
(44) Koenigs, W.; Knorr, E. *Ber. Deutsch. Chem. Ges.* **1901**, *34*, 957−981.
(45) Fischer, E.; Armstrong, E. F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2885−2900.
(46) Isbell, H. S. *Annu. Rev. Biochem.* **1940**, *9*, 65−92.
(47) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243−283.
(48) Helferich, B.; Bohn, E.; Winkler, S. *Ber. Dtsch. Chem. Ges.* **1930**, *63B*, 989−998.
(49) Helferich, B.; Gootz, R. *Ber. Dtsch. Chem. Ges.* **1931**, *64B*, 109−114.
(50) Helferich, B.; Wedemeyer, K. F. *Justus Liebigs Ann. Chem.* **1949**, *563*, 139−145.
(51) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10−C11.
(52) van Straten, N. C. R.; Kriek, N. M. A. J.; Timmers, C. M.; Wigchert, S. C. M.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1997**, *16*, 947−966.
(53) Koto, S.; Uchida, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2520−2523.