

Carbohydrate Chemistry

Bromine-Promoted Glycosidation of Conformationally Superarmed Thioglycosides

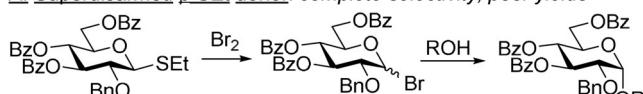
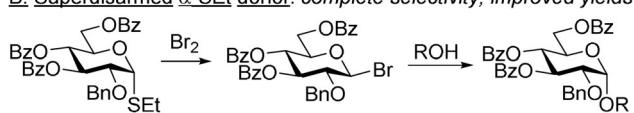
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Abstract: Presented herein is a study of the conformation and reactivity of highly reactive thioglycoside donors. The structural studies have been conducted using NMR spectroscopy and computational methods. The reactivity of these donors has been investigated in bromine-promoted glycosylations of aliphatic and sugar alcohols. Swift reaction times, high yields, and respectable 1,2-cis stereoselectivity were observed in a majority of these glycosylations.

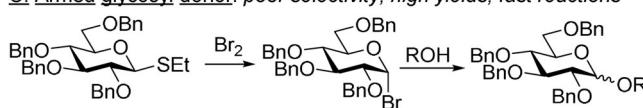
While understanding the structure and functions of carbohydrates is difficult,^[1] it is glycosylation, which is flawlessly executed by enzymes,^[2] that has proven to be a particularly challenging reaction to chemists. With the aid of modern methods, strategies, and technologies, the formation of many glycosidic bonds can now be achieved.^[3] The development of glycosylation reactions that will offer new capabilities for obtaining complex glycans with exclusive stereoselectivity and enhanced purity remains an important area of research in the field of synthetic chemistry. The goal of controlling glycosylation has been pursued in many ways, with the main focus recently shifting to studying stereoelectronics and conformation of the starting material and key reaction intermediates. Although some model studies have helped to establish general trends,^[4] practical application of the stereoelectronic and conformational factors to stereocontrol of glycosylations is still limited.

Fraser-Reid's seminal work on the armed-disarmed approach showed that the building block reactivity can be modulated through the choice of protecting groups.^[5] In recent years, the scope of the original armed-disarmed concept has been expanded, and a number of reactivity levels that extend beyond the traditional armed-disarmed boundary have been established.^[6] Following other early work in the area,^[7] our group reported that 2-O-benzyl-3,4,6-tri-O-benzoyl protected donors

are less reactive (superdisarmed) than their disarmed per-Bz counterparts.^[8] This unexpected protecting group effect was explained by the existence of the O-2/O-5 cooperative effect that takes into consideration the stabilization of reaction intermediates, rather than only the electronics of the starting material. While studying the activation of superdisarmed thioglycosides with Br₂, we developed conditions at which the β -bromide was the only intermediate leading to products (Scheme 1 A).^[9] The oxacarbenium ion either did not form or

A. Superdisarmed β -SEt donor: complete selectivity, poor yieldsB. Superdisarmed α -SEt donor: complete selectivity, improved yields

C. Armed glycosyl donor: poor selectivity, high yields, fast reactions

Scheme 1. Previous glycosidations of thioglycosides with Br₂.

had no contribution to the formation of glycosides. As a result, the nucleophilic displacement of the β -bromide intermediate took place in the concerted fashion leading to exclusive α -stereoselectivity of all glycosylations. Since the α -bromide remained totally unreactive in this reaction, α -thioglycoside precursor was found to be a more suitable precursor to generate the desired β -bromide intermediate stereoselectively (Scheme 1B). This strategic adjustment led to improved yields, however, unreactive glycosyl acceptors still produced only moderate yields.

To enhance the reaction rates and achieve more practical yields, we also investigated per-benzylated armed thioglycosides (Scheme 1C). Although those reactive donors could indeed be glycosylated quite rapidly in the presence of Br₂, providing good yields, a decreased stereoselectivity was encountered.^[9] These reactions proceeded via the intermediacy of the α -bromide that was sufficiently reactive in the armed series to couple with an acceptor. Low temperature NMR experiments^[10] showed that the β -bromide was also present at the early stage of the reaction. However, it was thought to be

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Supporting information, including full experimental details and compound characterization, and the ORCID identification number(s) for the author(s) of this article can be found under: <https://doi.org/10.1002/chem.201901969>.

an insignificant intermediate en route to the product formation due to its rapid anomerization into the α -counterpart.

Described herein is our dedicated effort to extend the bromine-promoted glycosylation reaction to the investigation of glycosyl donors of the superarmed series. There are two known concepts for superarming glycosyl donors. The first concept, wherein the enhancement of reactivity was achieved by changing the equatorial-rich 4C_1 conformation to an axial-rich skew-boat conformation by creating steric congestion with *tert*-butyldimethylsilyl (TBS) protecting groups at the C-2, -3 and -4, was introduced by Bols and co-workers.^[11] The second concept introduced by our group involves the electronic superarming using conventions of the O-2/O-5 cooperative effect. According to this effect, intermediates obtained from the 2-O-benzoyl-3,4,6-tri-O-benzyl-protected glycosyl donors are stabilized both anchimerically by the ester substituent at O-2 and electronically by the O-5 that is surrounded by electron-rich ethers.^[12] Bols' and our groups have also jointly developed glycosyl donors with combined conformational and anchimeric superarming.^[13] However, none of the superarmed donors developed to date can be applied to the stereoselective synthesis of 1,2-*cis* glycosides. The development of highly reactive (superarmed) α -stereoselective glycosyl donors would be very useful for all investigators working on synthesizing 1,2-*cis*-linked glycans in solution and solid supports.^[14]

With a goal of investigating superarmed glycosyl donors in application to 1,2-*cis* glycosylation, we began studying conformational properties of a series of β -ethylthio glycosides **β-1–3**, prepared from a common diol precursor **β-1**.^[13b] 1H NMR spectrum was recorded at rt and the coupling constants were consistent with those expected for the standard 4C_1 chair conformation, typical for α -D-glucose derivatives.^[15] We have also recorded a ^{13}C NMR spectrum, and the list of signals is included in Table 1. Diol precursor **β-1** was then protected with TBS groups at C-3 and C-4 positions to obtain compound **β-2**. 1H and ^{13}C NMR spectra were recorded at rt. The coupling constants obtained from the 1H spectrum clearly showed an increasing distortion in the conformation of **β-2** from the standard 4C_1 conformation observed for **β-1**. The *J* values were consistent with the previously reported values for similar compounds.^[6, 11a–c] The difference was particularly noticeable in the values for $J_{2,3}$ and $J_{3,4}$. Thus, $J_{2,3}$ decreases noticeably from 9.2 Hz in **β-1** to 3.9 Hz in **β-2** and $J_{3,4}$ decreases from 8.7 Hz in **β-1** to 5.0 Hz in **β-2**. This change was also associated with a shift of the anomeric proton downfield from 4.51 ppm in **β-1** to 4.79 ppm in **β-2**. This shift could be a sign of a particular distribution of functional groups around the ring. The remaining ring protons H-2–5 are all shifted downfield when TBS groups are added.

A further conformational change was observed for 3,4-di-O-triisopropylsilyl (TIPS) glucoside **β-3** as judged by the coupling constants of $J_{2,3}=J_{3,4}=J_{4,5}=0$ Hz. The value could be related to compound **β-3** adopting an axial-rich conformation to release the steric strain caused by bulky silyl groups at C-3 and C-4. All ring proton signals H-2–5 in **β-3** experience even greater downfield $\Delta\delta$ shift than those recorded for **β-2**, while the

Table 1. NMR data for thioglycosides **β-1–3**.

Cmpd	Signal	1H NMR [ppm]	<i>J</i> [Hz]	^{13}C NMR [ppm]	
				^{13}C NMR [ppm]	
β-1	H/C-1	4.51 (d)	$J_{1,2}=9.7$	85.06	
	H/C-2	3.28 (dd)	$J_{2,3}=9.2$	80.87	
	H/C-3	3.63 (dd)	$J_{3,4}=8.7$	77.95	
	H/C-4	3.47 (dd)	$J_{4,5}=9.2$	70.13	
	H/C-5	3.55–3.59 (m)	ND	77.82	
	H/C-6	4.57 (br d) 4.69–6.62 (m)	$J_{6a,6b}=12.1$	64.16	
β-2	H/C-1	4.79 (d)	$J_{1,2}=8.3$	82.81	
	H/C-2	3.42 (dd)	$J_{2,3}=3.9$	82.50	
	H/C-3	3.91–3.86 (m)	$J_{3,4}=5.0$	76.44	
	H/C-4	3.80 (t)	$J_{4,5}=5.0$	71.68	
	H/C-5	3.97–3.91 (m)	$J_{5,6a}=7.4$ $J_{5,6b}=4.9$	79.41	
	H/C-6	4.41 (dd) 4.61 (dd)	$J_{6a,6b}=11.3$	65.52	
β-3	H/C-1	5.05 (d)	$J_{1,2}=8.5$	81.23	
	H/C-2	3.60 (d)	$J_{2,3}=0$	83.09	
	H/C-3	4.16 (bs)	$J_{3,4}=0$	70.89	
	H/C-4	4.27 (bs)	$J_{4,5}=0$	75.71	
	H/C-5	4.24 (t)	$J_{5,6a}=6.9$ $J_{5,6b}=6.9$	80.79	
	H/C-6	4.50 (dd) 4.62 (dd)	$J_{6a,6b}=11.0$	66.13	

shifts for the H-6 protons are not affected by the 3,4-di-O-silylation.

Interesting trends have also been observed by comparing the ^{13}C NMR spectra of compounds **β-1–3**. The chemical shifts of C-1, C-2 and C-5 were found to be particularly diagnostic of the conformational changes undergone by the ring. The trend identified is in shifting of the C-1 and C-3 signals upfield, whereas C-2, C-4 and C-5 shift downfield. For example, the C-1 signal moves from 85.06 for **β-1** to 82.81 of **β-2** and to 81.23 ppm for **β-3**. In contrast, C-5 shifts from 77.82 to 79.41 to 80.79 ppm in the same sequence of compounds.

Due to the significant changes in the coupling constants, ring distortion was anticipated. Computational experiments were set up to investigate whether the *in silico* data would support the experimental data. A series of computational studies was performed on the compounds **β-1–3**. Computational models of thioglycosides **β-2** and **β-3** were built by implementing the following workflow: 1) Monte Carlo/Energy Minimization (MC/EM) conformational search was carried out at the molecular mechanics level (OPLS2005 force field) leaving all dihedral angles free to move; 2) Representative minimum-energy geometries of MC/EM search was optimized at the DFT B3LYP/6-31G* level of theory; 3) The obtained stationary points were confirmed as minima by calculating vibrational frequencies at the same level of theory and their thermochemical properties, including the final denoted total Gibbs free energy, were computed. DFT minimum energy structures and relative energy dif-

Table 2. DFT B3LYP/6-31G* minimum energy structures of thioglycosides β -2 and β -3 with relative Gibbs free energies.

Cmpd	Conformation	Relative energy [kcal mol ⁻¹]
β -2	4C_1 chair	0.00
	1C_4 chair	0.75
	3O boat	1.32
	2S_0 skew-boat	2.53
β -3	3S_1 skew-boat	0.00
	1C_4 chair	2.24
	2S_0 skew-boat	4.72

ferences, resulting from these computational studies, are summarized in Table 2.

In the case of compound β -2, the standard 4C_1 chair conformation is the most stable, whereas the axial-rich 1C_4 chair and 3O boat conformations lie at 0.75 and 1.32 kcal mol⁻¹, respectively, above the minimum energy structure, likely contributing to the conformational equilibrium. Interestingly, the axial-rich skew-boat conformation 3S_1 was located by DFT calculations as the lowest energy minimum of the 3,4-di-O-TIPS glucoside β -3 (Figure 1), followed by the 1C_4 chair at 2.24 kcal mol⁻¹. The

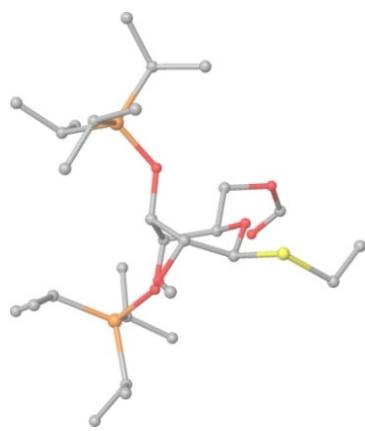


Figure 1. DFT-optimized 3S_1 skew-boat conformation of 3,4-di-O-TIPS thioglycoside β -3 (hydrogens and phenyl groups have been omitted for clarity in the ball and stick 3D-representation).

computational data achieved for thioglycosides β -2 and β -3 match well the experimental trend, with the calculated coupling constant values of the most stable skew-boat conformation of β -3 being very close to the experimental ones (see the Supporting Information, Tables S1 and S2).

To study the reactivity of thioglycoside β -2, the respective bromide 4 was generated by the reaction with Br_2 following previously established reaction conditions.^[9] We theorized that the activation of superarmed donors with Br_2 will allow us to investigate whether the conformational superarming may offer additional stabilization modes to the anticipated β -bromide intermediate. When donors in the traditional 4C_1 conformation are used for the synthesis of β -bromides, the latter are able to

undergo conformational changes to adopt the axial or pseudoaxial orientation (Figure 2).^[16] Since this adopted conformation is unstable, the β -bromide equilibrates into the thermodynamically stable α -counterpart and hence returns to its original 4C_1 conformation. Conversely, if the starting donor is already

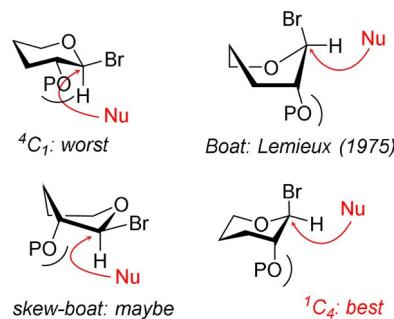
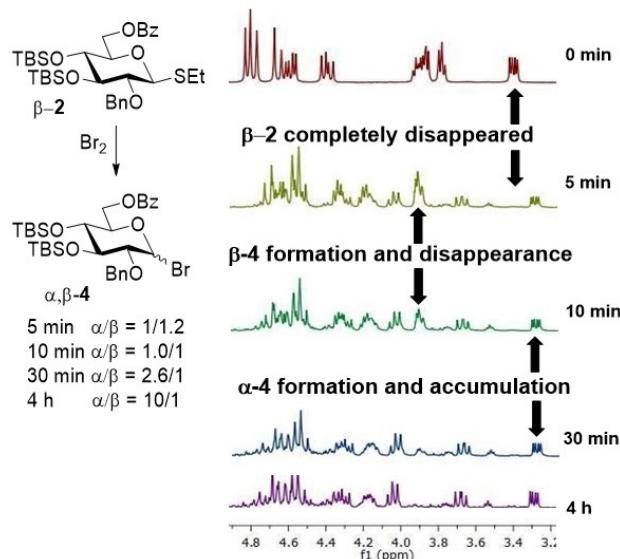


Figure 2. Conformation and stereoselectivity of β -bromides.

present as a skew-boat, as determined for the conformationally superarmed donors, the formation of β -bromide will additionally reinforce the all-axial conformation. If the axial β -bromide is stabilized by the anomeric effect, as in compounds with the preferred 1C_4 conformation (Figure 2), it will be both kinetically and thermodynamically stable and will not equilibrate (or will equilibrate much slower) into the α -counterpart. The analogy is found in Matsuda and Shuto's study of xylose derivatives and their observation of altered anomeric effect and reversed stereoselectivity in glycosylations.^[17] However, the hexose chair is much more difficult to flip due to the CH_2OR substituent at C-5 that has a strong propensity to reside equatorially.^[18]

Thus, bromide 4 obtained from 3,4-di-O-TBS donor β -2 was studied using a 300 MHz NMR as depicted in Scheme 2. Molecular bromine was injected into a frozen solution of the donor



Scheme 2. Conversion of 3,4-di-O-TBS β -SEt glucoside β -2 into α,β -bromides 4.

in CDCl_3 . The mixture was allowed to melt at -50°C and then ^1H NMR spectra were recorded at different time points. The starting material has been completely consumed within the first 5 min of the reaction monitoring, as judged by disappearance of the diagnostic signal for H-2 at 3.42 ppm. The presence of both α - and β -bromides **4** was also detected at this timepoint. The signal for H-1 at 6.50 ppm is diagnostic, but it cannot be used for quantifying the ratios of bromides because it coincides for both anomers. In this respect, reaction monitoring using more diagnostic signals at 3.94 ppm for H-2, H-3 of β -**4** and at 3.25 ppm for H-2 of α -**4** was proven most convenient.

As shown in Scheme 2, the anomeric mixture of bromides **4** has almost completely converted into the α -anomer at 30 min timepoint. Also evident at this timepoint is the presence of a decomposed by-product due to the anticipated partial loss of TBS protecting groups. This was an indication that the chosen starting β -thioglycoside is probably not the most suitable precursor for generating the β -bromide, even with the assistance of the TBS groups. It should be noted that we also attempted to convert thioglycoside **β-3** into the corresponding bromide. Unfortunately, this attempt was largely unsuccessful due to a very rapid cleavage of TIPS groups in the presence of Br_2 , perhaps due to a significant weakening of the O–Si bonds due to the steric congestion that these compounds experience.

In the attempt of achieving a more stereocontrolled formation of the reactive β -bromide intermediate, we turned our attention to investigating α -configured SEt donor. The analogy can be found in our previous study wherein superdisarmed α -SEt precursor produced the corresponding β -bromide predominantly.^[9] Starting from diol **α-1**, we obtained TBS and TIPS protected thioglycosides, **α-2** and **α-3**, respectively. The coupling constants calculated from their proton NMR spectra clearly demonstrated the conformational changes taking place. Thus, in the series of compounds **α-1**, **α-2** and **α-3**, the $J_{2,3}$ value decreases from 9.5 to 7.4 to 3.7 Hz. Coupling constants $J_{3,4}$ and $J_{4,5}$ behave similarly showing a steady decrease (Table 3). Differently from the β -series, no dramatic signal shifts were observed in the ^1H and ^{13}C NMR spectra of the α -series. As a matter of fact, the chemical shift difference between **α-1** and **α-2** is minimal, with somewhat more significant changes observed for **α-3**. This observation may be an indication of notable changes taking place upon transition from TBS to sterically more demanding TIPS groups.

The computational data for α -thioglycosides was also consistent with the experimental observations. Computational models of thioglycosides **α-2** and **α-3** were built by implementing the same protocol as that applied to the β -series. Only $^4\text{C}_1$ and $^1\text{C}_4$ chair conformations were located as minimum energy structures, showing the importance of the axial-rich $^1\text{C}_4$ chair geometry for compound **α-3** always higher than that for **α-2**, according to both relative SCF DFT/B3LYP and Gibbs free energies (see Supporting Information, Tables S3 and S4).

To study the reactivity of this series of compounds, the NMR monitoring of the formation of anomeric bromide **4** from thioglycoside **α-2** was conducted. The procedure used herein was the same as that applied to the β -counterpart of **2** (vide

Table 3. NMR data for thioglycosides **α-1–3**.

Cmpd	Signal	^1H NMR [ppm]	J [Hz]	^{13}C NMR [ppm]
α-1	H/C-1	5.44 (d)	$J_{1,2}=5.4$	82.69
	H/C-2	3.64 (dd)	$J_{2,3}=9.5$	78.56
	H/C-3	3.85 (t)	$J_{3,4}=9.4$	73.60
	H/C-4	3.50 (t)	$J_{4,5}=9.4$	70.21
	H/C-5	4.32 (ddd)	$J_{5,6a}=5.1$ $J_{5,6b}=1.9$	69.86
	H/C-6	4.58–4.47 (m) 4.69 (dd)	$J_{6a,6b}=12.1$	63.98
α-2	H/C-1	5.41 (d)	$J_{1,2}=4.9$	82.54
	H/C-2	3.61 (dd)	$J_{2,3}=7.4$	79.25
	H/C-3	3.96–3.93 (m)	$J_{3,4}=6.0$	73.92
	H/C-4	3.65 (dd)	$J_{4,5}=8.7$	72.95
	H/C-5	4.35–4.31 (m)	$J_{5,6a}=7.0$ $J_{5,6b}=2.1$	71.65
	H/C-6	4.38 (dd) 4.59 (dd)	$J_{6a,6b}=11.5$	64.52
α-3	H/C-1	5.41 (d)	$J_{1,2}=3.4$	79.73
	H/C-2	3.68 (t)	$J_{2,3}=3.7$	78.31
	H/C-3	4.26–4.22 (m)	$J_{3,4}=2.7$	71.94
	H/C-4	3.96 (dd)	$J_{4,5}=4.9$	71.39
	H/C-5	4.42–4.37 (m)	$J_{5,6a}=7.9$ $J_{5,6b}=3.4$	75.12
	H/C-6	4.45 (dd) 4.74 (dd)	$J_{6a,6b}=11.8$	63.48

supra). After 5 minutes, only β -bromide **4** was detected. At the 10-minute timepoint, the intermediate is still largely β -**4**, and only a small peak at $\delta \approx 3.3$ ppm is indicating the beginning of the anomerization process to α -**4**. Only after 2 hours, the reactive bromide β -**4** has completely anomerized to α -**4**. Computational models of α - and β -bromides **4** were built by implementing the same protocol applied for thioglycosides yet using the LACVP basis set due to the presence of bromine atoms. Only standard $^4\text{C}_1$ chair conformations were achieved for compound α -**4**, whereas a distorted ^{14}B boat (or an unusual $^4\text{S}_2$ skew-boat) conformation was located by DFT calculations as the lowest energy minimum of compound β -**4** (Tables S5 and S6).

Having acquired the evidence of adequate stability of the reactive intermediate β -**4**, glycosidations of donor **α-2** with model glycosyl acceptors were conducted. At first, when Br_2 was added to the reaction mixture containing donor **α-2** and a glycosyl acceptor at -50°C we observed that the formation of the desired disaccharide was accompanied by the formation of multiple by-products. These products were formed as a result of competing side reactions including hydrolysis and partial deprotection of the TBS groups. Therefore, to suppress the side reactions, we chose to add a sub-stoichiometric amount of a base to each glycosylation reaction mixture. Three basic additives were investigated: triethylamine (TEA), *N,N*-diisopropylethylamine (DIPEA) and 1,8-diazabicycloundec-7-ene (DBU), and all three provided comparable results. Under these reac-

tion conditions, glycosidation of donor α -2 with primary 6-OH glycosyl acceptor 5 afforded the desired disaccharide 6 in high yields of 82–95% and with complete α -stereoselectivity (entry 1, Table 4). Glycosidation of donor α -2 with secondary 2-OH glycosyl acceptor 7 afforded the desired disaccharide 8 in good yields of 74–79% and with good α -stereoselectivity ($\alpha/\beta=8$ –13/1, entry 2). Highly reactive aliphatic alcohols such as iPrOH, cyclohexanol, and benzyl alcohol were investigated, affording the target glucosides 9–11 in high yields 78–99%, albeit unremarkable stereoselectivity ($\alpha/\beta=2$ –5/1, entries 3–5). This poor stereoselectivity may be a result of a direct displacement of the anomeric α -bromide with powerful nucleophiles that does not take place with sugar acceptors. 3,4-di-O-TIPS protected donor α -3 provided a similar reactivity trend, but its glycosidations were compromised by the competing silyl group cleavage, even in the presence of a base (see the Supporting Information for additional experimental data).

In conclusion, we expanded the application of Br_2 -mediated glycosidation of thioglycosides to glycosyl donors of the super-

armed series. Over the course of this study, we investigated the formation of the reactive intermediates that were monitored and characterized by NMR spectroscopic techniques. An extensive conformational analysis of the donor through coupling constants values and carbon-hydrogen correlation was performed. Furthermore, the stability of β -bromide in solution over time was studied using NMR. The experimental data are supported by the molecular mechanic calculations and the DFT studies. Glycosylation reactions were performed with a group of standard acceptors, achieving high yields and high to complete stereoselectivity with sugar acceptors. These results complement our other recent studies dedicated to the activation of glycosyl halides.^[19]

Acknowledgements

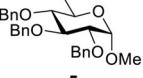
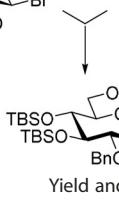
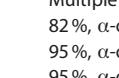
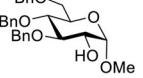
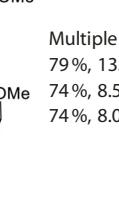
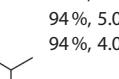
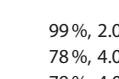
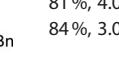
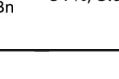
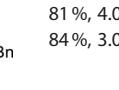
This work was supported by the National Institute of General Medical Sciences (U01GM120673) and the National Science Foundation (CHE-1800350).

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbohydrate chemistry • glycosylation • stereocontrolled reactions • synthesis

Table 4. Glycosidation of 3,4-di-O-TBS donor α -2.

Entry	Acceptor	Base	Product	Yield and α/β ratio
1	 5	none		Multiple products
		TEA	 6	82%, α -only
		DBU	 6	95%, α -only
		DIPEA	 6	95%, α -only
2	 7	none		Multiple products
		TEA	 8	79%, 13.0/1
		DBU	 8	74%, 8.5/1
		DIPEA	 8	74%, 8.0/1
3	iPrOH	TEA	 9	99%, 5.0/1
		DBU	 9	94%, 5.0/1
		DIPEA	 9	94%, 4.0/1
4	CyOH	TEA	 10	99%, 2.0/1
		DBU	 10	78%, 4.0/1
		DIPEA	 10	78%, 4.0/1
5	BnOH	TEA	 11	99%, 3.0/1
		DBU	 11	81%, 4.0/1
		DIPEA	 11	84%, 3.0/1

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Manuscript received: April 29, 2019

Revised manuscript received: July 3, 2019

Accepted manuscript online: July 8, 2019

Version of record online: August 20, 2019