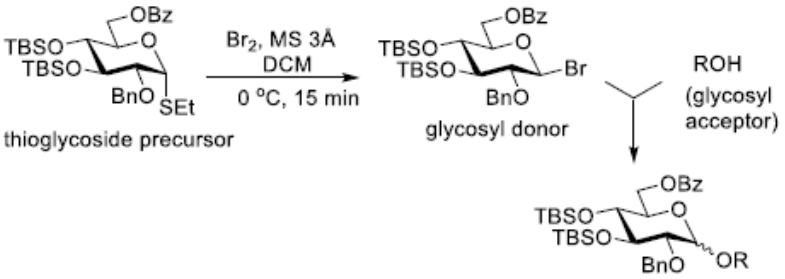
Bromine-promoted glycosidation of conformationally superarmed thioglycosides

Matteo Panza,[a] Monica Civera,[b] Jagodige P. Yasomanee,[a] Laura Belvisi,[b,*] and Alexei V. Demchenko[a,*]

[a] Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, Missouri 63121, USA

[b] Department of Chemistry, University of Milan, 20133 Milan, Italy



ABSTRACT: Presented herein is our study of the conformation and reactivity of highly reactive thioglycoside donors. The structural studies have been conducted using NMR spectroscopic 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.

Introduction

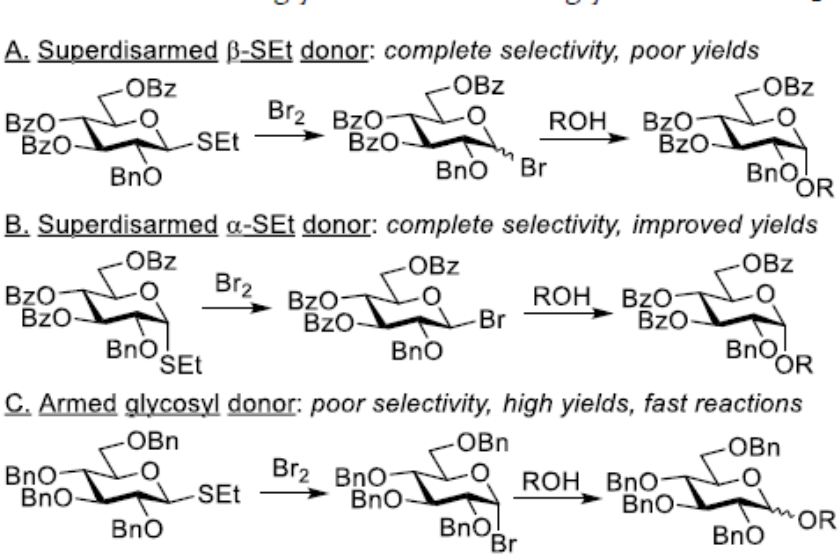
While understanding the structure and functions of carbohydrates is difficult,[1] it is glycosylation that is flawlessly executed by enzymes[2] has proven a particularly challenging reaction to chemists. With the aid of modern methods, strategies, and technologies, the formation of many glycosidic bonds 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 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 O2/O5 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 1A).[9] The oxacarbenium ion either did not form or 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 fond 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 glycosidated 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 an insignificant intermediate *en route* to the product formation due to its rapid anomerization into the α-counterpart.

Scheme 1. Previous glycosidations of thioglycosides with Br_2



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 *t*-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 O2/O5 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]

Results and discussion

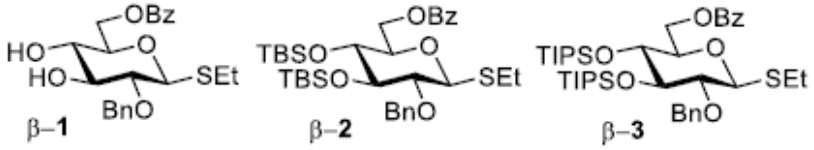
With a goal of investigating superarmed glycosyl donors in application to 1,2-*cis* glycosylation, we began studying conformational properties of a series of β-ethylthio glycosides β-**1-3**, prepared from a common diol precursor β-**1**.[15] 1H spectrum was recorded at rt and the coupling constants were consistent with those expected for the standard 4C1 chair conformation, typical for D-glucose derivatives.[16] We have also recorded a 13C 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 13C 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 4C1 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 in β-**1** to 3.9 Hz in β-**2** and $J_{3,4}$ decreases from 9.2 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 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-3,4. All ring proton signals H-2-5 in β-**3** experience even greater downfield Δδ shift than those recorded for β-**2**, while the shifts for the H-6 protons are not affected by the 3,4-*O*-silylation.

Interesting trends have also been observed by comparing the 13C 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 were 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 differences, resulting from these computational studies, are summarized in Table 2.

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



Cmpd	Signal	^{1}H NMR, ppm	*J*, Hz	^{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

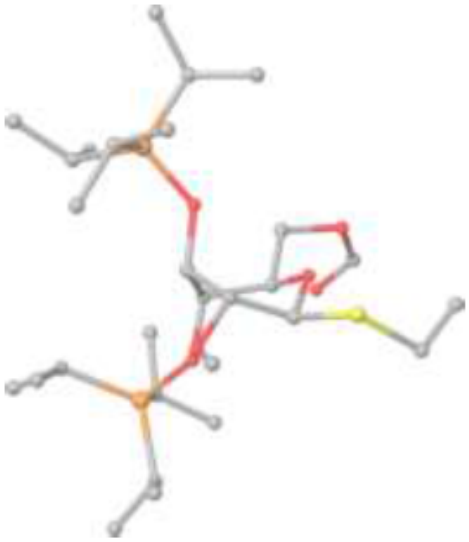
Table 2. DFT B3LYP/6-31G* minimum energy structures of thioglycosides β-**2** and β-**3** with relative Gibbs free energies

Cmpd	Conformation	Relative energy
β-2	^{4}C$_1$ chair	0.00 kcal mol^{-1}
	^{1}C$_4$ chair	0.75 kcal mol^{-1}
	^{3,O}B boat	1.32 kcal mol^{-1}
	^{2}S$_O$ skew-boat	2.53 kcal mol^{-1}
β-3	^{3}S$_1$ skew-boat	0.00 kcal mol^{-1}
	^{1}C$_4$ chair	2.24 kcal mol^{-1}
	^{2}S$_O$ skew-boat	4.72 kcal mol^{-1}

In the case of compound β-**2**, the standard 4C1 chair conformation is the most stable, whereas the axial-rich 1C4 chair and 3,OB boat conformations lie 0.75 and 1.32 kcal mol-1, respectively, above the minimum energy structure, likely contributing to the conformational

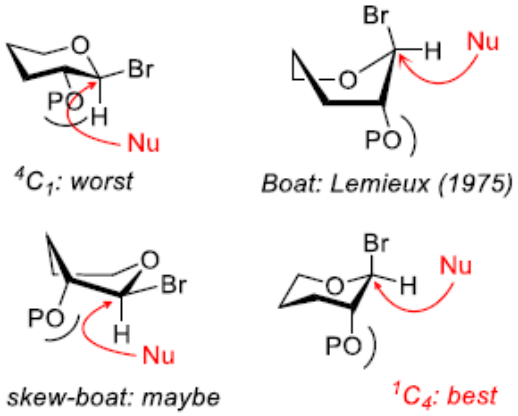
equilibrium. Interestingly, the axial-rich skew-boat conformation 3S1 was located by DFT calculations as the lowest energy minimum of the 3,4-OTIPS glucoside β-**3** (Figure 1), followed by the 1C4 chair at 2.24 kcal mol-1. The computational data achieved for thioglycosides β-**2** and β-**3** match 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).

Figure 1. DFT-optimized $^{3}S_{1}$ skew-boat conformation of the 3,4-OTIPS thioglucoside β-3 (hydrogens and phenyl groups have been omitted for clarity in the ball and stick 3D-representation).



To study the reactivity of thioglycoside β-**2**, the respective bromide **4** was generated by the reaction with Br2 following previously established reaction conditions.[9] We theorized that the activation of superarmed donors with Br2 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 4C1 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).[17] Since this adopted conformation is unstable, the β-bromide equilibrates into the thermodynamically stable α-counterpart and hence returns to its original 4C1 conformation. Conversely, if the starting donor is already 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 1C4 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.[18] However, the hexose chair is much more difficult to flip due to the CH2OR substituent at C-5 that has a strong propensity to reside equatorially.[19]

Figure 2. Conformation and stereoselectivity of β-bromides



Thus, bromide **4** obtained from 3,4-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 in CDCl3. 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.

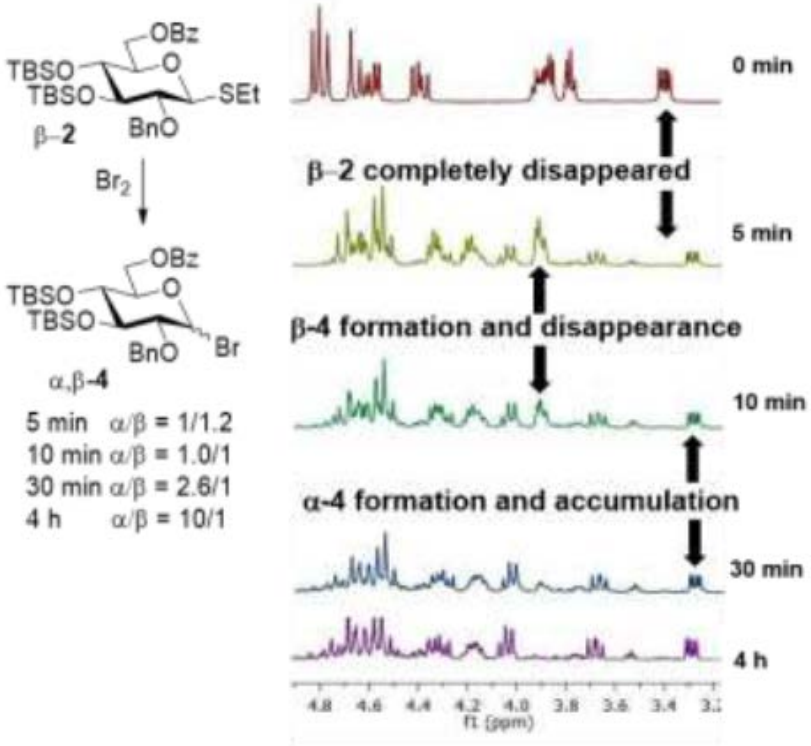
As shown in Scheme 2, the anomeric mixture of bromides **4** has almost completely converted into the α-anomer at 30 min timepoint. Also evident at this timepoint is the presence of a decomposed by-product due to the anticipated partial loss of TBS protecting groups. This was an indication that the chosen 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 the presence of Br2, 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 13C 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 4C1 and 1C4 chair

conformations were located as minimum energy structures, showing the importance of the axial-rich $^1C_4$ 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).

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

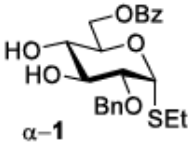


To study the reactivity of this series of compounds, the NMR monitoring of the formation of anomeric bromide **4** from thioglycoside α-**2** was conducted. The procedure used herein was the same as that applied to the β-counterpart of **2** (*vide supra*). After 5 minutes, only β-bromide **4** was detected. At the 10-minute timepoint, the intermediate is still largely β-**4**, and only a small peak at δ ≈ 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 $^4C_1$ chair conformations were achieved for compound α-**4**, whereas a distorted $^{1,4}B$ boat (or an unusual $^4S_2$ skew-boat) conformation was located by DFT calculations as the lowest energy minimum of compound β-**4** (Tables S5-S6).

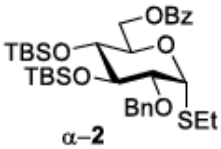
Having acquired the evidence of adequate stability of the reactive intermediate β-**4**, glycosidations of donor α-**2** with model glycosyl acceptors were conducted. At first, when Br2 was added to the reaction mixture containing donor α-**2** and a glycosyl acceptor at -50°C we observed that the formation 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 substoichiometric 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 reaction 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 (α/β = 8-13/1, entry 2). Highly reactive aliphatic alcohols such as *i*PrOH, cyclohexanol, and benzyl alcohol were investigated, affording the target glucosides **9-11** in high yields 78-99%, albeit unremarkable stereoselectivity (α/β = 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-OTIPS 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 SI for additional experimental data).

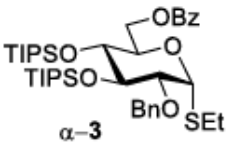
Table 3. NMR data for thioglycosides α-**1**-**3**



α–**1**



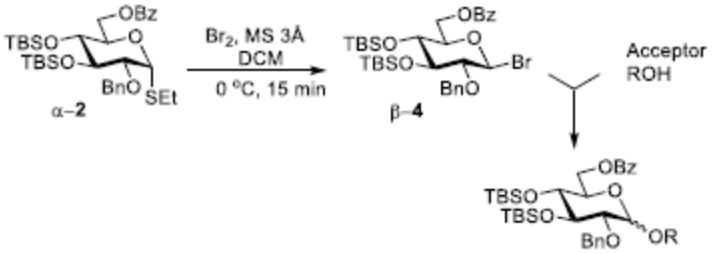
α–**2**

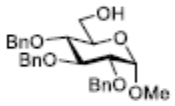
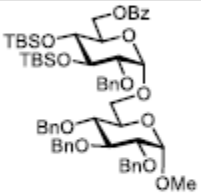
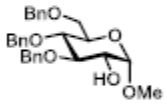
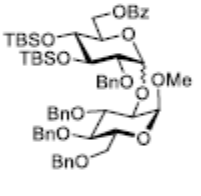
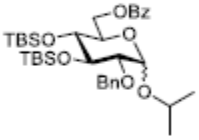
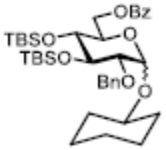
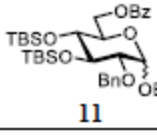


α–**3**

Cmpd	Signal	^{1}H 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

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



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

In conclusion, we expanded the application of Br2-mediated glycosidation of thioglycosides to glycosyl donors of the superarmed 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 sugar acceptors. These results complement our other recent studies dedicated to the activation of glycosyl halides.[20]

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, Missouri 63121, USA; demchenkoa@umsl.edu

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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