Organic LETTERS

Letter

pubs.acs.org/OrgLett

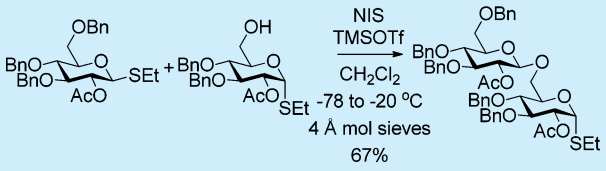
Investigation of α-Thioglycoside Donors: Reactivity Studies toward Configuration-Controlled Orthogonal Activation in One-Pot Systems

Raymond Smith, Helge Müller-Bunz, and Xiangming Zhu*

Centre for Synthesis and Chemical Biology, UCD School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

Supporting Information

ABSTRACT: The influence of anomeric configuration upon thioglycoside donors remains relatively unexplored. Utilizing methodology developed for the stereoselective and high-yielding synthesis of α-glycosyl thiols, a series of α-thioglycosides were synthesized, and their reactivity was compared to that of their β-counterparts. The highly selective activation observed for anomeric pairs containing a 2-*O*-acyl moiety and additional findings are reported. Application of a pair of "superarmed" thioglycosides to a one-pot oligosaccharide system is also described, in which selectivity is a result of configuration-based orthogonal activation.



Over the last few decades, a series of developments have led to thioglycosides becoming one of the most versatile and frequently employed classes of glycosyl donor.[1,2] Acting as quite efficient donors in their own right, as well as serving as convenient precursors to a variety of alternative donors,[3,4] their high stability under a wide range of conditions and their ability for selective activation has made them key building blocks in many oligosaccharide synthetic strategies from a variety of different perspectives.[5] The use of thioglycosides was central to Nicolaou's solid-supported total synthesis of a heptasaccharide phytoalexin elicitor,[6] in which all the glycosylations were carried out using thiophenyl and thiomethyl donors. Wong's famous reactivity study toward the development of a system for automated oligosaccharide synthesis involved extensive investigation of protecting group patterns applied to *S*-tolyl thioglycosides.[7] Such dependence on the stability and versatility of thioglycosides continues to be demonstrated in new and innovative ways, with recent examples including the development by Bowers and co-workers of a system for activation of *S*-PMP glycosides with visible light.[8]

As with all other varieties of glycosyl donor, reactivity modulation of thioglycosides is a continually developing field. Ever since Fraser-Reid's first description of the armed−disarmed concept,[9] researchers have put painstaking effort into finding the correct protecting group patterns to achieve their desired relative donor reactivities. Such methods have been incorporated in the development of an automated system for oligosaccharide synthesis.[7] Knowledge of the influence of protecting groups was further enhanced by Demchenko's observations on the specific contributions of protecting groups in the 2-position along with the combined influence of substituents on the remaining positions, later coined the "O2-O5 co-operative effect."[10] One of the most recent developments has been Bols' work on conformational arming, whereby bulky silyl protecting groups have been employed to force donors into a twist-boat conformation to enhance leaving group ability.[11,12]

One potential contributor to thioglycoside reactivity which remains relatively unexplored is the role of anomeric configuration. The bearing this can have upon reactivity is well documented in the context of other donor classes, for example, generation of α-glycosides from α-glycosyl bromides and chlorides using halide ion-catalyzed glycosylation to exploit higher β-glycosyl halide reactivity.[13] Fraser-Reid also observed consistently higher β-donor reactivity for a series of *n*-pentenyl glycosides.[14] Configuration-based reactivity modulation was also briefly investigated by Seeberger et al. during studies of glycosyl phosphate esters as donors.[15] They also recorded a faster reaction for β-anomers. While this quality has been explored quite well for the above glycosyl donors, relatively little investigation has been carried out for thiolgycoside donors.

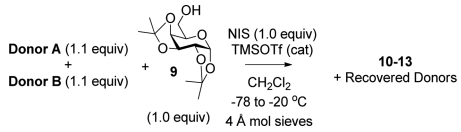
Of course, the relative lack of investigation into this area is somewhat understandable. α-Thioglycosides are notoriously difficult to synthesize by conventional means. Reactions of alternative donors with aglycon thiols typically lead to anomeric mixtures heavily in favor of the β-product.[16,17] Similarly, α-thioglycoside synthesis from the corresponding α-glycosyl thiols has always been hampered by the lack of efficient procedures to generate these precursors, with β-thiols being the favored products of standard synthetic routes.[18,19]

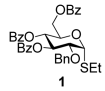
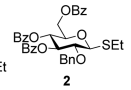
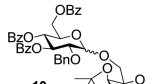
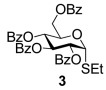
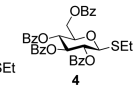
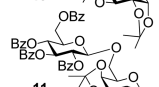
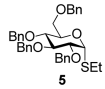
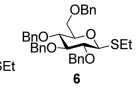
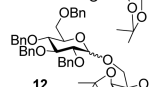
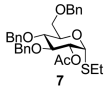
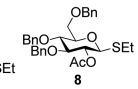
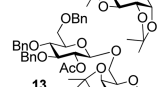
The past decade has seen the development of several new approaches which can circumvent this issue, for example, stereoselective generation of α-thioglycoside precursors by rearrangement of *p*-nitrobenzoylxanthate glycosides[20] and $TiCl_4$-mediated anomerization of *S*-glucuronides.[21] Recently, a high-yielding method for the synthesis of pure α-glycosyl thiols has been developed in our laboratory by stereoselective ring-opening of 1,6-anhydrosugars using $(TMS)_2S$ and TMSOTf.[22] This method was subsequently applied to the synthesis of a series of α-thioglycosides including the first *S*-linked analogues of

Received: May 31, 2016

DOI: 10.1021/acs.orglett.6b01572
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Determination of α-Thioglycoside Reactivity Using Competitive Glycosylation



entry	donor A	donor B	time (min)	product(s)	yield (%)[a]	product ratio (α/β)	donor recovery (%)[b] A	B	recovery ratio A:B
1	 **1**	 **2**	60	 **10**	61	3.5:1	44	80	1:1.8
2	 **3**	 **4**	55	 **11**	65	β only	96	35	2.7:1
3	 **5**	 **6**	75	 **12**	86	2:1	75	35	2.1:1
4	 **7**	 **8**	60	 **13**	79	β only	98	-[c]	>19:1
5	**1**	**4**	80	**10**[d]	68	2.9:1	32	93	1:2.9
6	**2**	**3**	90	**10**[d]	66	2:1	32	98	1:3.1
7	**5**	**8**	65	**12, 13**	26 (**12**) 47 (**13**)	2.7:1 (**12**) β only (**13**)	72	37	1:9.1
8	**6**	**7**	70	**12**[d]	55	4.6:1	9	85	1:9.4
9	**1**	**3**	90	**10**[d]	69	1.8:1	15	95	1:6.3
10	**5**	**7**	55	**12**[d]	86	4.9:1	11	88	1:8
11	**1**	**7**	105	**13**[d]	74	β only	97	12	8.1:1

[a]Calculated from isolated product mass following column chromatography. [b]Determined by integration of representative signals in the ^{1}H NMR and total recovered donor mass. [c]Not observable on the ^{1}H NMR spectrum. [d]No additional products observed.

maradolipid[23] and the immunostimulant glycolipid KRN7000.[24] Following on from the importance of thioglycosides in oligosaccharide synthesis, we saw an opportunity to explore the role that could be played by α-thioglycoside donors, particularly those containing a 2-*O*-acyl functionality. On the basis of the relative lack of knowledge on the influence of anomeric configuration upon thioglycoside reactivity, we felt the most obvious avenue to explore was whether we could carry out selective activation of thioglycosides with the orientation of the leaving group as the key differentiating factor.

We originally hypothesized that we could synthesize a series of α-linked thioglycoside donors which would have lower reactivity than their β-counterparts, thus introducing another group of donors of intermediate reactivity. However, some studies have indicated that the reactivity of different anomers can vary depending on the leaving group and protecting groups.[25,17] This seemingly contradictory information led us to speculate on whether a combination of several factors could govern the relative reactivities of anomers. If so, which ones would predominate under different conditions? We theorized that the higher α-reactivity observed for sulfonium salts was most likely a consequence of the anomeric effect. Interaction of the lone pair of *O*5 with the σ^* orbital of the leaving group should theoretically result in a slight lengthening of the anomeric bond, thus making it more labile upon activation.

To carry out a thorough analysis we began by synthesizing anomers representative of each $^4C_1$ donor reactivity class, that is, superdisarmed (**1**, **2**), disarmed (**3**, **4**), armed (**5**, **6**), and superarmed (**7**, **8**, Table 1). Donors **2**, **4**, **6**, and **8** were synthesized from tetra-*O*-acetyl-β-D-glucosyl thiol in accordance with literature procedures and data. α-Linked donors **1**, **3**, **5**, and **7** were derived from α-thiols synthesized using our ring-opening procedure.

To ascertain relative reactivity of these thioglycosides, we performed a series of competitive glycosylations (Table 1) in which galactoside **9** was placed in a flask with both anomers of a donor before reaction with 1.0 equiv promoter. We employed NIS for the initial tests due to its widespread usage for glycosylation with thioglycosides, with TMSOTf as a Lewis acid catalyst. Reactions were carried out with slow warming from −78 °C. Relative reactivity was determined by recovery of the donor starting materials and examination of the relative intensities of representative peaks on the ^{1}H NMR spectrum.

As displayed in Table 1 (entries 1−4), all thioglycoside pairs demonstrate a noticeable difference in reactivity. It seems that 2-*O*-acyl substituents, as well as enhancing the reactivity of β-donors, seem to cause a far greater disparity in α/β reactivity relative to compounds lacking any neighboring participating group. This agrees with recent work by Demchenko and Bols, in which comparison between two anomers of a conformationally armed system containing a 2-*O*-benzoyl group demonstrated a significant disarming influence of the benzoyl group upon the α-donor.[26] It is also supported by examples provided by Boons[25] and Crich[16] for *S*-dicyclohexylmethyl thioglycosides and SBox glycosides, respectively.

We believe that arming through anchimeric assistance by 2-*O*-acyl groups, as discussed by Demchenko in his first description of the *O*2/*O*5 co-operative effect, is rendered impossible in the case of α-configured donors. The relative orientation of orbitals brought about by the axially oriented leaving group means that the carbonyl lone pairs are incapable of the required interaction with the σ^* orbital of the C−S bond. The reactivity-enhancing

DOI: 10.1021/acs.orglett.6b01572
Org. Lett. XXXX, XXX, XXX−XXX

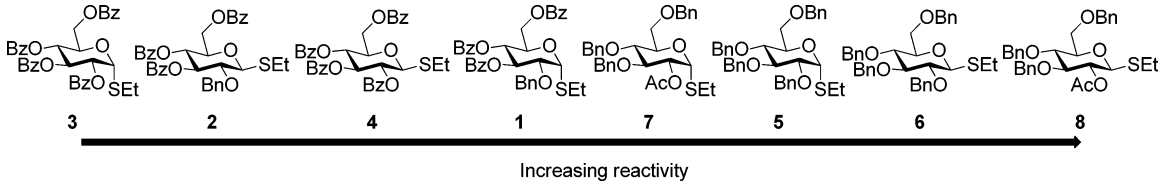


Figure 1. Thioglycoside reactivity sequence incorporating α-thioglycoside donors.

qualities previously associated with 2-*O*-acyl groups as a result of neighboring group participation are thus negated, preventing any co-operative effect from taking place and leaving them to act in a solely electron-withdrawing capacity as originally put forward by Fraser-Reid.

It should be noted that, although the recovery ratios for the armed, disarmed, and superdisarmed systems may seem poor at first glance, this is a consequence of the sluggish nature of these reactions at low temperatures which can often lead to incomplete conversion. For these two comparisons the reactivity difference is best illustrated by examination of the percentage donor recovery.

While preferential activation of a single anomer could be achieved in all cases to some extent, we were particularly surprised by the degree of selectivity for the so-called "superarmed" system. Despite being theoretically the most reactive pairing, this showed almost exclusive activation of the β-donor to the extent that it could not be observed by ^{1}H NMR of the recovered starting material.

Anomeric bond length was briefly considered as another contributing factor to the observed reactivity patterns. However, X-ray analysis of the superdisarmed, disarmed (acetylated for crystallization purposes), and armed systems indicated longer α−C-S bonds of 0.023, 0.026, and 0.025 Å respectively (see Supporting Information). Such small differences would indicate that such a contribution, if any, would be negligible.

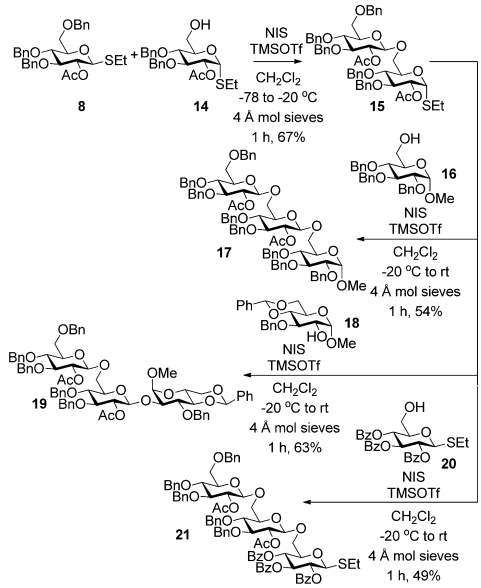
An unexpectedly higher reactivity was observed for **6** in comparison with **5**; this appears to go against known trends for thioglycoside donors with nonparticipating substituents in the 2-position.[27,28] However, repeated tests verified that this result was legitimate. Additionally, competition between superdisarmed pair **1** and **2** conforms to literature data—most likely a consequence of lower β-nucleophilicity due to electron-withdrawing effects upon the endocyclic oxygen by the 3-, 4-, and 6-*O*-benzoyl groups. It is our suggestion that this decreases the electron density of this atom, reducing lone-pair repulsion with the nucleophilic sulfur. Coupled with the optimal antiperiplanar alignment of the *O*5 lone pair and the C−S σ^* orbital[29,12] in compound **1** the outcome is higher α-reactivity. Conversely, the armed system possesses greater electron density at *O*5 due to the use of benzyl substituents, thus increasing the nucleophilicity of the β-configured sulfur atom and its tendency to interact with electrophiles. As such, it may be possible that the preferential reaction of **6** over **5** is determined by initial interaction with the activated NIS as opposed to the relative reactivities of the sulfonium intermediates.

Following our results for direct anomeric comparisons, we decided to investigate the relative order of reactivity within the α-donor series (entries 9−11). On the basis of the observation that the change in configuration clearly restores the typical electron-withdrawing properties of the 2-*O*-acyl group, we expected donors **3** and **7** to be less reactive than the corresponding 2-*O*-benzyl compounds. Therefore, we also chose to examine α- and β-donors of different reactivity categories to establish a complete picture of their reactivity relationships (entries 5−8).

As predicted, the combined influences of an acyl participating group and an α-configured leaving group had a major impact on where lie the relative positions of these donors within the known order of reactivity. This combination was seen to render disarmed donor **3** less reactive than either superdisarmed species, while very little activation of **7** was observed in the presence of armed anomers **5** and **6**. Interestingly, the presence of a 2-*O*-benzyl group in α-donor **1** led to increased reactivity greater than that of **4**, an unexpected result which indicates the effects of an arming substituent in the 2-position acting in tandem with an α-oriented leaving group are enough to surpass the reactivity enhancing qualities of anchimeric assistance in these less reactive systems. Again, a contrasting pattern when examining the more electron-rich donors **5** and **8** indicates that electronic effects upon the endocyclic oxygen could be playing a significant role in these relative reactivities. Overall, these results indicate a reactivity order as laid out in Figure 1. We can therefore conclude that disarmed thioglycoside **3** is the least reactive donor in the entire study, not just in the α-series.

The high degree of selectivity between superarmed anomers, in addition to them being two of the most synthetically useful donors involved in the study, led us to explore this disparity in reactivity further in the context of one-pot oligosaccharide chemistry (Scheme 1). For this purpose we synthesized α-superarmed acceptor **14**. Glycosylation of **14** with **8** under identical conditions to those for the competitive studies allowed for efficient conversion to disaccharidyl thioglycoside **15**, which was isolated as a white solid in 67% yield.

Scheme 1. One-Pot Synthesis of Trisaccharides 17, 19, and 21



This success led us to attempt one-pot synthesis of trisaccharides. As such, upon completion of glycosidation of

DOI: 10.1021/acs.orglett.6b01572
Org. Lett. XXXX, XXX, XXX−XXX

donor **8** with acceptor **14**, 6-OH α-methylglucoside acceptor **16** was introduced followed by additional NIS. As expected, trisaccharide **17** was produced in a very good yield of 54% (average of 73% per glycosylation step), with unreacted **16** and **17** also isolated. This was, to the best of our knowledge, the first example of a one-pot oligosaccharide where the relative reactivity of two anomers was a controlling factor in selective donor activation. Encouraged by this result, we chose to explore the scope of this chemistry further by varying the position of the glycosidic linkage. Hence, 2-OH acceptor **18** was used in place of **16** in order to obtain 1 → 6;1 → 2 trisaccharide **19** in 63% yield (79% per step). Following this success with electron-rich acceptors, the compatibility of this system with less reactive acceptors was tested. Glycosylation with benzoylated thioglycoside acceptor **20** generated trisaccharide donor **21** in a reasonable yield of 49% (70% per step). Not only did this demonstrate the flexibility of this one-pot system with regard to acceptor reactivity, but it also served to show the potential for configuration-controlled orthogonal activation to be used in the construction of larger oligosaccharides.

In conclusion, this investigation has shown that anomeric configuration can have a strong bearing on thioglycoside reactivity, the degree of which is heavily dependent on the nature of the 2-*O*-substituent. The extent of this influence is such that differences in reactivity due to configuration can be observed even under relatively strong NIS-promoted competitive conditions. Of particular importance is that an α-configured leaving group removes the stabilizing, arming capabilities of 2-*O*-acyl substituents such that a perbenzoylated α-thioglycoside can remain unreacted under conditions capable of promoting a typical "superdisarmed" system. Hence, α-configuration in combination with a neighboring 2-*O*-acyl group can be said to have a disarming effect. The synthetic utility of this phenomenon was demonstrated through efficient coupling of two superarmed anomers. The resulting disaccharidyl thioglycoside can be readily reacted with a variety of acceptors, making this system easily applicable to one-pot oligosaccharide strategies. We also observed that the influence of 2-*O*-benzyl substituents in these comparisons is heavily dependent on the nature of remote protecting groups. This seems to suggest that electron density at *O*5 may also have an impact on the relative reactivity of α- and β-thioglycosides. We believe that these observations will have a significant impact on future approaches to designing one-pot oligosaccharide syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01572.

Experimental details, X-ray data and characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiangming.zhu@ucd.ie

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to acknowledge University College Dublin, Meath County Council and the Science & Technology Department of Zhejiang Province (2013C24004) for financial support.

■ REFERENCES

(1) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900.
(2) Lian, G.; Zhang, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 13.
(3) Wolfrom, M. L.; Groebke, W. *J. Org. Chem.* **1963**, *28*, 2986.
(4) Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyriéres, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *188*, 81.
(5) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769.
(6) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; DeRoose, F. *J. Am. Chem. Soc.* **1997**, *119*, 449.
(7) Zhang, Z.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734.
(8) Wever, W. J.; Cinelli, M. A.; Bowers, A. A. *Org. Lett.* **2013**, *15*, 30.
(9) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.
(10) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215.
(11) Pedersen, C. M.; Nordström, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222.
(12) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *J. Org. Chem.* **2013**, *78*, 7234.
(13) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.
(14) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434.
(15) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545.
(16) Crich, D.; Li, M. *Org. Lett.* **2007**, *9*, 4115.
(17) Mydock, L. K.; Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2011**, *13*, 2928.
(18) Gamblin, D. P.; Garnier, P.; van Kasteren, S.; Oldham, N. J.; Fairbanks, A. J.; Davis, B. G. *Angew. Chem.* **2004**, *116*, 846.
(19) Jana, M.; Misra, A. K. *J. Org. Chem.* **2013**, *78*, 2680.
(20) Ané, A.; Josse, S.; Naud, S.; Lacône, V.; Vidot, S.; Fournial, A.; Kar, A.; Pipelier, M.; Dubreuil, D. *Tetrahedron* **2006**, *62*, 4784.
(21) Pilgrim, W.; Murphy, P. V. *J. Org. Chem.* **2010**, *75*, 6747.
(22) Zhu, X.; Dere, R. T.; Jiang, J.; Zhang, L.; Wang, X. *J. Org. Chem.* **2011**, *76*, 10187.
(23) Zeng, X.; Smith, R.; Zhu, X. *J. Org. Chem.* **2013**, *78*, 4165.
(24) Dere, R. T.; Zhu, X. *Org. Lett.* **2008**, *10*, 4641.
(25) Geurtsen, R.; Holmes, D.; Boons, G.-J. *J. Org. Chem.* **1997**, *62*, 8145.
(26) Heuckendorff, M.; Premathilake, H. D.; Pornsuriyasak, P.; Madsen, A. O.; Pedersen, C. M.; Bols, M.; Demchenko, A. V. *Org. Lett.* **2013**, *15*, 4904.
(27) Park, J.; Kawatkar, S.; Kim, J. H.; Boons, G. J. *Org. Lett.* **2007**, *9*, 1959.
(28) Nokami, T.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J. I. *Chem. - Eur. J.* **2009**, *15*, 2252.
(29) Perrin, C. L.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 2839.

DOI: 10.1021/acs.orglett.6b01572
Org. Lett. XXXX, XXX, XXX−XXX