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Tuning Effect of Silyl Protecting Groups on the Glycosylation Reactivity of Arabinofuranosyl Thioglycosides

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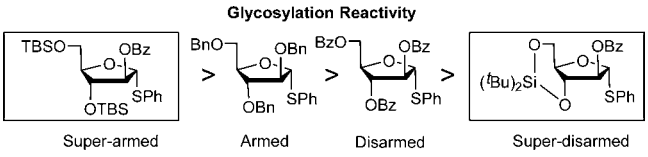
ABSTRACT



The tuning effect of silyl protecting groups on the glycosylation reactivity of arabinofuranosyl phenyl thioglycoside donors is presented. Silyl ethers on the 3-, 5-, and 3,5-positions of the arabinofuranose ring are found to have an arming effect on the donor reactivity, whereas the cyclic 3,5-acetal type protecting groups reduce the reactivity.

The stereoelectronic characteristics of protecting groups play a significant role in carbohydrate reactivity.[1] The armed–disarmed concept, which has proven to be a powerful tool in the concise synthesis of a *cis*–*trans* linked trisaccharide sequence, relies upon the fact that benzylated (armed) sugars are always more reactive than their acylated (disarmed) analogues.[2]

In order to facilitate the synthesis of complex oligosaccharides and glycoconjugates, a wider range of saccharide building blocks with different anomeric reactivity is required. In this respect, Wong and co-workers quantified the relative reactivity of numerous thioglycoside donors[3] and developed a computerized program for the design of synthetic schemes for one-pot multistep chemoselective assemblies of many important oligosaccharides.[4] They recently further studied the graded arming of *p*-tolyl thioglucosides by variously positioned silyl groups and the application of these findings in the reactivity-based one-pot assembly of linker-attached Lc_4 and $IV^2Fuc\text{-}Lc_4$, which are components of the human embryonic stem cell surface.[5] Bols et al. reported that bulky silyl group substituted pyranose thioglycosides have superior reactivity compared with the benzylated thioglycosides.[6] The enhanced reactivity can be explained by the stereoelectronic effects associated with the conformational change caused by the silyl protection.

On the other hand, cyclic protecting groups were found to have a torsionally deactivating effect on pyranoside reactivity. Fraser-Reid and co-workers first disclosed that the oxidative hydrolysis of a series of acetalated pyranosyl *n*-pentenyl glycosides proceeds less readily than for their torsion-free analogues.[7] Later, the Ley group showed that

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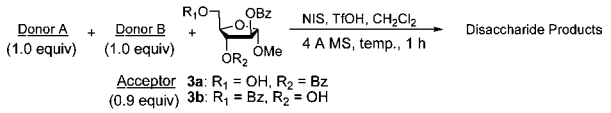
Table 1. Competition Glycosylation Reactions[a]



entry	donor A	donor B	temp	disaccharide product (yield)[b]
1	**1a**	**2a**	-80→-70 °C	**4**[c], 85%
2	**1b**	**2a**	-80→-60 °C	**5a**, 82%; **5b**[d], 13%
3	**1b**	**2b**	-80→-60 °C	**5a**, 86%
4	**1c**	**2b**	-80→-60 °C	**5c**, 85%
5	**1d**	**2c**	-80→-50 °C	**6a**, 65%; **6b**, 11%
6	**1e**	**2d**	-80→-50 °C	**7**, 70%
7	**1f**	**2a**	-80→-55 °C	**5b**[e], 91%
8	**1f**	**2e**	-80→-20 °C	**8a**, 29%; **8b**, 55%
9	**1g**	**2b**	-80→-40 °C	**9**, 77%
10	**1g**	**2e**	-50→-30 °C	**10**, 76%
11	L-**1b**	L-**2b**	-80→-60 °C	L-**5a**, 91%
12	L-**1f**	L-**2e**	-80→-30 °C	L-**8a**, 49%; L-**8b**,[18] 55%

[a] Glycosylations were run with donors A/B, acceptor **3a** (for entries 1–5, 7–8, and 11–12) or **3b** (for entries 6 and 9–10), NIS (1.2 equiv), and TfOH (0.1 equiv), 4 Å molecular sieves (MS) in dry CH_2Cl_2 in 1 h. [b] Isolated yield. [c] α/β = 1/1. The α/β ratios in entries 1, 2, and 7 were determined by ^{1}H NMR analysis of the corresponding anomer mixtures. [d] α/β = 3/1. [e] α/β = 3/1.

thioglycosides, bearing a dispiroketal (dispoke) or cyclohexane-1,2-diacetal (CDA) protecting group, have reactivities between armed and disarmed thioglycosides.[8] Furthermore, Boons et al. reported that 2,3-*O*-carbonate-masked ethyl thioglucosides can act as acceptors in chemoselective glycosylations with disarmed thioglycosides due to their reduced reactivity.[9]

Arabinofuranosides are widely distributed in living organisms.[10] Both D- and L-arabinosides are found, with the D-form being the major component of mycobacterial cell walls and the L-form being an important constituent of plant cell walls. Because of their biological relevance, the synthesis of arabinose-containing oligosaccharides has received considerable attention in the past decade.[11] But to date, systematical study of the effect of protecting groups on the glycosylation reactivity of furanosyl donors has yet to occur.[12] Establishment of the relative reactivity of glycosyl building blocks can not only provide valuable insight into the nature of a given furanose donor but also pave the way to the development of new furanosylation chemistry. In our search for new methods to synthesize oligofuranoses,[13] we recently reported a novel regioselective furanosylation approach and its application in the one-pot synthesis of natural oligoarabino- and galactofuranosides.[13a] We now present, in this Letter, the tuning effect of silyl protections on the reactivity of arabinosyl thioglycoside donors. This work extends the conventional armed–disarmed concept.

Our studies began with the design and preparation of a set of D- and L-arabinofuranose phenyl thioglycoside

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derivatives protected as silyl ethers and 3,5-*O*-acetals (Table 1, **1a**–**g**, L-**1b**, and L-**1f**) by known or slightly modified experimental procedures (see the Supporting Information). With these compounds, a series of three-component competition glycosylations were run to assess the influence of silyl protecting groups on glycosylation reactivity. In these experiments, both a silylated thioarabinoside (donor A, 1.0 equiv) and a nonsilylated armed or disarmed thioarabinoside (donor B, 1.0 equiv) would be mixed in the same reaction vessel in dry dichloromethane with a model acceptor arabinoside **3a**[13c] or **3b**[14] (0.9 equiv), respectively. Upon addition of the *N*-iodosuccinimide (NIS, 1.2 equiv)/trifluoromethanesulfonic acid (TfOH, 0.1 equiv) promoter system,[15] the two donors would then compete to couple with the acceptor to form disaccharide products. The product ratio will reflect the inherent reactivity of the donors. The results of these competition glycosylations are summarized in Table 1.

In the first instance, the competitive reaction between the fully *tert*-butyldimethylsilyl (TBS) protected donor **1a** and the fully benzylated donor **2a**[16] with 5-OH acceptor **3a** gave (1→5)-linked disaccharide **4** as a mixture of anomers (α/β = 1/1) in 85% yield (Table 1, entry 1). No coupling product between **2a** and **3a** was detected under these reaction conditions. More than 50% of the added **2a** was recovered after workup. Next, the glycosylation reaction of the donors with a mixed protecting group pattern was examined. Predominant activation of 3,5-di-*O*-TBS-2-*O*-Bz protected **1b** over **2a** took place, giving **5a** as the major product along with a minor quantity of **5b** (entry 2). So, these results can be attributed to the greater anomeric reactivity of the per- and disilylated donors **1a**,**b** relative to that of the per-benzylated armed donor **2a**. Subsequently, when compared with the less armed **2b** having 3,5-dibenzyl-2-Bz substituents, **1b** and its 3,5-di-*O*-*tert*-butyldiphenylsilyl (TBDPS) protected analogue **1c** could be exclusively activated to glycosylate with **3a**, to afford solely the disaccharides **5a** and **5c** with complete stereoselectivity in good yield, respectively (entries 3–4). The mono-TBS masked substrates **1d**,**e** were observed to be more reactive toward glycosylation with **3a** or **3b** than the corresponding 3- or 5-*O*-Bn blocked counterparts **2c**,**d** (entries 5–6, respectively).

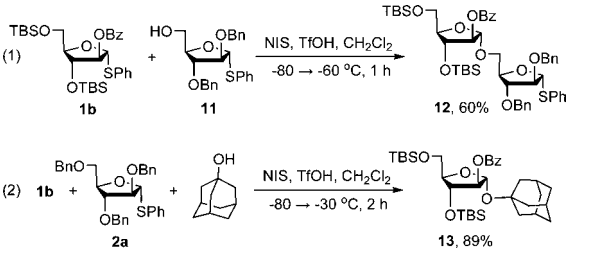
We further sought to test the reactivity of thioglycosides **1f**[13c] and **1g** protected as cyclic 3,5-*O*-di-*tert*-butylsilylene (DTBS) or 3,5-*O*-tetraisopropyldisiloxanylidene (TIPDS) acetals. In previous work by Crich et al., a slow activation for 3,5-acetalated *p*-tolyl thioglycoside and sulfoxide donors was observed.[17] Here, completely selective activation was still retained in the three-component reaction of **1f**, **2a**, and **3a**. Only disaccharide **5b** (α/β = 3/1), the coupling product of **2a** with **3a**, was formed (Table 1, entry 7). When **1f** was compared with per-benzoylated **2e**,[13c] a 1:1.9 mixture of **8a** and **8b**[18] was obtained (entry 8). Judging from the results of both reactions, it is clear that the 3,5-silylene acetal function remarkably decreases the donor reactivity, rendering **1f** even less reactive than the fully disarmed donor **2e**. The deactivation effect of an annulated 3,5-acetal moiety was further demonstrated by the TIPDS-protected **1g**, which was confirmed to exhibit reactivity that is between moderately armed (**2b**) and disarmed (**2e**) donors (entries 9–10). The different glycosylation behavior of **1f** and **1g** is probably due to the different torsional strains induced by the respective 3,5-*O*-acetal groups in the sugar rings. Compared with the TIPDS unit, the more conformationally rigid DTBS group further limits formation of the corresponding arabinofuranosyl oxacarbenium ion, thereby resulting in a decline in reactivity for **1f**.

Similar observations were made in the L-arabinose series. L-**1B** and L-**1f** were verified by the competition reactions to be more and slightly less reactive than the corresponding armed L-**2b** and disarmed L-**2e** (Table 1, entries 11–12).

The above silylated thioglycosyl donors may prove useful for the synthesis of oligoarabinoses. Of particular promise should be the 3,5-di-TBS/TBDPS (**1b**/**c**) and 3,5-DTBS (**1f**) protected thioglycosides because of their exceedingly high or low reactivity which widens the spectrum of furanosyl donor reactivity. However, their abilities to ensure stereoselective construction of 1,2-*trans* glycosidic linkages via neighboring group participation are equally important.

According to Scheme 1, eq 1, the coupling between **1b** and the armed 5-OH thioglycoside **11** proceeded smoothly to furnish α-linked disaccharide thioglycoside **12** as the only condensation product in good yield. It could undergo chemoselective activation in the presence of **2a**, reacting with the hindered 1-adamantanol, to yield the corresponding 1,2-*trans* glycoside **13** in 89% yield (eq 2).

Scheme 1. Selective Activation of **1b**



It is now possible to perform one-pot glycosylations that were previously not possible by the use of these super-armed/disarmed glycosyl donors. Two such examples are outlined in Scheme 2. It is worth pointing out that these reactions were carried out as a true automated one-pot glycosylation, as in both cases the three glycosylating agents and the activating reagents are mixed simultaneously, and not added sequentially. Thus, on activation

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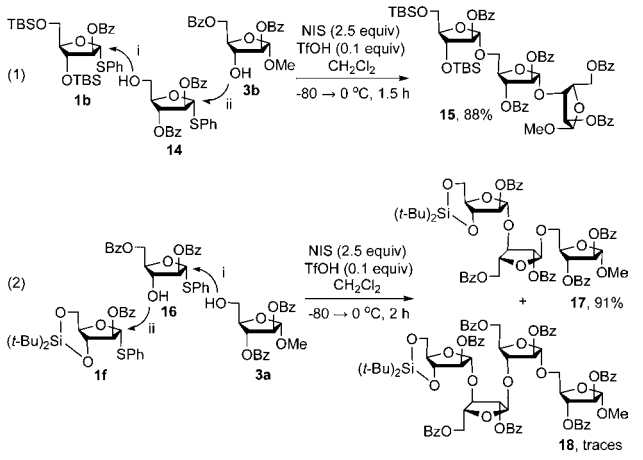
(15) NIS/TfOH has been screened as the appropriate activator for discriminating the reactivity levels of the donor substrates. Other activator systems, such as NIS, NIS/AgOTf, or DMTST, did not give results as those of NIS/TfOH.

(16) Hiranuma, S.; Kajimoto, T.; Wong, C.-H. *Tetrahedron. Lett.* **1994**, *35*, 5257.

(17) Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553.

(18) Kawabata, Y.; Kaneko, S.; Kusakabe, I.; Gama, Y. *Carbohydr. Res.* **1995**, *267*, 39.

Scheme 2. Automated One-Pot Glycosylation

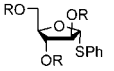
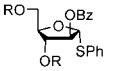
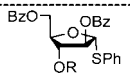
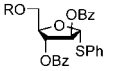


with NIS (2.5 equiv)/TfOH (0.1 equiv) at −80 °C and warming to 0 °C in CH_2Cl_2, triarabinoside **15** was rapidly assembled within 1.5 h from nonreducing end to reducing end in 88% yield, based on the reactivity difference of the three reactants: the superarmed donor **1b**, the disarmed thioglycoside acceptor **14**,[13c] and the 3-OH acceptor **3b** (eq 1). On the other hand, methyl glycoside acceptor **3a** was coupled to disarmed 3-OH thioglycoside acceptor **16**[13a] and then the superdisarmed donor **1f** to produce an excellent 91% yield of trisaccharide **17** together with a trace amount of tetrasaccharide **18** (eq 2). A trisaccharide with the same sugar frame as that of **17** has been prepared in our earlier study through a one-pot glycosylation protocol which was based on our developed regioselective glycosylation strategy.[13a] In that synthesis, a standard disarmed phenyl 2,3,5-tri-*O*-acetyl-α-D-thioarabinofuranoside donor rather than **1f** was employed to glycosylate with **16** and **3a**. But the total yield was in lower 70% yield. We reason that the improved yield of the automated one-pot procedure is attributable largely to the increased difference in reactivity between the donors **1f** and **16**.

Interestingly, during our study of arabinose thioglycoside reactivity, we observed a good correlation between the chemical shifts of anomeric protons and the corresponding silyl ether protected donor reactivity (Table 2). For example, the anomeric H-1 resonance of the most reactive **1a** is significantly further upfield than that of the less reactive **2a**, while the H-1 resonance of the latter is more upfield than that of the least reactive **2e** (δ_H 5.324 vs 5.610 vs 5.849 ppm, respectively). The same correlation is observed as well for each set of mixed protected thioglycosides.[19] As the stability of the positively charged oxacarbenium species seems to

(19) For a similar correlation between chemical shifts of anomeric hydrogens and pyranosyl thioglycosides reactivity, see ref 3.

Table 2. Relation between the Chemical Shifts of the Anomeric Protons of Thioarabinosides and Their Reaction Reactivity

donor	R	δ_{H1} (ppm)	reactivity order
	**1a**: TBS	5.324	**1a** > **2a** > **2e**
	2a: Bn	5.610	
	2e: Bz	5.849	
	**1b**: TBS	5.579	**1b** ≈ **1c** > **2b**
	1c: TBDPS	5.541	
	2b: Bn	5.731	
	**1d**: TBS	5.656	**1d** > **2c**
	2c: Bn	5.759	
	**1e**: TBS	5.789	**1e** > **2d**
	2d: Bn	5.826	

be mainly affected by the electron density at the anomeric center, the chemical shift of anomeric proton might be useful in explaining the observed reactivity order of these furanose thioglycosides.

In conclusion, the relative anomeric reactivity of a variety of silylated arabinose thioglycosides has been experimentally determined. Silyl ethers on the furanose ring are found to effectively enhance the reactivity. The highly reactive 3,5-di-TBS-2-Bz protected thioarabinose is able to condense with the traditionally armed thioglycoside as well as the very unreactive acceptor. A 3,5-cyclic acetal protection generally has a disarming effect on the reactivity. These findings offer a wider range of sugar building blocks of different anomeric reactivity and have allowed us to realize the first facile automated one-pot furanosylation. In addition, we observed a good correlation between the reactivity and the chemical shift of the anomeric hydrogen by ^{1}H NMR spectroscopy. Further exploration of these novel superarmed/disarmed thioglycoside molecules in the synthesis of oligoarabinoses and extensive investigation into the mechanism of the silyl protection mediated reactivity tuning are now in progress.

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Supporting Information Available. Experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, 2D NMR spectra for compounds **12**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.