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

LETTERS XXXX Vol. XX, No. XX 000-000

ORGANIC

Xing-Yong Liang.<sup>†,§</sup> Hua-Chao Bin.<sup>†,§</sup> and Jin-Song Yang<sup>\*,†,‡</sup>

TBSO

**ÓTBS** 

Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education, Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

vjs@scu.edu.cn

## Received April 25, 2013

## 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.<sup>1</sup> The armeddisarmed 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.<sup>2</sup>

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<sup>3</sup> and developed a computerized program for the design of synthetic schemes for one-pot multistep chemoselective assemblies of many important oligosaccharides.<sup>4</sup> They recently further studied the graded arming of *p*-tolyl thioglucosides by variously positioned silvl groups and the application of these findings in the reactivity-based one-pot assembly of linker-attached Lc<sub>4</sub> and IV<sup>2</sup>Fuc-Lc<sub>4</sub>, which are components of the human embryonic stem cell surface.<sup>5</sup> Bols et al. reported that bulky silyl group substituted pyranose thioglycosides have superior reactivity compared with the benzylated thioglycosides.<sup>6</sup> The enhanced reactivity can be explained by the stereoelectronic effects associated with the conformational change caused by the silvl 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.<sup>7</sup> Later, the Ley group showed that

<sup>&</sup>lt;sup>†</sup> West China School of Pharmacy.

<sup>&</sup>lt;sup>‡</sup>West China Hospital.

<sup>&</sup>lt;sup>§</sup> These authors contributed equally.

<sup>(1)</sup> Fraser-Reid, B.; Jayaprakash, K. N.; López, J. C.; Gómez, A. M.; Uriel, C. In Frontiers in Modern Carbohydrate Chemistry; Demchenko, A. V., Ed.; American Chemical Society: Washington, DC, 2007; p 91.

<sup>(2) (</sup>a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid,

B. J. Am. Chem. Soc. 1988, 110, 5583. (b) Fraser-Reid, B.; Wu, Z.; Udodong, U.; Ottosson, H. J. Org. Chem. 1990, 55, 6068.

<sup>(3)</sup> Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. J. Am. Chem. Soc. 1999, 121, 734.

<sup>(4)</sup> Selected examples: (a) Polat, T.; Wong, C.-H. J. Am. Chem. Soc. 2007, 129, 12795. (b) Duron, S. G.; Polat, T.; Wong, C.-H. Org. Lett. 2004, 6, 839. (c) Mong, T. K.-K.; Lee, H.-K.; Duron, S. G.; Wong, C.-H. Proc. Natl. Acad. Sci. U.S.A. 2003, 100, 797.

<sup>(5)</sup> Hsu, Y.; Lu, X.-A.; Zulueta, M. M. L.; Tsai, C.-M.; Lin, K.-I.; Hung, S.-C.; Wong, C.-H. J. Am. Chem. Soc. 2012, 134, 4549.

<sup>(6) (</sup>a) Jensen, H. H.; Pedersen, C. M.; Bols, M. Chem.-Eur. J. 2007, 13, 7576. (b) Pedersen, C. M.; Marinescu, L. G.; Bols, M. Chem. Commun. 2008, 2465. (c) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. J. Am. Chem. Soc. 2007, 129, 9222.

<sup>(7)</sup> Fraser-Reid, B.; Wu, Z.-F.; Andrews, C. W.; Skowronski, E. J. Am. Chem. Soc. 1991, 113, 1434.

Table 1. Competition Glycosylation Reactions<sup>a</sup>



<sup>*a*</sup> 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<sub>2</sub>Cl<sub>2</sub> in 1 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup>  $\alpha/\beta = 1/1$ . The  $\alpha/\beta$  ratios in entries 1, 2, and 7 were determined by <sup>1</sup>H NMR analysis of the corresponding anomer mixtures. <sup>*d*</sup>  $\alpha/\beta = 3/1$ .

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

Arabinofuranosides are widely distributed in living organisms.<sup>10</sup> 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.<sup>11</sup> But to date, systematical study of the effect of protecting groups on the glycosylation reactivity of furanosyl donors has yet to occur.<sup>12</sup> 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,<sup>13</sup> we recently reported a novel regioselective furanosylation approach and its application in the one-pot synthesis of natural oligoarabino- and galactofuranosides.<sup>13a</sup> 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

<sup>(8) (</sup>a) Ley, S. V.; Priepke, H. W. M. Angew. Chem., Int. Ed. Engl. 1994, 33, 2292. (b) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. J. Chem. Soc., Perkin Trans. 1 1998, 51.

<sup>(9)</sup> Zhu, T.; Boons, G.-J. Org. Lett. 2001, 3, 4201.

<sup>(10)</sup> Lowary, T. L. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; p 2005.

<sup>(11)</sup> For reviews, see: (a) Lowary, T. L. *Curr. Opin. Chem. Biol.* 2003, 7, 749. (b) Peltier, P.; Euzen, R.; Daniellou, R.; Nugier-Chauvin, C.; Ferrières, V. *Carbohydr. Res.* 2008, 343, 1897. (c) Imamura, A.; Lowary, T. L. *Trends Glycosci. Glycotech.* 2011, 23, 134.

<sup>(12)</sup> Lowary and co-workers reported the influence of the reactivity of D-arabinofuranosyl thioglycosides on the glycosylation stereoselectivity; see: Yin, H.-F.; Lowary, T. L. *Tetrahedron. Lett.* **2001**, *42*, 5829.

<sup>(13) (</sup>a) Deng, L.-M.; Liu, X.; Liang, X.-Y.; Yang, J.-S. J. Org. Chem. **2012**, 77, 3025. (b) Zhu, S.-Y.; Yang, J.-S. *Tetrahedron* **2012**, 68, 3795. (c) Liang, X.-Y.; Deng, L.-M.; Liu, X.; Yang, J.-S. *Tetrahedron* **2010**, 66, 87.

derivatives protected as silvl 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 silvlated thioarabinoside (donor A, 1.0 equiv) and a nonsilvlated 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,<sup>15</sup> 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 3agave  $(1 \rightarrow 5)$ -linked disaccharide **4** as a mixture of anomers  $(\alpha/\beta = 1/1)$  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 disilvlated 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.<sup>17</sup> Here, completely selective activation was still retained in the three-component reaction of 1f, 2a, and 3a. Only disaccharide 5b ( $\alpha/\beta = 3/1$ ), the coupling product of 2a with 3a, was formed (Table 1, entry 7). When

1f was compared with per-benzoylated 2e,<sup>13c</sup> a 1:1.9 mixture of **8a** and **8b**<sup>18</sup> was obtained (entry 8). Judging from the results of both reactions, it is clear that the 3,5-silvlene acetal function remarkably decreases the donor reactivity. rendering 1f even less reactive than the fully disarmed donor 2e. The deactivation effect of an annulated 3.5acetal moiety was further demonstrated by the TIPDSprotected 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  $\alpha$ -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 superarmed/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

<sup>(14)</sup> Wang, Z.-W.; Prudhomme, D. R.; Buck, J. R.; Park, M.; Rizzo, C. J. J. Org. Chem. **2000**, 65, 5969.

<sup>(15)</sup> 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.

<sup>(16)</sup> Hiranuma, S.; Kajimoto, T.; Wong, C.-H. Tetrahedron. Lett. 1994, 35, 5257.

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

<sup>(18)</sup> 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<sub>2</sub>Cl<sub>2</sub>, 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.<sup>13c</sup> 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.<sup>13a</sup> In that synthesis, a standard disarmed phenyl 2,3,5-tri-O-acetyl-a-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 onepot 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** ( $\delta_{\rm H}$  5.324 vs 5.610 vs 5.849 ppm, respectively). The same correlation is observed as well for each set of mixed protected thioglycosides.<sup>19</sup> 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	$\delta_{\! m H1}$ (ppm)	reactivity order
ROLOR	1a: TBS	5.324	1a > 2a > 2e
OR SPh	<b>2a</b> : Bn	5.610	
	<b>2e</b> : Bz	5.849	
ROCOBZ	1b: TBS	5.579	$1b \approx 1c > 2b$
OR SPh	1c: TBDPS	5.541	
	<b>2b</b> : Bn	5.731	
BzO OBz	1d: TBS	5.656	1d > 2c
OR SPh	<b>2c</b> : Bn	5.759	
ROOBZ	1e: TBS	5.789	1e > 2d
OBz SPh	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 silvlated 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 <sup>1</sup>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 silvl protection mediated reactivity tuning are now in progress.

Acknowledgment. The financial support from the NSFC (21172156, 21021001), the 973 program (2010CB833202), and the Ministry of Education (NCET-08-0377, 20100181-110082) is highly appreciated.

**Supporting Information Available.** Experimental details, <sup>1</sup>H and <sup>13</sup>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.