## **Communications**



# Thioglycoside Synthesis

K. N. Baryal, D. Zhu, X. Li, J. Zhu\* \_\_\_\_\_

Umpolung Reactivity in the Stereoselective Synthesis of S-Linked 2-Deoxyglycosides



Take control! An unprecedented sulfenylation of stereochemically defined 2deoxyglycosyl lithium species with asymmetric sugar-derived disulfide acceptors enabled the stereoselective synthesis of both  $\alpha$ - and  $\beta$ -S-linked 2-deoxyoligosaccharides. Reductive lithiation of 2-deoxyglycosyl phenylsulfides at -78 °C provides predominantly axial glycosyl lithium species, which upon warming isomerize to predominantly equatorial lithium species (see scheme).

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#### Thioglycoside Synthesis

## **Umpolung Reactivity in the Stereoselective Synthesis of S-Linked** 2-Deoxyglycosides\*\*

Kedar N. Baryal, Danyang Zhu, Xiaohua Li, and Jianglong Zhu\*

Dedicated to Professor Samuel J. Danishefsky

2-Deoxysugars, especially 2,6-dideoxy- and 2,3,6-trideoxysugars, are an important class of carbohydrates and exist in numerous biologically active natural products and clinical agents, including anthracyclines,<sup>[1]</sup> angucyclines,<sup>[2]</sup> aureolic acid antibiotics,<sup>[3]</sup> avermectins,<sup>[4]</sup> enediynes,<sup>[5]</sup> pluramycins,<sup>[6]</sup> lomaiviticins,<sup>[7]</sup> vancomycin,<sup>[8]</sup> and cardiac glycosides.<sup>[9]</sup> These sugars play a critical role in the biological activity of these compounds as well as their stability and solubility.<sup>[10]</sup> As a result, considerable effort has been devoted to the stereoselective synthesis of 2-deoxyglycosides and the study of their structure-activity relationships.<sup>[11]</sup> Despite the significance of 2-deoxysugar subunits, the glycosidic linkage of 2deoxyglycosides has been found to be susceptible to hydrolysis in acid media or by glycosyl hydrolases. This reactivity has made it difficult to pinpoint the biological role of these 2deoxysugars, has resulted in toxicity<sup>[12]</sup> and reduced activity<sup>[13]</sup> of the parent molecules, and has limited their use as clinical agents.

Thioglycosides (S-linked glycosides),<sup>[14]</sup> in which the glycosidic oxygen atom is replaced with a sulfur atom, are resistant towards enzymatic cleavage as well as chemical degradation. Furthermore, thioglycosides maintain the biological activity of their parent O-linked glycosides and are tolerated by most biological systems. Therefore, they are an important tool for structural biology<sup>[15]</sup> and attractive therapeutic agents. Because of these characteristics, the preparation of S-linked 2-deoxysugars for comparison of their physical, chemical, and biological properties with those of their natural O-linked counterparts is beneficial. Although a number of protocols are available for the synthesis of thioglycosides,<sup>[14,16]</sup> there is no efficient method for the stereoselective construction of S-linked 2-deoxyoligosaccharides,<sup>[17]</sup> and in particular, S-linked 2-deoxy-β-oligosaccharides. Previously, 2-deoxythioglycosides 3 were obtained with moderate to good anomeric stereoselectivity through the thioglycosylation of 2-deoxyglycosyl acetates<sup>[18]</sup>/chlorides  $\mathbf{1}^{[19]}$  or 2-deoxyglycals  $\mathbf{2}^{[20]}$  with simple thiol-containing nucleophiles (Scheme 1 a). Herein, we report an unprecedented sulfenylation of stereochemically defined 2-deoxyglycosyl

a) Previous synthesis of S-linked 2-deoxyglycosides



b) This study



Scheme 1. Strategies for the synthesis of S-linked 2-deoxyglycosides.

lithium species with asymmetric sugar-derived disulfide acceptors for the stereoselective synthesis of both  $\alpha$ - and  $\beta$ -S-linked 2-deoxyoligosaccharides (Scheme 1 b).

According to our approach, the reductive lithiation of a mixture of 2-deoxy  $\alpha$ - and  $\beta$ -glycosyl phenylsulfide **4** with a suitable radical-anion reductant should afford predominantly intermediate 5 with an axial lithium substituent at low temperature.<sup>[21,22]</sup> The 2-deoxyglycosyl lithium species 5 may then react with a sugar-derived asymmetric disulfide (e.g. 6) to afford the desired S-linked 2-deoxy-α-oligosaccharide (in this case 7).<sup>[23]</sup> We used a steric effect to promote the desired regioselectivity by installing a tertiary alkyl group (e.g., tertbutyl) at one end of the disulfide 6. Thus, the sulfur atom close to the sugar moiety should be more accessible for nucleophilic attack of the glycosyl lithium species, and the desired product 7 should be formed. Furthermore, upon warming, the axial lithium intermediate 5 should isomerize<sup>[21b,c,22]</sup> to the corresponding thermodynamically more stable equatorial lithium species 8, which may react with disulfide 6 to give the S-linked 2-deoxy- $\beta$ -oligosaccharide 9. Thus, S-linked 2-deoxy  $\alpha$ - and  $\beta$ oligosaccharides may be obtained selectively from the same 2deoxyglycosyl phenylsulfide precursors through facile temperature control.

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 <sup>[\*]</sup> K. N. Baryal, D. Zhu, Dr. X. Li, Prof. Dr. J. Zhu Department of Chemistry and School of Green Chemistry and Engineering, The University of Toledo
 2801 W. Bancroft Street, Toledo, OH 43606 (USA)
 E-mail: Jianglong.Zhu@Utoledo.edu

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The generation of nucleophilic glycosyl lithium reagents by reductive lithiation, a process invented by Cohen and coworkers,<sup>[21]</sup> for the stereoselective synthesis of C-glycosides was reported previously by the research groups of Sinaÿ,<sup>[17c,24]</sup> Beau,<sup>[25]</sup> Kessler,<sup>[26]</sup> and others.<sup>[27]</sup> Although the synthesis of  $\alpha$ -C-glycosides from readily available  $\alpha$ -glycosyl lithium intermediates is straightforward, the generation of  $\beta$ -glycosyl lithium species for the synthesis of  $\beta$ -C-glycosides has remained a challenge. Previous efforts towards the preparation of  $\beta$ -glycosyl lithium species involved the synthesis of  $\beta$ glycosylstannanes and a subsequent tin-lithium exchange.<sup>[28]</sup> Alternatively, the  $\beta$ -C-glycosides can be synthesized by an indirect approach involving sequential deprotonation of a glycosylsulfone, electrophile addition, and stereoselective reductive desulfonation.<sup>[29]</sup> Therefore, the development of a more effective method for the selective preparation of  $\beta$ glycosyl lithium species is particularly appealing. Furthermore, although these studies<sup>[27]</sup> highlighted umpolung approaches in the stereoselective synthesis of C-glycosides, the sulfenylation of glycosyl lithium intermediates for the stereoselective synthesis of S-linked glycosides has not been disclosed thus far.

2-Deoxyglycosyl phenylsulfide donors 4 were prepared from the corresponding readily available glycals through Re<sup>V</sup> catalysis.<sup>[20,30]</sup> In our hands, compounds **4a**, **4b**, and **4d** were obtained as a mixture of  $\alpha$  and  $\beta$  anomers, whereas **4c**, **4e**, and **4 f** were isolated as the pure  $\alpha$  isomer (Scheme 3).<sup>[30]</sup> Since both 2-deoxy  $\alpha$ - and  $\beta$ -glycosyl phenylsulfides can undergo reductive lithiation to afford the stereochemically pure axial lithium ( $\alpha$ -lithium) species,<sup>[21]</sup>  $\alpha/\beta$  anomeric mixtures of **4a**, 4b, and 4d were used directly for reductive lithiation. Furthermore, asymmetric sugar-derived tert-butyldisulfide acceptors, 6a-d, were synthesized<sup>[30]</sup> by reactions of thiosugars<sup>[31]</sup> with *tert*-butyl methanethiosulfonate<sup>[32]</sup> in the presence of a tertiary amine base (Scheme 2).<sup>[33]</sup> For example, Lfucal (10) was converted into the corresponding methyl glycoside, which underwent regioselective silvl protection to afford 11 (59% over two steps). Next, the triflation of 11, followed by  $S_N 2$  displacement with cesium thioacetate, provided thioester 12 (86% over two steps). The reduction of thioacetate 12 with lithium aluminium hydride furnished



**Scheme 2.** Reagents and conditions: a) cat. CSA, MeOH; b) TBSCl, Et<sub>3</sub>N, DMF, 59% over two steps; c) Tf<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C; d) CsSAc, THF, 86% over two steps; e) LiAlH<sub>4</sub>, Et<sub>2</sub>O,  $-30^{\circ}C \rightarrow RT$ ; f) tBuSSO<sub>2</sub>Me, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C $\rightarrow RT$ ; g) TBSCl, imidazole, DMF, 78% over three steps. CSA = camphorsulfonic acid, DMF = *N*,*N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMSE = 2-trimethylsilylethyl.

the corresponding thiosugar with concomitant cleavage of the *tert*-butyldimethylsilyl ether. The reaction of this thiosugar with *tert*-butyl methanethiosulfonate, followed by silyl reprotection, gave the disulfide acceptor **6a** (78% over three steps). The sugar-derived C6 disulfide acceptor **6b**, C4 disulfide acceptor **6c**, and C3 disulfide acceptor **6d** were obtained by a similar strategy.<sup>[30]</sup>

With 2-deoxyglycosyl phenylsulfides 4a-f and sugarderived disulfides 6a-d in hand, we carried out the key Sglycosylation reactions based on umpolung reactivity. Reductive lithiation<sup>[21,22]</sup> of a mixture of 2-deoxy  $\alpha$ - and  $\beta$ -glycosyl donors 4a (1.2 equiv) at -78°C with lithium 4,4'-di-tertbutylbiphenyl (LiDBB)<sup>[34]</sup> generated the corresponding highly stereochemically pure axial-lithium intermediate, which subsequently reacted with the C6-disulfide acceptor 6b to afford the S-linked disaccharide 13 in 87% yield with excellent  $\alpha$  selectivity ( $\alpha/\beta > 40:1$ ; Scheme 3). Under the same conditions, the S- $(1\rightarrow 6)$ -linked 2-deoxydisaccharides 14 and 15 were prepared in excellent yield with excellent  $\alpha$  selectivity from the 2-deoxyglycosyl phenylsulfide donors 4c and 4d, respectively. The S- $(1\rightarrow 4)$ -linked 2-deoxydisaccharides 16-21 were also synthesized in good to excellent yield and with excellent  $\alpha$  selectivity from the corresponding 2-deoxy L- or D-glycosyl lithium species and the L- or Dolivoside-derived C4-disulfide acceptor 6a or 6c. Furthermore, the S- $(1\rightarrow 3)$ -linked 2-deoxydisaccharides 22 and 23 were prepared in good yield with excellent  $\alpha$  selectivity from the corresponding 2-deoxyglycosyl lithium species and the Dolivoside-derived C3-disulfide acceptor 6d. Under the typical reaction conditions, only a slight excess of the 2-deoxyglycosyl phenylsulfide 4, used either pure or as an anomeric mixture, was necessary for the synthesis of S-linked 2-deoxy-α-glycosides in high yield. Benzyl (Bn) and p-methoxybenzyl (PMB) ether protecting groups are compatible with this type of Sglycosylation.

Next, we studied the anomerization of the axial 2-deoxy glycosyl lithium species 5d to the corresponding equatorial glycosyl lithium species 8d as well as the synthesis of the Slinked  $\beta$ -L-olivose-(1 $\rightarrow$ 4)- $\alpha$ -L-olivose derivative **24** (Table 1). Initially, it was found that when the axial 2-deoxyglycosyl lithium intermediate 5d (1.2 equiv) was allowed to stand at 0°C for 30 min before being cooled to -78°C and treated with the disulfide acceptor 6a, the desired S-(1 $\rightarrow$ 4)-linked 2deoxydisaccharide 24 was isolated in 32 % yield with excellent anomeric selectivity ( $\beta/\alpha > 40:1$ ; Table 1, entry 1). Epimerization of the axial 2-deoxyglycosyl lithium intermediate 5d (1.2 equiv) at -20 °C for 45 min<sup>[35]</sup> and subsequent treatment with disulfide 6a at -78 °C improved the yield of 24 to 53% $(\beta/\alpha > 40:1;$  Table 1, entry 2). However, incomplete epimerization of 5d at -30 °C for 45 min led to the production of 24 as a mixture of  $\alpha$  and  $\beta$  anomers in 54 % yield with moderate stereoselectivity ( $\beta/\alpha$  4.3:1; Table 1, entry 3). In all these experiments, the yield of product 24 as calculated on the basis of recovered disulfide acceptor 6a was nearly quantitative. Therefore, competitive deprotonation of  $THF^{\left[22\right]}$  by the glycosyl lithium species during epimerization was believed to be the major side reaction. In the hope that the use of less acidic solvents would suppress competitive deprotonation,<sup>[22]</sup> the epimerization was attempted at -20°C in hexane/THF

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**Scheme 3.** Synthesis of S-linked 2-deoxy- $\alpha$ -glycosides. General conditions: 2-deoxyglycosyl phenylsulfide (1.2 equiv), LiDBB (2.6 equiv), -78 °C, 15 min; then disulfide acceptor (1.0 equiv), THF, -78 °C, 2 h. In each case, the yield of the isolated product is given. [a] The yield of isolated 14 $\alpha$  is given. [b] The 2-deoxyglycosyl phenylsulfide **4b** (1.5 equiv) was used. Bn = benzyl, LiDBB = lithium 4,4'-di-*tert*-butylbiphenyl, MOM = methoxy-methyl, PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

(2:1 v/v) for 45 min; however, these conditions led to incomplete epimerization and afforded the S-(1 $\rightarrow$ 4)-linked 2-deoxydisaccharide **24** as a mixture of  $\alpha$  and  $\beta$  anomers in

 $\textit{Table 1:}\ Optimization of the stereoselective synthesis of S-linked 2-deoxy-\beta-glycosides.^{[a]}$ 



[a] General conditions: 2-deoxyglycosyl phenylsulfide **4d** (1.2 equiv), LiDBB (2.6 equiv), -78 °C, 15 min; then epimerization; then disulfide acceptor **6a** (1.0 equiv), THF, -78 °C, 5 h. [b] Yield of isolated **24**. [c] The total yield of the isolated product **24** as a mixture of  $\alpha$  and  $\beta$  anomers is given. [d] The reaction was carried out with **4d** (1.5 equiv) and LiDBB (3.3 equiv). [e] The reaction was carried out with **4d** (2.0 equiv) and LiDBB (4.4 equiv). 56% yield with low stereoselectivity ( $\beta/\alpha$  1.1:1; Table 1, entry 4). When the amount of the glycosyl phenylsulfide donor **4d** used was increased to 1.5 equivalents, the yield of product **24** improved to 71% (Table 1, entry 5), and it was finally discovered that the use of 2.0 equivalents of **4d** was sufficient to afford the desired 2-deoxy- $\beta$ -disaccharide **24** in 93% yield with excellent  $\beta/\alpha$  selectivity (entry 6). To the best of our knowledge, this reaction is the first synthetically useful example of the successful epimerization of an axial glycosyl lithium intermediate to its equatorial anomer for stereoselective oligosaccharide synthesis.

Following the development of optimal conditions for the anomerization of an axial 2-deoxyglycosyl lithium species to its equatorial anomer, we investigated the scope of this  $\beta$ -thioglycosylation based on umpolung reactivity. As shown in Scheme 4, the S-linked  $\beta$ -L-olivose- $(1\rightarrow 6)$ - $\alpha$ -diacetone-D-galactose **25** and S-linked  $\beta$ -L-oliose- $(1\rightarrow 6)$ - $\alpha$ -diacetone-D-galactose **26** were obtained in excellent yield with excellent  $\beta$  selectivity. The S-linked  $\beta$ -L-olivose  $(1\rightarrow 4)$ - $\alpha$ -L-olivose **27**, S-linked  $\beta$ -L-olivose- $(1\rightarrow 4)$ - $\alpha$ -D-olivose **28**, and S-linked  $\beta$ -L-oliose- $(1\rightarrow 4)$ - $\alpha$ -D-olivose **29** were also produced in good yield with excellent  $\beta$  selectivity. Furthermore, the S-linked  $\beta$ -L-olivose- $(1\rightarrow 3)$ - $\beta$ -D-olivose **30** and S-linked  $\beta$ -L-olivose- $(1\rightarrow 3)$ - $\beta$ -D-olivose **31** were synthesized in good to excellent yield with excellent  $\beta$  selectivity.

We demonstrated the utility of this efficient approach for the stereoselective synthesis of both  $\alpha$ - and  $\beta$ -S-linked 2-

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84%, >40:1 (β/α)

**Scheme 4.** Synthesis of S-linked 2-deoxy- $\beta$ -glycosides. General conditions: 2-deoxyglycosyl phenylsulfide (2.0 equiv), LiDBB (4.4 equiv), -78 °C, 15 min; then left to stand at -20 °C for 45 min; disulfide acceptor (1.0 equiv), THF, -78 °C, 5 h. In each case, the yield of the S-linked 2-deoxy- $\beta$ -glycoside is given.

deoxyglycosides in the preparation of an S-linked 2-deoxytrisaccharide, the S-linked methyl- $\alpha$ -L-rhodinose- $(1\rightarrow 4)$ - $\beta$ -Dolivose- $(1 \rightarrow 4)$ - $\alpha$ -L-olivoside **35** (Scheme 5). Accordingly, the  $\alpha$ -2,3,6-trideoxyglycosyl lithium species derived from 4-O*tert*-butyldimethylrhodinosyl phenylsulfide  $32^{[30]}$  reacted with the disulfide acceptor **6c** to afford the protected S-linked  $\alpha$ -Lrhodinose- $(1\rightarrow 4)$ - $\alpha$ -D-olivosyl phenylsulfide **33** in 87% yield with excellent  $\alpha/\beta$  selectivity. Next, reductive lithiation of the glycosyl phenylsulfide 33, followed by epimerization  $(-30 \,^{\circ}\text{C},$ 45 min)<sup>[36]</sup> and subsequent treatment with the disulfide acceptor 6a, afforded the desired S-linked 2-deoxytrisaccharide 34 in 90% yield with excellent  $\beta/\alpha$  selectivity. Finally, global removal of the silyl protecting groups in 34 with tetran-butylammonium fluoride (TBAF) gave the desired final product 35. Notably, this experiment showed that S-linked 2deoxydisaccharides bearing a phenylsulfide group at the reducing end, such as 33, can be employed as suitable precursors for the generation of the corresponding glycosyl



 $\ensuremath{\textit{Scheme 5.}}$  Stereoselective synthesis of an S-linked 2-deoxytrisaccharide.

lithium species for the synthesis of elongated S-linked analogues of 2-deoxyoligosaccharide subunits in biologically active natural molecules.

In summary, a novel approach to the stereoselective synthesis of S-linked 2-deoxy  $\alpha$ - and  $\beta$ -glycosides has been developed on the basis of an unprecedented sulfenylation of stereochemically defined 2-deoxyglycosyl lithium species with asymmetric sugar-derived disulfide acceptors. In this Sglycosylation based on umpolung reactivity, anomeric selectivity is dictated by stereochemically defined glycosyl lithium intermediates, which can be obtained through the reductive lithiation of readily available 2-deoxyglycosyl phenylsulfides and subsequent temperature-controlled anomerization. Whereas metastable glycosyl thiols or thiosugars were commonly employed in previous syntheses of thioglycosides, our S-glycosylation takes advantage of relatively stable asymmetric sugar-derived tert-butyldisulfides for the stereoselective construction of the S-glycosidic linkage. Furthermore, this approach was successfully used for the stereoselective synthesis of a complex S-linked 2-deoxytrisaccharide. Application of this methodology to the synthesis of Slinked analogues of naturally occurring bioactive 2-deoxysugars and comparative studies of the physical, chemical, and biological properties of these compounds are currently under way.

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