Thioglycoside Synthesis

DOI: 10.1002/anie.201301682

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

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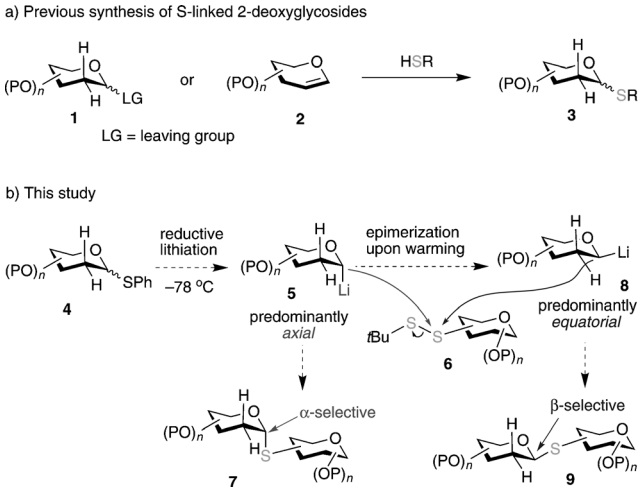
Dedicated to Professor Samuel J. Danishefsky

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,[1] angucyclines,[2] aureolic acid antibiotics,[3] avermectins,[4] enediynes,[5] pluramycins,[6] lomaiviticins,[7] vancomycin,[8] and cardiac glycosides.[9] These sugars play a critical role in the biological activity of these compounds as well as their stability and solubility.[10] As a result, considerable effort has been devoted to the stereoselective synthesis of 2-deoxyglycosides and the study of their structure–activity relationships.[11] Despite the significance of 2-deoxysugar subunits, the glycosidic linkage of 2-deoxyglycosides 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 2-deoxysugars, has resulted in toxicity[12] and reduced activity[13] of the parent molecules, and has limited their use as clinical agents.

Thioglycosides (S-linked glycosides),[14] 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[15] 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,[14,16] there is no efficient method for the stereoselective construction of S-linked 2-deoxyoligosaccharides,[17] 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[18]/chlorides **1**[19] or 2-deoxyglycals **2**[20] with simple thiol-containing nucleophiles (Scheme 1a). Herein, we report an unprecedented sulfenylation of stereochemically defined 2-deoxyglycosyl lithium species with asymmetric sugar-derived disulfide acceptors for the stereoselective synthesis of both α- and β-S-linked 2-deoxyoligosaccharides (Scheme 1b).



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

According to our approach, the reductive lithiation of a mixture of 2-deoxy α- and β-glycosyl phenylsulfide **4** with a suitable radical-anion reductant should afford predominantly intermediate **5** with an axial lithium substituent at low temperature.[21,22] 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**).[23] We used a steric effect to promote the desired regioselectivity by installing a tertiary alkyl group (e.g., *tert*-butyl) 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[21b,c,22] to the corresponding thermodynamically more stable equatorial lithium species **8**, which may react with disulfide **6** to give the S-linked 2-deoxy-β-oligosaccharide **9**. Thus, S-linked 2-deoxy α- and β-oligosaccharides may be obtained selectively from the same 2-deoxyglycosyl phenylsulfide precursors through facile temperature control.

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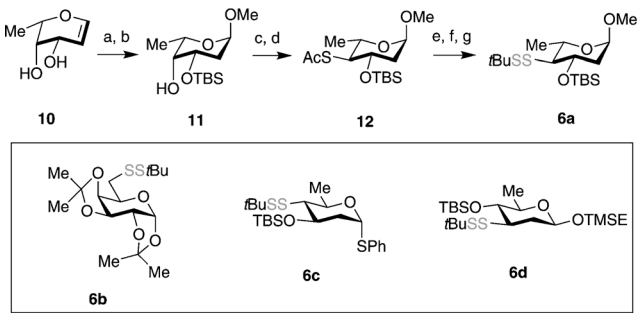
[**] Presented in part at the 244th American Chemical Society National Meeting, Philadelphia, PA, USA, August 19–23, 2012, CARB-13. We are very grateful to the National Science Foundation (CHE-1213352) and the University of Toledo for supporting this research. We thank Professors Peter Andreana and Steve Sucheck for proofreading this manuscript and Joseph Duffey, Hanin Dughayli, and Mallory Walker for experimental assistance.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301682.

The generation of nucleophilic glycosyl lithium reagents by reductive lithiation, a process invented by Cohen and coworkers,[21] for the stereoselective synthesis of C-glycosides was reported previously by the research groups of Sinaÿ,[17c,24] Beau,[25] Kessler,[26] and others.[27] Although the synthesis of α-C-glycosides from readily available α-glycosyl lithium intermediates is straightforward, the generation of β-glycosyl lithium species for the synthesis of β-C-glycosides has remained a challenge. Previous efforts towards the preparation of β-glycosyl lithium species involved the synthesis of β-glycosylstannanes and a subsequent tin–lithium exchange.[28] Alternatively, the β-C-glycosides can be synthesized by an indirect approach involving sequential deprotonation of a glycosylsulfone, electrophile addition, and stereoselective reductive desulfonation.[29] Therefore, the development of a more effective method for the selective preparation of β-glycosyl lithium species is particularly appealing. Furthermore, although these studies[27] 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^{V} catalysis.[20,30] In our hands, compounds **4a**, **4b**, and **4d** were obtained as a mixture of α and β anomers, whereas **4c**, **4e**, and **4f** were isolated as the pure α isomer (Scheme 3).[30] Since both 2-deoxy α- and β-glycosyl phenylsulfides can undergo reductive lithiation to afford the stereochemically pure axial lithium (α-lithium) species,[21] α/β anomeric mixtures of **4a**, **4b**, and **4d** were used directly for reductive lithiation. Furthermore, asymmetric sugar-derived *tert*-butyldisulfide acceptors, **6a**–**d**, were synthesized[30] by reactions of thiosugars[31] with *tert*-butyl methanethiosulfonate[32] in the presence of a tertiary amine base (Scheme 2).[33] For example, L-fucal (**10**) was converted into the corresponding methyl glycoside, which underwent regioselective silyl protection to afford **11** (59% over two steps). Next, the triflation of **11**, followed by S_N2 displacement with cesium thioacetate, provided thioester **12** (86% over two steps). The reduction of thioacetate **12** with lithium aluminium hydride furnished

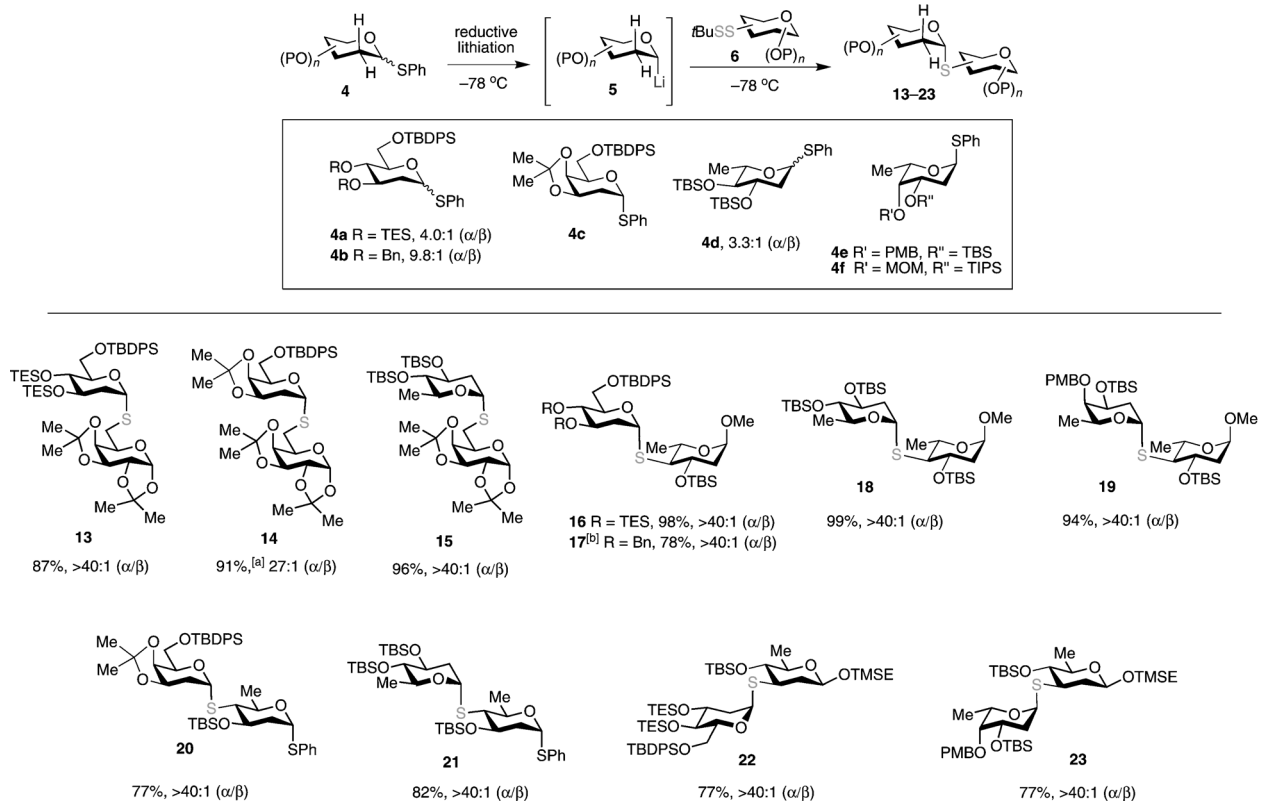


Scheme 2. Reagents and conditions: a) cat. CSA, MeOH; b) TBSCl, Et_3N, DMF, 59% over two steps; c) Tf_2O, pyridine, CH_2Cl_2, 0°C; d) CsSAc, THF, 86% over two steps; e) $LiAlH_4$, Et_2O, −30°C→RT; f) *t*BuSSO$_2$Me, Et_3N, CH_2Cl_2, 0°C→RT; g) TBSCl, imidazole, DMF, 78% over three steps. CSA = camphorsulfonic 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.[30]

With 2-deoxyglycosyl phenylsulfides **4a**–**f** and sugar-derived disulfides **6a**–**d** in hand, we carried out the key S-glycosylation reactions based on umpolung reactivity. Reductive lithiation[21,22] of a mixture of 2-deoxy α- and β-glycosyl donors **4a** (1.2 equiv) at −78°C with lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB)[34] 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 α selectivity (α/β > 40:1; Scheme 3). Under the same conditions, the S-(1→6)-linked 2-deoxydisaccharides **14** and **15** were prepared in excellent yield with excellent α selectivity from the 2-deoxyglycosyl phenylsulfide donors **4c** and **4d**, respectively. The S-(1→4)-linked 2-deoxydisaccharides **16**–**21** were also synthesized in good to excellent yield and with excellent α selectivity from the corresponding 2-deoxy L- or D-glycosyl lithium species and the L- or D-olivoside-derived C4-disulfide acceptor **6a** or **6c**. Furthermore, the S-(1→3)-linked 2-deoxydisaccharides **22** and **23** were prepared in good yield with excellent α selectivity from the corresponding 2-deoxyglycosyl lithium species and the D-olivoside-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 S-glycosylation.

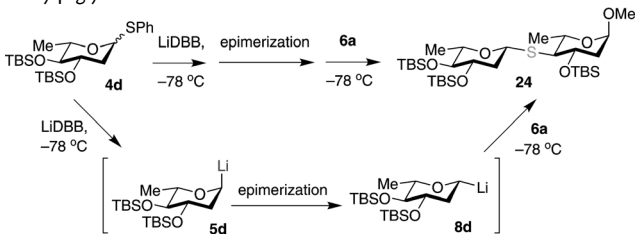
Next, we studied the anomerization of the axial 2-deoxy glycosyl lithium species **5d** to the corresponding equatorial glycosyl lithium species **8d** as well as the synthesis of the S-linked β-L-olivose-(1→4)-α-L-olivose derivative **24** (Table 1). Initially, it was found that when the axial 2-deoxyglycosyl 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→4)-linked 2-deoxydisaccharide **24** was isolated in 32% yield with excellent anomeric selectivity (β/α > 40:1; Table 1, entry 1). Epimerization of the axial 2-deoxyglycosyl lithium intermediate **5d** (1.2 equiv) at −20°C for 45 min[35] and subsequent treatment with disulfide **6a** at −78°C improved the yield of **24** to 53% (β/α > 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 α and β anomers in 54% yield with moderate stereoselectivity (β/α 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[22] 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,[22] the epimerization was attempted at −20°C in hexane/THF



Scheme 3. Synthesis of S-linked 2-deoxy-α-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**α is given. [b] The 2-deoxyglycosyl phenylsulfide **4b** (1.5 equiv) was used. Bn = benzyl, LiDBB = lithium 4,4′-di-*tert*-butylbiphenyl, MOM = methoxymethyl, 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→4)-linked 2-deoxydisaccharide **24** as a mixture of α and β anomers in 56% yield with low stereoselectivity (β/α 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-β-disaccharide **24** in 93% yield with excellent β/α 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.

Table 1: Optimization of the stereoselective synthesis of S-linked 2-deoxy-β-glycosides.[a]

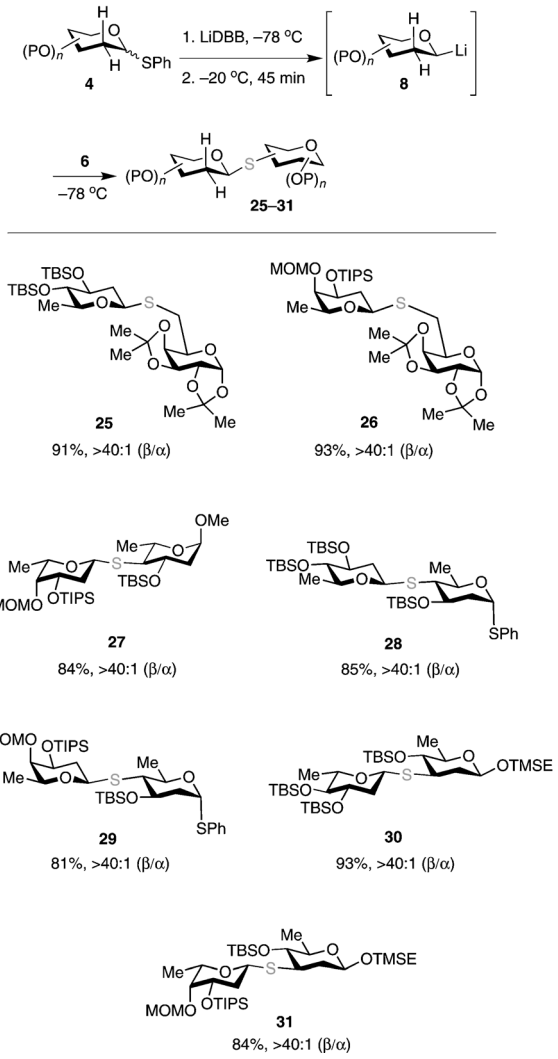


Entry	Epimerization conditions	Yield [%][b] (β/α)
1	0 °C, THF, 30 min	32 (>40:1)
2	−20 °C, THF, 45 min	53 (>40:1)
3	−30 °C, THF, 45 min	54[c] (4.3:1)
4	−20 °C, hexane/THF (2:1 v/v), 45 min	56[c] (1.1:1)
5[d]	−20 °C, THF, 45 min	71 (>40:1)
6[e]	−20 °C, THF, 45 min	93 (>40:1)

[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 α and β 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).

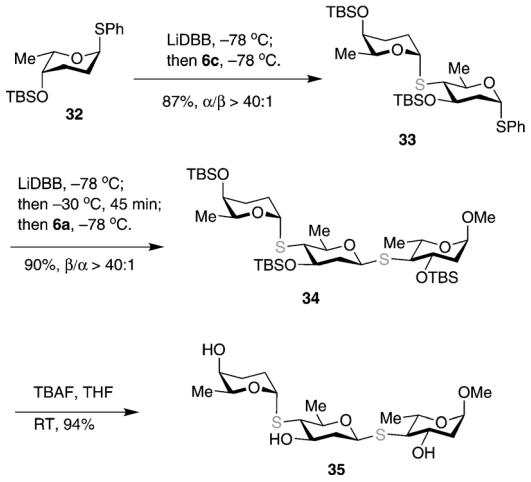
Following the development of optimal conditions for the anomerization of an axial 2-deoxyglycosyl lithium species to its equatorial anomer, we investigated the scope of this β-thioglycosylation based on umpolung reactivity. As shown in Scheme 4, the S-linked β-L-olivose-(1→6)-α-diacetone-D-galactose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

We demonstrated the utility of this efficient approach for the stereoselective synthesis of both α- and β-S-linked 2-



Scheme 4. Synthesis of S-linked 2-deoxy-β-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-β-glycoside is given.

deoxyglycosides in the preparation of an S-linked 2-deoxytrisaccharide, the S-linked methyl-α-L-rhodinose-(1→4)-β-D-olivose-(1→4)-α-L-olivoside **35** (Scheme 5). Accordingly, the α-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 α-L-rhodinose-(1→4)-α-D-olivosyl phenylsulfide **33** in 87% yield with excellent α/β selectivity. Next, reductive lithiation of the glycosyl phenylsulfide **33,** followed by epimerization (−30 °C, 45 min)[36] and subsequent treatment with the disulfide acceptor **6a**, afforded the desired S-linked 2-deoxytrisaccharide **34** in 90% yield with excellent β/α selectivity. Finally, global removal of the silyl protecting groups in **34** with tetra-*n*-butylammonium fluoride (TBAF) gave the desired final product **35**. Notably, this experiment showed that S-linked 2-deoxydisaccharides bearing a phenylsulfide group at the reducing end, such as **33**, can be employed as suitable precursors for the generation of the corresponding glycosyl



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 α- and β-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 S-glycosylation 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 S-linked analogues of naturally occurring bioactive 2-deoxysugars and comparative studies of the physical, chemical, and biological properties of these compounds are currently under way.

Received: February 26, 2013
Revised: May 15, 2013
Published online: June 18, 2013

Keywords: 2-deoxysugars · glycosyl lithium intermediates · glycosylation · thioglycosides · umpolung

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