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Extended applications and potential limitations of ring-fused 2,3-oxazolidinone thioglycosides in glycoconjugate synthesis

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Abstract—The utility of ring-fused 2,3-oxazolidinone derivatives of 2-amino-2-deoxy-thioglycosides in the synthesis of glycopeptide intermediates and building blocks for the synthesis of heparan sulfate oligosaccharides is reported. These unique ring-fused monosaccharides afford a novel and efficient route to alpha-*O*-linked 2-amino-2-deoxy amino acid derivatives and heparan sulfate oligosaccharide intermediates.

Stereoselective formation of α-linked glycosides of 2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-galactose is critical to the synthesis of numerous natural products and biologically important glycoconjugates including glycosylphosphatidylinositols, glycopeptides, glycoproteins and glycosaminoglycans.[1] Previous work in this laboratory demonstrated the utility of ring-fused 2,3-oxazolidione derivatives of phenyl 2-amino-2-deoxy-1-thio-glucopyranosides as versatile intermediates in the stereoselective formation of α-linked disaccharides (Fig. 1).[2] Additional advantages of the ring-fused 2,3-oxazolidinone monosaccharides as synthetic intermediates for the synthesis of 2-amino-2-deoxy-hexopyranoside containing glycoconjugates is their efficient conversion to highly functionalized, selectively protected, derivatives and their commercially viable synthesis on large scale in high yield.

Initial success in the efficient preparation and use of ring-fused 2,3-oxazolidione derivatives of phenyl 2-amino-2-deoxy1-thio-glucopyranoside in the synthesis of α-linked disaccharides suggested that these novel monosaccharides would be useful intermediates for the stereoselective synthesis of numerous biologically important glycoconjugates.[2] To this end, a series of ring-fused 2,3-oxazolidinone protected monosaccharide and disaccharide 2-amino-2-deoxy-1-thio-glycopyranosides was prepared to investigate extending this stereoselective coupling strategy to (1) the synthesis of glyco-amino acid intermediates for glycopeptide synthesis and (2) to the synthesis of advanced intermediates for preparing heparan sulfate oligosaccharides.

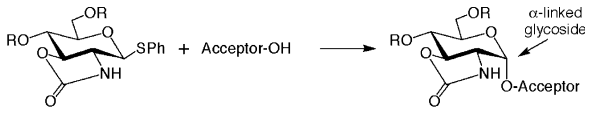

Figure 1.

The successful application of ring fused 2,3-oxazolidinone derivatives of phenyl 2-amino-2-deoxy-1-thio-glucopyranosides in the formation of α-*O*-linked serine and threonine intermediates is shown (Fig. 2).[3] Donor **1**, previously shown to be efficient in the stereoselective formation of α-linked disaccharides,[2] provided high yields of both α-*O*-linked serine (**4**) and α-*O*-linked threonine (**5**). Phenylthioglycoside **2**,[4] having C-6 benzyl and C-4 TBS protecting groups, afforded high yield of the α-linked threonine conjugate, which is set up for one-step deprotection at C-3 or C-4 for elongation of the saccharide. A slightly lower yield was observed using **2** because modest loss of the TBS protecting group occurs during the coupling reaction. This is not unexpected; loss of the TBS group from donors and acceptors has been observed in our laboratory when using PST to activate thioglycosides. This side reaction is more pronounced if care is not taken to quench the reaction at low temperature immediately upon completion.

Coupling of fused-ring 2,3-oxazolidinone galactosamine derivatives **3** to threonine, the predominant linkage in many biologically important *O*-linked glycoproteins,

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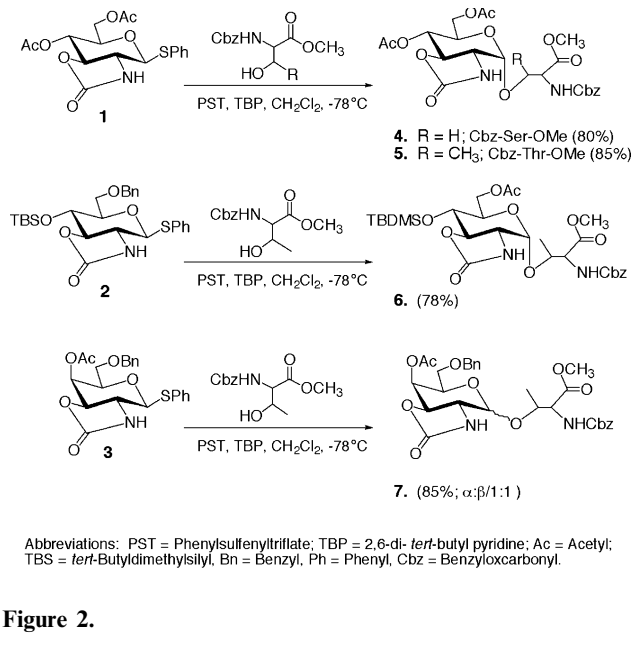
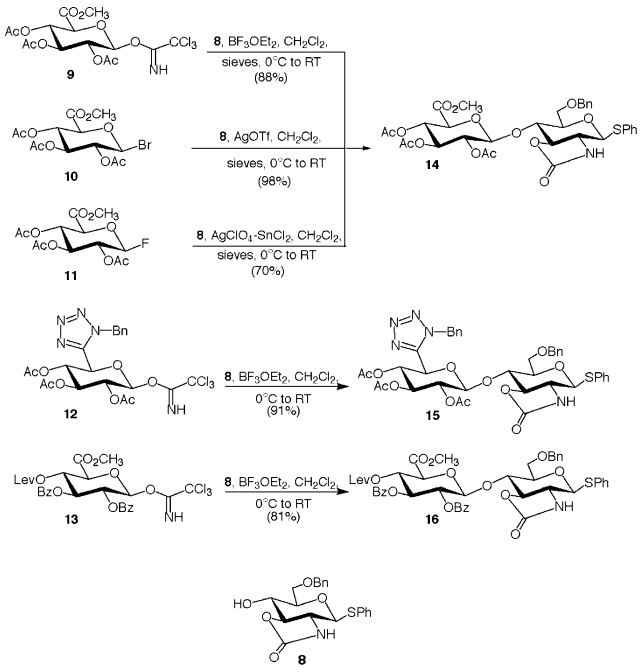


Figure 2.



Scheme 1.

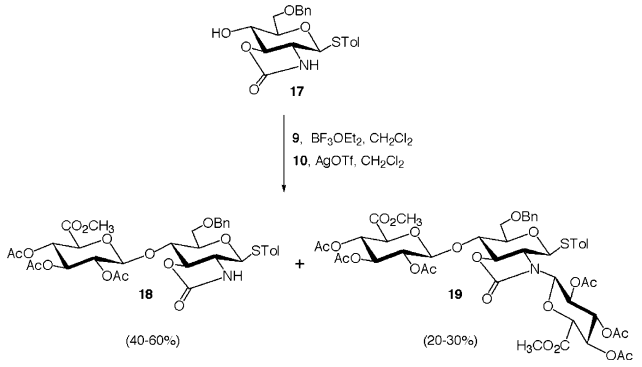
also proceeded in high overall yield.[5] However, poor enantioselectivity was observed and modification of reaction conditions did not improve stereoselectivity of this coupling reaction.[5] This poor stereoselectivity for the galactosamine derivative is not entirely unexpected. Reports for various 2-azido-2-deoxy-D-galactose donors including sulfoxide, thiophenyl and selenylphenyl donors bearing the non-participating C-2 azide group have typically afforded poor to modest yields in amino acid coupling reactions, with varied stereoselectivity for formation of the α-linked galactoside.[6]

Based on previous success in the coupling of ring-fused 2,3-oxazolidinonyl thioglycosides to a glucuronic acid acceptor in the synthesis of the repeating disaccharide unit of heparan sulfate,[2] we set out to prepare a series of disaccharides where the glucuronic acid is linked to the 4-position of a 2,3-oxazolidinonyl protected thioglycoside donor. It was anticipated that these novel disaccharide thioglycosides would serve as important intermediates for the efficient synthesis of chain elongated heparan sulfate oligosaccharides (Scheme 1).[7]

Coupling of known trichloroacetimidates **9**, **12** and **13** to oxazolidinone acceptor **8** afforded good to excellent yield of disaccharides **14**–**16**.[8] The known glucuronyl fluoride, **11**, and bromide, **10**, also afforded high yields of **14**. Considering glucuronic acid derivatives are known to be relatively deactivated glycosyl donors, these results exemplify the possible increased reactivity of the 4-hydroxy group in 2,3-oxazolidine protected glucopyranosides,[9] the utility of ring-fused 2,3-oxazolidinone derivatives of phenyl 2-amino-2-deoxy1-thioglycopyranosides as excellent, highly functionalized, glycosyl acceptors and demonstrates their compatibility with a number of orthogonal glycosylation strategies.

It was anticipated that the ring-fused 2,3-oxazolidinone-protected thioglycoside located at the reducing end of these disaccharides would afford stereoselective formation of α-linked glycosides, thus providing disaccharide building blocks for the synthesis of chain-elongated heparan sulfate oligosaccharides.[7] However, activation of disaccharides **14**–**16** using PST was not efficient. In fact, these disaccharides were simply not activated under standard coupling conditions at −78°C, which affords outstanding coupling of the monosaccharide donors. While modest levels of activation could be obtained at 0°C, glycoside coupling at this temperature was only achieved with simple alcohols such as methanol with a concomitant loss of stereocontrol.[10] Attempts to activate these disaccharide donors with a number of other known thioglycoside activating agents were also unsuccessful at low temperatures, and as expected afforded incomplete activation or loss of stereocontrol at higher activation temperatures (−20°C to room temperature).

The inability to efficiently activate the above disaccharides is consistent with similar observations suggesting that 2,3-oxazolidinone protection of monosaccharide thioglycosides deactivates (disarms) the D-hexopyranoside ring system to glycosyl activation. Boons recently reported similar disarming of 2,3-carbonate protected thioglycoside derivatives.[11] Therefore, further deactivation of this ring system by the C-4 glucuronide substituent appears to severely impede thioglycoside activation and subsequent glycoside bond formation. In a first effort to improve activation of these disaccharides we prepared *p*-methylphenyl thioglycoside **17**, which was anticipated to be more readily activated than the phenylthio-disaccharides (Scheme 2). Glycosylation of **17** with glucuronic acid donors **9** and **10** under the same conditions employed for preparing **14** afforded only modest yields of the target disaccharide, with concomitant formation of *N*-glycosylated trisaccharide



Scheme 2.

19 (Scheme 2).[12] Employing a two- to three-fold excess of acceptor **17** only modestly reduced formation of trisaccharide **19**. One explanation for this result is that *N*-glycosylation competes with *O*-glycosylation, and *N*-glycosylation imparts increased reactivity of the 4-hydroxy group of the 2,3-oxazolidinone protected sugar. Thus, the *N*-glycosylated disaccharide has a more reactive 4-hydroxy group than **17**, leading to the competitive formation of trisaccharide **19** even when excess **17** is employed. Unfortunately, activation of **18** and use as a glycosyl donor as described for **14** was not efficient, affording little improvement over that observed for **14**.

Based on the results of this work and previous reports,[2,9] it is clear that fused-ring 2,3-oxazolidinone protected thioglycosides are useful intermediates for the synthesis of highly functionalized α-linked 2-amino-2-deoxy-D-glucopyranosides. However, two hurdles to the ready use of the 2,3-oxazolidinone protected sugars in the synthesis of larger oligosaccharides are apparent. First, further deactivation of the 2,3-oxazolidinonyl thioglycoside ring system upon coupling other sugars to the 4-hydroxy group may limit utility of the subsequent highly disarmed 1-thio-disaccharides in subsequent glycosylation reactions. Second, the oxazolidinone nitrogen is more readily glycosylated than a typical amide nitrogen, and thus its presence in a growing saccharide chains may complicate the iterative linking of sugar units.

In conclusion, we have successfully demonstrated the application of fused-ring 2,3-oxazolidinone derivatives to the stereoselective formation of α-*O*-linked glycoamino acid conjugates. We have also demonstrated that the 4-hydroxy group of fused-ring 2,3-oxazolidinones affords high yield glycosyl coupling with a variety of glucuronic acid donors to give the key glucuronic acid-β(1–4)-glucosamine linkage that is the major repeating disaccharide unit in heparan sulfate. A limitation to the utility of the fused-ring 2,3-oxazolidinones appears to be the propensity for *N*-glycosylation. One way to avoid *N*-glycosylation is to protect the oxazolidinone nitrogen, however, the behavior of *N*-substituted 2,3-oxazolidinyl thioglycosides as glycosyl donors is unknown. Toward this end, we are currently studying the activation and stereoselectivity of diverse *N*-protected 2,3-oxazolidinone protected thioglycosides toward developing a series of armed and disarmed glycosyl donors that are refractory to *N*-glycosylation.

Acknowledgements

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2. Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461.
3. Standard activation of thioglycosides using PST was employed for all coupling reactions in Figure 2 as previously reported in reference 2. The structure of all products were confirmed by mass spectroscopic and ^{1}H NMR analysis. The alpha configuration of products are (**4**, δ 5.13, $J_{1,2}=2.4$ Hz; **5**, δ 5.01, $J_{1,2}=2.4$ Hz; **6**, δ 5.23, $J_{1,2}=3.7$ Hz; **7**, δ 5.2, $J_{1,2}=3.2$ Hz). In addition, both anomers were available for definitive assignment of alpha-beta isomers in all cases because oxidation of the thioglycosides to sulfoxide followed by triflic anhydride-mediated glycosylation afforded alpha:beta mixtures in 50–55% overall yields. These sulfoxide results further demonstrate the high enantioselectivity possible using PST-mediated coupling of 2,3-oxazolidinone protected thioglycosides.
4. Thioglycoside **2** was prepared in one step by introducing the TBS group onto the 4-position of the corresponding C-4 hydroxy derivative previously prepared in our laboratory (see Ref. 2).
5. Fused-ring 2,3-oxazolidinone protected galactosamine derivative **3** was prepared as described in Ref. 2.
6. Previous reports include: Coupling of a 2-azido galactosyl sulfoxide to serine afforded a 1:1 α/β mixture (Hamilton Andreotti, A.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 3352–3353). Coupling of 2-azido galactosyl fluoride, selenylphenyl and thiophenyl donors have been reported to give serine and threonine coupling in 65–87% yields of varied α/β selectivity [(a) Singh, L.; Nakahara, Y.; Ito, Y.; Nakahara, Y. *Carbohydr. Res.* **2000**, *325*, 132–142; (b) Jiaang, W.-T.; Chang, M.-Y.; Tseng, P.-H.; Chem, S.-T. *Tetrahedron Lett.* **2000**, *41*, 3127–3130; (c) Miyajima, K.; Nekado, T.; Ikeda, K.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 1676–1682).
7. Recent reports describing glycosaminoglycan oligosaccharide synthesis using modular disaccharide building blocks include: Haller, M. F.; Boons, G.-J. *Eur. J. Org. Chem.* **2002**, 2033–2038; Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem. Eur. J.* **2003**, *9*, 140–169.
8. Select data for saccharides **14**–**18**: (**14**) $R_f=0.30$ (2:3, ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 9H,

CH_3), 3.23 (dd, 1H, H′-2), 3.36 (m, 1H, H′-6), 3.53 (m, 1H, H′-5), 3.76 (s, 3H, OCH_3), 4.12 (m, 1H, H′4), 4.17, 4.37 (m, 1H, $PhCH_2$), 4.23 (m, 1H, H′-6), 4.61 (m, 1H, H′-3), 4.68 (d, 1H, H′-1), 5.06 (s, 1H, NH), 5.13 (d, 1H, H-1), 5.10 (m, 1H, H-5), 5.55–5.60 (m, 2H, H-2 and H-4), 5.98 (d, 1H, H-3), 7.22–7.40, 7.53 (10H, Ar-H). Mass spec. (ESI) m/z 726.16 ($M+Na^+$). (**15**) $R_f=0.41$ (2:3, ethyl acetate:hexane); ^1H NMR ($CDCl_3$) δ 1.89, 2.01, 2.08 (s, 9H, CH_3), 3.27 (dd, 1H, H′-2), 3.46 (m, 1H, H′-6), 3.78, 3.84 (m, 2H, H′-6), 3.92, 4.14 (m, 2H, $PhCH_2$), 4.08 (m, 1H, H-5), 4.19 (m, 1H, H′-4), 4.53 (m, 1H, H′-3), 4.63 (d 1H, H′-1, 4.8 (dd 1H, H-4), 5.06 (s, 1H, H-2), 5.28 (s, 1H, NH), 5.50 (m, 1H, H-1), 5.55 (m, 1H, H-3), 5.58–5.73 (m, 2H, $PhCH_2N$), 7.23–7.37, 7.48 (m, 15H, Ar-H). Mass spec. (ESI) m/z 827.20 ($M+Na^+$). (**16**) $R_f=0.55$ (1:1, ethyl acetate:hexane); ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H, CH_3CO), 2.37–2.65 (m, OCH_2CH_2O), 3.32 (dd, 1H, H′-2), 3.51–3.59 (m, 3H, H′-5 and 2H′-6), 3.78 (s, 3H, CH_3), 4.07 (m, 1H, $PhCH_2$), 4.13 (m, 1H, H′-4), 4.20 (d, 1H, H-5), 4.31 (d, 1H, $PhCH_2$), 4.35 (d, 1H, H′-3), 4.65 (d, 1H, $J=9.4$ Hz, H′-1), 4.79 (d, 1H, $J=8.5$ Hz, H-1), 5.08 (s, 1H, NH), 5.42–5.47 (m, 1H, H-2 and H-4), 5.65 (dd, 1H, H-3), 7.11, 7.22, 7.28–7.37, 7.48, 7.88 (m, 15H, Ar-H). Mass spec. (ESI) m/z 906.33 ($M+Na^+$). (**17**) $R_f=$ 0.55 (2:1, ethyl acetate:hexane); ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.15 (s, OH), 3.33 (dd, 1H, H-2), 3.62 (m, 1H, H-5), 3.79–3.91 (m, 2H, H-6), 4.03 (dd, 1H, H-4), 4.15 (dd, 1H, H-3), 4.59–4.67 (m, 2H, $PhCH_2$), 4.70 (d, 1H, $J=8.6$ Hz, H-1), 5.20 (s, 1H, NH), 7.12–7.44 (m, 9H, Ar-H). (**18**) $R_f=0.45$ (2:1, ethyl acetate:hexane); ^1H NMR ($CDCl_3$) δ 2.10 (s, 9H, CH_3), 2.35 (s, 3H, CH_3), 3.70–4.0 (m, 3H), 3.81 (s, 3H, OCH_3), 4.08 (d, 1H) 4.22–4.30 (m, 2H) 4.5–4.7 (m, 3H, H′-3, $PhCH_2$), 5.00–5.4 (m, 4H), 5.6 (d, 1H), 7.22–7.50 (9H, Ar-H). Mass spec. (ESI) m/z 740 ($M+Na^+$).

9. During the preparation of this manuscript Crich reported that oxazolidinone protection of *N*-acetylglucosamine confers high reactivity on the 4-hydroxy group in glycosylation, see: Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297–1300.
10. We consistently obtain high yields (80–95%) of the β-methyl glycosides of monosaccharide and disaccharide 2,3-oxazolidinone protected thioglycosides on glycosidation with methanol using PST activation.
11. Zhu, T.; Boons, G.-J. *Org. Lett.* **2001**, *3*, 4201–4203.
12. Trace amounts of *N*-glycosylated trisaccharides had been observed during glycosylation of **8**. It is not obvious why glycosylation of **17** affords increased competition of *N*-glycosylation compared to **8**, although the more electron donating *p*-methylphenyl substituent at the anomeric center is likely altering electron density on the oxazolidinone nitrogen. Although complicated by signal overlap, ^1H NMR of **19** showed that the exchangeable *N*–H of the oxazolidinone was no longer detectable and that two glucuronic acid glycosides were present. Mass spec. **19** (ESI) m/z 1056 ($M+Na^+$).