Oxazolidinone Protected 2-Amino-2-deoxy-D-glucose Derivatives as Versatile Intermediates in Stereoselective Oligosaccharide Synthesis and the Formation of α-Linked Glycosides

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Many natural products and biologically significant glycoconjugates contain *N*-substituted 2-amino-2-deoxy-D-glycopyranoside residues.[1] We have recently been exploring the introduction of structural diversity into one family of these important glycoconjugates, the glycosaminoglycans (GAGs).[2] A major obstacle to synthesizing GAG oligosaccharides, as well as other glycoconjugates containing 2-amino-2-deoxy-D-glycopyranoside residues, is the difficulty to readily prepare structurally diverse 2-amino sugars that also display high stereoselectivity during glycoside bond-forming reactions. Here, we report the synthesis of ring-fused 2,3-oxazolidinone derivatives of 1-phenylthio-glycopyranosides and demonstrate the utility of these novel glycosyl donors and synthetic intermediates in stereoselective oligosaccharide synthesis and the formation of α-linked glycosides.

While there are a number of strategies to obtain "*β*-linked" 2-amino-D-glycopyranosides[3] (found in hyaluronate and dermatan sulfate GAGs), the formation of "α-linked" 2-amino-D-glucopyranosides (found in heparin and heparan sulfate (HS) GAGs) relies almost exclusively on employing 2-azido-glycosyl donors.[4] Glycosidation of the 2-azido donors affords α/*β*-mixtures of the coupled products, although the α-isomer usually predominates. Methods to prepare the 2-azido sugars are also generally expensive and often inefficient, posing limitations to commercialization of glycoconjugates synthesized via these intermediates.[5] Moreover, the synthesis of oligosaccharides containing multiple different *N*-substituted α-linked 2-amino sugars is severely limited because these syntheses must use 2-azido donors for each glycoside forming reaction, making it problematic to differentiate the multiple amine groups. An additional significant obstacle to preparing galactosamine-containing glycoconjugates (e.g. chondroitin sulfates and glycopeptides) is the high cost and inaccessibility of galactosamine derivatives as synthetic intermediates.

In an effort to address these problems, we envisioned ring-fused 2,3-oxazolidinone derivatives of phenyl 2-amino-2-deoxy-1-thio-glucopyranosides as versatile intermediates for the stereoselective synthesis of α-linked and *β*-linked glycoconjugates. (Figure 1).

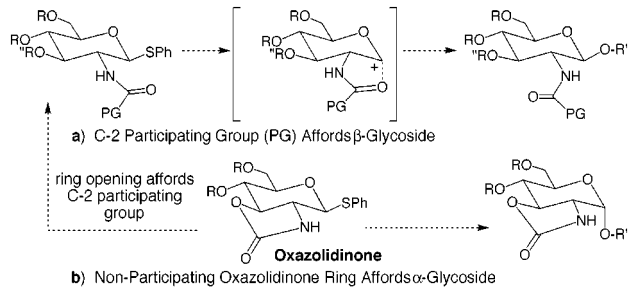
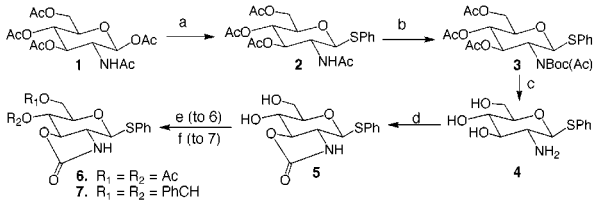


Figure 1. Ring-fused oxazolidinones of 2-amino-D-glycopyranosides are versatile intermediates to α-linked and *β*-linked saccharides.

Scheme 1[a]



[a] Reagents and conditions: (a) PhSH, $SnCl_4$, 60 °C, CH_2Cl_2 (98%). (b) Boc_2O, DMAP, 60 °C, THF (97%). (c) (i) Na^0, MeOH (98%); (ii) TFA, MeOH (80%). (d) NPCC, $NaHCO_3$, CH_3CN/H_2O (80%). (e) Ac_2O, pyridine (90%). (f) $PhCH(OMe)_2$, CSA, 60 °C, DMF (90%).

Oxazolidinone **5** was the first common intermediate targeted (Scheme 1). The phenylthio group protects the anomeric position until selectively activated for glycoside bond formation.[6] Selective differentiation of all hydroxyl groups in **5** is facilitated by the fused oxazolidinone ring, which protects and differentiates the C-3 hydroxyl group.

Two steps in Scheme 1 require comment. First, direct hydrolysis of acetamide **2** to form **4** is not efficient on large scale (10 g or more) because separating **4** from salts and byproducts is problematic. Converting **2** to *tert*-butoxycarbonyl (Boc) protected **3**, which is readily deacetylated, circumvents this problem.[7] Removal of the Boc group affords **4** in excellent yield from **1**. Second, treatment of **4** with *p*-nitro-phenoxycarbonyl chloride (NPCC) or phenyl chloroformate using modifications of reported methods affords oxazolidinone **5** in high yield: 80% and 93% yield, respectively.[8] Synthesis of these ring-fused oxazolidinones is versatile, efficient, and cost-effective when compared to preparing the 2-azido counterparts as synthetic intermediates.

Employing phenylsulfenyltriflate (PST) for the activation and glycosidation of thioglycoside **6** affords the formation of α-linked glycosides in excellent yield, Table 1.[9] In fact, glycoside bond formation using this novel donor/activator pair proceeds with nearly 100% stereoselective formation of the α-linked glycosides.[10] This very efficient glycosylation strategy rivals, even surpasses, the stereoselectivity and yields of current methods utilizing the 2-azido donors to make α-linked glycosides of 2-amino-D-hexopyranosides.

In addition to promoting the stereoselective formation of α-linked glycosides, the ring-fused oxazolidinone provides a

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(1) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720.

(2) For a recent review of GAGs and their functions in cell-surface recognition and the regulation of receptor functions and cytotoxic events see: Bernfield, M.; Gotte, M.; Park, P. W.; Reizes, O.; Fitzgerald, M. L.; Lincecum, J.; Zako, M. *Annu. Rev. Biochem*. **1999**, *68*, 729−77.

(3) A participating group at position 2 of hexopyranoside glycosyl donors is required to obtain *β*-linked glycosides. A number of groups for amine protection have been employed for this purpose, including *N*-tetrachlorophthaloyl (Debenham, J. S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 3302−3303), *N*-thiodiglycoloyl (Castro-Palomino, J. C.; Schmidt, R. R. *Tetrahedron Lett*. **2000**, *41*, 629−632), Troc (Yeung, B. K. S.; Hill, D. C.; Janicka, M.; Petillo, P. A. *Org. Lett*. **2000**, *9*, 1279−1282), methoxycarbonyl (Yeung, B. K. S.; Adamski-Werner, S. L.; Bernard, J. B.; Poulenat, G.; Petillo, P. A. *Org. Lett*. **2000**, *20*, 3135−3138), and acetamido-glycosylation (Di Bussolo, V.; Liu, J.; Huffman, L. G.; Gin, D. Y. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 204−207).

(4) A nonparticipating group at position 2 of the donor (such as 2-azido) is required to obtain α-linked glycosides that are then converted to the 2-amino-2-deoxy-D-glycopyranoside product.

(5) For recent reports regarding the preparation of 2-azido saccharides see: (a) Seeberger, P. H.; Roehrig, S.; Schell, P.; Wang, Y.; Christ, W. *Carbohydr. Res*. **2000**, *328*, 61−69. (b) Vasella, A.; Witzig, C.; Chiara J. L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073−2077.

(6) See: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(7) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185−4188.

(8) PC Kumar, R.; Remers, W. A. *J. Org. Chem.* **1978**, *43*, 3327.

(9) Specific reaction conditions are available in the Supporting Information. For a discussion of this method to activate phenythioglycosides see: Crich, D.; Sun, S. *J. Am. Chem. Soc*. **1998**, *120*, 455−456.

(10) *β*-Glycoside has been observed when sufficiently low temperatures were not maintained during the course of the reaction.

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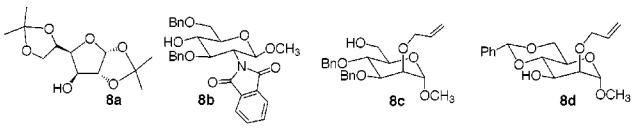
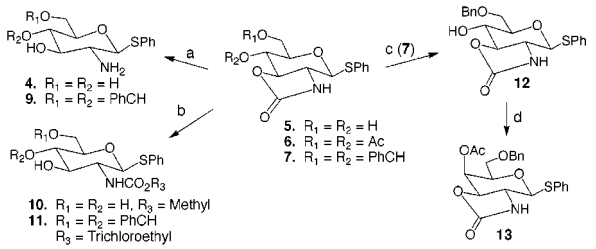
Table 1. Ring-Fused Oxazolidinone of D-Glucosamine Affords the Stereoselective Formation of α-Linked Glycosides in High Yield



glycosyl acceptor	**8a**	**8b**	**8c**	**8d**
glycosyl donor	**6**	**6**	**6**	**6**
isolated yield (%) of α-linked disaccharide[a]	97	75	90	95

[a] No β-glycoside was detected. A complete discussion of reaction conditions and procedures is presented in the Supporting Information.

Scheme 2[a] Oxazolidinone Donors as Versatile Intermediates



[a] Reagents and conditions: (a) NaOH, H_2O/THF, 75−80%. (b) Cs_2CO_3, R−OH, 85−95%. (c) $NaCNBH_3$, HCl, Et_2O/THF, 98%. (d) (i) Tf_2O, pyridine; (ii) NaOAc, DMF, 86%.

versatile protecting group for 2-amino sugar synthesis.[11] Important functional group interconversions of these 2,3-oxazolidinonyl glycosyl donors are demonstrated (Scheme 2).

Hydrolytic ring opening (deprotection) of oxazolidinones **5**−**7** under mild conditions affords **4** and **9**, respectively.[12] Similarly, treatment of **6** and **7** with an alcohol in the presence of mild base readily affords ring-opening deprotection of the C-3 hydroxyl group with concomitant generation of the C-2 carbamate protected amine (**10**, **11**). It is notable that this opening of the oxazolidinone ring with alcohol provides an extremely efficient synthetic route to differentially protected "β-selective" glycosyl donors.[3]

Entry into the D-galactosamine series of 2-amino sugars is readily achieved through regiospecific inversion of stereochemistry at C-4 or the ring-fused oxazolidinones (Scheme 2, conversion of **12** to **13**).[13] This novel route for preparing highly functionalized galactosamine derivatives, where each position on the sugar ring is differentially protected, is a significant improvement over current methods to synthesize these valuable, hard to obtain, intermediates.

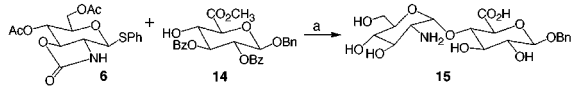
The highly versatile chemistry and reaction pathways shown here for the ring-fused oxazolidinones are widely applicable to efficiently preparing cost-effective intermediates for the synthesis of many biologically important glycoconjugates. For example, monosaccharides **10**, **11**, and **13** are ideal synthetic intermediates

(11) Oxazolidinone protection of other amino alcohols is known.

(12) Molecular modeling shows the ring-fused oxazolidinone ground-state energy to be higher than similar monocyclic structures.

(13) For the synthesis of galactosamine from glucosamine using similar chemistry for C-4 inversion see: Chaplin, D.; Crout, D. H. G.; Bornemann, S.; Hutchinson, D. W. *J. Chem. Soc., Perkin Trans. 1* **1992**, 235−237.

Scheme 3[a] Synthesis of Deprotected HS Disaccharide



[a] Reagents and conditions: (a) (i) PST, CH_2Cl_2, −78 °C (75%); (ii) NaOH, H_2O/THF (80%).

for preparing the 3-linked amino-sugars found in hyaluronate, the chondroitin sulfates, and many glycopeptides/glycoproteins. Similarly, **7** and **12** are ideal intermediates for the preparation of the 4-linked glucosamine residue units present in heparin, heparan sulfate, bacterial peptidoglycan, and glycosylphosphatidylinositol anchors.

A primary reason for exploring the chemistry of ring-fused 2,3-oxazolidinone derivatives of the 1-thio-glucopyranosides was our need to prepare versatile synthetic intermediates for the introduction of structural diversity into GAG and GAG-like oligosaccharides. Indeed, stereoselective coupling of oxazolidinone **6** with glucuronic acid **14** followed by hydrolysis readily affords high yield of the major, α-linked, repeating disaccharide unit of heparan sulfate in fully deprotected form (**15**, Scheme 3). The mild conditions required for oxazolidinone opening do not promote β-elimination of the 4-linked uronic acid, a significant limitation of many base-labile protecting groups in GAG synthesis.

In conclusion, ring-fused 2,3-oxazolidinone derivatives of phenyl 2-amino-2-deoxy-1-thio-glucopyranosides are highly versatile intermediates for stereoselective oligosaccharide synthesis. Notable advantages of these new synthetic intermediates that will be applicable to a diverse range of amino-sugar syntheses include the following:

(1) The ring-fused oxazolidinone moiety is an effective "nonparticipating" group for the stereoselective synthesis of "α"-linked glycosides of 2-amino-2-deoxy-D-hexopyranoses.

(2) Highly functionalized galactosamine derivatives are efficiently synthesized in high yield from oxazolidinonyl-protected glucosamine intermediates.

(3) Cleavage of the ring-fused oxazolidinones with alcohol affords an efficient route to "β-selective" glycosyl donors.

(4) The oxazolidinone-containing glycosyl donors and synthetic intermediates obtained from D-glucosamine can be readily prepared on large scale, in high yield, at low cost.

We are currently employing ring-fused 2,3-oxazolidinone derivatives of D-glycopyranoside intermediates in the stereoselective synthesis of highly substituted GAG oligosaccharides. The methods outlined here have broad utility in the synthesis of many diverse glycoconjugates containing *N*-substituted 2-amino-2-deoxy sugar residues.

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Supporting Information Available: Experimental procedures and spectral/analytical data for key intermediates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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