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Synthesis of C-Linked Glycopyranosyl Serines via a Chiral Glycine Enolate Equivalent

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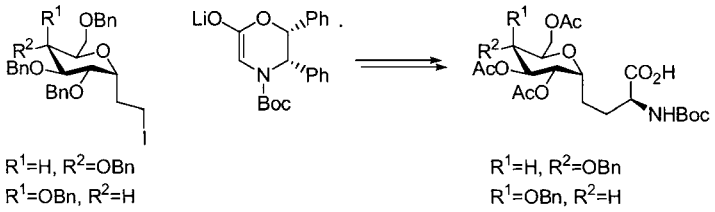
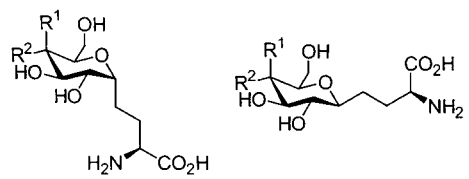
ABSTRACT



The stereoselective preparation of C-linked D-gluco- and D-galactopyranosyl L-serines in their α and *β* forms is herein reported. The syntheses require the conversion of the allyl *C*-glycopyranosides into their iodoethyl derivatives, which then undergo substitution with the Williams' chiral glycine enolate equivalent. Deprotection and acetylation affords Boc-protected amino acids for peptide synthesis.

Posttranslational protein glycosylation not only confers structural stability to proteins but also is important for intercellular recognition and has been implicated in tumor cell metastasis, viral infection, immunogenic responses, and leukocyte recruitment to sites of inflammation.[1] Carbohydrates that are linked to the peptide through the serine or threonine side-chain oxygen constitute an important class of *O*-glycoconjugates. However, the utility of these substances as therapeutics is hampered in many cases by their degradation under acidic conditions, by metabolism involving glycosidase enzymes, and by their propensity to undergo basic elimination affording dehydroalanine derivatives during solid-phase synthesis.[2] In an attempt to alleviate the stability issues due to the anomeric oxygen linkage and to provide analogues for biochemical studies in glycobiology, the methylene isosteres, D-*C*-glycopyranosyl L-serines, **1a**, **1b**, **2a**, and **2b** have received considerable attention (Figure 1).

Synthetic approaches to carbon-linked glycosyl amino acids have been reviewed.[3] With regard to *C*-glycopyranosyl serine syntheses, there are two points of stereocontrol that must be addressed, namely, the stereocenter at the anomeric carbon of the *C*-glycoside and at the α-carbon of the serine. Many approaches begin with the established stereocenter at the *C*-glycoside and add a chiral oxazolidine or oxazolidinone, which can later be converted to the amino acid.[4] Several groups have used similar chiral oxazolidine or oxazolidinone precursors to form the C-glycosidic bond, thus generating the anomeric stereochemistry.[5] Others initiate their



1a R^1=H, R^2=OH **2a** R^1=H, R^2=OH
1b R^1=OH, R^2=H **2b** R^1=OH, R^2=H

Figure 1. Methylene-isosteres of **1** α- and **2** *β*-glycosyl L-serine.

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(2) (a) Dwek, R. A. *Chem. Rev*. **1996**, *96*, 683. (b) Sjolin, P.; Kihlberg, J. *J. Org. Chem*. **2001**, *66*, 2957.

(3) Dondoni, A.; Marra, A. *Chem. Rev*. **2000**, *100*, 4395.

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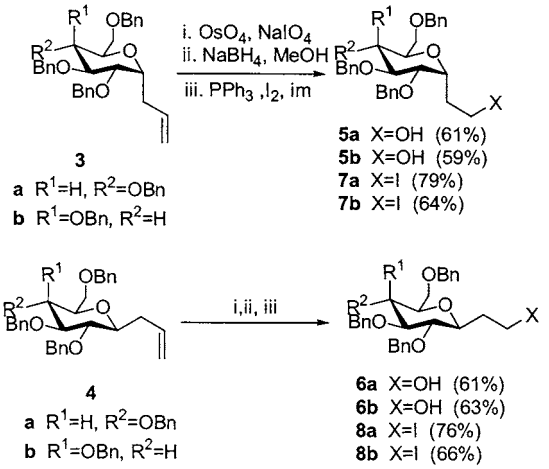
syntheses from the established *C*-glycosides and carry out a de novo synthesis of the serine stereocenter in the final steps.[6] Our work falls in the latter category, as the readily available α- or *β*-allyl tetra-*O*-benzyl *C*-glucose and *C*-galactose precursors provide configurationally defined substrates on which to build.[7] This report demonstrates the utility of the optically active Boc-protected 5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (available in 99% ee) as a chiral glycine equivalent to provide the α-serine stereochemistry via enolate alkylation. This chiral oxazinone enolate has been thoroughly developed by Williams,[8] and in this paper we report the successful use of this enolate for the preparation of D-*C*-glucosyl and D-*C*-galactosyl *N*-Boc L-serines.

The conversion of the allyl side chain into the iodoethyl substituent was accomplished in the same manner for both anomers and both *C*-glycosides (Scheme 1).[9] α-Alkenes **3a**

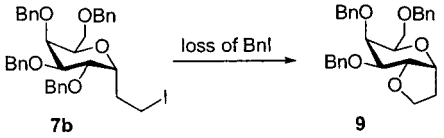
Scheme 1



and 3**b**, available by deacetylation and benzylation of the *C*-allyl tetra-*O*-acetylglycosides, and *β*-alkenes **4a** and **4b** were oxidatively cleaved using catalytic osmium tetroxide and sodium periodate to cleanly provide the aldehydes. While some of these aldehydes have been previously reported,[10] it has been shown that carbonyls in the side chain of *C*-glycosides may equilibrate the anomeric position by elimination and Michael addition of the pyranose oxygen.[11] Therefore, our aldehydes were immediately reduced using $NaBH_4$ in methanol to give the corresponding alcohols **5a**, **5b**, **6a**, and **6b**.[12] Conversion to iodides **7a**, **7b**, **8a**, and **8b** was achieved by the action of triphenylphosphine, imidazole, and iodine.[13]

β-Iodoethyl *C*-glycosides **8a** and **8b** are stable for extended periods of time at 4 °C, although they are prone to elimination to the *C*-vinyl glycoside if kept at room temperature. Interestingly, in the α-anomer series, *C*-glycoside **7b** forms bicyclic structure **9** with concomitant loss of the *C*-2 *O*-benzyl group over the course of 1 month at 4 °C (Scheme 2). It has been observed that this process can be

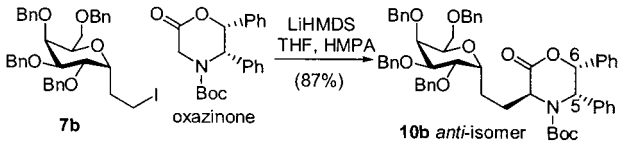
Scheme 2



catalyzed by use of excess iodine in the step leading to **7b**. Presumably the more stable cis-fused 6,5-ring system, possible only with the α-anomers, affords a lower energy reaction pathway to the cyclization product. A closely related 5-exo-type cyclization with a cis-ring fusion has been reported by Nicotra.[14]

With the iodides in hand, the key C−C bond-forming step entailed the stereoselective alkylation of a chiral, nonracemic (5*S*,6*R*)-oxazinone enolate by the iodides, illustrated on the α-Gal iodide **7b** (Scheme 3). As prescribed by Williams,

Scheme 3



the base, LiHMDS, was added slowly to the solution of **7b**, oxazinone, and HMPA in THF due to enolate instability. Using a 1:1:1 mixture of **7b**, oxazinone, and base led to recovery of more than 50% of the starting iodide; therefore,

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(6) (a) Debenham, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9897. (b) Debenham, S. D.; Cossrow, J.; Toone, E. J. *J. Org. Chem.* **1999**, *64*, 9153. (c) Fuchss, T.; Schmidt, R. R. *Synthesis* **1998**, 753. (d) Arya, P.; Ben, R. N.; Qin, H. *Tetrahedron Lett.* **1998**, *39*, 6131. (e) Ben, R. N.; Orellana, A.; Arya, P. *J. Org. Chem.* **1998**, *63*, 4817. (f) Lay, L.; Meldal, M.; Nicotra, F.; Panza, L.; Russo, G. *Chem. Commun.* **1997**, 1469. (g) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. *J. Org. Chem* **1996**, *61*, 8350.

(7) α-Anomers: (a) Ponten, F.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 7463. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223. (c) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479. *β*-Anomers: (d) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

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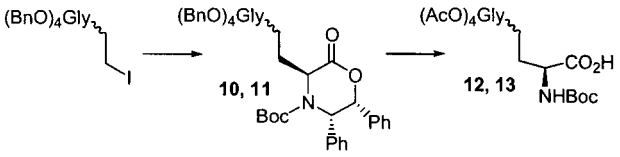
Table 1. Williams' Chiral Glycine Enolate Alkylation Results and Yield of the Deprotection Step



iodide	alkylation yield	deprotection yield
α-Glc **7a**	**10a** 71%[a]	**12a** 73%
α-Gal **7b**	**10b** 87%	**12b** 77%
β-Glc **8a**	**11a** 76%[b]	**13a** 86%
β-Gal **8b**	**11b** 73%	**13b** 68%

[a] Recovered 16% starting iodide and 8% elimination product. [b] Only 90% pure, contaminated with unreacted oxazinone.

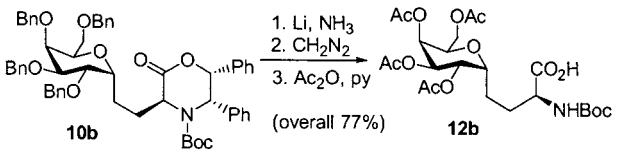
a 3-fold excess of oxazinone and base were employed supplying a 76% yield of alkylation product **10b** in 6 h with 13% recovered starting material. Extending the reaction time to 14 h led to an 87% yield of product.[15] Use of the sodium enolate, generated with NaHMDS, was explored but led to complex mixtures. The lithium enolate yielded cleaner reactions in all cases as judged by TLC and isolated yield of desired product.

As expected, the alkylation occurs on the less hindered top-face of the enolate, opposite the phenyl substituents, to give anti-addition product **10b**, which was the only isolated product in this case. The stereochemical assignment was based on the difference in chemical shift between H-5 and H-6 on the oxazinone moiety in DMSO-d_6 at 368 K. Williams has reported the empirical observation that the anti-isomers have a $\Delta\delta$ of 0.94−1.10 ppm, while the $\Delta\delta$ values for the syn-isomers are 0.60−0.70 ppm.[16] In our alkylations, only α-Glc iodide **7a** led to any isolated syn-isomer. In this case, the anti:syn ratio was 93:7. The chemical shift differences were 0.98 ppm for anti-isomer **10a**, whereas the syn-isomer had a $\Delta\delta$ of 0.61 ppm, in accordance with the observation by Williams.

The original *C*-glycosidic stereocenter is maintained throughout these transformations, as indicated by the downfield chemical shifts of the C-1 proton for all α-isomers (4.05−4.24 ppm) in comparison to H-1 on the β-glycosides (3.35−3.56 ppm). Furthermore, the H-1 to H-2 coupling constants for the α-isomers are in agreement with an axial to equatorial coupling; the $J_{1,2}$ = 3.8 Hz for **10b** is representative.

Table 1 summarizes the nonoptimized alkylation step and the final deprotection results to afford *C*-glucosyl and *C*-galactosyl *N*-Boc L-serines. The removal of the oxazinone chiral auxiliary requires treatment with lithium in ammonia, which deprotects the glycoside benzyl ethers as well. Workup with acetic anhydride and pyridine supplies products suitable for peptide synthesis on the free carboxylic acid (Scheme 4). The products were characterized as their methyl esters by treatment with diazomethane and provided spectroscopic data in agreement with the results of others.[4d,f,5e,6a]

Scheme 4



The well-precedented allyl *C*-glycosides, in both α- and β-forms, afford convenient starting substrates, and the ability to achieve excellent diastereoselection in the key oxazinone alkylation and the relatively short, five-step synthesis make this an attractive route for the preparation D-*C*-glycosyl *N*-Boc L-serines. Furthermore, the unnatural D-serines, via the antipodal oxazinone, would also be available through this versatile route.

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Supporting Information Available: Experimental procedures and characterization for compounds **5a**,**b**−**13a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) A solution of iodide (0.501 mmol) and 4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (0.492 g, 1.50 mmol) in THF (14 mL) was cooled to −78 °C, and to this was added a 1 M solution of LiHMDS (1.50 mmol). The reaction mixture was allowed to warm to room temperature overnight. Brine was added (3 mL), and the mixture was diluted with EtOAc (30 mL). The organic layer was separated, washed with more brine, dried with $MgSO_4$, concentrated, and chromatographed.

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