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Studies on the Stereoselective Synthesis of *C*-Allyl Glycosides

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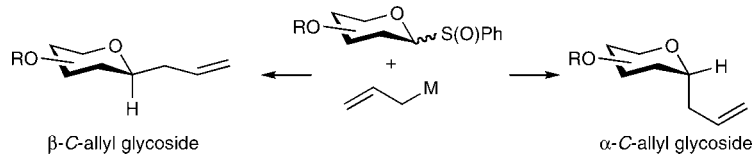
ABSTRACT



An investigation was carried out to explore the use of sulfoxide donors as common precursors to stereoisomeric *C*-glycoconjugates of glycoprotein and glycolipid tumor antigens. A study focusing on the effects of reaction conditions and substrate structure on the stereoselectivity of allylation was carried out. Although conditions were realized to selectively afford α-allylation products in good to excellent yields, the search for conditions favoring *β*-selectivity proved less successful.

Studies examining the pivotal roles of carbohydrates in biological processes, including promising applications to the treatment of disease,[1] have stimulated considerable effort to make available natural and unnatural glycoconjugates by chemical synthesis.[2] It was with such objectives in mind that we have examined the preparation of *C*-glycoamino acid derivatives of tumor-associated carbohydrate antigens for use in cotranslational synthesis of stable *C*-glycopeptides.[3,4] This strategy calls for the preparation of a *C*-allyl carbohydrate core that is subsequently elaborated into a selected oligosaccharide structure, then elaborated into the *C*-linked amino acid via olefin metathesis.[5] With our attention initially directed toward cancer-linked mucin glycopeptide antigens, the requisite α-*C*-allyl galactosamine core (**1**, Figure 1) was

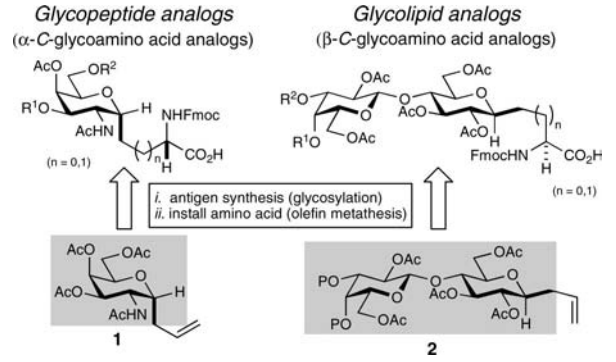


Figure 1. Target structures for C-linked cancer antigens.

concisely realized through radical-mediated allylation of peracetylated galactosamine chloride.[6] Anticipating the application of this strategy toward the preparation of *C*-analogs of glycolipid cancer antigens,[7] our attention was turned to the

(1) For reviews on glycobiology and disease: (a) Varki, A. *Glycobiology* **1993**, *3*, 97–130. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720. (c) Brockhausen, I.; Schutzbach, J.; Kuhns, W. *Acta Anat.* **1998**, *161*, 36–78. (d) DeMarco, M. L.; Woods, R. J. *Glycobiology* **2008**, *18*, 426–440.

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(3) McGarvey, G. J.; Benedum, T. E.; Schmidtmann, F. W. *Org. Lett.* **2002**, *4*, 3591–3594.

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(5) Schmidtmann, F. W.; Benedum, T. E.; McGarvey, G. J. *Tetrahedron Lett.* **2005**, *46*, 4677–4681.

(6) Ciu, J.; Horton, D. *Carbohydr. Res.* **1998**, *309*, 319–330.

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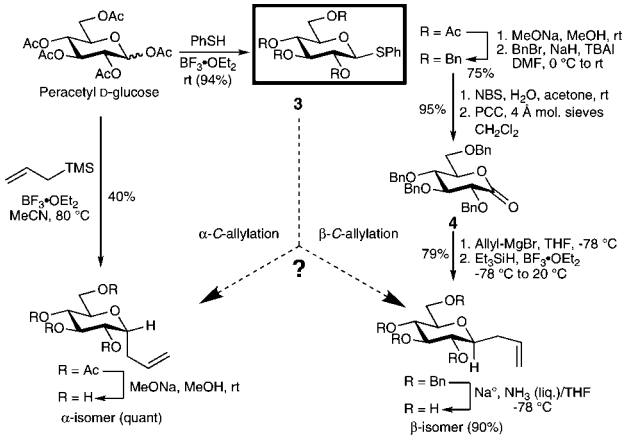
realization of the β-*C*-allyl lactose core (**2**) structure of these antigens. Implementation of this strategy required us to examine the means by which stereoselective C-allylation may be realized to establish the desired stable anomeric stereochemistry prior to subsequent elaboration.[8,9]

We chose D-glucose as an easily available model upon which to explore methods of stereoselective *C*-allylation. Conveniently, both of the target isomers could be delivered using established means. Specifically, the α-isomer may be obtained through ionic allylation of the inexpensive peracetyl derivative of D-glucose with allyl-$SiMe_3$,[10] whereas the β-isomer can be realized through stereoelectronically guided reduction of a lactol intermediate derived from allyl anion addition to benzyl protected lactone **4** (R = Bn, Scheme 1).[11]

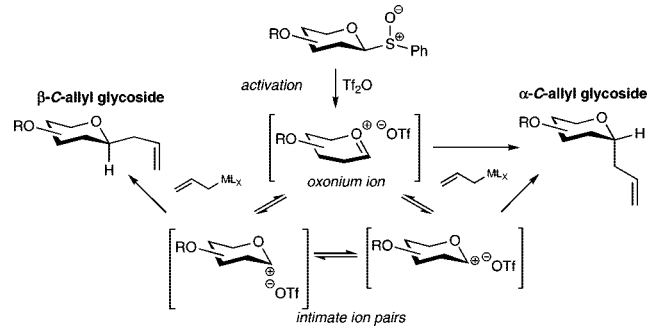
Scheme 1. Preparation of α- and β-*C*-Allyl Glucose



The modest yield for the α-isomer, the rather lengthy route leading to the β-isomer, as well as limitations these routes impose on protecting groups prompted us to explore more convenient and efficient means to these stereoisomeric *C*-glycosides.

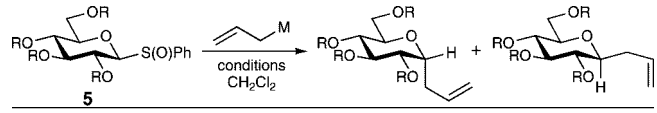
It was with this in mind that we speculated that both α-*C*-allyl and β-*C*-allyl isomers might be accessed by stereodivergent allylation of the stable thioglycoside intermediate **3**. The seminal studies of Crich and co-workers[12] provided us a working hypothesis by which anticipated allylation reaction may be viewed as resulting from a series of equilibrating ion pairs (Scheme 2).[13] It was suggested that the initially formed oxonium ion[14] or β-isomer of a resulting

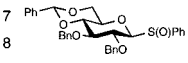
Scheme 2. Stereochemical Course of Glycosylation

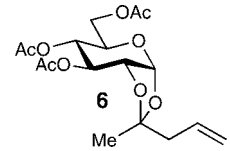


intimate ion pair could afford the α-allylation product, while isomerization of the intimate ion pair would presumably favor the more stable α-isomer[15] to offer a means to the β-allyl product. It was anticipated that adjustment in the sequence of donor activation and introduction of the nucleophile could affect the interception of this equilibrium and influence the stereochemical course of the reaction.

Table 1. Effect of Reaction Conditions and Protecting Group on Steroselectivity



entry	R (substrate)	conditions[a]	M	yield[b]	α/β ratio[c]
1	benzyl	A[d]	$SiMe_3$	49%	16:1
2	**benzyl**	**A**	**$SiMe_3$**	**90%**	**>19:1**
3	benzyl	B	$SiMe_3$	86%	>19:1
4	benzyl	C	$SiMe_3$	56%	>19:1
5	benzyl	A	$SnBu_3$	73%	2.2:1
6	**benzyl**	**B**	**$SnBu_3$**	**76%**	**1:3**
7	^{t}BuMe$_2$Si	A	$SiMe_3$	74%	>19:1
8	^{t}BuMe$_2$Si	B	$SnBu_3$	70%	>19:1
9	acetate	A	$SiMe_3$	77%	compound **6**
10	acetate	B	$SnBu_3$	62%	compound **6**
11	pivoyl	A	$SiMe_3$	52%	1.2:1
12	pivoyl	B	$SnBu_3$	45%	1:1
13	benzoyl	A	$SiMe_3$	35%	3.5:1
14	benzoyl	B	$SnBu_3$	30%	1:1.6
15	trichloroacetate	A	$SiMe_3$	NA	decomposition
16	trichloroacetate	B	$SnBu_3$	NA	decomposition
17		A	$SiMe_3$	56%	>19:1
18		B	$SnBu_3$	71%	>19:1



[a] Reaction Conditions: **A**: sulfoxide (1.0 equiv), allyl-M (2.5 equiv), Tf_2O (1.1 equiv), DTBMP, −78 °C to rt. **B**: sulfoxide (1.0 equiv), Tf_2O (1.1 equiv), DTBMP, −78 °C, 10 min; allyl-M (2.5 equiv), −78 °C to rt. **C**: allyl-M (2.5 equiv), Tf_2O (1.1 equiv), DTBMP, −78 °C.; sulfoxide (1.0 equiv), −78 °C to rt. [b] Yields are of chromatographically purified products. [c] α/β ratio determined through NMR observation of the C-2 ^{1}H of the allyl group in the crude reaction mixture.[18] [d] Reaction carried out in the absence of DTBMP.

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(8) For reviews on approaches to the synthesis of *C*-glycosides: (a) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913–9959. (b) Lee, D. Y. W.; He, M. S. *Curr. Top. Med. Chem.* **2005**, *5*, 1333–1350. (c) Yuan, X. J.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393–1430. (d) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133–1167.

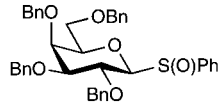
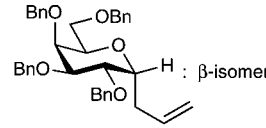
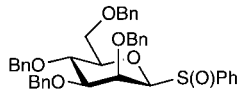
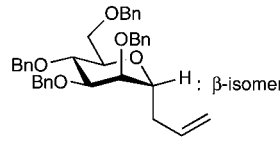
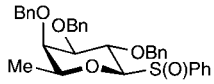
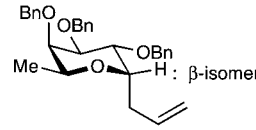
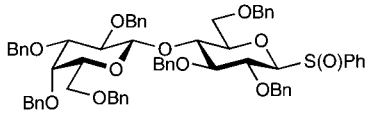
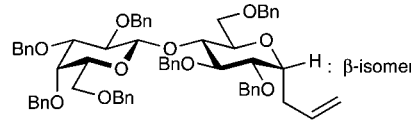
(9) For a previous approach to stereoisomeric *C*-glycosides: Shao, H.; Wang, Z.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130–2131.

(10) Horton, D.; Miyake, T *Carbohydr. Res.* **1988**, *184*, 221–229.

(11) Brenna, E.; Fuganti, C.; Grasselli, P.; Serra, S.; Zambotti, S. *Chem.−Eur. J.* **2002**, *8*, 1872–1878.

(12) For a thorough review: Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115–251, and references cited therein.

Table 2. Effect of Substrate on Stereoselectivity

entry	donor	reaction conditions[a]	products	yield	product : β-isomer[b]
1		conditions **A**, M=$SiMe_3$		75%	>19:1
2		conditions **B**, M=$SnBu_3$		85%	1:1
3		conditions **A**, M=$SiMe_3$		80%	>19:1
4		conditions **B**, M=$SnBu_3$		63%	1:1.5
5		conditions **A**, M=$SiMe_3$		87%	1:1.7
6		conditions **B**, M=$SnBu_3$		61%	1:2
7		conditions **A**, M=$SiMe_3$		70%	>19:1
8		conditions **B**, M=$SnBu_3$		74%	2:1

[a] Conditions **A**: see Table 1, entry 2; Conditions **B**: see Table 1, entry 6. [b] α/β ratio determined through NMR observation of the C-2 ^{1}H of the allyl group in the crude reaction mixture.[18]

In an effort to focus on the details attending the interception of the cationic intermediates, we chose to explore the potential of pre- and postactivation of an anomeric sulfoxide with respect to the presence of the nucleophile[16] using readily available perbenzyl glucose derivative **5** (R = Bn, Table 1).[17] Initial attempts to activate the sulfoxide using Tf_2O in the presence of allyl-$SiMe_3$ resulted in only a modest yield of products favoring the α-product (16:1, Entry 1).[18] A significant improvement in yield was observed when 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) 1.2 equiv was introduced to act as an acid scavenger to cleanly afford the α-product (entry 2).[19] In an effort to access the β-isomer, activation of the sulfoxide was carried out prior to introduction of the allyl nucleophile (Conditions **B**) to once again afford the α-isomer in good yield (entry 3). Conditions of inverse addition were also examined (Conditions **C**) to similarly afford the α-isomer, but in diminished yield (entry 4).

In an effort to promote interception of the more stable, and presumably less reactive, α-isomer of the intimate ion pair (Scheme 2), we chose to examine a more reactive nucleophile in the form of allyl-$SnBu_3$. In the event, application of Conditions **A** using the allylstannane led to significantly diminished α-selectivity (entry 5). Activation of the sulfoxide prior to introduction of the nucleophile (Conditions **B**) led to a good yield of product favoring the β-isomer (entry 6). Attempts to improve β-selectivity by varying the amount of DTBMP and changing the solvent (EtCN) proved ineffective. Nonetheless, conditions have been identified to selectively realize either the α- or β-isomer of this substrate in good to excellent yields (highlighted entries 2 and 6).

We next chose to examine the effect of protecting groups on promoting β-selectivity to this allylation reaction. Entries 7−18 describe the application of Conditions **A** and **B** to a variety of protected D-glucose sulfoxides. It is noteworthy that silyl protection gave the only the α-anomer regardless of the conditions applied (entries 7 and 8). Ester protection proved problematic, however. The acetate protected acceptor yielded only acetal **6**, evidence that the desired neighboring participation took place but with an undesirable capture of the nucleophile (entries 9 and 10).[20] Benzoyl and pivolyl protection proved only slightly better, affording low yields of allyl anomers with modest to poor selectivity (entries 11−14), while trichloroacetate protection (TCA) led only to decomposition (entries 15 and 16). The benzylidene protected substrate offered no advantages over substrate **5** (R = Bn), affording the α-anomer in modest to good yields regardless of the conditions applied (entries 17 and 18).[21]

Armed with these results, attention was turned to the stereoselective *C*-allylation of carbohydrate substrates other than D-glucose (Table 2). Using the conditions found best for the diastereoselective allylation of D-glucose (Table 1, entries 2 and 6), other perbenzylated donors were examined (Table 2). The galactose and mannose donors followed the trend noted for glucose, affording cleanly the α-anomer using conditions **A** with allyl-TMS (entries 1 and 3) and showing significant shift toward the β-anomer under conditions **B** with allyl-$SnBu_3$ (entries 2 and 4). The fucose donor, on the other hand, proved poorly stereoselective under either set of reaction conditions (entries 5 and 6). Finally, perbenzylated lactose was examined in an effort to advance our efforts toward *C*-allyl glycosides of the glycolipid cancer antigens. While the

α-anomer could be obtained cleanly using conditions **A** with allyl-$SiMe_3$, the desired β-isomer was not available using the alternative reaction conditions (entries 7 and 8). These results would seem to serve to illustrate how structural differences can affect the stereoselectivity of the incipient cation intermediates in this glycosyl transfer reactions.[14]

In summary, it has been found that thioglycosides, via their corresponding sulfoxides, offer convenient access to α-*C*-allyl glycosides that are useful intermediates for further elaboration into a variety of *C*-glycosides.[22] Unfortunately, access to the β-anomers of these *C*-glycosides through manipulation of both reaction conditions and donor structure has shown limited success to date. Realization of *C*-analogs of β-linked glycoconjugates will require alternative approaches, and we will report on our efforts in this regard in due course.

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Supporting Information Available: Experimental details and physical data are available for the new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For discussions regarding the basis for stereoselection in sulfur-mediated glycosylations: (a) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115–251. (b) Crich, D.; Sun, S. X. *J. Org. Chem.* **1996**, *61*, 4506–4507. (c) Crich, D.; Sun, S. X. *J. Org. Chem.* **1997**, *62*, 1198–1199. (d) Crich, D.; Sun, S. X. *J. Am. Chem. Soc.* **1998**, *120*, 435–436. (e) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020. (f) Crich, D.; Sun, S. X. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223. (g) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.

(14) For a comprehensive discussion of the current understanding of the mechanism of cationic glycosylation: Bennet, A. J.; Kitos, T. E. *J.Chem. Soc., Perkin Trans. 2* **2002**, 1207–1222.

(15) NMR experiments have shown this to be the favored anomeric stereochemistry: (a) Crich, D.; Sun, S. X. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223. (b) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.

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(17) Compound **5** was prepared by the methods given in: (a) Xia, J.; Alderfer, L.; Piskorz, D. R.; Locke, R. D.; Matta, K. L. *Carbohydr. Res.* **2000**, *328*, 147–163. (b) Khiar, N.; Martin-Lomas, M. *J. Org. Chem.* **1995**, *60*, 7017–7021.

(18) Product identities were confirmed by chromatographic separation of the isomers and comparison with pure allylated products prepared by independent synthesis (see Supporting Information).

(19) It is surmised that DTBMP is scavenging extraneous protons in the reaction mixture, though the presence of this base has also been noted to effect the stereoselectivity of glycosylations.[13b]

(20) Whitfield, D. M.; Nukata, T. *Carbohydr. Res.* **2007**, *342*, 1291–1304.

(21) For a discussion addressing the use of cyclic protecting groups, see: (a) Crich, D.; Subramanian, V.; Hutton, T. K. *Tetrahedron* **2007**, *63*, 5042–5049. (b) Litiens, R. E. J. N.; van den Bos, J. L.; Codee, J. D. C.; Overkleeft, H. S.; van der Marel, G. *Carbohydr. Res.* **2007**, *342*, 419–429.

(22) McGarvey, G. J.; Schmidtmann, F. W.; Benedum, T. E.; Kizer, D. E *Tetrahedron Lett.* **2003**, *44*, 3775–3779.