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C-Glycosides of 2-Amino-2-deoxy Sugars. *β*-*C*-Glycosides and 1,1-Disubstituted Variants

Yan Liu and Timothy Gallagher*

School of Chemistry, University of Bristol, Bristol BS8 1TS, UK

t.gallagher@bristol.ac.uk

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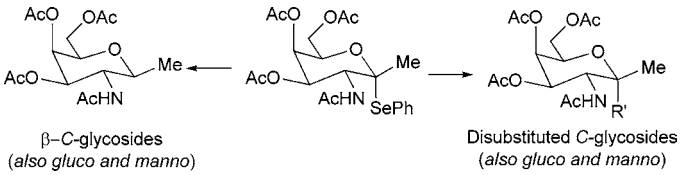
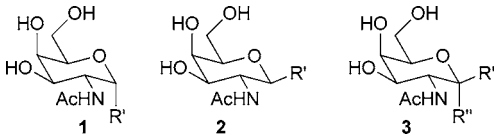
ABSTRACT



C(1)-Substituted anomeric selenides, derived from azidoselenation of C(1)-methylated glycals, provide access to anomeric radical reactivity that has been used to generate *β*-*C*-glycosides and 1,1-disubstituted *C*-glycosides based on *galacto*, *gluco*, and *manno* variants of *N*-acetyl-2-amino sugars.

N-Acetyl-2-amino-2-deoxy sugars play an integral role in the structure and function of both *O*- and *N*-glycopeptides.[1] As a result, the corresponding *C*-glycosides[2] of these important carbohydrate units represent a potentially valuable set of molecular tools with which to probe the various roles played by complex glycoconjugates, and a number of methods now exist for the synthesis of both α- and *β*-*C*-glycoside variants of 2-amino-2-deoxy sugars exemplified by **1** and **2** respectively.[3] We recently described two complementary entries to α-*C*-glycosides **1** that were based on on the trapping of an anomeric radical, derived from either an α- or *β*-anomeric selenide, with an alkene.[4] Importantly, this chemistry also proved applicable to more complex substrates providing, for example, disaccharide-based α-*C*-glycoside derivatives of *N*-acetyl lactosamine.



Although this chemistry complements other methods[3] for generating α-*C*-glycosides of 2-amino-2-deoxysugars, we were interested in exploring related reaction pathways to provide other less available *C*-glycoside variations of 2-amino sugars. In this paper we describe anomeric radical reactivity that provides (i) an alternative entry to *β*-*C*-glycosides of 2-amino-2-deoxy sugars **2** and (ii) disubstituted *C*-glycoside derivatives **3**.

(1) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720. Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495−4537. For recent discussions on the synthesis and significance of mucin-like glycoproteins, see: Marcaurelle, L. A.; Bertozzi, C. R. *Glycobiology* **2002**, *12*, 69R−77R.

(2) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. Postema, M. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. Levy, D.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. Skrydstrup, T.; Vauzeilles, B.; Beau, J.-M. In *Carbohydrates in Chemistry and Biology. The Chemistry of Saccharides*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, Chapter 20, pp 495−530.

(3) A comprehensive listing of earlier methods for the synthesis of *C*-glycosides related to 2-amino-2-deoxy sugars has been presented.[4] For more recent reports, see: Pachamuthu, K.; Gupta, A.; Das, J.; Schmidt, R. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2002**, 1479−1483. Ohnishi, Y.; Ichikawa, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 997−999. Dondoni, A.; Mariotti, G.; Marra, A. *J. Org. Chem.* **2002**, *67*, 4475−4486. McGarvey, G. J.; Schmidtmann, F. W.; Benedum, T. E.; Kizer, D. E. *Tetrahedron Lett.* **2003**, *44*, 3775−3779. Palmier, S.; Vauzeilles, B.; Beau, J. M. *Org. Bioorg. Chem.* **2003**, *1*, 1097−1098. Gaurat, O.; Xie, J.; Valery, J. M. *J. Carbohydr. Chem.* **2003**, *22*, 645−656. Xie, J. *Carbohydr. Res.* **2003**, *338*, 399−406. Miquel, N.; Vignando, S.; Russo, G.; Lay, L. *Synlett* **2004**, 341−343. Wen, X. H.; Hultin, P. G. *Tetrahedron Lett.* **2004**, *45*, 1773−1775.

(4) SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051−4054. Grant, L.; Liu, Y.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2002**, *4*, 4623−4625.

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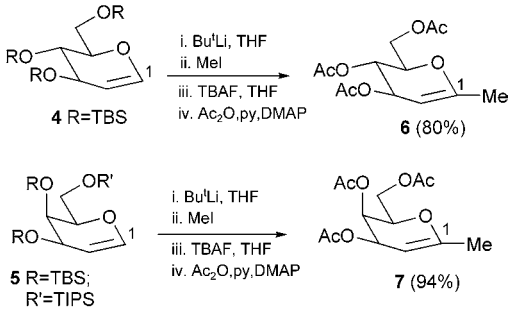
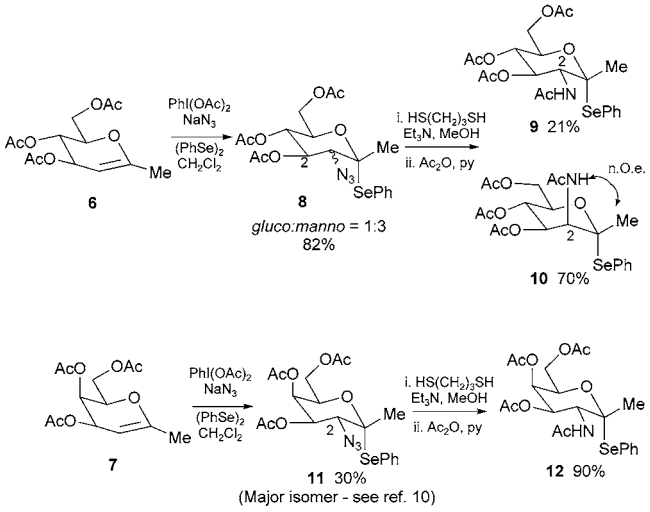
The strategy adopted involves the use of C(1)-substituted glycals as the key carbohydrate precursors, and there are a number of elegant methods known for assembling glycals of this type.[5] To establish the viability of this strategy, we have focused on C(1)-methylated glycals **6**[5a] and **7**, which were obtained by lithiation[6] and methylation of the corresponding per-O-silylated glucal and galactal derivatives **4** and **5** respectively. The resulting C(1)-methyl glycals (conventional sugar numbering is used throughout this paper) were desilylated and O-acetylated to provide **6** (80% overall yield from **4**) and **7** (94% overall yield from **5**) (Scheme 1).

Scheme 1. Synthesis of *C*(1)-Methyl Glycals



The requisite selenyl and acetamido moieties at C(1) and C(2), respectively, were then introduced via azidoselenation.[7] This involved (i) addition of azide radical to the glycal and trapping of the intermediate anomeric radical by diphenyl diselenide, followed by (ii) azide reduction and N-acetylation (Scheme 2).

Scheme 2. Azidoselenation of *C*(1)-Methyl Glycals

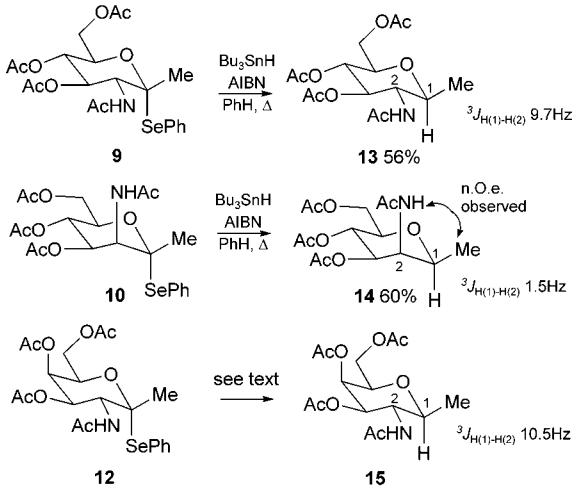


Azidoselenation of glucal **6** was, as anticipated on the basis of earlier studies,[8] not especially selective, and adduct **8** was isolated in 82% yield as an inseparable 1:3 mixture of epimers at C(2). Interestingly and unexpectedly, this addition process favored the *manno* isomer (see below) in contrast to the analogous reaction involving tri-*O*-acetyl-D-glucal (which lacks the methyl substituent at C(1)) that favors the *gluco* adduct.[9] Following azide reduction and N-acetylation, the *gluco* and *manno* isomers **9** and **10** (now separable) were obtained in 21% and 70% overall yields, respectively, and their reactivity was then evaluated independently.

Azidoselenation of the C(1)-methylated galactal derivative **7** was significantly more stereoselective though less efficient, and the *N*-acetyl 2-amino-2-deoxy-1-methylgalactose derivative **11** was obtained in 30% yield.[10] Reduction and N-acetylation of **11** gave **12** in 90% yield.

Initial studies to define the reactivity of selenides **9**, **10**, and **12** focused on simple reduction with the expectation that trapping of the resulting anomeric radical would occur from the α face[11] and thereby provide an entry to *β*-*C*-glycosides based on 2-amino sugars. In the event, reduction of both **9** and **10** provided the corresponding *β*-*C*-glycosides **13** and **14** in reasonable yields (Scheme 3). We did not carry out a

Scheme 3. Generation of *β*-*C*-Glycosides



separate reduction of the *galacto* adduct **12**, but the corresponding reduction product *β*-*C*-glycoside **15** was isolated

(5) For general entries to C(1)-substituted glycals, see: (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 925−926. (b) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926−927. (c) Lesimple, P.; Beau, J. M.; Jaurand, G.; Sinay, P. *Tetrahedron Lett.* **1986**, *27*, 6201−6204. (d) Friesen, R. W.; Loo, R. W. *J. Org. Chem.* **1991**, *56*, 4821−4823. (e) Dubois, E.; Beau, J.-M. *Carbohydr. Res.* **1992**, *228*, 103−120. (f) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem.* **1994**, *72*, 1262−1272. (g) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4755−4759. (h) Lui, L.; Postema, M. H. D. *J. Am. Chem. Soc.* **2001**, *123*, 8602−8603. (i) Postema, M. H. D.; Piper, J. L. *Tetrahedron Lett.* **2002**, *43*, 7095−7099. (j) Postema, M. H. D.; Piper, J. L. *Org. Lett.* **2003**, *5*, 1721−1723. (k) Postema, M. H. D.; Piper, J. L.; Liu, L.; Shen, J.; Faust, M.; Andreana, P. *J. Org. Chem.* **2003**, *68*, 4748−4754. (l) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797−1801.

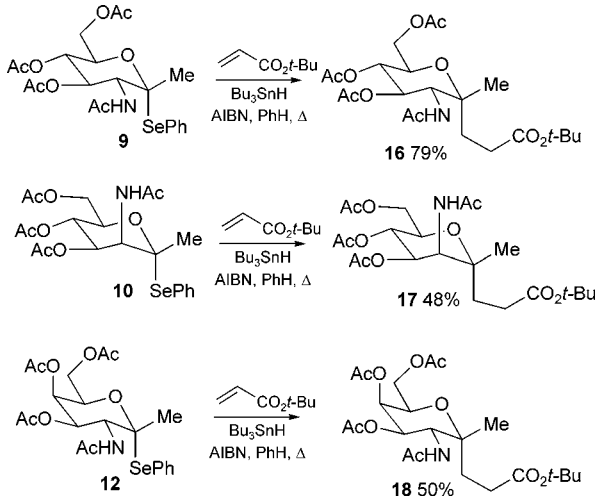
(6) The glycal lithiation procedures used have been described previously: Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913−916. Jäkel, C.; Dötz, K. H. *J. Organomet. Chem.* **2001**, *624*, 172−185.

(7) Czernecki, S.; Randriamandimby, D. *Tetrahedron Lett.* **1993**, *34*, 7915−7916. Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Org. Chem.* **1994**, *59*, 8256−8260. Santoyo-González, F.; Calvo-Flores, F. G.; Garcia-Mendoza, P.; Hernández-Mateo, F.; Isac-Garcia, J.; Robles-Díaz, R. *J. Org. Chem.* **1993**, *58*, 6122−6125.

as the major product (43%) when we attempted to trap the anomeric radical derived from **12** with styrene (see Scheme 5). The assignment of β-*C*-glycosides **13**, **14**, and **15** was based on ^{1}H NMR for which $^3J_{H(1)-H(2)}$ and $^3J_{H(2)-H(3)}$ were diagnostic, and in the case of **14**, this assignment was confirmed by NOE experiments.

Selenides **9**, **10**, and **12** also offered an additional opportunity as an entry to 1,1-disubstituted *C*-glycosides represented by **3**. This would require C−Se homolysis to generate the requisite anomeric radical and trapping of this species with a suitable alkene, rather than simple reduction. We anticipated that the new C−C bond would form on the α face, but a concern was the hindered and potentially unreactive nature of the intermediate anomeric radical. However, this did not prove to be a barrier to C−C bond formation, and our results are presented in Scheme 4.

Scheme 4. Generation of 1,1-Disubstituted *C*-Glycosides



Homolysis of *gluco* isomer **9** in the presence of *tert*-butyl acrylate led to the disubstituted *C*-glycoside **16** in 79% isolated yield. Similar transformations were carried out using the *manno* and *galacto* adducts **10** and **12** to provide *C*-glycosides **17** (48%) and **18** (50%), respectively.

Although earlier precedent[4,14b] indicated that C−C bond formation would occur on the α face of the anomeric center, a more rigorous assignment of the stereochemical outcome was demanded, and the structure of 1,1-disubstituted *C*-glycosides **16**−**18** was based on NOE studies, as illustrated in Figure 1.[12]

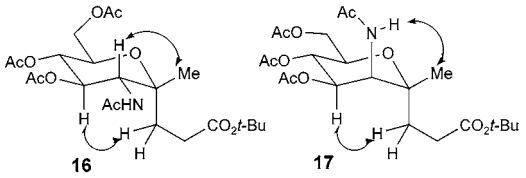
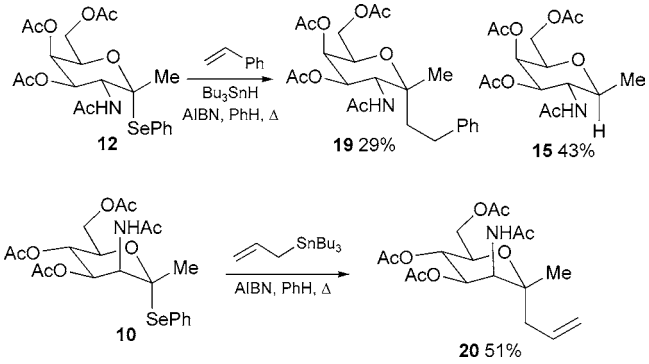


Figure 1. Stereochemical assignment of *C*-glycosides **16** and **17** (key NOE are indicated by arrows).

One area of potential application of *C*-glycosides **1** is as glycosyltransferase inhibitors to block *O*-glycopeptide synthesis, and the *galacto* variant **1** (R′= CH_2CH_2Ph) has begun to play a role in this respect.[13] It was therefore of interest to assemble a disubstituted variant of **1**, namely, the 1,1-disubstituted *galacto* derivative **19**.

Exposure of selenide **12** to Bu_3SnH in the presence of styrene (20 equiv) gave the target *C*-glycoside **19** in 29% yield (Scheme 5). Although this is a low yield, it must be

Scheme 5. Generation of 1,1-Disubstituted *C*-Glycosides Based on Styrene and Keck Allylation



appreciated that styrene is not generally an efficient trap for anomeric radicals[4] (electron-deficient alkenes being much

(8) For a discussion of the stereoselectivity of this process and strategies for enhancing *gluco* selectivity, see: Seeberger, P. H.; Roehrig, S.; Schell, P.; Wang, Y.; Christ, W. J. *Carbohydr. Res.* **2000**, *328*, 61−69. As far as we are aware, no study of the azidoselenenation (or related processes) have been reported for C(1)-substituted glycals.

(9) In the case of adduct **10**, a NOESY experiment linking the C(1) methyl group and the NH moiety supported the structure shown in Scheme 2, i.e., α-SePh. The anomeric configurations of **9** and **12** have not been rigorously determined, but this is not likely to be significant in terms of the generation and reactivity of the corresponding anomeric radical.[4]

(10) Azide radical addition to **7** has not yet been optimized but also gave, after azide reduction and N-acetylation, trace amounts of the *talo* isomer [axial NHAc at C(2)], which was assigned on the basis of ^{1}H NMR.

(11) For leading references to the stereoselective reduction of anomeric radicals, see: Crich, D.; Lim, L. B. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2205−2208. Schmid, W.; Christian, R.; Zbiral, E. *Tetrahedron Lett.* **1988**, *29*, 3643−3646. Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210−2222.

(12) For **16** and **17**, we have also observed a NOE between H(5) and the CH_2 of the C(1) substituent, not shown in Figure 1. Similar diagnostic NOE observations were made in the case of *C*-glycoside **18**, as well as *C*-glycosides **19** and **20** (Scheme 5).

(13) Simple *O*-glycosides (e.g., **1** (R′= OBn) of 2-amino-2-deoxy sugars act as competitive inhibitors of the glycosylation of GalNAc in vivo. This has significant implications for the expression of mucins and the intracellular trafficking of other glycoproteins. Gouyer, V.; Leteurtre, E.; Zanetta, J. P.; Lesuffleur, T.; Delannoy, P.; Huet, G. *Front. Biosci.* **2001**, *6*, D1235−D1244. Huet, G.; Gouyer, V.; Delacour, D.; Richet, C.; Zanetta, J. P.; Delannoy, P.; Degand, P. *Biochimie* **2003**, *85*, 323−330. Delacour, D.; Gouyer, V.; Leteurtre, E.; Ait-Slimane, T.; Drobecq, H.; Lenoir, C.; Moreau-Hannedouche, O.; Trugnan, G.; Huet, G. *J. Biol. Chem.* **2003**, *278*, 37799−37809.

(14) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829−5831. (b) Cui, J. R.; Horton, D. *Carbohydr. Res.* **1998**, *309*, 319−330.

more effective in this regard), and this case is likely compounded by the more hindered nature of the intermediate anomeric radical derived from **12**. That this was a slow process in terms of C−C bond formation was supported by the observation that the reduction product **15** (see also Scheme 3) was the major compound isolated from this reaction.

Finally, C-allylation of selenide **10** under Keck allylation conditions[14] proceeded smoothly to provide *C*-glycoside **20** in 51% yield (Scheme 5). The introduction of an allyl moiety is significant in terms of the functionality associated with the *C*-glycoside component, and this and related adducts are currently being exploited to provide access to novel carbohydrate-based tools.

In summary, we have validated a new entry to β-*C*-glycosides of *N*-acetyl-2-amino-2-deoxy sugars. This is based on extending the synthetic utility of anomeric selenides as precursors to *C*-glycosides via C−Se homolysis and alkene trapping. Further, this chemistry provides access to a novel subclass of *C*-glycoside derivatives, namely, the disubstituted 2-acetamido variants exemplified by **16**−**20**, and we now plan to extend this strategy to a broader range of C(1)-substituted glycals.

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

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