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Radical-Mediated Synthesis of α-*C*-Glycosides Based on *N*-Acyl Galactosamine

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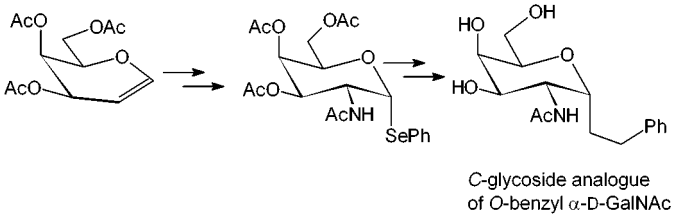
ABSTRACT

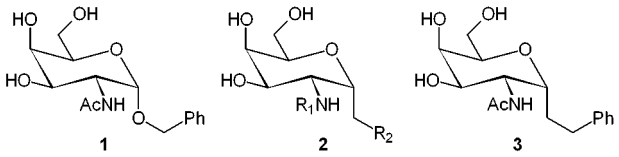


***C*-Glycosides of *N*-acyl 2-amino-2-deoxygalactose (acyl = MeCO, CF_3CO, *t*-BuOCO) are available in a stereoselective manner by trapping of an anomeric radical with an activated alkene. Using anomeric selenides, radical generation and trapping is carried out under conditions that avoid competitive reduction, and this chemistry has been applied to the synthesis of the novel *C*-glycoside analogue of *O*-benzyl α-D-GalNAc.**

Molecules that are effective inhibitors of glycosylation are valuable as tools for probing the significance of conjugating carbohydrates to proteins and lipids,[1] and recent results[2,3] based on the inhibitory properties of *O*-benzyl α-D-GalNAc **1** have furthered current understanding of the regulation of *O*-glycosylation and mucin metabolism.

This simple monosaccharide exhibits a differential action[2] on a family of GalNAc transferases, and a cellular product of *O*-benzyl GalNAc inhibition specifically blocks sialic acid transfer, which is an additional regulatory process of physiological significance.[3]

In the course of our studies, uncertainties arose regarding the stability of **1**, which appears to be processed in some cell lines. As a result, we have initiated a parallel program to explore the corresponding *C*-glycosyl variants represented by general structure **2**, with a key target being *C*-glycoside **3** as a stable analogue of **1**.



The chemical stability and favorable conformational properties associated with *C*-glycosides have encouraged the development of a wide range of synthetic strategies,[4] within which radical-based methods have found broad application. While nucleophilic radical character at the anomeric site has

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(3) Delannoy, P.; Kim, I.; Emery, N.; DeBolos, C.; Verbert, A.; Degand, P.; Huet, G. *Glycoconjugate J.* **1996**, *13*, 717−726. Nakano, T.; Matsui, T.; Ota, T. *Anticancer Res.* **1996**, *16*, 3577−3584. Huet, G.; Hennebicq-Reig, S.; de Bolos, C.; Ulloa, F.; Lesuffleur, T.; Barbat, A.; Carrière, V.; Kim, I.; Real, F. X.; Delannoy, P.; Zweibaum, A. *J. Cell Biol.* **1998**, *141*, 1311−1322. Ulloa, F.; Franci, C.; Real, F. X. *J. Biol. Chem.* **2000**, *275*, 18785−18793

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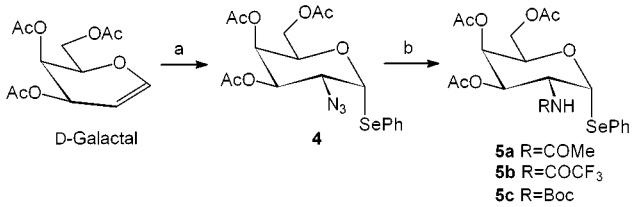
been applied successfully to elaborate 2-alkoxy, 2-fluoro, and 2-deoxysaccharides, as well as higher sugars, this process has yet to encompass fully 2-amino and 2-acetamido sugars.[5] Keck-type allylations (using allyl tributylstannane) have been described,[6] but this method provides only the *C*-allyl variant. Czernecki[5k] and Sinaÿ[5p] have shown that anomeric selenides do provide radicals, but these have only been trapped in intramolecular processes.

More recently, Fessner[7] has captured the radical derived from 1-bromo-*N*-(trifluoroacetyl)-α-D-glucosamine with vinyl phosphonates to give the corresponding *C*-glycosides.

While anomeric halides (see above) are generally a valuable source of anomeric radicals, there are limitations associated with using glycosyl bromides of 2-amino sugars.[8] For this reason, we have examined alternative radical precursors with the additional aim of providing access to a broad range of other 2-amino *C*-glycosyl derivatives, and our initial results, which focus on the *galacto* series, are described in this paper.

1-(Phenylselenyl)-2-azido-2-deoxy-α-D-galactose (**4**) provides an attractive starting point and is readily available via azide radical addition to D-galactal, as described by both Czernecki[9] and Santoyo-González[10] (Scheme 1). Selenide **4**

Scheme 1[a]



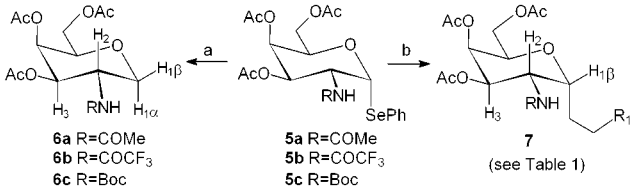
[a] Reagents and conditions: (a) $PhI(OAc)_2$, NaN_3, PhSeSePh (82%); (b) **5a**: MeCOSH (95%); **5b**: Et_3N, $HS(CH_2)_3SH$, then $(F_3CCO)_2O$ (75%); **5c**: Et_3N, $HS(CH_2)_3SH$, then Boc_2O (80%).

is readily handled, and homolytic C−Se bond cleavage is a well established and efficient method for radical generation.[5k,p,11] Further, the primary amine (arising from azide reduction) is easily converted to the *N*-acetyl derivative **5a**, as well as the *N*-trifluoroacetyl and *N*-Boc variants **5b** and **5c**, respectively, all of which exhibit good stability.

Using "standard" as well as a series of modified conditions for radical generation, reaction of **5a** in the presence of either methyl acrylate or styrene failed to give any *C*-glycoside.[12] C−Se cleavage occurred, but only reduction product **6a** was observed, which was generally obtained in quantitative yield.

The key to the successful trapping of an anomeric radical derived from **5** (other than by reduction) involves use of Et_3B as initiator at room temperature. Under these conditions, we were able to generate the desired radical and capture this species with a series of activated alkenes to give the corresponding α-*C*-glycosides **7** in 17−93% yield (Scheme 2 and Table 1).

Scheme 2[a]



[a] Reagents and conditions: (a) see footnote 12; (b) Et_3B, *n*-Bu_3SnH, PhMe, *hν*, ultrasound, rt.

Importantly, the α-anomer **7** was observed, and the corresponding *β*-isomer has not been detected. We have found that a combination of irradiation (200 or 400 W) and use of an ultrasonic bath also improved yields and reaction times. Reduction of the intermediate radical resulting in **6a**−**c** does still compete and remains the principle side reaction observed.

(4) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier Science Publishers: Amsterdam, 1995. Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: USA, 1995. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717.

(5) For other synthetic approaches to *C*-glycosides of 2-amino sugars, see (a) Nicotra, F.; Russo, G.; Ronchetti, F.; Toma, L. *Carbohydr. Res.* **1983**, *124*, C5−C7. (b) Hoffmann, M. G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 2403−2419. (c) Giannis, A.; Münster, P.; Sandhoff, K.; Steglich, W. *Tetrahedron* **1988**, *44*, 7177−7180. (d) Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 297−298. (e) Abel, S.; Linker, T.; Giese, B. *Synlett* **1991**, 171−172. (f) Grondin, R.; Leblanc, Y.; Hoogsteen, K. *Tetrahedron Lett.* **1991**, *32*, 5021−5024. (g) Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 3109−3112. (h) Kim, K. I.; Hollingsworth, R. I. *Tetrahedron Lett.* **1994**, *35*, 1031−1032. (i) Leteux, C.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2647−2655. (j) Ayadi, E.; Czernecki, S.; Xie, J. A. *J. Chem. Soc., Chem. Commun.* **1996**, 347−348. (k) Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193−9194. (l) Petrušová, M.; BeMiller, J. N.; Petruš, L. *Tetrahedron Lett.* **1996**, *37*, 2341−2344. (m) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442−6445. (n) Wang, L. X.; Fan, J. Q.; Lee, Y. C. *Tetrahedron Lett.* **1996**, *37*, 1975−1978. (o) Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678−6681. (p) Rubinstenn, G.; Esnault, J.; Mallet, J. M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327−1336. (q) Cui, J. R.; Horton, D. *Carbohydr. Res.* **1998**, *309*, 319−330. (r) Urban, D.; Skrydstrup, T.; Beau, J. M. *J. Org. Chem.* **1998**, *63*, 2507−2516. (s) Urban, D.; Skrydstrup, T.; Beau, J. M. *Chem. Commun.* **1998**, 955−956. (t) Westermann, B.; Walter, A.; Diedrichs, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 3384−3386. (u) Cipolla, L.; La Ferla, B.; Lay, L.; Peri, F.; Nicotra, F. *Tetrahedron: Asymmetry* **2000**, *11*, 295−303. (v) Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677−5680. (w) Dondoni, A.; Mariotti, G.; Marra, A. *Tetrahedron Lett.* **2000**, *41*, 3483−3487.

(6) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829−5831. Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079−4094. For carbohydrate-based applications of this methodology, see: Giese, B.; Linker, T.; Muhn, R. *Tetrahedron* **1989**, *45*, 935−940. Paulsen, H.; Matschulat, P. *Liebigs Ann. Chem.* **1991**, 487−495. Waglund, T.; Claesson, A. *Acta Chem. Scand.* **1992**, *46*, 73−76. See also ref 5m.

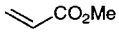
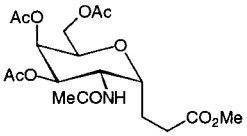
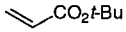
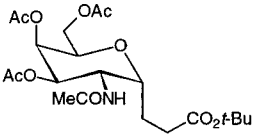
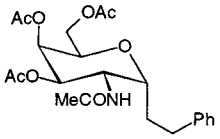
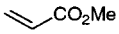
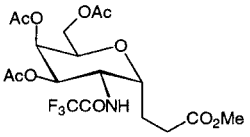
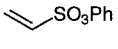
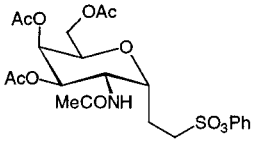
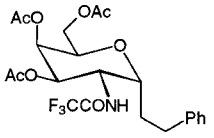
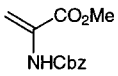
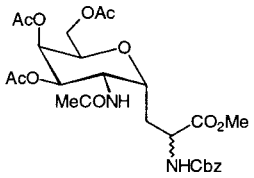
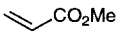
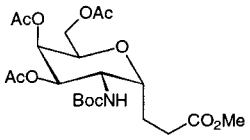
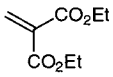
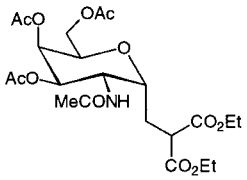
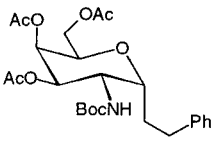
(7) Junker, H. D.; Fessner, W. D. *Tetrahedron Lett.* **1998**, *39*, 269−272. Junker, H. D.; Phung, N.; Fessner, W. D. *Tetrahedron Lett.* **1999**, *40*, 7063−7066.

(8) Horton[5q] has reported the successful Keck-type allylation process using anomeric chlorides and xanthates of 2-amido sugars. Attempts to use 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glycopyranosyl bromide as a radical precursor led only to the corresponding oxazoline. *N*-Trifluoroacetyl derivatives, as used by Fessner,[7] are less prone to oxazoline formation.

(9) Czernecki, S.; Randriamandimby, D. *Tetrahedron Lett.* **1993**, *34*, 7915−7916. Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Org. Chem.* **1994**, *59*, 8256−8260.

(10) Santoyo-González, F.; Calvo-Flores, F. G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Robles-Díaz, R. *J. Org. Chem.* **1993**, *58*, 6122−6125. See also: Giuliano, R. M.; Davis, R. S.; Boyko, W. J. *J. Carbohyd. Chem.* **1994**, *13*, 1135−1143.

Table 1. α-*C*-Glycosides **7** Derived from Selenides **5a**−**c**

Selenide	Radical Trap	*C*-Glycoside **7** (%)[a] (yield of **6**)	Selenide	Radical Trap	*C*-Glycoside **7** (%)[a] (yield of **6**)
5a		 **7a** (93 %) (**6a**: not detected)	**5a**		 **7f** (90 %) (**6a**: not detected)
5a		 **7b** (37 %) (**6a**: 60 %)	**5b**		 **7g** (74 %) (**6b**: not detected)
5a		 **7c** (58 %) (**6a**: 16 %)	**5b**		 **7h** (39 %) (**6b**: 31 %)
5a		 **7d** (17 %)[b] (**6a**: 69 %)	**5c**		 **7i** (37 %) (**6c**: 8 %)
5a		 **7e** (21 %) (**6a**: 76 %)	**5c**		 **7j** (39 %) (**6c**: 63 %)

[a] Isolated yields are after chromatography. [b] A 2:1 inseparable mixture of isomers was observed, provisionally assigned as diastereoisomers at the α-amino acid center, rather than epimers at C(1).

The structure of adducts **7** was based primarily on ^{1}H analysis, and complete proton assignments were made using ^{1}H−^{1}H and ^{1}H−^{13}C correlations. Anomeric stereochemistry (at C(1), using conventional sugar numbering) was based on the signal attributed to H(2), since H(1) was not well resolved.[13] A sound basis for this protocol was provided by the ^{1}H NMR spectrum obtained for the reduction product **6a**: $J_{H(1\alpha)-H(2)}$ = 11.0; $J_{H(1\beta)-H(2)}$ = 5.1; $J_{H(2)-NH}$ = 7.7; $J_{H(2)-H(3)}$ = 11.2 Hz. Comparing these data to the half-line

(11) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054−7056. Gupta, V.; Besev, M.; Engman, L. *Tetrahedron Lett.* **1998**, *39*, 2429−2432. Abe, H.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 4315−4325. Shuto, S.; Terauchi, M.; Yahiro, Y.; Abe, H.; Ichikawa, S.; Matsuda, A. *Tetrahedron Lett.* **2000**, *41*, 4151−4155.

(12) A variety of reaction conditions and reagents were studied: Bu_3SnH, Et_3B (at temperatures other than at rt and also in the absence of a hydride source) or AIBN, PhH or PhMe, at room temperature, 40 °C, 60 °C, and at reflux. $Bu_3SnSnBu_3$ and $(TMS)_3Si-H$ were also examined under various conditions, without success. When reaction of **5a** with Bu_3SnH was carried out without an alkene trap, quantitative reduction to give **6a** was observed.

(13) *C*-Glycosides **7** exist predominantly in the $^4C_1$ chair conformation [data for **7a**: $J_{H(2)-H(3)}$ = 9.5, $J_{H(3)-H(4)}$ = 3.1, $J_{H(4)-H(5)}$ = 3.1 Hz]. As a result, and using data available from reduction product **6a**, H(2) was predicted to exhibit a bandwidth ($W_{1/2}$) of 23.8 or 29.7 Hz for the α- and *β*-*C*-glycoside configurations, respectively. For **7a**, we observed 23.5 Hz, and for all other cases where H(2) was resolved, a consistent pattern was followed. It has been reported[5s] that the $^4C_1$ conformation is preferred for both peracetylated *C*-glycosides (related to **7**) and deprotected variants (such as **3**). It is interesting to note that alternative conformations are associated with variants carrying *O*-benzyl protecting groups.[5p]

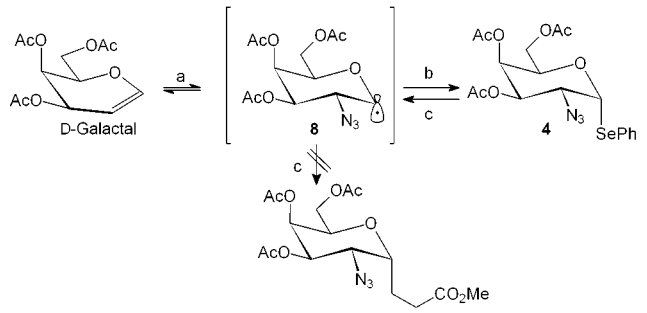
(14) Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J. Org. Chem.* **1991**, *56*, 6809−6813. Tingoli, M.; Tiecco, M.; Testaferri, L.; Temperini, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1883−1884.

width ($W_{1/2}$) of the H(2) signal for the *C*-glycosides **7** (e.g., **7a** $W_{1/2}$ = 24 Hz) allowed assignment of the α-stereochemistry shown in Table 1.

The *C*-glycosides shown in Table 1 represent a versatile group of functionalized *galacto* derivatives, and the successful trapping of styrene to give, e.g., **7b** is noteworthy. More generically, the use of an anomeric selenide (as opposed to a bromide) provides *C*-glycosides with differential and orthogonal protection of the 2-amino moiety (NAc vs $NCOCF_3$ vs NBoc). Further, an ability to incorporate both carboxylates, e.g., **7a** and **7f**, and sulfonates**,** e.g., **7c**, offers added flexibility in terms of future chemical modification of both the core *galacto* and the side chain *C*-glycosyl components.

A potentially more direct route toward the target *C*-glycosides has also been evaluated (Scheme 3). Addition of

Scheme 3[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, NaN_3; (b) $(PhSe)_2$; (c) $H_2C{=}CHCO_2Me$ and conditions (a); (c) Et_3B *n*-Bu_3SnH, PhMe, hν, ultrasound, room temperature.

$N_3^\bullet$ to D-galactal is postulated[14] to proceed via the 2-azido anomeric radical **8**, but to date all attempts to trap this intermediate with methyl acrylate have failed. Only D-galactal was recovered.[15]

Finally, the acetylated *C*-glycoside **7b** was deprotected (cat. NaOMe, MeOH, then Dowex 50 H^+ resin) in quantitative yield to give **3**, the *C*-glycoside analogue of benzyl α-D-GalNAc **1**. The biological evaluation of **3**, as well as a series of other novel *O*- and *C*-glycosyl variants, is now underway.

In summary, the radical-based strategy that has already found widespread application within 2-alkoxy and 2-deoxy sugars can be applied generally to the synthesis of *C*-glycosyl derivatives of 2-amino sugars. The success of this process derives from (i) use of anomeric selenides as the source of radical reactivity, which enables a range of *N*-protecting groups to be employed, and (ii) suppression of the competitive reduction of the intermediate radical by use of mild reaction conditions.

Azidoselenation is applicable to other glycals,[9,16] and this offers an opportunity to extend the radical-based methodology and make available a range of other 2-amino *C*-glycosyl derivatives.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR and other characterization data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Selenide **4** undergoes cleavage (AIBN, PhH at reflux, and also with Et_3B, Scheme 3) followed by rapid elimination of $N_3^\bullet$ to give D-galactal. Santoyo-Gonzalez, F.; Calvo-Flores, F. G.; Hernandez-Mateo, F.; Garcia-Mendoza, P.; Isac-Garcia, J.; Perez-Alvarez, M. D. *Synlett* **1994**, 454−456.

(16) For stereoselective approaches to *gluco* variants based on azidonitration, see: Seeberger, P. H.; Roehrig, S.; Schell, P.; Wang, Y.; Christ, W. J. *Carbohydr. Res.* **2000**, *328*, 61−69.