ORGANIC LETTERS

2002
Vol. 4, No. 26
4623−4625

Galacto, Gluco, Manno, and Disaccharide-Based *C*-Glycosides of 2-Amino-2-deoxy Sugars

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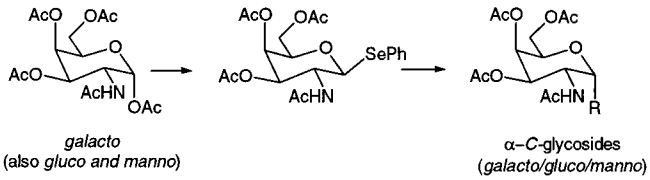
Received September 26, 2002

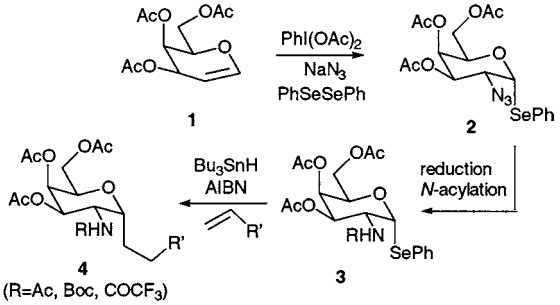
ABSTRACT



Starting from readily available precursors, selenoglycosides derived from GalNAc, GlcNAc, and ManNAc were prepared by either a one- or a two-step process. The anomeric selenides underwent facile C–Se homolysis to provide the corresponding anomeric radicals, which were trapped with alkenes to give *C*-glycosides. This provides a general entry to α-*C*-glycosides based on 2-amino-2-deoxy sugars that is also applicable to disaccharide variants.

C-Glycosides based on biologically significant carbohydrates represent potentially useful probes for determining carbohydrate function and regulation.[1] 2-Amino-2-deoxy sugars are important components of oligosaccharides and of both *N*- and *O*-glycopeptides,[2] and we recently described a stereochemically efficient entry to α-*C*-glycosides **4** based on *N*-acylgalactosamine (Scheme 1).[3] This process offers the added advantage that the nature of the N-substituent associated with the *C*-glycoside **4** can be varied (*N*-Ac vs *N*-Boc vs *N*-$COCF_3$).

Scheme 1. Azidoselenation as an Entry to α-Selenoglycosides



Central to this strategy was the use of an α-selenide **3** as a stable precursor to the corresponding anomeric radical, and **3** was constructed via **2**, the product of azidoselenation of 3,4,6-tri-*O*-acetyl-D-galactal **1**.

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(1) 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., Sinaÿ, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, Chapter 20, pp 495−530.

(2) For reviews of synthetic studies associated with glycosylation of 2-amino-2-deoxy sugars, see: Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167−1195. 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. Simple *O*-glycosides of 2-amino-2-deoxy sugars can 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.

(3) SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051−4054.

10.1021/ol0269695 CCC: $22.00
Published on Web 11/27/2002

The approach shown in Scheme 1 is flexible in terms of the target *C*-glycosides,[4,5] but the use of azidoselenation[6] as a key step in this sequence has significant limitations.

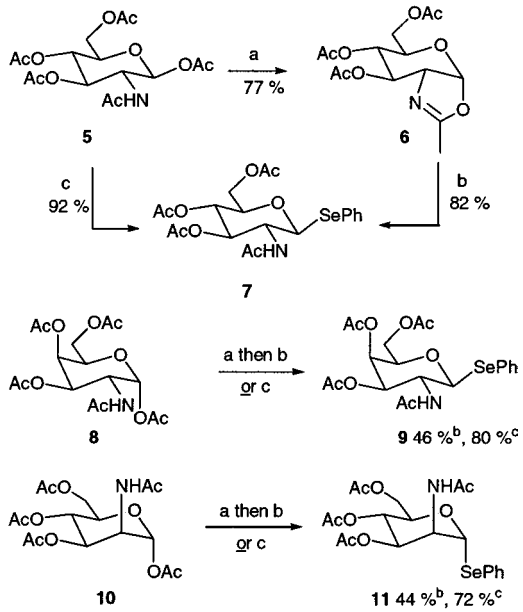
While this addition process works well for derivatives of D-galactal (e.g., **1**), the use of the corresponding peracetylated D-glucal leads to a mixture of the D-gluco and D-manno adducts. The radical addition can be controlled to favor the gluco adduct,[7] but the manno isomer is much less accessible. Furthermore, disaccharide-based glycals, e.g., D-maltal, are poor substrates for this radical addition reaction, leading to very low yields of adducts.[8]

We now report procedures that address these limitations associated with azidoselenation, and these enable selective access to β-anomeric selenides based on the galacto and gluco configurations, as well as the α-anomeric selenide corresponding to the manno configuration. This selenium-based method has also been applied to two representative disaccharides, which also function as substrates for *C*-glycoside synthesis.

The solution involves direct synthesis of the anomeric selenides from the corresponding and readily available 2-*N*-acetamido sugars. Two approaches are presented, which are illustrated in Scheme 2.[9]

In a two-step protocol, peracetylated *N*-acetyl-D-glucosamine **5** was reacted with TMSOTf or $BF_3{\cdot}Et_2O$ to give oxazoline **6**. Exposure of **6** to PhSeH in the presence of camphorsulfonic acid (CSA) gave the target β-selenide **7** in 63% overall yield. Alternatively, **7** is available in one operation and in 92% yield by direct treatment of **5** with $PhSeSiMe_3$ and TMSOTf. These procedures are applicable to the galactosamine and mannosamine derivatives starting from the commercially available peracetylated pyranosides

Scheme 2. One- and Two-Step Selenoglycosylation Procedures[a]



[a] Reagents and conditions: (a) TMSOTf, $Cl(CH_2)_2Cl$, 50 °C; (b) PhSeH (2 equiv), CSA (cat.), $Cl(CH_2)_2Cl$, reflux; (c) PhSeTMS (2 equiv), TMSOTf, $Cl(CH_2)_2Cl$, 50 °C. [b]Overall yield for the two-step procedure (via the corresponding oxazoline). [c]Yield for the one-step procedure.

8 and **10** and provide the corresponding β-selenide **9** (galacto) and α-selenide **11** (manno), respectively.[10]

Crucial to the incorporation of this chemistry into the radical-mediated strategy for *C*-glycoside synthesis (as outlined in Scheme 1) was validation of **7**, **9**, and **11** as precursors to the corresponding anomeric radicals. In this sense, it is important to recognize that azidoselenation of tri-*O*-acetyl-D-galactal **1** leads (ultimately) to the α-selenide **3**, whereas the chemistry outlined in Scheme 2 leads to the isomeric β-selenide **9**. Nevertheless, **9** did undergo smooth C−Se homolysis, and the resulting radical was trapped efficiently by either *tert*-butyl acrylate or styrene to give the α-*C*-glycosides **12a**[3] and **12b**[3] in 68 and 41% yields, respectively (Scheme 3).[11,12] These products were identical to those prepared from the corresponding α-selenide **3**.

In a similar fashion, the β-gluco selenide **7** and the α-manno isomer **11** underwent C−Se cleavage and addition to *tert*-butyl acrylate and styrene to give the α-*C*-glycosides **13a** and **13b** and **14a** and **14b**, respectively. The stereochemistry of *C*-glycoside **13a**, which adopts a $^4C_1$ conforma-

(4) A comprehensive listing of earlier methods for the synthesis of *C*-glycosides related to 2-amino-2-deoxy sugars has been presented earlier. For more recent reports, see: Rohrig, C. H.; Takhi, M.; Schmidt, R. R. *Synlett* **2001**, 1170−1172. Yang, G. L.; Franck, R. W.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **2001**, *3*, 197−200. Westermann, B.; Walter, A.; Florke, U.; Altenbach, H. J. *Org. Lett.* **2001**, *3*, 1375−1378. 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.

(5) For methods involving the generation and trapping of an anomeric radical, see: (a) Abel, S.; Linker, T.; Giese, B. *Synlett* **1991**, 171−172. (b) Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193−9194. (c) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442−6445. (d) Cui, J. R.; Horton, D. *Carbohydr. Res.* **1998**, *309*, 319−330. (e) Junker, H. D.; Fessner, W. D. *Tetrahedron Lett.* **1998**, *39*, 269−272. (f) Junker, H. D.; Phung, N.; Fessner, W. D. *Tetrahedron Lett.* **1999**, *40*, 7063−7066.

(6) For studies relating to the azidoselenation of glycals, see: Czernecki, S.; Randriamandimby, D. *J. Carbohydr. Chem.* **1996**, *15*, 183−190. Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Chem. Soc., Chem. Commun.* **1994**, 35−36. Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Org. Chem.* **1994**, *59*, 8256−8260. Czernecki, S.; Randriamandimby, D. *Tetrahedron Lett.* **1993**, *34*, 7915−7916. Santoyo-González, F.; Calvo-Flores, G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Robles-Díaz, R. *J. Org. Chem.* **1993**, *58*, 6122−6125.

(7) Seeberger, P. H.; Roehrig, S.; Schell, P.; Wang, Y.; Christ, W. J. *Carbohydr. Res.* **2000**, *328*, 61−69.

(8) Santoyo-González, F.; Calvo-Flores, G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Robles-Díaz, R. *Carbohydr. Res.* **1994**, *260*, 319−321.

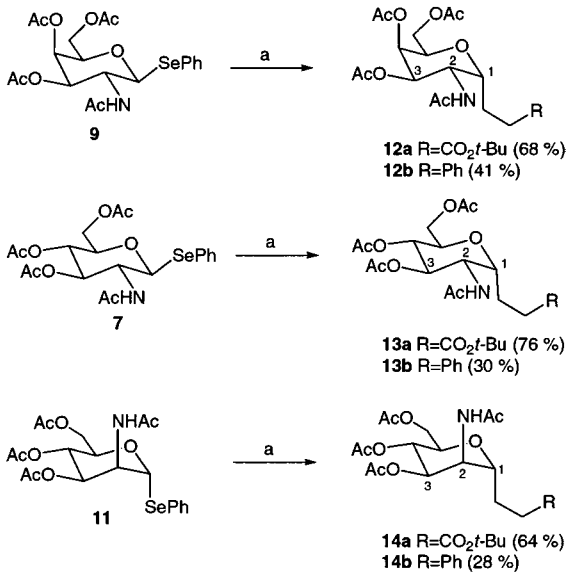
(9) Selenoglycosides of 2-amino-2-deoxy sugars have found application in *O*-glycosylation processes. Mehta, S.; Pinto, B. M. *Tetrahedron Lett.* **1991**, *32*, 4435−4438. Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269−3276. Carriere, D.; Meunier, S. J.; Tropper, F. D.; Cao, S.; Roy, R. *J. Mol. Catal. A-Chem.* **2000**, *154*, 9−22.

(10) The α-anomer of **6** gave **7** in 68% yield using the one-step procedure. In the two-step protocol, we obtained >95% yields of oxazolines (cf. **6**), but the subsequent ring opening with PhSeH/CSA was less efficient. The stereochemical assignment of anomeric selenides **7**, **9**, and **11** is based primarily on ^1H NMR. See the Supporting Information.

(11) β-Anomer **9** was less reactive than α-anomer **3**. α-Anomer **3** reacted at room temperature, using Bu_3SnH in PhMe, with Et_3B/O_2 as initiator, whereas **9** was unreactive under these conditions. Similar differences were observed between **7** and the corresponding α-anomer.

(12) Reaction of **7** with *tert*-butyl acrylate using tris(trimethylsilyl)silane (TTMS), AIBN, PhH, reflux gave **13a** in 93% yield. The same reaction, but replacing AIBN with Et_3B/O_2 as initiator, gave **13a** in 71% yield.

Scheme 3. Synthesis of Galacto-, Gluco-, and Manno-Based α-*C*-Glycosides[a]



[a] Reagents and conditions: (a) $H_2C{=}CHCO_2$-*t*-Bu or $PhCH{=}CH_2$ (20 equiv), *n*-Bu_3SnH, AIBN, PhH, reflux.

tion, was established by ^{1}H NMR: H(2) δ 4.51 (td, $^3J_{2,3} = {}^3J_{2,NH}$ 8.5 Hz, $^3J_{1,2}$ 3.8 Hz). In the case of *C*-glycoside **14a**, assignment of the α-configuration of the predominant $^4C_1$ conformer was again made using ^{1}H NMR: H(2) δ 4.46 (dt, $^3J_{2,NH} = 8.9$ Hz, $^3J_{1,2} = {}^3J_{2,3}$ 3.9 Hz).[13]

The other significant problem associated with azidoselenation is the failure of disaccharide-based glycals to undergo efficient addition,[14] which limits the use of azidoselenation to monosaccharide substrates. However, direct formation of selenoglycosides from disaccharides is feasible, and is illustrated in Scheme 4 for hepta-*O*-acetyl−*N*-acetyl-D-lactosamine **15**.[15]

The synthesis of the target selenoglycoside **16** was achieved using the one-step procedure from **15** in 73% yield, using the conditions developed for the monosaccharide variants (Scheme 2). The configuration of β-selenide **16** was confirmed by ^{1}H NMR (H(2) dd, $^3J_{1,2} = 10$ Hz and $^3J_{2,3} = 9.5$ Hz).

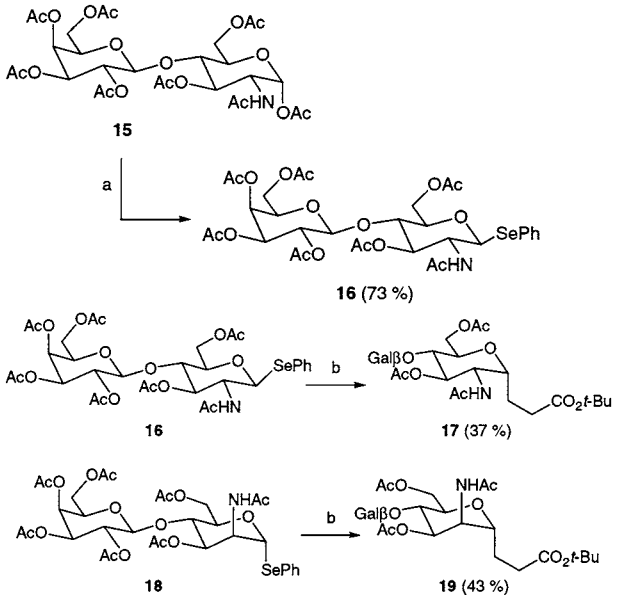
tert-Butyl acrylate served as an effective trap for the anomeric radical derived from **16**, and the α-*C*-glycoside **17** was isolated in 37% yield.[16] Similarly, selenoglycoside **18**, derived from the peracetylated derivative of disaccharide β-D-Gal*p*-1→ 4-D-Man*p*NAc,[17] underwent C−Se bond homolysis and addition to *tert*-butyl acrylate to provide α-*C*-glycoside **19** in 43% yield.[18]

(13) Conventional sugar numbering has been used for simplicity, and full spectroscopic details are available in the Supporting Information. When styrene, a less reactive trap, was used, the major byproduct was the corresponding peracetylated 1,5-anhydro-2-deoxy-D-pyranose.

(14) Santoyo-González et al.[8] have reported that azidoselenation of disaccharide-based glucals is low yielding and slow (1−3 weeks). In our hands, the adduct derived from peracetylated D-maltal was obtained in <10% yield after 1 week.

(15) Hepta-*O*-acetyl−*N*-acetyl-D-lactosamine **15** was obtained from lactulose using the Heynes rearrangement. Wrodnigg, T. M.; Stutz, A. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 827−828.

Scheme 4. Disaccharide-Based Selenoglycosides and Application to *C*-Glycoside Synthesis[a]



[a] Reagents and conditions: (a) TMSOTf, TMSSePh (1.5 equiv), $Cl(CH_2)_2Cl$, rt, 6 days; (b) $H_2C{=}CHCO_2$-*t*-Bu (20 equiv), *n*-Bu_3SnH, AIBN, PhH, reflux.

In summary, both α- and β-selenoglycosides provide viable sources of anomeric radical reactivity that are well suited to the synthesis of *C*-glycoside analogues of 2-amino-2-deoxy sugars. Application of "conventional" glycosylation conditions provides the requisite selenoglycosides (**7**, **9**, **11**, **16**, and **18**) in good yield directly from commercially available starting materials. Most significantly, the results reported in this paper extend our earlier work[3] by providing a more general entry to this potentially important class of *C*-glycosides.

Acknowledgment. We thank EPSRC and Roche Discovery for the provision of a CASE award (to K.E.W.) and EPSRC (Grant No. GR/R46601).

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.

OL0269695

(16) On the basis of ^{1}H NMR, the conformation of the gluco ring of **18** deviates from the expected $^4C_1$ arrangement: $^3J_{3,4} = {}^3J_{2,3} = 3.4$ Hz. Horton[5d] has observed similar effects for *C*-glycosides based on GlcNAc, which exist as an equilibrium between $^4C_1$ and $^1C_4$ conformers. As a consequence, the stereochemical assignment of **17** remains tentative.

(17) The Heynes rearrangement of lactulose generates a 3: 1 mixture of *N*-acetyllactosamine (major component) and the isomeric disaccharide β-D-Gal*p*-1→ 4-D-Man*p*NAc.[15] (This disaccharide is also available from Dextra Laboratories, Reading, U.K.). Using the "one step" procedure, selenoglycoside **18** was obtained in 91% yield from hepta-*O*-acetyl-β-D-Gal*p*-1→4-D-Man*p*NAc.

(18) In addition to producing *C*-glycosides **17** and **19**, reaction of both **16** and **18** gave the corresponding 1,5-anhydro-2-deoxy-D-pyranoses, which were isolated in 44% and 40% yields, respectively.