ORGANIC LETTERS

2013
Vol. 15, No. 22
5818–5821

Oxidative Cyclizations, the Synthesis of Aryl-Substituted C-Glycosides, and the Role of the Second Electron Transfer Step

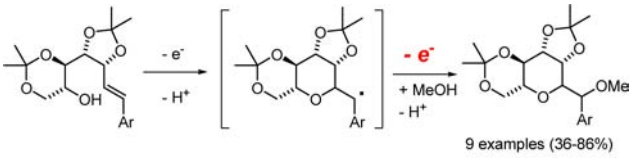
Jake A. Smith and Kevin D. Moeller*

Department of Chemistry, Washington University in St. Louis, St. Louis, Missouri 63130, United States

moeller@wustl.edu

Received October 6, 2013

ABSTRACT



Efficient removal of the second electron is critical for a successful cyclization.

Anodic oxidation reactions have been used to synthesize aryl- and biaryl-substituted C-glycosides. The reactions take advantage of the tendency for alcohol nucleophiles to trap nonpolar radical cations. The addition of the alcohol to the radical cation appears to be reversible, and the success of the cyclizations is dependent on the ease with which the resulting benzylic radical is oxidized.

C-Glycosides represent an important class of chemical probes that can be used to examine the role sugars play in numerous biological processes and recognition events.[1] Their utility is derived from the increase in stability imparted to them by the absence of the anomeric carbon. One such C-glycoside of interest (**2**) is illustrated in Scheme 1.[2] C-glycoside **2** is a proposed, stable analog of a family of mannose derivatives (**1**) that are effective FimH antagonists.[3] FimH is an adhesive protein that plays a role in the development of *Escherichia coli* urinary tract infections.[4] Small molecule inhibitors of FimH help to prevent bacterial entry into the bladder epithelium.[5] It is tempting to suggest that a more stable C-glycoside analog of **1** might prove to be a potent inhibitor of FimH. However, does the C-glycoside analog retain the activity of the original mannose derivatives, what stereoisomer of the C-glycoside is preferred at the anomeric carbon, and can a C-glycoside analog tolerate functionality ($-OR_3$) on the carbon bound to the original anomeric carbon of the sugar without a loss of activity? Can a C-glycoside be attached to a microelectrode array so that binding of the C-glycoside to its biological target can be monitored in "real time"?[6]

In order to answer these questions, an efficient method for the synthesis of the C-glycoside analogs is needed. To meet this need, we have been exploring oxidative cyclizations that allow for the two-step conversion of any sugar into a C-glycoside.[7] For example, the chemistry illustrated

(1) For a reviews, see: (a) Yin, J.; Linker, T. *Org. Biomol. Chem.* **2012**, *10*, 2351. (b) Levy, D. E.; Fuegedi, P. *Organic Chemistry of Sugars* **2006**, 269. (c) Dondoni, A.; Mauer, A. *Chem. Rev.* **2000**, *100*, 4395.

(2) For C-glycosides like **2**, see: (a) Araki, S.; Morita, K.; Yamaguchi, M.; Zhao, Z.; Wilson, T. J.; Lilley, D. M. J.; Harusawa, S. *J. Org. Chem.* **2009**, *74*, 2350. (b) Albrecht, H. P.; Repke, D. B.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1836. (c) Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Hayakawa, I.; Kigoshi, H. *J. Org. Chem.* **2009**, *74*, 3370. (d) Jung, J. H.; Lee, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 5698. (e) Popsavin, M.; Psopsavin, V.; Vukojević, G.; Csanádi, J.; Miljković, D. *Carbohydr. Res.* **1994**, *260*, 145. (f) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404. (g) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M. D.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475.

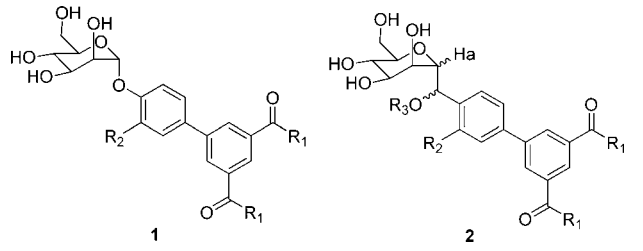
(3) Han, Z.; Pinkner, J. S.; Ford, B.; Obermann, R.; Nolan, W.; Wildman, S. A.; Hobbs, D.; Ellenberger, T.; Cusumano, C. K.; Hultgren, S. J.; Janetka, J. W. *J. Med. Chem.* **2010**, *53*, 4779.

(4) Waksman, G.; Hultgren, S. J. *Nat. Rev. Microbiol.* **2009**, *7*, 765.

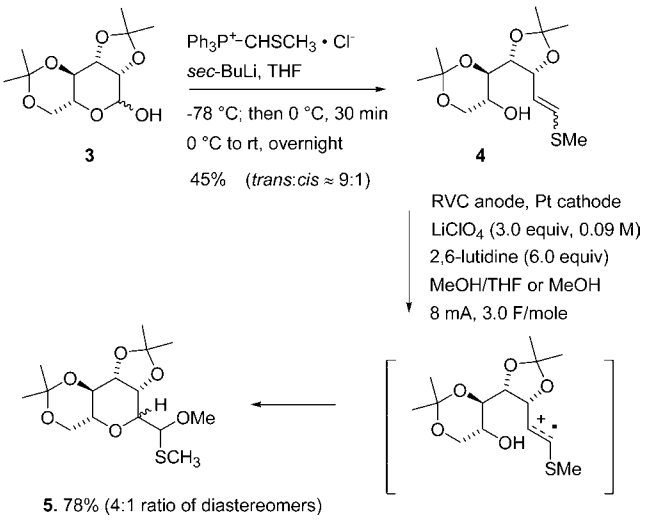
(5) (a) Rosen, D. A.; Pinkner, J. S.; Walker, J. N.; Elam, J. S.; Jones, J. M.; Hultgren, S. J. *Infect. Immun.* **2008**, *76*, 3346. (b) Chen, S. L.; Hung, C. S.; Pinkner, J. S.; Walker, J. N.; Cusumano, C. K.; Li, Z.; Bouckaert, J.; Gordon, J. I.; Hultgren, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 22439. (c) Abraham, S. N.; Sun, D.; Dale, J. B.; Beachey, E. H. *Nature* **1988**, *336*, 682. (d) Martinez, J. J.; Mulvey, M. A.; Schilling, J. D.; Pinkner, J. S.; Hultgren, S. J. *EMBO J.* **2000**, *19*, 2803. (e) Mulvey, M. A.; Lopez-Boado, Y. S.; Wilson, C. L.; Roth, R.; Parks, W. C.; Heuser, J.; Hultgren, S. J. *Science* **1998**, *282*, 1494. (f) Wright, K. J.; Seed, P. C.; Hultgren, S. J. *Cell. Microbiol.* **2007**, *9*, 2230. (g) Hung, C. S.; Bouckaert, J.; Hung, D.; Pinkner, J.; Widberg, C.; DeFusco, A.; Auguste, C. G.; Strouse, R.; Langermann, S.; Waksman, G.; Hultgren, S. J. *Mol. Microbiol.* **2002**, *44*, 903.

10.1021/ol402826z
Published on Web 11/07/2013

Scheme 1



Scheme 2



in Scheme 2 highlights a Wittig olefination–anodic oxidation strategy for converting pyranose sugars into C-glycosides that have a protected aldehyde bound to the "anomeric" carbon. The anodic cyclization works by generating a radical cation intermediate from the vinylsulfide that is then trapped by an alcohol nucleophile. The loss of a second electron followed by trapping by methanol leads to the final product. In principle, the thioacetal in C-glycoside **5** can be used to transform the product into a variety of analogs. However, in practice such efforts were thwarted when attempts to selectively deprotect the thioacetal were unsuccessful.

Reexamination of the cyclization reaction suggested a potentially efficient solution to this problem. The trapping of a radical cation by an alcohol nucleophile is aided by the use of a less-polar radical cation.[8] So, is an enol ether-type substrate needed for the reaction or can a styrene derived radical cation be used to trigger the cyclization?[9,10] If the answer is yes, then the C-glycosides could be accessed directly and the troublesome deprotection of **5** completely avoided.

Initial efforts to answer this question focused on oxidation substrates **6a**–**h**. The results of these studies are summarized in Table 1. The optimized reactions are highlighted in bold print. The first substrate studied was the 4-methoxyphenyl derivative **6a**. Substrate **6a** was selected because of its low oxidation potential ($E_{p/2}$ = +1.16 V vs Ag/AgCl), hence the ease with which it can be oxidized to form a radical cation intermediate. After a brief optimization, the oxidative cyclization originating from **6a** worked nicely and afforded an 84% isolated yield of the desired product. The product was obtained as a 3/4 mixture of α/β-isomers at the anomeric carbon and a roughly 1:1 mixture of isomers at the benzylic position. The reaction proceeded better when lithium methoxide was used as a base instead of the 2,6-lutidine commonly employed in oxidative cyclizations. The benefit of using the more basic, less hindered methoxide base was consistent with prior mechanistic evidence that suggested the trapping of a radical cation by an alcohol nucleophile is aided by deprotonation of the alcohol in the transition state for the cyclization.[11]

With the success of the initial cyclization, the scope of the method was examined. In general, the reactions could be optimized in order to afford good yields of the cyclic product. Yet while the cyclizations were successful, they were not like previously studied anodic cyclizations where a single set of optimized reaction conditions could be used to accomplish the transformation with a variety of substrates. Fortunately, the conditions needed for

(6) For selected examples, see: (a) Tesfu, E.; Roth, K.; Maurer, K.; Moeller, K. D. *Org. Lett.* **2006**, *8*, 709. (b) Stuart, M.; Maurer, K.; Moeller, K. D. *Bioconjugate Chem.* **2008**, *19*, 1514. (c) Fellet, M. S.; Bartels, J. L.; Bi, B.; Moeller, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 16891. (d) Sullivan, M. G.; Utomo, H.; Fagan, P. J.; Ward, M. D. *Anal. Chem.* **1999**, *71*, 4369. (e) Zhang, S.; Zhao, H.; John, R. *Anal. Chim. Acta* **2000**, *421*, 175. (f) Hintsche, R.; Albers, J.; Bernt, H.; Eder, A. *Electroanalysis* **2000**, *12*, 660. (g) Gardner, R. D.; Zhou, A.; Zufelt, N. A. *Sens. Actuators, B* **2009**, *136*, 177. (h) Beyer, M.; Nesterov, A.; Block, I.; König, K.; Felgenhauer, T.; Fernandez, S.; Leibe, K.; Torralba, G.; Hausmann, M.; Trunk, U.; Lindenstruth, V.; Bischoff, F. R.; Stadler, V.; Breitling, F. *Science* **2007**, *318*, 1888. (i) Devaraj, N. K.; Dinolfo, P. H.; Chidsey, C. E. D.; Collman, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 1794. (j) Wassum, K. M.; Tolosa, V. M.; Wang, J.; Walker, E.; Monbouquette, H. G.; Maidment, N. T. *Sensors* **2008**, *8*, 5023. (k) Kerkoff, H. G.; Zhang, X.; Mailly, F.; Nouet, P.; Liu, H.; Richardson, A. *VLSI Design* **2008**, Article ID 437879 (doi:10.1155/2008/437879). (l) Zhang, Y.; Wnag, H.; Nie, J.; Zhang, Y.; Shen, G.; Yu, R. *Biosens. Bioelectron.* **2009**, *25*, 34. (m) Maurer, K.; Yazvenko, N.; Wilmoth, J.; Cooper, J.; Lyon, W.; Danley, D. *Sensors* **2010**, *10*, 7371. (n) Li, X.; Tian, Y.; Xia, P.; Luo, Y.; Rui, Q. *Anal. Chem.* **2009**, *81*, 8249. (o) Chan, E. W. L.; Yousaf, M. N. *ChemPhysChem* **2007**, *8*, 1469.

(7) Xu, G.; Moeller, K. D. *Org. Lett.* **2010**, *12*, 2590.

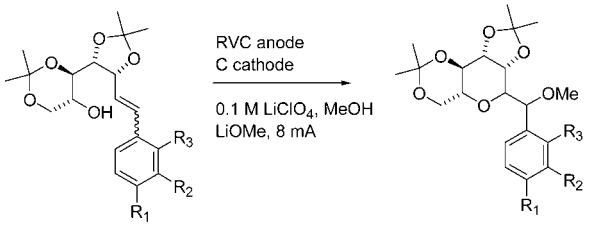
(8) (a) Tang, F.; Moeller, K. D. *J. Am. Chem. Soc.* **2007**, *129*, 12414. (b) Tang, F.; Moeller, K. D. *Tetrahedron* **2009**, *65*, 10863. (c) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839.

(9) For related examples of alcohol additions to nonenol ether derived olefins, see: (a) Il'chibaeva, I. B.; Kagan, E. Sh.; Tomilov, A. P. *Russ. J. Org. Chem.* **2001**, *37*, 16666. (b) Barba, I.; Chinchilla, R.; Gomez, C. *J. Org. Chem.* **1990**, *55*, 3270. (c) He, L.; Horiuchi, C. A. *J. Chem. Res. (S)* **2000**, 172. (d) Johnston, L. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1993**, *115*, 6564. (e) Johnston, L. J.; Schepp, N. P. *Pure Appl. Chem.* **1995**, *67*, 71. (f) Nair, V.; Balagopal, L.; Menon, R. S.; Ros, S.; Srinivas, R. *ARKIVOC* **2003**, *VIII*, 199. (g) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. *Chem. Commun.* **2005**, 1303. (h) Vargas, R. R.; Pardini, V. L.; Viertler, H. *Tetrahedron. Lett.* **1989**, *30*, 4037. (i) Raoult, E.; Sarrazin, J.; Tallec, A. *J. Appl. Electrochem.* **1984**, *14*, 639.

(10) For a very nice complementary photoelectron reaction, see: Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577.

(11) (a) Campbell, J. M.; Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 18383. (b) Zipse, H. *J. Am. Chem. Soc.* **1995**, *117*, 11798. (c) Oyama, M.; Nozaki, K. N.; Nagaoka, T.; Okazaki, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 33. (d) Mangion, D.; Arnold, D. R. *Acc. Chem. Res.* **2002**, *35*, 297. (e) Horner, J. H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* **2004**, *126*, 14979.

Table 1. Oxidation Studies



6a. R_1 = OMe, R_2 = R_3 = H
6b. R_1 = H, R_2 = H, R_3 = OMe
6c. R_1 = H, R_2 = OMe, R_3 = H
6d. R_1 = SMe, R_2 = R_3 = H
6e. R_1 = R_2 = R_3 = H
6f. R_1 = Me, R_2 = R_3 = H
6g. R_1 = Me, R_2 = H, R_3 = Me
6h. R_1 = Ph, R_2 = R_3 = H

7a. R_1 = OMe, R_2 = R_3 = H
7b. R_1 = H, R_2 = H, R_3 = OMe
7c. R_1 = H, R_2 = OMe, R_3 = H
7d. R_1 = SMe, R_2 = R_3 = H
7e. R_1 = R_2 = R_3 = H
7f. R_1 = Me, R_2 = R_3 = H
7g. R_1 = Me, R_2 = H, R_3 = Me
7h. R_1 = Ph, R_2 = R_3 = H

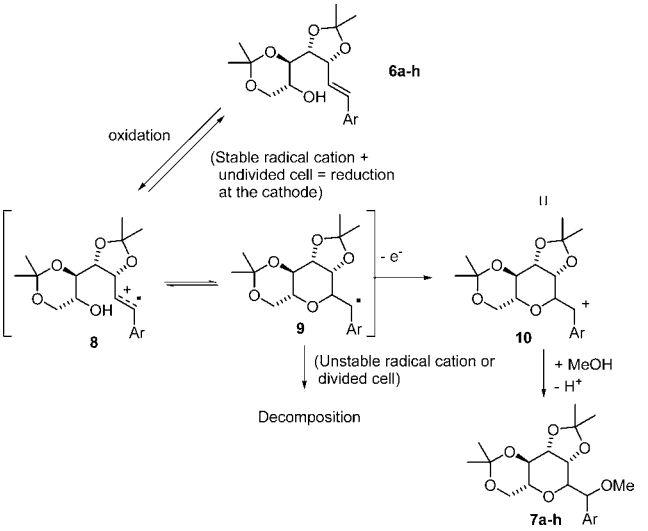
entry	subst.	$E_{p/2}$[a]	F/mol	α/β	% yield
1	**6a**	**1.16 V**	**2.2**	**0.75**	**84**
2	**6b**	**1.20 V**	**2.2**	**2.04**	**70(17)**[b]
3	6b	1.20 V	10	1.11	57
4	**6c**	**1.20 V**	**2.2**	**1.82**	**48(27)**[b]
5	6c	1.20 V	10	1.09	48
6	**6d**	**1.17 V**	**2.2**	**1.25**	**36(18)**[b]
7	**6e**	**1.34 V**	**10**	**0.85**	**74(5)**[b]
8[c]	6e	1.34 V	2.2	0.97	65(18)[b]
9	6e	1.34 V	2.2	2.6	22(60)[b]
10	**6f**	**1.38 V**	**10**	**0.87**	**86**
11	6f	1.38 V	2.2	1.12	36(25)[b]
12	**6g**	**1.17 V**	**10**	**0.95**	**76**
13	6g	1.17 V	2.2	1.2	55(26)[b]
14[c]	**6h**	**1.19 V**	**2.2**	**0.82**	**71(3)**[b]
16	6h	1.19 V	2.2	1.44	44(19)[b]
17	6h	1.19 V	10	0.60	40

[a] Cyclic voltammetry conditions. [b] Yield of recovered starting material. [c] These reactions were run with 1 M electrolyte.

optimization of each reaction could be understood by consideration of the mechanistic picture illustrated in Scheme 3. In this scheme, an initial oxidation of the substrate would lead a radical cation (**8**) that would then undergo a reversible cyclization[11a] to form the stable radical **9**. Oxidation of **9** to form a cation followed by solvent trapping led to the product. For a successful cyclization, the second oxidation step to form cation **10** proved critical.

If the cyclic radical **9** was easily oxidized to form cation **10**, then the reaction proceeded nicely to the product. If the cyclic radical **9** was not easily oxidized, then the reaction did not proceed well. Take for example the oxidation of substrates **6a**–**c**. All three subtrates oxidize at roughly the same potential, indicating that the oxidation of all three led to the formation of radical cation **8** with equal ease. However, only the oxidation of the 4-methoxystyrene derivative (**6a**) and the 2-methoxystyrene derivative (**6b**) (Table 1, entries 1 and 2) afforded a high yield of product. Both of these substrates have an electron-donating methoxy group in a location that aids the second oxidation step. This is not the case for the meta-substituted 3-methoxystyrene derivative **6c**.

Scheme 3

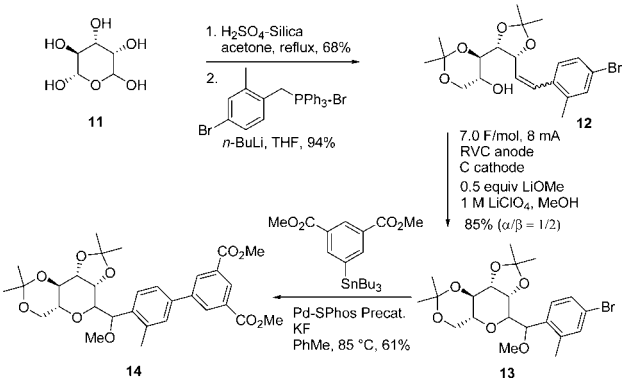


A similar observation was made for the substrate having a thioether substituent at the para-position of the phenyl ring (**6d**/ entry 6). The oxidation potential of **6d** was again consistent with the potentials measured for the successful methoxy-substituted substrates **6a** and **6b**, but the yield of the reaction was poor. In this case, the poor resonance overlap of the thioether lone pairs with the aromatic π-system leads to only a weak interaction between the substituent and the radical in **9**. Hence, the thioether substituent would aid the first oxidation step (an oxidation at sulfur) but not the second.

When a less electron-rich styrene was used (substrate **6e**), the reaction led to a surpising low current efficiency (entry 9). The passage of 2.2 F/mol of charge through the reaction led to only a 22% yield of the product along with 60% of the recovered starting material. The low current efficiency proved to be a result of the cathode being present in the reaction. When the oxidation of **6e** was conducted in a divided cell, the passage of 2.2 F/mol of charge through the cell led to complete consumption of the starting material, although the yield of the cyclic product remained low. The observation that the presence of the cathode in the undivided-cell reaction causes the low current efficiency (entry 9) is consistent with the reduction of radical cation **8** at the cathode to regenerate the substrate (Scheme 3). The reduction of radical cation **8** at the cathode would be aided by the fast, reversible formation of a stable cyclic radical **9**. The reversible formation of **9** would lower the concentration of the highly reactive radical cation in solution and thereby serve to increase its lifetime.

The poor current efficiency for the oxidation of **6e** in an undivided cell can be addressed by either passing more current through the cell (entry 7) or increasing the amount of electrolyte added to the reaction (entry 8). The passage of more current is a brute-force method to overcome the inefficiency of the reaction. It works when the reactive intermediates generated by the initial oxidation are relatively

Scheme 4



stable. In such cases, the initial cyclization led to a poor conversion of substrate but a high yield of recovered starting material. The oxdiation of substrates **6f** and **6g** also benefited from this approach.

The use of more electrolyte improved the current efficiency of the reaction by accelerating the oxidation of radical **9** to cation **10**. This occurs because the addition of more electrolyte to the reaction increases the concentration of the counterion needed to balance the charge of cation **10** as it is being generated at the anode. The faster the positive charge is balanced, the easier the oxidation, and the higher the yield of cyclic product obtained. In the case of substrate **6e**, the passage of 2.2 F/mol of charge through the reaction in the presence of 1 M electrolyte led to a 65% yield of product along with 18% of the recovered starting material (entry 8).

The use of more electrolyte also proved very effective for the oxidative cyclization originating from the biphenyl substrate **6h**. In this case, the low mass balance of the initial reaction (entry 16) did not bode well for the passage of additional charge through the cell (entry 17). However, the use of 1 M electrolyte and 2.2 F/mol of charge for the oxidation of substrate **6h** led to a 71% isolated yield of the desired C-glycoside.

With the success of the reactions in Table 1, attention was turned toward the synthesis of C-glycoside analog **2**. For this effort, the best strategy appeared to be one in which a bromostyrene derivative would be used for the anodic cyclization (Scheme 4). The required biaryl system would then be constructed following the cyclization. In this way, a variety of biaryl systems could be assembled by simply varying the final step of the sequence. A methyl group was included on the aromatic ring because it both increases the potency of mannose inhibitors of FimH[3] and aids the anodic cyclization by increasing the electron-richness of the ring. With the methyl group present, the anodic cyclization proceeded in an 85% isolated yield to form C- glycoside **13** as a 1/2 ratio of α/β-isomers. The product from the cyclization was then readily converted into the desired functionalized biphenyl devivative **14**. Overall, the synthetic route allowed for the conversion of mannose into the protected C-glycoside **14** in only four steps.

In conclusion, the oxidative coupling of styrene derivatives to alcohols offers a rapid approach to the synthesis of both phenyl and biphenyl substituted C-glycoside derivatives. The cyclization reactions are reversible and afford a stable benzylic radical intermediate. Oxidation of this cyclic benzyl radical is critical for reaction success. This second oxidation step is aided by either proper substitution of the substrate or an increase in the electrolyte concentration used for the electrolysis. Alternatively, reactions that have a high mass balance can be optimized by simply passing more current through the reaction. In examples where both more current and increased electrolyte concentration lead to a significant benefit, the conditions using more current are preferred since the reactions can be run with sunlight as the source of energy for the electrolysis.[12] Hence, the use of excess current is environmentally less problematic than the use of excess salt. Work to capitalize on the method to explore the biological activity of C-glycosides is underway along with efforts to provide a stereoselective synthesis of the C-glycoside products.

Acknowledgment. We thank the National Science Foundation (CHE-1151121) for their generous support of this work.

Supporting Information Available. A sample experimental procedure is included for the oxidation reaction along with characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Anderson, L. A.; Redden, A.; Moeller, K. D. *Green Chem.* **2011**, *13*, 1652.

The authors declare no competing financial interest.