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Preparation of α-*C*-Glycosides from Glycals

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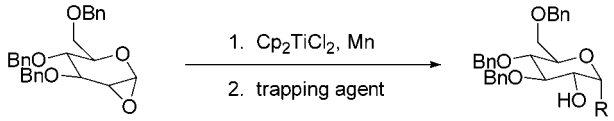
ABSTRACT



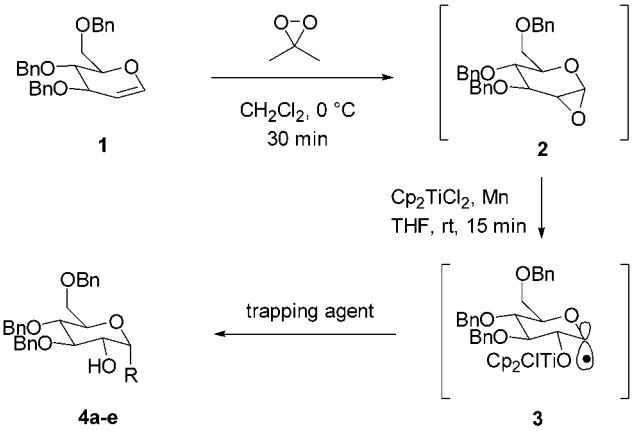
A novel approach to simple *C*-glycosides is reported. Reductive ring opening of 1,2-anhydro sugars with titanocene(III) chloride produces an anomeric radical that can be trapped with a variety of agents. The reaction stereospecifically affords α-glycosides and produces a free *C*-2 hydroxyl group allowing for further elaboration.

C-Glycosides are conformationally rigid, stable glycoside analogues that are of great interest.[1] Many methods have been developed for constructing these compounds. Free-radical chemistry has found specific application in the formation of α-*C*-glycosides.[2] The popular method of Giese employs the trapping of anomeric radicals derived from glycosyl halides.[3] However, this method requires the handling of rather sensitive glycosyl halide substrates and employs stoichiometric amounts of hazardous tin-based reagents to effect the radical formation. Other more recent methods have been developed, but they also involve cleavage of an activated anomeric bond.[4] It occurred to us that the titanocene-mediated ring opening of carbohydrate-derived epoxides might provide a unique route to anomeric radicals and *C*-glycosides.

The titanocene-mediated cleavage of epoxides has been known for over a decade and has been the subject of much study and use.[5] Typically, the regioselectivity of these reactions is guided by the stability of the two possible radicals resulting from the reductive cleavage of either C−O bond of the epoxide. To date, the only examples of selectivity employ increasing substitution to gain radical stabilization and regioselectivity. We reasoned that cleavage of a 1,2-anhydro glycal could, instead, be guided by the anomeric radical stabilization.

As previously reported, treatment of tri-*O*-benzyl glucal (**1**) with dimethyl dioxirane (DMDO) cleanly afforded 1,2-anhydro sugars (**2**) in near quantitative yields.[6] We found that addition of a trapping agent followed by a dropwise addition of titanocene(III) chloride into a THF solution of **2** affords a single product (**4a−e)** after chromatographic isolation (Scheme 1 and Table 1).

Scheme 1



(1) (a) Levy, D E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995. (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: London, 1995.

(2) For a review, see: Toto, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700. Also see: Praly, J.-P. *Adv. Carbohydr. Chem. Biochem.* **2001**, *56*, 65.

(3) Giese, B.; Dupuis, J.; Leising, M.; Nix, M.; Lindner, H. J. *Carbohydr. Res.* **1987**, *171*, 329.

(4) (a) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204. (b) SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051.

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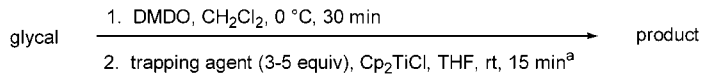
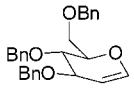
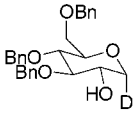
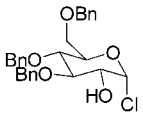
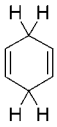
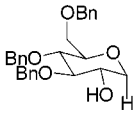
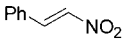
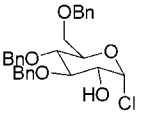
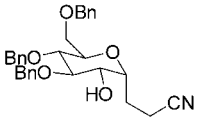
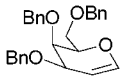
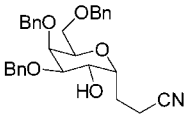
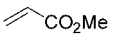
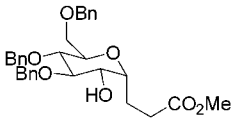
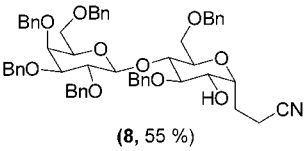
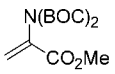
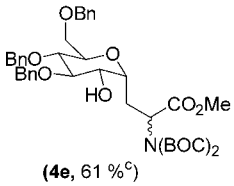
Table 1. *C*-Glycosides and Reduced Sugars Prepared from 1,2-Anhydro Carbohydrates

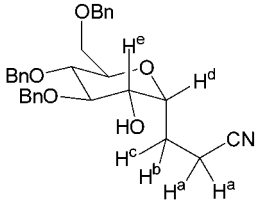


entry	glycal	trapping agent	product (yield[b])	entry	glycal	trapping agent	product (yield)
1	 (**1**)	Bu_3SnD	 (**4a**, 50 %)	6	**1**		 (**4f**, 10 %)
2	**1**		 (**4b**, 53 %)	7	**1**		 (**4f**, 47 %)
3	**1**		 (**4c**, 61 %)	8	 (**5**)		 (**6**, 54 %)
4	**1**		 (**4d**, 56 %)	9	hexa-(*O*)-benzyl lactal (**7**)		 (**8**, 55 %)
5	**1**		 (**4e**, 61 %[c])				

[a] Please refer to Supporting Information for full experimental details. [b] Overall yield for the two-step sequence after chromatographic isolation. [c] Isolated as a mixture of diastereomers, the exact ratio of which was not determined.

Tributyltin deuteride was employed as a source of deuterium atom to examine the regio- and stereochemical course of this reaction. We found that the product incorporated the label exclusively in the α-configuration (entry 1, Table 1), clearly implicating radical **3** as the primary reactive intermediate in these reactions.[7] In addition, the coupling constants to the anomeric proton (H^d) also confirm the formation of α-glycosides (Figure 1). As an example, the small observed value (2.9 Hz) between H^d and H^e is indicative of the assigned configuration for product **4c**. In addition, the anomeric coupling values of 10.4 and 2.9 Hz are in accord with predictions for α-*C*-glycosides.[1] This result contrasts with organometallic opening of these epoxides, which typically lead to *β*-glycosides (Scheme 2).[8]

With this knowledge in hand, our conditions were applied to a variety of trapping agents and unsaturated sugars to show the versatility of the sequence. The results are shown in Table 1. In all cases, only the α-glycoside was isolated; unless indicated, no other products were observed.[9] This method not only is compatible with simple monosaccharides but also

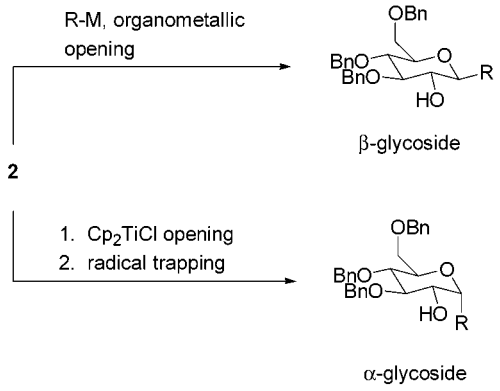


J (H^d/H^e) = 2.9 Hz
J (H^d/H^c) = 2.9 Hz
J (H^d/H^b) = 10.4 Hz

Figure 1. Anomeric coupling constants for product **4c**.

(5) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1994**, *116*, 986. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (c) Gansäuer, A. *Synlett* **1998**, 801.

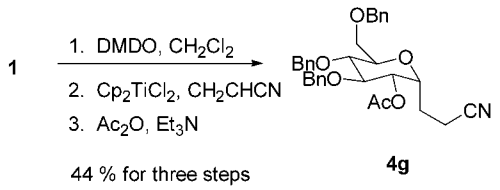
Scheme 2



is useful for disaccharides as well (entry 9). This suggests that the methodology could also be applied toward oligosaccharide synthesis. Also, we are interested in utilizing this chemistry in the construction of glycoproteins.[10] Entry 5 shows our initial efforts in this regard employing a dehydroalanine[11] derivative as a trapping agent. We intend to further study these reactions to improve both yield and stereochemical control.

An interesting and potentially useful point is the formation of a free *C*-2 hydroxyl group on the sugar. Although the selective formation of an allyl α-*C*-glycoside and subsequent deprotection of the neighboring *C*-2 benzyl ether has been described,[12] our method allows for the introduction of the *C*-glycoside *and* the concomitant formation of a free *C*-2 hydroxyl unit in a single transformation. In addition, we can introduce greater molecular diversity into the *C*-glycoside through the use of a variety of trapping agents. The resulting free alcohol can be manipulated to form disaccharides or glycosylamines or be orthogonally protected, if desired. As seen in Scheme 3, we have achieved this orthogonal

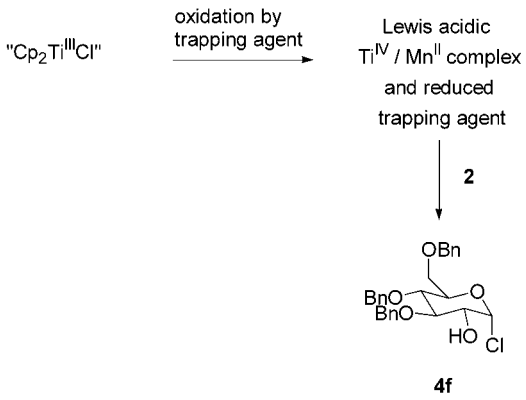
Scheme 3



protection in situ by adding acetic anhydride and triethylamine to the reaction mixture after the initial epoxide cleavage and trap.

Of note are attempted trapping reactions with acrolein and *β*-nitro styrene (entries 5 and 6, Table 1). In both cases we identified the chlorohydrin product **4f** derived from acid-promoted ring opening of the epoxide as the product. We reasoned that the trapping agent was preferentially reacting with the low-valent titanium reagent instead of the anhydro sugar. As illustrated in Scheme 4, the combination of

Scheme 4



titanium(IV) and manganese(II) salts are apparently Lewis acidic enough to promote the ring opening of the epoxide; capture by chloride affords **4f**.[13]

These results suggested that the process might be limited by the reduction potential of the trapping agent. In an effort to provide a quantitative assessment of this view, we examined the reduction potential of the electron-deficient alkenes shown in Table 2. We observed that there is a definitive window within which the potential must reside in order to effectively trap the anomeric radical. Acrolein and *β*-nitro styrene are preferentially reduced by the titanocene(III) complex, preventing the free-radical cleavage of the epoxide. Unactivated olefins such as styrene and 1-hexene are apparently not electrophilic enough to react with the nucleophilic anomeric radical (our attempts at trapping with these olefins were unsuccessful).[14] Thus, we conclude that if the redox potential falls within the range of ca. −2.7 to −2.9 (vs $Ag/AgNO_3$) the anomeric radical will be success-

(6) Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(7) This representation of **3** may be overly simplified, but it allows one to see the impact of anomeric stabilization leading to the observed products. For more on the conformations of these types of radicals, see refs 3 and 14.

(8) For examples, see: (a) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671. (b) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380. Rainier has published a report using boron- and aluminum-mediated alkylations to form α-*C*-glycosides: Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707.

(9) In addition to deuterium trapping and NMR data, to our knowledge all examples of trapping reactions of anomeric radicals leads predominantly, if not exclusively, to α-configured products.

(10) For reviews, see: Dondoni, A.; Marra, A. *Chem Rev.* **2000**, *100*, 4395. (b) Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317.

(11) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, *24*, 3697.

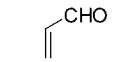
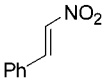
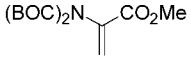
(12) Nicotra, F.; Cipolla, L.; Lay, L. *J. Org. Chem.* **1997**, *62*, 6678.

(13) Gansäuer has reported that the $ZnCl_2/Cp_2TiCl$ reagent is capable of opening epoxides, though the $MnCl_2/Cp_2TiCl$ system appears to be less Lewis acidic. See ref 5b.

(14) For a review on anomeric radicals, see: Descotes, G. *J. Carbohydr. Chem.* **1988**, *7*, 1. Also see ref 2.

(15) Reduction potentials were recorded in freshly distilled and degassed THF using a glassy carbon working electrode and a 0.01 M $Ag/AgNO_3$ in acetonitrile reference electrode. This electrode has a potential of ca. 0.3 V versus SCE.

Table 2. Reduction Potentials of Studied Trapping Agents and Their Observed Reactivity[15]

trapping agent	E_{pc} (V)	reactivity
	-1.8	quenches
	-2.55	quenches
	-2.73	traps
	-2.83	traps
	-2.93	traps
	> -3.3	unreactive
	> -3.3	unreactive

fully intercepted to form the glycoside. We believe these data will serve as a guideline as to the variety of trapping agents that can be employed in similar titanocene-promoted and -catalyzed reactions.

In conclusion, we have developed a new method for the production of *C*-glycosides. This method is unique in several ways: (1) It employs non-tin-based chemistry and 1,2-anhydro sugars for the formation of anomeric radicals. (2) To our knowledge, this is the first example of a regioselective titanocene-mediated epoxide opening in which the regioselectivity is not governed by the substitution of the epoxide. (3) It is not only regioselective but stereoselective as well, yielding only α-glycosides. An extra benefit is the formation of an unprotected *C*-2 alcohol that can be manipulated if desired or protected in situ.

Acknowledgment. We wish to thank the UCSB Committee on Research for their financial support. J.P. would also like to thank the Graduate Division of UCSB for a grant that assisted in the completion of this work. Mass spectral data was collected on instrumentation partially funded by the Army Research Office (DAAD19-00-0026).

Supporting Information Available: Full experimental details for C-glycosidation reactions, spectral data for previously undescribed compounds **4c**−**g**, **6,** and **8**, and description of the decoupling experiments used to determine the anomeric conformation. This material is available free of charge via the Internet at http://pubs.acs.org.

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