

Preparation of α -C-Glycosides from Glycals

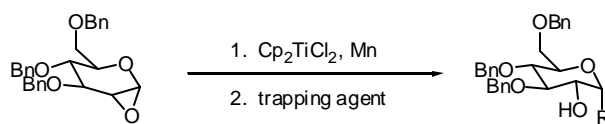
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Received Date (will be automatically inserted after manuscript is accepted)

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 continue to be highly desired synthetic targets.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**

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

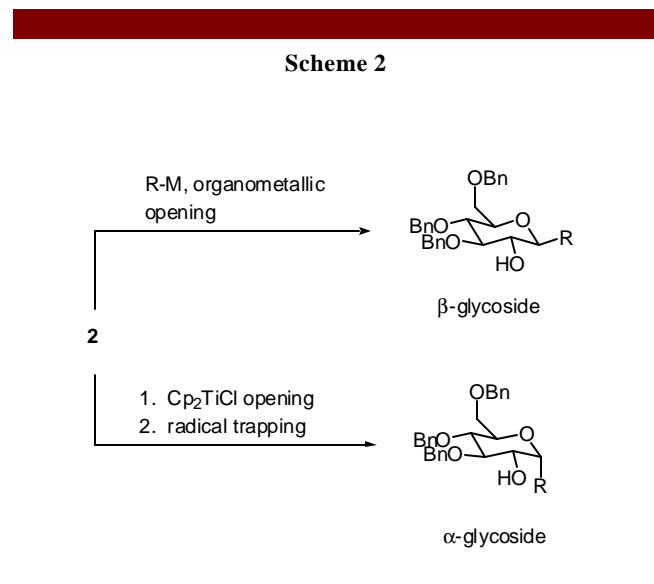
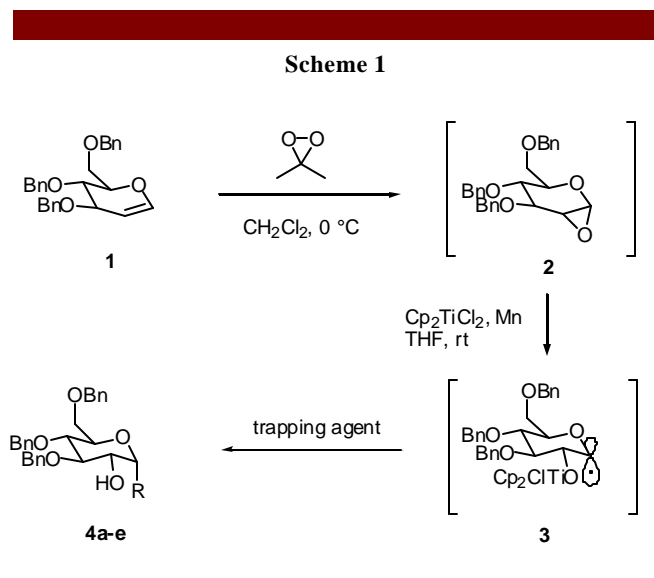
³ (a) Giese, B.; Dupuis, J.; Leising, M.; Nix, M.; Lindner, H. J. *Carbohydr. Res.* **1987**, 171, 329. (b) Giese, B.; Dupuis, J.; Nix, M. *Org. Synth.*

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, 4051-4054.

⁵ (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1994**, 116, 986-997. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, 120, 12849-12859. (c) Gansäuer, A. *Synlett* **1998**, 801-809.

⁶ Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1989**, 111, 6661-6666.

affords a single product (**4a-e**) after chromatographic



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.^{7,8} This result

⁷ This representation of **3** may be overly simplified, but 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 references 3 and 13.

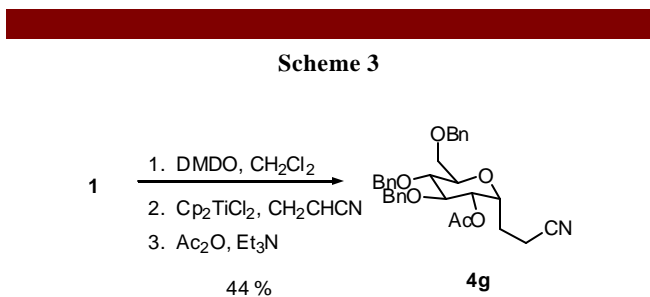
⁸ We do not have conclusive evidence that all products are α -configured. However, in addition to deuterium trapping and NMR data, to our knowledge all examples of trapping reactions of anomeric radicals leads to predominantly if not exclusively α -configured products.

isolation (Scheme 1 and Table 1).

contrasts with organometallic opening of these epoxides, which typically lead to β -glycosides (Scheme 2).⁹

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 seen. This method is not only compatible with simple monosaccharides, but is useful 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. Entry 5 shows our initial efforts in this regard employing a dehydroalanine¹⁰ derivative as a trapping agent. We intend to further study these reactions to improve both yield and stereochemical control.

An interesting and potentially useful is the formation of a free C-2 hydroxyl group on the sugar. While the selective formation of an allyl α -C-glycoside and subsequent deprotection of the neighboring C-2 benzyl ether has been described,¹¹ 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, glycosyl amines or be orthogonally protected, if desired. As seen in Scheme 3, we have achieved this orthogonal 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

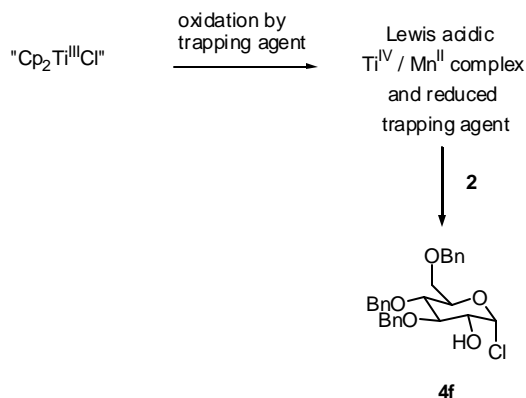
⁹ For examples see: (a) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671-8726. (b) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380-1386. Rainier has published a report using boron and aluminum mediated alkylations to α -C-glycosides: Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707-2709.

¹⁰ Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, *24*, 3697-3703.

¹¹ Nicotra, F.; Cipolla, L.; Lay, L. *J. Org. Chem.* **1997**, *62*, 6678-6681.

sugar. The combination of titanium (IV) and manganese (II) salts are apparently Lewis acidic enough to promote the ring-opening of the epoxide. Capture by chloride affords **4f**.¹²

Scheme 4



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).¹³ We believe this data can serve as a guideline as to the range 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*.

¹² Gansäuer has reported that the ZnCl₂/Cp₂TiCl reagent is capable of opening epoxides, though the MnCl₂/Cp₂TiCl system appears to be less Lewis acidic. See reference 2 (b).

¹³ For reviews on anomeric radicals see: (a) Praly, J-P. *Adv. Carbohydr. Chem. Biochem.* **2001**, 56, 65-151. (b) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700-717. (c) Descotes, G. *J. Carbohydr. Chem.* **1988**, 7, 1-20.

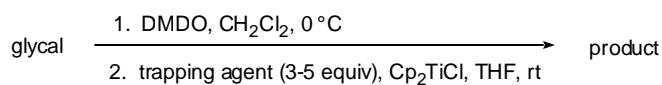
Acknowledgements: We wish to thank the UCSB Committee on Research for their financial support. J. P. would also like to thank the Graduate Division of UCSB for a grant that assisted in the completion of this work.

Supporting Information Available: Experimental details for C-glycosidation reactions and spectral data for previously undescribed compounds **4c-g**, **6** and **8**.

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

Table 2. Reduction potentials of studied trapping agents and their reactivity.¹⁴

¹⁴ Reduction potentials were recorded in freshly distilled and degassed THF using a glassy carbon working electrode and a 0.01 M Ag/AgNO₃ in acetonitrile reference electrode. This electrode has a potential of ca. 0.3 V versus SCE.



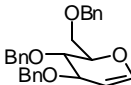
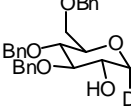

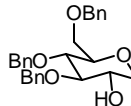
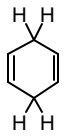
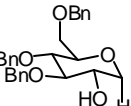
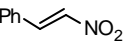
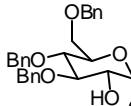

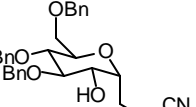
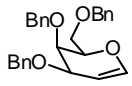

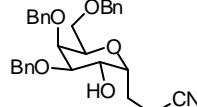
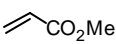
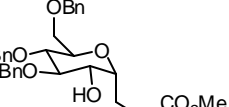

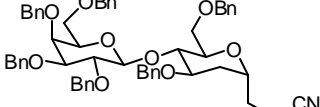
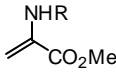
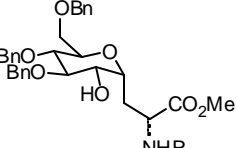
entry	glycal	trapping agent	product (yield ^a)	entry	glycal	trapping agent	product (yield)
1		Bu ₃ SnD	 (4a, 50 %)	6	1		 (4f, 10 %)
2	1		 (4b, 53 %)	7	1		 (4f, 47 %)
3	1		 (4c, 61 %)	8			 (6, 54 %)
4	1		 (4d, 56 %)	9	hexa-(O)-benzyl lactal (7)		 (8, 55 %)
5	1		 (4e, 61 % ^c)				

Table 1. C-glycosides and reduced sugars prepared from 1,2-anhydro carbohydrates.

^a Overall yield for the two step sequence after chromatographic isolation. ^b Initial addition was followed by addition of acetic anhydride (2 equiv) and triethylamine (3 equiv). ^c Isolated as a mixture of diastereomers, the exact ratio of which was not determined.