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Aluminum- and Boron-Mediated C-Glycoside Synthesis from 1,2-Anhydroglycosides

Jon D. Rainier* and Jason M. Cox

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

rainier@u.arizona.edu

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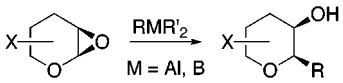
ABSTRACT

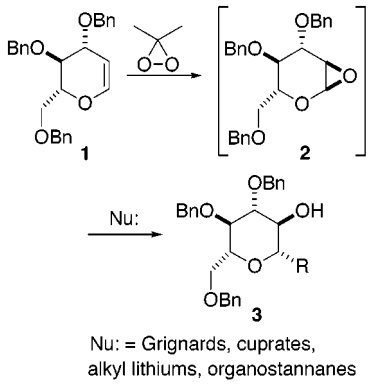


This letter describes a single flask strategy to the synthesis of α-C-glycosides from glycals. This protocol couples a glycal epoxidation reaction with a C-2 alkoxy-directed carbon–carbon bond-forming reaction.

Due to their increased stability to hydrolysis as well as their presence in a number of interesting natural products, C-glycosides have received a great deal of attention from the synthesis and medicinal chemistry community.[1] While this attention has led to a number of elegant approaches to their synthesis, to the best of our knowledge there is no readily available method that enables one to predictably generate α- or *β*-C-glycosides from a single glycosyl donor.

Among the many glycosyl donors that have been utilized in C-glycoside synthesis, 1,2-anhydroglycosides have received a significant amount of attention of late. This is largely due to their utility in the synthesis of C-glycosides having a trans-relationship between the C-2 hydroxy group and the anomeric C−C bond through their coupling with carbon nucleophiles.[2,3] Another reason that these epoxides have become attractive is that they can be generated from the reaction of the corresponding glycal with dimethyldioxirane under very mild conditions.[4] This enables one to bypass the isolation of relatively unstable glycosides containing anomeric leaving groups, as it is not necessary to isolate the epoxide prior to the addition of carbon nucleophiles (Scheme 1).

Scheme 1



Nu: = Grignards, cuprates, alkyl lithiums, organostannanes

In the course of our recently completed formal total synthesis of hemibrevetoxin B using C-glycoside technology

(1) (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier Science: Tarrytown, New York, 1995. (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, Florida, 1995.

(2) For anti-selective epoxide openings, see ref 3 and (a) Klein, L. L.; McWhorter, W. W., Jr.; Ko, S. S.; Pfaff, K.-P.; Kishi, Y.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7362. (b) Bellosta, V.; Czernecki, S. *J. Chem. Soc., Chem. Commun.* **1989**, 199. (c) Best, W. M.; Ferro, V.; Harle, J.; Stick, R. V.; Tilbrook, D. M. G. *Aust. J. Chem.* **1997**, *50*, 463. (d) Timmers, C. M.; Dekker, M.; Buijsman, R. C.; van der Marel, G. A.; Ethell, B.; Anderson, G.; Burchell, B.; Mulder, G. J.; Van Boom, J. H. *Bioorg. Med. Chem. Lett.* **1997**, 7, 1501. (e) Guo, J. S.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 187. (f) Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709. (g) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.

(3) (a) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (b) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601.

(4) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

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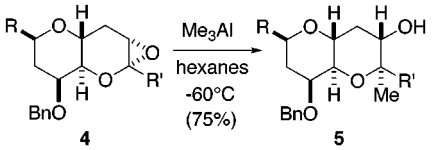
we found that trimethylaluminum efficiently transferred a methyl group to bicyclic epoxide **4** in a syn-fashion to provide **5** (eq 1).[5−7] While the reaction proceeded reasonably well in a number of solvents, we were intrigued by the observation that the highest coupling yields occurred when the reaction was carried out in nonpolar solvents. This led us to suspect that the transfer of a methyl group from an intermediate aluminate complex might be important.



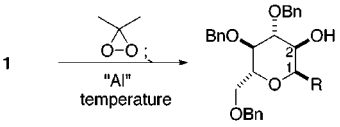
4 **5**

We set out to explore the scope of this chemistry, as it would complement the aforementioned anti-selective addition of other carbon nucleophiles to glycal epoxides. That is, if the aluminum chemistry proved to be general we would be able to construct either α- or *β*-C-glycosides from a single glycal epoxide by simply varying the counterion on the nucleophile.

With these goals in mind, we set out to investigate the coupling of 3,4,6-tri-*O*-benzyl-D-glucal epoxide **2** with alkyl, aryl, alkynyl, vinyl, and allyl aluminum reagents (Table 1). As had occurred in the **4** → **5** transformation, the transfer of a methyl group from Me_3Al occurred from the same face as the C-2 alkoxy group and resulted in a syn relationship between the newly formed C−O and C−C bonds (entry 1).[8] As the addition of dimethyl cuprate to **2** gives the corresponding anti-addition product,[9] this experiment effectively demonstrates that it is possible to control the C-glycoside stereochemistry by simply varying the counterion on the nucleophile.

The aluminum chemistry was also applicable to other nucleophiles; the corresponding alkynyl,[10] vinyl, phenyl, and furyl aluminum reagents also provided α-C-glycosides in high yield when coupled with **2**.[9] Interestingly, while both dimethylalkynyl aluminum[11] and trimethyl aluminum transferred alkynyl and methyl groups, respectively, at low temperature,[8] the transfer of a vinyl group from dimethylvinyl aluminum required relatively elevated temperatures to effect transfer in moderate yields. Unfortunately, at elevated temperatures methyl transfer became competitive with vinyl transfer (entry 4). These problems were circumvented by turning to trivinylaluminum. α-Vinyl glycoside **8** was isolated in 76% yield when 6 equiv of trivinyl aluminum were used, and the reaction was allowed to warm from −65 °C to room temperature (entry 6).[12]f Fewer equivalents of trivinylaluminum gave lower yields of **8** with significant quantities of oligomeric sugars (entry 5). By using the conditions that were optimized for the vinyl addition, the transfer of phenyl from triphenyl aluminum and 2-furyl from trifuryl aluminum gave the corresponding α-C-glycosides **9** and **10** in 79% and 85% yield, respectively (entries 7 and 8).[12] In our hands, allyl transfer from triallyl aluminum has been more problematic and has yielded mixtures of α- and

Table 1



entry	"Al"	equiv. (Al)	temperature	R	product	yield
1	$AlMe_3$	3	-95°C	Me	**6**	82%
2	Me_2Al—≡—TMS	3	-95°C	≡—TMS	**7**	80%
3	Me_2Al	3	-65°C		**8**	24%[a]
4	Me_2Al	3	-65°C → rt		**8**	40%[b]
5	$Al(\sim)_3$	3	-65°C → rt		**8**	59%[c]
6	$Al(\sim)_3$	6	-65°C → rt		**8**	76%
7	$AlPh_3$	6	-65°C → rt		**9**	79%
8	$Al(furyl)_3$	6	-65°C		**10**	85%
9	$Al(\sim)_3$	6	0°C		**11**	73%[d]

[a]Major products were methyl glycoside **8** (40%) and anomeric chloride and/or diol from hydrolysis of the epoxide or anomeric chloride upon workup.
[b]Major by-product was methyl glycoside **8** (44%).
[c]Major by-products were glycosidic dimers and higher oligomers.
[d]Product was isolated as a 2.3:1 mixture of α:β C-glycosides.

(5) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231.

(6) We are aware of one other report of the addition of trimethyl aluminum to glycal epoxides giving the product from syn-facial epoxide opening. See Bailey, J. M.; Craig, D.; Gallagher, P. T. *Synlett* **1999**, 132.

(7) For syn-selective epoxide opening reactions with acetylide anion in the presence of $ZnCl_2$ see: Leeuwenburgh, M. A.; Timmers, C. M.; van der Marel, G. A.; van Boom, J. H.; Mallet, J.−M.; Sinay, P. G. *Tetrahedron Lett.* **1997**, *38*, 6251.

(8) Procedure for the addition of trimethylaluminum to **2**: To a solution of 3,4,6-tri-*O*-benzyl-D-glucal (50 mg, 0.12 mmol) and CH_2Cl_2 (1.5 mL) at 0 °C was added dimethyldioxirane (1.8 mL of a 0.1 M solution in acetone, 0.18 mmol) dropwise. After 10 min the reaction mixture was concentrated. The resulting white solid was taken up in CH_2Cl_2 (6.0 mL) and cooled to −90 °C. To this solution was added $AlMe_3$ (0.060 mL of a 2.0 M solution in hexanes, 0.12 mmol) quickly. After 5 min the reaction was quenched with 0.5 M HCl (2 mL) and allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (5 × 5 mL), washed with brine (1 × 5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) afforded 44 mg (82%) of alcohol **6** as a colorless oil.

(9) The relative stereochemistry from epoxide opening was established by comparing the C-1, C-2 ^1H NMR *J* values for the *β*- and α-C-glycosides of the C-2 alcohols or the corresponding C-2 acetates. For the *β*-C-glycosides, $J_{1,2}$ ranged from 9.2 to 10 Hz. (a) ref 3. (b) Rainier, J. D.; Allwein, S. A.; Cox, J. M. Unpublished results). For the corresponding α-C-glycosides, $J_{1,2}$ ranged from 4.2 to 5.9 Hz.

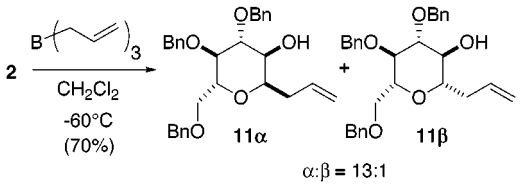
(10) We have been unable to generate the corresponding *β*-alkynyl glycoside from the addition of acetylide anions to **4**. Van Boom has generated α-alkynyl glycosides from alkynyl zinc additions. See ref 7.

(11) The aluminum reagents were prepared by coupling commercially available aluminum chlorides (Me_2AlCl or $AlCl_3$) with the appropriate Grignard or lithium reagent. See: Paley, R. S.; Snow, S. R. *Tetrahedron Lett.* **1990**, *31*, 5853.

(12) Procedure for the addition of trivinyl aluminum to **2**: A solution of **2**[8] (0.12 mmol) and CH_2Cl_2 (2 mL) at 0 °C was added to a solution of trivinylalane (0.72 mmol) and CH_2Cl_2 (12.0 mL) dropwise over 1 h at −60 °C. After warming to room temperature and stirring for an additional 1 h, the reaction mixture was cooled to 0 °C and quenched with HCl (0.5 N (aq), 2 mL). The mixture was extracted with CH_2Cl_2 (5 × 5 mL), washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) afforded 42 mg (76%) of alcohol **8** as a colorless oil.

β-allyl glycosides (entry 9). Presumably, β-allyl products come from a competitive intermolecular allyl transfer reaction.[13]

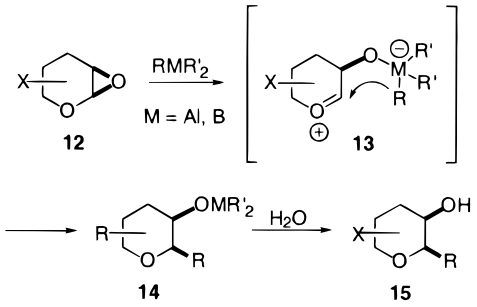
We were of the opinion that the presence of $MgCl_2$ from the synthesis of triallylaluminum was responsible for the somewhat disappointing results with triallylaluminum.[13] In an effort to overcome these problems, we targeted the transfer of allyl from triallylborane. We were attracted to boron for two reasons. First, when reacting with **2**, it should transfer its ligands intramolecularly via a "borate" complex. Second, triallylborane can be purified.[14] In the event, we were extremely pleased to find that the exposure of **2** to freshly distilled triallylborane at −60 °C resulted in a 13:1 mixture of α- and β-allyl-glycosides respectively in 70% yield (eq 2).



The syn addition reactions appear to be occurring via the mechanism outlined in Scheme 2. Aluminum or boron complexation to the epoxide is followed by oxonium ion formation to provide **13**. Intramolecular ligand transfer to the oxonium ion then gives the isolated products after hydrolysis.

To conclude, we have demonstrated that C-glycosides having a cis relationship between a C-2 alkoxy group and a C-1 carbon−carbon bond can be generated via the addition of aluminum or boron reagents to glycal epoxides. These coupling reactions nicely complement the previously reported anionic couplings to these same epoxides and represent the first examples of the predictable formation of α- or β-C-glycosides from a single glycosidic donor. Current efforts are focused on the continued examination of these reactions as well as their application to the synthesis of fused polyether-containing natural products.

Scheme 2



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Supporting Information Available: Spectroscopic data for compounds **6**−**11** and the corresponding C-2 acetates. This material is free of charge via the Internet at http://pubs.acs.org.

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(13) We believe that the intermolecular addition is occurring from an aluminum "ate" complex (possibly chlorotriallyl aluminate). Thus far, we have not been able to purify triallyl aluminum.

(14) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51*, 427.