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Haloacetal Radical Cyclizations of α- and β-Hydroxyhydrazones

Gregory K. Friestad*,† and Gina M. Fioroni‡

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, and Department of Chemistry, University of Vermont, Burlington, Vermont 05405

gregory-friestad@uiowa.edu

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ABSTRACT

Haloacetal radical cyclizations of α- and β-hydroxyhydrazones provide a direct access to aminosugarlike compounds. Stereocontrol of this process is influenced by stereogenic centers of both the hydroxyhydrazone and the acetal. The outcomes are consistent with chair and twist transition states with the anomeric alkoxy group in pseudoaxial orientations.

Stereocontrolled construction of C−C bonds using radical addition to imino acceptors[1,2] may be accomplished using a tether to transmit stereochemical information from a vicinal stereocenter (Figure 1). Previously, we exploited silyl ethers

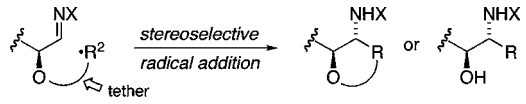

Figure 1. Use of a tether for stereocontrolled radical addition to C═N bonds.

as temporary tethers for this purpose in an approach to *anti*-1,2-amino alcohols.[3] The C−C bond is formed under neutral conditions without the complications associated with additions of basic organometallic reagents such as competing enolization.

The Ueno−Stork reaction (haloacetal radical cyclization) was first introduced by Ueno[4] for the functionalization of butyrolactones and by Stork[5] for the construction of bicyclic acetals and lactones in the early 1980s, and numerous synthetic applications have followed.[6] Despite the broad utility of the Ueno−Stork haloacetal cyclization for addition to alkenes, imine acceptors have rarely been used.[7]

† University of Iowa.
‡ University of Vermont.

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We envisioned application of 5- and 6-*exo* haloacetal cyclizations for direct access to aminosugars[8] (Figure 2). As a

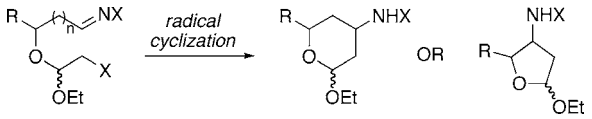


Figure 2. Potential access to aminopyranoside or aminofuranoside structures via haloacetal radical cyclization.

prelude to aminosugar synthesis, we initiated a study of the stereochemical outcome of these reactions with imino acceptors. Here we report haloacetal cyclizations of acyclic α- and *β*-hydroxyhydrazones and their stereochemical consequences.

The stereoselectivity of haloacetal radical cyclizations using acyclic precursors would be expected to be influenced heavily by the anomeric acetal stereogenic center. Interestingly, Renaud and co-workers showed that either relative configuration of bromoacetal **1** (Figure 3a) leads to the same

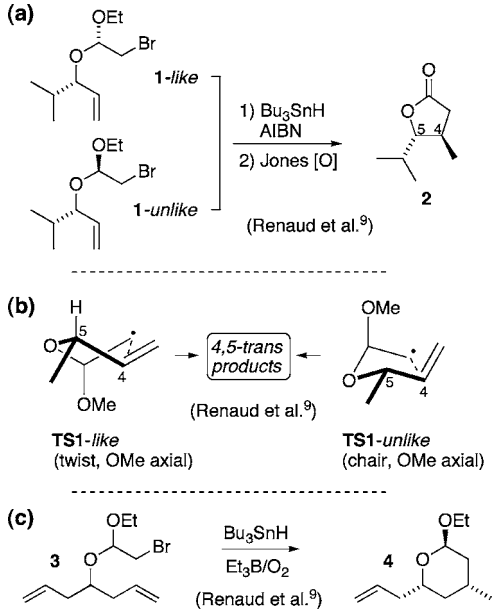
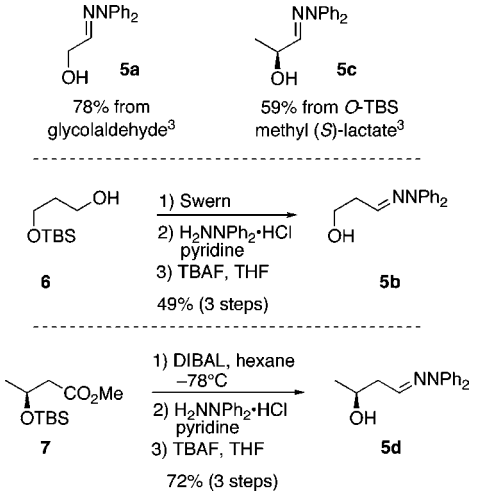


Figure 3. Anomeric effect on the stereochemistry of haloacetal radical cyclization.[9] (a) Stereoconvergence of **1**-*like* and **1**-*unlike*, inconsistent with the classical Beckwith−Houk model. (b) Calculated transition states (UHF/6-311G**) with axial alkoxy substituents, introducing a twist transition state for cyclization of **1**-*like*. (c) Product **4** suggests a similar anomeric effect in 6-*exo* cyclization.

4,5-*trans*-lactone **2** after radical cyclization and oxidation.[9] This apparent contradiction was resolved by calculations in collaboration with Schiesser, which found only transition states with axial anomeric alkoxy groups, e.g., **TS1**-*like* and **TS1**-*unlike* (Figure 3b). For cyclization of **1**-*like*, the twist transition state benefits from anomeric stabilization while avoiding 1,3-diaxial interactions of the corresponding chairlike transition state. Similarly, 6-*exo* cyclization of **3** via a chairlike transition state with OEt axial is consistent with exclusive formation of **4** (Figure 3c). These findings emphasize the important role of the anomeric effect in a refined Beckwith−Houk model.

First, several cyclization substrates were prepared. For 5-*exo* cyclization substrates, the α-hydroxyhydrazones **5a** and **5c** (Scheme 1) were obtained from glycolaldehyde and (*S*)-

Scheme 1. Access to α- and *β*-Hydroxyhydrazones



lactate, respectively, as previously described.[3] An achiral *β*-hydroxyhydrazone was obtained from monosilyl ether **6**[10] by Swern oxidation and condensation with diphenylhydrazine hydrochloride in pyridine (59% yield, two steps). Desilylation with tetrabutylammonium fluoride (TBAF) then provided **5b** in 76% yield.

Chiral *β*-hydroxyhydrazone **5d** was synthesized from methyl (*S*)-3-hydroxybutyrate (Scheme 1). Reduction of ester **7**[11] with DIBAL afforded the aldehyde, which was condensed with diphenylhydrazine to give the corresponding hydrazone

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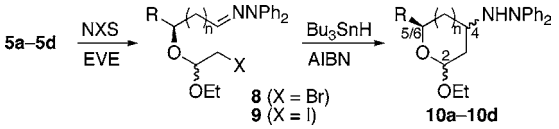
in 78% yield (two steps). Desilylation led to the corresponding β-hydroxyhydrazone **5d** in 92% yield.

The alcohols **5** were treated with either NBS or NIS and ethyl vinyl ether to give the cyclization substrates **8** or **9**, respectively, in yields ranging from 38 to 49% (Table 1).

Table 1. Haloacetal Radical Cyclizations of Hydrazones



hydroxy-hydrazone	R, X	haloacetal (yield)	cyclization (yield)	configurations[a] (product ratio)
5a ($n = 0$)	H, Br	**8a** (48%)	**10a** (69%)	cis:trans[b] (2:1)
5a ($n = 0$)	H, I	**9a** (47%)	**10a** (68%)	cis:trans[b] (2:1)
5b ($n = 1$)	H, Br	**8b** (44%)	**10b** (48%)	trans:cis (3:1)
5b ($n = 1$)	H, I	**9b** (38%)	**10b** (70%)	trans:cis (3:1)
5c ($n = 0$)	Me, Br	**8c** (36%)	**10c** (52%)	2α,4α:2β,4α (3:1)
5c ($n = 0$)	Me, I	**9c** (49%)	**10c** (64%)	2α,4α:2β,4α (3:1)
5d ($n = 1$)	Me, Br	**8d** (44%)	**10d** (47%)	2α,4β:2β,4α: 2β,4β (3:1:1)
5d ($n = 1$)	Me, I	**9d** (44%)	**10d** (41%)	2α,4β:2β,4α: 2β,4β (3:1:1)

[a] Assigned by ^{1}H NMR spectra (coupling constants for **10b** and **10d**, NOE difference for **10c**). [b] Assigned by analogy with that reported by Renaud et al.[9]

These were all obtained as inseparable 1:1 mixtures of diastereomeric acetals. Although the bromides appeared to be more stable during standard manipulations, they did not offer any improvement in yield. Still, adequate quantities were available to address our questions of stereocontrol.

Radical cyclizations of **8** and **9** were next examined (Table 1). Treatment of bromide **8a** with tributyltin hydride and AIBN in benzene (0.02 M) at reflux afforded **10a** in 69% yield (entry 1). The same reaction of iodide **9a** gave 68% yield (entry 2). Similarly, **8b** and **9b** were cyclized to afford **10b** in 48 and 70% yields, respectively.

Having demonstrated both 5- and 6-*exo* cyclization, we examined the diastereoselectivity of the process using chiral

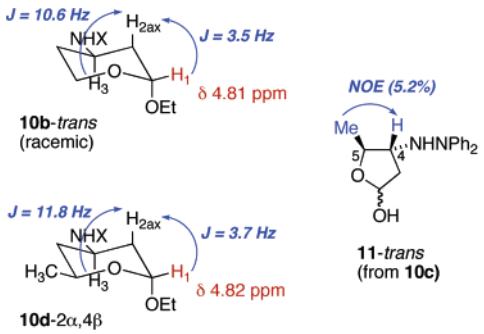


Figure 4. Selected diagnostic data for assignment of relative configurations of the major diastereomers of **10b**−**d**. Further data are provided in Supporting Information.

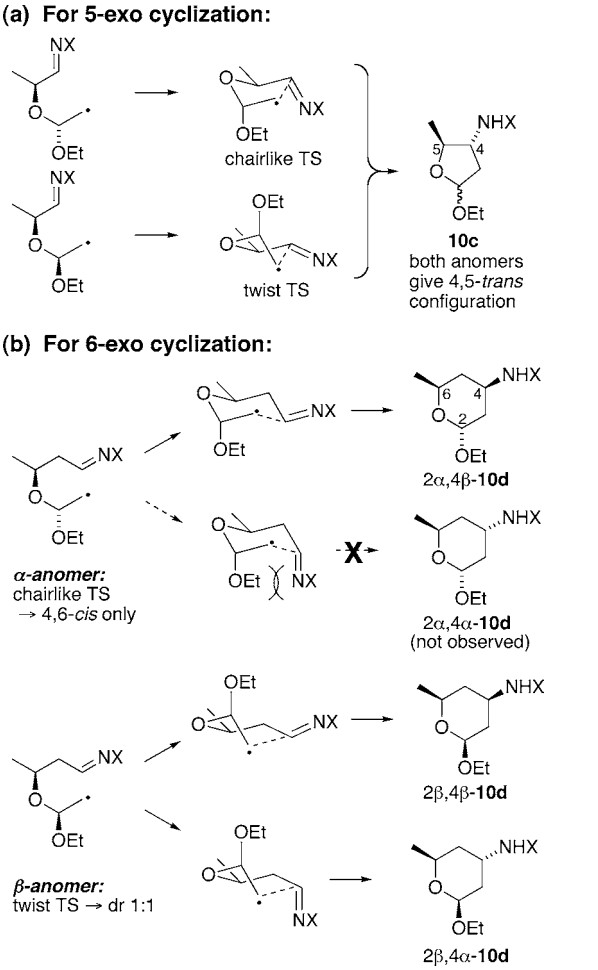


Figure 5. Proposed stereocontrol models for formation of **10c** and **10d** (X = NPh_2). (a) Alternative acetal configurations undergo 5-*exo* cyclization via chair or twist transition states to the same 4,5-trans relative configuration. (b) Alternative acetal configurations lead to matched (α-anomer) and mismatched (β-anomer) double diastereoselection in 6-*exo* cyclization. The α-anomer restricts the conformational freedom of the hydrazone through dipole repulsion between OEt and the imino nitrogen.

cyclization substrates derived from enantiomerically pure α-hydroxyhydrazones **5c** and **5d**. Upon 5-*exo* cyclization as described above, haloacetals **8c** and **9c** each gave the same mixture **10c**, consisting of two of the four possible diastereomers,[12] with the 2α,4α configuration favored (dr 3:1). The 6-*exo* cyclizations of **8d** and **9d** formed **10d** as three diastereomers (dr 3:1:1), of which the 2α,4β relative configuration was favored.

Relative configurations were determined by standard NMR methods. For the 5-*exo* cyclization product **10c**, the configuration was examined using the derived hemiacetal **11** (Figure 4), obtained as a mixture of diastereomers via acid-catalyzed hydrolysis (47% yield, dr 3:1). For the major diastereomer, a 5.2% NOE enhancement was found at the vicinal hydrogen upon irradiating the methyl group, diag-

(12) Formation of trace amounts of other diastereomers has not been excluded.

nostic for the trans relative configuration C4 and C5. In the 6-*exo* haloacetal cyclization, the relative configurations of the diastereomers of compounds **10b** and **10d** were determined through analysis of coupling constants (Figure 4).[13]

The stereocontrol in the cyclization reactions can be rationalized using the Renaud−Schiesser model incorporating twist transition states and the anomeric effect. For the 5-*exo* cyclizations leading to **10c**, both the chairlike and the twist transition states offer stabilization from the anomeric effect while minimizing steric repulsions, and both form the 4,5-trans relative configuration (Figure 5a). In the case of 6-*exo* cyclizations, the scenario is more complex because the α- and *β*-anomers (acetal diastereomers) do not converge to the same configuration at C4. The favored diastereomer (2α,4*β*-**10d**) has an acetal configuration different from both of the minor diastereomers. This shows that one acetal (2α) undergoes cyclization with complete selectivity (or there would be a fourth diastereomer found), while the other acetal (2*β*) is nonselective, giving a 1:1 mixture of products. The effects of the two stereocontrol elements are observed in matched and mismatched double diastereoselection.

The synthetic implications of the stereoselectivity bear further discussion. For the 5-*exo* cyclization sequence from **5c** to **10c**, the stereoconvergence renders the acetal configuration irrelevant for applications in which the acetal is ultimately oxidized or hydrolyzed. In contrast, to take full advantage of the excellent matched double diastereoselection available in 6-*exo* cyclization of **5d** to **10d**, a selective preparation of the 2α acetal configuration would be required.

Broader application will benefit from further optimization in two key aspects: First, the formation of haloacetals requires improved methodology; yields under these conditions were compromised by decomposition and incomplete mass balance.[14] Second, the method at present is limited to aldehyde hydrazones; a 6-*exo* radical cyclization of an acyclic ketone hydrazone was unsuccessful under these conditions, leading only to reductive dehalogenation.

In conclusion, 5-*exo* and 6-*exo* haloacetal radical cyclizations have been applied for the first time to aldehyde hydrazone acceptors. Analysis of the stereocontrol shows that the cyclizations are influenced by stereogenic centers in both the α- or *β*-hydroxyhydrazone precursor and the acetal.

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Supporting Information Available: General procedures and characterization data for **5b**, **5d**, and **8**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We speculate that oxidative processes involving the hydrazone may contribute to the incomplete mass balance.