Acyclic 1,4-Stereocontrol via Reductive 1,3-Transpositions

Wei Qi and Matthias C. McIntosh*

119 Chemistry Building, University of Arkansas, Fayetteville, Arkansas 72701 mcintosh@uark.edu

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ABSTRACT



One-pot reduction/allylic diazene rearrangement of lactic acid- and mandelic acid-derived α , β -unsaturated tosyl hydrazones leads to 1,4-*syn* or 1,4-*anti-E*-2-alkenyl arrays in high yield and diastereoselectivity. Either the *syn* or the *anti* diastereomer can be prepared by choosing the appropriate alkene stereoisomer of the hydrazone. The *E*-alkenes led to the 1,4-*syn* isomers, while the *Z*-alkenes led to the 1,4-*anti* isomers, both with \geq 20:1 diastereoselectivity.

The allylic diazene rearrangement (ADR) in its simplest form is the retro ene reaction of 1-diazo-2-propene to afford molecular nitrogen and propene (Scheme 1).¹ The ADR is



often encountered as the final step in the reductive 1,3transposition of α , β -unsaturated tosylhydrazones to the reduced alkenes.² More recently, the ADR has been employed in reductive Mitsunobu reactions,³ reductive alkylations,⁴ and in reductive transpositions of Diels–Alder adducts of 1-hydrazino dienes.^{5,6}

If the terminal carbon of the alkene of the allylic diazene is prochiral, a stereocenter can be installed via the ADR. Indeed, the ADR has been employed in a variety of cyclic systems to establish sp³ stereocenters.^{2,5,6} However, to our knowledge there have been no reports of the use of the reaction to install sp³ stereocenters in acyclic systems.

We envisioned that diastereoselective reduction of an α,β unsaturated tosylhydrazone could be achieved under the influence of an α -alkoxy stereocenter (Scheme 2). An unsaturated sulfonyl hydrazone containing an alkoxy group at the α -stereocenter might participate in either Felkin– Anh or Cram chelation-controlled reduction of the hydrazone imine. The suprafacial nature of the rearrangement, coupled with allylic strain-induced conformational constraints,^{4a,7} should result in diastereoselective transfer of

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the diazene hydrogen to one face of the prochiral alkene carbon.

Hydroxy and alkyl groups possessing 1,4-*syn* and/or 1,4*anti* relationships are encountered in a variety of biologically significant marine natural products, including amphidinolide J,⁸ reidispongiolide A,⁹ mycoticin,¹⁰ okadaic acid,¹¹ halichlorine,¹² pinnaic acid¹³ and many others. A diastereoselective acyclic reductive 1,3-transposition would greatly expand the utility of the reaction. We report herein the realization of this transformation in the generation of both 1,4-*syn* and 1,4-*anti* constructs.

A necessary first step of the proposed reductive transposition is the diastereoselective reduction of acyclic α -alkoxy sulfonyl hydrazones (Scheme 2). Although there was little precedent for this transformation,¹⁴ we were encouraged by a number of reports of diastereoselective reduction of acyclic α -hydroxy or α -alkoxy oximes using a variety of reducing agents.¹⁵

We chose to test the viability of the reductive transposition on lactic acid- and mandelic acid-derived substrates (Scheme 2, R₂ = Me or Ph). Siloxymethyl, siloxyethyl, and ethenyl were chosen as the R₄ substituents, since these groups would be useful in post-rearrangement manipulations that might be employed in natural product synthesis.

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Thus, tosyl hydrazone **1a** was prepared in four steps from (S)-(+)-lactic acid (Scheme 3).¹⁶ During optimization studies



on the reductive transposition, we found that a modification (addition of 2 weight equiv of silica gel) of the Kabalka conditions¹⁷ greatly accelerated the hydrazone reduction step. After addition of NaOAc and heating of the reaction mixture, the 1,4-*syn-E*-2-alkenyl product **2a** was isolated in high yield and diastereoselectivity (≥ 20 :1 dr based on ¹H NMR analysis).¹⁸ Importantly, Mosher ester analysis of a derivative of **2a** revealed that *no detectable racemization of the* α -*alkoxy stereocenter had occurred during the entire reaction sequence from* (*S*)-(+)-*lactic acid to* **2a**.¹⁶

The 1,4-*syn* adducts **2b** and **2c** were prepared in a directly analogous fashion (Figure 1). Each was isolated in very good



Figure 1. Reductive transposition products 2b-f.

yield and uniformly high level of isomeric purity (dr \ge 20: 1). Solely the *E*-alkene isomer was detected by ¹H NMR analysis.

The mandelic acid-derived hydrazones afforded equally high levels of diastereoselectivity in the reductive transposition to give adducts 2d-f (Figure 1). The er of adduct 2dwas identical to that of its Weinreb amide precursor,^{16,19} indicating that no detectable racemization of the alkoxybearing stereocenter had occurred in its conversion to 2d.

In order to access the corresponding 1,4-*anti* diastereomers, tosyl hydrazones **2g** and **2h** possessing Z-alkenes were

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(19) The er of the Weinreb amide leading to **2d** was 3:1.



prepared (Scheme 4). Although the stereoselectivity in the hydrazone formation step was not as high (70:30 and 65:35 E:Z, respectively), the *E*-hydrazone isomer could nevertheless be crystallized in isomerically pure form from the mixture.

Gratifyingly, treatment of hydrazones **1g** and **1h** under the same conditions as before yielded the 1,4-*anti-E*-2-alkenyl diastereomers **2g** and **2h** in good yield and $\geq 20:1$ dr. As with **2a**-**f**, only the *E*-alkene isomer was detected by ¹H NMR analysis.

The reductive transposition described herein has several features that recommend its use: (i) the ready accessibility of the α -alkoxy tosylhydrazone precursors,¹⁶ (ii) the mild reaction conditions for effecting the transformation, and (iii) the ability to prepare either the 1,4-*syn* or 1,4-*anti* diastereomers.

This method described herein is complementary to other methods used for acyclic 1,4-stereocontrol, such as the Claisen²⁰ and 2,3-Wittig²¹ rearrangements, and the S_N2' reactions of organometals.²² Our own applications to complex molecule synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, ¹H- and ¹³C NMR spectra of compounds **1a**-**h** and **2a**-**h**, X-ray crystal structure data of the hydrazone leading to **2f**, Mosher ester analyses of **2a**,d. This material is available free of charge via the Internet at http://pubs.acs.org.

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