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

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Abstract

One-pot reduction/allylic diazene rearrangement of lactic 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 1,3-transposition 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 sp^3 stereocenters.^{2,5,6} However, to our knowledge there have been no reports of the use of the reaction to install sp^3 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 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 reidispungiolide A,⁹ mycoticin,¹⁰ okadaic acid,¹¹ halichlorine,¹² pinnaic acid¹³ and many

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Supporting Information Available: Experimental procedures, characterization data, ^1H - and ^{13}C -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>.

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 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.

Thus, tosyl hydrazone **1a** was prepared in 4 steps from (*S*)-(+)-lactic acid (Scheme 3).¹⁶ During optimization studies on the reductive transposition, we found that a modification (addition of 2 weight eq 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 ($\geq 20:1$ *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 yield and uniformly high level of isomeric purity (*dr* $\geq 20:1$). 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 **2d** was identical to that of its Weinreb amide precursor,^{16,19} indicating that no detectable racemization of the alkoxy-bearing 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 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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Figure 1.
Reductive Transposition Products **2b–f**

Scheme 1.
The Allylic Diazene Rearrangement

Scheme 2.
Acyclic Diastereoselective Reductive Transposition

Scheme 3.
Reductive Transposition of Hydrazone **1a**

Scheme 4.
Preparation of 1,4-anti Adducts **2g,h**.