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 ≥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). The ADR is often encountered as the final step in the reductive 1,3-transposition of α,β-unsaturated tosylhydrazones to the reduced alkenes. More recently, the ADR has been employed in reductive Mitsunobu reactions, reductive alkylations, and in reductive transpositions of Diels-Alder adducts of 1-hydrazino dienes.

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. 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, 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, reidispongiolide A, mycoticin, okadaic acid, halichlorine, pinnaic acid, and many

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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.
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, 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.

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). During optimization studies on the reductive transposition, we found that a modification (addition of 2 weight eq of silica gel) of the Kabalka conditions 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). 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.

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 ≥ 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, 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 ≥ 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; (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 Claisen rearrangements, and the S₂N₂’ reactions of organometals. Our own applications to complex molecule synthesis will be reported in due course.
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References


16. See Supporting Information.


18. The 1,4-cis configuration of 2a was confirmed by its conversion to the known cis-2-methyl-5-hexanolide (see Supporting Information).

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


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 $2_g, h$.

$1_g \ n = 1$
$1_h \ n = 2$

$2_g, 85%$
$2_h, 80%$