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

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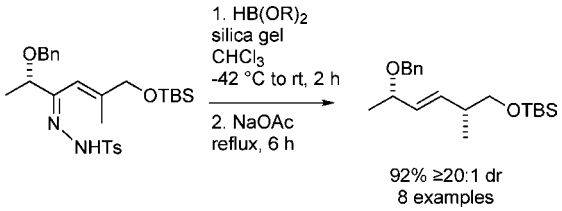
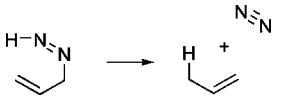
ABSTRACT



One-pot reduction/allylic diazene rearrangement of lactic 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 ≥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]

Scheme 1. Allylic Diazene Rearrangement



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

(1) Bumgardner, C. L.; Freeman, J. P. *J. Am. Chem. Soc*. **1964**, *86*, 2233; Jabbari, A.; Sorensen, E. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 3105.

(2) For representative examples, see: Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923; Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501; Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935; Silvestri, M. G.; Bednarski, P. J.; Kho, E. *J. Org. Chem.* **1985**, *50*, 2798; Steinmeyer, A.; Neef, G. *Tetrahedron Lett.* **1992**, *33*, 4879; Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009; Tanaka, T.; Maeda, K.; Mikamiyama, H.; Funakoshi, Y.; Uenaka, K.; Iwata, C. *Tetrahedron* **1996**, *52*, 4257; Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305; Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59; Hutchison, J. M.; Lindsay, H. A.; Dormi, S. S.; Jones, G. D.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2006**, *8*, 3663; Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838. For a review, see: Ripoll, J.-L.; Vallée, Y. *Synthesis* **1993**, 659.

(3) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841. (c) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572.

(4) (a) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208. (b) Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891.

(5) Sammis, G. M.; Flamme, E. M.; Xie, H.; Ho, D. M.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8612.

(6) See also: Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898.

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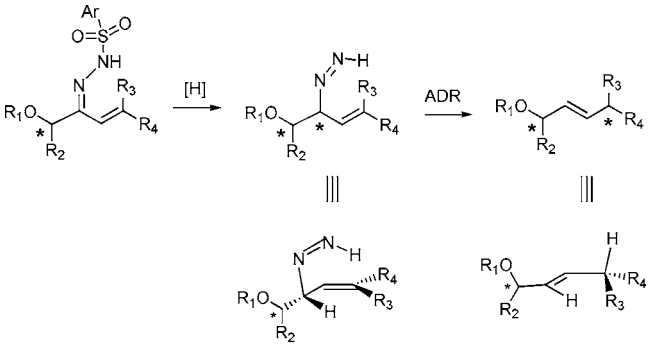
Scheme 2. Acyclic Diastereoselective Reductive Transposition



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 acid[13] 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, R_2 = Me or Ph). Siloxymethyl, siloxyethyl, and ethenyl were chosen as the R_4 substituents, since these groups would be useful in post-rearrangement manipulations that might be employed in natural product synthesis.

(7) For reviews of allylic strain directed reactions, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841; Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(8) Kobayashi, J.; Sato, Ishibashi, M. *J. Org. Chem.* **1993**, *58*, 2645.

(9) D'Auria, M. V.; Gomez-Paloma, L.; Minale, L.; Zampella, A.; Verbist, J.-F.; Roussakis, C.; Dibitus, C.; Patissou, J. *Tetrahedron* **1994**, *50*, 4829.

(10) Wasserman, H. H.; Van Verth, J. E.; McCaustland, D. J.; Borowitz, I. J.; Kamber, B. *J. Am. Chem. Soc.* **1967**, *89*, 1535.

(11) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469.

(12) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.

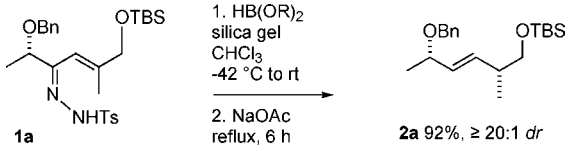
(13) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.

(14) Goma, Yuki; Matsumoto, Yoichi. *Reduction of optically active imines*. Jpn. Kokai Tokkyo Koho 2001064244, 2001.

(15) Iida, H.; Yamazaki, N.; Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1040; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1987**, 746; Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415; Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271; Uneyama, K.; Hao, J.; Amii, H. *Tetrahedron Lett.* **1998**, *39*, 4079; Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265; Boukhris, S.; Souizi, A. *Tetrahedron Lett.* **1999**, *40*, 1669; Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893.

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

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



on the reductive transposition, we found that a modification (addition of 2 weight equiv of silica gel) of the Kabalka conditions[17] 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 ^{1}H 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

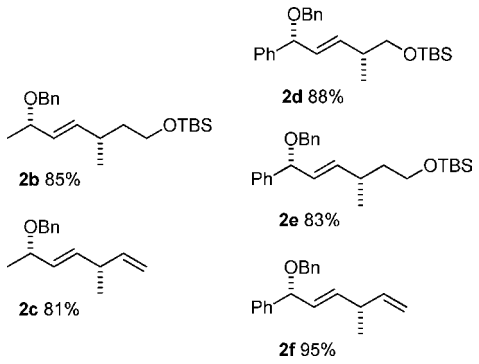


Figure 1. Reductive transposition products **2b**−**f**.

yield and uniformly high level of isomeric purity (dr ≥ 20:1). Solely the *E*-alkene isomer was detected by ^{1}H 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

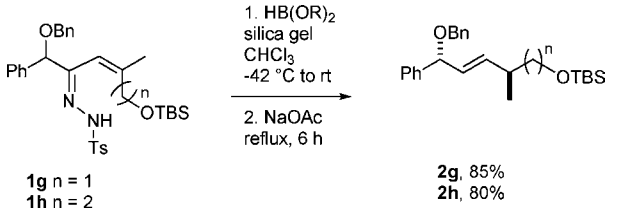
(16) See Supporting Information.

(17) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574.

(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.

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



1g n = 1
1h n = 2

2g, 85%
2h, 80%

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 ^{1}H 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 Claisen[20] and 2,3-Wittig[21] 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, ^{1}H- 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.

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(20) See, for example: Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103; Kim, D.; Shin, K. J.; Kim, I. Y.; Park, S. W. *Tetrahedron Lett.* **1994**, *35*, 7957. For reviews, see: Hiersemann, M., Nubbemeyer, U., Eds. *The Claisen Rearrangement: Methods and Applications*; Wiley-VCH: Weinheim, 2007.

(21) For a review, see: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(22) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864; Ibuka, T.; Nakai, K.; Habashita, H.; Bessho, K.; Fujii, N. *Tetrahedron* **1993**, *49*, 9479.