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Sulfoxide-Directed Enantioselective Synthesis of Functionalized Dihydropyrans

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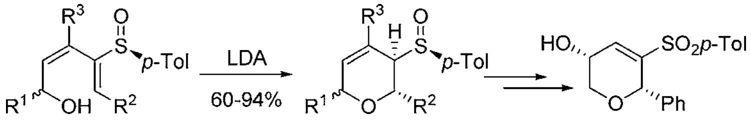
ABSTRACT



The highly selective base-promoted cyclization of enantiopure sulfinyl dienols affords allylic sulfinyl dihydropyrans.

Functionalized dihydro- and tetrahydropyrans are common constituents of bioactive natural products,[1] and this has led to the development of a number of synthetic approaches to these targets.[2] Several years ago we observed that vinyl oxiranes **A** (Scheme 1) displayed an undesired S_N2' reactivity with complex secondary alcohols present in the reaction media to produce adducts **B** with high selectivity.[3] In connection with our interest in the design of sulfoxide-based synthetic procedures, especially those that allow for multiple chirality-transfer operations,[4] and with our involvement in the synthesis of functionalized tetrahydrofurans,[5] we envisioned that an intramolecular variant of this process entailing the cyclization of *cis*-hydroxy oxiranes **D** to hydroxy dihydropyrans **F** could be a viable process. If successful, we perceived that dihydropyrans **F** had a useful array of functionality for synthetic purposes either at sulfoxide or sulfone oxidation states.[6]

Alternatively, dienyl sulfoxides **C** were also identified as suitable precursors of dihydropyrans **E** with a stereochemically labile allylic sulfoxide functionality, upon treatment with base.[7,8] Dienols **C** are available by Stille couplings

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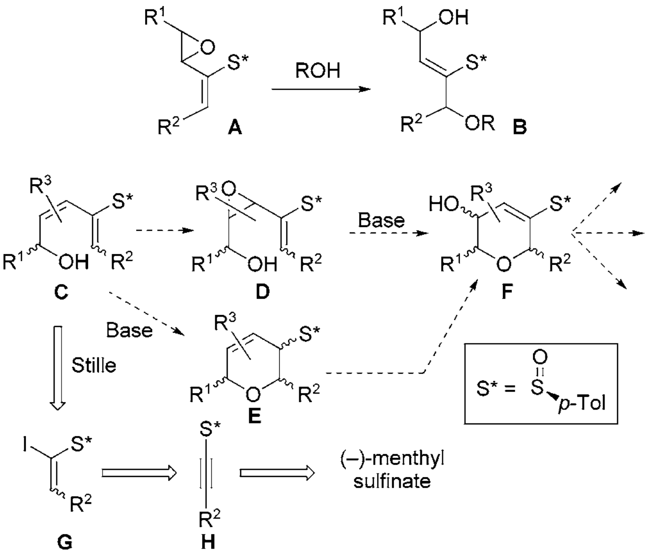
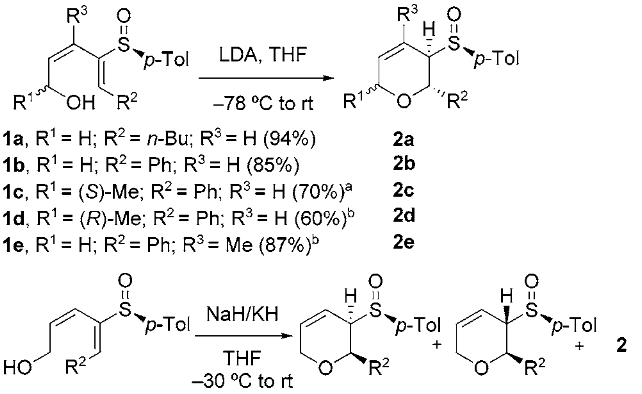
between vinyl stannanes and stereodefined iodo alkenyl sulfoxides **G**, which are prepared from alkynyl sulfoxides **H** by stereocontrolled hydrostannylation and tin−halogen exchange.[9] In this report we describe our preliminary studies on the efficient base-induced cyclization of hydroxy dienyl sulfoxides **C** to produce good to excellent yields of allylic sulfoxides **E**. In addition, we have outlined a simple protocol for producing enantiopure sulfones related to **F** from intermediates **E** and we have sketched some exploratory experiments on the reactivity of these compounds.

Scheme 1. Proposed Sulfinyl-Mediated Synthesis of Dihydropyrans



Scheme 2. Base-Induced Synthesis of Sulfinyl Dihydropyrans



1a, R^1 = H; R^2 = *n*-Bu; R^3 = H (94%)	**2a**
1b, R^1 = H; R^2 = Ph; R^3 = H (85%)	**2b**
1c, R^1 = (*S*)-Me; R^2 = Ph; R^3 = H (70%)[a]	**2c**
1d, R^1 = (*R*)-Me; R^2 = Ph; R^3 = H (60%)[b]	**2d**
1e, R^1 = H; R^2 = Ph; R^3 = Me (87%)[b]	**2e**

3a, R^2 = *n*-Bu (NaH, 65%)	**4a** (96)	–	**2a** (4)
3b, R^2 = Ph (KH, 67%)[c]	–	**5b**	**2b** (traces)

[a] An additional 17% vinyl sulfoxide was obtained. [b] Diastereomerization at sulfur took place upon standing in solution (70:30 and 50:50 mixture for **2d** and **2e**, respectively). [c] An additional 12% vinyl sulfoxide was obtained.

Scheme 2 gathers our preliminary results on this chemistry. Substrate **1a** was chosen as a representative example to pursue the monoepoxidation to produce the desired vinyl oxirane related to **D**. After considerable experimentation with fruitless results, we chose to examine the cyclization of dienol **1a**. Optimal results were obtained with LDA to produce an excellent yield of allylic sulfoxide **2a** as a single isomer.[9] Phenyl-substituted diene **1b** behaved similarly, affording dihydropyran **2b**. The influence of an additional stereocenter in the dienol was then addressed, and while **1c** underwent a smooth cyclization to yield **2c**, along with a small amount of an isomeric vinyl sulfoxide, diastereomer **1d** gave a slightly lower yield of the expected product **2d** as practically a single isomer that underwent diastereomerization at sulfur upon standing in solution. This protocol was also found to be compatible with additional substitution on the double bond with methyl-substituted substrate **1e** leading to an excellent yield of **2e** that isomerized at sulfur upon standing in solution.

In contrast with the above results, *E*,*Z* substrates **3a** and **3b** were found to be less reactive and slightly less selective. Thus, optimal conditions involved the use of NaH for **3a** and KH for **3b** and small amounts of **2a** and **2b** could be detected in the ^{1}H NMR of the crude reaction mixtures. In addition, the main products in these cases, **4a** and **5b**, had different stereochemistry at C-2 and C-3. Indeed, while **4a** was a 2,3-*cis* isomer, **5b** was a 2,3-*trans* isomer.[10]

Scheme 3 gathers a range of results that illustrate some aspects of the reactivity of these allylic sulfoxides, namely, their sigmatropic rearrangements to allylic alcohols and their oxidation to produce enantiopure allylic sulfones, versatile synthetic intermediates.[11] It should be noted that diastereomeric sulfoxides **2b** and **5b** displayed remarkable differences in the rate and yield of their sigmatropic rearrangements,

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(7) For synthetic applications of allylic sulfoxides, see: (a) Hua, D. H.; Venkataraman, S.; Chan-Yu-King, R.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741−4748 and previous papers by this group. (b) Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423−5433 and previous papers by this group. (c) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147−155.

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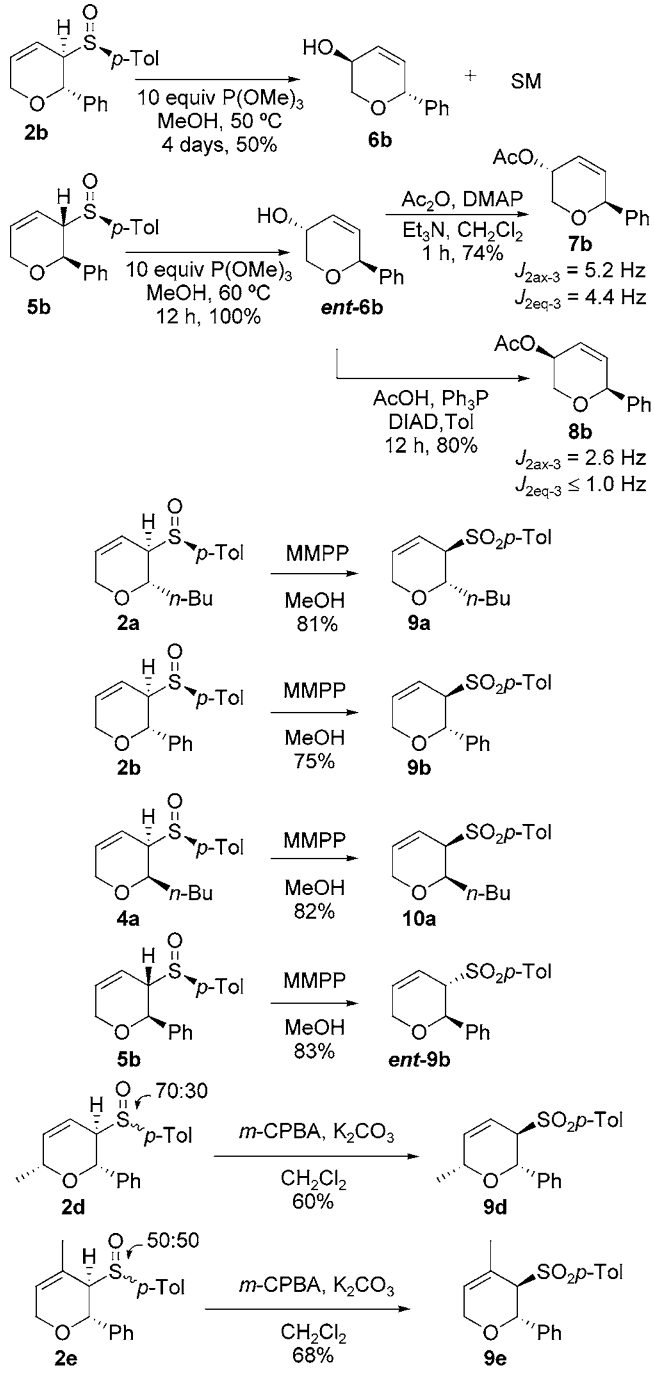
(9) All new products were fully characterized by standard techniques. The optical purity and absolute stereochemistry of the final products were established by detailed ^{1}H NMR analysis of the methoxy phenyl acetate of hydroxy oxirane **16**. The stereochemistry of dihydropyranyl sulfoxides and sulfones was established by detailed ^{1}H NMR analysis (see Supporting Information). For the synthesis of dienols, see: Paley, R. S.; de Dios, A.; Estroff, L. A.; Lafontaine, J. A.; Montero, C.; McCulley, D. J.; Rubio, M. B.; Ventura, M. P.; Weers, H. L.; Fernández de la Pradilla, R.; Castro, S.; Dorado, R.; Morente, M. *J. Org. Chem.* **1997**, *62*, 6326−6343. The *Z* vinyl stannanes were prepared from the appropriate propargyl alcohols in one step as described in: Havranek, M.; Dvorak, D. *Synthesis* **1998**, 1264−1268.

(10) This cyclization presumably entails nucleophilic attack on the α face of dienols **1** and **3**, consistent with literature knowledge (ref 8), followed by protonation of the intermediate metalated allylic sulfoxide with retention, in most cases. The 2,3-trans stereochemistry found for **5b** is tentatively attributed to steric hindrance between the bulky phenyl and sulfinyl substituents.

(11) For reviews, see: (a) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107−124. (b) Pyne, S. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21b, p 2068.

Scheme 3. Structural Assignments: Sigmatropic Rearrangements and Oxidations

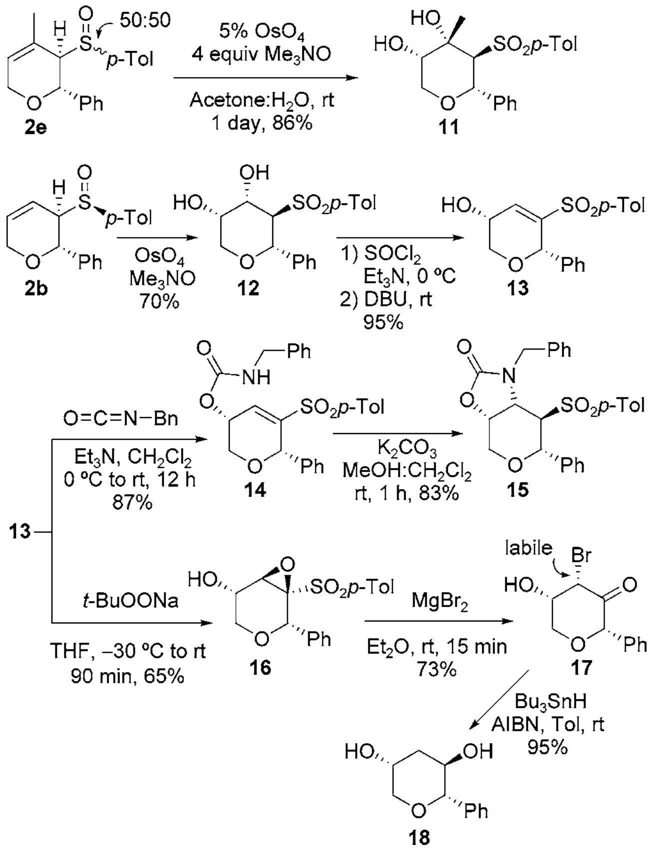


giving rise to allylic alcohols **6b** and ***ent*-6b**.[12] The spectral features of **6b** did not allow for a conclusive stereochemical assignment, and therefore a comparison was made for acetates **7b**, obtained by acetylation of ***ent*-6b**, and **8b**, derived from Mitsunobu inversion of ***ent*-6b**.[13]

The oxidation of several substrates under standard conditions gave additional support to the stereochemical assignments carried out at the sulfoxide stage. Thus, while **2a** and **4a** gave diastereomeric allylic sulfones **9a** and **10a**, respectively, **2b** and **5b** led to enantiomeric products. Finally, oxidation of diastereomeric mixtures of **2d** and **2e** gave single isomers of sulfones **9d** and **9e**, respectively.

At this stage we focused our efforts on carrying out exploratory experiments on the reactivity of our sulfinyl dihydropyrans to gain insight on the design of synthetic applications of the methodology. The dihydroxylation of diastereomeric mixtures of sulfoxides **2e** gave an excellent yield of sulfonyl diol **11** (Scheme 4).

Scheme 4. Survey of Synthetic Applications of Sulfinyl Dihydropyrans



Encouraged by this result, we examined in detail the dihydroxylation of model substrate **2b** that led to a good yield of diol **12** as a single isomer,[14] that was transformed smoothly to hydroxy vinyl sulfone **13**, structurally related to our initial objective **F** (Scheme 1).[15] The functionality in **13** allowed for straightforward formation of carbamate **14**, which cyclized to oxazolidinone **15** in excellent yield.[16] It

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[12] For alternative routes to related compounds, see: (a) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013−2015. (b) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, *4*, 293−295. (c) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2003**, *5*, 2173−2176.

[13] For reviews, see: (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335−668. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127−164.

[14] All attempts to obtain the related sulfinyl diol using OsO_4 under controlled conditions led to mixtures of starting material, allylic sulfone, sulfinyl diol, and sulfonyl diol **12**.

[15] Rayner, C. M.; Westwell, A. D.; Thornton-Pett, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 847−859.

[16] Hirama, M.; Hioki, H.; Ito, S.; Kabuto, C. *Tetrahedron Lett.* **1988**, *29*, 3121−3124.

should be mentioned that, aside from the sulfone-bearing center, the relative stereochemistry of **15** is enantiomeric to that found in the neurotoxin Dysiherbaine.[17] Finally, the nucleophilic epoxidation of **13** gave sulfonyl oxirane **16** as a single isomer that underwent oxirane cleavage, with $MgBr_2$,[18] to produce bromo pyranone **17** initially as a single isomer that underwent rapid epimerization at the bromine-substituted center. Treatment of this mixture with Bu_3SnH/AIBN unexpectedly resulted in not just removal of bromine but also rapid and stereoselective carbonyl reduction to afford diol **18** as a single isomer in excellent yield.

In conclusion, the first examples of the base-promoted intramolecular cyclization of 2-sulfinyl dienols to afford sulfinyl dihydropyrans have been described. This strategy allows for creation of two asymmetric centers within a synthetically useful dihydropyran framework in an expedient manner.[19] The configurational stability of the allylic sulfoxide in most cases is noteworthy. We are currently exploring the scope, limitations, and synthetic applications of the methodology.

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Supporting Information Available: Experimental procedures and characterization for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Isolation: (a) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112−4116. Syntheses: (b) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638. (c) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216−5217. (d) Sasaki, M.; Koike, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 3923−3926. (e) Phillips, D.; Chamberlin, A. R. *J. Org. Chem.* **2002**, *67*, 3194−3201. (f) Kang, S. H.; Lee, Y. M. *Synlett* **2003**, 993−994.

[18] de Reinach-Hirtzbach, F.; Durst, T. *Tetrahedron Lett.* **1976**, 3677−3680. For a recent application, see: Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789−1797.

[19] Enantiopure propargyl alcohols, precursors to the required stannanes (ref 9), are readily available. See: El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020 and previous papers by this group. This suggests that our methodology should be broadly applicable.