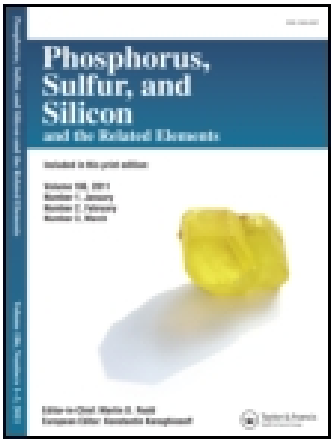

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Base-Induced Enantioselective Synthesis of Sulfinyl Dihydropyrans

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Base-Induced Enantioselective Synthesis of Sulfinyl Dihydropyrans

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2-Sulfinyl dienols undergo an efficient base-promoted cyclization to produce sulfinyl dihydropyrans with creation of two asymmetric centers. The configurational stability of the allylic sulfoxide in most cases is noteworthy. Simple manipulations lead to a variety of functionalized tetrahydropyrans.

Keywords Allylic sulfoxides; asymmetric synthesis; dihydropyrans; tetrahydropyrans

INTRODUCTION

Substituted dihydro- and tetrahydropyrans are common structural elements in natural products that possess important therapeutic properties, and this had led to the development of a number of synthetic approaches to these targets. Cationic, anionic, and radical cyclizations, hetero-Diels–Alder cycloaddition, ring-closing metathesis, and addition of organometallic reagents to glycals are frequently used strategies for the synthesis of these heterocycles.[1] Although many of them allow for the creation of the pyran skeleton in a stereocontrolled manner, a general approach that includes a variety of substitution patterns is still a challenge for organic chemists.

In recent years we have been engaged in the development of synthetic procedures involving vinyl sulfoxides, especially those that allow for subsequent sulfur-based chirality transfer operations.[2] In connection with our involvement in the synthesis of functionalized tetrahydrofurans,[3] we envisioned that a base-promoted cyclization of

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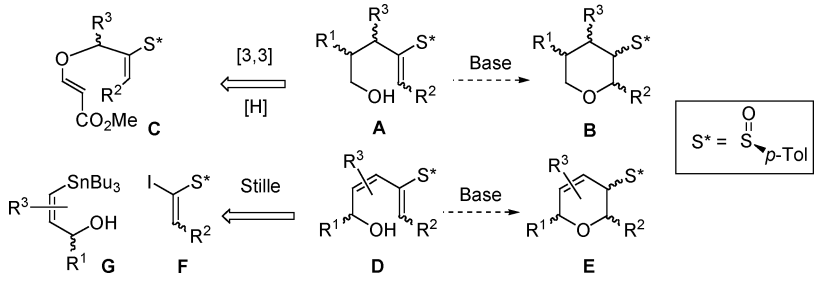
hydroxy dienyl and vinyl sulfoxides would be a viable entry to dihydro- and tetrahydropyrans (Scheme 1).



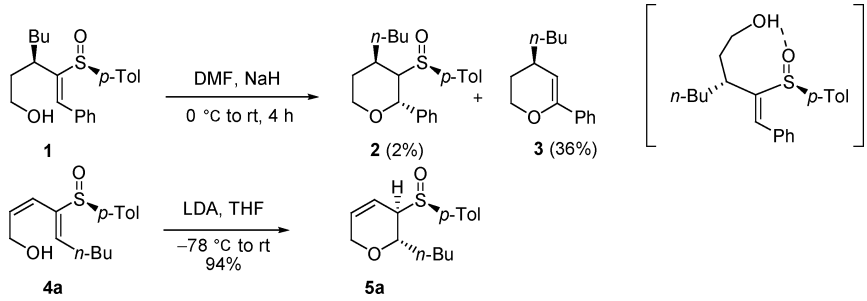
SCHEME 1 Proposed base-induced cyclization of hydroxy vinyl sulfoxides.

This approach would involve the stereocontrolled synthesis of compounds of general structure **A** and **D**, easily accessible by methodologies previously reported in our group. Substrates **A** could be prepared by sigmatropic rearrangement of sulfinyl acrylates **C**[4] with subsequent reduction and substrates **D** by Stille coupling of the corresponding iodo alkenyl sulfoxides.[5] Considering the scope of both methodologies, this strategy, if successful, would be a general method for the synthesis of dihydro- and tetrahydropyrans with a regio- and stereodefined substitution pattern and a useful array of functionality for synthetic purposes either at sulfoxide or sulfone states.[6]

RESULTS AND DISCUSSION

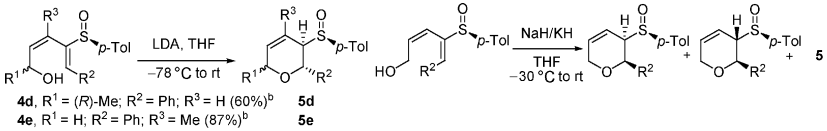
We chose substrates **1** and **4a** as representative examples to test the base-promoted cyclization (Scheme 2). The treatment of **1** with different bases (LDA, NaH) in THF did not result in any cyclization and only unreacted starting material was recovered. We thought that the low reactivity of **1** was due to a coordination of the hydrogen of the hydroxyl group and the sulfinylic oxygen. Indeed, when we changed to a more polar solvent such as DMF, the cyclization took place but elimination of the sulfinyl group could not be avoided under these conditions.

At this point we decided to examine the cyclization of dienol **4a**, hoping that the presence of a cis double bond would avoid the problems found with **1**. To our delight, optimal results were obtained with LDA to produce an excellent yield of allylic sulfoxide **5a** as a single isomer.[7] To test the scope of the methodology, we synthesized dienols **4b–e** with a different substitution pattern (Scheme 3). Diene **4b**, with a phenyl substituent, behaved similarly, affording dihydropyran **5b**. Substrates with an additional sterocenter were then examined and while **4c**



SCHEME 2 Base-promoted cyclization of hydroxy dienyl and vinyl sulfoxides.

underwent a smooth cyclization to yield **5c**, along with a small amount of an isomeric vinyl sulfoxide, diastereomer **4d** gave a slightly lower yield of the expected product **5d** 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 **4e** leading to an excellent yield of **5e** that isomerized at sulfur upon standing in solution.

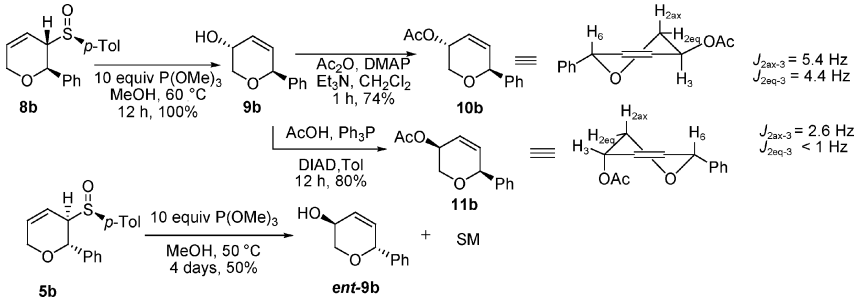


SCHEME 3 Synthesis of sulfinyl dihydropyrans.

The influence of the geometry of the vinyl sulfoxide moiety was then addressed with dienols **6a** and **6b**. In contrast with their *Z* isomers, NaH or KH was needed and small amounts of **5a** and **5b** could be detected in the ^{1}H NMR of the crude reaction mixtures. This cyclization presumably entails nucleophilic attack on the α face of dienols **4** and **6**, followed by protonation of the intermediate metalated allylic sulfoxide with retention, in most cases. The 2,3-trans stereochemistry found for **8b** is tentatively attributed to steric hindrance between the bulky phenyl group and sulfinyl substituents.

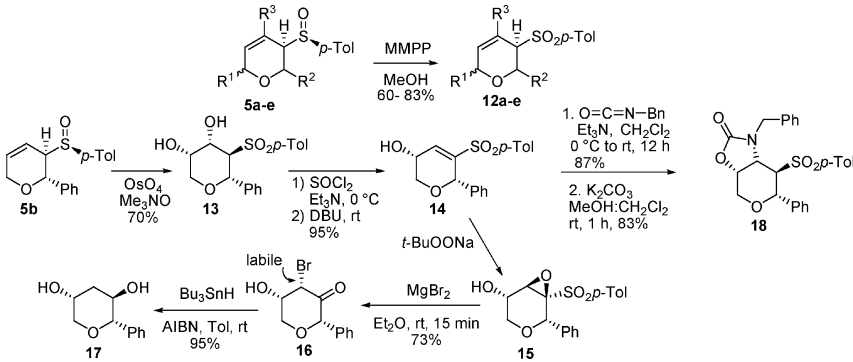
Scheme 4 illustrates some aspects of the reactivity of these allylic sulfoxides that allowed us to establish the relative cis-trans stereochemistry at C-2 and C-3 in dyhydropyrans **5b** and **8b** from the sulfoxide-sulfenate adduct **9b**. The relative stereochemistry of this adduct was established by synthesis of the acetate **10b** and the corresponding Mitsunobu-inversion product **11b** and comparison of their spectral features. The coupling constants between H_3-H_{2eq} and H_3-H_{2ax} establish a pseudoaxial arrangement for H_3 in **10b** (J_{3-2ax} = 5.1 Hz,

$J_{3-2eq} = 4.4$ Hz) and a pseudoequatorial arrangement for H_3 in **11b** ($J_{3-2ax} = 2.6$ Hz, $J_{3-2eq} < 1$ Hz).



SCHEME 4 Structural assignments: sigmatropic rearrangements.

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 (Scheme 5). The oxidation of several substrates under standard conditions yielded enantiopure allylic sulfones, versatile synthetic intermediates, and gave additional support to the stereochemical assignments carried out at the sulfoxide stage.



SCHEME 5 Synthetic applications.

Then we examined in detail the dihydroxylation of model substrate **5b** that led to a good yield of diol **13** as a single isomer. Diol **13** was transformed smoothly to hydroxy vinyl sulfone **14** that, under nucleophilic epoxidation conditions, gave sulfonyl oxirane **15** as a single isomer. The reaction of **15** with $MgBr_2$ produced bromo pyranone **16** 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 **17** as a single isomer in excellent yield. Finally the functionality in **14** allowed for straightforward formation of a carbamate that cyclized to oxazolidinone **18** in excellent yield. It should be mentioned that, aside from the sulfone-bearing center, the relative stereochemistry of **19** is enantiomeric to that found in the neurotoxin Dysiherbaine.

In conclusion, a new approach to substituted dihydro- and tetrahydropyrans has been described. The base-promoted intramolecular cyclization of 2-sulfinyl dienols affords sulfinyl dihydropyrans with the creation of two asymmetric centers in an expedient manner. The configurational stability of the allylic sulfoxide in most cases is noteworthy. In addition the base-promoted cyclization of 1-hydroxy-4-vinyl sulfoxides has been outlined. We are currently exploring the scope, limitations, and synthetic applications of both methodologies.

EXPERIMENTAL PROCEDURE

Synthesis of (−)-(2*S*,3*R*,R_S)-2-*n*-butyl-3-(*p*-tolylsulfinyl)-3,6-dihydro-2*H*-pyran, 5a

To a solution of the dienyl sulfoxide **4a** (20 mg, 0.070 mmol) in THF (10 mL/mmol of sulfoxide), at −78°C, under an argon atmosphere, was added 1.1 equiv of a freshly prepared 0.5 M LDA solution (0.15 mL, 0.077 mmol) in THF. The mixture was allowed to warm to room temperature (rt), monitored by TLC until completion (4 h), and quenched with a saturated solution of NH_4Cl and water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous $MgSO_4$, and filtered. Purification by chromatography (10–50% EtOAc-hexane) afforded 18 mg (0.066 mmol, 94%) of **5a** as a colorless oil.

Data for **5a**: R_f = 0.34 (50% EtOAc-hexane). $[\alpha]_D^{20} = -218.8$ (c = 0.75). **^{1}H NMR (300 MHz)-COSY** δ 0.88 (t, 3 H, J = 7.1 Hz, Me-*n*-Bu), 1.25–1.54 (m, 5 H), 1.74 (m, 1 H), 2.39 (s, 3 H, Me-*p*-Tol), 3.07 (m, 1 H, H-3), 4.09 (m, 2 H, H-6), 4.32 (dm, 1 H, J = 9.5 Hz, H-2), 5.14 (ddd, 1 H, J = 10.2, 4.9, 2.5 Hz, H-4), 5.95 (dtd, 1 H, J = 10.2, 2.5, 1.0 Hz, H-5), 7.29 (d, 2 H, J = 7.8 Hz, *p*-Tol), 7.53 (d, 2 H, J = 8.3 Hz, *p*-Tol). **^{13}C NMR (50 MHz)-HSQC** δ 14.0 (Me-*n*-Bu), 21.5 (Me-*p*-Tol), 22.5, 27.9, 30.7, 60.8 (C-6), 66.1 (C-3), 69.9 (C-2), 116.6 (C-4), 125.5 (2 C), 129.7 (2 C), 132.6 (C-5), 138.9, 142.0. **IR** (film): 3038, 2932, 2857, 1651, 1596, 1493, 1462, 1380, 1302, 1210, 1182, 1082, 1037, 1016, 812 cm^{-1}. **MS** (ES): 579 $[2M + Na]^+$, 301 $[M + Na]^+$, 279 $[M + 1]^+$ (100%).

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