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Hydroxyl-Directed Stereoselective [2,3] Sigmatropic Rearrangement of γ-Hydroxyalkyl γ-Alkoxyallylic Sulfoxides

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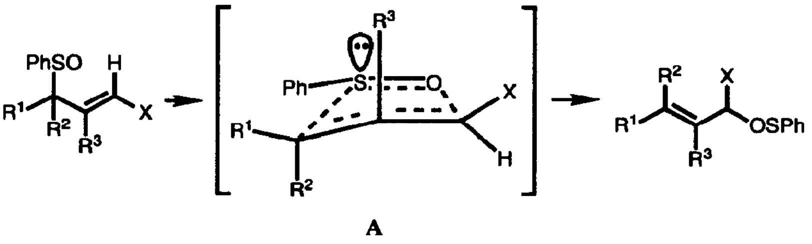
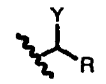
Abstract: *The [2,3] sigmatropic rearrangement of γ-hydroxyalkyl γ-methoxyallyl sulfoxides occurs in a highly stereoselective manner to give δ-hydroxy-(E)-enals; a novel mechanism involving interaction between the hydroxy oxygen and the sulfinyl sulfur is proposed.*

Previously we disclosed that [2,3] sigmatropic rearrangement of allylic sulfoxides (Mislow-Evans rearrangement) took place with an extremely high *E* preference when an alkyl group branched at the β-position of a sulfinyl group was involved (Scheme 1).[1] This, for the first time, provided conclusive evidence for the steric effect of the alkyl groups situated α to the sulfinyl group that had been postulated for long time:[2] a bulkier group R^1 occupies a pseudoequatorial position in a five-membered cyclic transition state [A].

Scheme 1



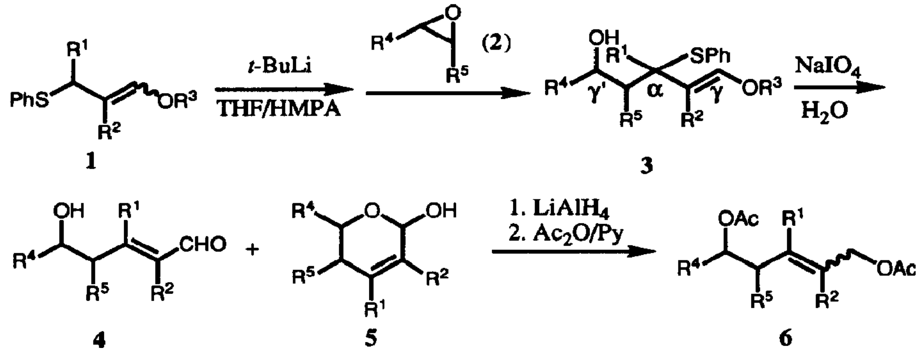
$R^1 =$ 

Y = alkyl, hydroxyl, alkoxyl

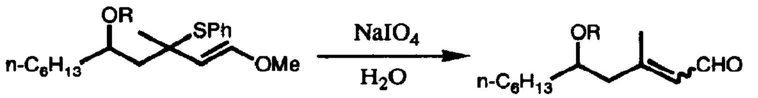
$R^2, R^3 =$ alkyl, H   X = H, alkoxyl

The continuing study has led us to an unexpected finding that a hydroxy group at the γ-position also induces the high *E* selectivity in the Mislow-Evans rearrangement of γ-alkoxyallyl sulfoxides. Treatment of γ-alkoxyallyl sulfides **1** to *t*-BuLi followed by oxirane **2** (1.5 equiv.) afforded smoothly hydroxy γ-alkoxyallyl sulfides **3** in 80-95% yields (Scheme 2).[3] Exposure of **3** to $NaIO_4$ in dioxane-H_2O (5:1) at room temperature furnished (*E*)-δ-hydroxy enals **4** exclusively (Table 1).[4] This, however, does not mean that no (*Z*)-isomers are formed. These compounds were transformed in situ to hemiacetals **5** which cannot be isolated by column chromatography. As such, the *E*/*Z* ratio was determined by converting the mixture of **4** and **5** to diacetates **6**. Remarkably, the high *E* preference holds even for tri- and tetrasubstituted double bonds.

Scheme 2



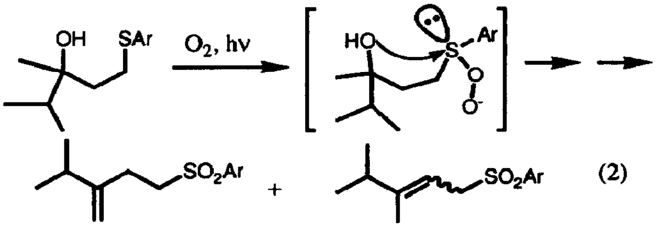
Such high selectivity cannot be attained when the hydroxy group is converted to methoxy and *t*-butyldimethylsiloxy groups (eq. 1). Apparently, the hydroxy group is unique in that it gives rise to the high *E* selectivity and the reaction is not governed by steric origin. Clennan et al. unambiguously proved that photooxidation reaction of γ-hydroxy sulfides proceeds via a five-membered transition state (eq. 2).[5] We hence propose a transition state [B] where the interaction between the hydroxy oxygen and the sulfinyl sulfur leads the hydroxyl-carrying residue to occupy the pseudoequatorial position.[6,7] The invalidity of the methoxy and siloxy groups for the high selectivity may be due to the bulkiness of these groups as compared with the hydrogen: the O-S interaction is hampered by repulsion between the RO group and the phenyl group on the sulfur.



(1)

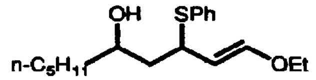
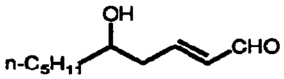
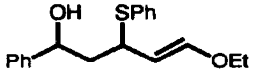
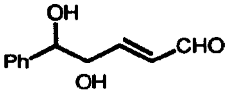
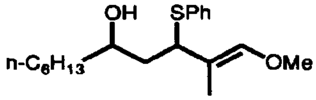
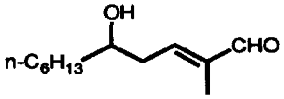
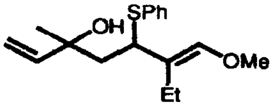
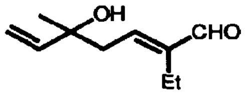
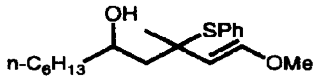
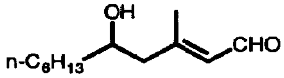
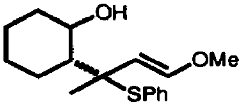
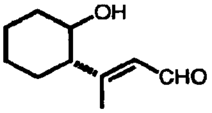
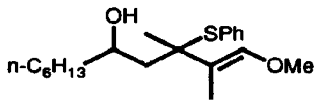
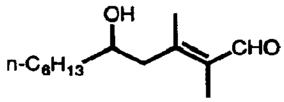
R = Me: yield 66%, *E*:*Z* = 64:36

= OTBS: yield 92%, *E*:*Z* = 52:48

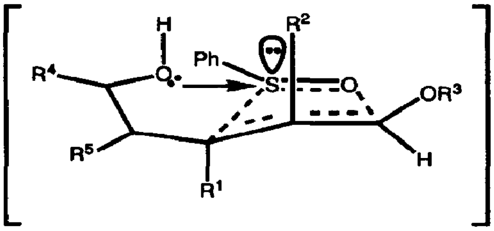


(2)

Table 1. Conversion of **3** to **4**.

3	4	yield/%	*E*:*Z*
		88	99:1
		80	99:1
		97	99:1
		88	99:1
		66	90:10
		45[a)]	97:3
		58[a)]	90:10

a) Overall yield based on **1** through two steps.



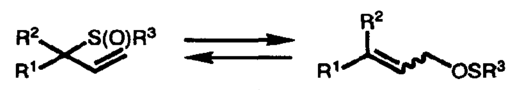
B

Another notable feature is lack of the selectivity with simple allylic sulfides (eq. 3). The γ-alkoxy group

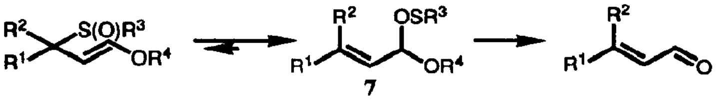
 (3)

70%; *E*:*Z* = 6:4

thus plays a key role for controlling the stereochemistry. As is well known, the sulfinyl-to-sufenyloxy transformation is an equilibrium process, rendering the reaction thermodynamically controlled.



When a γ-alkoxy group is present, the [2,3] sigmatropic rearrangement provides α,β-unsaturated sulfenyl acetals 7 which may be spontaneously hydrolyzed to enals. As a consequence, the equilibrium is shifted in favor of 7 and the reaction proceeds under kinetic control. It has been disclosed that β-substituted alkyl groups results in the high *E* selectivity even for simple allylic sulfides without γ-alkoxy group.[1] It follows therefore that the O-S interaction is not so powerful as the steric hindrance at the β-position in biasing the transition state geometry.



In summary, stereochemistry of [2,3] sigmatropic rearrangement of γ-alkoxyallylic sulfoxides is readily controlled by a hydroxy group at the γ'-position of the sulfinyl group. This reaction offers not only a novel mechanistic elucidation for Mislow-Evans rearrangement but also a synthetic method arriving at otherwise difficult-to-obtain δ-hydroxy α,β-unsaturated derivatives.

References

(1) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1989**, *54*, 2779.

(2) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563.

(3) Typical Procedure. To a THF solution (3 ml) containing (*E*)-1-ethoxy-3-phenylthio-1-propene (194 mg, 1 mmol) and HMPA (0.68 ml, 3.9 mmol) was slowly added *t*-BuLi (2.2 N pentane solution, 0.59 ml, 1.3 mmol) during a period of 10 min at -78 °C. After the solution being stirred for 3 min, 1,2-epoxyheptane (171 mg, 1.5 mmol) was added during a period of 5 min at this temperature. The reaction mixture was stirred for 15 min at -78 °C and quenched with aqueous NH_4Cl (1 ml). Usual workup and column chromatography on silica gel afforded (*E*)-1-ethoxy-5-hydroxy-3-phenylthio-1-decene (270 mg, 88%, syn:anti = 1:1). All compounds in this study gave satisfactory NMR and HRMS spectral data.

(4) Typical Procedure. A mixed solution of 5:1 dioxane-water (3 ml) containing 1-ethoxy-5-hydroxy-3-phenylthio-1-decene (211 mg, 0.69 mmol) and $NaIO_4$ (293 mg, 1.4 mmol) was stirred at room temperature for 1.5 h. The reaction mixture was extracted with ethyl acetate. Usual workup and column chromatography on silica gel furnished (*E*)-5-hydroxy-2-decenal (102mg, 88%)

(5) Clennan, E. L.; Yang, K. *J. Am. Chem. Soc.* **1990**, *112*, 4044.

(6) The intramolecular interaction between γ-hydroxy oxygen and the sulfinyl sulfur has been well elucidated by X-ray crystallography: Kucsman, A.; Kapovits, I. In *Organic Sulfur Chemistry*; Bernardi, F., Csizmadia, I. G.; Mangini, A. Eds.; Elsevior: Amsterdam, 1985; Chapter 4.

(7) Although oxidation of 3 leads to a diastereomeric mixture of the corresponding sulfoxides, the high stereoselectitives can be explained as follows. One diastereomer that involves a hydroxy-carrying group at the pseudoequatorial position undergoes the [2,3] sigmatropic rearrangement preferentially while the less reactive counterpart epimerizes due to acidic reaction conditions of $NaIO_4$-promoted oxidation (pH 2 - 4). For facile epimerization of sulfoxides under acidic conditions, see Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L. Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958.

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