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Asymmetric Desymmetrization of σ-Symmetrical Diols: The Role of Chelation in the Diastereoselective Acetal Cleavage Induced by the Chiral α-Sulfinyl Carbanion

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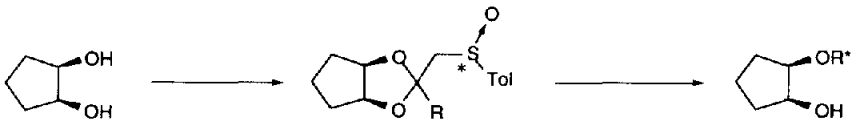
Abstract: The reaction mechanism of β-elimination in α-sulfinyl acetals was investigated using the chiral 3-oxo-thiochroman-1-oxide derivatives **1a** and **1b**. Our results show that the reaction is kinetically controlled with the C—O bond *syn* to the sulfinyl oxygen being cleaved exclusively. This reaction seems to proceed *via* six-membered ring chelation intermediates.

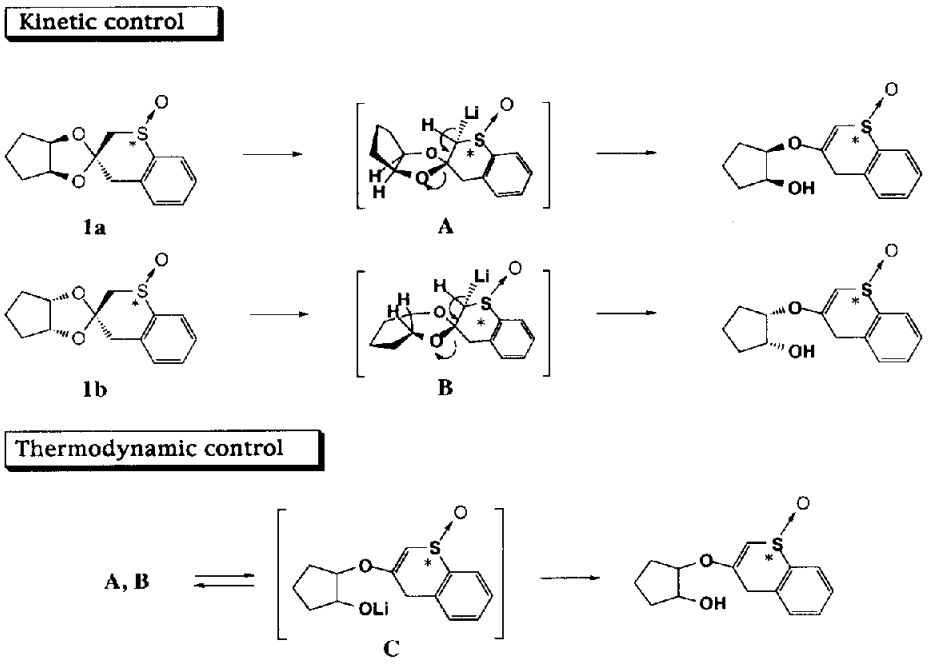
Asymmetric desymmetrization of *meso* diols has been studied as a powerful method for obtaining useful chiral building blocks from readily available materials.[1] Recently, we reported a novel chemical asymmetric desymmetrization of a σ-symmetrical diol using diastereoselective β-elimination caused by the chiral α-sulfinyl carbanion, and concluded that the diasteroselectivity in our reaction was due to kinetically controlled β-elimination (Scheme 1).[1a-f] However, we could not exclude the possibility of a thermodynamically controlled reaction mechanism.[1c,d] In addition, we were also interested in the stereochemical aspects of the reaction. Although considerable effort has been made to identify the reaction mechanism due to the unique characteristics of the chiral α-sulfinyl carbanion,[2] this research has focused on the reaction with electrophiles. To the best of our knowledge, this is the first report regarding a reaction mechanism involving β-elimination caused by the chiral α-sulfinyl carbanion.

To elucidate the reaction mechanism, we synthesized the cyclic α-sulfinyl acetals **1a** and **1b**, in which methylene protons adjacent to the sulfinyl group are conformationally restricted. If this reaction mechanism is kinetically controlled, we should expect that different products would be preferentially produced from **1a** and **1b** *via* diastereoselective β-elimination. On the other hand, if it is thermodynamically controlled, the same stable product would be obtained from both **1a** and **1b** *via* equilibrium between the closed form **A** and **B** and the cleaved form **C** (Scheme 2).

Scheme 1

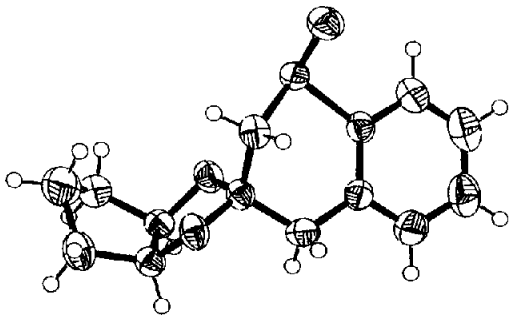


Scheme 2



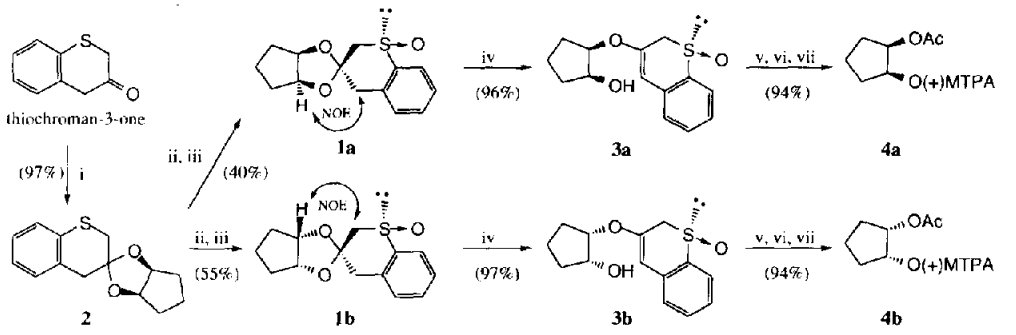
The chiral α-sulfinyl acetals **1a** and **1b** were synthesized as follows (Scheme 3). Thiochroman-3-one[3] was acetalized with *cis*-1,2-bis(trimethylsiloxy)cyclopentane and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[4] to give the sulfide **2** as a 1 : 1 diastereomeric mixture. The mixture of **2** was oxidized with *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (Davis' reagent)[5] to give the chiral sulfoxides **1a** and **1b**, each in 4 : 1 enantioselectivity. After the diastereomeric isomers were separated with column chromatography, their major enantiomeric isomers were purified by chiral HPLC (DAICEL; Chiralcel OB) to give sulfoxides **1a** and **1b** with high enantiomeric excess. The configurations at the spiro center of acetals **1a** and **1b** were determined based on the observation of the nuclear Overhauser effect (NOE) between the angular methine protons of the bicyclic ring and the methylene protons at the α- or γ-position of the sulfinyl group. This was also unambiguously confirmed by single-crystal X-ray analysis of the racemic **1a** (Fig. 1). The absolute stereochemistry of the sulfoxide of acetals **1a** and **1b** was determined to be the *R*-configuration.[6] Diastereoselective β-

Fig. 1 ORTEP Drawing of **1a**



elimination was then carried out by treating **1a** and **1b** with 3 equivalents of lithium diisopropylamide (LDA) at −78°C to give exclusively the diastereomeric isomers **3a** and **3b** accompanied by migration of the olefin to the β, γ-position, respectively. The absolute configuration of the cyclopentane rings was determined to be (1*R*, 2*S*) for **3a** and (1*S*, 2*R*) for **3b** after respective conversion into the known compounds **4a** and **4b**.[14]

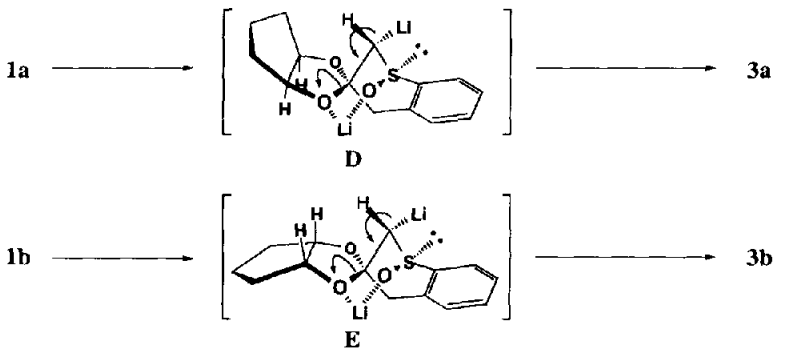
Scheme 3



i, *cis*-1,2-Bis(trimethylsiloxy)cyclopentane, TMSOTf (0.1 equiv.), CH_2Cl_2, room temp.; ii, Davis' reagent, CH_2Cl_2, room temp.; iii, separation; iv, LDA (3equiv.), THF, −78°C; v, (+)-MTPACl, Et_3N, DMAP, CH_2Cl_2, −50°C; vi, O_3, MeOH, −78°C; vii, Raney Ni(W2), EtOH, room temp.

These results show that these reactions are kinetically controlled rather than thermodynamically controlled and the C—O bond *syn* to the sulfinyl oxygen is selectively cleaved. We propose the mechanism shown in Scheme 4. In this mechanism, the lithium cation coordinates to the sulfinyl oxygen and one of the acetal oxygens to give stable six-membered ring chelation intermediates **D** and **E**. The proton *syn* to the sulfinyl oxygen is *syn* to both of the C—O bonds in the chelation intermediates, thereby being difficult to cause elimination. Therefore, the stereoelectronically favored *trans* elimination proceeds selectively to give **3a** and **3b**, respectively.

Scheme 4



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References and Notes

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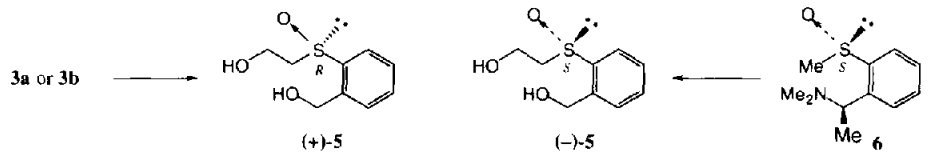
6 The absolute configuration was determined by comparing the specific rotation of the diol (+)-**5** transformed from **3a** or **3b** with that of the diol (–)-**5** transformed from **6** with a known *S*-configuration on a sulfur atom.



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