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Synthesis and Stereoselective Reduction of Chiral β-Ketosulfoxide from (+)-Camphor

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Abstract: A chiral β-ketosulfoxide derived from (+)-camphor was reduced with different hydride reagents to afford chiral β-hydroxysulfoxides in excellent diastereoselectivities and yields.

Chiral alcohols play an important role in the synthesis of natural products, drugs, and flavoring agents. The efficient stereoselective reduction is an interesting topic in organic chemistry[1], one of the most useful reactions has been the reduction of β-ketosulfoxides, which leads to functionalized chiral alcohols[2]. A number of β-ketosulfoxides have been reported which provide chiral alcohols in different diastereoselectivities[3].

We describe here a facile preparation of a chiral β-ketosulfoxide from (+)-camphor and its application in asymmetric synthesis of a chiral alcohol. Our working project is as follows. If a thioether is connected with a chiral bulky group, diastereoselective oxidation can lead to chiral sulfoxide. At the same time, the chiral bulky group may also construct a beneficial block to hydride attack to ketone in the subsequent reduction procedure.

3-(Methylthio)-1,7,7-trimethylbicyclo-[2.2.1]-heptan-2-one **1** was prepared from (+)-camphor and methyl thiotosylate[4] according to the literature procedure[5], as a mixture of endo and exo products (endo:exo 1:5.4 by ^{1}H-NMR analysis). After ketalization of the mixture, the thermodynamic endo product **2** was obtained in 95% yield. Oxidation[6] of compound **2** with 1 equiv. of 3-chloroperbenzoic acid in CH_2Cl_2 at -78°C afford **3a** and **3b** with the ratio of 11:1 (by ^{1}H-NMR analysis) in 96% yield, which were separated from each other by chromatography (the absolute configuration of **3** was derived from **5a**). **3a** was treated with n-BuLi and methyl benzoate in THF at -78°C to yield β-ketosulfoxide **4** in 74% yield.

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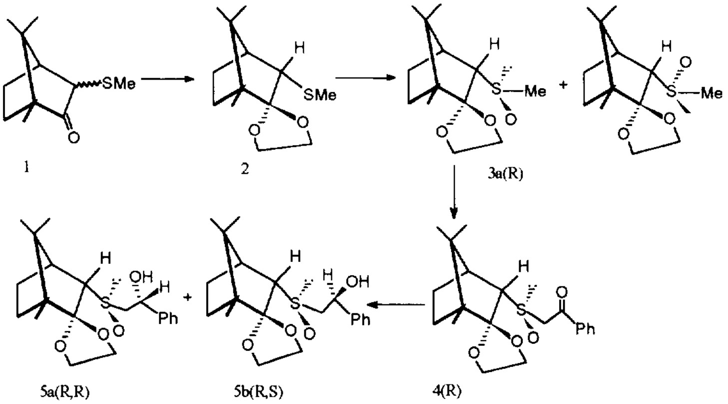

The foregoing β-ketosulfoxide **4** was then reduced[7]. A variety of reducing reagents were investigated. Table 1 lists the results. The ratio of **5a**:**5b** was determined by HPLC analysis[8]. The absolute configuration of **5** has been confirmed by an X-ray structure of **5a** (Figure 1).

Table 1. Reduction of the β-ketosulfoxide (**4**) with different reducing reagents[a].

Entry	Reduction reagent	Yield[b](%)	Ratio[c](**5a**:**5b**)
1	LAH	89	49.5:50.5
2	$NaBH_4$	98	20.5:70.5
3	DIBAL	94	3:97
4	DIBAL/$ZnCl_2$	98	100:0

a. All reactions were carried out at -78°C in THF.
b. Isolated yield.
c. The ratio was determined by HPLC analysis.

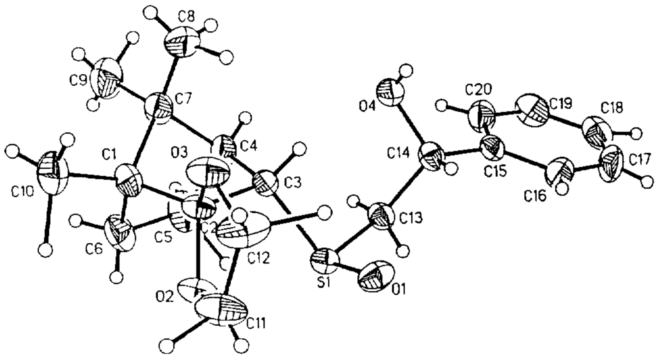

Figure 1. X-ray structure of **5a**

The reduction of **4** with a small hydride (LAH) gave a 49.5:50.5 mixture of β-hydroxysulfoxides, while the moderately active hydride ($NaBH_4$) afforded slight diastereoselectivities in favour of the S-alcohol, and the bulky hydride (DIBAL) yielded S-alcohol **5b** as the predominant product. In the presence of $ZnCl_2$, the reduction of **4** with DIBAL gave a completely reversed result with the formation of diastereoisomer **5a**. The activity of LAH is too high to differentiate the Re or Si-face of carbonyl group. The activity of $NaBH_4$ is lower than that of LAH, and the reduction with $NaBH_4$ gave a moderate diastereoselectivity. The results with DIBAL may be rationalized by taking into account their transition state (Figure 2).

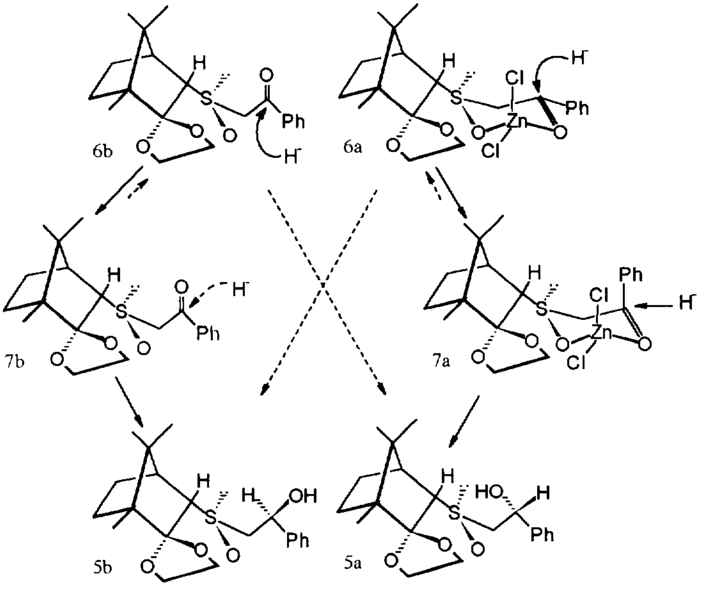

Figure 2. The transition state of reduction

In the absence of Lewis acid, the bulky hydride attacked preferably on the carbonyl group from the lone pair side (conformation **7b**) perhaps because of the block action of ketal portion, S-alcohol was the major product. In the presence of a chelating metal, the β-ketosulfoxide coordinated with $ZnCl_2$ to form a chelated conformation **6a** or **7a**, the ketalized camphoryl group constructed a large hindrance to the axial attack of bulky hydride, the equatorial attack of bulky hydride leaded to **5a** with 100% diastereoselectivity.

In summary, our experimental route provides easy and efficient ways to prepare a chiral β-ketosulfoxide. The reduction of resulting chiral β-ketosulfoxide with DIBAL or DIBAL/$ZnCl_2$ afforded both of diastereoisomers in extremely high stereoselectivity. Further work providing detail about the effect of different substitutents connected to carbonyl group on diastereoselectivity in the DIBAL reduction system are in progress.

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7. General procedure for reduction. A solution of β-ketosulfoxide (0.138mmol) and anhydrous $ZnCl_2$ (0.414 mmol) in 3 ml of dry THF was stirred for 1 h at room temperature under N_2. After cooling to -78°C, the mixture was slowly added a solution of DIBAL(0.2mmol) in 2 ml of dry THF, the resulting solution was stirred for 2 h at -78°C until completion of the reaction. The mixture was hydrolyzed with methanol and 10% NaOH solution and extracted with AcOEt to yield the diastereoisomer mixture of β-hydroxysulfoxides. For $NaBH_4$ reduction, the β-ketosulfoxide was added to $NaBH_4$ solution.
8. HPLC analyses were performed on Shimadzu LC-6AD. Compound **5a**, mp 140-141°C, $[\alpha]_D{}^{26}$=-0.54(1.3, CH_2Cl_2). ^{1}H-NMR($CDCl_3$) δ 0.828(s, 3H), 0.842(s, 3H), 1.087(s, 3H), 1.225-2.105(m, 5H), 2.746-2.796(dd, J=2.1, 12.9Hz, 1H), 2.926-3.003(dd, J=10,2, 12.9Hz, 1H), 3.245-3.267(dd, J=2.1, 4.5Hz, 1H), 3.663-4.025(m, 4H), 5.405-5.444(dd, J=2.1, 10.2Hz, 1H), 7.262-7.475(m, 5H). Compound **5b**, mp 88-90°C, $[\alpha]_D^{25}$=+72.6(1.2, CH_2Cl_2). ^{1}H-NMR($CDCl_3$) δ 0.836(s, 3H), 0.866(s, 3H), 1.108(s, 3H), 1.253-2.187(m, 5H), 2.760-2.811(dd, J=2.1, 13.1Hz, 1H), 3.011-3.088(dd, J=10.2, 13.1Hz, 1H), 3.254-3.276(dd, J=2.4, 4.4Hz, 1H), 3.716-4.156(m, 4H), 5.375-5.455(ddd, J=2.1, 3.8,10.2Hz, 1H), 7.262-7.453(m, 5H).

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