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# A Convenient Preparation of (1S)-(+)-10-Mercaptoisoborneol from (1S)-(+)-10-Camphorsulfonyl Chloride with High Diastereoselectivity

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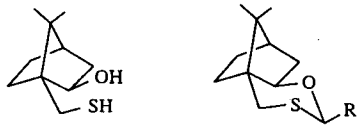
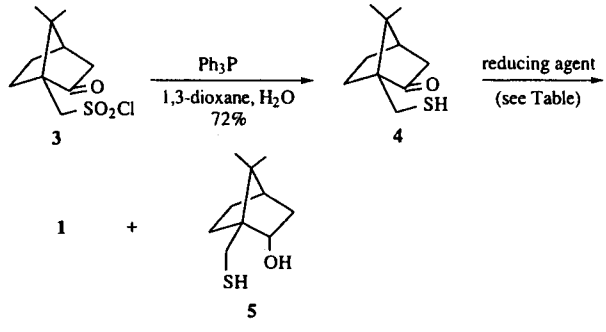
Chiral auxiliaries and catalysts derived from (+)-10-mercaptoisoborneol (exo-2-hydroxy-10-mercaptonorbornane, **1**) are used in various asymmetric syntheses.[1-5] Recently, 1,3-oxathianes **2** prepared from **1** have been used as highly effective chiral catalysts for the asymmetric epoxidation of aldehydes.[6]




**1** **2**

According to the literature,[1] thiol **1** was obtained by reduction of (+)-10-camphorsulfonyl chloride (**3**) with excess lithium aluminum hydride (chloride : hydride=1 : 4 molar ratio) in ether, followed by chromatographic separation of a 4 : 1 mixture of **1** and 10-mercaptoborneol (**5**). Because a large excess of pyrophoric reducing agent is employed, handling of this reagent and acidic workup need a careful manipulation. Also, the stereoselectivity in the ketone reduction is not so high. In this paper, we wish to describe a highly stereoselective method of obtaining **1**, which does not use $LiAlH_4$, rendering this method applicable to a large scale preparation, as shown in Scheme 1.




**Scheme 1.**

First, sulfonyl chloride **3** was converted to (+)-camphor-10-thiol (**4**) with triphenylphospine in dioxane-water co-solvent.[7] Thiol **4** could be easily separated from the reaction mixture by extraction with 5 M NaOH solution followed by acidification and extraction of the resulting thiol with hexanes. Sublimation of the crude product at reduced pressure gave the crystalline ketone **4** in 72% yield. Next, we studied the diastereoselective reduction of ketone **4** (Table 1). Reduction with $LiAlH_4$ or *i*-$Bu_2AlH$ gave *exo*-isomer **1** in high selectivity (>95% de). Similarly, $NaBH_4$ in EtOH showed a high *exo*-selectivity.[8] After reduction, removal of the minor *endo*-isomer **5** (polar) by silica gel column chromatography (hexanes : ethyl acetate=20 : 1) gave the diastereomerically pure *exo*-thiol **1**. This thiol is slowly oxidized to the disulfide when exposed to the air. Therefore, it should be kept under an inert atmosphere in a cold place.

## Experimental Part

The $^1H$ and $^{13}C$ NMR spectra were recorded with a Vari-

**Table 1.** Reduction of ketone **4** with reducing agents[a]

| Reducing Agent | Solvent | Temp. (°C) | Time | 1/5[b] |
|---|---|---|---|---|
| $LiAlH_4$ | THF | −78 | 3 h | ≥95/5 |
| $LiAlH_4$ | THF | 0 | 3 h | ≥95/5 |
| $LiAlH_4$ | ether | −78 | 3 h | 92/8 |
| LiAlH4 | ether | 0 | 3 h | ≥95/5 |
| $NaBH_4$ | ethanol | rt | 2 day | 95/5 |
| *i*-$Bu_2AlH$ | toluene | −78 | 3 h | 95/5 |

[a] Chemical yield was >95% in all cases. [b] The ratio was determined by the integration of two sets of peaks around 3.97 ppm (*exo*) and 4.35 ppm (*endo*) in $^1H$ NMR spectrum. It should be noted that the ratio determined by the $^1H$ NMR method can have an error of ±5%.

an Gemini 200 spectrometer in $CDCl_3$ using TMS as an internal standard. The FT-IR spectra were measured on a Nicholet 500 spectrometer as KBr disks. Optical rotations were measured on a Jasco DIP-370 digital polarimeter.

(+)-Camphor-10-thiol (**4**). A solution of (+)-10-camphorsulfonyl chloride (**3**, 18.0 g, 71.8 mmol) in a mixture of 240 mL of dioxane and 60 mL of water was treated with triphenylphospine (75.3 g, 287 mmol). The clear mixture was stirred for 2 days at room temperature, and then refluxed for 1 h. The reaction mixture was concentrated in vacuo. The resulting syrupy residue was extracted with hot hexanes (200 mL $\times$3). As the hexanes solution cooled to room temperature, a white precipitate (phosphine oxide) was formed, which was discarded. The hexanes solution was extracted with 5 M NaOH solution (100 mL$\times$5) and the combined NaOH extract cooled in an ice bath was acidified by careful addition of concentrated HCl (250 mL). The thiol was separated as a white solid, which was extracted with ethyl acetate (200 mL$\times$3). The organic solution was dried ($Na_2SO_4$) and concentrated in vacuo to give a white solid. Finally, purification by vacuum sublimation (125-135 °C, 0.05 mmHg) yielded 9.47 g (72%) of the thiol **4** as a colorless crystal, mp 65-66 °C (lit.[7] 65-67 °C); $[\alpha]_D^{20}$=+5.2 (c=1.02, $CHCl_3$); $^1$H NMR ($CDCl_3$) **d** 4.00-3.98 (m, 1H), 2.79 (dd, 1H, *J*=9.5 and 13 Hz), 2.58 (dd, *J*=5.3 and 13 Hz), 2.15 (bs, 1H), 1.28 (dd, 1H, *J*=9.5 and 5.3 Hz), 1.05 (s, 3H), 0.83 (s, 3H), and others; $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2, 60.3, 47.5, 43.4, 42.9, 26.7, 26.3, 21.0, 20.0, 19.5; IR (KBr) cm$^{-1}$ 1731.

(1*S*)-(+)-10-Mercaptoisoborneol (**1**). To a solution of $NaBH_4$ (2.06 g, 54.2 mmol) in EtOH (100 mL), cooled in an ice bath was added a solution of ketone **4** (5.00 g, 27.1 mmol) in EtOH (20 mL) over 10 min under a nitrogen atmosphere. The whole mixture was stirred for 2 days. Then, the excess NaBH4 was destroyed with dilute HCl solution. The product was extracted with EtOAc (100 mL$\times$2). The combined extract was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. Finally, column chromatography of the residue (eluent; hexanes : EtOAc=20 : 1) on silica gel gave 4.73 g (93% yield) of the product as a solid, mp 73-74 °C (lit.[1] 76-78 °C; lit.[3] 7 0); $[\alpha]_D^{20}$=−56.0 (c=1.15, $CHCl_3$)

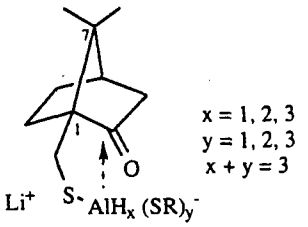



**Figure 1.**

(lit.[1] $[\alpha]_D^{24}$=−55.4; lit.[3] $[\alpha]_D^{24}$=−57.44 (c=10, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$. 3.97 (apparent t, 1H, *J*=4.7 Hz), 2.79 (dd, 1H, *J*=9.5, 13 Hz), 2.56 (dd, 1H, *J*=5.4, 13 Hz), 1.28 (dd, 1H, *J*=9.5, 5.4 Hz), 1.05 (s, 3H), 0.83 (s, 3H), and others; $^{13}$C NMR ($CDCl_3$) $\delta$ 76.4, 52.9, 47.4, 45.7, 39.4, 30.3, 26.8, 23.7, 20.5, 19.9; IR (KBr) cm$^{-1}$ 3467, 2950, 1393, 1373, 1071, 1033.

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8. The high selectivity may be ascribed to the model above (Figure 1) where the carbon-sulfur bond is *anti* to the C1-C7 bond and the hydrogen atom is transferred intramolecularly to the less hindered si face of the carbonyl bond.

# Highly Overlapping $^1$H NMR Signal Assignments of 12,13-Diepimeric Coenzyme F430 by the Compensated ROESY Experiment

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Coenzyme F430 is a nickel(II)-containing cofactor of the methyl coenzyme M reductase (Component C which was found in the cells of methanogenic bacteria) that is involved in the bio-catalytic reduction of methyl coenzyme M (2-methylthioethanesulfonic acid, $CH_3$-S-CoM).[1,2] Coenzyme F430 is known to be mediated in the reductive demethylation of methyl coenzyme M, using reducing equivalents from 7-mercaptoheptanoylthreonine phosphate (HS-HTP). The products of this reaction are methane and the heterodisulfide of methyl coenzyme M and HS-HTP (CoM-S-S-HTP).[3-5]