# Synthesis of a New Class of Chiral β-Mercaptoalcohols from Amino Acids

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**The syntheses of three new optically active β-mercaptoalcohols, (*R*)-1,1-diphenyl-2-mercapto-3-methyl-1-butanol, (*R*)-1,1-diphenyl-2-mercapto-4-methyl-1-pentanol, and (*R*)-1,1-diphenyl-2-mercapto-1-benzenepropanol from the corresponding amino acids are described. The enantiomeric excesses of these β-mercaptoalcohols were determined by $^1$H NMR as their (*S*)-mandeloyl derivatives.**

**Keywords** β-mercaptoalcohols, amino acids, synthesis

## Introduction

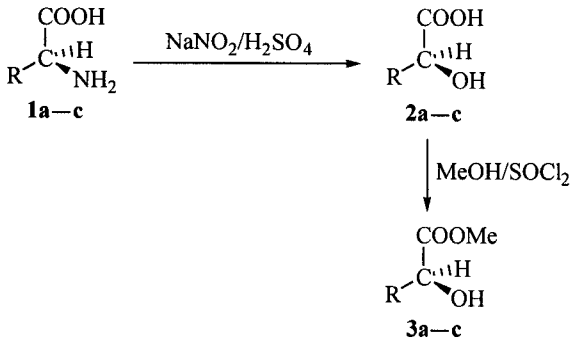
The chiral ligands with two heteroatoms taken among N and O, such as N, O (aminoalchols) and N, N (diamines) ligands, have received considerable attention in enantioselective reduction of prochiral ketones.[1] We are aware that few mercaptoalcohols with the S atom at a chiral center have been reported in literature, except that several optically active mercaptoalcohols, derived from camphor, have been used as catalysts in asymmetric reduction of prochiral ketones.[2-3]

Mercaptoalcohols are a rare class of natural products. In this paper, we wish to report the syntheses of three new optically active β-mercaptoalcohols, which possess a SH group attached to a chiral carbon, from readily available natural amino acids.

## Results and discussion

The synthesis of α-hydroxy acid methyl esters (**3a—c**) from the corresponding amino acids valine, leucine, and phenylalanine is shown in Scheme 1. The α-hydroxy acids (**2a—c**) were prepared by using the literature method[4] with modifications from the corresponding amino acids. Improved yields were obtained by slowly simultaneous addition of three fold excess of sodium nitrite and 1 mol/L $H_2SO_4$. In the preparation of **3a** from **2a**, following the procedure described by Vigneron,[5] a low yield (45%) was obtained. It was found that much better result (yield 82%) could be obtained by esterifying **2a** with methanol-thionyl chloride. Then this method was employed in the preparations of **3b** and **3c**.

**Scheme 1**




**a**: R=$(CH_3)_2CH$; **b**: R=$(CH_3)_2CHCH_2$; **c**: R=$PhCH_2$

Our first attempt to convert **3a** to the corresponding mercaptoalcohol **7a** is shown in Scheme 2. (*S*)-2-Hydroxy-3-methylbutanoic acid methyl ester (**3a**) was treated with excess of phenyl magnesium bromide to give (*S*)-1,1-diphenyl-3-methyl-1,2-butanediol (**4**),[5] which

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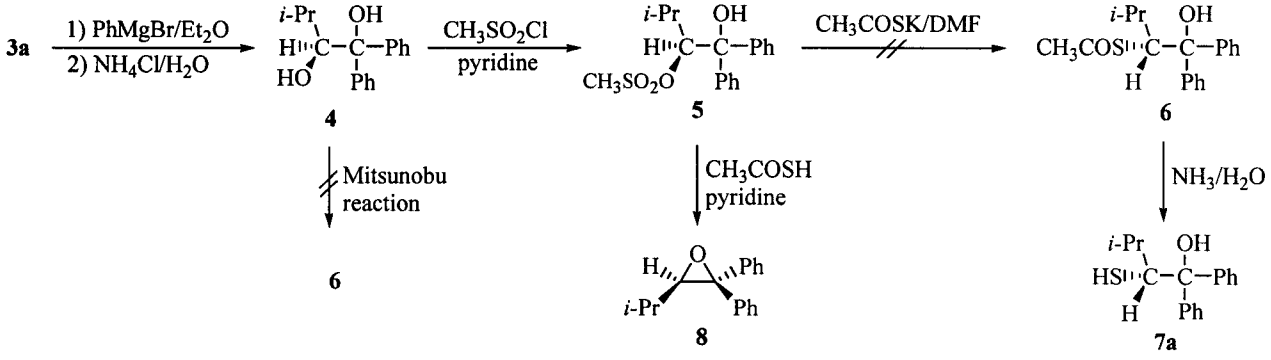
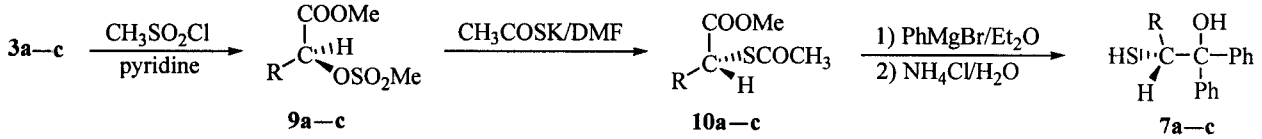
was then mesylated to obtain **5**. Unfortunately, conversion of **5** to **6** by reacting **5** with potassium thioacetate under $S_N2$ reaction conditions can be achieved neither in DMF at 20—60 ℃ nor in refluxing toluene in the presence of 18-crown-6 as catalyst. When **5** was refluxed with thioacetic acid in pyridine,[6] an optical active epoxide **8**, instead of **7a**, was obtained. Our second effort is to convert **4** and 1,1-diphenyl-1,2-propanediol,[7] which has a structure similar to **4**, to the thioesters by reacting with $PPh_3$, DEAD and thioacetic acid (the Mitsunobu reaction),[8] but we failed either, probably due to the steric hindrance around the reaction center.

**Scheme 2**



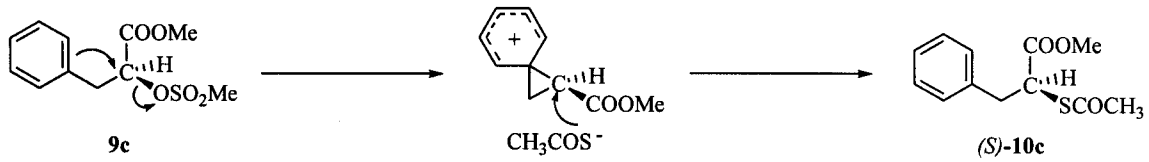

The actually successful synthesis is shown in Scheme 3. **3** was mesylated to obtain the ester **9**, which was treated with $KSCOCH_3$ in DMF to give **10**. Treating **10** with phenyl magnesium bromide gave the target compound β-mercaptoalcohols **7**. The racemic β-mercaptoalcohols were prepared by the same manner. Attempts to separate the enantiomers of **7a—c** or their cyclic derivatives of acetone by HPLC on a chiral stationary-phase columns were failed. However, the enantiomeric excesses of **7a—c** can be determined by $^1H$ NMR as their (*S*)-mandeloyl derivatives. The enantiomeric excess of **7c** is much lower than those of **7b** and **7a**, probably due to occurance of neighbouring group participation during the nucleophilic substitution (Scheme 4).

**Scheme 3**




**a**: R=$(CH_3)_2CH$; **b**: R=$(CH_3)_2CHCH_2$; **c**: R=$PhCH_2$

**Scheme 4**




## Experimental

Melting points were measured in capillaries and uncorrected. Optical rotations were measured at 589 nm (Na D line) on a WZZ-1 polarimeter. $^1H$ NMR spectra were recorded at 400 MHz, chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane (TMS); and $^{13}C$ NMR were performed at 400

MHz; A Varian Inova-400 was used. Infrared spectra were recorded on a Nicilet Avatar 360 FT-IR. For preparative column chromatography, silica gel (H60) was used, with the solvent system given in the text. Organic solvents were dried and distilled prior to use.

*Preparation of (S)-2-hydroxy-3-methylbutanoic acid* (**2a**)

To a vigorously stirred suspension of *L*-valine (10.0 g, 85.0 mmol) in 40 mL of water, a solution of $NaNO_2$ (17.6 g, 255 mmol) in 90 mL of water and 1 mol/L $H_2SO_4$(128 mL) were added dropwise simultaneously from two separate dropping funnels, at −5—0 ℃ within 3 h. Then the mixture was stirred for 9 h in ice-water bath. After being stirred overnight at room temperature, the solution was saturated with sodium chloride, extracted with diethyl ether (6 × 50 mL). The combined extracts were dried over magnesium sulfate and concentrated to dryness on a rotavapor. The residue was recrystallized from diethyl ether/petroleum ether to obtain the white product, yield 88%, m.p. 63—65 ℃; $[\alpha]_D^{14}$ + 24.1 (*c* 1.04, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ: 0.93 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.07 (d, *J* = 7.2 Hz, 3H, $CH_3$), 2.13—2.20 (m, 1H, $(CH_3)_2CH$), 4.15 (d, *J* = 3.2 Hz, 1H, CHOH;) $^{13}$C NMR ($CDCl_3$) δ: 16.31, 19.26 (2 × $CH_3$), 32.48 [$(CH_3)_2CH$], 75.27 (CHOH), 179.42 (C = O); IR ν: 3430 (OH), 2642 (COOH), 1720 (CO) cm$^{-1}$; Anal. calcd for $C_5H_{10}O_3$: C 50.84, H 8.53; found C 50.65, H, 8.49.

**2b** and **2c** were similarly prepared:

(*S*)-2-*Hydroxy*-4-*methylpentanoic acid* (**2b**) Yield 72%, m.p. 80—82 ℃; $[\alpha]_D^{25}$ − 24.3 (*c* 1.52, 1 mol/L NaOH); $^1$H NMR ($CDCl_3$) δ: 0.98 (d, *J* = 6.4 Hz, 6H, 2 × $CH_3$), 1.63—1.66 (m, 2H, $CH_2$), 1.90—1.92 (m, 1H, $(CH_3)_2CH$), 4.28—4.32 (m, 1H, CHOH); $^{13}$C NMR ($CDCl_3$) δ: 21.88, 23.69 (2 × $CH_3$), 24.94 ($(CH_3)_2CH$), 43.68 ($CH_2$), 69.35 (CHOH), 180.93 (C = O); IR ν: 3427(OH), 2703, 2628(COOH), 1709(C = O) cm$^{-1}$. Anal. calcd for $C_6H_{12}O_3$: C 54.53, H 9.15; found C 54.39, H 9.28.

(*S*)-2-*Hydroxy*-3-*phenylpropanoic acid* (**2c**) Yield 88%, m.p. 123—124 ℃; $[\alpha]_D^{22}$ − 30.2 (*c* 1.52, $Me_2CO$); $^1$H NMR ($CDCl_3$) δ: 2.98—3.25 (m, 2H, $CH_2$), 4.53 (s, 1H, CH), 7.26—7.34 (m, 5H, $C_6H_5$); $^{13}$C NMR ($CDCl_3$) δ: 40.65 ($CH_2$), 71.45 (CHOH), 127.64, 129.09, 130.01, 136.33 ($C_6H_5$), 178.16 (C = O); IR ν: 3447 (OH), 2592 (COOH), 1733 (C = O) cm$^{-1}$; Anal. calcd for $C_9H_{10}O_3$: C 65.05, H 6.07; found C 65.13, H 6.10.

*Preparation of (S)-2-hydroxy-3-methylbutanoic acid methyl ester* (**3a**)

To a well stirred round-bottomed flask containing anhydrous methanol (40 mL) at −10 ℃, thionyl chloride (10 mL) was added dropwise. The mixture was stirred for further 10 min at this temperature, then **2a** (4.5 g, 38 mmol) was added in one portion. After stirred at room temperature for 2 d, the mixture was evaporated under reduced pressure. The residue was dissolved in 40 mL of diethyl ether, washed with 5% $NaHCO_3$ solution to remove any acid, and then washed with water to neutral, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude products were purified by vacuum distillation. Yield 73%, b.p. 50.5 ℃/1.33 kPa; $[\alpha]_D^{13}$ + 22.3 (*c* 1.17, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ: 0.87 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.03 (d, *J* = 7.2 Hz, 3H, $CH_3$), 2.06—2.10 (m, 1H, $(CH_3)_2CH$), 2.68 (d, *J* = 6.0 Hz, 1H, OH), 3.80 (s, 3H, $OCH_3$), 4.06 (dd, *J* = 6.4, 3.6 Hz, 1H, CHOH); $^{13}$C NMR ($CDCl_3$) δ: 16.46, 19.19 (2 × $CH_3$), 32.60 [$(CH_3)_2CH$], 52.82 ($OCH_3$), 75.51 (CHOH), 175.83 (C = O); IR ν: 3504 (OH), 1736 (C = O) cm$^{-1}$; Anal. calcd for $C_6H_{12}O_3$: C 54.53, H 9.15; found C 54.34, H 8.95.

**3b** and **3c** were similarly prepared:

(*S*)-2-*Hydroxy*-4-*methylpentanoic acid methyl ester* (**3b**) Colorless liquid, yield 83%, b.p. 66 ℃/1.07 kPa; $[\alpha]_D^{25}$ − 20.8 (*c* 1.36, 1 mol/L NaOH); $^1$H NMR ($CDCl_3$) δ: 0.95 (q, *J* = 6.6, 4.4 Hz, 6H, 2 × $CH_3$), 1.54—1.57 (m, 2H, $CH_2$), 1.86—1.91 (m, 1H, $(CH_3)_2CH$), 2.62 (bs, 1H, OH), 3.79 (s, 3H, $OCH_3$), 4.22 (bs, 1H, CHOH); $^{13}$C NMR ($CDCl_3$) δ: 22.02, 23.71 (2 × $CH_3$), 24.87 [$(CH_3)_2CH$], 43.98 ($CH_2$), 52.96 ($OCH_3$), 69.53 (CHOH), 176.80 (C = O); IR ν: 3564 (OH), 1739 (C = O) cm$^{-1}$; Anal. calcd for $C_7H_{14}O_3$: C 57.51, H 9.65; found C 57.36, H 9.50.

(*S*)-2-*Hydroxy*-3-*phenylpropanoic acid methyl ester* (**3c**) Colorless waxy material, yield 79%, b.p. 124 ℃/667 kPa; $[\alpha]_D^5$ − 8.3 (*c* 0.96, EtOH); $^1$H

NMR ($CDCl_3$) δ: 2.94—3.00, 3.11—3.16 (m, 2H, $CH_2$), 3.78 (s, 3H, $OCH_3$), 4.47 (dd, $J$ = 6.8, 4.8 Hz, 1H, CH), 7.20—7.32 (m, 5H, $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 41.02 ($CH_2$), 52.98 ($CH_3$), 71.74 (CH), 127.41, 128.92, 129.93, 136.72 ($C_6H_5$), 175.07 (C = O); IR ν: 3445 (OH), 1738 (C = O) $cm^{-1}$; Anal. calcd for $C_{10}H_{12}O_3$: C 66.65, H 6.71; found C 66.52, H 6.58.

*Preparation of* (*S*)-1, 1-*diphenyl*-3-*methyl*-1, 2-*butanediol* (**4**)

**4** was prepared from **3a** following the description in literature[4]. Yield 77%, m.p. 110—111 ℃, $[\alpha]_D^4$ − 140.5 (*c* 0.84, $C_6H_6$).

*Preparation of* (*S*)-1, 1-*diphenyl*-3-*methyl*-2-(*methanesulfonyloxy*)-1-*butanol* (**5**)

To a stirred solution of (*S*)-1,1-diphenyl-3-methyl-1,2-butanediol (**4**) (0.5 g, 2.0 mmol) in 4 mL of pyridine at 0 ℃, 0.24 mL of methanesulfonyl chloride was dropped in. After stirred for 10 h, 50 mL of water was added, extracted with ethyl ether (3 × 30 mL). The combined extracts were washed successively with 10% citric acid solution, 5% $NaHCO_3$ solution, and water, dried over anhydrous magnesium sulfate and the solvent was removed. The crude product is pure enough for the next step. An analytical sample was obtained by recrystallization from alcohol. Yield 86%, m.p. 116—117 ℃; $[\alpha]_D^4$ + 15.4 (*c* 0.78, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 1.05 (d, $J$ = 7.2 Hz, 3H, $CH_3$), 1.07 (d, $J$ = 7.6 Hz, 3H, $CH_3$), 2.06—2.12 (m, 1H, $(CH_3)_2CH$), 2.20 (s, 3H, $SO_2CH_3$), 2.67 (s, 1H, OH), 5.64 (d, $J$ = 2.0 Hz, 1H, CHOMs), 7.26—7.69 (m, 10H, 2 × $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 17.90, 22.60 (2 × $CH_3$), 29.55 [$(CH_3)_2CH$], 38.80 ($CH_3$), 81.43 (COH), 92.56 (CHOMs), 125.83, 126.19, 127.90, 128.01, 129.04, 143.40, 145.96 (2 × $C_6H_5$); IR ν: 3528 (OH), 1449 ($C_6H_5$) $cm^{-1}$; Anal. calcd for $C_5H_{10}O_3$: C 64.65, H 6.63; found C 64.44, H 6.53.

**9a—c** were similarly prepared from **3a—c**: The crude products of **9a—b** were purified by chromatography (acetone/petroleum ether = 1:4); **9c** was extracted with $CHCl_3$ and purified by recrystallization from ethyl alcohol.

(*S*)-3-*Methyl*-2-(*methanesulfonyloxy*) *butanoic acid methyl ester* (**9a**) Colorless oil, yield 78%, b.p. 112 ℃/133 Pa, $[\alpha]_D^{20}$ − 39.2 (*c* 1.56, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 0.97 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 1.08 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 2.30—2.35 (m, 1H, $(CH_3)_2CH$), 3.15 (s, 3H, $SO_2CH_3$), 3.81 (s, 3H, $OCH_3$), 4.89 (d, $J$ = 4.4 Hz, 1H, $CHOSO_2$); $^{13}C$ NMR ($CDCl_3$) δ: 17.03, 18.95 (2 × $CH_3$), 31.27 [$(CH_3)_2CH$], 39.34 ($SO_2CH_3$), 52.98 ($OCH_3$), 82.64 ($CHOSO_2$), 169.65 (C = O); IR ν: 1755 (C = O) $cm^{-1}$; Anal. calcd for $C_7H_{14}O_5S$: C 39.99, H 6.71; found C 39.86, H 6.63.

(*S*)-4-*Methyl*-2-(*Methylsulfonyloxy*) *pentanoic acid methyl ester* (**9b**) Colorless oil, yield 74%, b.p. 124—125 ℃/266 Pa; $[\alpha]_D^{22}$ − 59.3 (*c* 1.08, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 0.97 (d, $J$ = 6.0 Hz, 3H, $CH_3$), 0.98 (d, $J$ = 6.0 Hz, 3H, $CH_3$), 1.68—1.72, 1.81—1.88 (m, 3H, $CH_2$, $(CH_3)_2CH$), 3.16 (s, 3H, $SO_2CH_3$), 3.80 (s, 3H, $OCH_3$), 5.08 (dd, $J$ = 9.8, 4.0 Hz, 1H, $CHOSO_2$); $^{13}C$ NMR ($CDCl_3$) δ: 21.62, 23.38 (2 × $CH_3$), 24.72 [$(CH_3)_2CH$], 39.63 ($SO_2CH_3$), 41.02 ($CH_2$), 53.19 ($OCH_3$), 76.91 (CHOH); 170.67 (C = O). IR ν: 1758 (C = O) $cm^{-1}$; Anal. calcd For $C_8H_{16}O_5S$: C 42.84, H 7.19; found C 42.72, H 7.19.

(*S*)-2-(*Methylsulfonyloxy*)-3-*phenylpropanoic acid methyl ester* (**9c**) White solid, yield 62%, m.p. 72—73 ℃, $[\alpha]_D^{22}$ − 29.2 (*c* 1.82, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 2.77 (s, 3H, $SO_2CH_3$), 3.11—3.16, 3.28—3.33 (m, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$), 5.18 (dd, $J$ = 8.8, 4.0 Hz, 1H, CH), 7.26—7.34 (m, 5H, $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 38.65 ($CH_2$), 38.96 ($SO_2CH_3$), 53.34 ($CH_3$), 79.10 (CH), 128.02, 129.20, 129.94, 135.33 ($C_6H_5$), 169.32 (C = O); IR ν: 1763 (C = O) $cm^{-1}$; Anal. calcd for $C_{11}H_{14}O_5S$: C 51.15, H 5.46; found C 51.26, H 5.50.

*Preparation of* (*R*)-3, 3-*diphenyl*-2-(1-*methylethyl*)-*oxirane* (**8**)

A mixture of **5** (0.15 g, 0.45 mmol), benzene (10 mL), pyridine (1.4 mL, 17 mmol) and thioacetic acid (0.40 mL, 5.6 mmol) was refluxed for 11 h, washed successively with 10% citric acid solution, 5% $NaHCO_3$ solution and water, dried over magnesium sul-

fate. The volatiles were removed under reduced pressure. The residue was subjected to chromatography (acetone/petroleum ether) to afford **8**. White solid, yield 28%, m.p. 95—96 ℃; $[\alpha]_D^{20}$ + 94.3 (*c* 0.55, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 0.75 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.01 (d, *J* = 6.4 Hz, 3H, $CH_3$), 2.55—2.64 (m, 1H, $(CH_3)_2CH$), 4.21 (d, *J* = 10.4 Hz, 1H, CH), 7.20—8.00 (m, 10H, 2 × $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 21.02, 22.47 (2 × $CH_3$), 32.36 (CH), 61.84 (CH), 127.48, 128.98, 129.15, 129.27, 133.27, 138.10, 139.04 (2 × $C_6H_5$), 201.11 ($C(C_6H_5)_2$); IR ν: 1672 ($C_6H_5$), 1214 (C-O-C) $cm^{-1}$; Anal. calcd for $C_5H_{10}O_3$: C 85.67, H 7.61; found C 85.79, H 7.58.

*Preparation of* (*R*)-2-*acetylthio*-3-*methyl*-*butanoic acid methyl ester* (**10a**)

The reactions were carried out under dry nitrogen atmosphere. To a solution of **9a** (2.1 g, 10 mmol) in 30 mL of DMF a solution of 1.37 g (12 mmol) $CH_3COSK$[9] in 30 mL of DMF was dropped in. The reaction mixture was stirred at room temperature until **9a** cannot be detected by TLC. Water (50mL) was added, and the mixture was extracted with ethyl ether. The combined extracts were washed with 5% $NaHCO_3$ solution and water, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to chromatography (acetone/petroleum ether) to afford colorless oil, yield 68%, $[\alpha]_D^{25}$ + 107.9 (*c* 1.94, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 0.98 (d, *J* = 6.4 Hz, 3H, $CH_3$), 1.00 (d, *J* = 6.8 Hz, 3H, $CH_3$), 2.23—2.45 (m, 1H, $(CH_3)_2CH$), 2.37 (s, 3H, $COCH_3$), 3.73 (s, 3H, $OCH_3$), 4.12 (d, *J* = 6.4 Hz, 1H, $CHOSO_2$); $^{13}C$ NMR ($CDCl_3$) δ: 14.57, 19.96 (2 × $CH_3$), 20.70 ($COCH_3$), 30.88 [$(CH_3)_2CH$], 53.68 ($OCH_3$), 61.83 (CHS), 171.68 (C = O), 194.59 (C = O). IR ν: 1737 (C = O), 1700 (C = O) $cm^{-1}$; Anal. calcd for $C_8H_{14}O_3S$: C 50.50, H 7.24; found C 50.47, H 7.34.

Similarly were prepared **10b** and **10c**:

(*R*)-2-*Acetylthio*-4-*methyl*-*pentanoic acid methyl ester* (**10b**) Colorless oil, yield 88%, $[\alpha]_D^{22}$ + 83.0 (*c* 1.26, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 0.90—1.01 (m, 6H, 2 × $CH_3$), 1.55—1.63, 1.78—1.85 (m, 3H, $CH_2$, $(CH_3)_2CH$), 2.37 (s, 3H, $COCH_3$), 3.73 (s, 3H, $OCH_3$), 4.24 (t, *J* = 7.6 Hz, 1H, $CHOSO_2$); $^{13}C$ NMR ($CDCl_3$) δ: 22.57, 22.72 (2 × $CH_3$), 26.54 [$(CH_3)_2CH$], 30.66 (CH), 40.88 ($SO_2CH_3$), 44.64 ($CH_2$), 53.07 ($OCH_3$), 173.01 (C = O), 194.43 (C = O); IR ν: 1740 (C = O), 1698 (C = O) $cm^{-1}$; Anal. calcd for $C_9H_{16}O_3S$: C 52.92, H 7.89; found C 52.68, H 7.82.

(*R*)-*α*-*Acetylthio*-3-*phenylpropanoic acid methyl ester* (**10c**) Colorless oil, yield 72%, $[\alpha]_D^{22}$ + 11.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 2.33 (s, 3H, $COCH_3$), 2.99—3.05, 3.23—3.28 (m, 2H, $CH_2$), 3.67 (s, 3H, $OCH_3$), 4.44 (t, *J* = 7.6 Hz, 1H, CH), 7.20—7.31 (m, 5H, $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 30.71 (CH), 38.40 ($COCH_3$), 47.56 ($CH_2$), 53.10 ($OCH_3$), 127.52, 128.95, 129.58, 137.59 ($C_6H_5$), 171.98 (C = O), 193.96(C = O); IR ν: 1740(C = O), 1698(C = O) $cm^{-1}$; Anal. calcd for $C_{12}H_{14}O_3S$: C 60.48, H 5.92; found C 59.85, H 5.86.

*Preparation of* (*R*)-1,1-*diphenyl*-2-*mercapto*-3-*methyl*-1-*butanol* (**7a**)

The reactions were carried out under dry nitrogen atmosphere. To a solution of **10a** (1.0 g, 3.7 mmol) in dry ethyl ether (10 mL) at 0 ℃, a solution of 30 mL of phenyl magnesium bromide in 20 mL of dry ethyl ether was added. After stirred for 6 h, the temperature allowed to raise to room temperature and stirred overnight. The flask was kept in an ice bath, and 100 mL saturated aqueous solution of ammonium chloride was added cautiously, then the mixture was extracted with ethyl ether (3 × 30 mL). The combined extracts were washed with water, dried over magnesium sulfate and concentrated to dryness. The residue was subjected to chromatography (benzene/cyclohexane) to afford **7a**, pale yellow waxy material, yield 20%, 75% *ee*, m.p. 78—80 ℃; $[\alpha]_D^{25}$ + 135.0 (*c* 0.78, $C_6H_6$); $^1H$ NMR ($CDCl_3$) δ: 0.97 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.03 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.11 (d, *J* = 4.8 Hz, 1H, SH), 1.88—1.96 (m, 1H, $(CH_3)_2CH$), 3.45 (s, 1H, OH), 4.14 (dd, *J* = 4.8, 2.0 Hz, 1H, CHCHSH), 7.17—7.58 (m, 10H, 2 × $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 17.94, 24.22 (2 × $CH_3$), 28.63 [$(CH_3)_2CH$], 56.65 (CHSH), 81.16 (CHSH), 125.68, 125.93, 126.97, 127.32, 128.70, 129.00, 144.62, 147.97

(2 × $C_6H_5$); IR ν: 3483 (OH), 2576 (SH), 1598, 1486, 1448 ($C_6H_5$) $cm^{-1}$; Anal. calcd. for $C_{17}H_{20}OS$: C 74.96, H 7.40; found: C 75.05, H 7.46.

Similarly were prepared **7b** and **7c**:

(*R*)-1, 1-*Diphenyl*-2-*mercapto*-4-*methyl*-1-*pentanol* (**7b**) Pale yellow waxy material, yield 28%, 71% *ee*, m.p. 56—58 ℃; $[\alpha]_D^{20}$ + 60.9 (*c* 0.16, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ: 0.79 (d, *J* = 6.8 Hz, 3H, $CH_3$), 0.83 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.08—1.15, 1.38—1.45 (m, 2H, $CH_2$), 1.76 (d, *J* = 7.2 Hz, 1H, SH), 1.84—1.88 (m, 1H, $(CH_3)_2$**C**H), 4.06—4.11 (m, 1H, **C**HSH), 5.43 (s, 1H, OH), 7.10—7.62 (m, 10H, 2 × $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 21.30, 24.19 (2 × $CH_3$), 26.55 [$(CH_3)_2CH$], 40.38 ($CH_2$), 49.13 (CHSH), 80.35 (C), 125.90, 126.04, 127.09, 127.42, 128.66, 128.98, 144.25, 147.37 (2 × $C_6H_5$); IR ν: 3462 (OH), 2556 (SH), 1598, 1490, 1448 ($C_6H_5$) $cm^{-1}$; Anal. calcd for $C_{18}H_{22}OS$: C 75.48, H 7.74; found C 75.26, H 7.79.

(*R*)-1,1-*Diphenyl*-2-*mercapto*-1-*benzenepropan*-*ol* (**7c**) Pale yellow waxy material, yield 20%, 18% *ee*, m.p. 88—90 ℃; $[\alpha]_D^{20}$ + 18.3 (*c* 0.49, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ: 1.63 (d, *J* = 7.2 Hz, 1H, SH), 2.54—2.58, 2.83—2.86 (m, 2H, $CH_2$), 4.40—4.44 (m, 1H, CH), 5.71 (s, 1H, OH), 7.12—7.74 (m, 15H, 3 × $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ: 38.07 ($CH_2$), 53.00 (CH), 80.26 (C), 125.80, 126.02, 127.09, 127.40, 127.66, 128.92, 128.98, 129.10, 129.44, 139.90, 144.09, 146.82 (3 × $C_6H_5$); IR ν: 3483 (OH), 2576 (SH), 1598, 1492, 1448 ($C_6H_5$) $cm^{-1}$; Anal. calcd. for $C_{21}H_{20}OS$: C 78.71, H 6.29. found C 78.76, H 6.33.

*General procedure for Determination of enantiomeric excess of* **7**

To a stirred solution of **7** (1 mmol) in 3 mL pyridine at 0 ℃ a solution of (*R*)-(-)-methylmandoloyl chloride (3 mmol)[10] was dropped. After stirred for 10 h, 20 mL water was added, extracted with ethyl ether (3 × 30 mL). The combined extracts were washed successively with 10% citric acid solution, 5% $NaHCO_3$ solution, and water, and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was subjected to chromatography (acetone/petroleum ether) to afford the disastereomeric mixture. The $^1H$ NMR chemical shifts of methoxyl group in the derivatives are shown in Table 1.

**Table 1** $^1H$ NMR chemical shifts of methoxyl group in the disastereomeric mixture derived from **7a—c**

| Substrate | $OCH_3{}^{RR}$ | $OCH_3{}^{SR}$ | *ee* (%) |
|---|---|---|---|
| **7a** | 3.40 | 3.21 | 75 |
| **7b** | 3.37 | 3.20 | 71 |
| **7c** | 3.17 | 3.06 | 18 |

$^{RR}$ or $^{SR}$ indicated the structure of diastereomer

## References


1 (a) Itsuno, S.; Ito, K,; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2887.
(b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am Chem. Soc.* **1987**, *109*, 5551.
(c) Hulst, R.; Heres, H.; Peper, N.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1373.
(d) Froelich, O.; Bonin, M.; Quirion, J. C.; Husson, H. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2335.

2 Fiaud, J. C.; Maze, F.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 3647.

3 Yang, T. K.; Li, D. S. *Tetrahedron: Asymmetry* **1999**, *10*, 405.

4 (a) Kim, H. O.; Olsen, R. O.; Choi, O. S. *J. Org. Chem.* **1987**, *52*, 4531.
(b) Focella, A.; Bizzarro, F.; Exon, C. *Synth. Commun.* **1991**, *21*, 2165.

5 Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1977**, *33*, 507.

6 Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765.

7 Curphey, T. J.; Trivedi, L. D.; Layloff, T. *J. Org. Chem.* **1974**, *39*, 3831.

8 (a) Mitsunobu, O. *Synthesis* **1981**, 1.
(b) Cory, E. J.; Cimprich, K. A. *Tetrahedron Lett.* **1992**, *33*, 4099.
(c) Schedel, H.; Quaedflieg, P. J. L. M.; Broxterman, Q. B.; Bisson, W.; Duchateau, A. L. L.; Maes, I. C. H.; Herzschuh, R.; Burger, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2125.

9 Juaristi, E.; Cruz-Sanchez, J. S. *J. Org. Chem.* **1988**, *53*, 3334.

10 Jamea, A. D.; Moscher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732.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