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Asymmetric Reduction of α-(Dimethylthiocarbamoylthio) Carbonyl Compounds with Bakers' Yeast

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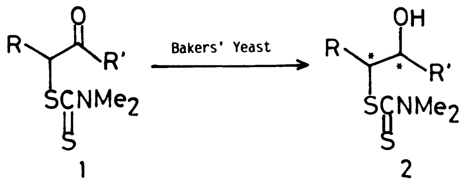
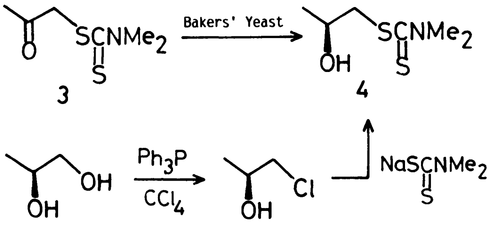
Treatment of α-(dimethylthiocarbamoylthio) ketones with bakers' yeast afforded the corresponding chiral alcohols in high yields with high enantiomeric excess (in most cases, more than 96% ee). α-(Dimethylthiocarbamoylthio) aldehydes were reduced to give chiral α-(dimethylthiocarbamoylthio) alcohols in 69—92% yields with 32—63% ee, which were converted to chiral 1,2-epithio derivatives.

Recently, asymmetric reduction of ketones with bakers' yeast (Saccharomyces cerevisiae) has been widely utilized for the preparation of chiral building blocks.[1] It is well-known that the reduction of β-keto esters by bakers' yeast affords optically active β-hydroxy esters.[1] Generally speaking, ketones α-substituted by an electron-withdrawing group are inclined to be reduced with bakers' yeast. Ketones α-substituted by sulfur atoms are also reduced to give chiral alcohols. For example, asymmetric reductions of compounds such as 1,3-dithians,[2] sulfides,[3] sulfones[4] with bakers' yeast are reported. Here, we describe an asymmetric reduction of α-(dimethylthiocarbamoylthio) ketones 1 with bakers' yeast, leading to chiral alcohols 2. Ketones 1 can be obtained in high yield by the reaction of α-halo ketones with sodium dimethyldithiocarbamate, which is commercially available and can be easily prepared by the reaction of dimethylamine and carbon disulfide in the presence of sodium hydroxide.[5]

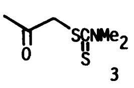
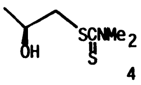
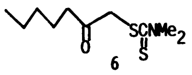
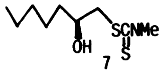
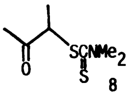
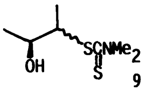
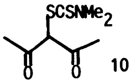
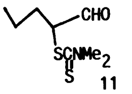
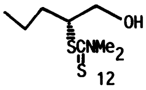
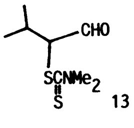
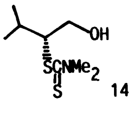
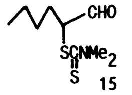
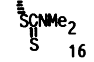
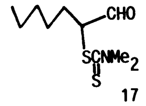


Various ketones 1 were prepared and treated with bakers' yeast in tap water in the presence of glucose. The reaction gave chiral alcohols 2 in good yield. Enantiomeric excess of the chiral alcohols obtained was determined by ^1H NMR analysis in the presence of chiral shift reagent ($Eu(hfc)_3$) and/or by HPLC analysis for the corresponding esters of (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA).[6] These results are shown in Table 1.



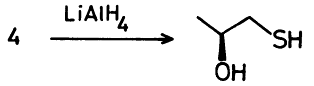
Treatment of α-(dimethylthiocarbamoylthio)acetone (3) with bakers' yeast gave the corresponding chiral alcohol 4 with more than 96% ee in unusually

Table 1. Asymmetric Reduction of α-(Dimethylthiocarbamoylthio)-Substituted Carbonyl Compounds with Bakers' Yeast

Ketone	Product	Reaction time/day	Yield[a)] %	ee %
 3	 4	6	91	>96
 6	 7	6	39	>96
 8	 9	4	82[b)]	>96[c)]
 10	3	4	25	—
	4	4	39	77
 11	 12	5	92	55
 13	 14	9	69	32
 15	 16	10	78	46
 17	 18	9	75	63

a) Isolated yield. b) Isolated as a diastereomeric mixture: erythro/threo=72/28. c) Both of erythro and threo.

high yield (91%). The absolute configuration was determined to be *S* by the independent synthesis of **4** via (*S*)-1-chloro-2-propanol from (*S*)-(+)-1,2-propanediol, as shown in experimental section. Reduction of **4** with $LiAlH_4$ gave 1-mercapto-2-propanol (**5**) in 83%

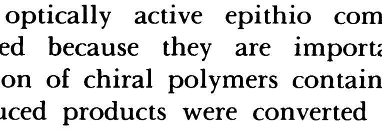


5

yield. Chiral reduction of 1-(dimethylthiocarbamoylthio)-2-heptanone (**6**) with bakers' yeast afforded optically pure (*S*)-(+)-1-(dimethylthiocarbamoylthio)-2-heptanol (**7**) in 39% yield. Treatment of 3-(dimethylthiocarbamoylthio)-2-butanone (**8**) with bakers' yeast yielded the diastereomeric mixture of the corresponding alcohols **9** with the ratio of erythro/threo (72/28) in 82% yield. Optical purities of each isomer separated by preparative HPLC were more than 96% ee. Treatment of 3-(dimethylthiocarbamoylthio)-2,4-pentanedione (**10**) with bakers' yeast gave a mixture of hydrolysis product **3** and its reduced product **4**. Absolute configuration of the chiral alcohols **7** and **9** was presumed to be *S* by comparison of the symbol of the optical rotation of **4**. This fact consists with the results obtained on the reduction of other sulfur-substituted ketones.[3,4]

Furthermore, α-(dimethylthiocarbamoylthio) aldehydes were also reduced with bakers' yeast to give chiral alcohols unexpectedly, although the optical purity was not high. For example, 2-(dimethylthiocarbamoylthio)pentanal (**11**) was reduced with bakers' yeast to give the corresponding alcohol **12** in 92% yield with 55% ee. As shown in the table, some aldehydes such as **13**, **15**, and **17** were also reduced with bakers' yeast to give the corresponding chiral alcohols **14**, **16**, and **18** in good yields.

Some optically active epithio compounds are synthesized because they are important for the preparation of chiral polymers containing sulfur.[7] The reduced products were converted to the thioepoxides and the absolute configuration was determined as *R* by comparison of the direction of the optical rotation with that of known epithio compounds.[7] Compound **12** was treated with sodium hydride to give (*R*)-(+)-1,2-epithiopentane (**19**) in 40% yield. Compound **14** was also treated with sodium hydride to give a known compound, (*R*)-(+)-3-methyl-1,2-epithiobutane (**20**).[7]



12, $R=CH_2CH_2CH_3$ **19**, $R=CH_2CH_2CH_3$

14, $R=CH(CH_3)_2$ **20**, $R=CH(CH_3)_2$

The present reduction with bakers' yeast afforded chiral (dimethylthiocarbamoylthio) alcohols in good yield, which would be useful for the synthesis of sulfur containing natural products[8] and chiral thiiranes[7] because the reaction conditions are mild and the procedures are simple and economically feasible.

Experimental

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Analytical spectra were obtained with the following instruments: IR, Jasco Model A-102; ^1H NMR (60 MHz), JEOL JNM-PMX60SI apparatus; ^1H NMR (100 MHz) and ^{13}C NMR (25 MHz), JEOL JNM-FX100 apparatus. Optical rotations were measured on a Jasco DIP-4 spectrometer. HPLC analysis was performed with a Yanagimoto liquid chromatograph L-2000 fitted with a Yanapak SA-I (6-mm o.d.×250-mm length) and with a Sumipax OA-3000 (4-mm o.d.×250-mm length) for the determination of enantioselectivity.

Fermentation was carried out at 31—35 °C by using industrial bakers' yeast purchased from Oriental Yeast Co., Ltd. All glasswares were sterilized by boiling water before use. The amount of consumed glucose was checked by test paper for that of glucose in urine. During the fermentation, additional glucose was added when the concentration became less than 0.5%. α-Chloro aldehydes were prepared by the reaction of aldehydes with sulfuryl chloride.[9]

α-(Dimethylthiocarbamoylthio)acetone (3). To a solution of 5 g (35 mmol) of sodium dimethyldithiocarbamate in 30 ml of methanol was added dropwise 3.9 g (42 mmol) of chloroacetone with cooling. The mixture was stirred overnight at room temperature and then poured into water. After the mixture was concentrated in vacuo, the organic material was extracted with dichloromethane. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated to give 5.46 g (88%) of **3**: mp 50—51 °C (from ethyl acetate); IR (KBr) 1715, 1498, 1355, 1255, 1155, and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.33 (s, 3H, $COCH_3$), 3.49 (s, 6H, $N(CH_3)_2$), 4.18 (s, 2H, CH_2). Found: C, 40.78; H, 6.17; N, 7.68%. Calcd for $C_6H_{11}NOS_2$: C, 40.65; H, 6.26; N,7.90%.

(*S*)-(+)-1-(Dimethylthiocarbamoylthio)-2-propanol (4). To a mixture of KH_2PO_4 (1 g), $NH_4H_2PO_4$ (1 g), $MgSO_4$ (0.5 g), $CaCO_3$ (2.5 g), glucose (90 g), and boiled water (450 ml) was added 9 g of bakers' yeast at 32 °C. After bubbles formed (ca. 20 min), 3 g (16.9 mmol) of **3** was added and then the mixture was stirred at 32 °C for 57 h. The organic layer was extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to give 3.22 g of an oil, which was chromatographed on SiO_2 (hexane/CH_2Cl_2=5/1) to give 2.74 g (91%) of **4**: bp 240 °C (10 mm) (short-pass distillation); mp 50—51 °C (from ether); $[\alpha]_D^{13}$ +52.2° (*c* 0.20, $CHCl_3$); IR (neat) 3400, 2990, 2940, 1500, 1375, 1255, 1145, 1120, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (d, *J*=6 Hz, 3H, $\underline{H}_3CHOH$), 2.97 (s, 1H, OH), 3.43 (m, 8H, $(C\underline{H}_3)_2N$, $C\underline{H}_2S$), 4.00 (m, 1H, $CH_3C\underline{H}OH$). Found: C, 39.78; H, 6.88; N, 7.20%. Calcd for $C_6H_{13}NOS_2$: C, 40.19; H, 7.31; N, 7.81%.

Independent Synthesis of 4. To 1.15 g (4.4 mmol) of triphenylphosphine was added a solution of 313 mg (4.12 mmol) of (*S*)-(+)-1,2-propanediol ($[\alpha]_D^{26}$ +16.9° (neat)) in 3 ml of CCl_4 under an atmosphere of nitrogen. The mixture was heated under reflux for 4 h and then cooled to room temperature. A mixed solvent of hexane and ether (3/1) was added and the mixture was filtered. After concentration of the filtrate, the residue was added dropwise into a solution of 630 mg (4.4 mmol) of sodium dimethyldithiocarbamate in 5 ml of methanol and then the mixture was heated under reflux for 4 h. After evaporation of the solvent, the residue was poured into water. The organic layer was extracted with ethyl acetate. The extracts were washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave 256 mg of the crude product, which was purified by preparative TLC (hexane/ethyl acetate, 1/1) to give 43 mg (5.8%) of **4**: R_f 0.34—0.51; $[\alpha]_D^{27}$ +33.3° (*c* 0.96, $CHCl_3$). IR and ^1H NMR data were identical with those of an authentic sample prepared above.

(*S*)-(+)-1-Mercapto-2-propanol (5). To a stirred mixture of $LiAlH_4$ (150 mg, 3.95 mmol) and dry ether (5 ml) was added a solution of **4** (471 mg, 2.63 mmol) in 5 ml of dry ether at −20 °C. The mixture was stirred for 2 h at −20 °C and then quenched with dilute HCl. The organic layer was extracted with ether and the combined extracts were washed with water, dried over $MgSO_4$, and concentrated. Removal of the solvent gave 142 mg (59%) of **5**: $[\alpha]_D^{22}$ +86.1° (*c* 2.42, $CHCl_3$); IR (neat) 3400, 3000, 1260, 1125, 1070 cm^{-1}. ^1H NMR data were identical with those of the literature.[10]

1-(Dimethylthiocarbamoylthio)-2-heptanone (6). To a solution of 1.92 g (16.9 mmol) of 2-heptanone in 15 ml of ether was added 2.70 g (0.87 ml, 16.9 mmol) of bromine at 0 °C. After the brown color disappeared, the mixture was poured into water and the organic materials were extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ and water, and dried over $MgSO_4$. Concentration of the solvent gave 3.17 g (97%) of a mixture of 3-bromo-2-heptanone and 1-bromo-2-heptanone (4/1): IR (neat) 1720, 1460, 1350, 1220 cm^{-1}; ^1H NMR (CCl_4) δ=0.91 (t, 3H, CH_3), 1.10—1.65 (m, 4H, $(CH_2)_2$), 1.70—2.20 (m, 2H, $C\underline{H}_2CHBr$), 2.27 (s, 3H, $C\underline{H}_3CO$), 4.17 (t, 1H, $C\underline{H}Br$). To a solution of 1.43 g (10.0 mmol) of sodium dimethyldithiocarbamate in 10 ml of methanol was added dropwise 1.50 g of the brominated 2-heptanone described above and the mixture was stirred overnight. After evaporation of the solvent, the residue was poured into water. The organic materials were extracted with CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated. The crude oil (2.55 g) was chromatographed on SiO_2 to give 1.06 g (74%) of 3-(dimethylthiocarbamoylthio)-2-heptanone: IR (neat) 1710, 1500, 1250, 1150, 1050, 980 cm^{-1}; ^1H NMR (CCl_4) δ=0.91 (t, 3H, CH_3), 1.10—2.00 (m, 6H, $(CH_2)_3$), 2.19 (s, 3H, $C\underline{H}_3CO$), 3.47 (s, 6H, $N(CH_3)_2$), 4.82 (t, 1H, $C\underline{H}SCSN$). The last fraction gave 60 mg (16%) of **6**: ^1H NMR (CCl_4) δ=0.92 (t, 3H, CH_3), 1.1—2.0 (m, 6H, $(CH_2)_3$), 2.65 (t, 2H, $C\underline{H}_2CO$), 3.50 (s, 6H, $N(C\underline{H}_3)_2$), 4.20 (s, 2H, $C\underline{H}_2SCSN$). Found: C, 51.68; H, 7.94; N, 6.01%. Calcd for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.20; N, 6.00%.

(*S*)-(+)-1-(Dimethylthiocarbamoylthio)-2-heptanol (7). To a mixture of KH_2PO_4 (0.2 g), $NH_4H_2PO_4$ (0.2 g), $MgSO_4$ (0.1 g), $CaCO_3$ (0.5 g), glucose (10 g), and boiled water (100 ml) was added 1 g of bakers' yeast at 32 °C. After bubbles formed (ca. 15 min), 0.125 g (0.534 mmol) of **6** was added and then the mixture was stirred at 35 °C. After 84 h, 1 g of bakers' yeast was added. After 113 h, 2 g of glucose was added. After 5.5 h, the organic layer was extracted twice with ethyl acetate and CH_2Cl_2. The combined extracts were washed with water and dried over $MgSO_4$. Concentraion of the solvent gave 0.116 g of the crude product, which was purified with column chromatography to give 55 mg (39%) of **7**: ^1H NMR (CCl_4) δ=0.9 (t, 3H, CH_3), 1.1—1.8 (m, 8H, $(CH_2)_4$), 3.1—3.6 (m, 9H, $C\underline{H}_2C\underline{H}OH$, $N(C\underline{H}_3)_2$), 3.68 (d, 2H, $CHOHC\underline{H}_2$); $[\alpha]_D^{32}$ +12.0° (*c* 0.50, $CHCl_3$); >95% ee by ^1H NMR analysis in the presence of $Eu(hfc)_3$. Found: C, 51.07; H, 8.69; N, 5.83%. Calcd for $C_{10}H_{21}NOS_2$: C, 51.02; H, 8.99; N, 5.95%.

3-(Dimethylthiocarbamoylthio)-2-butanone (8). To a mixed solution of sodium dimethyldithiocarbamate in 10 ml of methanol was added 1.50 g of a mixture of 3-chloro-2-butanone and 3,3-dichloro-2-butanone (5/6)[9] with ice cooling. The mixture was stirred overnight and concentrated. The organic layer was extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. The residual oil (1.93 g) was purified with column chromatography (hexane/ethyl acetate, 10/1) to give 0.545 g (52%) of **8**: IR (neat) 1710, 1500, 1250, 1050, 980 cm^{-1}; ^1H NMR (CCl_4) δ=1.44 (d, *J*=8 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 3.50 (s, 6H, $N(CH_3)_2$), 4.87 (q, 1H, $C\underline{H}SCSN$). Found: C, 43.85; H, 6.71; N, 7.24%. Calcd for $C_7H_{13}NOS_2$: C, 43.95; H, 6.85; N, 7.32%.

3-(Dimethylthiocarbamoylthio)-2-butanol (9). To a mixture of $NH_4H_2PO_4$ (0.6 g), KH_2PO_4 (0.6 g), $MgSO_4$ (0.3 g), $CaCO_3$ (1.28 g), glucose (30 g), and boiled water (300 ml) was added 3 g of bakers' yeast at 32 °C. After bubbles formed (ca. 20 min), 0.722 g (4.52 mmol) of **8** was added and then the mixture was stirred at 35 °C. After 64 h, 10 g of glucose was added. After 96 h, the organic layer was extracted twice with ethyl acetate and CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated. The residual oil (0.285 g) was chromatographed on SiO_2 to give 0.60 g (82%) of **9** as a mixture of erythro and threo (72/28): IR (neat) 3340, 1500, 1370, 1050, 980 cm^{-1}; ^1H NMR (CCl_4) δ=1.25 (m, 6H, $2CH_3$), 2.20 (s, 1H, OH), 3.43 (s, 6H, $N(CH_3)_2$), 4.03 (m, 2H, $C\underline{H}OHC\underline{H}SCS$). Found: C, 43.59; H, 7.96; N, 7.12%. Calcd for $C_7H_{15}NOS_2$: C, 43.49; H, 7.82; N, 7.25%. Each component was separated by preparative HPLC (column, SA-I(6ϕ×25 mm); eluent, hexane/ethyl acetate/ethanol (20/5/1)). *erythro*-**9**: $[\alpha]_D^{25}$ +109.4° (*c* 1.70, $CHCl_3$); IR (neat) 3430, 1500, 1381, 1260, 990, 980 cm^{-1}; ^1H NMR (CCl_4) δ=1.15 (d, *J*=6 Hz, 3H, $C\underline{H}_3CHOH$), 1.32 (d, *J*=6 Hz, 3H, $C\underline{H}_3CHSCS$), 2.55 (s, 1H, OH), 3.45 (s, 6H, $N(CH_3)_2$), 4.10 (m, 2H, $C\underline{H}C\underline{H}$); $J_{CH\text{-}CH}$=3.2 Hz , determined by ^1H NMR in the presence of 10% $Eu(hfc)_3$; >96% ee, no paired peaks in the presence of 40% $Eu(hfc)_3$. *threo*-**9**: $[\alpha]_D^{25}$ −51.4° (*c* 1.07, $CHCl_3$); IR (neat) 3420, 1500, 1372, 1250, 980, 962 cm^{-1}; ^1H NMR (CCl_4) δ=1.19 (d, *J*=6 Hz, 3H, $C\underline{H}_3CHOH$), 1.36 (d, *J*=6 Hz, 3H, $C\underline{H}_3CHSCS$), 2.40 (s, 1H, OH), 3.44 (s, 6H, $N(CH_3)_2$), 3.98 (m, 2H, $>CH\text{–}CH<$); $J_{CH\text{-}CH}$=4.8 Hz, determined by ^1H NMR in the presence of 10% $Eu(hfc)_3$; >96% ee, no paired peaks in the presence of 40% $Eu(hfc)_3$.

3-(Dimethylthiocarbamoylthio)-2,4-pentanedione (10). To a solution of 2.18 g (15.2 mmol) of sodium dimethyldithiocarbamate in 10 ml of methanol was added dropwise 2.01 g (15 mmol) of 3-chloro-2,4-pentanedione[11] with ice cooling. The mixture was stirred for 9 h at room temperature. After concentration of the solvent, the residue was poured into water and the organic layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated. The crude product (3.56 g) was purified with column chromatography (hexane/ethyl acetate, 20/1) to give 2.20 g (67%) of **10**: ^{1}H NMR (CCl_4) δ=2.06 (s, 6H, $2CH_3$), 3.50 (s, 6H, $N(CH_3)_2$), 17.32 (s, 1H, C=C-OH). Found: C, 43.49; H, 5.85; N, 6.12%. Calcd for $C_8H_{13}NO_2S_2$: C, 43.81; H, 5.97; N, 6.39%.

Reduction of 10 with Bakers' Yeast. Compound **10** (1.01 g, 4.59 mmol) was treated with bakers' yeast for 4 days, as described in the preparation of **9**. The crude product was chromatogaphed on SiO_2 (hexane/ethyl acetate, 20/1) to give 0.206 g (25%) of **3** as the first fraction. The second fraction gave 0.318 g (39%) of **4**: $[\alpha]_D^{25}$ +40.2 (*c* 2.56, $CHCl_3$): 77% ee. Spectral data were identical with those of the samples prepared above.

2-(Dimethylthiocarbamoylthio)pentanal (11). To a solution of 12.0 g (83.9 mmol) of sodium dimethyldithiocarbamate in 40 ml of methanol was added dropwise 9.57 g (79.4 mmol) of 2-chloropentanal with ice cooling. The mixture was stirred for 12 h at 25 °C and then for 1 h at 30—40 °C. After concentration of the solvent, the organic layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated. The residue (14.9 g) was distilled to give 10.2 g (63%) of **11**: bp 127—129 °C (0.3 mm); IR (neat) 1720, 1500, 1380, 1250, 980 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.00 (t, *J*=6 Hz, 3H, CH_3), 1.20—2.20 (m, 4H, $(CH_2)_2$), 3.50 (s, 6H, $N(CH_3)_2$), 4.75 (t, *J*=6 Hz, 1H, C$\underline{H}$SCS), 9.37 (s, 1H, C$\underline{H}$O). Found: C, 47.08; H, 7.34; N, 6.62%. Calcd for $C_8H_{15}ONS$: C, 46.79; H, 7.36; N, 6.82%.

Other aldehydes (**13**, **15**, **17**) were also prepared by the method described above.

2-(Dimethylthiocarbamoylthio)-3-methylbutanal (13): 53% yield; bp 133—135 °C (0.3 mm); IR (neat) 2950, 1720, 1500, 1470, 1250 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.95 (d, *J*=6.5 Hz, 3H, CH_3), 1.10 (d, *J*=6.5 Hz, 3H, CH_3), 2.45 (m, 1H, $(CH_3)_2C\underline{H}$), 3.50 (s, 6H, $N(CH_3)_2$), 4.85 (d, *J*=5 Hz, 1H, C$\underline{H}$CHO), 9.42 (s, 1H, CHO). Found: C, 46.72; H, 7.18; N, 7.03%. Calcd for $C_{18}H_{15}NOS_2$: C, 46.79; H, 7.36; N, 6.82%.

2-(Dimethylthiocarbamoylthio)hexanal (15): 63% yield; bp 80 °C (1.5 mm) (bath temperature); IR(neat) 2950, 1720, 1500, 1380, 1255, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.89 (t, 3H), 1.11—2.13 (m, 6H), 3.46 (d, 6H), 4.75 (t, *J*=6.5 Hz, 1H), 9.50 (s, 1H). Found: C, 49.52; H, 7.80, N, 6.21%. Calcd for $C_9H_{17}NOS_2$: C, 49.28; H, 7.81; N, 6.39%.

2-(Dimethylthiocarbamoylthio)heptanal (17): 96% yield; IR (neat) 1720, 1500, 1380, 1250, 1150, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.86 (t, *J*=6 Hz, 3H), 1.07—1.56 (m, 8H), 3.45 (s, 6H), 4.70 (t, *J*=6 Hz, 1H), 9.36 (s, 1H).

(*R*)-(+)-2-(Dimethylthiocarbamoylthio)-1-pentanol (12). To a mixture of $NH_4H_2PO_4$ (1 g), KH_2PO_4 (1 g), $MgSO_4$ (0.5 g), $CaCO_3$ (2.5 g), glucose (40 g), and boiled water (500 ml) was added 5 g of bakers' yeast at 35 °C. After bubbles formed, 1.77 g (8.63 mmol) of **11** was added and then the mixture was stirred at 35 °C. After 21, 47, 69, 94, and 106 h, 5 g of bakers' yeast was added. After 5 days, the organic layer was extracted twice with ethyl acetate and CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated. The residual oil (1.85 g) was chromatographed on SiO_2 (hexane/ethyl acetate, 10/1) to give 1.64 g (92%) of **12**: $[\alpha]_D^{35}$ +30.3° (*c* 4.02, $CHCl_3$): IR (neat) 3300, 1500, 1362, 1240, 980 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.10 (t, 3H, CH_3), 1.30—2.00 (m, 4H, $(CH_2)_2$), 3.50 (s, 6H, $N(CH_3)_2$), 3.61 (d, 2H, C$\underline{H}_2$OH), 4.10 (m, 1H, C$\underline{H}$SCS). Found: C, 46.40; H, 8.15; N, 6.46%. Calcd for $C_8H_{17}ONS$: C, 46.34; H, 8.27; N, 6.76%.

MTPA Ester of 12. To a solution of **12** (0.248 g, 1.20 mmol), CCl_4 (5 ml), and pyridine (5 ml) was added 0.146 g (0.577 mmol) of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[6] The mixture was stirred for 27 h at room temperature and then poured into water. The organic layer was extracted with ether and the combined extracts were washed with dilute HCl, saturated $NaHCO_3$, and water, and dried over $MgSO_4$. After removal of the solvent, the residue (0.34 g) was purified with preparative TLC (hexane/ethyl acetate, 2/1) to give 91 mg (39%) of MTPA ester of **12**: R_f 0.36—0.53; IR (neat) 1755, 1250, 1165, 1020, 980 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.95 (t, *J*=6 Hz, 3H, CH_3), 1.1—1.9 (m, 4H, $(CH_2)_2$), 3.40 (s, 6H, $N(CH_3)_2$), 3.50 (s, 3H, OCH_3), 4.0—4.5 (m, 3H, OCH_2CHSCS), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=13.8 (q), 20.1 (t), 32.6 (t), 50.8 (d), 51.0 (d), 55.5 (q), 68.0 (t), 127.5 (d), 128.4 (d), 129.6 (d), 132.3 (s); 54.6% ee, determined by the peak ratio of δ 50.8 and 51.0 ($\underline{C}$HSCS). Found: C, 51.18; H, 5.84; N, 3.28%. Calcd for $C_{18}H_{24}O_3NS_2F_3$: C, 51.04; H, 5.71; N, 3.31%.

(*R*)-(+)-2-(Dimethylthiocarbamoylthio)-3-methyl-1-butanol (14). Compound **13** (4.09 g, 19.9 mmol) was treated with bakers' yeast as shown in the preparation of **12**. The crude product (3.76 g) was chromatographed on SiO_2 (hexane/ethyl acetate, 10/1—2/1) to give 1.58 g (39% yield, 69% yield based on the consumed **13**): TLC (hexane/ethyl acetate, 2/1), R_f 0.26; $[\alpha]_D^{26}$ +29.6° (*c* 1.34, $CHCl_3$); 32% ee, determined by ^{1}H NMR in the presence of Eu(hfc)$_3$; IR (neat) 3450, 1500, 1375, 1255, 980 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.01 (d, *J*=6 Hz, 3H, CH_3), 1.05 (d, *J*=6 Hz, 3H, CH_3), 2.12 (s, 1H, OH), 2.30 (m, 1H, $C\underline{H}(CH_3)_2$), 3.44 (s, 6H, $N(CH_3)_2$), 3.69 (d, *J*=6 Hz, 2H, CH_2), 4.08 (m, 1H, CHSCS). Found: C, 46.41; H, 8.15; N, 7.02%. Calcd for $C_8H_{17}NOS_2$: C, 46.33; H, 8.27; N, 6.76%. The later fraction gave 1.80 g of **13**: TLC (hexane/ethyl acetate, 2/1), R_f 0.44.

(*R*)-(+)-2-(Dimethylthiocarbamoyl)-1-hexanol (16). Aldehyde **15** (0.370 g, 1.69 mmol) was treated with bakers' yeast, as shown in the preparation of **12**. The crude product (2.9 g) was chromatographed on SiO_2 (hexane/ethyl acetate, 10/1) to give 0.29 g (78%) of **16**: $[\alpha]_D^{17}$ +39.6° (*c* 1.39, $CHCl_3$); IR (neat) 3400, 2940, 1500, 1250, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.94 (t, *J*=6 Hz, 3H, CH_3), 1.14—2.00 (m, 6H), 2.41 (s, 1H), 3.50 (s, 6H), 3.66 (d, *J*=5.5 Hz, 2H), 4.00 (m, 1H); 46% ee, determined by ^{13}C NMR spectrum of the MTPA ester. Found: C, 48.79; H, 8.74; N, 6.44%. Calcd for $C_9H_{19}NOS_2$: C, 48.83; H, 8.65; N, 6.33%.

MTPA Ester of 16. To a mixture of **16** (0.1 g, 0.457 mmol), CCl_4 (5 ml), and pyridine (5 ml) was added 0.115 g (0.455 mmol) of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[6] The mixture was stirred for 20 h at room temperature. After quenched with water, the organic layer was extracted with ether. The ethereal layer was washed with dil HCl, saturated $NaHCO_3$, and water, and then dried over $MgSO_4$. Concentration of the solvent gave the crude product, which was purified with preparative TLC (hexane/ethyl acetate, 2/1) to afford 68 mg (34%) of MTPA ester of **16**: R_f 0.45—0.55; IR (neat) 2950, 1750, 1500, 1250, 1165, 980 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.89 (t, *J*=6 Hz, 3H), 1.1—2.0 (m, 6H), 3.40 (s, 6H), 3.51 (s, 3H), 3.9—4.6 (m, 3H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=13.8 (q), 22.4 (t), 28.9 (t), 30.1 (t), 41.4 (q), 45.5 (q), 50.8 (d), 51.1 (d), 57.9 (t), 127.4 (d), 128.4 (d), 129.6 (d), 132.2 (s), 166.2 (s), 195.6 (s); 46% ee, determined by the peak ratio of δ 50.8 and 51.1 ($\underline{C}$HSCS). Found: C, 52.03; H, 6.12; N, 3.11%. Calcd for $C_{19}H_{26}F_3NO_3S_2$: C, 52.16; H, 5.99; N, 3.20%.

(*R*)-(+)-2-(Dimethylthiocarbamoylthio)-1-heptanol (18). Aldehyde **17** (2.23 g, 9.56 mmol) was treated with bakers' yeast for 9 days, as shown in the preparation of **12**. The crude product (2.2 g) was chromatographed on SiO_2 (hexane/ethyl acetate, 20/1) to give 1.69 g (75%) of **18**: $[\alpha]_D^{26}$ +39.6° (*c* 5.00, $CHCl_3$): IR (neat) 3425, 1500, 1375, 1255, 980 cm^{-1}; ^1H NMR (CCl_4) δ=0.95 (t, 3H), 1.13—1.90 (m, 8H), 2.82 (s, 1H), 3.50 (s, 6H), 3.70 (m, 2H), 4.00 (m, 1H). Found: C, 51.23; H, 8.89; N, 6.12%. Calcd for $C_{10}H_{21}NOS_2$: C, 51.02; H, 8.99; N, 5.95%.

MTPA ester of 18 was prepared by the reaction of **18** (116 mg, 0.498 mmol) with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[6] as described above. The crude product (0.25 g) was purified by preparative TLC (hexane/ethyl acetate, 2/1) to give 117 mg (52%) of MTPA ester of **18**: $[\alpha]_D^{26}$ +3.16° (*c* 3.16, $CHCl_3$); IR (neat) 2950, 1755, 1380, 1250, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.89 (t, *J*=5.5 Hz, 3H), 1.05—2.0 (m, 8H), 3.35 (s, 3H), 3.41 (s, 3H), 3.55 (s, 3H), 4.0—4.7 (m, 3H), 7.4 (broad S, 5H): ^{13}C NMR ($CDCl_3$) δ=13.9 (q), 22.3 (t), 26.4 (t), 30.4 (t), 31.5 (t), 41.4 (q), 45.3 (q), 50.9 (d), 51.1 (d), 55.5 (q), 68.0 (t), 127.5 (d), 128.3 (d), 129.5 (d), 132.2 (s), 166.2 (s), 195.5 (s); 63% ee, determined by the peak ratio of δ 50.9 and 51.1 ($\underline{C}$HSCS). Found: C, 53.26; H, 6.17; N, 3.04%. Calcd for $C_{20}H_{28}F_3NO_3S_2$: C, 53.20; H, 6.25; N, 3.10%.

(*R*)-(+)-1,2-Epithiopentane (19). To a stirred mixture of NaH (0.661 g, 16.5 mmol) and THF (3 ml) was added a solution of 2.75 g (13.3 mmol) of **12** in 5 ml of THF at 0 °C during a period of 45 min. The mixture was stirred for 30 min at 0 °C and for 2 h at room temperature. After the mixture was poured into water, the organic layer was extracted with ether, washed with water, dried over $MgSO_4$, and concentrated. Short-pass distillation of the residue gave 0.523 g (40%) of **19**: $[\alpha]_D^{24}$ +8.0° (*c* 1.0, $CHCl_3$); IR (neat) 2890, 1460, 1261, 1040, 915 cm^{-1}; ^1H NMR (CCl_4) δ=0.98 (t, *J*=6 Hz, 3H, CH_3), 1.11 (m, 4H, CH_2CH_2), 2.04 (apparent d, *J*=5 Hz, 1H, CH_2S), 2.38 (apparent d, *J*=6 Hz, 1H, CH_2), 2.78 (m, 1H, CHS); ^{13}C NMR ($CDCl_3$) δ=13.7 (q), 22.5 (t), 25.8 (t), 35.7 (d), 38.6 (t); mass spectrum (70 eV) *m/z* 102 (M^+), 87, 74, 73, 70, 69, 64, 59. Found: C, 58.68; H, 9.57%. Calcd for $C_5H_{10}S$: C, 58.77; H, 9.86%.

(*R*)-(+)-3-Methyl-1,2-epithiobutane (20).[7] To a stirred mixture of 0.20 g (5.00 mmol) of NaH (60% in oil) and 1 ml of ether was added dropwise a solution of 1.03 g (4.98 mmol) of **14** in 3 ml of ether at 0 °C. The mixture was stirred for 2 days at 0 °C and then poured in ice water, and acidified with 10% HCl. The organic layer was extracted with ether, washed with water, dried over $MgSO_4$, and concentrated. Short-pass distillation of the residue afforded 18 mg (4%) of **20**: bp 70—90 °C (100 mm)(bath temperature); $[\alpha]_D^{26}$ +4.2° (*c* 3.52, $CDCl_3$); IR (neat) 2950, 1660, 1460, 1260, 1040 cm^{-1}: ^1H NMR ($CDCl_3$) δ=1.06 (d, *J*=6 Hz 6H, $2CH_3$), 1.22 (m, 1H, $C\underline{H}(CH_3)_2$), 2.14 (apparent d, *J*=5 Hz, 1H, CH_2S), 2.42 (apparent d, *J*=5 Hz, 1H, CH_2S), 2.65 (m, 1H, CHS).

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