ENZYMATIC SYNTHESIS OF (1*R*, 2*S*)- AND (1*S*, 2*R*)-2-METHYL-2,3-EPOXY-1-PHENYLPROPANOLS

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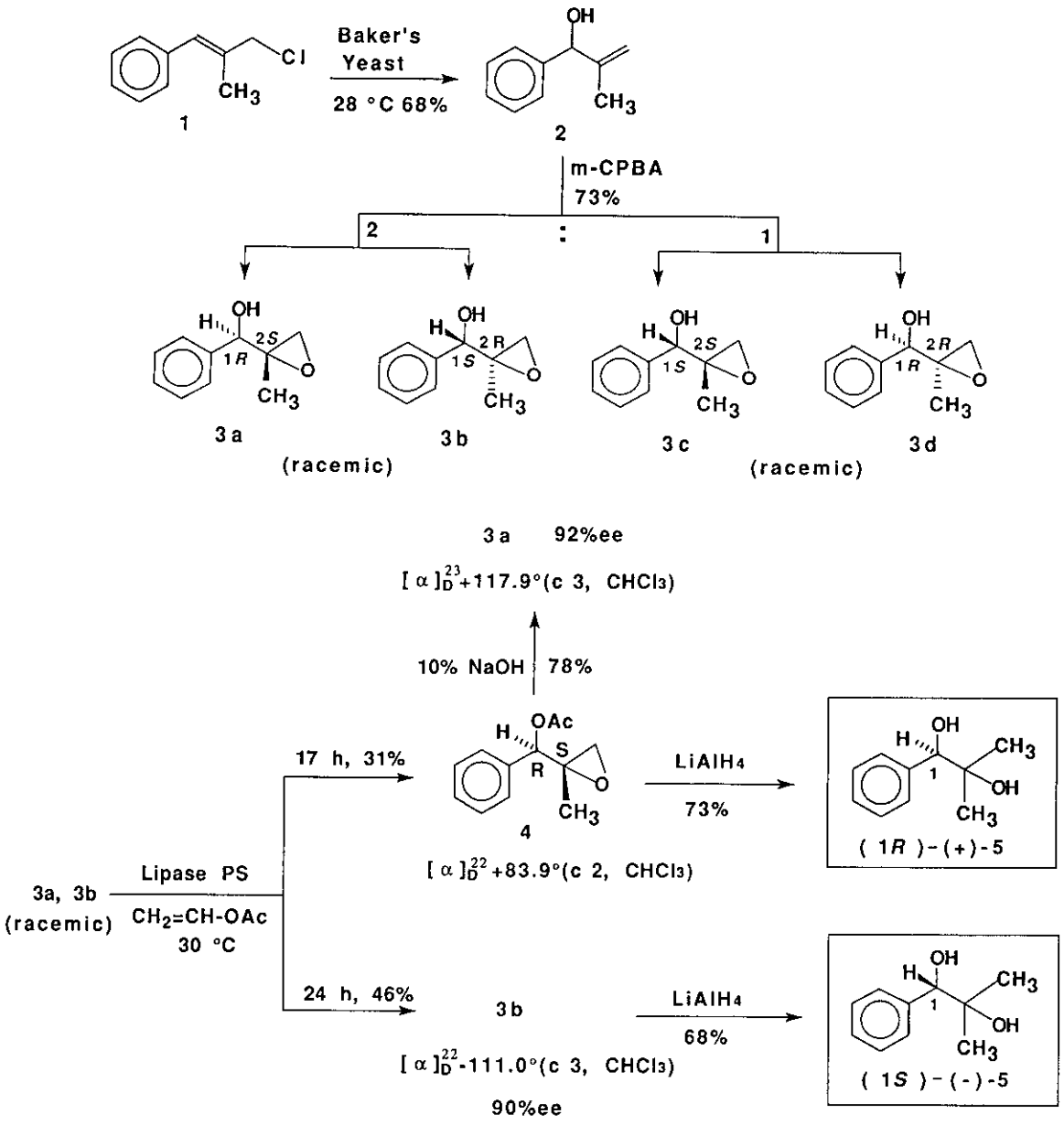
Abstract –(1*R*, 2*S*)- and (1*S*, 2*R*)-2-methyl-2,3-epoxy-1-phenylpropanols were prepared from α–methylcinnamyl chloride by use of baker's yeast and lipase PS.

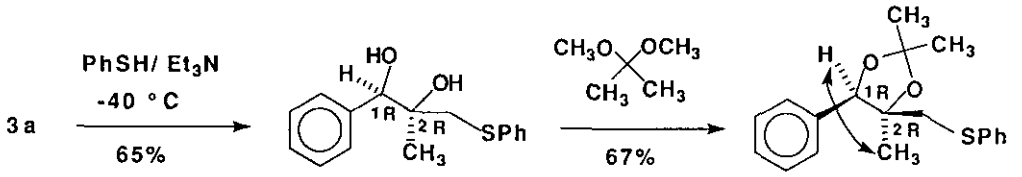
Optically active epoxides have potential as an important key building block for the synthesis of a wide variety of optically active compounds such as natural products.[1] In previous paper, we reported the enzymatic syntheses of chiral epoxy alcohols, which are expected to be chiral intermediates for syntheses of biologically active compounds such as β-blocker,[2] from epoxy ketone.[3,4,5b] Now for a further extention and development of syntheses of new chiral epoxy alcohols, we report here the synthesis and determination of absolute configuration of (1*R*, 2*S*)- and (1*S*, 2*R*)-2-methyl-2,3-epoxy-1-phenylpropanols (3a, 3b) starting from α–methylcinnamyl chloride (1) by use of baker's yeast and lipase PS (*Pseudomonas* sp., Amano). At first, when α–methylcinnamyl chloride (1) was fermentated with baker's yeast for 36 h at 28 °C, rearrangement[3] occurred to give 1-phenylallyl alcohol (2)[6] in 68% yield. Two pairs of racemic epoxy alcohols (3a, 3b) and (3c, 3d) (2 : 1) were separated by silica gel column chromatography (total yield 73%) after epoxidation of **2** with *m*-chloroperbenzoic acid. Enzymatic treatment of the epoxy alcohols (3a, 3b) with vinyl acetate in *t*-butyl methyl ether in the presence of lipase PS[3,5] for 17 or 24 h at 30 °C gave the optically active acetate (4) and alcohol (3b) in chemical yields of 31 and 46%, respectively. However, the same reaction for racemic epoxy alcohols (3c, 3d) was very sluggish (under the above

conditions, esterification proceeded only in 27% chemical yield in three weeks and the optical yield was very low, 56%ee)(Scheme 1).



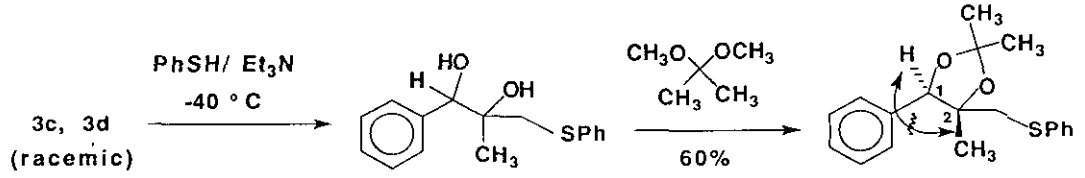
Scheme 1

The absolute configurations and the optical purities at C_1 of the epoxides (4) and (3b) were determined by converting them with lithium aluminum hydride into known (1*R*)- and (1*S*)-1-phenyl-2-methyl-1,2-propanediols [(+)-(5)] and [(-)-(5)][7], respectively and by ^{1}H-nmr spectral analyses (400 MHz) of (*R*)- and (*S*)-methoxy(trifluoromethyl)phenylacetic acid derivatives of **5**.[8] While the stereochemistry at C_2 of 3a was confirmed by the ^{1}H-nmr spectral analysis of acetonide [(1*R*, 2*R*)-7a] prepared from diols [(1*R*, 2*R*)-6a], which was produced in 65% yield by regioselective ring opening of epoxy alcohol (3a, obtained by hydrolysis from **4** in 78% chemical yield) with thiophenol in the presence of triethylamine at -40 °C.



[α]$_D^{21}$+36.1°(c 3, CHCl$_3$)
(1R,2R)-6a

NOE effect (4.7%)
(1R,2R)-7



6c, 6d
(racemic)

no NOE effect

7c, 7d
(racemic)

Scheme 2

In the ^{1}H-nmr spectrum (400 MHz) of [(1*R*, 2*R*)-7a], NOE enhancement (4.7%) between methyl proton and C_1 proton was observed, however, in the racemic acetonide (7c, 7d), NOE effect was absence. Thus the absolute configurations of **3a** and **3b** were finally determined from those of **(1R, 2R)-6a** and **(1R, 2R)-7** (Scheme 2).

EXPERIMENTAL

^{1}H-Nmr spectra were recorded on JEOL PMX-60si (60 MHz) or JNM-GMX-400 (400 MHz)-spectrometers with tetramethylsilane as an internal standard. Ms were recorded on a JEOL JMN-DX 303. For column chromatography, silica gel (Wacogel C-200, from Wako Pure chemical industried, Ltd.) was used. The optical purities(%ee) were calculated from the ^{1}H-nmr spectrum of the (-)- or (+)-MTPA ester.

Treatment of α-Methylcinnamyl Chloride (1) with Baker's Yeast.

A mixture of α-methylcinnamyl chloride (1)(1 g) and baker's yeast (50 g)(purchased from Oriental Yeast Co, Ltd.) in water (300 ml) was fermented for 63 h at 30 °C. The mixture was extracted continuously with $CHCl_3$ using a Soxlet apparatus and the extract was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (30 g) column chromatography using CH_2Cl_2 as eluent to yield 1-phenyl-2-methylallyl alcohol (2)[6](0.6 g , 68%). ^{1}H-Nmr ($CDCl_3$) δ: 1.61(3H, s), 4.96 (1H, dq, *J*= 1.0, 1.7 Hz), 5.14 (1H, s), 5.21 (1H, dq, *J*=1.0, 1.0 Hz), 7.27-7.43(5H, m)

Epoxydation of 1-Phenyl-2-methylallyl Alcohol (2) with *m*-Chloroperbenzoic Acid.

To a solution of 1-phenyl-2-methylallyl alcohol (2)(3.4 g, 22 mmol) in $CHCl_3$ (25 ml), 80% *m*-chloroper- benzoic acid (6.4 g, 34 mmol) was slowly added and the mixture was stirred for 10 h at room temperature. Potassium carbonate (30 g, 0.2 mol) and water (5 ml) were added to the mixture and the mixture was continued to stir for 1 h at room temperature. The mixture was extracted with $CHCl_3$ and the extract was washed with saturated brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (120 g) column chromatography using hexane-CH_2Cl_2 (1: 1) as eluent to give two pairs of racemic 1-phenyl-2-methyl-2,3-epoxypropyl alcohols(3a, 3b)(0.87 g, 22%) and (3c, 3d)(0.67 g, 18%).

3a, 3b(mixture): an oil. *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15, H, 7.37. Found: C, 73.18; H, 7.61.

^{1}H-Nmr ($CDCl_3$) δ: 1.26 (3H, s), 2.66 (1H, d, *J*= 4.6 Hz), 3.17 (1H, d, *J*=4.6 Hz), 4.69 (1H, s), 7.28-7.39 (5H, m).

3c, 3d(mixture): an oil. *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15, H, 7.37. Found: C, 73.08; H, 7.53. ^{1}H-Nmr ($CDCl_3$) δ: 1.20 (3H, s), 2.70 (1H, d, *J*= 4.6 Hz), 3.04 (1H, d, *J*=4.6 Hz), 4.49 (1H, s), 7.28-7.39 (5H, m).

Kinetic Resolution of the Epoxy Alcohols (3a, 3b).

a) Synthesis of (1*R*,2*S*)-1-Phenyl-2-methyl-2,3-epoxypropyl Acetate (4).

To a solution of the epoxy alcohols (3a, 3b) (0.30 g, 2 mmol) and vinyl acetate (1.5 g, 17 mmol) in *tert*-butyl methyl ether (80 ml), lipase PS (Amano)(0.3 g) was added and the mixture was stirred for 17 h at 30 °C. Esterification was monitored by ^{1}H-nmr (60 MHz). The lipase PS was then filtered off and the filtrate was evaporated under reduced pressure to give the residue which was purified by silica gel (120 g) column chromatography using hexane-CH_2Cl_2 (1: 1) as eluent to give (1*R*, 2*S*)-1-phenyl-2-methyl-2,3-epoxypropyl acetate (4) (0.29 g, 31%, 92%*ee*) as an oil. $[\alpha]_D^{22}$ + 83.9° (*c* 2, $CHCl_3$), ^{1}H-nmr ($CDCl_3$) δ: 1.25 (3H, s), 2.62 (1H, d, *J*=4.9 Hz), 2.82 (1H, d, *J*=4.9 Hz), 5.76 (1H, s), 7.31-7.39 (5H, m). Further elution afforded the epoxy alcohol (3b) but in low optical yield.

b) Synthesis of (1*S*,2*R*)-1-Phenyl-2-methyl-2,3-epoxypropyl Alcohol(3b).

To a solution of the epoxy alcohols (3a, 3b)(0.5 g, 3 mmol), and vinyl acetate (2.0 g, 20 mmol) in *tert*-butyl methyl ether (100 ml), lipase PS (Amano)(0.8 g) was added and the mixture was stirred for 24 h at 30 °C. Esterification was monitored by ^{1}H-nmr (60 MHz). The lipase PS was then filtered off and the filtrate was evaporated under reduced pressure to give the residue which was purified by silica gel (120 g) column chromatography using CH_2Cl_2 as eluent to give (1*S*, 2*R*)-1-phenyl-2-methyl-2,3-epoxypropyl alcohol (3b) (0.23 g, 46%, 90%*ee*) as an oil. $[\alpha]_D^{22}$ - 111.0° (c 3, $CHCl_3$). In addition, the acetate(4) was also isolated but in low optical yield.

c) Hydrolysis of (1*R*, 2*S*)-1-Phenyl-2-methyl-2,3-epoxypropyl Acetate (4) with 10% NaOH.

To a solution of (1*R*, 2*S*)-1-phenyl-2-methyl-2,3-epoxypropyl acetate (4) (167 mg, 1 mmol) in MeOH (3ml), aqueous 10% NaOH (5 ml, 12 mmol) was added dropwise at 0 °C. After 2 h, the mixture was extracted with $CHCl_3$ and the extract was washed with saturated brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (10 g) column

chromatography using CH_2Cl_2 as eluent to give (1*R*, 2*S*)-1-phenyl-2-methyl-2,3-epoxypropyl alcohol (3a) (60 mg , 38% , 92%ee), $[\alpha]_D^{23}$ + 114.0° (c 4, $CHCl_3$).

Lithium Aluminum Hydride Reduction of (1*R*, 2*S*)-1-Phenyl-2-Methyl-2,3-epoxypropyl Acetate (4).

To a suspension of lithium aluminum hydride (150 mg, 3 mmol) and THF (20ml), (1*R*, 2*S*)-1-phenyl-2-methyl-2,3-epoxypropyl acetate (4) (106 mg, 0.5 mmol) in THF(2 ml) was added slowly at 0 °C and the mixture was refluxed for 30 min. Aqueous 10% NaOH was added very slowly at 0 °C, and the precipitated solid was filtered off. The filtrate was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (5 g) column chromatography using CH_2Cl_2 as eluent to give (1*R*)-2-methyl-1-phenyl-1,2-propanediol (1*R*)-(+)-5 (46 mg, 46%), $[\alpha]_D^{22}$ + 15.3° (c 3.2, EtOH)[for (*S*)-alcohol, lit.,[7] $[\alpha]_D$ - 16.5° (c 2, EtOH)]. ^{1}H-Nmr ($CDCl_3$) δ : 1.09 (6H, s), 4.21(1H, s), 7.31-7.40 (5H, m).

Lithium Aluminum Hydride Reduction of (1*S*, 2*R*)-1-Phenyl-2-methyl-2,3-epoxypropyl Acetate (4).

To a suspension of lithium aluminum hydride (180 mg, 4 mmol) and THF (20 ml), (1*S*, 2*R*)-1-phenyl-2,3-epoxy-2-methylpropyl acetate (4)(126 mg, 0.6 mmol) in THF (2 ml) was added slowly at 0 °C and the mixture was refluxed for 30 min. Aqueous 10% NaOH was added very slowly to the mixture at 0 °C, and the precipitated solid was filtered off. The filtrate was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (4 g) column chromatography using CH_2Cl_2 as eluent to give (1*S*)-1-phenyl-2-methyl-1,2-propanediol [(1*S*)-(-)-5](68 mg , 68%), $[\alpha]_D^{22}$ -14.0° (c 6, EtOH). ^{1}H-Nmr spectrum was completely identical with that of **(1*R*)-(+)-5**.

Reaction of (1*R*, 2*S*)-1-Phenyl-2-methyl-2,3-epoxypropyl Alcohol (3a) with Thiophenol.

To a solution of (1*R*, 2*S*)-1-phenyl-2-methyl-2,3-epoxypropyl alcohol (3a)(456 mg, 3 mmol), and thiophenol(2 ml, 18 mmol) in $CHCl_3$ (3 ml), triethylamine (6 drops) was added at -30 °C and the mixture was allowed to stand until room temperature. Aqueous 10% NaOH (2 ml, 5 mmol) was added and the

mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (5 g) column chromatography using CH_2Cl_2 as eluent to give (1*R*, 2*R*)-1-phenyl-2-methyl-3-phenylthio-1,2-propanediol [(1*R*, 2*R*)- 6a] (64 mg , 65%) *as an oil.* $[\alpha]_D^{22}$ + 46.5° (*c* 3, $CHCl_3$). Ms m/z: 274 (M^+). *Anal.* Calcd for $C_{16}H_{18}O_2S$: C, 69.97, H, 6.56. Found: C, 69.57; H, 6.01.^{1}H-Nmr ($CDCl_3$) δ: 1.22 (3H, s), 2.89 (1H, d, *J*=13.2 Hz), 3.39 (1H, d, *J*=13.2 Hz), 4.73 (1H, s), 7.12-7.40 (10H, m).

Reaction of Racemic 1-Phenyl-2-methyl-2,3-epoxypropyl Alcohol (6c, 6b) with Thiophenol.

To a solution of racemic 1-phenyl-2-methyl-2,3-epoxypropyl alcohol (6c, 6d)(156 mg, 0.1 mmol), thiophenol(2 ml, 18 mmol) in $CHCl_3$ (3 ml), triethylamine (5 drops) was added *at -30 °C and the* mixture was allowed to stand until room temperature (1. 5 h). Aqueous 10% NaOH (2 ml, 5 mmol) was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine and dried over Na_2SO_4. *The solvent was removed under* reduced pressure to give racemic 1-phenyl-2-methyl-3-thiophenyl-1,2-propanediol (6c, 6d) (110 mg , 59%) as an oil. Without further purification, a mixture of **6c** and **6d** was immediately used for the synthesis of acetonide (7c, 7d).

Sythesis of (1R, 2R)-1,2-Isopropylidenedioxy-1-phenyl-2-methyl-3-*thiophenyl*-propane (7a).

To a solution of (1*R*, 2*R*)-1-phenyl-2-methyl-3-phenylthio-1,2-propanediol (6a) (38 mg, 0.1 mmol), 2,2-dimethoxypropane (100 mg, 0.9 mmol) in CH_2Cl_2 (10 ml), PPTS (50 mg, 0.2 mmol) was added and the mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure at 20 °C to give the residue which was purified by silica gel (4 g) column chromatography *using hexane*-CH_2Cl_2 (1 : 1) as eluent to give acetonide (1*R*, 2*R*)-(7a)(30 mg , 67%) as an oil. $[\alpha]_D^{23}$ + 72.0° (c 3, $CHCl_3$). Ms m/z: 314 (M^+). *Anal.* Calcd for $C_{19}H_{22}O_2S$: C, 72.58, H, 7.05. Found: C, 72.56; H, 7.36. ^{1}H-Nmr ($CDCl_3$) δ: 1.49 (3H, s), 1.54 (3H, s), 1.56 (3H, s), 2.25 (1H, d, *J*=12.2 Hz), 3.09 (1H, d, *J*=12.2 Hz), 5.00 (1H, s), 7.07-7.43 (10H, m).

Synthesis of Racemic 1,2-Isopropylidenedioxy-1-phenyl-2-methyl-3-phenylthio-propane (7c, 7d).

To a solution of racemic 1-phenyl-2-methyl-3-phenylthio-1,2-propanediol (6c, 6d) (109 mg, 0.4 mmol) and 2,2-dimethoxypropane (176 mg, 1.6 mmol) in CH_2Cl_2 (20 ml), PPTS (80 mg, o.3 mmol) was added and the mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure at 20 °C to give the residue which was purified by silica gel (4 g) column chromatography using hexane-CH_2Cl_2 (1 : 1) as eluent to give racemic acetonides (7c, 7d)(76 mg , 67%) as an oil. Ms m/z: 314 (M^+). *Anal.* Calcd for $C_{19}H_{22}O_2S$: C, 72.58, H, 7.05. Found: C, 72.35; H, 7.19. ^{1}H-Nmr ($CDCl_3$) δ: 0.92 (3H, s), 1.52 (3H, s), 1.60 (3H, s), 3.14 (1H, d, *J*=13.6 Hz), 3.36 (1H, d, *J*=13.6 Hz), 5.29 (1H, s), 7.16-7.47 (10H, m).

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