Asymmetric Synthesis of (2*R*,3*S*)-2,3-Epoxyoctanal, a Key Intermediate of 14,15-Leukotriene A_4

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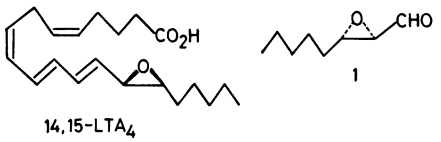
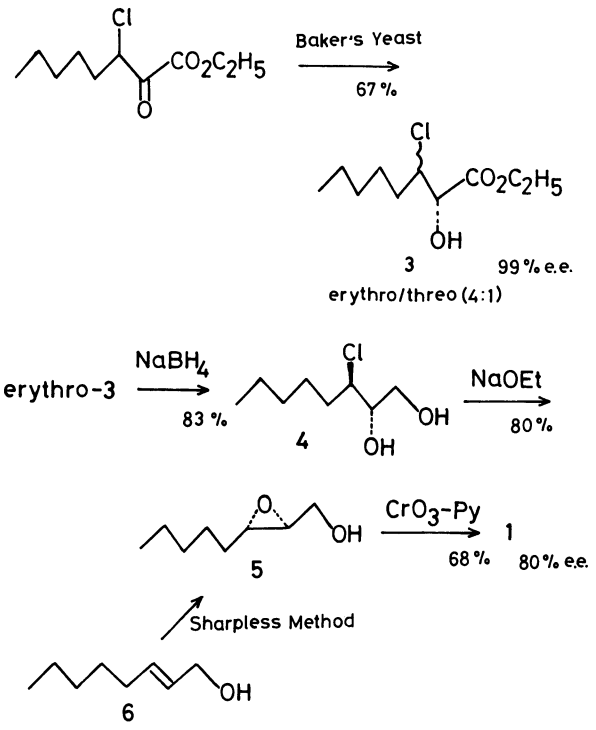
Synopsis. Asymmetric reduction of ethyl 3-chloro-2-oxooctanoate with baker's yeast gave ethyl 3-chloro-2-hydroxyoctanoate (**3**) [(2*S*,3*R*)/(2*S*,3*S*), 4:1] in 67% yield with >99% e.e. Chlorohydrin (2*S*,3*R*)-**3** was converted to the titled compound in 34% total yield with 80% e.e. via the reduction, dehydrochlorination, and oxidation, successively. (2*R*,3*R*)-2,3-Epoxyoctanal was also prepared from (2*S*,3*S*)-**3** in 33% total yield with 94% e.e.

Samuelsson[1] has reported that (5*Z*,8*Z*,10*E*,12*E*)-icosatetraenoic acid (14,15-LTA_4) is formed by oxidation of arachidonic acid with 15-lipoxygenase and is a key intermediate in further biological transformations. Because of the unavailability of unstable metabolites from natural sources, the synthesis becomes important. Zamboni et al.[2] reported a stereospecific synthesis of 14,15-LTA_4 by using (2*R*,3*S*)-2,3-epoxyoctanal (**1**) as a key intermediate. However, reports on the

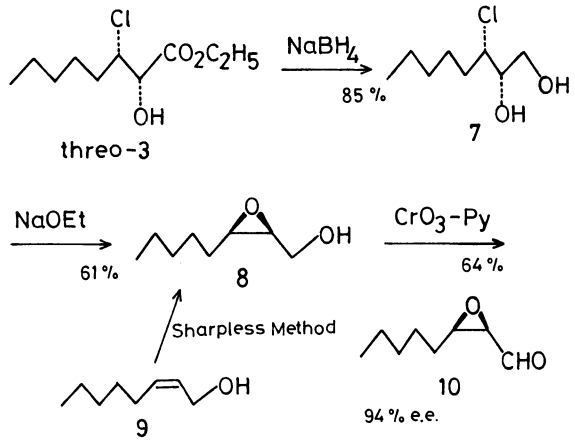


synthesis of **1** are quite few.[3] Here we describe a convenient synthesis of **1** using chiral reduction with fermenting baker's yeast. The reaction sequence is shown in Scheme 1.



Scheme 1.

The starting material, ethyl 3-chloro-2-oxooctanoate (**2**) is readily available by Darzen type condensation which was developed by us.[4] Treatment of **2** with fermenting baker's yeast gave a 4:1 mixture of ethyl *erythro*(2*S*,3*R*)- and *threo*(2*S*,3*S*)-3-chloro-2-hydroxyoctanoate (**3**) in 67% yield. Each isomer was separated by preparative HPLC. Optical purities of both isomers were estimated as >99% e.e. respectively by ^1H NMR analysis in the presence of chiral shift reagent (europium tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato] (Eu(hfc)$_3$)) and HPLC analysis of its 3,5-dinitrophenylcarbamate. Reduction of *erythro*-**3** with $NaBH_4$ gave diol **4** in 83% yield. Treatment of **4** with two equivalent of NaOEt yielded (2*S*,3*S*)-2,3-epoxyoctanol (**5**) in 80% yield and the subsequent oxidation of **5** with CrO_3-pyridine afforded aldehyde **1** in 68% yield. Enantiomeric excess was estimated as 80% e.e. by comparison of the optical rotation with that of the literature.[3] Decrease of the optical purity would be attributable to the racemization in the course of the reduction and dehydrochlorination. Furthermore we prepared **5** from *trans*-2-octen-1-ol by Sharpless method[2,5] and confirmed the structure of **5** obtained via baker's yeast reduction. Absolute configuration of α-carbon of **3** was determined to be S from that of **1**.



Scheme 2.

Similarly, *threo*-**3**, a minor product by the baker's yeast reduction, was also converted to *cis*-2,3-epoxyoctanol (**8**) via *threo*-diol **7**, as shown in Scheme 2. The spectral data of epoxide **8** was identical with that of the sample prepared by the epoxidation[5] of *cis*-2-octen-1-ol. Oxidation of **8** with CrO_3-pyridine gave (2*R*,3*R*)-2,3-epoxyoctanal (**10**) with 94% e.e. in 64% yield. The coupling constant (5.0 Hz) between two protons of the epoxide ring was a characteristic value for *cis*-epoxide.[6] Compound **10** will be useful for the synthesis of an unnatural form of 14,15-LTA_4.

Our system provides a convenient route to **1**, **8**, and

10 because of availability of the starting material, simplicity of the experiment, and no use of heavy metal.

Experimental

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Infrared (IR) spectra were obtained with a JASCO Model A-102 infrared spectrophotometer. ^{1}H NMR spectra (60 MHz) were recorded with a JEOL JNM-PMX60SI apparatus. ^{1}H NMR (100 MHz) and ^{13}C NMR spectra (25 MHz) were obtained with a JEOL JNM-FX100 apparatus, using $CDCl_3$ as a solvent. Optical rotations were measured on a JASCO DIP-4 spectrometer. Column chromatography was accomplished with 100—200 mesh Wakogel C-200. High-performance liquid chromatography (HPLC) was obtained with Yanagimoto liquid chromatograph L-2000 fitted with Yanapak SA-I (6 mm o.d.×250 mm) and with Sumipax OA-3000 (4 mm o.d.×250 mm) for the determination of enantioselectivity.

Fermentation was carried out in a thermostat-bath at 31—35 °C, using industrial baker's yeast purchased from Oriental yeast Co. LTD. All glasswares were sterilized by boiling water before use.

Ethyl 3-chloro-2-oxooctanoate (**2**) was obtained by the method described in our previous papers.[4]

Ethyl 3-Chloro-2-hydroxyoctanoate (3). To a mixture of KH_2PO_4 (1 g), $NH_4H_2PO_4$ (1 g), $MgSO_4$ (0.25 g), $CaCO_3$ (2.5 g), glucose (75 g), and boiled water (1 l) was added 8 g of baker's yeast at 35°C. After 20 min, 2.00 g (9.07 mmol) of **2** was added and the mixture was stirred for 4 d at 35 °C. The organic materials were extracted 5 times with ethyl acetate (total 1 l), washed with brine, and dried over $MgSO_4$. Removal of the solvent gave 1.39 g of an oil, which was chromatographed on SiO_2 (hexane/ethyl acetate, 20 : 1—1 : 1) to afford 1.33 g (67%) of **3**. HPLC analysis (SA-I, 6 mm o.d.×250 mm; hexane/ethyl acetate (10 : 1), 1.25 ml min^{-1}) showed two peaks at R_t 16.7 and 22.9 min with the 29 : 71 ratio of the integrated peak area. Each component was separated by preparative HPLC. Peak 1: *threo*(2S,3S)-**3**; R_t 16.7 min; $[\alpha]_D^{25}$ −16.0°(*c* 1.45, $CHCl_3$): IR (neat) 3525, 2950, 1745, 1265 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.90 (t, 3H, *J*=6 Hz), 1.40—2.30 (m, 8H), 1.30 (t, 3H, *J*=6.5 Hz), 4.15 (q, 2H, *J*=6.5 Hz), 4.20 (m, 2H). Found: C, 54.01; H, 8.55%. Calcd for $C_{10}H_{19}ClO_3$: C, 53.93; H, 8.60%. Peak 2: *erythro*(2S,3R)-**3**; R_t 22.9 min; $[\alpha]_D^{25}$ +2.3° (*c* 2.20, $CHCl_3$): IR (neat) 3470, 2975, 1740, 1220 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.90 (t, 3H, *J*=6 Hz), 1.5—2.0 (m, 8H), 1.30 (t, 3H), 4.20 (m, 2H), 4.2 (q, 2H, *J*=6.5 Hz). Found: C, 53.99; H, 8.35%. Calcd for $C_{10}H_{19}ClO_3$: C, 53.93; H, 8.60%.

Determination of Enantiomeric Excess of 3. (A) *threo*-**3**: >95% e.e. by ^{1}H NMR (CCl_4) analysis in the presence of 75% (mol/mol) Eu(hfc)$_3$: one singlet at 2.30 ppm ($CO_2CH_2C\underline{H}_3$) when decoupled with the peak of 6.15 ppm ($CO_2C\underline{H}_2CH_3$). *erythro*-**3**: >95% e.e. by ^{1}H NMR (CCl_4) analysis in the presence of 75% (mol/mol) Eu(hfc)$_3$ in a similar manner as described above. On the other hand, ^{1}H NMR (CCl_4) of (±)-*threo*-**3**[7] in the presence of 75% (mol/mol) Eu(hfc)$_3$ showed two singlets at 2.93 and 2.83 ppm ($CO_2CH_2C\underline{H}_3$) when decoupled with the peak of 7.95 ppm ($CO_2C\underline{H}_2CH_3$). (B) To a mixture of **3** (0.46 mmol), dry toluene (1 ml), and 3,5-dinitrophenyl isocyanate (105 mg, 0.5 mmol) was added 0.5 ml of dry pyridine. The mixture was heated at 80 °C for 1 h and cooled. The precipitate was filtered off and washed with ether. Concentration of the filtrate gave crude 3,5-dinitrophenylcarbamate (DNPC) of **3**, which was analyzed by HPLC [column, Sumipax OA-3000 (4φ×250 mm)].

DNPC of *threo*-**3**: >99% e.e.; HPLC [hexane/ethyl acetate/ethanol (20 : 1 : 0.5), 0.8 ml min^{-1}], a single peak at R_t 4.3 min; ^{1}H NMR (CCl_4) δ=0.86 (t, 3H, *J*=6.5 Hz), 1.30—1.90 (m, 8H), 1.35 (t, 3H, *J*=6.5 Hz), 4.32 (m, 3H), 5.38 (d, 1H, *J*=3.2 Hz), 8.63 (s, 3H). ^{1}H NMR (CCl_4) in the presence of 50% Eu(hfc)$_3$ showed no paired peak.

DNPC of *erythro*-**3**: >99% e.e.; HPLC [hexane/ethyl acetate/ethanol (20 : 1 : 0.5), 0.8 ml min^{-1}], a single peak at R_t 6.0 min; ^{1}H NMR (CCl_4) δ=0.86 (t, 3H, *J*=6.5 Hz), 1.30—1.90 (m, 8H), 1.35 (t, 3H, *J*=6.5 Hz), 4.40 (m, 3H), 5.40 (d, 1H, *J*=3.2 Hz), 8.65 (s, 3H).

(2*S*,3*S*)-3-Chloro-1,2-octanediol (4). To a mixture of $NaBH_4$ (98 mg, 1.54 mmol) and ethanol (3 ml) was added dropwise a solution of *erythro*-**3** (0.342 g, 1.54 mmol) in dry ethanol (2 ml) at 0 °C. The mixture was stirred for 7 h at room temperature, and then poured into ice water. The organic materials were extracted with dichloromethane and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product (290 mg) was chromatographed on SiO_2 (hexane/acetone (10 : 1)) to give 193 mg (83%) of **4**: $[\alpha]_D^{25}$ +18.7° (*c* 1.00, $CHCl_3$): IR (neat) 3400 (OH), 1460, 1075, 790 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.85 (t, 3H, *J*=6 Hz, $C\underline{H}_3(CH_2)_4$), 1.1—2.3 (m, 8H, $CH_3(C\underline{H}_2)_4$-), 3.65 (m, 2H, $C\underline{H}Cl\underline{C}HOH$), 4.40 (m, 2H, $C\underline{H}_2OH$). Found: C, 53.07; H, 9.78%. Calcd for $C_8H_{17}ClO_2$: C, 53.18; H, 9.49%.

(2*S*,3*S*)-2,3-Epoxyoctanol (5). Method A: from 4. To a solution of sodium ethoxide (95 mg, 1.4 mmol) in absolute ethanol (4 ml) was added dropwise a solution of **4** (228 mg, 1.27 mmol) in absolute ethanol (3 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 6.5 h at 25 °C. After the mixture was poured into ice water, the organic materials were extracted with dichloromethane. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residual oil (201 mg) was chromatographed on SiO_2 (hexane/acetone (10 : 1)) to give 146 mg (80%) of **5**: HPLC analysis [SA-I, 4.0 o.d.×250 mm; hexane/ethyl acetate (5 : 1), 0.8 ml min^{-1}], a single peak at R_t 24.2 min; $[\alpha]_D^{26}$ −27.2° (*c* 0.75, $CHCl_3$). Recrystallization from pentane gave 91.4 mg of **5**: mp 29.5—30 °C; $[\alpha]_D^{25}$ −36.8° (*c* 0.61, $CHCl_3$) [lit,[2] $[\alpha]_D$ −44° (*c* 1.0, $CHCl_3$)]: IR (neat) 3425 (OH), 2950, 1460, 1030, 885 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.90 (t, 3H, *J*=6.5 Hz, $C\underline{H}_3(CH_2)_4$), 1.45 (m, $CH_3(C\underline{H}_2)_4$), 2.82 (m, 2H, C_2-H, C_3-H), 3.10 (s, 1H, OH), 3.60 (br t, 2H, *J*=4 HZ, $C\underline{H}_2OH$); ^{13}C NMR ($CDCl_3$) δ=13.9 (q,), 22.5 (t), 25.6 (t), 31.5 (t), 56.1 (d), 58.7 (d), 61.9 (t).

Method B: by Sharpless Epoxidation.[5] To a stirred mixture of dry dichloromethane (16 ml), titanium tetraisopropoxide (455 mg, 0.48 ml, 1.60 mmol),diethyl (+)-tartrate (329 mg,1.6 mmol) was added dropwise a solution of trans-2-octen-1-ol[8] (204 mg, 1.6 mmol) in dry dichloromethane (4 ml) at −23 °C. *t*-Butyl hydroperoxide (TBHP) (1 ml, 3.62 mmol), which was extracted from commercial TBHP (70% aqueous solution) with dichloromethane and dried over $MgSO_4$ and 4 A molecular sieves, was added and then the mixture was stirred for 9.3 h at −23 °C. Aqueous tartaric acid (10%, 20 ml) was added and the mixture was stirred for 30 min at −23 °C and then for 1 h at room temperature. The organic materials were extracted with ether, and the ethereal extract was stirred with 1 M NaOH (20 ml) (1M=1 mol dm^{-3}) at 0 °C for 30 min and separated, washed with water, and dried over $MgSO_4$. Removal of the solvent gave 296 mg of an oil which was chromatographed on SiO_2 (hexane/acetone (20 : 1)) to give 151 mg (65.4%) of **5**: HPLC analysis [SA-I, 6.0 o.d.×250 mm; hexane/ethyl acetate (2 : 1), 1.1 ml min^{-1}], a single peak at R_t 21.3 min; $[\alpha]_D^{26}$ −38.1° (*c* 1.48, $CHCl_3$). IR and ^{1}H NMR data were identical with those of the sample prepared in Method A.

(2*R*,3*S*)-2,3-Epoxyoctanal (1).[2,3] To dry chromium oxide (997 mg, 9.97 mmol) was added dropwise a solution of dry pyridine (1.1 ml, 13.7 mmol) in dry dichloromethane (11 ml) at room temperature. After the mixture was stirred for 30 min, a solution of **5** (147 mg, 1.02 mmol) in dry dichlorome-

thane (4 ml) was added. The mixture was stirred for 4 h at 25 °C and the organic materials were extracted with ether. The ethereal extract was washed with 5% NaOH (10 ml), dil HCl (10 ml), saturated $NaHCO_3$, and brine successively, and dried over $MgSO_4$. Removal of the solvent gave the crude product, which was purified by column chromatography (SiO_2, hexane/acetone (15 : 1)) to afford 91 mg (68%) of **1**: $[\alpha]_D^{25}$ +64.6° (*c* 0.87, $CHCl_3$) [lit,[3] $[\alpha]_D^{25}$ +80.4° (*c* 1.39, $CHCl_3$)], 80% e.e.: IR (neat) 1735 (C=O), 1260, 1020, 805 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (t, 3H, *J*= 6.5 Hz, $C\underline{H}_3(CH_2)_4$), 1.40 (m, 8H, $CH_3(C\underline{H}_2)_4$), 3.00 (m, 2H, C_2-H, C_3-H), 8.85 (d, 1H, *J*=6.4 Hz, CHO).

(2*S*,3*S*)-3-Chloro-1,2-octanediol (7). To a stirred mixture of $NaBH_4$ (52 mg, 0.81 mmol) and ethanol (3 ml) was added *threo*-**3** (180 mg, 0.81 mmol) at 0 °C. The mixture was stirred for 7 h at room temperature, and poured into ice water. The organic materials were extracted with dichloromethane and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product (176 mg) was chromatographed on SiO_2 (hexane/acetone (10 : 1)) to give 122 mg (85%) of **7**: $[\alpha]_D^{26}$ −23.2 ° (*c* 2.12, $CHCl_3$); IR (neat) 3400 (OH), 1460, 1040, 875 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (t, 3H, *J*=6 Hz, CH_3), 1.0—2.0 (m, 8H, $(CH_2)_4$), 3.0—4.1 (m, 6H, $CHClCHOHCH_2OH$).

(2*S*,3*R*)-2,3-Epoxyoctanol (8). Method A: from 7. To a solution of sodium ethoxide (54 mg, 0.8 mmol) in absolute ethanol (6 ml) was added dropwise a solution of **7** (116 mg, 0.65 mmol) in absolute ethanol (1 ml) at 0 °C. The mixture was stirred for 9.5 h at 25 °C, and then poured into ice water. The organic materials were extracted with dichloromethane. The combined extracts were washed with water and dried over $MgSO_4$. Removal of the solvent gave an oil (118 mg), which was chromatographed on SiO_2 to give 57 mg (61%) of **8**:[9] $[\alpha]_D^{26}$ −6.12° (*c* 1.42, $CHCl_3$); IR (neat) 3420, 1460, 1030, 880 cm^{-1}; ^1H NMR (CCl_4)δ=0.90 (t, 3H, *J*=6 Hz, CH_3), 1.1—1.8 (m, 8H, $(CH_2)_4$), 2.95 (m, 3H, C_2-H, C_3-H, OH), 3.60 (m, 2H, CH_2OH): ^{13}C NMR ($CDCl_3$) δ=14.0 (q), 22.5 (t), 26.3 (t), 27.9 (t), 31.6 (t), 57.0 (d), 57.2 (d), 60.7 (t).

Method B: by Sharpless Epoxidation.[5] *cis*-2-Octen-1-ol[10] (252 mg, 1.97 mmol) was oxidized at −10 — − 23 °C for 13.5 h by TBHP (1.1 ml, 3.54 mmol) in the presence of titanium tetraisopropoxide (560 mg, 1.97 mmol) and diethyl (+)-tartrate (405 mg, 1.97 mmol), as shown in the preparation of **5**. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate (10 : 1)), giving 206 mg (78%) of **8**: $[\alpha]_D^{26}$ −6.44°(*c* 1.46, $CHCl_3$). IR and ^1H NMR data were identical with those of the sample prepared by method A.

(2*R*,3*R*)-2,3-Epoxyoctanal (10). In the same manner as shown in the preparation of **1**, alcohol **8** (191 mg, 1.33 mmol) was treated with CrO_3 (1.04 g, 10.4 mmol) and pyridine (1.65 g, 20.7 mmol) in dichloromethane (22 ml) at 30 °C for 4.5 h. The same work up as shown in **1** gave 121 mg (64%) of **10**: TLC (hexane/acetone, 3 : 1), one spot at R_f 0.42. Analytical sample was purified with column chromatography (SiO_2; hexane/acetone, 5 : 1) to afford 77 mg of pure **10**: $[\alpha]_D^{27}$ +134.6° (*c* 1.47, $CHCl_3$); 94% e.e. by ^1H NMR in the presence of 98% Eu(hfc)$_3$, two paired peaks at 18.0 and 17.6 ppm (intensity ratio of 97 : 3): IR (neat) 2950, 2840, 1730, 1470, 1050, 835 cm^{-1}; ^1H NMR (CCl_4) δ=0.92 (br. t, 3H, *J*=5 Hz, CH_3), 1.3—1.9 (m, 8H, $(CH_2)_4$), 3.16 (apparent d, 2H, *J*=2.8 Hz, 2 CHO-), 9.35 ppm (d, 1H, *J*=5.8 Hz, CHO); ^1H NMR (CCl_4) in the presence of 13% Eu(hfc)$_3$, δ=1.0 (br. t, 3H, CH_3), 1.2—2.3 (m, 6H, $(CH_2)_3$), 2.56 (m, 2H, C_4-H), 4.35 (m, 1H, C_3-H), 4.76 ppm (t, 1H, *J*=5 Hz, C_2-H).

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