A Convenient Synthesis of Enantiomerically Pure (2*S*,3*S*)- or (2*R*,3*R*)-3-Hydroxyleucine

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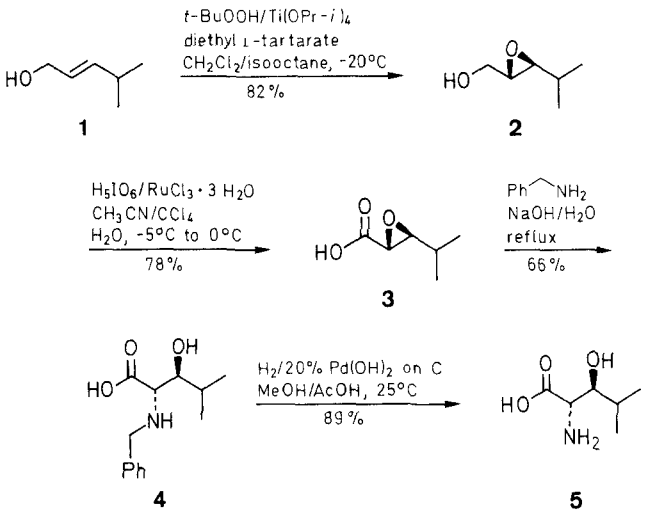
Both enantiomers of *erythro*-3-hydroxyleucine are available by asymmetric epoxidation of (*E*)-4-methyl-2-penten-1-ol (**1**) followed by ruthenium tetroxide catalyzed oxidation to the corresponding glycidic acid **3**, epoxide opening by benzylamine, and hydrogenolysis using palladium hydroxide on carbon.

The amino acid (2*S*,3*S*)-3-hydroxyleucine (**5**) is incorporated into the structures of the natural peptide antibiotics telomycin,[1] azinothricin,[2] and A83586C.[3] We recently encountered a need for multi-gram quantities of **5** in optically pure form for synthetic efforts in the peptide area. Previous stereospecific syntheses of racemic *erythro*-3-hydroxyleucine have utilized the epoxidation of (*E*)-4-methylpent-2-enoic acid followed by nucleophilic opening of the epoxide by an amine,[4,5] or the base-catalyzed condensation of *N*,*N*-bis(trimethylsilyl)glycine trimethylsilyl ester with isobutyraldehyde.[6] The aldol reaction of chiral oxazolidinones[7] and the electrophilic amination of chiral β-hydroxyesters[8,9] have recently been described for the asymmetric synthesis of *erythro*-β-hydroxy-α-amino acids. We now describe the use of the catalytic Sharpless epoxidation[10] in combination with subsequent epoxide opening using benzylamine[4] for a practical synthesis of (2*S*,3*S*)-3-hydroxyleucine (**5**) in optically pure form. Utilizing the opposite enantiomer of diethyl tartrate in the epoxidation reaction, we have also prepared (2*R*,3*R*)-3-hydroxyleucine by the same method.

The allylic alcohol (*E*)-4-methyl-2-penten-1-ol (**1**) was obtained by the condensation of isobutyraldehyde with triethyl phosphonoacetate followed by reduction of the resulting unsaturated ester with diisobutylaluminum hydride. Asymmetric epoxidation[11-14] of allylic alcohol **1** using catalytic titanium(IV) isopropoxide and (+)-diethyl L-tartrate proceeded smoothly to yield epoxide **2** in greater than 95% enantiomeric excess as determined by NMR analysis of the derived MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] esters.[11,12,15,16] Oxidation to the glycidic acid derivative **3** was accomplished using catalytic ruthenium(III) chloride in the presence of a stoichiometric amount of periodic acid.[17] The small amount of ruthenium tetroxide present at the end of the reaction was quenched by the addition of 2-propanol prior to workup. When the reaction was carried out by addition of ruthenium trichloride trihydrate to the mixture of periodic acid and alcohol **2**, NMR analysis of the acid **3** indicated contamination by up to 15% of isobutyric acid. The amount of this byproduct, apparently derived from oxidative cleavage of either epoxide **2** or **3**, could be reduced to less than 5% by carefully adding the epoxy alcohol to the cold reaction mixture already containing periodic acid and ruthenium trichloride. Prolonged heating of the epoxide **3** in the distillation resulted in a decrease in yield. In a larger-scale oxidation (15 g of epoxy alcohol **2**) the crude product was divided between

two flasks for distillation. With this simple precaution, acid **3** was isolated in 69% yield.



The transformation of the chiral epoxide **3** into (2*S*,3*S*)-3-hydroxyleucine (**5**) was readily accomplished in two steps adapted from those used by Lipshutz and co-workers for the racemic compound.[4] The opening of the epoxide at C-2 by benzylamine proceeded smoothly in aqueous solution. After extraction of the excess benzylamine, amino acid **4** precipitated as analytically pure material upon neutralization of the aqueous solution. NMR analysis indicated that product isolated in this manner contained none of the amino acid resulting from regioisomeric epoxide attack. Variable amounts of epoxide opening at C-3 have been observed in related cases.[18,19] To complete the synthesis, it was found that hydrogenolysis to remove the *N*-benzyl group could be achieved at room temperature in a low-pressure apparatus using Pearlman's catalyst (20% palladium hydroxide on carbon).[20] Thus, either (2*S*,3*S*)- or (2*R*,3*R*)-3-hydroxyleucine may be prepared in four steps from (*E*)-4-methyl-2-penten-1-ol (**1**) with no chromatography or tedious purification of intermediates.

All reagents were of commercial quality from freshly opened containers. (+)-Diethyl L-tartrate, $Ti(OC_3H_7\text{-}i)_4$, *tert*-butyl hydroperoxide in isooctane, $FeSO_4 \cdot 7H_2O$, L-tartaric acid, $RuCl_3 \cdot 3H_2O$, H_5IO_6, and benzylamine were purchased from Aldrich Chemical Co. (+)-Diethyl L-tartrate and $Ti(OC_3H_7\text{-}i)_4$ were distilled prior to use. Reagent quality solvents were used without purification except for additional drying as indicated. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Microanalyses were determined by the Merck analytical laboratory using a Control Equipment elemental analyzer 240X. Optical rotations were measured at the Na-D line at 25°C using a Perkin-Elmer 241 polarimeter. IR spectra were measured on a Perkin-Elmer 1310 infrared spectrophotometer. ^{1}H-NMR spectra were obtained on Varian XL-200 spectrometer using TMS as standard for $CDCl_3$ and DMSO-d_6 solutions and DSS (2,2-dimethyl-2-silapentane-5-sulfonic acid sodium salt) for D_2O solutions.

(2*S*,3*S*)-2,3-Epoxy-4-methyl-1-pentanol (2):

CH_2Cl_2 (300 mL, dried over 3 A molecular sieves) and powdered 4 A molecular sieves (6.0 g) are added to a flame-dried 1-L round-bottom flask containing a magnetic stirring bar and fitted with a septum inlet, internal thermometer, and pressure-equalizing addition funnel attached to an N_2 inlet. The stirred suspension is cooled to −20°C before (+)-diethyl L-tartrate (2.48 g, 12.0 mmol) is added via syringe, followed by $Ti(OC_3H_7\text{-}i)_4$ (2.98 mL, 2.84 g, 10 mmol). *tert*-Butyl hydroperoxide (133 mL, 3 M soln. in isooctane, 400 mmol, dried overnight over 3 Å molecular sieves) is added from the addition funnel over 10 min and the mixture is stirred at −20°C for another 30 min. A solution (dried over 3 A molecular sieves) of (*E*)-4-methyl-2-penten-1-ol (**1**; 20 g, 200 mmol) in CH_2Cl_2 (100 mL) is added via a double-ended needle over a 45 min period, maintaining the temperature between −20° and −15°C during the addition. After stirring at −20°C for 2.5 h, the mixture is then allowed to warm to 0°C and is poured slowly into a 1-L flask containing a 0°C solution of $FeSO_4 \cdot 7H_2O$ (66 g, 240 mmol) and L-tartaric acid (20 g, 130 mmol) in water (200 mL). The resulting two-phase mixture is stirred 15 min with cooling. The aqueous phase is separated and extracted with Et_2O (2 × 100 mL). The combined organic layers are stirred with Na_2SO_4 and decanted to remove a small amount of aqueous phase, then treated with a precooled (0°C) solution of NaOH (6 g, 150 mmol) and NaCl (1 g) in water (18 mL). This two-phase mixture is stirred at 0°C for 1 h before being diluted with water (100 mL). The aqueous phase is separated and extracted with Et_2O (4 × 100 mL). The combined organic layers are dried (Na_2SO_4), decanted, and concentrated on a rotary evaporator. The residue is distilled through a 1 × 10 cm Vigreux column to give epoxide **2** as a colorless liquid; yield: 18.96 g (82%); bp 43–46°C/0.9 mbar; $[\alpha]_D$ −32.7° (*c* = 1.01, $CHCl_3$) {Lit.[11] $[\alpha]_D$ −32.5° (*c* = 0.062, $CHCl_3$); for enantiomer, Lit.[12] $[\alpha]_D$ +32.2° (*c* = 2.7, CH_2Cl_2)}.

IR (CCl_4): ν = 3640–3250 cm^{-1} (OH).

^{1}H-NMR (200 MHz, $CDCl_3$ with D_2O): δ = 0.97 (d, 3 H, *J* = 7 Hz, CH_3), 1.03 (d, 3 H, *J* = 7 Hz, CH_3), 1.58 [octet, 1 H, *J* = 7 Hz, C<u>H</u>$(CH_3)_2$], 2.76 [dd, 1 H, *J* = 7 Hz, 2 Hz, C<u>H</u>CH$(CH_3)_2$], 2.97 (dt, 1 H, *J* = 4.5 Hz, 2 Hz, C<u>H</u>CH_2OH), 3.61 (dd, 1 H, *J* = 12 Hz, 4.5 Hz, C<u>H</u>OH), 3.91 (dd, 1 H, *J* = 12 Hz, 2 Hz, C<u>H</u>OH).

(2*R*,3*S*)-2,3-Epoxy-4-methylpentanoic Acid (3):

Caution! This reaction generates RuO_4, a volatile toxic compound. All steps, particularly those preceeding the isopropanol quench, should be carried out with adequate precautions.

A 500-mL round-bottom flask fitted with a mechanical stirrer, addition funnel, and internal thermometer is charged with CCl_4 (80 mL), CH_3CN (80 mL), water (120 mL), and H_5IO_6 (21.58 g, 94.6 mmol). The mixture is stirred as $RuCl_3 \cdot 3H_2O$ (225 mg, 0.86 mmol) is added and the flask is then cooled to −5°C in a salted ice bath. (2*S*,3*S*)-2,3-Epoxy-4-methyl-1-pentanol (**2**; 5 g, 43 mmol) dissolved in a mixture of CH_3CN (5 mL) and CCl_4 (5 mL) is added from the addition funnel over 20 min, producing a 3°C increase in reaction temperature. The mixture is stirred for 1 h at −5°C followed by 1 h at 0°C. The excess oxidant is then quenched by the addition of 2-propanol (5 mL) at 0°C. The flask is allowed to warm to 15°C over 30 min, with the color changing from orange to dark brown. After separation of the layers, the aqueous phase is extracted with CH_2Cl_2 (250 mL). The two organic layers are combined, then the aqueous layer is extracted with additional CH_2Cl_2 (2 × 250 mL). The organic layers are washed in succession with brine (40 mL), dried (Na_2SO_4), decanted, and concentrated to a weight of approximately 6.5 g. Rapid Kugelrohr distillation at 0.13 mbar (oven preheated to 90°C, receiver cooled to below 0°C) produces acid **3** as a yellow oil (NMR spectra of this material showed a small amount (< 5%) of isobutyric acid); yield: 4.34 g (78%); $[\alpha]_D$ −15.2° (*c* = 0.52, 95% EtOH).

$C_6H_{10}O_3$	calc.	C 55.37	H 7.74
(130.1)	found	55.29	7.90

IR (CCl_4): ν = 3400–2400 (OH); 1730 cm^{-1} (C=O).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.01 (d, 3 H, *J* = 7 Hz, CH_3), 1.05 (d, 3 H, *J* = 7 Hz, CH_3), 1.68 [octet, 1 H, *J* = 7 Hz, C<u>H</u>$(CH_3)_2$], 3.02 [dd, 1 H, *J* = 6 Hz, 2.5 Hz, 2.5 Hz, C<u>H</u>CH$(CH_3)_2$], 3.30 (d, 1 H, *J* = 2.5 Hz, C<u>H</u>CO_2H).

(2*S*,3*S*)-*N*-Benzyl-3-hydroxyleucine (4):

Water (8.6 mL) is added to compound **3** (4.5 g, 34.6 mmol) in a 100-ml round-bottom flask. The mixture is cooled by an ice bath as benzylamine (11.25 mL, 11.04 g, 103 mmol) is added to the stirred

reaction. After 5 min, 5 N NaOH (5.63 mL, 28.1 mmol) is added. The mixture is then heated to reflux for 2 h under a N_2 atmosphere. After cooling the reaction in an ice bath, 5 N NaOH (1.4 mL, 7 mmol) is added. The aqueous phase is washed with Et_2O (27 mL, followed by 2 × 10 mL), then acidified to pH 5.2 with 2 N HCl. The resulting mixture is stirred for 30 min at 0 °C before being filtered. The precipitate is washed with ice-cold water (2 × 10 mL), ice-cold acetone (3 × 10 mL), and Et_2O (2 × 10 mL) to give **4** as a colorless solid, which is dried under vacuum; yield: 5.44 g (66%); mp 224–225 °C (for racemate, Lit.[4] mp 224–228 °C); $[\alpha]_D$ +19.0° (c = 0.51, 2 N aq. HCl).

$C_{13}H_{19}NO_3$	calc.	C 65.80	H 8.07	N 5.90
(237.3)	found	65.69	7.85	5.94

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 0.76 (d, 3H, J = 6 Hz, CH_3); 0.84 (d, 3H, J = 6 Hz, CH_3); 1.90 (m, 1H, J = 6 Hz, $CH(CH_3)_2$); 3.10 (d, 1H, J = 6 Hz, NHCHCO); 3.34 (t, 1H, J = 6 Hz, CHOH); 3.70 (d, 1H, J = 13 Hz, CHPh); 3.89 (d, 1H, J = 13 Hz, CHPh); 7.18–7.32 (m, 5H, Ph).

MS (FAB): m/z = 260 (M + Na, 100%); 238 (M + 1, 62%).

(2*S*,3*S*)-3-Hydroxyleucine (5):

(2*S*,3*S*)-*N*-Benzyl-3-hydroxyleucine (**4**; 15.0 g, 63.21 mmol) is dissolved in MeOH (300 mL) and HOAc (150 mL), and hydrogenated for 6 h at 2.7 atm using 20% $Pd(OH)_2$ on carbon (3.0 g). The resulting mixture is centrifuged and the supernatant is decanted. The separated solid is washed with distilled water and MeOH until the black catalyst is free of precipitated product. After evaporation of the combined supernatant and washes, the crystalline residue is dissolved in distilled water (170 mL), with warming if neccessary. The solution is filtered through a 0.45 micron filter, cooled in an ice bath, and then stirred as MeOH (200 mL) is added dropwise. After standing 2 h at 0 °C, the mixture is filtered. The precipitate is washed with cold MeOH/water (1:1, 30 mL) to give **5** as a colorless crystalline solid which is dried under vacuum; yield: 5.87 g. The mother liquor and washes are evaporated and the residue is dissolved in distilled water (65 mL). Cooling to 0 °C, addition of MeOH (90 mL), filtration, and washing with cold MeOH/water (1:1, 10 mL) gives a second crop of **5** of equivalent purity; yield: 2.44 g (89% total); mp 220–223 °C; $[\alpha]_D$ +37° (c = 0.99, 1 N aq. HCl) {Lit.[1] mp 218–222 °C; $[\alpha]_D$ +35° (c = 0.41, 1 N aq. HCl)}.

^{1}H-NMR (200 MHz, D_2O): δ = 0.99 (d, 3H, J = 6.5 Hz, CH_3), 1.00 (d, 3H, J = 6.5 Hz, CH_3), 1.87–2.09 [m, 1H, J = 9, 6.5 Hz, $CH(CH_3)_2$], 3.57 (dd, 1H, J = 9, 3 Hz, CHOH), 3.94 (d, 1H, J = 3 Hz, CHNH).

Received: 24 March 1989; revised: 27 July 1989

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