A CONCISE ROUTE TO (*S*)-PHENYLALANINE FROM (*R*)-EPICHLOROHYDRIN

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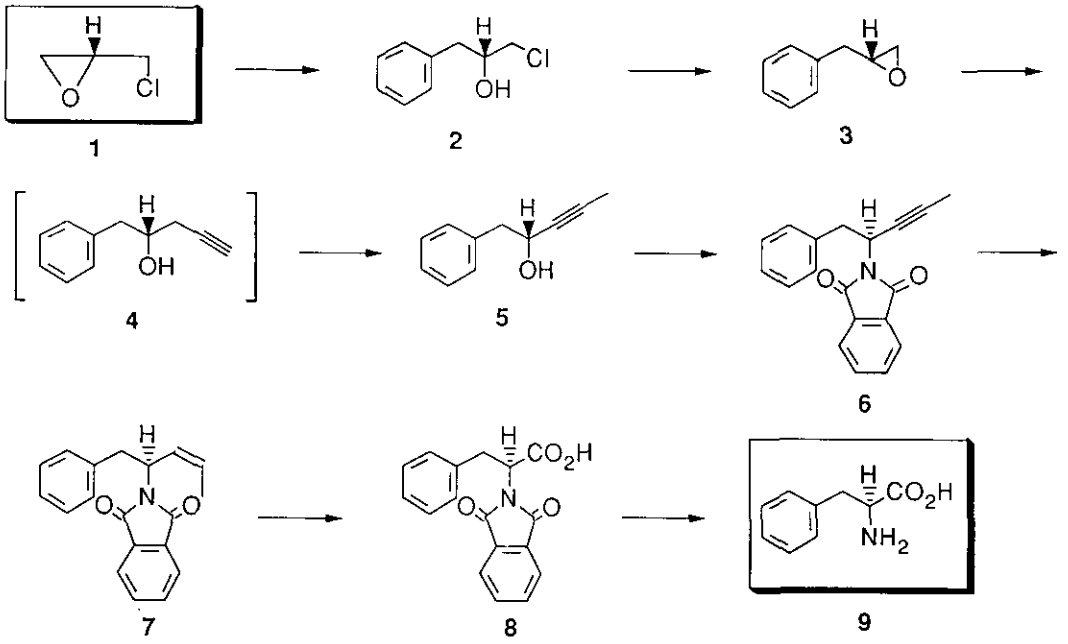
Abstract——— A concise route to (*S*)-phenylalanine has been established starting from (*R*)-epichlorohydrin.

(*S*)-Phenylalanine[1] (**9**) is an important amino acid not only as an essential component in human nutrition but also as a synthetic intermediate of a variety of biologically active compounds. We report herewith a concise synthesis of (*S*)-phenylalanine (**9**) starting from (*R*)-epichlorohydrin (**1**) which is available in a large quantity by fermentation[2] as well as by chemical conversion from D-mannitol.[3]

Reaction of **1** with phenyllithium in the presence of copper (I) cyanide afforded the chlorohydrin **2**, in 93% yield, which on exposure to powdered sodium hydroxide in ether gave (*R*)-3-phenyl-



Scheme 1

1,2-epoxypropane[4] (**3**) in 89% yield. Upon treatment with lithium acetylide ethylenediamine complex in dimethyl sulfoxide at room temperature followed by potassium *tert*-butoxide in the same reaction flask at the same temperature, **3** furnished the internal acetylene **5** directly in 80% yield via the spontaneous acetylene migration[5] of the initially formed terminal acetylene **4**. Employing the Mitsunobu reaction[6] **5** was transformed into the phthalimide **6** in 91% yield with inversion of the chirality. After partial hydrogenation of **6** on Lindlar catalyst the resulting *cis*-olefin **7** was oxidized with ruthenium oxide[7] to give (*S*)-*N*-phthaloylphenylalanine (**8**) in 72% overall yield. Since conversion of **8** into (*S*)-phenylalanine **9** as well as reversion of the latter into the former has already been established[8] in good yield, respectively, the present synthesis implies a formal synthesis of (*S*)-phenylalanine (**9**). The present method may be generally applicable to the synthesis of other α-amino acids possessing (*S*)-configuration.

Acknowledgment

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EXPERIMENTAL

Optical rotations were measured with a JASCO-DIP4 automatic polarimeter. Mass spectra were recorded with a JEOL-O1SG-2 instrument, ir spectra with a JASCO A102 spectrophotometer, and ^{1}H nmr spectra on JEOL-JNM-FX90A (90 MHz) and/or JEOL-JNM-GX500 (500 MHz) spectrometers. Reactions were carried out under argon except hydrogenation.

(*R*)-1-Chloro-2-hydroxy-3-phenylpropane (2) ——— To a stirred solution of CuCN (5.32 g, 59.4 mmol) in THF (50 ml) was added phenyllithium (2.6 M in cyclohexane-ether) (45.73 ml, 119 mmol) dropwise at –90 °C. After 30 min, (*R*)-epichlorohydrin (>98% ee) (**1**) (5.0 g, 54.1 mmol) in THF (10 ml) was added dropwise to the mixture at –45 °C and the stirring was continued for 90 min at the same temperature. The mixture was treated with sat. aq. NH_4Cl and extracted with ether. The extract was washed with sat. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (250 g) using Et_2O-hexane (1:9 v/v) as eluent to give **2** (8.39 g, 93%): bp 94 °C/18 mmHg (Kugelrohr); $[\alpha]_D^{25}$ –3.72° (*c* 1.02, $CHCl_3$). Ir (film) ν max: 3400 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.20 (1H, d, *J*=5.2 Hz, exchangeable with D_2O), 2.90 (2H, d, *J*=6.6 Hz), 3.47 – 3.62 (2H, m), 3.90 – 4.20 (1H, m), 7.29 (5H, m); Mass (m/z): 170 (M$^+$), 91 (100%). *Anal.* Calcd for $C_9H_{11}ClO$: C 63.35, H 6.50, Cl 20.78. Found: C 63.04, H 6.54, Cl 20.28.

(*R*)-3-Phenyl-1,2-epoxypropane (3) ——— A suspension of powdered NaOH (120 mg, 3.0 mmol) and **2** (171 mg, 1.0 mmol) in ether (3.0 ml) was stirred at room temperature for 2 h. The mixture was diluted with ether and washed with brine. After dried over $MgSO_4$, the organic layer was evaporated and the residue was chromatographed on a silica gel column (5 g) using Et_2O-hexane (1:4 v/v) as eluent to give **3** (119 mg, 89%): bp 94 –96 °C/18 mmHg (Kugelrohr); $[\alpha]_D^{26}$ +1.34° (*c* 1.19, $CHCl_3$). Ir (film) ν max: 1605, 1500 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.54 (1H, dd, *J*=2.4, 7.7 Hz), 2.70 – 2.90 (3H, m), 3.07 – 3.25 (1H, m), 7.25 (5H, m); Mass (m/z): 134 (M$^+$), 91 (100%). Calcd for $C_9H_{10}O$: 134.0731 (M). Found: 134.0726 (M$^+$).

(*R*)-4-Hydroxy-5-phenyl-2-pentyne (5) ——— A mixture of **3** (3.71 g, 27.7 mmol) and lithium acetylide ethylenediamine complex (4.25 g, 41.5 mmol) in DMSO (40 ml) was stirred at room temperature for 30 min, then *t*-BuOK (6.83 g, 60.9 mmol) was added to the mixture and the stirring was further continued for 16 h at the same temperature. After treating the reaction mixture with 5% HCl, the acidic mixture was extracted with benzene. The extract was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (80 g) using Et_2O-hexane (1:1 v/v) as eluent to give **5** (3.56 g, 80%): $[\alpha]_D^{28}$ +4.05° (*c* 1.58, $CHCl_3$). Ir (film) ν max: 3350, 2240, 1600 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.83 (3H, d, *J*=2.0 Hz), 2.95 (2H, d, *J*=3.0 Hz), 4.50 (1H, m), 7.30 (5H, m); Mass (m/z): 160 (M^+), 91 (100%). Calcd for $C_{11}H_{12}O$: 160.0888 (M). Found: 160.0909 (M^+).

(*S*)-5-Phenyl-4-phthalimino-2-pentyne (6) ——— To a stirred solution of **5** (2.87 g, 17.9 mmol) in THF (100 ml) was added triphenylphosphine (5.17 g, 19.7 mmol), phthalimide (2.90 g, 19.7 mmol), and diethyl azodicarboxylate (3.1 ml, 21.5 mmol) and the stirring was continued for 20 min. After evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column (300 g) using Et_2O-hexane (1:7 v/v) as eluent to give **6** (4.72 g, 91%): mp 93 – 94 °C; $[\alpha]_D^{28}$ –139.86° (*c* 1.33, $CHCl_3$). Ir (Nujol) ν max: 2250, 1775, 1715 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.82 (3H, d, *J*=2.2 Hz), 3.39 (2H, d, *J*=7.6 Hz), 5.25 (1H, m), 7.20 (5H, m), 7.60 – 7.82 (4H, m); Mass (m/z): 289 (M^+). *Anal.* Calcd for $C_{19}H_{15}NO_2$: C 78.87, H 5.23, N 4.84. Found; C 78.57, H 5.46, N 5.12.

(*Z*)-(*S*)-5-Phenyl-4-phthalimino-2-pentene (7) ——— **6** (480 mg, 1.64 mmol) in benzene (10 ml) was hydrogenated over Lindlar catalyst (24 mg) for 45 min at atmospheric pressure. After removal of the catalyst by filtration, the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (10 g) using Et_2O-hexane (1:3 v/v) as eluent to give **7** (473 mg, 99%): mp 83 – 84 °C; $[\alpha]_D^{28}$ –57.34° (*c* 1.08, $CHCl_3$). Ir (Nujol) ν max: 1775, 1710, 1610 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.61 (3H, dd, *J*=2.0, 7.6 Hz), 3.25 (2H, m), 5.10 – 5.80 (2H, m), 5.90 – 6.25 (1H, m), 7.20 (5H, m), 7.50 – 7.80 (4H, m); Mass (m/z); 291 (M^+). *Anal.* Calcd for $C_{19}H_{17}NO_2$: C 78.33, H 5.88, N 4.81. Found: C 78.23, H 5.98, N 4.62.

(*S*)-*N*-Phthaloylphenylalanine (8) ——— A suspension of **7** (466 mg, 1.6 mmol), $NaIO_4$ (3.42 g, 16.0 mmol), and $RuCl_3 \cdot 3H_2O$ (9.2 mg, 2.2 mol%) in a mixture of CH_3CN-CCl_4-H_2O (2:2:3) (7.0 ml) was stirred at room temperature for overnight. After dilution with CH_2Cl_2 the mixture was extracted with sat. aq. $NaHCO_3$ and the aqueous extract was made acidic with conc. HCl. Extraction of the mixture with Et_2O and the extract was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave crystalline residue which was chromatographed on a silica gel column using AcOH-AcOEt (5:95 v/v) as eluent to give **8** (338 mg, 72%): mp 182 – 184 °C (lit.[8b] mp 183 – 185 °C); $[\alpha]_D^{25}$ –197.52° (*c* 1.05, EtOH) [lit.[8b] $[\alpha]_D$ –212° (*c* 1.92, EtOH)]. Ir (Nujol) ν max: 3470, 1775, 1710 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 3.59 (2H, d, *J*=8.1 Hz), 5.23 (1H, t, *J*=8.1 Hz), 7.20 (5H, br.s), 7.55 – 7.85 (4H, m), 10.0 (1H, br); Mass (m/z): 295 (M^+). Calcd for $C_{17}H_{13}NO_4$: 295.0844 (M). Found: 295.0817 (M^+).

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