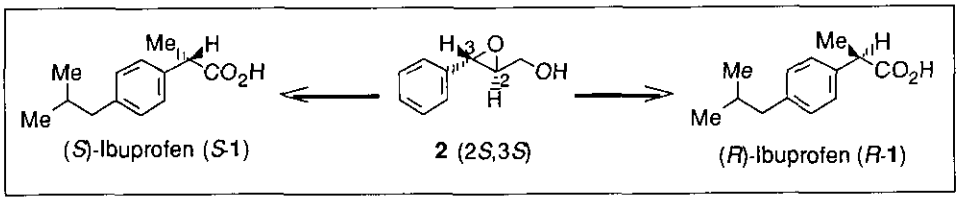
ENANTIODIVERGENT SYNTHESIS OF BOTH ENANTIOMERS OF IBUPROFEN FROM (2*S*,3*S*)-3-PHENYLGLYCIDOL

Seiichi Takano,* Masashi Yanase, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

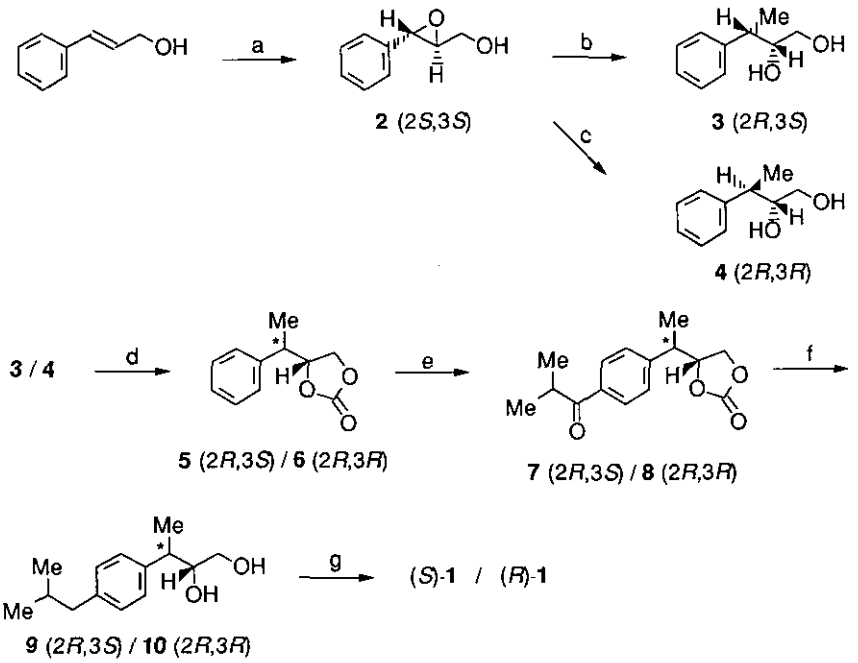
Abstract —— Enantiodivergent synthesis of both enantiomers of ibuprofen, a potent orally active anti-inflammatory agent, has been first established using (2*S*,3*S*)-3-phenylglycidol as a common starting material.

Ibuprofen (**1**) *is a potent orally active anti-inflammatory* agent and used in racemic forms since it was proven that less active (*R*)-enantiomer [(*R*)-**1**] is readily inverted to the active (*S*)-forms [(*S*)-**1**] in human.[1] Enantioselective synthesis of ibuprofen (**1**) is, therefore, not primarily important for the production of the drug itself, but it is still significant from both synthetic and pharmacological points of view.[2] We report herewith an efficient enantioselective synthesis of both (*S*)- and (*R*)-enantiomers of ibuprofen (**1**) *utilizing a single* (2*S*,3*S*)-3-*phenylglycidol* (**2**) *readily accessible* from *trans*-cinnamyl alcohol by the Sharpless chiral epoxidation.[3]



Scheme 1

(2*S*,3*S*)-3-Phenylglycidol (**2**) underwent regioselective methylation at C_3 to give the (2*R*,3*S*)-1,2-glycol (**3**) with retention of the stereochemistry[4,5] on treatment with 1.5 equiv. of trimethylaluminum in methylene dichloride at –70 °C. Immediate treatment of **3** with diethyl carbonate in the presence of potassium carbonate afforded the cyclic carbonate (**5**) in 59% overall yield. On the other hand, reaction of the same epoxide (**2**) with the higher order organocuprate, generated from methyllithium and copper (I) cyanide,[6] in ether at –50 °C afforded the (2*R*,3*R*)-1,2-glycol (**4**), selectively, with inversion of the stereochemistry,[5] which was transformed similarly to the cyclic carbonate (**6**) in 75% overall yield.



Scheme 2

a, Sharpless chiral epoxidation; b, Me_3Al, CH_2Cl_2, –70 °C; c, $Me_2Cu(CN)Li_2$, Et_2O, –50 °C. d, $(EtO)_2CO$, K_2CO_3, 80 °C; e, $Me_2CHCOCl$, $AlCl_3$, CS_2; f, NH_2-NH_2·H_2O, KOH, $O(CH_2CH_2OH)_2$, ~180 °C; g, $RuCl_3$·$3H_2O$, $NaIO_4$, MeCN/CCl_4/H_2O (2:2:3).

On the Friedel-Crafts acylation using 2-methylpropionyl chloride and aluminum trichloride in carbon disulfide, the former carbonate (**5**) afforded the ketone (**7**) in 43% yield, while the latter (**6**) afforded the isomeric ketone (**8**) in 62% yield. Both of the ketones, on treatment with hydrazine hydrate in diethylene glycol at 180 °C, furnished the corresponding isomeric 1,2-glycols, (2*R*,3*S*)-**9** and (2*R*,3*R*)-**10**, respectively, in 56 and 73% yields, with concomitant removal of the carbonate moiety under the conditions. Finally, both **9** and **10** were oxidized with ruthenium oxide[7] to afford optically active ibuprofen (**1**) with the corresponding chirality; **9** gave the (*S*)-acid [(*S*)-**1**] in 93% yield, while **10** gave the (*R*)-acid [(*R*)-**1**] in 77% yield.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. Mass spectra were recorded with a JEOL-OISG-2 instrument, ir spectra with a JASCO A102 spectrophotometer, and ^{1}H-nmr spectra on JEOL-JNM-FX90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Reactions were carried out under argon.

(2*R*,3*S*)-1,2-*O*-Carbonyl-3-phenylbutane-1,2-diol (5)

To a stirred solution of (2*S*,3*S*)-3-phenylglycidol[8] (**2**) (1.50 g, 41.3 mmol) in CH_2Cl_2 (75 ml) is added trimethylaluminum (2.0 M in toluene) (20.7 ml, 62.0 mmol) dropwise at –70 °C. After 33 h at the same temperature, the mixture was treated with 30% NH_4OH and the organic layer was separated and washed with brine. The aqueous layer was extracted with ether and the extract was washed with brine. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give the crude 1,2-diol (**3**) as a colorless oil which was immediately used for the next reaction without purification.

The crude **3** in diethyl carbonate (25 ml, 0.21 mol) was heated with K_2CO_3 (11.4 g, 82.6 mmol) at 80 °C for 66 h. The mixture was taken up into ether and insoluble inorganic materials were removed by filtration through Celite. The organic layer was evaporated under reduced pressure and the residue was purified by chromatography on a silica gel column (250 g) using a mixture of Et_2O/hexane (1:1 v/v) as eluent to give pure **5** as a colorless oil: yield 4.68 g (59% overall from **2**); $[\alpha]_D^{27}$ +14.40° (*c* 3.88, $CHCl_3$). Ir (film): ν max 1800, 1170 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.45 (3H, d, *J*=7.1 Hz), 2.82 - 2.15 (1H, m), 3.94 - 4.32 (2H, m), 4.72 (1H, dd, J=7.6, 16.1 Hz), 7.12 - 7.40 (5H, m); Mass: m/z 192 (M^+). *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.91; H, 6.34.

(2*R*,3*R*)-1,2-*O*-Carbonyl-3-phenylbutane-1,2-diol (6)

To a stirred solution of CuCN (6.27 g, 70.0 mmol) in ether (200 ml) was added methyllithium (1.4 M in ether) (100 ml, 140 mmol) dropwise at –68 °C and the mixture was stirred for further 1 h at –50 °C. To this mixture was added **2**[8] (4.2 g, 28.0 mmol) in ether (50 ml) dropwise at the same temperature and the mixture was stirred for 30 min at the same temperature. After the addition of sat. NH_4Cl, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give the crude 1,2-diol (**4**) as a colorless oil which was directly used for the next reaction.

The crude **4** in diethyl carbonate (33.6 ml, 0.29 mol) was heated with K_2CO_3 (7.73 g, 56.0 mmol) at 80 °C for 25 h. The mixture was treated as for **3** to give pure **6** after purification by column chromatography (SiO_2) using a mixture of Et_2O/hexane (2:1 v/v) as eluent: yield 5.27 g (75% overall from **2**); mp 66 - 67 °C; $[\alpha]_D^{26}$ –7.74° (*c* 1.11, $CHCl_3$). Ir (Nujol): ν max 1780 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.39 (3H, d, *J*=7.1 Hz), 2.94 - 3.25 (1H, m), 4.06 - 4.51 (2H, m), 4.74 - 4.97 (1H, m), 7.18 - 7.42 (5H, m); Mass: m/z 192 (M^+), 105. *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.74; H, 6.23.

(2*R*,3*S*)-1,2-*O*-Carbonyl-3-[4-(2-methylpropionyl)phenyl]butane-1,2-diol (7)

To a stirred solution of aluminum trichloride (5.02 g, 37.6 mmol) in carbon disulfide (50 ml) was added 2-methylpropionyl chloride (3.95 ml, 37.7 mmol) dropwise at 0 °C. After 30 min, a solution of **5** (2.41 g, 12.6 mmol) in carbon disulfide (10 ml) was added at the same temperature and the mixture was further stirred at room temperature for 20 h. The mixture was treated with 10% HCl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (100 g) using a mixture of Et_2O/hexane (4:1 v/v) as eluent to give pure **7** as colorless crystals: yield 1.41 g (43%); mp 39

- 40 °C; $[\alpha]_D^{30}$ +4.54° (*c* 2.33, $CHCl_3$). Ir (Nujol): ν max 1790, 1670, 1600 cm^{-1}; ^1H-nmr: δ 1.22 (6H, d, *J*=6.8 Hz), 1.47 (3H, d, *J*=6.8 Hz), 3.10 (1H, m), 3.53 (1H, m), 3.96 - 4.39 (2H, m), 4.82 (1H, dd, *J*=7.8, 15.4 Hz), 7.32 (2H, dd, *J*=1.6 and 8.5 Hz), 7.95 (2H, dd, *J*=2.0, 8.5 Hz); Mass: m/z 262 (M^+). *Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.67; H, 6.83.

(2*R*,3*R*)-1,2-*O*-Carbonyl-3-[4-(2-methylpropionyl)phenyl]butane-1,2-diol (8)

To a stirred solution of aluminum trichloride (1.78 g, 13.2 mmol) in carbon disulfide (10 ml) was added 2-methylpropionyl chloride (1.40 ml, 13.2 mmol) dropwise at 0 °C. After 30 min, a solution of **6** (1.28 g, 6.67 mmol) in carbon disulfide (3 ml) was added at the same temperature and the mixture was further stirred at room temperature for 35 h. The mixture was treated as for **5** to give pure[9] **8** as a colorless oil after purification by column chromatography (SiO_2) using a mixture of Et_2O/hexane (2:1 v/v) as eluent: yield 1.08 g (62%); $[\alpha]_D^{26}$ +11.3° (*c* 1.04, $CHCl_3$). Ir (film): ν max 1800, 1680, 1605 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 1.22 (6H, d, *J*=6.8 Hz), 1.41 (3H, d, *J*=7.1 Hz), 3.07 - 3.36 (1H, m), 3.39 - 3.69 (1H, m), 4.07 - 4.58 (2H, m), 4.75 - 4.99 (1H, m), 7.35 (2H, dd, *J*=1.6 and 8.1 Hz), 7.95 (2H, dd, *J*=2.0 and 8.6 Hz); Mass: m/z 262 (M^+), 219. *Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.73; H, 7.00.

(2*R*,3*S*)-3-[4-(2-Methylpropyl)phenyl]butane-1,2-diol (9)

A mixture of **7** (303 mg, 1.16 mmol), 98% hydrazine hydrate (0.29 ml, 5.8 mmol), and KOH (325 mg, 5.80 mmol) in diethylene glycol (3 ml) was heated at 110 °C for 45 min and 180 °C for 2.5 h. After cooling, the mixture was diluted with ether and the organic layer was washed sequentially with brine, 5% HCl, sat. $NaHCO_3$, and brine, and dried over $MgSO_4$. The mixture, after evaporation of the solvent under reduced pressure, was purified on a silica gel column (5 g) using a mixture of Et_2O/hexane (2:1 v/v) as eluent to give pure[9] **9** as a colorless oil: yield 143 mg (56%); $[\alpha]_D^{19}$ +4.29° (*c* 1.54, $CHCl_3$). Ir (film): ν max 3375 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 0.88 (6H, d, *J*=6.6 Hz), 1.32 (3H, d, *J*=6.8 Hz), 1.83 (1H, m), 2.43 (2H, d, *J*=7.3 Hz), 2.73 (3H, m), 3.25 - 3.50 (2H, m), 3.60 - 3.82 (1H, m), 7.08 (4H, m); Mass: m/z 222 (M^+), 161. *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.79; H, 9.77.

(2*R*,3*R*)-3-[4-(2-Methylpropyl)phenyl]butane-1,2-diol (10)

A mixture of **8** (60 mg, 0.23 mmol), 90% hydrazine hydrate (37 μl, 0.69 mmol), and KOH (38 mg, 0.69 mmol) in diethylene glycol (1 ml) was heated at 120 °C for 30 min and 180 °C for 3 h. After cooling, the mixture was treated as for **7** to give pure **10** as a colorless oil after purification by silica gel column chromatography using a mixture of Et_2O/hexane (4:1 v/v) as eluent: yield 37 mg (72%); $[\alpha]_D^{26}$ +16.22° (*c* 0.91, $CHCl_3$). Ir (film): ν max 3400 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 0.90 (6H, d, *J*=6.4 Hz), 1.24 (3H, d, *J*=7.1 Hz), 1.62 - 2.07 (1H, m), 2.39 (2H, d, J=2.0 Hz), 2.45 (2H, m), 2.66 - 2.89 (1H, m), 3.45 - 3.83 (3H, m), 7.10 (4H, m); Mass: m/z 222 (M^+). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.15; H, 9.84.

(*S*)-Ibuprofen [(*S*)-1]

A mixture of **9** (413 mg, 1.86 mmol), $NaIO_4$ (1.59 g, 7.44 mmol), and $RuCl_3 \cdot 3H_2O$ (10.7 mg, 0.04 mmol) in MeCN/CCl_4/H_2O (2:2:3 v/v) (7 ml) was stirred at 0 °C for 3 h. The mixture was taken to sat. $NaHCO_3$ and the combined $NaHCO_3$ layers were acidified by addition of conc. HCl. The acidic mixture was throughly extracted with ether and the combined extract was dried over

$MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified on a silica gel column (20 g) using a mixture of Et_2O/hexane (2:3 v/v containing 0.5% of acetic acid) as eluent to give (*S*)-ibuprofen [(*S*)-**1**] as colorless crystals: yield 355 mg (93%); mp 75 - 76 °C (lit.[2] mp 75 - 76 °C); $[\alpha]_D^{24}$ +59.51° (*c* 3.66, 95% EtOH) [lit.[2] $[\alpha]_D^{25}$ +60° (*c* 2.95, 95% EtOH)]. Ir (Nujol): ν max 3000 - 2600, 1700 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 0.89 (6H, d, *J*=6.6 Hz), 1.49 (3H, d, *J*=7.3 Hz), 1.53 - 1.91 (1H, m), 2.44 (2H, d, *J*=7.3 Hz), 3.70 (1H, dd, *J*=7.3 and 14.3 Hz), 7.04 (2H, d, *J*=8.0 Hz), 7.18 (2H, d, *J*=8.0 Hz), 9.6 (1H, br s, exchangeable); Mass: m/z 206 (M^+), 163. Spectral data and chromatographic behavior (tlc) were identical with those of an authentic material in racemic forms.

(*R*)-Ibuprofen [(*R*)-1]

A mixture of **10** (38 mg, 0.17 mmol), $NaIO_4$ (146 mg, 0.68 mmol), and $RuCl_3 \cdot 3H_2O$ (0.45 mg, 0.017 mmol) in $MeCN/CCl_4/H_2O$ (2:2:3 v/v) (1 ml) was stirred at room temperature for 3 h. The mixture was treated as for **9** to give (*R*)-ibuprofen [(*R*)-**1**] as colorless crystals: yield 27 mg (77%); mp 75 - 76 °C (lit.[2] mp 75 - 76 °C); $[\alpha]_D^{22}$ –58.71° (*c* 1.84, 95% EtOH) [lit.[2] for (*S*)-enantiomer; $[\alpha]_D^{25}$ +60° (*c* 2.95, 95% EtOH)]. Spectral data and chromatographic behavior were identical with those of an authentic material in racemic forms as well as those of (*S*)-enantiomer [(*S*)-**1**] prepared as above.

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8. Optically pure **2**, [mp 50 - 51 °C; $[\alpha]_D^{26}$ –50.4° (*c* 2.4, $CHCl_3$)], was used as starting material. Optically pure material could be obtained by recrystallization of the crude product[3] from a mixture of petroleum ether (bp 30 - 60 °C) and ether.
9. Retention of the original optical integrity was confirmed at this stage by measurement of ^{1}H-nmr spectra (500 MHz) of MTPA esters. Cf. S. Takano, M. Takahashi, M. Yanase, Y. Sekiguchi, Y. Iwabuchi, and K. Ogasawara, *Chemistry Lett.*, 1988, 1827.

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