SYNTHESIS OF (*S*)-(+)-α-METHOXYMETHYLDIHYDROCOUMARIN: ABSOLUTE CONFIGURATION OF THE REDUCED PRODUCT IN ENANTIOSELECTIVE RADICAL-MEDIATED REDUCTION†

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Abstract — (*S*)-(+)-α-Methoxymethyldihydrocoumarin was synthesized starting from (*R*)-2-benzyl-3-hydroxypropyl acetate. Consequently, the absolute configuration of the reduced product obtained by radical-mediated reduction of α-iodo-α-methoxymethyldihydrocoumarin was determined to be *R*.

Asymmetric induction in radical-mediated reactions using organotin reagents has been currently focused in synthetic organic chemistry.[1] Although diastereoselective radical reactions have been reported, little has been known about the enantioselective radical reaction.[2] Recently,[2a] we have reported the first example of an efficient enantioselective radical-mediated reduction of alkyl halide using organotin compound in the presense of a chiral ligand and a Lewis acid; the synthesis of optically active α-methoxymethyldihydrocoumarin (**2**) could be achieved by treatment of α-iodolactone (**1**) with tributyltin hydride coupled with a chiral amine and magnesium iodide as shown in Scheme 1. However, the absolute configuration of the reduced product (**2**) obtained by the asymmetric reaction was not determined, because **2** had not been known previously in optically active form. We describe here the synthesis of the title compound and the absolute configuration of the reduced product (**2**).

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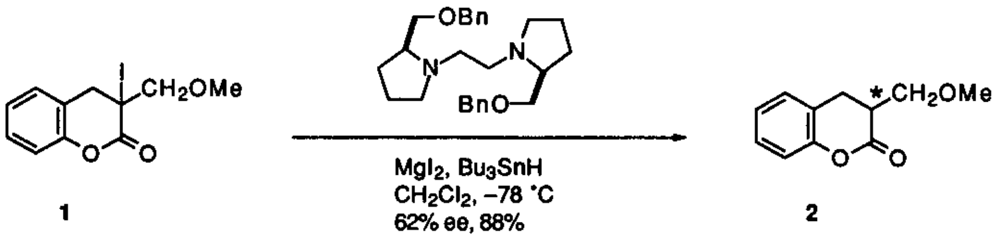
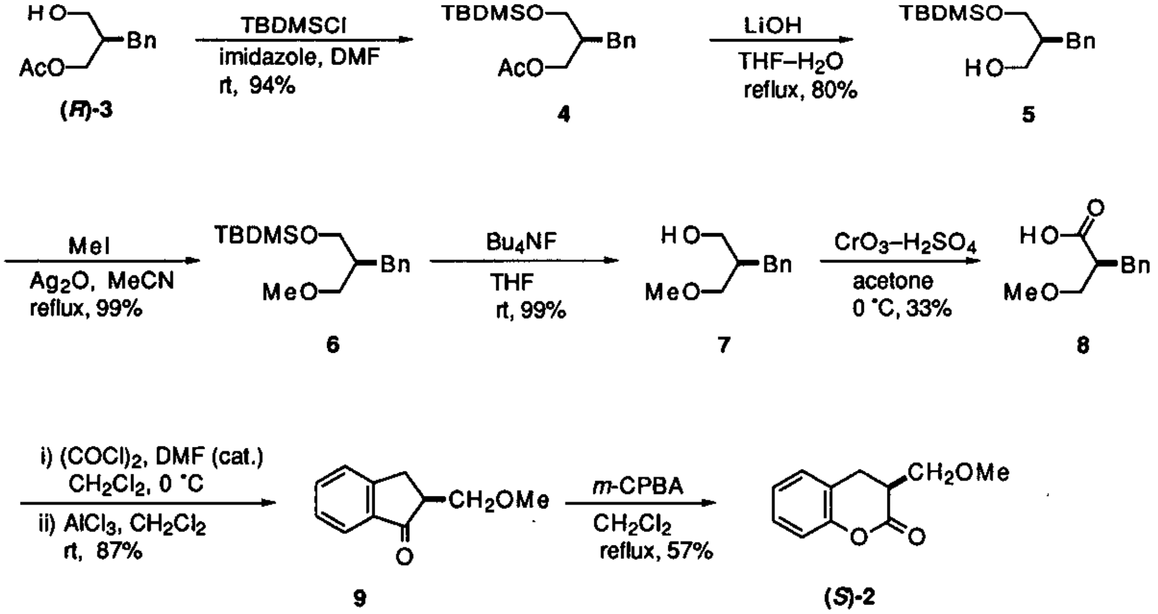
† This paper is dedicated to the memory of Professor Emeritus Shun-ichi Yamada.



Scheme 1

In our synthetic strategy, (*R*)-2-benzyl-3-hydroxypropyl acetate (**3**)[3], which is prepared from 2-benzylpropanediol by lipase-catalyzed transesterification reported by Achiwa *et al.*, was chosen as a starting chiral synthon. The synthesis of (*S*)-(+)-**2** is shown in Scheme 2.



Scheme 2

The hydroxyl group of (*R*)-**3** {97% optical yield; $[\alpha]_D$ +28° (*c*, 1.32, $CHCl_3$)} was protected with *t*-butyldimethylsilyl (TBDMS) group to form **4** in 94% yield, hydrolysis of which with LiOH in THF–H_2O gave alcohol (**5**) in 80% yield. For methylation of the hydroxyl group, at first, **5** was treated with NaH and MeI in DMF to give methyl ether (**6**). However, the specific rotation did not show significant value. This result suggested that racemization occurred by the treatment of **5** with NaH. Therefore, methylation under neutral conditions was considered. The reaction of **5** with MeI in MeCN in the presence of Ag_2O was carried out to afford desired optically active methyl ether (**6**) {$[\alpha]_D$ –11° (*c*, 1.22, MeOH)} in 99%

yield. Deprotection of TBDMS group in **6** using Bu_4NF gave alcohol (**7**) {$[\alpha]_D$ +13° (*c*, 1.02, MeOH)}in 99% yield, Jones oxidation of which provided carboxylic acid (**8**) in 33% yield. Indanone (**9**) was obtained in 87% yield by the treatment of **8** with $(COCl)_2$ in the presence of a catalytic amount of DMF followed by Friedel-Crafts acylation using $AlCl_3$ in CH_2Cl_2. Finally, Baeyer-Villiger reaction of **9** with *m*-CPBA afforded (*S*)-α-methoxymethyl-dihydrocoumarin (**2**) in 57% yield. The enantiomeric exess (ee) was determined to be 40% by HPLC analysis using a chiral column, although partial racemization stage has not been clear. The specific rotation of (*S*)-**2** synthesized from (*R*)-**3** showed $[\alpha]_D$ +8° (*c*, 1.19, benzene). Thus, we concluded that *S*-enantiomer of α-methoxymethyldihydrocoumarin (**2**) has plus sign of rotation. Consequently, the absolute configuration of **2** {62% ee; $[\alpha]_D$ −12° (*c*, 1.01, benzene)} in the enantioselective radical-mediated reduction previously reported[2a] was determined to be *R* (Scheme 1).

EXPERIMENTAL

All melting points were measured on a Yanagimoto (hot plate) melting point apparatus and are uncorrected. IR spectra were performed with a Hitachi 260-10 spectrophotometer and ^{1}H-NMR (270 MHz) and ^{13}C-NMR (67.5 MHz) spectra were recorded with a JEOL EX-270 (270 MHz) spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard. Mass spectra were measured on a Hitachi M-80, a JEOL JMS D-300 or a JEOL JMS-SX102A spectrometer. Column chromatography was performed on silica gel.

(*S*)-2-Benzyl-3-*tert*-butyldimethylsilyloxypropyl acetate (4)

To a solution of (*R*)-2-benzyl-3-hydroxypropyl acetate (**3**)[3] {optical yield: 97%; $[\alpha]_D$ +28° (*c*, 1.32, $CHCl_3$)}(5 g, 24.0 mmol) in DMF (70 mL) were added imidazole (2.7 g, 39.7 mmol) and TBDMSCl (4 g, 26.5 mmol). The whole was stirred at rt for 2 h. The mixture was diluted with AcOEt (100 mL)-benzene (50 mL). The resulting mixture was washed successively with water (100 mL), 0.5N HCl (50 mL), water (50 mL), saturated $NaHCO_3$, and saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by distillation to afford **4** (7.3 g, 94%) as an oil: bp 140-145 °C / 4 mmHg; $[\alpha]_D$ +1° (*c*, 1.39, benzene); IR (neat) 2940, 2850, 1740, 1600 cm^{-1}; ^{1}H-NMR δ 0.03 (6H, s), 0.88 (9H, s), 2.02 (3H, s), 2.02–2.14 (1H, m), 2.58 (1H, dd, *J* = 7.1, 13.7 Hz), 2.69 (1H, dd, *J* = 7.8, 13.7 Hz), 3.49 (1H, dd, *J* = 5.3, 10.2 Hz), 3.55 (1H, dd, *J* = 4.8, 10.2 Hz), 4.03 (2H, d, *J* = 5.9 Hz), 7.13–7.26 (5H, m); ^{13}C-NMR δ −5.6, −5.5, 20.9, 25.9, 34.2, 42.2, 61.8, 64.3, 126.0, 128.3, 129.1, 139.8, 171.1; MS *m/z* 307 (M^+–15). HRMS calcd for $C_{17}H_{27}O_3Si$ (M^+–15) 307.1727, found 307.1706.

(*S*)-2-Benzyl-3-*tert*-butyldimethylsilyloxypropanol (5)

A solution of acetate (4) (7.2 g, 22.2 mmol) and $LiOH•H_2O$ (1.9 g, 44.3 mmol) in THF (45 mL)-water (20 mL) was refluxed for 25 h. The solvent was removed under reduced pressure, and the crude product was diluted with Et_2O (300 mL). The resulting mixture was washed successively with water (100 mL) and saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by distillation to afford **5** (5 g, 80%) as an oil: bp 145 °C / 1.5 mmHg; $[\alpha]_D$ –18° (*c*, 1.08, MeOH); IR (neat) 3600–3200, 2950, 2860, 1600 cm^{-1}; ^1H-NMR δ 0.03 (6H, s), 0.85 (9H, s), 1.90–2.03 (1H, m), 2.57 (2H, d, *J* = 7.6 Hz), 2.67 (1H, br), 3.54–3.63 (2H, m), 3.68–3.75 (2H, m), 7.12–7.24 (5H, m); ^{13}C-NMR δ –5.6, 18.2, 25.9, 34.2, 43.9, 65.8, 66.2, 126.0, 128.4, 129.0, 140.1; MS *m/z* 280 (M^+). HRMS calcd for $C_{16}H_{28}O_2Si$ (M^+) 280.1856, found 280.1835.

(*S*)-2-Benzyl-3-*tert*-butyldimethylsilyloxypropyl methyl ether (6)

To a solution of alcohol (5) (2.1 g, 7.5 mmol) in MeCN (5 mL) were added MeI (4 mL, 64 mmol) and Ag_2O (3 g, 12.9 mmol). The whole was refluxed for 18 h. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane : benzene = 2 : 1, then benzene) followed by bulb-to-bulb distillation to give **6** (2.2 g, 99%) as an oil: bp 140 °C / 2 mmHg; $[\alpha]_D$ –11° (*c*, 1.22, MeOH); IR (neat) 2930, 2850, 1600 cm^{-1}; ^1H-NMR δ 0.04 (6H, s), 0.88 (9H, s), 1.90–2.06 (1H, m), 2.58 (1H, dd, *J* = 7.1, 13.5 Hz), 2.66 (1H, dd, *J* = 7.6, 13.5 Hz), 3.28 (3H, s), 3.28 (2H, d, *J* = 5.6 Hz), 3.50 (1H, dd, *J* = 5.4, 9.9 Hz), 3.54 (1H, dd, *J* = 5.3, 9.9 Hz), 7.14–7.25 (5H, m); ^{13}C-NMR δ –5.5 (SiC and $SiCH_3$), 25.9, 34.2, 43.4, 58.8, 62.2, 72.3, 125.8, 128.2, 129.2, 140.6; MS *m/z* 294 (M^+). HRMS calcd for $C_{17}H_{30}O_2Si$ (M^+) 294.2013, found 294.1988.

(*R*)-2-Benzyl-3-methoxypropanol (7)

A solution of ether (6) (2.2 g, 7.3 mmol) and $Bu_4NF•xH_2O$ (4 g) in THF (50 mL) was stirred for 2 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane : AcOEt = 2 : 1, then 1 : 1) followed by bulb-to-bulb distillation to afford **7** (1.3 g, 99%) as an oil: bp 160 °C / 2 mmHg; $[\alpha]_D$ +13° (*c*, 1.02, MeOH); IR (neat) 3600–3200, 2900, 1600 cm^{-1}; ^1H-NMR δ 2.05–2.18 (1H, m), 2.52 (1H, br), 2.61 (1H, dd, *J* = 7.3, 13.5 Hz), 2.67 (1H, dd, *J* =

7.6, 13.5 Hz), 3.34 (3H, s), 3.39 (1H, dd, J = 6.9, 9.2 Hz), 3.50 (1H, dd, J = 4.3, 9.2 Hz), 3.63 (1H, dd, J = 6.6, 10.9 Hz), 3.73 (1H, dd, J = 3.6, 10.9 Hz), 7.17–7.32 (5H, m); ^{13}C-NMR δ 34.9, 42.9, 59.6, 66.1, 76.2, 126.5, 128.9, 129.5, 140.4; MS *m/z* 180 (M^+). HRMS calcd for $C_{11}H_{16}O_2$ (M^+) 180.1148, found 180.1146.

(*S*)-2-Benzyl-3-methoxypropionic acid (8)

To a solution of alcohol (7) (680.6 mg, 3.78 mmol) in acetone (10 mL) was added dropwise Jones reagent at 0 °C until the solution turned brown. The reaction mixture was stirred until TLC analysis indicated complete oxidation of the alcohol (7). The mixture was quenched with *i*-PrOH and filtered. After addition of water, the filtrate was extracted with Et_2O (50 mL x 3). The organic extracts were washed with saturated NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was diluted with Et_2O. The resulting mixture was extracted with saturated $NaHCO_3$ (50 mL x 3). The extracts were washed with Et_2O, and then acidified with 30% H_2SO_4. The aqueous solution was extracted with Et_2O (50 mL x 3). The extracts were washed with saturated NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **8** (240.4 mg, 33%) as an oil: $[\alpha]_D$ –4° (*c*, 1.05, *c*-hexane); IR (neat) 3700–2300, 1710, 1600 cm^{-1}; ^{1}H-NMR δ 2.84 (1H, dd, J = 6.9, 12.2 Hz), 2.89–2.99 (1H, m), 3.04 (1H, dd, J = 6.3, 12.2 Hz), 3.35 (3H, s), 3.47–3.56 (2H, m), 7.18–7.33 (5H, m); ^{13}C-NMR δ 34.1, 47.2, 59.0, 71.8, 76.5, 126.6, 128.5, 128.9, 138.4, 178.4; MS *m/z* 194 (M^+). HRMS calcd for $C_{11}H_{14}O_3$ (M^+) 194.0943, found 194.0944.

(*S*)-2-Methoxymethylindanone (9)

To a solution of acid (8) (75.7 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) were added $(COCl)_2$ (0.05 mL, 0.57 mmol) and a catalytic amount of DMF (2 drops) at 0 °C. The whole was stirred at 0 °C for 30 min. The solvent was removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (4 mL). To this solution was added $AlCl_3$ (98.4 mg, 0.74 mmol) at 0 °C. The reaction mixture was stirred at rt for 30 min. After addition of saturated $NaHCO_3$, the mixture was extracted with Et_2O (50 mL x 3). The extracts were washed with saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane : Et_2O = 4 : 1) followed by bulb-to-bulb distillation to afford **9** (59.4 mg, 87%) as an oil: bp 123 °C / 2 mmHg; $[\alpha]_D$ –23° (*c*, 1.41, benzene); IR (neat) 2900, 1705, 1600 cm^{-1}; ^{1}H-NMR δ 2.88–2.96 (1H, m), 3.10–3.36 (2H, m), 3.34 (3H, s), 3.69–3.80 (2H, m), 7.33–7.39 (1H, m), 7.46–7.49 (1H, m), 7.56–7.62 (1H, m), 7.74–

7.77 (1H, m); ^{13}C-NMR δ 30.4, 47.9, 59.1, 72.3, 123.9, 126.6, 127.3, 134.9, 136.8, 154.3, 206.5; MS *m/z* 176 (M^+). HRMS calcd for $C_{11}H_{12}O_2$ (M^+) 176.0837, found 176.0845.

(*S*)-2-Methoxymethyldihydrocoumarin (2)

A solution of indanone (**9**) (50.1 mg, 0.29 mmol) and 70% *m*-CPBA (500 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was refluxed for 12 h. The solvent was removed under reduced pressure, and the crude product was taken up in Et_2O (30 mL). After filtration, the filtrate was diluted with hexane, and then washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) followed by bulb-to-bulb distillation to give **2** (31 mg, 57%) as an oil: bp 120 °C / 2 mmHg; 40% ee; HPLC [chiralcel OB; hexane : 2-propanol = 50 : 1; flow rate 0.5 mL / min]; $[\alpha]_D$ +8° (*c*, 1.19, benzene); IR (neat) 2925, 1760, 1600 cm^{-1}; ^{1}H-NMR δ 2.89–3.17 (3H, m), 3.41 (3H, s), 3.68 (1H, dd, *J* = 6.9, 9.6 Hz), 3.85 (1H, dd, *J* = 4.1, 9.6 Hz), 7.03–7.26 (4H, m); ^{13}C-NMR δ 27.0, 39.7, 59.2, 70.7, 116.6, 122.5, 124.4, 128.2 (CH x 2), 151.5, 168.9; MS *m/z* 192 (M^+). HRMS calcd for $C_{11}H_{12}O_3$ (M^+) 192.0785, found 192.0788. These spectral data were identical with those for the reduced product obtained by enantioselective radical reaction.[2a]

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