

Enantioselective Radical-Mediated Reduction of α -Alkyl- α -iododihydrocoumarins in the Presence of a Chiral Magnesium Iodide

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Abstract

An enantioselective reduction of α -alkyl- α -iododihydrocoumarins **1** by radical-mediated reactions using magnesium iodide and a chiral diamine **2** is described. The reactions of **1** with tributyltin hydride or triphenyltin hydride in the presence of a chiral Lewis acid generated from magnesium iodide and **2** at $-78\text{ }^\circ\text{C}$ in ether- CH_2Cl_2 took place to afford reduced products **3**. The determination of the absolute configurations of **3b–3d** by chemical correlation with **3a** is also described. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Enantioselective reaction; Radical-mediated reduction; Chiral Lewis acid; Absolute configuration

1. Introduction

Asymmetric induction in radical reactions using organotin reagents has been the focus of current investigation in synthetic organic chemistry, and diastereoselective radical reactions are well known as useful methods for the synthesis of optically active compounds. Chirality transfer using stereogenic centers adjacent to the radical center has been reported.¹ Lewis acids have been shown to influence diastereoselective radical-mediated reactions.¹ Recently, we have reported the first example of enantioselective radical-mediated reduction of α -iodolactone **1a** with tributyltin hydride in the presence of a chiral Lewis acid.² Enantioselective carbon-carbon bond-forming reactions by radical-mediated additions and allylations using chiral Lewis acids have also appeared.³ Other successful methods employed chiral organotin hydrides in the enantioselective radical-

mediated reduction of haloesters or haloketone.⁴ Radical reactions catalyzed by optically active thiol are also known.⁵ The present paper deals with the details of a radical-mediated reduction of α -alkyl- α -iododihydrocoumarins **1** and the determination of the absolute configurations of reduced products **3**.⁶

2. Results and Discussion

A radical generated at the α position to the carbonyl group possibly exists as an enol form so that the unpaired electron overlaps with a carbonyl π -bond.⁷ Although the π -system of an achiral enol radical is symmetrical, it was expected that the enantiotopic face of an enol radical could be distinguished in a chiral environment. To substantiate this expectation, we planned the reactions of the radicals, starting from α -iodo carbonyl compounds with a hydrogen radical in the presence of a chiral Lewis acid (Figure 1).

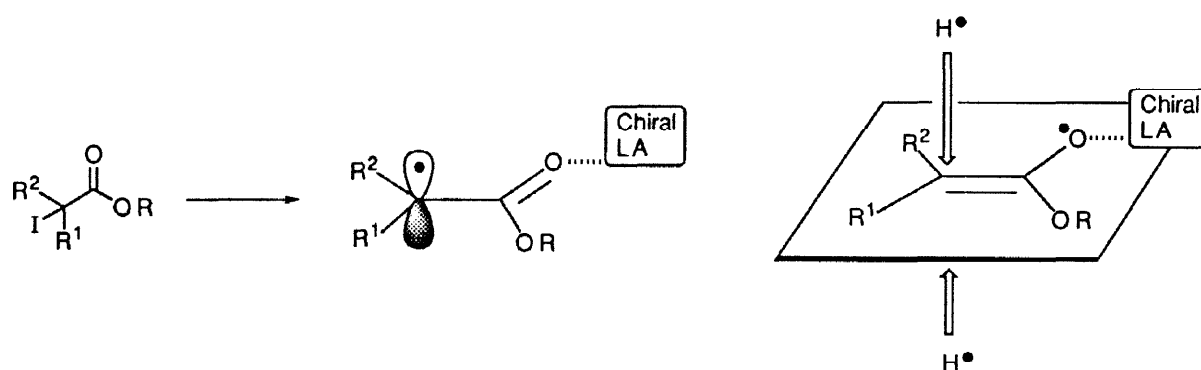
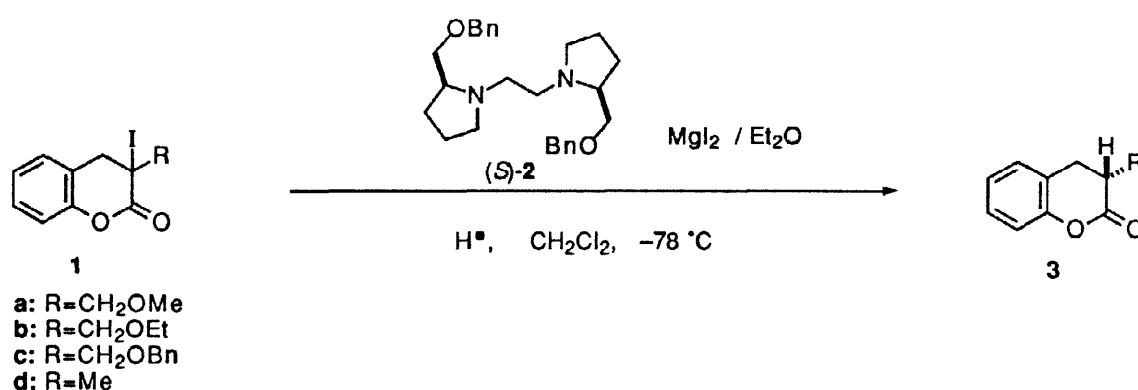


Figure 1



Scheme 1 Reagents: i, (*S*)-**2**, MgI₂ in Et₂O; ii, Bu₃SnH, Ph₃SnH or (Me₃Si)₃SiH

*C*₂-symmetric diamine **2**, which was easily synthesized from (*S*)-proline by a method similar to that described in the literature,⁸ was used for preparation of chiral Lewis acids. At first, we chose α -methoxymethyl- α -iodolactone **1a** as a model substrate. It is reported that MgI₂ is an effective Lewis acid in the diastereoselective radical-mediated reactions of α -halo- β -alkoxy esters without an initiator.^{9,10,11} Thus, the

reduction of **1a** with an equimolar amount of Bu₃SnH was carried out by use of MgI₂ (ether solution) and a chiral diamine **2** in CH₂Cl₂ at –78 °C as shown in Scheme 1.¹² The results are summarized in Table 1.

Table 1
Enantioselective radical-mediated reduction of α -iodolactone **1**^a

Run	Substrate	Concentration of 1 (mM)	Reagent	Yield (%) ^b	ee (%)	Confign
1	1a	11	Bu ₃ SnH	75	12	<i>R</i>
2	1a	21	Bu ₃ SnH	81	18	<i>R</i>
3	1a	36	Bu ₃ SnH	88	62	<i>R</i>
4	1a	67	Bu ₃ SnH	83	52	<i>R</i>
5	1a	36	Bu ₃ SnH	50	43 ^c	<i>R</i>
6	1a	37	Ph ₃ SnH	74	39	<i>R</i>
7	1a	36	(Me ₃ Si) ₃ SiH	<i>d</i>	–	–
8	1b	21	Bu ₃ SnH	76	24	<i>R</i>
9	1b	37	Bu ₃ SnH	84	65	<i>R</i>
10	1b	35	Ph ₃ SnH	83	62	<i>R</i>
11	1c	21	Bu ₃ SnH	80	28	<i>R</i>
12	1c	38	Bu ₃ SnH	89	58	<i>R</i>
13	1c	35	Ph ₃ SnH	85	46	<i>R</i>
14	1d	35	Bu ₃ SnH	78	30	<i>S</i>
15	1d	30	Bu ₃ SnH ^e	82	33	<i>S</i>

^a All reactions were carried out according to Scheme 1, unless otherwise noted. For details, see experimental section.

^b Isolated yield. ^c Reaction was carried out at –50 °C. ^d No reaction. ^e 2 equiv. of Bu₃SnH was used.

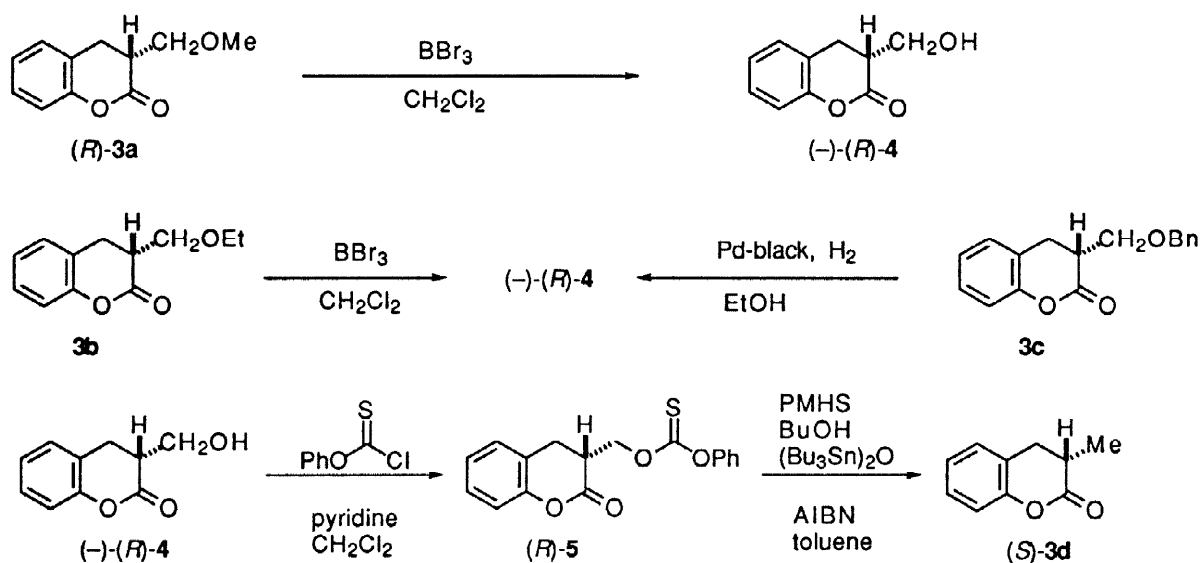
The degree of asymmetric induction was found to be dependent on the volume of the CH₂Cl₂ used as a solvent. The reactions under dilution conditions (11 mM and 21 mM) gave low enantioselectivities (run 1: 12% ee and run 2: 18% ee). These results are probably ascribed to the presence of the enol radical uncomplexed with the chiral Lewis acid. The best result was obtained by the reaction at 36 mM of **1a**. This reaction proceeded smoothly to afford an optically active reduced product **3a** in 88% isolated yield and 62% enantiomeric excess (ee) with *R* configuration (run 3).¹³ The reaction at –50 °C gave slightly lower selectivity, 43% ee (run 5).

When only ether was used as a solvent, the reaction mixture became a suspension, and the reaction at -78 to -50 °C for 16 h gave racemic **3a** in 66% isolated yield.

The reaction of **1a** with an equimolar amount of Ph_3SnH at -78 °C for 5 h resulted in 39% ee (run 6). This reaction required a long time for completion, while the reactions with Bu_3SnH mentioned above were completed within 40 min. When tris(trimethylsilyl)silane was used, the reaction did not proceed (run 7).

Next, we became interested in the asymmetric induction in the reactions of other α -alkoxymethyl- α -iodolactones. The reactions of **1b** and **1c** with Bu_3SnH gave similar results as in the case of **1a**. The reduction under high concentration of **1b** and **1c** gave (*R*)-**3b** (84% isolated yield, 65% ee) and (*R*)-**3c** (89% isolated yield, 58% ee), whereas the enantioselectivity was decreased under dilution conditions (runs 9 and 12 vs 8 and 11). When Ph_3SnH was used, (*R*)-**3b** and (*R*)-**3c** were obtained in 83% isolated yield with 62% ee and 85% isolated yield with 46% ee, respectively (runs 10 and 13).

The asymmetric reductions of α -methyl- α -iododihydrocoumarin **1d**, which does not contain an oxygen atom in the side chain, were also examined. The reduction with an equimolar amount of Bu_3SnH at -78 °C resulted in 30% ee with *S* configuration. When excess amount of Bu_3SnH (2 equiv.) was used, 33% ee was obtained.¹⁴ The sense of asymmetric induction was identical to that of α -alkoxymethyl- α -iododihydrocoumarins **1a–1c** (runs 14 and 15 vs 3, 9 and 12).



The absolute configurations of **3b**, **3c** and **3d** were determined by chemical correlation with (*R*)-**3a**¹³ as shown in Scheme 2. Hence, treatment of **3b** with BBr_3 in CH_2Cl_2 provided 3-(hydroxymethyl)-3,4-dihydrocoumarin (*-*)-**4** which proved to be identical, with the exception of enantiomeric purity, to the sample prepared from (*R*)-**3a** by the same procedure. Hydrogenolysis of **3c** also gave **4**, the sign of specific rotation of which showed minus. Therefore, the absolute configurations of **3b** and **3c** are determined to be *R*. It is noted that hydrogenolysis of **3c** affords the desired product **4** without any racemization while partial

racemization occurs in the reactions of both **3a** and **3b** with BBr_3 . The absolute configuration of **3d** was determined by use of (–)-**4** obtained above. Thionocarbonate **5** derived from (–)-**4** was deoxygenated using $\text{TMSO}(\text{SiHMeO})_n\text{-TMS}$ (PMHS) by the method described in the literature¹⁵ to afford **3d** which proved to be identical, with the exception of enantiomeric purity, to the sample obtained by the enantioselective reduction of **1d**. Thus, the absolute configuration of **3d** is found to be *S*. The determination of the absolute configurations of **3b–3d** was also carried out by comparison of the retention times (R_t) of the major enantiomers in HPLC analysis.

3. Conclusion

In conclusion, it was found that optically active α -alkyldihydrocoumarins **3** were synthesized by the enantioselective radical-mediated reduction of the corresponding iodides **1** with a chiral Lewis acid and organotin hydride. The sense of asymmetric induction was found to be independent of the substrates used. Further investigation toward development of a more effective chiral Lewis acid is currently under way.

4. Experimental

General

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 or a Horiba FT-210 spectrophotometer. ¹H NMR (270 MHz) and ¹³C NMR (67.5 MHz) spectra were recorded with a JEOL EX-270 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. Specific rotation was measured on a JASCO DIP-360 digital polarimeter. The enantiomeric excess (ee) of **3** was determined by HPLC analysis using chiral columns (DAICEL). Column chromatography was performed on silica gel.

Typical procedure for the preparation of MgI_2

Under argon atmosphere, a solution of I_2 (101.6 mg, 0.4 mmol) in Et_2O (4 mL) was added to Mg (20 mg, 0.8 mmol) at room temperature. The whole was shielded from light and stirred at room temperature until the mixture turned colorless (ca. 2.5 h). The resulting mixture was filtered by transfer into a syringe equipped with a filter, and a half-volume of the mixture was used for asymmetric reactions.

Preparation of (*S*)-*N,N'*-1,1'-ethylenebis(2-benzoyloxymethylpyrrolidine) (*S*)-**2**

(*S*)-**2** was prepared from (*S*)-proline by a method similar to that described in the literature.⁸ The crude product [(*S*)-**2**, oil, 3.25 g] in MeOH (10 mL) was mixed with a solution of picric acid (5.5 g, 19.2 mmol) in

MeOH (20 mL). The resulting yellow precipitates were collected by filtration and recrystallized from benzene (250 mL) to give optically pure (*S*)-2-dipicrate (5.8 g) as yellow plates of mp 154–155 °C, $[\alpha]_{\text{D}}^{29} +29.6$ (*c* 1.03, CHCl₃). Anal. Calcd for C₃₈H₄₂N₈O₁₆·1/3 H₂O: C, 52.29; H, 4.93; N, 12.84. Found: C, 52.61; H, 4.61; N, 12.45. A suspension of this dipicrate (1 g, 1.15 mmol) in hexane (20 mL) was mixed with a solution of NaOH (110 mg, 2.8 mmol) in H₂O (40 mL) under stirring. After all had dissolved, the organic layer was separated, and the aqueous layer was extracted with hexane (20 mL x 2). The extracts were washed successively with H₂O and saturated aqueous NaCl, and dried over K₂CO₃. The solvent was removed under reduced pressure to give (*S*)-2 (quantitative); colorless oil: bp 240–250 °C / 1 mmHg (bulb-to-bulb distillation); $[\alpha]_{\text{D}}^{27} -88.8$ (*c* 1.03, CHCl₃); IR (CHCl₃) 2940, 2850, 2800, 1450 cm⁻¹; ¹H NMR δ 1.57–1.96 (8H, m), 2.15–2.24 (2H, m), 2.36–2.49 (2H, m), 2.58–2.68 (2H, m), 2.96–3.09 (2H, m), 3.08–3.15 (2H, m), 3.34 (2H, dd, *J* = 6.5, 9.3 Hz), 3.50 (2H, dd, *J* = 4.6, 9.3 Hz), 4.51 (4H, s), 7.22–7.36 (10H, m); ¹³C NMR δ 22.9, 28.4, 54.7, 54.8, 63.9, 73.3, 73.6, 127.4, 127.6, 128.3, 138.5; MS *m/z* 407 (M⁺¹), 408 (M⁺); 409 (M⁺¹); HRMS calcd for C₂₆H₃₆N₂O₂ 408.2746 (M⁺), found 408.2760.

General procedure for enantioselective radical-mediated reduction of **1** in the presence of MgI₂ and **2**

To a solution of MgI₂ (0.2 mmol) in Et₂O (0.12–0.16 M solution) was added a solution of the chiral diamine [(*S*)-**2**] (82 mg, 0.2 mmol) in CH₂Cl₂ (2 mL). The mixture was stirred for 25 min at room temperature. The resulting mixture was cooled to –78 °C. A solution of **1** (0.2 mmol) in CH₂Cl₂ (2 mL) was added, and stirring was continued for 30 min. The resulting mixture was diluted with CH₂Cl₂ to the concentrations listed in Table 1, and stirring was continued for 15 min. Bu₃SnH or (Me₃Si)₃SiH (0.2 mmol) was added at –78 °C to the clear solution obtained above, and the whole was stirred for 40 min at the same temperature. After addition of aqueous NH₄Cl, the mixture was extracted with benzene (20 mL x 2). The extracts were washed with saturated aqueous NaCl, and dried over MgSO₄. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) to give optically active **3**.

For run 4, the reaction was carried out by use of a solution of MgI₂ (0.4 mmol) in Et₂O (1 mL), [(*S*)-**2**] (164 mg, 0.4 mmol) in CH₂Cl₂ (3.5 mL), **1a** (127.2 mg, 0.4 mmol) in CH₂Cl₂ (1.5 mL) and Bu₃SnH (0.11 mL, 0.4 mmol).

For run 5, the reaction was carried out at –50 °C.

For runs 6, 10 and 13, the reactions were carried out at –78 °C for 5 h by use of Ph₃SnH (0.56 mL, 0.22 mmol).

For run 15, the reaction was carried out by use of Bu₃SnH (0.11 mL, 0.4 mmol).

(*R*)-3-(Methoxymethyl)-3,4-dihydrocoumarin (**3a**): 88%; colorless oil: bp 120 °C / 2 mmHg (bulb-to-bulb distillation); 62% ee; HPLC [chiralcel OB; hexane : 2-propanol = 50 : 1; flow rate 0.5 mL / min; R_t: minor enantiomer (*S*): 34.1 min, major enantiomer (*R*): 37.5 min]; $[\alpha]_{\text{D}}^{25} -12$ (*c* 1.01, benzene); IR (CHCl₃) 3000, 2925, 1760, 1600 cm⁻¹; ¹H-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 $\text{C}_{11}\text{H}_{12}\text{O}_3$ (M^+) 192.0785, found 192.0788.

(*R*)-3-(Ethoxymethyl)-3,4-dihydrocoumarin (**3b**): 84%; colorless oil; bp 130–140 °C /1.5 mmHg (bulb-to-bulb distillation); 65% ee; HPLC [chiralcel OB; hexane : 2-propanol = 50 : 1; flow rate 0.5 mL / min; R_t: minor enantiomer (*S*): 22.9 min, major enantiomer (*R*): 27.1 min]; $[\alpha]_{\text{D}}^{25} -11$ (c 1.95, benzene); IR (neat) 2960, 2850, 1760, 1605 cm^{-1} ; ^1H NMR δ 1.22 (3H, t, $J = 6.9$ Hz), 2.88–3.20 (3H, m), 3.52–3.63 (2H, m), 3.66–3.76 (1H, m), 3.88–3.93 (1H, m), 7.02–7.12 (2H, m), 7.20–7.28 (2H, m); ^{13}C NMR δ 15.0, 27.0, 39.7, 66.8, 68.5, 116.6, 122.6, 124.4, 128.1, 128.2, 151.4, 169.0; MS m/z 206 (M^+); HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_3$ 206.0942 (M^+), found 206.0944.

(*R*)-3-(Benzyloxymethyl)-3,4-dihydrocoumarin (**3c**): 89%; 58% ee; HPLC [chiralcel OD; hexane : 2-propanol = 9 : 1; flow rate 1 mL / min; R_t: major enantiomer (*R*): 13.9 min, minor enantiomer (*S*): 18.2 min]. colorless semisolid; mp 47–55 °C (hexane), 76% ee, $[\alpha]_{\text{D}}^{25} -13$ (c 1.45, benzene); IR (KBr) 3061, 3021, 2935, 2921, 2858, 1770, 1613, 1587, 1134, 1108 cm^{-1} ; ^1H NMR δ 2.79–3.21 (3H, m), 3.76 (1H, dd, $J = 6.7, 9.8$ Hz), 3.95 (1H, dd, $J = 3.8, 9.8$ Hz), 4.58 (2H, s), 6.90–7.12 (2H, m), 7.18–7.39 (7H, m); ^{13}C NMR δ 27.1, 39.8, 68.3, 73.5, 116.6, 122.5, 124.4, 127.7, 127.8, 128.2, 128.3, 128.5, 137.8, 151.5, 168.9; MS m/z 268 (M^+); HRMS calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3$ 268.1099 (M^+), found 268.1104.

(*S*)-3-Methyl-3,4-dihydrocoumarin (**3d**): 82%; Colorless semisolid; mp 45–55 °C; 33% ee; HPLC [chiralcel OB; hexane : 2-propanol = 9 : 1; flow rate 1 mL / min; R_t: minor enantiomer (*R*): 10.5 min, major enantiomer (*S*): 14.2 min]; $[\alpha]_{\text{D}}^{28} -3.4$ (c 1.03, benzene); IR (KBr) 3090, 3037, 2987, 2939, 1754, 1614, 1587, 1157 cm^{-1} ; ^1H NMR δ 1.37 (3H, d, $J = 5.9$ Hz), 2.70–3.74 (3H, m), 7.02–7.27 (4H, m); ^{13}C NMR δ 15.4, 31.6, 34.2, 116.6, 122.8, 124.2, 127.9, 128.2, 151.8, 171.5; MS m/z 162 (M^+); HRMS calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2$ 162.0680 (M^+), found 162.0693(M^+).

Conversion of (*R*)-**3a** into (*R*)-3-(hydroxymethyl)-3,4-dihydrocoumarin (**4**)

To a solution of (*R*)-**3a**¹³ (49% ee; 98.1 mg, 0.51 mmol) in CH_2Cl_2 (2 mL) was added a solution of BBr_3 (0.15 mL, 1.59 mmol) in CH_2Cl_2 (1 mL) at -78 °C. The whole was stirred at -78 °C for 1 h, and then warmed to -40 °C over a period of 2 h. After being stirred for 90 min at -25 °C, the reaction was quenched with saturated NaHCO_3 . The resulting mixture was extracted with Et_2O (20 mL x 2). The extracts were washed with saturated aqueous NaCl , and dried over MgSO_4 . The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene- Et_2O) to give (*R*)-**4** (46.1 mg, 51%); colorless semisolid; mp 35–40 °C; 12% ee (partially racemized); HPLC [chiralcel OB; hexane : 2-propanol = 9 : 1; flow rate 1 mL / min; R_t: minor enantiomer (*S*): 15.5 min, major enantiomer (*R*): 18.8 min]; $[\alpha]_{\text{D}}^{28} -2.8$ (c 1.06, THF); IR (KBr) 3490–2965, 2960, 2900, 1760, 1615, 1590 cm^{-1} ; ^1H NMR δ 2.69 (1H, t, $J = 6.5$ Hz, OH), 2.81–3.10 (3H, m), 3.90–4.01 (2H, m), 7.04–7.36 (4H, m); ^{13}C NMR δ 26.3, 41.6, 61.8, 116.7, 122.5, 124.6, 128.2, 128.4, 151.2, 170.9; MS m/z 178 (M^+); HRMS calcd for $\text{C}_{10}\text{H}_{10}\text{O}_3$ 178.0630 (M^+), found 178.0624.

Conversion of 3 b into (R)-3-(hydroxymethyl)-3,4-dihydrocoumarin (4)

To a solution of **3b** (58% ee: 135.5 mg, 0.66 mmol) in CH₂Cl₂ (13 mL) was added a solution of BBr₃ (0.39 mL, 4.13 mmol) in CH₂Cl₂ (13 mL) at –78 °C. The whole was warmed to –25 °C over a period of 90 min. After being stirred for 1 h at –25 °C, the reaction was quenched with saturated NaHCO₃. The resulting mixture was extracted with Et₂O (20 mL x 2). The extracts were washed with saturated aqueous NaCl, and dried over MgSO₄. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene-Et₂O) to give (*R*)-**4** (54.5 mg, 47%); 44% ee (partially racemized); HPLC [chiralcel OB; hexane : 2-propanol = 9 : 1; flow rate 1 mL / min; R_t: minor enantiomer (*S*): 14.7 min, major enantiomer (*R*): 17.6 min]; [α]²⁴_D –6.8 (*c* 0.98, THF). Spectral data were identical with those for the product obtained from **3a**.

Conversion of 3 c into (R)-3-(hydroxymethyl)-3,4-dihydrocoumarin (4)

A solution of **3c** (51% ee, 179 mg, 0.67 mmol) in EtOH (50 mL) was hydrogenated over Pd-black (200 mg) under H₂ (1 atm) at room temperature for 6 h. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene-Et₂O) to give (*R*)-**4** (118.4 mg, 99%); 51% ee; HPLC [chiralcel OB; hexane : 2-propanol = 9 : 1; flow rate 1 mL / min; R_t: minor enantiomer (*S*): 14.9 min, major enantiomer (*R*): 17.8 min]; [α]²⁴_D –7 (*c* 1.10, THF). Spectral data were identical with those for the product obtained from **3a**.

Conversion of (R)-4 into (S)-3 d

To a solution of (*R*)-**4** (51% ee, 155 mg, 0.87 mmol) in CH₂Cl₂ (9 mL) phenyl chlorothionoformate (0.129 mL, 0.96 mmol) and pyridine (0.085 mL, 1.1 mmol) were added at 0 °C. The resulting solution was stirred for 30 min at room temperature. The mixture was diluted with Et₂O, and washed successively with 0.5 N HCl, H₂O and saturated aqueous NaCl, and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) followed by rinsing with petroleum ether to give (*R*)-**5** (185 mg, 68%); colorless solid; mp 116–120 °C; [α]²⁸_D –8.6 (*c* 1.07, benzene); IR (KBr) 3062, 2900, 1763, 1614, 1589 cm^{–1}; ¹H NMR δ 3.10–3.29 (3H, m), 4.83 (1H, dd, *J* = 6.4, 11.4 Hz), 5.03 (1H, dd, *J* = 4.5, 11.4 Hz), 7.06–7.46 (9H, m); ¹³C NMR δ 27.1, 38.6, 71.3, 116.8, 121.7, 121.8, 124.7, 126.7, 128.2, 128.6, 129.6, 151.3, 153.3, 167.6, 194.7; MS *m/z* 314 (M⁺); HRMS calcd for C₁₇H₁₄O₄S 314.0613 (M⁺), found 314.0612.

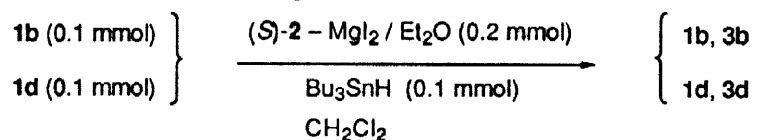
Deoxygenation of (*R*)-**5** (75 mg, 0.24 mmol) was carried out by the same method described in the literature¹⁵ using TMSO-(SiHMeO)_{*n*}-TMS (PMHS) (0.071 mL), BuOH (0.119 mL, 1.3 mmol), AIBN (16.2 mg, 0.096 mmol) and (Bu₃Sn)₂O (0.016 mL, 0.03 mmol). The crude product was purified by preparative thin-layer chromatography (benzene) to give (*S*)-**3d** (15 mg, 39%); [α]²⁸_D –5 (*c* 1.12, benzene). Spectral data were identical with those for the product obtained by the reduction of **1d**.

References and Notes

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