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# Studies on Antidiabetic Agents. VI.[1] Asymmetric Transformation of (±)-5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione(Ciglitazone) with Optically Active 1-Phenylethylamines

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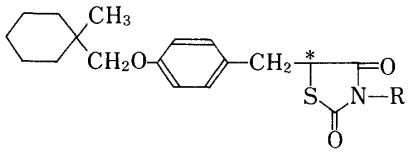
Optical resolution of a new antidiabetic agent, (±)-5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (**1**, ciglitazone) with (−)- and (+)-1-phenylethylamine (PEA) in ethyl acetate resulted in almost complete asymmetric transformation to give the salts, (−)-**1**·(−)-PEA and (+)-**1**·(+)-PEA, respectively, in up to quantitative yields. Optical purities of (−)- and (+)-**1** obtained from the salts were determined by nuclear magnetic resonance and their absolute configurations were confirmed chemically. The optical isomers showed essentially the same antidiabetic and hypolipidemic activities.

**Keywords**——antidiabetic agent; asymmetric transformation; ciglitazone; optical resolution; 2,4-thiazolidinedione

A new antidiabetic agent, (±)-5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (**1**, ciglitazone[2]), which has been selected from a number of 2,4-thiazolidinedione derivatives,[3] has an asymmetric center at the C-5 position of the thiazolidine ring. Since there have been only a few reports on the difference of activities between enantiomers of hypoglycemic[4a,b] or hypolipidemic agents,[5] we tried to resolve **1** to test the activities of the enantiomers.



**1**: R=H (ciglitazone)
**2**: R=$CH_3$

Fig. 1

Optical resolution was carried out using optically active 1-phenylethylamine (PEA) as a diastereomer-salt-forming agent. (±)-Ciglitazone (**1**, Fig. 1) was dissolved in ethyl acetate and 1 eq of (−)-PEA was added. When the solution was allowed to stand at room temperature for 24 h, a single salt, (−)-**1**·(−)-PEA ($[\alpha]_D^{20}$ −104°, mp 120—121 °C), was deposited in 79.4% yield based on (±)-**1**. A further crop obtained in 17.6% yield also showed the same physical properties and the other salt was not isolated. The salt thus obtained showed no change of melting point or optical rotation after recrystallization, and was converted to (−)-**1** ($[\alpha]_D^{20}$ −120°, mp 126—127 °C) by acid treatment. By the same procedure, (+)-**1**·(+)-PEA ($[\alpha]_D^{20}$ +104°, mp 120—121 °C) was obtained in 97.0% yield from (±)-**1** and (+)-PEA and converted to (+)-**1** ($[\alpha]_D^{20}$ +120°, mp 126—127 °C).

The optical purities of the resolved enantiomers were examined by nuclear magnetic

resonance (NMR) spectroscopy using a chiral shift reagent.[6] Thus (−)-, (+)- and (±)-**1** were converted to the N-methyl derivatives (−)-, (+)- and (±)-**2** (Fig. 1), respectively, by treatment with diazomethane, and their NMR spectra were measured in $C_6D_6$ containing tris(3-heptafluoropropylhydroxymethylene-*d*-camphorate)europium(III)[Eu(hfc)$_3$]. Although the N-methyl signal of (±)-**2** was observed as two peaks at 5.7 ppm [due to (−)-**2**] and 6.0 ppm [due to (+)-**2**], those of (−)-**2** and (+)-**2** appeared as single peaks at the expected positions, indicating that (−)- and (+)-**1** were optically pure.

These results clearly demonstrate that (±)-ciglitazone (**1**) was resolved with optically active PEAs through a second-order asymmetric transformation, which seems to be due to the optical lability of the proton at the C-5 position of the thiazolidine ring. Asymmetric transformation is a unique method for obtaining optically active compounds and is known in many optically labile compounds.[7,8] The optical lability of **1** was demonstrated by the mutarotation of (−)-**1**·(−)-PEA and of (−)-**1** in the presence of other bases (Fig. 2). This was also observed in the NMR spectra of (−)-**1**·(−)-PEA in $CDCl_3$ containing $D_2O$. The signal due to the proton at the C-5 position of the thiazolidine ring disappeared in 1 h, indicating rapid racemization through enolization (Fig. 3).

The absolute configurations of the resolved enantiomers were determined chemically by

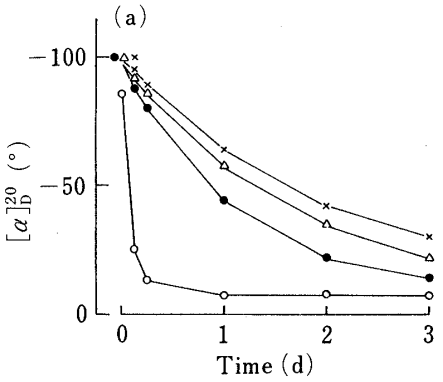



Fig. 2. (a) Mutarotation of (−)-**1**·(−)-PEA ($c$=1.0)

Solvent: ○, EtOH; ●, $CHCl_3$–EtOH (2%, v/v); △, AcOEt; ×, $CHCl_3$.

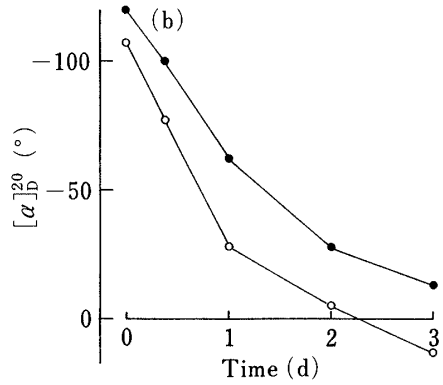
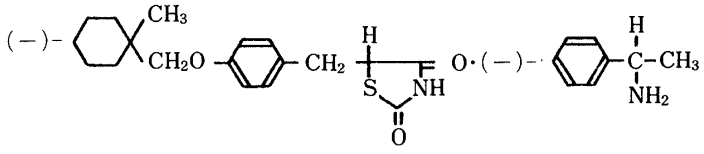



Fig. 2. (b) Mutarotation of (−)-**1** in AcOEt ($c$=1.0)

Solvent: ○, +(+)-PEA (1 eq); ●, + $isoPr_2NH$ (2.4 eq).



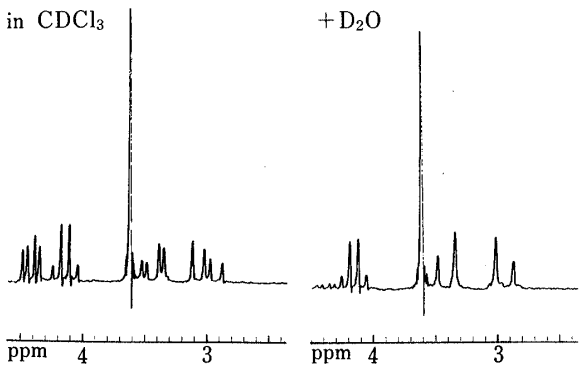




Fig. 3. NMR Spectrum of (−)-**1**·(−)-PEA

the route shown in Chart 1. 2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionic acid [(±)-**3**][9] was resolved successfully using (−)-PEA to give (−)-**3**, which was converted to the ester (−)-**4**. Treatment of (−)-**4** with KSCN provided (+)-**7**, which was then hydrolyzed with ethanolic hydrochloric acid to afford (−)-**1** along with the α-carbamoylthiopropionate (−)-**8**, although considerable racemization during this procedure was noted. The configuration of (−)-**3** was confirmed to be *R* by its transformation to the known (*R*)-(−)-**6**.[4a] Therefore all the absolute configurations are as designated in Chart 1.

The hypoglycemic and hypolipidemic activities of (*S*)-(−)-**1** and (*R*)-(+)-**1** in genetically obese and diabetic mice, yellow KK,[10] are shown in Table I.[11] All the resolved isomers and the racemate exhibited essentially the same activities. This result may suggest that each isomer easily racemizes in the animal body or, more plausibly that there is only one active form which is accumulated by asymmetric transformation at the drug-acting site that is itself asymmetric.

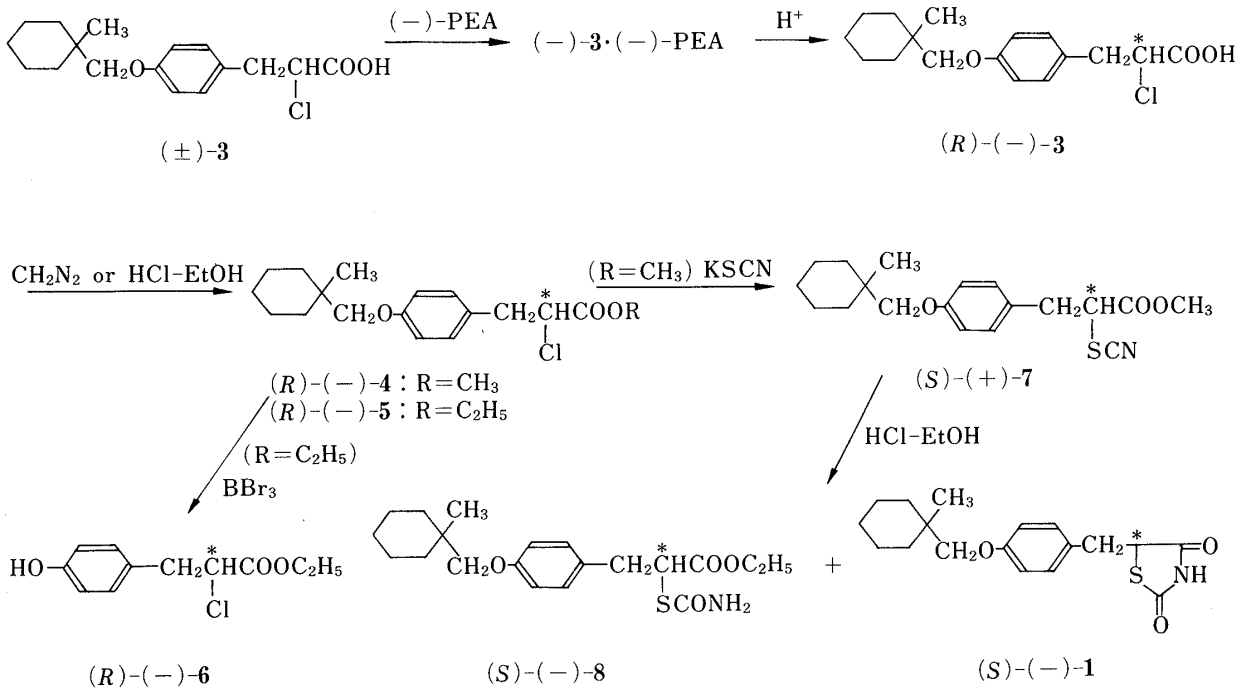



Chart 1

TABLE I. Hypoglycemic and Hypolipidemic Activities of Ciglitazone and the Resolved Isomers

| Compound | Dose (% in diet) | Blood glucose[a] | Plasma triglyceride[a] |
|---|---|---|---|
| (±)-**1** | 0.02 | 27[b] | 15 |
| | 0.05 | 53[c] | 40[b] |
| (−)-**1** | 0.02 | 39[d] | 35 |
| | 0.05 | 58[c] | 48[e] |
| (+)-**1** | 0.02 | 25[b] | 32 |
| | 0.05 | 55[c] | 33 |

*a*) Maximum reductions in blood glucose and plasma triglyceride levels at the dosage of 0.05 or 0.02% (w/w) in the diet were calculated as percentages of the control value.
*b*) $p<0.05$, *c*) $p<0.001$, *d*) $p<0.01$, *e*) $p<0.02$ *versus* control. Mean ±SD ($n=5$).

## Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrometer. NMR spectra were recorded on a Varian EM-390 or a Varian XL-100 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, and the following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are given in Hz. Optical rotations were measured on a Perkin-Elmer 141 or a Jasco DIP-181 polarimeter.

**Asymmetric Transformation of (±)-5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione 1-Phenylethylamine Salt**——a) (−)-(5*S*)-5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (−)-(1*S*)-1-Phenylethylamine Salt[(−)-**1**·(−)-PEA]: (±)-**1** (10.0 g) was dissolved in AcOEt (100 ml) and (−)-PEA (3.6 g) was added thereto. The solution was allowed to stand at room temperature for 24 h to give (−)-**1**·(−)-PEA as crystals (10.8 g, 79.4%), mp 120—121 °C, $[\alpha]_D^{20}$ −104° (*c* = 0.82, $CHCl_3$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200—2500, 1680. NMR $\delta$: 1.04 (3H, s), 1.44 (2H, d, *J* = 7), 1.47 (10H, br s), 3.0 (1H, dd, *J* = 14 and 9), 3.44 (1H, dd, *J* = 14 and 4), 3.63 (2H, s), 4.15 (1H, q, *J* = 7), 4.42 (1H, dd, *J* = 9 and 4), 5.05 (3H, s), 6.85 (2H, d, *J* = 9), 7.15 (2H, d, *J* = 9), 7.35 (5H, s). *Anal.* Calcd for $C_{26}H_{34}N_2O_3S$: C, 68.69; H, 7.53; N, 6.16. Found: C, 68.70; H, 7.62; N, 6.07. The filtrate was concentrated *in vacuo* and the residue was dissolved in AcOEt (40 ml). The solution was allowed to stand at room temperature for 24 h to give the second crop of (−)-**1**·(−)-PEA (1.8 g, 13.2%), mp 120—121 °C, $[\alpha]_D^{20}$ −104° (*c* = 0.85, $CHCl_3$). The filtrate was concentrated *in vacuo* and the residue was dissolved in AcOEt (10 ml). The solution was allowed to stand at room temperature for 24 h to give the third crop of (−)-**1**·(−)-PEA (0.6 g, 4.4%), mp 120—121 °C, $[\alpha]_D^{20}$ −104° (*c* = 0.85, $CHCl_3$).

b) (+)-(5*R*)-5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (+)-(1*R*)-1-Phenylethylamine Salt [(+)-**1**·(+)-PEA]: From (±)-**1** (10.0 g) and (+)-PEA (3.6 g), (+)-**1**·(+)-PEA was similarly obtained: the first crop, 10.8 g {79.4%, mp 120—121 °C, $[\alpha]_D^{20}$ +104° (*c* = 0.95, $CHCl_3$)}. The IR and NMR spectra of this sample were identical with those of (−)-**1**·(−)-PEA. *Anal.* Calcd for $C_{26}H_{34}N_2O_3S$: C, 68.69; H, 7.53; N, 6.16. Found: C, 68.58; H, 7.58; N, 6.20; the second crop, 1.8 g {13.2%, mp 120—121 °C, $[\alpha]_D^{20}$ +104° (*c* = 0.90, $CHCl_3$)}; the third crop, 0.6 g {4.4%, mp 120—121 °C, $[\alpha]_D^{20}$ +104° (*c* = 0.80, $CHCl_3$)}.

**(−)-(5*S*)-5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione[(−)-1]**——1 N HCl (10 ml) was added to a stirred suspension of (+)-**1**·(−)-PEA (4.6 g) in $Et_2O$ (50 ml) and the mixture was stirred at room temperature for 10 min. The organic layer was separated and the usual work-up gave (−)-**1** as crystals (3.2 g, 96.1%). Recrystallization from 85% EtOH gave colorless plates, mp 126—127 °C, $[\alpha]_D^{20}$ −120° (*c* = 1.0, $CHCl_3$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3160, 3050, 1750, 1685. NMR ($C_6D_6$) $\delta$: 1.0 (3H, s), 1.38 (10H, br s), 2.65 (1H, dd, *J* = 14 and 9), 3.04 (1H, dd, *J* = 14 and 4), 3.45 (2H, s), 3.80 (1H, dd, *J* = 9 and 4), 6.75 (2H, d, *J* = 9), 6.90 (2H, d, *J* = 9). *Anal.* Calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.89; H, 6.88; N, 4.11.

**(+)-(5*R*)-5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione[(+)-1]**——Treatment of (+)-**1**·(+)-PEA (4.6 g) with 1 N HCl (10 ml) in a manner similar to that used for the preparation of (−)-**1** gave (+)-**1** as crystals (3.2 g, 96.1%). Recrystallization from 85% EtOH gave colorless plates, mp 126—127 °C, $[\alpha]_D^{20}$ +120° (*c* = 1.13, $CHCl_3$). The IR and NMR spectra of this sample were identical with those of (−)-**1**. *Anal.* Calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.95; H, 6.84; N, 4.05.

**(±)-3-Methyl-5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione[(±)-2]**——A solution of $CH_2N_2$ in $Et_2O$ (*ca.* 3%, w/w, 10 ml) was added dropwise to a stirred and ice-cooled solution of (±)-**1** (1.0 g) in $Et_2O$ (40 ml) and the whole was stirred at room temperature for 30 min. The usual work-up of the mixture gave (±)-**2** as crystals (0.9 g, 86.5%). Recrystallization from cyclohexane gave colorless prisms, mp 89—90 °C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1750, 1670. NMR ($C_6D_6$) $\delta$: 1.0 (3H, s), 1.38 (10H, br s), 2.60 (3H, s), 2.66 (1H, dd, *J* = 14 and 9), 3.10 (1H, dd, *J* = 14 and 4), 3.44 (2H, s), 3.78 (1H, dd, *J* = 9 and 4), 6.75 (2H, d, *J* = 9), 6.92 (2H, d, *J* = 9). *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.48; H, 7.11; N, 4.01.

**(−)-3-Methyl-(5*S*)-5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione[(−)-2]**——Treatment of (−)-**1** (90 mg) with $CH_2N_2$ in a manner similar to that used for the preparation of (±)-**2** gave (−)-**2** as crystals (70 mg, 74.6%). Recrystallization from cyclohexane gave colorless prisms, mp 111—112 °C, $[\alpha]_D^{20}$ −128° (*c* = 0.55, $CHCl_3$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1750, 1670. The NMR spectrum of this sample was identical with that of (±)-**2**. *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.61; H, 7.19; N, 4.12.

**(+)-3-Methyl-(5*R*)-5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione[(+)-2]**——Treatment of (+)-**1** (90 mg) with $CH_2N_2$ in a manner similar to that used for the preparation of (±)-**2** gave (+)-**2** as crystals (70 mg, 74.6%). Recrystallization from cyclohexane gave colorless prisms, mp 111—112 °C, $[\alpha]_D^{20}$ +128° (*c* = 0.57, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.79; H, 7.10; N, 4.09.

**Resolution of (±)-2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionic Acid[(±)-3]**——(±)-**3**[9] (63 g) was dissolved in EtOH (400 ml) and (−)-PEA (24.8 g) was added thereto. The solution was allowed to stand at room temperature for 4 h. The resulting precipitate was collected by filtration, and recrystallized five times from EtOH to afford (−)-**3**·(−)-PEA (10.2 g, 11.6%), mp 162—163 °C, $[\alpha]_D^{20}$ −0.8° (*c* = 0.45, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3100—2100, 1605, 1590. NMR $\delta$: 1.0 (3H, s), 1.43 (10H, br s), 1.46 (3H, d, *J* = 7), 2.71 (1H, dd, *J* = 14 and 9), 3.06

(1H, dd, $J=14$ and 4), 3.56 (2H, s), 3.9—4.3 (2H, m), 6.75 (2H, d, $J=9$), 7.0 (2H, d, $J=9$), 7.35 (5H, br), 7.80 (3H, br). *Anal.* Calcd for $C_{25}H_{34}ClNO_3$: C, 69.51; H, 7.93; N, 3.24. Found: C, 69.27; H, 7.90; N, 3.10. The (−)-**3**·(−)-PEA salt (9.7 g) in AcOEt (100 ml) was treated with 1 N HCl (34 ml) at room temperature for 15 min, and the organic layer was separated, washed with $H_2O$, dried ($MgSO_4$) and concentrated to give (−)-**3** as crystals (6.3 g, 90.0%). Recrystallization from hexane gave colorless prisms, mp 94—95 °C, $[\alpha]_D^{20}$ −7.0° ($c=1.16$, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1710. NMR $\delta$: 1.0 (3H, s), 1.43 (10H, br s), 3.05 (1H, dd, $J=14$ and 7), 3.31 (1H, dd, $J=14$ and 7), 3.60 (2H, s), 4.39 (1H, t, $J=7$), 6.81 (2H, d, $J=9$), 7.10 (2H, d, $J=9$), 10.56 (1H, br s). *Anal.* Calcd for $C_{17}H_{23}ClO_3$: C, 65.69; H, 7.46. Found: C, 65.60; H, 7.16.

**Methyl (−)-(2*R*)-2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate[(−)-4]**——A solution of (−)-**3** (6.0 g) in $Et_2O$ (100 ml) was treated with a solution of $CH_2N_2$ in $Et_2O$ (*ca.* 5%, w/w, 50 ml) at room temperature for 15 min and the usual work-up gave the title compound as a crude oil, which was chromatographed on $SiO_2$ (100 g) with $Et_2O$–hexane (1 : 10, v/v) to give (−)-**4** as a pure oil (5.9 g, 94.1%), $[\alpha]_D^{20}$ −14.8° ($c=2.46$, MeOH). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1745. NMR ($C_6D_6$) $\delta$: 1.02 (3H, s), 1.40 (10H, br s), 2.95 (1H, dd, $J=14$ and 7), 3.24 (3H, s), 3.26 (1H, dd, $J=14$ and 7), 3.45 (2H, s), 4.51 (1H, t, $J=7$), 6.66 (2H, d, $J=9$), 6.95 (2H, d, $J=9$). *Anal.* Calcd for $C_{18}H_{25}ClO_3$: C, 66.55; H, 7.76. Found: C, 66.36; H, 7.85. The NMR spectrum of this compound (30 mg) in $C_6D_6$ (0.4 ml) containing Eu(hfc)$_3$ (100 mg) showed two O-methyl signals at 6.2 ppm [due to (−)-**4**] and at 6.3 ppm [due to (+)-**4**] in a ratio of 30 : 1 (optical purity: *ca.* 93.5%).

**Ethyl (−)-(2*R*)-2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate[(−)-5]**——A mixture of (−)-**3** (490 mg) and 17% HCl–EtOH (w/w), 8 ml) was stirred at room temperature for 2 h, poured into $H_2O$ and extracted with $Et_2O$. The usual work-up of the $Et_2O$ extract gave an oily residue which was chromatographed on $SiO_2$ (20 g) with $Et_2O$–hexane (1 : 50, v/v) to give (−)-**5** as an oil (485 mg, 90.8%), $[\alpha]_D^{20}$ −16.1° ($c=1.0$, EtOH). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1735. NMR $\delta$: 1.01 (3H, s), 1.21 (3H, t, $J=7$), 1.43 (10H, br s), 3.06 (1H, dd, $J=14$ and 7), 3.30 (1H, dd, $J=14$ and 7), 3.59 (2H, s), 4.16 (2H, q, $J=7$), 4.36 (1H, t, $J=7$), 6.82 (2H, d, $J=9$), 7.10 (2H, d, $J=9$). *Anal.* Calcd for $C_{19}H_{27}ClO_3$: C, 67.34; H, 8.03. Found: C, 67.51; H, 7.93.

**Ethyl (−)-(2*R*)-2-Chloro-3-(4-hydroxyphenyl)propionate[(−)-6]**——$BBr_3$ (0.2 ml) was added dropwise to a stirred and ice-cooled solution of (−)-**5** (339 mg) in $CH_2Cl_2$ (10 ml). The mixture was stirred at room temperature for 15 min, poured into ice-$H_2O$ and extracted with $CH_2Cl_2$. The usual work-up of the $CH_2Cl_2$ extract gave an oil, which was chromatoraphed on $SiO_2$ (20 g) with $Et_2O$–hexane (1 : 3, v/v) to give (−)-**6** as an oil (180 mg, 78.6%), $[\alpha]_D^{20}$ −27.6° ($c=0.6$, EtOH) {lit. (*S*)-(+)-**6**: $[\alpha]_D^{22}$ +30.4° ($c=2.0$, EtOH)[4a]}. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3480, 1730. NMR $\delta$: 1.21 (3H, t, $J=7$), 3.06 (1H, dd, $J=14$ and 7), 3.27 (1H, dd, $J=14$ and 7), 4.17 (2H, q, $J=7$), 4.37 (1H, t, $J=7$), 5.53 (1H, br s), 6.74 (2H, d, $J=9$), 7.06 (2H, d, $J=9$). *Anal.* Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73. Found: C, 57.60; H, 5.55.

**Methyl (+)-3-[4-(1-Methylcyclohexylmethoxy)phenyl]-(2*S*)-2-thiocyanatopropionate[(+)-7]**——A mixture of (−)-**4** (5.4 g), KSCN (2.4 g) and DMSO (60 ml) was stirred at 90 °C for 2 h, poured into $H_2O$ and extracted with $Et_2O$. The usual work-up gave an oil, which was chromatographed on $SiO_2$ (100 g) with $Et_2O$–hexane (1 : 5, v/v). The first part of the eluate gave (−)-**4** (2.6 g, 48.1%), $[\alpha]_D^{20}$ −8.2° ($c=2.77$, MeOH). The following part of the eluate gave (+)-**7** as crystals (2.4 g, 41.4%). Recrystallization from hexane gave colorless needles, mp 59—60 °C, $[\alpha]_D^{20}$ +10.8° ($c=2.06$, $C_6H_6$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2140, 1730. NMR ($C_6D_6$) $\delta$: 1.04 (3H, s), 1.39 (10H, br s), 2.90 (1H, dd, $J=14$ and 7), 3.01 (1H, dd, $J=14$ and 7), 3.22 (3H, s), 3.45 (2H, s), 3.47 (1H, t, $J=7$), 6.65 (2H, d, $J=9$), 6.87 (2H, d, $J=9$). *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.95; H, 7.10; N, 3.98. The NMR spectrum of this compound (30 mg) in $C_6D_6$ (0.5 ml) containing Eu(hfc)$_3$ (100 mg) showed two O-methyl signals at 5.65 ppm [due to (−)-**7**] and at 5.80 ppm [due to (+)-**7**] in a ratio of 1 : 3 (optical purity: 50%).

**Hydrolysis of Methyl (+)-3-[4-(1-Methylcyclohexylmethoxy)phenyl]-(2*S*)-2-thiocyanatopropionate[(+)-7]**——A mixture of (+)-**7** (1.5 g), 2 N HCl (50 ml) and EtOH (50 ml) was stirred under reflux for 4 h, diluted with $H_2O$ and extracted with $CHCl_3$. The usual work-up gave an oily residue which was chromatographed on $SiO_2$ (50 g) with $Et_2O$–hexane (1 : 3, v/v). The first part of the eluate gave (−)-**1** as crystals (0.125 mg, 8.7%). Recrystallization from $Et_2O$–hexane gave colorless plates, mp 126—127 °C, $[\alpha]_D^{20}$ −27.5° ($c=1.17$, $CHCl_3$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3160, 3050, 1750, 1685. The NMR spectrum of this sample was identical with that of (±)-**1**.[9] *Anal.* Calcd for $C_{18}H_{23}NO_3S$: C, 64.83; H, 6.95; H, 4.20. Found: C, 64.80; H, 6.91; N, 4.09. The following part of the eluate gave (−)-**8** as an oil (0.67 g, 41.1%), $[\alpha]_D^{20}$ −31.3° ($c=3.64$, $C_6H_6$). IR $\nu_{max}^{neat}$ $cm^{-1}$: 3420, 3320, 3180, 1720, 1680. NMR ($C_6D_6$) $\delta$: 0.87 (3H, t, $J=7$), 1.0 (3H, s), 1.36 (10H, br s), 2.8—3.5 (2H, m), 3.47 (2H, s), 3.88 (2H, q, $J=7$), 4.56 (1H, t, $J=7$), 5.03 (2H, br), 6.70 (2H, d, $J=9$), 7.06 (2H, d, $J=9$).

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## References and Notes

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