Total Synthesis of (*S*)-(+)-Curcudiol, and (*S*)-(+)- and (*R*)-(−)-Curcuphenol[1)]

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A highly enantioselective synthesis of the versatile chiral synthons possessing one stereogenic center, (*S*)- and (*R*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (3) was achieved based on the enzymatic reaction of (±)-3 with commercially available lipases MY-30 or OF-360 from *Candida rugosa*. Application of (*S*)-3 and (*R*)-3 to the total syntheses of (*S*)-curcuphenol (1), (*S*)-curcudiol (2), and (*R*)-curcuphenol (1), respectively, is described.

Key words bisabolane sesquiterpene; enantioselective hydrolysis; lipase; total synthesis

The phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources.[2)] Among them, (S)-(+)-curcuphenol (**1**), isolated from the marine sponge *Epipolasis* sp. strongly inhibits the activity of gastric H, K-ATPase,[3)] while (*R*)-(−)-curcuphenol (**1**), isolated from the Caribbean gorgonians *Pseudopterogorgia rigida* and *Lasianthaea podocephala*, exhibits antibacterial activities against *Staphylcoccus aureus* and *Vibrio anguillarum*.[4)] Accordingly, the establishment of an efficient and general synthetic route to both enantiomers of these sesquiterpenoids is of significance. Although racemic syntheses of bisabolane sesquiterpenes have been developed,[5)] useful asymmetric synthesis bearing a benzylic asymmetric center have not been reported except for a few examples.[6)] We now report that (*S*)-**1**, (*R*)-**1**, and (*S*)-curcudiol (**2**) have been synthesized based on enzymatic resolution using immobilized lipase in organic solvent.

The most intriguing point of the present synthesis is the preparation of the optically active primary alcohols possessing one stereogenic center of (*S*)- and (*R*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (**3**). This was successfully achieved by carrying out enantioselective hydrolysis of the reported (±)-acetate **4**[7)] using immobilized lipase. The desired racemic (±)-**3** had previously been obtained by us in the reaction of methyl (4,5)-epoxy-(2*E*)-pentenoate and *m*-methoxytoluene in the presence of $BF_3 \cdot Et_2O$.[7)]

Initially, (±)-**4** was subjected to screening experiments using several types of commercially available lipases. Among them, the two lipases MY-30 and OF-360 from *Candida rugosa* were found to be effective. When (±)-**4** was subjected to enantioselective hydrolysis using MY-30 in water-saturated isopropyl ether, the alcohol (*S*)-**3** (27%, 80% ee) and unchanged (*R*)-**4** (69%, 36% ee) were obtained. On the other hand, asymmetric hydrolysis of (±)-**4** using OF-360 gave (*S*)-**3** (60%, 51% ee) and (*R*)-**4** (38%, 83% ee). The desired stereochemistry of **3** was found to be governed by the selection of lipase. Then immobilized lipases MY-30 and OF-360 were obtained by illumination of a mixture consisting of the photo-crosslinkable resin prepolymer ENTP-4000,[8)] a photosensitizer such as benzoin ethyl ether and the crude lipases MY-30 and OF-360, respectively. Using the immobilized lipases afforded much better results, as shown in Table 1 [entry 2, (*S*)-**3**, 85% ee; entry 4, (*R*)-**4**, 90% ee]. The alcohol (*S*)-**3** with 80% enantiomeric excess was subjected to enantioselective acetylation using OF-360 in the presence of isopropenyl acetate in isopropyl ether to afford (*S*)-**4** [74%, 90% ee $[\alpha]_D$ −7.2° (*c*=0.46, MeOH)] and (*S*)-**3** (16%, 30% ee).

Treatment of (*S*)-**4** and (*R*)-**4** (entry 4, 90% ee) with MeONa in MeOH produced (*S*)-**3** [90% ee, $[\alpha]_D$ −15.1° (*c*=0.67, MeOH)] and (*R*)-**3** (90% ee), respectively. The enantiomeric purity of the obtained chiral compounds was determined by HPLC on a Chiralcel OD (250×4.6 mm) column. To confirm the absolute configuration of the present

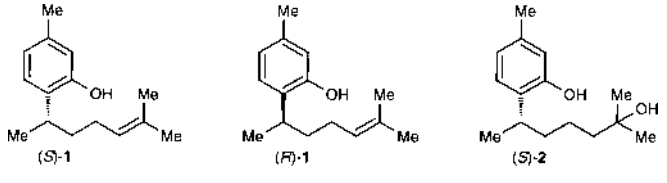


Chart 1

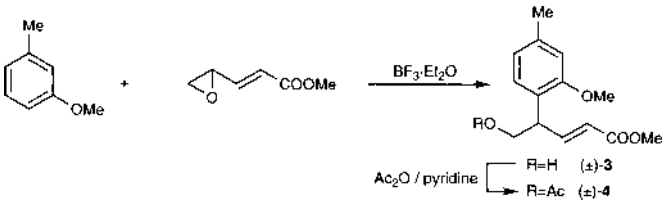
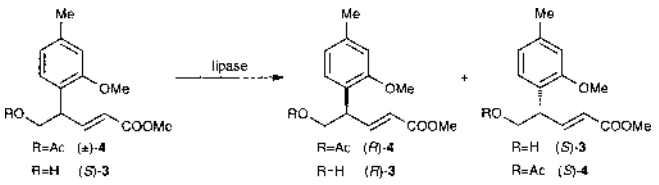


Chart 2

Table 1



Entry	Substrate (g)	Lipase	Products (%, % ee)	
1	(±)-**4** (1)	MY-30 (*Candida rugosa*)	(*R*)-**4** 69 (36)	(*S*)-**3** 27 (80)
2	(±)-**4** (1)	Immobilized lipase (MY-30)	(*R*)-**4** 77 (24)	(*S*)-**3** 22 (85)
3	(±)-**4** (1)	OF-360 (*Candida rugosa*)	(*R*)-**4** 38 (83)	(*S*)-**3** 60 (51)
4	(±)-**4** (1)	Immobilized lipase (OF-360)	(*R*)-**4** 40 (90)	(*S*)-**3** 52 (58)
5[a)]	(*S*)-**3** (0.4)	OF-360	(*S*)-**4** 74 (90)	(*S*)-**3** 16 (30)

a) Optically active (*S*)-**3** (80% ee) was employed.

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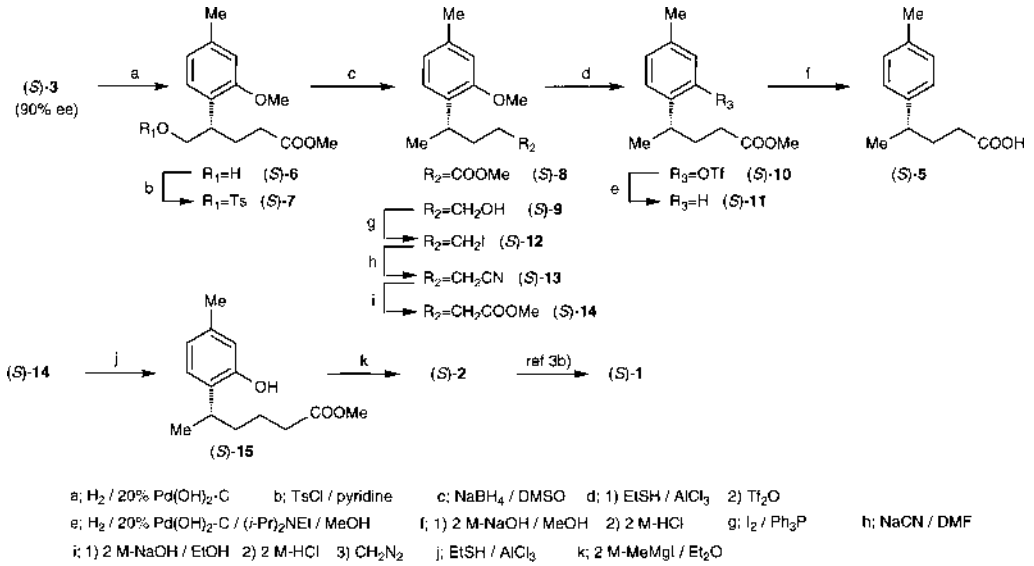

Chart 3

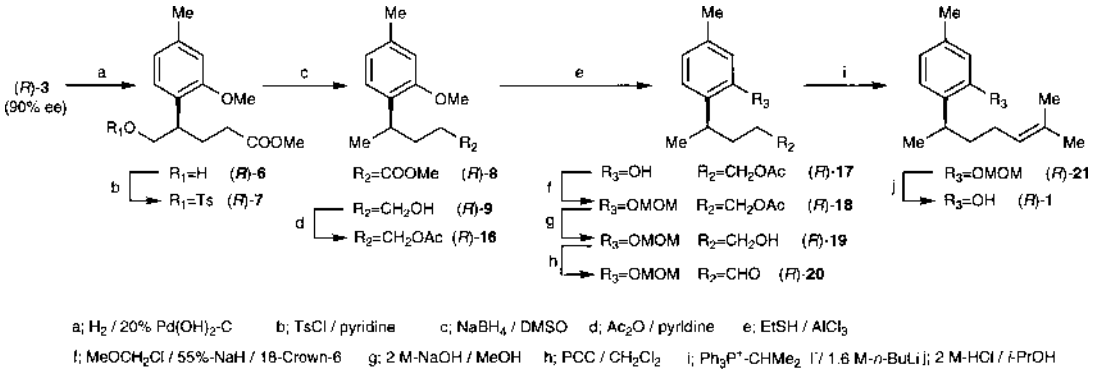

Chart 4

(−)-**3**, (−)-**3** was successfully converted to the reported acid (*S*)-(+)-4-(*p*-tolyl)pentanoic acid **5**.[9] Catalytic hydrogenation of (*S*)-**3** gave (*S*)-**6**, followed by treatment with tosyl chloride (TsCl) to afford the tosylate (*S*)-**7** [$[\alpha]_D$ +16.9° (*c*=0.99, MeOH)] in 83% overall yield from (*S*)-**3**. $NaBH_4$ reduction of (*S*)-**7** provided the 4-arylpentanoate (*S*)-**8** [42% yield, $[\alpha]_D$ +7.1° (*c*=1.32, MeOH)] and the corresponding alcohol (*S*)-**9** [40% yield, $[\alpha]_D$ +4.5° (*c*=1.68, MeOH)]. Demethylation of (*S*)-**8** with a combination of $AlCl_3$ and ethanethiol (EtSH),[9] followed by the treatment with trifluoromethanesulfonic anhydride (Tf_2O) gave the triflate (*S*)-**10**, which was subjected to catalytic hydrogenolysis to afford the (+)-(*p*-tolyl)pentanoate (*S*)-**11** [$[\alpha]_D$ +29.1° (*c*=0.89, MeOH)] in 48% overall yield from (*S*)-**8**. An alkaline hydrolysis of (*S*)-**11** provided a carboxylic acid (*S*)-**5** [92% yield, $[\alpha]_D$ +25.1° (*c*=0.55, MeOH) corresponding to 90% ee], of which the spectral data ($[\alpha]_D$) were identical to those [$[\alpha]_D$ +29.1° (*c*=0.99, MeOH)] of the reported (*S*)-**5**.[10] Thus the absolute configuration of the present (−)-**3** was determined to be *S*. Then total synthses of (*S*)-curcudiol (**2**), (*R*)- and (*S*)-curcuphenol (**1**) formally derived from (*S*)-**2**,[3b] were achieved from (*S*)-**3** (90% ee) and (*R*)-**3** (90% ee), respectively. Conversion of (*S*)-**9** into the one-carbon homologation product (*S*)-**13** was achieved by the standard procedure. The alcohol (*S*)-**9** was treated with iodine in the presence of triphenylphosphine (Ph_3P) to give an iodide (*S*)-**12** [$[\alpha]_D$ +5.8° (*c*=0.78, MeOH)] in 48% yield, which was reacted with NaCN in dimethylformamide (DMF) to provide a cyanide (*S*)-**13** [$[\alpha]_D$ −0.9° (*c*=1.22, MeOH)] in 99% yield. Alkaline hydrolysis of (*S*)-**13** followed by successive esterification gave the methyl ester (*S*)-**14** [$[\alpha]_D$ +6.2° (*c*=1.15, MeOH)] in 54% overall yield from (*S*)-**13**. Demethylation of (*S*)-**14** with a combination of $AlCl_3$ and EtSH provided the phenol (*S*)-**15**, which was treated with Grignard reagent to afford (*S*)-curcudiol (**2**) [$[\alpha]_D$ +9.9° (*c*=4.96, $CHCl_3$) corresponding to 90% ee] in 91% overall yield from (*S*)-**14**. The spectral data ($[\alpha]_D$, ^{1}H- and ^{13}C-NMR) of the synthesized (*S*)-**2** were identical to those [$[\alpha]_D$ +9.2° (*c*=10.8, $CHCl_3$)][3b] of natural product (*S*)-**2**, which is reported to convert into (*S*)-curcuphenol (**1**) in the literature.[3]

The synthesis of (*R*)-curcuphenol (**1**) from (*R*)-**3** (90% ee) was carried out in basically by the same way as for (*S*)-**3**. Conversion of (*R*)-**3** into the alcohol (*R*)-**9** was achieved by the same route [(*R*)-**7**, 83% overall yield from (*R*)-**3**, (*R*)-**8** (47% yield), and (*R*)-**9** (26% yield)] as in the previous case. Acetylation of (*R*)-**9** gave the corresponding acetate (*R*)-**16** [90% yield, $[\alpha]_D$ −2.6° (*c*=2.31, $CHCl_3$)], which was subjected to demethylation to afford the phenol (*R*)-**17**. The

phenol (*R*)-**17** was treated with methoxymethyl chloride (MOMCl) to give the MOM ether (*R*)-**18** [$[\alpha]_D$ −3.1° (*c*=1.88, $CHCl_3$)] in 94% overall yield from (*R*)-**16**. Hydrolysis of (*R*)-**18** gave an alcohol (*R*)-**19** [$[\alpha]_D$ −3.9° (*c*=1.47, $CHCl_3$)] in 98% yield, which was subjected to pyridinium chlorochromate (PCC) oxidation to provide an aldehyde (*R*)-**20**. The Wittig reaction of (*R*)-**20** afforded an olefin (*R*)-**21** [$[\alpha]_D$ −9.8° (*c*=1.01, $CHCl_3$)] in 62% overall yield from (*R*)-**19**. Deprotection of (*R*)-**21** gave (*R*)-curcuphenol (**1**) [62% yield, $[\alpha]_D$ −20.9° (*c*=1.73, $CHCl_3$) corresponding to 90% ee], for which the spectral data [$[\alpha]_D$, ^{1}H-, ^{13}C-NMR, and high-resolution mass spectra (HR-MS)] were identical with those [$[\alpha]_D$ −23.6° ($CHCl_3$)][3c] of natural product (*R*)-**1**.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on JEOL EX-400 (400 MHz) or a JEOL α-500 (500 MHz) spectrometers with tetramethylsilane (TMS) as an internal standard in $CDCl_3$. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), multiplet (m), and broad (br). Carbon substitution degrees were established by distortionless enhancement by polarization transfer (DEPT) pulse sequence. HR-MS were obtained with a JEOL JMS-DX 303 spectrometer. IR spectra were recorded on a Hitachi 260-30 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Immobilization of Lipase on Photo-Crosslinkable Resin Prepolymer (ENTP-4000) Typical immobilization procedures with photocross-linkable resin prepolymer are as follows. One gram of ENTP-4000 is mixed with 10 mg of the photosensitizer benzoin ethyl ether. The mixture is melted completely at 60 °C. The powdered lipase (100 mg) is added to the molten mixture under continuous mixing. The prepolymer–lipase mixture is layered on a sheet of transparent polyester film (thickness, *ca*. 0.5 mm). The layer is covered with transparent thin film and then illuminated with chemical lamps (wavelength range, 300—400 nm) for 3 min. The gel film thus formed is cut into small pieces (0.5×0.5×0.5 mm) and used for the bioconversion reaction.

Enzymatic Resolution of (±)-4 i) Table 1, Entry 1: A suspension of (±)-**4** (0.2 g), lipase MY-30 (0.1 g) in H_2O-saturated isopropyl ether (10 ml) was incubated at 33 °C for 3 d. This scale experiment was carried out five times simultaneously (total amount of (±)-**4** was 1 g). After the reaction mixture was filtered, the precipitate was washed with diisopropyl ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (50 g) to give (*R*)-**4** (0.69 g, 69%, 36% ee) from *n*-hexane : AcOEt=10 : 1 eluate and (*S*)-**3** (0.231 g, 27%, 80% ee) as a homogeneous oil from *n*-hexane : AcOEt=4 : 1 eluate. The NMR data of (*S*)-**3** were identical to those of the reported (±)-**3**.[7]

ii) Table 1, Entry 2: A suspension of (±)-**4** (0.25 g), immobilized lipase MY-30 (0.1 g) in H_2O-saturated isopropyl ether (10 ml) was incubated at 33 °C for 3 d. This scale experiment was carried out four times simultaneously (total amount of (±)-**4** was 1 g). The reaction mixture was worked up in the same way as for i) to give (*R*)-**4** (0.77 g, 77%, 24% ee) and (*S*)-**3** (0.188 g, 22%, 85% ee).

iii) Table 1, Entry 3: A suspension of (±)-**4** (0.2 g), lipase OF-360 (0.1 g) in H_2O-saturated isopropyl ether (10 ml) was incubated at 33 °C for 3 d. This scale experiment was carried out five times simultaneously (total amount of (±)-**4** was 1 g). The reaction mixture was worked up in the same way as for i) to give (*R*)-**4** (0.38 g, 38%, 83% ee) and (*S*)-**3** (0.514 g, 60%, 51% ee).

iv) Table 1, Entry 4: A suspension of (±)-**4** (0.2 g), immobilized lipase OF-360 (0.1 g) in H_2O-saturated isopropyl ether (10 ml) was incubated at 33 °C for 3 d. This scale experiment was carried out five times simultaneously (total amount of (±)-**4** was 1 g). The reaction mixture was worked up in the same way as for i) to give (*R*)-**4** (0.4 g, 40%, 90% ee) and (*S*)-**3** (0.445 g, 52%, 58% ee).

v) Table 1, Entry 5: A suspension of (*S*)-**3** (80% ee, 0.2 g), lipase OF-360 (0.1 g) and isopropenyl acetate (0.2 g) in isopropyl ether (10 ml) was incubated at 33 °C for 3 d. This scale experiment was carried out two times simultaneously (total amount of (*S*)-**3** was 0.4 g). The reaction mixture was worked up in the same way as for i) to give (*S*)-**4** [0.346 g, 74%, $[\alpha]_D^{26}$ −7.2° (*c*=0.46, MeOH) corresponding to 90% ee] and (*S*)-**3** (0.064 g, 16%, 30% ee).

Methyl (4*S*)-(2-Methoxy-4-methylphenyl)-5-hydroxypentanoate (3) To a solution of (*S*)-**4** (90% ee, 0.346 g, 1.18 mmol) in MeOH (10 ml) was added 0.5 M MeONa/MeOH (3 ml) at 0 °C and the whole mixture was stirred at the same temperature for 1 h. After 7% aqueous $NaHCO_3$ and ether were added to the reaction mixture, the organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (15 g, *n*-hexane : AcOEt=4 : 1) to afford (*S*)-**3** (0.293 g, 99%) as a homogeneous oil. (*S*)-**3**: $[\alpha]_D^{24}$ −15.1° (*c*=0.67, MeOH). The NMR data of (*S*)-**3** were identical to those of the reported (±)-**3**.[5c]

Methyl (4*R*)-(2-Methoxy-4-methylphenyl)-5-hydroxypentanoate (3) To a solution of (*R*)-**4** (90% ee, 0.852 g, 2.92 mmol) in MeOH (20 ml) was added 0.5 M MeONa/MeOH (6 ml) at 0 °C and the whole mixture was stirred at the same temperature for 1 h. After 7% aqueous $NaHCO_3$ and ether were added to the reaction mixture, the organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=4 : 1) to afford (*R*)-**3** (0.722 g, 99%) as a homogeneous oil. (*R*)-**3**: $[\alpha]_D^{24}$ +13.6° (*c*=0.65, MeOH). The NMR data of (*R*)-**3** were identical to those of the reported (±)-**3**.[5c]

Methyl (4*S*)-(2-Methoxy-4-methylphenyl)-5-tosyloxypentanoate (7) A solution of (*S*)-**3** (90% ee, 0.558 g, 2.3 mmol) in AcOEt (10 ml) was hydrogenated over 20% Pd–C (50 mg) at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated quantitatively to give (*S*)-**6** as a colorless oil. Crude (*S*)-**6** was dissolved in pyridine (5 ml), then TsCl (0.56 g, 2.95 mmol) was added to the solution, and the whole mixture was allowed to stand for 12 h at room temperature. Ether and 7% aqueous $NaHCO_3$ were added to the reaction mixture, and the organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (15 g, *n*-hexane : AcOEt=7 : 1) to afford (*S*)-**7** [0.75 g, 83% yield from (4*S*)-**3**)] as a homogeneous oil. (*S*)-**7**: $[\alpha]_D^{24}$ +16.9° (*c*=0.99, MeOH). The NMR data of (*S*)-**7** were identical to those of the reported (±)-**7**.[5c]

Methyl (4*S*)-(2-Methoxy-4-methylphenyl)pentanoate (8) and (4*S*)-(2-Methoxy-4-methylphenyl)pentanol (9) A solution of (*S*)-**7** (0.931 g, 2.29 mmol) and $NaBH_4$ (0.43 g, 2.29 mmol) in dimethyl sulfoxide (DMSO) (10 ml) was warmed for 2 h at 80 °C, then allowed to cool. Small amounts of acetone, ether, and 7% aqueous $NaHCO_3$ were added to the reaction mixture and the organic layer was separated. The organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=7 : 1) to afford (*S*)-**8** (0.227 g, 42% yield) as a homogeneous oil from *n*-hexane : AcOEt=20 : 1 eluate and (*S*)-**9** (0.191 g, 40% yield) as a homogeneous oil from *n*-hexane : AcOEt=10 : 1 eluate. (*S*)-**8**: $[\alpha]_D^{26}$ +7.1° (*c*=1.32, MeOH), (*S*)-**9**: $[\alpha]_D^{27}$ +4.5° (*c*=1.68, MeOH). The NMR data of (*S*)-**8** and (*S*)-**9** were identical to those of the reported (±)-**8**[5c] and (±)-**9**,[5c] respectively.

Methyl (4*S*)-(4-Methylphenyl)pentanoate (11) i) To a solution of (*S*)-**8** (0.203 g, 0.86 mmol) in EtSH (1 ml) was added a mixture of $AlCl_3$ (0.57 g, 4.2 mmol) in EtSH (3 ml) at 0 °C, and the whole mixture was stirred for 1 h at the same temperature. After ether and 0.2 M aqueous HCl were added to the reaction mixture, the organic layer was washed with saturated brine ether and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil. ii) To a solution of the above oil and Et_3N (0.26 g, 2.6 mmol) in CH_2Cl_2 (2 ml) was added a solution of Tf_2O (0.37 g, 1.3 mmol) in CH_2Cl_2 (0.5 ml) at 0 °C and the whole mixture was stirred at the same temperature. The reaction mixture was diluted with ice-water and the organic layer was washed with 7% aqueous $NaHCO_3$, and saturated brine. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=20 : 1) to afford (*S*)-**10** (0.226 g). iii) A solution of (*S*)-**10** (0.226 g) and Hünig base [(iso-Pr)$_2$NEt, 0.087 g, 0.7 mmol] in MeOH (10 ml) was hydrogenated over 20% Pd–C (30 mg) at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated to give a residue. After ether and 0.2 M aqueous HCl were added to the residue, the organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=30 : 1) to afford (*S*)-**11** [0.085 g, 48% overall yield from (*S*)-**8**]. (*S*)-**11**: $[\alpha]_D^{22}$ +29.1° (*c*=0.89, MeOH); NMR: δ: 1.25 (3H, d, *J*=7 Hz), 1.81—1.96 (2H, m), 2.14—2.22 (2H, m), 2.31 (3H, s), 2.67 (1H, q, *J*=10 Hz), 3.61 (3H, s), 7.06 (2H, d, *J*=8 Hz), 7.10 (2H, d, *J*=8 Hz). FAB-MS Calcd for $C_{13}H_{18}O_2$ (M^+, *m*/*z*): 206. Found: 206. *Anal.* Found: C, 75.40; H, 8.75. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

(4*S*)-(4-Methylphenyl)pentanoic Acid (5) A solution of (*S*)-**11** (0.064 g, 0.31 mmol) and 2 M aqueous NaOH (1 ml) in MeOH (2 ml) was stirred at 50 °C for 1 h. After the reaction mixture was diluted with H_2O and ether, the water layer was acidified with 2 M aqueous HCl and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave an acid (*S*)-**5** (0.055 g, 92%) as a homogeneous oil. (*S*)-**5**: $[\alpha]_D^{21}$ +25.1° (*c*=0.55, MeOH; corresponding to 90% ee); NMR: δ: 1.25 (3H, d, *J*=7 Hz), 1.81—1.96 (2H, m), 2.17—2.25 (2H, m), 2.30 (3H, s), 2.69 (1H, q, *J*=13 Hz), 7.05 (2H, d, *J*=8 Hz), 7.10 (2H, d, *J*=8 Hz). HR-MS (EI) Calcd for $C_{12}H_{16}O_2$ (M^+, *m*/*z*): 192.1150. Found: 192.1129.

1-Iodo-(4*S*)-(2-methoxy-4-methylphenyl)pentane (12) Triphenyl phosphine (Ph_3P, 0.79 g, 3 mmol), imidazole (0.26 g, 3.7 mmol) and iodine (0.9 g, 3.7 mmol) were added to a solution of (*S*)-**9** (0.312 g, 1.5 mmol) in Et_2O (5 ml) and MeCN (5 ml) at 0 °C and the whole mixture was stirred for 0.5 h at room temperature. The reaction mixture was filtered with the aid of Celite and the filtrate was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=100 : 1) to afford (*S*)-**12** (0.229 g, 48%) as a homogeneous oil. (*S*)-**12**: $[\alpha]_D^{24}$ +5.8° (*c*=0.78, MeOH). The NMR data of (*S*)-**12** were identical to those of the reported (±)-**12**.[5c]

(4*S*)-(2-Methoxy-4-methylphenyl)hexanenitrile (13) A solution of (*S*)-**12** (0.229 g, 0.85 mmol) in DMF (1 ml) was treated with NaCN (0.06 g, 1.3 mmol), and the whole mixture was stirred for 12 h at room temperature. After ether and 7% aqueous $NaHCO_3$ were added to the reaction mixture, the organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of organic solvent gave a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=30 : 1) to afford (*S*)-**13** (0.155 g, 99%) as a homogeneous oil. (*S*)-**13**: $[\alpha]_D^{25}$ −0.9° (*c*=1.22, MeOH). The NMR data of (*S*)-**13** were identical with those of the reported (±)-**13**.[5c]

Methyl (5*S*)-(2-Methoxy-4-methylphenyl)hexanoate (14) A solution of (*S*)-**13** (0.155 g, 0.7 mmol) in EtOH (5 ml) was treated with 2 M aqueous NaOH (1 ml) and the whole mixture was refluxed for 12 h. After cooling, the reaction mixture was acidified with 2 M aqueous HCl, and extracted with ether, then treated with CH_2N_2. The ether layer was dried over $MgSO_4$ and evaporated to give a residue. It was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=30 : 1) to afford (*S*)-**14** (0.096 g, 54% overall yield from (*S*)-**13**) as a homogeneous oil. (*S*)-**14**: $[\alpha]_D^{24}$ +6.2° (*c*=1.15, MeOH). The NMR data of (*S*)-**14** were identical to those of the reported (±)-**14**.[5c]

(*S*)-Curcudiol (2) i) To a solution of (*S*)-**14** (0.096 g, 0.38 mmol) in EtSH (1 ml) was added a mixture of $AlCl_3$ (0.31 g, 2.3 mmol) in EtSH (1 ml) at 0 °C, and the whole mixture was stirred for 1 h at the same temperature. After ether and 0.2 M aqueous HCl were added to the reaction mixture, the organic layer was washed with saturated brine ether and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil. ii) A 2 M MeMgI ether solution (0.6 ml) was added to a solution of the above crude oil in ether (1 ml) and the whole mixture was stirred for 2 d at room temperature. Under ice-cooling, 2 M aqueous HCl was added to the reaction mixture and it was extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=4 : 1) to afford (*S*)-**2** (0.083 g, 91% yield from (*S*)-**14**) as a homogeneous oil. (*S*)-**2**: $[\alpha]_D^{24}$ +9.9° (*c*=4.96, $CHCl_3$). FAB-MS Calcd for $C_{15}H_{24}O_2$ (M^+, *m*/*z*): 236. Found: 236. The spectral data (^{1}H-, ^{13}C-NMR, IR, and FAB-MS) were identical to those of the reported (±)-**2**.[5c]

Methyl (4*R*)-(2-Methoxy-4-methylphenyl)-5-tosyloxypentanoate (7) Compound (*R*)-**3** (90% ee, 1.563 g, 6,2 mmol) was converted into (*R*)-**7** (2.103 g, 83% overall yield from (*R*)-**3**) by the same way as for the preparation of (*S*)-**7** from (*S*)-**3**. (*R*)-**7**: $[\alpha]_D^{26}$ −14.3° (*c*=1.26, MeOH). The NMR data of (*R*)-**7** were identical with those of the reported (±)-**7**.[5c]

Methyl (4*R*)-(2-Methoxy-4-methylphenyl)pentanoate (8) and (4*R*)-(2-Methoxy-4-methylphenyl)pentanol (9) $NaBH_4$ reduction of (*R*)-**7** (2.102 g, 5.2 mmol) in the same way as for the preparation of (*S*)-**8** and (*S*)-**9** from (*S*)-**7** gave (*R*)-**8** (0.574 g, 47% yield) and (*R*)-**9** (0.28 g, 26% yield). (*R*)-**8**: $[\alpha]_D^{24}$ −10.0 (*c*=1.91, MeOH), (*R*)-**9**: $[\alpha]_D^{25}$ −4.8° (*c*=1.84, MeOH). The NMR data of (*R*)-**8** and (*R*)-**9** were identical to those of the reported (±)-**8**.[5c]

(4*R*)-(2-Methoxy-4-methylphenyl)pentyl Acetate (16) A solution of (*R*)-**9** (0.265 g, 1.3 mmol) and Ac_2O (0.2 g, 2 mmol) in pyridine (1 ml) was allowed to stand for 1 d at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, and saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=10 : 1) to afford (*R*)-**16** (0.287 g, 90%) as a homogeneous oil. (*R*)-**16**: $[\alpha]_D^{29}$ −2.6° (*c*=2.31, $CHCl_3$). The NMR data of (*R*)-**16** were identical to those of the reported (±)-**16**.[5c]

(4*R*)-(2-Methoxymethyloxy-4-methylphenyl)pentyl Acetate (18) i) To a solution of (*R*)-**16** (0.173 g, 0.69 mmol) in EtSH (1 ml) was added a mixture of $AlCl_3$ (0.46 g, 3.5 mmol) in EtSH (2 ml) at 0 °C, and the whole mixture was stirred for 30 min at the same temperature. After ether and 0.2 M aqueous HCl were added to the reaction mixture, the organic layer was washed with saturated brine ether and dried over $MgSO_4$. Evaporation of the organic solvent gave crude (*R*)-**17**. The NMR data of (*R*)-**17** were identical to those of the reported (±)-**17**.[2] ii) To a stirred solution of (*R*)-**17** in MeCN (2 ml) at 0 °C, 55% NaH (0.09 g, 2.1 mmol), 18-crown-16 (0.024 g, 0.07 mmol), MOMCl (0.11 g, 1.38 mmol) were added, and the whole mixture was stirred for 1 h at 0 °C. After ether and aqueous NH_4Cl were added to the reaction mixture, the ether layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=9 : 1) to afford (*R*)-**18** (0.183 g, 94% overall yield from (*R*)-**16**) as a homogeneous oil. (*R*)-**18**: $[\alpha]_D^{23}$ −3.1° (*c*=1.88, $CHCl_3$). The NMR data of (*R*)-**18** were identical to those of the reported (±)-**18**.[5c]

(4*R*)-(2-Methoxymethyloxy-4-methylphenyl)pentanol (19) A solution of (*R*)-**18** (0.164 g, 0.58 mmol) in MeOH (1 ml) was treated with 2 M aqueous NaOH (0.5 ml), and the whole mixture was warmed at 50 °C for 10 min, and then allowed to cool. After ether was added to the reaction mixture, the ether layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=5 : 1) to afford (*R*)-**19** (0.136 g, 98%) as a homogeneous oil. (*R*)-**19**: $[\alpha]_D^{22}$ −3.9° (*c*=1.47, $CHCl_3$). The NMR data of (*R*)-**19** were identical to those of the reported (±)-**19**.[5c]

Protected (4*R*)-curcuphenol (21) i) PCC (0.67 g, 3.1 mmol) was added to a mixture of (*R*)-**19** (0.147 g, 0.62 mmol) and Celite 545 (2 g) in CH_2Cl_2 (5 ml) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and filtered. The filtrate was subjected to short column chromatography to give the aldehyde (*R*)-**20**. ii) This was added to a solution of triphenylisopropylphosphonium iodide (0.54 g, 1.24 mmol) and 1.6 M *n*-BuLi in hexane (0.78 ml, 1.24 mmol) in tetrahydrofuran (THF, 10 ml) under stirring and the whole mixture was stirred for 2 d at room temperature. After ether and aqueous NH_4Cl were added to the reaction mixture, the ether layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=50 : 1) to afford (*R*)-**21** (0.10 g, 62% overall yield) as a homogeneous oil. (*R*)-**21**: $[\alpha]_D^{26}$ −9.8 ° (*c*=1.01, $CHCl_3$). The NMR data of (*R*)-**21** were identical to those of the reported (±)-**21**.[5c]

(*R*)-Curcuphenol (1) A mixture of 2 M aqueous HCl (1 ml) and isopropanol (1 ml) was added to a solution of (*R*)-**21** (0.1 g, 0.38 mmol) in isopropanol (0.5 ml). The whole reaction mixture was warmed at 60 °C for 30 min. After ether was added to the reaction mixture, the ether layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=5 : 1) to afford (*R*)-**1** (0.052 g, 62%) as a homogeneous oil. (*R*)-**1**: $[\alpha]_D^{23}$ −20.9° (*c*=1.73, $CHCl_3$). HR-MS Calcd for $C_{15}H_{22}O$ (M^+, *m*/*z*): 218.1617. Found: 218.1689. The spectral data (^{1}H-, ^{13}C-NMR, IR, HR-MS) were identical with those of the reported (±)-**1**.[5c]

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References and Notes

1) A part of this work was published as a preliminary communication: Ono M., Ogura Y., Hatogai K., Akita H., *Tetrahedron: Asymmetry*, **6**, 1829—1832 (1995).
2) ApSimon J. (ed.), "The Total Synthesis of Natural Product," Vol. 5, John Wiley and Sons, New York, 1983, pp. 35—45.
3) *a*) Fusetani N., Sugano M., Matsunaga S., Hashimoto K., *Experientia*, **43**, 1234—1235 (1987); *b*) Wright A. E., Pomponi S. A., McConnell O. J., Kohmoto S., McCarthy P., *J. Nat. Prod*., **50**, 976—978 (1987); *c*) Ghisalberti E. L., Jefferies P. R., Stuart A. D., *Aust. J. Chem*., **32**, 1627—1630 (1979).
4) McEnroe F. J., Fenical W., *Tetrahedron*, **34**, 1661—1664 (1978).
5) Synthesis of (±)-curcuphenol; *a*) Tanaka J., Nobutani K., Adachi K., *Nippon Kagakukaishi*, **1988**, 1065—1073; *b*) Shama M. L., Chand T., *Indian J. Chem*., **36B**, 553—556 (1997); Synthesis of (±)-curcuphenol and (±)-curcudiol; *c*) Ono M., Yamamoto Y., Akita H., *Chem. Pharm. Bull*., **43**, 553—558 (1995).
6) *a*) Sugawara T., Ogasawara K., *Tetrahedron*: *Asymmetry*, **9**, 2215—2217 (1998); *b*) Fuganti C., Serra S., *Synlett*, **1998**, 1252—1254; *c*) Fuganti C., Serra S., *J. Chem. Soc*., *Perkin Trans. 1*, **2000**, 3758—

3764.
7) Ono M., Todoriki R., Yamamoto Y., Akita H., *Chem. Pharm. Bull.*, **42**, 1590—1595 (1994).
8) Fukui S., Tanaka A., *Adv. Biochem. Engng./Biotechnol.*, **29**, 1—33 (1984).
9) Node M., Nishide K., Fuji K., Fujita E., *J. Org. Soc.*, **45**, 4275—4277 (1980).
10) Verbit L., Rao A. S., Clark-Lewis J. W., *Tetrahedron*, **24**, 5839—5845 (1968).