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TOTAL SYNTHESIS OF (*S*)-(+)- AND (*R*)-(-)-CURCUDIOLS BASED ON 1,2-ARYL MIGRATION *VIA* PHENONIUM ION

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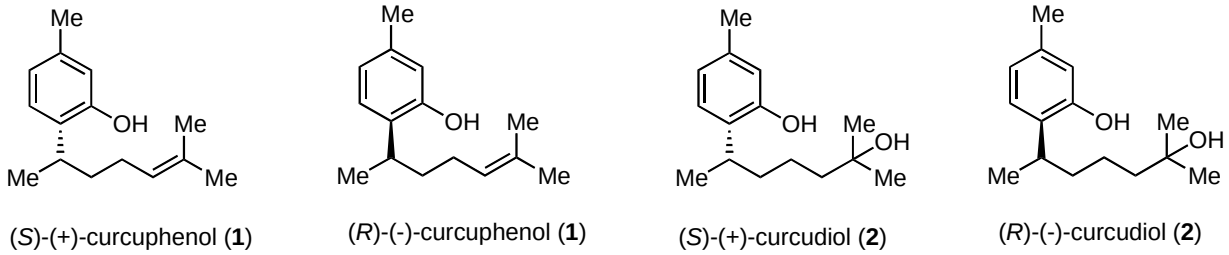
Abstract- Total synthesis of (*S*)-(+)- and (*R*)-(-)-curcudiols (**2**) was achieved based on the 1,2-aryl migration of the (4*R*,5*R*)- and (4*S*,5*S*)-4-aryl-5-tosyloxy-(2*E*)-hexenoates (**9**) derived from (4*R*,5*R*)- and (4*S*,5*S*)-4-epoxy-(2*E*)-hexenoates (**3**), respectively.

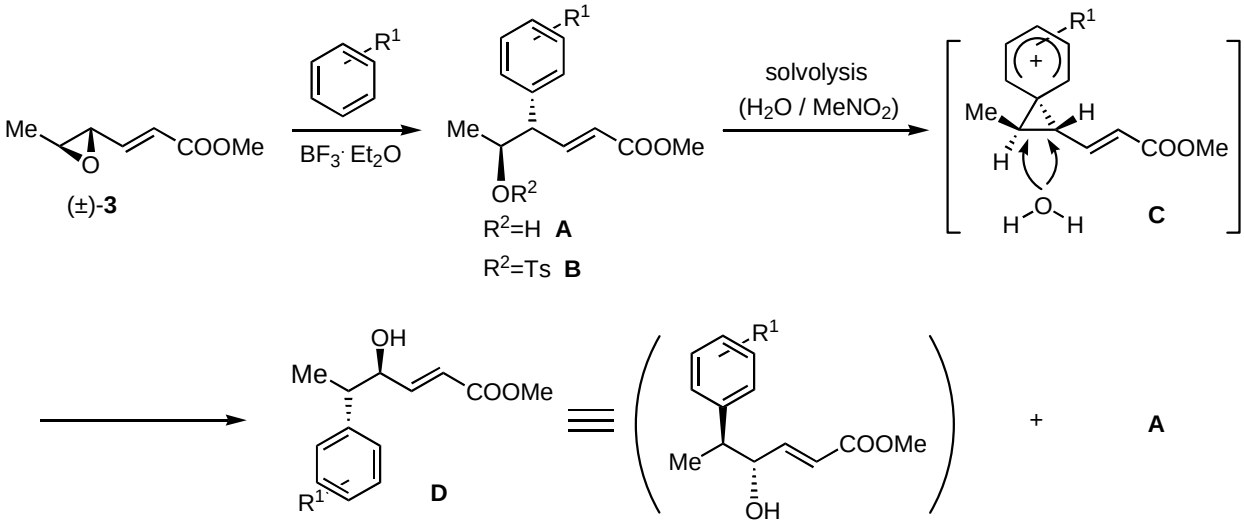
The phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources.[1] Among them, (*S*)-(+)-curcuphenol (**1**) and (*S*)-(+)-curcudiol (**2**), isolated from the marine sponge *Epipolasis* sp. strongly inhibit the activity of gastric H, K-ATPase,[2] while (*R*)-(-)-curcuphenol (**1**), isolated from the Caribbean gorgonians *Pseudopterogorgia rigida* and *Lasianthaea podocephala*, exhibits antibacterial activities against *Staphylcoccus aureus* and *Vibrio anguillarum*.[3] The structure of (*S*)-**2** was determined by spectral methods and confirmed by dehydration of (*S*)-**2** to form (*S*)-**1**.[2] Accordingly, the establishment of an efficient and general synthetic route to both enantiomers of these sesquiterpenoids is of significance. Racemic syntheses of bisabolane sesquiterpenes have been developed,[4] and moreover, useful asymmetric synthesis of these sesquiterpenes bearing a benzylic asymmetric center have been reported.[5] We now report that (*S*)- and (*R*)-curcudiols (**2**) have been synthesized based on 1,2-aryl migration via phenonium ion. (Scheme 1.)

We previously reported that the $BF_3{\cdot}Et_2O$-assisted reaction of (4,5)-epoxy-2(*E*)-hexenoate (**3**) with benzene analog bearing electron-donating group gave (4,5-*anti*)-4-aryl-5-hydroxy-(2*E*)-hexenoate **A**.[6] Moreover, solvolysis of (4,5-*anti*)-4-aryl-5-tosyloxy-(2*E*)-hexenoate **B** derived from **A** in water-saturated $MeNO_2$ gave 1,2-aryl migration product **D** along with complete inversion in good yield.[6] In the case of

this reaction, an intermolecular attack of the nucleophile (H_2O) to the σ-bridged phenonium ion **C** proceeded selectivity at the C(4)-position to provide the (4,5-*anti*)-5-aryl-4-hydroxy-(2*E*)-hexenoate **D**. (Scheme 2.)

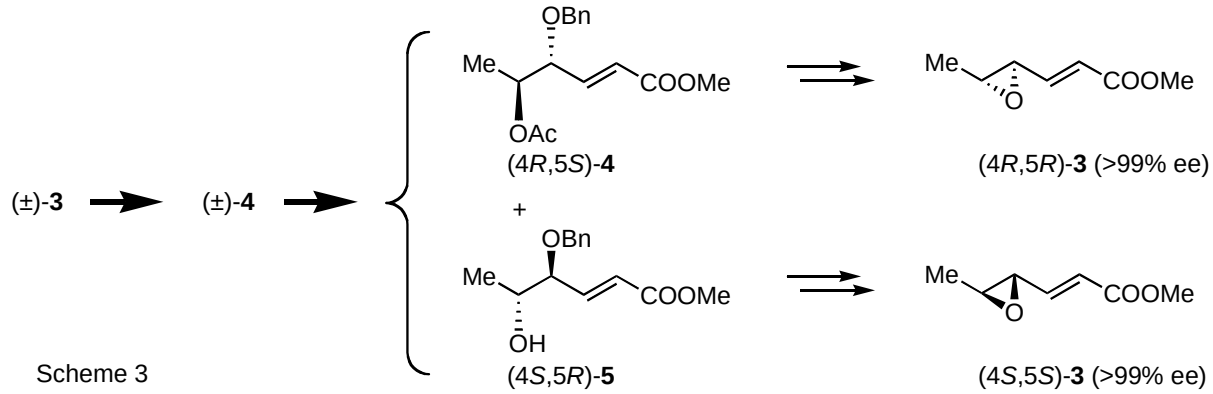


Scheme 1



Scheme 2

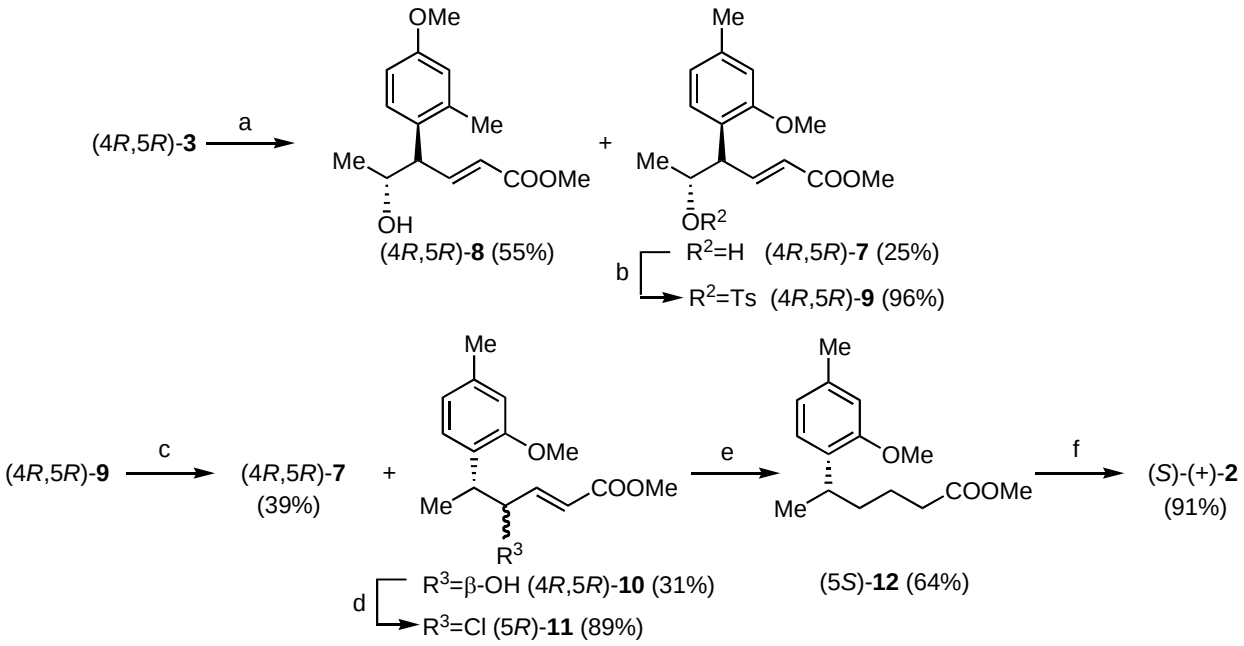
If this reaction were applied for the chiral (4,5-*trans*)-4-epoxy-(2*E*)-hexenoates ((4*R*,5*R*)-**3** or (4*S*,5*S*)-**3**), the chiral (4,5-*anti*)-5-aryl-4-hydroxy-(2*E*)-hexenoate **D** could be obtained. Actually, chiral compound ((4*R*,5*R*)-**3** or (4*S*,5*S*)-**3**) was obtained based on the lipase-catalysed asymmetric hydrolysis of (±)-(4,5-*trans*)-5-acetoxy-4-benzyloxy-(2*E*)-hexenoate (**4**) as shown in Scheme 3.[7]



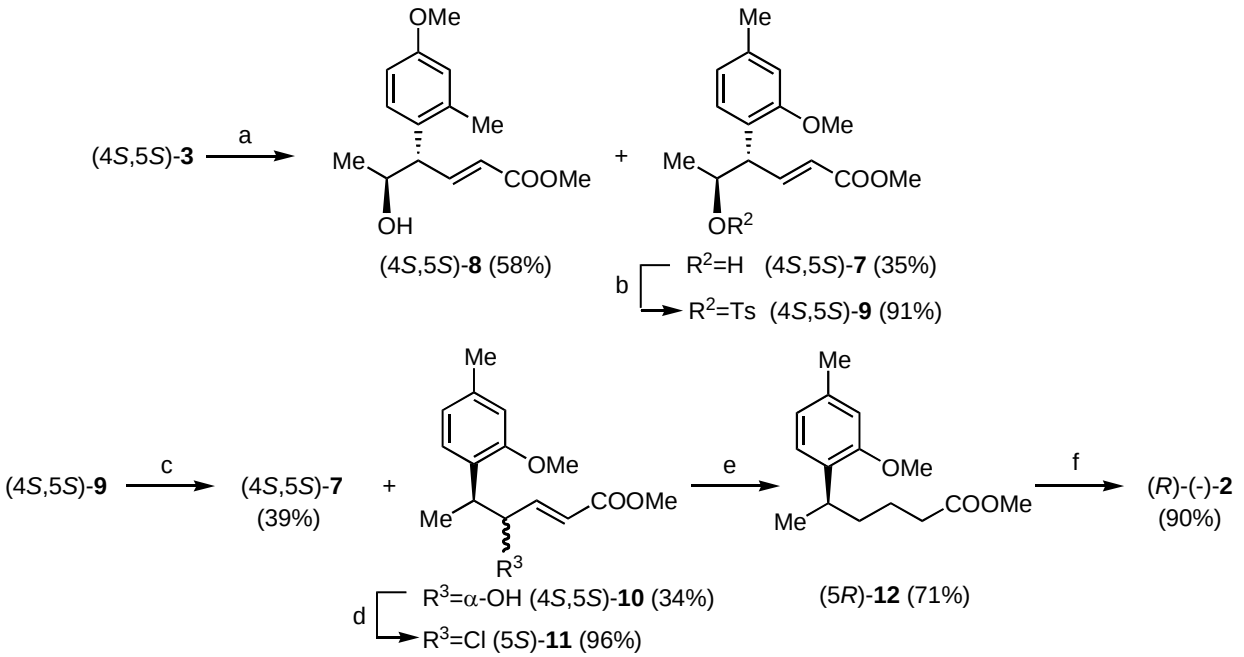
Scheme 3

The reaction of (4*R*,5*R*)-**3** and *m*-methoxytoluene gave (4*R*,5*R*)-**7** (25% yield) and its regioisomer (4*R*,5*R*)-**8** (55% yield). The structures of (4*R*,5*R*)-**7** and (4*R*,5*R*)-**8** were confirmed by the direct comparison of (±)-**7** and (±)-**8**, respectively.[6] Treatment of (4*R*,5*R*)-**7** with tosyl chloride (TsCl)

afforded the corresponding tosylate (4*R*,5*R*)-**9** (96% yield), which was subjected to solvolysis in water-saturated $MeNO_2$ to provide the 1,2-migration product (4*R*,5*R*)-**10** (31% yield) along with (4*R*,5*R*)-**7** (39% yield).



Scheme 4. a; 2-methoxytoluene / $BF_3 \cdot Et_2O$ / CH_2Cl_2 b; Ts_2O / pyridine c; $MeNO_2$ / H_2O
d; NCS / Ph_3P / MeCN e; H_2 / 20% $Pd(OH)_2$-C f; 1) EtSH / $AlCl_3$ 2) MeMgI / THF



Scheme 5. a; 2-methoxytoluene / $BF_3 \cdot Et_2O$ / CH_2Cl_2 b; Ts_2O / pyridine c; $MeNO_2$ / H_2O
d; NCS / Ph_3P / MeCN e; H_2 / 20% $Pd(OH)_2$-C f; 1) EtSH / $AlCl_3$ 2) MeMgI / THF

Treatment of (4*R*,5*R*)-**10** with *N*-chlorosuccinimide (NCS) and triphenylphosphine (Ph_3P) gave a single isomer (5*R*)-**11** (89% yield), which was subjected to hydrogenolysis to afford the saturated ester (5*S*)-**12** (64% yield). Demethylation of (5*S*)-**12** with a combination of $AlCl_3$ and EtSH[8] provided the phenol,

which was treated with Grignard reagent to afford (*S*)-(+)-curcudiol (**2**) ([α]$_D$ +9.9°, c = 4.96, $CHCl_3$) in 91% overall yield. The spectral data including specific rotation were identical with those ([α]$_D$ +9.2°, c = 10.8, $CHCl_3$) of the natural (*S*)-(+)-curcudiol (**2**).[2b] (Scheme 4.) The synthesis of (*R*)-(-)-curcudiol (**2**) was achieved from (4*S*,5*S*)-**3** by the same way as for the synthesis of (*S*)-(+)-**2**. (scheme 5.)

CONCLUSION

Total synthesis of (*S*)-(+)- and (*R*)-(-)-curcudiols (**2**) was achieved based on the 1,2-aryl migration of the (4*R*,5*R*)-and (4*S*,5*S*)-4-aryl-5-tosyloxy-(2*E*)-hexenoates (**9**) derived from (4*R*,5*R*)- and (4*S*,5*S*)-4-epoxy-(2*E*)-hexenoates (**3**), respectively.

EXPERIMENTAL

^{1}H-NMR spectra were recorded by a JEOL EX 400 spectrometer (Tokyo, Japan). Spectra were taken with 5-10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. Mass spectra and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-600H (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl (4*R*,5*R*)-4-(4'-methyl-2'-methoxyphenyl)-5-hydroxy-2(*E*)-hexenoate 7 and Methyl (4*R*,5*R*)-4-(2'-methyl-4'-methoxyphenyl)-5-hydroxy-2(*E*)-hexenoate 8

To a solution of (4*R*,5*R*)-**3** (1.903 g, 13.4 mmol) and *m*-methoxytoluene (4.91 g, 40.2 mmol) in CH_2Cl_2 (25 mL) was added $BF_3{\cdot}Et_2O$ (0.008M, 1.67 mL, 13.4 mmol) at –78°C, and the whole mixture was stirred for 1 h at –78°C, and for 1 h at –20°C. The reaction mixture was diluted with brine and extracted with CH_2Cl_2 . The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (250 g, *n*-hexane:AcOEt=5:1) to afford (4*R*,5*R*)-**7** (0.879 g, 25%) and (4*R*,5*R*)-**8** (1.937 g, 55%) as a colorless oil, respectively, in elution order. (4*R*,5*R*)-**7**: [α]$_D^{23}$ +12.9° (c = 0.49, $CHCl_3$). IR (neat): 3444, 1695 cm^{-1}. ^{1}H-NMR: δ 1.10 (3H, d, *J* = 6 Hz), 1.74 (1H, br.s), 2.33 (3H, s), 3.71 (3H, s), 3.77 (1H, ddd, *J* = 1, 7, 8.5 Hz), 3.80 (3H, s), 4.17 (1H, dq, *J* = 7, 6 Hz), 5.89 (1H, dd, *J* = 1, 15.6 Hz), 6.69 (1H, s), 6.74 (1H, d, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 7.5 Hz), 7.33 (1H, dd, *J* = 8.5, 15.6 Hz). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7. 63. Found: C, 67.72; H, 7.69. MS (FAB) m/z: 265 (M^++1). (4*R*,5*R*)-**8**: [α]$_D^{23}$ -5.0° (c = 0.83, $CHCl_3$). IR (neat): 3443, 1720 cm^{-1}. ^{1}H-NMR: δ 1.12 (3H, d, *J* = 6.5 Hz), 1.74 (1H, br.s), 2.31 (3H, s), 3.58 (1H, ddd, *J* = 2, 7.5, 8 Hz), 3.71 (3H, s), 3.78 (3H, s), 4.10 (1H, dq, *J* = 6.5, 7.5 Hz), 5.86 (1H, dd, *J* = 2, 15.5 Hz), 6.73 (1H, s), 6.75 (1H, d, *J* = 7.5 Hz), 7.08 (1H, d, *J* = 1, 7.5 Hz), 7.23 (1H, dd, *J* = 8, 15.5 Hz). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7. 63. Found: C, 67.86; H, 7.74. MS (FAB) m/z: 265 (M^++1).

Methyl (4*R*,5*R*)-4-(4'-methyl-2'-methoxyphenyl)-5-tosyloxy-2(*E*)-hexenoate 9

To a solution of (4*R*,5*R*)-**7** (0.879 g, 3.3 mmol), pyridine (0.53 g, 6.7 mmol) in benzene (30 mL) was added *p*-toluenesulfonic anhydride (Ts_2O, 1.52 g, 4.7 mmol), and the whole mixture was stirred for 1 d at 45°C. The reaction mixture was diluted with H_2O, which was extracted with ether. The organic layer was washed with 1M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (36 g, *n*-hexane:AcOEt=5:1) to afford (4*R*,5*R*)-**9** (1.339 g, 96%) as a colorless oil. (4*R*,5*R*)-**9**: $[\alpha]_D^{24}$ -17.8° (c = 0.67, $CHCl_3$). IR (neat): 1715, 1506 cm^{-1}. ^{1}H-NMR: δ 1.28 (3H, d, *J* = 6.4 Hz), 2.30 (3H, s), 2.43 (3H, s), 3.69 (3H, s), 3.72 (3H, s), 3.78 (1H, t, *J* = 8.4 Hz), 5.02 (1H, dq, *J* = 8.4, 6.4 Hz), 5.67 (1H, br s), 5.73 (1H, d, *J* = 15.8 Hz), 6.64 (1H, br d, *J* = 7.5 Hz), 6.86 (1H, d, *J* = 7.5 Hz), 6.99 (1H, dd, *J* = 8.4, 15.8 Hz), 7.24 (2H, d, *J* = 8.2 Hz), 7.66 (2H, d, *J* = 8.2 Hz). Anal. Calcd for $C_{22}H_{26}O_6S$; C, 63.14; H, 6.26. Found: C, 63.35; H, 6.36. MS (FAB) m/z: 419 (M^++1).

Solvolysis of (4*R*,5*R*)-9

A solution of (4*R*,5*R*)-**9** (1.339 g, 3.2 mmol) in water-saturated nitromethane (200 mL) was stirred for 3 d at 50°C. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (40 g) to afford the starting (4*R*,5*R*)-**9** (0.208 g, 16% recovery) from *n*-hexane:AcOEt=50:1 elution, (4*R*,5*R*)-**10** (0.264 g, 31%) from *n*-hexane:AcOEt=10:1 elution, (4*R*,5*R*)-**7** (0.329 g, 39%) from *n*-hexane:AcOEt=5:1 elution. Compound (4*R*,5*R*)-**7** was identical with the above-mentioned (4*R*,5*R*)-**7**. (4*R*,5*R*)-**10**: $[\alpha]_D^{22}$-20.2° (c = 0.51, $CHCl_3$). IR (neat): 3474, 1719 cm^{-1}. ^{1}H-NMR: δ 1.24 (3H, d, *J* = 7 Hz), 2.34 (3H, s), 3.45 (1H, dq, *J* = 4, 7 Hz), 3.72 (3H, s), 3.82 (3H, s), 4.47-4.52 (1H, m), 6.03 (1H, dd, *J* = 2, 16 Hz), 6.70 (1H, s), 6.76 (1H, d, *J* = 8 Hz), 6.94 (1H, dd, *J* = 4, 16 Hz), 7.05 (1H, d, *J* = 8 Hz). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.32; H, 7.61. MS (FAB) m/z: 265 (M^++1).

Methyl (5*R*)-4-chloro-5-(4'-methyl-2'-methoxyphenyl)-2(*E*)-hexenoate 11

To a solution of NCS (0.3 g, 2.2 mmol) and Ph_3P (0.59 g, 2.2 mmol) in MeCN (8 mL) was added a solution of (4*R*,5*R*)-**10** (0.199 g, 0.8 mmol) in MeCN (4 mL) at 0°C, and the whole mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (35 g, *n*-hexane:AcOEt = 20:1) to afford (5*R*)-**11** (0.190 g, 89%) as a homogeneous oil. (5*R*)-**11**: $[\alpha]_D^{23}$ +40.7 ° (c = 0.52, $CHCl_3$). IR (neat): 1725, 1457 cm^{-1}. ^{1}H-NMR: δ 1.36 (3H, d, J = 9 Hz), 2.32 (3H, s), 3.53 (1H, quintet, *J* = 7 Hz), 3.70 (3H, s), 3.80 (3H, s), 4.75 (1H, dt, *J* = 2, 7 Hz), 5.92 (1H, dd, *J* = 2, 15 Hz), 6.65 (1H, s), 6.93 (1H, dd, *J* = 8, 15 Hz), 6.73 (1H, d, *J* = 8 Hz), 7.04 (1H, d, *J* = 8 Hz). Anal. Calcd for $C_{15}H_{19}O_3Cl$: C, 63.71; H, 6.77. Found: C, 63.85; H, 6.86. MS (FAB) m/z:

282 (M^+).

Methyl (5*S*)-(2'-methoxy-4'-methylphenyl)hexanoate 12

A solution of (5*R*)-**11** (0.130 g, 0.46 mmol) in AcOEt (10 mL) was hydrogenated over 20% $Pd(OH)_2$-C (0.4 g) at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 50:1) to afford (5*S*)-**12** (0.074 g, 64%) as a colorless oil. (5*S*)-**12**: $[\alpha]_D^{21}$ +5.0° (c = 0.74, $CHCl_3$); IR (neat): 1738 cm^{-1}. NMR: δ 1.18 (3H, d, *J* = 7 Hz), 1.48-1.68 (4H, m), 2.28 (2H, t, *J*=6 Hz), 2.32 (3H, s), 3.15 (1H, sixtet, *J*=7 Hz), 3.64 (3H, s), 6.66 (1H, s), 6.73 (1H, d, *J* = 8 Hz), 7.03 (1H, d, *J* = 8 Hz). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.66; H, 9.08. MS (FAB) m/z: 250 (M^+).

(*S*)-Curcudiol 2

i) To a solution of (5*S*)-**12** (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, 1.2 mmol) 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 (5*S*)-**12**) as a homogeneous oil. (*S*)-**2**: $[\alpha]_D^{24}$ +9.9° (c = 4.96, $CHCl_3$). IR (neat): 1738 cm^{-1}. NMR: δ 1.18 (3H, s), 1.19 (3H, s), 1.23 (3H, d, *J* = 7 Hz), 1.28-1.72 (6H, m), 2.26 (3H, s), 3.07 (1H, sextet, *J*=7 Hz), 6.58 (1H, s), 6.72 (1H, d, *J* = 8 Hz), 7.03 (1H, d, *J* = 8 Hz). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.04; H, 10.45. MS (FAB) m/z: 236 (M^+). The spectral data (^{1}H-NMR, ^{13}C-NMR, IR, and FAB-MS) were identical to those of the reported (±)-**2**.[4c]

Methyl (4*S*,5*S*)-4-(4'-methyl-2'-methoxyphenyl)-5-hydroxy-2(*E*)-hexenoate 7 and Methyl (4*S*,5*S*)-4-(2'-methyl-4'-methoxyphenyl)-5-hydroxy-2(*E*)-hexenoate 8

To a solution of (4*S*,5*S*)-**3** (0.569 g, 4 mmol) and *m*-methoxytoluene (1.47 g, 12 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (0.008 M, 0.5 mL, 4 mmol) at –78°C, and the whole mixture was stirred for 1 h at –78°C, and for 1 h at –20°C. The reaction mixture was worked up in the same way as for (4*R*,5*R*)-**3** to afford (4*S*,5*S*)-**7** (0.365 g, 35%) and (4*S*,5*S*)-**8** (0.615 g, 58%). (4*S*,5*S*)-**7**: $[\alpha]_D^{22}$ -12.9° (c = 2.27, $CHCl_3$). (4*S*,5*S*)-**8**: $[\alpha]_D^{24}$ +5.8° (c = 1.17, $CHCl_3$). NMR data of (4*S*,5*S*)-**7** and (4*S*,5*S*)-**8** were identical with those of (4*R*,5*R*)-**7** and (4*R*,5*R*)-**8**, respectively.

Methyl (4*S*,5*S*)-4-(4'-methyl-2'-methoxyphenyl)-5-tosyloxy-2(*E*)-hexenoate 9

To a solution of (4*S*,5*S*)-**7** (1.142 g, 4.3 mmol), pyridine (1.36 g, 17.2 mmol) in benzene (30 mL) was added *p*-toluenesulfonic anhydride (Ts_2O, 3.1 g, 9.5 mmol), and the whole mixture was stirred for 1 d at 45°C. The reaction mixture was worked up in the same way as for (4*R*,5*R*)-**7** to afford (4*S*,5*S*)-**9** (1.646 g, 91%). (4*S*,5*S*)-**9**: $[\alpha]_D^{22}$ +19.7° (c = 0.65, $CHCl_3$). NMR data of (4*S*,5*S*)-**9** were identical with those of (4*R*,5*R*)-**9**.

Solvolysis of (4*S*,5*S*)-9

A solution of (4*S*,5*S*)-**9** (1.581 g, 3.8 mmol) in water-saturated nitromethane (200 mL) was stirred for 4 d at 50°C. The reaction mixture was worked up in the same way as for (4*R*,5*R*)-**9** to afford (4*S*,5*S*)-**10** (0.339 g, 34%) and (4*S*,5*S*)-**7** (0.393 g, 39%). Compound (4*S*,5*S*)-**7** was identical with the above-mentioned (4*S*,5*S*)-**7**. (4*S*,5*S*)-**10**: $[\alpha]_D^{22}$ +18.5° (c = 0.5, $CHCl_3$). NMR data of (4*S*,5*S*)-**10** were identical with those of (4*R*,5*R*)-**10**.

Methyl (5*S*)-4-chloro-5-(4'-methyl-2'-methoxyphenyl)-2(*E*)-hexenoate 11

To a solution of NCS (0.39 g, 2.9 mmol) and Ph_3P (0.77 g, 2.9 mmol) in MeCN (8 mL) was added a solution of (4*S*,5*S*)-**10** (0.260 g, 1 mmol) in MeCN (4 mL) at 0°C, and the whole mixture was stirred for 2 h at the same temperature. The reaction mixture was worked up in the same way as for (4*R*,5*R*)-**10** to afford (5*S*)-**11** (0.265 g, 96%). (5*S*)-**11**: $[\alpha]_D^{27}$ -40.1° (c = 0.5, $CHCl_3$). NMR data of (5*S*)-**11** were identical with those of (5*R*)-**11**.

Methyl (5*R*)-(2'-methoxy-4'-methylphenyl)hexanoate 12

A solution of (5*R*)-**11** (0.215 g, 0.8 mmol) in AcOEt (10 mL) was hydrogenated over 20% $Pd(OH)_2$-C (0.4 g) at room temperature under atmospheric pressure of hydrogen. The reaction mixture was worked up in the same way as for (5*S*)-**11** to afford (5*R*)-**12** (0.134 g, 71%). (5*R*)-**12**: $[\alpha]_D^{26}$ -4.2° (c = 0.31, $CHCl_3$). NMR data of (5*R*)-**12** were identical with those of (5*S*)-**12**.

(*R*)-Curcudiol 2

i) To a solution of (5*R*)-**12** (0.114 g, 0.5 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 worked up in the same way as for (5*S*)-**12** to give a crude oil. ii) A 2 M MeMgI ether solution (1 mL, 2 mmol) 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. The reaction mixture was worked up in the same way as for (5*S*)-**12** to afford (*R*)-**2** (0.097 g, 90% yield from (5*R*)-**12**). (*R*)-**2**: $[\alpha]_D^{23}$ -13.5° (c = 0.33, $CHCl_3$). NMR data of (*R*)-**2** were identical with those of (*S*)-**2**.

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