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First synthesis of (+)- and (−)-elvirol based on an enzymatic function

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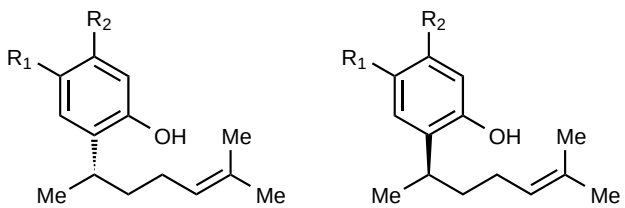
Abstract—A highly enantioselective synthesis of versatile chiral synthons possessing one stereogenic center, (*S*)- and (*R*)-4-aryl-5-hydroxy-(2*E*)-pentenoate **3** was achieved based on the enzymatic reaction of (±)-**4** with commercially available lipase 'OF-360' from *Candida rugosa*. An application of (*S*)-**3** and (*R*)-**3** to the total syntheses of (*S*)-elvirol **1** and (*R*)-elvirol **1**, respectively, is described. © 2001 Published by Elsevier Science Ltd.

1. Introduction

In 1969 the isolation of a new bisabolane sesquiterpene from *Elvira biflora* (Compositae) was reported and this phenol was called elvirol **1** whose structure did not obey the isoprene rule.[1] Although this phenol contains one stereogenic center, no reference was made to any optical activity in the natural compound. The phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources.[2] Among them, curcuphenol **2** being a structural isomer of elvirol **1** (Scheme 1), was isolated as two optically active forms. (*S*)-(+)-Curcuphenol **2**, isolated from the marine sponge *Epipolasis* sp. inhibits strongly the activity of gastric H, K-ATPase,[3] while (*R*)-(−)-curcuphenol **2**, isolated from a Caribbean gorgonian *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 elvirol **1** is of significant value from the standpoint of biological activity. Although racemic syntheses of elvirol **1** have been developed in past years,[5] a useful asymmetric synthesis bearing construction of a benzylic asymmetric center has not been reported so far.[6] We now report that (*S*)-**1** and (*R*)-**1** have been synthesized based on enzymatic resolution using lipase in an organic solvent.



Scheme 1.

2. Results and discussion

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** (Scheme 2). This was successfully achieved by carrying out an enantioselective hydrolysis of (±)-acetate **4** derived from (±)-**3** using lipase. The desired (±)-**3** was already obtained in the reaction of methyl (4,5)-epoxy-(2*E*)-pentenoate and *p*-methoxytoluene in the presence of $BF_3 \cdot Et_2O$ by us.[7]

Initially, (±)-**4** was subjected to screening experiments using several kinds of commercially available lipases. Among them, lipase 'OF-360' from *Candida rugosa* was found to be effective. When (±)-**4** was subjected to enantioselective hydrolysis using 'OF-360' in water saturated isopropyl ether for a short time (15 h), alcohol (*S*)-**3** (24%, 76% e.e.) and the unreacted (*R*)-**4** (71%, 24% e.e.) were obtained (entry 1, Table 1). On the other hand, asymmetric hydrolysis of (±)-**4** using 'OF-360' for a prolonged period (240 h) gave (*S*)-**3** (50%, 56% e.e.) and (*R*)-**4** (49%, 56% e.e.) (entry 4, Table 1). Alcohol (*S*)-**3** with 76% e.e. was subjected to enantioselective acetylation using 'OF-360' in the presence of isoprop-

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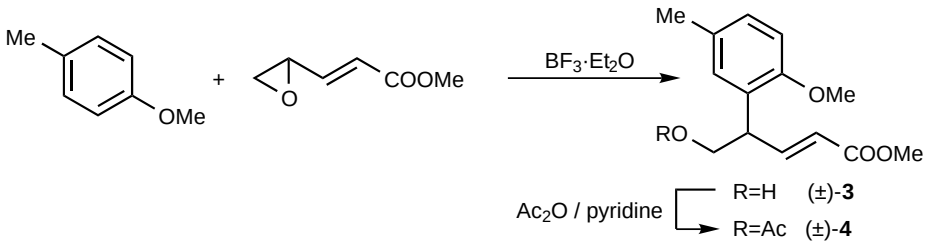
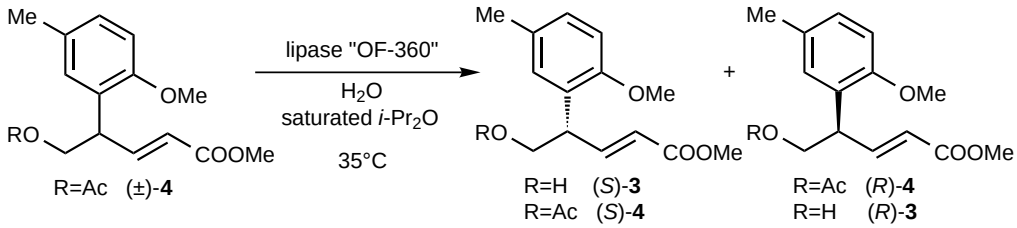


Scheme 2.

Table 1.

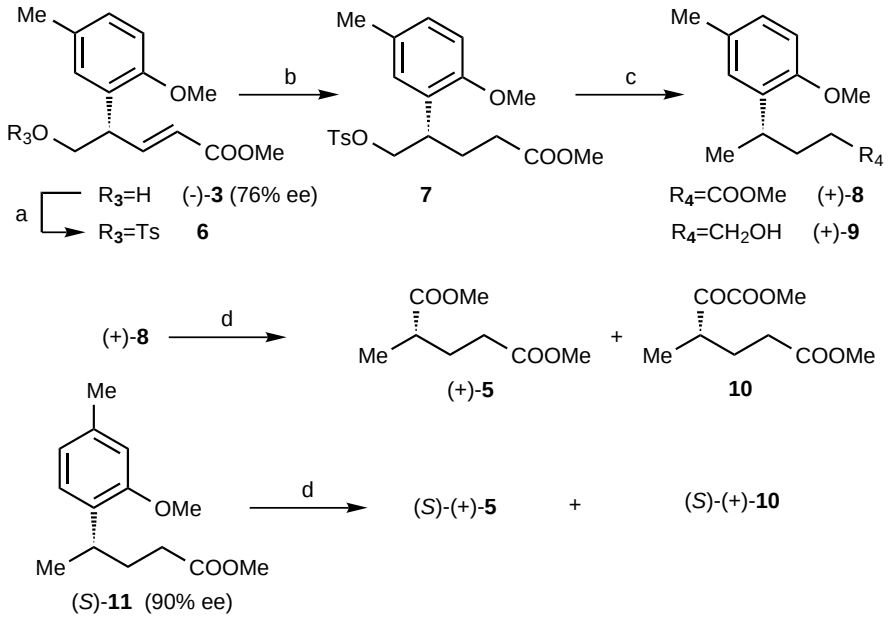


Entry	Substrate	Time (h)	Products (%, % ee)
1	(±)-**4** (10)	15	(*S*)-**3** 24 (76) (*R*)-**4** 71 (24)
2	(S)-**3** (76% ee, 2.03)	48	(*S*)-**3** 23 (64) (*S*)-**4** 70 (80)
3	(S)-**4** (80% ee, 1.66)	12	(*S*)-**3** 40 (92) (*S*)-**4** 50 (70)
4	(±)-**4** (10)	240	(*S*)-**3** 50 (56) (*R*)-**4** 49 (56)
5	(R)-**4** (56% ee, 3.35)	240	(*R*)-**3** 54 (28) (*R*)-**4** 36 (96)

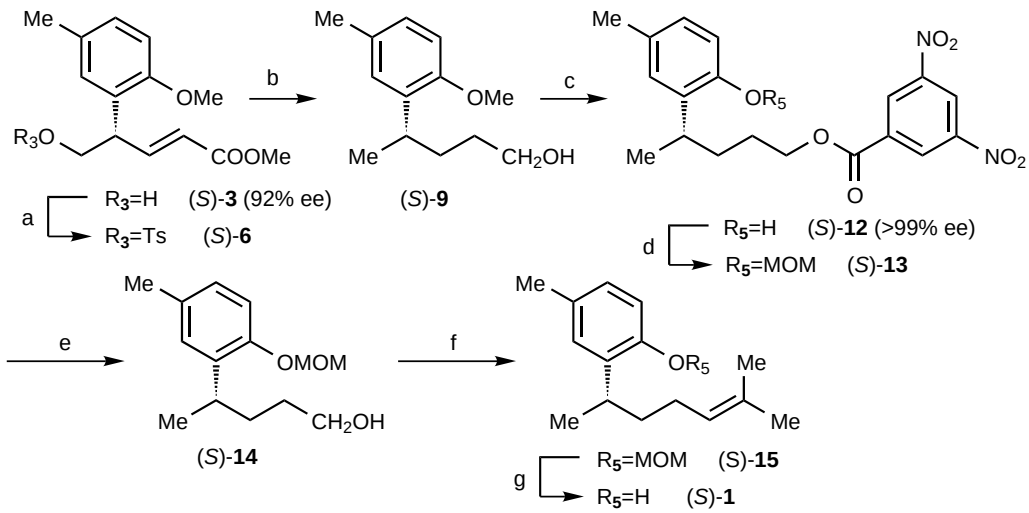
enyl acetate in isopropyl ether to afford (*S*)-**4** (70%, 80% e.e.) and (*S*)-**3** (23%, 64% e.e.) (entry 2, Table 1). The acetate (*S*)-**4** possessing 80% e.e. was again subjected to enantioselective hydrolysis to afford (*S*)-**3** (40%, 92% e.e., $[\alpha]_D$ −9.0 ($c=0.5$, $CHCl_3$)) and (*S*)-**4** (50%, 70% e.e.) (entry 3, Table 1). The acetate (*R*)-**4** with 56% e.e. was also subjected to enantioselective hydrolysis to afford (*R*)-**3** (54%, 28% e.e.) and (*R*)-**4** (36%, 96% e.e., $[\alpha]_D$ +11.3 ($c=0.5$, $CHCl_3$)) (entry 5, Table 1). The enantiomeric purity of the obtained chiral compounds was determined by HPLC on a Chiralcel AD (250×4.6 mm) column.

In order to confirm the absolute configuration of the present (−)-**3**, it was successfully converted to the optically active dimethyl 2-methylglutarate **5**. Treatment of (−)-**3** (76% e.e.) with tosyl chloride (TsCl) gave tosylate **6** (Scheme 3) in 77% yield. Catalytic hydrogenation of **6** followed by $NaBH_4$ reduction of **7** provided 4-arylpentanoate (+)-**8** (43% overall yield, $[\alpha]_D$ +8.9 ($c=1.45$, $CHCl_3$) corresponding to 76% e.e.) and alcohol (+)-**9** (31% overall yield, $[\alpha]_D$ +7.4 ($c=0.94$, $CHCl_3$) corresponding to 76% e.e.). Oxidative cleavage of the aromatic ring of (+)-**8** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3{\cdot}3H_2O$ followed by esterification with CH_2N_2 provided (+)-**5** (20% yield, $[\alpha]_D$ +14.6 ($c=1.07$, $CHCl_3$) corresponding to 76% e.e.) and α-keto ester **10** (22% yield). For a comparison, authentic (*S*)-**5** was derived from the reported (*S*)-4-arylpentanoate **11**.[8] The same oxidative cleavage of the aromatic ring of (*S*)-**11** (90% e.e.) as for (+)-**8** gave (*S*)-(+)-**5** (33% yield, $[\alpha]_D$ +15.8 ($c=0.72$, $CHCl_3$) corresponding to 90% e.e.) and α-keto ester (*S*)-(+)-**10** (10% yield, $[\alpha]_D$ +2.4 ($c=0.26$, $CHCl_3$) corresponding to 90% e.e.). The spectral data ($[\alpha]_D$, ^1H NMR) of (+)-**5** derived from (+)-**8** were identical with those of the authentic (*S*)-(+)-**5** and thence the absolute configurations of (−)-**3** and (+)-**4** were determined to be (*S*) and (*R*), respectively.

The total syntheses of (*S*)- and (*R*)-elvirol **1** were achieved from (*S*)-**3** (Scheme 4) (92% e.e.) and (*R*)-**3** (Scheme 5) (96% e.e.), respectively. Treatment of (*S*)-**3** with *p*-toluenesulfonic anhydride (Ts_2O) in pyridine gave tosylate (*S*)-**6** (85% yield) which was subjected to the following treatment: (1) catalytic hydrogenation, (2) $NaBH_4$ reduction, (3) $LiAlH_4$ reduction, to afford alcohol (*S*)-**9** (70% overall yield from (*S*)-**6**, $[\alpha]_D$ +8.0 ($c=0.5$, $CHCl_3$) corresponding to 92% e.e.). Demethylation of (*S*)-**9** with a combination of $AlCl_3$ and ethanethiol (EtSH) provided a phenol, which was treated with 3,5-dinitrobenzoyl chloride to afford the corresponding 3,5-dinitrobenzoate (*S*)-**12** in 59% overall yield from (*S*)-**9**. Recrystallization of (*S*)-**12** from AcOEt gave the enantiomerically pure (*S*)-**12** (mp 120–122°C, $[\alpha]_D$ +10.0 ($c=0.5$, $CHCl_3$)) which was treated with methoxymethyl chloride (MOMCl) in the presence of Hünig's base to afford the corresponding MOM ether (*S*)-**13** (Scheme 4) ($[\alpha]_D$ +4.6 ($c=0.66$, $CHCl_3$)) in 88% yield. Alkaline treatment of (*S*)-**13** with K_2CO_3 in MeOH provided alcohol (*S*)-**14** ($[\alpha]_D$ +9.9 ($c=0.51$, $CHCl_3$)) in 93% yield. Pyridinium chlorochromate (PCC)-oxidation of (*S*)-**14** followed by Wittig reaction afforded olefin (*S*)-**15** ($[\alpha]_D$ +19.6 ($c=0.16$, $CHCl_3$)) in 19% overall yield from (*S*)-**14**. Deprotection of (*S*)-**15**



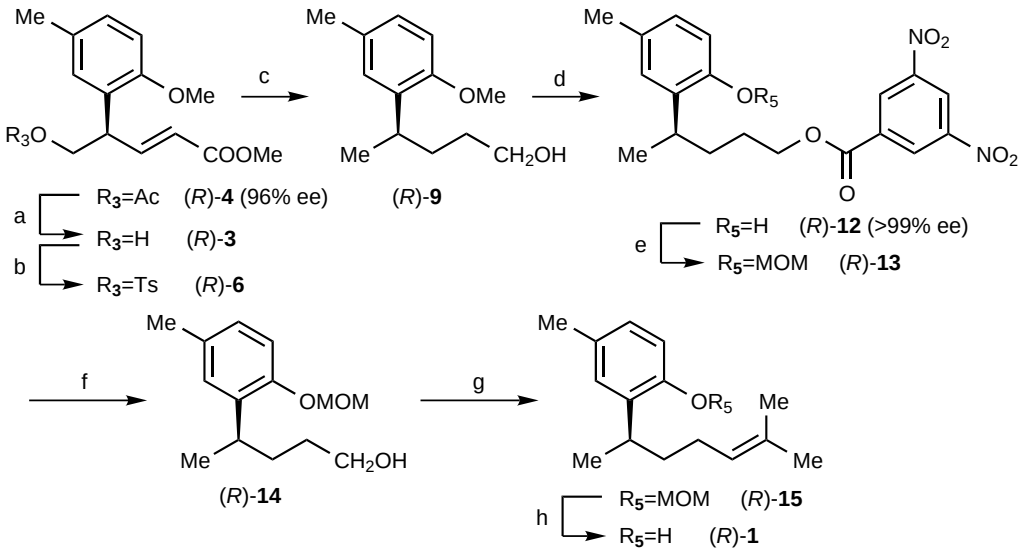
Scheme 3. (a) TsCl/pyridine, (b) H_2/20% $Pd(OH)_2$-C; (c) $NaBH_4$/DMSO; (d) $NaIO_4/RuCl_3 \cdot 3H_2O$ (2 mol%)/CCl_4/MeCN/H_2O.



Scheme 4. (a) Ts_2O/pyridine; (b) (1) H_2/20% $Pd(OH)_2$-C, (2) $NaBH_4$/DMSO, (3) $LiAlH_4$; (c) (1) EtSH/$AlCl_3$, (2) 3,5-dinitrobenzoyl chloride; (d) MOMCl/(*i*-Pr)$_2$NEt; (e) K_2CO_3/MeOH; (f) (1) PCC/CH_2Cl_2, (2) (*iso*-Pr)-$P^+Ph_3I^-$/*n*-BuLi/THF; (g) 2 M HCl/*i*-PrOH.

gave (*S*)-elvirol **1** (34% yield, $[\alpha]_D$ +36.1 ($c=0.46$, $CHCl_3$)), whose NMR data were identical with those of the natural product **1**.[1]

The synthesis of (*R*)-elvirol **1** from (*R*)-**4** (96% e.e.) was carried out fundamentally in the same way as that of (*S*)-**3**. Deprotection of (*R*)-**4** to give alcohol (*R*)-**3** ($[\alpha]_D$ +8.5 ($c=0.51$, $CHCl_3$)) followed by tosylation gave tosylate (*R*)-**6** in 85% overall yield. Successive treatment of (*R*)-**6** in the same way as for (*S*)-**6** afforded alcohol (*R*)-**9** (82% overall yield from (*S*)-**6**, $[\alpha]_D$ −9.5 ($c=0.5$, $CHCl_3$) corresponding to 96% e.e.). Demethylation of (*R*)-**9** followed by treatment with 3,5-dinitrobenzoyl chloride gave the corresponding 3,5-dinitrobenzoate (*R*)-**12** in 50% overall yield from (*R*)-**9**. Recrystallization of (*R*)-**12** from AcOEt gave the enantiomerically pure (*R*)-**12** (mp 120–122°C, $[\alpha]_D$ −11.6 ($c=0.5$, $CHCl_3$)) which was treated with methoxymethyl chloride (MOMCl) to afford the corresponding MOM ether (*R*)-**13** in 86% yield. Alkaline treatment of (*R*)-**13** with K_2CO_3 in MeOH gave alcohol (*R*)-**14** ($[\alpha]_D$ −10.0 ($c=0.5$, $CHCl_3$)) in 74% yield. Pyridinium chlorochromate (PCC)-oxidation of (*R*)-**14** followed by the Wittig reaction then afforded olefin (*R*)-**15** ($[\alpha]_D$ −18.7 ($c=0.16$, $CHCl_3$)) in 39% overall yield from (*R*)-**14**. Deprotection of (*R*)-**15** gave (*R*)-elvirol (**1**) (58% yield, $[\alpha]_D$ −37.1 ($c=0.23$, $CHCl_3$)), whose NMR data were identical with those of (*S*)-**1**.



Scheme 5. (a) NaOMe/MeOH; (b) Ts_2O/pyridine; (c) (1) H_2/20% $Pd(OH)_2$-C, (2) $NaBH_4$/DMSO, (3) $LiAlH_4$; (d) (1) EtSH/$AlCl_3$, (2) 3,5-dinitrobenzoyl chloride; (e) MOMCl/(*i*-Pr)$_2$NEt; (f) K_2CO_3/MeOH; (g) (1) PCC/CH_2Cl_2, (2) (*iso*-Pr)-$P^+Ph_3I^-$/*n*-BuLi/THF; (h) 2 M HCl/*i*-PrOH.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL EX 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS-DX 303 spectrometer. IR spectra were recorded a Jasco FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). 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.

3.2. (±)-Methyl 5-acetoxy-4-(2′-methoxy-5′-methylphenyl)-(2*E*)-pentenoate 4

A solution of (±)-**3** (0.99 g, 3.96 mmol) in pyridine (20 mL) was treated with Ac_2O (0.93 g, 9.11 mmol) and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 8:1) to give a colorless oil (±)-**4** (0.93 g, 80%). (±)-**4**: IR (neat): 1740 cm^{-1}; ^1H NMR: 2.03 (3H, s), 2.26 (3H, s), 3.72 (3H, s), 3.80 (3H, s), 4.19 (1H, br. q, J = 7.5 Hz), 4.30 (1H, dd, J = 6, 10 Hz), 4.39 (1H, dd, J = 9, 10 Hz), 5.87 (1H, dd, J = 2, 16 Hz), 6.78 (1H, d, J = 9 Hz), 6.90 (1H, d, J = 2 Hz), 7.03 (1H, dd, J = 2, 9 Hz), 7.15 (1H, dd, J = 7, 16 Hz). Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90%. Found: C, 65.41; H, 7.29. FAB MS m/z: 293 (M^++1).

3.3. Enzymatic resolution of (±)-4

(i) Table 1, entry 1; a suspension of (±)-**4** (1 g), lipase OF-360 (0.2 g) in H_2O-saturated-isopropyl ether (20 mL) was incubated at 33°C for 15 h. This scale experiment was simultaneously carried out ten times (total amount of (±)-**4** was 10 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** (7.13 g, 71%, 24% e.e.) from *n*-hexane:AcOEt = 10:1 eluent and (*S*)-**3** (2.038 g, 24%, 76% e.e.) as a homogeneous oil from *n*-hexane:AcOEt = 4:1 eluent. The NMR data of (*S*)-**3** were identical with those of the reported (±)-**3**.[7]

(ii) Table 1, entry 2; a suspension of (*S*)-**3** (76% e.e., 1 g), lipase OF-360 (0.2 g) and isopropenyl acetate (1 g) in isopropyl ether (20 mL) was incubated at 33°C for 48 h. This scale experiment was simultaneously carried out twice (total amount of (*S*)-**3** was 2.03 g). The reaction mixture was worked up in the same way as for (i) to give (*S*)-**4** (1.67 g, 70%, 80% e.e.) and (*S*)-**3** (0.467 g, 23%, 64% e.e.).

(iii) Table 1, entry 3; a suspension of (*S*)-**4** (80% e.e., 0.8 g), lipase OF-360 (0.2 g) in H_2O-saturated-isopropyl ether (20 mL) was incubated at 33°C for 12 h. This scale experiment was simultaneously carried out twice (total amount of (*S*)-**4** was 1.66 g). The reaction mixture was worked up in the same way as for (i) to give (*S*)-**4** (0.83 g, 50%, 70% e.e.) and (*S*)-**3** (0.569 g, 40%, $[\alpha]_D^{23}$ −9.0 (c = 0.5, $CHCl_3$) corresponding to 92% e.e.).

(iv) Table 1, entry 4; a suspension of (±)-**4** (1 g), lipase OF-360 (0.2 g) in H_2O-saturated-isopropyl ether (20 mL) was incubated at 33°C for 240 h. This scale experiment was simultaneously carried out ten times (total amount of (±)-**4** was 10 g). The reaction mixture was worked up in the same way as for (i) to give (*R*)-**4** (4.9 g, 49%, 56% e.e.) and (*S*)-**3** (4.281 g, 50%, 56% e.e.).

(v) Table 1, entry 5; a suspension of (*R*)-**4** (56% e.e., 1.1 g), lipase OF-360 (0.3 g) in H_2O-saturated-isopropyl ether (20 mL) was incubated at 33°C for 240 h. This scale experiment was simultaneously carried out three times (total amount of (*R*)-**4** was 3.35 g). The reaction mixture was worked up in the same way as for (i) to give (*R*)-**4** (1.206 g, 36%, $[\alpha]_D^{26}$ +11.3 ($c=0.5$, $CHCl_3$) corresponding to 96% e.e.) and (*R*)-**3** (1.549 g, 54%, 28% e.e.).

3.4. Methyl 5-tosyloxy-4-(2′-methoxy-5′-methylphenyl)-(2*E*)-pentenoate 6

A solution of (−)-**3** (76% e.e., 0.46 g, 1.84 mmol) in pyridine (10 mL) was treated with TsCl (0.53 g, 2.78 mmol), and the 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 2 M aqueous HCl, saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 10:1) to afford **6** (0.576 g, 77% yield) as a homogeneous oil. Compound **6**: IR (neat): 1725 cm^{-1}; ^1H NMR: 2.22 (3H, s), 2.44 (3H, s), 3.70 (3H, s), 3.71 (3H, s), 4.12 (1H, br. q, $J=7$ Hz), 4.27 (2H, d, $J=7$ Hz), 5.80 (1H, dd, $J=2$, 16 Hz), 6.70 (1H, d, $J=8$ Hz), 6.77 (1H, d, $J=2$ Hz), 7.01 (1H, dd, $J=2$, 8 Hz), 7.02 (1H, dd, $J=7$, 16 Hz), 7.30 (2H, d, $J=8$ Hz), 7.70 (2H, d, $J=8$ Hz). Anal. calcd for $C_{21}H_{24}O_6S$: C, 62.36; H, 5.98. Found: C, 61.94; H, 5.92%. FAB MS *m*/*z*: 404 (M^+ +1).

3.5. Preparation of methyl 4-(2′-methoxy-5′-methylphenyl)pentanoate (+)-8 and 4-(2′-methoxy-5′-methylphenyl)pentanol (+)-9

A solution of **6** (76% e.e., 0.576 g, 1.4 mmol) in AcOEt (10 mL) was hydrogenated over 20% Pd-C (20 mg) at room temperature under an atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated to give (*S*)-**7** as a colorless oil quantitatively. A solution of (*S*)-**7** and $NaBH_4$ (0.31 g, 8.1 mmol) in DMSO (10 mL) was warmed for 3 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 which was chromatographed on silica gel (17 g) to afford (+)-**8** (0.145 g, 43% yield) as a homogeneous oil from *n*-hexane:AcOEt = 30:1 eluent and (+)-**9** (0.094 g, 31% yield) as a homogeneous oil from *n*-hexane:AcOEt = 15:1 eluent. (+)-**8**: $[\alpha]_D^{24}$ +8.9 ($c=1.45$, $CHCl_3$), IR ($CHCl_3$): 1735 cm^{-1}; ^1H NMR: 1.23 (3H, d, $J=7$ Hz), 1.88–1.94 (2H, m), 2.14–2.29 (2H, m), 2.29 (3H, s), 3.19 (1H, sextet, $J=7$ Hz), 3.63 (3H, s), 3.78 (3H, s), 6.74 (1H, d, $J=9$ Hz), 6.92–7.00 (2H, m). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.90; H, 8.33%. FAB MS *m*/*z*: 236 (M^+). (+)-**9**: $[\alpha]_D^{24}$ +7.4 ($c=1.45$, $CHCl_3$), IR (neat): 3343 cm^{-1} (OH); ^1H NMR: 1.20 (3H, d, $J=8$ Hz), 1.40–1.69 (5H, m), 2.28 (3H, s), 3.17 (1H, sextet, $J=8$ Hz), 3.60 (2H, t, $J=6$ Hz), 3.78 (3H, s), 6.74 (1H, d, $J=8$ Hz), 6.94 (1H, dd, $J=2$, 8 Hz), 6.96 (1H, s). Anal. calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.49; H, 9.88%. FAB MS *m*/*z*: 208 (M^+).

3.6. Oxidative cleavage of aromatic ring of (+)-8

To a solution of (+)-**8** (0.145 g, 0.61 mmol) in MeCN (1 mL) was added $NaIO_4$ (2.63 g, 12.3 mmol) and H_2O (1.5 mL) at 0°C. A mixture of $RuCl_3 \cdot 3H_2O$ (10 mg) in CCl_4 (1 mL) was added to the above reaction mixture, and the whole mixture was vigorously stirred at room temperature for 6 h and stood for 12 h. The reaction mixture was filtered with the aid of Celite and the precipitate was washed with MeCN. The filtrate and washing were combined and concentrated to give a residue which was acidified with 2 M aqueous HCl. The acidic layer was extracted with ether and the organic layer was washed with saturated brine, dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was treated with an excess of CH_2N_2–ether solution to afford a crude oil. It was chromatographed on silica gel (10 g) to afford (+)-**5** (0.021 g, 20% yield) as a homogeneous oil from *n*-hexane:AcOEt = 40:1 eluent and (+)-**10** (0.027 g, 22% yield) as a homogeneous oil from *n*-hexane:AcOEt = 20:1 eluent. (+)-**5**: $[\alpha]_D^{26}$ +14.6 ($c=1.07$, $CHCl_3$), ^1H NMR: 1.18 (3H, d, $J=7$ Hz), 1.74–1.82 (1H, m), 1.93–2.01 (1H, m), 2.29–2.40 (2H, m), 2.51 (1H, sextet, $J=7$ Hz), 3.67 (3H, s), 3.68 (3H, s). ^{13}C NMR: 17.1 (q), 28.6 (t), 31.7 (t), 38.7 (d), 51.6 (q), 51.6 (q), 173.5 (s), 176 (s). FAB MS *m*/*z*: 174 (M^+). (+)-**10**: $[\alpha]_D^{27}$ +3.2 ($c=1.35$, $CHCl_3$), ^1H NMR: 1.18 (3H, d, $J=7$ Hz), 1.72–1.82 (1H, m), 2.02–2.11 (1H, m), 2.29–2.40 (2H, m), 3.30 (1H, sextet, $J=7$ Hz), 3.68 (3H, s), 3.89 (3H, s). ^{13}C NMR: δ 15.4 (q), 26.7 (t), 31.2 (t), 41.3 (d), 51.7 (q), 53.0 (q), 161.8 (s), 173.3 (s), 196.8 (s). Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.00; H, 6.78%. FAB MS *m*/*z*: 203 (M^++1).

3.7. Oxidative cleavage of the aromatic ring of methyl 4-(2′-methoxy-4′-methylphenyl)pentanoate (*S*)-11

To a solution of (*S*)-**11** (90% e.e., 0.289 g, 1.2 mmol) in MeCN (2 mL) was added $NaIO_4$ (5.23 g, 24 mmol) and H_2O (3 mL) at 0°C. A mixture of $RuCl_3 \cdot 3H_2O$ (20 mg) in CCl_4 (2 mL) was added to the above reaction mixture, and the whole mixture was vigorously stirred at room temperature for 6 h and stood for 12 h. The reaction mixture was worked up in the same way as for (+)-**8** to give (*S*)-**5** (0.072 g, 33% yield) and (*S*)-**10** (0.026 g, 10% yield). (*S*)-**5**: $[\alpha]_D^{25}$ +15.8 ($c=0.72$, $CHCl_3$). The NMR data of (*S*)-**5** were identical with those of (+)-**5**. (*S*)-**10**: $[\alpha]_D^{24}$ +2.4 ($c=0.26$, $CHCl_3$). The NMR data of (*S*)-**10** were identical with those of (+)-**10**.

3.8. 4-(2′-Methoxy-5′-methylphenyl)pentanol (*S*)-9

(i) To a solution of (*S*)-**3** (92% e.e., 1.50 g, 6 mmol) in benzene (20 mL) was added Ts_2O (3.91 g, 12 mmol) and pyridine (0.95 g, 12 mmol) and the mixture was stirred at 40°C for 12 h at room temperature. The reaction mixture was worked up in the same way as for the preparation of **6** to afford (*S*)-**6** (2.056 g, 85% yield) as a homogeneous oil. The NMR data of (*S*)-**6** were identical with those of the previous **6**.

(ii) A solution of (*S*)-**6** (92% e.e., 2.056 g, 5.08 mmol) in MeOH (12 mL) was hydrogenated over 20% Pd–C (0.2 g) at room temperature under an atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated to give (*S*)-**7** (1.79 g) as a colorless oil quantitatively. Compound (*S*)-**7**: ^{1}H NMR: 1.86–1.95 (1H, m), 2.03–2.11 (1H, m), 2.12–2.18 (2H, m), 2.22 (3H, s), 2.43 (3H, s), 3.27–3.34 (1H, m), 3.60 (3H, s), 3.67 (3H, s), 4.13 (1H, dd, $J=7$, 10 Hz), 4.17 (1H, dd, $J=7$, 10 Hz), 6.67 (1H, d, $J=8$ Hz), 6.78 (1H, d, $J=2$ Hz), 6.97 (1H, dd, $J=2$, 8 Hz), 7.27 (2H, d, $J=8$ Hz), 7.67 (2H, d, $J=8$ Hz).

(iii) A solution of (*S*)-**7** (1.79 g, 4.4 mmol) and $NaBH_4$ (0.83 g, 21.9 mmol) in DMSO (12 mL) was warmed for 2 h at 80°C, then allowed to cool. The reaction mixture was worked up in the same way as for the preparation of (+)-**8** and (+)-**9** to afford a mixture (2.45 g) of (+)-**8** and (+)-**9**.

(iv) To a suspension of $LiAlH_4$ (0.6 g, 15.8 mmol) in THF (20 mL) was added a solution of the above mixture in THF (20 mL) and the whole mixture was stirred at room temperature for 3 h. 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 which was chromatographed on silica gel (60 g) to afford (*S*)-**9** (0.745 g, 70% overall yield from (*S*)-**6**) as a homogeneous oil from *n*-hexane:AcOEt = 10:1 eluent. (*S*)-**9**: $[\alpha]_D^{26}$ +7.97 ($c=0.5$, $CHCl_3$). The NMR data of (*S*)-**9** were identical with those of (+)-**9**.

3.9. 4-(2′-Hydroxy-5′-methylphenyl)pentanyl 3,5-dinitrobenzoate (*S*)-12

(i) To a solution of (*S*)-**9** (0.20 g, 0.96 mmol) in EtSH (3 mL) was added a mixture of $AlCl_3$ (0.64 g, 4.8 mmol) in EtSH (1 mL) at 0°C, and the mixture was stirred for 0.5 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 and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (10 g) to afford (4*S*)-(2′-hydroxy-5′-methylphenyl)pentanol (0.169 g, 91% yield) as a homogeneous oil from *n*-hexane:AcOEt = 4:1 eluent. (4*S*)-(2′-Hydroxy-5′-methylphenyl)pentanol: $[\alpha]_D^{24}$ +11.0 ($c=0.72$, $CHCl_3$), IR (neat): 3400 cm^{-1} (OH); ^{1}H NMR: 1.24 (3H, d, $J=7$ Hz), 1.45–1.74 (4H, m), 2.05 (1H, m), 2.26 (3H, s), 3.12 (1H, sextet, $J=7$ Hz), 3.70 (2H, t, $J=6$ Hz), 6.10 (1H, br. s), 6.67 (1H, d, $J=8$ Hz), 6.85 (1H, dd, $J=2$, 8 Hz), 6.94 (1H, d, $J=2$ Hz). Anal. calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.42.%. FAB MS m/z: 194 (M^+).

(ii) A solution of above diol (0.16 g, 0.82 mmol) in pyridine (2 mL) was treated with 3,5-dinitrobenzoyl chloride (0.16 g, 0.7 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 20:1) to give a colorless crystal (*S*)-**12** (0.208 g, 65% yield). Recrystallization of (*S*)-**12** from AcOEt gave an optically pure (*S*)-**12** (0.18 g). (*S*)-**12**: mp 120–122°C: IR (KBr): 3388, 1710, 1544 cm^{-1}; $[\alpha]_D^{23}$ +10.0 ($c=0.5$, $CHCl_3$) corresponding to >99% e.e.: ^{1}H NMR: 1.28 (3H, d, $J=7$ Hz), 1.67–1.86 (4H, m), 2.26 (3H, s), 3.16 (1H, sextet, $J=7$ Hz), 4.42–4.45 (2H, t, $J=6$ Hz), 4.91 (1H, s), 6.64 (1H, d, $J=8$ Hz), 6.85 (1H, dd, $J=2$, 8 Hz), 6.95 (1H, s), 9.14 (2H, d, $J=2$ Hz), 9.21 (1H, t, $J=2$ Hz). Anal. calcd for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21. Found: C, 58.38; H, 5.16; N, 7.39%. FAB MS m/z: 388 (M^+).

3.10. 4-(2′-Methoxymethyloxy-5′-methylphenyl)pentanyl 3,5-dinitrobenzoate (*S*)-13

To a solution of (*S*)-**12** (0.178 g, 0.46 mmol) in MeCN (1 mL) was added *N*,*N*-diisopropylethylamine (1.6 g, 12.4 mmol) and chloromethylmethyl ether (MOMCl; 0.67 g, 8.82 mmol) at 0°C and the mixture was stirred at 40°C for 12 h. After ether was added to the reaction mixture, the organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (10 g) to afford (*S*)-**13** (0.174 g, 88% yield) as a homogeneous oil from *n*-hexane:AcOEt = 20:1 eluent. (*S*)-**13**: $[\alpha]_D^{24}$ +4.6 ($c=0.66$, $CHCl_3$), IR (neat): 1729, 1564 cm^{-1}; ^{1}H NMR: 1.26 (3H, d, $J=7$ Hz), 1.66–1.85 (4H, m), 2.28 (3H, s), 3.27 (1H, sextet, $J=7$ Hz), 3.47 (3H, s), 4.42 (2H, t, $J=6$ Hz), 5.15 (1H, d, $J=6$ Hz), 5.17 (1H, d, $J=6$ Hz), 6.94 (1H, dd, $J=2$, 8 Hz), 6.97 (1H, d, $J=8$ Hz), 6.99 (1H, d, $J=2$ Hz), 9.13 (2H, d, $J=2$ Hz), 9.21 (1H, t, $J=2$ Hz). Anal. calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48. Found: C, 58.49; H, 5.74, N, 6.31.%. FAB MS m/z: 432 (M^+).

3.11. 4-(2′-Methoxymethyloxy-5′-methylphenyl)pentanol (*S*)-14

A mixture of (*S*)-**13** (0.154 g, 0.36 mmol) and K_2CO_3 (40 mg) in MeOH (2 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O, washed with saturated brine and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (10 g) to afford (*S*)-**14** (0.079 g, 93% yield) as a homogeneous oil from *n*-hex-

ane:AcOEt = 4:1 eluent. (*S*)-**14**: $[\alpha]_D^{22}$ +9.9 ($c = 0.51$, $CHCl_3$), IR (neat): 3353 cm^{-1}; ^1H NMR: 1.22 (3H, d, $J = 7$ Hz), 1.41–1.71 (4H, m), 2.28 (3H, s), 3.20 (1H, sextet, $J = 7$ Hz), 3.46 (3H, s), 3.60 (2H, t, $J = 6$ Hz), 5.15 (2H, s), 6.92 (1H, dd, $J = 2$, 8 Hz), 6.95 (1H, d, $J = 8$ Hz), 6.98 (1H, d, $J = 2$ Hz). Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.03; H, 9.50%. FAB MS m/z: 238 (M^+).

3.12. 2-Methyl-(6*S*)-(2′-methoxymethyloxy-5′-methyl)-phenyl-2-heptene (*S*)-15

(i) Pyridinium chlorochromate (PCC, 0.4 g, 1.86 mmol) was added to a mixture of (*S*)-**14** (0.077 g, 0.33 mmol) and Celite 545 (0.2 g) in CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was stirred for 2 h at room temperature and filtered. The filtrate was subjected to short column chromatography (*n*-hexane:AcOEt = 20:1) to give an aldehyde (0.06 g). (ii) This was added to a solution of triphenylisopropylphosphonium iodide (0.22 g, 0.5 mmol) and *n*-BuLi in hexane (1.6 M, 0.32 mL, 0.5 mmol) in tetrahydrofuran (THF, 3 mL) under stirring and the whole mixture was stirred for 1.5 h at room temperature. After ether and aqueous NH_4Cl 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 which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to afford (*S*)-**15** (0.016 g, 19% overall yield from (*S*)-**14**) as a homogeneous oil. (*S*)-**15**: $[\alpha]_D^{27}$ +19.6 ($c = 0.16$, $CHCl_3$). IR (neat): 1011 cm^{-1}; ^1H NMR: 1.20 (3H, d, $J = 7$ Hz), 1.53 (3H, s), 1.67 (3H, s), 1.50–1.59 (1H, m), 1.59–1.68 (1H, m), 1.86–1.97 (2H, m), 2.27 (3H, s), 3.17 (1H, sextet, $J = 7$ Hz), 3.47 (3H, s), 5.12 (1H, br. t, $J = 7$ Hz), 5.14 (2H, s), 6.91 (1H, dd, $J = 2$, 8 Hz), 6.94 (1H, d, $J = 8$ Hz), 6.97(1H, d, $J = 2$ Hz). FAB MS m/z: 262 (M^+).

3.13. (*S*)-Elvirol 1

A solution of (*S*)-**15** (0.016 g, 0.06 mmol), 2 M aqueous HCl (0.5 mL) in isopropanol (1 mL) was warmed at 60°C for 3.5 h. 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 which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 50:1) to afford (*S*)-**1** (0.0046 g, 34%) as a homogeneous oil. (*S*)-**1**: $[\alpha]_D^{20}$ +36.1 ($c = 0.46$, $CHCl_3$). IR (neat): 3409 cm^{-1}; ^1H NMR (CCl_4:$CDCl_3$ = 5:1): 1.17 (3H, d, $J = 7$ Hz), 1.49 (3H, br.s), 1.48–1.54 (1H, m), 1.61–1.68 (1H, m), 1.62 (3H, br.s), 1.82–1.95 (2H, m), 2.21 (3H, s), 3.00 (1H, sextet, $J = 7$ Hz), 5.05 (1H, t, $J = 7$ Hz), 6.53 (1H, d, $J = 8$ Hz), 6.68 (1H, dd, $J = 2$, 8 Hz), 6.80 (1H, d, $J = 2$ Hz). ^{13}C NMR ($CDCl_3$): 17.67 (q), 20.73 (q), 21.00 (q), 25.73 (q), 26.10 (t), 31.67 (d), 37.28 (t), 115.31 (d), 124.61 (d), 127.05 (d), 127.62 (d), 130.03 (s), 132.06 (s), 132.80 (s), 150.77 (s). Anal. HRMS calcd for $C_{15}H_{22}O$ (M^+, m/z): 218.1677. Found: 218.1670. The spectral data (^1H NMR) were identical with those of the reported (±)-**1**.[5b]

3.14. Methyl 5-hydroxy-4-(2′-methoxy-5′-methylphenyl)-(2*E*)-pentenoate (*R*)-3

To a solution of (*S*)-**4** (96% e.e., 0.593 g, 2 mmol) in MeOH (1 mL) was added 0.5 M MeONa/MeOH (6 mL) at 0°C and the whole mixture was stirred at the same temperature for 30 min. After 7% aqueous $NaHCO_3$ and Et_2O 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 which was chromatographed on silica gel (30 g, *n*-hexane:AcOEt = 5:1) to afford (*R*)-**3** (0.46 g, 90% yield) as a homogeneous oil. The spectral data of (*R*)-**3** were identical with those of (*S*)-**3**. $[\alpha]_D^{26}$ +8.5 ($c = 0.51$, $CHCl_3$).

3.15. 4-(2′-Methoxy-5′-methylphenyl)pentanol (*R*)-9

(i) Tosylate (*R*)-**6** was prepared in 95% yield in the same way as for the preparation of (*S*)-**6**. The spectral data of (*R*)-**6** were identical with those of (*S*)-**6**. (ii) The successive treatment of (*R*)-**6** in the same way as for the conversion of (*S*)-**6** to (*S*)-**9** gave (*R*)-**9** in 78% overall yield from (*R*)-**3**. The spectral data of (*R*)-**9** were identical with those of (*S*)-**9**. $[\alpha]_D^{26}$ −9.5 ($c = 0.5$, $CHCl_3$).

3.16. 4-(2′-Hydroxy-5′-methylphenyl)pentanyl 3,5-dinitrobenzoate (*R*)-12

3,5-Dinitrobenzoate (*R*)-**12** was prepared in 50% overall yield from (*R*)-**9** in the same way as for the preparation of (*S*)-**12**. The spectral data of (*R*)-**12** were identical with those of (*S*)-**12**. Mp 120–122°C. $[\alpha]_D^{23}$ −11.6 ($c = 0.5$, $CHCl_3$).

3.17. 4-(2′-Methoxymethyloxy-5′-methylphenyl)pentanyl 3,5-dinitrobenzoate (*R*)-13

The MOM ether (*R*)-**13** was prepared in 86% yield in the same way as for the preparation of (*S*)-**13**. The spectral data of (*R*)-**13** were identical with those of (*S*)-**13**.

3.18. 4-(2′-Methoxymethyloxy-5′-methylphenyl)pentanol (*R*)-14

The MOM alcohol (*R*)-**14** was prepared in 74% yield in the same way as for the preparation of (*S*)-**14**. The spectral data of (*R*)-**14** were identical with those of (*S*)-**14**. $[\alpha]_D^{22}$ −10.0 ($c = 0.5$, $CHCl_3$).

3.19. 2-Methyl-(6*R*)-(2′-methoxymethyloxy-5′-methyl)-phenyl-2-heptene (*R*)-15

The MOM ether of elvirol (*R*)-**15** was prepared in 39% overall yield from (*R*)-**14** in the same way as for the preparation of (*S*)-**15**. The spectral data of (*R*)-**15** were identical with those of (*S*)-**15**. $[\alpha]_D^{27}$ −18.7 ($c = 0.16$, $CHCl_3$).

3.20. (*R*)-Elvirol 1

The (*R*)-Elvirol **1** (30 mg) was prepared in 58% yield from (*R*)-**15** in the same way as for the preparation of (*S*)-**1**. The spectral data of (*R*)-**1** were identical with those of (*S*)-**1**. $[\alpha]_D^{30}$ −37.1 ($c=0.23$, $CHCl_3$).

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