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Enantioselective synthesis of (*R*)- and (*S*)-curcumene and curcuphenol: an efficient chemoenzymatic route

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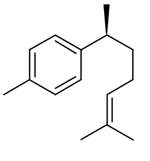
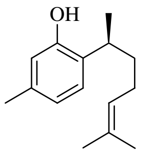
Abstract—An efficient enantioselective synthesis of curcumene and curcuphenol is described. The key intermediates, substituted butanoates **7a** and **7b** and their acids **8a** and **8b** are obtained in high enantiopurity (>99% ee) by a lipase-catalyzed kinetic resolution process. The enantiopure intermediates thus obtained were utilized for the total synthesis of the target compounds.

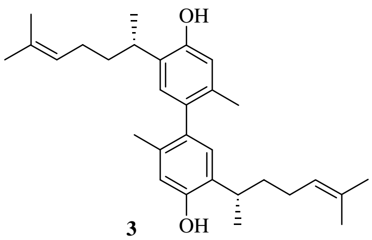
1. Introduction

Isolated from diverse natural sources, bisabolene sesquiterpenes are an important class of compounds showing a wide range of biological activities that vary with stereochemistry.[1] They are characterized by a benzylic stereogenic centre, and often carry a methyl group at this position. Amongst the numerous bisabolene sesquiterpenoids, the simplest (+)-curcumene **1** has been isolated from rhizomes of *Curcuma aromatica salisb* and is recognized as an odour component of distantly related corals, along with other members.[2] The phenolic sesquiterpene (+)-curcuphenol **2** is a major metabolite in different sponge genera and is known to possess potent H/K-ATPase inhibitory, antiplasmodial and cytotoxic activities.[3] Interestingly, its enantiomer, (−)-curcuphenol, which is isolated from gorgorian corals, exhibits antibacterial activity.[4] Recently, dimers of curcuphenols (e.g., **3**) have been isolated and assessed for their biological activities.[5] The difficulty in the introduction of a benzylic stereogenic centre in these compounds and their varied biological activities has made them challenging as well as attractive synthetic targets. Several non-racemic syntheses have been reported based on new asymmetric methodologies[6] and microbial approaches.[7] Since the biological activity of bisabolene enantiomers varies considerably,[4c,d] this underlines the need for methods to provide access to both enantiomers. In continuation of our efforts towards the development of chemoenzymatic routes for biologically active compounds,[8] we herein report the preparation of the target compounds in high enantiopurity.


(*S*)-**1**



(*S*)-**2**



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2. Results and discussion

Our synthetic approach to these sesquiterpenoids starts with commercially available substituted acetophenones such as 4-methyl-2-hydroxy acetophenone **4** and 4-methyl

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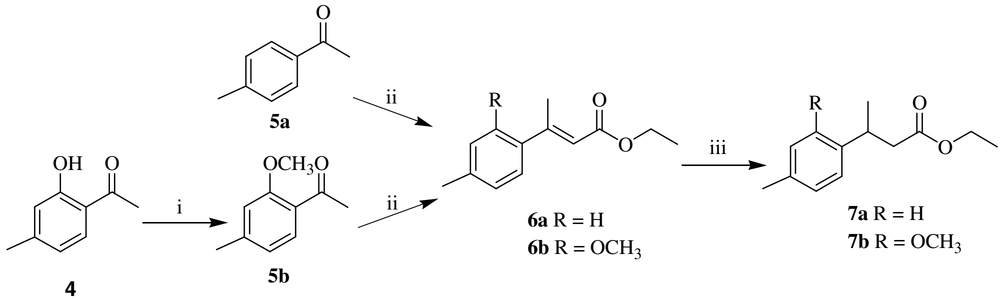


Scheme 1. Reagents: (i) Me_2SO_4, K_2CO_3, acetone; (ii) NaH, $(EtO)_2$ $POCH_2CO_2Et$, THF; (iii) H_2, 10% Pd–C, MeOH.

acetophenone **5a**. Compound **4** is protected as a methyl ether using dimethyl sulfonate and potassium carbonate under refluxing conditions to provide **5b**. These acetophenones **5a** and **5b** are converted to their α,β-unsaturated esters **6a** and **6b** by a Horner–Wadsworth–Emmons reaction using triethylphosphonoacetate and sodium hydride. The reduction of the olefinic bond of the unsaturated esters by catalytic hydrogenation provides the required key intermediates **7a** and **7b** as depicted in Scheme 1.

These intermediates have been investigated for their resolution by employing lipases. In the development of an efficient resolution protocol, the selection of the lipase plays an important role. Therefore, in the present study, ten commercially available lipases obtained from different sources have been screened for the hydrolysis of the racemic 3-substituted butanoates **7a** and **7b**. Some of the results obtained are summarized in Table 1. It has been observed that for the hydrolysis of racemic ester **7a**, lipases from *Candida cylindracea* (CCL), porcine pancreatic lipase (PPL), *Candida rugosa* (CRL) have shown low enantioselectivity, whereas papain (latex from *Carica papaya*), lipozyme (*Mucor miehei*) have shown no significant conversion after prolonged reaction time. The lipase from *Pseudomonas cepacia* (PS) and its immobilized forms PS-C, PS-D (immobilized on ceramic particles and diatomaceous earth, respectively) and lipase from *Pseudomonas fluorescens* (AK-20, Amano) provided encouraging results, with respect to conversion and enantioselectivity. Amongst them, lipase PS-D and PS have been found to provide the acid with 96% ee and 90% ee and the ester with 72% ee and 81% ee, respectively. However, excellent enantiopurity of the acid (99% ee) has been obtained from lipase PS-C and AK-20 with 92% ee and 86% ee of the ester, respectively.

In the screening of lipases for the hydrolysis of ester **7b**, similar results have been obtained. Lipases such as CRL, PPL, CCL and lipozyme were found to exhibit lower enantioselectivities while lipases PS-D and AK-20 have provided the acid with high enantiopurity (99% ee) and the ester with 76% ee and 83% ee, respectively. However, excellent enantiopurities of the acid (>99% ee) have been obtained from lipase PS-C and PS with 94% ee and 90% ee of the ester, respectively (Scheme 2). Moreover, this process is also useful in the preparation of enantiomerically enriched β-aryl carboxylic acids and in the literature where one of the methods describes the resolution of 3-phenyl methyl butanoate by lipase-catalyzed enantioselective hydrolysis.[9]

Table 1. Lipase-mediated hydrolysis of ester (±)-**7a** and (±)-**7b**[a]

Entry	Lipase	Time[b] (h)	ee (%)		c[e] (%)	Time[b] (h)	ee (%)		c[e] (%)
			Ester[c] (*R*)-**7a**	Acid[d] (*S*)-**8a**			Ester[f] (*R*)-**7b**	Acid[d] (*S*)-**8b**	
1	PS-C	15	92	99	48	16	94	>99	48
2	PS-D	18	72	96	42	17	76	99	43
3	PS	18	81	90	44	17	90	>99	47
4	AK-20	15	86	99	46	16	83	99	45
5	CCL	24	20	62	24	24	17	56	21
6	PPL	24	18	61	23	24	16	58	21
7	CRL	24	—	55	—	24	9	69	13
8	Lipozyme	—	—	—	—	36	12	60	16

[a] Conditions: 30 mg of (±)-**7a**, or **7b**, 15 mg of lipase (50% w/w), 3 mL of 0.1 M phosphate buffer NaH_2PO_4–Na_2HPO_4 (pH 7), temperature 30 °C.

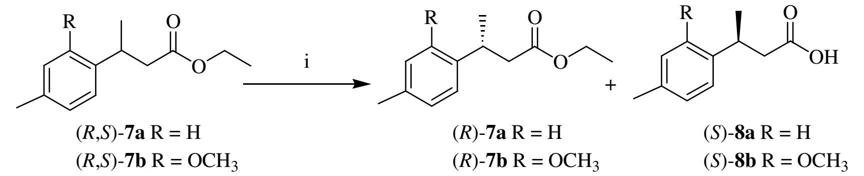
[b] Time taken for ester hydrolysis.

[c] Determined by chiral HPLC analysis employing Daicel Chiralcel AD-H column (0.46 × 25 cm); eluent: hexane/2-propanol = 95:0.5; flow rate: 0.5 mL/min; detector: 220 nm.

[d] Determined by chiral HPLC analysis employing Daicel Chiralcel AD-H column (0.46 × 25 cm); eluent: hexane/2-propanol/trifluoroacetic acid = 95:5:0.1; flow rate: 0.5 mL/min; detector: 220 nm.

[e] Conversion (c) is calculated from enantiomeric excess of substrate esters **7a**, **7b** (ee_s) and product acid **8a**, **8b** (ee_p) using the formula $c = ee_s/(ee_s + ee_p)$.

[f] Determined by chiral HPLC analysis employing Daicel Chiralcel AS-H column (0.46 × 25 cm); eluent: hexane/2-propanol = 99.5:0.5; flow rate: 0.5 mL/min; detector: 220 nm.



Scheme 2. Reagents: (i) Lipase PS-C, phosphate buffer pH 7.

Based on the above investigations, the lipase-catalyzed hydrolysis of the racemic substituted ethyl butanoates **7a** and **7b** was performed with the lipase from *P. cepacia* immobilized on ceramic particles (PS-C) in 0.1 M phosphate buffer (pH 7.0) at 30 °C. The conversion and enantiopurity of the esters and acids were analyzed at regular intervals with chiral HPLC and the reactions were stopped at about 50% of conversion. The required acids (*S*)-**8a** and (*S*)-**8b** were obtained in high enantiopurity (>99% ee) and the remaining esters (*R*)-**7a** and (*R*)-**7b** with 92% ee and 94% ee, respectively. However, in a previous report, the chiral synthons required in the synthesis of curcuphenol were obtained in enantiomeric excesses of up to 90% by sequential lipase-mediated hydrolysis and acetylation processes in two steps.[7c]

The enantiomerically pure acids (*S*)-**8a** and (*S*)-**8b** obtained by lipase-mediated resolution were reduced to the corresponding primary alcohols (*S*)-**9a**, (*S*)-**9b** by treatment with lithium aluminium hydride, which were then transformed to tosyl sulfonates (*S*)-**10a** and (*S*)-**10b** under mild conditions using tosyl chloride with triethyl amine as base. The cross coupling of tosylates with 2-methyl-1-propenyl magnesium bromide was catalyzed by copper bromide-dimethyl sulfide complex to provide the target compound curcumene (*S*)-**1** and methylated curcuphenol (*S*)-**11**. This copper reagent has been previously utilized for the S_N2 displacement of tosylates in the total synthesis of bisabolol.[10] Finally, cleavage of curcuphenol methyl ether (*S*)-**12** was carried out by using boron tribromide to provide the desired curcuphenol (*S*)-**2** (Scheme 3).

The other enantiomers of the target compounds, (*R*)-**1** and (*R*)-**2**, were also synthesized from (*R*)-**7a** and (*R*)-**7b** following the same sequential route.

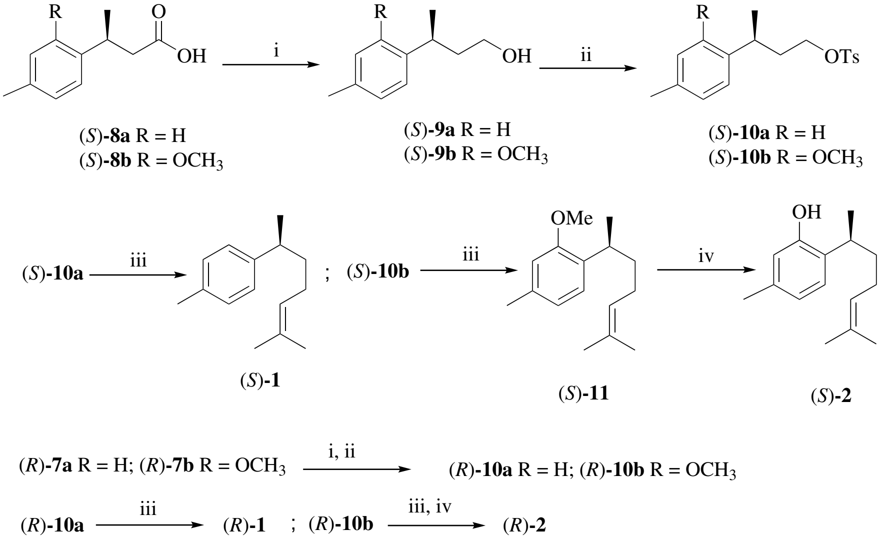
3. Conclusion

In conclusion, we have developed a simple and efficient chemoenzymatic route for the synthesis of enantiomeric pairs of curcumene and curcuphenol employing lipase-mediated kinetic resolution process in high enantiopurity. This protocol also provides an alternative route for the synthesis of related members of the bisabolene family.

4. Experimental

4.1. Materials and methods

Enzymatic reactions were carried out on an ‘Innova-4080 incubator-shaker’ at 200 rpm. Infrared spectra of neat sample are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (PPM, δ) on a 300 MHz instrument. Coupling constants are reported in Hertz (Hz). LSIMS mass spectra were recorded on Autospec



Scheme 3. Reagents: (i) LAH, THF; (ii) TsCl, TEA, DMAP, CH_2Cl_2; (iii) $(CH_3)_2C{=}CHMgBr$, $CuBr{\cdot}Me_2S$, THF; (iv) BBr_3, CH_2Cl_2.

M. with 7 kV acceleration voltage and 25 kV gun voltage. HPLC analysis was performed on an instrument that consisted of a Shimadzu SCL-10A system controller, SPA-M10A Diode array detector. The pH was checked by Cole parmer pH/ORP, 5652-10. Specific rotations were recorded on a SEPA-300 Horiba high sensitive polarimeter, fixed with a sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

Substituted acetophenones **4** and **5a**, triethyl phosphonoacetate, LAH, tosyl sulfonyl chloride, 2-methyl-1-propenyl magnesium bromide, copper iodide-dimethyl sulfide complex (used from new Aldrich bottle) and solvents were obtained commercially and used without purification. *P. cepacia* lipase immobilized on ceramic particles (PS-C) was purchased from Amano (Nagoya, Japan).

4.3. 4-Methyl-5-methoxy acetophenone 5b

To a solution of 4-methyl-5-hydroxy acetophenone **4** (3.5 g, 23.3 mmol) and anhydrous K_2CO_3 (8 g, 58.3 mmol) in 40 mL of dry acetone was added dimethyl sulfate (2.45 mL, 25.6 mmol) after which it was refluxed overnight. The reaction mixture was filtered through a Celite pad, after which acetone was evaporated under reduced pressure followed by the addition of water and extraction by ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and residue purified by silica gel column chromatography to give 3.5 g of protected phenol **5b** as a pale yellow liquid. Yield: 92%; IR (neat): 1669, 1606, 1258, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (3H, s), 2.56 (3H, s), 3.90 (3H, s), 6.71 (1H, s), 6.77 (1H, d, $J = 7.5$ Hz), 7.64 (1H, d, $J = 7.5$ Hz); EIMS (*m*/*z*): 164 (M^+); Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.49. Found: C, 73.01; H, 7.21.

4.3.1. Ethyl (*E*,*Z*)-3-(4-methylphenyl)-2-butenoate 6a. To a stirred suspension of NaH (60% in mineral oil, 1.06 g, 26.8 mmol) in dry THF (25 mL) at 0 °C, triethyl phosphonoacetate (4.8 mL, 26.8 mmol) was added dropwise under nitrogen over a period of 30 min and left for 15 min. To the resulting mixture, ketone **5a** (3 g, 22.3 mmol) was added slowly and the reaction mixture was refluxed for 2 h. The reaction mixture was quenched with a saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel to afford 3.69 g of pure ester *E*-**6a** as a colourless liquid. Yield: 81%; IR (neat): 1713, 1627, 1160, 816 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (3H, t, $J = 7.2$ Hz), 2.37 (3H, s), 2.55 (3H, d, $J = 1.6$ Hz), 4.17 (2H, q, $J = 7.2$ Hz), 6.07 (1H, d, $J = 1.6$ Hz), 7.12 (2H, d, $J = 8.0$ Hz), 7.35 (2H, d, $J =$ 8.0 Hz); EIMS (*m*/*z*): 204 (M^+); Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.39; H, 7.85. The last eluted fractions gave 0.45 g of ester *Z*-**6a** as a colourless liquid. Yield: 10%; IR (neat): 1712, 1627, 1162, 816 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, t, $J = 6.7$ Hz), 2.16 (3H, d, $J = 1.511$ Hz) 2.36 (3H, s), 3.99 (2H, q, $J = 6.7$ Hz), 5.84 (1H, d, $J = 1.5$ Hz), 7.06–7.12 (4H, m); EIMS (*m*/*z*): 204 (M^+); Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.41; H, 7.86.

4.3.2. Ethyl (*E*,*Z*)-3-(2-methoxy-4-methylphenyl)-2-butenoate 6b. To a stirred suspension of NaH (60% in mineral oil, 0.87 g, 21.9 mmol) in dry THF (25 mL) at 0 °C, triethyl phosphonoacetate (4 mL, 20.1 mmol) was added dropwise under nitrogen over a period of 30 min and left for 15 min. To the resulting mixture, ketone **5b** (3 g, 18.3 mmol) was added slowly and the reaction mixture was refluxed for 2 h. The reaction mixture was quenched with a saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel to afford 3 g of pure ester *E*-**6b** as a colourless liquid. Yield: 72%; IR (neat): 1717, 1628, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, $J = 7.3$ Hz), 2.34 (3H, s), 2.43 (3H, d, $J = 1.4$ Hz), 3.79 (3H, s), 4.15 (2H, q, $J = 7.3$ Hz), 5.81 (1H, s), 6.63 (1H, s), 6.67 (1H, d, $J = 7.3$ Hz), 6.98 (1H, d, $J = 7.3$ Hz); EIMS (*m*/*z*): 234 (M^+); Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.71; H, 7.72. The last eluted fractions gave 0.68 g of ester *Z*-**6b** as a colourless liquid. Yield: 16%; IR (neat): 1725, 1609, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, t, $J = 7.0$ Hz), 2.13 (3H, d, $J =1.5$ Hz), 2.36 (3H, s), 3.78 (3H, s), 3.97 (2H, q, $J = 7.0$ Hz), 5.88 (1H, d, $J = 1.5$ Hz), 6.66 (1H, s), 6.71 (1H, d, $J = 7.8$ Hz), 6.86 (1H, d, $J = 7.8$ Hz); EIMS (*m*/*z*): 234 (M^+); Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.71; H, 7.72.

4.3.3. Ethyl 3-(4-methylphenyl)butanoate 7a. The unsaturated esters *E*,*Z*-**6a** (3.75 g, 18.3 mmol) were dissolved in methanol (35 mL) and stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (0.8 g) for 3 h. The catalyst was removed by filtration on a Celite pad and the filtrate was concentrated and purified by column chromatography to give 3.56 g of **7a** as a colourless liquid. Yield: 95%; IR (neat): 1735, 1166, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, t, $J = 7.0$ Hz), 1.27 (3H, d, $J = 7.0$ Hz), 2.31 (3H, s), 2.37–2.62 (2H, m), 3.11–3.31 (1H, m), 4.05 (2H, q, $J = 7.0$ Hz), 7.06 (4H, s); EIMS (*m*/*z*): 206 (M^+); Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.63; H, 8.74.

4.3.4. Ethyl 3-(2-methoxy-4-methylphenyl)butanoate 7b. The unsaturated esters *E*,*Z*-**6b** (3.2 g, 13.6 mmol) were dissolved in methanol (30 mL) and stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (0.7 g) for 3 h. The catalyst was removed by filtration on a Celite pad and the filtrate was concentrated and purified by column chromatography to give 3.13 g of **7b** as a pale yellow liquid. Yield: 97%; IR (neat): 1735, 1259, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22–1.29 (6H, m), 2.33 (3H, s), 2.44 (1H, dd, $J = 8.6$ Hz, $J = 15.1$ Hz), 2.63 (1H, dd, $J = 5.7$ Hz, $J = 15.1$ Hz), 3.47–3.65 (1H, m), 3.84 (3H, s), 4.08 (2H, q, $J = 7.2$ Hz), 6.62 (1H, s), 6.67 (1H, d, $J = 7.9$ Hz), 7.00 (1H, d, $J = 7.9$ Hz); EIMS (*m*/*z*): 236 (M^+); Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.49.

4.4. General procedure for the lipase-mediated hydrolysis of ethyl 3-(4-methylphenyl)butanoate 7a

To a solution of the racemic ester (3 g, 14.5 mmol) in 40 mL of 0.1 M phosphate buffer, pH 7.0, was added 0.9 g of lipase PS-C. The reaction was performed at room temperature with magnetic stirring. The pH of the reaction mixture was adjusted to 7.0 by the concomitant addition of 0.05 M NaOH solution with a pH meter. The progress of the reaction was monitored by chiral HPLC and after approximately 45% conversion, the reaction mixture was filtered and extracted with ethyl acetate. The aqueous layer was acidified with a 2% HCl solution, saturated with sodium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure after which the residue was purified by column chromatography. The enantiopure products were analyzed by HPLC and compared with the corresponding racemic products. Acid (*S*)-**8a** (1.17 g) was obtained as a white coloured solid. Yield: 45%; mp: 95 °C; 99% ee [determined by the HPLC analysis using Chiralcel AD-H column (hexane/2-propanol/TFA = 95:5:0.1) with 0.5 mL/min flow rate ($t_{\text{major}} = 13.87$, $t_{\text{minor}} = 14.74$ min); $[\alpha]_D^{25} = +34.2$ (*c* 1.0, $CHCl_3$)]; IR (neat): 2966, 1701, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, d, $J = 6.9$ Hz), 2.31 (3H, s), 2.42–2.69 (2H, m), 3.11–3.32 (1H, m), 7.06 (4H, s); EIMS (*m*/*z*): 178 (M^+); Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.88. Unreacted ester (1.64 g) was recovered. Yield: 55%; 92% ee {determined by the HPLC analysis using Chiralcel AD-H column (hexane/2-propanol = 99.5:0.5) with 0.5 mL/min flow rate ($t_{\text{major}} = 11.92$, $t_{\text{minor}} = 12.87$ min); $[\alpha]_D^{25} = -26.2$ (*c* 3.5, $CHCl_3$)}.

4.4.1. General procedure for the lipase-mediated hydrolysis of ethyl 3-(2-methoxy-4-methylphenyl)butanoate 7b. To a solution of racemic ester (3 g, 12.7 mmol) in 40 mL of 0.1 M phosphate buffer, pH 7.0, was added 0.9 g of lipase PS-C. The reaction was performed at room temperature with magnetic stirring. The pH of the reaction mixture was adjusted to 7.0 by concomitant addition of 0.05 M NaOH solution with a pH meter. The progress of the reaction was monitored by chiral HPLC and after approximately 46% conversion, the reaction mixture was filtered and extracted with ethyl acetate. The aqueous layer was acidified with a 2% HCl solution, saturated with sodium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure after which the residue was purified by column chromatography. The enantiopure products were analyzed by HPLC and compared with the corresponding racemic products. Acid (*S*)-**8b** (1.21 g) was obtained as a viscous liquid. Yield: 46%; 99% ee [determined by the HPLC analysis using Chiralcel AD-H column (hexane/2-propanol/TFA = 95:5:0.1) with 0.5 mL/min flow rate ($t_{\text{major}} = 13.97$, $t_{\text{minor}} = 14.94$ min); $[\alpha]_D^{25} = +16.2$ (*c* 2.5, $CHCl_3$)]; IR (neat): 1707, 1506, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, d, $J = 7.5$ Hz), 2.31 (3H, s), 2.47 (1H, dd, $J = 9.0$ Hz, $J = 15.8$ Hz), 2.67 (1H, dd, $J = 9.0$ Hz, $J = 15.8$ Hz), 3.48–3.63 (1H, m), 3.81 (3H, s), 6.60 (1H, s), 6.66 (1H, d, $J = 7.5$ Hz), 6.99 (1H, d, $J = 7.5$ Hz); LC–MS (*m*/*z*): 231 $(M+Na)^+$; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.72. Unreacted ester (*R*)-**7b** (1.61 g) was recovered. Yield: 54%; 94% ee [determined by the HPLC analysis using Chiralcel AS-H column (hexane/2-propanol = 99.5:0.5) with 0.5 mL/min flow rate ($t_{\text{major}} = 13.06$, $t_{\text{minor}} = 14.12$ min); $[\alpha]_D^{25} = -2.7$ (*c* 1.0, $CHCl_3$)].

4.4.2. (*S*)-3-(4-Methylphenyl)-1-butanol 9a. To a stirred suspension of lithium aluminium hydride (0.2 g, 5.6 mmol) in 5 mL of dry THF was added a solution of (*S*)-**8a** (1 g, 5.6 mmol) in 15 mL of THF at 0 °C and stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated Na_2SO_4 in an ice bath and the slurry was filtered over Celite pad. The aqueous layer was extracted with ethyl acetate, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel to give 0.85 g of alcohol (*S*)-**9a** as a colourless liquid. Yield: 93%; $[\alpha]_D^{25} = +30.1$ (*c* 1.0, $CHCl_3$); IR (neat): 3352, 1514, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, d, $J = 7.3$ Hz), 1.72–1.86 (2H, m), 2.31 (3H, s), 2.72–2.92 (1H, m), 3.38–3.60 (2H, m), 7.04 (4H, s); EIMS (*m*/*z*): 164 (M^+); Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.4; H, 9.79.

4.4.3. (*R*)-3-(4-Methylphenyl)-1-butanol 9a. Prepared from (*R*)-**7a** by the same procedure described for (*S*)-**9a**. Yield: 91%; $[\alpha]_D^{25} = -29.6$ (*c* 1.0, $CHCl_3$).

4.4.4. (*S*)-3-(2-Methoxy-4-methylphenyl)-1-butanol 9b. To a stirred suspension of lithium aluminium hydride (0.2 g, 5.2 mmol) in 5 mL of dry THF was added a solution of (*S*)-**8b** (1.1 g, 5.2 mmol) in 15 mL of THF at 0 °C and stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated Na_2SO_4 in an ice bath and the slurry was filtered over Celite pad. The aqueous layer was extracted with ethyl acetate, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel to give 0.9 g of alcohol (*S*)-**9b** as a colourless liquid. Yield: 92%; $[\alpha]_D^{25} = +21.6$ (*c* 1.0, $CHCl_3$); IR (neat): 3422, 1505, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, d, $J = 6.9$ Hz), 1.48–1.86 (2H, m), 2.26 (3H, s), 3.19–3.32 (3H, m), 3.37–3.46 (1H, m), 3.76 (3H, s), 6.57 (1H, s), 6.64 (1H, d, $J = 7.7$ Hz), 6.95 (1H, d, $J = 7.7$ Hz); LC–MS (*m*/*z*): 217 $(M+Na)^+$; Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.12; H, 9.30.

4.4.5. (*R*)-3-(4-Methylphenyl)-1-butanol 9b. Prepared from (*R*)-**7b** by the same procedure described for (*S*)-**9b**. Yield: 92%; $[\alpha]_D^{25} = -20.2$ (*c* 1.0, $CHCl_3$).

4.4.6. (*S*)-3-(4-Methylphenyl)butyl 4-methyl-1-benzenesulfonate 10a. A solution of alcohol (*S*)-**9a** (0.75 g, 4.5 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.79 mL, 5.7 mmol) and tosyl chloride (0.94 g, 4.9 mmol) in a catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred at room temperature for 6 h, quenched with the addition of water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography to afford 1.19 g of tosylated product (*S*)-**10a** as a pale yellow liquid. Yield: 82%; $[\alpha]_D^{25} = +37.7$ (*c* 1.0, $CHCl_3$); IR (neat): 2961, 1360, 1176 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (3H, d, $J = 6.7$ Hz), 1.73–2.02 (2H, m), 2.30 (3H, s), 2.46 (3H, s), 2.67–2.90 (1H, m), 3.70–4.02 (2H, m), 6.85–7.07 (4H, m), 7.30 (2H, d, $J = 7.6$ Hz), 7.73 (2H, d, $J = 7.6$ Hz); EIMS (*m*/*z*): 318 (M^+); Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.90; H, 6.96. Found: C, 67.86; H, 6.92.

4.4.7. (*R*)-3-(4-Methylphenyl)butyl 4-methyl-1-benzenesulfonate 10a. Prepared from (*R*)-**9a** by the same procedure described for (*S*)-**10a**. Yield: 83%; $[\alpha]_D^{25} = -35.5$ (*c* 1.0, $CHCl_3$).

4.4.8. (*S*)-3-(2-Methoxy-4-methylphenyl)butyl 4-methyl-1-benzenesulfonate 10b. A solution of alcohol (*S*)-**9b** (0.75 g, 3.8 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.67 mL, 4.8 mmol) and tosyl chloride (0.79 g, 4.1 mmol) in a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 6 h, quenched with the addition of water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography to afford 1.12 g of tosylated product (*S*)-**10b** as a pale yellow liquid. Yield: 84%; $[\alpha]_D^{25} = +14.2$ (*c* 3.6, $CHCl_3$); IR (neat): 2960, 1359, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, $J = 6.9$ Hz), 1.79–2.01 (2H, m), 2.30 (3H, s), 2.44 (3H, s), 3.11–3.24 (1H, m), 3.76 (3H, s), 3.86–3.94 (2H, m), 6.57 (1H, s), 6.62 (1H, d, $J = 7.5$ Hz), 6.87 (1H, d, $J = 7.5$ Hz), 7.27 (1H, d, $J = 7.9$ Hz), 7.71 (1H, d, $J = 7.9$ Hz); EIMS (*m*/*z*): 348 (M^+); Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.49; H, 6.94. Found: C, 65.39; H, 6.89.

4.4.9. (*R*)-3-(2-Methoxy-4-methylphenyl)butyl 4-methyl-1-benzenesulfonate 10b. Prepared from (*R*)-**9b** by the same procedure described for (*S*)-**10b**. Yield: 82%; $[\alpha]_D^{25} = -13.6$ (*c* 1.0, $CHCl_3$).

4.4.10. (*S*)-Curcumene 1. A suspension of copper bromide-dimethyl sulfide complex (0.24 g, 1.1 mmol) in 10 mL of dry THF was treated with a 2-methyl-1-propenyl magnesium bromide solution (11.7 mmol, in 0.5 M solution of THF) at −60 °C. 0.75 g of (*S*)-**10a** (2.3 mmol) as a solution in 5 mL of THF was added dropwise and then warmed to 0 °C to room temperature and stirred for 3–4 h. Saturated NH_4Cl solution was added and the aqueous layer was extracted with diethyl ether. The ether layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual mass was chromatographed on silica gel to afford 0.32 g of (*S*)-curcumene **1**. Yield: 67%; $[\alpha]_D^{25} = +42.7$ (*c* 1.0, $CHCl_3$), {lit.[2c] $[\alpha]_D^{20} = +43.5$ (*c* 1.0, $CHCl_3$)}; IR (neat): 2859, 1513, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, d, $J = 7.1$ Hz), 1.55 (3H, s), 1.57–1.68 (2H, m), 1.69 (3H, s), 1.82–1.98 (2H, m), 2.34 (3H, s), 2.56–2.74 (1H, m), 5.13-5.05 (1H, m), 7.03–7.12 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.67, 20.92, 22.49, 25.73, 26.18, 38.46, 39.00,124.55, 126.88, 128.93, 131.36, 135.13, 144.63; EIMS (*m*/*z*): 202 (M^+); Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.01; H, 10.92.

4.4.11. (*R*)-Curcumene 1. Prepared from (*R*)-**10a** by the same procedure described for (*S*)-**1**. Yield: 65%; $[\alpha]_D^{25} = -39.8$ (*c* 1.2, $CHCl_3$).

4.4.12. (*S*)-Methylated curcuphenol 11. A suspension of copper bromide-dimethyl sulfide complex (0.23 g, 1.5 mmol) in 10 mL dry THF was treated with 2-methyl-1-propenyl magnesium bromide solution (15 mmol, in 0.5 M solution of THF) at −60 °C. 1.05 g of (*S*)-**10b** (3 mmol) as a solution in 5 mL of THF was added dropwise and then warmed to 0 °C to room temperature and stirred for 3–4 h. Saturated NH_4Cl solution was added and the aqueous layer was extracted with diethyl ether. The ether layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual mass was chromatographed on silica gel to afford 0.5 g of methylated curcuphenol (*S*)-**11**. Yield: 72%; $[\alpha]_D^{25} = +7.1$ (*c* 1.0, $CHCl_3$), {lit.[7a] $[\alpha]_D^{20} = +7.8$ (*c* 1.0, $CHCl_3$)}; IR (neat): 1611, 1505, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, $J = 6.6$ Hz), 1.33–1.76 (2H, m), 1.53 (3H, s), 1.67 (3H, s), 1.79–1.99 (2H, m), 2.31 (3H, s), 3.02–3.20 (1H, m), 3.79 (3H, s), 5.08 (1H, t), 6.62 (1H, s), 6.68 (1H, d, $J = 7.3$ Hz), 6.99 (1H, d, $J = 7.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.57, 21.09, 21.36, 25.70, 26.27, 31.40, 37.15, 55.27, 111.43, 121.08, 124.88, 126.52, 131.00, 132.80, 136.15, 156.13; EIMS (*m*/*z*): 232 (M^+); Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.67; H, 10.36.

4.4.13. (*R*)-Methylated curcuphenol 11. Prepared from (*R*)-**10b** by the same procedure described for (*S*)-**11**. Yield: 74% $[\alpha]_D^{25} = -5.8$ (*c* 1.0, $CHCl_3$).

4.4.14. (*S*)-Curcuphenol 2. To a solution of (*S*)-**11** (0.45 g, 1.9 mmol) in 10 mL of dry THF was added boron tribromide (0.23 mL, 2.4 mmol) under nitrogen at −78 °C and warmed to room temperature and stirred for 1 h. The reaction mixture was poured in ice-cold water and stirred for half an hour. The aqueous layer was extracted with CH_2Cl_2, washed with brine solution, dried with anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure and the residue obtained was chromatographed to provide 0.31 g of (*S*)-curcuphenol **2.** Yield: 68%; $[\alpha]_D^{25} = +23.5$ (*c* 1.3, $CHCl_3$), {lit.[3c] $[\alpha]_D^{20} = +24.6$ (*c* 1.0, $CHCl_3$)}; IR (neat): 3453, 1618, 1583, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, $J = 6.9$ Hz), 1.51 (3H, s), 1.54–1.65 (2H, m), 1.67 (3H, s), 1.84–1.96 (2H, m), 2.26 (3H, s), 2.84–3.03 (1H, m), 4.60 (1H, br s), 5.03–5.12 (1H, m), 6.56 (1H, s), 6.64 (1H, d, $J = 7.9$ Hz), 6.98 (1H, d, $J = 7.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 20.9, 21.1, 25.7, 26.2, 31.5, 37.3, 116.2, 121.7, 124.7, 126.9, 130.0, 131.9, 136.5 152.9; EIMS (*m*/*z*): 218 (M^+); Anal. Calcd for $C_{15}H_{22}O$: C, 85.52; H, 10.16. Found: C, 85.47; H, 10.07.

4.4.15. (*R*)-Curcuphenol 2. Prepared from (*R*)-**11** by the same procedure described for (*S*)-**2**. Yield: 65%; $[\alpha]_D^{25} = -20.9$ (*c* 1.0, $CHCl_3$).

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