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Total synthesis of (*R*)- and (*S*)-turmerone and (7*S*,9*R*)-bisacumol by an efficient chemoenzymatic approach

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ABSTRACT

An enantioselective synthesis of (*R*)-, (*S*)-turmerone and (7*S*,9*R*)-bisacumol is described. The enantiomerically pure key intermediates, a substituted butanoate ester and acid are utilized in the synthesis of both enantiomers of turmerone. The lipase catalyzed resolution studies of the acetate of bisacumol have been exploited towards the total synthesis of the naturally occurring cytotoxic sesquiterpene, (7*S*,9*R*)-bisacumol with high diastereoselectivity (94% de).

1. Introduction

Biocatalysis has increasingly become a useful tool for organic chemists in the synthesis of biologically active natural and unnatural products.[1] The sesquiterpenoid class of natural products possessing a bisabolane framework are interesting synthetic targets because they exhibit a diverse range of biological activities.[2] Curcuphenol **1** is an important member of this class of compounds and its individual isomers display different biological effects.[3] The target sesquiterpene, (*S*)-(+)-*ar*-turmerone **2** is one of the primary constituents of essential oils obtained from the rhizomes of *Curcuma longa* and is reported to exhibit cytotoxic, anti-inflammatory inhibition of platelet aggregation, and anti-venom properties.[4] It is a significantly more potent platelet inhibitor than aspirin against platelet aggregation induced by collagen.[5] Its unnatural isomer (*R*)-**2** has been utilized as a demonstration target in the development of new synthetic methodologies[6] and is also a precursor for other sesquiterpenes such as (*R*)-*ar*-himachalene **3,** a sex pheromone produced by the male flea beetle *Aphthona flava.*[7] (7*S*,9*R*)-Bisacumol **4**, another sesquiterpene, is isolated from the rhizomes of *Curcuma xanthorrhiza, Curcuma zedaria* and the leaves of *Baccharis dracunculifolia,*[8] and exhibits potent cytotoxic activity, particularly against leukaemia (Fig. 1).[9]

Several racemic and some stereoselective syntheses of turmerone **2** have already been reported.[2,10] Usually, asymmetric approaches either employ environmentally unsustainable metal-based catalysts or microbial processes to provide the single isomeric form. To the best of our knowledge, there is only one report on the synthesis of (7*S*, 9*R*)-**4**.[11] In a continuation of our earlier investigations towards the development of chemoenzymatic routes for biologically active compounds and their intermediates,[12] we herein report the enantioselective synthesis of both forms of turmerone, as well as the total synthesis of (7*S*,9*R*)-bisacumol in high enantiopurity.

2. Results and discussion

2.1. Synthesis of enantiomerically pure (*R*)- and (*S*)-*ar*-turmerone

Herein, for the synthesis of the target sesquiterpenoids, the enantiomerically pure substituted butanoate ester and acid were obtained by lipase-mediated resolution as reported[12c] in our previous studies. The kinetic resolution of the racemic butanoate **5** was performed by the lipase from *Pseudomonas cepacia* immobilized on ceramic particles (PS-C) at a neutral pH to provide acid (*S*)-**6** in 99% ee and ester (*R*)-**5** in 92% ee (Scheme 1).

The enantiomerically pure acid (*S*)-**6** was reduced to the primary alcohol (*S*)-**7** by employing lithium aluminium hydride as the reducing agent in quantitative yield. The oxidation of (*S*)-**7** to aldehyde (*S*)-**8** was carried out by a Swern oxidation protocol in good yields. The nucleophilic addition of the Grignard reagent, 2-methyl-1-propenyl magnesium bromide to aldehyde (*S*)-**8** provides a diastereomeric mixture of bisacumol **4**. The oxidation of **4** using oxalyl chloride and dimethyl sulfoxide affords the target compound (*S*)-turmerone **1**. Similarly, the enantiomerically pure ester (*R*)-**5** was subjected to reduction, followed by oxidation and nucleophilic addition to provide (*R*)-turmerone **1** in good yield. The direct reduction of acid (*S*)-**6** and ester (*R*)-**5** to the aldehyde (*S*)-**8** was found to be sluggish and low yielding. In the literature, (*R*)-**1** has been utilized in the synthesis of (*R*)-*ar*-himachalene **5**, which is a male pheromone component produced by the flea *A. flava* (Scheme 2).

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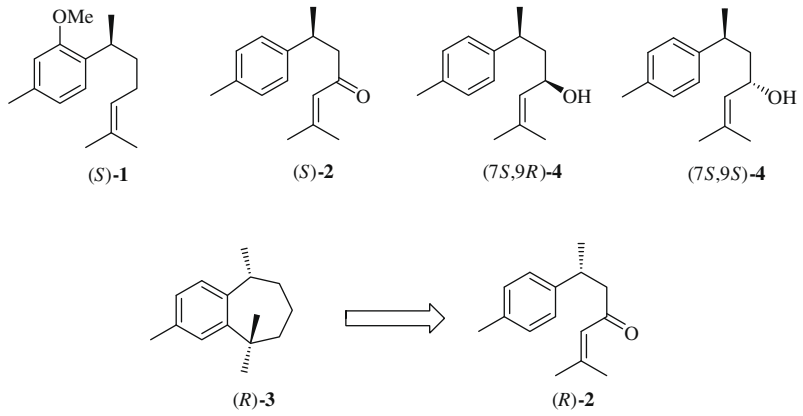
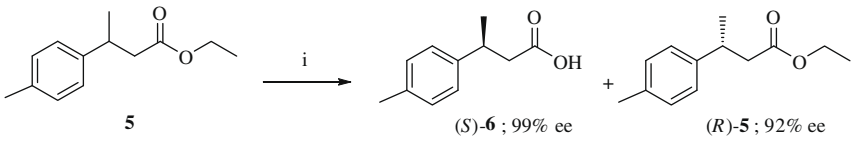


Figure 1.

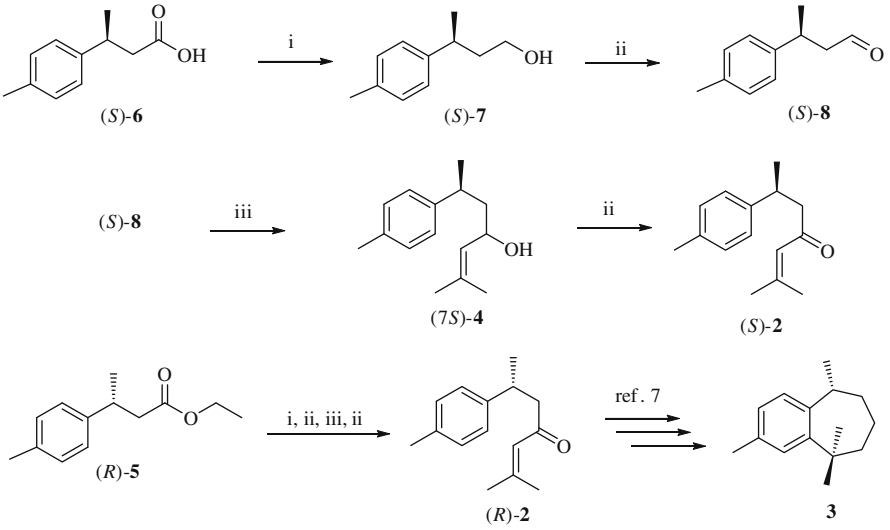


Scheme 1. Reagents and conditions: (i) lipase PS-C, phosphate buffer, pH 7, 30 °C.

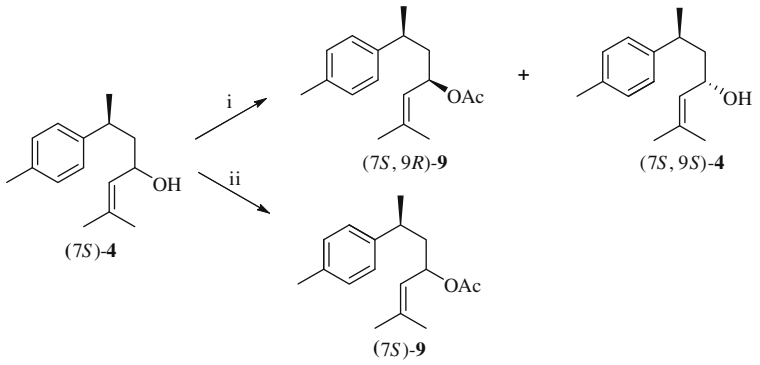
2.2. Lipase-mediated kinetic resolution: synthesis of (7*S*,9*R*)-bisacumol

The diastereomeric mixture of bisacumol **4** has been subjected to lipase-mediated kinetic resolution to obtain the naturally occurring (7*S*,9*R*)-bisacumol **4**. Lipases from different sources were screened for the transesterification of bisacumol (7*S*)-**4** using isopropenyl acetate as acyl donor in diisopropyl ether at temperatures up to 45 °C. However, even after a prolonged reaction time (7–8 days), little conversion (5–7%) was observed. This prompted us to investigate the lipase-catalyzed hydrolysis of bisacumol acetate **9** in order to achieve an effective kinetic resolution. Acetate **9** was synthesized in good yield by the acetylation of (7*S*)-**4** with acetic anhydride, employing triethyl amine as the base in a catalytic amount of 4-dimethylaminopyridine (Scheme 3).

Herein, eight commercially available lipases from different sources have been screened for the hydrolysis of the racemic acetate of bisacumol **9**, as the selection of the lipase plays an important role in the development of an efficient resolution protocol. Some of the results obtained are summarized in Table 1. It has been observed that for the hydrolysis of racemic acetate **9**, all the enzymes screened provide the acetate (7*S*,9*S*)-**9** in low enantioselectivity with enantiomeric excesses in the range of 25–62% after incubation for 7 days. The lipase from *Pseudomonas fluorescens* (AK-20) and the immobilized form of *Candida antartica* (CAL-B) afforded the alcohol in around 85% de and the acetate in 54% de and 43% de, respectively. The rate of hydrolysis for the lipase from *Candida rugosa* (AYS) is comparatively higher but it provides the required alcohol in lower enantiopurity. The lipases from *P. cepacia* (PS) and its immobilized forms PS-C and PS-D (immobilized on



Scheme 2. Reagents and conditions: (i) LAH; THF, rt; (ii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C; (iii) 2-methyl-1-propenyl magnesium bromide, THF, −60 °C.



Scheme 3. Reagents and conditions: (i) lipase, IPA, DIPE, 45 °C; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2.

Table 1
Lipase-mediated hydrolysis of bisacumol acetate **9**[a]

Entry	Lipase	Time[b]	Alcohol (7*S*,9*R*)-**4** de[c] (%)	Acetate (7*S*,9*S*)-**9** de[d] (%)	*c*[e] (%)
1	PS	7	91	60	40
2	PS-C	7	94	62	41
3	PS-D	7	88	42	32
4	AYS	7	60	85	57
5	AK-20	7	85	54	39
6	CAL-B	7	84	43	34
7	PPL	7	82	25	23
8	Lipozyme	7	75	28	27

[a] Conditions: 30 mg of acetate **9**, 15 mg of lipase (50% w/w), 3 mL of 0.1 M phosphate buffer NaH_2PO_4–Na_2HPO_4 (pH 7), temperature 35 °C.
[b] Time taken for the acetate hydrolysis in days.
[c] Determined by HPLC analysis employing Daicel Chiralcel AD-H column (0.46 × 25 cm); eluent: *n*-hexane:2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 230 nm.
[d] Determined by HPLC analysis employing Daicel Chiralcel OB-H column (0.46 × 25 cm); eluent: *n*-hexane:2-propanol = 99:1; flow rate: 0.25 mL/min; detector: 230 nm.
[e] Conversion (*c*) is calculated from the enantiomeric excess of the substrate acetate (de_s) and product alcohol (de_p) using the formula: $c = de_s/(de_s + de_p)$.

ceramic particles and diatomaceous earth, respectively) give better results with respect to the enantiopurity of the required alcohol. Amongst them, lipase PS and PS-D provide the alcohol in 91% de and 88% de, respectively, whereas the acetate was obtained in 60% de and 42% de, respectively. However, the lipase PS-C afforded the naturally occurring bisacumol (7*S*,9*R*)-**4** in 94% de and its acetate (7*S*,9*S*)-**9** in 62% de. Increasing the reaction time caused the enantiopurity of the required bisacumol to decrease.

Based on the above investigations, the lipase-mediated kinetic resolution of the racemic acetate of bisacumol **9** was performed with the lipase from *P. cepacia* immobilized on ceramic particles (PS-C) in 0.1 M phosphate buffer (pH 7.0) at 35 °C. The conversion and enantiopurity of the ester and acid were analyzed at regular intervals by employing chiral columns on HPLC and the reaction was stopped at around 40% conversion. The naturally occurring bisacumol (7*S*,9*R*)-**4** was obtained in 94% diastereomeric excess and the remaining acetate (7*S*,9*S*)-**9** in 62% de. Acetate (7*S*,9*S*)-**9** was deacetylated by employing anhydrous potassium carbonate in refluxing methanol to afford (7*S*,9*S*)-*epi*-bisacumol **4** in lower enantiopurity (Scheme 4).

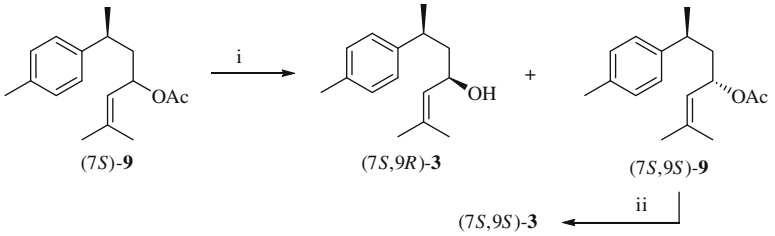
3. Conclusion

In conclusion, we have developed an efficient chemoenzymatic route for the synthesis of both enantiomers of *ar*-turmerone, (7*S*, 9*R*)-bisacumol and (7*S*, 9*S*)-*epi*-bisacumol in high enantiopurity. In addition to the total synthesis of the target compounds, this protocol provides an alternative route for the synthesis of related members of the bisabolene family such as (*R*)-*ar*-himachalene, a male pheromone component produced by the flea *A. flava*.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on an 'Innova-4080 incubator-shaker' at 200 rpm. Infrared spectra of neat samples 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



Scheme 4. Reagents and conditions: (i) lipase PS-C, phosphate buffer, pH 7, 30 °C; (ii) and. K_2CO_3, MeOH.

Autospec 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. Specific rotations were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

Lithium aluminium hydride, oxalyl chloride, dimethyl sulfoxide, 2-methyl-1-propenyl magnesium bromide 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. Lipase-mediated hydrolysis of ethyl 3-(4-methylphenyl) butanoate 5

To a solution of racemic ester **5** (5.0 g, 24.2 mmol) in 50 mL of 0.1 M phosphate buffer, pH 7.0, 1.5 g of lipase PS-C was added. The reaction was performed at room temperature with magnetic stirring. The pH of the reaction mixture was adjusted to 7.0 with a pH meter by concomitant addition of 0.05 M NaOH solution. The reaction was stopped at around 45% conversion and purified to give 1.94 g of acid (*S*)-**6** as a white solid. Yield: 45%; mp: 95 °C; 99% ee [determined by the HPLC analysis using Chiralcel AD-H column (*n*-hexane:2-propanol:TFA = 95:5:0.1) with 0.5 mL/min flow rate (t_{major} = 13.75, t_{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%. In addition to the acid, 2.58 g of unreacted ester (*R*)-**5** was recovered. Yield: 52%; 92% ee [determined by the HPLC analysis using Chiralcel AD-H column (*n*-hexane:2-propanol = 99.5:0.5) with 0.5 mL/min flow rate (t_{minor} = 11.54, t_{major} = 12.23 min); $[\alpha]_D^{25} = -26.2$ (*c* 3.5, $CHCl_3$)]; 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.

4.4. (*S*)-3-(4-Methylphenyl)-1-butanol 7

To a stirred suspension of lithium aluminium hydride (0.4 g, 10.6 mmol) in 10 mL of dry THF was added a solution of (*S*)-**6** (1.9 g, 10.6 mmol) in 20 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 a 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 1.62 g of alcohol (*S*)-**7** as a colourless liquid after purification. 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.

4.5. (*R*)-3-(4-Methylphenyl)-1-butanol 7

Prepared from (*R*)-**5** by the same procedure described for (*S*)-**7**. Yield: 91%; $[\alpha]_D^{25} = -28.6$ (*c* 1.0, $CHCl_3$).

4.6. (*S*)-3-(4-Methylphenyl)butanal 8

To a stirred solution of oxalyl chloride (0.87 mL, 10.1 mmol) in 15 mL of dry dichloromethane at −78 °C, dimethyl sulfoxide (0.81 mL, 11.4 mmol) dissolved in 10 mL of dry DCM was added dropwise and stirred for over 15 min. To the resulting system, (*S*)-**7** (1.5 g, 9.1 mmol) dissolved in 5 mL of dry DCM was added dropwise and the reaction mixture was stirred for 1.5–2 h at −78 °C, followed by addition of triethylamine (3.04 mL, 22.7 mmol). The system was warmed to 0 °C and quenched with addition of water. The aqueous layer was extracted with dichloromethane, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on column chromatography to give 1.22 g of aldehyde (*S*)-**8** as colourless liquid. Yield: 83%; $[\alpha]_D^{25} = +41.9$ (*c* 1.0, $CHCl_3$), {lit[10c] $[\alpha]_D^{20} = +39.6$ (*c* 1.0, $CHCl_3$)}; IR (neat): 2926, 1698, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 7.1 Hz), 2.34 (3H, s), 2.52–2.79 (2H, m), 3.22–3.41 (1H, m), 7.04 (4H, s), 9.68 (1H, s); EIMS (*m/z*): 162 (M^+); Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.40; H, 8.65.

4.7. (*R*)-3-(4-Methylphenyl)butanal 8

Prepared from (*R*)-**7** by the same procedure described for (*S*)-**8**. Yield: 85%; $[\alpha]_D^{25} = -35.2$ (*c* 1.0, $CHCl_3$), {lit[6a] $[\alpha]_D^{20} = -58.0$ (*c* 0.84, $CHCl_3$)}.

4.8. (7*S*)-Bisacumol 4

To a stirred solution of aldehyde (*S*)-**8** (1.0 g, 6.2 mmol) in 10 mL of dry THF, 2-methyl-1-propenyl magnesium bromide solution (12.3 mmol, in 0.5 M solution of THF) was added dropwise at −60 °C and stirred for 1 h. The reaction was quenched by adding saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether. The ether layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on column chromatography to give 0.96 g of a diastereomeric mixture of (7*S*)-**4** as a colourless liquid. Yield: 72%; IR (neat): 3352, 2924, 1448, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, d, *J* = 7.3 Hz), 1.55 and 1.58 (3H, s, diastereomeric), 1.73 and 1.78 (3H, s, diastereomeric), 1.75–1.86 (1H, m), 1.89–1.98 (1H, m), 2.31 and 2.32 (3H, s, diastereomeric), 2.67–2.92 (1H, m), 4.14–4.25 (1H, m), 5.15 (1H, d, *J* = 10.2 Hz), 7.05–7.13 (4H, m); EIMS (*m/z*): 218 (M^+); Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.50; H, 10.13.

4.9. (7*R*)-Bisacumol 4

Prepared from (*R*)-**8** by the same procedure described for (7*S*)-**4** to provide diastereomeric mixture of (7*R*)-**4.** Yield: 73%.

4.10. (*S*)-Turmerone 2

To a stirred solution of oxalyl chloride (0.11 mL, 1.3 mmol) in 2–3 mL of dry dichloromethane at −78 °C, dimethyl sulfoxide (0.10 mL, 1.4 mmol) in 1–2 mL of dry DCM was added dropwise and stirred for over 15 min. To the resulting system, a diastereomeric mixture of (7*S*)-**4** (0.25 g, 1.1 mmol) dissolved in 2 mL of dry DCM was added dropwise and the reaction mixture was stirred for 1.5–2 h at −78 °C, followed by the addition of triethylamine (0.26 mL, 2.8 mmol). The system was warmed to 0 °C and quenched with addition of water. The aqueous layer was extracted with dichloromethane, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on column chromatography to give 0.13 g of the target molecule (*S*)-**2** as a colourless liquid. Yield: 53%; $[\alpha]_D^{25} = +80.2$ (*c* 1.2, $CHCl_3$), {lit[11] $[\alpha]_D^{20} = +82.7$ (*c* 6.8, $CHCl_3$)}; IR

(neat): 2960, 1692, 1517, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, d, J = 7.0 Hz), 1.87 (3H, s), 2.02 (3H, s), 2.32 (3H, s), 2.53–2.79 (2H, m), 3.21–3.36 (1H, m), 6.02 (1H, s), 7.02 (4H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.66, 20.92, 21.98, 27.51, 35.21, 52.70, 124.42, 126.74, 129.12, 135.48, 144.02, 155.62, 199.94; EIMS (m/z): 216 (M^+); Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.21; H, 9.26.

4.11. (*R*)-Turmerone 2

Prepared from the diastereomeric mixture of (7*R*)-**4** by the same procedure described for (*S*)-**2**. Yield: 52%; $[\alpha]_D^{25} = -67.8$ (c 1.0, $CHCl_3$), {Lit[6a] $[\alpha]_D^{20} = -58.0$ (c 6.8, $CHCl_3$)}.

4.12. (7*S*)-Bisacumol acetate 9

A solution of a diastereomeric mixture of alcohol (7*S*)-**4** (0.50 g, 1.7 mmol) in CH_2Cl_2 (8 mL) was treated with triethylamine (1.15 mL, 8.2 mmol) and acetic anhydride (0.51 mL, 5.5 mmol) at 0 °C in a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 3 h and quenched with the addition of water followed by extraction with CH_2Cl_2. The organic layer was washed with sodium bicarbonate solution, followed by a brine solution and dried over anhydrous Na_2SO_4. The residue obtained on removal of solvent under reduced pressure was purified by column chromatography to provide 0.65 g of pure acetate (7*S*)-**9**. Yield: 92%; IR (neat): 2926, 1734, 1241, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 and 1.25 (3H, d, J = 7.5 Hz, diastereomeric), 1.55 and 1.60 (3H, s, diastereomeric), 1.68 and 1.72 (3H, s, diastereomeric), 1.74–2.02 (2H, m), 1.92 and 1.99 (3H, s, diastereomeric), 2.31 (3H, s), 2.57–2.77 (1H, m), 4.99–5.11 (1H, m), 5.24–5.42 (1H, m), 7.02–7.12 (4H, m); EIMS (m/z): 260 (M^+); Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.36; H, 9.24.

4.13. Lipase-mediated hydrolysis: Synthesis of (7*S*,9*R*)-bisacumol 4

To a solution of acetate (7*S*)-**9** (0.6 g, 2.3 mmol) in 5 mL of 0.1 M phosphate buffer, pH 7.0, was added 0.2 g of lipase PS-C. The reaction was performed at 35 °C 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 HPLC and after approximately 40% conversion, the reaction mixture was filtered and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure and the residue obtained was purified by column chromatography. The enantiopure products were analyzed by HPLC and compared with the corresponding racemic products. Then, 0.24 g of naturally occurring bisacumol (7*S*, 9*R*)-**4** was obtained as a colourless liquid. Yield: 40%; 94% de [determined by the HPLC analysis using Chiralcel AD-H column (*n*-hexane: 2-propanol = 90:10) with 0.5 mL/min flow rate (t_{major} = 9.89, t_{minor} = 10.79 min); $[\alpha]_D^{25} = +14.8$ (c 1.0, $CHCl_3$), {lit[11] $[\alpha]_D^{20} = +15.6$ (c 8.4, $CHCl_3$)}; IR (neat): 3353, 2925, 1447, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, d, J = 7.1 Hz), 1.55 (3H, s), 1.73 (3H, s), 1.75–1.86 (1H, m), 1.89–1.98 (1H, m), 2.31 (3H, s), 2.67–2.92 (1H, m), 4.14–4.25 (1H, m), 5.15 (1H, d, J = 10.2 Hz), 7.05–7.13 (4H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.20, 20.92, 22.91, 25.62, 35.62, 45.89, 66.85, 126.86, 128.06, 128.99, 133.82, 135.35, 143.98; EIMS (m/z): 218 (M^+); Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.55; H, 9.89. 0.32 g of unreacted acetate (7*S*,9*S*)-**9** was recovered. Yield: 55%; 62% de [determined by the HPLC analysis using Chiralcel OB-H column (*n*-hexane:2-propanol = 99:1) with 0.25 mL/min flow rate (t_{major} = 21.22, t_{minor} = 23.13 min); $[\alpha]_D^{25} = -21.4$ (c 1.0, $CHCl_3$). The spectroscopic data of the acetate were identical to that of **9**.

4.14. (7*S*,9*S*)-*epi*-Bisacumol 4

To (7*S*,9*S*)-**9** (0.2 g, 0.7 mmol) in methanol (20 mL), anhydrous K_2CO_3 (0.3 g, 2.1 mmol) was added and stirred at room temperature for 2 h. Potassium carbonate was removed by filtration through a Celite pad and the solvent evaporated under reduced pressure. The residue was purified by column chromatography to afford 0.15 g of (7*S*, 9*S*)-**4** as colourless liquid. Yield: 92%, $[\alpha]_D^{25} = +4.1$ (c 1.0, $CHCl_3$), {lit[11] $[\alpha]_D^{20} = +9.4$ (c 9.7, $CHCl_3$)}. IR (neat): 3352, 2925, 1446, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, d, J = 7.1 Hz), 1.57 (3H, s), 1.75 (3H, s), 1.75–1.86 (1H, m), 1.89–1.98 (1H, m), 2.33 (3H, s), 2.69–2.91 (1H, m), 4.18–4.26 (1H, m), 5.14 (1H, d, J = 10.0 Hz), 7.05–7.12 (4H, s). The other spectroscopic data were identical to that of (7*S*, 9*R*)-**4**.

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