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The enantiomers of *Iralia*®: preparation and odour evaluation

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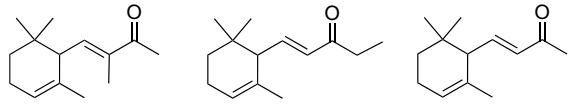
Abstract—The enantiomers of methyl ionones **1** and **2** were prepared by an enzyme-catalysed approach. Their odour properties were evaluated by skilful perfumers.

1. Introduction

Methyl ionones **1** and **2** (Scheme 1) are important violet odourants, which have not been found in nature. They were first prepared by Tiemann in 1893[1] by reaction of citral with ethyl methyl ketone, followed by cyclisation. They were commercialised as a mixture by Firmenich in 1903 under the trade name of *Iralia*®. In 1905, François Coty made use of *Violettone*® (α-ionone, **3**) and *Iralia*® to create the great classic *L'Origan*,[2] a perfume with a warm oriental character.



Scheme 1.

Modern fine and functional perfumery is always searching new odourants to enrich the panel of odourous molecules to be used in commercial products. This search is performed either by an accurate investigation of the relationship between odour and structure or by serendipitous discoveries.[3] With the aim of providing a contribution to the knowledge of the odour properties of molecules, we have been preparing in recent years the enantiomerically pure stereoisomers of chiral commercial fragrances by enzyme-mediated methods. Unpredictable examples of enantioselectivity in the odour perception of chiral odourants have been identified.[4]

Herein we report on the preparation of the enantiomers of the chiral methyl ionones **1** and **2**, and on the evaluation of their odour properties by skilful perfumers.

2. Results and discussion

Commercial α-isomethylionone **1** (Isoraldeine 95—Givaudan) was reduced with sodium boron hydride in CH_2Cl_2/methanol 2:1 to give a 1:1 mixture of the two diastereoisomeric alcohols (±)-**4a** and (±)-**4b** (Scheme 2). These latter derivatives were converted into 4-nitrobenzoates (±)-**5a** and (±)-**5b**, and were crystallised from methanol (four crystallizations). The crystalline product was found to be the single diastereoisomer (±)-**5a** (de = 98%, ^{1}H NMR), whose relative configuration was established by X-ray diffraction analysis (Fig. 1). The mother liquors were enriched in the other diastereoisomer (±)-**5b**, which was recovered with de = 94% (^{1}H NMR), after three crystallizations from hexane.

Racemic alcohol **4a**, obtained by saponification of ester (±)-**5a**, was submitted to Lipase PS—mediated transesterification in *t*-butyl methyl ether in the presence of vinyl acetate. After 24 h, acetate (−)-**6a** and alcohol (+)-**4a** were recovered as pure compounds from the reaction mixture by column chromatography. According to the same procedure, acetate (+)-**6b** and alcohol (−)-**4b** were obtained starting from racemic **5b**. Then, MnO_2 oxidation of alcohol (−)-**4a**, prepared from (−)-**6a** (Scheme 3), afforded (−)-**1** (ee = 98%, chiral GC), while the reaction of (+)-**4b**,

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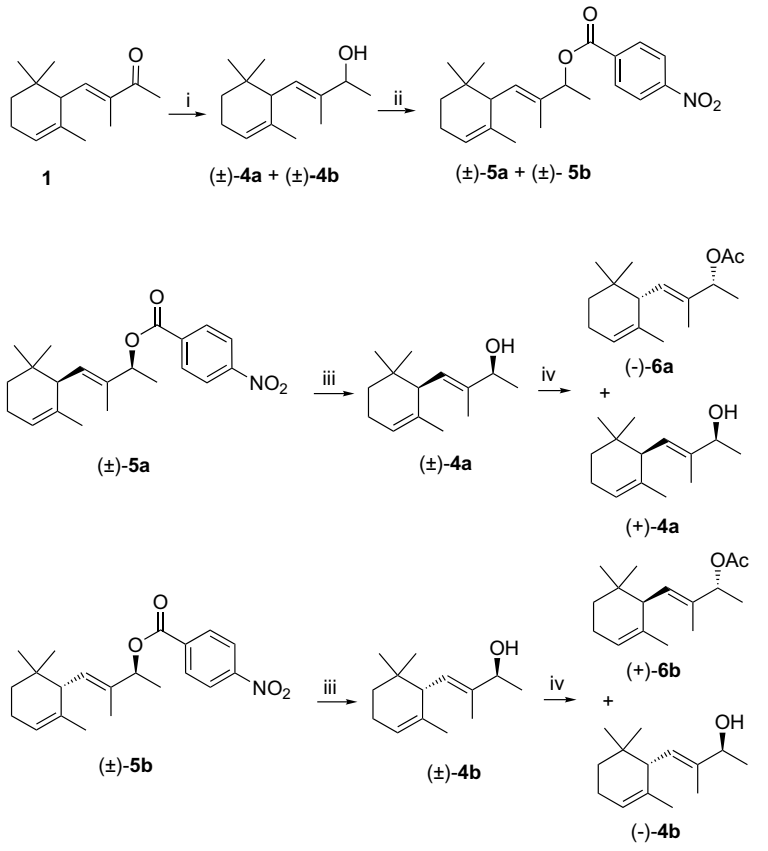


Scheme 2. Reagents: (i) $NaBH_4$, CH_2Cl_2, MeOH; (ii) *p*-nitrobenzoyl chloride, pyridine; (iii) MeOH, KOH; (iv) *t*-ButOMe, vinyl acetate, lipase PS; column chromatography.

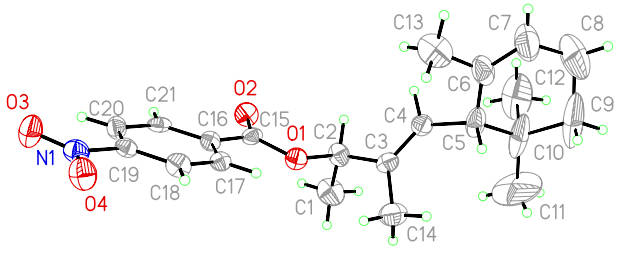
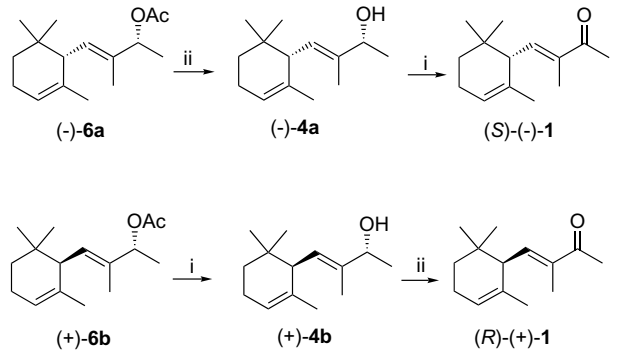


Figure 1.

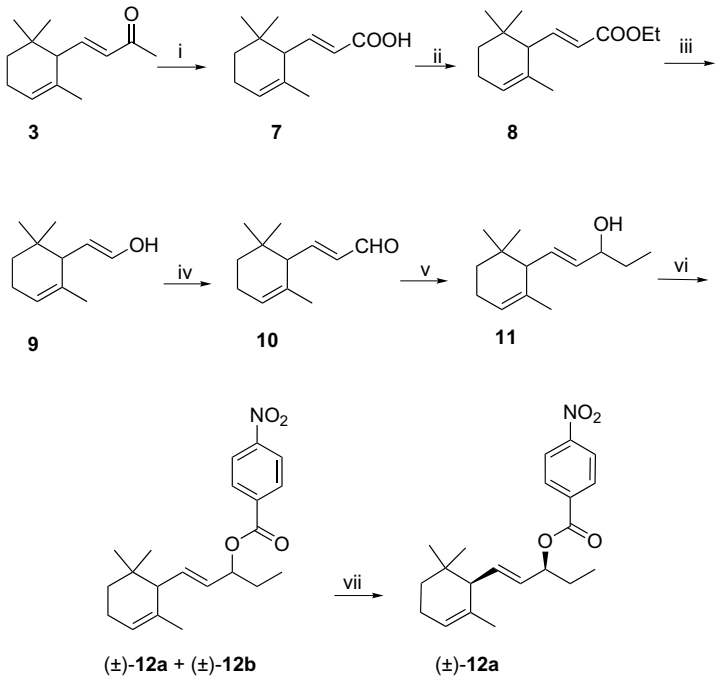


Scheme 3. Reagents: (i) MeOH, KOH; (ii) MnO_2, CH_2Cl_2.

obtained from (+)-**6b**, gave enantiomer (+)-**1** (ee = 94%, chiral GC). Oxidation of (+)-**4a** and of (−)-**4b** afforded (+)- and (−)-**1**, respectively, showing ee = 89% and 87% (chiral GC). The enantiomeric excesses of (−)-**6a**, (+)-**4a**, (+)-**6b** and (−)-**4b** were thus derived from the enantiomeric excesses of their corresponding oxidation products.

Racemic α-methyl ionone **2** was prepared according to the sequence reported in Scheme 4. Commercial α-ionone **3** was submitted to ipobromite degradation to give carboxylic acid **7**. The latter was converted into ethyl ester **8** and reduced with Redal to give alcohol **9**, which was oxidised to afford the unsaturated aldehyde **10**. Addition of ethyl magnesium bromide gave α-methylionol as a 1:1 mixture of the two diastereoisomers (±)-**11a** and (±)-**11b**. These latter derivatives were converted into the 4-nitrobenzoate esters (±)-**12a** and (±)-**12b**. Repeated crystallizations from methanol gave diastereoisomer (±)-**12a** as a single crystalline compound, whose relative configuration was established by X-ray diffraction analysis (Fig. 2). Nitrobenzoate (±)-**12a** was hydrolysed (Scheme 5) to afford (±)-**11a**, which was submitted to Lipase PS mediated acetylation in the presence of vinyl acetate in *t*-butylmethyl ether solution.

Acetate (−)-**13a** (ee = 98%, chiral GC) and unreacted alcohol (+)-**11a** (ee = 93%, chiral GC of the corresponding ace-



Scheme 4. Reagents: (i) NaOH aq, Br_2; (ii) EtOH, H_2SO_4; (iii) REDAL; (iv) MnO_2, CH_2Cl_2; (v) EtMgBr, THF (vi) *p*-nitro benzoyl chloride, pyridine; (vii) crystallisations from methanol.

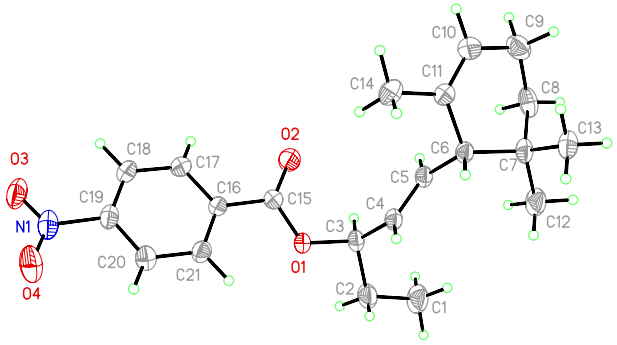


Figure 2.

tate) were recovered after column chromatography. Alcohol (−)-**11a**, obtained by hydrolysis of (−)-**13a**, and its enantiomer (+)-**11a** were converted into (−)- and (+)-**2**, respectively, by oxidation with Mn(IV)oxide. The enantiomeric excesses of these two samples of ionone **2** were derived from those of the starting materials (−)-**13a** and (+)-**11a**.

2.1. Configuration assignment

The absolute configurations of the enantiomers of methyl ionones **1** and **2** were established according to Scheme 6. We assumed that in the two series of compounds, Lipase PS acetylated the stereocentre showing the same configuration in both diastereoisomers. The 1:1 mixture of (±)-**4a** and (±)-**4b** was submitted to Lipase PS acetylation to afford two enantiopure diastereoisomeric acetates (chiral GC), which were hydrolysed and converted into benzoates (2*R*)-**14a** and (2*R*)-**14b**. These derivatives were submitted to ozonolysis, followed by treatment with PPh_3. After column chromatography, (*R*)-(−)-**15**[5] was recovered. An (*R*)-configuration was thus assigned to the stereogenic carbon atom bearing the OH group acetylated by lipase PS in both diastereoisomers. The X-ray analysis of *p*-nitrobenzoate (±)-**12a** allowed us to establish the relative configuration of the two stereogenic centres, thus the (*S*)-configuration could be assigned to the ionone enantiomer obtained from (−)-**6a**.

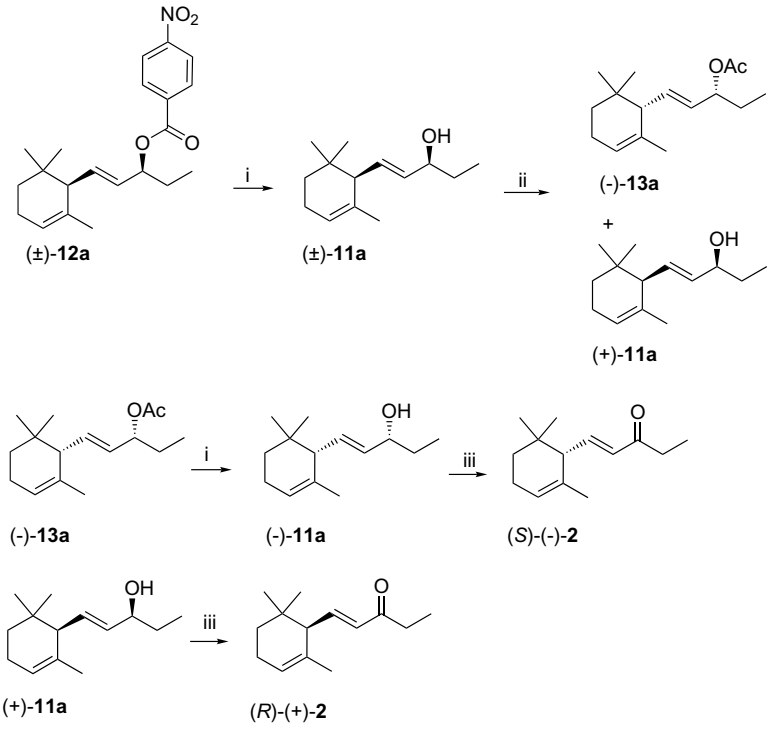
The same procedure was applied to the 1:1 mixture of **11a** and **11b**: the ozonolysis of benzoates (3*R*)-**16a** and (3*R*)-**16b** afforded (*R*)-(+)-**17**.[6] At the end of the correlation, an (*S*)-configuration was assigned to the ionone enantiomer obtained from (−)-**13a**.

3. Olfactory evaluation

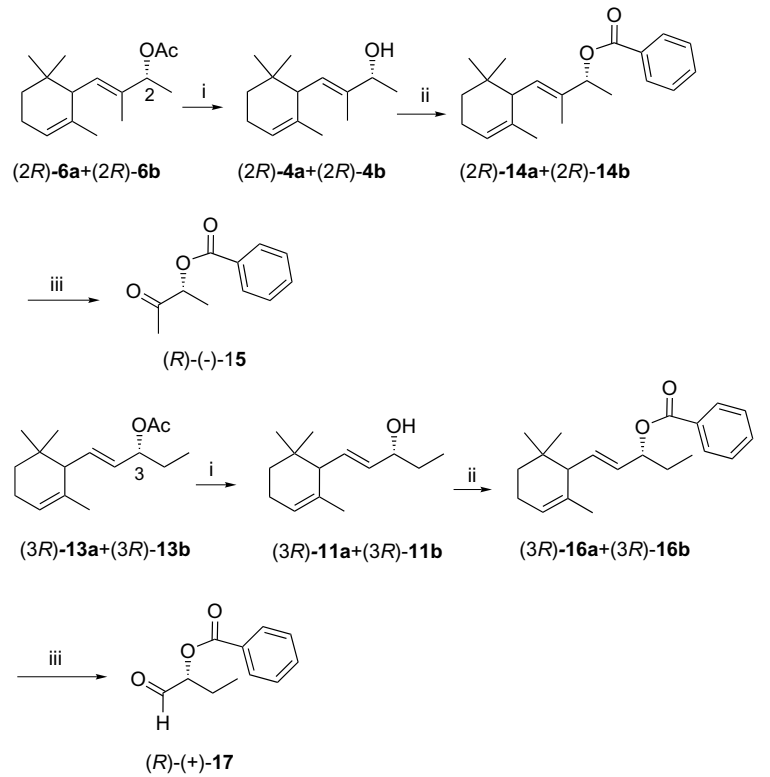
(*R*)-(+)-**1** (ee = 94%): odour threshold 0.079 ng/L air: typical dry warm ionone note, irisone, clean tea-like, also on blotter more intense and dryer than (−)-**1**.

(*S*)-(−)-**1** (ee = 98%): odour threshold 0.83 ng/L air; about ten times weaker floral note in the direction of iris and ionone, with hesperidic—citric elements and sweet fruity damascone-like aspects. More rich and complex in odour than (+)-**1**.

(*R*)-(+)-**2** (ee = 93%): odour threshold 0.53 ng/L air; woody, powdery, floral odour in the direction of the ionone



Scheme 5. Reagents: (i) MeOH, KOH; (ii) *t*-ButOMe, vinyl acetate, lipase PS; column chromatography; (iii) MnO_2, CH_2Cl_2.



Scheme 6. Reagents: (i) KOH, MeOH; (ii) PhCOCl, pyridine; O_3, CH_2Cl_2–MeOH; then PPh_3.

family, but less powerful and less intense. Dry-down linear, after 4 h woody-ionone, somewhat orris-like, and after 24 h woody-ionone, fruity, raspberry-type.

(*S*)-(−)-**2** (ee = 98%): odour threshold 0.24 ng/L air; woody, powdery, floral odour in the direction of the ionone family, but less powerful and less intense. Dry-down linear,

after 4 h woody-ionone, somewhat orris-like, and after 24 h woody-ionone, only very slightly fruity.

4. Conclusion

The enantiomers of methyl ionones **1** and **2** were prepared by an enzyme-mediated approach, and their absolute configurations were established by chemical correlation. The odour properties of each single enantiomer were evaluated by skilful perfumers. In a previous work,[7] we reported the odour descriptions of α-ionone enantiomers: they showed very similar odour (floral-woody note, with an additional honey aspect), with (*R*)-**3** being slightly weaker (odour threshold: 3.2 ng/L air) than its (*S*)-enantiomer (odour threshold: 2.7 ng/L air).

As for methyl ionone **1**, the (*R*)-enantiomer was found to be one order of magnitude stronger than its enantiomer, while the two enantiomers of compound **2** proved to be very similar both in odour and strength, as the enantiomers of parent compound **3**. The odour thresholds of the enantiomers of **1** and **2** are lower than those of (*R*)- and (*S*)-**3**. Subtle structural variations, such as the addition of one methyl group, can produce interesting effects on the odour strength of a compound.

5. Experimental

5.1. General

(*E*)-3-Methyl-4-(2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-one (α-isomethyl ionone or γ-methylionone) was a commercial product (Isoraldeine 95, Givaudan). Lipase PS from Pseudomonas cepacia (Amano Pharmaceuticals Co., Japan) was employed in this work. GC/MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature program was employed: 60° (1 min)/6°/min/150° (1 min)/12°/min/280° (5 min). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer (400 MHz ^{1}H, 100.6 MHz ^{13}C), in $CDCl_3$ solution at rt unless otherwise stated, using TMS as an internal standard; *J* values are given in Hertz. All the chromatographic separations were carried out on silica gel columns. Chiral GC analyses were performed on a DANI-HT-86.10 gas chromatograph using a Chirasil-DEX-CB column in the following conditions: (i) compounds **1** and **13a**: 70 °C (1 min) −3.5 °C/min −140 °C (6 min) −20 °C/min −180 °C (5 min), (−)-**1** $t_R = 14.31$ min, (+)-**1** $t_R = 14.79$ min; (−)-**13a** $t_R = 17.85$ min, (+)-**13a** $t_R = 17.94$ min. Optical rotations were measured on Dr. Kernchen Propol digital automatic polarimeter. Microanalyses were determined on a Carlo Erba 1106 Analyzer. Derivative **7** was prepared from α-ionone **3** according to Ref. [8] and was converted into ethyl ester **8** by reaction with ethanol/H_2SO_4 cat.

Crystal data for (±)-**5a**: $C_{21}H_{27}NO_4$, Mr = 357.4; monoclinic, $P2_1/n$, $a = 7.387(1)$, $b = 6.355(1)$, $c = 43.730(6)$ Å, $\beta = 94.21(1)°$, $V = 2044.8(5)$ Å^3, $Z = 4$, Dc = 1.161 g cm^{-3}, $F(000) = 384$, μ (CuKα) = 0.644 mm^{-1}; colourless crystal (0.6 × 0.4 × 0.2 mm).

Crystal data for (±)-**12a**: $C_{21}H_{27}NO_4$, Mr = 357.4; triclinic, $P\bar{1}$, $a = 8.538(1)$, $b = 10.212(1)$, $c = 12.603(1)$ Å, $\alpha = 91.07(1)°$, $\beta = 109.32(1)°$, $\gamma = 103.03(1)°$, $V = 1005.05(2)$ Å^3, $Z = 2$, Dc = 1.181 g cm^{-3}, $F(000) = 384$, μ (CuKα) = 0.656 mm^{-1}; colourless crystal (0.6 × 0.4 × 0.3 mm).

For both structures, diffraction data were collected on a Siemens P4 diffractometer with graphite monochromated CuKα radiation ($\lambda = 1.54179$ Å), using $\theta/2\theta$ scan technique. The structures were solved by direct methods[9] and refined by full-matrix least-squares on F^2 (SHELX97, SHELDRICK, 1999)[10]. In (±)-**5a**, the atoms of the cyclohexenyl group show very high atomic displacement factors possibly due to positional disorder. However, there were no remarkable peaks in the difference Fourier map and the disorder remained unresolved.

5.1.1. (*RS*,*E*)-3-Methyl-4-((*SR*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (±)-4a and (*RS*,*E*)-3-methyl-4-((*RS*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (±)-4b. $NaBH_4$ (1.72 g, 0.045 mol) was added to a solution of commercial **1** (25.0 g, 0.121 mol) in CH_2Cl_2/MeOH (150 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, poured into ice and extracted with CH_2Cl_2. The organic phase was dried over $NaSO_4$ and evaporated, to give a 1:1 mixture (23.1 g, 92%) of (±)-**4a** and (±)-**4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (br s, 1H, C*H*C=C of the cyclohexene ring of both diastereomers), 5.20 (d, 1H, $J = 10.5$ Hz, CH–*CH*=C of both diastereomers), 4.26 (m, 1H, *CH*OH of both diastereomers), 2.44 (d, 1H, $J = 10.5$ Hz, H–C(1) cyclohexene ring of both diastereomers), 2.00 (m, 2H, CH_2C= of both diastereomers), 1.71 (s, 3H, CH_3C=C of both diastereomers), 1.58–1.50 (m, 3H, CH_3C=C of both diastereomers), 1.45 (m, 1H, *H*–C(5) cyclohexene ring of both diastereomers), 1.27 (d, 3H, $J = 6.4$ Hz, CH_3CH of both diastereomers), 1.18 (dt, 1H, $J = 13.1$, 5.4 Hz, *H*–C(5) cyclohexene ring of both diastereomers), 0.89 (s, 3H, one CH_3–C(6) cyclohexene ring of both diastereomers), 0.80 and 0.77 (2s, 3H, one CH_3–C(6) cyclohexene ring of both diastereomers); GC/MS $t_R = 16.84$ min (single peak), *m*/*z* (%) 208 (M$^+$, 4), 181 (27), 150 (75), 109 (100).

5.1.2. (*RS*,*E*)-3-Methyl-4-((*SR*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-yl 4-nitrobenzoate (±)-5a and (*RS*,*E*)-3-methyl-4-((*RS*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-yl 4-nitrobenzoate (±)-5b. A solution of *p*-nitro benzoyl chloride (30.7 g, 0.166 mol) in CH_2Cl_2 (100 mL) was added at 0 °C to a solution of the 1:1 mixture of diastereoisomeric alcohols (±)-**4a** and (±)-**4b** (23.0 g, 0.110 mol) in pyridine (100 mL). The reaction mixture was stirred at room temperature for 1 h, poured into ice, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, to give a residue which was crystallised four times from methanol affording (±)-**5a** (de = 98%, by ^{1}H NMR): 8.03 g, 20%. From the mother liquors of the first crystallisation, compound (±)-**5b** showing de = 70% (^{1}H NMR) was recovered, and

brought to de = 94% by means of three crystallisations from hexane (5.89 g, 15%).

Data of (±)-**5a**: mp 85–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35–8.15 (m, 4H, aromatic hydrogens), 5.54 (q, 1H, $J = 6.4$ Hz, C*H*OCO), 5.43–5.28 (m, 2H, vinylic hydrogens), 2.47 (d, 1H, $J = 10.9$ Hz, H–C(1) cyclohexene ring), 2.00 (m, 2H, CH_2C=), 1.80 (d, 3H, $J = 1.5$ Hz, CH_3C=C), 1.52 (m, 3H, CH_3C=C), 1.48 (d, 3H, $J = 6.4$ Hz, CH_3CH), 1.40 (dt, 1H, $J = 13.0$, 7.4 Hz, *H*–C(5) cyclohexene ring), 1.18 (dt, 1H, $J = 13.0$, 5.4 Hz, *H*–C(5) cyclohexene ring), 0.89 (s, 3H, CH_3–C(6) cyclohexene ring), 0.75 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): 163.7, 150.3, 136.2, 134.6, 134.5, 130.5, 129.5, 123.4, 120.7, 77.6, 48.4, 32.4, 32.1, 27.3, 26.4, 22.9, 22.6, 19.4, 12.4; GC/MS: $t_R = 28.15$ min, *m*/*z* (%) 301 (M^+-56, 42), 190 (32), 150 (50), 134 (100). $C_{21}H_{17}NO_4$: Calcd C, 70.56; H, 7.61; N, 3.92. Found: C, 70.65; H, 7.73; N, 3.81.

Data of (±)-**5b**: mp 43–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35–8.15 (m, 4H, aromatic hydrogens), 5.55 (q, 1H, $J = 6.4$ Hz, C*H*OCO), 5.42–5.33 (m, 2H, vinylic hydrogens), 2.46 (d, 1H, $J = 10.9$ Hz, H–C(1) cyclohexene ring), 2.00 (m, 2H, CH_2C=), 1.79 (d, 3H, $J = 1.5$ Hz, CH_3C=C), 1.53 (m, 3H, CH_3C=C), 1.48 (d + m, 4H, $J = 6.4$ Hz, CH_3CH + *H*–C(5) cyclohexene ring), 1.20 (dt, 1H, $J = 13.0$, 5.4 Hz, *H*–C(5) cyclohexene ring), 0.88 (s, 3H, CH_3–C(6) cyclohexene ring), 0.79 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): 163.8, 150.3, 136.3, 134.6, 134.1, 130.5, 130.2, 123.4, 120.7, 77.9, 48.6, 32.4, 32.0, 27.3, 26.5, 22.9, 22.6, 19.2, 12.2; GC/MS: $t_R = 28.04$ min, *m*/*z* (%) 301 (M^+-56, 30), 190 (35), 150 (45), 134 (100), 119 (100). $C_{21}H_{17}NO_4$: Calcd C, 70.56; H, 7.61; N, 3.92. Found: C, 70.48; H, 7.52; N, 4.05.

5.1.3. (*RS*,*E*)-3-Methyl-4-((*SR*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (±)-4a. Derivative (±)-**5a** (7.90 g, 0.022 mol) was hydrolysed with KOH (1.88 g, 0.033 mol) in methanol (100 mL). After the usual work-up, racemic alcohol (±)-**4a** (3.79 g, 83%) was recovered: mp 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (br s, 1H, C*H*C=C of the cyclohexene ring), 5.19 (d, 1H, $J = 10.5$ Hz, CH–*CH*=C), 4.26 (q, 1H, $J = 6.4$ Hz, *CH*OH), 2.44 (d, 1H, $J = 10.5$ Hz, H–C(1) cyclohexene ring), 2.00 (m, 2H, CH_2C=), 1.71 (d, 3H, $J = 1.5$ Hz, CH_3C=C), 1.56 (m, 3H, CH_3C=C), 1.46 (m, 1H, *H*–C(5) cyclohexene ring), 1.27 (d, 3H, $J = 6.4$ Hz, CH_3CH), 1.18 (dt, 1H, $J = 13.1$, 5.4 Hz, *H*–C(5) cyclohexene ring), 0.89 (s, 3H, CH_3–C(6) cyclohexene ring), 0.77 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): 139.2, 135.1, 126.5, 120.2, 73.7, 48.3, 32.4, 31.8, 27.1, 26.6, 22.9, 22.6, 21.7, 11.8. $C_{14}H_{24}O$: Calcd C, 80.71; H, 11.61. Found: C, 80.66; H, 11.54.

5.1.4. (*RS*,*E*)-3-Methyl-4-((*RS*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (±)-4b. Derivative (±)-**5b** (5.70 g, 0.016 mol) was hydrolysed with KOH (1.34 g, 0.024 mol) in methanol (80 mL). After the usual work-up, racemic alcohol (±)-**4b** (2.82 g, 85%) was recovered: mp 71–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (br s, 1H, C*H*C=C of the cyclohexene ring), 5.20 (d, 1H, $J = 10.8$ Hz, CH–*CH*=C), 4.25 (q, 1H, $J = 6.3$ Hz, *CH*OH), 2.44 (d, 1H, $J = 10.8$ Hz, H–C(1) cyclohexene ring), 2.00 (m, 2H, CH_2C=), 1.71 (s, 3H, CH_3C=C), 1.52 (s, 3H, CH_3C=C), 1.44 (m, 1H, *H*–C(5) cyclohexene ring), 1.27 (d, 3H, $J = 6.3$ Hz, CH_3CH), 1.20 (m, 1H, *H*–C(5) cyclohexene ring), 0.90 (s, 3H, CH_3–C(6) cyclohexene ring), 0.80 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): 139.1, 135.1, 126.2, 120.2, 73.5, 48.3, 32.2, 31.8, 27.1, 26.6, 22.9, 22.6, 21.7, 11.8. $C_{14}H_{24}O$: Calcd C, 80.71; H, 11.61. Found: C, 80.79; H, 11.69.

5.1.5. (*R*,*E*)-3-Methyl-4-((*S*)-2,6,6-trimethylcyclohex-2-enyl)-but-3-en-2-yl acetate (−)-6a and (*S*,*E*)-3-methyl-4-((*R*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (−)-4a. A mixture of (±)-**4a** (3.60 g, 0.017 mol), lipase PS (1.00 g), and vinyl acetate (10 mL) in *t*BuOMe (50 mL) was stirred at rt for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and submitted to column chromatography (hexane/ethyl acetate 9/1). The first eluted fractions gave acetate (−)-**6a** (1.44 g, 34%). The last eluted fractions afforded unreacted alcohol (+)-**4a** (1.09 g, 31%).

Data of (−)-**6a**: $[\alpha]_D^{20} = -203.1$ (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (br s, 1H, C*H*C=C of the cyclohexene ring), 5.29–5.17 (m, 2H, CH–*CH*=C + *CH*OAc), 2.44 (d, 1H, $J = 10.9$ Hz, H–C(1) cyclohexene ring), 2.04 (s, 3H, OAc), 1.99 (m, 2H, CH_2C=), 1.70 (d, 3H, $J = 1.5$ Hz, CH_3C=C), 1.53 (m, 3H, CH_3C=C), 1.43 (dt, 1H, $J = 13.1$, 7.4 Hz, *H*–C(5) cyclohexene ring), 1.31 (d, 3H, $J = 6.5$ Hz, CH_3CH), 1.20 (dt, 1H, $J = 13.1$, 5.2 Hz, *H*–C(5) cyclohexene ring), 0.88 (s, 3H, CH_3–C(6) cyclohexene ring), 0.75 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.2, 135.1, 134.9, 128.2, 120.5, 75.5, 48.4, 32.4, 32.2, 27.4, 26.3, 22.9, 22.6, 21.3, 19.4, 12.5; GC/MS: $t_R = 18.98$ min, *m*/*z* (%) 190 (M^+- 60, 50), 134 (100), 119 (95). $C_{16}H_{26}O_2$: Calcd C, 76.75; H, 10.47. Found: C, 76.84; H, 10.38.

Data of (+)-**4a**: mp 59–63 °C; $[\alpha]_D^{20} = +292.9$ (*c* 1.02, $CHCl_3$). ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding racemic compound.

5.1.6. (*R*,*E*)-3-Methyl-4-((*R*)-2,6,6-trimethylcyclohex-2-enyl)-but-3-en-2-yl acetate (+)-6b and (*S*,*E*)-3-methyl-4-((*S*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (−)-4b. A mixture of (±)-**4b** (2.70 g, 0.013 mol), lipase PS (0.800 g), and vinyl acetate (10 mL) in tBuOMe (50 mL) was stirred at rt for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and submitted to column chromatography (hexane/ethyl acetate 9/1). The first eluted fractions gave acetate (+)-**6b** (1.01 g, 31 %). The last eluted fractions afforded unreacted alcohol (−)-**4b** (0.757 g, 28%).

Data for (+)-**6b**: $[\alpha]_D^{20} = +278.8$ (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (m, 1H, C*H*C=C of the cyclohexene ring), 5.31–5.20 (m, 2H, CH–*CH*=C + *CH*OAc), 2.42 (d, 1H, $J = 10.9$ Hz, H–C(1) cyclohexene ring), 2.03 (s, 3H, OAc), 2.00 (m, 2H, CH_2C=), 1.69 (d, 3H, $J = 1.4$ Hz, CH_3C=C), 1.51 (m, 3H, CH_3C=C), 1.44 (m, 1H, *H*–C(5) cyclohexene ring), 1.30 (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.20 (m, 1H, *H*–C(5) cyclohexene ring), 0.88 (s, 3H, CH_3–C(6) cyclohexene ring), 0.78 (s, 3H, CH_3–C(6)

cyclohexene ring); ^{13}C NMR: 170.2, 134.9, 134.8, 128.9; 120.5; 75.7; 48.4; 32.3; 32.0; 27.3; 26.4; 22.9; 22.6; 21.3; 19.2; 12.2. $C_{16}H_{26}O_2$: Calcd C, 76.75; H, 10.47. Found: C, 76.66; H, 10.54. GC/MS: $t_R = 18.78$ min, *m*/*z* (%) 190 (M^+-60, 46), 134 (100), 119 (95).

Data for (−)-**4b**: mp = 78–81 °C; $[\alpha]_D^{20} = -285.3$ (*c* 0.95, $CHCl_3$); ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding racemic compound.

5.1.7. (*R*,*E*)-3-Methyl-4-((*S*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (−)-4a. Hydrolysis of (−)-**6a** (1.30 g, 5.2 mmol) with KOH (0.437 g, 7.8 mmol) in MeOH (30 mL) gave after the usual work-up a residue which was crystallised from hexane, to afford alcohol (−)-**4a** (0.894 g, 86 %): mp 60–62 °C; $[\alpha]_D^{20} = -321.5$ (*c* 1.08, $CHCl_3$). ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding racemic compound.

5.1.8. (*R*,*E*)-3-Methyl-4-((*R*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-ol (+)-4b. Hydrolysis of (+)-**6b** (0.740 g, 2.96 mmol) with KOH (0.248 g, 4.44 mmol) in MeOH (25 mL) gave, after the usual work, up a residue, which was crystallised from hexane, to afford alcohol (+)-**4b** (0.535 g, 87%): mp = 80–83 °C; $[\alpha]_D^{20} = +308.3$ (*c* 0.95, $CHCl_3$); ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding racemic compound.

5.1.9. (*S*,*E*)-3-Methyl-4-(2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-one (−)-1. A mixture of alcohol (−)-**4a** (0.870 g, 4.18 mmol) and MnO_2 (1.2 equiv) in CH_2Cl_2 (20 mL) was refluxed for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (hexane/ethyl acetate 95:5) to afford (−)-**2** (0.724 g, 84%): ee = 98% (chiral GC); $[\alpha]_D^{20} = -450$ (*c* 1.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (dd, 1H, $J = 10.9$, 1.3 Hz, C*H*=CCO), 5.47 (m, 1H, *CH*=C of the cyclohexene ring), 2.66 (d, 1H, $J = 10.9$ Hz, H–C(1) cyclohexene ring), 2.31 (s, 3H, OAc), 2.07 (m, 2H, CH_2C=), 1.86 (d, 3H, $J = 1.5$ Hz, CH_3C=C), 1.58–1.45 (m, 4H, CH_3C=C + *H*–C(5) cyclohexene ring), 1.27 (dt, 1H, $J = 13.1$, 5.2 Hz, *H*–C(5) cyclohexene ring), 0.94 (s, 3H, CH_3–C(6) cyclohexene ring), 0.82 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): 200.2, 145.2, 137.8, 133.2, 121.9, 50.2, 32.7, 31.7, 27.1, 26.9, 25.6, 22.9, 22.7, 11.7; GC/MS: $t_R = 17.31$ min, *m*/*z* (%) 206 (M^+, 12), 191 (5), 150 (67), 135 (100). $C_{14}H_{22}O$: Calcd C, 81.50; H, 10.75. Found: C, 81.56; H, 10.69.

5.1.10. (*R*,*E*)-3-Methyl-4-(2,6,6-trimethylcyclohex-2-enyl)-but-3-en-2-one (+)-1. A mixture of alcohol (+)-**4b** (0.490 g, 2.36 mmol) and MnO_2 (1.2 equiv) in CH_2Cl_2 (20 mL) was refluxed for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (hexane/ethyl acetate 95:5) to afford (+)-**2** (0.427 g, 88%): ee = 94% (chiral GC); $[\alpha]_D^{20} = +430$ (*c* 1.25, $CHCl_3$). ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding enantiomer. $C_{14}H_{22}O$: Calcd C, 81.50; H, 10.75. Found: C, 81.56; H, 10.69.

5.1.11. (*E*)-3-(2,6,6-Trimethylcyclohex-2-enyl)prop-2-en-1-ol 9. Compound **8** (60.0 g, 0.270 mol) was reduced with Redal (92 mL, 3.5 M in toluene) at 0 °C in toluene solution (500 mL). After the usual work-up, alcohol **9** was recovered and purified by column chromatography (hexane/ethyl acetate 7/3) (33.6 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (dt, 1H, $J = 15.2$, 5.7 Hz, C=C*H*CH_2), 5.49 (dd, 1H, $J = 15.2$, 5.7 Hz, C*H*=CHCH_2), 5.40 (m, 1H, C=CH of the cyclohexene ring), 4.13 (m, 2H, CH_2OH), 2.12 (d, 1H, $J = 9.0$ Hz, H–C(1) cyclohexene ring), 1.99 (m, 2H, CH_2C=), 1.59 (s, 3H, CH_3C=C), 1.43 (dt, 1H, $J = 13.6$, 8.0, *H*–C(5) cyclohexene ring), 1.17 (dt, 1H, $J = 13.6$, 4.8, *H*–C(5) cyclohexene ring), 0.89 (s, 3H, CH_3–C(6) cyclohexene ring), 0.82 (s, 3H, CH_3–C(6) cyclohexene ring); GC/MS: $t_R = 14.93$ min, *m*/*z* (%) 180 (M^+, 10), 165 (5), 124 (100). $C_{12}H_{20}O$: Calcd C, 79.94; H, 11.18. Found: C, 79.88; H, 11.23.

5.1.12. (*E*)-3-(2,6,6-Trimethylcyclohex-2-enyl)acrylaldehyde 10. A mixture of alcohol **9** (33.4 g, 0.186 mol) and MnO_2 (1.2 equiv) in dichloromethane (300 mL) was refluxed for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (hexane/ethyl acetate 95:5) to afford aldehyde **10** (23.4 g, 71%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (d, 1H, $J = 7.9$, *CHO*), 6.68 (dd, 1H, $J = 15.2$, 9.6, C*H*=), 5.49 (dd, 1H, $J = 15.2$, 7.9 Hz, C=C*H*CHO), 5.54 (m, 1H, C=CH of the cyclohexene ring), 2.42 (d, 1H, $J = 9.6$ Hz, H–C(1) cyclohexene ring), 2.06 (m, 2H, CH_2C=), 1.58 (m, 3H, CH_3C=C), 1.47 (m, 1H, *H*–C(5) cyclohexene ring), 1.24 (m, 1H, *H*–C(5) cyclohexene ring), 0.95 (s, 3H, CH_3–C(6) cyclohexene ring), 0.88 (s, 3H, CH_3–C(6) cyclohexene ring); GC/MS: $t_R = 14.83$ min, *m*/*z* (%) 178 (M^+, 25), 163 (19), 122 (81), 107 (100). $C_{12}H_{18}O$: Calcd C, 80.85; H, 10.18. Found: C, 80.78; H, 10.24.

5.1.13. (*SR*,*E*)-1-((*RS*)-2,6,6-Trimethylcyclohex-2-enyl)-pent-1-en-3-ol 11a and (*RS*,*E*)-1-((*RS*)-2,6,6-trimethylcyclohex-2-enyl)pent-1-en-3-ol 11b. Aldehyde **10** (23.0 g, 0.129 mol) was dropped into a solution of ethylmagnesium bromide (from 0.193 mol of ethyl bromide and 0.219 mol of Mg) in Et_2O (500 mL) at 10 °C. The mixture was refluxed for 1 h, poured into ice, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and evaporated to give a residue, which was submitted to column chromatography (hexane/ethyl acetate 7:3). A 1:1 mixture of alcohols **11a** and **11b** was obtained (21.7 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47–5.42 (m, 2H, C*H*=*CH* of both diastereomers), 5.40 (m, 1H, C=C*H* of the cyclohexene ring of both diastereomers), 4.05–3.99 (m, 1H, C*H*OH of both diastereomers), 2.11 (m, 1H, H–C(1) cyclohexene ring of both diastereomers), 2.00 (m, 2H, CH_2C= of both diastereomers), 1.67–1.37 (m, 6H, CH_3C=C of both diastereomers + CH_2CH_3 of both diastereomers + *H*–C(5) cyclohexene ring of one diastereomers), 1.20–1.14 (m, *H*–C(5) cyclohexene ring of both diastereomers), 0.93–0.88 (m, 6H, CH_3CH_2 of both diastereomers + one CH_3–C(6) cyclohexene ring of both diastereomers), 0.84 and 0.81 (2s, 3H, one CH_3–C(6) cyclohexene ring of both

diastereomers); GC/MS: $t_R = 16.16$ min (single peak) *m/z* (%) 208 (M^+, 6), 190 (10), 152 (73), 123 (67), 95 (100).

5.1.14. (*RS*,*E*)-1-((*SR*)-2,6,6-Trimethylcyclohex-2-enyl)pent-1-en-3-yl 4-nitrobenzoate 12a and (*RS*,*E*)-1-((*RS*)-2,6,6-trimethylcyclohex-2-enyl)pent-1-en-3-yl 4-nitrobenzoate 12b. To a solution of the 1:1 mixture of alcohols **11a** and **11b** (21.6 g, 0.103 mol) in pyridine (100 mL), a solution of 4-nitrobenzoyl chloride (28.6 g, 0.155 mol) in CH_2Cl_2 (50 mL) was added at 0 °C. After 2 h at room temperature, the usual work-up allowed the recovery of the corresponding mixture of 4-nitrobenzoates **12a** and **12b**, which was crystallised four times from methanol to afford derivative, to afford derivative **12a** as a single diastereoisomer (de = 98%, ^{1}H NMR; 7.72 g, 21%): mp 64–67 °C; δ 8.31–8.16 (m, 4H, aromatic hydrogens), 5.64 (dd, 1H, $J = 14.7$, 9.4, CH–*CH*=C), 5.49 (dd, 1H, $J = 14.7$, 7.4, C=C*H*CHOCOAr), 5.45–5.38 (m, 2H, *CH*O-COAr + C=C*H* of the cyclohexene ring), 2.13 (d, 1H, $J = 9.4$, H–C(1) cyclohexene ring), 1.99 (m, 2H, CH_2C=), 1.90–1.72 (m, 2H, CH_2CH_3), 1.54 (m, 3H, CH_3C=C), 1.38 (dt, 1H, $J = 13.3$, 7.8, *H*–C(5) cyclohexene ring), 1.16 (dt, 1H, $J = 13.3$, 5.1, *H*–C(5) cyclohexene ring), 0.99 (t, 3H, $J = 7.4$, CH_3CH_2), 0.89 (s, 3H, CH_3–C(6) cyclohexene ring), 0.82 (s, 3H, CH_3–C(6) cyclohexene ring); GC/MS: $t_R = 27.50$ min, *m/z* (%) 301 (M^+-56, 6), 190 (27), 134 (100), 119 (100). $C_{12}H_{27}NO_4$: Calcd C, 70.56; H, 7.61; N, 3.92. Found: C, 70.62; H, 7.68; N 3.86.

5.1.15. (*SR*,*E*)-1-((*RS*)-2,6,6-Trimethylcyclohex-2-enyl)-pent-1-en-3-ol 11a. *p*-Nitroderivative **12a** (7.62 g, 0.0213 mol) was hydrolysed by reaction with KOH (1.79 g, 0.032 mol) in methanol (50 mL) at room temperature. After the usual work-up, alcohol **11a** was recovered by column chromatography (hexane/ethyl acetate 7/3) (3.46 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47–5.27 (m, 3H, vinylic hydrogens), 4.03–3.89 (m, 1H, C*H*OH), 2.06 (m, 1H, H–C(1) cyclohexene ring), 1.95 (m, 2H, CH_2C=), 1.62–1.32 (m, 6H, CH_3C=C + CH_2CH_3 + *H*–C(5) cyclohexene ring), 1.13 (dt, 1H, $J = 13.1$, 4.8, *H*–C(5) cyclohexene ring), 0.87 (t, 3H, $J = 7.1$, CH_3CH_2), 0.85 (s, 3H, CH_3–C(6) cyclohexene ring), 0.78 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 134.5, 133.8, 132.4, 120.8, 74.3, 53.9, 31.7, 31.4, 30.8, 27.4, 26.7, 22.9, 22.7, 9.6. $C_{14}H_{24}O$: Calcd C, 80.71; H, 11.61. Found: C, 80.78; H, 11.57.

5.1.16. (*R*,*E*)-1-((*S*)-2,6,6-trimethylcyclohex-2-enyl)pent-1-en-3-yl acetate and (−)-13a and (*S*,*E*)-1-((*R*)-2,6,6-trimethylcyclohex-2-enyl)pent-1-en-3-ol (+)-11a. A mixture of (±)-**11a** (3.36 g, 0.016 mol), lipase PS (1 g), and vinyl acetate (10 mL) in tBuOMe (50 mL) was stirred at rt for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and submitted to column chromatography (hexane/ethyl acetate 9/1). The first eluted fractions gave acetate (−)-**13a** (1.33 g, 33%). The last eluted fractions afforded unreacted alcohol (+)-**11a** (0.971 g, 29%).

Data for (−)-**13a**: $[\alpha]_D = -178.5$ (*c* 01.14, $CHCl_3$); ee = 98% (chiral GC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (dd, 1H, $J = 15.6$, 8.9, CH–*CH*=C), 5.40 (m, 1H, C*H*=C of the cyclohexene ring), (5.35, dd, 1H, $J = 15.6$, 7.2, C=C*H*CHOCO), 5.13 (q, 1H, $J = 7.2$, *CH*OAc), 2.09 (d, 1H, $J = 8.9$, H–C(1) cyclohexene ring), 2.03 (s, 3H, OAc), 1.98 (m, 2H, CH_2C=), 1.63 (m, 2H, CH_2CH_3), 1.55 (m, 3H, CH_3C=C), 1.40 (dt, 1H, $J = 12.6$, 8.2, *H*–C(5) cyclohexene ring), 1.16 (dt, 1H, $J = 12.6$, 4.5, *H*–C(5) cyclohexene ring), 0.89 (t, 3H, $J = 7.1$, CH_3CH_2), 0.88 (s, 3H, CH_3–C(6) cyclohexene ring), 0.80 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.2, 134.9, 133.6, 129.7, 121.1, 76.1, 54.0, 31.8, 31.7, 27.5, 27.3, 26.9, 22.9, 22.7, 21.2, 9.5. GC/MS: $t_R = 18.32$ min, *m/z* (%) 190 (M^+-60, 6), 190 (80), 123 (86), 105 (100). $C_{16}H_{26}O_2$: Calcd C, 76.75; H, 10.47. Found: C, 76.82; H, 10.41.

Data for (+)-**11a**: $[\alpha]_D = +274.2$ (*c* 1.06, $CHCl_3$); ee = 93% (chiral GC of the corresponding acetate). ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding racemic compound.

5.1.17. (*R*,*E*)-1-((*S*)-2,6,6-Trimethylcyclohex-2-enyl)pent-1-en-3-ol (−)-11a. Acetate (−)-**13a** (1.23 g, 4.92 mmol) was hydrolysed by reaction with KOH (0.413 g, 7.38 mmol) in methanol (30 mL). After the usual work up, alcohol (−)-**11a** (0.941 g, 92%) was recovered by column chromatography (hexane/ethyl acetate 7/3): $[\alpha]_D = -289.3$ (*c* 1.21, $CHCl_3$); ee = 98% (chiral GC of the corresponding acetate). ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the corresponding racemic compound.

5.1.18. (*R*,*E*)-1-(2,6,6-Trimethylcyclohex-2-enyl)pent-1-en-3-one (+)-2. A mixture of alcohol (+)-**11a** (0.950 g, 4.57 mmol) and MnO_2 (1.2 equiv) in CH_2Cl_2 (20 mL) was refluxed for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (hexane/ethyl acetate 95:5) to afford (+)-**3** (0.762 g, 81%): $[\alpha]_D = +376.8$ (*c* 0 1.05, $CHCl_3$); ee = 93% (chiral GC of the corresponding alcohol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, 1H, $J = 15.6$, 9.5, CH–*CH*=C), 6.07 (d, 1H, $J = 15.6$, C=C*H*CO), 5.49 (m, 1H, C*H*=C of the cyclohexene ring), 2.59 (q, 2H, $J = 7.3$, CH_2CH_3), 2.27 (d, 1H, $J = 9.5$, H–C(1) cyclohexene ring), 2.04 (m, 2H, CH_2C=), 1.56 (m, 3H, CH_3C=C), 1.45 (dt, 1H, $J = 13.4$, 8.3, *H*–C(5) cyclohexene ring), 1.21 (dt, 1H, $J = 13.4$, 4.8, *H*–C(5) cyclohexene ring), 1.11 (t, 3H, $J = 7.3$, CH_3CH_2), 0.93 (s, 3H, CH_3–C(6) cyclohexene ring), 0.85 (s, 3H, CH_3–C(6) cyclohexene ring); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 201.0, 147.6, 131.9, 131.1, 122.5, 54.2, 33.1, 32.4, 31.1, 27.7, 26.7, 22.9, 22.7, 8.1; GC/MS: $t_R = 17.07$ min, *m/z* (%) 206 (M^+, 33), 191 (13), 150 (30), 135 (35), 121 (100). $C_{14}H_{22}O$: Calcd C, 81.50; H, 10.75. Found: C, 81.45; H, 10.79.

5.1.19. (*S*,*E*)-1-(2,6,6-Trimethylcyclohex-2-enyl)pent-1-en-3-one (−)-2. A mixture of alcohol (−)-**11a** (0.930 g, 4.47 mmol) and MnO_2 (1.2 equiv) in CH_2Cl_2 (20 mL) was refluxed for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (hexane/ethyl acetate 95:5) to afford (−)-**3** (0.718 g, 78%): $[\alpha]_D = -397.1$ (*c* 1.20, $CHCl_3$); ee = 98% (chiral GC of the corresponding alcohol); ^{1}H, ^{13}C NMR and MS spectra were in accordance with those of the enantiomer. $C_{14}H_{22}O$: Calcd C, 81.50; H, 10.75. Found: C, 81.58; H, 10.80.

5.1.20. (*R,E*)-3-Methyl-4-((*RS*)-2,6,6-trimethylcyclohex-2-enyl)but-3-en-2-yl benzoates (2*R*)-14a and (2*R*)-14b. A 1:1 mixture of (2*R*)-**4a** and (2*R*)-**4b** (1.00 g, 4.81 mmol) (obtained from the acetates produced by lipase PS acetylation of the 1:1 mixture of racemic **4a** and **4b**) was dissolved in pyridine (10 mL) and treated with PhCOCl (1.01 g, 7.21 mmol) at 0 °C. After the usual work-up a 1:1 mixture of (2*R*)-**14a** and (2*R*)-**14b** (1.27 g, 85%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.00 (m, 2H, aromatic hydrogens), 7.60–7.25 (m, 3H, aromatic hydrogens), 5.50 (m, 1H, C*H*OCO of both diastereomers), 5.40–5.30 (m, 2H, vinylic hydrogens of both diastereomers), 2.42 (d, 1H, $J = 10.9$ Hz, H–C(1) cyclohexene ring of both diastereomers), 1.99 (m, 2H, $CH_2C=$ of both diastereomers), 1.80–1.35 (m, 7H, $CH_3C=C + CH_3CH + H$–C(5) cyclohexene ring of both diastereomers), 1.20 (m, 1H, $J = 13.0$, 5.4 Hz, *H*–C(5) cyclohexene ring of both diastereomers), 0.88 (s, 3H, CH_3–C(6) cyclohexene ring of both diastereomers), 0.77 and 0.75 (2s, 3H, CH_3–C(6) cyclohexene ring of both diastereomers); GC/MS: $t_R = 25.16$ and 25.24 min, *m*/*z* (%) 312 (M^+, 2), 256 (15), 190 (30), 135 (29), 105 (100). $C_{21}H_{28}O_2$: Calcd C, 80.73; H, 9.03. Found: C, 80.67; H, 9.11.

5.1.21. (*R,E*)-1-((*RS*)-2,6,6-Trimethylcyclohex-2-enyl)pent-1-en-3-yl benzoate (3*R*)-16a and (3*R*)-16b. A 1:1 mixture of (3*R*)-**11a** and (3*R*)-**11b** (1.00 g, 4.81 mmol) (obtained from the acetates produced by lipase PS acetylation of the 1:1 mixture of racemic **11a** and **11b**) was dissolved in pyridine (10 mL) and treated with PhCOCl (1.01 g, 7.21 mmol) at 0 °C. After the usual work-up a 1:1 mixture of (3*R*)-**16a** and (3*R*)-**16b** (1.25 g, 83%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.00 (m, 2H, aromatic hydrogens), 7.70–7.40 (m, 3H, aromatic hydrogens), 5.70–5.35 (m, 4H, C*H*OCO + vinylic hydrogens of both diastereomers), 2.12 (d, 1H, $J = 8.7$ Hz, H–C(1) cyclohexene ring of both diastereomers), 1.98 (m, 2H, $CH_2C=$ of both diastereomers), 1.78 (m, 2H, CH_2CH_3 of both diastereomers), 1.57 (m, 3H, CH_3CH of both diastereomers), 1.42 (m, 1H, *H*–C(5) of the cyclohexene ring of both diastereomers), 1.15 (m, 1H, *H*–C(5) cyclohexene ring of both diastereomers), 0.97 (t, $J = 7.5$, CH_2CH_3), 0.88, 0.87, 0.81, and 0.80 (4s, 6H, $2CH_3$–C(6) cyclohexene ring of both diastereomers); GC/MS: $t_R = 24.69$ min (single peak) *m*/*z* (%) 312 (M^+, 2), 256 (5), 190 (33), 105 (100). $-C_{21}H_{28}O_2$: Calcd C, 80.73; H, 9.03. Found: C, 80.79; H, 8.95.

5.1.22. (*R*)-3-Oxobutan-2-yl benzoate. The 1:1 mixture of benzoates (2*R*)-**14a** and (2*R*)-**14b** (1.10 g, 3.52 mmol) was treated with O_3 at −78 °C in CH_2Cl_2/MeOH 1:1 solution (50 mL). The mixture was quenched with PPh_3 (2.77 g, 0.0106 mol) and after the usual work-up, the residue was submitted to CC (hexane/AcOEt 8:2), to obtain (−)-(*R*)-**15** (0.350 g, 57%): $[\alpha]_D^{20} = -33.1$ (*c* 1.16, CH_2Cl_2), lit.[5] for (*R*)-**15** $[\alpha]_D^{20} = -35.7$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR[5]: 8.20–8.00 (m, 2H, aromatic hydrogens), 7.40–7.30 (m, 3H, aromatic hydrogens), 5.25 (q, 1H, $J = 6.5$, C*H*OCO), 2.20 (s, 3H; CH_3CO), 1.50 (d, 3H, $J = 6.5$, CH_3CH); GC/MS: $t_R = 16.31$ min, *m*/*z* (%) 192 (M^+, 2), 149 (25), 105 (100).

5.1.23. (*R*)-1-Oxobutan-2-yl benzoate (*R*)-17. The 1:1 mixture of benzoates (3*R*)-**16a** and (3*R*)-**16b** (1.10 g, 3.52 mmol) was treated with O_3 at −78 °C in CH_2Cl_2/MeOH 1:1 solution (50 mL). The mixture was quenched with PPh_3 (2.77 g, 0.0106 mol) and after the usual work-up, the residue was submitted to CC (hexane/AcOEt 8:2), to obtain (+)-(*R*)-**17** (0.372 g, 55%): $[\alpha]_D^{20} = +41.0$ (*c* 1.00, $CHCl_3$), for (*R*)-**17** lit.[6a] $[\alpha]_D^{20} = +43.2$ (*c* 1.0, $CHCl_3$), lit.[6b] $[\alpha]_D^{20} = +41$ (*c* 0.07, $CHCl_3$); ^{1}H NMR:[6a,b] 9.30 (s, 1H, C*H*O), 8.20–8.00 (m, 2H, aromatic hydrogens), 7.40–7.30 (m, 3H, aromatic hydrogens), 5.18 (m, 1H, C*H*OCO), 2.00–1.90 (m, 2H, CH_2CH_3), 1.23 (t, 3H, $J = 6.5$, CH_3CH_2).

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References

1. Tiemann, F. *to Haarmann & Reimer*, Ger. Patent 75,120, 1893.
2. Ohloff, G. 'Düfte', Wiley-VCH, Helvetica Chimica Acta, Zürich, **2004**.
3. Sell, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6254–6261.
4. Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1–42; Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Chem. Biodiv.* **2004**, *1*, 1888–1898; Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *J. Mol. Cat. B: Enzym.* **2004**, *32*, 33–51; Brenna, E. *Curr. Org. Chem.* **2003**, *7*, 1347–1367.
5. Barros, M. T.; Leitao, A. J.; Maycock, C. D. *Tetrahedron Lett.* **1995**, *36*, 6537–6540.
6. (a) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron: Asymmetry* **1994**, *5*, 927–934; (b) Martre, A.-M.; Mousset, G.; Rhlid, R. B.; Veschambre, H. *Tetrahedron Lett.* **1990**, *31*, 2599–2602.
7. Brenna, E.; Fuganti, C.; Serra, S.; Kraft, P. *Eur. J. Org. Chem.* **2002**, 967–978.
8. Buchecker, R.; Egli, R.; Regel-Wild, H.; Tscharner, C.; Eugster, C.-H.; Uhde, G.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 2548–2562.
9. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G. P.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115–119.
10. Sheldrick, G. M. SHELXL-*97. Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.