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Lipase-catalyzed resolution of *p*-menthan-3-ols monoterpenes: preparation of the enantiomer-enriched forms of menthol, isopulegol, *trans*- and *cis*-piperitol, and *cis*-isopiperitenol

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Abstract—A study on the enzymic resolution of the most common *p*-menthan-3-ol monoterpene isomers is described. Enantioenriched alcohols **1**, **5**, **10**, **11** and **12** are obtained by means of the lipase-mediated kinetic acetylation of the corresponding racemic materials. The stereochemical aspects of the enzymic process have been investigated. We found that the structural features of the starting *p*-menthan-3-ol as well as the kind of lipase used, impacted strongly on the enantioselectivity of the resolution. The potentialities of this approach for preparative purposes are discussed.

1. Introduction

The 3-oxygenated monoterpenes of *p*-menthane family are important natural compounds. They are widespread in nature and are used extensively in flavour and fragrance industries and as pharmaceuticals, cosmetics, agrochemicals and cooling substances. Many industrial processes of syntheses, extraction and transformations of terpenes are correlated to this class of compounds because of the high commercial requirement of (−)-menthol. All the most common *p*-menthan-3-ols isomers **1**–**13** (Fig. 1) are intermediates in the preparation of (−)-menthol [1–3] and are used as starting building blocks in several syntheses of fine chemicals and natural compounds with biological activity.

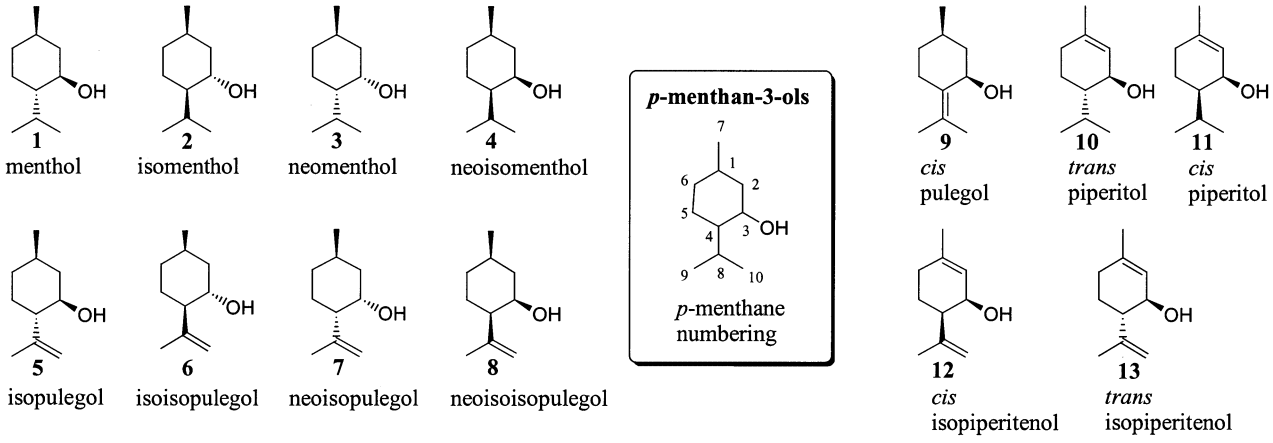

Figure 1. The most common *p*-menthan-3-ols.

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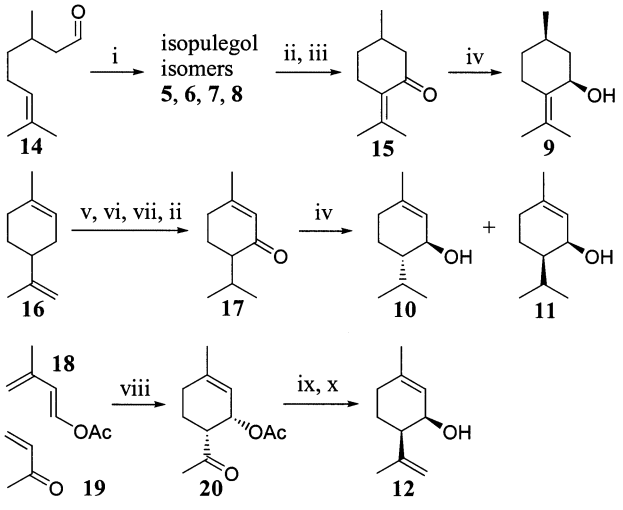
It is well known that the enantiomer and diastereoisomer composition of these products determine their activity features.[4] This is the case of the eight saturated *p*-menthan-3-ols isomers where only (−)-menthol **1** is used since it gives the best organoleptic performance. Moreover, recent studies have showed that while the mixture of the isopulegol isomers **5**–**8** has been used conventionally as a perfume ingredient, its main component (−)-isopulegol **5** is odourless[5] and can be used as a cooling agent. Therefore, several new methods of enantioselective synthesis[2,6] and of resolution of racemic material[7–14] have been developed in recent years.

As part of a program of preparation of enantiopure odorants, we have previously shown that enantiomer-enriched *p*-menthan-3,9-diols are easily obtainable by means of the lipase-mediated acetylation of racemic materials.[15] The latter approach seems to be rather flexible and accordingly, we extended the acquired enzymic methodology to the study of the resolution of *p*-menthan-3-ols **1**–**13**.

Although many processes for the enzyme-mediated preparation of (−)-menthol **1** are described in the literature,[7–14] a similar approach to the preparation of the enantiopure compounds **5**–**13** is still lacking. In light of these observations we report here the results of our studies on the preparation of racemic compounds **5**–**13** and on their lipase-mediated resolution.

2. Results and discussion

Our study first involved the preparation of the racemic starting materials. Racemic menthol **1** is commercially available while the syntheses of racemic **5**–**12** were performed by slight modification of some reported procedures (Scheme 1). Cyclisation of citronellal under Lewis acid catalysis ($SnCl_4$)[16] afforded a mixture of the isopulegol isomers **5**–**8** in the ratio: 66/30/3/1 respectively. These latter were used for the preparation of *cis*-pulegol **9** by sequential oxidation, base-catalyzed isomerization[17] and $LiAlH_4$ reduction.[18] The latter reaction afforded only the *cis*-isomer whereas the *trans*-isomer was not formed because of its great instability.



Scheme 1. *Reagents and conditions*: (i) $SnCl_4$ cat., CH_2Cl_2; (ii) CrO_3/H_2SO_4, acetone; (iii) NaOH cat., EtOH; (iv) $LiAlH_4$, Et_2O; (v) H_2, PtO_2, EtOH; (vi) O_2, MeOH, rose bengal, light; (vii) Na_2SO_3 aq.; (viii) benzene, reflux; (ix) Ph_3PCH_2, THF; (x) KOH, MeOH.

Piperitol isomers **10** and **11** were prepared from racemic limonene **16** by a multistep sequence. Regioselective hydrogenation of the disubstituted double bond by means of platinum catalysis followed by a photooxidation reaction with oxygen and bengal rose as sensitizer gave a mixture of hydroperoxides which were reduced to the related alcohols.[19] The latter mixture contained mostly *p*-menth-2-en-1-ol that gave piperitone **17** by oxidation with Jones' reagent. Treatment of the crude mixture with the oxidant followed to the chromatographic separation of **17** and $LiAlH_4$ reduction[20] of the latter gave the separable *trans*-piperitol **10** (51%) and the *cis*-piperitol **11** (42%).

Although various syntheses of isopiperitenol are described in the literature,[3,21–23] few of them are highly diastereoselective affording a mixture of *cis*- and *trans*-isopiperitenol **12** and **13**. Since we were interested in the study of each single diastereoisomer we looked for a more selective pathway. We found that the Diels–Alder reaction of methyl-vinyl ketone **19** and 1-acetoxy-3-methyl 1,3-butadiene **18** gave 6-(acetyl)-3-methylcyclohex-2-en-1-yl acetate **20** with good diastereoselectivity (90%) though a similar reaction employing 1-silyloxy-3-methyl 1,3-butadiene[16] gave inferior selectivity (75%). The following Wittig methylenation of the ketone functionality allowed the construction of the entire *p*-menthane framework. Subsequent KOH hydrolysis of the acetate moiety afforded *cis* piperitol **12** without variation of the diastereoisomeric ratio. In order to obtain diastereoselectively *trans* piperitol **13**, we tried the isomerization reaction of compound **20**, however under both acid and base catalysis the substrate undergoes elimination with the formation of dienic ketone.

Each of the obtained *p*-menthan-3-ol was treated with vinyl acetate in ^{t}BuOMe solution in the presence of lipases. The reactivity of the substrates towards the irreversible acetylation reaction was tested by monitoring at regular time intervals the distribution of chemical species (GC analysis) and by isolation and full characterization of the products. The results of this study, seen together (Table 1 and Scheme 2), lead to some interesting conclusions.

Porcine pancreatic lipase does not catalyse the acetylation reaction for any of the substrates used and only a trace of acetates was detected in few cases **1** and **10**. Both *candida rugosa* lipase and lipase PS are good catalysts for the same reaction although the latter enzyme seems to be superior in terms of efficiency and enantioselectivity.

Table 1. Results of the enzyme-mediated acetylation of *p*-menthane-3-ol (±)-**1**, (±)-**5**–**8**, (±)-**9**, (±)-**10**, (±)-**11** and (±)-**12**

	Enzyme	Time (days)	Configuration of the reacting enantiomer	Ee of recovered alcohol (%)	Ee of acetylated product (%)	Enantiomer ratio	Conversion
(±)-**1**	PPL	21	[b]	[b]	[b]	[b]	0.01
	CRL	14	1*R*,3*R*,4*S*	60	94	60	0.390
	PS	14	1*R*,3*R*,4*S*	78	97	156	0.446
(±)-**5**–**8**	PPL	80	[a]	[a]	[a]	[a]	[a]
	CRL	60	1*R*,3*R*,4*S*	[b]	95	[b]	[b]
	PS	50	1*R*,3*R*,4*S*	[b]	98	[b]	[b]
(±)-**9**	PPL	30	[a]	[a]	[a]	[a]	[a]
	CRL	30	[b]	0	[b]	[b]	[b]
	PS	30	1*R*,3*R*	8	[b]	[b]	[b]
(±)-**10**	PPL	21	[b]	[b]	[b]	[b]	0.01
	CRL	21	3*S*,4*S*	59	90	35	0.396
	PS	10	3*S*,4*S*	81	99	501	0.450
(±)-**11**	PPL	21	[a]	[a]	[a]	[a]	[a]
	CRL	21	3*S*,4*R*	71	90	40	0.441
	PS	14	3*S*,4*R*	91	99	638	0.479
(±)-**12**	PPL	21	[a]	[a]	[a]	[a]	[a]
	CRL	28	3*R*,4*R*	55	89	298	0.382
	PS	8	3*R*,4*R*	92	99	662	0.482

[a] The substrate was not acetylated.
[b] Data not determined.

Racemic menthol **1** was converted by CRL and lipase PS into the (−)-menthyl acetate **21** with good enantioselectivity though the e.e. of the recovered alcohol was moderate. Hydrolysis of **21** gave (−)-menthol **1** in good accord with the processes described in the patent literature.

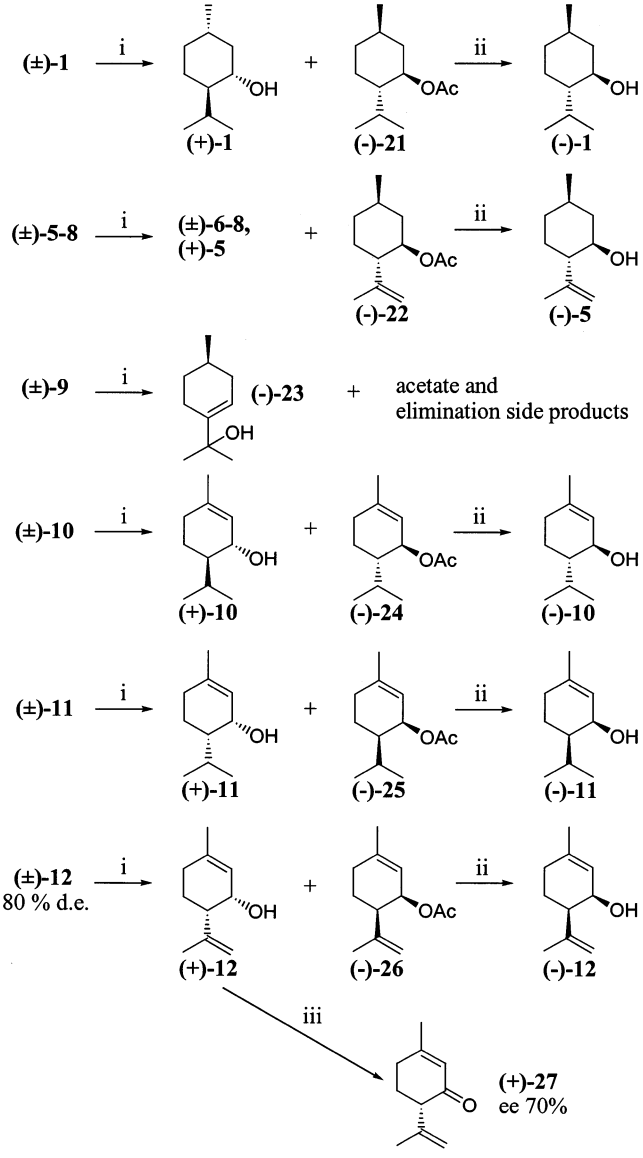
The mixture of the isopulegol isomers **5**–**8** was acetylated very slowly and both CRL and lipase PS afforded only the (−)-isopulegol acetate **22** with good to excellent enantioselectivity and complete diastereoselectivity. Hydrolysis of the latter acetate gave (−)-isopulegol with high enantiomeric purity. This fact is noteworthy since (−)-**5** is a relevant product for industrial processes, fine chemical production or for its cooling activity. The industrial preparation of (−)-**5** is correlated to the synthesis of enantiopure citronellal which is manufactured mainly by the Takasago Co. in the process of asymmetric isomerization of geranyl and neryldiethylamine. Since this latter reaction is performed by the proprietary technology based on the chiral Rh(I)-BINAP catalyst, the preparation of enantiopure isopulegol remains restricted to the owner of this process. Otherwise, by our resolution method, (−)-**5** is obtained straightforwardly from commercially available racemic citronellal without troublesome chemical manipulation.

Concerning the acetylation of the isomeric monounsaturated alcohols **9**, **10** and **11** the behaviour was again different. Racemic **9** was slowly converted in its acetate but with concomitant isomerisation to tertiary alcohol **23** and its acetate. Isolation gave only alcohol **23** with very low enantiomeric enrichment (8% e.e. by PS lipase and 0% e.e. by CRL). Otherwise, *trans*-piperitol **10** and *cis*-piperitol **11** were converted by lipase PS in enantiopure acetate (−)-**24** and (−)-**25**, respectively whereas the unreacted (+)-**10** and (+)-**11** show good enantiomeric purity. The same reactions performed with CRL gave analogous results although with inferior selectivity. Moreover, since natural (−)-(*R*)-piperitone is available in moderate e.e. (60–90%) by extraction from *eucalyptus dives*, the piperitols resulting from its reduction are not good chiral building blocks for asymmetric synthesis. Taking advantage of the above-described selectivity, we designed a method for the purification of these easy available materials. Separate treatment of natural (+)-**10** and (−)-**11** with lipase PS in our reaction conditions (see experimental) afforded enatiopure (+)-**10** and (−)-**25**, respectively. The saponification of this latter gave enantiopure (−)-**11**.

Relating to the resolution of the dienic alcohol **12**, we obtained similar results. Racemic isopiperitenol **12** was converted by CRL and lipase PS to the acetate (−)-**26** with good to excellent enantioselectivity (89 and 99% e.e., respectively) whereas recovered alcohol (+)-**12** showed moderate to good enantioenrichment by CRL (55% e.e.) and lipase PS (92% e.e.) respectively. Although the starting material (±)-**12** was not a single diastereoisomer (90% of *cis* derivative) the isolated products showed comparable d.e.s confirming that both lipases are not diastereoselective. Moreover, in order to assign the absolute stereochemistry of (+)- and (−)-*cis* isopiperitenol, we converted (+)-**12** in the (+)-isopiperitenone **27** by MnO_2 oxidation. Since the latter ketone is known[24] to have the (*S*)-configuration (+)-*cis* isopiperitenol and (−)-*cis* isopiperitenol have (3*S*,4*S*) and (3*R*,4*R*) configurations. On the other hand, the oxidation of (+)-**12** (92% e.e.) afforded (+)-**27** with significantly lower e.e. (70%). Judging from these experimental data, it is clear that (3*R*,4*S*)-*trans* isopiperitenol **13** was acetylated by CRL and lipase PS similar to piperitenol **10** and **11**.

3. Conclusions

The preparation and the study of the enzyme-mediated resolution of racemic *p*-menthan-3-ols **1**–**13** are described. Some general results have been achieved. Porcine pancreatic lipase does not catalyse the acetylation reaction whereas CRL and lipase PS afforded the acetates in good and excellent enantioselectivity respectively with the single exception of *cis*-pulegol **9**. The latter reaction is also diastereoselective for the *p*-menthan-3-ol without a double bond in the cyclohexanic rings **1**–**4** and **5**–**8** as confirmed from the patent literature **1**–**4** and from the present work **5**–**8**. In the latter case the enzymic process performed on the racemic mixture of the eight-isopulegol isomers afforded exclusively the relevant (−)-isopulegol **5** in enantiopure form. Otherwise the alcohol with one unsaturation on C(1) **10**–**13**, are acetylated without diastereoselectivity and with an enantiodiscrimination depending exclusively from the C(3) configuration. The latter selectivity allowed us to prepare the enantiomeric form of *trans*- and *cis*-piperitol either by resolution of the corresponding racemic materials and from the natural enantioenriched material by enzyme-based purification. At last, the dienic *cis*-isopiperitenol **12** was resolved and the absolute stereochemistry of the enantiomers assigned by chemical correlation.



Scheme 2. *Reagents and conditions*: (i) Lipase, vinyl acetate *t*-butylmethylether; (ii) KOH, MeOH; (iii) MnO_2, CH_2Cl_2.

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded in $CDCl_3$ solution at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^{1}H). The chemical-shift is based on internal tetramethylsilane. IR spectra were recorded on a Perkin–Elmer 2000 FTIR spectrometer. Mass spectra were measured on a Finnigan-MAT TSQ 70 spectrometer. Melting points were measured on a Reichert melting-point apparatus, equipped with a Reichert microscope, and are uncorrected. Optical rotations were determined on a Propol automatic digital polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns. Lipase PS from *Pseudomonas cepacia* (Amano Pharmaceuticals Co., Japan), *Candida rugosa* lipase (CRL; Sigma, type VII), porcine pancreatic lipase (PPL, Sigma, type II) were employed. GC: DANI-HT-86.10 gas chromatograph; enantiomer and diastereoisomer excesses determined on a Chirasil DEX-CB column (25 m×0.25 mm; Chrompack) with the following temp. program: Analysis of menthol acetate: 30°–3°/min −180°; t_R 21.72, 22.93. Analysis of the isopulegol acetate: 30°–0.5°/min −90° −20°/min–180°; t_R 73.87, 75.97. Analysis of the piperitol acetate and isopiperitenol acetate: 50°(3 min)–0.5°/min −70°–20°/min–180°; t_R (*trans* piperitol acetate) 45.10, 45.39; t_R (*cis* piperitol acetate) 44.86, 45.20; t_R (*cis* isopiperitenol acetate) 45.22, 45.79.

4.2. Synthesis of the racemic substrates 5–13

4.2.1. Isopulegol isomers 5–8. To an ice-cooled and stirred solution of citronellal **14** (60 g, 389 mmol) in dry CH_2Cl_2 (500 mL) is added dropwise a solution of $SnCl_4$ (2 mL, 17 mmol) in CH_2Cl_2 (20 mL) maintaining the temperature below 5°C. After the addition is complete, stirring is continued for 1 h and then a solution of saturated $NaHCO_3$ (200 mL) is added. The organic solvent was evaporated and the residue was steam distilled. The distillate was extracted with ether (3×200 mL), and the organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled to give a mixture of the isopulegol isomers **5**–**8** (50 g, 83%), sum of isomers (by GC analysis) 96%; isopulegol/neoisopulegol/isoisopulegol/isoneoisopulegol ratio: 66/30/3/1.

4.2.2. *cis*-Pulegol 9. Jones reagent (2.7 M, 60 mL) was added dropwise to a stirred solution of the mixture of the isopulegol isomers **5**–**8** (25 g, 162 mmol) in acetone

(100 mL) at 0°C. The reaction was stirred at the same temperature until all starting material was consumed and then poured in a mixture of water (100 mL) and crushed ice (100 g). The resulting mixture was extracted with diethyl ether (3×100 mL) and the organic phase was washed with water (100 mL) and brine. The solvent was eliminated by concentration at reduced pressure and the residue was dissolved in ethanol (100 ml) and treated with catalytic NaOH (1 g). The solution was heated at reflux for 1 h, then the ethanol was eliminated in vacuo and the residue partitioned between diethyl ether and water. The organic phase was washed with 5% aq. HCl (50 mL) and brine and then concentrate at reduced pressure. The distillation of the residue gave pure pulegone **15** (19.8 g, 80%). A solution of the obtained pulegone (15 g, 99 mmol) in dry diethyl ether (50 mL), was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (3.76 g, 99 mmol) in dry diethyl ether (150 mL) at 0°C. When the addition was complete the mixture was stirred at rt until no more starting ketone was detected by TLC analysis. The reaction was quenched by dropwise addition of water (10 mL) and a 10% aqueous solution of NaOH (20 mL). The ether layer was separated, was washed with brine, was dried (Na_2SO_4) and the solvent evaporated in vacuo. Distillation of the residue (bp 68–70°/0.8 mmHg) afforded *cis* pulegol **9** (12 g, 79%).

4.2.3. Piperitol isomers 10 and 11. Racemic limonene **16** (dipentene, 137 g, 1 mol) in absolute ethanol (500 mL) was hydrogenated at atmospheric pressure and rt using PtO_2 as catalyst. After 1 mol of hydrogen was absorbed, the catalyst was removed by filtration and the solution was diluted with additional ethanol (500 mL), treated with bengal rose (1 g) and irradiated at rt in a Rayonet photochemical apparatus (120 W high-pressure Hg lamp) with continuous purging of dry oxygen. When the photooxidation was complete (10 days) the resulting mixture of peroxides was added dropwise to a cooled (0°C) and stirred solution of Na_2SO_3 (250 g) in water (1 L). The reaction was stirred at rt overnight and then extracted with ether (3×200 mL). The organic phase was washed with brine, concentrated in vacuo and the residue was dissolved in acetone (300 mL). The obtained solution was cooled to 0°C and treated under stirring with 2.7 M Jones reagent (250 mL). After stirring for 2 h, the reaction was diluted with water (600 mL), extracted with ether (3× 200 mL) and the organic phase was concentrated under reduced pressure. The residue was purified by chromatography (hexane–diethyl ether, 95/5) and distillation (bp 70°C/0.5 mmHg) to give pure piperitone **17** (41 g, 27%).

A solution of the obtained ketone **17** (20 g, 132 mmol) in dry diethyl ether (60 mL), was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (5 g, 132 mmol) in dry diethyl ether (200 mL) at 0°C. When the reduction was complete (2 h), the reaction was quenched by dropwise addition of water (15 mL) and a 10% aqueous solution of NaOH (25 mL). The ether layer was separated, washed with brine, dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by chromatography eluting with hexane–diethyl ether (95:5→80:20) to give pure *cis*-piperitol **11** (6.4 g, 42%), ^{1}H NMR, δ, ppm: 5.63 (1H, dm, $J=5.5$ Hz, H-C(2)), 4.13 (1H, bt, $J=3.5$ Hz, H-C(3)), 2.02–1.91 (2H, m), 1.80–1.55 (2H, m), 1.69 (3H, s, Me(7)), 1.45–1.10 (2H, m), 1.00 and 0.96 (6H, d+d, $J=6.6$ Hz, Me(9) and Me(10)); m/z (EI): 154 (M^+, 4), 139 (34), 121 (3), 112 (9), 111 (10), 93 (16), 91 (12), 84 (100), 83 (42), 77 (14), 69 (10), 55 (20), 41 (33); FT-IR (film) 3380, 2956, 1674, 1474, 1449, 1429, 1384, 1047, 1023, 957, 902, 848, 803 cm^{-1} and *trans*-piperitol **10** (10.4 g, 51%), ^{1}H NMR, δ, ppm: 5.39 (1H, s, H-C(2)), 4.01 (1H, bs, H-C(3)), 2.12–1.88 (3H, m), 1.76–1.60 (1H, m), 1.68 (3H, s, Me(7), 1.57 (1H, d, $J=7$ Hz, OH), 1.40–1.17 (2H, m), 0.97 and 0.84 (6H, d+d, $J=6.9$ Hz, Me(9) and Me(10)); m/z (EI): 154 (M^+, 6), 139 (34), 121 (3), 112 (8), 111 (12), 93 (17), 91 (13), 84 (100), 83 (43), 77 (14), 69 (11), 55 (24), 41 (36); FT-IR (film) 3325, 2959, 1676, 1467, 1385, 1159, 1049, 1027, 986, 899 cm^{-1}.

4.2.4. Isopiperitenol isomers 12 and 13. A solution of methyl vinyl ketone **19** (30 mL, 360 mmol) and 1-acetoxy-3-methyl 1,3-butadiene **18**[25] (40 g, 317 mmol) in benzene (200 mL) was heated at reflux under nitrogen for 6 h. After cooling at rt the solvent was removed under reduced pressure and the residue was purified by chromatography eluting with hexane–ethyl acetate (9:1) to give pure 6-(acetyl)-3-methylcyclohex-2-en-1-yl acetate **20** (53.2 g, 85%) as a diastereoisomer mixture (*cis*/*trans* 9:1 by GC), ^{1}H NMR (*cis* isomer), δ, ppm: 5.64 (2H, m, H-C(1) and H-C(2)), 2.60 (1H, dt, $J=$ 11.3, 3.6 Hz, H-C(6)), 2.30–1.72 (4H, m, H-C(4) and H-C(5)), 2.18 (3H, s, OAc), 1.99 (3H, s, acetyl), 1.74 (3H, Me-C(3)); m/z (EI): 153 (45), 136 (22), 121 (42), 111 (26), 93 (100), 79 (35), 43 (92); FT-IR (film) 2939, 1732, 1721, 1432, 1372, 1239, 1158, 1065, 1018, 956 cm^{-1}. A sample of the obtained **20** (22 g, 112 mmol), dissolved in dry THF (60 mL), was added to 1 M (triphenylphosphonio)methanide (140 mmol) previously prepared by reaction of $(Ph_3PMe)I$ (58.5 g, 145 mmol) in THF (200 mL) with 10 M BuLi in hexane (14.5 mL). The resulting mixture was heated under reflux for 2 h, cooled to rt and then poured into cool (0°C) H_2O (300 mL). The quenched mixture was extracted with diethyl ether (2×200 mL), and the organic phase was successively washed with sat. NH_4Cl solution and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in hexane/Et_2O 3:1, and the triphenylphosphine oxide was eliminated by crystallization (ice-bath cooling). The liquid phase was evaporated and treated with methanolic KOH (70 mL of 20% solution) stirring at rt until no more starting acetate was detected by TLC analysis. The mixture was diluted with water (200 mL) and extracted with diethyl ether (3×100 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography and bulb-to-bulb distillation to give pure isopiperitenol (11.8 g, 70%) as a diastereoisomer mixture of **12** and **13** (*cis*/*trans* 9:1 by GC), ^{1}H NMR (*cis* isomer), δ, ppm: 5.68 (1H, dq, $J=5$, 1.5 Hz, H-C(2)), 5.00 (1H, s, H-C(9)), 4.81 (1H, s, H-C(9)), 4.13 (1H, bt, $J=4$ Hz, H-C(3)), 2.18–1.98 (3H, m), 1.89–1.67 (2H, m), 1.83 (3H, s, Me(10)), 1.72 (3H, s, Me(7)),

1.62–1.49 (1H, m, OH); *m*/*z* (EI): 152 (M^+, 5), 134 (7), 121 (12), 119 (9), 109 (14), 91 (13), 84 (100), 83 (54), 69 (12), 56 (12), 41 (15); FT-IR (film) 3422, 2930, 1672, 1648, 1449, 1376, 1245, 1154, 1068, 957, 885, 815 cm^{-1}

4.3. Lipase-mediated resolution of the racemic substrates

4.3.1. General procedure. A mixture of the suitable racemic substrate (5 g), lipase (3 g), vinyl acetate (5 mL) and ^{t}BuOMe (30 mL) was stirred at rt and the formation of the acetate monitored by TLC analysis. The reaction was stopped at about 50% of conversion by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was purified by chromatography eluting with hexane–diethyl ether (95:5→80:20) to give alcohol acetate and unreacted alcohol. The acetate was then dissolved in methanol (10 mL) and treated with KOH (2 g) in methanol (15 mL) stirring at rt until no more starting material was detected by TLC analysis. The mixture was diluted with water (70 mL) and extracted with diethyl ether (3×30 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography and bulb-to-bulb distillation to give the enantiomeric form of the unreacted alcohol.

4.3.2. Resolution of racemic menthol 1. Racemic **1** was resolved according to the general procedure. The use of lipase PS as catalyst gave (−)-menthyl acetate **21** (99% GC), $[\alpha]_D^{20}=-80.5$ (*c* 2, $CHCl_3$), chiral GC (t_R 21.72) e.e. = 97%, and (+)-menthol **1** (99% GC), $[\alpha]_D^{20}=+36.9$ (*c* 2, EtOH); chiral GC (t_R 22.93) e.e. = 78%. The use of CRL as catalyst gave (−)-menthyl acetate (99% GC), $[\alpha]_D^{20}=-78.5$ (*c* 2, $CHCl_3$), chiral GC e.e. = 94%, and (+)-menthol (99% GC), $[\alpha]_D^{20}=+29.5$ (*c* 2, EtOH); chiral GC e.e. = 60%. Saponification of the acetate samples gave pure (−)-menthol, $[\alpha]_D^{20}=-48.9$ (*c* 2, EtOH) and $[\alpha]_D^{20}=-47.1$ (*c* 2, EtOH) respectively.

4.3.3. Preparation of enantiopure (+)-isopulegol 5 from racemic isopulegol isomers 5–8. A mixture of the four racemic isopulegol isomers **5**–**8** (15 g, 97 mmol) was used as substrate in the general procedure of resolution. The use of lipase PS as catalyst gave (−)-isopulegol acetate **22** (3.6 g, 18 mmol), (98% GC), $[\alpha]_D^{20}=-17.9$ (*c* 1, $CHCl_3$), lit.[26] $[\alpha]_D^{20}=+17.3$ (*c* 2, $CHCl_3$), chiral GC (t_R 73.87) e.e. = 98% and a mixture of the unreacted isopulegol isomers **5**–**8** (11.2 g, 72 mmol). Saponification of the acetate gave pure (−)-isopulegol **5** (2.3 g, 15 mmol) (99% GC), $[\alpha]_D^{20}=-13.6$ (*c* 1, $CHCl_3$). The use of *candida rugosa* lipase as catalyst gave (−)-isopulegol acetate (2.9 g, 15 mmol), (97% GC), $[\alpha]_D^{20}=-17.6$ (*c* 1, $CHCl_3$), chiral GC e.e. = 95% and a mixture of the unreacted isopulegol isomers **5**–**8** (11.4 g, 74 mmol). Saponification of the acetate gave pure (−)-isopulegol (2 g, 13 mmol) (99% GC), $[\alpha]_D^{20}=-13.4$ (*c* 1, $CHCl_3$).

4.3.4. Enzymic acetylation of racemic *cis* pulegol. Racemic **9** was acetylated according to the general procedure. Either the use of lipase PS or CRL as catalyst afforded a mixture consisting in unreacted **9**, its acetate, the isomerized alcohol **23** and its acetate. All the attempt to the separation of the mixture by chromatography or distillation gave alcohol **23** (98% GC), ^{1}H NMR, δ, ppm: 5.70 (1H, m, H-C(3)), 2.13–1.92 (3H, m), 1.81–1.48 (4H, m), 1.32–1.08 (1H, m), 1.31 and 1.30 (6H, s+s, Me(9) and Me(10)), 0.95 (3H, d, $J=6.1$ Hz, Me(7)); *m*/*z* (EI): 154 (M^+, 13), 139 (100), 121 (29), 107 (7), 95 (15), 81 (22), 67 (6), 59 (18), 43 (44); FT-IR (film) 3358, 2924, 1457, 1373, 1153, 949, 899, 843; and a inseparable mixture of its acetate and some elimination side products. When lipase PS was used as catalyst, the obtained alcohol **23** show $[\alpha]_D^{20}=-7.2$ (*c* 2, $CHCl_3$), lit.[27] $[\alpha]_D^{20}=+92.9$ ($CHCl_3$), e.e. = 8%, while CRL gave racemic **23**.

4.3.5. Resolution of racemic *trans*-piperitol. Racemic **10** was resolved according to the general procedure. The use of lipase PS as catalyst afforded (−)-*trans*-piperitol acetate **24** (98% GC), $[\alpha]_D^{20}=-144.6$ (*c* 2, $CHCl_3$), lit.[28] $[\alpha]_D^{20}=+119$ (*c* 1.16, $CHCl_3$), chiral GC (t_R 45.10) e.e. = 99%, ^{1}H NMR, δ, ppm: 5.33 (1H, m, H-C(2)), 5.27 (1H, m, H-C(3)), 2.05 (3H, s, OAc), 2.02–1.92 (2H, m), 1.80–1.60 (2H, m), 1.69 (3H, MeC(7)), 1.56–1.31 (2H, m), 0.95 and 0.84 (6H, d+d, $J=6.9$ Hz, Me(9) and Me(10)); *m*/*z* (EI): 196 (M^+, 1), 154 (12), 136 (32), 121 (100), 111 (7), 93 (62), 84 (68), 77 (22), 69 (14), 55 (13), 43 (57); FT-IR (film) 2960, 1732, 1438, 1370, 1240, 1159, 1020, 970, 904 cm^{-1} and (+)-*trans*-piperitol **10** (98% GC), $[\alpha]_D^{20}=+24$ (*c* 2, EtOH), lit.[20] $[\alpha]_D^{17}=+28$ (*c* 2, EtOH), chiral GC (t_R 45.39) e.e. = 81%. The use of CRL as catalyst gave (−)-*trans*-piperitol acetate (98% GC), $[\alpha]_D^{20}=-130$ (*c* 2, $CHCl_3$), chiral GC e.e. = 90%, and (+)-*trans*-piperitol (98% GC), $[\alpha]_D^{20}=+17.5$ (*c* 2, EtOH); chiral GC e.e. = 59%. Saponification of the acetate samples gave pure (−)-*trans*-piperitol $[\alpha]_D^{20}=-30.4$ (*c* 2, EtOH) and $[\alpha]_D^{20}=-27.3$ (*c* 2, EtOH), respectively.

4.3.6. Resolution of racemic *cis*-piperitol. Racemic **11** was resolved according to the general procedure. The use of lipase PS as catalyst gave (−)-*cis*-piperitol acetate **25** (98% GC), $[\alpha]_D^{20}=-376$ (*c* 2, $CHCl_3$), lit.[28] $[\alpha]_D^{20}=-284$ (*c* 1.11, $CHCl_3$), chiral GC (t_R 44.86) e.e. = 99%, ^{1}H NMR, δ, ppm: 5.64 (1H, m, H-C(2)), 5.23 (1H, m, H-C(3)), 2.12–1.87 (1H, m), 2.02 (3H, s, OAc), 1.86–1.24 (4H, m), 1.70 (3H, s, Me(7)), 1.21–1.07 (1H, m), 0.95 and 0.89 (6H, d+d, $J=6.7$ Hz, Me(9) and Me(10)); *m*/*z* (EI): 196 (M^+, 1), 154 (14), 136 (37), 121 (100), 111 (10), 93 (92), 84 (78), 77 (25), 69 (20), 55 (13), 43 (73); FT-IR (film) 2960, 1736, 1675, 1445, 1370, 1243, 1017, 951, 901 cm^{-1} and (+)-*cis*-piperitol **11** (98% GC), $[\alpha]_D^{20}=+184$ (*c* 2, EtOH), lit.[20] $[\alpha]_D^{20}=-246$ (*c* 2, EtOH), chiral GC (t_R 45.20) e.e. = 91%. The use of CRL as catalyst gave (−)-*cis*-piperitol acetate (98% GC), $[\alpha]_D^{20}=-339$ (*c* 2, $CHCl_3$), chiral GC e.e. = 90%, and (+)-*cis*-piperitol (98% GC), $[\alpha]_D^{20}=+126$ (*c* 2, $CHCl_3$); chiral GC e.e. = 71%. Saponification of the acetate samples gave pure (−)-*cis*-piperitol, mp 32°C, $[\alpha]_D^{20}=-203$ (*c* 2, EtOH) and $[\alpha]_D^{20}=-182$ (*c* 2, EtOH), respectively.

4.3.7. Preparation of enantiopure (+)-*trans*- and (−)-*cis*-piperitol from natural (−)-piperitone. A sample of natural (−)-piperitone **17** (from *eucalyptus dives*) 59% e.e.

{$[\alpha]_D^{20} = -11$ (*c* 3.5, $CHCl_3$), lit.[29] $[\alpha]_D^{20} = +18.6$ (*c* 3.45, $CHCl_3$), was reduced as described above to give (−)-*cis*-piperitol **11** {$[\alpha]_D^{20} = -107.5$ (*c* 2, EtOH)} and (+)-*trans*-piperitol **10** {$[\alpha]_D^{20} = +19.1$ (*c* 2, EtOH)}. The two alcohols were submitted to the general procedure of acetylation using lipase PS as catalyst and the reaction was stopped at about 70 and 30% of conversion, respectively. The two mixtures were purified by chromatography to give enantiopure (+)-*trans* piperitol {$[\alpha]_D^{20} = +30.5$ (*c* 2, EtOH) 98% e.e.} and (−)-*cis*-piperitol acetate {$[\alpha]_D^{20} = -378.2$ (*c* 2, $CHCl_3$) 99% e.e.}. The latter acetate give after saponification (−)-*cis*-piperitol {$[\alpha]_D^{20} = -206$ (*c* 2, EtOH)}.

4.3.8. Resolution of racemic *cis*-isopiperitenol. A mixture of racemic **12** and **13** (*cis*/*trans* 9:1) was used as substrate in the general procedure of resolution. The use of lipase PS as catalyst gave (−)-*cis*-isopiperitenol acetate **26** (98% GC), $[\alpha]_D^{20} = -378$ (*c* 2, $CHCl_3$), chiral GC (t_R 45.22) e.e. = 99%, d.e. 80%, ^{1}H NMR (*cis*-isomer), δ, ppm: 5.60 (1H, m, H-C(2)), 5.37 (1H, m, H-C(3)), 4.85 (1H, s, H-C(9)), 4.73 (1H, s, H-C(9)), 2.22–2.00 (3H, m), 1.97 (3H, s, OAc), 1.97–1.60 (2H, m), 1.77 and 1.73 (6H, s+s, Me(7) and Me(10)); *m*/*z* (EI): 194 (M^+, 1), 179 (1), 152 (27), 134 (84), 126 (13), 119 (45), 105 (18), 91 (35), 84 (100), 77 (16), 43 (26); FT-IR (film) 2935, 1732, 1674, 1648, 1441, 1371, 1239, 1021, 957, 910, 890 cm^{-1}; and (+)-*cis*-isopiperitenol **12** (98% GC), $[\alpha]_D^{20} = +213$ (*c* 2, $CHCl_3$), chiral GC (t_R 45.79) e.e. = 92%, d.e. 80%. The use of CRL as catalyst gave (−)-*cis*-isopiperitenol acetate (98% GC), $[\alpha]_D^{20} = -297$ (*c* 2, $CHCl_3$), chiral GC e.e. = 89%, d.e. 86% and (+)-isopiperitenol (98% GC), $[\alpha]_D^{20} = +79$ (*c* 2, $CHCl_3$); chiral GC e.e. = 55%, d.e. 76%. Saponification of the acetate samples gave pure (−)-*cis*-isopiperitenol $[\alpha]_D^{20} = -228$ (*c* 2, EtOH) and $[\alpha]_D^{20} = -210$ (*c* 2, EtOH), respectively.

4.4. Determination of the absolute configuration of *cis*-piperitenol

4.4.1. Preparation of isopiperitenone. A solution of (+)-*cis*-isopiperitenol **12** (1.5 g, 9.9 mmol, {$[\alpha]_D^{20} = +213$ (*c* 2, $CHCl_3$), e.e. = 92%, d.e. 80%} in CH_2Cl_2 (30 mL) was treated with MnO_2 (4 g, 46 mmol) stirring at rt for 2 h. The reaction was filtered and the solution was concentrated under reduced pressure. The residue was purified by chromatography (hexane–ether, 95:5) and bulb-to-bulb distillation (oven temp. 80–85°/0.6 mmHg) to afford pure (98% GC) (*S*)-(+)-isopiperitenone **27** (1.3 g, 8.7 mmol, 87%, $[\alpha]_D^{20} = +30.1$ (*c* 2, $CHCl_3$)), lit.[24] $[\alpha]_D^{20} = +49$ (*c* 0.96, $CHCl_3$); ^{1}H NMR, δ, ppm: 5.90 (1H, bq, $J = 1.5$ Hz, H-C(2)), 4.95 (1H, m, H-C(9)), 4.76 (1H, m, H-C(9)), 2.95 (1H, dd, $J = 5.3$, 10.3 Hz, H-C(4)), 2.40–2.30 (2H, m), 2.20–1.99 (2H, m), 1.96 (3H, s, Me(7)), 1.75 (3H, bq, $J = 0.7$ Hz, Me(10)); *m*/*z* (EI): 150 (M^+, 19), 135 (28), 122 (6), 117 (1), 107 (7), 91 (4), 82 (100), 67 (4), 54 (13); FT-IR (film) 3075, 2936, 1671, 1648, 1438, 1380, 1319, 1201, 1025, 891 cm^{-1}.

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