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A Chemoenzymatic, Preparative Synthesis of the Isomeric Forms of *p*-Menth-1-en-9-ol: Application to the Synthesis of the Isomeric Forms of the Cooling Agent 1-Hydroxy-2,9-cineole

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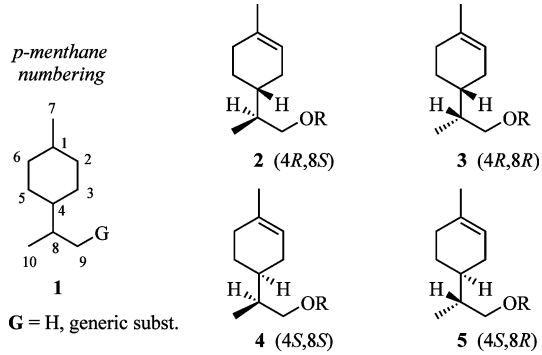
A preparative-scale synthesis of the four *p*-menth-1-en-9-ol isomers **2a**–**5a** has been achieved by means of two chemoenzymatic processes. Both synthetic pathways start from the enantiomeric forms of limonene that are converted into *p*-mentha-1,8-dien-9-al isomers **12** and **15**. The baker's yeast mediated reduction of the latter aldehydes afforded compounds **3a** and **5a**, respectively, with very high enantioselectivity. Moreover, chemical reduction of **12** and **15** gives the mixtures of enantiopure diastereoisomers **2a**/**3a** and **4a**/**5a**, respectively. PPL (*Porcine pancreas* lipase) mediated resolution of the latter mixtures followed by fractionating crystallization of derivatives **2b**–**5b** allowed the enantio- and diastereoisomerically pure alcohols **2a**–**5a** to be obtained. Compounds **2a**–**5a** have then been used as starting materials for the preparation of four isomers of the cooling agent 1-hydroxy-2,9-cineole (**6**–**9**).

Introduction

A great number of natural compounds show the general *p*-menthane structure **1** (Scheme 1). The most well known are the *p*-menthane terpenes and the sesquiterpenes of the bisabolene family that widely occur in nature as a constituents of a large number of essential oils.



Scheme 1. Structures and numbering of *p*-menth-1-en-9-ol isomers **2**–**5**.

Among these compounds, the most challenging are those that contain two contiguous secondary stereogenic centres: one in the cyclohexene ring and the other in the side chain.[1] Since many products of this kind show biological activity, which is strictly related to their absolute configuration, their syntheses need a high degree of stereocontrol. It is worthy to note that the formation of the C(4)–C(8) bond with simultaneous creation of two new asymmetric centres is a demanding synthetic reaction. The use of the four *p*-menth-1-en-9-ol isomers **2a**–**5a** as common chiral building blocks is an attractive alternative to the use of the above-mentioned stereoselective approach.

In view of the ready availability of both enantiomers of limonene, the specific transformation of the latter terpenes into the alcohols **2a**–**5a** was first investigated in 1966[2] and was improved a few years later.[3] The method consists of the hydroalumination or hydroboration of the C(8)=C(9) bond of limonene, followed by oxidation of the corresponding organoalane or organoborane derivatives, respectively, to afford the *p*-menth-1-en-9-ol isomers. These reactions proceed with high regioselectivity and very low (or no) diastereoselectivity, and the mixtures of enantiopure diastereoisomers are not easily separable. Fractionating crystallization of the corresponding 3,5-dinitrobenzoyl ester allows the large-scale preparation of alcohols **3a** and **4a**, whereas alcohols **2a** and **5a** can be obtained in very low yields (3–4%) only by a tedious process based on the use of mother liquors that are derived from the crystallization of **3b** and **4b**. Until now, this path remains the most simple and direct method of preparing the above-mentioned building blocks. As a consequence of this fact, many syntheses of natural products are based on the use of *p*-menth-1-en-9-ol as a mixture of enantiopure diastereoisomers,[4] and only few of them have employed the pure isomers.[5]

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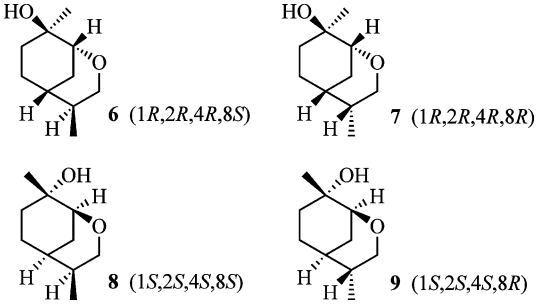
As part of a project aimed at the preparation of a new cooling agent with the *p*-menthane structure,[6] we recently discovered that 1-hydroxy-2,9-cineole (**6**–**9**, Scheme 2) exhibits a definite cooling effect. In order to start with a valuable structure–activity relationship (SAR) study, we needed to evaluate all the latter isomers in their pure form. Since the isomers of 1-hydroxy-2,9-cineole have been synthesized starting from the *p*-menth-1-en-9-ol isomers,[5a] we focused our attention on the large-scale preparation of the latter alcohols. Moreover, our previous interest in the use of biocatalysis for the enantioselective synthesis of terpene-[7] and sesquiterpene[8] derivatives led us to develop a chemoenzymatic approach to the compounds **2**–**5**.



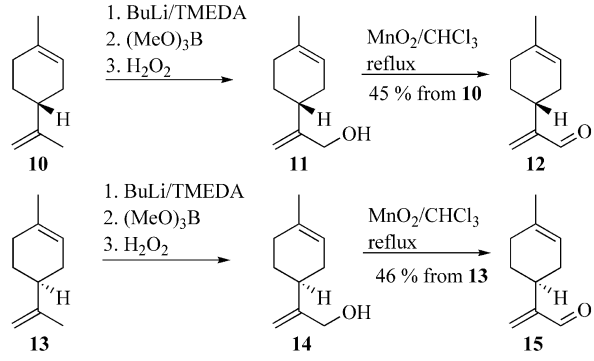
Scheme 2. Structures of the 1-hydroxy-2,9-cineole isomers (**6**–**9**).

Herein, we report the accomplishment of our plan by means of two different synthetic strategies. The first one afforded compounds **3a** and **5a** and is based on the baker's yeast mediated diastereoselective reduction of the C(8)=C(10) bond of *p*-mentha-1,8-dien-9-al isomers **12** and **15**. The second strategy afforded the four isomers **2a**–**5a** by means of the lipase-mediated resolution of the mixtures of enantiopure diastereoisomers **2a/3a** and **4a/5a**.

Results and Discussion

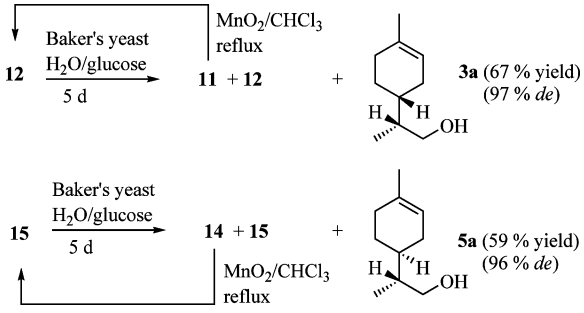
As mentioned above, limonene enantiomers are cheap and commercially available enantiopure starting materials for the synthesis of alcohols **2a**–**5a**. We selected aldehydes **12** and **15** (Scheme 3) as precursors for the latter alcohols. We envisaged that the diastereoselective reduction of the disubstituted double bond will be achieved by microbial reduction. It is known that the baker's yeast reduction of activated di- and trisubstituted olefins proceeds with high enantioselectivity.[8b–8d,9] Preliminary studies, aimed at the synthesis of the bisabolene sesquiterpenes, have shown that 3-(4-methylcyclohex-3-enyl)-but-2-enal isomers are good substrates for this type of transformations.[8c] In order to verify the applicability of the latter approach, we prepared a large amount of the two *p*-mentha-1,8-dien-9-al isomers.

The selective metalation at C(10) of (+)-limonene **10** and (–)-limonene **13** was performed by using a *n*-butyllithium/TMEDA complex.[10] According to a method described in the patent literature, the allyllithium intermediates were treated with trimethylborate, and the obtained organoborane derivatives were oxidized in situ with hydrogen peroxide to afford alcohols **11** and **14**, respectively.[11] The yields were



Scheme 3. Synthesis of the *p*-menth-1,8-dien-9-al enantiomers **12** and **15**.

satisfactory, although the metalation was not completely regioselective. Indeed, also the perillic alcohol was afforded in about 10% of the *p*-menthenol mixture. Luckily, perillaldehyde is easily separable from *p*-mentha-1,8-dien-9-al by chromatography. Therefore, manganese dioxide oxidation of the impure alcohols **11** and **14**, followed by purification afforded aldehydes **12** and **15**, respectively. The latter compounds were then submitted to microbial reduction (Scheme 4).



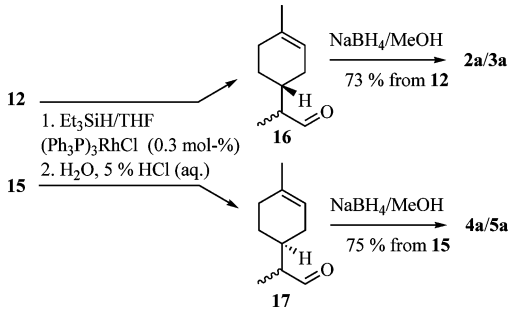
Scheme 4. Baker's yeast mediated synthesis of **3a** and **5a**.

The experimental conditions were the same for each substrate (see Experimental Section), and we decided to perform the baker's yeast reduction in the presence of a nonpolar resin. This technique allowed a large-scale reduction, since high concentration of substrate (7 g L^{-1}) was achieved and the workup procedure was simplified. The results of the biotransformations were very good. The reduction of the conjugated double bond by baker's yeast gave high yields of saturated alcohols (67–59% of isolated products), and the diastereoisomeric ratio of the products was independent of the enantiomeric form of the substrates. The new chiral centre was formed with high preference for the (*R*) absolute configuration, which confirms the general trend of the enantioselectivity for the reduction of this type of aldehydes.[9] Since the microbial transformation gave also allyl alcohols (**11** and **14**) and unreacted aldehydes, the entire reaction mixture was submitted to treatment with manganese dioxide. Thus, after chromatographic separation, the saturated alcohols were isolated, and the starting aldehydes could be resubjected to microbial reduction. Overall, the process allows the diastereoselective, large-scale preparation

of alcohol **3a** (97% *de*) and alcohol **5a** (96% *de*) from aldehyde **12** and **15**, respectively.

However, we are interested in preparing all the isomeric forms of the latter alcohols. Our previous study on the lipase-mediated resolution of *p*-menthan-3,9-diols[7d] showed that the acetylation of the 9-hydroxy group is seldom diastereoselective. Therefore, we decided to prepare the mixtures of enantiopure diastereoisomers **2a/3a** and **4a/5a**, respectively, in order to submit them to enzyme-mediated resolution.

The latter alcohols were prepared by a two-step procedure starting again from the *p*-mentha-1,8-dien-9-al isomers (Scheme 5). The aldehydes **12** and **15** were treated with triethylsilane in the presence of a catalytic amount of Wilkinson's catalyst.[12] The reduction of the conjugated double bond followed by the in situ hydrolysis of the obtained triethylsilylenolether intermediates afforded aldehydes **16** and **17**, respectively. The latter compounds were purified by chromatography and then reduced with sodium borohydride to give two mixtures of enantiopure diastereoisomers **2a/3a** and **4a/5a**, respectively.



Scheme 5. Regioselective chemical reduction of aldehydes **12** and **15**.

Each of the two mixtures of alcohols was treated with vinyl acetate in *t*BuOMe solution in the presence of different lipases [PPL (*Porcine pancreas* lipase) type II, CRL (*Candida rugosa* lipase) type VII and lipase PS (*Pseudomonas cepacia*)]. The reactivity of each substrate towards the irreversible acetylation was tested by monitoring the product distribution at regular time intervals by chiral GC analysis. The results of this study are collected in the Table 1 and present some interesting observations. All the lipases mediate the acetylation of the alcohols, but the diastereoselectivity is strongly dependent on the type of lipase used. PPL showed a higher selectivity with a preference for the conversion of the (8*S*) isomer. In contrast, lipase PS showed low selectivity, whereas CRL converted the (8*R*) isomer, although with poor selectivity. Noteworthy, the absolute configuration of the stereocentre at position 4 did not affect the stereochemical course of the acetylation.

Interestingly, these results are in partial contrast with those previously obtained for the acylation of the very closely related substrate *p*-menthane-3,9-diol,[7d] where lipase PS showed a higher enantioselectivity. Unexpectedly, the present study displays some similarity between the kinetic resolution of *p*-menth-1-en-9-ol and those described

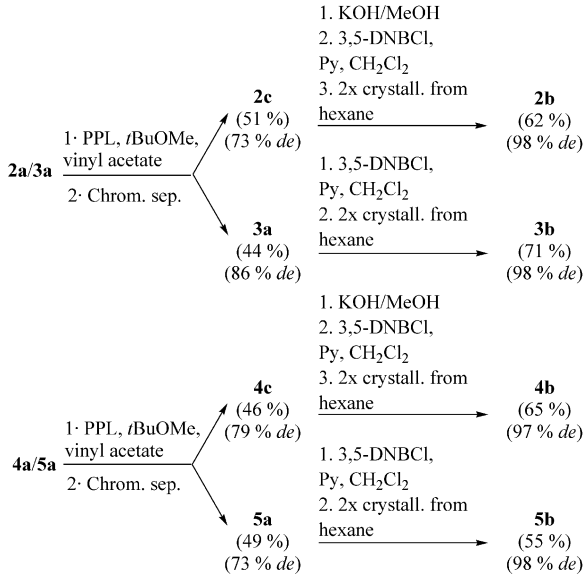
Table 1. Results of the enzyme-mediated acetylation of *p*-menthane-9-ol **2a/3a** and **4a/5a**.

Entry	Enzyme	Acetylated product configuration; *de* [%][a]	Enantiomer ratio (*E*)[b]	Conversion
2a/3a	PPL	4*R*,8*S*; 73	17	0.54
	CRL	4*R*,8*R*; 25	1.9	0.40
	PS	4*R*,8*S*; 29	2.3	0.49
4a/5a	PPL	4*S*,8*S*; 79	18	0.48
	CRL	4*S*,8*R*; 21	1.8	0.50
	PS	4*S*,8*S*; 38	3.1	0.48

[a] Chiral GC analysis. [b] $E = \ln[1 - c \times (1 + de_p)]/\ln[1 - c \times (1 - de_p)]$.

for the 2-arylpropan-1-ol (primary alcohols)[13] – both show the preferential acetylation of the (*S*) enantiomer by PPL with a higher selectivity.

Taking advantage of these experimental findings, we performed the resolution of the two mixtures of enantiopure diastereoisomers **2a/3a** and **4a/5a** with PPL as catalyst (Scheme 6).

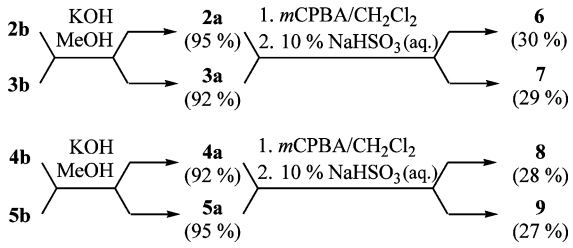


Scheme 6. PPL-mediated resolution of the two mixtures of alcohols **2a/3a** and **4a/5a**.

The enzymatic acetylation was interrupted at about 50% conversion and acetates **2c** and **4c** were separated from the unreacted alcohols **3a** and **5a**, respectively. The achieved new set of derivatives was further manipulated in order to increase its diastereoisomeric purity. Acetates **2c** and **4c** were hydrolyzed, thus all alcohols were converted into the corresponding 3,5-dinitrobenzoyl esters. Two crystallizations from hexane afforded derivative **2b**–**5b** with a diastereoisomeric excess up to 97%. Finally, hydrolysis of the latter compounds gave the desired set of enantio- and diastereoisomerically pure alcohols **2a**–**5a**. The described procedures compare favourably with previously reported syntheses and allow the preparation of the title compounds in larger scales and in high isomeric purities.

In accord with our first pursuit, we employed these building blocks for the synthesis of the 1-hydroxy-2,9-cine-

ole isomers (Scheme 7). It is known[5a] that the epoxidation of *p*-menth-1-en-9-ol affords a 1:1 mixture of epoxides and, because of steric reasons, only one of these two diastereoisomers is prone to acid-catalyzed cyclization to give cineole derivatives. Although this process allows the preparation of the target compounds in a yield below 50%, it has the advantage to be direct and does not require demanding reactions. Moreover, we found that the isolation of the mixture of epoxides is not necessary because quenching with sodium sulfite already catalyzes the cyclization.



Scheme 7. Synthesis of the 1-hydroxy-2,9-cineole isomers (**6**–**9**).

Thus, overall, the latter two-step process could be performed in just "one pot". According to this observation, we treated the set of alcohols **2a**–**5a** with *m*-chloroperbenzoic, acid and after complete epoxidation, we added sodium sulfite to the reaction mixture. After a few hours, workup and chromatographic separation afforded the 1-hydroxy-2,9-cineole isomers (**6**–**9**), which were further purified by crystallization from hexane. Spectroscopic data of these compounds are in good agreement with those previously reported,[5a] whereas optical rotation measurements showed higher values, which clearly demonstrates the good isomeric purity of the starting alcohols. Evaluation of the cooling properties of compounds **6**–**9** are still in progress and will be reported in due course.

Conclusions

In summary, we have developed an efficient methodology for the large-scale preparation of the four isomers of *p*-ment-1-en-9-ol. The starting materials are the two enantiomeric forms of *p*-mentha-1,8-dien-9-al that are, in turn, prepared from the cheap and commercially available limonene enantiomers. Baker's yeast mediated reduction of the latter aldehydes directly provides the (8*R*) isomers in very good yields and in a stereoselective fashion. In addition, the combination of the lipase-mediated resolution of the mixture of enantiopure diastereoisomers with fractionating crystallization allows the preparation of all isomeric forms of the target alcohols in high purity.

A first use of these chiral building blocks is in the preparation of four isomers of 1-hydroxy-2,9-cineole. Moreover, we will exploit their use for the preparation of natural bisabolane sesquiterpenes.

Experimental Section

General Remarks: All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. Lipase from *Porcine pancreas* type II (Sigma, 147 units/mg), lipase from *Candida rugosa* type VII (Sigma, 1150 units/mg) and lipase from *Pseudomonas cepacia* (Amano Pharmaceuticals Co., Japan, 30 units/mg) were used in this work. Fresh baker's yeast (DSM Bakery Ingredients Italy s.p.a.) was bought in a local market and used without further manipulations. TLC: Merck silica gel 60 F254 plates. Column chromatography (CC): silica gel. GC-MS analyses: HP-6890 gas chromatograph equipped with a 5973 mass detector, with a HP-5MS column (30 m × 0.25 mm, 0.25 μm firm thickness; Hewlett Packard) with the following temperature program 60 °C (1 min) – 6 °C/min – 150 °C (1 min) – 12 °C/min – 280 °C (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1/30; t_R given in min: t_R(**2a**–**5a**) 13.2, t_R(**2b**–**5b**) 29.5, t_R(**2c**–**5c**) 16.3, t_R(**6**, **9**) 13.1, t_R(**7**, **8**) 14.0, t_R(**11**, **14**) 13.0, t_R(**12**, **15**) 11.1, t_R(**16**, **17**) 13.4; mass spectra: *m*/*z* (rel. %). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a CHIRASIL DEX CB-Column with the following temperature program 60 °C (0 min) – 2 °C/min – 80 °C (0 min) – 1 °C/min – 85 °C (0 min) – 0.2 °C/min – 88 °C (0 min) – 25 °C/min – 180 °C (2 min); t_R given in min: t_R(**2c**) 24.7, t_R(**3c**) 25.0, t_R(**4c**) 23.8, t_R(**5c**) 24.1. Optical rotations: Jasco-DIP-181 digital polarimeter. ^{1}H- and ^{13}C NMR spectra: $CDCl_3$ solutions at room temperature; Bruker-AC-400 spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm relative to internal $SiMe_4$ (=0 ppm), *J* values in Hz. The diastereoisomeric excesses of alcohols **3a**–**5a** and of the esters **3b**–**5b** were determined by ^{1}H NMR spectroscopic analysis by using the signals arising from the C(10) methyl group (doublet) for the determination of the diastereoisomeric purities. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrometer; films; $\tilde{\nu}$ in cm^{-1}. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected. Microanalyses were determined on an analyzer 1106 from Carlo Erba.

Procedure for Preparation of *p*-Mentha-1,8-dien-9-al: To a cooled (0 °C) and well-stirred solution of 1.2 M *n*-butyllithium in hexane (834 mL, 1 mol) was added dropwise under nitrogen *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (108 g, 1.1 mol). To the resulting yellow solution, (+)-limonene (205 g, 1.5 mmol) was added slowly, and the mixture was stirred overnight at room temperature. The dark red solution of metalated limonene obtained was then cooled to –78 °C, and trimethyl borate (115 g, 1.1 mol) was added dropwise. The reaction was warmed to –30 °C and then treated over a 2 h period with 30% aqueous hydrogen peroxide solution (170 mL, 1.5 mol). The mixture was then quenched with water (200 mL) and diluted with diethyl ether (400 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 200 mL). The combined organic solution was washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was distilled to give recovered (+)-limonene (89 g, 0.65 mol) and a 9:1 mixture of *p*-mentha-1,8-dien-9-ol **11** and (+)-perillic alcohol (83 g, 545 mmol). The latter oil was dissolved in $CHCl_3$ (300 mL) and treated with MnO_2 (200 g, 2.3 mol), and the mixture was stirred at reflux for 8 h. The residue obtained upon filtration and evaporation of the $CHCl_3$ phase was purified by column chromatography with hexane/diethyl ether (95:5–8:2) as eluent to give pure (+)-*p*-mentha-1,8-dien-9-al **12** (67.9 g, 453 mmol, 45% based on *n*-butyllithium) and (+)-perillaldehyde (6.5 g, 43 mmol).

The procedure described above was repeated with (–)-limonene to afford (–)-*p*-mentha-1,8-dien-9-al **15** (69.1 g, 461 mmol, 46% based on *n*-butyllithium) and (–)-perillaldehyde (6.2 g, 41 mmol).

(*R*)-*p*-Mentha-1,8-dien-9-al (12): $[\alpha]_D^{20}$ = +76 (*c* = 1.5, $CHCl_3$), ref.[14] $[\alpha]_D^{20}$ = +88 (*c* = 0.03, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1694, 1622,

1437, 941, 796 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.55 (s, 1 H), 6.26 (s, 1 H), 6.00 (s, 1 H), 5.43–5.38 (m, 1 H), 2.76–2.67 (m, 1 H), 2.23–2.03 (m, 2 H), 1.98–1.74 (m, 3 H), 1.66 (s, 3 H), 1.52 (dddd, J = 12.7, 11.3, 10.6, 5.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 154.6, 133.7, 133.1, 120.0, 31.4, 30.6, 29.8, 27.5, 23.4 ppm. MS (EI): m/z (%) = 150 (15) [M$^+$], 135 (13), 122 (100), 107 (36), 91 (41), 79 (74), 67 (63), 53 (31), 39 (26). $C_{10}H_{14}O$ (150.22): calcd. C 79.96, H 9.39; found C 79.85, H 9.40.

(*S*)-*p*-Mentha-1,8-dien-9-al (15): $[\alpha]_D^{20}$ = –73.9 (c = 1.5, $CHCl_3$). IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of **12**. $C_{10}H_{14}O$ (150.22): calcd. C 79.96, H 9.39; found C 79.80, H 9.40.

Baker's Yeast Reduction of Aldehydes 12 and 15: A 10-L open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (5 L) and glucose (300 g). Fresh baker's yeast (1.5 kg) was added in small pieces to the stirred mixture, and the fermentation process was allowed to proceed for 2 h. Aldehyde **12** (50 g, 333 mmol), adsorbed on the resin AMBERLITE XAD 1180 (Rohm and Haas Company, 250 g), was added in one portion. Vigorous stirring was continued for 4 d at room temperature. During this time, more baker's yeast (250 g) and glucose (100 g) were added after 24 and 48 h since fermentation began. The resin was then separated by filtration through a sintered glass funnel (porosity 0, >160 μm), and the water phase extracted again with further resin (50 g). The combined resin crops were extracted with diethyl ether (4 × 150 mL), and the organic solution was washed with brine. The dried organic phase (Na_2SO_4) was concentrated under reduced pressure to give an oil (57 g). The latter was dissolved in $CHCl_3$ (200 mL) and treated with MnO_2 (100 g, 1.15 mol), and the mixture was stirred at reflux for 8 h. The residue obtained upon filtration and evaporation of the $CHCl_3$ phase was purified by column chromatography using hexane/diethyl ether (9:1–3:1) as eluent to give recovered aldehyde **12** (10.1 g, 67 mmol) and alcohol **3a** (34.5 g, 224 mmol, 67%).

The procedure described above was repeated with aldehyde **15** (50 g) to afford recovered aldehyde **15** (10.9 g, 73 mmol) and alcohol **5a** (30.5 g, 198 mmol, 59%).

(4*R*,8*R*)-*p*-Menth-1-en-9-ol (3a): 98% chemical purity (GC), 97% *de* (by NMR analysis), $[\alpha]_D^{20}$ = +106 (c = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = +104 (neat), ref.[3c] $[\alpha]_D^{20}$ = +106.79 (neat). IR (neat): $\tilde{\nu}$ = 3340, 1450, 1378, 1040, 799 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39–5.35 (m, 1 H), 3.64 (dd, J = 10.6, 5.1 Hz, 1 H), 3.49 (dd, J = 10.6, 6.5 Hz, 1 H), 2.08–1.88 (m, 3 H), 1.83–1.68 (m, 2 H), 1.64 (s, 3 H), 1.61–1.50 (m, 2 H), 1.46 (br. s, 1 H), 1.33 (dddd, J = 12.7, 11.7, 11, 5.5 Hz, 1 H), 0.91 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9, 120.6, 66.4, 40.2, 35.2, 30.7, 27.7, 27.2, 23.4, 13.2 ppm. MS (EI): m/z (%) = 154 (23) [M$^+$], 136 (21), 121 (56), 107 (49), 94 (100), 79 (67), 67 (62), 55 (29), 41 (25). $C_{10}H_{18}O$ (154.25): calcd. C 77.87, H 11.76; found C 77.80, H 11.80.

(4*S*,8*R*)-*p*-Menth-1-en-9-ol (5a): 97% chemical purity (GC), 96% *de* (by NMR analysis), $[\alpha]_D^{20}$ = –95 (c = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{25}$ = –94 (c = 0.92, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3335, 1451, 1378, 1042, 798 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39–5.34 (m, 1 H), 3.64 (m, 1 H), 3.49 (m, 1 H), 2.08–1.87 (m, 3 H), 1.87–1.69 (m, 2 H), 1.64 (s, 3 H), 1.59–1.46 (m, 2 H), 1.34 (br. s, 1 H), 1.25 (dddd, J = 12.6, 11.4, 10.9, 5.7 Hz, 1 H), 0.93 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9, 120.7, 66.3, 39.9, 35.3, 30.6, 29.8, 25.5, 23.3, 13.6 ppm. MS (EI): m/z (%) = 154 (28) [M$^+$], 136 (23), 121 (63), 107 (54), 94 (100), 79 (64), 67 (52), 55 (23), 41 (16). $C_{10}H_{18}O$ (154.25): calcd. C 77.87, H 11.76; found C 77.85, H 11.75.

Chemical Reduction of Aldehydes 12 and 15: A solution of aldehyde **12** (25 g, 167 mmol) in dry THF (40 mL) was treated under nitrogen with Et_3SiH (28.7 mL, 180 mmol) and $(Ph_3P)_3RhCl$ (0.5 g, 0.54 mmol). The mixture was stirred and heated at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with THF (100 mL), water (30 mL) and 5% aqueous HCl (10 mL). The stirring was continued for a further 2 h, then the mixture was diluted with water (500 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography by using hexane/diethyl ether (95:5–9:1) as eluent to afford aldehyde **16** (20.1 g, 132 mmol). The latter oil was dissolved in methanol (60 mL) and treated at 0 °C with $NaBH_4$ (2.4 g, 63 mmol) whilst stirring. After complete reduction of **16** (1 h, TLC monitoring), the reaction mixture was diluted with diethyl ether (250 mL) and treated with 5% aqueous HCl (100 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 100 mL). The combined organic solution was washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was distilled (b.p. 70–75 °C/0.5 Torr) to give a 1:1 mixture (NMR analysis, 96% chemical purity by GC) of alcohols **2a** and **3a** (18.8 g, 122 mmol, 73%).

The procedure described above was repeated with aldehyde **15** (25 g) to afford a 1:1 mixture (NMR analysis, 95% chemical purity by GC) of alcohols **4a** and **5a** (19.3 g, 125 mmol, 75%).

PPL-Mediated Separation of the Diastereoisomers 2a/3a and 4a/4b: A mixture of alcohols **2a/3a** (15 g, 97 mmol), PPL (5 g), vinyl acetate (15 mL) and *t*BuOMe (70 mL) was stirred at room temperature, and the formation of the acetate was monitored by TLC analysis. The reaction was stopped at about 54% conversion (GC analysis) by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was purified by chromatography using hexane/diethyl ether (95:5–8:2) as eluent to give acetate **2c** (9.9 g, 50 mmol, 51%, 73% *de* by chiral GC analysis) and unreacted alcohol **3a** (6.6 g, 43 mmol, 44%, 86% *de* by chiral GC analysis of the corresponding acetate). The acetate was then dissolved in methanol (10 mL) and treated with KOH (5 g, 89 mmol) in methanol (30 mL) whilst stirring at room temperature until no more starting material was detected by TLC analysis. The mixture was diluted with water (80 mL) and extracted with diethyl ether (3 × 80 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was treated with pyridine (30 mL) and a solution of 3,5-dinitrobenzoyl chloride (13 g, 56 mmol) in CH_2Cl_2 (60 mL). After complete conversion of the starting alcohol, the mixture was diluted with water (300 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phase was washed with aqueous $NaHCO_3$ (5% solution), brine and then dried (Na_2SO_4). Concentration at reduced pressure gave an oil, which was purified by CC (hexane/Et_2O, 9:1) and crystallized twice from hexane to give pure ester **2b** (10.8 g, 31 mmol, 62%).

In a similar manner, alcohol **3a** (6.5 g, 42 mmol) was treated with pyridine (30 mL) and a solution of 3,5-dinitrobenzoyl chloride (11 g, 48 mmol) in CH_2Cl_2 (50 mL). After complete conversion of the starting alcohol, workup and chromatographic purification, the corresponding 3,5-dinitrobenzoyl ester was obtained, which was crystallized twice from hexane to give pure **3b** (10.4 g, 30 mmol, 71%).

(4*R*,8*S*)-*p*-Menth-1-en-9-yl 3,5-Dinitrobenzoate (2b): 99% chemical purity by GC, up to 98% *de* by NMR analysis, m.p. 74–75 °C. $[\alpha]_D^{20}$ = +46 (c = 1.5, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = +41.85 (c = 0.965, $CHCl_3$). IR (nujol): $\tilde{\nu}$ = 1722, 1633, 1545, 1346, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (br. t, J = 2 Hz, 1 H), 9.12 (br. d, J = 2 Hz, 2 H), 5.36 (br. s, 1 H), 4.46 (dd, J = 10.8, 5.4 Hz, 1 H),

4.32 (dd, *J* = 10.8, 7.1 Hz, 1 H), 2.12–1.76 (m, 6 H), 1.64 (s, 3 H), 1.64–1.52 (m, 1 H), 1.35 (dt, *J* = 11.5, 6 Hz, 1 H), 1.07 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 148.7, 134.2, 134.1, 129.3, 122.2, 120.2, 70.2, 36.8, 35.9, 30.4, 29.5, 25.7, 23.3, 14.2 ppm. MS (EI): *m*/*z* (%) = 348 (1) [M$^+$], 195 (17), 149 (14), 136 (30), 121 (32), 107 (25), 94 (100), 79 (25). $C_{17}H_{20}N_2O_6$ (348.35): calcd. C 58.61, H 5.79, N 8.04; found C 58.75, H 5.80, N 8.10.

(4*R*,8*R*)-*p*-Menth-1-en-9-yl 3,5-Dinitrobenzoate (3b): 99% chemical purity by GC, up to 98% *de* by NMR analysis, m.p. 95–96 °C. $[\alpha]_D^{20}$ = +37.8 (*c* = 1.5, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = +36.7 (*c* = 0.77, $CHCl_3$). IR (nujol): $\tilde{\nu}$ = 1721, 1632, 1546, 1345, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (br. t, *J* = 2 Hz, 1 H), 9.12 (br. d, *J* = 2 Hz, 2 H), 5.37 (br. s, 1 H), 4.48 (dd, *J* = 10.8, 5.5 Hz, 1 H), 4.31 (dd, *J* = 10.8, 7.1 Hz, 1 H), 2.12–1.91 (m, 4 H), 1.91–1.74 (m, 2 H), 1.64 (s, 3 H), 1.64–1.52 (m, 1 H), 1.41 (dt, *J* = 11.6, 6 Hz, 1 H), 1.05 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 148.7, 134.2, 134.0, 129.3, 122.2, 120.2, 70.3, 36.9, 35.8, 30.5, 27.9, 27.0, 23.3, 13.8 ppm. MS (EI): *m*/*z* (%) = 348 (1) [M$^+$], 195 (19), 149 (15), 136 (34), 121 (33), 107 (30), 94 (100), 79 (25). $C_{17}H_{20}N_2O_6$ (348.35): calcd. C 58.61, H 5.79, N 8.04; found C 58.80, H 5.80, N 8.00.

A sample of the ester **2b** (8.7 g, 25 mmol) was hydrolyzed with KOH (2.5 g, 44 mmol) in refluxing methanol (40 mL). After workup and bulb-to-bulb distillation (oven temperature 75–80 °C/0.5 Torr), pure alcohol **2a** (3.65 g, 23.7 mmol, 95%) was obtained.

According to the procedure described above, the hydrolysis of a sample of the ester **3b** (6.3 g, 18 mmol) afforded pure **3a** (2.55 g, 92%).

(4*R*,8*S*)-*p*-Menth-1-en-9-ol (2a): 98% chemical purity by GC, up to 98% *de* by NMR analysis $[\alpha]_D^{20}$ = +102 (*c* = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = +97.27 (*c* = 1.033, $CHCl_3$), ref.[3c] $[\alpha]_D^{20}$ = +103.1 (neat). IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of alcohol **5a**. $C_{10}H_{18}O$ (154.25): calcd. C 77.87, H 11.76; found C 77.80, H 11.75.

(4*R*,8*R*)-*p*-Menth-1-en-9-ol (3a): 98% chemical purity by GC, up to 98% *de* by NMR analysis, $[\alpha]_D^{20}$ = +106 (*c* = 1, $CHCl_3$), IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of alcohol **3a** obtained by the baker's yeast reduction procedure. $C_{10}H_{18}O$ (154.25): calcd. C 77.87, H 11.76; found C 77.75, H 11.71.

The separation procedure described above was repeated starting from the mixture of alcohol **4a** and **5a** (17 g, 110 mmol). The PPL-mediated acetylation was stopped at about 48% conversion to give acetate **4c** (10.1 g, 51 mmol, 46%, 79% *de* by chiral GC analysis) and unreacted alcohol **5a** (8.3 g, 54 mmol, 49%, 73% *de* by chiral GC analysis of the corresponding acetate). Acetate **4c** was hydrolyzed, and both the obtained alcohol and alcohol **5a** were then converted to the corresponding 3,5-dinitrobenzoyl esters, which were then crystallized twice from hexane to give pure **4b** (11.5 g, 33 mmol, 65%) and **5b** (10.4 g, 30 mmol, 55%), respectively.

(4*S*,8*S*)-*p*-Menth-1-en-9-yl 3,5-Dinitrobenzoate (4b): 98% chemical purity by GC, up to 97% *de* by NMR analysis, m.p. 94–95 °C. $[\alpha]_D^{20}$ = –33 (*c* = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = –34.0 (*c* = 3.27, $CHCl_3$). IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of **3b**. $C_{17}H_{20}N_2O_6$ (348.35): calcd. C 58.61, H 5.79, N 8.04; found C 58.75, H 5.75, N 7.99.

(4*S*,8*R*)-*p*-Menth-1-en-9-yl 3,5-Dinitrobenzoate (5b): 98% chemical purity by GC, up to 98% *de* by NMR analysis, m.p. 72–73 °C. $[\alpha]_D^{20}$ = –43 (*c* = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = –39.91 (*c* = 1.152, $CHCl_3$). IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of **2b**. $C_{17}H_{20}N_2O_6$ (348.35): calcd. C 58.61, H 5.79, N 8.04; found C 58.80, H 5.80, N 8.00.

A sample of the ester **4b** (9.1 g, 26 mmol) was hydrolyzed with KOH (2.5 g, 44 mmol) in refluxing methanol (40 mL). After workup and bulb-to-bulb distillation (oven temperature 75–80 °C/0.5 Torr), pure alcohol **4a** (3.8 g, 24.7 mmol, 95%) was obtained.

According to the procedure described above, hydrolysis of a sample of the ester **5b** (8 g, 23 mmol) afforded pure **5a** (3.25 g, 21.1 mmol, 92%).

(4*S*,8*S*)-*p*-Menth-1-en-9-ol (4a): 98% chemical purity by GC, up to 98% *de* by NMR analysis, $[\alpha]_D^{20}$ = –104 (*c* = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = –103.1 (*c* = 4.79, benzene). IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of alcohol **3a** obtained by the baker's yeast reduction procedure. $C_{10}H_{18}O$ (154.25): calcd. C 77.87, H 11.76; found C 77.65, H 11.70.

(4*S*,8*R*)-*p*-Menth-1-en-9-ol (5a): 98% chemical purity by GC, up to 97% *de* by NMR analysis, $[\alpha]_D^{20}$ = –97 (*c* = 1, $CHCl_3$), ref.[3a] $[\alpha]_D^{20}$ = –94.0 (*c* = 0.92, $CHCl_3$). IR, ^{1}H NMR, ^{13}C NMR and MS data in accordance with those of alcohol **5a** obtained by the baker's yeast reduction procedure. $C_{10}H_{18}O$ (154.25): calcd. C 77.87, H 11.76; found C 77.95, H 11.75.

Procedure for the Preparation of 1-Hydroxy-2,9-cineole (6–9) Starting from Alcohols 2–5: A solution of alcohol **2a** (3 g, 19.5 mmol) in CH_2Cl_2 (50 mL) was treated with MCPBA (6.67 g of a 75% wet acid, 29 mmol) whilst stirring at 0 °C until no more **2a** was detected by TLC analysis (3 h). The reaction mixture was then treated with a saturated aqueous solution of $NaHSO_3$ (20 mL) and stirred at room temperature for 3 h. The mixture was diluted with water (80 mL) and extracted with CH_2Cl_2 (2 × 80 mL). The organic layer was washed in turn with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), and dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by CC (hexane/Et_2O, 9:1) and crystallized from hexane to give pure cineole **6** (0.98 g, 5.8 mmol, 30%).

(1*R*,2*R*,4*R*,8*S*)-1-Hydroxy-2,9-cineole (6): 98% chemical purity by GC, m.p. 82–83 °C. $[\alpha]_D^{20}$ = –79.1 (*c* = 1, $CHCl_3$), ref.[5a] $[\alpha]_D^{20}$ = –65.5 (*c* = 1.78, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3325, 3267, 1457, 1372, 1212, 998, 898 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (dd, *J* = 11.4, 6.6 Hz, 1 H), 3.54 (br. d, *J* = 4.5 Hz, 1 H), 3.31 (t, *J* = 11.4 Hz, 1 H), 2.01–1.90 (m, 2 H), 1.87–1.71 (m, 3 H), 1.54 (br. s, 1 H), 1.43–1.32 (m, 2 H), 1.21 (s, 3 H), 1.20 (br. s, 1 H), 0.85 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.9, 71.4, 66.5, 33.5, 31.7, 30.8, 28.1, 27.9, 21.4, 18.4 ppm. MS (EI): *m*/*z* (%) = 170 (9) [M$^+$], 152 (11), 137 (4), 134 (5), 123 (6), 110 (100), 97 (90), 79 (8), 71 (19), 55 (12), 43 (26). $C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.60, H 10.65.

The procedure described above was repeated starting from alcohol **3a** (2.8 g, 18.2 mmol), **4a** (3.1 g, 20.1 mmol) and **5a** (3.5 g, 22.7 mmol) to give cineole **7** (0.9 g, 5.3 mmol, 29%), **8** (0.95 g, 5.6 mmol, 28%) and **9** (1.04 g, 6.1 mmol, 27%), respectively.

(1*R*,2*R*,4*R*,8*R*)-1-Hydroxy-2,9-cineole (7): 99% chemical purity by GC, m.p. 92–93 °C. $[\alpha]_D^{20}$ = –32.5 (*c* = 1, $CHCl_3$), ref.[5a] $[\alpha]_D^{20}$ = –22.4 (*c* = 1.19, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3311, 3254, 1444, 1372, 1236, 1068, 989, 913, 827 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (dd, *J* = 11.8, 7.3 Hz, 1 H), 3.52 (t, *J* = 11.8 Hz, 1 H), 3.44 (br. s, 1 H), 2.19–2.05 (m, 2 H), 1.85–1.60 (m, 6 H), 1.35 (br. s, 1 H),1.28 (s, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.6, 71.2, 68.2, 36.1, 33.8, 30.3, 30.0, 28.4, 21.8, 15.4 ppm. MS (EI): *m*/*z* (%) = 170 (8) [M$^+$], 152 (7), 134 (3), 137 (3), 123 (5), 110 (100), 97 (43), 71 (18), 55 (7), 43 (21).

$C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.63, H 10.67.

(1*S*,2*S*,4*S*,8*S*)-1-Hydroxy-2,9-cineole (8): 97% chemical purity by GC, m.p. 91–92 °C. $[\alpha]_D^{20}$ = +30.9 (*c* = 1, $CHCl_3$). IR, ^1H NMR, ^{13}C NMR and MS data in accordance with those of **7**. $C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.75, H 10.62.

(1*S*,2*S*,4*S*,8*R*)-1-Hydroxy-2,9-cineole (9): 98% chemical purity by GC, m.p. 80–81 °C. $[\alpha]_D^{20}$ = +78.4 (*c* = 1, $CHCl_3$). IR, ^1H NMR, ^{13}C NMR and MS data in accordance with those of **6**. $C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.70, H 10.65.

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