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Chemoenzymatic preparation of the *p*-menth-1,5-dien-9-ol stereoisomers and their use in the enantiospecific synthesis of natural *p*-menthane monoterpenes

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ABSTRACT

A study on the preparation and synthetic exploitation of the isomeric forms of *p*-menth-1,5-dien-9-ol is reported. The latter alcohols were prepared in high enantiomeric purity from the easily available enantiomers of carvone. Thus, a chemoenzymatic procedure based on lipase-mediated acetylation, allowed the separation of their diastereoisomeric forms. Moreover, the purity of the chiral building blocks obtained was improved by fractional crystallisation of their 3,5-dinitrobenzoyl derivatives. A number of synthetic applications have also been described. The stereospecific cyclisation of the isomerically pure dienic alcohols gave the isomeric forms of the terpenes dill and *epi*-dill ether, which were hydrogenated diastereoselectively to the corresponding (1*R*)- or (1*S*)-derivatives depending on the catalyst used. The oxidation of the latter ethers turned out to be stereoselective, affording either the corresponding *p*-menthan-9-oic lactone or the keto-acid derivatives depending on the starting isomer used.

1. Introduction

The general *p*-menthane framework **1** (Fig.1) occurs frequently in the chemical scaffold of a large number of natural terpenes and sesquiterpenes. These compounds show a great structural variability, the presence of one or two unsaturations at C(1) and C(5), respectively, being common and also oxidation at C(3) by the introduction of an oxygen atom. Furthermore, the latter functional group allows the formation of bicyclic compounds with the introduction of another stereocentre. Overall, both a large number of compounds and isomers are possible. Some relevant examples of monocyclic sesquiterpenes of this type include α-zingiberene and the α-turmerone isomers **2**, which can be isolated from a number of essential oils, comprising those of ginger[1] and turmeric.[2] In addition, several bicyclic monoterpenes of type **3** are the key components of different flavours. It should be noted that dill ether[3] is the most important constituent of the dill herb from an organoleptic point of view. Moreover, wine lactone[4] is a very powerful odourant, which owes its name to its first isolation source. Further saturated lactones of type **3** can be found in mint[5] and have attracted great synthetic interest[6] for their potential application in the flavour and fragrance industry. Indeed, some isomers of these *p*-menthane lactones, exhibit a strong and suitable coumarin-like flavour without the toxicological constraints of the coumarin itself.

All of these compounds, although different from each other, share the same difficulties in their stereoselective synthesis. In particular, the most challenging point is the specific preparation of the two contiguous secondary stereocentres at C(4) and C(8). Since the products described above show many relevant biological activities that are definitely related to their absolute configuration, their synthesis requires a very high degree of stereocontrol.

In this context, we have previously reported the stereoselective preparation of some *p*-menth-1-en-ols[7] and their use as chiral building blocks in the mono- and sesquiterpene synthesis. The latter studies face the aforementioned topic by a biocatalytic approach that allows the introduction of a C(8) stereocentre using either an enzyme-mediated resolution[7a] or a baker's yeast-mediated reduction.[7] The starting substrates for the aforementioned transformations already contain the C(4) asymmetric centre and were easily prepared from the chiral pool.

Herein, taking advantage of these acquired methodologies, we selected the isomeric forms of the *p*-menth-1,5-dien-9-ol **4** as suitable chiral building blocks for the synthesis of terpenes of type **2** and **3**. In fact, the latter alcohol can be obtained as a mixture of diastereoisomers from carvone enantiomers,[8] thus controlling the C(4) stereocentre. We envisaged that these types of compounds were good substrates for a lipase-mediated resolution process. Substituted 2-cyclohexenyl-propanols have been resolved via PPL[7a] allowing the separation of the stereoisomers, which show

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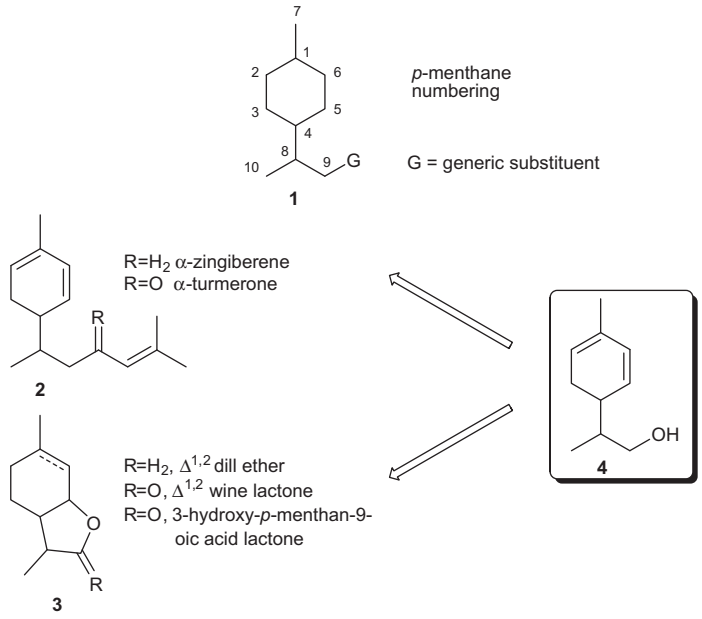


Figure 1. General structure of the *p*-menthane framework and structures of some relevant mono and sesquiterpenes having the same skeleton.

different C(8) absolute configurations. The combined use of the latter findings could afford all the isomeric forms of alcohol **4**, which are obvious precursors of sesquiterpenes of type **2**. Moreover, the high reactivity of the 1,5-dienic system turned out to be a useful tool in the synthesis of the bicyclic compounds of type **3**. Herein we report the results of these studies, comprising of an effective chemo-enzymatic protocol for the preparation of the *p*-menth-1,5-dien-9-ol stereoisomers and their exploitation as chiral building blocks in the field of natural product synthesis.

2. Results and discussion

2.1. Preparation of the *p*-menth-1,5-dien-9-ol stereoisomers

As introduced before, *p*-menth-1,5-dien-9-ol was previously obtained from carvone[8] by a two step process. We followed this synthetic method, carrying out some modifications in order to make it suitable for larger scale preparation.

First we submitted the tosylhydrazone of the (*S*)-carvone **5** (Scheme 1) to the Shapiro reaction, carefully controlling the experimental conditions, especially the temperature (see Section 4) minimized the side reactions, thus affording the *p*-mentha-1,5,8-triene **6** in higher purity. Overheating of the reaction favours the aromatization of **6** to give 1-isopropenyl-4-methyl benzene, which in turn is converted into 2-(*p*-tolyl)-propan-1-ol via a hydroboration. The latter compound is not separable by chromatography[†] and is itself a good substrate for PPL mediated acetylation.[9] Performing the base addition at low temperature, followed by slow decomposition of the hydrazone, meant that the overall amount of this side compound was less than 5% of the alcohol mixture.

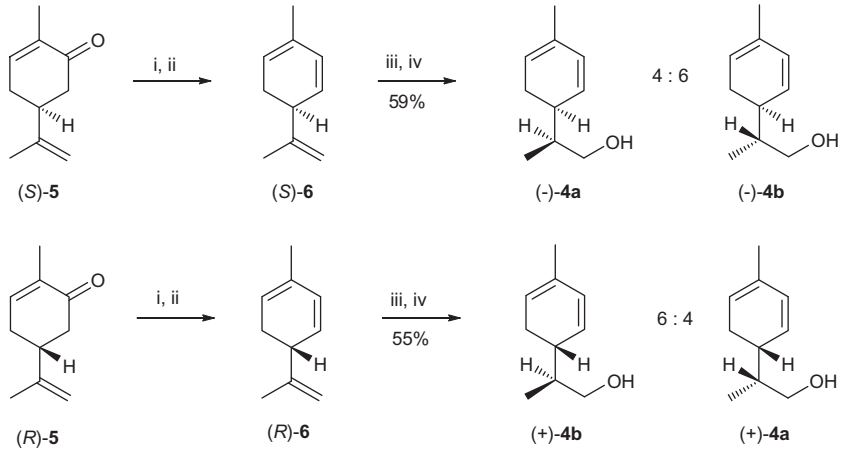
In order to make the process less expensive, the regioselective hydroboration of (*S*)-**6** was performed using the less expensive disiamylborane instead of 9-BBN. The latter reagent did not show any diastereoselectivity, whereas disiamylborane afforded, after oxidation of the intermediated borane with $NaOH/H_2O_2$, alcohols (−)-**4a** and (−)-**4b** in a 4:6 ratio, respectively. As demonstrated earlier, the reaction conditions employed did not affect the C(4) stereocentre, thus giving rise to a couple of enantiopure diastereoisomers. Their relative configurations were unambiguously assigned by chemical correlation with the known isomeric forms of dill ether (see Section 2.2). Since both enantiomers of carvone are commercially available in high enantiomeric purity, the described pathway was carried out starting from (*R*)-**5** to give, through the intermediate of (*R*)-**6**, alcohols (+)-**4b** and (+)-**4a** in a 6:4 ratio, respectively. The diastereoisomeric alcohols are not separable by chromatography either as acetate or nitrobenzoate derivatives. The 4:6 couple of diastereoisomers **4a**/**4b** was converted in the corresponding 3,5-dinitrobenzoate ester in order to study their fractional crystallisation. These experiments again afforded disappointing results and we observed a significant increase in the diastereoisomeric ratio only after ten crystallisations from hexane.

For these reasons, we selected a completely different separation process based on the lipase-mediated esterification. We have previously demonstrated that PPL catalyses the irreversible acetylation of (2*S*)-substituted-propanol and affords the corresponding esters with good enantioselectivity.[9] When the *p*-menth-1-en-9-ol[7a] stereoisomers were used as substrates, PPL catalysed the enantioselective acetylation of the (8*S*) enantiomers independent of the C(4) configuration. The latter good enantioselectivity, coupled with the lack of diastereoselectivity, allowed the separation of the diastereoisomers.

Since the *p*-menth-1,5-dien-9-ol isomers are very similar to the aforementioned alcohols, we tested the PPL-mediated acetylation of the diastereoisomers **4a** and **4b**. We first treated a mixture of (−)-**4a** and (−)-**4b** with vinyl acetate in the presence of PPL as a catalyst. The acetate **5a** (Scheme 2) obtained turned out to be the ester of (4*S*,8*S*)-*p*-menth-1,5-dien-9-ol, thus confirming our initial insight.

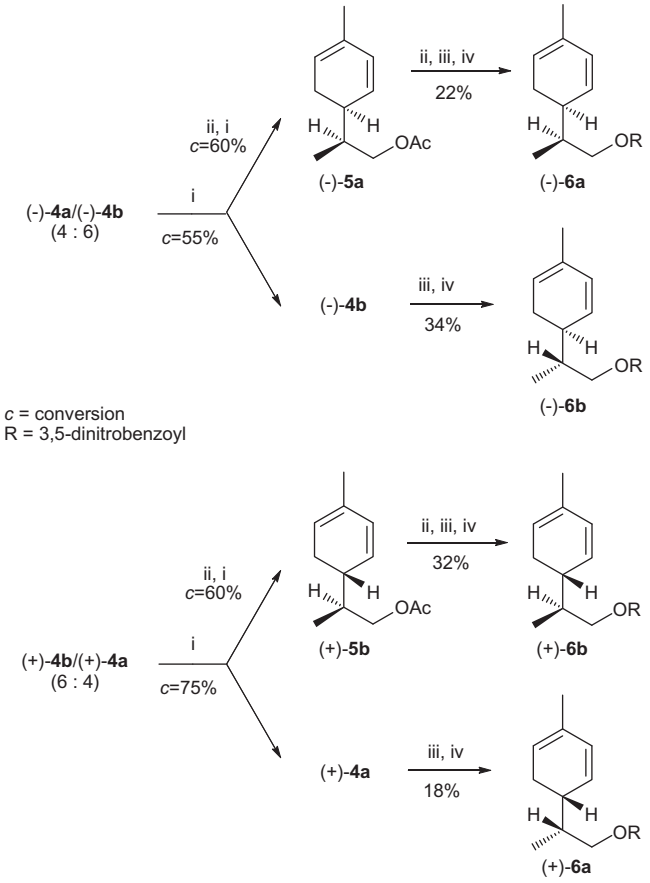
Since we required all the isomers in high purity, we performed the above resolution by means of a two step procedure. A 4:6 mixture of alcohols (−)-**4a** and (−)-**4b** was acetylated until 55% conversion. The following chromatographic separation afforded the unreacted alcohol (−)-**4b** and acetate **5a** in very good and low diastereoisomerical purity, respectively. Thus, the latter acetate was treated with NaOH in methanol and the derived alcohol was

[†] 2-(*p*-Tolyl)-propan-1-ol 3,5-dinitrobenzoate is separable from *p*-menth-1,5-dien-9-ol 3,5-dinitrobenzoate by chromatography.



Scheme 1. Synthesis of the *p*-menth-1,5-dien-9-ol stereoisomers from carvone enantiomers. Reagents and conditions: (i) $TsNHNH_2$, MeOH, HCl cat.; (ii) BuLi, Et_2O −60 °C then rt; (iii) disiamylborane, THF, 0 °C then rt; (iv) NaOH/H_2O then H_2O_2.

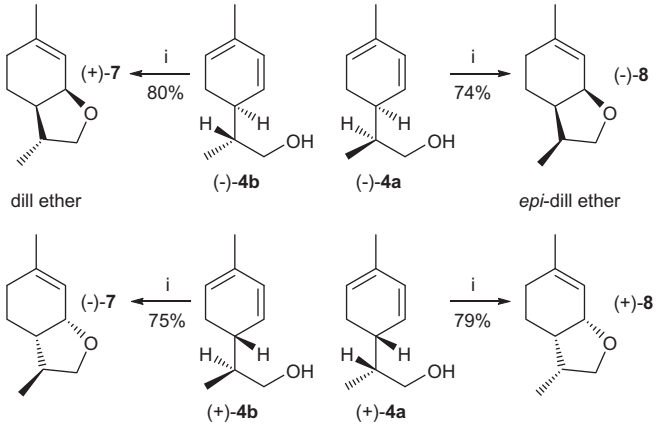
submitted again to the PPL-mediated acetylation until the reaction reached about 60% conversion. Analysis of the obtained acetate (−)-**5a** showed a very good diastereoisomeric purity. Both *p*-menth-1,5-dien-9-ol isomers were obtained, thus confirming the overall efficiency of the enzymatic process. In addition, both the chemical and diastereoisomeric purity of the latter chiral synthons, as well as their chemical stability, could be increased. The diastereoenriched alcohols were converted into the corresponding 3,5-dinitrobenzoyl esters (−)-**6a** and (−)-**6b** which were crystallised from hexane with a concurrent increase in purity. With these results in hand, we repeated the PPL-mediated separation protocol starting from a 6:4 mixture of alcohols (+)-**4b** and (+)-**4a**. In this case, with the major (8*S*)-diastereoisomer, the first acetylation reaction was stopped at the 75% conversion whereas the second one was interrupted when it reached 60% conversion. The obtained acetate (+)-**5b** and alcohol (+)-**4a** were converted into their corresponding 3,5-dinitrobenzoyl esters (+)-**6b** and (+)-**6a** whose crystallisations confirmed a further increase in purity.



Scheme 2. Lipase-mediated resolution of the *p*-menth-1,5-dien-9-ol stereoisomers. Reagents and conditions: (i) PPL, vinyl acetate, *t*-BuOMe then chromatography; (ii) NaOH, MeOH, rt; (iii) 3,5-dinitrobenzoyl chloride, Py, CH_2Cl_2, rt; (iv) crystallisation from hexane.

2.2. Acid-mediated cyclisation of the *p*-menth-1,5-dien-9-ol stereoisomers, synthesis of the dill ether

In accordance with our first aim, we exploited the obtained chiral building blocks for the synthesis of natural *p*-menthane monoterpenes. First, we tested the reactivity of the 1,5-dienic system towards the intramolecular addition of the alcohol functional group. A relevant finding was that either Brønsted acids or Lewis acids efficiently catalysed the cyclisation of the *p*-menth-1,5-dien-9-ol isomers to give the corresponding 3,9-epoxy-*p*-menth-1-ene ethers. Moreover, the reaction proceeded with complete diastereoselectivity and the formation of the new C–O bond gives rise only to the bicyclic ethers with a *cis*-configuration at the 3,4-positions of the *p*-menthane framework. The experiments, carried out using isomerically pure starting alcohols, afforded the corresponding ethers as a single isomer, thus confirming



Scheme 3. Acid-catalysed cyclisation of the *p*-menth-1,5-dien-9-ol stereoisomers. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, Et_2O, rt.

that the pre-existing stereocentres were left unaffected under the cyclisation conditions (Scheme 3).

Accordingly, alcohols (−)- and (+)-**4b** were treated with $BF_3{\cdot}OEt_2$ in diethyl ether to give (+)- and (−)-dill ether **7**, respectively. Using the same experimental conditions, the alcohols (−)- and (+)-**4a** afforded (−)- and (+)-*epi*-dill ether **8**, respectively. We chose $BF_3{\cdot}OEt_2$ as the catalyst since it gave better results in terms of higher yields and lower amounts of side products. Other acids did efficiently catalyse the cyclisation (Table 1).

Table 1
Results of the acids-mediated cyclisation of the *p*-menth-1,5-dien-9-ol

Acid	Reaction conditions[a]	Yields[b] (%)
HCl aq (37%) 2 equiv	Et_2O, 17 h	53
HCl aq (37%) 0.2 equiv	Et_2O, 24 h	47
H_2SO_4 (96%), 1.1 equiv	Et_2O, 5 h	81
$BF_3{\cdot}OEt_2$ 1.1 equiv	Et_2O, 15 h	80
$SnCl_4$ 1.1 equiv	CH_2Cl_2, 13 h	16

[a] (−)-**4b** was used as the starting alcohol for all the entries.
[b] Yield of (+)-**7** after purification and bulb to bulb distillation

We observed that concentrated HCl aq converted alcohol **4b** into ether **7** in about 50% yield, using either a catalytic amount of acid or an excess. Since increasing of the acid catalyst reduced the reaction time, we settled on the use of a stoichiometric amount. Accordingly, concentrated sulfuric acid afforded the bicyclic ether with the highest yield (81%) and the shortest reaction time. As described above, Lewis acids are effective catalysts for the latter cyclisation and both $BF_3{\cdot}OEt_2$ and $SnCl_4$ transformed alcohol **4b** although with very different yields. It is noteworthy that the relative amount of the side products changed significantly upon which acid was used. Concentrated sulfuric acid and $SnCl_4$ did not leave unreacted alcohol and afforded a number of degradation/polymerization products. Otherwise, concentrated HCl and $BF_3{\cdot}OEt_2$ gave the dill ether and the starting alcohol together with a minor extent of side products.

Overall, these results represent a new synthetic pathway to dill ether stereoisomers. Indeed the previously reported enantiospecific preparations[10] of this relevant flavour were performed using a completely different approach which was based on the cyclisation of different *p*-menth-1-en-diols instead of the ring closure triggered by acid activation of the 1,5-dienic system.

2.3. Stereoselective hydrogenation of the dill and *epi*-dill ethers

Having an effective method for the synthesis of the dill ether isomers, we turned our attention to their further exploitation. Indeed, the C(1) double bond could be transformed with the introduction of at least one more stereocentre. We focused our attention on the hydrogenation reaction, since the saturated ethers obtained by this means have been used[11] as starting materials in the synthesis of *p*-menthane lactone isomers, which are of interest in the fields of flavour and fragrance.

The hydrogenation has been roughly investigated in some previous work,[10d,11] which indicate that high diastereoselectivity can be obtained when PtO_2 is employed as catalyst. The use of further catalysts was not examined leaving the study of this transformation incomplete. Therefore, we performed the hydrogenation reaction selecting different catalysts and using either dill or *epi*-dill isomers as substrates (Table 2 and Scheme 4).

As previously described, PtO_2 in ethanol diastereoselectively catalyses the reduction of either (+)-**7** or (−)-**8** to give the corresponding (1*R*)-derivatives as the main products. The distereoselectivity was good, especially for the hydrogenation of the *epi*-dill ether. It is noteworthy, that when using PtO_2, we obtained a significant amount of *p*-menthan-9-ol isomers, likely formed through the C(3)–O hydrogenolysis process. In addition, a minor amount of the 3,9-epoxy-*p*-menthane isomers, conceivably derived by the metal-catalysed epimerization at C(8), was detected in the reaction mixtures. Therefore we tried the hydrogenation using rhodium-based catalysts, which do not usually give hydrogenolysis. As expected, both Rh/Al_2O_3 and $(Ph_3P)_3RhCl$ gave only trace amounts of the *p*-menthan-9-ol and afforded the saturated ethers with low diastereoselectivity.

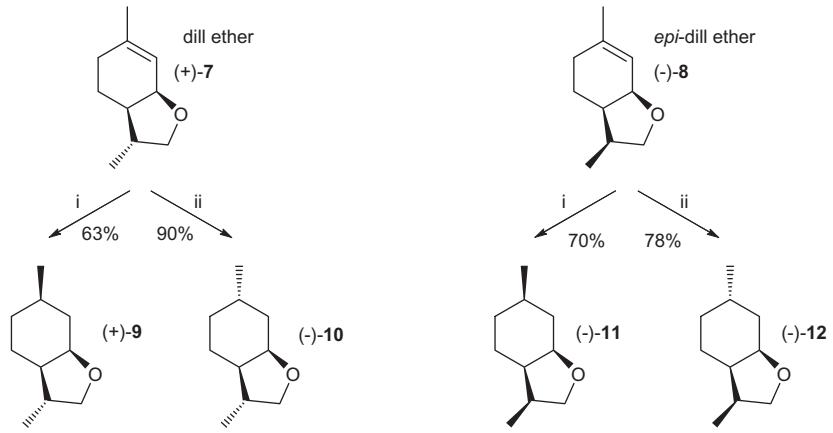
Moreover, Rh/Al_2O_3 gave a considerable quantity of isomerisation-derived compounds whereas the Wilkinson's catalyst left a large part of the starting ethers unreacted even after a long reaction time. Worse results were obtained when using palladium on activated charcoal, which showed a lower selectivity but a high activity towards the epimerization and hydrogenolysis reactions. A breakthrough was achieved by mean of Raney Ni. The latter metal showed an opposite diastereoselectivity to that of all the previously studied catalysts affording (1*S*) derivatives with very high selectivity. In addition, the latter reaction did not give hydrogenolysis products and the unwanted isomers were formed in very small amounts. These results demonstrate that it is possible to prepare all four isomers **9**–**12** by using different catalysts. Accordingly, dill ether and *epi*-dill were hydrogenated using either PtO_2 or Raney-Ni as catalyst to afford ether (+)-**9** or (−)-**10**, and ether (−)-**11** or (−)-**12**, respectively (Scheme 4).

The saturated derivatives obtained were further purified by chromatography in order to increase their diastereoisomeric purity and make them suitable as starting materials in the next step. For the sake of completeness, the above described reactions were

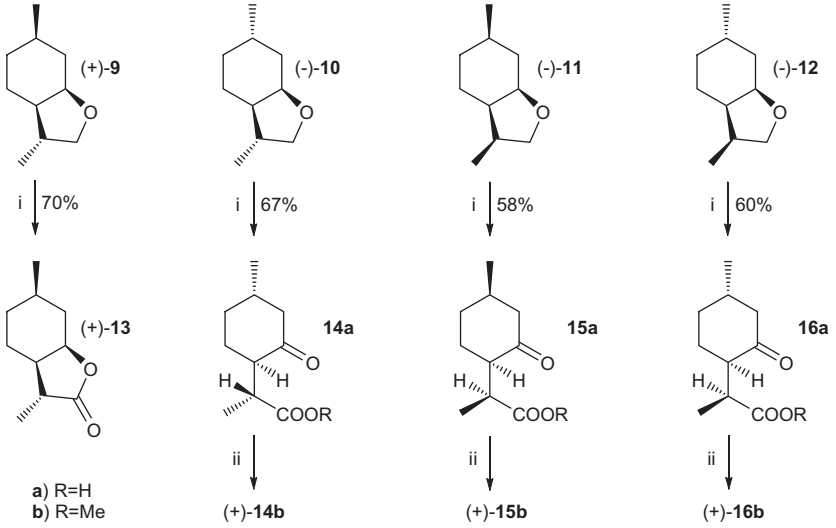
Table 2
Results of the hydrogenation of the dill and *epi*-dill ethers

3,9-Epoxy-*p*-menth-1-ene	Catalyst	Condition[a]	3,9-Epoxy-*p*-menthane[b] (%)				Unreacted[b] (%)	*p*-Menthan- 9-ol[b,c] (%)
			(1*R*,3*R*,4*R*,8*R*) (+)-**9**	(1*S*,3*R*,4*R*,8*R*) (−)-**10**	(1*R*,3*R*,4*R*,8*S*) (−)-**11**	(1*S*,3*R*,4*R*,8*S*) (−)-**12**		
(3*S*,4*R*,8*R*) (+)-**7**	PtO_2	EtOH, 2 h	68	10	—	7	—	15
	Rh/Al_2O_3	EtOH, 2 h	53	22	—	24	—	1
	Pd/C	AcOEt, 1 h	36	16	1	35	—	12
	$(Ph_3P)_3RhCl$	EtOH, 48 h	31	10	—	1	58	—
	Raney Ni	EtOH, 2 h	5	95	—	—	—	—
(3*S*,4*R*,8*S*) (−)-**8**	PtO_2	EtOH, 2 h	2	—	79	4	—	15
	Rh/Al_2O_3	EtOH, 2 h	—	17	67	15	—	1
	Pd/C	AcOEt, 1 h	2	8	35	15	—	40
	$(Ph_3P)_3RhCl$	EtOH, 48 h	1	—	17	4	78	—
	Raney Ni	EtOH, 2 h	—	4	7	89	—	—

[a] The hydrogenation was performed at rt, using H_2 at atmospheric pressure.
[b] Yield determined by GC analysis.
[c] As a mixture of isomers.



Scheme 4. Stereoselective hydrogenation of the dill and *epi*-dill ethers. Reagents and conditions: (i) PtO_2, EtOH, H_2/atmospheric pressure, rt; (ii) Raney Ni, EtOH, H_2/atmospheric pressure, rt.



Scheme 5. Oxidation of the 3,9-epoxy-*p*-menthane isomers **9**–**12**. Reagents and conditions: (i) $RuCl_3{\cdot}nH_2O$ cat., CCl_4/CH_3CN, $NaIO_4/H_2O$ rt; (ii) CH_2N_2, Et_2O, 0 °C.

repeated starting from (−)-dill ether and (+)-*epi* dill ether with almost identical results.

2.4. Regioselective oxidation of the 3,9-epoxy-*p*-menthane stereoisomers

As aforementioned, racemic ethers **9** and **11** were oxidised[11] by RuO_4 to give the corresponding lactones, which were further transformed in the mint flavour mintlactone. More recently,[6] the stereoisomers of the *p*-menthan-9-oic lactones were comprehensively studied in order to achieve their olfactory evaluation. Indeed these compounds turned out to be relevant odourants of potential industrial applications giving a distinctive coumarinic odour note. In addition, lactone **13** and its C(9) epimer can be found in the essential oil of *Mentha suaveolens*[5a] and are therefore regarded as natural, although their absolute configurations are still unassigned.

Having both enantiomeric forms of ethers **9**–**12** in hand, we assessed their oxidation. We submitted ethers (+)-**9**, (−)-**10**, (−)-**11** and (−)-**12** to the RuO_4 mediated oxidation process (Scheme 5).

The reactions were performed using a catalytic amount of $RuCl_3$ and a large excess of $NaIO_4$ as oxidant, while a mixture of CCl_4 and CH_3CN[12] was used as solvent in order to increase the efficiency of the oxidation. Only ether (+)-**9** gave the corresponding lactone (+)-**13** in good yields. The other diastereoisomers were transformed in the corresponding keto-acids **14a**–**16a** while only trace amounts of lactones were detected. In order to control this over-oxidation process, we stopped the reactions at early stage but we again obtained the keto-acids close to the unreacted ethers. Concerning the structure assignment of **14a**–**16a**, it should be noted that the enantiomers of the latter compounds were previously obtained by photo-oxidation of natural menthofurane.[13] Isomer **14a** is a crystalline compound and its melting point matched that reported[14] for the corresponding enantiomer. In addition, the NMR analyses of the three acids **14a**–**16a** were in rough agreement with those described. In spite of these first confirmations the given analytical characterizations are not adequate enough to unambiguously confirm the chemical structures of the aforementioned compounds. Both the CG and the NMR analyses of the keto acids showed very broad signals, thus making the purity determination and the structure assignation difficult. This effect was due to the concurrent presence of the open keto-acid form and of the bicyclic lactol form, conceivably existing in a tautomeric equilibrium in solution. Therefore, we blocked the compounds **14a**–**16a** in their open form by converting them into the corresponding keto esters by a diazomethane treatment. The analytical data of the obtained compounds (+)-**14b**, (+)-**15b** and (+)-**16b** were in good agreement

with the given structures and showed that the oxidation of the ethers (−)-**10** and (−)-**12** proceeded with complete stereocontrol to give diastereoisomerically pure (+)-**14b** and (+)-**16b**. Conversely, ether (−)-**11** gave keto derivative (+)-**15b** impure with (−)-**14b** (a 4:1 ratio), clearly demonstrating a partial epimerization at C(4). All the above described experiments were then repeated starting from ether (−)-**9**, (+)-**10**, (+)-**11** and (+)-**12** with comparable results (see Section 4).

3. Conclusion

The present study highlights the usefulness of the *p*-menth-1,5-dien-9-ol stereoisomers as chiral building blocks in terpene synthesis. Different outcomes were achieved. First, we have developed a chemo-enzymatic procedure based on the lipase-mediated acetylation, which allows the separation of the diastereoisomeric *p*-menth-1,5-dien-9-ol isomers. The latter alcohols were in turn prepared in high enantiomeric purity from the easily available carvone enantiomers. Moreover, the purity of the chiral building blocks obtained was improved by fractional crystallisation of their stable 3,5-dinitrobenzoyl derivatives. As a first synthetic application, we have described the acid-mediated cyclisation of the isomerically pure dienic alcohols to give the isomeric forms of the terpenes dill and *epi*-dill ether. With the aim of preparing odour active compounds, we hydrogenated the latter ethers and found two diastereoselective pathways to the 3,9-epoxy-*p*-menthane isomers. The regioselective oxidation of the saturated ethers afforded either the enantiomeric forms of the natural lactone **13** or the keto-acids **14a**–**16a**, depending on the substrate used. Further studies with the purpose of using *p*-menth-1,5-dien-9-ol stereoisomers as chiral building blocks in terpenes and sesquiterpenes synthesis are currently ongoing and will be reported in due course.

4. Experimental

4.1. General

All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. (*S*)-Carvone (95% ee) and (*R*)-carvone (98% ee) were purchased from Fluka and from Aldrich, respectively. Lipase from *Porcine pancreas* (PPL) type II, Sigma, 147 units/mg was employed in this work. TLC: Merk Silica Gel 60 F_{254} plates. Column chromatography (CC): silica gel. GC–MS analyses: *HP-6890* gas chromatograph equipped with a 5973 mass detector, using an HP-5MS column (30 m × 0.25 mm, 0.25 μm film thickness; Hewlett Packard) with the following temp programme: 60° (1 min)−6°/min−150° (1 min)−12°/min−280° (5 min); carrier gas, He; constant flow 1 ml/min; split ratio, 1/30; t_R given in min: t_R(**4a**) 13.20, t_R(**4b**) 13.27, t_R(**5a**) 15.93, t_R(**5b**) 15.98, t_R(**6a**) 29.31, t_R(**6b**) 29.36, t_R(**7**) 11.24, t_R(**8**) 12.30, t_R(**9**) 10.69, t_R(**10**) 9.86, t_R(**11**) 10.90, t_R(**12**) 10.47, t_R(**13**) 16.52, t_R(**14b**) 17.00, t_R(**15b**) 16.74, t_R(**16b**) 16.50. Optical rotations: Jasco-DIP-181 digital polarimeter. ^{1}H and ^{13}C Spectra: $CDCl_3$ solutions at rt; Bruker-AC-400 spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm rel to internal $SiMe_4$ (=0 ppm), *J* values in Hz. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected.

4.2. Preparation of *p*-menth-1,5-dien-9-ol isomers

At first, BuLi (28.3 mL of a 10 M solution in hexane) was added dropwise under nitrogen to a stirred and cooled (−60 °C) suspension of (*S*)-carvone tosylhydrazone (30 g, 94.3 mmol) in dry diethyl ether (300 mL). After the addition was complete, the reaction was kept at 0 °C for 1 h and then was left to reach room temperature and stirred for another 2 h. The mixture was then quenched by addition to crushed ice (1 Kg). The organic layer was separated and the aqueous phase was extracted with ether (100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was used immediately in the next step. The triene obtained as above was dissolved in dry THF (100 mL) and then treated at 0 °C under nitrogen with a freshly prepared solution of disiamylborane (78 mL of 1.2 M solution in THF). When the addition was complete, the resulting clear solution was stirred at rt overnight after which sodium hydroxide (80 mL of an aqueous 4 M solution) was added slowly. The resulting mixture was treated with an excess of hydrogen peroxide (35% solution in water, 60 mL, 698 mmol). The reaction was very exothermic and so the oxidant was added dropwise while keeping the reaction temperature below 30 °C by external cooling (ice bath). When the addition was complete, the reaction mixture was stirred for a further 4 h, then was diluted with water (250 mL) and extracted with Et_2O (3 × 100 mL). The organic phase was sequentially washed with 5% aq $Na_2S_2O_5$ (100 mL) and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ether (9:1–3:1) as eluent to afford pure (4*S*)-*p*-menth-1,5-dien-9-ol (8.45 g, yield 59%) as a 4:6 mixture of the (4*S*,8*S*)- and (4*S*,8*R*)-isomers, respectively (by NMR analysis).

The above procedure was repeated starting from (*R*)-carvone tosylhydrazone (30.1 g, 94.6 mmol) to give pure (4*R*)-*p*-menth-1,5-dien-9-ol (7.9 g, 55% yield) as a 6:4 mixture of the (4*R*,8*S*)- and (4*R*,8*R*)-isomers, respectively (by NMR analysis).

4.3. General procedure for lipase-mediated acetylation

A solution of *p*-menth-1,5-dien-9-ol (70 mmol), PPL (8 g), vinyl acetate (20 mL) and *t*-BuOMe (80 mL) was stirred at rt and the formation of the acetylated compounds was monitored by TLC analysis. The reaction was stopped at the reported conversion (see below) by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was then purified by chromatography using hexane–diethyl ether (95:5–3:1) as eluent.

The above general procedure was used in the acetylation of the 4:6 mixture of the (4*S*,8*S*)- and (4*S*,8*R*)-*p*-menth-1,5-dien-9-ol isomers, respectively (10.2 g, 67 mmol). The reaction was stopped at about 55% conversion and the unreacted alcohol (−)-**4b** was treated with pyridine (30 mL) and a solution of 3,5-dinitrobenzoylchloride (7.6 g, 33 mmol) in CH_2Cl_2 (40 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 phases were washed with aq $NaHCO_3$ (5% solution), brine and then dried (Na_2SO_4). Concentration at reduced pressure gave an oil which was purified by chromatography (hexane/Et_2O 9:1) and crystallized twice from hexane to give pure (4*S*,8*R*)-*p*-menth-1,5-dien-9-ol 3,5-dinitrobenzoate (−)-**6b** (7.8 g, 22.5 mmol, 34% yield); mp 68–69 °C, $[\alpha]_D^{20} = -104.5$ (*c* 2.1, $CHCl_3$), 99% chemical purity by GC, 97% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.73 (m, 3H), 2.09-2.29 (m, 3H), 2.35–2.46 (m, 1H), 4.33 (dd, *J* = 7.0, 11.0 Hz, 1H), 4.47 (dd, *J* = 5.9, 11.0 Hz, 1H), 5.44–5.51 (m, 1H), 5.73 (dd, *J* = 3.7, 9.7 Hz, 1H), 5.88 (dt, *J* = 9.7, 1.8 Hz, 1H), 9.14 (br d, *J* = 2.1 Hz, 2H), 9.22 (br t, *J* = 2.1 Hz, 1H). ^{13}C NMR (100 MHz) δ 14.6, 20.9, 25.1, 35.1, 36.0, 69.7, 119.8, 122.2, 128.3, 129.0, 129.3, 131.3, 134.0, 148.7, 162.5. GC–MS *m*/*z* (rel intensity) 346 (M^+, 2), 281 (1), 207 (2), 195 (11), 149 (12), 132 (100), 119 (71), 105 (20), 93 (41), 77 (15), 65 (4).

The acetate was then dissolved in methanol (10 mL) and treated with NaOH (5 g, 125 mmol) in methanol (20 mL) with stirring at rt 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 submitted again to the lipase-mediated acetylation and the reaction was stopped at 60% conversion. The obtained (4*S*,8*S*)-*p*-menth-1,5-dien-9-ol acetate (−)-**5a** (4.1 g, 21.1 mmol) showed $[\alpha]_D^{20} = -129.3$ (*c* 2, $CHCl_3$), 91% chemical purity by GC, 91% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.9 Hz, 3H), 1.71 (m, 3H), 1.80–1.92 (m, 1H), 1.98–2.21 (m, 2H), 2.04 (s, 3H), 2.28–2.39 (m, 1H), 3.92 (dd, *J* = 7.0, 10.9 Hz, 1H), 4.07 (dd, *J* = 6.0, 10.9 Hz, 1H), 5.42–5.48 (m, 1H), 5.69 (dd, *J* = 9.7, 3.6 Hz, 1H), 5.82 (dt, *J* = 9.7, 1.8 Hz, 1H). ^{13}C NMR (100 MHz) δ14.2, 20.8, 20.9, 26.2, 35.2, 35.8, 67.1, 120.1, 128.0, 128.7, 131.2, 171.0. GC-MS *m*/*z* (rel intensity) 194 (M^+, 1), 134 (59), 119 (51), 105 (44), 92 (100), 77 (30), 61 (8), 43 (25).

The above acetate was hydrolysed with NaOH in methanol. After work-up, the crude alcohol was converted into the corresponding 3,5-dinitrobenzoate ester and crystallized twice from hexane to give (4*S*,8*S*)-*p*-menth-1,5-dien-9-ol 3,5-dinitrobenzoate (−)-**6a** (5.2 g, 22% yield), mp 67–68 °C, $[\alpha]_D^{20} = -97.1$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 96% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.9 Hz, 3H), 1.73 (m, 3H), 2.06–2.18 (m, 2H), 2.18-2.29 (m, 1H), 2.36–2.47 (m, 1H), 4.33 (dd, *J* = 7.1, 11.0 Hz, 1H), 4.45 (dd, *J* = 6.0, 11.0 Hz, 1H), 5.45–5.52 (m, 1H), 5.75 (dd, *J* = 3.7, 9.7 Hz, 1H), 5.88 (dt, *J* = 9.7, 1.8 Hz, 1H), 9.14 (br d, *J* = 2.1 Hz, 2H), 9.22 (br t, *J* = 2.1 Hz, 1H). ^{13}C NMR (100 MHz) δ 14.6, 21.0, 25.8, 35.6, 36.0, 69.5, 120.0, 122.3, 127.9, 129.1, 129.3, 131.4, 134.1, 148.7, 162.5. GC–MS *m*/*z* (rel intensity) 346 (M^+, 3), 281 (6), 207 (12), 195 (11), 149 (13), 134 (76), 119 (69), 105 (35), 93 (100), 91 (66), 77 (34), 65 (7).

The above general procedure used a 6:4 mixture of the (4*R*,8*S*)- and (4*R*,8*R*)-*p*-menth-1,5-dien-9-ol isomers, respectively (9.8 g, 64.5 mmol). The PPL-catalysed acetylation was stopped at about 75% conversion and the unreacted alcohol (+)-**4a** was converted into the corresponding 3,5-dinitrobenzoate and crystallized twice from hexane to give pure (4*R*,8*R*)-*p*-menth-1,5-dien-9-ol 3,5-dinitrobenzoate (+)-**6a** (4.1 g, 18% yield), mp 61–62 °C, $[\alpha]_D^{20} = +101.7$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 96% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**6a**.

The acetate was hydrolysed and the resulting alcohol was submitted again to the lipase-mediated acetylation. The reaction was stopped at 60% conversion. The obtained (4*R*,8*S*)-*p*-menth-1,5-dien-9-ol acetate (+)-**5b** (5.3 g, 27.3 mmol) showed $[\alpha]_D^{20} = +169.0$ (*c* 1.7, $CHCl_3$), 91% chemical purity by GC, 95% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.9 Hz, 3H), 1.71 (m, 3H), 1.89–1.98 (m, 1H), 2.02–2.17 (m, 2H), 2.04 (s, 3H), 2.27–2.39 (m, 1H), 3.94 (dd, *J* = 7.0, 10.9 Hz, 1H), 4.05 (dd, *J* = 6.0, 10.9 Hz, 1H), 5.41–5.47 (m, 1H), 5.65 (dd, *J* = 9.7, 3.6 Hz, 1H), 5.81 (dt, *J* = 9.7, 1.8 Hz, 1H). ^{13}C NMR (100 MHz) δ 14.2, 20.9, 20.9, 24.7, 35.0, 35.9, 67.3, 120.0, 128.6, 129.2, 131.2, 171.1. GC–MS *m*/*z* (rel intensity) 194 (M^+, <1), 134 (52), 119 (31), 105 (41), 92 (100), 77 (30), 61 (7), 43 (22).

The above acetate was hydrolysed with NaOH in methanol. After work-up, the crude alcohol was converted into the corresponding 3,5-dinitrobenzoate ester and crystallized from hexane to give (4*R*,8*S*)-*p*-menth-1,5-dien-9-ol 3,5-dinitrobenzoate (+)-**6b** (7.1 g, 32% yield), mp 68–69 °C, $[\alpha]_D^{20} = +103.5$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**6b**.

The hydrolysis of dinitrobenzoates **6a** and **6b** was performed with NaOH in methanol as described for the hydrolysis of acetates **5a** and **5b**. Accordingly, the reaction was almost quantitative and the following alcohols were obtained:

(4*S*,8*S*)-*p*-Menth-1,5-dien-9-ol (−)-**4a**; $[\alpha]_D^{20} = -209.1$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 96% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 7.0 Hz, 3H), 1.49 (br s, 1H), 1.65–1.81 (m, 1H), 1.72 (m, 3H), 1.99–2.21 (m, 2H), 2.31–2.42 (m, 1H), 3.48 (dd, *J* = 6.6, 10.8 Hz, 1H), 3.64 (dd, *J* = 6.0, 10.8 Hz, 1H), 5.43–5.49 (m, 1H), 5.71 (dd, *J* = 3.6, 9.8 Hz, 1H), 5.82 (dt, *J* = 9.8, 1.8 Hz, 1H). ^{13}C NMR (100 MHz) δ 14.1, 21.0, 26.2, 35.2, 39.1, 65.8, 120.3, 128.5, 128.8, 131.3. GC–MS *m*/*z* (rel intensity) 152 (M^+, 10), 137 (36), 119 (35), 105 (25), 93 (97), 91 (100), 77 (50), 65 (11), 40 (34).

(4*S*,8*R*)-*p*-Menth-1,5-dien-9-ol (−)-**4b**; $[\alpha]_D^{20} = -213.9$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 97% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.93 (d, *J* = 6.9 Hz, 3H), 1.38 (br s, 1H), 1.71 (m, 3H), 1.73–1.83 (m, 1H), 2.00–2.20 (m, 2H), 2.30–2.41 (m, 1H), 3.50 (dd, *J* = 6.4, 10.8 Hz, 1H), 3.61 (dd, *J* = 6.1, 10.8 Hz, 1H), 5.42–5.47 (m, 1H), 5.70 (dd, *J* = 3.7, 9.7 Hz, 1H), 5.81 (dt, *J* = 9.7, 1.8 Hz, 1H). ^{13}C NMR (100 MHz) δ 14.1, 21.0, 25.1, 34.9, 39.4, 66.0, 120.1, 128.4, 129.7, 131.2. GC–MS *m*/*z* (rel intensity) 152 (M^+, 12), 137 (35), 119 (19), 109 (10), 105 (23), 93 (100), 91 (93), 77 (50), 65 (11), 39 (10).

(4*R*,8*R*)-*p*-Menth-1,5-dien-9-ol (+)-**4a**; $[\alpha]_D^{20} = +218.4$ (*c* 1, $CHCl_3$), 99% chemical purity by GC, 96% diastereoisomeric purity. ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**4a**.

(4*R*,8*S*)-*p*-Menth-1,5-dien-9-ol (+)-**4b**; $[\alpha]_D^{20} = +229.3$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity. ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**4b**.

4.4. General procedure for the cyclisation of *p*-menth-1,5-dien-9-ol isomers

A suitable acid catalyst (see Table 1) was added dropwise to a solution of the *p*-menth-1,5-dien-9-ol isomer (6 mmol) in dry ether (40 mL). After stirring at rt for 5–24 h (see Table 1), the mixture was quenched by the addition of aq $NaHCO_3$ (5% solution, 100 mL) and extracted with ether (2 × 50 mL). The combined organic phases were washed with brine and then dried (Na_2SO_4). Concentration by distillation of the solvent through a vigreux column gave an oil, which was purified by chromatography eluting with hexane/ether (95:5–9:1) as eluent to afford pure ether **7** or **8**.

The cyclisation of alcohol (−)-**4b** ($BF_3{\cdot}OEt_2$) afforded (3*S*,4*R*,8*R*)-3,9-epoxy-*p*-menth-1-ene (+)-**7** (dill ether) in 80% yield; $[\alpha]_D^{20} = +3.3$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity, Lit.[10a] $[\alpha]_D^{20} = +8.1$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.8 Hz, 3H), 1.45–1.56 (m, 1H), 1.65–1.77 (m, 5H), 1.80–1.97 (m, 2H), 1.97–2.09 (m, 1H), 3.30 (dd, *J* = 6.9, 8.3 Hz, 1H), 4.06 (dd, *J* = 7.3, 8.3 Hz, 1H), 4.21–4.27 (m, 1H), 5.50–5.53 (m, 1H). ^{13}C NMR (100 MHz) δ 17.5, 23.6, 24.1, 28.1, 37.9, 43.9, 73.9, 75.0, 121.0, 138.6. GC–MS *m*/*z* (rel intensity) 152 (M^+, 5), 151 (6), 138 (11), 137 (100), 124 (6), 109 (33), 107 (5), 95 (12), 93 (14), 91 (16), 79 (15), 69 (24), 55 (9), 41 (10).

The cyclisation of alcohol (−)-**4a** ($BF_3{\cdot}OEt_2$) afforded (3*S*,4*R*,8*S*)-3,9-epoxy-*p*-menth-1-ene (−)-**8** (*epi*-dill ether) in 74% yield; $[\alpha]_D^{20} = -129.3$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 96% diastereoisomeric purity, Lit.[10a] $[\alpha]_D^{20} = -133.4$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta\delta$ 1.00 (d, *J* = 6.9 Hz, 3H), 1.20–1.33 (m, 1H), 1.58 (dm, *J* = 12.8 Hz, 1H), 1.73 (s, 3H), 1.85–2.03 (m, 3H), 2.49–2.63 (m, 1H), 3.45 (dd, *J* = 7.9, 9.8 Hz, 1H), 3.93 (dd, *J* = 7.9, 8.1 Hz, 1H), 4.15–4.19 (m, 1H), 5.58–5.62 (m, 1H). ^{13}C NMR (100 MHz) δ 11.6, 19.1, 23.5, 29.7, 37.0, 40.1, 72.3, 76.1, 120.2, 140.0. GC–MS *m*/*z* (rel intensity) 152 (M^+, 4), 151 (4), 138 (9), 137 (100), 124 (4), 109 (26), 107 (6), 95 (10), 93 (14), 91 (15), 79 (14), 69 (21), 55 (8), 41 (10).

The cyclisation of alcohol (+)-**4b** ($BF_3{\cdot}OEt_2$) afforded (3*R*,4*S*,8*S*)-3,9-epoxy-*p*-menth-1-ene (−)-**7** in 75% yield; $[\alpha]_D^{20} = -3.4$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 98% diastereoisomeric purity, Lit.[10a] $[\alpha]_D^{20} = -7.3$ (*c* 1, $CHCl_3$), ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (+)-**7**.

The cyclisation of alcohol (+)-**4a** ($BF_3{\cdot}OEt_2$) afforded (3*R*,4*S*,8*R*)-3,9-epoxy-*p*-menth-1-ene (+)-**8** in 79% yield; $[\alpha]_D^{20} = +143.0$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity, Lit.[10a] $[\alpha]_D^{20} = +127.9$ (*c* 1, $CHCl_3$), ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**8**.

4.5. General procedure for the hydrogenation of the dill/*epi*-dill ether isomers

A solution of the unsaturated ether (6 mmol) in absolute ethanol (30 mL) was treated with the appropriate catalyst (see Table 2) and was hydrogenated at rt and at atmospheric pressure. After consumption of the stoichiometric amount of hydrogen, the catalyst was removed by filtration and the solution was diluted with water (150 mL). The mixture was extracted with ether (2 × 70 mL) and the combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was distilled off through a vigreux column and the residue was purified by chromatography eluting with hexane/ether (95:5–9:1) as eluent to afford the 3,9-epoxy-*p*-menthane isomer.

Hydrogenation of ether (+)-**7** with PtO_2 as catalyst gave (1*R*,3*R*,4*R*,8*R*)-3,9-epoxy-*p*-menthane (+)-**9** in 63% yield; $[\alpha]_D^{20} = +88.5$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, 97% diastereoisomeric purity, Lit.[10d] $[\alpha]_D^{20} = -69.5$ (for the opposite enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.6 Hz, 3H), 0.86–1.02 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 1.25–1.39 (m, 1H), 1.38–1.47 (m, 1H), 1.55–1.68 (m, 1H), 1.68–1.83 (m, 3H), 2.11–2.26 (m, 1H), 3.35 (t, *J* = 8.5 Hz, 1H), 4.04 (dt, *J* = 6.4, 10.5 Hz, 1H), 4.08 (t, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz) δ 15.9, 22.3, 23.5, 29.5, 29.9, 33.9, 38.4, 44.7, 74.1, 78.7. GC–MS *m*/*z* (rel intensity) 154 (M^+, 39), 139 (13), 123 (5), 109 (8), 97 (100), 83 (47), 69 (30), 55 (17), 41 (22).

Hydrogenation of ether (+)-**7** with Raney-Ni as catalyst gave (1*S*,3*R*,4*R*,8*R*)-3,9-epoxy-*p*-menthane (−)-**10** in 90% yield; $[\alpha]_D^{20} = -17.0$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity, Lit.[10d] $[\alpha]_D^{20} = +11.2$ (for the opposite enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78–0.89 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 1.10–1.23 (m, 2H), 1.47–1.67 (m, 4H), 1.92–2.05 (m, 2H), 3.33 (dd, *J* = 3.5, 8.5 Hz, 1H), 3.95–3.99 (m, 1H), 4.14 (dd, *J* = 7.4, 8.5 Hz, 1H). ^{13}C NMR (100 MHz) δ 19.8, 22.2, 26.5, 28.3, 33.4, 36.8, 39.7, 44.9, 73.9, 75.8. GC–MS *m*/*z* (rel intensity) 154 (M^+, 23), 139 (15), 121 (8), 109 (9), 97 (100), 83 (43), 69 (31), 55 (18), 41 (24).

Hydrogenation of ether (−)-**8** with PtO_2 as catalyst gave (1*R*,3*R*,4*R*,8*S*)-3,9-epoxy-*p*-menthane (−)-**11** in 70% yield; $[\alpha]_D^{20} = -51.9$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 95% diastereoisomeric purity, Lit.[10d] $[\alpha]_D^{20} = +46.5$ (for the opposite enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H), 1.29–1.51 (m, 4H), 1.54–1.64 (m, 1H), 1.65–1.79 (m, 2H), 1.82–1.92 (m, 1H), 2.32–2.45 (m, 1H), 3.42 (dd, *J* = 8.4, 8.9 Hz, 1H), 3.86 (t, *J* = 8.4 Hz, 1H), 3.96–4.02 (m, 1H). ^{13}C NMR (100 MHz) δ 12.4, 17.1, 20.3, 25.9, 30.0, 34.5, 37.6, 40.8, 72.3, 78.7. GC–MS *m*/*z* (rel intensity) 154 (M^+, 45), 139 (16), 123 (9), 107 (8), 97 (100), 83 (38), 69 (29), 55 (17), 41 (25).

Hydrogenation of ether (−)-**8** with Raney Ni as catalyst gave (1*S*,3*R*,4*R*,8*S*)-3,9-epoxy-*p*-menthane (−)-**12** in 78% yield, $[\alpha]_D^{20} = -46.4$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 93% diastereoisomeric purity, Lit.[10d] $[\alpha]_D^{20} = +39.2$ (for the opposite enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–0.91 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.07–1.21 (m, 2H), 1.44–1.53 (m, 1H), 1.53–1.62 (m, 1H), 1.62–1.70 (m, 1H), 1.70–1.79 (m, 1H), 1.97 (dm, *J* = 14.5 Hz, 1H), 2.37–2.54 (m, 1H), 3.44 (dd, *J* = 7.9, 10.2 Hz, 1H), 3.92 (dd, *J* = 7.9, 8.3 Hz, 1H), 3.96–4.01 (m, 1H). ^{13}C NMR (100 MHz) δ 11.6, 22.1, 22.2, 26.7, 33.4, 37.6, 37.8, 41.1, 72.3, 79.3. GC–MS *m*/*z* (rel intensity) 154 (M^+, 24), 139 (13), 136 (18), 123 (11), 109 (11), 97 (100), 83 (39), 69 (30), 55 (18), 41 (26).

Hydrogenation of ether (−)-**7** with PtO_2 as catalyst gave (1*S*,3*S*,4*S*,8*S*)-3,9-epoxy-*p*-menthane (−)-**9** in 65% yield; $[\alpha]_D^{20} = -89.1$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, 97% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (+)-**9**.

Hydrogenation of ether (−)-**7** with Ni-Raney as catalyst gave (1*R*,3*S*,4*S*,8*S*)-3,9-epoxy-*p*-menthane (+)-**10** in 86% yield; $[\alpha]_D^{20} = +17.1$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 98% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**10**.

Hydrogenation of ether (+)-**8** with PtO_2 as catalyst gave (1*S*,3*S*,4*S*,8*R*)-3,9-epoxy-*p*-menthane (+)-**11** in 70% yield; $[\alpha]_D^{20} = +52.2$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 96% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**11**.

Hydrogenation of ether (+)-**8** with Raney-Ni as catalyst gave (1*R*,3*S*,4*S*,8*R*)-3,9-epoxy-*p*-menthane (+)-**12** in 80% yield, $[\alpha]_D^{20} = +47.6$ (*c* 2, $CHCl_3$), 99% chemical purity by GC, 95% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (−)-**12**.

4.6. General procedure for the oxidation of the ether isomers 9–12

A solution of ether **9**–**12** (3 mmol) and ruthenium trichloride hydrate (20 mg) in CCl_4/CH_3CN (1:1, 20 mL) was treated with a suspension of $NaIO_4$ (4 g, 18.7 mmol) in water (20 mL). The heterogeneous mixture was stirred vigorously at rt until the starting ether was no longer detectable by TLC analysis (1–20 h). The reaction was then diluted with water (80 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed in turn with 5% aq Na_2SO_3 (80 ml) and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ether (9:1–3:1) as eluent to afford compound **13**, **14a**–**16a**. Keto acids **14a**–**16a** were further characterized by analysis of the corresponding methyl ester derivatives **14b**–**16b**. Accordingly, a small sample (100 mg, 0.54 mmol) of the acids was treated with an excess of diazomethane (2 mL of a 1 M solution in diethyl ether) at 0 °C. The reaction was kept for 1 h at this temperature. Thus, the solvent was removed in vacuo and the residue was analysed.

Oxidation of ether (+)-**9** gave (1*R*,3*R*,4*R*,8*R*)-3,9-epoxy-*p*-menthan-9-one (+)-**13** in 70% yield, mp 62 °C (hexane), $[\alpha]_D^{20} = +48.7$ (*c* 1, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity, Lit.[6a] $[\alpha]_D^{20} = +45.7$ (*c* 0.9, $CHCl_3$), mp 55–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–1.07 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.31–1.46 (m, 1H), 1.55 (dm, *J* = 13.5 Hz, 1H), 1.60–1.72 (m, 1H), 1.85 (dm, *J* = 14.6 Hz, 1H), 2.04–2.12 (m, 1H), 2.16–2.25 (m, 1H), 2.41–2.52 (m, 1H), 4.48 (dt, *J* = 11.0, 6.8 Hz, 1H). ^{13}C NMR (100 MHz) δ 13.2, 22.0, 24.0, 28.6, 29.4, 35.3, 37.8, 41.7, 77.4, 179.5. GC–MS *m*/*z* (rel intensity) 168 (M^+, <1), 139 (2), 124 (6), 109 (26), 95 (44), 81 (100), 67 (47), 55 (23), 41 (23).

Oxidation of ether (−)-**10** gave (1*S*,4*R*,8*R*)-3-oxo-*p*-menthan-9-oic acid **14a** in 67% yield, mp 93–96 °C, lit.[14] mp 95 °C (for the opposite enantiomer); the (1*S*,4*R*,8*R*)-3-oxo-*p*-menthan-9-oic acid methyl ester (+)-**14b** was obtained as a colourless oil showing the following analytical data: $[\alpha]_D^{20} = +21.1$ (*c* 1.7, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.5 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.28–1.48 (m, 2H), 1.74–1.90 (m, 1H), 1.88–1.96 (m, 1H), 2.00–2.16 (m, 2H), 2.37 (ddd, *J* = 2.3, 3.9, 13.2 Hz, 1H), 2.63–2.78 (m, 2H), 3.68 (s, 3H). ^{13}C NMR (100 MHz) δ 14.1, 22.3, 29.0, 33.8, 35.3, 38.5, 50.1, 51.6, 51.9, 176.8, 210.5.GC–MS *m*/*z* (rel intensity) 198 (M^+, 7), 166 (46), 151 (12), 139 (24), 111 (100), 95 (39), 88 (37), 69 (90), 55 (45), 41 (28).

Oxidation of ether (−)-**11** gave (1*R*,4*R*,8*S*)-3-oxo-*p*-menthan-9-oic acid **15a** (thick oil) in 58% yield; the (1*R*,4*R*,8*S*)-3-oxo-*p*-menthan-9-oic acid methyl ester (+)-**15b** was obtained as a colourless oil showing the following analytical data: $[\alpha]_D^{20} = +51.9$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, 75% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.98 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.53–1.67 (m, 1H), 1.79–1.89 (m, 3H), 2.08–2.16 (m, 1H), 2.17–2.29 (m, 1H), 2.44 (dd, *J* = 5.1, 13.5 Hz, 1H), 2.52–2.60 (m, 1H), 2.80–2.89 (m, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz) δ 15.0, 19.8, 26.8, 30.1, 32.7, 39.2, 48.1, 51.5, 52.7, 175.4, 210.9. GC–MS *m*/*z* (rel intensity) 198 (M^+, 13), 166 (66), 151 (14), 139 (28), 111 (100), 95 (44), 88 (40), 69 (97), 55 (50), 41 (31).

Oxidation of ether (−)-**12** gave (1*S*,4*R*,8*S*)-3-oxo-*p*-menthan-9-oic acid **16a** (thick oil) in 60% yield; the (1*S*,4*R*,8*S*)-3-oxo-*p*-menthan-9-oic acid methyl ester (+)-**16b** was obtained as a colourless oil showing the following analytical data: $[\alpha]_D^{20} = +22.2$ (*c* 1.9, $CHCl_3$), 99% chemical purity by GC, 98% diastereoisomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.31–1.44 (m, 1H), 1.57 (dq, *J* = 3.3, 12.9 Hz, 1H), 1.80–1.94 (m, 2H), 1.95–2.06 (m, 2H), 2.38 (ddd, *J* = 2.3, 3.7, 13.3 Hz, 1H), 2.51–2.59 (m, 1H), 2.74–2.84 (m, 1H), 3.66 (s, 3H). ^{13}C NMR (100 MHz) δ 14.8, 22.2, 30.1, 33.9, 35.3, 39.1, 50.6, 51.5, 52.5, 175.8, 210.0. GC–MS *m*/*z* (rel intensity) 198 (M^+, 13), 166 (60), 151 (11), 139 (25), 111 (98), 95 (44), 88 (39), 69 (100), 55 (53), 41 (33).

The above oxidation procedure was repeated starting from ethers (−)-**9**, (+)-**10**, (+)-**11** and (+)-**12** to give compounds (−)-**13**, (−)-**14b**, (−)-**15b**, and (−)-**16b**, respectively showing the following analytical data:

(1*S*,3*S*,4*S*,8*S*)-3,9-Epoxy-*p*-menthan-9-one (−)-**13** in 65% yield, mp 62 °C (hexane), $[\alpha]_D^{20} = -48.5$ (*c* 1, $CHCl_3$), 99% chemical purity by GC, 99% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (+)-**13**.

(1*R*,4*S*,8*S*)-3-Oxo-*p*-menthan-9-oic acid methyl ester (−)-**14b**, colourless oil, $[\alpha]_D^{20} = -21.0$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, 98% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (+)-**14b**.

(1*S*,4*S*,8*R*)-3-Oxo-*p*-menthan-9-oic acid methyl ester (−)-**15b**, colourless oil, $[\alpha]_D^{20} = -47.9$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, 70% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (+)-**15b**.

(1*R*,4*S*,8*R*)-3-Oxo-*p*-menthan-9-oic acid methyl ester (−)-**16b**, colourless oil, $[\alpha]_D^{20} = -22.6$ (*c* 2, $CHCl_3$), 96% chemical purity by GC, 98% diastereoisomeric purity, ^{1}H NMR, ^{13}C NMR, MS spectra were in accordance with those of (+)-**16b**.

References

1. Millar, J. G. *J. Nat. Prod.* **1998**, *61*, 1025–1026.
2. Golding, B. T.; Pombovillar, E. *J. Chem. Soc., Perkin Trans.1* **1992**, 1519–1524.
3. (a) Wust, M.; Mosandl, A. *Eur. Food Res. Technol.* **1999**, *209*, 3–11; (b) Blank, I.; Sen, A.; Grosch, W. *Food Chem.* **1992**, *43*, 337–343.
4. Guth, H. *Helv. Chim. Acta* **1996**, *79*, 1559–1571.
5. (a) Sutour, S.; Bradesi, P.; de Rocca-Serra, D.; Casanova, J.; Tomi, F. *Flavour Frag. J.* **2008**, *23*, 107–114; (b) Näf, R.; Velluz, A. *Flavour Frag. J.* **1998**, *13*, 203–208.
6. (a) Gaudin, J. M. *Tetrahedron* **2000**, *56*, 4769–4776; (b) Serra, S.; Fuganti, C. *Helv. Chim. Acta* **2002**, *85*, 2489–2502.
7. (a) Serra, S.; Fuganti, C.; Gatti, F. G. *Eur. J. Org. Chem.* **2008**, 1031–1037; (b) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 97–101.
8. Ronn, M.; Andersson, P. G.; Backvall, J. E. *Acta Chem. Scand.* **1998**, *52*, 524–527.
9. Serra, S. *Tetrahedron: Asymmetry* **2011**, *22*, 619–628.
10. (a) Serra, S.; Fuganti, C. *Helv. Chim. Acta* **2004**, *87*, 2100–2109; (b) Reichert, S.; Mosandl, A. *J. High Res. Chromatogr.* **1999**, *22*, 631–634; (c) Brunke, E.-J.; Rojahn, W. *Dragoco Rep.* **1984**, *31*, 67; (d) Ohloff, G.; Schulte-Elte, K. H.; Willhalm, B. *Helv. Chim. Acta* **1966**, *49*, 2135–2150.
11. Kitagawa, I.; Tsujji, S.; Nishikawa, F.; Shibuya, H. *Chem. Pharm. Bull.* **1983**, *31*, 2639–2651.
12. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
13. (a) Foote, C. S.; Wuesthoff, M. T.; Burstain, I. G. *Tetrahedron* **1967**, *23*, 2601–2608; (b) Woodward, R. B.; Eastman, R. H. *J. Am. Chem. Soc.* **1950**, *72*, 399–403.
14. Davison, M.; Kikolski, E. M.; Mostafavi, D.; Lalancette, R. A.; Thompson, H. W. *Acta Crystallogr., Sect. C* **2005**, *61*, O249–O252.