Enzyme-Mediated Preparation of Enantiomerically Pure *p*-Menthan-3,9-diols and Their Use for the Synthesis of Natural *p*-Menthane Lactones and Ethers

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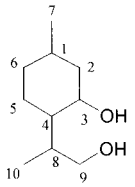
The diastereoselective preparation of the *p*-menthane-3,9-diols (±)-**12**, (±)-**13a**, (±)-**13b**, and (±)-**18** and the study of their enzymic resolution is described (*Scheme 1*). The corresponding enantiomer-enriched diols obtained by means of the lipase-mediated kinetic acetylation of the racemic diols are suitable synthetic precursors of many relevant *p*-menthane monoterpenes. Their usefulness is shown in the preparation of different natural products of this class that are interesting for industrial purposes because of their odor qualities, *i.e.*, of the enantiomeric form of 3-hydroxy-*p*-menthan-9-oic acid lactone **1**, of mintlactone **2**, of the 3,9-epoxy-*p*-menth-1,8(10)-diene **10**, and of the pheromone vesperal **11** (*Schemes 2* and *3*).

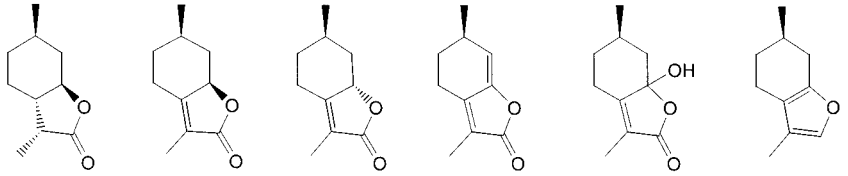
1. Introduction. – Among the monoterpenes of the *p*-menthane family, many natural products show O-functionalization in both positions 3 and 9 of the *p*-menthane framework. Several compounds of different chemical structures belong to this class, and most of them are well-known as flavoring ingredients. The 3-hydroxy-*p*-menthan-9-oic acid lactone **1**, (−)-mintlactone ((−)-**2**), (+)-isomintlactone (**3**), (1*R*)-menthofurolactone (**4**), (1*R*)-3-hydroxymintlactone **5** as well as (+)-menthofuran (**6**) were found in peppermint oil [1], whilst the isomeric (+)-mintlactone and (−)-isomintlactone are key aroma components of the wood of *Bursera graveolens* [2]. Moreover, the odorants (−)-wine lactone (**7**) [3], (+)-dill ether (**8**) [4], racemic linden ether (**9**) [5a], (+)-3,9-epoxy-*p*-mentha-1,8(10)-diene ((+)-**10**) [6] together with the structurally related pheromone (+)-vesperal ((+)-**11**) [7a] have been found in different natural sources.

In this context, *p*-menthane lactones are very interesting compounds since the most prominent members of this class, as lactones **1**–**4**, are used as commercial flavoring ingredients [8]. Moreover, recent studies have highlighted the relevance of the isomeric wine lactone [3] and of the analogous saturated *p*-menthane lactones [9] due to the low threshold and the powerful coumarin-like odor properties, respectively. In addition, these studies show that either the isomer or the enantiomer composition of these lactones determined their olfactory features.

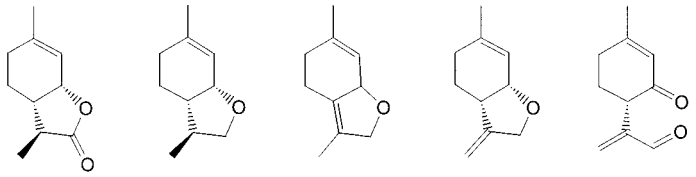
In light of these observations, it seemed desirable to develop new synthetic methods for the stereoselective preparation of this kind of compound. Several enantioselective synthesis of these natural lactones [3][9][10] and ethers [5b] have been reported, but the need for expensive enantiomerically pure starting materials is the main obstruction limiting their large-scale preparation. On the other hand, different isomeric *p*-menthane-3,9-diols that are easily prepared in the racemic form from low-cost industrial products, may be converted to the suitable *p*-menthane lactones and ethers



p-menthane numbering



(+)-**1** (–)-**2** **3** **4** **5** **6**



7 **8** **9** (+)-**10** (+)-**11**

by known and straightforward methods. We envisage that enzymic resolution of these diols can afford useful chiral building blocks of great utility in the preparation of the above-mentioned natural compounds. We focused our attention on three kinds of diols: the *p*-menthane-3,9-diols, the *p*-menth-8(10)-ene-3,9-diols, and the *p*-mentha-1,8(10)-diene-3,9-diols, which share the same framework but differ in the number of C=C bonds observed from the naturally occurring products **1**–**11**. We prepared a set of four diastereoisomerically pure diols, (±)-**12**, (±)-**13a**, (±)-**13b**, and (±)-**18**, showing the above-mentioned structural characteristics, and, next, we tested their reactivity toward the irreversible acetylation catalyzed by three different lipases (lipase PS, CCL, and PPL). This kind of exploitation was previously applied in the preparation of enantiomerically pure ionone [11] and irone odorants [12] starting from racemic materials. Accordingly, we extended this acquired enzymic methodology to the preparation of enantiomerically pure *p*-menthane odorants. We found that both the kinetics and enantioselectivity in the acetylation step are strongly affected by the kind of enzyme used and also by the configurational features of the substrates. By means of this enzymic selectivity, we obtained the two enantiomeric forms of diols (±)-**12**, (±)-**13a**, and (±)-**18**, which were then converted by chemical manipulation to both enantiomeric forms of lactone (±)-**1**, mintlactone (±)-**2**, ether (±)-**10**, and vesperal (±)-**11**.

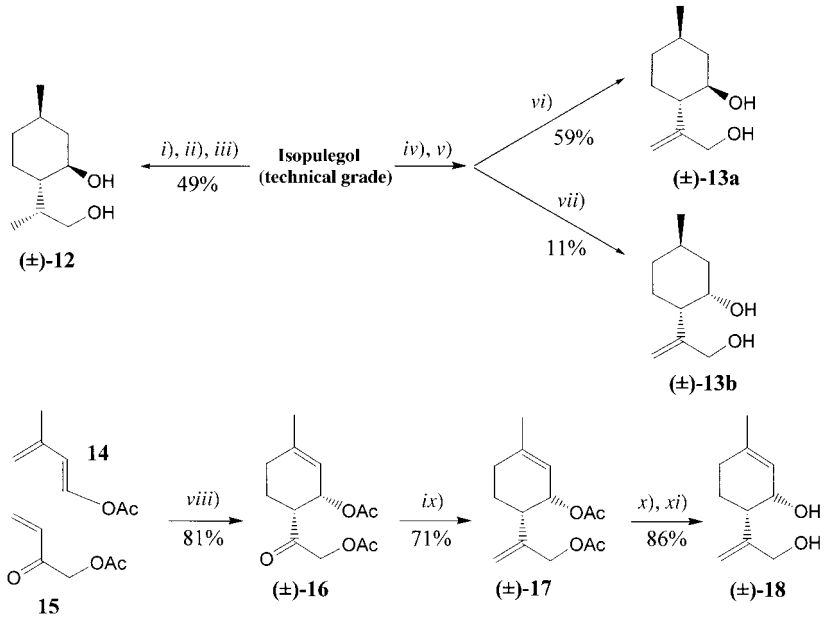
2. Results. – 2.1. *Synthesis of Racemic Diols (±)-***12**, *(±)-***13a**, *(±)-***13b**, *and (±)-***18**. To establish unambiguously both the enantioselectivity and diastereoselectivity in the lipase-catalyzed acetylation of *p*-menthane-3,9-diols, we prepared the four diastereo-

isomerically pure diols (±)-**12**, (±)-**13a**, (±)-**13b**, and (±)-**18** by modification of reported procedures (*Scheme 1*).

Diol (±)-**12** shows the same relative configuration as lactone (±)-**1**, and it was previously [13] obtained from isopulegol by hydroboration as a key synthetic step. Since this reaction proceeds with high diastereoselectivity, the availability of the enantiomeric form of (±)-**12** and (±)-**1** [10i] is relegated to the preparation of enantiomerically pure isopulegol. Accordingly, we treated commercially available racemic isopulegol with $BH_3 \cdot Me_2S$, and subsequent oxidation with $NaOH/H_2O_2$ gave a diastereoisomer mixture of diols. Purification of the latter by crystallization afforded diol (±)-**12** in up to 98% diastereoisomer purity.

In the same way, we focused our attention on compounds (±)-**13a** and (±)-**13b**, which show the same relative configurations at C(1) and C(3) as mintlactone and isomintlactone, respectively. These two diols are formally obtained by oxidation of the allylic methyl group of isopulegol and neoisopulegol, which are the main components of the commercial material. This kind of functionalization was well-studied in the past, and several procedures to this end have been reported [13–15]. We, therefore, treated commercially available racemic isopulegol with 3-chloroperbenzoic acid (*m*ClPBA), and the mixture of epoxides obtained was submitted to a ring-opening rearrangement by means of lithium diisopropylamide in refluxing THF. The crude diols were then

Scheme 1



i) $BH_3 \cdot Me_2S$, THF. *ii*) H_2O_2, NaOH. *iii*) Crystallization from hexane. *iv*) *m*ClPBA, CH_2Cl_2. *v*) lithium diisopropylanide, THF, reflux. *vi*) CC, crystallization from hexane/AcOEt. *vii*) CC, crystallization from Et_2O. *viii*) **14** + **15**, benzene, reflux. *ix*) Ph_3PCH_2, THF, reflux. *x*) KOH, MeOH, reflux. *xi*) Crystallization from hexane/AcOE.

purified by chromatography and crystallization to afford diastereoisomerically pure (±)-**13a** and (±)-**13b**.

Structural considerations of compounds **7**–**11** suggested that a third kind of diol showing at least one unsaturation at C(1) and *cis* relative configuration at C(3) and C(4) should be investigated. To this end, we selected the diol (±)-**18**, which was previously prepared in the synthesis of (+)-vesperal ((+)-**11**) [7a]. According to the latter method, we built up the cyclohexene ring with the required *cis* relative configuration at C(3) and C(4) by *Diels-Alder* reaction of diene **14** [16] and vinyl ketone **15** [17]. The resulting ketone (±)-**16** was obtained in good diastereoselectivity (95%), and the following *Wittig* methylenation afforded the diacetate (±)-**17** showing the entire *p*-menthane framework. Subsequent KOH hydrolysis of the acetate moieties gave crude diol (±)-**18**, which was further purified by crystallization to give (±)-**18** in 99% diastereoisomer purity.

2.2. *Lipase-Catalyzed Acetylation of Diols* (±)-**12**, (±)-**13a**, (±)-**13b**, *and* (±)-**18**. Each of the four diastereoisomerically pure diols (±)-**12**, (±)-**13a**, (±)-**13b** and (±)-**18** was treated with vinyl acetate in ^{t}BuOMe solution in the presence of lipases (lipase PS, CCL, and PPL). The reactivity of each substrate toward the irreversible acetylation was tested by monitoring at regular time intervals the product distribution by GC analysis. After good conversion (45–100%) of the starting diols, the products were isolated and fully characterized. The results of this study are collected in the *Table* and allow some interesting considerations.

Table. *Results of Enzyme-Mediated Acetylation of Diols (±)-***12**, *(±)-***13a**, *(±)-***13b**, *and (±)-***18**

	Enzyme	Time [days]	ee of recovered alcohol[a])	ee of monoacetylated product[a])[b])	ee of diacetylated product[a])	Enantiomer ratio	Conversion
(±)-**12**	PPL	4	72	6	*c*	1.9	0.923
	CCL		17	55	*c*	4	0.236
	PS		92	64	*c*	15	0.59
(±)-**13a**	PPL	21	*a*	0, *b*	*c*		
	CCL		*a*	0, *b*	*c*		
	PS		*a*	92	99	662	0.482
(±)-**13b**	PPL	21	*a*	0, *b*	*c*		
	CCL		*a*	0, *b*	*c*		
	PS		*a*	0, *b*	*c*		
(±)-**18**	PPL	28	*a*	0, *b*	*c*		
	CCL		*a*	0, *b*	*c*		
	PS		*a*	94	99	712	0.487

[a]) The GC analysis of the reaction mixture showed that none of the compound (*a*), more than 90% of the compound (*b*), and less than 5% of the compound (*c*) was detected. [b]) Compounds (±)-**13a**, (±)-**13b**, and (±)-**18** were monoacetylated by each lipase in less than 36 h.

All the lipases used mediated the acetylation of the primary alcohol functions, but, when these groups were allylic (compounds (±)-**13a**, (±)-**13b**, and (±)-**18**), the reaction was very fast (less then 36 h), and no enantioselectivity was observed in this step. Otherwise, the saturated diol (±)-**12** reacted slowly, and, after four days, *ca*. 50% of the starting diol was acetylated. The enantioselectivity of this step was dependent on the

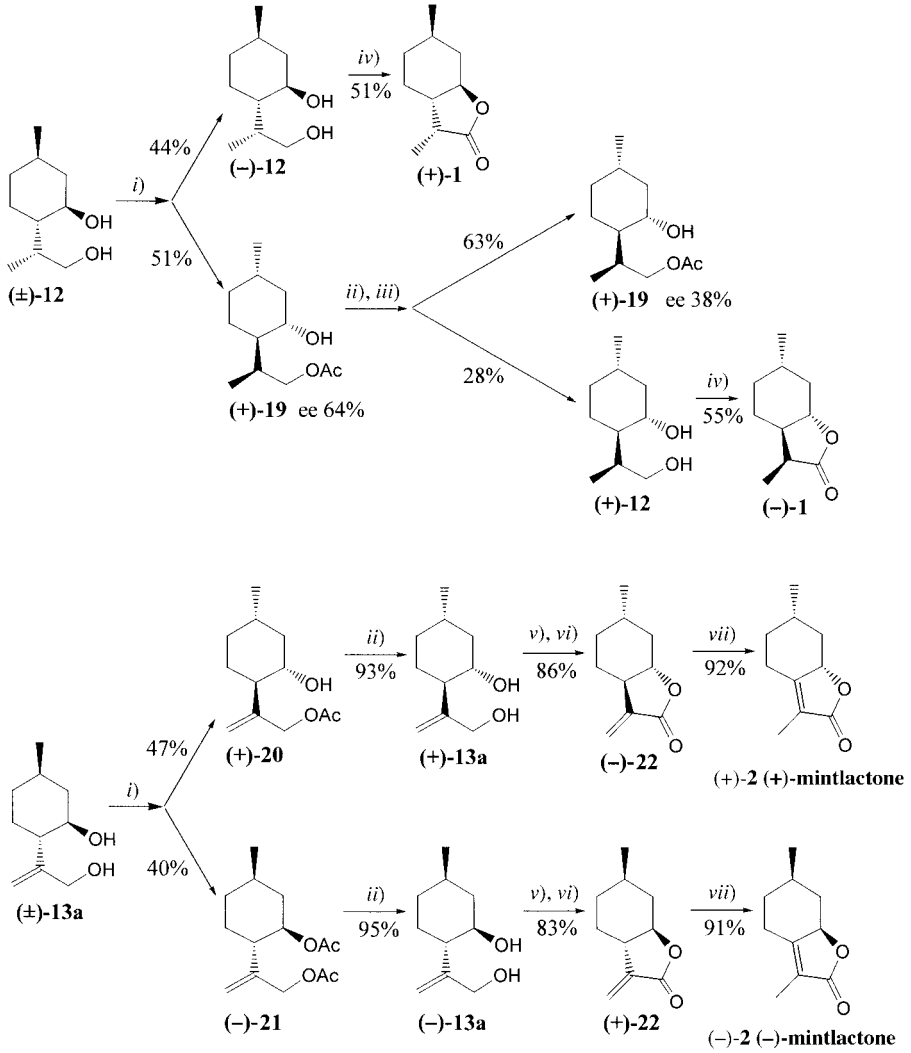
kind of lipase used. Lipase PS showed higher selectivity with a preference for the conversion of the (+)-isomer. Differently, PPL showed the lowest selectivity, whereas CCL, though with poor selectivity, converted the (−)-isomer. The monoacetylated compounds obtained were not further acetylated by the above-mentioned enzymes, even after long reaction time.

Concerning the acetylation of the secondary-alcohol group, the behaviors of the diols (±)-**13a**, (±)-**13b**, and (±)-**18** were again different. Compounds (±)-**13a** and (±)-**18** were slowly converted to the enantiomerically pure diacetates (99% ee) and to the enantiomer-enriched (92 and 94% ee, resp.) monoacetylated derivatives only when lipase PS was used as a catalyst. Otherwise, (±)-**13b**, which differed from (±)-**13a** only in the *cis* relative configuration at C(3) and C(4), was not converted by any of the enzymes used.

2.3. *Preparation of Enantiomer-Enriched Diols (+)- and (−)-***12**, *(+)- and (−)-***13a**, *and (+)- and (−)-***18** *and Their Conversion to the Natural Products (+)- and (−)-***1**, *(+)- and (−)-***2**, *(+)- and (−)-***10**, *and (+)- and (−)-***11**. Taking advantage of the above-described enzymic selectivity, we devised a large-scale method for the preparation of all the enantiomeric forms of diols (±)-**12**, (±)-**13a**, and (±)-**18** and then to the natural products (+)- and (−)-**1**, (+)- and (−)-**2**, (+)- and (−)-**10**, and (+)- and (−)-**11**. We first treated (±)-**12** with lipase PS in the presence of vinyl acetate and ^{t}BuOMe as solvent allowing the reaction to proceed to >50% conversion (*Scheme 2*). The unreacted diol (−)-**12** was isolated in satisfactory enantiomer purity (92% ee), whereas acetylated (+)-**19** showed lower purity (64% ee). To obtain enantiomerically pure (+)-**12**, we exploited the reverse selectivity of CCL toward acetylation of (−)-**12**. Accordingly, (+)-**19** was hydrolyzed and the crude diol obtained submitted to CCL-mediated acetylation forcing again the reaction to >50% of conversion. The isolation procedure provided, besides (+)-**19** (38% ee), the unreacted diol (+)-**12** in good enantiomer purity (94% ee). The oxidation of diols (+)- and (−)-**12** was accomplished by means of $KMnO_4/CuSO_4 \cdot 5\,H_2O$ [10i] in CH_2Cl_2 solution to afford natural lactone (+)-**1** and its enantiomer (−)-**1**, respectively.

On the other hand, the enantiomeric forms of (±)-**13a** and (±)-**18** were prepared by a more direct pathway. Treatment of (±)-**13a** with lipase PS in the presence of vinyl acetate and ^{t}BuOMe as solvent gave diacetate (−)-**21** in very high enantiomer purity (99% ee) and the monoacetylated (+)-**20** also in good enantiomer purity (92% ee) (*Scheme 2*). Thus, KOH hydrolysis of the acetate moieties provided (−)- and (+)-**13a**, respectively. The conversion of the latter diols to *trans-p*-menthene lactones **22** [10a] [14] [15] [18] was performed according to the two-step procedure reported by *Friedrich* and *Bohlmann* [14]. The reaction of (−)- and (+)-**13a** with MnO_2 gave the related hydroxy-aldehydes, which were directly converted to (+)- and (−)-**22**, respectively, by oxidation with Ag_2CO_3 on *Celite*. Moreover, to obtain the enantiomeric form of mintlactone, we examined the isomerization reaction of the exocyclic C=C bond of **22**. Although *Ogasawara* and co-workers [10b] achieved this transformation by means of $RhCl_3 \cdot 3\,H_2O$ as catalyst, we were unable to achieve satisfactory results using either the latter salt or $[RhCl(Ph_3P)_3]$. On other hand, we found that the more effective rhodium(I) hydride complex $[RhH(Ph_3P)_4]$ [19] was an efficient catalyst for this kind of isomerization. Accordingly, the reaction of (+)- and (−)-**22** with $[RhH(Ph_3P)_4]$ (10 mol-%) in refluxing toluene afforded enatiomerically pure (−)-mintlactone ((−)-**2**) and (+)-mintlactone ((+)-**2**), respectively, both in good chemical yields.

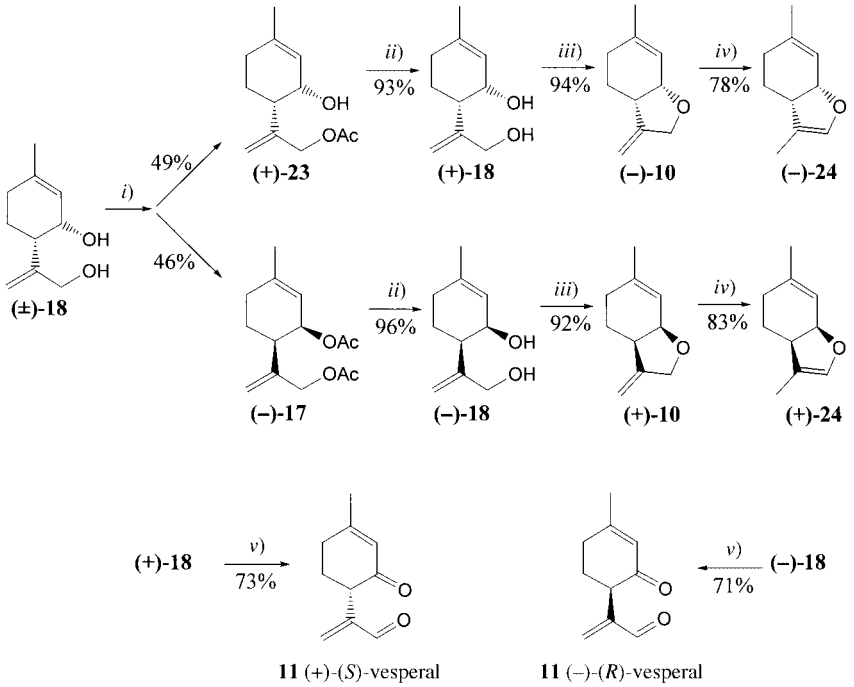
Scheme 2



i) Vinyl acetate, *t*BuOMe, lipase PS. *ii*) KOH, MeOH, reflux. *iii*) Vinyl acetate, *t*BuOMe, CCL. *iv*) $KMnO_4$/$CuSO_4 \cdot 5H_2O$, CH_2Cl_2. *v*) MnO_2, CH_2Cl_2. *vi*) 10% Ag_2CO_3/*Celite*, benzene, reflux. *vii*) [$RhH(Ph_3P)_4$ (cat.), toluene, reflux.

Finally, as described for compound (±)-**13a**, treatment of (±)-**18** with lipase PS in presence of vinyl acetate and *t*BuOMe as solvent gave the diacetate (−)-**17** in very high enantiomer purity (99% ee) and the monoacetylated (+)-**23** also in good enantiomer purity (94% ee) (*Scheme 3*). The subsequent KOH hydrolysis of the acetate moieties provided (−)- and (+)-**18**, respectively. The reaction of the latter diols with a catalytic amount of 5% aqueous HCl solution in Et_2O as solvent smoothly provided the ethers

Scheme 3



i) Vinyl acetate, *t*BuOMe, lipase PS. *ii*) KOH, MeOH, reflux. *iii*) 5% aq. HCl soln. (cat.), Et_2O. *iv*) $[RhH(Ph_3P)_4]$ (cat.), toluene, reflux. *v*) *Dess-Martin* reagent, CH_2Cl_2.

(+)- and (–)-**10**, respectively, in very good yields. Confirmatory experiments were performed, treating the above-mentioned diols with 1 equiv. of *p*-toluenesulfonyl chloride in pyridine solution. The ethers obtained by this means were chemically identical to those prepared by the acidic catalyst and showed comparable optical-rotation values. These results clearly demonstrate[1]) that no racemization or double-bond isomerization occurred during the ring closure in acidic media. Moreover, ether (+)-**10**[2]) showed identical spectroscopic data and a similar optical-rotation value to those recorded for the natural compound found in *Ledum palustre* L. [6], which is also known as wild rosemary or Labrador tea and is used in folk medicine by the native peoples of North America.

Furthermore, with the aim of preparing both enantiomers of linden ether **9**, we tried the isomerization of (–)- or (+)-**10** by means of the $[RhH(Ph_3P)_4]$ catalyst. Surprisingly enough, the ethers (–)- and (+)-**10** were regiospecifically isomerized to the thermodynamically less-stable enol ethers (–)- and (+)-**24**, respectively, in good yields

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[1]) Since the reaction of diol (+)- or (–)-**18** with 1 equiv. of *p*-toluenesulfonyl chloride in a deficiency of base afforded only the 9-(tosyloxy) derivative, the S_N2 process in this ring closure conserves the starting configuration.

[2]) The (+)-**10** obtained was evaluated by an expert perfumer who described its aroma feature as sweet mint and spearmint like, suitable for fresh-fruits- and spearmint-aroma formulations.

and without apparent racemization (*Scheme 3*). Analysis of the reaction mixtures showed that linden ether **9** could also not be formed by prolonging the reflux for many days.

Finally, since the absolute configurations of diols (+)- and (−)-**18** and ether (+)- and (−)-**10** were not determined before, we correlated these two compounds with the pheromone vesperal, whose absolute configuration was previously assigned [7a]. Thus, the oxidation of (+)- and (−)-**18** with *Dess-Martin* periodinane provided (+)-(*S*)-vesperal ((+)-**11**) and (−)-(*R*)-vesperal ((−)-**11**), respectively (*Scheme 3*). Therefore, the absolute configuration of the natural ether (+)-**10** and of the diol (−)-**18** is (3*R*,4*R*) (*p*-menthane numbering).

3. Conclusions. – The lipase-mediated resolution of different *p*-menthan-3,9-diols is described in this work. The high-quality results obtained in terms of chemical yields and enzyme selectivity allows the preparation of the enantiomeric diols (+)- and (−)-**12**, (+)- and (−)-**13a**, and (+)- and (−)-**18** in high optical purity. These diols are easily converted to the enantiomerically pure *p*-menthane terpenes (−)-and (+)-**1**, (+)- and (−)-**2**, (−)- and (+)-**10**, and (+)- and (−)-**11**, respectively, which are of both industrial and academic interest. Moreover, the first enantiospecific synthesis of natural ether (+)-**10** allows us to assign unambiguously its absolute configuration. Since the racemic starting materials are straightforwardly available from industrial sources, the overall chemo-enzymatic sequence may be regarded as a general and useful procedure for the enantioselective preparation of many relevant *p*-menthane compounds. Studies devoted to the enantioselective synthesis of the structurally related wine lactone, dill ether, and linden ether are still in progress and will be reported in due course.

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Experimental Part

1. *General*. Lipase PS from *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan, 30 U mg^{-1}), *Candida cylindracea* lipase (CCL; *Sigma*, type VII, 880 U mg^{-1}), porcine pancreatic lipase (PPL, *Sigma*, type II, 147 U mg^{-1}) and technical-grade isopulegol (sum of isomers: 96%; isopulegol/neoisopulegol/isoisopulegol/isoneoisopulegol 66:30:3:1) were employed. TLC: *Merck* silica gel *60 F_{254}* plates. Column chromatography (CC): silica gel. 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 115° (3 min) −0.5°/min −130° −8°/min −180° (1 min); analysis of (±)-(1*RS*,3*RS*,4*SR*,8*RS*)-*p*-menthane-3,9-diol diacetate: t_R 17.59, 18.01; analysis of (±)-(1*RS*,3*RS*,4*SR*)-*p*-menth-8(10)-ene-3,9-diol diacetate: t_R 17.45, 17.88; analysis of (±)-(1*RS*,3*RS*,4*RS*)-*p*-mentha-1,8(10)-diene-3,9-diol diacetate: t_R 16.42, 16.53; t_R in min. Optical rotations: *Jasco DIP-181* digital polarimeter. ^{1}H-NMR Spectra: $CDCl_3$ solns. at r.t.; *Bruker AC-250* spectrometer at 250 MHz (^{1}H); chemical shifts in ppm rel. to internal $SiMe_4$ (= 0 ppm), *J* values in Hz. Mass spectra: *Finnigan-Mat TSQ-70* spectrometer; *m/z* (rel. %). IR Spectra: *Perkin-Elmer 2000-FT-IR* spectrometer; films: $\tilde{\nu}$ in cm^{-1}. Microanalyses were determined on an analyzer *1106* from *Carlo Erba*.

2. *Racemic Diols (±)-***12**, **-13**, *and* **-18**. The diols (±)-**12**, **-13**, and **-18** were prepared by partial modification of known procedures.

2.1. *(±)-(1*RS,*3*RS,*4*SR,*8*RS*)*-p-Menthane-3,9-diol (=(β*RS,*1*SR,*2*RS,*4*RS*)-2-Hydroxy-β,4-dimethylcyclohexaneethanol*; (±)-**12**). Borane · methyl sulfide (57 ml, 0.6 mol) in dry THF (100 ml) was added dropwise to a cooled (0°) soln. of technical-grade isopulegol (80 g, 0.519 mol) in dry THF (400 ml) under N_2. The resulting clear soln. was warmed to r.t. and stirred at r.t. for 2 h. Then, 4N aq. KOH (250 ml) was added slowly, and the resulting mixture was warmed to 50° for 2 h. After this time, 35% aq. H_2O_2 soln. (350 ml, 3.6 mol) was added dropwise keeping the temp. < 30° by external cooling (ice bath). After the addition, the mixture was stirred at

r.t. overnight. The main part of THF was evaporated, the aq. mixture extracted with Et_2O (3×250 ml), the org. phase successively washed with 5% aq. $Na_2S_2O_5$ soln. (100 ml) and brine, dried (Na_2SO_4), and evaporated, and the residue (90 g) dissolved in hexane (250 ml) and stored at $-10°$ for 3 days. The crystalline precipitate was further purified by a second crystallization: (±)-**12** (44 g, 49%). M.p. 82–84°. Chemical purity 99% (GC of the corresponding diacetate), de 98% (GC). IR: 3270, 2953, 2921, 2871, 1457, 1375, 1216, 1106, 1024, 668. ^{1}H-NMR: 4.36 (*s*, OH–C(3), OH–C(9)); 3.64 (*dd*, *J* = 10.8, 5.1, H–C(9)); 3.56 (*dd*, *J* = 10.8, 3.4, H–C(9)); 3.43 (*ddd*, *J* = 10, 10, 4.2, H–C(3)); 1.96 (*dm*, *J* = 12, 1 H); 1.89–1.75 (*m*, 1 H); 1.63 (*dm*, *J* = 12, 1 H); 1.56 (*dm*, *J* = 12, 1 H); 1.50–1.13 (*m*, 3 H); 1.04–0.80 (*m*, 2 H) (H–C(1), H–C(4), H–C(8), CH_2(5), CH_2(6), CH_2(2)); 0.95 (*d*, *J* = 7.3, Me(10)); 0.91 (*d*, *J* = 6.5, Me(7)). MS: 173 (53, $[M+1]^+$), 172 (30, M^+), 155 (4), 139 (5), 124 (17), 123 (9), 112 (22), 97 (29), 95 (34), 81 (100), 71 (68), 67 (50), 55 (45), 41 (19). Anal. calc. for $C_{10}H_{20}O_2$: C 69.72, H 11.70; found: C 69.63, H 11.68.

2.2. *(±)-(1*RS,*3*SR,*4*SR*)- and (±)-(1*RS,*3*SR,*4*SR*)*-p-*Menth-8(10)-ene-3,9-diol* (=*(1*RS,*2*RS,*4*SR*)*- and *(1*RS,*2*RS,*4*RS*)-2-Hydroxy-4-methyl-β-methylenecyclohexaneethanol*; (±)-**13a** and (±)-**13b**, resp.). At 0°, 3-chloroperbenzoic acid (100 g of a 75% wet acid, 0.435 mol) was added portionwise to a soln. of technical-grade isopulegol (60 g, 0.389 mol) in CH_2Cl_2 (300 ml). The mixture was stirred for 2 h, and then the 3-chlorobenzoic acid formed was filtered off over a *Celite* pad. The clear soln. obtained was washed with 5% aq. Na_2SO_3 soln. (100 ml) and sat. aq. $NaHCO_3$ soln. (100 ml), dried (Na_2SO_4), and evaporated. The residue, dissolved in dry THF (100 ml), was added dropwise to a stirred 3M lithium diisopropylamide soln. in THF (400 ml, 1.2 mol) under N_2. The resulting mixture was heated under reflux for 2 h and then poured into ice, acidified with 5% HCl soln. (900 ml), and extracted with AcOEt (3×250 ml). The org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to CC (hexane/AcOEt 7:3). The 1st eluted fraction was further purified by crystallization from Et_2O: pure (±)-**13b** (7.12 g, 11%). M.p. 110°. Chemical purity 99%, de 97% (GC of the corresponding diacetate). IR: 3379, 2923, 1649, 1456, 1385, 1263, 1121, 1075, 1048, 952, 911. ^{1}H-NMR: 5.81 (br. *d*, *J* = 1.1, H–C(10)); 5.00 (br. *s*, H–C(10)); 4.13 (br. *d*, *J* = 12.7, H–C(9)); 4.05 (br. *d*, *J* = 12.7, H–C(9)); 3.97 (*m*, H–C(3)); 2.56 (br. *s*, OH–C(3), OH–C(9)); 2.19 (br. *d*, *J* = 12.5, H–C(4)); 1.98–1.70 (*m*, 4 H); 1.51–1.39 (*m*, 1 H), 1.18 (*ddd*, *J* = 12.5, 11.4, 2.4, 1 H), 1.09–0.91 (*m*, 1 H) (CH_2(2), CH_2(6), CH_2(5), H–C(1)); 0.89 (*d*, *J* = 6.3, Me(7)). MS: 171 (60, $[M+1]^+$), 170 (23, M^+), 167 (30), 152 (16), 137 (9), 123 (24), 109 (42), 108 (41), 95 (52), 93 (100), 81 (73), 79 (72), 69 (59), 67 (75), 57 (26), 55 (51), 41 (53). Anal. calc. for $C_{10}H_{18}O_2$: C 70.55, H 11.66; found: C 70.65, H 11.65.

The 2nd eluted fraction was further purified by crystallization from hexane/AcOEt 4:1: pure (±)-**13a** (39.2 g, 59%). M.p. 102–103°. Chemical purity 99%, de 98% (GC of the corresponding diacetate). IR: 3319, 2951, 2920, 2854, 1651, 1458, 1377, 1126, 1097, 1044, 897. ^{1}H-NMR: 5.19 (br. *d*, *J* = 1.1, H–C(10)); 5.04 (*s*, H–C(10)); 4.12 (br. *d*, *J* = 12.7, H–C(9)); 4.05 (br. *d*, *J* = 12.7, H–C(9)); 3.53 (*ddd*, *J* = 10.4, 10.4, 4.2, H–C(3)); 2.93 (br. *s*, OH–C(3), OH–C(9)); 2.08–1.86 (*m*, 2 H), 1.78–1.60 (*m*, 2 H), 1.62–1.42 (*m*, 1 H), 1.43–1.24 (*m*, 1 H), 1.10–0.84 (*m*, 2 H) (H–C(4), CH_2(2), CH_2(6), CH_2(5), H–C(1)); 0.95 (*d*, *J* = 6.4, Me(7)). MS: 171 (20, $[M+1]^+$), 170 (7, M^+), 167 (3), 153 (5), 152 (17), 137 (9), 123 (24), 109 (43), 108 (41), 95 (57), 93 (100), 81 (92), 79 (76), 69 (56), 67 (75), 55 (48). Anal. calc. for $C_{10}H_{18}O_2$: C 70.55, H 11.66; found: C 70.68, H 11.68.

2.3. *(±)-(3RS,4*RS*)*-p-*Mentha-1,8(10)-diene-3,9-diol* (=*(1*RS,*2*RS*)-2-Hydroxy-4-methyl-β-methylenecyclohex-3-eneethanol*; (±)-**18**). A mixture of diene **14** (56 g, 444 mmol) and ketone **15** (45 g, 352 mmol) in dry benzene (300 ml) was heated for 12 h under reflux and a static atmosphere of N_2. The mixture was cooled and evaporated. The residue was purified by CC (hexane/AcOEt 9:1): pure *6-[(acetyloxy)acetyl]-3-methylcyclohex-2-en-1-yl acetate* (=*2-(acetyloxy)-1-[2-(acetyloxy)-4-methylcyclohex-3-en-1-yl]ethanone*; (±)-**16**; 72.8 g, 81%) as a diastereoisomer mixture (*cis*/*trans* 95:5 by GC). IR: 2940, 2835, 1732, 1672, 1431, 1371, 1239, 1079, 1063, 1045, 1020, 956, 905. ^{1}H-NMR: 5.62 (*m*, H–C(2)); 5.56 (*m*, H–C(1)); 4.84 (*d*, *J* = 16.7, 1 H, AcOCH_2); 4.72 (*d*, *J* = 16.7, 1 H, AcOCH_2); 2.79–2.68 (*m*, H–C(6)); 2.20–1.86 (*m*, CH_2(4), CH_2(5)); 2.16 (*s*, MeCOO); 2.01 (*s*, MeCOO); 1.75 (*s*, Me–C(3)). MS: 211 (3, $[M-\text{MeCO}]^+$), 194 (8), 169 (4), 152 (39), 151 (30), 139 (20), 134 (46), 121 (66), 110 (25), 101 (22), 93 (100), 91 (53), 77 (38).

A sample of the obtained (±)-**16** (50 g, 197 mmol), dissolved in dry THF (100 ml), was added to 1M (triphenylphosphonio)methanide (250 ml) previously prepared by reaction of (Ph_3PMe)Br (89.2 g, 252 mmol) in THF with 10M BuLi in hexane (25.1 ml). The resulting mixture was heated under reflux for 4 h, cooled to r.t. and then poured into cool (0°) H_2O (500 ml). The quenched mixture was extracted twice with Et_2O ($2 \times$ 300 ml), and the org. phase was successively washed with sat. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in hexane/Et_2O 3:1 (100 ml), and the triphenylphosphine oxide was eliminated by crystallization (ice-bath cooling). The liquid phase was evaporated and purified by CC: pure p-*mentha-1,8(10)-diene-3,9-diol diacetate* (=*2-(acetyloxy)-4-methyl-β-methylenecyclohex-3-eneethanol acetate*;

(±)-**17**; 35.2 g, 71%). Colorless oil (*cis*/*trans* 95 :5 by GC). IR: 2938, 1740, 1653, 1436, 1372, 1241, 1022, 958, 911. ^{1}H-NMR: 5.64–5.55 (*m*, H–C(2)); 5.38–5.28 (*m*, H–C(3)); 5.17 (*s*, H–C(10)); 5.01 (*s*, H–C(10)); 4.65 (*d*, *J* = 13.2, H–C(9)); 4.52 (*d*, *J* = 13.2, H–C(9)); 2.34 (*dm*, *J* = 12.5, H–C(4)); 2.15–1.79 (*m*, 3 H), 1.76–1.62 (*m*, 1 H), (CH_2(6), CH_2(5)); 2.08 (*s*, MeCOO); 1.97 (*s*, MeCOO); 1.74 (*s*, Me(7)). MS: 209 (6, [*M* – MeCO]$^+$), 192 (11), 177 (1), 150 (34), 135 (29), 132 (100), 117 (59), 105 (22), 92 (70), 91 (58), 84 (87), 79 (21), 77 (20).

A sample of (±)-**17** (30 g, 119 mmol) was treated with KOH (28.1 g, 500 mmol) in MeOH (200 ml) under reflux for 2 h. The mixture was poured in ice and extracted with Et_2O (3 × 200 ml). The dried (Na_2SO_4) org. phase was evaporated and the residue purified by CC (hexane/AcOEt 7 :3) and crystallization (hexane/AcOEt 3 :1): pure (±)-**18** (17.2 g, 86%). M.p. 58–60°. Chemical purity 98% and de 99% (GC of the corresponding diacetate). IR: 3403, 2931, 2907, 1679, 1653, 1442, 1385, 1297, 1274, 1156, 1108, 1065, 1051, 1025, 958, 896. ^{1}H-NMR: 5.64 (*m*, H–C(2)); 5.24 (*s*, H–C(10)); 5.02 (*s*, H–C(10)); 4.19–4.03 (*m*, H–C(3), CH_2(9)); 2.70 (br. *s*, OH–C(3), OH–C(9)); 2.29 (*dm*, *J* = 12.5, H–C(4)); 2.12–1.93 (*m*, 2 H), 1.92–1.75 (*m*, 1 H), 1.66–1.53 (*m*, 1 H) (CH_2(6), CH_2(5)); 1.72 (*s*, Me(7)). MS: 169 (3, [*M* + 1]$^+$), 168 (23, *M*$^+$), 153 (2), 150 (7), 135 (18), 133 (15), 122 (9), 105 (7), 94 (10), 91 (22), 84 (100), 83 (82), 79 (29), 61 (23), 56 (24), 55 (20). Anal. calc. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.30, H 9.60.

3. *Lipase-Mediated Acetylation of Diols* (±)-**12**, (±)-**13**, and (±)-**18**. 3.1. *General Procedure* (*GP*). A mixture of the suitable (±)-diol (50 mmol), lipase (see *Table*), and vinyl acetate (30 ml) in ^{t}BuOMe (100 ml) was stirred at r.t. and the conversion to acetate monitored by TLC. The reaction was stopped by filtration of the enzyme and evaporation of the filtrate. The residue was purified by CC (hexane/AcOEt): unreacted diol, monoacetylated diol, and diacetylated diol. The enantiomer composition of the products was determined by chiral GC analysis of the corresponding diacetate (see *Table*).

3.2. *(–)-(1*R*,3*R*,4*S*,8*R*)- and (+)-(1*S*,3*S*,4*R*,8*S*)*-p-*Menthane-3,9-diol* (=*(β*R*,1*S*,2*R*,4*R*)*- and *(β*S*,1*R*,2*S*,4*S*)*-2-Hydroxy-β,4-dimethylcyclohexaneethanol*; (–)-**12** and (+)-**12**, resp.). According to the *GP*, lipase-PS-mediated acetylation of (±)-**12** (16 g, 93 mmol) gave the less-polar monoacetate (+)-**19** (10.1 g, 51%) and unreacted (–)-**12** (7.1 g, 44%).

*Data of (+)-(1*S*,3*S*,4*R*,8*S*)*-p-*Menthane-3,9-diol 9-Acetate* (=*(β*S*,1*R*,2*S*,4*S*)-2-Hydroxy-β,4-dimethylcyclohexaneethanol α-Acetate*; *(+)*-**19**): $[\alpha]_D^{20} = +32.6$ (*c* = 2, $CHCl_3$). Chiral GC: ee 64%, chemical purity 97%. IR: 3440, 2952, 2922, 2870, 1740, 1457, 1394, 1370, 1243, 1039, 983, 923. ^{1}H-NMR: 4.23 (*dd*, *J* = 10.7, 5.7, H–C(9)); 3.86 (*dd*, *J* = 10.7, 7.7, H–C(9)); 3.51 (*ddd*, *J* = 10.5, 10.5, 4.2, H–C(3)); 2.31–2.15 (sym. *m*, 1 H), 2.01–1.91 (*m*, 1 H), 1.72–1.60 (*m*, 2 H), 1.54–1.32 (*m*, 1 H), 1.33–1.19 (*m*, 1 H), 1.17–0.8 (*m*, 3 H) (H–C(8), H–C(4), H–C(1), CH_2(5), CH_2(6), CH_2(2)); 2.06 (*s*, MeCOO); 1.95 (*s*, OH–C(3)); 0.99 (*d*, *J* = 7, Me(10)); 0.92 (*d*, *J* = 6.4, Me(7)). MS: 214 (1, *M*$^+$), 196 (1), 171 (2), 154 (19), 139 (25), 136 (24), 121 (28), 112 (100), 97 (54), 95 (37), 81 (62), 69 (42), 55 (38). Anal. calc. for $C_{12}H_{22}O_3$: C 67.26, H 10.35; found: C 67.40, H 10.20.

Data of (–)-**12**: M.p. 102–104°. $[\alpha]_D^{20} = -18.5$ (*c* = 1.9, $CHCl_3$). Chiral GC: ee 92%, chemical purity 98%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**12**.

A sample of the monoacetate (+)-**19** (12.8 g, 60 mmol) was treated with KOH (5.05 g, 90 mmol) in MeOH (70 ml) under reflux for 2 h. The mixture was poured in ice and extracted with Et_2O (3 × 100 ml). The dried (Na_2SO_4) org. phase was evaporated and the crude diol obtained submitted to CCL-mediated acetylation according to the *GP*. Purification by CC gave the less-polar monoacetate (+)-**19** (8.1 g, 63%) and unreacted (+)-**12** (2.9 g, 28%).

Data of (+)-**19**: $[\alpha]_D^{20} = +19.5$ (*c* = 2, $CHCl_3$). Chiral GC: ee 38%, chemical purity 97%. IR, ^{1}H-NMR, MS: in accordance with that of starting (+)-**19**.

Data of (+)-**12**: M.p. 103–104°. $[\alpha]_D^{20} = +19.2$ (*c* = 1.9, $CHCl_3$). Chiral GC: ee 94%, chemical purity 98%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**12**.

3.3. *(–)-(1*R*,3*R*,4*S*)- and (+)-(1*S*,3*S*,4*R*)*-p-*Menth-8(10)-ene-3,9-diol* (=*(1*S*,2*R*,4*R*)*- and *(1*R*,2*S*,4*S*)*-2-Hydroxy-4-methyl-β-methylenecyclohexaneethanol*; (–)-**13a** and (+)-**13a**, resp.). According to the *GP*, lipase-PS-mediated acetylation of (±)-**13a** (10 g, 59 mmol) gave the less-polar diacetate (–)-**21** (6 g, 40%) and monoacetate (+)-**20** (5.9 g, 47%).

*Data of (–)-(1*R*,3*R*,4*S*)*-p-*Menth-8(10)-ene-3,9-diol Diacetate* (=*(1*S*,2*R*,4*R*)*-2-(Acetyloxy)-4-methyl-β-methylenecyclohexaneethanol Acetate*; (–)-**21**): $[\alpha]_D^{20} = -43.4$ (*c* = 2, $CHCl_3$). Chiral GC: ee 99%, chemical purity 98%. IR: 2930, 2871, 1737, 1655, 1456, 1373, 1245, 1130, 1089, 1028, 984, 906, 842. ^{1}H-NMR: 5.08 (*d*, *J* = 1.1, H–C(10)); 5.01 (*s*, H–C(10)); 4.78 (*ddd*, *J* = 10.7, 10.7, 4.4, H–C(3)); 4.57 (*d*, *J* = 13.5, H–C(9)); 4.49 (*d*, *J* = 13.5, H–C(9)); 2.17–1.95 (*m*, 2 H), 1.90–1.77 (*dm*, *J* = 13.4, 1 H), 1.76–1.63 (*dm*, *J* = 14, 1 H), 1.65–1.48 (*m*, 1 H), 1.47–1.28 (*dq*, *J* = 13, 3.4, 1 H), 1.08–0.85 (*m*, 2 H) (H–C(4), H–C(1), CH_2(2), CH_2(5), CH_2(6)); 2.09 (*s*, MeCOO); 1.98 (*s*, MeCOO); 0.93 (*d*, *J* = 6.4, Me(7)). MS: 212 (1), 194 (12), 179 (3), 161 (7),

152 (100), 134 (68), 123 (21), 119 (36), 109 (28), 108 (31), 95 (27), 93 (49), 81 (34), 79 (26), 67 (15), 55 (13). Anal. calc. for $C_{14}H_{22}O_4$: C 66.12, H 8.72; found: C 65.95, H 8.70.

*Data of (+)-(1S,3S,4R)-*p*-Menth-8(10)-ene-3,9-diol 9-Acetate* (=*(1R,2S,4S)-2-Hydroxy-4-methyl-β-methylenecyclohexaneethanol α-Acetate*; (+)-**20**): M.p. 58–59°. $[\alpha]_D^{20} = +38.9$ ($c = 2$, $CHCl_3$). Chiral GC: ee 92%, chemicl purity 98%. IR: 3367, 2938, 2921, 2860, 1734, 1652, 1447, 1391, 1371, 1242, 1096, 1049, 1024, 901, 847, 756. ^{1}H-NMR: 5.21–5.16 (*m*, H–C(10)); 5.13–5.09 (*m*, H–C(10)); 4.57 (*s*, CH_2(9)); 3.55 (*ddd*, $J = 10.5$, 10, 4.2, H–C(3)); 2.20 (br. *s*, OH–C(3)); 2.10 (*s*, MeCOO); 2.10–1.98 (*dm*, $J = 12.5$, 1 H), 1.92 (*ddd*, $J = 12.5$, 10, 3.4, 1 H), 1.81–1.62 (*m*, 2 H), 1.61–1.41 (*m*, 1 H), 1.41–1.21 (*dq*, $J = 13$, 3.4, 1 H), 1.09–0.83 (*m*, 2 H) (H–C(4), H–C(1), CH_2(2), CH_2(5), CH_2(6)); 0.95 (*d*, $J = 6.4$, Me(7)). MS: 194 (1, $[M - H_2O]^+$), 179 (1), 170 (2), 161 (1), 152 (29), 137 (22), 123 (53), 109 (75), 108 (89), 95 (57), 93 (100), 81 (53), 79 (50), 69 (33), 67 (36), 55 (25). Anal. calc. for $C_{12}H_{20}O_3$: C 67.89, H 9.50; found: C 68.00, H 9.55.

Treatment of the diacetate (–)-**21** and monoacetate (+)-**20** with KOH/MeOH under the conditions described above gave the diols (–)-**13a** (95%) and (+)-**13a** (93%), respectively.

*Data of (–)-*__13a__: M.p. 102–103°. $[\alpha]_D^{20} = -52.1$ ($c = 1$, EtOH). Chiral GC: ee 99%, chemical purity 99%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**13a**.

*Data of (+)-*__13a__: M.p. 102–103°. $[\alpha]_D^{20} = +47.6$ ($c = 1$, EtOH). Chiral GC: ee 92%, chemical purity 99%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**13a**.

3.4. *(–)-(3R,4R)- and (+)-(3S,4S)-*p*-Mentha-1,8(10)-diene-3,9-diol* (=*(1R,2R)-* and *(1S,2S)-2-Hydroxy-4-methyl-β-methylenecyclohex-3-eneethanol*; (–)-**18** and (+)-**18**, resp.). According to the *GP*, lipase-PS-mediated acetylation of (±)-**18** (7.1 g, 42.3 mmol) gave the less-polar diacetate (–)-**17** (4.9 g, 46%) and monoacetate (+)-**23** (4.4 g, 49%).

*Data of (3R,4R)-*p*-Mentha-1,8(10)-diene-3,9-diol Diacetate* (=*(1R,2R)-2-(Acetyloxy)-4-methyl-β-methylenecyclohex-3-eneethanol Acetate*; (–)-**17**): $[\alpha]_D^{20} = -279.4$ ($c = 2$, $CHCl_3$). Chiral GC: ee 99%, chemical purity 99%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**17**. Anal. calc. for $C_{14}H_{20}O_4$: C 66.65, H 7.99; found: C 66.80, H 8.00.

*Data of (3S,4S)-*p*-Mentha-1,8(10)-diene-3,9-diol 9-Acetate* (=*(1S,2S)-2-Hydroxy-4-methyl-β-methylenecyclohex-3-eneethanol α-Acetate*; (+)-**23**): $[\alpha]_D^{20} = +169.9$ ($c = 2$, $CHCl_3$). Chiral GC: ee 94%, chemical purity 97%. IR: 3460, 2935, 2832, 1737, 1673, 1652, 1449, 1376, 1235, 1155, 1110, 1067, 1027, 957, 907, 848, 817. ^{1}H-NMR: 5.70–5.62 (*m*, H–C(2)); 5.25 (*s*, H–C(10)); 5.07 (*s*, H–C(10)); 4.69–4.54 (*m*, CH_2(9)); 4.20–4.12 (*m*, H–C(3)); 2.22 (*dm*, $J = 12.5$, 1 H), 2.16–1.93 (*m*, 3 H), 1.93–1.76 (*m*, 1 H), 1.67–1.54 (*m*, 1 H) (H–C(4), OH–C(3), CH_2(5), CH_2(6)); 2.11 (*s*, MeCOO); 1.73 (*s*, Me(7)). MS: 192 (2, $[M - H_2O]^+$), 177 (1), 167 (1), 150 (20), 135 (37), 132 (18), 122 (15), 117 (19), 107 (10), 91 (24), 84 (100), 83 (34), 79 (14), 67 (19), 55 (8). Anal. calc. for $C_{12}H_{18}O_3$: C 68.54, H 8.63; found: C 68.70, H 8.55.

Treatment of the diacetate (–)-**17** and monoacetate (+)-**23** with KOH/MeOH under the conditions described above gave the diols (–)-**18** (96%) and (+)-**18** (93%), respectively.

*Data of (–)-*__18__: M.p. 72–73°. $[\alpha]_D^{20} = -219.6$ ($c = 2$, $CHCl_3$). Chiral GC: ee 99%, chemical purity 98%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**18**.

*Data of (+)-*__18__: M.p. 71–72°. $[\alpha]_D^{20} = +204.8$ ($c = 2$, $CHCl_3$). Chiral GC: ee 94%, chemical purity 97%. IR, ^{1}H-NMR, MS: in accordance with that of (±)-**18**.

4. *Lactones* **1**, **22**, *and* **2**. 4.1. *(+)-(1R,3R,4S,8R)- and (–)-(1S,3S,4R,8S)-3-Hydroxy-*p*-menthan-9-oic Acid Lactone* (=*(3R,3aS,6R,7aR)-* and *(3S,3aR,6S,7aS)-Hexahydro-3,6-dimethylbenzofuran-2(3H)-one*; (+)-**1** and (–)-**1**, resp.). A soln. of diol (–)-**12** (1.9 g, 11 mmol) in CH_2Cl_2 (40 ml) was treated with $KMnO_4/CuSO_4 \cdot 5\,H_2O$ according to [10i]. The obtained heterogeneous mixture was stirred at r.t. for 10 h. Then workup afforded crude lactone, which was purified by CC (hexane/AcOEt 9:1): pure (+)-**1** (0.95 g, 51%).

The same method was applied to the oxidation of diol (+)-**12** (1.5 g, 8.7 mmol): (–)-**1** (0.8 g, 55%).

*Data of (+)-*__1__: $[\alpha]_D^{20} = +104.2$ ($c = 1.2$, $CHCl_3$). Chemical purity 97% (GC). IR: 2933, 2871, 1781, 1457, 1379, 1293, 1200, 1101, 1044, 993, 964, 849, 798. ^{1}H-NMR: 4.00 (*ddd*, $J = 11.1$, 11.1, 3.8, H–C(3)); 2.64 (*quint.*, $J = 7.6$, H–C(8)); 2.25 (*ddd*, $J = 11.1$, 3.7, 3.7, H–C(2)); 2.01–1.87 (*m*, 1 H), 1.87–1.71 (*m*, 2 H), 1.69–1.48 (*m*, 1 H), 1.43–1.19 (*m*, 1 H), 1.17–0.98 (*m*, 1 H) (H–C(4), H–C(6), H–C(5), H–C(1), H–C(5), H–C(6)); 1.24 (*ddd*, $J = 11.1$, 11.1, 11.1, H–C(2)); 1.15 (*d*, $J = 7.6$, Me(10)); 1.02 (*d*, $J = 6.6$, Me(7)). MS: 167 (1, $[M - 1]^+$), 139 (1), 124 (7), 109 (23), 95 (26), 82 (21), 81 (100), 68 (20), 67 (48), 55 (17), 41 (16). Anal. calc. for $C_{10}H_{16}O_2$: C 71,39, H 9.59; found: C 71.45, H 9.55.

*Data of (–)-*__1__: $[\alpha]_D^{20} = -106.7$ ($c = 1.2$, $CHCl_3$). Chemical purity 98% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**1**.

4.2. *(+)-(1R,3R,4S)- and (–)-(1S,3S,4R)-3,9-Epoxy-*p*-menth-8(10)-en-9-one* (=*(3aS,6R,7aR)-* and *(3aR,6S,7aS)-Hexahydro-6-methyl-3-methylenebenzofuran-2(3H)-one*; (+)-**22** and (–)-**22**, resp.). Diol (–)-**13a** (2.4 g,

14.1 mmol) in CH_2Cl_2 (100 ml) was stirred with MnO_2 (6 g, 69 mmol) at r.t. for 3 h. Filtration and evaporation afforded the crude hydroxy-aldehyde, which was dissolved in dry benzene (100 ml) and stirred with 10% Ag_2CO_3 on *Celite* (45 g, 16.3 mmol). The mixture was heated under reflux for 12 h, then cooled, and filtered. The filtrate was evaporated and the residue purified by CC (hexane/AcOEt 9:1). Bulb-to-bulb distillation of the product (oven temp. 105–110°/0.2 Torr) afforded pure (+)-**22** (1.95 g, 83%).

The same method was applied to the oxidation of diol (+)-**13a** (2.2 g, 12.9 mmol): (−)-**22** (1.85 g, 86%).

*Data of (+)-***22**: M.p. 40–41°. $[\alpha]_D^{20} = +69.6$ ($c = 2$, $CHCl_3$). Chemical purity 99% (GC). IR: 2945, 2925, 2862, 1771, 1678, 1455, 1403, 1354,1250, 1230, 1180, 1123, 994, 944, 842, 819, 697. ^{1}H-NMR: 6.06 (*d*, *J* = 3.1, H−C(10)); 5.39 (*d*, *J* = 3.1, H−C(10)); 3.73 (*ddd*, *J* = 11.0, 11.0, 3.6, H−C(3)); 2.36 (*tq*, *J* = 11.0, 3.1, H−C(4)); 2.12 (*dq*, *J* = 12.5, 3.1, H−C(5)); 2.27 (*dm*, *J* = 11.8, 1 H), 1.85 (*dm*, *J* = 13.4, 1 H), 1.75–1.53 (*m*, 1 H), 1.45–1.25 (*m*, 2 H) (H−C(6), H−C(5), H−C(1), CH_2(2)); 1.14 (*ddd*, *J* = 12.5, 12.2, 3.9, H−C(6)); 1.04 (*d*, *J* = 6.5, H−C(7)). MS: 167 (1, $[M+1]^+$), 166 (11, M^+), 165 (6), 151 (4), 138 (85), 133 (5), 123 (25), 120 (23), 110 (31), 109 (44), 95 (58), 94 (100), 81 (60), 79 (55), 67 (46), 55 (38), 41 (29). Anal. calc. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.35, H 8.45.

*Data of (−)-***22**: M.p. 40–41°. $[\alpha]_D^{20} = -62.1$ ($c = 1.6$, $CHCl_3$). Chemical purity 98% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**22**.

4.3. *(−)-(1*R*,3*R*)- and (+)-(1*S*,3*S*)-3,9-Epoxy*-p-*menth-4(8)-en-9-one* (=*(−)-* and *(+)-Mintlactone* (=*(6*R*,7a*R*)-* and *(6*S*,7a*S*)-5,6,7,7a-Tetrahydro-3,6-dimethylbenzofuran-2(4*H*)-one*; (−)-**2** and (+)-**2**, resp. A soln. of lactone (+)-**22** (0.8 g, 4.8 mmol) in dry toluene (40 ml) was heated under reflux and N_2 with a cat. amount of $[RhH(Ph_3P)_4]$ (10 mol-%) until no more (+)-**22** was detected by GC (20 h). The mixture was then cooled and the solvent evaporated. The residue was purified by CC (hexane/AcOEt 8:2) and bulb-to-bulb distillation (oven temp. 105–110°/0.2 Torr): pure (−)-**2**. Colorless oil (0.73 g, 91%).

The same method was applied to the isomerization of lactone (−)-**22** (0.5 g, 3 mmol): (+)-**2** (0.46 g, 92%).

*Data of (−)-***2**: $[\alpha]_D^{20} = -61.3$ ($c = 2$, EtOH). Chemical purity 99% (GC). IR: 2954, 2930, 2872, 1756, 1688, 1456, 1330, 1300, 1099, 1075, 1031, 998, 858, 767, 753, 685. ^{1}H-NMR: 4.63 (br. *dd*, *J* = 11.2, 6.0, H−C(3)); 2.80 (*ddd*, *J* = 14.0, 4.4, 2.0, 1 H), 2.20 (br. *ddd*, *J* = 14, 14, 5.5, 1 H) (CH_2(5)); 2.48–2.36 (*m*, 1 H), 2.01–1.88 (*m*, 1 H), 1.81–1.61 (*m*, 1 H), 1.12–0.92 (*m*, 2 H) (CH_2(6), CH_2(2), H−C(1)); 1.81 (*t*, *J* = 1.6, Me(10)); 1.01 (*d*, *J* = 6.6, Me(7)). MS: 167 (10, $[M+1]^+$), 166 (100, M^+), 151 (2), 138 (28), 137 (57), 123 (18), 110 (22), 109 (36), 95 (34), 81 (38), 67 (34). Anal. calc. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.15, H 8.50.

*Data of (+)-***2**: $[\alpha]_D^{20} = +56.2$ ($c = 2$, EtOH). Chemical purity 99% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (−)-**2**.

5. p-*Menthane Ether* **10** *and* **24**. 5.1. *(+)-(3*R*,4*R*)- and (+)-(3*S*,4*S*)-3,9-Epoxy*-p-*mentha-1,8(10)-diene* (=*(3a*R*,7a*R*)-* and *(3a*S*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-6-methyl-3-methylenebenzofuran*; (+)-**10** and (−)-**10**, resp.). To a soln. of diol (−)-**18** (2.1 g, 12.5 mmol) in Et_2O (200 ml), 5% aq. HCl soln. (2 ml) was added. The mixture was stirred at r.t. for 1 h an then washed with H_2O (50 ml) and brine (100 ml). The org. layer was separated, dried (Na_2SO_4), and concentrated atmospheric pressure by distillation of the solvent through a short *Vigreux* column. The crude product was purified by CC (hexane, hexane/Et_2O 9:1). The fractions containing (+)-**10** were concentrated again at atmospheric pressure. Further purification by bulb-to-bulb distillation (oven temp. 90–95°/20 Torr) gave pure (+)-**10** (1.73 g, 92%). Colorless oil.

The same procedure was applied to diol (+)-**18** (2.5 g, 14.9 mmol): (−)-**10** (2.1 g, 94%).

*Data of (+)-***10**: $[\alpha]_D^{20} = +42.5$ ($c = 1.2$, $CHCl_3$). Chemical purity 98% (GC). IR: 2927, 2834, 1672, 1449, 1381, 1058, 1033, 942, 927, 906, 884. ^{1}H-NMR: 5.56–5.50 (*m*, H−C(2)); 4.97 (*q*, *J* = 2.2, H−C(10)); 4.93 (*q*, *J* = 2.2, H−C(10)); 4.46–4.36 (*m*, 1 H), 4.35–4.23 (*m*, 2 H) (H−C(3), CH_2(9)); 2.62 (*m*, H−C(4)); 2.18–1.81 (*m*, 2 H), 1.80–1.54 (*m*, 2 H) (CH_2(6), CH_2(5)); 1.73 (*s*, Me(7)). MS: 150 (9, M^+), 136 (9), 135 (100), 122 (32), 117 (4), 107 (7), 105 (6), 93 (11), 91 (21), 79 (38), 77 (13). Anal. calc. for $C_{10}H_{14}O$: C 79.96, H 9.39; found: C 80.15, H 9.40.

*Data of (−)-***10**. $[\alpha]_D^{20} = -37.8$ ($c = 2$, $CHCl_3$). Chemical purity 96% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**10**.

5.2. *(+)-(3*R*,4*R*)- and (−)-(3*S*,4*S*)-3,9-Epoxy*-p-*mentha-1,8(9)-diene* (=*(3a*R*,7a*R*)-* and *(3a*S*,7a*S*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran*; (+)-**24** and (−)-**24**, resp.). A soln. of (+)-**10** (0.9 g, 6 mmol) in dry toluene (40 ml) was heated under reflux and N_2 in the presence of a cat. amount of $[RhH(Ph_3P)_4]$ (10 mol-%) until no more (+)-**10** was detected by GC (36 h). The mixture was then cooled, and both the solvent and the catalyst were removed by CC (hexane; hexane/Et_2O 9:1). The fractions containing (+)-**24** were concentrated at atmospheric pressure by distillation of the solvent through a short *Vigreux* column. The residue was further purified by bulb-to-bulb distillation (oven temp. 95–100°/20 Torr): pure (+)-**24** (0.75 g, 83%). Colorless oil.

The same method was applied to the isomerization of ether (−)-**10** (0.6 g, 4 mmol): (−)-**24** (0.47 g, 78%).

Data of (+)-**24**: $[\alpha]_D^{20} = +146.7$ ($c = 1.5$, $CHCl_3$). Chemical purity 95% (GC). IR: 2962, 2925, 2882, 2857, 1667, 1448, 1434, 1380, 1257, 1091, 915, 891, 839. ^{1}H-NMR: 6.04 (*t*, *J* = 1.4, H–C(9)); 5.63–5.57 (*m*, H–C(2)); 4.71 (*dm*, *J* = 8.8, H–C(3)); 2.59 (*td*, *J* = 8.8, 4.4, H–C(4)); 2.06–1.72 (*m*, 3 H), 1.45–1.26 (*m*, 1 H) (CH_2(6), CH_2(5)); 1.77 (*s*, Me(7)); 1.65 (*t*, *J* = 1.4, Me(10)). MS: 151 (11, $[M+1]^+$), 150 (100, M^+), 135 (21), 121 (41), 117 (16), 115 (9), 107 (16), 105 (18), 93 (40), 91 (50), 82 (19), 79 (30), 77 (28), 65 (7). Anal. calc. for $C_{10}H_{14}O$: C 79.96, H 9.39; found: C 79.85, H 9.35.

Data of (–)-**24**: $[\alpha]_D^{20} = -129.2$ ($c = 2$, $CHCl_3$). Chemical purity 95% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**24**.

6. *(–)-(*R*)- and (+)-(*S*)-Vesperal* (*=(1*S*)- and (1*R*)-4-Methyl-α-methylene-2-oxocyclohex-3-eneacetaldehyde*; (+)-**11**). Triacetoxy-periodinane (0.6 g, 1.4 mmol) was added portionwise to a cooled (0°) soln. of (–)-**18** (0.2 g, 1.2 mmol) in CH_2Cl_2 (40 ml) under N_2. The mixture was stirred for 1 h at 0° and then allowed to warm to r.t. After 24 h, the mixture was treated with sat. $Na_2S_2O_3$ soln. (30 ml) and sat. $NaHCO_3$ soln. (30 ml). The aq. layer was extracted with CH_2Cl_2 (2 × 40 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue purified by CC (hexane/AcOEt 8:2): pure (–)-**11** (140 mg, 71%). White solid.

The same procedure was applied to oxidize (+)-**18** (0.3 g, 1.8 mmol): (+)-**11** (215 mg, 73%).

Data of (–)-**11**: M.p. 52°. $[\alpha]_D^{20} = -50.6$ ($c = 1.1$, CH_2Cl_2). Chemical purity 97% (GC). IR: 3057, 2940, 1695, 1668, 1640, 1426, 1380, 1318, 1215, 952, 880. ^{1}H-NMR: 9.57 (*s*, CH(9)=O); 6.30 (*s*, H–C(10)); 6.21 (*s*, H–C(10)); 5.96 (*s*, H–C(2)); 3.46 (*dd*, *J* = 12.1, 4.9, H–C(4)); 2.55–2.38 (*m*, 1 H), 2.37–2.23 (*m*, 1 H), 2.21–2.00 (*m*, 2 H) (CH_2(6), CH_2(5)); 1.99 (*s*, Me(7)). MS: 164 (10, M^+), 162 (14), 149 (19), 145 (14), 136 (20), 135 (28), 121 (6), 108 (7), 105 (10), 91 (17), 82 (100), 77 (9), 65 (5), 54 (15). Anal. calc. for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 73.05, H 7.45.

Data of (+)-**11**: M.p. 50°. $[\alpha]_D^{20} = +46.2$ ($c = 1$, CH_2Cl_2). IR, ^{1}H-NMR, MS: in accordance with those of (–)-**11**.

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