Natural *p*-Menthene Monoterpenes: Synthesis of the Enantiomeric Forms of Wine Lactone, Epi-wine Lactone, Dill Ether, and Epi-dill Ether Starting from a Common Intermediate

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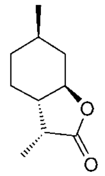
A concise synthesis of the enantiomeric forms of wine lactone (**5**), epi-wine lactone (**14**), dill ether (**6**), and epi-dill ether (**15**) was accomplished starting from the enantiomeric forms of *p*-mentha-1,8(10)-diene-3,9-diol (**8**) (*Scheme 3*). The latter compounds were previously prepared in high optical purity by means of lipase-mediated kinetic resolution, and they were the common building blocks for this divergent synthesis. The key steps were a number of chemo- and diastereoselective reactions of which the oxidation of **8** to the lactone **7** (see *Table 1*), the diastereoselective reduction of **7** to the lactones **14** and **5** (see *Table 2*), and the reduction of enol-ether **16** to ether **15** were studied comprehensively. The effectiveness of this new synthetic approach allows the preparation of the title *p*-menthane monoterpenes, which are of considerable interest to the perfume industry, in high yield and in a few simple experimental steps.

1. Introduction. – The 3,9-dioxygenated *p*-menthane monoterpenes are well-known natural products. Recently, we have reported [1] the enzyme-mediated preparation of a number of enantiomerically pure *p*-menthan-3,9-diols and their use for the synthesis of some *p*-menthane lactones and ethers belonging to this class. By means of this approach, we obtained both enantiomeric forms of several natural compounds of different chemical structures such as the 3-hydroxy-*p*-menthan-10-oic acid lactone (**1**), mintlactone (**2**), (+)-3,9-epoxy-*p*-menth-1,8(10)-diene (**3**), and vesperal (**4**).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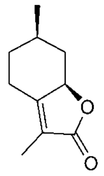
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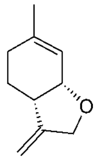
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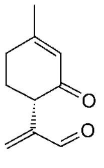
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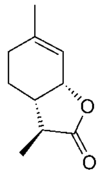
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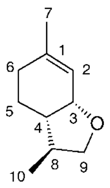

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In connection with our continuing interest in the development of synthetic approaches to enantiomerically pure flavors and fragrances, we extended our studies on the preparation of *p*-menth-1-ene lactones and ethers showing *cis* configuration at the 3,4 position of the *p*-menthane framework. The latter kind of compound has been found in Nature, and different researches have demonstrated that both the character and intensity of their odors are related to relative and absolute configurations [2]. This is the case for wine lactone (**5**), which was first identified as an animal metabolite [3] then recognized as a key flavor compound of different white wines [4], and, recently, it was found in orange juice and black pepper [5]. The eight possible isomers of wine lactone were prepared by *Guth* [6], and the olfactory evaluation revealed that natural **5** is the most-powerful isomer with an odor threshold < 0.04 pg/l, whereas the weakest isomers show a threshold $> 10^6$ pg/l. These characteristics clearly demonstrate that odor features are dramatically influenced by the configuration. A similar case is that of dill ether (**6**), which is the most-important constituent of dill essential oil from an organoleptic point of view [7]. Its absolute configuration was elucidated by stereoselective synthesis [8], and, only recently, the preparation of its eight isomeric forms [9a–c] allowed to establish that **6** shows a high odor-activity value and is the character-impact compound of dill-herb flavor. It is noteworthy that **5** and **6** show the same absolute configuration and a *cis* relationship at the 3,4 position. Moreover, wine lactone and dill ether share the difficult accessibility by chemical synthesis, particularly in enantiomerically pure form.

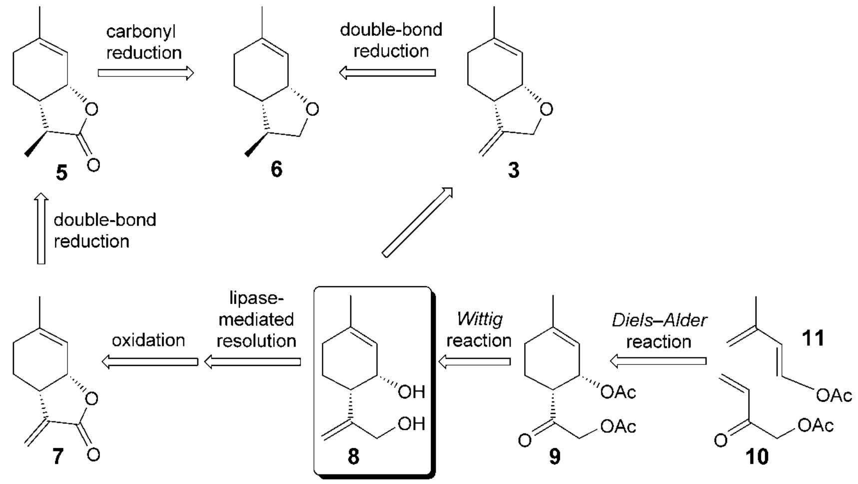
In this context, the first preparation of enantiomerically pure wine lactone (**5**) is due to *Guth* [6] who, starting from (+)- and (−)-limonene, prepared the eight isomers of wine lactone as a mixture of diastereoisomers and then separated these by chromatography. Again starting from an enantiomerically pure building block, *Chavan* and co-workers [10] described the conversion of (+)-isolimonene to (−)-wine lactone and its 8-epimer by means of iodolactonization as the key step. An enantioselective asymmetric synthesis of the same two compounds was reported by *Bergner* and *Helmchen* [11]. The latter approach is based on a Pd-catalyzed enantioselective allylic substitution and involved the use of asymmetric ligands and a number of chemical manipulations.

Dill ether (**6**) was prepared first by *Ohloff* and co-workers [12] before its isolation in Nature. This synthetic pathway started from (−)- and (+)-limonene and afforded, besides some 2,9-epoxy-*p*-menthene isomers, the 3,4-*cis*-configured stereoisomer of **6** as a couple of enantiomerically pure diastereoisomers. *Mosandl* and co-workers [9a,b] reported two synthetic methods for the preparation of 3,4-*cis*- and 3,4-*trans*-configured stereoisomers of **6** starting from the eight isomers of wine lactone, which, in turn, were obtained by the *Guth* procedure from (−)- and (+)-limonene.

Based on these observations, it seemed desirable to develop a new synthetic method to the enantiomerically pure forms of **5** and **6** by means of a procedure not necessarily involving troublesome diastereoisomer separation, low-yielding steps, or the use of expensive catalyst and enantiomerically pure starting materials.

According to our retrosynthetic analysis (*Scheme 1*), we anticipated that diol **8** could be a useful building block for the preparation of both wine lactone and dill ether. We have previously prepared the enantiomeric form of **8** in high enantiomeric purity by lipase-mediated acetylation of the racemic material [1]. This latter was obtained by diastereoselective *Diels–Alder* reaction of the easily available vinyl ketone **10** and diene **11** followed by *Wittig* methylenation and hydrolysis. To achieve our synthesis plan, diol **8** should be chemoselectively oxidized to lactone **7** and then diastereoselectively reduced to **5**. The latter compound is the direct precursor of **6**, which should be obtained also by chemoselective reduction of ether **3**, the latter being again easily available from **8**.

Scheme 1. Retrosynthetic Analysis



2. Results. – 2.1. *Oxidation of Diols (+)- and (–)-***8**. The preparation of wine lactone (**5**) by our synthetic pathway required the preparation of α,β-unsaturated lactone **7**. The chemoselective oxidation of **8** is an intriguing synthesis step since both OH groups are in an allylic position. Therefore, compounds derived from the oxidation of the secondary OH group such as keto-aldehyde **4** and lactol **13** and those showing partial oxidation at C(9) such as lactol **12** are possible products of the reaction (*Scheme 2*). To find the best procedure to obtain **7**, we tested different oxidants (*Table 1*). With transition-metal reagents, the oxidation of **8** afforded a mixture of lactone **7** and keto-aldehyde **4** without formation of the lactols **12** and **13**. Pyridinium chlorochromate (PCC) gave mainly **4**, whilst MnO_2 in the same solvent showed reverse selectivity. Even though the reagent Ag_2CO_3 on *Celite* [13] was described as an

Scheme 2

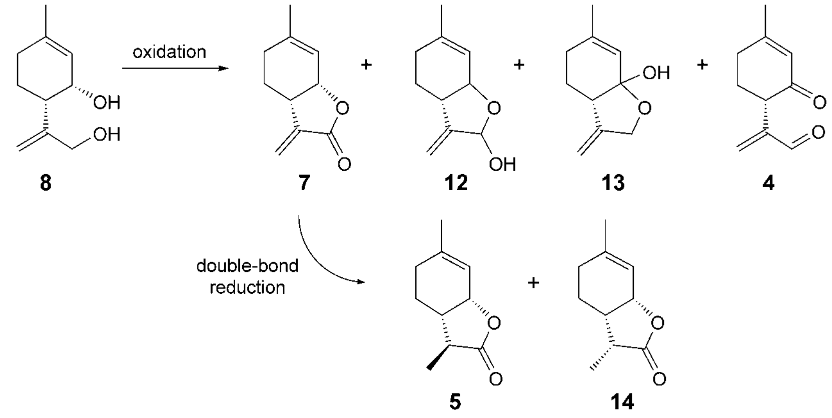


Table 1. *Oxidation of Diol* **8**

Oxidant [a]	Conditions (solvent, time, temp.)	Product distribution [%] [b]				
		8	**7**	**12/13**	**4**	unidentified
PCC (2.1 equiv.)	CH_2Cl_2, 2 h, r.t.	0[c]	24	0[c]	68	8
MnO_2 (5 equiv.)	CH_2Cl_2, 4 h, reflux	0[c]	60	0[c]	38	2
Ag_2CO_3/*Celite* (5 equiv.)	benzene, 6 h, reflux	0[c]	73	0[c]	25	2
IBX (5 equiv.)	DMSO, 6 h, r.t.	16	2	54	22	6
BAIB (3 equiv.), TEMPO (cat.)	CH_2Cl_2, 4 h, r.t	0[c]	97	0[c]	2	1
DMP (2.1 equiv.)	CH_2Cl_2, 5 h, r.t.	0[c]	6	0[c]	89	5

[a] PCC = pyridinium chlorochromate, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; BAIB = bis(acetato-κ*O*)phenyliodine; TEMPO = 2,2,6,6-tetramethylpyridin-1-yloxy; DMP = *Dean–Martin* periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one. [b] The products distribution was measured after workup by GC analysis. [c] The compound was not detected by GC analysis.

excellent chemoselective oxidant for the preparation of butenolides starting from 1,4 diols [14], we observed that the latter reagent was fairly superior to MnO_2.

Hypervalent iodine oxidants demonstrated a considerably different behavior over the previously mentioned reagents. The selective transformation of *p*-menthan-3,9-diols [15a] to the corresponding 9-hydroxy-lactols by means of *o*-iodoxybenzoic acid (= 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; IBX) in DMSO [15b] was previously reported. In our hands, the latter approach proceeded without chemoselective control affording predominantly a mixture of lactols **12** and **13** besides keto-aldehyde **4**, unreacted **8**, and a trace of lactone **7**. Further, the use of *Dess–Martin* periodinane (= 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; DMP) [16] gave selectively **4** free of any lactol isomers, besides a small amount of **7**. Surprisingly enough, the use of catalytic TEMPO (= 2,2,6,6-tetramethylpiperidin-1-yloxy) and [bis(acetoxy)-iodo]benzene (= bis(acetato-κ*O*)-phenyliodine; BAIB) [17] as the co-oxidant was the best methodology for the preparation of lactone **7**. The latter approach was previously used for the selective oxidation of 1,5-diols to δ-lactone, and, in the present work, we describe its usefulness also for the conversion of 1,4-diols **8** to γ-lactone **7**. Indeed, this procedure is the most selective and effective of those tested (see *Table 1*) yielding enantiomerically pure **7** in up to 97% yield with complete transformation of the starting diol **8**.

2.2. *Reduction of Lactone* **7**. According to our retrosynthetic analysis, we studied the reduction of **7** to wine lactone (**5**) and/or its 8-epimer **14**. Some problems of regio- and diastereoselectivity arose since only the C(8)=C(10) bond should be reduced giving two possible isomers. All the reducing agents tested (*Table 2*) left the C(1)=C(2) unaffected but showed different activities on the conjugated C(8)=C(10) bond. In all cases, the main reduction product was epi-wine lactone (**14**). The use of Mg turnings in MeOH [18] was the most effective procedure, since all starting **7** was reduced, and the smallest amount of unidentified by-products (< 1%) was formed. Different results were obtained with the hydrides as reducing agents. Both $NaBH_4$ in EtOH and *in situ* formed copper hydride (Bu_3SnH/LiCl/CuI) [19] in THF reduced **7** efficiently showing a slightly superior diastereoselectivity in the formation of **14** than Mg in MeOH. The reduction with silicon [20] and tin [21] hydrides afforded, besides the lactones **14** and **5**, a

Table 2. *Reduction of Lactone* **7**

Reducing agent	Conditions (solvent, time, temp.)	Product distribution [%)][a])			
		7	**5**	**14**	unidentified
Mg	MeOH, 3 h, r.t.	0[b])	13	86	1
NaBH$_4$	EtOH 1.5 h, r.t.	0[b])	5	92	3
Et$_3$SiH, [RhCl(PPh$_3$)$_3$] (cat.)	benzene, 4 h, r.t.	0[b])	4	26	70[c])
Bu$_3$SnH, [PdCl$_2$(PPh$_3$)$_2$] (cat.)	THF, 4 h, r.t.	5	6	51	38 [c])
Bu$_3$SnH/LiCl/CuI	THF, 1 h, –60°; then 2 h, 0°	1	7	90	2

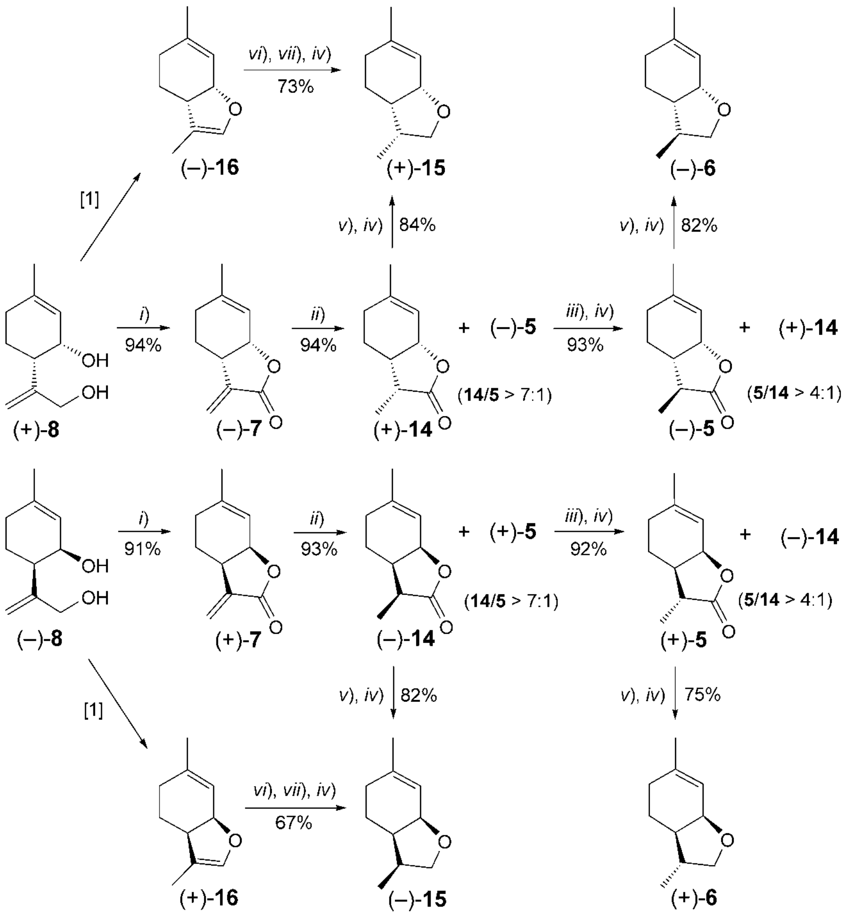
[a]) The product distribution was measured after workup by GC analysis. [b]) The compound was not detected by GC analysis. [c]) GC/MS Analysis showed that more than 95% of the unidentified compounds corresponded to a single isomer of lactone **7**. The isolation procedure afforded an inseparable mixture of lactone **14** and the unidentified compound; its structure was determined as 3,9-epoxy-*p*-mentha-1,4(8)-dien-9-one by MS and ^{1}H-NMR analysis.

considerable amount of 3,9-epoxy-*p*-mentha-1,4(8)-dien-9-one, which is an isomer of **7**. This is probably due to the Rh^{I} and Pd^{II} catalyst used in association with Et$_3$SiH and Bu$_3$SnH that allowed both reduction and isomerization of the conjugated C=C bond.

2.3. *Enantiomerically Pure Epi-wine Lactone* (**14**) *and Wine Lactone* (**5**). Taking advantage of the above-described results, we devised a method for the preparation of all the enantiomeric forms of lactones **14** and **5**. The enantiomerically pure (+)- and (–)-**8** were oxidized with BAIB/TEMPO to afford enantiomerically pure (–)- and (+)-**7**, respectively (*Scheme 3*). The next step was the reduction of the conjugate C=C bond by means of Mg in MeOH. Lactones (–)- and (+)-**7** afforded epi-wine lactones (+)- and (–)-**14**, respectively, besides a small amount of isomeric (–)- and (+)-**5**, respectively. The enantiomers (+)- and (–)-**14** were easily separated from their epimers (–)- and (+)-**5**, respectively, by chromatography, and their optical rotation values compared favorably with reported data [10][11] thus establishing that our synthetic pathway does not involve racemization. Furthermore, with the objective to prepare both enantiomers of wine lactone (**5**), we experimented with the basic epimerization of **14**. Thus, treatment with ^{t}BuOK in ^{t}BuOH [22] of either pure **14** or the mixture **14**/**5** (>7:1) obtained as above gave a new mixture **5**/**14** (>4:1) where **5** was the main component. By means of the latter synthetic sequence, natural wine lactone (–)-**5** and lactone (+)-**5** were prepared from (–)- and (+)-**7**, respectively, in enantiomerically pure form and with an overall yield of *ca.* 55%.

2.4. *Enantiomerically Pure Dill Ether* (**6**) *and Epi-Dill Ether* (**15**). The transformation of lactones **5** and **14** to the dill ether (**6**) and epi-dill ether (**15**) [23], respectively, was achieved by a slight modification of a known procedure [9a,b]. It was reported that the LiAlH$_4$ reduction of these lactones affords smoothly the corresponding diastereoisomeric diols that could be cyclized to the related ethers by treatment with an acid catalyst. This ring closure affords stereospecifically the bicyclic ethers with 3,4-*cis* configuration. Consequently, starting from enantiomerically pure lactones with these structural features, the overall process affords the corresponding ethers without any epimerization. Therefore, we submitted the lactone (–)- or (+)-**5** to LiAlH$_4$ reduction, and the reaction mixture was quenched directly with an excess of diluted aq. HCl solution (*Scheme 3*). After isolation, the natural dill ether (–)-**6**, and its

Scheme 3



i) BAIB, CH_2Cl_2, TEMPO (cat.). *ii*) Mg, MeOH. *iii*) ^{t}BuOK, ^{t}BuOH. *iv*) 3% aq. HCl soln. *v*) $LiAlH_4$, Et_2O. *vi*) 70% aq. $HClO_4$ soln. (cat.), THF/H_2O 2:1. *vii*) $NaBH_4$.

enantiomer (+)-**6**, respectively, were obtained in chemically and isomerically pure form as confirmed by comparison of their analytical data with those reported [9]. Analogously, the same procedure was applied to (+)- and (–)-**14** to afford pure epi-dill ether (+)- and (–)-**15**, respectively.

Finally, we studied a more-straightforward approach to (+)- and (–)-**15**. As mentioned in our retrosynthetic analysis, ether **3** could be a suitable precursor of dill ether by chemoselective reduction of the C(8)=C(10) bond. Accordingly, we transformed the diols (+)- and (–)-**8** to the ethers (–)- and (+)-**3**, respectively, by treatment with a catalytic amount of HCl. The following isomerization by means of a rhodium hydride catalyst [1] gave the enol ethers (–)- and (+)-**16**, respectively. The activated C(8)=C(9) bond of the latter compounds was selectively reduced by means of a one-pot procedure that involved hydration, reduction, and cyclization (*Scheme 3*). Hence,

(−)- and (+)-**16** were dissolved in a THF/water mixture and treated with a catalytic amount of $HClO_4$. The starting materials were smoothly converted in the corresponding lactols, which were treated with an excess of $NaBH_4$. The mixtures were quenched with diluted HCl solution, and the isolation procedure afforded epi-dill ethers (+)- and (−)-**15**, respectively. It is noteworthy that this synthesis path is highly diastereoselective since the latter compounds were obtained with 93 and 94% de, respectively, without any chromatographic separation.

3. Conclusions. – A new enantiospecific approach to the isomeric forms of natural wine lactone and dill ether is described in this work. The enantiomeric forms of *p*-mentha-1,8(10)-diene-3,9-diol (**8**) were the common building blocks for this divergent synthesis. The key steps were a number of chemo- and diastereoselective reactions that were optimized. The high-quality results obtained in terms of chemical yields and selectivity allows the preparation of all the enantiomeric forms of wine lactone (**5**), epi-wine lactone (**14**), dill ether (**6**), and epi-dill ether (**15**). Since the starting enantiomerically pure building blocks are straightforwardly prepared by resolution of the corresponding racemic diol that is easily available by chemical synthesis, the overall synthetic pathway may be regarded as a useful procedure for the enantioselective preparation of these *p*-menthene compounds.

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Experimental Part

1. *General*. All moisture-sensitive reactions were carried out under a static atmosphere of N_2. All reagents were of commercial quality, with the exception of Ag_2CO_3 on *Celite*, '*o*-iodoxybenzoic acid' (IBX), *Dess–Martin* periodinane (DMP), and hydridotetrakis(triphenylphosphine)rhodium, which were prepared according to [13], [15b], [16], and [24], respectively. Lipase PS from *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan, 30 U mg^{-1}) was employed in this work. TLC: *Merck* silica-gel *60 F_{254}* plates. Column chromatography (CC): silica gel. GC: *HP-6890* gas chromatograph; diastereoisomer excesses (de) determined with a *HP-5* column (30 m × 0.32 mm; *Hewlett-Packard*) with the following temp. program 60° (1 min) – 6°/min – 150° (1 min) – 12°/min – 280° (5 min); t_R in min racemic **7**, **5**, **14**, **6**, and **15**: t_R 17.50, 16.75, 17.76, 10.78, and 11.77, resp. M.p.: *Reichert* apparatus, equipped with a *Reichert* microscope; uncorrected. Optical rotations: *Jasco DIP-181* digital polarimeter. IR Spectra: *Perkin-Elmer 2000-FT-IR* spectrometer; films; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: $CDCl_3$ solns. at r.t.; *Bruker-AC-250* spectrometer at 250 MHz; chemical shifts δ in ppm rel. to internal $SiMe_4$ (= 0 ppm), *J* values in Hz. Mass Spectra: *Finnigan-Mat-TSQ-70* spectrometer; *m/z* (rel. %). Microanalyses: analyzer *1106* from *Carlo-Erba*.

2. *Enantiomerically Pure Starting Materials*. 2.1. *(+)-(3*S*,4*S*)- and (−)-(3*R*,4*R*)-*p*-Mentha-1,8(10)-diene-3,9-diol (=(1*S*,2*S*)- and (1*R*,2*R*)-2-Hydroxy-4-methyl-β-methylenecyclohex-3-ene-1-ethanol*; (+) and (−)-**8**, resp.). The resolution procedure was performed according to [1] with lipase PS as catalyst, vinyl acetate as acetyl donor, and ^{t}BuOMe as solvent.

Data of (+)-**8**: M.p. 72°. $[\alpha]_D^{20} = +207.2$ ($c = 2$, $CHCl_3$). Chiral GC: ee 95%, chemical purity (GC) 97%.

Data of (−)-**8**: M.p. 73°. $[\alpha]_D^{20} = -220$ ($c = 2$, $CHCl_3$). Chiral GC: ee 99%, chemical purity (GC) 98%.

2.2. *(−)-(3*S*,4*S*)- and (+)-(3*R*,4*R*)-3,9-Epoxy-*p*-mentha-1,8(9)-diene (=(3a*S*,7a*S*)- and (3a*R*,7a*R*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran*; (−)- and (+)-**16**, resp.). According to [1], from (+)- and (−)-**8**, resp.

Data of (−)-**16**: $[\alpha]_D^{20} = -132.2$ ($c = 2$, $CHCl_3$). Chemical purity (GC) 97%.

Data of (+)-**16**: $[\alpha]_D^{20} = +146.5$ ($c = 2$, $CHCl_3$). Chemical purity (GC) 97%.

3. *Oxidation of Diol* **8**. 3.1. *Keto-aldehyde* **4** *and Lactols* **12** *and* **13**. The product distribution after oxidation of **8** was analyzed by GC and GC/MS. The keto-aldehyde **4** (t_R 16.55) was obtained as described previously [1]. Lactol **12** was obtained by DIBAH reduction [25] of lactone **7**. Compound **12** was unstable and rapidly

decomposed after workup to give a diastereoisomer mixture of dimeric compounds. For this reason, the lactols obtained on oxidation of **8** were not isolated and were characterized only by GC/MS.

Data of **12**: t_R 15.05 (br.). MS: 166 (4, M^+), 148 (18), 137 (16), 119 (13), 105 (24), 91 (39), 84 (100), 83 (65), 79 (28), 77 (26), 65 (11), 55 (21), 39 (23). *Data of* **13**: (t_R 15.29, br.). MS: 166 (5, M^+), 148 (14), 137 (18), 119 (8), 108 (14), 105 (16), 91 (26), 84 (100), 83 (64), 77 (16), 65 (9), 55 (16), 39 (18).

3.2. *(+)-(3*R*,4*R*)- and (−)-(3*S*,4*S*)-3,9-Epoxy-*p*-mentha-1,8(10)-dien-9-one* (*=(3a*R*,7a*R*)-* and *(3a*S*,7a*S*)-3a,4,5,7a-Tetrahydro-6-methyl-3-methylenebenzofuran-2(3*H*)-one*; (+)- and (−)-**7**, resp.). A soln. of (−)-**8** (2.2 g, 13.1 mmol) in CH_2Cl_2 (60 ml) was treated with [bis(acetoxy)iodo]benzene (BAIB, 12.8 g, 39.7 mmol) and 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO; 0.3 g, 1.9 mmol) and stirred at r.t. until no more (−)-**8** was detected by TLC (4 h). The mixture was then poured in ice (100 g), treated with sat. aq. $Na_2S_2O_3$ soln. (100 ml) and extracted with Et_2O (2 × 150 ml). The combined org. phase was washed with sat. aq. $NaHCO_3$ soln. (80 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated and the residue purified by CC (hexane/AcOEt 9 : 1): pure (+)-**7** (1.96 g, 91%).

The same method was applied to (+)-**8** (1.8 g, 10.7 mmol): (−)-**7** (1.65 g, 94%).

*Data of (+)-***7**: M.p. 53°. $[\alpha]^{20}_{\mathrm{D}} = +75.3$ ($c = 2$, $CHCl_3$). Chemical purity (GC) 97%. IR: 1756, 1744, 1668, 1450, 1441, 1383, 1319, 1246, 1194, 1114, 959, 946, 816, 651. ^{1}H-NMR: 6.24 (*d*, $J = 2.4$, ^{1}H−C(10)); 5.60 (*d*, $J = 2.4$, ^{1}H−C(10)); 5.59 (*m*, H−C(2)); 4.90 (*m*, H−C(3)); 3.11 (*m*, H−C(4)); 2.12 – 1.84 (*m*, 3 H), 1.84 – 1.66 (*m*, 1 H) (CH_2(6), CH_2(5)); 1.75 (*s*, Me(7)). ^{13}C-NMR: 170.3; 142.2; 138.9; 120.9; 118.2; 74.7; 37.2; 26.5; 24.3; 23.7. MS: 165 (3, $[M+1]^+$), 164 (25, M^+), 150 (9), 149 (100), 136 (31), 121 (16), 117 (5), 105 (32), 93 (17), 91 (33), 79 (24), 77 (20), 65 (8), 53 (19). Anal. calc. for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 73.20, H 7.35.

*Data of (−)-***7**: M.p. 52 – 53°. $[\alpha]^{20}_{\mathrm{D}} = -71.6$ ($c = 2$, $CHCl_3$). Chemical purity (GC) 97%. IR, ^{1}H-NMR, MS: in accordance with that of (+)-**7**.

4. *Epi-wine Lactone* (**14**) *and Wine Lactone* (**5**). 4.1. *Reduction of Lactone* **7**: *(+)-(3*R*,4*S*,8*R*)- and (−)-(3*S*,4*R*,8*S*)-3,9-Epoxy-*p*-menth-1-en-9-one (=(3*R*,3a*S*,7a*R*)-* and *(3*S*,3a*R*,7a*S*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one*; (+)- and (−)-**14**, resp.). A soln. of (−)-**7** (0.5 g, 3 mmol) in MeOH (30 ml) was treated with Mg turnings (0.3 g, 12.5 mmol) under stirring at r.t. until no more (−)-**7** was detected by TLC (3 h). The mixture was then poured into a cooled (0°) 3% aq. HCl soln. (150 ml) and extracted with Et_2O (3 × 100 ml). The combined org. phase was washed with brine (150 ml), dried (Na_2SO_4), and evaporated, and the residue purified by CC (hexane/AcOEt 9 : 1): pure (+)-**14** (350 mg, 70%) and (+)-**14**/(−)-**5** 55 : 45 (by GC; 120 mg, 24%).

The same method was applied to the reduction of (+)-**7** (0.5 g, 3 mmol): (−)-**14** (365 mg, 73%) and (−)-**14**/(+)-**5** 51 : 49 (by GC; 100 mg, 20%).

*Data of (+)-***14**: M.p. 58 – 59°. $[\alpha]^{20}_{\mathrm{D}} = +121.2$ ($c = 1$, $CHCl_3$). Chemical purity 98%, d.e. 99% (GC). IR: 1752, 1670, 1449, 1384, 1352, 1203, 1172, 943, 887. ^{1}H-NMR: 5.68 (*m*, H−C(2)); 4.64 (*m*, H−C(3)); 2.91 (*dq*, $J = 7.3$, 7.2, H−C(8)); 2.36 (*dm*, $J = 13.5$, H−C(4)); 2.11 – 1.89 (*m*, CH_2(6)); 1.79 (*s*, Me(7)); 1.76 – 1.63 (*m*, ^{1}H−C(5)); 1.29 – 1.09 (*m*, ^{1}H−C(5)); 1.20 (*d*, $J = 7.2$, Me(10)). ^{13}C-NMR: 178.8; 144.0; 116.9; 74.6; 40.2; 37.8; 28.8; 23.7; 19.6; 9.2. MS: 167 (2, $[M+1]^+$), 166 (31, M^+), 152 (9), 151 (100), 138 (9), 123 (13), 122 (18), 107 (42), 95 (21), 93 (92), 91 (44), 79 (41), 77 (28), 69 (9), 67 (11), 65 (8), 55 (25). Anal. calc. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.20, H 8.45.

*Data of (−)-***14**: M.p. 59 – 60°. $[\alpha]^{20}_{\mathrm{D}} = -124.1$ ($c = 1$, $CHCl_3$). Chemical purity 97%, d.e. > 99% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**14**.

4.2. *Isomerization of* **14**/**5**: *(−)-(3*R*,4*S*,8*S*)- and (+)-(3*S*,4*R*,8*R*)-3,9-Epoxy-*p*-menth-1-en-9-one* (*=(3*S*,3a*S*,7a*R*)-* and *(3*R*,3a*R*,7a*S*)-3a,4,5,7a-Tetrahydro-3,6-dimethyl-benzofuran-2(3*H*)-one*; (−)- and (+)-**5**, resp.). A sample of (+)**14**/(−)-**5** 87 : 13 (350 mg, 2.1 mmol) in *t*BuOH (20 ml) was treated with ^{t}BuOK (360 mg, 3.2 mmol). The resulting mixture was stirred at r.t. for 3 h and then poured in a cooled (0°) 3% aq. HCl soln. (100 ml) and extracted with Et_2O (3 × 60 ml). The combined org. phase was washed with brine (80 ml), dried (Na_2SO_4), and evaporated and the residue (350 mg) purified by CC (hexane/AcOEt 9 : 1): pure (−)-**5** (220 mg, 63%) and (+)-**14**/(−)-**5** 56 : 44 (by GC; 105 mg, 30%).

The same method was applied to (−)**14**/(+)-**5** 88 : 12 (400 mg, 2.4 mmol): (+)-**5** (270 mg, 67%) and (−)-**14**/(+)-**5** 58 : 42 (by GC; 100 mg, 25%).

*Data of (−)-***5**: M.p. 50 – 51°. $[\alpha]^{20}_{\mathrm{D}} = -13.1$ ($c = 1$, $CHCl_3$). Chemical purity 98%, d.e. 99% (GC). IR: 1766, 1673, 1450, 1383, 1323, 1211, 1173, 1149, 973, 950, 899, 712. ^{1}H-NMR: 5.51 (*m*, H−C(2)); 4.90 (*dm*, $J = 5$, H−C(3)); 2.43 (*dq*, $J = 7.3$, 7.2, H−C(8)); 2.33 – 2.20 (*m*, H−C(4)); 2.12 – 1.93 (*m*, CH_2(6)); 1.92 – 1.66 (*m*, CH_2(5)); 1.74 (*s*, Me(7)); 1.26 (*d*, $J = 7.2$, Me(10)). ^{13}C-NMR: 179.8; 140.8; 118.8; 75.5; 40.3; 37.6; 25.9; 23.7; 22.3; 14.0. MS: 167 (2, $[M+1]^+$), 166 (22, M^+), 152 (9), 151 (100), 138 (10), 123 (13), 122 (6), 107 (24), 95 (17), 93 (51), 91 (28), 79 (27), 77 (18), 69 (9), 67 (8), 65 (5), 55 (18). Anal. calc. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.20, H 8.50.

*Data of (+)-***5**: M.p. 49–51°. $[\alpha]_{\mathrm{D}}^{20} = +16.4$ ($c = 1$, $CHCl_3$). Chemical purity 98%, d.e. 99% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (−)-**5**.

5. *Dill Ether* (**6**) *and Epi-dill Ether* (**15**). 5.1. *Reduction of Lactone* **5** *and* **14**: *(−)-(3*R*,4*S*,8*S*)- and (+)-(3*S*,4*R*,8*R*)-3,9-Epoxy-*p*-menth-1-ene (=(3*S*,3a*S*,7a*R*)-* and *(3*R*,3a*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-3,6-dimethylbenzofuran*; (−)- and (+)-**6**, resp.) *and (+)-(3*R*,4*S*,8*R*)- and (−)-(3*S*,4*R*,8*S*)-3,9-Epoxy-*p*-menth-1-ene (=(3*R*,3a*S*,7a*R*)-* and *(3*S*,3a*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-3,6-dimethylbenzofuran*; (+)- and (−)-**15**, resp.). A soln. of (−)-**5** (100 mg, 0.6 mmol) in dry Et_2O (10 ml) was added dropwise to a suspension of $LiAlH_4$ (50 mg, 1.3 mmol) in dry Et_2O (10 ml). After stirring for 1 h at r.t., the mixture was cautiously treated with an excess of 3% aq. HCl soln. (50 ml) and further stirred for 1 h. The mixture was then diluted with Et_2O (20 ml), the aq. phase extracted with Et_2O (20 ml), the combined org. phase washed with brine (50 ml), dried (Na_2SO_4), and evaporated, and the residue purified by bulb-to-bulb distillation (oven temp. 95–100°/25 Torr): pure (−)-**6** (75 mg, 82%).

The same method was applied to (+)-**5** (80 mg, 0.48 mmol), to (+)-**14** (130 mg, 0.78 mmol), and to (−)-**14** (120 mg, 0.72 mmol): (+)-**6** (55 mg, 75%), (+)-**15** (100 mg, 84%), and (−)-**15** (90 mg, 82%), resp.

*Data of (−)-***6**: $[\alpha]_{\mathrm{D}}^{20} = -7.3$ ($c = 1$, $CHCl_3$). Chemical purity 99%, d.e. 99% (GC). IR: 1673, 1449, 1380, 1081, 1028, 991, 956, 925, 897, 836. ^{1}H-NMR: 5.52 (*m*, H−C(2)); 4.24 (br. *s*, H−C(3)); 4.06 (*dd*, $J = 8.3$, 7.5, ^{1}H−C(9)); 3.30 (*dd*, $J = 8.3$, 7, ^{1}H−C(9)); 2.08–1.97 (*m*, H−C(8)); 1.97–1.80 (*m*, CH_2(6)); 1.77–1.66 (*m*, H−C(4), ^{1}H−C(5)); 1.70 (*s*, Me(7)); 1.56–1.45 (*m*, ^{1}H−C(5)); 1.05 (*d*, $J = 6.9$, Me(10)). ^{13}C-NMR: 138.8; 121.1; 75.1; 74.1; 44.0; 38.0; 28.2; 24.2; 23.7; 17.7. MS: 152 (5, M^+), 151 (6, $[M-1]^+$), 138 (11), 137 (100), 124 (6), 119 (1), 109 (33), 107 (5), 95 (12), 93 (14), 91 (16), 79 (15), 77 (12), 69 (24), 67 (11), 55 (10). Anal. calc. for $C_{10}H_{16}O$: C 78.90, H 10.59; found: C 78.85, H 10.55.

*Data of (+)-***6**: $[\alpha]_{\mathrm{D}}^{20} = +8.1$ ($c = 1$, $CHCl_3$). Chemical purity 99%, d.e. 99% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (−)-**6**.

*Data of (+)-***15**: $[\alpha]_{\mathrm{D}}^{20} = +127.9$ ($c = 1$, $CHCl_3$). Chemical purity 99%, d.e. 99% (GC). IR: 1673, 1592, 1449, 1380, 1083, 1052, 1025, 995, 930, 899. ^{1}H-NMR: 5.61 (*m*, H−C(2)); 4.18 (br. *s*, H−C(3)); 3.94 (*t*, $J = 8.2$, ^{1}H−C(9)); 3.46 (*dd*, $J = 10$, 8.2, ^{1}H−C(9)); 2.68–2.44 (*m*, H−C(8)); 2.07–1.83 (*m*, H−C(4), CH_2(6)); 1.74 (*s*, Me(7)); 1.66–1.52 (*m*, ^{1}H−C(5)); 1.37–1.15 (*m*, ^{1}H−C(5)); 1.00 (*d*, $J = 7.2$, Me(10)). ^{13}C-NMR: 140.2; 120.0; 76.1; 72.3; 40.1; 37.0; 29.7; 23.6; 19.0; 11.6. MS: 152 (4, M^+), 151 (4, $[M-1]^+$), 138 (9), 137 (100), 124 (4), 119 (2), 109 (26), 107 (6), 105 (3), 95 (10), 93 (14), 91 (14), 79 (13), 77 (11), 69 (21), 67 (8), 55 (8). Anal. calc. for $C_{10}H_{16}O$: C 78.90, H 10.59; found: C 78.80, H 10.60.

*Data of (−)-***15**: $[\alpha]_{\mathrm{D}}^{20} = -133.4$ ($c = 1$, $CHCl_3$). Chemical purity 99%, d.e. 99% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**15**.

5.2. *Reduction of Enol Ether* **16**. A soln. of (−)-**16** (250 mg, 1.67 mmol) in THF (50 ml) was treated with H_2O (20 ml) and 70% aq. $HClO_4$ soln. (0.2 ml, 2.3 mmol). The mixture was stirred at r.t. until no more (−)-**16** was detected by TLC (36 h) and then treated with an excess of $NaBH_4$ (320 mg, 8.46 mmol). The mixture was set aside for 1 h, quenched with 3% aq. HCl soln. (100 ml), and further stirred for 1 h. After dilution with Et_2O (40 ml), the aq. phase was extracted with Et_2O (40 ml), the combined org. phase washed with brine (50 ml), dried (Na_2SO_4), and evaporated, and the residue purified by bulb-to-bulb distillation (oven temp. 95–100°/25 Torr): (+)-**15** (185 mg, 73%).

The same method was applied to (+)-**16** (200 mg, 1.33 mmol): (−)-**15** (135 mg, 67%).

*Data of (+)-***15**: $[\alpha]_{\mathrm{D}}^{20} = +125.4$ ($c = 1$, $CHCl_3$). Chemical purity 98%, d.e. 93% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**15**.

*Data of (−)-***15**: $[\alpha]_{\mathrm{D}}^{20} = -129.4$ ($c = 1$, $CHCl_3$). Chemical purity 98%, d.e. 94% (GC). IR, ^{1}H-NMR, MS: in accordance with that of (+)-**15**.

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