8. Monoterpenoid Chemistry

Part 3[1])

Stereoselective Synthesis of the Major Oxygenated Metabolites of *trans*-Sobrerol

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The stereoselective synthesis of the major oxygenated metabolites of *trans*-sobrerol (**1**) in optically active and/or racemic form is described.

(±)-*trans*-Sobrerol (= (2*RS*,6*SR*)-*p*-menth-6-ene-2,8-diol; **1**), a well known mucolytic agent, has been widely used for the treatment of chronic bronchopulmonary diseases [2]. In previous studies [3–5], one of us (*P.V.*) demonstrated that **1** is extensively excreted in the free form and as conjugates, probably with glucuronic acid. Hydroxylation and oxidation of **1** at the allylic positions and, to a small extent, hydroxylation at Me–C(α), leading to **2**–**11** appear to be the metabolic pathway for **1** in man and in animals. It must be assumed that these biotransformations occur both simultaneously and successively. However, in the previous studies, no authentic samples were available for comparison, and structures were based on NMR and MS evidence. Since these metabolites might potentially contribute to the pharmacological and therapeutical properties of **1**, we have prepared substantial amounts of them, in optically active and/or racemic forms[2]), to allow further characterization and pharmacological evaluation. Development of practical syntheses of oxidized metabolites of **1** has been hampered by the lack of methods for regio- and stereocontrolled introduction of oxygenated functions into ring positions of the *p*-menthane skeleton. Accordingly, a variety of standard procedures afforded only complex mixtures in which the target compounds were present in traces or not at all. Since acid-catalyzed rearrangement of α-pinene epoxide (**12**) affords smoothly *trans*-sobrerol (**1**) [6], we reasoned that analogous reactions of appropriately substituted α-pinene epoxides might provide the desired *p*-menthane derivatives.

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[1]) Part 2, see [1].

[2]) Racemic and optically active forms are denoted *(Exper. Part)* by the letters **a** and **b**, respectively. Unless otherwise stated, the structural formulae of optically active compounds in this paper represent their absolute configuration.

Synthesis of Metabolites **2**, **3** *and* **5**. Myrtenyl chloroacetate (**13**), obtained by oxidation of β-pinene (**14**) [7] (→**15**) followed by conventional chloroacetylation (chloroacetyl chloride, THF, 4-(dimethylamino)pyridine, r.t.), provides a convenient common starting point for the synthesis of **2**, **3**, and **5**. Thus, treatment of **13** with *m*-chloroperbenzoic acid in CH_2Cl_2 in the presence of solid $NaHCO_3$ gave the *trans*-epoxide **16**. Subsequent acid-catalyzed rearrangement (acetone/0.1 N HCl 1:1, r.t.) resulted in stereospecific opening of the bicyclo[3.1.1]heptane system, thus securing the C(4) and C(6) chiral centers in **17**, mild hydrolysis (K_2CO_3, MeOH, r.t.) of which led to **2** in a 49% overall yield. The GC/MS and ^{1}H-NMR of **2** showed a pattern identical with that obtained from the authentic urinary metabolite M6 [4].

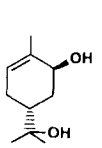
The required enone **5** (metabolite M10 [4]) was synthesized from **17** by mild oxidation (MnO_2, CH_2Cl_2, r.t.; →**18**) followed by hydrolysis of the chloroester moiety (thiourea, $NaHCO_3$, EtOH/H_2O) [8].

In order to obtain **3**, the secondary OH group of **17** was converted into the corresponding acetate (→**19**) and then the chloroester selectively cleaved as described above to yield **20**. In the latter, the primary OH group was now available for oxidation. However, this proved to be surprisingly difficult. A number of reagents were tried, all of which gave low yields and/or were unreliable. Since pyridinium-chlorochromate oxidation was easily performed on a related compound [9], the problem appeared to arise from the interference of the protecting group at C(6). Protection of the secondary OH group in **17** as the (*tert*-butyl)dimethylsilyl derivative (→**21**) was undertaken in the hope that oxidation would be facilitated. This indeed proved to be the case. Thus, **21** was subjected to hydrolysis in the presence of thiourea in order to unmask the primary alcohol (→**22**), and with a variety of oxidants the desired transformation went smoothly. In particular, oxidation of **22** under the *Swern* conditions (oxalyl chloride, DMSO, Et_3N, CH_2Cl_2) [10] afforded the aldehyde **23** (80%). Completion of the synthesis of **3** involved oxidation with $NaClO_2$ in *t*-BuOH/H_2O in the presence of cyclohexene as chlorine scavenger [11] to yield the protected acid **24**, followed by brief exposure to Bu_4NF in THF to afford **3** in a 56% overall yield. The GC/chemical-ionization MS(CH_4) of **3** as permethylated derivative showed a pattern identical with that obtained from the authentic permethylated metabolite M7 [4].

Synthesis of Metabolites Arising from Biooxidation at the Ring. Several methods for the oxidation of **1** to **4** were investigated. *Jones* and *Collins* oxidations, pyridinium chlorochromate, and pyridinium dichromate all gave mixtures and/or low yields of the desired product. The one reagent which did prove suitable for this conversion was activated MnO_2 in CH_2Cl_2 which gave **4** (85%), whose physical data matched those of 8-hydroxycarvonacetone, previously described by *Schmidt* [12].

Our stereospecific routes to the remaining metabolites proceeded through the bicyclo[3.1.1]hept-2-en-6-ol system using the rigid nature of this framework to establish the required configurations. We felt that *syn*-chrysanthenol (**25**), readily accessible from verbenone (**26**) *via* chrysanthenone (**27**) [13] [14], possessed suitable functionality for modification to the compounds **6**–**9** and **11**. Protection of the OH group with chloroacetyl chloride gave **28** and its sequential treatment with *m*-chloroperbenzoic acid and diluted HCl in acetone at r.t. gave the dihydroxy monochloroacetate **29** in 43% overall yield. The assignment of the configuration of **29** seems secure on the basis of the

assumption that the O-atom has entered (→**30**) exclusively from that surface of the π system which is opposite to that occupied by the *gem*-dimethyl group, in line with precedent [13]. Finally, mild alkaline hydrolysis of **29** gave the triol **6** (87%) which upon oxidation with *Jones'* reagent afforded a 51% yield of hydroquinone derivative **11** [5]. The physical data of **6** matched those of urinary metabolite M4 [3].



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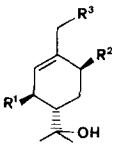
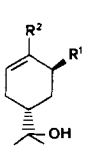
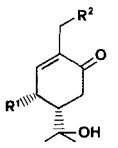


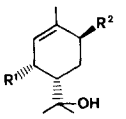
2 $R^1 = H$; $R^2, R^3 = OH$
7 $R^1, R^2 = OH$; $R^3 = H$
17 $R^1 = H$; $R^2 = OH$; $R^3 = CH_2ClCOO$
19 $R^1 = H$; $R^2 = AcO$; $R^3 = CH_2ClCOO$
20 $R^1 = H$; $R^2 = AcO$; $R^3 = OH$
21 $R^1 = H$; $R^2 = (t\text{-Bu})Me_2SiO$; $R^3 = CH_2ClCOO$
22 $R^1 = H$; $R^2 = (t\text{-Bu})Me_2SiO$; $R^3 = OH$
39 $R^1 = OH$; $R^2 = AcO$; $R^3 = H$



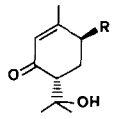
3 $R^1 = OH$; $R^2 = CO_2H$
23 $R^1 = (t\text{-Bu})Me_2SiO$; $R^2 = CHO$
24 $R^1 = (t\text{-Bu})Me_2SiO$; $R^2 = CO_2H$



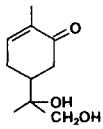
4 $R^1, R^2 = H$
5 $R^1 = H$; $R^2 = OH$
9 $R^1 = OH$; $R^2 = H$
18 $R^1 = H$; $R^2 = CH_2ClCOO$
31 $R^1 = CH_2ClCOO$; $R^2 = H$



6 $R^1, R^2 = OH$
29 $R^1 = CH_2ClCOO$; $R^2 = OH$
32 $R^1 = CH_2ClCOO$; $R^2 = AcO$
33 $R^1 = OH$; $R^2 = AcO$
36 $R^1 = CH_2ClCOO$; $R^2 = (t\text{-Bu})Me_2SiO$
37 $R^1 = OH$; $R^2 = (t\text{-Bu})Me_2SiO$



8 R = OH
34 R = AcO
38 $R = (t\text{-Bu})Me_2SiO$



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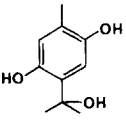

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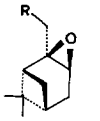
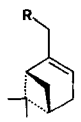


12 R = H
16 $R = CH_2ClCOO$

14

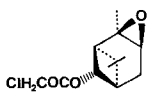


13 $R = CH_2ClCOO$
15 R = OH

25 R = OH
28 $R = CH_2ClCOO$

26

27



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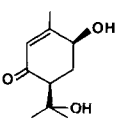

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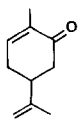

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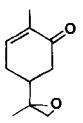

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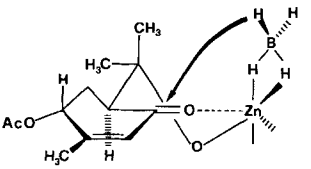

42

With the oxygenation at both allylic positions assured, we proceeded to the synthesis of **7**, **8**, and **9**. Oxidation of **29** with pyridinium chlorochromate in CH_2Cl_2 in the presence of anhydrous NaOAc [15] provided the protected enone **31** (85%). Cleavage of the chloroacetate according to *Naruto et al.* [8] gave the crystalline dihydroxy-enone **9** (78%). The exchange of the protecting group between C(3) and C(6) in **29** was accomplished by acetylation (→**32**), followed by selective hydrolysis of the chloroacetate (→**33**). Oxidation of **33** with the mildly acidic pyridinium chlorochromate smoothly afforded the enone **34**, but its treatment with K_2CO_3 in MeOH did not lead to the desired diol **8**. Instead, a base-catalyzed epimerization at C(6) occurred, resulting in a 40% of **35**. Maintenance of the correct configuration at C(6) evidently needed alternative protection of the secondary OH group. Accordingly, when **29** reacted with (*tert*-butyl)dimethylsilyl chloride in DMF in the presence of imidazole, **36** was obtained. Conversion of the latter to **8** [5] was effected in three steps in 41% overall yield by selective hydrolysis of the chloroacetate (→**37**), oxidation of allylic alcohol with MnO_2 (→**38**), followed by exposure to 0.1 N HCl in MeCN at r.t.

The enone **34** served for the synthesis of **7** by reduction of the carbonyl group in the desired stereochemical sense. Thus, while reduction of **34** with $NaBH_4$ in $EtOH/H_2O$ in the presence of $CeCl_3 \cdot 6H_2O$ [16] gave a 2:1 mixture of **33** and **39** (65%), the use of $Zn(BH_4)_2$ in Et_2O [17] resulted in good *erythro*-selectivity (**39**/**33** = 15:1) leading to the desired **39** in 68% isolated yield. The basis of the observed stereochemical outcome could involve initial chelation of the reducting agent involving the metal atom, the OH and CO group as shown in **42** (chelation-controlled transition state). Attack of the hydride can now occur from the less hindered side giving **39**. Usual alkaline hydrolysis (K_2CO_3, MeOH, r.t.) of the AcO group of **39** provided **7**, whose spectroscopic data matched those of the authentic metabolite M2 [3].

Selective epoxidation (*m*-chloroperbenzoic acid, CH_2Cl_2, $NaHCO_3$) of the isolated double bond of *rac*-carvone (**40**) to give **41** [18], followed by solvolytic ring opening of the oxirane function afforded **10** in 52% yield. The GC/MS of **10** (as methyloxime/trimethylsilyl derivative) showed a pattern identical with that obtained from the authentic urinary metabolite, M^+ 357 [5]. In this case, no attempt was made to find conditions that would allow separation of the diastereoisomeric epoxides of **40**, and hence **10** must be regarded as a mixture of diastereoisomeric diols.

Preliminary pharmacological data indicate a fair to good activity profile for most of the metabolites.

Experimental Part

General. M.p. (uncorrected): *Büchi* apparatus. TLC: plates from *Merck*. Flash chromatography (FC) [19]: silica gel *60* (0.040–0.063 mm). Optical rotations: CH_2Cl_2 solns. (unless otherwise stated); *Perkin-Elmer-241* polarimeter. IR spectra: *Perkin-Elmer-275* spectrophotometer; nujol mull (unless otherwise stated). ^{1}H-NMR spectra; *Bruker WP-80* (80 MHz) in $CDCl_3$ (unless otherwise stated) with TMS as internal standard (= 0 ppm) with *J* in Hz. *rac*-Verbenone was prepared from *trans*-verbenol by *Jones* oxidation [20]. *rac*-α-Pinene and (−)-myrtenol were purchased from *Fluka*.

1. rac-*Myrtenol Chloroacetate* (= *(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl Chloroacetate;* **13a**). To a soln. of **15a** (3.0 g, 19 mmol) in dry THF (70 ml) was added $CH_2ClCOCl$ (2.2 ml, 28 mmol) in pyridine (2.5 ml), and the resulting mixture was stirred at r.t. for 3 h. The mixture was then poured into Et_2O (100 ml) and washed

with 2N H_2SO_4, sat. $NaHCO_3$ soln., H_2O, and finally with brine. After evaporation, the residue was flash-chromatographed with cyclohexane/CH_2Cl_2 1:1 to give **13a** as colourless oil (4.2 g, 93%). IR (film): 1755, 1740, 1655. ^{1}H-NMR: 0.86 (*s*, 3H–C(9)); 1.17 (*d*, *J* = 8.5, H–C(7)); 1.28 (*s*, 3H–C(8)); 2.40 (*ddd*, H–C(7)); 4.03 (*s*, CH_2Cl); 4.54 (*q*, *J* = 1.5, CH_2O); 5.60 (*oct.*, *J* = 1.5, H–C(3)).

(–)-*Enantiomer* **13b**: $[\alpha]_D^{20} = -43.9°$ (*c* = 1.85).

Using the same procedure as before, *rac-syn*-chrysanthenol (**25a**) was converted into rac-syn-*chrysanthenol chloroacetate* (= *2,7,7-trimethylbicyclo[3.1.1]hept-2-en-6-yl chloroacetate*; **28a**) in 95% yield. Colourless oil. IR: 1765, 1735, 1655. ^{1}H-NMR: 0.92 (*s*, CH_3–C(7)); 1.42 (*s*, CH_3–C(7)); 1.68 (*dt*, *J* = 2.0, 1.6, CH_3–C(2)); 4.01 (*s*, CH_2Cl); 4.45 (*s*, H–C(6)); 5.26 (*oct.*, *J* = 1.6, H–C(3)).

2. *(4*RS,*6*SR*)-6,8-Dihydroxy*-p-*menth-1-en-7-yl Chloroacetate* (**17a**). A soln. of **13a** (4.2 g, 18.4 mmol) in dry CH_2Cl_2 (50 ml) was treated at 0° with $NaHCO_3$ (1.68 g, 20 mmol) followed by freshly purified *m*-chloroperbenzoic acid (3.44 g, 20 mmol). The resulting slurry was stirred overnight at r.t. and then poured into sat. Na_2SO_3 soln., and the product was extracted with CH_2Cl_2. The combined org. layers were washed with $NaHCO_3$ soln. and brine, dried, and evaporated to give 3.98 g (95%) of epoxide **16a**, which was not further purified. The latter was dissolved in 40 ml of acetone, and 40 ml of 0.1N HCl were added. The mixture was stirred at r.t. for 3 h, poured onto AcOEt (50 ml) and washed with sat. $(NH_4)_2SO_4$ soln. The aq. layer was extracted with AcOEt and the combined org. layers were dried and evaporated. FC of the thick oily residue with AcOEt/cyclohexane 1:1 afforded 2.98 g (62%) of **17a** as colourless needles, m.p. 89–90° (Et_2O). IR: 3350, 3250, 1760, 1730. ^{1}H-NMR: 1.16 (*s*, $2CH_3$); 4.06 (*s*, CH_2Cl); 4.21 (*m*, H–C(6)); 4.60, 4.83 (*AB*, *J* = 10.8, CH_2O); 5.95 (br. *d*, *J* = 5.2, H–C(2)).

*(4*R,*6*S*)-Enantiomer* **17b**: M.p. 85–86° (Et_2O). $[\alpha]_D^{20} = -79.6°$ (*c* = 0.1).

Using the same procedures as before, **28a** was converted into *(3*RS,*4*SR,*6*SR*)-6,8-dihydroxy*-p-*menth-1-en-3-yl chloroacetate* (**29a**) in 45% yield. Colourless oil. IR (film): 3380, 1730, 1670. ^{1}H-NMR: 1.25 (*s*, $2CH_3$); 1.82 (br. *s*, CH_3–C(1)); 2.76 (br. *s*, 2OH); 4.02 (*s*, CH_2Cl); 4.09 (*m*, H–C(6)); 5.34 (br. *d*, *J* = 5.5, H–C(3)); 5.71 (*dq*, *J* = 5.5, H–C(2)).

3. *(4*RS,*6*SR*)-6-Acetoxy-8-hydroxy*-p-*menth-1-en-7-yl Chloroacetate* (**19a**). Compound **17a** (7.0 g, 26.6 mmol) was dissolved in dry THF (100 ml) and treated with Ac_2O (3.8 ml, 40 mmol) in the presence of 4-(dimethylamino)pyridine (0.5 g, 4 mmol). The mixture was allowed to stand at r.t. for 3 h, AcOEt and 2N H_2SO_4 were added, the org. layer was separated, washed with sat. $NaHCO_3$ soln., H_2O, and brine, dried, and evaporated. The oily residue afforded, after FC using cyclohexane/AcOEt 3:2. **19a** (7.6 g, 94%) as a thick oil. IR: 3490, 3420, 1710. ^{1}H-NMR: 1.19 (*s*, $2CH_3$); 2.06 (*s*, AcO); 5:42 (*dd*, *J* = 4.0, 1.7, H–C(6)); 6.11 (br. *dq*, *J* = 5.8, 1.4, H–C(2)).

*(4*R,*6*S*)-Enantiomer* **19b**: $[\alpha]_D^{20} = -71.5°$ (*c* = 0.94).

Using the same procedure as before, **29a** was converted into *(3*RS,*4*SR,*6*SR*)-6-acetoxy-8-hydroxy*-p-*menth-1-en-3-yl chloroacetate* (**32a**) in nearly quantitative yield, m.p. 94° (Et_2O). IR: 3550, 1735, 1675. ^{1}H-NMR: 1.30 (*s*, $2CH_3$); 1.79 (br. *s*, CH_3–C(1)); 2.10 (*s*, AcO); 4.10 (*s*, CH_2Cl); 5.35 (*m*, $w_{1/2}$ = 6, H–C(6)); 5.46 (br. *d*, *J* = 6.0, H–C(3)); 5.98 (*dq*, *J* = 5.7, H–C(2)).

4. *(4*RS,*6*SR*)-6-[(*tert*-Butyl)dimethylsilyloxy]-8-hydroxy*-p-*menth-1-en-4-yl Chloroacetate* (**21a**). To a stirred soln. of **17a** (5.0 g, 19 mmol) in DMF (20 ml) were added imidazole (4.1 g, 60 mmol) and (*tert*-butyl)-dimethylsilyl chloride (4.6 g, 30 mmol) at r.t. Then the mixture was stirred at r.t. for 14 h. After dilution with brine, the aq. layer was extracted with Et_2O. The combined org. extracts were washed with H_2O. Concentration of the dried solvent afforded an oily residue which was purified by FC using cyclohexane/AcOEt 4:1 to yield **21a** (6.5 g, 90%) as a nearly colourless oil. ^{1}H-NMR: 0.85 (*s*, $(CH_3)_3CSi$); 1.14 (*s*, $2CH_3$); 4.02 (*s*, CH_2Cl); 4.25 (br. *t*, *J* = 3.0, H–C(6)); 4.54, 4.70 (*AB*, *J* = 12.5, CH_2O); 5.88 (br. *d*, *J* = 4.8, H–C(2)).

*(4*R,*6*S*)-Enantiomer* **21b**: $[\alpha]_D^{20} = -41.8°$ (*c* = 0.14).

Using the same procedure as before, **29a** was converted into *(3*RS,*4*SR,*6*SR*)-6-[(*tert*-*butyl*)dimethylsilyl-oxy]-8-hydroxy*-p-*menth-1-en-3-yl chloroacetate* (**36a**) in 76% yield, colourless oil. IR (film): 3570, 3450, 1740, 1675. ^{1}H-NMR: 0.88 (*s*, $(CH_3)_3CSi$); 1.16, 1.24 (2*s*, $2CH_3$); 1.75 (br. *s*, CH_3–C(1)); 4.01 (*s*, CH_2Cl); 4.03 (*m*, H–C(6)); 5.33 (br. *d*, *J* = 5.5, H–C(3)); 5.72 (*dq*, *J* = 5.5, H–C(2)).

5. *(4*RS,*6*SR*)-6-[(*tert*-*Butyl*)dimethylsilyloxy]*-p-*menth-1-en-7,8-diol* (**22a**). To a stirred soln. of **21a** (5.2 g, 13 mmol) in 50 ml of EtOH/H_2O 95:5 were added thiourea (1.14 g, 15 mmol) and solid $NaHCO_3$ (1.26 g, 15 mmol). The resulting mixture was refluxed for 5 h, while the reaction was monitored by TLC. The solvent was evaporated and the residue partitioned between AcOEt and sat. NaH_2PO_4 soln. The combined org. layers were washed with H_2O, dried, and evaporated to afford, after FC using cyclohexane/AcOEt 3:2, pure **22a** (3.2 g, 77%), m.p. 93° ($(i\text{-Pr})_2O$). ^{1}H-NMR: 0.12 (*s*, $(CH_3)_2Si$); 0.88 (*s*, $(CH_3)_3CSi$); 1.22 (*s*, $2CH_3$); 1.75 (2*s*, 2OH); 4.07 (*s*, CH_2OH); 4.31 (*m*, H–C(6)); 5.80 (br. *d*, *J* = 5.0, H–C(2)).

(4R,6S)-Enantiomer **22b**: M.p. 121°. $[\alpha]_D^{20} = -69.5°$ ($c = 1.07$).

Using the same procedure as before, compounds **20**, **5**, **33**, **9**, and **37** were obtained from the corresponding chloroacetates. *(2RS,4SR)-7,8-Dihydroxy-*p*-menth-6-en-2-yl Acetate* (**20a**): Yield 84%. M.p. 74° (Et_2O). IR: 3490, 3420, 1710. ^{1}H-NMR: 1.33 (*s*, $2CH_3$); 2.10 (*s*, AcO); 4.01 (br. *s*, CH_2OH); 5.53 (*m*, H–C(2)); 6.02 (br. *d*, $J = 5.0$, H–C(6)).

(2S,4R)-Enantiomer **20b**: Two crystalline forms, m.p. 52 and 78°. $[\alpha]_D^{20} = -163.9°$ ($c = 0.76$).

rac-*7,8-Dihydroxy-*p*-menth-6-en-2-one* (**5a**): Yield 90%. Colourless oil. IR (film): 3480, 1665. ^{1}H-NMR: 1.21 (*s*, $2CH_3$); 2.40 (br. *s*, 2OH); 4.22 (br. *s*, CH_2OH); 6.94 (br. *d*, $J = 5.5$, H–C(3)).

(4R)-Enantiomer **5b**: $[\alpha]_D^{20} = -23.4°$ ($c = 0.5$, EtOH).

*(2RS,4RS,5SR)-5,8-Dihydroxy-*p*-menth-6-en-2-yl Acetate* (**33a**): Yield 88%. M.p. 132° (Et_2O). ^{1}H-NMR: 1.21, 1.41 (2*s*, $2CH_3$); 1.72 (br. *s*, CH_3–C(1)); 2.09 (*s*, AcO); 3.91 (2*s*, 2OH); 4.48 (*m*, H–C(5)); 5.35 (br. *t*, $J = 2.7$, H–C(2)); 5.83 (*dq*, $J = 5.8$, 1.4, H–C(6)).

*(4RS,5SR)-5,8-Dihydroxy-*p*-menth-6-en-2-one* (**9a**): M.p. 97° (Et_2O). IR: 3220, 1680, 1655. ^{1}H-NMR: 1.21, 1.40 (2*s*, $2CH_3$); 1.79 (br. *s*, CH_3–C(1)); 1.98 (*dd*, $J = 17.0$, 13.0, H–C(3)); 2.50 (*ddd*, $J = 17.0$, 4.3, 0.9, H–C(3)); 4.66 (br. *dd*, $J = 5.9$, 3.1, H–C(5)); 6.70 (*dq*, $J = 5.9$, 1.4, H–C(6)).

*(3RS,4SR,6SR)-6-[(*tert*-Butyl)dimethylsilyl]oxy-*p*-menth-1-en-3,8-diol* (**37a**): Yield 81%. M.p. 135° (Et_2O/hexane). IR: 3230, 1675. ^{1}H-NMR: 0.18 (*s*, $(CH_3)_2Si$); 1.27, 1.48 (2*s*, $2CH_3$); 1.80 (br. *s*, CH_3–C(1)); 3.42 (*s*, OH); 4.13 (*m*, $w_{1/2} = 6$, H–C(6)); 5.69 (*dq*, $J = 5.1$, 1.4, H–C(2)).

6. *(4RS,6SR)-6-[(*tert*-Butyl)dimethylsilyloxy]-8-hydroxy-*p*-menth-1-en-7-al* (**23a**). To a rapidly stirred soln. of 1.92 ml (22 mmol) of oxalyl chloride in 55 ml of CH_2Cl_2 at −78° was added 3.2 ml (45.8 mmol) of DMSO over 5 min. After stirring for an additional 15 min, 5.1 g (17 mmol) of **22a** in 25 ml of CH_2Cl_2 was added over 5 min. After stirring for 20 min, 12 ml of Et_3N was added, and the mixture was allowed to warm to r.t. Sat. $NaHCO_3$ soln. was added, and the mixture was extracted with Et_2O. The combined extracts were dried and the solvent removed. The residue was flash chromatographed with cyclohexane/AcOEt 4:1 to afford **23a** (4.09 g, 80%) as colourless needles, m.p. 52° (hexane). IR: 3460, 1670, 1640. ^{1}H-NMR: 0.86 (*s*, $(CH_3)_3CSi$); 1.20, 1.24 (2*s*, $2CH_3$); 4.73 (br. *t*, $J = 2.8$, H–C(6)); 6.85 (*dd*, $J = 4.8$, 2.3, H–C(2)); 9.44 (*s*, CHO).

(4R,6S)-Enantiomer **23b**: M.p. 49° (hexane). $[\alpha]_D^{20} = -57.0°$ ($c = 1.09$). IR: 3530, 1675, 1650.

7. *(4RS,6SR)-6-[(*tert*-Butyl)dimethylsilyloxy]-8-hydroxy-*p*-menth-1-en-7-oic Acid* (**24a**). A soln. of 80% $NaClO_2$ (10 g) and KH_2PO_4 (10 g) in H_2O (100 ml) was added dropwise over 30 min to a stirred soln. of **23a** (3.6 g, 12 mmol) in *t*-BuOH (250 ml) in the presence of cyclohexene (60 ml). The resulting two-phase system was stirred vigorously overnight at r.t. and then concentrated to remove volatile components. The residue was taken up in 0.1N NaOH (150 ml) and washed with Et_2O. The aq. soln. was acidified (pH 3) with 10% H_2SO_4 and extracted with AcOEt. The combined org. layers were washed with sat. $(NH_4)_2SO_4$ soln., dried, and concentrated. FC with AcOEt/cyclohexane 1:1 afforded **24a** (2.50 g, 66%) as colourless needles, m.p. 165° (AcOEt). IR: 3380, 1690, 1645. ^{1}H-NMR: 0.07, 0.13 (2*s*, $(CH_3)_2Si$); 0.86 (*s*, $(CH_3)_3CSi$); 1.22 (*s*, $2CH_3$); 4.70 (br. *t*, $J = 2.7$, H–C(6)); 5.80 (br. *s*, 2OH); 7.17 (*dd*, $J = 5.2$, 2.0, H–C(2)).

(4R,6S)-Enantiomer **24b**: M.p. 167° (AcOEt). $[\alpha]_D^{20} = -5.3°$, $[\alpha]_{365}^{20} = -16.6°$ ($c = 0.9$, DMF).

8. *(4RS,6SR)-6,8-Dihydroxy-*p*-menth-1-en-7-oic Acid* (**3a**). To a soln. of **24a** (5.0 g, 15.9 mmol) in 100 ml of THF was added 1M Bu_4NF in THF (16 ml, 16 mmol). The soln. was stirred until TLC indicated that the starting material was no longer present (10 h). The solvent was removed, and the residue was diluted with H_2O and extracted with $CHCl_3$. The org. layers were washed with brine and dried. Evaporation afforded white crystals which were recrystallized from MeOH to give **3a** (2.75 g, 86%); m.p. 223°. IR: 3340, 3290, 1675, 1635. ^{1}H-NMR ((D_6)DMSO): 1.05 (*s*, $2CH_3$); 1.60–2.45 (*m*, 4H); 4.05 (*m*, 3OH); 4.44 (br. *t*, $J = 2.7$, H–C(6)); 6.89 (*dd*, $J = 5.4$, 2.4, H–C(2)).

(4R,6S)-Enantiomer **3b**: M.p. 236°. $[\alpha]_D^{20} = 121.5°$ ($c = 1.2$, DMF).

9. *(4RS,6RS)-6,8-Dihydroxy-*p*-menth-1-en-3-one* (**35a**). To a rapidly stirred soln. of **34a** (1.0 g, 44 mmol) in MeOH (25 ml) was added K_2CO_3 (0.7 g, 5 mmol) at r.t. After 3 h, the mixture was evaporated, and the resulting residue was partitioned between AcOEt and NaH_2PO_4 soln. The org. layer was washed with H_2O, dried and evaporated. Crystallization of the residue from $(i\text{-Pr})_2O$ gave **35a** (460 mg, 57%), m.p. 110–111°. IR: 3370, 1630. ^{1}H-NMR: 1.26 (*s*, $2CH_3$); 1.87 (*ddd*, $J = 13.7$, 13.7, 10.0, H–C(5)); 2.06 (br. *s*, CH_3–C(1)); 2.29 (*dd*, $J = 13.7$, 2.7, H–C(4)); 2.38 (*ddd*, $J = 13.7$, 4.3, 2.7, H–C(5)); 2.50 (*d*, $J = 6.5$, OH–C(6)); 4.41 (*ddd*, $J = 10.0$, 6.5, 4.3, H–C(6)); 4.78 (*s*, $(CH_3)_2CO\mathit{H}$); 5.85 (br. *s*, H–C(2)).

Using the same procedure as before, compounds **2**, **6**, and **7** were obtained from the corresponding chloroacetates. *(2RS,4SR)-*p*-Menth-6-en-2,7,8-triol* (**2a**): Yield 90% from **17a**, colourless needles, m.p. 111° (Et_2O).

^{1}H-NMR: 1.05 (*s*, $2CH_3$); 3.91 (br. *d*, *J* = 5.4, CH_2OH); 3.97 (*s*, OH); 4.00 (*m*, H–C(3)); 4.37 (*d*, *J* = 5.1, HO–C(2)); 4.49 (*t*, *J* = 5.4, CH_2OH); 5.63 (br. *d*, *J* = 3.2, H–C(6)).

(2S,4R)-Enantiomer **2b**: M.p. 113°. $[\alpha]_D^{20} = -119.7°$ (*c* = 1.08, EtOH).

(2RS,4RS,5SR)-p-*Menth-1-en-2,5,8-triol* (**6a**): Yield 87% from **29a**, m.p. 127° (Et_2O). IR: 3470, 3350, 3250, 1670. ^{1}H-NMR ((D_6)DMSO): 1.10, 1.22 (2*s*, $2CH_3$); 1.68 (br. *s*, CH_3–C(1)); 3.81 (*dt*, *J* = 5.6, 3.0, H–C(2)); 4.11 (*m*, H–C(5)); 4.15 (br. *s*, OH); 4.51 (*d*, *J* = 5.6, HO–C(2)); 5.47 (*dq*, *J* = 5.6, 1.4, H–C(6)).

(2RS,4RS,5RS)-p-*Menth-1-en-2,5,8-triol* (**7a**): Yield 90% from **39a**, m.p. 117° ($(i\text{-Pr})_2O$). IR: 3220, 1680. ^{1}H-NMR: 1.09, 1.14 (2*s*, $2CH_3$); 1.67 (*t*, *J* = 1.5, CH_3–C(1)); 3.73 (*m*, OH); 4.05 (br. *d*, *J* = 8.5, H–C(5)); 4.67 (*d*, *J* = 5.9, HO–C(5)); 5.07 (*s*, OH); 5.19 (*d*, *J* = 3.4, HO–C(2)); 5.24 (*m*, H–C(6)).

10. *(4RS,6SR)-6-[(*tert*-Butyl)dimethylsilyloxy]-8-hydroxy*-p-*menth-1-en-3-one* (**38a**). A soln. of **37a** (2.25 g, 7.5 mmol) in dry CH_2Cl_2 (50 ml) was stirred at r.t. in the presence of activated MnO_2 (15 g) for 48 h. The mixture was filtered through a short *Celite* pad and the solvent evaporated. FC with cyclohexane/AcOEt 4:1 gave **38a** (2.0 g, 89%) as colourless needles, m.p. 79° (hexane). IR: 3440, 1655. ^{1}H-NMR: 1.19 (*s*, $2CH_3$); 1.90 (*s*, $(CH_3)_3CSi$); 1.95 (br. *s*, CH_3–C(1)); 2.81 (*dd*, *J* = 11.2, 5.2, H–C(4)); 4.18 (*t*, *J* = 3.0, H–C(6)); 4.90 (*s*, OH); 5.71 (*m*, H–C(2)).

Using the same procedure as before, compounds **4** and **18** were obtained. rac-*8-Hydroxy*-p-*menth-6-en-2-one* (**4a**): Yield 85%from **1a**, colourless oil. ^{1}H-NMR: 1.16 (*s*, $2CH_3$); 1.75 (br. *s*, CH_3–C(1)); 6.71 (br. *dq*, *J* = 5.2, 1.4, H–C(6)).

(4R)-Enantiomer **4b**: M.p. 41° (hexane). $[\alpha]_D^{20} = -41.8°$ (*c* = 1, EtOH). IR: 3420, 1670, 1640.

rac-*8-Hydroxy-6-oxo*-p-*menth-1-en-7-yl Chloroacetate* (**18a**): Yield 85% from **17a**, colourless oil. IR (film): 3450, 1750, 1665. ^{1}H-NMR: 1.16 (*s*, $2CH_3$); 4.00 (*s*, CH_2Cl); 4.76 (br. *s*, CH_2O); 7.04 (br. *d*, *J* = 5.6, H–C(2)).

(4R)-Enantiomer **18b**: $[\alpha]_D^{20} = -20.4°$ (*c* = 0.56, EtOH).

11. *(2RS,4SR)-8-Hydroxy-5-oxo*-p-*menth-6-en-2-yl Acetate* (**34a**). Diol **33a** (5.0 g, 22 mmol) was dissolved in dry CH_2Cl_2 (100 ml) under N_2 at r.t., and recrystallized pyridinium chlorochromate (8.8 g, 44 mmol) was added followed by anh. NaOAc (4.4 g). Stirring was continued for 1 h, and the mixture was poured into Et_2O (500 ml). The Et_2O soln. was filtered through *Florisil* and evaporated to afford an oily residue which was purified by FC with cyclohexane/AcOEt 2:1 leading to **34a** (4.2 g, 85%) as colourless oil. IR: 3460, 1740, 1660. ^{1}H-NMR: 1.72 (*ddd*, *J* = 14.6, 11.9, 7.2, H–C(3)); 1.91 (*d*, *J* = 1.4, CH_3–C(1)); 2.06 (*s*, AcO); 2.13 (*s*, $2CH_3$); 2.22 (*ddd*, *J* = 14.6, 6.5, 5.4, H–C(3)); 2.61 (*dd*, *J* = 11.9, 4.8, H–C(4)); 4.53 (*s*, OH); 5.41 (*dd*, *J* = 7.2, 6.5, H–C(2)); 5.90 (*q*, *J* = 1.4, H–C(6)).

Using the same procedure as before, **29a** was converted into *(3RS,4SR)-8-hydroxy-6-oxo*-p-*menth-1-en-3-yl chloroacetate* (**31a**) in 85% yield. ^{1}H-NMR: 1.25, 1.30 (2*s*, $2CH_3$); 2.05 (*s*, OH); 1.82 (*d*, *J* = 1.4, CH_3–C(1)); 2.19 (*ddd*, *J* = 12.8, 5.1, 2.8, H–C(4)); 2.60 (*ddd*, *J* = 16.9, 5.1, 1.0, H–C(5)); 2.83 (*dd*, *J* = 16.9, 12.8, H–C(5)); 4.06 (*s*, CH_2Cl); 5.58 (*ddd*, *J* = 2.8, 1.0, H–C(3)); 6.81 (*dq*, *J* = 5.7, 1.4, H–C(2)).

12. rac-*8,9-Dihydroxy*-p-*menth-6-en-2-one* (**10a**). The epoxides **41a** were obtained by *m*-chloroperbenzoic-acid treatment [18] of *rac*-carvone (**40a**) and isolated in 88% yield after FC (AcOEt/cyclohexane 1:1). The mixture **41a** (5.5 g, 33.1 mmol) was immediately dissolved in acetone/0.1N HCl 4:1 (60 ml) and kept at r.t. for 3 h. AcOEt and sat. $(NH_4)_2SO_4$ soln. were then added, and the aq. layer was extracted twice with AcOEt. The combined org. layers were washed with H_2O, dried, and the solvent evaporated. The resultant oily residue was purified by FC using AcOEt/cyclohexane 1:1 to yield **10a** (3.61 g, 59%) as a colourless oil. IR (film): 3390, 1660. ^{1}H-NMR: 1.21 (*s*, CH_3–C(8)); 1.73 (br. *s*, CH_3–C(1)); 2.90 (br. *s*, 2OH); 3.40, 3.56 (*AB*, *J* = 11.0, CH_2OH); 6.74 (*m*, H–C(6)).

13. *5,8-Dihydroxycarvacrol* (= *2-(1-Hydroxy-1-methylethyl)-5-methylbenzene-1,4-diol;* **11**). A soln. of **6a** (5.6 g, 30.1 mmol) in dry, freshly distilled acetone (from $KMnO_4$, 65 ml) was stirred, cooled (−20°), and treated with *Jones* reagent (70 ml; prepared by adding 96.7 ml of conc. H_2SO_4 soln. to a cold (0°) stirred soln. of 111.25 g of CrO_3 in 450 ml of H_2O). The mixture was allowed to reach −5° within 2 h. Upon completion of the reaction (*TLC*), 20% $NaHSO_3$ soln. was added dropwise and the mixture extracted with Et_2O. The combined Et_2O extracts were washed with H_2O, brine, and evaporated. FC using AcOEt/cyclohexane 1:1 gave **11** (2.79 g, 51%) as colourless needles, m.p. 102° (hexane/Et_2O). IR: 3400, 3270, 3130. ^{1}H-NMR: 1.55 (*s*, $2CH_3$); 2.10 (*s*, CH_3–C(1)); 5.02 (*s*, OH); 6.55 (2*s*, H–C(3), H–C(6)); 7.18 (*s*, OH); 9.02 (*s*, OH).

14. *(4RS,6SR)-6,8-Dihydroxy*-p-*menth-1-en-3-one* (**8a**). A soln. of **38a** (3.0 g, 10 mmol) in MeCN/0.1N HCl 9:1 (50 ml) was stirred overnight. Evaporation gave a residue which, after FC with AcOEt/cyclohexane 1:1, afforded **8a** (1.4 g, 75%) as colourless oil. IR (film): 3400, 1650. ^{1}H-NMR: 1.16, 1.20 (2*s*, $2CH_3$); 1.90 (*s*, OH); 1.92

(*ddd*, J = 13.9, 12.8, 3.7, H–C(5)); 2.01 (*d*, J = 1.5, CH_3–C(1)); 2.19 (*ddd*, J = 3.7, 3.0, H–C(5)); 4.88 (*s*, OH); 5.80 (*q*, J = 1.5, H–C(6)).

15. *(2*RS,*4*RS,*5*RS*)-5,8-Dihydroxy-*p*-menth-6-en-2-yl Acetate* (**39a**). To an ice-cold soln. of **34a** (5.5 g, 24.1 mmol) in dry Et_2O (60 ml) were added 60 ml of 0.4M $Zn(BH_4)_2$ in Et_2O (prepared according to [21]) under N_2 with stirring. After 1 h at 0°, sat. $(NH_4)_2SO_4$ soln. (10 ml) was added and stirring continued for an additional 30 min. Then, the org. layer was dried and evaporated. The residue was analyzed by ^{1}H-NMR (200-MHz, *Varian XL-200*): 15:1 mixture of diastereoisomers **39a** and **33a**. Purification by careful FC with AcOEt/cyclohexane 7:3 afforded first 3.68 g (68%) of **39a** as colourless needles, m.p. 121° (Et_2O). ^{1}H-NMR: 1.17, 1.23 (2*s*, $2CH_3$); 1.67 (br. *s*, CH_3–C(1)); 2.04 (*s*, AcO); 5.10 (br. *t*, H–C(2)); 4.29 (*m*, H–C(5)); 5.59 (*dq*, J = 5.6, H–C(6)).

Further elution provided 195 mg of the more polar **33a** as a white foam.

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