8. Stereochemistry-Activity Relationships in Olfaction. Odorants Containing a Proton Donor/Proton Acceptor Unit

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Summary

A novel class of odorants is described where the odor is associated with the interaction of two functional groups, one being an H-donor (AH function), and the other an H-acceptor (B function). Generally, odor occurs only if the distance between the two structural elements (AH/B system) is less than 3 Å. Bifunctional derivatives of the *p*-menthane and iridane series served as models for deriving this rule. The stereospecificity of odor perception was an important prerequisite for its establishment.

It is known that hydroxycarbonyl compounds having a molecular weight up to about 250 may possess a pronounced odor. In other cases, however, bifunctional compounds of this type are completely odorless. No molecular explanation for this contrasting behaviour has been offered. While engaged in work on structure-activity relationships in olfaction we have been able to account for this discrepancy by invoking the stereochemistry of the molecules giving rise to the effects, as illustrated by the formulas below. *The compounds in red are odorants, whereas the uncolored molecules were found to be virtually odorless.* Examination of *Dreiding* models shows the distance between the hydrogen atom of the hydroxyl group and the carbonyl group to be less than 3 Å in the odoriferous compounds, but more than 3 Å in the odorless molecules. A single exception to this rule has been found.

In the bifunctional unit of compound **1** the distance between the functional groups is 2.2 Å, assuming a chair conformation for the ring and an axial conformation for the aldehyde group. In the diequatorial conformation of compound **2** the distance between the functional groups is about 6 Å. Base-catalyzed equilibration showed the equilibrium between **1** and **2** to be mainly (92%) on the side of **2** with concomitant disappearance of the odor. The required distance for this particular type of fragrance already reaches the limit of about 3 Å in odoriferous compound **3**. This value is largely exceeded in the odorless hydroxyaldhyde **4**. We presume that in the cyclohexene derivatives **5**–**8** the carbonyl group occupies an axial position since only in this case – independent of whether the ring is in a half-chair or a half-twist conformation – the bifunctional unit can be adjusted to the required distance

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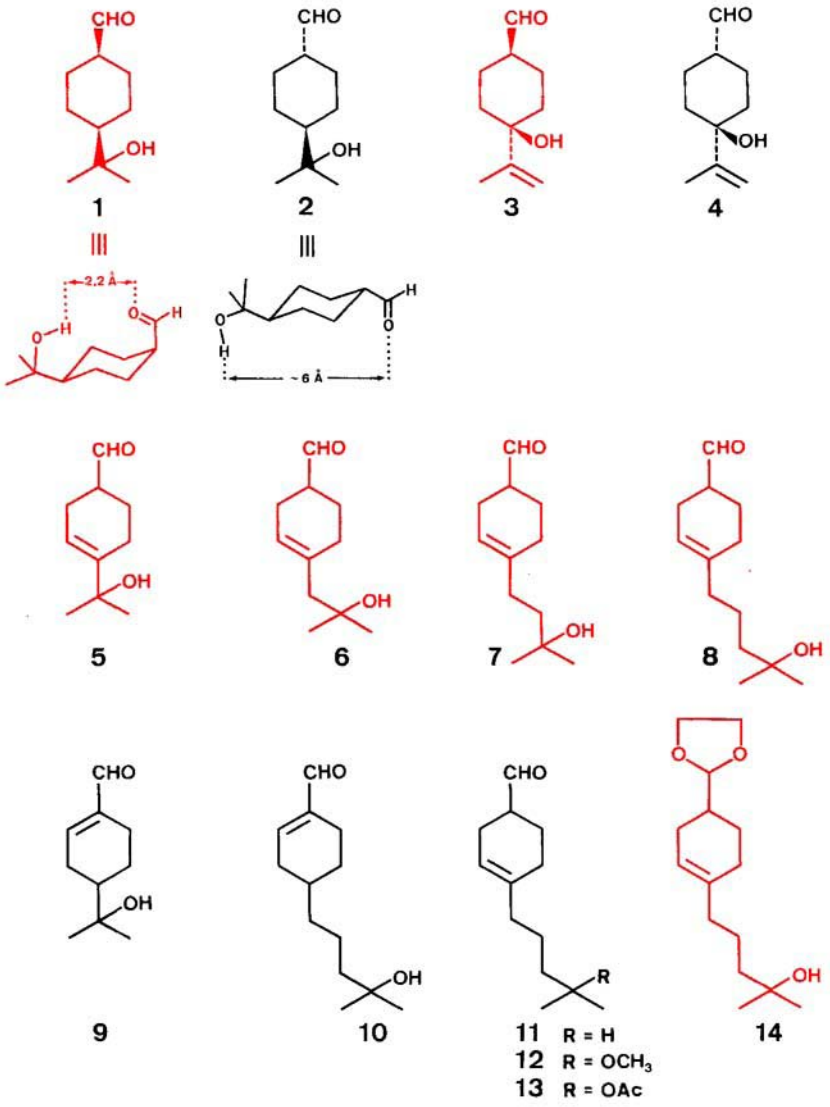
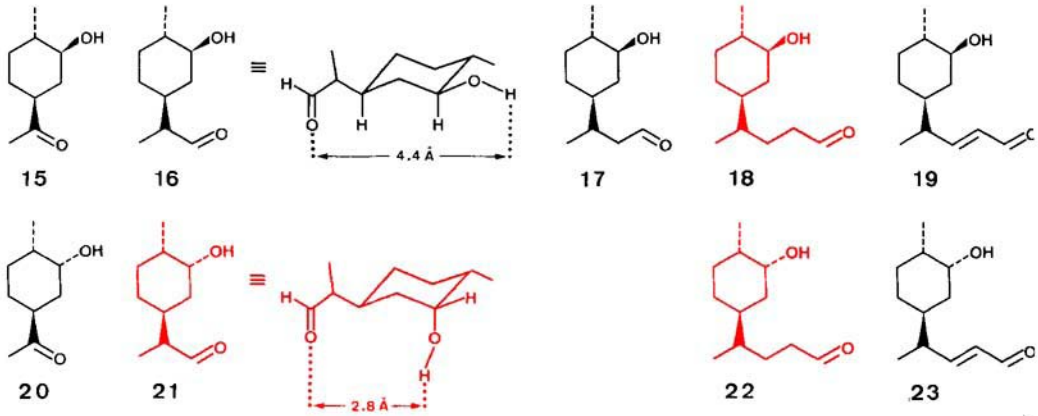


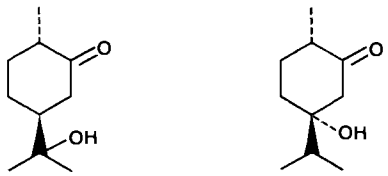
(≦3.0 Å). If the aldehyde group is attached to a trigonal C-atom, as in **9** and **10**, approach of the functional groups to less than 4 Å is not possible, and as a result the compounds are odorless. If the functional group in the side chain is replaced by an H-atom as in **11**, the typical odor of lily of the valley of **8** disappears[1]). If the H-donor function OH is converted into a second acceptor function by alkylation (→ **12**) or acetylation (→ **13**), odorless compounds are obtained. Conversely, no limitation to a carbonyl group exists in the case of the H-acceptor function. Other electroneg-

[1]) The odor of compound **11** is comparable to that of the *Diels-Alder* adduct from acrolein and myrcene.



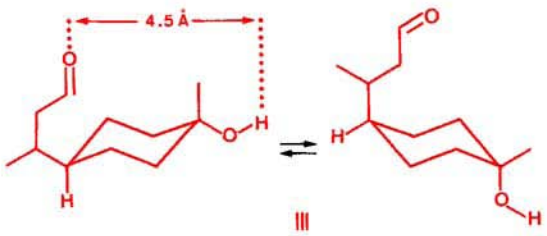
ative centers, such as acetal groups, can also exercise this function. Indeed, **14** has an odor closely similar to that of LYRAL® (**8**).

The spacing principle of the bifunctional unit also proved to be clearly effective in the case of the diastereoisomeric pairs **15**–**23**. Owing to the axial conformation of the hydroxyl group, the hydroxycarbonyl compounds of the (1′*S*, 3′*R*, 4′*S*)-series **20**–**22** showed odoriferous properties approaching the odor of lily of the valley already with the second member (**21**), whereas among the homologs of the (1′*S*, 3′*S*, 4′*S*)-series **15**–**18** with a diequatorial *cis*-arrangement of the oxygen-containing substituents the same odoriferous properties appear only with compound **18** (*ca.* 1 Å). Introduction of an (*E*) double bond into the α,β-position of the aldehyde group prevents an approach of the H-donor and H-acceptor function; hence both hydroxyaldehydes **19** and **23** are odorless.



If the position of the functional groups is reversed, as in the case of the two hydroxyketones **24** and **25**, the required distances of < 3 Å are not reached, and these two compounds are odorless.

Surprisingly, in the case of the stereoisomeric pairs **26**–**35** having substituents in the 1- and 4-position of the ring this phenomenon is reversed. The compounds **31**–**35** (with *cis*-arrangement of the hydroxyl group and the oxo-substituted side chain), which if the rule is met should possess odoriferous properties already from the second member **32** on (2.5 Å), all proved to be odorless. On the other hand, in the case of compounds **26**–**30** (with *trans*-arrangement of the corresponding groups) the characteristic lily of the valley odor is perceived from the third member **28** (4.5 Å and less) onwards.



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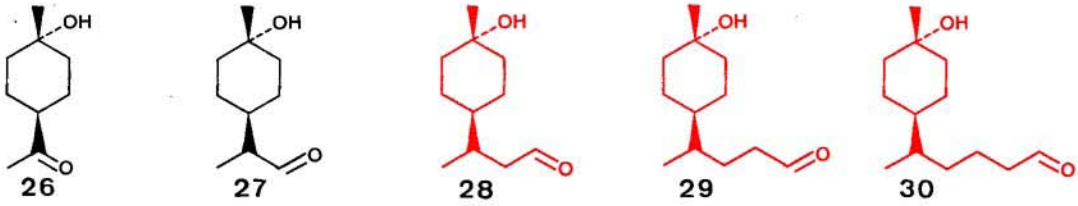

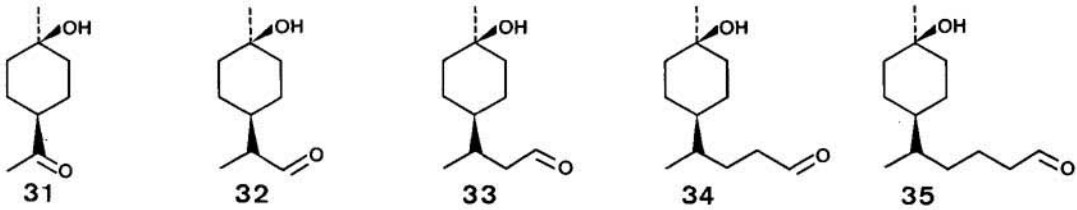

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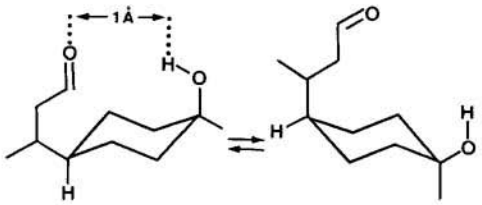
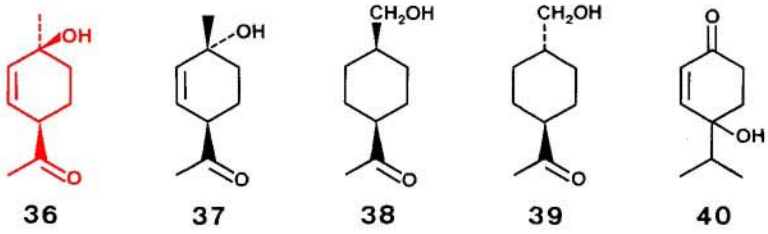
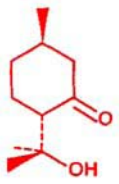




Compounds of type **36** and **37** again behave 'normally' after introduction of a double bond in the 2-position of the cyclohexane ring. Indeed, molecule **36** with the functional groups at a distance of less than 3 Å in the half-chair form possesses a pronounced odor, whereas the *trans*-arrangement of the functional groups, as in **37**, does not induce any receptor activity. Again, no odor was detected in the case of the



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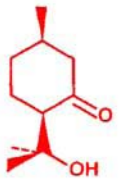

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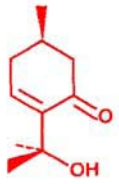

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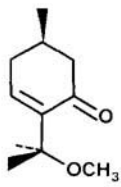

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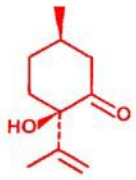

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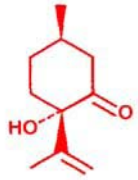

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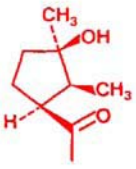

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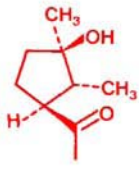

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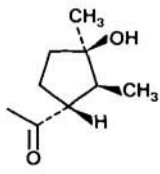

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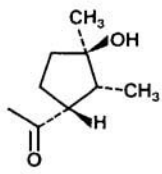

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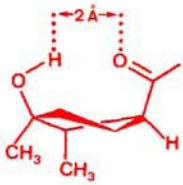
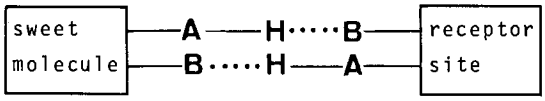


pair of stereoisomers **38** and **39** which behave like the isomers **26** and **31** bearing a tertiary hydroxyl group. The α,β-unsaturated hydroxyketone **40** is also odorless.

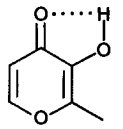
Compounds with the functional groups at the positions shown in **41**, **42**, **43**, **45** and **46** all have a minty odor, independently of the arrangement of their bifunctional unit. If the proton-donor group of **43** is blocked by the formation of ether **44**, the odor is lost as in the case of compound **12**.

Similar phenomena are observed with compounds **47**–**50** having a cyclopentane ring. Only **47** and **48** with a *cis*-bifunctional unit had a flowery odor, the corresponding *trans*-compounds **49** and **50** being completely odorless. Base-catalyzed equilibration showed that **48** and **49** represent the thermodynamically more stable compounds. Thus, it was possible to convert the intensely odoriferous diastereoisomer **47** into an odorless compound **49**, whereas the odorless ketone **50** was transformed into a strong odorant **48**.

Discussion. – In his work on stimulants of sweet taste *Shallenberger* [1–3] postulates that the interaction between a sweetener and its receptor molecule requires a complementary proton-donor (AH) and proton-acceptor (B) group forming a strong intermolecular hydrogen bonding system as shown in the following figure. Besides the average distance of about 3 Å, the torsion angle between the AH and B moieties in the sweet molecule must be about 60° [2]. Hydrophobic interaction of an apolar area of the sweetener with the receptor system is an additional parameter for an efficient binding [4].



The caramel odor appears to fit the ideally molecular requirements of an AH/B-system as discussed above. The common molecular feature of heated food aroma is a strictly planar enol-carbonyl moiety of alkyl-substituted five- or six-membered cyclic α-diketones, stabilized by strong hydrogen bonding [5] [6]. Thus, maltol (**51**) and FURANEOL® (**52**) are typical representatives of burnt flavor [7].



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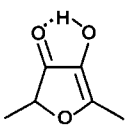

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Finally an olfactory mutant (HPB-1) of *Drosophila melanogaster* was specifically attracted by twelve chemicals having a bifunctional unit which consists of a proton-donor (AH) and proton-acceptor (B) group, the minimal distances between which are 1.65 to 2.5 Å. Among the selected attractants which repelled the parent strain (AA 75) are maltol (**51**), salicylaldehyde and related compounds [8]. However, there is a variety of chemicals containing the same molecular features which are definitely non-specific odors. This discrepancy makes the interpretation of the results difficult.

The bio-mechanistic approach to sweet taste, caramel flavor and bifunctional pheromones led us to postulate that the AH/B-system is also essential for the chemoreception of the odorant model described here. This novel class of odorants characterized by a three point-interaction with a hypothetical receptor system has been recognized. The prerequisite for the release of odor is a bifunctional unit which is composed of an H-donor and an H-acceptor moiety. Topologically, these functional groups can be distributed over the hydrophobic portion of the molecule, which seems to be the third point of molecular interaction. The critical condition for the triggering of the receptors is the distance between the proton-donor AH and the proton-acceptor B (AH/B-system) which, as a rule, has to adjust to a value of less than 3 Å. Concomitantly an intramolecular hydrogen bond may be but has not necessarily to be formed. Rather, it is assumed that the AH/B-system of the odorant molecule interacts with a complementary system of the receptor site through an intermolecular hydrogen bridge. The adjustment of the distance between the polar structural elements in the AH/B-system can be achieved by the stereochemistry of

the odorant molecule. The pairs of stereoisomers investigated in this paper rigorously follow the 'all or nothing principle'.

While most of the odorant molecules have a flowery (lily of the valley) odor, the bifunctional system can also develop other odors such as minty, woody or woodruff-like notes. Due to insufficient examples it is not yet possible to determine clearly which of the molecular parameters can be made responsible for the specific odor quality. At present, we can conclude that in addition to steric factors the electronic environment of the bifunctional unit exerts a decisive influence on the odor characteristics of the model.

In order to evaluate the scope and limitation of this molecular event, we plan extensive work on structural modification.

Origin of various compounds. – The synthesis of the following compounds is given in detail in the exper. part: **1**–**7**, **9**, **10**, **15**–**23**, and **26**–**39**. The acrolein adduct of myrcene, as well as LYRAL® (**8**), was prepared according to the method of *Kogami et al.* [9]. Partial hydrogenation of LYRAL® in presence of Pd/C led to the formation of its dihydroproduct **11**. Acetal **14** was obtained from **8** by the method described for the preparation of compound **62** (s. exper. part); methylation [10] of **14** and subsequent treatment with 10% HCl solution at RT. for 48 h afforded the methyl ether **12**. Acetoxy-aldehyde **13** was obtained by acetylation [11] of **8**.

(–)-4-Hydroxycarvomenthone (=*c*-4-hydroxy-*r*(1)-*p*-menthan-2-one; **25**) was obtained as in [12]. (–)-8-Hydroxycarvomenthone (=*trans*-8-hydroxy-*p*-menthan-2-one; **24**) [13] was prepared by hydration of (–)-dihydrocarvone (=*trans*-8-*p*-menthen-2-one) [14]. 4-Hydroxycryptone (=4-hydroxy-4-isopropyl-2-cyclohexen-1-one; **40**) was discovered as a new natural product in *angelica* root oil and synthesized by an independent method [15]. Compounds **41**–**46** were obtained as in [16]. The diastereoisomeric 1,2-dimethyl-3-acetyl-cyclopentan-1-ols (**47**–**50**) are taken from [17].

Particular emphasis was put on the origin of allyl alcohols **68** and **69**, which were used as starting materials. Both allyl alcohols were obtained in larger quantities by photooxygenation of (+)-limonene [18]. The C-atom carrying the hydroxyl group in (+)-*t*(4)-*p*-2,8-menthadien-*r*-1-ol (**68**; $[\alpha]_D^{20} = +180°$) had the (*R*)-configuration according to the method of *Horeau* [19] ($[\alpha]_D^{20} = +11°$ of the α-phenylbutyrate). (+)-*c*(4)-*p*-2,8-Menthadien-*r*-1-ol (**69**) [18] ($[\alpha]_D^{20} = +67.9°$) did not react under the same conditions, this fact being indicative of the axial poisition of the hydroxyl groups [20] and of the (*S*)-configuration at C(1), as previously found [18]. Furthermore, the *cis*- and *trans*-β-terpineol (=*t*(4)- and *c*(4)-8-*p*-menthen-*r*-1-ol; **70** and **71**) was linked with the allyl alcohol **68** and **69** through the hydroxyketone **26** and **31**, respectively. The configuration of alcohols **68**–**71** and their completely saturated derivatives **72** and **73** was independently determined by their gas chromatographic data, mass, ^{1}H-NMR. and ^{13}C-NMR. spectra (*cf. Table* in section 11 of the exper. part).

The authors are indebted to Dr. *B. Maurer* for valuable suggestions, Dr. *B. Willhalm* and Mr. *W. Thommen* for the measurement and interpretation of the NMR. and mass spectra, and to Mrs. *Chantal Vallier-Mugny*, Miss *Beatrice Frei* and Miss *Nicole Iff* for their skilful technical assistance. Miss *Gertrud Lingesleben* is responsible for the lay-out of this paper, which she did with great skill and patience.

Experimental Part

General. – All melting points (m.p.) are uncorrected. Specific rotations $[\alpha]_D$ (for solutions) and rotations α_D (for neat liquids) were measured in a 1 dm tube on the models Polatronic 1 *(Schmidt & Haensch)* and *Perkin-Elmer* 141 polarimeter. UV. spectra: λ_{max} (ε) in nm. IR. spectra were recorded as films or in solutions (solvent specified in each case) on a *Perkin-Elmer* A-21 spectrophotometer; absorption maxima are given in cm^{-1}. ^1H- and ^{13}C-NMR. spectra were recorded on a *Varian* A-60 instrument and/or on a *Bruker* HFX-90 instrument, using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as an internal standard; abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br. = broad, J = spin-spin coupling constant (Hz), $w_{1/2}$ = half width (Hz). Mass spectra were measured on a *Atlas* CH-4 mass spectrometer, using an inlet temperature of *ca.* 150° and electrons of 70 eV energy; only the most intense fragment ions are reported as *m/e* (% base peak). Gas chromatography (GC.) was carried out on *Varian Aerograph* instruments (models 1700 and 2700), using *Carbowax* 20 M or SE-30, 10% on *Chromosorb* W 95, 60–80 mesh (4 mm × 3 m).

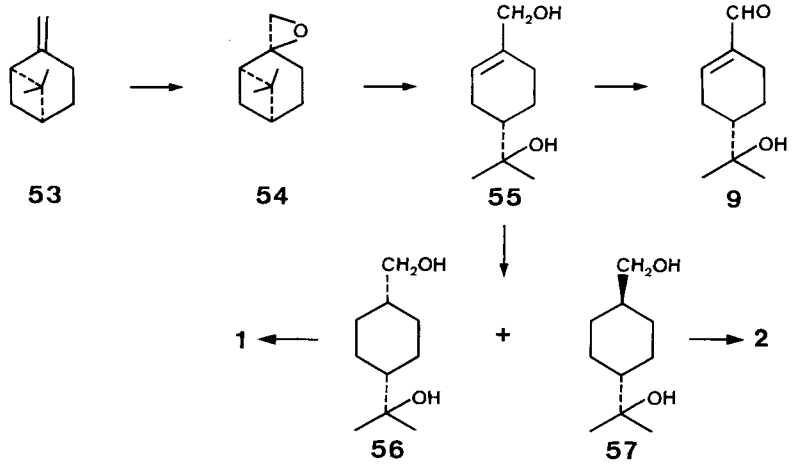
1. *Synthesis of* cis- *and* trans-*8-hydroxy*-p-*menthan-7-al* (**1** *and* **2**) *and* (–)-*(4S)-8-hydroxy-1*-p-*menthen-7-al* (**9**).

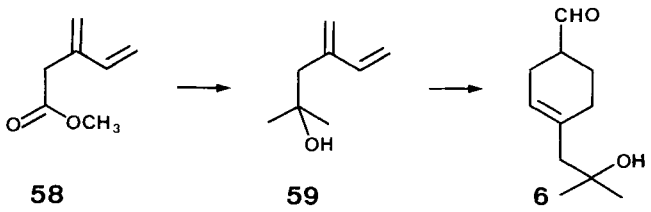
The reaction of 272 g of β-pinene (= 2(10)-pinene; **53**) ($a_D^{20} = -19.5°$) with buffered peracetic acid [21] yielded 266 g (87.5%) of pure expoxide **54** having the following constants: b.p. 33–35°/0.05 Torr, $[\alpha]_D^{20} = +7.2°$ ($c = 9$, $CHCl_3$), $d_4^{20} = 0.9723$, $n_D^{20} = 1.4769$.

A mixture of 150 g of **54** and 1.5 l of water was vigorously stirred and continuously mixed with small portions of solid CO_2. After 4 h the mixture was extracted 4 times with ether, and the ether extract concentrated. The resulting odorless *(4S)-1*-p-*menthene-7,8-diol* (**55**; 152 g = 90%) contained small quantities of perilla alcohol [= (4*S*)-1,8-*p*-menthadien-7-ol] which was removed by fractional distillation. **55**: $[\alpha]_D^{20} = -61.7°$ ($c = 10$, $CHCl_3$).

A solution of 35 g of **55** in 2.5 l of methylene chloride was stirred for 20 h with 350 g of activated MnO_2 at RT. After removal of the MnO_2 by filtration, evaporation of the solvent, and distillation (b.p. 65–69°/0.1 Torr) 28 g of pure *(4S)-8-hydroxy-1*-p-*menthen-7-al* **9** (81%) were obtained, $[\alpha]_D^{20} = -147°$ ($c = 10$, $CHCl_3$), $I_{ox} = 100.2\%$. – UV. (ethanol): 234 (13570). – IR. (film): 3400, 1670. – ^1H-NMR. (CCl_4): 1.16 (*s*, 6 H, 3 H–C(9), 3 H–C(10)); 9.44 (*s*, 1 H, H–C(7)). – MS: 168 (M^+, 0), 150 (17), 135 (4), 121 (5), 110 (51), 95 (20), 79 (23), 67 (6), 59 (100), 43 (38).

A solution of 5 g of **55** in ethyl acetate was shaken in H_2 over PtO_2 until complete disappearance of the starting material. The cis- *and* trans-p-*menthane-7,8-diols* (**56** and **57**; 4.9 g) were obtained as odorless products in the ratio 1:1, and separated by chromatography on SiO_2. – ^1H-NMR. of **56**: 3.68 (*d*, $J = 7$, 2 H, 2 H–C(7)); recognizable by Eu(fod)$_3$-shift reagent was H–C(1): $w_{1/2} = 17$. ^1H-NMR. of **57**: 3.47 (*d*, $J = 6$, 2 H, 2 H–C(7)); recognizable by Eu(fod)$_3$-shift reagent was H–C(1): $w_{1/2} = 27$. The NMR. signals of the 2 H–C(7) were similar to both those of *cis*- and *trans*-8-*p*-menthen-7-ol [22].





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A solution of 100 mg of **56** was heated under reflux in benzene with Ag_2CO_3 for 5 h according to *Fetizon* [23], to give 70 mg of *cis*-8-hydroxy-*p*-menthan-7-al (**1**). GC. showed this to contain 10% of *trans*-8-hydroxy-*p*-menthan-7-al (**2**), and it had a very powerful flowery-woody odor note.

When subjected to the same reaction, diol **57** yielded pure **2** which was practically odorless.

Equilibrium test. Stirring 100 mg of pure **2** at RT. in 2 ml of methanol containing 50 mg of KOH allowed equilibrium to be reached after 16 h, when 8% of **1** and 92% of **2** (by GC.) were present. A *ca.* (1:3)-mixture (50 mg) of **1** and **2** reacted in the same manner to yield 9% of **1** and 91% of **2** after 17 h.

2. *Synthesis of* (±)-*4-(2'-hydroxy-2'-methylpropyl)-3-cyclohexene-1-carbaldehyde* (**6**).

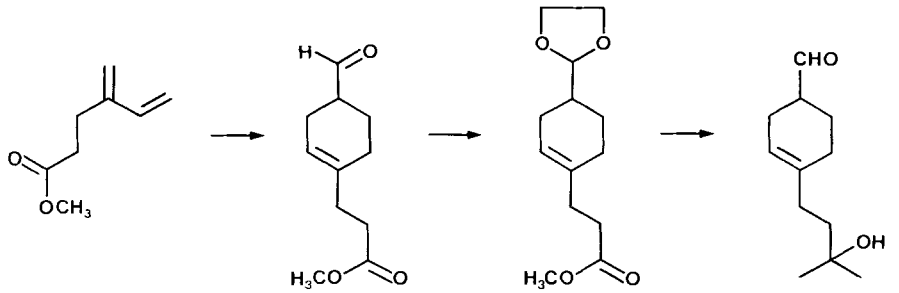
A solution of 19 g of NaOH in 250 ml of water was added dropwise to a mixture of 18 g of 3-methylidene-4-pentenal [24], 55 g of $AgNO_3$, 125 ml of water and 50 ml of ethanol with vigorous stirring. The resulting organic acid (12.3 g) was converted by means of diazomethane in ether into *methyl 3-methylidene-4-pentenoate* (**58**), b.p. 65° (bath temp.)/50 Torr. – ^{1}H-NMR.: 3.23 (*s*, 2 H, 2 H–C(2)); 3.84 (*s*, 3 H, CH_3O); 5.25 (*m*, 4 H, CH_2=C(3), 2 H–C(5)); 6.45 (*d*×*d*, J_1 = 11, J_2 = 17, 1 H, H–C(4)).

Ester **58** (1 g) was heated under reflux for 1 h with a *Grignard* solution prepared from 1 g of Mg and 3 ml of CH_3I. The product was decomposed with icecold hydrochloric acid, washed with water until neutral and distilled in a bulb tube to give 0.88 g of *2-methyl-4-methylidene-5-hexen-2-ol* (**59**). – ^{1}H-NMR.: 1.22 (*s*, 6 H, 3 H–C(1), H_3C–C(2)); 2.45 (*s*, 2 H, 2 H–C(3)); 5.25 (*m*, 4 H, H_2C=C(4), 2 H–C(6)); 6.47 (*d*×*d*, J_1 = 11, J_2 = 17, 1 H, H–C(5)).

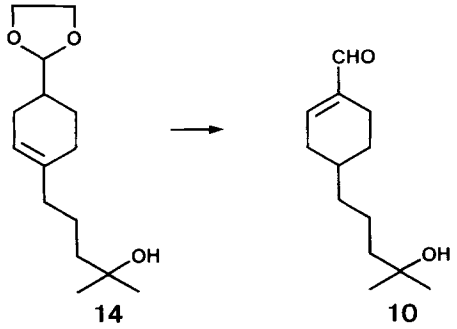
To 320 mg of **59** and 300 mg of acrolein (freshly distilled) in 10 ml of toluene were added with ice-cooling 20 drops of a $SnCl_4$ solution (0.2 ml of $SnCl_4$ in 5 ml of toluene). After 5½ h a small quantity of dilute $NaHCO_3$ was added to the mixture. Filtration through SiO_2 and washing with ether yielded 168 mg of pure *Diels-Alder*-adduct **6** having a LYRAL-like odor with a fresher tonality than **8**. – IR. (film): 3420, 2700, 1710. – ^{1}H-NMR.: 1.2 (*s*, 6 H, 3 H–C(3'), H_3C–C(2')); 5.5 (br.*s*, 1 H, H–C(3)); 9.7 (*s*, 1 H, CH=O). – MS.: 182 (M^+, 0), 122 (28), 119 (55), 118 (55), 86 (70), 84 (100), 59 (85), 47 (33), 43 (30), 36 (60).

3. *Synthesis of* (±)-*4-(3'-hydroxy-3'-methylbutyl)-3-cyclohexene-1-carbaldehyde* (**7**).

Treatment of 42 g of 4-methylidene-5-hexenal [25] in 400 ml of methanol with *Caros* acid (peroxymonosulfuric acid) [26], and distillation of the product on a spinning band column gave *methyl 4-methylidene-5-hexenoate* (**60**) in excellent yield. A mixture of 35 g of **60**, 28 g of acrolein and 3 g of $SnCl_4 \cdot 5\ H_2O$ in 150 ml of toluene was heated under reflux for 5 h, and after cooling washed with water until neutral. Yield of *methyl 4-formyl-1-cyclohexene-1-propionate* (**61**): 43 g (88%). – IR. (film): 3450, 2900, 2700, 1725.



60 61 62 7



14 10

A mixture of 9.7 g of **61**, 4 g of glycol and 0.1 g of *p*-toluenesulfonic acid was heated under reflux in 50 ml of benzene for 5 h with elimination of water. After washing with water and distillation in a bulb tube *methyl 4-(1',3'-dioxolan-2'-yl)-1-cyclohexene-1-propionate* (**62**) was obtained as a GC. pure product. – IR. (film): 1740, 1160. – ^{1}H-NMR.: 3.6 (*s*, 3 H, CH_3O); 3.83 (br.*s*, 4 H, 2 H–C(4'), 2 H–C(5')); 4.67 (*m*, 1 H, H–C(2')); 5.4 (*m*, 1 H, H–C(2)).

A *Grignard* reaction was carried out in the usual manner using 5.3 g of **62** with 6.4 g of CH_3I and 1.1 g of magnesium in ether. After distillation in a bulb tube the hydroxyacetal was obtained in 85% yield. This product, when shaken with 1% H_2SO_4 at RT. for 24 h, yielded **7**. The latter had the characteristic lily of the valley odor. – IR. (film): 3450, 2700, 1725. – ^{1}H-NMR.: 1.17 (*s*, 6 H, 3 H–C(4'), H_3C–C(3')); 5,38 (*m*, 1 H, H–C(3)); 9.55 (br. *s*, 1 H; CH=O).

4. *Synthesis of* (±)*-4-(4'-hydroxy-4'-methylpentyl)-1-cyclohexene-1-carbaldehyde* (**10**).

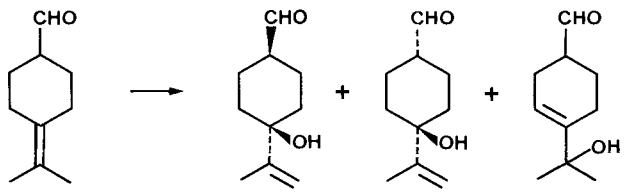
A solution of 70 g of acetal **14** in 300 ml of ethyl acetate was shaken in H_2 over 1 g of Pd/C until the starting material had disappeared. After filtration 68 g (~ 97%) of hydrogenation product were obtained which were heated to 80° in 100 ml of glacial acetic acid for 11 h yielding 40 g (~ 72%) of a stereoisomeric mixture of saturated hydroxyaldehydes. A solution of 5.2 g of bromine in 200 ml of $CHCl_3$ was slowly added at – 10° with vigorous stirring to the mixture of these hydroxyaldehydes in 200 ml of $CHCl_3$ to which 12 g of $CaCO_3$ had been added. After careful treatment with ice-cold $NaHCO_3$-solution and water 50 g (~ 91%) of the desired monobromohydroxyaldehyde were obtained. This product, when heated in 60 g of pyridine to 120° for 2 h, yielded 34 g (94%) of the odorless **10**. – IR. (film): 3400, 2700, 1680, 1640. – ^{1}H-NMR.: 1.22 (*s*, 6 H, 3 H–C(5'), H_3C–C(4')); 6.76 (*m*, 1 H, H–C(2)); 9.4 (*s*, 1 H, CH=O). – MS.: 210 (M^+, 0), 192 (10), 117 (8), 109 (37), 107 (30), 81 (18), 79 (25), 59 (100), 43 (68), 41 (30), 31 (53), 29 (34), 28 (42), 27 (20).

5. *Formation of* **3**, **4** *and* **5** *by photooxygenation of 4(8)-*p*-menthen-7-al* (**63**).

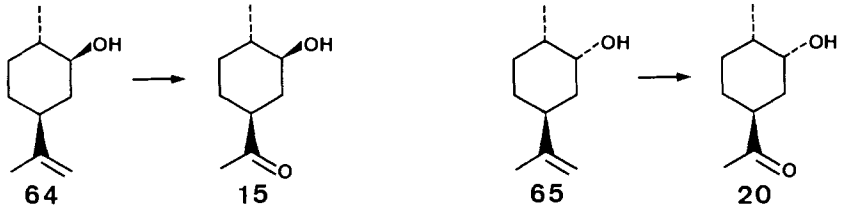
The compound **63** (10 g), obtained by treating a mixture of hydroxyaldehydes **1** and **2** with $KHSO_4$ [27], was subjected to photooxygenation in 80 ml of methanol in the presence of 500 mg of *Rose Bengal* until 1 mol of O_2 had been absorbed [16]. Subsequent reduction with dimethyl sulfide gave a mixture of the hydroxyaldehydes **3**–**5** in a ratio of 35:24:41. It was separated into the pure compounds by prep. GC.

t-*4-Hydroxy-8-*p*-menthen-*r*-7-al* (**4**; peak 1) was an odorless compound. – IR. (film): 3400, 2700, 1723, 897. – ^{1}H-NMR.: 1.7 (*s*, 3 H, 3 H–C(10)); 4.85 (*m*, 2 H, 2 H–C(9)); 9.6 (*s*, 1 H, H–C(7)). – MS.: 168 (M^+, 3), 150 (11), 140 (22), 97 (60), 84 (97), 69 (76), 43 (100), 41 (70), 39 (30), 28 (31), 28 (62).

c-*4-Hydroxy-8-*p*-menthen-*r*-7-al* (**3**; peak 2) had an extraordinarily strong woody-flowery odor with a hotspicy undertone and was reminiscent of **1**. – IR. (film): 3400, 2700, 1723, 893. – ^{1}H-NMR.: 1.78 (*s*.



63 3 4 5



3 H, 3 H–C(10)); 4.81 and 4.99 (2*s*, 2 H, 2 H–C(9), one signal shows allylic coupling); 9.67 (*s*, 1 H, H–C(7)). – MS.: 168 (M^+, 1), 150 (3), 140 (12), 97 (33), 84 (57), 69 (43), 43 (73), 41 (41), 31 (23), 29 (30), 28 (100).

(±)-8-*Hydroxy-3*-p-*menthen-7-al* (**5**; *peak 3*). The odor of **5** recalls **3** and LYRAL® (**8**). – IR. (film): 3400, 2700, 1723, 840. – ^{1}H-NMR.: 1.25 (*s*, 6 H, 3 H–C(9), 3 H–C(10)); 5.7 (br.*s*, 1 H, H–C(3)); 9.63 (*s*, 1 H, H–C(7)). – MS.: 168 (M^+, 0), 150 (14), 135 (7), 121 (34), 107 (13), 93 (16), 91 (14), 79 (21), 59 (12), 43 (100), 31 (14), 29 (15), 28 (14), 27 (13).

6. Synthesis of (+)-*(1'*S,*3'*S,*4'*S)- *and* (−)-*(1'*S,*3'*R,*4'*S)-*1-(3'-hydroxy-4'-methylcyclohexyl) ethanone (***15** and **20**).*

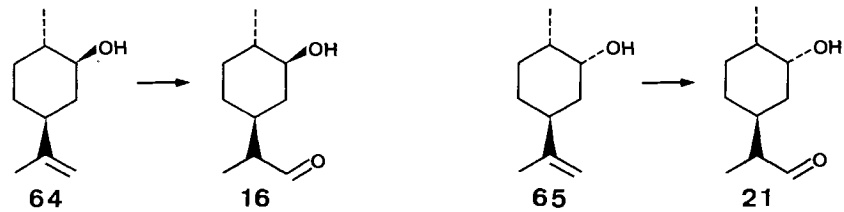
(+)-Dihydrocarveol (=(1*S*, 2*S*, 4*S*)-8-*p*-menthen-2-ol; **64**; 4 g) [14] (α_D^{20} = +32.8° (neat); [14]: −33°, ethanol) in 30 ml of methanol was treated at −15° with ozone and subsequently hydrogenated in the presence of Pd/C until absorption had ceased to give 4.2 g of **15** which were purified by chromatography on 100 g of SiO_2 with hexane/ether 55:45. The odorless **15** had m.p. 59° (hexane/ether) and $[\alpha]_D^{20}$ = −42.8° (*c* = 9, $CHCl_3$). – IR: (film): 3400, 2900, 1705. – ^{1}H-NMR.: 1.0 (br.*s*, 3 H, H_3C–C(4')); 2.1 (*s*, 3 H, 3 H–C(2)); 3.4 (*m*, 1 H, H–C(3')). – MS.: 156 (M^+, 2), 138 (14), 113 (27), 95 (71), 81 (57), 71 (24), 57 (28), 55 (40), 43 (100), 41 (30).

(−)-Neodihydrocarveol (=(1*S*,2*R*,4*S*)-8-*p*-menthen-2-ol; **65**) [15], treated in the same manner as **64**, yielded liquid odorless **20** with α_D^{20} = −28,2° (neat). – IR: (film): 3400, 2900, 1700. – ^{1}H-NMR.: 0,92 (*d*, *J* = 5, 3 H, H_3C–C(4')); 2.1 (*s*, 3 H, 3 H–C(2)); 3.7 (*m*, 1 H, H–C(3')). – MS.: 156 (M^+, 3), 138 (6), 123 (5), 113 (9), 95 (72), 84 (57), 71 (26), 57 (26), 55 (32), 43 (100), 41 (27), 29 (79).

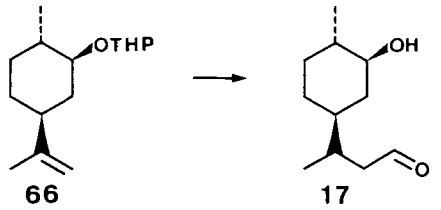
7. Synthesis of (+)-*(2*R+S, *1'*S, *3'*S, *4'*S)- *and* (−)-*(2*R+S, *1'*S, *3'*R, *4'*S)-*2-(3'-hydroxy-4'-methylcyclohexyl)propanal (***16** and **21**)[2]).*

(+)-Dihydrocarveol (**64**) was first converted into its tetrahydropyranyl ether and then hydroborated [28]. The resulting hydroxyether was subjected to a *Fetizon* oxidation [23] [29]. Compound **16** was obtained as an odorless product by purification on SiO_2 by means of hexane/ether 7:3; α_D^{20} = +19.9° (neat). – IR. (film): 3450, 2900, 2700, 1725. – ^{1}H-NMR.: 1.0 (*d*, *J* = 5, 3 H, CH_3CH); 1.07 (*d*, *J* = 6, 3 H, CH_3CH); 3.1 (*m*, $w_{1/2}$ = 16, 1 H, H–C(3')); 9.7 (*d*, *J* = 2, 1 H, H–C(1)). – MS.: 170 (M^+, 1), 152 (13), 137 (5), 113 (25), 95 (100), 94 (84), 81 (40), 55 (62), 43 (67), 41 (65), 29 (41).

Treating **65** in the same manner gave **21** having a pleasant flowery scent; α_D^{20} = −29° (neat). – IR. (film): 3470, 2900, 2700, 1725. – ^{1}H-NMR.: about 1.0 (superimposed *d*, 6 H, 2 CH_3CH); 3.8 (*s*, $w_{1/2}$ = 5, 1 H, H–C(3')); 9.4 (*d*, *J* = 2, 1 H, H–C(1)). – MS.: 170 (M^+, 4), 152 (8), 137 (10), 123 (28), 113 (52), 95 (100), 94 (69), 81 (53), 67 (43), 58 (65), 57 (69), 55 (82), 43 (75), 41 (85), 29 (54).



[2]) The mention *R*+*S* indicates that the ratio is not necessary 1:1 as in a racemate (RS), the synthesis leading to diastereomers.



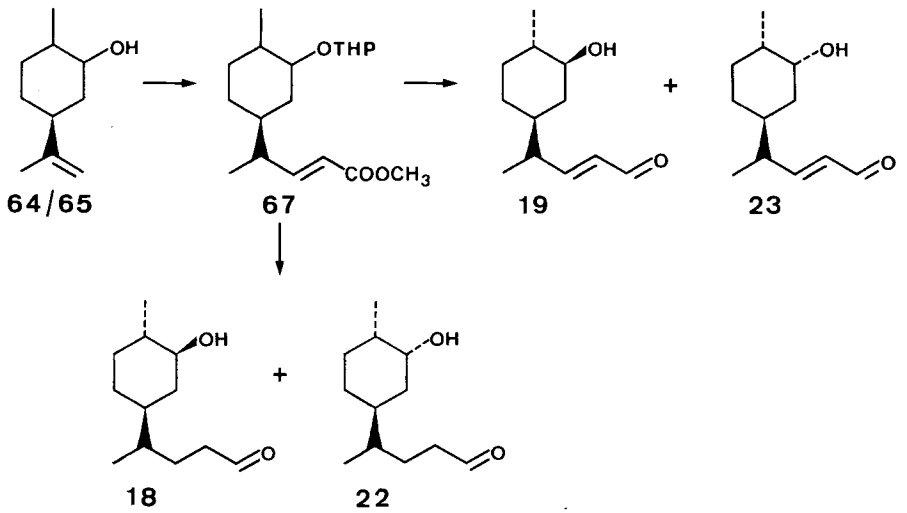
8. *Synthesis of (3*R+S, *1'*S, *3'*S, *4'*S*)-3-(3'-hydroxy-4'-methylcyclohexyl)butanal* (**17**).

A 1.6M solution of 9-borabicyclo [3.1.1]nonane [30] in THF, followed by 340 ml of a 0.2M solution of $LiAlH(OCH_3)_3$ in THF was added to 2.5 g of dihydropyranyl ether **66** from **64** [14] [31] in 50 ml of THF. The resulting solution took up 1.1 l of CO within 4 h. The subsequent treatment was carried out in a known manner [30]. The purification was performed by repeated chromatography on SiO_2 in ether giving 5 mg of pure **17** as an odorless product; $[\alpha]_D^{20} = +6.23°$ ($c = 0.4$, $CHCl_3$). – IR. ($CDCl_3$): 3500, 1735. – ^{1}H-NMR.: 0.9 (*d*, $J = 6$, 3 H, CH_3CH); 0.97 (*d*, $J = 5$, 3 H, CH_3CH); 3.1 (*m*, $w_{1/2} = 26$, 1 H, H–C(3')); 9.7 (*d*, $J = 2$, 1 H, H–C(1)).

9. *Synthesis of (4*R+S, *1'*S, *3'*S, *4'*S*)-4-(3'-hydroxy-4'-methylcyclohexyl)pentanal* (**18**), *(4*R+S, *1'*S, *3'*R, *4'*S*)-4-(3'-hydroxy-4'-methylcyclohexyl)pentanal* (**22**), *(4*R+S, *1'*S, *3'*S, *4'*S, *2*E*)-4-(3'-hydroxy-4'-methylcyclohexyl)-2-pentenal* (**19**), *and (4*R+S, *1'*S, *3'*R, *4'*S, *2*E*)-4-(3'-hydroxy-4'-methylcyclohexyl)-2-pentenal* (**23**).

A mixture of the diastereoisomeric *p*-menthenols **64** and **65** (3:2; 9.2 g) was allowed to react with dihydropyran and $POCl_3$ according to a known method [31], and 14 g of the resulting tetrahydropyranyl ethers (98.5%; b.p. 160° (bath temp.)/0.01 Torr) were mixed with diborane (2.9 g of $NaBH_4$, 12 ml of BF_3/etherate in diglyme) in 50 ml of THF [28] to yield 12.2 g (79%) of the primary alcohol (b.p. 200° (bath temp.)/0.01 Torr). Subsequent treatment with 30 g of CrO_3 and 48 g of pyridine in 750 ml of CH_2Cl_2 [32] yielded 10.8 g (89%) of an aldehyde mixture (b.p. 180° (bath temp.)/0.01 Torr). When mixed with 10 g of methyldimethylphosphonoacetate and 1.5 g of NaH in 40 ml of diisopropyl ether under *Horner-Wittig* conditions [33], this aldehyde mixture was converted into 11 g (83%) of the diastereoisomeric *methyl 4-(4'-methyl-3'-tetrahydropyranyloxy-1'-cyclohexyl)-2-pentenoates* (**67**).

VITRIDE® (21 ml, 70% in benzene) [34] was added within 30 min to 10 g of **67** in 50 ml of toluene, the temp. rising to 50°. After the usual treatment (ice/dilute H_2SO_4 and subsequent extraction with ether) the product was obtained in a quantitative yield. It was treated for 4 h at RT. with 50 g of activated MnO_2 in 250 ml of CH_2Cl_2. A mixture of 2 g of the resulting oxidation product with 20 ml of 15% H_2SO_4-



solution was stirred for 10 h at RT. Then the mixture of the diastereoisomeric **19** and **23** was extracted with ether yielding 1.1 g (78%) which were separated by chromatography on 300 g of SiO_2 with cyclohexane/ether 3:2. Both **19** and **23** were odorless. **19**: $[\alpha]_D^{20} = +17.5°$ ($c = 5.8$, $CHCl_3$). – ^{1}H-NMR.: 1.03 (*d*, $J = 5$, 3 H, CH_3CH); 1.1 (*d*, $J = 7$, 3 H, CH_3CH); 3.84 (br.*s*, $w_{1/2} = 8$, 1 H, H–C(3′)); 6.0 (*d*×*d*, $J_{AX} = 8$, $J_{AB} = 16$, 1 H, H–C(2)); 6.77 (*d*×*d*, $J_{AX} = 8$, $J_{AB} = 16$, 1 H, H–C(3)); 9.47 (*d*, $J = 8$, 1 H, H–C(1)). **23**: $[\alpha]_D^{20} = -3.5°$ ($c = 5$, $CHCl_3$). – ^{1}H-NMR.: 0.935 (*d*, $J = 7$, 3 H, CH_3CH); 1.02 (*d*, $J = 5$, 3 H, CH_3CH); 3.84 (br. *s*, $w_{1/2} = 8$, 1 H, H–C(3′)); 6.0 (*d*×*d*, $J_{AX} = 8$, $J_{AB} = 16$, 1 H, H–C(2)); 6.77 (*d*×*d*, $J_{AX} = 8$, $J_{AB} = 16$, 1 H, H–C(3)); 9.47 (*d*, $J = 8$, 1 H, H–C(1)).

The mixture of the diastereoisomers **67** (37 g) in 500 ml of ethanol was hydrogenated in the presence of Pd/C until the starting material had disappeared. After chromatography on SiO_2 in cyclohexane/ether 3:2 10.5 g (28%) of a saturated product ($[\alpha]_D^{20} = +12°$) were obtained. This product in 50 ml of THF was treated with 2 g of $LiAlH_4$ in 200 ml of THF. The reduction product (8 g, 83%; b.p. 200° (bath temp.)/0.01 Torr) clearly showed two pairs of diastereoisomers in the GC. After treatment with CrO_3 [32] and then 15% H_2SO_4 the mixture (5.4 g, 97%) was separated into **18** and **22** by chromatography (3 times) on SiO_2 in cyclohexane/ether 3:2. These aldehydes had a flowery scent. **18** (50 mg): $[\alpha]_D^{20} = +15°$ ($c = 4.6$, $CHCl_3$). – IR.: 3500, 2720, 1725. – ^{1}H-NMR.: 0.9 (*d*, $J \simeq 7$, 3 H, CH_3CH); 0,97 (*d*, $J = 7$, 3 H, CH_3CH); 3.13 (*m*, $w_{1/2} = 22$, 1 H, H–C(3′)); 9.73 (*t*, $J \simeq 1.5$, 1 H, H–C(1)).

22 (150 mg): $[\alpha]_D^{20} = -22°$ ($c = 8.5$, $CHCl_3$). – IR.: 3500, 2720, 1730. – ^{1}H-NMR.: 0.866 (*d*, $J = 7$, 3 H, CH_3CH); 0.935 (*d*, $J = 6$, 3 H, CH_3CH); 3.87 (br.*s*, $w_{1/2} = 7$, 1 H, H–C(3′)); 9.73 (*t*, $J \simeq 2$, 1 H, H–C(1)).

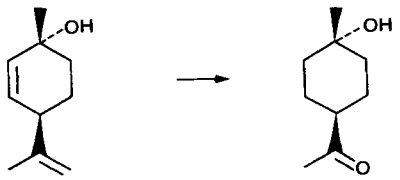
10. *Synthesis of 1-(*t*-4′-hydroxy-4′-methyl-*r*-1′-cyclohexyl)ethanone* (**26**) *from* (+)-*(1*R,*4*R)-*2,8*-p-*menthadien-1-ol* (**68**).

10.1. *Application of* Horeau's *method* [19]. Alcohol **68** was obtained pure ($d_4^{20} = 0.9406$, $n_D^{20} = 1.4901$, $\alpha_D^{20} = +180°$; [18]: $n_D^{20} = 1.4881$, $\alpha_D^{25} = +180.2°$) by distillation of the photooxygenation products of (+)-limonene ($\alpha_D^{20} = +101.8°$ (neat)) [18], and was identical with the alcohol prepared from the epoxide of (+)-2-carene [35].

A mixture of **68** (25 mg), 0.2 ml of α-phenylbutyric acid anhydride and 0.5 ml of pyridine was stirred for 48 h at RT. and then neutralized against phenolphthalein with 0.5N potassium hydroxide (consumption 2.94 ml). After extracting 5 times with petroleum ether the ester of **68** with $[\alpha]_D^{20} = +11°$ was obtained. Generally, axial alcohols have shorter retention times than the corresponding equatorial alcohols [13] and show stronger molecular peaks [36]. On the other hand, the $H_3C(7)$-group presents no significant chemical shift differences in the ^{1}H-NMR. spectrum. In the stereoisomeric compounds the ^{13}C chemical shift data show the expected differences in all cases[3])[4]).

10.2. At −15° 6.4 g of **68** were treated with the amount of ozone calculated for one double bond and subsequently hydrogenated over Pd/C in a watercooled vessel. After evaporation of the solvent 5.2 g of the product distilled (bulb tube, b.p. 90°/0.1 Torr). Chromatography on SiO_2 (hexane/ethyl acetate 1:1) yielded **26** as an odorless oil in pure form. – IR. (film): 3400, 1700. – ^{1}H-NMR.: 1.18 (*s*, 3 H, H_3C–C(4′)); 2.12 (*s*, 3 H, 3 H–C(2)). – MS.: 156 (M^+, 5), 141 (8), 138 (16), 123 (6), 113 (2), 95 (46), 71 (96), 58 (34), 43 (100).

11. *Synthesis of 1-(*c*-4′-hydroxy-4′-methyl-*r*-1′-cyclohexyl)ethanone* (**31**) *from* (+)-*(1*S,*4*R)-*2,8*-p-*menthadien-1-ol* (**69**) *and* trans-*β-terpineol* (= *c(4)-8*-p-*menthen-r-1-ol;* **71**).

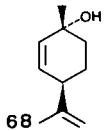
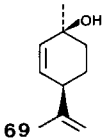
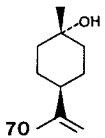
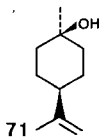
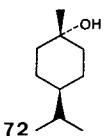
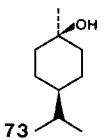


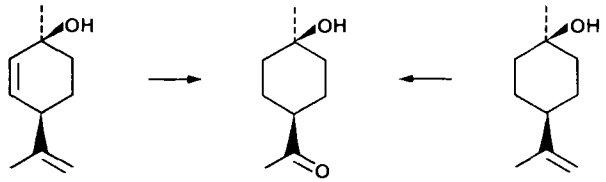
68 **26**

[3]) Among the monoterpene alcohols which we investigated only *trans-β*-terpineol (= *c*(4)-8-*p*-menthen-*r*-1-ol; **71**) had been studied. The published data are in complete agreement with our measurements [37].

[4]) The chemical shifts of the $H_3C(7)$ in **72** and **73** correspond to the signals of the equatorial (31.3 ppm) and axial (25.3 ppm) methyl groups in the case of their *t*-butyl-homologous alcohols (*i.e. t*-butyl instead of isopropyl) [38].

Table. *Physical data of the* tert. *alcohols* **68–73**

Compound	Retention time		MS:		^{1}H-NMR.	^{13}C-NMR.								
	Carbo-wax	SE-30	M^+ (rel.int.)	$M^+ - 18$ (rel.int.)	$H_3C-C(1)$	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
 **68**	110	62	4.9	78	1.23	68.6	36.4	25.3	42.7	130.5	134.8	29.0	147.3	110.8	21.1
 **69**	89	57	9.1	27	1.20	67.4	36.8	24.9	43.5	131.8	134.2	29.6	148.1	110.6	20.8
 **70**	117	72	0	69	1.17	70.6	40.3	29.4	44.7	29.1	40.3	25.7	149.6	108.8	21.1
 **71**	90	65	0.5	49	1.18	68.8	38.9	27.0	44.8	27.0	38.9	31.5	150.3	108.4	20.9
 **72**	83	72	1.9	1.6	1.20	70.9	40.3	27.2	43.6	27.2	40.3	25.7	32.1	20.1	20.1
 **73**	62	63	3.2	1.8	1.20	69.1	39.0	25.2	43.6	25.2	39.0	31.4	32.7	19.9	19.9



69 **31** **71**

Alcohol **69** separated from the photooxygenation product of (+)-limonene ($a_D^{20} = +101.3°$ (neat)) [11] had the following constants: $d_4^{20} = 0.9407$, $n_D^{20} = 1.4907$, $a_D^{20} = +67.9°$ ([18]: $d_4^{20} = 0.9398$, $n_D^{20} = 1.4900$, $a_D^{20} = +67.3°$). Alcohol **69** (15.7 g) was partially ozonized and completely hydrogenated under the conditions described under 10. Thus **31** (11.8 g) was obtained as an odorless oil identical with the product described below.

Light-induced addition of H_2O to limonene [39] gave **71** with the following constants: m.p. 32°, $n_D^{20} = 1.4759$, $d_4^{20} = 0.9239$. – IR. (film): 3320, 1640, 884. – ^{1}H-NMR.: 1.182 (*s*, 3 H, 3 H–C(7)); 1.69 (*s*, 3 H, 3 H–C(10)); 4.62 (br. *s*, 2 H, 2 H–C(9)). – MS.: 154 (M^+, 0.5), 136 (49), 121 (37), 111 (14), 107 (36), 93 (57), 81 (33), 71 (100), 55 (34), 43 (88).

A solution of 25 g of **71** in 250 ml of methanol was treated with ozone at −15°. After reductive treatment in the manner described under 9, 12 g of pure **31** were obtained as an odorless oil, b.p. 75° (bath temp.)/0.01 Torr. – IR. (film): 3380, 1700. – ^{1}H-NMR.: 1.154 (*s*, 3 H, H_3C–C(4')); 2.08 (*s*, 3 H, 3 H–C(2)). – MS.: 156 (M^+, 2), 141 (3.5), 138 (33.2), 123 (13), 113 (1), 95 (61), 71 (90), 58 (34), 43 (100).

70 **27**

12. *Synthesis of* (±)-t*(4)*-r-*1-hydroxy*-p-*menthan-9-al* (**27**).

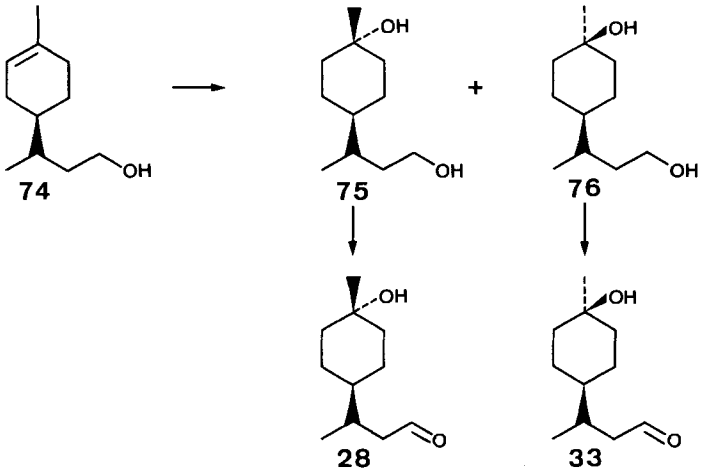
cis-β-Terpineol (= *t*(4)-8-*p*-menthen-*r*-1-ol; **70**) [39] (5 g) were hydroborated with B_2H_6 and oxidized following a method described for isopulegol [40]. The resulting 5.5 g of diol were allowed to react with CrO_3/pyridine complex (7g of CrO_3 in 77 ml of H_2O/pyridine 1:10) to produce 2.6 g (47%) of odorless **27** which was purified on SiO_2 (ether/hexane 7:3). – IR. (film): 3380, 2700, 1720. – ^{1}H-NMR.: 1.02 (*d*, *J* = 6.5, 3 H, 3 H–C(10)); 1.15 (*s*, 3 H, 3 H–C(7)); 9.5 (*d*, *J* = 2, 1 H, H–C(9)). – MS.: 170 (M^+, 0), 152 (0.8), 112 (50), 94 (27), 71 (96), 43 (100).

Light-induced addition of H_2O to limonene [39] gave the terpineol **70** used above with the following constants: m.p. 36°, $n_D^{20} = 1.4832$, $d_4^{20} = 0.9358$. – IR. (film): 3330, 1640, 885. – ^{1}H-NMR.: 1.168 (*s*, 3 H, 3 H–C(7)); 1.675 (*s*, 3 H, 3 H–C(10)); 4.6 (br.*s*, 2 H, 2 H–C(9)). – MS.: 154 (M^+, 0), 136 (69), 121 (44), 111 (9), 107 (47), 93 (49), 81 (17), 71 (100), 55 (33), 43 (85).

13. *Synthesis of* (±)-c*(4)*-r-*1-hydroxy*-p-*menthan-9-al* (**32**).

Under identical conditions, *trans*-β-terpineol (**71**) [39] yielded the odorless stereoisomer **32**. – IR. (film): 3400, 2690, 1720. – ^{1}H-NMR.: 1.025 (*d*, *J* = 7, 3 H, 3 H–C(9)); 1.165 (*s*, 3 H, 3 H–C(7)); 9.5

71 **32**



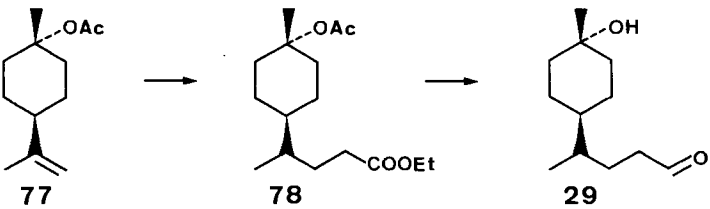
(*d*, J=2, 1 H, H–C(10)). – MS.: 170 (M^+, 0), 152 (1.9), 112 (46), 94 (55), 71 (100), 59 (46), 43 (96), 31 (90).

14. *Synthesis of* (±)-*3-(*t-*4'-hydroxy-4'-methyl-*r-*1'-cyclohexyl)butanal* (**28**) *and* (±)-*3-(*c-*4'-hydroxy-4'-methyl-*r-*1'-cyclohexyl)butanal* (**33**).

To a solution of 40 g of $Hg(OAc)_2$ in 120 ml of water, 120 ml of THF and 1 ml of 50% H_2SO_4 were added 19 g of alcohol **74** [41], and the mixture was stirred in a water bath for 18 h [42]. Subsequently, 130 ml of 3M NaOH and then 130 ml of 0.5M $NaBH_4$ in 3M NaOH were added. A diol mixture was obtained (19 g) after extraction with ether which, according to GC., consisted of 70% of **75** and 30% of **76**. The pure diols were treated separately with Ag_2CO_3/*Celite* in benzene [23], and yielded the pure stereoisomers **28** and **33**, respectively. Compound **28** had a strong scent of lily of the valley. – IR. (film): 3400, 2700, 1720. – ^{1}H-NMR.: 0.91 (*d*, J=6.5, 3 H, 3 H–C(4)); 1.13 (*s*, 3 H, H_3C–C(4')); 9.82 (*m*, 1 H, H–C(1)). – MS.: 184 (M^+, 0), 166 (1), 151 (4), 128 (10), 95 (10), 71 (100), 55 (17), 43 (49).

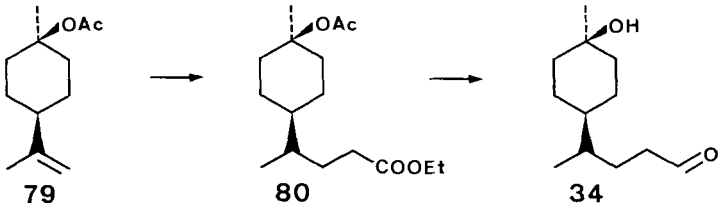
Compound **33** was odorless. – IR. (film): 3420, 2720, 1725. – ^{1}H-NMR.: 0.9 (*d*, J=6, 3 H, 3 H–C(4)); 1.17 (*s*, 3 H, H_3C–C(4')); 9.7 (br.*s*, 1 H, H–C(1)). – MS.: 184 (M^+, 0), 166 (1.3), 151 (3), 71 (100), 43 (53).

15. *Synthesis of* (±)-*4-(*t-*4'-hydroxy-4'-methyl-*r-*1'-cyclohexyl)pentanal* (**29**) *and* (±)-*4-(*c-*4'-hydroxy-4'-methyl-*r-*1'-cyclohexyl)pentanal* (**34**).

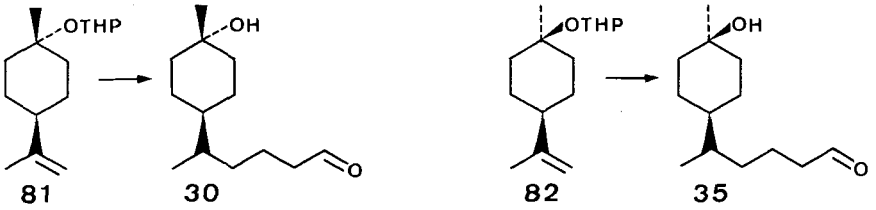


cis-β-Terpenyl acetate (=[*t*(4)-8-*p*-menthen-*r*-1-yl] acetate; **77**, 19 g) in 50 ml of THF was treated with 9-borabicyclo [3.1.1]nonane, then with ethyl bromoacetate [43] yielding 2 g (7%) of acetoxyester **78**. After reduction of the latter with an excess of $LiAlH_4$ the product was oxidized to the strongly odoriferous **29** in excellent yield by the *Fetizon* method [23]. – IR. (film): 3400, 2700, 1725. – ^{1}H-NMR.: 0.844 (*d*, J=5, 3 H, 3 H–C(5)); 1.13 (*s*, 3 H, H_3C–C(4')); 9.68 (*m*, 1 H, 1 H–C(1)). – MS.: 198 (M^+, 0), 180 (2.5), 155 (19), 137 (40), 95 (23), 81 (1), 71 (100), 55 (33), 43 (74).

trans-β-Terpenyl acetate (=[*c*(4)-8-*p*-menthen-*r*-1-yl]acetate; **79**), treated in the manner described above, yielded *via* diester **80** the odorless **34**. – IR. (film): 3400, 2700, 1717. – ^{1} H-NMR.: 0.875 (*d*, J=5,



79 80 34



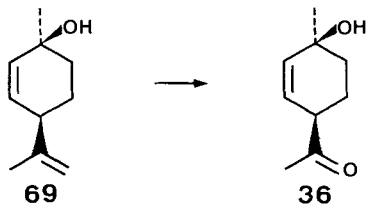
81 30 82 35

3 H, 3 H–C(5)); 1.15 (*s*, 3 H, H_3C–C(4′)); 9.78 (*t*, *J* = 1.5, 1 H, H–C(1)). – MS.: 198 (M^+, 0), 180 (6.5), 155 (15), 137 (41), 71 (100), 55 (30), 43 (64).

16. *Synthesis of* (±)-*5-(*t*-4′-hydroxy-4′-methyl-*r*-1′-cyclohexyl)hexanal* (**30**) *and* (±)-*5-(*c*-4′-hydroxy-4′-methyl-*r*-1′-cyclohexyl)hexanal* (**35**).

The tetrahydropyranyl ether of *cis*-β-terpineol (= *t*(4)-*r*-1-tetrahydropyranyloxy-8-*p*-menthene; **81**) was converted by hydroboration into the corresponding trialkylborane which, after removal of excess diborane by the addition ol limonene, was treated with an excess of freshly distilled acrolein [44]. The product was separated from impurities by means of *Girard* P reagent. Ether cleavage was carried out by means of conc. HCl solution at RT. (15 h). After chromatography on SiO_2 10 g of **30** were obtained. This aldehyde had a powerful and pleasant scent of lily of the valley like the two lower members **28** and **29** of the homologous series. – IR. (film): 3400, 2700, 1720. – ^{1}H-NMR.: 0.844 (*d*, *J* = 5, 3 H, 3 H–C(6)); 1.13 (*s*, 3 H, H_3C–C(4′)); 9.68 (*m*, 1 H, H–C(1)). – MS.: 212 (M^+, 0), 194 (7), 95 (40), 71 (100), 55 (43), 43 (64).

In the same manner the tetrahydropyranyl ether of *trans*-β-terpineol (= *c*(4)-*r*-1-tetrahydropyranyloxy-8-*p*-menthene; **82**) was transformed into **35** which was virtually odorless. – IR. (film): 3400, 2700, 1725. – ^{1}H-NMR.: 0.875 (unresolved *d*, *J* ≃ 4, 3 H, 3 H–C(6)); 1.155 (*s*, 3 H, H_3C–C(4′)); 9.7 (br.*s*, 1 H, H–C(1)). – MS.: 212 (M^+, 0), 194 (7), 95 (40), 71 (100), 55 (43), 43 (64).



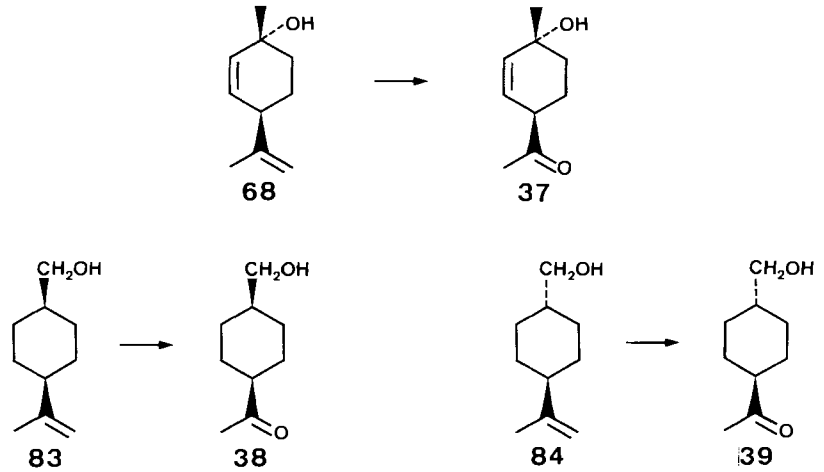
69 36

17. *Synthesis of* (+)-*(1′*R*,4′*S*)-1-(4′-hydroxy-4′-methyl-2′-cyclohexen-1′-yl)ethanone* (**36**).

(+)-(1*S*,4*R*)-2,8-*p*-Menthadien-1-ol (**69**; 2 g) [18], dissolved in the ten-fold quantity of methanol, was treated with an ozone/air mixture until 70% of the quantity of ozone calculated for one double bond had been absorbed. After addition of a large excess of dimethyl sulfide (5 ml) the mixture was allowed to stand for 2 days at RT. (negative iodide starch paper test). Prep. TLC. yielded pure **36** which had a faint spicy odor; $\alpha_D^{20} = +9.3°$ (neat). – IR. (film): 3430, 1710. – ^{1}H-NMR.: 1.22 (*s*, 3 H, H_3C–C(4′)); 2.12 (*s*, 3 H, 3 H–C(2)); 2.94 (*t*, *J* = 6, 1 H, H–C(1′)); 5.7 (*s*, 2 H, H–C(2′), H–C(3′)).

18. *Synthesis of* (+)-*(1′*R*,4′*R*)-1-(4′-hydroxy-4′-methyl-2′-cyclohexen-1′-yl)ethanone* (**37**).

(+)-(1*R*,4*R*)-2,8-*p*-Menthadien-1-ol (**68**) [18] [35], when treated under the same conditions as **69** above, yielded the practically odorless **37**; $\alpha_D^{20} = +7°$ (neat). – IR. (film): 3400, 1710. – ^{1}H-NMR.: 1.20



(*s*, 3 H, H_3C–C(4′)); 2.15 (*s*, 3 H, 3 H–C(2)); 2.98 (*t*, J=6, 1 H, H–C(1′)); 5.68 (*s*, 2 H, H–C(2′), H–C(3′)).

19. *Synthesis of* cis- *and* trans-*1-(4′-hydroxymethyl-cyclohexyl)ethanone (***38** *and* **39**).

cis-8-*p*-Menthen-7-ol (**83**; 3.8 g) [22] were ozonized in 50 ml of methanol at – 30° and subsequently hydrogenated over Pd/C. The product was filtered (2.7 g yield) and purified by chromatography on SiO_2 in hexane/ether 9:1. Pure **38** was virtually odorless. – IR. (film): 3350, 1705. – ^{1}H-NMR.: 2.12 (*s*, 3 H, 3 H–C(2)); 3.35 (*d*, J=4, 2 H, CH_2OH). – MS.: 156 (M^+, 3), 138 (10), 95 (100), 81 (13), 67 (30), 55 (22), 43 (93).

When starting from *trans*-8-*p*-menthen-7-ol (**84**) [22] and applying the same procedure, the *trans*-derivate **39** was obtained as a practically odorless product. – IR. (film): 3450, 1705. – ^{1}H-NMR.: 2.1 (*s*, 3 H, 3 H–C(2)); 3.32 (*d*, J=7, 2 H, CH_2OH). – MS.: 156 (M^+, 3), 138 (11), 95 (100), 81 (11), 67 (29), 55 (21), 43 (83).

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