Structure–Odor Relationships in Monoterpenelactones

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Twelve γ -, δ - and ϵ -monoterpenelactones were synthesized, with seven compounds (**5**, **6**, **7**, **8**, **13**, **13'**, and **15**) being newly formed. The odor of the monoterpenelactones was found to be dependent on the size of their rings and their conformation. Substitution of the equatorial methyl group at C(3) in the δ - and ϵ -monoterpenelactones with a planar molecular shape was necessary for the monoterpenelactones to produce a pronounced maple-like odor.

A considerable quantity of γ - and δ -lactones with the number of carbon atoms from 6 to 16 has been found in milk fat¹⁾ and butter oil,²⁾ the organoleptic properties of which were described as being creamy, sweet, coconut-like, peach-like and milky. On the other hand, the odor of mentholactone (**7'**) is tenacious, and reminiscent of maple syrup or brown sugar. The purpose of this paper is to further describe the relationship between the structures of γ -, δ - and ϵ -monoterpenelactones and their olfactive properties.

Photooxygenation of citronellal (**1**) and subsequent reduction of the resulting hydroperoxides gave hydroxy acids (**2**, **3** and **4**),³⁾ which were subsequently dehydrated to give mono-

terpenelactones (**5**, **6**, **7** and **8**) as shown in Scheme 1. Monoterpenelactones **12** and **13** were synthesized from nerolic acid (**9**) in a similar manner (Scheme 2).

The relative stereochemistry of (R^* , R^*)- and (R^* , S^*)-3,7-dimethyl-6-octen-5-olide (**5** and **6**) was then determined. Inspection of the Drieding models showed that the (R^* , R^*) and (R^* , S^*) isomers had the C-3 CH_3 and C-5 $\text{CH}=\text{C}(\text{CH}_3)_2$ groups in *cis*- and *trans*-1,3 relationships, respectively, and would be expected to exist preferentially in conformations which avoided diaxial opposition of these groups. The nuclear Overhauser effects (NOEs) and coupling constants for the monoterpenelactones in C_6D_6 are shown in Fig. 1. The

Scheme 1

Scheme 2

Fig. 1. NOEs (%) $\curvearrowright$ and Coupling Constants (Hz) $\longleftrightarrow$ for Monoterpenelactones in C_6D_6 .

equatorial protons at the C-2 and C-4 positions of **5** were assigned by the observation of the W-coupling, $^4J_{2\beta,4\beta} = 2.1$ Hz. The large vicinal coupling constants ($^3J_{2\alpha,3} = 11.0$ Hz, $^3J_{3,4\alpha} = 11.7$ Hz, $^3J_{4\alpha,5} = 11.7$ Hz) have been associated with an approximate diaxial interaction in a half-chair form.⁴⁾ The equatorial protons at C-2 and C-4 of **6** were assigned by the observation of the W-coupling, $^4J_{2\beta,4\beta} =$

0.9 Hz, the $^4J_{2\beta,4\beta}$ value of **6** being smaller than that of **5**. For **6**, the $J_{3,4\alpha}$, $J_{4\beta,5}$, $J_{3,4\beta}$ and $J_{4\alpha,5}$ values were similar (7.1, 7.7, 6.0 and 4.5 Hz). The stereochemistry of the δ -lactone ring in **6** was tentatively assigned as a half-boat form on the basis of the coupling constants and the NOE data (see Fig. 1).

The 1H -NMR spectra of **7** and **8** in C_6D_6 showed the presence of exomethylene protons

at δ 4.74 and 4.98 (1H each) and at δ 4.73 and 4.96 (1H each), respectively. Mentholactone (**7'**) and iso-mentholactone (**8'**)⁵⁾ were obtained by hydrogenizing **7** and **8**, respectively. Accordingly, these facts led us to conclude that **7** and **8** were (*R**,*S**)- and (*R**,*R**)-3,7-dimethyl-7-octen-6-olide, respectively. The long-range couplings (*W*) between H_{α} -2 and H_{α} -4 in **7** ($^4J_{2\alpha,4\alpha}=1.8$ Hz) and **8** ($^4J_{2\alpha,4\alpha}=1.4$ Hz) are particularly revealing, since the geometry in the half-chair conformation requires these protons in a planar *W* conformation. The NOE experiments were in agreement with these conformations (see Fig. 1).

The observed coupling constants between H-2 and the allyl protons at C-4 in **12** ($^4J_{2,4\beta}=0.7$ Hz; $^4J_{2,4\alpha}=2.1$ Hz) suggested that $\phi_1=45\pm3^\circ$ and $\phi_2=70\pm4^\circ$. ϕ_1 and ϕ_2 are the dihedral angles between the vinyl plane and allylic carbon-hydrogen bonds, H_{β} -C₄ and H_{α} -C₄, respectively.⁶⁾ The NOEs between the

H_3 -9 and H_2 -4 were in agreement with this conformation as shown in Fig. 1. In a similar manner to that for the conformation analysis of **12**, the preferred conformation of **13** in C_6D_6 was established by the coupling constants between H-2 and the allyl protons at C-4 ($^4J_{2,4\beta}=0.7$ Hz; $^4J_{2,4\alpha}=1.4$ Hz) and by the NOE experiments (see Fig. 1).

Hydrogenation of **7**, **8** and **13** yielded **7'**, **8'** and **13'**, respectively.⁷⁾ 3,7-Dimethyl- γ -octalactones (**14** and **16**) were prepared by the procedure reported by Miyawaki and Yukawa.⁸⁾ The method developed for the synthesis of γ -crotonolactone⁹⁾ was employed with a slight modification for the synthesis of **15**. The relative stereochemistry of these compounds was confirmed by an analysis of their NOEs and/or coupling constants as shown in Figs. 1 and 2.

The odor thresholds (detection threshold, *T*) of the monoterpenelactones and their odor

Fig. 2. Structures and NOEs (%) ($\curvearrowright$) for γ -Monoterpenelactones **14**–**16** in $CDCl_3$.

Table I. OLFACTIVE PROPERTIES OF MONOTERPENELACTONES

No.	Odor description		<i>T</i> (ppm)
	Neat	At 10–20 times higher concentration than the threshold	
5	Dry, maple-like, spicy, oily, floral	Sweet, maple-like, burnt, metallic	1.3
6	Sweet, maple-like, fenugreek-like, spicy, floral	Sweet, chemical, metallic	0.2
12	Cane-sugar-like, maple-like, green	Sweet, maple-like, burnt	0.4
7	Sweet, maple-like, strong, cis-jasmone-like	Sweet, maple-like, roasted, metallic	0.2
8	Dark, maple-like, walnut-like, floral	Coffee-like, roasted	1.6
13	Fenugreek-like, maple-like, spicy	Roasted, sweet, metallic	0.5
7'	Sweet, maple-like, fenugreek-like	Sweet, maple-like, roasted	0.3
8'	Green, dusty, earthy	Sweet, chemical	1.0
13'	Fenugreek-like, maple-like, earthy, spicy	Metallic, sweet, cosmetic	0.2
14	Milky, fatty, sweet, strong	Milky, mild, sweet	0.01
15	Milky, fatty, coconut-like	Slightly sweet, herbaceous	0.1
16	Milky, coconut-like	Milky, mild, earthy	0.02

descriptions neat and at 10–20 times higher concentration than their threshold values are shown in Table I. All of the δ - and ϵ -monoterpenelactones neat, except **8'**, had a maple-like, burnt or roasted odor, which is suitable as a flavor ingredient. Particularly, ϵ -lactone **7** had the most marked maple-like and roasted odor ($T=0.2$ ppm). The maple-like odor of neat **6** and **13'** disappeared at a 10–20 times higher concentration than the odor threshold value. γ -Monoterpenelactones **14–16** had very low odor threshold values and did not possess a maple-like odor, having instead a milky or herbaceous odor. Also, the δ - and ϵ -lactones without a methyl group at C(3) possessed little or no maple-like odor. The substitution of a methyl group at C(3) in the δ - and ϵ -lactones might be necessary for the emergence of a maple-like odor. Replacement of the isopropyl group at C(6) in the ϵ -lactones by an isopropenyl group resulted in an increase in the strength of the maple-like odor. Compounds **8'** and **8**, which had an axial methyl group at C(3), had little or no maple-like odor. These results show that the axial methyl group at C(3) had a negative effect on the maple-like odor.

The aroma compounds developed during food processing, mostly by caramelization,

toasting, baking and roasting, are mainly associated with a respective caramel-like, sweet, nutty and burnt odor impression. It has been suggested that a caramel-like flavor impression (such as that of maltol, furaneol and cyclotene (maple lactone, **17**))¹⁰⁾ is produced by a "three-point interaction".¹¹⁾ According to this theory, on approaching a receptor surface carbonyl, the hydroxy and alkyl (and/or alkenyl) groups of these compounds meet with a corresponding proton donor site (AH), proton-acceptor site (B), and the hydrophobic pocket (X), respectively. In addition, it has been considered that the strong hydrogen bond of a planar alkyl-enol-carbonyl substructure present in cyclic dicarbonyl compounds is required.

The caramel-like odor molecules reported here, however, had no hydroxy group, indicating that the hydrogen bond was not a requirement for a caramel-like odor. Additionally, we would point out that there was some interaction between the molecular functional groups and olfactory receptor site (AH, X) as shown in Fig. 3. The steric barrier for the approach of the monoterpenelactone to the active site of the hypothetical receptor molecule arose from an axial methyl group at C(3) for **8'** (see Fig. 3). The molecular shape of **7** was

Fig. 3. Specific Receptor Interactions of **7** ($T=0.2$ ppm), **8**, **17** ($T=0.3$ ppm) and **18**.

A is the receptor site corresponding to the electronegative group, and X is the receptor site corresponding to the hydrophobic group.

close to that of cyclotene (**17**), and this was also a planar cyclic compound possessing two oxygen atoms and the methyl group as shown in Fig. 3. 3-Ethyl-2-hydroxy-2-cyclopenten-1-one (**18**) has been reported to possess a stronger, sweeter and more caramel character than **17**.¹⁰ The fact that the odor strength increased if a methyl group was substituted by an ethyl group indicates the latter's ideal occupation of the hydrophobic pocket in the cavity of the active site.

Experimental

IR spectra were measured as films on a Hitachi 260-10 spectrometer. ¹H-NMR spectra were recorded in CDCl₃ or C₆D₆ with TMS as an internal standard on a Bruker AM-400 spectrometer. Simulation and iterative refinement of the ¹H-NMR patterns for **5–8**, **7**, **8**, **12**, **13** and **13'** were performed by using the PANIC program.¹² Mass spectra were recorded at 70 eV on a Hitachi M-80B spectrometer, and GLC analyses were performed with a Hewlett-Packard 5710-A. HPLC analyses were performed on a Waters M6000A [column, Cosmosil 5SL, 10 mm ϕ $\times$ 25 cm; solvent, EtOAc–*n*-hexane (1 : 9), 2 ml/min; detected by refractive index].

Methylene blue (MB)-sensitized photooxygenation of citronellal acid (1). EtOH solutions (300 ml) containing **1** (1 g) and MB (0.04 g) were irradiated for one hour in an oxygen stream, using a water-cooled 400W high-pressure mercury lamp (Riko UVL-400HA) in a Pyrex container. The solvent was removed and the photolysate was subjected to silica gel column chromatography (Merck) with an EtOAc eluent to remove the MB. After evaporating the EtOAc, the obtained hydroperoxides were reduced by adding 2 ml of a 50% dimethyl sulfide–benzene solution at 0°C and then by stirring for 4 hr. After evaporating the solvent, the residual oil was chromatographed on a silica gel (50 g) column. The elution was carried out with (1) 10% EtOAc in *n*-hexane (500 ml, FA-1), (2) 33% EtOAc in *n*-hexane (200 ml, FA-2) and (3) EtOAc (400 ml, FA-3). 3,7-Dimethyl-7-hydroxy-5-octenoic acid (**2**, 503 mg) and 3,7-dimethyl-6-hydroxy-7-octenoic acid (a c. 1 : 1 mixture of **3** and **4**, 405 mg) were isolated from the fractions as FA-3 and FA-2, respectively.

Synthesis of 5 and 6. A solution of **2** (100 mg) and CHCl₃ (0.1 ml) was dissolved in benzene (10 ml) followed by silica gel (0.1 g) addition. The resulting mixture was refluxed for 30 min. The reaction mixture was filtered and evaporated to yield a yellow oil which was purified by preparative HPLC to give **5** (40 mg, 44%) and **6** (18 mg, 20%). **5**, EI-MS *m/z* (rel. int.): 168.1143 (M⁺, C₁₀H₁₆O₂, calcd.

168.1150, 43%), 153 (84), 56 (100). IR $\nu_{\max}$ (KBr) cm⁻¹: 1725, 1675, 1250. **6**, EI-MS *m/z* (rel. int.): 168.1148 (M⁺, C₁₀H₁₆O₂, calcd. 168.1150, 32%), 153 (84), 56 (100). IR $\nu_{\max}$ (film) cm⁻¹: 1730, 1680, 1230.

Synthesis of 7 and 8. A solution of a c. 1 : 1 mixture of **3** and **4** (190 mg) and CHCl₃ (0.2 ml) was dissolved in benzene (20 ml). Ac₂O (0.3 g) and AcONa (0.5 g) were then added, and the resulting mixture was refluxed for 1 hr. The reaction mixture was filtered and evaporated to yield a yellow oil, which was purified by preparative HPLC to give **7** (57 mg, 33%) and **8** (63 mg, 37%). **7**, EI-MS *m/z* (rel. int.): 168.1145 (M⁺, C₁₀H₁₆O₂, calcd. 168.1150, 16%), 69 (100). IR $\nu_{\max}$ (film) cm⁻¹: 3075, 1725, 1650, 1270, 900. **8**, EI-MS *m/z* (rel. int.): 168.1151 (M⁺, C₁₀H₁₆O₂, calcd. 168.1150, 13%), 69 (100). IR $\nu_{\max}$ (film) cm⁻¹: 3080, 1725, 1650, 1260, 900.

Synthesis of nerolic acid (9). According to the reported procedure,¹³ neral (10 g) afforded **9** (6.6 g, 60%).

MB-sensitized photooxygenation of nerolic acid (9). Compound **9** was photooxygenated as already described. The reaction mixture was then separated into five fractions, F-1 (*n*-hexane, 200 ml), F-2 (EtOAc–*n*-hexane = 1 : 10, 400 ml), F-3 (EtOAc–*n*-hexane = 1 : 5, 350 ml), F-4 (EtOAc–*n*-hexane = 1 : 2, 350 ml), and F-5 (EtOAc, 400 ml). Compounds **10** (393 mg) was obtained from F-5. The subsequent preparative TLC (eluting with EtOAc–*n*-hexane = 3 : 2) of F-3 and F-4 gave **11** (*R*_f 0.35, 375 mg).

(2Z,5E)-3,7-Dimethyl-7-hydroxy-2,5-octadienoic acid (10). EI-MS *m/z* (rel. int.): 166.1005 (M⁺ – H₂O, C₁₀H₁₄O₂, calcd. 166.0994, 8%), 151 (19), 121 (100). IR $\nu_{\max}$ (film) cm⁻¹: 3450, 3300–2500, 1685, 1640, 1160, 980. NMR δ_{H} (CDCl₃): 1.31 (6H, s), 1.90 (3H, d, *J* = 1.4 Hz), 3.36 (2H, d, *J* = 6.7 Hz), 5.61 (1H, dt, *J* = 15.6, 6.7 Hz), 5.72 (1H, dt, *J* = 15.6, 1.1 Hz), 5.72 (1H, m), 6.3 (2H, br. s).

(Z)-3,7-Dimethyl-6-hydroxy-2,7-octadienoic acid (11). mp 75°C. EI-MS *m/z* (rel. int.): 166.0999 (M⁺ – H₂O, C₁₀H₁₄O₂, calcd. 166.0994, 26%), 151 (6), 97 (100), 96 (98), 95 (81). IR $\nu_{\max}$ (CHCl₃) cm⁻¹: 3590, 3300–2500, 3070, 1685, 1635, 1250, 905. NMR δ_{H} (CDCl₃): 1.72–1.77 (5H, m), 1.94 (3H, d, *J* = 1.3 Hz), 2.44 and 2.91 (1H each, ddd, *J* = 12.4, 8.4, 5.6 and 12.4, 8.4, 8.4 Hz, respectively), 4.04 (1H, dd, *J* = 7.8, 4.8 Hz), 4.85 and 4.98 (1H each, m), 5.76 (1H, m), 6.4 (2H, br. s).

Synthesis of 3,7-dimethyl-2,6-octadien-5-olide (12). A solution of **10** (200 mg) and CHCl₃ (0.2 ml) was dissolved in benzene (20 ml). Silica gel (0.2 g) was then added, and the resulting mixture was refluxed for 30 min. The reaction mixture was filtered and evaporated to yield a yellow oil, which was purified by preparative TLC (eluting with EtOAc–*n*-hexane = 1 : 2) to yield **12** (*R*_f 0.3–0.4, 105 mg).¹⁴

Synthesis of 3,7-dimethyl-2,7-octadien-6-olide (13). A solution of **11** (183 mg) and CHCl_3 (0.2 ml) was dissolved in benzene (20 ml). *p*-TsOH (0.01 g) was then added, and the resulting mixture was refluxed for 1 hr. The reaction mixture was subjected to alumina column chromatography, using an Et_2O eluent to remove the acid. The resulting mixture was separated by preparative TLC (eluting with EtOAc -*n*-hexane = 1:1) to give **13** (*Rf* 0.4–0.7, 95 mg). **13**, EI-MS *m/z* (rel. int.): 166.1001 (M^+ , $\text{C}_{10}\text{H}_{14}\text{O}_2$, calcd. 166.0994, 6%), 151 (5), 95 (100). IR ν_{max} (film) cm^{-1} : 3080, 1695, 1660, 1645, 1280, 910.

*Synthesis of (*R**,*S**)- and (*R**,*R**)-3,7-dimethyl-6-octanolide (7' and 8') and 3,7-dimethyl-2-octen-6-olide (13').* Hydrogenation of **7**, **8** and **13** over Pd/CaCO_3 yielded **7'**, **8'** and **13'**, respectively.⁷⁾ **13'**, EI-MS *m/z* (rel. int.): 168.1155 (M^+ , $\text{C}_{10}\text{H}_{16}\text{O}_2$, calcd. 168.1150, 1%), 125 (100). IR ν_{max} (film) cm^{-1} : 3050, 1695, 1640, 1280.

*Synthesis of (*R**,*S**)- and (*R**,*R**)-3,7-dimethyl-4-octanolide (14 and 16).* These compounds were prepared by the procedure reported by Miyawaki and Yukawa.⁸⁾ TLC (eluting with 1:1 Et_2O -*n*-hexane) of the product (100 mg) gave **14** (*Rf* 0.50, 29 mg) and **16** (*Rf* 0.42, 62 mg).

Synthesis of 3,7-dimethyl-2-octen-4-olide (15). This compound was prepared by the method described by Price and Judge,⁹⁾ using a *c.* 1:2 mixture of **14** and **16** (85 mg, 0.5 mmol) as the starting material. Preparative GLC of the reaction mixture gave **15** (56 mg, 67%). **15**, EI-MS *m/z* (rel. int.): 168.1144 (M^+ , $\text{C}_{10}\text{H}_{16}\text{O}_2$, calcd. 168.1150, 10%), 153 (3), 98 (100), 69 (100). IR ν_{max} (film) cm^{-1} : 3100, 1755, 1645, 1170.

Sensory evaluation. Threshold values for the lactones were determined by the "2/5 test" (selecting the same two out of five samples).¹⁵⁾ The panelists (seven males) ranged in age from approximately 22 to 29 years of age. Each had extensive experience and proven reliability in odor

judgements. The sessions were conducted mid-morning each day.

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