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Article

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Structure-Odor Relationship Study on Geraniol, Nerol and Their Synthesized Oxygenated Derivatives

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Abstract

Despite being isomers having the same citrus-like, floral odor, geraniol, **1,** and nerol, **3**, show different odor thresholds. To date, no systematic studies are at hand elucidating the structural features required for their specific odor properties. Therefore, starting from these two basic structures and their corresponding esters, namely geranyl acetate, **2,** and neryl acetate, **4**, a total of 12 oxygenated compounds was synthesized and characterized regarding retention indices (RI), mass spectrometric (MS) and nuclear magnetic resonance (NMR) data. All compounds were individually tested for their odor qualities and odor thresholds in air (OT). Geraniol, the *Z*-isomer, with an OT of 14 ng/L, was found to be more potent than its *E*-isomer, nerol, which has an OT of 60 ng/L. However, 8-oxoneryl acetate was the most potent derivative within this study exhibiting an OT of 8.8 ng/L, while 8-oxonerol was the least potent with an OT of 493 ng/L. Interestingly, the 8-oxo derivatives smell musty, fatty, while the 8-hydroxy-derivatives show odor impressions similar to those of **1** and **3**. 8-Carboxygeraniol was found to be odorless, while its *E*-isomer, 8-carboxynerol, showed fatty, waxy and greasy impressions. Overall, we observed that oxygenation on C-8 affects mainly the odor quality, while the *E/Z* position of the functional group on C-1 affects the odor potency.

Keywords

8-Hydroxygeraniol; Odor threshold in air; Retention indices; Gas Chromatography-Olfactometry; Mass Spectrometry.

Introduction

Geraniol, **1**, or (2E)-3,7-dimethylocta-2,6-dien-1-ol, and its *Z*-isomer nerol, are fragrant substances of great value.[1] The smell of geraniol has previously been described as sweet, fruity and berry-like, while nerol has been reported as having floral, citrus-like and sweet smell properties.[2] Geraniol, **1**, and geranyl acetate, **2**, are major components of the essential oil of *Cymbopogon martinii*, Roxb. Wats. var. motia known as palmarosa which is commonly obtained from its leaves and flowering tops.[3] Besides being used as a scenting substance in soaps, perfumes and cosmetics, palmarosa oil is a potent mosquito repellent, antiseptic and has also pain-relieving properties.[3] Various studies further show that **1** has anti-tumor activity against various cancer cells, both *in vitro* and *in vivo.*[4, 5] Geraniol, **1**, has been reported to exert several other pharmacological effects such as antimicrobial, antibacterial, anti-inflammatory, and anti-oxidant effects, as well as neuro-protectivity and hepato-protectivity.[6] **1** has also been shown to exert anticonvulsant effects which has been proven to be independent of benzodiazepine receptors.[7] Nerol, **3**, or (2*Z*)-3,7-dimethylocta-2,6-dien-1-ol, is a monoterpene which can be found in various medicinal plants such as *Lippia* spp and *Melissa officinalis* L. These species are renowned for their antimicrobial, antioxidant and antiviral properties due to the presence of nerol.[8-10] It was also shown that **3,** just like several other monoterpene alcohols, exerts an anxiolytic effect in mice and can also be used for the treatment of anxiety and restlessness.[11] In addition, nerol is not only applied as an odorant in fragrances, soaps, and shampoos but is also added to household cleaners and detergents.[12] Neryl acetate, **4**, was found as one of the major compounds isolated from the essential oil of the curry plant *Helichrysum italicum (*Asteraceae*)* which is known for its anti-inflammatory, antioxidant, fungicidal, and astringent effects.[13]

Moreover, the essential oil of *H. italicum* is used as an emollient and as a fixative in perfumes due to its intense odor.[13] Still, the smell of neryl acetate is described in literature as rose-like, and not spicy, curry-like as one might assume from its dominant presence in *H. italicum* essential oil.[14]

Apart from the natural occurrence of the above-mentioned compounds **1**-**4**, a series of derivatives has been observed both in plants and animals. After oral administration of geraniol, 8-hydroxygeraniol and 8-carboxygeraniol were isolated as metabolic products from the urine of rats.[15] Interestingly, the carbon 8-hydroxylation of geraniol and nerol is also the first step in the biosynthesis of indole alkaloids in the higher plant *C. roseus.*[15] 8-Hydroxygeraniol and 8-hydroxynerol were further found as glycosidically bound monoterpenes in Shiraz and Muscat of Alexandria leaves and berries,[16] and as aglycones in nectarines.[17] 8-Carboxygeraniol, also known as foliamenthoic acid, was isolated in small amounts from Tongling white ginger, and was found as a secoiridoid derivative, foliamenthin, in *Menyanthes trifoliata.*[18] Geranyl and neryl acetates, **2**, and **4**, are also present in the peel and leaf oils of lemon and lime species belonging to the family of Rutaceae,[19] as well as in the peel, flowers (neroli) and leaves (petitgrain) of bitter orange (*Citrus aurantium* L.).[20] Geranyl acetate can be further found in sweet flag leaves at different growing phases.[21] Its odor was described in literature as woody, floral and rosy.[2] Among the oxidation products of the acetates, **2**, and **4**, the 8-oxogeranyl acetate is the only compound that was found as constituent of the attractant pheromone blend that is secreted by the Australian predaceous bug, *Oechalia schellenbergii* [22] (Table 1). Apart from that, no systematic data is available, on the odor characteristics of these metabolites or derivatives, or of any other physiological effects of these compounds on humans or animals. To close this gap, the aim of our study was to systematically evaluate the odor qualities and odor thresholds of these substances as we previously did in a comparative approach for the related derivatives of linalool and linalyl acetate.[23] To achieve this aim, we synthesized, starting from geraniol, nerol and their acetates, reported metabolites and hypothetical derivatives of these acyclic monoterpenes following the same study design as in our previous investigation. The aim was to allow for a comprehensive analytical and olfactory evaluation, and to establish an extended substance library aiding future analytical research, thereby comprising data on retention indices (RI values) as well as mass spectrometric and nuclear magnetic resonance data.

Materials and Methods

Chemicals

Geraniol, nerol, geranyl acetate, neryl acetate, selenium dioxide, sodium borohydride, methanol anhydrous, ethanol, dioxane, *tert*-butyl alcohol, 2-methyl-2-butene, sodium chlorite, sodium dihydrogen phosphate, ethyl acetate, hexane, magnesium sulfate were purchased from Aldrich (Steinheim, Germany), and diethyl ether from Fisher Scientific (Loughborough, UK).

General methods

All reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were dried before use to remove moisture using appropriate drying agents. All reactions were monitored by thin-layer chromatography (TLC) using Kieselgel 60 F_{254} plates (Merck, Darmstadt, Germany). Visualization of the reaction components was achieved using ultraviolet (UV) fluorescence (254 nm) and potassium permanganate ($KMnO_4$) staining. Column chromatography was carried out over silica gel 60. The yields reported are after purification. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in deuterated solvents and chemical shifts (δ) are quoted in parts per million (ppm) calibrated to tetramethylsilane (TMS) (^{1}H and ^{13}C). Coupling constants (*J*) were measured in Hertz (Hz). The identity of all intermediates and synthetic products was determined by electron ionization mass spectrometry (EI-MS).

Nuclear Magnetic Resonance (NMR) Spectra

^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) on Avance 360 and Avance 600 spectrometers (Bruker Biospin, Rheinstetten, Germany) at room temperature operated at 360 or 600 MHz (^{1}H) and 90 or 150 MHz (^{13}C), respectively, with TMS as internal standard.

Gas chromatography-olfactometry (GC/O) and GC-Electron Ionization -Mass Spectrometry (GC-EI-MS)

GC-O analyses were performed with a Trace GC Ultra (Thermo Fisher Scientific GmbH, Dreieich, Germany) by using the following capillaries: FFAP (30 m × 0.32 mm i.d. fused silica capillary, free fatty acid phase FFAP, film thickness 0.25 µm; Chrompack, Mühlheim, Germany) and DB5 (30 m × 0.32 mm i.d. fused silica capillary DB-5, film thickness 0.25 µm; J&W Scientific, Fisons Instruments, Mainz-Kastel, Germany). The helium carrier gas flow was set for FFAP and DB5 capillary columns at 2.5 mL/min and 1.2 mL/min, respectively. The compounds eluting at the end of the capillaries were split with a Y-splitter, ratio 1:1 (v/v) (J&W Scientific) and transferred via two deactivated capillaries (0.5 m x 0.2 mm) (J&W Scientific) to a flame ionization detector and a heated sniffing port (temperature: 250 °C). The samples were applied onto the capillary using a cold-on-column injector at 40 °C. After 2 min, the oven was heated at a rate of 10 °C/min to 240 °C and held for 7 min (DB-FFAP) or to 280 °C and held for 5 min (DB-5), respectively.

GC-EI MS analyses were performed with an MSD 5975C (Agilent Technologies, Waldbronn, Germany) and an ITQ 900 (Thermo Fisher Scientific, Dreieich, Germany) with the capillaries described above. Mass spectra in the electron impact mode (EI-MS) were generated at 70 eV.

Retention indices (RI)

Linear retention indices (Table 1) were determined by GC-O using mixtures of individual odorants dissolved in dichloromethane together with a series of *n*-hydrocarbons (C6–C34) dissolved in *n*-pentane, according to the method previously described.[24]

Evaluation of odor quality

The odor qualities were determined during GC-O evaluation with the aid of seven panelists (one male, six females, aged 28-33) who were trained volunteers from the University of Erlangen, exhibiting no known illness at the time of examination and with audited olfactory function.

In preceding weekly training sessions the assessors were trained for at least half a year in recognizing orthonasally about 140 selected known odorants such as linalool, benzaldehyde, *E*-2-nonenal, and vanillin at different concentrations according to their odor qualities and in naming these according to an in-house developed flavor language. The odorants were presented to the panel in 140 mL Weck jars (J. Weck GmbH u. Co. KG, Wehr-Öflingen, Germany) as aqueous solutions that were prepared following two protocols: 1) Either an ethanolic stock solution of the odorant was prepared by dissolving the reference compounds in ethanol abs. in given concentrations, followed by dilution of the odorant stock solution with tap water to reach about a ten-fold concentration of the odorant above its respective odor threshold in water, so that clear smell perception was ensured, thereby taking care, that ethanol content remained limited to a minimum, or 2) the pure odorant was directly weighed and dissolved in tap water, again with the goal of reaching about a ten-fold concentration of the odor threshold value in water of the respective compound.

With regard to the GC-O experiments that were carried out on the synthesized compounds, samples were evaluated by each panelist repeatedly on different days, as they performed dilution analyses, as well as on different capillary columns (DB-FFAP and DB-5). Thereby, panelists were informed about elution times of the compounds to ensure that inhalation corresponded with substance elution from the sniffing port, and were asked to relate the naming of their sensory impressions to smell impressions that they recalled from training, if possible.

Determination of odor thresholds

Odor thresholds were determined in air following the procedure described by Czerny et al. [25] using *E*-dec-2-enal as an internal odor standard. According to this procedure, E-dec-2-enal and the respective target compound were dissolved in dichloromethane at known concentrations, in each case providing one stock solution comprising both odorants. This stock solution was diluted step-wise by a factor 1:2 (v/v), and all dilutions were applied to HRGC/O until no odor was perceivable. From the flavor dilution (FD) factors and the relative concentrations of standard and target compound, the odor threshold values in air were then calculated as previously described.[25] The detection odor thresholds of the panel were calculated as the geometric mean of the individual thresholds according to Czerny et al. [26]

Syntheses, general procedures

Procedure 1.

Generally, the method of Wakayama et al. [27] was used (Figure 1). Compounds **1-4** and selenium dioxide (SeO_2) (1 eq.) were dissolved in dioxane/ethanol (9:1, v/v), and the solution was heated at 80 °C for 5 h. After removal of selenium deposit by double filtration, the solvent was removed under reduced pressure using a rotary evaporator. The residue was purified twice by flash chromatography on silica gel 60 (Merck), with a mobile phase of hexane/ethyl acetate, affording the crude compounds **5-8.**

(2E, 6E)-8-Hydroxy-2,6-dimethylocta-2,6-dienal (5), 8-Oxogeraniol. Compound **5** was prepared following procedure 1 from **1** (1.9 g, 12.9 mmol) and SeO_2 (1.4 g, 12.9 mmol) in 30 mL dioxane/ethanol (9:1, v/v). Flash chromatographic purification with hexane/ethyl acetate (1:1, v/v) yielded 268 mg (12.4 %) of **5** as yellow oil. ^1H NMR (360 MHz, $CDCl_3$) δ ppm 9.38 (s, 1 H), 6.46 (t, *J*=6.70 Hz, 1 H), 5.45 (t, *J*=6.24 Hz, 1 H), 4.11 (d, *J*=7.04 Hz, 2 H), 2.49 (q, *J*=7.57 Hz, 2 H), 2.10 - 2.15 (m, 2 H), 1.75 (s, 3 H), 1.70 (s, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm 194.7, 153.2, 139.1, 137.3, 124.1, 40.1, 27.0, 16.0, 8.8. MS (EI) *m/z* (%) (rel.int.): 168 [M^+] (1), 136(8), 135(81), 121(88), 105(66), 91(88), 79(100), 77(73), 67(26), 55(45).

(2E, 6E)-3,7-Dimethyl-8-oxoocta-2,6-dien-1-yl acetate (6), 8-Oxogeranyl acetate. Compound **6** was prepared following procedure 1 from **2** (2.1 g, 10.5 mmol) and SeO_2 (1.2 g, 10.5 mmol) in 30 mL dioxane/ethanol (9:1, v/v). Flash chromatographic purification with hexane/ethyl acetate (3:1, v/v) yielded 438 mg (20 %) of **6** as pale yellow oil. ^1H NMR (360 MHz, $CDCl_3$) δ ppm 9.37 (s, 1 H), 6.43 (t, *J*=7.20 Hz, 1 H), 5.37 (t, *J*=7.04 Hz, 1 H), 4.58 (d, *J*=7.04 Hz, 2 H), 2.48 (q, *J*=7.34 Hz, 2 H), 2.22 (t, *J*=7.72 Hz, 2 H), 2.02 - 2.04 (m, 3 H), 1.73 (s, 6 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 195.1, 171.0, 153.3, 140.3, 140.0, 119.6, 61.1, 37.7, 27.0, 21.0, 16.4, 9.2.MS

(EI) *m/z* (%) (rel.int.): 210 [M^+] (1), 150(3), 135(56), 121(100), 107(39), 91(72), 79(55), 77(48), 67(16), 55(18).

(2E, 6Z)-8-Hydroxy-2,6-dimethylocta-2,6-dienal (7), 8-Oxonerol.

Compound **7** was prepared following procedure 1 from **3** (2.16 g, 14 mmol) and SeO_2 (3 g, 27 mmol) in 30 mL dioxane/ethanol (9:1, v/v). Flash chromatographic purification with hexane/ethyl acetate (6:1 to 1:1, v/v) yielded 200 mg (8.5 %) of **7** as yellow oil. ^1H NMR (360 MHz, $CDCl_3$) δ ppm 9.39 (s, 1 H), 6.46 (td, *J*=7.27, 1.14 Hz, 1 H), 5.50 (t, *J*=6.93 Hz, 1 H), 4.14 (d, *J*=7.00 Hz, 2 H), 2.45 - 2.48 (m, 2 H), 2.26 - 2.31 (m, 2 H), 1.78 (s, 3 H), 1.75 (s, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm 195.1, 153.2, 139.8, 138.4, 125.5, 58.9, 30.5, 27.5, 23.2, 9.2. MS (EI) *m/z* (%) (rel.int.): 168 [M^+] (1), 149(8), 135(38), 121(46), 107(33), 105(41), 91(93), 79(100), 77(89), 67(33), 55(55).

(2Z, 6E)-3,7-Dimethyl-8-oxoocta-2,6-dien-1-yl acetate (8), 8-Oxoneryl acetate.

Compound **8** was prepared following procedure 1 from **4** (2 g, 10.1 mmol) and SeO_2 (1.2 g, 10.3 mmol) in 20 mL dioxane/ethanol (9:1, v/v). Flash chromatographic purification with hexane/ethyl acetate (6:1 to 1:1, v/v) yielded 171 mg (8 %) of **4** as yellow oil. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 9.39 (s, 1 H), 6.33 - 6.62 (m, 1 H), 5.43 (t, *J*=7.18 Hz, 1 H), 4.48 - 4.64 (m, 2 H), 2.48 (q, *J*=7.55 Hz, 2 H), 2.26 - 2.35 (m, 2 H), 2.04 (s, 3 H), 1.80 (s, 3 H), 1.75 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 195.1, 170.9, 152.9, 140.8, 139.8, 120.5, 60.7, 30.5, 27.3, 23.2, 21.0, 9.2. MS (EI) *m/z* (%) (rel.int.): 210 [M^+] (1), 150(4), 135(63), 121(100), 105(45), 91(74), 79(67), 77(55), 67(16), 55(19).

Procedure 2.

Generally, the method of Liu et al. [28] was used (Figure 1). Compounds **5-8** and sodium borohydride ($NaBH_4$) (2 eq.) were dissolved in dry methanol. The solution was stirred at -10 °C. After 1 h, water was added and the reaction mixture was extracted with dichloromethane. The organic layer was dried over sodium sulfate. After removal of the solvent, the residue was purified by flash chromatography on silica gel 60 (Merck), with a mobile phase of hexane/ethyl acetate, affording the crude compounds **9-12**. As this approach has been previously reported as rather a mild-selective procedure,[29] all target compounds were specifically analyzed by GC-MS and NMR and compared to data reported in literature to exclude potential side-reactions.

(2E,6E)-2,6-Dimethylocta-2,6-diene-1,8-diol (9), 8-Hydroxygeraniol. Compound **9** was prepared following procedure 2 from **5** (117 mg, 0.69 mmol) and $NaBH_4$ (78 mg, 2.1 mmol) in 10 mL dry methanol. Flash chromatographic purification with hexane/ethyl acetate (3:1, v/v) yielded 83.6 mg (70 %) of **9** as colorless oil. ^1H NMR (360 MHz, $CDCl_3$) δ ppm 5.34 - 5.46 (m, 2 H), 4.14 (d, *J*=6.81 Hz, 2 H), 3.99 (s, 2 H), 2.12 - 2.19 (m, 4 H), 1.68 (s, 3 H), 1.58 (s, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm 139.1, 135.2, 125.6, 124.0, 69.0, 59.3, 39.1, 27.1, 16.2, 13.8.MS (EI) *m/z* (%) (rel.int.): 169 [M^+-1] (1), 151(5), 137(9), 121(20), 119(35), 105(24), 93(40), 91(100), 67(99), 55(22). The ^1H NMR data fully agreed with an earlier report.[30]

(2E, 6E)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (10), 8-Hydroxygeranyl acetate.

Compound **10** was prepared following procedure 2 from **6** (17.5 mg, 0.083 mmol) and $NaBH_4$ (41 mg, 1.1 mmol) in 10 mL dry methanol. Flash chromatographic purification with hexane/ethyl acetate (3:1, v/v) yielded 11.4 mg (64.5 %) of **10** as colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 5.31 - 5.39 (m, 2 H), 4.58 (d, *J*=7.18 Hz, 2 H), 3.99 (d, *J*=4.91 Hz, 2 H), 2.17 (q, *J*=7.43 Hz, 2 H), 2.07 - 2.12 (m, 2 H), 2.05 (s, 3 H), 1.70 (s, 3 H), 1.66 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 171.2, 141.7, 135.3, 125.2, 118.7, 68.9, 61.4, 39.0, 25.6, 21.0, 16.4, 13.7. MS (EI) *m/z* (%) (rel.int.): 212 [M^+] (1), 152(5), 134(14), 121(8), 119(76), 105(24), 93(30), 91(100), 79(69), 67(82), 55(19). The NMR spectral data agreed with Holsclaw et al. [31]

(2E, 6Z)-2,6-Dimethylocta-2,6-diene-1,8-diol (11), 8-Hydroxynerol.

Compound **11** was prepared following procedure 2 from **7** (25 mg, 0.15 mmol) and $NaBH_4$ (97 mg, 2.5 mmol) in 20 mL dry methanol. Flash chromatographic purification with hexane/ethyl acetate (1:1, v/v) yielded 18.6 mg (72.9 %) of **11** as colorless oil. ^1H NMR (360 MHz, $CDCl_3$) δ ppm 5.34 - 5.51 (m, 1 H), 4.83 - 4.91 (m, 1 H), 4.05 - 4.08 (m, 2 H), 3.98 (brs, 2 H), 2.12 - 2.17 (m, 4 H), 1.73 (s, 3 H), 1.65 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 138.6, 135.6, 125.0, 124.8, 68.6, 58.9, 25.3, 23.3, 13.7. MS (EI) *m/z* (%) (rel.int.): 171 [M^++1] (1), 151(2), 137(10), 121(7), 119(26), 105(15), 93(28), 91(100), 79(88), 67(71), 55(16). The ^1H NMR data agreed with Ono et al. [32]

(2Z, 6E)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (12), 8-Hydroxyneryl acetate.

Compound **12** was prepared following procedure 2 from **8** (66 mg, 0.3 mmol) and $NaBH_4$ (29 mg, 0.7 mmol) in 10 mL dry methanol. Flash chromatographic purification with hexane/ethyl acetate (2:1, v/v) yielded 32.5 mg (48 %) of **12** as colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 5.39 (brs, 1 H), 5.34 - 5.38 (m, 2 H), 4.57 (d, *J*=7.18 Hz, 2 H), 3.99 (s, 2 H), 2.13 - 2.18 (m, 4 H), 2.05 (s, 3 H), 1.77 (s, 3 H), 1.67 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 171.1, 142.0, 135.6, 125.0, 119.6 , 68.7, 61.2, 31.7, 26.0, 23.4, 21.0, 13.63. MS (EI) *m/z* (%) (rel.int.): 212 [M^+] (1), 137(10), 121(7), 119(74), 105(23), 93(26), 91(100), 79(67), 67(77), 55(14), 51(11). The NMR data fully agreed with Tomooka et al. [33]

Procedure 3.

Pinnick oxidation was used for the following syntheses [34] (Figure 1). The aldehydes **5-8** were dissolved in *tert*-butyl alcohol and 2-methyl-2-butene. A solution of sodium chlorite ($NaClO_2$) (9.2 eq., 80%) and sodium dihydrogen phosphate (NaH_2PO_4) (6.9 eq.) in water was added drop-wise over a 10 min period. The reaction mixture was stirred at room temperature (25-30 °C) overnight. Volatile components were then removed under vacuum, the residue was dissolved in 30 mL water and this was extracted twice with 15 mL portions of hexane. The aqueous layer was acidified to pH 3 with HCl and extracted three times with 20 mL of ether. The combined ether layers were washed with 50 mL cold water, dried, purified by flash chromatography on silica gel 60 (Merck), with a mobile phase of hexane/ethyl acetate and concentrated to give **13-16**.

(2E, 6E)-8-Hydroxy-2,6-dimethylocta-2,6-dienoic acid (13), 8-Carboxygeraniol. Compound **13** was prepared following procedure 3 where compound **5** (2.3 g, 14.1 mmol) was dissolved in 50 mL tert-butyl alcohol and 20 mL 2-methyl-2-butene. A solution of $NaClO_2$ (11.7 g, 161 mmol) and NaH_2PO_4 (11.6 g, 97 mmol) in 40 mL water was added dropwise over a 10 min period. Flash chromatographic purification with hexane/ethyl acetate (6:1 to 1.5:2, v/v) yielded 832 mg (32 %) of **13** as pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 6.76 (td, *J*=7.25, 1.50 Hz, 1 H), 5.43 (td, *J*=7.00, 1.50 Hz, 1 H), 4.16 (d, *J*=7.00 Hz, 2H), 2.33 (q, *J*=7.50 Hz, 2H), 2.16 (t, J=7.50 Hz, 2H), 1.81 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 172.1, 146.5, 139.4, 127.1, 124.6, 58.9, 40.4, 27.3, 16.4, 12.8. MS (EI) *m/z* (%) (rel.int.): 166 [M^+-H_2O] (1), 151(19), 148(100), 121(17), 117(16), 105(42), 91(77), 79(50), 77(61), 67(23), 65(30).

(2E, 6E)-8-Acetoxy-2,6-dimethylocta-2,6-dienoic acid (14), 8-Carboxygeranyl acetate.

Compound **14** was prepared following procedure 3 where compound **6** (175 mg, 0.83 mmol) was dissolved in 25 mL *tert*-butyl alcohol and 6 mL 2-methyl-2-butene. A solution of $NaClO_2$ (694 mg, 9.5 mmol) and NaH_2PO_4 (691 mg, 5.7 mmol) in 10 mL water was added dropwise over a 10 min period. Flash chromatographic purification with hexane/ethyl acetate (3:1, v/v) yielded 75.4 mg (40 %) of **14** as pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 6.86 (td, *J*=7.27, 0.94 Hz, 1 H), 5.30 - 5.42 (m, 1 H), 4.59 (d, *J*=7.18 Hz, 2 H), 2.34 (q, *J*=7.43 Hz, 2 H), 2.14 - 2.22 (m, 2 H), 2.05 (s, 3 H), 1.83 (s, 3 H), 1.72 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 173.4, 171.2, 143.9, 140.8, 127.5, 119.2, 61.2, 37.8, 27.0, 20.9, 16.4, 12.0.MS (EI) *m/z* (%) (rel.int.): 226 [M^+] (1), 166 (8), 150(7), 122(11), 121(100), 105(46), 91(37), 77(26), 67(10), 55(5).

(2E, 6Z)-8-Hydroxy-2,6-dimethylocta-2,6-dienoic acid (15), 8-Carboxynerol.

Compound **15** was prepared following procedure 3 where compound **7** (25 mg, 0.15 mmol) was dissolved in 20 mL *tert*-butyl alcohol and 5 mL 2-methyl-2-butene. A solution of $NaClO_2$ (174 mg, 2.4 mmol) and NaH_2PO_4 (210 mg, 2.3 mmol) in 10 mL water was added dropwise over a 10 min period. Flash chromatographic purification with hexane/ethyl acetate (1:1, v/v) yielded 10 mg (37 %) of **15** as yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 6.83 (br. dt, *J*=6.70, 1.20, 1.20 Hz, 1 H), 5.48 (br. t, *J*=7.50, 7.50 Hz, 1 H), 4.12 (d, *J*=7.50 Hz, 2 H), 2.28 - 2.36 (m, 2 H), 2.20 - 2.27 (m, 2 H), 1.84 (s, 3 H), 1.73 - 1.78 (m, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 168.2, 141.4, 140.7, 127.1, 119.2, 60.5, 30.8, 27.2, 23.2, 12.4. MS (EI) *m/z* (%) (rel.int.): 166 [M^+-H_2O] (1), 151(3), 148(100), 133(3), 121(8), 105(10), 91(12), 79(8), 77(11), 67(4), 65(5).

(2E, 6Z)-8-Acetoxy-2,6-dimethylocta-2,6-dienoic acid (16), 8-Carboxyneryl acetate.

Compound **16** was prepared following procedure 3 where compound **8** (65 mg, 0.31 mmol) was dissolved in 15 mL *tert*-butyl alcohol and 5 mL 2-methyl-2-butene. A solution of $NaClO_2$ (290 mg, 4.0 mmol) and NaH_2PO_4 (290 mg, 2.4 mmol) in 10 mL water was added dropwise over a 10 min period. Flash chromatographic purification with hexane/ethyl acetate (2:1, v/v) yielded 13.3 mg (19 %) of **16** as yellow oil. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 6.87 (t, *J*=6.99 Hz, 1 H), 5.42 (t, *J*=7.37 Hz, 1 H), 4.56 (d, *J*=7.18 Hz, 2 H), 2.33 (q, *J*=7.30 Hz, 2 H), 2.24 - 2.28 (m, 2 H), 2.05 (s, 3 H), 1.85 (s, 3 H), 1.79 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 173.0, 171.1, 144.0, 141.2, 128.0, 120.2, 61.0, 31.2, 27.3, 23.3, 21.0, 12.0. MS (EI) *m/z* (%) (rel.int.): 226 [M^+] (1), 166(8), 151 (7), 148(5), 121(100), 105(48), 91(40), 77(33), 67(11), 55(6).

Results and Discussion

The odor qualities of **1**-**4**, and their synthesized oxygenated derivatives were investigated by trained panelists using GC-O. The obtained odor attributes are shown in Table 2. This procedure offers the advantage that compounds that might be present as odor-active impurities accompanying the reference compound are separated from the target odorants during the chromatographic separation step. Consequently, an influence of such components on the results is ruled out. Also, odor thresholds can be compared to each other on an absolute basis without interference with any matrix system as would be the case e.g. when determining odor thresholds in water, oil or solid matrices. Potential pitfalls may arise in GC-O if panelists do not take care to inhale at the time point of odorant elution from the GC column so that they specifically need to be instructed on elution times as done in the present study. Moreover, the chromatographic shape of the substances may vary between different columns of different polarity. Accordingly, it is recommendable to perform the experiments on capillaries with different polarities, as is done in the present study. Results obtained were reproducible and consistent as the components were evaluated more than once on different columns at different days. In addition, no changes in odor were observed when panelists olfactorily evaluated different steps of concentration. It is worth mentioning that any impurity that might be still present with our synthesized compounds did not interfere in the odor property owing to the fact that elution by GC-O on different capillary columns revealed the pure compounds without any interferences from even minute amounts that may occur for example from organo-selenium by-products.

In general, geraniol, **1**, geranyl acetate, **2**, and nerol, **3**, shared the main attributes citrus-like, floral, sweet and fruity with the sole exception of neryl acetate, **4**, which was described with unexpected odor attributes, namely clove-like and phenolic. Panelists (three out of seven) specifically reported an olfactory similarity to the characteristic clove constituent 4-eugenol.

Geraniol, **1**, was categorized by our panel as smelling citrus-like as in previous studies.[35] However, this odor descriptor was more clearly specified by some individuals to smell like orange peel and neroli. Additional odor attributes named for **1** were fresh and fatty as perceived by 43% of the subjects while only 29% gave the attributes soapy and sweet. The odor of geranyl acetate, **2**, was further described as sweet and floral by 28% of the panel, while only two panelists used the terms soapy and fruity. On the other hand, other odor attributes like soapy and floral were given to nerol, **3**, by 29% of the panel. Apart from that, 44-55% of the panel used the attribute lemon-like as a more precise descriptor for **3**. The odor of neryl acetate, **4**, was perceived by 42% of the panel as floral, sweet and by 29% as clove-like, phenolic as previously mentioned. Only one panelist perceived **4** as fatty-dusty. Despite being rated by the panelists as an intense odorant, one panelist was anosmic to **4** even when directly smelling the substance in its pure oil-form from the bottle.

Regarding the odor qualities of the oxygenated derivatives, most of the 8-oxo derivatives were predominantly described by our panel as fatty, musty whereas the 8-oxogeranyl acetate, **6**, and the 8-oxoneryl acetate, **8**, were rated as citrus-like by 42% and 57% of the panel, respectively. On the other hand, the 8-hydroxy derivatives showed odor attributes comparable to those of the respective parent alcohols or acetates. Accordingly, these attributes comprised the main impressions citrus-like, floral, soapy and fruity. In addition to these smell impressions, half of the panel rated the smell of 8-hydroxynerol, **11**, rather unexpectedly, as sweet and vanilla-like. Apart from that, it is interesting to note that 8-hydroxyneryl acetate, **12**, was the sole substance that all panelists unequivocally agreed on as being citrus-like, with the exception of only one panelist who was anosmic to this substance.

In contrast to this, all 8-carboxy derivatives showed plasticine-like, greasy and waxy smells, with the sole exception of 8-carboxygeraniol, **13,** which was unequivocally perceived as odorless by all panelists, even at a concentration of 500 µg/mL. However, this plasticine-like odor could not be further specified by the panel, as they could not relate this impression to specific odor references. Nevertheless, this is most likely due to the fact that the smell of plasticine as product of daily use is rather a complex odorant mixture than a single compound.

Interestingly, one panelist described the smell of both 8-carboxynerol, **15**, and 8-carboxyneryl acetate, **16**, as green and dill-like. Moreover, these two attributes were consistently reported by this panelist whenever smelling the two substances, even at different concentrations and on different days. On the other hand, sweet and coconut-like were recorded as attributes by 43% of the panel for the 8-carboxygeranyl acetate, **14**, while only one subject named coconut-like for its isomer, **16**. The same panelist who was anosmic to neryl acetate, **4**, as mentioned earlier, was also anosmic to the 8-carboxynerol **15** at the concentrations evaluated in this study, i.e. a concentration of 220 µg/mL.

With regard to the odor thresholds of the investigated compounds, it became clear, as shown in Figure 2A, that geraniol is the most potent compound (14 ng/L_{air}) compared to its acetate, **2**, and its corresponding oxygenated derivatives **5, 6, 9, 10** and **14**. Thereby, 8-hydroxygeraniol, **9**, with an OT of 340 ng/L_{air}, was the least potent compound in this substance group. In general, the OT values of geranyl acetate, **2**, and its oxygenated derivatives ranged between these OT values, and predominantly between 22 ng/L_{air} and 66 ng/L_{air}.

It can be observed that oxidation of C-8 of geraniol to 8-oxogeraniol led to an increase in the odor threshold by a factor of 13 (194 ng/L_{air}), thereby turning the citrus-like odor of geraniol to a fatty-musty smell. Reduction of the aldehyde group to the corresponding alcohol, the 8-hydroxygeraniol, retained the citrus-like, fresh odor but led to a further decline in odor potency (340 ng/L_{air}). Further oxidation of the 8-oxogeraniol to the 8-carboxygeraniol resulted in total odor loss. This demonstrates that an increase in polarity at C-8 obviously reduces odor potency. This finding is in agreement with our observations in our previous structure-odor relationship study of linalool and its C-8 oxygenated derivatives.[23] Accordingly, it appears that not only the presence of the OH-group at C-1 in geraniol or at C-3 in linalool defines the citrusy character and high odor potency, but that modification at C-8 also influences both odor quality and potency.

Despite being isomers and having comparable smell, nerol, **3**, was found to be less potent than **1** by a factor of 4 (odor threshold: 60.5 ng/L_{air}). Still, it is the most potent substance among its oxygenated derivatives, comparable to what we observed for geraniol. Introduction of the aldehyde function at C-8 of nerol, giving 8-oxonerol, not only changed the smell from citrus-like to musty but also increased the threshold to 493 ng/L_{air}. On the other hand, a hydroxy-function at C-8, giving 8-hydroxynerol, retained the citrus-like main impression but additionally provoked a sweet, vanilla-like note that was perceived by almost half of the panel. The 8-carboxynerol was found to be the most potent odorant amongst the nerol oxidation derivatives with a threshold value of 268 ng/L_{air}; however, it exhibited a greasy, waxy odor. Apparently, increase of the polarity of the C-8 oxygenated functional group in nerol results in an increase of potency which is opposite to the observations made for linalool and geraniol and their derivatives. This consideration is, however, made regardless of the odor quality of the respective compounds which also changed as discussed before.

Regarding the acetate derivatives, 8-oxogeranyl acetate was found to be the most potent compound (22 ng/L_{air}) among the geranyl acetate derivatives; it was dominated by a musty, dusty odor character. The alcoholic derivative, 8-hydroxygeranyl acetate, retained the citrus-like odor but with a 3-fold higher odor threshold value (65 ng/L_{air}). Thus, the odor quality and threshold value of the 8-hydroxygeranyl acetate are nearly similar to those of the geranyl acetate. An acid moiety at C-8 in the 8-carboxygeranyl acetate produced a decrease in the odor threshold value to 39 ng/L_{air}; however, the smell turned from citrus-like to sweet-coconut and plasticine-like.

Overall, the term musty was used as a main descriptor for the odor of all the 8-oxo derivatives, mainly 8-oxogeraniol, 8-oxogeranyl acetate and 8-oxonerol. The panel was not able to further specify this musty odor by any other sensory terminology but additionally reported the terms citrus-like (two panelists) in case of 8-oxoneryl acetate, and fatty (all panelists) for all 8-oxo derivatives. It has been previously reported that the term musty is a general term comprising such divergent impressions like dusty, papery, earthy or moldy.[36] Interestingly, and in line with these previous reports, the term musty was further specified by two panelists by the additional term dusty in case of the 8-oxogeranyl acetate, and by only one panelist in case of the 8-oxonerol. Although geosmin and 2-methylisoborneol are compounds that are most commonly associated with musty odor,[36] there are no common structural features between these substances and the odorants investigated within the present study. According to Jong and Birmingham [37] 2-octanone and 3-octanone are two compounds produced by mushrooms which also possess a musty odor. However, none of these substances elicits a comparable musty impression as perceived for the compounds of the present study. Nevertheless, one might postulate that the carbonyl moiety is a common functional group of these 8-carbon chain ketones and our 8-oxo derivatives, and might be responsible for the musty odor perceived by the panel. On the other hand, the same structural feature did not affect the pleasant odors of the 8-oxolinalool and 8-oxolinalyl acetate as no musty smell was recorded for these compounds.[23]

As discussed above, neryl acetate, with a relatively high odor threshold among its derivatives (96 ng/L_{air}), showed unexpected odor attributes, namely clove-like and phenolic. These descriptors are not common among this substance group, and have never been reported before for this substance. Interestingly, the smell of neryl acetate has been previously described as rose-like.[14] However, the method of smell determination was not detailed in this study, so that it is unclear where these differences originate. Potentially, the differing impressions of the previous study arose from other side-products or contaminations, as application of GC-O as analytical strategy was not mentioned in the experimental part of the study. Interestingly, clove-like and phenolic would relate to a completely different substance class, namely guaiacol and phenol derivatives such as 4-vinylguaiacol.[38] One might hypothesize that the presence of a 4-carbon chain with a double bond at C-2 and a methoxy or an acetoxy group at C-1 might be the common structural feature responsible for this smell impression as illustrated in Error! Reference source not found..

From the data compiled in Table 3, where all individual threshold values of the participants are shown, it becomes evident that inter-individual variation in sensitivity to these substances was pronounced. For example, 8-oxogeraniol was found to have the highest individual OT value (637 ng/L_{air}); yet, on average, it was not the least potent compound amongst the geraniol derivatives. It is interesting to note that no single panelist was especially sensitive to all compounds; however, one panelist recorded the lowest OT values for three compounds, namely geraniol (2.8 ng/Lair), geranyl acetate (18.8 ng/L_{air}) and 8-hydroxygeranyl acetate (27 ng/L_{air}).

As can be seen from the data shown in Figure 2B, the lowest OT values were determined in the nerol substance group with 8.8 ng/L_{air} for 8-oxoneryl acetate and 27 ng/L_{air} for 8-carboxyneryl acetate, respectively, followed by nerol with a threshold value of 60 ng/L_{air}. On the other hand, 8-oxonerol was found to be the least potent compound in this study, with a threshold value of 493 ng/L_{air}.

When analyzing the data of individual panelists, the absolute lowest and highest individual OT values were recorded for two nerol derivatives, with 0.41 ng/L_{air} for 8-

oxoneryl acetate and 6480 ng/L$_{air}$, for 8-oxonerol, respectively. Interestingly, these two values were obtained from the same panelist; moreover, this panelist was also exceptional in other terms, i.e. anosmic to 8-hydroxyneryl acetate. Overall, the odor threshold values showed that, for each substance, at least two panelists showed comparable OT values regardless of the odor quality perceived. In addition, not more than one subject was anosmic to each compound as previously mentioned, with a total of five cases within the whole study.

From the above results, several insights into structure-odor relationships can be deduced for the investigated geraniol and nerol derivatives. With the exception of 8-oxo and 8-carboxygeranyl acetate, all *E*-isomer derivatives showed lower odor threshold values than their respective *Z*-analogues. Accordingly, the *E/Z* configuration greatly affects the potency of the compounds regardless of the odor quality. An aldehyde group at C-8 changed the odor completely from citrus-like to musty, with 8-oxoneryl acetate showing somewhat exceptional behavior as this substance retained the citrus-like odor but was, in case of two panelists, associated with a musty nuance. Comparing the results of this investigation with our previous study on linalool and its derivatives, [23] some links in structure-odor relationships become obvious. First, substituting C-8 with an OH-group enhances the dominance of the citrus-like character; this is especially true for compounds bearing an acetate moiety at C-1. In addition, 8-hydroxy C-1 acetates are more potent than their respective 8-hydroxy C-1 alcohols. Next, a carboxyl group at C-8 is responsible for plasticine-like, greasy impressions as these were named for all odor-active acid derivatives. Last, it could be demonstrated that increase of the polarity of the oxygen-bearing group at C-8 of geraniol or linalool [23] decreases the odor potency until the odor disappears. In contrast to this, the polarity is directly related to the odor potency for the oxygenated derivatives of nerol. More specifically, in this case a carboxyl function at C-8 of nerol is more potent than an aldehyde group, regardless of the odor quality.

To sum up, our study shows that geraniol, **1**, nerol, **3**, their acetates (**2** and **4**) and their corresponding oxygenated derivatives, **5-16,** were found to be odor active with the sole exception of 8-carboxygeraniol. Odor threshold and odor quality determinations revealed that structural changes on the basic skeleton of these monoterpenes lead to derivatives that can be more potent or more pleasant with regards to their smell character than the parent monoterpene itself. The 8-oxo and 8-hydroxy derivatives of geraniol, geranyl acetate and neryl acetate showed comparable smells for all panelists whereas oxygenated derivatives of nerol showed very divergent odor characteristics amongst panelists, with for example high variations in odor thresholds for 8-oxonerol and very divergent assignment of odor attributes for 8-carboxynerol. Furthermore, cases of anosmia were recorded five times for four panelists; three panelists for either 8-hydroxygeraniol, 8-carboxygeranyl acetate, or 8-hydroxyneryl acetate, whereas one panelist showed anosmia to both 8-carboxynerol and neryl acetate.

Overall, the structure-odor relationship of these monoterpene alcohols can be summarized as follows; the OH group at C1 is the sole contributor to the odor quality and potency of both isomers **1** and **3**. Replacing this OH by an acetate group led only to a remarkable decrease in the potency but not the odor quality, with the sole exception of neryl acetate: for this substance the odor turned from the characteristic citrus-, lemon-like impression of nerol to a clove-like, phenolic note. On the other hand, an OH at C-8 preserved the common citrus-like smell of the parent monoterpenes, but not the potency, irrespective whether C-1 bears an OH or an acetate group. However, a carbonyl group at C-8 led to the appearance of a musty note that was either relatively pure (8-oxogeraniol) or accompanied by other odor notes (8-oxoneryl acetate). Last but not least, substitution of C-8 by a highly polar functional group, the carboxy group, turned the odor of all derivatives to waxy, greasy and plasticine-like.

Accordingly, our study demonstrates that potentially naturally occurring nerol and geraniol derivatives might be of sensory relevance as was previously demonstrated for the corresponding linalool derivatives. Future studies will need to elucidate if these substances contribute to certain smells in nature, or if they can impart other physiological effects, apart from pure smell sensation.

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Figures captions

Figure 1: Synthetic pathways of the target oxygenated compounds of geraniol, nerol and their acetates.

Figure 2: Influence of the oxygenated functional groups on the odor thresholds of (A) geraniol, geranyl acetate and their oxygenated derivatives, (B) nerol, neryl acetate and their oxygenated derivatives. Displayed are individual odor thresholds as reported by seven panelists.

Figure 3: Common structure features that are potentially responsible for the common clove-like odor of both compounds.

Table 1: Retention Indices and Occurrence of the Acyclic Monoterpenes and Their Derivatives.

Compound	Odorant	RI [a]		Previously identified
		DB5	FFAP	
1	Geraniol	1260	1850	Examples: Palmarosa (*Cymbopogon martinii* (Roxb.) Poaceae, [3, 39] *Ocimum gratissimum* Lamiaceae, [40] lemon balm (*Melissa officinalis* L.) Laminaceae. [41]
2	Geranyl acetate	1382	1768	Examples: Palmarosa (*Cymbopogon martinii* (Roxb.) Poaceae, [3, 39] *Citrus limon* (L.) Burm. and *Citrus aurantifolia* (Christm.) Swing (family Rutaceae), [19] Sweet Flag (*Acorus calamus* L.) Araceae. [21]
3	Nerol	1233	1766	*Lippia* spp [9] and *Melissa officinalis* L. [8] *Warionea saharae* Benth & Coss. (Asteraceae), [42] *Xeranthemum cylindraceum* and *X. annum* Astraceae, [43] sweet orange essential oil (*Citrus sinensis* (L.) Osbeck). [44]
4	Neryl acetate	1363	1720	*Helichrysum italicum* (Roth) G.Don subsp. italicum (Asteraceae), [13] *Citrus limon* (L.) Burm. and *Citrus aurantifolia* (Christm.) Swing (family Rutaceae), [19] *Citrus aurantium* L. (Rutaceae). [20]
5	8-Oxogeraniol	1516	2400	Fruits of *Amomum tsao-ko* Zingiberaceae, [45] component of the secretion of male scent organs of African milkweed butterflies (Danainae). [46]

6	8-Oxogeranyl acetate	1620	2350	Pheromone blend from Australasian predaceous bug, *Oechalia schellenbergii* (Heteroptera: Pentatomidae). [22]
7	8-Oxonerol	1494	2462	not reported
8	8-Oxoneryl acetate	1600	2315	not reported
9	8-Hydroxygeraniol	1531	2642	Fruits of *Euterpe oleracea* Mart. (Arecaceae), [47] leaves and grape berries from *Vitis vinifera* Muscat of Alexandria and Shiraz Cultivars, [16] yellow-fleshed Nectarines (*Prunus persica* L. Cv. Springbright), [17] as a geraniol metabolite in urine of rats. [15]
10	8-Hydroxygeranyl acetate	1631	2512	not reported
11	8-Hydroxynerol	1505	2600	Yellow-fleshed Nectarines (*Prunus persica* L. Cv. Springbright), [17] leaves and grape berries from *Vitis vinifera* Muscat of Alexandria and Shiraz Cultivars. [16]
12	8-Hydroxyneryl acetate	1619	2500	not reported
13	8-Carboxygeraniol	1665	3228	From tongling white ginger *Zingiber officinale* Roscoe, Zingiberaceae, [48] flowers of *Osmanthus fragrans* var*. aurantiacus,* [49] leaves of *Tecoma chrysantha* JACQ, [18] as a geraniol metabolite in urine of rats. [15]

14	8-Carboxygeranyl acetate	1809	3125	not reported
15	8-Carboxynerol	1659	3207	not reported
16	8-Carboxyneryl acetate	1765	3088	not reported

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[a] Retention indices were determined as described by van den Dool and Kratz [24]

Table 2: Odor Qualities Defined by Panelists and Median of the Odor Threshold of All Compounds.

Compound	Odor qualities [a]							OT [ng/L_{air}]	
	PA	PB	PC	PD	PE	PF	PG	Range	Media
1	Citrus, fresh, floral, sweet	Citrus, fresh, fatty	Citrus, floral	Citrus, Orange-peel, neroli	Citrus, fresh, floral, sweet	Fatty, sweet, fruity	Citrus, soapy	2.8-23.1	23.1
2	Fruity	Fatty, sweet	Citrus, floral.	Citrus, fresh	Citrus, sweet, floral	Soapy	Lemon-like	18.8-150.7	75.3
3	Citrus, fresh	Floral, sweet, fresh	Citrus, floral	Lemon-peel, balsamic, fruity	Citrus, fresh, lemon-like	Soapy, citrus	Lemon, soapy	11.3-180.2	89.8
4	Anosmia	Phenolic	Clove, floral	Clove, floral	Clove, sweet, floral	Fatty, dusty	Phenolic, sweet	27-432	121.5
5	Fatty, musty, old	Sweet-sour, herb	Fatty, musty	Floral, soapy, fresh	Fatty, musty	Fatty, musty	Citrus, fresh	39.8-637.2	318.6
6	Fatty, musty	Sweet, fresh	Orange-peel, dusty, fatty	Cumin, spicy	Fatty, musty, lemon-like	Fatty, soapy, dusty	Citrus, greasy	6.8-108	13.5
7	Fatty,	Sweet, green,	Fatty,	Sandal-wood,	Fatty, musty	Fatty,	Fatty,	50.6-	405

	musty	herb	musty	balsamic		dusty	citrus	6480	
8	Citrus, fatty, musty	Sweet	Wax, plastic	Balsamic, cumin	Citrus, fatty, musty	Fatty, citrus	Citrus, sweet, fatty	0.41-26.2	13.1
9	Fatty, soapy	Fresh, herb	Anosmia	Floral, citrus, sweet	Fatty, citrus	Fatty, fruity	Citrus	135-540	405
10	Fatty, citrus	Grassy, fresh	Floral, body-lotion	Orange, fruity	Citrus, soapy	Citrus, soapy	Citrus, soapy	27-108	54
11	Citrus, sweet, fresh	Sweet, vanilla	Citrus	Balsamic, woody	Vanilla, sweet	Vanilla, sweet	Citrus	112.7-1803	450.9
12	Citrus, floral, soapy	Citrus, sweet	Citrus	Citrus	Citrus	Anosmia	Citrus	27-216	81
13	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	-	-
14	Floral, sweet, coconut	Grassy, dill	Plasticine	Anosmia	Plasticine, greasy	Coconut, sweet	Sweet	14-112.3	42.1
15	Anosmia	Green, dill	Plasticine	Fatty, greasy	Fatty, waxy, greasy	Fatty, waxy	Pungent	74.3-4752	74.3
16	Sweet, roasted	Dill, green	Plasticine, waxy	Acidic.	Plasticine, waxy, greasy	Coconut, fatty	Herbal, green	6.8-216	27

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[a] Odor qualities as perceived at the sniffing port.

Table 3: Odor Thresholds of Panelists for All Compounds.

Compound	Odorant	OT [ng/L_{air}] [a,b]							Group [c]
		PA	PB	PC	PD	PE	PF	PG	
1	Geraniol	23.1	23.1	23.1	23.1	11.53	11.53	2.88	14.05
2	Geranyl acetate	75.33	18.83	150.66	37.66	150.66	150.66	18.83	61.79
3	Nerol	179.50	22.52	180.15	11.26	89.77	180.15	22.52	60.55
4	Neryl acetate	***n.o.***	432	216	27	27	27	432	96.21
5	8-Oxogeraniol	637.2	39.82	637.2	318.6	39.82	79.65	637.2	194.18
6	8-Oxogeranyl acetate	6.75	13.5	54	13.5	27	13.5	108	22.14
7	8-Oxonerol	1620	50.62	810	202.5	202.5	6480	405	493.75
8	8-Oxoneryl acetate	13.09	26.19	13.09	26.19	3.27	0.41	26.19	8.81
9	8-Hydroxygeraniol	540	270	***n.o.***	540	135	270	540	340.17
10	8-Hydroxygeranyl acetate	54	54	108	54	108	108	27	65.82
11	8-Hydroxynerol	901	112.72	901	225.45	450.9	1803	225.45	450.76
12	8-Hydroxyneryl acetate	216	54	54	216	27	***n.o.***	108	85.72
13	8-Carboxygeraniol	-	-	-	-	-	-	-	-
14	8-Carboxygeranyl acetate	14.04	56.16	56.16	***n.o.***	28.08	28.08	112.32	39.71
15	8-Carboxynerol	***n.o.***	74.25	594	74.25	74.25	4752	74.25	210
16	8-Carboxyneryl acetate	27	13.5	6.75	216	6.75	54	54	27

[a] n.o. : No odor perceived by the panelist.

[b] Odor thresholds in air were determined as described by Ullrich and Grosch [50]

[c] Group odor threshold was calculated as a geometric mean of the individual thresholds of panelists.

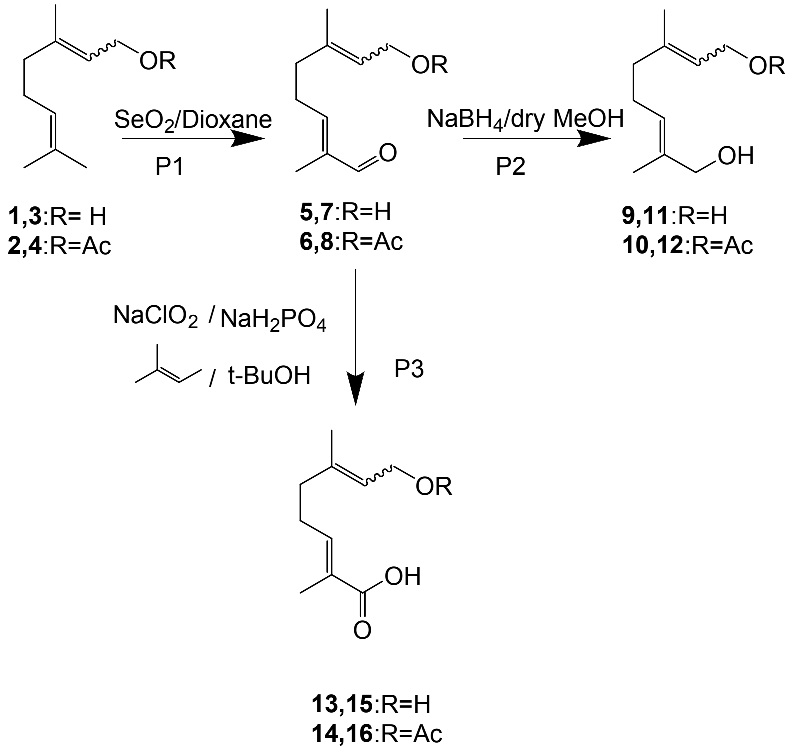
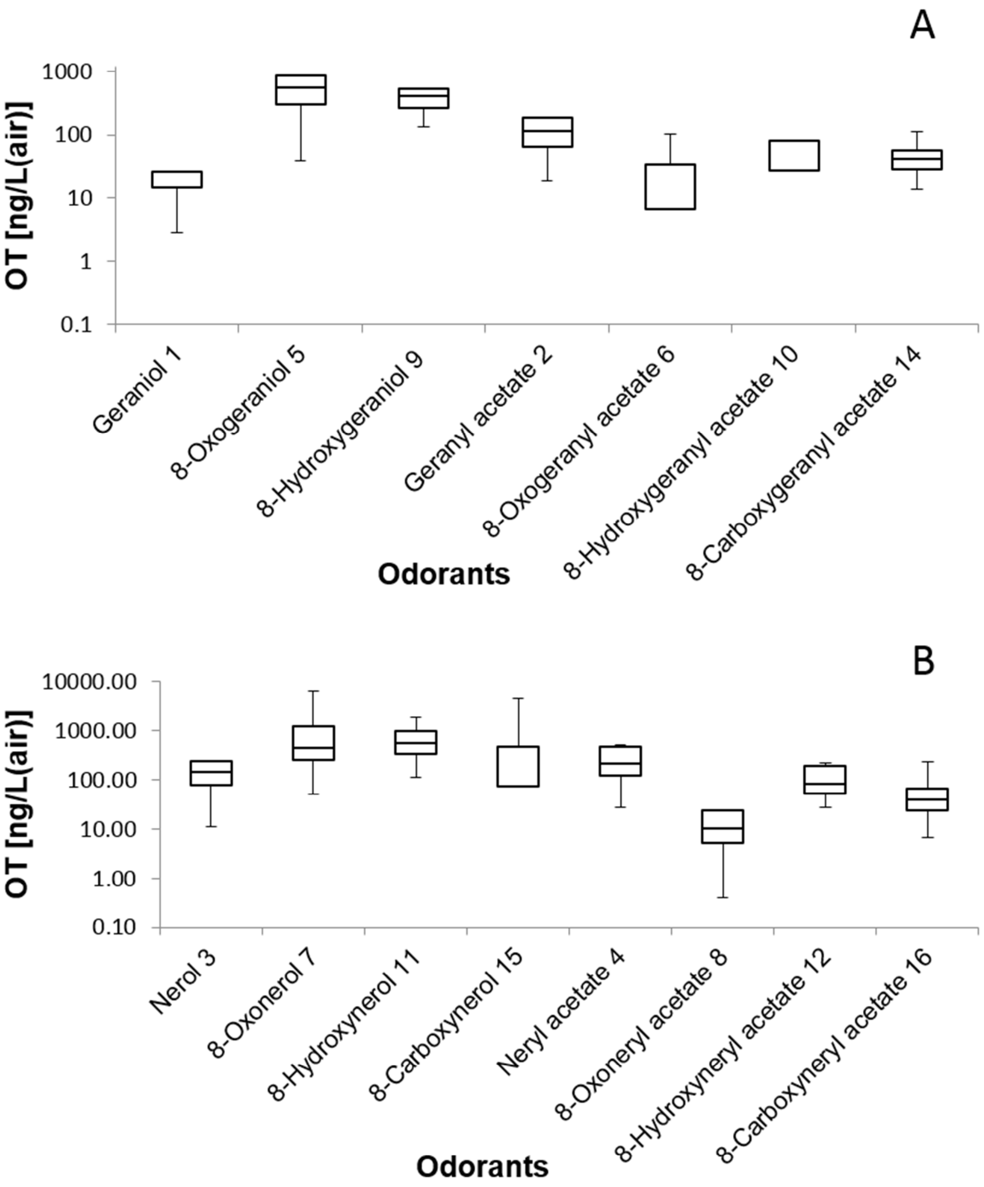

OR
SeO2/Dioxane
P1
1,3:R= H
2,4:R=Ac
OR
O
5,7:R=H
6,8:R=Ac
NaBH4/dry MeOH
P2
OR
OH
9,11:R=H
10,12:R=Ac
NaClO2 / NaH2PO4
/ t-BuOH
P3
OR
OH
O
13,15:R=H
14,16:R=Ac

Figure 1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OT [ng/L(air)]
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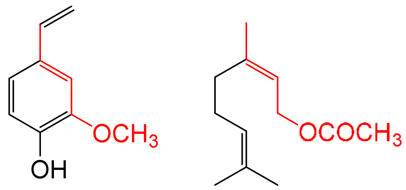
100
10
1
0.1
Geraniol 1
8-Oxogeraniol 5
8-Hydroxygeraniol 9
Geranyl acetate 2
8-Oxogeranyl acetate 6
8-Hydroxygeranyl acetate 10
8-Carboxygeranyl acetate 14
Odorants
B
OT [ng/L(air)]
10000.00
1000.00
100.00
10.00
1.00
0.10
Nerol 3
8-Oxonerol 7
8-Hydroxynerol 11
8-Carboxynerol 15
Neryl acetate 4
8-Oxoneryl acetate 8
8-Hydroxyneryl acetate 12
8-Carboxyneryl acetate 16
Odorants

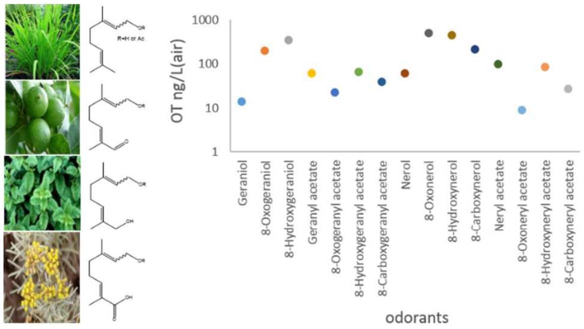
Figure 2

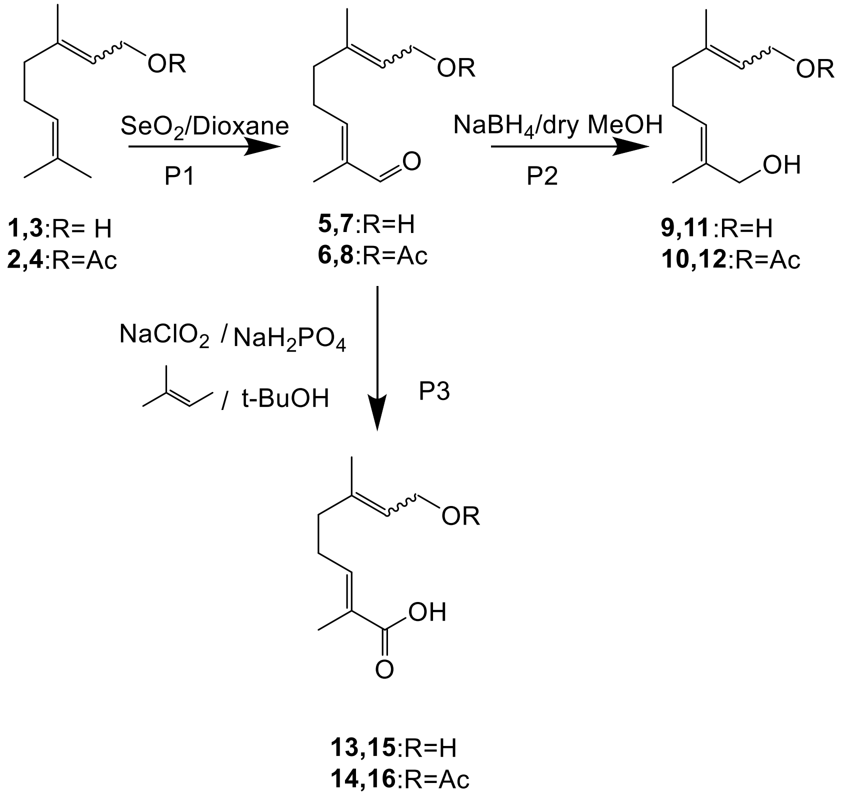


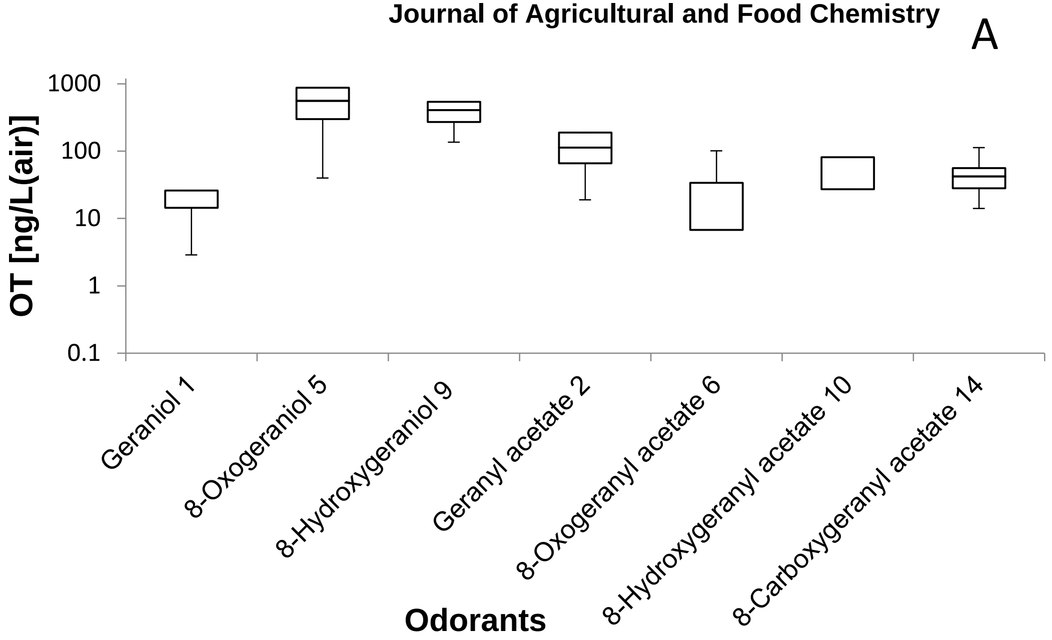
4-Vinyl guaiacol Neryl acetate **4**

Figure 3

For table of contents only




OR
SeO$_2$/Dioxane
P1
NaBH$_4$/dry MeOH
P2
O
OH
1,3:R= H
2,4:R=Ac
5,7:R=H
6,8:R=Ac
9,11:R=H
10,12:R=Ac
NaClO$_2$ / NaH$_2$PO$_4$
/ t-BuOH
P3
OH
O
13,15:R=H
14,16:R=Ac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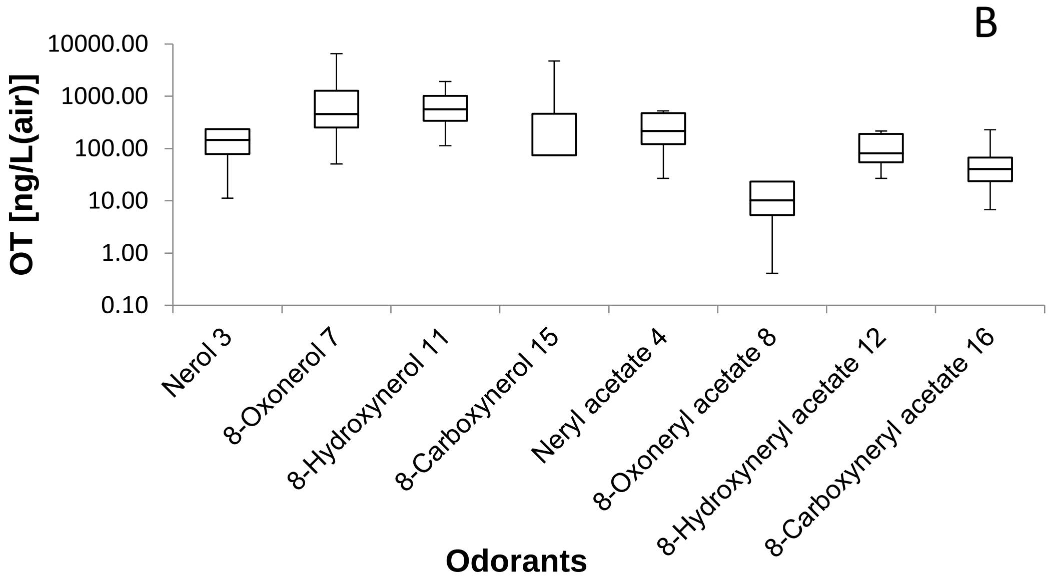
Geranyl acetate 2
8-Oxogeranyl acetate 6
8-Hydroxygeranyl acetate 10
8-Carboxygeranyl acetate 14
Odorants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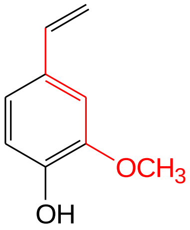
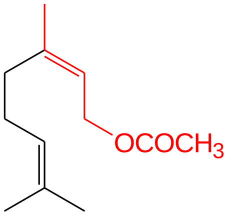
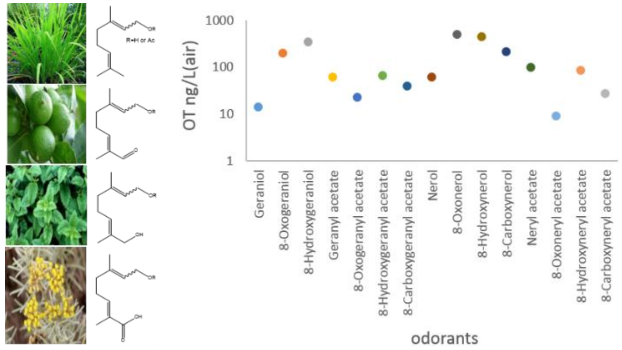
Odorants



4-Vinyl guaiacol



Neryl acetate **4**


OR
R=H or Ac
OR
O
OR
OH
OR
OH
O
1000
100
10
1
OT ng/L(air)
Geraniol
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8-Hydroxygeraniol
Geranyl acetate
8-Oxogeranyl acetate
8-Hydroxygeranyl acetate
8-Carboxygeranyl acetate
Nerol
8-Oxonerol
8-Hydroxynerol
8-Carboxynerol
Neryl acetate
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8-Hydroxyneryl acetate
8-Carboxyneryl acetate
odorants