

# PERFUMER & FLAVORIST

## Sensory Properties of Optical Isomers

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It has long been known that optically active stereoisomers—optical antipodes or enantiomers—can have different sensory qualities. The most illustrative examples of this phenomenon are the enantiomers of carvone and menthol.

Especially during the last decade the interest in the separation and determination of the sensory properties of natural enantiomers has resulted in a large number of publications.

This increasing interest was initiated by the development of new chromatographic separation techniques on optically active stationary phases and arose from the need to prove the naturalness of certain enantiomers.

Numerous enantiomers have already been isolated and/or synthesized and their sensory properties have been investigated. These sensory properties of the compounds concern their odor qualities and threshold values in certain media. Because the determination of the sensory properties is a rather subjective task due to intra- and inter-individual differences, it is not surprising that some confusion exists about these properties. The sensory properties of a series of volatile enantiomers, which are important in flavors and fragrances, will be discussed in this article.

### Introduction

Optical activity in organic compounds is possible. When the compound has four different substituents at one or more carbon atoms, the central carbon atom is asymmetric and can give rise to left-handed and right-handed molecules, which are called optical antipodes or enantiomers. The occurrence of enantiomers is also called chirality, which stems from the Greek word *cheir* (hand). Another word for chirality is *handedness*.

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In the case of flavors and natural isolates with volatile constituents that contain an asymmetric carbon atom, optical activity is not only possible; it's probable. Generally, in fact, these compounds will be mostly either left- or right-handed. Flavors and natural products often contain either the right-handed or the left-handed compounds, and the sensory properties of these constituents can be different.

The occurrence of an excess of one of the enantiomers in a mixture, say fruit flavor, is defined by the percentage of the enantiomeric excess. The enantiomeric excess concentration is the absolute value of the difference of the percentages of the two enantiomers.

R- (rectus) and S- (sinister) are symbols for the absolute configuration of the enantiomers. The R-enantiomer is a clockwise system and the S-enantiomer a counterclockwise system for the four different substituents attached to the asymmetric carbon atom. The addition of (+) or (-) indicates the real rotation of polarized light by the enantiomer. The (+)-enantiomer, formerly called (d), is dextrorotatory and the (-)-enantiomer, formerly called (l), is levorotatory.

Beets<sup>1</sup> reviewed chirality of olfactory stimulants and covered the history of this subject until 1978. He also reviewed chirality of gustatory stimulants, such as the enantiomers of nonvolatile amino acids. Examples included  $\alpha$ -substituted amino acids of which one antipode has a sweet taste and the other a bitter taste.

In 1989 Pickenhagen<sup>2</sup> reviewed enantioselectivity in odor perception. He also determined the sensory properties of the enantiomers of muscone and (E)- $\alpha$ -damascone.

More recently Chastrette et al.<sup>3</sup> reported on the role of chirality in structure-odor relationships. They studied the influence of chirality on odors of 16 enantiomeric pairs according to the dispersion/hydrogen bonding theory of receptor-odorant interaction.

Jones and Elliot<sup>4</sup> investigated the individual and substance differences in the discriminability of ten pairs of enantiomers.

Mosandl et al.<sup>5-13</sup> in particular have extensively reported on the separation and qualitative sensory properties of a large number of enantiomers. Recently Mosandl<sup>12</sup> wrote an excellent review about the analytical advances in the quality assessment of flavors and fragrances. A great part of this review was devoted to chirality evaluation.

Very recently Werkhoff et al.<sup>14</sup> wrote a thorough review on the chiroscopic analysis in essential oil, fragrance and flavor research. They mentioned the progress in the area of chiroscopic analysis achieved by the modified cyclodextrins as chiral stationary phase in gas chromatography. The analysis was illustrated with several examples of volatile natural isolates.

Although a great deal is known about the sensory properties of enantiomers, some confusion and differences of opinion remain about these properties.

The rest of this article discusses the qualitative and quantitative properties of optical enantiomers based on a survey of the available literature.

## Linear Aliphatic Compounds

A series of volatile natural compounds with an asymmetric carbon atom can be derived from isoleucine by Strecker degradation, followed by reduction, oxidation and esterification. In this group of compounds about 50 2-methylbutanoates and 2-methylbutyl esters have been identified in foods and beverages.<sup>15</sup> All these esters can occur in (R)- and (S)-form. The (R)- and (S)-forms mostly have different sensory qualities.

Several pairs of enantiomers in this series have been separated, isolated and synthesized by Mosandl's group<sup>5-13</sup> to determine the sensory properties. The odor descriptions of a series of aliphatic enantiomers are shown in Table I. Mosandl<sup>6</sup> mentioned that the (S)-enantiomer of 2-methylbutanoic acid predominates (being at least 80%, and in most cases more than 95%) in the flavors of apple, strawberry, papaya, black currant, pineapple, and many other fruits. Meanwhile, the (R)-enantiomer of 2-methylbutanoic acid has been detected in the extract of *Veratrum album*.

The enantiomers of 4-methylhexanoic acid were found by Ohloff<sup>16,17</sup> to have different odor intensities, the odor of the (R)-(+)-enantiomer being stronger and more fatty.

Most secondary aliphatic alcohols and many of the tertiary aliphatic alcohols contain an asymmetric carbon atom. Threshold values in air have been determined<sup>18</sup> for the enantiomers of 2-butanol. No significant differences have been found between the enantiomers of 2-butanol.

The sensory properties of the enantiomers of 2-octanol have been studied in more detail. According to an investigation by Guillot and Babin<sup>19</sup> the threshold value in air of (S)-(+)-2-octanol is 3.2 times lower than the threshold value of the (R)-(-)-enantiomer. Stuiver<sup>20</sup> repeated these measurements and found that the threshold of (S)-(+)-2-octanol was about 3.5 times lower than the threshold of its antipode. Punter<sup>18</sup> found that threshold values of the 2-octanol (R)- and (S)-enantiomers differed by a factor 3. However, he observed that the (R)-(-)-enantiomer has the lower threshold value. Table II presents some standardized odor threshold values in air, and, based on values of Stuiver<sup>20</sup> and

Punter,<sup>18</sup> shows small differences between the enantiomers of 2-butanol and 2-octanol.<sup>70</sup>

### Lactones

All alkyl-substituted  $\gamma$ - and  $\delta$ -lactones contain at least one asymmetric carbon atom, so that a series of enantiomers exists.

$\gamma$ -Lactones and  $\delta$ -lactones occur in many food flavors. Optically active  $\gamma$ -lactones have been found in many fruit flavors, such as strawberries, raspberries, peaches, apricots, mangoes, papayas and passion fruits. Chiral  $\delta$ -lactones are generally present in lower concentrations in fruit flavors but they are important constituents of the flavors of dairy products, such as milk, cream, butter and cheese.

The odor descriptions of  $\gamma$ - and  $\delta$ -jasmin lactones have been studied in detail by several researchers.

During a thorough study of stereoisomeric flavor compounds, Mosandl and Guenther<sup>65</sup> investigated the structures and sensory qualities of a series of  $\gamma$ -lactones, which are shown in Table III.

$\gamma$ -Jasmin lactone is (Z)-7- $\gamma$ -decenolactone and occurs in peaches, nectarines, mangoes, and yellow passion fruits as well as in the natural isolates peppermint oil and jasmin absolute. Werkhoff et al.<sup>14</sup> mentioned that  $\gamma$ -jasmin lactone in flavors has a very characteristic enantiomer distribution with a definite excess of the dextrorotatory enantiomer. Fischer et al.<sup>21</sup> found that (S)- $\gamma$ -jasmin lactone was approximately 50 times weaker than the (R)-enantiomer, as shown in Table IV.

Guichard et al.<sup>22</sup> isolated and synthesized the enantiomers of (Z)-6- $\gamma$ -dodecenolactone and determined their sensory properties. The odor of the enantiomers was qualified as flowery, fruity, coconut, peach and apricot. No

**Table III. Sensory qualities of  $\gamma$ -alkyl  $\gamma$ -lactones in an aqueous solution of 10% sugar and 0.015% citric acid**

difference in the odor quality between the enantiomers was found, but there was a difference in the odor intensity. The odor of each pure enantiomer was assessed by sniffing the column effluent. The detection threshold value calculated for the (S)-enantiomer was 2-3 times lower than that of the (R)-form.

### Terpenoid Hydrocarbons

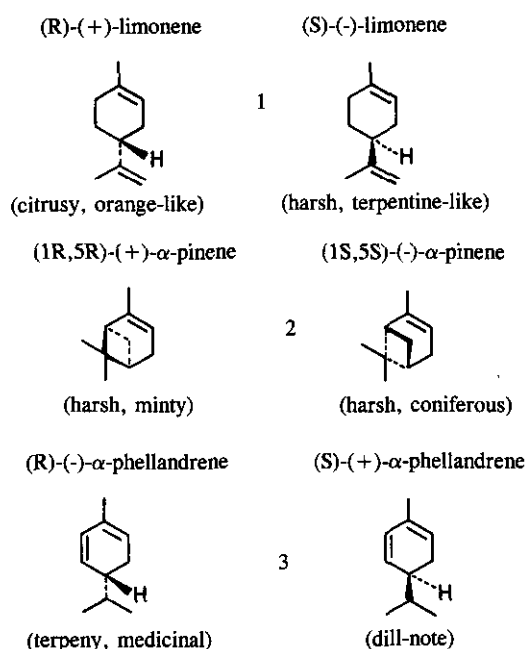
Up to 20 optically active monoterpene hydrocarbons have been found in nature. Examples are  $\alpha$ -pinene,  $\beta$ -pinene, limonene, camphene,  $\alpha$ -phellandrene,  $\beta$ -phellandrene,  $\alpha$ -thujene, sabinene and  $\delta$ -3-carene. The gas chromatographic separation of these enantiomers is now well established.<sup>13,14,23,24</sup>

Little is known about the sensory properties of the enantiomers of the monoterpene hydrocarbons. The odor descriptions of some monoterpene hydrocarbons are shown in Table V and the threshold values in Tables II and VI.

The optical enantiomers of limonene [1] are the best studied, but some confusion exists about their sensory properties. In the opinion of Werkhoff et al.<sup>14</sup> and literature they cited, (R)-(+)- and (S)-(-)-limonene as well as the racemate are very common as con-

**Table IV. Sensory qualities of jasmin lactones<sup>14,21</sup>**

Compound	Odor and flavor
racemic $\gamma$ -jasmin lactone (Z-7- $\gamma$ -decenolactone)	fruity, tropical fruit-like, peach, apricot, prune, strawberry, coconut creamy, sweet, flowery
(S)-(+)- $\gamma$ -jasmin lactone	creamy, milky, soft, caramel, fruity $\gamma$ -decalactone-like, weakly peach-like
(R)-(-)- $\gamma$ -jasmin lactone	racemate-like, fruity, intensive peach-like, coconut, distinctly stronger than (S)-(+)-antipode
racemic $\delta$ -jasmin lactone (Z-7- $\delta$ -decenolactone)	creamy buttery, milky, fatty, peach, apricot, fruity, sweet, flowery, coumarin-like, coconut
(S)-(+)- $\delta$ -jasmin lactone	fatty, creamy, less intensive than racemate
(R)-(-)- $\delta$ -jasmin lactone	milky, coconut, fruity, less intensive than racemate, distinctly stronger than (S)-(+)-antipode



**Figure 1. Terpenoid hydrocarbons**

stituents of many flavors and essential oils. The absolute configuration of limonene in orange, grapefruit and lemon juice and peel oil has recently been determined by Schurig et al.<sup>25</sup> The enantiomeric excess was 96-99% (R)-(+)-limonene.

Racemic limonene is a liquid with lemon-like odor. It has been reported<sup>14</sup> that (R)-(+)-limonene has a typical and powerful orange odor whereas the (S)-(-)-form possesses a lemon note including a turpentine-like character. (R)-(+)-limonene occurs in high concentration in the peels of all citrus fruits, and is often isolated from sweet orange peel oil. As a consequence this (R)-(+)-limonene contains traces (<0.1%) of olfactively important sweet orange constituents, such as octanal and decanal.

Very pure (R)-(+)- and (S)-(-)-limonene both have a harsh, terpene-like odor, however the (R)-(+)-enantiomer has a fresh, slightly citrusy note and the (S)-(-)-enantiomer a turpentine-like note. Randebrock<sup>26</sup> investigated the threshold values in air of the enantiomers of limonene, which are shown in Table II. No significant difference was found between the two enantiomers.

(1S,5S)-(-)- $\alpha$ -Pinene and (1R,5R)-(+)- $\alpha$ -pinene occur in natural isolates and fruit flavors, such as gum turpentine, eucalyptus oil and mango fruits. Both enantiomers [2] have harsh, terpene-like odors, the (1S,5S)-(-)-enantiomer being somewhat more coniferous and the (1R,5R)-(+)-enantiomer somewhat more fresh minty. Lindell<sup>27</sup> determined the threshold values of the enantiomers of  $\alpha$ -pinene in air, which differed by a factor of about 1.6 (see Table II).

Different authors sometimes found large differences in general sensitivity. By standardizing the threshold values,<sup>70</sup> these differences can become much smaller. In this respect, it should be noted that the threshold values found by Randebrock<sup>26</sup> when standardized<sup>69</sup> are a factor of about 30 too low, which means that the threshold values of limonene and  $\alpha$ -pinene in Table II are probably much closer to each other than they appear at first sight.

Blank et al.<sup>28</sup> determined the sensory properties of (S)-(+)- and (R)-(-)- $\alpha$ -phellandrene [3]. (S)-(+)- $\alpha$ -Phellandrene occurs in dill herb and has a characteristic dill note, but its antipode has a terpene-like, medicinal odor. The odor threshold value in water of the (R)-(-)-enantiomer is

2-3 times that of the (S)-(+)-enantiomer.

### Oxygenated Monoterpenes

Terpenoid alcohols occur widely in nature, in both essential oils and flavors. The alcohols are important for the sensory properties of some oils. The odor descriptions of terpenoid enantiomers are shown in Table V. Some threshold values of these compounds can be seen in Tables II and VI.

In 1962 Ohloff and Klein<sup>29</sup> synthesized the enantiomers of linalool [4] and determined their sensory qualities. (S)-(+)-Linalool was found to have an odor reminiscent of petitgrain and lavender. Its antipode, (R)-(-)-linalool, had a woody lavender note. Christoph<sup>31</sup> determined the sensory properties of the enantiomers of linalool. The (S)-(+)- had a more citrusy fruity note and its threshold value in air was 3.5-4 times that of the (R)-(-)-enantiomer.

The enantiomers of citronellol [5] were prepared by Rienaecker and Ohloff.<sup>32</sup> The (S)-(-)-enantiomer has a floral, rose-like odor, typically reminiscent of geranium oil, whereas the (R)-(+)-enantiomer has a citronella oil-like odor character.

$\alpha$ -Terpineol is a colorless, crystalline solid. The (R)-(+)-enantiomer has a floral typically lilac odor; it occurs in mango. The (S)-(-)-enantiomer has a coniferous odor char-

acter; this isomer has been detected in litchis. The racemic mixture was found in yellow passion fruit.<sup>14</sup>

The enantiomers of 7-hydroxydihydrocitronellal [6] were synthesized by Skorianetz et al.<sup>33</sup> and were found to have different odor qualities. (S)-(-)-Hydroxydihydrocitronellal has a lily-of-the-valley odor. The odor of its antipode is weaker and has green, leaf-like and minty notes.

Theimer and McDaniel<sup>34</sup> synthesized a series of monoterpene derivatives starting from natural (R)-(+)- $\alpha$ -pinene and (S)-(-)- $\beta$ -pinene. The pinenes were isomerized into each other giving two pairs of enantiomers. These enantiomers were converted into pinocarveol, which was converted into myrtenal, myrtenal acetal, pinocarvyl propionate and pinoacetaldehyde, representing two enantiomers from  $\alpha$ -pinene and two enantiomers from  $\beta$ -pinene. Four solutions of equal concentration were prepared—one from each of the four chemicals. Smelling strips from each of the four solutions were presented in random order to volunteers who were asked to match the four strips into two pairs according to odor similarity. In all cases, odor differences within pairs of enantiomers were found to be significantly greater than the differences within pairs of the same enantiomer prepared from different starting material.

Blank et al.<sup>35</sup> found that the threshold value of 3,9-epoxy-1,4(8)-p-menthadiene, so-called linden ether, equaled that of (3S,4R,8R)-3,9-epoxy-1-p-menthene and was ten times greater than the threshold value of menthofuran and one-twentieth the threshold value of (3R,4S,8R)-3,9-epoxy-1-p-menthene.

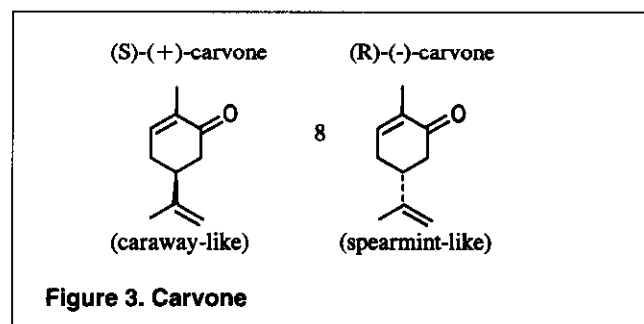
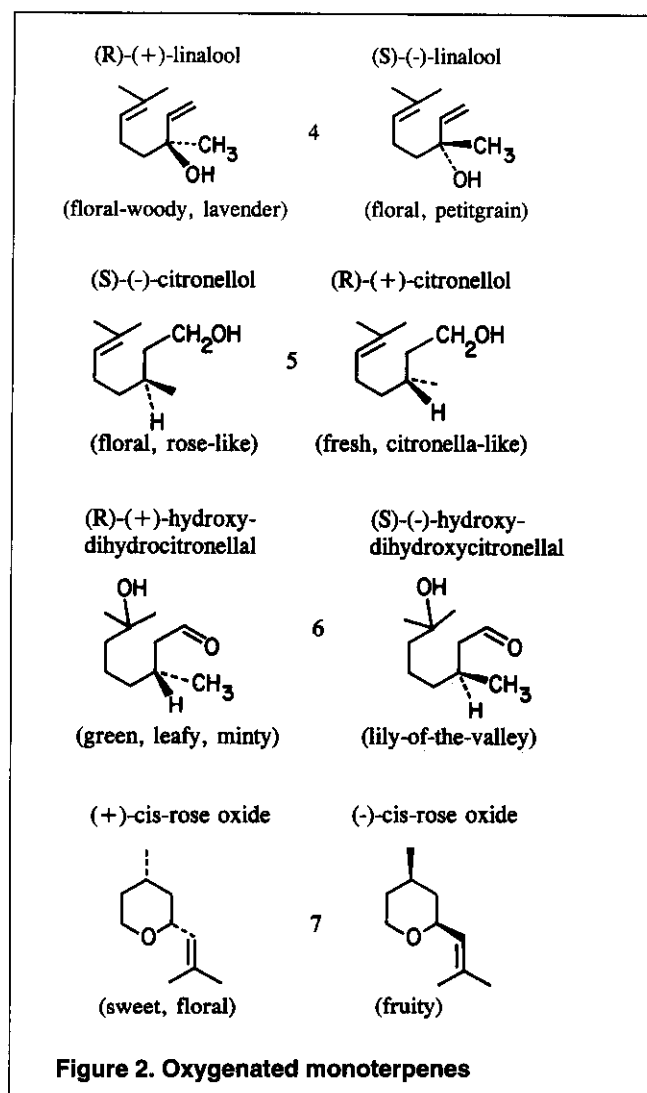
In 1990 Tateba and Mihara<sup>36</sup> synthesized a series of  $\gamma$ ,  $\delta$ - and  $\epsilon$ -monoterpene lactones and isolated three pairs of conformational enantiomers (e.g., cis- and trans-3,7-dimethyl- $\gamma$ -octalactone, mentholactone and isomentholactone and their dehydroderivatives). They found a significant difference between the sensory properties of the antipodes.

The enantiomers of rose oxide [7] were studied by Ohloff.<sup>16</sup> (+)-cis-Rose oxide has a sweet odor, whereas its antipode (-)-cis-rose oxide has a powerful, fruity odor character.

### Menthol, Isomers and Derivatives

The absolute configurations of the menthol and its isomers and derivatives are as follows: l-menthol (1R,3R,4S), l-isomenthol (1S,3R,4S), l-neomenthol (1S,3R,4R), l-neoisomenthol (1S,3S,4S), l-menthone (1R,4S), l-isomenthone (1S,4S); and d-menthol (1S,3S,4R), d-isomenthol (1R,3S,4R), d-neomenthol (1R,3R,4R), d-menthone (1S,4R), d-isomenthone (1R,4R). For the sake of simplicity the old prefixes d- and l- will be used in the following and in Table VII.

The sensory properties of (d)- and (l)-menthol have been



### Carvone

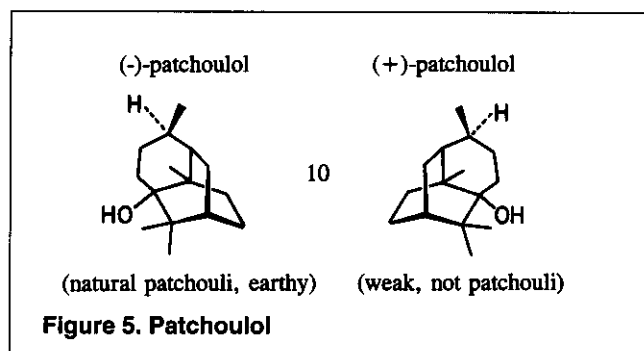
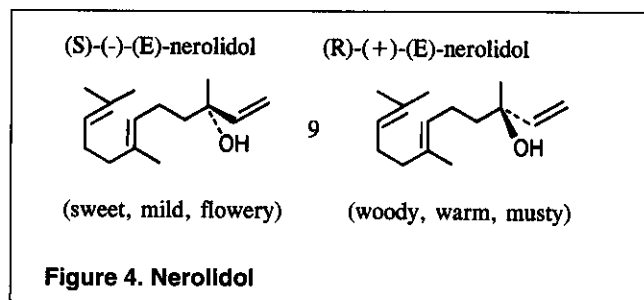
The sensory properties of the enantiomers of carvone [8] have been studied by several authors.<sup>31, 39-46, 58</sup> Natural (R)-(-)-carvone was isolated from spearmint oil and (S)-(+)-carvone from caraway oil. Both enantiomers were also synthesized from the enantiomeric limonene. Sensory evaluation demonstrated that the two (S)-(+)-carvones (natural and synthetic) on the one hand and the two enantiomeric (R)-(-)-carvones on the other had the same odor quality and intensity, but that the former have a caraway character while the latter have an odor of spearmint.

Polak et al.<sup>46</sup> mentioned that although the odor qualities of enantiomers tend to be similar, in the case of carvone it is unequivocally proven by enantiomeric inter-conversion that the qualitative odor differences were real and not due to traces

studied by Doll and Bournot<sup>37</sup> and in more detail by Emberger and Hopp.<sup>38</sup>

Doll and Bournot<sup>37</sup> found that the sensory qualities of the enantiomers were significantly different when a minimum concentration was exceeded. Moreover they determined that in air the threshold values of the antipodes were the same. The intensity for l-menthol was 3.3-3.5 times greater than the intensity for d-menthol. The cooling taste effect was significantly stronger for l-menthol than for d-menthol; this finding was confirmed by Emberger and Hopp.

An excellent study on the sensory qualities of the enantiomers of menthol, its epimers and acetates, was carried out by Emberger and Hopp.<sup>38</sup> They determined the sensory qualities of the enantiomers of all menthol isomers, menthone, isomenthone and menthyl acetate. They found a clear difference between the odor qualities of the enantiomers of menthol (Table V). Their quantitative results are summarized in Table VII. The differences in flavor thresholds of the various pairs of enantiomers are small. Greater differences can be seen in the cooling effect thresholds of the various enantiomer pairs.



of odorous by-products. These researchers found an odor threshold concentration range of 1-4000 ppb in water for (S)-(+)-carvone and of 0.7-2000 ppb for (R)-(-)-carvone. The ratio range of the threshold values of the enantiomers varied among subjects by two orders of magnitude.

According to Pelosi and Viti<sup>43</sup> the (R)-(-)-enantiomer of carvone represents the best example of the minty primary odor.

Christoph<sup>31</sup> determined the sensory properties of the enantiomers of carvone. He found the odor quality for the (S)-(+)-enantiomer caraway-like, whereas its (R)-(-)-antipode had a spearmint character. The threshold value in air of the (S)-(+)-enantiomer was 3-4 times greater than that of its (R)-(-)-antipode.

### Nerolidol

Schubert et al.<sup>47</sup> recently separated nerolidol [9] into its four enantiomers. Distinct sensory properties of all enantiomers and a chiroselective capillary gas chromatographic method to resolve the enantiomeric pairs of (Z)- and (E)-nerolidol were described. The odor descriptions of the nerolidol isomers are shown in Table V.

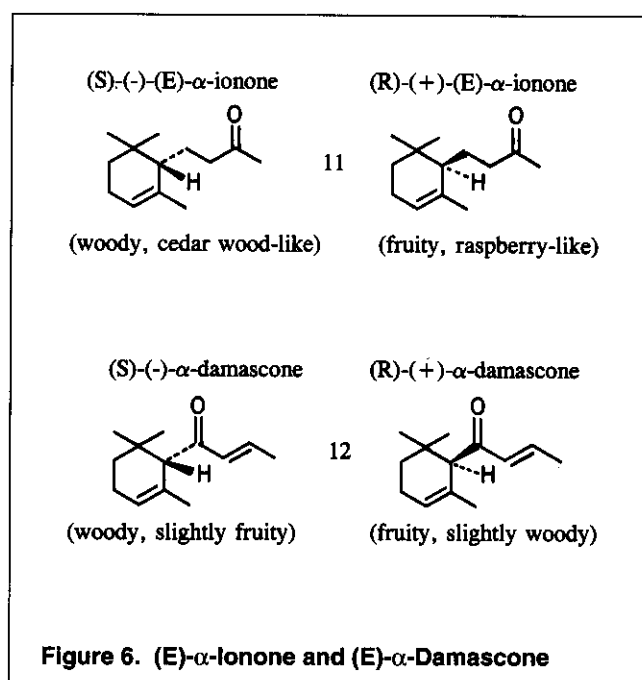
### Patchoulol

Naef et al.<sup>63</sup> investigated the enantiomers of patchoulol [10]. They found that (-)-patchoulol has a natural patchouli, earthy and celery odor and that (+)-patchoulol has a weak odor, not reminiscent of patchouli.

### (E)- $\alpha$ -Ionone and (E)- $\alpha$ -Damascone

The sensory properties of the enantiomers of (E)- $\alpha$ -ionone [11] and of (E)- $\alpha$ -damascone [12] have been studied in detail.

Naves<sup>48</sup> found that (R)-(+)-(E)- $\alpha$ -ionone and (S)-(-)-



(E)- $\alpha$ -ionone had the same odor quality and threshold value, which was twelve times greater than the threshold concentration of the racemate. A similar observation was made for a methyl homologue (neo-iso- $\alpha$ -ionone).<sup>49</sup> This phenomenon has not been found again.

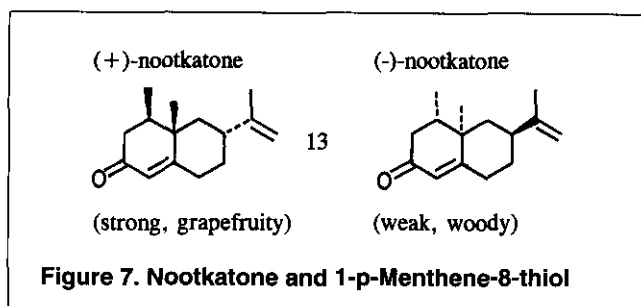
Polak et al.<sup>46</sup> found threshold concentration ranges of 0.03-328 ppb in water for (R)-(+)-(E)- $\alpha$ -ionone and of 0.1-656 ppb for (S)-(-)-(E)- $\alpha$ -ionone. They reported that the olfactory threshold ratio for  $\alpha$ -ionone enantiomers varied among subjects by 3-4 orders of magnitude.

More recently the enantiomers of (E)- $\alpha$ -ionone have been isolated by Werkhoff et al.<sup>50,51</sup> They found that natural (+)-(E)- $\alpha$ -ionone in general has an (R)-configuration, with an enantiomeric excess of over 90%, with the exception of  $\alpha$ -ionone in boronia oil where it was about 82%. These researchers also determined the sensory properties of the enantiomers, which are quite different, as shown in Tables V and VI. The relative sensitivities for both enantiomers of ionone were found to diverge widely for different flavorists.

The sensory properties of (R)-(+)- and of (S)-(-)- $\alpha$ -damascone were determined by Pickenhagen<sup>2</sup> during a study of enantioselectivity in odor perception. Organoleptic comparison of the two forms was carried out. It was found that the (R)-(+)-enantiomer has a "cork" and green apple animal note and the (S)-(-)-form has a more floral odor, reminiscent of rose petals, also having a winy character. The threshold values in water were found to be 1.5 ppb for the (S)-(-)- and 100 ppb for its (R)-(+)-antipode.

Werkhoff et al.<sup>50,51</sup> isolated the enantiomers of (E)- $\alpha$ -damascone from natural sources and determined the sensory qualities as described in Table VI. In contrast to the findings of Pickenhagen,<sup>2</sup> however, Werkhoff et al. were unable to establish striking differences in the flavor threshold values of the enantiomers.



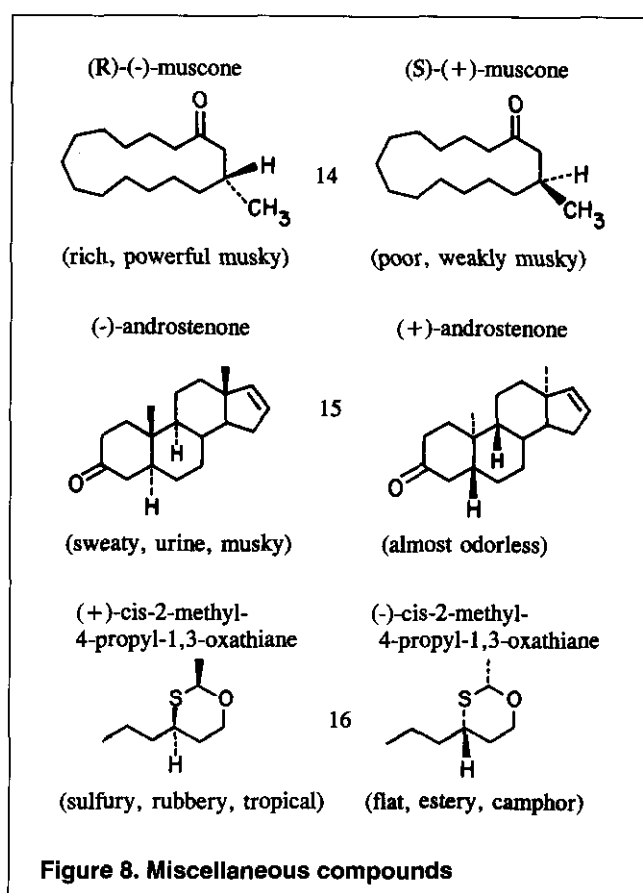


### Nootkatone and 1-p-Menthene-8-thiol

(+)-Nootkatone is a sesquiterpene ketone, which is one of the character impact compounds for the grapefruit flavor.

Haring et al.<sup>52</sup> determined the sensory properties of the enantiomers of nootkatone [13]. (+)-Nootkatone has a grapefruity odor, a bitter taste, and its odor threshold value in water is 0.8 ppm. (-)-Nootkatone has a soft woody odor, is virtually tasteless, and its odor threshold in water is 600 ppm. Haring et al.<sup>52</sup> also studied the sensory properties of the enantiomers of some analogues of nootkatone, such as tricyclonootkatone, tetrahydronootkatone and  $\alpha$ -vetivone.

The other character-impact compound of grapefruit is 1-p-menthene-8-thiol, which consists of two enantiomers. Demole et al.<sup>53</sup> isolated these compounds from grapefruit juice and determined their sensory properties. The flavor detection threshold values in water were 0.00002 ppb for



the (R)-(+)-enantiomer and 0.00008 for the (S)-(-)-enantiomer. Qualitatively, there was no significant difference between the sensory properties of the racemic mixture and of the optically active (R)-(+)-enantiomer, while the (S)-(-)-enantiomer appeared to have a somewhat more fruity and natural aroma than its antipode. The mixture behaved like a mixture of both forms.

Mosandl<sup>7</sup> more recently determined the sensory qualities of the two enantiomers of 1-p-menthene-8-thiol and found a striking difference for the odor qualities of the enantiomers in comparison with the findings of Demole.<sup>53</sup> Mosandl determined the odor character of the (R)-(+)-enantiomer as a pleasant, fresh grapefruit juice and of the (S)-(-)-enantiomer as an extremely obnoxious sulfur note.

### Miscellaneous Compounds

Acree et al.<sup>54</sup> studied the odor threshold of enantiomers of methyl epijasmonate. They found, for instance, for (+)-methyl epijasmonate a threshold value in water of 3 ppb while the (-)-methyl epijasmonate was found to be odorless.

In 1992 Polak and Provasi<sup>55</sup> studied the odor sensitivity to geosmin enantiomers. The threshold values in water were 0.078 ppb for the (+)-enantiomer and 0.0095 ppb for the (-)-enantiomer.

Finato et al.<sup>56</sup> synthesized a series of new earthy odorants, including a group of enantiomeric fenchol derivatives such as (R)- and (S)-enantiomers of 2-methyl-, 2-ethyl-, 2-

butyl- and 2-ethynylfenchol. The qualitative sensory properties of the enantiomers were different. The main odor quality for the enantiomers was earthy or camphoraceous. The secondary notes were woody, musk and moldy.

Theimer et al.<sup>57</sup> studied the sensory qualities of the enantiomers of C-10-substituted cyclohexanones. Ratios of odor strength as high as 20:1 and one case of urine odorless versus odorous between chiral enantiomers were observed. Liquid enantiomers were found to be stronger than solid enantiomers. At very high concentrations all the compounds had woody-type odors with no observed cases of anosmia.

The sensory properties of the enantiomers of muscone [14], (R)-(-)- and (S)-(+)-3-methylcyclopentadecanone, have been described by Pickenhagen.<sup>2</sup> The two products show distinct differences in their odor. The natural (R)-(-)-enantiomer is described by a panel of perfumers as "very nice musky note, rich and powerful," whereas the (S)-(+) is "poor and less strong." Threshold values determined in water with a panel of 18-20 members show values of 61 ppb for the (R)-(-)-enantiomer and 223 ppb for its (S)-(+)-antipode.

Ohloff et al.<sup>59</sup> and Pickenhagen<sup>2</sup> described the sensory properties of the enantiomers of Ambrox.\* The absolute configurations (R) and (S) were not indicated. Sensory comparison of the two forms showed that the (+)-enantiomer has a dominant woody note and a threshold value in water of 2.6 ppb; the (-)-form has the warm musky, animal note and a threshold value of 0.3 ppb.

Pickenhagen<sup>2</sup> also referred to the completely different sensory properties of the enantiomers of androstenone [15], which were recently reviewed by Chastrette et al.<sup>3</sup> and by Zinkevich and Aronov.<sup>67</sup>

Recently Hummel et al.<sup>60</sup> studied the olfactory discrimination of nicotine-enantiomers by smokers and nonsmokers. Subjects were able to discriminate between the two enantiomers of nicotine. Whereas both groups reported the (R)-(+)-enantiomer to cause an unpleasant sensation, the (S)-(-)-enantiomer was perceived as pleasant by smokers, but as unpleasant by nonsmokers. Estimates of detection thresholds of the two enantiomers did not differ significantly. Also, there were no significant differences between thresholds of smokers and nonsmokers.

Masuda and Mihara<sup>61</sup> studied the odor evaluation of both enantiomers of five alkoxy-pyrazines. The qualitative sensory properties were given. The threshold values in water varied between 2 and 200 ppb; three alkoxy-pyrazines showed a significant difference between the (+)- and (-)-enantiomers.

The enantioselective synthesis of (+)- and (-)-cis-2-methyl-4-propyl-1,3-oxathiane [16] and their olfactive properties were studied by Pickenhagen and Bronner-Schindler in 1984.<sup>62</sup> One year later Mosandl and Heusinger<sup>66</sup> investigated the enantiomers of a series of homologous alkyl-

\* Firmenich registered tradename

substituted 1,3-oxathianes and could not confirm the findings of Pickenhagen.

p-Menthan-3-one-8-thiol is a character-impact compound of buchu leaf oil. The compound contains two asymmetric carbon atoms in its molecule and hence consists of four optical stereoisomers, that is, two pairs of enantiomers. Koepke and Mosandl<sup>8</sup> isolated the four enantiomers and determined their olfactive qualities, which are shown in Table V.

### Chirality and Odor Perception

From the study of the sensory properties of more than 50 pairs of enantiomers, what can be learned with respect to the primary process of odor perception?

Several of the before-mentioned publications<sup>1-4</sup> deal with this subject. Regarding chirality and odor perception the following simple comparison can be made. When a person as a receiver (read: receptor site) shakes hands with another human being (read: stimulant), the former surely knows which hand he received: left or right (handedness). In other words during the primary process of odor perception the receptor site, which is optically active, can distinguish between the optically active stimuli. In odor perception it is believed that the initial event is the interaction of odorants with specific receptors on the cilia of olfactory sensory neurons. Buck and Axel<sup>68</sup> recently confirmed that

receptors are parts of proteins and found that several hundred different types of receptors may be involved in those interactions. How the interaction between receptor site and stimulus occurs is not yet understood. Some publications<sup>1,3</sup> mention a kind of chemical bonding, however a physical event also may be involved (compare with the handshaking process).

The discrimination between two enantiomers may occur on the optically active site of one and the same receptor; also a differentiation may take place on different receptor sites caused by so-called multiplicity. This multiplicity is the ability of the molecule to trigger different receptor sites at different concentrations.

Summarizing, one may conclude that optically active receptor sites, of which many exist, can distinguish between the enantiomers by means of a chemical and/or a physical interaction. Possible examples of chemical interactions are enantiomers of carvone, nootkatone, and androstenone. Examples of physical interactions are enantiomers of hydrocarbons and of spherical molecules such as camphor and homologues.

### Concluding Remarks

The sensory properties of over 50 pairs of volatile enantiomers were discussed. One observed tendency is that nonpolar (hydrocarbons) and slightly polar compounds show no difference or moderately significant differences in their odor qualities and threshold values. Strongly polar and bipolar compounds showed significant differences in their sensory properties.<sup>1</sup>

More or less in agreement with the findings of Chastrette et al.,<sup>3</sup> three main categories of pairs of enantiomers can be distinguished:

- The sensory properties of the two enantiomers differ slightly in intensity or in quality (terpenoid hydrocarbons and spherical camphoraceous compounds).
- The enantiomers have the same main character but differ in secondary notes and in intensity (aliphatic and monoterpenoid alcohols and some esters).
- The odors of the two enantiomers differ both in quality and in intensity (carvone, nootkatone, androstenone, bifunctional compounds).

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