The Nose as a Stereochemist. Enantiomers and Odor

Ronald Bentley*

Department of Biological Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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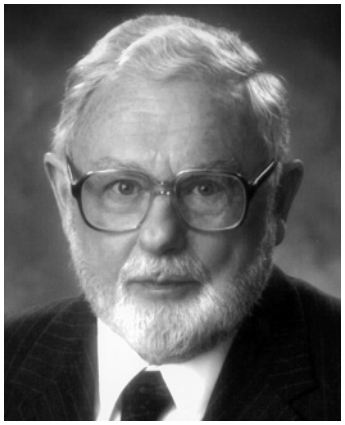

Ronald Bentley received a Ph.D. degree from Imperial College, London, for work on the chemistry and attempted synthesis of penicillin (1943–1946). As a Commonwealth Fund Fellow at Columbia University, New York (College of Physicians and Surgeons), he studied the use of stable isotopes in biochemical investigations, 1946–1947. Subsequently (1948–1952), he was responsible for a mass spectrometric facility for stable isotope analysis at The National Institute for Medical Research, London. He joined the Faculty of the University of Pittsburgh in 1953, becoming Professor of Biochemistry in the Department of Biological Sciences in 1960, and was retired (mandatory) at age 70 in 1992 as Professor Emeritus. In the summer of 1960, he was a Public Health Service Special Fellow at Hopkins Marine Station, Stanford University, and he held a John Simon Guggenheim Memorial Foundation Fellowship at the Institute of Biochemistry, University of Lund, Sweden, in 1963–1964. His research focused on the biosynthesis of various microbial secondary metabolites and of ubiquinone and menaquinone (vitamin K_2). Moreover, he did research on carbohydrate conformations and developed an interest in stereochemistry. A two volume text, *Molecular Asymmetry in Biology*, was published in 1969–1970. Following retirement, he has written on a variety of topics and was one of six general editors for *The Oxford Dictionary of Biochemistry and Molecular Biology* (1997, revised 2000). He received the Waksman Outstanding Educator Award of the Society for Industrial Microbiology in 2002 and takes pride in becoming a 50 year member of the American Chemical Society in 2003.

1. Chirality in Biology—Introduction

A chiral structure is one for which the mirror-image form cannot be superimposed on the original by rotation or translation; the two forms are enantiomers. Chirality is pervasive in Nature at several levels.[1,2] There are many examples in terms of body structures; one is that the human left hand cannot be superimposed on the mirror-image right hand. Similarly, there are behavioral asymmetries such as left- and right-handedness. Furthermore, macrobiomolecules tend to be homochiral, that is, made up from units of the same chirality. Thus, with few exceptions, the protein amino acids all have the L configuration and nucleic acids contain only D-ribose or D-deoxyribose. Polysaccharides are less exclusive, but important materials such as cellulose and amylose are homochiral containing only D-glucose. For small biomolecules, there are often roles for both enantiomers; D-amino acids are required for formation of bacterial cell walls and vitamin C (L-ascorbic acid) is a carbohydrate of the L configurational series.

Although many other human senses are now recognized, it has been customary for centuries to speak of the five human senses—hearing, sight, smell, taste, and touch. Of these five classical human senses hearing is not usually associated with chiral influences, although there is evidence that the right and left ear process sounds differently.[3,4] The other four senses are, however, generally responsive to chiral influences. Clearly, sight and touch can distinguish a left-handed from a right-handed structure. With taste, the situation is unequivocal. In 1886, Piutti found that D-asparagine had a sweet taste, while L-asparagine was tasteless.[5] Although there are individual variations, there are now well-recognized taste differences for enantiomers of many compounds. To take only two examples of considerable commercial significance, *N*-L-α-aspartyl-L-phenylalanine (known as, aspartame) has a very strong sweet taste; the DD enantiomer is bitter. Monosodium L-glutamate, MSG, has the characteristic umami taste, the D enantiomer does not.[2]

Enantioselectivity with the remaining human sense, that of smell, is the focus of this review. Several words describe the property of a material that makes it perceptible to the olfactory sense, and to some extent they are synonymous—aroma, scent, smell, odor. Odor is defined as "an emanation that is perceived by the sense of smell" and can refer to an emanation composed of several compounds.[6] Odorant is defined as "any substance capable of stimulating the sense of smell" and refers to a single molecule.[6] It is now well

* Telephone, (412) 531-4290; e-mail, rbentley@pitt.edu; address for correspondence, 37 Thornwood Drive, Pittsburgh, PA 15228-2452.

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recognized that enantiomers of many chemical compounds are perceived differently as odorants by the human nose; in plain terms, they smell differently. This situation is adequately described for the present purpose by stating that enantiomers of many chiral compounds may show differences in odor. This phrasing for the human case—enantiomers show differences in odor (and variants thereof)—seems unambiguous and is in line with similar phrases used by others, for example, "enantiomers have different odors",[7] "chiral isomers can differ in odor",[8] and "enantiomers of odorous compounds might differ in their smell".[9] It is in line with general chemical usage. Thus, H_2S is said to have an odor of rotten eggs, and Cl_2 has an irritating and suffocating odor; these two materials show differences in odor and can be distinguished by the sense of smell. In the wider sense, enantiomers can be distinguished by organisms lacking a nose. In those situations, it is appropriate to state that enantiomers are perceived differently (see later).

There are general reviews concerning odor and structure[7,10] and one that includes microencapsulated fragrance samples.[11] One interesting source is a lengthy review of papers over a 75 year period on perfume and aroma chemistry published in *Helvetica Chimica Acta* that contains a total of 459 citations.[12] Other reviews deal more specifically with enantioselectivity and odor.[9,11,13−15] An invaluable source of specific information is a listing of 361 enantiomer pairs giving details of odor and odor thresholds. The list is organized into 11 groups based on structure (e.g., cyclic terpenoid odorants) or odor type (e.g., sandalwood-type odorants).[16]

These reviews are mostly written by individuals with dedicated interests in perfumery and the use of fragrances. They are apparently intended for those with similar concerns, professionals who do not need to think twice about a description such as "earthy, slightly camphoraceous, powdery cellar note" (ref 13, p 9). They tend to be organized around the odorant types that are particularly important to perfumers—woody, floral, musk, etc. As the quote just given indicates, they make fascinating reading particularly for the colorful language reminiscent of that of enophiles.

In contrast, this review, intended for a more general chemical/biochemical audience, emphasizes chemistry and stereochemistry and has a narrow focus on the human nose. It is eclectic, rather than comprehensive—a tasting or, more accurately, a sniffing menu. It is a review neither of the biology of olfaction nor of the physiology of the olfactory receptor molecules. These are certainly fascinating and important topics, but to include them here would give a review of unmanageable length. These topics are discussed in biology texts and encyclopedias;[17] a recent review is comprehensive and provides more than 150 citations.[18] Moreover, the important Nobel Prize Lectures of Axel[19] and Buck[20] are now easily available. Despite the enormous volume of information on olfaction, there is still much to learn.[21] The important and interesting insect pheromones are noted briefly in section 9.

2. Enantioselectivity

The reaction of enantiomers with enzymes and protein receptors is usually enantioselective, although there are numerous exceptions.[2] Thus, on one hand, D-amino acid oxidase, EC 1.3.3.3, is specific for D amino acid isomers and the L enantiomers are not substrates; this enzyme is enantioselective. On the other hand, nicotine dehydrogenase, EC 1.2.99.4, converts (*R*)-nicotine to (*R*)-6-hydroxynicotine and the enantiomeric (*S*)-nicotine to (*S*)-6-hydroxynicotine; this enzyme is not enantioselective. Enantioselectivity is also very common with physiological events such as the actions of insect pheromones, plant growth regulators, and drugs.[2] In dealing with enzymes and physiological responses, there is, in fact, a wide range of observations from nonspecific to complete enantiospecificity. As will be seen, there is a similar broad range of responses in dealing with odor perception. In some cases, both enantiomers have the same odor; in others, one enantiomer is odorous and the other without odor. In many cases, there are strong differences in odor types between two enantiomers, and furthermore, there may be differences between detection thresholds.

It has long been known that many secondary metabolites (natural products) occur as separate enantiomers in, for instance, different plants; in some cases both will also occur in various proportions and sometimes as racemic mixtures.[22] Among these natural products are odorants such as the materials in the so-called essential oils. Those having pleasing or interesting odors are, of course, much valued. In the perfume, fragrance, and food industries, highly trained individuals with extensive exposure to many fragrances and odors play vital roles. Since some perfumes cost more than $2000 per ounce, the stakes are high. In many cases, to eliminate human variability, a panel of "judges" will be used to evaluate an odor or odor intensity. Materials with unpleasant odors may also be of concern, for instance, in environmental situations. One such compound is the musty smelling compound geosmin (see later).

The chemical basis for any type of enantioselectivity is simple; while enantiomers have identical chemical reactivities under symmetrical conditions (absence of any chiral reagent or influence), diastereoisomers—stereoisomers that are not enantiomers—behave differently under symmetrical conditions. Pasteur was the first to make use of this fact to resolve the racemic "paratartaric acid" into the two enantiomeric forms (Pasteur did not use this terminology).[23] He treated paratartaric acid, termed here (±T), with a base, the optically active cinchonicine (an isomer of cinchonine), termed here (+C), to form two salts:

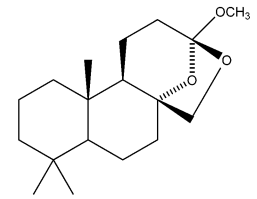
$$2(\pm T) + 2(+C) \rightarrow (+T)(+C) + (-T)(+C)$$

Since the two salts, (+T)(+C) and (−T)(+C), were diastereoisomers, not enantiomers, their properties differed and separation was possible; Pasteur accomplished this by crystallization. Regeneration of the acids from the two diastereoisomeric salts yielded (+T) and (−T). This basic principle of diastereoisomer formation has been widely adapted in many ways for the separation of enantiomers. One technique, generally used in odor research with enantiomers, is enantioselective gas−liquid chromatography using a chiral stationary phase.[24]

The macrobiomolecules found in enzymes and protein receptors (such as the olfactory receptors) are chiral, usually containing a multiplicity of individual chiral centers. The "products" formed by interaction of say, an olfactory receptor, (+OR), with the enantiomers of an odorant, (+O) and (−O), will be in a diastereoisomeric relationship, (+OR)-(+O) and (+OR)(−O); hence the process has the potential to be enantioselective. In fact, the presence of a diastereoisomeric relationship or situation is a necessary but not sufficient condition for recognition (selectivity).[25] The other

requirement is for specific contact points between receptor and odorant, but this condition will not be discussed here.

In chemical terms, for a compound to have an odor, it must have a degree of volatility; hence, there is an upper limit for the molecular mass of an odorant. This limit is reached by 13-methoxy-8α,13;13,20-diepoxy-14,15,16-tris-norlabdane, $C_{18}H_{30}O_3$ (**1**), relative molecular mass $M_r = 294$,



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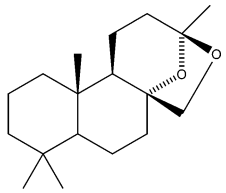

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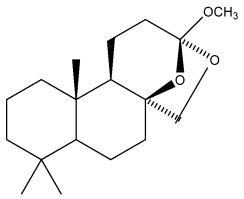

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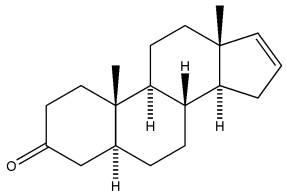

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a compound with a powerful, amber-like odor ("une odeur de type boisé-ambré").[26] The intensity of the odor was comparable to that of the previously known ketal (**2**), $C_{18}H_{30}O_2$, $M_r = 278$. Interestingly, the epimer **3** had little odor ("très peu odorant"). A close approximation to this upper limit is found with androstenone (**4**), (5*S*,8*R*,9*S*,10*S*,-13*R*,14*S*)-(+)-5α-androst-16-en-3-one, $M_r = 272$, having the characteristic odor of urine; the enantiomer is odorless. Similarly, the related alcohol (3*R*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*)-(+)-5α-androst-16-en-3α-ol, $M_r = 274$, has an animalic, musk-like odor with strong sandalwood tonality; the odor of the enantiomer is much weaker. At the other end of the scale are materials with low molecular masses, such as H_2S ($M_r = 34$) and CS_2 ($M_r = 76$).

While the basic chemistry for odor recognition of enantiomers is straightforward, depending on the formation of diastereoisomeric intermediates, the actual physiological mechanism is complex and not well understood.[10,27−34] It may be noted, however, that a theory by L. Turin proposes inelastic electron tunneling to account for the biological transduction of molecular vibrations.[35,36] Recent experiments to test predictions of the theory found no evidence to support it.[37] The subject is controversial, in part because of the publication of a book, *The Emperor of Scent*, essentially a mouthpiece for Turin's views.[38]

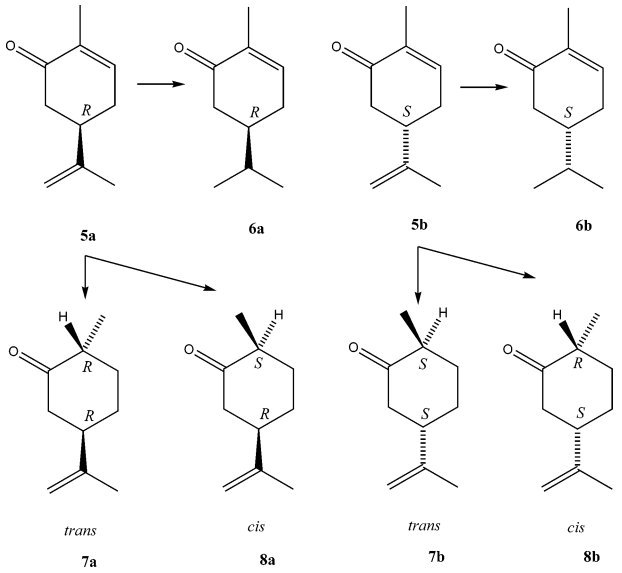
3. Proof for Enantioselectivity in Odor

One of the first indications that enantiomers might have different odors came in 1874 when two essential oils containing either (1*R*,2*S*,4*R*)-(+)-borneol (Borneo-camphor oil from *Dryobalanops aromatica*) or the enantiomeric (1*S*,2*R*,4*S*)-(−)-borneol (Ngai-camphor oil from *Blumea balsamifera*) were found to have different odors; Borneo-camphor oil had a weak camphor-like odor, unpleasantly peppery, while Ngai-camphor oil had an odor of camphor or turpentine. This and other early examples have been reviewed.[9] In view of the emphasis on homochirality in Nature, it is interesting to note that borneol, in addition to occurring in the individual enantiomeric forms as just quoted, is also a natural product that occurs as a racemate.

This work with borneol illustrates one of the many difficulties in dealing with odor discrimination. The materials examined were natural essential oils, complex mixtures of varying compositions, rather than pure enantiomers. The nose is very sensitive to impurities in compounds being tested, even at low levels. For reliable results, the sample of one enantiomer should contain neither any different chemical compound(s) nor any of the other enantiomer. These conditions demand very precise analytical methods that were not attained in much early work. In a few instances, a single enantiomer was tested against a racemic mixture, another unreliable operation. These early results should not be ignored but regarded as preliminary evidence for enantioselectivity with an odorant.

The year 1971 may be taken as that in which it was settled, once and for all, that enantiomers of certain compounds can have different odors and, as well, different odor intensities. In that year, three separate research groups investigated odor sensations with the enantiomers of carvone. Each group used very carefully purified samples and rigorous stereochemical methodology.

Russell and Hills noted that "the degree to which odor perception depends on structure has remained unsettled".[39] Using gas−liquid chromatography (GLC), they carefully purified commercial samples of (*R*)-(−)- and (*S*)-(+)-carvone (**5a** and **5b**, respectively), purity being defined by capillary

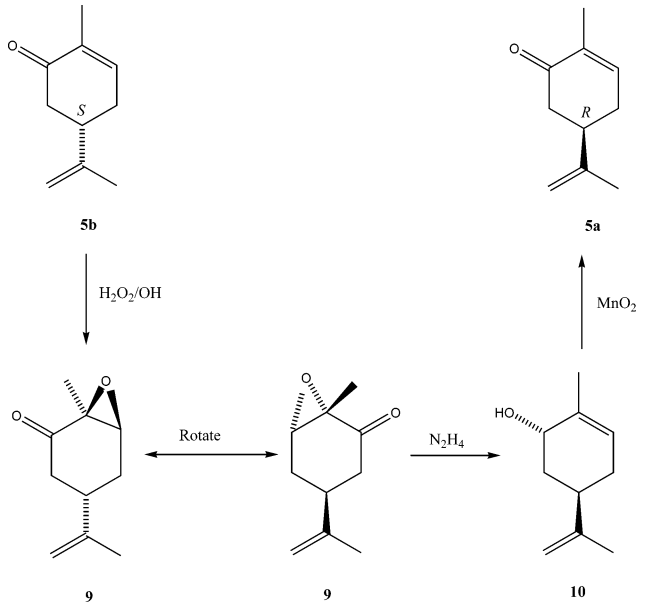


GLC, proton magnetic resonance spectroscopy, and mass spectrometry. Reduction of **5a** and **5b** with $NaBH_4/PtCl_4$ gave carvonacetone samples (**6a** and **6b**) and with Zn/OH^- samples of *trans*- (**7a**, **7b**) and *cis*-dihydrocarvones (**8a**, **8b**). A panel of trained judges described **5b**, **6b**, and **7b**, as having the odor of caraway. The enantiomeric compounds, **5a**, **6a**, and **7a**, were described as having spearmint odors. For compounds, **8a** and **8b**, there was difficulty in describing the odors (musty, woody), but the two enantiomers could be distinguished. This work clearly indicated that the carvone enantiomers could be distinguished by odor.

Leitereg et al. also carefully purified commercial carvone samples by distillation and preparative GLC to >99.9% purity.[40] In addition, (*S*)-(+)-carvone was synthesized from (*R*)-limonene and (*R*)-(−)-carvone from (*S*)-limonene by the

following reactions: limonene → limonene nitrosochloride (reagent, ethyl nitrite, HCl); limonene nitrosochloride → carvoxime (reagent, K *tert*-butoxide); carvoxime → carvone. The synthetic samples were also carefully purified. The characteristic odors, caraway for (*S*)-(+)-carvone and spearmint for (*R*)-(−)-carvone, were confirmed using a variety of careful testing procedures. Moreover, the threshold values in water were different for the two synthetic samples: (*S*)-(+)-carvone, 130 ppb, and (*R*)-(−)-carvone, 2 ppb.

Moreover, Friedman and Miller used carefully controlled stereochemical methods to interconvert carvone enantiomers ("chiral inversion") considerably reducing any possibility of contamination.[41] Thus from (*S*)-(+)-carvone (**5b**), (*R*)-(−)-carvone (**5a**) was prepared by way of the intermediates **9** and **10**. To continue the process, a second chiral inversion



converted (*R*)-(−)-carvone (**5a**) back to (*S*)-(+)-carvone (**5b**). With each chirality change, there was a corresponding, reproducible change in odor:

(*S*)-(+)-caraway → (*R*)-(−)-spearmint → (*S*)-(+)-caraway

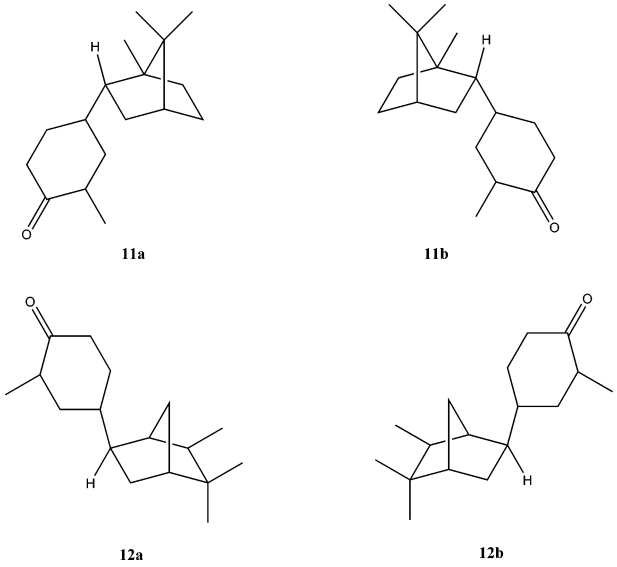
(*R*)-(−)-spearmint → (*S*)-(+)-caraway → (*R*)-(−)-spearmint

These workers found that 8−10% of the population cannot detect the two carvone odors; they suffer from carvone anosmia. As did Leitereg et al.,[40] they prepared synthetic samples of carvone from limonene. By reversing this process, that is, converting carvone to limonene, they confirmed differences for the purified limonene enantiomers, (*R*)-(+)-limonene having the odor of orange and (*S*)-(−)-limonene having the odor of lemon. They reported some other examples and also pointed out that this phenomenon was not universal. Thus, enantiomers of camphor and 2-octanol had identical odors.

These landmark papers clearly established that in some cases the human nose could detect odor differences for enantiomers. The conclusion relied on extremely careful purification techniques, rigorous stereochemical operations, and the use of panels of trained judges, rather than of individuals. Such precise, careful work has provided and continues to provide important information. A very recent example concerns two woody odorants (Georgyone and Arborone); structural requirements were considered in detail as well as possible binding modes.[42]

4. Enantioselectivity and Odor Intensity

In the work just described, different odor intensities were observed for the carvone enantiomers. In fact, enantiodifferentiation in terms of odor intensity or threshold is now well recognized and commonly observed. At one extreme, one enantiomer may have an odor, while the other is odorless. This possibility was probably first recognized in 1977 in connection with nonsteroidal compounds having an odor of urine.[8] This odor was initially observed with some steroids in 1944, a typical case being that of the previously discussed androstenone (**4**). For 4-(2-*endo*-bornyl)-2-methylcyclohexanone, one enantiomer (**11a**) was consistently found to have



a urine odor (albeit at a low intensity of 1 compared to androstenone, 1000) while the other (**11b**) was without odor. It was stated that "This is perhaps the first case in which chirality is the sole differentiating cause between odorous and odorless molecules". (Interested readers should be aware that the authors did not use the conventional CIP system for specifying absolute configurations. The enantiomers described as *d*- and *l*-camphor [i.e., (1*R*,4*R*)-(+)-bornan-2-one and (1*S*,4*S*)-(−)-bornan-2-one, respectively] were used as reference materials, with *d* and *l* then applied as configurational descriptors for related compounds. This results, for instance, in the enantiomers **12a** and **12b** being described as *d*(−)-*exo* and *l*(+)-*exo* (a strange combination!). The intensities of the urine odor, relative to androstenone, were 200 for **12a** and 10 for **12b**.

There are now several cases where one enantiomer is found to be odorous and the other enantiomer is odorless. As already noted for androstenone, the naturally occurring material, (5*S*,8*S*,9*S*,10*R*,13*R*,14*S*)-(+), has the very characteristic urine odor, but the enantiomer, (5*R*,8*R*,9*R*,10*S*,13*S*,-14*R*)-(−), is now known to be odorless.[9]

The case of androstenone exemplifies another difficulty of working with odor perception—there is considerable human variation in evaluating the odor. Roughly 50% of the adult population is anosmic for this material even at high levels. For the remainder, 15% detect a subtle odor, either not unpleasant or even pleasant, while 35% report the

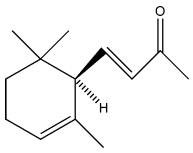
unpleasant stale urine odor and detect it at low levels.[43] There is a significant genetic component to these differences. Moreover, for some anosmic individuals, the ability to perceive androstenone can be induced by systematic exposure to the odorant.[44] Other workers have also shown that prior experience can affect odor perception.[45]

Human variation has been carefully investigated for 10 enantiomeric pairs;[46] only the enantiomers of carvone, limonene, and α-pinene were significantly discriminated, and those of 2-butanol, camphor, β-citronellol, fenchone, menthol, rose oxide, and α-terpineol were not. Some of the reported results were at variance with earlier ones. Moreover, there were marked individual differences in discrimination performance. It was concluded that enantioselectivity for odor in humans is not a general phenomenon but is restricted to some substances.

Since two of the substances (carvone, limonene) that were discriminated contained an isopropenyl group at the stereogenic center, further studies of similarly structured compounds were undertaken. Further substances for which the enantiomers could be distinguished were as follows: dihydrocarvone, dihydrocarveol, and dihydrocarvyl acetate, isopulegol, limonene oxide, perillaalcohol, and perillaaldehyde.[47] Again, there was considerable individual variation. It was suggested that the structural requirements for discrimination were as follows: (i) an isopropenyl group at the stereogenic center, (ii) a methyl group at the *para* position of the six-membered ring, or (iii) an oxygen-containing group at the *meta* position.

Sensitivity to odor depends on many factors such as physiological, psychological, and pathological conditions (ref 10, p 57). In general, females have a greater odor sensitivity than do males, and sensitivity is dependent on age; there is a marked sensitivity decrease after age 70 that becomes pronounced for octogenarians (as this writer can attest). Moreover, in the human population, 1.2% of individuals lack any sense of smell, a condition known as total anosmia.

In studies with α-ionone, the relative sensitivities also diverged widely, with some individuals being more sensitive to (+)-α-ionone than to the (−) enantiomer. For other individuals, the opposite was true.[48] It was suggested that there were at least two receptor types with opposite chiral selectivity and that their distribution varies independently in the human population. There has been some controversy about the ionone situation. Whereas the (*R*)-(+)-(*E*) enantiomer (**13a**) was at one time described as violet-like, fruity,



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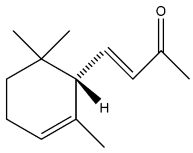

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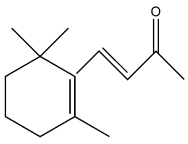

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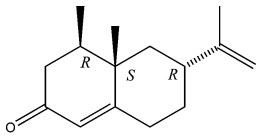
raspberry-like, flowery, and strong impact and the (*S*)-(−)-(*E*) enantiomer (**13b**) as woody, cedar wood-like, raspberry, and β-ionone-like, other workers using samples of high enantiomeric excess and chemical purity assign the same olfactory description to each enantiomer—floral-woody note, with an additional honey aspect.[13] The (*R*)-(+) isomer was slightly weaker than the enantiomer. Some difficulties may be due to the presence of traces of β-ionone (**14**), a compound characterized by a high rate of anosmia.

While generalizations relating to odor perception are usually elusive, it appears that the odor/odorless situation for enantiomers requires a material with $M_r > 224$. The smallest of nine molecules reported in a review both have $M_r = 224$.[9] They are isomers of the methyl jasmonate family and are discussed in detail later.

In addition to the maximum qualitative odor differences of odor/odorless, there are many examples of quantitative odor differences. Perhaps one of the smallest is the 2-fold difference for enantiomers of *cis*-2-methyl-4-propyl-1,3-oxathiane; the threshold for the (2*S*,4*R*)-(+) isomer is 2 ppb, and for the enantiomeric (2*R*,4*S*)-(−), it is 4 ppb. Readers may appreciate the fulsome odor descriptions of these materials. The (2*S*,4*R*)-(+) isomer is "typical sulfurous, with a rubbery onion note; in addition, there is a fruitiness reminiscent of grapefruit peel, mango, and passion fruit", while (2*R*,4*S*)-(−) was found weaker (compare thresholds) and "without the pronounced sulfur character and possessing a fresh note with more iris character".[49] For further detailed discussion of oxathianes and other olfactory descriptions, see later.

One of the larger differences is found for nootkatone, a sesquiterpenoid ketone of the eremophilane series. The (4*R*,4a*S*,6*R*)-(+) enantiomer (**15**) has a grapefruit odor, while



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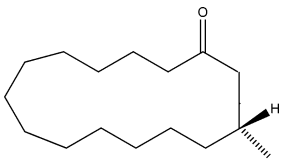
the enantiomeric (4*S*,4a*R*,6*S*)-(−) isomer is woody and spicy. The threshold concentration for **15** in the vapor phase is 30 ppm and for its enantiomer, it is ∼66000, a 2200-fold difference (here, ppm means one volume of saturated vapor diluted a million times with air).[50]

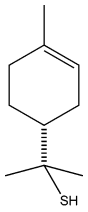
As just indicated, there is much variation in the threshold levels for odorant detection. A material requiring a relatively high concentration is muscone, the major odor component of the male musk deer (*Moschus moschiferous*). The musk odorants are widely used in perfumery and many materials with the characteristic odor—warm, sensual, animal, and natural that is long lasting and can act as a fixative—have been synthesized. The natural material is (*R*)-(−)-3-methyl cyclopentadecanone (**16**); the odor is described as



16

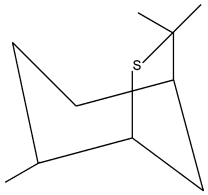
"rich, powerful, musky" and the odor threshold is 61 ppb.[13,16,51] For the (*S*) enantiomer ("poor, weakly musky"), it is 233 ppb.

On the other hand, some odorants are detectable at very high levels of dilution. One example is (*R*)-(+)-1-*p*-menthen-8-thiol (**17a**) with a pleasant odor of fresh grapefruit juice;



17a

the threshold value for detection is 0.00002 ppb. To illustrate the intensity of this odor, it has been noted that 1 g in 10 million metric tons of water could be detected by odor.[52] This compound illustrates the previously noted fact that in assigning odor, purity is essential. The (*S*)-(−)-1-*p*-menthen-8-thiol was at one time described as having an extremely obnoxious sulfur note. However, it is now known that this sulfur odor is due to the presence of an impurity, 2,8-epithio-*cis*-*p*-menthane (**18**).[53] The (*S*)-(−)-1-*p*-menthen-8-thiol,



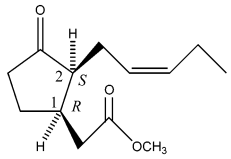
18

obtained in a state of purity by enantioselective GLC, was shown by on-line olfactometry to have a weak, nonspecific odor.

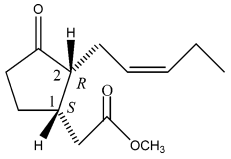
5. Compounds with More than One Chiral Center

There are many examples of enantioselectivity for materials with a single chiral center as the previously discussed cases of carvone, limonene and (*R*)-(+)-1-*p*-menthen-8-thiol attest. It is probable that a larger number of odorants contain more than one chiral center;[16] in a few cases, there are as many as six (e.g., androstenone). For compounds with two chiral centers, there are four stereoisomers. Although often described as four diastereoisomers, this usage is imprecise; there are two pairs of enantiomers, *RR*/*SS* and *RS*/*SR*, and for any one isomer, there are two diastereoisomers. Thus for *RR* and *SS*, the diastereoisomers are, in each case, *RS* and *SR*. For *RS* and *SR*, the diastereoisomers are *RR* and *SS*. In such cases, it is usual to consider diastereoselectivity as well as enantioselectivity.

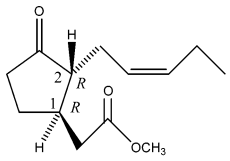
The methyl jasmonates, with two chiral carbons, are of interest for both enantio- and diastereoselectivity with respect to odor and to lack of odor. Methyl epijasmonate with the (1*R*,2S)-(+)-(*Z*) configuration (**19a**) has a strong, jasmine-like odor with a detection threshold of 3 ppb; the enantiomer (**19b**) is odorless. One diastereoisomer, methyl jasmonate, (1*R*,2*R*)-(−)-(*Z*) (**20a**), has only a weak odor (threshold > 70 ppb); the other diastereoisomer, (1*S*,2*S*)-(+)-(*Z*) (**20b**), is odorless.[16] For these compounds, there is both enantio- and diastereoselectivity. In the jasmine plant (*Jasminium grandiflorum*) the (1*R*,2*S*) (**19a**) and (1*R*,2*R*) (**20a**) diastereoisomers occur in the ratio 3:97.[13]



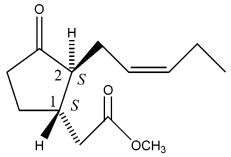
19a



19b



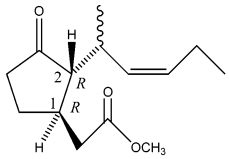
20A



20b

The jasmonate situation is complicated by a further stereochemical feature, a double bond in the five carbon side chain. In the examples just noted, this bond had the *Z* stereodescriptor. This arrangement is clearly influential as shown by its reduction to the dihydro form. Whereas the (1*S*,2*S*)-(+)- and (1*S*,2*R*)-(−)-methyl jasmonates are odorless, the dihydro forms do have odor but in some cases relatively high recognition thresholds: (1*S*,2*S*)-(+)-dihydro—floral, fatty, *cis*-jasmone, 15 360 ppb—and (1*S*,2*R*)-(−)-dihydro—herbal, fatty, tea-like, tobacco, 12 500 ppb. As with methyl jasmonate, the (1*R*,2*S*)-(+)-dihydro isomer has the most intense odor (15 ppb) and the (1*R*,2*R*) is about 16-fold less intensive.[16] The dihydro forms have been useful in perfumery, and a mix of (1*R*,2*S*)-(+)- and (1*R*,2*R*)-(−)-dihydro forms is used under the trade name Hedione and is found in perfumes such as Eau Sauvage, Rive Gauche, and Chanel No. 19.

In a further structural modification, homologues of (1*R*,2*R*)-methyl jasmonate and (1*R*,2*R*)-methyl dihydrojasmonate with a methyl substituent at C(1) of the five carbon side chain were prepared.[54] The substances were actually racemic mixtures [i.e., (1*R*,2*R*) and (1*S*,2*S*)] and were diastereoisomeric with reference to the methyl group at C(1) of the side chain. The odor of **21** was described as "floral, jasminic note,



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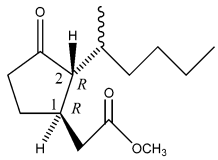
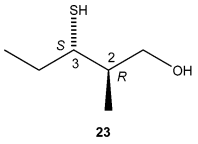


22

more indolic than *Hedione*® and has a fruity-raspberry undertone"; **22** "smells floral, *Hedione*®-like, but with a citrus connotation. It is finer, not as powerful, but more long-lasting than *Hedione*®".

A material found as an aroma component of onions is 3-thio-2-methyl-pentanol with four stereoisomers.[55] All four have the same general odor that is concentration dependent. At 1 ppm in 5% saltwater, the odor is "sulfuric, burnt gum, sweaty, onion", but at 0.5 ppb, it is "meat broth, sweaty, onion, leek"—in either case, quite a combination! The odor threshold of "the racemic mixture" (mix of all four stereoisomers?) in water was 0.15 ppb. However, the values for the separate stereoisomers in water, given in units of micrograms per liter, were somewhat different; note that 1 μg L^{-1} is equivalent to 1 ppb: (2*R*,3*S*) *anti*, 0.04; (2*S*,3*R*) *anti*, 0.03; (2*R*,3*R*) *syn*, >12; (2*S*,3*S*) *syn*, >30. In the original

paper, the *syn* forms are apparently incorrectly identified in terms of the CIP descriptors. The thresholds in air are almost unbelievably low; for the (2*R*,3*S*) stereoisomer (**23**), it is



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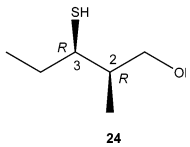
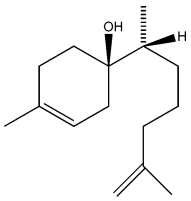


24

0.00007−0.0002 ng L^{-1} and for its enantiomer 0.003−0.007 ng L^{-1}. For the other isomers, for example, (2*R*,3*R*) *syn* (**24**), thresholds in air could not be determined since they contained small amounts of (2*R*,3*S*) and (2*S*,3*R*) isomers. The (2*R*,3*S*) structure is probably the most intense odor yet discovered and is comparable with the just discussed (*R*)-(+)-1-*p*-menthen-8-thiol. Note that there are wide differences involving diastereoselectivity between the (2*R*,3*S*) form and the diastereoisomers, (2*R*,3*R*) and (2*S*,3*S*); there are similar differences between the (2*S*,3*R*) isomer and the same two diastereoisomers.

A compound with two chiral centers where only one of the four stereoisomers has an odor has been identified.[56] This material, iso-β-bisabolol, was isolated from sandalwood oils, and all four isomers were synthesized chemically. The (6*R*,7*R*) isomer (**25**) had a "strong, floral, *muguet*-like (i.e.,



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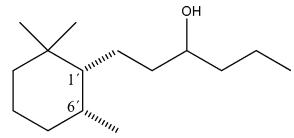
lily of the valley), very pleasant odor"; the enantiomer (6*S*,7*S*) and the two diastereoisomers (6*R*,7*S*) and (6*S*,7*R*) were odorless. With the possible exception of androstenone (2^6 stereoisomers!), this is claimed as the first rigorously diastereo- as well as enantiospecific odorant in terms of odor/odorless. The odor detection thresholds were 0.785 μg L^{-1} (water) and 0.081 μg L^{-1} (air); some individuals were anosmic to this alcohol.

A material used extensively in perfumery as various isomeric mixtures is 1-(2,2,6-trimethylcyclohexyl)hexan-3-ol; with three chiral centers, there are eight stereoisomers. A mix of two racemic diastereoisomers with the side chain substituent in either *cis* (**26**) or *trans* (**27**) orientation was marketed under the trade name Timberol. Timberol has a "powdery-woody odor with animal, steroid-type undertones".[13] The woody-animal odor was mainly associated with the *trans* structure (**27**); that is, there was a diastereoselectivity. In conformational terms, this odorous form has the two substituents in equatorial positions.

A different preparation, Norlimbanol, was a 1:1 mixture of the two racemic *trans* isomers, **28a**/**28b** and **29a**/**29b**. In testing the individual isomers, the following results were obtained: **28a** (1′*R*,3*S*,6′*S*)-(+), powerful, long-lasting, very nice woody-amber (best of the series); **28b** (1′*S*,3*R*,6′*R*)-(−), no animalic character, very weak; **29a** (1′*R*,3*R*,6′*S*)-(+), no animalic character, very weak; **29b** (1′*S*,3*S*,6′*R*)-(−), resembles **28a** but much less powerful. Clearly, the desired odor is strongly associated with the 3*S* configuration of the side chain hydroxyl; there is marked enantioselectivity but less marked diastereoselectivity. The (1′*R*,3*S*,6′*S*)-(+) ster-



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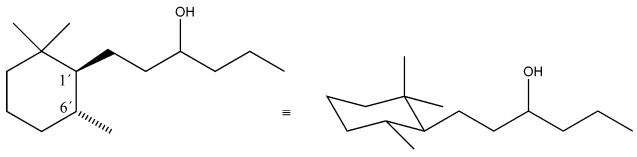

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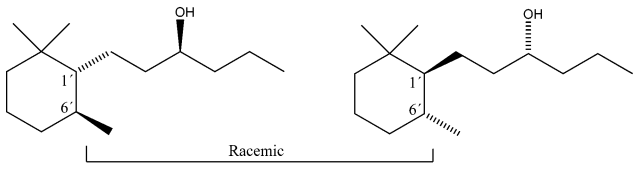
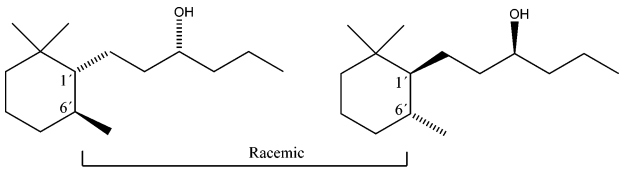


28a **28b**

eoisomer, **28a**, is being used in perfumery as "Dextro Norlimbanol".[13]



29a **29b**

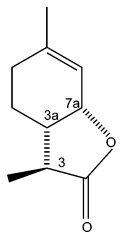
Also with three chiral centers is 3a,4,5,7-tetrahydro-3,6-dimethylbenzo-furan-2(3*H*)-one, "wine lactone", an important flavor component of white wines such as Gewürztraminer, providing a coconut and sweet odor. All of the eight stereoisomers have been prepared and evaluated. The thresholds, ng L^{-1} (air), are given in Table 1. The naturally

Table 1. Threshold Values in Air for Stereoisomers of Wine Lactone

configurations	threshold, ng L^{-1}
(3*S*,3a*S*,7a*R*)[a]	0.00001−0.00004
(3*S*,3a*S*,7a*S*)	0.007−0.014
(3*S*,3a*R*,7a*R*)	0.05−0.2
(3*R*,3a*S*,7a*S*)	8−16
(3*R*,3a*R*,7a*R*)	14−28
(3*S*,3a*R*,7a*S*)	80−160
(3*R*,3a*R*,7a*S*)[b]	>1000
(3*R*,3a*S*,7a*R*)	>1000

[a] Isomer naturally occurring in wine. [b] This is the enantiomer of the most intense isomer.

occurring isomer, (3*S*,3a*S*,7a*R*) (**30**), has the lowest threshold value.[57,58] The very large difference in threshold between



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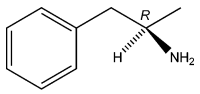
the natural material, (3*S*,3a*S*,7a*R*), and its enantiomer is remarkable.

6. Nitrogen Compounds

Chemists are familiar with intense odors of nitrogen compounds such as aniline, indole, nitrobenzene, putrescine, and pyridine. Less familiar are some nitrogenous natural products with characteristic odors that may contribute to a flower or fruit scent. For instance, two compounds with a structural relationship to aniline are *o*-aminoacetophenone and methyl anthranilate. The former has the strong floral character of flowers of the family *Castanopsis*, and the latter is the character impact compound of Concord grapes and is an odor component in several essential oils (e.g., bergamot, neroli, ylang-ylang). Interestingly, the regioisomers, methyl *m*- and *p*-anthranilates are odorless (ref 10, p 19). Neroli oil also contains, inter alia, 0.1% of indole; this material, usually associated with an unpleasant, fecal-like odor, gives a powerful, exotic floral note at high dilution (ref 10, p 143).

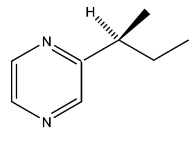
There are only a few cases where enantiomers of nitrogenous compounds have been studied for odor. A very simple case, described in 1971, is that of amphetamine (1-methyl-2-phenylethylamine); it involves a nitrogen atom directly attached to a chiral center. The (*R*)-(−) enantiomer (**31**) has



31

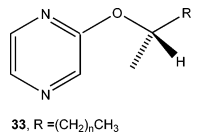
a musty odor, while the (*S*)-(+) isomer is fecal in nature.[41] The more potent (*S*)-(+) isomer for central nervous system stimulation is sold in sulfate form as dextroamphetamine sulfate, and the (*R*)-(−) isomer as levamphetamine (levamfetamine). Amphetamine is enantioselective with respect to both physiology and odor. In an interesting footnote, it was reported that the odor differences for the amphetamine enantiomers were known for several decades (i.e., prior to 1971) by individuals involved in their manufacture. "Unfortunately, this knowledge was not disseminated since it was not deemed significant".[41]

Pyrazines have received some attention in terms of enantiomeric differences. These materials often have a roasty-toasty odor and are some of the strongest smelling compounds with typical thresholds of about 0.002 ppb. Castoreum, a perfumery material obtained from dried odorous glands of the Canadian beaver, *Castor fiber*, is a complex mixture containing 0.2% of basic nitrogenous compounds. Conspicuous are eight alkaloids of the nupharidine series and several pyrazines including the achiral tetramethylpyrazine (ref 10, p 220). Neroli oil contains at low levels 2-methoxy-3-isobutylpyrazine, and this pyrazine is the characteristic odor component of green bell peppers. The regioisomer, 2-methoxy-3-*sec*-butylpyrazine (2-methoxy-3-[1-methylpropyl]-pyrazine) has the typical odor of green peas (ref 10, p 180). It is present in galbanum oil, isolated from the dried latex of *Ferula galbaniflua* and related species, and is used in perfumery for an intense green leaf scent with a woody-balsamic base note. It is a compound with a single chiral center; the natural enantiomer (**32**) has the (*S*)-(+) configuration. The odors of the two enantiomers are about the same—a burdock-like, green, and earthy odor—but the odor thresholds are different: (*S*)-(+), 0.10 ppb, and (*R*)-(−), 0.01 ppb.[59]



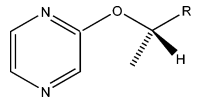
32

Odor characteristics of some synthetic alkoxypyrazines (**33**) are given in Table 2.[60] In addition, two 2-menthoxypyrazine enantiomers were prepared, both having a fruity, sweet smell; the menthol component was (−)-menthol. Odor thresholds, (1′*R*,2′*S*,5′*R*)-(−) (**34**) 2 ppb, and (1′*S*,2′*R*,5′*S*)-(+), 10 ppb.



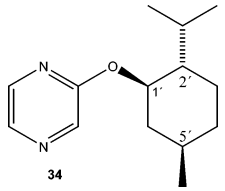
33, R =$(CH_2)_nCH_3$

Table 2. Odors of Synthetic Alkoxypyrazines



33, R =$(CH_2)_nCH_3$

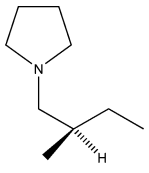
side chain, R	threshold, ppb (*S*)-(+)	threshold, ppb (*R*)-(−)	odor
$n = 1$	100	100	green, dusky
$n = 2$	100	100	fatty, metallic, green
$n = 4$	70	200	green, metallic, fatty, burdock
$n = 5$	30	90	green, fishy, amine-like, fatty



34

In recent work, chiral nitrogen compounds have been identified in the volatiles produced by roasting spotted shrimp, *Sergia lucence* (heating to 160 °C in a stream of air). The roasting produces a strong and pleasant odor ("very tasty"), and these shrimp are widely used in traditional Japanese cuisine.[61] A GLC and GLC−MS analysis revealed about 200 compounds in the volatiles, with 13 containing sulfur and 80 containing nitrogen. Of most interest were certain pyrrolidine and imine structures with either one or two chiral centers.

The simplest pyrrolidine structure was 2-(methylbutyl)-pyrrolidine (**35** = the *R* enantiomer). The (*R*) enantiomer had a "roasted-seafood note (strong, metallic)", while the (*S*) isomer had a "seafood-like note (strong, mild)". With a further methyl substituent, (2′-methylbutyl)-2-methylpyrrolidine, a second chiral center was present (**36** = 2*R*,2′*R* enantiomer). The odors of the four stereoisomers were as follows: (2*R*,2′*R*), irritating roasty note (metallic); (2*S*,2′*S*),



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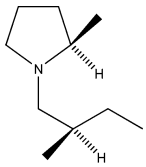
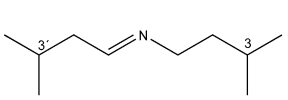


36

chocolate-like note (mould-like, weak); (2*R*,2′*S*), green note (weak, roast); (2*S*,2′*R*), mouldy note (earthy, chocolate-like).[61]

Further components of the roasted shrimp aroma are imines—2[or 3]-methyl-*N*-(3′[or 2′]-methylbutylidene)butanamine.[62] There are four such structures, one being achiral, two having a single chiral center, and one having two chiral centers. All of the possible isomers have been prepared, and the odors have been evaluated; the descriptions are somewhat lengthy and have been abbreviated here. The achiral material, 3-methyl-*N*-(3′-methylbutylidene)-butanimine (**37**), was described as oily, fish guts pickled in salt, bacon-like element with sweet chocolate, cocoa, jam. The two imines with a single chiral center are shown in the (*R*) configuration as **38** and **39**. Odors are as follows:[62] (*R*)-**38**, heavier esteric odor than (*S*)-**38**, fruity, cereal-like, slightly fishy scent; (*S*)-**38**, amine, internal organs of shrimp, cocoa-like element with sweet butter-like odor; (*R*)-**39**, heavy, strong seafood element, seaweed with sweet butter-like odor; (*S*)-**39**, light, strong seafood element, fruity including apple, pineapple, chinese quince, pear.



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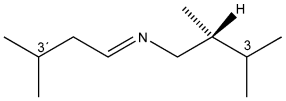

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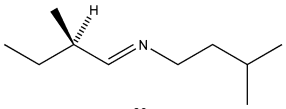

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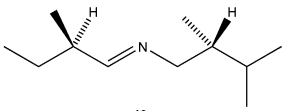


40

The single structure with two chiral centers is shown as the (*R*,*R*) isomer, **40**. Odors were rated as follows for the four stereoisomers of **40**: (*R*,*R*), mild sweet fruity, slightly phenolic element including peel of mango, apple, citrus; (*S*,*S*), light, metallic, oily, seafood with sweet butter-like and esteric scent; (*R*,*S*), seafood, fish odor with phenolic, esteric, fruity element; (*S*,*R*), metallic, slightly heavy cocoa-like with esteric, fruity element, sweeter than (*S*,*S*), image of burned fish, shrimp.

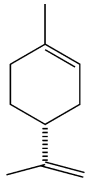
A reader of this paper[62] has an amazing sense of a whole meal in one sniff—seafood, butter, fruit, cocoa! The authors suggest that some of these imines might find use as seafood flavors and also as fruit flavors such as mango.

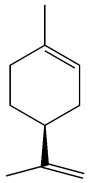
7. Sulfur Compounds

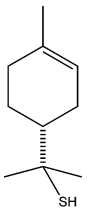
The rotten egg odor of H_2S, the pungent smell of SO_2, and the unpleasant odors of some thiols (mercaptans) give sulfur a poor reputation in the aroma area. However, sulfur compounds are commonly found as secondary metabolites in both plants and microorganisms and in many cases have pleasant rather than offensive odors—an example is the previously noted grapefruit aroma of (*R*)-(+)-1-*p*-menthen-8-thiol.

Sulfur-containing aroma chemicals vary in structure from methional, $CH_3-S-CH_2-CH_2-CHO$ (odor of bread or vegetables) to more complex heterocyclic structures such as oxathianes (see later).[63] They are some of the strongest odorants so far known.[64] An outstanding example is the substantial contribution of sulfur compounds to the odor/taste properties of yellow passion fruits (*Passiflora edulis* f. *flavicarpa*). These fruits have a "floral, estery aroma with an exotic tropical sulfur note".[65] In a recent comprehensive study, more than 100 sulfur volatiles were detected after enrichment by preparative multidimensional capillary GC, and 47 of them were specifically identified. Of these, 35 were reported for the first time in passion fruit and 23 were previously unknown sulfur-containing natural products. The identified compounds covered a wide range of chemical structures, the simplest being diethyl disulfide, $C_2H_5-S-S-C_2H_5$.

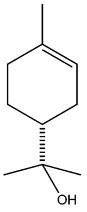
There are many instances of odor differences with enantiomers of sulfur-containing compounds. It is interesting to examine the effect of oxygen and sulfur by comparison of limonene (*p*-mentha-1,8-diene) with α-terpineol (1-*p*-menthen-8-ol) and the previously discussed 1-*p*-menthen-8-thiol. (*R*)-(+)-Limonene (**41a**) has an orange odor, and both the (*R*)-(+) enantiomers of 1-*p*-menthen-8-thiol (**17a**) and α-terpineol (**42a**) retain a fruity or floral characteristic. (*S*)-(−)-Limonene (**41b**) is described as either turpentine or lemon; the thiol (**17b**) is nearly odorless, and the alcohol (**42b**) is tarry.[9]


41a

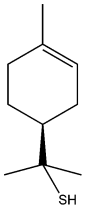

41b



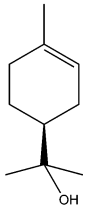
17a



42a

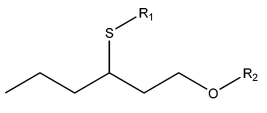


17b



42b

Another instructive case is provided by 3-thio- (**43**, $R_1 = R_2 = H$) and 3-methylthiohexanols (**43**, $R_1 = CH_3$, $R_2 = H$) and esters of these structures that occur in passion fruit.[65] The "parent" molecule is 3-thiohexanol, $CH_3(CH_2)_2-CH(SH)-(CH_2)_2-OH$; it shows an intense sulfur odor with both enantiomers. The corresponding methoxy structure, 1-methoxyhexane-3-thiol, has been isolated as an odor signal compound from flowering clary-sage plants, *Salvia sclarea*.[66] The odor was described as both intriguing and repulsive, reminiscent of human armpit perspiration. Both enantiomers of this material were synthesized. The characteristic odor was only found with the (*S*) enantiomer (**44**); this isomer



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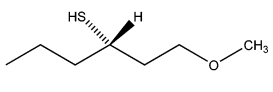

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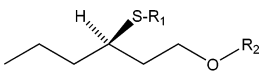
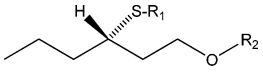
Table 3. Odors for Enantiomeric 3-Thio- and 3-Methylthiohexanols and Their Esters



43a



43b

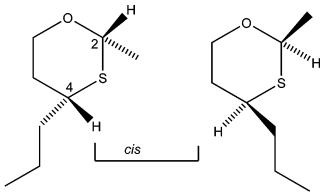
$R_1 = R_2 = H$	intense sulfur odor	intense sulfur odor[a]
$R_1 = H$, $R_2 = COCH_3$	tropical fruit	sulfur, herbaceous
$R_1 = H$, $R_2 = CO(CH_2)_2CH_3$	tropical fruit	sulfur, oniony
$R_1 = H$, $R_2 = CO(CH_2)_4CH_3$	herbaceous, fresh sulfur	burnt sulfur
$R_1 = CH_3$, $R_2 = H$	herbaceous, weak	exotic, fruity
$R_1 = CH_3$, $R_2 = COCH_3$	fruity	intense sulfur, herbaceous
$R_1 = CH_3$, $R_2 = CO(CH_2)_2CH_3$	fruity, very weak	oniony
$R_1 = CH_3$, $R_2 = CO(CH_2)_4CH_3$	fruity, very weak	weak oniony, roasty

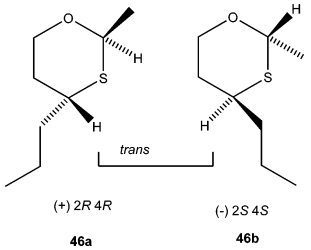
[a] Note that in this case there is no enantiomeric difference.

also had strong connotations of burnt sulfur and alliaceous notes. In contrast, the (*R*) enantiomer was merely sulfury, herbaceous, and onion-like. The detection thresholds were very low: (*S*) = 0.04×10^{-3} ng L^{-1} air and (*R*) = 1.09×10^{-3} ng L^{-1} air. In the volatiles from the plant, the (*S*)/(*R*) ratio was 6:4.

Returning now to the enantiomers of 3-substituted hexanols and their esters, results are summarized in Table 3. In general, the (*R*) enantiomers (**43a**) have a typical, fruity aroma; however, this situation is reversed with 3-methylthiohexanol where the (*S*) enantiomer has an exotic, fruity odor.[67] Two of the 3-thiohexyl alkanoates (**43b**, $R_1 = H$, $R_2 = COCH_3$, and **43b**, $R_1 = H$, $R_2 = CO(CH_2)_2CH_3$) occur in passion fruit as the (*S*) isomers.[68]

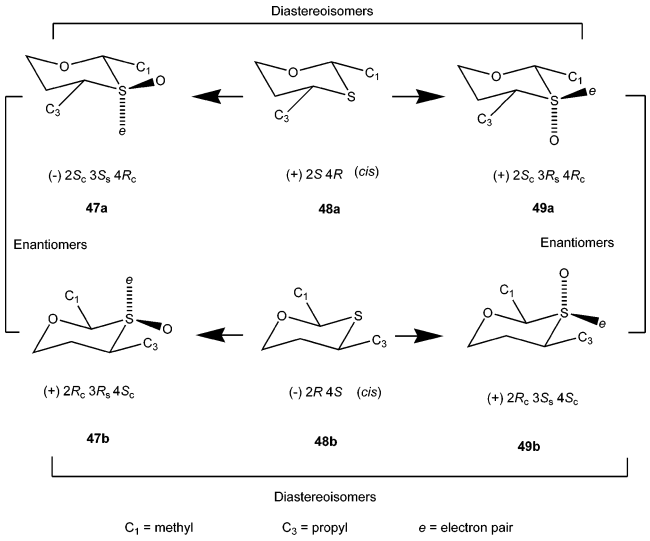
Another passion fruit flavor compound with interesting stereochemical features is 2-methyl-4-propyl-1,3-oxathiane. This compound exists in *cis* and *trans* forms, and early work established a 10:1 *cis*/*trans* mixture in passion fruit juice. There are four stereoisomers, two *cis*, (+)-(2*S*,4*R*) (**45a**) and (−)-(2*R*,4*S*) (**45b**), and two *trans* enantiomers, (+)-(2*R*,4*R*) (**46a**) and (−)-(2*S*,4*S*) (**46b**). All four have been obtained





and evaluated with respect to odor: **45a**, fatty, fruity-green, tropical fruits, grapefruit; **45b**, sulfurous, herbaceous green, roasty linseed oil-like, onion; **46a**, green-grass root, earthy red radish note; **46b**, sulfurous, slight bloomy-sweet odor, less intense than **46a**. In other words, there are clear differences among the enantiomeric forms. The (4*R*) configured materials tend to be fruity or grassy, and the (4*S*) materials tend to be sulfurous.[69,70] In passion fruit volatiles, the major component is the *cis* (2*R*,4*S*) stereoisomer (**45b**); there are smaller amounts of the *trans* (2*S*,4*S*) (**46b**). In perfumery, a preparation of 2-methyl-4-propyl-1,3-oxathiane is used under the trade name Oxane. This is a singularly unfortunate choice since in chemical terminology oxane refers to tetrahydropyran and other materials.

In addition to chirality at carbon, chirality at sulfur is also possible in compounds such as sulfonium salts, sulfoxides, and sulfoximines and plays an important role in the chemical reactions of biology.[71] However, this writer is unaware of any case where odor differences have been found for enantiomers with chirality dependent only on sulfur. Nevertheless, studies on the *S*-oxides (sulfoxides) of the *cis*-2-methyl-4-propyl-1,3-oxathiane do indicate an influence of sulfur chirality for compounds with two chiral carbons and one chiral sulfur. For 2-methyl-4-propyl-1,3-oxathiane-3-*S*-oxide, eight stereoisomeric forms are possible, four for the *cis* series and four for the *trans* series. The four *cis* oxides have been prepared and evaluated for odor; they will be discussed here in terms of conformations of the six-membered ring of 2-methyl-4-propyl-1,3-oxathiane (four carbons, one oxygen, one sulfur). These *cis* structures are most likely in a chair conformation with both methyl and propyl groups occupying equatorial positions.[69] The two enantiomeric forms of the parent *cis* oxathianes, (+)-(2*S*,4*R*) (**45a**) and (−)-(2*R*,4*S*) (**45b**), can be rewritten in conformational structures as **48a** and **48b**, respectively. On formation



of the *S*-oxides, each enantiomer gives rise to two diastereoisomers, one with the oxygen equatorial and one with the oxygen axial. From **48a** are derived (−)-(2S_c,3S_s,4R_c), equatorial oxygen (**47a**) and (+)-(2S_c,3R_s,4R_c), axial oxygen (**49a**) (the subscripts c and s refer to CIP descriptors at carbon

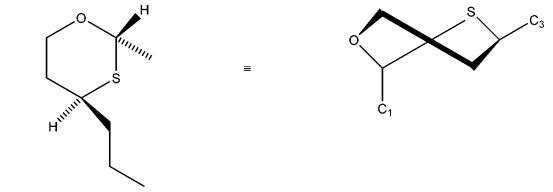
and sulfur, respectively[71]). Similarly, from **48b** are derived (+)-(2R_c,3R_s,4S_c), equatorial oxygen **47b** and (−)-(2R_c,3S_s,4S_c), axial oxygen, **49b**. That there are differences with respect to enantioselectivity and diastereoselectivity is indicated by the odor evaluations[72] shown below.

(-)-(2S_c, 3S_s, 4R_c), eq O, **47a**		(+)-(2S_c, 3R_s, 4R_c), ax O, **49a**
Intensive, exotic fruit note, very volatile	Diastereoisomers	Intensive, green sulfur note (reminiscent of fresh rhubarb)
Enantiomers		Enantiomers
(+)-(2R_c, 3R_s, 4S_c), eq O, **47b**		(-)-(2R_c, 3S_s, 4S_c), ax O, **49b**
Intensive, pungent green foul sulfur note (H_2S)	Diastereoisomers	Grassy, green long-lasting, unpleasant sulfur note

eq O =equatorial oxygen, ax O = axial oxygen

Although a Firmenich patent is said to indicate the presence of a 2-methyl-4-propyl-1,3-oxathiane-3-oxide in yellow passion fruit,[72] this material was not identified in a comprehensive tabulation.[65]

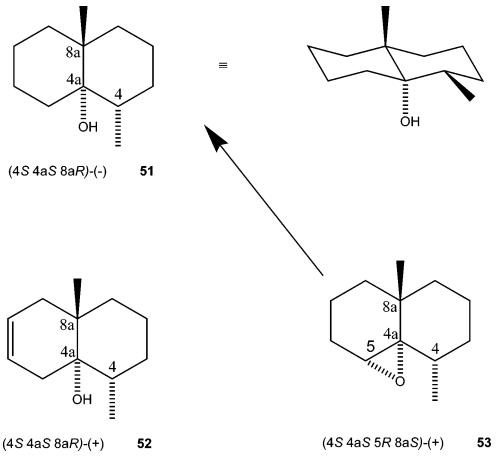
Formation of the *S*-oxides for the *trans* forms of 2-methyl-4-propyl-1,3-oxathiane has not been reported. It is, however, of interest that the *trans* compounds (**46a** and **46b**) apparently adopt twist conformations (**50a** and **50b**) rather than a chair.[69]



8. Malodorous—Or Not?

In perfumery, certain animalic odorants are much prized. The material secreted by an abdominal gland of a small deer, *Moschus moschiferous*, does not sound promising for perfume use in view of a "pyridinic, urinaceous odor" that is penetrating and persistent (ref 10, p 199). Nevertheless, musk odorants are important for perfumers (see earlier). This is also true for a fatty yellow secretion of the civet cat. In part, there is a concentration and fixative effect.

An odorant with a double-headed character is geosmin, *trans*-1,10-dimethyl-*trans*-9-decalol (or 4,8a-dimethyl-octahydronaphthalen-4a-ol) produced by a number of microorganisms. Most attention has been focused on the (4*S*,4a*S*,8a*R*)-(−) stereoisomer (**51**) that is produced by *Streptomyces* sp. and *Penicillium* sp.[73] It is also present in some wines[74] and in secretions of the millipede *Niponia nodulosa*.[75] At appropriate concentrations, (−)-geosmin has an unpleasant, moldy, musty, earthy odor and can cause problems in water supplies, in foods, especially in fish, and in wines.[73] The



enantiomer, (4*R*,4a*R*,8a*S*)-(+)-geosmin, has been prepared synthetically and has the same odor quality. However, the odor thresholds are different: for the (−) isomer, 0.0095 ± 0.0013 ppb, and for the (+) isomer, 0.078 ± 0.012 ppb.[76] There was considerable human variability in evaluating these enantiomers. Since the geosmin molecule contains three chiral centers, there are eight stereoisomers in all; there is apparently no information for the remaining six of these structures.

(−)-Geosmin apparently plays a flavor role in beets (*Beta vulgaris*). In cooked beet juice at concentrations <5.8 μg L^{-1}, it provides a characteristic "beet" flavor, but at higher concentrations, the result is "earthy". Evidence indicates that geosmin is actually a metabolic product in beets.[77] There is apparently some use of geosmin in the fragrance industry, and a 0.1% solution in dipropylene glycol is commercially available. It is said to have an "intense green, earthy, herbal note" and may be used to boost a variety of fragrance types, for example, those used in soaps, shampoos, and detergent powders.[78]

Compounds related to geosmin have also been investigated. A dominant component of the flower scent of some cacti (*Rebutia marsoneri*, *Dolichothele longimamma*, *Sulcorebutia kruegeri*) is (+)-dehydrogeosmin. The odor has a "strong, camphoraceous, earthy-musty tonality which is reminiscent of freshly ploughed soil".[79] Hydrogenation of the (−) enantiomer of natural (+)-dehydrogeosmin yields the (nonnatural) (+) enantiomer of geosmin. Hence, the configuration of the natural (+)-dehydrogeosmin is (4*S*,4a*S*,8a*S*), **52** (note the influence of the CIP sequence rules at the 8a position). Both natural (4*S*,4a*S*,8a*S*)-dehydrogeosmin and its enantiomer were prepared synthetically and had comparable odor qualities. The natural (+) stereoisomer exhibited a fresher and stronger camphoraceous tonality than the (−) isomer, with differences in the recognition thresholds: natural (+), 140 pg L^{-1} in air, and unnatural (−) isomer, 10 pg L^{-1} in air. The six other stereoisomers have not been described.

A further structural variation related to geosmin is the epoxytrinor-eudesmane sesquiterpene isolated from the North German liverwort, *Lophocolea bidentata*. This structure contains four chiral centers, and hence there are 16 possible stereoisomers. The configuration of the natural (+) material is (4*S*,4a*S*,5*R*,8a*S*) (**53**), and reduction yields (−)-geosmin. It is described as a "highly fragrant" material, apparently quite unlike the typical musty geosmin odor. Although the enantiomer, (−)-(4*R*,4a*R*,5*S*,8a*R*) was obtained synthetically, as were another enantiomeric pair, (4*S*,4a*R*,5*S*,8a*S*) and (4*R*,4a*S*,5*R*,8a*R*), no odor descriptions were given.[80]

9. A Wider View of the Perception of Enantiomers

While the focus of this review is on the human nose, the sense of smell is highly developed in many animals; it was the use of hunting dogs to follow an animal's trail that gave rise to the word scent. As might be expected, enantiomers are perceived differently in many cases, with carvone enantiomers often being used as experimental materials. The emphasis in this work is primarily on physiology, rather than on stereochemistry; all that can be attempted here is to point the reader to recent publications: rats;[29−31,81,82] mice;[28,32] squirrel monkeys;[83] fish;[84−89] honeybees (nonpheromonal substances).[90,91]

Another very large topic is that of the role of chirality in insect pheromones; in these creatures, the antennae are usually the principal olfactory sites. An excellent review by Mori[92] and a fascinating text by Eisner[93] are available. The variety of observed responses is truly remarkable—Mori lists 10 response categories. The most common relationship is that activity is present in only one enantiomer of the pheromone, and the other does not inhibit this action; examples include (+)-brevicomin (pine sawfly pheromone) and (+)-faranal (trail pheromone of the pharaoh's ant). In other cases, while only one enantiomer is bioactive, the other is inhibitory. Thus, (+)-dispalure attracts males of the gypsy moth (*Lymantria dispar*) and (−)-dispalure suppresses this response. In a few remarkable cases, individual enantiomers are inactive and both must be present for bioactivity; for example, sulcatol, an aggregation pheromone produced by males of an ambrosia beetle (*Gnathotrichus sulcatus*). Moreover, insects can use chirality to segregate different species and males from females. There are recent papers describing the reaction of moths[33,94] and pine weevils (*Hylobius abietis*)[95] to plant derived enantiomers. Cotton bollworm moths have the ability to change their response to α-pinene enantiomers as a result of experience; they can learn to discriminate in favor of an enantiomer.[96] A similar human situation was noted earlier.[45]

10. Practical Applications

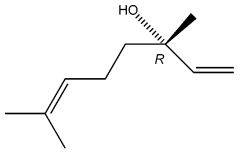
It should be clear from the foregoing that the relationship between stereochemical structure and odor, in terms of both enantio- and diastereoselectivity, is an important consideration for those working with perfumes and fragrances. One very important issue, of much concern in the food and flavor industries, is the authenticity of materials such as the essential oils derived from various plants. Similarly, wholly natural materials are prized in aromatherapy and in "green chemistry" generally. Moreover, there are legal regulations in several countries concerning natural versus nonnatural substances. Authenticity assessment has been described as a permanent challenge in food flavor and essential oil analysis.[97]

A solution to the challenge came from studies of the enantiomeric composition of some natural products. In the world of chiral natural products, a considerable number occur in nature as both enantiomeric isomers; moreover, the number occurring as racemates is larger than usually realized.[22] Examples of naturally occurring racemates are known for alkaloids, monoterpenes, sesquiterpenes, and many miscellaneous compounds. However, from a defined, specific source, the enantiomer composition of a product will generally be invariant. Thus, in an enantiomeric analysis of 13 samples of authentic essential oils of *Lavandula* species, the (*R*) enantiomer of linalyl acetate was present at >99% in 12 cases and at 98.8% in the remaining sample.[98] Clearly, if an unscrupulous operator has added less expensive synthetic material (normally a racemate), the presence of (*S*)-linalyl acetate would indicate the adulteration. Hence determination of the enantiomeric composition of a specific compound in a product sample is one way to verify its authenticity.

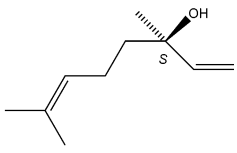
As a further illustration of a simple case involving racemate detection to indicate a problem, consider ethyl 2-methylbutyrate; this natural product is an impact flavor compound of apples and apple juices. In genuine samples, the (*S*) enantiomer is present with high enantiomeric purity (>99.5%). Detection of racemic material in a preparation definitely proves the addition of synthetic material.[97]

Very sophisticated analytical methods are now available[24] to analyze samples for enantiomeric composition. Beginning about 1988, selectively modified cyclodextrins were synthesized and used as chiral stationary phases for enantioselective capillary gas chromatography ("enantio-cGC") and enantioselective multidimensional gas chromatography ("enantio-MDGC").

Several publications concern the authenticity of the previously mentioned lavender oil, in which major components are linalool and linalyl acetate. The (*R*)-(−) enantiomer of linalool (**54a**) has the characteristic, floral, woody lavender



54a



54b

note and is the predominant isomer in authentic lavender oil, both as the alcohol itself (at least 85%) and as linalyl acetate (at least 95%).[24,97,98] Hence the presence of larger amounts of the (*S*)-(+) enantiomer indicates a lack of authenticity. A similar situation involving linalool and its acetate is presented by bergamot oil; the major components of the natural oil are also the (*R*) enantiomers.[24]

Orange juice is popular because of its pleasant and complex citrus flavor; however, adulteration has been a significant problem for the beverage industry.[99] The problem has been tackled by investigating the enantiomeric composition of chiral terpenes in commercial preparations. Again, linalool is an important component, but a mirror image situation is found in sweet orange oil, where the (*S*) enantiomer of linalool is the major component (94−96%).[100] The (*S*)-(+) enantiomer (**54b**) has a petitgrain odor (bitter or sour orange).[16] Significant adulteration was observed in several orange beverages by determination of enantiomeric composition. Other cases using enantiomeric compositions concern pulegone isomers (mint odors)[101] and monoterpenes in oils of *Salvia* sp.[102] In a study of *Pelargonium* species, the monoterpene nerol oxide was added to the list of naturally occurring racemates.[103]

The ingenuity of analysts is awe inspiring, so it is not surprising that a further element has been added to gas chromatographic methods. This technology depends on the large variations in stable isotope ratios found in nature, for example, the ratio $^2H/^1H$. Synthetic and natural materials can often be discriminated by their δ^2H_{SMOW} values. If the ratio, $^2H/^1H = R$, then

$$\delta^2\mathrm{H}_{\mathrm{SMOW}}\,(\%) = \frac{R_{\mathrm{sample}} - R_{\mathrm{SMOW}}}{R_{\mathrm{SMOW}}} \times 1000$$

SMOW refers to standard mean ocean water and is sometimes further specified as V-SMOW (Vienna standard mean ocean water). In general, depleted ^{2}H concentrations are associated with natural products, and the more enriched or less negative δ^2H values are associated with synthetic materials.

In early work, values for natural linalool, determined by isotope ratio mass spectrometry (IRMS), were significantly lower than those for synthetic material: $-297\% \pm 26\%$ and $-196\% \pm 59\%$, respectively.[104] When it became possible to determine isotope ratios on-line by gas chromatography−pyrolysis−isotope ratio mass spectrometry (GC−P−IRMS), early work suggested that it was not possible to distinguish synthetic (−207% to −301%) from natural linalool (−234% to −333%), although a distinction was possible with linalyl acetate.[105]

However, further investigation and definition of conditions did indicate a discrimination: synthetic linalool, $\delta^2\mathrm{H}_{\mathrm{V-SMOW}}$ −185% to −209%, and natural linalool, −265% to −307%.[106] The method does appear to be reliable for both linalool and linalyl acetate. In examination of eight commercial samples of lavender oil, it was possible to show that in five cases there was adulteration with synthetic linalool and linalyl acetate based on enantiomeric composition. These five samples could also be clearly identified as adulterated on the bais of the $\delta^2\mathrm{H}_{\mathrm{V-SMOW}}$ values of linalool and linalyl acetate. For three samples, there was a blend with synthetic linalyl acetate (enantiomeric ratios), but these could not be distinguished by isotope ratios due to similar $\delta^2\mathrm{H}_{\mathrm{V-SMOW}}$ values of linalyl acetate.

Developments continue. A recent publication describes a multicolumn switching device that has been developed for measuring isotope ratios; it was applied to the authentication of (*E*)-α(*β*)-ionone from raspberries and raspberry products.[107]

It may also be noted that a similar question of authenticity has been explored for terpenoids (borneol, camphor, fenchone, isomenthone, menthol, menthone) in pharmaceutical materials derived from natural sources.[108] Large discrepancies of enantiomer composition were found particularly for borneol and fenchone in certain pharmaceutical preparations.

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12. References

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