**Review Article**

**Enantioselectivity of the Musk Odor Sensation**

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**ABSTRACT**  This brief review, the summary of a talk at the Symposium on Biological Chirality 2000 in Szeged, Hungary, illustrates what chiral recognition tells us about the molecular parameters of the musk odor sensation. While the enantioselectivity of odor perception is strong evidence for the key role of proteinogenic receptors in the molecular mechanism of olfaction, the quantitative and qualitative odor differences of enantiomers are often not very pronounced, as in the case of muscone (17/26). In those cases, however, where there is strong enantiodiscrimination, we find most intense musk odorants with very low odor thresholds, such as (–)-(12R)-12-methyl-9-oxa-14-tetradecanolide (35), (12R:9Z)-12-methyl-14-tetradec-9-enolide ((R)-Nirvanolide®, 38), and (–)-(4S,7R)-1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]2-benzopyran [(–)-(4S,7R)-Galaxolide®, 57], the latter being rather rigid. We thus can assume the geometry of the musk receptor to be fairly complementary to these compounds, which therefore can serve as templates for the design of new musk odorants. *Chirality* 13:388–394, 2001.

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Chiral recognition of substrates is one of the most characteristic phenomena of biological activity, simply because receptors, proteins built from enantiopure amino acids, themselves are chiral. Thus, if an active agent possesses a chiral center, one would expect a diastereomeric interaction. And thus, enantiomeric odorants should differ in both their qualitative and quantitative characteristics.

For olfaction, there is strong biochemical evidence that signal transduction in vertebrates occurs via activation of G-protein-coupled receptors, stimulation of adenylyl cyclase, opening of cyclic nucleotide-gated channels, and subsequent membrane depolarization. The first family of odorant receptor genes, which encode these G-protein-coupled receptors with seven-transmembrane spanning topology, was discovered by Buck and Axel in 1991. Functional evidence that these receptors indeed mediate responses to odorants was provided 7 years later by Zhao et al. Before these landmark discoveries, one of the strongest indications for the key role of proteinogenic receptors in the molecular mechanism of olfaction was the enantioselectivity of odor perception.4,5

Carvone (4/5) is perhaps the best known and most prominent case for olfactory enantiodifferentiation. While (–)-(4R)-carvone (4) is reminiscent of spearmint, its enantiomer 5 smells caraway-like. Both compounds are main components of the respective essential oils and are commercially isolated from these. To exclude that certain impurities of very low thresholds were responsible for the odor differences, both enantiomers were prepared via limonene nitrosochlorides. As shown in Scheme 1, (–)-(4R)-limonene (1) was treated with ethyl nitrite and hydrogen chloride and the resulting nitrosocarbonyl (2) was dehydrohalogenated by action of potassium tert-butoxide in dimethyl sulfoxide to provide the carvoxime 3. This was then hydrolyzed in refluxing 5% oxalic acid to give the enantiomerically pure (–)-(4R)-carvone (4), which indeed showed a characteristic spearmint odor. The olfactory properties of the (+)-(4S)-enantiomer (5) were confirmed in an analogous manner, and in addition it was found to be about 65 times (2 ppb vs. 130 ppb in water) weaker than 4.6

Less known, but also very impressive, is the olfactory disparity of the enantiomers of α-ambrinol (7/8). They were resolved by fractional crystallization of the diastereomeric mixture of its (–)-(1S)-camphane acid esters 6 from pentane/diethyl ether mixtures (Scheme 2). The diastereomerically pure esters were then reduced with lithium aluminum hydride to provide 7 and 8 with enantiomeric excesses of >99.5%. While the natural (–)-α-ambrinol (7) possesses an animalic, indol- or skatol-like naphthalenic odor, its enantiomer 8 was found to exhibit a strong, dry, earthy, musty note that is typical for geosmine. However, the odor thresholds of the enantiomeric α-ambrinols differ only by a factor of 1.5–2.

An important example for extreme threshold difference is (Z)-methyl jasmonate (Scheme 3). It was separated as depicted in Scheme 3 by transesterification to the diastereomeric trans-configurated (–)-bornyl jasmonates 10 and

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which were separated by preparative HPLC. Saponification with ethanolic potassium hydroxide and esterification with diazomethane provided the diastereomeric mixtures 12/13 and 14/15, respectively, which were again separated by preparative HPLC to provide all four methyl jasmonate isomers 12–15. Of these methyl jasmonates, only the (1R)-diastereoisomers 12 and 13 have a smell, while their enantiomers 14 and 15 were found to be odorless. The diastereoisomers 12 and 13 both possess a typical floral, jasminic, slightly fruity odor, but the odor threshold of 12 is about 20 times lower than that of 13. Therefore, the odor of methyl jasmonate is almost entirely due to (+)-(1R;2S)-methyl epijasmonate (12), for which we measured a threshold of 0.012 ng/L air.

Quite astonishingly, however, these cases of high olfactory stereodiscrimination are really an exception and, in general, the enantioselectivity in odor perception is relatively small! The odors of (+)- and (–)-camphor, for instance, cannot be distinguished at all, and many enantiomeric pairs of γ- and δ-lactones, like δ-decalactone, with its typical peach note, smell almost identical. So it seems that odorant–receptor interactions are usually not so stereospecific, even if in most cases there are slight differences.

### MUSK ODORANTS

Almost everyone who has ever smelled perfumes (and is not anosmic to musks) has smelled some musk odorants because they form an essential part of the dry down of almost every perfumery creation. However, if you should not have a clear idea about what musk smells like, go into a perfumery shop and spray CK be (C. Klein, 1996) or Bvlgari pour homme (Bulgari, 1995) on a smelling strip made from blotter-paper. What you will smell after 6–8 h on that blotter, when the more volatile part has evaporated, are musk odorants. Alternatively, you can also find a rub-and-smell figure on musks in a recent review article on the chemistry of odorants.

Highly substituted nitroarenes like Musk Ketone (16) were the first commercial musk odorants (Fig. 1). They had been discovered by Albert Baur in the search for new...
explosives and remarkably possess significantly lower odor thresholds than the natural lead (–)-(3R)-muscone (17), which is the principal odorous constituent of the secretion of the male musk deer Moschus moschiferus, from which the term “musk” was derived. The structure of 17 was elucidated by Leopold Ruzicka in 1926. Just 1 year later, Max Kerschbaum found 15-pentadecanolide (18) in Angelica root oil (Archangelica officinalis Hoffm. syn. Angelica archangelica L.). It became one of the most important macrocyclic musk odorants and is known under the trade names Cyclopentadecanolide® (Haarmann & Reimer), Exaltolide® (Firmenich), Pentalide® (Soda Aromatics), and Thibetolide® (Givaudan).

Yet the comparatively high price of the macrocycles at that time did not allow them to supersede the nitro-musks, even though the photochemical reactivity of the latter caused disoloration and skin sensitization problems. These problems, however, led to the development of the so-called polycyclic musks, the first of which, Phantolide® (19) was introduced in 1952. Galaxolide® (20) marks the next milestone in the musk-odorant timeline (Fig. 1). It possesses a lower threshold, an even higher chemical stability than 19, and is still the most-used musk today. Because of their better biodegradability, macrocycles and other biodegradable musks, however, are constantly gaining ground.

The first example of a new class of musks was Cyclo-musk® (21) discovered in 1975 by BASF.10 Another remarkable structure is the epoxy musk Moxalone® (22) introduced into perfumery by Givaudan in 1983. Finally, the recently developed, Nirvanolide® (23)11 demonstrates that macrolides can possess thresholds as low as nitro-musks—over 100 years after Musk Ketone® (16) was discovered.

**Macrocyclic Musks**

The odor properties of the enantiomeric muscones (17/26), were reported as late as 1989.4 Both were prepared by diastereoselective cyclopropanation, directed via chelation control by a homochiral protecting group (Scheme 4). Reductive opening of the cyclopropane ring employing lithium metal in liquid ammonia and tert-butanol led to the optically active muscols that were oxidized to the target compounds with pyridinium dichromate.12 The odor difference as well as the difference in thresholds of the muscone enantiomers 17 (95.5% ee) and 26 (97.7% ee) were, however, not very pronounced. While the musk note of the naturally occurring (–)-(3R)-muscone (17) was described as ‘very nice, rich and powerful,’ the musk note of its (+)-(3S)-enantiomer 26 was found ‘poor and less strong.’ The odor threshold in water differed only by a factor of 3.8, i.e., 61 ppb for 17 and 233 ppb for 26.4

The first example for qualitative odor differences of enantiomeric macrocyclic musks was 12-methyl-13-tridecanolide (29/30).13 While 13-tridecanolide is not musky, the (+)-(12R)-12-methyl-13-tridecanolide (29) possesses a musk note with a sandalwood tonality, and its (–)-(S)-enantiomer 30 has an animalic musk tonality with camphoraceous aspects. Both enantiomers were prepared by ring enlargement of cyclodecanone (27) with a chiral building block (Scheme 5). Central intermediates were 13-methyl-11-oxabicyclo[8.4.0]tetradec-1(10)-enes like 28; the enantiomeric purity of the resulting target molecules was 98.8% ee (29) and 99.3% ee (30). Both enantiomers of 12-methyl-13-tridecanolide were found in Angelica root oil (Archangelica officinalis Hoffm. syn. Angelica archangelica L.) in a ratio of 72 (29) : 28 (30).14 The dimethyl-macrolide (–)-(12S;13R)-12-methyl-13-tetradecanolide is devoid of any

![Scheme 4. Synthesis and odor of the enantiomeric muscones (17/26).](image-url)
musk note but has an animalic cedarwood profile with camphoraceous aspects, while its enantiomeric (+)-(12R;13S)-12-methyl-13-tetradecanolide possesses a strong woody odor with pronounced musk character. The enantiomers of the 13-tetradecanolides emanate similar woody combination odors with only a faint musk-like character.17

\( (-)-(12R)-12\text{-methyl-9-oxa-14-tetradecanolide (35)} \) was the first example of only one enantiomer of a macrocyclic musk odorant smelling and it possessed the lowest threshold reported for a macrocyclic musk at that time; its enantiomer was odorless on GC/olfactometry. A key step in the enantioselective synthesis (Scheme 6) was the desymmetrization of 3-methylglutaric anhydride (31) with \((-)-(1S)-1\text{-naphth-1-yl})ethanol. Borane reduction of 32, THP protection, LAH reduction, Williamson reaction with \(\sigma\)-bromoheptyl-OBO, and Collaud cyclization by polymerization/depolymerization of the resulting \(\sigma\)-hydroxycarboxylic acid 34 provided the (R)-configured methyl oxamacrolide 35 with 87.2% ee. Its odor threshold was determined by GC/olfactometry as 0.09 ng/L air and its intense musky, fruity, powdery odor was reminiscent of the nitro musk Musk Ambrette, with additional woody, myrrh-type facets.

Even lower than that of 35 is the threshold of the related (12R;9Z)-12-methyl-14-tetradec-9-enolide (38, \(R\)-Nirvanolide) with 0.05 ng/L. It was synthesized from 33 by pyridinium-chlorochromate oxidation, Wittig olefination, deprotection, Appel bromination, and macrocyclization under high dilution (Scheme 7). It possesses an intense musky, fruity, powdery odor with lactonic nuances, and its enantiomer turned out to be odorless on GC/olfactometry as well.

**Alicyclic Musks**

Cyclomusk (21) was the first representative of this latest class of musk odorants, but nothing is known about the odor properties of its stereoisomers. However, for Helvetolide the \((+)-(1^{S}1^{R})-2-[1^{S}3^{S}3^{S}\text{-dimethylcyclohexyl)]ethoxy]-2-methylpropyl propionate (41) was claimed to be more intense and more musky than its \((-)-(1^{R}1^{S})\)-enantiomer, which, however, was reported to be quite similar in tonality. As depicted in Scheme 8, 41 can be prepared from \((+)-(3S)\)-dihydromyrcene (39), which itself is accessible by pyrolysis of \((+)-(1R;2S;5R)\)-pinane or \((-)\-
(1S;2S;5S)-pinane. Cyclization of 39 by treatment with acetic acid containing a catalytic amount of sulfuric acid provided after alkaline hydrolysis of the intermediate acetates (+)-(1S;1'R)-1-(3',3'-dimethylcyclohexyl)ethanol (40). Acid-catalyzed ring opening of isobutylene oxide with 40, and esterification with propionic anhydride concluded the stereospecific synthesis of 41. Also for 1'R-(3'S,3'R-dimethylcyclohexyl)ethoxycarbonylmethyl propionate, the musk odor is mainly due to the (1'S;1'R)-stereoisomer.

**Polycyclic Musks**

Polycyclic musks are not only interesting because of their commercial importance but also because their relatively rigid structures make them ideally suited for molecular-modeling studies. However, not many odor descriptions and thresholds of enantiomeric polycyclic musks exist. The first one concerns Fixolide® (= Tonalide®, 46/47), the (–)-(3S)-isomer 46 of which has a strong musky odor with good fixation properties, while its (+)-(3R)-enantiomer 47 possesses just a light and sweet aromatic odor. 46 was synthesized from (–)-(4S)-pyrocine (42) by Friedel-Crafts alkylation of toluene, halogenative decarboxylation, hydrogenolytic dehalogenation, and subsequent Friedel-Crafts acetylation, as shown in Scheme 9. Its enantiomer 47 is available on the same route but starting from (+)-(4R)-pyrocine.

The aldehyde 53 in Scheme 10 constitutes a constitutional isomer to Fixolide® (= Tonalide®, 46/47) and was claimed to be much stronger than its parent compound. Its enantioselective protonation of the lithium enolate of 2,2,4,5-tetramethylhex-4-en-3-one (48) with (–)-(1R;2S)-N-isopropyl-ephedrine. Friedel-Crafts alkylation of 1,2-xylene employing the resulting (–)-(4R)-2,2,4,5-tetramethylhex-5-en-3-one provided 50 with 80–85% ee. Lithium-aluminum reduction followed by acid-catalyzed elimination, Wagner–Meerwein rearrangement, and cyclization led to the C₂-symmetric tetrahydrooctamethynaphthalene 52. Ceric-ammonium-nitrate oxidation of 52 in the last step then provided the aldehyde 53 with 77% ee. The musky, very earthy, slightly ambery odor of the (–)-(6S;7S)-5,6,7,8-tetrahydro-3,5,5,6,7,8,8-heptamethynaphthalene-2-carbaldehyde (53) was perceived much stronger than that of its (+)-(6R;7R)-enantiomer, which is less earthy, with an additional woody tonality. Close in odor to these aldehydes are the corresponding nitriles, of which also the (–)-(6S;7S)-enantiomer is the more characteristic and intense one.

**Scheme 8.** Synthesis of (+)-(1'S;1'R)-Helvetolide® (41).

**Scheme 9.** Synthesis and odor of the Fixolide® enantiomers 46 and 47.

**Scheme 10.** Synthesis of a constitutional aldehyde to Fixolide® by enantioselective protonation of the lithium enolate of 48.
The odor of the commercially most important polycyclic musk odor Galaxolide® (57–60) was found to be due almost entirely to its (–)-(4S)-isomers 57 and 58 (Scheme 11).25 All four Galaxolide® isomers 57–60 were synthesized by Friedel–Crafts alkylation of pentamethylindane (54) with (–)-(2S)- and (+)-(2R)-methyloxirane, respectively, and acid-catalyzed reaction of the products 55 and 56 with paraformaldehyde. The formed diastereomeric pairs 57/58 and 59/60 were separated by flash chromatography of their η-aryltricarbonylchromium complexes, which afterwards were decomposed by oxidation. Interestingly, the configuration at C-4 has a decisive influence on the odor threshold, while the configuration at C-7 is of minor importance. The (–)-(4S,7R)-isomer 57 possesses the lowest odor threshold, with 0.63 ng/L, and the most typical, very pleasant musk character. The (–)-(4S,7R)-configured 58 is only slightly less intense, with a threshold of 1.0 ng/L and a musk note with dry aspects. However, with 130 ng/L (59) and 440 ng/L (60) the (+)-(4R)-configured Galaxolide®-isomers are weak to odorless, with uncharacteristic or even fruity nuances. Thus, the methyl group at C-7 of Galaxolide® seems to be situated in a hydrophobic bulk region of the olfactory receptor, which is not very shape-dependent, while the C-4 methyl group determines the profile of the odorant that is oriented on the receptor by the osmophoric ether oxygen. Or transferred into the old (1894) but vivid “lock-and-key” model of Emil Fischer: The osmophoric (most polar functional) group “inserts” the molecule into the receptor, the profile “codes” the information, and bulky substituents provide a “firm grip.” Together these molecular features make up the olfactophore, the “key” for a given odor note (Fig. 2).

Interestingly, enantioselective biotransformations of Fixolide® (= Tonalide®, 46/47) and Galaxolide® (57–60) have been reported for tench (Tinca tinca) and crucian carp (Carassius carassius), respectively; in the latter case the (–)-(4S)-isomers (57/58), which are also the olfacto- rily most active ones, were found to be metabolized preferentially.26 The stereochemistry of the Fixolide®-isomers 46 and 47 in tench and tench liver was not assigned. For a detailed review on recent developments in fragrance chemistry and the current trends in musk odorants, see Ref. 9.

CONCLUSION

High stereodifferentiation, as in the case of (–)-(12R)-12-methyl-9-oxa-14-tetradecanolide (35), (12R,9Z)-12-methyl-14-tetradec-9-enolide (38), and (–)-(4S,7R)-Galaxolide® (57), indicates that the musk odorant fits the complementary binding site of the receptor very well. This results in very intense musk odorants with extremely low thresholds, while their enantiomers are (almost) odorless. With the help of such stereoisomers, we thus can gain insight into

Scheme 11. Synthesis and olfactory characterization of all four Galaxolide® isomers 57–60.

Fig. 2. The molecular parameters of a musk odorant transferred into a “lock-and-key” model.
the receptor geometry—and we can draw the following conclusions:

- If both enantiomers of a given odorant possess similar odor thresholds, the stereogenic element either hinders the interaction with the receptor or is situated in a hydrophobic bulk region, the geometry of which is of secondary importance.
- Because the stereogenic element of chiral fragrant substances with extremely low thresholds is likely situated in a profile region, the odor of powerful chiral odorants is likely to be due to just one enantiomer, while the other is expected to be odorless or very weak and uncharacteristic.
- If there are no such examples of high enantioselectivity for a given class of odorants, it is likely that more intense odorants of that family can be discovered, and by placing stereogenic elements in different parts of the molecule one can locate profile and bulk regions (Fig. 2).

**LITERATURE CITED**


