

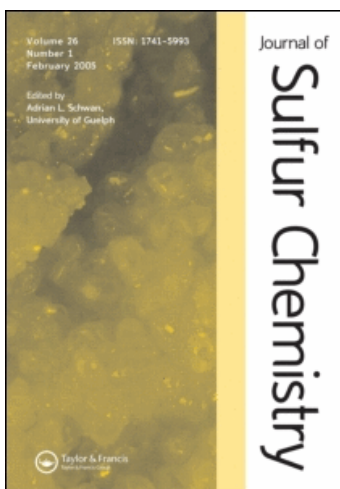
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Journal of Sulfur Chemistry

Publication details, including instructions for authors and subscription information:

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SULFUR-CONTAINING ODORANTS IN FRAGRANCE CHEMISTRY

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To cite this Article Goeke, Andreas(2002) 'SULFUR-CONTAINING ODORANTS IN FRAGRANCE CHEMISTRY', *Journal of Sulfur Chemistry*, 23: 3, 243 – 278

To link to this Article: DOI: 10.1080/01961770208050160

URL: <http://dx.doi.org/10.1080/01961770208050160>

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SULFUR-CONTAINING ODORANTS IN FRAGRANCE CHEMISTRY

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(Received 11 March 2002; in final form 24 April 2002)

Sulfur-containing compounds are some of the strongest odorants. The perception of their odors often depends on their concentration as well as on their chemical, diastereo- and enantiomeric purity. Even if present only in trace amounts, they may change the overall olfactory impressions of fragrant mixtures, which makes the art of composing perfumes both difficult as well as rewarding. In the fruity area, compounds such as 8-mercapto-*p*-menthan-3-one (37), *p*-menthene-8-thiol (59), 3-mercapto-hexanol (62) and Oxane® (100) have gained unimpeachable superiority in terms of imparting natural fruitiness and freshness which transmits also into other olfactory domains. With regard to fragrance chemistry, the article gives a review of the particular odor properties, structure–odor correlations, biological significance and of the biochemical generation of sulfur-containing odorants.

Keywords: Sulfur-containing odorants; Fragrances; Structure–activity relationships; Natural scents

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1. INTRODUCTION

Sulfur-containing odorants live a shadowy existence in fragrance chemistry. The reasons are most often their obnoxious, unpleasant odors when smelled at high concentration, their instability towards oxidation and, in addition, the prejudiced generalization of these facts leading to the opinion that these compounds cannot be reliably incorporated into perfumes.

In flavor chemistry, there is a completely different understanding, and this subject is inseparably connected to many sulfur-containing odorants, above all the so-called character impact sulfur compounds [1], i.e. those chemicals which are mainly responsible for the sensory properties of a specific natural scent. Such compounds for instance were isolated from onion, garlic, radish, cress and other vegetables as well as from truffle, meat, fish, bread and coffee (1–21, Fig. 1).

Apart from these more or less flavor (foodstuff) related materials, character impact sulfur compounds and many other sulfur-containing odorants which add an olfactory facet to a natural scent were also found in various fruits, essential oils, absolutes and resins. It is the overlapping domain with perfumery that is reviewed in this article. The positive and unique features of sulfur-containing odorants even led to new concepts in perfume composing, in particular with regard to fruity fragrances. Their

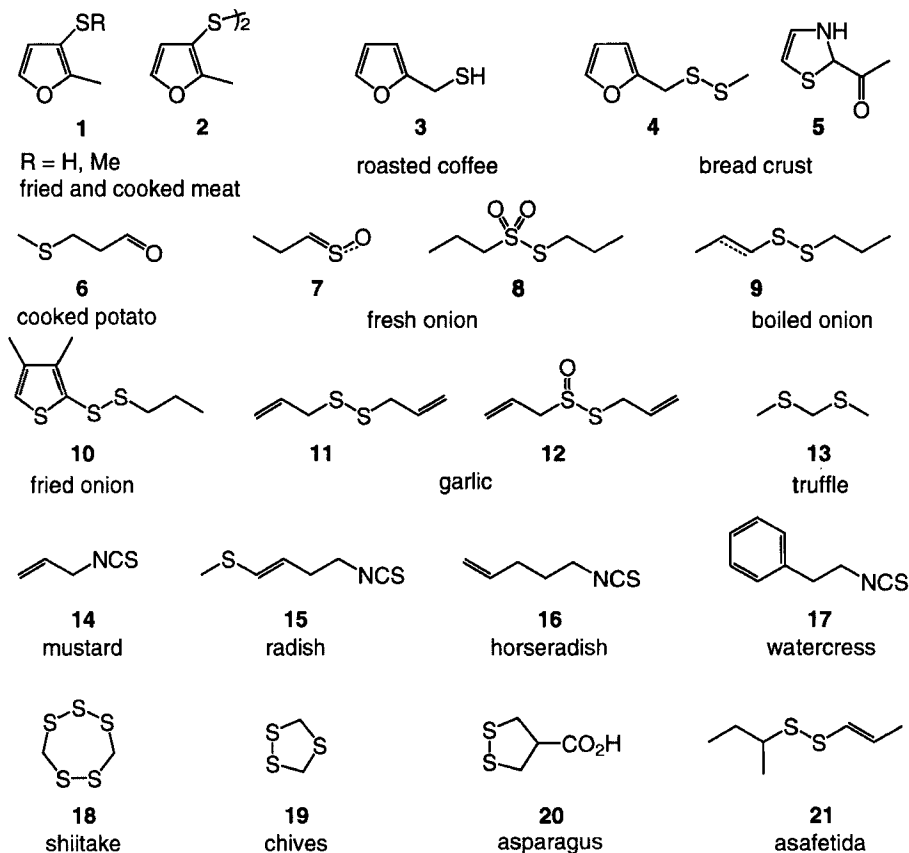


FIGURE 1

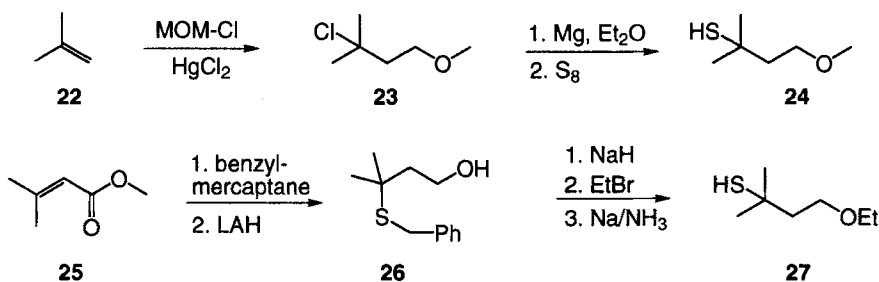
odor characteristics, structure–odor correlations, as well as their biological significance and biochemical generation known so far, will be discussed.

2. FRUITY ODORS

2.1. Blackcurrant (Cassis) and Buchu

Burgeon de cassis, the essential oil from the flower buds of blackcurrant shrubs (*Ribes nigrum*), has a very characteristic odor, much appreciated in perfumery. Due to the high price, its use has been limited in the past, but with respect to the applicability of sulfur-containing odorants in perfumery, the history of the cassis odor family constitutes a good example of how closely difficulties and benefits are related.

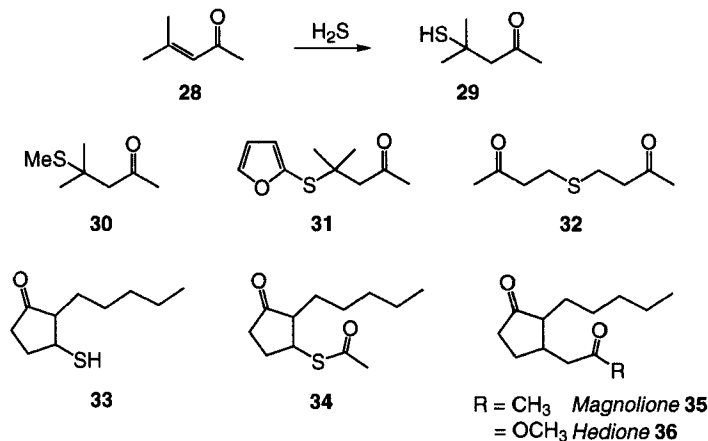
From various species of *Ribes*, only 4-methoxy-2-methyl-2-butanethiol **24** was detected as character impact odorant [2]. In appropriate dilution its odor is typically cassis, with floral and fruity-green aspects. Later, **24** was identified in olive oil [3], green tea [4] and *Ruta*-species [5]. According to Scheme 1, **24** was first prepared by mercuriation of isobutylene with chloromethyl methyl ether (MOM-Cl), followed by Grignard reaction with sulfur [6]. The corresponding ethyl ether **27** was claimed to share these interesting organoleptic properties [7].



SCHEME 1

However, rather than **24**, 4-mercapto-4-methyl-pentanone (**29**) seems to play an important role, when cassis type odors occur in natural scents. Its “history” is quite interesting: In 1968, 4-mercapto-4-methyl-pentanone was identified as the source of the obnoxious tom-cat urine off-odor in freshly painted chill-rooms of slaughterhouses and meat stores [8]. Apparently, the compound was formed by H₂S (from meat) addition to mesityl oxide (Scheme 2), present as a 0.4% impurity in a thinner of the paint. The odor of **29** is very unpleasant mercaptan-like at higher concentration, turns cat urine-like (where it was indeed found) [9] at concentrations higher than 0.001% but acquires a very natural crisp cassis note at trace amounts of lower than 10⁻⁵%. Although the cassis–catty odor relation might be perceived as disturbing for the hedonic claims given for perfumes, the importance of **29** in compositions was demonstrated early, e.g. for raspberry flavors, wherein **29** imparts an interesting note of *Baie Rouge* (oil of pink pepper berries) [10], or for hesperidic perfumes, when seasoned with traces of **29** have enriched fruity fresh characters [11]. Compound **29** was also shown to be responsible for the cassis aspects of wines from *Sauvignon* grapes [12]. This and other sulfur-containing odorants (*vide infra*) are being deliberated

during fermentation from *S*-cysteine conjugates [13] (rather than from *S*-cysteine conjugate sulfoxides, that were identified earlier from e.g. *Allium* species) and a method of quantifying the amount of those conjugates in grape must was proposed as a measure of the aromatic potential of *Sauvignon* wines [14]. In recent years, **29** was identified for the first time as an olfactorily important key constituent of various natural scents like box tree [15], broom [16], green tea [17], and grapefruit [18].



SCHEME 2

The methylmercaptan adduct **30** of mesityl oxide, sold as *Corps Cassis* (*Oxford*), finds occasional application in perfumery. 4-Methyl-4-furfurylthio-2-pentanone **31** was patented as a compound with a roasted aroma having a cassis connotation [19]. Other cassis-like mercaptan conjugates like **32**, **33** and **34** also occur in the patent literature [10]. Apparently, **33** imparts an impression of exotic fruits, in particular mango, while **32** and **34** rather create cassis tonalities. However, in our own GC-sniff experiments, **34** reveals a floral jasminic-fruity odor similar to that of *Hedione*[®] (**36**) and *Magnolione*[®] (**35**), potent benchmark odorants of this family (Scheme 2).

The essential oil of the leaves of buchu (*Barosma betulina*), native to southern parts of Africa, is regarded as an important alternative for the preparation of blackcurrant flavors and for fragrances. Already in 1969, Lamparsky and Schudel identified 8-mercapto-*p*-menthan-3-one (**37**) as its powerful organoleptic principal [20]: the H₂S adduct on (–)-pulegone, contained in about 10% in the essential oil [21,22]. A mixture of all possible diastereomers of **37**, also on the market as *Corps Cassis* (*Givaudan*), create an intense fruity cassis impression, accompanied by minty and burnt undertones, typical for sulfur notes. The sensory properties of **37a** and **37b** were already described by Ohloff and Sundt, who favored the *trans*- over the *cis*-compound [22]. Köpfe and Mosandl synthesized all enantiomers of **37a,b** in order to determine the organoleptic differences (Table I) [23]. They found **37b** to be the most typical, intense fruity odorant, while the (1*R*)-isomers (from (+)-pulegone) were reported to possess less pleasant characteristics. A variety of other menthanone and menthone derivatives such as **38–40** [24] and, more recently **41–50** (Fig. 2) [25], were identified as trace constituents of buchu oil. The thioacetate **38** has been known for a longer time to contribute to the cassis aspect, and the sensory properties were chiroselectively evaluated (Table I): **38a** seems to have the most interesting organoleptic properties [26].

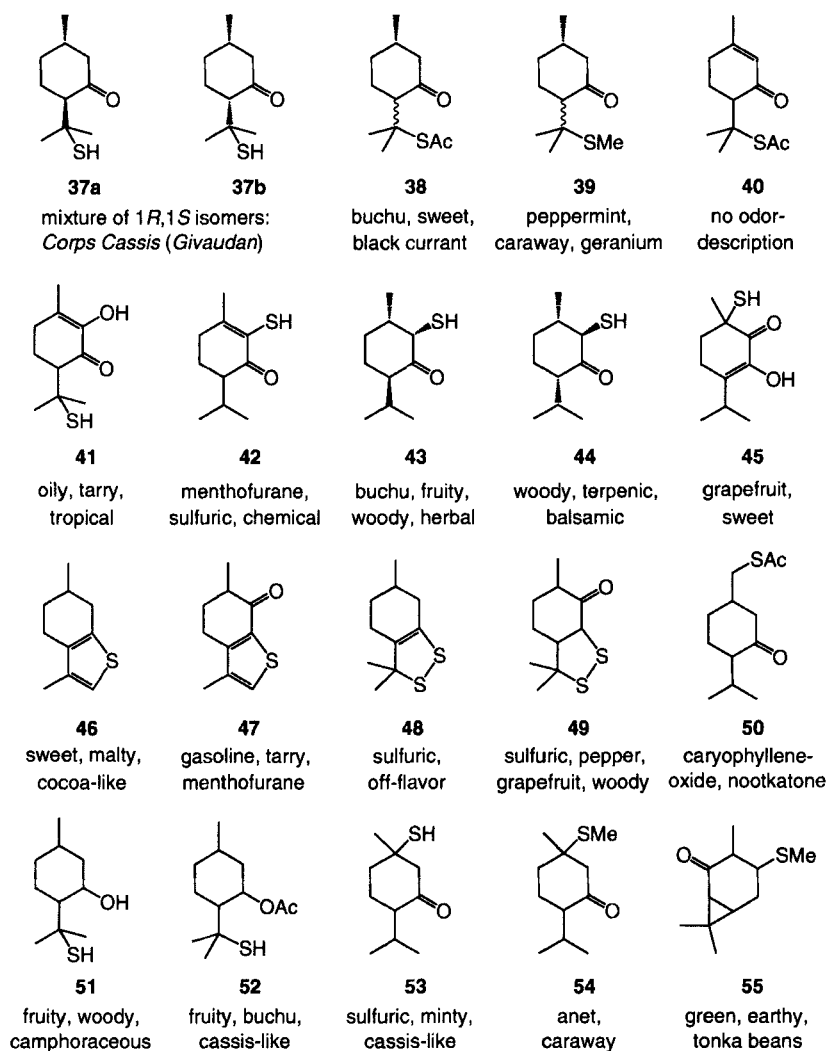
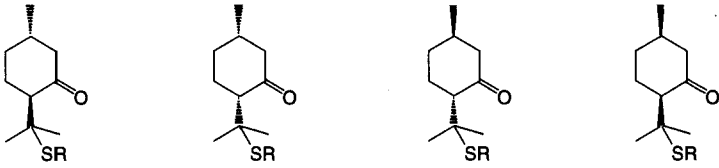


FIGURE 2

On the basis of the qualitative odor descriptions of these and several synthetic analogues **51**–**55** (Fig. 2) [27,28] and regarding the odor thresholds of a few of these compounds, some structure–odor correlations can be summarized. Generally, the odor of sulfur-containing compounds is very much dependent on their concentration, a dependence which is believed to be brought about by the ability to trigger different receptor sites in the olfactory bulb of the nose (so-called multiplicity of compounds). Regarding the extremely low odor thresholds, it is obvious that subanalytical traces of sulfur-containing impurities may have a significant influence on the perception of a “chemically pure” sulfur compound.

The strongest and most typical cassis or buchu odorants are those having a free tertiary mercapto-group in a 2–4 Å distance to a carbonyl group [29]. The steric bulk around the mercapto-group is of importance, since primary or secondary mercapto ketones are not very potent or lose their cassis character. Flexible 2-mercapto-ketones

TABLE I Sensory evaluation of menthanone derivatives



No.	Sensory evaluation (0.1% in water)			
	(1 <i>S</i> ,4 <i>S</i>)- a	(1 <i>S</i> ,4 <i>R</i>)- b	(1 <i>R</i> ,4 <i>R</i>)- a'	(1 <i>R</i> ,4 <i>S</i>)- b'
37 (H)	Sulfuric, tropical fruit, clear buchu-leaf note, strong	Blackcurrant, passionfruit, most intense fruity note	Onion, slightly fruity, rotton	Rubber, burnt, sulfuric, unpleasant
38 (Ac)	Green, blackcurrant, exotic fruit, intensive	Strong, sweet, slightly pungent	Musty, sulfuric, intensive	Delicate fruity, sweet

like **60** may also attain a larger distance to the carbonyl group by *gauche* conformations. This factor, and, compared to **44**, increased steric bulk around the mercapto-group leaves some cassis character to **43**. This is also demonstrated by a number of linear 2-mercapto-ketones **65–68** that were described in a patent of IFF [30] (Fig. 3). The strong cassis/buchu odor of 3-mercapto-heptanone (**65**) is gradually overshadowed by green, minty and grape-type tonalities, as the chainlength or the steric bulk are increasing. The same tendency is visible for the perfumistically important mercapto-hexanol derivatives **62–64** (*vide infra*), that in contrast to **61** do possess fruity properties. Apparently, the hydrogen bond donor **62** is less cassis-like than the acceptor **63**, an impression that is reaffirmed by the comparison of **37** and **51**.

Compounds with fixed *syn*-conformation like in thiodiosphenol (**42**) lack the blackcurrant note. A SH–CO distance larger than 4 Å like in piperitylmercaptan **53** also diminishes this note. The circumstances for nonproton-donating methylmercaptan conjugates are ambiguous: Small molecules like **30** possess a quite intense cassis odor, while **39** or **54** do not even have sulfuric odor notes. Sulfuric aspects of **55** may be caused by impurities.

Regarding these assumptions, the quite strong cassis odor of some isomers of **38** is surprising. Although these compounds presumably did not contain free thiols (having different retention times at GC-sniff conditions), the hydrolysis of thioacetates in the mucosa of the olfactory bulb cannot be excluded. The hydrolytic activities of various enzymes on odorants [31,32] and pheromones [33] have been assumed to play an important role in olfaction.

Finally, the generally known isosterism between sulfur atoms of sulfides and *cis*-double bonds, which is apparent in the olfactory resemblance of thiophene and benzene, offers an intelligible reason for the noncassis type odors of **46** and **47**.

2.2. Grapefruit

Since the beginning of perfume creation, hesperidic ingredients like lemon, yuzu and orange oils have been used to generate fresh and clean impressions. In recent years, perfumes with grapefruit-like nuances were particularly *en vogue*. For a long time,

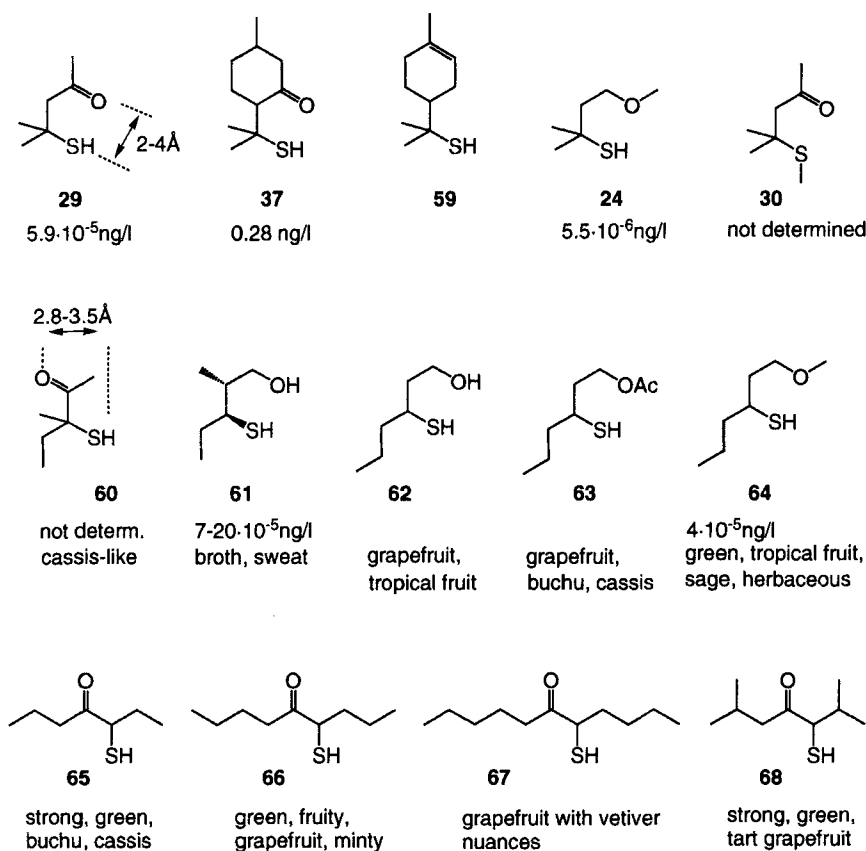
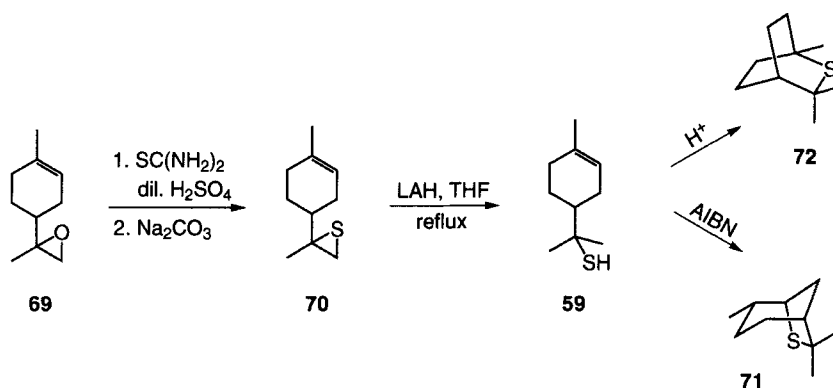


FIGURE 3

it has been assumed that volatile sulfur-containing compounds contribute to the flavors of grapefruit and orange juice [34] as well as to their essence [35]. Traces of H₂S, MeSH, Et₂S and SO₂ were detected in the headspace of fresh grapefruit juice, but the evaluation of the contribution of these volatiles were hampered by the transient nature of freshly squeezed juice [36].

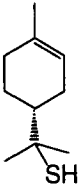
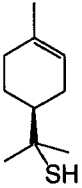
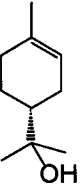
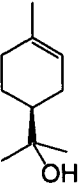


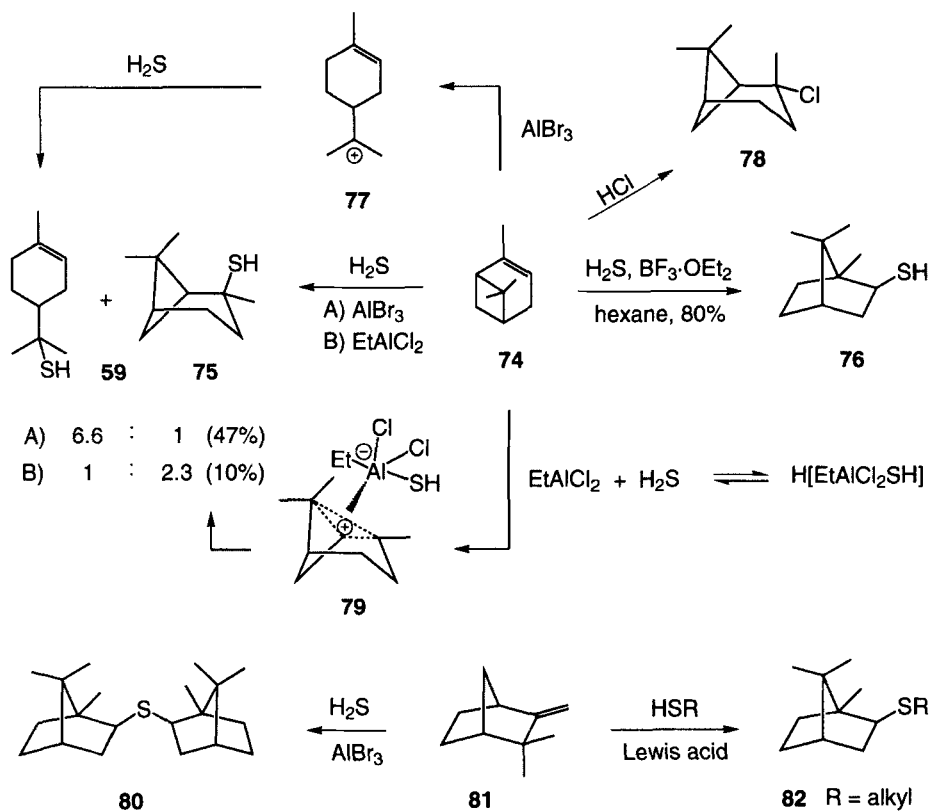
SCHEME 3

In 1982, 1-*p*-menthene-8-thiol **59** was shown to be an extremely potent constituent of grapefruit juice (*Citrus paradisi* Macfayden) [37,38], which adds the typical gaseous fresh fruity character to the substantive warm juicy woody aspects, being usually associated with the sesquiterpenes nootkatone, and dihydro-nootkatone. Later on, **59** was also identified in orange [39], yuzu [40] and must [41]. Racemic **59** as well as the (+)-*R* (94% ee) and the (–)-*S*-enantiomer (56% ee) were synthesized according to Scheme 3. Since (*R*)-limonene (> 90% ee) was identified in grapefruit oil, it was assumed to be the precursor for **59**, and a high excess of (*R*)-**59** was anticipated for the natural **59**. Natural (*S*)-limonene was less optically pure, and (–)-*S*-**59** was prepared in only 54% ee. The sensory evaluation based on these purities furnished no significant organoleptic differences [38]. However, several years later, Mosandl *et al.* revised these results after having separated (+)- and (–)-**59** by means of a GC column with a chiral stationary phase, from which both antipodes were directly smelled and evaluated (so-called GC-sniff method) [42]. The astonishing results are summarized in Table II together with the results reported for terpineol, which nicely demonstrates the olfactory impact of the mercapto-group. An earlier finding [43], which attributed an obnoxious sulfur note to (*S*)-**59** was thereby corrected: this isomer contained sulfuric smelling **71** (Scheme 3) which is co-occurring in grapefruit oil, due to stereoselective radical cyclization. The H⁺-promoted Markownikoff-type cyclization product **72** was not yet detected in grapefruit oil [38].

The fascinating odor properties of **59** stimulated the interest to further investigate the usually complex reaction mixtures of sulfur with terpenes. The formation of odorant volatiles from the reaction of sulfur with limonene had been described already in 1922 [44], and its mechanism was later elucidated [45] to explain the formation of many aromatic, mono- and bicyclic sulfides and mercaptans [46]. Similar and unusual products were detected from reactions of other terpenes with H₂S.

TABLE II Olfactory properties of **59** and terpineol (**73**)

			
<i>Odor evaluation (GC-sniff)</i>			
<i>(R)</i> - 59	<i>(S)</i> - 59	<i>(R)</i> - 73	<i>(S)</i> - 73
Grapefruit-like, strong impact <i>taste</i> threshold: 2×10^{-5} ppb	Weak, nonspecific, nearly odorless	Flowery, sweet, lilac	Tarry, reminiscent of cold pipe

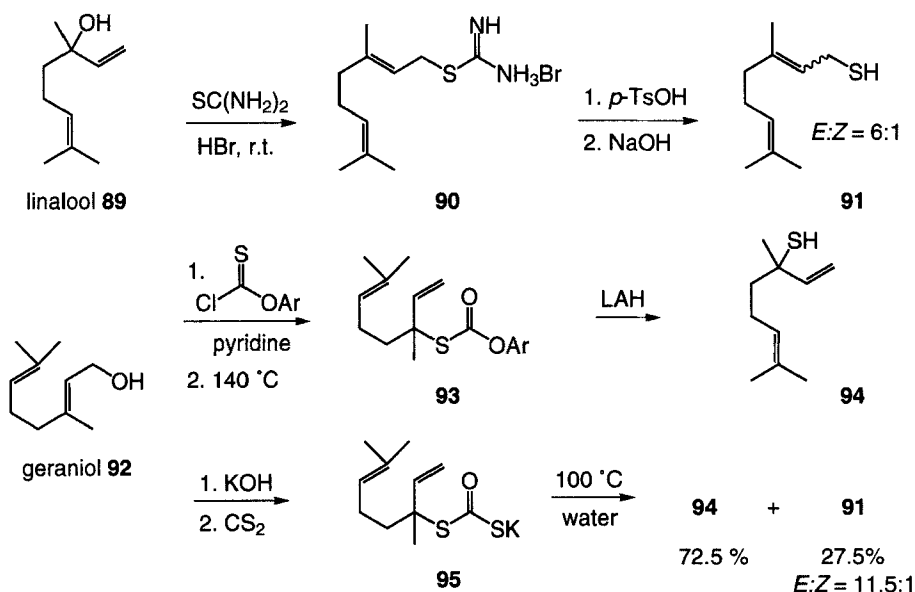
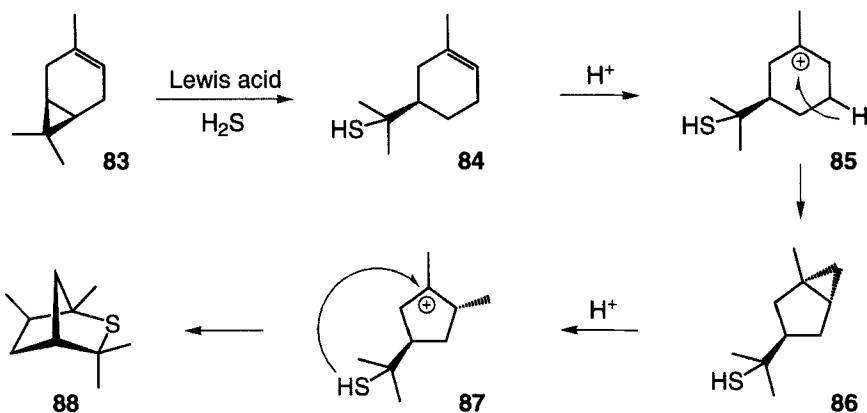


SCHEME 4

Electrophilic thiolation of α - and β -pinene mainly led, depending on the reaction conditions, to **59**, **75** or to thioborneol **76** (Scheme 4) [47]. Strongly acidic AlBr_3 promotes the pinene-menthene-isomerization, prior to hydrogen sulfide addition. This chemistry is analogous to the well known preparation of terpineol catalyzed by strong protic acids. On the other hand, weaker *Lewis* acids stereoselectively catalyze the *anti*-addition of H_2S , leading to *trans*-pinane-2-thiol **75**. This selectivity is opposite to the *syn*-addition of HCl on pinene leading to **78** [48] which is an important step in the camphor synthesis. An interaction of the thioaluminate with the nonclassical carbenium ion **79** was reasoned to be the source of this selectivity. Compared to these findings, the high yielding preparation of thioborneol from α -pinene is a surprising result [49]. Camphene was also thiolated in high yield into diisobornylsulfide **80** [47] or alkyl-bornyl-sulfides **82** [50].

Interesting cationic rearrangements led for instance to the formation of **88** by reaction of H_2S with 3-carene (**83**) (Scheme 5) [51]. *Lewis* acid catalyzed insertion into the carene-cyclopropane unit is followed by protonation and ring contraction to **86**, reprotonation with ring opening and intramolecular trapping of the cation by the mercapto-group in **87**. However, none of the many compounds identified showed similarly strong odor-properties like **59**. Perfumery materials such as thiocineol or thiolimonene are complex reaction mixtures which contain **59** in varying amounts,

with contents of up to 40% [52]. Because of its strength, **59** is always the olfactory principal in these mixtures, and depending on the starting terpene, other compounds are more or less a matrix for **59**, and have usually little influence on the character of perfume creations.



Long before the importance of **59** was known, thiolinalool **94** and thiogeraniol **91** have been used in perfumery to impart grapefruit-like impressions. The compounds were prepared by a substitution reaction of geranyl bromide with H_2S in the presence of base, or, more efficiently, by reacting linalool or geraniol under allylic rearrangement

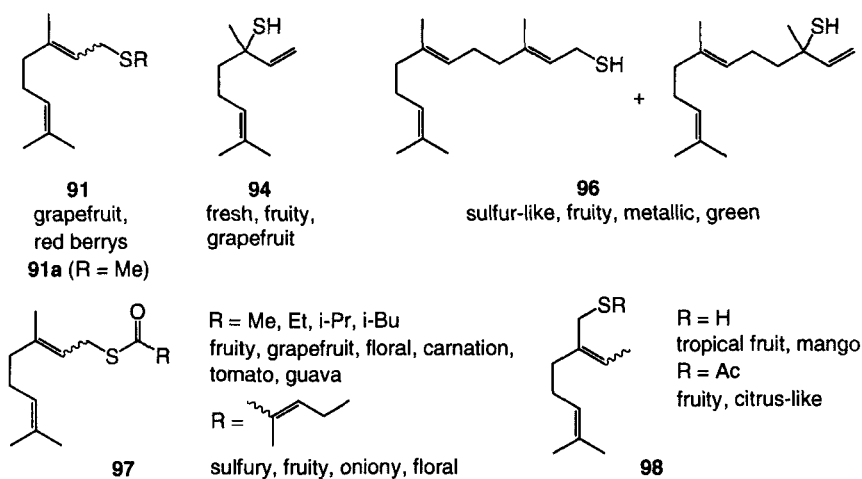


FIGURE 4

conditions with thiourea and subsequent hydrolysis of the thiuronium salts [53] (Scheme 6). (3,3)-Sigmatropic rearrangements of arylthiono- into thiolo-carbonates **93** were also applied [54]. The rearrangements occurred during distillation of the crude thionocarbonate. A similar rearrangement of allylic thionochloroformates was recently shown to proceed at room temperature [55]. An inexpensive alternative to convert olfactorily important allylic alcohols into their corresponding thiols is feasible by the thermal rearrangement of xanthogenate anions **95** [56]. The reaction proceeds either in (3,3)- or (1,3)-fashion with subsequent elimination of COS. From an olfactory point of view, thiofarnesol **96** was found to be especially interesting, displaying fruity, metallic and green notes. Similar reactions of *O*-allyl-*S*-alkyl-dithiocarbonates were reported to be catalyzed by phenolic compounds [57] and by *Lewis* acids [58]. By (3,3)-sigmatropic rearrangement, the latter reaction produced selectively the geranyl and neryl sulfides at room temperature. The COS elimination was assumed to occur via a retro-ene-type fragmentation. In addition, various thiogeranyl esters **97** and their use in flavors and fragrances were also patented (Fig. 4). Generally, the fruity-grapefruit note of these compounds is accompanied by floral-green aspects [59]. More tropical fruit, mango-like nuances were attributed to some constitutional isomers **98** and their corresponding acetates [60]. Interestingly, **91a** was identified as a pheromone constituent of male danaine butterfly *Idea leuconoe* [61].

Usually, thiogeraniol (**91**) and thiolinalool (**94**) contain small amounts of α -terpineol (~5%). It is not surprising that traces of mercaptoterpeneol **59** were also identified in these mixtures which olfactorily dominate the overall character. As for terpineol, **59** is generated by a substitution of a leaving group in **99** as depicted in Scheme 7.

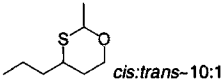
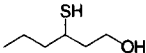
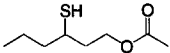
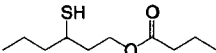
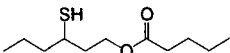
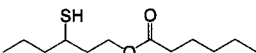
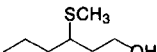
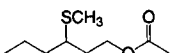
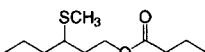
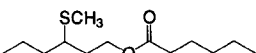


SCHEME 7

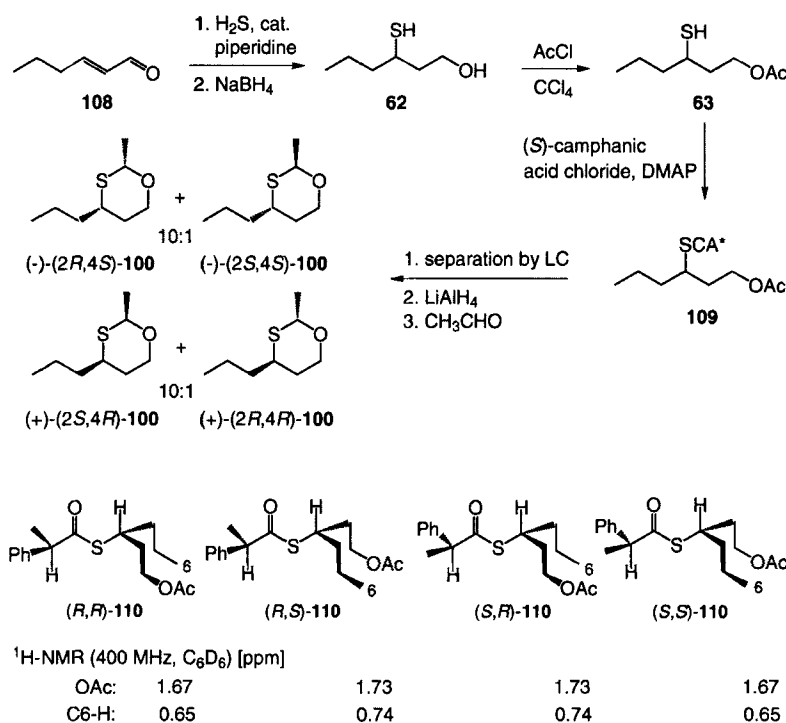
2.3. Passionfruit

Taste and odor of yellow passionfruit are characterized by particularly sweet, warm, fruity-exotic impressions that are appreciated not only in flavor but also in fragrance applications. An investigation of the volatile aroma compounds of Hawaiian passionfruit juice (*Passiflora edulis* f. *flavicarpa*) in 1972 revealed the presence of sulfur-containing compounds: from 539 kg of juice, 6.55 g of concentrated aroma were isolated, containing 0.24% of organically bound sulfur [62]. Winter *et al.* were the first to demonstrate that the attractive organoleptic properties of this fruit are associated with 3-methylthio-hexanol **104** and the oxathiane **100** [63–65] (Table III). Later on, **62** and various esters were also identified as important character-donating key constituents [66,83]. In recent years, mercaptohexanol **62** and its acetate **63** were identified in grapefruit juice [67] and in several white [68] and red wines [69]. Its cysteinylated aroma precursors were identified in must [70] as well as in passionfruit juice [71,72]. In perfumery, the oxathiane **100**, available under the name *Oxane*[®], is being used favorably.

TABLE III 3-Mercaptohexanol (**62**) and its derivatives isolated from passionfruit

No.	Structure	Odor description	Ref.
100	 <i>cis:trans</i> -10:1	Fruity, tropical fruit, green, slightly burnt	[63]
62		Grapefruit, tropical fruits, fresh fruit character	[63,83]
63		Grapefruit, blackcurrant, passionfruit, buchu, mango	[66,83]
101		Fruity, grapefruit, blackcurrant, mango, passionfruit, guave	[66,83]
102		Tropical fruit, passionfruit, buchu	[66,83]
103		Grapefruit, blackcurrant, buchu, tropical fruit	[66,83]
104		Fruity, juicy, melon-like, green, fatty	[83]
105		Fruity, sweet, mango, passionfruit, stronger than 104	[66,83]
106		Sulfury, fruity, caramel-like, caraway-like	[66,83]
107		Faintly fruity, green, tropical fruit	[66,83]

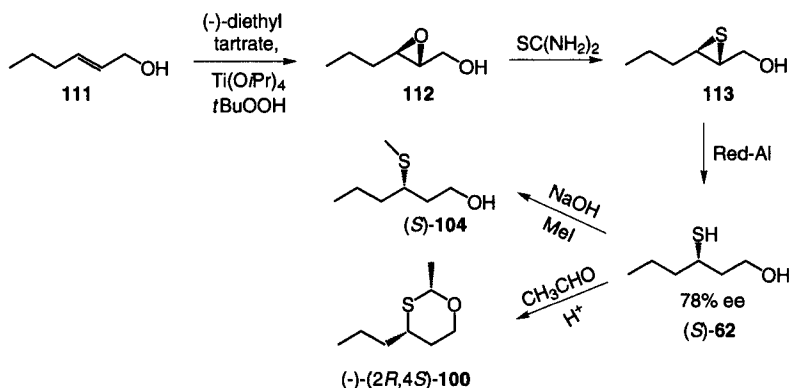
As in the case of menthanethiol **59**, the appealing properties triggered the interest to learn more about the structure–odor correlation, especially regarding the oxathiane **100**. Heusinger and Mosandl reported the synthesis and assignment of the absolute configuration of all four stereoisomers [73] (Scheme 8): racemic **62** was converted into the diastereomeric camphanic acid derivatives **109** which were then separated by preparative liquid chromatography. Reduction of the diastereomers with LiAlH_4 followed by acetalization with acetaldehyde generated the oxathianes with optical purities of $> 99.5\%$ ee. The absolute configuration was assigned by correlation with the known configuration of hydratropic acid in analogy to a method developed by Schmierer and Helmchen [74]: the four most stable conformations of the diastereomeric phenyl-propionic acid-*S*-esters **110** have the CH–COS–CH-plane in common. Residues that stand in a *cisoid* relationship to the phenyl groups are shielded in a different way than those which are in a *transoid* arrangement. As a consequence, an up-field shift of $^1\text{H-NMR}$ signals of the substituents in a *cisoid* position is observed. In Scheme 8, the shifts of the acetyl group- and of the C6-protons are exemplified.



SCHEME 8

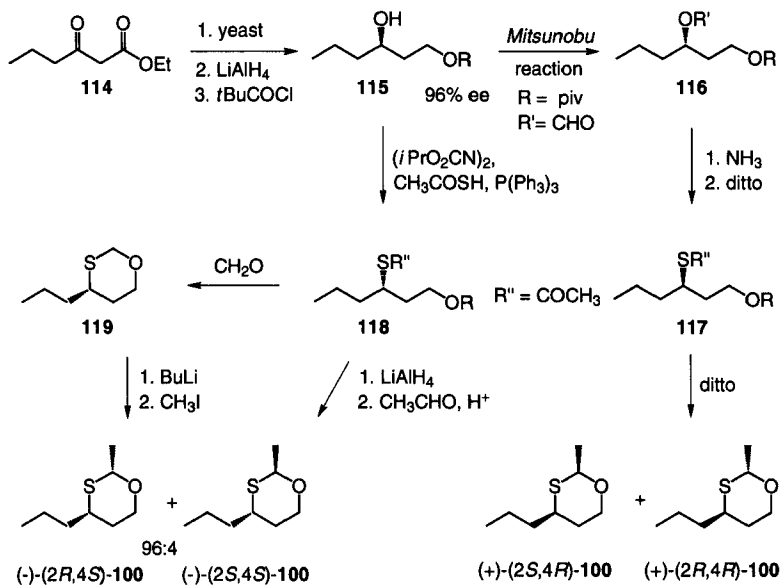
The absolute configuration of the natural occurring *cis*-isomer was determined to be (–)-(2*R*,4*S*)-**100** [75]. It is worth mentioning that its optical purity is $> 98\%$ ee, but that of its precursor **62** varies in a broad range from 16 to 82% ee, always in favor of the (*S*)-isomer [76]. Two other enantioselective syntheses of Oxane[®] and its derivatives were reported (Scheme 9). Pickenhagen *et al.* applied a *Katsuki–Sharpless* oxidation of hexenol, followed by conversion of the resulting epoxide into the episulfide

113 [77]. Reduction with Red-Al and acetalization led to $(-)-(2R,4S)$ -**100**. Its optical purity was presumably similar to that of **62**, showing an ee of 78%. $(+)$ -*trans*-**100** was likewise prepared with 52% ee.



Küntzel and Fráter chose a yeast reduction of ketoester **114** as the key step in their enantioselective synthesis of **100** and obtained **115** in 96% ee (Scheme 10) [78]. By subsequent *Mitsunobu* reactions, both enantiomers of pivaloyl-protected mercapto-hexanols were obtained which were converted into the oxathianes with ees of 88–95%. In an attempt to enhance the *cis-trans* selectivity of $(-)$ -*cis*-**100**, the 1,3-oxathiane **119** was alkylated favoring the diequatorial *cis*-isomer in a ratio of 96:4.

In addition, derivatives of **117** ($R = R' =$ alkyl and aryl ester groups) were claimed to also emanate notes of tropical fruits [79].



The *S*-oxides of *Oxane*[®] were also identified in the essential oil and juice of passionfruit. The oxidation of (+)- and (-)-*cis*-**100** led to two pairs of *S*-oxides **120**, with the equatorial and axial oxides in a ratio of 3 : 1 [80].

The olfactory properties of the optical isomers mentioned above as well as those of some artificial derivatives **119** and **121** (Fig. 5) are compiled in Table IV. No differences were reported for (*S*)- and (*R*)-**62** [73]. However, it may well be that these extremely strong odorants (olfactometer odor threshold 0.94 pg, cf. Fig. 3) were evaluated at too high concentrations. Without the relative configuration being determined, our investigations indicate differences at high dilution: one isomer has a sweet-grapefruit-like nuance, the other possesses more green-fruity aspects. The differences between the enantiomeric methylthio-hexanols **104** are more pronounced, (*S*)-**104** being more fruity, the (*R*)-isomer more herbaceous-green. In contrast, the powerful exotic fruit odor of the mercapto-hexylacetate **63** is due to the (*R*)-isomer, while the (*S*)-isomer displays an intensive sulfuric note. The methylthio-hexylacetates **105** show the same tendencies, but the fruity character of the (*R*)-isomer is no longer particularly tropical. The odor notes of the isomers of **100** also do not seem to be dramatically different: [75,82] green and fruity nuances vary a little and typical passionfruit impressions were rather attributed to the *cis*-(2*S*,4*R*)-isomer than to the

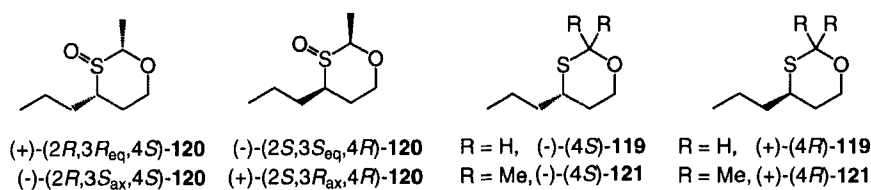


FIGURE 5

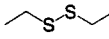
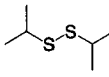
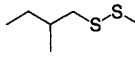
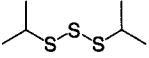


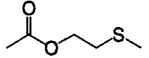
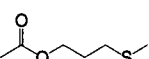
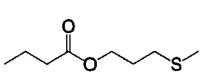
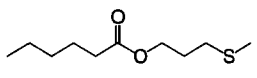
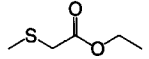
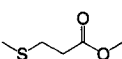
TABLE IV Odor descriptions of enantiomeric passion fruit odorants

No.	Configuration	Odor description	Ref.
62	(+)-(3 <i>S</i>)	Intensive sulfurnote	[73]
62	(-)-(3 <i>R</i>)	Intensive sulfurnote	[73]
104	(+)-(3 <i>S</i>)	Exotic fruity	[73]
104	(-)-(3 <i>R</i>)	Herbaceous, weak	[73]
63	(3 <i>S</i>)	Intensive, sulfuric, herbaceous	[81]
63	(3 <i>R</i>)	Penetrating, tropical fruits, passionfruit	[81]
105	(3 <i>S</i>)	Intensive sulfuric, herbaceous	[81]
105	(3 <i>R</i>)	Fruity, not specifically tropical fruit	[81]
100	(-)-(2 <i>R</i> ,4 <i>S</i>)	Sulfuric, herbaceous-green, roasty sulfuric, blackcurrant, fruity, raspberry	[82/75]
100	(+)-(2 <i>S</i> ,4 <i>S</i>)	Sulfuric, bloomy-sweet, less strong than (2 <i>R</i> ,4 <i>S</i>)- 100	[82/75]
100	(+)-(2 <i>S</i> ,4 <i>R</i>)	Fatty, green fruity, tropical fruits, grapefruit fresh, fruity, exotic fruit, passionfruit, green	[82/75]
100	(+)-(2 <i>R</i> ,4 <i>R</i>)	Green-grass root, earthy, raddish	[82/75]
120	(+)-(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)	Intensive, pungent, green, rotten	[80]
120	(-)-(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>)	Green-grass, longlasting sulfur note	[80]
120	(-)-(2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)	Intensive, exotic fruits, volatile	[80]
120	(+)-(2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)	Intensive, green, reminiscent of rhubarb	[80]
119	(-)-(4 <i>S</i>)	Artificial, sulfuric, burnt rubber-like	[82]
121	(-)-(4 <i>S</i>)	Typical carrot note, sweet	[82]
119	(+)-(4 <i>R</i>)	Artificial fruity, fatty, slight grapefruit note	[82]
121	(+)-(4 <i>R</i>)	Slight fruity, soft lemon note	[82]

naturally occurring *cis*-(2*R*,4*S*)-**100**. This trend can also be observed within the group of (4*R*)-*S*-oxides, which are more fruity in odor than the green (4*S*)-**120**. Regarding the *cis*-*trans* isomeric oxathianes, the diastereomeric *trans*-forms impart less pronounced nuances, and adding (e.g. in **121**) or removing (e.g. in **119**) a methyl group in the 2-position led to less attractive odor tonalities [82]. Regarding the information given in the references cited above, the odor strength of the passionfruit compounds is decreasing in the order **62** \approx **63** > **105** > **104** > *Oxane*[®] (**100**, GC odor threshold \approx 3ng/L [78]).

In addition to these 3-mercapto-hexanol based odorants, Werkhoff *et al.* recently identified a large number of different sulfur-containing compounds, 23 of which have not been described in natural aromas and scents before [83]. Except for a number of olfactorily unimportant high molecular weight disulfides, odor descriptions were given which are summarized in Table V accompanied by some taste threshold

TABLE V Volatile sulfur compounds identified in passionfruit

No.	Structure	Odor description (taste thresh. in water)
122		Sulfuric, rubbery, carbide-like, sweet
123		Sulfuric, oniony, roasted onion, tropical fruit, durian-like
124		Sulfury, rubbery, onion-like
125		Oniony, leek-like, durian-like, sulfuric, roasted onion, metallic
126		Roasty, coffee-like, shiitake, oniony, metallic
127		Fatty, roasty, nutty, roasted peanut, bread crust-like, popcorn, cocoa
128		Sulfuric, rotten, creamy, cauliflower, kohlrabi
129		Herbaceous, mushroom-like, cabbage, asparagus, potato
130		Sulfuric, cheese-like, mushroom-like (10–20 ppb)
131		Tropical fruit note, methional-like, canned pineapple (500 ppb)
132		Fruity, sweet, juicy, radish-like
133		Sulfuric, tropical fruit note, radish-like, cabbage (150 ppb)

(continued)

TABLE V Continued

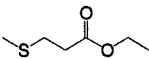
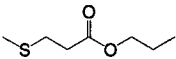
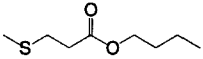
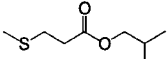
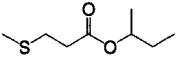
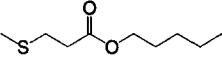
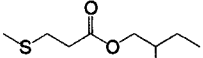
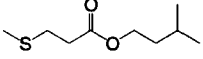
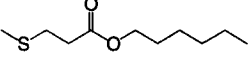
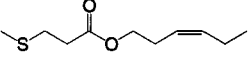
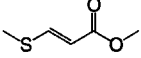
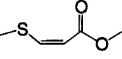
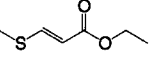
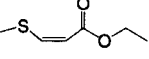
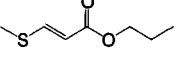
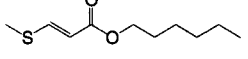
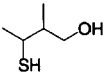
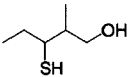
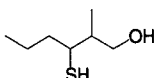
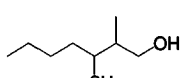
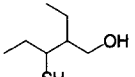
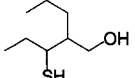
No.	Structure	Odor description (taste thresh. in water)
134		Fruity-herbaceous, sulfury, milk-like, cheese-like (300 ppb)
135		Vegetable-like, mushroom-like, cabbage
136		Sulfuric, rubbery, fruity, mushroom-like, kohlrabi, radish-like (1-2 ppm)
137		Rubbery, fruity, mushroom-like
138		Sulfuric, not fruity, cabbage
139		Fruity, somewhat pineapple-like, milk-like, green, raddish-like
140		Faintly fruity
141		Fruity, estery aroma, pineapple-like
142		Fruity, tropical fruit, mango, passionfruit, guave, geranium-like
143		Sulfuric, sweet, green, carbide-like, leek-like
144		Cheesy, yoghurt-like, pineapple-like, weak caramel character
145		Sulfuric, faintly cabbage-like, cauliflower
146		Sulfuric, sweet, metallic
147		Not fruity or pleasant, rotten, sour
148		Faintly fruity, sweet
149		Sulfuric, fruity, green, estery, rotten, faintly passionfruit-like

TABLE VI Odor properties of several 3-mercapto-alkanols

No.	Structure	Odor description	Odor thresh. ($\mu\text{g/L}$ water)
150		Meaty, sweat	0.23
61		Meaty, onion, leek, roasty, broth	0.63
151		Onion, meaty, rubber, tropical fruit, green	0.31
152		Tropical fruit, grapefruit, cassis, sulfuric, burnt, floral, onion	77
153		Rubber, onion, tropical fruit	1.4
154		Tropical fruit, sulfuric, fatty, green, meaty, onion	10.5

values. The olfactory contribution of each of these compounds on the overall impression of yellow passionfruit is not clear. Compound **142** and several compounds with a pineapple-like odor description (*vide infra*) may be of some importance.

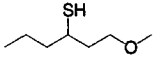
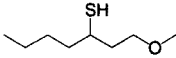
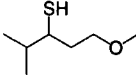
Various 3-mercapto-alkanols were also described in a patent of *Dragoco* [84]. Short chain derivatives **61** and **150** have sweaty sulfuric odors, even at high dilution. Compounds with longer alkyl chains showed again the tropical fruit characters but possessed higher odor thresholds (Table VI). Apparently, the odors of all the enantiomers of **61** are sweaty and broth-like, but the odor threshold of the isomers varied by a factor of 1000 [85].

Several mercapto methyl ethers were recently reported to occur in the top note of the steam distillate of clary sage (*Salvia sclarea* L.) and *Ruta* species [5,86]. Due to its herbaceous-green, alliaceous and perspiration profile, **64** was judged to be key to the fragrance of clary sage flowers and to the topnote of the freshly distilled oil (Table VII). Racemic **64** was prepared from *cis*-3-hexenol, similar to the method applied by Pickenhagen *et al.* (Scheme 9). Both enantiomers of **64** were synthesized with optical purities of > 95% ee, in analogy to the sequence of Küntzel, depicted in Scheme 10. Again, (*S*)-**64** was found to be the major natural isomer, and, as for mercapto-hexanol **62**, the optical purity of natural (*S*)-**64** was only 20% ee.

2.4. Diverse Fruits

Among the sulfur-containing volatiles of passionfruit, several methylthio-esters and methionol derivatives were also identified in pineapple (**122**, **133**, **134**, **144–147**)

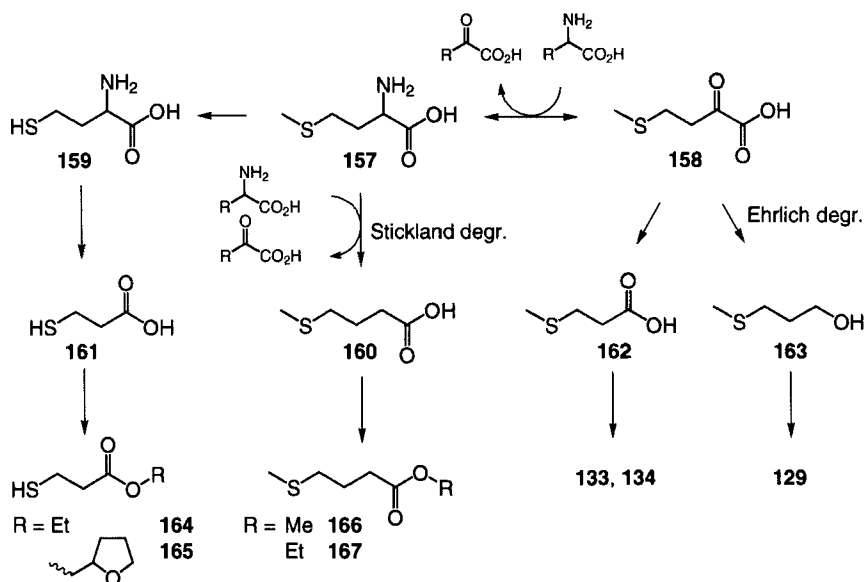
TABLE VII Sensory evaluations of compounds detected in clary sage oil

No.	Structure	Odor descriptions	Odor thresh. (ng/L air)
(±)-64		Flavor (0.5 ppb in water): green, tropical fruit, herbaceous, sage odor tonalities	0.36×10^{-3}
(S)-64		Burnt sulfur, alliaceous, association with human axillary perspiration	4×10^{-5}
(R)-64		Sulfuric, herbaceous, onion-like, lacks unique clary sage signal	1.09×10^{-3}
(±)-155		More onion-like than (±)-64, less diffusive	0.82×10^{-3}
(±)-156		Lack of character	4.3×10^{-2}

[87–89], apple (**128**, **129**) [90], melons of various cultivars (**122**, **128**, **129**, **132–134**) [91–95] and durian (**122**, **123**, **125**, **132**), [96,97] a sulfur-rich exotic fruit from South East Asia. ‘The durian fruit is a delicacy for the palate, but a nuisance for the nose’, [98] and cannot be further discussed here. Independent from these findings, β -methylthio acrylic esters [99] (like **144–147**) and methylthioacetates [100] (like **132**) were said to have useful perfumistic and flavor-enhancing properties.

These sulfur-containing odorants are of olfactory importance mainly for melons, where they occur in concentrations significantly higher than their odor thresholds [93]. Apparently, their formation and concentration are highest during fruit maturity. The compounds are thought to be biogenetically related to the methionine cycle, the major pathway of ethylene-formation in higher plants [101]. The intermediate 2-oxo-4-methylthiobutyric acid (**158**) may be oxidatively cleaved and esterified to **133** and **134** or reductively degraded via an Ehrlich degradation (Scheme 11) into methionol (**163**) which gives rise to compounds like **129**. The homologous **166** and **167** may be regarded as a usual Stickland reaction [89,102] products of methionine (**157**). The methyl ester **166** was claimed to impart a fruity, ylang-jasminic character to a floral perfume composition while **169** (Fig. 6) was described to accentuate the green floral part of that composition [103]. The ethyl mercapto propionate **164**, which was found to significantly contribute to the flavor of grapes [104], can be explained as a side product of *homo*-cysteine (**159**), generated from methionine by methyl-transferase.

Besides these pathways, plants have other means of controlling the concentration of cysteine and methionine, either by blocking the sulfate take-up via the roots or by degrading cysteine into volatile H_2S , which is given off by the respiratory system [105]. Methionine can be converted into methyl mercaptan, which may be retained in the leaves [106] and gives rise to dimethyl disulfide, also occurring in the aroma of pineapple and melon. The H_2S emission by higher plants is a significant contribution to the biogeochemical cycle of sulfur. Therefore, it is not surprising to find H_2S or methyl mercaptan in freshly prepared essential oils or absolutes since they seem to be omnipresent trace compounds in the sulfur metabolism of plants. Essential metabolic processes are extremely sensitive to fluctuations of the



SCHEME 11

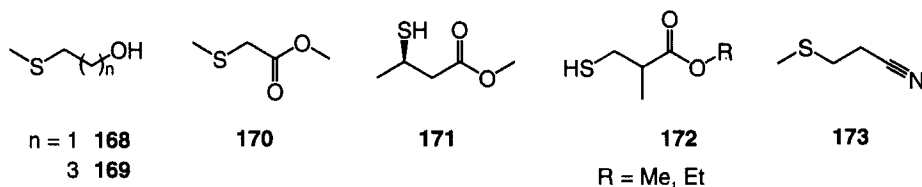


FIGURE 6

thiol–disulfide ratio and plants keep concentrations of methionine and in particular cysteine low [107]. As a consequence, these sulfur-containing odorants appear only as trace compounds, while the degradation products of nonsulfur amino acids, simple fruit esters, often represent a major part of essential oils.

Also **163**, **168** and **173** [93,95] were identified in melon, and **170** in pineapple [87] (Fig. 6). Methylthio propionitrile (**173**) is a side product of a different biogenetic transformation better known to occur in *Cruciferae*: the myrosinase promoted degradation of glucosinolates [108].

Recently, **171** was identified as the character-donating odor compound in *Garcinia epunctata* Stapf, which belongs to the *Clusiaceae* (Mangosteen family), native to the tropical rainforests of Gabon [109]. Expectedly, this compound possesses a strong blackcurrant-like note. Compared to the relatively low ee values of the natural mercaptohexanol derivatives (*vide supra*), naturally occurring (*R*)-**171** was reported to have an ee of 93%. The isomeric compounds **172** were described to have mild natural flavors useful for fruity fragrance compositions [110]. Compounds like **165** were also mentioned to enhance for instance the citrus character of perfumes [111].

3. GREEN SCENTS

3.1. Galbanum

Iran and Afghanistan are home of the giant fennel *Ferula galbaniflua*, from which a resin is collected in small drops (*tears*). Steam distillation of the resin produces an essential galbanum oil, appreciated for its green-spicy, leaf-like odor but also for its fixative properties. Essential oils from several other members of the *Ferula* family (e.g. *Ferula rubicaulis* Boiss.) are also commercially available under the same name. Its history apparently goes back to an ancient Egyptian perfume called *Metopian*, and to the Old Testament where it was mentioned as an ingredient of holy incense (Exodus, Ecclesiasticus) [112].

In olfactory terms, several characteristic minor compounds of the oil such as (3*E*,5*Z*)-undeca-1,3,5-triene (green, pineapple-like) and 2-methoxy-3-isobutylpyrazine (green pepper-like) impart much of the character of galbanum oil and were, together with the synthetic galbanum odorant Dynascone[®] (green, fruity-pineapple), the object of intensive research in fragrance chemistry [113]. In addition, several thioesters **174–178** with an isoprene skeleton were also found to be olfactorily important, but detailed odor descriptions were not communicated [114,115]. These compounds resemble **179**, claimed to enhance the aroma of perfume compositions. Compound **179** itself has a warm fruity, bread and yeast-like aroma of a strawberry tonality [116].

Several *S*-prenyl thioesters **180–182** were identified in the essential oils of *Rutaceae* [117], *Agathosma* [118] and *Diosmeae* species [119]. Thiol **183**, an important constituent of roasted coffee, is pungent, leek-like, and a penetrating ‘foxy, skunky’ odor dominates even at low concentrations [120] (Fig. 7).

3.2. Green, Herbaceous and Roasty Notes

Imaginative and fancy accords are trendy in perfumery and lead to unique creations. The characteristic scent of tomato leaves was imitated in “Les Belles” (N. Ricci, 1996) [113]. The natural scent of tomatoes is not brought about by a single character impact compound, but by a complex combination of several odorants. From these,

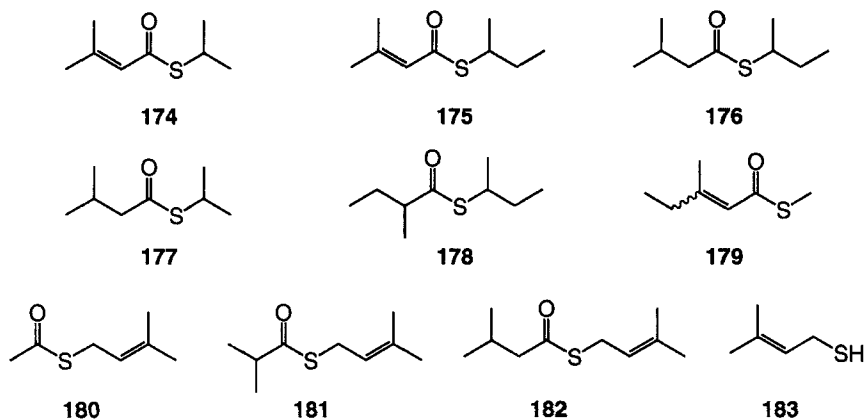
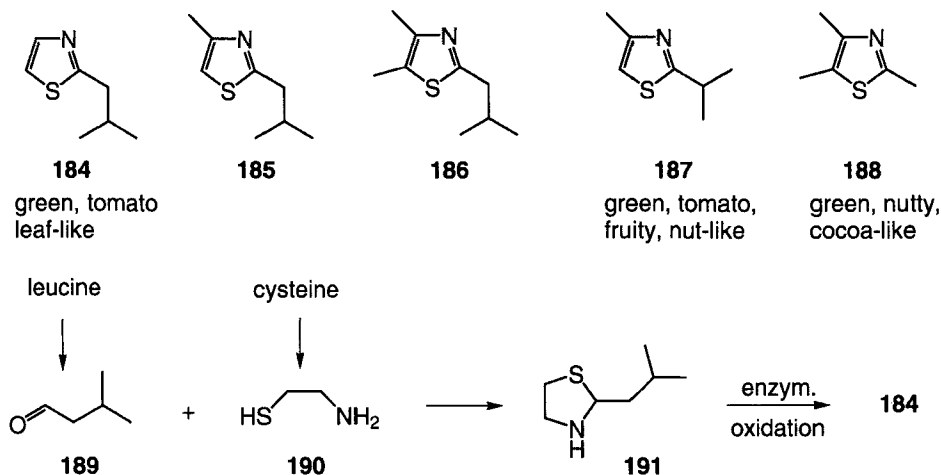


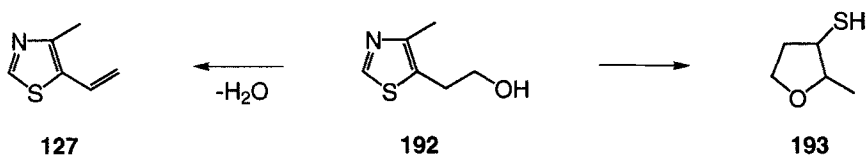
FIGURE 7

185 [121] and 2-isobutylthiazole (**184**) [122] contribute significantly to the particular fresh green note. Although the odor of **184** resembles that of tomato leaves, **184** was only isolated from the fruits. The proposed *in vivo* formation from **189** and cysteamine (**190**) is depicted in Scheme 12 [123]. The thiazoles **186–188** were identified in the essential oil of coriander (*Coriandrum sativum* L.) [124] that is for instance used in fine fragrances (“Gucci No. 1”, “Le Jardin d’Amour” and “Coriandre”) [112].



SCHEME 12

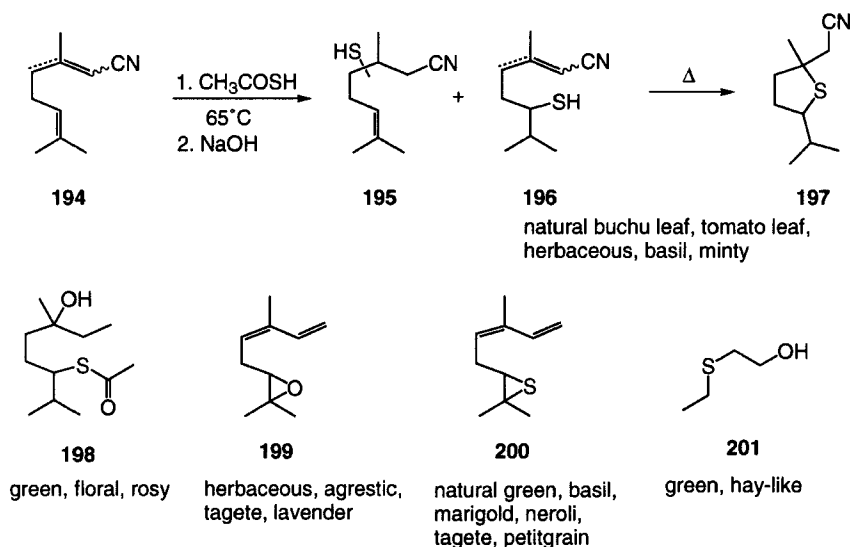
A lot of other alkylthiazoles were identified in heat-processed foods, Maillard reaction model systems and flavor concentrates of Likens–Nickerson extracts. Their formation as well as their flavor properties have been already reviewed [125–127]. It may very well be that one or another alkylthiazole is occasionally used as a trace compound in green accords. Another source of thiazoles in flavors is the thermal degradation of thiamine. In this context, the use of *Sulfurol* (**192**) in perfumery is worth mentioning (Scheme 13). This rare material was attributed a very tenacious sweet, animal-herbaceous odor and it has occasionally been used as a modifier in oriental and heavy floral fragrances [128]. Others, however, describe pure **192** as odorless and assign odors of varying qualities to trace impurities like the dehydration product **127** [129], frequently found in natural scents and processed food flavors, or to **193** which is a potent, well-known savory compound with a broth and meat-like flavor [130]. A diastereo- and enantioselective synthesis of **193** was reported [131]. In addition, the compound was identified as a degradation product of thiamine [132].



SCHEME 13

Other synthetic sulfur-containing odorants with tomato-leaf facets were prepared from geranonitrile and thioacetic acid (Scheme 14). Apparently, the odor notes of **195** and **196** were similar but more substantive than that of **197**. Thioacetic acid addition to dihydro linalool led to **198** with a green-floral odor [133].

Ocimene epoxide **199** (Myroxide[®]) has a clean agrestic note. Its sulfur analogue **200** covers far more olfactory areas, above all green and spicy nuances [134]. The green-smelling odorant **201** is an additional example for the isosterism between an *S*-atom and a *cis*-configured double bond [135] (*vide supra*): **201** has similar olfactory properties as *cis*-3-hexenol, a classic green, hay-like character compound.



SCHEME 14

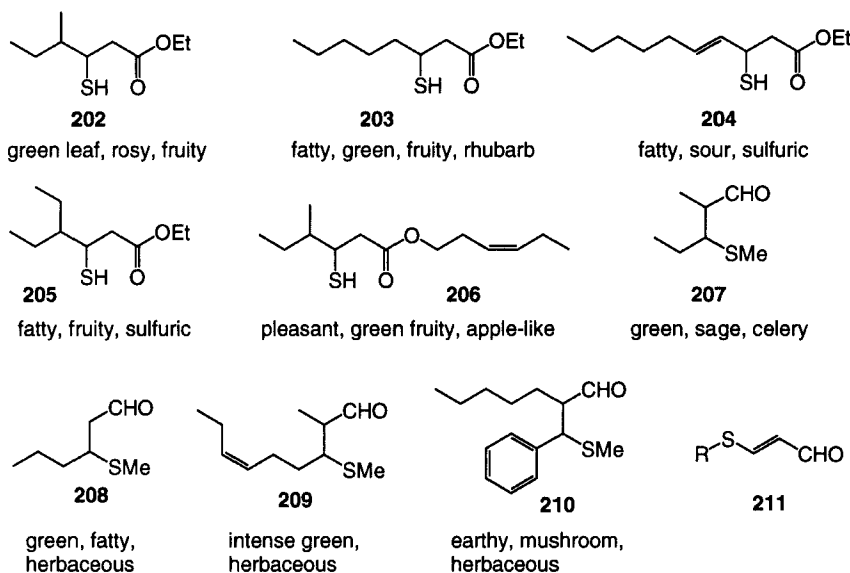


FIGURE 8

Finally, some $\text{H}_2\text{S}/\text{MeSH}$ adducts of longer chain α,β -unsaturated carboxylic acid esters **202–206** [136] and aldehydes **207–210** [137] were described in the patent literature (Fig. 8). As already discussed, the grapefruit-, cassis- and passionfruit-type notes that usually go together with short-chain β -mercapto-ketones, -acids and -ethers have changed in favor of green, fatty and herbaceous odor characteristics of the long-chain analogues. A variety of sulfide adducts of propargyl aldehyde with the general formula **211** were also claimed as useful fragrance ingredients [138].

4. SCENTS OF FLOWERS

The most obvious occurrence of sulfur-containing compounds in flowers is related to those which are bat-pollinated, such as quite a number of nocturnal blooming white cacti, exhibiting intense vegetable- or garlic-like odors. Usually, this olfactory stimulus is supported by conspicuous structures of the flowers that give acoustic guidance for their echo-locating guests [139]. The genuine, olfactorily dominating sulfur-containing compounds are low molecular weight dimethyl disulfide (**212**), its monosulfone **214** and methyl thioacetate **213** [140]. Higher oligosulfides (**215–223** [140,141], Fig. 9) were also identified in a number of species, especially after longer sampling times and their formation by disproportionation on the adsorbent during head space analysis cannot be excluded [140]. Compound **217** may be derived from CS_2 which was occasionally found in natural scents, e.g. that of the orchid *Dendrobium superbum* Rchb.f. [142].

Interestingly, the carcass- or cheese-like odors of many fly-pollinated flowers lack these sulfur-containing compounds but are rich in short-chain carboxylic acids [143].

However, dimethyl disulfide (**212**) which stimulates the appetite of bats at this high concentration, does also occur in the scents of roses and geranium oils where they may olfactorily add a certain sweetness. Indeed, judged by the 19 sulfur-containing odorants identified, roses are a quite “sulfur-rich” species. Since the dawn of history roses and rose oils belong to the most appreciated materials in perfumery. An early Caliph once said: “I am the king of sultans and the rose is king of sweet scented flowers; each of us is therefore worthy of the other” [112].

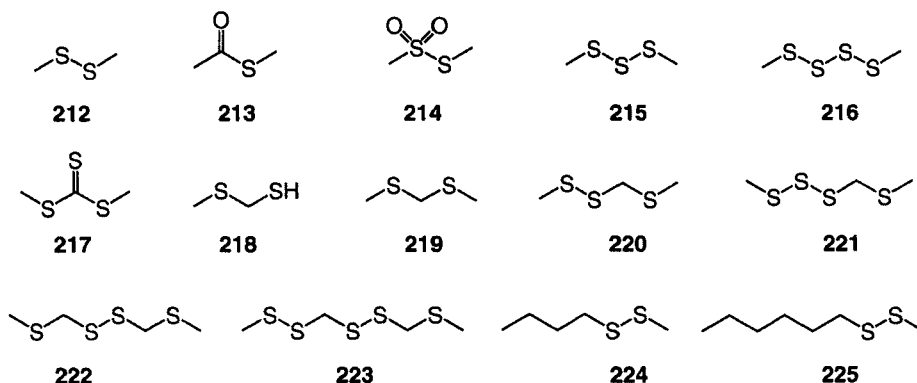


FIGURE 9

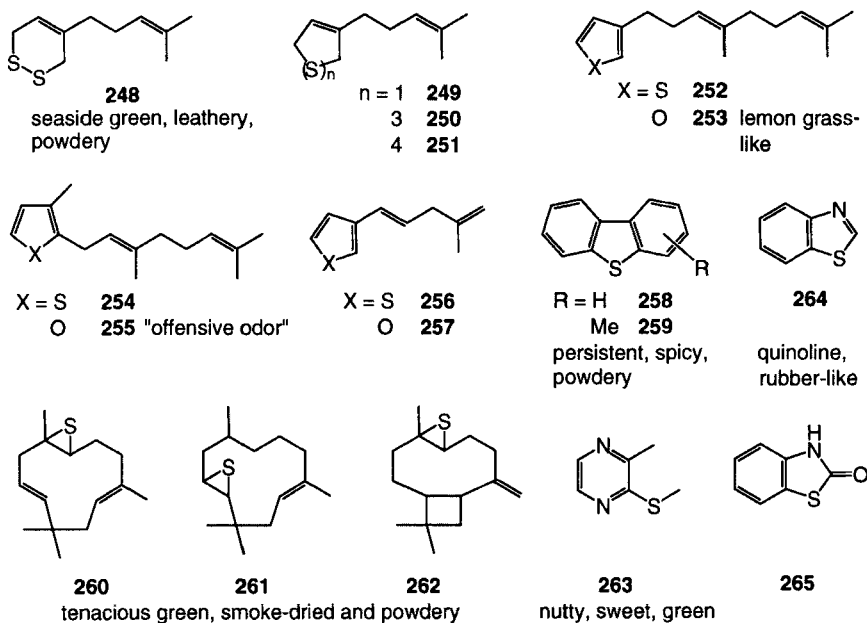


FIGURE 10

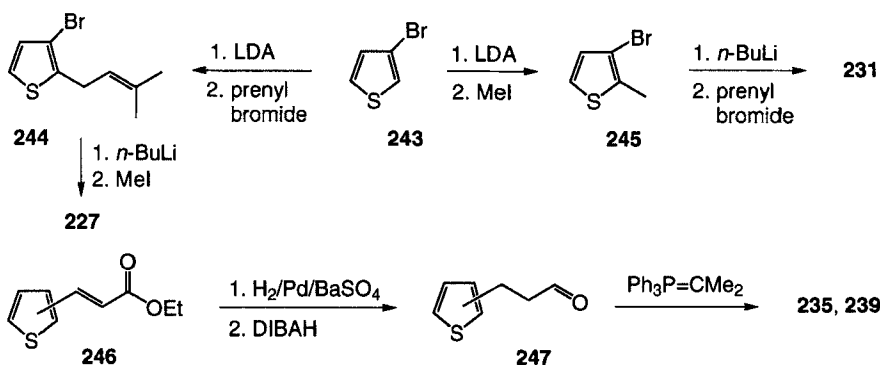
Besides dimethyl sulfide, **212**, **224** and **225**, rose thiophene **227**, the perillene *S*-analogue **235**, the disulfide **248**, thio-dendrolasin **252**, the epithiosesquiterpenes **260–262** (Fig. 10) as well as mintsulfide (**267**) and isomintsulfide (**268**, Scheme 16) were also found in rose oil [144,145]. Interestingly, dibenzothiophenes **258** and **259**, described as persistent spicy and powdery, were said to impart the naturalness of rose scent perceived when smelling rose petals to essential rose oil [146].

Rose furan **228** itself was isolated in 1968 and has a hesperidic odor [147]. Ohloff assumed that for perfumery it "will become increasingly important in the future" [148]. In contrast, the olfactory properties of **227** and in particular **235** were initially evaluated to be of little interest; the latter being described as strongly spicy, reminiscent of vulcanized rubber [149]. However, in a detailed study, Weyerstahl *et al.* clarified that the exchange of oxygen by sulfur in **227** and a number of constitutional isomers does not significantly change the olfactory properties (Table VIII) [150]. Compared to the corresponding furans, the homoallylic thiophenes **235**, **237**, **239** and **241** were given almost identical odor descriptions. Furthermore, rose thiophene (**227**) and thioperillene (**235**) did not show odor qualities superior to those of their isomers. Apparently, **237/238** and **241/242** displayed the strongest and most pleasant odors, but were not comparable to the structurally similar jasmone, a precious jasmine odorant. The *S*-analogue **256** of α -clausenane (**257**) (*lepalene* [152], isolated from *Clausena willdenovii*) [151] was also claimed to be useful in fragrance applications [153].

Rose thiophene (**227**) and its derivatives were prepared in high purity by routes starting from bromo thiophene (**243**). Thioperillene (**235**) and its isomers were synthesized by a Wittig route starting from thiophenyl acrylic acid esters (**246**) as depicted in Scheme 15 [150].

TABLE VIII Olfactory properties of rose furanes and rose thiophenes

Structure	Odor description	
	X = S	X = O
	227 fresh, citrusy, tagete, similar to 228	228 fresh, citrusy, tagete
	229 similar to above, less pleasant, rubber	230 similar to above, less fresh, dill
	231 less fresh than thiorose furan, more fruity	232 similar to above, dumper, less citrusy
	233 fresh, fatty, passionfruit	234 green, dill, melon, sweet
	235 bergamot, green, metallic, pear, mushroom	236 bergamot, metallic, mushroom, pear
	237 green, pear, fresh, violet, gassy, mushroom	238 green, fatty, violet, bergamot
	239 bergamot, green, mushroom, pear	240 green, mushroom, bergamot, pear
	241 green, fresh, pear, gassy, bergamot	242 green, pear, fresh, violet, metallic, melon



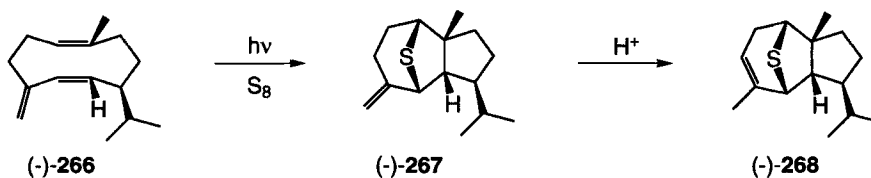
SCHEME 15

The higher homologues of **228** and **236** were also found in nature: An "offensive odor" [154] was assigned to sesqui-rose furan (**255**), identified in Japanese *Actinodaphne longifolia* (Blume) Nakai. *Dendrolasin* (**253**), first isolated from mandibular glands of the ant *Lasius* (*Dendrolasius*) *fuliginosus* Latr. [155] was described as lemon grass-like. However, in pure form the compound has only a weak odor. *Thio-dendrolasin* (**252**) was found in rose oil [145] but precise olfactory properties were not communicated. Having the above mentioned in mind, one can expect a citrus-like odor for **252**.

The compounds **235**, **248**, **250** and **251** were also identified in hop (*Humulus lupulus*), which is cultivated all over the world for the brewery industry. The bitter, green and herbaceous oil of the flower tops is occasionally used in perfumes with herbal characters.

Regarding the biosynthesis of these sulfur compounds, the occurrence of the dithia-cyclohexene **248** as well as the tri-, tetrasulfides **250** and **251**, but the nonoccurrence of the monosulfide **249** is an interesting finding. Since all these compounds were generated under a variety of *in vitro* photolysis reactions of myrcene (a frequently occurring monoterpene) and sulfur (applied to hop plants to fight mildew), it was reasoned that in certain plants a biogenetic pathway exists which adds sulfur to unsaturated systems [156]. Indeed, epithiospecific proteins were isolated from various plants, playing a role in regulating the release of elemental sulfur from glucosinolates [157,158].

The episulfides of humulene (**260** and **261**) and of caryophyllene (**262**) [159] as well as mintsulfides (**267** and **268**) were isolated from rose and hop oils. Very likely, these compounds are biogenetically related to the corresponding sesquiterpenes from which the sulfides can be prepared by irradiation in the presence of sulfur [160]. The triplet sulfur $S(^3P_J)$ addition to olefines was shown to be a stereoselective process [161] and the formation of (-)-mintsulfide from (-)-germacrene D (**266**) is likewise a stereoselective reaction (Scheme 16) [162]. Variations in the optical rotation of different samples of natural mintsulfide were correlated to the optical purity of germacrene D. Mintsulfide occurs also in quite a number of perfumistically important essential oils such as those of peppermint, spearmint, pepper, ylang ylang, narcissus, geranium, chamomile and davana. Although **267** was described to possess a heavy, woody and earthy odor, its intensity is presumably too low to contribute to these natural scents.



SCHEME 16

A number of unusual sulfur compounds were detected in the headspace samples of several springtime flowers (e.g. *Narcissus poeticus* L.) (**264** and **265**) [163] and the essential oil of orris (**263**) [164]. Usually, benzothiazoles and in particular pyrazines occur in a great number of different thermally treated food flavors, mainly those of coffee and cocoa. It is very likely that **263** was also generated by secondary processes.

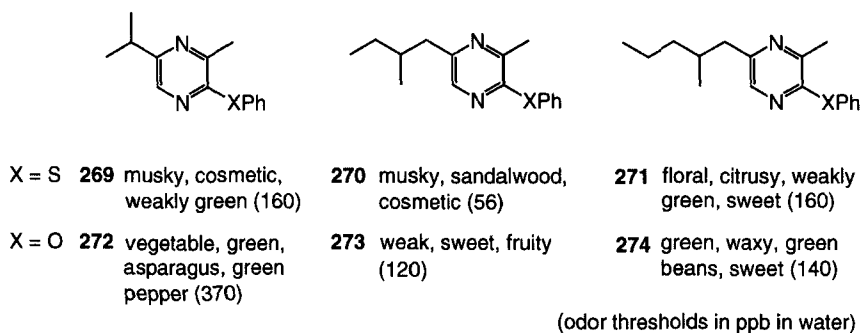


FIGURE 11

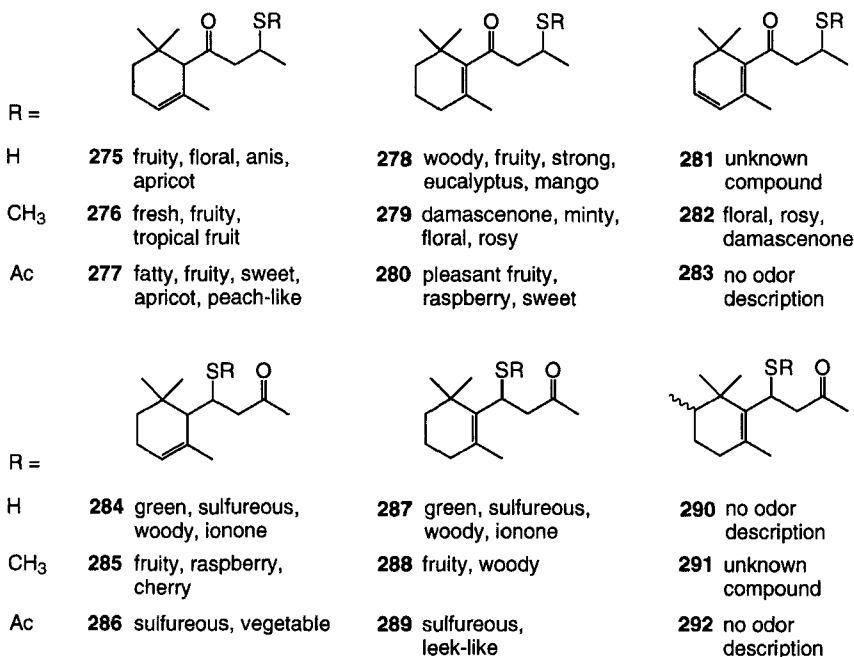


FIGURE 12

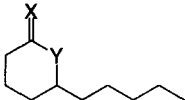
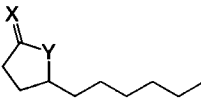
Most likely, **264** and **265** have to be regarded as nonbiogenetic but environmental contaminants. Syntheses, occurrence and olfactory properties of pyrazines have already been reviewed in detail [165], and several studies on structure–odor correlations were reported [166–168]. Therefore, a few remarks will suffice here: the vast majority of pyrazines have more or less green odors with sweet and/or roasted undertones. Regarding the odor strength of these potent materials, methoxy substituted pyrazines usually show the lowest odor thresholds, also in comparison with the corresponding sulfur derivatives [169]. Although it appeared that the oxygen atom of alkoxy- and phenoxy-groups can be replaced by a sulfur atom without significant changes of the quality of odors, in a limited number of cases differences were observed. These are depicted in Fig. 11 [170].

4.1. Synthetic Sulfur Compounds Related to Floral Odorants

The addition of methyl mercaptan, thioacetic acid or H₂S to well-known odorants represents a classic and simple protocol to modify the odors of the parent compounds. Therefore, it is not surprising to find a number of such adducts of damascenes [171–173] and ionones [174,175] in the patent literature. What was mentioned for the Hedione/Magnolione-type adducts **33** and **34** holds true here as well: the precious fruity, rosy characters of the damascenes, important for the reconstitution of the oils of rose *damascena* and *centifolia*, is still present in the sulfur adducts **275–283** but the characters are shifted towards a more sweet, ripe-fruit impression. The same was observed for the ionone/irone adducts **284–292** (Fig. 12). Although precise odor descriptions were not given for these compounds, or even negative attributes such as sulfurous or leek-like (**284**, **287**, **286**, **289**) [174] were reported, the effect created by these compounds when added to certain formulations becomes obvious: the compounds enhance the fresh fruity, in particular the raspberry-like characters of the mixtures in a more complex, faceted way than can be obtained by the presence of ionones alone.

The main use of γ - and δ -lactones relates to flavor compositions and perfumery accords of fruity (peach, mango, strawberry, etc.), creamy, milky or coconut notes. In perfumery, lactones find additional applications in floral accords, particularly of *Gardenia*, *Tuberose*, *Honeysuckle* and more general in floriantal formulations. A few attempts were made to combine the potent odor characteristics of lactones with unique effects that may be obtained by replacing oxygen by sulfur atoms. A drastic effect was indeed observed for *rac*-**297** (Table IX): compared to *rac*-**293**, not only the odor threshold was decreased, but the warm lactonic character was mingled with a fresh tropical fruit note. In contrast to *rac*-**294**, the γ -thiolactone *rac*-**298** had an increased odor threshold and a less pleasant, fatty rancid character [176]. In case of the corresponding thionolactones, no such big differences were observed. The individual odor properties between the enantiomers of **295** and **296** were said to be comparable to those of the corresponding lactones **293** and **294** [177]. Other thiono- and thiololactones will be shortly addressed in the following chapter.

TABLE IX Olfactory properties of some thiono- and thio-lactones

<i>X</i> (<i>Y</i>)	Odor description (odor thresh. (ng/L in air))			
O (O) (<i>R</i>)- 293	Fruity, sweet, milk-like (<i>rac</i> - 293 = 100 ^a)	(<i>R</i>)- 294	Fatty, sweet, fruity, coconut (<i>rac</i> - 294 = 11 ^a)	
O (O) (<i>S</i>)- 293	Fruity, sweet, creamy peach, buttery, stronger than (<i>R</i>)-	(<i>S</i>)- 294	Soft, sweet coconut with fruity-fatty aspects	
S (O) (<i>R</i>)- 295	Green, sweet, fruity (3)	(<i>R</i>)- 296	Fruity (0.2)	
S (O) (<i>S</i>)- 295	Sweet, fruity (3)	(<i>S</i>)- 296	Sweet, fruity (0.2)	
O (S) <i>rac</i> - 297	Tropical fruit, fresh (0.7/6 ^a)	<i>rac</i> - 298	Fruity, fatty, rancid (3/47 ^a)	

^aodor threshold in water (ppb).

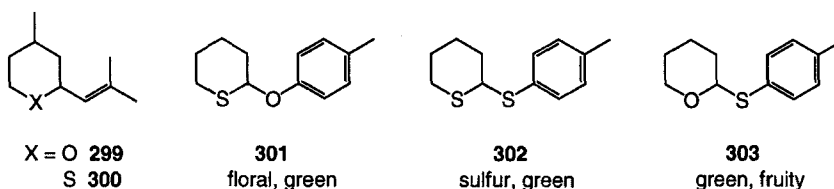


FIGURE 13

Finally, some tetrahydro pyranes and their corresponding sulfur analogues should be shortly discussed. Rose oxide (**299**), the most important constituent of this class, occurs in rose and geranium oils, and has a herbaceous geranium-like odor. It was the object of intensive research during the past four decades. Compound **299** and a number of similar compounds play an important role in perfumery to convey diffusivity and naturalness. Thio-rose oxide (**300**) was described as "olfactorily related" to rose oxide [178]. From a series of phenolic ethers, **301** was said to have a floral, green odor. One exocyclic oxygen atom seemed necessary to generate the floral character [179] (Fig. 13).

5. MUSK ODORS

Among the various chemical classes of musk odorants, macrocyclic lactones and ketones are the most advantageous in terms of good biodegradability and their favorable toxicological and ecological properties. Their structures are related to those of the natural isolates such as muscone, ambrettolide and pentadecanolide. Plenty of efforts were made to find reliable structure-odor correlations for musk odorants. For macrocycles, the musk odor and intensity depends on a subtle equilibrium of the ring size and geometry with hydrophobic parts and hydrogen-bond acceptors [113].

The finding that oxa-macrocyclic lactones also have musky odors, sometimes even associated with interesting olfactory shadings, led to efforts to incorporate sulfur instead of oxygen. Early results conveyed the impression that thia-macrolides (e.g. **315**, **316**) are generally weaker than their oxa-analogues [180,181].

However, Kraft and Cadalbert recently showed that both the quality and the odor strength strongly depend not only on the ring size of the lactones but also on the position of the sulfur atom with respect to the carbonyl groups: in even-numbered rings, a 1,7- and in odd-numbered rings a 1,6-distance between the sulfur atom and the carbonyl group (which corresponds to a 6.9 Å distance between the acceptor sides, regardless if counted from the ester or from the alkyl side of the carbonyl functionality) led to most intense compounds [182,183]. The odor thresholds were even lower than those of the corresponding carba-analogues. For example, **307**, prepared according to Scheme 17, has a similar, although a more green than floral character than ambrettolide (**308**), the odorant principle of ambrette seed oil (*Hibiscus abelmoschus* L.). The isosterism of a sulfur atom and a *cis*-double bond can explain that neither strength nor quality of the musk odor was diminished by replacement of **308** by **307**. Furthermore, based on these observations and on odor threshold data, a *Catalyst* olfactophore model was proposed that rendered the calculation of odor thresholds of thia-macrolides in good agreement with the measured data (Fig. 14) [184].

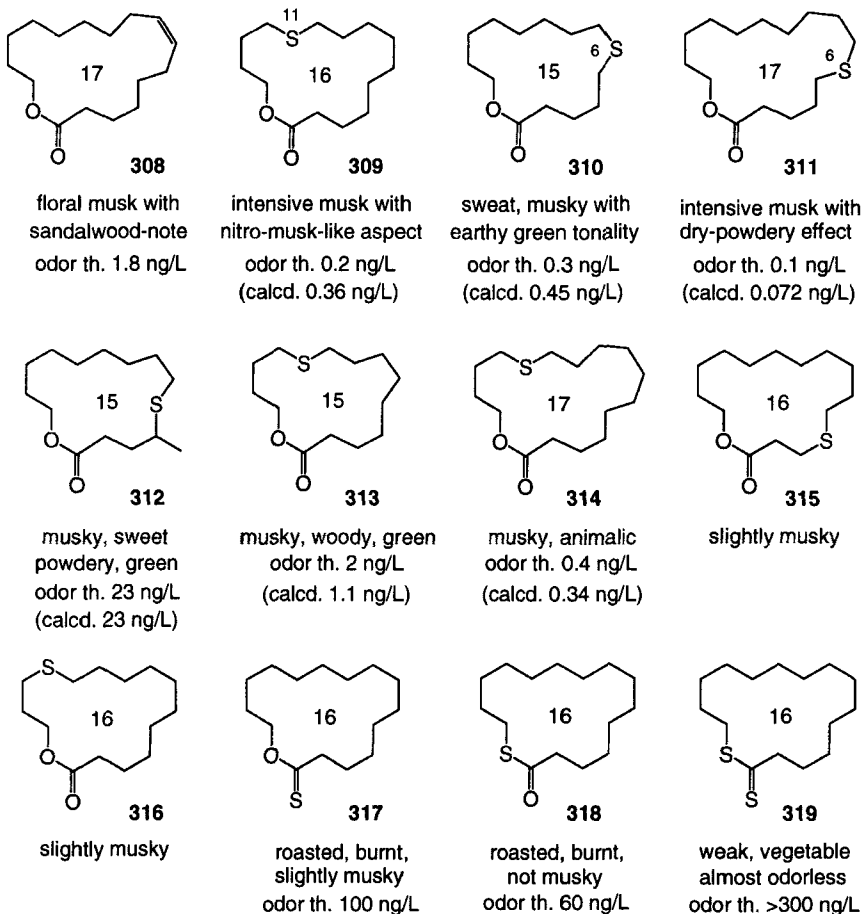
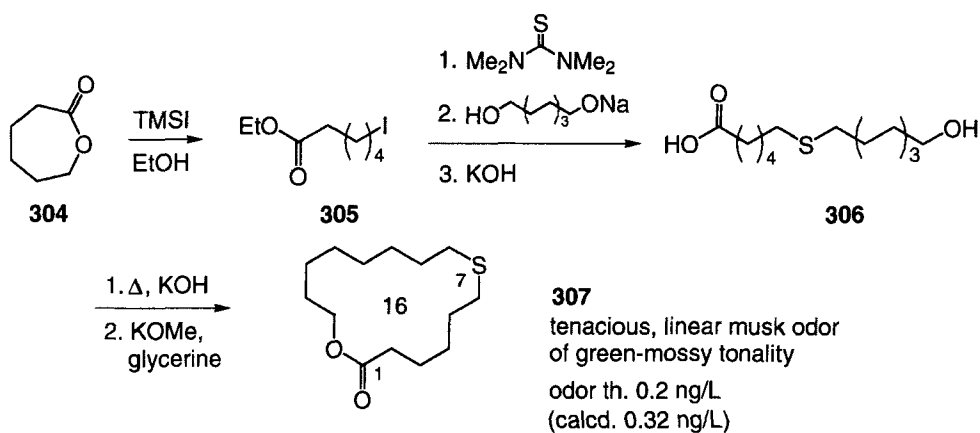


FIGURE 14



SCHEME 17

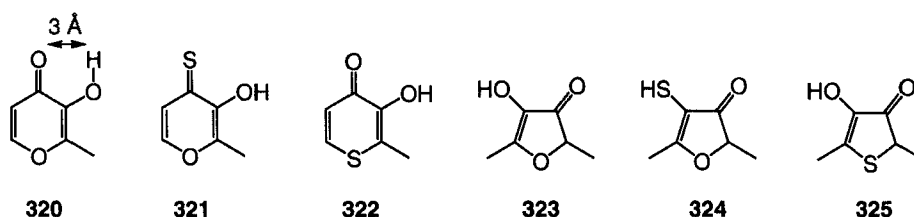


FIGURE 15

Thiolo-, thiono- and dithio-pentadecanolides (**317–319**) were also prepared [182]. None of them displayed interesting musky properties but only sulfuric, burnt notes of quite low intensity.

6. SWEET SCENTS

Generally, compounds with sweet, caramel-like odors possess a planar enol-carbonyl unit of cyclic dicarbonyl derivatives which is supposed to act as a H-donor (enol)/H-acceptor (carbonyl) pair of 3 Å distance at the olfactory receptor site [178]. Already 1861 maltol (**320**) was identified as the aromatic principle in the bark of larch trees [185], later also in roasted barley [186] and various species of pine [187] and in a variety of wines [188]. Compound **320** is formed upon heating of sugar- or starch-containing foodstuff [189]. A higher odor intensity was observed for the more hydrophobic ethyl analogue (ethyl maltol). However, for the (compared to **320** more hydrophobic) sulfur derivatives **321** and **322**, no significant change in odor quality was observed. The odors of **324** and **325** were claimed to be more intense than that of Furaneol® (**323**), but only minor changes in the odor quality were recognized. It was reasoned that mainly the structure of the bifunctional unit and not its chemical character (S vs. O) is of importance. The various odor tonalities are then created by the hydrophobic skeletons of the different molecules [178] (Fig. 15).

7. SUMMARY

Sulfur-containing compounds are some of the strongest odorants so far known. Their odors often depend on their concentrations and, above all, their chemical, diastereo- and enantiomeric purity. Even if present only in trace amounts, they may change the overall olfactory impressions of fragrant mixtures, which makes the art of composing perfumes both difficult as well as rewarding. In the fruity area, compounds like 8-mercapto-*p*-menthan-3-one (**37**), *p*-menthene-8-thiol (**59**), 3-mercapto-hexanol (**62**) and Oxane® (**100**) have gained unimpeachable superiority in terms of imparting natural fruitiness and freshness which transmits also into the floral and green domain. In other olfactory fields of perfumistic importance, effects of sulfur-containing compounds have been studied but applicable results are rare.

Acknowledgments

For many interesting discussions and constructive criticism, I am very grateful to Roman Kaiser and Philip Kraft, for proof-reading of the manuscript to Markus Gautschi and Mechthild Rennebaum.

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