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Odds and Trends: Recent Developments in the Chemistry of Odorants**

Philip Kraft,* Jerzy A. Bajgrowicz, Caroline Denis, and Georg Fráter

Fragrance chemistry is, together with the closely related area of flavor chemistry, one of the few domains, if not the only one, in which chemists can immediately experience structure–activity relationships. This review presents structure–odor correlations and olfactophore models for the main odor notes of perfumery: "fruity", "marine", "green", "floral", "spicy", "woody", "amber", and "musky". New trendsetters and so-called captive odorants of these notes are introduced, and recent activities and highlights in fragrance chemistry are summarized. The design of odorants, their chemical synthesis, and their use in modern perfumery is discussed. Our selection is guided and illustrated by creative fragrances, and features new odorants which encompassed current trends in perfumery. New odorants for grapefruit and blackcurrant, for galbanum, and leafy top notes are presented. Compounds with fashionable marine, ozonic, and aquatic facets are treated, as well as new odorants for classical lily-of-the-valley, rose, and jasmine accords. Compounds with sweet and spicy tonalities are also discussed, as are the most recent developments for woody notes such as sandalwood and vetiver. We conclude with musky and ambery odorants possessing uncommon or unusual structural features. Some odor trends and effects are illustrated by microencapsulated fragrance samples, and areas where there is need for the development of new synthetic materials and methodologies are pointed out. Thus, chemists are invited to explore fragrance chemistry and participate in the design and synthesis of new odorants. This review gives the latest state of the art of the subject.

Keywords: fragrances · macrocycles · molecular modeling · structure–activity relationships · terpenoids

1. Introduction

Albert Eschenmoser once said,[1] "We all agree […] that the emphasis in synthetic research is shifting toward the *synthesis of properties*, and not just compounds". In this sense, fragrance chemistry is certainly a very interesting area for research; indeed, one of the few where synthetic chemists can immediately explore and experience structure–activity relationships: simply by smelling.

In fact, the *synthesis of properties* is not just en vogue, it was already the goal at the very beginning of modern organic chemistry—and the isolation and identification of olfactorily active principles of valuable odoriferous natural products was an important chapter. For example, the olfactory properties of coumarin (**1**), previously accessible only by isolation from tonka beans, were key for Perkin to work on its structure elucidation and an industrially feasible synthesis.[2] In 1876, coumarin (**1**) became available on the market, and inspired Jean-François Houbigant to break with the traditional perfumery of Eaux de Cologne. By combining coumarine with oakmoss, geranium, and bergamot he created an accord that was not an attempt to imitate a natural scent, but a new fantasy smell. The result was "Fougère Royale" (1882), a fragrance that set a trend and finally resulted in a whole family of related perfumes, the so-called Fougère family. Thus, the birth of modern perfumery began with coumarin (**1**). Scheme 1 presents a brief overview of other odorants that played a decisive role in the evolution of perfumery, each one together with an illustrative example of an important use in a fine fragrance.

New perfumery trends were almost always directed by new fragrance synthetics, or as Ernest Beaux, the creator of "Chanel N° 5", said in 1952: "We'll have to count on chemists to find new substances, if we are to make new and original notes. Yes, the future of perfumery is in the hand of

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chemistry".[3] In this review we intend to show the chemistry behind the recent trends in perfumery, to illustrate the design of new molecules, and to summarize some recent developments in fragrance chemistry. Processes and perfumery compounds with a more general technical and industrial relevance were treated in complementary reviews.[4]

2. Fruity Odorants

2.1. An Olfactophore Model for Fruity Odorants

Even without any knowledge of perfumery every chemist will remember the fruity odor of aliphatic esters from his early studies in chemistry. In our discussion of odor notes we will therefore also start with fruity odorants, and by following the odor transitions of prominent raw materials of perfumery we will continue with green, leafy notes, marine-smelling molecules, floral, and then spicy odorants. We will conclude with woody, ambery, and finally musky perfumery synthetics that form the base note, the dry-down of a perfume.[4] Some of the macrocyclic musks also possess fruity aspects so that the olfactory spectrum presented becomes a full circle at the end of our overview (Figure 1).

Fruity notes are very popular in perfumery. They are now present in almost every feminine fragrance, and are used more and more in masculine perfumes as well. However, not many new fruity odorants were introduced in recent years; instead, already known materials such as lactone **6** have become increasingly used.

Esters are certainly prototypes for fruity odorants. But even if they are very simple in structure, their odor is difficult to predict. Boelens et al.[5] stated the following structure–odor correlations for aliphatic esters:

1) Aliphatic esters up to C_8 are strongly fruity.
2) For the acyl moiety there is a decrease in fruitiness along the series $C_3 - C_5 > C_1, C_2 > C_6 - C_8$.
3) For the alkoxy group there is a decrease in fruitiness with $C_1 - C_5 > C_6 - C_{10}$.

But apples are not pears, and their odors are quite distinct and cannot be grouped together for structure–odor correlations.[6]


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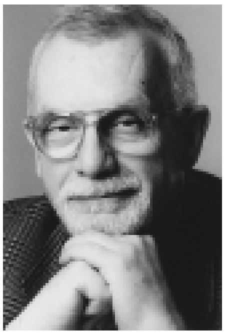
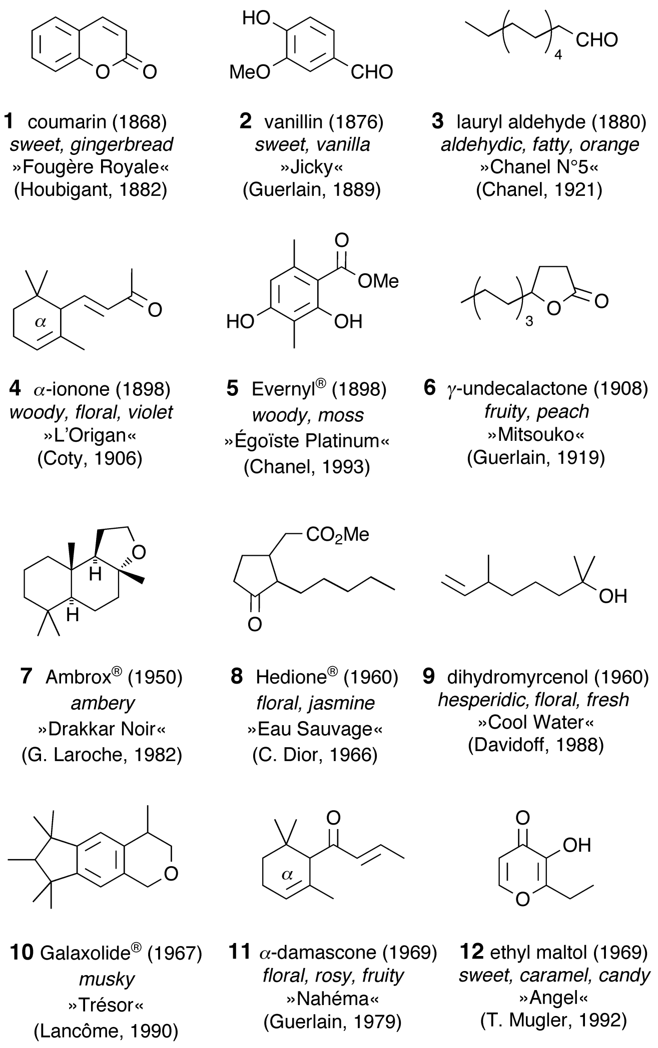

G. Fráter

Philip Kraft, born in 1969, received his diploma and doctorate degree from the University of Kiel, by carrying out syntheses of medium and large ring compounds under the supervision of Professor W. Tochtermann. From 1990–1994, he was a scholarship holder of the Studienstiftung des Deutschen Volkes, and from 1994–1996 recipient of a Chemiefond Stipendium des Verbandes der Chemischen Industrie. In 1996, he joined Givaudan Roure Research Ltd. and is currently laboratory head in Organic Synthesis.

Jerzy A. Bajgrowicz, born in 1950, graduated from the Technical University of Cracow, and received his doctorate from the Technical University of Wroclaw in 1977. Following several years of research on azaaromatics and amino acids at his alma mater, the Ecole Normale Supérieure of Rabat, and the University of Montpellier he joined Laboratoires Fournier in 1985. After four years in the pharmaceutical industry he moved to Givaudan Roure, where he is currently leading the Fragrance Ingredients group.

Caroline Denis, born in 1973, studied chemistry at the University of Nice. In 1996, she joined the Givaudan Roure Perfumery School in Grasse, continued her perfumery training in Applied Research in Argenteuil, and became junior perfumer at the start of 1999. Currently, she is working as perfumer in Dübendorf on perfumery briefs as well as in the evaluation of new research compounds and on the composition of demo formulas with new odorants.

Georg Fráter, born in 1941, obtained his doctorate working with Professor H. Schmid at the University of Zürich, and then spent postdoctoral years in Leiden and Edmonton. After more than ten years of agrochemical research with Hoffmann-La Roche, he joined Givaudan Roure, and is currently head of its Research Center in Dübendorf. He is also a senior lecturer at the University of Zürich.



1 coumarin (1868)
sweet, gingerbread
»Fougère Royale«
(Houbigant, 1882)

2 vanillin (1876)
sweet, vanilla
»Jicky«
(Guerlain, 1889)

3 lauryl aldehyde (1880)
aldehydic, fatty, orange
»Chanel N°5«
(Chanel, 1921)

4 α-ionone (1898)
woody, floral, violet
»L'Origan«
(Coty, 1906)

5 Evernyl® (1898)
woody, moss
»Égoïste Platinum«
(Chanel, 1993)

6 γ-undecalactone (1908)
fruity, peach
»Mitsouko«
(Guerlain, 1919)

7 Ambrox® (1950)
ambery
»Drakkar Noir«
(G. Laroche, 1982)

8 Hedione® (1960)
floral, jasmine
»Eau Sauvage«
(C. Dior, 1966)

9 dihydromyrcenol (1960)
hesperidic, floral, fresh
»Cool Water«
(Davidoff, 1988)

10 Galaxolide® (1967)
musky
»Trésor«
(Lancôme, 1990)

11 α-damascone (1969)
floral, rosy, fruity
»Nahéma«
(Guerlain, 1979)

12 ethyl maltol (1969)
sweet, caramel, candy
»Angel«
(T. Mugler, 1992)

Scheme 1. Trendsetting odorants of the past.

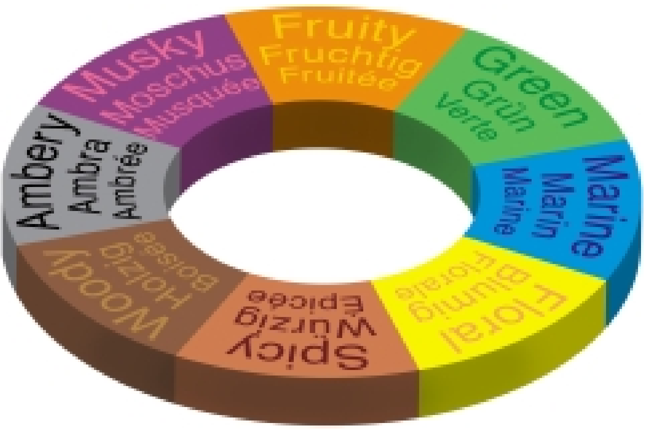
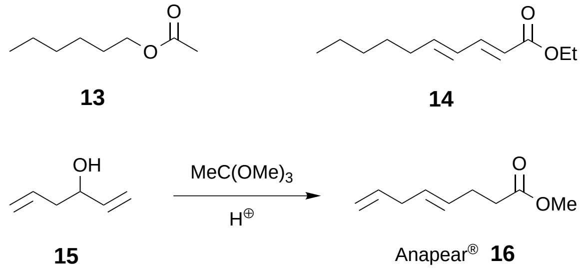


Figure 1. The olfactory spectrum.

After peach, coconut, and apple, it is now pear, grapefruit, and blackcurrant that are in fashion. The pear trend started in personal care products such as "Elsève alpha jojoba" shampoo (L'Oréal, 1995), which contained 3.5% of hexyl acetate (**13**), and "P'tit DOP Douche + Bain Super Relaxing" (Lascad/L'Oréal, 1997), which contained about 25% of **13**. This trend then spread to fine fragrances such as "Tempore Donna" (Laura Biagiotti, 1999), where **13** was used in a pear-chocolate accord that was blended with vanilla. We also find **13** in "D&G feminine" (Dolce & Gabanna, 1999) with its sensual pear-musk interplay. A blackcurrant note joins the pear-musk theme in "2020 Courrèges" (Courrèges, 1997). Here the pear note is mainly a consequence of about 5% of ethyl (2*E*,4*E*)-deca-2,4-dienoate (**14**), which like **13** is a natural constituent of pears.[7]

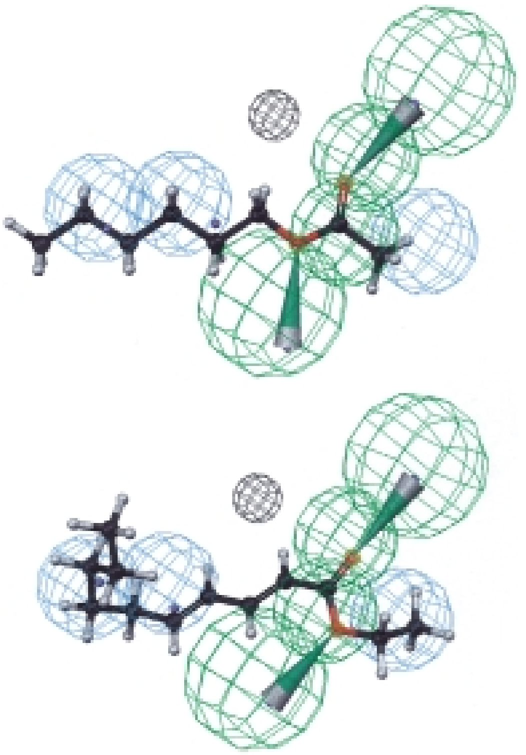
Anapear (**16**) is a new powerful odorant with a fruity-green pear note. It is synthesized by an orthoester–Claisen rearrangement of hexa-1,5-dien-3-ol (**15**), as outlined in Scheme 2.[8] It has just started to be used, for example, in "Emporio Armani Elle" (G. Armani, 1998).



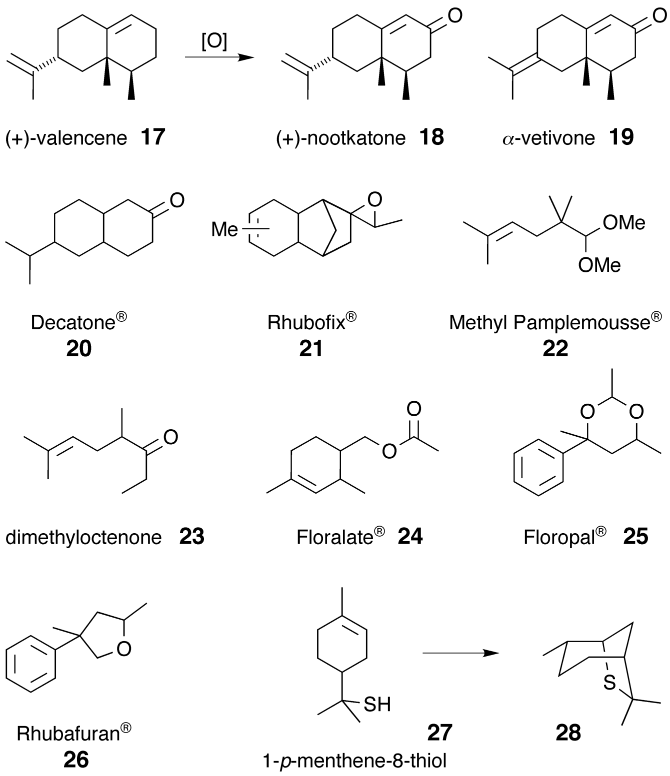
Scheme 2. Pear odorants.

A data set of quantitatively assessed odorants for pear esters was published by Sell,[6] and this has been used in the generation of several models that relate the molecular structure to the pear odor of the compounds.[6, 9, 10] A distance of approximately five carbon atoms, corresponding to approximately 6.3 Å, between a hydrophobic part and a hydrogen-bond-accepting oxygen atom as well as the absence of steric bulk in the vicinity of the alkoxy oxygen atom were found to be important requirements for a pear-type odor. By using the data set of Sell[6] and including the commercially important pear odorants **13**, **14**, and **16**, we generated the CATALYST[11] olfactophore model shown in Scheme 3.

An olfactophore model (a special case of a pharmacophore model) is a representation of generalized molecular features (hydrophobic groups, hydrogen-bond donors and acceptors) that are key for a given odor. It corresponds to the binding properties and geometries of the receptor. In the pear model of Scheme 3 both oxygen atoms of each ester moiety fit with the hydrogen-bond acceptors (depicted in green) that orient the molecule within the binding site of the receptor. Two hydrophobic pockets (depicted in cyan) are located 7.2/7.9 Å and 5.3/5.9 Å away from the hydrogen-bond acceptors on one side, and a third one is situated on the opposite side at a distance of 2.5/3.1 Å. An excluded volume (shown in black), inaccessible to the odorant molecule, was placed 2.9/4.0 Å away to account for steric demands of the receptor. The model covers a conformational energy barrier of 3 kcal mol^{-1}. Within this energy barrier the conformer that best fits the model is selected, and the estimated activity is calculated on the basis of its mapping with the features. Scheme 3 illustrates the mapping of **13** and **14**, respectively, to this pear olfactophore.



Scheme 3. Olfactophore model for pear odorants. Top: with **13**; bottom: with **14**.



Scheme 4. Grapefruit odorants.

These olfactophore models (hypotheses based on the *molecular similarity* of known odorants) can provide some insight into the molecular parameters responsible for a given odor, and they are helpful for the computer-aided design of new odorants. Despite all the uncertainties of these models, such a pragmatic approach is inevitable, because our limited knowledge on the mechanism of olfaction[12–14] and the odorant receptors does not yet allow a de novo design of odorants based on the *molecular complementarity* to a receptor surface.[4]

2.2. Grapefruit and Blackcurrant

"Pleasures for Men" (E. Lauder, 1997), "Aqua Allegoria Pamplelune" (Guerlain, 1999), and "L'eau de Kenzo masc" (Kenzo, 1999) with around 3.5 % of Methyl Pamplemousse (**22**; see Scheme 4), are recent examples of the grapefruit trend. Bergamot, lemon, and orange oil (so-called hesperidic notes) have always been used to give freshness and lift to a fragrance. Grapefruit accords offer a new way of doing so without being reminiscent of the traditional Eaux de Cologne.

The prototype odorant of this note, the naturally occurring nootkatone (**18**), can be obtained by oxidation of valencene (**17**; Scheme 4). Despite its good substantivity, **18** remains too expensive for many applications. It differs from α-vetivone ((+)-isonootkatone, **19**), one of the main components of vetiver oil (see Section 7.3), only by the position of the nonconjugated double bond. The olfactory properties of these two octalinones are similar in many respects, and thus grapefruit aspects are also present in vetiver oil. The odor of nootkatone (**18**) is mimicked by the perfumery synthetics Decatone (**20**) and Rhubofix (**21**), the latter being a complex mixture of regio- and stereoisomers.

Grapefruit odorants have many facets, hesperidic – citrusy, fruity rhubarb, and cassis-type, as well as green and woody tonalities. Many of these facets are present in "Good life" (Davidoff, 1998), and they all revolve around an overdose of 8.5 % of Methyl Pamplemousse (**22**): fruity aspects are reinforced by blackcurrant notes, green by a fig-leaf tonality, and woody by a classical moss accord. Other grapefruit odorants with mainly hesperidic, citrusy, fresh facets are dimethyloctenone (**23**) and Floralate (**24**; Scheme 4). Floropal (**25**) and Rhubafuran (**26**) are two examples of grapefruit odorants with fruity rhubarb undertones.

Grapefruit accords are also often based on sulfur-containing compounds in chemically and olfactorily complex mixtures such as thiolimonene, thiocineole, or thiogeraniol. These are obtained by treating the corresponding terpenes with sulfur, hydrogen sulfide, or thiourea. Their main odor vectors are the enantiomers of 1-*p*-menthene-8-thiol (**27**),[13] which are the potent character-donating constituents of grapefruit juice[14] and easily cyclize to 2,8-*epi*-thio-*p*-menthane (**28**). 8-Mercapto-*p*-menthone (**29**; Scheme 5), identified in buchu leaf oil,[15, 16] is also an olfactorily important component of the thioterpene mixtures. It possesses a blackcurrantlike odor.

Other blackcurrant odorants include 4-methoxy-2-methylbutan-2-thiol (**30**), a major constituent of the cassis bud aroma,[17, 18] Corps Cassis (**31**), and Oxane (**32**, Scheme 5), the 4*S*-*cis* and 4*S*-*trans* stereoisomers of which were found in yellow passion fruits.[19–21] Labienoxime (**33**)[22] and the bicyclic Buccoxime (**34**) belong to another important family

“Khas Khas”

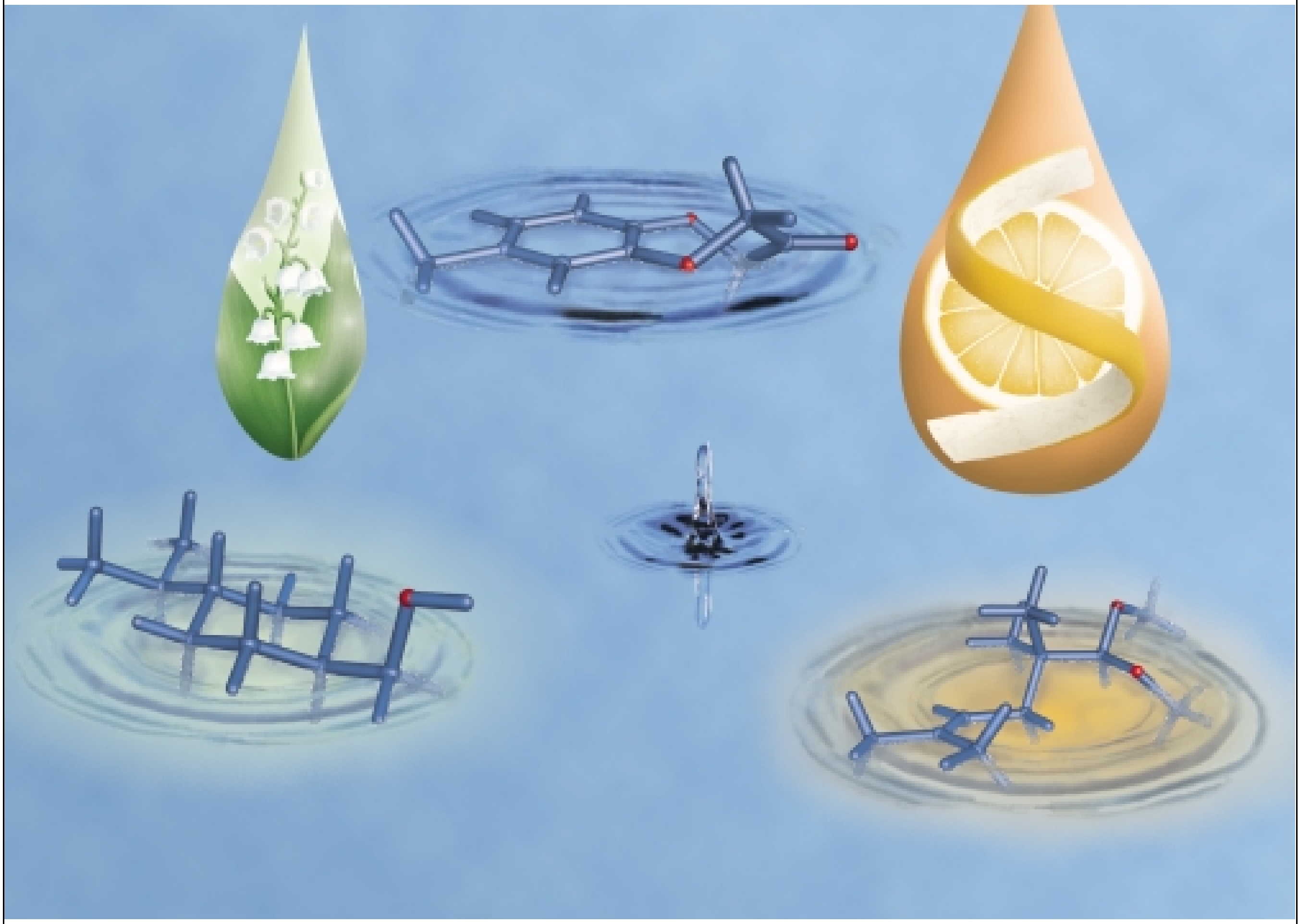
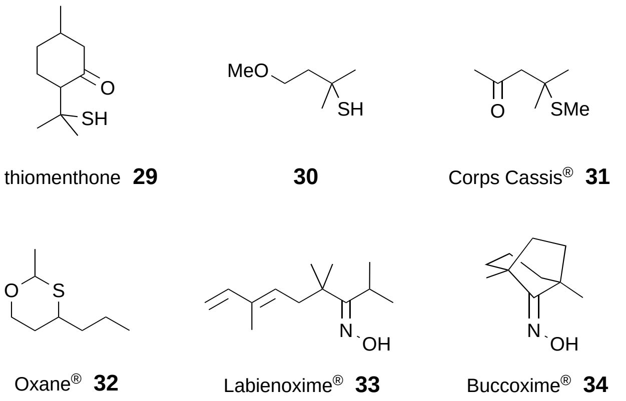


Figure 2. “Khas Khas”—a modern feminine fragrance featuring Methyl Pamplemousse (**22**), Calone 1951 (**84**), Melonal (**90**), Tropional (**85**), Mayol (**96**), Florol (**97**), and vetiver oil.

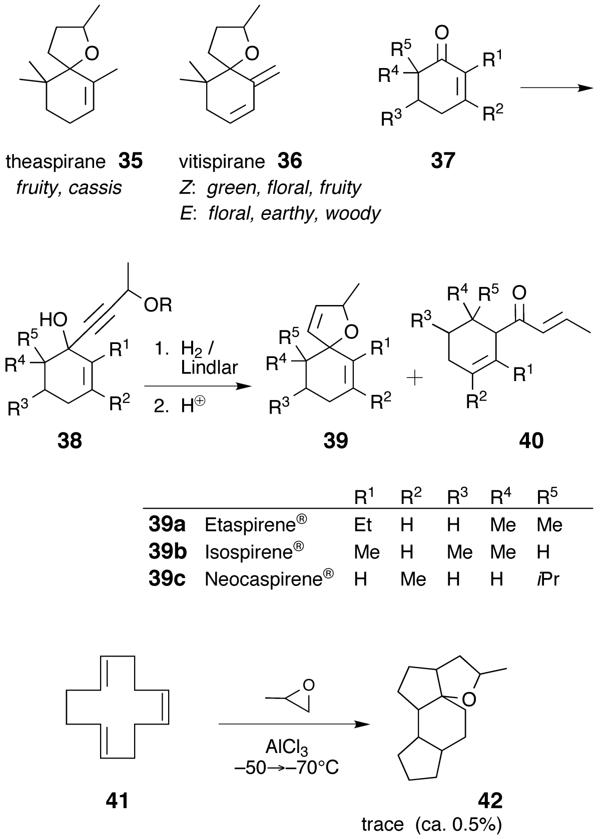
••• *Microencapsulated fragrance: Rub and smell!*



Scheme 5. Sulfur- and nitrogen-containing blackcurrant-type odorants.

of chemicals with blackcurrant smell, the ketoximes, which usually have a more green and metallic odor.

The family of the blackcurrant-smelling spirocyclic ethers **39** (Scheme 6) is synthetically demanding. They resemble natural vitispiranes (**36**, found in grape juice, wine, spirits, vanilla, blackberry, etc.), and theaspiranes (**35**, found in raspberries, tea, rose, quince, etc.), but seem to originate from the damascone (**11**)/damascenone chemistry, as presented in Scheme 6.[23, 24] An interesting structure–odor relationship study with nineteen spirocyclic ethers was published by van der Weerd.[25] Recently, the polycyclic ether **42**, which also possesses the 1-oxaspiro[4.5]decane substructure, was patented[26] as having a very intense and substantive blackcurrant odor.



		R^1	R^2	R^3	R^4	R^5
39a	Etaspirene®	Et	H	H	Me	Me
39b	Isospirene®	Me	H	Me	Me	H
39c	Neocaspirene®	H	Me	H	H	*i*Pr

Scheme 6. Spiroethers with a fruity, blackcurrant scent.

In general, blackcurrant odorants are extremely powerful, and are therefore usually used in the form of perfumery bases: Oxane (**32**) in the green-fruity-floral "Cassis base 345 B", and Neocaspirene (**39c**) in the fruity-exotic "Dewfruit". These bases are easy to work with, even in higher concentration. For instance, about 18% of cassis bases were employed in the floral-fruity feminine fragrance "Le monde est beau" (Kenzo, 1997).

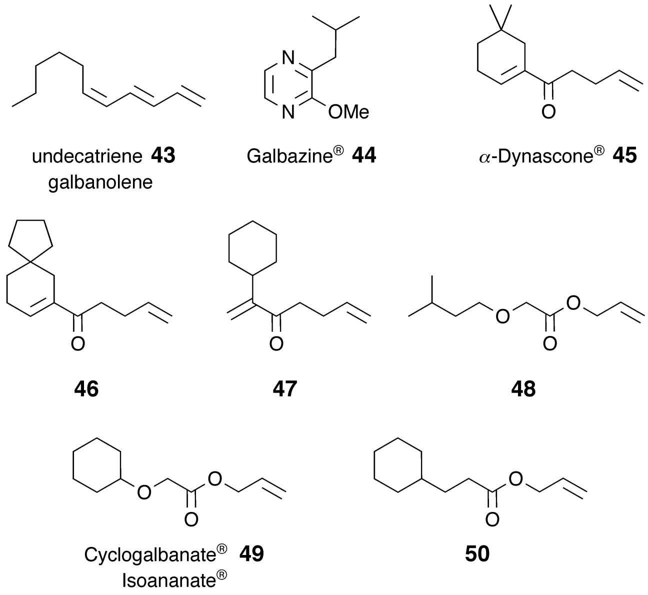
Last but not least, there are also examples for the direct use of blackcurrant odorants. Etaspirene (**39a**) gives a lot of volume and diffusivity to "Pleasures" (E. Lauder, 1995), and Buccoxime (**34**) links the blackcurrant and grapefruit accords in "Good life". Furthermore, these odorants opened the way to fantasy notes, such as the tomato-leaf accord of "Les Belles" (N. Ricci, 1996).

In Figure 2 the microencapsulated feminine fragrance "Khas Khas" illustrates how a grapefruit accord, composed of Methyl Pamplemousse (**22**) can exalt the hesperidic aspects of vetiver. This vetiver note is modernized by a marine accord (see Section 4.2), and blended with trendy floral odorants such as Mayol (**96**) and Florol (**97**; see Scheme 17). This perfume demonstrates how modern perfumery synthetics enable the use of a rather traditional ingredient of masculine perfumery, such as vetiver oil, in a floral-woody-aquatic feminine fragrance.

3. Green Notes

3.1. An Olfactophore Model for Galbanum Notes

The characteristic, harsh green odor of galbanum oil (*Ferula galbaniflua* Boiss. et Buhse and *Ferula rubicaulis* Boiss) arises to a great extent from minor constituents, of which (3*E*,5*Z*)-undeca-1,3,5-triene (**43**)[27] and 2-methoxy-3-isobutylpyrazine (Galbazine, **44**) are the most important (Scheme 7). Both



Scheme 7. Galbanum-pineapple odorants.

“ChocoMinty”

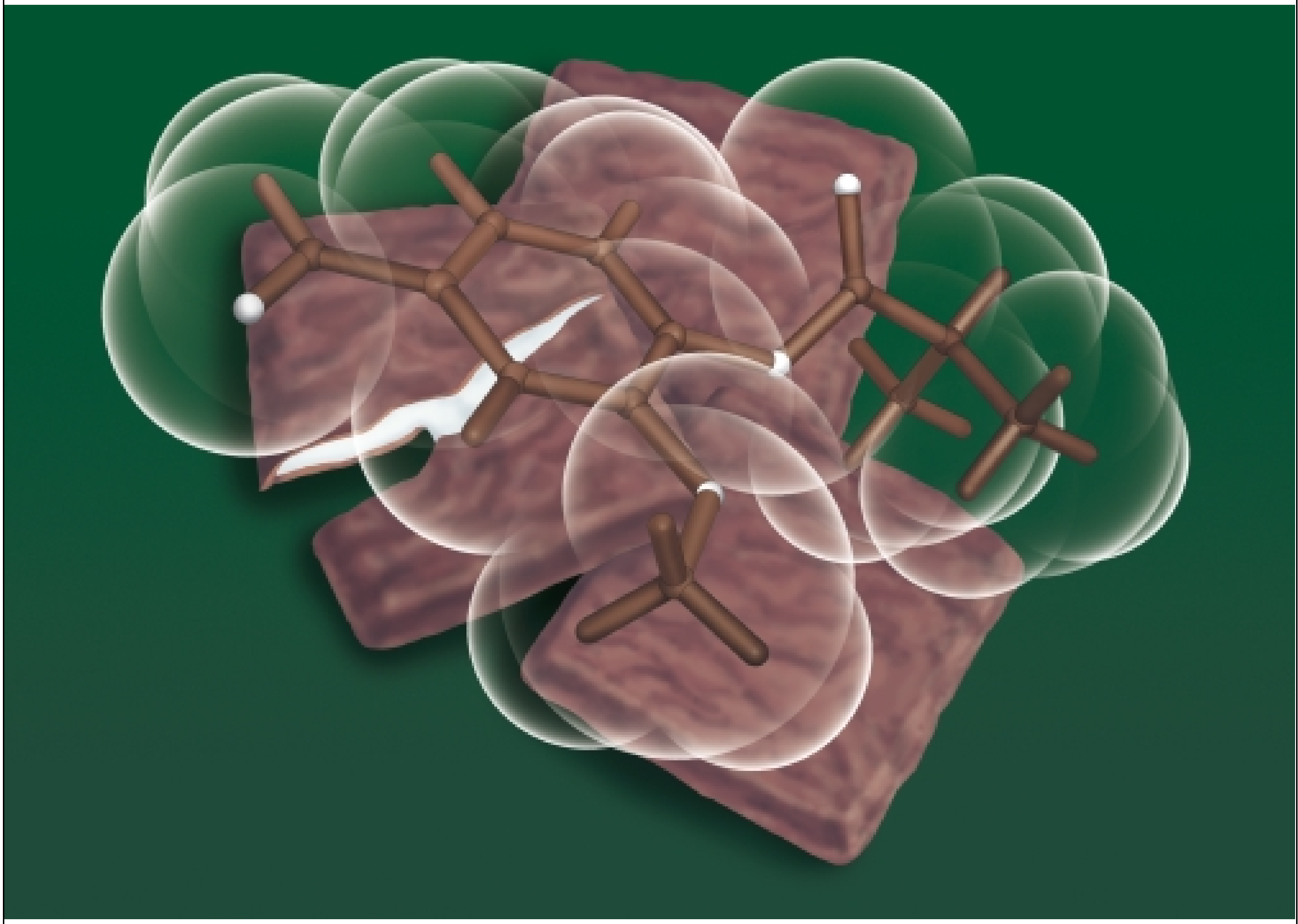
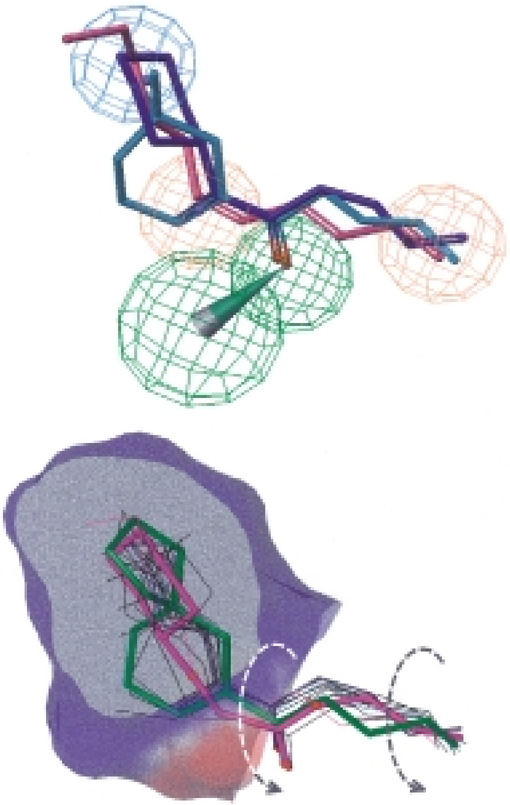


Figure 3. “ChocoMinty”—a fresh gourmande note featuring Isobutavan (**134**).

••• *Microencapsulated fragrance: Rub and smell!*

compounds are available to the perfumer as synthetic products. The galbanumlike odor of another important perfumery raw material, Dynascone (**45**, main odor vector), is accompanied by a fruity, pineapple-type note. Compound **45** was found by serendipity among the impurities of synthetic α-damascone (**11**).[28, 29]

An analysis of the structural requirements for the green, galbanum odor[30] led to a family of hypothetical olfactophores composed of one nonaromatic hydrophobic function (blue sphere), one oriented hydrogen-bond acceptor (green spheres), and two customized functions representing an electron-rich fragment that is either an ether or an aliphatic double bond (orange spheres).[11] The generated olfactophore hypotheses consist of a bulky hydrophobic part with an electron-rich link to the pent-4-en-1-one or allyloxycarbonyl side chain. Different positions of the side chain are possible because of the flexibility of the latter. A proposal for the 3D shape of the hydrophobic pocket, corresponding to the Conolly surface of the aligned active structures that are colored according to their electrostatic potential, is also depicted in Scheme 8.[31] This feature is of important discriminating power; slight changes, for example, ring enlargement by one carbon atom or shift of a methyl substituent by one position in the ring, can lead to a total loss of the green-galbanum component in the olfactory profile. Even more restrictive is the presence of both hydrogen-bond acceptors. Two recently revealed galbanum odorants of very low odor threshold and outstanding substantivity, **46** and **47** (Scheme 7),[30, 32, 33] map very well this *combinatorial*[34, 35] olfactophore. Not surprisingly, the even more flexible undecatriene **43** with a green-galbanum odor without fruity aspects also fits to it, except for the hydrogen-bonding function. It can be postulated that the C-3 double bond is playing the role of a weak hydrogen-bond acceptor. Another possibility consists of the generation of an oxygen function at this position (through a metabolic process), prior to the receptor–ligand interactions.



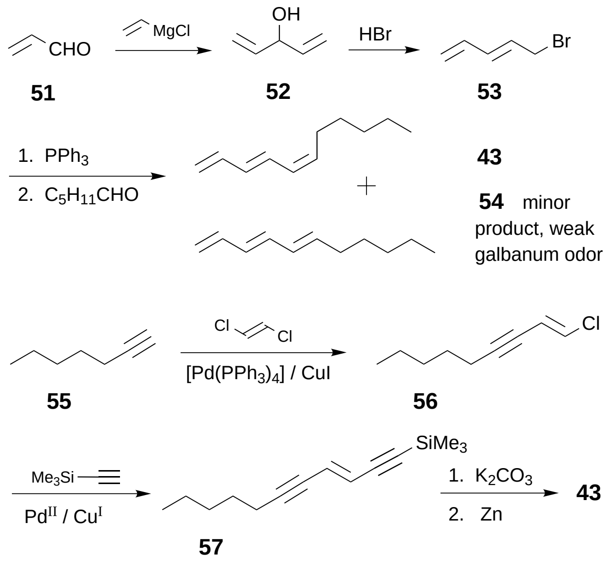
Scheme 8. Galbanum olfactophore model. Top: One of the best hypotheses mapped by undecatriene **43** (magenta), α-Dynascone (**45**, cyan), and **47** (blue). Bottom: All the active structures of the training set aligned on this hypothesis. The galbanum-like **46** (green) and much more pineapple-smelling **49** (pink) are highlighted. Hydrogen atoms are omitted for clarity.

3.2. Galbanum Notes

The complex galbanum odor blends with many different accords. As early as 1945, galbanum was overdosed in “Vent Vert” (Balmain, 1945) in a green-floral accord. In “Chanel 19” (Chanel, 1970) galbanum shows its efficiency with floral and woody notes. More recently, with the development of synthetic galbanum odorants, galbanum is used in fragrances to impart fruity-green, especially pineapple notes.

The main representatives of this odorant family are the 1-substituted pent-4-en-1-ones **45**–**47** and the allyl glycolates **48** and **49** (Scheme 7), which can be considered as their 2-oxa analogues. The odors of the esters are much more fruity, reminiscent of the pineapple scent. Their weaker galbanum note disappears completely in the absence of the ether function close to the carbonyl group, which mimics the α,β-conjugated double bond of the corresponding ketones. This is the case for allyl cyclohexylpropionate (**50**), which smells almost exclusively pineapplelike.

Since the first isolation of undecatriene **43** from galbanum oil in 1964,[27] several synthetic methods for the preparation of this impact chemical have been developed. One of the most industrially viable processes, using vinyl chloride, acrolein, and hexanal as building blocks, is depicted in Scheme 9, together with the most recently published one.[36] The main step of the latter is the Pd/Cu-catalyzed coupling of tri-



Scheme 9. Syntheses of (3*E*,5*Z*)-undeca-1,3,5-triene (**43**).

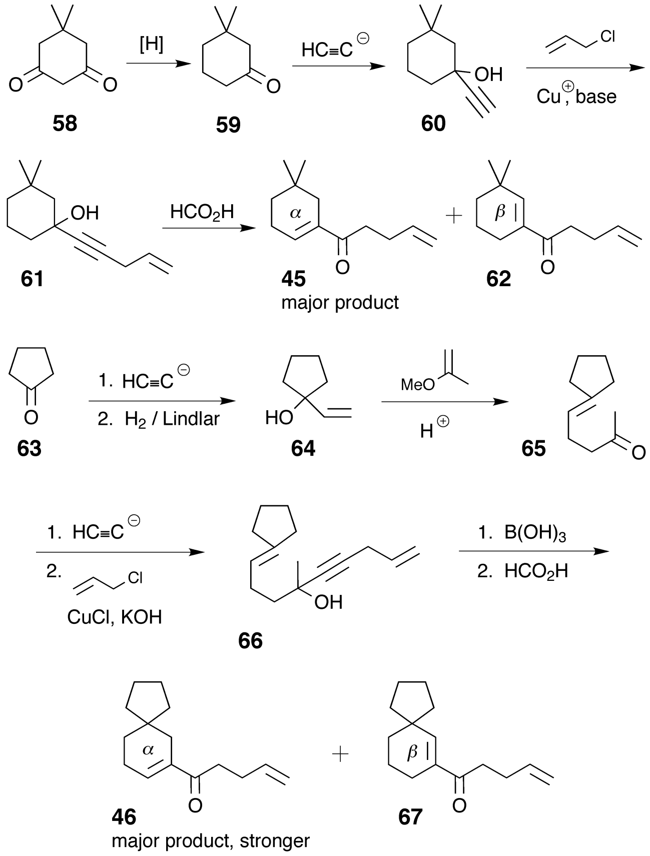
“W-A-S”

Figure 4. “**W**-A-S.”—a woody-ambery-spicy masculine perfume featuring Georgywood (**170**), Spirambrene (**200**), Okoumal (**196**), and black and pink pepper oil.

••• *Microencapsulated fragrance: Rub and smell!*

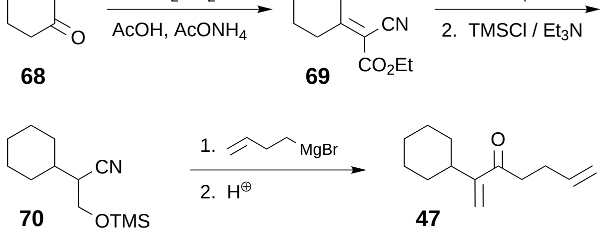
methylsilylacetylene with chloroenynes. Interestingly, **43** (=galbanolene) was also found in algae, where it plays the same pheromone role (sperm attractant) as another structurally similar arachidonic acid metabolite,[37] dictyopterene A (**77**, see Scheme 13; Section 4.1).

α-Dynascone (**45**), in a mixture with its weaker β isomer (**62**), had long been used as a captive material (that is, a material used only in-house and not sold to others) before it was introduced recently to the market. One of the possible synthetic routes to this valuable material starts with a partial reduction of dimedone (**58**), with the crucial step being the last Rupe rearrangement of the propargylic alcohol **61** (Scheme 10).



Scheme 10. Syntheses of **45** and **46**.

The more substantive galbanum odorant **46** can be obtained starting from cyclopentanone. The synthesis ends by dehydration followed by a tandem ring closure and Rupe rearrangement (Scheme 10).[32] Significantly simpler and less expensive is the synthesis of **47** (Scheme 11), which comprises an elegant one-pot reaction: Grignard addition, imine hydrolysis, hydroxyl deprotection, and dehydration.[30]



Scheme 11. Preparation of **47**. TMS = Me_3Si.

Dynascone (**45/62**), allyl amyl glycolate (**48**), and Cyclogalbanate (**49**) are often used in perfumery, with or without natural galbanum oil. We find galbanum oil, allyl amyl glycolate (**48**), and Cyclogalbanate (**49**), for example, in "Elements Aqua" (H. Boss, 1997). Dynascone (**45/62**) and allyl amyl glycolate (**48**) have also contributed in the development of the modern Fougère family with the important accord of **48**, **45/62**, dihydromyrcenol (**9**), and Ambrox (**7**). "Cool Water" (Davidoff, 1988) and "Egoïste Platinum" (Chanel, 1993) are prominent representatives of modern Fougère perfumes.

3.3. The Green of Leaves

Green notes in perfumery are very diverse. Very often green odor means freshly cut grass, but it can also mean the smell of leaves. In "Premier Figuier" (L'Artisan Parfumeur, 1995), galbanum oil is combined with many other green notes around Glycolierral (**72**) to give a fig-leaf accord. Glycolierral (**72**) has an ivy-leaf odor, and for this note it is used in "J'adore" (C. Dior, 1999). Another fresh green, leafy note with floral undertones is Undecavertol (**74**), which possesses more violet-leaflike facets. This compound requires a careful dosage because of its strength. In "Extravagance d'Amarige" (Givenchy, 1998) it was used in around 0.1% and blended with allyl amyl glycolate **48** and some other violet-leaf odorants, such as methyl non-2-enoate (Neofolione) and methyl non-2-ynoate (methyl octine carbonate). Undecavertol (**74**) was even used in around 0.4% and blended with 0.3% of Cyclogalbanate (**49**) in "Sunwater" (Lancaster, 1997). Birch leaves are trendy too, and "Birch Leaf Givco" was for example used in "Escape for Men" (C. Klein, 1993). It is a base with a very natural smell that contains Undecavertol (**74**) together with a natural, fresh, green, leafy, aldehydic odorant called Vernaldehyde (**76**).

Glycolierral (**72**) and Vernaldehyde (**76**) are prepared starting from the common terpenes phellandrene (from eucalyptus oil) and myrcene, respectively (Scheme 12). The Diels–Alder condensations with acrolein and methacrolein (formed in situ by Mannich condensation of propional and formaldehyde) lead to the corresponding aldehydes that are transformed to the final regioisomer mixtures **72** and **76** by simple ketalization or partial hydrogenation. Undecavertol (**74**)[38] is also prepared in a simple two-step process, which consists of an aldol condensation of propanal, and the Grignard addition of pentylmagnesium bromide.

4. Marine-Type Molecules

4.1. The Olfactory Impression of a Seashore

Which molecules hit our olfactory receptors when we walk along a wet seashore? At least some of them are linear or alicyclic $C_{11}H_{14}$ to $C_{11}H_{18}$ hydrocarbons, which serve as mating pheromones of various species of brown algae.[39]

"Muskberry"

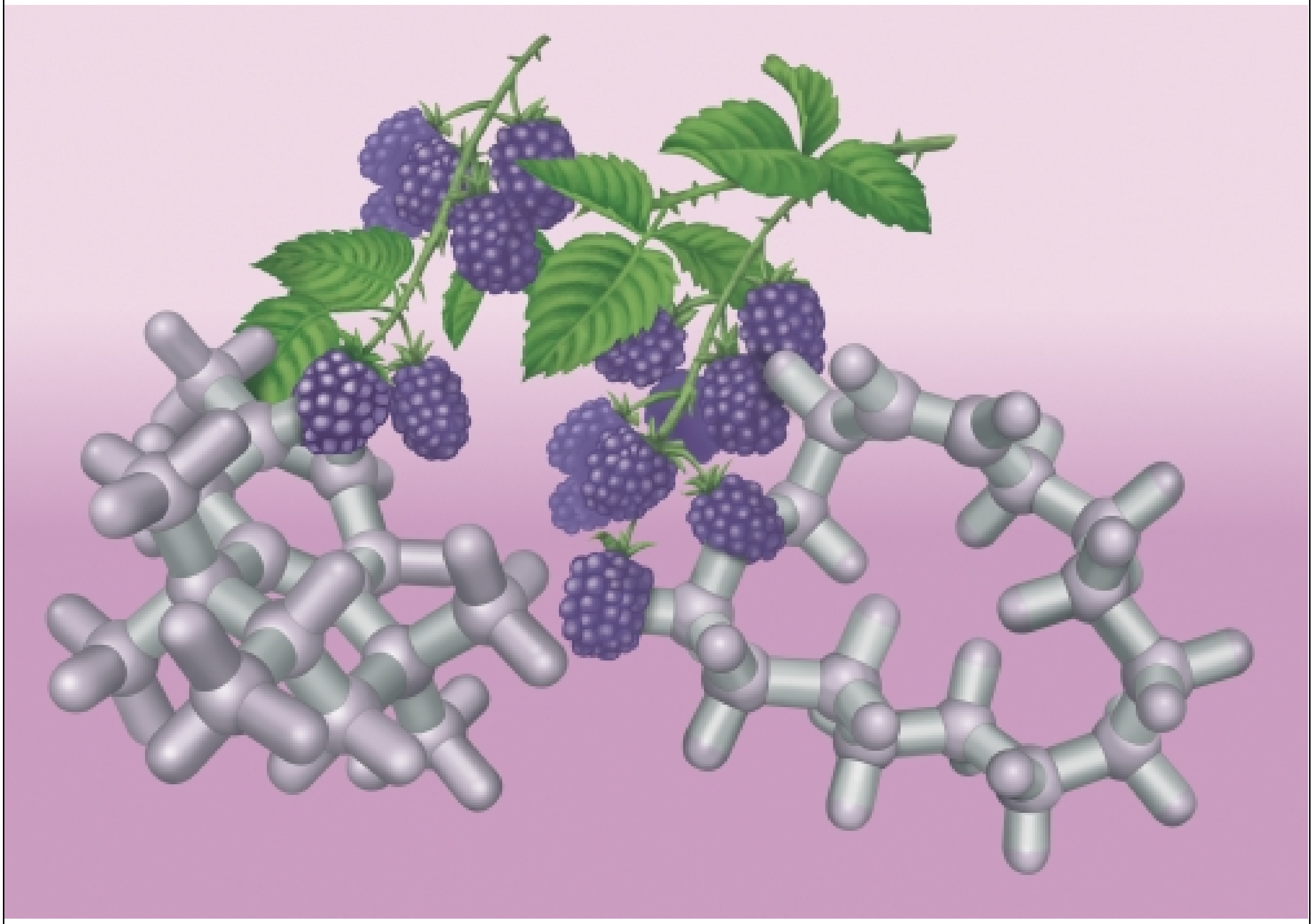
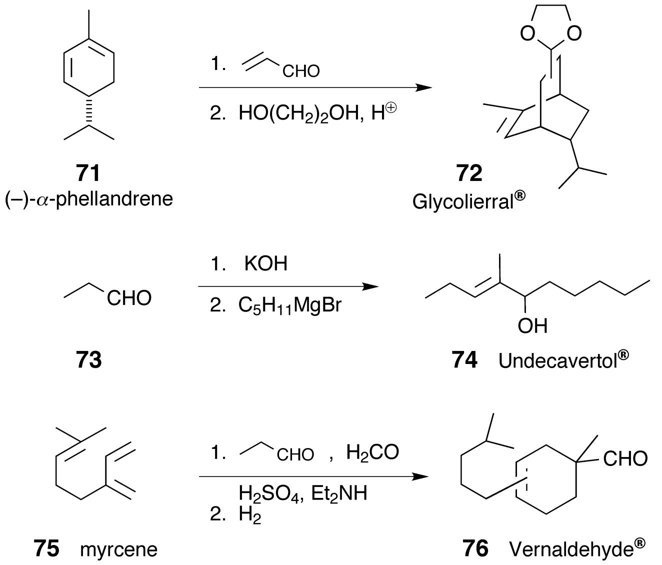


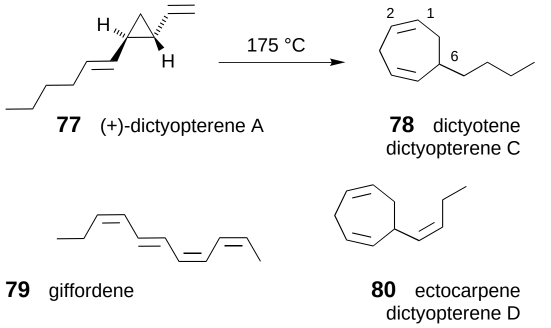
Figure 5. "Muskberry"—a fruity-musky accord featuring Habanolide (**254**) and Moxalone (**212**).

••• *Microencapsulated fragrance: Rub and smell!*



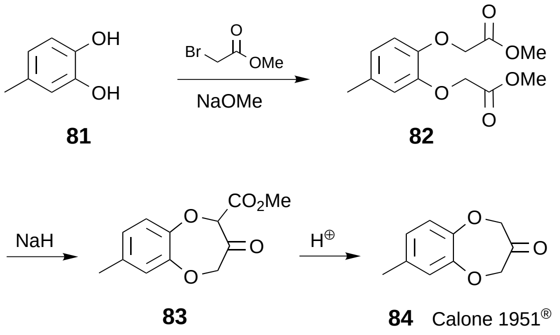
Scheme 12. Synthesis of some green-leaf odorants.

(+)-Dictyopterene A (**77**), which possesses a characteristic odor of seawater, was the first of these odoriferous hydrocarbons to be isolated from algae.[40] The Cope rearrangement of **77** gives dictyotene (**78**; Scheme 13),[41] the (−) isomer of which also was found to be present in marine brown algae. The odor of **78** is fishy, somewhat reminiscent of salmon roe. Giffordene (**79**) with its typical sea-algae odor is the odoriferous principle of *Giffordia mitchellae* (Harvey) Hamel,[42] and the green, tomato-leaflike smelling ectocarpene (**80**) is secreted by the brown algae *Ectocarpus siliculosus*.[43]



Scheme 13. Some odorants of algae.

When it comes to creating the olfactory impression of a seashore in perfumery, Calone 1951 (**84**) is the material of choice. The benzodioxepanone **84**,[44] a very unusual structure for a fragrant substance, possesses a typical marine sea-breeze note with floral nuances, and is manufactured from homopyrocatechol (**81**) as outlined in Scheme 14. A Williamson reaction with methyl bromoacetate is followed by a classical Dieckmann condensation, and hydrolysis and decarboxylation of the resulting intermediate **83** in the last step provides the commercial product **84**.[44]



Scheme 14. Industrial synthesis of Calone 1951 (**84**).

4.2. Marine, Watermelon, and Ozonic Notes

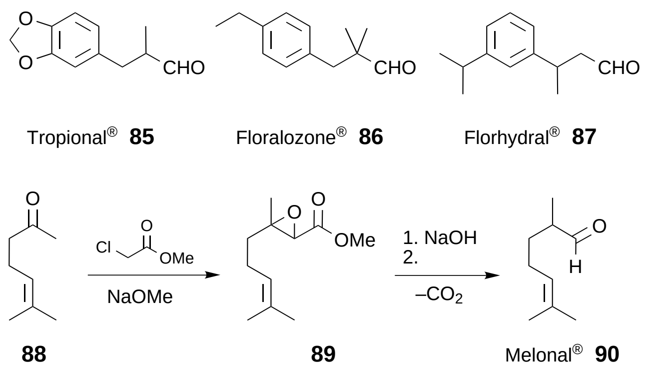
With the launches of "New west for her" (Aramis, 1990) and "Escape for her" (C. Klein, 1991) a marine trend was initiated in feminine perfumery, based on a very simple combination of two raw materials: Calone 1951 (**84**) and Tropional (**85**). In "L'Eau d'Issey" (I. Miyake, 1992), a watermelon note was added to this accord with Melonal (**90**). Finally, ozonic aspects were added to these marine and watery facets by Floralozone (**86**), to form a typical aquatic accord that can be found in fragrances such as "Cool Water fem" (Davidoff, 1996), "L'Eau d'Eden" (Cacharel, 1996), and "Polo Sport Woman" (R. Lauren, 1996). The evolution of the aquatic accord is shown in Table 1.

These accords were also employed in masculine perfumes. "L'Eau d'Issey masc" (I. Miyake, 1994) with about 13% of Tropional (**85**), 0.4% of Calone 1951 (**84**), and 0.4% of Melonal (**90**) is a prominent example. However, the compounds can also be used to give just an ozonic or marine inflection. In "Allure" (Chanel, 1996) we find some 2% of Tropional (**85**) and around 0.05% of Floralozone (**86**), and in "Good life woman" (Davidoff, 1999) a trace of Calone 1951 (**84**) and some Florhydral (**87**), which conveys a fresh, marine, and ozonic touch.

The chemical structures of these aldehydes are depicted in Scheme 15. The industrial synthesis of Melonal (**90**) by Darzen's glycidic ester condensation of 6-methylhept-5-en-2-one (**88**), subsequent hydrolysis, and decarboxylation is also presented.

Table 1. Evolution of the aquatic accord.

	"New West for her" (1990)	"Escape for her" (1991)	"L'Eau d'Issey" (1993)	"L'Eau d'Eden" (1996)	"Cool water fem" (1996)	"Polo Sport W" (1996)
Calone 1951 (**84**) [%]	1.2	0.8	0.6	0.17	0.4	0.45
Tropional (**85**) [%]	7.5	3.7	2	1.5	4.3	4.8
Melonal (**90**) [%]	–	–	0.02	0.03	0.02	0.12
Floralozone (**86**) [%]	–	–	–	0.1	0.07	0.04
ratio **84**:**85**	0.21	0.16	0.3	0.11	0.09	0.09



Scheme 15. Aldehydes with marine odor notes.

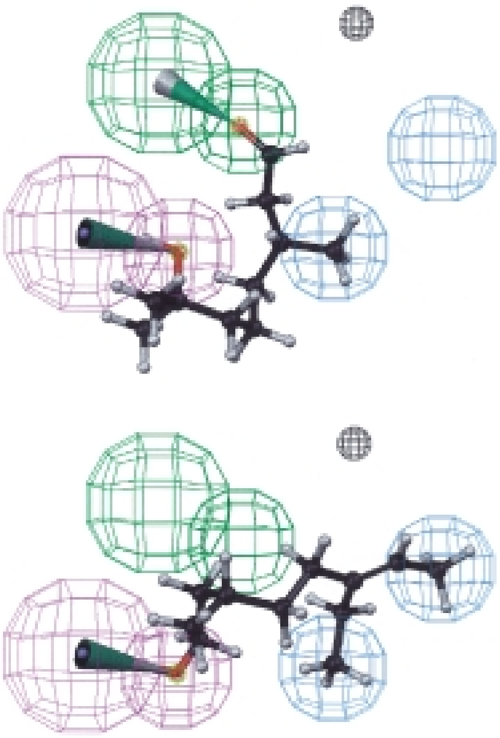
5. Floral Odorants

5.1. A Muguet Olfactophore

The complex scent of lily of the valley flowers (*Convallaria majalis* L.), in perfumery often called muguet, is delicate floral, with a distinct touch of greenness, surrounded by fresh, rosy-lemony nuances. It has something in common with the scent of rose, jasmine, and lilac blossoms; and therefore, cannot be imitated by a single compound. Odorants with muguet character also often possess other different aspects, which makes structure–odor correlations difficult.[10] However, even though no single odorant duplicates the natural scent, hydroxycitronellal (**91**; scheme 17)[45] reproduces the odor of lilly of the valley quite closely. Therefore, it is generally considered as the prototype of muguet odorants, and can be found in the typical muguet perfume "Diorissimo" (C. Dior, 1956).

Boelens et al.[46, 47] assumed an aldehyde group, a γ,δ-double bond or oxygen atom, and a maximum length of the molecules of 12–14 Å with a bulky group at the end to be necessary structural features of muguet odorants. However, 2,3-dihydrofarnesol (**92**; Scheme 17), which lacks an aldehyde group as well as a γ,δ-double bond or an ether function is an outstanding muguet odorant, and by headspace-GC analysis was even shown to be a true fragrance component of the living lily of the valley flowers.[48] On the basis of the observation that bifunctional compounds possess a muguet odor only if they can adopt a conformation in which the distance between the functional groups is less than 3 Å, Ohloff and Giersch[49] postulated a proton-donor-proton-acceptor unit at the binding site of the muguet receptor. But Pelzer et al.[48] pointed out that these conformations are relatively strained, and their work with energetically minimized muguet odorants resulted in two different structural fragments for each functional group. The hydroxy fragment is 2,5-disubstituted and consists of two hydrophobic residues 4.7 and 6.0 Å from the carbinol carbon atom, while the carbonyl fragment is 2,4-disubstituted and bears a C-4 double bond and two hydrophobic substituents 3.9 and 5.0 Å from the carbonyl carbon atom.[10, 48]

By allowing a relatively high conformational freedom of 15 kcal mol^{-1} for the compounds, we could however generate a CATALYST[11] olfactophore model (Scheme 16), which features a bifunctional unit of a hydrogen-bond donor (magenta) and acceptor (green), and maps well with both fragments of Pelzer's model. The donor, acceptor, and one of the two hydrophobic functions form a quasi equilateral triangle with a side length of 4.5 Å. The second hydrophobic binding pocket is situated 4.2 Å away from the first, 5.7 Å from the hydrogen-bond acceptor, and 8.1 Å from the hydrogen-bond donor. A small excluded volume (in black) accounts for steric constraints. The model incorporates structure–threshold data of a series of muguet alcohols. Scheme 16 presents the fit of (+)-(3*R*)-hydroxycitronellal[45] (3*R*)-**91** (upper part) and Meo Parf (**93**, lower part), a powerful muguet alcohol with rosy undertones, to this muguet olfactophore model.

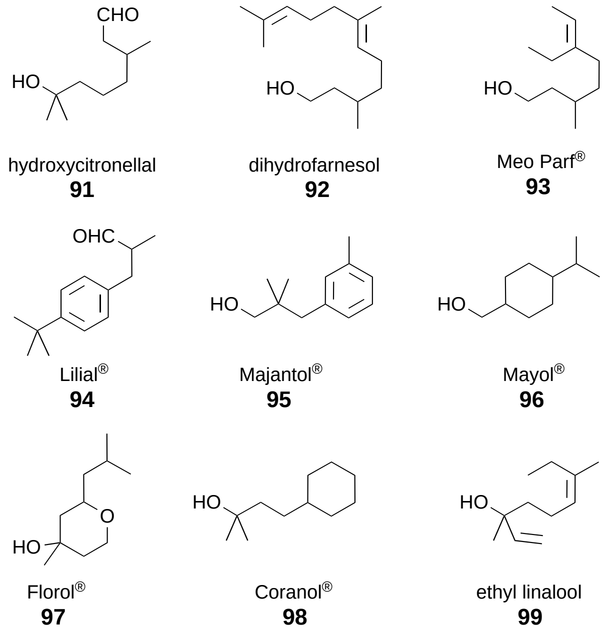


Scheme 16. Muguet olfactophore model. Top: with **91**; bottom: with **93**.

5.2. Muguet-Type Alcohols

The traditional muguet odorants, such as the well-known example Lilial (**94**; Scheme 17), were aldehydes, and in general, these muguet aldehydes are more powerful than muguet alcohols. However, aldehydes are more unstable, especially in oxidizing or alkaline media. The growing usage and scope of application of muguet odorants triggered a big demand to find alcohols of this odor note. Besides Meo Parf (**93**), Majantol (**95**), Mayol (**96**), and Florol (**97**), a derivative of rose oxide with a muguet odor and rose-petallike aspects, are representative muguet alcohols. In terms of odor, Mayol (**96**) is the closest to hydroxycitronellal (**91**), followed by Florol (**97**), Majantol (**95**), and Meo Parf (**93**), which already has a strong rosy inflection.

A muguet accord that contains Lilial (**94**) and Majantol (**95**) in the ratio of around 3:2 has been used in "Good Life"



Scheme 17. Floral, muguet-type odorants.

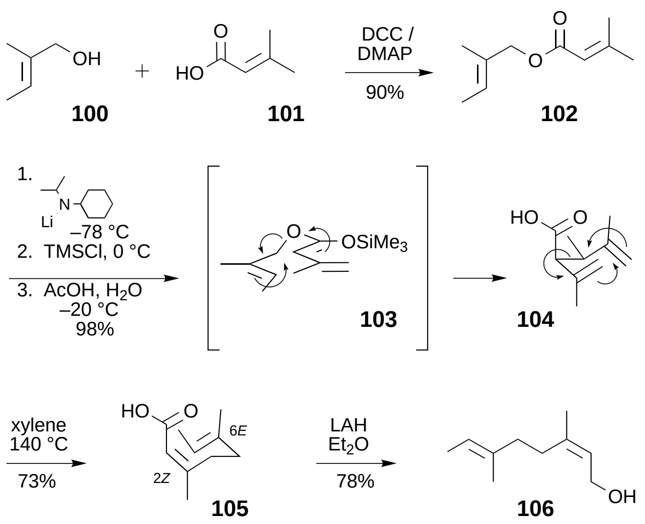
(Davidoff, 1998) and "Good Life woman" (Davidoff, 1999). In "Dolce vita" (C. Dior, 1995) overdoses of around 15 % of Majantol (**95**) and 6 % of Mayol (**96**) have been combined to harmonize the different floral parts, and to convey smoothness to the fragrance. Florol (**97**) was often used in combination with hydroxycitronellal (**91**) and Lilial (**94**) in muguet accords. Some examples are summarized in Table 2.

Table 2. Recent fragrances with a classical muguet accord.

	"XS for her" (1994)	"O oui" (1998)	"Dazzling Gold" (1998)	"J'adore" (1999)	"Fragile" (1999)
Florol (**97**) [%]	0.5	5.5	7	5.6	2.7
Lilial (**94**) [%]	3.5	5.5	8.5	7.5	3.2
hydroxycitronellal (**91**) [%]	2	2.5	5	1.7	3.3

Coranol (**98**), a captive odorant of Firmenich[50] with an intense floral odor similar to ethyl linalool (**99**) is only slightly reminiscent of lily of the valley. One of the first uses was in "Jean-Paul Gaultier" (J.-P. Gaultier, 1993) at a concentration of 0.3%. Coranol (**98**) also possesses a very fresh, clean dihydromyrcenol facet, and therefore has been used in high dosage in masculine fragrances, both in modern Fougère perfumes as well as in the oriental family, for example, in "L'Eau d'Issey masc" (I. Miyake, 1994) at 8%, "Bvlgari" (Bulgari, 1995) at 4.5%, "Dune masc" (C. Dior, 1997) at 8%, and "Jungle homme" (Kenzo, 1998) at 3.7% of **98**. Florol (**97**) and Coranol (**98**) were combined in the feminine "L'Eau d'Eden" (Cacharel, 1996), and more recently in "Romance" (R. Lauren, 1998) as well as in the masculine "L'Eau de Kenzo masc" (Kenzo, 1999) at 0.16, 3, and 1%, respectively, for Florol (**97**), and 3, 3.5, and 7% for Coranol (**98**).

An interesting analogue of Meo Parf (**93**) has recently been found in the constitutional nerol isomer **106**.[51] This was synthesized as outlined in Scheme 18 by Steglich esterification of tiglic alcohol (**100**) with senecioic acid (**101**), followed by a selective Ireland–Claisen rearrangement of the resulting ester **102**, subsequent Cope rearrangement, and LAH reduction of the formed product **105**. The shift from the typical rosy odor of nerol to the more muguet tonality of **106** by transposition of only one methyl group in the hydrophobic prenyl tail is impressive.[51]

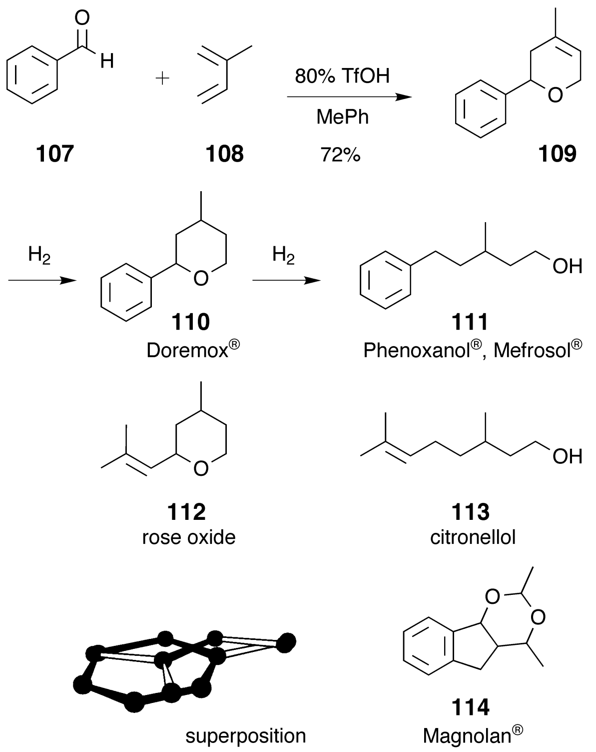


Scheme 18. Synthesis of a constitutional isomer (**106**) of nerol. DCC = dicyclohexylcarbodiimde; DMAP = 4-dimethylaminopyridine; LAH = lithium aluminum hydride.

5.3. Substantive Rose Scents

Substantivity[52] refers to the persistence of perfume materials or fragrances on blotters, on skin, or in the intended application. One important parameter that determines the substantivity of an odorant is its vapor pressure, which depends on the molecular weight. One way to increase the substantivity is consequently to increase the mass of a given molecule without affecting its shape a great deal. In terms of shape, the isobutenyl group, a very common structural element of terpenes, is similar to a phenyl ring (see the superposition in Scheme 19). Thus, both structural elements can be interchanged without alteration of the main odor characteristics. This isosterism has been demonstrated for many examples,[53, 54] whereby substituting a phenyl for an isobutenyl moiety has allowed more substantive, that is, long-lasting, odorants to be designed.

The most prominent case for this odorant design is Phenoxanol (**111**), which is constructed by replacing the isobutenyl group of citronellol (**113**) by a phenyl ring (Scheme 19). This results in a decrease of the vapor pressure by factor of 10, from 130000 $ng\,L^{-1}$ for **113** to about 12000 $ng\,L^{-1}$ for **111**, while the odor threshold of **111** at 0.8 $ng\,L^{-1}$ is also ten times lower than that of **113**. Doremox (**110**),[55] the corresponding analogue of rose oxide (**112**), is another precedent for increasing the substantivity of an odorant by replacing an isobutenyl moiety by a phenyl group. From the olfactory point of view, Phenoxanol (**111**) is richer and smoother than citronellol (**113**), and slightly fruity.



Scheme 19. Substantive rose odorants. Tf = F_3CSO_2.

Doremox (**110**) and rose oxide (**112**) both have floral, rosy, green odors, but Doremox (**110**) is less metallic, and has a pear-type undertone.

As illustrated in Scheme 19, the two perfumery synthetics Phenoxanol (**111**) and Doremox (**110**) are linked by common chemistry, which starts from the hetero-Diels–Alder reaction of benzaldehyde (**107**) with isoprene (**108**).[56] Recently, a lot of different catalyst systems have been elaborated for this reaction, including cationic palladium(II) complexes[57] and triflic acid,[58, 59] as shown for the synthesis of **109** in Scheme 19. The hetero-Diels–Alder adduct **109** is either hydrogenated to provide Doremox (**110**), or hydrogenolytically cleaved to afford Phenoxanol (**111**).

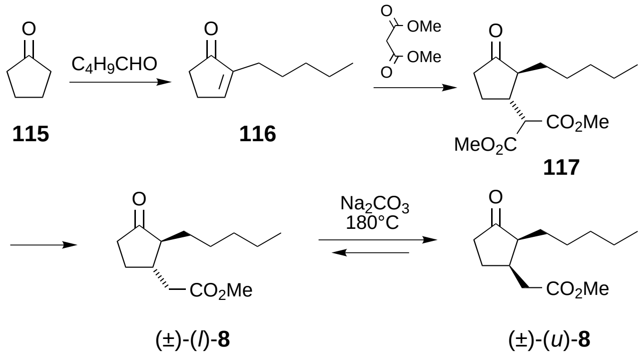
In "Birmane" (Van Cleef&Arpels, 1999), 0.6% of Phenoxanol (**111**) was mixed with other floral odorants such as Lilial (**94**) and additional rosy materials such as citronellol (**113**) to bring richness and volume, and to give a nice natural effect of rose absolute. In the floral-fruity "Bvlgari E.D.P." (Bulgari, 1994), around 2.5% of Phenoxanol (**111**) was used. Its effect was reinforced by natural rose absolute.

Roses are very diverse and all of them smell differently. This is also true for rosy odorants. Another substantive floral, rosy odorant is Magnolan (**114**),[60] the Prins reaction product of indene with acetaldehyde in the presence of formic acid. Compound **114** can convey the freshness of rose flower dew in compositions. Magnolan (**114**) is often used with muguet odorants. In "Comme des garçons 2" (Comme des garçons, 1999) about 9% was combined with around 2.8% of Mayol (**96**), and in "Sunwater" (Lancaster, 1997) 1.4% of **114** was used with 0.5% of Florol (**97**). In "In Love Again" (Yves Saint Laurent, 1998) 2.7% of Magnolan (**114**) was employed in combination with jasmine notes.

5.4. Jasmine and Transparent

Methyl dihydrojasmonate (Hedione, **8**) had its debut with around 2% incorporated in "Eau Sauvage" (Dior, 1966).[61] It confers a floral-jasmine, transparent, warm note on fragrances with the fresh-floral softness of lemons, and was already used in the high dosage of 8% in "Diorella" in 1972 (C. Dior). Just four years later, we find it in over 20% in "First" (Van Cleef&Arpels, 1976). Methyl dihydrojasmonate (**8**) indeed became a real phenomenon in fine perfumery, and today it is hard to find a formula without it. Up to now, the highest level of Hedione (**8**) is present in "Odeur 53" (Comme des garçons, 1998), at about 63%.

Scheme 20 details the industrial synthesis of **8** by aldol condensation of cyclopentanone with pentanal, subsequent Michael addition of methyl malonate, and decarboxylation. This process provides methyl dihydrojasmonate (**8**) in the thermodynamic equilibrium of about 90% (*l*)-**8** and 10% (*u*)-**8**. However, the *u* isomers of **8** are much more powerful (about 70 times) than the *l* isomers, and the odor of (*u*)-**8** is almost exclusively a result of the presence of the 1*R*,2*S*-(+) enantiomer, while (1*S*,2*R*)-**8** is very weak, and more earthy than floral in smell. Therefore, different processes have been worked out to increase the content of the *u* isomers by fractional distillation from the thermodynamic equilibrium, which is adjusted by heating **8** with bases such as sodium carbonate. Cepionate with around 30% of (*u*)-**8** was the first quality methyl dihydrojasmonate enriched in the *u* isomers.[62] Kharismal, Super Cepionate, and Hedione HC with up to 75% of (*u*)-**8** (Table 3) followed.[63] These new higher quality methyl dihydrojasmonates (**8**) avoid a dilution effect by the weak *l* isomers; however, (*u*)-**8** isomerizes back into the thermodynamic equilibrium outside the narrow range of pH 5–7. Hedione HC was used for instance in the floral, green, musky bestseller "Pleasures" (E. Lauder, 1995).

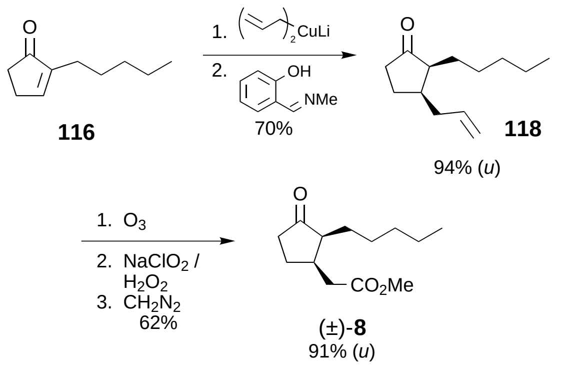


Scheme 20. Industrial Synthesis of Hedione (**8**).

Table 3. Qualities of methyl dihydrojasmonate (**8**).

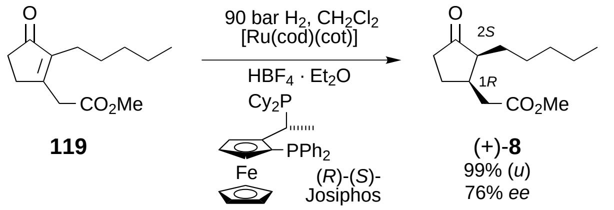
Product	*l*:*u*	Odor threshold [ng L^{-1}]
Hedione	ca. 90:10	0.3
Cepionate	ca. 70:30	0.1
Kharismal	ca. 40:60	0.05
Super Cepionate	ca. 30:70	0.04
Hedione HC	ca. 25:75	0.03

An interesting approach to the synthesis of (*u*)-**8** was developed by S. Ebert and N. Krause.[64, 65] As outlined in Scheme 21, 2-pentylcyclopent-2-en-1-one (**116**) was alkylated by lithium diallylcuprate. The protonation of the chiral enolate intermediate with *N*-methylsalicylaldimine proceeded with high diastereoselectivity, and **118** was isolated in 70% yield with a *u*:*l* ratio of 94:6. Ozonolysis, oxidation, and diazomethane esterification led to a methyl dihydrojasmonate (**8**) containing 91% of the *u* isomers.



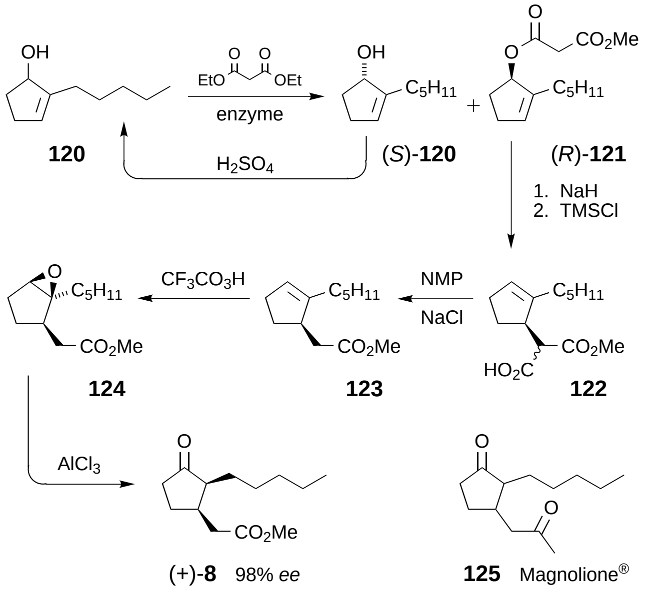
Scheme 21. Synthesis of (*u*)-methyl dihydrojasmonate ((±)-**8**) by diastereoselective protonation.

The next step in improving the odor intensity of methyl dihydrojasmonate (**8**) was the catalytic asymmetric hydrogenation of the cyclopentenone **119** with chiral ruthenium catalysts.[66, 67] Scheme 22 details the application of a recently claimed catalyst system comprising a Ru(II)-Josiphos complex in the presence of tetrafluoroborate to this reaction. (+)-(1*R*,2*S*)-Methyl dihydrojasmonate ((1*R*,2*S*)-**8**) was obtained in a *u*:*l* ratio of 99:1 with 76% *ee*.[67]



Scheme 22. (1*R*,2*S*)-(+)-Methyl dihydrojasmonate ((+)-**8**) by enantioselective hydrogenation. cod = 1,5-cyclooctadiene; cot = cyclooctatetraene; Cy = cyclohexyl.

An alternative industrially feasible route to (1*R*,2*S*)-**8** was elaborated by Fehr.[68, 69] As outlined in Scheme 23 the key step of this approach is the *syn*-selective epoxidation of the methyl cyclopent-2-enyl acetate **123** by highly electrophilic peracids, such as trifluoroperacetic acid.[70] The chiral starting material (*R*)-**121** was prepared either by kinetic enzymatic resolution of 2-pentylcyclopent-2-en-1-ol (**120**) or by asymmetric hydrogenation of the corresponding ketone. Chirality transfer by Claisen rearrangement of the malonate-derived allylic silyl ketene acetal led, after decarboxylation, to the central intermediate **123**. The already mentioned diastereoselective epoxidation, and a subsequent aluminum trichloride mediated rearrangement complete this synthesis of (1*R*,2*S*)-**8**.



Scheme 23. An alternative route to (+)-**8**. NMP = *N*-methylpyrrolidone.

Its advantages are the easy availability of **120** and the high enantiomeric purity of the final product.

Related to methyl dihydrojasmonate (**8**) both in structure and in odor is Magnolione (**125**, Scheme 23), which bears an acetyl group instead of the methyloxycarbonyl moiety. This substitution results in an increased odor strength, a better stability, and a more floral, intense jasminic note. In analogy to the synthesis of methyl dihydrojasmonate (**8**) in Scheme 20, it is accessible by reaction of 2-pentylcyclopent-2-en-1-one (**116**) with ethyl acetoacetate and decarbethoxylation of the resulting adduct.[71] Magnolione (**125**) was used in 13% in the chypre "Coriandre" (Couturier, 1973), but even the use of 0.7% of it in "Eden" (Cacharel, 1994) emphasizes the floral note of that fragrance.

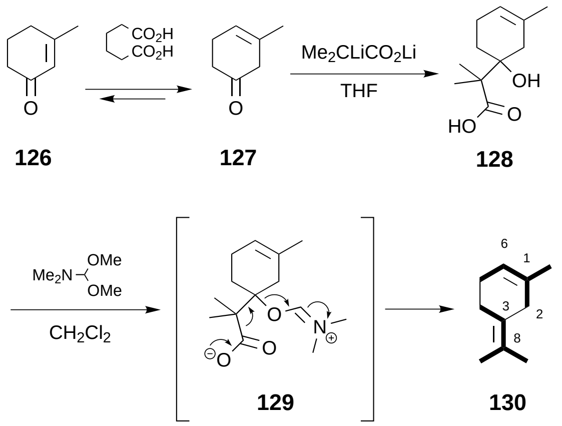
6. Spicy Tonalities

6.1. Pepper

Spices have always been associated with warmth and sensuality, and thus, just as in the kitchen, diverse spices are also used in perfumery. One prominent example is "Parfum Sacré" (Caron, 1990) with a combination of coriander (6%), nutmeg (2%), cardamom (0.5%), clove (0.7%), cinnamon bark (0.5%), and black pepper oil (1%). Recently, in "Les Belles: Délices d'Epices" (N. Ricci, 1999), cardamom, cinnamon, clove, and pepper were also combined.

Pepper is not only the most important spice of international trade, its essential oil has also become increasingly fashionable in perfumery. In the spicy-aromatic-musky male fragrance "Extreme Polo Sport" (R. Lauren, 1998), we even find an overdose of around 6% that determines the overall pepper note of that fragrance. The use of black pepper oil in "Contradiction" (C. Klein, 1997) is much more subtle; 0.2% of it provides more of a sparkling and piquant effect than confering a peppery note.

Black pepper oil has an intense, spicy, and peppery odor, reminiscent of cubebs (the dried unripe berry of an Indonesian pepper shrub) but with a milder taste that lacks the pungency of the spice. Around 90% of the oil is made up of hydrocarbons, and about 77% of this hydrocarbon fraction consists of monoterpenes,[72] of which α- and β-pinene (ca. 10% and 16%, respectively), 3-carene (ca. 36%), and limonene (ca. 24%) are the main constituents.[73] It is assumed that trace constituents of polar sesquiterpenoids of yet unknown structure play a decisive role in the characteristic pepper note of this essential oil;[74] however, as we just saw, the sparkling and piquant effects of black pepper oil, which are mainly due to the monoterpene fraction, are also very important in perfumery. In 1992, Kollmannsberger et al.[74] reported on two unidentified menthadienes in the monoterpene fraction that could contribute to this interesting effect. The mass spectrum of one of these unknown trace constituents of black pepper oil was rather similar to that of terpinolene, and by a short synthesis it was shown to be the corresponding *meta*-monoterpene *meta*-mentha-3(8),6-diene (isosylveterpinolene, **130**), the first established example of a naturally occurring *meta*-menthadiene.[75] The synthetic reference was prepared as outlined in Scheme 24 by deconjugation of 3-methylcyclohex-2-en-1-one (**126**), subsequent alkylation with lithium 2-lithio-2-methylpropanoate, and decarboxylative dehydration[76] of the resulting hydroxycarboxylic acid **128** by employing dimethylformamide dimethyl acetal. *meta*-Mentha-3(8),6-diene (**130**) possesses a pleasant green-herbal, terpenic odor reminiscent of parsley and carrot leaves, and a slightly metallic nuance; it is however, much weaker than limonene, and thus does not contribute considerably to the odor of black pepper oil.[75]

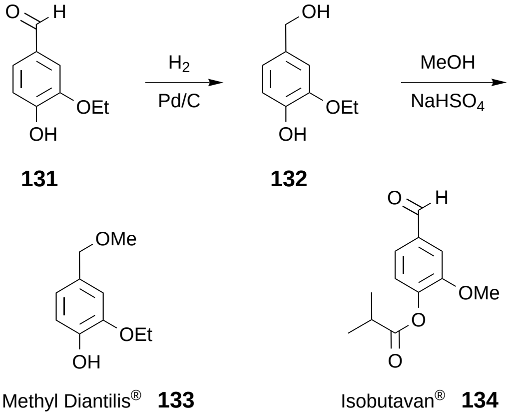


Scheme 24. Synthesis of isosylveterpinolene (**130**).

A different quality of pepper oil, that of pink pepper berries (*Shinus molle*), has been used in "Pleasures" (E. Lauder, 1995). It brings diffusivity, adds a creamy aspect, and blends well with musks.

6.2. Sweet Spice

Some spices and some spicy odorants also possess sweet aspects, close to vanilla. Methyl Diantilis (**133**) with its clove-carnation-powdery note is one example. It is synthesized as presented in Scheme 25 by hydrogenation of ethyl vanillin (**131**), and methylation of the benzylic hydroxy function formed in intermediate **132**.[77]



Scheme 25. Two derivatives of vanillin (**2**).

Methyl Diantilis (**133**) resulted from the search for derivatives of vanillin (**2**) that possess the sweet odor characteristics of **2** but do not lead to discoloration problems. Isobutavan (**134**), the isobutyrate of vanillin (**2**), is another product of this research, and is indeed less discoloring than vanillin (**2**). It has a sweet and creamy vanilla odor reminiscent of white chocolate, and at around 2% plays an important part in the base note of the oriental-ambery-gourmand fragrance "A*Men" (T. Mugler, 1996).

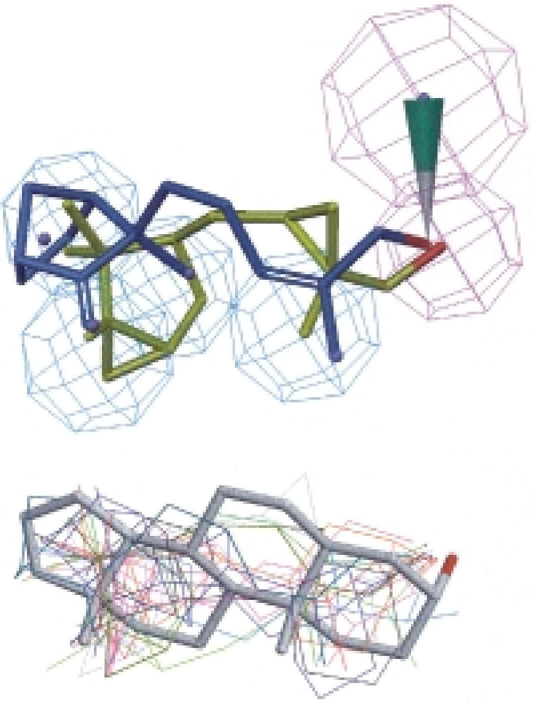
The interplay of spicy and sweet perfumery materials is very important in the oriental-spicy-gourmand perfume "Angel" (T. Mugler, 1992), where nutmeg, cardamom, and pepper oil were blended with a candy accord made mainly of ethyl maltol (**12**), vanillin (**2**), and coumarin (**1**). Many other feminine fragrances followed this gourmand trendsetter, for example "Sonia Rykiel" (S. Rykiel, 1997) and "Just me" (Montana, 1997).

The microencapsulated perfume base "ChocoMinty" in Figure 3 (see p. 2987) is a gustative note, in which a fresh minty accord is married with a sweet chocolate accord, formulated with 4% of Isobutavan (**134**). You can easily recognize the odor of a delicious candy!

7. Woody Odorants

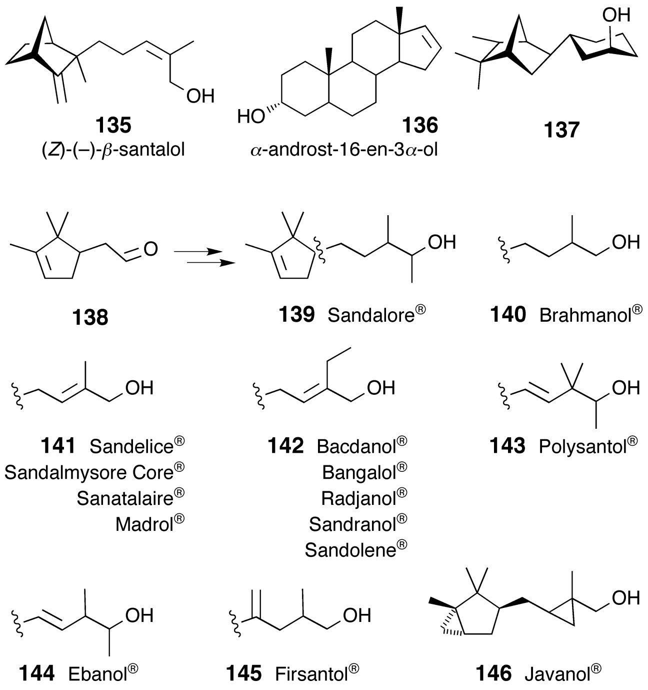
7.1. Sandalwood Olfactophores

The East Indian sandalwood oil (*Santalum album L.*) represents one of the most precious perfumery raw materials. It plays an important religious and cultural role in India, and has always been an indispensable constituent of fine fragrances worldwide. The rarity, and therefore high price of sandalwood oils made the search for synthetic substitutes inevitable, which has provided numerous structure–odor relationship data. Unfortunately, because of the complex stereoisomeric composition of sandalwood-smelling products—almost always of terpenic origin—most of these data were only of limited use for the generation of precise olfactophore models. Nevertheless, several such models have been proposed and reviewed.[4, 10] They all include a distance constraint between the osmophoric hydroxyl group (which orients the molecule on the receptor) and a bulky, lipophilic moiety. These models are, however, a source of some controversy. The situation improved during the last decade when more information on optically pure sandalwood odorants and their structurally related inactive counterparts became available. Recent models, based on this new data, and generated with the help of advanced molecular modeling tools, take into consideration the flexibility of structures within defined strain energy limits: 10 and 15 kcal mol^{-1} in the studies of Buchbauer et al.[78] and Bajgrowicz et al.,[35] respectively. The latter proposed the concept of a combinatorial olfactophore model based on the recent discovery of combinatorial receptor coding schemes that the mammalian olfactory system uses to encode odor entities.[79] The best hypothesis of this model is depicted in Scheme 26 together with the alignement of all the active stereoisomers used in the generation of the model.[11]



Scheme 26. Sandalwood olfactophore model. Top: Best hypothesis mapped by (*Z*)-(−)-*β*-santalol (**135**, cyan) and by Javanol (**146**, yellow). Bottom: Alignement of all the active structures used in the generation of the model on the best hypothesis; *α*-androst-16-en-3*alpha*-ol (**136**) is highlighted. Hydrogen atoms are omitted for clarity.

The lipophilic, bulky moiety is decomposed into three hydrophobic regions in this olfactophore model. The fourth one, which usually belongs to the flexible spacer, is placed in the vicinity of the osmophoric hydrogen-bond donor. It corresponds to the 18-Me group of *α*-androst-16-en-3*α*-ol (**136**, Scheme 27), which astonishingly also possesses a fine sandalwood scent, in contrast to the unpleasant, steroidal, animalic, and urinous odor of the ketone derivative, which is the sex pheromone of pigs.



Scheme 27. Strong sandalwood-smelling compounds.

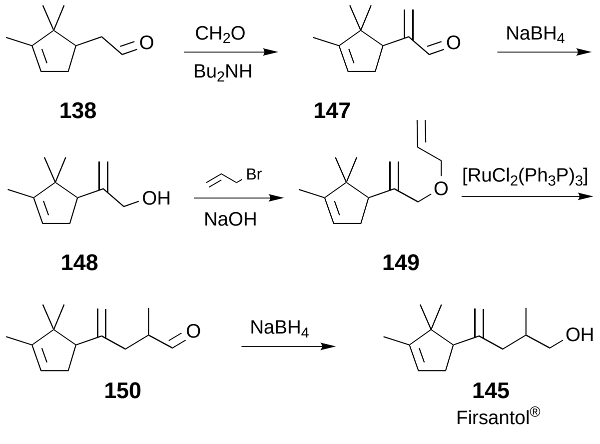
7.2. Derivatives of *α*-campholenic aldehyde

Despite many attempts no industrially viable process leading to *β*-santalol, the main olfactory constituent of sandalwood oils (ca. 25% of the weight of the oil), has yet been elaborated. The synthetic difficulties can be illustrated by the fact that the natural (*Z*)-(−)-*β*-santalol (**135**, Scheme 27) was first prepared only in 1990 in an 11-step synthesis starting with the Diels–Alder addition of cyclopentadiene to the *trans*-crotonate of (*R*)-pantolactone.[80] In relation to the price of natural sandalwood oils, which, however impressive for the fragrance market, does not allow a total synthesis of **135** to be competitive.

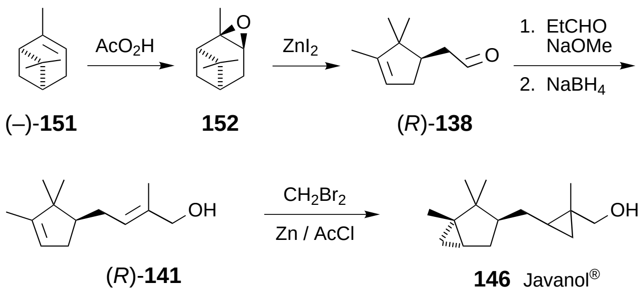
The recourse to synthetic analogues was a natural step. Complex mixtures of terpenylcyclohexanols, prepared by hydrogenation of acid-catalyzed condensation products of phenols (for example, guaiacol) with inexpensive terpenes (the most used was camphene) constituted the first generation of such products (for example, Sandela). Their main odor vectors of defined absolute configuration were claimed only recently. Compound **137** possesses the lowest odor threshold.[81] Today, the best and most used sandalwood oil substitutes (**139**–**146**, Scheme 27) are derivatives of *α*-campholenic aldehyde (**138**), which is prepared from inexpensive *α*-pinene (**151**), most of which comes as a by-product from the paper industry.

Initially, the products were prepared from mixtures of enantiomers of **138**, often of variable ratio. More recent studies pointed at dramatic odor differences of the diastereoisomers and enantiomers in this series, with the derivatives of (*R*)-(+)-*α*-campholenal ((*R*)-**138**) being most often, but not always, the better sandalwood odorants.[35, 82, 83] These studies gave rise to a series of "chiral switch" patents, an already well-established procedure in the pharmaceutical domain.

Among the usually simple and straightforward syntheses of campholenic aldehyde derivatives those of Firsantol (**145**, Scheme 28) and Javanol (**146**, Scheme 29) merit citation. The first one resulted from an elegant and cost-effective sequence consisting of an α-methylenation, reduction, etherification, and isomerization/Claisen rearrangement;[84] the latter from the first example of a successful industrial application of a double Simmons–Smith cyclopropanation process.[83]



Scheme 28. Synthesis of Firsantol (**145**).

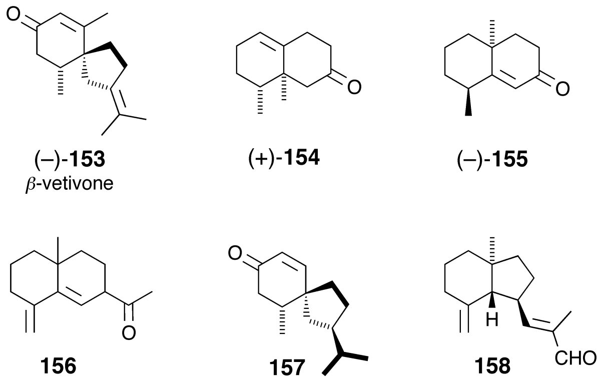


Scheme 29. Preparation of Javanol (**146**).

Sandalwood notes are often used in mixtures, together with sandalwood oil or without it. In the floral-oriental-woody "Samsara" (Guerlain, 1989) sandalwood oil was blended with Polysantol (**143**), while the sandalwood note of the oriental-spicy "Jako" (K. Lagerfeld, 1997) was created with Sandalore (**139**), Radjanol (**142**), and Ebanol (**144**). The method of using sandalwood odorants as well as the dosage varies a lot. As an example, two extremes for the use of Sandalore (**139**) illustrate this: "Boudoir" (V. Westwood, 1998) with 0.7% and "Chaos" (D. Karan, 1996) with 5% of Sandalore (**139**). Curiously, around 1% of the intermediate Firsantal (**150**) gives a woody-sandal-floral touch to the middle note of the recently launched "Ultra Violet" (P. Rabanne, 1999), while around 3% of the end product Firsantol (**145**) was employed in the woody-aromatic-musky fragrance "212 for men" (C. Herrera, 1999).

7.3. Vetiver Oil

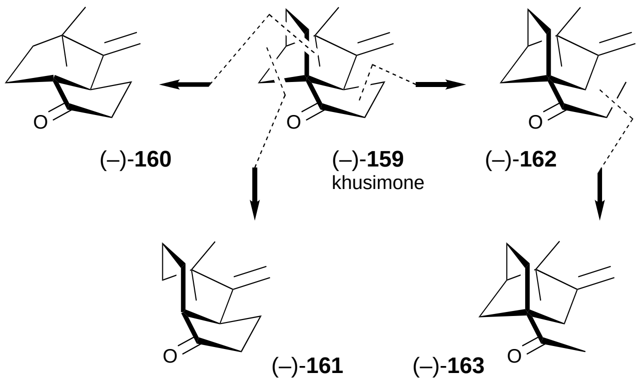
The odor of vetiver oil (*Vetiveria zizanoides* Stapf) still remains one of the unrevealed secrets of nature. This oil is available on the market in a lot of different qualities, and consequently a lot of different odor tonalities, but they all share a suave and sweet woody odor with earthy, green, fungi-type aspects and grapefruit, rhubarb undertones. However, there is a big controversy about which compounds contribute to this highly appreciated scent, which arises mainly from the carbonyl fraction that makes up some 12% of the vetiver oils.[85] Around 60% of this fraction consists of α- (**19**) and β-vetivone (**153**; Scheme 30), but their odor was said to be weak and uninteresting for perfumery.[85] According to Maurer[85] khusimone (**159**) and the two dimethyloctalones **154** and **155**,[86] which are present in the essential oil to about 0.15%, are responsible for the characteristic odor of vetiver oil. A technically feasible partial synthesis of khusimone (**159**) starting from vetivenic acid was worked out,[85] but **159** has not (yet) been introduced into perfumery.



Scheme 30. Compounds supposed to contribute to the typical odor of vetiver oil.

In contrast to this work at Firmenich, Mookherjee et al. of International Flavours & Fragrances (IFF) considered β-vetivone (**153**) the key odorant of vetiver oil,[87] together with the 2-acetyl-4a-methyl-8-methyleneoctaline **156**, which has a powerful woody-amber odor, and nordihydro-β-vetivone **157**, which has a strong rich, woody-peppery odor.[87] Mookherjee et al. described compounds **154** and **155** of Maurer as weak, green, rooty, and woody. Recent work by Spreitzer et al. on (−)- and (+)-β-vetivone (**153**)[88] as well as on their chiral partial structures[89, 90] showed, however, that neither β-vetivone (**153**) nor the partial structures possess the pleasant vetiver scent. The odor of the naturally occurring (−)-**153** was evaluated by Dragoco perfumers and found to be quinoline-like, reminiscent of cassis and grapefruit, while (+)-**153** exhibited an unpleasant cresolic, medicinal note.[88]

Therefore, khusimone (−)-**159** seems to be the only compound of vetiver oil which perfumers agree possesses a typical vetiver odor. This was the reason why Spreitzer et al.[91–93] synthesized *seco* structures of (−)-**159** to study the structure–odor relationship of the vetiver odor. Scheme 31 details three different *seco*-khusimones. (−)-**160** smelled weakly camphoraceous with a woody by-note,[91] while (−)-**162** was camphoraceous with a sweet-herbal by-note, and (−)-**163** cedarwoodlike.[92] *seco*-Khusimone (−)-**161** could not be evaluated since epimerization favored the corresponding *trans*-fused 3a*S*,8a*R* isomer. The odor of this isomer was



Scheme 31. *seco*-Khusimones (**160**–**163**) used to study the structure–odor relationship of the vetiver scent.

intense woody-camphoraceous, but lacked the typical vetiver odor descriptors.[93] Consequently, the typical odor descriptors of vetiver seem not to stem from these partial structures, and we are still far away from a synthetic vetiver odorant.

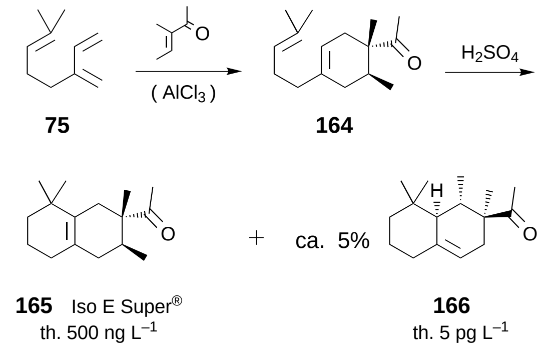
Only very recently, Weyerstahl et al.[94] discovered a new olfactorily important constituent of Haïtian vetiver oil, (*E*)-opposita-4(15),7(11)-dien-12-al (**158**; Scheme 30), which possesses a strong, green odor with undertones of mimosa and orris, and a woody tonality. The secrets of the vetiver odor remain, however, far from being unveiled, and much more work will be necessary to find synthetic substitutes.

Vetiver oil was used a great amount in the past, with "Vetiver" (Carven, 1957) and "Vetiver" (J. P Guerlain, 1959) being the best examples. But vetiver oil was also indispensable in the chypre family, for example, in "Mitsouko" (J. P Guerlain, 1919). Nowadays, vetiver oil is still used, but in much lower dosage. "Hugo Dark Blue" (H. Boss, 1999), "Christian Lacroix" (C. Lacroix, 1999), and "Azzura" (Azzaro, 1999) are some recent examples.

7.4. Woody!

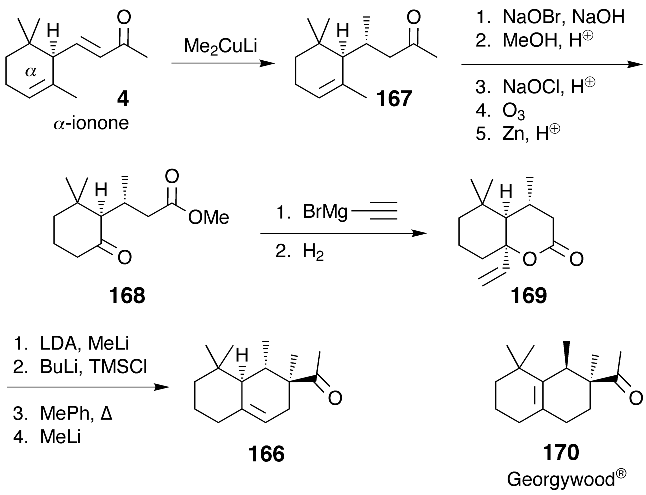
What Hedione (**8**) is to florals, Iso E Super is to woody notes. Iso E Super (**165**; see Scheme 32) is a very rich product with many facets, and some people smell a cedarwood note while others perceive it as transparent or musky, ionone-like. The musky-violet facets were exploited in "Fahrenheit" (C. Dior, 1988) with 25 % of Iso E Super (**165**) and in "Trésor" (Lancôme, 1991) with 18 % of it. The cedarwood side was important for "Féminité du Bois" (Shiseido, 1992) with 43 %, and for "Déclaration" (Cartier, 1998) with 35 % of it.

The industrial synthesis of Iso E Super (**165**) is shown in Scheme 32. The aluminum trichloride catalyzed Diels–Alder reaction of myrcene (**75**) with (3*E*)-3-methylpent-3-en-2-one gives predominantly regioisomer **164**, which is cyclized in the presence of sulphuric acid to provide **165** as the major product. However, it is not this compound that causes the woody odor of the commercial product, but a 5 % impurity that is formed during the cyclization step.[95] The odor threshold of this very powerful impurity **166** is about 100 000 times lower than that of the main product **165**.



Scheme 32. Industrial synthesis of Iso E Super (**165**). th. = threshold value.

The powerful impurity **166** was isolated by epoxidation of a commercial Iso E Super mixture, and a structure was proposed by 2D NMR experiments;[95] however, this required conformation by a directed synthesis. The stereoselective synthesis of **166** is summarized in Scheme 33.[95] Diastereoselective conjugate addition of lithium dimethylcuprate to α-ionone (**4**) gave **167**, which was further transformed by a haloform reaction, esterification, and ozonolysis of the double bond after isomerization with sodium hypochlorite. The resulting oxo methyl ester **168** reacted diastereoselectively with ethynylmagnesium bromide, and the Grignard intermediate was hydrogenated in the presence of Lindlar's catalyst to furnish vinyl lactone **169**. Ireland–Claisen rearrangement of **169** followed by methylation with methyllithium afforded the target molecule **166**, which was identical by all analytical methods to the material isolated from commercial Iso E Super.[95]

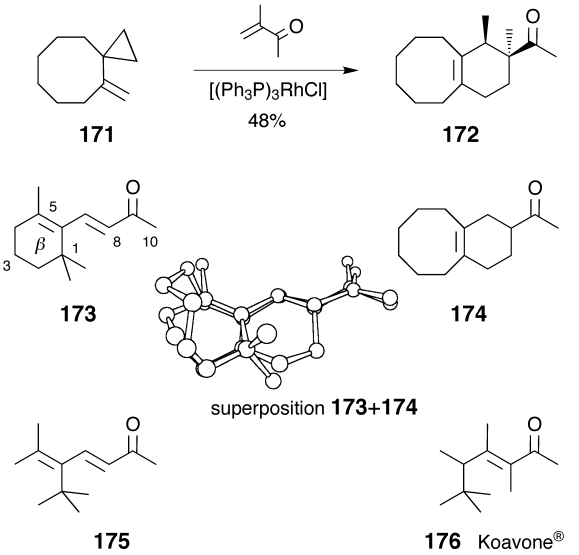


Scheme 33. Synthesis of the powerful impurity (**166**) of Iso E Super and the structure of a related woody odorant **170**. LDA = lithium diisopropylamide.

Clearly, this synthesis of **166** is not suited for an industrial scale, and the structure turned out to be too complex for an alternative synthetic procedure. However, out of several synthesized analogues, **170** was found to have an almost equal odor threshold, and it was even preferred in terms of its odor characteristics. Its industrial synthesis by a Diels–Alder reaction of homomyrcene with methyl isopropenyl ketone is straightforward,[4] and **170** has been introduced into perfumery by Givaudan as Georgywood. Among many examples, "Golden Moments" (P. Presley, 1999) with 5% of Georgywood (**170**) is the most prominent one.

What is "W-A-S"? Smell the microencapsulated fragrance in Figure 4 (see p. 2989): An original woody-ambery-spicy masculine fragrance with anisic and floral facets. The woody part is mainly composed of Georgywood (**170**), combined with musky notes. The ambery part consists of Okoumal (**196**) and Spirambrene (**200**, see Scheme 37), which bring warmth and sensuality to the fragrance and harmonize with the spicy accord mainly based on black and pink pepper oil.

Similar to Georgywood (**170**) in odor, structure, and excellent threshold value is **172**, which is accessible by an uncommon Diels–Alder-type reaction of 4-methylenespiro[2.7]decane (**171**) with methyl isopropyl ketone using Williamson's catalyst (Scheme 34).[96] A dimethylcyclohexene ring is almost equivalent in terms of shape to a cyclooctene moiety, and this is also reflected in the remarkable olfactory resemblance of 1-bicyclo[6.4.0]dodec-1(8)-en-10-ylethan-1-one (**174**) to β-ionone (**173**). The superposition in Scheme 34 shows the excellent overlap of both molecules.



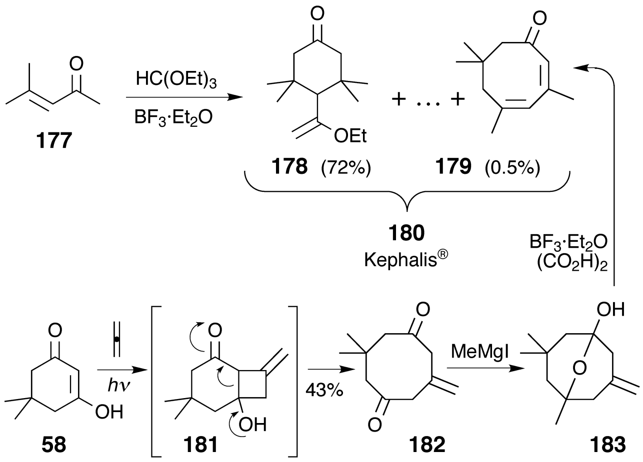
Scheme 34. Odorants **172** and **174** with the bicyclo[6.4.0]dodecene

In 1962, Sestanj[97] had already found that cutting out carbon atom C-3 does not alter the odor characteristics of β-ionone (**173**), and 5-*tert*-butyl-6-methylhepta-3,5-dien-2-one (**175**) indeed possesses a woody, floral odor close to that of **173**. This result incited researchers at IFF to synthesize related *seco*-ionones, and one of these compounds, Koavone (**176**), indeed became a commercial product. An analysis of the superposition of **176** and 10-methylionone,[98] one of the first applications of molecular modeling in fragrance chemistry, rationalized the similar odor profiles. Koavone (**176**) smells woody, floral, and ambery, and has mainly been used in consumer goods, in many different medias: In shampoos such as "Elsève multivitaminé 2 in 1" (L'Oréal, 1995), fabric softeners such as "Vernel cool fresh" (Henkel, 1996), soaps such as "Fa aqua" (Henkel, 1997), as well as deodorants such as "Dove sans alcool" (Lever, 1998). Nevertheless, the interest of Koavone (**176**) for fine fragrance perfumery was demonstrated by "Jazz" (Yves Saint Laurent, 1988) with a dosage of around 2%.

8. Ambery Notes

8.1. Ambery Ketones and Ketals

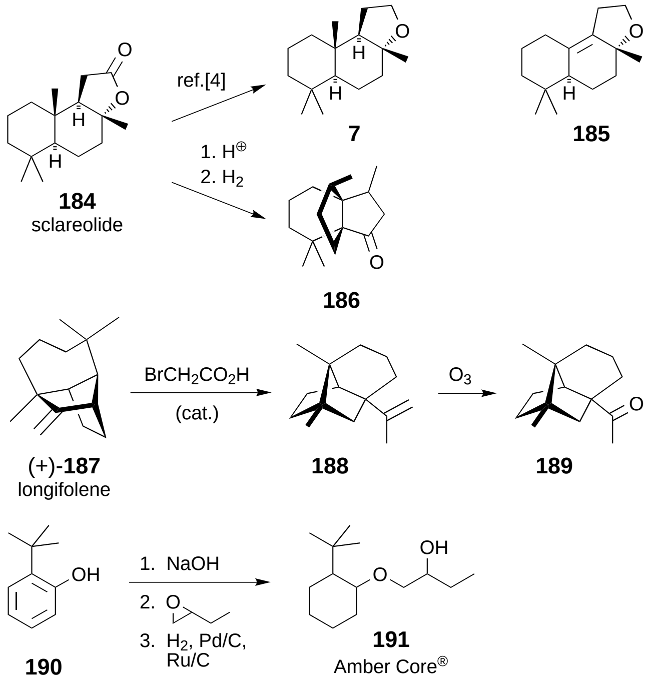
Many odorants share woody and ambery odor characteristics. Kephalis (**180**) is a typical example, since it possesses woody-piney as well as ambery-tobacco facets. These various facets have been exploited in "Yohji Homme" (Y. Yamamoto, 1999) with around 4% of Kephalis (**180**). This valuable perfumery raw material **180**[99] consists of a complex mixture of ketones, alcohols, and ethers obtained in an acid-catalyzed reaction of mesityl oxide with ethyl orthoformate.[100] In an attempt to improve the efficiency of the manufacturing process, a detailed analytical and synthetic study was undertaken and the synthesis of one of the trace constituents (**179**) contributing to the overall rich ambery scent was published (Scheme 35).[101]



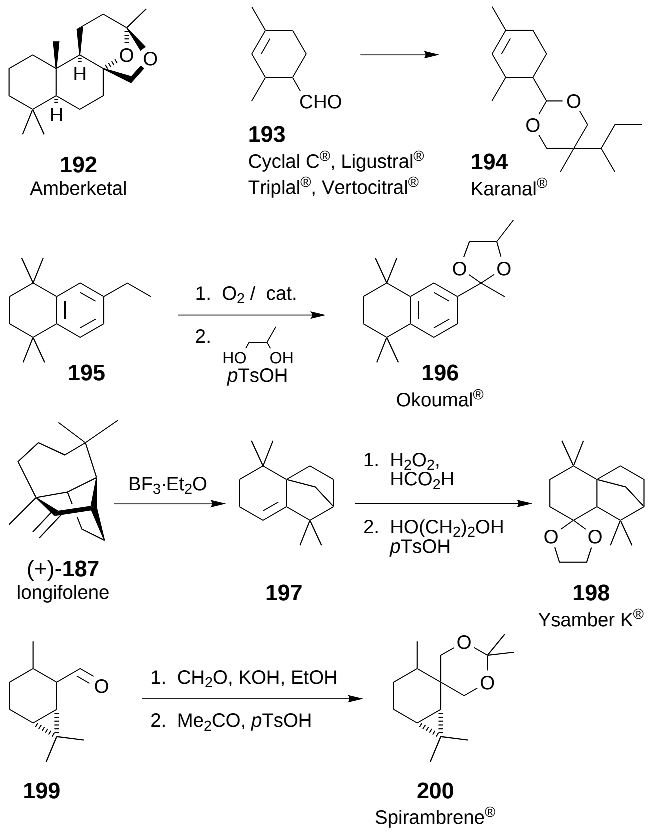
Scheme 35. The perfumery raw material Kephalis (**180**).

All three steps in the preparation of **179** were tandem transformations: de Mayo photocycloaddition/retroaldol ring enlargement, followed by Grignard addition/transannular acetalization, and ketal ring opening/dehydration/double-bond migration, which led to the conjugated system of **179**. Ambery and tobacco facets are indeed present in the odor profile of **179**, but these are astonishingly accompanied by a fruity, α-damascone note.[100]

Chemicals that smell like amber are mainly ethers, ketones (Scheme 36), and cyclic ketals (Scheme 37, Scheme 38) that are almost always derived from commonly occuring natural terpenes. The cyclic ether Ambrox (**7**) remains the prototype of what perfumers understand as ambery, which is actually a very unclear term derived from the multifacet odor of natural ambergris.[102] Interestingly, its nordidehydro analogue **185**[103] still exibits an intense amberlike odor, which corroborates the amber olfactophore model discussed below. From a molecular

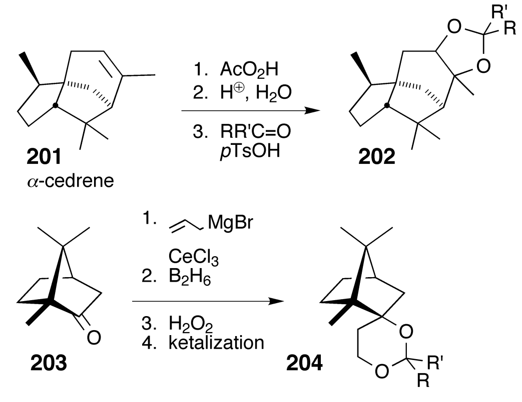


Scheme 36. Some of the best ambery odorants; cyclic ketals are excluded.



Scheme 37. Cyclic ambery ketals already introduced into perfumery. pTsOH = p-$H_3CC_6H_4SO_3H$.

modeling point of view, it is also interesting to compare the shapes of propellane **186**, obtained by an interesting acid-catalyzed transposition of sclareolide (**184**),[104, 105] and the recently published[106] 12-noralloisolongifolan-11-one (**189**, obtained from naturally abundant longifolene (**187**)) with those of the woody odorants Iso E Super (**166**), Georgywood (**170**), and their analogues (see Section 7.4). An ambery-woody borderline case is Amber Core (**191**),[107, 108] which should be envisaged as a noroxa analogue of the active stereoisomers of Timberol and Norlimbanol,[4] which are usually classified as woody.



Scheme 38. New cyclic ambery ketals. R, R′ = H, C1 – C6 alkyl.

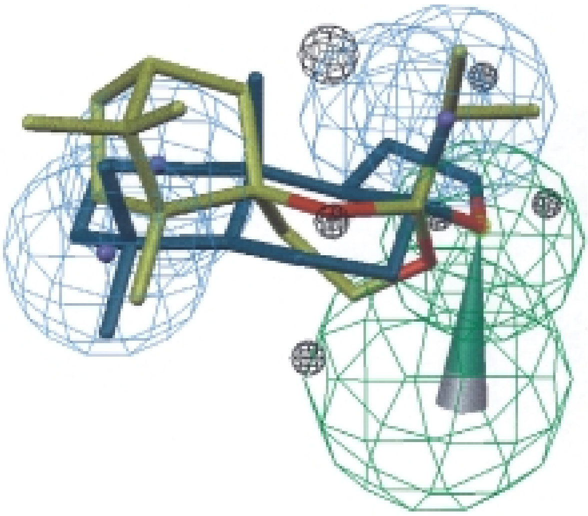
Cyclic ketals are steadily gaining ground among ambery odorants (Scheme 37 and 38). Amberketal (**192**)[109], Karanal (**194**),[110, 111] derived from the well-known green-smelling Ligustral (**193**), Okoumal (**196**)[112], Ysamber K (**198**),[113] and Spirambrene (**200**),[114] produced in two steps from 2-formylcarane (**199**), are the most prominent amongst the already commercialized perfumery products. Potential future introductions include the dioxolanes **202**[115] and the 1,3-dioxanes **204**,[116] obtained in straightforward transformations from α-cedrene (**201**) and camphor (**203**), respectively.

The use of Spirambrene (**200**) is very diverse and versatile. It is found in the floral-oriental feminine fragrance "Eden" (Cacharel, 1994) as well as in the marine masculine perfume "Kenzo pour Homme" (Kenzo, 1991). Okoumal (**196**) is a very powerful ambery odorant, which blends well with woody, especially sandalwood notes. The combination Okoumal/Ebanol (**196**/**144**) was found in "Escape for men" (C. Klein, 1993) and in "Hugo" (H. Boss, 1995). Karanal (**194**) and Amberketal (**192**) are also very powerful and long-lasting odorants. They have been used in "Diesel++masc" (Diesel, 1997) and in "Boss" (H. Boss, 1998), respectively.

8.2. Amber Olfactophore

Attempts to rationalize the structure – odor relationship of amber odorants have a long history.[4] From Ohloff's "triaxial rule", through Vlad's "ambergris triangle",[119] and oxygen accessibility criteria to the more recent CATALYST study[11, 117] based on the alignment of "chemical functions" in flexible structures, and repeated electron-topological investigations,[118] different concepts have been investigated to explain the presence or the absence of this noble scent, which depends on very slight structural modifications. An important argument for carrying out structure – odor correlations in this odor note is the relative rigidity of most of the compounds that smell like amber. In the most recent study in this domain, which uses the electronic-topological matrices of contiguity, Gorbachov and Rossiter[118] propose a new "active ambergris fragment" consisting of one oxygen atom and three carbon atoms, possessing certain atomic charges, and being separated by certain key distances.

Our 3D model of the amber olfactophore[117] (Scheme 39) contains four hydrophobic functions (blue spheres), and one oriented hydrogen-bond acceptor (green). The six excluded volumes (black), which tentatively correspond to the geometrical limits of the binding pocket of the putative amber olfactory receptor and significantly improve the predictability of the presence or absence of the ambery odor in examined structures, were added by a trial and error process. However imperfect, this model has been successfully applied to the design and lead development of the camphor derivatives **204** (Scheme 39). The best of these compounds **204** (R, R′ = H, *i*Pr) is depicted.



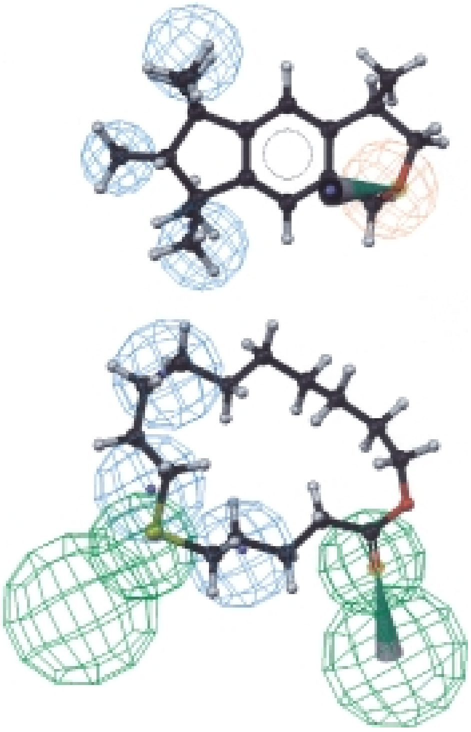
Scheme 39. Ambery olfactophore model mapped by Ambrox (**7**, blue) and one of the epimers of the best derivative **204** (R, R′ = H, *i*Pr, yellow). Hydrogen atoms are omitted for clarity.

9. Musk Odorants

9.1. Musk Olfactophore Models

Although quite a lot of data on substances with musk odor are accessible in the open literature,[119] our insight into the molecular parameters of musk odorants remains rather limited. This is because musk odorants belong to structurally very different chemical classes (for example, macrocyclic aliphatic compounds, polycyclic benzene derivatives, and nitro arenes) with different possible binding features.

Bersuker et al.[119] stated two independent features to be responsible for a musk odor. The first is a hydrogen-bond acceptor symmetrically flanked at a distance of 6.7 ± 0.5 Å by two hydrophobic binding pockets that are 2.5 ± 0.5 Å apart from each other. The second feature consists of two hydrophobic groups within a distance of 5.5 ± 0.5 Å to each other. However, Kansy et al.[120] could not confirm the prediction rate of Bersuker's hypothesis. Using the same data set[119] they proposed an olfactophore model consisting of three hydrophobic features 6.7, 8.0, and 5.6 Å away from the hydrogen-bond acceptor.[120] As is shown in the upper part of Scheme 40, the methyl groups of the pentamethylindane moiety of (4*S*,7*R*)-Galaxolide ((4*S*,7*R*)-**10**) fit well to these hydrophobic functions; however, this olfactophore model could not explain the importance of the *S* configuration of the 4-methyl group, which is crucial for the musk odor of **10**.[121] Thus, the conformationally constrained (4*S*,7*R*)-**10** seems to be better suited as a template for the design of musk odorants than this olfactophore model.



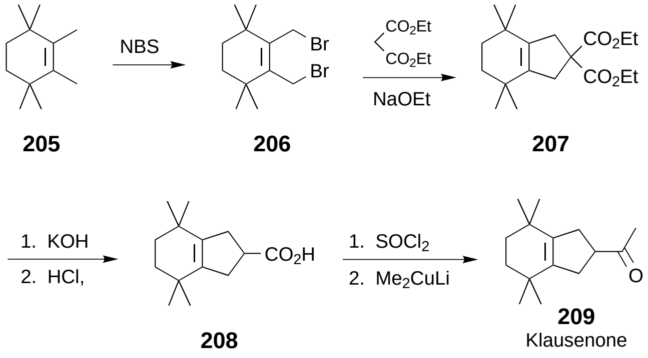
Scheme 40. Olfactophore models for musk odorants. Top: with **10**; bottom: with 6-thiahexadecanolide.

Other questions also remain open: Why is the threshold of the nitro musks about 20–30 times lower than that of the natural alicyclic lead substance (*R*)-(−)-muscone (**223**; see Scheme 44)?[122] Does the musk receptor possess more than one binding site for polar groups? Can more powerful macrocyles be designed by introducing additional polar groups? Is the function of double bonds restricted to conformational effects, or is it also of electronic importance?

To find some answers to these questions a series of thiamacrolides was synthesized.[123] A sulfur atom can mimic a double bond without restricting the conformational freedom of the macrocycle. A 1,7-distance of the sulfur atom and the carbonyl group in even-membered rings, and a 1,6-position of the sulfur atom and carbonyl group in odd-membered rings significantly lowered the thresholds of the compounds. A CATALYST[11] hypothesis was generated using the threshold data of 13 thiamacrolides smelling of musk, which allowed threshold values to be calculated with good accuracy. In the lower part of Scheme 40 the fit of 6-thiahexadecan-16-olide to this olfactophore hypothesis is shown. The model consists of two hydrogen-bond acceptors 6.9 Å away from each other, and three hydrophobic functions 4.1/2.8, 7.1/1.7, and 8.3/5.0 Å, respectively, away from the hydrogen-bond acceptors. The second hydrogen-bond acceptor could explain why some dicarbonyl compounds, such as for example 5-oxomuscone,[124] possess intense musk notes, while others are practically odorless.

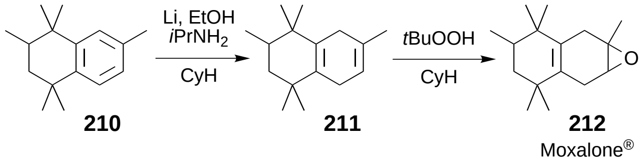
9.2. The Klausenone Story

In 1979, while working on the synthesis of aromatic retinoids, M. Klaus of F. Hoffmann-La Roche discovered by serendipity a compound with an intense musky odor and interesting damascone-like, woody nuances. Allylic bromination of 1,2,3,3,6,6-hexamethylcyclohex-1-ene (**205**) with NBS, followed by a malonic ester synthesis led to the diethyl ester **207**, which was hydrolyzed and decarboxylated to **208**, and finally transformed into the unexpected musk odorant **209** (Scheme 41). In comparison with other polycyclic musk odorants such as Galaxolide (**10**), the intense musk odor of the non-benzenoid 2-acetyl-2,3,4,5,6,7-hexahydro-1*H*-indene **209** was also truly amazing from a structural point of view, and the substance therefore soon became known as Klausenone—also at Givaudan Roure, at that time the flavor and fragrance division of Roche.



Scheme 41. The original synthesis of Klausenone (**209**). NBS = *N*-bromosuccinamide.

Efforts were first directed towards an industrially feasible synthetic route to Klausenone (**209**).[125] However, this turned out to be rather difficult, and the synthesis of derivatives was soon also investigated. Surprisingly, it turned out that the corresponding alcohol of Klausenone (**209**), obtained by LAH reduction of **209**, also possesses an intense musk odor, which showed that a carbonyl function was not a necessary requirement. Finally, the epoxide intermediate **212**, en route to a methylated Klausenone by a acid-catalyzed rearrangement, turned out to be the best musk odorant of all the derivatives synthesized (Scheme 42). It was introduced into perfumery by Givaudan as Moxalone (**212**). The industrial synthesis[126] starts from 1,1,2,4,4,7-hexamethyltetralin (**210**). As depicted in Scheme 42, an industrial Birch reduction and epoxidation employing *tert*-butylhydroperoxide complete the Moxalone synthesis.

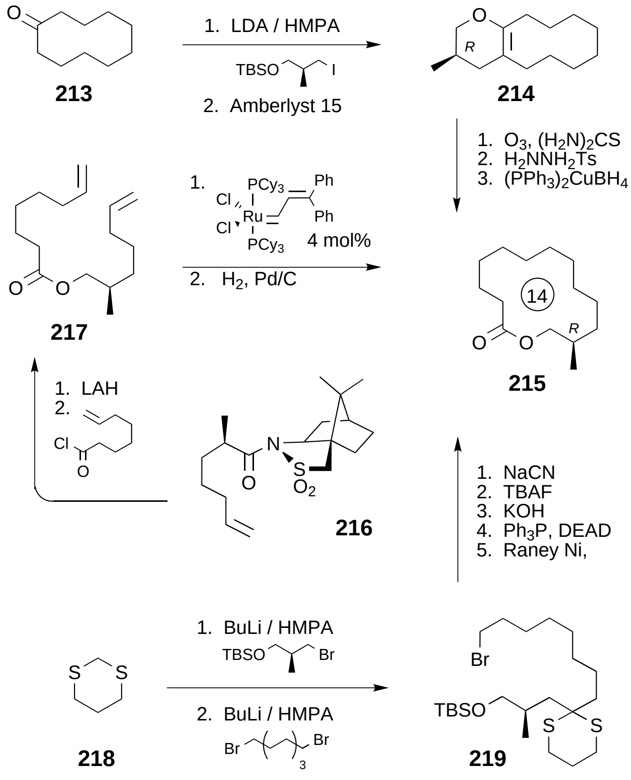


Scheme 42. Industrial synthesis of Moxalone (**212**).

Moxalone (**212**) was the first musk with an oxirane moiety. It possesses a rich musk odor with woody and fruity undertones, which distinguish it from the other musk odorants. Recently, it has been used in “Paris Baby Doll” (Yves Saint Laurent, 1999) at around 1.2 %, and also shows its efficiency in the unisex fragrance “CK be” (C. Klein, 1996).

9.3. Macrocyclic Musks

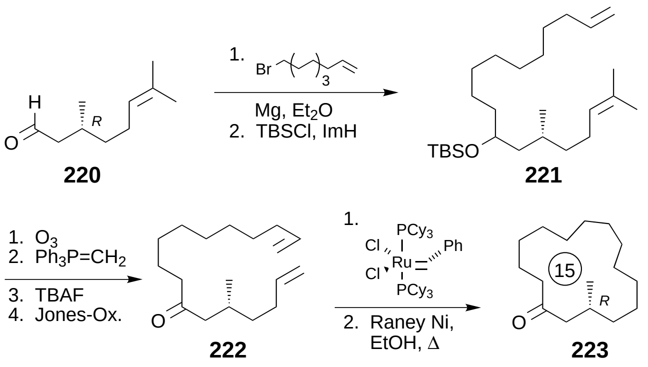
12-Methyl-13-tridecanolide (**215**; Scheme 43) was the first example showing the significance of methyl substituents in macrocyclic musk odorants. While the 13-tridecanolide possesses no musk odor, the enantiomers of 12-methyl-13-tridecanolide (**215**) differ distinctly in their musk odors: The 12*R*-(+) stereoisomer exhibits a sandalwood-musk note, while its 12*S*-(−) enantiomer has an animallike musk odor with camphoraceous aspects.[127, 128] Both enantiomers occur in Angelica root oil (*Archangelica officinalis* Hoffm.) in the ratio of 72:28 ((*R*)-**215**:(*S*)-**215**).[129]



Scheme 43. Synthetic approaches towards (12*R*)-(+)-methyl-13-tridecanolide (**215**). HMPA = hexamethyl phosphoramide, TBS = $tBuMe_2Si$, Ts = $H_3CC_6H_4SO_2$, TBAF = tetrabutylammonium fluoride, DEAD = diethyl azodicarboxylate.

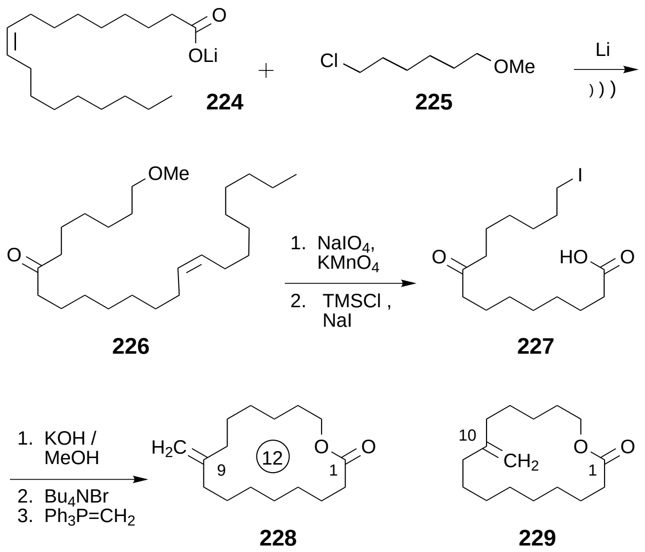
So far three different enantioselective approaches to this interesting natural product have been published (Scheme 43). The first one makes use of a ring-enlargement sequence with a chiral building block:[127] Cyclodecanone (**213**) was alkylated with a chiral building block derived from the methyl ester of (2*S*)-(+)-3-hydroxy-2-methylpropanoic acid. Amberlyst 15 mediated the cyclization to the bicyclic enol ether **214**, which was then subjected to ozonolysis and selective reduction of the resulting ketone group to provide the target molecule (12*R*)-(+)-**215** in 98.8% *ee*. Fürstner et al.[130, 131] applied a ring-closing metathesis to the synthesis of (12*R*)-(+)-**215**. The enantiomerically pure starting material **216** was prepared by alkylation of *N*-propionylbornane-10,2-sultam with 5-iodopent-1-ene. Reduction of amide **216** followed by esterification of the resulting alcohol provided the dienoate **217**, which was cyclized by the action of a Grubbs catalyst. As outlined in Scheme 43, reduction of the metathesis product then furnished the target molecule (12*R*)-(+)-**215**. The most recent approach of Noda et al.[132] utilizes 1,3-dithiane (**218**) as an auxiliary.[133] The carbon chain of **215** was constructed by alkylation of **218** with first a chiral building block and then 1,8-dibromooctane. Interconversion of the functional groups of **219**, subsequent macrolactonization, and reductive desulfuration completed this synthesis of enantiopure (12*R*)-(+)-**215** (Scheme 43).

As a consequence of the recently developed ruthenium and molybdenum alkylidene catalysts,[131, 134] ring-closing olefin metathesis has advanced to a widely applicable synthetic method for the preparation of macrocycles. An interesting application is the synthesis of enantiopure (*R*)-(−)-muscone (**223**; Scheme 44), the principal odorous constituent of the male musk deer.[135] The Grignard reaction of 1-bromodec-9-ene with commercially available (*R*)-(+)-citronellal (**220**) provided, after oxidation or protection of the alcohol function, a substrate that was already suitable for a ring-closing metathesis to form (*R*)-(−)-muscone (**223**). However, the *gem*-dimethyl substitution of one double bond of **221** rendered ring closure by metathesis impossible. Therefore, **221** had to be transformed into diene **222** with two terminal double bonds. As outlined in Scheme 44, this substrate smoothly underwent ring closure in the presence of 5 mol% of bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride to furnish the desired target molecule **223** after hydrogenation.



Scheme 44. Synthesis of (*R*)-(−)-muscone (**223**) by ring-closing metathesis. ImH = imidazole.

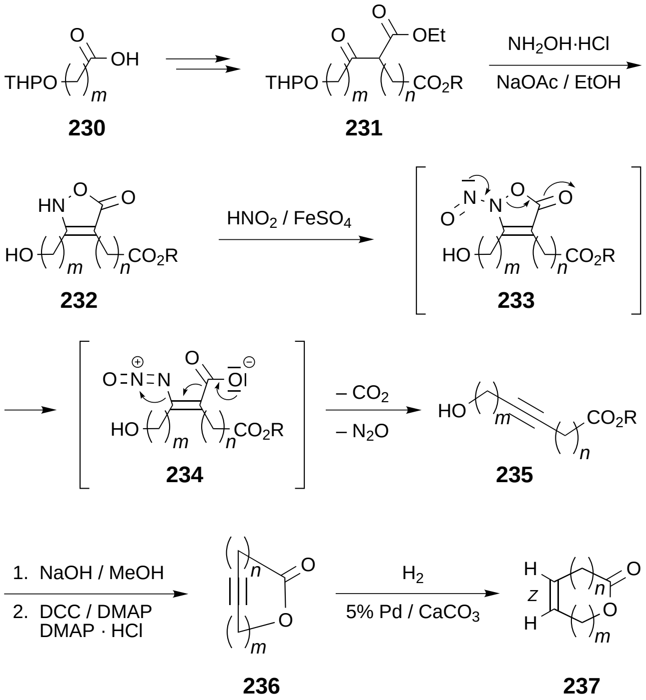
The synthesis of the first methylene macrolides is shown in Scheme 45.[136, 137] A Barbier reaction of chloroalkyl methyl ether **225** with lithium oleate led, after Lemieux oxidation and deprotection with Olah's reagent, to the ω-iodooxocarboxylic acid **227**. This compound was cyclized and methylenated by a standard Wittig reaction to provide 9-methylene-15-pentadecanolide (**228**), which emanated a strong sweet musk note with an animallike tonality. The 10-methylene analogue **229**, which is available from undecylenic acid, is even sweeter and more animallike, but has a waxy undertone.[136, 137]



Scheme 45. The first methylene macrolides.

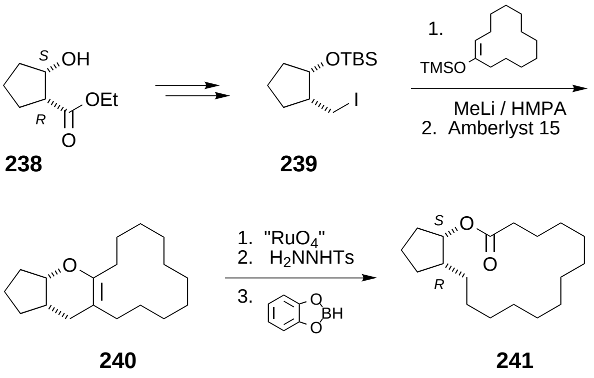
A general sequence for the synthesis of *Z*-configurated alkenolides is presented in Scheme 46. Starting from the THP-protected ω-hydroxycarboxylic acids **230**, Lehmann and Tochtermann[138] synthesized α-branched β-oxo esters **231** that were converted into isoxazolones **232** by treatment with hydroxylamine hydrochloride. By employing the method of Zard et al.,[139, 140] these compounds fragmented upon nitrosation to afford ω-hydroxyalkynoic acids **235**. Cyclization and hydrogenation with Lindlar's catalyst gave the 16-membered *Z*-alkenolides **237**, the olfactorily most interesting of which turned out to be (7*Z*)-pentadec-7-en-15-olide (**237**, $n = 5$, $m = 7$).[138]

As (9*E*)-hexadec-9-en-16-olide (*iso*-ambrettolide), synthesized from a main constituent of shellac (aleuritic acid), became an important perfumery material[4] it also seemed interesting to utilize fatty acids from other natural products in the synthesis of macrocyclic musks. Baba et al.[141] converted chaulmoogric acid (cyclopent-2-ene-1-tridecanoic acid), a main component of Chaulmoogra oil, into a mixture of macrobicyclic lactones that was reported to possess a musk odor. This process led to the synthesis of related macrobicyclic lactones with defined regio- and stereochemistry.[142] The preparation of (1*S*,16*R*)-(+)-2-oxabicyclo[14.3.0]nonadecan-3-one (**241**) by ring enlargement with a chiral building block, derived by yeast reduction from 3-oxocyclopentanecarboxy-



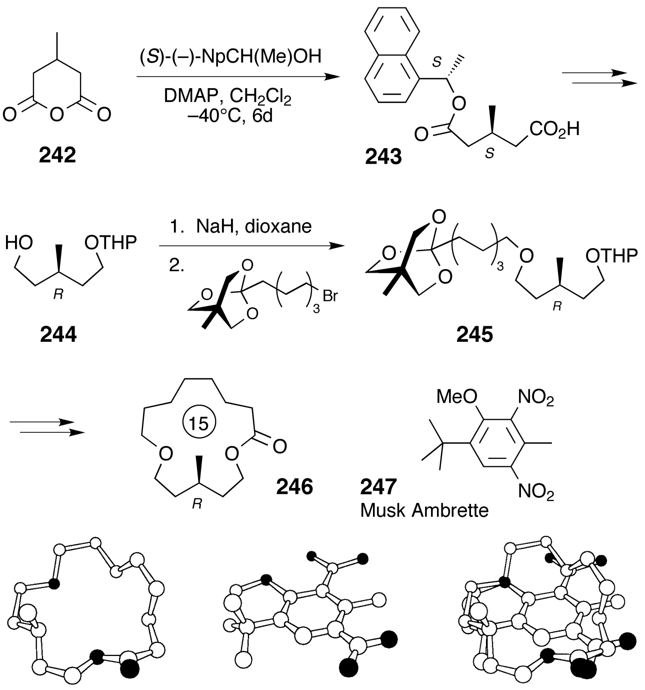
Scheme 46. A synthetic sequence towards *Z* alkenolides. THP = tetrahydropyran.

late, is outlined in Scheme 47. The smell of this macrobicyclic lactone was reminiscent of the olfactory impression of clean skin, with aldehydic, fatty, and woody aspects but only a slight musky touch.[142]



Scheme 47. Stereoselective synthesis of a macrobicyclic lactone (**241**) by ring enlargement.

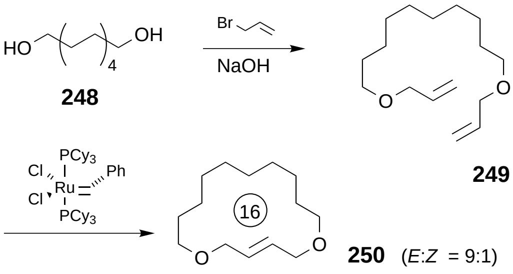
The synthesis of a macrocyclic musk that closely resembles the nitro musk Musk Ambrette (**247**) is presented in Scheme 48.[143, 144] The observation that only the *R* isomer **246** was responsible for these interesting odor characteristics, while its enantiomer was odorless in the GC olfactometry was unexpected.[143] The key step in the stereoselective synthesis of **246** was the desymmetrization of 3-methylglutaric anhydride (**242**) with (1*S*)-(−)-1-(1-naphthyl)ethanol.[145] Borane reduction, THP protection, LAH reduction, and a Williamson reaction with ω-bromoheptyl-OBO (OBO = 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane) led to the extremely powerful musk odorant **246** via intermediate **245**. The superposition



Scheme 48. A macrocyclic musk that closely resembles the nitro musk Musk Ambrette (**247**). (*S*)-(−)-Np = (*S*)-(−)-naphthyl.

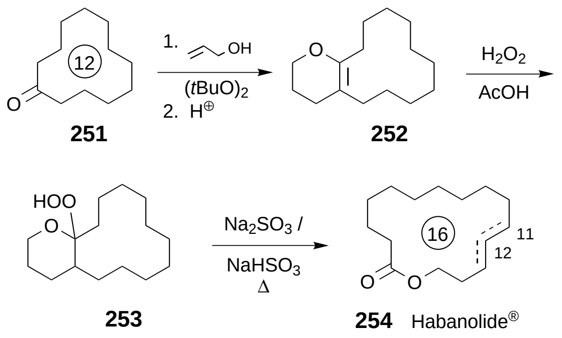
of the minimum-energy conformer of **246** with Musk Ambrette (**247**), also shown in Scheme 48, may account for the odor similarity of both compounds. An (ω-2)-methyl substituent as well as a 1,7-dioxa distance, both of which are present in **246**, were assumed to intensify the musk odor of macrocycles.[143]

A recent Takasago patent[146] claimes 1,6-dioxamacrocycles to be outstanding musk odorants. 1,6-Dioxacyclohexadec-3-ene (**250**) possesses a powdery musk note, and was synthesized as outlined in Scheme 49 by a Williamson reaction of decan-1,10-diol (**248**) with allyl bromide and subsequent ring-closing metathesis. This simple two-step process illustrates the search of industrial chemists for inexpensive routes to macrocyclic structures.



Scheme 49. 1,6-Dioxacyclohexadec-3-ene (**250**).

Habanolide (**254**)[147] is one of the least expensive macrocyclic musks currently available to the perfumer, and thus has recently become important in perfumery. Its industrial synthesis (Scheme 50) starts from cyclododecanone (**251**), and is the result of over 20 years of process research on the synthesis of pentadecan-15-olide.[148–151] Habanolide (**254**) blends very well with other macrocyclic musks and traditional ambery



Scheme 50. Industrial synthesis of Habanolide (**254**).

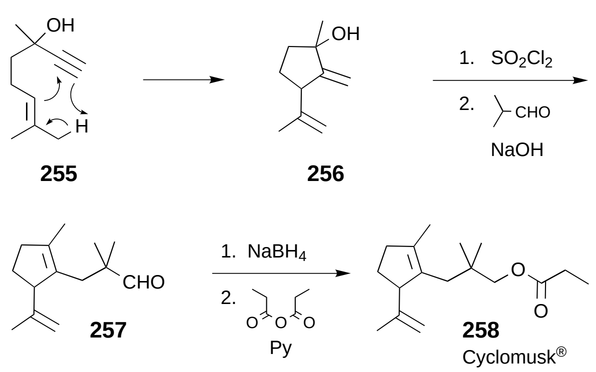
notes. “Bvlgari for men” (Bulgari, 1995) was one of the first examples where it was used in large amounts of around 10%. In the oriental-amber-musk family, we find an overdose of Habanolide (**254**) in “Salvatore Ferragamo pour Homme” (S. Ferragamo, 1999), and “Hypnotic Poison” (C. Dior, 1998) at around 16 and 17%, respectively.

Habanolide (**254**) also goes well with Helvetolide (**262**), and this combination of perfumery raw materials was used for example in “2020” (Courrèges, 1997) in the ratio of 2.3:1 and in “Herve Leger” (H. Leger, 1998) in the ratio of 0.6:1.

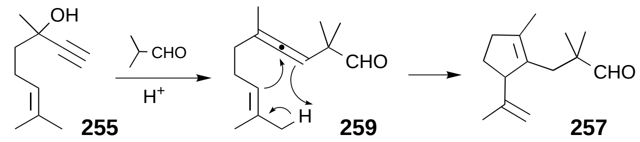
The microencapsulated base “Muskberry” in Figure 5 (see p. 2991) was built around a blackberry accord. It illustrates how the musk odorants Habanolide (**254**) and Moxalone (**212**) bring sensuality to a composition, and accentuate the perfumery side of this gustative odor.

9.4. Neither Macrocyclic Nor Benzenoid

When musks are mentioned, one usually thinks of macrocycles, polycyclic benzene derivatives, or nitro arenes.[4, 124] However, in 1975 BASF had already discovered a cyclopentenyl ester with a musky, warm, powdery odor and fruity, strawberry-type nuances.[152, 153] The compound, which was introduced as Cyclomusk (**258**), was manufactured as summarized in Scheme 51 by thermal cyclization of dehydrolinalool (**255**), subsequent halogenation under migration of the double bond, reaction of the resulting halide with isobutyraldehyde, reduction, and esterification of the resulting product with propionic anhydride. As shown in Scheme 52, the central intermediate **257** of this process is also accessible by direct thermal cyclization of the allene **259**, which is obtained by heating dehydrolinalool (**255**) with isobutyraldehyde in the presence of acid.[154]

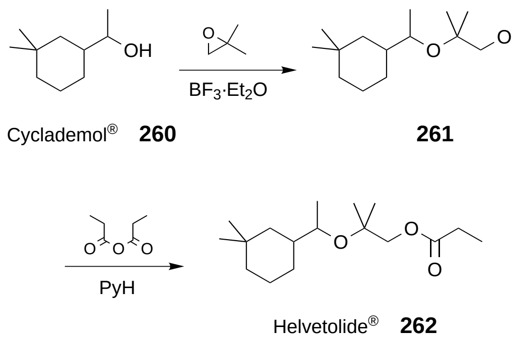


Scheme 51. Synthesis of Cyclomusk (**258**). Py = pyridine.



Scheme 52. Alternative route to the intermediate aldehyde of the Cyclomusk (**258**) synthesis.

Fifteen years later, in 1990, another representative of this uncommon class of musk odorants was discovered:[155] Helvetolide (**262**) with its musky-floral, fruity, pear-type odor. Its synthesis, as described in the corresponding patent,[155] is outlined in Scheme 53. An acid-catalyzed ring opening of isobutylene oxide with Cyclademol (**260**) afforded regioselectively the 2,2-dimethyl-3-oxaalcohol **261**, which was esterified to the corresponding propionate Helvetolide (**262**). In the floral-woody-musky feminine perfume “Ultra Violet” (P. Rabanne, 1999) around 3% of Helvetolide (**3**) was used in combination with other musks.



Scheme 53. Synthesis of Helvetolide (**262**).

10. Fragrance Forecast

With the pear-type nuances of the new musk Helvetolide (**262**) we return to the starting point of our journey into modern perfumery. We have seen how new odorants lead to new accords and then to new trends.

The traditional pyramidal building of perfumes seems to have changed, and perfumes become more and more rectangular. This allows the possibility of getting directly into the middle and base notes which give the character to a fragrance. Nevertheless, the top note is still important, and some perfumes can be distinguished most easily by this. That is also why impact odorants become more and more crucial.

We do not want to conclude this overview on recent developments in the chemistry of odorants without recalling the main trends, and without daring to take a look into the future. Again, we follow the olfactory circle of Figure 1. Fruity odorants are used to a great extent nowadays, and therefore, there seems to be a real need for innovative new fruity odorants such as Anapear (**16**) in the future. “Salvatore Ferragamo pour homme” (S. Ferragamo, 1999) is a recent example of a high dosage of fruity-lactonic notes, which previously were only used in such high concentrations in feminine fragrances. Grapefruit is still trendy in feminine as well as in masculine perfumes, and here the end is not yet in sight. Green perfumery materials have very diverse nuances, but the galbanum direction will continue to be important. New materials such as **46** and **47** with increased performance will open new possibilities for creation. In nature, the scent of leaves is ubiquitous and now begins to enter more and more into perfumery, with new accords such as that of tropical leaves in "Cerruti Image" (Cerruti, 1998). In the future, the family of green odors could be even further extended with vegetable odors. Marine and ozonic notes are still used, but not anymore in overdoses. However, odorants such as Calone 1951 (**84**), Tropional (**85**), Floralozone (**86**), and Florhydral (**87**) have made their way into the perfumer's palette, and are now commonly used. With the comeback of sensuality in perfumery, floral notes will probably boom in the next few years; even masculine perfumes will probably become more and more floral. Everybody is waiting for a new Hedione (**8**), not one just enriched in the powerful isomers, but a really new floral building block with different tonalities, maybe in the rosy, magnolia direction. Also Coranol (**98**) could get used in a similar way to Hedione (**8**), even though it is completely different in smell. But sensuality is not only evoked by floral but also by spicy materials, and this has been demonstrated in perfumery for decades. "L'Air du Temps" (N. Ricci) of 1948 was already composed of spicy odorants, and "Opium pour Homme" (Yves Saint Laurent, 1995) as well as "Jungle for men" (Kenzo, 1998) are some recent examples in place of many other masculine oriental-spicy perfumes. "Oscar for men" (O. de la Renta, 1999), a spicy woody perfume, shows that this spicy trend is not over yet; and new spicy odorants would give a boost to it. Likewise, new sweet and suave compounds such as Methyl Diantilis (**133**) would reinforce the sweet-spicy notes. Woody notes are clearly indispensable in perfumery, and they are well represented by synthetic odorants. Nevertheless, not all aspects of the woody family are equally well covered. Vetiver and patchouli are less common notes by far for perfumery synthetics than cedar and sandalwood notes. Therefore, perfumers are waiting for a transparent vetiver odorant, and an inexpensive patchouli-type material. Ambery compounds are well established in the perfumer's palette; thus, a real revolution is not expected in this family, unless we could really get close to the natural odor of ambergris tincture. After nitro musks, polycyclic musks, and macrocyclic musks, linear musks are now being developed. Completely new structures for musk odorants could also bear new side notes such as, for example, the anisic tonality in **246**, and this can inspire new signature accords.

However that may be, the ambition of the perfumer to create something outstanding will continue to depend on the fascination of the chemist to invent something never smelled before.

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