Pergamon

Tetrahedron 54 (1998) 7633–7703

TETRAHEDRON

Tetrahedron report number 456

Fragrance Chemistry

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Received 26 February 1998

Abstract: This Tetrahedron Report on fragrance chemistry summarizes the recent progress in the chemistry of important amber, sandalwood, wood, musk, and floral odorants. Some details of the olfactory mechanism, current models for structure-odour relationships, and the parameters of olfactory performance are also discussed.

Contents

1 INTRODUCTION

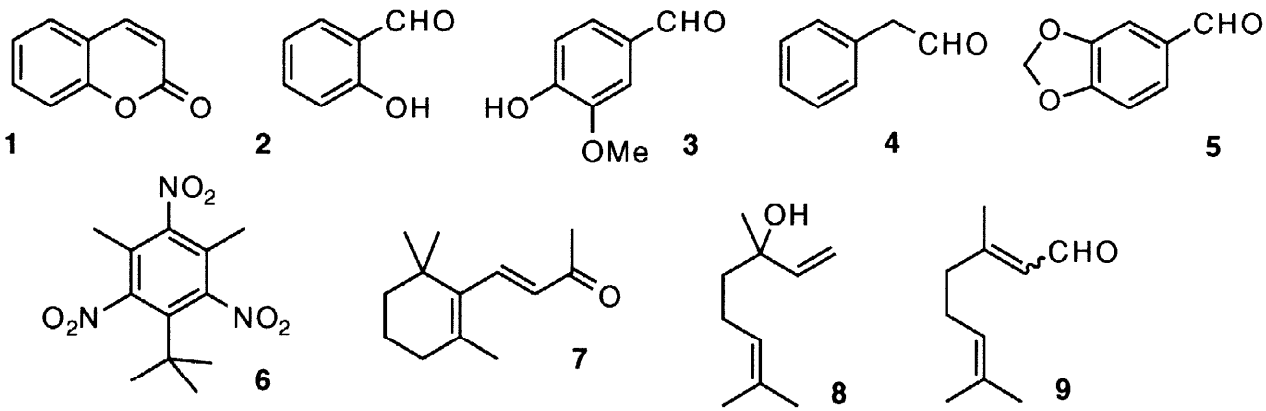
Fragrance chemistry is a fascinating blend of natural product, synthetic, analytical, and physical chemistry with a certain amount of creative fantasy for odours, and molecular structures. Besides the rigor and logic of isolation, analysis and synthesis, one is and should be carried away by serendipitous, artistic, intuitive moods.

In the broadest sense all compounds with a smell belong to the category of *fragrance chemistry*. In English the term *aroma chemicals* is used for both fragrance and flavour compounds, although there is no strict separation in practice. Thus, compounds with a sufficiently high vapour pressure will have an odour and this is normally the case up to a molecular weight of around 300, a relatively low polarity granted.

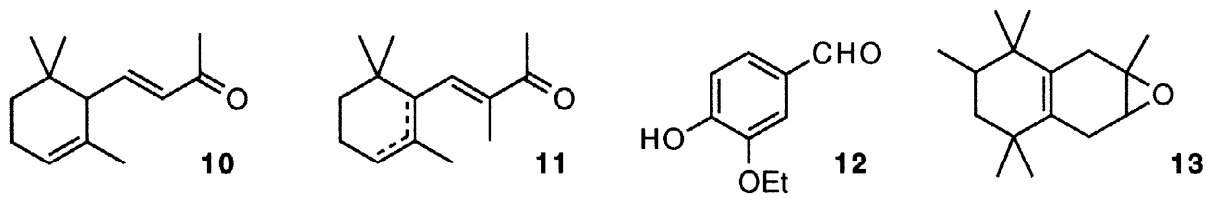
0040-4020/98/$19.00
PII: S0040-4020(98)00199-9

It is often incorrectly assumed that only compounds with a *pleasant* smell belong to the realm of *fragrance chemistry*.[1] Not only is *pleasant odour* a very subjective notion, but fragrance compositions often include single compounds which in higher concentrations or in pure form have an *animal*, *faecal*, *sulfurous* or *sweaty obnoxious* odour. Also, *fragrance chemistry* deals with malodour, in order to counteract it; therefore, the analysis and chemistry of *e.g.* sweat is also a topic of concern.

Fragrance chemistry[2,3] emerged from the very old tradition in virtually all civilizations of making fragrances from naturally occurring materials, mostly of plants but also of animal origin, as there are essential oils, exudates, balsams, and resins. In the second half of the 19th century, synthetic fragrance chemicals started to appear in the chemical literature and on the market: coumarin (**1**, 1866), salicylaldehyde (**2**, 1876), vanillin (**3**, 1876), phenylacetaldehyde (**4**, 1883), piperonal (**5**, 1890), the nitro musk Musk xylol (**6**, 1891), and β-ionone (**7**, 1893).



Over the last 100 years, synthetic fragrance chemistry has been a continuous success story. Organic chemists were able to offer the perfumers their *nature identical* raw materials in high and constant quality, and at low price, *e.g.* linalool (**8**), citral (**9**), α- and β-ionone (**10** and **7**). Moreover previously unknown synthetic molecules with new odour characteristics have become available and fantastic new possibilities for creation have revolutionized perfumery. Methyl ionone (**11**), an unnatural homologue of **7**/**10**, was first described in 1893 as being stronger than α- and β-ionone (**10** and **7**). Ethyl vanillin (**12**, 1894) is also stronger than its natural counterpart **3**. Both have been successfully used in the creation of the perfume »Shalimar« (Guerlain, 1925).



Today, most of the synthetic fragrance chemicals are in the price range of US$ 10–100 per kg, perhaps 10% in the range of US$ 100–250 per kg, and only a few above this. The natural fragrance ingredients, like essential oils, absolutes, and resins are, with a few exceptions, in the upper price range, and far above it: patchouli oil costs about US$ 20 per kg, lavender oil US$ 60 per kg, jasmin concrete US$ 600 per kg, and Turkish rose oil about US$ 2500 per kg. This is the reason, why in the last 25 years –since the analytical methods made it possible– perfumers were provided with many reconstitutions of expensive natural oils. In the so-called functional perfumery, that is the perfumery of soaps, detergents, and household goods, where prices must be kept very low, the compositions consist almost completely of synthetic materials. Today, only in fine fragrances the perfumer can afford to use some natural products.

In this review we were not aiming at a comprehensive coverage of *fragrance chemistry*. In our opinion this would neither be possible in the limited space, nor desirable for the reader. Rather we tried to show the beauty, difficulty and the multidisciplinary character of the topic. Some excellent publications cover a part of our theme up to *ca.* 1990.[3–7] A very special publication should also be mentioned here: Fragrance and Flavour Chemistry published in *Helvetica Chimica Acta* during its first 75 years.[8]

This review is intended to have a more practical character, giving preference to processes and compounds with technical and industrial relevance. This means, that the synthesis of a known fragrance chemical is included only if it is of some exceptional originality and elegance. It is a legitimate question, why new fragrance compounds are considered to be necessary, when there are some 2500 ingredients the perfumer can choose from. Yet, to be really unique, and to allow the creation of something outstanding, new compounds are indispensable. New odour tonalities give new possibilities for the creation. For instance, Moxalone® (**13**)[9] has a *musky-fruity* tonality, which is something new in this combination.

Besides the odour characteristics, other performance criteria like odour threshold, substantivity, toxicity, transparency, stability, and biodegradability, are also important parameters of odorants. The lower the threshold of a molecule, the more powerful it is, the higher impact it has in a composition. A higher impact means obviously also a relative price reduction because of possible lower dosage, and an advantage in respect to a possible environmental encumbrance.

The non-toxicity, of course, is a *conditio sine qua non*, and as such it must not be discussed here. *Substantivity*[10] means the behaviour of the fragrance in the application on skin, or hair, or fabric, e.g. the distribution and residuality of a perfume in its use in a laundry-washing process. High residuality on laundry can be achieved by high lipophilicity, which again can become problematic when biodegradability is addressed. To circumvent this problem relatively lipophilic precursors of relatively hydrophilic fragrance molecules have been proposed, which are cleaved in the washing process to ensure the desired residuality of the fragrance.[11] *Transparency* is a difficult to describe characteristic of a fragrance ingredient, meaning how it performs in mixtures; whether it is dominating or it lends itself to a harmonious accord. *Stability* in this context means the behaviour towards high pH of 9–10 as it prevails during the washing process, towards oxidants in bleach, and in special applications also towards low pH of 4–5. Last but not least, the biodegradability should be high. With all these requirements[12] it is clearly a demanding task to find and introduce new fragrance chemicals.

2 RATIONAL DESIGN OF ODORANTS

2.1 *Olfactory Mechanism—Molecular Complementarity*

The knowledge of the mechanism of olfaction, and particularly of its *primary event* involving odoriferous ligands and their receptors, would obviously facilitate the search for new and more efficient perfumery raw materials. It would help to optimise the structures of the known lead molecules, and make possible a *de novo* design of better performing compounds. Unfortunately, and despite all the recent research effort, the information on the molecular interactions between olfactory receptors and their ligands is almost non-existent.

In 1991, Buck and Axel reported their discovery of a large family of genes encoding putative odorant receptors,[13] possibly more than 1000 different proteins. They seem to belong to the largest group of receptors for neurotransmitters and hormones—the **seven-transm**embrane-domain (7TM), **G-p**rotein-coupled **r**eceptors (GPCRs). This super-family of proteins mediates numerous physiological phenomena, including vision. Studies of any GPCR represent a challenge because of the instability outside the membrane and crystallization difficulties. Even in the cases where functionally well defined specific receptors of endogenous ligands like retinal, histamine, serotonine, dopamine, tachykinin, thrombin, endothelin, or substance P (of enormous importance for the pharmaceutical research) are known,[14] little data on the tertiary structure of the receptor-ligand complex are available. Some information on the amino acids crucial for the recognition of such ligands has been provided by point mutation experiments and studies with chimeric analogues and labelled ligands. However, the large majority of the models generated thusfar,[14–16] of contested practical value, have been based on the only available 7TM

template, a model of bacteriorhodopsin obtained by using electron diffraction data of its 2D crystals.[17] While analysing such models one should never forget that bacteriorhodopsin, although functionally related to GPCRs, does not belong to this super-family of receptors and has only little sequence homology with them.

Buck and Axel's discovery triggered big expectations in the fragrance microcosm, but six years later the confirmed experimental data on specific odorant-receptor couples in vertebrates are still insufficient for any exploitable *molecular complementarity* search. The most relevant experimental facts in this direction have been provided by the groups of Breer,[18,19] Bargmann,[20] and most recently Firestein.[21] The first one expressed the new putative odorant receptor OR5 from rat in Sf9 insect cells, and observed a significant dose dependent increase in the cytosolic level of IP_3 –one of the second messengers involved in the olfactory signal transduction– upon extracellular stimulation with the odorants Lilial® [3-(4-tert-Butylphenyl)-2-methylpropanal, **14**] and Lyral® [4-(4-Hydroxy-4-methylpent-1-yl)-cyclohex-3-ene-1-carboxaldehyde, **369**]. The second elegant study, based on the chemotaxis of mutants of *C. elegans*, a worm with a very simple chemosensory system composed of 32 neurones, provided functional evidence for a specific interaction between the ODR-10 olfactory receptor protein and diacetyl in this species.[20] The OR-I7 gene,[13] expressed *in vivo* through adenovirus-mediated gene transfer in the olfactory epithelium of rat, responded selectively to *n*-octanal in an electro-olfactogram experiment.[21]

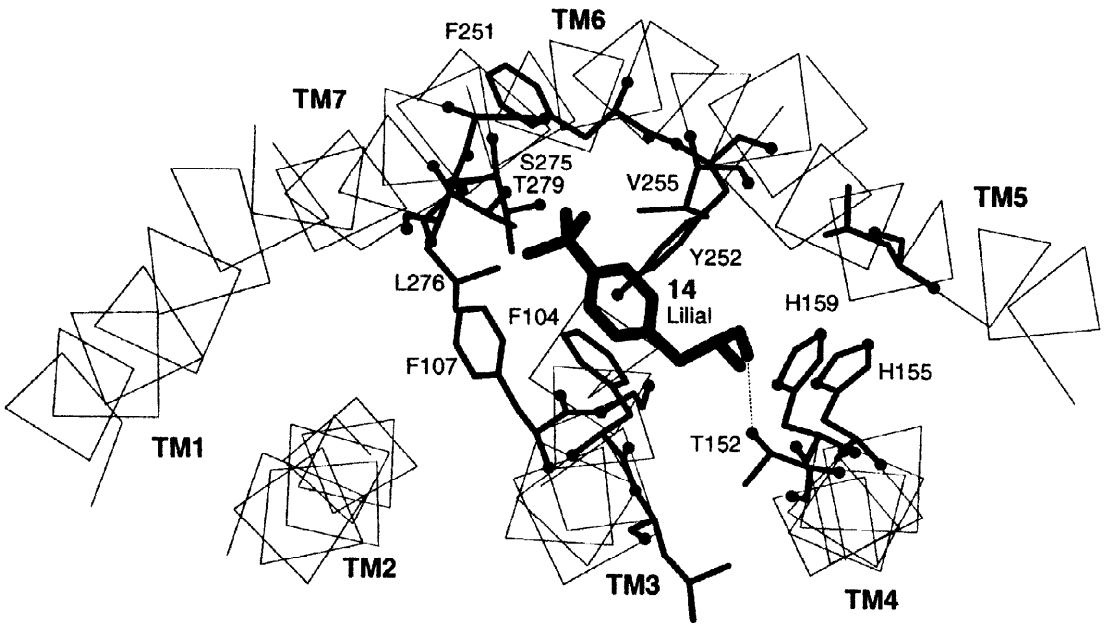
Another still unanswered question concerning the *primary event* in olfaction is how lipophilic odorant ligands make their way through the aqueous mucus layer covering the olfactory epithelium to the receptor? In other words, what are the *perireceptor events*?[22b] So called **o**dorant **b**inding **p**roteins (OBP), soluble proteins of low molecular weight with affinity to several structurally different odorants, were found abundantly in the nasal mucus. They belong to the family of ligand carrier lipocalins, and were historically the first proteins supposed to be involved in the molecular recognition of odorants.[23] Their role is still unclear and several hypotheses have been advanced:[24] They could influence odorant transport, its concentration near the receptor, the odorant signal termination, or even stabilise an active conformation of odorant receptors through interactions with their exterior portions. Recently, a bovine OBP membrane receptor, which seems not to be restricted to the olfactory tissues, was discovered.[25] Therefore, OBPs could play a broader role within the body. Some other proteins found in the nasal mucus of vertebrates such as olfactomedin[26] and vomeromodulin do not have proven functions either. Cytochrome P-450 is the most often mentioned among the degrading and detoxifying enzymes that seem also to influence the odour perception.[22b,27]

It should be noted here that odorants can interact with other parts of the nasal cavity. The trigeminal nerve responds to some airborn chemicals by triggering the sensation of piquancy, pungency, burning, astringency, tingling, and cooling.[28] The speculations concerning human pheromones,[29a–c] potentially important for the creation and marketing of perfumes, have been recently amplified by the work on the **vomero**nasal **o**rgan (VNO).[29] It appears to have a distinct mechanism of signal transduction,[29c–e] resembling that of odorants, but there is no clear evidence even for the presence of this organ, let alone its function in adult humans.[29a]

After the period of completing the catalogue of genes encoding for proteins specifically located in the olfactory epithelium, the main research activity is now focused on the signal transduction and the genetics of olfaction. Papers reporting the expression and isolation of putative odorant receptors have begun to appear,[19,30] but their functional relevance has not yet been proven. Both research and recent opinions on the olfactory mechanism have been extensively reviewed.[22,29b,31–33]

Based mainly on the results of Breer's group,[18] some speculative models of odorant receptor interactions have been generated. Singer and Shepherd[34a] tested docking of Lyral® to a model of the putative rat olfactory receptor encoded by the OR5 gene. They found a possible binding pocket composed of 6 amino acids of TM3 through TM7, not surprisingly situated close to the position of the binding site of retinal in bacteriorhodopsin used as template. The same authors obtained similar results with the I9 receptor[13]–benzaldehyde couple,[34b] and proposed a general *determinant*-based model for ligand-receptor interactions in olfactory receptors.[35] They suggested that odorant receptors contain an average of 2–4 subsites. Ligands contain a similar number of *determinants*, and the set of them in the active geometry is called *olfactophore*. Singer *et al.*[36] performed a correlated mutation analysis of putative odorant receptor sequences from rat, and proposed several substructures

involved in the ligand binding. The calculation of positive selection moments of the 6th TM of human olfactory receptors allowed similar conclusions.[37]



Top view of Lilial® (14) docked at a possible binding site of a model of the putative OR5 odorant receptor[38]

These studies prompted us to present our model[38] of the OR5 receptor interacting with Lilial® (**14**). The hydrogen bond between a hydroxyl bearing amino acid (Tyr or Thr) and the carbonyl group is the common receptor-ligand interaction in these models. Histidine residues of TM4, versatile in their binding interactions, appear to be of prime importance. Despite these very exciting speculations, indispensable for the progress of any science, the factual knowledge of the mechanism of olfaction does not yet allow the application of *molecular complementarity* search techniques to the design of optimal olfactory agonists and antagonists.

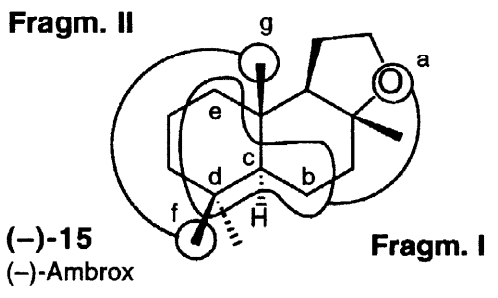
2.2 *Olfactophore Search—Molecular Similarity*

The approach based on *molecular similarity* among compounds of the same odour note is of more practical and immediate use in the search for more efficient odorants. Looking for the minimum structural requirement for a given type of odour is not new. It paralleled the search for primary odours, and has progressively been adopting the methods pioneered in medicinal chemistry. By analogy with the widely used term *pharmacophore*, *olfactophore* has been coined[35,39,40] for a set of structural features responsible for a defined odour-type sensation. We will use it rather than *osmophore* which has historically (since its introduction by Rupe in 1900[41] for interchangeable functional groups of odorants) served to design the (most) polar part of odoriferous compounds, probably responsible for the strongest interactions with their receptors.[42]

The acquisition of reliable structure-odour relationship (SOR) data constitutes the first and indispensable step in any *olfactophore* search. The selection of useful information from the chemical and perfumery literature is not easy because of the lack of unity in perfumers language, insufficient statistical significance of most of the published data and scarcity of results obtained with olfactorily pure single stereoisomers or their mixtures of known ratio and configuration. The complex problem of the efficient measurement of the odour quantity[43] and quality[44] makes the task even more difficult.

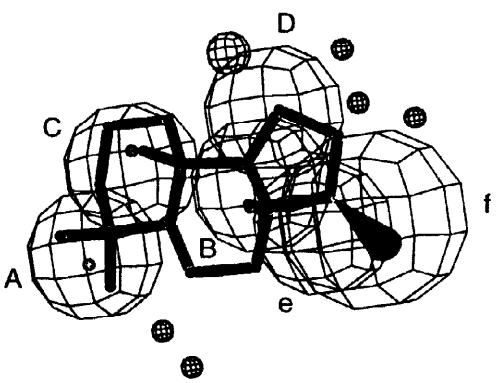
Taking into account only the lowest energy conformers of the often very flexible odorants constitutes another common reason for the lack of precision of the majority of *olfactophore-search* studies. The active shape of odorants can be dramatically different from their preferred conformers due to a possible gain of energy provided by the receptors and their environment in order to stabilize the ligand-receptor-G-protein complex.

Since this report focuses on the last decade of Fragrance Chemistry, we refer to the excellent reviews on structure-odour relationship[45] for older empirical rules, and models such as the *triaxial rule*,[46] and *ambergris triangle*[47] for amber odorants, or *musk*[48] and *sandalwood* rules.[49,50] The history and current state of the SOR research has been exhaustively reviewed in a recent paper.[51] Here, only the three most thoroughly studied *olfactophores*, corresponding to the odour notes described in the following synthetic part, *i. e. amber*, *sandalwood*, and *musk*, are considered.



The two (accessible) molecular fragments considered responsible for the amber odour[54]

Fragment I	O bond to a *quat.* C-atom + 4 carbons
Fragment II	2 methyl groups attached to a quaternary C-atom



Ambrox® (**15**) mapping the best CATALYST *hypothesis* of the amber *olfactophore*[38]

A–D hydrophobic *functions*
e→f oriented H-bond acceptor
small spheres = excluded volumes

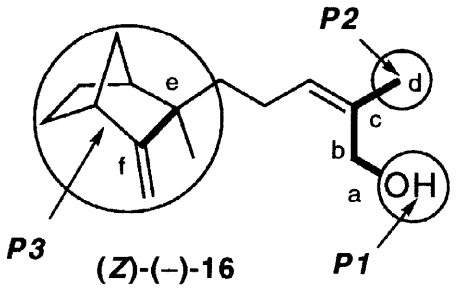
Amber: The domain of amber-like smelling compounds is particularly well suited for the *olfactophore* search. The available SOR data obtained with structurally rigid compounds of known absolute configuration allow to take into consideration a relatively small number of representative conformations. The difficult problem of how to define the multifacet amber type odour can be overcome by taking (–)-Ambrox® [(–)-**15**][52] as the reference.

The steric accessibility (SA) of the *osmophoric* oxygen of the analogues of this odorant was calculated using a probe radius of 1.4Å.[53] The lower limit of the measured van der Waals surface, critical for the amber odour, was found to be 5–6Å^2. This structural feature was used as a supplementary criterion in another study[54] based on the so-called electron-topological (ET) approach.[55] The two molecular fragments found indispensable for the amber odour –highlighted in the depicted (–)-Ambrox® molecule [(–)-**15**]– correspond to two electron-topological matrices of contiguity (ETMC). These are built using effective charges as diagonal elements, and Wiberg indices for bonded as well as *optimized* distances for unbonded atoms. The authors[54a] report an astonishingly high degree of prediction, about 95%. The ET method was also applied to other odour classes, comprising sandalwood[56] and musk.[57]

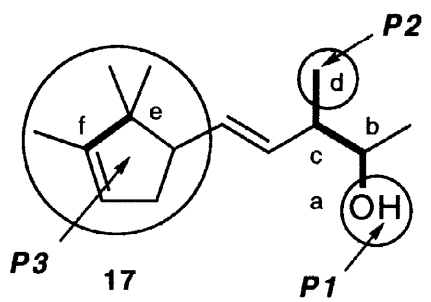
A different approach,[38] taking into account the flexibility of the ligands, is based on a broad coverage of an energetically reasonable conformational space,[58] with a ΔE arbitrarily fixed at 15 kcal/mol. An automated analysis[59] of the generated *conformational models*, which contained 2–79 conformers for each of the 23 carefully selected compounds of the *training set*, led to *hypotheses*—sets of abstract chemical features[60] displayed as spheres positioned in space, that contribute to the analysed physiological activity, *i. e.* amber odour. The following

selection of the best *hypothesis* and its fine-tuning by placing *excluded volumes* resulted in a model for the amber *olfactophore*, which proved useful in the rationalization of the SOR data, and in the design of new molecules with this smell.

The *triaxial rule*,[46] notwithstanding many exceptions,[61] continues to be applied in the SOR studies of amber odorants. It was applied in an analysis of the importance of the axial methyl groups of (–)-Ambrox® [(–)-**15**] and its analogues for their interactions with a hypothetical odorant receptor *via* an *axial hydrogen bond*.[62]



(*Z*)-(–)-16
(*Z*)-(–)-β-Santalol



17
Ebanol

Naipawer *et al.* [50] (1981)	$C_e \rightarrow O(H)$ (in a *reasonable* conformer)	*ca.* 4 Å
Chastrette *et al.* [71] (1990)	$C_e \rightarrow O(H)$ (in the *most stable* conformer)	6.5–7.1 Å
Buchbauer *et al.* [73] (1994)	*P1*→*P2*	2.9–3.0 Å
	P1→*P3*	6.3–6.4 Å
	P2→*P3*	5.9–6.0 Å
Dimoglo *et al.*[56] (1995)	$C_e \rightarrow C_d$	5.15 ± 0.15 Å
	$C_e \rightarrow O(H)$	6.60 ± 0.20 Å
	$C_f \rightarrow O(H)$	7.60 ± 0.20 Å

Sandalwood: Despite the quite abundant SOR literature on sandalwood odorants,[63] only few data for unequivocally defined, *i. e.* optically pure, structures are available. The optically pure (*Z*)-β-santalol, main odour vector of natural sandalwood oil,[64] 5α-androst-16-en-3α-ol,[65] and (1*S*,3*R*,6*R*,8*R*)-*tert*-butylbicyclo[4.4.0]decan-3-ol[66,67] have been until recently the only pure substances for which the *sandalwood odour* was reported. The first information on the single stereoisomers derived from campholenic aldehyde, which constitute the main class of synthetic sandalwood-type odorants, was only released in 1995.[68] The majority of sandalwood smelling compounds are fairly flexible except the steroid and the *tert*-butyldecalinol cited above. However, it should be mentioned that the latter is not always rated among the most active compounds of the natural sandalwood odour,[69] and that the odour of 5α-androst-16-en-3α-ol is quite often perceived as different from that of sandalwood.[65]

The classical *sandalwood rules*,[49,50] and results of more recent studies underline the importance of the distance between the hydroxy group and a bulky moiety, that preferably contains an electron-rich fragment, *i. e.* a double bond, an ether function or a cyclopropane ring. The often flexible spacer linking these fragments should be branched next to the hydroxyl bearing carbon. Different values for this distance, obtained in several studies, are not always easy to compare because of different locations of the center of the bulky group. The initially proposed approximately 4 Å distance between the hydroxyl oxygen and "a highly substituted or quaternary carbon atom" in at least one *reasonable* conformation[50] was sometimes found too short.[56,70,71] One should always keep in mind that most of the literature studies consider only the lowest energy conformers, which are certainly not the active conformers for all the ligands. The necessary structural features of the bulky part of a *sandalwood* smelling substance are also difficult to define. For some they are limited to a quaternary carbon atom, while others consider two adjacent tertiary or quaternary carbon atoms or a part of the molecular surface.

Other parameters have been used to augment the predictive power of such *olfactophore models*. Buchbauer, Wolschann *et al.* studied the conformations and molecular surfaces of sandalwood odorants.[72] In one of their recent works they applied the *active-analogue* approach[73,74] which takes into account the flexibility of the ligands. The analysis of sets of energetically allowed conformers of twelve active compounds, of which only two were single stereoisomers, together with six odourless analogues gave an *olfactophore* assumed by the authors to consist of three *osmophoric points*. They correspond to the hydroxy *osmophore*, a lipophilic substituent, and a bulky, rigid group, represented as a dummy atom in the middle of an alicyclic system. The sandalwood odour of (*Z*)-*dehydro-homo*-β-santalol[75a] and (*Z*)-*bis-homo*-β-santalol[75b] seems to confirm their findings, but the 7-oxa analogue of the natural β-santalol turned out to be odourless,[76] despite the fulfilment of all the steric requirements. This was rationalized by the difference in the electrostatic potential at the third point of their postulated sandalwood *olfactophore*.

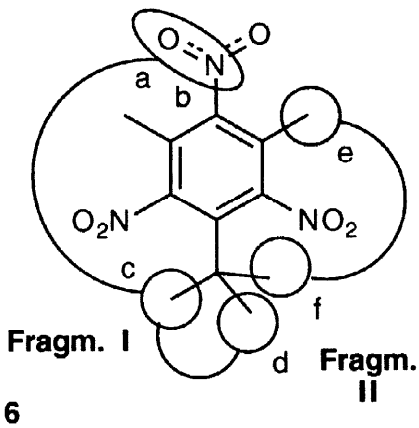
In addition to the distances between two fragments –atoms a+b+c+d, and atoms e+f, highlighted in the depicted sandalwood odorants– the sandalwood *olfactophore* generated by the already mentioned ET method[55] involves also some electronic interactions of the hydrophobic parts with the protein receptor. Frontier orbital calculations carried out by Dimoglo *et al.*[56] led to the proposal that atoms C_e and C_f act as electron donors, while atoms C_b, C_d and O(H), the latter with an electron density of –0.26±0.05 e, act as electron acceptors.

Two different *santalophore patterns* were obtained *via* a statistical evaluation of the empirical sandalwood rules,[49,50] for a set of 57 active and 82 inactive molecules, followed by comparison of four optimized structures (lowest-energy conformers) of intensively *sandalwood* smelling, and relatively rigid compounds.[71] They consist of a "*tert*-butyl group or an equivalent, and a hydroxyl group". A *superpattern*, defined as the envelope of the superimposed structures, possibly interacting with different parts of the sandalwood receptor, was proposed. The authors reported 100% correct predictions for a set of 17 active and inactive molecules, using this *superpattern*, and some angles and distances within the ligands.

Musk: The SOR work in the domain of musks has a long tradition. It started with the serendipitous finding of nitro musks at the end of the last century, and has been carried out since, most of the time separately within the main three classes of these important perfumery raw materials: macrocyclic, nitro, and non-nitro benzenoid, mainly polycylic musks. The slight differences between the typical musk odour of these chemical series brought about hypotheses of the existence of more than one musk receptor –or a set of receptors– and consequently not a unique musk *olfactophore*.[77] Another aspect of the musk SOR studies is the relation between this odour and that of the often considered as sandalwood-like 5α-androst-16-en-3α-ol and androstenone, so-called steroidal musks,[65] and suspected of having a pheromone function. As a result, the whole musk SOR domain appears rather confusing.

The work of Bersuker *et al.*[57] is one of the most documented recent studies aiming at a unique musk *olfactophore*. Using their ET approach,[55] they analysed 362 compounds belonging to all classes of musks as well as inactive analogues, and found two independent, sterically accessible, molecular fragments indispensable for the musk scent. The first one is a polar group (C=O, N=O, C≡N) of which the most electronegative atom is situated symmetrically from two methyl groups or methylene units at a distance of 6.7±0.5Å. The latter are separated by 2.5±0.5Å. The distance between two other methyl or methylene groups that constitute the second fragment should be 5.5±0.5Å. Additional considerations, based mainly on the necessary steric accessibility of these two fragments, allowed a very good predictability (97% for active, 94% for inactive compounds), which would be even higher if one applied their hypothesis, that some aromatic musks interact with the receptor in form of dimers.

These results were evaluated by Kansy *et al.*[40] using a single (as in the original study[57]) and a multiconformer approach, with the help of the MOLOC[78] and CATALYST[59] software, respectively. The results were deceiving: The overall predictability ratio was 54% for the first approach, in which the steric accessibility was not considered, and 59% in the second one. It was better, though still not satisfactory (65% overall, 84% for active, and only 30% for inactive compounds), when the Bersuker database was screened with a CATALYST *hypothesis*, generated automatically with a set of 40 selected compounds.

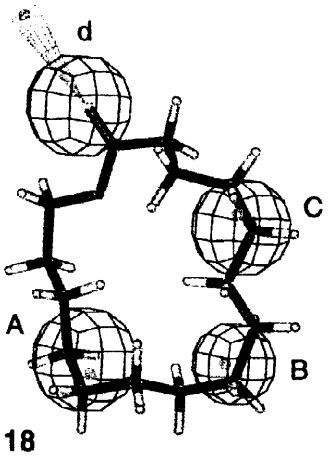


6
Musk Xylol

Two fragments indispensable for the musk scent [57]

Fragment I O (or N) symmetrically flanked by 2 Me or methylene groups
Fragment II 2 Me or methylene groups

$O \rightarrow C_c = O \rightarrow C_d = 6.7 \pm 0.5$ Å
$C_c \rightarrow C_d = 2.5 \pm 0.5$ Å
$C_e \rightarrow C_f = 5.5 \pm 0.5$ Å

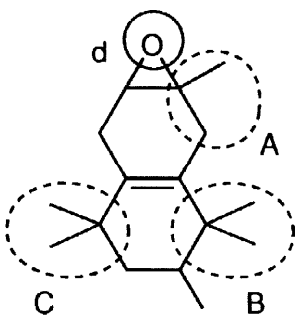


18
Exaltolide, Thibetolide

mapping the model of the musk *olfactophore* generated using CATALYST [40]

A–C hydrophobic *functions*
d H-bond acceptor

$A \rightarrow B = 3.6$ Å $B \rightarrow C = 4.0$ Å
$C \rightarrow d = 5.5$ Å $d \rightarrow A = 6.7$ Å
$d \rightarrow B = 8.0$ Å



13
Moxalone

Tentative positioning of the Compass model features [82] on Moxalone (**13**)

A–C appropriate surface shapes
d H-bond acceptor

Chastrette *et al.* also studied a large chemical domain of musks.[79] After having investigated single families of musks –nitrobenzenoids[79a] and polycyclic carbonyl compounds[79b]– they used a neural network to analyse a sample of 105 nitrobenzenes, carbonyl tetralins, and carbonyl indanes.[79c] Their structures were described by a simple common underlying skeleton, comprising a benzene ring with a *tert*-butyl or *pseudo tert*-butyl group, and a nitro or carbonyl group in *meta* position, and eight descriptors. They consisted of six steric descriptors –corresponding to five benzene-ring substituents and one of the heteroatoms– and two electronegativity descriptors related to the hydrogen-bond acceptor. After training, the musk odour predictability attained 80%—much better than the 66% of correct classification obtained using the discriminant method.

More frequent are studies of chemically restricted groups of relatively rigid musk compounds. Klopman and Ptchelintsev[80] used 23 structural descriptors (15 activating and 8 desactivating) and clog *P* in a QSAR equation of the musk odour of non-nitro aromatic musks, obtained using the CASE (computer automated structure evaluation) technology with 152 compounds. The subsequent *Multi-CASE* analysis identified nine structural determinants favourable for the *musky* scent as well as seven thwarting fragments. The system was able to predict the odour of 18 compounds out of a subset of 20 randomly selected compounds. An analysis showed some overlap between the structural requirements for *musky* odour in nitro and non-nitro musks. Similar QSAR studies with reported high-predictive power of the elaborated models, in which the lipophilicity of the compounds plays an important role, were recently carried out by Yoshii *et al.*,[81] and Jain *et al.*[82]

The flexible macrocyclic ketones and lactones, for which minor structural changes trigger dramatic changes in odour are conspicuously absent in these investigations. Another feature that a fragrance chemist would like to find in the musk QSAR studies is an evaluation of the predictive power of the generated *olfactophore* models, based on a large and diverse enough set of compounds not used in the generation of these models.

3 SYNTHESIS OF ODORANTS

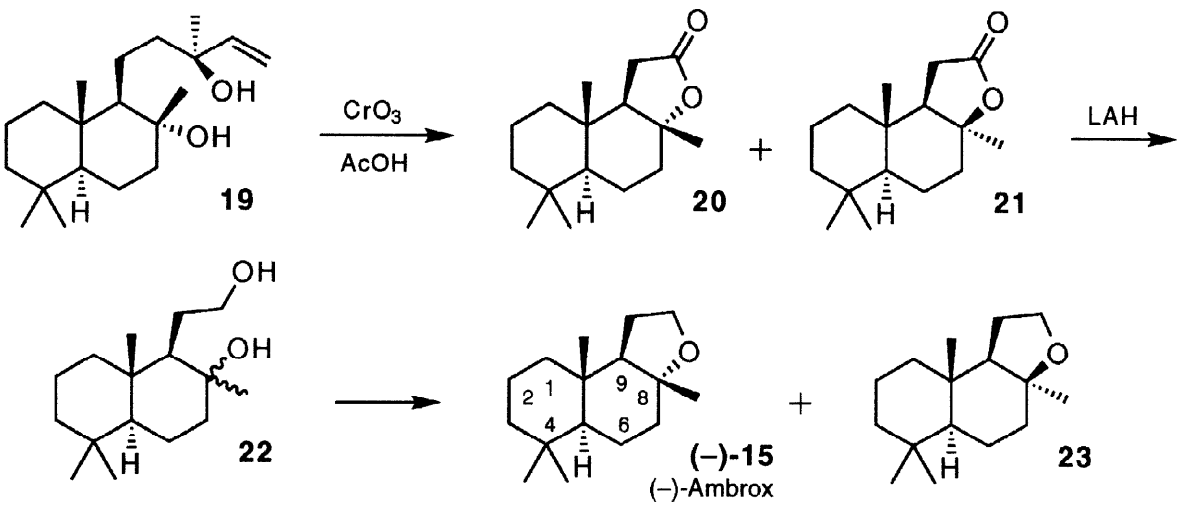
As certain chemical classes, certain skeletons or *olfactophores*, and certain functional groups or *osmophores* are key for an odour, we are going to discuss chemistry by odour types. And since there are odour transitions from *ambery* to *woody*, from *woody* to *sandalwood-like*, from *sandalwood-like* to *musky*, as well as from *musky* to *floral*, we will also proceed this way.

3.1. *Amber Odorants*

The commercially most important amber chemical is the tricyclic ether (–)-Ambrox® [(–)-**15**].[52] The history of this material, which is central to fragrance creation, is a fascinating chapter of natural product and synthetic chemistry with a commercial background.[83] Today (–)-**15** costs around US$ 1000 per kg, and its world consumption is 15–25 tons per year.

(–)-**15** was first prepared from (–)-sclareol (**19**)[84] by oxidation of the side chain and formation of the γ-lactones (+)-sclareolide (**20**) and (–)-*iso*-sclareolide (**21**), which have been reduced to the diols **22**. Cyclization of the diols then leads to the desired ether (–)-**15** and the 8-*epi*-isomer (+)-*iso*-Ambrox [(+)-**23**].

This synthesis is still the commercial one, as the diterpene sclareol is a relatively cheap (US$ 150–200 per kg) and abundant constituent of clary sage oil (*Salvia sclarea* L.). Besides technical improvements of the oxidation, reduction, and cyclization steps, it is difficult to compete with this old synthesis.

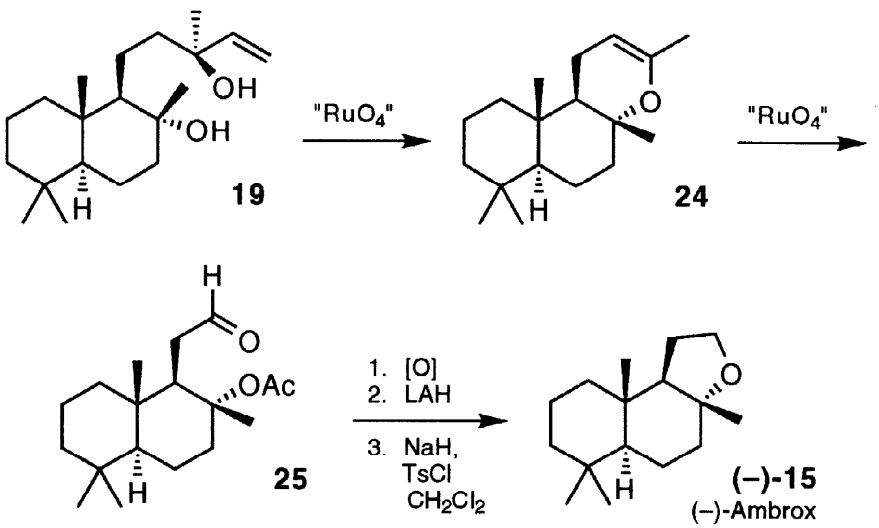


An impressive approach to (–)-**15** is the microbiological conversion of **19** to **20**, and to the (8*R*)-**22** diastereomeric diols by *Hyphozyma roseoniger*[85] or *Cryptococcus albidus*,[86] demonstrating an environmentally friendly oxidation.

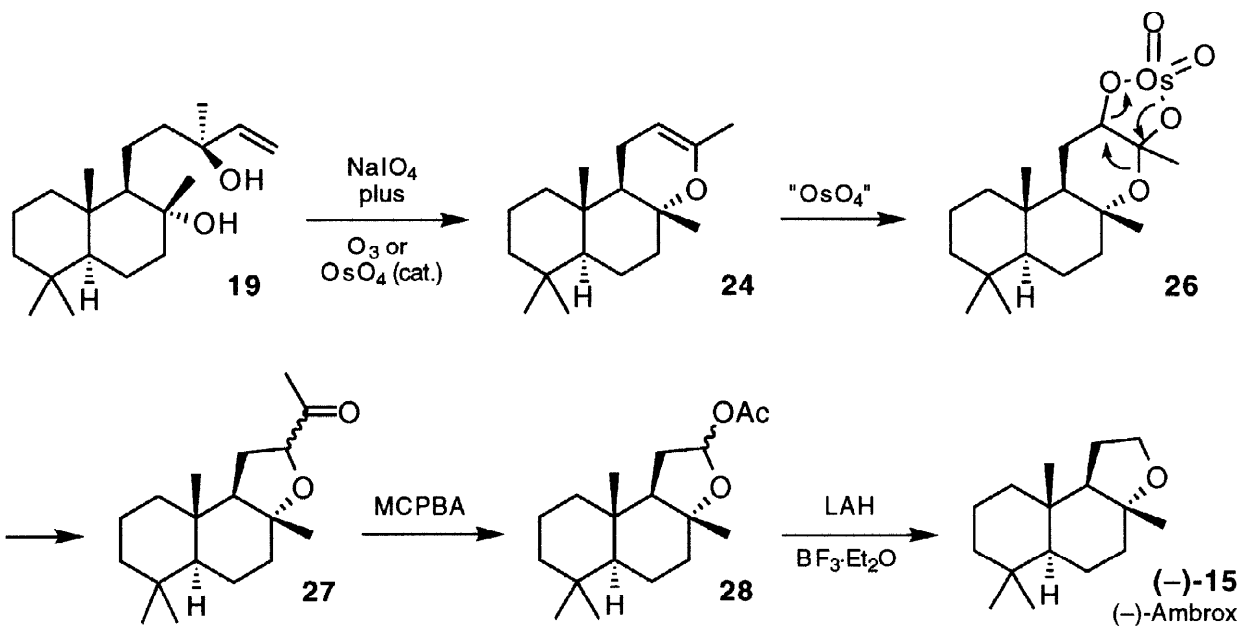
The ruthenium tetroxide oxidation of sclareol (**19**) to sclareolide (**20**) is strongly dependent on the reoxidation agent used. Sodium periodate gives only 18% yield of **20**, whereas calcium hypochlorite gives about 54%.[87] Mechanistically, the double-bond of (–)-sclareol is first cleaved to the corresponding α-hydroxy acid, which is further oxidized –under decarboxylation– to give a methyl ketone, that cyclizes in the course of the reaction to enol ether **24**. Ruthenium-tetroxide oxidation of **24** then provides the aldehyde **25**, that is converted *via* sclareolide (**20**) into the target molecule (–)-Ambrox [(–)-**15**].

Another ingenious oxidation of **19** has been described with the system OsO_4–$NaIO_4$ (1:70).[88] The final product of this oxidation **27** is isolated in high yield. The envisaged synthesis of (–)-**15** has been completed in high yield through a Baeyer–Villiger oxidation to the acetate **28** with subsequent reduction with lithium aluminium hydride in the presence of $BF_3 \cdot Et_2O$.

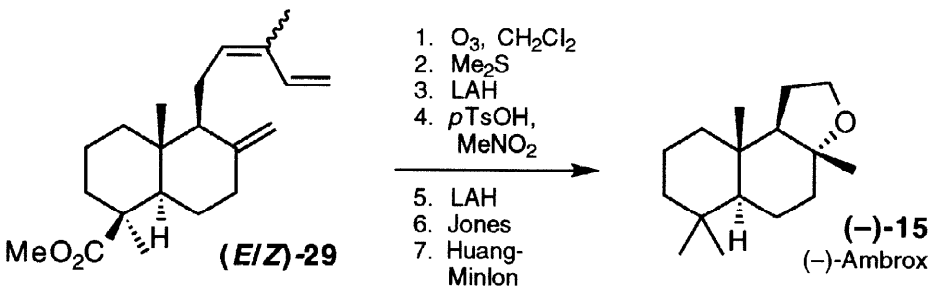
The above transformation **19**→**27** has been improved, and made more attractive for industrial application by the use of O_3–$NaIO_4$ (77% yield) instead of the toxic and expensive OsO_4.[89]



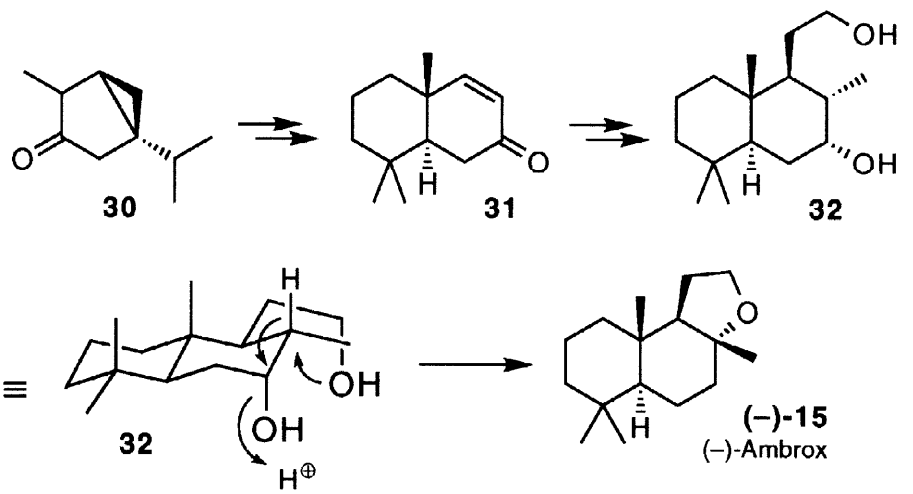
Apart from the well-established route to Ambrox [(–)-**15**] starting from **19**, different other natural products have been used as starting materials. Some of these syntheses have no industrial practical value for now, but they certainly have their educational and aesthetic merits showing the lively imagination of organic chemists.



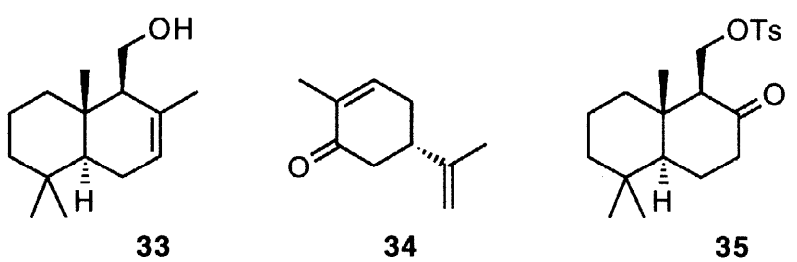
The communic acid methyl ester (*E*/*Z*-**29**), a close relative of sclareol (**19**), has been ozonized and reduced, and then cyclized under Büchi-conditions. In three more steps, necessary for the transformation $CO_2Me \rightarrow Me$, (–)-**15** was synthesized.[90]



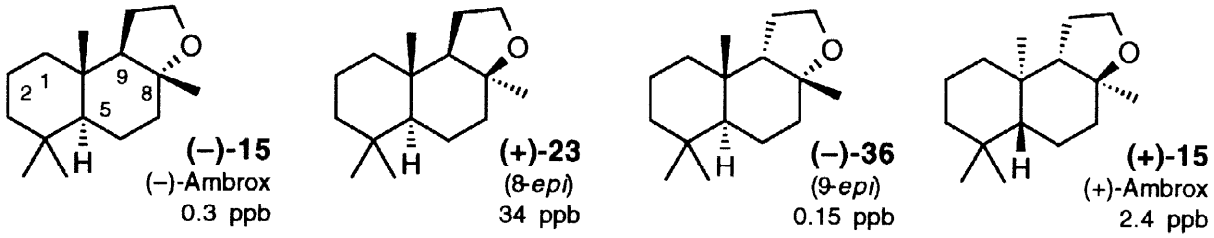
The monoterpene thujone (**30**), a waste material of the Canadian forest industry, is a less obvious starting material for the synthesis of (–)-**15**. Nevertheless it has been converted[91] to (–)-Ambrox in 15 steps through the intermediates **31** and **32**, culminating in a beautiful ring closure of the 1,5-diol moiety of **32** to the tetrahydrofuran ring of (–)-**15**.



Drimenol (**33**) has been transformed to (–)-**15** in six steps,[92] whereas (*S*)-(+)-carvone (**34**) needed some 13 steps[93] to reach the target. The enantiomerically pure tosylate **35**, which can be prepared from geranylacetone, furnished (–)-**15** after 15 steps.[94]

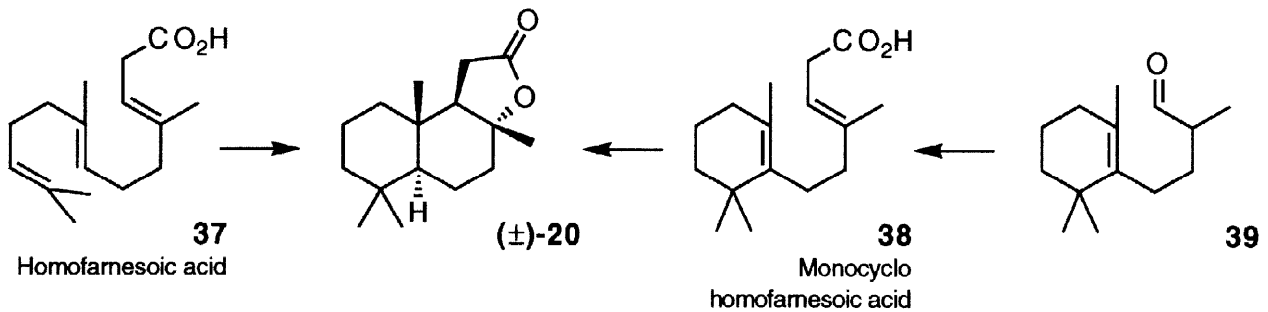


For the study of structure-odour relationship of ambery compounds the diasteromers,[95a] enantiomers,[95a] nor-compounds,[95b] ring-opened analogues[53b] and 5β-isomers[95b] of (–)-**15** have been prepared. While (–)-**15** has an odour threshold of 0.3 ppb, the 9-*epi* isomer (–)-**36** is even slightly more powerful with a threshold of 0.15 ppb. Yet, the enantiomer [(+)-**15**] is about 10 times weaker (2.4 ppb), and the 8-*epi* isomer (+)-**23** even 100 times weaker (34 ppb). The racemate (±)-**15** is only slightly weaker than (–)-**15** with a threshold of 0.5 ppb, and its odour is very similar to that of (–)-**15**.



Sclareol (**2**) constitutes the only practical starting material for (–)-**15**. Therefore, the available quantity of (–)-**15** is limited, and its price accordingly high. The increasing demand for this valuable amber odorant on the one hand, and the fact that racemic Ambrox [(±)-**15**] is olfactorily very similar to (–)-**15** on the other hand, prompted different laboratories to design new syntheses of (±)-**15**.

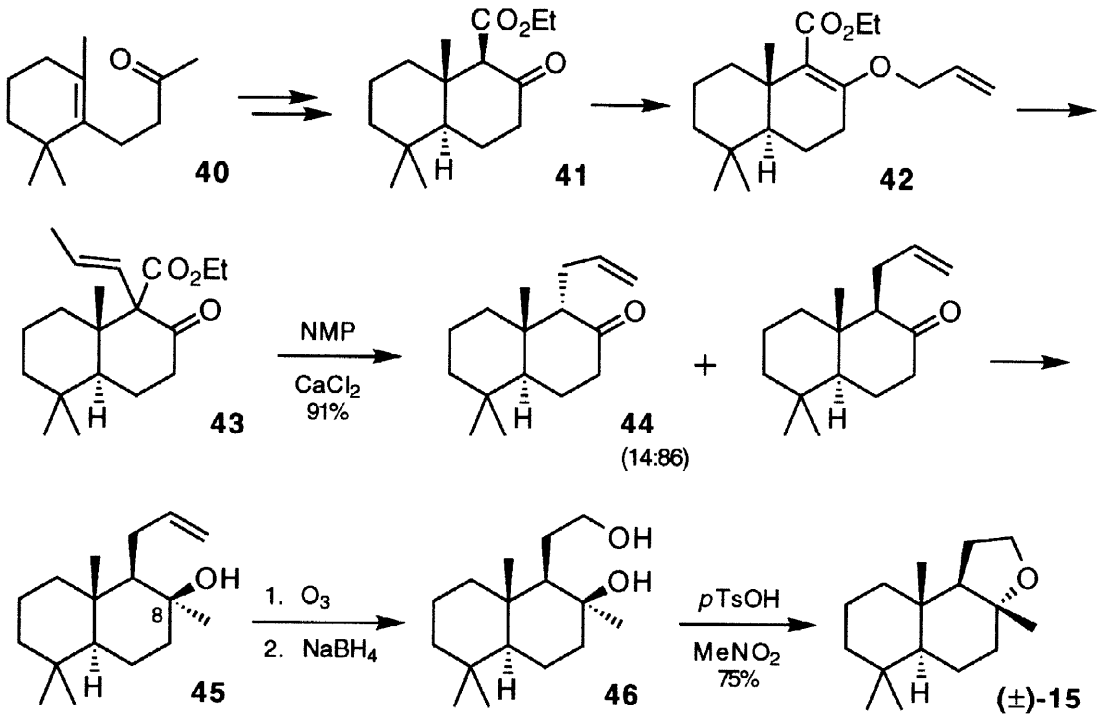
As long ago as the fifties the acid-catalyzed cyclizations of homofarnesoic acid (**37**) and monocyclo homofarnesoic acid (**38**) to racemic sclareolide [(±)-**20**] and its diastereomers were reported. [96,97,98]

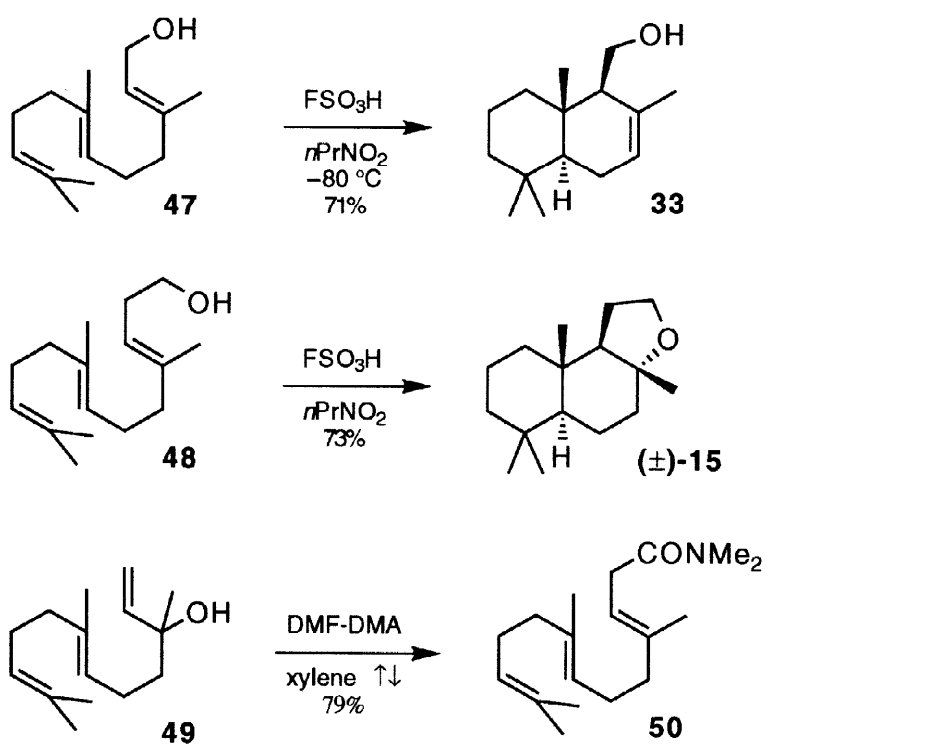


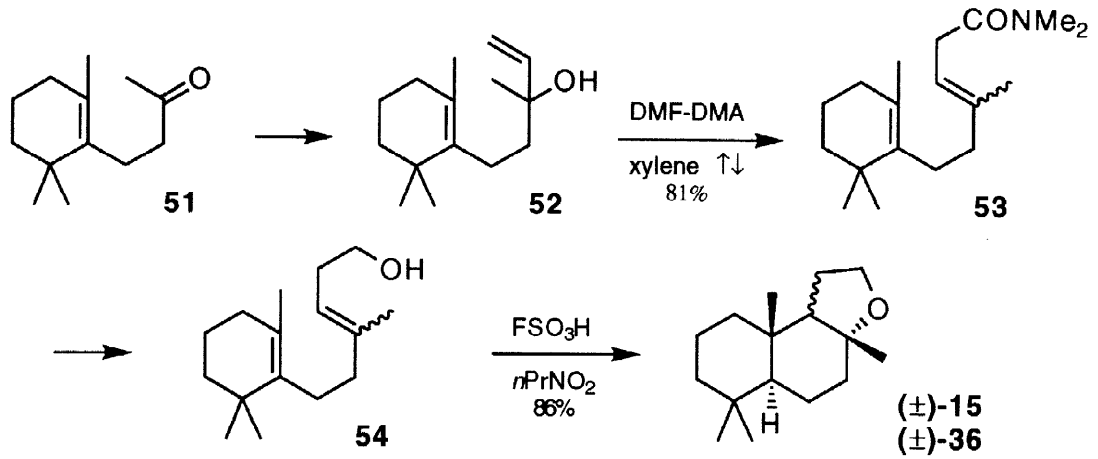
The cyclization of (*E*)-**37** has been studied in detail,[99] and it was found that at –78°C in dichloromethane, catalyzed with $SnCl_4$, (±)-**20** can be obtained in 82% yield. Similarly, treatment of (*E*)-**38** with trifluoroacetic acid at 0°C for 2 h provided (±)-**20** in 64% yield, whereas (Z)-**38** under the same conditions gave (±)-9-*epi*-**20** in similar yield.[100] In the cyclization of both **37** and **38** the stereochemistry of the double bonds (*E vs Z*) is translated to the stereochemistry of the products *via* the preferred chairlike transition state. Thus, the feasibility of this route to (±)-**20**, which subsequently is processed to (–)-**15** in two steps, depends on the availability of (*E,E*)-**37** and (*E*)-**38**, respectively. For the preparation of (*E,Z*)-**37** farnesyl bromide was treated with potassium cyanide and the resulting nitrile was hydrolyzed.[101] Another route to (*E,Z*)-**37** comprises the treatment of nerolidol with carbon monoxide in the presence of palladium dichloride.[102] (*E,Z*)-**38** can, for instance, be prepared from the dihydro C_{14}-aldehyde **39** *via* a Knoevenagel condensation with malonic acid,[103a] or with methyl cyanoacetate and subsequent hydrolysis.[103b] Wittig C_3-elongation of dihydro β-ionone (**40**) also furnishes **38**.[103c]

The readily available β-keto ester **41** [from dihydro β-ionone (**40**)] has been converted to (±)-**15** in six steps.[104] The introduction of the side chain had to be carried out by the detour through the *O*-allyl group (**41**→**42**→**43**→**44**), because C-alkylation of **41** failed. Grignard reaction with **44** furnished in high yield and stereoselectivity the tertiary alcohol **45** with the wrong stereochemistry on C-8. This has been very elegantly corrected in the cyclization step of the diol **46**. Kinetically controlled cyclization with a sterically favoured equatorial approach of the intramolecular nucleophile to the tertiary carbonium ion yielded (±)-**15** in good yield and high selectivity.

A couple of variations to this approach have been published,[105] but the breakthrough in the synthesis of *rac*-Ambrox [(±)-**15**] came about by the biomimetic, acid-catalyzed cyclization of the polyene alcohol homofarnesol (**48**).


CO2Et
O
40
41
42
43
NMP
CaCl2
91%
44
(14:86)
OH
8
1. O3
2. NaBH4
45
46
pTsOH
MeNO2
75%
(±)-15

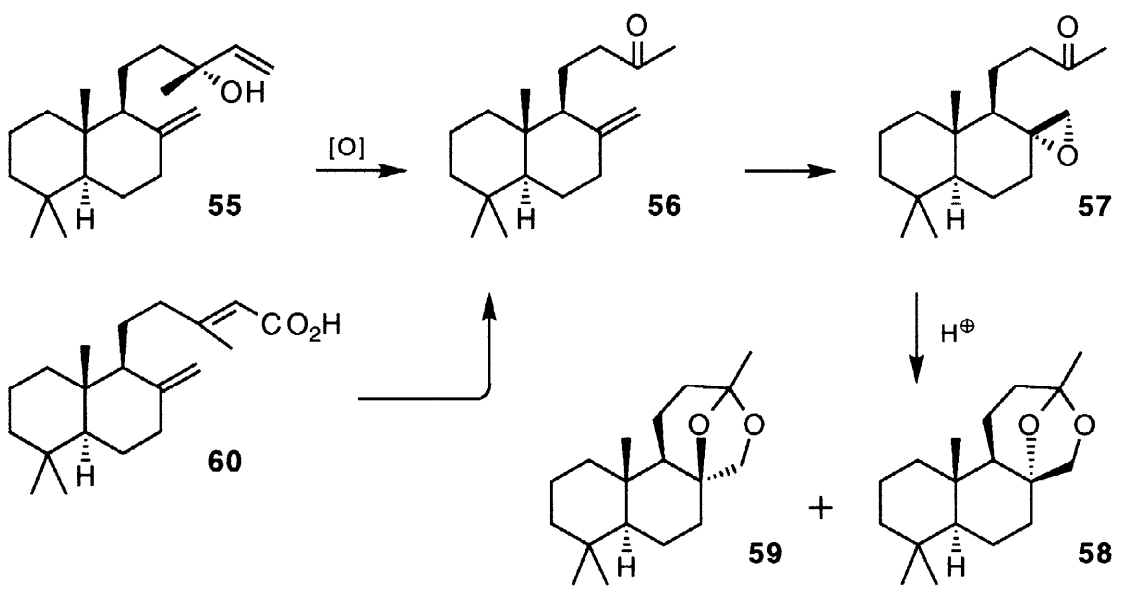

OH
47
FSO3H
nPrNO2
−80 °C
71%
33
48
73%
(±)-15
DMF-DMA
xylene ↑↓
79%
49
CONMe2
50

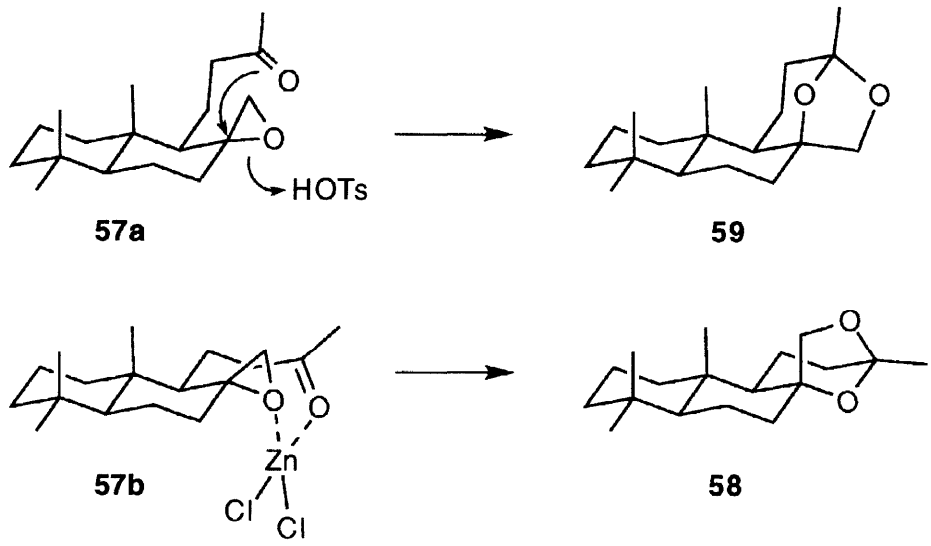


The lower homologue, (*E*,*E*)-farnesol [(*E*,*E*)-**47**] was first successfully cyclized to drimenol (**33**).[106] This low-temperature cyclization with fluorosulfonic acid was then used for the *one step* synthesis of (±)-**15** from (*E*,*E*)-homofarnesol [(*E*,*E*)-**48**] in 73% yield.[107]

A detailed study has been undertaken to understand and optimize this industrially important process.[108] All four stereoisomers of homofarnesol (**48**) were separately treated with fluorosulfonic acid, and the product mixtures analyzed. The most important result was, that under these conditions the isomerisation of (*E*,*E*)-**48** to (3*Z*,7*E*)-**48** is fast enough to compete with the cyclization. Thus, pure (*E*,*E*)-**48** furnishes a mixture of 40% (±)-**15** and 35 % (±)-**36** (9-*epi*-**15**). This isomerisation diminishes slightly the synthetic elegance, but since (–)-**36** is even more powerful than (–)-**15**, it is no problem from the olfactory point of view.

As with the corresponding homofarnesoic acid (**37**), the feasibility of the process depends on the accessibility of (*E*,*E*)-**48**, or the corresponding monocyclo homofarnesol (*E*)-**54**. (*E*)-Nerolidol [(*E*)-**49**] can be transformed to the separable 2:1 mixture of the amides **50**. (*E*,*E*)-**50** was reduced to (*E*,*E*)-**48**, and then cyclized with chlorosulfonic acid at –78°C in nitropropane to afford a mixture of (±)-**15** and (±)-**36** in 75 % yield.[109] (*E*)-Configurated monocyclo homofarnesol [(*E*)-**54**] has been prepared from dihydro-β-ionone (**51**) through the intermediates **52** and **53**. Cyclization of (*E*)-**54** under the same conditions provided the mixture of (±)-**15** and (±)-**36** in 86% yield.[109]





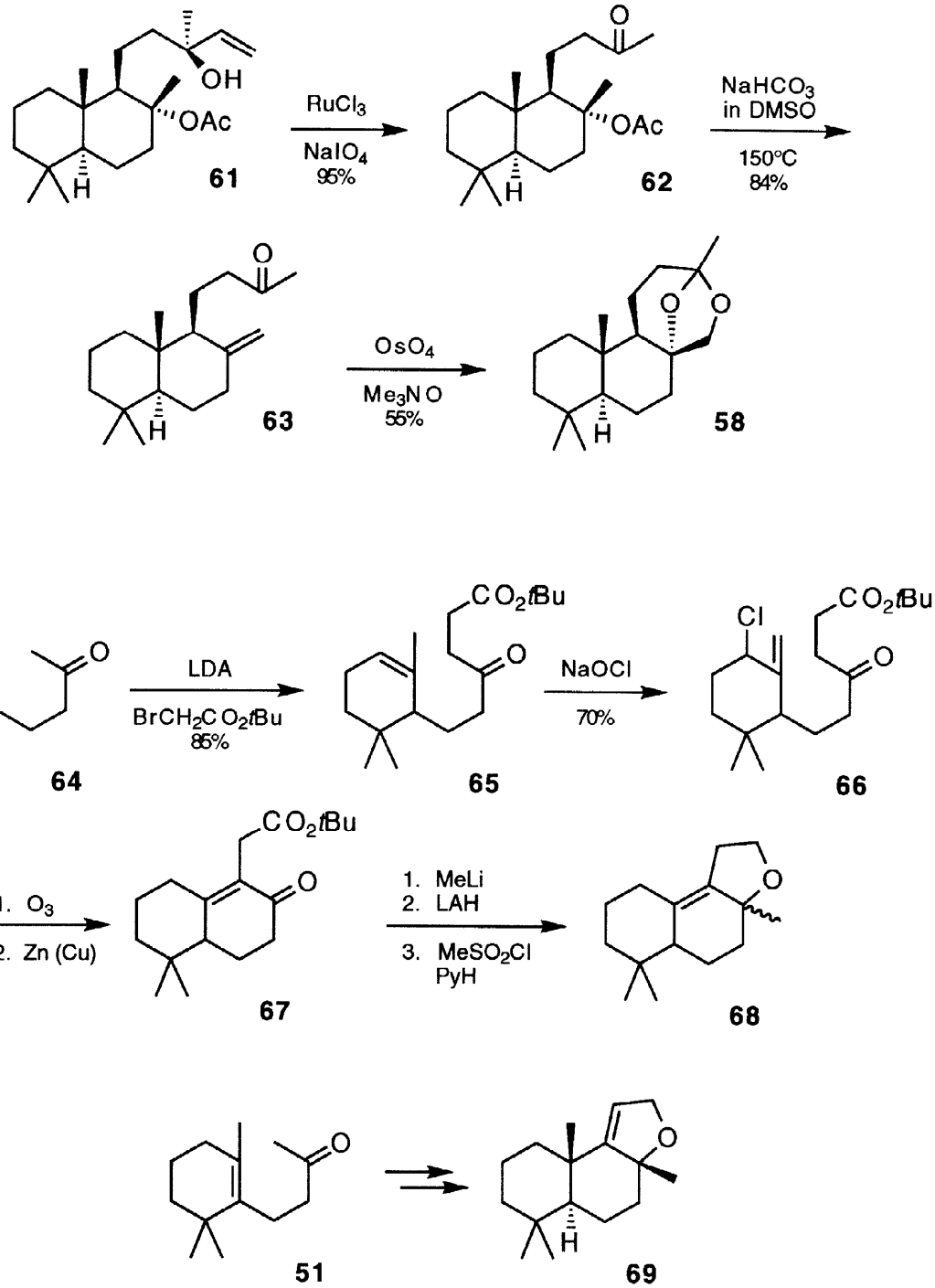
Next to Ambrox® (**15**), Amberketal (**58**) is one of the best known amber odorants. It also has already a long history, and its most straightforward preparation is that from manool (**55**),[110–113] which is a commercialized constituent of *Halocarpus biformis* (Podocarpaceae) from New Zealand.[114] This synthesis proceeds through the intermediate methylene ketone **56**, and each synthetic variant is judged on how it solves the problem of preparing **56** and by the ratio of **58** *vs.* **59**. The *epi*-8-isomer **59** is virtually odourless;[111] thus, the more selective the transformation to the powerful epimer **58**, the better.

Besides manool (**55**) also anticopalic acid (**60**) can be used as a starting material for **58** by oxidation of the corresponding ester.[115] The epoxidation of **56** with *m*-chloroperbenzoic acid is highly diastereoselective, and yields **57**. Treatment of **57** with *p*-toluenesulfonic acid in toluene furnishes selectively the odourless isomer **59**, whereas zinc chloride in dichloromethane at 18°C yields only **58**. This demonstrates the subtility of the ring closure.[115] It has been shown, that clays, *e. g.* vermiculite, also catalyze the ring closure of **57**→**58** stereoselectively.[115,116] The striking difference in the ring-closure reaction catalyzed with *p*-toluene sulfonic acid and zinc chloride, respectively, has been rationalized with **57a** for the case of protonation of the epoxide **57**, and subsequent attack of the carbonyl oxygen on the developing tertiary centre. In the case of the Lewis acid catalysis a complexation as in **57b** has been assumed, which would ensure an attack of the carbonyl group from the α-face, providing **58**. Communic ester (*E*/*Z*)-**29** was used as a natural triterpenic starting material for **58**.[117] The handicap of this approach is the necessary three-step sequence to convert the carbalkoxy group into the methyl group.

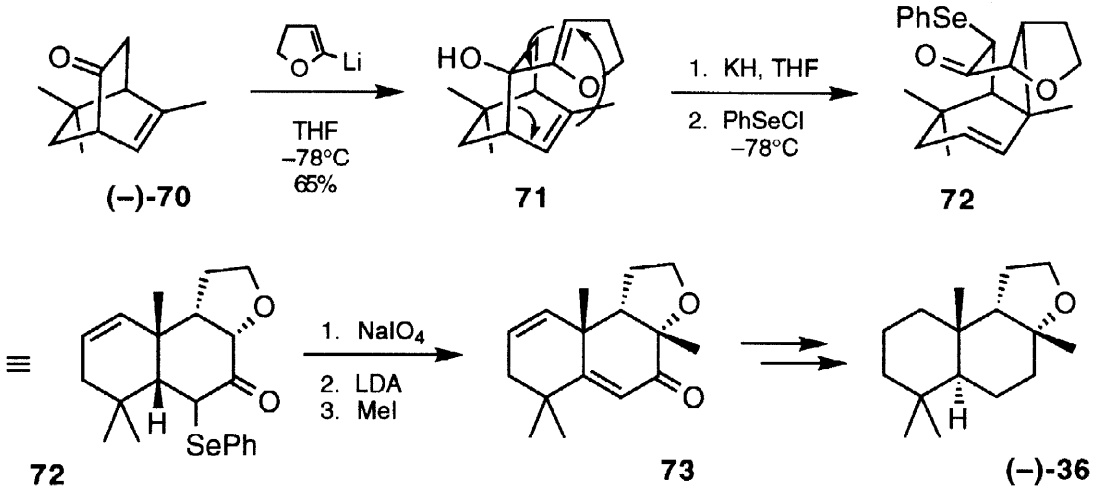
Sclareol (**19**) is better suited for the preparation of Amberketal (**58**), and has consequently been used for this purpose.[118–120] The monoacetate of sclareol (**61**) could be oxidized very efficiently to the ketoacetate **62** with a catalytic amount of ruthenium trichloride and a stoichiometric amount of sodium periodate. Pyrolysis of **62** led in high yield to the γ-isomer **63** as the main product, which finally was transformed into Amberketal (**58**) with a catalytic amount of osmium tetroxide and trimethylamine oxide.

The commercial importance of (–)-Ambrox® [(–)-**15**] and later that of (±)-Ambrox [(±)-**15**] prompted different, but mostly industrial laboratories to search for new analogues with the aim of being either cheaper or possessing additional odour aspects.

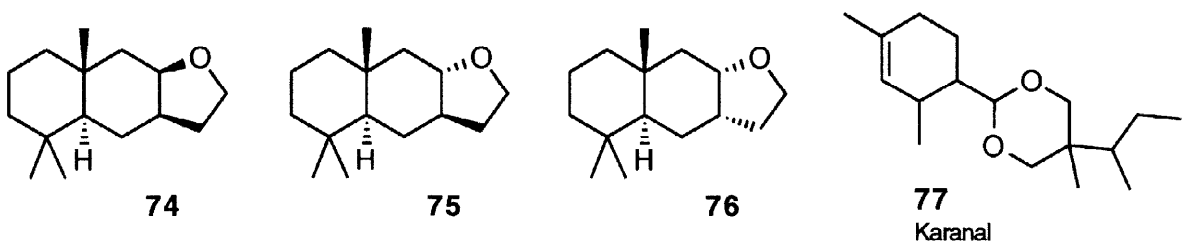
One of such attempts was the synthesis of *dehydro-nor*-Ambrox **68**.[121] Dihydro-α-ionone (**64**) was alkylated to give **65**, which by treatment with sodium hypochlorite was transformed into **66**. Ozonization, followed by ring closure and reduction, led to **67**, which after three additional steps gave the target **68**. This compound displays an *ambergris* aspect with a *warm, wood-tobacco* tonality. *Dehydro*-Ambrox (**69**), which has a *woody-ambery* character was prepared by using the β-isomeric starting material **51**.[122]



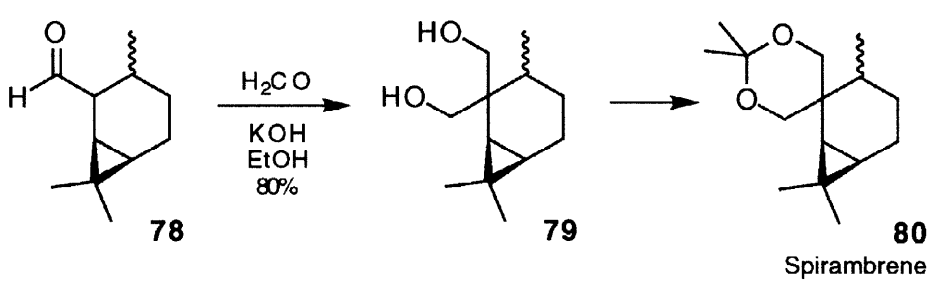
As already mentioned, the stereoisomer (–)-9-*epi*-Ambrox® [(–)-**36**] is more powerful than Ambrox® [(–)-**15**] itself, although only by a factor of two. In spite of this fact, this compound hardly earned any synthetic interest. One exception is a demonstration of the synthetic potential of the oxy-Cope rearrangement.[123,124] The enantiopure bicyclic ketone [(–)-**70**] was transformed to the oxy-Cope starting material **71** with lithium dihydrofuran. Under usual rearrangement conditions **71** yielded the corresponding enolate, which *in situ* reacted with phenylselenyl chloride to provide **72**. Introduction of the double bond by eliminiation and subsequent alkylation furnished **73**, which finally, after four more steps, gave the target molecule (–)-**36**.



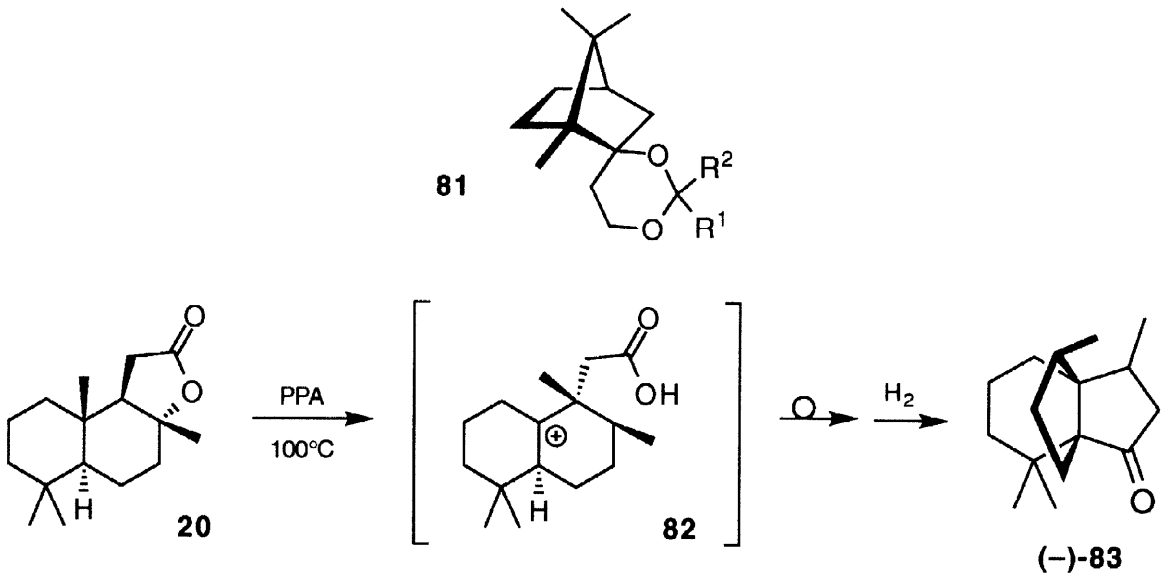
Calculations of the *steric accessibility* of the functional group led to the syntheses of three analogues **74**, **75**, and **76**, all of which possess a *typical ambergris odour*.[53]



Two interesting cases in the context of amber odorants are **77**[125] and **80**,[126] because they are structurally new in this field. **77** is derived from the commercial, *green, floral* smelling aldehyde, Cyclal C, and has been commercialized as Karanal® (Quest). It has an intense and persistent *amber-like* odour with *woody, floral and lily-like* tonalities.



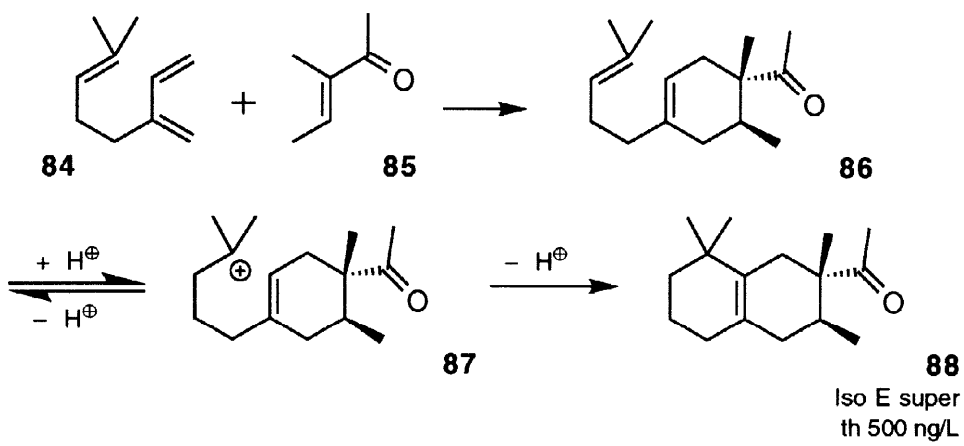
More interesting is the spiroketal **80**,[126] known as Spirambrene® (Givaudan Roure). It is synthesized from 2-formyl carane (**78**) in only two steps. Spirambrene® (**80**) displays a powerful *ambery, woody, slightly aldehydic* odour, and contributes significantly to »Kenzo pour homme« (Kenzo, 1991), and the beautiful creation »Oui-Non« (Kookaï,1993).



The *ambery-woody* compounds of the general formula **81** constitute another class of interesting new amber odorants.[127] They were found with the help of one of the amber *olfactophore* models presented in chapter 2.2.[38] Surprisingly, the propellane (–)-**83** has also an intense *ambery-woody* note.[128] The formation of dehydro-**83** from sclareolide (**20**) was completely unexpected, and can be rationalized through a series of (1,2)-shifts with **82** as plausible intermediate.[128]

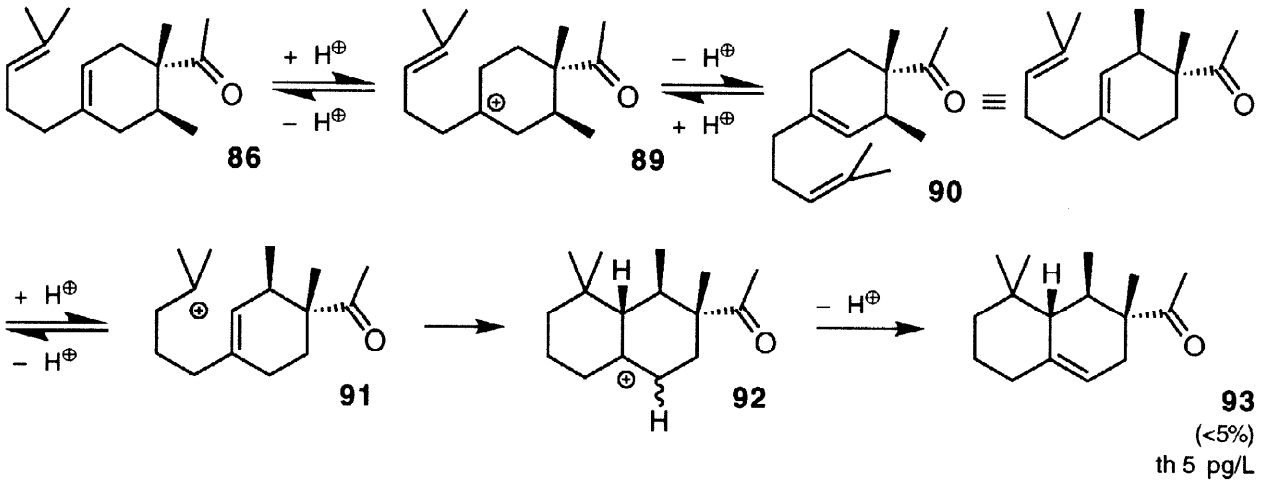
3.2 *Woody Odorants*

Perfumes like »Trésor« (Lancome, 1990), »Casmir« (Chopard, 1991), and »Dune« (Dior, 1991) marked a new style of perfumery technique—massive constructions around a comparatively small number of long-lasting synthetic materials, that could be used at very high levels, of up to 25%. The woody odorant Iso E super® (**88**) is perhaps the most important building block for this new type of formulation. Almost equal amounts of Hedione®, Galaxolide®, methyl ionone, and Iso E super® (**88**) make up some 80% of the formula of Trésor.[129]

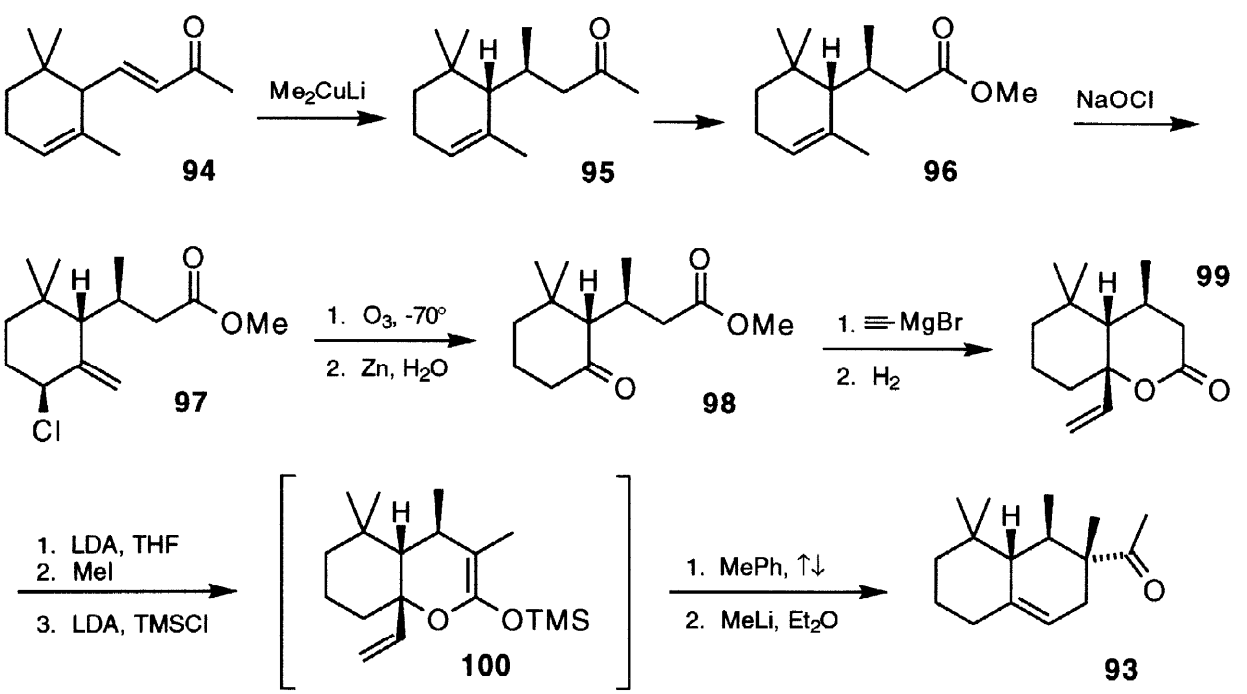


Iso E super® (**88**), that possesses a *rich, warm-woody odour with a shade of amber* was claimed in 1973 by IFF.[130] Its industrial synthesis starts with the Diels–Alder reaction of myrcene (**84**) with 3-methylpent-2-en-2-one (**85**), followed by an acid-catalyzed cyclization, which leads to **88**. Surprisingly, an analysis carried out at Givaudan Roure showed that the compound responsible for the *intense woody* odour of this product is not **88**, but a small impurity (<5%) with an odour threshold of 5 pg/L, and the structure **93**.

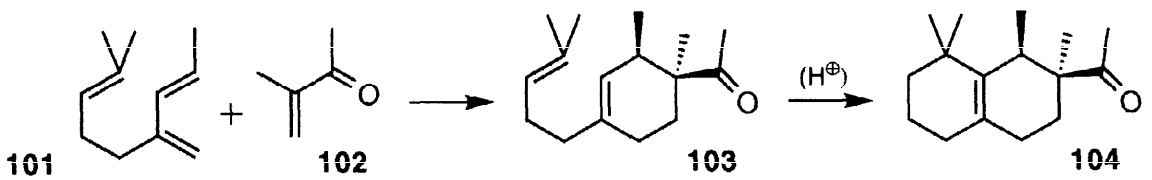
The formation of **93** in the industrial synthesis of **88** is not obvious at first sight. However, protonation of **86** does not lead only to **87** but also to **89**, which can give **90** due to a protonation-deprotonation equilibrium. Its cyclization provides **92**, and finally, after deprotonation, the active compound **93**.



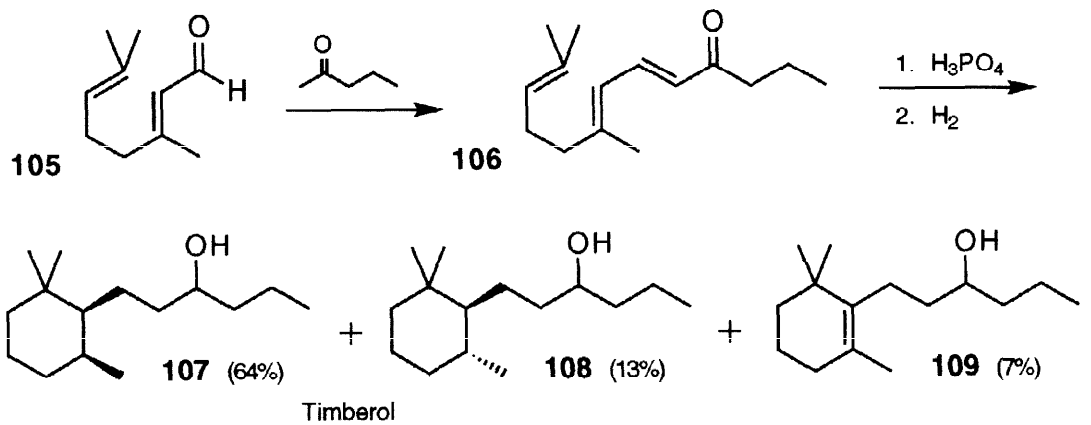
A synthesis of **93** was carried out in order to prove unequivocally its structure.[131,132] α-Ionone (**94**) was diastereoselectively β-methylated by cuprate addition, oxidized, and transformed into **97** by the action of sodium hypochlorite. An ozonolysis, and subsequent zinc reduction gave **98**, that after addition of ethynylmagnesium bromide, and hydrogenation furnished **99**. This was then methylated and transformed by [3,3]-sigmatropic Ireland-Claisen rearrangement[133] to provide after reaction with methyl lithium selectively the powerful impurity of Iso E super® **93**.

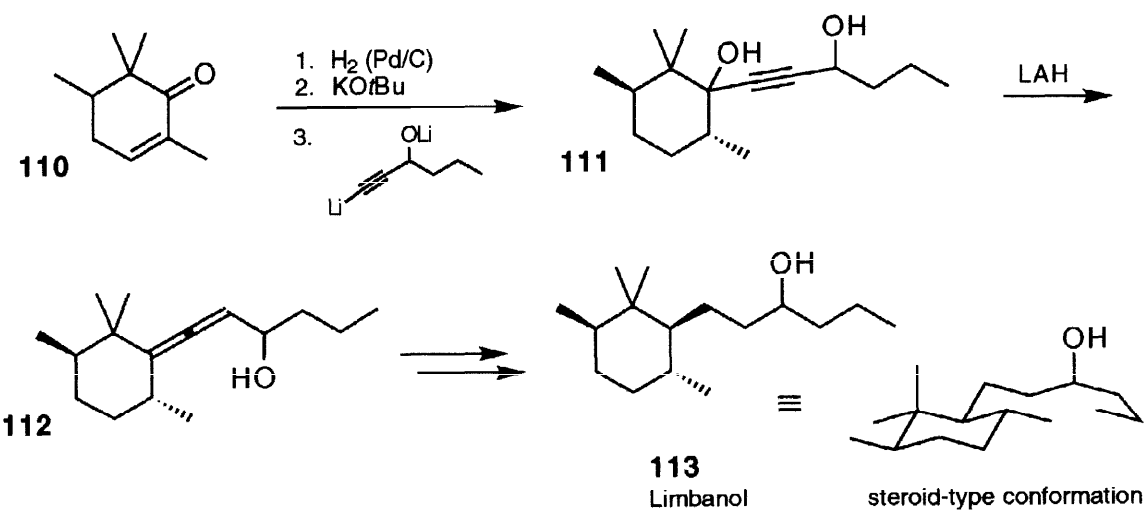


Apparently, this synthesis was far too complicated to be carried out on industrial scale. Therefore, numerous derivatives of **93** were synthesized, of which **104** turned out to be one of the best. The synthesis by Diels–Alder reaction of **101** with **102**, and subsequent cyclization is well suited for industrial production. The odour threshold of **104** is about the same as that of **93**, and its *elegant warm-woody, sweet-powdery* smell is even more attractive.



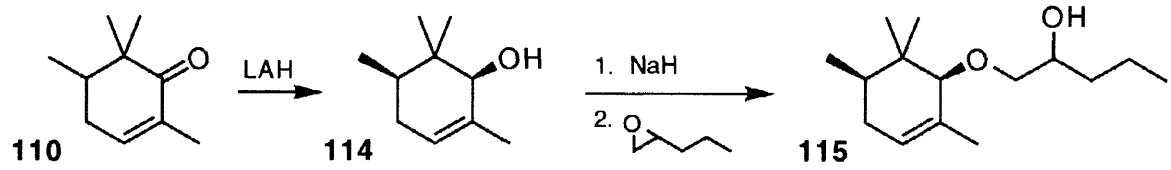
Another interesting commercial product of *woody* tonality is Timberol® (**107–109**) from Dragoco. It has a *powdery-woody odour with animal undertones*, and has been used, for example, in »Marbert Man« (Marbert, 1977) and »Basara« (Shiseido, 1993) in up to 4% and 6%, respectively. Its commercial synthesis[134] commences with a classical aldol condensation of citral (**105**) and 2-pentanone. Subsequent cyclization and complete hydrogenation provides a mixture of mainly **107**, **108**, and **109**.



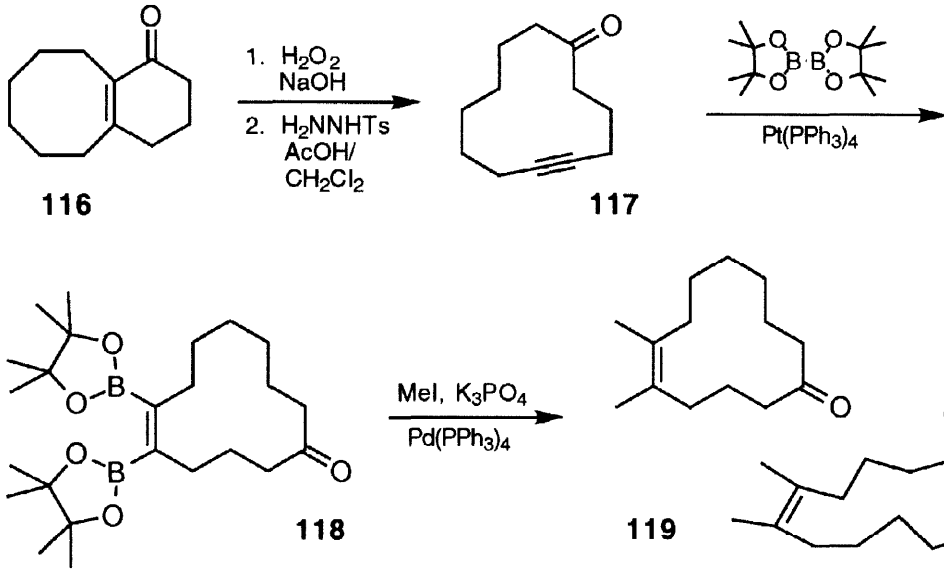


Because of the good performance of this mixture a Firmenich group[135] did an in-depth study around Timberol® (**107–109**), and found the (*E*)-derivative **108**, which makes up only 13% of the commercial product, to be mainly responsible for the odour characteristics. They attributed its *steroid-type sweaty-animal* undertones, to a steroid-type folding.[135] By transition from the ionone- to the irone-series they planned to accentuate the steroid-type shape; thus, intensifying the *woody* odour character. The resulting *neo*-tetrahydroirone analogue (**113**) is registered as Limbanol®.

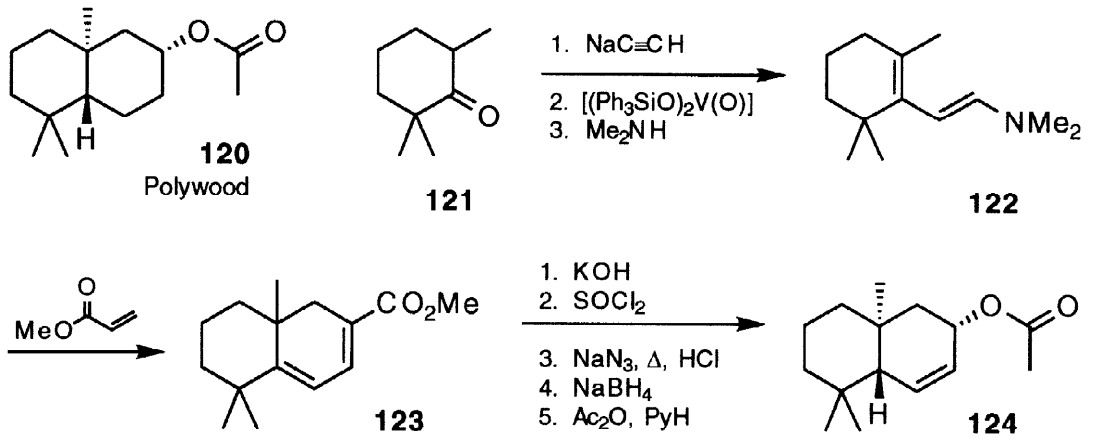
The first synthesis of Limbanol® (**113**) started from 2,5,6,6-tetramethylcyclohex-2-en-1-one (**110**),[136] which was hydrogenated, isomerized, and alkylated to provide **111**. Reaction with lithium aluminium hydride furnished **112**, that was then transformed to the target molecule **113**. As predicted, Limbanol® (**113**) possesses a *woody-animal, steroid-type* odour of higher intensity than that of Timberol® (**107–109**).



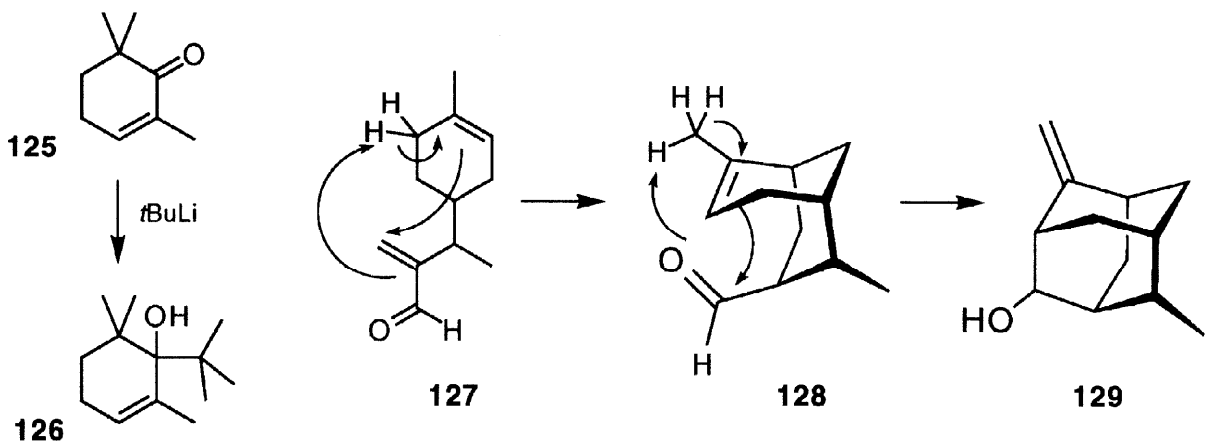
Yet, the *dehydro*-oxa-analog **115** turned out to be more accessible than Limbanol® (**113**), while being very similar in odour and almost equal in strength.[135] Reduction of **110** by lithium aluminium hydride, and nucleophilic opening of 1,2-epoxypentane constitutes a two-step sequence to a Limbanol®-type odorant.



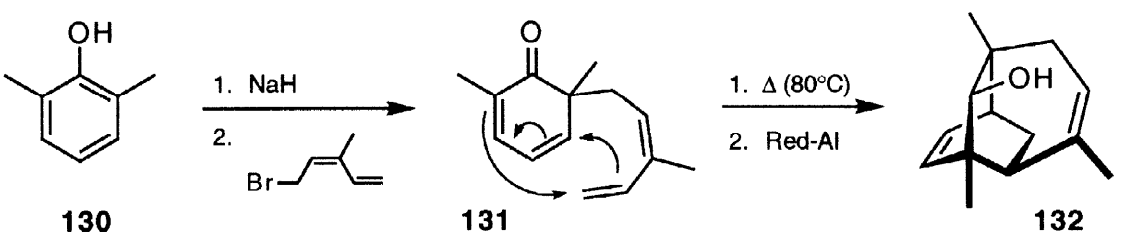
With the idea to mimic the B-C-D part of the steroid-type conformation of Limbanol (**113**) by a medium-sized ring, compound **119** and its corresponding alcohol were designed by molecular modelling.[137] The Eschenmoser–Ohloff fragmentation of **116** furnished cyclododec-5-yn-1-one (**117**), that was (*Z*)-dimethylated *via* diboration with dipinacolyl hypodiborate, and subsequent Suzuki coupling. While the corresponding alcohol turned out to be very weak, at least ketone **119** had an *animal woody* odour—in contrast to cyclododecanone, which has only a *camphoraceous* odour profile.[137]



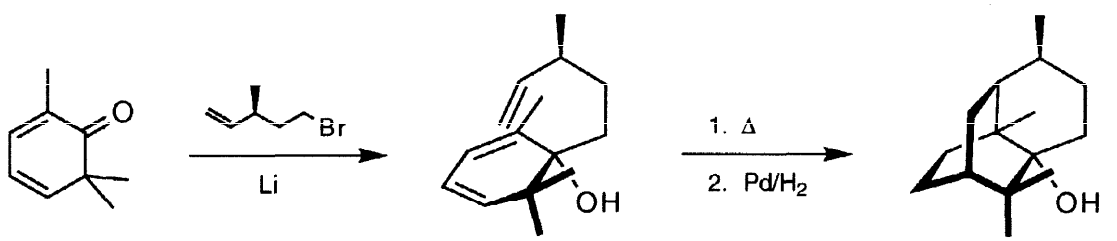
Polywood® (**120**), an old, *warm, dry-woody* smelling perfumery synthetic, was also object to some more research.[138,139] The dehydro derivative **124** of Polywood® (**120**) was prepared by a regioselective [4+2] dieneamine cycloaddition of methyl acrylate to **122**, using **121** as starting material. A five-step sequence led from the Diels–Alder adduct to the target compound **124** that possesses an accentuated *woody* odour note.[138]



A simple addition of *tert*-butyl lithium to the related starting material 2,6,6-trimethylcyclohex-2-en-1-one (**125**)[140] led the Firmenich group to the highly hindered tertiary alcohol **126**,[141] which showed a pronounced *patchouli-type, woody-earthy* odour. Similar in odour, though at first glance quite different in structure, is the captive material **129** of IFF.[142] An ene reaction transforms the dipentene derivative **127** *via* the intermediate **128** into the fragrant adamantane derivative **129** with a *patchouli-like, woody, piney-camphoraceous* odour.

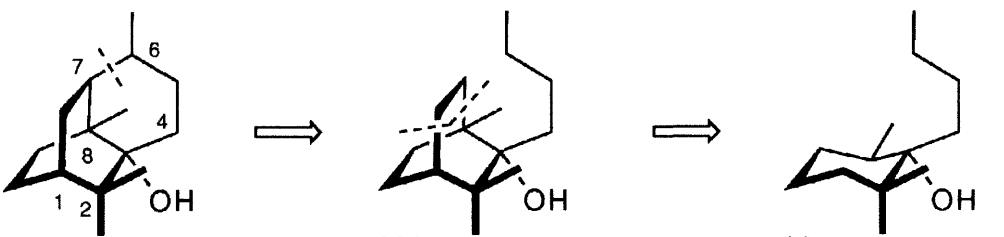


In 1971, an efficient synthetic sequence of C-alkylation to the dienone of **130**, Claisen rearrangement, and intramolecular Diels-Alder cycloaddition was developed,[143] that led from phenols to tricyclic ketones. Most interesting from the olfactory point of view was compound **132**, prepared from the corresponding unsaturated tricyclic ketone by reduction with sodium bis(2-methoxyethoxy)aluminium hydride. It possesses a *camphoraceous, patchouli, earthy-woody* odour, and its structure is related to that of the the odour vector of patchouli oil (–)-**135**.



133 **134** **(–)-135**
(–)-patchoulol

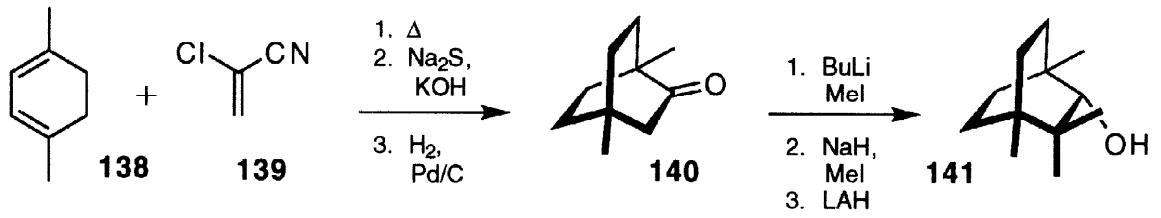
Patchouli (*Pogostemon cablin* Benth.) is a small shrub cultivated in India, the Philippines, Java, Sumatra, and Singapore. Its essential oil has a *powerful woody-balsamic odour with herbaceous, earthy, camphoraceous, and floral nuances in a well balanced manner.* The tricyclic alcohol, patchoulol (**135**), the structure elucidation of which took almost 100 years (from 1869–1967),[144] is most important for the characteristic odour of this essential oil. An elegant stereocontrolled synthesis of (–)-**135** was carried out by Näf *et al.*[145] in 1981. 2,6,6-Trimethyl-2,4-cyclohexadien-1-one (**133**) was alkylated with enantiopure (+)-3-methylpent-4-enyl bromide. An intramolecular Diels–Alder reaction in the next step, and subsequent hydrogenation furnished (–)-**135** in three steps. However, this as many other approaches to (–)-**135** or racemic (±)-**135** so far could not compete with the price of the natural product.



135
patchoulol

136 **137**

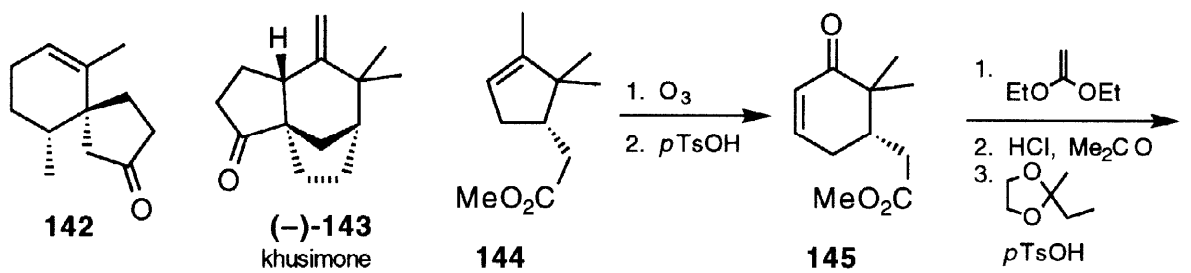
Therefore, work on the structural features responsible for the odour characteristics of **135** was carried out. Removal of the 8-methyl group increases the *woody*, and decreases the *camphoraceous* character.[146] Cutting out the C-6–C-7 bond gives compound **136**, that again had an intense *woody* odour, while the *earthy* and *camphoraceous* aspects of **135** were missing.[147] Removing also C-1–C-11 and C-7–C-8, however, results in a strong *camphoraceous, earthy odour with woody-powdery undertones.*[148] Other monocyclic analogs of **136** prepared by Weyerstahl *et al.*[148] by addition of alkyl lithium reagents to **125** also have at least one of the patchouli descriptors, *woody, earthy or camphoraceous.* As ill luck would have it, they missed **126**, though they prepared its *n*-butyl- and *iso*-butyl-analogues.[148]



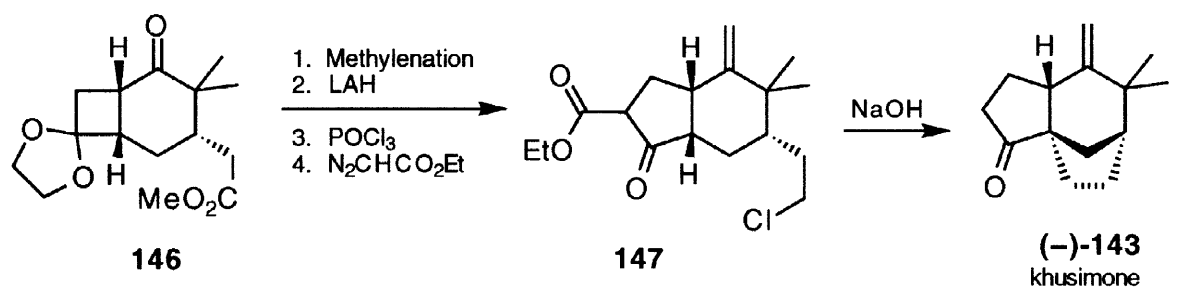
138 **139** **140** **141**

Looking at **129**, **132**, **135**, and some camphor derivatives,[149] it seems that *patchouli* odorants should be rigid, sterically hindered C_{12}–C_{15} secondary or tertiary alcohols. Compound **141** turned out to be the best of a series of bicyclo[2.2.2]octanes, that were synthesized by the Diels–Alder reaction of cyclohexa-1,3-dienes with the ketene equivalent **139**.[150] Hydrolysis, hydrogenation, and dimethylation of the resulting ketone furnished after lithium aluminium hydride reduction the odoriferous bicycloalcohol **141** with a *strong patchouli odour accompanied by woody-camphoraceous nuances*. Compared to patchouli oil, which because of its attractive price was for example used in an overdose of 40% in »Gentleman« (Givenchy, 1974), the compounds **126**, **129**, **132**, and also **141** are already competitive in terms of synthetic accessibility and production costs.

For vetiver oil, used in 20% in »Vetiver« (Guerlain, 1961), there are no such synthetics. Vetiver oil is the steam distillate from the roots of *Vetiveria zizanoides* Stapf.—a wild, tufted grass cultivated in Java, India, Réunion, and Haiti. The content of three sesquiterpenes, α- and β-vetivone and khusimol, always present in the oil, can attain 35%. They became fairly popular synthetic targets,[151] but there is no consensus[152] on their contribution to the *persistent, heavy, woody-earthy, somewhat sweet-sour and balsamic* scent of the vetiver oils. According to Büchi *et al.*[153a] this odour is mainly due to the spiroketone **142**, and (–)-khusimone [(–)-**143**].[153a]

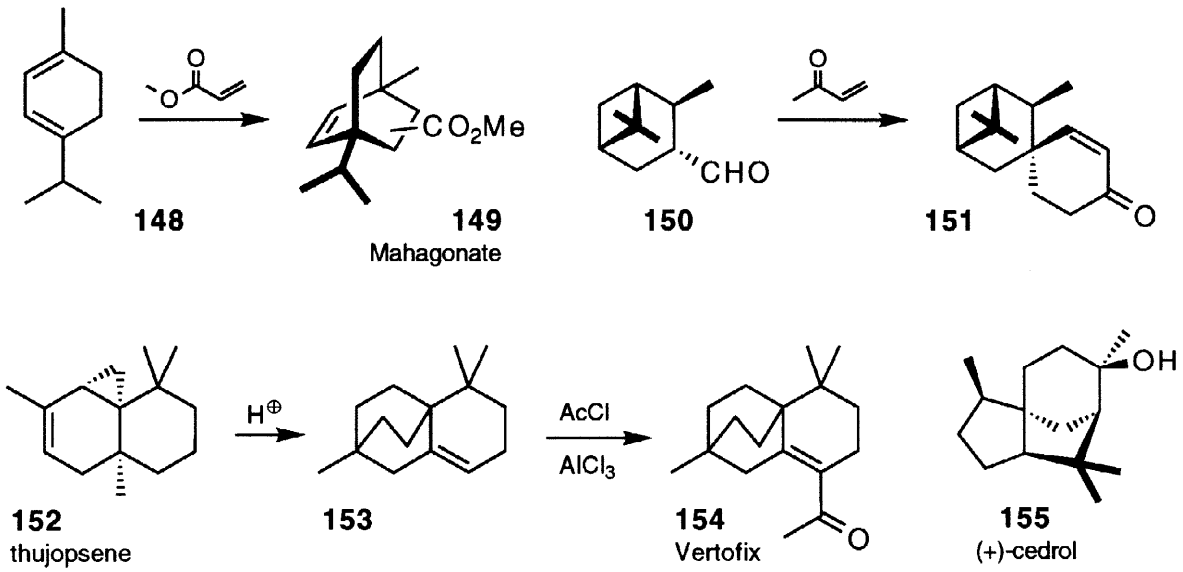


142 **(–)-143** khusimone **144** **145**



146 **147** **(–)-143** khusimone

Several syntheses of **142**[153b] and (±)-**143** have been reported,[153a] none of which could be carried out on an industrial scale at tolerable cost. Of these, the most inexpensive way to (±)-**143** was reported by Büchi *et al.*[153a] in 1976. The first stereoselective approach to natural (–)-khusimone [(–)-**143**] was reported by Liu and Chan,[154] who used (–)-α-campholenic ester **144** as starting material. Ozonization followed by aldol condensation provided **145**, which was further transformed by [2+2] cycloaddition of a ketene equivalent, methylenation, reduction of the ester moiety, halogenation of the resulting alcohol, and homologation of the cyclobutanone ring. Cyclization of **147**→(–)-**143** was accomplished in 70% yield by treatment with aqueous sodium hydroxide in refluxing methanol.[153] Needless to say, this synthesis is also far too complicated for an industrial production.



Even if there is no real synthetic *vetiver* odorant, some compounds in one way or another are reminiscent of vetiver oil, the most important being **149**, **151** and **154**. Mahagonate® (**149**), produced by Dragoco by Diels–Alder reaction of α-terpinene (**148**) and methyl acrylate under thermal or Lewis acid conditions, has a *woody, spicy, vetiver* odour. The α,β-unsaturated spiroketone **151** with some structural resemblance to **142** is easily accessible from (–)-3-formylpinane (**150**) by simple Robinson anellation with methyl vinyl ketone.[155] It possesses a *leathery-woody, vetiver-cedarwood type* odour, similar in many respects to that of Vertofix® (**154**).

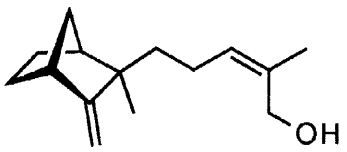
Vertofix® (**154**) is manufactured by Friedel–Crafts acylation of the hydrocarbon fraction of cedarwood oil with acetyl chloride or acetic anhydride and catalysts such as zinc chloride or aluminium chloride. Thujopsene (**152**), which constitutes some 40–50% of the hydrocarbon fraction, thereby undergoes acid-catalyzed rearrangement to the tricyclic olefin **153**, which then is acylated to **154**, the primary odorant of Vertofix® (**154**).[156] The odour of Vertofix® (**154**) is described as *warm, woody, reminiscent of vetiver and cedar, with leathery aspects.* With 12%, Vertofix® dominates the woody aspects of »Chanel No.19« (Chanel, 1970), and »Cacharel pour l' Homme« (Cacharel,1981) even contains an "overdose" of some 20% of it.

As cedarwood oil (*Juniperus virginiana* L.) is a by-product of the American timber industry, it is one of the most economical and abundant sources of sesquiterpenes. This makes it an attractive starting material for the synthesis of other odorants like Vertofix®. On the other hand, any attempt to introduce a new *cedarwood* odorant is a lost cause, simply because cedarwood oil is so inexpensive. (+)-Cedrol (**155**) is responsible for its *soft, woody odour, typical of cedarwood*, and it is isolated from the oil by fractional distillation followed by crystallization. The syntheses of **155** by Stork and Clarke,[157] and Corey *et al.*[158] can already be considered classics in total synthesis.

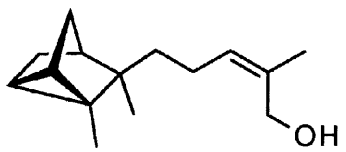
3.3 *Sandalwood Odorants*

The sandalwood oil constitutes one of the oldest and most expensive perfumery raw materials. Among different sandalwood oils, that of the heartwood and roots of *Santalum album* L. trees from the East Indian state of Karnataka (Mysore before 1973) is the most appreciated by perfumers.[159] Besides its unique olfactory properties, which make it play an important religious and social role in India, it also appears to have an important therapeutic value.[160]

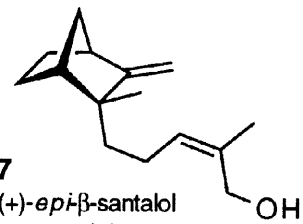
The multifaceted, persistent, natural and inimitable scent of sandalwood oil is due not only to its main constituents of more or less *sandalwood* odour, but also to the minor impact chemicals and possibly to synergistic effects of other, weak and odourless compounds. New, trace constituents (*e.g.* **158**, **163**, **165**,[161] **166**) are still being isolated and identified, and numerous papers have reviewed the rich domain of sandalwood scent, including the analytical studies.[63,162]



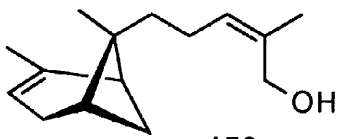
16
(*Z*)-(−)-β-santalol
typical sandalwood, woody, milky, urinous



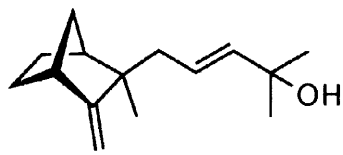
156
(*Z*)-(+)-α-santalol
woody, cedarwood



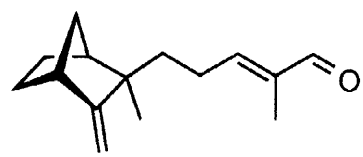
157
(*Z*)-(+)-*epi*-β-santalol
sweet, sandalwood



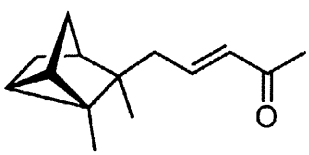
158
(*Z*)-α-*trans*-bergamotol
sandalwood, citrus



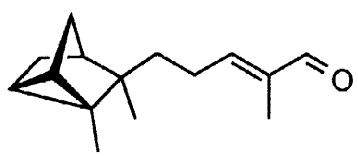
159
β-photosantalol A
sandalwood, animalic, musky



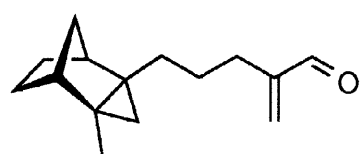
160
(*E*)-β-santalal
sweaty, sandalwood



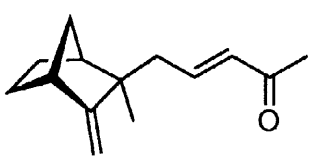
161
nor-α-santalenone
woody, sandalwood, ionone-like



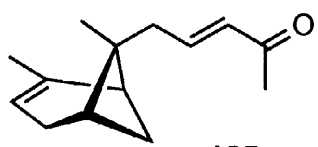
162
(*E*)-α-santalal
woody, cedarwood



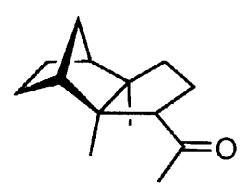
163
woody, ambergris, sandalwood



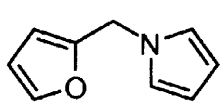
164
nor-β-santalenone
sweaty, woody, green, sandalwood



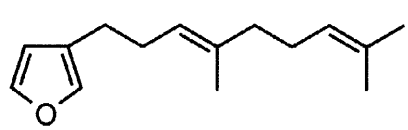
165
nor-α-*trans*-bergamotenone
fatty, nutty, milky, sandalwood



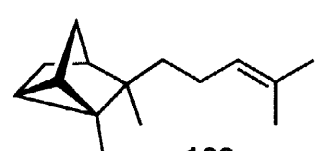
166
acetyldihydroalbene
woody, amber, ionone



167
N-furfurylpyrrole
roasty, pyrazine-like, herbaceous

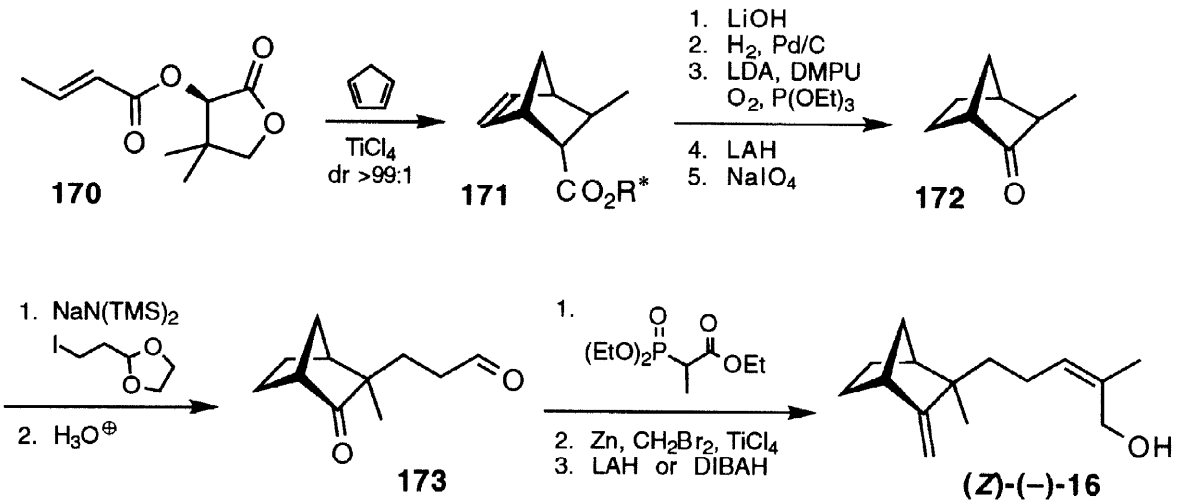


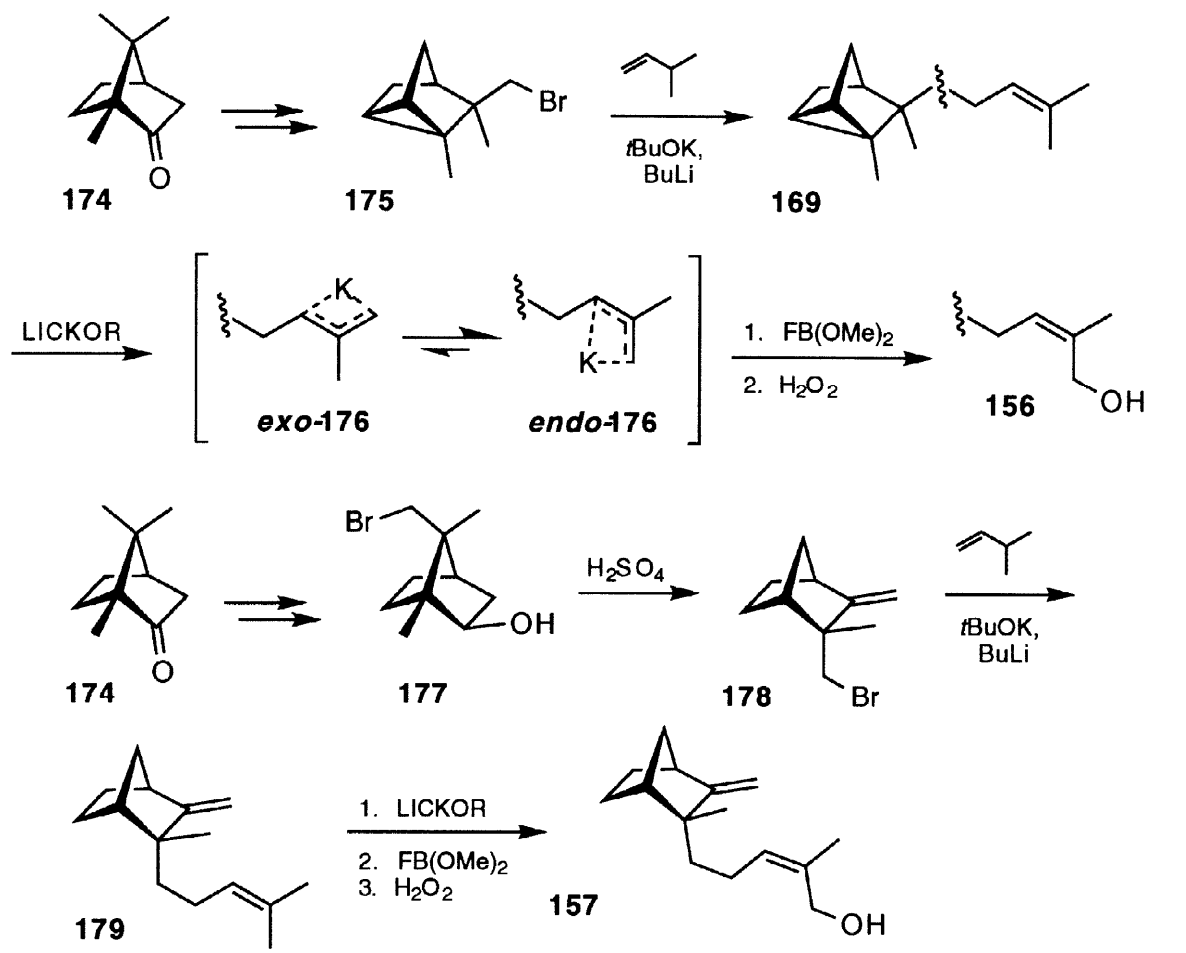
168
dendrolasine
green, fatty, nitrile-like, agrumen oils



169
α-santalene
woody, cedarwood

It is difficult to evaluate the contribution of the different constituents of sandalwood oil to the overall odour profile,[163] but (*Z*)-(−)-β-santalol (**16**) is unanimously considered as the main sandalwood, *i.e. lactonic, floral, woody, milky, musky (urinous, animal)*, odour vector. It accounts for approximately 25% of the oils weight. The importance of the most abundant (*Z*)-(+)-α-santalol (**156**, approx. 45–47%), bringing more *woody, cedarwood* character, is more controversial. α-Santalene (**169**), the main sesquiterpene hydrocarbon was ranked third among the most odour-intensive molecules in the oil by Nikiforov *et al.*,[164] but others grant it little sensory importance. The most recently identified *nor*-α-*trans*-bergamotenone (**165**),[161] despite its low concentration of <0.01%, is said to be of great importance to the overall odour of the oil. The depicted compounds **16**, and **156–169** are considered as the main contributors to the scent of the East Indian sandalwood oil.

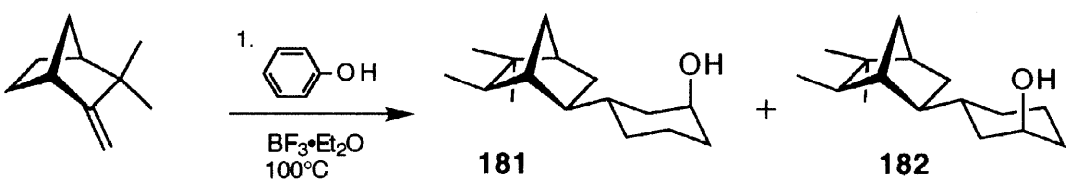

1. LiOH
2. H_2, Pd/C
3. LDA, DMPU
O_2, $P(OEt)_3$
4. LAH
5. $NaIO_4$
$TiCl_4$
dr >99:1
170
171
CO_2R^*
172
1. $NaN(TMS)_2$
2. $H_3O^{\oplus}$
173
1.
$(EtO)_2P$
OEt
2. Zn, CH_2Br_2, $TiCl_4$
3. LAH or DIBAH
(Z)-(−)-16


174
175
Br
tBuOK,
BuLi
169
LICKOR
K
exo-176
endo-176
1. $FB(OMe)_2$
2. H_2O_2
156
OH
174
Br
OH
177
H_2SO_4
178
Br
tBuOK,
BuLi
179
1. LICKOR
2. $FB(OMe)_2$
3. H_2O_2
157
OH

As with many other natural products, the components of sandalwood oil inspired total syntheses. These have been reviewed,[49b,63a] and recently focus has shifted to the constituents and isomers of minor olfactory importance, such as santalenes and *epi*-santalols. Therefore, we will mention only the most recent enantioselective syntheses of the three main santalols (**16**, **156**, and **157**).

In 1990, Krotz and Helmchen[64] reported the first synthesis of optically pure (*Z*)-(–)-β-santalol (**16**). It is based on the preferred *exo*-alkylation of 3-methyl-2-norbornanone (**172**), obtained through the asymmetric Diels–Alder cycloaddition of cyclopentadiene to *trans*-crotonate **170** with (*R*)-pantolactone used as auxiliary. Another crucial step of the synthesis is the oxidation of the dianion generated from the hydrolysed and hydrogenated **171**, and *in situ* reduction of the α-peroxide to the α-hydroxycarboxylic acid. In a similar way, they prepared β-santalene, (*E*)-β-santalol, and the corresponding enantiomers. Their olfactory evaluation consolidated the structure-odour relationship data: only natural (–)-β-santalols (*Z* >> *E*) smelled *sandalwood*-like.

Schlosser and Zhong applied their findings on the conformational mobility and the conformational preferences of allylpotassium type intermediates in the elegant syntheses of both (Z)-(+)-α-santalol (**156**)[165] and (Z)-(+)-*epi*-β-santalol (**157**).[166] They proceeded through the formal hydration of the corresponding santalenes, realised *via* regioselective metallation with the superbasic LICKOR reagent, followed by trapping with fluorodimethoxyboron and subsequent oxidation of the termodynamically favoured *endo*-conformer of the allylpotassium species **176**. This site selective functionalization of isoprene units should, in principle, also work with other santalenes for which numerous other stereoselective syntheses have been published.[167] Despite all the synthetic attempts aimed at (–)- or *rac*-β-santalol no industrially viable process has yet been found.



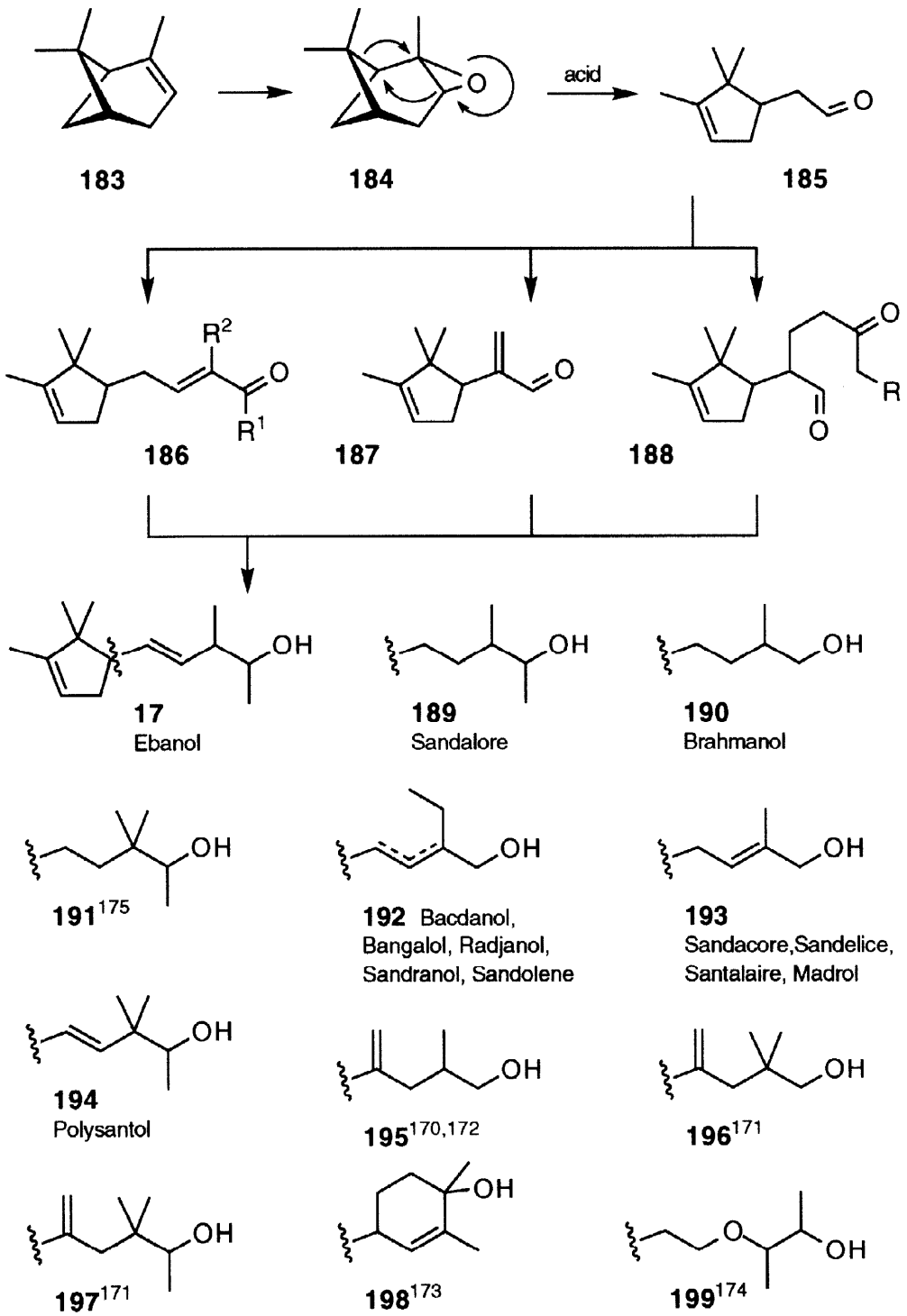
180 **181** **182**

in Sandela, Sandel H&R, Sandiff, Santalydol, etc.
sandalwood-like

The natural sandalwood oil always constituted a valuable ingredient of perfume compositions, but it has become scarce and even more expensive since 1974, when its price quintupled; it is now at about US$ 250–400 per kg depending on the origin and quality. The perfumers have therefore to rely on cheaper synthetic substitutes. Among them, two classes of compounds have been commercially successful. Both originated from the fortuitous findings of German chemists. The first class of compounds, terpenyl cyclohexanols, are obtained by acid-catalysed condensation of phenols (*e. g.* phenol, guaiacol) with cheap terpenes [camphene (**180**), pinenes], followed by hydrogenation to provide complex mixtures of secondary alcohols. The first paper reporting such products appeared in 1947,[168] but the relative configuration of the odoriferous minor isomers (**181, 182**) were revealed only in 1964.[169] The interest in these products culminated in 1970s, and has since then focused on a better chemically defined class of compounds, that of derivatives of α-campholenic aldehyde (**185**), of which the compounds **17** and **189–199** represent the most important commercialized, and recently patented compounds.

Both enantiomers of campholenal (**185**) are readily available from the corresponding α-pinenes (**183**) *via* acid catalysed transposition of their epoxides (**184**). The next steps towards final products are straightforward—aldol condensation and reduction of the enones to saturated or allylic alcohols, alternatively preceded by deconjugation (**17**; Ebanol®) or deconjugative α-methylation (**194**; Polysantol®). The synthesis of substituted 4-(2,2,3-trimethylcyclopent-3-enyl)pent-4-en-1-ols (*e. g.* **195–197**)[170, 171,172] begins by a cheap α-methylenation of **185**. The enal **187** is then reacted in the classical way *via* Wittig-Horner reaction, and Claisen or Carrol rearrangements. The cyclohexenol **198** was obtained *via* Robinson type cyclisation of dione **188**.[173] The synthesis of **199**, which differs from **189** (Sandalore®) by one oxygen atom inserted into the *spacer* is also simple: an opening of epoxybutane with reduced **185**, or LAH/$AlCl_3$ reduction of the corresponding dioxolane.[174]

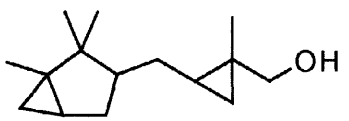
As usual, process modifications lowering the production costs follow the original patents, *e. g.* an improved process for producing alkyl-substituted butenols in which new catalysts are used for the two last steps has been



claimed.[176] Piperidinium acetate catalysed the formation of enone **186** (85% yield, azeotropic distillation of water), which was then hydrogenated in the presence of a Cu–Zn catalyst to give **193** with 81% yield and better purity.

The average market price of synthetic substitutes of sandalwood oil varies from US$ 20 per kg for terpenylcyclohexanols to about US$ 50–200 per kg for the campholenal derivatives **17** and **189–194**. This broad price range is justified by the difference in their performances: odour threshold compared to the vapour pressure of the product, substantivity, *naturalness*, *etc.* The most expensive, and the most appreciated by perfumers, seem to be the pent-4-en-2-ols **17** and **194**. However, there is still room for improvement. Recently, a new class of

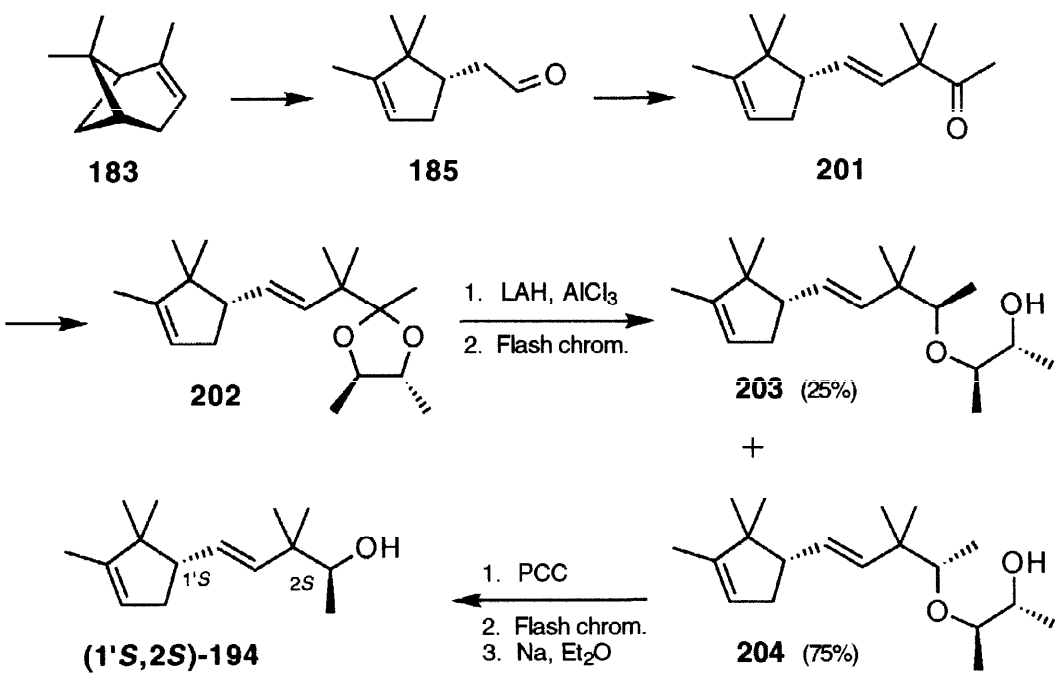
polycyclic derivatives of campholenal, containing one or two *bioisosteric* cyclopropane rings instead of the double bonds, *e. g.* **200**, has been claimed.[177] Some of these compounds are performing much better than the existing benchmark products in terms of any of the above-mentioned parameters, but would this outweigh the evident handicap consisting in the industrially difficult cyclopropanation step?



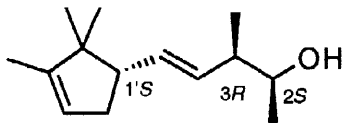
200

Until very recently little has been known on the structure-odour relationship of the enantiopure isomers of the commercial products. This information is now becoming available, often through the patent literature, and the manufacturers of these products begin to apply some degree of stereoselection in order to provide more intense odorants of higher quality for the same weight of raw material.

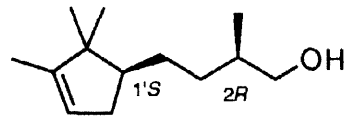
Four stereoisomers of Polysantol were obtained[68] *via* stereoselective reduction of acetals **202**, followed by chromatographic separation of the diastereomeric hydroxyethers **203/204**, PCC oxydation, and reduction of the corresponding oxoethers. The stereoisomers of **194** were also prepared by enzymatic hydrolysis of the corresponding chloroacetates. The typical sandalwood scent is most pronounced in the two (2*S*)-isomers, of which perfumers prefer the (1'*S*,2*S*)-**194**.



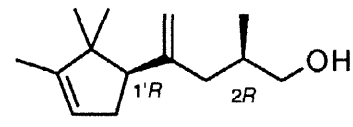
The known[178] relative-configuration-odour-relationship data of the four diastereomeric pairs constituting Ebanol (**17**) have recently been completed by the olfactory description of all eight stereoisomers of this product.[179] Similarly, the four isomers of **195** were prepared and evaluated.[170] The two sandalwood-smelling diastereomers of (2*R*)-**190**, prepared by asymmetric hydrogenation of **193** using the $Ru_2Cl_4[(R)\text{-Tol-BINAP}]_2NEt_3$ catalyst, are described in a recent patent.[180]



17
(1'*S*,2*S*,3*R*)>(1'*R*,2*S*,3*R*)
>>other 6 stereoisomers



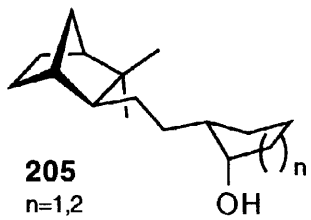
190
Intensity of the sandalwood-like scent
(1'*S*,2*R*)≅(1'*R*,2*R*)>>other 2



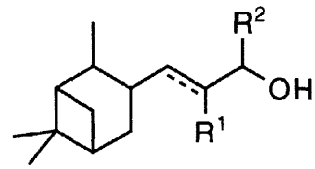
195
(1'*R*,2*R*)>(1'*R*,2*S*)
>other 2

This, and certainly soon more knowledge of the exact configuration of the best odour vectors should allow fine-tuning of the sandalwood *olfactophore* model, and enable a more rational design of still better sandalwood odorants. This *olfactophore* consists of a bulky moiety separated by a spacer from the hydroxyl group. After analysis of the above-detailed SOR data it is tempting to postulate, that the geometry of the immediate proximity of the *osmophoric* hydroxy group tolerates less variations than the orientation of the more distant lipophilic bulky group.

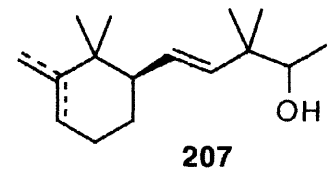
The bulky moiety of the norbornane in β-santalol (**16**), **181/182**, and analogues (*e. g.* **205**[181]) as well as that of the trimethylcyclopentenyl group in campholenal derivatives (**17**,**189–199**) can be replaced by structures of similar steric bulk (*cf.* **206**,[182] **207**,[183] **208**,[70] **209**,[184] **210**,[185] and **211**[186]). Even 2-methoxyisopropyl (*cf.* **212**[187]), and *tert*-butyl substituents (*e. g.* in **213**[67]) are apparently able to mimic this feature.



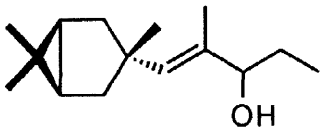
205
n=1,2



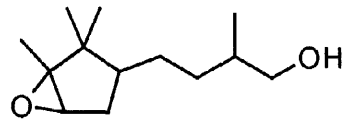
206
R^1=Me,Et; R^2=H,Me



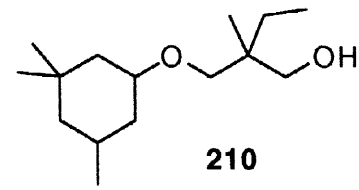
207



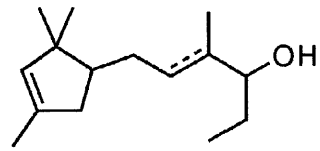
208



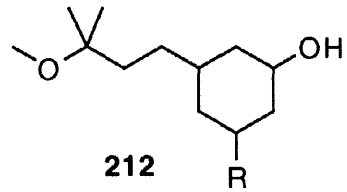
209
epoxybrahmanol



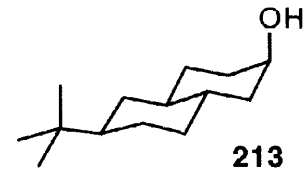
210



211



212



213

3.4 *Musk Odorants*

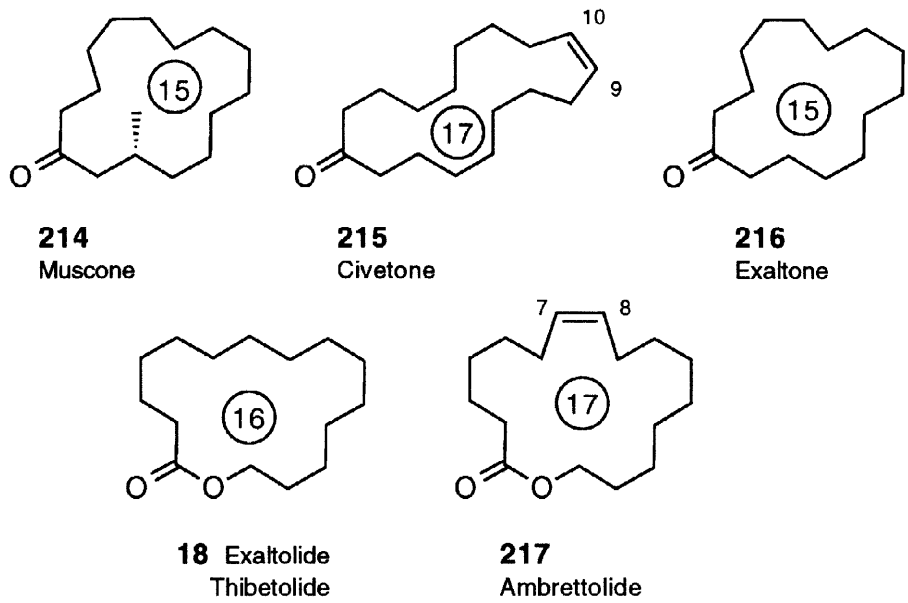
The musks are of central importance for the fragrance industry. They form the *bottom note* (the *dry out*) of a perfume composition, *i. e.* the musky undertone stays the longest on the skin or on the fabric (*substantivity*, *vide infra*). The *musk* odour is difficult to describe, it is often called *warm, sweet, powdery, animal, etc.*, it is longlasting,

tenacious, and substantive. The use of musks goes back to antiquity, and is itself a chapter of human cultural history.

The chemistry of the natural musk odorants started with the discovery of the macrocyclic musks, ketones and lactones, during the first half of this century, when their isolation from animal and plant sources and subsequent structure elucidation took place.

Muscone (**214**), civetone (**215**), and Exaltone® (**216**) are the main odorous principles from the animal kingdom, whereas the lactones Exaltolide® (**18**), and (Z)-Δ^7-ambrettolide (**217**) have been isolated from plants. The chemistry of macrocyclic musks has been reviewed.[188]

The class of nitro-musks was discovered by serendipity during the search for new explosives some hundred years ago,[189] when the structure of the above natural musks was not yet known, and the latter had an exorbitant price. Musk xylol (**6**), Musk ketone (**218**), Musk Tibetene (**219**), Musk Ambrette (**220**), and Moskene® (**221**) are the most prominent representatives of this class. It is a fascinating coincidence, that these penta- and hexa-substituted polynitro benzene derivatives display a *musky* odour, with an *ambery, sweet vanilla, powdery* character, and a touch of a highly esteemed *animal* tonality. Because of these odour chracteristics, and their very favourable price, especially compared to the natural and later the synthetic macrocyclic musks, the nitro musks became high-volume industrial chemicals.[190] During the 1980s their use began to decline. The reason is partly toxicological,[191–193] partly practical,[194] but mainly the introduction of a *third class* of high-performing musks to the market.



214 Muscone

215 Civetone

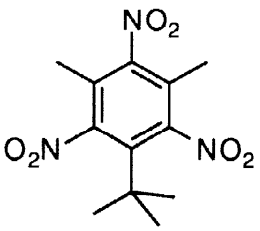
216 Exaltone

18 Exaltolide
Thibetolide

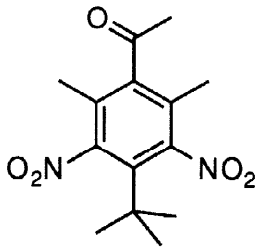
217 Ambrettolide

This third class of synthetic musks consists of polycyclic, aromatic compounds. Phantolide® (**222**),[195] Celestolide® (**223**),[196] Traseolide® (**224**),[197] Fixolide® or Tonalide® (**225**),[198] and Galaxolide® (**226**)[199] are the main representatives, the last two being the most important today. Their chemistry is text-book aromatic chemistry,[190] their odours are *musky with fruity and woody effects, and an animal undertone*. The polycyclic musks are today in the same price class as the nitro musks or even cheaper, *i.e.* US$ 15–20 per kg, and several thousands of tons are manufactured per year. Because of their low biodegradability, and their tendency to bio-accumulate, they are causing some concern today.[200–202]

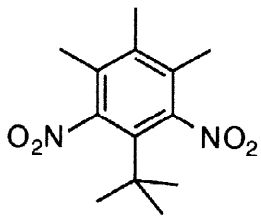
As can be imagined, to put up a unifying theory of the structure-odour relationship of these chemically very different classes of musk compounds remains a very demanding task, to say the least (*cf* chapter 2.2).



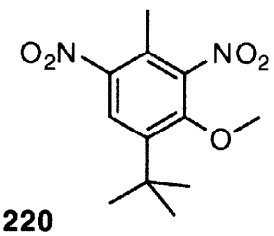
6
Musk xylol



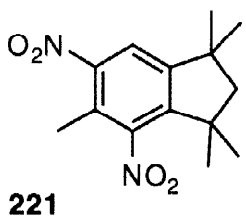
218
Musk ketone



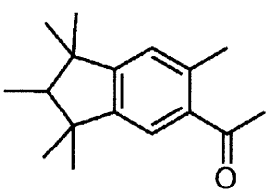
219
Musk Tibetene



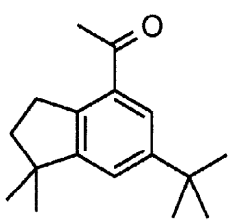
220
Musk Ambrette



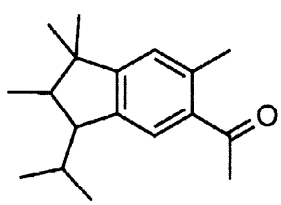
221
Moskene



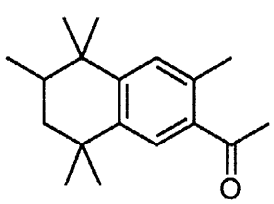
222
Phantolide



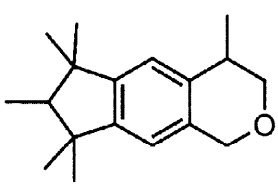
223
Celestolide



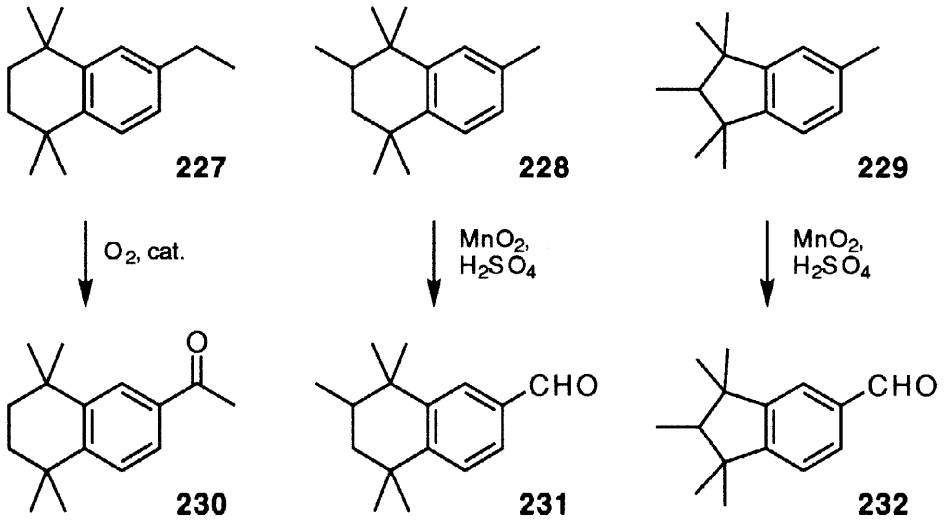
224
Traseolide



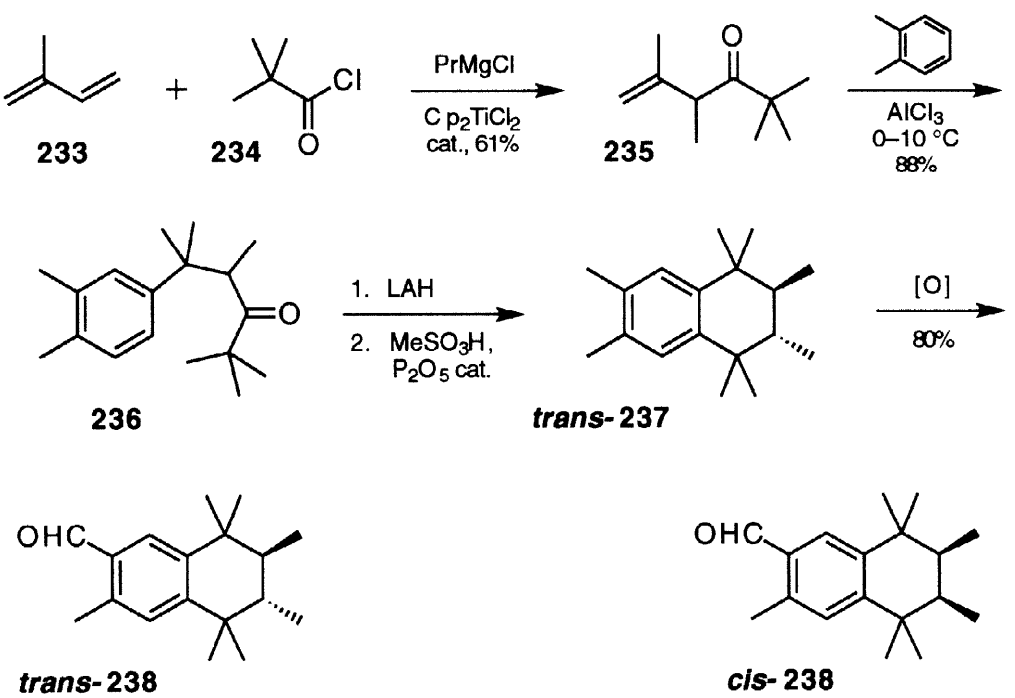
225
Fixolide, Tonalide



226
Galaxolide

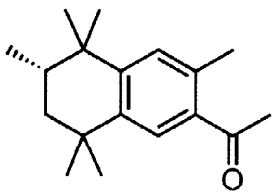


The chemistry of the nitro musks can be considered today as a closed chapter, and that of the nitro-free aromatic, polycyclic musks is also approaching an end. The aromatic hydrocarbons **227**, **228**, and **229**, which are the intermediates for the above polycyclic musks, have been oxidized to the carbonyl compounds **230**, **231**, and **232**, which are powerful musks, compound **231** possessing in addition a *woody, camphoraceous* note.[203] Interestingly, acetals and ketals of this series display a more *woody* odour (Okoumal®).[203, 204]

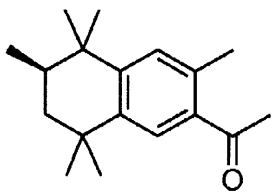


The aldehyde analogue of Fixolide®, *trans*-**238**, has been claimed to be stronger than Fixolide® (**225**) itself.[205] *trans*-**238** has been prepared by reacting isoprene (**233**) with pivaloyl chloride (**234**) to give **235**, which underwent a Friedel–Crafts reaction with *ortho*-xylene to provide **236**. The latter compound was then reduced,

and transformed *via* methyl-migration to the hydrocarbon *trans*-**237** as the main product (15% *cis*-isomer). Oxidation with ammonium cerium(IV) nitrate furnished *trans*-**238**. The diastereomeric *cis*-**238** is described as a strong musk, but weaker than *trans*-**238**.[206] Besides this recent example of diastereoselectivity of odour and/or odour strength there are a few cases of enantioselectivity of odour sensation known in the polycyclic musk field.

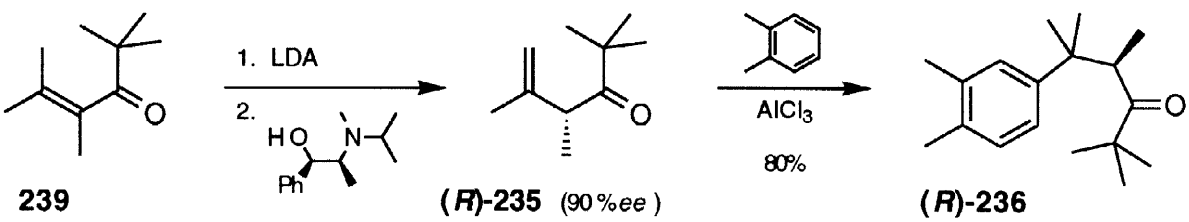


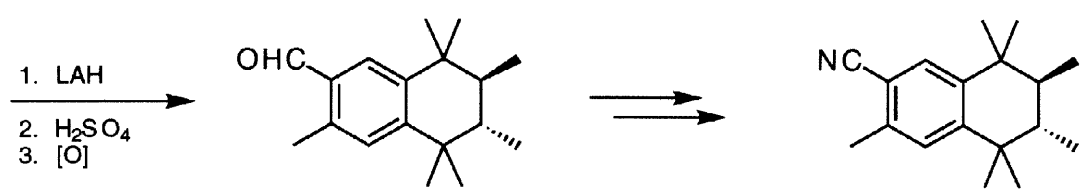
(*S*)-225



(*R*)-225

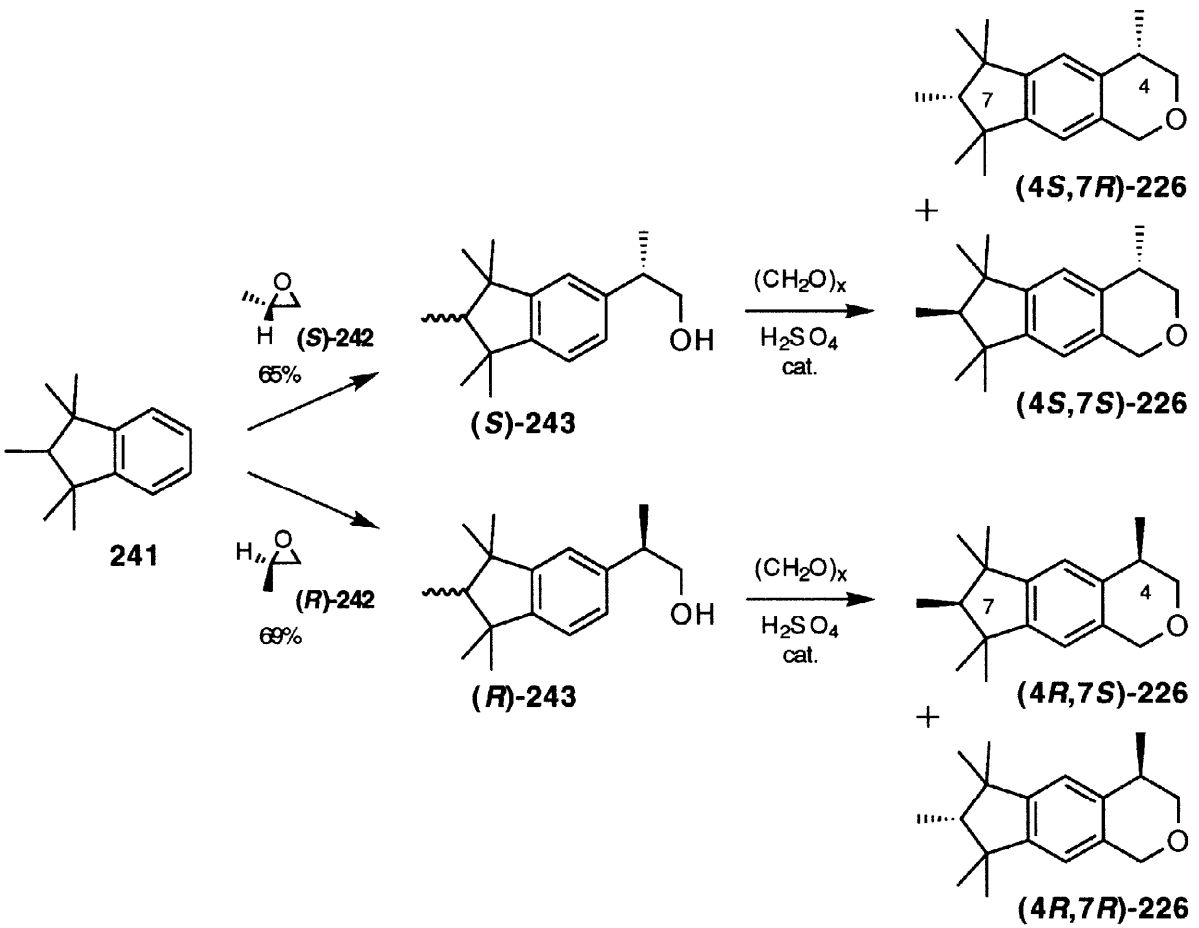
(*S*)-**225** (Fixolide®, Tonalide®) has the *characteristic, strong, musk* odour, whereas the enantiomer (*R*)-**225** displays a *light and sweet aromatic* odour.[207] The nitrile **240** has been prepared in both enantiomeric forms from (*R*)- and (*S*)-**235**, respectively, which have been prepared by enantioselective protonation of the enolate derived from **239** with (–)- and (+)-*N*-isopropylephedrin.[208,209] The further synthesis follows the route described before, with a slight loss of chirality. Of the two enantiomers, the (6*S*,7*S*)-**238** is the more powerful musk.

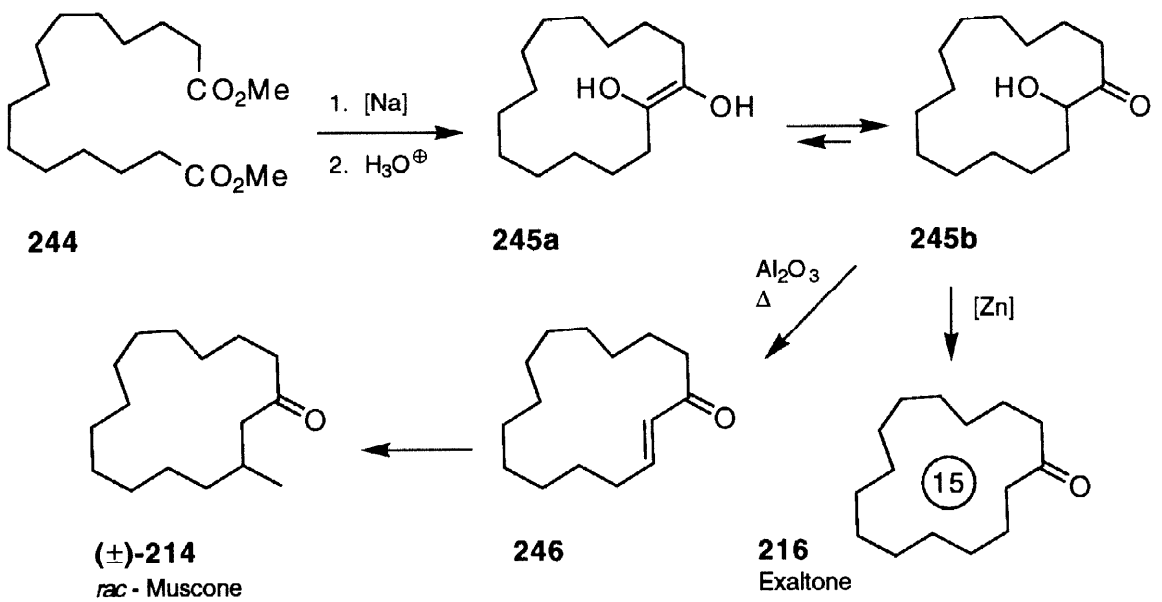




Galaxolide® (**226**) is a *ca.* 1:1:1:1 mixture of the four stereoisomers, *i.e.* two racemic, diastereomeric pairs. All the four isomers have been prepared, and evaluated olfactorily.[210] Pentamethylindan (**241**) was reacted with propylenoxides, (*S*)- and (*R*)-**242**, to give the diastereomeric mixtures (*S*)- and (*R*)-**243**, respectively. Ring closure to the isochromanes with formaldehyde under acid catalysis furnished the enantiomerically pure diastereomeric pairs *cis*-(4*S*,7*R*)-**226** and *trans*-(4*S*,7*S*)-**226**, and *cis*-(4*R*,7*S*)-**226** together with *trans*-(4*R*,7*R*)-**226**. The two main problems, the structure elucidation, *i. e.* the differentiation between the *cis*- and the *trans*-isomers of **226**, and the separation of the isomers, were solved as follows.

The chromecarbonyl complexes of **226** were prepared, separated by chromatography on silica gel, and further purified by crystallization. The pure $Cr(CO)_3$ complexes were then oxidized to provide the pure isomers of **226**. The structure assignment was performed by X-ray crystallography of the pure *rac-trans*-**226** (mp 67 °C), and the $Cr(CO)_3$ complex of (4*S*,7*R*)-**226**.

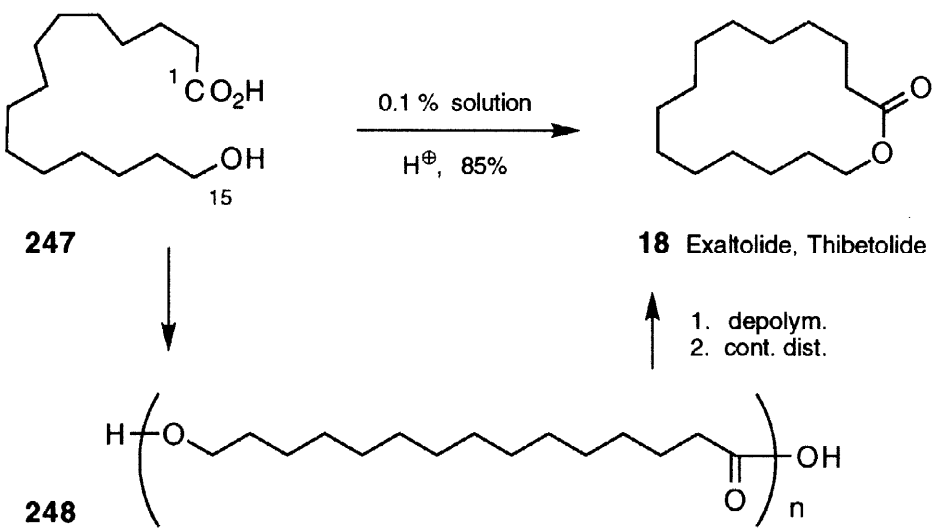

241
(S)-242
65%
(R)-242
69%
(S)-243
(R)-243
(CH2O)x
H2SO4
cat.
(4S,7R)-226
(4S,7S)-226
(4R,7S)-226
(4R,7R)-226


CO2Me
CO2Me
1. [Na]
2. H3O⊕
244
245a
245b
Al2O3
Δ
[Zn]
(±)-214
rac - Muscone
246
216
Exaltone

The stereochemistry of odour sensation in this case is particularly striking: The (4*S*)-isomers, *i.e.* *cis*-(4*S*,7*R*)-**226**, and *trans*-(4*S*,7*S*)-**226** are the powerful *musky* isomers, the *trans*-isomer [(4*S*,7*S*)-**226**] being slightly weaker by a factor of *ca.* 2, and slightly more *dry* than (4*S*,7*R*)-**226**. The (4*R*)-isomers, *cis*-(4*R*,7*S*)- and *trans*-(4*R*,7*R*)-**226** are weak to very weak, *ca.* 250 and 900 times weaker than (4*S*,7*R*)-**226**. This was in agreement with the original hypothesis based on the *matching* of androstenone and the stereoisomers of Galaxolide®,[210] the two products being related by a specific anosmia association.

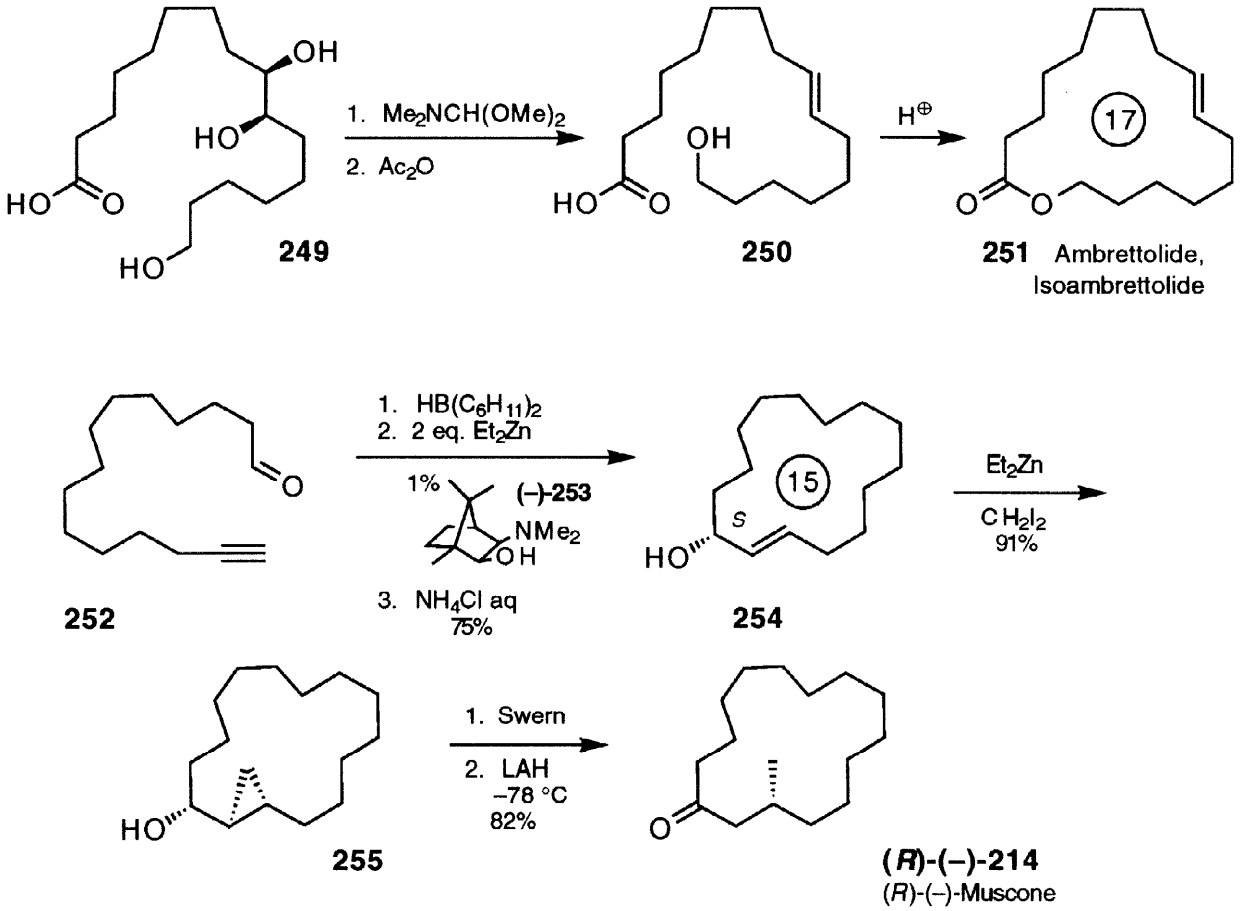
Today the importance of the macrocyclic musks is increasing again, because of their ready biodegradability. The stumbling-block for their really large-scale use has up to now been their relatively high price compared to the other classes of musks, the nitro- and nitro-free polycyclic musks. Any synthesis of both macrocyclic ketones, or macrocyclic lactones has its key step in the formation of the large ring (14–17 membered in the case of macrocyclic musks). The first approaches as well as the first industrial syntheses all used the technique of macrocyclization.[6] In connection with the synthesis of antibiotic macrolides new macrocyclization strategies have been developed during the last 20 years.[211,212] However, only a few of these methods are applicable in industry.

A major step forward in macrocyclization was the acyloin condensation of α,ω-diesters. Application of this reaction to dimethyl 1,15-pentadecanedioate(**244**) furnished **245a** / **245b**,[213,214] which was either treated with zinc in acidic media to provide Exaltone® (**216**) or dehydrated over alumina to the α,β-unsaturated ketone **246**. This ketone can be converted to muscone(**214**) by means of a Michael reaction with methyl magnesium bromide.[215] It is very important to realize, that the main difficulty in macrocyclization, namely dimerization and polymerization, normally makes high dilution (≤1 mM) necessary. The acyloin condensation, as a surface reaction on the sodium metal, circumvents this problem, and the reaction can be carried out under very practical conditions of around 1 M solutions.

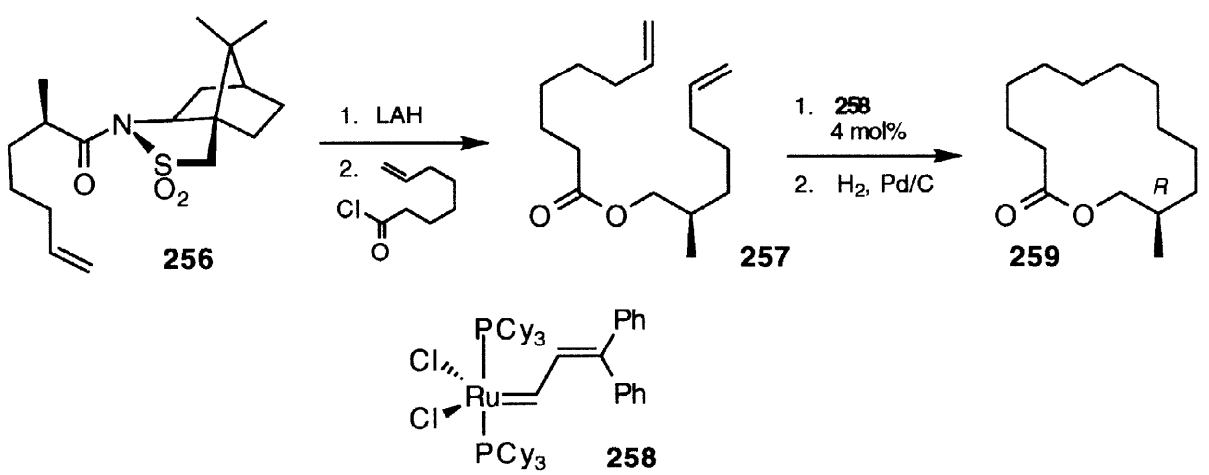


Using very high dilution ω-hydroxy pentadecanoic acid was cyclized directly to Exaltolide® (**18**),[216] but only the polymerisation-depolymerization process[217] allowed a large-scale preparation. In a further development glycerol esters of ω-hydroxy acids are prepared *in situ*, and the monomeric macrocyclic lactone formed in a reversible transesterification process is continuously distilled off.[218]

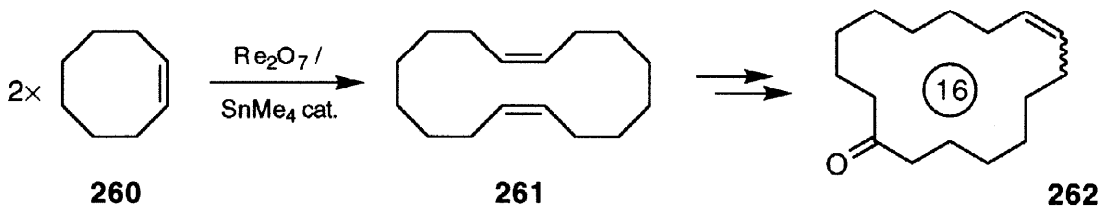
(*E*)-16-Hexadec-9-enolide (**251**, Ambrettolide®, Isoambrettolide®) is an industrially used, valuable fragrance ingredient. It is prepared from aleuritic acid (**249**), the main acidic constituent of shellac, by the dimethylamino-dioxolane mediated double-bond formation, followed by ring closure.[219,220] A one-pot variant has also been described, using two equivalents of dimethylformamide dimethyl acetal.[221]



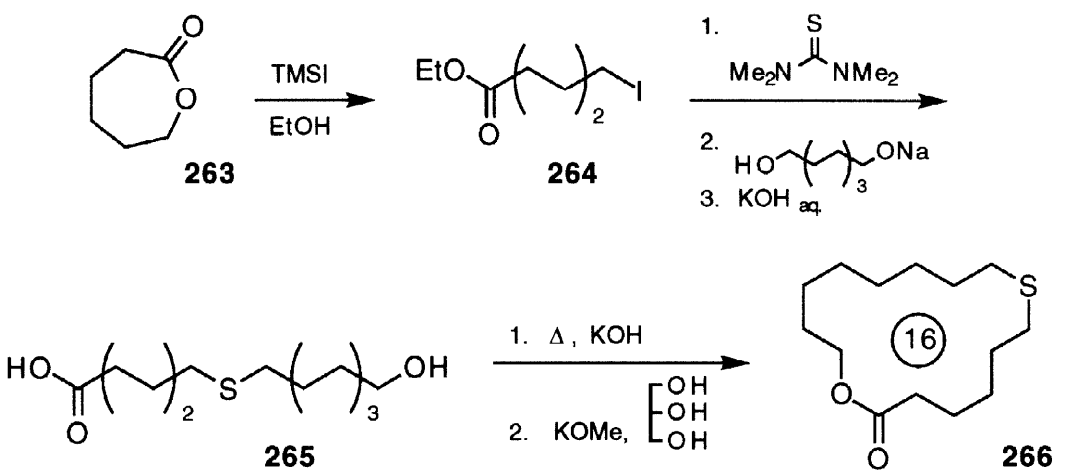
As an example of the muscone (**214**) chemistry the synthesis of the natural (*R*)-(–)-**214** is presented here. Oppolzer's route[222] follows a ring-closure strategy starting with 14-pentadecynal (**252**), which is hydroborated, and the resulting (*E*)-alkenylborane is transmetallated in a 0.05 M (!) solution with diethyl zinc in the presence of 1% of the chiral catalyst (–)-**253**, in order to make the ring closure to **254** highly enantioselective (92 %*ee*). The allylic alcohol **254** is then transformed to **255** by a stereoselective Simmons–Smith cyclopropanation, and the synthesis is finished with an oxidation and a reduction step.



Olefinmetathesis is an established technique for ring-closure of macrocycles,[223,224] but recently new catalytic systems have emerged[225] to give new impetus to this field. By a ring-closing methathesis employing the Grubbs catalyst **258**,[225] methyl diene **257** was transformed in 68% yield to (+)-(12*R*)-12-methyl-13-tridecanolide(**259**)[226]—the stereogenic centre was created *via* Oppolzer's bornane 10,2-sultame **256**. While the enantiomers of muscone (**214**) smell very similar, the enantiomers of 12-methyl-13-tridecanolide(**259**), which is a natural constituent of angelica root oil (*Archangelica officinalis* Hoffm.),[227] differ significantly in their odour characteristics: (+)-(12*R*)-**259** possesses a *musk note with a sandalwood tonality,* while (–)-(12*S*)-**259** has an *animal musk odour with camphoraceous aspects.*[228]

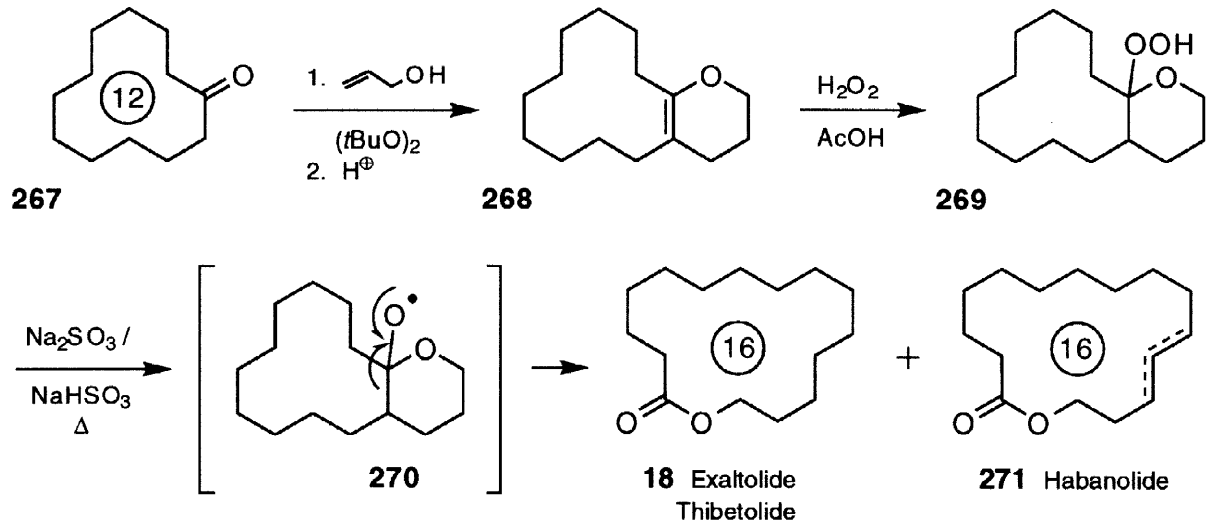


In contrast to the synthesis of **259**, ring-opening metathesis was used in the preparation of 1,9-cyclohexadiene (**261**), *en route* to the macrocyclic ketone **262**.[229] Cyclooctene (**260**) is dimerized under the catalytic influence of Re_2O_7 to **261**, which after monoepoxidation and rearrangement was transformed to the macrocyclic musk ketone (8*E*/*Z*)-cyclohexadec-8-enone(**262**).[230]

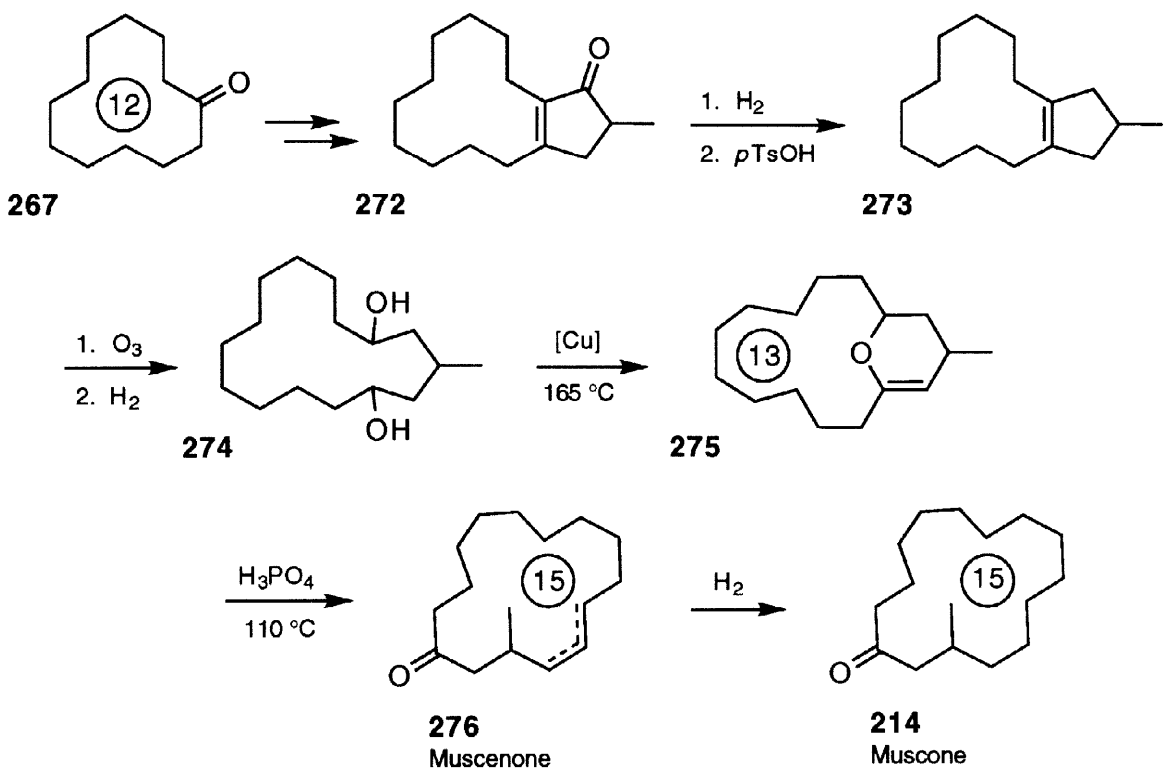


Very recently, powerful thia-macrolides have been described.[231] Starting with ε-caprolactone (**263**) the thia-lactone **266** has been prepared through the intermediates **264** and **265**. Compound **266** displays a *tenacious musk odour with a green-mossy* tonality, and with 0.2 ng/L an exceptionally low threshold value.

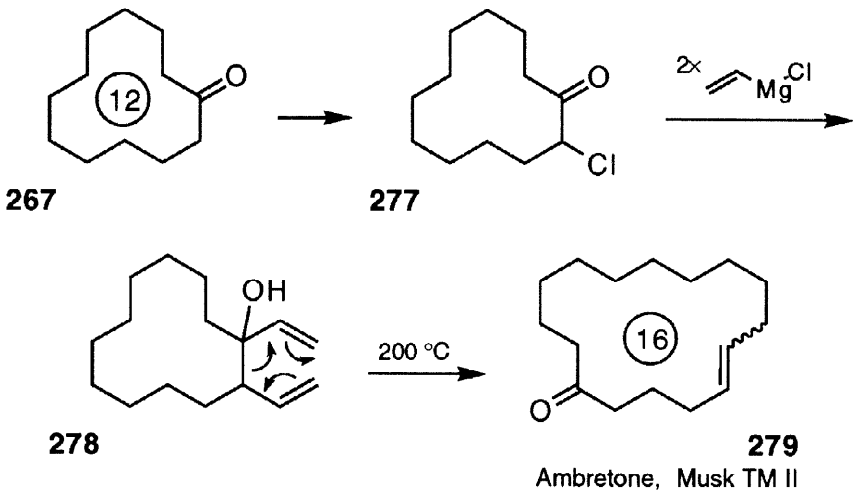
The other successful strategy to macrocyclic rings, besides the direct ring closure, is ring enlargement which is a standard synthetic strategy.[232] For the musk specialities this route became important when cyclododecanone (**267**) came to the market, at a reasonable price, as one of the downstream products of



the butadiene oligomerization in the early sixties. A few examples shall demonstrate here the utility of cyclododecanone (**267**) as a starting material.[233] **267** can be transformed in two steps into the bicyclic enolether **268**, which upon treatment with hydrogen peroxide (70%) yields the hydroperoxide **269**. The labile **269** then undergoes a fragmentation reaction to a mixture of Exaltolide® (**18**), and the *dehydro*-Exaltolides **271**.[234–236] This fragmentation has been studied in more detail under iron-copper catalysis.[237] The mixture of the *dehydro*-Exaltolides **271** has recently been introduced to the market under the name Habanolide® (**271**).[238]



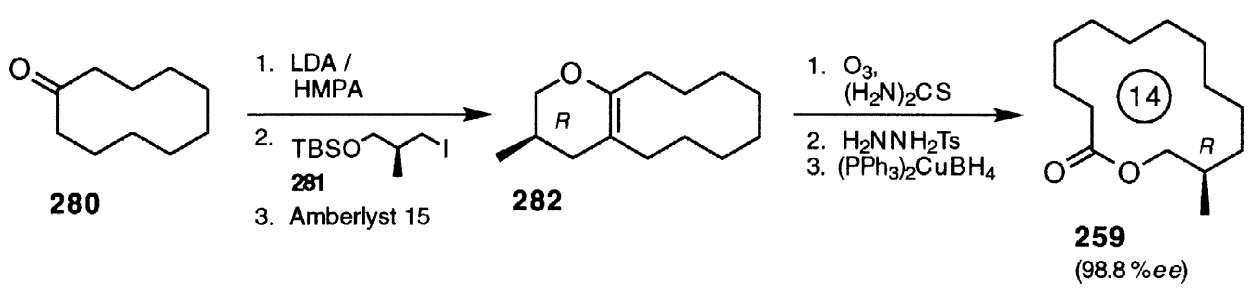
An early synthesis of muscone (**214**) starting from cyclododecanone(**267**) involved the reduction and dehydration of the bicyclic enone **272** to give **273**, which was ozonized and reduced to the ring-enlarged diol **274**.[239] Copper-catalyzed pyrolysis furnished the dihydropyran **275**, which upon treatment with acid yielded the dehydro-muscone **276**.



267 **277** **278** **279**

Ambretone, Musk TM II

An efficient ring-enlargement with four carbon atoms using the oxy-Cope rearrangement transforms cyclododecanone (**267**) into cyclohexadec-5-en-1-one (**279**),[240–242] which is a valuable, musky compound known under the trade names Ambretone®, and Musk TM II®. Chlorination of **267** with sulfuryl chloride yields **277**, which when treated with two mole equivalents of vinyl magnesium chloride provides the hydroxydivinyl compound **278** as a *cis/trans*-mixture. Thermal rearrangement of **278** furnishes the target compound (*E/Z*)-**279**.



280 **282** **259** (98.8 %*ee*)

Employing chiral building blocks readily available from bioorganic hydroxy acids, *e.g.* **281** from (+)-(2*S*)-methyl 3-hydroxy-2-methylpropanoate, macrolides could also be synthesized in high optical purity *via* a ring-enlargement sequence.[243] The first stereoselective synthesis of (+)-(12*R*)-12-methyl-13-tridecanolide (**259**) commenced with the HMPA-mediated alkylation of cyclodecanone (**280**) with chiral building block **281**, followed by Amberlyst®15 catalyzed cyclisation to **282**. Ozonolysis and selective reduction of the resulting carbonyl group furnished **259** with 98.8 %*ee*. This synthetic sequence was applied to several other macrolides with overall yields of isolated material up to 37%,[244] and enantiomeric excesses of up to 99.8 %*ee*.[245]

12-Methyl-13-tridecanolide (**259**) is not only interesting because of its *fine musk* odour and the significantly different odour of its enantiomer, its biogenesis in *Archangelica officinalis* Hoffm. is also not obvious. Only very recently was the final proof of structure made by coinjection with synthetic material,[246] and (+)-(12*R*)-**259** was

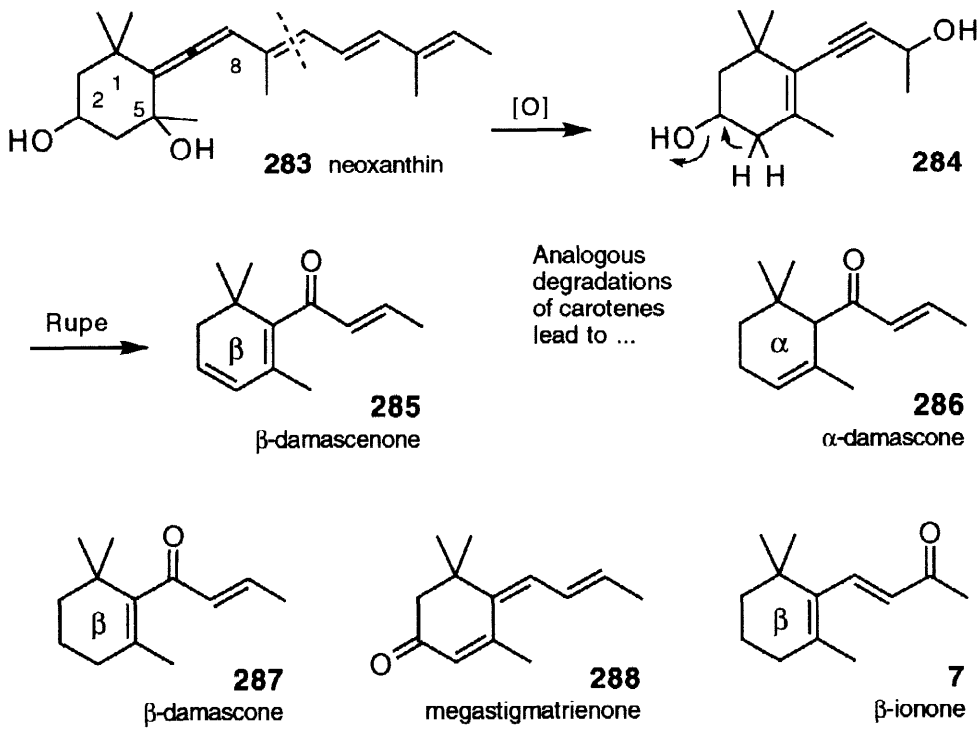
found to be the main enantiomer, though the ratio of (+)-(12*R*)-**259** to (–)-(12*S*)-**259** was only 72% to 28%.[246] This reminds us, that quite often nature is not just as selective as we may assume, or as synthetic chemistry is, for that matter.

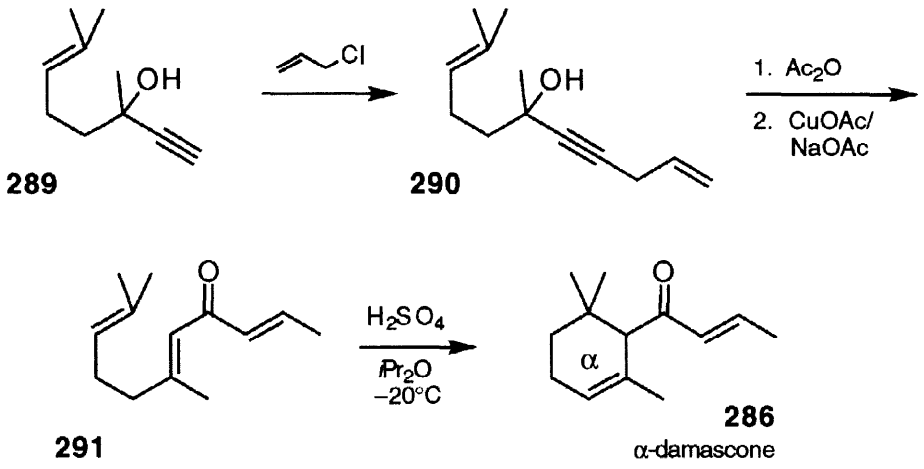
3.5 *Floral Odorants*

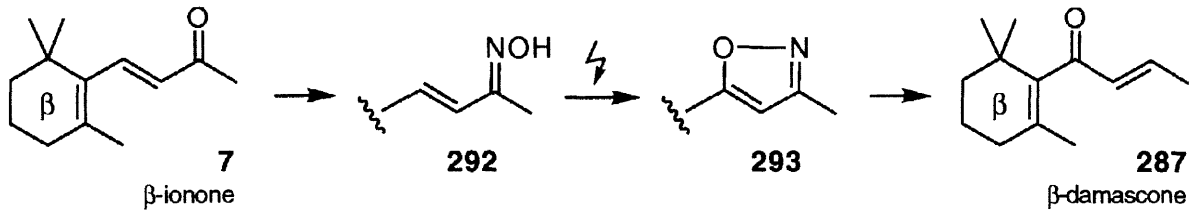
The kingdom of blooms is the domain of monoterpenes and C_{13}-degraded carotenes. β-Damascenone (**285**) is a prominent example of the latter class of compounds. Its biosynthesis has been suggested[247] to proceed *via* the oxidative degradation at C-9 of allenic carotenes such as neoxanthin (**283**). Dehydration of **284** followed by Rupe rearrangement could explain the formation of **285**, while deoxy-neoxanthin might be the biochemical precursor for α- and β-damascones (**286** and **287**). In a similar way megastigmatrienone (**288**) may be formed, while ionones, like β-ionone (**7**), are accessible by oxidative degradation of a great variety of carotenes.

The history of the isolation and structure elucidation of β-damascenone (**285**) from Bulgarian rose oil (*Rosa damascena*), as told by Kastner,[248] is one of the most exciting chapters of fragrance chemistry–the original analytical results were published 20 years later, in 1987.[249]

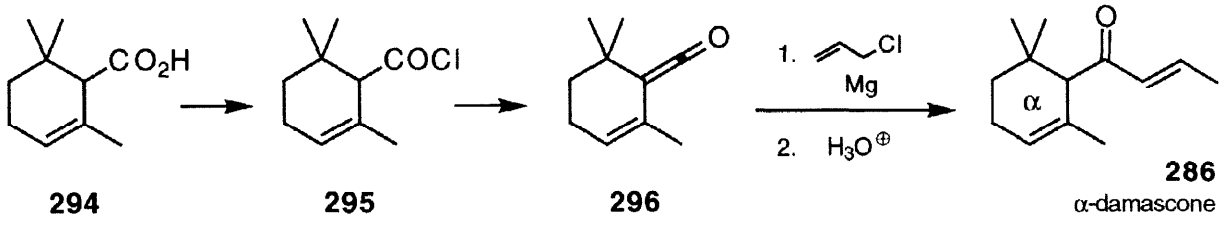
Three years after the structure elucidation of the damascones, in 1970, the first technical process to α-damascone was established and started from dehydrolinalool (**289**).[250] Coupling of **289** with allyl chloride led to **290**, which was transformed by $Cu^{\oplus}$-catalyzed Claisen rearrangement (Saucy-Marbet reaction) of the acetylenecarbinol acetate and isomerization to **291**. Acid-catalyzed cyclization finally gave α-damascone (**286**).





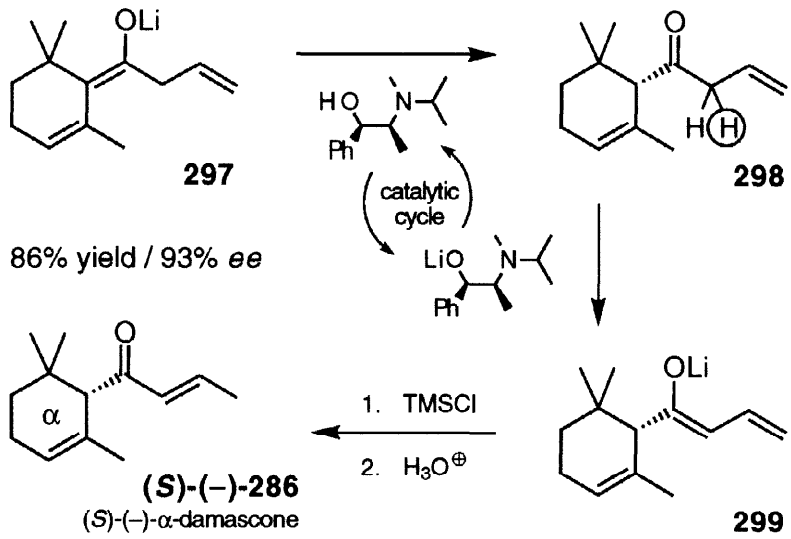


An interesting 1,3-transposition of the carbonyl group from ionones to damascones is possible *via* an isoxazole intermediate.[251] For instance, β-ionone (**7**) was transformed into its ketoxime **292**, which then was oxidized to the corresponding isoxazole **293**. Birch reduction and thermolysis, or acidic hydrolysis provided β-damascone (**287**).

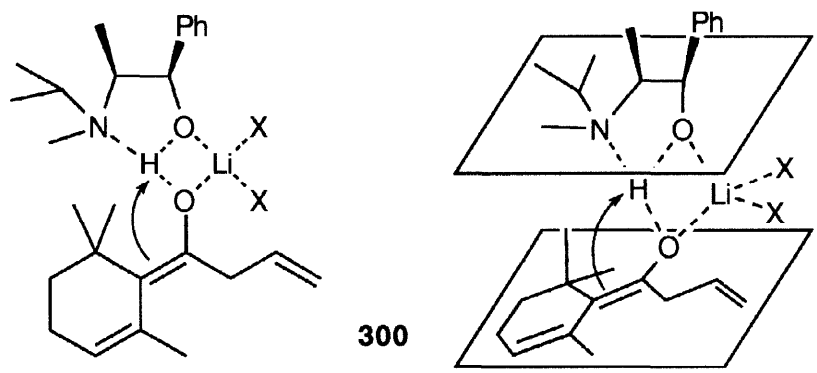


Another route to α-damascone (**286**) started from α-cyclogeranic acid **294**.[252] The latter was first transformed to its acid chloride **295**, then dehydrohalogenated to provide ketene **296**, which was further reacted with the Grignard reagent of allyl chloride, hydrolyzed and isomerized to the target molecule **286**.

While β-damascenone (**285**) smells *floral-waxy, typically of Bulgarian rose blooms*, β-damascone (**287**) is *floral-woody, somewhat tobacco-like*, and α-damascone (**286**) smells *floral-fruity, green, apple-like with a harsh camphoraceous cork-note*. This cork-stopper off-note is due to the (*R*)-(+)-α-damascone [(*R*)-(+)-**286**], whereas the (*S*)-(−)-isomer [(*S*)-(−)-**286**] is *linear, clean and more intense*—in addition it possesses a *pleasant wine-like nuance*. Fehr achieved a stereoselective synthesis of (*S*)-(−)-α-damascone [(*S*)-(−)-**286**], and developed an elegant method for the enantioselective protonation of enolates.[253]

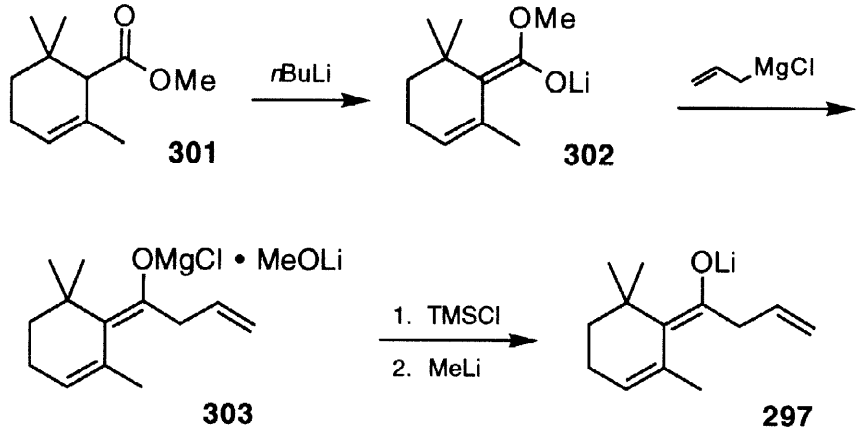


The most interesting, catalytic modification of this approach was published in 1994.[254] Lithium enolate **297** is stereoselectively protonated to give **298** by substoichiometric amounts of (1*R*,2*S*)-(−)-*N*-isopropylephedrine. The lithiated chiral auxiliary is protonated by an acidic allylic hydrogen of **298**, thus providing lithium enolate **299**, and regenerating the chiral auxiliary to close the catalytic cycle. Reaction of **299** with trimethylsilyl chloride and hydrolysis provides (*S*)-(−)-α-damascone [(*S*)-(−)-**286**] in 86% yield with 93% *ee*.

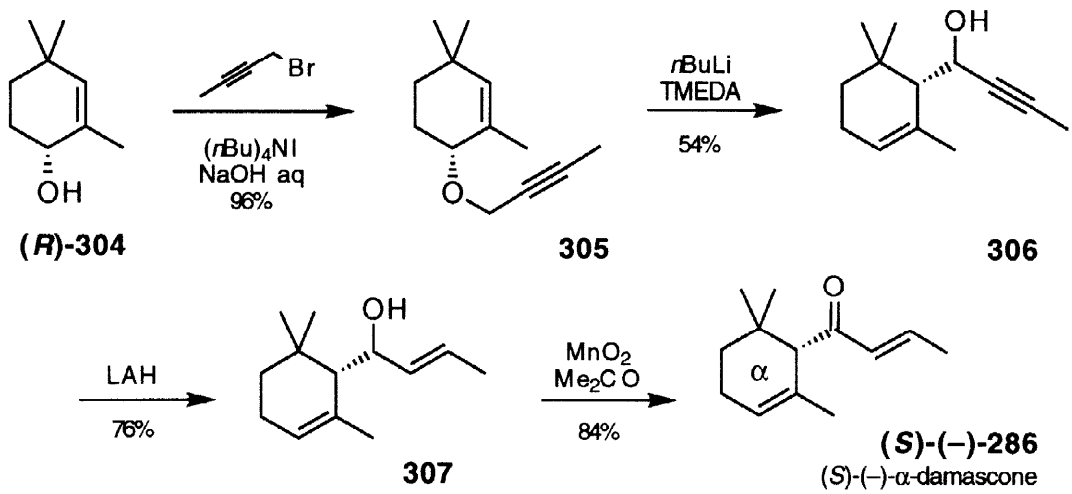


The high stereoselectivity of the protonation was rationalized by Fehr with model **300**, in which the proton is transferred *via* a nine-membered transition state with the nitrogen actively participating. The nitrogen atom, the proton, and the double bond are situated over each other, and the bulky phenyl as well as the methyl group of the chiral auxiliary point in the opposite direction.[255]

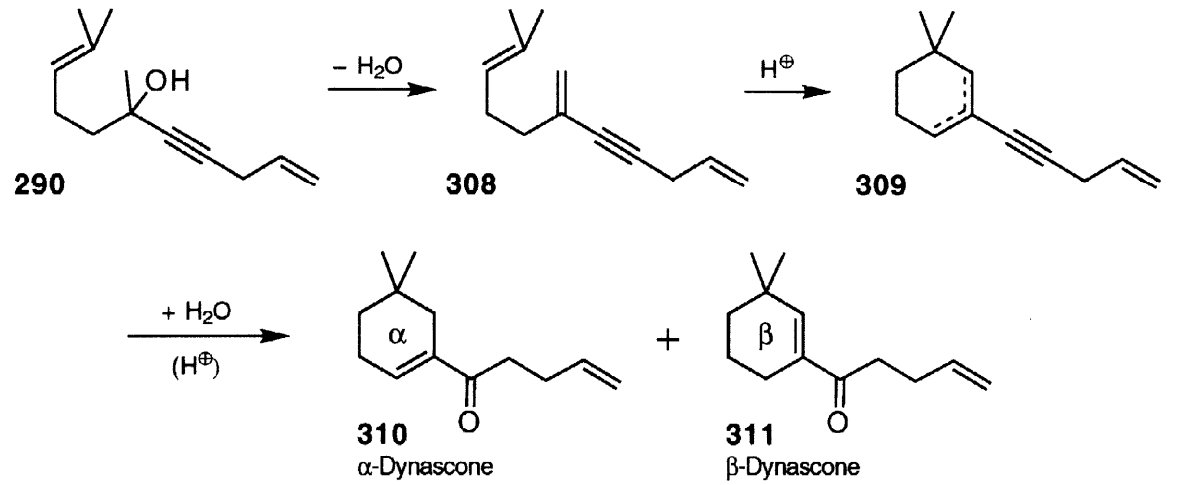
However, the synthesis of the enolate **297** is quite complicated. Methyl α-cyclogeranate (**301**) has first to be lithiated, reacted with allylmagnesium chloride to give **303**, and finally transmetallated *via* trimethylsilyl enol ether. That makes the technical application of this elegant stereoselective approach very demanding, and up to now (*S*)-(−)-α-damascone [(*S*)-(−)-**286**] has neither been used in perfumery nor seen on the market.

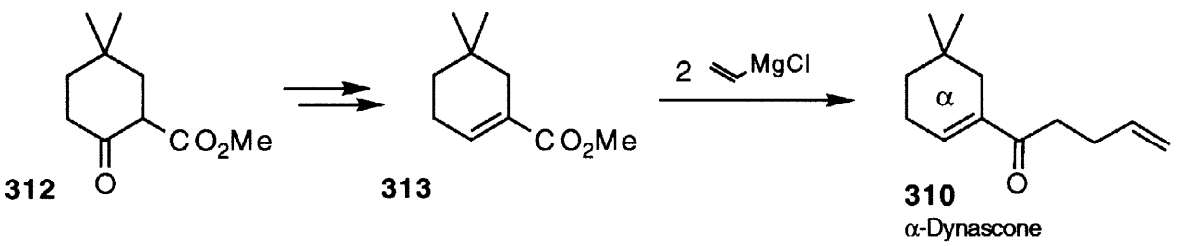


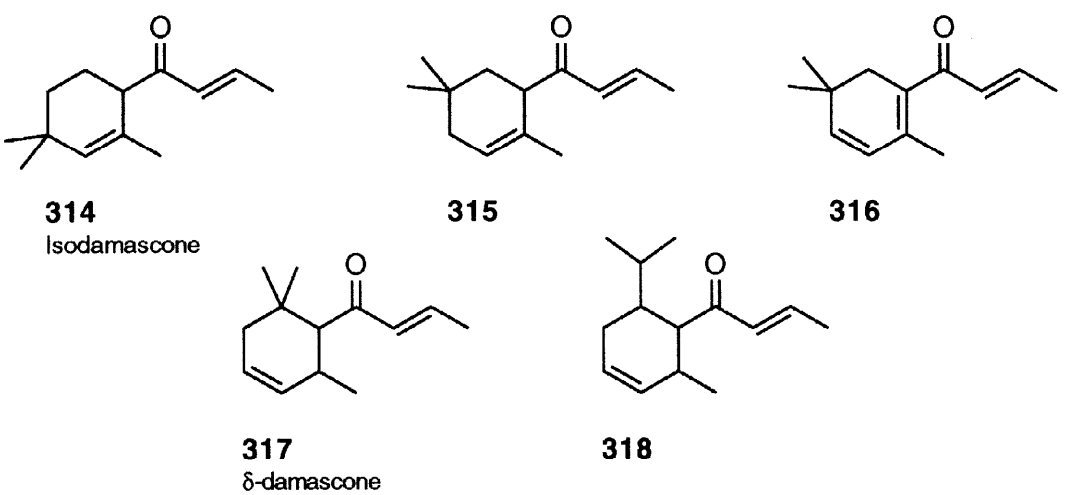
A more academic synthesis of (*S*)-(–)-α-damascone [(*S*)-(–)-**286**] was carried out by Mori *et al.*[256] The chiral building block (*R*)-**304**, prepared by enzymatic resolution of the corresponding acetate with pig liver esterase, was O-alkylated to give **305**. The chirality was then transferred by means of a [2.3]-Wittig rearrangement, and the triple-bond of the resulting product **306** was reduced with lithium aluminium hydride to provide **307**. Manganese dioxide oxidation of the allylic alcohol moiety furnishes the target molecule S-(–)-α-damascone [(*S*)-(–)-**286**].[256]



In addition to the *cork note* of (*R*)-(+)-α-damascone [(*R*)-(+)-**286**], the *green aspect* of technical α-damascone (**286**) varied in the early syntheses and often could not be tolerated. Analytical investigations showed this off-note to be due to a powerful impurity with the structure **310/311**.[257] This was formed by dehydration of **290**, acid-catalyzed cyclization of **308**, and hydrolysis of the product to the mixture of **310** and **311**.







The pure mixture **310/311** possesses a *green, galbanum-type* odour with *pineapple-like, hyacinth and metallic facets*, and was found so interesting, that it was immediately developed.[258] It has been named Dynascone®, and contributes, for example, markedly to »Cool Water« (Davidoff, 1988).

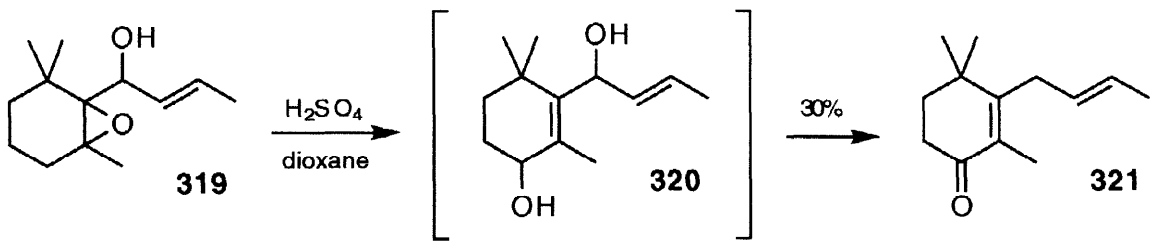
In contrast to α-Dynascone® (**310**), the β-isomer **311** is *much weaker, has no galbanum character, and is much more ionone-like,* thus less interesting. Hence, selective routes to α-dynascone (**310**) were developed,[257]

one of which starts from **312**, which is reduced and dehydrated to **313**. Double addition of a vinyl Grignard reagent to the methyl ester **313** then selectively yields α-Dynascone (**310**).

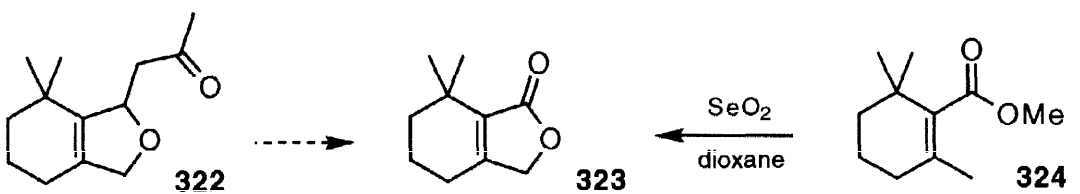
Naturally, the success of the damascones (**285–287**) and Dynascone (**310/311**) triggered a lot of work on derivatives, and related structures. Isodamascone® (**314**), introduced in 1971 by Dragoco, was one of the first, and one of the few outstanding derivatives.[259] The shift of the *gem*-dimethyl substituent from the C-1 to the C-3 position changes the α-damascone odour to a *fresher, apple-purée-like tonality,* though both still share many common aspects. Isodamascone® (**314**) has been used, for instance, in 1% in »Burberrys« (Burberrys, 1992).

The connecting link from α-damascone (**286**) to Isodamascone® (**314**) would be **315** with the *gem*-dimethyl substituent at C-2. Together with related structures, **315** was prepared by Weyerstahl *et al.* in 1996.[260] Its odour, however, was described as *apple-like, nutty and woody*, apparently the floral character was lost. From all the 2,2-dimethyl analogues only **316**, the β-damascenone (**285**) derivative, smelled *damascone-like with plum and fig undertones.*

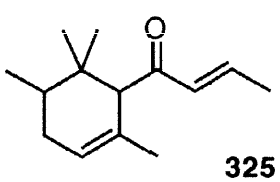
A shift of the double bond of α-damascone (**286**) from $\Delta^{4,5}$ to $\Delta^{3,4}$ leads to δ-damascone (**317**), a commercial product of IFF.[261] Increasing the steric bulk at C-1 by substituting the *gem*-dimethyl group by an isopropyl group, finally leads to **318**, which was patented by Quest.[262] The odour of **318** still is *damascone-like, with fruity-woody nuances.*



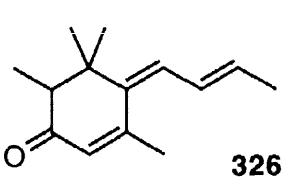
Epoxy β-damascol **319** now leads us to megastigmaenones. Its acid-catalyzed rearrangement *via* **320** gives the megastigmadienone **321**, which possesses a *very impressive fine floral-fruity odour with a tobacco note.*[263] It was isolated in trace quantities from Virginia tobacco and passion fruit.



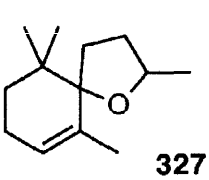
7,11-Epoxymegastigma-5(6)-en-9-one (**322**) was found by Kaiser to be present in the astonishing high amount of 79%[264] in the headspace of the strong *ionone-floral* smelling *Houlletia odoratissima* Lind. ex Lindl. ex Paxt., a rare terrestrial orchid native to the northern part of South America. Compound **322** was also found in 38% in the scent of the recently described Peruvian orchidaceae *Gongora cruciformis* Whitten & D. E. Benn,[265] together with 2% of a new compound, which was proposed to have the structure **323**.[266] This was confirmed by selenium dioxide oxidation of methyl β-cyclogeranate(**324**).[266]



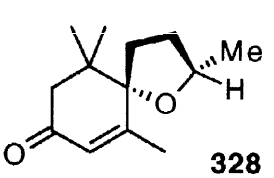
325
irone damascone



326
irone megastigmatrienone



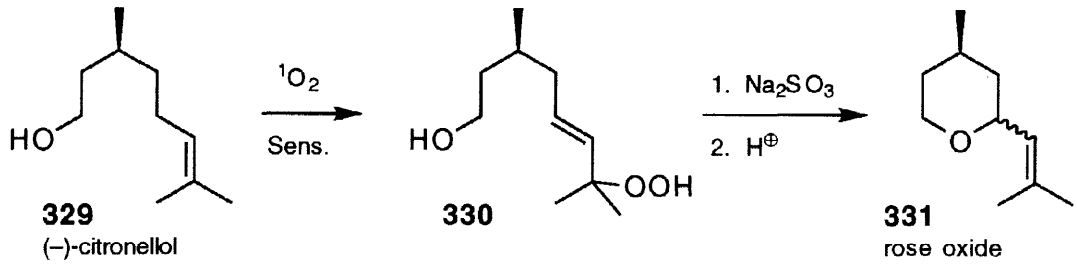
327
theaspirane



328
cis -theaspirone

To complete the chemistry of carotene degradation products, it should be mentioned that the irone homologues of damascone **325**,[267] and of megastigmatrienone **326**[268] have also been synthesized. The odour of the latter was evaluated as being similar to the *tobacco, sweet, plum, and orris-like* scent of megastigmatrienone **288**.[268]

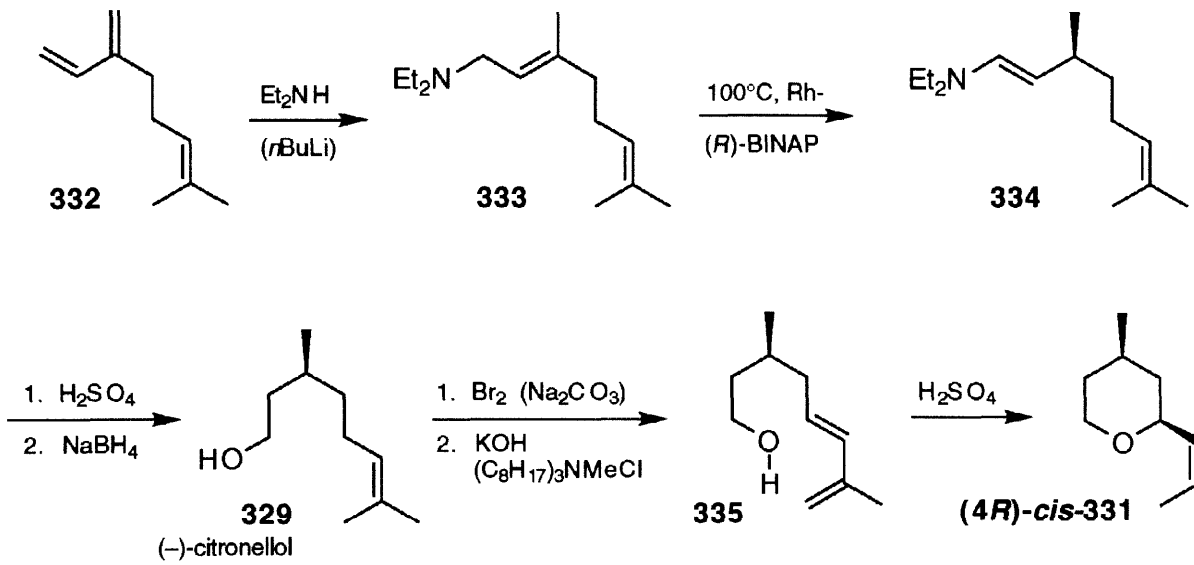
Derivatives of theaspirane (**327**) also belong to the class of degraded carotenoids, and some interesting work on the structure-odour correlation has been carried out in this class of compounds.[269] They have *fruity, especially blackcurrant-like odours* and therefore will not be discussed here. *cis*-Theaspirone (**328**), however, does belong to the floral odorants—it smells *orris-like, sweet-powdery, floral, and has tea-like nuances.*[270]



329 (–)-citronellol **330** **331** rose oxide

Only a few years earlier than β-damascenone (**285**), another trace constituent of Bulgarian rose oil had attracted the interest of perfumers and fragrance chemists. Following the identification of rose oxide (**331**) in 1961,[271] process development started immediately, and the monoterpene soon became an important perfumery ingredient. Some prominent examples include »Rive Gauche« (St. Laurent, 1971), »Metal« (Paco Rabanne, 1979), and »Drakkar Noir« (Guy Laroche, 1982) with 0.5 % of **331**. Its photochemical synthesis by Ohloff *et al.*[272] is a prominent example for the reactivity of singlet-oxygen in industrial production. (–)-Citronellol (**329**) is irradiated in methanol in the presence of oxygen with rose bengal as sensitizer. After consumption of one equivalent of oxygen, aqueous sodium sulfite is added to **330**. The reduced reaction product is then isolated and treated with dilute sulfuric acid to provide **331** as a diastereomeric mixture.

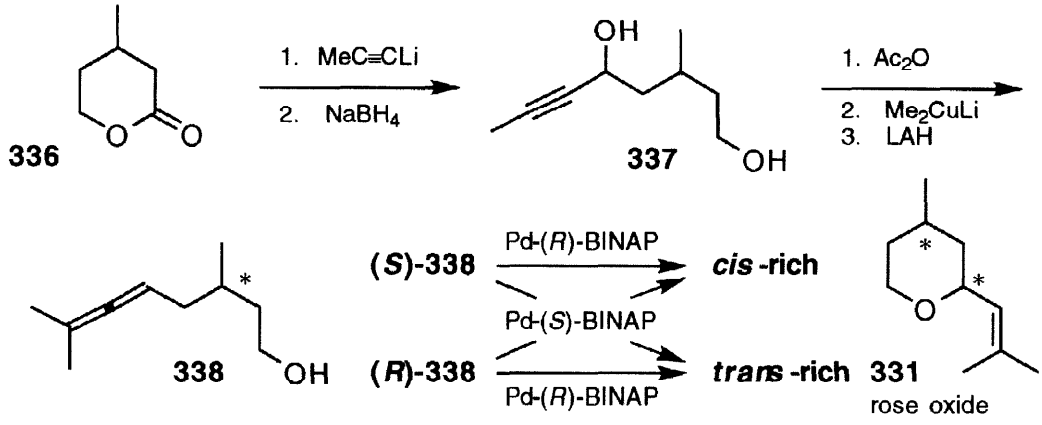
Though Ohloff *et al.*[273] had synthesized and evaluated the enantiomers of both *cis*- and *trans*-rose oxide, it was only recently found by Takasago that (4*R*)-*cis*-rose oxide [(4*R*)-**331**] has a threshold of 0.5 ppb,[274] ten times lower than that of its enantiomer (4*S*)-**331**.



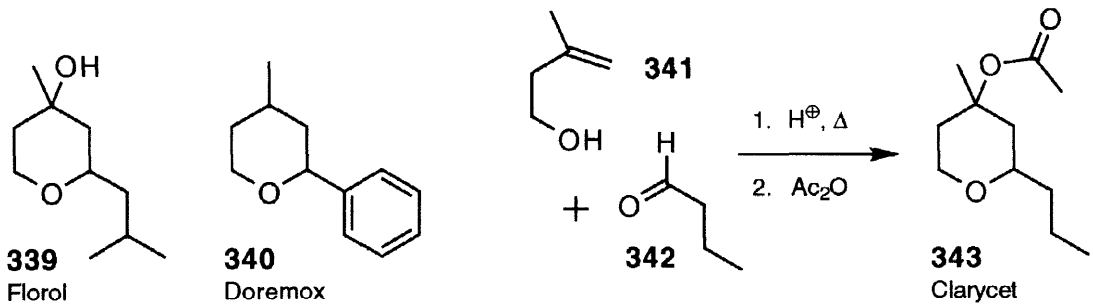
332 **333** **334**

329 (–)-citronellol **335** **(4*R*)-*cis*-331**

The elegant asymmetric isomerization[276] of allylamine **333**, which is also used in the Takasago (–)-menthol process,[275] provides the chiral enamine **334** in excellent 98 %*ee*. Enamine hydrolysis and reduction give (–)-citronellol (**329**), which is transformed to dehydrocitronellol (**335**) by bromine addition, and subsequent elimination in the presence of Aliquat® 336. The following acid-catalyzed cyclization to (*R*)-*cis*-rose oxide [(*R*)-*cis*-**331**] proceeds with high diastereoselectivity.[277]



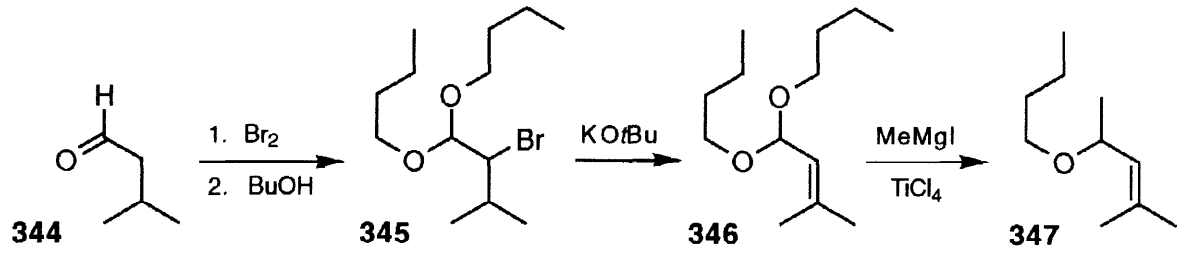
Another interesting approach to *cis*-rich (4*R*)-**331** is the Pd-BINAP catalyzed cyclization[274b] of allene **338**.[278] This is available from 3-methyl δ-valerolactone (**336**) by addition of 1-propynyl lithium, sodium borohydride reduction, esterification with acetic anhydride, alkylation by the Gilman reagent, and LAH reduction.[278] However, introducing the stereochemistry in the β-methyl lactone **336** remains the major problem of this approach. Once solved on an industrial scale, the diastereoselective cyclization by Pd-BINAP becomes attractive. For example, the *cis*-rich (4*R*)-*cis*-**331** was obtained from (*R*)-allene alcohol (*R*)-**338** by the use of the Pd-(*S*)-BINAP complex, while the *cis*-rich enantiomer (4*S*)-*cis*-**331** was produced from the (*S*)-allene alcohol (*S*)-**338** and the Pd-(*R*)-BINAP complex.



Besides the natural rose oxide (**331**), three analogues have attained commercial importance, *i. e.* Florol® (**339**), Doremox® (**340**),[279] and Clarycet® (**343**).[280] Doremox® (**340**) with its *strong floral-green, rose odour reminiscent of rose oxide* is a prime example for the old rule,[281] that isobutenyl can be replaced by phenyl without change in the odour characteristics. The most interesting variation of the rose oxide theme is Clarycet® (**343**) of IFF. It combines the *floral, green-rosy note with clary-sage, camomile-like and lavender aspects*, and is produced by acid-catalyzed reaction of 3-methylbut-3-en-1-ol (**341**) with butan-1-al (**342**), and subsequent esterification with acetic acid anhydride.[280]

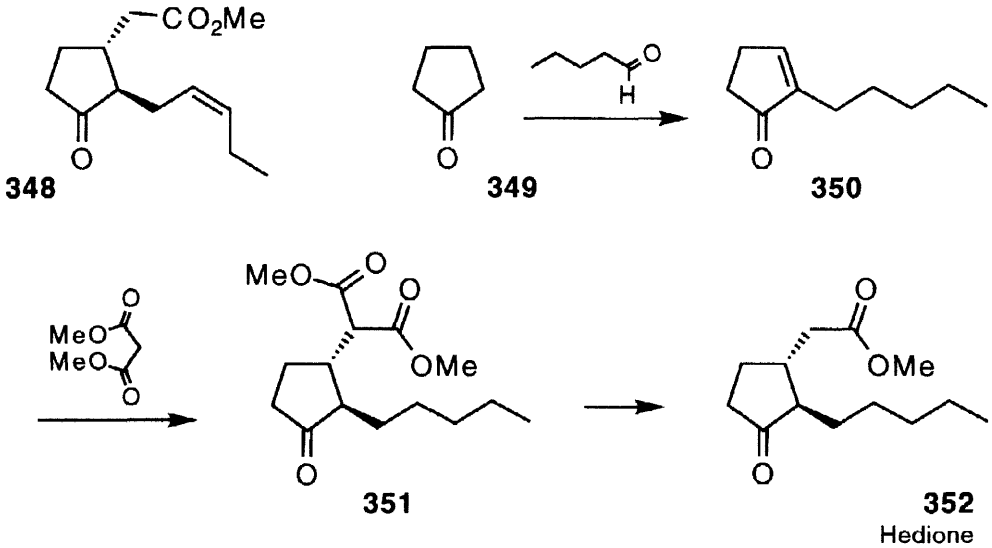
An in-depth study of the structural requirements for the rose oxide odour was carried out by Weyerstahl and Hoepfner in 1986.[282] They found an ether oxygen and an α-branching with an at least C_3-alkyl chain to be

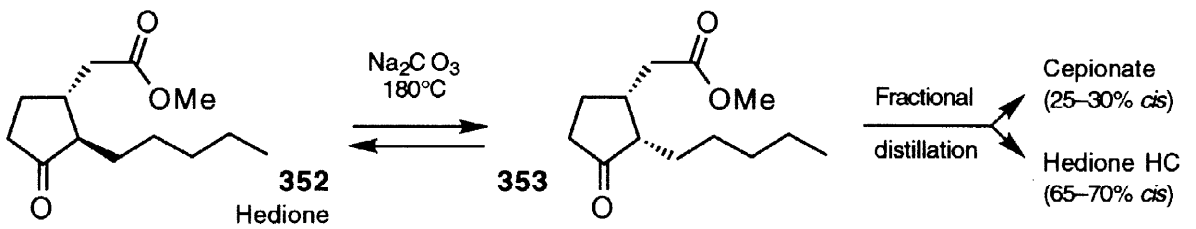
indispensable for the rose oxide odour. The six-membered ring can be replaced by a five-membered ring, and even imitated by alkyl groups.



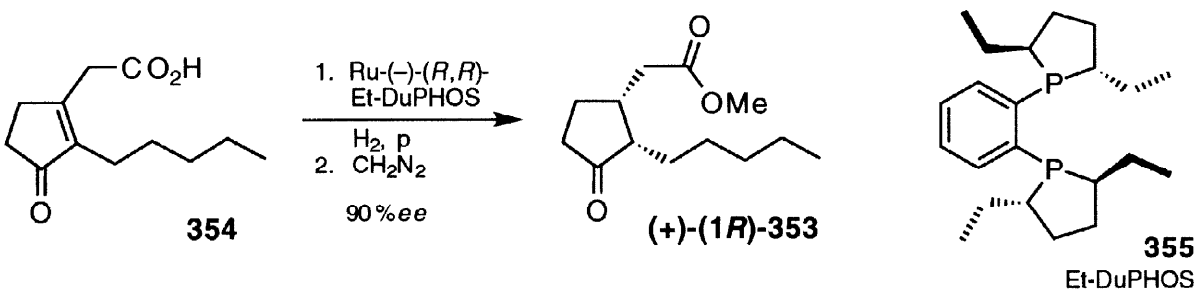
The best *seco*-analogue of rose oxide (**331**) was compound **347**, which has a *rose oxide odour with a herbaceous-fruity tonality.* Since prenal polymerized too readily, and formed 1,1,3-trialkoxy derivatives upon direct acetalization, the synthesis of **347** commenced with the bromo acetalization of isovaleraldehyde (**344**) with *n*-butanol. Elimination and Mukaiyama–Grignard reaction[283] then provided the target molecule **347**.[282]

What β-damascenone (**285**) and rose oxide (**331**) were for Bulganrian rose oil, so was methyl (–)-*trans*-(*Z*)-jasmonate (**348**) for jasmine absolute (*Jasminium grandiflorum* L.).[284] However, in this case it was not the natural product, but the dihydro derivative, commercially known as Hedione® (**352**) and first synthesized in the course of the structure elucidation of **348**, that became famous. Patented in 1960,[285] Hedione® (**352**) had its olfactory debut as a 3% constituent of »Eau Sauvage« (Dior, 1966). Later it was used at higher concentrations: 22% in »First« (Van Cleef & Arpels, 1976), and at about 30% in »Cristalle« (Chanel, 1993). Hedione® (**352**) with its *light, smooth-floral, sweet, jasmine-like* odour even set up a new fragrance category, the *eaux fraîches*, and was the starting point for the *unisex* fragrances. Its industrial synthesis from cyclopentanone (**349**) by aldol condensation with pentanal, subsequent isomerization to intermediate **350**, and Michael addition of malonic ester yields Hedione® (**352**) almost exclusively as the *trans*-isomer. However, it is the *cis*-isomer of **352** that is much more intense, and much more distinct in its odour characteristics.

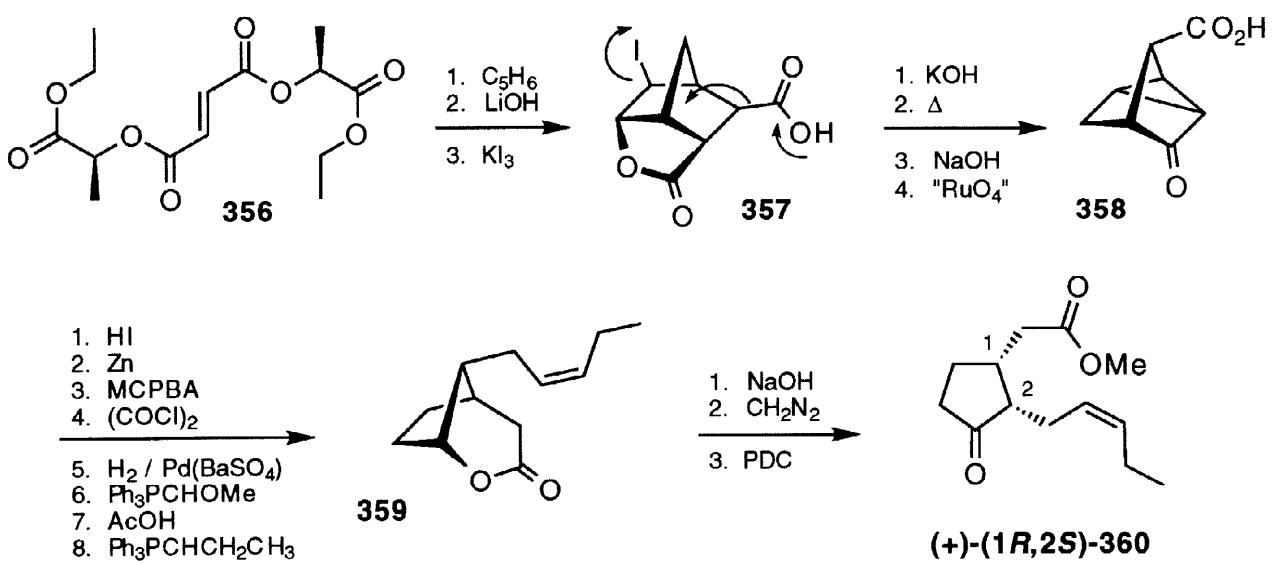




Therefore, in 1989 a process was worked out at Nippon Zeon to increase the amount of *cis*-isomer (**353**).[286] By heating **352** with sodium carbonate, about 10% of *cis*-isomer (**353**) is formed, which is further increased to about 25–30% by fractional distillation. The resulting product was introduced as Cepionate®. A *high-cis* quality of Hedione® (**353**) is also manufactured by Firmenich. This so called Hedione HC® (65–70% *cis*) was important for the creation of »CK one« (C. Klein, 1994). The use of the more expensive Hedione HC® is limited, because the *cis*-isomer (**353**) isomerizes outside a narrow 5.5–6.5 pH range.

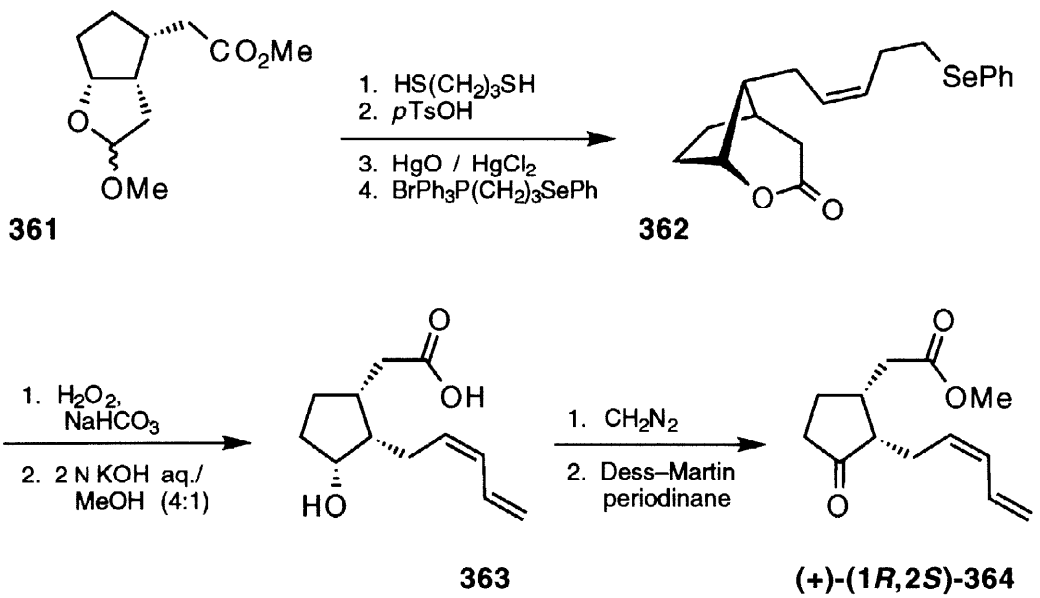


The next step to improve the qualtity of Hedione® (**352**) would be an industrial route to the (1*R*)-*cis* enantiomer (+)-(1*R*)-**353**, which is the most intense and most characteristic component of Hedione® (**352**). Catalytic asymmetric hydrogenation of the cyclopentenone **354** could be feasible on an industrial scale.[287] Using the ethyl DuPHOS ruthenium catalyst **355** the (+)-(1*R*)-*cis* enantiomer (+)-(1*R*)-**353** was prepared with 90 %*ee* and a *cis*/*trans* ratio of 96:4.[288]



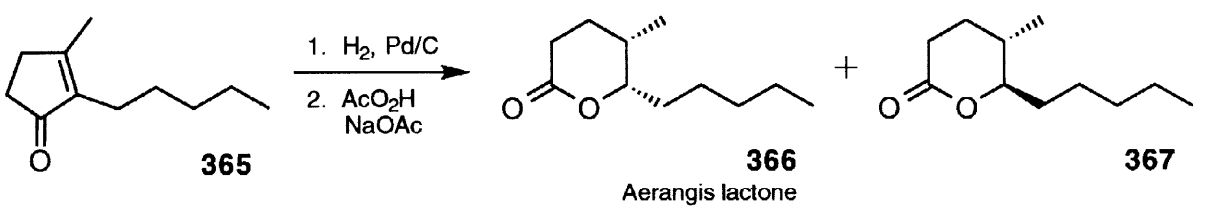
A 17-step synthesis of enantiopure (+)-(1*R*)-**353** starting from levoglucosenone, a pyrolytic product of cellulose, was also reported.[289]

It is again the (1*R*,2*S*)-enantiomer that carries the jasmine fragrance in the naturally occurring methyl jasmonate. Compared with the (+)-(1*R*,2*S*)-methyl *epi*-jasmonate [(+)-(1*R*,2*S*)-**360**], which has an odour threshold of 0.012 ng/L, the threshold of the epimeric (–)-(1*R*,2*R*)-**360** is 20 times higher, while the other jasmonates were described as odourless.[290] The first stereoselective synthesis of (+)-(1*R*,2*S*)-methyl *epi*-jasmonate [(+)-(1*R*,2*S*)-**360**] was carried out in 1990 by Helmchen, Goeke *et al.*,[291] starting with the stereoselective Diels-Alder cycloaddition of the fumaric ester of ethyl lactate **356** to cyclopentadiene. *Via* a decarboxylation-elimination reaction the tricyclic ketocarboxylic acid **358** was constructed, that was further transformed to the bicyclic lactone **359**. Hydrolysis, esterification and PCC oxidation finally provided the odoriferous target molecule (+)-(1*R*,2*S*)-**360**.



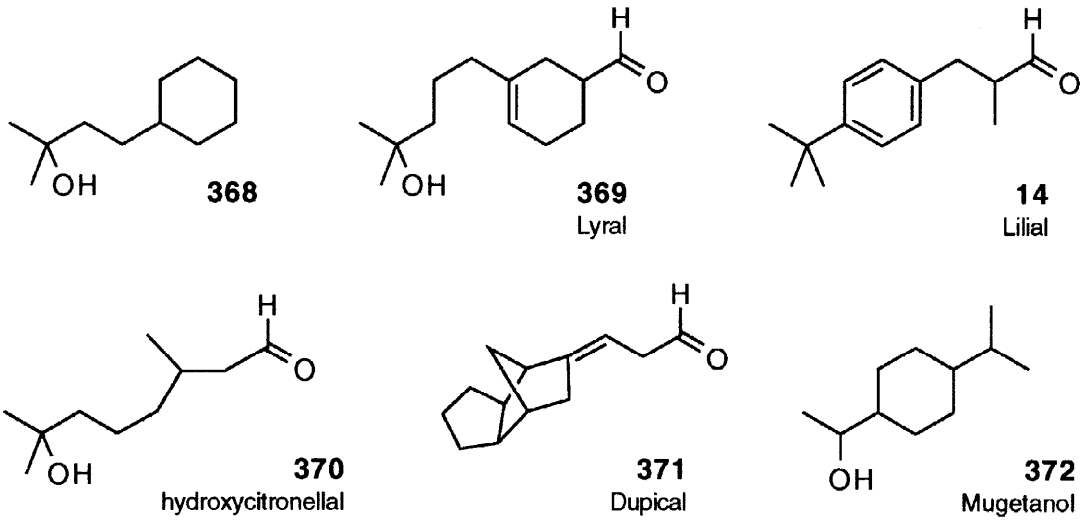
361 **362** **363** **(+)-(1*R*,2*S*)-364**

Cymbidium goeringii (Rchb. f.) Rchb. f. is a widespred Asian Orchid with a *pleasant, lily-of-the-valley-type, fresh-citrusy, floral odour.* While the *lily of the valley* aspect is due to nerolidol and (*E*,*E*)-farnesol, the *fresh-floral odour note reminiscent of ripe lemons and jasmine*, as discovered by Kaiser,[292] is caused by methyl *cis*-(*Z*)-dehydrojasmonate **364**. Its absolute configuration was determined by Kitahara *et al.*[293] to be (1*R*,2*S*) by a stereoselective synthesis starting from acetal ester **361**, which was converted to the bridged phenylselenide lactone **362** in four steps. Oxidative elimination of the phenylselenide moiety afforded the corresponding diene, which after alkaline hydrolysis provided **363**. Treatment with diazomethane and Dess–Martin oxidation completed the enantioselective synthesis of (+)-(1*R*,2*S*)-**364**, which was shown to be identical with the natural isolate by capillary GC.



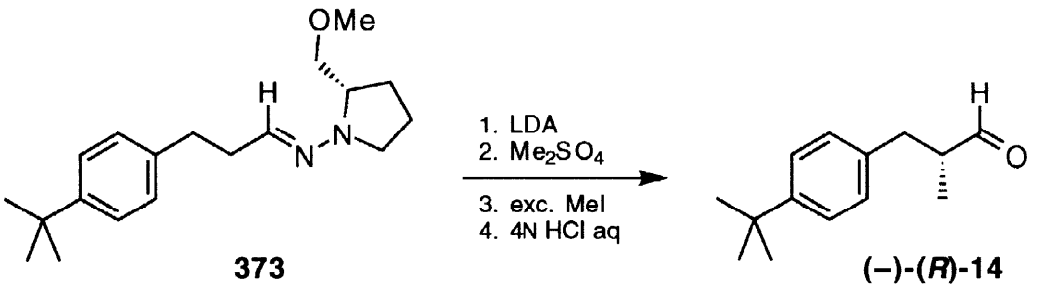
365 **366** Aerangis lactone **367**

Aerangis lactone (**366**) was discovered by Kaiser[294] as the main odour component of the African "moth orchids" *Aerangis confusa* J. Stewart and *Aerangis kirkii* (Rolfe) Schltr., and is characterized by aspects *reminiscent of tuberose and gardenia.* Its synthesis by hydrogenation of dihydrojasmone (**365**) and subsequent Baeyer–Villiger oxidation is straightforward.[294] By enantioselective multidimensional capillary GC, *cis*-(4*S*)-methyl-(5*S*)-decanolide was identified as the unique stereoisomer of Aerangis lactone [(4*S*,5*S*)-**366**, 99.9 %*ee*].[295]



In 1994, 1,1-dimethyl-3-cyclohexylpropan-1-ol (**368**) had its debut at 10% in »L'eau d'Issey pour homme« (Miyake,1994).[296] With its *sweet, floral, fresh-muguet, and lilac-like odour* it leads us to *lily-of-the-valley* odorants. Lilial®(**14**)[297] with >2500 t/a ,[298] Lyral® (**369**)[299] with 520 t/a,[298] and hydroxycitronellal (**370**) with 1100 t/a[298] are the commercially most important compounds of this class of odorants, and even in the 2D structural formulas their molecular similarities become apparent. Dupical® (**371**) of Quest,[300] and Mugetanol® (**372**) of H&R[301] are two more recently developed *lily-of-the-valley* odorants, though Mugetanol® (**372**) had actually been discovered and patented by Monsanto in 1975.[302] By transesterification with vinyl laurate in the presence of Pseudomonas lipase,[303] all stereoiomers of **372** were prepared. They all possess lily-of-the-valley odours, but the (–)-(1*S*)-*cis*-enantiomer [(–)-(1*S*)-**372**] turned out to the most intense and distinct one.

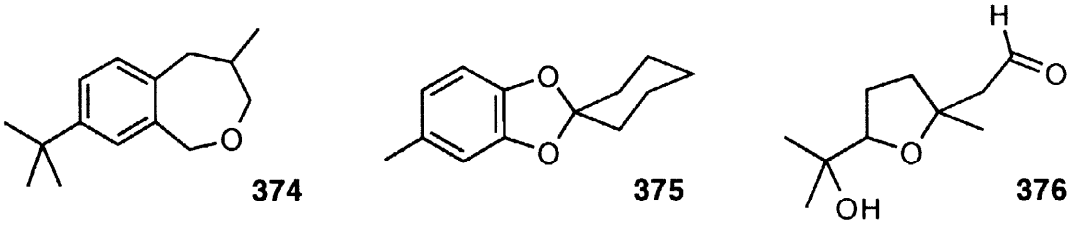
Lilial® (**14**) with its *very powerful, fresh, floral note reminiscent of lilly of the valley, lindenblossom, and cyclamen,* was used at 2% in the masculine Fougère »Paco Rabanne« (Rabanne, 1973), and even at 20% in the feminine *fruity-floral* fragrance »Calyx« (Prescriptives, 1987). To find out if an enantioselective approach to this important industrial product would pay in terms of odour intensity, Enders and Dyker[304] synthesized both enantiomers of Lilial® (**14**) *via* the SAMP/ RAMP hydrazone method. The SAMP hydrazone **373** was α-alkylated by deprotonation with lithium diisopropylamide and treatment with dimethyl sulfate. The resulting product was then cleaved by heating with excess methyl iodide, and subsequent hydrolysis with aqueous hydrochloric acid provided (–)-(*R*)-**14** in 95 %*ee*. This (–)-(*R*)-enantiomer was found to be the most intense, though the differences were small, and both enantiomers smelled of *lily of the valley.*



373 **(–)-(*R*)-14**

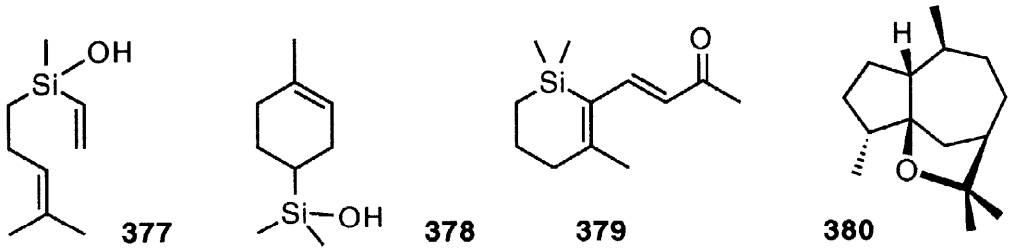
With the idea to fix the side chain of Lilial® (**14**) in a cyclic ether in an energetically favourable conformation Skouroumounis and Winter[305] synthesized compound **374**, which, however, was found to be *weak and vague, without the slightest lily-of-the-valley* aspect. The motivation for the synthesis of **374** and related ethers was the replacement of the labile aldehyde group of many lily-of-the-valley odorants by a more stable functional group.

After several attempts in this direction[306] Anselmi, Pelosi *et al.*[307] found in the easily accessible ketal **375** a *white-floral, lily-of-the-valley-like* odorant without aldehyde or hydroxy function. With regard to the occurrence of cyclic ethers in the essential oil of lily-of-the-valley (*Convallaria majalis* L.), Boelens *et al.*[300] synthesized the tetrahydrofuran derivative **376**,which biogenetically may arise from citral. Indeed, the synthezised compound **376** with some structural resemblance to hydroxycitronellal (**370**) was found to possess a *fresh, white-floral odour with a fruity-citrusy note.*



374 **375** **376**

At the end of this chapter, we revisit the terpenes. A series of sila derivatives of odoriferous terpenes has been synthezised by Wannagat *et al.*,[308] and summarized in two reviews.[309] The substitution of carbon by silicon increases the electronic charge on the adjacent oxygen, stretches the molecule, and increases its mass. In effect, the odour of the sila linalool **377** is shifted from *lily of the valley* to *hyacinth*, that of sila terpineol **378** from *lilac* to *lily of the valley*, and that of sila β-ionone **379** from *violet* to *freesia.*



377 **378** **379** **380**
liguloxide

That terpenes still have surprises in store can be seen in liguloxide (**380**), which was isolated from the essential oil of an *Olearia phlogopappa* clone.[310] One might expect a *floral-herbaceous* odour; however, liguloxide (**380**) was found to possess *a typical tomato ketchup* note.[310]

4 CONCLUDING REMARKS

As mentioned at the beginning, we did not aim at a comprehensive review. We chose from a wealth of material, publications and patents, led by our own interests, and those of our industry. We did not even touch the topics of *herbaceous-spicy* and *fruity* odorants. Nevertheless, we tried to show the interested reader the fantastic diversity of fragrance chemistry and its long and intellectually very rewarding passage from natural essences, tinctures, absolues *etc.*

A constantly recurring question is –and it is well justified– how to find a new odorant which fulfills the necessary conditions of it being: "new," "aesthetically pleasing," "non-toxic," "cheap," "stable and biodegradable," and "better / more useful" in comparison with the hundreds of existing compounds.

In section 2 we discussed the limited knowledge of the olfactory mechanisms, the sorry state of *structure-odour relationships* (SOR), and consequently of the *rational design* of new odorants. Thus, the finding of a new odorant with all the above mentioned attributes is still very empirical—based almost exclusively on a broad chemical knowledge, experience, fantasy, and instinct, but backed up with modern tools for carrying out *molecular similarity* studies.

Natural products are, as ever, an important source of leads, both for new odour tonalities, and for new structures. The *headspace* technique, *i.e.* the trapping of scent of the living flower is today a generally used method.[311–314] Trace components of essential oils can also contribute significantly to the odour characteristics, as was demonstrated by the identification of powerful alkaloids.[318]

It is well known that the perception of an odour is very subjective, influenced by physiology and psychology, which obviously makes a meaningful evaluation of odorants difficult. As Sell put it,[31] "odour is not a physical property."

In order to cancel out large individual differences of odours and their thresholds, normally a panel is used for the evaluation of new substances. In order to rate the odour strength the *odour value* (OV)[319] has been introduced:

$$OV = \frac{\text{vapour pressure (ng/L)}}{\text{threshold conc. (ng/L)}}$$

The OV of commercial odorants is in the range of $10–10^7$, the vapour pressure being 50 ng/L–50 mg/L, whereas the threshold is in the range of 2 pg/L to about 2 μg/L.[319,320] Without considering the hedonics, the higher the OV, the more powerful (useful) is the compound, in principle—although odour value alone does not account for all the complexity of odour perception.

Several attempts have been made to establish an alternative to the unsatisfactory, because so individual, descriptive method of characterizing odours. One of these approaches, at least for the similarity if not for the quality of odours, has been made by examining panel correlation diagrams, obtained from odour threshold measurements with odorants of similar and dissimilar odour notes.[321]

Substantivity, besides the odour quality and odour strength, is the most important characteristic of a fragrance molecule.[10] The substantivity defines the duration of perceptibility of a fragrance (molecule) on skin, hair, fabric, *etc.* Some of the fragrance molecules display themselves also a fixative influence on a mixture—they are substantive and fixative.[266,322–324] The substantivity of fragrances in detergents and softeners on laundry is of profound economical and ecological interest. The "more odour" remains on the laundry, the more effective is the fragrance, the less is washed out, and the less burdened is the ecosystem.[325–327] Especially in this context, it is essential that fragrance chemicals are biodegradable. One increasingly researched route for higher substantivity is that of precursors, the aim of which is to prepare a derivative of the desired compound that displays a better stability or a lower solubility, *etc.*, and that under the influence of a pH-temperature change or an enzyme releases the compound at the right place and the right time.[328] These compounds are supposed to be stable in detergent powders (pH up to 9) or in softeners (pH down to 2–3). They should not be washed out during the washing process, then be cleaved, and deposit the fragrance on the laundry.[11]

Acknowledgement

For proof-reading of the manuscript, and for useful comments we are most grateful to *P. Naegeli.*

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Note on Trademarks—Words which we know or have reason to believe constitute registered trademarks ® are designated as such in the text. However, neither the presence nor absence of such designation should be regarded as affecting the legal status of any trademark.

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Biographical sketch

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Georg Fráter, born 1941 in Budapest (Hungary), obtained his Ph. D. working with Professor H. Schmid at the University of Zürich, and spent postdoctoral years in Leiden, The Netherlands, and Edmonton, Canada. After more than ten years of agrochemical research with Hoffmann-La Roche, he joined Givaudan Roure in Switzerland, and became head of its synthetic chemistry research. Georg Fráter has authored a large number of publications and patents, and contributed significantly to modern synthetic methodology. He is also senior lecturer at the University of Zürich.

Jerzy A. Bajgrowicz, born 1950 in Wroclaw (Poland), graduated from the Technical University of Cracow, and obtained his doctorate in organic chemistry at the Technical University of Wroclaw in 1977. He spent several years doing research in the domain of azaaromatics and asymmetric synthesis of aminoacids, and teaching chemistry at his *alma mater*, then at the Ecole Normale Supérieure of Rabat (Morocco), and the University of Montpellier (France). After the next four years dedicated to the pharmaceutical research (Laboratoires Fournier, Dijon, France), in 1989, he joined Givaudan Roure Research, where he is now the head of the Fragrance Chemistry group. His main research interests are focused on the design –using CAMD techniques– and synthesis of new odorants.

Philip Kraft, born 1969 in Rendsburg (Germany), studied chemistry at the University of Kiel. He received his diploma in 1994, and obtained his doctorate *summa cum laude* in 1996, doing organic syntheses of medium and large ring compounds under the supervision of Professor W. Tochtermann. In 1996, he joined Givaudan Roure Research as a laboratory head in Organic Synthesis. He was awarded a scholarship of the *Studienstiftung des Deutschen Volkes* from 1990–94, the *Chemiefonds-Stipendium des Verbandes der Chemischen Industrie* 1994–96, and the faculty prize of the University of Kiel in 1997.