

Chapter 7

Aroma Chemicals IV: Musks

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7.1 Introduction

Monsieur Eme s'expliquait à présent pourquoi son choix s'était à l'époque – et si spontanément – porté sur le musc à l'exclusion de tout autre parfum, et il comprenait aussi pourquoi cette eau de toilette en particulier lui convenait si bien et servait si parfaitement sa stratégie de séduction et de conquête. La connotation sexuelle de son parfum lui apparut soudain dans toute sa clarté. L'espace d'un instant, Monsieur Eme fut lui-même un chevrotaïn porte-musc en rut . . .

P. Kemp, *Musc* [1]

Musk is the dried secretion from an internal pouch found between the hind legs of the male musk deer *Moschus spp.*, which resembles an ordinary deer with hare-like long ears, grey-brown body colour and two canine teeth protruding from its upper jaw. The musk deer measures approximately 60 cm, is 10–13 kg in weight, and inhabits the mountain forests of at least 13 countries in southern and eastern Asia and eastern parts of Russia. Its intensely smelling secretion serves for both territorial boundary marking and for attracting female partners over large distances, i.e. as a pheromone. To harvest the secretion, the animal was traditionally hunted. The main hunting season was in February and March, when hunger forces the animals to leave their inaccessible hiding-places in the mountains [2]. After killing the animal, the pouch was removed with the outer covering of hair and hide, and dried in the sun or on a heated stove. Most of the hair and hide was removed, and the musk pods (Figure 7.1) were soaked in water and then opened to yield fatty brownish grains. By extraction of these musk grains with alcohol, tinctures were prepared that were directly used in perfumery.

The best quality was Tonquin musk from Tibet and China, followed by Assam and Nepal musk, while Carbadine musk from some Russian and Chinese Himalayan regions was considered inferior [3, 4]. To obtain 1 kg of musk grains, between 30 and 50 animals had to be sacrificed, and thus musk tinctures were very expensive perfumery ingredients. At the beginning of the nineteenth century, the price of Tonquin musk grains was about twice their weight in gold. But despite this high price, musk tinctures were still used in perfumery till about 1979, when musk deers were protected from extinction by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) and complimentary national laws. Today, natural musk, the quantity legally permitted by CITES as well as that poached and illegally traded, continues to be used only in traditional east Asian medicine, as a sedative or stimulant to the heart and nerves, and most importantly as an aphrodisiac.



Figure 7.1 Dried musk pods in different views with hair and hide partially removed, approx. 4 cm (1.5 inches) in diameter.

The first olfactory impression when smelling musk tinctures is *animalic*, *sweet* and *ammoniacal*. But the more one studies its character, the more contrasting, vibrant and oscillating it becomes: *repulsive–attractive*, *chemical–warm*, *sweaty–balmy*, *acid–waxy*, *earthy–powdery*, *fatty–chocolate-like*, *pungent–leathery*, *resinous–spicy*, *fig-like*, *dry*, *nutty* and *woody*, to give just some impressions [5]. To get an idea about this olfactory richness, smell for instance »Musc Ravageur« of *Maurice Roucel* (Editions de Parfums Frederic Malle, 2000) [6], which extrapolates these facets into a well-balanced perfume.

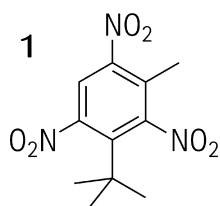
Considering this diversity of adjectives, it is understandable why biologists usually used the term ‘*moschata*’ or ‘*moschatellina*’ simply to indicate a strong smell, and thus several plant and animal species bear this designation: *Abelmoschus moschatus*, *Fragaria moschata*, *Adoxa moschatellina*, *Achillea moschata*, *Malva moschata*, *Mimulus moschatus*, *Fusarium moschatum*, *Aromia moschata*, *Cairina moschata*, *Hypsiprymnodon moschatus*, *Eledone moschata*, *Chrysolampus moschitus*, *Sterotherus moschatus*, *Nosotragus moschatus*, *Desmana moschata* and *Ovibus moschatus* [5]. The latter, musk ox, is even often incorrectly associated as the source of natural musk. In perfumery, however, musk is generally considered a prime olfactory descriptor. What then is ‘*musky*’, and what are ‘*musks*’?

The term ‘*musk*’ is an abstraction from the complex odour impressions of natural musk tinctures, especially from the dry-down, after the more volatile parts are evaporated. It refers to the *warm*, *sensual*, *sweet-powdery* tonality of the dry-down. This abstraction began in 1888, with the discovery of ‘*Musk Bauer*’ (1) by Albert Bauer [6]. The introduction of this musk as a 10% solution in acetanilide for about \$500 per kilo [7], which was half the price of musk tincture at that time, was such an immediate commercial success that several small fragrance companies were formed all over Europe. We will return to ‘*Musk Bauer*’ later, but for the moment let us keep in mind that the term ‘*musk*’ was coined even before the odorous principle of Tonquin musk was known.

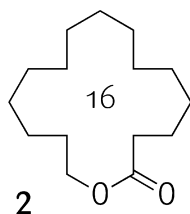
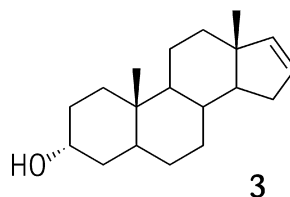
Today, younger perfumers hardly know Tonquin musk, and chemical benchmarks define the ‘*musky*’ odour impression, an impression that is most often associated with the odour of *baby skin*. Hence, the smooth, soft and intimate ‘*skin-on-skin*’ connotation of musks and their indispensability in perfumery to impart sensuality. Musks refine, exalt, fix, stimulate, balance and harmonise perfumery compositions; they have an erotic

effect, bring volume and diffusivity, and impart warmth and liveliness. Or in one phrase, they form the skeleton of a perfume. There is probably not a single fragrance on the market without containing any musk odorant. Actually, there is even one perfume with *just* musk: »Velviona« (Helmut Lang, 2001).

In terms of benchmarks, 15-pentadecanolide (2, Thibetolide[®], Exaltolide[®]) is probably the commercial musk with the least side notes; and thus, it will serve as the reference to what we understand as a *musk odorant*. Some steroids were claimed to emanate *musky* odours; however, they generally smell *urinous* and *animalic*, aspects present in natural musk tinctures, but not musky in terms of the above definition, even in dilution. An interesting steroid in terms of odour is α -androst-16-en-3 α -ol (3), but also this is not musky but *sandalwood-like* in dilution. That should suffice to avoid any confusion, which sometimes found its way into the literature. So let us now move on to the chemical structures of natural musk odorants.



Musk Bauer

Thibetolide[®]
Exaltolide[®] α -androst-16-en-3 α -ol

7.2 Natural musks

Bearing the commercial success of Musk Bauer (1) in mind, the apparent next question was, which compounds were responsible for the musk note of the natural Tonquin musk? Were these simple aromatic compounds like 1 or vanillin? Were they easy to manufacture? This was the motivation for Heinrich Walbaum [8] of Schimmel & Co, at that time the biggest fragrance manufacturer, to investigate musk-deer glands at the beginning of the twentieth century [9]. In 1906, he isolated the principal musk odorant, established that it was a ketone of the empirical formula $C_{16}H_{30}O$ with two double-bond equivalents, and named this new ketone 'muscone' (4) [10]. However, he had no clue about the chemical structure of muscone (4), the content of which varies from 0.5 to 2% in musk grains. And thus, the structure elucidation and synthesis of 4 remained high on the wish list of the young fragrance industry; and also on the wish list of Philippe Chuit, who had founded a small fragrance company with Martin Naef in Geneva. In 1920, he contacted Leopold Ruzicka at the ETH Zurich, who was looking for financial support and who previously had been working on irone in collaboration with the German company Haarmann & Reimer (now Symrise). In 1921, Ruzicka and Naef et Cie. (the later Firmenich) closed a co-operation contract [11] and, after work on nerolidol and farnesol, Ruzicka started the structure elucidation of muscone (4) at the end of 1922. Vigorous chromic acid oxidation of 4 yielded a series of aliphatic dicarboxylic acids that finally led to the conclusion that muscone was 3-methylcyclopentadecan-1-one (4) [12]. According to Baeyer's theory of

strain in multimembered rings [13], such macrocyclic compounds were thought to be too unstable to exist; thus, Ruzicka's finding opened a new chapter of organic chemistry, which, amongst other achievements, earned him a Nobel prize in 1939.

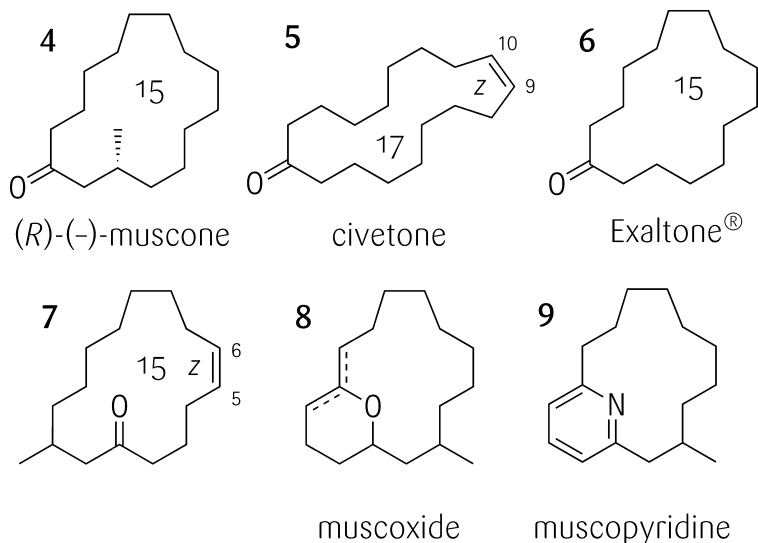
Ruzicka also investigated and elucidated the structure of civetone (5) [14], the musk odorous principle of the glandular secretion of the civet cat (*Viverra civetta*), which had been isolated in 1915 [15]. In comparison with 4, civetone (5) possesses a far more animalic musk character, perhaps due to a steroid-type folding that 5 could adopt. Even though such a steroid-type folding had already been proposed by Vladimir Prelog and Leopold Ruzicka [16] in 1943, and found its way into many organic chemistry textbooks, we shall not forget about the severe transannular strain it implies. It is virtually impossible for an odorant receptor to compensate for the resulting steric hindrance of the transannular hydrogens. The concept that due to attractive van der Waals interactions two opposite sides of a macrocycle would align just like aliphatic lipid chains, is simply wrong. To avoid transannular interactions, the *gauche* atoms in a macrocyclic ring tend to be separated as far as possible from each other. They form the corners of a triangle, a square or a pentagon, the sides of which consist of *trans*-configured aliphatic chains [17].

But let us not forget that Chuit was aiming at an industrial synthesis of muscone (4), no matter how interesting these macrocycles were from an academic point of view. Therefore, Ruzicka attempted the synthesis of macrocyclic ketones by pyrolysis of heavy metal salts of dicarboxylic acids, a method previously applied by Zelinsky [18] and Willstätter [19] to the synthesis of smaller ring systems. However, this cyclisation method [20] employing thorium salts gave only low yields of macrocyclic ketones in the order of 5–6%, and did not tolerate the β -methyl group of muscone (4). Therefore, in 1926 the *nor*-muscone, cyclopentadecanone (6, Exaltone®) was introduced to the market instead of muscone (4), at the exorbitant price of 50 000 CHF/kg [11] due to the low yields and the difficult purification. Cyclopentadecanone (6) possesses a pleasant musk note, and was later even identified in nature; it occurs in the scent glands of the Louisiana muskrat [21].

In-depth modern analyses of the odoriferous principles of Tonquin musk were carried out by Mookherjee and co-workers [22, 23] of IFF in 1970 and 1981. In the course of these studies, several new macrocycles were identified, the most interesting one in terms of odour being (5*Z*)-14-methylcyclopentadec-5-en-1-one (7). Other structurally interesting constituents are muscoxide (8) and muscopyridine (9), the latter of which was found by Ruzicka and co-workers [24] in 1946, and had been synthesised by Büchi and co-workers [25] in 1957.

The musk odorants of the animal kingdom are exclusively macrocyclic ketones. Today, *rac*-muscone (*rac*-4), civetone (5) and Exaltone® (6) are all important commercial products, and muscone continues to be a popular scientific target structure, especially for enantioselective synthesis of its naturally occurring (*R*)-(-)-isomer 4. With an odour threshold of 4.5 ng/l air [26] 4 is not even an extremely potent musk, and in water the threshold of the enantiomers differ only by a factor of 4, i.e. 61 ppb for 4 and 233 ppb for *ent*-4, while being similar in odour character [27]. However, the fascination for the genuine natural odorant motivated chemists to investigate several stereoselective syntheses, of which we present three recent ones.

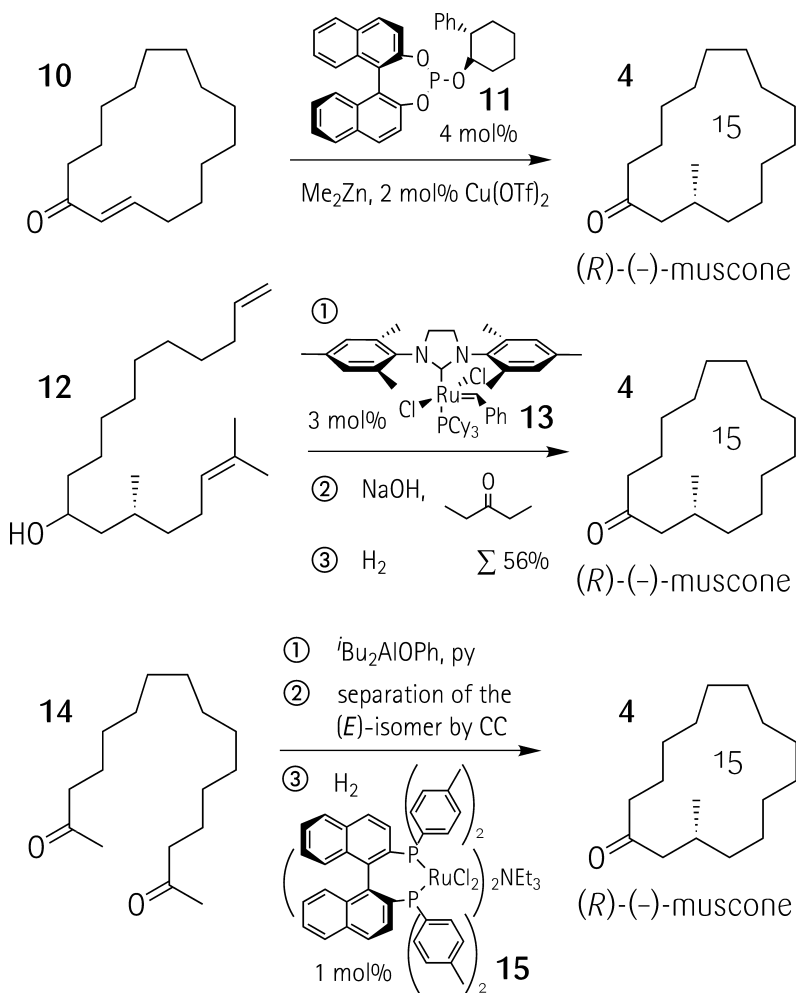
Alexakis and co-workers [28] investigated the copper-catalysed enantioselective Michael addition of dimethyl zinc to cyclopentadec-2-en-1-one (10). Out of various 2-arylcylohexal-substituted phosphites the ligand 11 turned out to be particularly



efficient for the 1,4-addition of organozinc reagents and furnished 4 with an enantiomeric excess of 79%. A very elegant synthesis of 4 was reported by Grubbs and co-workers [29]. The stereochemical information stems from (*R*)-(+)-citronellal, which is commercially available in high enantiomeric purity. A simple Grignard reaction with 1-bromodec-ene provides 12 that was subjected to ring-closing metathesis (RCM) in the presence of the second-generation ruthenium alkylidene 13. Following RCM, sodium hydroxide and 3-pentanone were added to initiate Ru-catalysed transfer hydrogenation to provide the macrocyclic ketone. Addition of gaseous hydrogen then resulted in the Ru-catalysed hydrogenation of the formed double bond and afforded 4 in overall 56% yield. Another approach was recently developed at Takasago [30]. Intramolecular aldol condensation of 2,15-hexadecadienone (14), prepared from 1,10-dibromodecane by double acetoacetic ester synthesis, furnished an (*E/Z*)-mixture of 3-methyl-2-cyclopentadecen-1-one. Silica-gel column chromatography (CC) afforded the pure (*E*)-isomer, which was required for the enantioselective reduction using the $\text{Ru}_2\text{Cl}_4[(S)\text{-}p\text{-tolyl-BINAP}]_2\text{NEt}_3$ catalyst system. Employing this catalyst, hydrogenation at room temperature at 70 atmospheres provided (*R*)-(-)-muscone (4) with >98% *ee*. If some day one of these three strategies will be applied on an industrial scale is an open question.

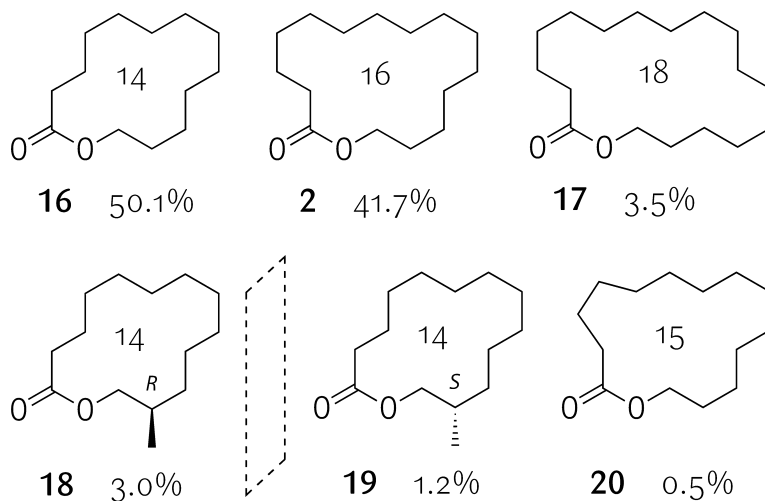
In the plant kingdom, musk odorants are exclusively macrolides, macrocyclic lactones. The most important one we have already met, 15-pentadecanolide (2, Thibetolide[®], Exaltolide[®]) was discovered in 1927 in Angelica root oil (*Archangelica officinalis* Hoffm. syn. *Angelica archangelica* L.) by Max Kerschbaum [31] of Haarmann & Reimer. At the same time, the competitor Firmenich introduced it into perfumery as Exaltolide[®], at the exorbitant price of 100 000 CHF/kg [11]. They had subjected their Exaltone[®] (6) to subsequent Baeyer–Villiger oxidation. The 15-pentadecanolide (2), thus obtained, has a more distinct and delicate musk note and is less animalic than 6, and like most macrolides, it smells slightly floral. The odour threshold of 2 was measured as 2.1 ng/l air [10].

In a recent in-depth analysis [32], 15-pentadecanolide (2) was shown to account for about 42% of the macrolide fraction of Angelica root oil. Besides some traces of

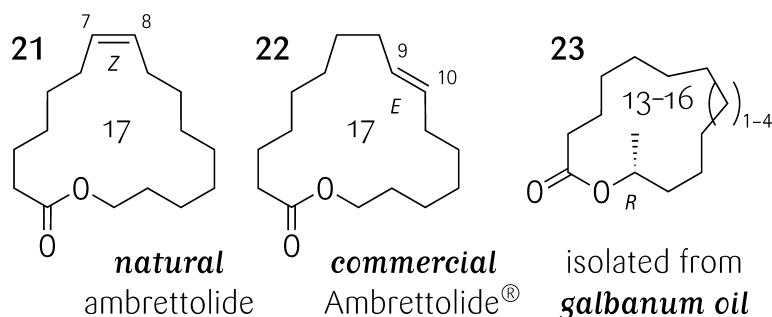


16-hexadecanolide, several other macrolides were detected. The main component is 13-tridecanolide (16), which makes about half of the macrolide fraction, accompanied by its 12-methyl derivative 18/19 occurring in around 4% of the macrolide fraction. This is followed by 3.5% of 17-heptadecanolide (17) and 0.5% of 14-tetradecanolide (20), so that the main components possess an odd number of ring-carbon atoms. However, excepting 18/19, no further ($\omega - 1$)-methyl macrolides occur, not even of the second-most abundant component 15-pentadecanolide (2). Though not occurring in nature, the corresponding 14-methyl-15-pentadecanolide is a very interesting musk odorant [33], and in an obvious analogy it has been termed 'muscolide' by Günther Ohloff [34]. Nevertheless, 12-methyl-13-tridecanolide (18/19), discovered in Angelica root oil by Taskinen [35], is an interesting musk odorant too, especially since it was the first example for which the importance of methyl substituents on the character of macrocyclic musks was demonstrated [36, 37]. The (R)-isomer 18 possesses a *clean musk note with strong sandalwood accents and a slight fruity undertone of pear*, while the enantiomer 19 differs

unambiguously by a *pronounced animalic musk note accompanied by camphoraceous aspects*. The *nor*-derivative **16** is much more *camphoraceous and rather cedarwood-like than musky*. Both enantiomers **18** and **19** occur in Angelica root oil [32] in the ratio of 72:28, and the major enantiomer **18** recently has become an attractive target for synthetic organic chemists [38]. These were the most important aspects on Angelica root oil, and if you are interested in an olfactory impression, smell »Angeliques sous la pluie« (Editions de Parfums Frederic Malle, 2000) [6], in which *Jean-Claude Ellena* interprets this theme.



Next to 15-pentadecanolide (**2**), the commercially second-most important natural musk is ambrettolide (**21**), or, more strictly, **21** rather than **22**, which is sold as Ambrettolide[®], i.e. a double-bond isomer. The reason for this is that it is not synthesised from ambrettolic acid, but from aleuritic acid, the main acidic constituent of shellac [39]. So do not get confused, what was isolated from Ambrette seed oil (*Hibiscus abelmoschus* L. syn. *Abelmoschus moschatus* M.) by Kerschbaum [31] in 1927 has the structural formula **21**. However, both compounds are relatively similar in smell: *Powerful musky, warm-aromatic with fruity-floral nuances and some reminiscence to genuine Ambrette seed oil*.



The four macrolides of the general formula 23, which were discovered by Roman Kaiser and Dietmar Lamparsky [40] of Givaudan in Galbanum oil (*Ferula galbaniflua* Boiss. et Buhse and *Ferula rubicaulis* Boiss. syn. *Peucedanum galbanifluum* Baill. and *Peucedanum rubicaule* Baill.), do not at all possess the character of their parent essential oil. Galbanum oil has a very *characteristic sharp spicy-green, leaf-like character with balsamic nuances*. The odour characteristics of the isolated ω -methyl macrolides 23 range from *fruity-woody* (12-tridecanolide) via *woody-cedar, balsamic* (13-tetradecanolide) to *distinct musky* (14-pentadecanolide and 15-hexadecanolide), and again the compounds with an odd number of ring-carbon atoms are the more abundant in the oil. It is interesting to note that, in comparison with 18 and 19, both enantiomers of 13-tetradecanolide smell very similar and both possess complex cedarwood-type odours [37], so an ω -methyl group probably sterically hinders the interaction with the musk receptor. We clearly see that methyl groups do matter.

This is stressed, because Max Stoll [41] of Firmenich summarised in 1936 his data on macrocycles derived from the natural leads in the following empirical rules (slightly abbreviated and adapted):

- (1) To smell musky the macrocyclic ring must contain 14–18 members.
- (2) One carbonyl or imino group must be present, but a second one will completely destroy the musk odour.
- (3) Lactones and oxa ketones are stronger than ketones, yet further oxa substituents diminish the odour intensity.
- (4) Methyl groups have almost no influence on the odour.

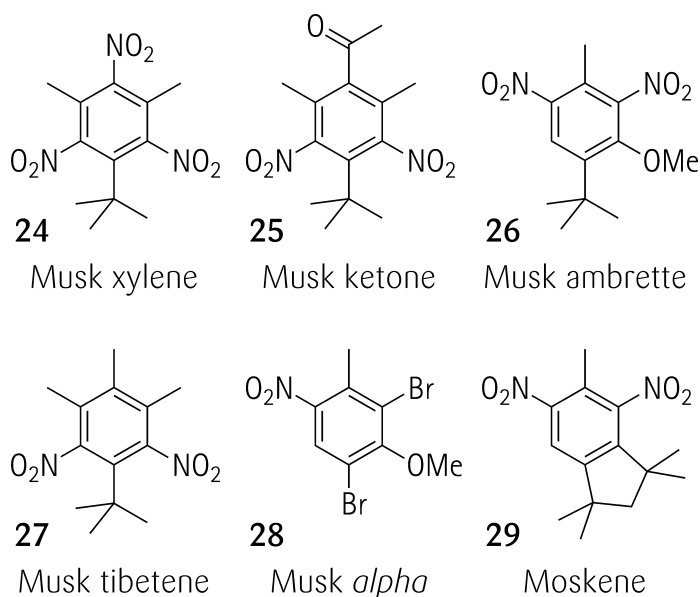
As a rule of thumb, these statements are quite practical, but one must be very careful as there are important exceptions to each of them. Above, we saw the importance of methyl groups. These exceptions provide interesting insights into the design of new powerful macrocycles. However, for the moment we leave it here, since for a long time macrocyclic musks had economically no chance against the easier-to-produce and consequently much cheaper nitro and polycyclic musks.

7.3 Nitro musks

So back to the nitro musks. Musk Bauer (1) had simply been discovered by serendipity [10], Albert Bauer had actually been searching for new explosives and had alkylated trinitrotoluene (TNT) by Friedel–Crafts reaction with *tert*-butyl halides [7]. Together with the *Société des produits chimiques de Thann et de Mulhouse* he patented and produced Musk Bauer (1), and motivated by its immediate success, systematically studied further derivatives. In short succession he discovered Musk xylene (24), Musk ketone (25) [42] and Musk ambrette (26) [43], all before the dawn of the twentieth century. These three musks 24–26 soon replaced Musk Bauer (1), and became the epitome of musks for the next 50 years. Many perfumes of that period, like for instance »Chanel N°5« by *Ernest Beaux* (Chanel, 1921), had over 10% of nitro musks incorporated, mainly 25. Musk ketone (25), with an excellent odour threshold of 0.1 ng/l air [10], is considered to resemble the natural Tonquin musk character quite closely, with a *sweet, powdery, mild animalic and warm character*. Musk xylene (24) is somewhat harsher, and due to its

cheaper price found more application in the soap and detergent segment. Musk ambrette (26) was special in adding a *heavy floral side note* to the *persistent sweet musk tonality* of the family. Consequently, it was often employed in floral perfumes, like for instance the floral salicylate prototype »L'Air du Temps« by *Francis Fabron* (Nina Ricci, 1948). Especially in these perfumes, Musk ambrette (26) was difficult to replace, when it was severely restricted [3] in use in 1981, and subsequently withdrawn from the market. Reasons for the restrictions of the nitro arenes were mainly a certain toxicity (neurotoxicity) and their phototoxicity, but besides they also caused ecological concerns due to their poor biodegradability.

Extensive research on nitro arenes – in the course of which also the wrong structures assigned to Musk ketone (25) and Musk ambrette (26) by Bauer were corrected – led to the introduction of three further nitro musks by Givaudan: Musk tibetene (27) [44], Musk *alpha* (28) and Moskene (29) [45]. Musk tibetene (27) discovered by M. S. Carpenter [44] in 1937 became the commercially most important one of these, being closer in odour to 25 than to 24. Musk *alpha* (28) is interesting for its unique blend of marine and musky tonalities, while Moskene was the first musk with an indanic skeleton [46].



In 1951, Carpenter [47] of Givaudan summarised his data on nitro musks in the following empirical rules (slightly modified):

- (1) To smell musky, nitro arenes must possess a *tert*-alkyl group (*tert*-butyl or *tert*-amyl) and a molecular weight below 300 u.
- (2) Either two nitro groups need to be present, or a nitro group and an alkoxy group (MeO, EtO or *i*PrO).
- (3) In alkoxy nitro arenes, the *tert*-alkyl group must be *ortho* to the alkoxy group in order to smell musky.

Of course, there are also exceptions to these simple rules: 2-Bromo-1-*tert*-butyl-4-methoxy-3,5-dinitrobenzene smells musky, while 2-bromo-5-*tert*-butyl-4-methoxy-1,3-dinitrobenzene with the *tert*-butyl group *ortho* to the methoxy group does not, and Musk *alpha* (28) is devoid of any *tert*-alkyl moiety.

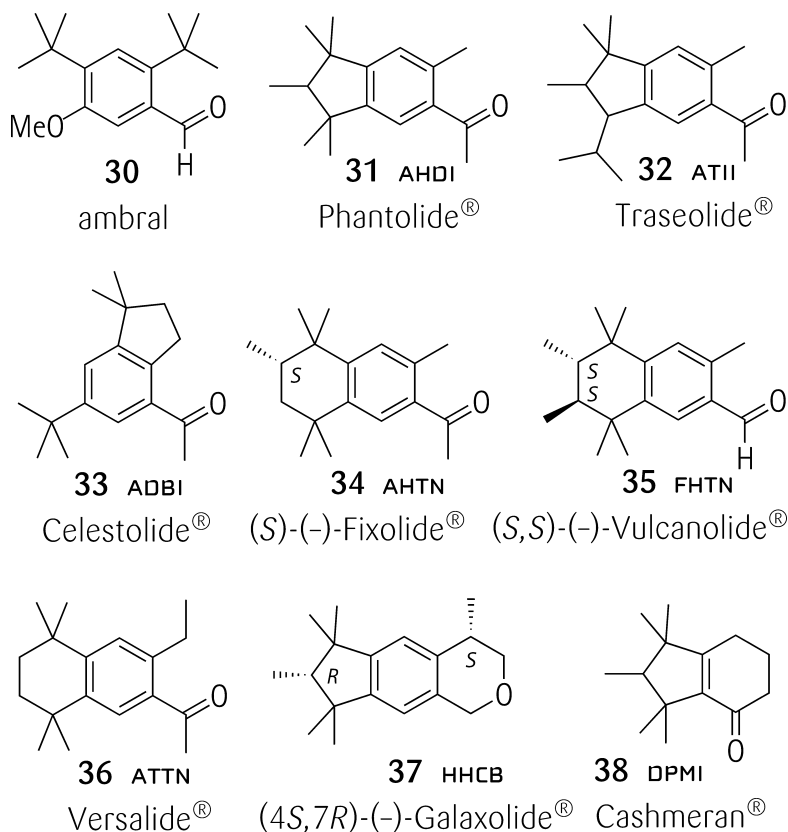
7.4 PCM – Polycyclic aromatic musks

In the beginning of 1948, Carpenter [47] himself had found the most striking exception to his postulated rules: 2,4-Di-*tert*-butyl-5-methoxybenzaldehyde (30), a fine persistent musk odorant without a nitro group. Though it was never introduced to the market, it became known as Ambral within Givaudan, and inspired chemists to synthesise many related nitro-free aromatic musks. Due to their photochemical reactivity and their instability in alkaline media, nitro musks decomposed and caused discolouration problems in functional products. If it were possible to synthesise aromatic musks without nitro groups, it would be possible to derive stable musks for functional perfumery, for cosmetics, laundry and detergents, for a huge market with enormous potential.

The first nitro-free aromatic musk to get introduced to perfumery was discovered by Kurt Fuchs in 1951, who assigned his invention to Polak's Frutal Works. It was introduced to the market one year later, even without the knowledge of its correct structure, which was reflected in its name 'Phantolide®' (AHDI, 31). When four years later [48] its structure was elucidated as acetyl indane, polycyclic arenes became the new lead structure for musk odorants. With an odour threshold of 6.7 ng/l air, Phantolide® (AHDI, 31) was not superior in terms of strengths; yet, due to its stability and hydrophobicity, its performance in washing powders and detergents was outstanding. Now, besides hedonics (*the pleasance*) and odour strength, the evolution in musk odorants was mainly directed towards stability in harsh media and hydrophobicity, a key factor in the deposition of odorants on the fabric during the washing process. This evolution gave rise to numerous polycyclic musks (PCM): Traseolide® (ATII, 32), Celestolide® (ADBI, Crysolide®, 33), Fixolide® (AHTN, Tonalide®, *rac*-34), Vulcanolide® (FHTN, *rac*-35), Versalide® (ATTN, 36) with the isochromane musk Galaxolide® (HHCB, Pearlide®, *rac*-37) as the culmination of this evolution to stability and hydrophobicity.

Galaxolide® (*rac*-37) was the result of systematic studies of M. G. J. Beets of IFF on the osmophoric group of PCMs, the most polar functional group of odorants, the one that is proposed to orient the odorant on the receptor site. So far, the known PCMs had all carbonyl functions, but Beets and Heeringa wanted to replace the carbonyl group by other functional groups in order to make them even more stable and hydrophobic. The recipe was an ether oxygen, placed in a rigid tetrahydropyran ring at the same position they assumed for the carbonyl oxygen of the other known PCMs. Galaxolide® (*rac*-37) was first synthesised in 1965, and already in the late 1960s, used in dosages up to 40% in fabric softeners such as ›Comfort‹ and ›Softlan‹, and in detergents like ›Coral‹ at 27%. But high doses were also incorporated in fine fragrances, for instance ›Trésor‹ by *Sophia Grojsman* (Lancôme, 1990) with its 21.4% of Galaxolide® (*rac*-37).

The odour threshold of the commercial isomeric mixture of Galaxolide® (*rac*-37) is 0.9 ng/l air. However, the different stereoisomers differ distinctly in their thresholds [49], and this provides some interesting insight into the molecular features of musks.



All four stereoisomers were synthesised by Friedel–Crafts alkylation of 1,1,2,3,3-pentamethylindane with (*S*)- and (*R*)-methyloxirane, acid-catalysed reaction with paraformaldehyde and separation of the diastereomeric pairs via their tricarbonyl chromium complexes. Interestingly, the configuration at C-4 was much more important than that at C-7, reflected in the odour threshold values of the four isomers: 0.63 ng/l air for **37**, 130 ng/l air for *ent*-**37**, 1.0 ng/l air for the (4*S*,7*S*)-(-)- and 440 ng/l air for the (4*R*,7*R*)-(+)-isomer [49], respectively. So the odour of commercial Galaxolide[®] (*rac*-**37**) is determined by the (4*S*)-(-)-isomers, while the 7-Me group seems to be situated in a hydrophobic bulk region of the receptor site, which is not very shape-dependent [26]. Transferred into the old (1894) but vivid ‘lock-and-key’ model (Figure 7.2) of Emil Fischer, the osmophoric ether group *inserts* the molecule into the receptor, the profile-determining 4-Me group *codes* the odour information and the bulky substituents provide a *firm grip*. Together, these molecular parameters make up the olfactophore, the *key* for the musk receptor.

But is there really only one musk receptor? In the series, Musk ketone (**25**), Phantolide[®] (**31**) and Galaxolide[®] (*rac*-**37**), there is some apparent molecular similarity, but do these benzenoid musks use different receptors than, for example, the macrocyclic musks? This is a very difficult question to answer. To gain some insight, the

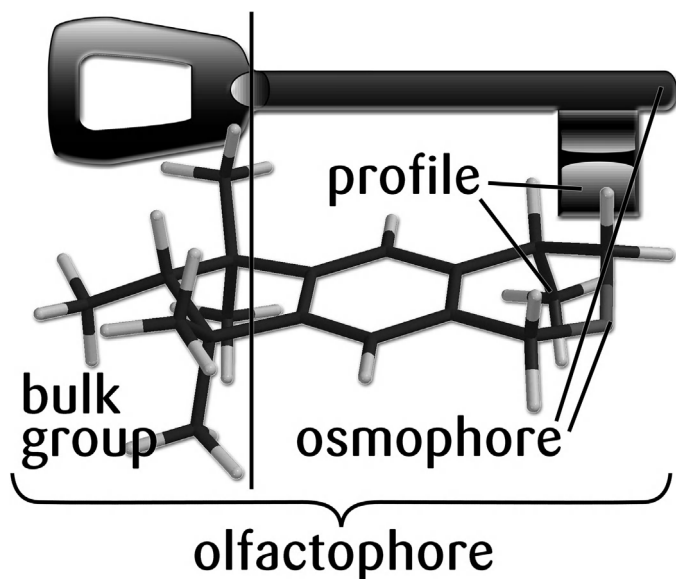
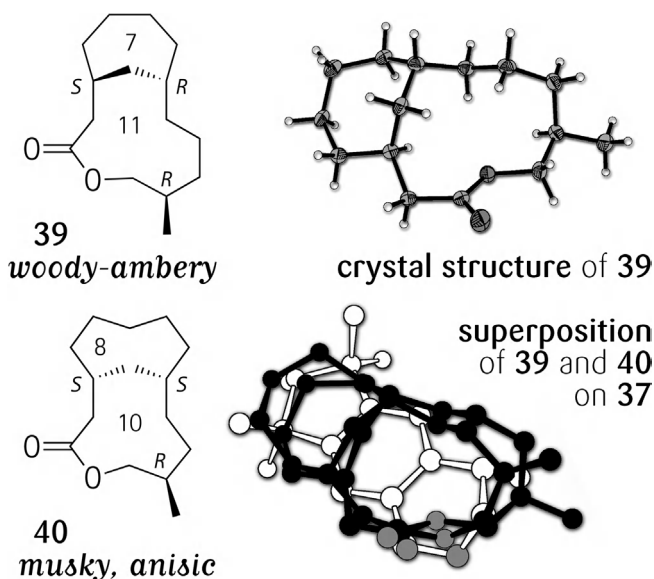


Figure 7.2 The molecular parameters of (4*S*,7*R*)-(-)-galaxolide (37) transferred into the 'lock-and-key' model.

macrolide **18** was conformationally constrained into a Galaxolide-like shape by introduction of methylene bridges between C-3 and C-8 or C-9. It was possible to obtain X-ray data of these rigid macrobicycles, shown here for (1*S*,6*R*,10*R*)-(+)-6-methyl-4-oxabicyclo[8.4.1]pentadecan-3-one (**39**). This macrobicyclic compound was the most powerful odorant, yet the least musky of the series, smelling *woody, cedarwood-like, ambery and slightly animalic*. The most musky macrobicyclic compound investigated [50] was **40**, and in the superposition analysis on the crystal structure of **37**, the methyl substituent of **40** superimposes very well with the (4*S*)-Me group of **37**. So, similar structural features may be key for a musk odour in both macrobicycles and benzenoid musks. However, **40** is weaker than **18**, and the conformation that **18** would need to adapt to mimic **40** or **37** is energetically quite unfavourable. So severe doubts remain, but it might be possible that there is just one musk receptor.

As for Galaxolide (**37**), the structures of the most powerful stereoisomers of Fixolide (**34**) [26] and of Vulcanolide (**35**) [51] are shown; however, no exact threshold data were reported in the literature for these compounds. Also given are the abbreviations that ecotoxicologists introduced for **31**–**38**. As a consequence of their massive production volumes, their excellent chemical stability, their non-biodegradability and their high octanol/water partition coefficient, PCMs have bioaccumulated in fish and other marine organisms, human fat and human milk [52]. Although no apparent toxicity has been reported [10], possible long-term effects [53] are difficult to foresee, and more and more PCM-free formulations appear on the market. DPMI (Cashmeran[®], **38**) is often considered a PCM by ecotoxicologists as well. Like HHCB (Galaxolide[®], *rac*-**37**) its industrial synthesis starts from pentamethylindane; yet, DPMI (**38**) is neither aromatic nor a typical musk odorant. It possesses a *woody-ambery and leathery odour with some*



powdery, vanilla-type, velvet nuance that has only a very faint musk-like tonality. That is why, from a perfumer's point of view, 38 is not considered a PCM.

Today, Galaxolide® (HHCB, *rac*-37) is still the most widely used musk with some 7000–8000 t/a production volume and a market price of around 15 CHF [10]. But macrocycles are gaining substantial market share. Whilst in 1998, 75% of the musk odorants used were polycyclic, it is expected that in 2008 macrocycles will make up 60–65% of the global musk market [10]. But to make this possible, far better synthetic processes for industrial macrocyclisation have had to be discovered. So what has happened in the meantime with the industrial macrocyclisation processes?

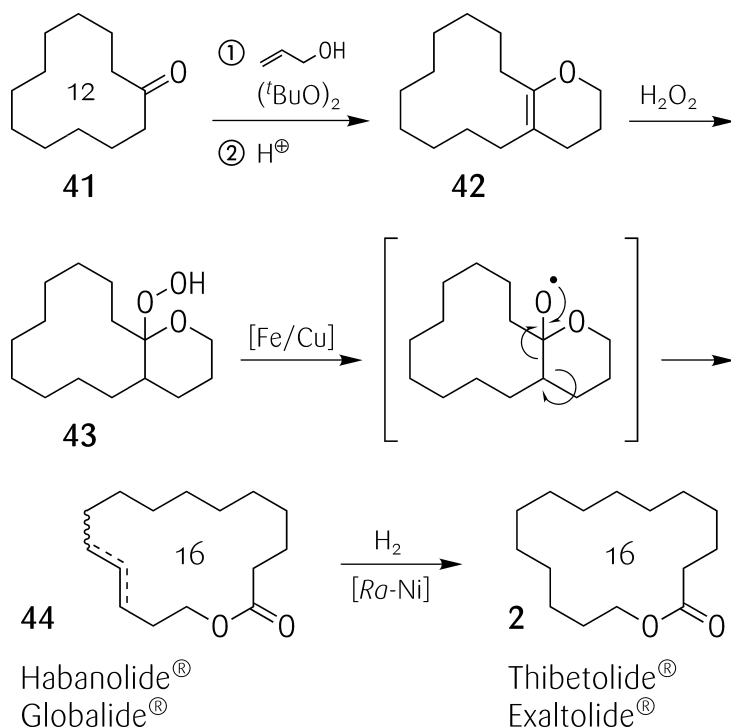
7.5 Evolution of the industrial synthesis of macrocycles

The first improvements in macrocyclisation were the Thorpe–Ziegler reaction for macrocyclic ketones, and acid-catalysed cyclisations of hydroxycarboxylic acids according to the Ruggli–Ziegler dilution principle. The next breakthrough was the Stoll–Hansley–Prelog process, an intramolecular version of the acyloin condensation, which does not require high-dilution conditions, as it is a heterogeneous reaction. As a result, the price of Exaltone® (6) dropped from 50 000 CHF/kg in the 1930s to about 500 CHF/kg in 1947 [11].

At that time, Exaltolide® (2) was still manufactured by Baeyer–Villiger oxidation of 6. This changed when E. W. Spanagel and W. H. Carothers at Du Pont [54] found a way to circumvent the necessity of high dilution also in the synthesis of macrocyclic lactones. 15-Hydroxypentadecanoic acid was polycondensed in the presence of Lewis acids at 180–250°C, and afterwards the monomeric 15-pentadecanolide (2) was distilled off *in vacuo* at 270°C/1 Torr. Consequently, the price of 2 decreased by a factor of ten, and its production rose from kilogram to ton scale. The real revolution in the synthesis of macrocycles started

however in the 1960s, when cyclododecanone (**41**) became an inexpensive industrial building block as the result of the cyclooligomerisation of butadiene, a process pioneered by G. Wilke of the MPI für Kohlenforschung [55]. Thus, ring expansion reactions based on cyclododecanone (**41**), which today reaches production volumes of 100 000 t/a, became the method of choice for the industrial synthesis of macrocyclic lactones and ketones [56].

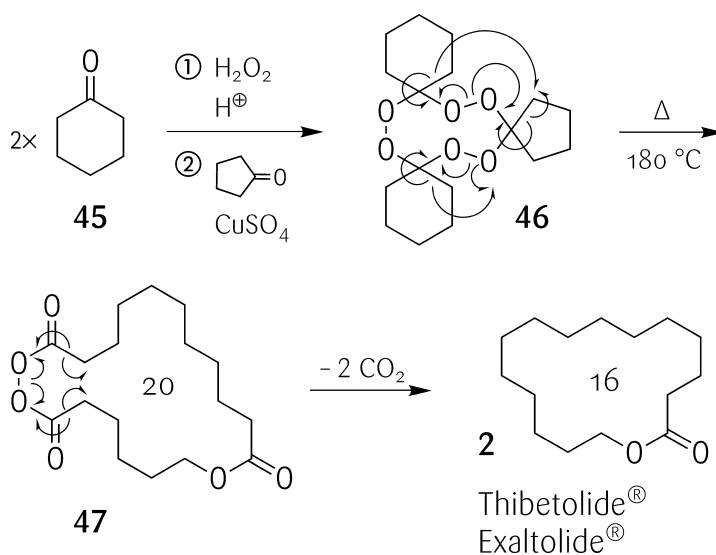
Radical addition of allyl alcohol to **41** with subsequent acid-catalysed cyclisation provides the bicyclic enol ether **42**, which is transformed to **43** by addition of hydrogen peroxide. Fragmentation of this hydroperoxide **43** in the presence of cupric acetate and iron sulfate furnishes an isomeric mixture of 11/12-pentadecen-15-olides (**44**), which already possesses an elegant musk note with metallic nuances and is commercially known as Habanolide® and Globalide® (**44**). Catalytic hydrogenation of **44** with Raney nickel completes the current industrial process [34] for 15-pentadecanolide (**2**), which is sold as Cyclopentadecanolide® (Symrise), Exaltolide® (Firmenich), Pentalide® (Soda Aromatics) or Thibetolide® (Givaudan) at around 60 CHF/kg.



Habanolide® and Globalide® (**44**) are only slightly less expensive, but became trendy because of their *metallic character reminiscent of hot-ironed linen*, usually considered an undesirable side aspect by perfumers. However, this daring ‘urban high-tech’ facet can provide some special radiant freshness for which the term of ‘white musks’ was coined. The prototype *white musk* accord was created by Alberto Morillas in answer of the

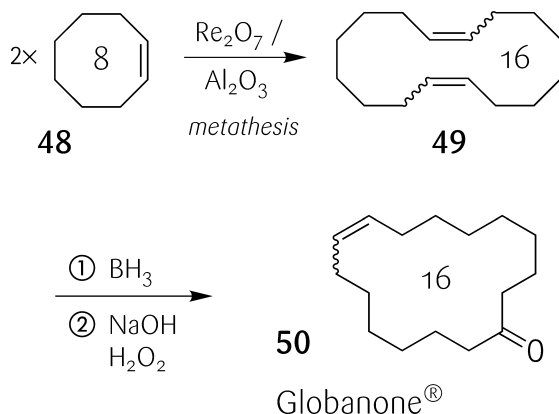
brief for »Emporio Armani White for Her« (Armani, 2001). His own code name for the winning submission was »cotton and linen«, and bergamot as well as mandarin oil, cassis, ginger and woody notes together with mint and fig leaves join in the *white musk* theme. The traditional hesperidic (*citrus-fruit like*) yet modern green »Cologne« (Thierry Mugler, 2002) and the intense white floral »Glow by J. Lo« (Lancaster, 2002) also feature *white musk* accords, which of course have nothing to do with the rare Arctic white musk-oxen, as some may have believed.

The Story process [57] developed in 1968 constitutes an industrial alternative to the presented ring-enlargement route to 15-pentadecanolide (2). In terms of production costs this process is very attractive; however, the handling of the trimeric peroxide 46 is quite tricky, and the industrial Story synthesis of 2 was discontinued after a severe explosion. The trimeric peroxide 46 was synthesised via the crystalline 1,1'-dihydroperoxydicyclohexyl peroxide, which is formed by treatment of cyclohexanone (45) and 90% hydrogen peroxide in the presence of perchloric acid at room temperature. Reacting this intermediate peroxide with cyclopentanone at 0–4°C in the presence of anhydrous cupric sulfate yielded the trisperoxide 46, which was thermally decomposed in boiling decane, presumably via decarboxylation of the intermediate diacyl peroxide 47. 15-Pentadecanolide (2) was obtained in about 25%, accompanied by about the same quantity of cyclotetradecane and smaller amounts of isomeric dilactones. The hazardous nature of the peroxides involved is obviously a severe restriction on this elegant and economic approach.

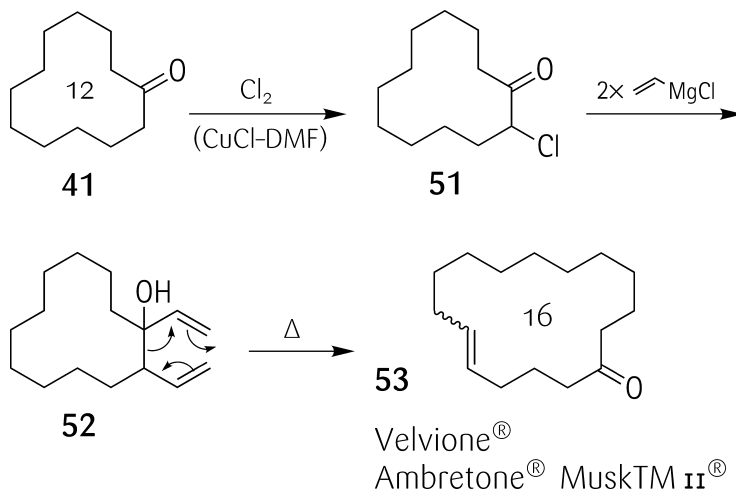


In the academic world, the RCM constitutes today the preferred method for the synthesis of macrocyclic compounds. For industrial syntheses of macrocyclic musks, Grubbs' catalysts are however still too expensive to compete with the established processes. Yet, one industrially important process involves ring-opening RCM of cyclooctene (48), employing not a Grubbs' catalyst but dirhenium heptoxide on alumina

in flow reactors. Monohydroboration of the resulting cyclohexadeca-1,9-diene (49) is followed by oxidation of the cycloalkenylborane to the corresponding alcohol and then further to the cycloalkenone 50 [56], which possesses a *slightly aldehydic and waxy musk odour* and has been introduced to perfumery as Globanone®.

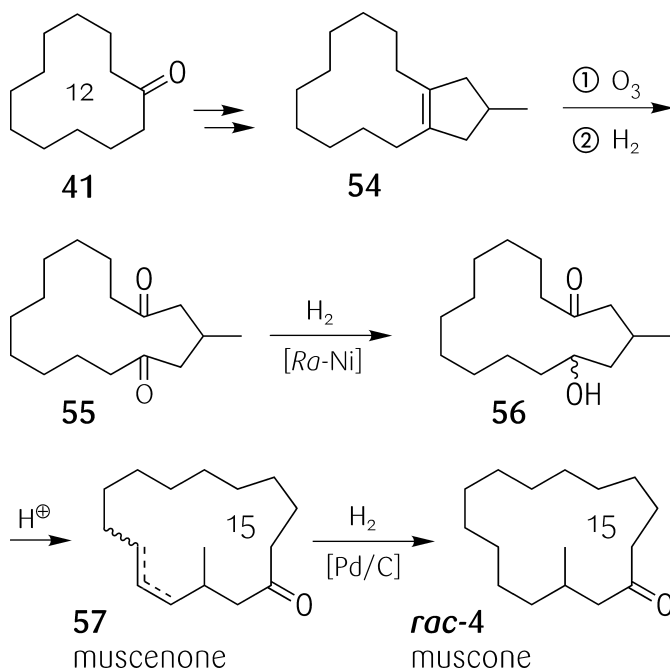


Shifting the double bond from C-8 to C-5 intensifies the musk odour of cyclohexadecanone, and renders the odour note more towards a *powdery nitro-musk* character. This product is known in perfumery as Ambretone (Takasago), Musk TM II (Soda Aromatics) and Velvione (Givaudan), and it is produced by oxy-Cope ring enlargement of cyclododecanone (41) [39]. Chlorination of 41 in the presence of copper(I)chloride–DMF affords 2-chlorocyclododecanone (51), which is reacted with two equivalents of vinyl magnesium chloride to provide the divinyl alcohol 52. Thermal oxy-Cope rearrangement of 52 leads to the final product 53. Velvione (53) was extensively used in the fine fragrance »Velviona« (Helmut Lang, 2001), but it is also economic and substantive enough to provide powdery volume and musky softness in laundry-care products.



7.6 Modern macrocyclic musks

To replace or even outperform PCMs and nitro musks in diverse applications, one can either lower the production price of macrocycles or increase their odour intensity, which means lowering their odour threshold. The latter option allows for more complex synthetic approaches and accordingly higher production costs. Muscenone (57), which had its debut in perfumery in 1993 with the floral feminine fine fragrance »Jean-Paul Gaultier« (Shiseido, 1993) created by Jacques Cavallier, was the first example for such high-performance modern musks.

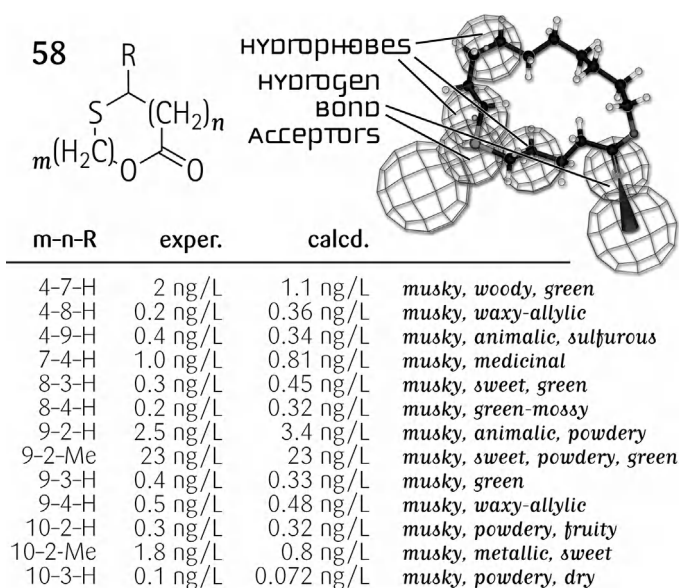


Muscenone (57) was first reported as intermediate in a muscone synthesis by A. Eschenmoser, G. Ohloff and co-workers [58] in 1971, but its value in perfumery was discovered only much later. Muscenone (57) is still an intermediate in the current industrial synthesis of muscone (*rac*-4), which commences from 14-methylbicyclo[10.3.0]pentadec-1(12)-ene (54), accessible by annulation of cyclododecanone (41). Ozonolysis of 54, followed by reductive work-up and further hydrogenation of one carbonyl group of 55 with *Raney* nickel, provides 56. Acid-catalysed elimination of the hydroxy function of 56 completes the synthesis of muscenone (57), which can then optionally be hydrogenated to muscone (*rac*-4). Muscenone (57) possesses a *very elegant and diffusive musk odour reminiscent of Musk ketone* (25), and with an olfactory threshold of 0.9 ng/l air, is as powerful as the benchmark musk Galaxolide® (*rac*-37).

Besides the ring size and methyl substituents, double bonds are an important feature to influence both character and strength of macrocyclic musks. Is the function of

double bonds restricted to conformational effects, or is it also of electronic importance? Can more powerful macrocyclic musks be designed by introducing additional polar groups?

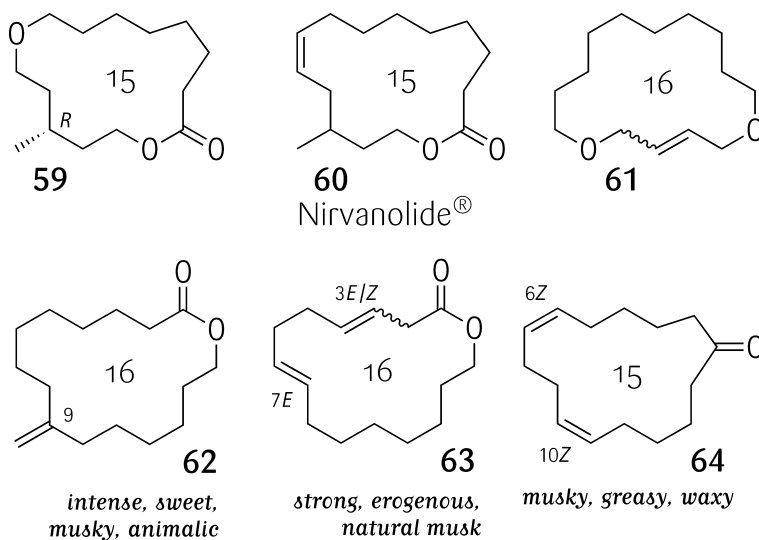
To answer these important questions, we developed a simple sequence [59] and synthesised a series of thiamacrolides **58**. As demonstrated by the olfactory similarity of *p*-xylene and 2,5-dimethylthiophene as well as by several (3*Z*)-hexenyl derivatives, a sulfur atom is able to mimic a double bond. For the thiamacrolides **58**, we found that a 1,7-distance of the sulfur atom and the carbonyl group in even-membered rings, and a 1,6-position of the sulfur atom and the carbonyl group in odd-membered rings significantly lowered the odour thresholds. An olfactophore model, featuring two hydrogen-bond acceptors and three hydrophobic-binding pockets, was generated with the Catalyst software [60], which predicts the experimental odour thresholds of these thiamacrolides **58**, quite accurately. The threshold of a given molecule is calculated on the basis of its degree of mapping with the hypothetical features of the receptor model [38]. The depicted olfactophore model clearly suggests that a second electronegative feature, besides a carbonyl or oxycarbonyl function, would be advantageous for the musk odour, and it also suggests a hydrophobic group right in the middle of these two hydrogen-bond acceptors.



This was the inspiration behind the synthesis of 4-substituted 1,7-dioxacycloalkan-8-ones [61], which indeed possessed very low odour thresholds in the range of 0.1–0.2 ng/l air. Of particular interest was 12-methyl-9-oxa-14-tetradecanolide; firstly because just the (*R*)-enantiomer **59** is responsible for the odour of the racemate, while the enantiomer is odourless on GC-olfactometry, and secondly because its odour is surprisingly reminiscent of the very characteristic Musk ambrette (**26**). One can indeed superimpose both molecules so that the *tert*-butyl group of **26** and the 12-methyl group of **59**, the nitro group of **26** and the oxycarbonyl group of **59**, and also the ether oxygens of both molecules overlie very well [38].

In Nirvanolide® (60), the latest captive macrocyclic musk of Givaudan, the second electronegative feature is a double bond. Again, the odour is due to the (*R*)-enantiomer [26]; however, even the racemate 60 has an odour threshold of 0.1 ng/l, just like Musk ketone (25). And with its *clean and sweet, powdery and persistent, and slightly animalic musk odour*, 60 is also odourwise quite close to Musk ketone (25), just like muscenone (57), but more powerful. Nirvanolide® (60) had its debut at 6.7% in the perfume »Forever Elizabeth« (Elizabeth Taylor, 2002) created by David Apel.

There are some other creative ways of making use of double bonds for modern macrocyclic musks. Williamson reaction of 1,10-decandiol with allyl bromide, followed by RCM, furnished 61, possessing a pleasant powdery musk note without a carbonyl function being present. This work of Takasago [38] also demonstrates the importance of two hydrogen-bond acceptors in a certain distance. Methylene macrolides have been described by W. Tochtermann and co-workers [62]. Especially interesting is the 9-methylene macrolide 62 with an *intense sweet musk note of animalic tonality*. This group also reported [63] the first double-unsaturated macrocyclic musk 63, which possesses a strong and erogenous natural musk note. Two stereochemically defined double bonds in a certain distance are an efficient way of confining the conformational freedom of macrocycles, and thus designing powerful musks. However, the industrial-scale synthesis of such dienolides is quite costly. C. Fehr *et al.* [64] recently developed an iterative fragmentation of tricyclic systems, by which they synthesised the cyclopentadecadienenone 64. Yet, in comparison with the pleasant musk note of 63, the greasy, waxy, relatively weak musk odour of 64 is rather disappointing.



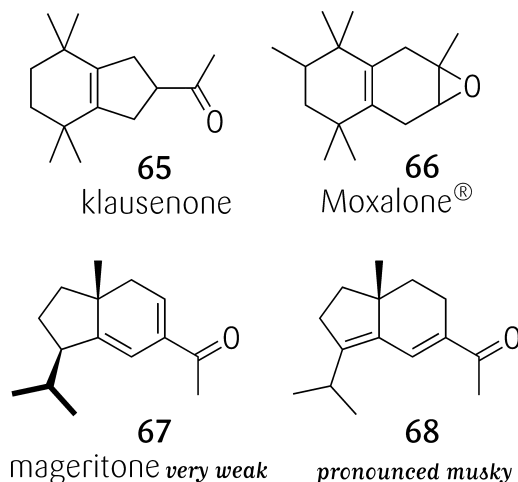
Today, Muscenone (57) and Nirvanolide® (60) are the quintessence of modern musk accords, in terms of power, diffusivity and character. Muscenone (57) and Nirvanolide® (60) are the perfumery materials of choice when it comes to replacing PCMs and nitro musks in older formulations.

7.7 New musk structures

In 1979, M. Klaus of F. Hoffmann-La Roche discovered by serendipity a new intense musk odorant with some damascone-like and woody nuances. In the course of synthetic work on aromatic retinoids he had synthesised the hexahydroindene **65**, which because of its powerful odour soon became internally known as klausenone (**65**) in Hoffmann-La Roche and also at Givaudan, at that time the flavour and fragrance division of Roche. As **65** is structurally not an aromatic polycycle, the musk odour of **65** was rather surprising. Attempts to develop an industrially feasible route to klausenone (**65**) turned out to be more difficult than anticipated, and thus derivatives were also investigated [38]. The corresponding alcohol, obtained by LAH reduction of **65**, possessed as well a pronounced musk note, indicating the carbonyl function was no prerequisite. Surprisingly, the epoxide intermediate **66**, *en route* to a methyl klausenone by acid-catalysed rearrangement, turned out to be the best musk odorant of the whole series and it was introduced into perfumery as Moxalone® (**66**). Moxalone® (**66**) had its debut in »Eden« (Cacharel, 1994) by Jean Guichard and was even at 0.62% an important cornerstone in the unisex fragrance »CK be« (C. Klein, 1996) created by René Morgenthaler.

In the late 1960s, J. Kula was doing his master's degree in the lab of Professor J. Kulescza on derivatives of carotol. Ozonolysis with reductive work-up and intramolecular aldol condensation of the intermediate oxo aldehyde gave a dihydroxy ketone, which was dehydrated to provide a mixture with a pleasant musky smell. Investigating this mixture, they believed the musk note to be due to its main component **67** which they called mageritone [65]. However, more than 30 years later J. Kula reinvestigated this chemistry, and found mageritone (**67**) only weak and uncharacteristic in smell. Instead the isomeric dienone **68**, present at only 5%, was found responsible for the musky odour of the mixture [66]. The tetrahydroindene musk **68** possesses a *dry musky odour* with an odour threshold of around 1 ng/l.

Caution is advisable, when the descriptor '*musky*' appears in the chemical literature, especially if perfumers were not involved in the evaluation of the compounds. For instance, K. H. Ney [67] reported an intense musk odour for ethyl 2-hydroxyimino-

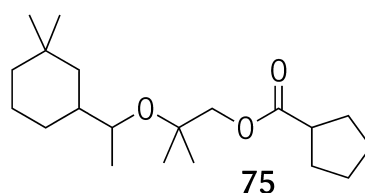
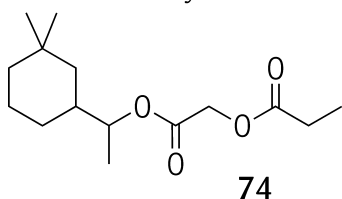
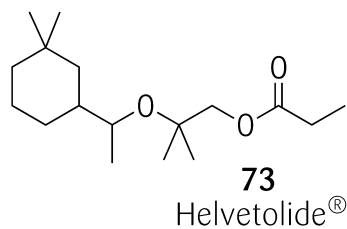
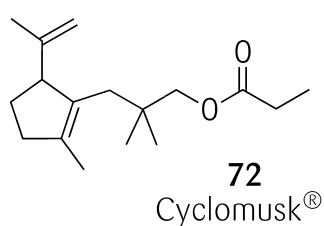
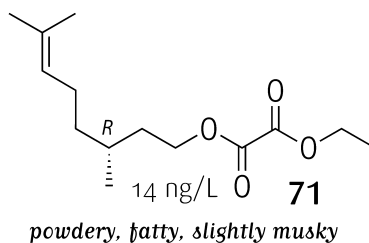
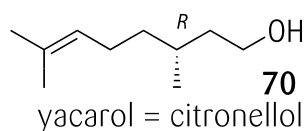
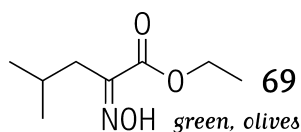


4-methyl-pentanoate (69), but when we resynthesised this compound, our perfumers described it as *relatively weak, green and only reminiscent of olives, but not of musk*.

A musky smell was also reported for the secretion of the alligators *A. sclerops* and *A. latirostris*, which live in the Paraná river region of Argentina [68]. The intense smelling secretion serves as mating pheromone, and had also been used as perfume by the natives. A ‘*musk-like*’ odour principle was even isolated and named *yacarovol* (70). However, investigations by G. Fester *et al.* [69] proved the identity of *yacarovol* with (*R*)-(+)-citronellol (70), which of course is no musk odorant but possesses a *sweet, typically rosy odour*. Probably due to animalic-smelling impurities, this rosy odour had been mistaken for musk.

However, the ethyl oxalate ester of (*R*)-(+)-citronellol 71 possesses some musky facets, though they are barely noticeable. If the product 71 is completely free from traces of 70, it smells *powdery, fatty and slightly musky* with an odour threshold of over 14 ng/l air. These musky facets have even been rationalised by molecular modelling calculations [70], but we should not consider 71 a musk odorant.

Yet, structurally not too far away, there is a class of compounds – neither macro- nor polycyclic or benzenoid – that indeed possesses a pronounced musk odour. Already in 1975, W. Hoffmann and K. von Fraunberg of BASF discovered the cyclopentenyl ester 72, which emanates a *warm, powdery musk odour with fruity, strawberry-like nuances* [38]. This compound 72 was introduced to perfumery as Cyclomusk[®], even though it is rather linear than cyclic in structure. But though its industrial synthesis, which commenced with the thermal cyclisation of dedydrolinalool, was not too expensive, 72 had no chance against



Galaxolide® (*rac*-37) in the late 1970s and was subsequently withdrawn from the market. Some 15 years later, however, Firmenich introduced another representative of this class to perfumery – Helvetolide® (73), which turned out to be far more successful. It was, for instance, used by Alberto Morillas at 8.8% in »Emporio Armani White for Her« (Armani, 2001), at 6.1% in »Miracle« (Lancôme, 2000) and at 3.8% in »Flower« (Kenzo, 2000). Interestingly, one *gem*-dimethyl group of 73 can be replaced by a carbonyl group without losing the musk odour. The fruity, blackberry-type nuance of 73 then turns into the more camphoraceous side note of 74. This ‘oxo-Helvetolide’ 74, which is known as Romandolide in Firmenich, was for instance used by Jacques Cavallier at 5.0% in »Absolu« (Rochas, 2002) and at 1.0% in »Murmure« (Van Cleef & Arples, 2002). Surprisingly, we have found that the corresponding cyclopentanoate of Helvetolide (75) still smells musky with an odour threshold of 1.4 ng/l air, and with a molecular weight of 324.27 u(!) for C₂₀H₃₆O₃, it holds the world record for the heaviest musk odorant, if not the heaviest odorant of all. Previously, one would not have believed it possible to construct musk odorants over 300 – so surprises are still possible in fragrance chemistry!

Let us conclude this chapter with an overview of the most important milestones in musk chemistry (Figure 7.3). Even before the odorous principle (*R*)-(-)-muscone (4) of

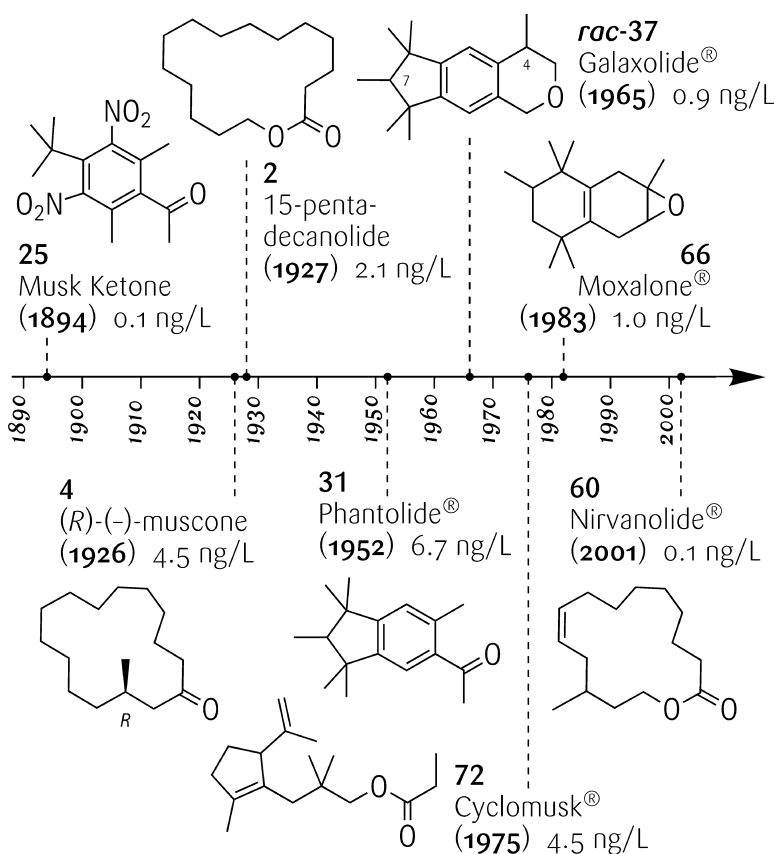


Figure 7.3 The timeline of musk odorants.

the Tonquin musk was known, nitro musks like Musk ketone (25) became the epitome of musks. And with a threshold of 0.1 ng/l air for 25, they became a very hard-to-beat benchmark, compared to the 4.5 ng/l air for 4 and 2.1 ng/l air for 15-pentadecanolide (2). The latter natural macrolide from the vegetal kingdom can be considered the most typical musk, but was, for a long time, too expensive to allow its use in consumer products. But discolouration problems in consumer products caused the decline of the nitro musks and PCMs like Phantolide® (31), as their first representative became the new standard. The evolution towards increased stability culminated in Galaxolide® (*rac*-37) with a threshold of 0.9 ng/l air. Yet, the lack of biodegradability of *rac*-37 ignited the search for new musk structures, for which Cyclomusk (72) and Moxalone (66) were the first commercial examples. But it also led to modern macrocyclic musks, with improved thresholds in the range of nitro musks, for which Nirvanolide (60) with 0.1 ng/l air is the prominent example.

Acknowledgements

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