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Fragrance Chemistry — Milestones and Perspectives

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Abstract: This mini-review on Fragrance Chemistry focuses on milestones in the timelines of musk, ionone/woody and sandalwood odorants, as well as on new perspectives arising from the development of fragrance precursors. After a brief introduction of the history of perfumery, its mutual interaction with the chemistry of odorants, and the current state of the fragrance industry, the whole spectrum of musk odorants is discussed from the accidental discovery of nitro musks like Musk Ketone® *via* the parallel evolution of benzenoid and macrocyclic musks, to new structures like Cyclomusk® and Moxalone®. Following a description of the structure elucidation of violet odorants, ionone and irone, Iso E Super® and the structurally related Georgywood®, but also Koavone® and Timberol® are treated. Weissenborn's discovery of terpenylcyclohexanols lead to sandalwood synthetics that today are mainly derivatives of campholenic aldehyde like Sandalore®, Sandal Mysore Core®, Polysantol®, Ebanol®, and Javanol®. Finally, lipase labile precursor systems, for instance digeranyl succinate, or UV-radiation labile ones like citronellyl coumarate and citronellyl cyclohexylglyoxylate are presented, and views on *'secondary benefits'*, *'anti-perfumes'* and exclusive *'Editions de Parfums'* conclude this overview on the driving forces and the serendipities in the chemistry of fragrant substances.

Keywords: Fragrance precursors · Ionones · Musks · Odorants · Sandalwood

'Sailing on the scent of your perfume
Only memories to guide
Distant thoughts inside ...'
G. Duke, 'Illusions' [1]

1. Introduction

From the fresh, sparkling shower gel in the morning to the sensual, seductive perfumes that surround us during a romantic candle-light dinner, we experience fragrances at almost any time and almost everywhere. Even our shopping is accompanied by pleasant scents, and when we reach out for personal and homecare products we very often have the choice between different fragrance variants of the same brand.

The use of perfumes has a long history: In biblical times people sacrificed 'through smoke' – *per fumum* – the treasures of nature to please the Gods [2]. Alcoholic extracts of plants and resins as well as composites thereof were used in the middle age as both perfume and medicine (*aqua mirabilis*), aphrodisiac and elixir of life (*aqua vitae*). After Napoleon Bonaparte had ordained by decree in 1810 that manufacturers and vendors had to make a distinction between pharmaceuticals and perfumes, *eaux de Colognes* were no longer drunk. The newly defined 'perfumes', still composed exclusively of natural ingredients, mainly essential oils, became more and more sophisticated, and consequently luxury items for monarchs and their entourage, aristocrats and patricians. The use of synthetic ingredients marked the beginning of modern perfumery at the end of the 19th century, and enriched the perfumers palette with new odor notes.

In 1882, Paul Parquet created 'Fougère Royale' around an accord composed of *coumarin*, oakmoss, geranium and bergamot, and with its launch by Houbigant the new era commenced. In the following years, major achievements in the synthesis of fragrant compounds as well as the discovery of new odorants catalyzed the creation of many landmark perfumes. *Vanillin* blended with resins, animalic notes and a floral accord with hesperidic elements, was the basis of 'Shalimar' created by Jacques Guerlain in 1919, the prime example of an oriental fragrance. And in 'Chypre' (1917), which gave the name to the third big fragrance family, François Coty already used the newly available *quinolines*, especially *iso*-butyl and *iso*-propyl quinoline, though leathery Chypre fragrances like 'Bandit' (Piguet, 1944) became fashionable only much later.

With the beginning of the age of fashion, the creativity of both designers and perfumers gave another boost to a rapidly growing industry. After World War II, the rise of the consumer purchasing power finally made perfumes available to everybody and led the way for their introduction into many functional products. Today, perfume is an everyday item, even sold in supermarkets, and people in general possess more than just one fragrance. Whereas 50 years ago a perfume was still considered a precious item, and women would use the same fragrance over many years (while men's fragrances were barely accepted that time), today men and women choose which fragrance to wear according to their daily mood.

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Behind the scenes, the Flavor and Fragrance (F&F) industry is striving constantly to lower prices and to increase quality and performance of perfumery ingredients, *i.e.* to make them more stable and last longer. The fragrance industry, situated in between the petrochemical and the pharmaceutical industry, has been growing over the last hundred years to an estimated market size of 7000 Mio CHF. While the production scale of fragrance compounds is closer to that of pharmaceuticals, the product prices are closer to those of the bulk-chemical industry. Some ingredients, namely those with an extremely low odor threshold, are produced in kilogram quantities only. At the other end, some perfumery ingredients, mainly for use in detergents and homecare products, are produced in quantities of up to 10 000 t/a, *e.g.* linalool (8000–10 000 t/a), 2-phenylethanol (7000–9000 t/a), benzyl acetate (7000–9000 t/a), Galaxolide® (7000–8000 t/a), Lilial (5000–6000 t/a), Hedione® (4000–5000 t/a) and Iso E Super® (2500–3000 t/year), *cf.* also [3].

In the following, we want to point the reader to some selected milestones of the most important odor notes and to give an idea of how Fragrance Chemistry developed, what driving forces were active, and which future direction the industry might take. A general overview on the developments of the F&F industry from the end of 1945–1994 was given by Paul Z. Bedoukian in his annual reviews [4], while processes and compounds of general technical and industrial relevance were summarized in a more recent review [5]. Information on the newest trends and highlights in the chemistry of odorants can be found in [6], and details on the production and uses of individual substances are treated in [7].

2. Timelines of Odor Notes

2.1. *Musks*

As for many other disciplines, serendipity is also a key factor in Fragrance Chemistry, and the fortunate finding of the aromatic nitro musks by Albert Baur in 1888 marks the origin of the timeline of musk odorants (Fig. 1). Baur was actually searching for new explosives when he noticed that the product of the Friedel-Crafts reaction of trinitrotoluene (TNT) with *tert*-butyl halides emanated a pleasant musky smell. 2-*tert*-Butyl-4-methyl-1,3,5-trinitrobenzene was an immediate commercial success and became known as 'Musk Baur' [8]. Baur became associated with a commercial firm, the 'Société des produits chimiques de Thann et de Mulhouse', and pursued his studies on nitro arenes systematically. In 1894, he discovered and developed Musk Ketone (**1**), which was prepared by nitrating acetylated *tert*-butyl-*m*-xylene [9]. Musk Ketone, possessing an excellent odor threshold of 0.1 ng/l, is considered to resemble the natural *Tonkin musk* closer than any other nitro musk, and until recently was amongst the most used perfumery ingredients.

Tonkin musk is the dried solidified secretion (*musk grains*) from a preputial follicle of the male musk deer (*Moschus moschiferus* L.), which inhabits the Himalayas from Afghanistan to China. Its odoriferous principle, (–)-(3*R*)-muscone (**2**), was isolated by Heinrich Walbaum of Schimmel & Co. in 1906 [10], and makes up only 0.5–2% of the musk grains. He was able to establish its molecular formula, and show that it was a ketone, but it was only 20 years later that Leopold Ruzicka, in the laboratory of M. Naef & Co. (today Firmenich), elucidated its structure [11] – and overturned Baeyer's theory of strain in multimembered rings [12]. Ruzicka and M. Naef & Co. were originally aiming at an industrial synthesis of muscone (**2**), which, with an odor threshold of 4.5 ng/l, was not even extremely powerful. However, their cyclization method employing thorium salts [13] did not tolerate the β-methyl substituent, and thus cyclopentadecanone, under the name of Exaltone®, was introduced instead – at the exorbitant price of 50 000 CHF/kg [14], while Musk Ketone (**1**) cost less than 100 CHF/kg at that time!

Considering the prices of the nitro musks, it was more than reckless from a commercial point of view to subject Exaltone®, which was produced in just about 6% yield from thapsic acid and had to be purified *via* its semicarbazone, to a Baeyer-Villiger oxidation. The resulting 15-pentadecanolide (**3**) possessed, however, superior olfactory characteristics, and was also introduced into perfumery

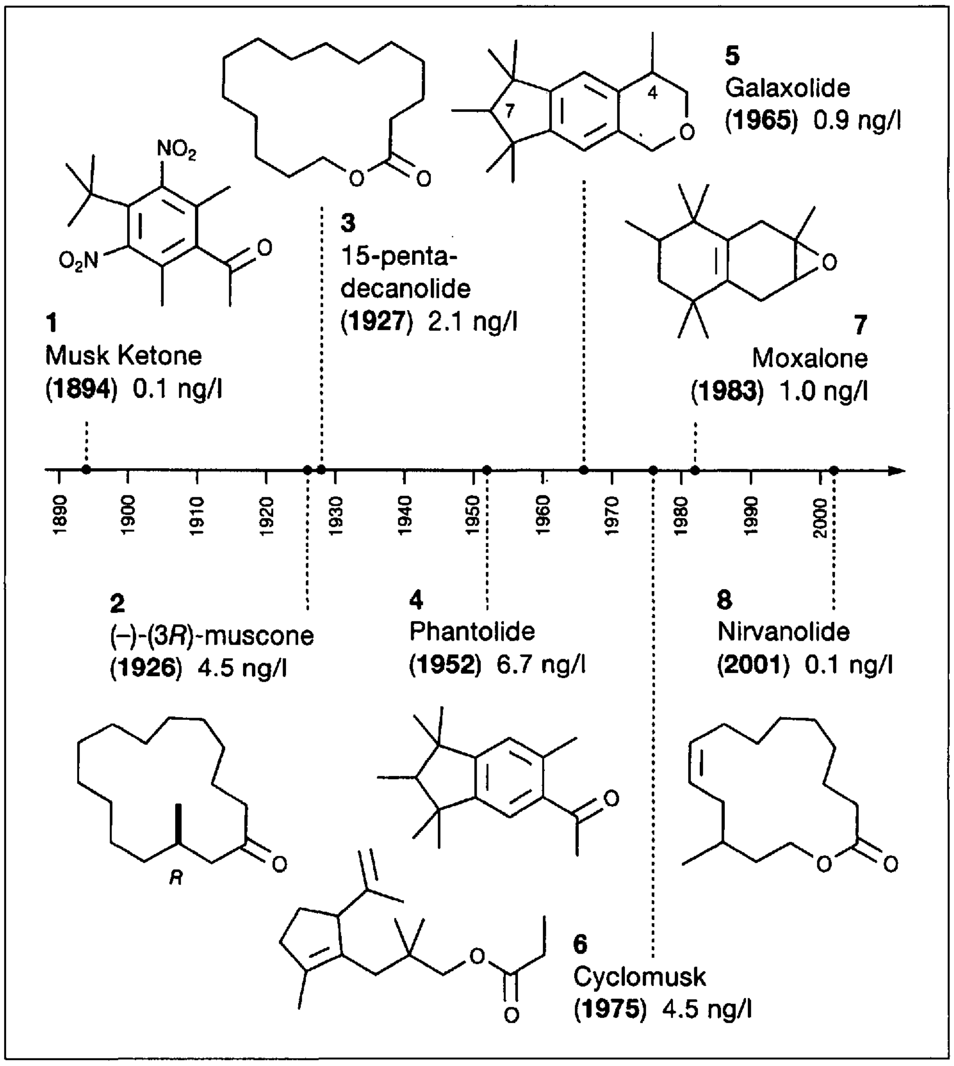

Fig. 1. The musk timeline

in 1927. Its price at that time was 100 000 CHF/kg (!) [14] – 1000 times more expensive than the excellent benchmark **1**, which is even 20 times stronger than **3** in terms of odor threshold (Fig. 1). For comparison, the price of natural muscone, based on the price of *Tonkin musk* and its content in **2**, would have been 'merely' around 300 000 CHF/kg at that time [15]. The high price that perfumers were willing to pay for **3** demonstrates the fascination for the real odoriferous principles of nature, the macrocyclic musks. At about the same time, Max Kerschbaum [16] of Haarmann & Reimer in Germany found 15-pentadecanolide (**3**) in Angelica root oil (*Archangelica officinalis* Hoffm. syn. *Angelica archangelica* L.).

With the improvements of the cyclopentadecanone synthesis by first the Thorpe-Ziegler reaction, and then by acid-catalyzed cyclization of the 15-hydroxypentadecanoic acid according to the Ruggli-Ziegler dilution principle, the selling price of **3** dropped to one fifth in the next eight years [14]. Another breakthrough in the synthesis of cyclopentadecanone was the Stoll-Hansley-Prelog process, the acyloin condensation of the dimethyl pentadecadienoate, which as a surface reaction did not require high dilution. Spanagel and Carothers [17] circumvented high-dilution conditions by polycondensation of the 15-hydroxypentadecanoic acid and subsequent distillation *in vacuo* at 270 °C/1 torr. As a consequence, the price of **3** decreased again by a factor of ten, while its production rose from kilogram to ton scale. In the early 60's, Wilke opened up an inexpensive industrial access to cyclododecanone by cyclooligomerization of butadiene [18], and this was the chance for new processes *via* ring-enlargement sequences [19] [20]. Today, **3** is sold under the trade names Cyclopentadecanolide® (Haarmann & Reimer), Exaltolide® (Firmenich), Pentalide® (Soda Aromatics), and Thibetolide® (Givaudan) for around 60 CHF/kg, while Musk Ketone (**1**) is today about 50 CHF/kg – an impressive result of process research.

The 'high' price of **1** today, is of course also the result of a drastic decline in usage over the years. This was not due to environmental or toxicological issues, but a consequence of the lack of stability of the nitro musks. Their photochemical reactivity and their instability in alkaline media led to decomposition and caused discoloration in functional products. In the late 1940's, chemists were therefore searching for nonnitro derivatives to increase the stability and the range of application of benzenoid musks. Kurt Fuchs discovered the first nonnitro indan musk **4** in 1951, and assigned his invention to Polak's Frutal Works [21]. It was introduced to the market only one year later, even without knowledge of the correct chemical structure of **4** – which was reflected in its name 'Phantolide®' (**4**). When the structure of **4** was elucidated four years later [22], it became apparent that it showed some shape similarity to Musk Ketone (**1**). Though the odor threshold of **4** is significantly higher than that of **1**, its superior performance in detergents and washing powders made Phantolide® (**4**) the new lead structure for musk odorants, and in the following years numerous derivatives were synthesized in the laboratories of the F&F industry. Some prominent introductions include Celestolide® (IFF), Tonalide® (PFW), Traseolide® (Quest) and Versalide® (Givaudan, *for structures see* [7]). Besides the odor intensity and character, the main performance and selection criterion was the hydrophobicity, one of the factors that make musk odorants deposit on the fabric during the washing process – in terms of volume, laundry care had already become the prime area of application for musk odorants.

In the late 1950's, M.G.J. Beets of IFF was, therefore, looking to replace the carbonyl group of the polycyclic musks by other (less polar) functional groups, for instance nitriles. His studies of the structural requirements for musk odorants [23] bore fruit in the discovery of the isochroman musk Galaxolide® (**5**) in 1965 [24]. Already in the late 60s, Galaxolide® (**5**) was used in up to 40% in fabric softeners such as 'Comfort' and 'Softlan', and in detergents like 'Coral' at 27% [25]. More recently, overdoses could also be found in alcoholic perfumes, like in 'Trésor' (Lancôme, 1990) with 20% of **5** and in 'Parfum Sacré' (Caron, 1990) with 25% [25]. *Even today*, it is still the most widely used musk.

'*Even today*', because the use of Galaxolide® (**5**) – and other polycyclic musks (PCM's) – is a much debated topic. Its massive production volume together with its excellent chemical stability, its non-biodegradability and its high octanol/water partition coefficient has led to bioaccumulation in fish, human fat and human milk [26]. Although risk assessments show that HHCB, as Galaxolide® (**5**) is called today by the toxicologists, is safe for the environment [27], perfume and homecare product houses frequently insist on PCM-free formulations [28]. Musk odorants like Cyclomusk® (**6**), which was found by serendipity by Werner Hoffmann and Karl von Fraunberg of BASF in 1975 [29], had no chance against **5** at the time of their introduction to the market. Now **6** constitutes an important lead for the development of new biodegradable musks, such as Helvetolide® of Firmenich [6]. Moxalone® (**7**) of Givaudan [30], also the result of a fortunate finding [6], demonstrates that polycycles do not have to be aromatic to smell musky – and that new structures with powerful musk notes still can be found.

Before these will be discovered, however, macrocyclic musks will take over a substantial market share. While 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 [31]. With a market price of around 15 CHF/kg, Galaxolide® (**5**) is obviously a benchmark difficult to beat in terms of cost. So on one hand cheaper macrocyclic intermediates (like Habanolide® [6]) are introduced and even more process research is carried out to lower the prices; on the other hand more intense macrocyclic musk odorants are intensively sought. While Max Stoll of Firmenich stated in 1935 [32] that methyl groups have almost no influence on the odor of macrocyclic musks, and that additional oxygen atoms in macrolides decrease the odor intensity, today there is no doubt that methyl groups and additional polar groups [33] are of critical importance for the odor intensity and character [34]. If the configuration of the methyl bearing carbon atom is inverted, macrocyclic musks can even become odorless [34]. A 1,7-dioxa substitution and a (ω-2)-methyl group increase the intensity of macrocyclic musk odorants dramatically, and 12-methyl-9-oxa-14-tetradecanolide is about one thousand times stronger than 13-methyl-11-oxa-14-tetradecanolide in terms of odor threshold [34]. The feature of a (ω-2)-methyl group and a polar moiety, in this case a double bond, is also present in Nirvanolide® (**8**) [35], the newest introduction of Givaudan. With an odor threshold of 0.1 ng/l it reaches the world record of Musk Ketone (**1**), and is currently the most powerful musk in perfumery. Its 17-membered analog was claimed by Quest at about the same time [36], so the race for the ultimate musk is again running, after Galaxolide® was dethroned!

2.2. *Ionone/Woody Odorants*

Empress Josephine's wedding dress was embroidered with violets for her marriage with Napoleon, 'crystallized violets' sprinkled with castor sugar are a delicacy, and violet petals have been used in cosmetic formulations and were spread amongst the laundry of those who could afford it. Today, with all the affordable violet-smelling toilet soaps available, one easily forgets that violet flower oil was the most expensive of all essential oils – at the times when it was still economic to be produced. For the production of one kilogram of this oil 33000 kg of violet blossoms for *ca.* 2.50 German gold mark per kilogram were needed [37]. That makes 82500 German gold marks for material costs alone per kilogram of the oil, much more than even the most precious musk grains.

This high price was the reason why a synthetic violet odorant was highest on the agenda of the young fragrance industry. Ferdinand Tiemann of the University of Berlin therefore started, in collaboration with Haarmann & Reimer in Holzminden and Laire & Co. in Paris, an extensive search for the odorous principle of violets (*Viola odorata* L., fam. Violaceae). However, violet flower oil was too expensive to be used for isolation and structure elucidation with traditional techniques. Therefore, assuming the same odorous principle, the similarly smelling but more readily available and much cheaper orris root oil (*Iris pallida* Lam., fam. Iridaceae) was used instead for these investigations. Another advantage of orris root oil was the high content of its odorous principle, which can reach up to 70–80% in the oil. *Via* its phenylhydrazone, Tiemann and Krüger [38] isolated the odorous principle *irone* and (incorrectly) determined its molecular formula by elemental analysis as $C_{13}H_{20}O$. This incorrect elemental analysis together with some oxidative degradation products let them believe that irone could be a base-catalyzed condensation product of acetone with citral. But the product of this reaction possessed '*a strange but not very characteristic odor*'; however, when they cleaned the glassware with diluted sulfuric acid, Tiemanns nose detected the typical scent of violets in bloom. What they had actually discovered was ionone (**9**), and because of the similar smell and their incorrect elemental analysis of the earlier isolated irone, they concluded that the latter compound must be a double-bond isomer of the synthesized ionone (**9**). The correct constitution of the irones, homologs of the ionones (**9**), was not established until more than 50 years later, in 1947, by Naves *et al.* of Givaudan [39], and independently by Ruzicka and co-workers at Firmenich [40].

The comedy of errors in the chemistry of ionones continued. Even in his review on violet odorants in 1951 [41] Schinz still believed that ionones did not occur in nature. A few years before, he and Ruzicka had isolated *parmone* from violet flower oil, which they believed to be the odorous principle of violets [42]. It was not until 1972 that Uhde and Ohloff [43] were able to show that *parmone* was a *phantome*, a mixture of (*R*)-(+)-α-ionone, (*R*)-(+)-dihydro-α-ionone, β-ionone and dihydro-β-ionone. Although Tiemann and Krüger had inaccurately analyzed orris root oil in the search of the odorous principle of violets, they had actually discovered what they were initially looking for. In the violet flower oil, Uhde and Ohloff found 8.22% of (*R*)-(+)-α-ionone and 0.22% of β-ionone [43]. A recent headspace analysis of violets in bloom [44] even gave 35.7% of α-ionones, 21.1% of β-ionone, and 18.2% of dihydro-β-ionone, which makes together 75% of the headspace.

This chemical confusion did however not injure the commercial success of the ionones (**9**). Together with the stronger methylionones, which were also discovered by Tiemann in 1893 [45], employing ethyl methyl ketone instead of acetone, the α-/β-ionones (**9**) revolutionized perfumery. Today almost every perfume includes them, since they blend well with basically all other perfumery materials. Another material that is comparably versatile and can be used in a similar way as the ionones was found 80 years later at IFF (Fig. 2). First named Isocyclemone E®, **10** resulted from an exploratory work submitting Diels-Alder adducts of myrcene with different dienophiles to the acid-catalyzed cyclization Tiemann had already made use of [46]. This is an example of how simple chemistry and inexpensive starting materials like myrcene, which is industrially easily available from β-pinene by pyrolysis, can inspire inventions in Fragrance Chemistry. Other products of this approach with myrcene include the aldehyde Cyclemone A®, the non-cyclized Precyclemone B®, the tricyclic Lactoscatone®, Myrac Aldehyde® and its myrcenol analog Lyral® [7]. The latter in particular became fairly popular, but no other myrcene derivative had more influence on perfumery than Iso E Super® (**10**), as a better quality of Isocyclemone E® was named later.

Curiously enough, the patented main constituent **10** [46] of Iso E Super® was found to be almost odorless by GC-olfactometry [47]. **10** possesses an odor threshold of around 500 ng/l, while the impurity **13** (*ca.* 5%) with a threshold of only 5 pg/l is responsible for the pleasant

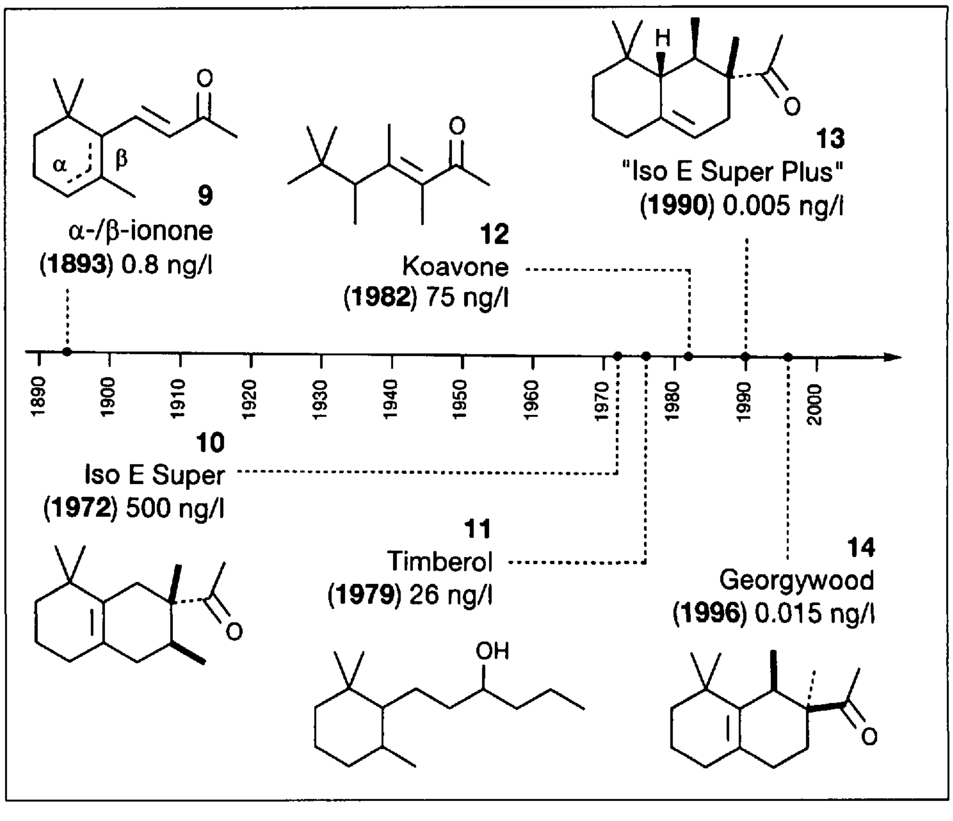

Fig. 2. The ionone/woody timeline

woody-ambery odor characteristics of Iso E Super® [47]. At Givaudan, this impurity **13** became known as 'Iso E Super Plus' and was patented in 1990 [48]. It served as a lead for more powerful woody-ambery odorants, of which Georgywood® (**14**), with an odor threshold of 15 pg/l, turned out to be one of the best. Its synthesis by Diels-Alder reaction of homomyrcene with methyl isopropenyl ketone and subsequent acid-catalyzed cyclization is straightforward [49]. Georgywood® (**14**), named after its inventor Georg Fráter, was not introduced into perfumery until 1996 and still is reserved for internal (*captive*) use only. Recently, Mark Erman of Millenium Specialty Chemicals [50] found conditions to enrich the content of **13** in the cyclization step of the Iso E Super® synthesis by employing phosphoric acid in methanol – so more than hundred years after Tiemann, there is still work on this cationic cyclization.

Before we leave the family of ionone/woody odorants we have to mention two more milestones: Timberol® (**11**) of Dragoco and Koavone® (**12**) of IFF. It had long been known that the diastereomeric mixture of the tetrahydroionols [51] possesses only very weak and uncharacteristic odor notes, but if the side chain is elongated by just two carbon atoms, a surprisingly powerful woody-powdery odorant of animalic, steroid-type tonality is obtained. 1-(2,2,6-Trimethylcyclohex-1-yl)hexan-3-ol (**11**) was discovered by Klein and Rojahn of Dragoco [52], and introduced into perfumery as Timberol®. Its success inspired the researchers of Firmenich to investigate the structure–odor correlation of related ionols [53], and they found the attractive steroid-type note of **11** to be mainly due to the *trans*-isomer with both cyclohexane ring substituents in equatorial positions. Firmenich introduced this compound as Norlimbanol® for captive use. Later also all four *trans*-enantiomers have been prepared in enantiomerically pure form, and the configuration of the hydroxy-bearing carbon atom was found to be of utmost importance [54][55]. Both (3*R*)-*trans*-diastereoisomers are odorless, while the (+)-(3*S*,1'*R*,6'*S*)-Norlimbanol® was found to be the most powerful and most steroid-like smelling stereoisomer of Timberol® (**11**). It has been introduced recently as 'Dextro-Norlimbanol' [56], but is also reserved for captive use only. In the future, we will probably also see '*overdoses*' of Timberol®-type notes in perfumery, though these materials cannot be used like an ionone (**9**) or like Iso E Super® (**10**). The Timberol® chapter, however, illustrates the strategy of switching to more and more powerful isomers of successful odorants.

Koavone® (**10**), acetyl diisoamylene, was the first (prominent) example for the application of molecular-modeling techniques in the design of odorants. A superposition analysis with 10-methyl ionone was applied to rationalize their similar odor profiles [57]. On paper, Koavone® (**10**) can be regarded as a *seco*-7,8-dimethylionone. Already in 1962, Sestanj [58] had shown that cutting out the carbon atom C(3) does not alter the odor characteristics of β-ionone (**9**). So either with the help of computers or by making use of Dreiding models the rational design of odorants definitely made important contributions to the palette of the perfumer, and certainly will continue to do so in the future. Koavone conveys lift and elegance to accords with methyl ionones and Iso E Super® (**10**) [56], though its threshold is certainly not outstanding.

2.3. *Sandalwood Synthetics*

In the late 1930's, at the I.G. Farbenindustrie, Abt. Riechstoffe, a number of diverse olefins were reacted with phenols in a random approach, targeting at floral odorants, and smelling for instance like violet, iris and lily of the valley [59]. The standard sequence consisted of acid-catalyzed alkylation, hydrogenation of the aromatic ring and oxidation to ketones. When Albert Weissenborn, a former student of Otto Wallach, hydrogenated a mixture of terpenylphenols obtained by boron trifluoride catalyzed alkylation of guaiacol with camphene, he discovered a product mixture with a strong sandalwood odor. Sandalwood oil (*Santalum album* L.), documented already 2000 BC in one of the oldest pieces of Indian literature, the Ramayana, has long been a precious ingredient not only of the Indian and Islamic culture but also of ancient European perfumery, and its affordable price allowed its use even in higher concentrations, mainly in oriental fine fragrances.

The patent describing Weissenborn's discovery was filed in 1942, but due to the events of World War II was published only ten years later [60]. Together with a vast amount of other chemical data of the I.G. Farben and other companies, the information was collected by US Army Intelligence, and was presented to the perfumery community by Byers in 1947 [61]. The Weissenborn process was soon applied by different companies, and the product was sold under different names such as Sandela®, (**16**) (Givaudan [62]), Sandel H&R™ (Haarmann & Reimer), Sandiff®, (IFF), Santalex®, (Takasago), and Santalydol™ (in Russia). It took more than half a century to identify the odorous principle that constituted initially only 0.5% of these complex isomeric mixtures. The relative configurations of the active stereoisomers, 3-*trans*-isocamphylcyclohexanols with axial OH groups (**16**), were established by Demole and coworkers in 1969 [63] and their absolute configurations published only two years ago in a Japanese patent [64]. The content of the sandalwood-smelling isomers **16** in these complex mixtures of terpenylcyclohexanols is still quite low, in spite of process improvements consisting mainly in oxidation of the hydrogenation product to the corresponding cyclohexanones and subsequent catalytic reduction. Using hydrogenation with a catalyst system comprising ruthenium, triphenylphosphine, ethylenediamine and potassium hydroxide in isopropanol, Takasago was able to increase the ratio of axial cyclohexanols [65][66] and the content of **16** rose from 8% in Santalex®, to 24% in Super Santalex [65]. The successful introduction of these first synthetic sandalwood oil substitutes triggered not only a more general use of sandalwood notes in perfumery, but also the synthesis of many other molecules structurally more or less similar to **16** and the santalols [5][6]. However, only Osyrol® (**17**, Bush Boake Allen [67]) turned out to be commercially successful and until today remains the only acyclic material of sandalwood smell.

The real breakthrough in sandalwood synthetics is however due to another fortuitous finding, claimed in 1968 in an East German patent [68], one year before Demole published the configuration of the odoriferous isocamphylcyclohexanols **16**. Using inexpensive α-campholenic aldehyde, Manfred Mühlstädt *et al.* of the VEB Miltitz, formerly the renowned and initially biggest flavor and fragrance company Schimmel & Co., were the first to prepare substituted 4-(2,2,3-trimethylcyclopent-3-enyl)butan-1-ols [68], just a few years before the price of natural sandalwood oil suddenly increased – from 40 $/kg in 1973 to approximately 210 $/kg at the end of 1974. The allylic alcohol **19** and its 2-ethyl analog were the first two representatives of this new class of sandalwood odorants, though the original description in the patent as 'fine, resembling musk and sandalwood' [68] was somehow misleading, since the musk facet is certainly not one of their main olfactory characteristics. Nevertheless, their real olfactory value for perfumery was discovered immediately.

The dramatic price increase in the early 1970's caused by the uncontrolled cutting of sandalwood trees, plagued also by the lethal spike disease, encouraged huge research efforts to find still better sandalwood oil substitutes derived from α-campholenal. Today, the substituted 4-(2,2,3-trimethylcyclopent-3-enyl)butan-1-ols represent the best synthetic sandalwood substitutes and the first compound of this family to be commercialized was Sandalore®, (**18**, Fig. 3, [69]). In the following years, numerous analogs followed, often bearing several different commercial names, *e.g.* Madrol™ (Dragoco), Sandal Mysore Core™ (Kao Soap), Sandelice®, (Henkel), and Santalaire™ (Haarmann & Reimer) for 2-methyl-4-(2,2,3-trimethylcyclopent-3-enyl)but-2-en-1-ol (**19**), which appeared already in the seminal patent of Mühlstädt *et al.* [68]. α-Campholenal, the starting material for all these synthetics is manufactured by epoxidation and acid-catalyzed rearrangement from inexpensive α-pinene, available from the pine and paper industries. Thus, a fast growing and ubiquitous tree is used to imitate the unique odor of a slow growing and endangered one.

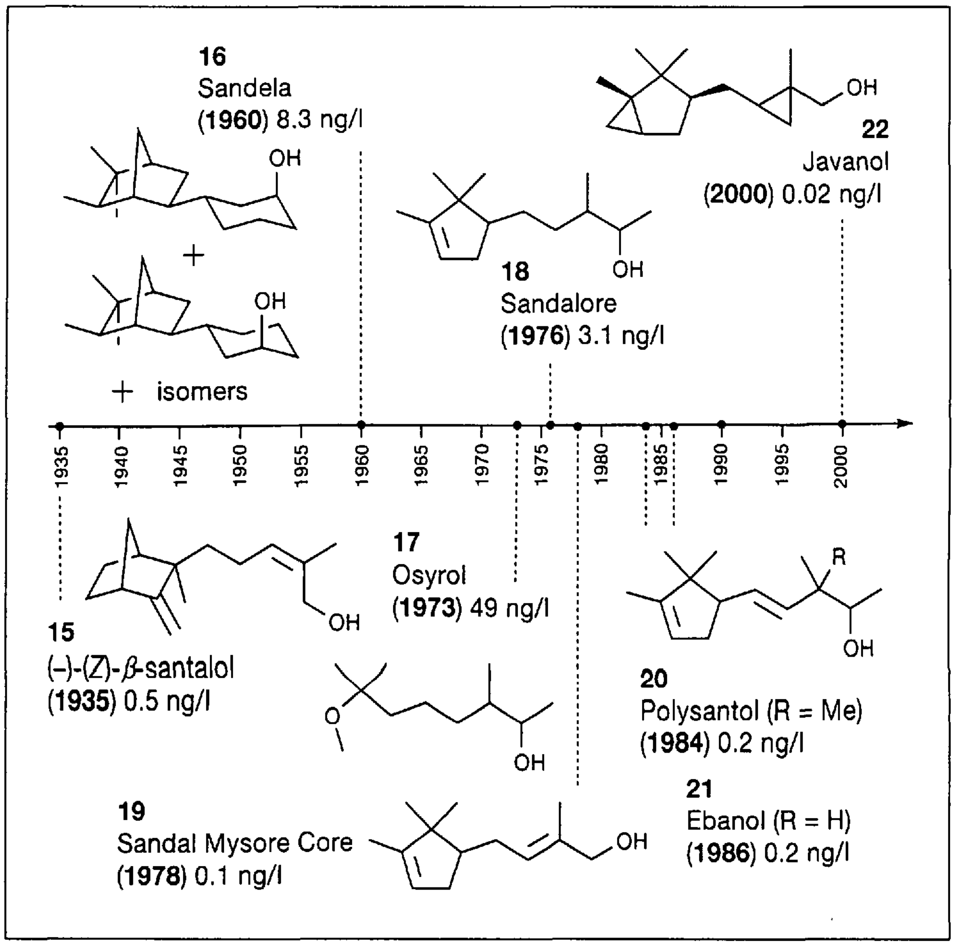

Fig. 3. The sandalwood timeline

The very presence and the quality of the sandalwood scent depends critically on the length and substitution pattern of the aliphatic chain between the *osmophoric* hydroxyl group and the bulky lipophilic moiety. In general, the introduction of a double bond in this aliphatic chain enhances the odor intensity, and indeed, the allylic alcohols Sandal Mysore Core™ (**19**) and its 2-ethyl analog Bacdanol®, have a stronger and more characteristic odor than their saturated analogs. Shifting the double bond closer to the lipophilic cyclopentene moiety further improved the odor characteristics, although the homoallylic alcohols, isomers of the two above-mentioned products and synthesized by Mühlstädt *et al.* [68], were found to possess 'characteristic woody-animal and soft-fruity odorous properties which differ substantially from the typical sandalwood or musk note of the corresponding allylic alcohols' [70]. More substituted derivatives, like Polysantol® (**20**) of Firmenich [71] and Ebanol® (**21**) of Givaudan [72], which had been discovered as an impurity in Sandalore®, seem to be the most appreciated sandalwood synthetics, at least today.

Because of their commercial importance and the industrial availability of both campholenal enantiomers obtained from α-pinene that, depending on the geographic origin of the pine trees, is *laevo* or *dextro* rotatory, the absolute and relative configurations of the campholenyl synthetics have been studied in detail. Already in the early 1980's, all four pairs of enantiomers that constitute Ebanol® (**21**) [72] have been investigated, and soon the elucidation of the absolute configuration of the campholenyl derivatives followed. This led to a series of so called *chiral-switch* patents [73–77] and corresponding 'super' qualities of already existing products. The most striking difference was observed for the enantiomers of Mühlstädt's first campholenal derivatives: the (+)-(*R,E*) and (–)-(*S,E*) enantiomers of **19** have GC odor thresholds of 0.06 and 4.0 ng/l, respectively [78]! In most cases the products derived from (+)-(*R*)-α-campholenal *ex* (–)-(1*S*)-α-pinene exhibit the most intense sandalwood odors.

Until the very recent introduction of Javanol® (**22**) [78], Polysantol® (**20**) and Ebanol® (**21**) possessed the highest intensity of all sandalwood odorants. **22** is also derived from (+)-(*R*)-α-campholenal, but differs from their relatives by having two cyclopropane rings that favorably modify its electronic shape [79]. They are industrially manufactured *via* a double Simmons-Smith cyclopropanation process, a rarity in the chemical industry.

Sandal Mysore Core™ (**19**), Polysantol® (**20**), Ebanol® (**21**) and Javanol® (**22**), all possess lower odor thresholds than that of the odorous principle of sandalwood oil, (–)-(*Z*)-β-santalol (**15**), the synthesis of which was never attempted on an industrial scale, though the first structure attribution by Ruzicka and Thomann [80] dates back to 1935. **15** constitutes *ca.* 25% of the oil and is structurally related – like camphene to tricyclene – to the main constituent of the oil, (+)–α-santalol with a significantly weaker, cedarwood-type scent. The double-bond geometry of **15**, initially proposed to be (*E*) [81], was corrected by Erman in 1967 [82], and the absolute configuration was elucidated as late as 1980 by Brunke *et al.* [83]. Finally, the first total synthesis of enantiomerically pure (–)-(*Z*)-β-santalol was carried out by Krotz and Helmchen [84] *via* asymmetric Diels-Alder condensation of cyclopentadiene with a chiral *trans*-crotonate, as recently as in 1990. First the relatively low price of the authentic sandalwood oil, then the discovery of the terpenylcyclohexanols **16** followed by the more powerful campholenal derivative **18** and the high-impact odorants **19**–**22** never made an industrial approach to **15** attractive, even though today sandalwood oil is priced around 550 CHF/kg, and despite many interesting synthetic ideas [85].

3. Future Perspectives

Today, the successful launch of a new fragrance or a new consumer product begins with a good understanding of the market, and ends with an advertisement campaign. Consequently, the development of fragrances involves a great deal of consumer research to understand the needs and preferences for certain odor notes. For fabric and homecare products there is an ever great demand for long-lasting '*fresh and clean*' notes.

Many substantive (*long-lasting*) odorants are known, but a great number of odorants are too volatile to be perceived more than a few hours after their application. This is the reason why more efficient and effective fragrance-delivery systems, especially for laundry-care products, are intensely sought. Delivery systems such as spray-dried and microencapsulated perfumes as well as inclusion complexes with cyclodextrins have been developed and are already in use to help decrease volatility, to improve stability, and to enable a slow release. Many efforts are still being made to improve these systems that are the topic of one of the following articles [86].

Another approach consists of employing fragrance precursors or '*properfumes*'. The use of '*prodrugs*', an inactive drug derivative which is converted in the body into its active form, is a well-established technology to improve *e.g.* the oral bioavailability or the penetration across biological membranes. This concept, widely used by the pharmaceutical industry, was introduced to functional perfumery by Firmenich in the mid 90's [87]. They made use of lipases that are employed in most detergents to degrade fatty stains to hydrolyze esters of fragrant alcohols. Digeranyl succinate (DGS, **23**) was the first fragrance precursor on the market, used in the fabric softener 'Lenor' [88]. **23** has a better affinity towards fabrics than geraniol (**24**) and is slowly cleaved by the lipase during the rinsing and drying cycle into geraniol (**24**) and succinic acid (**25**, Fig. 4a). In effect, geraniol is perceptible on the fabric much longer. The introduction of DGS (**23**) into functional perfumery has triggered the search for other precursor systems, which is illustrated by an increasing number of patent applications, *e.g.* sulfonates [89], betaine esters [90], β-keto esters [91] and carbonates [92] of fragrant alcohols. For stability reasons these systems can, however, generally not be used in detergents. This led to the development of precursors that are cleaved by hydrolysis during the laundry process, *e.g.* β-amino ketones derived from damascones and ionones (**9**) [93], or 2-acyl benzoates derived from fragrant alcohols [94], and fragrance chemists are still looking for new systems with improved stability and release properties.

The development of light-labile precursors is also a topic of current interest. Today many 'surfaces', *e.g.* fabrics, floors, hair and skin, are being fragranced and therefore light would constitute an ideal trigger. Upon exposure to light, coumarate **26** photoisomerizes to **27**, which by subsequent lactonization releases two widely used fragrance ingredients, coumarin (**28**) and citronellol (**29**, Fig. 4b, [95]). A. Herrmann *et al.* of Firmenich made use of a Norrish-type-II fragmentation of α-keto esters to generate fragrant aldehydes and ketones, *e.g.* to release citral (**32**) by light exposure of oxo-ester **30** (Fig. 4c, [96]). This system has the disadvantage that the diradical **31** formed is prone to undergo side reactions, which lead to byproducts [97] that may possess unpleasant odors. The fact that light is almost everywhere where fragranced products are used, makes this class of fragrance precursors very useful. We can therefore expect other interesting light-labile fragrance precursors that could find their way into consumer products.

Though fragrances are incorporated into functional products to impart a pleasant odor, some odorants possess also antimicrobial properties or other *second-*

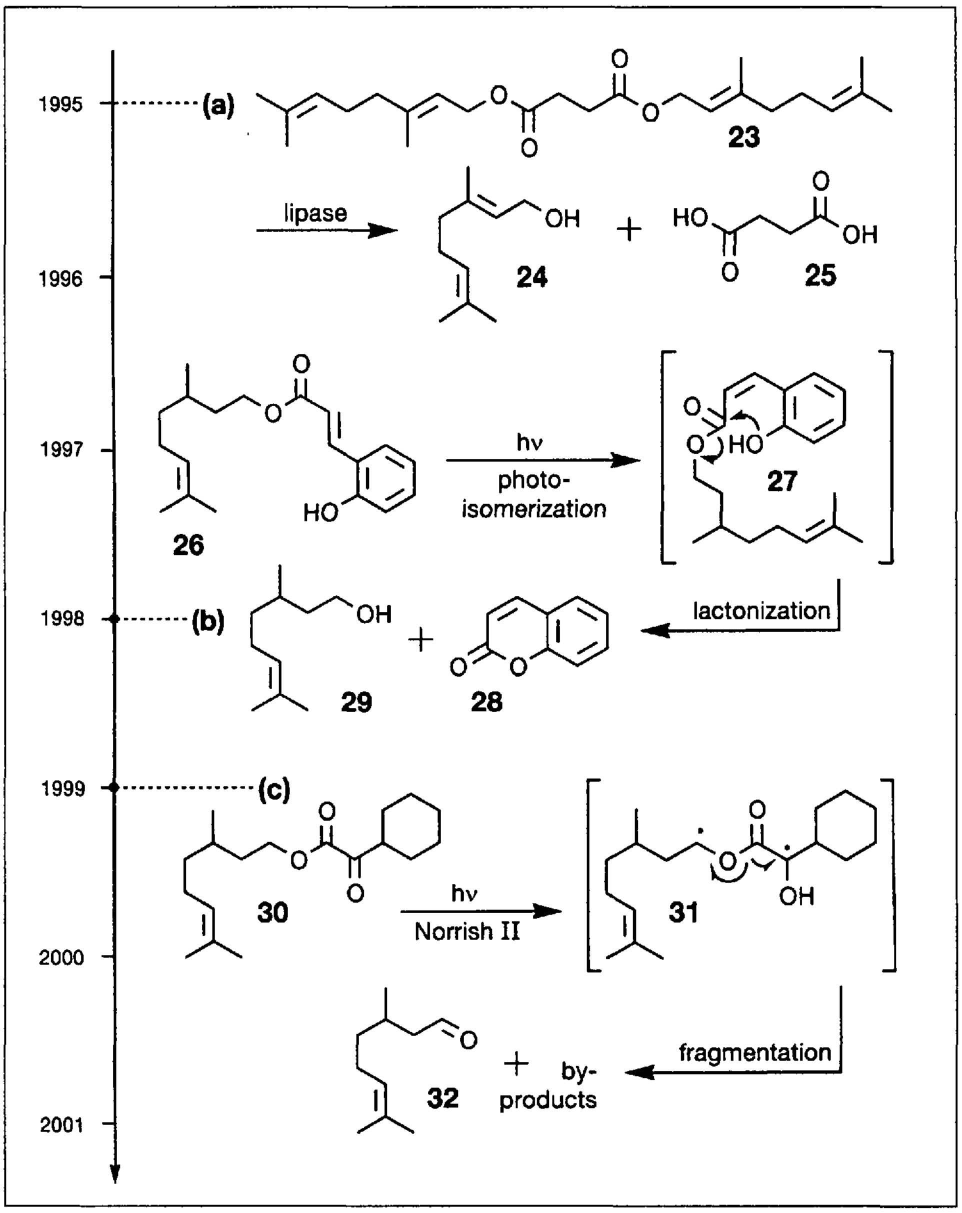

Fig. 4. Precursor technologies

ary benefits, like for instance insect repellent activity. It is therefore obvious to use fragrance materials also for their antimicrobial properties, and to improve these activities deliberately by structure modifications. Although this concept has been discussed for a long time, it only recently received more attention, since cases of resistance to the widely used antibacterial agents like Triclosan were reported. Fragrance ingredients such as eugenol, carvacrol and thymol are known to have bactericidal activity. However, their use is limited because at a certain concentration their odor becomes unpleasant. In order to overcome this problem, fragrance chemists have been looking for compounds that not only exhibit pleasant odor characteristics, even in higher concentrations, but also possess good antibacterial activity [98]. Today, new odorants are therefore routinely screened for these *secondary benefits*.

The search for performant molecules with new and innovative odor characteristics is, however, still the main focus of the industry and in almost every odor note there are still plenty of new odorants to be discovered; stronger in odor, more transparent or more easy to overdose, exhibiting better performance in special functional products, or possessing unique combinations of different odor tonalities. There are endless possibilities and variations, and in this article we have shown just some motivations and driving forces for the development of a few prominent odoants. Current trends in the chemistry of odorants were presented in a recent review [6].

We close this review with a glance at the latest trends in perfumery. Trends in perfumery have always influenced the development of new odorants. Traditionally there was a 'tickle-down' phenomenon of odor notes from luxury fine fragrances *via* mass-market perfumes into personal & laundry care, and even household products. Today, fine fragrances perfumers are inspired to a great extent by odor notes used in the cosmetic and toiletries segment. One example was the pear trend, which started in personal care products and then spread to fine fragrances [6]. The attribute *'fresh and clean'* is not only a catchy phrase when it comes to fabric care, but does frequently occur in fine-fragrance briefs. So *'fresh and clean'* green top notes are currently *en vogue* in fine fragrances, smell for instance 'Truth *fem.*' (C. Klein, 2000).

The Japanese designer Rei Kawakubo recently promoted the rebellious concept of *'anti-perfumes'* that should not be appealing to other persons, but should 'create around you the smell that you like' – 'your own air' [99]. Consequently these should be used not only on skin, but also on furniture and clothes, as air fresheners and pillow sprays, to clean overhead transparencies or CD boxes – all in one. The first two were named 'Odeur 53' [100] and 'Odeur 71' [101], playing with images like 'cellulosic smell', the 'mineral intensity of carbon', a 'salty taste of a battery' or 'the smell of dust on a hot light bulb'. What sounds like olfactory action paintings, are actually quite monolithic compositions, in the case of 'Odeur 53' with over 63% of one single odorant – a portrait of Hedione® [6]. The concept of sheer 'single-note' perfumes featuring, for instance, flowers (*soliflores* like 'Rosa Magnifica', Aqua Allegoria, Guerlain, 1998 [102]), leaves (*e.g.* 'Shiso', Comme des garçons, parfumsPARFUMS, 2001 [103]) or classic raw materials (*e.g.* 'PureVetiver', Azzaro Collection, 2000 [104]), is today a major trend. But why not do the same around new 'salty', 'milky' or 'vegetal' odorants in the future, as suggested by the Comme des garçons advertisement?

At the beginning of this paragraph, we mentioned market research and advertisement campaigns, certainly needed and justified for big international product launches. But recently the Internet has opened up a forum for smaller launches and more experimental perfumes that never existed before. For his 'Editions de Parfums' Frederic Malle gave (prominent) perfumers total freedom to create rare scents without norms or limits. These authentic artistic creations are all presented in the same bottle, with the name of the perfumer and the name of the fragrance as given by the perfumer [105]. Two examples are 'Angeliques sous la pluie' from Jean-Claude Ellena, a bouquet of angelicas after the rain, and 'Lipstick rose' from Ralf Schwieger, the symbolization of pure powdered floral harmony. These fragrances can be ordered *via* Internet [106] or bought in a little shop at the Rue de Grenelle in Paris; and needless to say there is no market research or advertisement campaign behind the range. Another paradise for unusual scents is the Salons du Palais Royal Shiseido at the Rue de Valois in Paris, managed by Serge Lutens [107]. Besides a series of exclusive eaux de parfums, 'Féminité du Bois' (Shiseido, 1992) with its overdose of 43% of Iso E Super® (**10**) also had its origins there. Shops of this kind could bear and catalyze new trends, and the people behind them could dare to use new and unusual odorants or to overdose existing materials long before these are accepted in market tests.

Note on trademarks

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

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