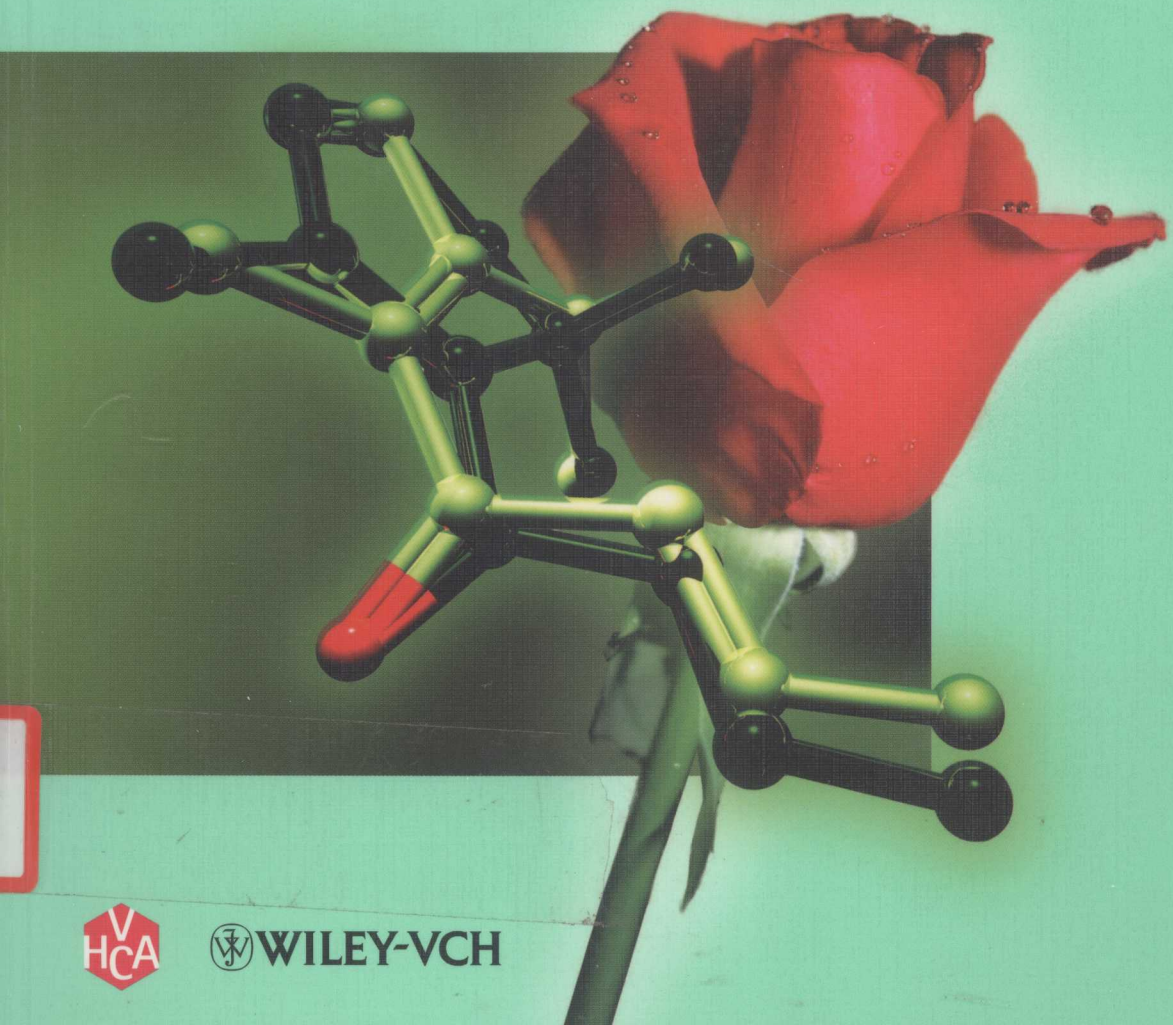
Günther Ohloff
Wilhelm Pickenhagen
Philip Kraft

Scent and Chemistry
The Molecular World of Odors



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Preface

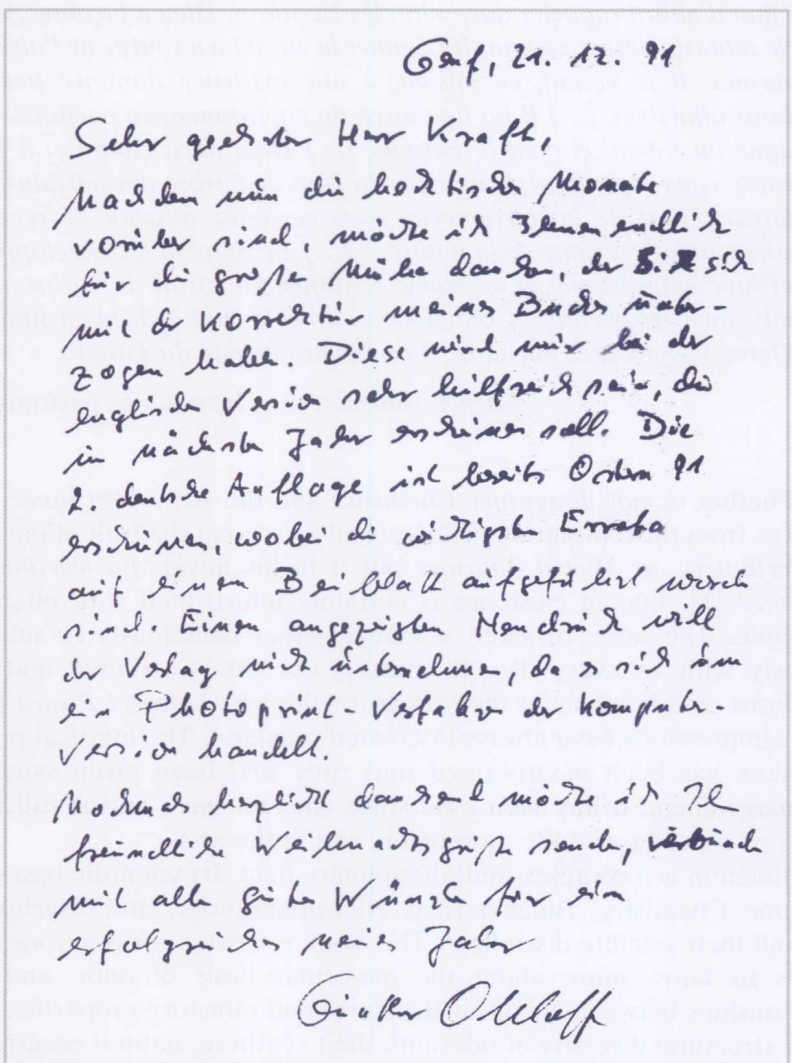
Il faut d'abord rappeler que, selon les Ecritures, Dieu a façonné Adam avec le sable du désert, et, pour lui donner la vie, il lui a soufflé de l'air dans les narines. Il le vouait, ce faisant, à une existence dominée par des émotions olfactives. [...] Il lui faut aussi un environnement parfumé. Il se mit donc au travail et créa le Paradis. [...] Dieu dit à Adam et à Eve: « Gardez-vous cependant de manger du fruit de l'arbre des parfums, car, connaissant l'art de la parfumerie, vous cesseriez aussitôt de recevoir gratuitement les parfums de la nature. » [...] Le Serpent les enveloppa de son effluve empoisonné et enjôlant: « Mangez du fruit de l'arbre de la connaissance des parfums. Connaissant l'art et la chimie de la parfumerie, vous ferez vos propres parfums, et ils égaleront ceux du Paradis. »

Michel Tournier, 'La légende des parfums' [1]

Whether or not, *Fragrance Chemistry* and the *Art of Perfumery* did emerge from the temptation of *Adam* and *Eve* to eat the fruit of the *Tree of Perfumery*, as *Michel Tournier* put it in his novel '*La légende des parfums*' [1], human existence is certainly intertwined with olfactory emotions. The sense of smell is indeed either consciously or subconsciously with us every day. It controls our intake of food and our emotions, and helps us in the search for the past (*Marcel Proust* [2]). Odor impressions have always fascinated mankind. The mystical power of odors has been incorporated into rites, and been given symbolic meaning. There, it has been used since ancient times, and is still used today as part of social life, in religion, and in the arts.

Olfaction is a complex multidisciplinary field. Its scientific bases are Organic Chemistry, Biochemistry, Neurophysiology, and Psychology with all their satellite disciplines. This book is written for everyone who wants to know more about the molecular basis of odor, and the relationships between chemical structures and olfactory properties. The great structural diversity of odorants, their synthesis, natural occurrence and their structure–odor correlation demonstrate what a fascinating science *Fragrance Chemistry* indeed is.

The first edition of this book, '*Scent and Fragrances – The Fascination of Odors and their Chemical Perspectives*' was published in 1994 as the English translation of the original German title '*Riechstoffe und Geruchssinn – Die molekulare Welt der Düfte*' by *Günther Ohloff* that appeared in 1990. Both the English and the original German version sold out quickly, which showed the massive interest with which they were met. Knowledge of the *Chemistry of Odorants* has significantly increased since *Günther Ohloff* (1924–2005) wrote his small but condensed



Genf, 21. 12. 91

Sehr geehrter Herr Kraft,

nachdem nun die hektischen Monate vorüber sind, möchte ich Ihnen endlich für die große Mühe danken, der Sie sich mit der Korrektur meines Buches unterzogen haben. Diese wird mir bei der englischen Version sehr hilfreich sein, die im nächsten Jahr erscheinen soll. Die 2. deutsche Auflage ist bereits Oktober 91 erschienen, wobei die wichtigsten Errata auf einem Beiblatt aufgeführt worden sind. Einen angepriesenen Handschlag will der Verlag nicht übernehmen, da es sich um ein Photoprint-Verfahren der kompletten Version handelt.

Nochmals herzlichen Dank und möchte ich Ihnen freundliche Weihnachtsgrüße senden, verbunden mit allen guten Wünschen für ein erfolgreiches neues Jahr

Günther Ohloff

Figure. *Letter of* Günther Ohloff *to* Philip Kraft, *for Christmas 1991*

magnum opus in 1990. We, therefore, concluded that a new and revised edition, which would take these developments into account, and which would correct some mistakes that had slipped in the first two editions (*cf. Fig.*), was highly in demand. With the original text featuring many original results of *Ohloff*'s research group at *Firmenich*, and our affiliation to *Symrise* (*W. P.*) and *Givaudan* (*P. K.*), respectively, the resulting book is truly cross-company.

This new and completely revised edition follows with some exceptions the successful format of the original text, but updates and complements it with special focus on the new developments in Genetics and Physiology of the human olfactory receptor system, the discovery and use of new odorants, and new studies in the correlation of chemical structures and olfactory properties.

As for the first edition, the intention is to inform the interested reader about the actual state of the art in the multidisciplinary field of human olfaction with an emphasis on *Fragrance Chemistry*. We are indebted to *Asta Ohloff* and *Ulrike Dexel* for their support of this project, and for sorting out copyright issues with *Springer-Verlag*. For the reproduction of photos and pictures, we are extremely grateful to *Roman Kaiser* and *Jean-Pierre Bachmann*, both of *Givaudan*, as well as to *Philip Goutel* (*Fig. 1.2*), *Hanns Hatt* (*Fig. 2.4*), *David Monniaux* (*Fig. 7.13*), *Sasha A. R. Pattinson* (*Fig. 7.14*), *Devendra Basnet* (*Fig. 8.1*), and *Doug Perrine* (*Fig. 8.6*). *Markus Gautschi* and *Andreas Muheim* of *Givaudan* are acknowledged for their approval to publish selected proprietary data such as the odor value map of sandalwood odorants (*Fig. 2.10*), and *Heinz-Jürgen Bertram* for his approval to display the *Symrise Fragrance Circle* (*Fig. 2.6*). For analytical data on perfumes, we are indebted to *Christine Ledard* and the respective perfumers of the mentioned fragrances. For help with literature references, we are grateful to *Andreas Schomburg*, and, for help in compiling the index, to *Fanny Grau*. Furthermore, *P. K.* thanks *Olivia Rosser* and *Tony McStea* for additional proof-reading. Finally, we would like to thank *M. Volkan Kısakürek* and *Thomas Kolitzus* of the *Verlag Helvetica Chimica Acta* for the excellent collaboration.

Should you spot any typos, mistakes, or even incorrect chemical formulas, please hit up the '*Scent and Chemistry*' wall on *Facebook* [5], and let us know. Needless to say, you can also leave your comments there. Get yourself involved in improving future editions: We would love to hear from you!

Wilhelm Pickenhagen and Philip Kraft

Geneva and Zürich, January 2011

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[5] http://www.facebook.com/pages/Scent-and-Chemistry/263202847040070; or look for 'Scent and Chemistry Facebook' in your web search engine. You can also tweet to us @ScentChemistry.

Contents

1. Historical Aspects

1.1. Scents of Time

The use of odors and odorants is, most certainly, much older than the recorded history of mankind, probably even older than *Homo sapiens*, and coincides with the hominid control of fire. Several Middle Pleistocene sites exhibit the exploitation and control of fire some 500,000 years ago. The presence of burned seeds, woods, and flint at the Acheulian site of *Gesher Benot Ya'aqov* suggests that these date back even to the Lower Pleistocene, some 0.79 million of years ago [1]. Thus, *Homo antecessor*, *Homo erectus*, and *Homo ergaster* were already able to burn resinoid woods, and prepare food by roasting, grilling, or cooking. The anthropologist *Richard Wrangham* speculates that cooking has been a biological requirement for hominid survival, and may have begun as far back as 1.7 million years ago [2][3]. It may very well have influenced our evolution in flattening our facial features to enable savoring of food by retronasal perception, while carnivores rarely savor their food, but rip, chomp, and swallow it [4]. Retronasal perception might even be the key to kissing, or the explanation for the evolution of pronounced female breasts that make it possible for babies to taste the milk and smell their mothers upon breastfeeding. Mouth-based smelling is a human trait and led very early on to the discovery of spices that made food more tasty, but also more healthy by acting as preservatives. Fragrant spices also served as the first medicines, and the belief that odors were a cause rather than an effect of illness, or that good smells would cure diseases, since they cover bad smells associated with these, extended well into the early 19th century; many odorants indeed possess antimicrobial properties.

Apart from the preparation of food, fire also served very early on in human history for the disposal of corpses, which called for neutralization and deodorization of the resulting stench during cremation rituals [5]. In this way, the burning of fragrant woods, odorous resins, and aromatic plants became linked to religion. Odors became bridges between the here and now, and the hereafter. Offered as a gift to the gods by all past civilizations, perfume spiritually elevates and renders the body divine,

and transforms places into sanctuaries [5]. This symbolism is documented in the ancient writings, and the word *perfume* derives in fact from '*per fumum*', meaning '*through smoke*', or by nebulization, by transformation of a substance into something airborne. In particular, the early fumigatory use of burning resins, woods, barks, and other parts of aromatic plants had widespread appeal. Such odor signals were assumed to possess magical properties and were sent to honor the Gods. The association of odor and sanctity was so explicit that the priests of the cult of *Osiris* chewed cedar gum to perfume their breath and create a scented aura of sacredness [5]. Odors were also supposed to protect the live and dead from any mishap, as well as to keep the healthy free of disease, to heal the sick, to form a link between man and his ancestors, or simply to give pleasure. Even today, especially in Buddhism, fumigation is synonymous with purification, both in the religious and in the hygienic sense of the word, and this practice soon expanded from the temples into the homes [5].

Incense and myrrh are two of the oldest known odorants [6]. It is written in ancient Assyrian tablets that incense was offered to the God of the Sun in Nineveh. During the reign of *Hammurabi*, one thousand talents (*ca.* 29,000 kg) of incense was burnt annually in the *Bel* temple of Babylon. At the time of the Pharaohs, 3000 BC, the Egyptians prepared incense offerings from a mixture of different resins such as myrrh and opopanax, often combined with cinnamon bark and other aromatic materials [7]. Odorous hardwoods had the same symbolic power. For example, cedarwood is mentioned in the *Epic of Gilgamesh*, 3200 BC, which is considered to be the oldest written document about the genesis of mankind. At that time, Egyptians had already developed the technology of producing cedarwood oil. This was one of the seven oils that the Pharaohs used in combination with tar and odorous resins to prepare balms for their dead [8]. Cedarwood was used because it was thought to last eternally. Sandalwood also constitutes one of the most ancient perfumery ingredients that has been used for more than 4000 years. The Bible considers sandalwood as one of the most important gifts. One of the oldest citations describes the *Queen of Sheba* who '*made a gift to Solomon of a great quantity of sandalwood and precious stones*' [9]. Sandalwood is much esteemed in Eastern cultures, especially in India.

From ancient times on, odor has been part of the language of writers, philosophers and physicians. *Homer*, for instance, reported which odor notes pleased the Greek Gods. In the *Odyssey*, the secret of the '*Bouquet of Venus*' that made *Aphrodite* irresistible was revealed. *Odysseus*, the king of *Ithaca*, was held prisoner by the magical odorants used by the sorceress *Circe*. The incredible beauty of *Helen of Troy*, whose abduction

caused the *Trojan* War, was ascribed to her cosmetic secrets. She was known to have shared these secrets with her admirers by showing them the recipes of the cosmetic products she used. This supposedly is the beginning of cosmetic and perfumery formulation.

The Greeks were experts in the art of extracting the aromatic principles of plants and resins using olive oil. Fat extraction of floral odors from freshly picked flowers, a technique for the production of concretes that had been known as *enfleurage* and was practiced in southern France from the 17th to the 19th century, was already known in Greece at the time of *Homer*. *Antiphanes* described the preparation and use of tinctures, lotions, essences, and creams to scent and moisturize each part of the body. The most important writers of classical antiquity such as *Herodotus*, *Horace*, *Ovid*, *Pliny*, and especially *Martial* often described cosmetic practices and the use of odorant products. According to the book of *Theophrastus*, rose, lily, and violet were the odors that were most liked by the Greeks at that time. It was reported by *Martial* that the Romans preferred the more masculine odors of saffron and balsams. Other odors *en vogue* in classical times were narcissus, iris, calamus, cinnamon, costus, vetiver, quince essence, thyme, and marjoram along with the biblical oil of nard. In his natural history, *Pliny the Elder* mentioned a cream which contained 27 of these aromatic ingredients. In ancient Greece, *Megallus* and *Peron* were famous Athenian perfumers, while, according to *Martial*, *Cosmus* and *Nicero* were the most important *Unguentarii* in Rome. While the Greeks made use of perfumes more moderately, the Romans were lavish with their scents. *Catullus* became an addict to odor orgies and decided to be '*nose only*'. However, critical voices were also heard. *Pliny the Elder* reminded his followers '*perfumery was the most redundant luxury*'. *Solon*, an Athenian statesman and lawmaker, forbade the use of perfume by Greek men. In contrast, *Aristotle* praised the aesthetic aspects of the sense of smell. He noted '*pleasant odors contribute to the wellbeing of mankind*'. *Anacreon* recommended that the '*use of lovely perfumes on one's head is the most effective remedy against illness*'. In fact, also in classical times a great number of odorants were used as therapeutic agents. Their use is described in '*Naturalis Historia*' by *Pliny the Elder* and '*De Materia Medica*' by *Dioscorides*.

The first studies on the sense of smell were performed in very ancient times. *Galen*, the founder of *galenism*, and personal physician to Emperor *Marcus Aurelius*, discovered the existence of the olfactory nerve. The first theory dealing with structure–activity relationships of odorants is ascribed to the Roman writer and philosopher *Titus Lucretius Carus* (98–54 BC). According to his book '*De Rerum Natura*' [10],

pleasant-smelling odorants were assumed to be of a smooth round geometry, whereas harsh compounds supposed possessed rough molecular surfaces. An odor of a compound was thought to be elicited by molecules passing through slots of complementary shape in the sensory organ. Thus, the '*lock and key*' principle, which *Emil Fischer* [11] used to describe the interaction of an enzyme with its substrate, was first mentioned over 2000 years ago.

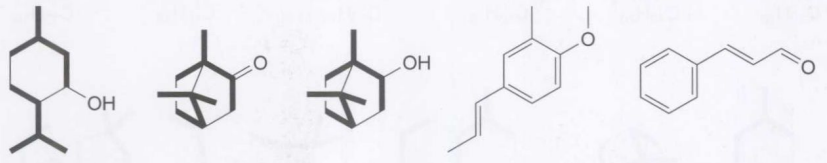
All classical fragrances were scented cosmetics and toiletries, so-called '*unguenta*', perfumed oils and lotions, and not alcoholic perfumes, as we know them today. The first still was invented by alchemists in Alexandria *ca.* 200–300 AD, and then perfected by the Persian philosopher and physician *Alī Sīnā Balkhi* (*Avicenna*, 980–1037) for the steam distillation of rose oil (attar of rose) from *Rosa centifolia* L., a rose highly prized by the Arabs. Rose oil and rose water were soon produced on a large scale and exported around the world. However, only in 1320 Italian distillers invented the serpentine cooler, which allowed the production of high-grade alcohol (from the Arabic *al-kuhūl*), and, in 1370, the first alcohol-based perfume appeared in France. It became known as '*L'Eau de Hongrie*' or '*Hungary Water*', since it was allegedly formulated at the command of the Queen of Hungary by her court alchemist. The name emphasizes on the water-clear appearance of this alcoholic perfume in contrast to the then-known oil-based fragrance formulations. These '*eaux*' were, however, not only applied externally as perfume, but also internally as medicines against various diseases. This explains the name '*Aqua Admirabilis*' that *Giovanni Maria Farina* (1685–1766) launched in Cologne in 1709. It soon became famous as '*Kölnisch Wasser*' or '*Eau de Cologne*'. Allegedly, *Napoléon Bonaparte* (1769–1821) used up to two bottles of *Eau de Cologne* per day, which he poured over his head and shoulders. Not only did *Napoléon* make *Eau de Cologne* famous all over the world, he also defined per decree the term *perfume* in 1810. According to this definition, perfumes had to be distinguished from medicines and were no longer allowed to be used internally. The composition of medicines for internal use had to be declared, and thus many perfume makers decided to drop any claims of therapeutic effects rather than to lay open their formulae. Thus, perfume became a beauty-care product and very soon a fashion item [12].

Despite the success of the *Eaux de Cologne* family, most of the perfumes of the 18th, 19th, and early 20th century were reconstitutions and interpretations of flower scents, so called *soliflores* [13]. Some prominent examples for such *soliflores* are '*Lily of the Valley*' (*Floris, ca.* 1750), '*Rose*' (*Molinard*, 1860), '*Jasmin*' (*Molinard*, 1860), '*Rose Jacqueminot*' (*Coty*, 1904), '*Jasmin de Corse*' (*Coty*, 1906), '*Violette*

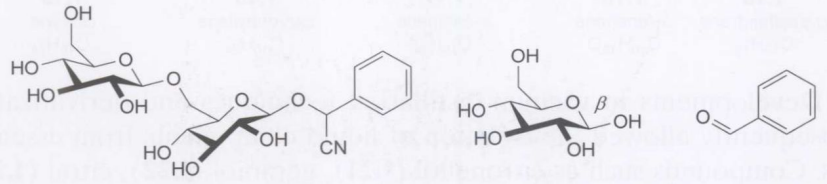
Pourpre' (*Houbigant*, 1907), '*Narcisse Noir*' (*Caron*, 1912), '*Gardénia*' (*Chanel*, 1925), and '*Le Muguet de Bois*' (*Coty*, 1942). This was due to the fact that the perfumers had only essential oils with which to compound, and while they could construct flowers that did not yield an essential oil, such as lily of the valley (*muguet*), from other essential oils, abstract creations were very difficult to achieve at the end of the 19th century. This technical stagnation was only overcome by the timely and rapid development of Organic Chemistry. Analysis of natural products and efficient synthetic preparation of their smelling principles led to an understanding of the molecular basis of essential oils.

1.2. Chemical Discoveries and Modern Perfumery

The beginnings of the analytical branch of Fragrance Chemistry trace back to 1818, when *Jacques-Julien Houtou de Labillardière* (1755–1834) established by elemental analysis that turpentine oil was characterized by a relation of five C- to eight H-atoms ($(C_5H_8)_x$) [14]. This relation was found to be identical for all terpene hydrocarbons. In 1833, *M. J. Dumas* [15] classified the essential oils into those containing only hydrocarbons such as turpentine and citron oil, those containing oxygenated compounds such as camphor and anise oil, and those with sulfur (mustard oil) or nitrogen compounds (oil of bitter almonds). He found the correct empirical formula of menthol (**1.1**), camphor (**1.2**), borneol (**1.3**), and anethole (**1.4**).



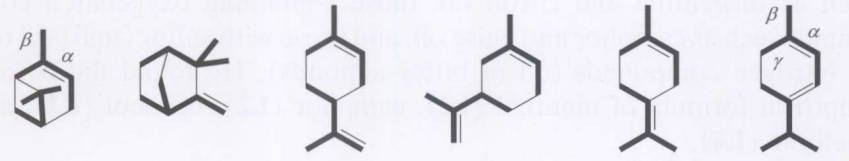
1.1 menthol $C_{10}H_{20}O$ | **1.2** camphor $C_{10}H_{16}O$ | **1.3** borneol $C_{10}H_{18}O$ | **1.4** anethole isoestragole | **1.5** cinnamaldehyde



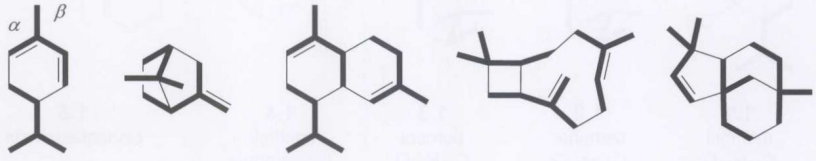
1.6 amygdalin | **1.7** β-D-glucopyranose | **1.8** benzaldehyde

In 1835, *Jean-Baptiste Dumas* (1800–1884) and *Eugène-Melchior Péligot* (1811–1890) isolated and characterized cinnamaldehyde (**1.5**) from cinnamon essential oil [16]. In their groundbreaking work on bitter almond oil, *Friedrich Wöhler* (1800–1882) and *Justus Liebig* (1803–1873) showed in 1837 that its typical odor was due to an enzymatic cleavage of amygdalin (**1.6**) in glucose (**1.7**), hydrogen cyanide, and benzaldehyde (**1.8**), the latter two compounds exhibiting a bitter almond odor [17]. Benzaldehyde (**1.8**), the principal odorant of the essential oil from bitter almonds, can be regarded as the first natural perfume material prepared synthetically [18].

Starting in 1884, *Otto Wallach* (1847–1931) elucidated in over 125 papers the structures of the most important terpenoid constituents of the most important essential oils, including α-pinene (**1.9**), camphene (**1.10**), limonene (**1.11**), sylvestrene (**1.12**), terpinolene (**1.13**), α-terpinene (**1.14**), α-phellandrene (**1.15**), α-fenchene (**1.16**), as well as the sesquiterpenes α-cadinene (**1.17**), caryophyllene (**1.18**), and clovene (**1.19**) [19]. The first perfumery raw materials were those which were easy to isolate from essential oils by crystallization such as camphor (**1.2**), borneol (**1.3**), and (+)-cedrol (**1.20**).



1.9 α-pinene $C_{10}H_{16}$ | **1.10** camphene $C_{10}H_{16}$ | **1.11** limonene $C_{10}H_{16}$ | **1.12** sylvestrene $C_{10}H_{16}$ | **1.13** terpinolene $C_{10}H_{16}$ | **1.14** α-terpinene $C_{10}H_{16}$



1.15 α-phellandrene $C_{10}H_{16}$ | **1.16** α-fenchene $C_{10}H_{16}O$ | **1.17** α-cadinene $C_{15}H_{24}$ | **1.18** caryophyllene $C_{15}H_{24}$ | **1.19** clovene $C_{15}H_{24}$

Developments in vacuum-distillation techniques and derivatization subsequently allowed the isolation of liquid components from essential oils. Compounds such as citronellol (**1.21**), geraniol (**1.22**), citral (**1.23**), (−)-linalool (**1.24**), cinnamaldehyde (**1.5**), and eugenol (**1.25**) represent a series of natural materials that inspired the perfumers of the 19th century.