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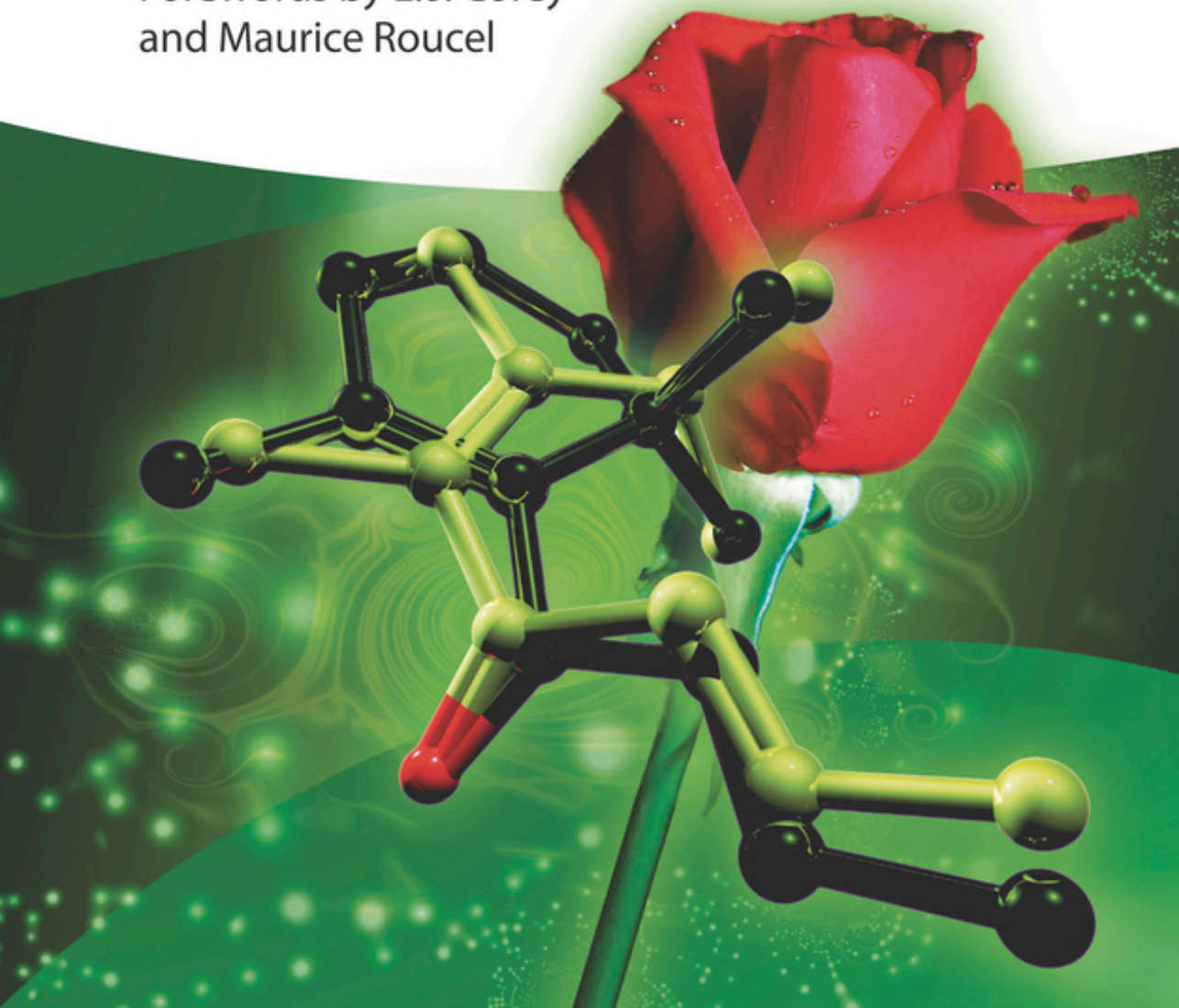
Günther Ohloff, Wilhelm Pickenhagen,
Philip Kraft, and Fanny Grau

Scent and Chemistry

The Molecular World of Odors

Second Edition

Forewords by E. J. Corey
and Maurice Roucel



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The Molecular World of Odors

Günther Ohloff[†]*, Wilhelm Pickenhagen, Philip Kraft, and Fanny Grau*

Second Edition

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Cover Illustration:
Taking up the motif of the original German edition, the cover illustration shows a superposition analysis of the modern trendsetting captive Pomarose on β-damascenone in front of a red rose photographed by *Jean-Pierre Bachmann*. This superposition analysis is shown from a different perspective in Fig. 6.2 on page 193 and is explained in the accompanying paragraph. The background features a fractal chaos generated from the light reflections on the surface as first featured on the corresponding Facebook page. Rendering and raytracing by Dr. Philip Kraft.

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Chemical Foreword

Since ancient times, humans have derived pleasure from naturally occurring fragrances, perfumes, scents, and spices. However, it is only in the last 100 years or so that science has revealed in great detail the many molecules responsible for these delightful properties and the fascinating connection between chemical structure and odor. At present, thousands of natural, older, and newer odorant substances are defined precisely as molecular structures and available by chemical synthesis. An enormous global commercial enterprise has evolved to provide aesthetically pleasing fragrances to meet a worldwide demand. The mystique of perfumes thrives as does global use.

Even more recently, we have begun to understand the nature of odor perception in terms of molecular receptors in the nose and the signal transmission between these, the olfactory bulb, and the brain.

This book, '*Scent and Chemistry: The Molecular World of Odors*', delivers an in-depth and authoritative exposition of every aspect of this multifaceted subject. It spans a vast terrain of topics, including historical, physiological, commercial, structural, and molecular basis of scent, and chemical synthesis of odorants.

Since I am a chemist, I was especially interested in the chemical structures of the many odorant molecules that are discussed in the book and the step-by-step pathways by which such molecules can be produced synthetically at scale. The large number of very interesting syntheses described by the authors adds great value for those in the field and for students of chemistry who will appreciate it as a treasure house of fascinating chemical structures and elegant reaction sequences.

I read this unique volume with great pleasure and satisfaction. For this reason, I extend warm thanks to the three distinguished authors and confident recommendation to potential readers.

Elias James Corey
Sheldon Emory Professor Emeritus
Harvard University
Nobel Laureate (Chemistry, 1990)
Cambridge, MA, USA
May 2021

Perfumistic Foreword: Synthetics or Naturals?

Many people think that only natural ingredients should be used to create and compose perfumes. This is a generally preconceived notion that is not shared by the creators of perfumes. I try to be open-minded and consider any odoriferous ingredient as perfumery ingredient, like a writer who utilizes every letter of the alphabet including 'X' and 'Z' to compose the words that make up his poems. Like all artists, musicians, painters, and all other creative people, we use what we deem interesting and useful for the realization of our ideas. What we are looking for is novelty, uniqueness, and beauty. The ingredients catalogue available 150 years ago to the creative perfumer was far less thorough than it is today, making it difficult to create new original notes by using only natural ingredients.

The invention of synthetic Organic Chemistry in 1828 by *Friedrich Wöhler* and its rapid development considerably improved the possibilities for new creations. It began with the synthesis of naturally occurring molecules like coumarin (**1.26**), vanillin (**1.27**), and others. The progress in chemical methodology, analysis, and synthesis led to the discovery of odorants that do not exist in nature and allowed the development of new sensory impressions, which then opened up new dimensions for perfume creations. Notes like '*lily of the valley*', among others, became available that could not be isolated from their natural environment, as well as lilacs and violets, whose extracts only had the name but did not possess the odor of the original flowers.

The synthesis and the use of fatty aldehydes contributed to the creation and originality of '*Chanel N°5*', that of hydroxycitrone (hydroxycitronellal), to the scent of lily-of-the-valley flowers. All that resulted in a plethora of new creations in the years around 1920, and this was only the beginning.

Ambrox (**1.41**), allyl amyl glycolate, *Calone* (**1.46**), and ethyl maltol (**1.47**) contributed to the creation of very successful new perfumes. *Hedione* (**1.39**); the damascones (**1.40**), even if their olfactory notes resemble those of natural origin; and the purely synthetic trendsetters like *Galaxolide* (**1.44**), *Iso E Super* (**1.45**), *Manzanate*, and *Vertofix* (**4.235**) as well as the more recent ones like *Ambrocenide* (**4.243**), *Helvetolide* (**8.106**), and *Romandolide* (**8.107**), which exhibit olfactory notes that have not yet been found in natural products, have vastly improved the diversity and originality of olfactory notes. Research into new products is ongoing; however,

new aspects like human and environmental safety and biodegradability have to be kept in mind in the development of new perfumery molecules.

We want to incite pleasure, not inconvenience. As an example, quite a few natural products are harmful to our health. Modern technologies, such as the separation of the furocoumarins from bergamot oil, allow us to avoid these inconveniences. The purity of synthetic materials is meticulously controlled and associated with lower production costs, thus more affordable, thereby conferring them with advantages in comparison to natural products that can vary from one year to another.

In addition, considering the actual production and use of fragrant materials of all kinds, it would be impossible today to rely solely on the availability of natural sources. Creativity in perfumery has evolved with new techniques as it is the case in music, paintings, and other arts – we are in a new era. Gone are the trips in horse carriages; cars and planes are our transportation means today. Natural ingredients are still used in perfumery, and it depends on the knowledge of the perfumer to use them advantageously.

Recent great successes as well as some historical ones depend to a great part on the use of synthetic materials and – if I am allowed to give my judgment – on the sensory quality of these perfumes. I think we have no reasons to hide behind our predecessors.

Maurice Roucel
Master Perfumer, Symrise
Chevalier de l'Ordre des Arts et des Lettres
Paris, France
April 2021

Preface to the Second Edition

Ese olor. Reconocía ese olor de algún lugar. Y se ponía nervioso. No era olor de comida, ni el olor de los pisos cuando se enceran. No era nada que formase parte de la rutina. Lo había sentido en el pasillo alguna vez, pero era difícil saber de dónde provenía. Quizá del techo o del suelo. […] No era el olor a rancio del Papapa, ni los perfumes dulzones de la mamá ni el desodorante del papá ni el olor a sudor y barro de Sergio. Era mejor. Desesperantemente mejor. ¿De dónde vendría? Sintió un impulso desconocido y se preocupó. Sabía que era malo. […] Cosas del olor.
That smell. He recognized that smell from somewhere. And it made him nervous. It wasn't the smell of food, nor was it the smell of floors being waxed. No ordinary smell at all. He had smelled it in the hallway once, but it was hard to tell where it was coming from. Maybe from the ceiling or the floor. […] It wasn't Grandpa's rancid smell, nor was it Mom's sweet perfume, nor Dad's deodorant, nor Sergio's smell of sweat and mud. It was better. Desperately better. Where would it come from? He felt an unfamiliar urge and became worried. He knew it was bad. […] The way smells are.

Santiago Roncagliolo, 'Pudor' [1].

If you are (still) reading this Preface, you most likely care for smells, scents, and odors. Even more so, you are probably deeply fascinated, impressed, and excited by these, and you want to understand why the things smell the way they do. Perhaps you even want to create and design new fragrant impressions, may that be on a molecular level or by compounding perfumes from natural and/or synthetic perfumery materials. Maybe you even read the first edition of '*Scent and Chemistry*' and crave for an updated and extended version – one with (even) more focus on perfumery? If that is the case, then we do hope that this new and revised second edition is for you!

The original German edition of '*Riechstoffe und Geruchssinn: Die molekulare Welt der Düfte*' by Günther Ohloff [2] was published 30 years ago, and the little booklet ('*das Büchlein*' as Ohloff called it) has since become the bible for fragrance chemists and *perfumistas* alike, growing from 233 in the original German, and 238 in its English translation '*Scent and Fragrances*', to 418 pages in the first English edition. What was intended as an account on the current state of our knowledge about

the sense of smell and its active principles, the odorant stimuli, has consequently turned into a solid little textbook on *Fragrance Chemistry*.

Fragrance Chemistry is no more and no less than the foundation of olfaction, a fascinating science that comprises structure–odor correlations as well as the *Organic Synthesis* of these structurally diverse active olfactory principles and the knowledge of their natural occurrence and the biochemistry, neurophysiology, and psychology of odorant perception. This book is written for everyone interested in the molecular basis of odor and the relationships between chemical structures and their olfactory properties. With the ease of access, the Internet has granted everyone to perfumery materials, *e.g.*, [3–5], virtually, everybody can now study the olfactory properties of perfumery raw materials, enjoy their fragrant sensations, and even create accords and perfumes with these. Likewise, there is a vast number of Internet sites, *e.g.,* [6–10], on which one can order perfume decants to build up a library of olfactory families, enjoy fragrant masterpieces, or study the composition of classic creations [11]. It was therefore only too logical that one of the major wishes expressed for the next edition of '*Scent and Chemistry*' was the addition of an introduction to the basic techniques, creation, and composition methods in perfumery. To this purpose, we are thus extremely pleased to welcome *Fanny Grau*, a successful perfumer with a PhD degree in *Organic Chemistry* who has worked in all categories and segments and is now very active in the vibrant Latin American fine fragrance market for *Symrise*. Not only does she know a lot about compounding and composition techniques but also on structure–odor correlations, and since she was also self-taught before her official perfumery training with *Marc vom Ende*, who just took over as the head of the *Symrise* perfumery school and also works as research and commercial perfumer, she has an unconventional, hands-on, or in modern speech '*fresh-and-fruity*' approach to teaching perfumery techniques.

This new edition of *Scent and Chemistry* therefore should even be more attractive to *perfumistas* and *scent aficionados* as the entry point into the *Molecular World of Odors*. Since olfactory art is currently emerging as a contemporary form of art [12–15], we would be most delighted to even reach olfactory artists, art critics, and art philosophers as well as aestheticians. Perfumes as such can already be works of art [16, 17], but so can be odorant molecules and their syntheses.

Since the concept of the book has proven successful over all these years, the overall structure and content outline were not changed. It was not our aim to include all new compounds or developments, such as, for instance, precursor technologies, for such an endeavor reviews such as Ref. [18] are far better suited. But those new materials and findings that we expect to make a lasting impact on perfumery were of course added, all errors were eliminated, and all figures updated – to the very best of our knowledge. In this respect, we would like to thank all the readers that spotted typos and mistakes or suggested improvements. For current market data, we are indebted to *Heinz-Jürgen Bertram*, Symrise. For eliminating typos and for useful input, we are very grateful to Professor *Albert Eschenmoser* (*Fig. 1*), ETH Zurich; to Professor *Konrad Tiefenbacher*, University of Basel; and to Professor *Ben List*, Max-Planck-Institut für Kohlenforschung who was just awarded the Nobel prize in Chemistry "for the development of asymmetric organocatalysis." For additional proof-reading *Philip Kraft* is greatly indebted to his colleagues *Johannes Panten* and *Alicia De Benito Cassado* (both *Symrise*) and his student intern *Anne Clisson*

Küsnacht, 15. Dezember 2011

Lieber Herr Kraft,

Recht herzlich bedanke ich mich für die Zusendung eines Exemplars des "neuen Ohloffs", der vor wenigen Tagen mich per Post erreicht hat. Für einen alten Terpenchemiker, insbesondere einen, der so langjährigen beruflichen Kontakt mit Günther Ohloff hatte, ist es ein Vergnügen, bei Durchblättern so viele der Terpenformeln zu sehen, die einem an die eigene chemisch Jugend erinnern. Zweifellos haben Sie durch die Neuherausgabe des Werkes Ihrem Fachgebiet einen grossen Dienst erwiesen; ich gratuliere Ihnen und wünsche Ihrem Werk viel Erfolg.

Da Sie mir schrieben, dass Sie für Hinweise auf eventuelle Fehler dankbar wären, will ich einige Unstimmigkeiten erwähnen, die mir beim Betrachten einiger Formelbilder aufgefallen sind. Auf Seite 6 ist eine Liste von Terpenen erwähnt, deren Konstitution von Otto Wallach aufgeklärt worden sei. Dies gilt sicherlich nicht für die aufgeführten Sesquiterpene; so viel ich mich erinnere, wurde das Cadinen von Ruzicka aufgeklärt (um 1924), und die Konstitution von Caryophyllen und dessen Cyclisationsprodukt Cloven um 1950, sowohl von Barton, als auch an der ETH. Ich lege Ihnen den Reprint eines Artikel bei, den ich vor Jahrzehnten über Ruzicka geschrieben hatte, und in welchem die Geschichte dieses und anderer Sesquiterpene diskutiert ist. Auf Seite 196 ist mir aufgefallen, dass der Formel 6.25 eine Methylgruppe fehlt, und auf Seite 252, wird die Konstitutionsermittlung des Patschouli Alkohols George Büchi zugeschrieben, was die (damals berühmte) Geschichte wohl zu sehr vereinfacht, denn Büchi hatte eine Patschoulialkohol-Struktur total synthetisiert, die sich durch die Röntgenanalyse von Dunitz als falsch erwies und in der im Buch zitierten Arbeit (in der auch Büchi als Coauthor vorkommt) korrigiert wurde.

Ich hatte seinerzeit im Labor von Hans Schinz (einem alten Mitarbeiter von Ruzicka und lebenslangem Firmenich-Angestellten)) meine Diss. gemacht. Das grösste Verdienst von Hans Schinz war die Isolierung und Strukturermittlung des Lavandulols mit seinem unregelmässigen Isoprengerüst. Das war damals eine kleine Sensation. Lavandulol ist auf Seite 243 erwähnt, aber leider - so empfinde ich - ohne Bezug auf Schinz.

Unstimmigkeiten finden in einem Buch solchen Inhalts und Umfangs wird man immer, es tut dem grossen Verdienst der Autoren des Werks keinerlei Abbruch.

Ich wünsche Ihnen frohe Weihnachten und ein glückliches (und in ihrem Alter) erfolgreiches neues Jahr-

Figure 1 Letter of *Albert Eschenmoser* to *Philip Kraft*, for Christmas 2011

(*École Normale Supérieure de Paris, ENS Ulm*). Certainly, also this edition will not be immaculate and error-free. So, let us know about any typos, mistakes, or incorrect formulas, you come across while reading as hopefully this will not be the last edition of our compact guide into the *Molecular World of Odors*.

Can you judge a book by its odor? For '*Scent and Chemistry*' we hope you can, both by the inspiring fragrant chemistry inside and by the odoriferous impressions it conjures while reading, and in addition we hope that the book also *feels* good and *smells* good in your hands!

August 2021

Wilhelm Pickenhagen
Philip Kraft, and Fanny Grau
Geneva, Zürich, and São Paulo

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Preface to the First Edition

Il faut d'abord rappeler que, selon les Écritures, 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 Ève : « 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. »

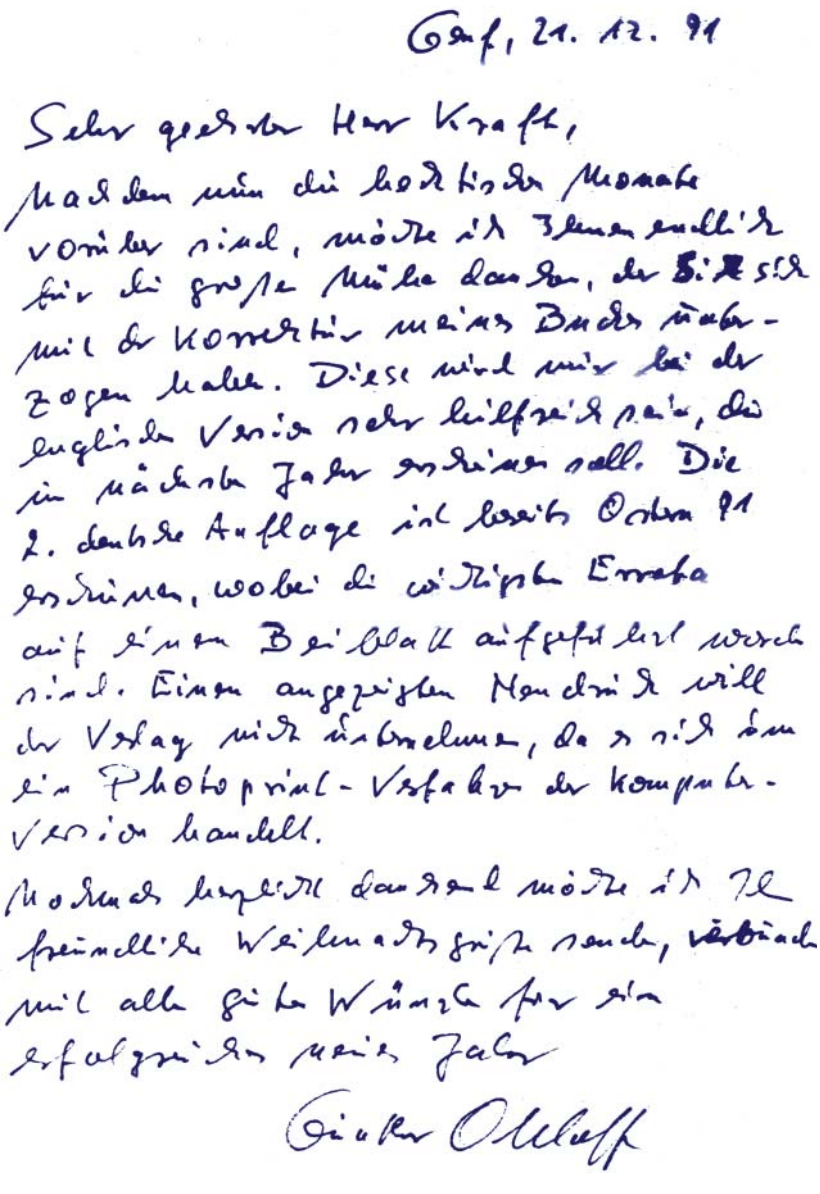
Michel Tournier, 'La légende des parfums' [1].

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 in the *Chemistry of Odorants* has significantly increased since *Günther Ohloff* (1924–2005) wrote his small but condensed *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. 2*), was highly in demand. With the



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 Ostern 91 erschienen, wobei die wichtigsten Errata auf einem Beiblatt aufgeführt sind. Einen ausgiebigen Handschlag will der Verlag mir überlassen, da es sich um ein Photoprint-Verfahren der kompletten Version handelt.

Nochmals herzlichst danke ich Ihnen freundliche Weihnachtsgrüße sende, verbunden mit allen guten Wünschen für ein erfolgreiches neues Jahr

Günther Ohloff

Figure 2 Letter of *Günther Ohloff* to *Philip Kraft*, for Christmas 1991

original text featuring many original results of *Ohloff*'s research group at *Firmenich*, and our affiliation to *Symrise* (*Wilhelm Pickenhagen*) and *Givaudan* (*Philip Kraft*), 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 indepted 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, *Philip Kraft* thanks *Olivia Rosser* and *Tony McStea* for additional proofreading. Finally, we would like to thank *M. Volkan Kısakürek* and *Thomas Kolitzus* of the *Verlag Helvetica Chimica Acta* for the very excellent collaboration.

Should you spot any typos, mistakes, or even incorrect chemical formulas, please hit up the '*Scent and Chemistry*' wall on *Facebook* [3] and let us know. Needless to say, you can also leave your comments there. Get yourselves involved in improving future editions. We would love to hear from you!

January 2011

Wilhelm Pickenhagen and Philip Kraft
Geneva and Zürich

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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 this dates back even to the Lower Pleistocene, some 0.79 million 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 consisted 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 skull 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 tastier but also healthier 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; besides 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]. 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 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, the transformation of a substance into something airborne. In particular, the early fumigatory use of burning resins, woods, barks,

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Günther Ohloff, Wilhelm Pickenhagen, Philip Kraft, and Fanny Grau.

and other parts of aromatic plant had widespread appeal. Such odor signals were supposed 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 were burnt in the *Bel* temple of Babylon annually. 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 constitutes also one of the most ancient perfumery ingredients that has been used far longer 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 brought about the *Trojan* War, was supposed to be due 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 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 nardin. In his natural history, *Pliny the Elder* made mention of a cream that contained twenty-seven 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 that '*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 research 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 supposed to be of a smooth round geometry, whereas harsh compounds were supposed to possess 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*', and 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 *Alí Sínā 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 from 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 Admirbilis*' that *Giovanni Maria Farina* (1685–1766) launched in Cologne in 1709. This soon became famous as '*Kölnisch Wasser*' or '*Eau de Cologne*'. Allegedly, *Napoléon Bonaparte*

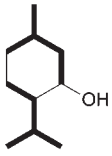
(1769–1821) used up to two bottles of *Eau de Cologne* per day, which he poured over his head and shoulders. Not only did *Napoléon* make *Eau de Cologne* famous all over the world, but he also defined per decree the term *perfume* in 1810. According to this definition, perfumes had to be distinguished 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 rather drop any claims of therapeutic effects than to lay open their formulas. Therefore, 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 to compound with, and while they could construct flowers that did not yield an essential oil, such as the 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. The analysis of natural products and efficient synthetic preparation of their smelling principles led to an understanding of the molecular basis of essential oils.

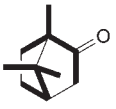
1.2 Chemical Discoveries and Modern Perfumery

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-atoms 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**).

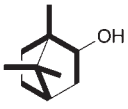
In 1835, *Jean-Baptiste Dumas* (1800–1884) and *Eugène-Melchior Péligot* (1811–1890) isolated and characterized cinnamaldehyde (**1.5**) from cinnamon essential oil [16]. In their groundbreaking work on bitter almond oil, *Friedrich Wöhler* (1800–1882) and *Justus Liebig* (1803–1873) showed in 1837 that 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 to be prepared synthetically [18].



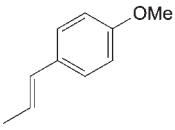
1.1
menthol
$C_{10}H_{20}O$



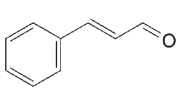
1.2
camphor
$C_{10}H_{16}O$



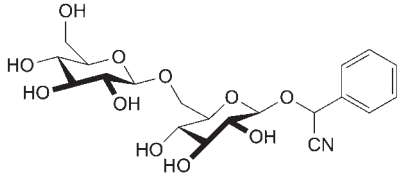
1.3
borneol
$C_{10}H_{18}O$



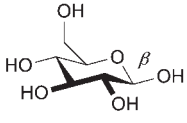
1.4
anethole
isoestragole



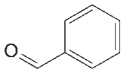
1.5
cinnamaldehyde



1.6
amygdalin



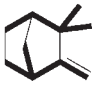
1.7
β-D-glucopyranose



1.8
benzaldehyde

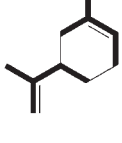
Starting in 1884 *Otto Wallach* (1847–1931) elucidated in over 125 papers the structures of the most important terpenoid constituents of the most important essential oils, including α-pinene (**1.9**), camphene (**1.10**), limonene (**1.11**), sylvestrene (**1.12**), terpinolene (**1.13**), α-terpinene (**1.14**), α-phellandrene (**1.15**), α-fenchene (**1.16**), and the sesquiterpenes α-cadinene (**1.17**), caryophyllene (**1.18**), and clovene (**1.19**) [19]. The exact constitution and stereochemistry of the sesquiterpenes **1.17**–**1.19** was, however, elucidated only later by the groups of *Ruzicka*, *Eschenmoser*, and *Barton* between 1924 and 1954 [20–22]. The first perfumery raw materials were those that 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
$C_{10}H_{16}$

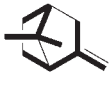


1.12
sylvestrene
$C_{10}H_{16}$

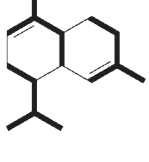
1.13
terpinolene
$C_{10}H_{16}$

1.14
α-terpinene
$C_{10}H_{16}$

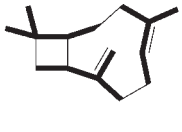
1.15
α-phellandrene
$C_{10}H_{16}$



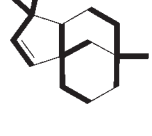
1.16
α-fenchene
$C_{10}H_{16}O$



1.17
α-cadinene
$C_{15}H_{24}$

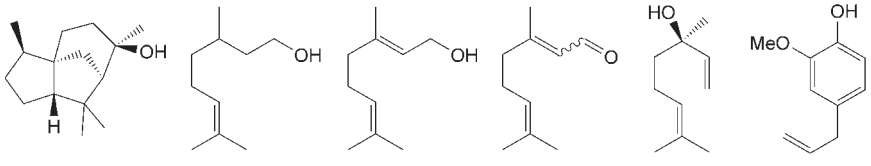


1.18
caryophyllene
$C_{15}H_{24}$



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. However, the development of modern perfumery with all of its creativity and artistic freedom became only possible with the commercial synthesis of pure nature identical and synthetic odorants (*Figs. 1.1–1.4*). These synthetic compounds allowed for the creation of fantasy perfumes, some of which are still in fashion today.



1.20 (+)-cedrol | **1.21** citronellol | **1.22** geraniol | **1.23** citral | **1.24** (−)-linalool | **1.25** eugenol

The age of modern perfumery dawned in 1868 when *William Henry Perkin* (1838–1907) synthesized coumarin (**1.26**; *Fig. 1.1*) by heating the sodium salt of salicylaldehyde with acetic anhydride [23]. Coumarin (**1.26**) with its distinctive note of freshly mown hay and marzipan is the smelling principle of tonka beans, from which *Friedrich Wöhler* had isolated it by extraction with 80% ethanol 12 years earlier [24]. In 1877, the modification of the *Perkin* reaction, involving boiling a mixture of acetic anhydride, anhydrous sodium acetate, and salicylaldehyde [25, 26], made coumarin (**1.26**) industrially accessible, and thus, *Paul Parquet*, chief perfumer and owner of *Houbigant*, could utilize **1.26** in the creation of a fragrance that should evoke the scent of fern – if ferns had any, since most of them are odorless [27]. The result was '*Fougère Royale*' (*Fig. 1.2*), which appeared on the market in 1884 and was such a success that many related fragrances were created around the central accord of oak moss, lavender, and coumarin (**1.26**). Even though '*Fougère Royale*' was discontinued in the 1950s, with an unsuccessful relaunch attempt in 1988, the *fougère* family still constitutes one of the main fragrance concepts, with such representatives as '*Paco Rabanne pour homme*' (*Paco Rabanne*, 1973) by *Jean Martel*, '*Drakkar Noir*' (*Guy Laroche*, 1982) by *Pierre Wargnye*, and '*Cool Water*' (*Davidoff*, 1988) by *Pierre Bourdon* [28]. In December 2010, finally even '*Fougère Royale*' reappeared on the market and was revived and modernized by *Rodrigo Flores-Roux* working alongside *Roja Dove* as creative director.

Ferdinand Tiemann (1848–1899) [29] can be considered the true founder of Fragrance Chemistry. He was involved in improving *Perkin's* access to coumarin (**1.26**) to industrial applicability [26], but more important even was his structure elucidation and synthesis of vanillin (**1.27**; *Fig. 1.1*) three years before, in collaboration with *Wilhelm Haarmann* (1847–1931). *Haarmann*, who descended from a wealthy old-established family background in Holzminden, had joined the laboratory of *August Wilhelm von Hofmann* (1818–1892) at the University of Berlin at about

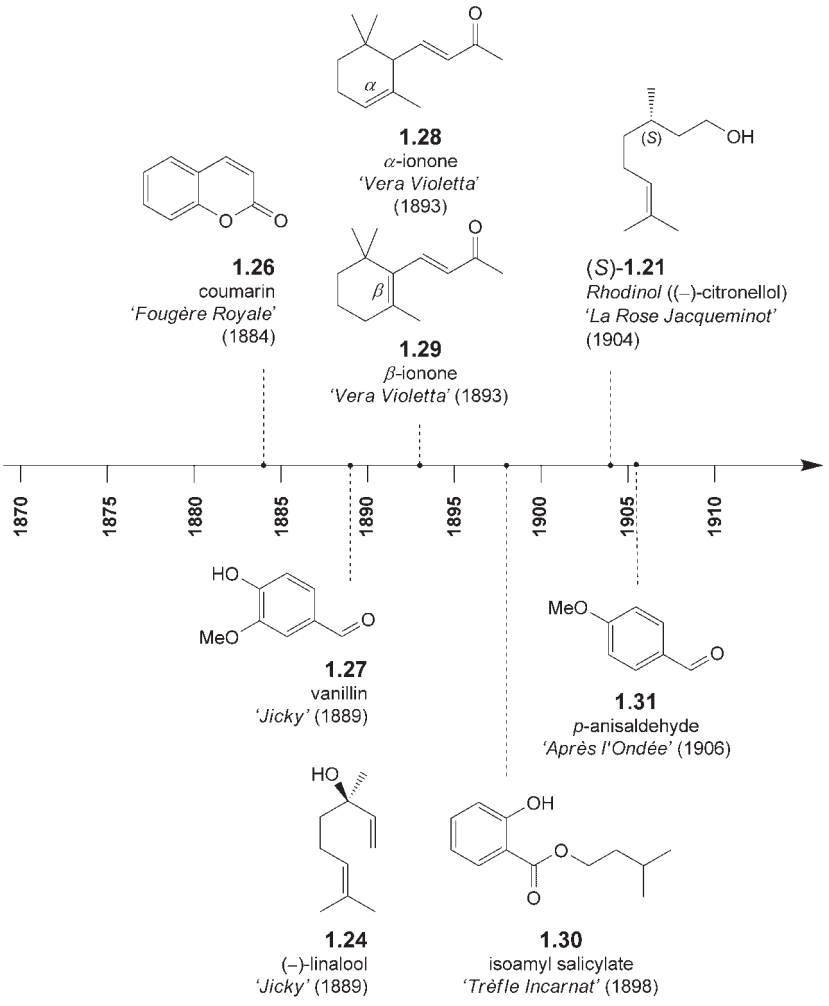


Figure 1.1 Timeline of the initial phase of modern perfumery featuring the most important perfumes in 1870–1910 that were influenced by new odorants

the same time as *Tiemann*, and they remained close friends even during the Franco–Prussian War of 1870. After the war they both returned to *Hofmann*'s laboratory to continue studies on coniferin, which was isolated from the cambium juice of conifers, especially pinewood. Upon degradation experiments of coniferin, their former colleague *Wilhelm Kubel* had observed a characteristic vanilla scent. In 1874, *Tiemann* and *Haarmann* synthesized vanillin (**1.27**) by hydrolysis of coniferin with the enzyme emulsin and oxidation of the resulting coniferyl alcohol with a mixture of potassium bichromate and sulfuric acid [30]. *Haarmann* decided to exploit this invention in his hometown Holzminden, where pinewood was in plentiful supply, and founded in 1874 the *Haarmann's Vanillinfabrik* (now *Symrise*), which later inspired the foundation of several other Flavor and Fragrance companies all over

Figure 1.2 Flacons of early milestone fragrances: '*Fougère Royale*' (*Houbigant*, 1884), '*Jicky*' (*Guerlain*, 1889), '*Trèfle Incarnat*' (*L. T. Piver*, 1898), '*Floramye*' (*L. T. Piver*, 1905), '*La Rose Jacqueminot*' (*Coty*, 1904), '*Quelques Fleurs*' (*Houbigant*, 1912), and '*Nuit de Noël*' (*Parfums Caron*, 1922). Source: Courtesy of *Philip Goutel*

Europe. *Tiemann*, on the other hand, wanted to continue his academic career but decided to dedicate his scientific work to the chemistry of fragrant materials. He immediately saw the use of a new reaction that was discovered in 1876 by *Karl Reimer* (1845–1883) in *Hofmann*'s laboratory for the industrial production of **1.27** from guaiacol by heating with chloroform and 4 equivalents of sodium hydroxide [31]. This *Reimer–Tiemann* reaction made vanillin (**1.27**) available at very attractive costs, which revolutionized perfumery.

Aimé Guerlain was the first to use **1.27** in his famous creation '*Jicky*' (*Guerlain*, 1889; *Fig. 1.2*) [32], in an accord with coumarin (**1.26**) and (−)-linalool (**1.24**), isolated from rose wood, as well as bergamot, lavender, sandalwood oil, and civet. Because of its sophisticated composition, '*Jicky*' can be regarded as the first modern perfume [28], and not taking the *Eaux de Cologne* into account, it is the oldest fine fragrance still on the market. *Frédéric Beigbeder*'s protagonist *Marc Maronnier* famously uses '*Jicky*' in his '*Mémoires d'un jeune homme dérangé*', albeit today it is considered a female fragrance [33]. At the end of the 19th century, '*Jicky*' was, however, found too *avant-garde* for women and thus had first been introduced as a male fragrance.

Perhaps the most precious and popular perfumery materials in the 19th century was violet flower oil ('*fleur de violette*'), for which *von Soden* estimated production costs exceeding 80,000 German gold marks per kilogram [34] due to the low content of essential oil in violet flowers (*Viola odorata* L.) [35]. The structure elucidation of the smelling principle of violet flowers was therefore of high economic interest. Yet, even the quantities of violet flower oil necessary for this work at that time turned out to be too expensive. Therefore, *Tiemann* and his co-worker *Paul Krüger* used the similarly smelling but much cheaper orris root oil (*Iris pallida* Lam.) in their investigations on the smelling principle of violets, assuming that the odor of both oils was due to the same natural product [36, 37]. An incorrect elemental analysis of the