

Chapter 1

Fragrance and Attraction

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The fragrance of flowers, fruits, and fauna of natural scents have long been highly popular. What makes this attraction possible? What is the chemistry of fragrance and flavors? This chapter is based on the plenary lecture given at the “Chemistry of Sex” symposium held during the 2018 Spring ACS meeting in New Orleans, Louisiana. This chapter will focus on the chemical basis of fragrance attraction and presents a rich tapestry of chemistry and the vibrant fragrance industry behind our emotional attraction to scents and perfumes. Perfumery examples delineating how minor changes in the structure, stereochemistry, shape, and chirality of a fragrance ingredient or a scent molecule influence its smell, pleasantness, and usefulness are highlighted. Thanks to the technological advances in the art of organic synthesis, perfumes, once the luxury of kings and queens, have now become available for everyone to enjoy. Brief glimpses of the power of synthetic chemistry and biotechnology in a quest for new scents are presented.

Introduction

Fragrance and attraction are intertwined through a multi-sensory communication of pheromones and neurotransmitters. Why are bees attracted to flowers? Why does a humming bird typically feed on red flowers? Besides pollination, it has been speculated that flowers developed fragrances, spicy smelling natural scents not only to attract insects but to also act as a defense mechanism to ward off plant eaters.

People are naturally attracted to smells that are pleasing, soothing, and calming. As a result, there has been a significant rise in the use of homecare fragrances, incense sticks, and candles. Fragrances have been known to evoke childhood memories and can touch our hearts, which has been used for beneficial purposes like aromatherapy. Fragrances also impart feeling like naturalness, cleanliness, softness, and pleasantness; as a result, they are widely used in personal hygiene and homecare products.

Flavor and Fragrance Business

Because of the enormous utility of fragrances, the attraction to fragrances and flavor has become a huge global business worth \$26.3 billion in 2017. The top five flavors and fragrance companies (1) control 61.5% of the total share of the market.

Hundreds of new fragrances are launched every year in an attempt to please and attract consumers with exhilarating scents that impart relaxing, soothing, energizing and joyful feelings. In spite of that, the bestselling fragrance for women in 2017 in the USA was Chanel No 5. Chanel No 5 was created in 1921 and has remained one of the most admired and beloved perfumes. It has stood the test of time, and appealed to every generation of users over the last 97 years. In addition, it is worth pointing out that one of the oldest continuously produced fragrance in the world is Jicky by Guerlain (2) that was launched in 1889.

Language of Fragrances

Let us now consider common descriptors that are used by perfumers to describe fragrance scents. There is an incredible odor diversity that exists in fragrance and olfaction today. These notes belong to the following five main odor categories:

- Fresh Notes
- Floral Notes
- Oriental Notes
- Woody Notes
- Animal Notes

Each of these notes are further comprised of many other widely used notes including: citrus, grapefruit, marine, green, galbanum, aromatic, fruity notes of apple, peach, pear, strawberry, nectarine, plum, and pineapple.

Floral notes comprise all of the most appreciated fragrant flowers like rose, jasmine, tuberose, gardenia, orange blossoms, violet, and lavender. Oriental notes include amber, incense, resins, and woody notes that are an essential part of every perfume. Woody notes primarily include sandal, cedar, patchouli, and vetiver class. Oudh and agar wood have gained popularity lately. Other classes of appreciated notes include spicy, leather, and mossy notes along with animal notes such as musk, ambergris, civet, and others. Sweet and gourmand notes are also well liked by consumers and perfumers alike.

Fragrance Design

Conceptually, fragrance creation or design uses an olfactive pyramid of various notes that are layered on top of each other like a piece of fine art. A fragrance can be comprised of up to hundreds of ingredients that are harmoniously blended like a musical symphony. These notes are divided into top, middle, and bottom notes.

Top Notes

Aroma chemicals having citrus, fruity, green, aldehydic, marine and ozone odor impart, freshness, juiciness, friskiness, and impact to the fragrance. A select group of top notes are shown in Figure 1.

Center Notes

The next part of the perfumery triangle are center notes which represent the heart and body of the fragrance. This group mainly includes floral notes such as rose, jasmine, violet, lily of the valley, muguet, tuberose, orange blossoms, iris, and others along with some long-lasting fruity, spicy, and herbaceous notes.

Base Notes

The last part of the perfumery triangle is known as the base or bottom notes that use fragrance ingredients belonging to sweet, powdery, musk, and woody (sandal, patchouli, cedar, vetiver, and amber) scent molecules. These ingredients impart longevity and substantivity to the fragrance.

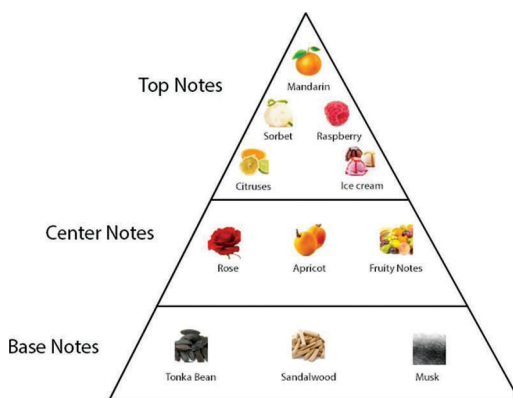


Figure 1. Perfumery Triangle.

Precious Essential Oils Used in Fragrances

As described earlier, a fragrance is a symphony of hundreds of aroma chemicals (3). These aromas are derived from various essential oils (4); absolutes made from select flowers, fruits, citrus, precious woods, taste enhancing spices, sweet and creamy absolutes, and amber and musk odorants; and aromatherapy materials. Modern fragrances contain both natural and synthetic fragrance ingredients that chemists have discovered in order to complement and enhance creativity, innovation, and differentiation. A compilation of diverse essential oils, taste enhancing spices, creamy and floral absolutes, and other natural notes used in perfumery include:

- Jasmine Absolute Indian;
- Rose Bulgarian, Turkish rose, tuberose, and gardenia;
- Orange blossom, violet, hyacinth, geranium, and lavender;
- Peony, iris, and orchids;
- Eucalyptus, citronella, and turpentine essential oils.
- Spice oils such as cinnamon, ginger, cardamom, clove, and nutmeg;
- Lemon, bergamot, citrus, grapefruit, and orange essential oils;
- Fruits like peach, pear, apple, nectarine, strawberry, and melon;
- Sandalwood essential oil;

- Cedar wood essential oil;
- Patchouli essential oil;
- Vertiver essential oil;
- Oudh wood or agar wood;
- Ambergis, which is now replaced with mostly synthetic and natural amber molecules;
- Musk tincture, which is also replaced with mostly synthetic and natural musk molecules;
- Natural vanilla, synthetic vanillin, coumarin, lactonic, sweet, and gourmand molecules; and
- Aromatherapy essential oils.

Analysis of Essential Oils

Fragrance chemists use instrumental analysis techniques, such as gas chromatography-mass spectrometry (GC-MS), NMR, IR, and UV, to analyze and identify various components that are present in the essential oils (5). GC-olfactometry (6) is an important technique that is used to identify key components of a given essential oil, fruit, or spice. In addition, synthesis can be used to corroborate the structure of an unknown aroma chemical present in these natural fragrance ingredients. Figure 2 describes some of the key components that have been identified in Italian lemon oil.

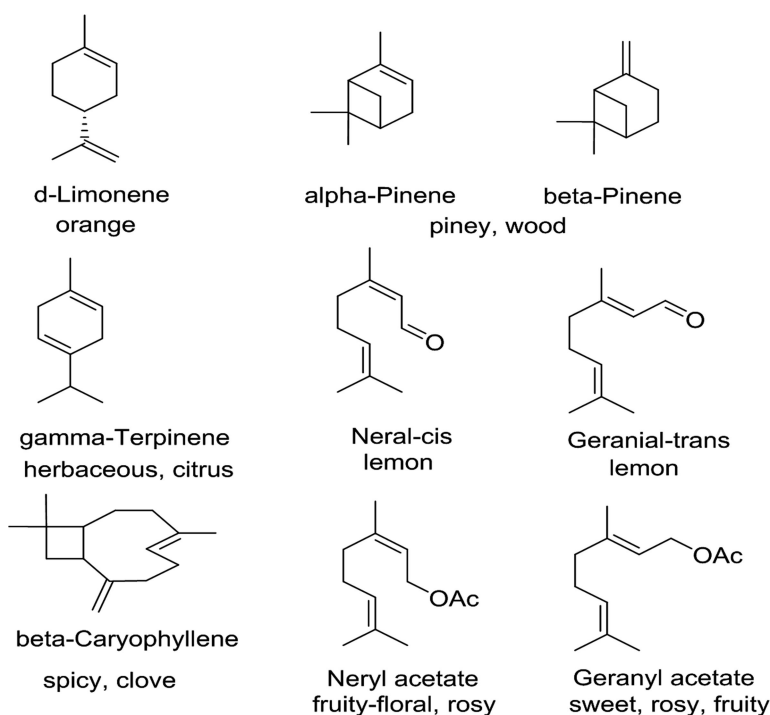


Figure 2. Key components of Italian lemon oil.

Search for New Molecules

There are multiple benefits of discovering new molecules including:

- Ensuring a consistent supply of a key odor that contributes to the fragrance ingredient of an essential oil;
- Providing a cost effective alternate for very expensive naturally occurring essential oils that are in short supply or for a source that has been labeled as endangered or unsustainable;
- Having quality assurance while also providing molecules for safety testing, as well as testing for stability in functional applications including biodegradability, human health, and toxicity compliance concerns;
- Proprietary status of new molecules enhances creativity and offers competitive advantage for the inventing company or individual; and
- New fragrances launched are difficult to copy.

As a result, several flavor and fragrance companies have invested huge resources in developing hundreds of new fragrance ingredients (7) that are superior in performance and odor to many naturally occurring aroma chemicals.

Synthetic Technologies Used for the Discovery of New Molecules

Over the last century, chemists have discovered new chemical reactions (8) and technologies (9) to create carbon-carbon bonds that are at the heart of synthesizing organic molecules. These endeavors have led to the synthesis of novel, unique, and complex structures. Many scientists have been awarded Nobel Prizes for their groundbreaking discoveries, which have been utilized in advancing the art of organic synthesis. A few such technologies that have wide utility in flavor and fragrance are cited as follows:

- Name Reactions: Diels-Alder reaction (Robert Diels and Kurt Alder shared the 1950 Nobel Prize in Chemistry), pericyclic, free radical, biomimetic reactions, Mannich reaction, Wittig reaction, and Prins reaction (discovered in 1912 by Dr. Prins who also worked at International Flavors & Fragrances [IFF]);
- Condensation: Aldol, Dieckman, Knoevenagel, Michael, Stobbe, acyloin, hydroformylation, and metathesis cyclization (Robert Grubbs, Richard Schrock, and Yves Chauvin shared the 2005 Nobel Prize in Chemistry);
- Rearrangements: Claisen, Carrol, Favorskii, Cope, and oxy-Cope;
- Organometallic: Grignard, organolithium and cuprates, Reformatsky, Simmons-Smith cyclopropanation, and ethynylation among others;
- Oxidation: per acids, CrO₃, NaIO₄, KMnO₄, H₂O₂, TEMPO, Ozone, and RuO₄ among others;
- Reductions: using vitride, diborane (Herbert C. Brown was awarded the Nobel Prize in 1979), LiAlH₄, and NaBH₄;
- Asymmetric: hydrogenation or reduction and chiral epoxidation (Barry Sharpless, Ryoji Noyori, and Williams Knowles shared the 2001 Nobel Prize in Chemistry);
- Functional group transformations: aldehyde, ketone, alcohol, ether, acetal and ketal, ester, lactone, epoxide, and nitriles among others; and
- Hetero atoms incorporation: N (pyridine, pyrazine, pyrimidine), O (furan, pyran), and S (thio analogs).

Discovery of IFF Classic Fragrance Molecules

Over the last 70 years, IFF scientists have discovered numerous differentiating aroma chemicals and developed commercial processes for fragrance ingredients like Galaxolide, Iso E Super, Cashmeran, Vertofix, Bacdanol, Lylal, Phenoxanol, phenyl ethyl alcohol, Helional, Canthoxal, Triplal, Trimofix, δ -Damascone, and Kharismal that have greatly influenced the fragrance industry. Many of these chemicals have become indispensable ingredients in perfumery.

The abundant availability of these unique and cost effective fragrance ingredients have allowed perfumers across the globe to create classic fragrances that have delighted and attracted consumers of both genders and all generations. Using these hedonically superior ingredients, IFF perfumers have created some of the world's most popular fragrances, which are presented in Figure 3.

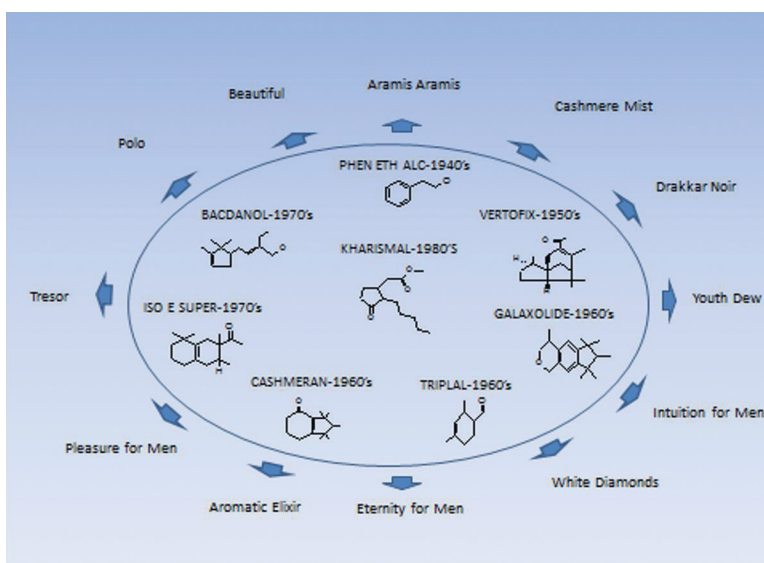


Figure 3. Iconic fragrances created using IFF classic fragrance ingredients.

Technologies Used To Synthesize Fragrance Molecules for Consumer Fragrances

Over the next few sections, examples of the technologies used in the development of recent aroma chemicals for creating fine and consumer fragrances are provided. Since consumer fragrances employ very harsh bases (with pH varying from 2–13), fragrances for detergents, shampoos, hair conditioners, softeners, soaps, shower gels, homecare, and fabcare must use ingredients with good chemical stability within that specific medium needed for functional application.

Examples of Diels-Alder Technology

Diels-Alder technology has been used extensively in the synthesis of numerous flavor and fragrance molecules that are used in consumer and fine fragrances. The odor description and structures of a few key ingredients like Lyrall, aldehyde AA, Isocyclocitral, Iso E Super, Isoprecyclemone B, Melafleur, Myrac aldehyde, Camek, Oriniff, and δ -damascone are shown in Figure 4.

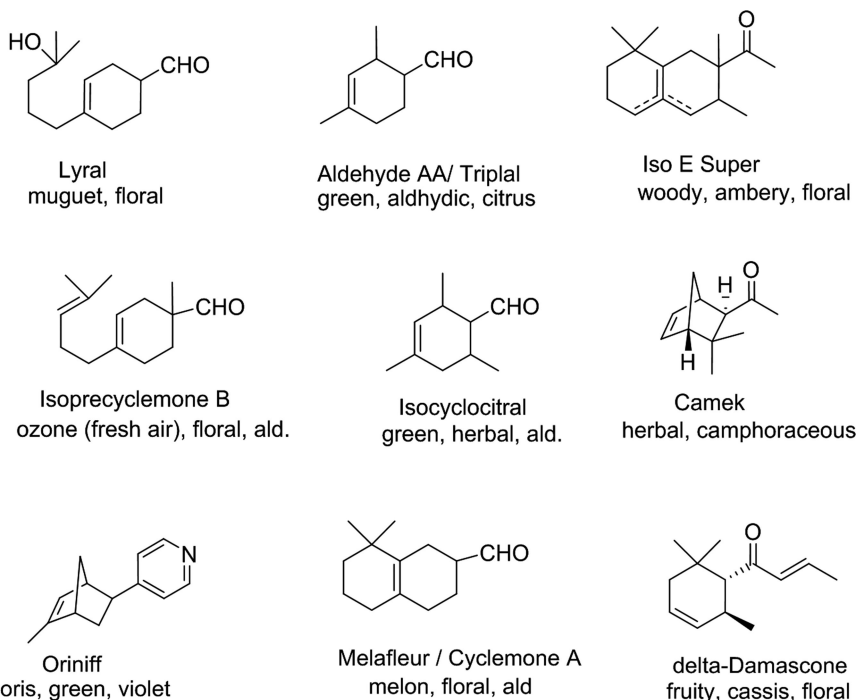


Figure 4. Fragrance ingredients based on Diels-Alder technology.

Use of Nitriles (10) in Perfumery by Functional Group Transformations

As previously stated, consumer fragrances in soaps, detergents, conditioners, and softeners employ very stringent conditions and harsh bases; because of this, perfumers need to use fragrance ingredients that would be stable in those environments. Fragrance ingredients with aldehyde groups play a large role in the design of functional perfumes, but unfortunately, aldehydes undergo many side reactions in the basic media such as aldol condensations and polymerizations.

It has been observed that a simple transformation of an aldehyde group into a nitrile group present in a fragrance ingredient not only enhances its base stability, but also retains its odor. Figure 5 highlights a select group of aromatic nitrile fragrance ingredients such as Fleuranil, Salicynalva, Khusinil, and a few acyclic nitrile fragrance ingredients such as Azuril, Peonile, Citralva, Citronalva, and Lemonalva that perform well in basic applications.

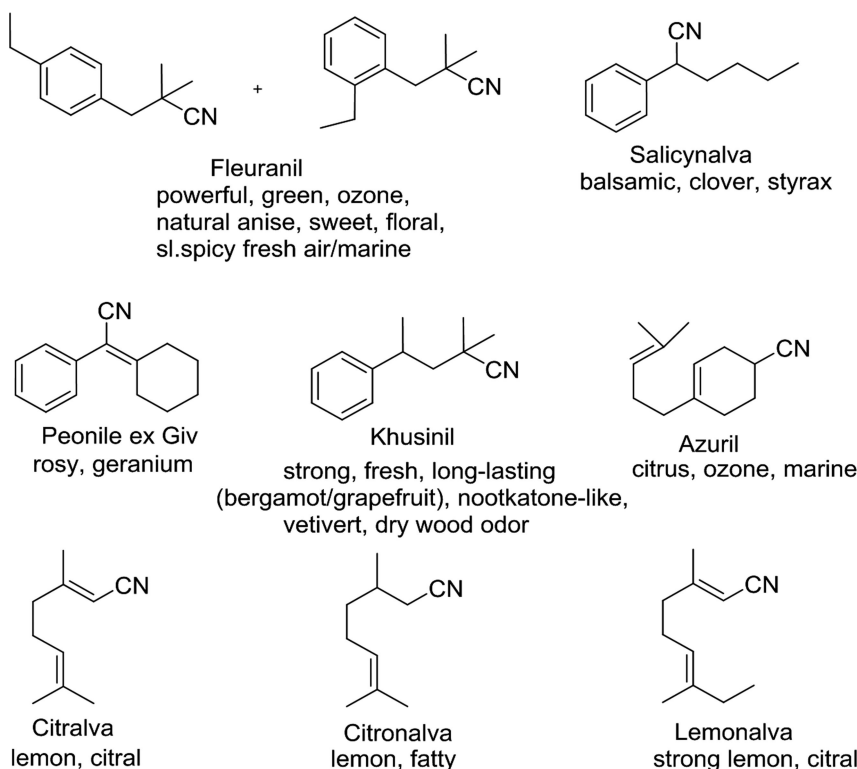


Figure 5. Examples of nitriles used in perfumery.

More Examples of Diverse Technologies Employed in the Discovery of New Molecules for Creation of Consumer Fragrances

Cassifix (11) was the first long-lasting cassis note discovered that did not contain a sulfur atom. It was prepared in four steps starting from campholenic aldehyde, which was converted to α -methylene campholenic aldehyde using a Mannich reaction, followed by its Diels-Alder reaction with Isoprene to produce a mixture of aldehydes. These aldehydes in the after chemical reduction, followed by cyclization with acid, produced Cassifix.

Prismantol, a spicy, ginger, woody note, was prepared using two technologies: hydroformylation of R-(+)-Limonene and an Ene reaction (12). Both Montaverdi and Vivaldie were derived from cis-3-Hexenol and are powerful green (13) odorants. Arctical and Ozofleur are functional fragrance ingredients that provide benefits to consumer fragrances due to their stability in high pH. Arctical (14) was developed as a base stable note in place of n-Decanal with its fresh, citrus, aldehydic notes. Figure 6 describes the structure and odor of new recently introduced ingredients.

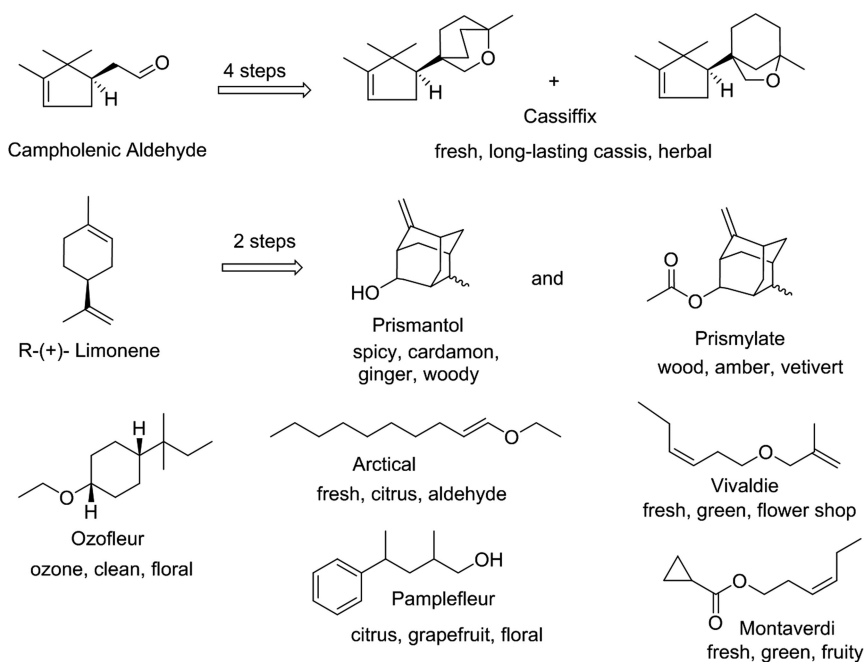


Figure 6. Fragrance ingredients for consumer fragrances.

Search for New Amber Notes

Amber notes are essential to the performance and attraction of a fragrance. Amber notes are widely used in perfume creation and there are very few fragrances that do not contain an amber odorant. In addition, amber odorants display an enormous functional diversity, and many amber molecules contain a functional moiety such as ketone, ether, epoxide, ketal, and primary or secondary or tertiary hydroxyl groups. Some molecules contain hydroxyl ether functionality.

Of the amber molecules used in fragrances, (–)-l-Ambrox is considered one of the most precious aroma ingredients and is known for its beautiful, enticing, woody, amber, soft, and velvety smell and for its long-lasting power both on skin and cloth. Because of this, several years ago, intensive effort was mounted to find a new amber molecule that would compete and complement the performance and utility of Ambrox. Figure 7 delineates the structure of key amber molecules such as l-Ambrox, Grisalva, and Galaxolide that contain an ether ring. It may be pointed out that an ether ring or functionality plays a key role in the performance of a few other desirable benchmark fragrance ingredients like Cedramber or Cassifix.

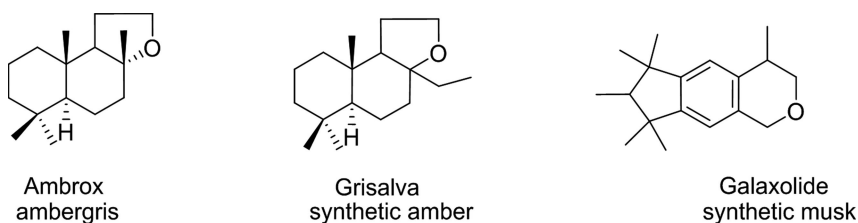


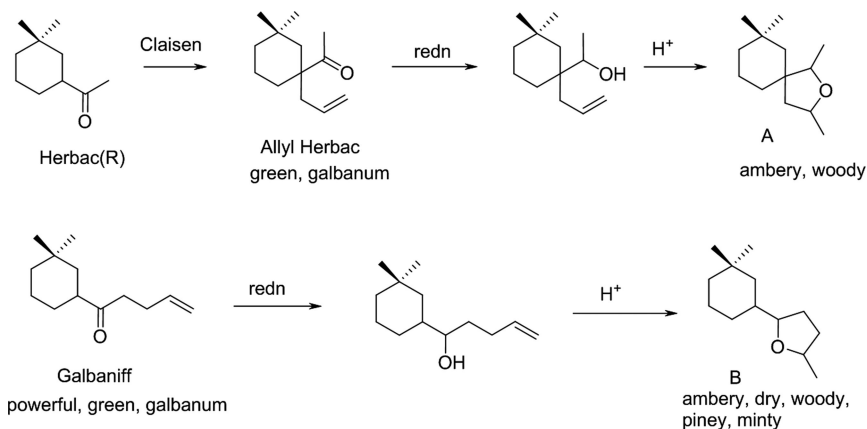
Figure 7. Structure of key fragrance ingredients with ether moiety.

Genesis of an Exploratory Idea in Quest of New Amber Molecules

Since the presence of a tetrahydrofuran ether ring in Ambrox is a key structural necessity for the performance of amber odor, we envisioned a new technology to prepare THF-ether-like molecules derived from the cyclization of γ , δ -unsaturated ketones. γ , δ -unsaturated ketones are readily accessible via the Claisen rearrangement of ketones.

To test this hypothesis, we took Herbac, a perfumery ingredient and converted it into allyl Herbac first and then to the desired THF-ether structure, A, using a two-step sequence shown in Scheme 1. Lithium aluminum hydride was used to reduce allyl herbac ketone to its alcohol derivative, which on acid cyclization produced structure A. Similarly, Galbaniff was converted to Structure B using the same technology.

Surprisingly, such a transformation led to a change in the odor of allyl Herbac and Galbaniff from green and galbanum to woody and amber. Inspired by this observation, this technology was used to prepare new THF-ether-like molecules on diverse structural backbones. For this discussion, please refer to our previously published (15) work.

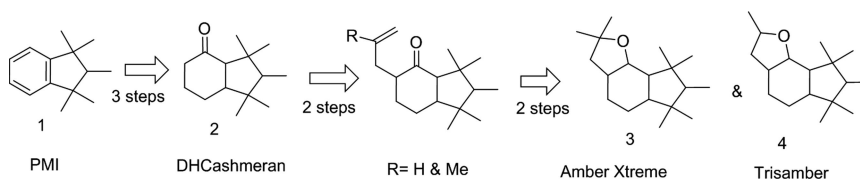


Scheme 1. Cyclization of allyl Herbac and Galbaniff to THF-ether derivatives.

Discovery of Amber Xtreme and Trisamber—Two New Amber Molecules

The goal of this exploration was to discover a new amber molecule. Therefore, we prepared new THF-ether-like molecules using this technology on diverse structural backbones and building blocks. One backbone that led to the discovery of Amber Xtreme and Trisamber was derived from Pentamethylindane, a key building block of Galaxolide, an IFF musk molecule. Pentamethylindane was converted into Dihydrocashmeran in three steps using the hydrogenation of a Cashmeran intermediate as depicted in Scheme 2.

Dihydrocashmeran was converted into Amber Xtreme and Trisamber using a multi-step synthetic technology (16, 17) employing a Claisen rearrangement to produce methallyl and allyl Dihydrocashmeran intermediates. These two intermediates were then converted to Amber Xtreme and Trisamber using a two-step sequence involving reduction followed by acid cyclization as delineated in Scheme 2.



Scheme 2. Route to Amber Xtreme and Trisamber.

It is worth mentioning that Amber Xtreme is primarily a mixture of two isomers: the *cis* isomer (Structure A) which is a much more powerful woody, amber odor profile, and the *trans* isomer (Structure B), which is described in Figure 8. From the structure-odor (18) point of view, note the stereo chemical comparison between the Amber Xtreme structure and the structure of (–)-l-Ambrox. It is no wonder that Amber Xtreme is ambery and complements (–)-l-Ambrox in its odor and performance profile.

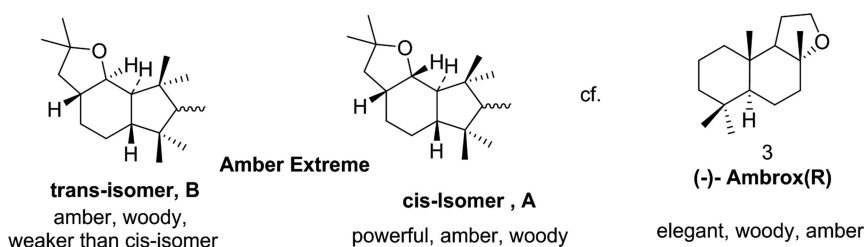


Figure 8. Odor differences between Amber Xtreme isomers.

Chirality in Fragrance Ingredients

Let me briefly share a few examples of how chirality (18) influences odor preferences or attraction for chiral isomers of certain fragrance ingredients. It is shocking and surprising to find that certain chiral isomers of well-known aroma chemicals can have a completely different odor. For example, enantiomer ingredients like (R)-Limonene has an orange odor versus (S)-Limonene, which has a lemony smell, while (–)-Carvone smells like spearmint versus (+)-Carvone, which smells like caraway. Among other diastereomeric chiral ingredients such as menthol, which has 3 chiral centers and 8 possible stereoisomers, only l-menthol has a cool, minty smell. For this reason, it is widely used in both perfumery and flavors.

Another dramatic observation of a chiral odor difference is noted with methyl jasmonate, a key component of jasmine essential oil. Methyl jasmonate has two chiral carbons and thus can exist in 4 diastereoisomers as shown in Figure 9. It was later determined that only the 1R, 2S-(+)-methyl jasmonate epimer has a true jasmine floral smell which is 70 times stronger than the other three diastereomers. In addition, strangely enough, the 1S, 2S-diastereomer was found to be odorless (19).

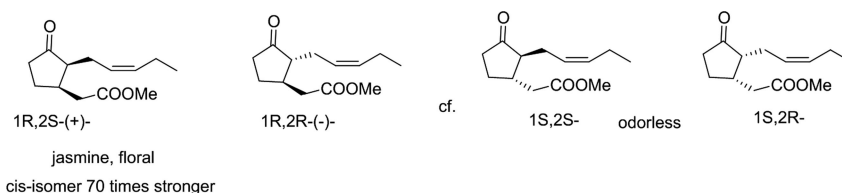


Figure 9. Odor differences among methyl jasmonate chiral diastereomers.

Among all the musk fragrance ingredients, Galaxolide is one of the largest produced musk molecules due to its outstanding performance and long-lasting odor. It was discovered by Dr. Beets, an IFF scientist, in 1957. Later, it was found that only the 4S, 7R- diastereomer (20) had the most powerful musk smell with a low threshold (0.63ng/L), which is depicted in Figure 10.

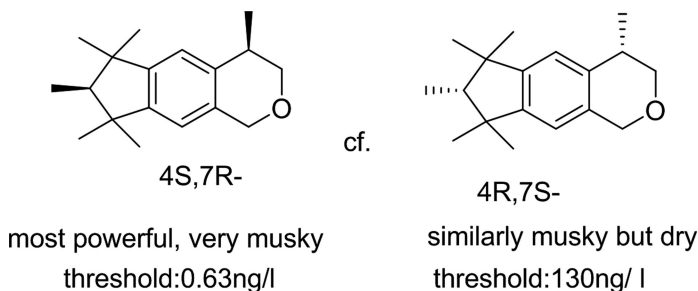


Figure 10. Odor differences among Galaxolide key chiral diastereomers.

3R(-)-Muscone

Muscone is another fragrance ingredient for which striking odor differences are observed among its enantiomers. Muscone is loved by consumers and perfumers for its rich, powerful, powdery musk smell. (-)-muscone has a desirable musky smell with a low threshold value of 61ppb versus 3S-(+)-muscone which has a very weak musk odor as shown in Figure 11. If one incorporates another methyl group at the 3-position of muscone structure then 3,3-dimethyl muscone becomes odorless. Such is the unpredictable power of chirality and structure-odor relationship.

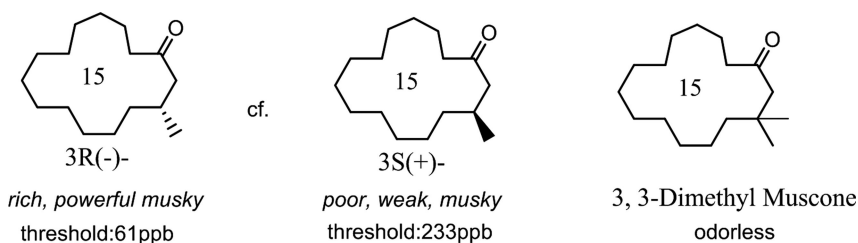


Figure 11. Odor differences of Muscone chiral enantiomers.

Cassifix vs. Ent-Cassifix

Another example of dramatic odor differences among chiral fragrance ingredients comes from our work which was carried out during the discovery of Cassifix. The Cassifix that was prepared from S-(-)-campholenic aldehyde, which is derived from 1S, 5S-(-)- α -pinene, and was found to be strongly cassis in odor. In contrast, ent-Cassifix was prepared from R-(+)-campholenic aldehyde, which is made from 1R, 5R-(+)- α -pinene as shown in Figure 12, and was found to have a very weak cassis odor.

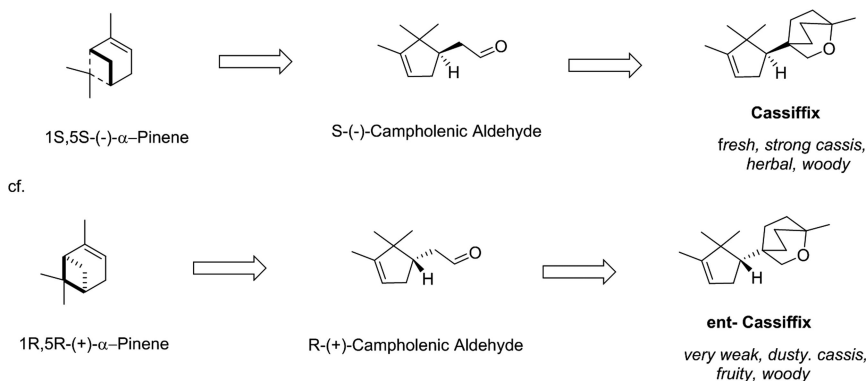


Figure 12. Odor differences among Cassifix and enantiomer ent-Cassifix.

In conclusion, it is fair to state that in spite of tremendous advances in biological and olfactory research and artificial intelligence in computer modeling, even today, no one can predict with certainty the odor of a new structure. As a result, structure-odor relationship prediction remains empirical in nature.

Living Flower Technology: A Tool for Capturing True to Nature Aroma of a Flower's Fragrance

Living Flower technology was pioneered by Dr. B. D. Mookherjee of the IFF in the 1980s. Use of such Living scents lead to the creation of many attractive fragrances. The idea behind this technology was to create a true natural scent of a blooming flower as shown in Figure 13.

This transformative technology was based on the fact that when a flower is plucked from the branch, the nutrition that is being provided by the root system of the flowering plant is severed, thus directly impacting the enzymatic chemistry of the flower leading to an observed change in the amount of chemical constituents of the essence. Using this technique led to the recreation of a natural flower scent. IFF has a database of hundreds of living accords of diverse flowers, fruits, and spices. In fact, the IFF botanical garden as shown in Figure 14 has a collection of 1500 unique plants from all over the globe. This has allowed IFF perfumers to create attractive and legendary fragrances.

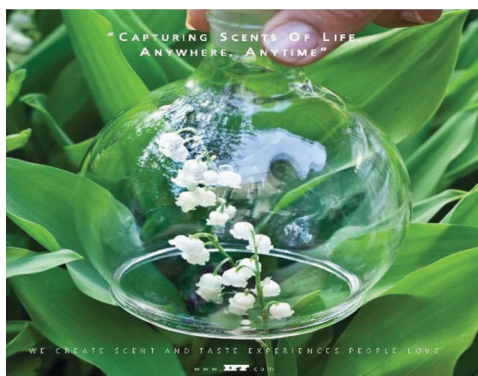


Figure 13. IFF headspace technology.



Figure 14. IFF botanical garden.

Future of Fragrances: Natural, Organic, Healthy, and Sustainable

Before concluding this article, let me express briefly a few thoughts about the future of fragrance design. Going forward, more and more consumers will use fragrances not just for sensory and esthetic benefit but they will also prefer to purchase scents that are healthy, holy, and sustainable. This trend of wellness is already gaining momentum. It is no wonder that there is an increasing interest in the use of natural essential oils in perfumes and aromatherapy. Concurrently, the use of niche fragrances is growing exponentially in the industry.

With regard to holy and healthy fragrances, Asian cultures have relied on the use of holy basil, sandal, natural spices and attars of select flowering plants for healing purposes for many years. There are numerous fragrance healing gardens in Kashmir, India dating back to the 1700's. Figure 15 depicts the Butchart Garden of Victoria, Canada, which is well known for its healing properties.

Many people regularly visit fragrant gardens like Butchart and surround themselves with the natural pleasant flora and fauna to rejuvenate and relieve stress. Many argue that visiting these gardens is a healthy alternative to using anti-anxiety medication.



Figure 15. Butchart Garden of Victoria, Canada.

Fragrance Technologies of the Future

In moving forward toward the goal of assuring sustainable fragrances, synthetic biotechnology will be a major source of key natural flavor and fragrance ingredients. In addition to using natural ingredients, synthetic biotechnology will also be used for the production of sustainable raw materials and essential oils needed for creating attractive fragrances. This is primarily due to dwindling resources, climate changes, and a lack of abundant, cost-effective key fragrance ingredients without which modern fragrances cannot be created.

Acknowledgments

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