

Artificial Synthesis of Natural Fragrance

Jiayun Zhen^{1†*}, Jiale Zhao^{2†}, Shuyang Zhang^{3†}

¹Beijing 101 High School International Department, Beijing, China

²HD Shanghai School, Shanghai, China

³Xi'an Tie Yi International Curriculum Center, Xi'an, China

*Corresponding Author. Email: zjy21d4@163.com

[†]All the authors contributed equally to this work and should be considered as co-first author.

Abstract. Natural essences are indispensable in the field of perfumery due to their unique flavor and “natural” properties. Many brands of perfume are known for adding natural essence. The increased cost and the environmental damage caused by using of natural essence are sometimes unavoidable, so since the Industrial Revolution, more molecular formulas of natural essence have been determined by scientists and synthesized artificially, aiming to gradually replace natural essence. Synthetic essences have replaced most natural essences in the field of perfumery due to their efficient industrial synthesis, similar smell to natural products, and low cost. This paper reviews the organic chemical basis of synthetic natural essence, focusing on hydrocarbons, oxygen-containing compounds, nitrogen/sulfur-containing compounds, and macrocyclic compounds, and systematically analyzes their structure, function, and synthesis pathways. Simultaneously, based on the technical maturity and wide application of artificial synthesis of natural essence, this paper will compare the differences between them and natural essence, which will also focus on the impact of the two on the environment and ecology.

Keywords: Natural essences, Artificial synthesis, Perfume, Olfactory system

1. Introduction

1.1. Definition

Essence, which is the material of perfume, can be divided into two groups: natural essence and artificial essence. Natural essence can be discovered in nature, while artificial essence can only be manmade, which cannot be found in nature. There are two ways to get natural essence: extracting from nature, like extracting Jasmine Absolute from jasmine, or synthesizing from simple raw materials. This paper will focus on exploring the artificial synthesis of natural essence and reviewing its synthetic development.

1.2. History of artificial flavors

In Ancient times, humans used natural flavors to help create more flavors in food. In the pre-19th century, the concept of 'artificial' flavors did not exist, but processes like fermentation and

distillation helped create more concentrated flavors for use in cooking and medicinal purposes. With the Industrial Revolution beginning, synthetic additives started to be produced, due to the widespread availability of processed food, which led to mass production. In 1843, methyl salicylate was produced and acted as the first artificial flavor in the world, and then, after 15 years, the synthesis of vanillin was another artificial flavor. During the 20th century, artificial flavors became more common and acceptable, but in the mid-20th century, there was a debate between artificial and natural flavors. An article mentioned that after revelations of troubling food industry productive practices and globalization of a complex and uneven food system, consumers are increasingly concerned with the origin of foods and numerous implications of an unhealthy diet [1]. Therefore, people's attitude shifted to natural products. Although the artificial industry faced a big trouble in this period, after 30-40 years, the industry continued to thrive because of lower cost and longer shelf life of synthetic flavors, which helped them survive in the market. Currently, both artificial and natural flavors have considerable sales volumes, but there is a clear trend towards using 'natural products' rather than artificial ones. And the overall conclusion about history is in figure 1.

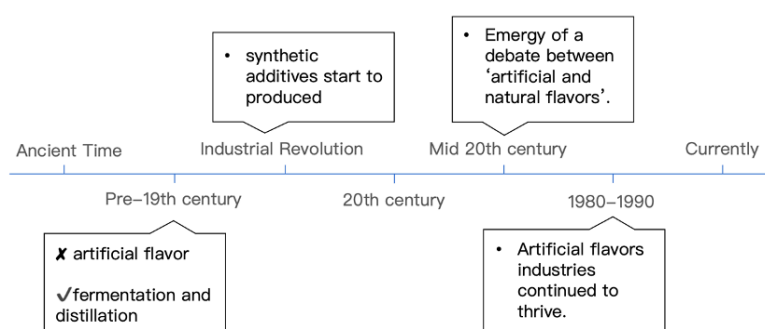


Figure 1. Timeline of the history of artificial from ancient times to current

1.3. Comparison between artificial and natural essence

About table 1, in 2017, Bloom J mentioned that some artificial flavors made in a laboratory could reach roughly 100 percent pure, but the same flavor obtained from a plant will not. Additionally, Bloom J notes that some natural chemicals can be toxic or even carcinogenic, whereas artificial flavors do not contain these harmful substances [2]. After 5 years, Mosia S, Nita Sukdeo N, and Pradhan A did an investigation using Refractory Index (RI) and Specific Gravity (SG) equipment at 20 °C. Among them, the Refractory Index and Specific Gravity are used to measure the concentration of substances or solutions and mass control, and the density of the substance and some physical properties separately. The result indicates that both RI and SG are higher in artificial flavors than in natural ones; therefore, artificial fragrances are more viscous [3]. For artificial flavors, the cost of synthesizing different flavors is relatively cheaper than abstract natural flavors, due to the need for sourcing raw materials from nature, which changes in the environment and seasons may affect the yield of plants. In addition, another direction to compare artificial and natural flavors is to compare the consumer preference. Consumer preferences depend on different ways, for example, people's attitude to artificial flavors can offer stronger, more intense flavors that are recognizable and familiar, but someone will be concerned about the synthetic origins of the flavors. On the other hand, people prefer using natural flavors because of their purity, safety, and authenticity, whereas natural flavors have less intensity or difficult to maintain consistently across large batches.

Table 1. Different properties of artificial and natural essence

	Artificial flavors	Natural flavors
Purities	Approximately 100% pure made in lab	Relatively poor purity
Viscosity	More viscous (higher SG&RG)	Less viscous (low SG&RG)
Ingredient	Would not contain harmful substance	May be toxic or even carcinogenic
Cost	Low	High
Consumer preference	Like: Can provide stronger and more intense flavors	Like: due to their purity, safety, and authenticity
	Dislike: Concerns about their synthetic origins.	Dislike: Less intense or difficult to maintain consistently

Overall, according to the comparison, it clearly shows that the benefits of using artificial fragrances outweigh the natural flavors, so artificial flavors are worthy of being invented.

2. Olfactory perception mechanism of humans

2.1. Structure of the human olfactory system

The human olfactory system can be roughly divided into olfactory receptors (ORs) shown in figure 2, olfactory sensory neurons (OSNs), olfactory bulbs (OBs), and the primary olfactory cortex in the brain.

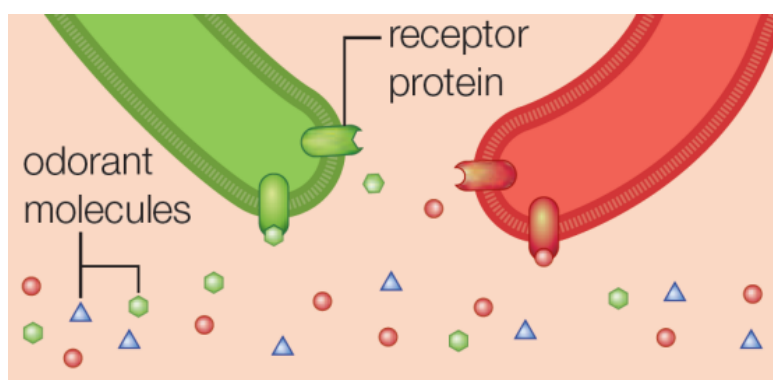


Figure 2. Structure of olfactory receptors

ORs are used to detect odor molecules in the environment. Human ORs belong to the G protein-coupled receptors (GPCRs) family, which contains about 400 functional OR genes and about 600 non-functional genes, making it the largest known gene family in the world [4]. OSNs are the primary sensory organs in vertebrates. Between 6 million and 10 million OSNs make up the neuroepithelium, which is arranged in the upper part of the nasal cavity of mammals. OSNs act as bipolar neurons, with a single dendrite extending to the surface of the tissue, dispersed into cilia. The axons at the other end are directly connected to areas of the brain [5]. OBs are parts of the telencephalon cortex. They are oblate oval in shape, one from each half of the human brain, and are responsible for processing information from the left and right nostrils. It is characterized by a buildup of nerve fibers arranged below the surface, known as glomeruli. When the axons of OSNs leave the olfactory epithelium, they converge to form the olfactory nerve, and the glomeruli are responsible for receiving this signal. All this system is showing in figure 3.

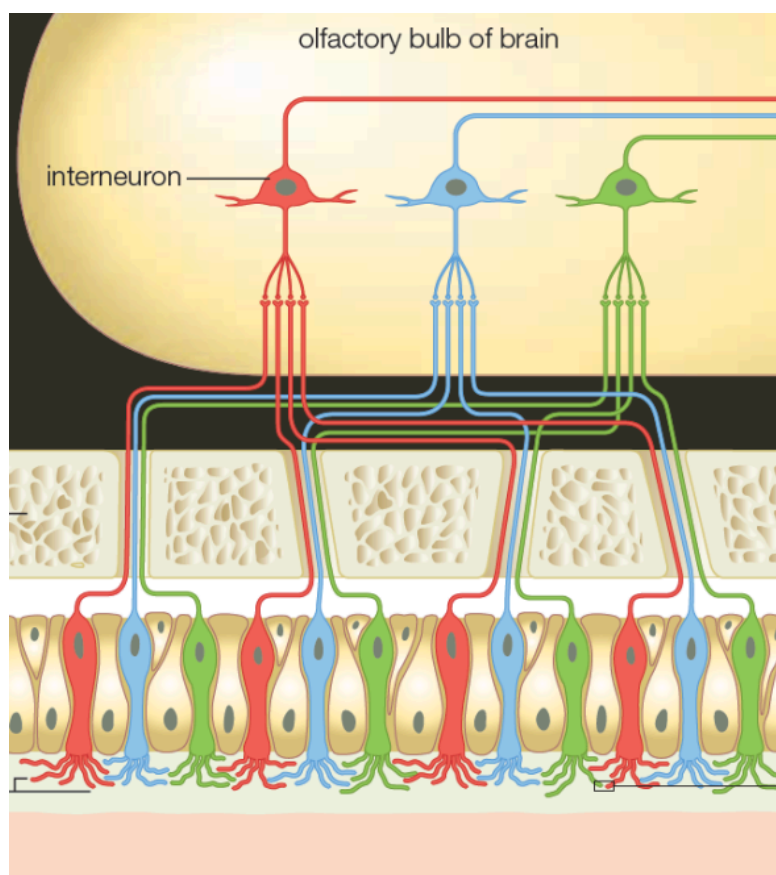


Figure 3. Structure of olfactory sensory neurons and olfactory bulbs

2.2. Binding of molecules to signaling due to nerve impulses

According to a study by Christian B. Billesbølle et al. [7], researchers use Cryo-electron microscopy(cryo-EM) to observe the structure and the reaction between propionic acid, which shows in figure 4, and OR52E1 (an olfactory receptor in the human body belonging to class A of the GPSRs family).

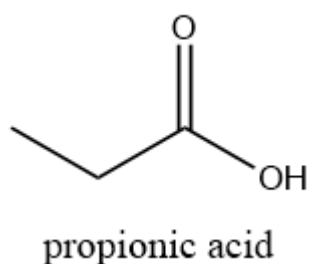


Figure 4. The molecule structure of propionic acid

OR51E2 contains seven transmembrane helices (TMs, a protein structure embedded in the phospholipid bilayer of the cell membrane and is the core structure of GPCRs). In this study, it was shown that propionic acid binds to closed pockets formed by TM3, TM4, TM5, and TM6, which was shown in figure 5.

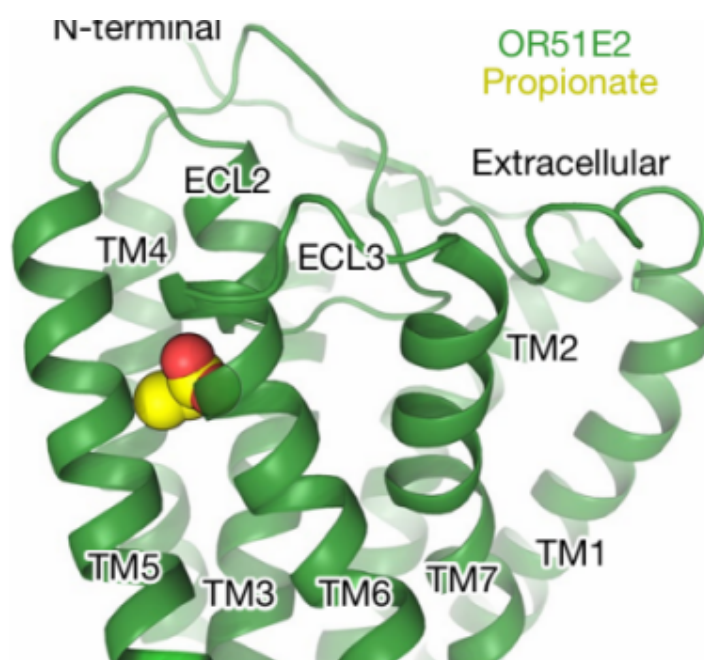


Figure 5. The binding site in OR51E2 of the propionic acid

The carboxyl group(-COOH) on propionic acid forms ionic bonds with the R262^{6x59} (Arginine) residue on TM6. It also forms hydrogen bonds with Q181 (Glutamine) on extra cellular loop2(ECL2) and S258^{6x55} (Serine) on TM6. At the same time, the aliphatic chain on propionic acid is also connected to H104^{3x33} (Histidine) of TM3 and L158^{4x60} (Leucine) of TM4 through van der Waals forces, as the figure 6 shows.

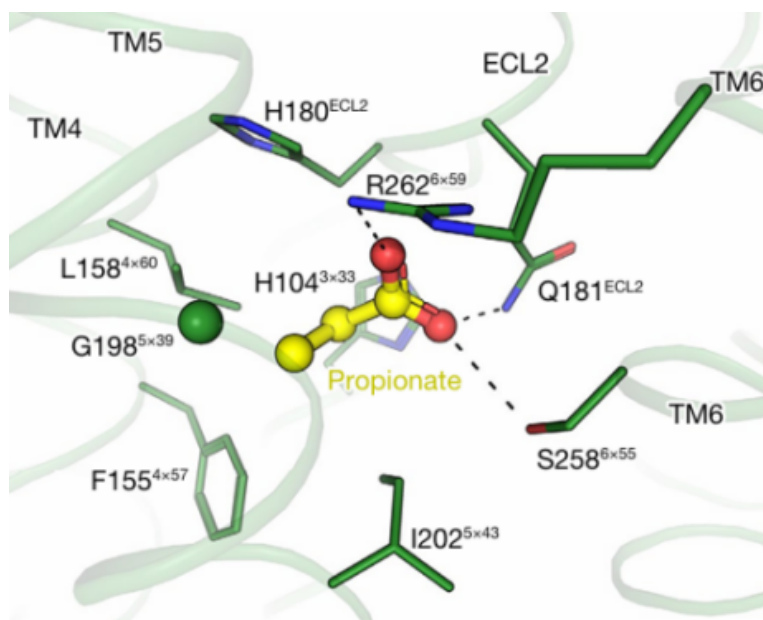


Figure 6. Bonds formed between OR and acid

Eventually, propionic acid and OR51E2 are tightly bonded. After they combined, the ECL3 of OR51E2 undergoes a conformational change because the action of propionic acid moved into the

pocket, driving TM6 to rotate, and then activating OR51E2 [7]. The activated OR51E2 will activate the G-protein on the receptor, which in turn lets the α subunit leave and activate adenylyl cyclase (AC). Cyclase converts ATP into cAMP, and cAMP will interact with ion channels of the OR to generate action potentials that convert odor signals into electrical signals for conduction, which demonstrates by figure 7 [6].

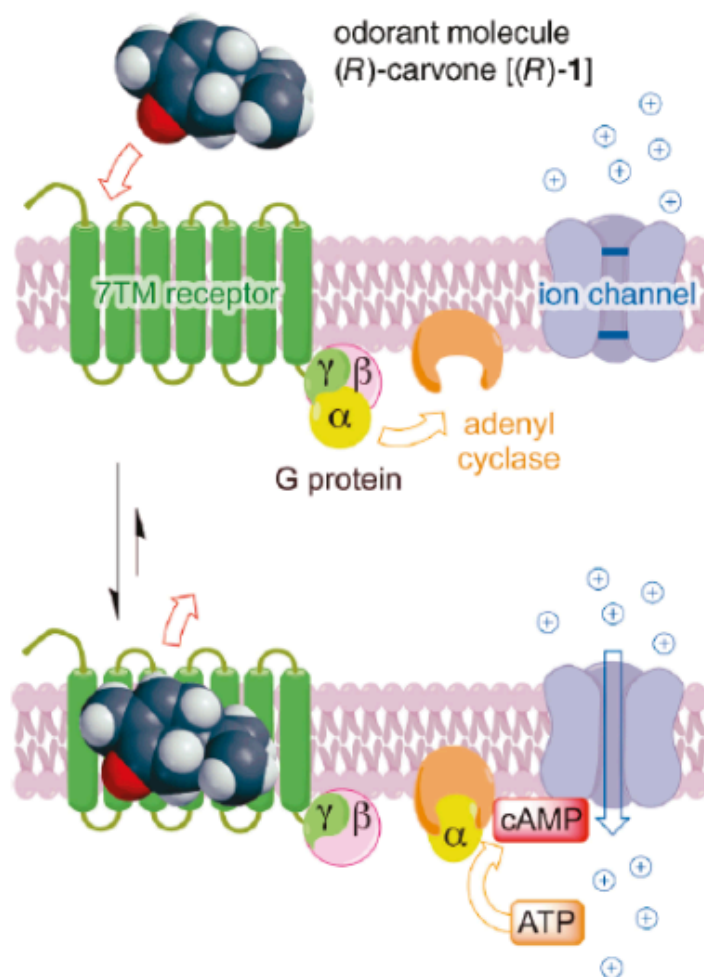


Figure 7. The biochemistry of odorant-receptor binding

2.3. Enantiomers and olfactory mechanisms

The diversity of molecules determines that the same molecule can have many different structural forms. Like enantiomers [8]. In human life, the application of different enantiomers can be seen everywhere. For example, carvone, limonene, citronellal, and so on. The amazing thing is that different enantiomers of the same molecule can be recognized by humans as completely different odors. This is to be discussed according to the human olfactory mechanism. The difference in odor between enantiomers can also be divided into several situations, as shown in the table 2 [9].

Table 2. Relative olfactory properties of enantiomers

Case	Relative Olfactory Properties
1	Only one enantiomer smells and the antipode is weak to odorless
2	Enantiomers smell similar but possess different intensities
3	Enantiomers smell similar and possess similar intensities
4	Enantiomers smell different

Carvone has two enantiomers, showing in figure 8, which is D(S)-Carvone and L(R)-Carvone. D-carvone has a smell of caraway, while L-carvone has a smell of mint [10].

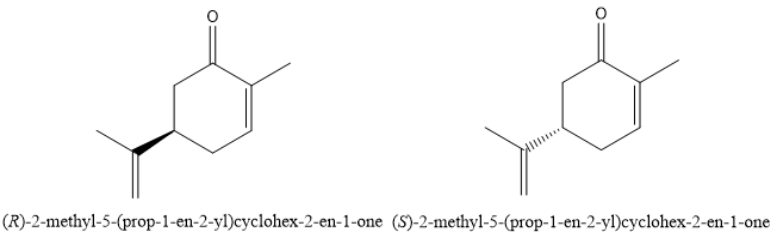


Figure 8. Enantiomers of carvone

Alexandra Kirner et al. investigated the effect of Concanavalin A (ConA) on the odor of two enantiomers of carvone in rats [8]. Before the experiment, rats had similar olfactory thresholds for D- and L-carvone. When the researchers dissolved ConA in Ringer's reagent and perfused it into the nasal mucosa of the rats under anesthesia, the response rate to D-carvone decreased, while the response rate to L-carvone did not change significantly.

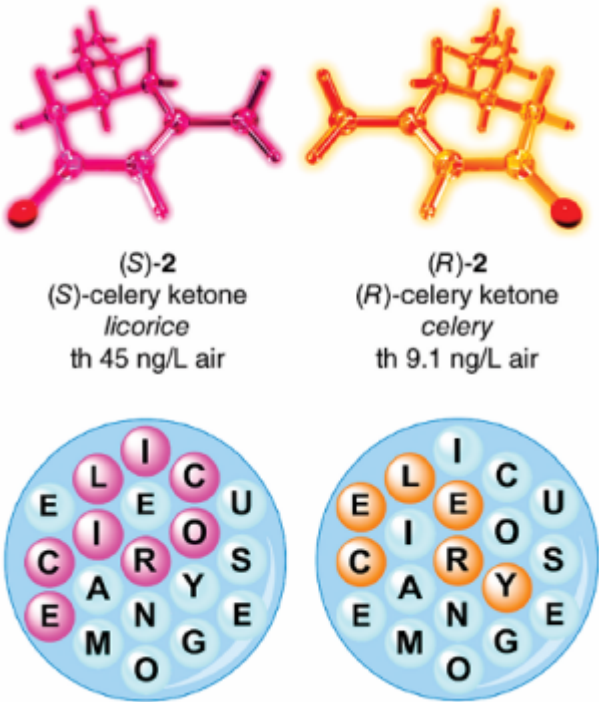


Figure 9. Receptors activated by carvone

The experimental results support this finding and may provide some ideas and inspiration for the mysteries of the human olfactory system. We can infer that since ConA blocks D-carvone but not L-carvone, there will be different ORs in OSNs to recognize the two enantiomers of carvone, which shows in figure 9. In other words, the brain has different patterns of interpreting D- and L-carvone signals, which may explain why humans have different odors for the two structures.

3. Classification of artificial flavors

Artificial flavors can be classified in various ways, for example, by flavor type, the source of the raw materials, the chemical structure, and different functionalities. The classification by chemical structures had been used.

3.1. Hydrocarbons and derivatives

The first chemical structure is hydrocarbons and derivatives. Under this category, terpenes and aromatic compounds are two branches. Terpenes are all made of repeated fusion of isoprene (C_5H_8) units. Tens of thousands of terpenes have been identified from plants around the world. The number of isoprene units, terpenes can be divided into seven categories: monoterpenes (with 10 carbon atoms), sesquiterpenes (15), diterpenes (20), disquiterpenes (25), triterpenes (30), tetraterpenes (40), and polyterpenes (>40). Most terpene compounds are related to primary metabolism in plants [11]. About aromatic compounds, they were defined in the early days of organic chemistry research as a class of substances with aromatic odors extracted from plant gums. With the deepening of research, unsaturated cyclic compounds containing special stability are gradually collectively referred to as aromatic compounds [12].

Vanillin is a typical artificial flavor that has the structure of hydrocarbons and derivatives. There are a number of methods that could form vanillin, such as the eugenol method, the guaiacol method, the lignin method, and the glyoxylic acid method [13]. However, some methods are inconvenient and unrealistic due to the high resource costs incurred in the cultivation of raw materials and production processes. Among them, the eugenol method is a classic method that uses expensive raw material. In a 2024 article, author Song, Jia-xin, mentioned that the eugenol method uses eugenol leaves as the raw material, but the natural raw material is expensive to produce, limited in quantity, and gradually being eliminated [14]. Therefore, according to various difficulties in making vanillin, the method using guaiacol as substrate is the most common one which is shown in Figure 10.

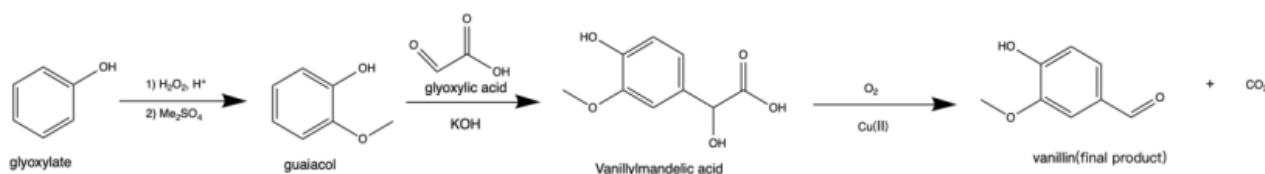


Figure 10. Synthetic pathway of vanillin

During this synthesis, the reaction uses guaiacol as a substrate, which is one of the most widely used methods for guaiacol conversion. To be more specific, this synthesis can be separated into several processes, but the last two are the most important. Firstly, the condensation reaction takes place between glyoxylate and guaiacol. Then, during the next step, glyoxylic acid reacts as an electrophilic reagent, and potassium hydroxide acts as a basic catalyst and provides a hydroxide ion (OH^-), which assists in nucleophilic attack. Also, the hydroxy group provided by guaiacol increases

its nucleophilicity, making it capable of attacking the aldehyde group (-CHO) on glyoxylic acid. Therefore, vanillymandelic acid has been successfully produced. About the final step, it is an oxidative decarboxylation reaction, which can be separated into 'oxidative' and 'decarboxylation'. For 'oxidative', it means vanillymandelic acid can be oxidized by oxygen and using copper and manganese as catalysts, and for 'decarboxylation', it indicates the removal of carboxylic acid in vanillymandelic acid and the release carbon dioxide when vanillin is finally produced.

This reaction uses copper and manganese salts as catalysts can lower the activation energy which enhancing the efficiency. Additionally, the glyoxylate method also has other advantages, including reducing the generation of by-products, which simplifies the subsequent separation and purification processes, thereby enhancing the purity and yield of vanillin. However, the Glyoxylic acid method has some limitations. Firstly, the high cost of glyoxalic acid largely increases the production cost and poses economic challenges for large-scale industrial production. Furthermore, because of the non-renewable nature of petroleum, the reliance on petroleum-based intermediates in vanillin production raises concerns regarding sustainability [15].

3.2. Oxygen-containing compounds

Oxygen-containing products are one type of essence that contains oxygen atoms in the structure, which can form different functional groups. There are six branches under this big type. They are lactones, ketones, aldehydes, esters, ethers, and alcohols. For lactone, the oxygen atoms in the structure can provide a longer-lasting aroma. Because the ring shape restricts molecules from moving randomly, in this case, the smell will spread more slowly than other kinds of flavors.

In this paragraph, we take one essence in the ether, called Ambrox, to give a simple explanation of the synthesis of oxygen-containing essence. In 1995, Roger and his group innovated a pathway to synthesize Ambrox with the starting material bicyclic Exo-methylene ketone, using a four-step reaction that can get the Bicyclic diol, which is an important intermediate to get the final product [16]. Since Bicyclic diol contains two O-H bonds, which allow the reduction to occur. Also, stereochemistry is used for the final ring-forming steps. From diol to Ambrox needs the help of p-toluene sulfonic acid. This pathway was chosen because it's easy to understand with basic chemistry methods, and because the natural way to get this kind of flavor is hard and expensive, but with the help of artificial synthesis, Ambrox can remission the high demand pressure of ambergris in the market. In this case, it reduces the potential risk of whale overfishing to a certain extent. However, the starting material is expensive, and some chemical agents used during the reaction are highly toxic, such as potassium cyanide.

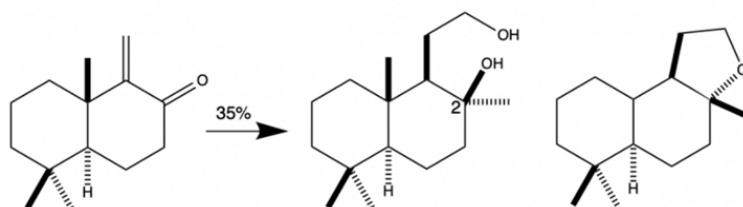


Figure 11. Method for synthesizing Ambrox using dicycle none as raw material

3.3. Nitrogen/sulfur-containing compounds

The third type of flavor is nitrogen or sulfur-containing compounds. This type is divided into three branches: Pyrazines, Indoles, and thiazoles. Indoles are being chosen to give a synthesis pathway.

Indoles usually can be distilled from Jasmine flowers [17], but they can also be obtained from artificial synthesis, which requires no need for plants. In 2017, Jian Gang Yu and his group improved the traditional Fisher indole synthesis pathway by adding ionic liquid([EMIM][BF₄]) [18]. In this reaction, phenyl hydrazine and propyl aldehyde react under 60 °C to form hydrazone, then hydrazone undergoes rearrangement with Zinc Chloride at 200 °C to yield 3-methylindole in just 4 minutes. Zinc chloride not only acts as a catalyst but also can neutralize NH₃ generated during indole ring formation. Figure 12 shows the synthesis way. In this improved method, the yield increases from 81% to 95.3% and reduces the reaction time from 20 minutes to 4 minutes. On the other side, after reaction, the ionic liquid can be reused and has no loss of reactivity. After three synthesis cycles, the yield remains over 90%. All in all, the new method compared with the traditional one is more environmentally friendly and able to be used in other kinds of indole compound synthesis.

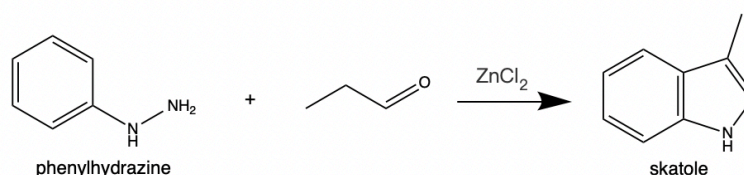


Figure 12. Fisher indole synthesis of 3-methylindole

3.4. Macrocyclic compounds

Macrocyclic compounds are cyclic compounds formed by many carbon atoms joined into rings. Macrocyclic compounds can be divided into macrocyclic ether and musk. Among them, musk is widely used in the field of perfumery. Musk is an important formulation of perfumes, and almost all musk used are polycyclic aromatics produced chemically from petrochemically derived raw materials. Natural musk includes macrocyclic lactones found in plants, as well as keto musks secreted in animal glands [19]. Among them is the representative variety of macrocyclic musk – muscone, extracting from the sachets of male musk, which have a deep musk aroma. They are widely used in the base notes of perfumes, giving a fragrance the most persistent smell. It is precisely because the natural extraction of muscone will endanger the safety of wild musk deer, many people do not hesitate to kill musk deer to obtain precious muscone, causing serious ecological problems and destroying biodiversity. Therefore, with the continuous development of organic chemical synthesis technology, natural muscone has gradually been replaced by artificial synthesis.

There are many ways to synthesize Muscone, including closed-loop method, loop expansion method, and methyl insertion method. Here, the methyl insertion method using cyclopentadecanone as raw material is used as an example to introduce the synthesis path of Muscone. The molecules mentioned in the paper are listed in the figure 13. Starting with cyclopentadecanone, which is the molecule 1 showing in the figure 13, in benzene, utilizing with ethylene glycol and toluene sulfonic acid to treat 1. As an acid catalyst, toluene sulfonic acid enhances the positive electricity of carbonyl carbons on 1, making it easier for the hydroxyl groups on ethylene glycol to attack, and generating ketal molecule 2 through Ketonation reaction.

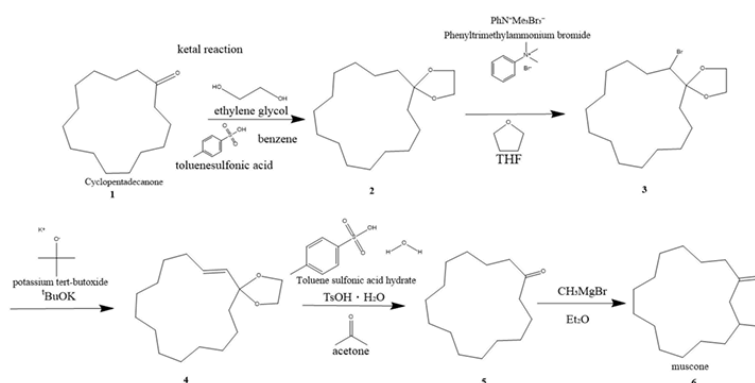


Figure 13. Synthesis path of muscone

Phenyltrimethylammonium bromide acts as a bromination reagent to provide bromine ions in the reaction. Molecule 2 and phenyltrimethylammonium bromide react in THF to undergo a nucleophilic substitution reaction to form bromo ketal molecule 3. Molecule 3 and tBuOK continue to react. Since tBuOK is a strong base, it will grab the β -hydrogen on molecule 3 to form a double bond product molecule 4. Ketal molecule 4 and toluene sulfonic acid hydrate react in acetone. Toluene sulfonic acid protonates the oxygen atoms of the ketal, and water molecules attack the carbon of ketal, decomposing the ketal and regenerating carbonyl, which shows in molecule 5. Molecule 5 and magnesium methyl bromide react in ether. As a Grignard reagent, the methyl group of magnesium methyl bromide attacks the carbonyl carbon of molecule 5, undergoes a nucleophilic addition reaction, forms a tetrahedral intermediate, and then hydrolyzes to form the Muscone, as shown in molecule 6 [20].

4. The application of fragrance

4.1. The application of fragrance

Fragrances are an indispensable part of life and have been widely used across consumer products, industrial sectors, the food industry, and even in psychological applications. For example, in the food industry, fragrances are used to enhance or replicate the taste of dishes and replace expensive or unavailable natural flavor sources, even if this severely deceives consumers. Also, in the pharmaceutical industry, flavors are used to mask bitterness or unpleasant taste in oral medications and also improve patient compliance, especially for children. Among them, perfume is the most popular way of using fragrance. According to data, the global perfume market size in 2020 will be about 390.6 billion yuan, of which China will account for 2.5% [21]. In 2023, the size of China's perfume market has reached 20.7 billion yuan, a year-on-year increase of 22.5%. After user surveys, it was found that 68.5% of perfume consumers were women, and 64.2% of consumers said that the use of perfume focuses on pleasing themselves and providing emotional value. It can be seen that the use of perfume is no longer limited to social and professional situations, but has begun to turn more to the expression of emotions [22].

4.2. Classification of perfume

Nowadays, perfumes on the market are made by diluting fragrances with alcohol and water. The classification of perfumes is varied, both by essence concentration and by note.

According to the concentration of fragrance, it can be divided into four categories, as shown in Table 3.

Table 3. Classification of the perfume by concentration of fragrance

Types of perfume	Concentration	Characteristics	Fragrance duration
Cologne (Eau de Cologne-EDC)	2%-5%	The fresher type First used for men's shaving or washing Lower price	Very short, about 1 hour But it is very diffusive
Eau de Toilette (EDT)	5%-15%	The most common and popular one Suitable for daily use	Generally 3-4 hours
Eau de Parfum (EDP)	15%-20%	Fully enjoy the front, middle, and back notes of a perfume	Reach more than 5 hours
Parfum	20%-40%	Strongest taste Rich aroma layers High price	Reaching 5-10 hours

5. Conclusion

According to the research, perfume occupy a huge market around the world which means it's becoming a necessity in our daily life, but It also receive a lot of misunderstood [21]. Since the public does not have access to such expertise. So, this paper can help readers have a better understanding of flavors.

This work explained why humans can smell flavors, and then we give out four types of flavors, which are divided by different structures. They are hydrocarbons and derivatives, oxygen-containing compounds, nitrogen or sulfur-containing compounds, and macrocyclic Compounds. As of now, the synthesis pathway of these compounds has been innovated a lot. This paper aims to raise public awareness of artificial fragrances, knowing the chemical principles behind perfumes, and the contribution of synthetic natural flavors to environmental protection. These synthesis methods not only have high yield and low pollution but also make perfume inexpensive and of decent quality. In this case, chemists need to explore more in this field, to innovate more high-yield but low-pollution synthesis pathways that not only protect the environment but also lower the cost of production.

Acknowledgement

Zhen Jiayun, Zhao Jiale, and Zhang Shuyang contributed equally to this work and should be considered co-first authors.

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