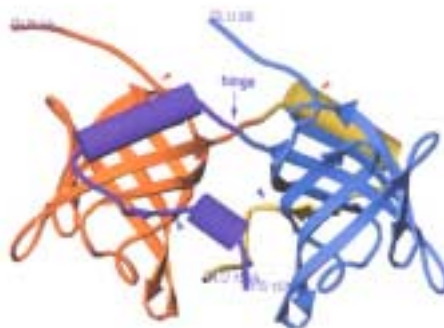


## Fragrance Chemistry

All civilizations, from antiquity to present time, have used fragrances for a variety of purposes. Before the advent of organic synthesis, fragrances were often limited to those found in the form of oils, balsams, exudates, and resins.<sup>1</sup> With development of organic synthesis during the 19<sup>th</sup> Century, fragrance chemistry advanced into industrial synthesis and distribution. Since that time, a great deal has been achieved in both the understanding of the biology of smell, olfaction, as well as the development of new and unique fragrances.

### Biology of Olfaction

Odorant binding proteins (OBPs) are small, water soluble proteins that are approximately 19 kDa in size.<sup>2</sup> OBPs belong to a family of carrier proteins known as lipocalins and reversibly bind a variety of different odorants in the nM to  $\mu$ M range.<sup>2</sup> The ability for OBP to bind such a wide array of odorants, as well as the selective localization in the lateral nasal cavity, suggest a physiological role in olfaction.<sup>3</sup> Bovine OBP was crystallized as a homodimer in which the two subunits are held together by noncovalent bonds.<sup>4</sup> Each monomer has an eight stranded  $\beta$ -barrel with an  $\alpha$ -helix. In the dimer, the  $\alpha$ -helix of one monomer completes the  $\beta$ -barrel of the other as shown in Figure 1. Based on a wealth of structure-activity relationship data, there are three



**Figure 1.** Crystal structure of Bovine OBP homodimer.

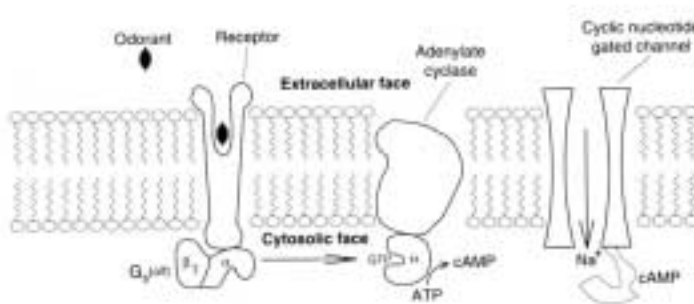
possible roles OBP could play in the process of olfaction.<sup>5</sup> The first would be to act as a buffer, lowering the concentration of odorants that bind to the olfactory receptors.<sup>6</sup> This action would trap most of the molecules that would otherwise inactivate the olfactory receptors for a long period of time. A second role of OBP could be to serve as a carrier protein like the lipocalins.<sup>7</sup> Most odorants are small hydrophobic molecules, poorly soluble in the aqueous mucus surrounding the olfactory receptors. OBP could bind odorants and transport them to the receptor. The third role OBP could play in olfaction is that of a transducer.<sup>8</sup> In this scenario, OBP would bind to the odorant and interact with the receptor as a complex. This model allows for discrimination of odors by OBP and not purely by the receptors in the olfactory epithelium.

The olfactory receptors belong to the largest group of receptors for neurotransmitters, **G-protein-coupled receptors (GPCRs)**. GPCRs are membrane bound proteins containing seven  $\alpha$ -helical domains that are connected by six loops (three extracellular and three intracellular).<sup>9,10</sup> These receptors are thought to be bound to the olfactory cilia of sensory neurons whose axons project into the olfactory bulb in the brain.<sup>11-14</sup> In order to elucidate the pathway for olfactory signal transduction, 18 different members of a multigene family that encodes seven transmembrane proteins whose expression is restricted to the olfactory epithelium were characterized.<sup>15</sup> Shown in Figure 2 is the protein encoded by cDNA clone I15, which is



**Figure 2.** Expression of I15, G-Protein Coupled Receptor

believed to transverse the cell membrane seven times. Amino acids in white circles illustrate positions at which 60% or more of the clones share the same residues, whereas those in black illustrate more variable residues. The high degree of variability in domains III, IV, and V suggest that odorant molecules may bind between these domains. This would allow for the discrimination of odorants by different GPCRs. The signal transduction process involving these receptors is shown in Figure 3. It is believed that odorants bind to the membrane bound



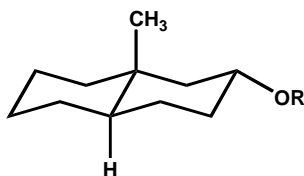
**Figure 3.** Mechanism of signal transduction in olfactory epithelium.

receptor which itself is bound to a GTP (guanosine triphosphate) binding protein also known as a G-protein. Binding of the odorant causes the  $\alpha$  domain ( $G_\alpha$ ) to dissociate from the  $\beta$  and  $\gamma$  domains.  $G_\alpha$  then binds to adenylyl cyclase which converts ATP into cAMP. cAMP acts as a second messenger and binds to a nucleotide gated channel which causes an influx of  $\text{Na}^+$  into the cell. This starts the signal transduction process which finally leads to odor discrimination and processing in the brain.

## Traditional Odorants

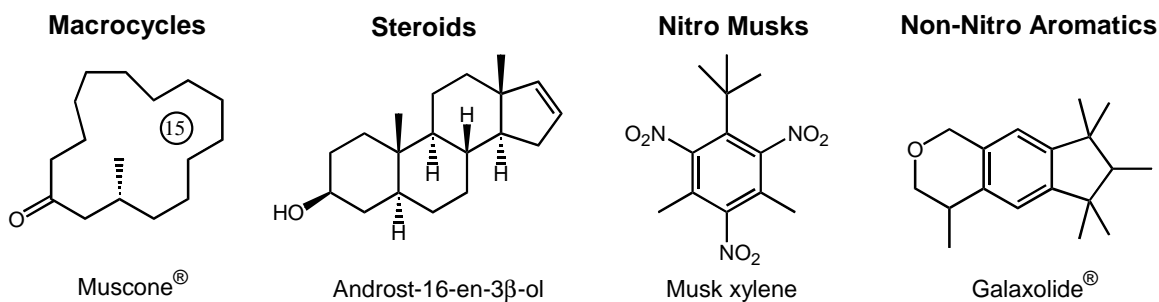
Two odorants that find prominent use in the field of fragrance chemistry and have been studied extensively during the last century are amber and musk.<sup>16</sup> Structure-odor relationships (SOR) that have been elucidated for these two odorants constitute an indispensable step in the search for new and unique fragrances.

Amber scented compounds are described as having an exotic, woody, incense-like odor. One important compound in the field of amber fragrances is (-)-Ambrox®. While Ambrox® is used in industry as a mixture of diastereomers, stereoselective construction of its diastereomers has provided insight into requirements for the amber scent.<sup>17</sup> One such observation is the Triaxial Rule.<sup>18</sup> This rule states that in order to obtain an amber like odor the compound must have a *trans* decalin system. Furthermore, if the *trans* decalin system contains a methyl substituent on a bridgehead carbon, there must be an equatorial oxygen at the 8-position as seen in Figure 4. If the system is a *cis* decalin, or if the 8-position is substituted with an axial oxygen, the compound will have reduced amber intensity or may be odorless altogether.



**Figure 4.** Triaxial Rule for amber odorants.

Musk represents an integral scent for the industry of fragrance chemistry and can be found in nearly 40% of personal hygiene and perfume products. This scent is often described as warm, sweet, and animalistic. There are four main classes of compounds that make up musk odorants: macrocycles, steroids, poly-nitro benzene derivatives, and non-nitro aromatics (Figure 5).<sup>19</sup> SOR data on these classes have provided insight into derivatives of musk odorants as well as the design and synthesis of new, unrelated, odorants with a wide variety of scents.

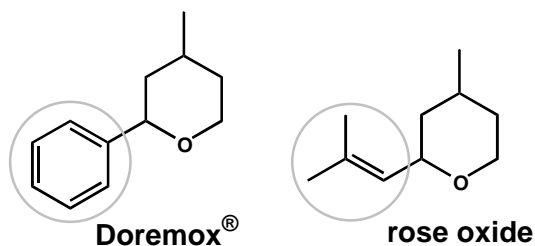


**Figure 5.** Four main classes of musk odorants.

## Current Trends

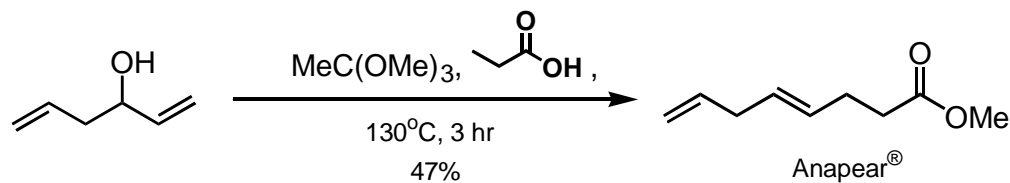
Fragrance chemistry is an ever changing field which is dependent on the trends of the age. Recent trends in fragrance chemistry include floral scents, fruity scents, and spicy scents just to name a few. Trends spawn the search for new and unique fragrances that are cost effective as well as desired by the public.<sup>20</sup>

Rose is currently an important scent in the class of floral fragrances and illustrates a parameter of fragrance chemistry that is important to the industry: substantivity.<sup>20</sup> The term substantivity refers to the persistence of perfume materials on skin or the intended application. One method of increasing substantivity is to increase the mass of an odorant without altering the shape. A common substitution seen in fragrance chemistry is replacement of an isobutylene group for a phenyl group. These two moieties are fairly similar in shape, yet the phenyl group is two carbons larger than isobutylene. An example of this alteration can be seen in the rose odorant, Doremox® (Figure 6).<sup>21</sup> The vapor pressure of Doremox® is 12000 ng/L while its isobutylene analogue, rose oxide, has a vapor pressure of 130000 ng/L.<sup>21</sup> This reduction in vapor pressure allows Doremox® to stay on the skin for a significantly longer period of time.



**Figure 6.** Increasing substantivity by changing isobutylene group into a phenyl group.

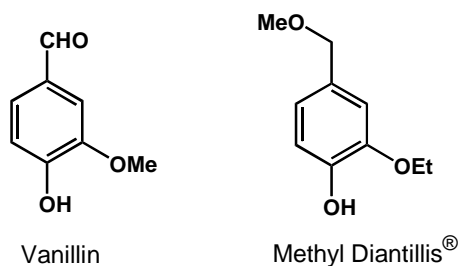
Another increasing trend in odorants within the last decade is the growing popularity of pear odorants. One such odorant, hexyl acetate, was first introduced to the market in personal hygiene products such as L’Oreal’s “Elseve alpha jojoba” shampoo introduced in 1995. The popularity of this odorant spawned a search for other novel pear scented compounds. Anapear® was discovered by Roman Kaiser of Givaudan-Roure International and is prepared by the Johnson ortho-ester variant of the Claisen Rearrangement as shown in Figure 7.<sup>22</sup>



**Figure 7.** Synthesis of Anapear®

Odorants of spice scent have been popular for over a decade and are still finding use in a wide variety of products. In the search for a novel vanilla type odor which would not cause

discoloration, Methyl Diantillis® was discovered (Figure 8). This molecule, while structurally similar to vanillin, possesses a creamy, vanilla odor reminiscent of white chocolate and can currently be found in fragrances such as “A \*Men” by a subdivision of Givaudan Corporation.<sup>23</sup>



**Figure 8.** Comparison in structure of Vanillin and Methyl Diantillis®

Fragrance chemistry is an industrially important science that requires the constant discovery of new and unique odorants. Because so little is known about the mechanism of olfaction, the discovery of new odorants requires both rational design through molecular similarities and serendipitous discovery. SOR data based on thoroughly studied odorants such as amber and musk provide insight into novel derivatives yielding a wide variety of new odorants.

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