Material study

Heterocyclic Oxygen-Containing Aroma Chemicals*

A look at the four groups that comprise this section of heterocyclic chemicals, and their importance to flavors and fragrances

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Of the ca. 20 million chemical compounds presently characterized, almost half are heterocyclic molecules. Heterocyclic molecules are significant due to their abundance in nature, and their chemical and biological importance. In the flavor and fragrance industry, heterocyclic compounds are of interest because of their varied occurrence in food flavors and their valuable organoleptic characteristics. Even though heterocyclic aroma chemicals are found only in minute amounts in foods, their powerful odors and low odor thresholds, as expressed by high φ values (see below), make them key in boosting flavors and fragrances.

The main heterocyclic aroma chemicals are oxygen-, sulfur- and nitrogen-containing rings. The oxygen-containing heterocyclic aroma chemicals belong to the oxirane, furan, pyran and oxepine groups. The sulfur-containing aroma chemicals belong to the thiophene family and, together with nitrogen, to the thiazole and dithiazine systems. Nitrogen-containing aroma chemicals belong to pyrrole, indole, pyridine, quinoline, pyrazine and quinoxaline systems and, together with sulfur, as mentioned above, the thiazole and dithiazine families. This article will describe the oxygen-containing heterocyclic aroma chemicals.

Due to the highly potent odor character of a majority of the heterocyclic compounds used in flavors and fragrances, the term φ Value will be used for some of the materials described. A relatively new concept, φ Value gives a better understanding of the odor intensity of a single molecule, taking into consideration its molecular mass (MM), analogous to ε value in UV/VIS data of particular molecules.

φ Value of a molecule is defined as the following:[1]

$$\varphi = \frac{MM \times 10^3}{\text{Threshold (ppm)}}$$

The oxygen-containing heterocyclic aroma chemicals belong to the following groups:

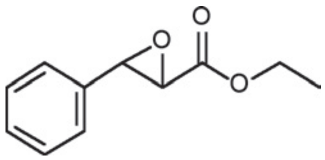
1. oxiranes (epoxides)
2. furans and hydrofurans
3. pyrans
4. oxepines

Oxiranes

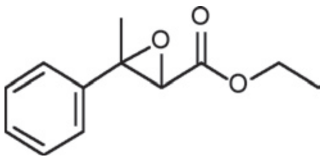
The epoxide-containing aroma chemicals are mainly glycidate esters, such as ethyl 3-phenylglycidate, ethyl 3-methyl-3-phenylglycidate and methyl anisylglycidate. Ethyl 3-phenylglycidate (16) (F-1), so-called "aldehyde C-16 special," is an artificial aroma chemical possessing a fruity, strawberry, fermented honey odor. It is applied mainly in fruit flavors (strawberry) and ice cream flavorings.[2] Ethyl 3-methyl-3-phenylglycidate (17) (F-2), so-called "aldehyde C-16" (strawberry aldehyde), is also an artificial aroma chemical with fruity,

*This is a part of a chapter that appeared in *Chemistry and Technology of Flavors and Fragrances*. M. Zviely, Edit., D.J. Rowe, Blackwell Publishing Ltd. (2004).

Ethyl 3-phenylglycidate (so-called aldehyde C16 special; 16) **F-1**

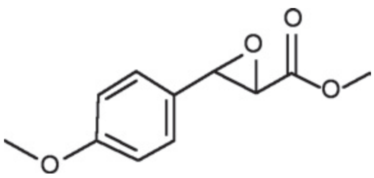


Ethyl 3-methyl-3-phenyl-glycidate (so-called aldehyde C16; 17) **F-2**



strawberry, fermented honey odor. It is applied to fruit flavors and ice cream flavorings such as strawberry, raspberry, cherry, grape, apricot and peach. Methyl anisylglycidate (18) (F-3), or methyl (4-methoxyphenyl) oxiranecarboxylate, has a fresh aromatic odor, fruity and somewhat reminiscent of berries.

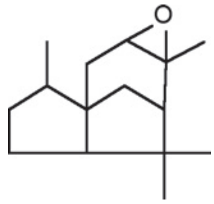
Methyl anisylglycidate (Anoxirane; 18) **F-3**



The synthesis of glycidates generally is accomplished using the Darzens condensation method (Darzens-Claisen reaction; glycidic ester condensation) (F-4).[3]

Other epoxides include α-cedrene epoxide (19) (F-5), which has a precious woody, tobacco and sandalwood odor that is reminiscent of ambergris. This epoxide is applied in soap compound and is useful in artificial patchouli.

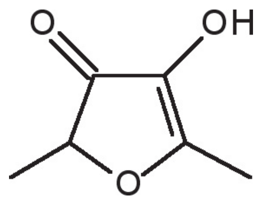
α-Cedrene epoxide (αndrane; 19) **F-5**



Furans and Hydrofurans

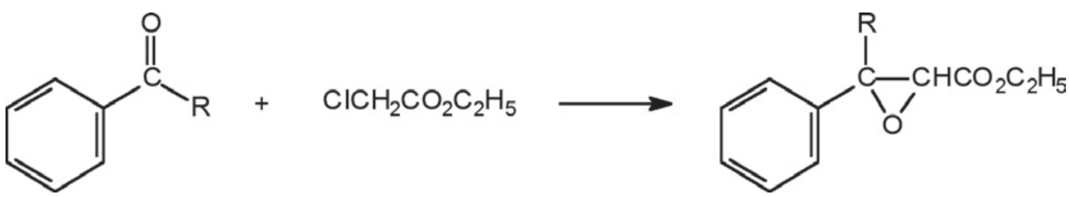
The five-membered ring of heterocyclic aroma chemicals containing only one oxygen atom consists of furans together with dihydrofurans and tetrahydrofurans. One of the most important molecules is 4-hydroxy-2,5-dimethyl-3(2H)-furanone (20) (F-6), also known by the name of Furaneol. This material occurs in strawberry, pineapple and in beef. It has a sweet, caramel-fruity (pineapplelike) odor and flavor with fried-meat aspects. 4-Hydroxy-2,5-dimethyl-3(2H)-furanone is applied mainly to fruity (strawberry) meat flavorings and ice cream formulations.

4-Hydroxy-2,5-dimethyl-3(2H)-furanone (Furaneol, Fraision; 20) **F-6**

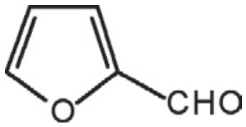


Another important molecule is furfural (furan-2-carboxaldehyde; 21) (F-7), occurring in almost every food flavor: dairy, cereals, roasted products, meat, etc. Furfural has a sweet caramel-like, nutty, baked bread, almond odor and flavor, and is applied in cereal, as well as roasted and meat flavorings.

Darzens condensation **F-4**

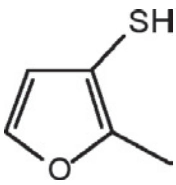


Furfural (21), φ 3.2 x 10^4 **F-7**



2-Methylfuran-3-thiol (22) (F-8), which occurs in meat and coffee, has a sulfurous coffee and meatlike odor and flavor upon extreme dilution. It is used mainly in roasted and meat flavorings.

2-Methylfuran-3-thiol (Oxycyclothione; 22) **F-8**



4-Hydroxy-2,5-dimethyl-3(2H)-furanone (20) can be synthesized by dimerization of methylglyoxal and cyclization of the diol-dione intermediate (F-9).[4] Another important route to 4-hydroxy-2,5-dimethyl-3(2H)-furanone (20) is shown in F-10.[5]

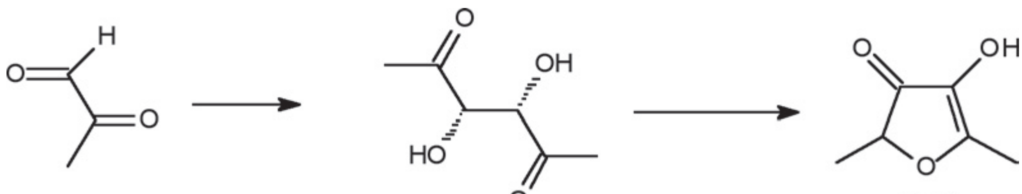
Furfural (21) is produced from plant residues that are rich in pentoses, such as bran, by treatment with dilute sulfuric acid, followed by steam distillation (F-11).[6] 2-Substituted furans are available also by direct reaction, e.g., 2-acetylfuran, and this is also true for pyrroles and thiophenes.

2-Methyltetrahydrofuran-3-one (dihydro-2-methyl-3(2H)-furanone; 23) (F-12) occurs in coffee, roasted filberts, beer, rum, roasted almond and potato chips. It has a breadlike, buttery top note, and a nutty and astringent flavor with a slight creamy almond nuance. 2-Methyltetrahydrofuran-3-one is used in roasted flavorings: almond, rum, cocoa, brandy and caramel.

2-Pentylfuran (24) (F-13) occurs in many foodstuff, such as fruits, vegetables, meat, roasted products, coffee, cocoa, tea and fish. The material has a green, waxy aroma with musty cooked caramellic nuances, and is used in fruit, vegetable, coffee, nut and bread flavorings.

Furfuryl mercaptan (Coffee Mercaptan, 2-furan-methanethiol; 25) (F-14) is found in coffee, chicken, beef, and grilled and roasted pork. Upon dilution it

Production of 4-hydroxy-2,5-dimethyl-3(2H)-furanone (20) through dimerization of methylglyoxal and cyclization of the diol-dione intermediate **F-9**



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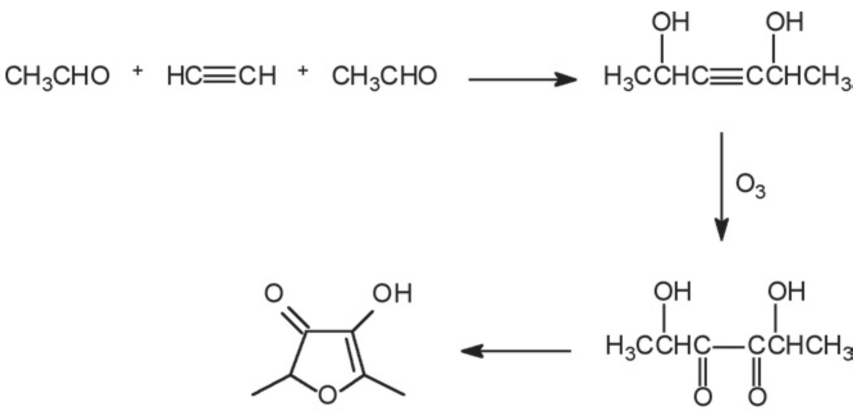
Another important route to 4-hydroxy-2,5-dimethyl-3(2H)-furanone (20) **F-10**



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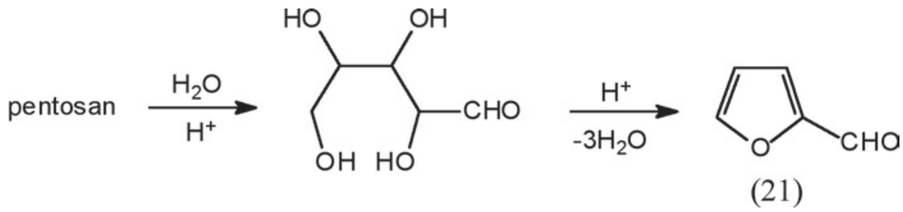
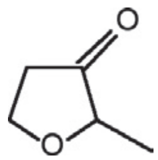
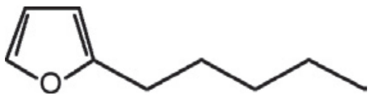
Production of furfural (21) from pentosan treated with dilute sulfuric acid, followed by steam distillation **F-11**



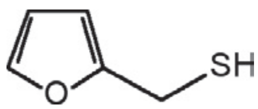
2-Methyltetrahydrofuran-3-one (Coffee Furanone; 23) **F-12**



2-Pentylfuran (24), φ 2.3 x 10^7 **F-13**



Furfuryl mercaptan (Coffee Mercaptane; 25), φ 2.6 x 109 **F-14**



has a strong coffeelike, sulfurous, roasted onion and garlic odor and flavor. Furfuryl mercaptan is used mostly in coffee, mocha and ice cream flavorings. It can be synthesized from furfuryl alcohol by reaction with thiourea in the presence of hydrogen chloride. The resulting S-furfurylisothioronium chloride is cleaved with sodium hydroxide to produce furfuryl mercaptan (25) (F-15).[7]

Some possible synthetic pathways toward 2-methyltetrahydrofuran-3-one (23) are shown in F-16.[8]

1,4-Cineole (1,4-epoxy-p-menthane; 26) (F-17) is a tetrahydrofuran derivative possessing fresh, cooling, camphoraceous, minty and eucalyptuslike odor, with terpenelike and green nuances.

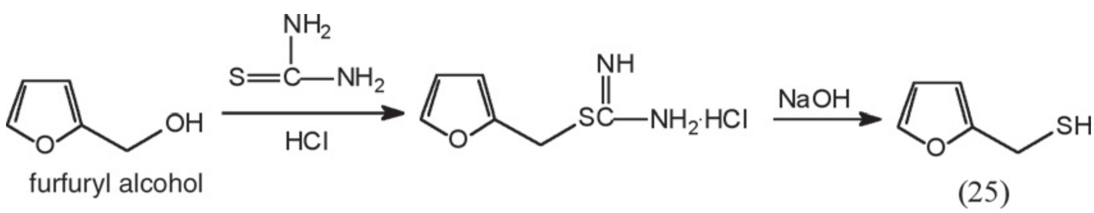
An interesting heterocyclic oxygen-containing molecule is dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan (27) (F-18), also known as Ambroxan. This molecule, which has a tetranorlabdanolic system, possesses a strong amber odor, enriched by dry and woody nuances. This compound is very useful as a modifier for all floral fragrance formulations. Its synthesis is shown in F-19.[9]

Another tetrahydrofuran worth mentioning is theaspirane (1-oxaspiro[4.5]-2,6,10,10-tetramethyl-6-decene; 28) (F-20). Theaspirane occurs in blackberry, raspberry, grape, teas, passion fruit and guava, and possesses a cooling minty, camphoraceous flavor, with an herbal and piney nuance. Theaspirane is used in tea, guava, mint, berry, citrus and grapefruit flavor formulations and in minty, herbal and woody fragrance compounds.

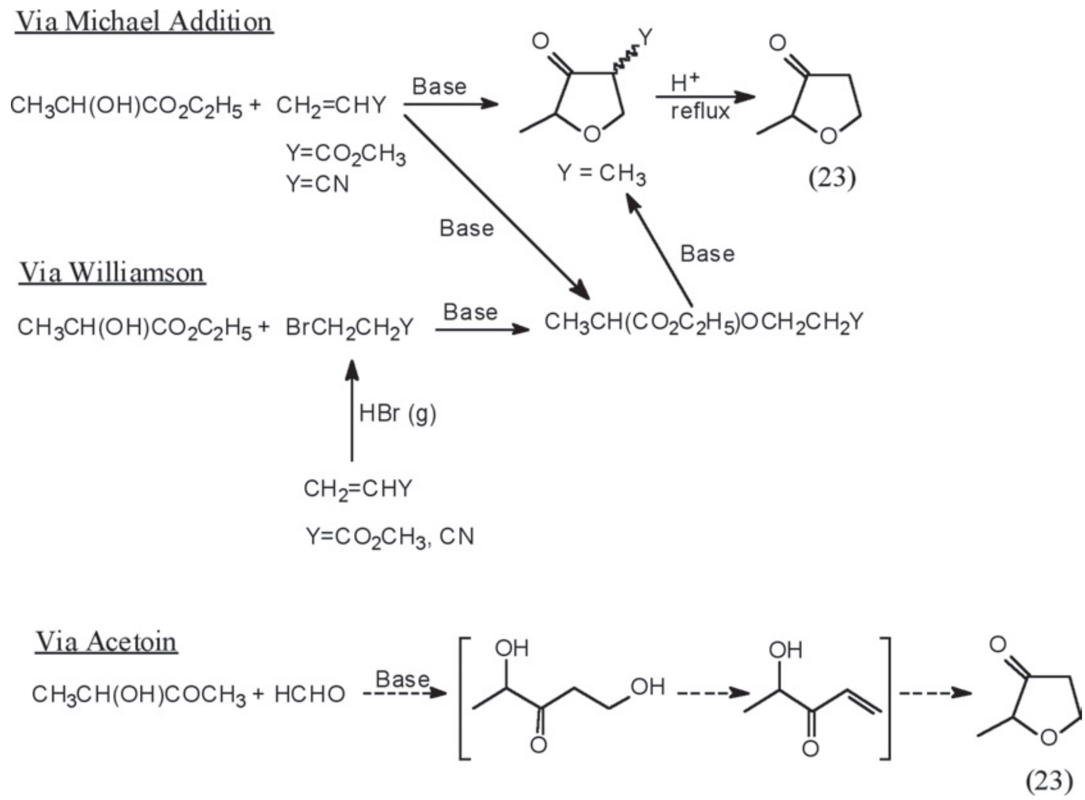
Pyrans

Three examples will be shown from this group of oxygen-containing heterocycles. 1,8-Cineole, or eucalyptol (29) (F-21), is a molecule occurring in many essential oils,

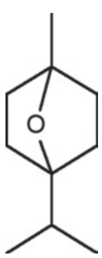
The production of furfuryl mercaptan through the synthesizing of furfuryl alcohol **F-15**



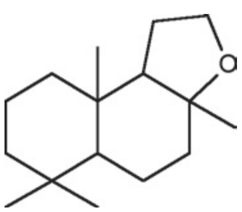
Possible synthetic pathways toward 2-methyltetrahydrofuran-3-one (23) F-16



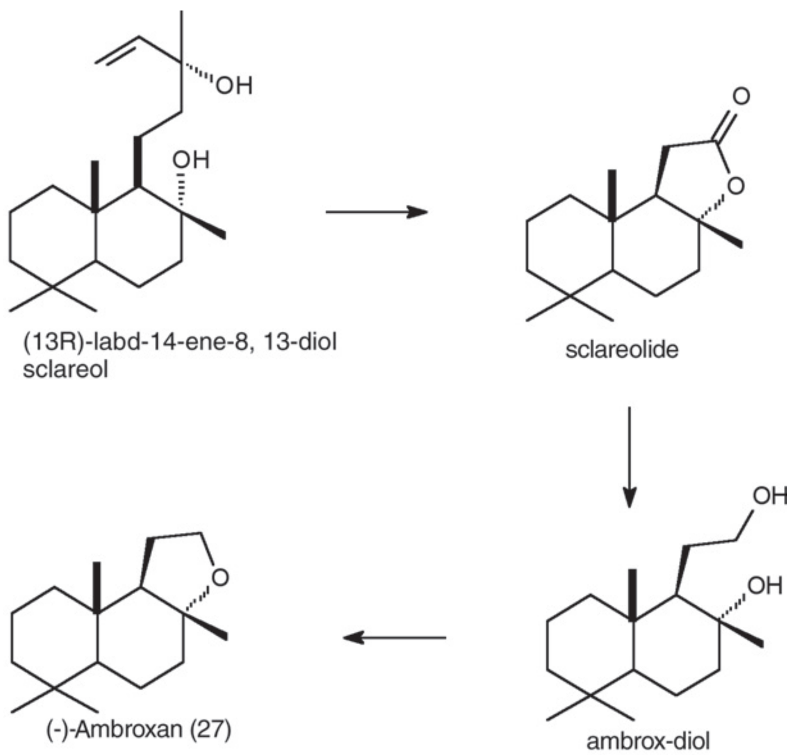
1,4-Cineole (26) F-17



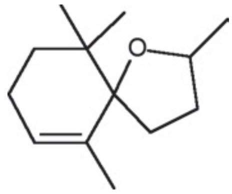
Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan (Ambroxan, Ambermor, L'ambroxin; 27), (+) isomer φ 7.88x10^{8}, (-) isomer φ 9.09x10^{7} F-18



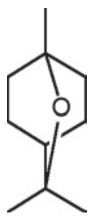
The synthesis of dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan (Ambroxan, Ambermor, L'ambroxin; 27) F-19



Theaspirane (Spiroxide; 28) **F-20**



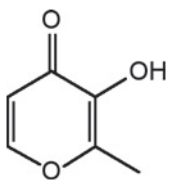
Eucalyptol (1,8-cineol; 29) **F-21**



including *Eucalyptus globulus*. Eucalyptol has a fresh, strong eucalyptuslike camphoraceous and minty odor, and a cooling taste. It is used in candies, toothpaste and chewing gum.

Maltol (30) (F-22), or 3-hydroxy-2-methyl-4-pyrone, can be found in strawberry, bread, dairy products, cocoa, coffee, barley, filberts and peanuts. It has a sweet, aromatic, caramellic cooked fruitlike odor, with fruit and berry notes. Maltol is used in fruit flavors and roasted food formulations such as strawberry, pineapple, caramel, brown sugar, brandy and butterscotch. The synthetic pathway for another maltol derivative, ethyl maltol, is shown in F-23. This one-pot

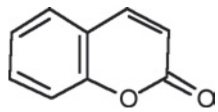
Maltol (30) **F-22**



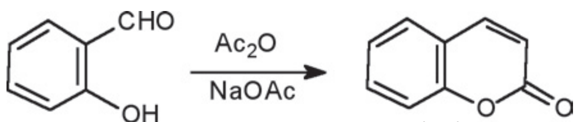
process starts with α-ethylfurfuryl alcohol and is treated with chlorine to produce 4-chloro-6-hydroxy-2-ethyl-2*H*-pyran-3(6*H*)-one, which doesn't need to be isolated and can be converted to ethyl maltol by aqueous hydrolysis.[10]

Coumarin (2*H*-1-benzopyran-2-one; 31) (F-24) occurs in bilberry, raspberry, mint oil, tea, soybean, cloudberry, matsutake and chicory. It has a sweet aromatic, somewhat coconutlike odor and flavor. It is used in sweet aromatic compounds for functional perfumery and in sweet aromatic, spicy formulations for candies and cookies. Coumarin is prepared from salicylic aldehyde and acetic anhydride, in the presence of sodium acetate (F-25).[11]

Coumarin (31) **F-24**



Production of coumarin (31) from salicylic aldehyde and acetic anhydride, in the presence of sodium acetate **F-25**



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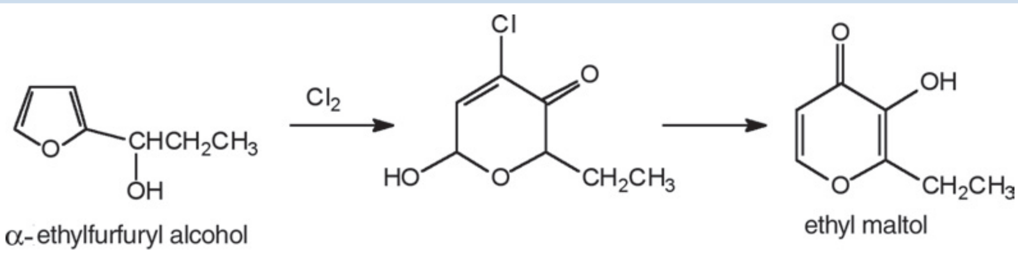
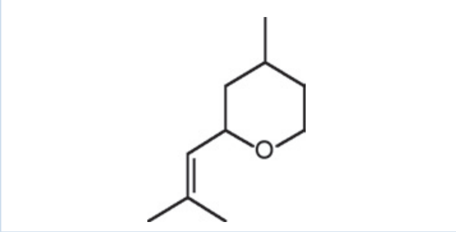
2-Isobutenyl-4-methyltetrahydropyran (rose oxide; 32) (F-26) is found in essential oils such as rose and geranium. It is described as floral, roselike, fruity, green, vegetative and herbal, and is applied in floral, roselike fragrances. One of the syntheses of rose oxide is shown in F-27. This route begins by acetylation of citronellol, followed by allylic bromination of citronellyl acetate. Elimination of hydrobromic

The synthetic pathway for ethyl maltol **F-23**



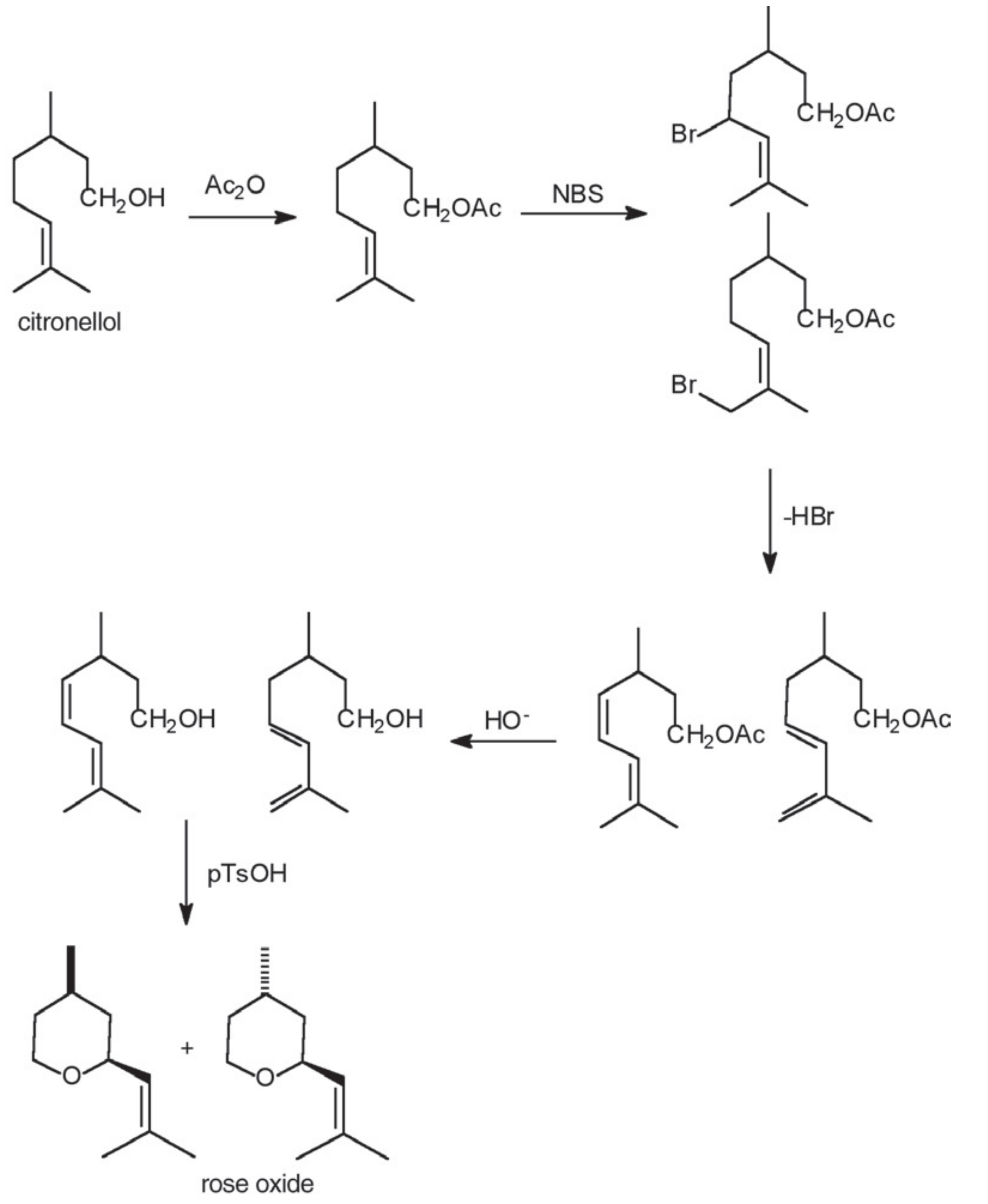
Rose oxide (32) **F-26**



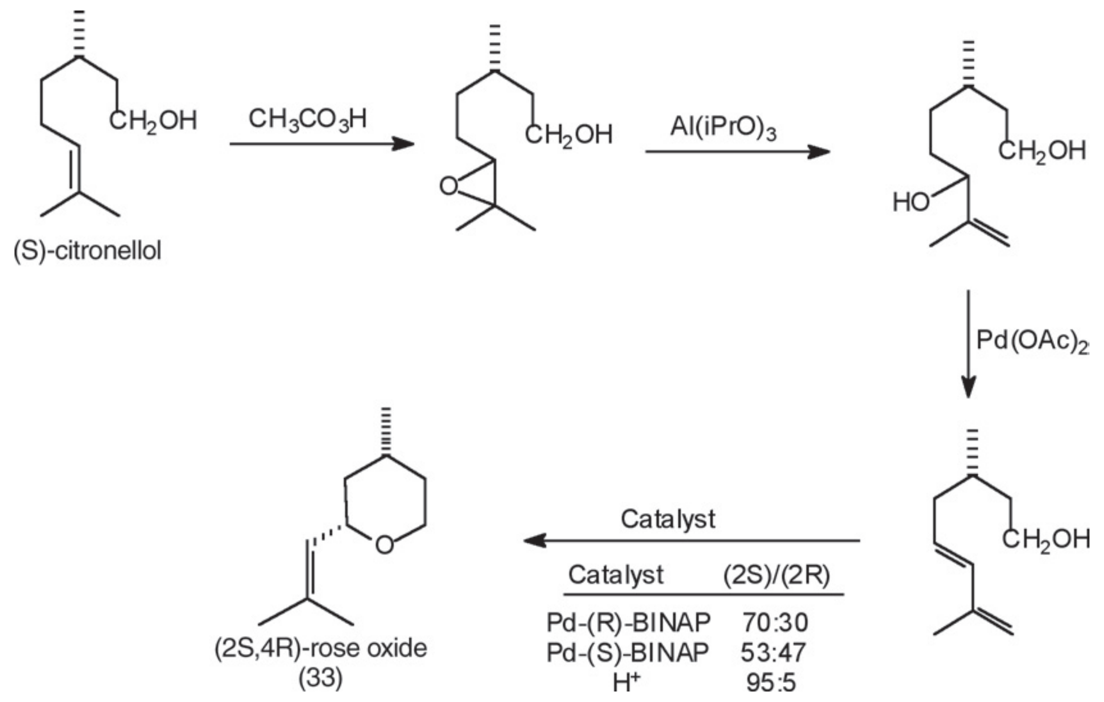
acid produces two acetylated dienes. Hydrolysis of theses dienes produces the alcohol dienes, which undergoes cyclization to yield *cis*- and *trans*-rose oxide isomers.[12]

The stereoselective synthesis of all four stereoisomers of rose oxide has been achieved starting from optically active citronellol.[13] Stereochemistry at the 4-methyl group is controlled by the chirality of the 3-methyl group in citronellol. For example, (4R)-rose oxide is obtained from (S)-citronellol and the (4S)-enantiomer from (R)-citronellol, respectively.

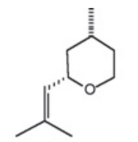
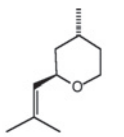
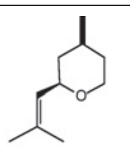
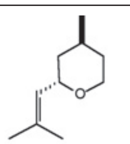
One of the syntheses of rose oxide (32) **F-27**



The stereoselective synthesis of all four stereoisomers of rose oxide **F-28**

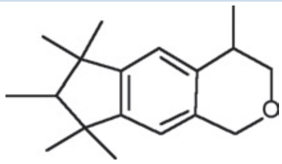


The φ value and odor description of four stereoisomers of rose oxide **T-1**

Rose oxide diasterioisomer	φ Value	Odor description
 (2S,4R)- rose oxide (33)	3.08×10^{7}	Floral-green; clean, light, rose, green, diffusive, strong
 (2R,4R)- rose oxide (34)	9.64×10^{5}	Floral-green; green herbal (minty), fruity
 (2R,4S)- rose oxide (35)	3.08×10^{6}	Herbal-green-floral; hay green, earthy, heavy
 (2S,4S)- rose oxide (36)	1.93×10^{6}	Herbal-green-floral; fruity, herbal rose, citrus (bitter peel)

Relative stereochemistry at the 2-position is controlled by the choice of catalyst for the cyclization in the last stage. Acid catalyzed cyclization of the (S)-diene produces (2S,4R)-rose oxide (33) with 95 percent *cis*-selectivity, whereas Pd-(S)-BINAP gives a 1:1 mixture of (2R,4R)- (34) and (2S,4R)- (33) isomers. The (2R,4R)-rose oxide (34) is obtained by column chromatographic separation of this mixture. Similarly, (2R,4S)- (35) and (2S,4S)- (36) rose oxide have been prepared from (R)-citronellol (F-28). T-1 shows that (2S,4R)-rose oxide (33) has the higher φ value of all isomers. The odor character of (2S,4R)-rose oxide (33) is greatly superior to the other isomers in terms of both quality and quantity.[14]

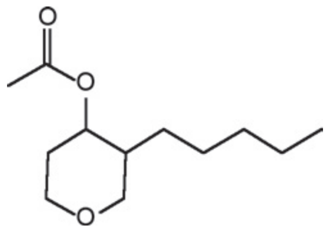
4,6,6,7,8,8-Hexamethyl-1,3,4,6,7,8-hexahydrocyclopenta[g]benzopyran (Galaxolide, Abbalide, Musk 50; 37) **F-29**



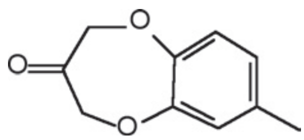
Another important pyran aroma chemical is 4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopenta[g]benzopyran (37) (F-29). This molecule has a powerful and clean musk odor characteristic resembling that of macrocyclic musks. This benzopyran is used in a wide range of perfume compounds, such as soap, perfumery, household products, cosmetics and alcohols.

The synthesis of 4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopenta[g]-benzopyran (37) starts from 1,1,2,3,3-pentamethylindane, which is prepared by cycloaddition of *tert*-amyl alcohol to α-methylstyrene. The pentamethylindane is hydroxylated with propylene oxide in a Friedel-Crafts reaction, using aluminum chloride as a catalyst. Ring closure of the resulting 1,1,2,3,3-pentamethyl-5-(β-hydroxyisopropyl)indane is accomplished with paraformaldehyde and a lower aliphatic alcohol via

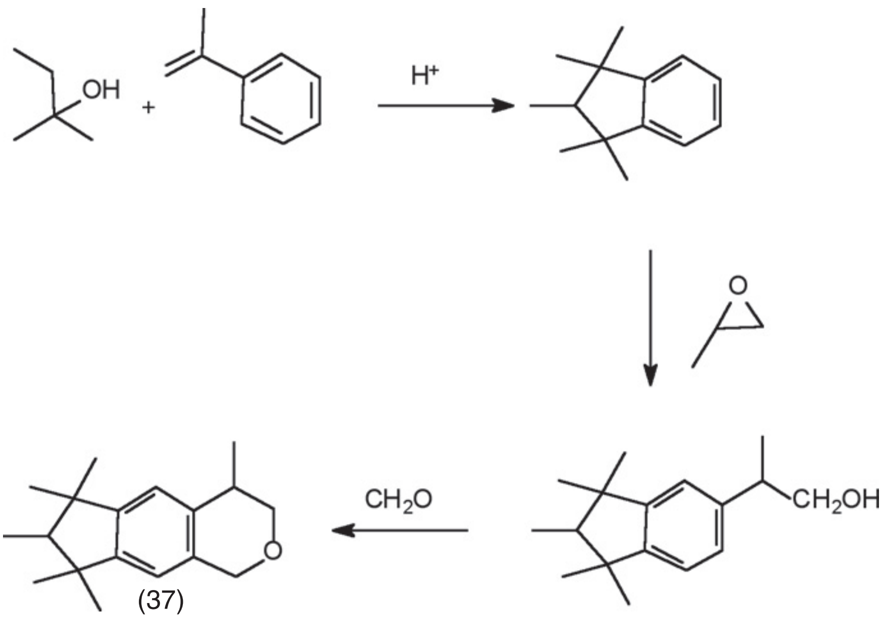
Tetrahydro-3-pentyl-2H-pyran-4-yl acetate (Jasmine Acetate; 38) **F-31**



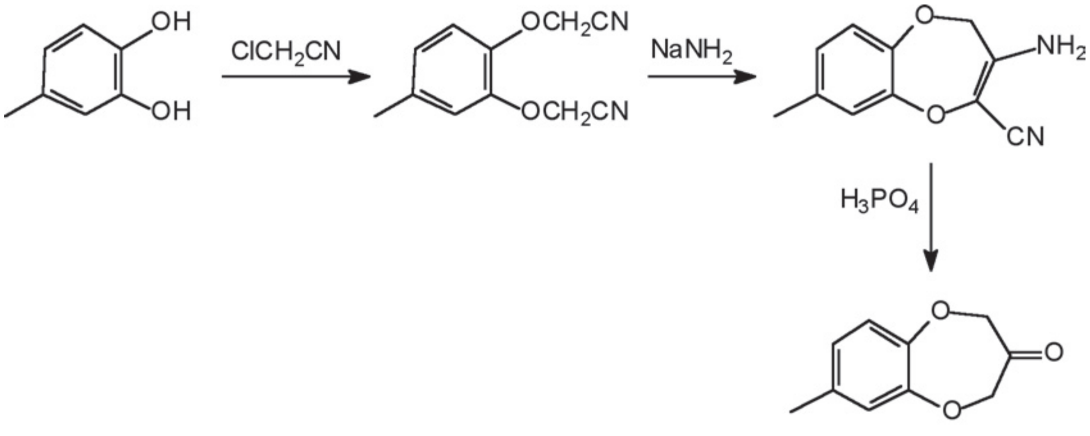
7-Methyl-3,4-dihydro-2H-benzodioxepin-3-one (Calone, Oxalone, Ganone, Aquamor; 39) **F-32**



Synthesis of 4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopenta[g]-benzopyran (37) **F-30**



7-Methyl-3,4-dihydro-2H-benzodioxepin-3-one (39) is synthesized from 4-methylcatechol **F-33**



(39)

the acetal, or with paraformaldehyde and a carboxylic acid anhydride via the acylate (F-30).[15,16]

Tetrahydro-3-pentyl-2H-pyran-4-yl acetate (38) (F-31) has an oily, plantlike, herbaceous lavender, slightly mushroom odor, with a floral tealike jasmine note. This material is prepared from octene, formaldehyde and acetic acid in the Prins reaction, and is obtained among other components. Jasmine Acetate is an economic substitute for jasmonates in floral compounds.

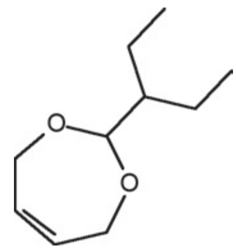
Oxepins

An important seven-membered ring is 7-methyl-3,4-dihydro-*2H*-benzodioxepin-3-one (39) (F-32), a fragrance ingredient having a fresh oceanic, floral odor, which is also diffusive with watermelon notes. This molecule is used in fragrances as an extremely valuable component for marine notes in compounds for alcoholic and cosmetic perfumery.

7-Methyl-3,4-dihydro-*2H*-benzodioxepin-3-one (39) is synthesized from 4-methylcatechol (F-33).[17] Condensation of 4-methylcatechol with two moles of chloroacetonitrile produces the double cyanomethyl ether, which cyclizes using sodium amide to obtain the α-aminocyano unsaturated dioxepine ring. Hydrolysis of this disubstituted ring in the presence of phosphoric acid yields the desired 7-methyl-3,4-dihydro-*2H*-benzodioxepin-3-one (39).

4,7-Dihydro-2-isopentyl-2-methyl-1,3-dioxepin (40) (F-34) has a citrus, herbal-floral odor, with notes of lemon, neroli and jasmine. It is used in a range of fragrances for cosmetic and functional perfumery for its herbal-floral note.

4,7-Dihydro-2-isopentyl-2-methyl-1,3-dioxepin (Karotin; 40) **F-34**



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