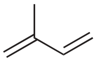
TERPENOIDS

1. Introduction

1.1. Definitions. Terpenoids (sometimes also referred to as isoprenoids) are defined as materials whose molecular structures contain carbon backbones that are made up of isoprene (2-methylbuta-1,3-diene) (**1**) units. Therefore, the number of carbon atoms in any terpenoid will be a multiple of five, although degradative and other metabolic processes can affect this. In such cases, the overall structure will still indicate the substance's terpenoid origins and they will still be considered to be terpenoids.



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The first terpenoids to be studied in detail contained two isoprene units and were called monoterpenoids. Consequently, the basic nomenclature system is based on 10 carbon units rather than the 5 of isoprene and this is shown in Table 1.

Carotenoids are a specific class of tetraterpenoids as will be explained below. Steroids are a subgroup of triterpenoids and are defined as those that produce Diels's hydrocarbon when distilled from zinc dust. They are covered in a separate chapter (qv).

The term "terpene" was originally applied to the hydrocarbons found in turpentine and is sometimes applied more generally to any unsaturated terpenoid hydrocarbon. Usually, it will indicate an unsaturated monoterpenoid hydrocarbon, the higher nonoxygenated homologues being referred to as sesquiterpenes, diterpenes, etc.

The junction between isoprene units is not random, but most often is formed through the so-called head-to-tail coupling as shown in Figure 1. In certain cases, a tail-to-tail coupling occurs, also shown in Figure 1. This coupling is a characteristic feature of the central coupling used to form the carotenoids and the triterpenoid squalene (**2**) (see Fig. 4) which is the precursor for the steroids. The explanation of the coupling systems lies in the biosynthesis as described in Figures 3 and 4.

After formation of a linear skeleton, the chain may be cross-linked to produce rings and further classification of terpenoids is based on the resulting ring systems. Some common ring systems are shown in Figure 2. A clear listing of the known ring systems can be found in the book by Devon and Scott (1). Both linear and cyclic structures can be functionalized by the introduction of oxygen or other heteroatoms. As the IUPAC names of terpenoids are often rather unwieldy, trivial names are in common use. The original trivial names usually indicate a natural source of the material, eg, pinene from pine species. Semisystematic names are often based on the ring system and the oxygenation pattern. For example, 1-methyl-4-isopropylcyclohexane is referred to as *p*-menthane and numbered as shown in Figure 2.

Greek letters are sometimes used to indicate the order in which the isomers were discovered or their relative abundance in an essential oil and sometimes to refer to the location of the double bond in isomeric olefins.

Terpenoids can be analyzed by the usual methods. For the volatile members of the family, gas chromatography–mass spectrometry (gc–ms) is a particularly useful tool. In laboratories (eg, those in the major fragrance companies), which are accustomed to analyzing mixtures of volatile terpenoids, gc–ms is the major analytical technique employed and such laboratories will have extensive libraries of mass spectra of terpenoids to assist in this. However, the mass spectral fragmentation patterns of closely related terpenoids are often so similar as to render definitive identification by ms alone, impossible. For these materials and those for which there is no reference (eg, compounds newly isolated from nature), nuclear magnetic resonance (nmr) spectroscopy is the analytical tool of choice. Physical techniques, eg, density, refractive index, and optical rotation, are relatively inexpensive and prove useful in quality control.

Being secondary metabolites, individual terpenoids may be common to a number of species or may be produced by only one organism. Comparison of the terpenoids produced by a plant will give an indication of which metabolic pathways operate in it and can therefore be used to aid in classification of species, a procedure known as chemical taxonomy.

1.2. Biosynthesis. The two key building blocks for terpenoids in nature are isopentenyl pyrophosphate (**3**) and pentenyl pyrophosphate (**4**). Coupling of these two isomeric materials under enzymic control, as shown in Figure 3, gives geranyl pyrophosphate (**5**), the precursor for all monoterpenoids. Subsequent addition of isopentenyl pyrophosphate (**3**) to geranyl pyrophosphate (**5**) in a similar way, produces farnesyl pyrophosphate (**6**), and hence sesquiterpenoids. Further repetition of the process leads on to the diterpenoids and higher.

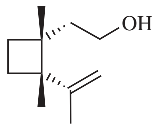
The mechanism of the tail-to-tail coupling is shown in Figure 4. In this example, a molecule of farnesyl pyrophosphate (**6**) reacts with one of nerolidyl pyrophosphate (**7**) forming the tail-to-tail link between the two chains. Reductive elimination of the pyrophosphate residue by enzyme bound TPNH gives squalene (**2**), which is the precursor for, *inter alia*, the steroids.

The linear terpenoid precursors can undergo many different cyclization processes. The longer the chain, the more different possibilities there are for cyclized structures. The cyclization processes are essentially carbocation reactions, with the initial cation being formed by loss of the pyrophosphate residue from the parent linear structure. Some cyclization processes for monoterpenoids are shown in Figure 5 and for sesquiterpenoids in Figure 6.

1.3. Biological Significance. Terpenoids play many roles in nature. Some are key to metabolic processes, eg, vitamin A (retinol) in sight, vitamin E (tocopherol) as an antioxidant, and vitamin D_2 (calciferol) in calcium transport. Chlorophyll also contains a terpenoid component in its structure.

The volatility of the lower terpenoids makes them particularly suitable for signaling between living organisms, as they can be carried through the air from the donor to the recipient of the signal. Such materials (semiochemicals) can carry messages between organisms of the same species (pheromones) or of different species (allelochemicals).

Some examples of terpenoid pheromones are grandisol (**8**), which is a sex attractant for the male boll weevil; neocembrene-A (**9**), which is a trail pheromone of the Australian termite species *Nasutitermes exitiosus*; and lineatin (**10**), which is the aggregation pheromone of *Trypodendron lineatum*. *d*-Limonene (**11**) is an example of an allomone (an allelochemical that benefits the sender) in that it is produced by the Australian tree *Araucaria bidwilli* and repels termites that would otherwise attack it. Nepetalactone is produced by catmint (*Nepeta cataria*) and is a mixture of two isomers (**12**) and (**13**), with the former being the major. It is insect repellent, but also induces grooming and rolling behavior in all felines, from domestic cats to lions and tigers. An account of pheromone induced behavior will be found in the book by Wyatt (2).



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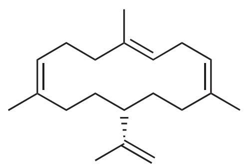

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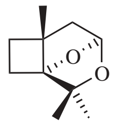

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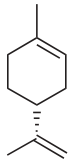

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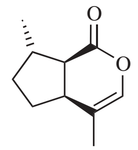

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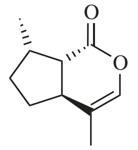

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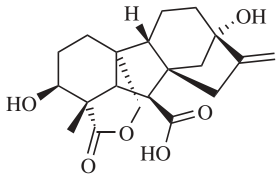

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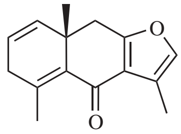

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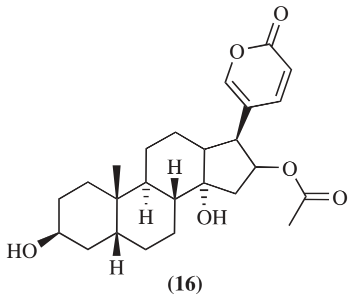

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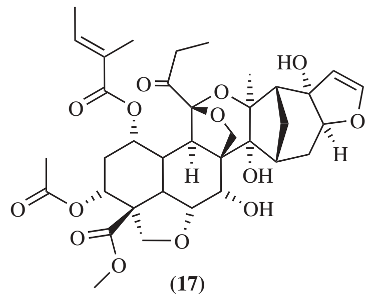

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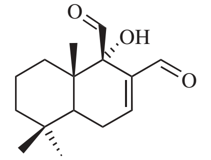

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Terpenoids are also used as hormones. In mammals, the role of steroids is vital and will be discussed in the article on steroids (see STEROIDS). The diterpenoid giberellic acid [77-06-5] (**14**) is a plant growth hormone.

Many plants produce defence secretions that form protective barriers when the structure of the plant is damaged and exposed to air. Examples include pine rosin and rubber. In some cases, the exudates contain antibacterial or antifungal components as is the case, eg, with myrrh. This is the resin of the shrub *Commiphora abyssinica* that contains a number of such compounds including the eudesmane derivative (**15**).

Defensive chemicals also include antifeedants that make the organism unattractive or toxic to would be predators. Examples include Bufotalin (**16**), which is produced by toads; azadirachtin (**17**), which is produced by *Melia azadirachta* and also by the Indian neem tree, *Azadirachta indica*; and warburganal (**18**) is produced by plants of the genus *Warburgia*.

1.4. Industrial Significance.

Terpenoids have been used as solvents and as ingredients in perfumery, cosmetics, medicine, and other applications throughout recorded history. Many are still extracted from natural sources, but modern chemistry also allows for production from petrochemical sources and from readily available terpenoid feedstocks, such as turpentine. The terpenoids used directly from nature as fragrance ingredients are usually extracted in the form of essential oils and these are covered in a separate chapter. The highest tonnage uses of terpenoids are as resins, solvents, fragrances and vitamins. The total volume of terpenoids used as fragrance ingredients is of the order of 50,000 tonnes/annum with a value in the order of $500M. Only a few of them (eg, menthol, geraniol and its esters, linalool and its esters, and citronellol and its esters) exceed 5000 tonnes/annum in volume. Since the market for vitamin E is more than double this figure, and it and related vitamins share a synthetic route with the others, the economic effect of the vitamin market on the fragrance terpenoid market is significant. Major suppliers are DSM (Switzerland), BASF (Germany), Kuraray (Japan), Millennium (USA) (now owned by Lyondell), and DRT (France). The fragrance house International Flavors and Fragrances (IFF) is also a significant supplier of terpenoid perfume ingredients through its factories in the United States and Spain. Indian and Chinese suppliers are increasingly important. Lower tonnage use would include food colors and medicines. Rubber is a polyisoprenoid, but will not be discussed here as it is covered in a separate chapter. Price increases in gum turpentine from China in late 2005 are having a very significant effect on pricing in the entire terpenoid market.

2. Major Industrial Synthetic Routes

The so-called rose alcohols (geraniol, nerol, citronellol, and linalool) together with the corresponding aldehydes citral and citronellal, lie at the heart of the major production routes in terpenoid chemistry as shown in Figure 7. In this figure, the basic feedstocks are contained in ellipses and it can be seen that there is a balance between natural (hence, renewable) and petrochemical feedstocks.

The most important natural feedstock is turpentine. It can be produced by tapping suitable conifers, a process that involves making an incision in the bark and collecting the exudate in cups. Such turpentine is called gum turpentine.

Wood turpentine is extracted mainly from tree stumps but the major source of turpentine is known as crude sulphate turpentine (CST) as it is a by-product of the Kraft paper process.

The composition of turpentine varies depending on the species of tree from which it is produced and plantations may contain a variety of species and chemotypes, therefore the composition of crude turpentine is subject to variation. The largest production is sulfate turpentine from the southeastern United States, which amounts to well over 100,000 tonnes/annum and in 2005 was priced under $2/gal. Second most important is Chinese gum turpentine, which is produced in about half that volume. Other significant sources include gum turpentine from Russia, Brazil, Portugal, India, and Mexico, and sulfate turpentine from Canada. These last few each being of the order of 10,000 tonnes/annum. Scandanavia and Chile are now also significant suppliers of CST.

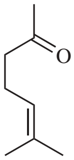
Fractional distillation of crude sulfate turpentine (CST) gives a "lights" fraction (1–2%), which contains *inter alia* some lower boiling sulfur compounds, such as methyl mercaptan, dimethyl sulfide, and dimethyl disulfide. This is followed by the α-pinene fraction (60–70%), and then the β-pinene (20–25%). The next fraction is referred to as "dipentene" (3–10%) and contains racemic limonene together with other *p*-menthadienes. Then, after the pine oil fraction (3–7%) comprising ethers and alcohols, comes a fraction (1–2%) containing the shikimates anethole [104-46-1] and estragole (also known as methylchavicol) [104-67-0], and the sesquiterpene hydrocarbon, β-caryophyllene [87-44-5].

The distillation removes much of the sulfur-containing impurity originating from the Kraft process but, for many applications, further desulfurization is necessary and a variety of techniques are employed for this (3–10).

The menthadienes are used in the manufacture of terpene resins and menthol. Pine oil is used in ore flotation, as a disinfectant, and as a fragrance ingredient, particularly in inexpensive cleaning products. The ethers anethole and estragole find use as flavor ingredients.

Turpentine from the western United States contains 12–43% of 3-carene. Indian turpentine contains ~60% of 3-carene together with ~15% of the sesquiterpene longifolene. Turpentine from Sweden, Finland, CIS, and Austria also all contain 3-carene. The two isomeric pinenes are, by far, the most important of these natural feedstocks, as far as conversion to other terpenoids is concerned.

The major petrochemical routes to the rose alcohols and the corresponding aldehydes are directed toward linalool and citral. This is partly for historic reasons as the earliest syntheses involved 6-methylhept-5-en-2-one (**19**) [110-93-0] as a key intermediate and the early industrial syntheses were developed from these academic routes. The other reason is that the major companies manufacturing terpenoids from petrochemical feedstocks are all producers of vitamins A, E and K, and citral is key to the synthesis of these.



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2.1. From α-Pinene. The most significant syntheses starting from α-pinene (**20**) are those of linalool (**23**), geraniol (**24**), nerol (**25**), and α-terpineol (**26**). These and some others are shown in Figure 8.

Linalool and geraniol are produced from α-pinene by the Millennium Company at their site in Colonel's Island, Georgia (11). Their process starts with hydrogenation of α-pinene using a special catalyst that gives a high selectivity for *cis*-pinane (**21**). This is necessary because the trans isomer is relatively unreactive in the subsequent reaction step. Autoxidation followed by catalytic hydrogenation of the intermediate hydroperoxide gives pinanol (**22**) with a cis/trans ratio of 75/25. The pinanols are distilled, and then pyrolyzed to give linalool (**23**). This pyrolysis, first reported by Ohloff and Klein (12), is run at relatively low conversion in order to minimize the formation of plinols (alcohols formed by ene cyclization of linalool). Before conversion to geraniol, the linalool must be freed of impurities boiling close to the former. This isomerization is carried out over a vanadate catalyst (13), which process is improved by first converting the linalool to its borate ester (14). A description of the mechanism of the reaction has been published (15). This gives a mixture of geraniol (**24**) and nerol (**25**) in a purity of 99% and with a geraniol/nerol ratio of 68/32. Geraniol is the preferred isomer and can be separated from nerol by distillation, though many commercial grades of "geraniol" are actually geraniol–nerol mixtures (see entry under geraniol and nerol in Section 4.2.1).

Treatment of α-pinene with aqueous acid gives α-terpineol (**26**), whereas anhydrous acid gives camphene (**27**). The former is used as pine oil, a disinfectant and a fragrance ingredient. The use of β- and USY-zeolites as catalysts for the hydration of α-pinene and camphene leads to more selective and less polluting processes (16,17). Pyrolysis of α-pinene gives a mixture containing dipentene (**28**) and ocimenes. Some further information is included later under the heading "ocimenes." Epoxidation of α-pinene gives pinene oxide (**29**), which is isomerized to give campholenic aldehyde (**30**), an important feedstock for a variety of sandalwood materials.

2.2. From β-Pinene. Figure 9 shows some of the major routes to terpenoids starting from β-pinene (**31**). The pyrolysis of β-pinene to produce myrcene (**32**) was first introduced by Glidden (SCM) in 1958 (18). The process is carried out at 500°C and gives a product containing 75–77% myrcene. Hydrochlorination of myrcene in the presence of a copper catalyst gives initially predominately linalyl chloride (**33**), which then isomerizes to give a mixture of linalyl (**33**) (2–4%), geranyl (**34**) (50–55%), and neryl (**35**) (40–50%) chlorides (19,20). The crude product from this reaction also contains bornyl and α-terpinyl chlorides as a consequence of traces of unchanged β-pinene in the pyrolysis product. These two, together with traces of other chlorinated impurities, make purification of the ultimate downstream products difficult. Bush, Boake, and Allen (BBA) and Union Camp both developed processes similar to those of Glidden and these are now owned and operated by the fragrance house International Fragrances and Flavors (IFF) at their site in Jacksonville, Florida. Direct hydrolytic conversion of the halides to the rose alcohols is complicated by a side reaction giving unacceptably high levels of α-terpineol (**26**) and so instead, the halides are converted to the corresponding acetates, (**36–38**), respectively, (or formates) by the addition of sodium acetate or sodium formate with a phase-transfer catalyst (PTC) (21,22). Saponification of the acetates or formates gives the alcohols and sodium acetate or formate for recycle. Fractionation of the crude alcohol mixture gives both geraniol (**24**) and nerol (**25**) as products, usually as mixtures; high-purity products are made by further distillation. This overall scheme suffers from three disadvantages. The levels of impurities create difficulties in preparing high-quality rose alcohols. The trace chlorinated compounds are a particular issue as they must be removed to below ppb levels. Second, the wastewater generated by the process must be treated and this adds to cost. Third, β-pinene is less abundant than its α-isomer, and hence less readily available and more expensive. The two isomers can be interconverted (23), but the thermodynamic equilibrium composition contains 96% α-pinene and only 4% β-pinene. Furthermore, α-pinene boils at 156°C at 760 mmHg and β-pinene at 165°C at 760 mmHg. This would make any attempt to produce β-pinene by equilibration of α-pinene, separation of the two by distillation and recycling of the α-pinene, very expensive in energy terms.

Prins reaction of β-pinene with formaldehyde gives the alcohol nopol (**39**) and its acetate [35836-72-7] (**40**) is used as a fragrance ingredient. Base-catalyzed addition of diethylamine to myrcene gives geranyl diethyl amine (**41**), which is converted to menthol (**42**) as described below.

2.3. From Methylbutenol and Methoxypropene.

The Swiss pharmaceutical company Hoffmann-La Roche started the first major synthetic production of terpenoids in 1957. The plant and processes now belong to DSM. The basic process has been refined over the last four decades and the current scheme is as shown in Figure 10 (24).

The addition of acetylene to acetone under Favorski–Babayan conditions gives methylbutynol (**43**) which can be hydrogenated to methylbutenol (**44**) using a Lindlar catalyst (25–29). When this is treated with methyl propenyl ether (the vinyl ether of acetone), trans-etherification takes place to give (**45**), which then undergoes a Claisen–Cope rearrangement to give methylheptenone (**19**) (30,31). Addition of acetylene produces dehydrolinalool (**46**), a key intermediate for subsequent conversions. For example, Lindlar hydrogenation gives linalool (**23**) and treatment with methyl propenyl ether gives ψ-ionone (**47**) the precursor for many ionones and vitamins.

Citral can also be produced from dehydrolinalool via a Meyer–Schuster rearrangement (32,33), rearrangement using a vanadate catalyst (34), or by rearrangement of its acetate in the presence of copper salts (35,36), trisilylorthovanadates (37), or vanadium catalysts in the presence of silanols (38) and yields of up to 90% can be obtained (39,40).

2.4. From Isobutylene, Acetone, and Formaldehyde. The process operated by Badische Anilin und Soda Fabrik (BASF) is shown in Figure 11. In the first chemical step, formaldehyde and acetone react under influence of a basic catalyst to produce methyl vinyl ketone. This then undergoes an ene reaction with isobutylene to give the methylheptenone isomer, 6-methylhept-6-en-2-one [10408-15-8] (**48**). Both reaction steps can be carried out in a single process operation lending further elegance to the overall scheme (41–43). Isomerization of this material to methylheptenone (**19**) is straightforward (44,45) and unconverted isobutylene and acetone can be recycled to the process, thus making it commercially feasible (46,47). Addition of acetylene to (**48**) and (**19**) gives the isomeric alcohols (**49**) and (**46**), respectively (48). When these materials are used for the preparation of ionones and vitamins, the *iso*-dehydrolinalool (**49**) offers an advantage in that it is more easily protonated than dehydrolinalool (**46**) and this helps in the cyclization reaction (49–51).

2.5. From Isoprenol. BASF have developed an ingenious process for the manufacture of citral as shown in Figure 12. The ene reaction of isobutylene with formaldehyde gives *iso*-prenol (**50**) (41,52). Isomerization of *iso*-prenol over a palladium catalyst gives prenol (**51**) (53). Oxidation of prenol using air as oxidant over a silver on silica catalyst, followed by isomerization, gives prenal (senecioaldehyde) (**52**) (54–56). Prenal and prenol are then heated together to form the enol ether (**53**), which undergoes a Claisen−Cope reaction to give the aldehyde (**54**) (57,58). This aldehyde is drawn twice in the figure to show its relationship to the compound from which it was formed and also to citral (**55**), which it produces through a Cope rearrangement (59–61). A similar process is operated by the Japanese company Kuraray.

2.6. From Isoprene. Hydrochlorination of isoprene [78-79-5] (**1**) produces prenyl chloride (**56**), together with some of the isomeric 3-chloro-3-methylbut-1-ene (**57**), the ratio between the two depending on reaction conditions. The former undergoes S_N2 reactions while the latter prefers S_N2', hence both alkylate preferentially at the primary carbon atom. Therefore, treatment of the chlorides with acetone in the presence of base, gives methylheptenone [110-93-0] (**19**), as shown in Figure 13 (62). This is the basis of a process developed by Rhone−Poulenc in which a phase-transfer catalyst is used to assist in the alkylation of acetone (63–65). A similar process is operated by Kuraray (66). Linalool produced in this way can be isomerized to geraniol using an orthovanadate catalyst (67).

Research into terpenoid chemistry continues as new structures are identified and academics and manufacturers strive to find ever more efficient synthetic methods. With the current accent on sustainability, catalytic methods have received particular attention and recent advances in this field have been reviewed by Swift (68).

While manufacturers of fine chemicals work to chemical and physical specifications, organoleptic specifications are also of crucial importance in the flavor and fragrance industry. Tolerances around analytical parameters are often greater than those around odor standards. The organoleptic quality is important in determining price and so, in most instances, various grades of a material will exist with very different prices. To the individual purchaser, the price will vary depending on the amount bought. Overall volume of use is determined by a combination of price and quality. For this reason and because both prices and volumes vary depending on prevailing economic conditions, all figures quoted are illustrative only and are based on average patterns over the decade 1995–2005.

In the following monographs on individual terpenoids, the following abbreviations are used for their physical properties.

Abbreviation	Property
CAS Registry No.	Chemical Abstracts registry number
formula	Empirical formula
FW	Formula weight
mp	melting point
bp	boiling point
d^{20}	density
${n_D}^{20}$	refractive index
$[\alpha]_D$	specific rotation[a]
vp	vapor pressure
vd	vapor density
fp	flash point
ait	auto ignition temperature
lel	lower explosive limit
tpa	metric tonnes per annum

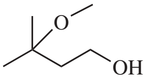
[a] If both enantiomers are found, the absolute value will be reported and it is to be understood that the laevo-enantiomer will have a negative value and the dextro-enantiomer will be positive. If only one enantiomer is described, the direction as well as the absolute value of rotation will be stated.

3. Hemiterpenoids

Hemiterpenoids are used mostly as intermediates in the synthesis of other terpenoids. The main exceptions are some esters of prenol that impart fruity top-notes in perfumery. Prenyl acetate (**58**, R = Me) and benzoate (**58**, R = Ph) are the two most important of these.

In addition to the methods described above, prenol (**51**) can be prepared from methylbutynol (**43**) by rearrangement to prenal (**52**) using a titanium alkoxide/copper chloride catalyst (69,70) followed by selective hydrogenation using a ruthenium rhodium tris(*m*-sulfonatoyl)phosphine trisodium salt (TPPTS) catalyst (71,72). However, it is more usual to prepare the prenyl esters by nucleophilic substitution of a carboxylate anion on prenyl chloride [503-60-6] (**56**) which, in turn, is available through hydrochlorination of isoprene [78-79-5] (**1**). This hydrochlorination often employs copper ions as catalysts. These processes are shown in Figure 14.

3-Methyl-3-methoxybutan-1-ol (MMB) (**59**) is one hemiterpenoid that has grown very significantly in importance since its launch in the 1980s to an annual production in the order of 12,000 tonnes in 2005. It is produced from isobutylene by Kuraray, has a mild camphoraceous odor, and has uses as a solvent in air fresheners and in a wide variety of cleaning applications.



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4. Monoterpenoids

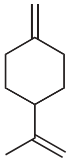
4.1. Monoterpenoid Hydrocarbons.

Linear Monoterpenoid Hydrocarbons. *Myrcene*

Myrcene	
CAS Registry No.	[123-35-3]
formula	$C_{10}H_{16}$
FW	136.23
bp	93°C at 9.33 kPa (70 mmHg)
bp	167°C at 101.3 kPa (760 mmHg)
d^{20}	0.7880 g/cm^3
$n_D{}^{20}$	1.4692
vp	7 mmHg (20°C)
vd	4.7 v air

Myrcene (**32**) is also known as β-myrcene and its systematic name is 7-methyl-3-methylene-1,6-octadiene. It is very widespread in nature. This is not surprising as it is formed in nature by elimination from geranyl pyrophosphate, the precursor of all monoterpenoids. It can also be formed by elimination of water from alcohols such as geraniol or linalool, and so its presence in natural extracts may be as an artifact (formed during the extraction process) rather than as a genuine plant metabolite.

Myrcene is not extracted commercially from natural sources. It can be prepared by dimerization of isoprene (**1**) (73–75), but the major industrial production route is by pyrolysis of β-pinene (**31**). This is carried out at 550−600°C (18) and gives a mixture containing 75−77 wt% myrcene together with limonene (**11**) (~9%), ψ-limonene (**60**) and other products of isomerization and dimerization. The crude material is usually used directly in further conversions. Its tendency to polymerize means that purification by distillation must be carried out carefully under reduced pressure, moderate temperatures, and preferably in the presence of a polymerization inhibitor. Inhibitors are also required if the material is to be stored or shipped.

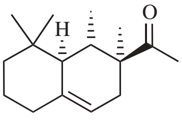


(60)

Myrcene has minimal use *per se* in fragrances, but it is of great importance as a feedstock for other fragrance ingredients. Consequently, its production volume is large (~30,000 tpa). The major materials made from myrcene are nerol, geraniol, linalool, citronellol, dimethyloctanol, citronellal, hydroxycitronellal, menthol, citral, and the ionones and methylionones. The role of myrcene in the commercial production of each of these will be discussed below under the relevant headings. Rhone–Poulenc have a process for addition of methyl acetoacetate to myrcene, catalyzed by rhodium tris(*m*-sulfonatoyl)phosphine trisodium salt (TPPTS), to give geranyl acetone, which is an intermediate for production of phytol and tocopheryl acetate (vitamin E) (76). Myrcene contains a 1,3-diene function, and is therefore capable of undergoing Diels-Alder reactions. This chemistry provides several other important fragrance ingredients. The production of two of these is shown in Figure 15.

Addition of myrcene to acrolein gives the aldehyde (**61**), which is known under trade names such as Myrac Aldehyde, Empetal, Acropal, and Vernaldehyde [37677-14-8] and has a natural, green, and aldehydic odor.

The aluminium chloride catalyzed addition of 3-methylpentan-3-ene-2-one (the aldol product of 2-butanone and acetaldehyde) gives the monocyclic ketone (**62**). Cyclization of this ketone using 85% phosphoric acid gives a mixture containing the isomeric bicyclic ketones (**63–65**), which was first commercialized by IFF under the trade name Iso E Super [54464-57-2] (71–79). The success of the material was such that it is now a major fragrance ingredient and, following expiry of the IFF patents, is being produced by a number of different companies under different tradenames. Later research (80) showed that the most organoleptically important component of the mixture was not one of the major components, but a minor, rearranged product (**66**) and this led to the development of an analogue known as Georgywood (**67**) (81).



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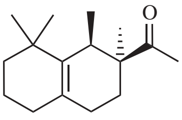


(67)

Lyral (**68**) [31906-04-4] is another important fragrance ingredient produced from myrcene. This hydroxy aldehyde has a sweet, light, floral (muguet) odor with excellent tenacity and radiance. More than 2000 tonnes are produced annually and sold under a variety of tradenames, such as Kovanol, HydroxyEmpetal, and Landolal in addition to the original, Lyral (82,83).

The most obvious synthesis of Lyral is to hydrate the double bond of Myrac Aldehyde (**61**) under acidic conditions. However, the aldehyde group is sensitive to acid and undergoes an intramolecular Prins reaction if this is attempted. It is therefore necessary to protect the aldehyde function prior to hydration, and this can be done by formation of an enamine or oxazolidine that can be removed by hydrolysis when hydration is complete (84,85).

Another approach is to react myrcene with sulfur dioxide under pressure to give myrcene sulphone (**69**). This can then be hydrated using sulfuric and the sulfur dioxide removed from the intermediate (**70**) by vapor-phase pyrolysis to produce myrcenol [543-39-5] (**71**). The sulfur dioxide can be recovered and recycled and the myrcenol purified by distillation. Diels-Alder addition of this with acrolein then produces Lyral (69,86). This synthetic sequence is shown in Figure 16.

Citronellene

Citronellene	
CAS Registry No.	[2436-90-0]
formula	$C_{10}H_{18}$
FW	138.25
bp	158–159°C at 101.3 kPa (760 mmHg) {(*R*)-enantiomer}
bp	155–156°C at 96 kPa (720 mmHg) {racemate}
d^{18}	0.761 g/cm^3 {racemate}
$n_D{}^{18}$	1.4385
$[\alpha]_D$	8.7°

Citronellene (**72**), 2,6-dimethylocta-2,7-diene or 3,7-dimethylocta-1,6-diene, is also commonly known as dihydromyrcene and occasionally as β-linalolene. It does not occur in nature and has no use *per se*, but is a valuable feedstock for a range of fragrance ingredients.

Hydrogenation of either α-pinene (**20**) or β-pinene (**31**) gives pinane (**21**) and pyrolysis of this produces citronellene (87). Any optical activity in the pinane is transferred to the citronellene (88). Typically, the pyrolysis is carried out at 550–600°C and the crude product contains ~50–60% citronellene, which can then be purified by fractional distillation.

The highest tonnage product from citronellene is dihydromyrcenol (**73**), which has a powerful, fresh lime-like odor and rose to prominence after its use to impart a new masculine freshness to the fragrances Drakkar Noir and Cool Water. Dihydromyrcenol is prepared by acid-catalyzed hydration of citronellene as shown in Figure 17 (89). The more electron-rich, trisubstituted, double bond reacts preferentially with acids and selectivity for the desired product is high. In some processes, formic acid is used as the catalyst, in which case, the intermediate product is a mixture of dihydromyrcenol and its formate. The formate is easily hydrolyzed by base (90). The mixture of the alcohol and formate is also used in perfumery under the name Dimyrcetol. Sulfuric acid is also used as a catalyst for the hydration (91). Concentrated sulfuric acid adds to the double bond and subsequent dilution with water causes hydrolysis of the intermediate sulfate ester. This gives a simpler process and a higher yield of dihydromyrcenol.

The fully saturated alcohol, tetrahydromyrcenol [18479-57-7] (**74**) is also a useful fragrance ingredient.

When dihydromyrcene is treated with formic acid at higher temperatures (50°C) than that required to produce dihydromyrcenol and its formate, an unexpected rearrangement occurs to produce α,3,3-trimethylcyclohexane methanol (**75**), known as cyclodemol, and its formate (92). The product is formed by cyclization of dihydromyrcene to the cycloheptyl carbonium ion, which rearranges to give the more stable cyclohexyl compound (93). The formate ester, α,3,3-trimethylcyclohexane methanol formate [25225-08-5] (**76**), is a commercially available product known as Aphermate, used to impart herbal, woody, ozone, and fruity notes in fragrance. Similarly, treatment of citronellene with sulfuric acid in refluxing acetic acid for 6–8 h, produces the acetate (**77**), which has both floral and musky notes and is known as Rosamusk or Cyclocitronellene Acetate. A series of musk compounds has been found, based on Rosamusk, but with an ethereal spacer between the cyclodemol fragment and the ester function. The most significant of these is Helvetolide (**78**), which is produced by Firmenich. Oxidation of cyclodemol gives the ketone known as Herbac (**79**), which has herbal, woody, minty, and fruity notes. All of these conversions are shown in Figure 18. Stereochemistry has an effect on the odor of all of these products and mechanistic studies have included stereochemical factors (94).

The acid-catalyzed addition of methanol to citronellene gives methoxycitronellene (**80**) in good yield (95). Epoxidation of the remaining double bond with peracetic acid gives 2-methoxy-7,8-epoxy-2,6-dimethyloctane (**81**) which, on hydrogenation using a nickel catalyst, gives primarily methoxycitronellol (**82**). If a small amount of base is added to the hydrogenation, the product is a mixture of 60% of the secondary alcohol, Osyrol or methoxyelgenol (**83**) and 40% of methoxycitronellol (**82**) (96,97). Osyrol [41890-92-0] possesses a woody, floral odor characteristic of sandalwood and has become established as a fragrance ingredient. This reaction sequence is shown in Figure 19.

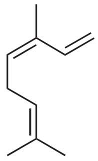
Figure 20 shows some other known chemistry of citronellene and dihydromyrcenol, in this case producing citronellol or hydroxycitronellal. However, these routes are not the major ones in use.

Epoxidation of dihydromyrcenol followed by hydrogenation gives hydroxycitronellol (**84**). Dehydration of this gives a mixture of citronellol (**85**) and an isomer, α-citronellol (**86**), which can easily be isomerized to citronellol (95). Oxidation of the primary alcohol function of diol (**84**) gives hydroxycitronellal (**87**) (qv).

Aluminium alkyls react by the Ziegler reaction with the least substituted double bond to give the tricitronellyl aluminium compound. Oxidation of the intermediate compound then produces the tricitronellyl aluminate (**88**), which is easily hydrolyzed with water to give citronellol (98,99). If the citronellene is optically active, optically active citronellol can be obtained (100).

(−)-Citronellol is a more valuable fragrance compound than the racemate. Although the Ziegler reaction provides a more direct method for producing primary alcohols, aluminium alkyl chemistry requires special handling and is fairly costly. The by-product aluminium salts usually require some treatment for disposal (101). For these reasons, this process has not been realized commercially.

Ocimenes. Both geometric isomers of β-ocimene (**89**) occur extensively in nature, whereas the isomers of α-ocimene (**90**) and allo-ocimene (**91**) and (**92**) occur in a more limited range of species. None of them are extracted or used commercially to a significant extent.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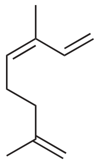
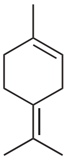

(90)

A mixture of 4- *trans*-6-*cis*-alloocimene [7216-56-0] (**91**) and 4-*trans*-6-*trans*-allo-ocimene [3016-19-1] (**92**) can be obtained by pyrolysis of α-pinene (**20**) (qv). Hydrochlorination of this mixture [637-84-7] followed by hydrolysis of the chlorides with aqueous base gives a mixture of three isomeric allo-ocimenols [18479-54-4] (**93–95**), which has been used as a fragrance ingredient under the trade name Muguol (102). More important is the mixture, in approximately equal proportions, of tetrahydromyrcenol [18479-57-7] (**96**) and tetrahydrolinalool [78-69-3] (**97**), which is formed from it by hydrogenation as shown in Figure 21. This latter mixture is sold as Tetrahydromuguol and has a lily of the valley fragrance as its name suggests.

Oxidation of allo-ocimene in the presence of a catalyst produces a polymeric peroxide (**98**), which can be thermally isomerized to produce allo-ocimene diepoxide [3765-28-4] (**99**) in 70–75% yield (103). The diepoxide has been used in the manufacture of resins and as an acid scavenger for halogenated solvents (104).

Monocyclic Monoterpenoid Hydrocarbons. Dipentene. The terms dipentene or *p*-menthadienes are used to indicate a mixture of monoterpenoid hydrocarbons and ethers usually produced as by-products from processes for the manufacture of other terpenoids. The major source is as a by-product from the manufacture of synthetic pine oil. Important components of dipentene are limonene (**28**), terpinolene (**100**), α-terpinene (**101**), camphene (**27**), 1,4-cineole (**102**), 1,8-cineole (**103**), α-pinene (**20**), *p*-cymene (**104**), 2,4(8)-*p*-menthadiene (**105**), α-phellandrene (**106**), β-phellandrene (**107**), and γ-terpinene (**108**). The *p*-menthadienes are isomerized to an equilibrium mixture by either strong acid or strong base. The equilibrium composition from acid catalyzed isomerization has been determined as 53.3% α-terpinene (**101**), 13.8% γ-terpinene (**108**), 29.8% 2,4(8)-*p*-menthadiene (**105**), and 3.1% 3,8-*p*-menthadiene (**109**) (105).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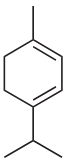
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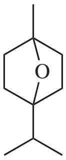
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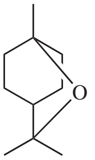
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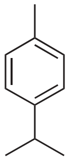
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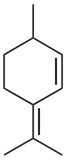
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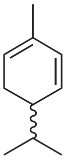
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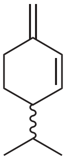
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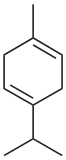
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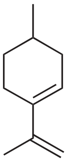

(109)

Dipentene is a good solvent for paints, varnishes, and enamels that contain synthetic resins, particularly phenolic resins. It is also used as an antiskinning agent and as a wetting agent in the dispersion of pigments. The solvency of dipentene for rubber and its swelling and softening properties make it useful in rubber reclaiming and in the processing of natural and synthetic rubbers. Dipentene is also formulated into a variety of cleaners similar to pine oil cleaners. About 25,000–30,000 tonnes are produced annually under tradenames, such as Solvenol.

Hydrogenation of a mixture of the *p*-menthadienes produces a mixture of *cis*-*p*-menthane [6069-98-3] and *trans*-*p*-menthane [1678-82-6]. Oxidation to a mixture of *p*-menthane hydroperoxides gives a useful polymerization initiator used in the rubber industry. A (−)-limonene and (+)-β-phellandrene mixture from sulfate turpentine has been used to produce terpene resins.

Limonene

Limonene

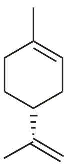
CAS Registry No.	[138-86-3]
CAS Registry No.	[7705-14-8] (racemate)
CAS Registry No.	[5989-27-5] (*R*)-(+)-enantiomer
CAS Registry No.	[5989-54-8] (*S*)-(−)-enantiomer
formula	$C_{10}H_{16}$
FW	136.23
bp	110°C at 13.33 kPa (100 mmHg)
bp	176.5°C at 101.3 kPa (760 mmHg)
d^{20}	0.8411 g/cm^3
$n_D{}^{20}$	1.4730
$[\alpha]_D$	126.3°
vp	<3 mmHg (14.4°C)
vd	4.7 v air
lel	6.1

Limonene is very widespread in nature. The richest sources are the oils contained in the peel of citrus fruits, which contain levels up to 90%. The major source of limonene is indeed from citrus peel, largely as a by-product of the fruit juice industry. Citrus fruit produce the (*R*)-enantiomer (**11**) and so the bulk of commercially available limonene is dextrorotatory. The laevorotatory enantiomer is available, but in much more restricted supply and at a higher price. (*R*)-Limonene production exceeds 50,000 tonnes/annum (106). Traditionally, the price was low, eg, \$0.8/kg in 1985 (82), but the need for readily biodegradable solvents drove it up in the mid-1990s. For example, by July 1995 it had risen to \$6.60/kg (107). It has since fallen back to ~\$2.5/kg in 2005 (108). Such price swings are not helpful to those who use limonene as a feedstock for synthesis. (*R*)-Limonene is used as such in perfumery. It has little odor value of its own, but contains trace odoriferous impurities originating from the oil, mostly orange, from which it was extracted (109,110). One important use for (*R*)-(+)-limonene is its use as a chiral starting material for the synthesis of (*R*)-(−)-carvone [6485-40-1] (**242**) (qv).

As mentioned above, limonene of varying degrees of optical purity is available from turpentine and from various turpentine cracking processes and finds use as a solvent and in the manufacture of terpene resins. It is used for aqueous cleaning compositions using carefully selected and proportioned surface-active agents and a coupling agent, usually a glycol or glycol ether (111). They are meant to replace halogenated hydrocarbon solvents and are biodegradable. Another process has produced a multiuse cleansing agent from (+)-limonene that is basically harmless to human skin (112). An application for printed circuit board cleaners has also been developed using dipentene and limonene with emulsifying surfactants to facilitate removal by rinsing in water (113).

Limonene (**11**) can be isomerized to terpinolene [586-62-9] (**100**) using liquid SO_2 and a hydroperoxide catalyst (*tert*-butyl hydroperoxide (TBHP)) (114). Another method uses a specially prepared *ortho*-titanic acid catalyst with a buffer, such as sodium acetate (115). A selectivity of ~70% is claimed at ~50% conversion when run at 150°C for 4 h. The chemistry of limonene has been reviewed by Thomas and Bessière (106).

Phellandrenes. Both α-phellandrene [99-83-2] (**106**) and β-phellandrene [555-10-2] (**107**) occur widely in essential oils. (−)-α-Phellandrene can be isolated from *Eucalyptus dives* oil. A particularly rich source of (*S*)-(−)-β-phellandrene is the lodgepole pine, *Pinus contorta*. (*S*)-(−)-β-Phellandrene [6153-17-9] (**110**) is found at a level of ~2% in the southeastern United States turpentine and processing the turpentine gives a fraction containing ~28% (−)-β-phellandrene and 62% (−)-limonene [5989-54-8] (**111**). The (−)- β-phellandrene in the fraction can be selectively hydrochlorinated to piperityl chloride (116) as the first step in an l-menthol synthesis, details are given below in the entry on menthol.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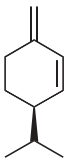
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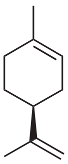
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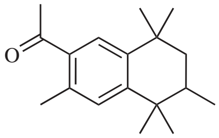

(112)

p-Cymene

***p*-Cymene**

CAS Registry No.	[99-87-6]
formula	$C_{10}H_{14}$
FW	134.22
bp	110°C at 13.33 kPa (100 mmHg)
bp	177°C at 101.3 kPa (760 mmHg)
d^{20}	0.8570 g/cm^3
$n_D{}^{20}$	1.4905
vp	1.5 mmHg (20°C)
vp	3.7 mmHg (37.7°C)
vd	4.62 v air
ait	436°C
lel	5.6%

p-Cymene (**104**) has been identified in >1800 essential oils and plant extracts. It is produced by vapor-phase dehydrogenation of *p*-menthadienes over catalysts, such as chromia–alumina (117). Disproportionation of *p*-menthadienes over a Cu–Ni catalyst gives a mixture of *p*-menthane and *p*-cymene (118). It has use as a solvent and heat-transfer fluid and as the starting material for the polycyclic musk known as Fixolide or Tonalide (**112**) (119). It is also possible to synthesize this musk by first dehydrogenating *p*-cymene to α-*p*-dimethylstyrene (120,121).

Bicyclic Monoterpenoid Hydrocarbons. *α-Pinene*

α-Pinene

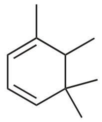
CAS Registry No.	[80-56-8]
CAS Registry No.	[508-32-7] racemate
CAS Registry No.	[7785-70-8] (*R*)-(+)-enantiomer
CAS Registry No.	[7785-26-4] (*S*)-(−)-enantiomer
formula	$C_{10}H_{16}$
FW	136.23
mp	−64°C
bp	89°C at 13.33 kPa (100 mmHg)
bp	156°C at 101.3 kPa (760 mmHg)
d^{20}	0.8595 g/cm^3
$n_D{}^{20}$	1.4658
$[\alpha]_D$	51.9°
vp	3 mmHg (20°C)
vd	4.7 v air
ait	255°C

α-Pinene (**20**) is very widespread in nature. The most significant sources commercially are, of course, the pine, fir, and spruce species that are used to produce turpentine, either gum or sulfate, as described above. The distillate from sulfate turpentine is sufficiently pure for further conversion.

By far, the most important use of α-pinene is as a feedstock for production of other terpenoids and a wide variety of fragrance ingredients. Some of the more important conversions are shown in Figure 8. α-Pinene undergoes thermal isomerization to ocimene and alloocimene, acid-catalyzed isomerization to camphene, hydration to pine oil/terpineol, and polymerization to terpene resins. Its epoxide is a useful intermediate and hydrogenation with subsequent oxidation leads on to the rose alcohols; linalool, nerol, and geraniol.

By using a supported palladium catalyst (23,122), α-pinene can be isomerized to an equilibrium mixture containing ∼4% β-pinene (**31**). This equilibration opens up the possibility of production of the latter from the former. The amount of β-pinene in equilibrium with α-pinene is low, but the use of an efficient fractional distillation column with continuous processing make the process feasible albeit energy intensive.

Pyrolysis of α-pinene, usually at ∼450°C, gives a mixture of dipentene and, by a retro-2 + 2 cleavage, *cis*- β-ocimene (**89**) (123,124). The latter rearranges to give ∼40–50 wt% of the two allo-ocimene isomers, ie, 4-*trans*-6-*cis*-allo-ocimene [7216-56-0] (**91**) and 4-*trans*-6-*trans*-allo-ocimene [3016-19-1] (**92**) (10). The mechanistic pathways for this rearrangement have been determined (125,126). Redistillation of the crude pyrolysate leads to the formation of allo-ocimene dimers and ∼10–15% (α) and (β) pyronene, (**113**) and (**114**), respectively, which are formed by cyclization of allo-ocimene. The pyrolysis conditions are usually optimized to give the maximum amount of allo-ocimene. Ocimenes can be produced by a technique using shorter contact time and rapid quenching or steam dilution (127).



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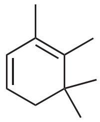

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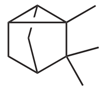


(115)

Acid-catalyzed isomerization of α-pinene gives a mixture of camphene (**27**) and tricyclene [508-32-7] (**115**). The process is carried out by heating with TiO_2 catalysts or other activated clays and the products are obtained in a 4:1 equilibrium mixture in about an 80% yield. Tricyclene undergoes reactions identical to those of camphene; therefore, the crude material is often used as such for further synthesis.

The hydrogenation of α-pinene to *cis*-pinane (**21**) is a process of major importance. Pyrolysis of the *cis*-pinane produces citronellene (**72**) (dihydromyrcene) as the major product in 50–60% yield (88). As described above under citronellene, dihydromyrcenol (**73**) produced from it, has become an important fragrance material. The most significant use of *cis*-pinane is based on oxidation to pinane hydroperoxide and its subsequent catalytic reduction to pinanol (**22**). The cis and trans isomers of pinanol are formed in a ratio of ∼80:20 (128,129).

Pyrolysis of the *cis*-pinanol gives linalool (**23**), which can be readily isomerized to nerol and geraniol using an *ortho*-vanadate catalyst (13). Because the isomerization is an equilibrium process, use of borate esters in the process improves the yield of nerol and geraniol to as high as 90% (14). One disadvantage of this route to the rose alcohols is the formation of the plinols (**116**). These cyclic alcohols are formed by an intramolecular ene reaction of linalool as shown in Figure 23. Since the ene reaction and the cleavage of pinanol are both thermal processes, it is impossible to prevent the formation of the plinols as by-products. Because of the closeness of their boiling points to that of linalool, separation is very difficult.

Another process of major importance is the acid catalysed hydration of α-pinene to give α-terpineol as is described in Section 4.2.2 under α-terpineol.

Epoxidation of α-pinene gives α-pinene oxide, which can be rearranged by Lewis acid catalysts to give campholenic aldehyde (**30**). This is a key feedstock for the production of sandalwood ingredients, and further details will be found below under the heading campholenic aldehyde.

β-*Pinene*

β-Pinene	
CAS Registry No.	[127-91-3] racemate
CAS Registry No.	[19902-08-0] (*R*)-(+)-enantiomer
CAS Registry No.	[18172-67-3] (*S*)-(−)-enantiomer
formula	$C_{10}H_{16}$
FW	136.23
mp	−61°C
bp	98°C at 13.33 kPa (100 mmHg)
bp	165°C at 101.3 kPa (760 mmHg)
d^{20}	0.8722 g/cm^3
$n_D{}^{20}$	1.4790
$[\alpha]_D$	22.6°
vp	2 mmHg (20°C)
vd	4.7 v air

Like the α-isomer, β-pinene occurs very widely in nature and, again like the α-isomer, the main source is from fractional distillation of turpentine. As it is the minor of the two isomers in turpentine, the price of β-pinene is usually somewhat higher than that of α-pinene.

Higher quality grades find direct use in perfume and flavor applications, but the main use for β-pinene is for cracking to myrcene, and hence production of further downstream fragrance ingredients, and in resin manufacture. It is prone to autoxidation and must be stored under conditions that preclude this.

The resins are made by Lewis acid (usually $AlCl_3$) polymerization of β-pinene, either as a homopolymer or as a copolymer with other terpenes, such as limonene. β-Pinene polymerizes much more easily than α-pinene and the resins are useful in pressure-sensitive adhesives, hot-melt adhesives and coatings, and elastomeric sealants.

The major manufacturing routes from β-pinene are shown in Figure 9. The details of rose alcohol and menthol production are given below under the headings for the individual products. One of the first syntheses of a new fragrance chemical from turpentine sources used formaldehyde with β-pinene in a Prins reaction to produce the alcohol, Nopol (**39**) (130). Nowadays, the corresponding acetate (**40**) is used more widely in fragrances, particularly for those destined for soaps, detergents, polishes, and other household products. The acetate can be made by direct esterification of Nopol (see Fig. 9).

Camphene

Camphene

CAS Registry No.	[79-92-5] racemate
CAS Registry No.	[5794-03-6] (+)-enantiomer
CAS Registry No.	[5794-04-7] (−)-enantiomer
formula	$C_{10}H_{16}$
FW	136.23
mp	48–52°C
bp	91°C at 13.33 kPa (100 mmHg)
bp	158–160°C at 101.3 kPa (760 mmHg)
d^{20}	0.84 g/cm^3
$[\alpha]_D$	108°

Camphene (**27**) is widespread in nature. It is produced commercially by the reaction of α-pinene (**20**) with a TiO_2 catalyst. Preparation of the catalyst has a great influence on the product composition and yield. Tricyclene (**115**) is formed as a coproduct, but its reactivity is very similar to that of camphene; thus the product is generally used as a mixture. The *p*-menthadienes and dimers produced as by-products are easily removed by fractional distillation and the camphene has a melting point range of 36–52°C, depending on its purity. The main use of camphene is as a feedstock for preparation of a variety of fragrance compounds and some of the reactions employed are shown in Figure 24.

Addition of acids, such as acetic, propionic, isobutyric, and isovaleric, produces useful isobornyl esters, the most important of which is isobornyl acetate [125-12-2] (**117**) (131). Isobornyl acetate possesses a fruity and woody odor and its perfumery use runs into thousands of tonnes per annum. The isobornyl esters of acrylic and methacrylic acids are also useful in preparing acrylic polymers. Similarly, addition of alcohols and glycols to camphene catalyzed by strong acids such as Amberlyst 15 ion-exchange resin produces useful camphane ethers (**118**) (132).

Saponification of isobornyl acetate produces isoborneol (*exo* -1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol [124-76-5]) (**119**), which can be oxidized or dehydrogenated to give camphor (**120**) (qv).

An important use of camphene is for the production of synthetic sandalwood materials. When camphene reacts with guaiacol (2-methoxyphenol) in the presence of a Brønsted or Lewis acid, a mixture of terpenylphenols is formed. Hydrogenation of the mixture results in hydrogenolysis of the methoxy group and gives a complex mixture of ~130 terpenylcyclohexanols, such as 3-(2-isocamphyl)cyclohexanol {[3407-42-9] for unspecified absolute stereochemistry or [4105-12-8] for the (1*R*,3*R*,1'*S*,2'*R*,4'*S*,6'*S*)-isomer} (133,134). The yield of the desired isomers in the final product can be improved by reversing the etherification pattern of the camphene–guaiacol adduct (135). A process has also been developed using catechol and camphene (136–139). These materials are available under various trade names, such as Candelum, Indisan, isobornylcyclohexanol (IBCH), Nardosandol, Sandel, Sandela, Sandenol, Sandeol, and Santalex. Each of these has a unique isomer distribution and odor profile and in several cases, different qualities exist under the same trade name. Total annual consumption is in hundreds of tonnes. In a brilliant piece of work, Demole showed that the active isomers were those with an *exo*-isocamphane ring attached in the 3-position relative to an axial hydroxy group in the cyclohexanol, ie, structures (**121**) and (**122**) (133,140).

Carene

Carene

CAS Registry No.	[13466-78-9] racemate
CAS Registry No.	[498-15-7] (*S*)-(+)-isomer
formula	$C_{10}H_{16}$
FW	136.23
bp	104°C at 13.33 kPa (100 mmHg)
bp	170°C at 101.3 kPa (760 mmHg)
d^{20}	0.8617 g/cm^3
$n_D{}^{20}$	1.4742
$[\alpha]_D$	17°

3-Carene (also known as delta-3-carene or Δ-3-carene) (**123**) is less widespread in nature than the pinenes. However, it is found in many turpentines and can be extracted from them by fractional distillation. Turpentine from the western United States and Canada averages ~25% 3-carene; much of it is unutilized although it is obtained in high optical purity. Turpentines from the Scandinavian countries, the CIS, Pakistan, and India all contain significant quantities of 3-carene.

Using strong bases, such as t-C_4H_9OK/dimethyl sulfoxide (DMSO), sodium on Na_2CO_3 or sodium on alumina, (1*S*,6*R*)-(+)-3-carene can be isomerized to an equilibrium mixture containing 40% of (+)-2-carene [4497-92-1] (**124**) (141–144). This serves as a potential starting point for menthol or menthone manufacture and will be discussed in more detail below in the relevant sections.

3-Carene has also been isomerized over an ε-alumina catalyst to a 50:50 mixture of dipentene and carvestrene (**125**). The crude mixture can be readily polymerized to a terpene resin or copolymerized with piperylene (145,146). Although 3-carene does not polymerize to produce terpene resins, copolymerization with phenol has been successfully commercialized by DRT in France (147).

The potential supply of 3-carene exceeds demand as a feedstock for synthesis of fragrance ingredients and consequently, much research has been invested in the area. The Prins reaction of 3-carene with formaldehyde in acetic acid gives mainly 2-carene-4-methanol acetate (**126**), which when saponified produces the

2-carene-4-methanol (**127**) (148). On reaction with acetic anhydride in the presence of zinc chloride, 3-carene gives 4-acetyl-2-carene (**128**) (149). These various products, shown in Figure 25, have been commercialized, but have not enjoyed great success.

4.2. Monoterpenoid Alcohols. *Linear Monoterpenoid Alcohols and Their Esters. Linalool*

Linalool	
CAS Registry No.	[78-70-6]
CAS Registry No.	[22564-99-4] racemate
CAS Registry No.	[126-90-9] (*S*)-(+)-isomer
CAS Registry No.	[126-91-0] (*R*)-(−)-isomer
formula	$C_{10}H_{18}O$
FW	154.25
bp	79.8°C at 1.33 kPa (10 mmHg)
bp	199°C at 101.3 kPa (760 mmHg)
d^{20}	0.8607 g/cm^3
$n_D{}^{20}$	1.4616
$[\alpha]_D$	22°
fp	76°C
solubility	<1% in water at 20°C, soluble in ethanol and mineral oil

Linalool (**23**) is more properly spelt linalöol and pronounced with two distinct o sounds, the first long and the second short. This gives an indication of one of its principal sources, Linaloe oil, the essential oil of the Indian tree *Bursera delpechiana*, which contains levels of ~30% linalool and 45–50% of its acetate. However, it is common practice nowadays to omit the diaeresis and even to spell the name with a single letter o. Other synonyms include linalyl alcohol, Licareol (extract from rosewood), and Coriandrol (extract from coriander). It occurs very widely in nature. The richest source is Ho leaf oil from China and Taiwan, which typically contains >90% linalool and levels as high as 97.5%, have been reported (150). Rosewood oil will typically contain 75–85% linalool and it is a major component of many flower (eg, ~80% in freesia and 75% in honeysuckle) and herb (eg, 65–80% in coriander) oils. Linalyl acetate is also a frequently encountered component of plant oils. Oils in which it plays a particularly important organoleptic role, include lavender (~50%) and citrus leaf oils (also ~50%).

Natural linalool is extracted mainly from three species. The largest is Brazilian rosewood of which ~100–150 tpa is produced. In recent years, there has been some concern about the endangering of the rosewood species by overharvesting and consequently about the sustainability of production of the oil. About 10 tpa is produced from Chinese and Taiwanese Ho leaf. Production from Linaloe oil is only a few tpa in India (151). Minor sources of natural linalool include shin and coriander oils (82). In the past, it was also extracted from lavender and bergamot.

The history, world consumption, and production, analogues, substitutes, and derivatives of linalool have been reviewed by Clark (151). Estimates of market size vary. Another source (83) estimates the total production volume of linalool and its esters as 6000 tpa, whereas Clark (151) states that the output of three of the main producers is 10,000 tpa. Such variances probably stem from the fact that linalool is used *per se* and as an intermediate for both other aroma chemical and vitamin manufacture and the result will depend on how the volume is estimated.

There are four main producers of linalool at present; BASF, DSM, Kuraray and Millennium, but other producers, Chinese in particular, are becoming important. The BASF process for manufacture of linalool (**23**) is described in Section 2.4. The process, apart from the final Lindlar hydrogenation of dehydrolinalool (**46**) is shown in Figure 11. Section 2.3 and Figure 10 show the DSM production route. Kuraray use the route described in Section 2.6. The first stages of this synthesis are shown in Figure 13, the methylheptenone (**19**) thus produced being converted to linalool (**23**) by ethynylation and subsequent Lindlar hydrogenation. Similarly, Section 2.1 and Figure 8 show the Millennium process, which starts from α-pinene.

Isoprene (2-methyl-1,3-butadiene) can be telomerized in diethylamine with *n*-butyllithium as the catalyst to a mixture of *N*,*N*-diethylneryl- and geranylamines. (*N*,*N*-Diethylgeranylamine is shown as structure **41** in Figure 9, the neryl isomer has the opposite double-bond geometry.) Oxidation of the amines with hydrogen peroxide gives the amine oxides, which, by the Meisenheimer rearrangement, and subsequent pyrolysis, produce linalool in an overall yield of ~70% (75,152,153).

Linalool can also be made from nerol and geraniol by the ortho-vanadate-catalyzed isomerization. Because linalool is lower boiling than nerol and geraniol, the isomerization can be run under distillation conditions to remove the linalool overhead while continually adding nerol and geraniol to the distillation kettle for further isomerization (14).

Linalool can also be made along with nerol and geraniol via the hydrochlorination of myrcene as shown in Figure 9. After conversion of the chlorides to acetates followed by saponification of the acetates, the mixture of alcohols is obtained. Fractionation of the mixture gives linalool in ~95% purity, but the presence of close boiling chlorinated impurities imparts a metallic note and prohibits manufacture of a perfumery-quality product.

The price of synthetic linalool is typically ~\$5–8/kg, natural grades costing at least twice that. Synthetic linalyl acetate has a similar price to that of the alcohol, natural acetate being much more expensive at ~\$45/kg (82,83).

Linalool is of major importance both as a material in its own right (it is generally considered to be the ingredient with the widest range of fragrance application) and as an intermediate for the production of a wide range of other terpenoids and derivatives.

Its fresh, clean floral odor with a nuance of citrus makes it a valuable floral blender and it is used widely in perfumery. As its odor is of a general floral character rather than that of a specific flower, it is used in all floral types, and is therefore found in a very wide range of fragrances. It has been estimated that it is present in 90% of all fine fragrances (154).

Linalool can be esterified to linalyl acetate [115-95-7] (**36**) by reaction with acetic anhydride. Linalyl acetate has a floral-fruity odor, reminiscent of bergamot and it also has some pear character. The acetate is also a high volume aroma chemical as it is widely used as a fresh and sweet blender. Linalool is subject to dehydration and to isomerization to nerol and geraniol during the esterification. However, if the acetic acid formed during the esterification is removed in a distillation column, the isomerization can be minimized and good yields of the acetate obtained (155). Many other esters of linalool are also used in perfumery.

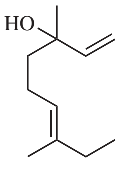
Linalool can be hydrogenated to dihydrolinalool [18479-49-7] and tetrahydrolinalool [78-69-3] (**97**), both of which are used in perfumery. The use of the latter has increased because of its superior performance in harsh media, such as household cleaners containing hypochlorite bleach (which attacks the double bonds of linalool).

Linalool can be converted to geranyl acetone by the Carroll reaction (156). After transesterification with ethyl acetoacetate, the intermediate ester thermally rearranges with loss of carbon dioxide. Linalool can also be converted to geranyl acetone by reaction with methyl isopropenyl ether. The linalyl isopropenyl ether rearranges to give geranyl acetone. Geranyl acetone is an important intermediate in the synthesis of isophytol [505-32-8], farnesol [106-28-5], and nerolidol [40716-66-3]. Isophytol is used in the manufacture of Vitamin E and thus linalool is a key intermediate in the synthesis of the latter. All of these reactions are shown in Figure 55 in the section on nerolidol.

Linalool has been used to prepare a mixture of terpenes useful for enhancing the aroma or taste of foodstuffs, chewing gums, and perfume compositions. Aqueous citric acid reaction at 100°C converts the linalool to a complex mixture, as shown in Figure 26. A few of the components include α-terpineol (34%) (**26**), Bois de Rose oxide (5.1%) (**129**), ocimene quintoxide (0.5%) (**130**), linalool oxide (furan form) (0.3%) (**131**), *cis*-ocimenol (3.28%) (**132**), and many other alcohols and hydrocarbons (157).

Epoxidation of linalool occurs at the more substituted double bond. Ring closure of this epoxide gives a mixture of the cis [5989-33-3] and trans [34995-77-2] isomers of the furan (**131**), and also the cis and trans isomers of the pyran (**133**) [14049-11-7] as shown in Figure 27. This mixture is known as linalool oxide, and sometimes erroneously as epoxylinalool or epoxydihydrolinalool. Linalool oxide has a sweet woody, floral powerful, sweet and penetrating odor with earthy undertones. It is used in perfumes and in essential oil reconstitutions in which it adds a “natural” note to linalool.

Various analogues of linalool have been produced over the years, but the only successful one is ethyl linalool (**134**). This is produced by DSM simply by substituting 2-butanone for acetone in the first stage of their synthesis and other suppliers are also in production.



(134)

Geraniol and Nerol

Geraniol	
CAS Registry No.	[106-24-1]
formula	$C_{10}H_{18}O$
FW	154.25
bp	131°C at 3.33 kPa (25 mmHg)
bp	230°C at 101.3 kPa (760 mmHg)
d^{20}	0.8770 g/cm^3
$n_D{}^{20}$	1.4756
vp	0.2 mmHg (20°C)
vd	5.31 v air
fp	93.3°C
solubility	very slightly in water, 1in 2 v/v in 70% alcohol, soluble in most organic solvents

Nerol	
CAS Registry No.	[106-25-2]
formula	$C_{10}H_{18}O$
FW	154.25
bp	128°C at 3.33 kPa (25 mmHg)
bp	225°C at 101.3 kPa (760 mmHg)
d^{20}	0.8735 g/cm^3
$n_D{}^{20}$	1.4736

The names of these two alcohols are derived from those of the plants from which they were first isolated, geraniol (**24**) from geranium and nerol (**25**) from neroli (orange flower). Other names for geraniol-rich grades include Gerallol, Meranol, Reuniol, Rhodeanol, Rhodinol, Roseneone, and Roseol and for nerol-rich grades; Allerol, Lorena, Neraniol, Nerodol, Nerolol, and Nerosol.

These two materials are most easily dealt with together since they often occur together in nature and syntheses usually also produce both simultaneously. The equilibrium mixture is comprized of 60% geraniol and 40% nerol. The isomers can be separated by efficient fractional distillation and products of many compositions are available. The odor profile varies with the isomer ratio among other factors. As an example of the variation in quality, Table 2 shows the geraniol–nerol balance in the products offered by a single supplier, IFF. Many of these also contain citronellol and/or other materials, such as dimethyloctanol.

In early literature, cis–trans referred to the CH_2OH versus the methyl group but more recently, the two larger groups are used. Therefore, early sources say geraniol is cis and nerol trans, whereas later sources say geraniol is trans and nerol cis. The natural sources, consumption, history, substitutes, synthesis, etc, of geraniol has been reviewed by Clark (154).

Both alcohols are widespread in nature, geraniol more so than nerol. The richest geraniol sources are *Monarda fistulosa* 93%, palmarosa (*Cymbopogon martini*) 80–85%, citronella (*Cymbopogon nardus, C. winterianus*) 30%, lemongrass (*Cymbopogon citratus*) 30%, and geranium 50%. Nerol is highest in rose, palmarosa, citronella, and davana.

The most important commercial source of natural geraniol is citronella (especially *Cymbopogon winterianus*) in which oil it is present at a level of ~30%. The oil also contains citronellol and citronellal and the geraniol must be separated from these by fractional distillation. Production is estimated at ~5000 tpa (154). Other significant sources are geranium (150 tpa from an oil containing 15–80%), Jamrosa (*Cymbopogon jwarancusa*) (100 tpa from an oil containing 80–85%), palmarosa (*Cymbopogon martini*) (80 tpa from an oil containing 75–85%) and Dhanrosa (*Cymbopogon flexuosus*) (10 tpa from an oil containing 80–85%) (154).

Nerol and linalool do not form complexes with calcium chloride thus permitting isolation of a pure grade of geraniol from palmarosa.

Citronella, palmarosa and geranium oils also serve as sources of natural grades of the corresponding esters. Geraniol prepared from β-pinene was the first synthetic terpenoid to be produced in bulk. Currently, the two largest suppliers are Millennium, who produce it from α-pinene by the route described in Section 2.1 and Figure 7 and IFF, using the former BBA plant and process ex β-pinene as described in Figure 9 and Section 2.2.

The prices of geraniol, nerol, and their esters are generally in the \$6–12/kg range though they are very dependent on quality and some high-grade materials derived from natural feedstocks will attract much higher prices.

Geraniol possesses a mild, sweet floral odor that is distinctly rose in character, and therefore is only used in rose perfumes. This means that it is used in a narrower range of fragrances than its isomer linalool. It is found in ~43% of fine fragrances, as opposed to 90% for linalool. Consequently, its volume of use is lower than that of linalool.

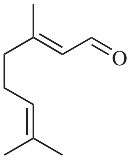
The odor of pure nerol is sweet, rosy refreshing and "wet" seashore (158). The purer it is, that is the less geraniol it contains, the more of the "wet" character there is.

There are many grades of both "geraniol" and "nerol" available on the market, all varying in odor quality and geraniol/nerol ratio. Production estimates (82,83,154) vary considerably and it is unclear whether or not some of these include feedstock material in addition to material for direct use. However, it is clear that current production of natural geraniol/nerol runs into hundreds of tonnes/annum and synthetic into thousands.

A wide variety of geranyl and neryl esters are in use as fragrance ingredients. The most significant is geranyl acetate [105-87-3], which has a sweet, fruity, floral, and slightly green odor. The world consumption of geranyl acetate has been estimated at 650 tpa and the next six largest esters have a joint annual production of several hundred tonnes (154).

A considerable amount of nerol and geraniol is used internally by the producers as intermediates for manufacture of other terpene products, particularly citral, ionones, methylionones, citronellol, citronellal, hydroxycitronellal, (±)-menthol, vitamins A and E, and carotenoids.

Nerol and geraniol can be converted to citronellol (**85**) by hydrogenation over a copper chromite catalyst (159). In the absence of hydrogen and under reduced pressure, citronellal (**135**) is produced (160). If a nickel catalyst is used, a mixture of nerol, geraniol, citronellol, and tetrahydrogeraniol (**136**) is obtained and such a mixture is also useful in perfumery.



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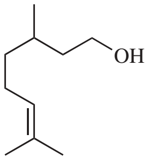

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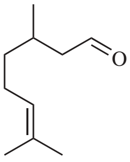

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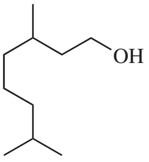


(136)

Complete hydrogenation of geraniol gives 3,7-dimethyloctan-1-ol, commonly known as tetrahydrogeraniol [106-21-8] (**136**). This saturated alcohol has an odor similar to that of citronellol and is increasingly popular as an ingredient because of its improved stability in harsher products, such as those containing bleach. It is estimated that the production volume of it and its esters grew from 300 tpa in 1985 to >700 tpa in 1995 (82,83) and growth has continued since then.

Nerol and geraniol can be converted to citral (**55**) in the vapor phase over a copper catalyst (161,162). Oppenauer oxidation of nerol and geraniol using catalytic amounts of aluminium isopropoxide and with aldehydes as the hydrogen acceptor also produces citral in good yields (163). The citral produced by this process gives a good intermediate product for producing high-quality ionones and methylionones.

Citronellol

Citronellol

CAS Registry No.	[106-22-9]
CAS Registry No.	[26489-01-0] racemate
CAS Registry No.	[1117-61-9] (*R*)-(+) enantiomer
CAS Registry No.	[7540-51-4] (*S*)-(−) enantiomer
formula	$C_{10}H_{20}O$
FW	156.27
bp	105°C at 1.47 kPa (11 mmHg)
bp	224°C at 101.3 kPa (760 mmHg)
d^{20}	0.8550 g/cm^3
$n_D{}^{20}$	1.4559
$[\alpha]_D$	5.3°
vp	0.02 mmHg (25°C)

Citronellol (**85**) is sold under various trade names, such as Cephrol and Corol, but more usually simply as citronellol. Similarly, the laevorotatory isomer is usually called (−)-citronellol or (*l*)-citronellol, but the trade name Levocitrol is also used. Some confusion arises from the use of the name Rhodinol, which has been used for the laevo-isomer, but also for various grades of mixtures of rose alcohols.

Citronellol is widespread in nature in both enantiomeric forms, the richest sources being rose and geranium. It is one of the components responsible for the insect repellent properties of citronella oil. Previously, it was extracted from various oils, especially citronella and geranium, or by hydrogenation of citronellal isolated from citronella oil. Nowadays, the major source, by far, is synthetic.

Citronellol is manufactured on a commercial scale by the hydrogenation of nerol and geraniol, which in turn are made either from α- or β-pinene (see Sections 2.1 and 2.2). Hydrogenation of nerol and geraniol over a copper chromite catalyst gives a high yield of citronellol (159). Fractional distillation of the crude product produces a perfumery-quality citronellol. Geraniol can also be hydrogenated selectively to citronellol, without forming tetrahydrogeraniol, through use of a Raney cobalt catalyst (164). However, partial hydrogenation using a nickel catalyst does give some tetrahydrogeraniol. The product contains nerol, geraniol, and tetrahydrogeraniol and has odor properties closer to materials derived from citronella oil, and is therefore useful as a perfumery material (105).

Optically active citronellol can be prepared in high optical purity by asymmetric hydrogenation of geraniol using a rhodium $[(S)\text{-BINAP}]_2^+$ catalyst (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (165–168).

Application of the Zeigler reaction to citronellene also produces citronellol as shown in Figure 20. Aluminum alkyls react by the Ziegler reaction with the least substituted double bond of citronellene (**72**) to give the tricitronellyl aluminum compound (**88**) (47). Oxidation of the intermediate compound then produces the tricitronellyl aluminate, which is easily hydrolyzed with water to give citronellol (98,99). If the citronellene is optically active, optically active citronellol can be obtained (100). However, this process has not been commercialized.

During a joint venture with Naarden International, Shell International developed a new route to citronellol, but this was never commercialized. The route starts with cyclodimerization of isoprene (**1**) to give 1,5-dimethylcycloocta-1,5-diene (**137**). Olefin metathesis with isobutene in the presence of a rhenium oxide catalyst produces 2,6-dimethylhepta-1,5-diene (**138**). The diene is hydroformylated to citronellal (**139**), which after hydrogenation produces citronellol (**85**) (169). Alternatively, the 1,5-dimethylcycloocta-1,5-diene can be partially hydrogenated and the monoene (**140**) then pyrolyzed to 2,6-dimethylocta-1,7-diene (**141**), which can be converted subsequently to citronellol in several steps (170). These processes are shown in Figure 28.

Citronellol can also be made by the selective hydrogenation of citral (**55**) and citronellal (**135**) using a chromium-promoted Raney nickel catalyst (171,172) or from citral using a palladium–ruthenium catalyst in the presence of trimethylamine (173).

Estimates of production of citronellol and its esters vary from just under 3000 tpa (83) to 6000 tpa (82). Prices are in the $5–10/kg range with natural extracts being slightly higher and optically pure materials considerably more.

Citronellol has a fresh rosy odor that finds extensive use in floral fragrances and also in flavors for citrus and other fruit notes. Its improved stability over geraniol, nerol, and linalool makes it particularly useful in fragrances for soaps, detergents, and other household products. The odor of the levorotatory isomer is much finer than that of the racemate. Citronellyl acetate [150-84-5], also known as Cephreine, has a fresh rosy and fruity note and is also a significant perfumery ingredient. The formate, propionate, butyrate, and isobutyrate esters are also used. Citronellol is also important as an intermediate in the synthesis of a number of other aroma chemicals.

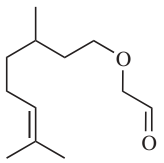
Dehydrogenation of citronellol over a copper chromite catalyst produces citronellal (**135**) in good yield (95). If the dehydrogenation is done under distillation conditions in order to remove the lower boiling citronellal as it is formed, polymerization or cyclization of citronellal is prevented. Citronellol can also be used to produce hydroxycitronellal (**87**) as discussed below under the heading hydroxycitronellal.

Citronellol is the key feedstock for the synthesis of rose oxide [16409-43-1] (**142**) as shown in Figure 29 (174). Dye-sensitized photooxidation of citronellol gives mixture of two allylic hydroperoxides (**143**) and (**144**). These are reduced using bisulfite to give the corresponding diols, (**145**) and (**146**), respectively, which are then treated with dilute sulfuric acid. Diol **145** cyclizes to rose oxide while diol **146** remains unchanged and is removed from product by distillation. Diol **146** is dehydrohydroxycitronellol and is used under trade names, such as Allofixine, Hydroxyol, and citronellol hydrate. It has a floral, sweet, green odor, and is used as a fixative. Use of (−)-citronellol in the above synthesis produces a mixture, in about equal proportions, of (−)-cis and (−)-trans rose oxides, (**147**) and (**149**), respectively.

Rose oxide provides a good example of the growing focus on chirality in the fragrance industry. It exists in four isomeric forms, two enantiomers each of two geometric isomers as shown in Figure 30 as structures (**147–150**), together with their odor thresholds. These thresholds were determined by Yamamoto and coworkers who found that the absolute stereochemistry at C4 is more important than that at C2 (175,176). The commonest of these in nature is the laevorotatory enantiomer of *cis*-rose oxide (**147**), which is found, eg, in rose and geranium oils. Not surprisingly, therefore, this is also the isomer with the finest rose character and the lowest odor threshold. The other isomers have more herbal character in their odor profile.

Rose oxide is found in a number of essential oils, but particularly those of rose and geranium. It is used to give dry, green, and rosy top-notes to fragrances. Racemates and optically pure (both laevo- and dextro-) forms are commercially available and used in fragrances. The homochiral products, especially the laevorotatory ones, command much higher prices than does the racemate.

Some other aroma chemicals prepared from citronellol include citronellyl oxyacetaldehyde (**151**), which has a muguet note and citronellyl methyl acetal (**152**), the mixed acetal with methanol of acetaldehyde, which has a floral, fruity, leafy, and green character. Surprisingly, ethyl citronellyl oxalate (**153**) has a musky character in addition to rosy and fruity notes.



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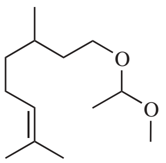

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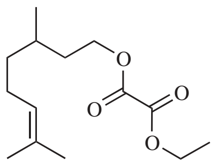


(153)

Monocyclic Monoterpenoid Alcohols and Their Esters. *α-Terpineol*

α-Terpineol	
CAS Registry No.	[98-55-5]
CAS Registry No.	[7785-53-7] (+)-enantiomer
CAS Registry No.	[10482-56-1] (−)-enantiomer
formula	$C_{10}H_{18}O$
FW	154.25
mp	37°C racemate
mp	41°C enantiomers
bp	14°C at 13.33 kPa (100 mmHg)
bp	219°C at 101.3 kPa (760 mmHg)
d^{20}	0.9336 g/cm^3
$n_D{}^{20}$	1.4831
$[\alpha]_D$	106.4°
solubility	very slightly soluble in water, soluble in alcohol and mineral oil

In commercial terms, α-terpineol, *p*-menth-1-en-8-ol (**26**) is intimately connected with pine oil and so both subjects will be covered together here.

α-Terpineol is very widespread in nature, usually occurring at relatively low levels in oils. Natural pine oil was a product derived from the extraction of aged pine stumps and sulfate pine oil is a product separated from crude sulfate turpentine in ~5% yield. The sulfate pine oil retains the sulfur odor of the sulfate turpentine and its use is therefore limited to ore flotation and solvent applications.

Acid-catalyzed hydration of α-pinene produces pine oil and this is one of the largest uses of turpentine (177–179). Mineral acids are used as catalysts, usually in a concentration of 20−40 wt% and temperatures of 30−100°C. An efficient surfactant, preferably one that is soluble in the acid-phase upon completion of the reaction, is needed to emulsify the α-pinene and acid. The surfactant can then be recycled with the acid. Phosphoric acid is the acid commonly used in the pine oil process. Its mild corrosion characteristics and its moderate strength make it more manageable, especially because the acid concentration is constantly changing in the process by the consumption of water. Phosphoric acid is also mild enough to prevent any significant dehydration of the alcohols formed in the process. Optimization of a process usually involves considerations of acid type and concentration, temperature, surfactant type and amount, and reaction time. The optimum process usually gives a maximum of alcohols with the minimum amount of hydrocarbons and cineoles.

The major component of pine oil is α-terpineol (**26**). Other components in the product include; β-terpineol (**154**), γ-terpineol (**155**), α-fenchol (**156**), borneol (**157**), terpinen-1-ol (**158**), and terpinen-4-ol (**159**), *p*-menthadienes (mainly limonene and terpinolene), 1,4-cineole (**102**), and 1,8-cineole (**103**). The mechanisms of some of these reactions are shown in Figure 31. The ethers, 1,4- and 1,8-cineole, are also formed by cyclization of the *p*-menthane-1,4- and 1,8-diols. The bicyclic alcohols, α-fenchol [512-13-0] and borneol (*endo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol [507-70-0]) are formed by the Wagner-Meerwein rearrangement of the pinanyl carbocation and subsequent hydration.

Fractional distillation of crude pine oil is used to generate a wide range of grades of pine oil and α-terpineol. Some grades of pine oil may constitute a blend of synthetic and natural pine oil. High-grade perfumery α-terpineol can be made by the partial dehydration of *p*-menthane-1,8-diol (terpin hydrate) under mildly acidic conditions (180,181).

World production of pine oil is estimated to be as high as 30,000 tpa, under 10% of which is natural (182). Production of pure grades of α-terpineol and its esters is ~3500 tpa (82,83). The price is very dependent on quality. The lowest grades sell for little over $1/kg, high-grade α-terpineol could sell for over four times that amount.

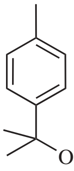
The largest use of pine oil is in the manufacture of cleaners and disinfectants. It is effective against gram-negative enterobacteria but not against gram-positive organisms. Lower grades, such as sulfate pine oil are used for the flotation of metallic sulfide ores, including copper, zinc, nickel, iron, and lead. In textiles, the most important property of pine oil is its ability to reduce surface tension and interfacial tension between fiber and solution. Pine oil allows ingredients in wet-processing baths to get into fibers and to work immediately. Also, because of its bacteriocidal activity, it is used in almost all wet processing of cotton, silk, rayon, and woollen goods. Pine oil production has declined as a result of the decrease in the amount of pine oil used in cleaner and disinfectant products. The pine oil content of those products has dropped from 70–90% to 10–30% (182).

Pure α-terpineol has a delicate sweet floral, lilac-type odor (though only present at very low levels, if at all, in lilac). Its odor qualities are greatly affected by impurities, and many fragrance houses buy cheap grades and redistill it to their perfumery quality. The monoterpenoid hydrocarbons tend to give a pine character, the other alcohols and the phenols give a medicinal quality. Low-cost, ready availability and stability to air, soap and household products make it a very useful ingredient.

α-Terpineol can be readily acetylated to its acetate using acetic anhydride (183). α-Terpinyl acetate [80-26-2] has a sweet, herbaceous, refreshing odor of the bergamot-lavender type similar to, but weaker than that of linalyl acetate. However, its better stability, especially in soap and household products, has ensured an important place for it on the perfumers' palette. Many other esters of α-terpineol are also used in perfumery but with lower overall tonnage than the acetate.

Hydrogenation of α-terpineol gives dihydroterpineol [498-81-7] as a mixture of cis and trans isomers (184). Dihydroterpinyl acetate [80-25-1], produced from the mixture, is also a useful fragrance ingredient. Both dihydroterpineol and dihydroterpinyl acetate have similar odors to their unsaturated counterparts, but are softer and sweeter. Their stability is even greater and they are both useful materials.

α-Terpineol can be dehydrogenated to give *p*-cymen-8-ol (**160**) (185) and this has been used by Quest International as a feedstock for production of an equivalent to the musk Tonalide (**112**) by cyclialkylation with 2,3-dimethylbut-1-ene and subsequent acetylation (186).



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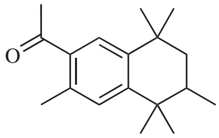


(112)

Menthol

Menthol	
CAS Registry No.	[89-78-1]
FW	156.27

There are eight isomeric forms of *p*-menthane-3-ol (2-isopropyl-5-methylcyclohexan-1-ol or 2-{1'-methylethyl}-5-methylcyclohexan-1-ol). The four different geometric isomers are known as menthol, neomenthol, isomenthol, and neoisomenthol, and each exists in two enantiomeric forms. Their structures are shown in Figure 32 together with trivial and systematic names, CAS numbers, specific rotations, taste, and cooling thresholds for each individual isomer and the size of the sensory cooling effect relative to that of *l*-menthol, which is given an arbitrary value of 100.

Of the eight isomers, the only one of significant commercial importance is (1*R*,3*R*,4*S*)-(−)-menthol, usually known as *l*-menthol (**42**). It is the commonest in nature and has the best organoleptic character of the eight. It has the lowest cooling threshold and the strongest cooling sensation. It has a good profile of clean, fresh, and minty taste with a low contribution of the musty and bitter components that mar the profile of many of the other isomers. Racemic menthol, known as (±)-menthol or *d,l*-menthol [15356-70-4], is used commercially, but mostly as an inexpensive substitute for optically pure *l*-menthol, particularly when the price of the latter is high. The racemate is prepared as an intermediate in the Symrise process for *l*-menthol production, as described below, and can also be prepared by acid catalyzed cyclization of racemic citronellal in a process analogous to that used by Takasago to prepare *l*-menthol from (+)-citronellal (also described below).

The remainder of this section describes the commercially important isomer *l*-menthol (**42**) the natural sources, world consumption, synthesis, properties, analogues, substitutes, and derivatives of which have been reviewed by Clark (187,188). The Leffingwell website (189) also contains a large amount of information on menthol.

(1*R*,3*R*,4*S*)-(−)-Menthol

CAS Registry No.	[2216-51-5]
formula	$C_{10}H_{20}O$
FW	156.27
bp	216°C at 101.3 kPa (760 mmHg)
mp	43°C
d^{20}	0.89 g/cm^3
${n_D}^{20}$	1.458
$[\alpha]_D$	−50.2°
vp	0.8 mmHg (20°C)
fp	93°C
solubility	0.04% in water, soluble in ethanol and mineral oil

l-Menthol occurs primarily in plants of the genus *Mentha*. The two most important of these commercially are *Mentha arvensis* (cornmint) and *Mentha piperita* (peppermint). *M. arvensis* oil contains between 70 and 75% *l*-menthol and is by far the most important source of it. It is grown primarily in India, China, and Paraguay. In 1985, it was estimated that China produced most of the world's supply of natural menthol (82). Thanks to a new breeds, such as Shivalik-88, Gompti, and Himalaya, India has become the world's largest supplier pushing China into second place (187).

Natural *l*-menthol is obtained by freezing the essential oil. The resultant crystals of *l*-menthol are then separated by filtration. The supernatant oil is called dementholized mint oil (DMO). Impurities in the crystals come from the essential oil and usually give a slight peppermint aroma to the crystallized *l*-menthol. The DMO, rich in *l*-menthone (~28%) and *l*-menthol (content depending on how aggressively the producer crashes out the menthol), can be further processed to give additional natural *l*-menthol.

There are many published syntheses of *l*-menthol and quite a few have been commercialized at some time. Obviously, it is important that any synthesis should give a homochiral product since only *l*-menthol is of significant commercial interest. Interestingly, the two most significant routes start from achiral precursors, one of them introducing chirality through resolution and the other through use of a chiral catalyst. These two will be discussed first. The other routes will be placed in alphabetical order of feedstock. All but one of these depends on a homochiral natural source in order to provide the chirality of the product.

The largest producer of synthetic *l*-menthol is Symrise. The route, as shown in Figure 33, was developed by Haarmann and Reimer (one of the companies that merged to form Symrise) and their then parent, Bayer. Several thousand tpa are produced by this route.

The synthesis starts with the alkylation of *m*-cresol (**168**) by propylene in the presence of an aluminium catalyst to produce thymol [89-83-8] (**169**) (190,191). Hydrogenation of thymol using a catalyst containing Co (49.7%), Mn (22.9%) and Cu (0.2%), gives a mixture of all eight stereoisomers, but rich in *dl*-menthol (192–195). The proportions of the diastereomeric pairs in the mixture are shown in Table 3, together with the boiling points (196) of each pair. The boiling points are sufficiently far apart that the pairs can be separated using an efficient distillation column. The unwanted isomers can be recycled to the hydrogenation reaction where they are reequilibrated.

The *dl*-menthol thus prepared was originally resolved through its 3,5-dinitrobenzoate ester, but it was later found that the benzoate served equally well. A super-saturated solution of the racemic benzoates is seeded with crystals of one enantiomer inducing that isomer to crystallise out (197). The opposite enantiomer is therefore concentrated in the mother liquor. The resolved esters can then be saponified to the corresponding alcohols and the benzoic acid recycled. It is possible to equilibrate any menthol isomer to the same equilibrium mixture (198), but in practice the other diastereomersare most easily recycled via the hydrogenation stage, along with the *d*-menthol. The recycles are so efficient that the overall yield of *l*-menthol from this route is >90%. The disadvantage of the process lies in terms of the labor, time, plant capacity and energy consumed in operating all of the separation and recycle processes.

Biochemical methods for the resolution of menthol are now being developed. Symrise have patented a method for the selective hydrolysis of *dl*-menthyl benzoate using a lipase (199). A lipase from, eg, *Candida rugosa*, will hydrolyze the benzoate of *l*-menthol, but not that of *d*-menthol. Thus treating the racemic benzoate with the lipase gives a mixture of *l*-menthol and *d*-menthyl benzoate, which are easily separated without recourse to fractional crystallization. Takasago developed a similar process somewhat earlier (200).

A South African government biochemical laboratory has developed a process that short-cuts that of Symrise more dramatically. They used a lipase from a *Pseudomonas* species to selectively acetylate only *l*-menthol out of the mixture produced by hydrogenation of thymol thus allowing easy separation of the *l*-menthol and recycle of all seven other isomers (201).

The other major producer of synthetic *l*-menthol is Takasago who manufacture >2000 tpa (188). Their route is shown in Figure 34. The key step, in which chirality is introduced, is the isomerization using a chiral rhodium complex developed by Professor Noyori of Nagoya University and which is part of the work for which he was awarded the Nobel Prize for chemistry in 2001 (202).

The synthesis starts with myrcene (**32**), which can be obtained from β-pinene as described above. Addition of the diethylamide anion gives geranyl diethyl amine (**41**). Isomerization using ruthenium (*S*)-BINAP gives the *N,N*-diethylenamine of *d*-citronellal (**170**) and this is easily hydrolyzed to *d*-citronellal (**171**). The isomerization (203–205) proceeds with an enantiomeric excess (ee) of >96% and the catalyst turn over number is 400,000, which makes the process very efficient. The remainder of the synthesis follows that of the standard synthesis of *l*-menthol from citronellal. The zinc-catalyzed ene reaction converts *d*-citronellal to *l*-isopulegol [89-79-2] (**172**) and this is hydrogenated to *l*-menthol (**42**). More detail on this chemistry is given below.

The abundant supply of 3-carene (**123**) and the commercial attractiveness of *l*-menthol, have prompted much research into routes from the former to the latter. Some of these are shown in Figure 35. It is reported (83) that the Indian company Camphor and Allied once manufactured 200 tpa by the route through intermediates (**173–177**) as described below, but it would appear that none of the other potential routes have been commercialized. These other routes will not be discussed here, but details can be found in the literature (142,143,189,206–211).

As described above, (+)-3-carene (**123**) is isomerized by strong base to give (+)-2-carene (**124**). Pyrolysis at relatively low (180°C) temperatures in the liquid phase produces (+)-*trans*-isolimonene [5133-87-1] (**173**) via a 1,5-sigmatropic shift. Any (+)-3-carene is unaffected and can be recovered by distillation and recycled to the isomerization reaction. Isomerization of (+)-*trans*-isolimonene to (+)-isoterpinolene (**174**) can be achieved with catalysts or by hydrochlorination/dehydrochlorination. Addition of hydrogen chloride gives the chloride (**175**). Treatment with sodium acetate results in formation of pulegyl acetate (**176**), which can be saponified to pulegol (**177**), and then hydrogenated to *l*-menthol (**42**).

Citronellal can be cyclized to *iso*-pulegol by means of the ene reaction. Hydrogenation of the *iso*-pulegol thus formed then gives menthol. Using *d*-citronellal (**171**) with appropriate reagents and conditions leads to *l*-menthol (**42**) as shown in Figure 36. Originally, the *d*-citronellol was extracted from Citronella oil, but material produced from myrcene as described above is now more important.

The cyclization reaction can be effected thermally or through use of acidic (both Lewis and Brønsted) catalysts, such as alumina, silica, and boric acid (212–222). The product mixture contains 70% (−)-isopulegol (**172**), 23% (+)-neoisopulegol (**178**), 8% (+)-isoisopulegol (**179**), and 2% (+)-neoisoisopulegol (**180**). Hydrogenation of this mixture produces a mixture of (−)-menthol (**42**) from (**172**); (+)-neomenthol (**163**) from (**178**); (+)-isomenthol (**165**) from (**179**); and (+)-neoisomenthol (**167**) from (**180**), as shown in Figure 36. As the asymmetric center of citronellal is unaffected by the reactions, all of the isopulegol and menthol isomers formed have the correct stereochemistry at C1 of the *p*-menthane skeleton. There are therefore two strategies for recycling unwanted isomers. The first is to purify the (−)-isopulegol (**172**) by crystallization and recycle (**178–180**) back to citronellal by pyrolysis (221,223,224). The second is to hydrogenate the mixture, separate the (−)-menthol by crystallization and treat the remainder with aluminium isopropoxide, which converts all of them, by Oppenauer oxidation, enolization, reketonization and Meerwein-Ponndorf-Verley reduction, to (−)-menthol, which is the thermodynamically most stable isomer (225).

A significant improvement to this process was made when it was discovered that zinc salts, such as the chloride and bromide, gave much higher selectivity for (−)-isopulegol, the ratio of the desired isomer to the others being ~94:6 (226–228). Further development has improved selectivity even further to a ratio of 99.7:0.3 through use of a tris(2,6-diarylphenoxy)aluminium catalyst (229).

Like (+)-3-carene, (+)-limonene (**11**) is a readily available natural homochiral feedstock and so, in principle, could be a useful starting material for (−)-menthol synthesis. At least one route has been reported (206,230). As shown in Figure 37, the synthesis starts with selective hydrogenation of the disubstituted double bond and epoxidation of the trisubstituted one to give the epoxide (**181**). Hydrolysis and selective acylation of the secondary alcohol then gives (**182**). Pyrolysis of the acetate gives the unsaturated alcohol (**183**), which can be isomerized by allylic acetolysis and hydrolysis to give a mixture of *d*-*cis*- and *l*-*trans*- piperitols, (**184**) and (**185**), respectively. The former is recycled to the previous stage and the latter hydrogenated to give *l*-menthol (**42**) and *l*-isomenthol (**164**) in a ratio of 3:1. The latter can be used to prepare menthone.

Takasago have patented a process for the preparation of (−)-menthol from mesityl oxide and methyl vinyl ketone (231). The key step, hydrogenation of piperitenone (**186**) to (+)-pulegone (**187**), uses their chiral hydrogenation technology. The process, shown in Figure 38, will provide a useful alternative to their process described above, when myrcene is in short supply.

It is possible to prepare *l*-menthol from *l*-α-phellandrene [99-83-2] (**188**), as shown in Figure 39 (206,217–219). Addition of HCl gives phellandrene hydrochloride (**189**) which, on solvolysis under weakly alkaline conditions to control the pH, produces a mixture of mainly *cis*- and *trans*-2-menthen-1-ol and a minor amount of piperitol. Treatment with dilute aqueous acid isomerizes the allylic alcohols to an equilibrium mixture in which (−)-*cis*-piperitol [65733-28-0] (**191**) and (+)-*trans*-piperitol [65733-27-9] (**192**) predominate. The two isomers can be separated by efficient fractional distillation (232). Alternatively, treatment of the chloride (**189**) with sodium acetate and acetic acid gives a mixture of isomeric piperityl acetates (**190**). Hydrolysis of these gives (−)-*cis*-piperitol (**191**) and (+)-*trans*-piperitol (**192**). The former is recycled to the acetolysis stage and the latter hydrogenated to (+)-isomenthol (**165**). An efficient method for hydrogenation of (+)-*trans*-piperitol has been patented by Kane and co-workers (233). The (+)-isomenthol must be distilled away from the small amount (5%) of (+)-menthol also produced in the hydrogenation. The (+)-isomenthol is then epimerized using sodium mentholate or aluminum isopropoxide to obtain the equilibrium mixture containing ~56% (−)-menthol (**42**), 30% (+)-neomenthol (**163**), 13% (+)-isomenthol (**165**), and 1% (+)-neoisomenthol (**167**) (234). After fractional distillation to produce the USP (−)-menthol, the other menthol isomers are recycled to produce additional (−)-menthol. This route is interesting in that, although the distinguishing feature of the *l*-menthol series is the stereochemistry at C1 of the *p*-menthane system, the natural chirality of *l*-α-phellandrene is based on C4 and the chirality at C1 is induced across the ring at the hydrogenation stage.

In a similar way, (*S*)-(−)-β-phellandrene [6153-17-9] (**110**) can be converted to (−)-menthol. As mentioned in Section 4.1.2, (*S*)-(−)-β-phellandrene is more readily available than the α-isomer as it is extracted from turpentine from the southeastern United States. Hydrochlorination gives the same piperityl chloride that is obtained from (−)-α-phellandrene (116). (−)-Phellandrene is also available from (−)-β-pinene (**31**) by treatment with bisulfite under radical conditions followed by pyrolysis of the resulting sulfonic acid (**193**) as shown in Figure 40 (235,236).

The ready availability of the pinenes makes them attractive potential feedstocks for *l*-menthol production. A number of routes have been published, but the only commercially successful one is that described above, which uses myrcene as an intermediate. One alternative approach is as shown in Figure 41 using citronellene, prepared from (−)-β-pinene, as a key intermediate. The difficult step is to convert the citronellene to citronellol and two ways of achieving this are shown. The first uses an aluminium alkyl as described above under citronellene and citronellol. The second uses hydrochlorination of the trisubstituted double bond followed by anti-Markownikoff addition of hydrogen bromide to the other, then selective solvolysis and elimination. A process along these lines was developed by Glidden in the 1960s (206,230), but was never commercialized.

(−)-Piperitone (**194**) can be extracted commercially form *Eucalyptus dives*. Reduction with lithium aluminium hydride gives a mixture of (−)-*cis*-piperitol (**190**) (36%) and (+)-*trans*-piperitol (**191**) (64%), which are then separated (237). The (+)-*trans*-piperitol is then hydrogenated over Raney-nickel to give *d*-isomenthol (**165**) containing 1% *d*-menthol. The *d*-isomenthol is purified and isomerized to (−)-menthol (**42**) (224). This route is shown in Figure 42 and it is estimated that the Australian company Keith Harris & Co once produced ~30 tpa of *l*-menthol using it (154).

(+)-Pulegone (**187**) is present at ~75% in the oil of pennyroyal (*Mentha pulegium*), which is grown commercially in Southern Europe and North Africa. Hydrogenation gives a mixture of (−)-menthone (**195**) and (+)-isomenthone (**196**) which, on Birch reduction, gives (−)-menthol (**42**) as shown in Figure 43 (238,239). It is estimated that the Spanish company Destillaciones Bordas once produced ~20 tpa of *l*-menthol using this route (154).

According to Clark (188), total world production of menthol in 1998 was ~12,000 tonnes of which 2500 tonnes was synthetic. In 2005, the annual production of synthetic menthol was almost double Clark's estimate. The total demand is relatively inelastic, and so movements in supply have dramatic effects on prices. A shortfall of 100 tonnes of natural can cause prices to double or triple, an excess of 1000 could cause them to halve. Historically, menthol prices have seen sharp peaks about every 5–10 years. The troughs in menthol prices are generally in the $10–20/kg range and the peaks are typically in the $40/kg region but have reached as high as $100/kg (151,154). When the natural material is expensive, the companies making synthetic material are in a stronger position and some processes with marginal economics become more attractive. Local economic conditions, such as import restrictions and feedstock availability, can also be important in determining the economics of any given process.

l-Menthol is known for its refreshing, diffusive odor characteristic of peppermint. However, its main uses stem from its physiological cooling effect. When applied to skin or mucus membranes, *l*-menthol creates the sensation of cooling independent of the actual temperature of the tissue concerned. This property makes it useful in toothpaste and other oral care products, in confectionery, tobacco, cosmetic products, and pharmaceuticals.

Some menthyl esters, such as the acetate [2623-23-6] and isovalerate, are used in flavors. Menthyl salicylate has been used as sunscreen active and menthyl valerate has been used as a mild sedative under the trade name Validol.

The cooling activity of *l*-menthol is strongly dependent on the thickness of the *stratum corneum*. Therefore, a dose which is pleasantly cooling to the skin of the face, might be intensely irritating to the eyes. *l*-Menthol is quite volatile and so, application to the face, (eg, in a shaving preparation) is likely to cause undesirable effects on the eyes. The peppermint odor can also be unwanted at times. Consequently, there has been a great deal of work carried out in the search for analogues that are less volatile and odorless.

The first successes came as a result of an extensive research programme by Wilkinson Sword Ltd. Their research team synthesized >1200 coolants and laid the foundations of structure–activity work on the cooling effect of menthol and related materials (240–257). Only two of these materials have been commercialized. The more successful of the two is known as WS-3 (**197**) and is supplied by Millennium, Givaudan, and Frutarom, the latter using the trade name Framidice. It is prepared from *l*-menthol (**42**) as shown in Figure 44. Substitution of the alcohol function of menthol by bromine proceeds with retention of configuration. Conversion of the bromide (**198**) by formation of the Grignard reagent and carboxylation of the latter, also proceeds with retention to give the acid (**199**). The acid is then converted to the amide (**197**) via the acid chloride. A recent patent claims the preparation of WS-3 and other coolants from the corresponding nitriles (258).

WS-3 is an almost odorless white powder with a cooling power of ~1.5 times that of *l*-menthol and it is used as a cooling agent in tobacco, oral care preparations, cosmetics, confectionery, and pharmaceutical preparations.

The other commercially available WS material is WS-23 (**200**), which is supplied by Millennium and Qaroma.

Since the introduction of WS-3, many other coolants have appeared on the market, mostly based on the menthol structure and, in fact, synthesized from menthol. These are shown in Figure 45. Three menthyl esters are produced. The lactate (**201**) is made by Symrise and sold under the trade name Frescolat ML, while the succinate (**202**) is available from Advanced Biotech as Koolada. Menthyl pyrrolidone carboxylate (**203**) is sold by Quest as Questice. Questice serves as a sustained release precursor for menthol, the ester function being cleaved by lipases. It therefore finds use in cosmetics since the release rate is affected by the moisture levels in the skin. Thus as the body tries to lose heat, eg, on exercise, Questice provides the desirable sensation of cooling. Some higher menthyl esters have been patented as coolants by Firmenich (259). Two menthyl ethers are also of interest as coolants. The mono- ether of propylene glycol (**204**) has been added to the FEMA/GRAS list and the monoglyceryl ether (**205**) is sold as Cooling Agent 10 by Takasago (260–262). It is reported that the ether with the (*S*)-enantiomer of glycerol (**206**) is twice as effective as a coolant than is that from racemic glycerol (263). Menthone glycerol acetal (**207**) is available from Symrise as Frescolat MGA (264) and the amide (**208**) has been patented by Hasegawa (265). The *cis*- and *trans*-*p*-menthane-3,8-diols (**209**) and (**210**) have also been patented as coolants by Takasago (266,267) and the lactic acid derivative (**211**) by Firmenich (268). Further derivatives continue to be patented (eg, WO Pat. 2,005,049,553, assigned to Givaudan, Jpn. Pat. 2,005,041,783 assigned to Osaka Yuki Kagaku Kpgyo and US 6899901 assigned to Takasago), but it remains to be seen which will become commercial realities. Freskomenthe (**212**) is not closely related to menthol, but is sold as a coolant by Givaudan.

Many physiological cooling agents also display properties of insect repellency and (**197**) (269), (**201**) (270), (**203**) (271), (**207**) (270), (**209**), and (**210**) (272,273) have all been claimed to do this.

Isopulegol

Isopulegol	
CAS Registry No.	[7786-67-6] racemate
CAS Registry No.	[104870-56-6] (+)-isomer
CAS Registry No.	[89-79-2] (−)-isomer
formula	$C_{10}H_{18}O$
FW	154.25
bp	74°C at 1.33 kPa (10 mmHg)
d^{20}	0.912 g/cm^3
$n_D{}^{20}$	1.47
$[\alpha]_D$	23.6°

Isopulegol occurs in some species including *Eucalyptus citriodora* and Citronella. It is synthesized from citronellal and is used in perfumery, eg, in geranium accords. It has been reported to have a minty herbaceous odor, however, Yamamoto has found that when (−)-isopulegol (**172**) is very pure, both chemically and enantiomerically, it has virtually no odor. However, it does impart a feeling of freshness, crispness, and coolness to citrus fragrances (274) and is sold as Coolant P by Takasago. Unilever has patented its use as a coolant in combination with menthyl lactate (**201**) and menthyl glyceryl ether (**205**) (275).

Thymol

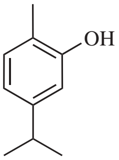
Thymol	
CAS Registry No.	[89-83-8]
formula	$C_{10}H_{14}O$
FW	150.22
mp	51.5°C
bp	115°C at 1.33 kPa (10 mmHg)
bp	233°C at 101.3 kPa (760 mmHg)
fp	101°C

Thymol is the trivial name for 2-isoproyl-5-methylphenol. Its natural sources, history, world consumption, substitutes, analogues, isomers, and derivatives have been reviewed by Clark (276).

Thymol (**169**) is found in a number of species, mostly from the *Thymus*, *Ocimum*, and *Monarda* families. It takes its name from thyme (*T. vulgaris*) of which it is an organoleptically important component. The levels present vary widely not only from species to species, but also from plant to plant within a species. As it is a phenol, it can be extracted from herb oils using aqueous sodium hydroxide and subsequent acidification. Such techniques were used to produce thymol in the past, particularly from thyme, oregano, and basil. Material isolated in this way tended to contain some carvacrol (**213**). This is a disadvantage as the medicinal, phenolic and tarry odor of carvacrol spoils the sweeter, herbal, and medicinal odor of thymol. Since thymol is easily prepared, as described above under menthol, the modern supply is entirely synthetic, mostly from Symrise. The major use for thymol is as an intermediate for menthol production.

Thymol has antibacterial, antifungal and antiparasitic properties. It is less toxic than phenol, the LD50 of thymol being 980 mg/kg for rats in contrast to 530 mg/kg for phenol. Its antibacterial properties mean that it inhibits plaque formation, and therefore it finds use in oral care applications. It has been used as a fungicidal treatment for fabrics and as an anthelmintic for both humans and animals. Synthetic thymol finds relatively little use in perfumes and flavors, oils, such as thyme and basil, being used in preference.

In addition to production of menthol, thymol is also used to prepare a number of indicator dyes, such as thymol blue (**214**) (red-yellow at pH 1.2–2.8 and yellow-blue at pH 8.0–9.2) and thymolphthalein (**215**) (colorless-blue at pH 8.8–10.5).



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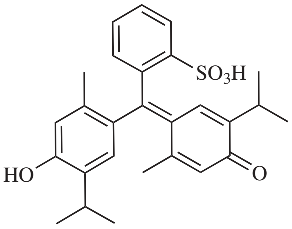

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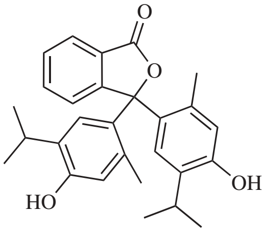


(215)

Bicyclic Monoterpenoid Alcohols and Their Esters. *Borneols*

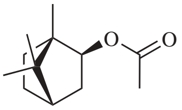
Borneols[a,b]

CAS Registry No.	[507-70-0] racemate
CAS Registry No.	[464-43-7] (+)-enantiomer (1-(*R*))
CAS Registry No.	[464-45-9] (−)-enantiomer (1-(*S*))
formula	$C_{10}H_{18}O$
FW	154.25
mp	210°C racemate
mp	208°C enantiomers
bp	212°C at 101.3 kPa (760 mmHg)
d^{20}	1.0110 g/cm^3
$[\alpha]_D$	38°
vp	33.5 mmHg (25°C)
vd	5.31 v air
CAS Registry No.	[124-76-5]
bp	214°C at 101.3 kPa (760 mmHg)
mp	212°C
$[\alpha]_D$	34

[a] Borneol is *endo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**157**).

[b] Isoborneol is (*exo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol [124-76-5] (**119**).

The preparation and uses of isoborneol (**119**) and its esters are described above in Section 4.1.3 under camphene. Optically pure (−)-borneol can also be prepared from (−)-pinenes (277). Borneol, isoborneol, and their acetates occur in a wide variety of herbs and other plants. They are used in perfumes for soaps and detergents for woody, camphor, and pine notes with a relatively low cost. Two monoethers of isoborneol with glycols are used as fixatives in perfumery. These are Arbanol (Millennium) (**216**) and Bornafix (IFF) (**217**). The major product in perfumery, by far, is isobornyl acetate [125-12-2] (**117**); borneol being used at about one-tenth the volume of the former. The most important use for isoborneol is as an intermediate for camphor. Estimates of total world tonnage of the two alcohols and their esters, vary from 1000 to 2000 tpa (82,83).



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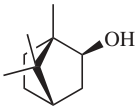

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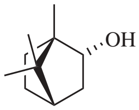

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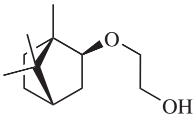

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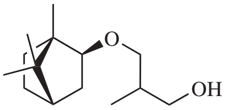

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4.3. Monoterpenoid Ethers. *1,8-Cineole*

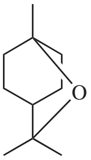
1,8-Cineole

CAS Registry No.	[470-82-6]
FW	154.25
mp	2°C
bp	108°C at 13.33 kPa (100 mmHg)
bp	177°C at 101.3 kPa (760 mmHg)
d^{20}	0.9245 g/cm^3
$n_D{}^{20}$	1.4574
fp	47–48°C
odor threshold	12 ppb
solubility	0.35%ww in water at 25°C, soluble in most organic solvents

1,8-Cineole (**103**) is also known as eucalyptol, cajeputol, cajuputol, kajeputol, 1,8-epoxy-*p*-menthane, 1,8-oxido-*p*-menthane and the anhydride of *p*-menthane-1,8-diol. It is very widespread in nature, which is not surprising since it is easily formed by trapping of the terpinyl carbocation by water or from acid-catalyzed cyclization of α-terpineol or similar reactions. Such reactions also explain its presence in pine oils and dipentene. Its natural sources, history, producers and capacity, pricing, imports, substitutes and analogues, and derivatives have been reviewed by Clark (278).

1,8-cineole is produced only from natural sources as these are sufficiently inexpensive to make synthesis uneconomic. Originally, it was produced from Cajeput oil, but the discovery of *Eucalyptus globulus*, the oil of which contains up to 95% 1,8-cineole, in 1788 led to the first commercial production from that source in 1854 in Australia, and then to its taking over as the dominant source. Australia remained the leading producer until 1945, but since then Brazil, Colombia, Spain, South Africa, Paraguay Portugal, China, and India have all started production. The largest producers are currently China and Portugal. Much of the oil is used per se and only about one-quarter of it is distilled to produce pure cineole. Tonnage estimates vary from 700 tpa (82) to 3300 tpa (278). The price of *E. globulus* oil varies with supply and demand and is usually in the \$5–8/kg range. Pure 1,8-cineole is in the \$8–10/kg range (278).

Cineole has a camphoraceous odor strongly reminiscent of eucalyptus. It has some use in fragrance and in oral care preparations, but the largest part is used in paramedical applications because of its antibacterial and decongestant properties.



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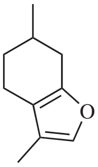


(218)

Menthofuran

Menthofuran	
CAS Registry No.	[494-90-6]
formula	$C_{10}H_{14}O$
FW	150.22
bp	79°C at 1.33 kPa (10 mmHg)
d^{20}	0.9676 g/cm^3
n_D^{20}	1.4855
$[\alpha]_D$	94.6°

Menthofuran (**218**) occurs in a variety of oils, mostly in mints and it is one of the characteristic components of *M. piperita* (peppermint). It can be prepared from pulegone and is mainly used in reconstitutions of peppermint oil (82). The commonest isomer is the (+)-form [17957-94-7]. Menthofuran can also be prepared from pulegone by sulfonation with fuming sulfuric acid followed by pyrolysis of the resulting sultone. Use of (+)-pulegone as feedstock gives (+)-menthofuran.

4.4. Monoterpenoid Aldehydes.

Citral

Citral	
CAS Registry No.	[5392-40-5]
formula	$C_{10}H_{16}O$
FW	152.23
bp	229°C at 101.3 kPa (760 mmHg)
d^{20}	0.888 g/cm^3
$n_D{}^{20}$	1.488
vp	0.2 mmHg (20°C)
vd	5 v air

Citral exists as two geometric isomeric forms, geranial (also known as citral a), which is the (*E*)-isomer and neral (also known as citral b), which has the (*Z*)-configuration. When the word citral is used, it usually implies a mixture of the two geometric isomers.

Geranial	
CAS Registry No.	[141-27-5]
bp	77°C at 0.24 kPa (1.8 mmHg)
bp	119°C at 2.7 kPa (20 mmHg)
bp	228°C at 101.3 kPa (760 mmHg)
d^{20}	0.8972 g/cm^3
$n_D{}^{20}$	1.4898

Neral	
CAS Registry No.	[106-26-3]
bp	76.5°C at 0.31 kPa (2.3 mmHg)
bp	120°C at 2.7 kPa (20 mmHg)
d^{20}	0.8869 g/cm^3
$n_D{}^{20}$	1.4869

Citral is widespread in nature, the two isomers usually both being present and in ratios that vary considerably, but usually within the 40:60–60:40 range. The richest sources are lemongrass (*Cymbogon citratus*), which contains 70–90% citral, and the fruit of *Litsea cubeba*, which typically contains 60–75%. It also occurs in lemon balm, ginger, basil, rose and, of course, citrus species. Lemons usually only contain a few percent of citral, but it is the principal component responsible for their characteristic odor. Special grades are produced by extraction from lemongrass and *Eucalyptus staigeriana*, but the only natural source, which competes economically as a source for citral as a feedstock, is Chinese *L. cubeba*.

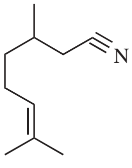
Citral can be prepared from both α- and β-pinene. These are initially converted to geraniol as described in Sections 2.1 and 2.2, respectively, and then oxidized to citral using either catalytic oxidative dehydrogenation or Oppenauer oxidation (161–163). The routes to citral used by the three main petrochemical suppliers, BASF, DSM, and Kuraray are described in Sections 2.3–2.5.

Citral has some use in fragrances and flavors owing to its lemon character. It is an intermediate of major importance in the production of other materials particularly ionones and vitamins. Most of the citral produced is used internally by the companies that make it and so it is very difficult to estimate total production figures. Its price is in the \$8–15/kg bracket (82).

The odor of citral is very desirable as there is a strong association between lemon odor and cleanliness in the mind of the consumer. However, citral is not a very robust molecule. For example, even attempts to purify it by distillation are likely to lead to isomerization (215) and addition of a mild acid, such as ascorbic acid, is needed to prevent this (279). In functional products, citral is subject to both acid and base reactions and to oxidation by air or by other components, such as hypochlorite bleach. Consequently, a great deal of research has been invested in the search for materials with the odor of citral, but with much better stability.

Some of the first citral analogues to appear were its dimethyl acetal [7549-37-3] and diethyl acetal [7492-66-2]. The acetal group is more stable than the aldehyde, but the improved stability is bought at the price of a poorer match to the odor of lemon. A major breakthrough came with the discovery of geranyl nitrile [31983-27-4]. Geranyl nitrile has also been known under such names as Citraldia, Citralva, Citranile, Citrylone, geranionitrile, Geranitrile, geranonitrile, Lemonitrile, LRG 183, LRT 7, or LRT 8 although some of these have fallen out of use. Geranyl nitrile is an example of the many instances in which the nitrile function plays a similar role to the aldehyde group as far as odor is concerned, yet it is much more stable to acids, bases, and oxidants. Thus, geranyl nitrile has an odor that is distinctly lemon in character and has therefore become an important fragrance ingredient. Its price is in the range \$10–15/kg and the market size is estimated as 1500 tpa (154). There are two routes that are used for commercial production, as shown in Figure 46. The products differ slightly in the balance of the isomers produced, in each case (**219**) is the major product, but it is also accompanied by (**220**), (**221**), and (**222**). In one route, the oxime (**223**) of citral (**55**) is dehydrated while in the other, the Döbner reaction of methylheptenone (**19**) with cyanoacetic acid gives geranyl nitrile in one pot.

Double bonds are susceptible to attack by oxidants, and also undergo acid-catalyzed reactions, and so citronellyl nitrile (**224**) and tetrahydrogeranyl nitrile (**225**) have also been developed as fragrance ingredients. Citronellyl nitrile is used to a lesser extent than geranyl nitrile and is more expensive. Tetrahydrogeranyl nitrile is also known under the trade names Hypo-Lem (IFF) and Virixal Nitrile (PCAS). Citronitrile (**226**) is an analogue of citral in which the isopropenyl group has been replaced by a benzene ring and the aldehyde by a nitrile.



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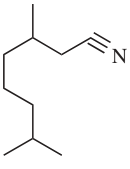

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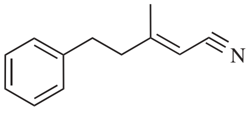


(226)

Citronellal

Citronellal	
CAS Registry No.	[106-23-0]
CAS Registry No.	[2385-77-5] (*R*)-(+) enantiomer
CAS Registry No.	[5949-05-3] (*S*)-(−) enantiomer
CAS Registry No.	[26489-02-1] racemate
formula	$C_{10}H_{18}O$
FW	154.25
bp	107°C at 2.0 kPa (15 mmHg)
bp	208°C at 101.3 kPa (760 mmHg)
d^{20}	0.8510 g/cm^3
$n_D{}^{20}$	1.4467
$[\alpha]_D$	15°

Citronellal (**135**) occurs in a number of essential oils. The richest sources are *Eucalyptus citriodora* (up to 85% citronellal content), some chemotypes of *Litsea cubeba* and citronella (*Cymbopogon nardus*) [typically 30–40% of the (+)-enantiomer]. Swangi Leaf Oil (*Citrus hystrix*) is rich in (−)-citronellal, as it accounts for 60–80% of the oil obtained from the leaves (280,281). *Backhousia citriodora* contains up to 80% of the (−)-enantiomer. Natural grades of citronellal are commercially available from *E. citriodora* and citronella, but the major sources of commercial material are from geraniol or myrcene as shown in Figure 7. Citronellal is accessible from citronellol (95) or geraniol by catalytic isomerization (95,160) or from citral by selective hydrogenation (282). The lithium catalyzed addition of diethylamine to myrcene and subsequent hydrolysis to citronellal (152) has become a commercially significant route. Citronellal can also be made by telomerization of isoprene (283). Synthetic citronellal costs ~$10/kg. It is estimated that ~400 tpa are used in perfumery and in flavors for its fresh, green, and citrus odor (83), however, the major use is as a starting material for menthol (227) and hydroxycitronellal production, each of which uses >1000 tpa of citronellal. These routes are described above under menthol in Section 4.2.2 and immediately below under hydroxycitronellal.

Citronellal (**135**) can also be converted to the *cis*- and *trans*-*p*-menthane-3,8-diols [92471-23-3] (**209**) and [91739-72-9] (**210**), respectively, by reaction with dilute acids as shown in Figure 47 (284,285). The glycol mixture can be readily purified by distillation and the two isomers easily separated. The glycols are useful as coolants and as insect repellents, as is citronellal itself, and are especially effective against mosquitos (286). Derivatives of the glycols have been prepared and are useful as insecticides and plant growth regulators (287).

Hydroxycitronellal

Hydroxycitronellal	
CAS Registry No.	[107-75-5]
formula	$C_{10}H_{20}O_2$
FW	172.26
bp	87°C at 0.13 kPa (1 mmHg)
bp	116°C at 0.67 kPa (5 mmHg)
d^{20}	0.9220 g/cm^3
$n_D{}^{20}$	1.4494
$[\alpha]_D$	10.5°

Hydroxycitronellal (**87**) is important in perfumery for its floral, muguet green, and sweet odor that finds use in a wide range of floral fragrances. It has been sold under many trade names, such as Anthosal, Centaflor, Cyclalia, Cyclia, Cyclodor, Cyclohydronal, Fixol, Fixonal, Hycelea, Hylea, Majal, Muguet synthetique, Muguettine principe, Storine, Tilleul, and a special grade prepared from citronellal ex citronella was called Laurine. Annual consumption is estimated at ~1000 tonnes (83) and the price would, typically be in the \$12–15/kg range. It is valued for its floral odor that is strongly reminiscent of muguet and also has some lime blossom character.

Direct hydration of citronellal to hydroxycitronellal is not possible because of the competing Prins reaction that produces isopulegol or the 3,8-*p*-menthanediols described above. However, it is possible to protect the aldehyde function by formation of a bisulfite, an enol acetate, an enamine, an imine or an oxazolidine (288–291). As an example, Figure 48 shows the use of diethanolamine as a protecting group. Addition of diethanolamine to citronellal (**135**) in the presence of an acid catalyst leads to the oxazolidine (**227**). When this is treated with conc. sulfuric acid, the acid adds to the double bond to give the sulfate ester (**228**). Addition of water results in hydrolysis of both the sulfate ester and the oxazolidine protecting group to produce hydroxycitronellal (**87**). It is also possible to hydrate citronellol, and then dehydrogenate the primary alcohol function of the resultant diol to produce hydroxycitronellal (292,293). The hydration can be effected by using a strong acid ion-exchange resin (294) and solvents, such as 2-propanol (295) or acetone (296). Hydroxycitronellol can also be produced from citronellene as shown in Figure 20.

Using chemistry based on their menthol process (as described above), Takasago can produce optically pure (−)-hydroxycitronellal and they claim that this enantiomer has a preferable odor and is a weaker skin sensitizer than the racemate (168,297).

The dimethyl acetal and methyl anthranilate Schiff's base of hydroxycitronellal are also important fragrance ingredients. The latter (**229**), is available under trade names, such as Anthralal, Arangol, Arerantae, Aurangeol, Auranol, Aurantea, Aurantein, Aurantion, Aurantine, Aurantol, Aurantolin, Aurantorcol, Aurentol, Auriol, Bigariol, and Bigaradia.

Campholenic Aldehyde

Campholenic Aldehyde

CAS Registry No.	[4501-58-0]
FW	152.23
bp	77°C at 1.33 kPa (10 mmHg)
$[\alpha]_D$	3°

Campholenic aldehyde (**30**) or campholene aldehyde occurs in nature, but in a limited range of species. It is produced commercially from α-pinene (**20**) by epoxidation and subsequent Lewis acid catalyzed rearrangement (298,299). Zinc bromide is the most effective catalyst for the rearrangement, but the chloride can also be used. As shown in Figure 49, the epoxidation and rearrangement both proceed stereoselectively, so that if the starting material is (+)-α-pinene (**230**), the epoxide is (+)-*cis*-α-pinene epoxide [1686-14-2] (**231**) and rearrangement gives (−)-campholenic aldehyde (**232**). The specific rotation of the aldehyde is very low and so it is difficult to check its enantiomeric purity, minor contaminants with high specific rotations proving particularly troublesome. Many commercial sources of pinene contain both enantiomers (usually not in equal proportions), and so the cheapest sources of campholenic aldehyde are usually of low enantiomeric purity. This has some significance as will be seen below.

Campholenic aldehyde is not used *per se* in perfumery, but is of importance as the precursor for a range of sandalwood materials. This is of increasing importance as the supply of natural sandalwood is insufficient to meet demand and overharvesting has put the future of the species (*Santalum album*) at risk.

The campholenic aldehyde derived sandalwood materials were discovered by the East German company VEB Miltitz in the late 1960s (300). They found that if campholenic aldehyde undergoes aldol condensation with an aldehyde or ketone and the resultant unsaturated ketone is reduced to an allylic alcohol (**233**), as shown in Figure 49, the products possess a fine odor reminiscent of sandalwood. The first of the series to be commercialized was the product (**234**) [28219-61-6] derived from an initial aldol with butanal. This material is now available under the trade names Anandol, Bacdanol, Balinol, Bangalol, Madrol, Radjanol, Sandolene, Sandranol, Santalinol, and Sriffol. Versions with high enantiomeric excess are known as Dartanol, and Laevosandol. In general, in this series, it has been found that the best sandalwood character is associated with those enantiomers prepared from (−)-campholenic aldehyde (**232**). Using propanal in place of butanal gives (**235**) [28219-60-5], which is known as Sandacore, Sandalmysore Core, Santacore, Santalaire, Santalice, and Santaliff. A high ee version of this material is sold under the name Hindinol. The saturated analogue of (**235**) is known as Brahmanol (**236**) [72089-08-8] (301). If the double bond in the cyclopentene ring is also reduced, the resulting product does not have a sandalwood odor. When a ketone, such as 2-butanone, is used in the aldol reaction, a mixture of products results as the ketone can react on either side of its carbonyl group. When both the aldehyde and side-chain double bond of the product mixture from 2-butanone are reduced, a mixture of saturated alcohols is formed. Only those isomers with the basic structure (**237**) rather than (**238**) possess a sandalwood odor (302,303). The former are the basis of the product known as Sandalore [65113-99-7]. One minor component of Sandalore is the unsaturated material (**239**) in which the double bond has moved rather than being hydrogenated. This minor component contributes a disproportionate amount to the odor of Sandalore and is now manufactured independently and sold under the names Ebanol [67801-20-1] and Ebalore (304,305). Alkylation of the intermediate ketone before reduction gives Polysantol (**240**) [107898-54-4], also known as Nirvanol and Suprasantol (306,307). Cyclopropanation of (**235**) gives Javanol (**241**) [198404-98-7], which is claimed to be the most powerful of all sandalwood chemicals in this series (308). The discovery of Javanol is a good example of the use of SAR and molecular modelling in fragrance ingredient discovery (309). Prices of these materials start in the \$20–40/kg range and rise to >\$200/kg. Many of them are produced and used internally by fragrance companies so it is difficult to estimate volumes, but the total figure is likely to be well >1000 tpa.

4.5. Monoterpenoid Ketones. *Carvone*

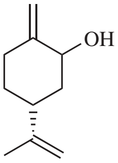
Carvone	
CAS Registry No.	[99-49-0] unspecified stereochemistry
CAS Registry No.	[6485-40-1] (*R*)-(−)-enantiomer
CAS Registry No.	[2244-16-8] (*S*)-(+)-enantiomer
FW	150.22
bp	98°C at 1.33 kPa (10 mmHg)
bp	157°C at 13.33 kPa (100 mmHg)
bp	23°C at 101.3 kPa (760 mmHg)
d^{20}	0.96 g/cm^3
$n_D{}^{20}$	1.4990
$[\alpha]_D$	62°
vp	0.4 mmHg (20°C)
vd	5.2 v air
fp	83°C
solubility	insoluble in water at 20°C, soluble in ethanol, mineral oil, and other organic solvents

Carvone, also known as *p*-mentha-6,8-dien-2-one and carvol, is a material of commercial importance and has been reviewed by Clark (310). There are two enantiomers of which the (*R*)-(−)- is the commoner and is used in much greater quantities. If the stereochemistry is not specified, it is usually the (*R*)-(−)-enantiomer, usually referred to as *l*-carvone, which is intended. Both isomers occur fairly widely in essential oils. The most significant natural sources of carvone are spearmint, dill, and caraway. The term spearmint is applied to various *Mentha* species including *M. cardiaca, M. gracilis, M. spicata*, and *M. viridis* and these usually contain 55–75% of the (*R*)-(−)-enantiomer (**242**). The (*S*)-(+)-enantiomer (**243**) is found in dill (*Anethum graveolens*) at levels of 30–65% and at 50–75% in caraway (*Carum carvi*).

Carvone is used both as a synthetic material and in the form of essential oils. Very little is isolated and purified from natural sources. The annual consumption of *l*-carvone from synthesis is ~1000 tonnes. The major suppliers of oils rich in *l*-carvone are Chinese. The enantiomer, *d*-carvone, has a much smaller usage, ~10 tpa of synthetic and just under 100 tpa as oils of dill or caraway.

Carvone is one of the classic examples of odor differences between enantiomers. In 1971, Friedman and Miller (311) interconverted the enantiomers using the reactions shown in Figure 50 and proved conclusively that the spearmint character of *l*-carvone and the dill–caraway character of *d*-carvone were intrinsic properties of the respective enantiomers and were not due to trace impurities. Thus epoxidation of *l*-carvone (**242**) gave (**244**), which could be reduced to *d*-*trans*-carveol (**245**) and that oxidized to *d*-carvone (**243**). Similarly, *d*-carvone could be converted via the epoxide (**246**) and *l*-*trans*-carveol (**247**) to *l*-carvone (**242**). In the same year, however, Leitereg and co-workers (312) carried out a well-constructed sensory evaluation of the carvone enantiomers and demonstrated that only about two-thirds of people can distinguish between them.

l-Carvone (**242**) is manufactured from *d*-limonene (**11**) by the route shown in Figure 51 (313,314). The starting material is available as a by-product from citrus (particularly orange) juice production. Addition of nitrosyl chloride (usually generated *in situ* from, eg, isopropyl nitrite and hydrochloric acid) gives the adduct (**248**), which exists in equilibrium with its dimer (**249**). Treatment of the adduct with a weak base gives carvoxime (**250**), which can be hydrolyzed or trans-oximated to produce *l*-carvone (**242**). The main companies who produce carvone in this way are Quest (Mexico), Formosa (Brazil), and Frutarom (Israel). The largest producer is Quest's Mexican site (310). New producers are now appearing in China and a significant recent development is the new process operated by Millennium in Georgia (USA) (315). In this new process, shown in Figure 52, limonene (**11**) is first epoxidized to (**251**) and the epoxide is rearranged to carveol (**252**) using a metal catalyst promoted by a phenol. The secret of this process lies in the catalyst as most rearrangement catalysts convert limonene oxide to the allylic alcohol with an exocyclic methylene group (**253**) and this material can neither be isomerized cost effectively to carveol nor oxidized cost effectively to carvone. Since both of the commercial routes to *l*-carvone depend on *d*-limonene as a feedstock, the price of the former tends to fluctuate in line with that of the latter. Typically, *l*-carvone is in the $15/kg price range (82,83,310). The price of *d*-carvone is typically about three times that of the *l*-isomer in consequence of the higher price of the *l*-limonene from which it is prepared.



(253)

By far, the most important use of *l*-carvone is as a spearmint flavor in oral care preparations, such as toothpastes and mouthwashes. Chewing gum is another significant use for *l*-carvone. The *d*-isomer is used in flavors, particularly for pickles, though usually in the form of dill or caraway essential oils. Carvone can be used to effect in small quantities in perfumery, but this represents a very small fraction of total consumption.

Menthone

Menthone	
CAS Registry No.	[89-8-5]
CAS Registry No.	[14073-97-3] (−)-isomer
CAS Registry No.	[3391-87-5] (+)-isomer
FW	154.25
mp	−6°C
bp	138°C at 13.33 kPa (100 mmHg)
bp	210°C at 101.3 kPa (760 mmHg)
d^{20}	0.8903 g/cm^3
$n_D{}^{20}$	1.4500
$[\alpha]_D$	29°
vp	0.5 mmHg (20°C)

The history and uses etc of menthone have been reviewed by Clark (316).

Menthone is sometimes referred to as *trans*-menthone, but the prefix is essentially redundant as the cis isomer is called isomenthone [31977-92-1]. Menthone and isomenthone can be interconverted by epimerization, the equilibrium mixture containing ∼70% menthone and 30% isomenthone. In fact, isolation of either in pure form is difficult because of the ease of interconversion. The direction of rotation of plane-polarized light switches on epimerization so that *l*-menthone (**195**) isomerizes to *d*-isomenthone [1196-31-2] (**196**) and *d*-menthone to *l*-isomenthone.

Menthone is fairly widespread in nature, the *l*-isomer being commoner than the *d*-. It is commonest in mints, pennyroyal, and sages, and these are also the oils containing the highest levels. Low levels are found in oils, such as geranium and rose.

By far the most significant sources of menthone are the dementholized oils from cornmint and peppermint. Synthetic material is available from oxidation of menthol, from carene (see Fig. 35) and from hydrogenation of thymol (317), but this accounts for only ∼30 of the 1330 tonnes of menthone produced annually (316). Menthone is used in mint reconstitutions and to some extent in other essential oil reconstitutions and perfumes.

Other materials used similarly include piperitone (**194**) and pulegone (**187**). The former is usually isolated from the oil of *Eucalyptus dives*, but some is also synthesized from limonene (82). It has a fresh minty, camphoraceous note, and finds some use in perfumes (largely for masking), but more in flavors, such as caraway and tarragon. It is also used as a mint flavor ingredient in oral care products.

Camphor

Camphor	
CAS Registry No.	[76-22-2] racemate
CAS Registry No.	[464-49-3] (*R*)-(+)-enantiomer
CAS Registry No.	[464-48-2] (*S*)-(−)-enantiomer
formula	$C_{10}H_{16}O$
FW	152.23
mp	179–181°C
bp	204°C at 101.3 kPa (760 mmHg)
$[\alpha]_D$	44°
vp	4 mmHg (70°C)
vd	5.24 v air
ait	465°C
lel	3.5%

Camphor (**120**) is widespread in nature in both enantiomeric forms. The richest source is the oil of camphor wood *Cinnamomum camphora*, from which the (+)-enantiomer is extracted commercially (318). It is also an important contributor to the odor of lavender and of herbs, such as sage and rosemary.

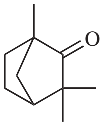
Most synthetic camphor is produced from α-pinene (**20**) via camphene (**27**), as shown in Figure 24. Addition of acetic acid to camphene gives isobornyl acetate (**117**), which is saponified to produce isoborneol (**119**) in good yield. Catalytic dehydrogenation of isoborneol then gives camphor. Catalysts include copper chromite (319) or metals, such as zinc, indium, gallium, and thallium (320).

Camphor production runs to many thousands of tonnes/annum. It is used in perfumes but, more importantly, as a plasticizer, preservative, disinfectant, and in paramedical applications. Its use in religious ceremonies in Asian countries is also a significant part of total consumption (321).

Fenchone

Fenchone	
CAS Registry No.	[1195-79-5] racemate
CAS Registry No.	[7787-20-4] (+)-isomer
CAS Registry No.	[4695-62-9] (−)-isomer
formula	$C_{10}H_{16}O$
FW	152.24
mp	5°C
bp	122°C at 13.33 kPa (100 mmHg)
bp	193°C at 101.3 kPa (760 mmHg)
d^{20}	0.9452 g/cm^3
$n_D{}^{20}$	1.4628
$[\alpha]_D$	70°

Fenchone (**254**) occurs in a number of essential oils, such as cedar leaf and lavender, and the (−)-isomer is particularly important in fennel. Synthetic material is made from pinene. Addition of carboxylic acids to α-pinene gives the corresponding esters of fenchol. These esters can be hydrolyzed to fenchol, which is then oxidized to fenchone. It is used mainly in reconstitution of fennel oils.



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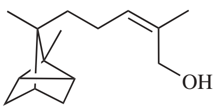
5. Sesquiterpenoids

Sesquiterpenoids contain three isoprene units and the precursor for them all, in nature, is farnesyl pyrophosphate as shown in Figure 3. Because there are now three double bonds in the molecule, as opposed to the two of monoterpenoids, the variety of possible cyclic structures is much greater, as shown in Figure 6. Skeletal rearrangements, migrations of methyl groups, and even loss of carbon atoms to produce norsesquiterpenoids all contribute further to the variety. There are probably >3000 sesquiterpenes that have been isolated and identified in nature. A large number of sesquiterpenoids possess interesting biological activities, but most are of academic interest only and have no commercial application outside folk medicine.

As a consequence of their higher molecular weight, sesquiterpenoids are less volatile than their monoterpenoid counterparts. This means that a smaller percentage find use in perfumery. However, some of those that do have an odor, have low thresholds and/or high intensities. They often have fixative properties and are generally used as base notes, in particular as woody notes, in perfumes. The use of sesquiterpenoids in perfumery was reviewed by McAndrew (322). Three of the most important sesquiterpenoid-rich oils are sandalwood, patchouli, and vetiver.

Sandalwood oil is obtained by distillation of the wood of the parasitic tree *Santalum album*. The isomeric alcohols α-santalol [115-71-9] (**255**) and β-santalol [115-71-9] (**256**) account for ~90% of the oil. Over-harvesting has taken the species to the brink of being endangered and supply is, consequently, now very short. Fortunately, the odor can be recreated using synthetic materials, such as the isobornylcyclohexanols (see under camphene in Section 4.1.3) and the campholenic aldehyde derivatives described in Section 4.4. Details of sandalwood chemistry can be found in Chapter 6 of the book by Sell (323).



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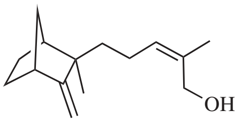

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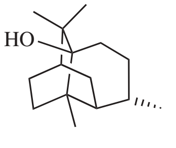
Patchouli oil is distilled from the fermented leaves of *Pogostemon cablin*. Its main constituent is patchouli alcohol [5986-55-0] (**257**), also known as patchoulol. However, this and the other major components have relatively little odor and the characteristic scent arises from some of the minor compounds present. Vetiver oil is distilled from the roots of the tropical grass *Vetivera zizanoides*. It contains a very large number of sesquiterpenoids, α-vetivone (**258**), β-vetivone (**259**), and khusimol (**260**) accounting for ~35% but, as with patchouli, it is a number of minor components that are responsible for its valuable odor. Details of patchouli and vetiver chemistry can be found in Chapter 7 of the book by Sell (323).



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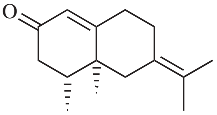

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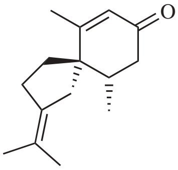

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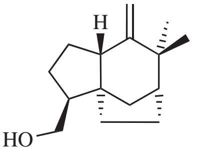

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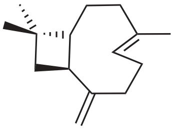
5.1. Caryophyllene

Caryophyllene	
CAS Registry No.	[87-44-5]
formula	$C_{15}H_{24}$
FW	204.35

Caryophyllene (**261**), often referred to as β-caryophyllene, is very widespread in nature, occurring in such diverse plants as pepper, Melissa, ylang–ylang, marigold, and the herbs sage and basil. The richest source is clove bud oil (*Eugenia caryophyllata*) from which it is extracted commercially, albeit as a by-product of eugenol production. It is used to produce a variety of materials that are used in perfumery. Examples include caryophyllene alcohol or caryolanol (**262**) (from acid-catalyzed hydration) and the epoxide [1139-30-6] (**263**) (from treatment with a per-acid), which has a woody odor with a hint of amber. The epoxide also occurs widely in nature and is useful in reconstituting essential oils. The caryophyllene molecule is very strained, having a trans-double bond in a nine-membered ring, to which a four-membered ring is fused. Thus, many of its reactions proceed with rearrangement. For example, acetylation gives a mixture of ketones known as acetylcaryophyllene. A description of its chemistry can be found in Chapter 7 of the book by Sell (323).



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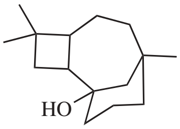

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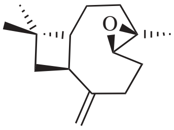

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5.2. Longifolene

Longifolene	
CAS Registry No.	[475-20-7]
formula	$C_{15}H_{24}$
FW	204.35
bp	254°C at 94.1 kPa (706 mmHg)
d^{20}	0.928 g/cm^3
$n_D{}^{20}$	1.504
$[\alpha]_D$	45°

Longifolene (**264**) occurs in and is commercially extracted from the oil of *Pinus longifolia.* It has a very strained ring system and exposure to acids causes an exothermic rearrangement to isolongifolene (**265**). Epoxidation of isolongifolene gives the corresponding epoxide (**266**), which undergoes acid-catalyzed rearrangement to isolongifolanone (**267**). This is valued in perfumery for its warm woody, amber odor, and is produced under trade names, such as Valanone B, Isolongifolanone, Timberone, and Piconia (324). The Prins reaction of isolongifolene with formaldehyde has also produced a number of useful products (325,326). The most significant of these is the mixture of acetates (**268**) and (**269**), which is known under the trade name of Amboryl Acetate. All of these reactions are shown in Figure 53. Further chemistry of longifolene is described in Chapter 7 of the book by Sell (323).

5.3. Cedrene, Cedrol, and Thujopsene. The name cedar is used to describe a variety of trees of the *Cedrus*, *Juniperus*, *Cupressus*, and *Thuja* families. In chemical terms, they fall into two main categories, those that are rich in cedrene, cedrol, and thujopsene, and those that are rich in atlantones. The second category is used *per se* in perfumery, eg, in the form of Atlas Cedarwood oil. The first category, which includes Texan, Virginian, and Chinese cedar, has a much larger production and the oils are used both *per se* and as feedstocks for a range of fragrance ingredients. Estimates of the production volume of these oils are of the order of 500 tpa, with prices in the range $8–16/kg for American oils and somewhat less for Chinese. Overharvesting is becoming an issue with cedarwood though the situation is not yet as severe as it is for sandalwood.

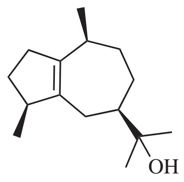
The main components of these cedarwood oils are α-cedrene [469-61-4] (**270**), cedrol [77-53-2] (**271**), and thujopsene [470-40-6] (**272**). The oils also contain a variety of minor components (327). Fractional distillation gives hydrocarbon and alcohol fractions. Cedrene and thujopsene are separated from the former and recrystallization of the latter gives cedrol. A crude alcoholic fraction containing both cedrol and isomers, such as widdrol (**273**) together with some ketonic material, is sold as cedrenol. Thujopsene is also isolated from Hiba Wood oil (83).

Acetylation of the alcohol mixture yields cedryl acetate [61789-42-2] (**274**). Cedryl methyl ether [19870-74-7], and [67874-81-1] (**275**), also known as Cedramber, is readily made by methylation of cedrol (328). Both the ester and the ether have woody–amber odors, and are therefore useful in perfumery. Cedrene oxide [11000-57-0] (**276**) also has a woody–amber smell of use in perfumery and Ambrocenide (**277**), another amber material, can be prepared from it by hydrolysis and reaction with acetone. These reactions and products are shown in Figure 54.

The most important cedarwood derivative, with production in the hundreds of tonnes/annum and prices of \$25–35/kg (82,83), is the mixture produced by acylation of the oil as shown in Figure 54. This product has a rich woody odor with cedar, amber, and musky character (329). Either the hydrocarbon fraction or the entire oil can be used as feedstock as, during the acylation process, the alcohols are dehydrated to the corresponding olefins, and these then react together with the original hydrocarbon oil components. The product is known under a range of trade names, such as acetylcedrene, Lignofix, Lixetone, methyl cedryl ketone, and Vertofix. The major component of the mixture is acetylcedrene (**278**), but the major contributor to the odor is the acetylation product [32388-56-0] (**279**) of rearranged thujopsene (330–332). The Friedel-Crafts reaction is normally carried out with sulfuric or polyphosphoric acids as catalysts but, interestingly, when titanic chloride was used, the acylation product of cedrene was not acetylcedrene but the odorless vinyl ether (**280**) (333).

5.4. Guaiol and Guaiazulene.

Guaiol [489-86-1] (**281**) and bulnesol [22451-73-6] (**282**) are the major components of Guaiacwood oil, which is distilled from the South American tree *Bulnesia sarmienti*. Both the oil and guaiol extracted from it are used as fixatives in perfumery. The acetylated oil and guaiyl acetate [134-28-1] are also used in this way. Guaiazulene [8030-55-5] (**283**) is prepared from guaiol by dehydration and dehydrogenation. It is used as an anti-inflammatory agent. Guaiazulene is also prepared from α-gurjunene [489-40-7] (**284**), which is the major component of Gurjun Balsam. This is obtained from Southeast Asian trees of the *Dipterocarpus* species and is used in a similar way to Guaicwood oil.



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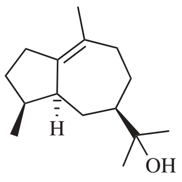

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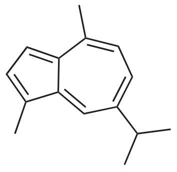

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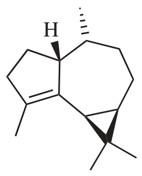

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5.5. Farnesol

Farnesol

CAS Registry No.	[4602-84-0] unspecified isomers
CAS Registry No.	[7541-49-3] unspecified-isomers
CAS Registry No.	[106-28-5] racemic (*E*,*E*)-isomer
formula	$C_{15}H_{26}O$
FW	222.37
bp	156°C at 1.6 kPa (12 mmHg)
d^{20}	0.8846 g/cm^3
$n_D{}^{20}$	1.4890

Farnesol (**285**), also known as farnesyl alcohol, occurs in many blossom oils. The trans-trans-isomer is commonest, but all four possible isomers do occur in nature and all share the same odor, reminiscent of muguet and linden blossom. A mixture of trans-trans- and trans-2-cis-6-isomers occurs, together with nerolidol, in Cabrueva oil (from *Myrocarpus frondosis*). Natural farnesol can be extracted from the oil but the yield is only 2–3%. Synthetic material is therefore the most important commercially. Farnesol is manufactured from nerolidol by isomerization over a vanadium catalyst (13). Farnesol provides an excellent background note in floral accords, such as muguet and lilac, and is also used in floral and oriental fragrances. It is also valued as a blender and fixative. Its acetate has a faint green-floral odor and is used as a fixative for rose bases.

5.6. Nerolidol

Nerolidol	
CAS Registry No.	[7212-44-4] racemic unspecified geometric isomer
CAS Registry No.	[40716-66-3] racemic 6-(*E*)-isomer
formula	$C_{15}H_{26}O$
FW	222.37
bp	114°C at 0.13 kPa (1 mmHg)
bp	145°C at 1.6 kPa (12 mmHg)
bp	276°C at 101.3 kPa (760 mmHg)
d^{20}	0.8778 g/cm^3
$n_D{}^{20}$	1.4898
$[\alpha]_D$	15°

Nerolidol (**286**) is also known as peruviol and exists as both enantiomeric forms of each of the cis and trans isomers. It occurs in many essential oils. For example, the (+)-trans isomer is found in Cabreuva oil and the (−)- in the oil of *Dalbergia parviflora* and a special grade of nerolidol is available from the former.

Most nerolidol in use is prepared synthetically from linalool (**23**). Treatment of linalool with diketene, ethyl acetoacetate, or isopropenyl methyl ether gives geranylacetone [396-70-1] (**287**) in an analogous way to that from which methylheptenone is obtained from methylbutenol. Addition of acetylene to geranylacetone gives dehydronerolidol [2387-68-0] (**288**), which can be hydrogenated to nerolidol using a Lindlar catalyst (334). Geranyl acetone can also be treated with vinyl Grignard reagent to produce nerolidol directly (335).

Synthetic nerolidol is a mixture of all four isomers. It has a long lasting, mild floral odor with green and woody aspects, and is somewhat reminiscent of lilies. It has good blending and fixative properties and is valued as a floral base note in fragrances (158).

Neroliodyl acetate also finds use in perfumery owing to its tenacious sweet woody and refreshing odor. Nerolidol is also used as a precursor for farnesol and for vitamins E (β-tocopherol) [148-03-8] (**289**) and K_1 [84-80-0] (**290**) as shown in Figure 55.

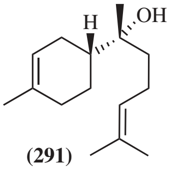
5.7. α-Bisabolol

α-Bisabolol

CAS Registry No.	[515-69-5]
CAS Registry No.	[23089-26-1] (−)-α-bisabolol
CAS Registry No.	[23178-88-3] (+)-α-bisabolol
CAS Registry No.	[72059-10-0] (−)-*epi*-α-bisabolol
CAS Registry No.	[78148-59-1] (−)-*epi*-α-bisabolol
CAS Registry No.	[76738-75-5] (+)-*epi*-α-bisabolol
formula	$C_{15}H_{26}O$
FW	222.37
bp	154–156°C at 1.6 kPa (112 mmHg)
d^{20}	0.93 g/cm^3
$n_D{}^{20}$	1.496
$[\alpha]_D$	52°

α-Bisabolol occurs in chamomile (336) and lavender (337) oils. Chamomile is recognized as a European medicinal plant, and bisabolol contributes to its healing and soothing effects. The richest natural source is the New Caledonian shrub *Myoporum crassifolium* Forst. Original reports found that the wood oil contained up to 80% of a diastereomer of α-bisabolol, which was named anymol (338,339). This has now been shown to be (−)-*epi*- α-bisabolol (**291**) in work that places the level at ~65% (340). All four stereoisomers are known in nature. For example, in addition to chamomile, (−)-α-bisabolol (**292**) occurs in the heartwood of *Vanillosmopsis erythropappa* (341), (+)-α-bisabolol (**293**) is a constituent of poplar bud extract *Populus balsamifera* and (+)-*epi*-α-bisabolol (**294**) is the main constituent (~30%) of the essential oil from the South African sage *Stevia stenophylla* (342).

α-Bisabolol has been found to reduce infections (343), have a spasmolytic effect similar to that of papaverine (344), have a beneficial effect on ultraviolet (uv) (345), and heat (346) burns, antiinflammatory properties (347), and to inhibit the growth of *Corynebacterium sp*. and *Staphylococcus epidermis*, the bacteria mainly responsible for the decomposition of human perspiration (348). It is available both as a homochiral isolate from plant sources and as a racemate from synthesis, through the acid-catalyzed cyclization of nerolidol (349). It is an almost colorless oil with a faint, sweet floral odor and has fixative properties in perfumery. However, its main use is as an antiphlogistic agent in cosmetics.



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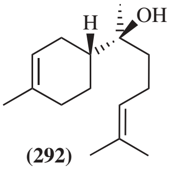

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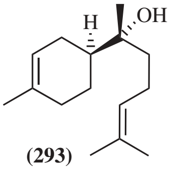

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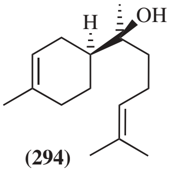

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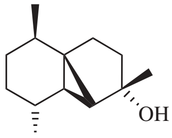

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5.8. Cubebol. (−)-Cubebol (**295**) occurs in a number of essential oils. The richest source is Cubeb Oil (*Piper cubeba*) in which it is present at ~10% (350). Patent applications have been filed by Firmenich claiming it as a cooling and refreshing agent, in combination with other cooling agents (351–353).

5.9. Nootkatone

Nootkatone

CAS Registry No.	[4674-50-4]
formula	$C_{15}H_{22}O$
FW	218.33
mp	39°C
n_D^{20}	1.52
$[\alpha]_D$	181°
fp	100°C

(+)-Nootkatone (**296**) was identified in grapefruit and found to be an important part of its taste (354). It has also been found in oranges and lemons.

Nootkatone is prepared by oxidation of either valencene (**297**) or nootkatene (**298**), as shown in Figure 56. Its usage is restricted largely by its intensity rather than its price although the latter is in thousands of dollars. Valencene has been isolated from orange juice and orange peel oil and is also found in lemon and grapefruit oils. However, the level of valencene in these oils is low. Nootkatene is readily obtainable from the wood of *Chamaecyparis nootkatensis* by steam distillation and can be converted to nootkatone by hydrochlorination and subsequent oxidation with Jones' reagent (355). Some chemotypes of the tree produce nootkatone that can therefore be extracted from them.

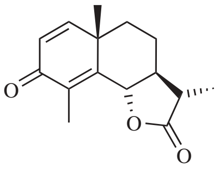
Nootkatone has a powerful, sweet, and citrus odor and is of importance in grapefruit flavors, contributing to both the aroma and the bitter taste (356).

5.10. α-Santonin

α-Santonin

CAS Registry No.	[481-06-1]
formula	$C_{15}H_{18}O_3$
FW	246.29

(−)-α-Santonin (**299**) is extracted from dried flower heads of Levant wormseed, *Artemisia maritima*, which grows in Turkestan and the Southern Urals. Some related species also provide santonin. It is almost tasteless, but has a bitter after-taste and has been used as an anthelmintic (for nematodes) in both human and veterinary medicine. It is unstable to light and the photochemical rearrangement that it undergoes is known as the Santonin rearrangement. Some of the fascinating chemistry of santonin has been reviewed in Chapter 7 of the book by Sell (323).



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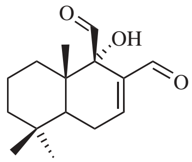

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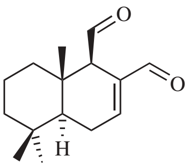

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5.11. Warburganal and Polygodial. Warburganal (**18**) and polygodial (**300**) are found in plants of the genus *Warburgia* (natives of East Africa) and belong to the drimane family of sesquiterpenes. They and many other members of the family, have a pungent taste and skin irritancy and possess a broad range of biological properties including antibacterial and antifungal activity, plant growth regulation, cytotoxic activity, phytotoxicity, piscicidal and molluscicidal activity, and are insect antifeedants. They have therefore been the subject of much research, reviewed by Jansen (357), but are still largely used only as plant extracts in cooking and folk medicine.

6. Diterpenoids

Diterpenoids contain four isoprene units and the natural precursor for them all is geranylgeranyl pyrophosphate. The potential variety of diterpenoids is even greater than that of sesquiterpenoids and, as with the latter, many of them possess interesting biological activities. As a result of their low volatility and consequent lack of odor, there are no diterpenoids that are used in perfumery, other than as solvents and diluents.

6.1. Phytol and Isophytol.

Phytol	
CAS Registry No.	[7541-49-3]
formula	$C_{20}H_{40}O$
FW	296.53
bp	204°C at 1.33 kPa (10 mmHg)
d^{20}	0.85 g/cm^3
$n_D{}^{20}$	1.403

As described above, phytol (**301**) and isophytol (**302**) can be manufactured from geranylacetone in a sequence exactly analogous to those for the production of geraniol and linalool from methylheptenone. Geranylacetone, in turn, can be obtained from either myrcene or linalool. Both phytol and isophytol are important as intermediates in the synthesis of Vitamins E and K and isophytol is used as a diluent in higher price fragrances (82).

6.2. Chlorophyll. The chlorophylls are esters of phytol. Chlorophyll-a [479-61-8] ($C_{55}H_{72}MgN_4O_6$, MW 892) has structure (**303**), as shown in Figure 57; chlorophyll-b [519-62-0] ($C_{55}H_{70}MgN_4O_7$, MW 906) is (**304**) and chlorophyll-c [18901-56-9] is a mixture of two materials, (**305**) ($C_{54}H_{70}MgN_4O_6$, MW 878) and an analogue containing a double bond in one of the porphyrin side chains (**306**) ($C_{54}H_{68}MgN_4O_6$, MW 876). Although phytol is commercially available, synthesis of chlorophyll from it would be totally uneconomic. All the chlorophyll in commercial use is extracted from leaves, principally those of grass, nettles, or alfalfa. It is used as a fat-soluble green dye (E140) in foods, such as fats and processed vegetables.

6.3. Rosin Acids

Rosin Acids

CAS Registry No.	[514-10-3] structure (**307**)
CAS Registry No.	[79-54-9] structure (**308**)
formula	$C_{20}H_{30}O_2$
FW	302.45
mp	152°C structure (**307**)
$[\alpha]_D$	−282° structure (**307**)

The resin of conifers contains a variety of diterpenoid acids generally referred to as rosin acids. Two of the more important of these are shown in Figure 58 as structures (**307**) and (**308**). The material with structure (**307**) is called abietic acid, but is also referred to as (−)-8(14),12-abietadien-18-oic acid; (1*R*, 4*aR*, 4*bR*,10*aR*)-1,2,3,4,4*a*,4*b*,5,6,10,10*a*-decahydro-1,4*a*-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid; [1*R*-(1*a*,4*ab*,4*ba*,10*aa*)]-1,2,3,4,4*a*,4*b*,5,6,10,10*a*-decahydro-1,4*a*-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid; (−)-13-isopropyl-podocarpa-7,13-dien-15-oic acid; (−)-abietic acid; 7,13-abietadien-18-oic acid; *l*-abietic acid; odomit B 10; or sylvic acid. Similarly, **308** is called levopimaric acid or is referred to as (1*R*,4*aR*,4*bS*,10*aR*)-1,2,3,4,4*a*,4*b*, 5,9,10,10*a*-decahydro-1,4*a*-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid; [1*R*-(1*a*,4*ab*, 4*ba*,10*aa*)]-1,2,3,4,4*a*,4*b*,5,9,10,10*a*-decahydro-1,4*a*-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid; 13-isopropyl-podocarpa-8(14),12-dien-15-oic acid; (−)-levopimaric acid; β-Pimaric acid; Δ-6,8(14)-abietadienoic acid; *l*-Pimaric acid or *l*-Sapietic acid. The diene systems of these acids is prone to autoxidation and so commercial products made from rosin acids are often either saturated or aromatic analogues, prepared by catalytic hydrogenation or dehydrogenation, respectively. Methyl esters, such as methyl abietate, (**309**) and (**310**) are the basis for solvents, such as Abalyn and Hercolyn. The polyethoxylation product (**311**) of abietylamine is used as a high-boiling, oil soluble acid scavenger under trade names such as Polyrad.

6.4. Taxanes

Paclitaxel	
CAS Registry No.	[33069-62-4]
formula	$C_{47}H_{51}NO_{14}$
FW	853.91
mp	213°C dec.
$[\alpha]_D$	−49°

The physiological activity of extracts from yew species has been known for millennia. In 1856, Lucas (358) isolated a mixture of alkaloids, which he called taxine and, 100 years later, Graf (359) showed this to be a mixture of at least seven compounds. Over 250 taxane diterpenoids are now known. Paclitaxel (**312**) was isolated from *Taxus brevifolia* (the Pacific Yew) in 1967 (360,361) and its structure determined by X-ray crystallography in 1971 (362). The discovery of its anticancer properties led to a huge amount of research into its extraction, synthesis, production, and application. Bristol-Myers Squibb trademarked the name Taxol for paclitaxel and they, other pharmaceutical companies and academic researchers have invested much into the study of paclitaxel and the search for active analogues and prodrugs. Some of the more significant materials in this series are shown in Figure 59.

Paclitaxel has shown promising results in fighting advanced stages of ovarian, breast, and a variety of other cancers. An excellent review of the history of its development as an anticancer drug, its mechanism of action and Structure–Activity Relationships (SARs) can be found in the introductory chapter of a thesis by Beusker (363). Its chemistry and pharmacology has been reviewed by Farina and co-workers (364) and a thesis by Damen (365) contains a comprehensive review of the chemistry, including synthesis, of paclitaxel and many of its analogues.

Taxus brevifolia is slow growing and the content of paclitaxel in its bark is very low. For example, one report states that 6 tonnes of bark, representing 2000−3000 trees, would be required to produce 1 kg of paclitaxel and this would be sufficient for the treatment of only 500 patients (366). Obviously, this would not be a feasible source of material and so alternatives were sought. The first total synthesis of paclitaxel was reported in 1994 (367) and a number have been published since then (368–373). However, none of these are of commercial use.

Preparation from fermentation using endophytic fungi from *Taxus* species has been studied as an alternative source of material, but the yields are low. For example, fermentation broth from *Taxomyced andeanane* contains only 24−50 ng/L of paclitaxel (374). Plant cell cultures are also the subject of much research but, again, yields tend to be low, eg, 153 mg/L/6 weeks (375,376). Work continues in this area and it is likely that commercial processes will be developed in time.

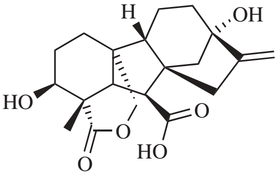
For the moment, commercial supply of paclitaxel is through a high yielding four-step sequence from 10-*O*-deacetylbaccatin III (**313**) (365,377). This material occurs in the leaves of the European yew (*Taxus baccata*) at a level of up to 1g/kg (378–380) and can be extracted from them in yields of up to 200 mg/kg (381).

Docetaxel (**314**) is also prepared from 10-*O*-deacetylbaccatin III and is available from Aventis (formerly Rhône-Poulenc Rohrer) as a drug under the trade name of Taxotere. Docetaxel differs from paclitaxel by having a *tert*-butoxy carbonyl group instead of a benzoyl group on the C13 side chain and a hydroxyl group instead of an acetoxyl group at C10. These structural changes give docetaxel better water solubility and hence better bioavailability than paclitaxel. The area of taxane diterpenoids remains one of great research interest and new production methods, new analogues and prodrugs are almost certain to appear in the future.

6.5. Gibberellic Acid

Gibberellic Acid	
CAS Registry No.	[77-06-5]
formula	$C_{19}H_{22}O_6$
FW	346.37

Gibberellic acid (**14**) is produced commercially by fermentation processes and is used as a growth promoter for plants, especially seedlings.



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7. Triterpenoids

Triterpenoids contain six isoprene units. Many of them are derived from squalene, which has a tail-to-tail link in the center of the chain as described above, and the steroids form a subset of these. Steroids will not de discussed in this chapter as they are described elsewhere in the encyclopedia.

7.1. Squalene and Squalane.

Squalene	
CAS Registry No.	[111-02-4]
formula	$C_{30}H_{50}$
FW	410.72
mp	−75°C
bp	285°C at 3.33 kPa (25 mmHg)
d^{20}	0.858 g/cm^3
$n_D{}^{20}$	1.494

Squalane	
CAS Registry No.	[111-01-3]
formula	$C_{30}H_{62}$
FW	422.82
mp	−38°C
bp	176°C at 0.0067 kPa (0.05 mmHg)
d^{20}	0.81 g/cm^3
$n_D{}^{20}$	1.452

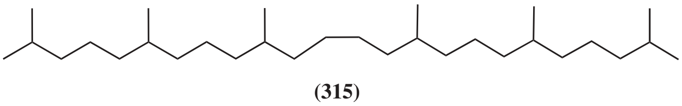
As described earlier, squalene (**2**) is the precursor to triterpenoids and steroids, and is therefore widespread in nature. Two sources of particular interest are shark liver and olive oil, both of which serve as feedstocks for commercial production. Most companies extracting squalene from shark oils are based in Japan and Australasia. Total production is of the order of several thousand tpa. Production from olive oil is about one-sixth of that figure, but the product commands a higher price because of its vegetable origin, and therefore better marketing platform. Significant producers of vegetable grade include the Dutch Company Uniqema.

Squalene is somewhat unstable to air because of the number of double bonds in the molecule. Hydrogenation gives squalane (**315**), which is a much more stable material, and therefore of greater commercial significance. Squalane can be synthesized from geranylacetone by coupling with diacetylene and subsequent hydrogenation (382) or by dimerization of dehydronerolidol followed by dehydration and hydrogenation (383), but these routes are not competitive with naturally derived material. Material referred to as synthetic squalane is actually hydrogenated polyisobutylene.

Consumption of squalene is low because of its instability, but it is used as a food supplement–folk medicine, particularly in Japan. It is claimed to have beneficial effects on the skin and in boosting the immune system though hard scientific evidence for this is somewhat lacking. When used as a food additive, it is usually in the form of shark liver oil extracts.

The market for squalane is larger and is based on its use in skin cosmetics. It is claimed to be a natural component of sebum and is rapidly absorbed into the skin. Claimed benefits include moisturizing properties, skin lubrication properties, barrier properties, and rejuvenating action both by promotion of skin cell growth and by inhibition of bacteria which retard cell growth.

(2)



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7.2. Betulin and Betulinic Acid.

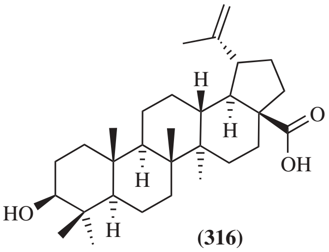
Betulin

CAS Registry No.	[473-98-3]
formula	$C_{30}H_{50}O_2$
FW	442
mp	252°C

Betulinic Acid

CAS Registry No.	[472-15-1]
formula	$C_{30}H_{48}O_3$
FW	456.70
mp	278°C
$[\alpha]_D$	+7.8°

Betulinic acid (**316**), also known as 3β-hydroxy-lup-20(29)-en-28-oic acid; 3β-hydroxy-lup-20(29)-en-28-oic acid; mairin; (+)-betulinic acid; β-betulinic acid; 3β-Hydroxylup-20(29)-en-28-oic acid; betulic acid or lupatic acid, is present in and extracted from the bark of the White Birch (*Betula alba*). Betulinic acid has anticancer properties that have been reviewed by Eiznhamer and Xu (384). Betulin (**317**) and betulinic acid also possess activities that are useful in the field of cosmetics. They inhibit the enzyme elastase thus correcting loss of skin elasticity; stimulate collagen synthesis; are antiinflammatory, and inhibit melanogenesis. The resultant market need is filled by use of purified bark extract [84012-15-7], rich in both triterpenes.



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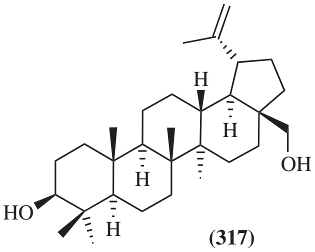

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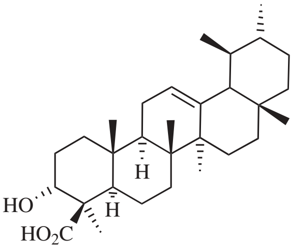
7.3. Boswellic Acids. Boswellic acids, such as β-boswellic acid (**318**), occur in the exudates of the Indian tree *Boswellia serrata*. This relative of the species used to produce frankincense, is known in Indian Ayurvedic medicine for its calming, soothing, and antiirritant properties, which are the result of the boswellic acids that they contain (385). These antiinflammatory properties are the result of their ability to inhibit 5-lipoxygenase, a key enzyme in the inflammatory pathway (386,387). The antiirritancy is specific in that it does not block production of prostaglandins and thromboxanes, and is therefore more effective than other antiirritants (388,389). Shrivastava, Singh, and Basniwal have reviewed the antiinflammatory and other activities of *B. serrata* and extracts of it (390). Extracts are available commercially, for example from Quest under the tradename of Soothex.



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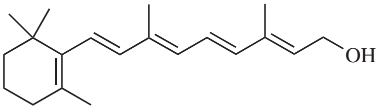
8. Carotenoids

The carotenoids are the most important group of the tetraterpenoids. The biogenetic precursor for the carotenoids is lycopene, which is formed by an initial tail-to-tail fusion of geranylgeranyl and geranyllinalyl pyrophosphates (in an analogous way to that shown for the formation of squalene in Fig. 4) followed by dehydrogenation. Cyclization at one or both ends of the chain then produces the mono- and bicyclic members of the family. Oxidation can occur at the ends of the chain to produce further carotenoids and oxidative degradation produces materials with fewer than the starting 40 carbon atoms. The geometrical configuration of the double bonds is usually trans. The prefix neo- is often used to designate isomers containing at least one cis configuration. The prefix apo- indicates carotenoids that are oxidative degradation products retaining more than one-half of the carotene structure. About 600 naturally occurring carotenoids have been identified and characterized (189,391). Carotenoids are widely distributed in plant, marine, and animal life and it has been estimated that nature produces ~100 million tpa of carotenoids, whereas synthetic production amounts to only several hundred tons per year (392,393).

An important function of certain carotenoids is their provitamin A activity. Retinol (**319**) is formed by cleavage of carotenoid precursors by an oxidative enzyme system present in the intestinal mucosa of animals and humans. This is then converted to 11-*cis*-retinal (**320**), which is then complexed to the protein opsin to form the pigment rhodopsin, which is responsible for vision (394). However, this will not be discussed further here as it is covered elsewhere.



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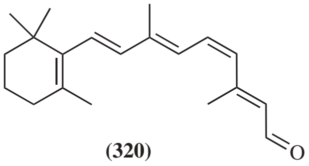

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The extended conjugation present in carotenoids means that they absorb visible light and are therefore colored. This makes them useful as dyes, particularly in animal and human food and in pharmaceuticals. However, it also renders them susceptible to degradation by light and air and commercial utilization thus requires stabilization in the form of emulsions, oil solutions and suspensions, and spray-dried forms (395).

8.1. Lycopene.

Lycopene [502-65-8] (**321**) is found in a wide variety of fruits and particularly in tomatoes. It has been shown to reduce the risk of prostate and other cancers (396,397). It has also been shown to lower the susceptibility of lymphocyte DNA to oxidative damage (398) and to protect from atherosclerosis by preventing plasma lipid oxidation to low density lipoprotein (LDL) (399,400). Lycopene, extracted from tomatoes, is used as a red food color, E 160(d).

8.2. Carotenes.

The three most important carotenes are α-carotene, β-carotene, and γ-carotene, all of which are widespread in nature. They are either extracted from carrots or prepared synthetically and are used as yellow colors [E 160(a)] in fat containing foods, such as cheese. β-Carotene is also known as solatene and is used as a sunscreen as well as a food color. The structures of these and other important carotenoids are shown in Figure 60.

α-Carotene

CAS Registry No.	[7488-99-5]
formula	$C_{40}H_{56}$
FW	536
mp	187°C
$[\alpha]_D$	+380°

One of the ring double bonds of α-Carotene (**322**) is not conjugated to the double bonds of the linear section of the molecule thus introducing a center of asymmetry and making the molecule optically active.

β-Carotene

CAS Registry No.	[7235-40-7]
formula	$C_{40}H_{56}$
FW	536
mp	181°C

β-Carotene (**323**) is prescribed in the treatment of the inherited skin disorder erythropoietic protoporphyria (EPP) to reduce the severity of photosensitivity reactions in such patients. The essential theoretical background relevant to the role of carotenoids as photoconductors has been reviewed (395). β-Carotene has also been used as a photoconductor in recording-media film.

γ-Carotene	
CAS Registry No.	[472-93-5]
formula	$C_{40}H_{56}$
FW	536
mp	178°C

γ-Carotene (**324**) differs from the two previous isomers in being cyclized at only one end.

8.3. Oxygenated Carotenoids.

Capsanthin	
CAS Registry No.	[465-42-9]
formula	$C_{40}H_{56}O_3$
FW	584
mp	176°C

Capsanthin (**325**) is extracted from paprika and is used as an orange food color, E 160(c).

Capsorubin	
CAS Registry No.	[470-38-2]
formula	$C_{40}H_{56}O_4$
FW	600
mp	201°C

Like capsanthin, capsorubin (**326**) is extracted from paprika and used as an orange food color, E 160(c).

β-*apo*-8'-Carotenal	
CAS Registry No.	[1107-26-2]
formula	$C_{30}H_{40}O$
FW	416
mp	139°C

β-apo-8'-Carotenal (**327**) occurs in egg yolk and orange peel. It is extracted from plant material and used as an orange food color, E 160(e).

Bixin	
formula	$C_{25}H_{30}O_4$
FW	536

Bixin (**328**) is one of a number of deeply colored carotenoid degradation materials that can be isolated from the pericarp of the fruit of the tree *Bixa orellana*. Extracts, known as Annatto, are used as yellow food colors E 160(b). Other components include the trans isomer and nor-bixin. The extraction and chemistry of Annatto has been reviewed by Preston and Rickard (401).

Crocetin	
formula	$C_{20}H_{24}O_4$
FW	328

Crocetin (**329**) occurs in the stigma of saffron flowers (*Crocus sativa*) together with crocin, the bis(glycoside) with gentiobiose of crocetin. It is used as a yellow color in foods, in the form of intact stigma rather than as an extracted dye.

9. Terpenoid Degradation Products

9.1. Carotenoid Degradation Products.

It is obvious that degradation of natural products will occur as a result of decay, but it also can be the product of metabolic processes that produce materials of use to the organism. Carotenoids are very widespread in nature, and so it is not surprising that we find many different carotenoid degradation products in plants and animals. As described in the preceding section, some of these degradation products retain sufficient extended conjugation to be useful as pigments. Others lose the color, but gain other properties, significantly odor, a result of the reduced molecular weight, and hence greater volatility. In terms of commercial importance, the most significant groups of these are the ionones, damascones, and safranic acid derivatives. The molecular structures of these materials all contain a 2,2,6-trimethylcyclohexyl fragment, derived from the ring at the end of the original carotenoid. Safranic acid derivatives have a single carbon attached to the 1-position of the ring, whereas the ionones and damascones have a chain of four carbon atoms at this position. The ionones and damascones differ in that the ionones are oxygenated at the third carbon away from the ring, whereas the damascones are oxygenated at the carbon attached to the ring. The nomenclature system for double bonds and substituents is shown in Figure 61. Double-bond positions are identified by Greek letters and the location of substituents in the ionone family by the prefixes *n*- and *iso*-. One potential source of confusion is that α-*iso*-methylionone is often referred to as γ-methylionone.

Ionones, Methylionones and Related Materials. The ionones are materials of major importance in perfumery. They occur naturally in a variety of flowers, fruits, leaves, such as tobacco and even roots, such as carrots. In odor terms, the ionones are associated with violet and, indeed, α- and β-ionones account for 57% of the volatile components of violet flowers (*Viola odorata*). β-Ionone also has a woody odor character and is of use, not only in perfumery, but also as a key intermediate in the synthesis of Vitamins A, E, and K. Annual production of ionones for perfumery use runs into hundreds of tonnes, but that of β-ionone is much higher because of its use as an intermediate for vitamin synthesis. The methylionones do not occur in nature, but their odor properties have made them valuable analogues of the natural materials. In perfumery, α-*iso*-methylionone is far more important than the ionones and its tonnage is ~10 times that of α- and β-ionones (82). Prices are in the $15–30 range and vary from one ionone–methylionone to another and from one quality to another. As a result of the manufacturing route, ionones and methylionones for fragrance use are often mixtures of various isomers and each producer will have its own composition signature(s).

Aldol condensation of citral with a ketone leads to materials known as ψ-ionones, as shown in Figure 62. Obviously, if acetone is used as the ketone, only one product, ψ-ionone [141-10-6] (**47**), is produced. If an asymmetric ketone, such as 2-butanone, is used, then two products will result, the so-called *n*-methyl-ψ-ionone [26651-96-7] (**330**, R = Me) and the *iso*-methyl-ψ-ionone [1117-41-5] (**331**, R = Me). Treatment of these ψ-ionones with an acid catalyst then gives a mixture of ionones, represented by structure (**332**) in which either R or R' is H and one of the three dotted lines represents a double bond. As discussed above and shown in Figure 10, dehydrolinalool (**46**) can be treated with an acetone equivalent, such as 2-methoxypropene, to yield ψ-ionone directly without going through citral, if the desired product is an ionone as opposed to a methylionone (402). Diketene (403) and acetoacetate esters (403) have also been used. Similarly, the methyl enol ether of 2-butanone can react with dehydrolinalool to give *iso*-methyl-ψ-ionone (404).

Sodium or potassium hydroxides are the catalysts usually employed in the aldol condensation. Excess ketone is normally used and recovered and recycled. The exact conditions employed will affect the *n*-/*iso*- ratio of the products. For example, if the reaction temperature is kept at 0–10°C, higher yields of the isomethylpseudoionones, which are the more thermodynamically stable isomers, are obtained. The aldol intermediates have more time to equilibrate to the more stable isomers at the lower temperature. Sodium and potassium hydroxides tend to favor *n* isomers, whereas quaternary ammonium hydroxides favor the iso materials (405). Cosolvents, such as methanol, also affect the isomer ratio and can be very important in getting a high yield of the *iso*-methyl-ψ-ionones (406). Each producer has invested considerable effort into optimizing ratios and guaranteeing consistency of product mix for each specified quality.

If phosphoric acid is used as the cyclization catalyst, the α-isomer predominates, whereas with sulfuric acid, the β-isomer is the major product. Use of boron trifluoride etherate in dimethylformamide gives predominantly the γ-isomer (407). The reactions are normally carried out at atmospheric pressure, but higher temperatures and pressures can be employed (408). Prolonged acid treatment will lead to the thermodynamically favored β-isomer.

Partially and totally hydrogenated ionones are also used in perfumery and hydrogenation of the ketone also gives the ionols (409). Hydrogenation improves the stability of the materials, but usually at the cost of odor quality. Some more detail on the more important ionones and analogues is given below and their structures are shown in Figure 63.

α-Ionone

CAS Registry No.	[6901-97-9] unspecified isomers
CAS Registry No.	[127-41-3] racemic (*E*)-isomers
formula	$C_{13}H_{20}O$
FW	192.30
bp	123°C at 1.33 kPa (10 mmHg)
bp	258°C at 101.3 kPa (760 mmHg)
d^{20}	0.9309 g/cm^3
${n_D}^{20}$	1.5020
$[\alpha]_D$	400°

α-Ionone (**333**) occurs widely in nature, eg, in violets, blackberries, plums, and tobacco. It has a warm, woody, floral odor with balsamic and sweet tones and is strongly reminiscent of violet flowers. It is used widely in perfumery.

β-Ionone

CAS Registry No.	[14901-07-6] unspecified isomers
CAS Registry No.	[79-77-6] (*E*)-isomer specified, absolute stereochemistry unspecified
formula	$C_{13}H_{20}O$
FW	192.30
bp	122°C at 0.93 kPa (7 mmHg)
bp	132°C at 1.33 kPa (10 mmHg)
bp	271°C at 101.3 kPa (760 mmHg)
mp	−35°C
d^{20}	0.9461 g/cm^3
${n_D}^{20}$	1.5202

β-Ionone (**334**) is also very widespread in nature being found in, among others, rose, osmanthus, raspberries, cherries, tobacco, carrots, and capsicums. It has a warm woody, dry, and fruity odor and is greener than α-ionone. However, it is less useful than the latter and is used particularly in woody perfumes. In production terms, it is the most important of all the ionones because of its use in vitamin manufacture.

γ-Ionone

CAS Registry No.	[76-76-5]
formula	$C_{13}H_{20}O$
FW	192.30
bp	82°C at 0.16 kPa (1.2 mmHg)
d^{20}	0.93170 g/cm^3
${n_D}^{20}$	1.4985

γ-Ionone (**335**) is not observed in nature, and is of minor importance in perfumery.

α-*n*-Methylionone

CAS Registry No.	[127-42-4] (*R*)–(*E*)-isomer
CAS Registry No.	[7779-30-8] unspecified isomers
formula	$C_{14}H_{22}O$
FW	206.33
bp	970°C at 0.35 kPa (9 mmHg)
d^{20}	0.92100 g/cm^3
$n_D{}^{20}$	1.4938

α-*n*-Methylionone (**336**) is also known as α-cyclocitrylidenebutanone and Cetone Alpha. It has a floral, sweet-oily odor of moderate tenacity and is used as a blender in perfumery.

β-*n*-Methylionone

CAS Registry No.	[127-43-5]
formula	$C_{14}H_{22}O$
FW	206.33
bp	102°C at 0.35 kPa (9 mmHg)
d^{20}	0.9370 g/cm^3
$n_D{}^{20}$	1.5155

β-*n*-Methylionone (**337**) is also known as β-methylionone, Cetone Beta, Iraldeine Beta, and Raldeine Beta. It has a warm woody odor of the same type as β-ionone and is the least important of the methylionones.

α-*iso*-Methylionone

CAS Registry No.	[127-51-5]
formula	$C_{14}H_{22}O$
FW	206.33
mp	−64°C
bp	131°C at 1.3 kPa (10 mmHg)
d^{20}	0.9345 g/cm^3
$n_D{}^{20}$	1.5019

α-*iso*-Methylionone (**338**) is also available under trade names, such as Iraldeine Gamma, Raldeine Gamma, and Noviraldiol and is also, somewhat confusingly, called γ-methylionone. It has a sweet floral odor with woody and tobacco nuances and is a very versatile ingredient. This makes it the most important of the entire ionone family as far as perfumery is concerned and annual production runs into thousands of tonnes.

β-*iso*-Methylionone

CAS Registry No.	[79-89-0]
formula	$C_{14}H_{22}O$
FW	206.33
bp	94°C at 0.4 kPa (3 mmHg)
d^{20}	0.9376 g/cm^3
$n_D{}^{20}$	1.5033

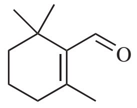
β-*iso*-Methylionone (**339**) is available under trade names, such as δ-methylionone, Rhodione Methyl Delta, Ironal Methyl Delta, Raldeine Delta, and Iraldeine Delta.

The use of delta in the name is potentially confusing as it could also signify a different position of the double bond which, in this case, it does not. It has a light warm, woody floral character with a distinct animalic–ambergris note. This makes it of great interest to perfumers, but its high price limits it to a very low level of use.

Timberol/*nor*-Limbanol

CAS Registry No.	[70788-30-6]
formula	$C_{15}H_{30}O$
FW	226.41
bp	150°C at 0.013 kPa (0.1 mmHg)
d^{20}	0.899 g/cm^3
$n_D{}^{20}$	1.473

One ionone analogue that has become an important perfumery ingredient is that which is known by the trade names of Timberol and *nor*-Limbanol (**340**). It is produced by reaction of citral with 2-pentanone, then cyclization in a manner exactly analogous to that of the ionones, then hydrogenation (410). It has a highly diffusive, powdery-woody odor and is used in a wide range of perfume formulations. There are two centers of asymmetry in the molecule, and hence, four stereoisomers. It was found that a mixture of the isomers with a trans relationship around the ring had a more interesting odor than a mixture of all four isomers (411). A mixture high in trans isomers can be produced from β-cyclocitral (**341**) by hydrogenation followed by aldol condensation with 2-pentanone, and then hydrogenation (412). Later, it was found that the most interesting individual isomer is the (+)-*trans*-*nor*-Limbanol (**342**), which has the lowest odor threshold of the four and a powerful, elegant woody character, and is very radiant (413–417). This material is also now also being used in fragrances.



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Damascones. The first member of this family to be identified was β-damascenone (**343**). It was isolated from the Damask rose, *Rosa damascena*, the oil of which contains ∼0.05% of it (418) and the structure was confirmed by synthesis (419). Since then, damascones have been identified in a wide variety of natural products. They are usually present at very low levels, but their powerful odors mean that they contribute much to the odor profiles of the plants and oils containing them. As an indication of this, the thresholds in air of some of the damascones, as given by Williams (420) in his review of their history is shown in Table 4. Just as their occurrence in nature has been found to spread from rose to other plant sources, so their use in perfumery has expanded from rose to a wide variety of applications. Their success in perfumery has resulted in a great deal of activity in the search for analogues (420–422).

The allylic transposition of the α,β-unsaturated ketone function in the side chain makes the damascones a much more challenging synthetic target than the corresponding ionones. Consequently, the damascones are much more expensive, prices being in the $250−1500/kg range. However, their intense odors mean that they can be used even at these prices. The major producer is Firmenich who make many hundreds of tonnes, in collaboration with DRT in France.

The original production method is shown in Figure 64 using α-damascone (**344**) as an example (423). Allylation of dehydrolinalool (**46**) gives the acetylenic alcohol (**345**), which is rearranged to (**346**) and cyclized to α-damascone. The product of this synthesis contained a tiny trace of another compound with a very intense odor. This material was isolated and characterized and it was found to have been formed by dehydration of alcohol (**345**) to the corresponding olefin (**347**), which then cyclized to (**348**) before hydrating to (**349**). This reaction by-product has now become an important perfumery ingredient in its own right and is sold under the trade name Dynascone (424).

A number of other routes to damascones have been devised (425,426), but the one that is currently used in production is that shown in Figure 65. The key sequence is shown at the top of the figure. Reaction of an ester with 2 equiv of allyl Grignard reagent gives a tertiary carbinol which can be pyrolyzed to a β,γ-unsaturated ketone. Isomerization using either acid or base then produces the corresponding α,β-unsaturated ketone (427). The synthesis of damascones starts with methylheptenone (**19**). A Wittig-Horner reaction followed by acid catalyzed cyclization gives a mixture of methyl α-cyclogeranate (**350**) and methyl β-cyclogeranate (**351**). Application of the allyl Grignard—ene—isomerization reaction sequence to (**350**) gives α-damascone (**344**). Methyl α-cyclogeranate can be converted to the diene-ester (**352**) and this, in turn, to β-damascenone (**343**). Similarly, methyl β-cyclogeranate can be converted to β-damascone (**353**). Deprotonation of methyl β-cyclogeranate with butyllithium gives the enolate (**354**) that can be treated with allyl Grignard reagent, and subsequently isomerized to give γ-damascone (**355**) (428).

α-Damascone	
CAS Registry No.	[24720-09-0]
CAS Registry No.	[23762-94-5] (*Z*)-isomer
formula	$C_{13}H_{20}O$
FW	192.30
bp	80°C at 0.000133 kPa (0.001 mmHg)
d^{20}	0.935 g/cm^3
${n_D}^{20}$	1.496
fp	>100°C

α-Damascone (**344**) has a floral, fruity, rose, and apple odor character. The (*S*)-(−)-enantiomer is found in tea and is >100 times stronger than its antipode (429–431).

β-Damascone	
CAS Registry No.	[23726-91-2]
CAS Registry No.	[23726-92-3] (*Z*)-isomer
formula	$C_{13}H_{20}O$
FW	192.30
bp	52°C at 0.000133 kPa (0.001 mmHg)
d^{20}	0.938 g/cm^3
${n_D}^{20}$	1.498
fp	>100°C

β-Damascone (**353**) is found in rose, osmanthus, tea, rum, and tobacco. It has a fruity, floral, blackcurrant, plum, rose, honey, and tobacco odor profile.

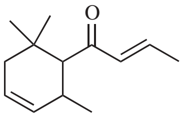
γ-Damascone	
CAS Registry No.	[35087-49-1]
formula	$C_{13}H_{20}O$
FW	192.30
bp	60°C at 0.0133 kPa (0.1 mmHg)
d^{20}	0.9335 g/cm^3
${n_D}^{20}$	1.494
fp	98°C

γ-Damascone (**355**) is fruitier than α- or β-damascone. However, its threshold of detection is an order of magnitude higher than either of these. It has a powerful floral, rosy, and fruity note with pine and green character.

δ-Damascone

CAS Registry No.	[57378-68-4]
formula	$C_{13}H_{20}O$
FW	192.30
d^{20}	0.932 g/cm^3
$n_D{}^{20}$	1.49
fp	>100°C

δ-Damascone (**356**) is not found in nature. It is also known as Dihydrofloriffone. It is very diffusive with a threshold similar to that of damascenone and has a fruity, blackcurrant, floral, and woody odor character.



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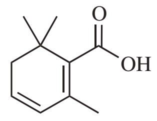
β-Damascenone

CAS Registry No.	[23726-93-4]
formula	$C_{13}H_{18}O$
FW	190.28
bp	116°C at 1.7 kPa (13 mmHg)
d^{20}	0.95 g/cm^3
$n_D{}^{20}$	1.51
fp	>100°C

β-Damascenone (**343**) is present in Bulgarian rose oil at a level of only 0.05%, but is a major contributor to the overall odor of the oil. Not surprisingly, it is used in reconstitutions of rose oil. It is also found in rose, apricot, beer, grape, mango, tomato, wine, rum, raspberries, passionfruit, and blackberries. Its detection threshold is one-tenth those of α- or β-damascone.

Safranic Acid Derivatives and Related Materials. Safranic acid (**357**) and cyclogeranic acid (**358**) and related materials are formed by degradation of the central chain of carotenoids right back to the carbon next to the cyclohexane ring at the end. The corresponding aldehydes safranal [116-26-7] (**359**) and β-cyclocitral [432-25-7] (**360**) both make important olfactory contributions to the oils containing them. Safranal is important to the odor of saffron and accounts for up to 70% of the volatiles in it. It also occurs in osmanthus, tea, grapefruit, and paprika among others. β-Cyclocitral is found in rum, tea, tomato, melon, paprika, peas, and broccoli. These aldehydes are not particularly stable in application and so their importance as top-notes has led to a search for more stable materials with similar odor types.



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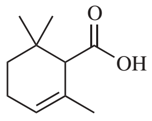

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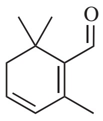

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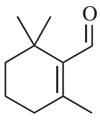

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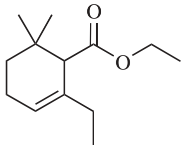
The first synthetic material in the family to be commercialized was Ethyl Safranate [35044-58-7]. It was prepared by the route shown in Figure 66 and found to have the same limit of detection as β-damascenone (432). The reaction sequence starts with a Robinson Annulation Reaction between mesityl oxide and ethyl acetoacetate to give the keto-ester (**361**), which is then reduced and dehydrated to produce a mixture of three isomers α- (**362**), β- (**363**), and γ- (**364**), the ratio between them depending on the reaction conditions. The α-isomer has a woody-ionone like odor, the β- is herbal and spicy and the γ- is fruity, reminiscent of apple and plum.

Another speciality in this area is Givescone (433–435), which is a mixture of two isomers (**365**) and (**366**), [57934-97-1] and [77851-07-1] and has a rosy, spicy, fruity, and woody odor. More recent introductions in the family include Romascone [0081752-87-6] (**367**) (436) and Myrascone [94333-50-3] (**368**). The former is damascone like, fruity, and blackberry like while the latter is dry herbal and fruity.



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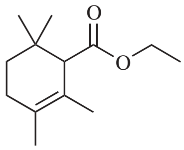

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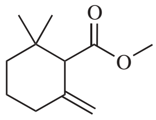

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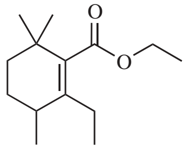

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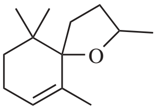
Other Carotenoid Degradation Products. There are a number of other groups of volatile carotenoid degradation products that occur in nature and contribute to the odors of the plants in which they are found. Many of these are commercially available in small quantities at high price. Examples include the theaspiranes (**369**), which are found in tea, passionfruit, and tobacco; vitispiranes (**370**) found in some oils, such as lemon balm; edulans (**371**) found in passionfruit, osmanthus, and tobacco; and dihydroactindiolide (**372**) found in tea, osmanthus, tomato, ambergris, and tobacco.



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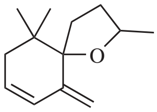

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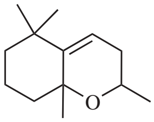

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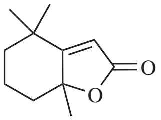

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9.2. Other Terpenoid Degradation Products.

Ambreine Degradation Products. The sperm whale, *Physeter catodon* (formerly *Physter macrocephalus*) produces, in its intestinal tract, a material known as ambergris. Ambergris is found washed up on beaches and in former days was also removed from whales that had been killed. Never a secure source of supply, the decline in whale numbers has made natural ambergris an increasingly rare commodity. Ambergris was found to be comprised of up to 46% cholestanol-type steroids, principally epicoprosterol (**373**), and 25–45% of the triterpene ambreine [473-03-0] (**374**) (437). Lumps of ambergris, usually ∼20 cm in diameter, but on occasions weighing up to 400 kg, are excreted into the sea where they undergo a series of degradative reactions in the presence of air, salt water, and light. As this happens, the ambergris fades from dark brown to pale gray and develops an odor that is highly prized in perfumery (438,439). There are many degradation products of ambreine, quite a number of which contribute to the characteristic, animalic, briny, ozonic, and faecal character of the odor. The degradative transformations have been reproduced *in vitro* (440–443) and this chemistry has been reviewed by Sell (323). Three degradation products of importance to perfumery are the naphthofuran [6790-58-5] (**375**), α-ambrinol [41199-19-3] (**376**), and dihydro-γ-ionone [13720-12-2] (**377**). As might be imagined from its relationship to the ionones, the last of these contributes to the tobacco notes of ambergris. It also serves as a starting material for the synthesis of α-ambrinol, to which it is easily converted by means of the Prins Reaction. The naphthofuran is by far the most important of all the ambreine degradation products. The structures of the ambergris products are shown in Figure 67.

3a,6,6,9a-tetramethyldodecahydronaphtho[2,1-b]furan

3*a*,6,6,9*a*-tetramethyldodecahydronaphtho[2,1-*b*]furan

CAS Registry No.	[6790-58-5]
formula	$C_{16}H_{28}O$
FW	236.40
mp	76°C
$[\alpha]_D$	−29°

This naphthofuran (**375**) is one of the most expensive fragrance ingredients typically costing well >$500/kg for enantiomerically pure grades and >$350/kg for racemic material. Despite its high price, it is used extensively in perfumery, albeit at low levels, not only for its powerful ambergris odor, but also for its enriching effect on fragrance compositions. In view of its value to perfumery, a great deal of effort has been, and continues to be, invested into the search for efficient synthetic routes to the naphthofuran. Annual worldwide production runs to several tens of tonnes and a variety of qualities is available under trade names, such as Amberlyn, Ambermore, Ambertone, Ambrofix, Ambrox, Ambroxan, Ambroxid, Ambroxid Rein, Ambroxide, Fixateur 404 and Sylvamberfor enantiopure materials derived from partial synthesis; Ambrox DL, Cetalox, and Synambran for racemic materials by total synthesis and Cetalox-laevo for enantiopure product from total synthesis.

The labdane family of diterpenoids offer an attractive source of feedstocks for synthesis as they share the same substitution pattern and stereochemistry around the naphthalene ring system. The residues from distillation of the essential oil of Clary Sage (*Salvia sclarea*) contain ~50% by weight sclareol (**378**) and this is the major starting material for 3*a*,6,6,9*a*-tetramethyldodecahydronaphtho[2,1-*b*]furan synthesis. The production routes are shown in Figure 68.

The key intermediate in this synthesis is sclareolide (**379**), which can be obtained by chromic acid oxidation of sclareol. Alternatively, permanganate oxidation of sclareol gives the naphthopyran (**380**), which can be ozonized to the acid-ester (**381**), which can then be saponified and lactonized to give sclareolide. Fermentation routes are now also available enabling sclareol to be converted to sclareolide without the need for heavy metal oxidants (444). Reduction of sclareolide with either lithium aluminium hydride or borane gives the diol (**382**), which can be cyclized to the desired ether. This synthesis suffers the disadvantages of the use of either chromium or manganese oxidants that creates an effluent problem and of overoxidation with a subsequent requirement for a vigorous reductant to return the material to the desired oxidation level. Consequently, much research has been invested into alternative routes and one ingenious example is that of Barton and co-workers (445,446) and further developed by Tse, Davey, and Payne (447,448), as shown in Figure 69. Ozonolysis of sclareol (**378**) with an oxidative work-up gives norlabdane oxide (**380**). Treatment of this pyran with hydrogen peroxide in the presence of a catalytic amount of iodine gives the ketone (**383**). Bayer-Villiger oxidation of the latter using peracetic acid gives the acetal acetate (**384**), which can be hydrogenated to the target naphthofuran.

Many other diterpenoids and also monoterpenoids and sesquiterpenoids have been used as starting materials for naphthofuran (**375**), but none of these syntheses are of commercial importance. An excellent review of these will be found in Chapter 2 of the thesis by Bolster (449). Chauffat and Morris have also reviewed the history of ambergris development (450). Both reviews cover partial syntheses from natural products and total syntheses.

One basic synthetic approach toward total synthesis involves the biomimetic cyclization of homofarnesic acid and derivatives thereof. The earliest syntheses of this type used acids, such as stannic chloride to cyclize homofarnesic acid (**385**) to sclareolide (see Fig. 70) that could then be reduced and cyclized in the conventional manner (451–459).

Cyclization of homofarnesol (**386**) rather than the acid offers the advantage of producing the naphthofuran directly rather than sclareolide. This was achieved by Vlad and co-workers using fluorosulfonic acid in nitropropane (460). However, although they started from (*E*,*E*)-homofarnesol, isomerization to the (3*Z*,7*E*)-isomer was fast enough that their product contained a mixture of the desired target (**375**) and the isomeric cis-fused furan (**387**). A mixture of these two isomers can also be prepared from the monocyclic precursor (**388**) (461–465). Both of these reactions are shown in Figure 71. The latter was the subject of many years of development work which eventually led to processes for the production of high purity racemic and enantiomerically pure products (450).

α-Ambrinol

α-Ambrinol	
CAS Registry No.	[41199-19-3]
formula	$C_{13}H_{22}O$
FW	194.32
d^{20}	0.95 g/cm^3
$n_D{}^{20}$	1.492

α-Ambrinol (**376**) is a pale yellow liquid with a powerful animalic, ambergris odor. It can be prepared from dihydro-γ-ionone as discussed above or from β-ionone by pyrolysis and subsequent hydrogenation (466). It is used at low levels in a wide variety of fragrances.

Ambergris Analogues. In view of the value of these nature identical ingredients and the difficulties in synthesizing them, it is not surprising that many analogues have been developed and are used in perfumery. The structures of some are shown in Figure 72. Ambra Oxide [76900-04-4] (**389**) is the pyran equivalent of 3*a*,6,6,9*a*-tetramethyldodecahydronaphtho[2,1-*b*]furan and Grisalva [68611-23-4] (**390**) is another close analogue. Some other ambergris materials in use, such as Karanal (**391**) (467) are not closely related to the natural materials, but do possess similar odors. Polywood [24238-95-7] is related to ambrinol, but has a woody odor rather than being animalic. It can be resolved via enzymic hydrolysis of the chloroacetates of the corresponding alcohol and it was found that the (+)-enantiomer (**392**) has a much richer and more voluminous odor than its antipode (**393**) (468).

Jeger's ketal (**394**), named after its discoverer, but also called Amberketal, Ambraketal, and Ketamber, is another material with a powerful ambergris odor. It is prepared from manool (**395**), extracted from the New Zealand tree *Dacrydium biforme*, by permanganate oxidation to the ketone (**396**) followed by osmylation of the double bond and spontaneous formation of the ketal from the resultant diol-ketone. It has also been synthesized from larixol (**397**), which is readily available from the European larch, *Larix decidua* (449).

Iripallidal Degradation Products. The triterpenoid iripallidal (**398**) occurs in the rhizomes of the iris, *Iris pallida*, and this degrades to give, among other products the irones. The natural extract is known as orris and owes its odor largely to the irones. These have the same nomenclature system as the ionones and are therefore known as α-irone [79-69-6] (**399**), β-irone [79-70-9] (**400**) and γ-irone [35124-16-4] (**401**). They are prepared commercially by the same route as the ionones, but starting from dimethylheptenone (**402**) instead of methylheptenone (**19**). The synthesis is technically more challenging because of the issue of regioselectivity in the cyclization of the ψ-irones. Interesting academic solutions to this problem have been published by Barton (469) and Eschinazi (470), and a synthesis of individual stereoisomers has been carried out by Brenna and co-workers (471). The irones are considerably more expensive than the ionones and have smoother, more buttery odors than their ionone counterparts. The structures are shown in Figure 73.

BIBLIOGRAPHY

"Terpene Resins" in *ECT* 1st ed., Vol. 13, pp. 700–704, by W. J. Roberts and A. L. Ward, Pennsylvania Industrial Chemical Corp.; "Terpenes and Terpenoids" in *ECT* 1st ed., Vol. 13, pp. 705–771, by R. S. Ropp, Hercules Powder Co.; J. E. Hawkins, University of Florida, E. G. Reitz, Chicago City Colleges (Wright Branch), P. de Mayo, Birkbeck College, University of London, and G. C. Harris, Hercules Powder Co.; in *ECT* 2nd ed., Vol. 19, pp. 803–838, by S. J. Autenrieth and A. B. Booth, Hercules Incorporated; "Camphor" in *ECT* 2nd ed., Vol. 4, pp. 54–58, by G. Etzel, Camphor & Allied Products Ltd.; "Terpenoids" in *ECT* 3rd ed., Vol. 22, pp. 709–762, by J. M. Derfer and M. M. Derfer, SCM Corp.; in *ECT* 4th ed., Vol. 23, pp. 833–882, by J. O. Bledsoe, Jr., Bush Boake Allen, Inc.; "Terpenoids" in *ECT* (online), posting date: December 4, 2000, by J. O. Bledsoe, Jr., Bush Boake Allen, Inc.

CITED PUBLICATIONS

1. T. K. Devon and A. I. Scott, *Handbook of Naturally Occurring Compounds*, Vol. 2, The Terpenes, Academic Press, New York, 1972.
2. T. D. Wyatt, *Pheromones and Animal Behaviour*, Cambridge University Press, England, 2003.
3. U.S. Pat. 3,655,803 (1972), F. L. Miller (to SCM Corp.).
4. U.S. Pat. 3,778,486 (1973), C. B. Hamby, Jr. (to SCM Corp.).
5. U.S. Pat. 3,325,553 (1967), J. M. Derfer (to The Glidden Co.); Can. Pat. 973,206 (1975), O. Prochazka (to Anglo Paper Products, Ltd.).
6. U.S. Pat. 3,660,512 (1977), C. B. Hamby, Jr., C. W. Barrett, and J. M. Derfer (to SCM Corp.); U.S. Pat. 3,359,342 (1967), J. M. Derfer (to The Glidden Co.).
7. U.S. Pat. 3,360,581 (1967), J. M. Derfer (to The Glidden Co.).
8. U.S. Pat. 3,420,910 (1969), C. Bordenca, J. M. Derfer, and C. B. Hamby, Jr. (to SCM Corp.).
9. Eur. Pat. 243,238 A1 (1987), F. Casbas, D. Duprey, J. Olivier, and R. Rolley (to Societe Nationale Elf Aquitaine).

10. L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, John Wiley & Sons, Inc., New York, 1967, p. 475.
11. J. Dorsky, in K. Bauer and D. Garbe, eds., *Common Fragrance and Flavour Materials*, VCH Verlag, Weinheim, 1985, p. 399.
12. U.S. Pat. 3,240,821 (1966), G. Ohloff, E. Klein, and G. Schade (to Studiengesellschaft Kohle).
13. U.S. Pat. 3,925,485 (1975), P. Chabardes and C. Grard (to Rhône-Poulenc).
14. U.S. Pat. 4,254,291 (1978), B. J. Kane (to SCM Corp.).
15. P. Chabardes, E. Kuntz, and J. Varagnat, *Tetrahedron* **33**, 2799 (1977).
16. J. C. van der Waal, H. van Bekkum, and J. Vital, *J. Mol. Catal.* **105**, 185 (1996).
17. H. Valente and J. Vital, *Proceedings of the 4th International Symposium on Heterogenous Catalysis and Fine Chemicals*, Basel, Switzerland, 1996, p. 214.
18. U.S. Pat. 2,420,131 (1947), L. A. Goldblatt and S. Palkin (to Glidden).
19. U.S. Pat. 2,882,323 (1959), R. Weiss (to Ameringen Häbler Inc.).
20. Eur. Pat. 132,544 (1984), P. W. Mitchell, L. T. McElligott, and D. E. Sasser (to Union Camp Corp.).
21. U.S. Pat. 3,031,442 (1958), R. L. Webb (to The Glidden Co.).
22. U.S. Pat. 3,076,839 (1963), R. L. Webb (to The Glidden Co.).
23. U.S. Pat. 3,278,623 (1966), J. M. Derfer (to The Glidden Co.).
24. J. Dorsky, *Perfumer Flavorist* **3**(6), 51 (1978).
25. W. Kimel, J. D. Surmatis, J. Weber, G. O. Chase, N. W. Sax, and A. Ofner, *J. Org. Chem.* **22**, 1611 (1967).
26. H. Lindlar, *Helv. Chim. Acta* **35**, 446 (1952).
27. U.S. Pat. 2,681,938 (1954), H. Lindlar (to Hoffmann-LaRoche, Inc.).
28. U.S. Pat. 3,674,888 (1972), M. Derrien and J. F. Le Page (to Institut Francais du Petrole, des Carburants et Lubrifiants).
29. W. Kimel, N. W. Sam, S. Kaiser, G. G. Eichmann, G. O. Chase, and A. Ofner, *J. Org. Chem.* **23**, 153 (1958).
30. Belg. Pat. 634,738 (1964), G. Saucy and R. Marbet (to Hoffmann-La Roche).
31. G. Saucy and R. Marbet, *Helv. Chim. Acta* **50**, 2091 (1967).
32. K. H. Meyer and K. Schuster, *Berichte* **55**, 819 (1922).
33. H. Rupe and E. Kambli, *Helv. Chim. Acta* **9**, 672 (1926).
34. Ger. Pat. 1,811,517 (1969), P. Charbardes (to Rhône-Poulenc).
35. Brit. Pat. 1,204,754 (1970), P. Chabardes and Y. Querou (to Rhône-Poulenc SA).
36. U.S. Pat. 3,920,751 (1975), P. Chabardes and Y. Querou (to Rhône-Poulenc SA).
37. Ger. Pat. 2,353,145 (1973), N. Hindley and D. A. Andrews (to Hoffmann-La Roche).
38. Jpn. Pat. 51,048,608 (1974), T. Hosogai, T. Nishida, and K. Itoh (to Kuraray).
39. H. Pauling, D. A. Andrews, and N. C. Hindley, *Helv. Chim. Acta* **59**, 1233 (1976).
40. U.S. Pat. 3,981,896 (1976), H. Pauling (to Hoffmann-LaRoche Inc.).
41. Ger.-AS Pat. 1,618,098 (1967), H. Müller, H. Overwien, and H. Pommer (to BASF).
42. Ger. Pat. 1,286,020 (1969), H. Pommer, H. Müller, and H. Overwien (to Badische Anilin- & Soda-Fabrik A-G).
43. Ger. Pat. 1,259,876 (1968), H. Pommer, H. Müller, and H. Overwien (to Badische Anilin- & Soda-Fabrik A-G).
44. U.S. Pat. 3,670,028 (1972), H. Müller, H. Köhl, and H. Pommer (to Badische Anilin- & Soda-Fabrik A-G).
45. Ger. Pat. 1,643,668 (1971), H. Pommer, H. Müller, H. Köhl, and H. Overwien (to Badische Anilin- & Soda-Fabrik A-G).
46. H. Pommer and A. Nurrenbach, *Pure Appl. Chem.* **43**(3–4), 527 (1975).
47. W. Reif and H. Grassner, *Chem. Ing. Tech.* **45**(10a), 646 (1973).
48. Ger. Pat. 1,643,710 (1967), H. Pasedach, W. Hoffmann, and W. Himmele (to Badische Anilin- & Soda-Fabrik A-G).

49. Ger. Pat. 973,089 (1959), W. Friedrichsen (to Badische Anilin- & Soda-Fabrik A-G).
50. Ger. Pat. 1,268,135 (1968), H. Pommer, H. Müller, and H. Overwien (to Badische Anilin- & Soda-Fabrik A-G).
51. U.S. Pat. 3,686,321 (1972), H. Müller and H. Overwien (to Badische Anilin- & Soda-Fabrik A-G).
52. P. R. Stapp, *Ind. Eng. Chem., Prod. Res. Dev.* **15**, 189 (1976).
53. Ger.-AS Pat. 1,901,709 (1969), H. Overwien and H. Müller (to BASF).
54. Ger.-AS Pat. 2,715,209 (1977), C. Dudeck and co-workers (to BASF).
55. Ger.-AS Pat. 2,715,208 (1977), B. Meissner and co-workers (to BASF).
56. W. F. Hölderich, in L. Guczi, F. Solymosi, and P. Tetenyi, eds., "*Studies in Surface Science and Catalysis*", Vol. 75, 1993, part A, p. 27.
57. Ger.-AS Pat. 2,625,074 (1976), A. Nissen and G. Kaibel (to BASF).
58. Eur. Pat. 21,074 (1989), A. Nissen and W. Aquila (to BASF).
59. Ger. Pat. 2,157,035 (1971), N. Götz and R. Fischer.
60. Eur. Pat. 344,043 (1988), P. Chabardes and J. Chasal.
61. J. Paust, *Pure Appl. Chem.* **63**, 45 (1991).
62. Ger. Pat. 2,356,866 (1974), Y. Tamai and co-workers (to Kuraray).
63. Fr. Pat. 1,548,516 (1968), M. Pichou (to Societe des Usines Chimiques Rhone-Poulenc).
64. Can. Pat. 766,787 (1967), W. C. Meuly and P. Gradeff (to Rhodia, Inc.).
65. Fr. Pat. 1,384,137 (1965), W. C. Meuly and P. Gradeff (to Rhône-Poulenc SA).
66. U.S. Pat. 3,983,175 (1976), Y. Tamai and co-workers (to Kuraray Co., Ltd.).
67. Jpn. Pat. 75,58 004 (1973), O. Yoshiaki and co-workers (to Kuraray).
68. K. A. D. Swift, *Topics Catal.* **27**(1–4), 143 (2004).
69. U.S. Pat. 4,007,137 (1977), J. M. Sanders, W. L. Schreiber, and J. B. Hall (to International Flavors & Fragrances, Inc.).
70. P. Chabardes, *Tetrahedron Lett.* **29**, 6253 (1988).
71. J. M. Grosselin and C. Mercier, *Organometallics* **10**, 2126 (1991).
72. J. M. Grosselin and C. Mercier, *J. Mol. Catal.* **63**, L26 (1990).
73. K. Takabe, A. Agata, T. Katagiri, and J. Tanaka, *Synthesis* 307 (1977).
74. U.S. Pat. 4,186,148 (1980), A. Murata, S. Tsuchiya, A. Konno, and J. Uchida (to Nissan Chemical Industries, Ltd.).
75. K. Takabe, T. Katagiri, and J. Tanaka, *Tetrahedron Lett.* **34**, 3005 (1975).
76. C. Mercier and P. Chabardes, *Pure Appl. Chem.* **66**, 1509 (1994) and references cited therein.
77. U.S. Pat. 3,907,321 (1975), J. B. Hall and J. M. Sanders (to International Flavors & Fragrances, Inc.).
78. U.S. Pat. 3,911,018 (1975), J. B. Hall and J. M. Sanders (to International Flavors & Fragrances, Inc.).
79. U.S. Pat. 3,929,677 (1975), J. B. Hall and J. M. Sanders (to International Flavors & Fragrances, Inc.).
80. C. Nussbaumer, G. Fráter, and P. Kraft, *Helv. Chim. Acta* **82**, 1016 (1999).
81. G. Fráter, J. A. Bajgrowicz, and P. Kraft, *Tetrahedron* **54**, 7633 (1998).
82. H. U. Däniker, *Flavors and Fragrances* (Worldwide), SRI International, 1987.
83. L. P. Somogyi, B. Rhomberg, and N. Takei, *Flavors and Fragrances*, SRI International, 1995.
84. U.S. Pat. 4,031,161 (1977), J. M. Sanders, W. I. Taylor, I. D. Hill, and J. J. Kryschuk (to International Flavors & Fragrances, Inc.).
85. K. Kogami, O. Takahashi, and J. Kumanothani, *Can. J. Chem.* **52**, 125 (1974).
86. U.S. Pat. 3,176,022 (1965), J. H. Blumenthal (to International Flavors & Fragrances, Inc.).
87. U.S. Pat. 4,018,842 (1977), L. A. Canova (to SCM Corp.).

88. U.S. Pat. 3,277,206 (1966), J. P. Bain (to The Glidden Co.).
89. U.S. Pat. 2,902,510 (1959), R. L. Webb (to The Glidden Co.).
90. U.S. Pat. 3,487,118 (1969), J. H. Blumenthal (to International Flavors and Fragrances, Inc.).
91. Fr. Pat. 2,597,861 (1987), J. Ibareq and B. Lahourcade (to Derives Resiniques et Terpeniques).
92. U.S. Pat. 3,847,975 (1974), J. B. Hall (to International Flavors and Fragrances, Inc.).
93. J. B. Hall and L. K. Lala, *J. Org. Chem.* **37**, 920 (1972).
94. Brit. Pat. 1,254,198 (1970), H. R. Ansari and B. J. Jaggers (to Bush Boake Allen).
95. U.S. Pat. 3,038,431 (1962), R. L. Webb (to The Glidden Co.).
96. U.S. Pat. 3,963,648 (1976), J. B. Nicholas and H. R. Ansari (to Bush Boake Allen).
97. Ger. Pat. 2,255,119 (1972), B. N. Jones, H. R. Ansari, B. N. Jaggers, and J. F. Janes (to Bush Boake Allen).
98. K. Ziegler, H. Martin, and F. Krupp, *Liebig Ann. Chem.* **629**, 14 (1960).
99. K. Ziegler, F. Krupp, and K. Zosel, *Liebig. Ann. Chem.* **629**, 241 (1960).
100. Ger. Pat. 1,118,775 (1961), R. Reinacker and G. Ohloff.
101. U.S. Pat. 2,961,452 (1960), R. A. Raphael (to The Glidden Co.).
102. U.S. Pat. 2,867,668 (1959), E. T. Theimer (to International Flavors & Fragrances, Inc.).
103. V. N. Kraseva, V. G. Cherkaev, and F. M. Raitses, *Katal. Reakts. Zhidk. Faze Tr. Vses. Konf., 2nd. Alma-Ata, Kaz. SSR* 593 (1966).
104. U.S. Pat. 3,468,854 (1969), E. E. Royals (to Tenneco Chemicals, Inc.).
105. R. B. Bates, E. S. Caldwell, and H. P. Klein, *J. Org. Chem.* **34**, 2615 (1969).
106. A. F. Thomas and Y. Bessière, *Nat. Prod. Rep.* **6**(3), 291 (1989).
107. *Chem. Mark. Rep.* 34 (July 10, 1995).
108. *Chem. Mark. Rep.* 267 (12) (March 21, 2005).
109. C. S. Sell, *Chem. Biodiv.* **1**, 1899 (2004).
110. M. H. Boelens, H. Boelens, and L. J. van Gemert, *Perfumer Flavorist* **18**, 2 (1993).
111. U.S. Pat. 4,511,488 (1985), G. B. Matta (to Penetone Corp.).
112. U.S. Pat. 4,533,487 (1985), C. L. Jones (to Pitre-Jones).
113. U.S. Pat. 4,640,719 (1987), M. E. Hayes, C. C. Hood, R. E. Miller, and R. Sharp (to Petroleum Fermentations, NV).
114. U.S. Pat. 4,544,780 (1985), S. E. Wilson (to Shell Oil Co.).
115. U.S. Pat. 4,551,570 (1985), W. E. Johnson, Jr. (to SCM Corp.).
116. U.S. Pat. 2,827,499 (1958), J. P. Bain, A. B. Booth, and E. A. Klein (to The Glidden Co.).
117. A. Stanislaus and L. M. Yeddanapalli, *Can. J. Chem.* **50**, 113 (1972).
118. U.S. Pat. 2,211,432 (1941), R. C. Palmer and C. H. Bibb (to Newport Ind. Inc.).
119. U.S. Pat. 3,856,875 (1974), T. E. Wood and E. Heilweil (to Givaudan).
120. Ger.-AS Pat. 1,045,399 (1963), E. H. Polak (to PFW).
121. Fr. Pat. 1,392,804 (1963), J. Stofberg, B. van der Wal, and K. N. Nieuwland.
122. U.S. Pat. 4,000,207 (1976), G. L. Kaiser (to SCM Corp.).
123. L. A. Goldblatt and S. Palkin, *J. Am. Chem. Soc.* **63**, 3517 (1941).
124. R. E. Fuguitt and J. E. Hawkins, *J. Am. Chem. Soc.* **67**, 242 (1945).
125. K. J. Crowley, *J. Org. Chem.* **33**, 3679 (1968).
126. K. J. Crowley and S. G. Traynor, *Tetrahedron* **34**, 2783 (1978).
127. U.S. Pat. 3,281,485 (1966), R. L. Blackmore.
128. U.S. Pat. 3,723,542 (1974), R. R. Riso (to Stepan Chemical Co.).
129. G. Ohloff and E. Klein, *Tetrahedron* **18**, 37 (1962).
130. J. P. Bain, *J. Am. Chem. Soc.* **68**, 638 (1946).
131. Jpn. Pat. 7,413,158 (1974), Y. Matoubara and H. Yada (to Yoshitomi Pharmaceutical Industries).

132. U.S. Pat. 3,354,225 (1967), B. J. Kane (to The Glidden Co.).
133. E. Demole, *Helv. Chim. Acta* **47**, 319 (1964).
134. U.S. Pat. 3,499,937 (1970), J. Dorsky and W. M. Easter, Jr. (to Givaudan Corp.).
135. Eur. Pat. 19,845 (1981), G. K. Lange and K. Bauer (to Haarmann and Reimer).
136. U.S. Pat. 4,014,944 (1976), J. B. Hall and W. J. Wiegers (to IFF).
137. U.S. Pat. 4,104,203 (1978), J. B. Hall and W. J. Wiegers (to IFF).
138. U.S. Pat. 4,131,555 (1978), J. B. Hall and W. J. Wiegers (to IFF).
139. U.S. Pat. 4,131,557 (1978), J. B. Hall and W. J. Wiegers (to IFF).
140. E. Demole, *Helv. Chim. Acta* **52**, 2065 (1969).
141. U.S. Pat. 3,407,241 (1968), A. B. Booth (to Hercules, Inc.).
142. U.S. Pat. 3,407,242 (1968), A. B. Booth (to Hercules, Inc.).
143. M. C. Brown and co-workers, *J. Am. Chem. Soc.* **89**, 1925 (1967).
144. U.S. Pat. 2,851,481 (1958), R. L. Webb (to Glidden).
145. U.S. Pat. 3,594,438 (1971), J. O. Bledsoe, Jr. (to SCM Corp.).
146. U.S. Pat. 3,466,267 (1969), J. M. Derfer (to SCM Corp.).
147. *Resins for Adhesives*, product brochure, Derives Resiniques et Terpeniques (DRT).
148. G. Ohloff, H. Farnow, and W. Phillip, *J. Liebigs Am. Chem.* **43**, 613 (1958).
149. P. J. Kropp, D. C. Heckert, and T. J. Flautt, *Tetrahedron* **24**, 1385 (1968).
150. S. T. Ohashi and co-workers, *Perfumer Flavorist* **22**(2), 1 (1997).
151. G. S. Clark, *Perfumer Flavorist* **13**(4), 49, 52 (1988).
152. K. Takabe, T. Katagiri, and J. Tanaka, *Chem. Lett.* **9**, 1025 (1977).
153. U.S. Pat. 4,247,480 (1981), A. Murata and co-workers (to Nissan Chemical Industries, Ltd.).
154. G. S. Clark, *Perfumer Flavorist* **23**(3), 19 (1998).
155. U.S. Pat. 3,661,978 (1972), P. S. Gradeff and B. Finet (to Rhodia, Inc.).
156. M. F. Carroll, *J. Chem. Soc.* 704 (1940).
157. U.S. Pat. 5,137,741 (1972), M. J. Zampino and B. D. Mookherjee (to IFF).
158. S. Arctander, *Perfume and Flavor Chemicals* (*Aroma Chemicals*), Vols. I–II, published by author, Montclair, N.J., 1969.
159. U.S. Pat. 3,346,650 (1967), B. J. Kane (to The Glidden Co.).
160. SU Pat. 118,498 (1959), V. N. Kraseva, A. A. Bag, L. L. Malkina, O. M. Khol'mer, and I. M. Lebedev.
161. Ger. Pat. 2,338,291 (1974), L. M. Polinski, I. Der Hang, and J. Dorsky (to Givaudan).
162. K. Kogami and J. Kumanotani, *Bull. Soc. Chem. Jpn.* **41**, 2508 (1968).
163. U.S. Pat. 4,055,601 (1977), W. J. Ehmann (to SCM Corp.).
164. U.S. Pat. 3,275,696 (1966), E. Goldstein (to Universal Oil Products Co.).
165. A. F. Thomas, in J. Apsimon, ed., *The Total Synthesis of Natural Products*, Vol. 2, John Wiley & Sons, Inc., New York, 1973, pp. 1–195.
166. U.S. Pat. 4,739,084 (1988), H. Takaya, J. Ohta, R. Noyori, N. Sayo, H. Kumobayashi, and S. Akutagawa (to Takasago Perfumery Co.).
167. U.S. Pat. 4,739,085 (1988), H. Takaya, J. Ohta, R. Noyori, N. Sayo, H. Kumobayashi, and S. Akutagawa (to Takasago Perfumery Co.).
168. S. Akutagawa and K. Tani, in I. Ojima, ed., *Catalytic Asymmetric Synthesis*, VCH, New York, 1993, p. 41.
169. Ger. Pat. 2,652,202 (1977), R. van Helden and A. J. de Jong (to Shell International Research).
170. Ger. Pat. 2,704,547 (1977), A. J. de Jong (to Shell International Research).
171. U.S. Pat. 4,029,709 (1977), R. S. DeSimone and P. S. Gradeff (to Rhodia, Inc.).
172. P. S. Gradeff and G. Formica, *Tetrahedron Lett.* 4681 (1976).
173. Ger.-OS Pat. 2,934,250 (1979), M. Horner, M. Irrgang, and A. Nissen (to BASF).
174. Ger. Pat. 1 137 730 (1961), G. O. Schenck, G. Ohloff, and E. Klein (to Studiengesellschaft Kohle).

175. T. Yamamoto, H. Matsuda, Y. Utsumi, T. Hagiwara, and T. Kanisawa, *Tetrahedron Lett.* **43**, 9077 (2002).
176. U.S. Pat. 5,858,348 (1999), H. Matsuda and T. Yamamoto.
177. U.S. Pat. 2,898,380 (1959), R. Herrlinger (to Hercules, Inc.).
178. U.S. Pat. 2,178,349 (1939), D. H. Sheffield (to Hercules, Inc.).
179. G. W. Gladden and G. Watson, *Perf. Ess. Oil Rec.* **55**, 793 (1964).
180. U.S. Pat. 2,521,399 (1950), S. G. Norton (to Hercules Powder Co.).
181. U.S. Pat. 2,628,258 (1953), J. E. Sapp, W. F. Gillespie, and P. A. McKim (to Gaylord Container Corp.).
182. *Synthetic Organic Chemicals, U.S. Production and Sales*, USITC Publication 2810, U.S. International Trade Commission, Washington, D.C., 1993, p. 3.
183. H. Paillard and P. Tempia, *Helv. Chim. Acta* **14**, 1314 (1931).
184. O. Zeitshel and H. Schmidt, *Bercher.* **60**, 1372 (1927).
185. U.S. Pat. 5,313,008 (1994), C. P. Newman (to Unilever).
186. U.S. Pat. 5,079,386 (1992), S. E. Meakins, K. R. Motion, and C. P. Newman (to Unilever).
187. G. S. Clark, *Perfumer Flavorist* **13**(5), 37 (1988).
188. G. S. Clark, *Perfumer Flavorist* **23**(3), 19 (1998).
189. Available at http://www. Leffingwell.com and references cited therein.
190. Brit. Pat. 776,204 (1957) (to Bayer).
191. R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.* **69**, 699 (1957).
192. Ger. Pat. 2,314,813 (1974), A. W. Biedermann (to Bayer).
193. N. E. Kologivova and co-workers, *Zh. Prikl. Khim.* **36**, 12, 2740 (1963).
194. H. Terada and O. Koby, *Kagaku Zasshi* **65**, 1841 (1962).
195. W. Hickel, H. Feltkamp, and S. Giger, *Annalen.* **37**, 1 (1960).
196. S. Dev, *Handbook of Terpenes*, CRC Press, Washington, D.C., 1982, pp. 204–207.
197. Ger. Pat. 2,109,456 (1972), J. Fleischer, K. Bauer, and R. Hopp (to Haarmann and Reimer).
198. U.S. Pat. 2,843,636 (1959), A. B. Booth (to Glidden).
199. Eur. Pat. 1,223,223 (2002), U. Bornscheuer, I.-L. Gatfield, E.-M. Hilmer, S. Vorlova, and R. Schmidt (to Haarmann and Reimer).
200. U.S. Pat. 3,607,651 (1971), T. Moroe, S. Hattori, A. Komatsu, and X. Yyzo (to Takasago).
201. WO Pat. 02/36795 A2 (2002), J. A. Chaplin and co-workers (to AECI).
202. S. Akutagawa, *Appl. Catal. A* **128**, 171 (1995) and references cited therein.
203. S. Inoue, H. Takaya, K. Tani, S. Otsuka, T. Sato, and R. Noyori, *J. Am. Chem. Soc.* **112**(12), 4897 (1990).
204. K. Tani and co-workers, *J. C. S. Chem. Commun.* **11**, 600 (1982).
205. S. Akutagawa, *Top. Catal.* **4**, **3**, 4271 (1997).
206. J. C. Leffingwell and R. E. Shackelford, *Cosmetics Perfumery* **89**(6), 69 (1974) and references cited therein.
207. U.S. Pat. 2,851,481 (1958), R. L. Webb (to Glidden Co.).
208. P. Z. Bedoukian, *Perfumer Flavorist* **5**, 8 (1983).
209. S. Dev and co-workers, *Tetrahedron* **44**(22), 6941 (1988).
210. Ind. Pat. IV 151863A (1983), S. Dev and co-workers (to Bhavara Chemicals Ltd.).
211. Council of Scientific and Industrial Research (India), part IN 147,337 1980, (*Chem. Abstr.* **94**, 1981, 15919w).
212. S. Kumura, *Bull. Chem. Soc. Jpn.* **10**, 330 (1935).
213. Brit. Pat. 942,054 (1961), P. L. Williams and B. T. D. Sully (to Bush, Boake, Allen).
214. Fr. Pat. 1,374,732 (1964), P. S. Williams and B. T. D. Sully (to A. Boake, Roberts and Co., Ltd.).
215. G. Ohloff, *Tetrahedron Lett.* **1**(32), 10 (1960).

216. B. D. Sully, *Chem. Ind.* 263 (1964).
217. P. C. Traas, in E. T. Theimer, ed., *Fragrance Chemistry*, Academic Press, New York, 1982, p. 165.
218. K. Bauer and D. Garbe, *Common Fragrance and Flavour Materials*, VCH, New York, 1985, p. 38.
219. P. Z. Bedoukian, *Perfumery and Flavouring Synthetics*, 3rd ed., Allured, 1986, p. 283.
220. Jpn. Pat. 8875 (157) (1958), S. Hashira and co-workers (to Takasago).
221. A. Boake, P. I. Williams, B. T. D. Sully, and D. I. Williams, *Perfumery and Essential Oil Record* 365 (1968).
222. U.S. Pat. 3,218,361 (1966), R. L. Webb (to Glidden).
223. V. Grignard and J. Doeuvre, *Compt. Rend.* **190**, 1164 (1930).
224. C. A. Henrick and co-workers, *J. Org. Chem.* **40**, 1 (1975).
225. G. Hückel and E. Jordan, *Arch. Pharm.* **66**, 294 (1961).
226. Y. Nakatani and K. Kawashima, *J. C. S. Chem. Commun.* 147 (1978).
227. Y. Nakatani and K. Kawashima, *Synthesis* 149 (1978).
228. Jpn. Pat. 116,348 (1978) (to Takasago).
229. Eur. Pat. 1,225,163 (2002), H. Yoji, I. Takesji, and O. Yoshiki (to Takasago).
230. R. Hopp, *Rec. Adv. Tobacco Sci.* **19**, 3 (1993).
231. U.S. Pat. 6,342,644 (2002), N. Sayo and T. Matsumoto (to Takasago).
232. U.S. Pat. 2,894,040 (1950), J. P. Bain, A. B. Booth, and W. Y. Gary (to The Glidden Co.).
233. U.S. Pat. 4,058,572 (1977), B. J. Kane, K. E. Irving, J. O. Bledsoe, and L. A. Canova (to Glidden).
234. T. Yoshida, A. Komatsu, and M. Indo, *Agr. Biol. Chem.* **29**, 824 (1965).
235. U.S. Pat. 4,224,240 (1980), B. J. Kane and S. G. Traynor (to SCM Corp.).
236. U.S. Pat. 4,136,126 (1979), L. M. Hirschy, B. J. Kane, and S. G. Traynor (to SCM Corp.).
237. A. MacBeth and J. S. Shannon, *J. Chem. Soc.* 2852 (1952).
238. J. Solodar, *J. Org. Chem.* **41**(21), 3461 (1976).
239. Jpn. Pat. 7,361,454 (1973), O. Obudal and co-workers (to Taigo Perfumery Co.).
240. H. R. Watson, in C. M. Apt, ed., *Flavor: Its Chemical, Behavioral & Commercial Aspects*, Westview Press, Boulder, Col., 1977, pp. 31–50.
241. H. R. Watson, R. Hems, D. G. Roswell, and D. J. Spring, *J. Soc. Cosmet. Chem.* **29**, 185 (1978).
242. U.S. Pat. 4,296,255 (1981), D. G. Rowsell, D. J. Spring, and R. Hems (to Wilkinson Sword).
243. U.S. Pat. 4,296,093 (1981), D. G. Rowsell, J. M. Gascoyne, and R. Hems (to Wilkinson Sword).
244. U.S. Pat. 4,230,688 (1980), D. G. Rowsell, D. J. Spring, and R. Hems (to Wilkinson Sword).
245. U.S. Pat. 4,226,988 (1980), H. R. Watson, D. G. Rowsell, and D. J. Spring (to Wilkinson Sword).
246. U.S. Pat. 4,193,936 (1980), H. R. Watson, D. G. Rowsell, and D. J. Spring (to Wilkinson Sword).
247. U.S. Pat. 4,178,459 (1979), H. R. Watson, D. G. Rowsell, and D. J. Spring (to Wilkinson Sword).
248. U.S. Pat. 4,153,679 (1979), D. G. Rowsell, D. J. Spring, and R. Hems (to Wilkinson Sword).
249. U.S. Pat. 4,150,052 (1979), H. R. Watson, D. G. Rowsell, and D. J. Spring (to Wilkinson Sword).
250. U.S. Pat. 4,070,496 (1978), D. G. Rowsell and D. J. Spring (to Wilkinson Sword).
251. U.S. Pat. 4,070,449 (1978), D. G. Rowsell and R. Hems (to Wilkinson Sword).

252. U.S. Pat. 4,060,091 (1977), H. R. Watson, D. G. Rowsell, and D. J. Spring (to Wilkinson Sword).
253. U.S. Pat. 4,059,118 (1977), H. R. Watson, D. G. Rowsell, and J. H. D. Browning (to Wilkinson Sword).
254. U.S. Pat. 4,034,109 (1977), D. G. Rowsell and R. Hems (to Wilkinson Sword).
255. U.S. Pat. 4,033,994 (1977), H. R. Watson, D. G. Rowsell, and J. H. D. Browning (to Wilkinson Sword).
256. U.S. Pat. 4,032,661 (1977), D. G. Rowsell and D. J. Spring (to Wilkinson Sword).
257. U.S. Pat. 4,020,153 (1977), D. G. Rowsell and D. J. Spring (to Wilkinson Sword).
258. U.S. Pat. 6,482,983 (2002), M. Y. Lebedev and M. B. Erman (to Millennium Speciality Chemicals).
259. U.S. Pat. 6,359,168 (2002), E. Frerot and N. Van Beem (to Firmenich).
260. U.S. Pat. 4,459,425 (1984), A. Amano, M. Moroe, and T. Yoshida (to Takasago).
261. Eur. Pat. 80,148 (1983), A. Amano, M. Moroe, and T. Yoshida (to Takasago).
262. Jpn. Pat. 60 25,908 [85 25,908] (1985) (to Kanebo).
263. U.S. Pat. 5,608,119 (1997), A. Amano and K. Tokoro (to Takasago).
264. U.S. Pat. 5,266,592 (1993), H. Grub, R. Pelzer, R. Hopp, R. Emberger, and H.-J. Bertram (to Haarmann & Reimer).
265. Jpn. Pat. 2004059474 (2004), O. Takazawa, H. Watanabe, and M. Iso (to T. Hasegawa Co.).
266. U.S. Pat. 5,959,161 (1999), H. Kenmochi, T. Akiyama, Y. Yuasa, T. Kobayashi, and A. Tachikawa (to Takasago).
267. U.S. Pat. 6,328,982 (2001), K. Shiroyama, K. Sawano, and H. Ohta (to Takasago).
268. WO Pat. 2005042680 (2005) (to Firmenich SA).
269. U.S. Pat. 20040028714 (2004), M. Gautschi and P. Blondeau (to Givaudan).
270. Ger. Pat. 19840321, J. Kalbe and G. Nentwig (to Bayer).
271. U.S. Pat. 6,451,844 (2002), S. D. Watkins and M. J. Hills (to Quest Int.).
272. Jpn. Pat. 60199804 (1985), N. Hiroyuki and co-workers.
273. U.S. Pat. 5,017,377 (1991), Sikinami and co-workers.
274. U.S. Pat. 5,773,410 (1998), T. Yamamoto (to Takasago).
275. U.S. Pat. 6,267,974 (2001), A. J. Suares, A. P. Znaiden, D. C. Feliciano, and M. Carrabotta (to Unilever).
276. G. S. Clark, *Perfumer Flavorist* **20**(1), 41 (1995).
277. Jpn. Pat. 5,368 (1952), B. Masumoto and T. Funahashi.
278. G. Clark, *Perfumer Flavorist* **25**, 3 (2000).
279. U.S. Pat. 5,094,720 (1992), D. E. Sasser (to Union Camp Corp.).
280. C. Moreuil and R. Huet, *Fruits* **28**, 703 (1973).
281. A. Sato, K. Asano, and T. Sato, *J. Essential Oil Res.* **2**, 179 (1990).
282. U.S. Pat. 3,971,830 (1976), P. S. Gradeff (to Rhodia Inc.).
283. K. Tani, T. Yamamgata, S. Otsuka, H. Kumobayashi, and S. Akutagawa, *Org. Syn.* **67**, 33 (1989).
284. H. E. Zimmerman and J. English, *J. Am. Chem. Soc.* **75**, 2367 (1953).
285. B. C. Clark, T. S. Chamblee, and G. A. Iacobucci, *J. Org. Chem.* **49**, 4557 (1984).
286. U.S. Pat. 5,130,136 (1992), Y. Shono, K. Watanabe, H. Sekihachi, H. Kakimizu, Y. Suzuki, and N. Matsuo (to Sumitomo Chem. Co., Ltd.).
287. Jpn. Pat. 01,283,253 (1989), H. Nishimura, S. Akimoto, and T. Yasukochi (to Nippon Oils and Fats Co., Ltd.).
288. U.S. Pat. 2,235,840 (1941), W. C. Meuly (to E. I. du Pont de Nemours & Co., Inc.).
289. U.S. Pat. 3,869,517 (1975), P. S. Gradeff and C. Bertrand (to Rhodia, Inc.).
290. U.S. Pat. 3,852,360 (1974), M. Vilkas and G. Senechal (to L'Air Liquide).
291. Ger.-AS Pat. 2,045,888 (1970), M. Vilkas and G. Senechal.
292. Jpn. Pat. 7,003,366 (1965), T. Kumano.

293. Ger.-AS Pat. 2,211,421 (1972), L. M. Polinski, B. Venugopal, E. Eschinasi, and J. Dorsky (to Givaudan).
294. Brit. Pat. 1,278,178 (1972), E. H. Eschinasi (to Givaudan).
295. U.S. Pat. 4,206,766 (1980), W. Hoffmann (to BASF).
296. U.S. Pat. 4,482,765 (1984), M. S. Pavlin (to Union Camp Corp.).
297. Ger. Pat. 3,044,760 (1980), S. Akutagawa and T. Taketomi (to Takasago).
298. B. Arbusow, *Ber.* **68**, 1430 (1935).
299. J. B. Lewis and G. W. Hedrick, *J. Org. Chem.* **30**, 4271 (1965).
300. East Ger. Pat. 68936 (1969) (to VEB Miltitz).
301. Ger. Pat. 2,827,957 (1978), E. J. Brunke and E. Klein (to Dragoco).
302. Swiss Pat. 629,461 (1977), W. M. Easter and R. E. Naipawer (to Givaudan).
303. U.S. Pat. 4,052,341 (1976), R. E. Naipawer and W. M. Easter (to Givaudan Corp.).
304. Eur. Pat. 203,528 (1985), R. E. Naipawer (to Givaudan SA).
305. U.S. Pat. 4,696,766 (1986), R. E. Naipawer (to Givaudan).
306. Eur. Pat. 155,391 (1984), K.-H. Schulte-Elte, B. Müller, and H. Pamingle (to Firmenich SA).
307. U.S. Pat. 4,610,813 (1984), K.-H. Schulte-Elte and B. L. Müller (to Firmenich).
308. Eur. Pat. 801,049 (1997), J. A. Bajgrowicz and G. Fráter (to Givaudan-Roure).
309. J. A. Bajgrowicz, I. Frank, G. Fráter, and M. Hennig, *Helv. Chim. Acta* **81**(7), 1349 (1998).
310. G. S. Clark, *Perfumer Flavorist* **14**(3), 35 (1989).
311. L. Friedman and J. G. Miller, *Science* **172**, 1044 (1971).
312. T. J. Leitereg, D. G. Guadagni, J. Harris, T. R. Mon, and R. Teranishi, *J. Agric. Food Chem.* **19**, 785 (1971).
313. U.S. Pat. 3,293,301 (1966), J. M. Derfer, B. J. Kane, and D. G. Young (to The Glidden Co.).
314. U.S. Pat. 3,014,047 (1961), J. P. Bain, W. Y. Gary, and E. A. Klein (to The Glidden Co.).
315. WO Pat. 2,003,004,448 (2003) (to Millennium Specialty Chemicals).
316. G. S. Clark, *Perfumer Flavorist* **19**(3), 41 (1994).
317. U.S. Pat. 3,124,614 (1958), L. J. Dankert and D. A. Pernoda (to Dow Chemical Company).
318. E. Guenther, *The Essential Oils*, Vol. IV, D. Van Nostrand Co., Inc., New York, 1950, pp. 256–328.
319. Y. Matsubara, M. Kasano, K. Tanaka, A. Takita, and K. Itsuki, *Chem. Abstr.* **84**, 31257c (1976).
320. Jpn. Pat. 77,48,645 (1977), Y. Ogino, Y. Saito, and K. Itoi.
321. E. Klein and W. Rojahn, *6th International Congress on Essential Oils*, paper No. 163, San Francisco, Calif., 1974.
322. B. A. McAndrew, *Perfumer Flavorist* **17**(4), 1 (1992).
323. C. S. Sell, *A Fragrant Introduction to Terpenoid Chemistry*, Royal Society of Chemistry, Cambridge, 2003.
324. T. S. Santhanakrishnau, R. Sohti, U. R. Nayak, and S. Dev, *Tetrahedron* **26**, 65 (1970).
325. G. Ferber, *Perf. Cosmet.* **68**, 18 (1978).
326. U.S. Pat. 4,100,110 (1978), H. R. Ansari, N. Unwin, and H. R. Wagner (to Bush Boake Allen).
327. G. C. Kitchens, J. Dorsky, and K. Kaiser, *Givaudanian* **1**, 3 (1971).
328. U.S. Pat. 3,373,208 (1968), J. H. Blumenthal (to International Flavors & Fragrances).
329. T. F. Wood, *Givaudanian* **1**, 3 (1970).
330. H. U. Däniker, A. R. Hochstetler, K. Kaiser, and G. C. Kitchens, *J. Org. Chem.* **37**, 1 (1972).

331. H. U. Däniker, A. R. Hochstetler, K. Kaiser, and G. C. Kitchens, *J. Org. Chem.* **37**, 6 (1972).
332. W. G. Dauben, L. E. Friedrich, P. Oberhänsli, and E. I. Aoyagi, *J. Org. Chem.* **37**, 9 (1972).
333. B. A. McAndrew, S. E. Meakins, C. S. Sell, and C. Brown, *J. Chem. Soc. Perkin Trans.* **I**, 1373 (1983).
334. O. Isler, R. Ruegg, L. Chopard-dit-Jean, H. Wagner, and K. Bernhard, *Helv. Chim. Acta* **39**, 897 (1956).
335. A. Ofner, W. Kimel, A. Holmgren, and F. Forrester, *Helv. Chim. Acta* **42**, 2577 (1959).
336. F. S. M. Zaoral and V. Herout, *Coll. Czech. Chem. Commun.* **16**, 626 (1953).
337. C. F. Seidel, P. H. Müller, and H. Schinz, *Helv. Chim. Acta* **27**, 738 (1944).
338. K. G. O'Brien, A. R. Penfold, and R. L. Werner, *Aust. J. Chem.* **6**, 166 (1953).
339. K. G. O'Brien, A. R. Penfold, M. D. Sutherland, and R. L. Werner, *Aust. J. Chem.* **7**, 298 (1954).
340. C. Menut, P. Cabalion, E. Hnawia, H. Aganiet, J. Waikedre, and A. Fruchier, *Flavour. Fragr. J.* **20**(6), 621 (2005).
341. E. Fleikamp, G. Nonnenmacher, and O. Isaac, *Z. Naturforsch.* (*B*) **36**, 114 (1981).
342. E.-J. Brunke and F.-J. Hammerschmidt, *Dragoco Rep.* **2**, 37 (1984).
343. M. Hava and J. Janku, *Rev. Czech. Med.* **3**, 130 (1957).
344. G. C. Dull, J. L. Fairley, R. Y. Gottshall, and E. H. Lucas, *Antibiot. Anmerkungen* 682 (1956–1957).
345. J. V. Janku and C. Zita, *Cs. Farmacie* **3**, 93 (1954).
346. C. Zita and B. Steklova, *Cs. Iek Ces* **94**, 204 (1955).
347. V. Yakoviev and A. von Schlichtergral, *Arzneim. Forschung* **19**, 615 (1969).
348. *Dracogo Rep.* **24**(4), 79 (1977).
349. C. D. Gutsche, J. R. Maycock, and C. T. Chang, *Tetrahedron* **24**, 859 (1968).
350. B. M. Lawrence, *Perfumer Flavorist* **5**(6), 27 (1980).
351. U.S. Pat. 6,214,788 (2001), M. I. Velazco, L. Wünsche, and P. Deladoey (to Firmenich).
352. Eur. Pat. Appl. 1,541,039 A1 (2005), M. I. Velazco, L. Wünsche, and P. Deladoey (to Firmenich).
353. Swiss Pat. 60699 (1999), M. I. Velazco, L. Wünsche, and P. Deladoey (to Firmenich).
354. G. L. K. Hunter and W. B. Brogden, *J. Food Sci.* **30**, 876 (1965).
355. Ger. Pat. 1,948,033 (1970), G. Ohloff (to Firmenich).
356. G. Ohloff, *Scent and Fragrances*, transl. by W. Pickenhagen and B. M. Lawrence, Springer-Verlag, Berlin, 1994, p. 136.
357. B. J. M. Jansen, *Total Synthesis of Insect Antifeedant Drimane Sesquiterpenes*, Ph.D. Thesis, University of Wageningen, 1997.
358. H. Lucas, *Arch. Pharm.* **85**, 145 (1856).
359. E. Graf, *Angew. Chem.* **68**, 249 (1956).
360. M. E. Wall and M. C. Wani, Taxane *Anticancer Agents—Basic Science and Current Status, ACS Symposium Series*, Vol. 583, ACS, Washington, D.C.
361. G. I. Georg, T. T. Chen, I. Ojima, and D. M. Vyas, eds., American Chemical Society, Washington, D.C., 1995, pp. 18–30.
362. M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Am. Chem. Soc.* **93**, 2325 (1971).
363. P. H. Beusker, Ph.D. Thesis, Catholic University of Nijmegen, 2002.
364. V. Farina, ed., *The Chemistry and Pharmacology of Taxol and Its Derivatives*, Pharmacochemistry Library, Vol. 22, Elsevier, Amsterdam, The Netherlands, 1995.
365. E. Damen, Ph.D. Thesis, Catholic University of Nijmegen, 2000.
366. S. Jennewein and R. Croteau, *Appl. Microbiol. Biotechnol.* **57**, 13 (2001).

367. (a) R. A. Holton and co-workers, *J. Am. Chem. Soc.* **116**, 1597 (1994); (b) R. A. Holton, and co-workers, *J. Am. Chem. Soc.* **116**, 1599 (1994); (c) R. A. Holton and co-workers, *ACS Symp. Ser.* **583**, 288 (1995).
368. (a) P. A. Wender and T. P. Mucciaro, *J. Am. Chem. Soc.* **114**(14), 5878 (1992); (b) P. A. Wender and co-workers, *J. Am. Chem. Soc.* **119**, 2757 (1997); (c) P. A. Wender and co-workers, *J. Am. Chem. Soc.* **119**, 2755 (1997).
369. L. A. Paquette, *ACS Symp. Ser.* **583**, 313 (1995).
370. (a) K. C. Nicolaou and co-workers, *nature* (*London*) **367**, 630 (1994); (b) K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros, and E. J. Sorensen, *J. Am. Chem. Soc.* **117**, 624 (1995); (c) K. C. Nicolaou and co-workers, *J. Am. Chem. Soc.* **117**, 634 (1995); (d) K. C. Nicolaou and co-workers, *J. Am. Chem. Soc.* **117**, 645 (1995); (e) K. C. Nicolaou, H. Ueno, J. J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, and R. Chadha, *J. Am. Chem. Soc.* **117**, 653 (1995); (f) K. C. Nicolaou and R. K. Guy, *Angew. Chem. Int. Ed. Engl.* **34**, 2079 (1995); (g) K. C. Nicolaou and co-workers, *nature* (*London*) **367**, 630 (1994).
371. (a) J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.* **34**, 1723 (1995); (b) S. J. Danishefsky and co-workers, *J. Am. Chem. Soc.* **118**, 2843 (1996).
372. (a) T. Mukaiyama, I. Shiina, H. Iwadare, H. Saitoh, Y. Tani, M. Hasegawa, and K. Saitoh, *Proc. Jpn. Acad. Ser. B* **73**, 95 (1997); (b) T. Mukaiyama and co-workers, *Chem. Eur. J.* **5**, 121 (1999).
373. (a) K. Morihira and co-workers, *J. Am. Chem. Soc.* **120**, 12980 (1998); (b) H. Kusama and co-workers, *J. Am. Chem. Soc.* **122**, 3811 (2000); (c) I. Kuwajima and H. Kusama, *Synlett* 1385 (2000).
374. A. Stierle, G. A. Strobel, and D. Stierle, *Science* **260**, 214 (1993).
375. Y. Yukimune, H. Tabata, Y. Higashi, and Y. Hara, *nature Biotechnol.* **14**, 1129 (1996).
376. U.S. Pat. 5,567,641 (1996), R. N. Patel, L. J. Szarka, and R. Partyka.
377. J. N. Denis, A. E. Greene, D. Guénard, F. Guéritte-Vögelein, L. Mangatal, and P. Potier, *J. Am. Chem. Soc.* **110**, 5917 (1988).
378. D. G. I. Kingston, A. A. Molinero, and J. M. Rimoldi, *Prog. Chem. Org. Nat. Prod.* **61**.
379. W. Herz, G. W. Kirby, R. E. Moore, W. Steglich, and C. Tamm, eds., Springer Verlag, New York, 1993, pp. 1–206.
380. E. Baloglu and D. G. I. Kingston, *J. Nat. Prod.* **62**, 1448 (1999).
381. G. Appendino, *Nat. Prod. Rep.* **12**, 349 (1995).
382. Y. Fujita and T. Nishida, *Kukagaku* **29**, 814 (1980).
383. Y. Fujita, Y. Ninagawa, T. Nishida, and K. Itoi, *Yuki Gosei Kagaku Kyokaishi* **37**, 224 (1979).
384. D. A. Eiznhamer and Z.-Q. Xu, *Idrugs* **7**(4), 359 (2004).
385. A. Leung and S. Foster, Olibanum, *Encyclopaedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*, 1996, pp. 389–390.
386. G. B. Singh and C. K. Atal, *Agents and Actions* **18**(3/4), 407 (1986).
387. G. Kesava Reddy, G. Chandrakasan, and S. C. Dhar, *Biochem. Pharmacol.* **38**(20), 3527 (1989).
388. H. Safayhi and co-workers, *J. Pharmac. Exper. Ther.* **261**, 1143 (1992).
389. H. Safayhi, E. R. Sailer, and H. P. Ammon, *Mol. Pharmacol.* **47**, 1212 (1995).
390. S. K. Shrivastava, G. K. Singh, and P. K. Basniwal, *Indian J. Nat. Prod.* **19**(4), 14 (2003).
391. T. W. Goodwin, ed., *Chemistry and Biochemistry of Plant Pigments*, 2nd ed., Academic Press, Inc., New York, 1976.
392. O. Isler, R. Rügg, and U. Schwieter, *Pure Appl. Chem.* **14**, 245 (1976).

393. O. Isler, *Pure Appl. Chem.* **51**, 447 (1979).
394. H. Kandori, *Chem. Ind.* 735 (1995).
395. K. Münzel, in J. C. Bauernfeind, ed., *Carotenoids as Colorants and Vitamin A Precursors, Technological and Nutritional Applications*, Academic Press, New York, 1981, pp. 781–813.
396. E. L. Giovanucci, A. Ascherio, E. B. Rimm, M. J. Stampfer, G. A. Colditz, and W. C. Willett, *J. Natl. Cancer Inst.* **87**, 1767 (1995).
397. E. L. Giovanucci, *J. Natl. Cancer Inst.* **91**, 317 (1999).
398. Riso and co-workers, *Am. J. Clin. Nutr.* **69**(4), 712 (1999).
399. S. Agarwal and A. V. Rao, *Lipids* **33**, 981 (1998).
400. Suganuma and Inakuma, *Biosci. Biotechnol. Biochem.* **63**(1), 78 (1999).
401. H. D. Preston and M. D. Rickard, *Food Chem.* **5**, 47 (1980).
402. Ger. Pat. 1,109,677 (1959), R. Marbet and G. Saucy (to Hoffmann La Roche).
403. Ger.-AS Pat. 1286019 (1967), H. Pommer, W. Reif, W. Pasedach, and W. Hoffmann (to BASF).
404. Brit. Pat. 865,478 (1961) (to Hoffmann-La Roche).
405. Brit. Pat. 812,727 (1959), M. G. J. Beets and H. van Essen (to Polak and Schwarz).
406. U.S. Pat. 3,840,601 (1974), P. S. Gradeff (to Rhodia, Inc.).
407. Fr. Pat. 1,355,944 (1962), G. Ohloff and G. Schade (to Studiengesellschaft Kohle).
408. U.S. Pat. 4,431,844 (1984), L. Janitschke, W. Hoffman, L. Arnold, M. Strözel, and H. J. Sheiper (to BASF).
409. Ger. Pat. 2,455,761 (1974), G. Blume, R. Hopp, and W. Sturm (to Haarmann and Reimer).
410. Ger. Pat. 2,807,584 (1978), E. Klein and W. Rojahn (to Dragoco Gerberding GmBH).
411. K. H. Schulte-Elte, W. Giersch, B. Winter, H. Pamingle, and G. Ohloff, *Helv. Chim. Acta* **68**(7), 1961 (1985).
412. Eur. Pat. 118,809 (1984), K. H. Schulte-Elte, G. Ohloff, B. L. Müller, and W. Giersch (to Firmenich).
413. Eur. Pat. 0 457,022 B1 (1991), K.-H. Schulte-Elte, C. Margot, C. Chapuis, D. P. Simmons, and D. Reichlin (to Firmenich).
414. U.S. Pat. 4,623,750 (1983), K.-H. Schulte-Elte and G. Ohloff (to Firmenich).
415. U.S. Pat. 4,626,381 (1983), K.-H. Schulte-Elte (to Firmenich).
416. U.S. Pat. 4,711,875 (1983), K.-H. Schulte-Elte and G. Ohloff (to Firmenich).
417. Eur. Pat. 121,828 (1983), K.-H. Schulte-Elte and H. Pamingle (to Firmenich).
418. E. Kovats, *J. Chromatogr.* **406**, 185 (1987).
419. E. P. Demole, P. Enggist, U. Säuberli, M. Stoll, and E. Kovats, *Helv. Chim. Acta* **53**, 541 (1970).
420. A. Williams, *Perfumer Flavorist* **27**(2), 18 (2002).
421. P. Weyerstahl and co-workers, *Liebigs Ann. Chem.* 809 (1996).
422. K. S. Ayyar, R. C. Cookson, and D. A. Kagi, *J. Chem. Soc. Chem. Commun.* 161 (1973).
423. K.-H. Schulte-Elte and co-workers, *Liebigs Ann. Chem.* 484 (1975).
424. A. F. Morris, F. Näf, and R. L. Snowden, *Perfum Flavor* **16**, 33 (1993).
425. G. Büchi and J. C. Vederas, *J. Am. Chem. Soc.* **94**, 9128 (1972).
426. K.-H. Schulte-Elte, B. L. Müller, and G. Ohloff, *Helv. Chim. Acta* **56**, 310 (1973).
427. Swiss Pat. 563,951 (1972), K.-H. Schulte-Elte (to Firmenich).
428. Eur. Pat. 260,472 (1987), C. Fehr and J. Galindo (to Firmenich).
429. C. Fehr and J. Galindo, *J. Am. Chem. Soc.* **110**, 6909 (1988).
430. Eur. Pat. 326,869 (1989), C. Fehr and J. Galindo (to Firmenich).
431. C. Fehr and J. Galindo, *J. Org. Chem.* **53**, 1828 (1988).
432. Brit. Pat. 1,456,152 (1974), H. J. Wille, W. M. B. Könst, and J. Kos (to Naarden International).

433. Fr. Pat. 2,296,611 (1976), P. A. Ochsner and H. Schenk (to Givaudan).
434. Fr. Pat. 2,327,226 (1977), H. Schenk (to Givaudan).
435. U.S. Pat. 4,006,108 (1977), P. A. Ochsner and H. Schenk (to Givaudan).
436. U.S. Pat. 5,015,625 (1991), C. Fehr and J. Galindo (to Firmenich).
437. E. J. Lederer, *J. Chem. Soc.* 2122 (1949).
438. G. Ohloff, in E. T. Theimer, ed., *Fragrance Chemistry*, New York, Academic Press, 1982.
439. C. S. Sell, *Chem. Ind.* **16**, 520 (1990).
440. B. D. Mookherjee and R. R. Patel, *Proceedings of the 7th International Conference of Essential Oils*, Kyoto, 1977; paper 137, 479. *Chem. Abstr.* **92**, 203412h (1980).
441. E. Lederer, *Fortschritte der Chemie Organischer Naturstoffe*, Vol. 6, Springer-Verlag, 1950, p. 120.
442. G. Ohloff, K.-H. Schulte Elte, and B. L. Muller, *Helv. Chim. Acta.* **60**, 2763 (1977).
443. K.-H. Schulte Elte, B. L. Muller, and G. Ohloff, *Nouv. J. Chim.* **2**, 247 (1978).
444. U.S. Pat. 5,155,029 (1992), M. I. Farbood, J. A. Morris, and A. E. Downey (to IFF).
445. D. H. R. Barton, S. I. Parekh, D. K. Taylor, and C.-L. Tse, *Tetrahedron Lett.* **35**, 5801 (1994).
446. U.S. Pat. 5,463,089 (1994), D. H. R. Barton, S. I. Parekh, D. K. Taylor, and C.-L. Tse (to Quest International).
447. Eur. Pat. 822,191 (1997), P. N. Davey, L. S. Payne, and C.-L. Tse (to Quest International).
448. Eur. Pat. 1,171,433 (2000), P. N. Davey and C.-L. Tse (to Quest International).
449. M. G. Bolster, Ph.D. Thesis, Wageningen Agricultural University, 2002.
450. C. Chauffat and A. Morris, *Perfumer Flavorist* **29**(2), 34 (2004).
451. G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.* **77**, 5068 (1955).
452. G. Lucius, *Angew. Chem.* **68**, 247 (1956).
453. G. Lucius, *Arch. Pharm.* **291**, 57 (1958).
454. G. Lucius, *Chem. Ber.* **93**, 2663 (1960).
455. A. Saito, H. Matsushita, and H. Kaneko, *Chem. Lett.* 729 (1983).
456. Ger. Pat. 3,240,054 (1982), G. Staiger and A. Macri (to Consortium Elektrochemische Industrie GmbH).
457. Eur. Pat. 107,857 (1985), G. Staiger and A. Macri (to Consortium Elektrochemische Industrie GmbH).
458. T. Kawanobe, K. Kogami, and M. Matsui, *Agric. Biol. Chem.* **50**, 1475 (1986).
459. Eur. Pat. 165,458 (1985), T. Kawanobe and K. Kogami (to Hasegawa).
460. P. F. Vlad, N. D. Ungur, and V. B. Perutskii, *Khim. Geterotslic. Soedin* 896 (1990).
461. Eur. Pat. 403,945 (1989), K.-H. Schulte-Elte, R. L. Snowden, C. Tarchini, B. Bär, and C. Vial (to Firmenich SA).
462. R. L. Snowden and S. M. Linder, *Tetrahedron Lett.* **32**, 4119 (1991).
463. R. L. Snowden, J.-C. Eichenberger, S. M. Linder, P. Sonnay, C. Vial, and K.-H. Schulte-Elte, *J. Org. Chem.* **57**, 955 (1992).
464. R. L. Snowden, J.-C. Eichenberger, W. Giersch, W. Thommen, and K.-H. Schulte-Elte, *Helv. Chim. Acta* **76**, 1608 (1993).
465. A. F. Barrero, J. Altarejos, E. J. Alvarez-Manzaneda, J. M. Ramos, and S. Salido, *J. Org. Chem.* **61**, 2215 (1996).
466. Ger. Pat. 2,733,928 (1977), H. Strickler (to Firmenich).
467. Eur. Pat. 276998 (1988), C. P. Newman, K. J. Rossiter, and C. S. Sell (to Unilever).
468. A. Gautier, C. Vial, C. Morel, M. Lander, and F. Näf, *Helv. Chim. Acta* **70**, 2039 (1987).
469. D. H. R. Barton and M. Mousseron-Canet, *J. Chem. Soc.* 271 (1960).
470. H. A. Eschinazi, *J. Am. Chem. Soc.* **81**, 2905 (1959).
471. E. Brenna, C. Fuganti, S. Ronzani, and S. Serra, *Helv. Chim. Acta* **84**, 3650 (2001).

GENERAL REFERENCES

J. L. Simonsen, *The Terpenes*, 3 volumes, Cambridge University Press, 1949.

E. Guenther, *The Essential Oils*, Vols. 1–6, Van Nostrand Co., Inc., Princeton, N.J., 1948–1952.

J. L. Simonson and co-workers, *The Terpenes*, Vols. 1–3, 2nd rev. ed., Cambridge University Press, New York, 1953 and 1957.

A. R. Pinder, *The Chemistry of the Terpenes*, Chapman and Hall, 1960.

P. Z. Bedoukian, *Perfumery and Flavoring Synthetics*, 2nd rev. ed., Elsevier Publishing Co., New York, 1967.

W. Templeton, ed., *An Introduction to the Chemistry of Terpenoids and Steroids*, Butterworths & Co., Ltd., London, 1969.

S. Arctander, *Perfume and Flavor Chemicals* (*Aroma Chemicals*), Vols. I–II, published by author, Montclair, N.J., 1969.

T. K. Devon and A. I. Scott, *Terpenes*, Vol. II, *Handbook of Naturally Occurring Compounds*, Academic Press, New York, 1972.

A. A. Newman, *Chemistry of Terpenes and Terpenoids*, Academic Press, London, 1972.

T. E. Furia and N. Bellanca, eds., *Fenaroli's Handbook of Flavor Ingredients*, 2nd ed., Vol. 2, CRC Press, Inc., Cleveland, Ohio, 1975.

A. F. Thomas and Y. Bessiere, in J. ApSimon, ed., *The Total Synthesis of Natural Products*, Vol. 4, John Wiley & Sons, Inc., New York, 1981.

S. Dev, *CRC Handbook of Terpenoids, Monoterpenoids*, Vols. I–II, CRC Press, Inc., Boca Raton, Fla., 1982.

S. Dev, A. P. S. Narula, and J. S. Jadav, *Handbook of Terpenoids*, 2 volumes, CRC Press, Inc., Boca Raton, Fla., 1982.

E. T. Theimer, ed., *Fragrance Chemistry*, Academic Press, New York, 1982.

W. F. Erman, *Studies in Organic Chemistry*, Vol. II, *Chemistry of the Monoterpenes: An Encyclopedic Handbook*, Marcel Decker, New York, 1985.

R. Croteau, *Chem. Rev.* **87**, 929 (1987).

H. U. Däniker, *Flavors and Fragrances* (Worldwide), SRI International, 1987.

Tse-Lok Ho, *Carbocycle Construction in Terpene Synthesis*, VCH, 1988.

D. F. Zinkel and J. Russell, eds., *Naval Stores*, Pulp Chemicals Association, Inc., New York, 1989.

P. M. Muller and D. Lamparsky, eds., *Perfumes, Art, Science and Technology*, Elsevier, New York, 1991.

P. J. Tesseire, *Chemistry of Fragrant Substances*, VCH Publishers, 1993.

R. A. Hill, *Terpenoids*, in *The Chemistry of Natural Products*, R. H. Thompson, ed., Blackie Academic and Professional, Chapman and Hall, 1993, pp. 106–139.

J. Mann, R. S. Davidson, J. B. Hobbs, D. V. Banthorpe, and J. B. Harbourne, *Natural Products: Their Chemistry and Biological Significance*, Longman, 1994.

G. Ohloff, *Scent and Fragrances, The Fascination of Odors and Their Chemical Perspectives*, transl. by W. Pickenhagen and B. M. Lawrence, Springer-Verlag, Berlin, 1994.

L. P. Somogyi, B. Rhomberg, and N. Takei, *Flavors and Fragrances*, SRI International, 1995.

K. Bauer, D. Garbe, and H. Surburg, *Common Fragrance and Flavor Materials*, 4th ed., Wiley-VCH, Weinheim, 2001.

D. H. Pybus and C. S. Sell, eds., *The Chemistry of Fragrances*, RSC, 1999.

C. S. Sell, *A Fragrant Introduction to Terpenoid Chemistry*, Royal Society of Chemistry, Cambridge, 2003.

H. Surburg and J. Panten, *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*, Wiley-VCH, New York, 2006.

C. S. Sell, ed., *The Chemistry of Fragrance*, RSC, 2006 (in press).

Electronic Sources

Available at www.Leffingwell.com.

Essential Oils Database, Boelens Aromachemical Information Systems, Huizen, The Netherlands.

Physical Properties and Spectral Data of Terpenoids

C. J. Pouchert, *The Aldrich Library of Infrared Spectra*, Aldrich Chemical Co., Inc., Milwaukee, Wis., 1974.

C. J. Pouchert and J. R. Campbell, *The Aldrich Library of NMR*, Vols. 1–11, Aldrich Chemical Co., Inc., Milwaukee, Wis., 1974.

J. G. Grasselli and W. M. Ritchey, *CRC Atlas of Spectral Data and Physical Constants of Organic Compounds*, 2nd ed., CRC Press Inc., Boca Raton, Fla., 1975.

W. Jennings and T. Shibamoto, *Qualitative Analysis of Flavor and Fragrance Volatiles by Glass Capillary Gas Chromatography*, Academic Press, New York, 1980; also includes retention indexes and mass spectral data.

A. A. Swigar and R. M. Silverstein, *Monoterpenes, Infrared, Mass,* ^{1}*H-NMR, and* ^{13}*C-NMR Spectra, and Kovats Indices*, Aldrich Chemical Co., Inc., Milwaukee, Wis., 1981.

R. P. Adams, *Identification of Essential Oil Components by Gas Chromatography/Quadropole Mass Spectrometry*, Allured Publishing Corp., Illinois, USA, 2001.

K.-H. Kubecza, *Essential Oil Analysis by Capillary Gas Chromatography and Carbon-13 NMR Spectroscopy*, 2nd ed., John Wiley & Sons, Inc., New York, 2002.

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Table 1. **Classification of Terpenoids**

Name	No. of isoprene units	No. of carbon atoms
hemiterpenoids	1	5
monoterpenoids	2	10
sesquiterpenoids	3	15
diterpenoids	4	20
sesterterpenoids	5	25
triterpenoids	6	30
tetraterpenoids	8	40
carotenoids	8	40
polyisoprenoids	>8	>40

Table 2. **Geraniol/Nerol Ratios in Commercial Products**

Name	% geraniol	% nerol
Geraniol 980 pure	>97	<3
Geraniol 7030	70–78	23–30
Geraniol Coeur	55–62	10–15
Geraniol 5020	48–58	24–30
Nerol 800	10–20	80–86
Nerol 850	7–16	83–88
Nerol 900	<5	90–98

Table 3. **Products of Hydrogenation of Thymol**

Name	% in Mixture	bp °C
dl-menthol (**42**)/(**161**)	62–64	216.5
dl-neomenthol (**162**)/(**163**)	18–20	212
dl-isomenthol (**164**)/(**165**)	10–12	218
dl-neoisomenthol (**166**)/(**167**)	1–2	214.6

Table 4. **Odor Thresholds of Damascones**

Compound	Threshold ng/L air
α-damascone	0.14
β-damascone	0.19
γ-damascone	4.5
δ-damascone	0.021
β-damascenone	0.013

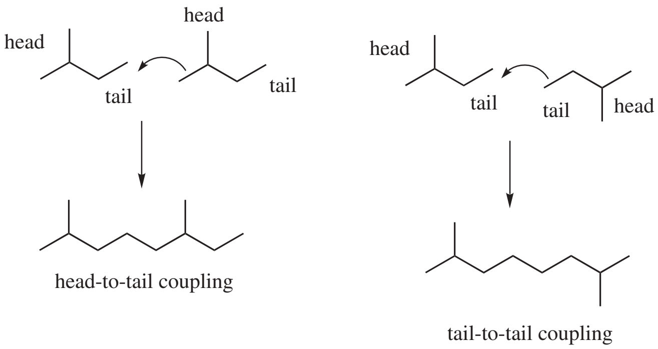


Fig. 1. Coupling of isoprene units.

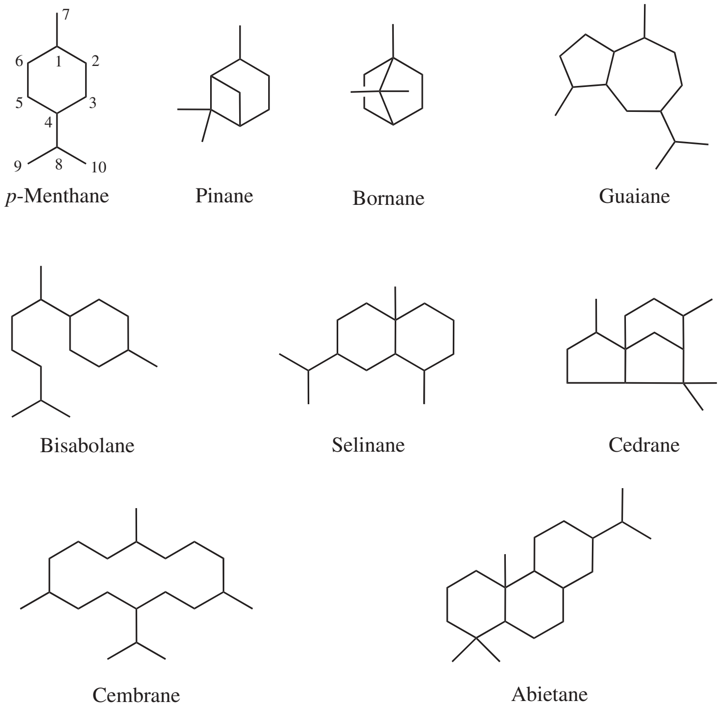


Fig. 2. Some common terpenoid skeletons.

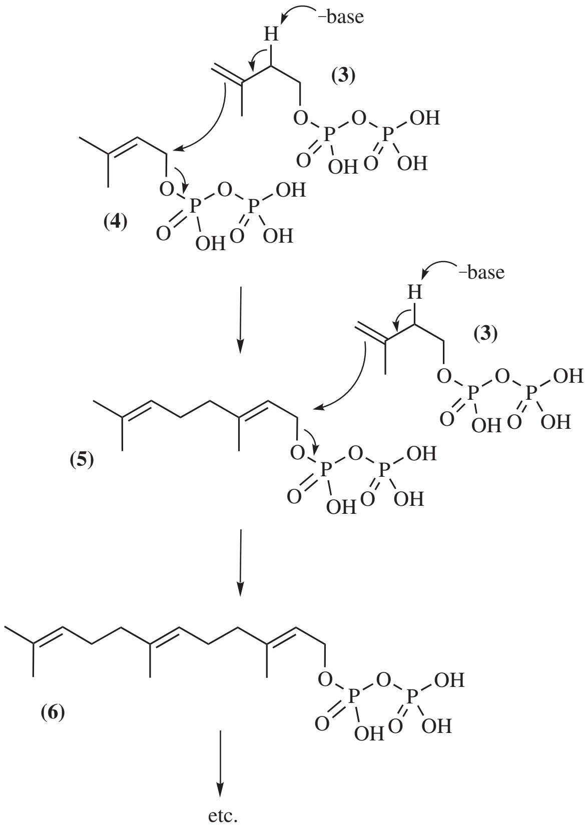


Fig. 3. Biosynthesis of the basic linear terpenoid skeletons.

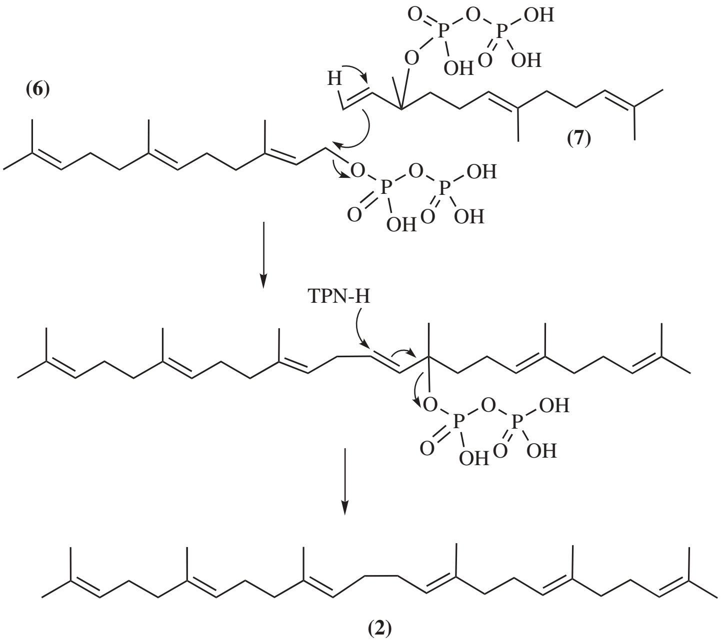


Fig. 4. An example of tail-to-tail coupling in terpenoids.

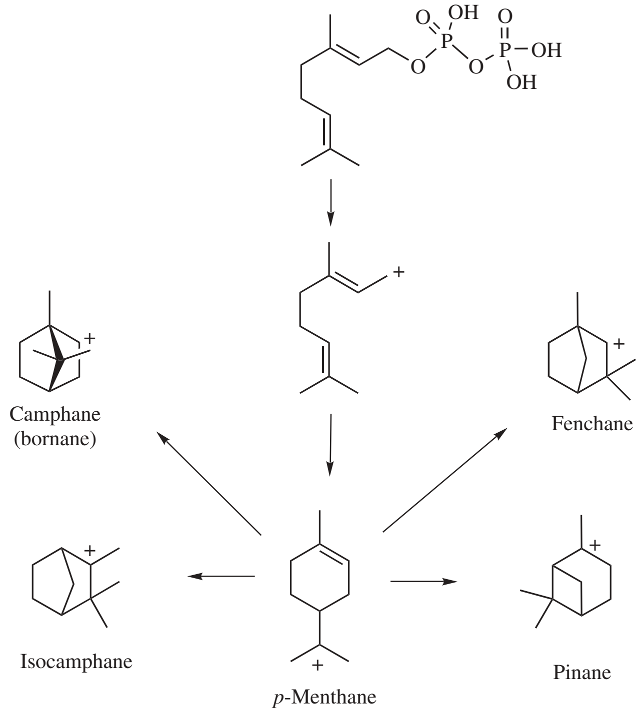


Fig. 5. Some biosynthetic routes to cyclic monoterpenoids.

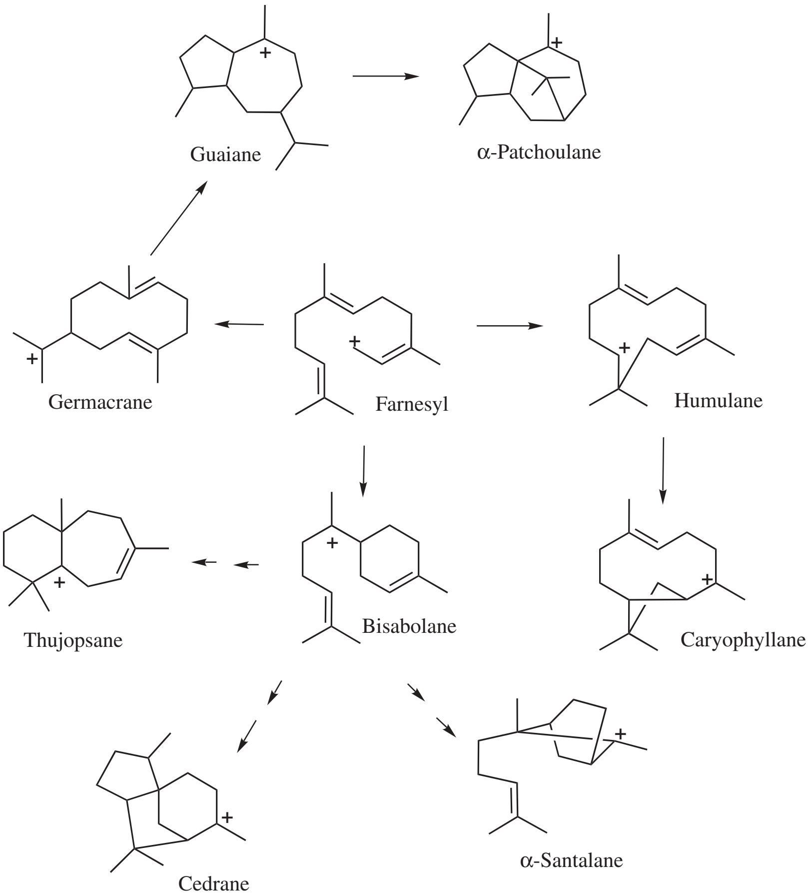


Fig. 6. Some biosynthetic routes to cyclic sesquiterpenoids.

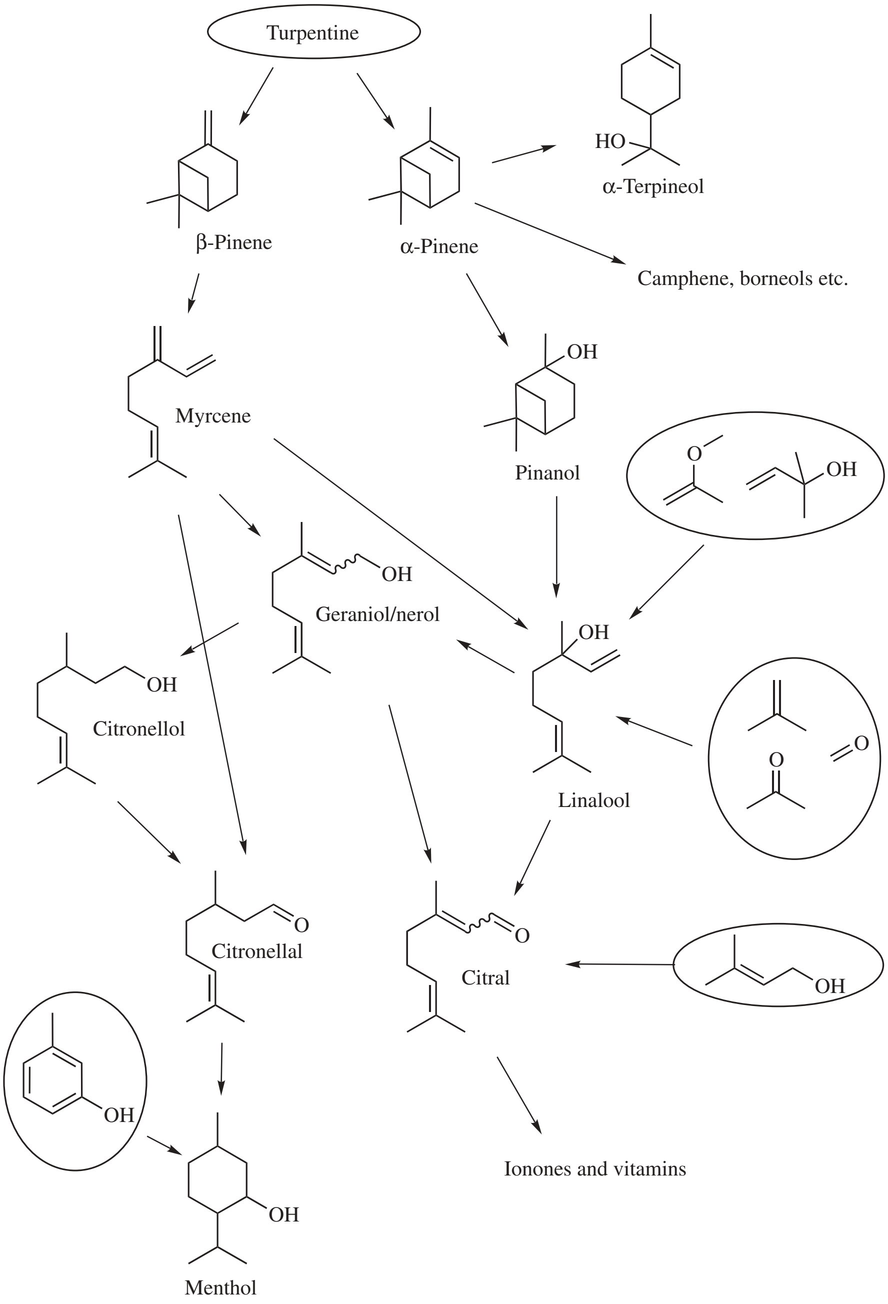


Fig. 7. The key terpenoid manufacturing routes.

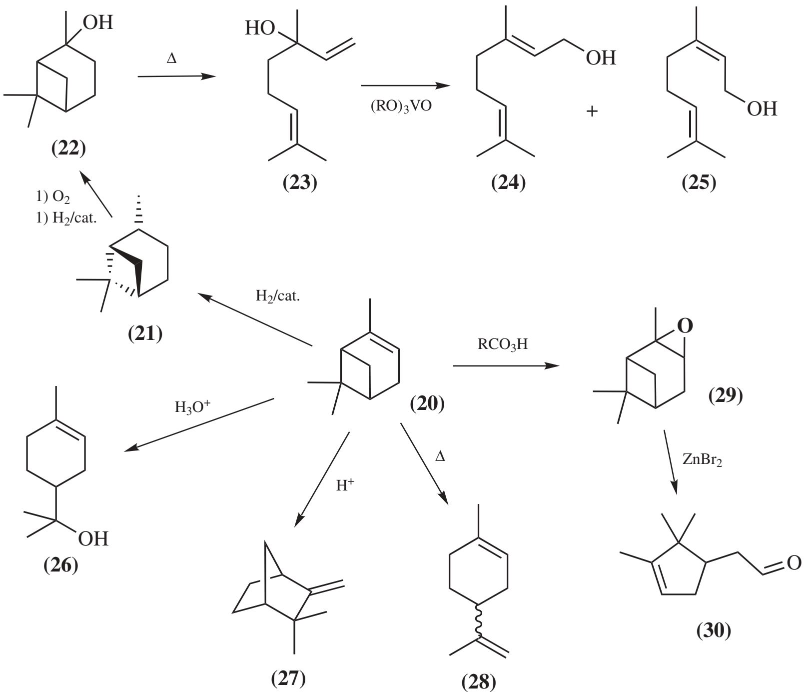


Fig. 8. Major products from α-pinene.

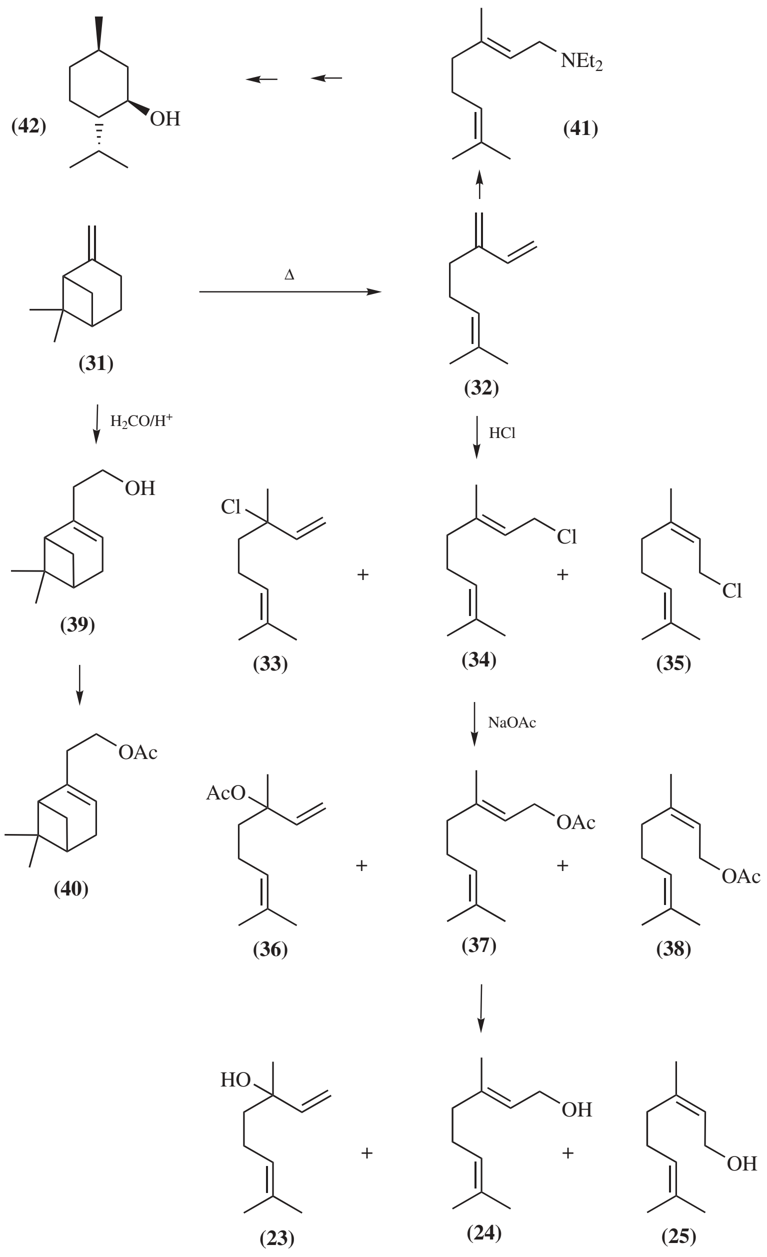


Fig. 9. Major products from β-pinene.

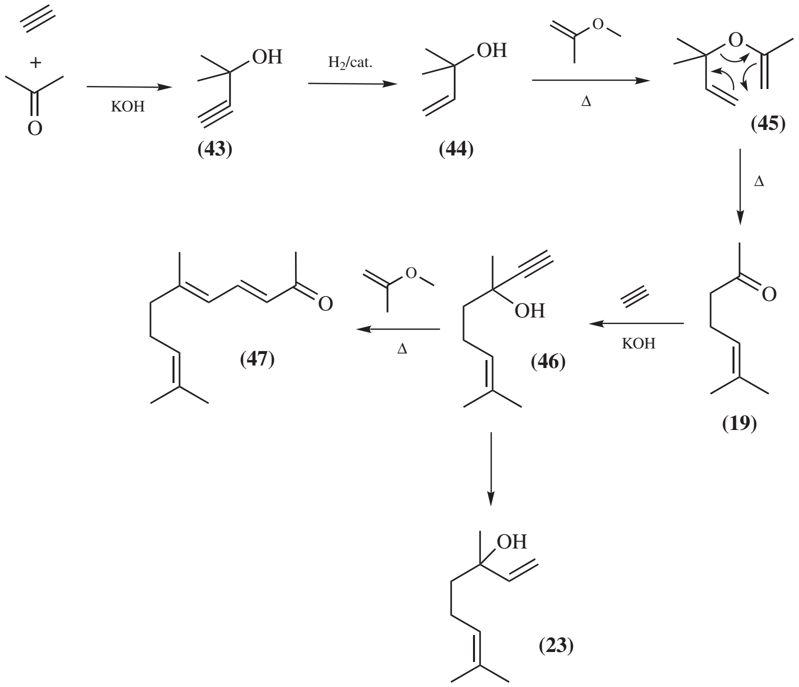


Fig. 10. Key features of the DSM process for terpenoid manufacture.

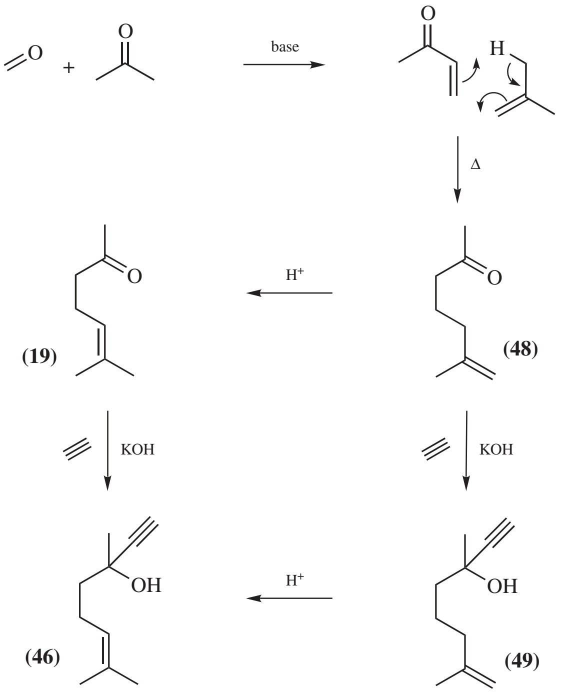


Fig. 11. Key features of the BASF process for terpenoid manufacture.

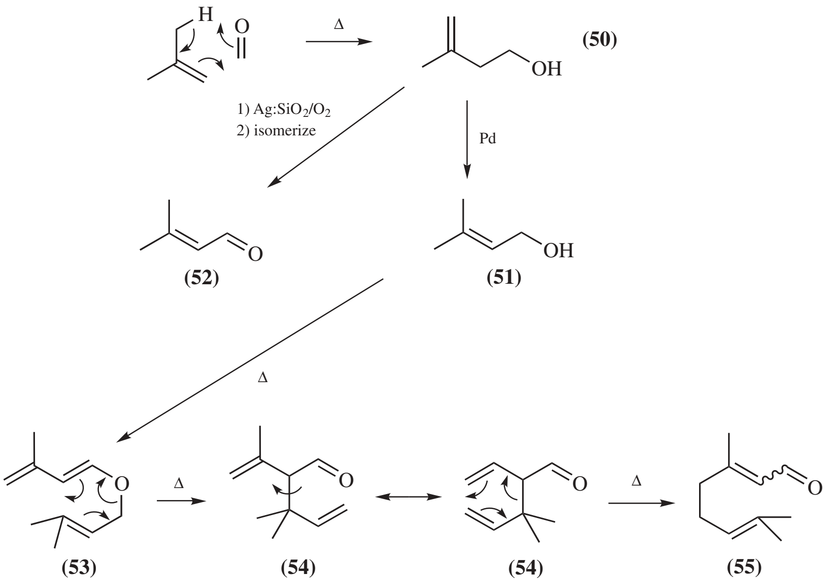


Fig. 12. Key features of the BASF process for manufacture of citral.

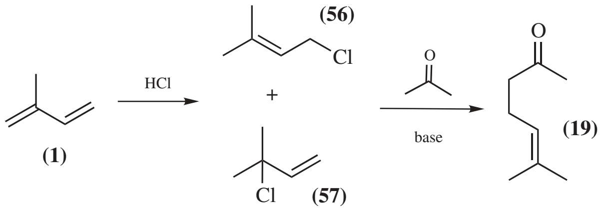


Fig. 13. Manufacture of terpenoids from isoprene via prenyl chloride.

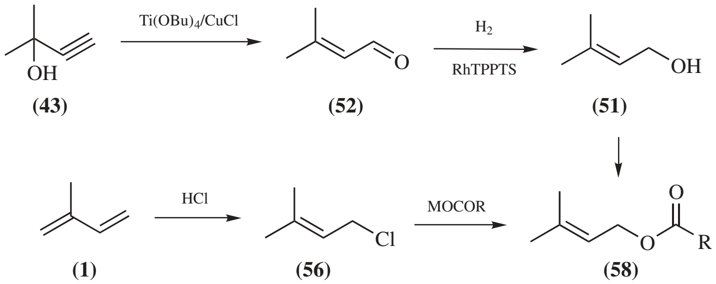


Fig. 14. Preparation of prenyl esters.

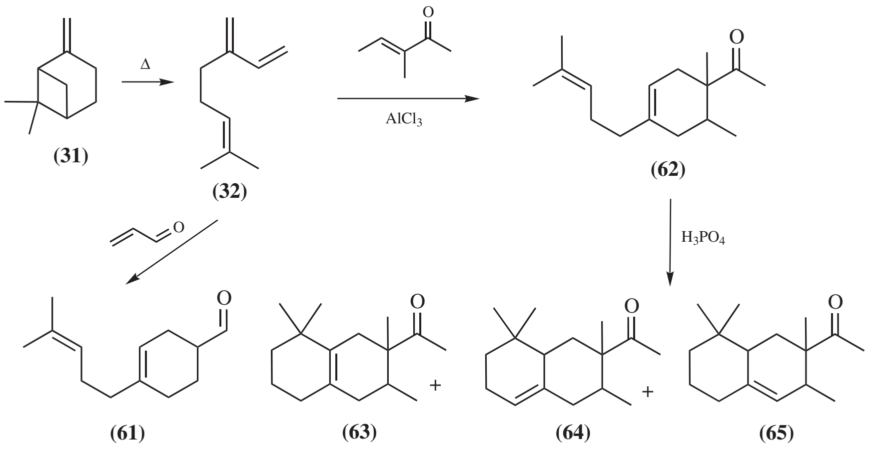


Fig. 15. Preparation of Myrac Aldehyde and Iso E Super.

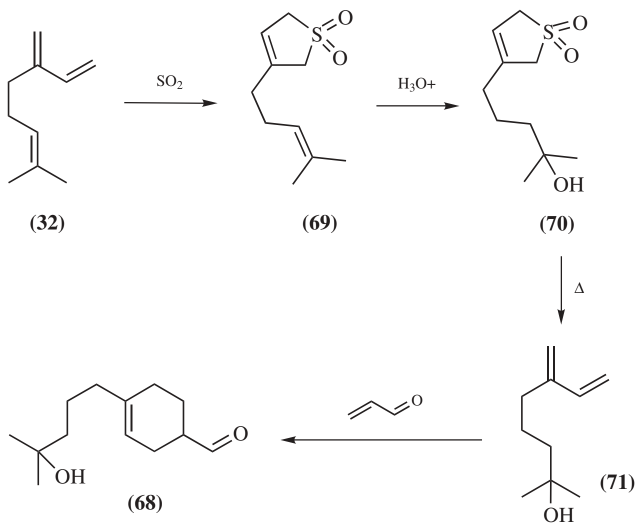


Fig. 16. Preparation of Lyral.

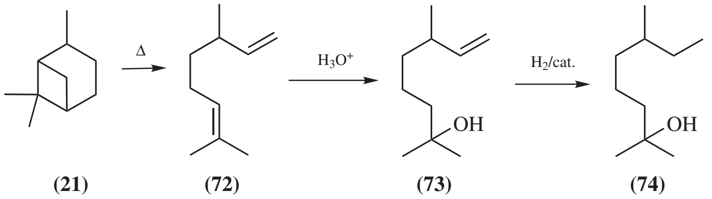


Fig. 17. Preparation of dihydromyrcenol and tetrahydromyrcenol.

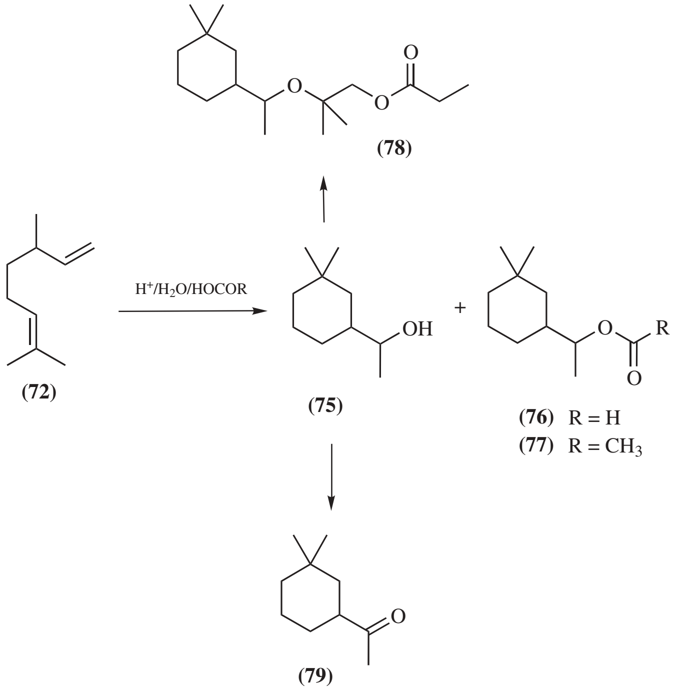


Fig. 18. Preparation of cyclodemol and its derivatives.

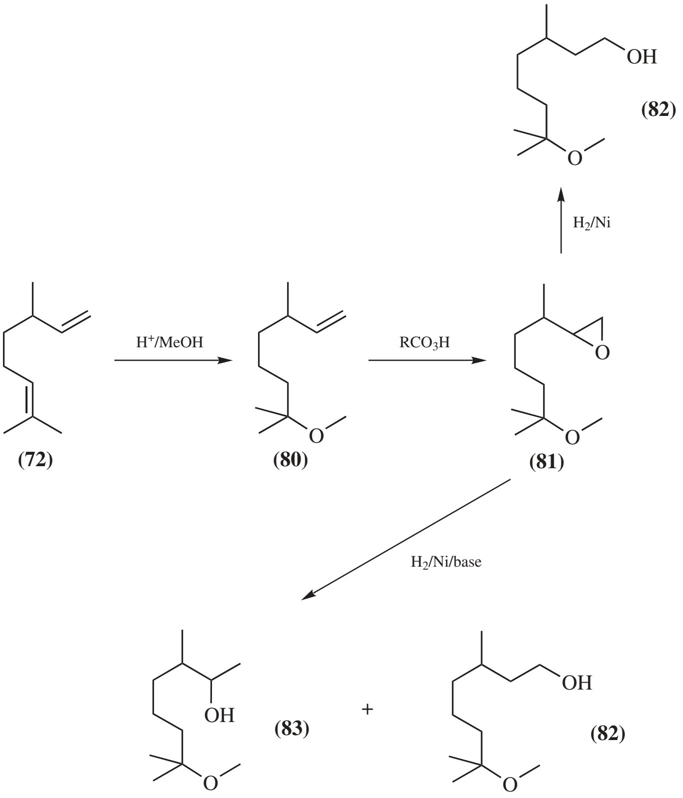


Fig. 19. Preparation of methoxycitronellol and Osyrol.

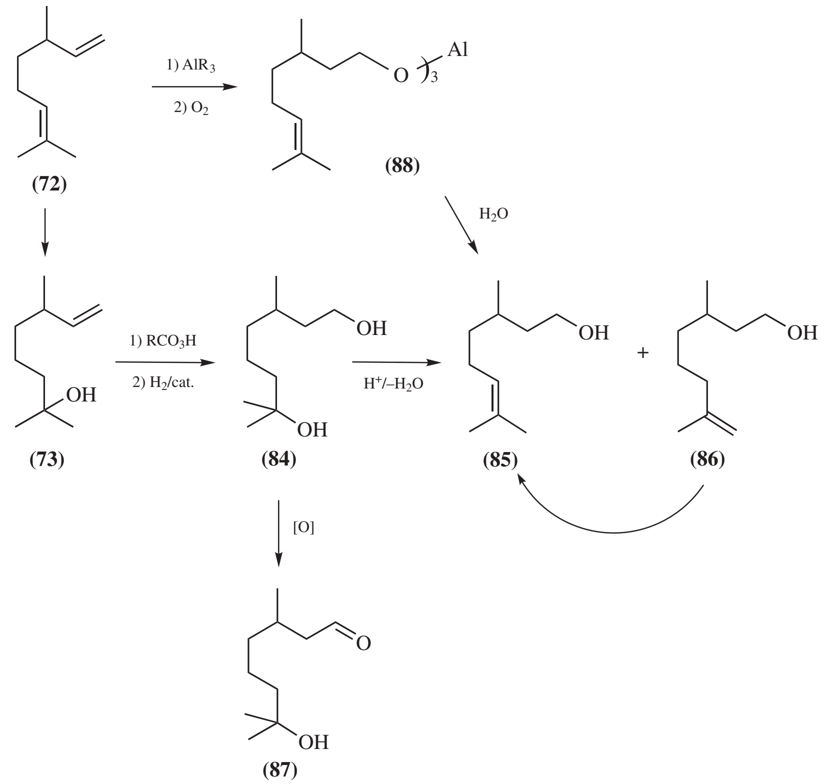


Fig. 20. Conversion of dihydromyrcenol to citronellol and hydroxycitronellal.

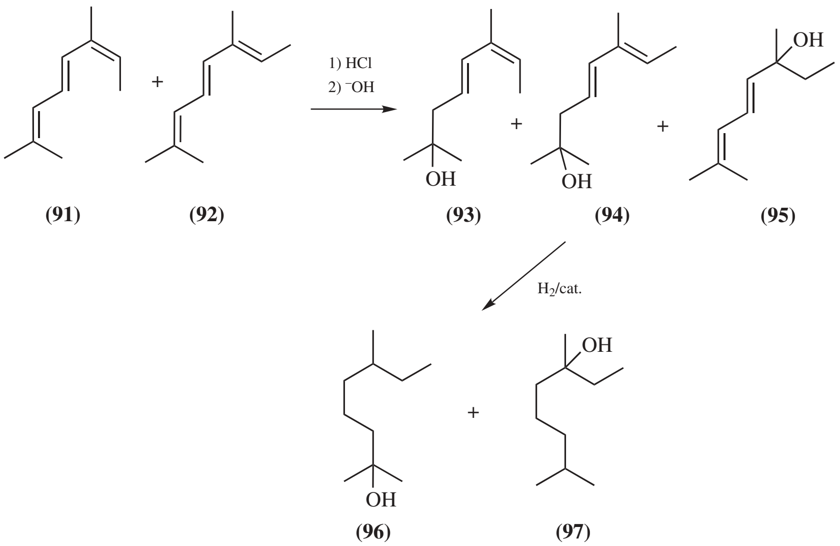
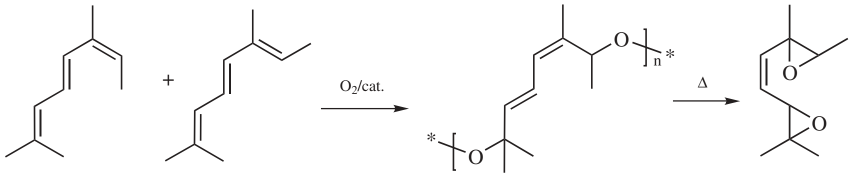
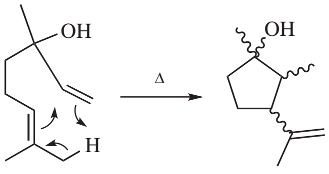


Fig. 21. Production of tetrahydromuguol from allo-ocimene.



(91) **(92)** **(98)** **(99)**

Fig. 22. Production of allo-ocimene epoxide.



(23) **(116)**

Fig. 23. Formation of plinols from linalool.

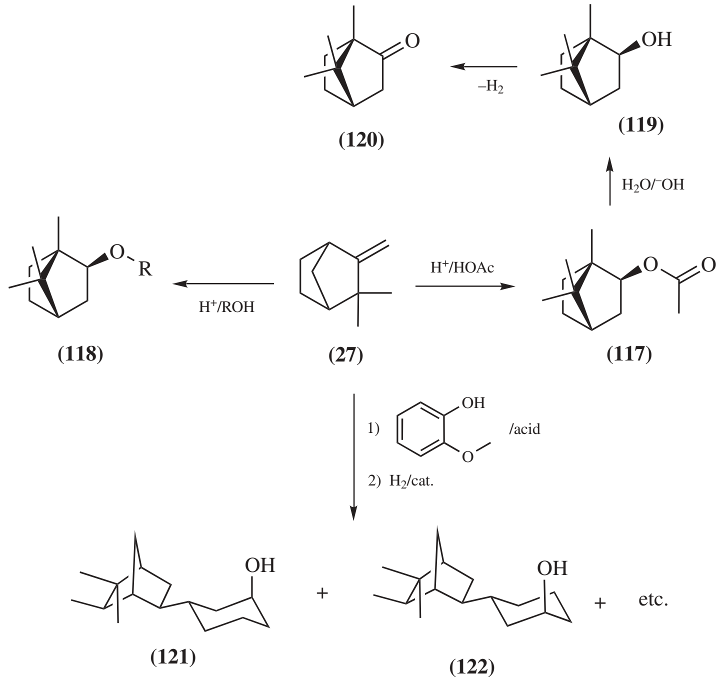


Fig. 24. Fragrance ingredients from camphene.

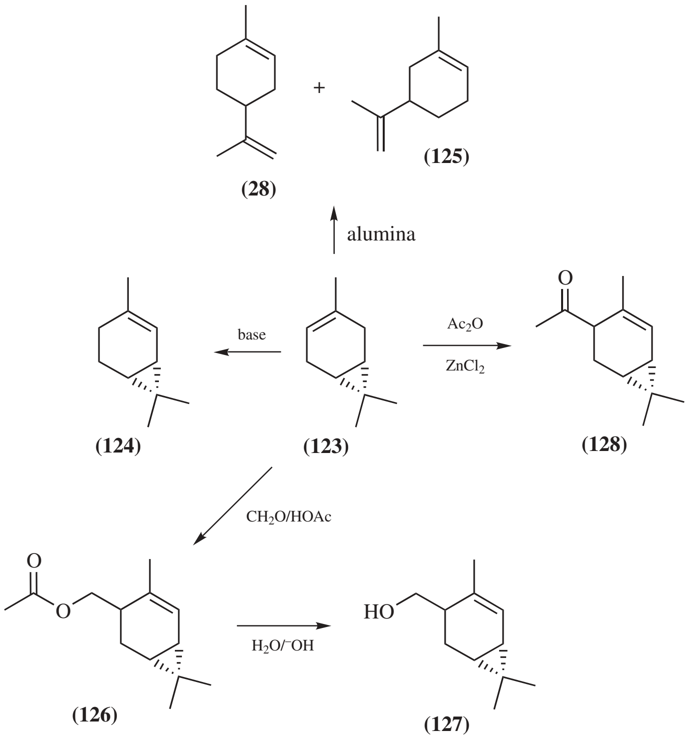


Fig. 25. Some reactions of 3-carene.

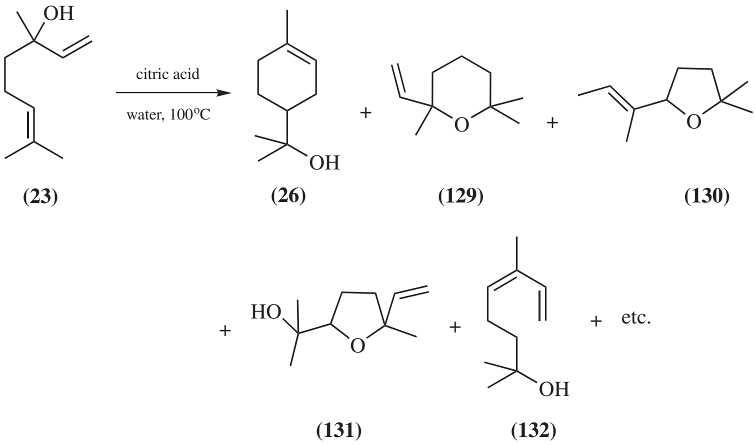


Fig. 26. Acid treatment of linalool.

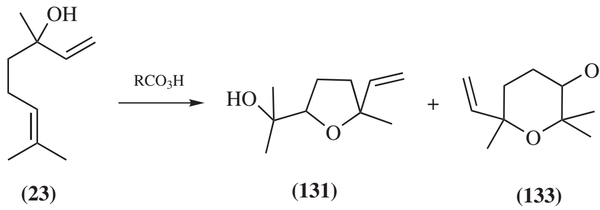


Fig. 27. Formation of linalyl oxide.

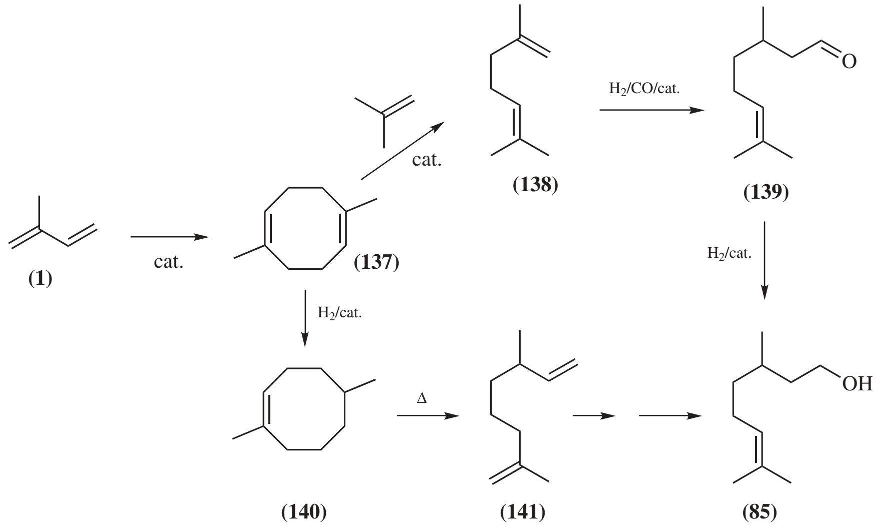


Fig. 28. Naarden/Shell routes to citronellol.

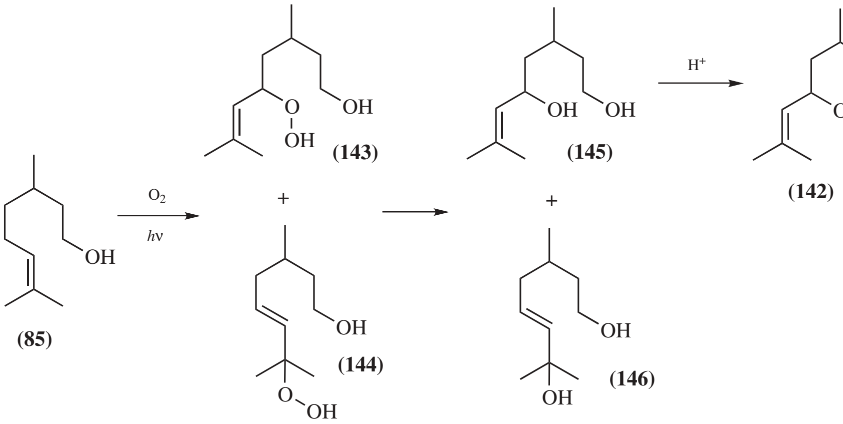
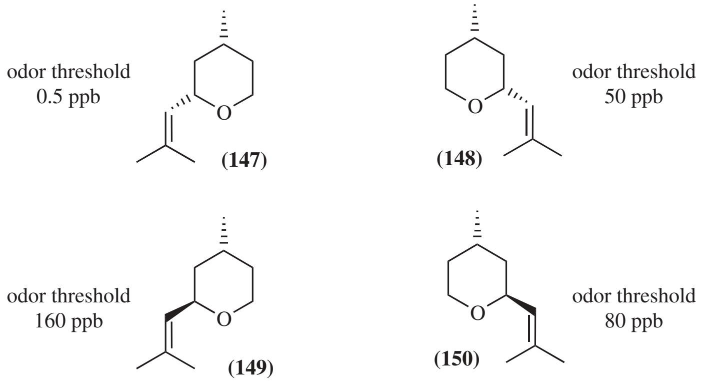


Fig. 29. Preparation of rose oxide.



odor threshold 0.5 ppb **(147)**

odor threshold 50 ppb **(148)**

odor threshold 160 ppb **(149)**

odor threshold 80 ppb **(150)**

Fig. 30. Isomers of rose oxide.

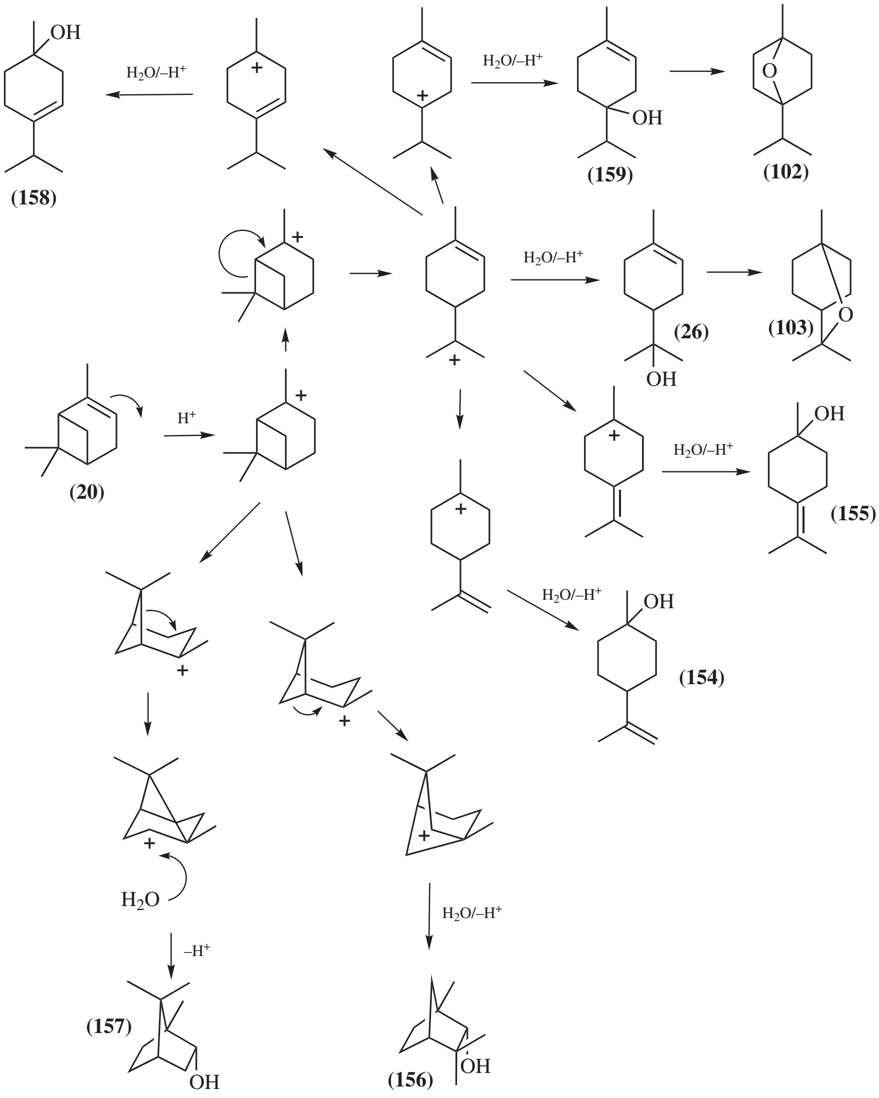
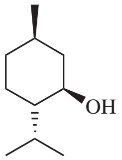
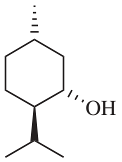


Fig. 31. Formation of pine oil components.

l-menthol
(1*R*,3*R*,4*S*)-(–)-menthol
[2216-51-5]
$[\alpha]_D$ –50.2°
taste threshold 0.4 ppm
cooling threshold 0.8 ppm
cooling effect vs *l*-menthol 100



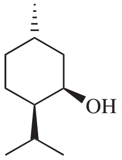
(42)



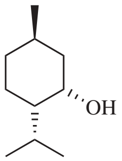
(161)

d-menthol
(1*S*,3*S*,4*R*)-(+)-menthol
[15356-60-2]
$[\alpha]_D$ 50.2°
taste threshold 0.3 ppm
cooling threshold 3.0 ppm
cooling effect vs *l*-menthol 27

l-neomenthol
(1*S*,3*R*,4*R*)-(–)-neomenthol
[20747-49-3]
$[\alpha]_D$ –20.9°
taste threshold 0.6 ppm
cooling threshold 25.0 ppm
cooling effect vs *l*-menthol 3



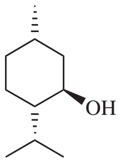
(162)



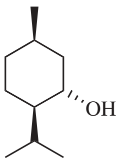
(163)

d-neomenthol
(1*R*,3*S*,4*S*)-(+)-neomenthol
[2216-52-6]
$[\alpha]_D$ 20.9°
taste threshold 0.5 ppm
cooling threshold 2.5 ppm
cooling effect vs *l*-menthol 32

l-isomenthol
(1*S*,3*R*,4*S*)-(–)-isomenthol
[20752-33-4]
$[\alpha]_D$ –25.9°
taste threshold 0.6 ppm
cooling threshold 30.0 ppm
cooling effect vs *l*-menthol 3



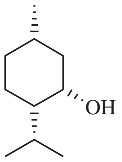
(164)



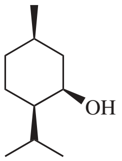
(165)

d-isomenthol
(1*R*,3*S*,4*R*)-(+)-isomenthol
[23283-97-8]
$[\alpha]_D$ 25.9°
taste threshold 0.7 ppm
cooling threshold 7.0 ppm
cooling effect vs *l*-menthol 11

l-neoisomenthol
(1*S*,3*S*,4*S*)-(–)-neoisomenthol
[64282-88-8]
$[\alpha]_D$ –2°
taste threshold 1.0 ppm
cooling threshold 6.0 ppm
cooling effect vs *l*-menthol 13



(166)



(167)

d-neoisomenthol
(1*R*,3*R*,4*R*)-(+)-neoisomenthol
[20752-34-5]
$[\alpha]_D$ 2°
taste threshold 0.2 ppm
cooling threshold 28.0 ppm
cooling effect vs *l*-menthol 3

Fig. 32. Isomers of menthol.

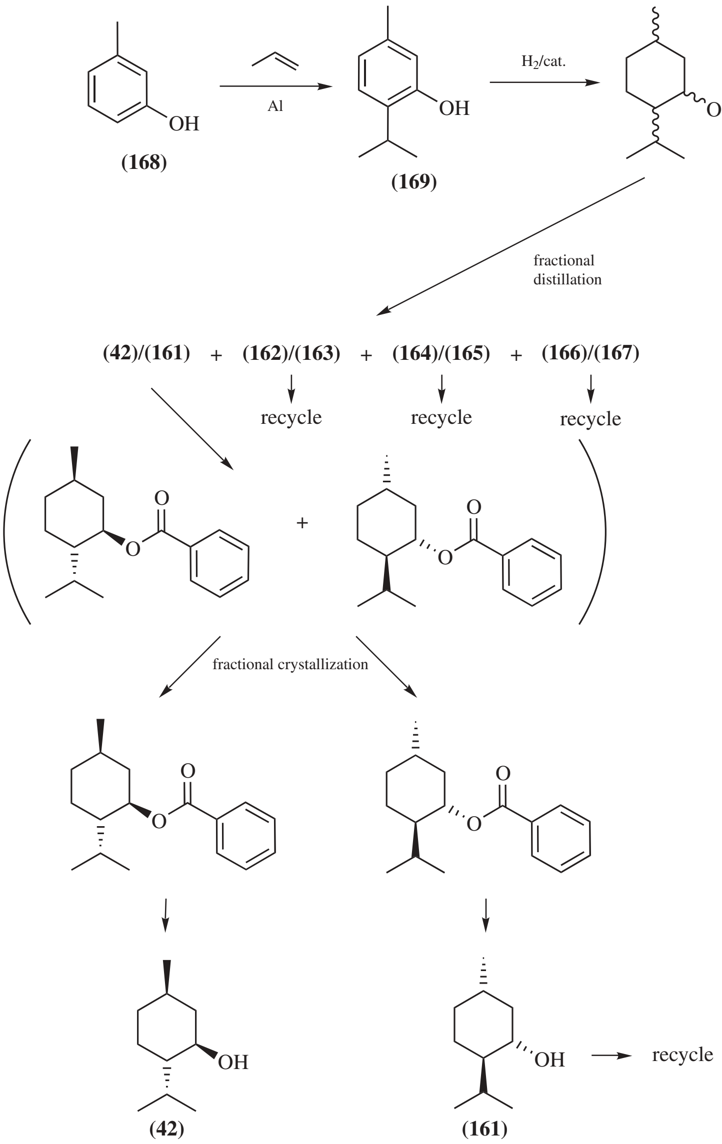


Fig. 33. Symrise process for *l*-menthol.

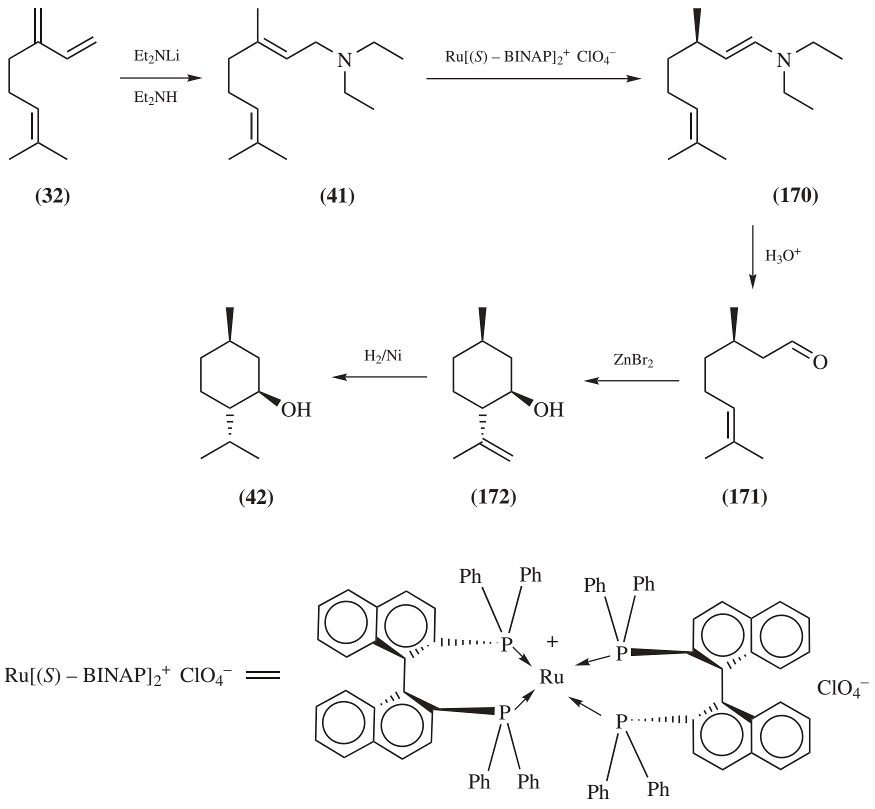


Fig. 34. The Takasago process for *l*-menthol.

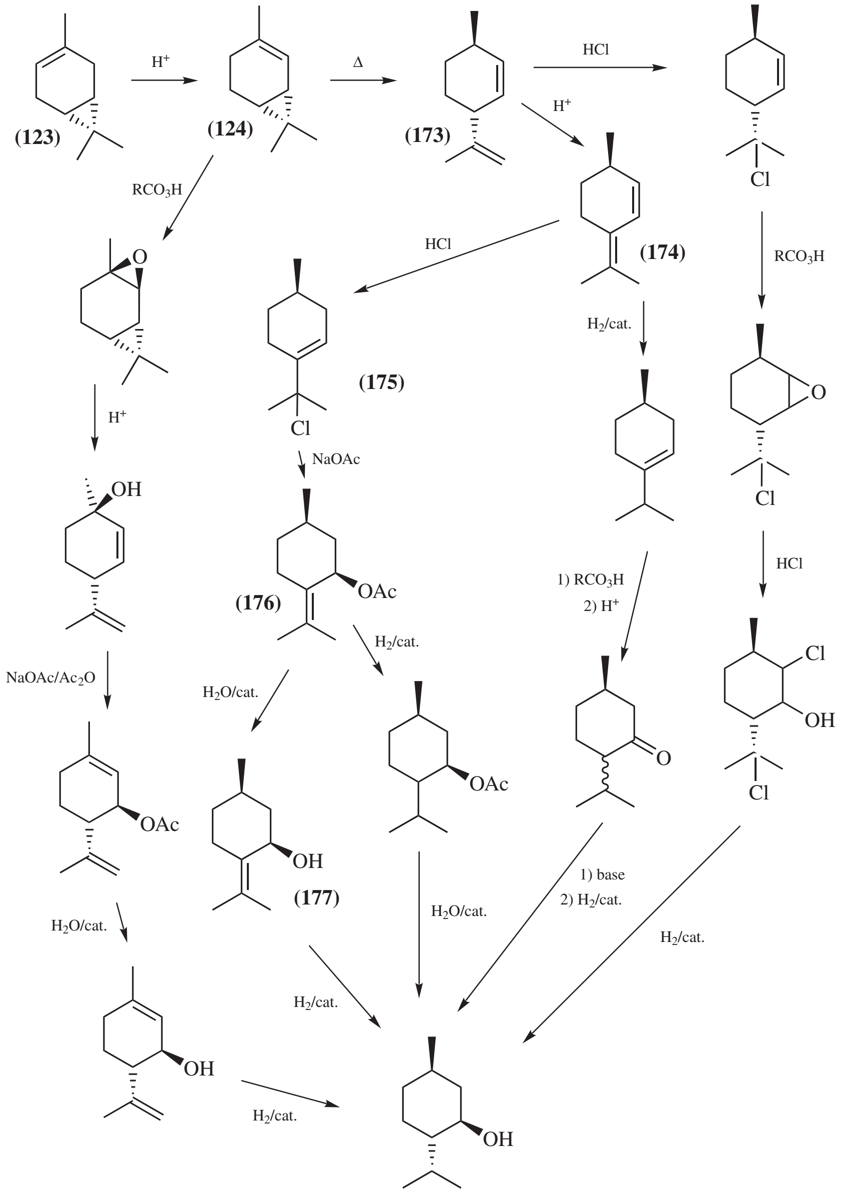


Fig. 35. *l*-Menthol from 3-carene.

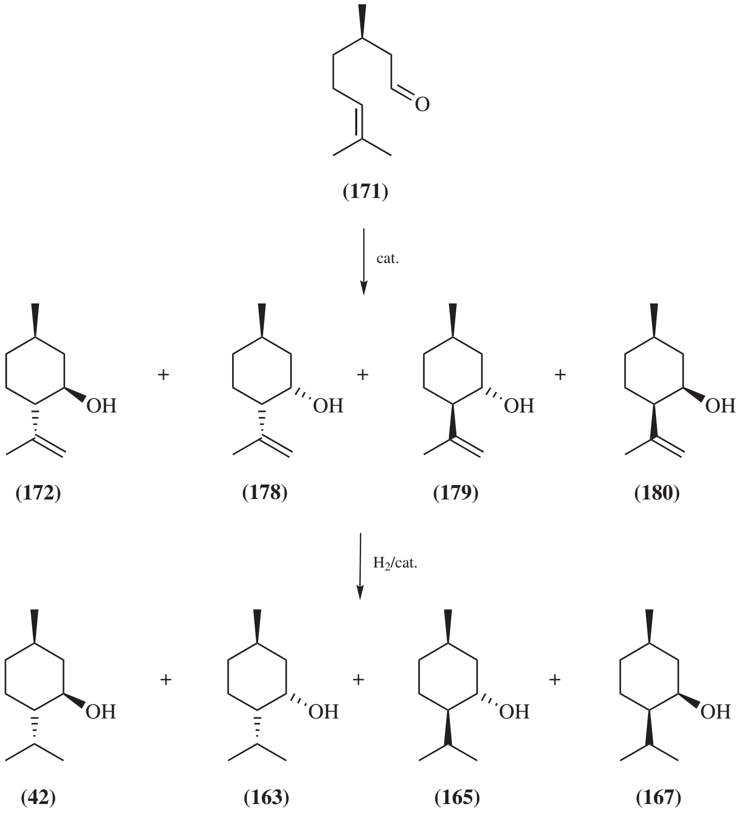


Fig. 36. Acid-catalyzed cyclization of *d*-citronellal and subsequent hydrogenation.

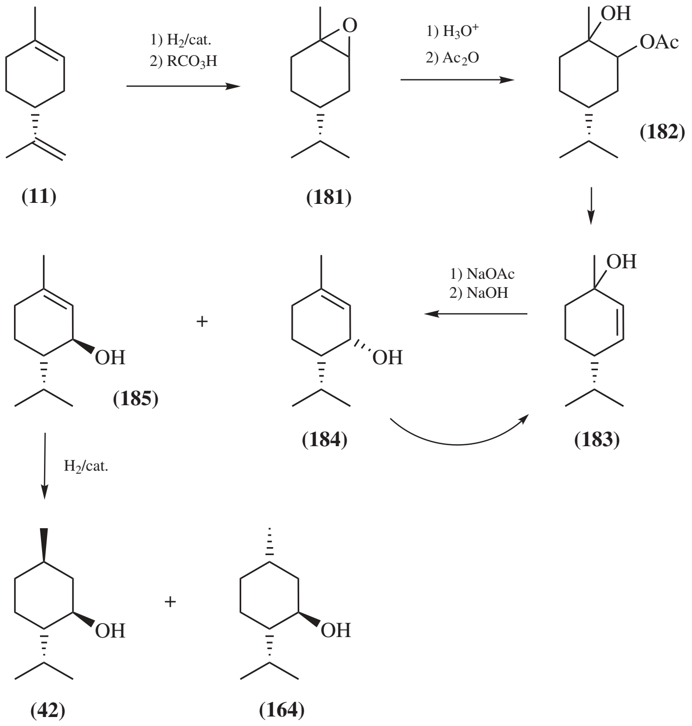


Fig. 37. (−)-Menthol from (+)-limonene.

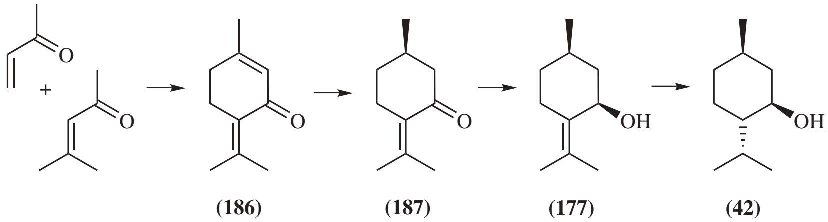


Fig. 38. *l*-Menthol from mesityl oxide.

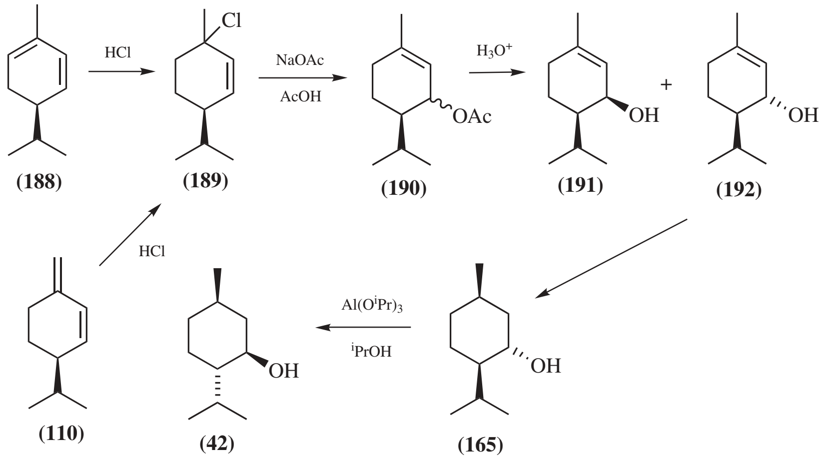


Fig. 39. *l*-Menthol from phellandrenes.

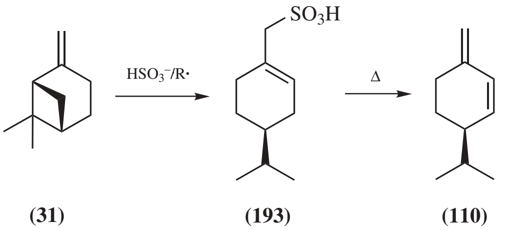


Fig. 40. Conversion of β-pinene to β-phellandrene.

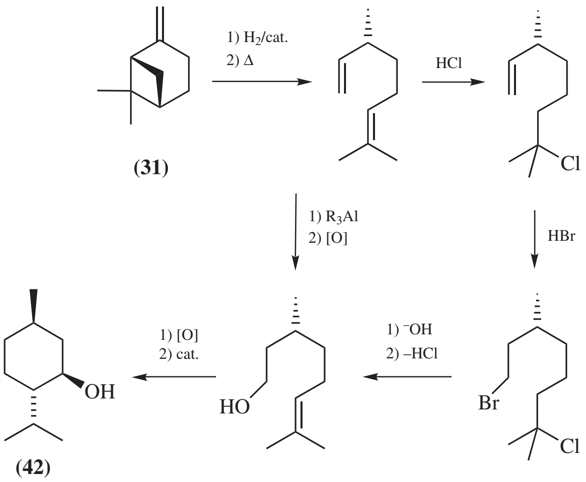
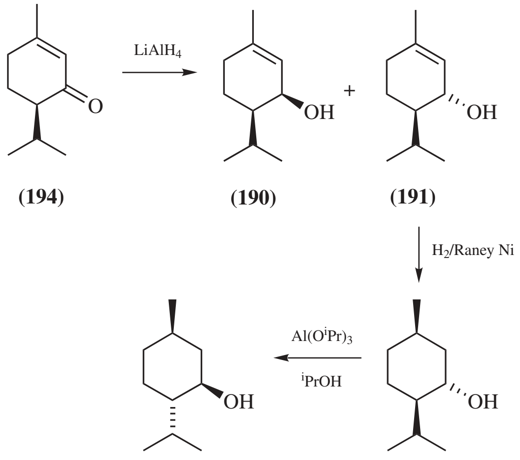


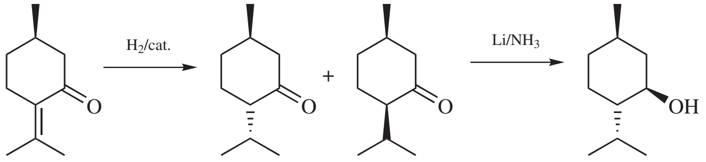
Fig. 41. *l*-Menthol from β-pinene.



(194) **(190)** **(191)**

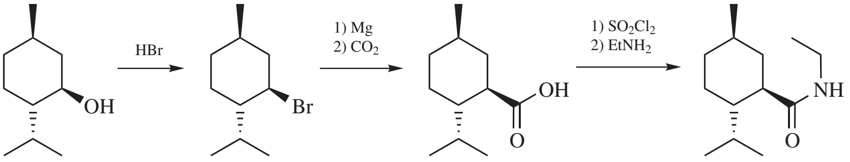
(42) **(165)**

Fig. 42. *l*-Menthol from *l*-piperitone.



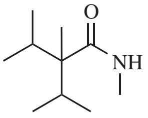
(187) **(195)** **(196)** **(42)**

Fig. 43. *l*-Menthol from *d*-pulegone.



(42) **(198)** **(199)** **(197)**

Fig. 44. Synthesis of WS-3.



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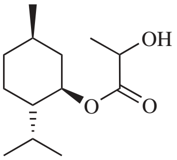
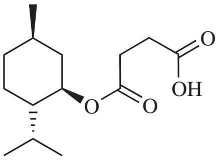
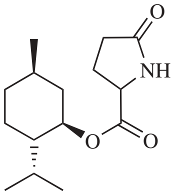


(201)



(202)



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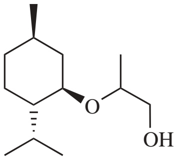
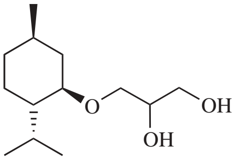
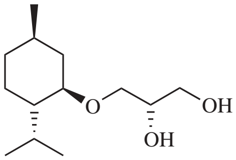


(204)



(205)



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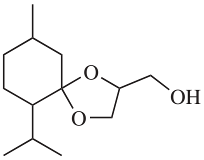

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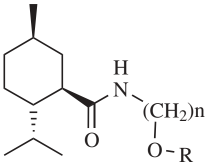

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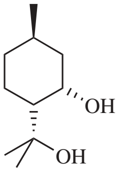
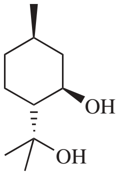


(209)



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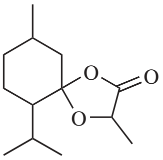

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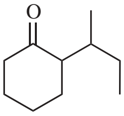
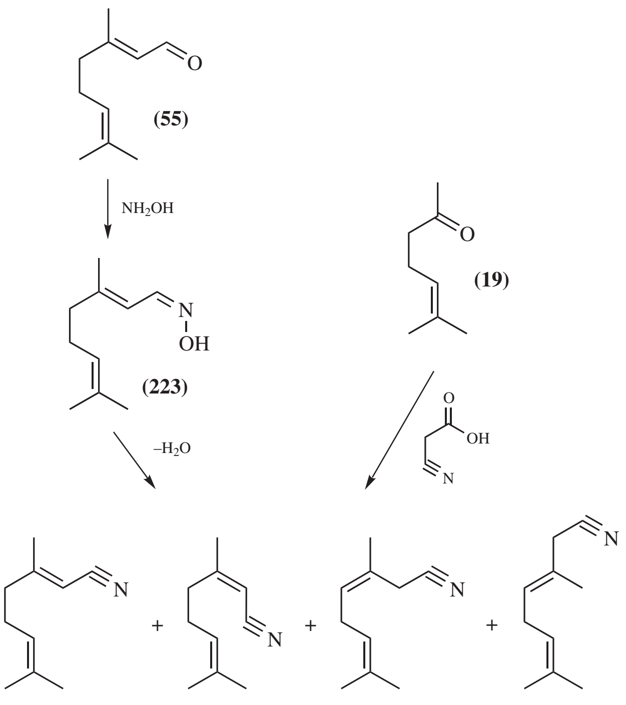


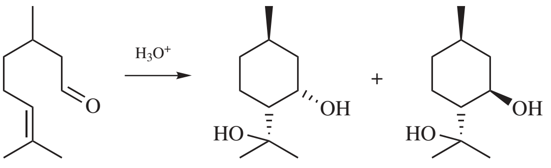
(212)

Fig. 45. Physiological cooling agents.



(219) (220) (221) (222)

Fig. 46. Preparation of geranyl nitrile.



(135) (209) (210)

Fig. 47. Cyclihydration of citronellal.

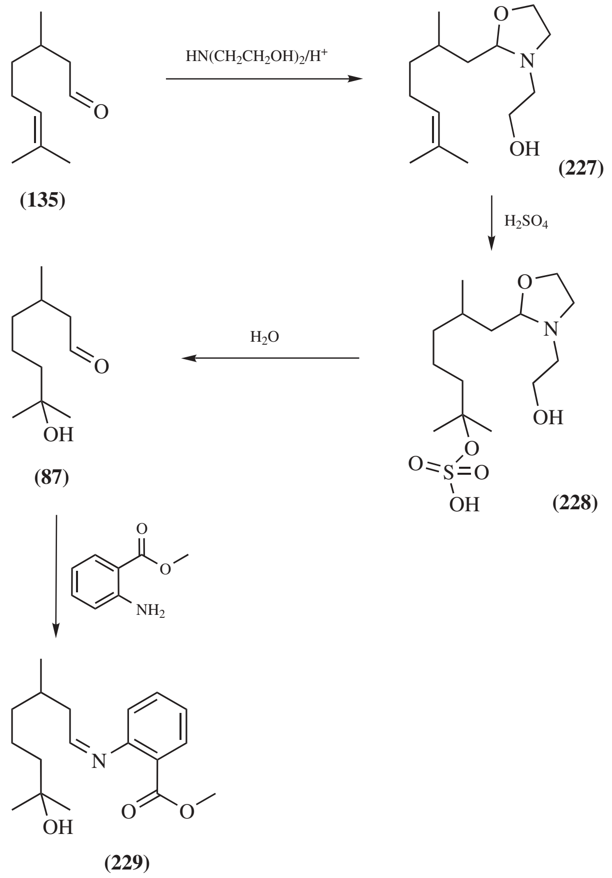


Fig. 48. Production of hydroxycitronellal from citronellal.

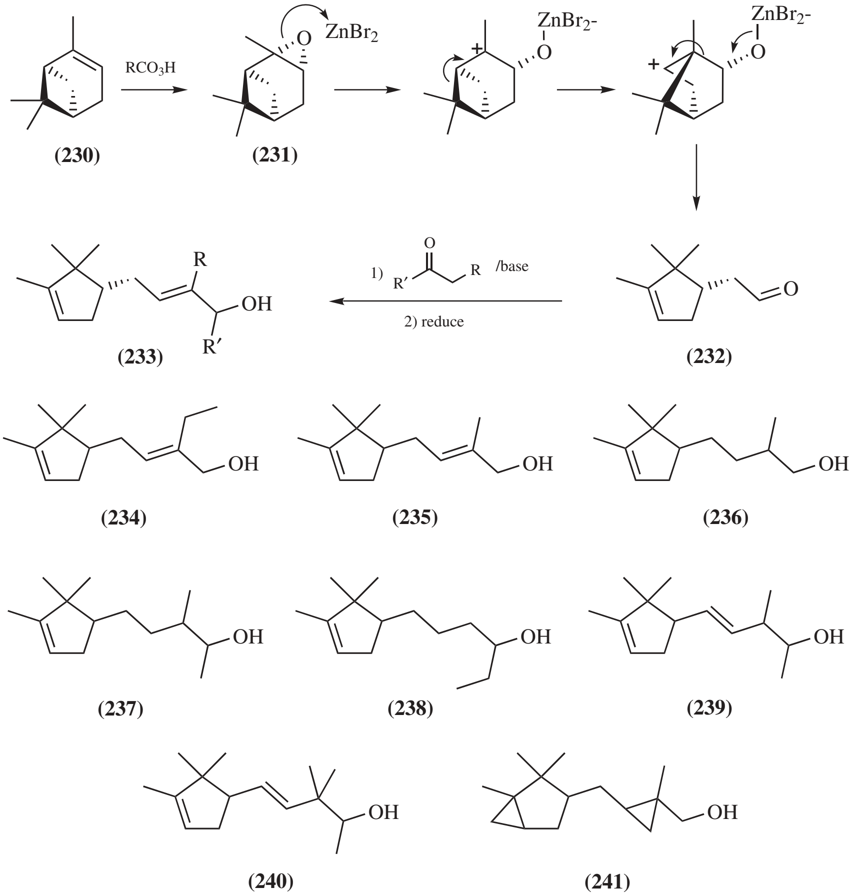


Fig. 49. Sandalwood materials made from campholenic aldehyde.

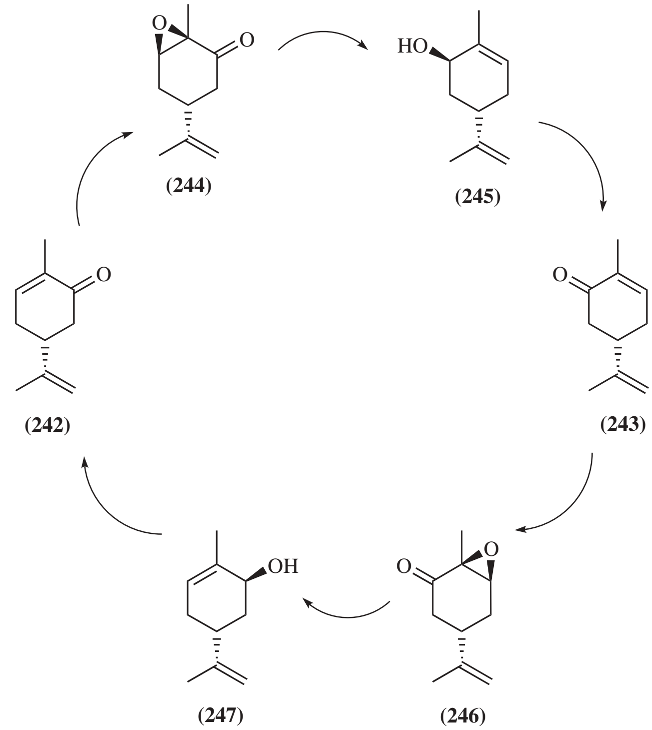


Fig. 50. Interconversion of carvone enantiomers.

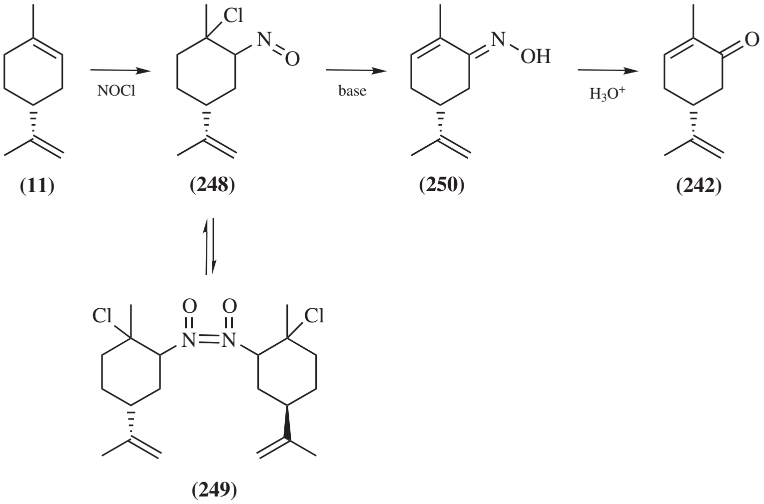


Fig. 51. Preparation of *l*-carvone from *d*-limonene using nitrosyl chloride.

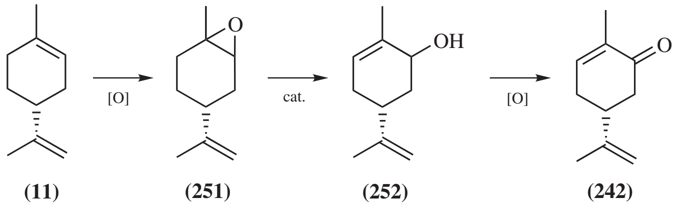


Fig. 52. Preparation of *l*-carvone from *d*-limonene via limonene oxide.

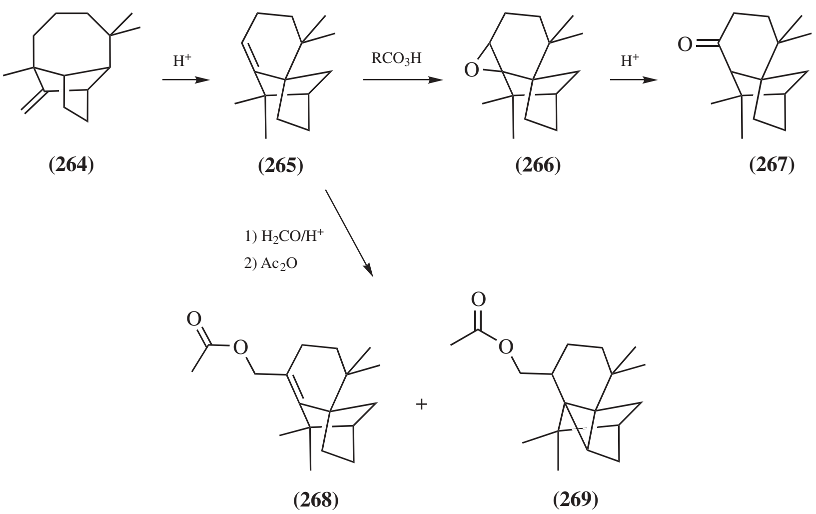


Fig. 53. Fragrance ingredients from longifolene.

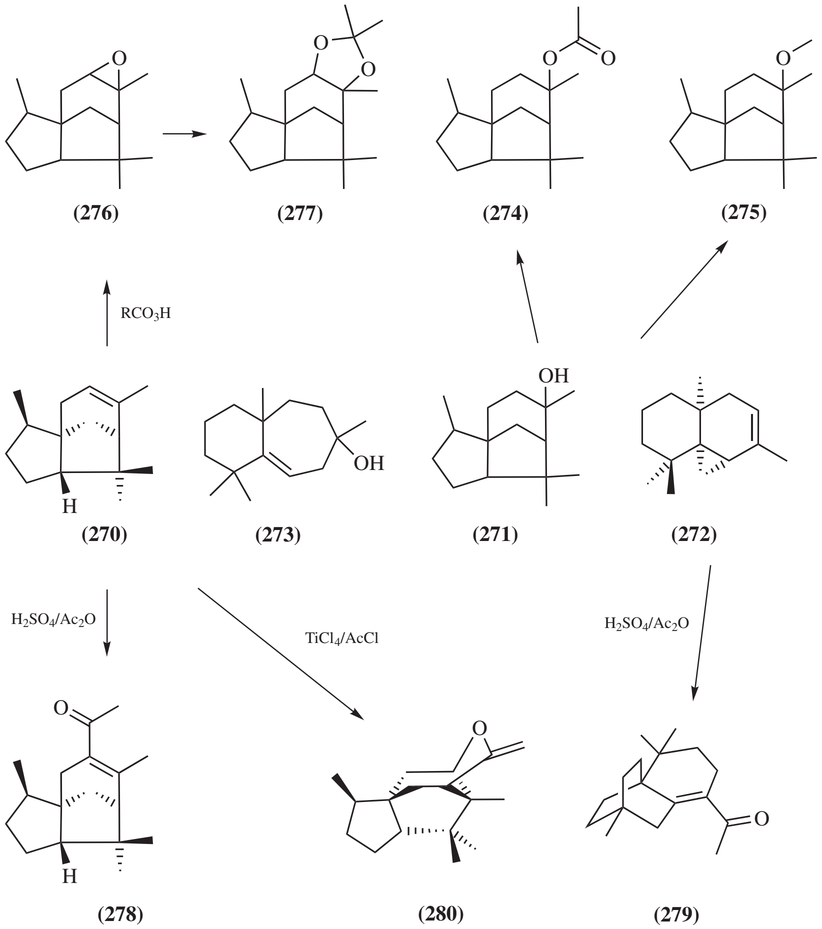


Fig. 54. Fragrance ingredients from Cedarwood oil.

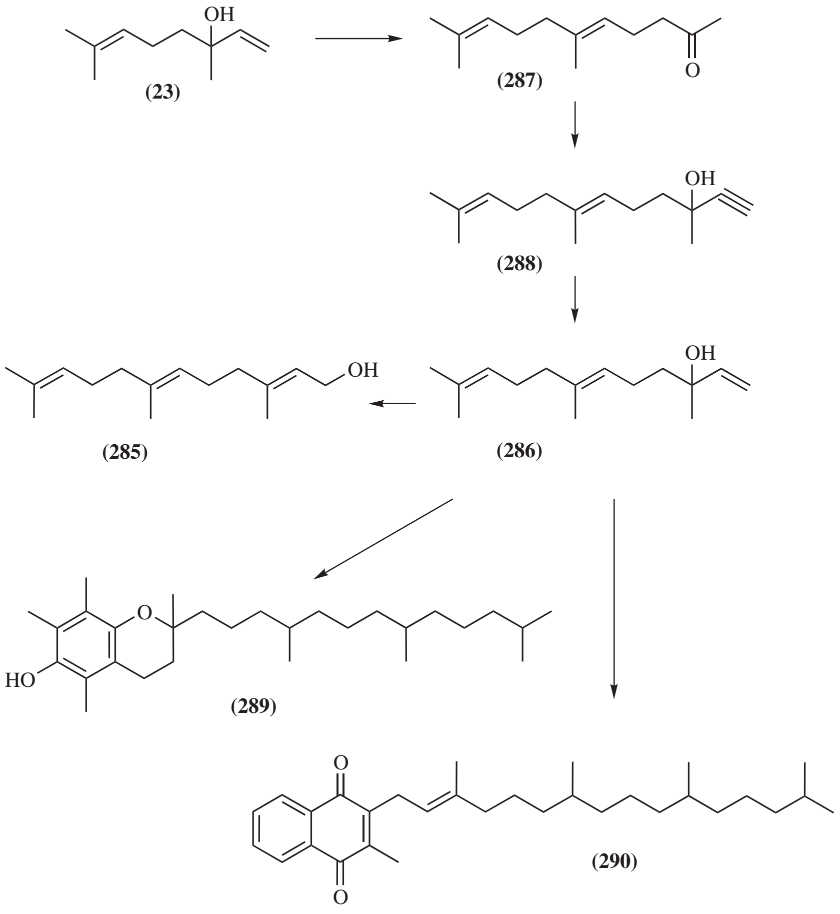


Fig. 55. Synthetic routes around nerolidol.

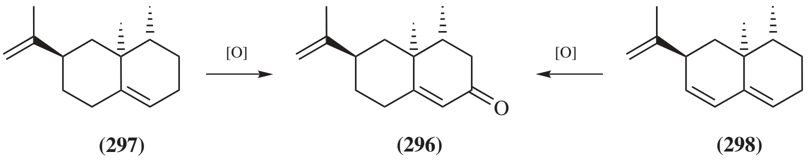
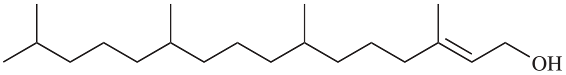
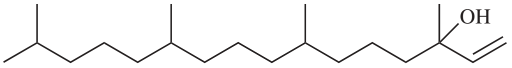


Fig. 56. Synthesis of nootkatone.



(301)



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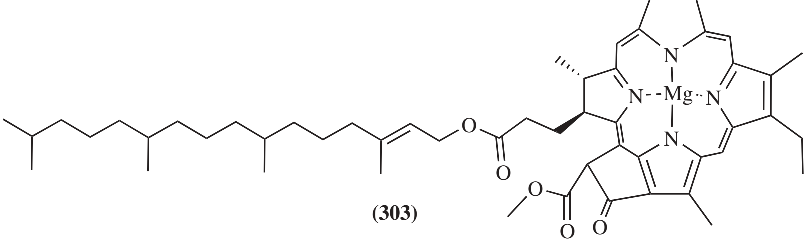

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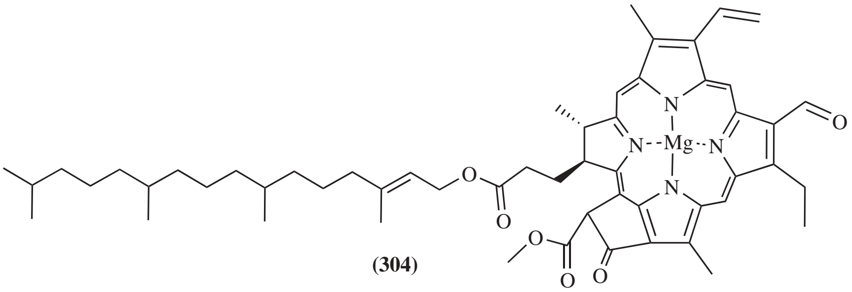

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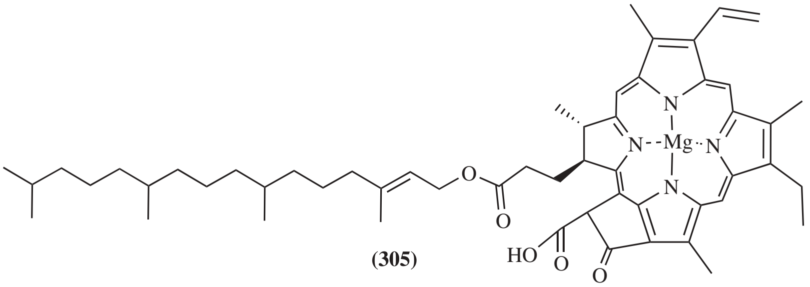

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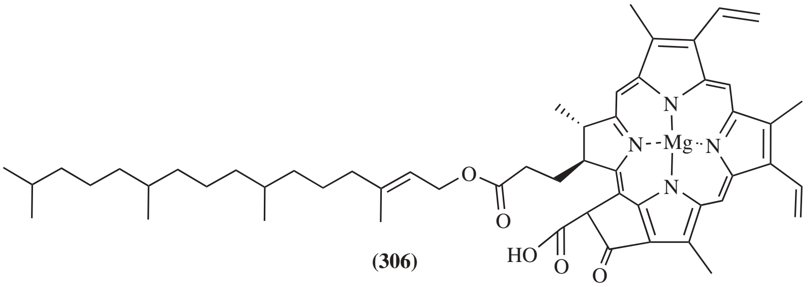
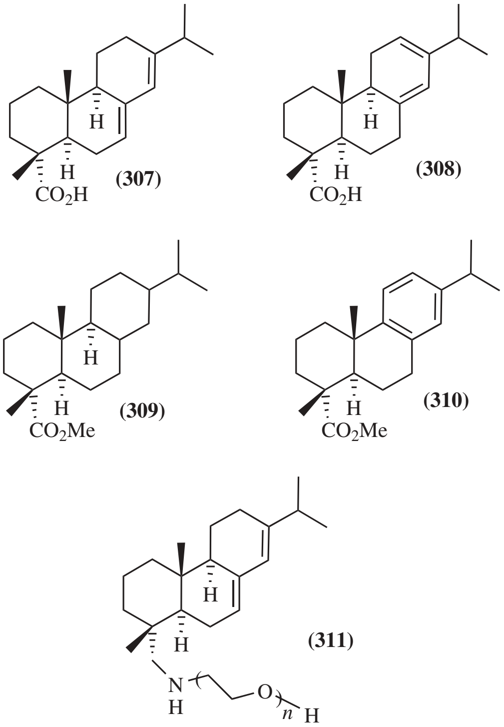


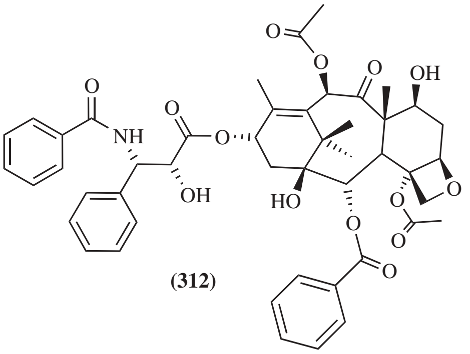
(306)

Fig. 57. Phytols and chlorophylls.



(307) **(308)** **(309)** **(310)** **(311)**

Fig. 58. Rosin acid derivatives.



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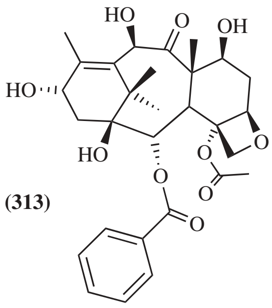

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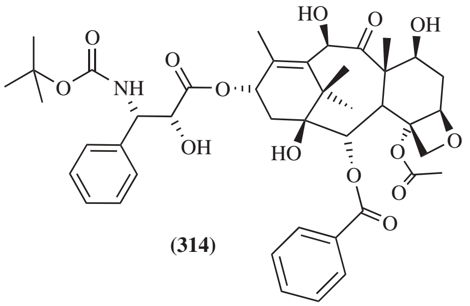


(314)

Fig. 59. Taxane diterpenoids.

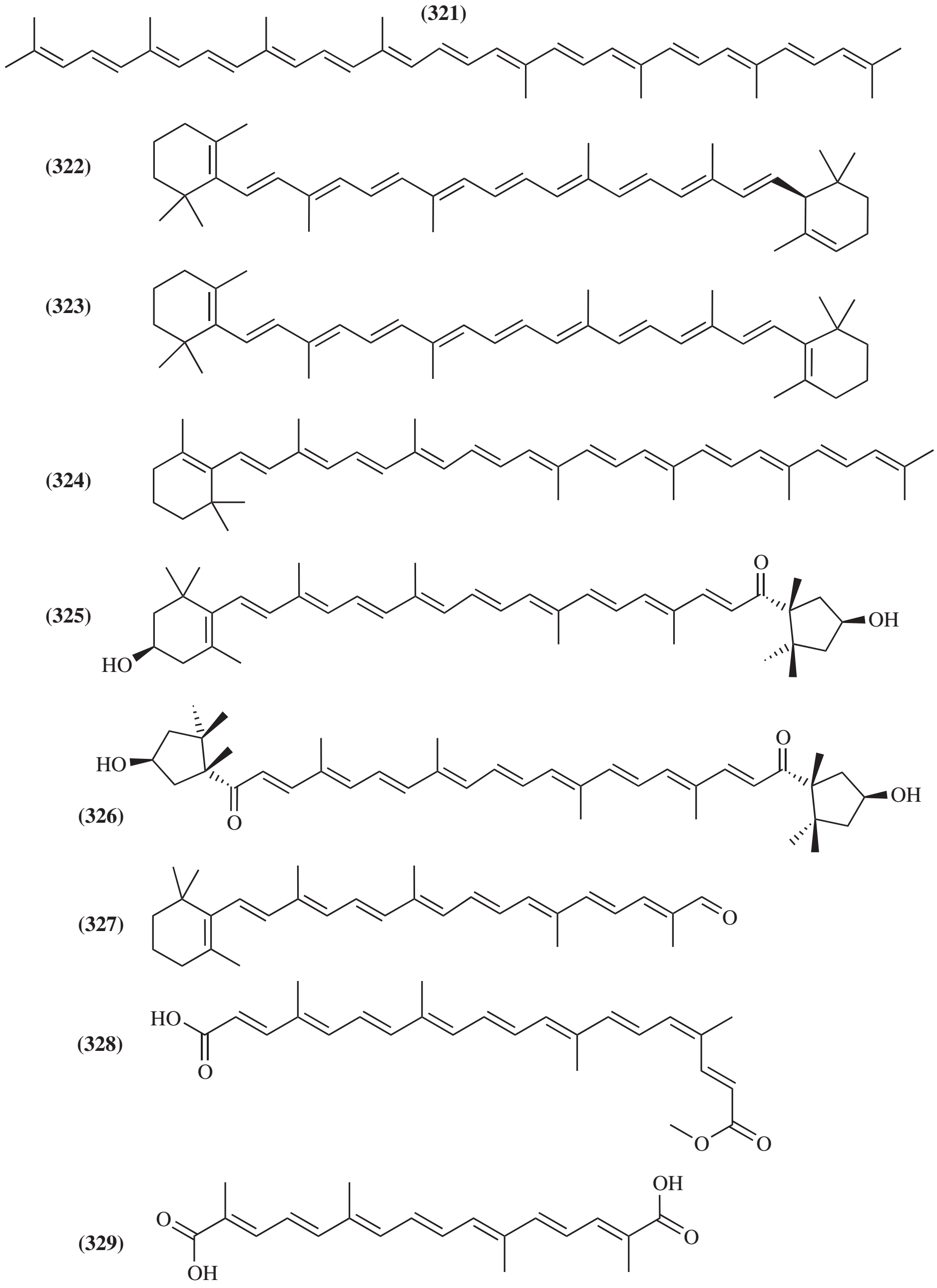


Fig. 60. Carotenoids.

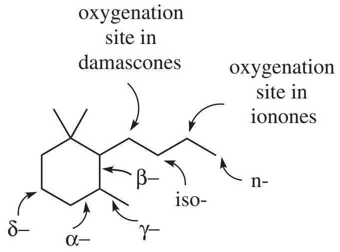


Fig. 61. Nomenclature in ionones and damascones.

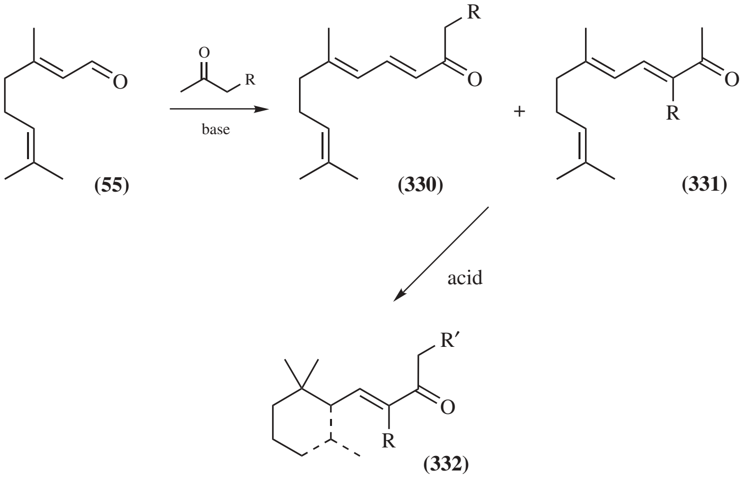


Fig. 62. Preparation of ionones.

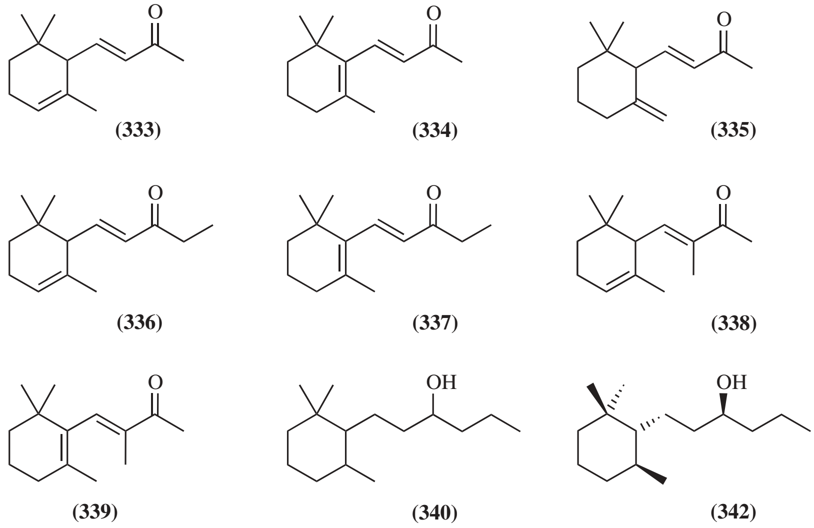


Fig. 63. Ionones and related materials.

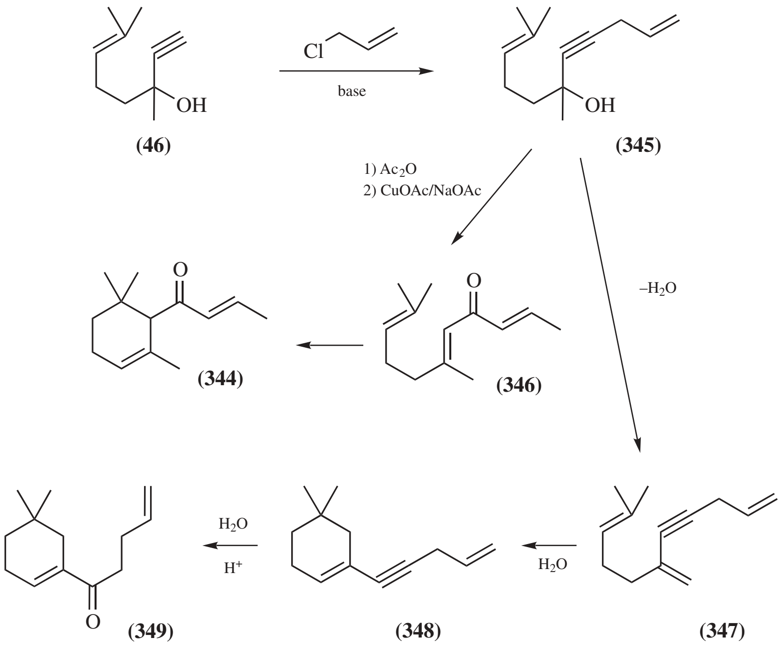
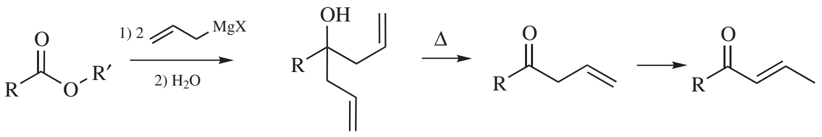


Fig. 64. The original damascones production route.



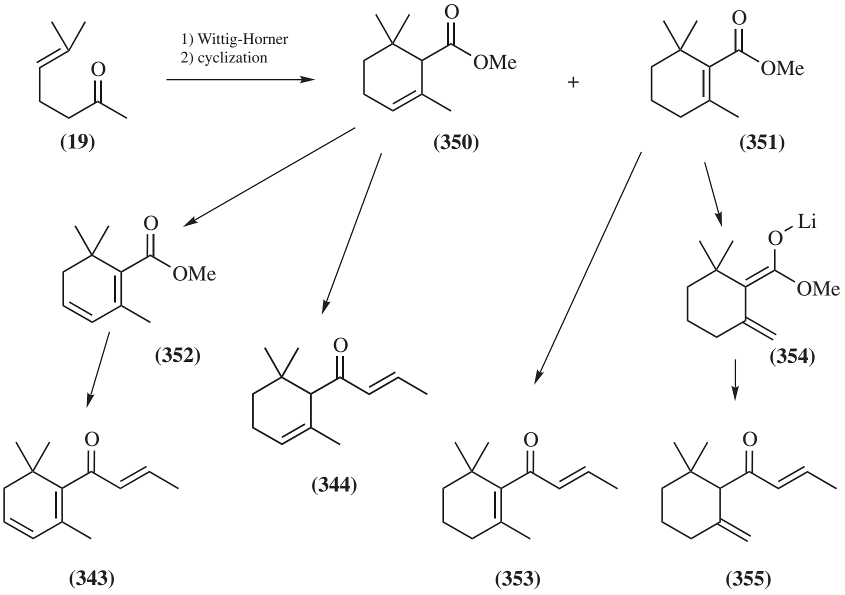


Fig. 65. Damascone production route.

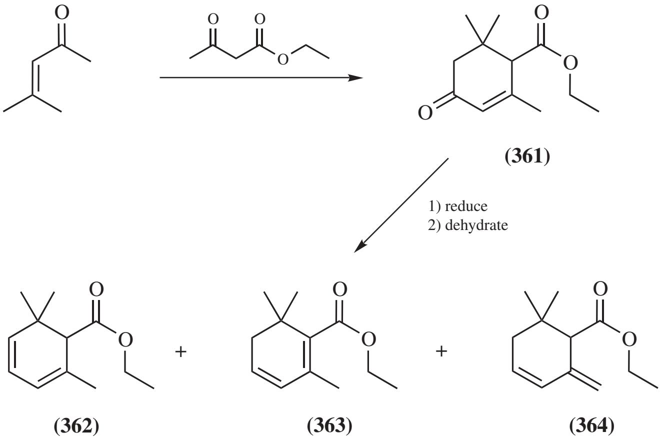


Fig. 66. Preparation of ethyl safranate.

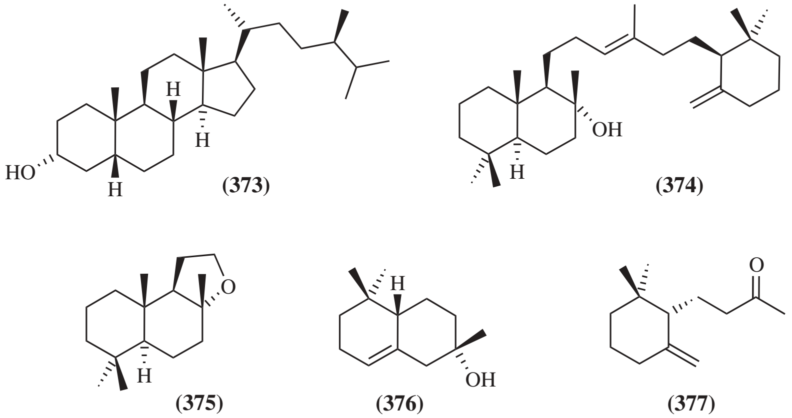


Fig. 67. Components of ambergris.

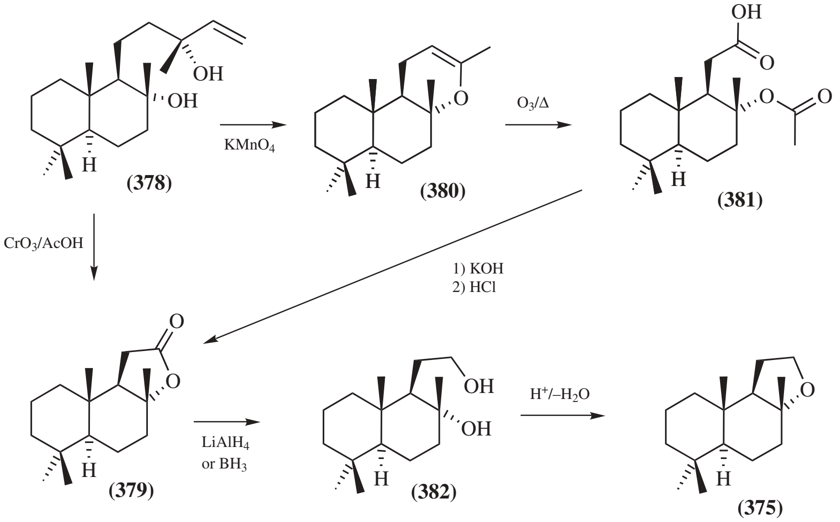


Fig. 68. Production of 3*a*,6,6,9*a*-tetramethyldodecahydronaphtho[2,1-*b*]furan from sclareol.

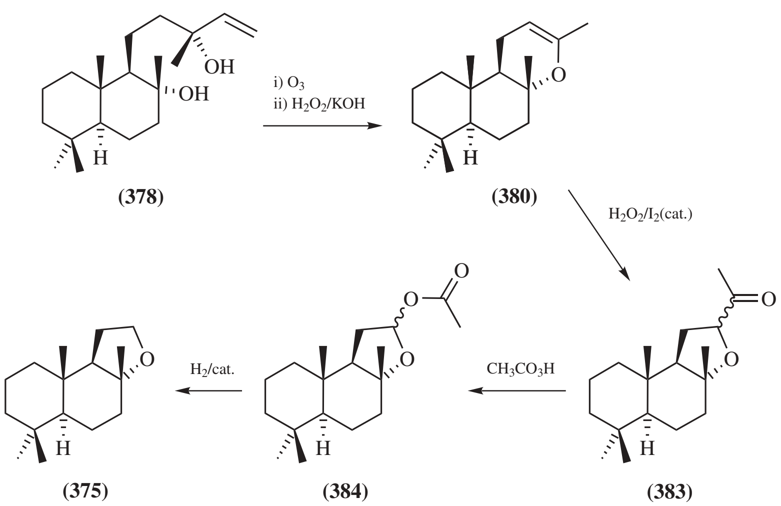


Fig. 69. Alternative route to 3*a*,6,6,9*a*-tetramethyldodecahydronaphtho[2,1-*b*]furan from sclareol.

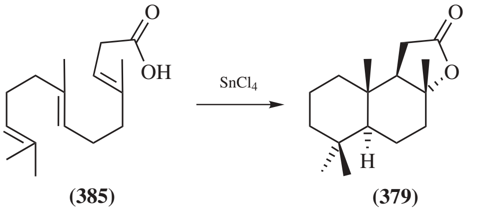


Fig. 70. Acid catalyzed biomimetic cyclization of homofarnesic acid.

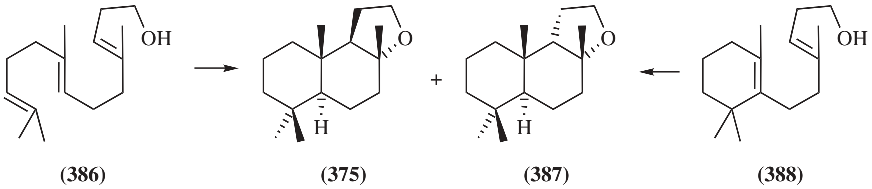
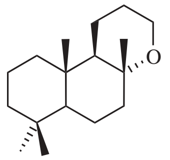


Fig. 71. Acid-catalyzed biomimetic cyclization of homofarnesol.



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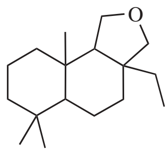

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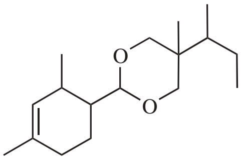

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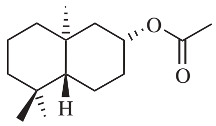

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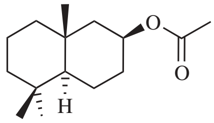

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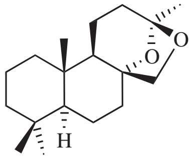

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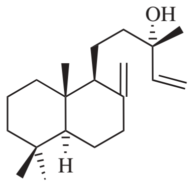

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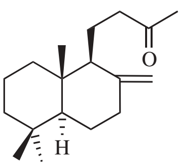

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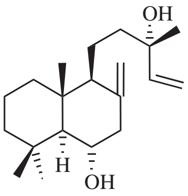
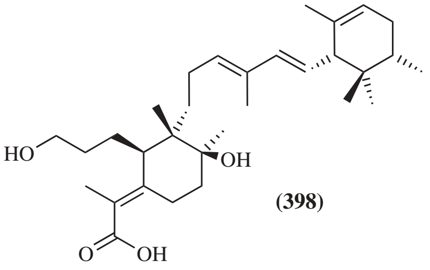


(397)

Fig. 72. Ambergris analogues.



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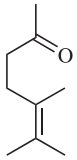

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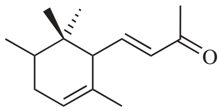

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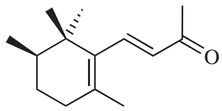

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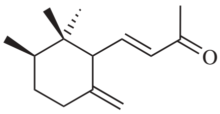

(401)

Fig. 73. Iripallidal and the irones.