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TECHNOLOGY OF MONOTERPENOID FRAGRANCES

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Table of Contents

1. Introduction

Fragrances of the monoterpenoid group include some of the most important scents and flavours produced by the industry. Many of the chemical compounds in this group are among the largest amounts produced, and numbering almost 3000 in total. The volume of monoterpenoid production stems primarily from demand on the flavour market, and are employed in the cosmetics, food, domestic detergents and pharmaceutical industries. The high demand necessitates expansion of the production capacity of existing facilities or the development of ever more advanced technologies. As a result, the branch of industry involved in monoterpenoid production is experiencing highly dynamic growth. One example is that of l-menthol, which is produced in large volumes, where the predicted growth in its demand drives the actions of all its producers. The present situation on the market is also the result of changes in legislation, which continuously adapts to maintain pace with technical progress, and applies both to the safety of fragrance use, including substances of the monoterpenoid group, and changes in environmental protection standards. So--called green or environmentally friendly technologies are enjoying great popularity.

This handbook is devoted to the production technologies for fragrances from the monoterpenoid group, for students of chemistry and related fields who desire more in-depth knowledge of the production technologies used in relation to the scents and flavours belonging to this group of chemical compounds. To date, no literature exists that shows this branch of the chemical industry in this manner. There are several good books on the subject of monoterpenoid flavours available in English; however, due to the number of chemical compounds described and a focus on how the substances are generated in nature and what characteristic reactions they may undergo, even these do not offer exhaustive coverage of specific technologies, generally only briefly touching on the subject.

This handbook describes only the most interesting examples of production technologies used for selected monoterpenoid compounds. The focus is on the production technologies for fragrances produced in large quantities (for this industry), such as citral and menthol. However, some of the production methods for monoterpenoid fragrances synthesised in smaller quantities than these two are presented as well (e.g. citronellol, linalool, and geraniol).

For all the technologies utilised to obtain the scents and flavours in question, and described in this handbook, other variants of the methods (depending on the producer) employed in their production are also presented.

Additionally, as an interesting aside, the GC-FID analysis chromatograms for the described chemical compounds are presented, from Perfumer's Apprentice. The monoterpenoid fragrances were analysed using a Bruker 430-GC gas chromatograph equipped with a FID detector and a capillary column, VF-1ms (15 m × 0.25 mm × 0.25 μm).

2. A brief history of monoterpenoid compound production

The monoterpenoid fragrance industry originated in the second half of the 19th century. Two periods can be distinguished: the first lasting until the 1950s (Fig. 1), and the second continuing to the present day (Fig. 2).

In the first period, as a result of the rapid progress of organic chemistry, the structures of compounds like d-limonene were determined, substances were isolated from natural resources by synthesis in laboratory conditions (citronellal, ionones), and the first industrial-scale plants were commissioned (linalool). This period is often considered to be the time when substances of synthetic origin first became very popular. They found uses not only in perfume products, but also in the food industry. This was appreciated by the scientific community and resulted in the awarding of a Nobel Prize to Otto Wallach, for example. He received it in 1910, partly for determining the structures of the multiple $C_{10}H_{16}$ terpene compounds (monoterpenoids) present in many essential oils. Based on these tests, the "isoprene principle" was formulated. The results of his assays and characteristic reactions were published in 1909 in the "Terpene und Campher" book (600 pages). Another Nobel Prize winner was Sir Robert Robinson, in 1947. His studies contributed to the narrowing down of the principle developed by Wallach [1].

The post-war period, on the other hand, was one of rapid growth in the fragrance production industry, including monoterpenoid compounds. All this was thanks to the development of analytical technologies and methods, enabling the structures of the newly obtained fragrances to be confirmed. Novel technologies for obtaining monoterpenoid fragrances were introduced, such as linalool in 1953. Takasago was the first company in the world to achieve synthetic l-menthol production, in 1955, based on an original technology developed two years before [2]. At the turn of 1973 and 1974, Haarmann & Reimer, then owned by Bayer, became the second producer of this compound in the world [3]. In the 1980s, Takasago developed a technology that is still utilised to produce l-menthol using myrcene as the initial substrate, and then in 2001 a researcher employed at Takasago, Professor Ryoji Noyori (one of the creators of this flavour's production method), received a Nobel Prize in chemistry for studies into chiral hydrogenation processes. It must be noted that processes utilising chiral systems are one of the company's main focus points [2].

The monoterpenoid compound production industry is one of the most dynamically growing branches of the chemical industry. Extensive funding goes

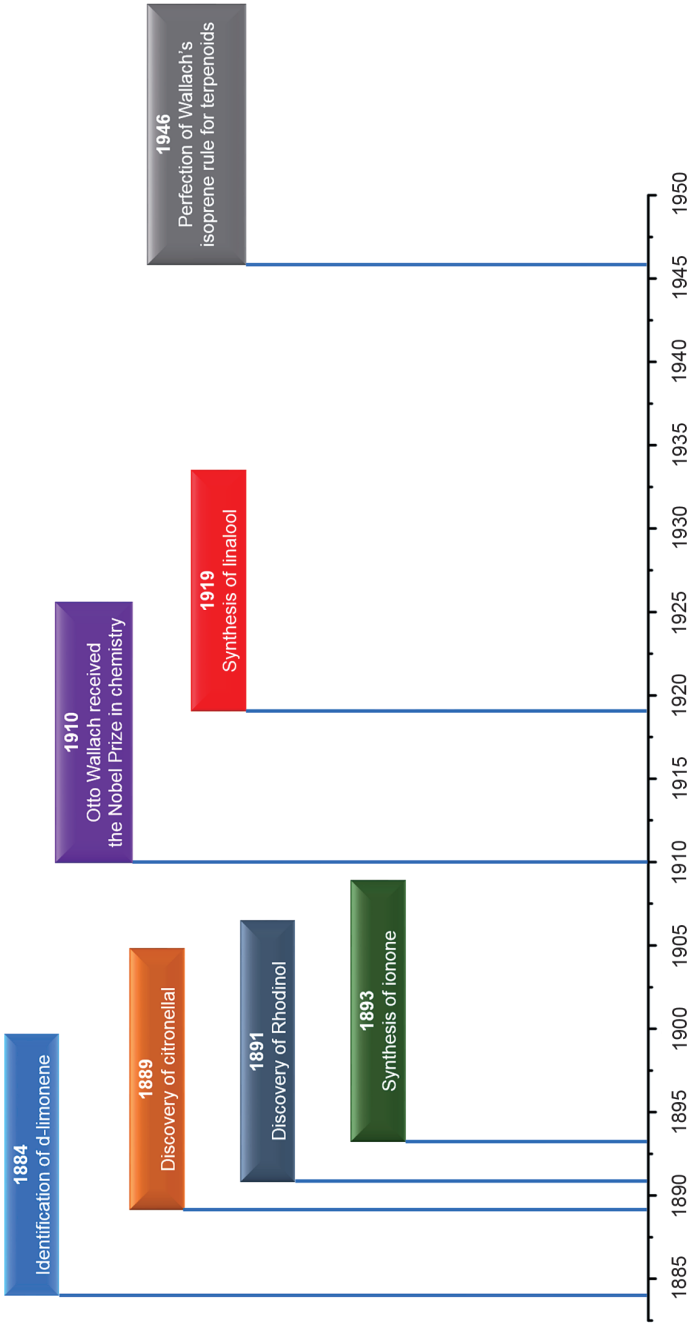

Fig. 1. Major dates in the history of monoterpenoid fragrances – period I*

* Figures and tables in this monograph without the sources mentioned were prepared by author.

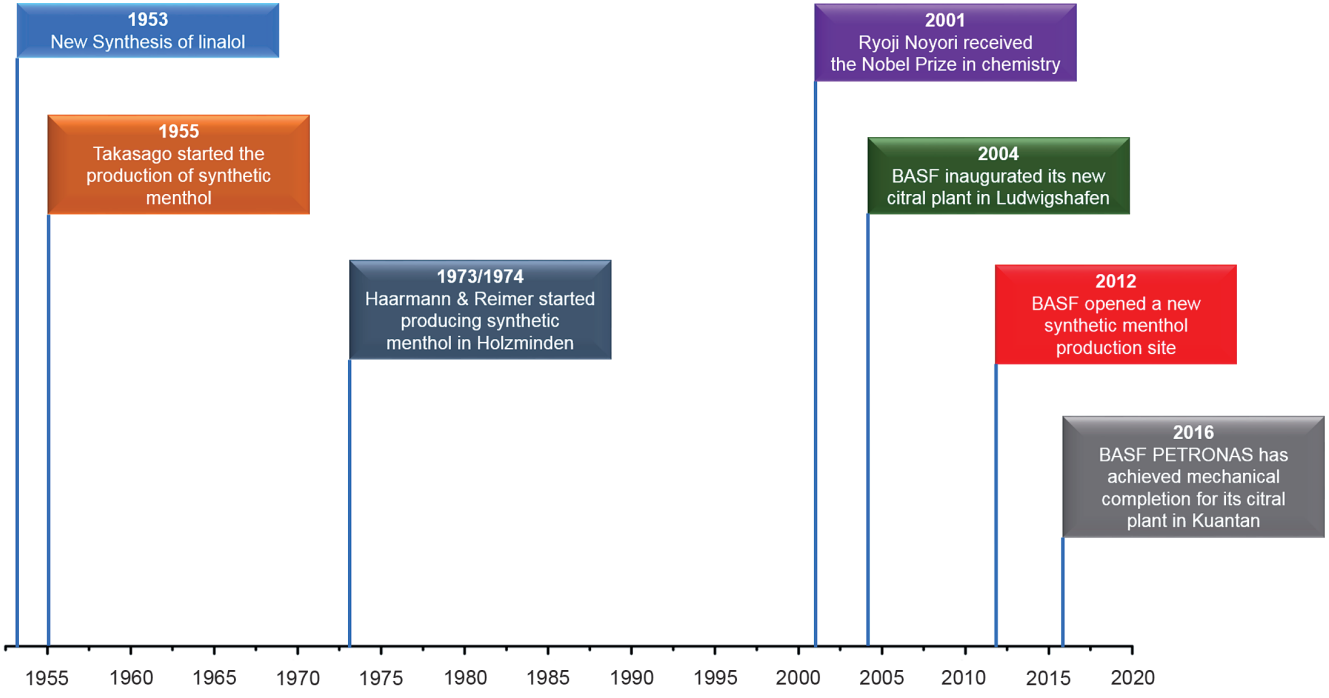

Fig. 2. Major dates in the history of monoterpenoid fragrances – period II

into research and development. This situation is necessitated in some cases by legal regulations concerning the use of certain fragrances, or simply the desire to introduce new, more competitive products. One example is BASF, which in 2004 in Ludwigshafen, at a cost of USD 370 M, commissioned a state of the art citral [4] and citral derivative synthesis unit, followed in 2012 by an l-menthol production unit based on terpene aldehyde [5]. In September 2016, the construction of a new unit to produce citral and citral precursors, as well as other citral-based compounds, was finished in Kuantan, Malaysia. The cost of this installation was about USD 500 M. Completion of the l-menthol production unit is scheduled for 2017, and is a joint venture involving BASF (60% shareholding) and an oil company, Petronas (40% shareholding) [6].

3. Main producers of monoterpenoid fragrances

Both products of natural origin, obtained through extraction or distillation, for example, and those produced using raw materials obtained from crude oil and natural gas processing are all available on the fragrance (including monoterpenoids) market. Many synthetic fragrances have their equivalents in nature, as do monoterpenoids. Of course, it should be noted that compounds belonging to the former group are usually more expensive than their synthetic equivalents. The increased demand for these substances frequently cannot be satisfied from natural sources alone, and this high demand leads to price increases, and the consequent need for production by the synthetic monoterpenoid flavour industry to cover such shortages. Demand drives the development of the technologies required to produce the desired compounds. One example is l-methanol, a compound produced in mass quantities, where the predicted increases in demand is driving the actions of producers. The production capacities of existing units (Symrise, Takasago) have been increased through facility expansion, or by creating new ones (BASF).

Monoterpenoid fragrances are produced both by the primary producers of flavours, as well as enterprises for whom the production of fragrances and their related products is not their sole focus.

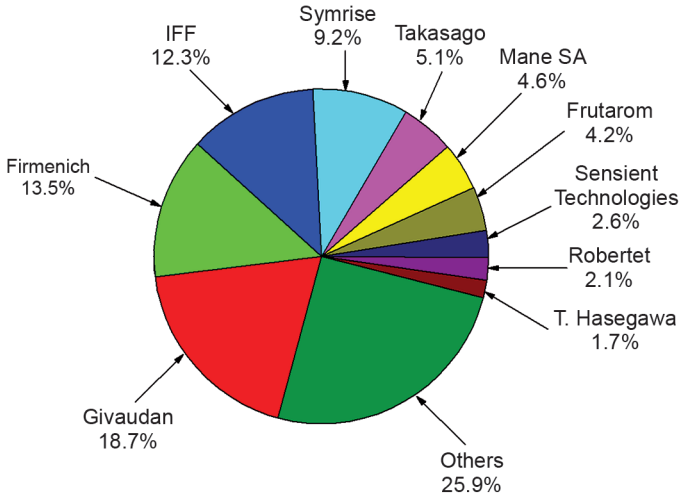

Fig. 3. Percentage share of the fragrance market held by individual producers in 2016

The former group includes such companies as Givaudan and Firmenich (Switzerland), IFF (USA), Symrise (Germany), and Takasago (Japan). Note that these five companies have an almost sixty percent share of the fragrance and food flavour market (Fig. 3) [7].

Interestingly, the above companies are not primary producers of monoterpenoid compounds.

The latter group includes BASF and DSM, and while the production of these substances is significant, it only constitutes a small portion of their production operations.

Among the five major fragrance producers, the greatest share in monoterpenoid fragrance production belongs to Symrise and Takasago. This is related in particular to the production of l-menthol, one of the most popular flavouring substances, and which has been produced by both companies for several decades. Additionally, Symrise may in the future become a major producer of terpene compounds in general, having multiple substances in its range. This is a result of acquiring Prinova from the Canadian capital group, TorQuest Partners, in 2016 for USD 379 M. The holding includes Renessenz, a company with over a hundred-year history and a leading producer of terpene-derived fragrances for the cosmetics and food industries [8].

Among those global companies whose portfolios are not limited to fragrance (including monoterpenoid) production, BASF is the largest. BASF, operating from its headquarters in Ludwigshafen, is involved in the production of various chemical products, and far more. This German company has branches around the world, and first became interested in fragrances in the 1930s, when it initiated the production of β-phenylethanol, colloquially referred to as "rose alcohol", one of the primary components of the most expensive essential oils: rose oil.

Since the 1960s, citral and other fragrances based on the same, as well as vitamins A and E, have been produced as well. Currently, BASF has about 100 flavours in its range. Some of these are monoterpenoid compounds, e.g. citral, of which it is the largest global producer, with about 2/3 of the total production of this compound. Even from the beginning of its production by BASF, this compound has been used to obtain menthol, citronellol, linalool, geraniol, and others. Some citral is processed by the vitamin production department [9].

A Dutch company, DSM, which has its headquarters in Heerlen and branches in many other countries, is the largest competitor for BASF, especially in the pharmaceutical market. This company began life in 1902 as a modest coal mining company [10]. In 2003, it acquired the vitamin department from Roche. A branch focused on vitamins and "fine chemicals" was established, known as DSM Nutritional Products. This company is also one of the main producers of citral, although it is also used to produce various other pharmaceutical products [11].

Aside from the above-mentioned primary producers of fragrances, and those for whom the production of monoterpenoid flavours is a significant, but not dominant part of business, there are also other, smaller companies that offer compounds of this kind.

4. Safe fragrance use

According to the CosIng (Cosmetic Ingredients) cosmetic ingredients database, nearly 3,000 fragrance ingredients, among which monoterpenoids form as sizeable group, are used in numerous products, such as detergents, hygiene products, cosmetics, aromatherapy products, and herbal products [12].

These include fragrances both of natural origin and obtained through chemical synthesis. Studies have demonstrated that about 1–3% of the European population are allergic to certain fragrances. In 2005, a list of chemicals belonging to the group of fragrances identified as allergenic agents was published in the European Union. The Scientific Committee on Consumer Safety (SCCS) identified the 26 most common allergenic fragrances. A better descriptor is: potentially allergenic substances, since only a small fraction of consumers are allergic to them, and sometimes only to one of them. If these substances are present in concentrations exceeding 0.001% in leave-on products and 0.01% in rinse-off products, listing them on the product label is mandatory [13] as a source of information for people allergic to these compounds, and so allows them to avoid health issues. Two subgroups can be distinguished within this group of compounds [14].

Subgroup A: Fragrances which, based on the current state of knowledge, are most commonly listed as well-identified allergens among consumers.

These include:

- pentylcinnamic aldehyde (or amylcinnamic aldehyde),
- pentylcinnamic alcohol (or amylcinnamic alcohol),
- benzyl alcohol,
- benzyl salicylate,
- cinnamic alcohol,
- cinnamic aldehyde,
- citral,
- coumarin,
- eugenol,
- geraniol,
- hydroxycitronellal,
- hydroxymethylpentylcyclohexenecarboxylic aldehyde (also known as Lyral).

Subgroup B: Fragrances that are more rarely mentioned in various studies as allergens. These include:

- anise alcohol,
- benzyl benzoate,
- benzyl cinnamate,
- citronellol,
- farnesol,
- hexylcinnamic aldehyde,
- 2-(4-tert-butylbenzyl)-propionic aldehyde (also known as lily aldehyde),
- d-limonene,
- linalool,
- methylheptyne carbonate,
- 3-methyl-4-(2,2,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (or α-isomethylionone).

Furthermore, the latter subgroup includes two plant extracts, namely oakmoss extract and tree moss extract.

Since publishing the list of 26 allergenic agents, this number has continued to grow as new items are added. Based on dermatological data, the SCCS has now identified a total of 82 substances (54 single compounds and 28 natural extracts) as potential sensitising agents. Of this group, 26 ingredients are classified as substances most commonly mentioned as well identified allergens, while 35 single compounds and 13 plant extracts as systems requiring further detailed studies. Nevertheless, the Committee recommends showing information about these ingredients on product labels to inform potential users about their presence [13].

Research into fragrances of both natural and synthetic origin continues. The obtained data is analysed by the International Fragrance Association (IFRA), which issues recommendations concerning specific fragrances. IFRA is the official organisation of the global perfume industry. It was established by fragrance producers in 1973, in Geneva, where its headquarters remains to this day, while the operations office is located in Brussels. It was founded by the following companies: Firmenich, Givaudan, IFF, Robertet, Symrise and Takasago. Its main purpose is to ensure fragrance raw material safety by:

- conducting scientific research,
- preparing production standards,
- preparing safety rules for use of fragrance raw materials.

The International Fragrance Association has created a classification of fragrances, comprising 11 categories, which are further subdivided into groups. Category 1 includes fragrances present in products that have the longest or most frequent contact with human body, e.g. mouth washes or such products as toys, while category 11 has fragrances present in products that come into contact with human body only sporadically (scented candles, for example).

All the results are collected in guidelines, known as IFRA Standards. These are prepared based on an analysis of all the available information on fragrances, both those published and those not. Each compound is listed with recommended amounts to be used depending on the category of the product of which they are to be an ingredient [15].

There are also continuously updated lists of prohibited substances and those limited to use in fragrances.

The scientific arm of IFRA is the Research Institute of Fragrance Materials (RIFM), established by American producers of fragrances in 1966. It is a non--profit organisation, financed by the fragrance and flavour industry. It is based in Woodcliff Lake in the USA. RIFM is a non-governmental organisation, which tests fragrances and publishes the most comprehensive database in the world concerning:

– safety of fragrance use,
– physicochemical data,
– toxicological data,
– ecotoxicological data.

For newly created fragrances, the procedure is presented in Fig. 4.

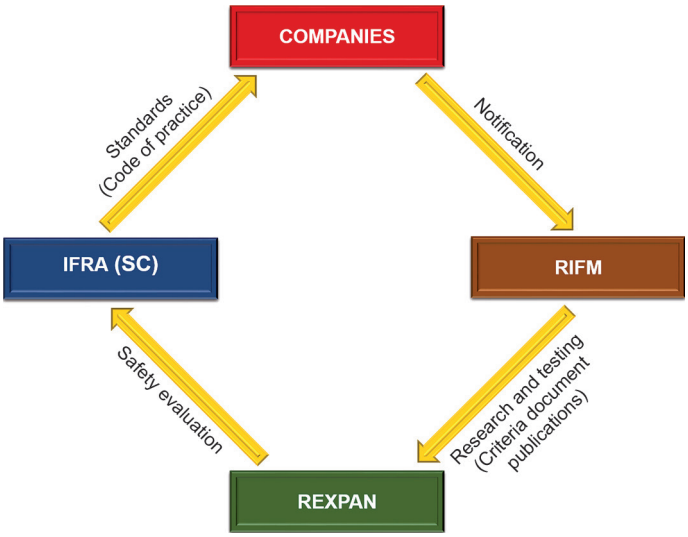

Fig. 4. Diagram of new fragrance safety assessment [16]

A producer submits their compound to RIFM, which conducts the necessary testing, then all the information (studies, tests and literature reviews) is transferred to the REXPAN database, which covers the safety of all chemical substances. Once the information is processed, i.e. a safety assessment is prepared, the data

is provided to the International Fragrance Association, which prepares the IFRA Guidelines. Such procedures are performed for new fragrances; additionally, all the data concerning compounds already present on the market continue to be updated.

5. Industrial production methods for selected monoterpenoids

As mentioned above, monoterpenoid compounds are the largest fragrance group, used in the cosmetics, food, and pharmaceutical industries. Among the substances used in these industries, several key monoterpenoid compounds can be identified. These are geraniol, linalool, citronellol, citronellal, and citral. Aside from being commonly used as fragrances, they also serve as substrates to obtain other compounds, e.g. menthol and rose oxide.

5.1. Citral

In nature, citral occurs as two isomers (Fig. 5): geranial (trans form, or citral a) and neral (cis form, or citral b). The ratio of citral isomers depends on the plant material of origin. Usually it remains within the range of 40:60 to 60:40. A sample citral chromatogram is shown in Fig. 6.

The richest sources of this compound are the oils lemon myrtle (Backhousia citriodora 90–98%), aromatic litsea (Litsea cubeba 70–85%), and lemongrass (Cymbopogon citratus 65–85%). Furthermore, various amounts of citral have been found in citruses.

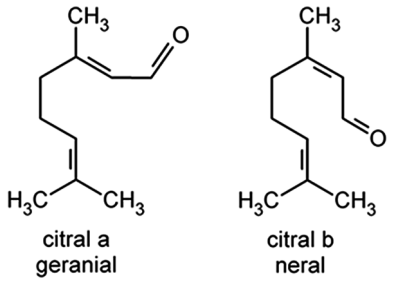

Fig. 5. Structural formulas of citral isomers

Citral has a characteristic sweet, fruity lemon odour, detectable for up to 24 hours at a detectability threshold of 40 ppb. It finds frequent use in the cosmetics, pharmaceutical and food industries.

In the food industry, it is a flavouring ingredient for: alcoholic and non-alcoholic beverages, pastries, meat products, cheese, ice-cream, chewing gum, candies, gelatine, and condiments, in amounts in the range 1–40 ppm (for chewing gum, 200 ppm). In the cosmetics and household chemicals industries, on the other hand, it is employed as a fragrance (aroma compound) in the production of soaps, detergents, creams and lotions, as well as perfumes [17]. Citral is a potential allergen, and consequently if its content exceeds the level approved for use in the given product the producer is obliged to list the full name of the fragrance on the product label.

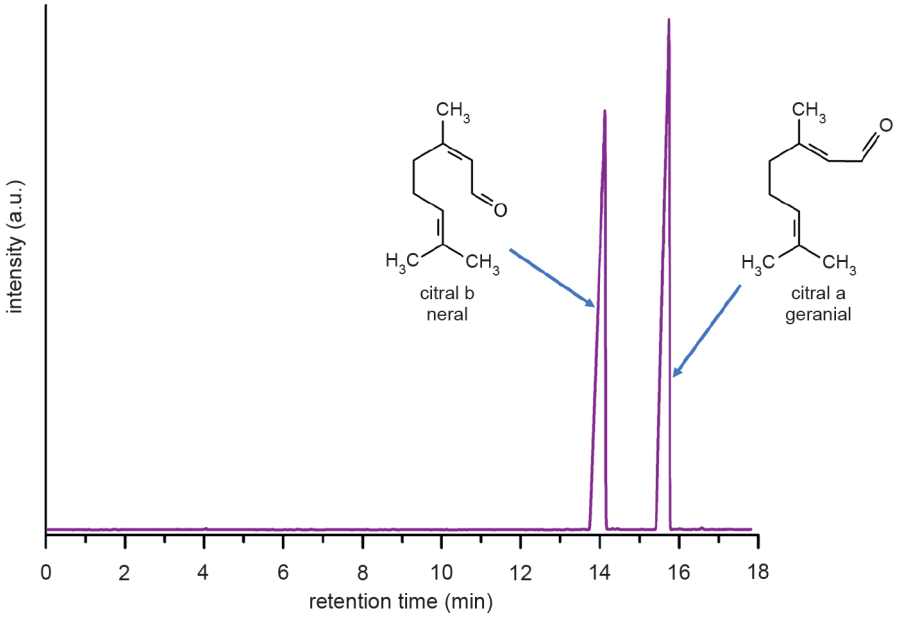

Fig. 6. Sample chromatogram of citral

It is included among the five most important terpene compounds used for producing other valuable chemical compounds, which include citronellal, hydroxycitronellal, menthol, citronellol, geraniol, farnesol, as well as ionones and their methyl derivatives (Fig. 7). It is also an important substrate in the synthesis of vitamins A and E, and other optically active carotenoids [18, 19].

Citral is a mass-produced compound. It has been classified as an HPV substance, i.e. one produced in volumes exceeding 1,000 tonnes/year (> 60,000 tonnes/year). The price of 1 kg of citral oscillates around USD 30 for the natural substance, or USD 17 for its synthetic equivalent.

On an industrial scale, it is currently produced using synthetic methods, with only very limited amounts obtained through the distillation of oil from lemongrass

or aromatic litsea (a few tons per year) [20]. Among the producers of this compound, both synthetic and natural, the foremost are BASF (Germany), Givaudan (Switzerland), Mane (France), Kuraray (Japan), and DSM (Netherlands) [21]. The most significant synthetic citral production technologies used are those utilised by BASF and DSM (Fig. 8).

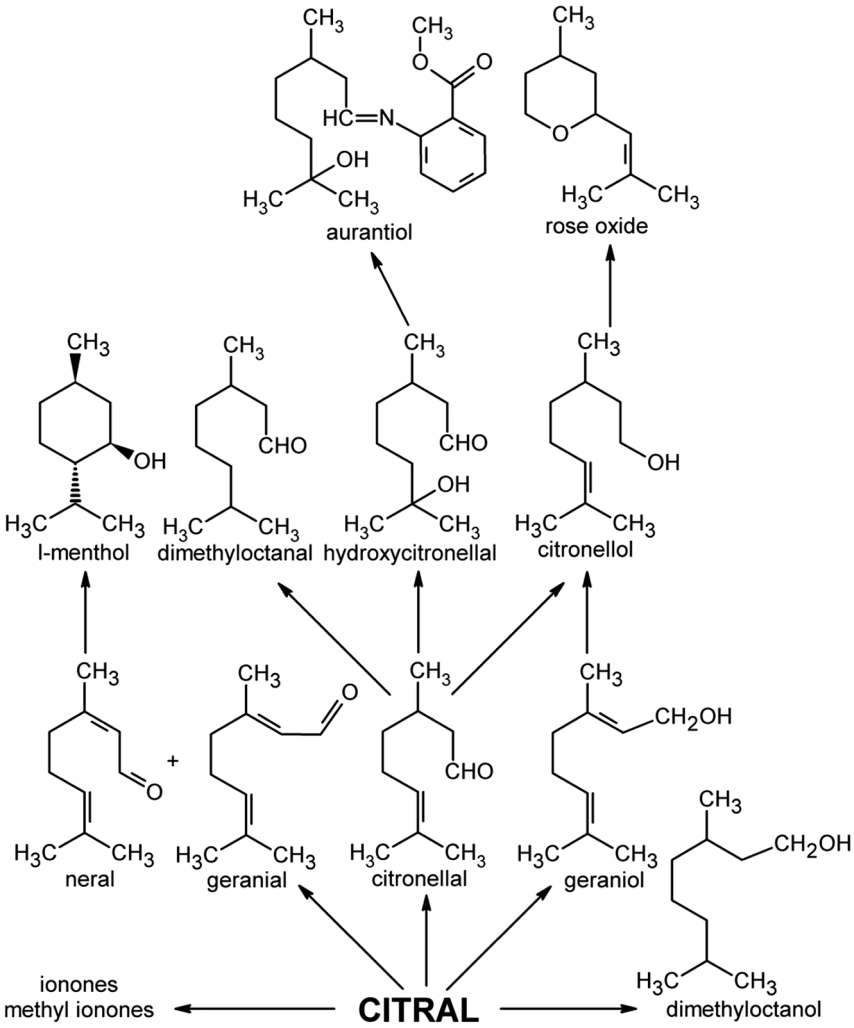

Fig. 7. Selected directions for citral use in the fragrance industry

BASF is currently the largest producer of synthetic citral. This terpene aldehyde serves as a basis for developing numerous technologies, notably menthol production, launched in 2012 and the latest to join this group. The advantage of this solution

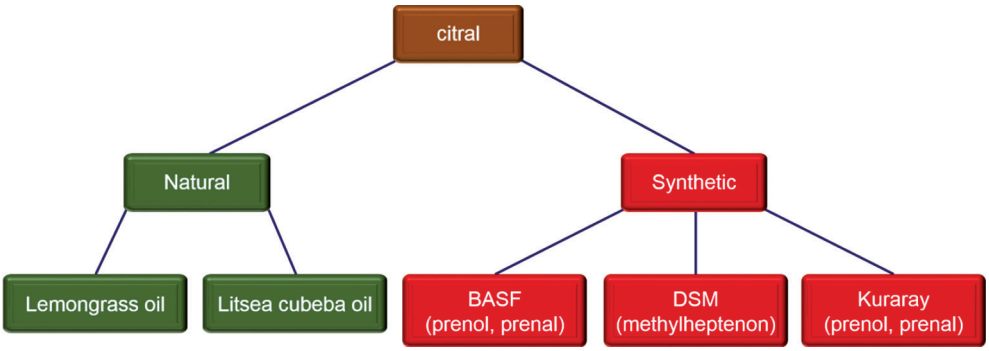

Fig. 8. Selected industrial methods of citral production

is also that all units necessary for production, both the materials for the citral production process and for its subsequent processing into other valuable compounds, are located at a single site, which markedly reduces costs of transport over longer distances (known as the Verbund strategy) [22, 23]. BASF's citral production unit forms a part of a larger project (worth approximately USD 370 M), intended primarily to increase the production capacity in the pharmaceutical sector (vitamins) and in the fragrance segment.

The term "Verbund" can be explained in short as an "integrated system" or "network of interconnections". It is the fulcrum of BASF's business. The term is understood as an internally coherent management philosophy in all fields and areas of business (Fig. 9). From constructing the facility/unit, to dialogue with

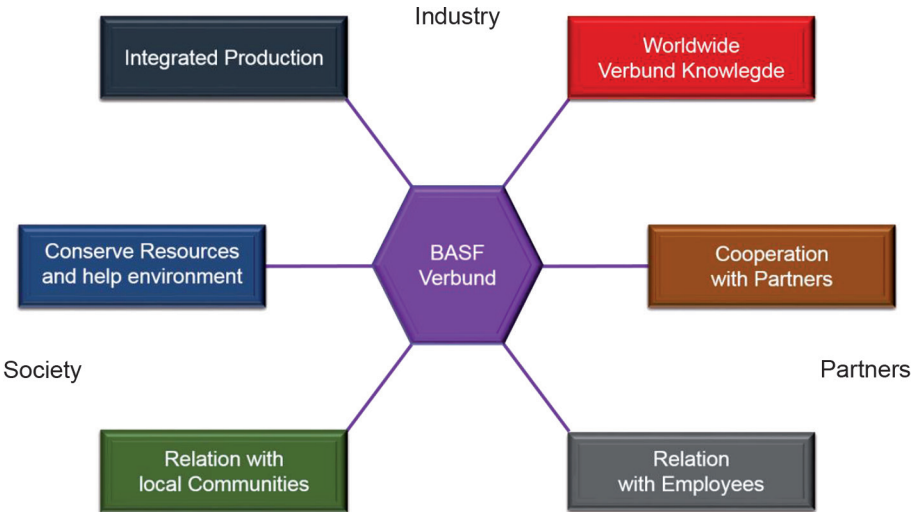

Fig. 9. "Verbund" strategy diagram [22]

customers in order to understand their expectations so that production profiles can be adjusted accordingly, to good relations with employees and local communities, and the social benefits stemming from environmental protection and social responsibility.

The Verbund concept was initiated at the headquarters and main chemical complex in Ludwigshafen, and today is implemented in five complexes around the world. At these locations, production, energy generation and consumption, logistics, and infrastructure have been integrated, partly through common service centres and the use of outsourcing, to maximise profitability and to take advantage of the economies of scale [22].

The citral production technology developed by BASF is based on prenol and prenal as synthesis substrates (Fig. 10) [24].

The production capacity of the latest unit, commissioned in 2004, is estimated at 40,000 tonnes/year. This is four times the amount of citral produced by the previous unit [25, 26]. If one desired to obtain a similar quantity from natural materials, an area the size of Mallorca would have to be sown with lemongrass [9].

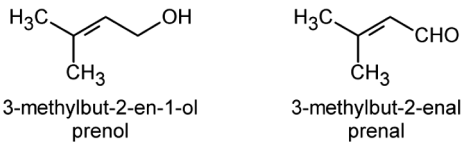

Fig. 10. Structural formulas of prenol and prenal

In September 2016, the construction of a new unit producing citral and citral precursors, as well as other citral-based compounds, was completed in Kuantan, Malaysia. The complex was built by Fluor [27], the investment costing approximately USD 500 M. Completion of the l-menthol production unit is scheduled for 2017, as a joint venture between BASF and Petronas [6].

It should also be noted that the technology employed by BASF is highly environmentally friendly. The only by-product generated during this citral synthesis is water. The entire process is characterised by high selectivity, i.e. the value of the atom efficiency coefficient, thanks to incorporating as many atoms present in the input reagents into the reaction process as possible [28]. Both of these input compounds used in geranial and neral synthesis occur naturally. Prenol can be found in citrus fruits, cranberries, blackcurrants, blueberries, grapefruits, tomatoes, white bread, coffee, hops, and passion fruit. It is used in plant protection products, fragrances, and pharmaceutical products [29].

Prenal, on the other hand, is found in blackberries, tomatoes, tea, passion fruit, raspberries, grapefruits, and white bread. In small amounts (ppm), the compound is used as a flavour in food, chewing gums, and non-alcoholic beverages [30].

The raw materials used in the prenol and prenal production process are formaldehyde and isobutene.

The source of methanal in BASF is a methanol oxidation process, conducted on a silver catalyst at a temperature of 600ºC in the presence of steam (Fig. 11). The reaction produces an aqueous solution of formaldehyde, which can be transferred directly to isoprenol synthesis. Methanal production units are located throughout the world (the Americas, Europe, Asia, and the Middle East) [31]. The largest producers are Asian and Pacific countries, including China (50% of world production) and the USA (14.5%). In 2015, the world methanal production was approximately 47 million tons, with 52 million tons predicted for 2017.

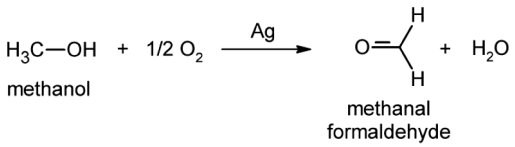

Fig. 11. Formaldehyde production reaction

2-methylprop-1-ene is obtained by BASF as a product of the steam cracking of naphtha, a fraction from crude oil distillation.

Table 1

Composition of C_4 fraction from naphtha steam cracking, obtained by BASF [32]

Product type	Percentage [% m/m]	
	Fraction with low octane number	Fraction with high octane number
1,3-butadiene	26	47
2-methylprop-1-ene (isobutene)	32	22
but-1-ene	20	14
trans-but-2-ene	7	6
cis-but-2-ene	7	5
butane	4	3
2-methylpropane (isobutane)	2	1
vinylacetylene, ethylacetylene; but-1,3-diene	2	2

The steam cracking unit at BASF Ludwigshafen is the single largest unit it owns. The unit covers an area of about 64,000 m^2 (comparable to 13 football fields). At the same time, it is the most important installation, the heart of the Verbund strategy. The first unit was commissioned in 1965 (Steamcracker I), while the second, with twice the capacity, in 1981 (Steamcracker II). Both units operate independently,

24 hours a day. This allows for overhauls or repairs to take place in one while the other unit remains unaffected. Naphtha cracking with steam takes place at a temperature of approximately 840°C. Together, the units process about 2 million tons of naphtha annually. BASF also has steam cracking units in Port Arthur (Texas, USA), Antwerp (Belgium), and Nanjing (China) [33].

The most important precursor necessary for citral production, prenol, is obtained through a two-stage process. First, isoprenol is formed as a result of the reaction between isobutene and formaldehyde (Fig. 12).

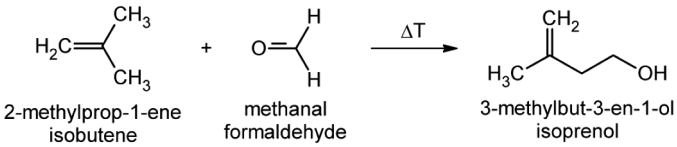

Fig. 12. Isoprenol production reaction

The isoprenol synthesis process flow is illustrated in Fig. 13 [34]. Thermal condensation of isobutene with formaldehyde (40% aqueous solution) occurs in a flow reactor (1) at a temperature of 250°C, and a pressure of 250 bar. Once out of the reaction space, the mixture is cooled to separate the unreacted alkene, which is recycled back into the process (2a). The remaining mixture is then rectified (2b) to separate isoprenol from water and any possible by-products [35]. Note that the process diagram shown here is part of a unit used by BASF in the isoprene production process (as a result of dehydrating isoprenol on a catalyst with acidic properties).

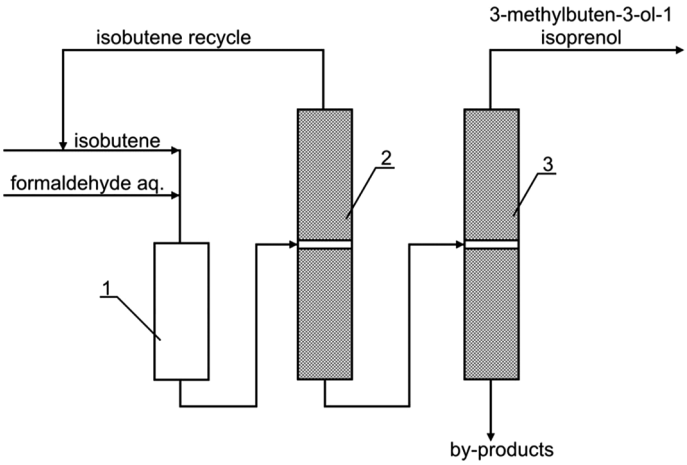

Fig. 13. Isoprenol synthesis unit diagram: 1 – reactor, 2, 3 – rectifying columns [34]

The isoprenol obtained from condensation is isomerised to prenol on a palladium catalyst deposited on active carbon in a continuous system at a temperature of 250°C (Fig. 14). Note that the catalyst is also a popular system used in hydrogenation reactions [35–38].

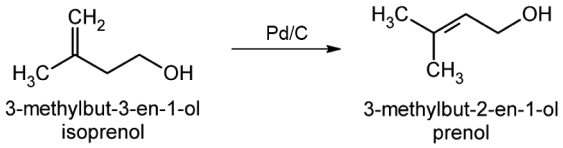

Fig. 14. Isomerisation of isoprenol to prenol

In order to obtain prenal, isoprenol is subjected to oxidising dehydrogenation in the presence of a silver catalyst [39] (Fig. 15) in a flow system (reaction duration is approx. 0.001 s). Note that this is the same catalyst used in the production of formaldehyde from methanol [40].

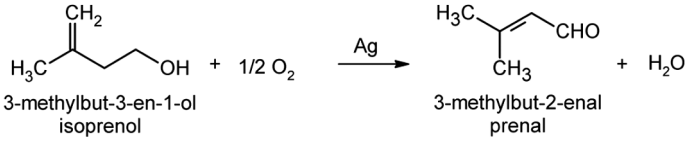

Fig. 15. Oxidative dehydrogenation of isoprenol to prenal

Isoprenol and air are heated in an evaporator (1) to a temperature of 70°C, then transferred to a vertical flow reactor [41, 42], where in its upper part (2) a silver catalyst bed (approx. 20 cm thick) is located, pre-heated to 460ºC. The oxidising dehydrogenation process occurs at a temperature of 500°C, and the mixture remains in the reactor space for 0.001 s. Furthermore, nitrogen is added as an inert agent. This results in the pressure in the system being higher than atmospheric pressure (1.07 bar).

When the post-reaction stream leaves the reactor, it is cooled in a condenser (3) to a temperature of 25°C and collected in a separator (4). Isoprenol and prenal are separated first, and the remaining components of the mixture are transferred to an absorption system comprising two columns (5 and 6) filled with Raschig rings washed with DMF. Next, the gaseous products are separated from the additional alcohol and aldehyde (Fig. 16). Aldehyde is obtained at 95% efficiency relative to initial alcohol [43, 44].

Several process stages can be identified within the BASF citral production method:

– synthesis of acetal from two molecules of prenol and one of prenal,
– elimination of one prenol molecule from acetal,

– Claisen rearrangement,
– Cope rearrangement.

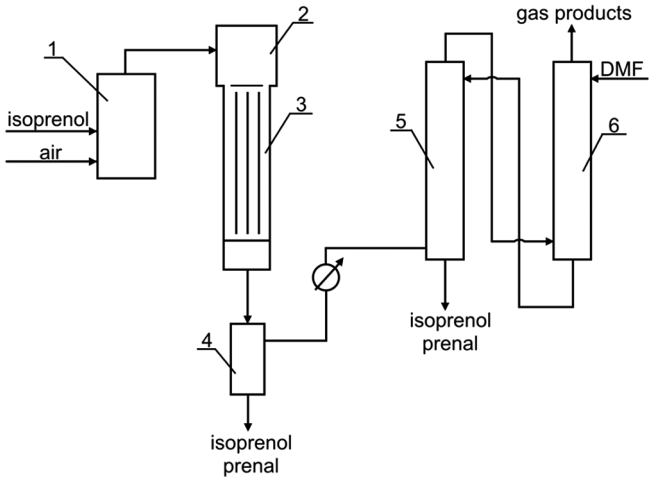

Fig. 16. Process diagram of oxidative dehydrogenation of isoprenol to prenal 1 – evaporator, 2 – reactor, 3 – condenser, 4 – separator, 5 and 6 – absorption columns [42]

During the first stage, acetal is formed (Fig. 17) from two molecules of prenol and one of prenal in the presence of a catalyst having acidic properties.

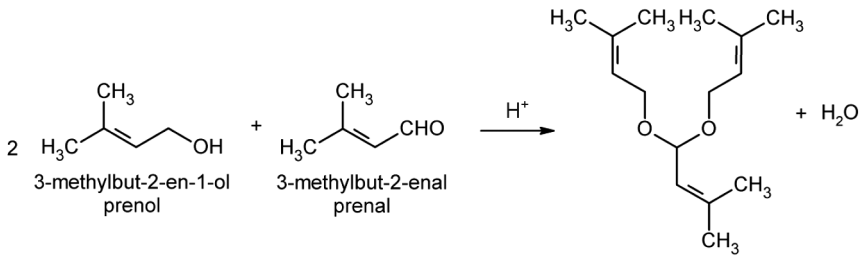

Fig. 17. Reaction of acetal formation from prenol and prenal

Directly after the acetal production reaction, the post-reaction mixture is transferred to a type of distillation column (1) (Fig. 18), where in the bottom (reaction) part (5), one prenol molecule of prenol is eliminated from the initial compound under the effects of a catalyst having acidic properties, as per the reaction in Fig. 19, producing citral precursor [45].

In the middle part of the column, the produced ether is separated from the prenol and prenal (from the acetal production process). The precursor is subsequently transferred to a reactor (6), where the temperature leads to rearrangement processes (Claisen and Cope, Figs. 20 and 21, respectively).

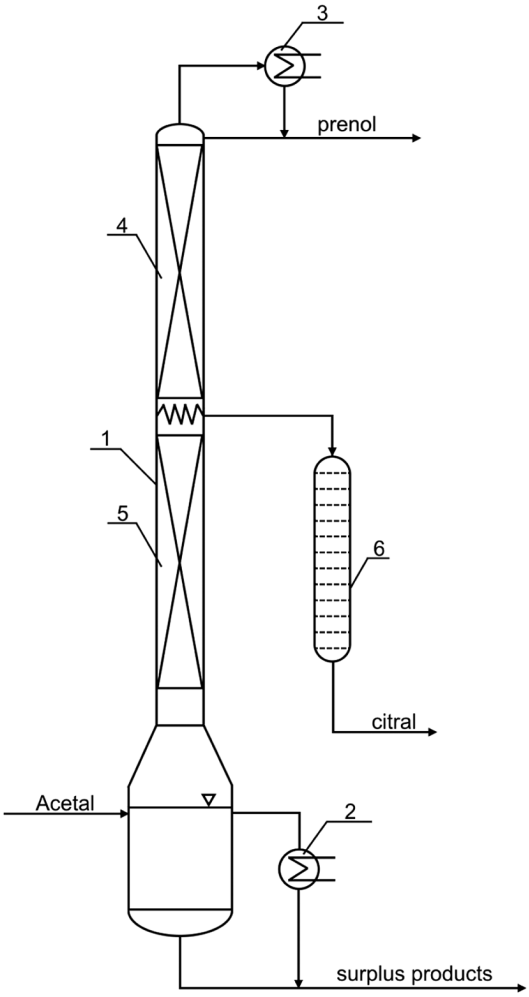

Fig. 18. Citral synthesis unit diagram 1 – distillation column, 2 – heat exchanger, 3 – condenser, 4 – distillation part of column, 5 – bottom (reaction) part of column, 6 – reactor [46]

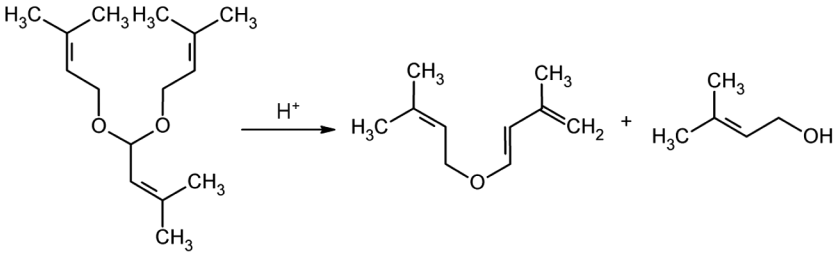

Fig. 19. Elimination of one prenol molecule from acetal

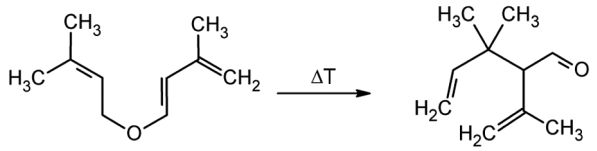

Fig. 20. Claisen rearrangement reaction

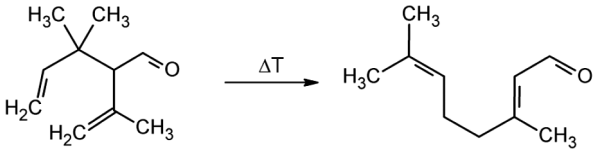

Fig. 21. Cope rearrangement reaction

In the distillation part (4), prenol is separated from the remaining components. This alcohol is recycled into the acetal formation process. The few by-products of acetal decomposition not described above are discharged from the bottom part of the column.

The citral production technology described above provides a substance of a very high purity, which can be used as a fragrance in perfumes, as a flavouring in the food industry, and as a substrate in menthol synthesis, which currently is also available as a component of pharmaceuticals.

Another major producer of synthetic citral is DSM. The initial compound in this citral production process is 6-methylhept-5-en-2-one, known also as 2-methylhept--2-en-6-one, or simply as methylheptenone (Fig. 22) [47, 48].

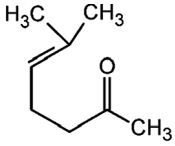

Fig. 22. Structural formula of methylheptenone

Methylheptenone has a characteristic fruity and herbal odour, and a creamy, fruity and cheesy flavour. In nature, it is found in many essential oils and in tomatoes. It is utilised by the perfume, food, and pharmaceutical industries, and forms an ingredient in fragrances (0.01% in the finished product) and flavourings (0.5––10 ppm in the end product). However, over 90% of the methylheptenone obtained synthetically is used to produce other fragrances, e.g. linalool and citral, as well as in the pharmaceutical industry for the production of medicines and vitamins (A and E). Among the methylheptenone producers, the major companies other than DSM are Givaudan (Switzerland), BASF (Germany), and Vigon International (USA) [49].

The methylheptenone production technology is multi-stage, although it utilises some of the most common compounds found in the petrochemical industry.

First, through the reaction of acetone and acetylene, the unsaturated alcohol 2-methylbut-3-yn-2-ol is formed (Fig. 23) [5].

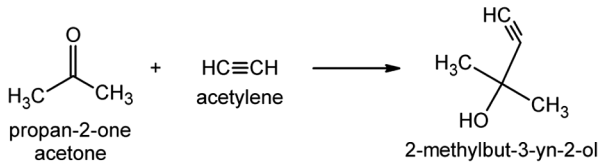

Fig. 23. 2-methylbut-3-yn-2-ol production reaction

During the next stage, 2-methylbut-3-yn-2-ol is subject to mild reduction (the triple bond transforms into a double one) in the presence of the Lindlar catalyst (Fig. 24) [51]. A more recent solution is to use a palladium nanoparticle-based catalyst system [52]. In this way, 2-methylbut-3-en-2-ol is formed [53].

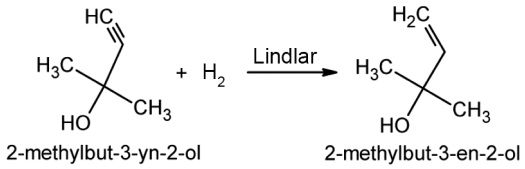

Fig. 24. 2-methylbut-3-yn-2-ol hydrogenation to 2-methylbut-3-en-2-ol

The final stage in the methylheptenone production process is a reaction between 2-methylbut-3-en-2-ol and isopropenylmethyl ether (Fig. 25) in the presence of a phosphorus catalyst (metaphosphoric acid chelate) [54]. The process is conducted on a continuous basis at 150°C in a methanol solution, and a pressure of approx. 10 bar. An excess of ether is used, compared to the stoichiometric amount [55].

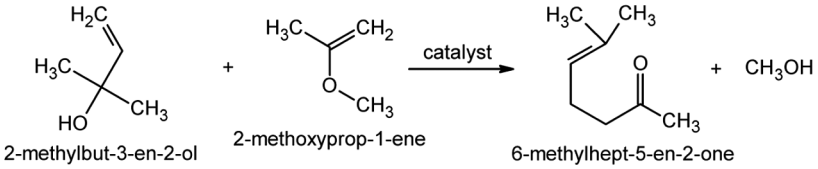

Fig. 25. Methylheptenone production reaction

The reaction of methylheptenone with acetylene produces dehydrolinalool (Fig. 26). Note that this compound is also a precursor in the linalool and pseudoionone production processes.

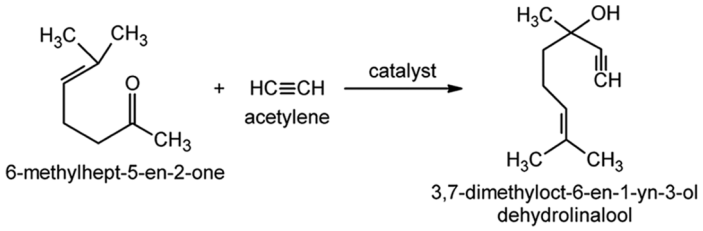

Fig. 26. Dehydrolinalool production reaction

The dehydrolinalool production process is conducted at a temperature of 15°C, and a pressure of 12 bar, and in the presence of a catalyst with alkaline properties [56, 57]. A process diagram is shown in Fig. 27.

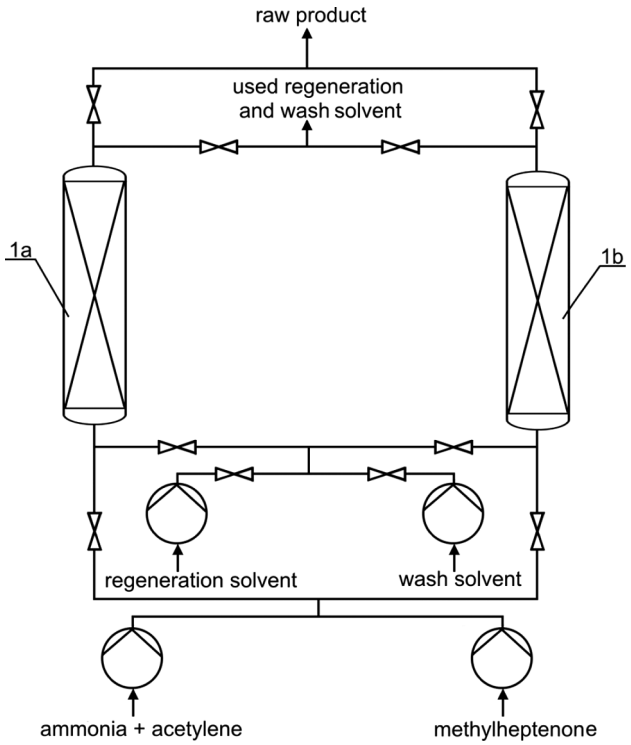

Fig. 27. Dehydrolinalool production process diagram: 1a, 1b – reactors/regenerators [56]

The system comprises two reactors operating alternately as a reactor-regenerator. Each contains an alkaline catalyst (based on AMBERSEP® 900 resin). The catalytic system is pre-washed with deionised water, and subsequently with methanol to remove the water and methylheptenone, in order to remove the methyl alcohol from

the system. Acetylene dissolved in ammonia (24% m/m, obtained at a temperature of 6°C and a pressure of 9 bar) and methylheptenone are introduced into a reactor prepared in the above manner [58, 59].

After leaving the reactor, the post-reaction mixture is transferred to a separator heated to 78°C, where dehydrolinalool and other reaction products are separated from the ammonia and acetylene mixture, which can then be recycled back into the process. When the catalyst is deactivated, the reactor is switched to regeneration, while its previous role is taken up by the other unit. To this end, the flow of the acetylene mixture in ammonia is stopped, while the flow of methylheptenone is maintained for a short time. To restore its activity, regenerating methanol (containing 5% m/m of KOH) is passed through the catalyst bed. Next, as at the beginning, the catalyst is washed with methanol and then methylheptenone. A system prepared in this manner is ready to take over the reactor role while the other one is deactivated to regenerate the catalyst bed.

The final stage is the rearrangement of dehydrolinalool to citral (Fig. 28), catalysed by a molybdenum catalyst (which has replaced the vanadium-based catalyst used previously, as it generated large amounts of by-products) [60]. The reaction is carried out at a temperature of approx. 100°C in a solution containing phenylacetic acid and DMSO.

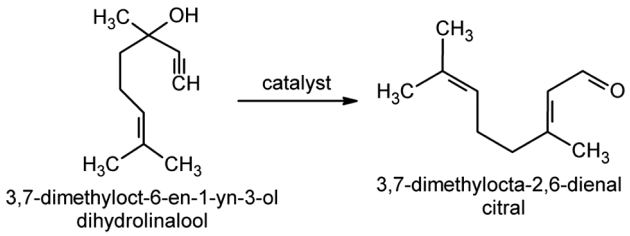

Fig. 28. Production of citral from dehydrolinalool

Citral is extracted from the post-reaction mixture and subsequently purified. The process yield is approx. 90%.

Note that, aside from the two citral production technologies discussed above, there is another one, developed by Kuraray (Japan), which is similar in execution to that utilised by BASF. This similarity stems from forming acetal from prenol and prenal at a certain stage [61, 62], its further decomposition, and then Claisen and Cope rearrangements. A number of differences exist during the prenol and prenal formation stages [63].

5.2. Menthol

Menthol is a cyclic monoterpenoid, possessing three chiral centres in its structure. Each of the four geometric isomers, known as menthol, neomenthol, isomenthol, and neoisomenthol, exists in two enantiomeric forms (Fig. 29) [1, 64].

The largest amounts of menthol occur in different varieties of Lamiaceae plants: peppermint (Mentha piperita), field mint (Mentha arvensis), round-leafed mint (Mentha rotundifolia), and wrinkled-leaf mint (Mentha crispata). Menthol is also found in the essential oils of many other plants.

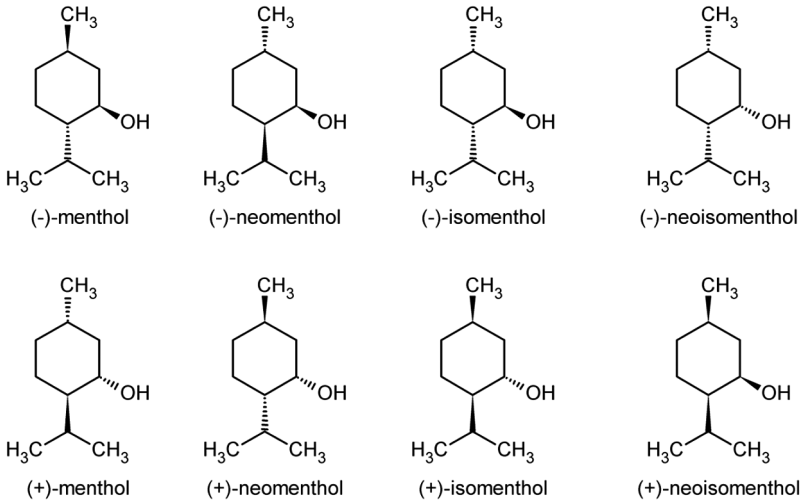

Fig. 29. Structural formulas of the eight menthol forms

Menthol causes a feeling of freshness on the skin and mucous membranes. This occurs because the compound attaches itself to thermoreceptors on the skin or mucous membranes. Thermoreceptors react to heat and cold, affecting the perception of ambient temperature.

Menthol, by attaching to a cold receptor, increases intra-cellular calcium concentration and causes the same stimulation of the nerve endings as occurs from contact with cold water. The organism thus experiences a feeling of freshness [65].

l-menthol is one of the best-selling fragrances in the world, and is necessary for the production of many consumer products (according to data from Givaudan). It is probably the most important flavouring ingredient used in mouth cavity hygiene products. Annual global demand, estimated at 25,000 to 30,000 tons, already exceeds total production capacity. It continues to grow as a result of using menthol in ever more new products [66]. A sample l-menthol chromatogram is shown in Fig. 30.

A frequent replacement for the expensive l-menthol enantiomer is a cheaper racemic mixture containing (±)-menthol.

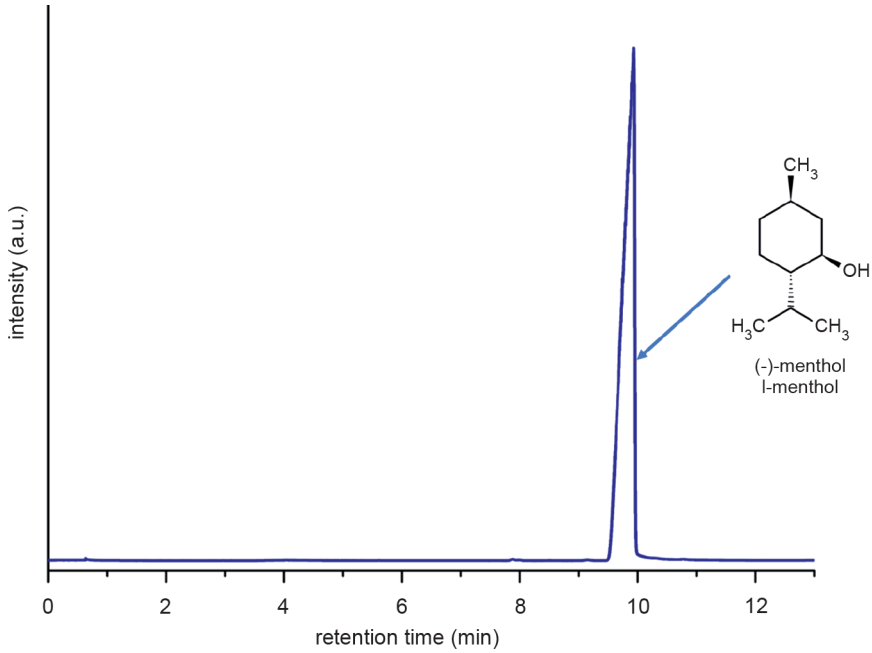

Fig. 30. Sample chromatogram of l-menthol

The pharmaceutical industry employs both natural and synthetic menthol, the former obtained from mint oil, in producing dermatological balms with cooling and slightly anaesthetising effects; rub-in mixtures soothing nerve pains and headaches; stomatological and laryngological preparations used for throat and nose mucous membrane inflammations; and other products (snuff tobacco, aerosols, nasal sticks, etc.).

The cosmetics and household chemical industries use menthol as an aroma chemical (fragrance) in the production of shampoos, soaps, detergents, creams, skin tonics, facial products, and mouthwashes.

The food industry, on the other hand, uses this compound in mint flavourings, in chewing gums and sweets.

According to IFRA recommendations, the l-menthol content in a fragrance concentrate should not exceed 8%, while for food products it should be no more than 1,100 ppm [67].

The high demand for menthol resulted in BASF taking an interest in this compound, with a new plant producing up to 10,000 tonnes/year production capacity. The prospect of a new player in this segment caused considerable commotion on

the market. The previously two largest producers, namely Symrise and Takasago, also declared that they would double the quantities of menthol used, to 6,000 and 3,000 tonnes/year, respectively [68]. The production volume is estimated at a little over 20,000 tonnes/year, resulting in a shortfall of several thousand tonnes compared to the predicted demand, while the price remains about 30 USD/kg for natural menthol, and 17 USD/kg for its synthetic equivalent.

The major producers of the enantiomer in the greatest demand, i.e. l-menthol, are Takasago (Japan), Symrise (Germany), Lanxess (Germany), and, most recently, BASF (Germany) [67].

At present, four main methods of menthol production can be identified (Fig. 31) [69].

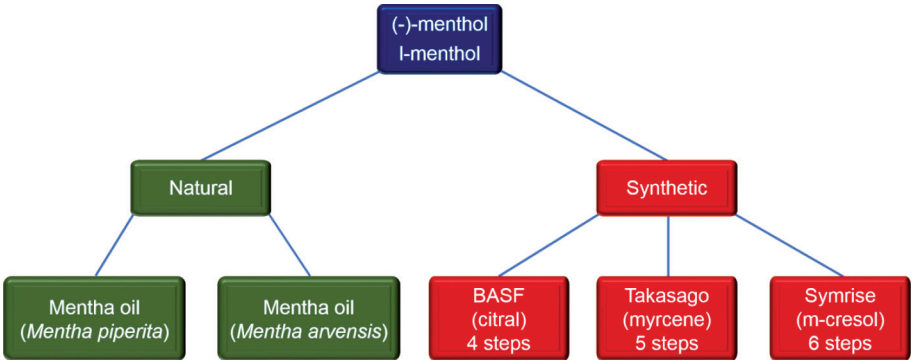

Fig. 31. Major production methods of l-menthol [69]

Originally, pure l-menthol was obtained typically from mint oil extracted from field mint (botanical name: Mentha arvensis). Currently, 22,000 tonnes is produced this way, with 18,000 tonnes from India. A hectare of crops yields 120–160 kg of oil per year. This is almost twice the rate for mint oil yield from peppermint, at 60–100 kg per hectare. For this reason, field mint oil continues to gain importance in trade [70].

As an interesting aside, even before World War II, menthol was produced by crystallisation from the essential oil obtained from this plant, mainly in Japan and China. In 1938, Japan was a global leader in menthol production, producing 886 tonnes of this compound, 375 of which was intended for export. However, this production method has its drawbacks; as the harvest yield and product quality may vary depending on weather conditions, leading to production shortfalls. This method of menthol production involves freezing out the natural oil, then filtering off the precipitated crystals. The major producers of natural menthol include India and China [71].

The other three methods of synthetic menthol production utilise products of the petrochemical industry as substrates. Among them, two use a chiral catalyst during the process (BASF and Takasago) [72].

The most modern l-menthol production unit is that commissioned in the summer of 2012 at the BASF plant in Ludwigshafen.

BASF has developed a new production process based on the aroma compound, citral. It is produced as part of BASF's Verbund strategy. The l-menthol plant production capacity is estimated at about 10,000 tonnes/year, and has made BASF one of the major producers of this compound. As previously mentioned, the production plant in Malaysia shared with Petronas will be completed in 2017, adding several thousand more tonnes to the market [6, 73].

The main advantage of the BASF method is that l-menthol is produced in a continuous process. According to BASF, this not only saves time, but also ensures a more efficient use of the raw materials, as it allows the production of a greater amount of l-menthol of at least 99.7% purity using the same amount of raw materials [74].

The menthol production process in this method is multi-staged [75–77]:

- production of a neral-rich fraction,
- catalytic hydrogenation of neral to (R)-citronellal,
- citronellal cyclisation to isopulegol in the presence of a catalyst with acidic properties,
- purification of isopulegol by crystallisation,
- catalytic hydrogenation of isopulegol to l-menthol,
- purification of l-menthol (distillation).

As mentioned above, the raw material for menthol synthesis at BASF is citral (citral b). This stage is one of the most important in the entire menthol production process. Studies have shown that the chiral catalyst utilised in the following stage exhibits enantiomeric selectivity towards (R)-citral, but only when neral is used, while no such activity has been found for geranial [78].

During the first stage, citral (a mixture of geranial and neral) is used to produce a fraction enriched with this compound (Fig. 32) [79].

A stream containing a mixture of both the aldehydes is preheated (1), and then introduced in the middle of a column (2) between the desorbing (3) and rectification (4) sections. Rectification in the column produces a fraction enriched in neral (containing less than 0.3% geranial), which is collected on the side of the column opposite the point of entry. Both parts, i.e. feed and fraction collection, are separated by a barrier (5).The process utilises repeated recycling of both the easily boiled components through a system comprising a condenser (6), condensate container (7), and a reflux pump (8), and those with higher boiling points, using a circulation pump (9) and a preheater (10) to improve the effectiveness of the geranial separation from neral.

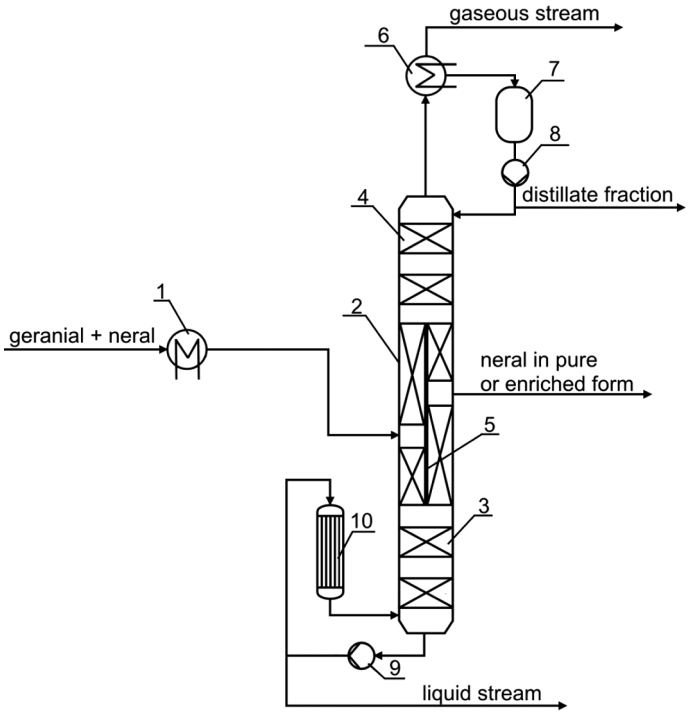

Fig. 32. Diagram of a unit for neral-enriched fraction production: 1 – heater, 2 – column enriching the fraction in neral, 3 – desorbing section, 4 – rectification section, 5 – separation barrier, 6 – condenser, 7 – condensate container, 8 – reflux pump, 9 – recirculation pump, 10 – evaporator [79]

During the second stage, the neral-enriched fraction is subjected to hydrogenation (Fig. 33). The process is carried out at a temperature of 30°C and a hydrogen pressure of 100 bar.

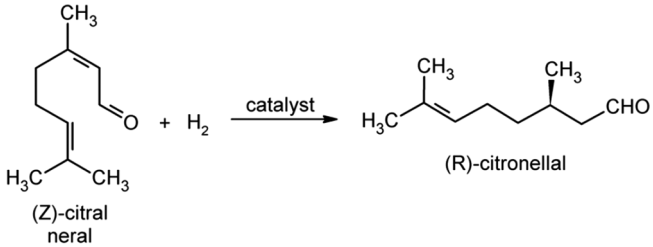

Fig. 33. Reaction of neral hydrogenation using a chiral catalyst

BASF's asymmetric catalytic hydrogenation of neral is a crucial stage in the menthol production process. To this end, a new high-performance rhodium

catalyst was specially developed, enabling synthesis of mainly the desired enantiomer from citral [80].

As can be seen in Fig. 34, there are three forms of rhodium catalyst (I, II, III), differing in their number of phosphine ligands [81]. Based on analyses supported by quantum-chemical tests, it has been determined that the active form is type II, as it has the optimum ligand to metal ratio (of 2) [25]. If a greater number of phosphine ligands is present (type I, Fig. 34), the resulting catalytic system exhibits a low activity and is quickly deactivated.

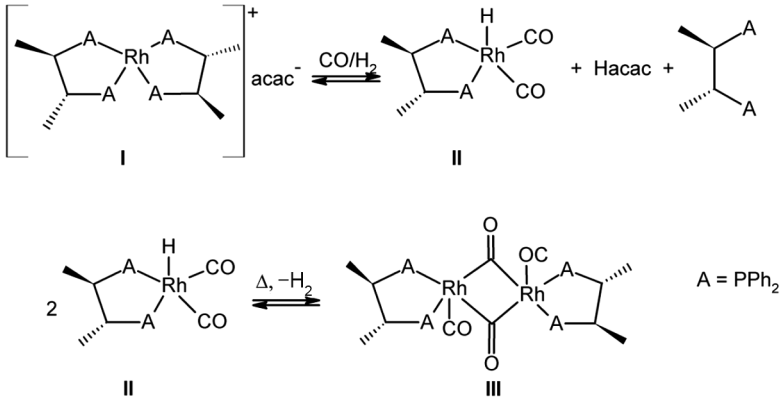

Fig. 34. Catalyst types utilised in the chiral hydrogenation of neral

Another important parameter that must be controlled during the process is the partial pressure of carbon oxide (CO). From the perspective of catalytic activity, CO content in the hydrogen stream must neither be too low or too high, but in both cases, a small amount of type II of the catalyst forms. The optimum concentration was found to be 1,000 ppm. With careful control of the above parameters, it is possible to carry out the hydrogenation reaction with satisfactory results.

Neral hydrogenation occurs according to the mechanism shown in Fig. 35. During the first stage, dissociation results in a CO molecule detaching from the type II catalytic system (Fig. 34), similar to a classic hydroformylation process. The active type of catalyst obtained in this way forms a π complex with a neral molecule, which subsequently undergoes an insertion reaction. During the next stage, the oxidising addition of hydrogen to rhodium produces a new complex. This is crucial for the rate at which the entire process occurs. Ultimately, the complex decomposes to an R-citronellal molecule and catalyst, which can be re-used in the next cycle.

A typical process flow is shown in Fig. 36. The main elements are reactor, catalyst regenerator, and distillation column.

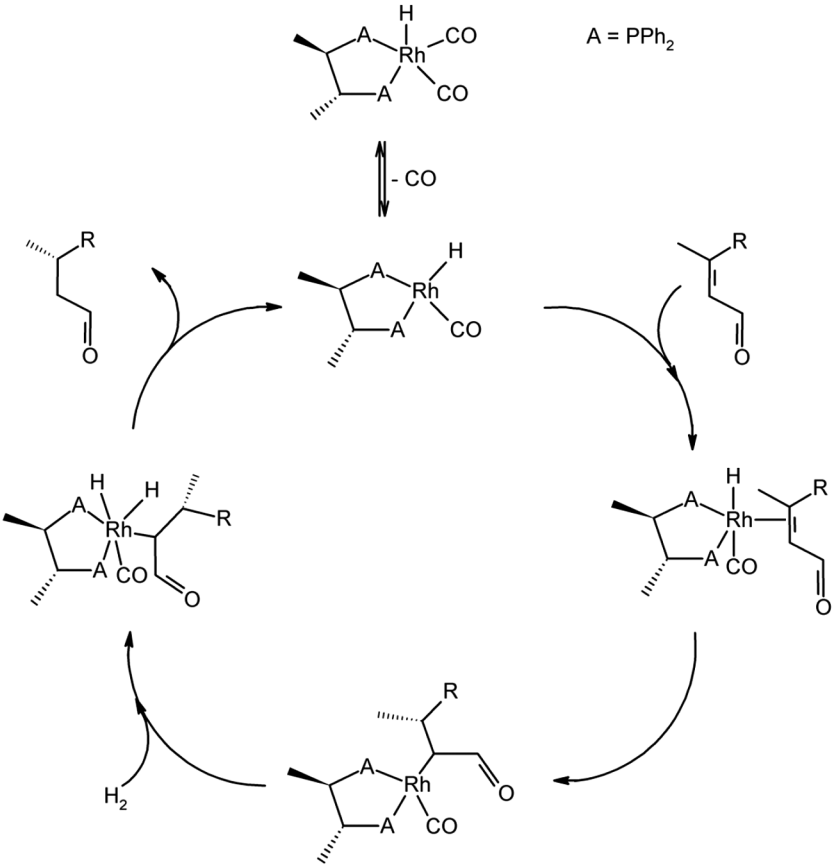

Fig. 35. Mechanism of the chiral hydrogenation of neral [25]

A problem that may occur during hydrogenation is loss of catalyst activity. An inactive catalyst form is created during distillation under reduced pressure. This can be easily observed due to its colour (brown-red). Optimisation tests of the catalytic system used have demonstrated that the quickest way to restore its effectiveness is the presence of higher CO concentrations, although the hydrogenation process occurs the easiest under low partial pressures of carbon oxide (approx. 1,000 ppm, as mentioned above). Further testing has demonstrated that complete elimination of CO from the reaction stream during hydrogenation is not possible, as it leads to a complete loss of activity by the catalyst due to the creation of its inactive, type III form (Fig. 34). It is an interesting relation, because most known hydrogenation processes are sensitive to the presence of CO. However, in this case, the introduction of small amounts of carbon oxide to the hydrogen stream enables the chiral hydrogenation process.

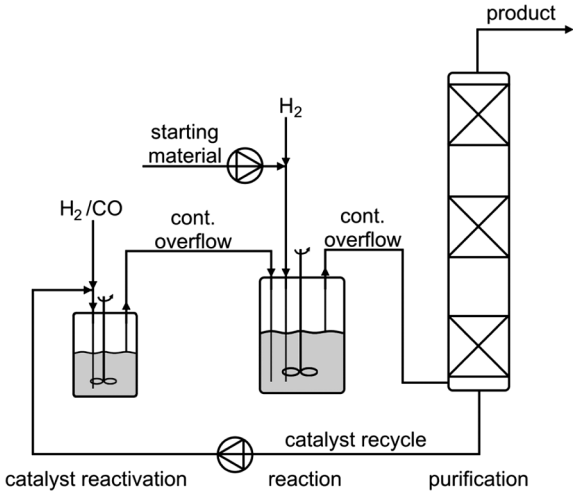

Fig. 36. Process diagram of the chiral hydrogenation of neral [78]

During the subsequent stage, the (R)-citronellal obtained through hydrogenation undergoes cyclisation to isopulegol (Fig. 37).

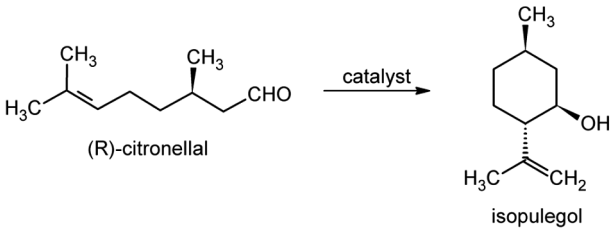

Fig. 37. Reaction of (R)-citronellal cyclisation to isopulegol

The cyclisation takes place, as is usual, at a low temperature (10°C, following a pre-cooling of the reaction mixture) in the presence of a catalyst, specifically bis(diarylphenoxy) aluminium, at a reagent-catalyst ratio of 100:1. A solvent is also used (reagent-solvent ratio of 1.5:1), which facilitates the reaction and additionally removes the heat generated from the system, limiting the occurrence of undesired reactions [82–85]. The process is carried out for 5 hours, and then isopulegol is separated from the post-reaction mixture by distillation under reduced pressure (100 mbar). The resulting compound is purified by crystallisation at a temperature of approx. 10°C [86, 87].

The final stage is hydrogenation of isopulegol (purity of at least 99%) to l-menthol (Fig. 38), carried out at a temperature of 100°C and a pressure of 50 bar,

in the presence of a nickel catalyst (nickel oxide) modified with zircon, copper, and molybdenum oxides [88, 89].

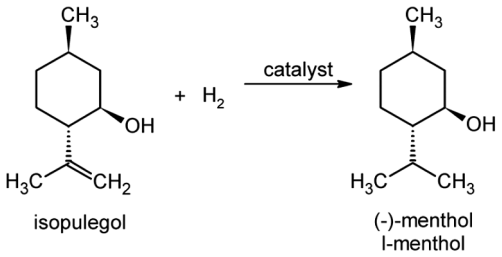

Fig. 38. Isopulegol hydrogenation to l-menthol

Pure l-menthol (99.7%) is obtained through distillation with the use of an approx. 60 m tall column [90]. The system, in this case used to purify l-menthol of undesired

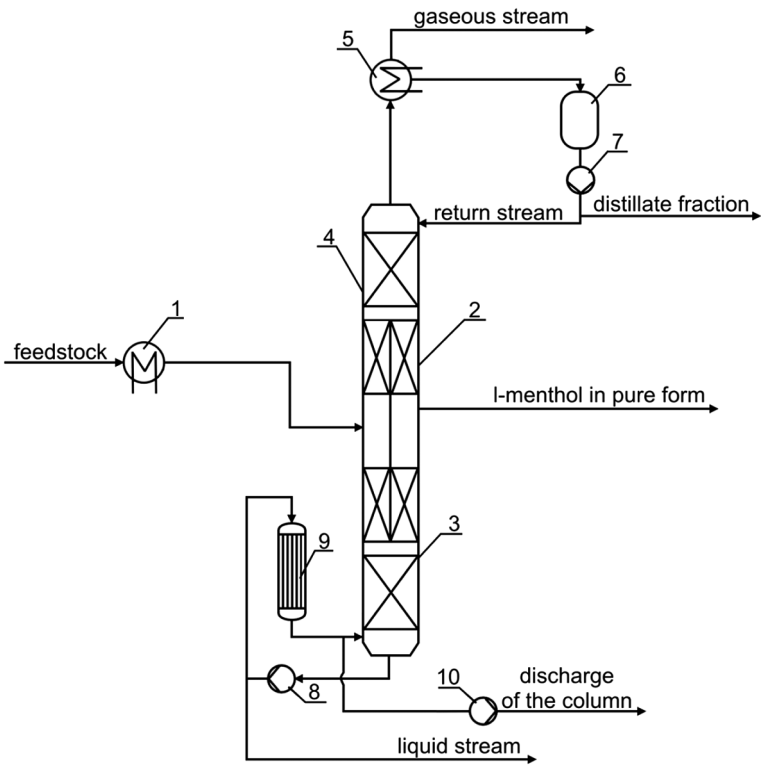

Fig. 39. Diagram of l-menthol purification unit: 1 – pre-heater, 2 – menthol purification column, 3 – desorption section of the column, 4 – rectification section of the column, 5 – condenser, 6 – condensate container, 7 – reflux pump, 8 – pump, 9 – pre-heater, 10 – pump [90]

compounds such as d-menthol or neomenthols and neoisomenthols, has a similar structure to that shown in Fig. 32, used for neral enrichment of the fraction used subsequently in hydrogenation.

After pre-heating (1), the material is introduced into a column used for l-menthol purification (2), about half way up. This comprises a desorption (3) and a rectification (4) section, operating at a pressure of approx. 100 mbar. Rectification in the column produces pure l-menthol (containing less than 0.3% of impurities, chiefly other enantiomers), which is collected on the side of the column opposite to the point of entry. The process utilises repeated recycling of both the easily boiled components through a system comprising a condenser (5), condensate container (6), and reflux pump (7), and those with higher boiling points using a pump (8) and pre-heater (9) to improve the effectiveness of the purification process. If needed, excess liquid components can be removed from the column using a pump (10).

The end product is formed, for example, as flakes 1 to 20 mm in diameter and approx.0.1–3 mm thick [91].

Another major producer of l-menthol is Takasago. This company has produced l-menthol since the 1950s (Fig. 40). Originally, the raw material used in the production of this fragrance was d-citronellal, obtained at 35% efficiency from citronella oil. Other compounds were obtained from the citronellal-depleted essential oil as well, specifically geraniol and its esters. The optical purity of the material used for l-menthol production was about 80%, with a total of 300 tonnes of the compound produced per year. Due to the increased demand for l-menthol, larger amounts of citronella oil were needed as well. Even producing 300 tonnes required 1,300 tonnes of the essential oil, which was 50% of the global demand. As a result, in 1972 Takasago began using thymol as the raw material, which is obtained from a product of crude oil processing, m-cresol. l-Menthol was obtained by distilling a mixture containing 4 pairs of menthol enantiomers. The problems that then occurred on the fuel market, with its dramatic rise in crude oil prices, encouraged Takasago to seek an alternative raw material for the production of l-menthol. d-Limonene, obtained from cheap orange oil, was used as the initial substrate. This method was similar to that based on thymol, as separation of the resulting enantiomer mixture was a necessary step as well. Up until 1980, both technologies (thymol- and limonene-based) were used concurrently. As a result of another crisis on the crude oil market, d-Δ^3-karene, obtained from turpentine distillation, began to be used as the raw material [71].

The l-menthol production technology employed today dates back to the 1980s. The production plant for this compound is located in Iwata, in the Suzuka prefecture of Japan (Fig. 40). Note that l-menthol has been in production there since 1968 [92].

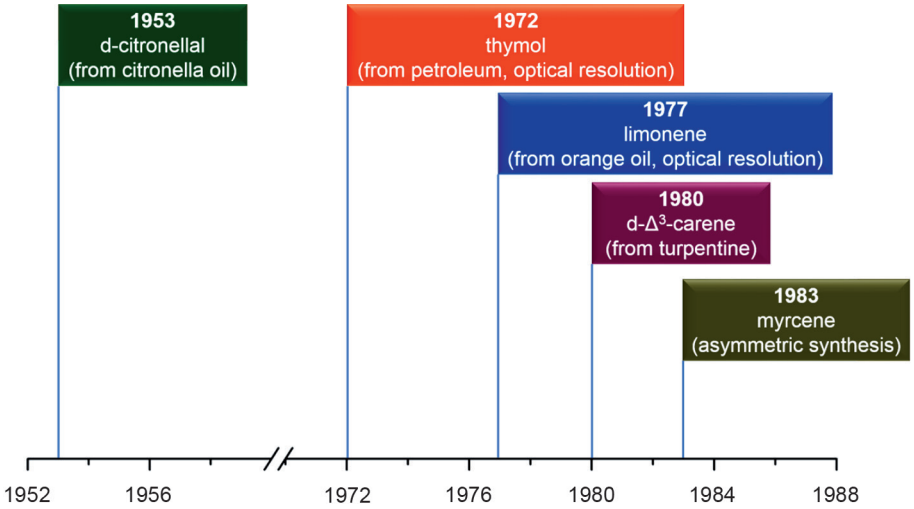

Fig. 40. History of l-menthol production by Takasago [71]

The production volume of l-menthol and its derivatives is estimated at approx. 3,000 tonnes/year [93]. Unlike the l-menthol production method in use by BASF, described earlier, a chiral catalyst is applied in the isomerisation reaction as well. This catalytic system has been developed by a group led by Professor Ryoji Noyori from Nagoya University [94]. It must be noted that for this and other achievements related to chiral systems and hydrogenation processes, he received the 2001 Nobel Prize in chemistry [95]. In general, the system utilised belongs to BINAP rhodium catalysts. Both ligands of this type are shown in Fig. 41.

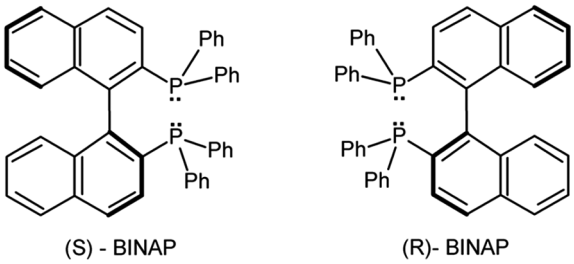

Fig. 41. BINAP ligands (2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene)

Such systems are created through the reaction between 1,1'-binaphthol and $(C_6H_5)_3PBr_2$ (triphenylphosphine dibromide), carried out at a temperature of 320°C [96, 97].

The l-menthol production technology developed by Takasago has multiple stages (the five stages shown in Fig. 30). The first stage is to produce diethylgeranylamine

from myrcene, which is subsequently transformed into (R)-citronellalenamine with the use of a chiral catalyst. The resulting enamine is subjected to hydrolysis to (R)-citronellal. The last two stages are similar to those familiar from the BASF technology, i.e. cyclisation of (R)-citronellal to isopulegol, which is subsequently hydrogenated to l-menthol [98].

As mentioned above, the raw material used by Takasago is myrcene [99]. This compound occurs commonly in nature, although interestingly it is not obtained from plant material. Industrial methods of myrcene production are based on the pyrolysis of β-pinene, which depending on the specific process variant is carried out at temperatures ranging from 500 to 600°C (Fig. 42). After the pyrolysis process, myrcene is separated from the post-reaction mixture with the use of fractional distillation, carried out under reduced pressure and in the presence of polymerisation inhibitors. Such compounds must also be present during storage of this monoterpene hydrocarbon.

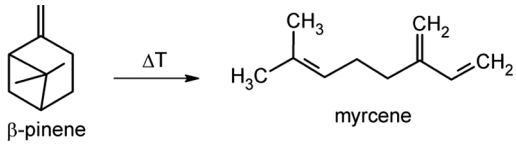

Fig. 42. β-Pinene pyrolysis reaction

β-Pinene belongs to monoterpene hydrocarbons. As a result of its transformation at high temperatures, compounds other than myrcene are also obtained, both from the decomposition of the original pinene, and as reaction products (e.g. limonene and its various dimers). β-Pinene is most commonly obtained from turpentine, where its content is between 10 and 20% [100]. Additionally, α-pinene is subjected to isomerisation to provide the desired amounts of this compound, as it is significantly less expensive than its β equivalent, and its content in turpentine is several times higher. Currently, a cheap source of pinenes is sulfate turpentine, a by-product of the paper industry.

Myrcene is produced on a large scale, with an annual production volume of about 30,000 tonnes. It is not used directly as a fragrance, but serves as a basis for obtaining other valuable aromatic compounds, such as nerol, geraniol, linalool, citronellol, menthol, and many others.

The first stage of the technology developed by Takasago is amination with the use of diethylamine in the presence of a catalyst with alkaline properties, which could be lithiumor naphthyllithium (Fig. 43) [101]. The process is carried out at a temperature of 50°C for 5 hours. The yield of the desired product is approximately 85%, while stereoselectivity in relation to diethylgeranylamine is 95%.

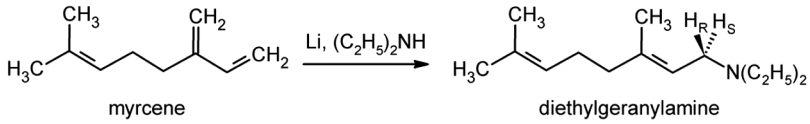

Fig. 43. Production of diethylgeranylamine from myrcene

The diethylgeranylamine is then subjected to enantioselective isomerisation (Fig. 44). This is carried out at a temperature of approx. 80°C in the presence of THF [102]. The process catalyst is the catalytic system mentioned earlier, developed by Professor Noyori's group. They have found that an allyl migration of hydrogen in allylamine occurs if a BINAP catalyst is used (with the ligand structure shown in Fig. 41) [103].

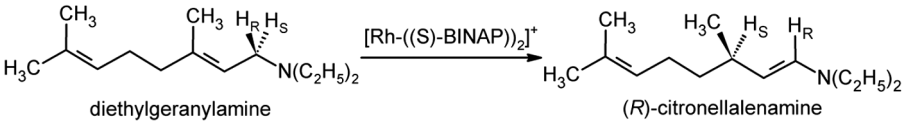

Fig. 44. (R)-citronellalenamine production from diethylgeranylamine with the use of a chiral catalyst

Once isomerisation has finished, the post-reaction mixture (THF, enamine and catalyst) is distilled under reduced pressure (initially 0.5 bar, down to 3 mbar at the end). The solvent and product are separated, and the catalyst is precipitated from the post-distillation residue by adding n-heptane. The mechanism of the isomerisation reaction is shown in Fig. 45. The transformation product is obtained with high enantioselectivity (97.6%), an optically active enamine [(R)-citronellalenamine].

It must be noted that throughout the years, various modifications to the catalyst have occurred, as well as differing methods of carrying out the process of enantioselective isomerisation in order to increase the desired compound yield. Examples of different solutions that have been used and their effects on the TON value (turnover number – the number of moles of the substrate that the catalyst can transform before deactivation) are shown in Table 2.

The first version of Takasago's technology utilised a [Rh-(-)-BINAP(COD)]ClO_4 catalyst, containing a single binaphthalene ligand and a cyclooctadiene one [105].

As can be seen, the difference in TON values between the original catalyst and the current version (with two binaphthalene ligands in its structure) is substantial. Like many other chiral catalysts, materials of this type are very expensive, so they need to be characterised by high efficiency, reflected by the TON value. For the first version of the Takasago catalyst, this was a mere 100. In order to achieve the planned production capacity, and consequently process profitability, of approx. 2,000 tonnes/year, the TON value has to be above 100,000 while maintaining high

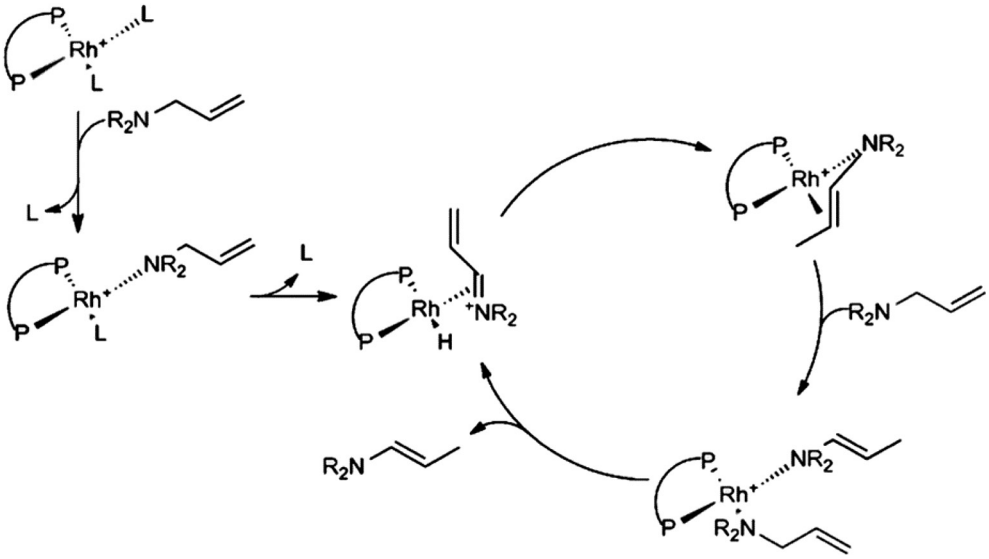

Fig. 45. Diagram of BINAP catalyst action during the menthol synthesis process at Takasago [104]

Table 2

TON values for individual variants of the process [106]

Process modification	TON
[Rh-((S)-BINAP)COD]ClO_4 catalyst Non-purified raw material	100
[Rh-((S)-BINAP)COD]ClO_4 catalyst Raw material purified with the use of Vitride®	1,000
[Rh-((S)-BINAP)COD]ClO_4 catalyst After removing amines (poisons)	8,000
[Rh-((S)-BINAP))$_2$]ClO_4 catalyst	80,000
[Rh-((S)-BINAP))$_2$]ClO_4 catalyst Used again	400,000

selectivity in forming the main reaction product [107]. Such a low value was caused partly by the presence of various catalyst poisons in the reaction stream, and chiral catalytic systems are highly sensitive to the presence of various chemical compounds. The BINAP catalyst is similar. Notable chemical agents include oxygen, moisture, carbon dioxide, quaternary amines, and, particularly, 2-[2-(N,N--diethylamine)ethyl]-6-methylhepta-1,5-diene (present in amounts of approx. 0.07% in commercial allylamine). Consequently, the allylamine is dried and subjected to a reducing agent, a toluene solution of $NaAlH_2(OC_2H_4OCH_3)_2$, otherwise known

as Vitride, with the undesired amine removed through fractional distillation. However, the greatest impact was achieved by replacing the cyclooctadiene ligand with another BINAP fragment. The latest catalytic system $[Rh(S)\text{-}BINAP)_2]ClO_4$ (Fig. 46) is obtained through the reaction of $[Rh(COD)BINAP]ClO_4$ with BINAP in a hydrogen atmosphere. Most importantly, it is thermally stable and additionally it can be reused, after distillation. In the current variant of the process, the ratio of substrate to catalyst is 8,000, while the TON value oscillates around 400,000 (four times the assumed value necessary to achieve process profitability). According to Takasago, for the fifteen years since the commissioning of the technology, 250 kg of the BINAP catalyst (in its different versions) was used to produce 28,700 tonnes of (-)-menthol [108].

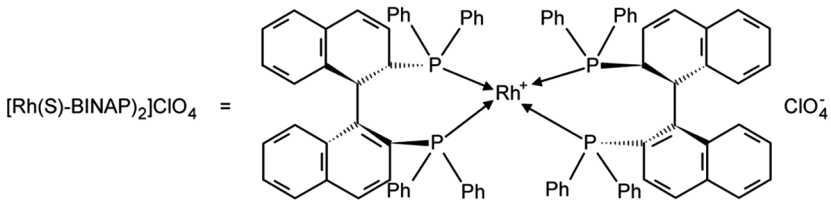

Fig. 46. Structural formula of the chiral catalyst currently utilised by Takasago

During the following stage, (R)-citronellalenamine is subjected to hydrolysis with the use of a catalyst with acidic properties (Fig. 47).

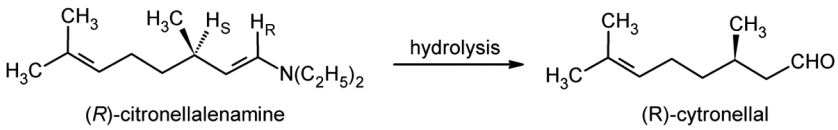

Fig. 47. Hydrolysis of (R)-citronellalenamine

The final two stages, involving the cyclisation of (R)-citronellal to isopulegol (Fig. 48) and hydrogenation of the latter to l-menthol (Fig. 60), are identical to

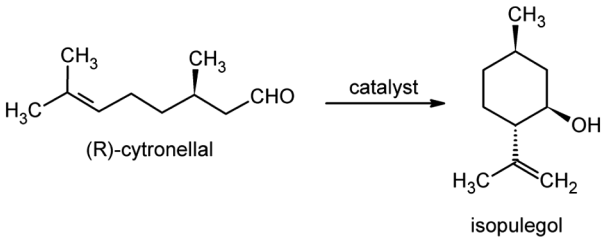

Fig. 48. Reaction of (R)-citronellal cyclisation to isopulegol

the menthol production process used by BASF, described earlier. The cyclisation occurs in the presence of an aluminium catalyst (previously $ZnBr_2$) at a temperature of approx. 110ºC. Isopulegol yield is 98% [109–112].

The final stage is isopulegol hydrogenation to l-menthol (Fig. 49).

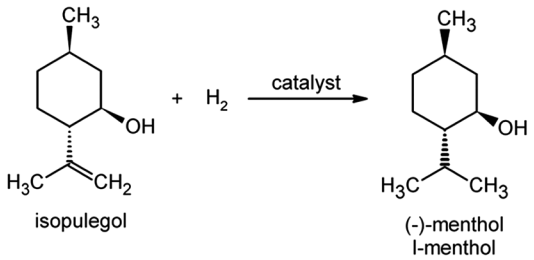

Fig. 49. Isopulegol hydrogenation to l-menthol

The process is carried out at a temperature of 80°C and a hydrogen pressure of 30 bar [113]. The hydrogenation lasts 3 hours and occurs in the presence of a catalyst, in this case Raney nickel.

Symrise (previously Haarmann & Reimer, then part of Bayer) has produced menthol using the same method since 1973. It owns production plants in Holzminden (Germany, which doubles as the company headquarters) and in Byshy Park (USA) [3].

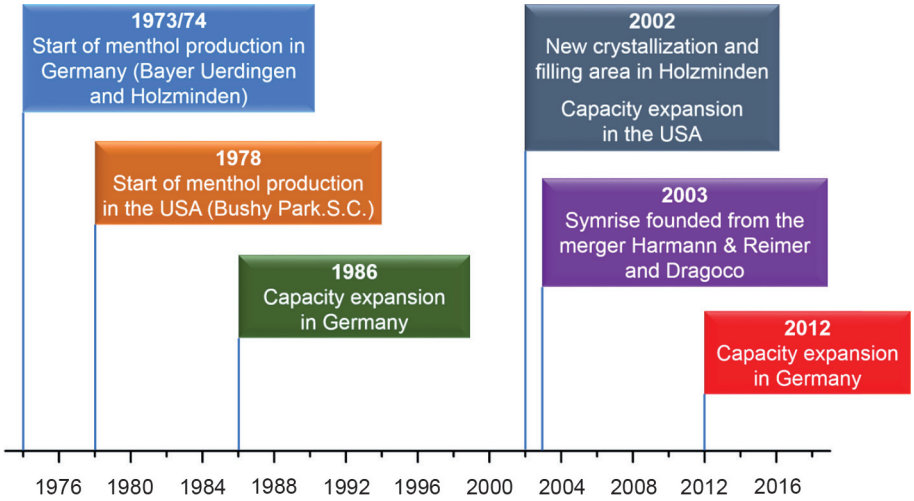

Fig. 50. History of menthol production by Symrise [3]

Production of this fragrance is conducted in close cooperation with another German company, Lanxess (Fig. 51) [114].

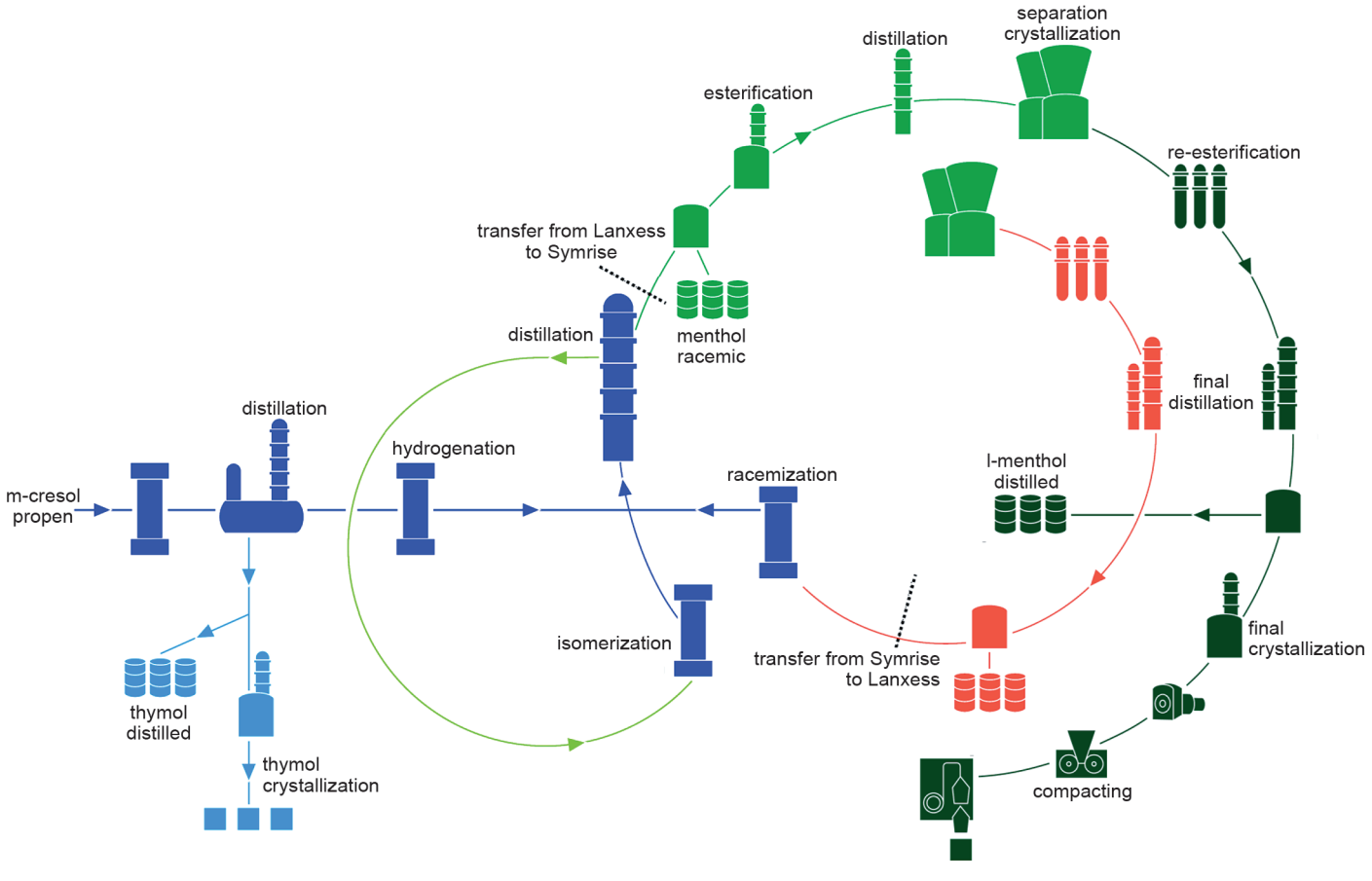

Fig. 51. Diagram of menthol production by Symrise, in cooperation with Lanxess [114]

Lanxess AG was founded in 2004 as a result of Bayer AG detaching a part not related to health protection. The company is based in Cologne. In terms of sales, Lanxess is the fourth largest chemical concern in Germany. It is engaged in the production of polymers, semi-products and specialist chemical agents, rubber, and others.

Both partners have invested several tens of million USD (with Symrise investing about 20 million) in the last few years to double the menthol production capacity [115, 116].

This move was caused by demand for this compound, and by the predictions of Givaudan (a major power in the market of fragrances used in cosmetics and food flavourings) regarding the continued demand for menthol. Symrise produces menthol of a very high purity, so it is suitable not only for the cosmetics but also the food and pharmaceutical industries.

A diagram of menthol production based on solutions employed in Symrise is shown in Fig. 52 [117]. This is a process that, among the three major synthetic menthol production technologies, comprises the highest number of stages (six). Additionally, unlike the other two methods presented earlier, it does not require the use of a catalyst with chiral properties.

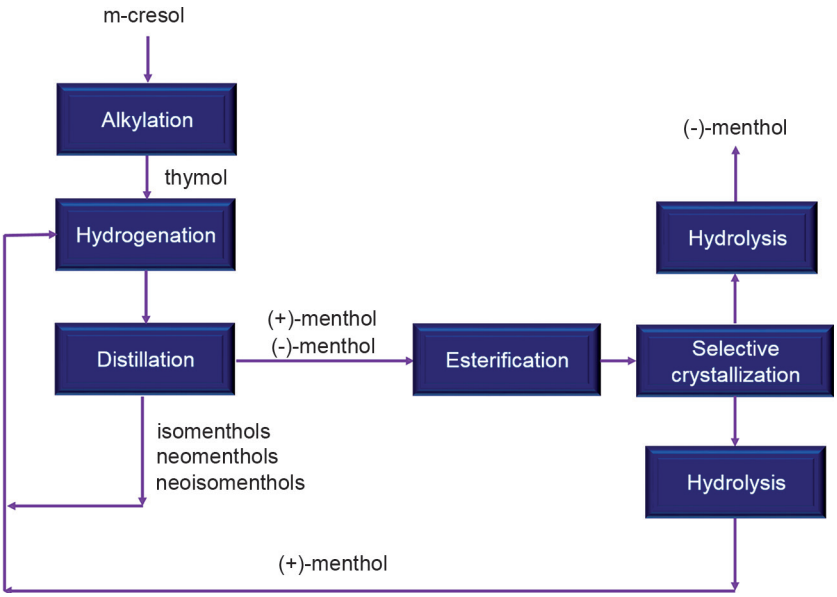

Fig. 52. Diagram of menthol production according to the technology employed by Symrise [117]

The following stages can be identified within the technology introduced by Symrise (Fig. 52):

– thymol production through alkylation of m-cresol,
– hydrogenation of thymol to a mixture of menthol enantiomers,
– distillation intended to separate the menthol fraction (l- and d-menthol),
– transesterification of the menthol fraction with methyl benzoate,
– selective crystallisation (separation of l-menthyl benzoate),
– hydrolysis of l-menthyl benzoate to produce l-menthol.

The substrate used by Symrise for menthol synthesis is m-cresol, supplied to Symrise by Lanxess. The most modern cresol production plant is located in Leverkusen, and was commissioned in November 2013 for a cost estimated at over EUR 20 M.

Compared to the old plant, the new one optimises energy consumption in cresol production. Launching the facility increased the amount of cresols available on the market by about 20%. The characteristic element of the unit is a 46-metre distillation column, used to separate the cresol mixture into individual isomers.

m-Cresol is subjected to alkylation with propylene. Before the input mixture is introduced into the reactor, the raw materials are pre-heated to about 300°C. The pre--heated reagents are introduced at the bottom of the reactor, while thymol is collected at the top. Alkylation occurs at a temperature of 360°C and a pressure of 50 bar in the presence of an aluminium catalyst and a small quantity of cyclohexylamine (several hundred ppm), the addition of which reduces the amount of by-products formed (below 1% in the post-reaction stream) [118]. The primary product of the reaction is thymol (Fig. 53).

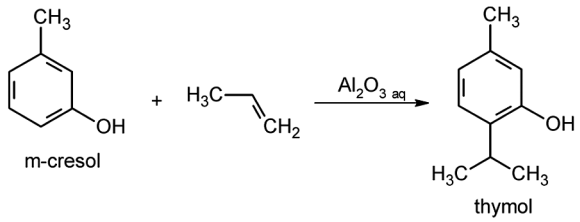

Fig. 53. Production of thymol from m-cresol

A more recent solution is to use a zeolite catalyst (e.g. mordenite) in hydrogen form during alkylation. This enables the thymol production process to be carried out at a pressure of 1–2 bar at a temperature of about 250°C [119].

The next stage is the hydrogenation of thymol, which occurs in the presence of a Co – Mn – Cu catalyst (Co – 49.1%, Mn – 22.9%, Cu – 0.2%) [120].

The process is carried out at a temperature of 180–210ºC and a pressure of 100 bar. The hydrogenation results in an equilibrium mixture comprising eight stereoisomers, but with a preponderance of d- and l-menthol (above 60%, see Table 3).

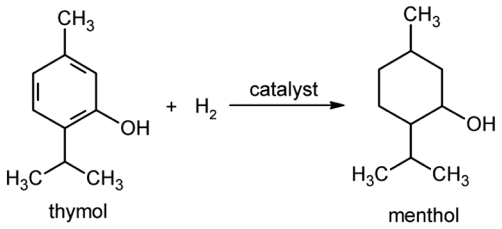

Fig. 54. Hydrogenation of thymol to menthol

Table 3

Products of thymol hydrogenation. Based on [1]

Compound	Content [%]	T_{boil} [°C]
d,l-menthol	62–64	216.5
d,l-neomenthol	18–20	212
d,l-isomenthol	10–12	218
d,l-neoisomenthol	1–2	214.6

As can be seen, the boiling points of the enantiomer pairs differ from one another. Consequently, it is possible to separate them using high-performance distillation columns (about 50 m high).

Undesired isomers are recycled into the hydrogenation process, where the equilibrium composition of all eight menthol isomers is restored.

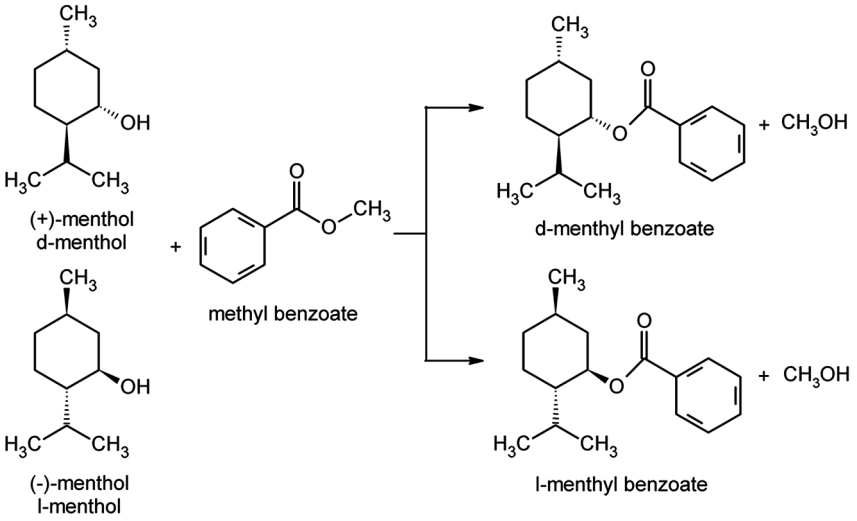

Fig. 55. Transesterification of methyl benzoate

The racemic mixture of l- and d-menthol is subjected to transesterification using methyl benzoate (Fig. 55). The reaction produces a mixture of l- and d-menthyl benzoates, which can be separated using fractional crystallisation.

A diagram of the separation of these esters is shown in Fig. 56 [121]. The saturated solution of (-)-menthol and (+)-menthol is placed in a tank (1), equipped with an effective stirring system and cooling coils. The contents of the tank are removed by two pumps (2, 3) (two separate streams), which move the solution through the filtering system (4, 5) to remove any crystals that are still be present in the saturated solutions. Next, both filtrate streams are transferred to the first heat exchanger, where they are heated to 2°C, because if the solutions are a little below saturation then any crystal nuclei present in the system disappears after passing through the filters.

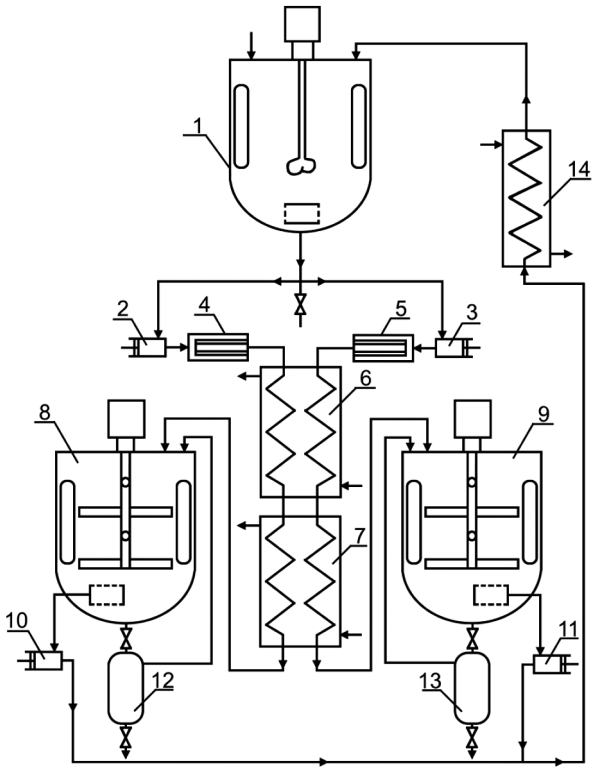

Fig. 56. Diagram of separation of l- and d-menthyl benzoate mixture: 1 – ester tank, 2, 3 – dosing pumps, 4, 5 – filters, 6, 7 – heat exchangers, 8, 9 – ester tanks, 10, 11 – force pumps, 12, 13 – l-menthol benzoate tanks, 14 – heat exchanger [121]

In the next heat exchanger (7), the streams are cooled to about 1°C below saturation and transferred to two 250-litre tanks (8, 9), which are also equipped

with stirring systems and cooling coils. Because the solutions are oversaturated, crystallisation may occur; crystallisation nuclei, e.g. optically pure l-menthol benzoate, are added to accelerate the process. The precipitated crystals of the benzoate ester of l-menthol are separated from their liquid of origin by filtering into tanks (12, 13), while the solution containing d-menthol benzoate is moved by pumps (10, 11) through a heat exchanger (14) to the tank with the initial mixture of both esters. Another option is that shown in Fig. 52, i.e. recycling d-menthol after hydrolysis (Fig. 57) and adding to the mixture in the thymol reduction process.

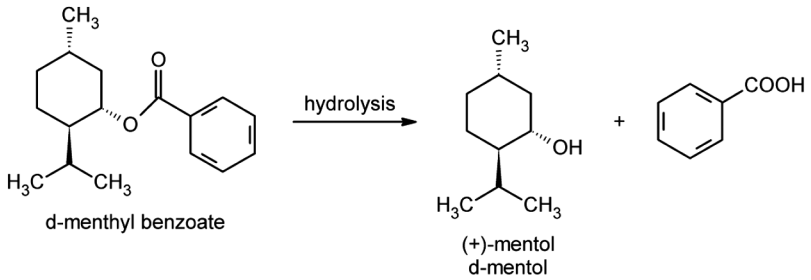

Fig. 57. Hydrolysis of d-menthyl benzoate

The final stage is hydrolysis of the precipitated l-menthyl benzoate in order to produce pure l-menthol (Fig. 58). In both cases, the hydrolysis occurs in the presence of a lipase (Candida rugosa) [122].

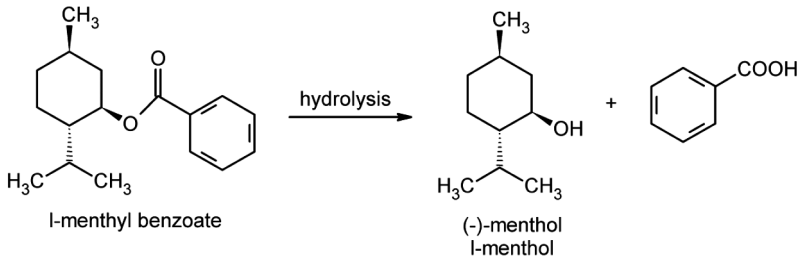

Fig. 58. Hydrolysis of l-menthyl benzoate

When analysing the above technology, one very important conclusion can be drawn: Specifically, it is possible to recycle practically any of the menthol isomers into the hydrogenation process, but whether it is done depends primarily on whether it is economical. Note that no operation or process related to recycling individual compounds is cheap.

5.3. Geraniol

Geraniol (Fig. 59), or trans-3,7-dimethylocta-2,6-dien-1-ol, belongs to the group of monoterpene alcohols. It has a characteristic scent similar to geranium, where its presence was first discovered, and hence its name. The scent remains detectable for over 24 hours. It is present in many essential oils (about 250), together with another isomeric compound, nerol [19]. The isomer ratio (geraniol to nerol) is 60:40. This ratio is maintained in synthetic geraniol production as well. It can be found in rose and lemon oils (where it is one of the main components), lavender and geranium oils (in small quantities), as well as many spice plants (nutmeg), vegetables (carrot, coriander), and fruit (bergamot orange, orange, blueberries, blackberries) [1]. Pure geraniol, originating both from synthesis and from natural materials (completely devoid of nerol or only containing small amounts) can be obtained using fractional distillation (Fig. 60). Geraniol has anti-oxidative properties. It is also one of the better known allergens in cosmetics. However, its sensitising effect is weak, meaning it can be used in greater quantities (even up to 50%) in products than other allergens.

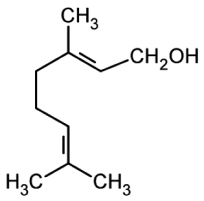

Fig. 59. Structural formula of geraniol

Geraniol is a compound highly popular as a component of various flower scent compositions (it imitates rose scent well, and is an inexpensive replacement). It finds use in personal hygiene products, soaps, detergents, and in perfume products (top note). Moreover, in quantities from 1 to 10 ppm, it is also used in fruit flavourings, e.g. peach, raspberry, grapefruit, apple, plum, blueberry, orange, and pineapple [123]. Due to its common use, about 7,000 tonnes/year is produced, by synthetic methods and by obtaining it from plant material (Fig. 61).

Producers of this compound include: BASF (Germany), Takasago (Japan), IFF, Penta International, Renessenz (both from the USA), and Robertet (France) [124]. The numerous group of producers means that geraniol can be found under many trade names, such as Geraniol (this name applies both to the pure isomer and to an isomer mixture, therefore a number specifying the percentage content of the main compound is given), Gerallol, Meranol, Reuniol, Rhodeanol, Rhodinol, Roseneone and Roseol.

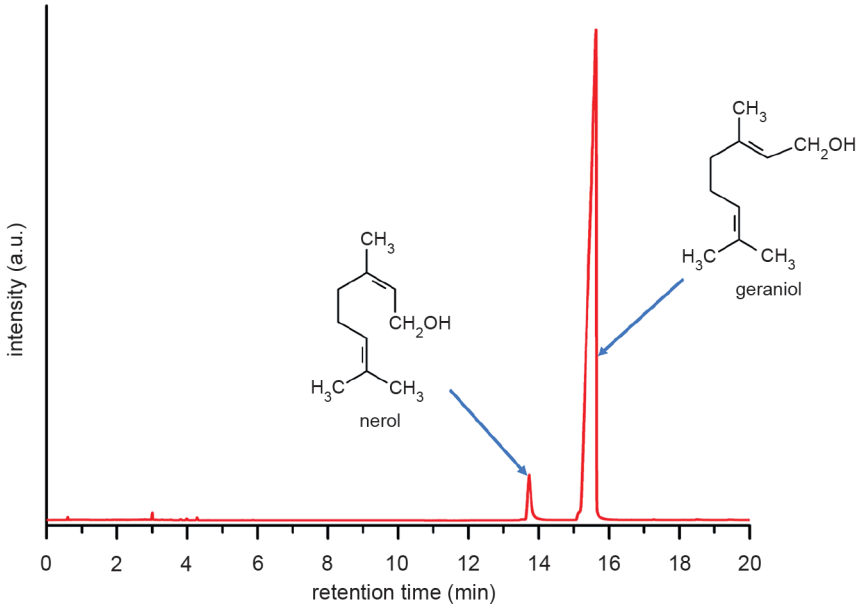

Fig. 60. Sample chromatogram of geraniol

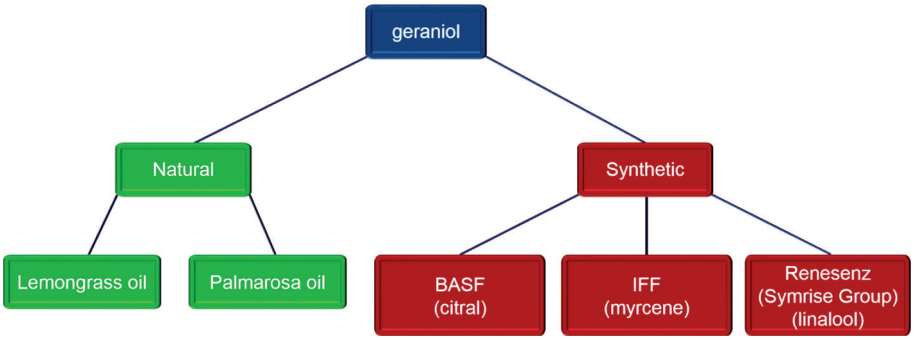

Fig. 61. Selected industrial methods of geraniol production

Geraniol is obtained by BASF from citral. Like menthol, it is produced as part of the Verbund strategy implemented by BASF.

As previously mentioned, the raw material is citral, produced in large quantities by BASF in Ludwigshafen. It is subjected to hydrogenation (Fig. 62), carried out in the presence of a Ru-Fe/C catalyst (5% ruthenium and 1% iron on active carbon) [125, 126].

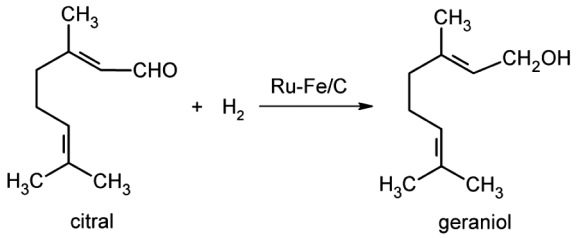

Fig. 62. Hydrogenation of citral to geraniol

The process is carried out in a continuous manner (Fig. 63) in the liquid phase, with the catalyst system in a suspension composed of citral (70% m/m), methanol (27% m/m), and trimethylamine (3% m/m). The suspension is transferred together with hydrogen to a mixing nozzle (1), then introduced into a hydrogenation reactor (2). This is a bubble column with appropriately designed partitions. The process is carried out at a temperature of 80°C and a hydrogen pressure

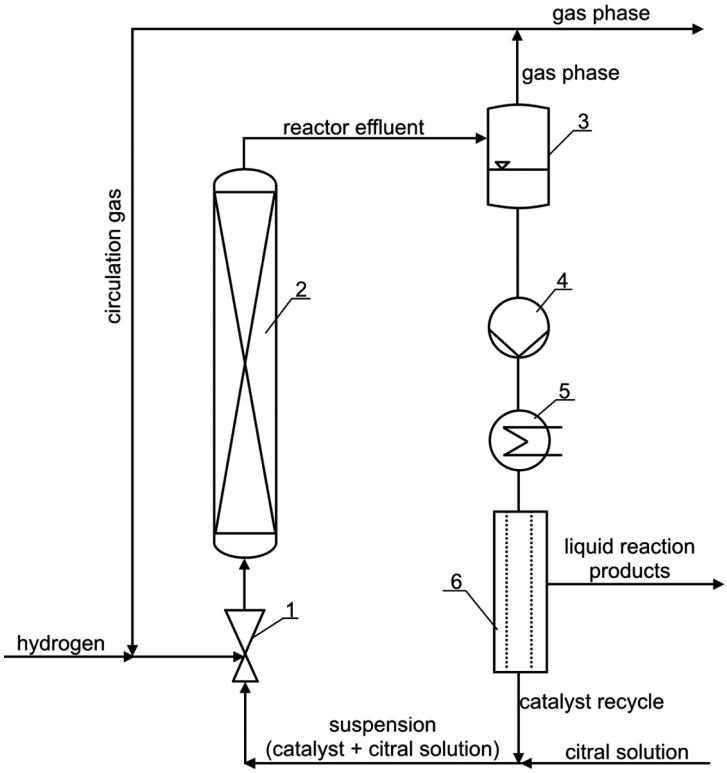

Fig. 63. Diagram of citral to geraniol hydrogenation unit: 1 – mixing nozzle, 2 – reactor with packing, 3 – separator, 4 – pump, 5 – heat exchanger, 6 – cross-flow filter [127]

of 22 bar. After leaving the reactor, the post-reaction mixture is transferred to a separator (3) to separate the gaseous phase from the suspension with the catalytic system. To prevent undesired reactions, the gaseous phase is only partially recycled into the reactor, the rest being removed from the system. The suspension of liquid substances and catalyst is moved by a pump (4) to a heat exchanger (5) to be heated to the desired temperature, and is subsequently filtered using cross-flow filters (6). Once separated, the catalyst is added to a fresh batch of citral solution and in this way is recycled into the reaction [127].

As a result of executing the hydrogenation process in this manner, 90% of the citral undergoes the reaction, mainly transforming into geraniol and citral, produced with a selectivity in excess of 94%. Additionally, a small amount of citronellol is produced (selectivity a little over 1%). As mentioned earlier, to obtain pure geraniol (without nerol), the resulting mixture of isomers undergoes fractional distillation.

In another variant of the hydrogenation process, a higher hydrogen pressure (30 bar) is applied. This enables a higher efficiency of citral conversion (96%), although the selectivity of producing the geranial and nerol mixture drops to 92%, while the amount of produced citronellol increases [127].

Another important producer of geraniol is IFF. In 1997, a plant producing this terpene alcohol was commissioned in Jacksonville, Florida. Due to the growing demand for geraniol in 2000, after upgrading the plant for USD 10 million, IFF increased the facility's production capacity by 250%, to 8,000 tonnes/year. Throughout the years, it has produced geraniol in unchanged quantities and in only one location (Jacksonville).

The raw material in the geraniol technology developed by IFF is myrcene, obtained in a similar manner to the Takasago menthol synthesis technology, from β-pinene pyrolysis (Fig. 64). Both α-pinene and β-pinene are obtained through fractional distillation of turpentine. The former isomer's content in the raw material is almost 3 times higher than that of the latter compound. Additionally, β-pinene is a more versatile substance in terms of potential use, and consequently has a higher commercial value. α-Pinene is most commonly transformed into β-pinene through isomerisation in the presence of noble metal-based catalysts. Thanks to such catalytic systems, β isomer is produced with high selectivity.

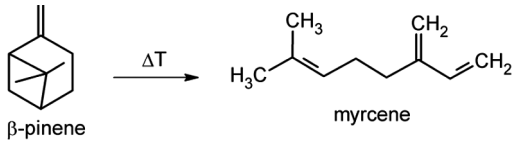

Fig. 64. β-Pinene pyrolysis reaction

It is worth noting that since the beginning of the 1980s, geraniol has been produced from myrcene by another American company, Renessenz, which currently belongs to Symrise [128].

During the first stage, β-pinene is subjected to pyrolysis carried out at a temperature of 555–600°C, with a very short duration spent in the reactor. Myrcene is produced with 90% efficiency. The other compounds obtained in the process are pseudomyrcene and 1,2-dimethyl-3-isopropenylcyclopentane. Pure myrcene is separated by fractional distillation.

During the next stage, myrcene reacts with hydrogen chloride (hydrochlorination) in the presence of CuCl as a catalyst, and a small amount of a quaternary ammonium salt. As a result of the reaction, geranyl and neryl chlorides are formed as the main products, as well as smaller quantities of linalyl chloride (Fig. 65).

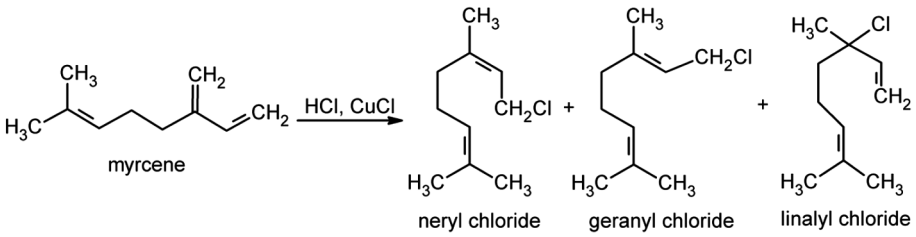

Fig. 65. Hydrochlorination of myrcene

Using copper (II) chloride as the catalytic system here would lead to a reverse situation, where linalyl acetate would become the dominant reaction product. The process flow is shown in Fig. 66.

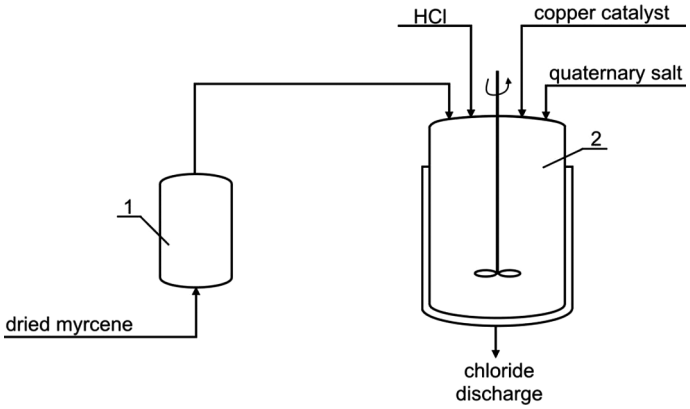

Fig. 66. Diagram of myrcene hydrochlorination: 1 – cooled tank, 2 – hydrochlorination reactor [129]

Purified and dried myrcene, which prevents its polymerisation, is stored in a cooled tank (1) at a temperature of approx. 10°C, because dimerisation occurs at higher temperatures. From the storage tank, it is then transferred to a hydrochlorination reaction (2), where gaseous hydrogen chloride, a catalyst, and a quaternary ammonium salt, e.g. methyltrioctylammonium chloride, are introduced. The hydrochlorination process is carried out at a temperature of 10°C for about 8 hours [129].

After removing the catalyst, the raw mixture of chlorides is transformed into geranyl, neryl, and linalyl acetates through a reaction with sodium acetate in the presence of a phase transfer catalyst (PTC) or triethylamine (Fig. 67).

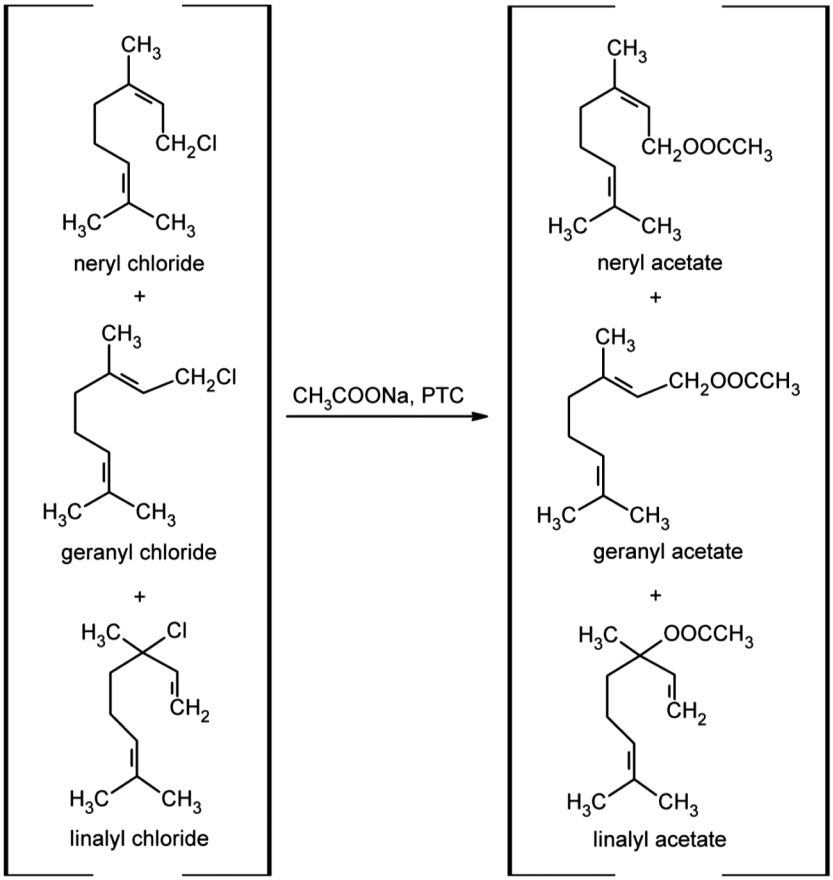

Fig. 67. Esterification of neryl, geranyl, and linalyl chlorides

The process produces mainly geranyl acetate (50–55%), neryl acetate (40–50%), and small amounts of linalyl acetate.

The resulting acetates are subjected to saponification to their corresponding terpene alcohols, while the remaining sodium acetate is recycled into the process (Fig. 68). The mixture of geraniol, nerol, and linalool is separated by fractional distillation to obtain the first of these compounds in particular (with 98% purity) [130].

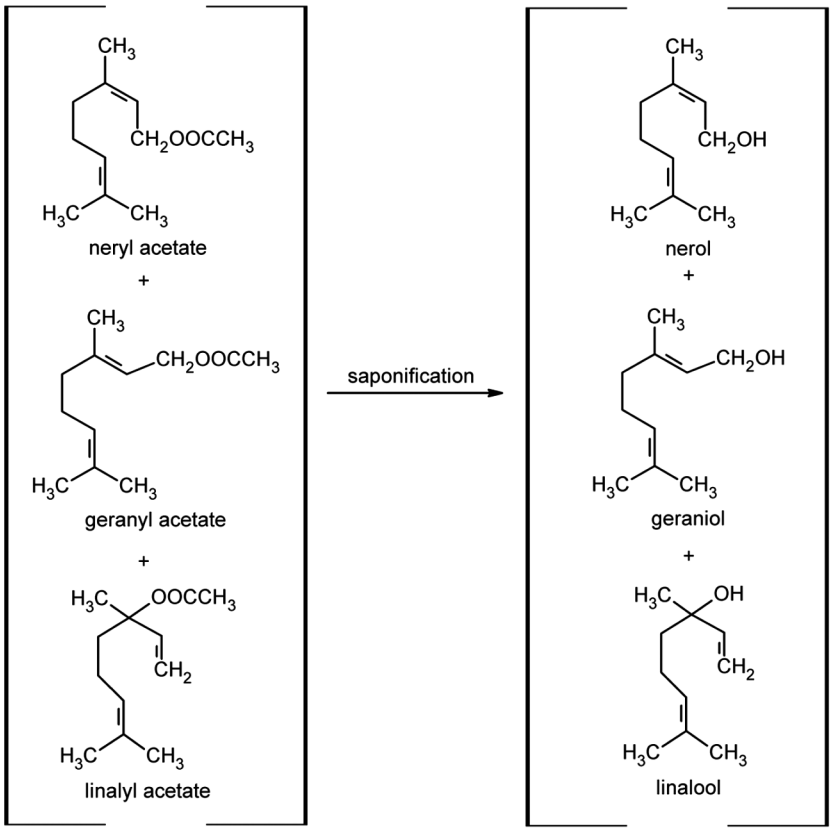

Fig. 68. Hydrolysis of neryl, geranyl, and linalyl chlorides

In 1982, SCM Corporation (now Renessenz, part of Symrise) announced the commissioning of a geraniol production unit that utilised α-pinene, which occurs in larger quantities than its β equivalent. Consequently, the large amounts of turpentine required from which to isolate the β-pinene became unnecessary. In this way, even during the raw material selection stage, the technology relies on a less expensive substrate [131].

The plants that produce geraniol and the linalool necessary for its production are located in Brunswick (Georgia, USA). The raw material (α-pinene), on the other

hand, is obtained in Jacksonville (Florida, USA). The Jacksonville plant houses units for the fractional distillation of turpentine. Aside from the discussed terpene hydrocarbon, its β form is produced as well. Both α- and β-pinene are used to produce various fragrance compounds, e.g. antelol, synthetic pine oil, and many others.

During the first stage, another terpene alcohol is produced: linalool. The method of linalool production developed by Renessenz is discussed in detail in Section 5.4. Geraniol, on the other hand, is produced by obtaining a linalyl ester through transesterification and subsequently isomerising it to the esters of geraniol and nerol [132]. During the first stage, diisobutyllinalyl borate is produced as a result of transesterification between triisobutyl borate and linalool (Fig. 69).

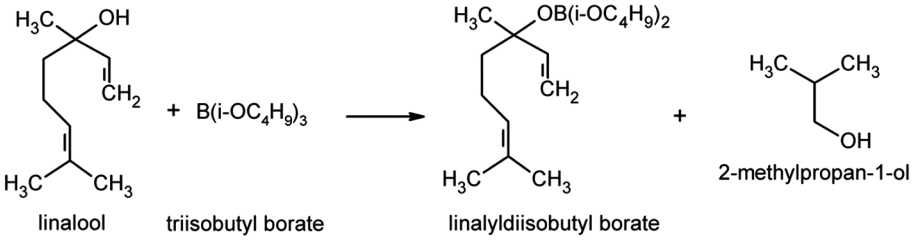

Fig. 69. Transesterification between linalool and triisobutyl borate

Under the effect of a vanadium catalyst (e.g. trihexyl orthovanadate), the borate ester of linalyl is isomerised to diisobylgeranyl and diisobutylneryl borates, which

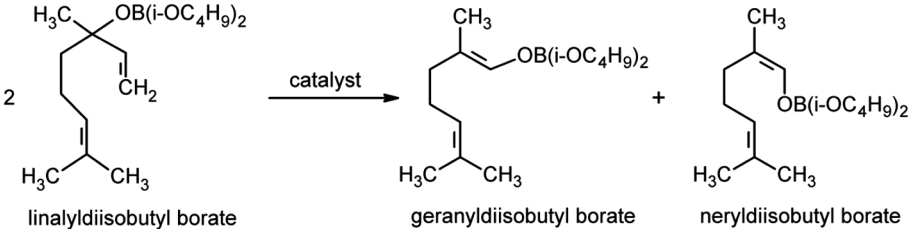

Fig. 70. Isomerisation of linalyldiisobutyl borate

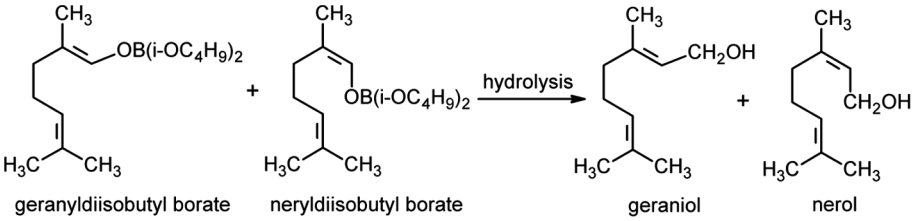

Fig. 71. Hydrolysis of geranyldiisobutyl and neryldiisobutyl borates

are then subjected to hydrolysis. The process produces a mixture of geraniol and nerol, which is subjected to purification and isolation of the former of these terpene alcohols.

5.4. Linalool

Linalool (Fig. 72) is one of the most interesting terpene alcohols occurring in nature. It has a pleasant, flowery scent with a lemony and slightly terpene note. The scent remains detectable for about 12 hours. A typical chromatogram of linalool is shown in Fig. 73.

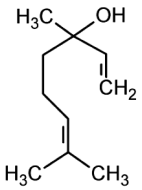

Fig. 72. Structural formula of linalool

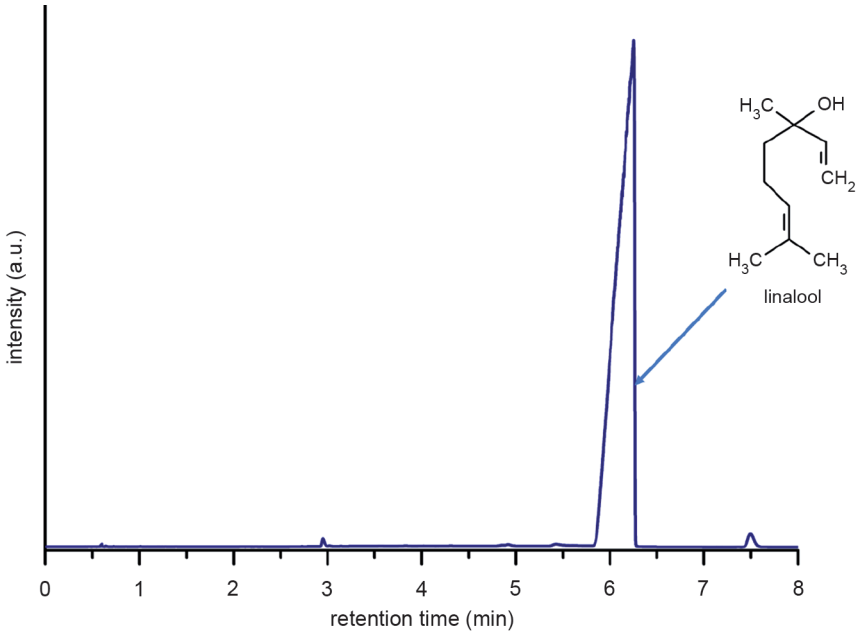

Fig. 73. Sample chromatogram for linalool

In plant material, it can be found both non-combined and very frequently in the form of esters (in more than two hundred different plants). It is a component of: oil obtained from Brazilian rosewood (making up even 90% of the composition) and oil obtained from coriander (70%), geranium, bergamot orange, and ylang--ylang (also known as cananga tree). Small quantities can also be found in lemon oil and other flower oils.

The interest in this compound is very high. Due to its structure, it can be a substrate in the synthesis of other terpene compounds, among them terpineol, geraniol and citral. It serves the same role in nature, as a compound participating in the biosynthesis of other terpenoids. Furthermore, it can be used in the production of citronellol, vitamin A, and other sesquiterpenes [133].

Pure linalool is used in large amounts in soaps and detergents. This stems from its high stability in many products, and from the fact that it is not susceptible to discolouration. Additionally, the mild character and freshness of its scent are important for fragrance compositions based on synthetic compounds, as it confers a sense of naturality. For this reason, linalool is commonly employed in flower fragrances, but also in non-flower perfumery products.

From among the linalool esters, linalyl acetate has the greatest importance. It is a component of many essential oils, among which oil obtained from bergamot orange and petigrain are notable. Similarly to the pure alcohol, it is used in large quantities in soaps and detergents, including high alkalinity products.

Linalool is produced by many methods. Both chemical compounds from crude oil and natural gas processing, and those isolate from natural materials are used (Fig. 74). Pure linalool can be obtained through fractional distillation of oils from Brazilian rosewood or coriander. Between these two most popular materials of natural origin, Brazilian rosewood oil is the most important.

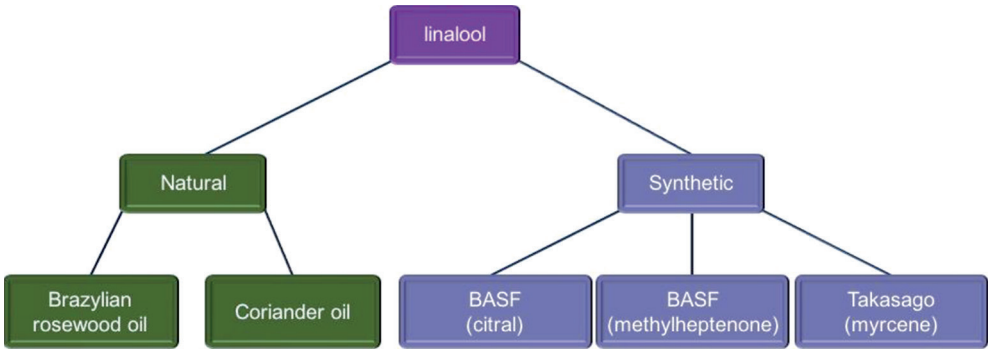

Fig. 74. Selected industrial methods of linalool production

Producers of linalool (natural and synthetic) include: BASF (Germany), Renessenz, Prinova (USA), DSM Nutritional (Denmark) and Takasago (Japan) [134].

It is one of the older linalool production technologies. BASF produces linalool using methylheptenone (specifically, 6-methylhept-5-en-2-one). First, however, an isomer of this compound is obtained – specifically, 6-methylhept-6-en-2-one, through a single-stage process. The raw materials are isobutene, formaldehyde and acetone (Fig. 75). The process is carried out at a temperature of 250°C and a pressure of approx. 150 bar [34].

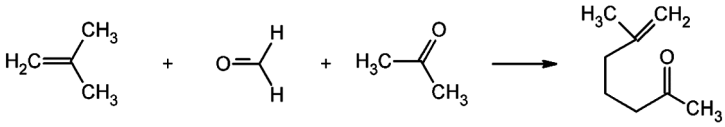

Fig. 75. Methylheptenone production reaction

Under the above conditions of pressure and temperature, the three substances utilised can react not only to form methylheptenone, but also between each other, producing various other chemical compounds. These include both low-mass compounds and multi-molecule formations. For example, formaldehyde undergoes the Cannizzaro reaction (Fig. 76), while isobutene molecules react to form dimethylhexene and trimethylcyclopentane (Fig. 77).

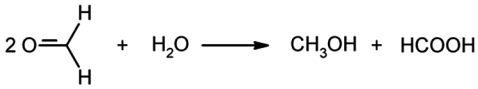

Fig. 76. Cannizzaro reaction

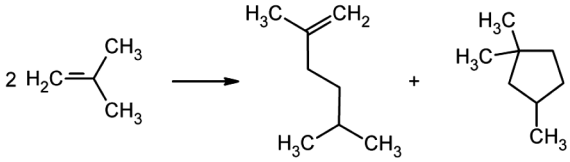

Fig. 77. Isobutene dimerisation

The other reactions are: formation of mesityl oxide (from acetone, Fig. 78), 3-methylbut-3-en-1-ol, and ultimately, as a result of its dehydration, isoprene (from isobutene and formaldehyde, Fig. 79), or the formation of ketobutanol, which transforms easily into methylvinylketone (through the reaction of acetone and formaldehyde, Fig. 80).

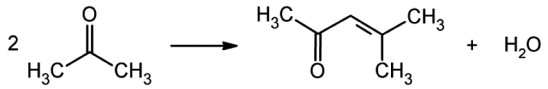

Fig. 78. Condensation of acetone

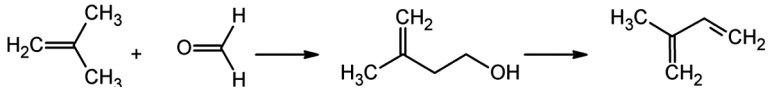

Fig. 79. Production of isoprene from isobutene and methanal

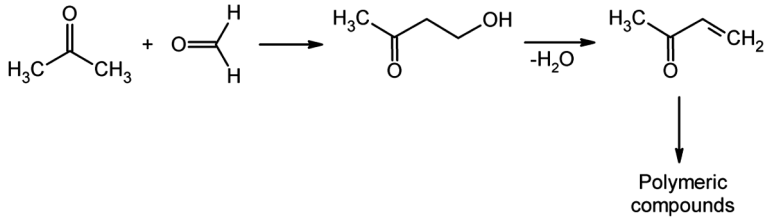

Fig. 80. Production of polymeric compounds from acetone and formaldehyde via an intermediate methylvinylketone stage

For this reason, precise control of the methylheptenone production process is necessary, to limit the occurrence of non-beneficial reactions as much as possible. The methylheptenone production process is shown in Fig. 81.

Isobutene, acetone, and an aqueous solution of formaldehyde are separately pre-heated (2) to the desired temperature, then transferred to a high-pressure reactor (1). After leaving the reaction space, isobutene and acetone are distilled from the product and the unreacted substrate stream in pressure columns (4), to be recycled into the process. The remaining components of the post-reaction mixture are separated by distillation carried out in multiple columns (4). By-products with low boiling points are isolated first, then others with higher boiling points. Finally, pure 6-methylhept-6-en-2-one is obtained.

During the next stage, 6-methylhept-6-en-2-one is subjected to isomerisation to 6-methylhept-5-en-2-one (Fig. 82).

The process is carried out for 4 hours at a temperature of 150°C and atmospheric pressure. The isomerisation is catalysed by palladium (II) chloride [135]. As in the previous case, the post-reaction mixture is transferred to a distillation system to isolate pure 6-methylhept-5-en-2-one.

The direct precursor in linalool production is dehydrolinalool. One method used for its production (proposed by DSM) is shown in Section 5.1, for citral production based on this compound. The technology proposed by BASF is also based on the 6-methylhept-5-en-2-one reaction with acetylene (Fig. 83).

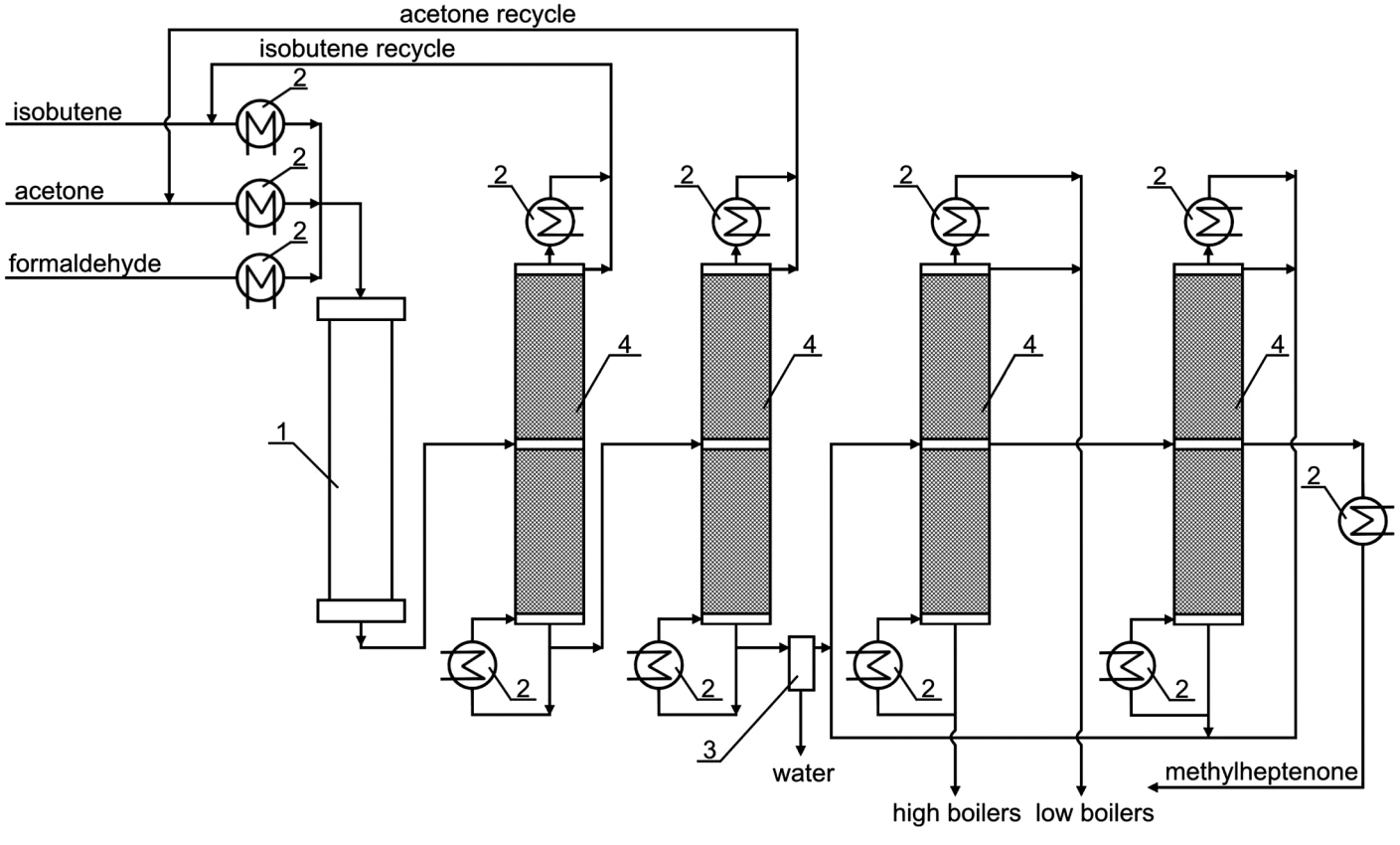

Fig. 81. Methylheptenone production reaction diagram 1 – high–pressure reactor, 2 – heat exchangers, 3 – distillation columns [34]

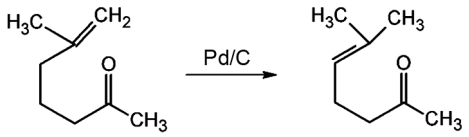

Fig. 82. 6-methylhept-5-en-2-one production reaction

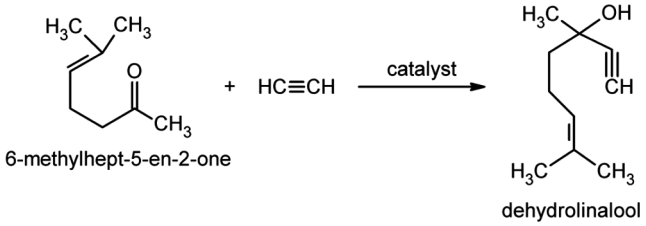

Fig. 83. Dehydrolinalool production reaction

As with dehydrolinalool production by DSM (Section 5.1), BASF also utilises ion exchange resin with alkaline properties and an ammonia solution of acetylene as a catalyst [136]. The method of preparing the catalyst for operation is identical as well, i.e. first it is washed with sodium hydroxide, then water is added to restore neutral pH, which is followed by methanol to reduce the water residue level to below 0.1% m/m. The dehydrolinalool production process is carried out in a pipe reactor at a pressure of approx. 25 bar and a temperature of 40°C. The post-reaction mixture is subjected to distillation. The acetone isolated in its course is recycled into the process. After a time, the catalyst becomes deactivated. To restore its original activity, actions similar to its first use are performed.

The final stage in the linalool production technology employed by BASF is dehydrolinalool hydrogenation (Fig. 84), carried out in the presence of a Lindlar catalyst (palladiumon a substrate partially deactivated with lead).

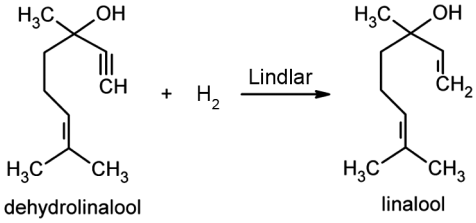

Fig. 84. Linalool production reaction

The process has two stages. The first reactor, heated to 80°C, is introduced with dehydrolinalool and hydrogen at a pressure of approx. 1.2 bar, then the mixture containing about 15% of unreacted raw materials is transferred to another reaction

system. During the second stage, also at a temperature of 80°C and a partial hydrogen pressure of 0.1 bar (hydrogen is partially replaced with an inert gas), the remaining dehydrolinalool is hydrogenated. The use of this solution enables the initial raw material to react completely. Linalool production selectivity in the hydrogenation process can be as high as 99.5% [137, 138].

An alternative method of linalool production, proposed by BASF, is the isomerisation of a geraniol and nerol mixture [139]. This solution can utilise pure geraniol [140], its mixture with nerol [141], and, most importantly, a fraction taken directly from citral hydrogenation to these alcohols, which aside from these substances can also contain citronellol (Section 5.3) [142]. Regardless of the raw material used for isomerisation, transformation into linalool occurs in the presence of a tungsten catalyst. The process is carried out in a continuous manner, without a solvent, in a homogeneous system at a temperature of 160ºC under reduced pressure (about 130 mbar), in a reactor resembling a distillation column. The geraniol/nerol mixture is introduced at the bottom and subsequently undergoes isomerisation to linalool. The resulting product is continuously distilled from the reaction mixture, if its content in the liquid phase is at least 8%. Concurrently, the raw material is fed to replace the removed linalool at an identical rate. The citronellol and other by--products generated in the reaction remain in the liquid phase and are not removed. This distillation residue can be used as a raw material e.g. in the production of tetrahydrogeraniol (Section 5.9).

The linalool production process employed by Renessenz (formerly SCM Corporation) is a part of a larger technology that enables production of other useful aroma compounds based on a substance of natural origin, α-pinene [143]. Renessenz has a history of over a hundred years, and together with Prinova belongs to Prinova Holdings. This Holding has been acquired by Symrise for USD 397 million from a Canadian company, TorQuest Partners. Renessenz is a leader in the production of fragrances for the cosmetics and food industries, obtained using terpenes. Its production facilities are Jacksonville Plant, located in Jacksonville (Florida), and Colonels Island Plant in Brunswick (Georgia). The terpene compounds utilised in the production process are obtained from natural materials.

The linalool production process employed by Renessenz is a part of a larger technology that enables the production of other useful aroma compounds based on a substance of natural origin, α-pinene [143].

Among these compounds, Ebanol® and geraniol are the most notable. The precursor used to produce the above-mentioned terpene alcohol is linalool.

The linalool production technology is multi-staged. During the first stage, α-pinene, isolated from sulfate turpentine, is subjected to hydrogenation (Fig. 85).

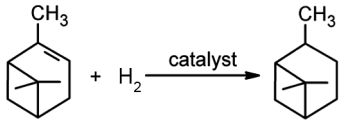

Fig. 85. Hydrogenation of α-pinene to pinane

The hydrogenation is carried out at a temperature of approx. 50°C and a pressure of 150 bar in the presence of a nickel catalyst (in a newer version, a ruthenium one) [144].

A typical diagram of pinene hydrogenation to pinane is shown in Fig. 86. Hydrogen from a storage tank (1) is transferred by a control valve (4) to a mixer (5), where α-pinene containing less than 5 ppm of sulfur compound impurities (2) is delivered using a pump (3). The mixture formed flows through a reactor (7), where the catalyst is located. The temperature within the reaction space is controlled by two heat exchangers placed upstream (6) and downstream (8) of the reactor. The post-

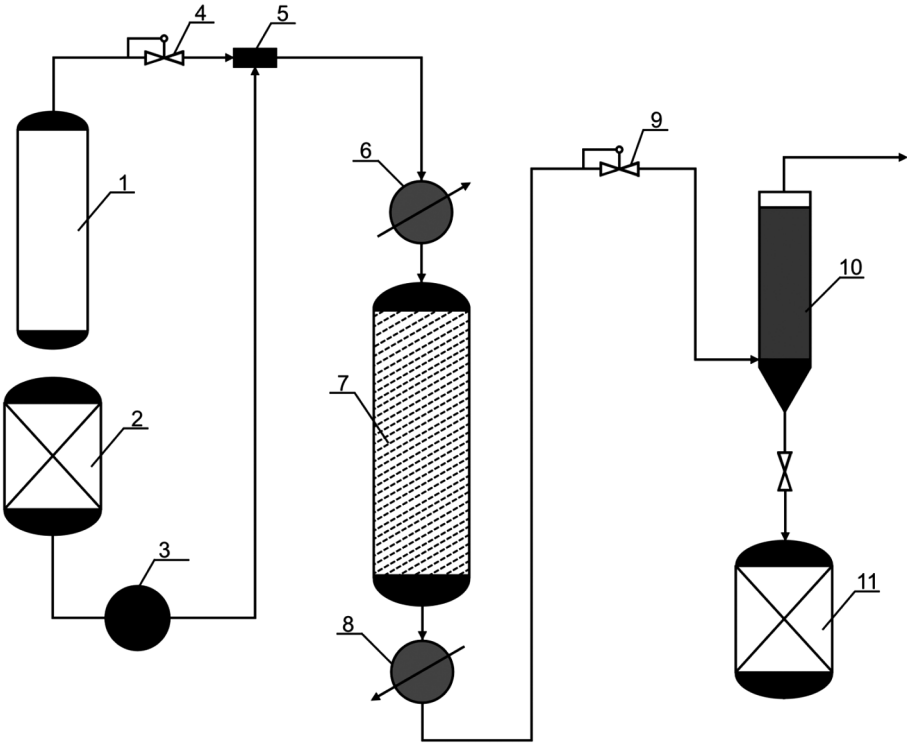

Fig. 86. Diagram of α-pinene hydrogenation: 1 – hydrogen tank, 2 – α–pinene tank, 3 – pump, 4, 9 – control valves, 5 – mixer, 6, 8 – heat exchangers, 10 – separator, 11 – pinane tank [145]

-reaction mixture is decompressed to atmospheric pressure (9) and transferred to a separator (10), which separates the gaseous phase (recycled into the process if needed) from the liquid phase, which contains the main reaction product (cis-pinane), as well as small amounts of unreacted α-pinene and a by-product generated during the hydrogenation (trans-pinane), which are stored in a tank (11). The α-pinene conversion rate is 99%, while cis-pinane is produced at a 99% selectivity.

During the next stage, the pinane mixture (mainly cis and small amounts of trans) is oxidised to hydroxides (Fig. 87). The reaction occurs at a temperature of 70°C, and is catalysed with a cobalt catalyst. Aside from these two compounds, large quantities of oxidation by-products are also generated. 2-pinane hydroxide is isolated from the post-reaction mixture [146].

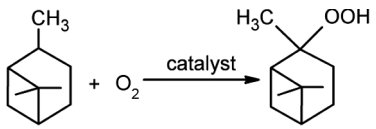

Fig. 87. Pinane oxidation

This hydroxide is decomposed during a reduction process (Fig. 88), carried out at 50°C in the presence of a palladium catalyst on a substrate (Pd/C) [147].

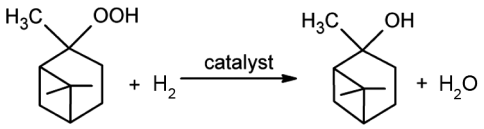

Fig. 88. Pinane hydroxide reduction

The decomposition reaction produces pinan-2-ol, which during the last stage is transferred to a pyrolysis process (Fig. 89), where the primary product is linalool.

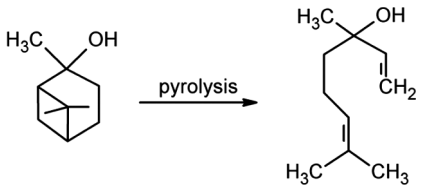

Fig. 89. Linalool production reaction

Depending on the variant, the pyrolysis process is carried out at temperatures ranging from 450 to 600°C. The temperature and geometry of the reactor affect the types of by-product generated (e.g. cyclopentanols, also called plinols) [146].

The total efficiency of linalool production from α-pinene is approx. 30% (remember the broad range of undesired compounds generated during each stage, starting with pinane mixture oxidation).

5.5. Citronellal

Citronellal, systematic name 3,7-dimethyl-6-octenal (Fig. 90). Occurs in two isomeric forms as (R)-citronellal and (S)-citronellal. It is the main component: citronellol oil (Cymbopogon nardus, 40–50%), lemon eucalyptus oil (Eucalyptus citriodora, approx. 85%), and lemon balm (Melissa officinalis, approx. 35%), from which it is obtained by steam distillation, or through extraction methods [148]. The presence if citronellal has been confirmed in over 50 other essential oils, but it can also be found in tomatoes and cardamom. This compound also has insect--discouraging properties, being particularly effective against mosquitoes (it can be used in producing various repellents), and has anti-fungal properties [149].

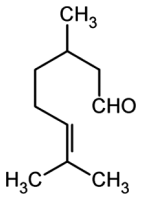

Fig. 90. Structural formula of citronellal

Citronella, whose chromatogram is shown in Fig. 91, has an intense citrus scent similar to citral, although less sweet or fruity.

The citronellal scent lasts for more than 48 hours, which is longer than citral. It finds uses as an ingredient of fragrance compositions, mainly citrus scents [20]. Synthetic citronellal is in no practical way inferior to its natural equivalent, such as that obtained from citronella oil, and may therefore serve as its replacement. The recommended citronellal content in fragrance concentrates ranges from 1 to 3%.

The use of citronellal in food products is rather negligible (below 10 ppm in a product), chiefly stemming from the substance's instability.

Citronellal is also the starting compound used in various technologies to produce other aroma compounds, including hydroxycitronellal, dimethyloctanal, geranonitrile and citronellylnitrile.

At present, both natural and synthetic citronellal are available commercially (Fig. 92). Both pure (R)-citronellal and the isometric mixture (R+S) are produced. Producers and distributors of this compound include BASF (Germany), Robertet

(France), Takasago (Japan), as well as Vigon International (USA) and Penta International (USA) [150].

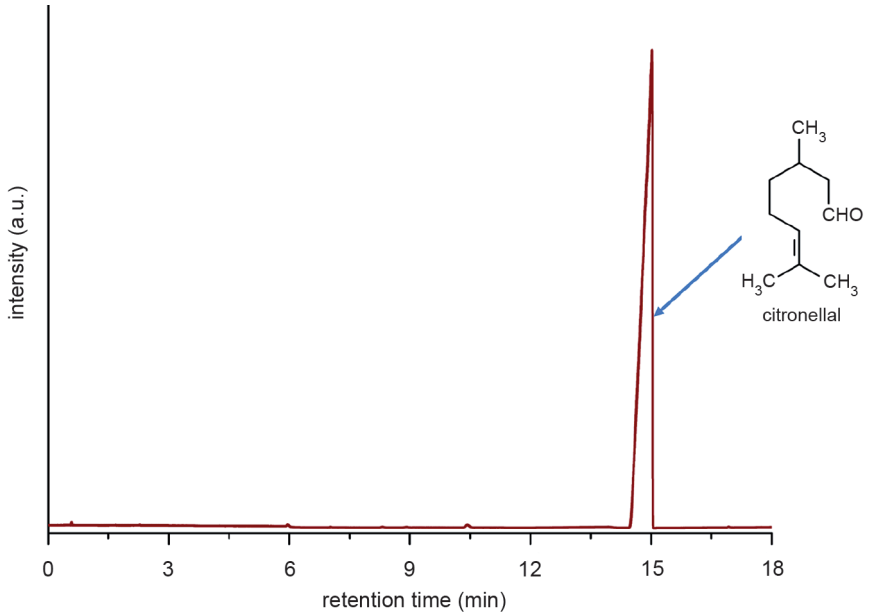

Fig. 91. Sample chromatogram of citronellal

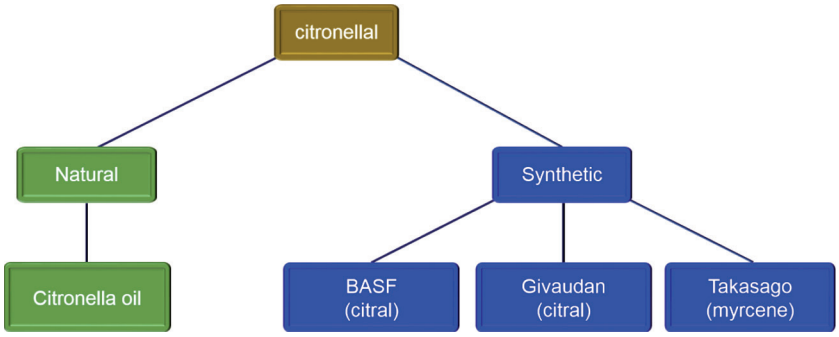

Fig. 92. Selected industrial methods of citronellal production

Among the major producers of synthetic citronellal, whose market is relatively small compared to the natural substance, is BASF. This produces the compound from citral as part of the Verbund strategy, as is the case with many other fragrances at BASF.

As previously mentioned, the raw material is citral, produced in large quantities by Ludwigshafen. The difficulty in executing this process stems from the presence

of two double carbon-carbon bonds and a functional group (carbonyl). As a result, mild conditions must be maintained during the process to limit the possible complete hydrogenation of this compound. Research conducted by BASF has demonstrated that an effective catalytic system that can be employed in this process is palladium deposited on active carbon. Hydrogenation is carried out on a mixture of geranial and neral (Fig. 93).

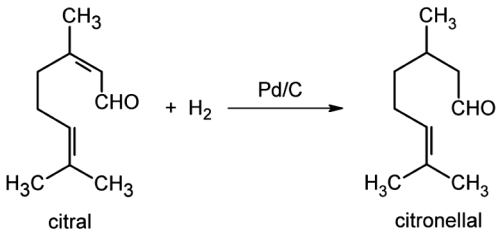

Fig. 93. Hydrogenation of citral to citronellal

The hydrogenation process can be carried out in a tank reactor or continuously. The latter method is more effective in citronellal production A sample diagram of a citral hydrogenation unit is shown in Fig. 94.

First to be prepared is a catalyst suspension in a solution containing: citral (70% m/m), methanol (27% m/m), and trimethylamine (3% m/m). The suspension is mixed in a mixing nozzle (1) with hydrogen and transferred to a hydrogenation reactor (2) operating at a temperature of 70°C and a pressure of 8 bar.

After leaving the reactor, the post-reaction mixture is transported to a separator (3) to separate the gaseous phase from the suspension with the catalytic system. A portion of the gaseous phase is recycled into the hydrogenation process to prevent undesired reactions, while the remainder is removed from the system. The suspension of liquid substances and catalyst, with the gaseous products removed, is transferred by pump (4) to a heat exchanger (5) to be heated to the desired temperature, and subsequently filtered using cross-flow filters (6). Once separated, the catalyst is added to a fresh batch of citral solution, and in this way it is recycled into the reaction [151, 152]. The resulting mixture of liquid substances is then subjected to fractional distillation.

Citronellal is produced in this process with a selectivity of 95%, with almost all citral undergoing the reaction (99.5%).

Givaudan also produces citronellal through the hydrogenation of citral. As with the BASF solution described above, the catalyst used in the hydrogenation reaction is palladium deposited on active carbon. The process itself, however, is carried out at a temperature of 40–50°C and a pressure of 3 bar in an alkaline environment (ammonium carbonate is added) [153].

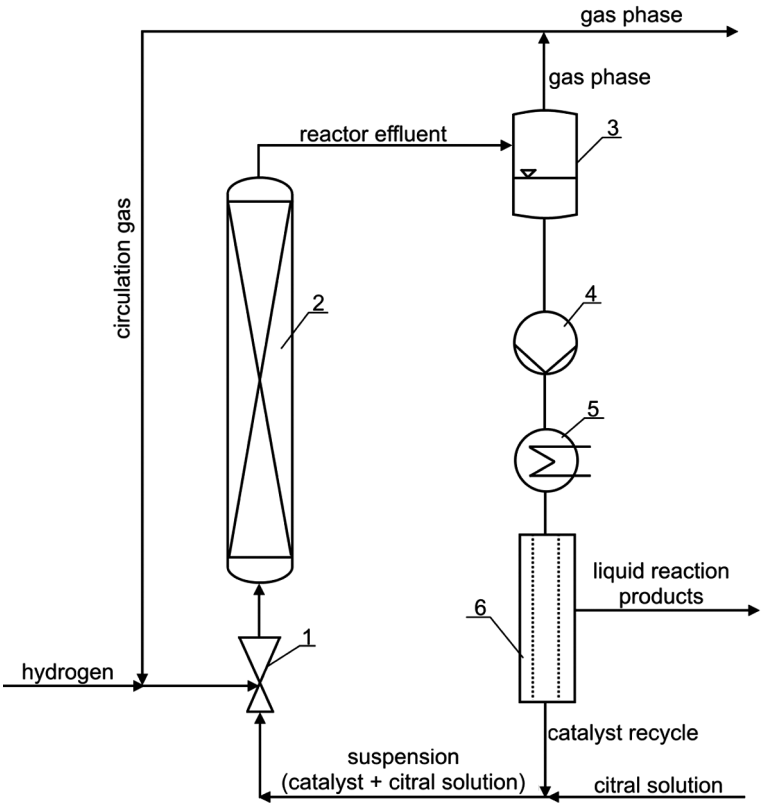

Fig. 94. Diagram of citral to citronellal hydrogenation unit [46] 1 – mixing nozzle, 2 – reactor with packing, 3 – separator, 4 – pump, 5 – heat exchanger, 6 – cross-flow filter [151]

The third producer of citronellal is Takasago, producing an isomer of this compound, (R)-citronellal. It is an intermediate in the production of one of the most important fragrances it synthesises, i.e. l-menthol. The specific method of (R)--citronellal production is described in Section 5.2, concerning l-menthol.

5.6. Hydroxycitronellal

Another compound obtained using citral is hydroxycitronellal (Fig. 95), with the systematic name 7-hydroxy-3, 7-dimethyloctanal. This aldehyde has a scent similar to lily of the valley.

Hydroxycitronellal has a scent stability of 218 hours, and is a naturally occurring compound (Fig. 96 shows a sample chromatogram of this terpene aldehyde).

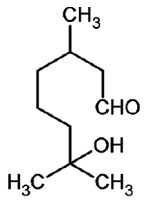

Fig. 95. Structural formula of hydroxycitronellal

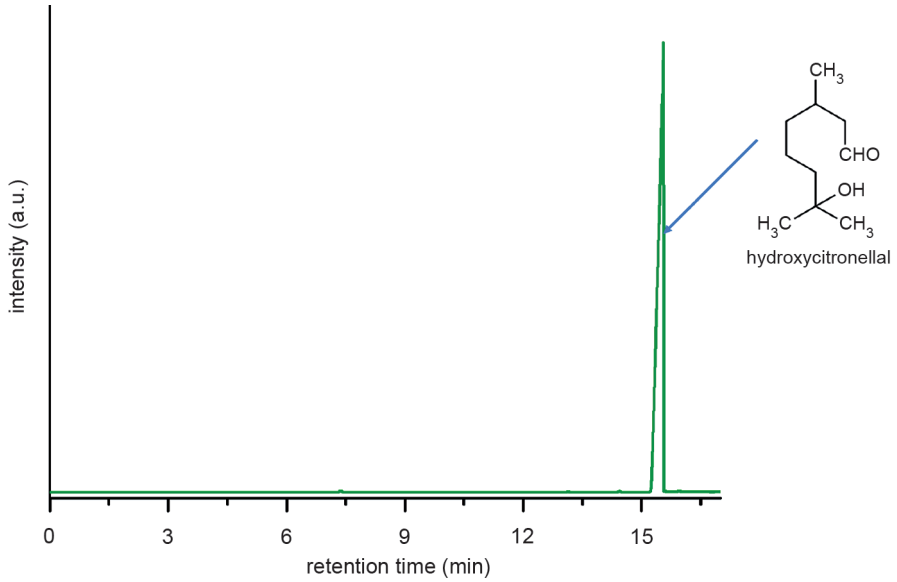

Fig. 96. Sample chromatogram of hydroxycitronellal

It is a component of various oils: key lime, sweet orange, petitgrain, tangerine, sandalwood, and ylang-ylang (cananga tree). The compound has found use in many cosmetic and household chemical products, among them soaps, shampoos, detergents, and perfumery, surface cleaning and care preparations. Hydroxycitronellal is a compound with low stability at high and low pH values. It is frequently converted to more stable acetals, e.g. dimethyl acetal.

In perfumery products, hydroxycitronellal can be found, for example, in colognes (combined with citrus notes, characteristic for such products), as well as in eau de toilette and oriental-type perfumes. IFRA classifies this aldehyde as a potential allergen and, depending on the category of the product where it is used, the quantity is strictly limited to specified levels [154].

The maximum hydroxycitronellal content depends on the type of product in which it is used. In laundry detergents and fabric softeners it is 70 ppm, in dishwashing

liquids a higher level is acceptable (90 ppm), while the lowest level (10 ppm) is permitted in toilet and other surface cleaning agents.

Hydroxycitronellal is produced through chemical synthesis in amounts of about 1,000 tonnes/year. The price ranges from 7 to 12 dollars per kilogram. Fig. 97 shows selected methods used to produce this compound.

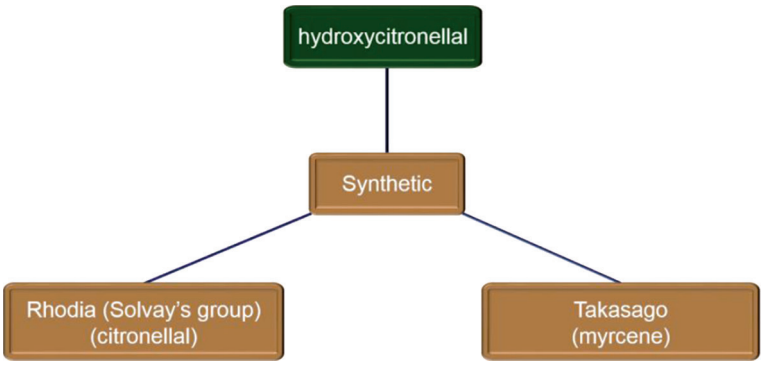

Fig. 97. Selected industrial methods of hydroxycitronellal production

Commercially, hydroxycitronellal is available under many different trade names, including: Anthosal, Centaflor, Cyclalia, Cyclia, Cyclosia® Base, Fixol, Cyclodor, Fixonal, Cyclohydronal and l-Laurinal.

This aldehyde is also used to obtain the most common Shiff base, i.e. Aurantiol® (Fig. 98).

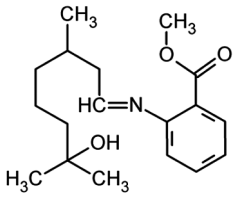

Fig. 98. Structural formula of Aurantiol®

Hydroxycitronellal is produced and distributed by BASF (Germany), Firmenich (Switzerland), Takasago (Japan), Penta International (USA) and many other, lesser known companies [155].

The starting compound used in hydroxycitronellal production is citronellal. A direction hydration of citronellal to hydroxycitronellal is not possible due to a competing reaction which produces isopulegol (menthol precursor). In order to prevent this undesired reaction, the aldehyde group must first be protected.

One technology of hydroxycitronellal production is that developed by Rhodia, which is part of Solvay. The starting compound is citronellal, and the process has three stages.

First the carbonyl group is protected. To this end, the aldehyde is subjected to a reaction with acetic anhydride to produce the enol form of the ester (Fig. 99).

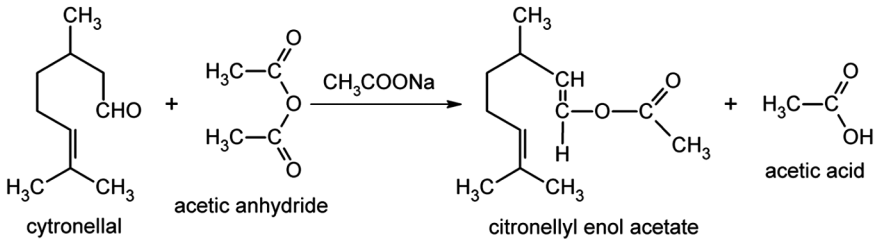

Fig. 99. Creation of the enol form of the citronellol ester

The process is carried out at the boiling point of the reaction mixture, in the presence of sodium acetate. The acetic acid formed during the reaction may cause the cyclisation of both citronellal (to isopulegol) and the produced monoester of acetic acid. As a result, it is continuously removed from the reaction environment. As both the mono and diester enable the synthesising of the same end product, from the economic standpoint there is no need to use an acetic anhydride excess [156]. The resulting mixture is subjected to fractional distillation in order to obtain the pure enol form of citronellol acetate.

During the next stage (Fig. 100), a water molecule is attached to the double bond, creating the hydroxy form of the ester produced in the preceding reaction.

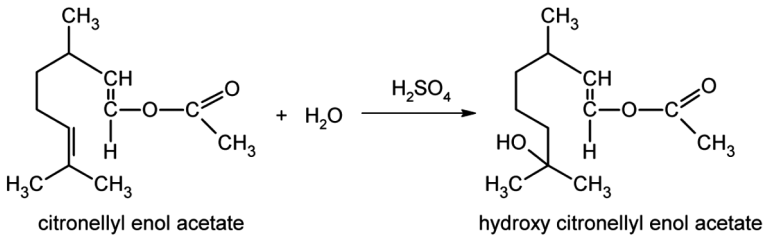

Fig. 100. Hydration of the enol form of the citronellol ester

The hydration is carried out using an aqueous solution of sulfuric acid (approx. 70%) at a temperature of 18ºC. The ratio of acid to ester is slightly higher than 1. The unreacted raw material, forming about 20% of the quantity, is recycled into the hydrogenation process. The hydroxyl form of the acetic acid ester is produced with an efficiency of 75% compared to the reacted starting compound [157].

During the last stage, the functional group protecting the carbonyl group is removed (Fig. 101).

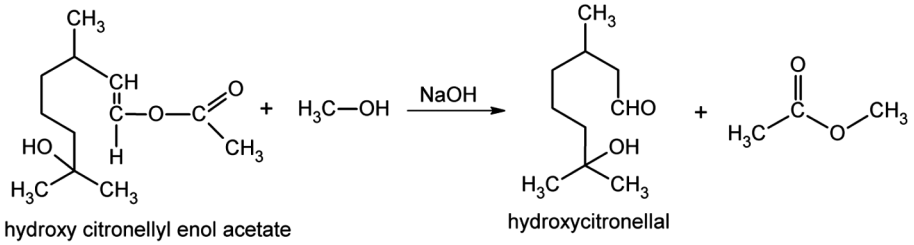

Fig. 101. Hydrolysis of the produced hydroxyester

To this end, the compound obtained from the reaction in Fig. 101 is subjected to alcoholysis using methanol in an alkaline environment. Compared to aqueous solutions of hydroxides, the use of an alcoxide does not cause the degradation of the produced hydroxycitronellal, which is sensitive to high and low pH values. The reaction is carried out at a temperature of 68°C for 6 hours. Methyl alcohol is distilled out of the system, while the precipitated catalyst is dissolved in water. When the aqueous phase is removed, the reaction product is extracted from the organic phase with isopropyl ether. Hydroxycitronellal is obtained with 97% efficiency [158].

Another method of hydroxycitronellal production, developed by Takasago, is based on 7-hydroxygeranylamine as its starting compound. The above amine is produced in a reaction between myrcene and diethylamine in the presence of an alkaline metal, e.g. lithium [159].

The resulting 7-hydroxygeranylamine is transformed during the next stage into 7-hydroxygeranylenamine through isomerisation (Fig. 102). The process is carried out in a solution containing THF as the solvent, sodium phenolate, and a palladium catalyst modified with triphenylphosphines. The reaction is carried out at a temperature of 150°C for 15 hours. To produce hydroxycitronellal of high purity, the catalyst is decomposed first by adding a small amount of water to the system. The post-reaction mixture is distilled under reduced pressure to isolate the 7-hydroxygeranylenamine. The enamine is produced with an efficiency in excess of 80% [160].

Fig. 102. Isomerisation of 7-hydroxygeranylamine to 7-hydroxygeranylenamine

During the final stage (Fig. 103), the 7-hydroxygeranylenamine obtained in the last reaction is hydrolysed to produce hydroxycitronellal. The catalyst in this process is a diluted mineral acid, such as 1 mole of sulfuric acid. The diluted aqueous solution of the catalyst enables gradual hydrolysis of the enamine and the release of 7-hydroxycitronellal into the reaction environment.

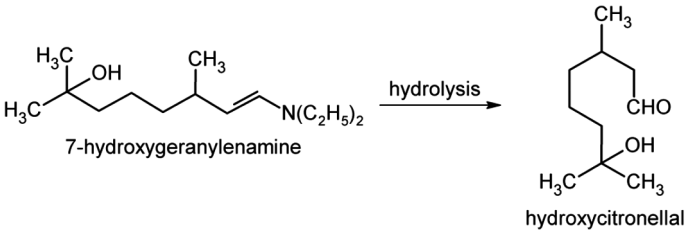

Fig. 103. Hydrolysis of 7-hydroxygeranylenamine

5.7. Citronellol

Citronellol (Fig. 104), also known under the systematic name 3,7-dimethyloct-6-en-1-ol, is another important monoterpene alcohol. A sample citronellol chromatogram is shown in Fig. 105.

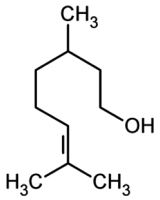

Fig. 104. Structural formula of citronellol

This alcohol can occur in two isomeric forms as (R)-citronellol and (S)-citronellol. Both compounds can be found in essential oils, e.g. Lemon-scented boronia (Boronii citriodora – approx. 80%), lemon eucalyptus (Eucalyptus citriodora – 15 to 20%), geranium and rose (50%), sandalwood and clary sage [20].

Citronellol finds use in cosmetics and food products [161]. In the cosmetics industry, it is used for products with fresh, long lasting rose scents (above 48 hours). It is also an indispensable ingredient of blossom compositions. Citronellol is characterised by high stability in various cosmetic products. It can be used in quantities of up to 30% in fragrance concentrates [162].

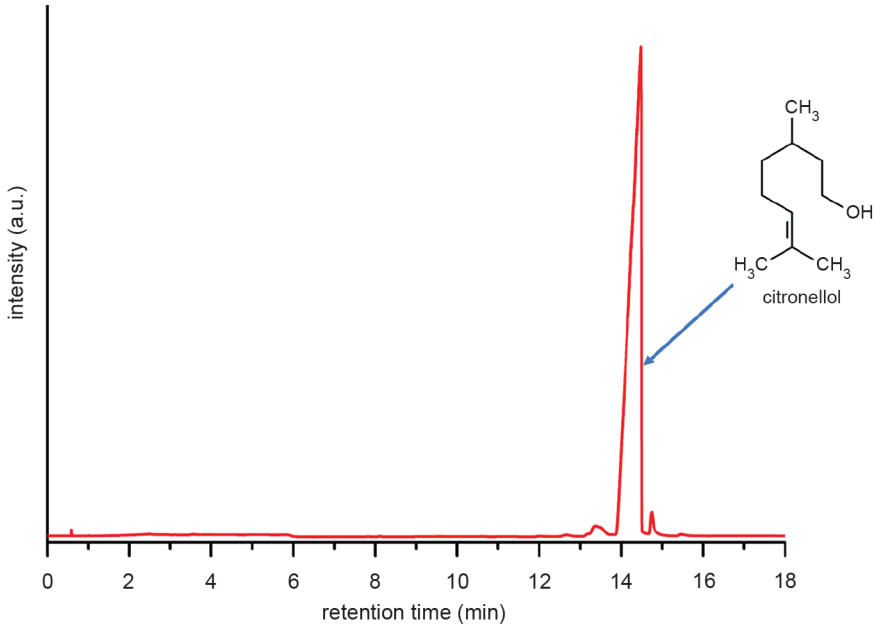

Fig. 105. Sample chromatogram of citronellol

The food industry uses it as an ingredient of concentrates imitating fruit scents such as: citrus, cherry, strawberry, peach, and fruit mixes. For such products, the recommended amount of citronellol is up to 60 ppm.

Aside from the above-mentioned applications, citronellol can also be used in the synthesis of another fragrance of great importance, rose oxide.

At present, both natural and synthetic citronellol are available commercially (Fig. 106). Its producers include such companies as: BASF (Germany), IFF and Renessenz (USA), Mane (France) and Takasago (Japan) [162].

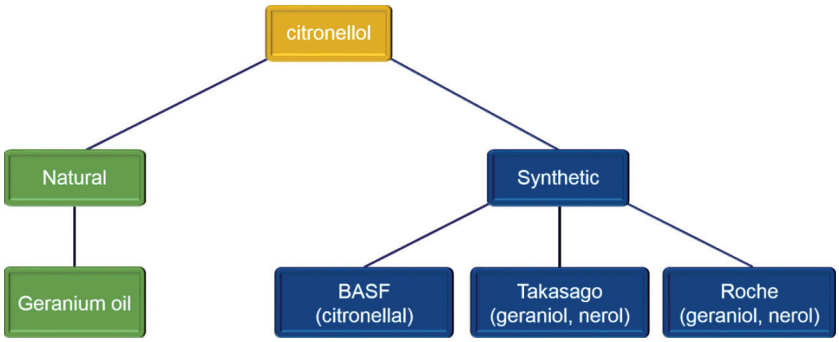

Fig. 106. Selected citronellol production technologies

Citronellol is produced in amounts of several thousand tonnes per year (between 3,000 and 6,000 tonnes). This applies both to the alcohol itself and its derivatives. The price ranges from 5 to 10 dollars per kilogram (depending on purity). Various citronellol production technologies provide, as the reaction product, either a mixture of (R)-citronellol and (S)-citronellol isomers (with traditional hydrogenation catalysts), or both of these compounds as pure R and S forms (with chiral catalysts, which selectively produce one form).

The raw material in the technology employed by BASF is citronellal, produced in the citral hydrogenation process (Fig. 107).

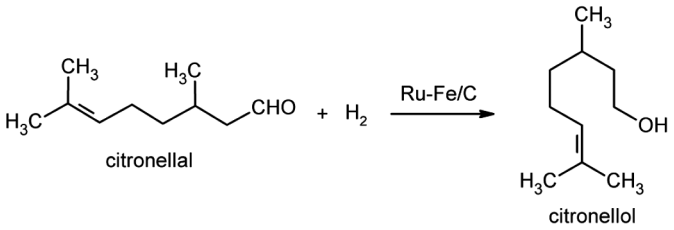

Fig. 107. Hydrogenation of citronellal to citronellol

Note that the process generates a mixture of (R)-citronellol and (S)-citronellol, the first of the citronellol production process variants listed above.

As with the conventional process of citral hydrogenation to geraniol, here too a Ru-Fe/C catalyst is used, with the same composition as before (5% ruthenium and 1% iron on active carbon). The catalytic system is in a suspension comprising citronellal (70% m/m), methanol (27% m/m), and trimethylamine (3% m/m), i.e. the same composition as with citral hydrogenation, with the only difference being that here the starting compound is citronellal [163, 164].

As can be seen in Fig. 108, the process uses a unit identical to that employed for the geraniol (Section 5.3) or citronellal (Section 5.5) production technologies discussed earlier.

The produced suspension is, together with hydrogen, first introduced into a mixing nozzle (1), then moved to a hydrogenation reactor (2), which is a bubble column with specially designed partition barriers. The process is carried out at a temperature of 80°C and a hydrogen pressure of 20 bar. After leaving the reactor, the post-reaction mixture is separated in a separator (3) into the gaseous phase and a suspension containing the product, solvent, unreacted citronellal, and catalyst. The gaseous phase is also partially recycled into the reactor to prevent side reactions. The suspension of liquid substances and the catalyst is transferred by a pump (4) to a heat exchanger (5) to be heated to the desired temperature, and is subsequently filtered using cross-flow filters (6). Once separated, the catalyst is added to a fresh batch of citronellal solution and recycled into the reaction [165].

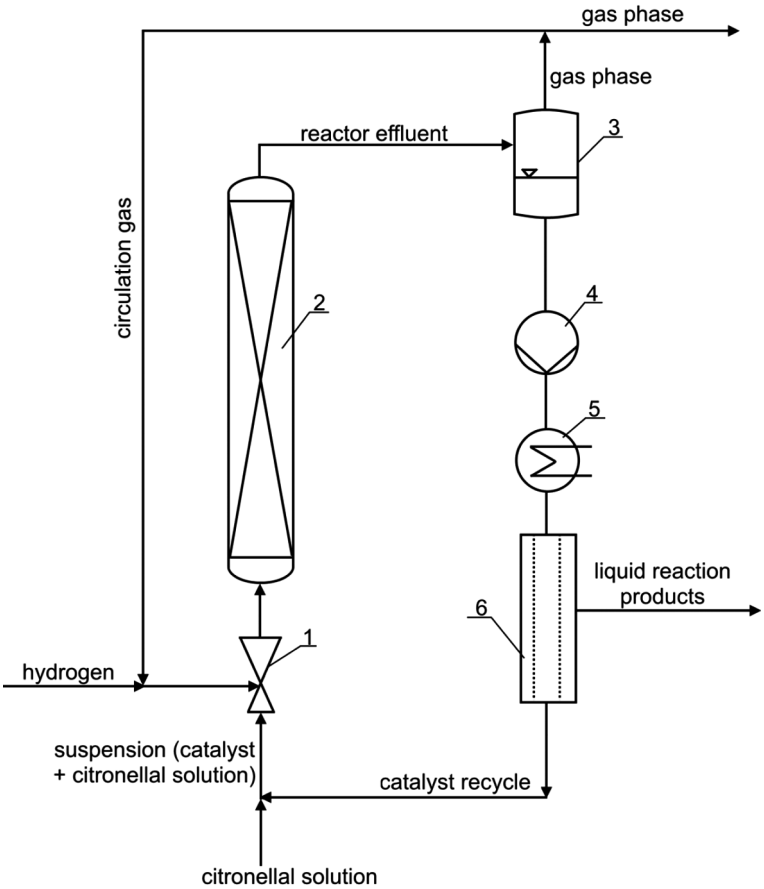

Fig. 108. Citronellol production diagram 1 – mixing nozzle, 2 – reactor with packing, 3 – separator, 4 – pump, 5 – heat exchanger, 6 – cross-flow filter [165]

For citronellal hydrogenation to citronellol, the conversion rate of the starting aldehyde is 95%, while the desired alcohol is produced with 99% selectivity.

Takasago specialises in fragrance production processes, including monoterpenoids, with the use of chiral catalysts. It is no different with citronellol. Both geraniol and nerol can be used as the raw material for synthesis [166]. A catalytic system enabling the production of only the specific desired citronellol isomer can be used as required (Fig. 109). Unlike menthol synthesis, where a rhodium catalyst containing BINAP ligands is utilised, a ruthenium system containing only a single binaphthalene fragment is utilised for geraniol and nerol hydrogenation reactions (Fig. 110) [167, 168].

The hydrogenation process is carried out at a temperature of 20°C and a pressure of 30 bar in the presence of methanol as a solvent. The TON value in this case is

50,000 [170, 171]. In this way, the company produces 300 to 500 tonnes of various isomeric forms of citronellol every year. The hydrogenation processes generate products with an enantiomeric purity of 96–99%.

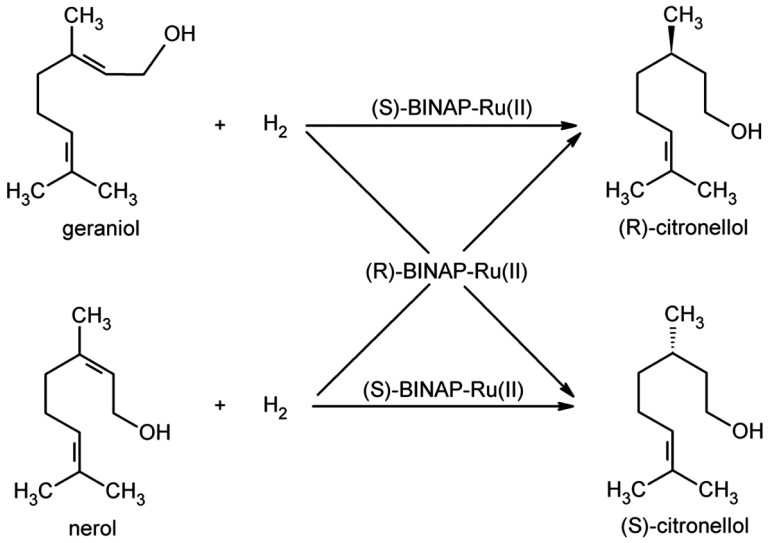

Fig. 109. Diagram of nerol and geraniol hydrogenation with the use of chiral catalysts

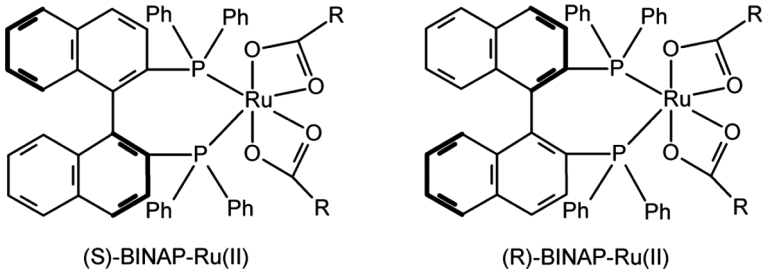

Fig. 110. Structural formula of catalysts used for chiral hydrogenation of nerol and geraniol to citronellal [169]

The catalytic systems applied in (R)-citronellol and (S)-citronellol production are also successfully utilised as catalysts in the hydrogenation reactions of α,β-unsaturated esters of carboxylic acids, lactones and ketones, as well as the alkaloids isoquinoline, morphine, and synthetic analogues of morphine.

Aside from the already discussed methods of citronellol production, there is also the technology developed by Roche; to date, a pilot plant has been commissioned to produce only (R)-citronellol (from geraniol and nerol) for pharmaceutical purposes.

Similar to the Takasago technology, the catalyst used in the process is a ruthenium--based chiral system, Ru(MeO-Biphep)$_2$ (Fig. 111) [172].

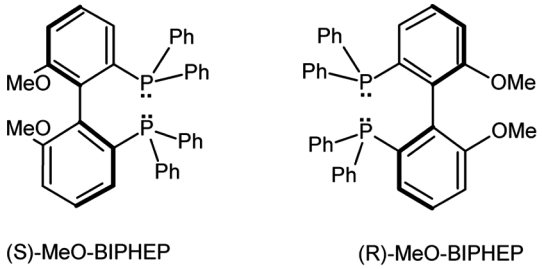

Fig. 111. MeO-Biphep ligands

The hydrogenation is carried out at a temperature of 20°C and a pressure of 60 bar. Methanol is also the solvent in this case. Unlike the Takasago technology, the TON value does not exceed 20,000. The process produces (R)-citronellol of 99% enantiomeric purity.

5.8. Ionones and methylionones

As was mentioned in the section concerning citral, fragrances produced with its participation are ionones (Fig. 112) and their methyl derivatives (Fig. 113).

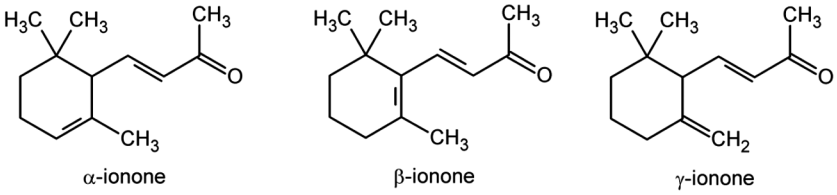

Fig. 112. Ionone compounds

In the case of ionones and their methyl derivatives, the compounds of the greatest importance, utilised in various sectors of industry, whether cosmetics, household chemicals or pharmaceuticals, are α- and β-ionone and α-isomethylionone.

α-Ionone, with the systematic name 4-(2,6,6-trimethylcyclohex-2-enyl)-but--3-en-2on, has a viola scent with wood notes, which is a result of the presence of a small amount of the β isomer (chromatogram shown in Fig. 114).

Its scent is detectable for 112 hours. The presence of this compound, in small quantities, has been found in brown boronia (Boronia megastigma) and acacia

(Acacia farnesiana) oils, almonds, plums, blackcurrants, raspberries, whiskey, and tobacco. Due to the low content of this compound in natural materials, the price of α-ionone obtained this way is very high [1, 19].

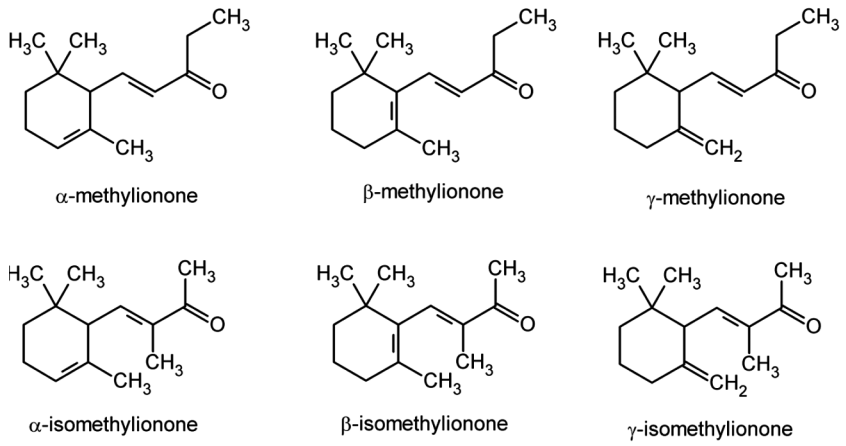

Fig. 113. Methyl derivatives of ionones

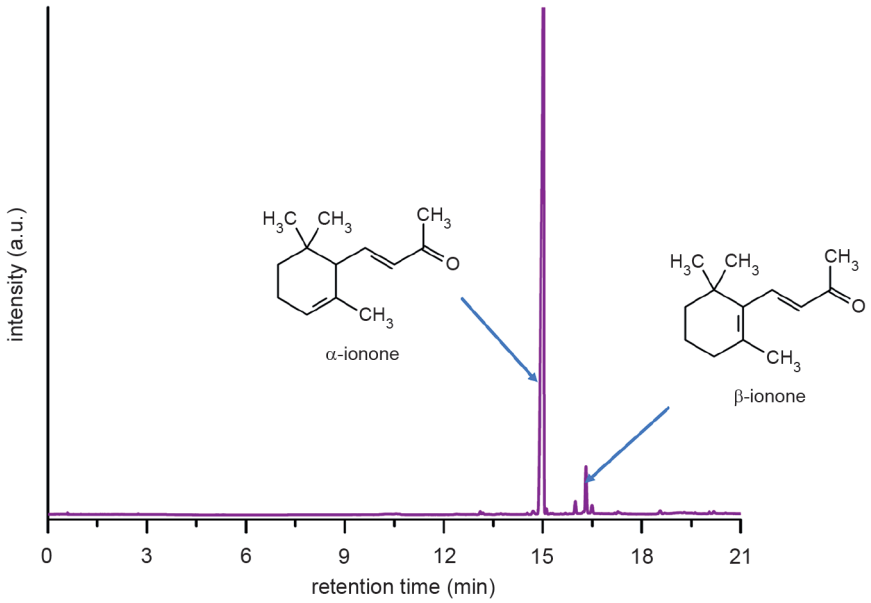

Fig. 114. Sample chromatogram of α-ionone

This ketone is widely used in various products, in cosmetics such as shampoos, soaps, eau de toilettes, and makeup, as well as non-cosmetic products, such as

household cleaning agents. In perfumery products, it is used in wood, flower, and citrus compositions. Additionally, the cosmetics industry uses this compound to produce various fruit scent compositions, e.g. peach, raspberry, grapefruit, plum, and blueberry. Annual production of this compound is estimated at 100 to 1,000 tonnes. It is available under many trade names, e.g. Irisone Alpha, Alphaline 70, Alpha-Ionone Extra 70 and 80, Ionone Alpha, and Alpha-Ionone Natural. Producers include Givaudan (Switzerland), DSM Nutritional (Netherlands), Takasago (Japan), IFF (USA), and WEN International, Inc. (China) [173].

Another important isomer among the ionones, perhaps the most important, is β-ionone. The systematic name of this compound is 4-(2,6,6-trimethylcyclohex--1-enyl)-but-3-en-2-one. It has an intensive wood scent with fruit tones. The detectability threshold is approx. 0.007 ppb, and the scent remains detectable for 112 hours. As with α-ionone, the presence of the β isomer has been found in brown boronia (Boronia megastigma) oil, as well as almonds, peaches, tomatoes, oranges, tobacco, and carrots. Trace amounts also occur in river and lake waters, as a result of biotransformations in various species of algae. The β-Ionone present in tomatoes and carrots confers a subtle sweet flavour to them [174].

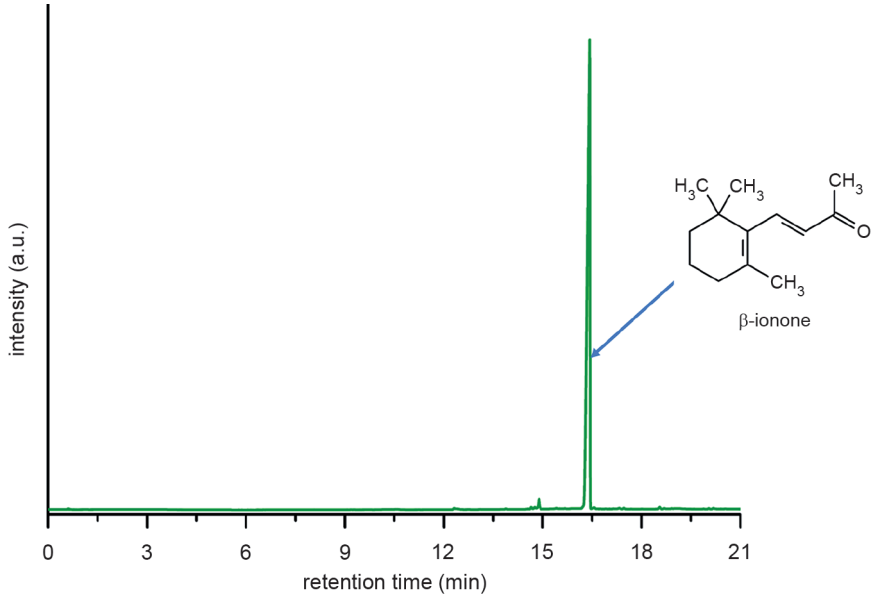

Fig. 115. Sample chromatogram of β-ionone

Among all the isomers of ionones and their methyl derivatives, β-ionone is produced in the largest quantities. The production volume of this compound is estimated at approx. 10,000 tonnes/year. It is available under such names as:

Beta-Ionone R, Ionone Beta, Beta-Ionone, Beta-Ionone Extra 70 and 80, and Ionone Beta Natural.

Synthetic β-ionone is mainly used to produce compounds necessary in the synthesis of vitamin A [175] and other optically active carotenoids [177, 178]. It is estimated that over 75% of the β-ionone produced is used by the industry producing this group of compounds. The remainder is used in the production of cosmetics and household chemicals. It is utilised in perfumery products with viola accords, as well as those of a wood and fruit character [179].

Many producers of this compound synthesise it only to cover their own needs, mainly as a material for vitamin A production. Examples here are BASF (Germany) and DSM (Netherlands). Only 30% of the β-ionone produced by these two concerns is sold to other entities. Furthermore, producers and distributors also include Takasago (Japan), Givaudan (Switzerland), and Vigon International, Inc. (USA).

The most important compound among both the n-methyl and isomethyl derivatives of ionones is α-isomethylionone. Its systematic name is 3-methyl-4-(2,6,6-trimethyl--2-cyclohexenyl)-4-buten-2-one. A sample chromatogram of this aroma compound is shown in Fig. 116. A certain lack of consistency in the naming applied by certain producers must be mentioned here. Specifically, α-isomethylionone can be found under the name of gamma ionone, which would suggest that it is the third, after

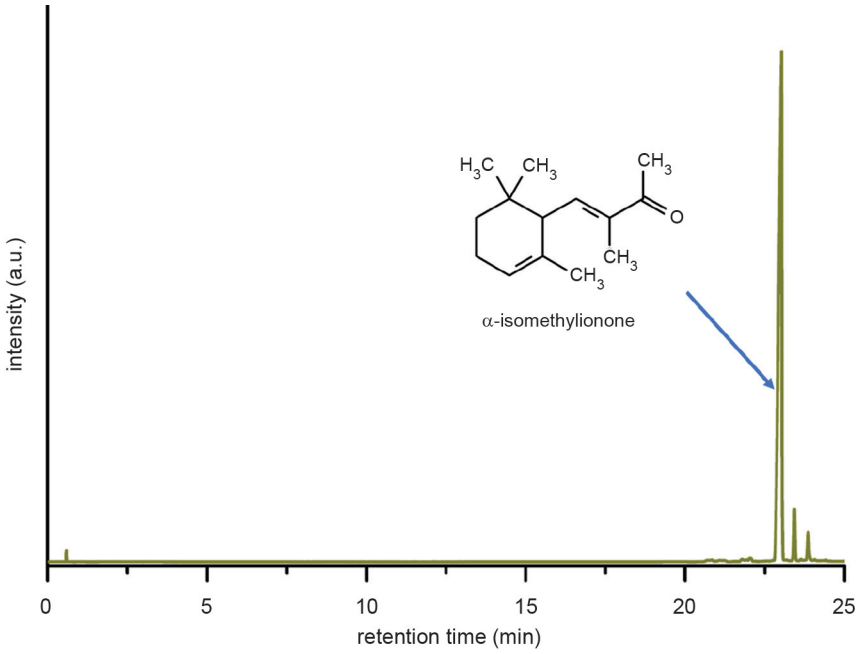

Fig. 116. Sample chromatogram of α-isomethylionone

α and β, isomer of ionones (Fig. 113), while in fact we are dealing with a methyl derivative of α-ionone (Fig. 114).

This compound has a scent (viola) classified as flowery, with wood and fruit notes. The scent remains detectable for 124 hours. α-Isomethylionone is a highly popular and frequently used compound. It finds use in various cosmetics, such as: after-shaves, shampoos, hair care and bath products, moisturising creams, perfumes and colognes, and skin care preparations. The compound can be found in such products of the perfumery industry as: Chanel No. 19 (1971), Chanel Coco, Yves Saint Laurent Paris (1983) and Lancôme Trésor (1990).

α-Isomethylionone is among the known potential allergens, so the recommended quantity is precisely specified by IFRA. Commercially, it is available under various names: Isoraldeine® Cetone Alpha, Gamma-Methyl Ionone, Gamma-Methyl Ionone EQ, and Isoraldeine 95 (Gamma Methyl Ionone 83%)

Its production volume is estimated at several hundred tonnes. The main producers and distributors include Givaudan (Switzerland), Takasago (Japan), Vigon International (USA), and others [181].

The processes employed in the industry are based on condensation reactions followed by cyclisation, most commonly carried out in homogeneous systems [182]. It should be noted that the largest producers of these compounds synthesise them in an almost identical manner (with minor variations in process parameters, solvents, and catalytic systems).

First, pseudoionone is obtained through the aldol condensation of citral with acetone (Fig. 117). Pseudoionone is a compound that does not occur naturally in large quantities [183, 184].

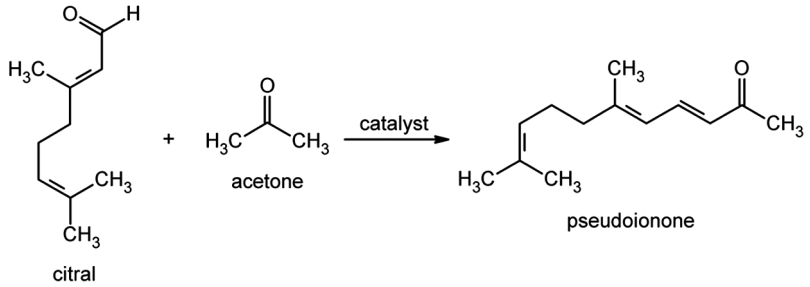

Fig. 117. Condensation of citral with acetone

However, if butan-2-one (methylethylketone) is used instead of acetone, the condensation products will be: methylpseudoionone and isomethylpseudoionone (Fig. 118). These reactions occur in the presence of alkaline catalysts.

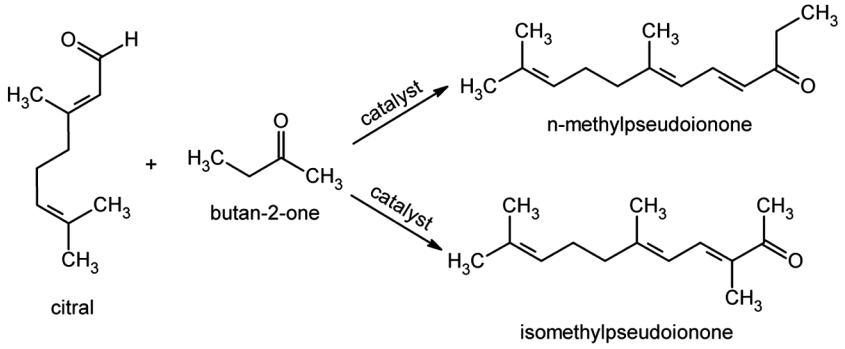

Fig. 118. Condensation of citral with butan-2-one

During the next stage, the obtained pseudoionones and (iso)methylspeudoionones are subjected to cyclisation with the use of acidic catalysts (Figs. 119–121). These processes result in 9 isomers of ionones and their methyl derivatives.

As noted above, BASF is one of the more important producers of ionones and their methyl derivatives. During the first stage of the industrial method of producing ionones from citral and acetone (or butan-2-one), pseudoionone (or methylpseudoionones) is formed. In the case of pseudoionone production,

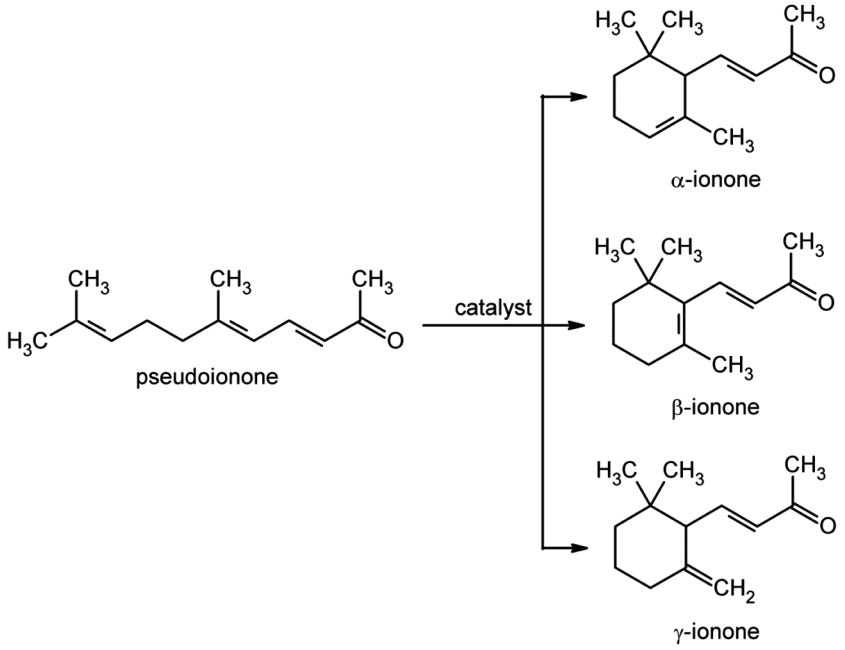

Fig. 119. Cyclisation of pseudoionone

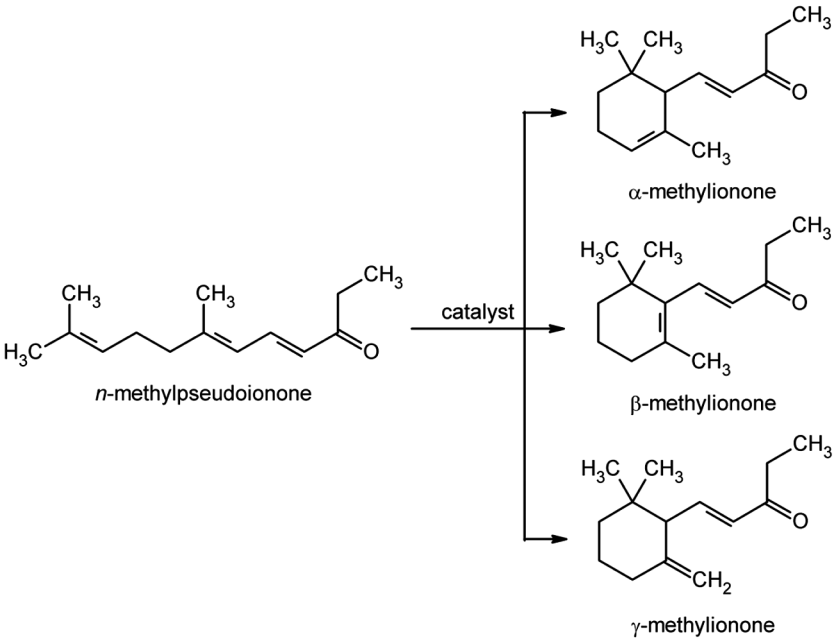

Fig. 120. Cyclisation of n-methylpseudoionone

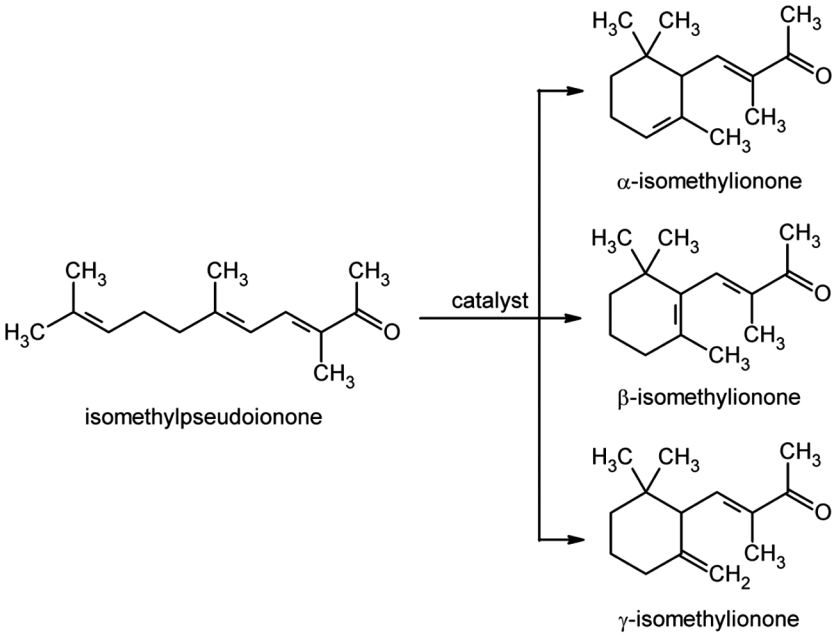

Fig. 121. Cyclisation of isomethylpseudoionone

aldol condensation is carried out at a temperature of 112°C in the presence of a 5% aqueous NaOH solution, serving as a catalyst. The process is conducted in pipe reactors. The mixture is pre-heated to 108ºC, then pumped to the reaction system. The aldolisation reaction is exothermic, causing the temperature to rise to the desired value (112°C). The mixture remains in the reaction space for 2 minutes, and Citral conversion rate reaches 93%. After leaving the reactor, acetone is distilled from the post-reaction mixture and recycled into the process, while the remaining mixture is cooled. After neutralisation with an acid solution, the organic phase is separated from the aqueous one. Pseudoionone is purified using distillation under reduced pressure (50 mbar) [185].

Methylpseudoionone is produced in a similar manner, with the difference that the process is carried out at temperatures of approx. 120–130°C, depending on the concentration of the sodium hydroxide solution utilised. The main reaction product is methylpseudoionone; there are also small amounts of isomethylpseudoionone produced [186], which also form a valuable precursor in the production of aroma compounds (particularly α-isomethylionone). To obtain a pure isomethylpseudoionone, the aldol condensation process is carried out in the presence of milder alkaline catalysts, which are quaternary ammonium hydroxides.

A newer solution, proposed by BASF, which eliminates the need to neutralise the post-reaction mixture and separate the organic and inorganic phases, is to carry out the condensation continuously, using a catalytic system deposited on a specially designed substrate. A diagram of this version of the process is shown in Fig. 122.

The main element of the unit is a reactor shaped like a distillation column (1), with a reaction area split into two sections. The top section houses a special packing with the catalyst (cylinders a few millimetres in size, with 5% praseodymium deposited on γ-Al_20_3), while the bottom section only contains packing with a geometry that prevents the catalyst from moving to the bottom section of the column.

Above the top and below the bottom reaction area are two separation areas (2, 3), additionally fitted with elements improving the efficacy of the separation. The condensation process is carried out at a temperature of about 90°C and a pressure of about 3 bar. Reagent streams (citral and acetone) are introduced above the top reaction area. The post-reaction stream is collected from the bottom section of the reaction column, and contains pseudoionone (about 25% m/m), unreacted acetone (about 62% m/m), citral (about 9%), and small amounts of water, diacetone alcohol (a product of two acetone molecules condensing), and mesityl oxide. The stream is transferred to a heat exchanger, commonly known as a reboiler (6), and heated to 124°C. The volatile components generated inside, in the form of a vapour, are recycled into the reaction, while the high boiling point fraction (enriched with the main reaction product) is removed in a liquid form.

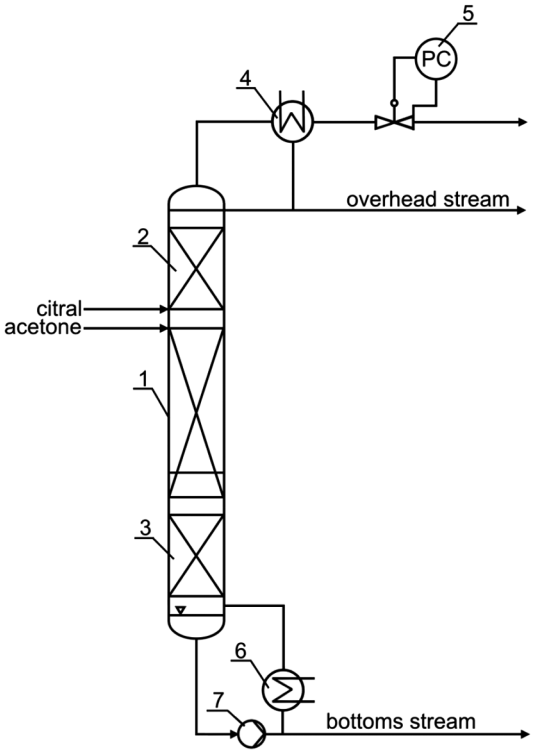

Fig. 122. Diagram of pseudoionone production with the use of a heterogeneous catalyst: 1 – reaction distillation column, 2, 3 – separation areas, 4 – condenser, 5 – pressure controller, 6 – reboiler, 7 – force pump [187]

At the top, the volatile components of the post-reaction mixture are collected (96% m/m acetone and 4% m/m water), which are then, after condensing (4), partially recycled into the reaction as reflux [187, 188].

A reaction system designed this way can operate 24 hours a day, and the selectivity of the pseudoionone production process is approx. 97% and 84% for the citral and acetone, respectively, while the efficiency compared to the aldehyde is almost 67% [189].

As previously mentioned, ionone production is a two-stage process. The next stage of ionone synthesis is cyclisation of the pseudoionones. To this end, a particular type of pump is used, where the cyclisation reaction occurs (Fig. 123). The main compound that the presented unit is focused on is β-ionone. This is, of course, related to the high demand for this compound in the pharmaceutical industry, which uses it as a base for vitamin production.

A solution of pseudoionone in hexane is prepared, the purpose of which is to collect the heat from the exothermic cyclisation reaction. The solution is additionally

cooled in a heat exchanger (1) to a temperature below 10°C before it enters the reaction pump. The specific temperature value depends on the amount of both the starting pseudoionone undergoing the reaction and the sulfuric acid used for cyclisation. The cooled pseudoionone solution in hexene is transferred to the pump (2) mentioned above. The mixing chamber of the pump enables mixing of the pseudoionone with the acid, and allows the reaction itself to be carried out. The time that the mixture spends inside the reaction area (below 10 s) depends on the raw material that is being subjected to the cyclisation reaction, and on the product that is generated in the process. The process is carried out at a pressure of approx. 2 bar. After leaving the pump, the post-reaction mixture is cooled in a heat exchanger (3), usually to about 10°C, then transported to another pump (4), where water is introduced to dilute the sulfuric acid present in the post-reaction mixture. Before being transferred to a separator (6), the resulting mixture is cooled in a heat exchanger (5) to a temperature of 40°C. If needed, the system can include additional reaction pumps. The top phase in the separator is subjected to fractional distillation to isolate the pure reaction products. β-Ionone production efficiency exceeds 80%. It must be noted that, depending on the concentration of the catalyst utilised, it is possible for the same unit to produce a mixture of products containing mainly β-ionone (when the concentration of the H_2SO_4 aqueous solution exceeds 90%) or α-ionone (for diluted acids – below 60%), and in a similar manner, a mixture of methyl derivatives of ionones [190, 191].

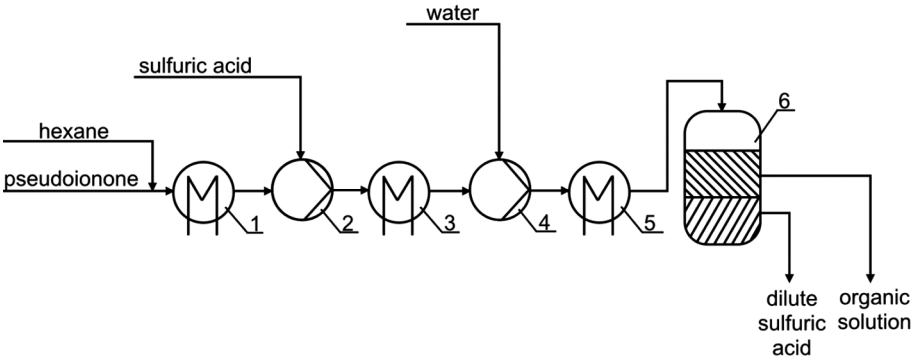

Fig. 123. Diagram of a unit for ionone production at BASF: 1, 3, 5 – heat exchangers, 2, 4 – reaction pumps, 6 – separator [190]

Similarly to BASF, DSM is also a major producer of ionones, focusing exclusively on the production of β-ionone, used as a starting compound in the synthesis of vitamin A and others.

As noted above, the first stage is to produce pseudoionone through aldol condensation of citral and acetone. As with the new solution proposed by BASF,

DSM carries out the pseudoionone production process using a heterogeneous catalytic system instead of an aqueous solution of sodium hydroxide. One variant is to use an ion exchange resin containing alkaline functional groups, e.g. Ambersept 900 OH. The pseudoionone production process takes place at a temperature of 60°C and lasts 3 hours. Next, the catalyst is separated from the organic phase, from which pseudoionone is then isolated. The aldolisation process yield is 62%. After washing with ethanol, the catalyst can be reused [192].

A newer solution proposed by DSM is to carry out the pseudoionone production process in the presence of lanthanum oxide, serving as the catalyst for the aldol condensation of citral and acetone [193, 194]. The process is carried out at a temperature of 200°C for 3 hours at a pressure of 25 bar. Peudoionone production efficiency is approx. 60%. After the process, the catalyst is regenerated by calcination at a temperature of 900°C, and recycled into the condensation process.

During the second stage, pseudoionone is subjected to cyclisation in the presence of sulfuric acid. Additionally, various organic solvents are used to collect the heat generated in the process. The most effective are chlorine derivatives of organic compounds, especially alkanes, e.g. methylene chloride. However, using these substances means that they need to be removed from the produced pseudoionone, especially if it is to be used in the production of the precursors employed in vitamin synthesis. For this reason, carbon dioxide has replaced these solvents, as it has no adverse effect on the end product [195]. A diagram of this version of the process is shown in Fig. 124.

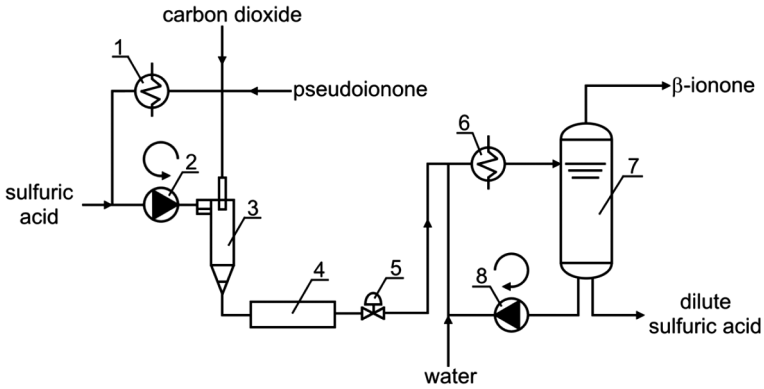

Fig. 124. Diagram of β-ionone production by DSM: 1 – heat exchanger, 2 – centrifugal pump, 3 – cyclone, 4 – reactor, 5 – pressure reduction valve, 6 – heat exchanger, 7 – separator, 8 – centrifugal pump [196]

Pseudoionone is mixed with a circulating stream of carbon dioxide, at a pressure of 80–100 bar. A small amount of CO_2 is also introduced into a 98% sulfuric

acid stream. The two streams are combined, forming an emulsion system, which is pumped to a hydrocyclone separating the light organic phase circulating in the system from the heavier phase (containing sulfuric acid, pseudoionone, and others), which is transferred to a reactor.

The cyclisation process occurs at a temperature of 0°C. After leaving the reaction space, the post-reaction mixture is decompressed to atmospheric pressure, and subsequently diluted with water, and cooled (the heat generated during dilution is collected). The organic phase is separated from the aqueous solution of sulfuric acid in a separator. β-ionone production efficiency is approx. 70%.

5.9. Dimethyloctanol

Dimethyloctanol (Fig. 125), otherwise known as tetrahydrogeraniol or dihydrocitronellol (See Fig. 126 for a sample chromatogram). Its systematic name is 3,7-dimethyloctan-1-ol.

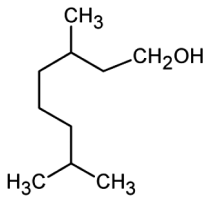

Fig. 125. Structural formula of dimethyloctanol

Tetrahydrogeraniol has a fresh, lightly citrus scent resembling rose with wax accents in the background. The scent remains detectable for 24 hours. It occurs in lemon and thyme oils.

Dimethyloctanol finds use in products from the cosmetics, household chemicals and food industries. It is used as a component of various fragrance compositions, as well as an agent masking the unpleasant odour of a product. This popularity stems from the great stability of this alcohol, regardless of the environment in which it is present. As a flavouring for food products, it is usually utilised in products with fruity scents, which include ice creams, chewing gums, candies, and non-alcoholic beverages. The tetrahydrogeraniol content in products of this group is recommended to not exceed 50 ppm. In the cosmetic and household chemicals industries, it is used in a broad range of products, including detergents due to its high resistance to high and low pH values. In this case, its content in the product should not exceed 10%.

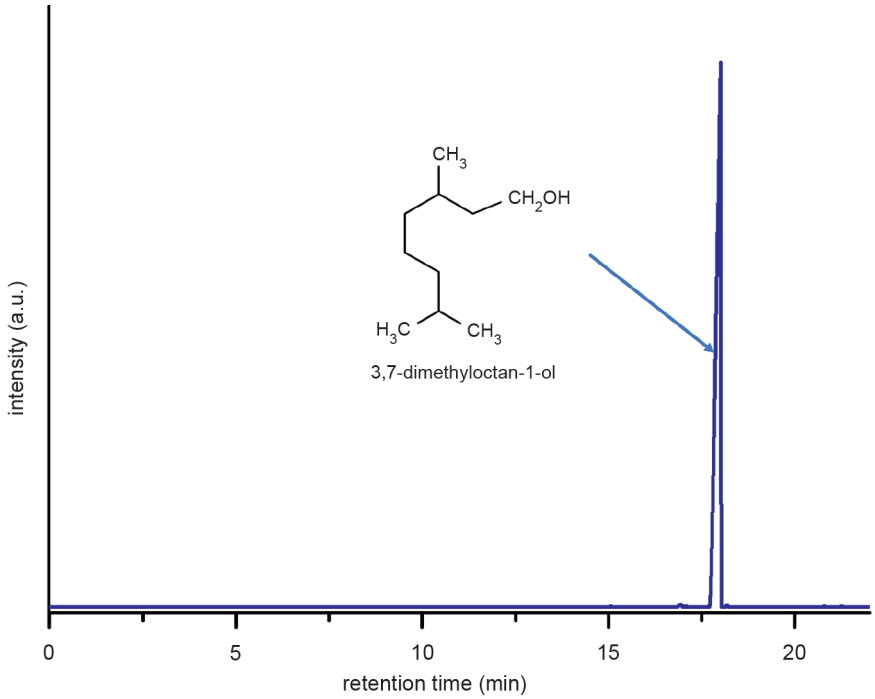

Fig. 126. Sample chromatogram of dimethyloctanol

It can be found under such trade names as: Tetrahydrogeraniol, l-Dihydro Citronellol, and Dimethyl Octanol. Producers and distributors include BASF, Takasago, IFF, as well as Berjé and Ernesto Ventós [197].

The reaction producing tetrahydrogeraniol through complete hydrogenation of such unsaturated precursors as citral, geraniol, neral, and citronellal has been known since the beginning of the 20th century. Today, however, processes based on the relatively expensive pure forms of these compounds have little economic justification. Therefore, post-distillation resides from the production processes of linalool, geraniol, nerol, citronellol, and citronellal, containing small amounts of linalool, as well as geraniol and nerol, can be used as the raw material in the dimethyloctanol production reaction. Note that both by-product fractions from individual processes or mixtures combining the post-distillation residues from multiple processes can be used. There are two reasons behind the requirements concerning the low content of geraniol, nerol, and linalool. In the case of geraniol or nerol hydrogenation, a problem arises when separating the saturated reaction product (tetrahydrogeraniol) from unsaturated starting compounds. Another problem is related to linalool. Specifically, if a raw material containing this terpene alcohol is used, the employed catalytic system should enable not only complete hydrogenation

of this compound, but also its isomerisation (moving the hydroxide group to the beginning of the carbon chain). Otherwise, the product of complete hydrogenation will be tetrahydrolinalool [198].

Dimethyloctanol is produced according to such a solution at BASF. The raw material for the process is the fraction originating from geraniol production, which contains mainly citronellol and isonerol, and no more than 10% of geraniol/nerol and linalool. The requirements concerning the content of the latter three compounds are related to the issues described above. The catalytic systems are usually palladium (5%) deposited on active carbon, or Raney nickel. It has been found that the best solution is to use the second of these catalysts. Hydrogenation conditions, on the other hand, depend on the raw material utilised in the process. This applies to temperature, pressure, and hydrogenation duration [199, 200]. Correct selection of the raw materials (low content of the three mentioned compounds) and parameters (temperature and pressure) enable the compounds to react almost completely (99%), transforming into dimethyloctanol as a result.

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A b s t r a c t

In this monography were described only the most interesting examples of production technologies used for selected monoterpenoid compounds. The focus is on the production technologies for fragrances produced in large quantities (for this industry), such as citral and menthol. However, some of the production methods for monoterpenoid fragrances synthesised in smaller quantities than these two are presented as well (e.g. citronellol, linalool, and geraniol).

For all the technologies utilised to obtain the scents and flavours in question, and described in this handbook, other variants of the methods (depending on the producer) employed in their production are also presented.

Технология монотерпеноидович ароматов

С о д е р ж а н и е

В этой монографии описаны только наиболее интересные примеры технологии получения отобранных монотерпеноидович соединений. Поэтому основное внимание в первую очередь уделяется технологиям получения ароматов, производимых в значительных количествах (как это отрасль химической промышленности), таких как цитраль или вышеупомянутых ментола. Но есть также методы, чтобы получить монотерпеноидович ароматов, полученных в меньших количествах по сравнению с двумя ранее (например, цитронелолу, линалолу или жераниолу).

Для всех технологий, описанных в монографии представлены различные варианты методов (в зависимости от производителя), применимые к их производству.

Technologia monoterpenoidowych związków zapachowych

Streszczenie

W niniejszej monografii zostały opisane tylko najbardziej interesujące przykłady technologii uzyskiwania wybranych związków monoterpenoidowych. Skupiono się zatem przede wszystkim na technologiach otrzymywania substancji zapachowych wytwarzanych w znacznych ilościach (jak na tę gałąź przemysłu chemicznego), takich jak na przykład cytral czy też wspomniany powyżej mentol. Przedstawiono również metody uzyskiwania monoterpenoidowych substancji zapachowych otrzymywanych w mniejszych ilościach w porównaniu z dwoma wcześniejszymi (np. cytronelolu, linalolu czy też geraniolu).

W przypadku wszystkich opisanych w publikacji technologii służących do otrzymywania tytułowych aromatów przedstawiono różne warianty metod (zależnie od producenta) mających zastosowanie przy ich produkcji.