Chiral chemistry in flavours & fragrances

John and **Diane Leffingwell** of **Leffingwell & Associates** discuss the importance of chirality in the flavours and fragrances industry

Industrial chemists usually associate chirality positively with the top selling blockbuster chiral drugs, such as Lipitor (Atorvastatin), Plavix (Clopidogrel) and Nexium (Esomeprazole). But chirality also plays a very important role in flavour and fragrance chemistry. In this short review we will examine the chemistry and odour properties of such important chiral materials as menthol, carvone, methyl dihydrojasmonate, ambergris (Ambrox) and sandalwood odourants (β-santalol).

Menthol

Menthol is a $C_{10}H_{20}O$ terpenoid alcohol with three chiral centres leading to eight possible stereoisomers (four enantiomeric pairs). Only the (-)-menthol enantiomer possesses the intense cooling and clean, desirable minty odour. For example, the (+)-menthol enantiomer is less cooling and possesses an undesirable musty off-note odour. This note is also present in racemic menthol.

(-)-Menthol is one of the largest volume chiral chemicals with a 2009 production volume estimated at about 21,000-22,000 tonnes. Prior to World War II, production was almost totally from *Mentha arvensis* oil and was controlled by Japan and China. In 1939, Japan exported 260 tonnes of menthol, while China's exports in 1940 were 191 tonnes.

With the advent of war, shipments to the allied countries ceased and major shortages occurred. Seeing an opportunity, Japanese and Chinese immigrants in Brazil began planting *M. arvensis* for menthol production. In 1941, Brazil produced five tonnes of menthol, rising to 1,200 tonnes by 1945.[1]

In the 1960s, Brazil's production peaked at about 3,000 tonnes as China again began supplying menthol. During the 1960s, an oversupply of menthol caused the price to fall as low as $7.70-8.80/kg, with processors then reducing production levels. This ultimately led to worldwide shortages with pricing rising for a short time to over $50/kg.

In 1958, India began extensive plantings of *M. arvensis* but, until the late 1980s, India's quality was variable and often had low menthol content. In the 1980s, new strains were introduced that gave improved oil yields with menthol contents of 75-85%. By 1996, India was producing 6,000 tonnes/year of *M. arvensis* oil and had surpassed China as the major producer of menthol.[2]

We estimate that India produced about 34,000-35,000 tonnes of mentha oil in 2009 but that this fell by about 25% to 27,000-28,000 tonnes last year, due to reduced plantings and weather conditions. While the bulk of this production is used for local menthol crystallisation, large amounts of oil and crude menthol fractions are also exported to Brazil, Taiwan and Japan for further menthol production.

For 2010, we project that 'natural' (-)-menthol production worldwide will be about 12,500 tonnes with synthetic (-)-menthol production at about 6,800 tonnes, for a total of about 19,300 tonnes. This represents a decline of about 14%,

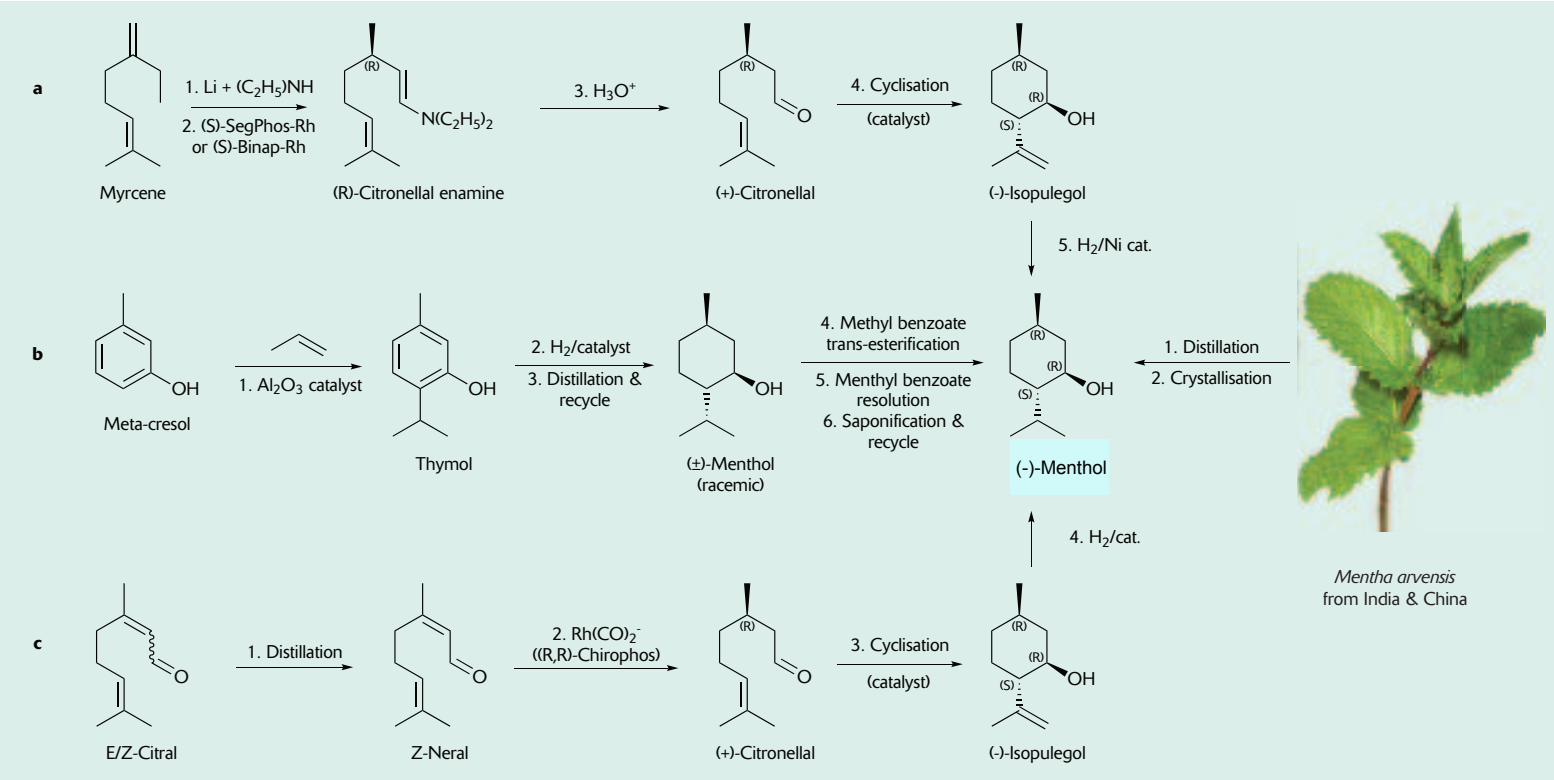


Figure 1 - Routes to (-)-menthol

Mentha arvensis from India & China

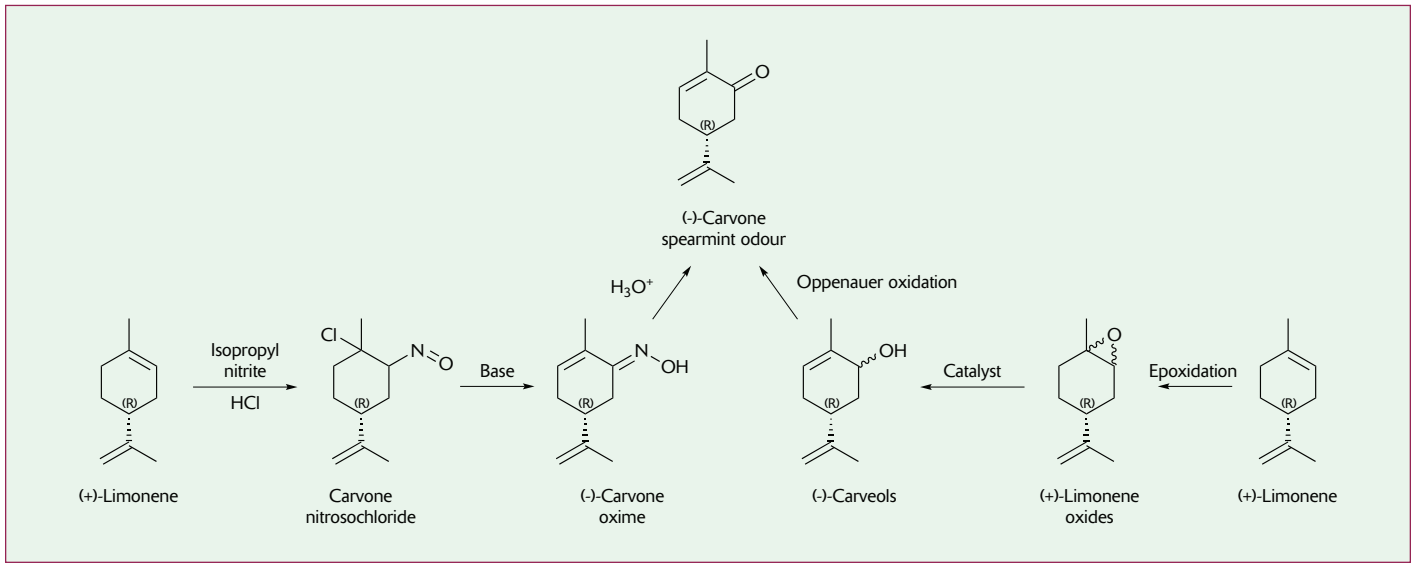


Figure 2 - Routes to (-)-carvone

due primarily to the drop in natural production. Consumption remains strong, putting upward pressure on prices. Symrise indicates that demand for menthol has been rising at a double-digit rate for years.[3]

In the 1970s both Takasago and Haarman & Reimer (now part of Symrise) introduced commercially viable routes to synthetic (-)-menthol. Takasago's process (Figure 1a) uses myrcene as the starting material, which is converted to N,N-diethylgeranylamine and then asymmetrically isomerised via the chiral rhodium (S)-Binap (or SegPhos) complex to the optically active enamine of citronellal.

Hydrolysis yields (+)-citronellal, which is cyclised to (-)-isopulegol by classical methods. On hydrogenation, the isopulegol gives (-)-menthol in high optical purity. In his 2001 Nobel lecture Professor Ryoji Noyori said that the process "resulted from a fruitful academic-industrial collaboration".[4]

The Symrise process (Figure 1b) starts with meta-cresol being converted to thymol, which on hydrogenation gives a racemic mixture of menthol isomers. Distillation provides racemic dl-menthol, which is reacted with methyl benzoate to give racemic menthyl benzoate.

Optical resolution is achieved by selective crystallisation of the benzoate ester followed by saponification to yield (-)-menthol. In a tribute to German engineering, the Symrise process, which employs extensive recycles, gives an overall yield of >90%.[5] In 2009, we estimate that Symrise's production was about 4,000+ tonnes, while Takasago's was about 1,500+ tonnes.

In June 2010, BASF announced that it would enter the (-)-menthol market by building the world's largest production plant, which is scheduled to be operational in 2012. Nearly simultaneously, Symrise announced plans to double its own capacity. Takasago is doing the same. Once all this is in place, we anticipate synthetic menthol potentially will be larger than natural production.

The new BASF process (Figure 1c) starts with E/Z-citral from which Z-neral is separated by distillation. Asymmetric hydrogenation of neral with a chiral rhodium catalyst yields (+)-citronellal, which can be converted to (-)-menthol via (-)-isopulegol.[6]

The carvones

Chemists in the flavours and fragrances industry recognised in the early 20th century that certain enantiomeric chemicals, such as menthol and carvone, had different organoleptic properties. By the late 1950s, processes had been developed for the industrial syntheses of (-)-menthol from optically active terpenoids and (-)-carvone was being manufactured from (+)-limonene by Norda in the 1960s.

However, academics did not generally accept the premise that optical enantiomers could have different odours until the early 1970s, when two papers appeared that unequivocally proved that that the carvone enantiomers were dramatically different in odour character.[7] (-)-Carvone is the main constituent in spearmint oil and is the primary spearmint odour contributor. (+)-Carvone is the main constituent in caraway oil and is primarily responsible for its caraway odour.

(-)-Carvone is used extensively to extend and supplement spearmint oil in flavourings and oral care products. It is produced from purified citrus (+)-limonene, by two procedures. The classical route is via the nitrosochloride followed by a weak base to form carvone oxime. The oxime is converted to (-)-carvone by acid hydrolysis in the presence of a hydroxylamine acceptor, such as acetone.[8]

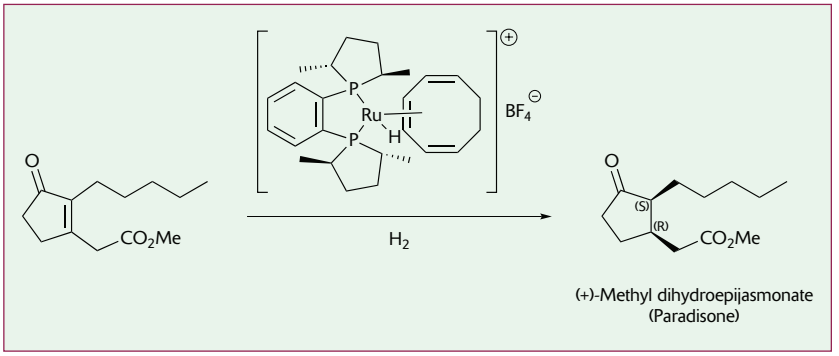
The other route is by the rearrangement of (+)-limonene oxide to (-)-carveol using a catalyst consisting of a combination of metal salts and phenolic compounds. The (-)-carveol is subsequently oxidised to (-)-carvone by an Oppenauer oxidation (Figure 2).[9] (+)-Carvone is also synthesised industrially in a similar manner from (-)-limonene.

The methyl dihydrojasmonates

Methyl dihydrojasmonate (Hedione) is closely related to methyl jasmonate, which occurs in jasmine oil. It has a typical fruity, jasmine-like odour. Hedione was discovered in 1959 in Firmenich's laboratories and its first perfumery use was in Dior's Eau Sauvage in 1966.[10]

As is the case with the methyl jasmonates, only the *cis* or *epi*-methyl dihydrojasmonates possess the intense jasmine

Figure 3 - Enantioselective synthesis of (+)-methyl dihydroepijasmonate



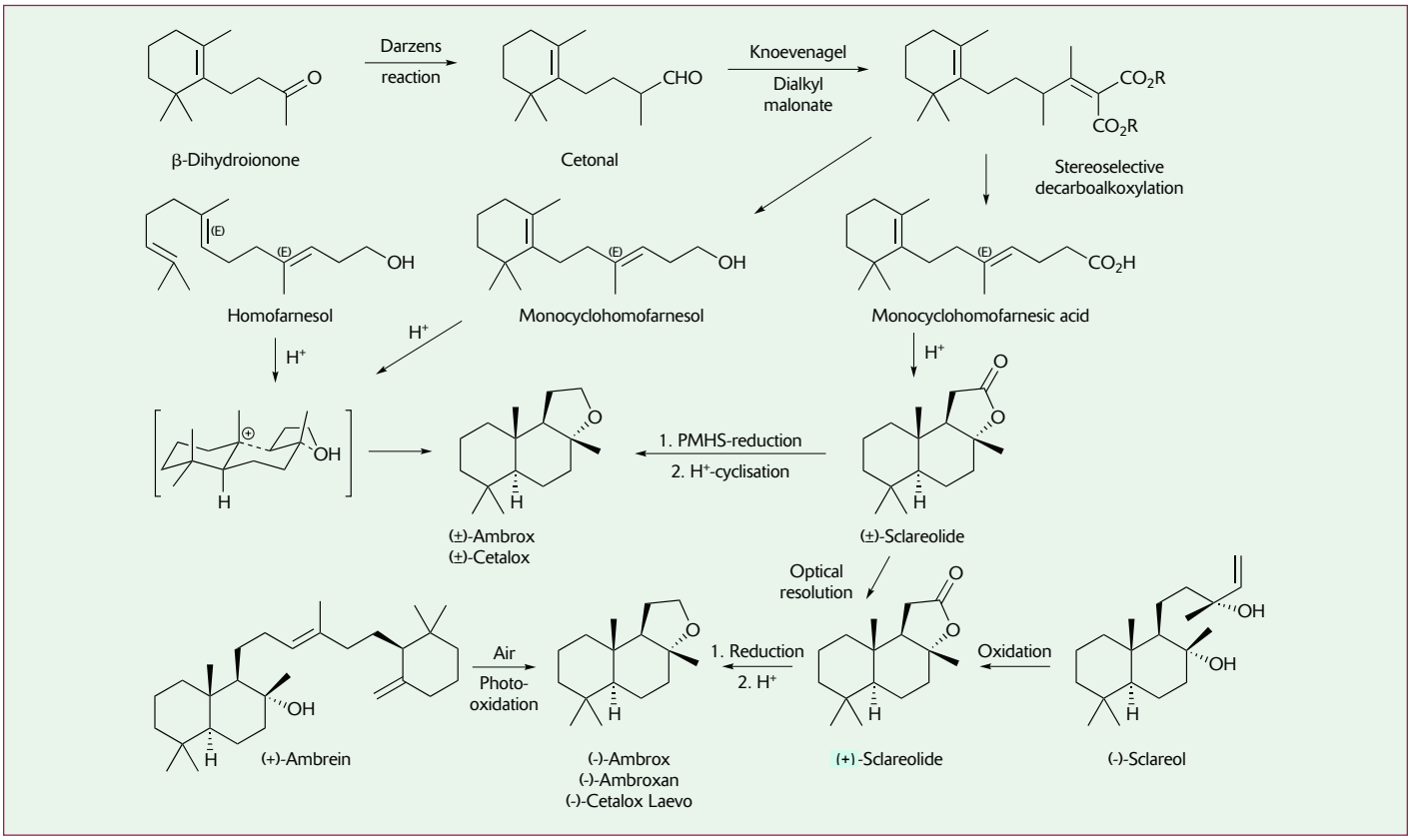


Figure 4 - Routes to Ambrox

odour. Several grades enriched in the *cis* isomer are now available: IFF's Kharismal (>57% *cis*), Zeon's Super Cepionate (>70% *cis*) and Firmenich's Hedione HC (~75% *cis*).

The *cis* isomer tends to isomerise into the weaker *trans* form outside the narrow pH range of 5-7, which limits its use primarily to fine fragrances. However, the success of the methyl dihydrojasmonates is proved by the fact that it is used in almost all fine fragrances and is Firmenich's top seller in terms of volume.[11]

Of the enantiomeric *cis* isomers, the 1R,2S-(+)-epi-methyl dihydrojasmonate (Paradisone), which is 800 times more powerful than its enantiomer, is most desired. Perfumer Arcadi Boix Camps from Auram Art & Perfume indicates a perfume blotter of Paradisone in a 70 m^3 room "diffuses the space with the angelic aromas of one million flowers" and calls its synthesis is "one of chemistry's miracles."[12] Figure 3 shows its synthesis by enantioselective catalytic hydrogenation.[13]

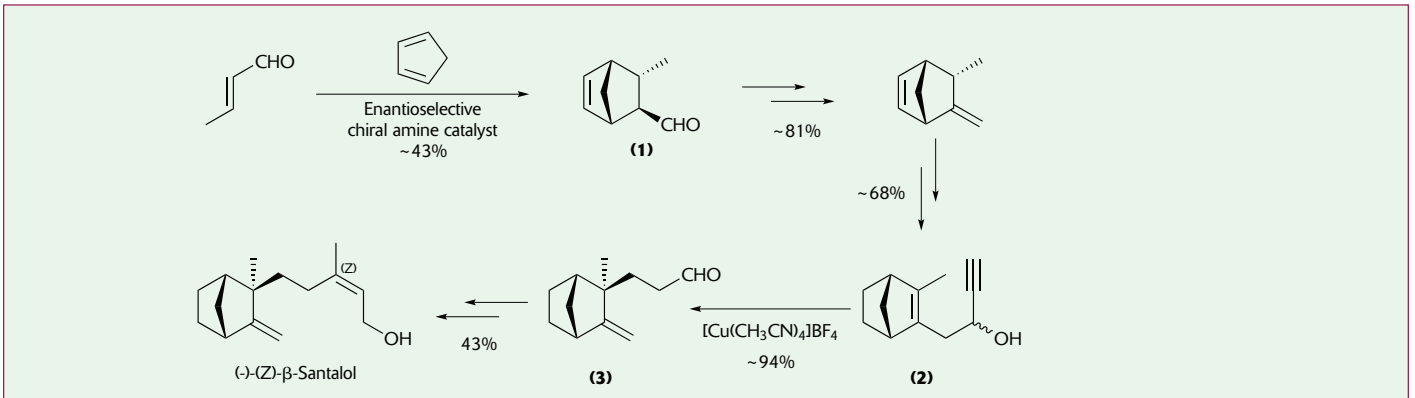
Ambergris

The trading of Ambergris (or Ambra) dates back at least to the 9th century BC and it has been used as a medicine, a spice in Asian cuisine and as an aphrodisiac. By the 14th century AD, ambergris had become one of the most valued perfumery ingredients, along with musk and civet. Today, the trade is almost non-existent, due to the global moratorium on commercial whaling.

Ambergris is a rare product that is produced in the digestive tract of the sperm whale (*Physeter macrocephalus*) as a pathological waxy substance, presumably to protect it from injuries caused by the sharp beaks of the giant squid (a major dietary staple). When expelled from the whale, ambergris floats and is exposed to air, sunlight and the waves. In this process, the substance changes from a light-coloured material to a dark to grey-amber shade and develops its characteristic aroma.

Due to its value in perfumery, Firmenich started an extensive research program on ambergris's composition in the 1930s.[14] This research, carried out by Max Stoll's group, in collaboration with Leopold Ruzicka, centered on the triterpene ambrein which comprises about 25-45% ambergris. On degradation, it was shown to have a relationship to the diterpenes manool and sclareol.[15]

Figure 5 - Enantioselective synthesis of (-)-(Z)-β-santalol



Both Edgar Lederer in Paris and Ruzicka's group reported the structure of ambrein in 1946.[16] Lederer became a Firmenich consultant in 1947. As early as 1942, Ruzicka had found that oxidation of sclareol with $KMnO_4$ produced sclareolide, like ambrein.[17,15] This would lead eventually to a commercial synthesis of Ambrox in 1950.[18] However not until 1977 did IFF workers report the presence of Ambrox in ambergris tincture.[19]

In the 1950s, Firmenich launched several specialities, notably Fixateur 404 (1952), based on approximately 10% Ambrox, and Grisambrol (1954), which contained both Ambrox and β-ambrinol.[14] Fixateur 404 was rapidly accepted for its ambergris note in fine perfumery in the 1950s and 1960s.

By the 1970s, Ambrox attracted use in other products, such as soaps and detergents. When Henkel introduced its version of this molecule - Ambroxan, which is now marketed by Kao - in the 1970s, Firmenich released Ambrox as an ingredient. The supply widened as other companies released their versions.

Since Ambrox was originally produced only from sclareol, derived from clary sage, which occasionally was in short supply, an extensive research effort soon began by fragrance companies and in academia, to find reliable processes at a lower total cost. By the early 1990s, totally synthetic versions of racemic Ambrox diastereomer isomers were introduced under the tradenames Ambrox DL (Firmenich, 1988), Synambran (Wacker, now Symrise) and Fixambrene (Givaudan-Roure).

Whilst it is beyond the scope of this article to review the hundreds of publications on this subject, Roger Snowden has presented an outstanding paper on the complexities of Ambrox syntheses.[20] For commercial synthesis, the major starting materials investigated have been homofarnesic acid, homofarnesol, monocyclohomofarnesic acid and monocyclohomofarnesol.[21-24] Figure 4 shows the totally synthetic routes and those from natural materials.

Commercially, the main totally synthetic version of Ambrox supplied by Firmenich is Ambrox DL (>50% (±) Ambrox and <50% diastereoisomers) from monocyclohomofarnesol. Cetalox, introduced in 1993, (>96% (±) Ambrox) is produced from monocyclohomofarnesic acid and Cetalox Laevo, introduced in 2004 (>99% (-)-Ambrox) is presumably produced via the optical resolution of the intermediate (±)-sclareolide.[25]

Whilst Ambroxan-type products and Cetalox Laevo have the highest purity, all of the Ambrox type products are widely used in perfumery for their ambergris, animal, amber, woody notes. We estimate that production of these materials exceeds 20 tonnes/year.

Sandalwood

Although several species of sandalwood are available in commerce, the most prized is that of *Santalum album L*. which is today in extremely short supply. Historically, India was the major producer, but this wood has been over-harvested and the government now bans exports, although illegal harvesting and smuggling continues to exacerbate the problem.

East Indian Sandalwood oil, produced by steam distillation, is a highly valued perfume raw material, with a current price close to $2,300/kg. Because of the lack of reliable supply and high cost, it has largely been replaced by synthetic substitutes or the lesser quality Australian sandalwood oil from *Santalum spicatum*.

The two major constituents of East Indian Sandalwood oil are (+)-(Z)-α-santalol and (-)-(Z)-β-santalol, which together compose 70-90% of the oil in a ratio of about 70:30. Of the two, only the latter is considered the 'gold standard' for sandalwood odour as it adds a urinaceous, animalic sandalwood tonality to the oil.[26]

In 1990, Krotz & Helmchem synthesised both enantiomers of (Z)-β-santalol and found that only the (-)-enantiomer had the typical sandalwood odour of the natural oil while (+)-(Z)-β-santalol was described as odourless.[27] Until recently, no potential industrial synthesis of (-)-(Z)-β-santalol has been achieved.

In 2009, Charles Fehr and co-workers designed 'the right cat for the desired odour' in a synthesis of the prized fragrance (–)-β-santalol.[28] The route uses a highly enantio- and exo-selective Diels-Alder reaction between cyclopentadiene and crotonaldehyde to form the intermediate **1** (Figure 5) using the chiral amine catalyst, (S)-2-[Bis-(3,5-bistrifluoromethylphenyl)-trimethylsilyloxymethyl]pyrrolidinium perchlorate.

This is transformed into an enynol (**2**) which undergoes a highly selective copper-catalysed cyclisation-fragmentation reaction to form (**3**) from which (-)-(Z)-β-santalol can be formed by classical procedures. Totally synthetic (-)-(Z)-β-santalol is not yet commercially available, but do not count the fragrance chemists out - it may be just around the corner.

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* - Hedione, Paradisone, Ambrox & Cetalox are trademarks of Firmenich SA; Kharismal is a trade name of International Flavors & Fragrances; Cepionate is a trademark of Zeon Corporation; Ambroxan is a trademark of Kao Corporation; Synambran is a trademark of Symrise AG

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Corrections: The structures shown in "Red" should have appeared in the original article

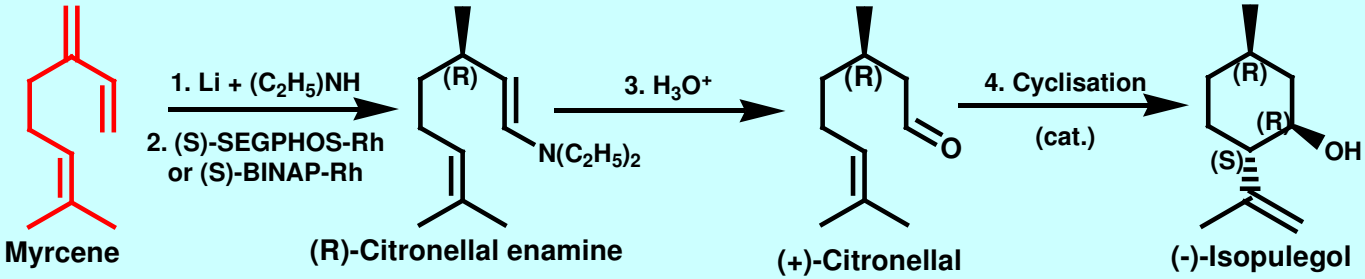

Figure 1. Routes to (-)-Menthol

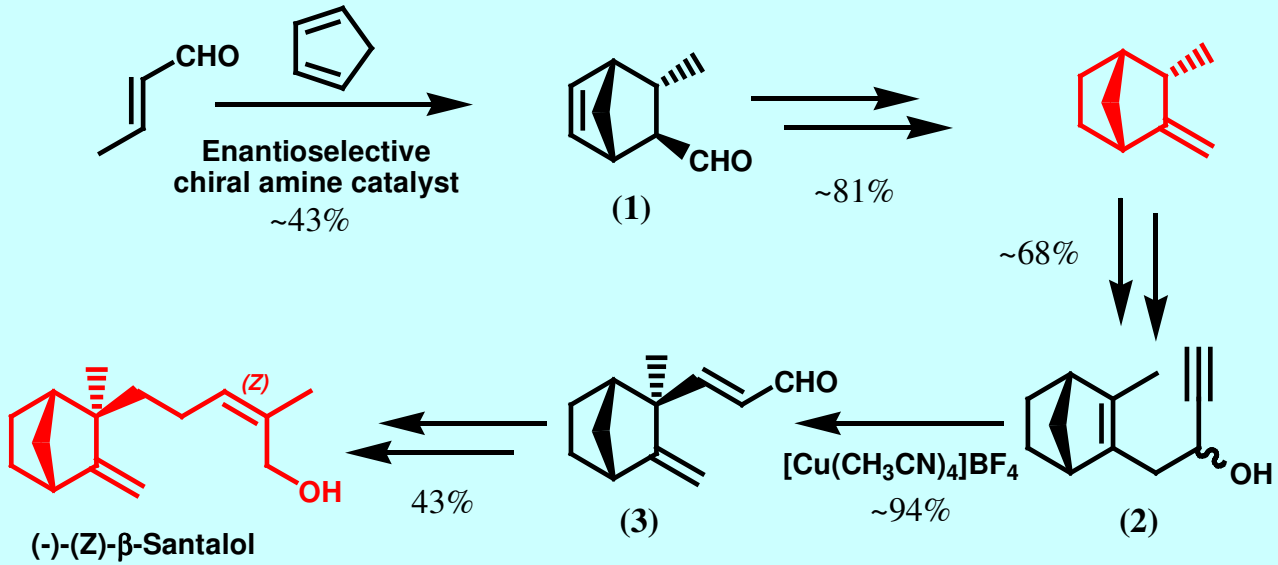

Figure 5. Enantioselective Synthesis of (-)-(Z)-β-Santalol

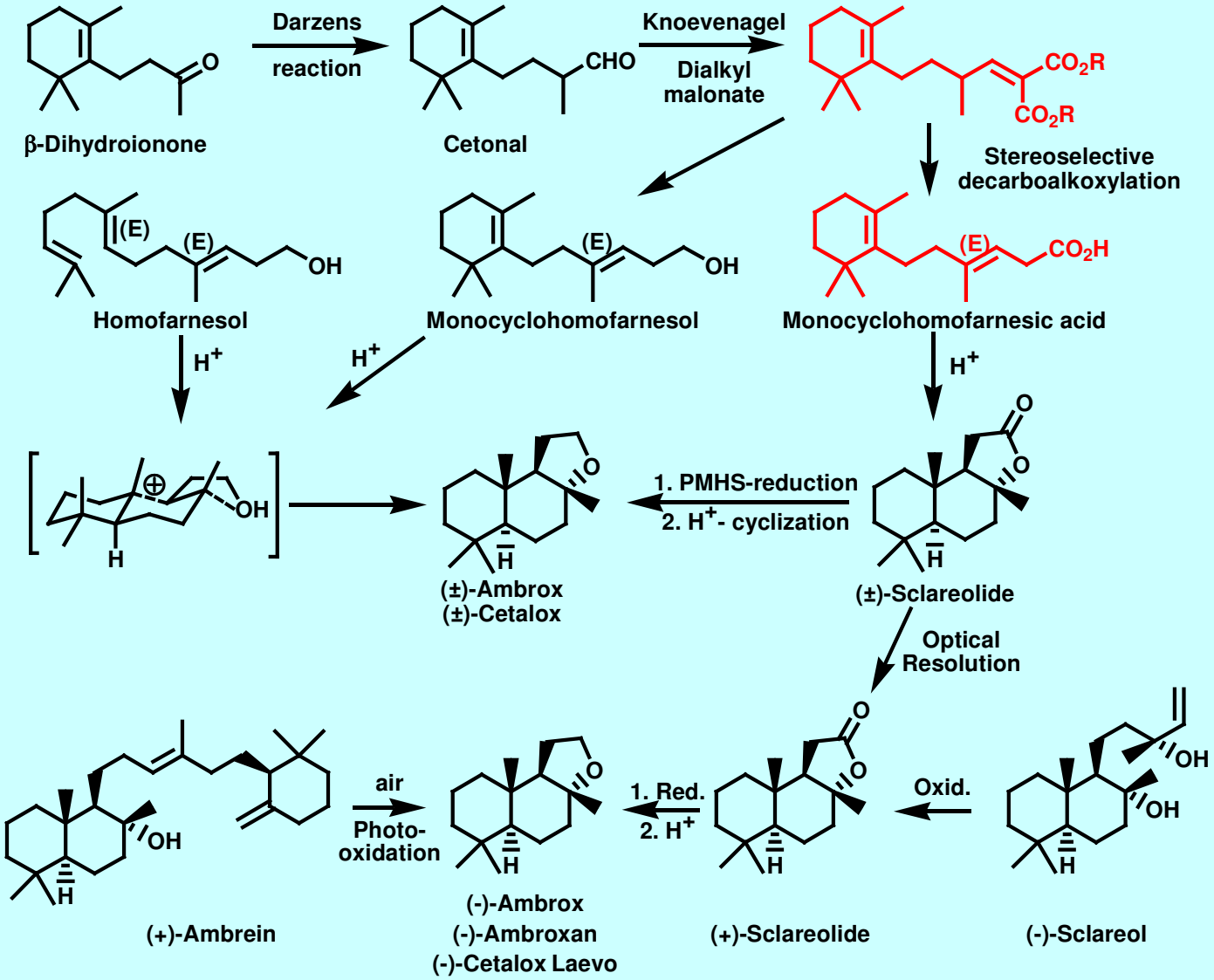

Figure 4. Routes to Ambrox