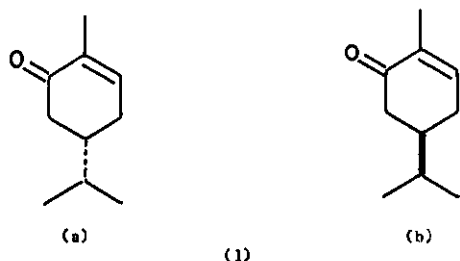


Synthetic Routes to Carvone

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Carvone (1),¹ p-mentha-6,8-diene-2-one, formerly designated as carveol,² is a common and important constituent of essential oils. It occurs in (+)-, (-)-, and (\pm)-forms. (+)-Carvone (1a) is the main component (50-60%) of the caraway (*Carum carvi*) and dill (*oleum anethi*) oils; the (-)-variety (1b) is found in spearmint oil (up to 70%) and in kuromoji oil.^{3a} (\pm)-Carvone is pre-



sent in gingergrass oil.^{3a} (The pronounced differences in odor and taste of the optical isomers of carvone effectively illustrate the importance of stereoisomerism from an organoleptic point of view.^{4,5}) This α,β -unsaturated ketone is used extensively as an odorant and flavorant, and has considerable economic value. But the carvoniferous oils are expensive and subject to price fluctuations. Therefore, several synthetic routes have been developed to provide a substitute for the natural product or a partial replacement of it. These synthetic routes will be reviewed in this article.

Syntheses from limonene

About 80 million pounds of (+)-limonene (2) per year is potentially available from the citrus industry but only a quarter of this amount is currently recovered and marketed.⁶ This abundant raw material constitutes an excellent starting point for the production of carvone.

Via nitrosochlorination. In the approach shown in Chart 1, (+)-limonene (2) is converted,

through the intermediates of (+)-limonene nitrosochloride (3) and (-)-carvoxime (4), into (-)-carvone (1b). It is worthwhile to note that this synthesis involves the reversal of the optical rotation of limonene.⁷ The original nuclear double bond, which is arbitrarily fixed in the Δ^1 -position with respect to the asymmetric C₄-atom, is shifted to the Δ^6 -position and this results in the optical inversion.⁷ From (-)-, (+)-, and (\pm)-limonene this synthesis affords (+)-, (-)-, and (\pm)-carvone respectively.⁷

Originally discovered by Tilden and Shennstone,⁸ the fundamental nitrosochlorination reaction can be effected by the action of gaseous nitrosyl chloride⁹⁻¹¹ and of methyl nitrite,⁷ ethyl nitrite,^{7,12-15} butyl nitrite,¹⁶ amyl nitrite¹² or nitrogen trioxide¹⁷ in the presence of hydrochloric and sulfuric or acetic acid. Solvents such as ethanol,¹³ isopropyl alcohol,^{11,15} liquid sulfur dioxide⁹ and carbon tetrachloride¹⁰ and temperatures varying from 15 to -70° have been recommended.^{7,9,11} By this process, nitrosochloride consisting of a mixture of α - and β -varieties is obtained,¹⁸ but its splitting is not required for conversion into the oxime. The nitrosochlorides are unstable, sensitive to heat and acid, and are liable to violent decomposition by autocatalytic reaction at room temperature; their satisfactory dehydrohalogenation demands great and expensive dilution.^{7,15} The reagents recommended for dehydrohalogenation include ethanol,¹⁹ methanol²⁰ alcoholic solution of sodium and potassium hydroxide,²¹ sodium methylate,²² pyridine,^{9,13-16,23} urea,^{9,10} and dimethylformamide.¹⁵ Pyridine affords carvoxime in 90-95% yield,^{9,13} but urea in the presence of absolute isopropyl alcohol gives 99% yield.⁹

For the final step in the synthesis, one can proceed directly without the purification of carvoxime.² The hydrolysis is accomplished by hydrochloric,⁷ sulfuric,^{9,15,20} phosphoric,^{7,11} oxalic acid,^{13,14} and acetic acid-iron combination.²⁴

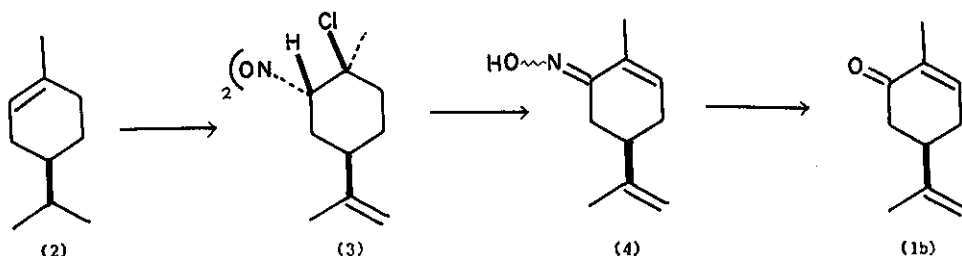


Chart 1. (-)-Carvone from (+)-limonene via nitrosochlorination.

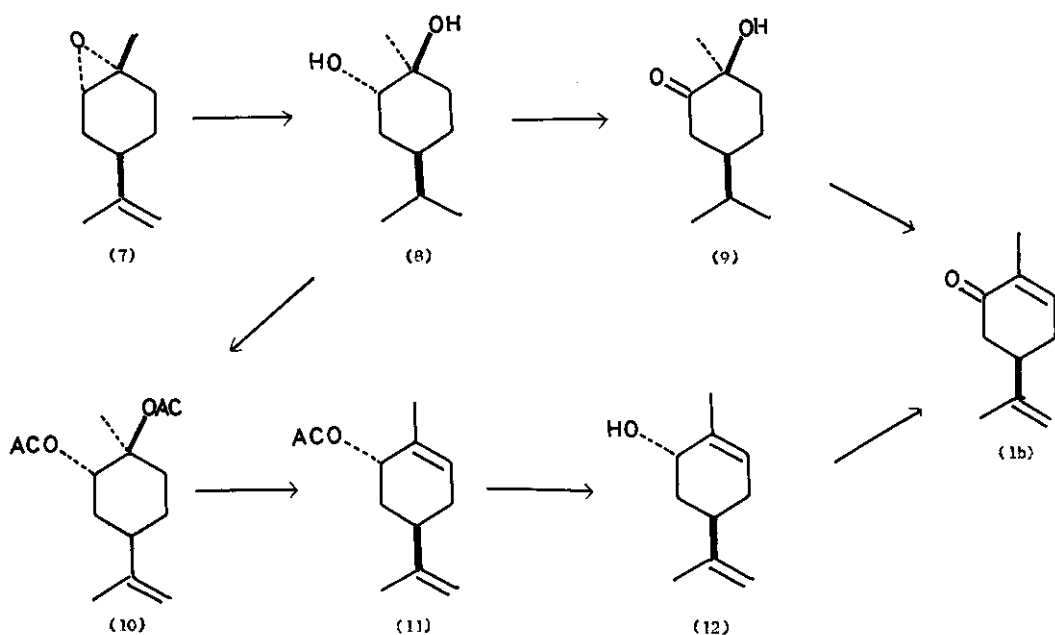


Chart 2. (-)-Carvone from (+)-limonene via epoxidation.

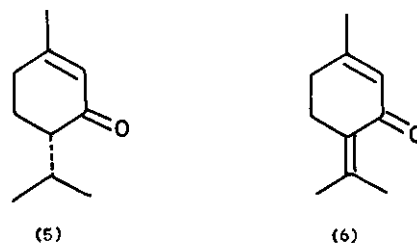
Hydrolysis is often incomplete and accompanied with racemization and isomerization.^{7,8} However, satisfactory conversion is feasible if the reaction is carried out at pH 0.7 to 0.9,^{8,13,15} or by the addition of hydroxylamine acceptors such as acetone,¹¹ methyl ethyl ketone,¹¹ cyclohexanone,¹¹ formaldehyde,¹¹ acetaldehyde,¹¹ glyoxal,²⁵ paraldehyde,²⁶ or CuSO_4 .²⁷

Under carefully controlled conditions, the nitrosochloride in alcohol solution can be converted into carboxime hydrochloride and hydrolyzed in the same operation to carvone.^{7,11} The generated carvone is recovered by steam and purified by distillation. If exceedingly pure carvone is required, then it must be extracted by bisulfite addition²⁸ or hydrogen sulfide complexing²⁹⁻³² followed by vacuum fractionation.

By allylic oxidation. Eschinazi^{7,33} has claimed two practical methods for the allylic oxidation of the C₆ atom in limonene to yield carvone. Essentially these methods rest on photo-oxidation and on oxidation utilizing the butyl chromate reagent of Oppenauer and Oberrauch.³⁴ The carvone obtained by the above allylic oxidations retains the original optical rotation. Thus we have fascinating routes to (+)-carvone from the inexpensive (+)-limonene. These methods yield a mixture of carvone and isopiperitenone (5) without admixture with nitrogenous compounds.⁷ This product is claimed to fulfill the high standards of odor purity in perfumery;⁷ however, its application in flavors is doubtful.

Tert-butyl chromate or aerial oxidation of (+)-limonene (2) at 50° for 36 hr in benzene with or without acetic acid and acetic anhydride yields (±)-carvone (20%);^{35,36} (+)-isopiperitenone (5) (13%), and piperitenone (6) (3%) are by-products.

On oxidation with molecular oxygen in acetic acid at 50° in the presence of cobalt acetate, limonene gives (±)-carvone as the principal



product (40%).³⁷ Performance of several initiators like Co(II)bis- and Co(III)tris- (acetylacetonate), Mn acetate, and Ni acetate have been reported.

Wilson and Shaw⁶ have recently reported the oxidation of (+)-limonene with tert-butyl perbenzoate and peracetate to an ester mixture which, on hydrolysis followed by oxidation of the resulting alcohol with chromic acid, yields (-)-carvone and piperitenone (6) in 23% and 15% overall yields respectively. Optically pure (-)-carvone (1b) can be recovered from the mixture by distillation.

Carvone is also prepared by auto-oxidation of limonene at room temperature followed by oxidation of the resulting carveol with dichromic acid.³⁸

Via epoxidation (Chart 2). Two methods have been reported by Linder and Greenspan.³⁹ In one, the epoxide (7) derived from (+)-limonene is hydrolyzed to the glycol (8), which is then oxidized to the keto alcohol (9) and dehydrated to (-)-carvone (1b). The yield of carvone from the glycol is approximately 9.2%. In the second, the glycol (8) is converted to the diacetate (10), which in turn is pyrolyzed to carveol acetate (11), then saponified to carveol (12), and finally oxidized to (-)-carvone (1b). The overall yield of carvone from the epoxide is approximately 7%.

Synthesis from α -terpinyl acetate (Chart 3)

We shall now turn our attention to the conver-

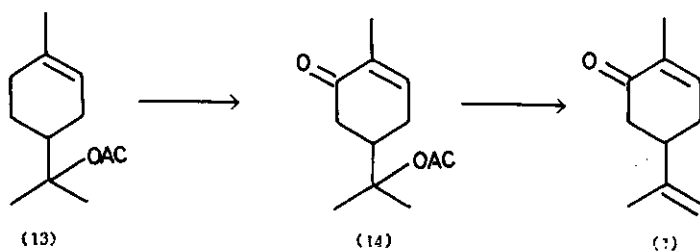


Chart 3. Carvone from α -terpinyl acetate.

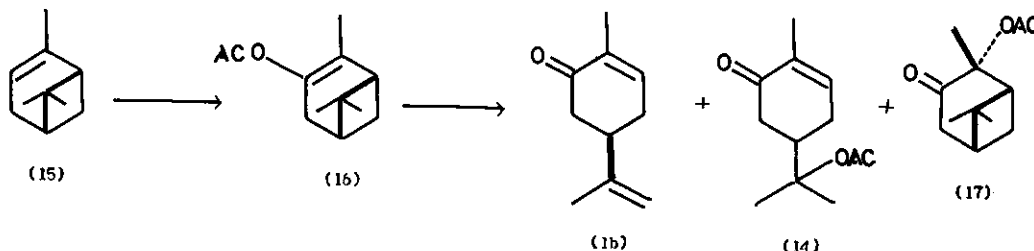


Chart 4. (-)-Carvone from (-)- α -pinene by electro-oxidation.

sion of (\pm)- α -terpinyl acetate (13) into (\pm)-carvone through pyrolysis of 8-acetoxycarvotanacetone (14).^{40,41} With tert-butyl chromate, the acetate (13) undergoes facile oxidation of the methylene group in C₆ position in the ring, affording the desired α,β -unsaturated ketone (14). Decomposition of 14 is carried out by distillation through a Vigreux column at atmospheric pressure in an oil bath, the temperature of which is gradually raised from room temperature to 340° during the operation. The neutral portion (66%) of the pyrolysate contains 72% of (\pm)-carvone.

Syntheses from α -pinene

Electro-oxidation (Chart 4). An elegant method of preparation of (-)-carvone (1b) from (-)- α -pinene (15) consists of the anodic oxidation

of the enol acetate of isopinocampone (16) in methylene chloride-acetic acid solvent.⁴² The required 16 is secured from (-)- α -pinene (15) through hydroboration-oxidation followed by reaction between the resulting ketone and isopropenyl acetate. During anodic oxidation (-)-carvone (1b), 8-acetoxy-p-menth-6-en-2-one (14), and an acetoxy ketone (17) are formed. The conversion to 1b is controlled by the nature of the solvent used and the supporting electrolyte. Maximum yield of 1b (approximately 64%) is obtained when methylene chloride-acetic acid (8:1) is used as a solvent, along with tetraethylammonium p-toluene sulfonate as supporting electrolyte.

Oxidation with peracids. A German patent⁴³ covers the production of carvone from α -pinene

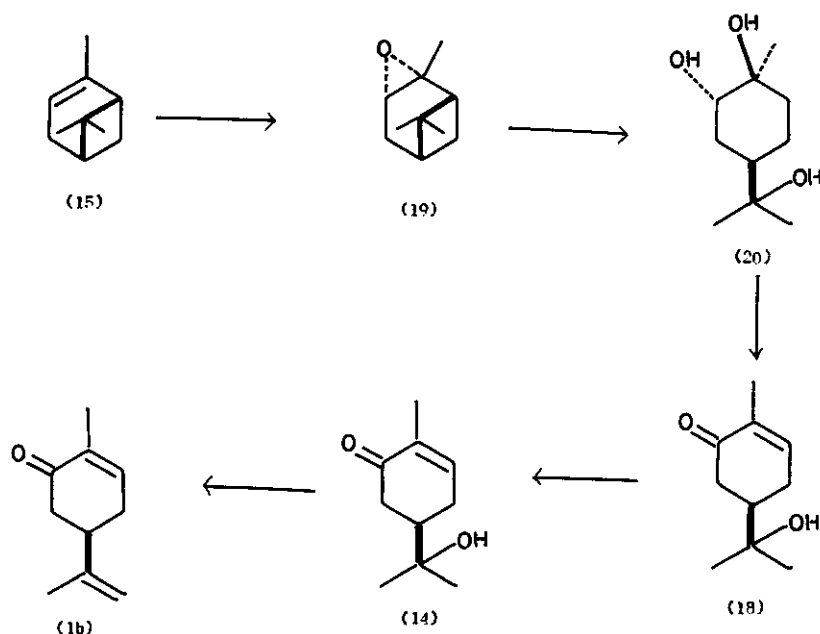


Chart 5. (-)-Carvone from (-)- α -pinene via epoxidation.

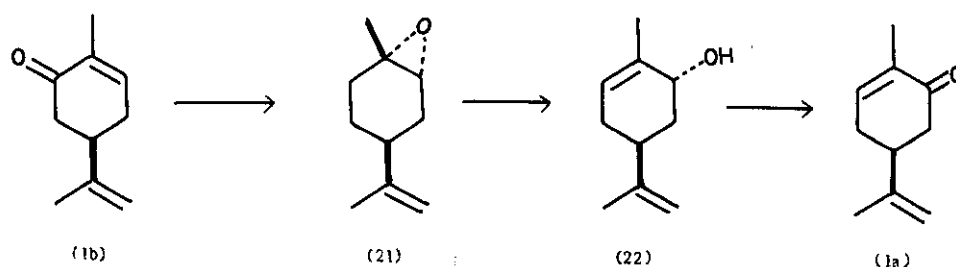


Chart 6. Isomerization of (-)-carvone.

by performic acid oxidation of the latter and dehydrating the resulting 8-hydroxycarvotanacetone (18) with *p*-toluene sulfonic acid; the yield is 7-13%. The process is applicable to the preparation of racemic carvone or its optical isomers.

Via epoxidation (Chart 5). Reference has already been made to the pyrolysis of 8-acetoxycarvotanacetone for the production of carvone.⁴⁰ The necessary 8-hydroxycarvotanacetone (18) can also be conveniently obtained from (-)- α -pinene (15) through the intermediates α -pinene oxide (19) and sobrerol (20). Since sobrerol is susceptible to racemization by acids, a nonacid oxidizing agent should be employed for its conversion to 8-hydroxycarvotanacetone. Any suitable carboxylic acid ester can be used, although the acetate is preferred because it is so readily and cheaply prepared. The carvone obtained in the pyrolytic operation retains the optical rotation of the same sign as the starting pinene.⁴⁴

Interconvertibility of carvone enantiomers

Of great significance is the conversion of (-)-carvone to its enantiomer (and *vice versa*) as illustrated in Chart 6.⁴⁵⁻⁴⁸ Base catalyzed epoxidation of (-)-carvone (1b) gives the epoxy ketone (21). Upon hydrazine reduction 21 furnishes trans-carveol (22) which is oxidized to (+)-carvone (1a) with MnO_2 .⁴⁸

Summary

Methods leading to (-)-, (+)-, and (\pm)-carvone have been reviewed. The technical production of (-)-carvone is based on the widely available (+)-limonene; the most favored route is that epitomized in Chart 1. Though the steps involved are simple, their exploitation is a well-guarded secret. There is no similar commercial-scale production of (+)-carvone⁴⁹ because the basic materials for its synthesis are not as readily available. However, sooner or later the rising demand for this ketone will ensure that it, too, will be produced synthetically.

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Perfumer's Notebook

By Calamondin

PERFUMES—EFFECT OF THE PRODUCT MEDIUM

The perfumer formulating a fragrance for a product usually has some odor profile in mind. The odor of the oil will suggest the general character of the fragrance, but changes as it is incorporated into the medium are the rule rather than the exception. Let us consider some reasons for such changes. They may occur immediately, within a short time, or on longer aging but here we are concerned with the changes in odor induced by the product without particular regard to time.

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Dilution is the first influencing factor. The temperature/volatility curve has been discussed previously.* That ratio is one which can be experimentally determined. We are now considering one which is not susceptible to physical measurement. It is the change in odor intensity with dilution, a ratio characteristic of or peculiar to each odorant. On dilution each odorant naturally undergoes a reduction in odor strength and a change in how the nose perceives the odor. The ratio of perceived odor strength to change in concentration varies widely for the palette of odor materials the perfumer uses. As a result a well balanced concentrate may be out of balance at use level. It explains how a fragrance compounded at the bench and seemingly possessing a good balance of topnote, contrast, and body may lose much of these features when diluted by the product.

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A second phenomenon, and one likely to have a greater influence on balance or profile than dilution, is reaction with the medium into which the perfume is incorporated. The reaction may be chemical in nature or it may be due to differential solubility of the perfume components in the product medium. An example is the performance of a perfume containing substantial amounts of phenyl ethyl alcohol in a product which has an appreciable content of water. The greater solubility of PEA in the water phase tends

to reduce its odor effect relative to that in the concentrate.

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The chemical reactions which can occur are numerous. For example, when perfumes containing phenyl acetic acid or a phenol, such as eugenol, are introduced into a weakly alkaline medium, as a toilet soap, significant change will occur. The alkalinity of the soap almost completely neutralizes the phenyl acetic acid with loss of odor. The weakly acidic eugenol is noted to display less intensity from soap than from the concentrate, or from a neutral medium. Some lactones are observed to be less odorous even in a weakly alkaline medium. Such changes as are mentioned are not due to aging but to a more or less immediate reaction between perfume and medium.

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Difference in the solubilities of the components of a perfume in a product is another cause of unexpected changes in odor from that indicated by the concentrate. When perfuming emulsions the odor profile may depend upon whether the emulsion is oil-in-water or water-in-oil, that is whether water or oil is the external phase. Somewhat different fragrance effects are observed if the two emulsion types are perfumed with a concentrate containing significant amounts of alcohols with some water solubility, such as phenyl ethyl alcohol, geraniol, linalol, etc. Some years ago an experimenter reported differences in odor when oil-in-water and water-in-oil emulsions were perfumed with a linalol/linalyl acetate blend. The differences were substantial and due to the different solubility of the alcohol and ester in the two phases.

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Soaps exhibit differences in their solvent action for odorant chemicals resulting in change of profile as a blend is introduced. The perfumer preparing to formulate a fragrance for a toilet soap will do well to first incorporate many single substances prior to compounding in order to compare odorants for their fragrance yield. This phenomenon is separate from the neutralization or enhancement of perfumery raw materials by the base odor of the product and from any neutralization of acidic components.

In addition to testing of individual perfume components in a product it is a useful technique

* See April/May 1977 Perfumer & Flavorist Perfumer's Notebook.