Laevo-menthol—syntheses and organoleptic properties

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Laevo- or (−)-menthol is one of the most important flavorings used in the tobacco industry. Menthol is used extensively in pharmaceuticals, cosmetics, toothpastes, chewing gum, and other toilet goods as well as in cigarettes. The current annual world production is estimated to be in excess of 3 million pounds, of which the tobacco industry consumes approximately 25%.

The majority of (−)-menthol is obtained by freezing the oil of *Mentha arvensis* to crystallize the menthol present. This "natural" menthol is then physically separated by centrifuging the supernatant liquid (called dementholized cornmint oil) away from the menthol crystals. Any residual impurities are due to traces of *Mentha arvensis* oil, and these often impart a slight peppermint aroma to the menthol crystals.[1,2]

Considerable effort has been devoted to the production of (−)-menthol by synthetic or semi-synthetic means from other more readily available raw materials (Fig. 1). Historically, the price of naturally derived (−)-menthol has fluctuated widely. When natural prices are high (e.g., $8/lb) synthetic menthol has been able to compete economically. However, until very recently natural menthol prices have normally been in the $3.50-6.00/lb range and synthetic (−)-menthol production has been only marginally profitable at best. Currently, factors such as currency fluctuations and short crops are having a marked effect. Prices, at least for the short term, have escalated as much as 100%.

DEMENTHOLIZED CORNMINT OIL (ex *Mentha arvensis*)

(+)-CITRONELLAL (ex *Citronella Oil*)

(−)-B-PINENE (ex Eastern U.S. Turpentine; *Pinus palustris, Pinus rigida, Pinus echinata, Pinus elliottii, Pinus virginiana, Pinus banksiana*)

(+)-*delta*-3-CARENE (ex Western U.S. Turpentine; *Pinus contorta, Pinus ponderosa, Larix occidentalis*)

(+)-PULEGONE (ex Spanish Pennyroyal Oil)

(−)-PIPERITONE (ex Australian *Eucalyptus dives* Oil)

(−)-*alpha*-PHELLANDRENE (ex *Eucalyptus numerosa, Eucalyptus phellandra, Eucalyptus dives*)

(+)-LIMONENE (ex Lemon Oil or Orange Oil; via steam distillation of waste citrus peels)

RACEMIC MENTHOL (ex Thymol or racemic Citronellal; via optical resolution)

Fig. 1. Potential raw materials for synthesis of (−)-menthol.

This article reviews the various synthetic sequences and potential raw materials for (−)-menthol production as well as a new procedure for the total synthesis from (+)-limonene, a citrus by-product. The organoleptic properties of the menthol isomers and intermediates from this new synthesis sequence are discussed, along with the importance of the stereochemical aspects on chemoreception.

Synthetic laevo-menthol

From racemic menthol. A major synthetic effort on (−)-menthol has been based on the optical resolution of racemic menthol which can be derived either by the reduction of thymol (ex petrochemical sources) or from racemic-citronellal (ex β-pinene → citral →). The difficulty in the classical menthol resolution techniques is that from a pound of racemic menthol no more than one-half pound of (−)-menthol can theoretically be obtained. Of course, the (+)-menthol which is separated can be isomerized to racemic menthol,[3] but such recycles and resolution techniques are expensive.

Racemic menthol can be separated into its optical antipodes in a number of ways. In general, these methods are based on formation of the crystalline derivative of an optically active material which is then separated by fractional crystallization. Common classical derivatives are materials such as the alkaloid salt of the acid phthalate,[4] campholic acid,[5] and menthoxyacetic acids.[6] More recently a patent was issued wherein a supersaturated solution of a benzoic acid derivative of (±)-menthol is seeded with the (+)- or (−)- form of the derivative to induce selective crystallization.[7] Another novel procedure wherein racemic menthol is resolved over an optically active polymer has appeared.[8]

The discovery of chemical methods for asymmetric reductions[9] offers promise for the future that thymol can be catalytically reduced in such a manner that proper asymmetry would be introduced at C-1 in the menthol mixture produced. Provided the desired optical asymmetry is present at C-1, the remaining asymmetric centers at C-3 and C-4 can be manipulated to give (−)-menthol with little trouble. At present, however, this breakthrough is only an anticipation of things to come.

The stereoselective synthesis of (−)-menthol from readily available optically active terpenoids possessing properly disposed asymmetric center(s) offers intrinsically the most attractive routes to this alcohol without the necessity of optical resolution. Examples of such synthetic possibilities have led to several commercially exploitable procedures which should be mentioned.

From dementholized cornmint oil. Dementholized "cornmint" oil is the supernatant oil obtained from freezing naturally occurring (−)-menthol from oil of *Mentha arvensis*. In compositions this dementholized cornmint oil is similar in many

respects to the peppermint oil obtained from *Mentha piperita* and is valuable in its own right for peppermint flavorings. Considerable quantities of this relatively inexpensive by-product oil (from natural menthol production) have historically been processed by enriching the residual (−)-menthol present by chemical conversion of menthyl acetate (via ester hydrolysis) and menthone isomers (via mild reduction techniques) into additional (−)-menthol. The (−)-menthol can then be separated and purified by distillation derivative crystallization or as the borate ester.[1,10] A typical analysis of dementholized cornmint oil is shown:[11]

Component	Percentage
α-Pinene	1.8
β-Pinene	2.3
(+)-Limonene	6.2
Cineole	0.5
3-Octanol	2.0
(−)-Menthone*	27.6
(+)-Isomenthone*	6.0
(−)-Isopulegol*	4.6
(+)-Neomenthol*	2.6
(+)-Neoisopulegol*	.1.6
(−)-Menthol*	31.7
(+)-Neoisomenthol*	1.0
(+)-Isomenthol*	1.0
(−)-Menthylacetate*	2.9
(+)-Piperitone*	6.1

*All convertible to (−)-menthol by chemical means.

From citronella oil (Figs. 2, 3). The production of (−)-menthol from citronella oil is probably the most popularized synthetic of the procedures, since it is used as an illustration in many organic chemical textbooks. This process has been used commercially both in the United States and abroad whenever the price ratio of citronella oil to natural menthol was advantageous. (+)-Citronellal is separated from citronella oil by fractional distillation and then subjected to cyclization procedures. Classically, t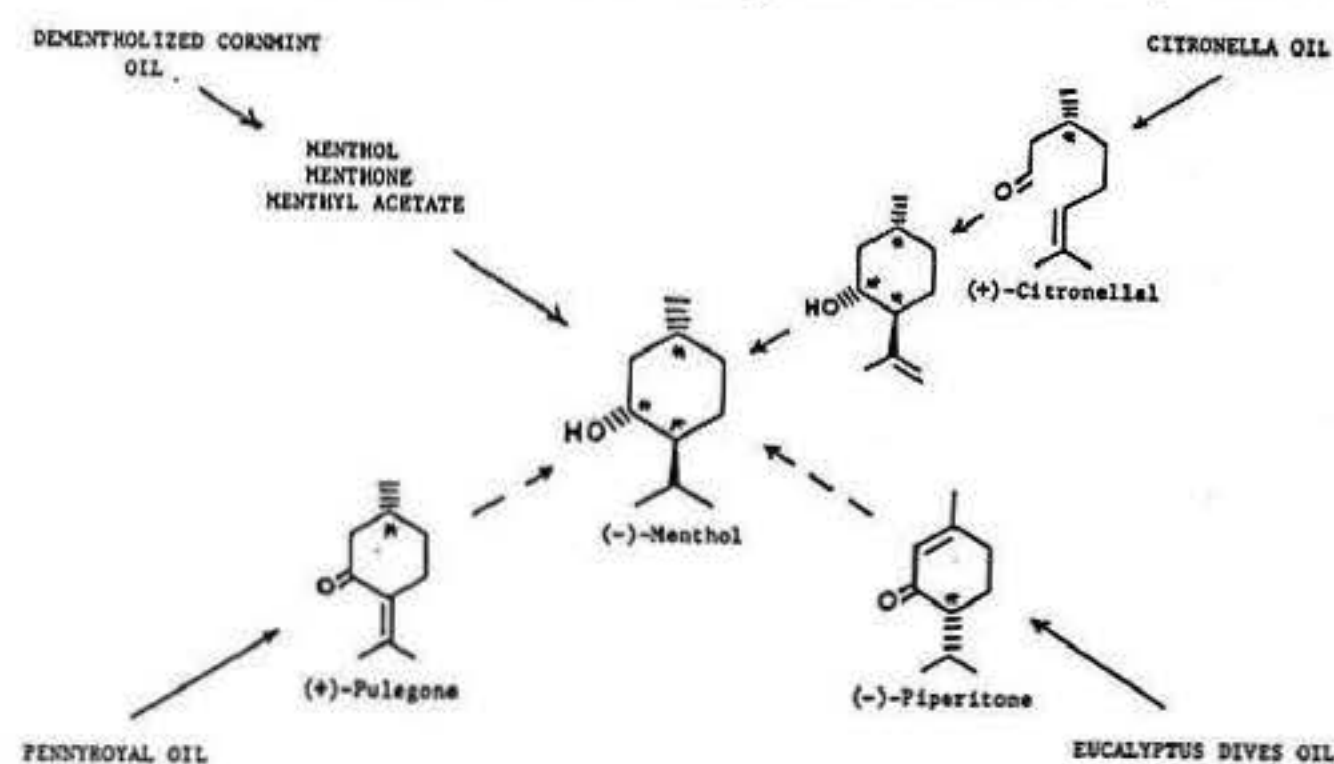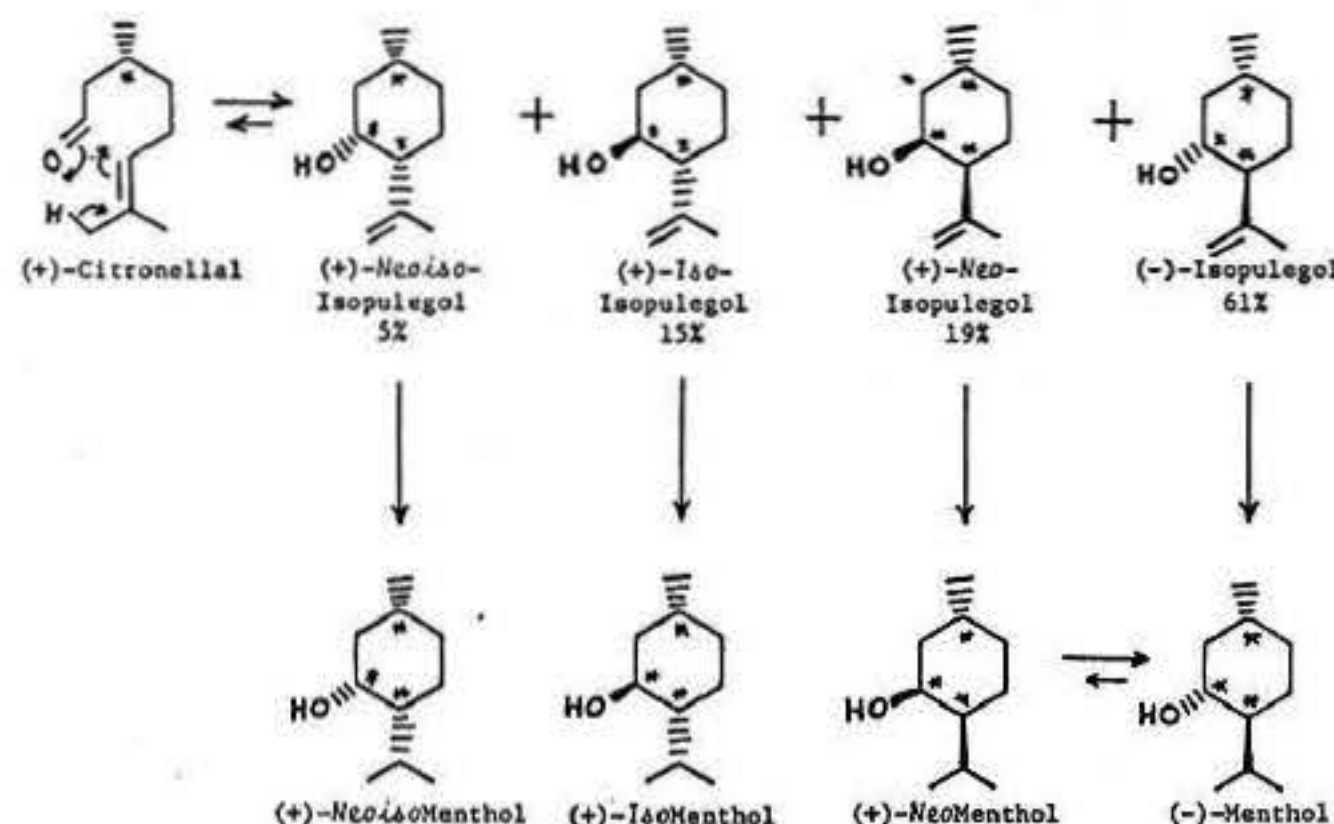his cyclization is carried out in protonic media (formic acid, phosphoric acid, acetic anhydride, or solid loff has shown that thermal cyclization occurs acidic catalysts such as silica). More recently, Oh-cleanly and in high yield.[12,13] The resultant iso-pulegol isomers formed possess the necessary asymmetric center at C-1 of the p-menthane skeleton for (−)-menthol production. The (−)-isopulegol can be physically separated[13] and directly hydrogenated to (−)-menthol, while the remaining isopulegol isomers are recycled to an equilibrium mixture.[13] Alternatively, the total isomeric mixture of isopulegols can be hydrogenated to an isomeric menthol mixture. (−)-Menthol is separated and purified through high efficiency distillation columns and recrystallization (of derivatives). The remaining isomeric menthols can be isomerized catalytically to an equilibrium mixture favoring the desired (−)-menthol isomer.[1] This process of physical separation of (−)-menthol or (−)-isopulegol and isomer equilibration can be continued at will and is an integral part of the commercial production of (−)-menthol from (+)-citronellal. The retention of optical activity in this process is determined completely by the fact that the initial asymmetric center in (+)-citronellal is carried through the entire sequence unchanged. Configurations at C-3 and C-4 in the resultant p-menthane skeleton are manipulated to always correctly relate to C-1. Maintenance of such a center of spatial configuration is mandatory for any successful (−)-menthol synthesis from optically active starting materials.

From (+)-pulegone (Fig. 4). The manufacture of (−)-menthol from (+)-pulegone (ex Spanish pennyroyal oil) similarly is dependent on configuration at C-1 in the present material.[14] In this process the 4,8-double bond is catalytically hydrogenated and then the mixture of (−)-menthone and (+)-*isomenthone* so produced is reduced by sodium in alcohol to give predominantly (−)-menthol. Reduction of menthones by nascent hydrogen generated *in situ* is the preferred procedure inasmuch as this system allows epimerization of the isopropyl group and preferential reduction to an all-equatorial substituent system, presumably via the enolate.[1]
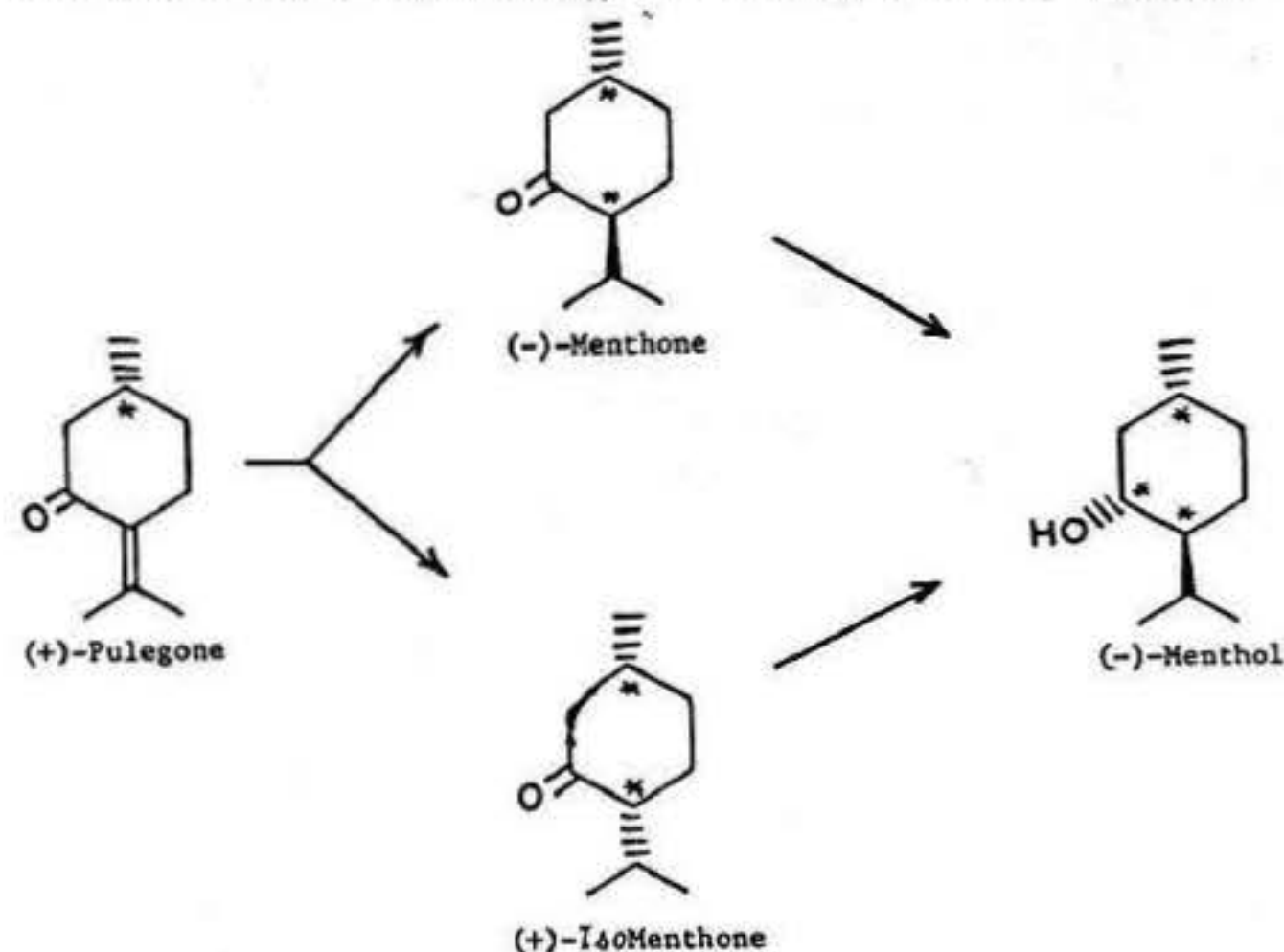

Fig. 2.

Fig. 3. (−)-Menthol from (+)-citronellal.

Fig. 4. (−)-Menthol from (+)-pulegone.

From (−)-piperitone (Fig. 5). (−)-Piperitone is a major constituent of Australian oil of *Eucalyptus dives*. This material presents a somewhat different case because the optical activity is due solely to
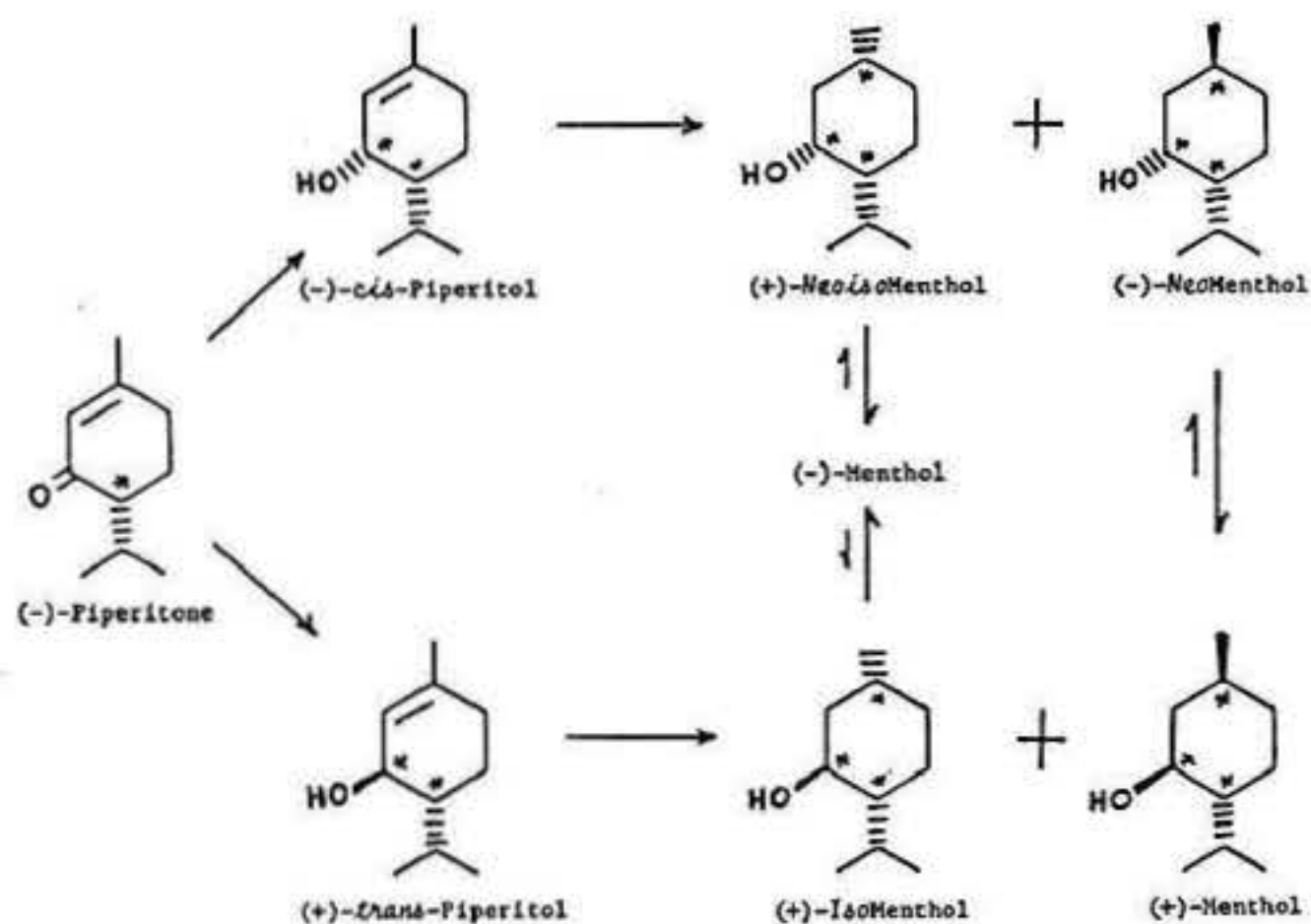
Fig. 5. (—)-Menthol from (—)-piperitone.

the asymmetric C-4 carbon which possesses the opposite configuration present in (—)-menthol. This means that to achieve the correct configuration we must selectively induce the correct asymmetry at C-1 and then invert C-4 in the final product. Because C-4 is adjacent to the ketone carbonyl, (—)-piperitone is easily racemized in the presence of either acidic or basic substances. For this reason much effort has been expended to find a simple procedure for preparing optically pure piperitone from a partially racemized mixture.[15,16]

Hydrogenation of the 1,2-double bond of (—)-piperitone produces (+)-menthone and (+)-isomenthone. Since these ketones are of the opposite optical series with respect to C-1, on reduction with sodium in alcohol, (+)-menthone gives (+)-menthol while (+)-isomenthone gives (—)-menthol. This drawback precludes production of (—)-menthol by this sequence due to partial racemization.[17] Alternatively, (—)-piperitone may be reduced[18] to a mixture of (+)-trans-piperitol and (—)-cis-piperitol (64% trans and 36% cis) using LiAlH$_4$. Hydrogenation of (+)-trans-piperitol with Raney nickel produces (+)-isomenthol (major product) and (+)-menthol (minor product), while (—)-cis-piperitol affords (—)-neomenthol (major product) and (+)-neoisomenthol (minor product). Isomerization of (+)-isomenthol and (+)-neoisomenthol in the presence of oxidation-reduction catalysts can produce (—)-menthol; (—)-neomenthol, however, isomerizes to (+)-menthol. As can be seen, this process is plagued with isomer separation of materials whose configurations at requisite asymmetric centers are antipodal. For this reason, (—)-menthol of high optical purity is rarely ever produced from (—)-piperitone without some optical resolution being required at a final purification stage. A more direct approach at (—)-menthol production from the antipodal (+)-cis and (—)-trans-piperitols will be discussed later.[19]

From α-phellandrene (Fig. 6). The same stereochemical complexities that plague menthol production from (—)-piperitone also are encountered if (—)-α-phellandrene is used as the raw material. Addition of hydrogen chloride to phellandrene affords phellandrene hydrochloride (predominantly, 1-chloro-2-menthene) which can be converted to a mixture of optically active cis and trans piperityl
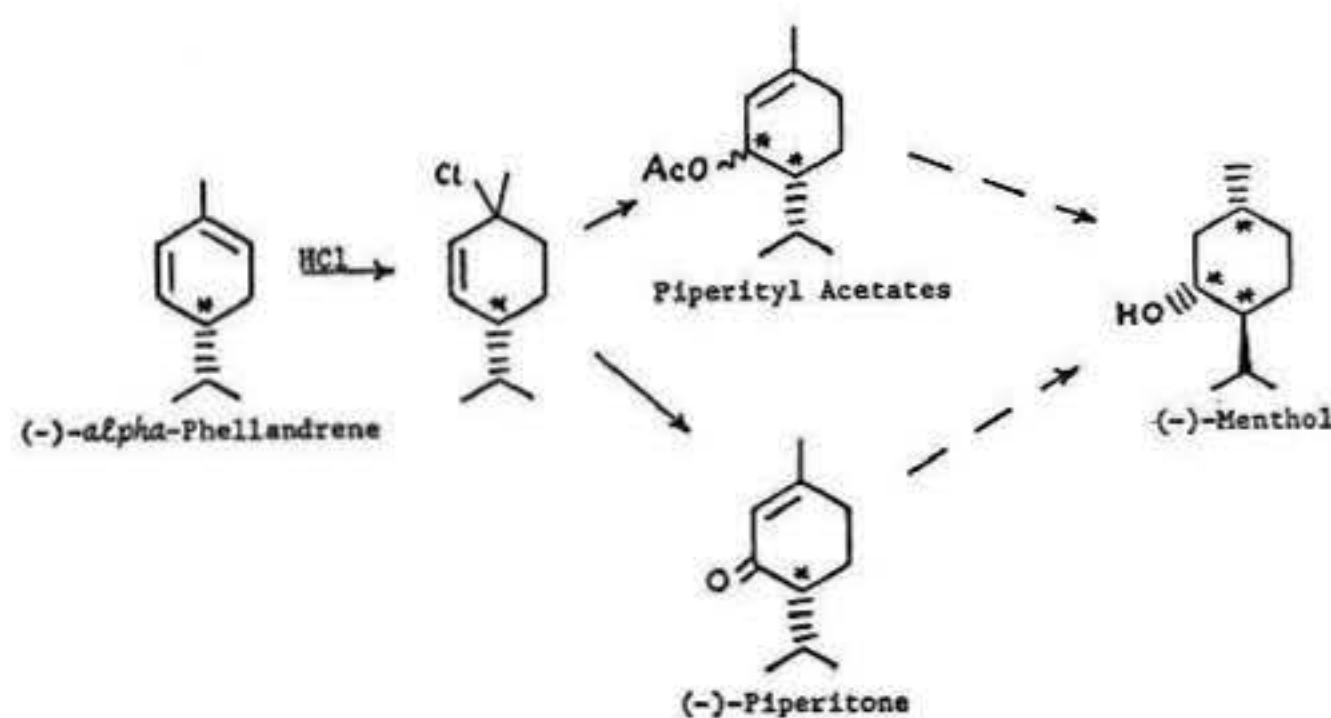

Fig. 6. (—)-Menthol from (—)-α-phellandrene.

acetates by allylic displacement with sodium acetate in acetic acid.[20,21] Hydrolysis affords (—)-cis-piperitol and (+)-trans-piperitol. Alternatively, phellandrene hydrochloride may be oxidized with chromic acid to give (—)-piperitone.[22] Either sequence puts one into exactly the same situation as previously described for converting natural (—)-piperitone to (—)-menthol.

From (—)-β-pinene (Fig. 7). A more successful approach in which asymmetric centers are controlled so as to avoid isomeric materials with opposing antipodes in the synthetic sequence has been developed by Glidden-Durkee (SCM Corporation). (—)-β-Pinene of very high optical purity occurs as a major constituent in both gum and sulfate turpentine produced in the eastern United States. Typically, these types of turpentine contain 60-65% α-pinene and 20-35% (—)-β-pinene from which the latter is commercially separated by fractional distillation for use as a raw material in resins and for perfume and flavor materials such as geraniol, linalool, citral, nopol, and a multitude of related aromatics.[23-28] Hydrogenation of (—)-β-pinene affords predominantly (—)-cis-pinane with the requisite asymmetry at C-1 required for conversion all the way to (—)-menthol. Pyrolysis of (—)-cis-pinane affords optically active 2,6-dimethyl-2,7-octadiene which can be converted to (+)-citronellol by several routes. One procedure involves protection of the 2,3-double bond by reaction with HCl to form 2-chloro-2,6-dimethyl-7-octene followed by anti-Markownikoff addition of HBr. Solvolysis of the intermediate bromo-chloro compound affords a mixture of α- and β-citronellol (either directly or more usually as the ester). [Only the β-isomer is desired and so the α-double bond is subjected to isomerization to the β position.] Alternatively, direct treatment of 2,6-dimethyl-2,7-octadiene with organoaluminum compounds such as aluminum triisobutyl (or alkyl boranes) and
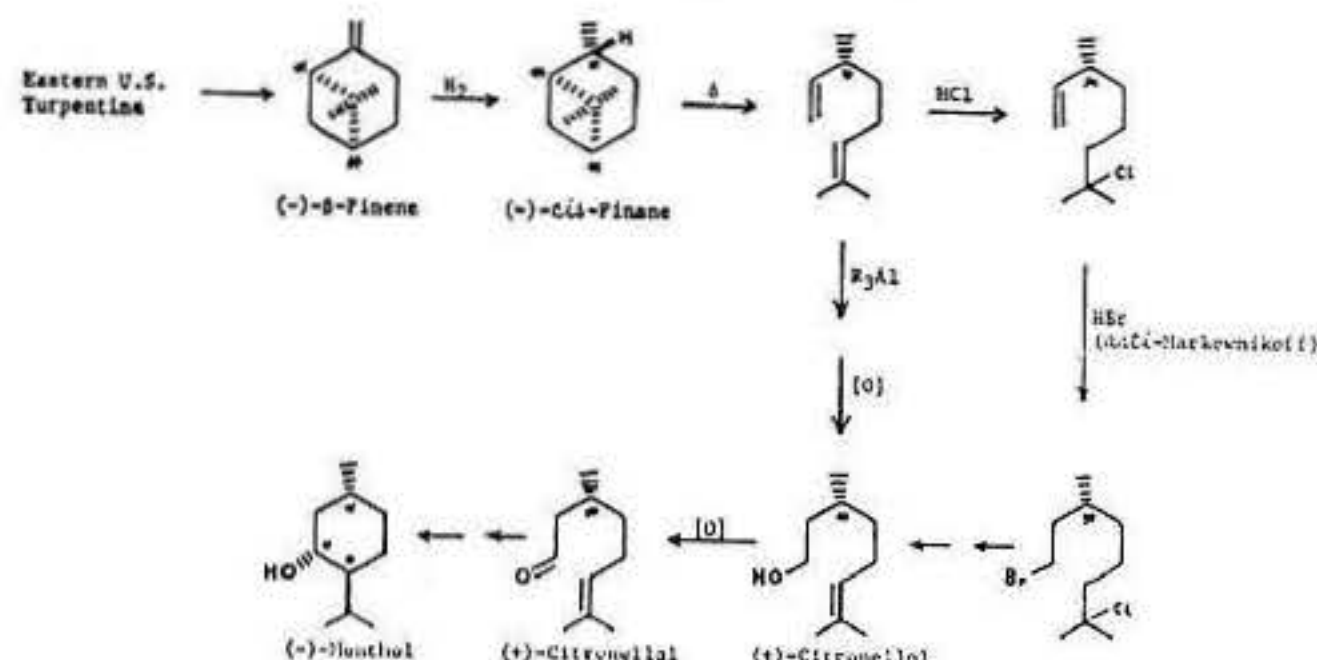

Fig. 7. (—)-Menthol from (—)-β-pinene.

oxidation-hydrolysis affords (+)-β-citronellal in high yield. This latter sequence offers considerable advantages over the former, provided appropriate safety precautions are employed. Catalytic oxidation of (+)-citronellol gives (+)-citronellal, in good yield, which is then convertible to (−)-menthol by classical procedures. The degree of optical purity of the final product obtained via this procedure is highly dependent on excluding the small percentage of *trans*-pinane produced in hydrogenation of (−)-β-pinene. Pyrolysis of this latter material affords antipodal 2,6-dimethyl-2,7-octadiene which when carried through the sequence gives (+)-menthol. While seemingly insignificant because of the small percentage generated, this can play a distinct role in the final optical purity of the menthol produced.

From (+)-3-carene (Fig. 8). (+)-Δ-3-Carene from Western U.S. turpentine[29] provides another monoterpene raw material for the potential production of (−)-menthol. Catalytic isomerization[30,31] provides the needed (+)-Δ-2-carene required for either of two alternate synthetic routes.

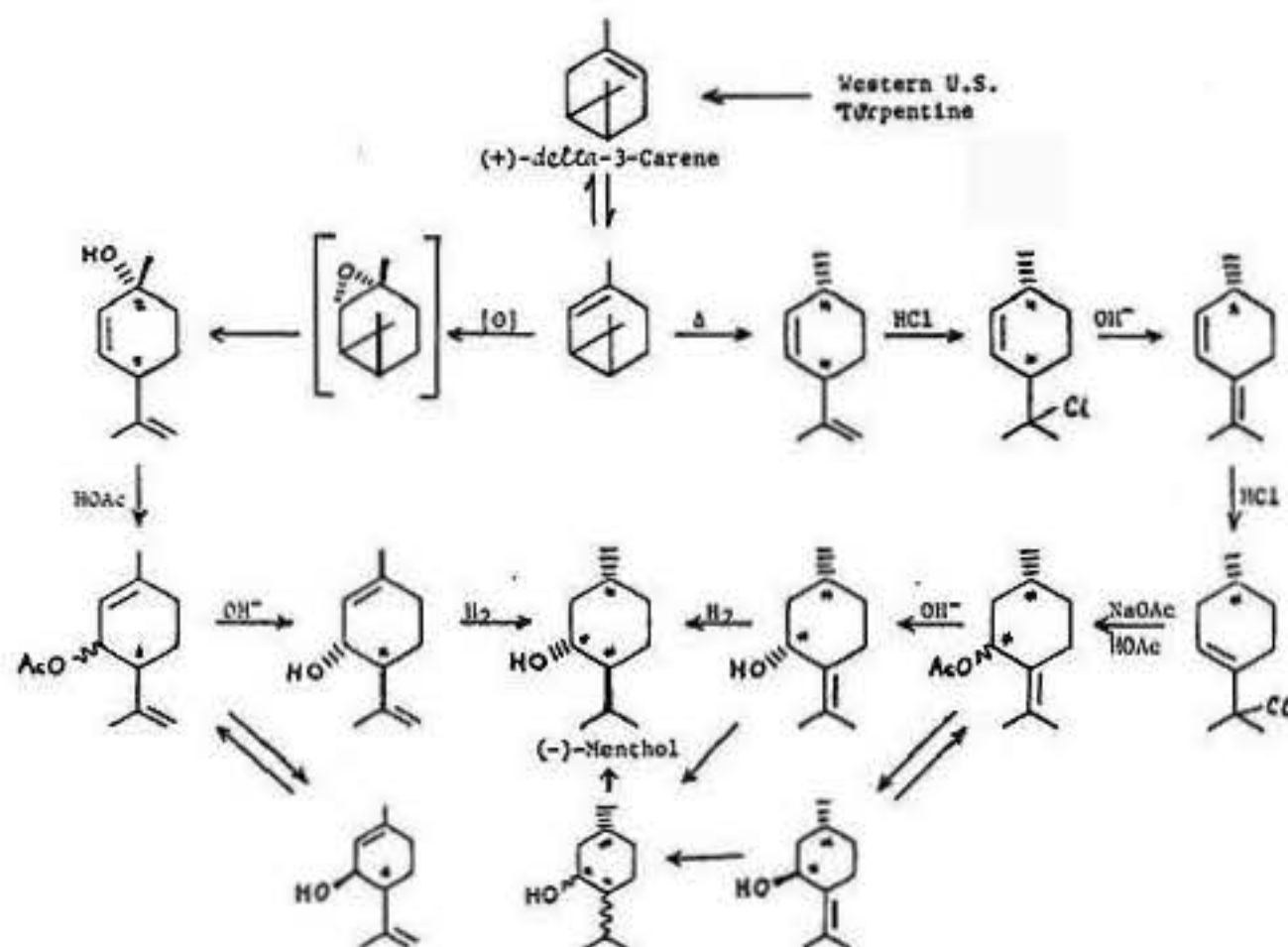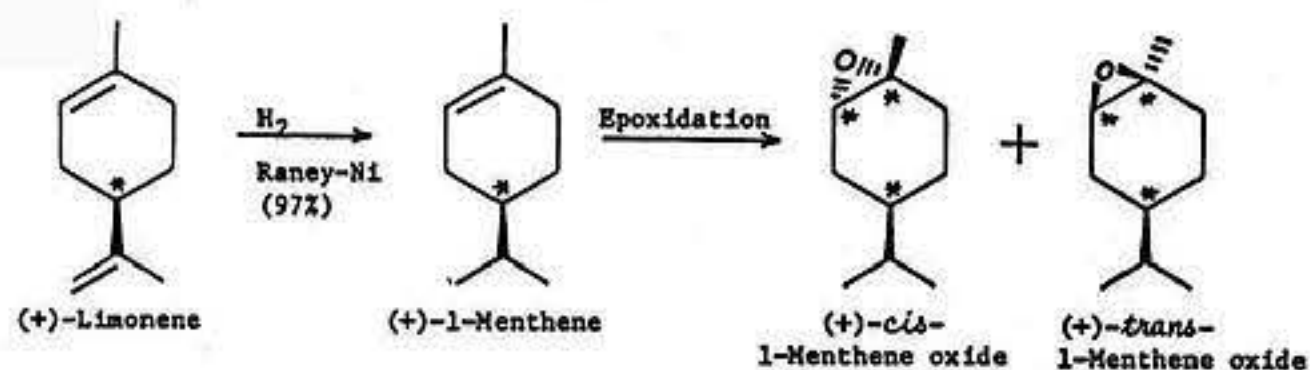

Fig. 8. (−)-Menthol from (+)-Δ-3-carene.

In one approach, reaction of (+)-2-carene with peracid yields (+)-*cis*-2,8-p-menthadien-1-ol via the intermediate *cis*-2-carene epoxide.[32] Allylic displacement[33] with acetic or formic acid in a buffered solution affords a mixture of *cis*- and *trans*-piperitenyl acetates (or formates) which on hydrolysis give (+)-*cis*- and (−)-*trans*-piperitenol. These isomeric alcohols are separated by fractional distillation and the *cis*-isomer is recycled by the same buffered carboxylic acid system used above to mixed *cis*/*trans* piperitenyl esters.[33] In this manner pure (−)-*trans*-piperitenol is obtained with minimum losses due to (+)-*cis* isomer formation. The (−)-*trans*-piperitenol is desired here so as to be able to selectively obtain (−)-menthol directly on hydrogenation. Hydrogenation over Pd/C affords better than 70% (−)-menthol along with some undesired (−)-*iso*menthol. Efficient fractional distillation gives (−)-menthol of good purity. Unfortunately, the (−)-*iso*menthol obtained in the last step of this synthesis is of the opposite optical series, but since this can be catalytically converted to racemic menthol under strong catalytic conditions,[3] this by-product is salable.

A second route, developed by Hercules, Inc., involves pyrolysis of (+)-*delta*-2-carene to (+)-*trans*-2,8-p-menthadiene[30,34] with generation of an asymmetric center at C-1 which is carried through the remainder of the synthesis. Isomerization of this 2,8-menthadiene to (+)-2,4(8)-p-methadiene can be accomplished either catalytically in the presence of strong bases[30] (e.g., potassium t-butoxide) or via hydrochlorination-dehydrochlorination. Treatment of (+)-2,4(8)-p-menthadiene with hydrogen chloride affords 8-chloro-3-p-menthene which can be reacted with sodium acetate and acetic acid to give mixed (*cis*/*trans*) pulegol esters via allylic displacement.[35] Hydrolysis affords (−)-*cis* and (+)-*trans*-pulegol. Because the absolute configuration of C-1 is fixed in this system, reduction of either pulegol isomer provides menthol isomers which can be readily equilibrated to predominantly (−)-menthol. More specifically, reduction of (−)-*cis*-pulegol affords (−)-menthol and (+)-neoisomenthol, while (+)-*trans*-pulegol gives (+)-isomenthol and (+)-neomenthol. Purification of equilibrated menthol isomers is carried out as previously mentioned (e.g., fractional distillation and crystallization of menthol derivatives). This latter process is intrinsically one of the most attractive potential routes to (−)-menthol developed to date.

From (+)-limonene (Figs. 9-15). At this point I would like to describe a route to (−)-menthol developed at R. J. Reynolds from (+)-limonene, the abundant by-product terpene derived from steam distilling orange and lemon peels. (+)-Limonene of high optical purity was hydrogenated to (+)-1-menthene over a Raney-Ni catalyst (97% yield). A rather protracted study was undertaken at this point on methods of epoxidation of (+)-1-menthene with a view to economics (and stereoselectivity). From our previous study[36] we knew that reaction of 1-menthene with peracids produced essentially a 1:1 mixture of *cis*/*trans* epoxides. We had also found that direct acetic acid-sodium acetate solvolysis of (+)-*trans*-1-menthene oxide would give predominantly the desired (+)-1-hydroxy-neocarvomenthylacetate,[37] whereas similar treatment of the *cis* epoxide gave only 1-acetoxyneocarvomenthol. Without belaboring the theoretical implications, it should be pointed out that this study demonstrated for the first time that 1,4-disubstituted-1-cyclohexenes which were previously considered to be attacked in a non-stereoselective manner by electrophilic reagents, could be directed to give predominantly either the *cis*[39] or *trans*[40] epoxides, as desired. The discovery that air oxidation of (+)-1-menthene in acetaldehyde gave a reasonably good yield of (+)-1-menthene epoxides provided an economical process. Since none of the epoxidation processes studied was completely stereospecific, the idea of direct solvolysis to 1-hydroxyneocarvomenthylacetate was abandoned. Instead, since both the *cis* and *trans* epoxide produce (+)-1-hydroxyneocarvomenthol on hydrolysis, this intermediate was prepared from the mixed epoxides and then converted by acetylation to the desired hydroxyacetate.

Pyrolysis of (+)-1-hydroxyneocarvomenthylacetate gave a mixture of 8 parts of (−)-*trans*-2-men-

Fig. 9.

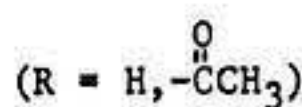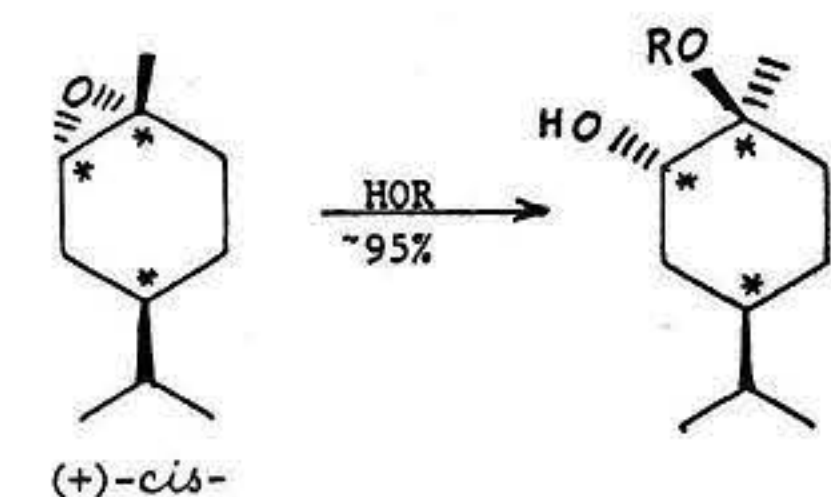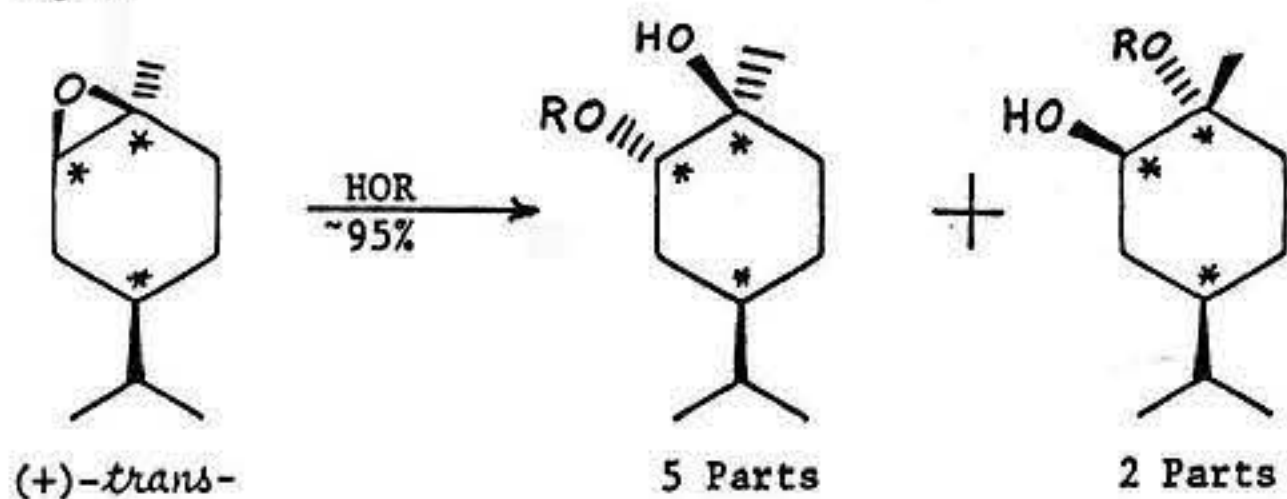| Reagent	Solvent	Yield	cis:trans Epoxide Product Ratio
Peracids	CH_2Cl_2	90%	53:47
O_2	------	3-15%	70:30
O_2/AcH	CH_2Cl_2	54%	75:25
HOCl/OH⁻	H_2O	25-35%	22:78
HOBr/OH⁻	H_2O	80%	10:90

Fig. 10. Solvolysis of menthene oxides.

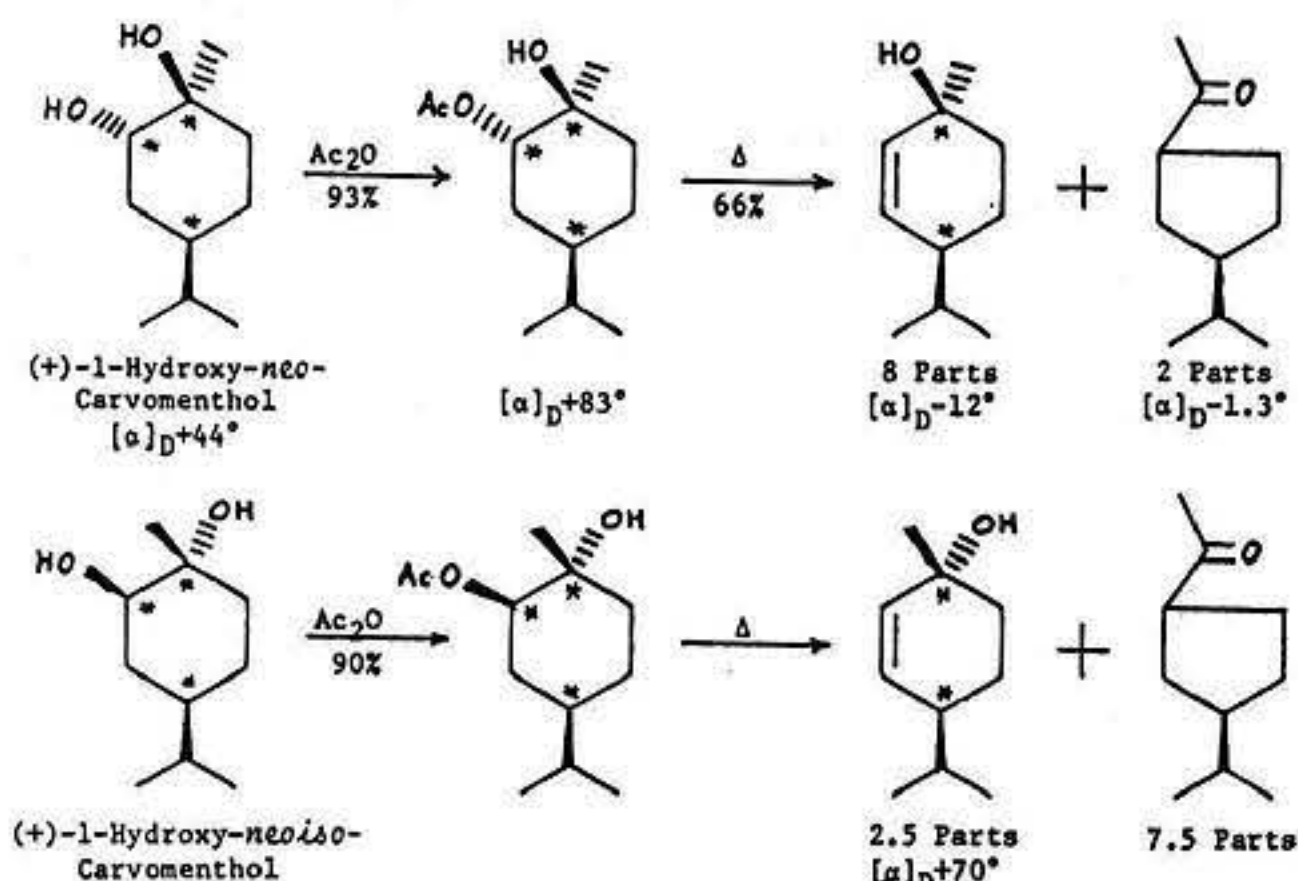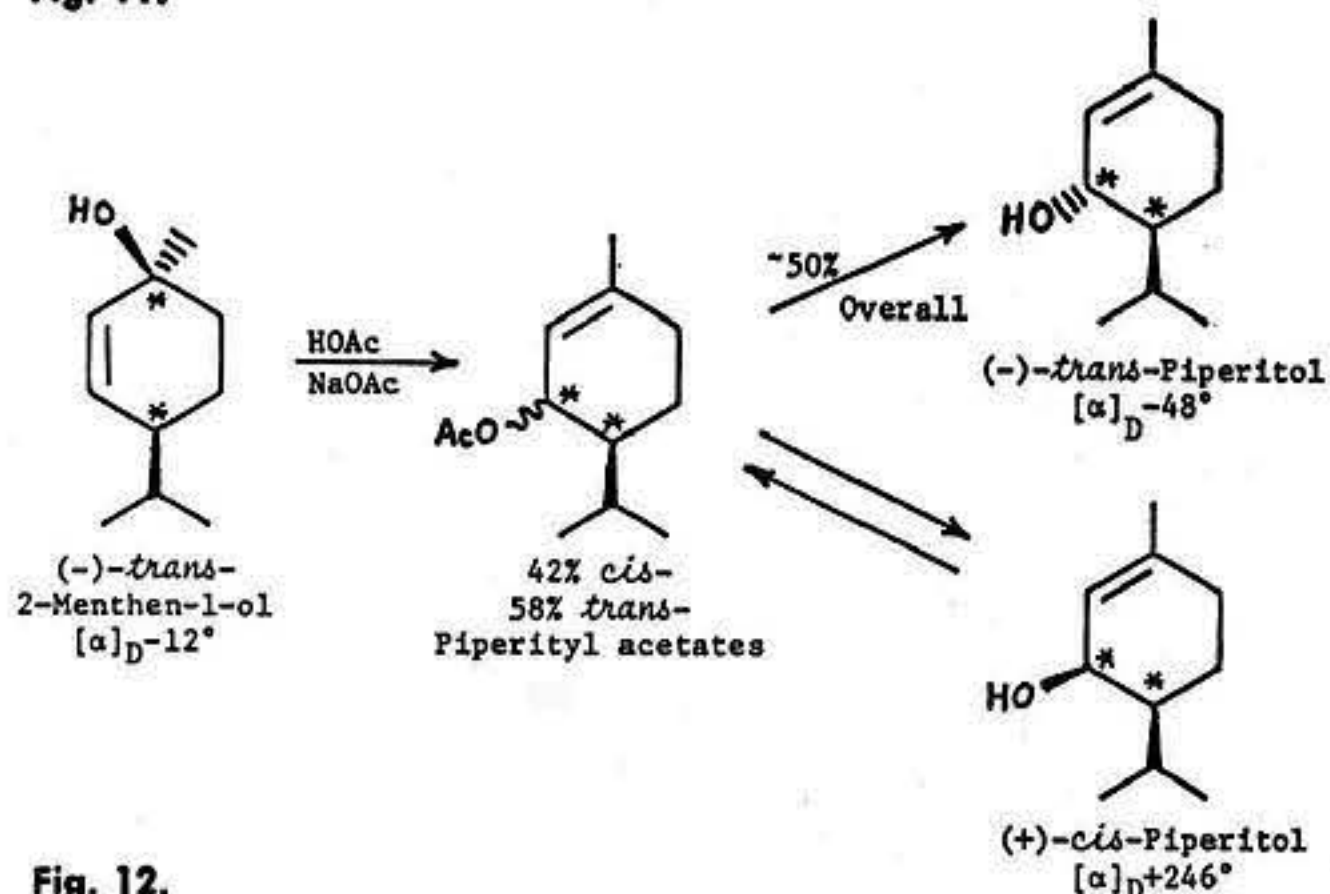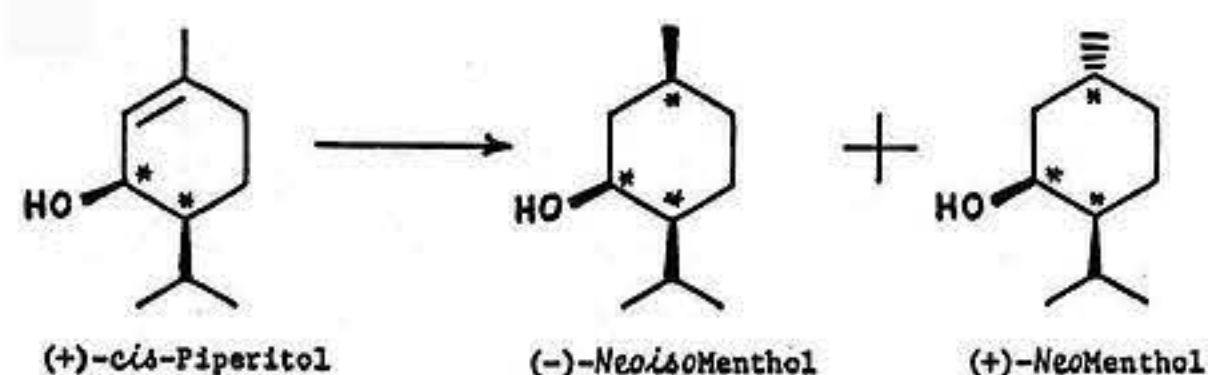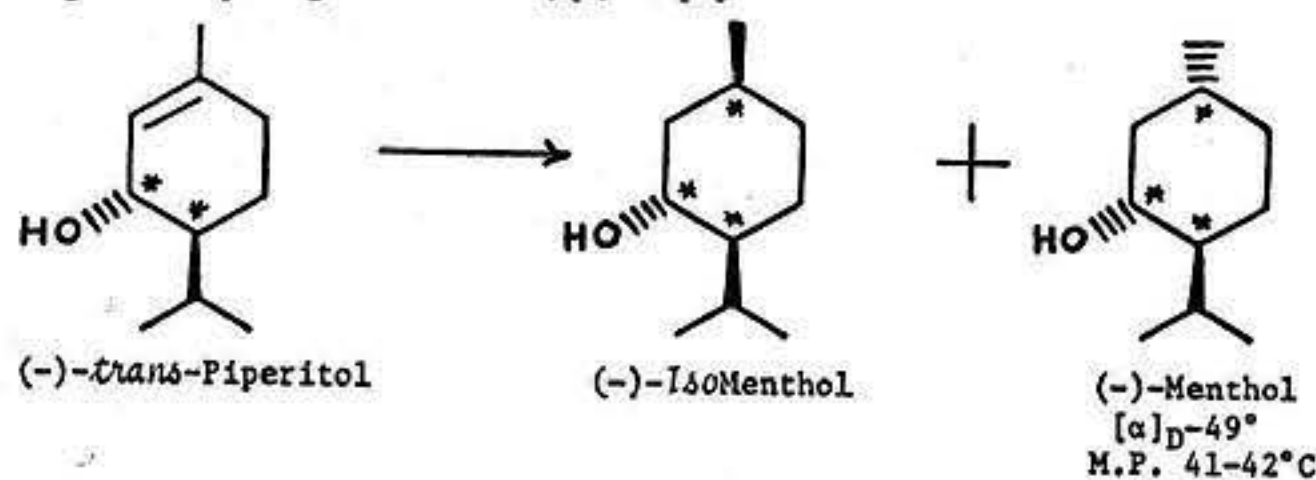Fig. 11.

Fig. 12.

Fig. 13. Hydrogenation of (+)-cis-piperitol.

Catalyst	Solvent	% (−)-NeoisoMenthol	% (+)-NeoMenthol
5% Pd/C	EtOAc	43	57
5% Pd/C	EtOH	50	50
5% Pt/C	EtOH	50	50
5% Ru/C	H_2O	73	27
PtO$_2$	EtOAc	29	71
5% Rh/C	EtOAc	45	55

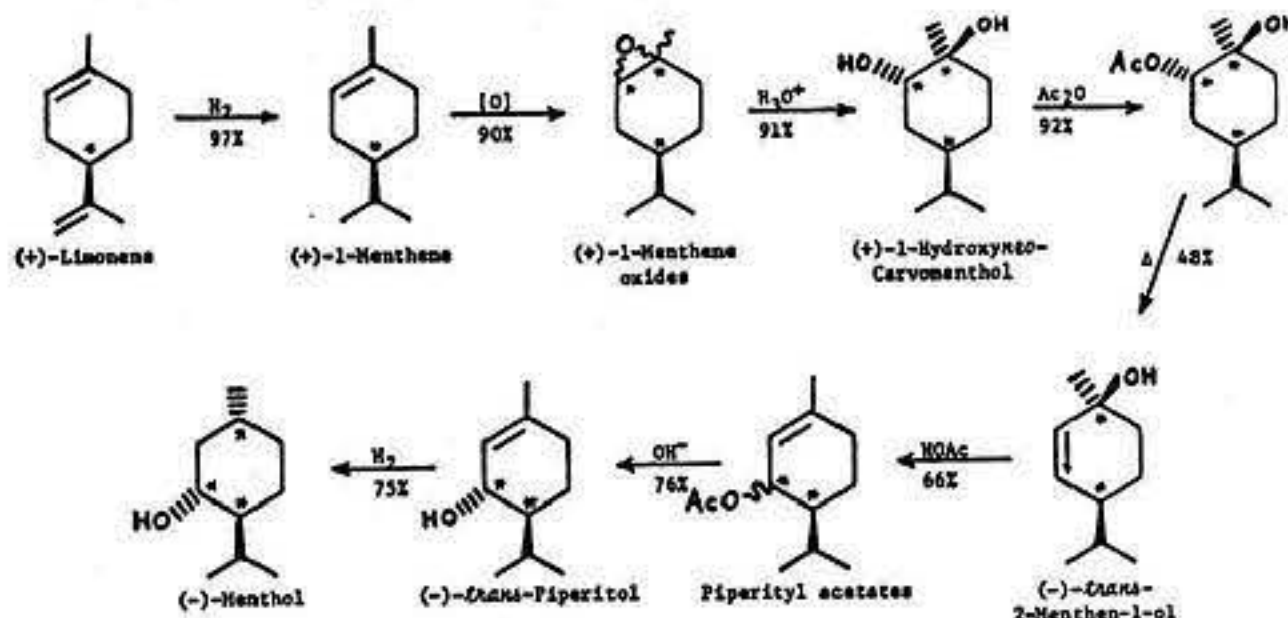| Catalyst	Solvent	% (−)-IsoMenthol	% (−)-Menthol
5% Pd/C	H_2O	31	69
5% Pd/C	EtOAc	27	73
5% Ru/C	H_2O	55	45
PtO$_2$	EtOAc	45	55
5% Pd/C	EtOH	25	75
5% Pd/Al$_2$O$_3$	EtOH	30	70

Fig. 14. Hydrogenation of (−)-trans-piperitol.

Fig. 15. (−)-Menthol from (+)-limonene; summary.

thene-1-ol and 2 parts of the novel ring contraction product, 3-isopropylcyclopentyl methyl ketone. The small amount of 1-hydroxyneoisocarvomenthylacetate formed in the hydrolysis/acetylation sequence (derived from the *trans* epoxide)[87] gave 2.5 parts of (+)-cis-2-menthene-1-ol and 7.5 parts of 3-isopropylcyclopentyl methyl ketone. A study of such pyrolytic ring contractions of cyclohexyl-1,2-hydroxyacetates has been published.[41] Although the pyrolysis products can be purified at this stage, it is more practical on a large scale to subject the crude pyrolysate to solvolysis in acetic acid/sodium acteate wherein the 2-menthene-1-ols[41a] are converted to a mixture of the piperityl acetates[33] through allylic substitution-rearrangement (42% cis/58% trans). Inasmuch as the isomeric cis and trans piperityl acetates are separable only with difficulty by fractional distillation, it is most convenient to take the crude mixtures of acetic acid solvolyzed crude pyrolyzate and hydrolyze the total mixture with base to give the corresponding mixed (+)-cis and (−)-trans-piperitols. These iso-

meric alcohols are readily separable by distillation along with the 3-isopropylcyclopentyl methyl ketone formed during the pyrolysis step. This latter ketone, although of no further interest to us in our menthol synthesis, is interesting from several other standpoints. First, reduction to 1-(3-isopropylcyclopentyl)-1-ethanol provides the interesting linalool-muguet floral type perfumery material reported by Eschinasi;[42] and second, the ketone itself is very closely related to an interesting burley tobacco isolate (3-isopropenylcyclopentyl methyl ketone)[43] and itself possesses distinct burley tobacco flavor characteristics.[44,45]

Having separated the (+)-cis and (−)-trans-piperitols, we had several alternative courses of action for obtaining (−)-menthol. First, "selective" hydrogenation of (+)-cis-piperitol stereospecifically to (+)-neomenthol would "fix" the absolute configuration at C-1 so that upon equilibration of the C-3, C-4 asymmetric centers, (−)-menthol would be the predominant product. Unfortunately, in all cases some (−)-neoisomenthol was produced and because this alcohol possesses the opposite absolute configuration at C-1, upon isomerization it would yield (+)-menthol. For this reason we decided to recycle the (+)-cis-piperitol back into the solvolysis system used on the (−)-trans-2-menthene-1-ol for production of equilibrated piperityl acetates. In this way the cis-piperitol was converted to a 42% cis/58% trans mixture from which additional (−)-trans-piperitol was obtained after ester hydrolysis. By continuously repeating this procedure during production a maximum amount of (−)-trans-piperitol is obtained, and since the solvolysis system is used in the preceding sequence, it is quite convenient to feed the (+)-cis-piperitol stream back in at this stage.

Having abandoned any real consideration of reducing cis piperitol to menthol isomers, we now undertook a brief study on the direct reduction of (−)-trans-piperitol to (−)-menthol. It shortly became apparent that 5% Pd/C in ethanol would provide 75% (−)-menthol and 25% (−)-isomenthol. Fortunately, these two isomers are separable by efficient fractional distillation and (−)-menthol of high purity was readily obtained. Since the (−)-isomenthol formed is of the opposite optical series, the only utility this material has is for production of menthone (by oxidation) or racemic menthol via isomerization techniques.[8]

Organoleptic properties of menthol isomers. The above examples illustrate the basic routes to (−)-menthol from available optically active terpenes. Let us now turn to the organoleptic properties of some of the menthol isomers and particularly to the reason why (−)-menthol is preferred over racemic or (+)-menthol.

(−)-Menthol has been utilized for many years for its cooling properties which are desirable in certain topical and ingested applications. Although arguments have raged in scientific circles for half a century, about the physiological response of enantiomers, until recently the reason for such differences was poorly understood. Industrially it was recognized a long time ago that (−)-menthol possessed more cooling power than (+)-menthol. Published reports, however, range from (+)-menthol having no cooling power[28] to the more recent findings that it has about ⅔ the cooling power of the laevo isomer.[46] But if the only difference was cooling power, why then was racemic menthol so totally unsuited for use in flavor applications as a replacement for (−)-menthol? As was pointed out at a recent symposium on Gustation and Olfaction,[47] the dextro and laevo forms of menthol fall into that small but scientifically significant group of enantiotopic materials that possess distinctively different aromas. This may simply be explained by the fact that action of odorant molecules with chemoreceptors can be three dimensionally dependent.

Picture for a moment the olfactory reception apparatus. Surrounding the olfactory nerve cell is a highly organized bimolecular leaflet lipoprotein membrane. On one side (outer) the fluid possesses a high sodium ion concentration while on the inner side of the membrane a high potassium ion concentration is found. The differential ion concentration sets up an electrical voltage potential.[48] Spanning the biomembrane are transmembrane channels which act as ion pumps. It is known that these transmembrane channels are comprised of helical protein structures and this is the mechanism by which ion selective permeation biomembranes can occur.[49] Such protein channels possess discrete preferred 3-dimensional conformations. Obviously, this is a dynamic system and ion permeation is a continuously pulsating process even in the equilibrium state.[50] When an odorant contacts these biomembrane structures in the olfactory epithelium a measurable electrical impulse occurs, presumably corresponding to alteration in the cationic permeability of the biomembrane. The adsorption-desorption process of odorants at the lipid boundary interface presents a novel system which may also possess some 3-dimensional preferences.[51] Interaction of chemical odorant messengers with the protein structure composing the biomolecular transmembrane channel by complexing via hydrogen bonding or sulphydryl groups of the helical "ion pump"[52] causes conformational deformation of the helical structure, thus altering the rate and pulsation order code of the ion pump. The change in the transmitter code and electrical potential results in the specific odorant message.

The general mechanism presented above supports the basic ideas elaborated by Davies[50] and is in all probability valid for certain other forms of chemoreception (e.g., taste, anesthesia).[53] That such processes are 3-dimensionally dependent is not surprising and, in fact, it is amazing that such considerations were ignored until recently.[54] As this mechanism is further studied, better correlations to molecular structure and odor will undoubtedly supersede the very elementary information presently being proposed.[55]

The marked change in odor characteristics of the other menthol isomers is certainly not surprising when one considers the basic 3-dimensional dependence of odor reception.

Figures 16 and 17 present the organoleptic prop-

Material	Structure	Tobacco Flavor Effect
(-)-Isomenthol		Musty, camphoraceous
(+)-Neomenthol		Pine, camphoraceous
(+)-Menthol		Musty, resinous, weak cooling
(±)-Menthol		Cooling, musty, resinous
(-)-Menthol		Strong cooling

Fig. 16. Tobacco flavor of isomeric menthols.

Material	Structure	Tobacco Flavor Effect
(+)-Limonene		Smoothing, hydrocarbon note
(+)-Limonene oxides (1:1 cis/trans)		Sweet citrus
(+)-1-Menthene oxides (1:1 cis/trans)		Mint, sweet, smoothing
(+)-1-Hydroxyneo-Carvomenthol		Mint, adds body
(-)-trans-2-Menthen-1-ol		Musty, herbaceous, floral
(+)-3-Isopropylcyclopentyl Methyl Ketone		Adds body, strong burley tobacco note
(-)-trans-Piperitol		Musty, herbaceous, floral

Fig. 17. Tobacco flavor of aromatic intermediates from synthetic menthol study.

erties of the various menthol isomers studied along with the intermediates from the final menthol synthesis described. While these evaluations were made in the course of studying the organoleptic properties of aromatic materials on tobacco,[44] there are similarities in the odors of the materials alone.

References

1. For an excellent review, see "Peppermint Oils and Menthol," Dragoco Publication, Holzminden, Germany.
2. R. Huet, Fruits, **27**, No. 6, 469 (1972).
3. A. B. Booth, U.S. Patent 2,843,636.
4. R. H. Pickard and W. O. Littlebury, J. Chem. Soc. 119 (1912); see also E. L. Russell and K. A. Hanover, U.S. Patent No. 3,201,-455 (1965).
5. J. Read and W. J. Grubb, J. Chem. Soc., 188 (1931).
6. J. Read and W. J. Grubb, German Patent 600,983.
7. Haarmann and Reimer GmbH, Belgium Patent No. 779,888 (1972).
8. M. B. Epstein and F. Gerecht, U.S. Patent No. 3,305,591 (1967).
9. R. E. Harmon, S. K. Gupta, and D. J. Brown, Chem. Rev., **73**, 21 (1973) and references therein.
10. M. M. Chopra, M. C. Nigam, and P. R. Rao, Parfumerie und Kosmetik, **53**, 282 (1972).
11. Analysis of dementholized cornmint oil obtained from Biddle-Sawyer (ex Brazil); VPC percentages not corrected for detector response variables; temperature and flow programmed 4% FFAP column.
12. G. Ohloff, Tet. Letters, **10** (1960).
13. R. L. Webb, U.S. Patent No. 3,218,361 (1965).
14. E. Gildemeister and Fr. Hoffman, Die Atherischen Ole, Vol. IIIb, Akademie-Verlag, Berlin (1962) pp. 103-104.
15. J. W. Blagden and W. E. Huggett, U.S. Patent No. 1,960,134 (1934).
16. J. W. Blagden and W. E. Huggett, U.S Patent No 2,264,928 (1941).
17. See J. W. Blagden and W. E. Huggett, U.S. Patent No. 2,237,980 for an alternate procedure.
18. A. K. MacBeth and J. S. Shannon, J. Chem. Soc., 2852 (1952).
19. See also, A. Blumann, Perfumery and Essential Oil Record, **45**, 252 (1954).
20. W. E. Huggett and H. T. Porter, British Patent No. 532,614 (1941).
21. J. P. Bain, A. B. Booth, and E. A. Klein, U.S. Patent No. 2,827,-499 (1958).
22. G. Ohloff and G. Schade, U.S. Patent No. 3,070,629 (1962).
23. C. Bordenca, Amer. Perf. and Cosmetics, **80**, 7, 19 (1965).
24. Y. R. Naves, Rev. Ind. Chim. Belg., No. 8, 1 (1962).
25. Y. R. Naves, Russ. Chem. Rev., **37**, No. 10, 779 (1968).
26. B. D. Sully, Chem. and Ind., 263 (1964).
27. W. B. Fordham, Rep. Prog. Appl. Chem., **50**, 326 (1965).
28. J. M. Derfer, Tappi, **46**, No. 9, 513 (1963).
29. For a review of the major chemical constituents of various turpentine species, see J. Drew and G. D. Pylant, Jr., ibid., **49**, No. 10, 430 (1966).
30. A. B. Booth, U.S. Patent No. 3,407,242 (1968) and 3,422,029 (1969).
31. S. P. Acharya and H. C. Brown, J. Am. Chem. Soc., **89**, 1925 (1967).
32. G. Ohloff and W. Giersch, Helv. Chim. Acta, **51**, 1328 (1968).
33. J. P. Bain, U.S. Patent No. 2,935,526 (1960); see also J. P. Bain, A. B. Booth, and W. Y. Gary, U.S. Patent No. 2,894,040 (1959).
34. K. Gollnick and G. Schade, Tetrahedron, **22**, 123 (1966).
35. R. L. Webb, U.S. Patent No. 2,851,481 (1958).
36. J. C. Leffingwell and E. E. Royals, Tetrahedron Letters, 3829 (1965).
37. E. E. Royals and J. C. Leffingwell, J. Org. Chem., **31**, 1937 (1966).
38. E. E. Royals and J. C. Leffingwell, J. Am. Chem. Soc., **80**, 2067 (1964).
39. J. C. Leffingwell and R. E. Shackelford, Canadian Patent No. 854,722 (1970).
40. J. C. Leffingwell and R. E. Shackelford, Canadian Patent No. 854,266 (1970).
41. J. C. Leffingwell and R. E. Shackelford, Tetrahedron Letters, 2003 (1970).
41a. Alternatively, 2-menthen-1-yl derivatives obtained by alternate methods can be employed at this stage for conversion to piperityl esters. See for example, G. O. Schenk, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, Ann., **674**, 93 (1964); G. O. Schenk, O.-A. Neumuller, G. Ohloff and S. Schroeter, ibid., **687**, 26 (1965); H. Kuczynski and A. Zabza, Bull. Acad. Polon. Sci., Ser. Sci. Chim., **9**, 551 (1961); Roczniki Chem., **37**, 773 (1963); J. P. Bain, W. Y. Gary and E. A. Klein, U.S. Patent No. 3,014,047 (1961); R. L. Webb, U.S. Patent No. 3,028,418 (1962).
42. E. H. Eschinasi, The Givaudanian, July-August, 7 (1962).
43. D. L. Roberts and W. A. Rohde, Tobacco Sci., **174**, No. 9, 107 (1972).
44. J. C. Leffingwell, H. J. Young, and E. Bernasek, Tobacco Flavoring for Smoking Products, R. J. Reynolds Tobacco Co., Winston-Salem, N.C. (1972) p. 41.
45. J. C. Leffingwell and R. E. Shackelford, U.S. Patent No. 3,689,-562 (1972).
46. R. R. Johnson, "Comparison of d- and l-Menthol as Cigarette Flavorants," 26th Tobacco Chemists Research Conference, Williamsburg, Va., October, 1972.
47. J. C. Leffingwell in Gustation and Olfaction, G. Ohloff and A. F. Thomas, Ed., Academic Press, New York, 1971, p. 144.
48. H. H. Friedman, D. A. MacKay, and H. L. Rosano, Ann. N.Y Acad Sci., Vol. **116**, Art. 2, p. 602 (1964).
49. D. W. Urry, Research/Development, 30 (1973) and references therein.
50. J. T. Davies, Handbook of Sensory Physiology, **IV**, Chemical Senses, 1, Olfaction, L. M. Beidler, Ed., Springer-Verlag, Berlin, (1971) p. 322-350.
51. F. M. Menger, Quart. Rev., **26**, 229 (1972).
52. J. M. Rozental and D. M. Norris, Nature, **244**, 371 (1973) and references therein.
53. H. Eyring, J. W. Woodbury and J. S. D'Arrigo, Anesthesiology, **38**, 415 (1973).
54. G. Ohloff, Chemie in Unserer Feit, No. 5, 114 (1971); G. F. Russell and J. I. Hills, Science, **172**, 1043 (1971); L. Friedman and J. G. Miller, ibid., **172**, 1045 (1971); E. T. Theimer and E. M. Klaiber, Abstracts, 166th ACS National Meeting, Chicago, August, 1973, AGFD, No. 29.
55. J. E. Amoore, Molecular Basis of Odor, C. C. Thomas, Springfield, Ill., 1970.