A STUDY OF PULEGENIC ACID, ITS ISOMERS, AND ITS CONVERSION TO LACTONES

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ABBREVIATIONS

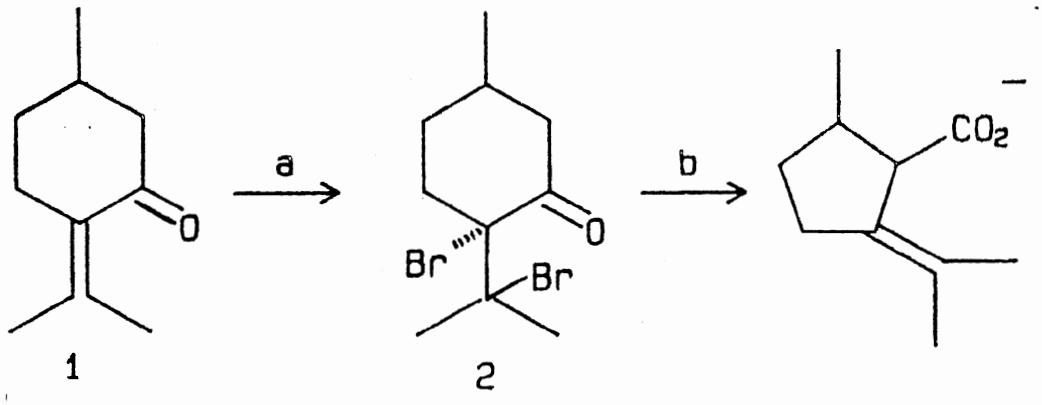
Ac	=	acetate group: $-O-\overset{\overset{\displaystyle O}{\|}}{C}CH_3$
bp	=	boiling point
Et	=	ethyl group: $-C_2H_5$
g	=	gram
GLC	=	gas-liquid chromatography
GC/MS	=	gas-liquid chromatography/mass spectrometry
h	=	hour or hours
L	=	liter
m/e	=	mass to electron charge ratio
Me	=	methyl group: $-CH_3$
mL	=	milliliter
mmol	=	millimole
mol	=	mole
mp	=	melting point
PPA	=	polyphosphoric acid

CHAPTER I

INTRODUCTION AND HISTORICAL

Pulegenic acid (2-isopropylidene-5-methyl-1-cyclopentane-carboxylic acid) was first reported by O. Wallach[1a-h] in a series of papers between 1895 and 1918. Wallach proposed a four-membered ring for pulegenic acid and the lactone derived from it. This was later revised. Pulegenic acid (as salts) is generally prepared as shown in Scheme 1. A glossary is included as Appendix A to assist the reader in quickly identifying the numbered structures.

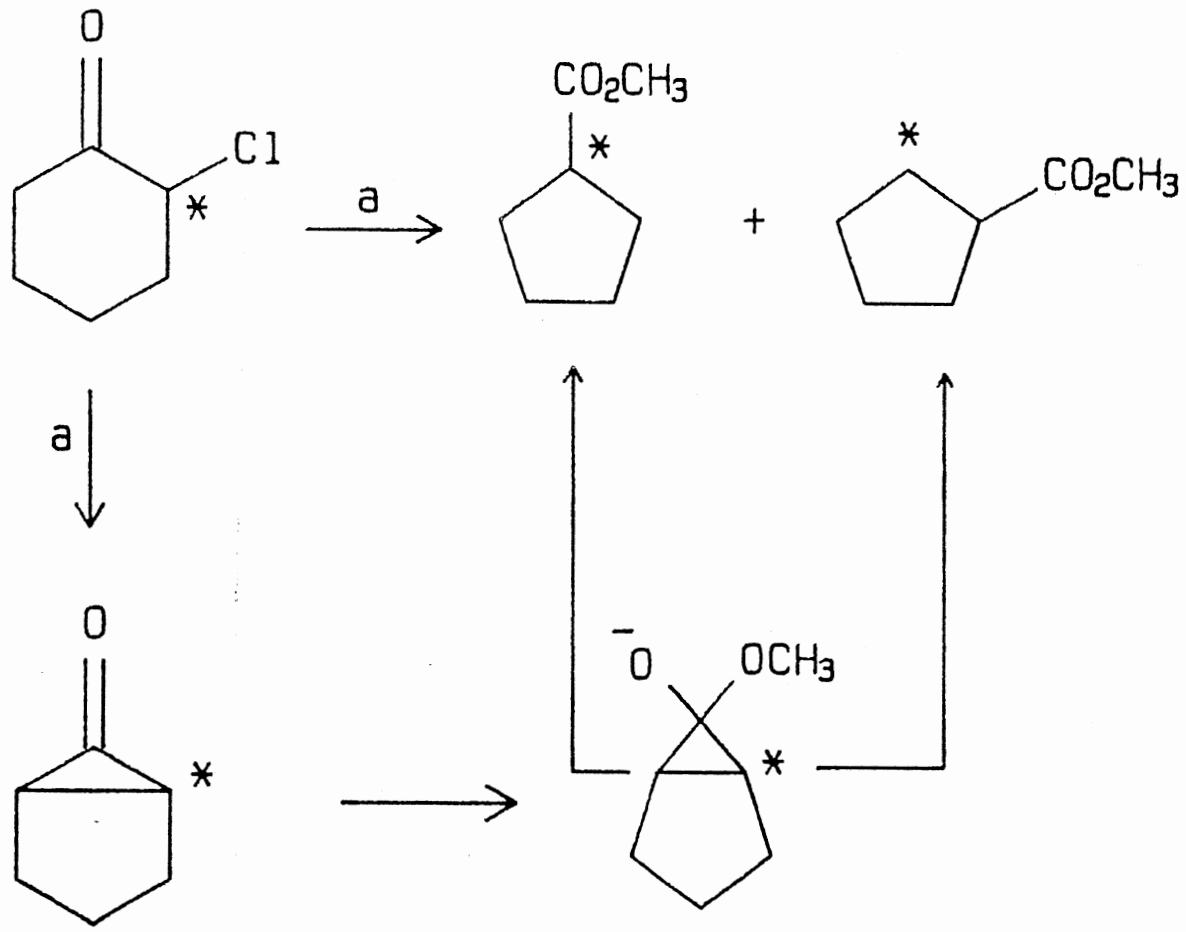
Scheme 1. Preparation of the Salt of Pulegenic Acid



[a]Br_2/NaOH. [b]NaOH.

The ring contraction of pulegone dibromide (Scheme 1) is an example of the Favorskii reaction shown in Scheme 2.

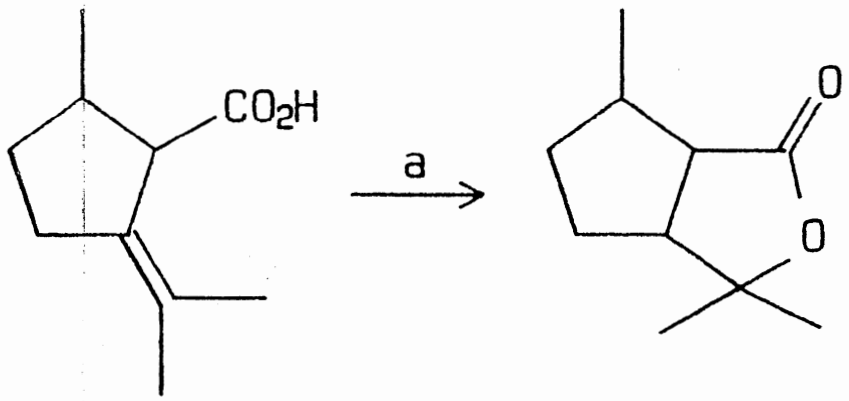
Scheme 2. Favorskii Rearrangement Mechanism



[a]CH_3O^-. CH_3OH. Δ

This reaction is an anionic rearrangement wherein an *alpha*-haloketone is converted to the conjugate base of a carboxylic acid and may proceed by way of a cyclopropanone intermediate.[1i,j]

Wallach[1f] carried out the synthesis of pulegenic acid and converted it to the same lactone **4b** obtained by hydrogenating carvenolide (**5**) shown in Scheme 4. Wallach[1g] also converted pulegenic acid, as shown below, to a mixture of *gamma*-lactones. At that time he was unaware that pulegenic acid and these lactone products were mixtures of isomers. He later investigated the different isomeric possibilities for pulegenic acid and the position of the double bond.[1g]



[a]H^+.

H. Rupe and K. Schafer[2] studied hydrogenation of the double bond of pulegenic acids and the preparation of the methyl esters.

The pulegenic acids were used as intermediates in various reactions either to synthesize model compounds for comparisons or as intermediates with the stereochemistry of the acids remaining unknown as late as 1962.[3a-i]

In 1962 Wolinsky *et al.* established their stereochemistry. These results are valuable because of the close structural relationship of the pulegenic acids to various naturally occurring alkaloids and terpenoids. With an established stereochemistry, their use as intermediates in natural product synthesis became possible.[5,6] Wolinsky[4,5] and Cavill[6] showed that the Favorskii rearrangement reaction of pulegone dibromide resulted in two isomeric acids. Both groups found that by using different alkaline reagents, the ratios of the isomers could be changed. Aqueous potassium hydroxide produced a variable mixture of isomers, whereas sodium methoxide caused a preponderance of one isomer. Attempts to separate these isomers, however, were unsuccessful. Their stereochemical assignments (*cis*- and *trans*-configuration shown in Figure 1) are based on spectral properties and by comparing with products synthesized from known compounds. Other possible isomers arising from conjugation with the carboxyl groups were ruled out since the ultraviolet spectra of the acids showed only end adsorption. In addition, their NMR spectra failed to show signals characteristic of vinyl protons.

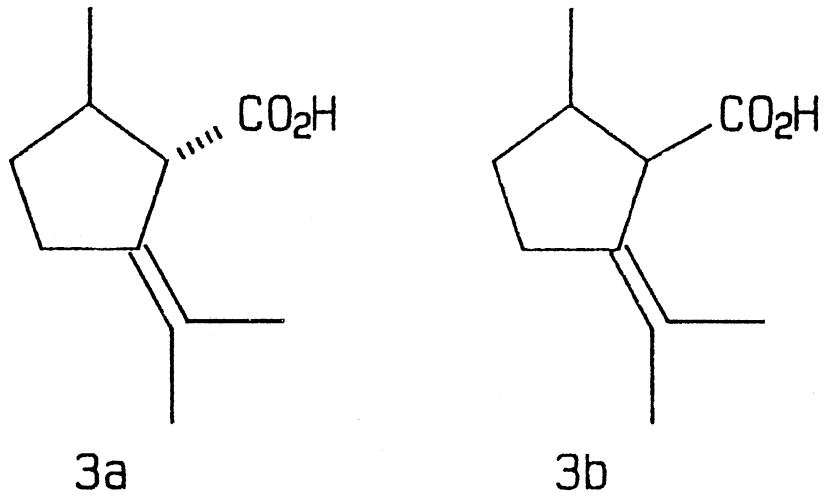
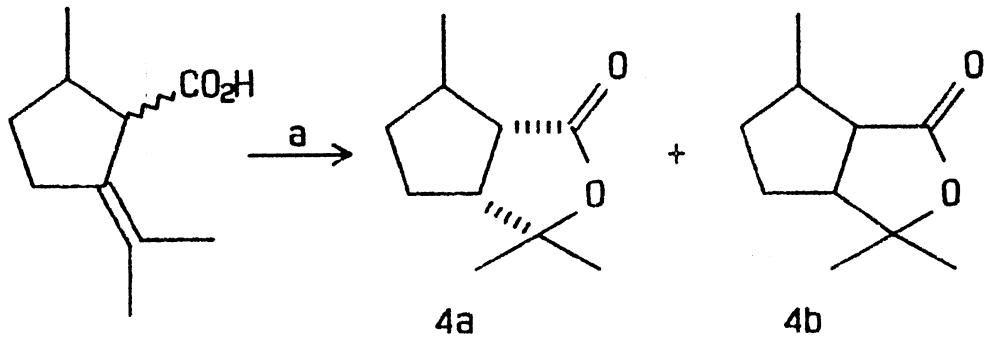


Figure 1. Isomers of Pulegenic Acid

With dilute hydrochloric acid, the pulegenic acids were converted to the corresponding lactones **4a** and **4b** as shown in Scheme 3. These isomers were separated by gas-liquid chromatography (GLC).[5]

Scheme 3. Lactone Isomers Derived From Pulegenic Acid



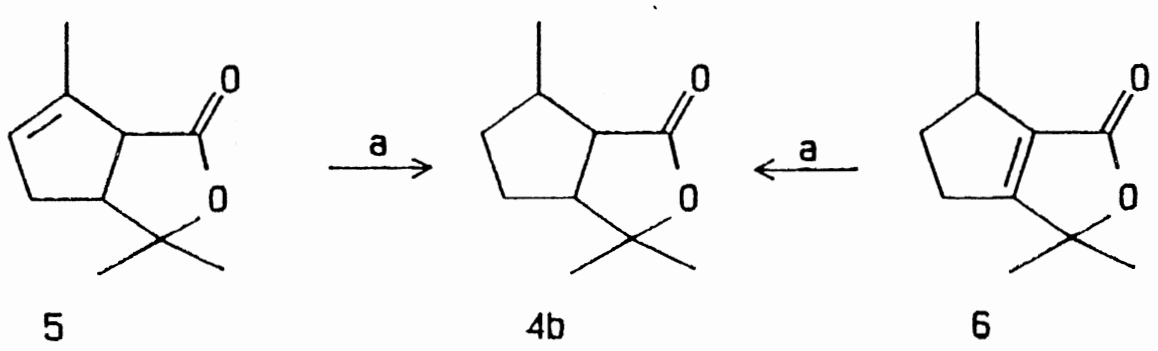
[a]H_2O. HCl.

The pulegenic acids prepared using aqueous potassium hydroxide followed by treatment with hydrochloric acid yielded a mixture of **4a:4b** (40:60).

The acids produced from the sodium methoxide treatment followed by hydrolysis gave **4a:4b** (92:8). These mixtures on treatment with lithium aluminum hydride gave the same isomeric ratios of *cis*- and *trans*-2-hydroxymethyl-3-isopropylidene-1-methylcyclopentane which indicated that epimerization had not occurred during lactonization.

As stated previously, the stereochemistry assigned to lactones and their parent pulegenic acids was supported by the formation of lactone **4b** upon catalytic hydrogenation of carvenolide (**5**) as well as from lactone **6**.[1f] Hydrogen addition can be expected to occur stereospecifically from the least-hindered side of **5** and **6** to give a *cis-cis* configuration (Scheme 4). The lactone **4b** was assumed to have the thermodynamically stable *cis*-ring-fusion as shown.

Scheme 4. Hydrogenation of Carvenolide (**5**) and Lactone **6** to *cis,cis*-Lactone **4b**



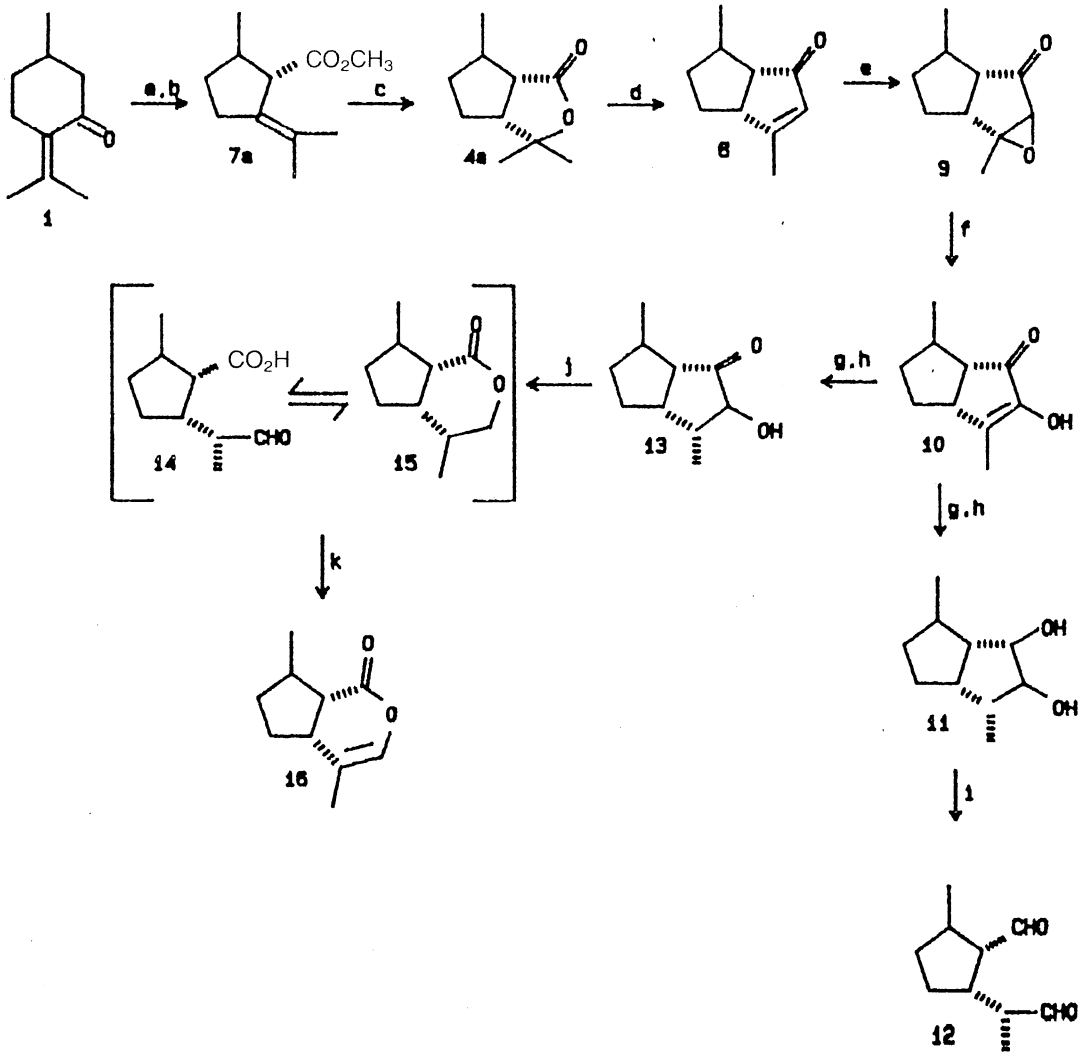
[a]H_2. PtO_2. EtOAc.

Wolinsky[4] stated that the data from the Favorskii rearrangement reflects that pulegone dibromide is a mixture of *cis*- and *trans*-isomers in which *cis* and *trans* refers to the orientation of the methyl group of the six-membered ring and the bromoisopropyl group. With aqueous potassium hydroxide, the dibromide rearranges to afford a kinetically controlled mixture of *trans*-**3a** and *cis*-**3b**. With sodium methoxide, the methyl esters are produced initially and these were subjected to epimerization to the more thermodynamically stable *trans*-ester **7a** (Scheme 7) and finally to *trans*-acid **3a** during reaction workup.

In 1963, Achmad and Cavill[7] wrote a brief, but packed, paper on the use of *trans*-pulegenic acid in the synthesis of the enantiomers of natural iridodial and nepetalactone as shown in Scheme 5. Several different reactions were discussed, but no experimental data were given. They took advantage of the basic nepetane skeleton of pulegenic acid which makes it valuable in the synthesis of iridodial, nepetalactone, iridomyrmecin, and other natural products.

These authors[7] carried out the Favorskii rearrangement on the dibromide of (+)-pulegone using sodium methoxide in methanol to provide *trans*-pulegenic acid (**3a**) in excellent yield. This acid was lactonized to **4a** in 10N hydrochloric acid and then converted to the bicyclooctenone **8**, in 28% yield, using a phosphorus pentoxide/phosphoric acid mixture. The bicyclooctenone **8** was epoxidized with alkaline hydrogen peroxide to the oxoepoxide **9**. This compound was converted into the bicyclooctenone **10** with sulfuric acid in acetic acid. The product was hydrogenated and hydrolyzed to diol **11**. Diol **11** was cleaved with sodium periodate in ethanol to dialdehyde **12** which is the enantiomer of natural iridodial. Treatment of **12** with aqueous acetic acid gave a product having GLC retention time and infrared spectrum in agreement with those of the natural iridodial.

Scheme 5. Synthesis of Iridodial (**12**) and Nepetalactone (**16**)



[a]Br_2/AcOH.
[b]NaOMe/MeOH.
[c]10N HCl. MeOH.
[d]P_2O_5/H_3PO_4.
[e]H_2O_2/OH.
[f]H_2SO_4/AcOH.
[g]H_2/Adam's Catalyst.
[h]Hydrolysis.
[i]NaI_2O_4/EtOH. AcOH.
[j]$Pb(OAc)_4$/AcOH.
[k]Pyrolysis.

Next, Achmad and Cavill synthesized nepetalactone (**16**). Their first approach was to try peracid oxidation of the bicyclooctenone **8** in an attempt to directly form the nepetalactone enantiomer.[7] However, they were unable to effect such a reaction, but thought it should be possible. Our experience with this reaction confirms their results. This will be discussed later. They then resorted to use of the keto-enolacetate **10** which was hydrogenated and hydrolyzed to the hydroxy ketone **13**. Oxidation of **13** with lead tetra-acetate in acetic acid gave nepetalic acid (**15**) which on pyrolysis was converted into the enantiomer of natural nepetalactone (**16**).

In that same year, Achmad and Cavill[8] published their observations on the formation of pulegenic acid through the Favorskii rearrangement. They proposed the mechanism shown in Scheme 6 which accounts for the differing ratios of the pulegenic acids using aqueous alkali versus ethoxide in ethanol. They also pointed out the value of the nepetane skeleton of pulegenic acid as a starting material in the synthesis of cyclopentanoid monoterpenes of insect and plant origin. The *trans*-relationship of the carboxyl and ring methyl substituent in pulegenic acid suggested a regiospecific route for synthesis of the cyclopentanoid monoterpenes. In preparation for their synthesis, Achmad and Cavill investigated, in detail, the Favorskii rearrangement of both pulegone dibromide and pulegone epoxide.[8] They reacted pulegone dibromide with sodium ethoxide to yield essentially one isomer of pulegenic acid (**3a**). Interestingly, in the experimental description given below, at no point is there a procedure to suggest hydrolysis from the ethyl ester to acid; however, the acid is reported as the initial product:

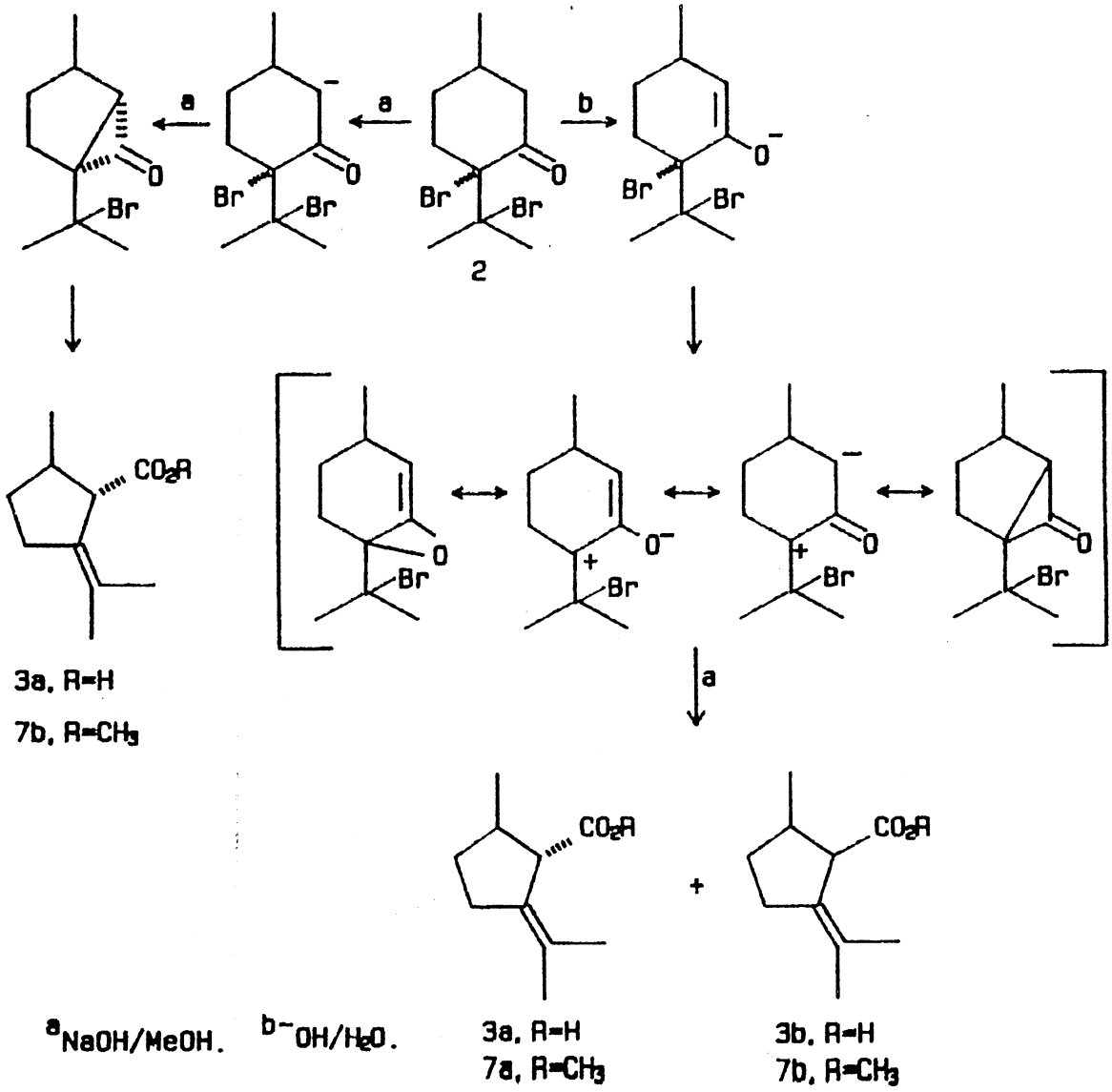
> **(b) Favorskii Rearrangement of Pulegone Dibromide.** -(i) Freshly prepared dibromide (from D-pulegone (70 g) and bromine (42 g) was added (1.5 h) to a well-stirred solution of sodium ethoxide (from 33 g Na) in ethanol (500 mL). The mixture was further refluxed for 4 h. After cooling, and removal of excess solvent, water (300 mL) was added, and the mixture extracted with ether (5X50 mL) to remove excess pulegone. The aqueous layer, after acidification (dil. sulfuric acid) was extracted with ether (4X50 mL)

> and the ethereal layer washed (water) and dried. The solvent was evaporated, then distillation gave the *trans*-pulegenic acid (**3a**) as an almost colorless liquid (25.2 g, b.p. 124°-128°C/3 mm, n(26,D) 1.4800.

It would be expected that the ethyl ester would be the initial product as was observed when methoxide in methanol was used.[9] Their pulegenic acid (**3a**) was converted to its methyl ester using diazomethane. This ester was equilibrated with sodium methoxide in methanol to give a 70:30 ratio of the original *trans*-ester and its epimer. They assigned the *trans*-configuration to the original ester since it was thought to be the more stable product from base-catalyzed epimerization. Therefore, the minor product would be the *cis*-isomer. The rearrangement of pulegone dibromide to pulegenic acid was repeated using sodium methoxide in dimethoxyethane to give the *trans*-acid as was done with ethoxide, but with a 15% decrease in yield.[9]

These authors believed that both regiospecific and nonregiospecific Favorskii rearrangements take place depending on the reagent (methoxy or hydroxyl). Their mechanism appears in Scheme 6. The regiospecific Favorskii rearrangement requires that the cyclopropanone system be formed with direct displacement of the halide ion by the enolate ion and consequent inversion at the carbon atom bearing the halogen substituent. With the use of hydroxyl ion, the rearrangement involves a resonance-stabilized dipolar intermediate or its equivalent to result in a mixture of stereoisomers. Their evidence is the isolation of a single acidic constituent, *trans*-pulegenic acid (**3a**), from the Favorskii rearrangement of pulegone dibromide in the presence of sodium ethoxide in ethanol. This is necessary for a regiospecific transformation assuming that the pulegone dibromide is indeed one isomer. The nonregiospecific transformation would result in a mixture of isomers as observed in the hydroxyl-induced rearrangement or from the existence of two isomers of pulegone dibromide.

Scheme 6. Mechanisms to Account for Isomers of Pulegenic Acid



A later paper by Wolinsky and Chan[9] presented an alternate rationalization of the ratio of pulegenic acid isomers. They reported that pulegone dibromide (**2**) is converted by sodium methoxide in methanol or sodium ethoxide in ethanol into an equilibrium mixture of 26% *cis*- and 74% *trans*-methyl and -ethyl pulegenate, respectively. The dibromide of pulegone is converted to a mixture of *cis*- and *trans*-pulegenic acids (**3a** and **3b**) by

treatment with aqueous alkali, whereas, with sodium methoxide followed by hydrolysis, *trans*-pulegenic acid (**3a**) is the predominate or the only product. Their explanation for the stereochemistry of the Favorskii rearrangement reflects the likelihood that pulegone dibromide is a mixture of isomers and that regiospecific rearrangement with aqueous alkali affords a kinetically controlled mixture of product acids. Thus, with sodium methoxide, methyl esters result and these are epimerized to the more thermodynamically stable *trans*-ester which in turn is converted to the *trans*-acid during reaction workup.

Cavill[8a] contradicted this by insisting that pulegone dibromide is a single isomer which rearranges regiospecifically with sodium ethoxide. In aqueous alkali, the resonance-stabilized intermediate leads ultimately to the observed mixture of *cis*- and *trans*-acids.

When pulegone dibromide was heated with sodium methoxide in anhydrous methanol and the reaction mixture was poured into dilute acid (to avoid basic hydrolysis), both isomers (26% *cis*- and 74% *trans*-methyl pulegenate) were obtained as shown in Table I.[8]

TABLE I

EQUILIBRATION EXPERIMENTS FOR PREPARING PULEGENIC ACID ISOMERS

Reactant	Base	Product	% *cis*	% *trans*
Pulegone dibromide	$NaOH/H_2O$	Pulegenic acid	45-60	40-55
Pulegone dibromide	$NaOH/MeOH/H_2O$	Pulegenic acid	8	92
Pulegone dibromide	$NaOH/EtOH/H_2O$	Pulegenic acid	0	100
Pulegone dibromide	NaOEt/EtOH	Pulegenic acid	26	74
Pulegone dibromide	NaOMe/MeOH	Pulegenic acid	26	74
trans-methyl pulegenate **7a**	NaOMe/MeOH	Pulegenic acid	23	77

Also, equilibration of pure *trans*-methyl pulegenate with sodium methoxide afforded a mixture of 23% *cis*- and 77% *trans*-methyl pulegenates (**7a** and **7b**).[8]

In the methoxide catalyzed reaction, the first isolatable product was a thermodynamically controlled mixture of *cis*- and *trans*-pulegenates with the *trans*-ester **7a** predominating. This divergence in isomer composition between the esters isolated when water is excluded from the reaction mixture and the acids isolated when water is added during the reaction workup was explained as follows.[9]

When the hydrolysis of the ethyl and methyl pulegenates is examined as the hydrolysis of each pure ester or mixture of *cis*- and *trans*-isomers, analysis shows in every instance that there was predominant or exclusive formation of *trans*-pulegenic acid (**3a**) depending

on whether the methyl or ethyl esters were used. Equilibration of the *cis*- and *trans*-esters must obviously compete with their saponification. This is not surprising in view of the relatively high acidity of the proton of the methine group at C-2 which is flanked by activating carboalkoxy and isopropylidene groups. Moreover, the hydrolysis of the *trans*-esters probably proceeds more rapidly than hydrolysis of the relatively more sterically hindered *cis*-esters, with the greatest rate differential expected for the bulkier ethyl esters.

To determine whether epimerization competes with the hydrolysis of the *trans*-esters, the equilibrium mixture of *cis*- and *trans*-esters was subjected to the action of limited amounts of alkali.[8]

If equilibration proceeds faster than the hydrolysis of the *trans*-ester, the composition of the recovered ester should remain unaltered. On the other hand, if the hydrolysis of the *trans*-ester is the fastest step, then the recovered ester will be enriched in the *cis*-isomer.[8] The proportion of *trans*-isomer was found to increase indicating that the slower hydrolysis rate of the *cis*-isomer was the determining factor.

Thus the Favorskii rearrangement of pulegone dibromide with alkoxides affords a thermodynamically controlled mixture of *cis*- and *trans*-pulegenates. The regioselective formation of *trans*-pulegenic acid is a consequence of the facile epimerization of the *cis*-ester and the retarded rate of hydrolysis of this ester.

To conclude this historical view, a brief discussion of some uses of pulegenic acid is given below.

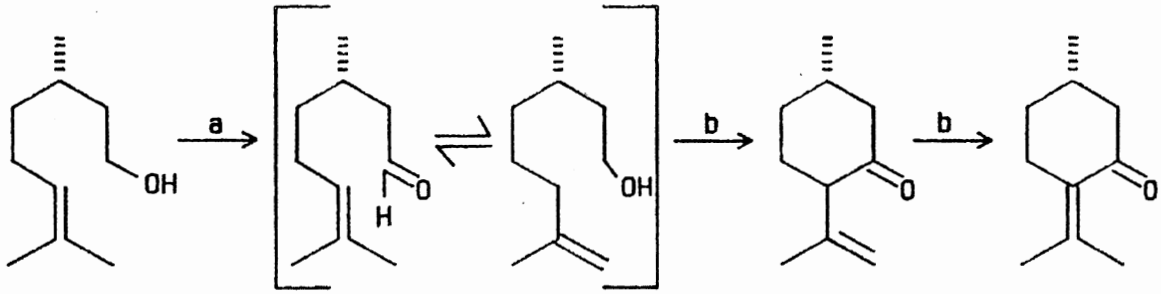
Varech *et al.*[10] in 1965 found pulegenic acid useful in conformational analysis in the cyclopentane series and in the preparation of some mono- and disubstituted cyclopentane derivatives with known absolute configuration.

Wolinsky *et al.*[5] in 1965 used *trans*-pulegenic acid as the starting material for the synthesis of 6 out of 8 possible iridolactones and *cis-trans*-pulegenolide.

Eisenbraun *et al.*[11] converted (+)-pulegone to (−)-(1R)-*cis*- and (+)-(1S)-*trans*-2-isopropylidene-(5R)-N, N-trimethylcyclopentanemethylamines and their dideuterio derivatives by reacting with Br_2, dimethylamine, and $LiAlH_4(D_4)$. They also repeated an earlier route involving conversion of the (+)-pulegone to pulegenic acid and prepared its acid chloride followed by treatment with dimethylamine and $LiAlH_4$ to show that their new synthesis route provided cleaner products. The internal conjugated product was not the major component.

(S)-(−)-pulegone occurs in the volatile oils of numerous plants; however, there are at present no commercial suppliers. A convenient synthesis, shown in Scheme 7, of (S)-(−)-pulegone from (−)-citronellol was described by Corey *et al.*[12] The needed (−)-citronellal was made by high-temperature hydroalumination of `(+)-pinane, followed by oxidation of the acyclic organoaluminum compound to (−)-citronellol. In turn (−)-citronellal was obtained by oxidation with 2.5 equiv of Pyridininum chlorochromate in dry methylene chloride. This product was cyclized directly to isopulegol by the acidic chlorochromate and then oxidized to (−)-isopulegone. Ethanolic sodium hydroxide was used to convert (−)-isopulegone to (−)-pulegone.

Scheme 7. S-(−)-Pulegone Synthesis



[a]Pyridinium chlorochromate. CH_2Cl_2. [b]NaOH/EtOH.

Paquette *et al.*,[13] in a 1981 paper, describe polycyclopentanoids which are biologically active polyquinane natural products. Thus there is a need for functionalized bicyclo(3.3.0)octane building blocks so more complex target molecules can be synthesized.

The reaction of **1** with Br_2 in acetic acid is known to be sluggish and unpredictable with significant amounts of unreacted starting material recovered. A substantial improvement was made through adaptation of the conditions of Marz and Norman[14] which involve slow addition of the halogen to a cold (−10°C) buffered ($NaHCO_3$) ethereal solution of the α,β-unsaturated ketone. The dibromide was then directly added to methanolic sodium methoxide solution and allowed to stir at room temperature overnight. In a typical experiment, a 2:1 ratio of isomers was obtained and these were efficiently separated by high-pressure liquid chromatography.[14]

CHAPTER II

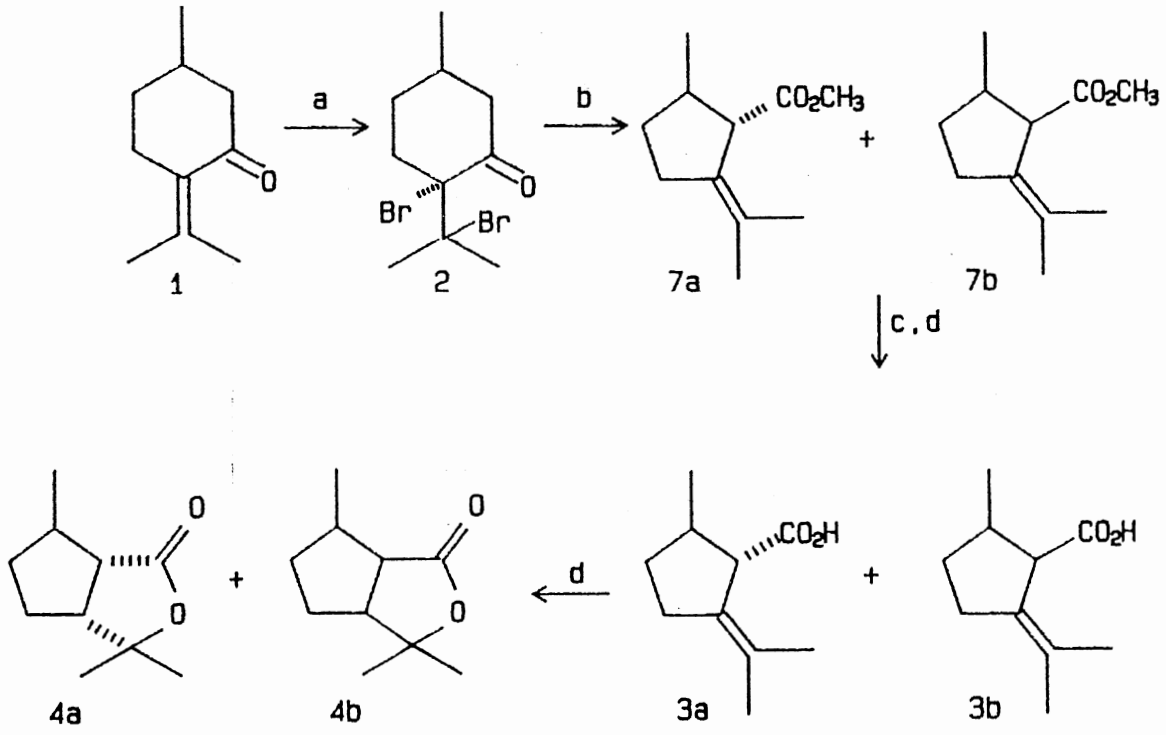
RESULTS AND DISCUSSION

This study was undertaken with two objectives. First, to develop a more direct and efficient synthesis of the two pulegenic acid lactones **4a** and **4b**. These were to be used as standards for comparison with nepetalactones from earlier work.[15a-j] Second, to produce enantiomers of natural nepetalactone (**16**) and the nepetolactones. In general, the Favorskii rearrangement reaction and various transformations using pulegenic acid (**3**) were explored. In the process of studying these reactions, emphasis was placed on the use of gas chromatography/mass spectrometry (GC/MS) and ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) as quick, informative analytical tools to help explain reactions and to identify products. The instrumental work will be discussed (especially the GC/MS spectra) in detail in a separate chapter. Structure numbers can be identified through use of the glossary of compounds in Appendix A.

The (R)-(+)-pulegone (**1**) used as starting material was determined to be 95+% pure by GC/MS. The impurities (see Figure 2) were an isomer of pulegone (**19**) and a saturated cyclic ketone, probably menthone (**20**) since it is a common mint constituent. Neither of these would be expected to interfere with our planned use of **1**.

(+)-Pulegone (**1**) was brominated to the dibromide **2** which proved unstable in our attempts to purify it. Therefore, **2** was added immediately to a solution of sodium methoxide in methanol which effected the Favorskii rearrangement-ring contraction from the six-membered to the five-membered ring as seen in Scheme 8.

Scheme 8. Synthesis of Pulegenic Acids **3a** and **3b** As Well As Their Lactones



[a]Br_2/AcOH. [b]NaOEt. EtOH. [c]NaOH. H_2O. [d]HCl. H_2O.

This resulted in the formation of a mixture of methyl pulegenates **7a** and **7b** which were shown by GC/MS analysis to be a 70:30 mixture of isomers along with the minor components shown in Figure 2.

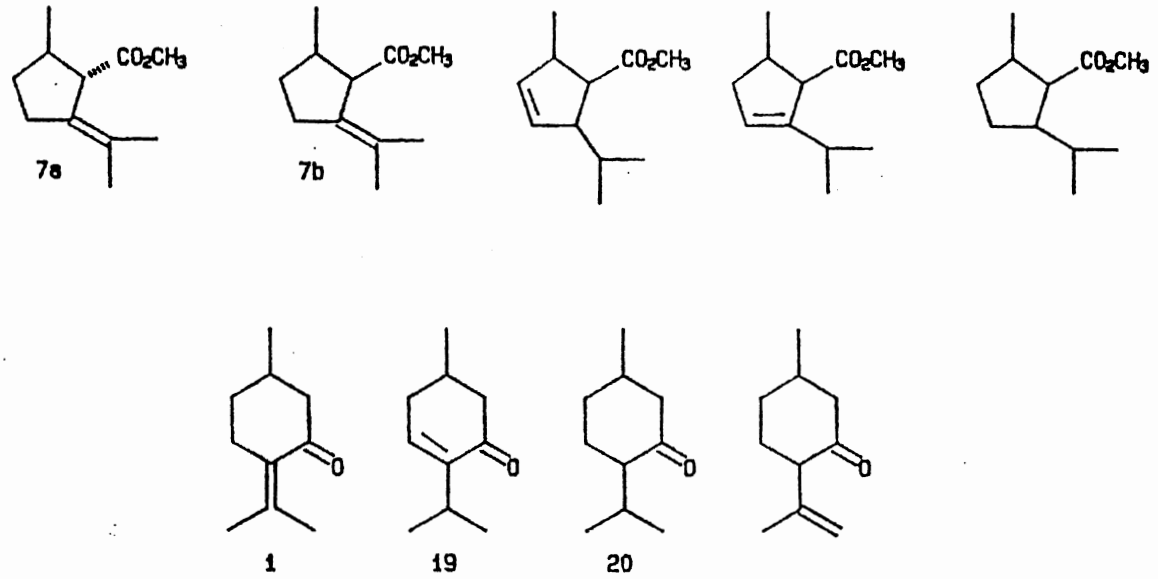
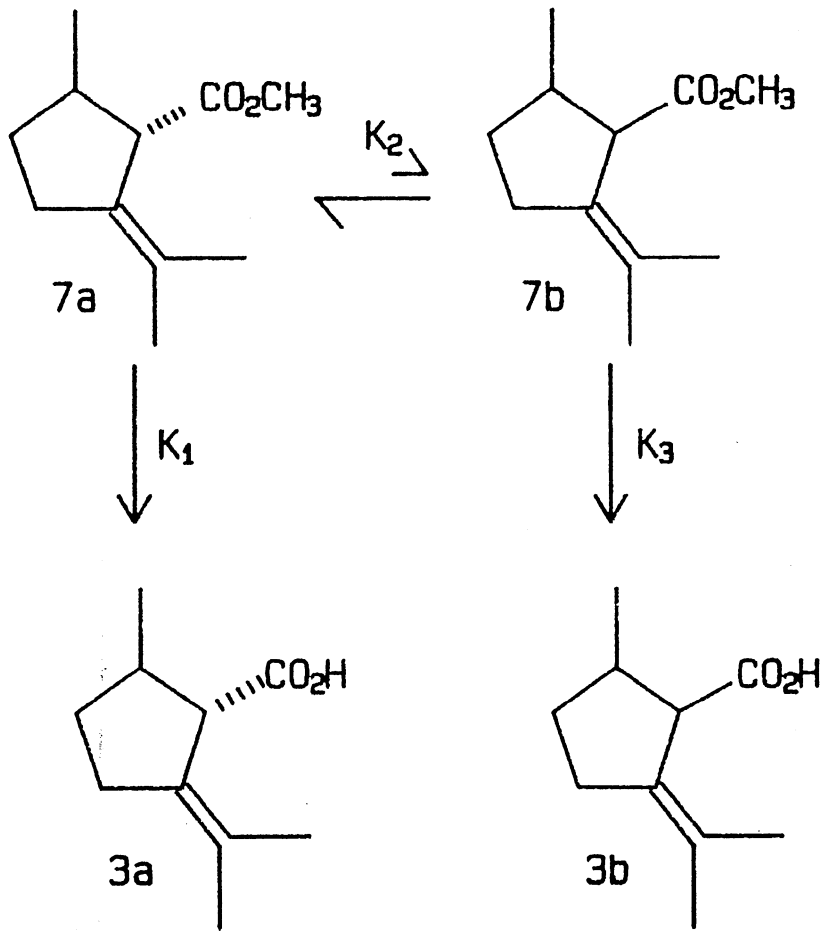


Figure 2. Methyl Pulegenates and Observed Minor Products

We assumed that the major product was the previously described thermodynamically more stable *trans*-methyl pulegenate (**7a**).[4-6] Other compounds found in the reaction were the saturated and unsaturated ester impurities and the original ketone impurities from pulegone. Upon distillation, the methyl pulegenate isomers **7a** and **7b** were isolated in the same 70:30 ratio previously described.[4-6] However, saponification of these esters changed the isomer distribution to favor the more stable *trans*-isomer with a final 95:5 ratio of *trans*- to *cis*-pulegenic acids (**3a** and **3b**). The shift toward the *trans*-isomer occurs through epimerization and selective saponification as illustrated in Scheme 9 and as was first discussed by Wolinsky.[9] With the equilibrium favoring the *trans*-isomer and the faster saponification rate for the *trans*- versus the *cis*-isomer, the *cis*-methyl ester on exposure to alkali is converted almost exclusively to the *trans*-stereochemistry.

Scheme 9. Epimerization and Hydrolysis of **3a**

Where: $K_1 > K_2 > K_3$.



To confirm this assumption, we carried out the Favorskii rearrangement on pulegone (**1**) using ethanol as the solvent to obtain the ethyl esters (**27a** and **27b**) of pulegenic acid. Approximately the same ratio of isomers was found for the ethyl esters as for the methyl esters. Morever, upon saponification of the ethyl esters to pulegenic acid, only one isomer

was produced. This shows that indeed the saponification rate between the *cis*- and *trans*-esters is different. The larger ethyl group as compared to the methyl group shows a greater selectivity.

As the next step in our synthesis study, we prepared the gamma-lactones **4a** and **4b** from the pulegenic acids as shown in Scheme 8. The lactonization was carried out using different acidic cyclizing agents to optimize the yield. Hydrochloric acid (two concentrations), Amberlyst-15 (A-15, a sulfonic acid resin), acidic alumina, and hot sulfolane were tried and the products were analyzed. The last two reagents did not produce the lactones and gave very complex mixtures. The first two reagents worked well. Three reactions were run using a 95:5 mixture of *trans*-pulegenic acid **3a** and *cis*-pulegenic acid **3b** added to a 1:4 mixture of water and hydrochloric acid, a 4:1 mixture of water and hydrochloric acid, and A-15 in refluxing benzene. The ratio of the lactones **4a** and **4b** was different for each condition shown in Table II.

TABLE II

LACTONIZATION OF 3a WITH ACID CATALYSTS

Pulegenic Acid			Lactones	
3a	**3b**	Reagent	*trans*-**4a**	*cis*-**4b**
95+	5	1:4 H_2O:HCl	82	18
95+	5	4:1 H_2O:HCl	97	3
95+	5	A-15	99	1

An explanation of what might cause a change in isomer distribution is lacking. All three reactions gave good yields and were easily carried out with the A-15 catalyst giving the highest yield of lactone **4a**. This catalyst was selected since it is an insoluble sulfonic acid resin in bead form and, thus, can easily be removed from the reaction mixture which permits compositional monitoring of the reaction progress. When an aliquot of the sample is removed from the reaction flask, it also is removed from A-15 and the reaction ceases. The worst case is when the reaction mixture has been stirring for an extended time and the resin has been ground into powder. Again filtration is sufficient to stop the reaction. We were thus able to follow the conversion rate of the pulegenic acid to the lactone using A-15. These data are given in Table III.

TABLE III

REACTION TIMES FOR THE LACTONIZATION OF *trans*-PULEGENIC ACID (3a)

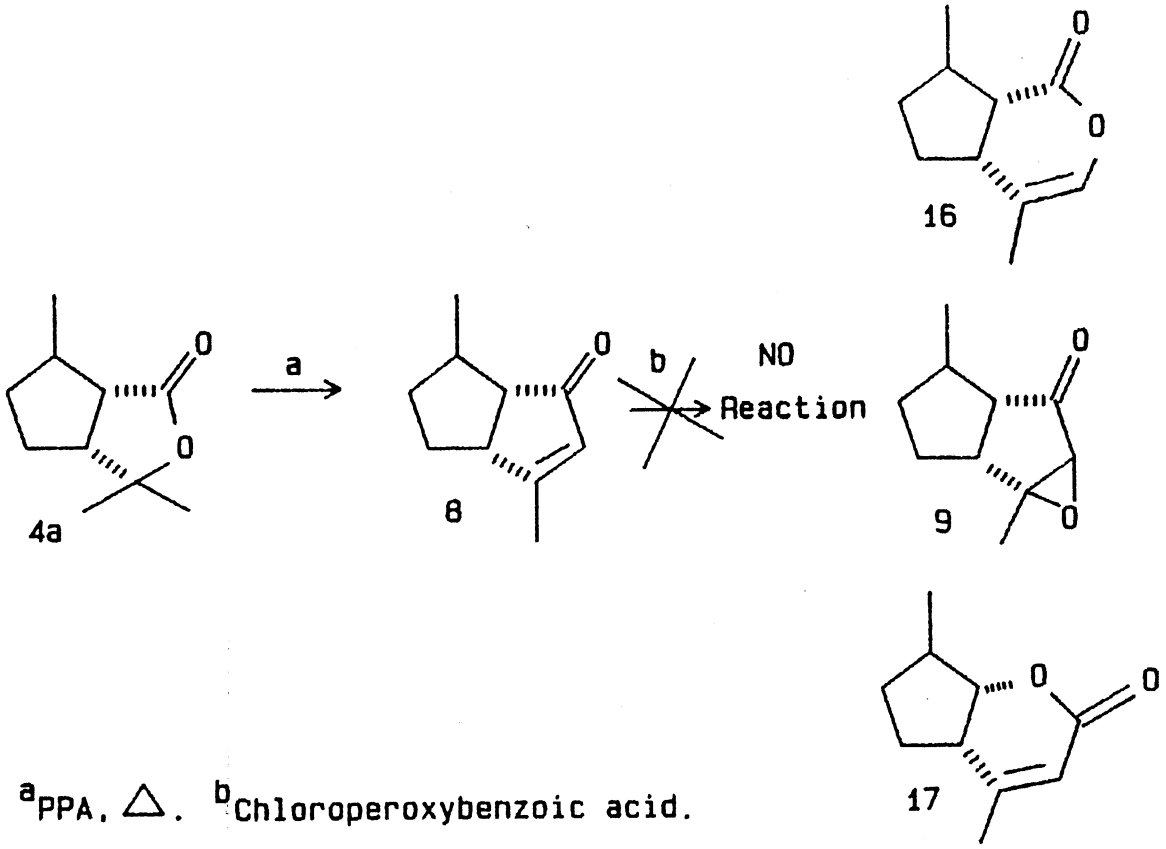
Time of Reaction (h)	Acid, **3a** (%)	Lactones, **4a** and **4b** (%)
1	47	53
2	15	85
16	0	100

After 1 hour at reflux in benzene in the presence of A-15, about half of the pulegenic acid had lactonized. In 2 hours, only 15% of the original pulegenic acid remained, and by 16 hours, no acid remained.

The *trans*-configuration of purified (99% pure) lactone **4a** (steric relationship of the methyl group in the cyclopentane ring with the adjacent carbonyl carbon) was confirmed by comparing its melting point to literature values.[9] The *trans*-lactone **4a** has the lower melting point, 19°C, while the *cis*-lactone **4b** melts at 47°C. Our lactone was a liquid at room temperature and easily crystallized in a refrigerator. The melting point was measured as approximately 16°C by inserting a thermometer in a sample vial and recording the temperature when the sample began to melt and when half of the material was melted.

The unsaturated ketone **8**, as shown is Scheme 10, was prepared from the *trans*-gamma-lactone (**4a**) and *trans*-pulegenic acid (**3a**).

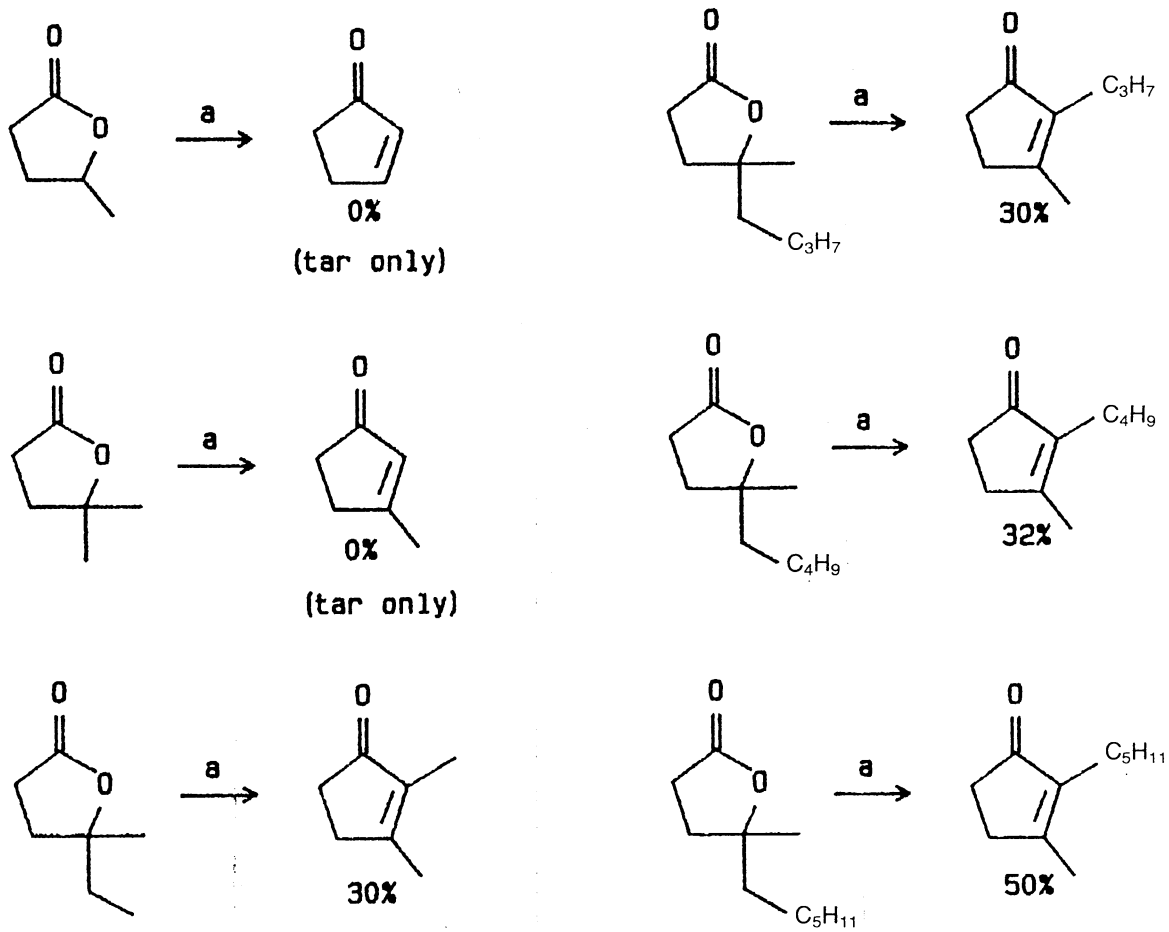
Scheme 10. Attempted Conversion of Pulegenic Lactone to Nepetalactone



Different reagents and several different reaction temperatures were investigated in this conversion. First, a reagent consisting of a mixture of methanesulfonic acid and phosphoric acid was tried.[15a,b] Room temperature and 50°C runs were made. The former reaction yielded only starting material and approximately 3% of **8**, while the latter yielded no product or recoverable starting material. In the next series of reactions, polyphosphoric acid[17a-f] (either commercially prepared or laboratory prepared from phosphorous pentoxide and phosphoric acid) was used. The only differences in the reaction conditions were the temperatures and starting material. The temperature ranged from 45° to 100°C with the lower temperatures giving the best yields. The selected temperature range should be between 45° and 65°C, and the starting material of choice is the lactone over the acid. When

the lactone was used as the reactant, only unsaturated ketone **8** was isolated after distillation. However, starting with pulegenic acid, both lactones and **8** were found as products no matter how long or hot the reaction conditions. The best yield of **8** agreed with the low yield (20%) reported in the literature.[9] This low yield is due both to the difficulty of conversion and the polymerization of the α,β-unsaturated ketone **8** after it is formed. Studies[17a,18] using various substituted saturated lactones demonstrated that the yield improved, if the position alpha to the lactone ether oxygen is sterically hindered or better totally substituted. Scheme 11 shows the types of substituted lactones that have been studied and the product yields.[18] The methyl and dimethyl substituted lactones modeling our lactones **4a** and **4b** gave no desired product, only black tar.

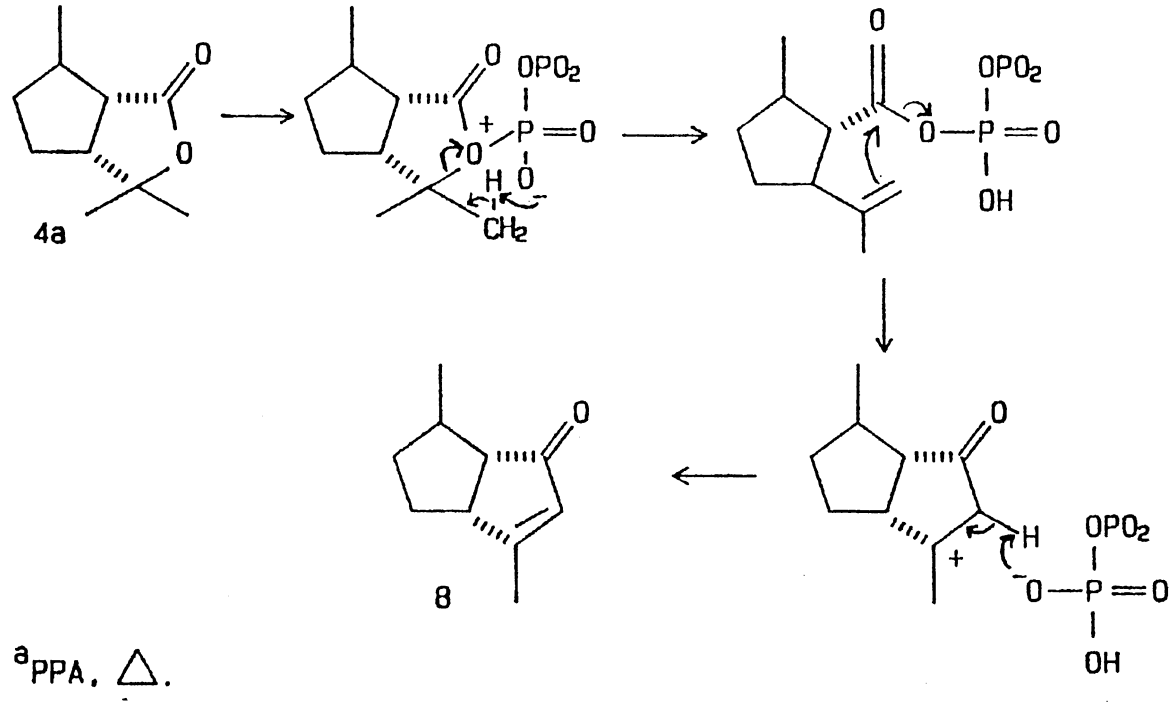
Scheme 11. Steric Effect of Substituents on Formation of Unsaturated Ketones



[a]PPA, △ .

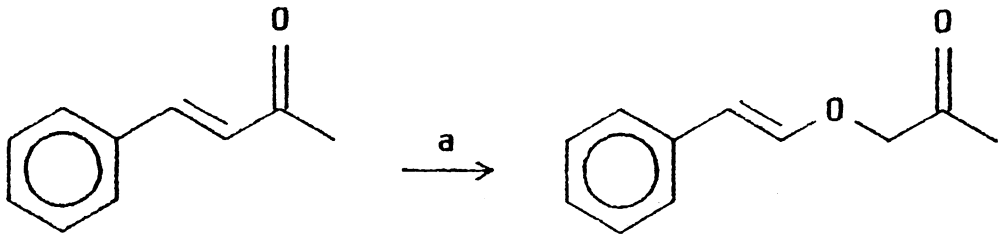
These authors[18] stated that, since the resulting α,β-unsaturated ketone lacked steric hindrance around the double bond, polymerization occurred. However, by studying the proposed mechanism scheme (see Scheme 12) for the PPA-induced alkylation, it becomes apparent that the less substituted lactones, such as the two that gave no unsaturated ketone, would be more difficult to form since again with less substitution polymerization is more likely.

Scheme 12. Mechanism of the Reaction of PPA on Lactone **4a**



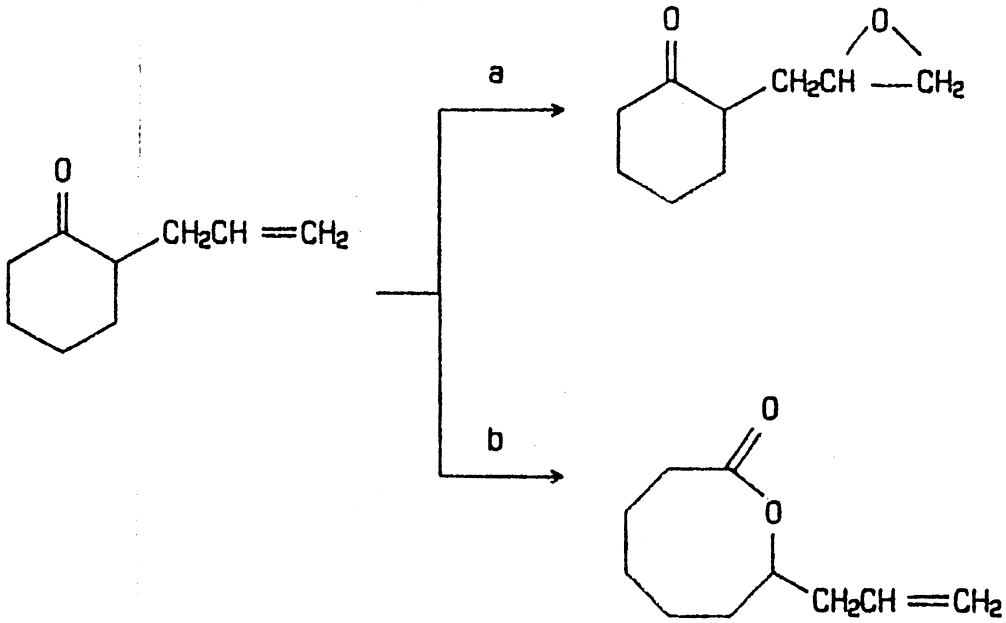
Enough of **8** was synthesized, however, to allow trial of the reaction shown in Scheme 10.

An efficient path to nepetalactone **16**, as suggested by Cavill *et al.*,[7] would be the peroxidation of unsaturated ketone **8**. It was hoped that a Baeyer-Villiger rearrangement would insert an oxygen to form the desired lactone. Cavill *et al.*[7] treated **8** with *para*-chloroperoxybenzoic acid, but no reaction was observed. A search of the literature was made to learn the character and limitations of this reaction.[19a-g] For a successful Baeyer-Villiger rearrangement, a stabilized carbonium ion must result. This stabilization is usually provided by a phenyl group in the β-position to the double bond as shown for the following example.



Otherwise, the double bond reacts to form the epoxide.[19a] Payne[20] showed that 2-allylcyclohexanones also undergo Baeyer-Villiger rearrangement shown in Scheme 13.

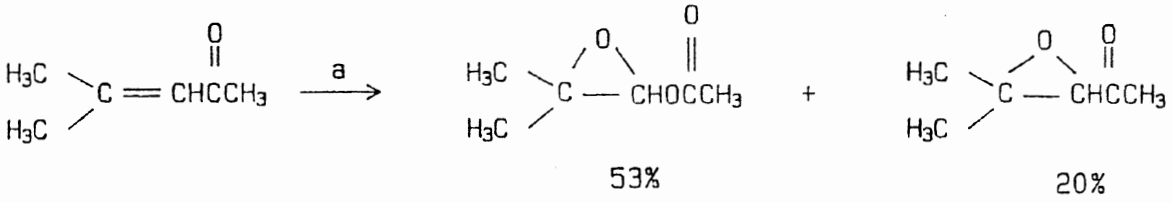
Scheme 13. Baeyer-Villiger Rearrangement of 2-Allylcyclohexanone



[a]C_6H_5CN. H_2O_2. [b]CH_3CO_3H.

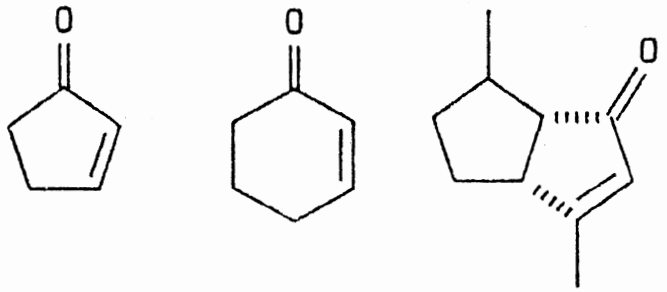
Payne and Williams[19c] found that the peroxidation of mesityl oxide yielded 3,3-dimethyl-2-acetoxyoxirane when treated with peroxyacetic acid (see Scheme 14).

Scheme 14. Peroxidation of Mesityl Oxide



[a]CH_3CO_3H.

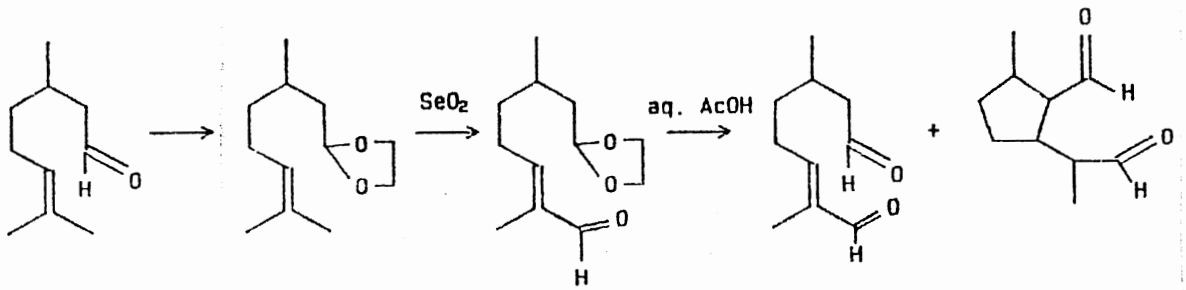
The peroxidation reaction was tried on the two model compounds, **21** and **22**, shown below as well as on compound **8**.



21 22 8

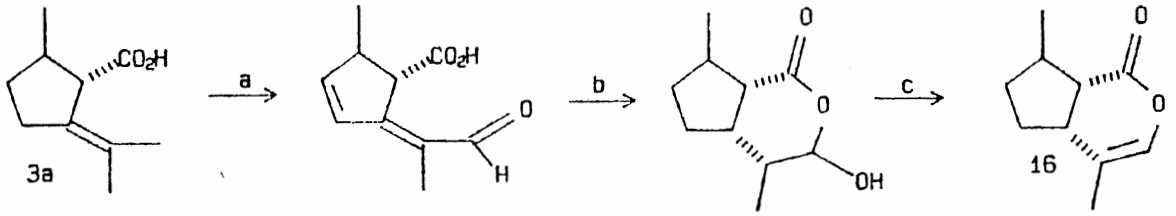
Compounds **21** and **22** failed to react and **8** gave only a small amount of a product that by GC/MS had the correct molecular weight (one oxygen added). Most of the starting material was recovered. The actual structure of the new product remains unknown. The mass spectrum, with an apparent loss of two methyl groups from the parent ion, suggests that the lactone is formed in preference to the epoxide. Though the potential of this reaction is of interest, the low yield discouraged us from proceeding.

Another oxidative approach to the conversion of pulegenic acid to nepetalactone was investigated. As shown below, Robinson[21a] and Achmad and Cavill[6] used selenium dioxide to synthesize iridodial from citronellal by oxidizing the terminal methyl of the isopropylidene group, followed by a condensation of the resultant unsaturated dialdehyde.



From this study, we decided that allylic oxidation reaction using selenium dioxide had the potential of placing an oxygen at the correct position in the pulegenic acid skeleton to subsequently form nepetalic acid (**15**) which, in turn, could be converted to nepetalactone (**16**) as shown in Scheme 15.

Scheme 15. Conversion of Pulegenic Acid to Nepetalactone (**16**)



[a]SeO_2. AcOH. Δ. [b]H_2. Pd/C. [c]Δ.

Considerable research has been done to oxidize alkenes at the allylic position to produce aldehydes using selenium.[21a-x] Guillemonat[21b] reviewed the literature and carried out allylic hydroxylation of olefins using selenium dioxide. He developed the following rules for predicting the point of attack and the reaction products:

1. Hydroxylation occurs *alpha* to the more highly substituted end of the double bond.

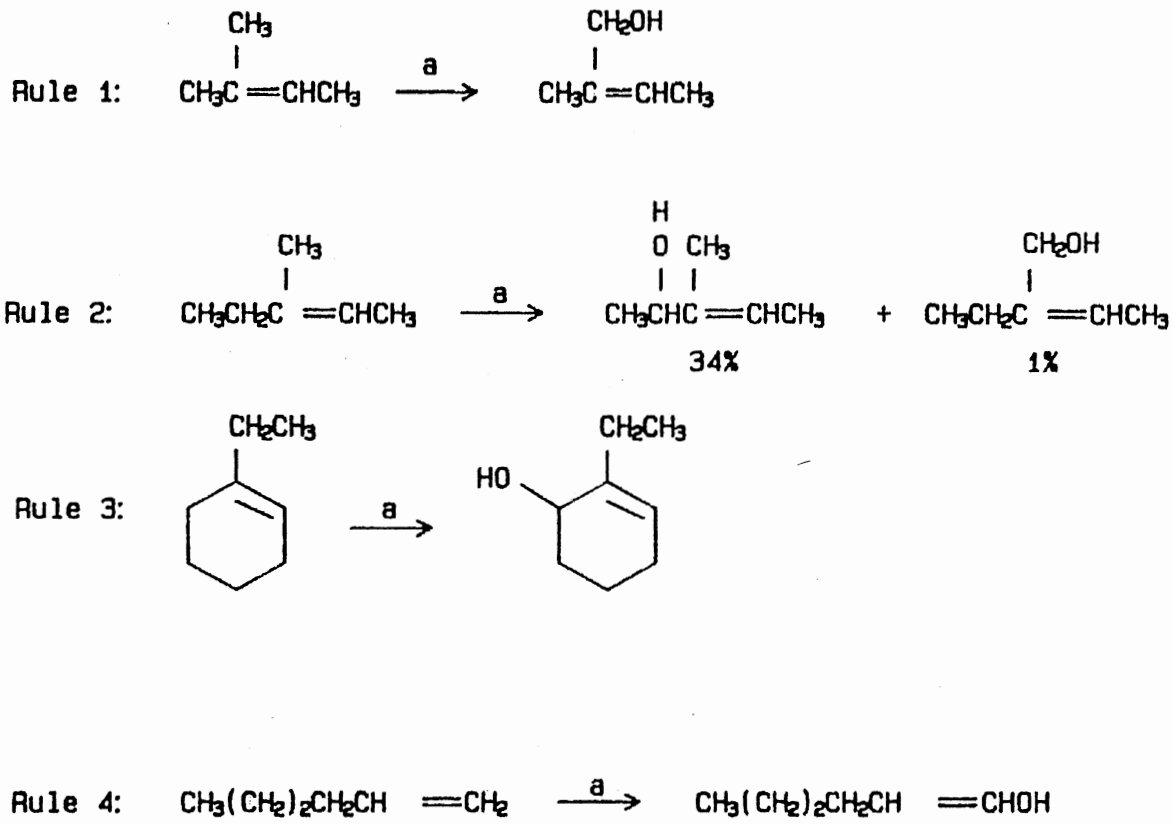
2. The order of facility of oxidation is $CH_2 > CH_3 > CH$.

3. When the double bond is in a ring, oxidation whenever possible occurs within the ring and again *alpha* to the more substituted end of the double bond.

4. Oxidation of a terminal double bond affords a primary alcohol with allylic migration of the double bond.

Examples are presented in Scheme 16 which illustrates each of these rules.

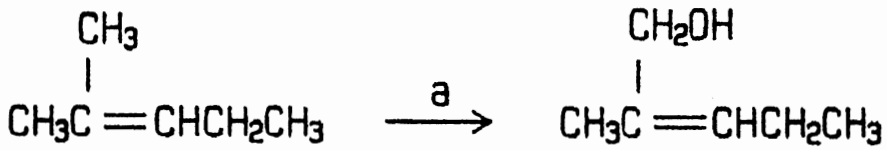
Scheme 16. Examples of Guillemonat's Rules



[a]SeO_2.

Scheme 17 shows an example when Rule 1 takes precedence over Rule 2.

Scheme 17. Guillemonat's Rule 1 Takes Precedence Over Rule 2

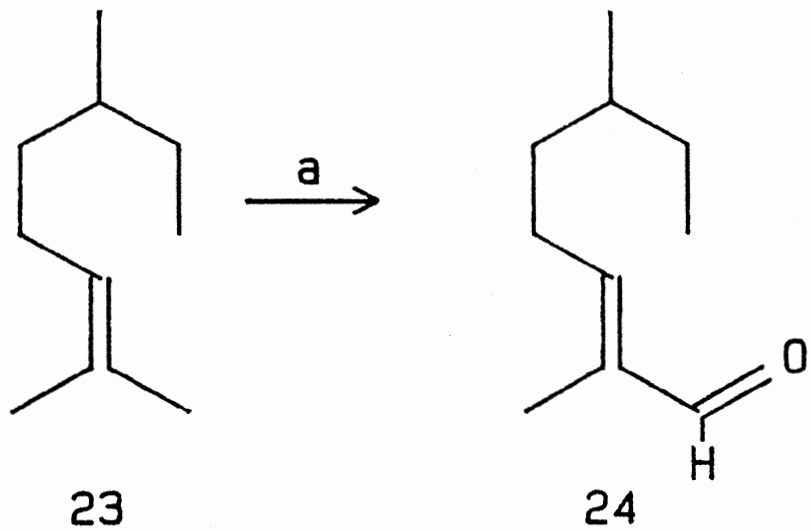


[a]SeO_2.

The products formed from the selenium dioxide oxidation depend on the solvent used: acetic acid gives the acetate, ethanol gives an ether, and water gives an α,β-unsaturated ketone (which probably arises from oxidation of the alcohol first formed).[21c]

To establish procedures, 2,6-dimethyloctene (**23**) was oxidized as shown in Scheme 18. Methanol and two equivalents of SeO_2 were used to obtain the expected allylic aldehyde along with a minor methoxy-containing product. The position of the carbonyl was confirmed by proton NMR.

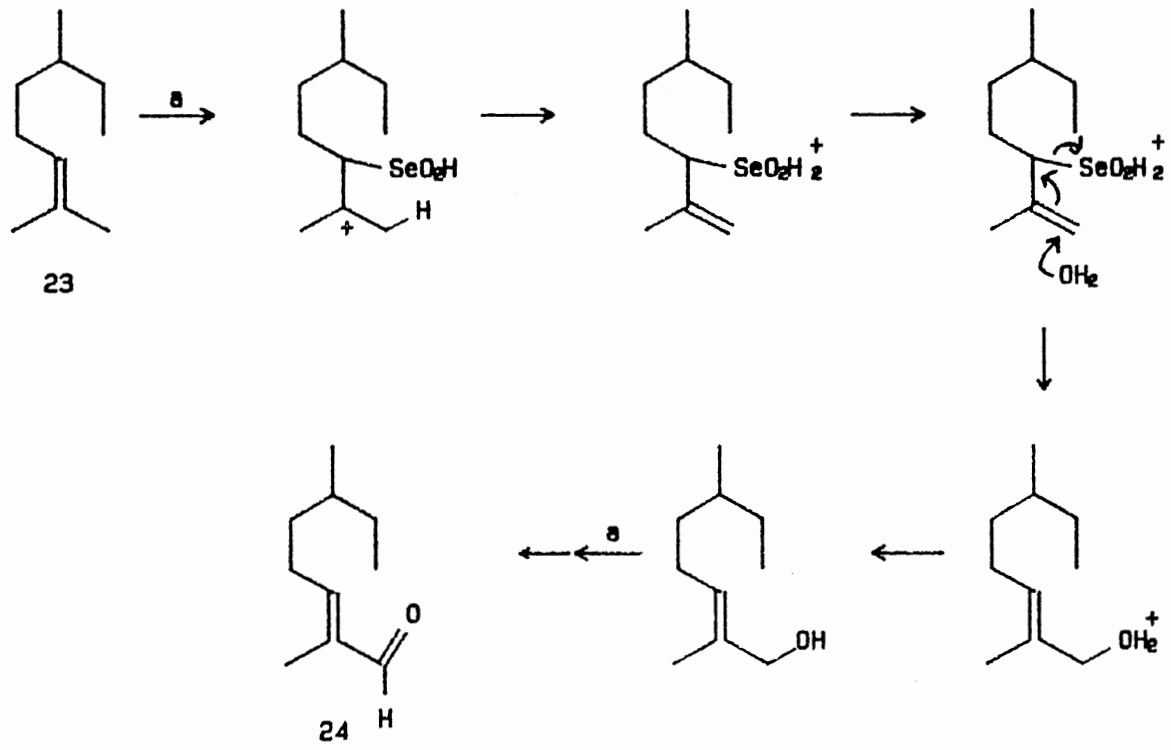
Scheme 18. SeO_2 Oxidation of Compounds **23** to **24**



[a]SeO_2. MeOH.

The mechanism of reaction for selenium dioxide is shown in Scheme 19.

Scheme 19. Mechanism for the SeO_2 Oxidation of **23** to **24**



[a]SeO_2. $MeOH/H_2O$.

This procedure was applied to pulegenic acid. The products predicted from Guillemonat's Rules are shown in Figure 3.

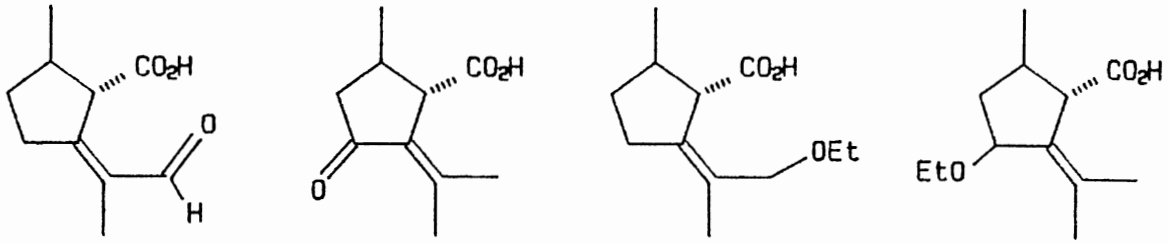
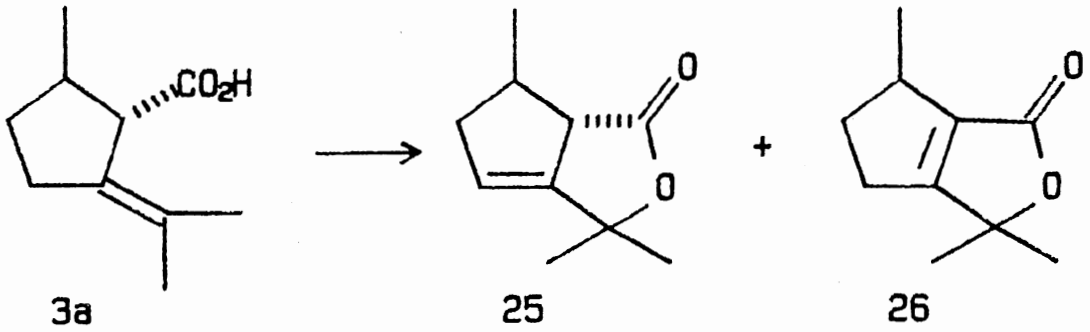


Figure 3. Predicted Possible Products of SeO_2 Oxidation of **3a**

However, upon carrying out this oxidation reaction, the two major products shown in Scheme 20 were formed. That these products were lactones was established by their insolubility in alkali. GC/MS and NMR analysis confirmed the structures.

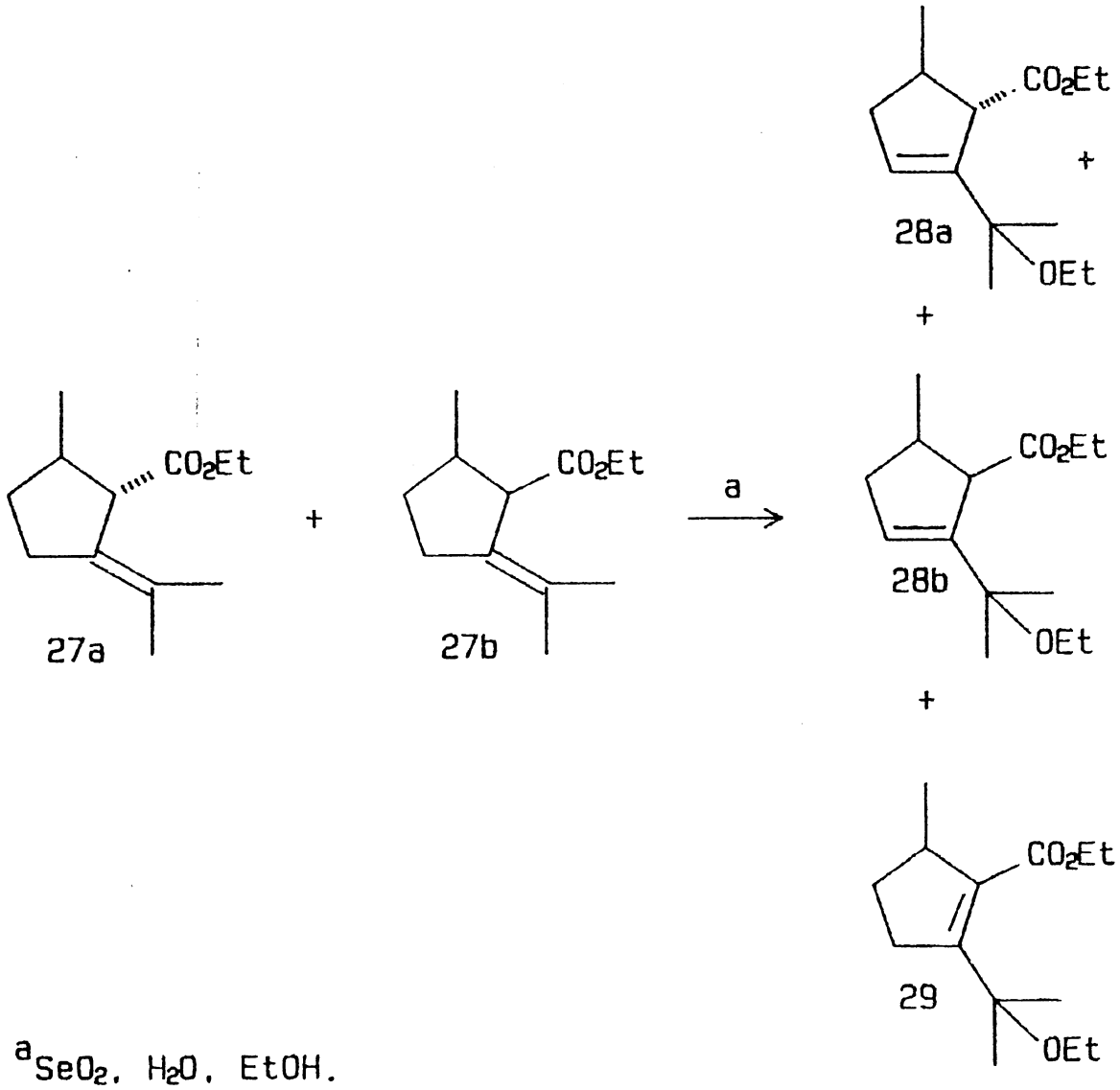
Scheme 20. SeO_2 Oxidation of **3a**



[a]SeO_2. H_2O. EtOH.

Therefore, no oxygen was added to pulegenic acid which was unexpected and at first difficult to explain. To examine this further, another experiment was carried out in which only one equivalent of SeO_2 and ethyl pulegenates (**7a** and **7b**) were used. Three products were formed as shown in Scheme 21.

Scheme 21. SeO_2 Oxidation of **27a** and **27b** to **28a**, **28b,** and **29**



These products showed a molecular weight of 240, which suggested addition of an ethoxy group to the ethyl pulegenates. Figure 4 lists the possible double bond and ethoxyl group arrangements and shows the ones that can be eliminated through use of ^{1}H NMR, which indicated that the double bond is in the ring because the adsorption of one vinylic proton was observed.

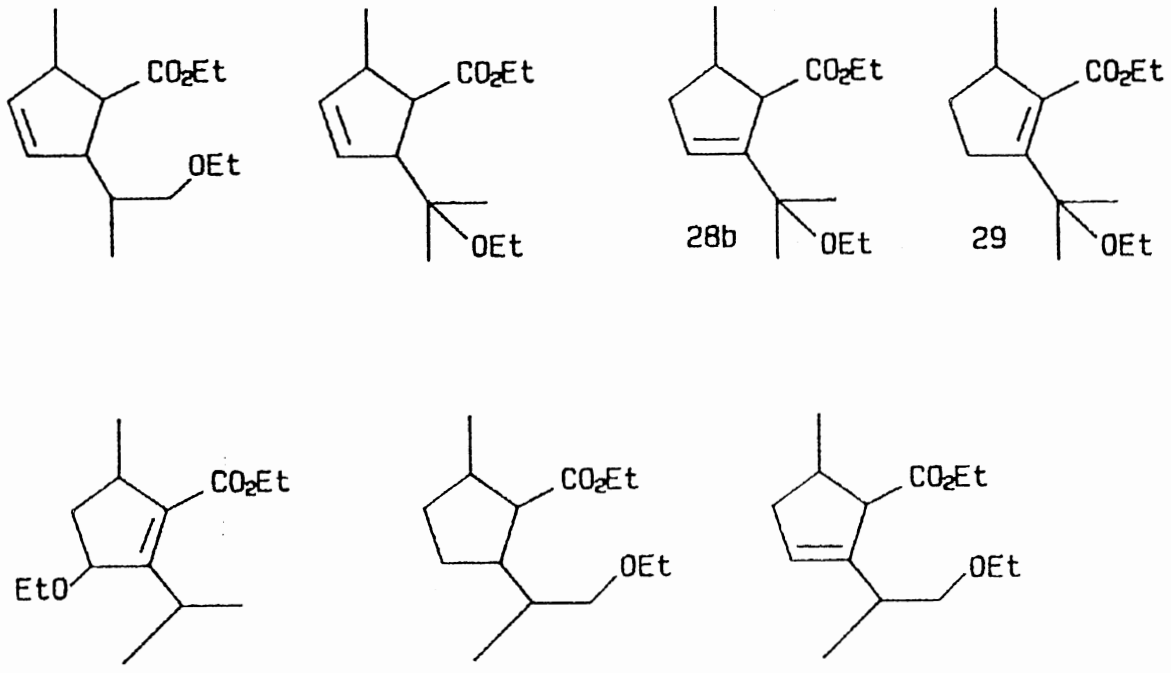
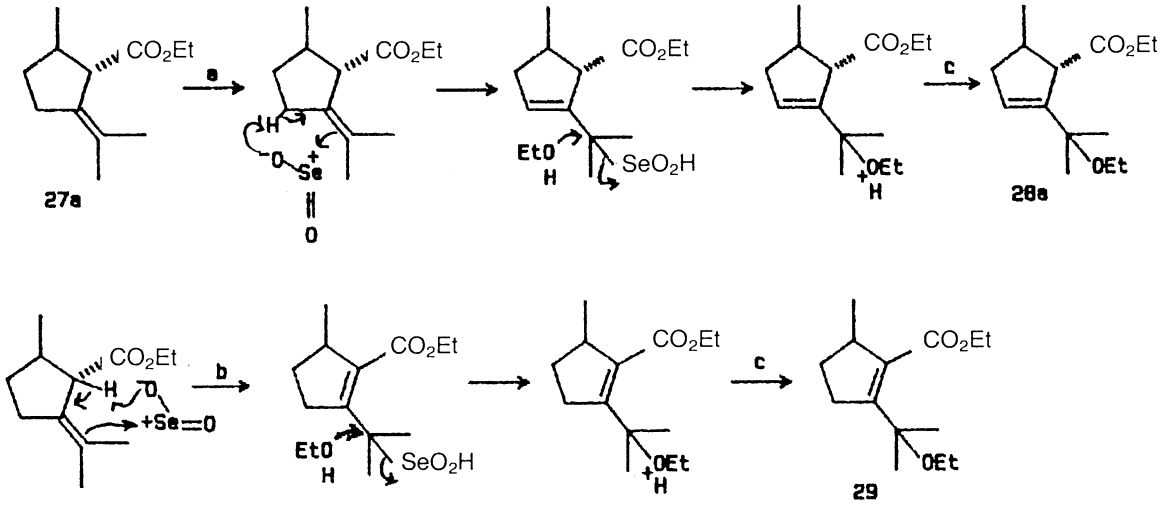


Figure 4. Possible Structures of the Products of SeO_2 Oxidation of Ethyl Pulegenate

Apparently the original double bond in the pulegenic ester migrated into the ring. This suggests that attack must occur initially on the allylic positions on the five-membered ring, thus causing double bond migration as shown in Scheme 22.

Scheme 22. Mechanism Proposed to Explain SeO_2 Oxidation of Ethyl Pulegenates

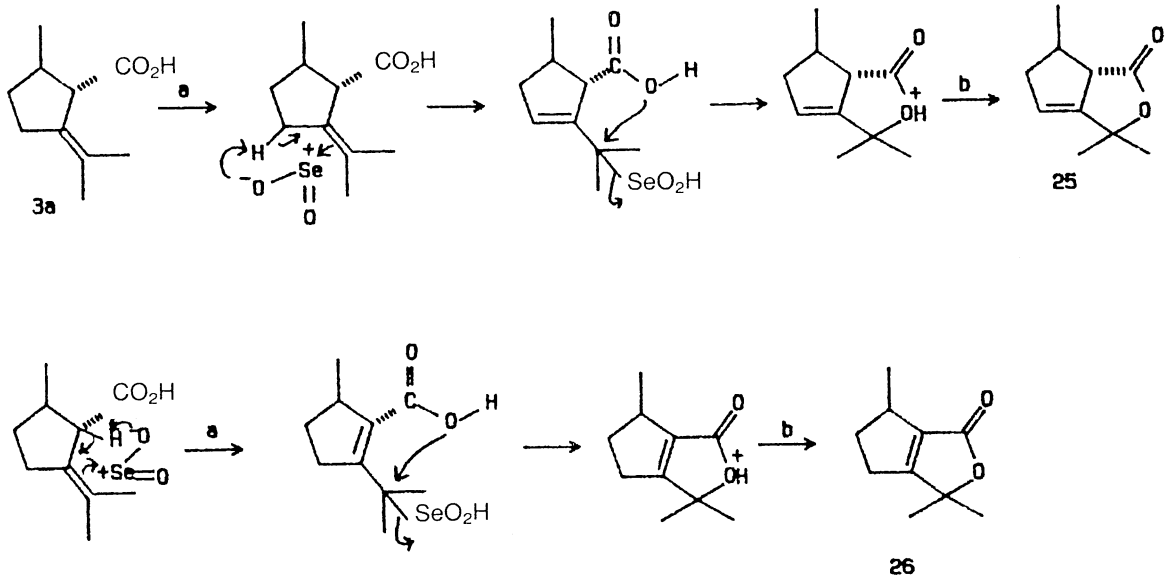


[a]SeO_2. EtOH. [b]EtOH. [c]Loss of H^+.

This is supported by the GC/MS data (see next section for details) which shows three products of which two have very similar mass spectra and the third an entirely different fragmentation pattern. Also, the existence of three products instead of four (starting material consisted of two isomers) suggests that the differing position between the two isomers was destroyed. This would be the case if the double bond position was as in compound **29**.

With this new evidence, a similar mechanism to that presented in Scheme 22 can be proposed to explain the formation of the unsaturated lactones from pulegenic acid (**3a**). In Scheme 23, the allylic positions in the ring react initially, thus moving the double bond to the ring and creating an activated position for addition of SeO_2 at the tertiary position in the isopropyl group. Then, before an ethoxy group displaces the Se group as in Scheme 22, intramolecular cyclization of the carboxyl group forms the lactone.

Scheme 23. Proposed Mechanism to Explain Products From the SeO_2 Oxidation of **3a**



[a]SeO_2. H_2O. EtOH. [b]Loss of H^+.

Therefore, the structure needed for synthesis of nepetalactone is not realized.

CHAPTER III

EXPLANATION OF GAS CHROMATOGRAPHY/ MASS SPECTROMETRY DATA

A series of reactions starting with pulegone (**1**) and proceeding through various products were studied. For each of these reactions, the GC/MS analysis proved interesting and useful in understanding the type and number of products that were formed. A large volume of information is obtained from this technique. There is the temptation to try to evaluate and use all of the data. Since much time can be spent identifying minor components, an arbitrary minimum occurrence level of 5% was set. However, an isomer of the predominate product was sought at lower levels.

It must also be recognized that some speculation on the structure of the components found in these reactions is necessary, since no attempt was made to isolate them and no other analytical techniques on these minor components were used for identification.

GC/MS is a quick, informative technique that allows judgments to be made on the course of the reaction and provides information about the major and minor products and how much starting material is present at the conclusion of the reaction.

GC/MS of Pulegone (1)

The purity of the starting material of the reaction sequence is important in evaluating the effects of the reagents. If the starting material is not pure, other materials can enter into the reaction causing the appearance of unexpected minor products.

The total ion chromatogram in Figure 5 shows there are at least six different identifiable peaks; however, only two are major. The two small peaks at scans 353 and 361 (1 scan = 1 second) account for about 1% of the sample. They both have parent ions of m/e 154, indicating they are isomers of the saturated form (**20**) of pulegone.

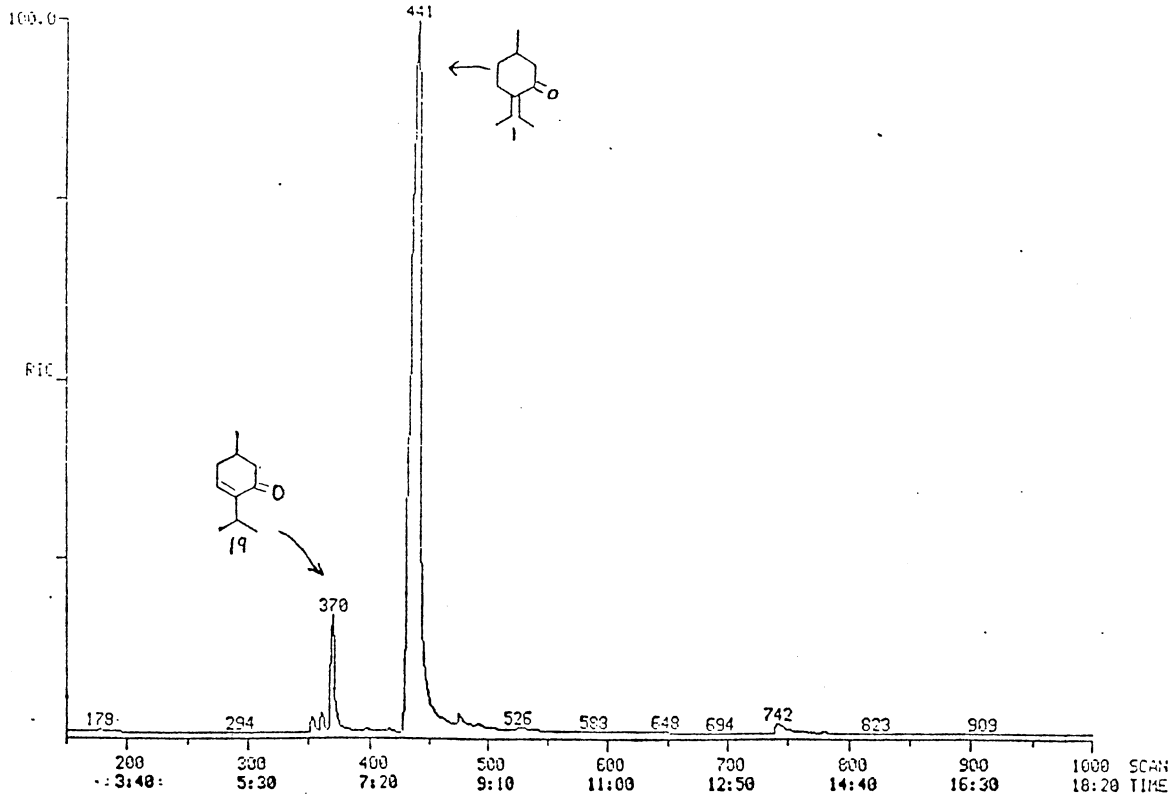
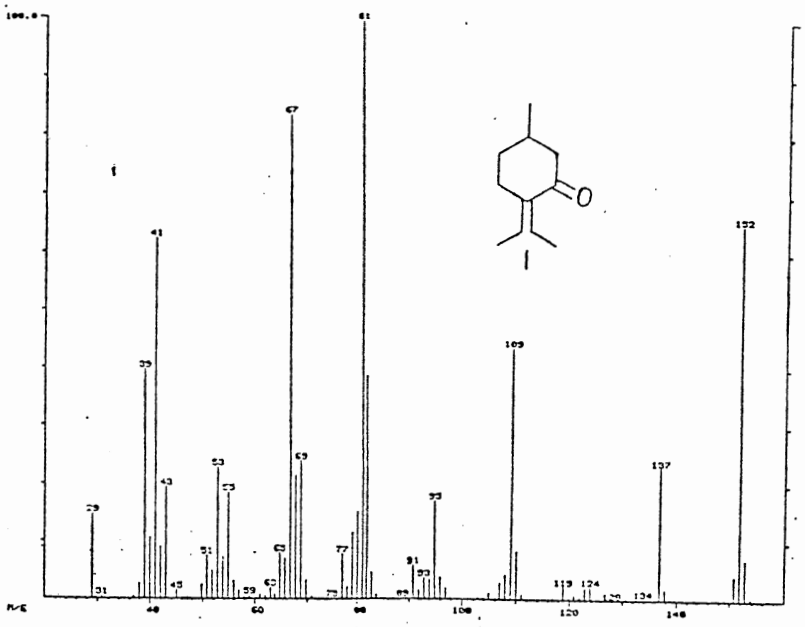
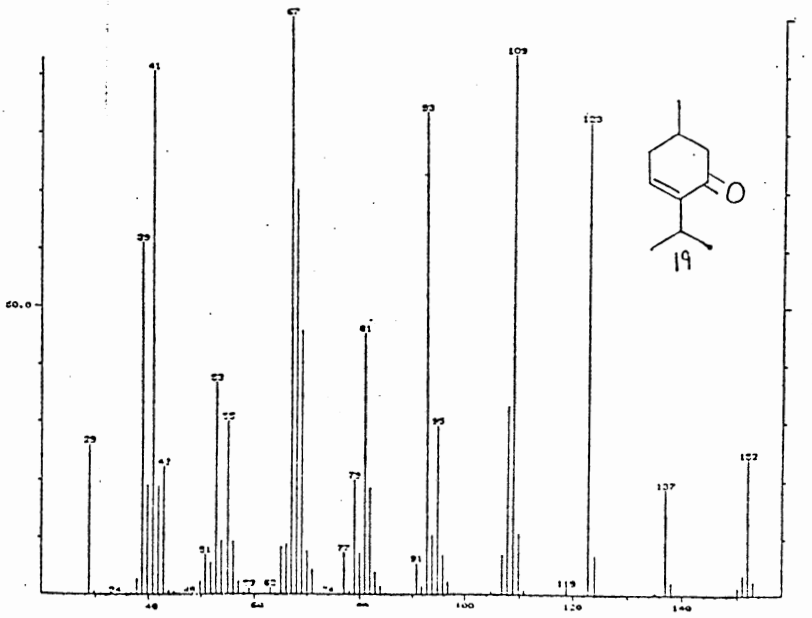


Figure 5. Total Ion Chromatogram of Pulegone (**1**)

At scan 370, **19** an isomer of pulegone appears. Pulegone (**1**) appears at scan 441. The earlier peak represents an isomer with the double bond in a different position than that of pulegone. The fragmentation patterns for **1** and **19** are shown in Figure 6 a and b.



a. Scan 441; Compound **1**



b. Scan 370; Compound **19**

Figure 6. Mass Spectra of Pulegone and an Isomer

A minor component with parent ion of m/e 222 is found at scan 742 into the total ion chromatogram. At the present time the identity has not been determined, but it probably is sesquiterpenoid.

Favorskii Rearrangement Reaction GC/MS Data

Treatment of pulegone, as discussed above, with bromine and then with sodium methoxide in methanol resulted in a reaction mixture represented by the total ion chromatogram in Figure 7. The total ion chromatogram shows major components at scans 438 and 446 which are the desired products, methyl pulegenates (**7a** and **7b**), from the Favorskii rearrangement of pulegone dibromide (**2**).

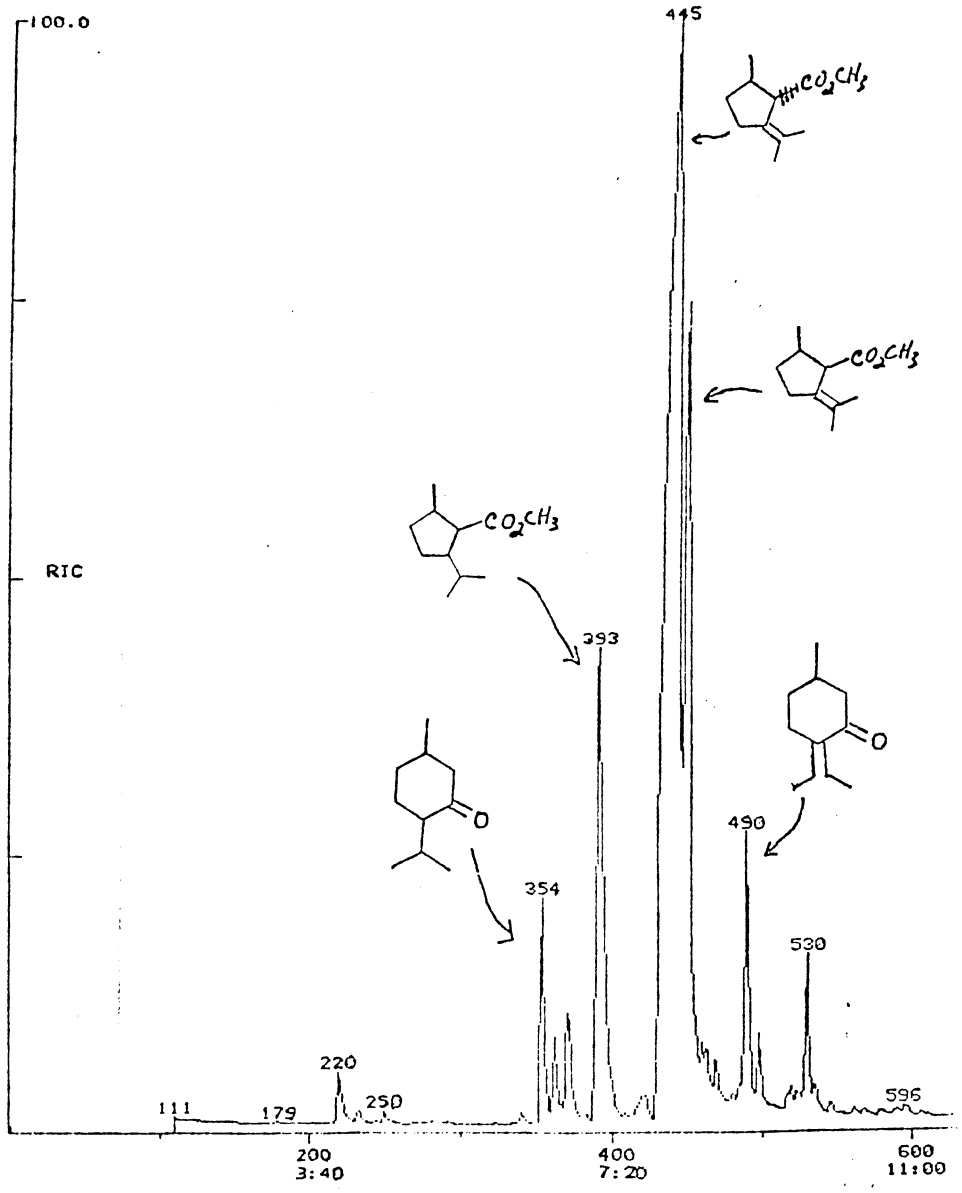


Figure 7. Total Ion Chromatogram of Products From Favorskii Reaction of Pulegone

Two impurities from the original pulegone are identified in the reaction mixture as menthone **20** at scan 354 and a pulegone isomer at scan 371. There is a component at scan 380 which has a parent ion of m/e 164 or 182 that has not been identified. The effect of having an impurity in the starting pulegone is seen by the occurrence of the compound (m/e

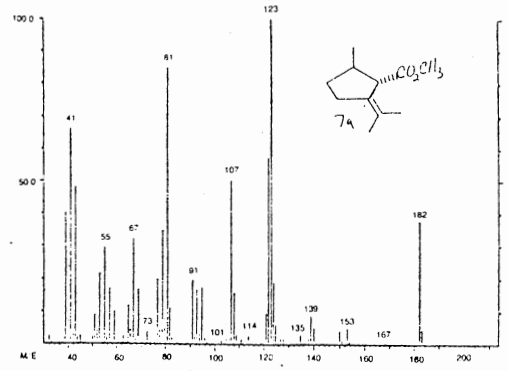
184) represented by the peak at scan 392. This unknown has a fragmentation indicating that it is a saturated methyl pulegenate. This component probably is the product of the Favorskii rearrangement on the brominated menthone impurity or possibly an artifact in the conventional Favorskii rearrangement itself.

At scans 438 and 446, the methyl pulegenates (**7a** and **7b**) occur with a parent ion m/e of 182. These isomers occur in about an 80:20 ratio based on peak areas. Mass spectrometry is usually not effective in distinguishing isomers. However, when combined with gas chromatography in this example, it clearly provided the needed data.

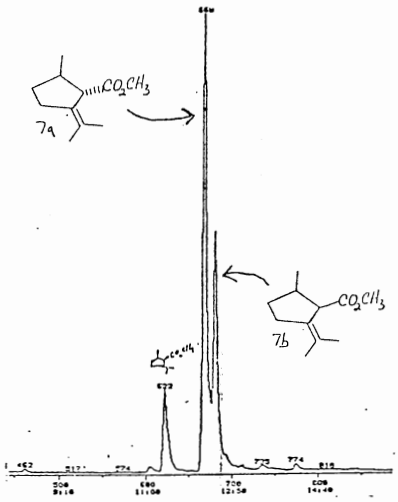
Some remnant of the starting material, pulegone, is seen at scan 490.

GC/MS Information on Methyl Pulegenate

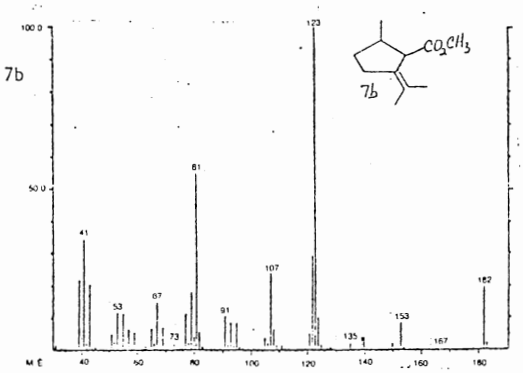
The total ion chromatogram and mass spectra of purified methyl pulegenates, **7a** and **7b**, are shown in Figure 8 a, b, and c. Both isomers give essentially the same fragmentation patterns, with the *trans*-isomer **7a** providing a stronger parent ion intensity than the *cis*-isomer **7b**. The two isomers are separated by 10 scans on the total ion chromatogram, with the *trans*-isomer eluting first.



b. Scan 668; Compound **7a**



a. Total Ion Chromatogram of **7a** and **7b**



c. Scan 679; Compound **7b**

Figure 8. GC/MS Data on Methyl Pulegenates (**7a** and **7b**)

After hydrolysis of the methyl pulegenates, **7a** and **7b**, to their acids, **3a** and **3b**, the ratio of the isomers significantly changed to a 97:3 ratio (see Figure 9). This later ratio was established through GC/MS studies of their methyl esters prepared through use of diazomethane to esterify the acids.

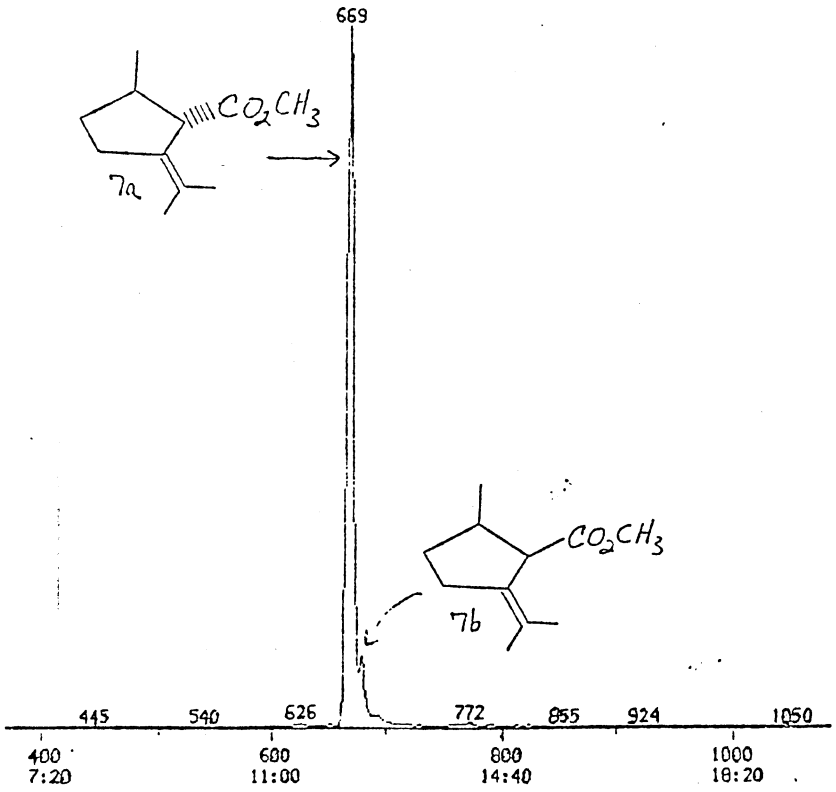


Figure 9. Total Ion Chromatogram of Methyl Ester **7a** After Purification

GC/MS Data on the Neutral Fraction of the Hydrolysis of Methyl Pulegenate

The total ion chromatogram of the neutral fraction from the conversion of the methyl pulegenates (**7a** and **7b**) to pulegenic acids (**3a** and **3b**) is given in Figure 10. Some unreacted methyl pulegenate is present along with pulegone starting material and other components associated with possible impurities from pulegone.

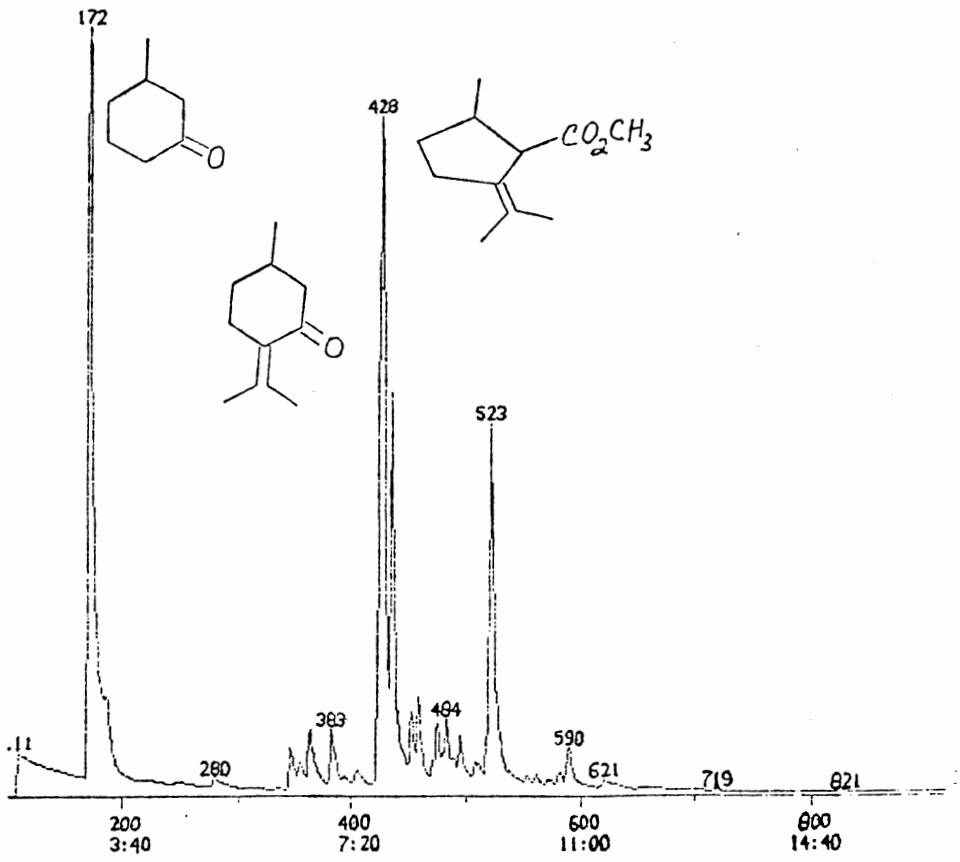
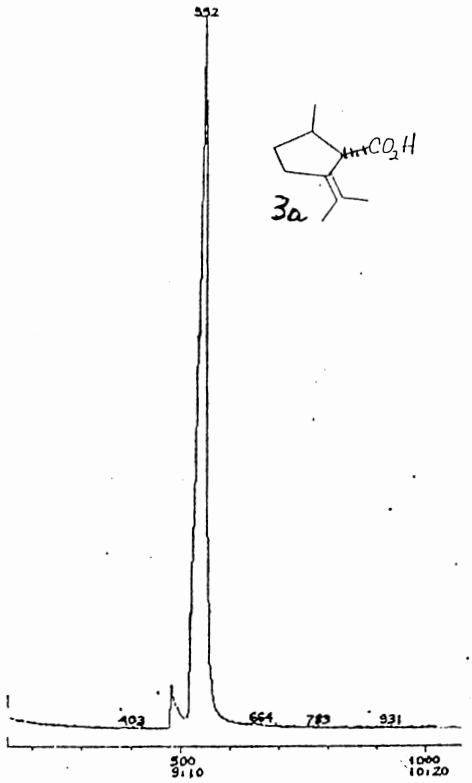


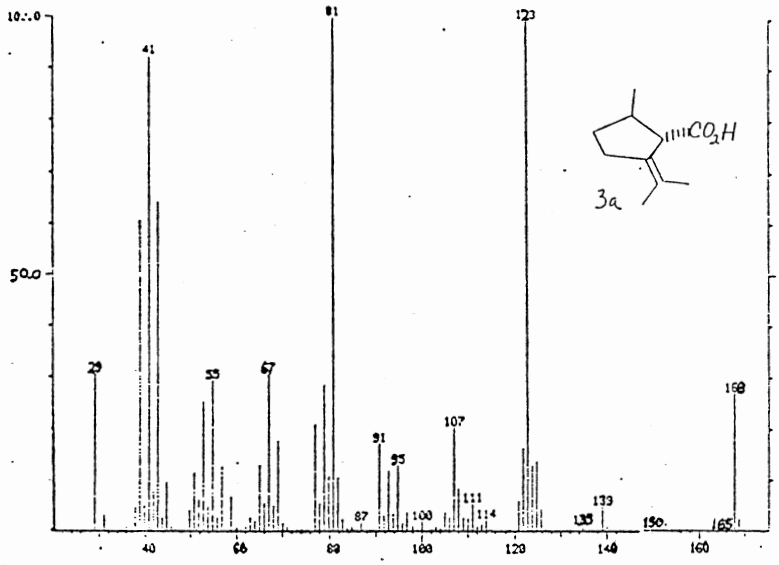
Figure 10. Total Ion Chromatogram of the Neutral Products Extracted From Saponification of Esters **7a** and **7b**

Pulegenic Acid GC/MS Data

Over 95% of one isomer was observed in the total ion chromatogram of the pulegenic acid product. The acid itself could be chromatographed since it passed through the column and remained unaltered (see Figure 11). This is not the usual behavior of carboxylic acids. The ion fragmentation pattern, as shown in Figure 11 b, is representative of an organic acid through loss of m/e 45 ($-HCO_2$). In this case, the loss of the carboxyl group is more significant than loss of a methyl group. If methyl loss were significant, then m/e at 153 and 109 would be more intense. A loss of C_3H_6 (m/e 42) occurs after the decarboxylation (m/e 123 to 81).



a. Total Ion Chromatogram of **3a**



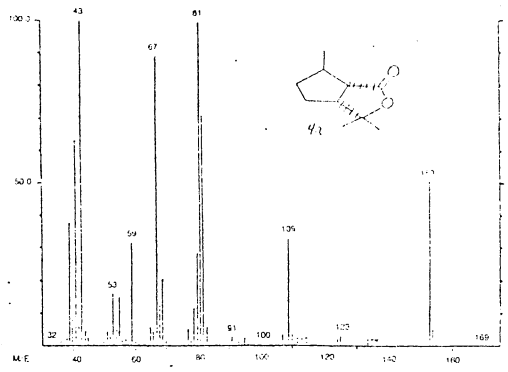
b. Scan 552; Pulegenic Acid **3a**

Figure 11. GC/MS Data on Pulegenic Acid (**3a**)

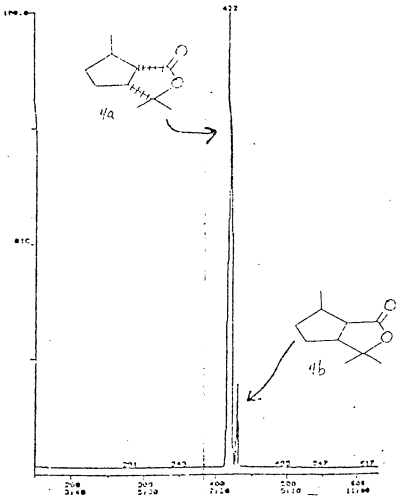
GC/MS Study of the Lactonization of Pulegenic Acid

The acid-catalyzed lactonization of pulegenic acid was studied by GC/MS to document the differences between the two lactone isomers (**4a** and **4b**).

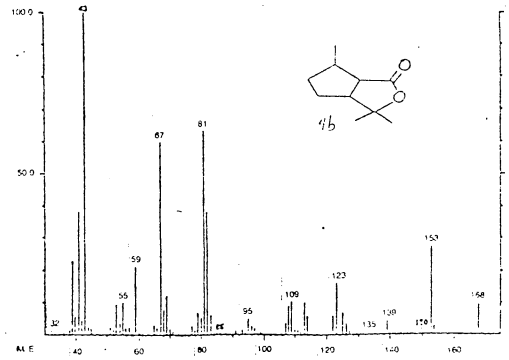
The major isomer eluted at scan 422 and the minor one 8 scans later (430) in a 95:5 ratio (see Figure 12). The fragmentation patterns for the lactones differ from those of pulegenic acids, as seen in Figure 12 b and c. As mentioned earlier, carboxylic acids show a characteristic loss of m/e 45, whereas lactones **4a** and **4b** lose a methyl group (m/e 15). Also, isomers **4a** and **4b** register different fragmentation patterns. The major isomer, the *trans*,*cis*-lactone **4a**, does not show a parent ion at m/e 168 but does lose carbon dioxide (m/e 44) after loss of a methyl group, whereas the minor isomer, *cis*,*cis*-lactone **4b** occurring later in the total ion chromatogram, has a parent ion (m/e 168) and loses both methyl and ester function (CO_2) from the parent ion. This is a case where the differences in structure of isomers significantly influences the fragmentation pattern of the mass spectrum.



b. Scan 422; Lactone **4a**



a. Total Ion Chromatogram of **4a** and **4b**



c. Scan 427; Lactone **4b**

Figure 12. GC/MS Data on Lactones **4a** and **4b**

GC/MS Data for Polyphosphoric Acid (PPA)

Rearrangement of Lactones 4a and 4b

Lactone **4a** was rearranged to the unsaturated ketone **8** using PPA. Only one isomer of the unsaturated ketone was observed and it was assumed to be **8**. There was some starting material present as shown in Figure 13. However, after distillation, the pure unsaturated ketone **8** was recovered.

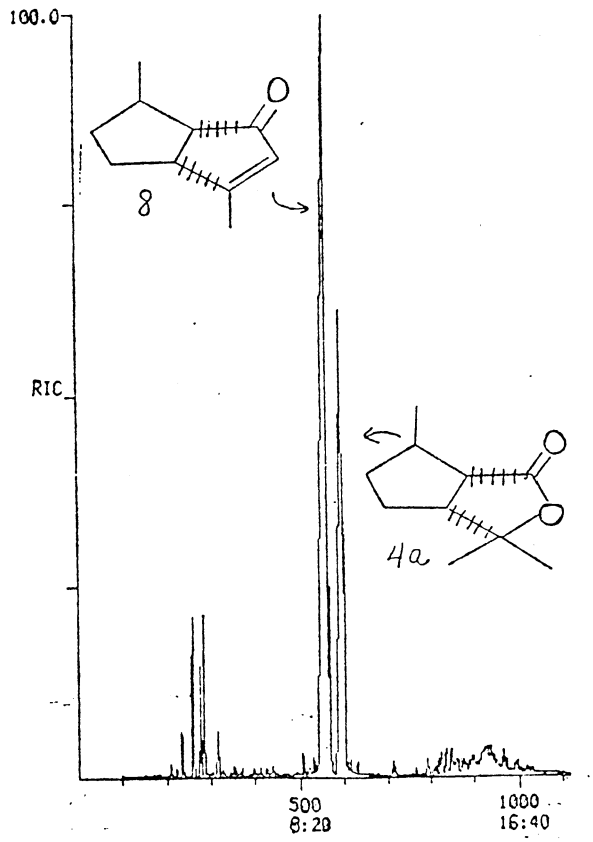
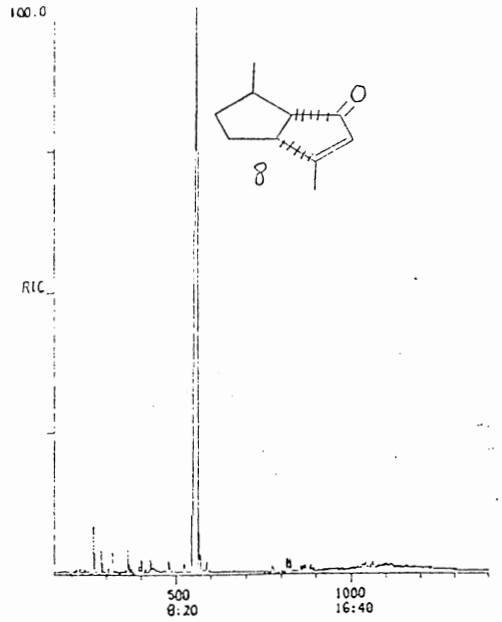
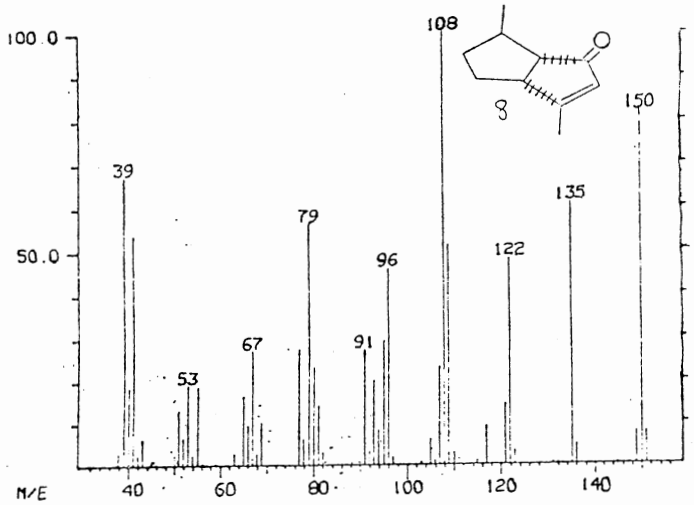


Figure 13. Total Ion Chromatogram of Reaction Mixture From PPA Treatment of **4a**

Its total ion chromatogram and mass spectrum are shown in Figure 14.



a. Total Ion Chromatogram of **8**



b. Unsaturated Ketone **8**

Figure 14. GC/MS Data on Distilled Unsaturated Ketone **8**

GC/MS Data on Selenium Dioxide

Oxidation of Allylic Positions

An unsaturated hydrocarbon, 2,6-dimethyl octene (**23**) was treated with SeO_2 to cause oxidation at the allylic methyl positions, as shown in Figure 15.

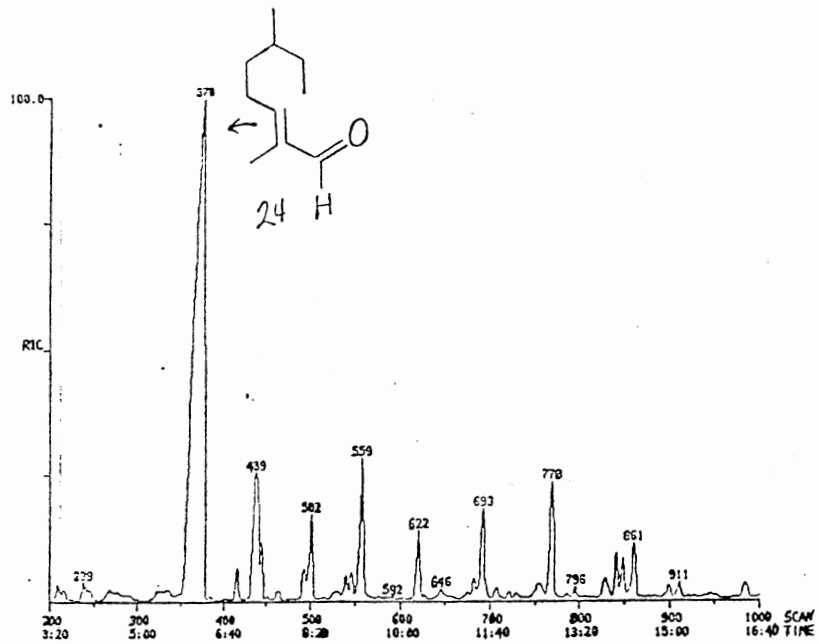
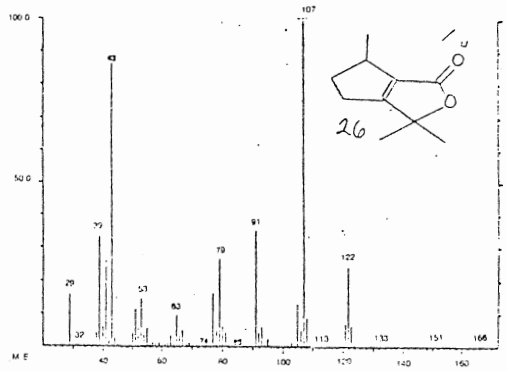
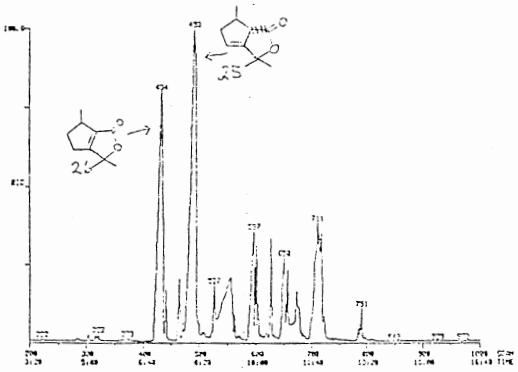


Figure 15. Total Ion Chromatogram of SeO_2 Oxidation of **23**

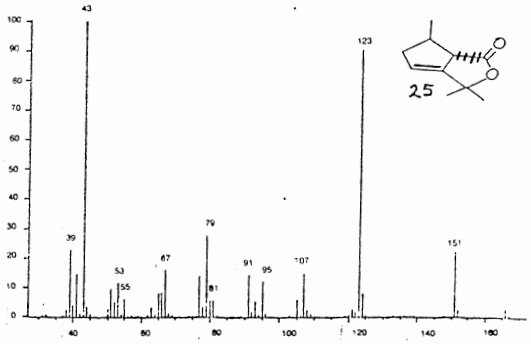
This SeO_2 oxidation was extended to pulegenic acid (**3a**) with interesting results. Two major products were formed, as shown in the total ion chromatogram in Figure 16 a. These two compounds (scans 434 and 493) gave mass spectra, shown in Figure 16 b and c. These compounds are believed to have the structures **26** and **25**, respectively. The fragmentation patterns support these structures as does the NMR data.



b. Scan 434; Compound **26**



a. Total Ion Chromatogram of **25** and **26**



c. Scan 493; Compound **25**

Figure 16. GC/MS Data on SeO_2 Oxidation Products of Pulegenic Acid (**3a**)

Further investigation of this reaction was carried out using one equivalent of SeO_2. This time the two ethyl pulegenates (**7a** and **7b**) were used. Three major products were obtained as shown in the total ion chromatogram in Figure 17. Since the starting material consisted of two (Figure 17) isomers (*cis*- and *trans*-isomers of ethyl pulegenate), it is expected that products would exist in pairs resulting in four products.

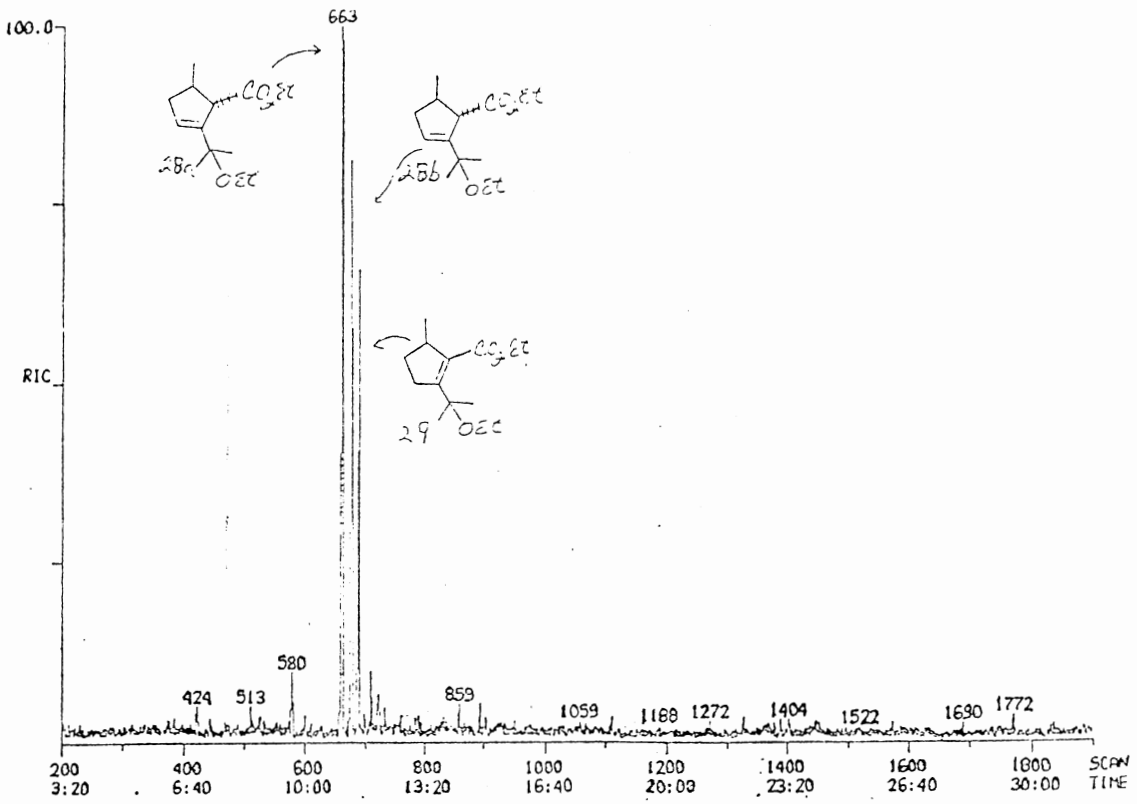
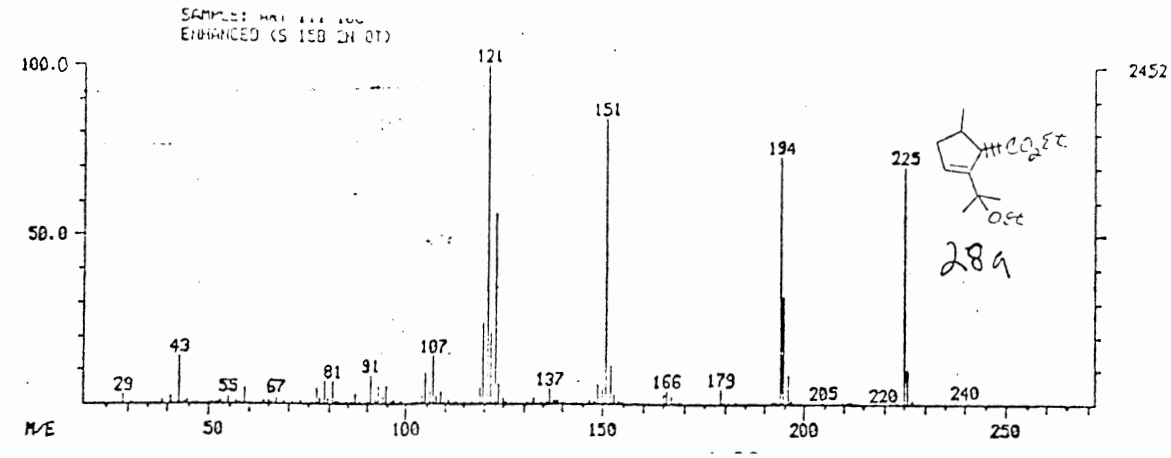
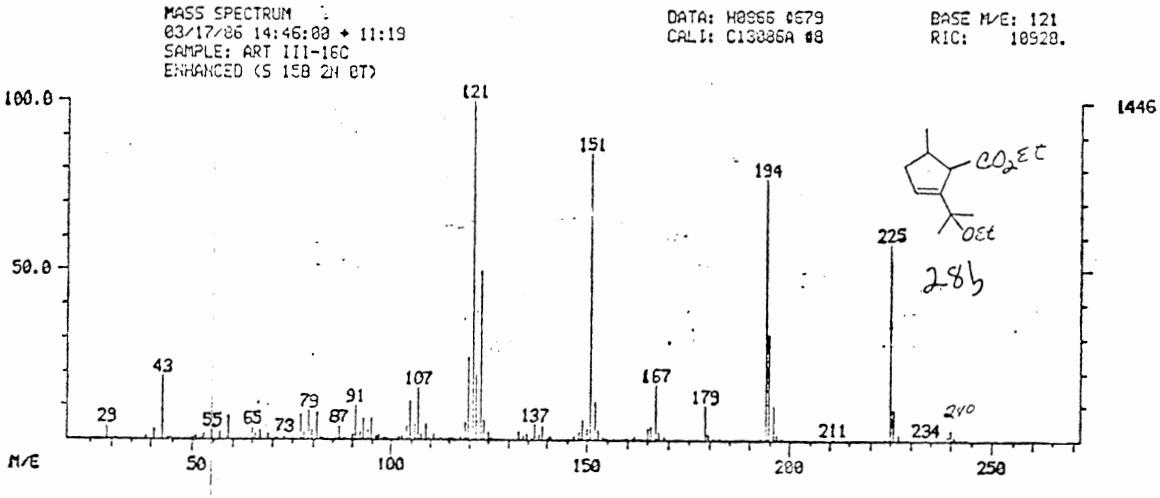


Figure 17. Total Ion Chromatogram of Products From the SeO_2 Oxidation of Ethyl Pulegenates (**7a** and **7b**)

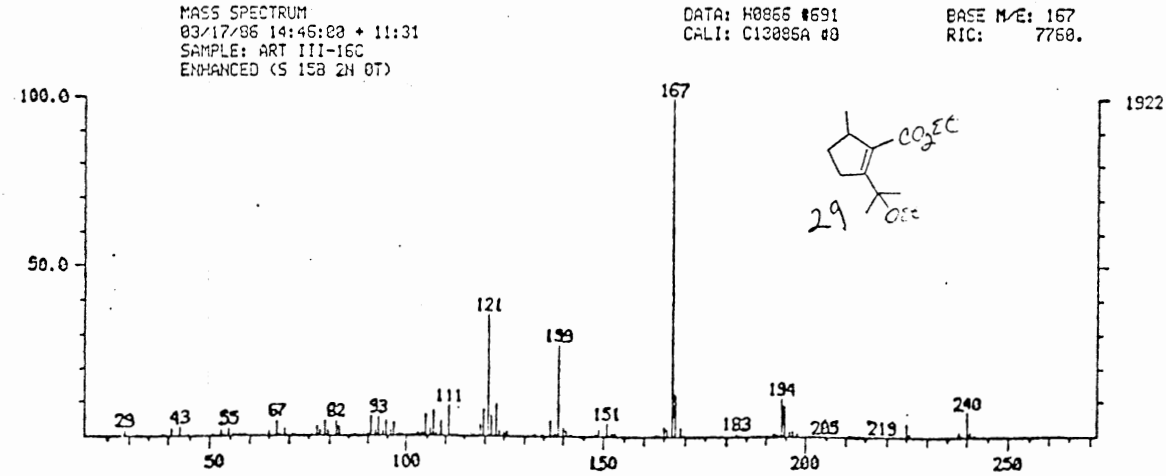
Since there are only three products, one must exist in an arrangement which destroys the original stereochemical differences. Examination of mass spectra of the products of this reaction in Figure 18 a, b, and c shows that two of the products have almost identical fragmentation patterns. These compounds, represented by scans 663 and 679, have a parent ion of m/e 240 and then lose a methyl group (m/e 15) which results in m/e 225. There is also loss of C_2H_{60} (m/e 46) to give m/e 194, whereas the compound represented by scan 691 has a predominate loss of CO_2Et (m/e 73) from the parent ion m/e 240 to m/e 167. These data are consistent with the proposed structures of compounds **28a**, **28b**, and **29**.



a. Scan 663; Compound **28a**



b. Scan 679; Compound **28b**



c. Scan 691; Compound **29**

Figure 18. Mass Spectra of Products From SeO_2 Oxidation of Ethyl Pulegenates (**7a** and **7b**)

CHAPTER IV

EXPERIMENTAL SECTION

Instrumentation. Compound identification was performed using Finnigan 4023 and Kratos MS25Q gas chromatography/mass spectrometers. The gas-liquid chromatographic gradient condition was 60° to 280°C at 8° per minute using a DB-1, 30-meter column with a 1.0-micron film thickness. Nuclear magnetic resonance data were obtained with an IBM Instrument, Inc., NR/300 FT NMR and Bruker Pulse NMR CXP spectrometers.

Favorskii Rearrangement of Pulegone Dibromide (2). Pulegone (**1**) (480 g) was dissolved in 630 mL of acetic acid. Bromine (420 g) was added over 0.75 h at 0°C to this solution. The volume of the solution was reduced by aspirating most of the acetic acid. The reddish purple solution produced white fumes during the stripping. The dibromide was freed of acetic acid by adding isohexane (2,000 mL), washing with water (3X400 mL), and with saturated sodium bicarbonate (2X400 mL). Half of the isohexane was stripped from the dibromide, and the resulting residue darkened in color and more white fumes evolved. The fuming and a pink tint to the bicarbonate wash both indicate some decomposition of the dibromide.

Sodium (180 g) was added to 4.2 L of absolute methanol under a blanket of dry nitrogen during 0.25 h. The solution containing the dibromide was slowly added to the

sodium methoxide in methanol during 1 h. As the solution was added, isohexane was removed by distillation. Next, methanol was distilled and the remaining solution was heated to reflux for 2.5 h. The reaction mixture was cooled to 12°C and filtered through Dicalite. It was extracted with ethyl ether (approximately 1,500 mL). The ether extract was washed with water (3X1000 mL) which left the water layer reddish brown and the ether layer a light brown. A residual white solid was formed in the reaction flask which was found to be inorganic salts. The ether was stripped away leaving an oil which after distillation yielded an 80:20 mixture of *trans*-:*cis*-methyl pulegenates (**7a** and **7b**) in approximately 70% yield.

Hydrolysis of Methyl Pulegenates (7a and 7b) to Pulegenic Acids (3a and 3b). The methyl pulegenates (**7a** and **7b**) were hydrolyzed to the pulegenic acids by dissolving 90.9 g of the ester in 455 mL of 95% ethanol and then mixing this solution with 22 g of sodium hydroxide dissolved in 182 mL of water. This mixture was heated at reflux for 3 h with ethanol being distilled and replaced by water as needed. After all the ethanol was removed, heating was continued to steam distill neutral products. The residue was extracted with ether to remove nonvolatile neutral compounds and the ether layer was backwashed with water. This gave 24.4 g of neutral products. The alkaline layer was then acidified to release the pulegenic acids which were extracted with ether to give 45.1 g of acids **3a** and **3b**. Distillation gave a yellow oil bp 90°-105°C/0.5 mm.

The isomer distribution had changed to 95:5 for *trans*-:*cis*-pulegenic acid (**3a** and **3b**).

Conversion of Pulegenic Acids (3a and 3b) to Lactones (4a and 4b) by Acidic Reagents. Three reactions were performed to check the effect of conditions and reagents on the lactonization of the pulegenic acid (**3a** and **3b**).

1. Pulegenic acid (**3a** and **3b**) (2.7 g) added to 20 mL of 4:1 H_2O:HCl, and this mixture was heated at reflux for 2 h. This produced a 95% yield of the gamma-lactones **4a** and **4b** in a 97:3 ratio.

2. Pulegenic acid (2.7 g) was added to 1:4 H_2O:HCl, and the mixture was heated at reflux for 2 h. This produced a 95% yield of gamma-lactones **4a** and **4b** in an 80:20 ratio.

3. Pulegenic acid (2.7 g) was added to 270 mL of benzene containing 0.3 g of Amberlyst-15. This mixture was heated at reflux for 16 h, and the reaction mixture was sampled to follow the progress of the reaction.

   a. At 1 h, there were 47% of acids **3a** and **3b** and 53% of lactones **4a** and **4b** present.

   b. At 2 h, there were 15% of acids **3a** and **3b** and 53% of lactones **4a** and **4b** (97:3) present.

   c. At 16 h, all of acids **3a** and **3b** were consumed and only lactones **4a** and **4b** (99:1) were observed.

Several other methods of lactonization were attempted to check isomer ratios. The methyl esters (**7a** and **7b**) were heated with A-15 as above, but no reaction was observed. Sulfolane and the pulegenic acids (**3a** and **3b**) were heated together to give a multitude of various undesired products. Pulegenic acids (**3a** and **3b**) were even passed through acidic alumina; however, this also was unsuccessful.

The *trans*,cis-lactone **4a** distilled at 85°C/3 mm.

Conversion of Lactones (4a and 4b) to the Bicyclooctenone (8). A 5-g sample of a mixture of lactones **4a** and **4b** was stirred into PPA at 80°C. The reaction mixture turned brownish yellow. The reaction was maintained at 80°C for 5.5 h and then poured into ice and the flask was washed with ice water. The reaction mixture was extracted with isohexane. The isohexane layer was washed with water and bicarbonate solution. Distillation yielded **8** in an 18% yield.

Several polyphosphoric acid (PPA) reactions at different temperatures were run. Temperatures ranging from 45° to 110°C were tried. At lower temperatures, no reaction was observed, and at higher temperatures, the yields were extremely low. The best result was obtained at 80°C.

Allylic Oxidation Using Selenium Dioxide. The incorporation of oxygen as the hydroxyl or aldehyde/ketone of olefinic systems can be effected using selenium dioxide. It was desirable to place a carbonyl on one of the allylic methyl groups in pulegenic acid (**3a**) to enable synthesis of nepetalactone **16**. A model hydrocarbon (**23**) was tried first to gain familiarity with the reaction procedures.

Conversion of 2,6-Dimethyloctene (23) to 2,6-Dimethyl-2-Octenal (24) Using Acetic Acid and Methanol Solvents. 2,6-Dimethyl-2-octene (**23**) (2 g, 14.0 mmol) was mixed into acetic acid (75 mL). Seven drops of water were added to selenium dioxide powder (3 g, 27 mmol) to dissolve it. The dissolved selenium dioxide was added to the acetic acid mixture and the solution brought to reflux. As the solution warmed up, it slowly took on a yellow tint that changed to brown and finally black. After an hour at reflux, a noticeable amount of black precipitate (selenium metal) was present. The reaction mixture

was cooled, filtered, extracted with ether (3X), concentrated, and the resulting oil was analyzed by GC/MS and NMR and found to be the allylic aldehyde (**24**).

This reaction was carried out in methanol using the same reaction conditions and quantities of compounds. However, no selenium metal precipitated and most of the starting material **23** was recovered. According to GC/MS data, some product **24** was formed.

Conversion of Ethyl Pulegenates to Compounds 28a, 28b, and 29. Esters (5.0 g, 27.2 mmol) and 80 mL ethanol were added to a 250-mL flask containing a magnetic stirrer and fitted with a reflux condenser. Selenium dioxide (1.6 g, 14.4 mmol) was added and stirred to aid solution. Some of the selenium dioxide remained at the bottom of the flask, but once the solution became hot, no selenium remained undissolved. The reaction mixture was heated at reflux for 24 h, cooled, and treated as described above. A dark oil was recovered weighing 5.3 g which distilled at 45°-60°C/1 mm to give a mixture of **28a**, **28b**, and **29**.

Reaction of Pulegenic Acid (3a) With Selenium Dioxide. Compound **3a** (13 g, 77.4 mmol) was dissolved in ethanol (250 mL) and added to selenium dioxide powder (17.2 g, 155 mmol) dissolved in a minimum of water (7 to 10 drops) to make a solution. The combined material was heated to reflux. The reaction solution turned from light yellow to orange, then brown, and finally to a dark brown at reflux. The collected selenium metal did not exceed 2 g. GC/MS analysis of the reaction mixture shows it to be complex. After distillation at 60°-80°C/1 mm, 9.4 g of a yellow-orange oil was recovered which from GC/MS data was shown to contain two major components (see Figure 16 a). These two components were identified as **25** and **26**.

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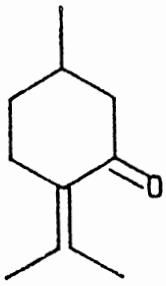
APPENDIX A

GLOSSARY OF STRUCTURES



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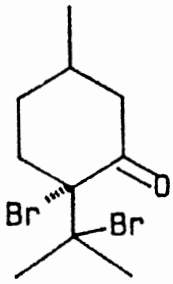

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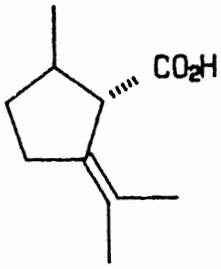

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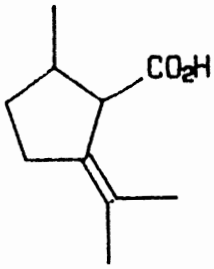

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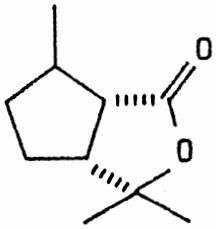

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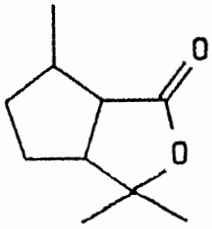

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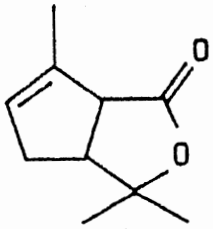

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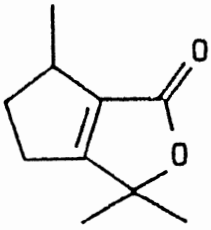

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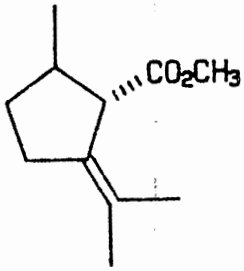

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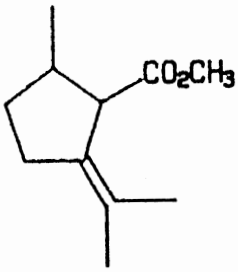

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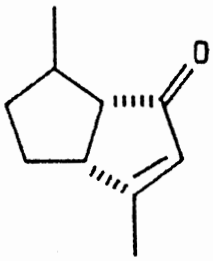

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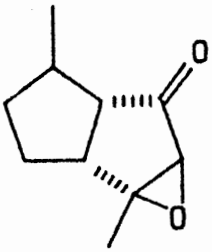

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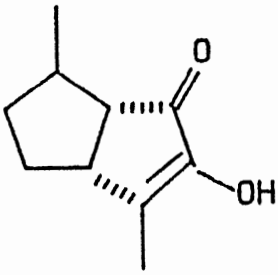

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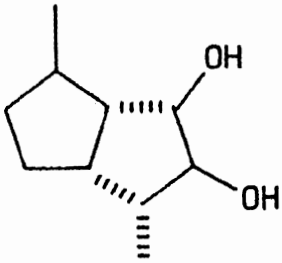

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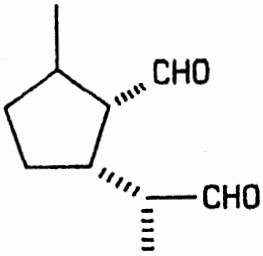

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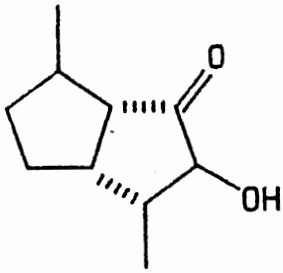

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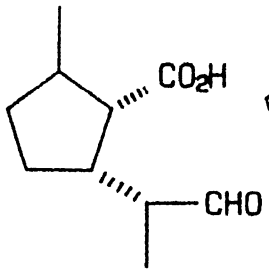

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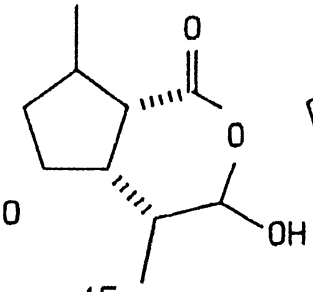

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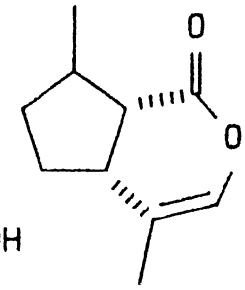

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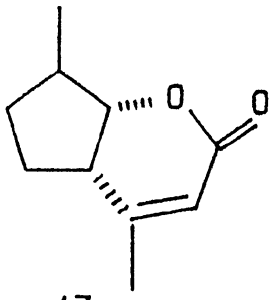

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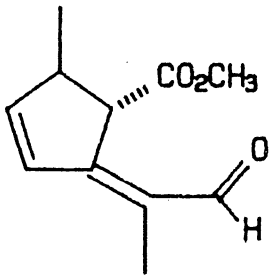

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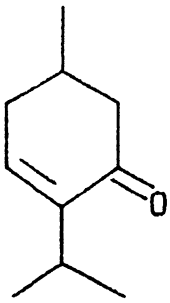

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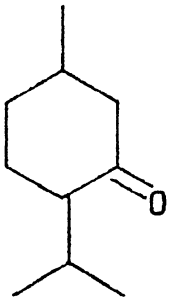

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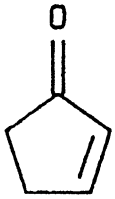

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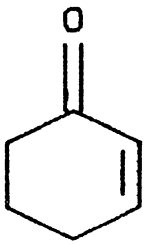

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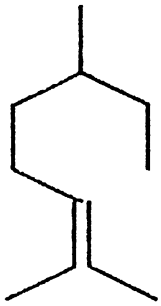

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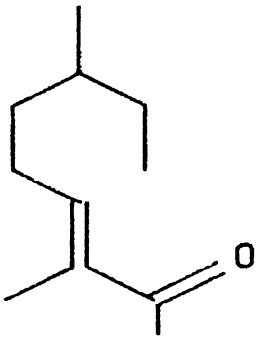

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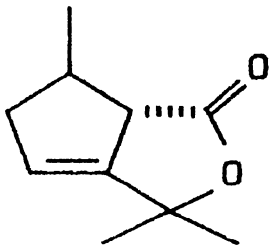

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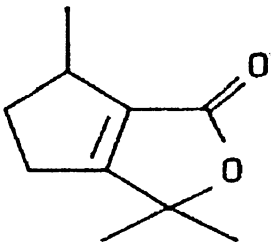

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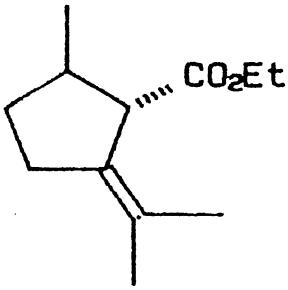

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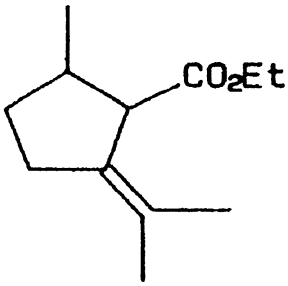

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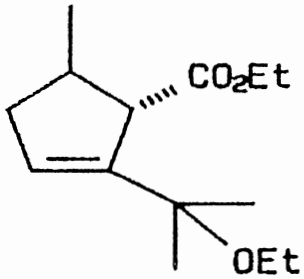

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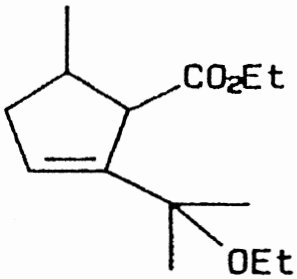
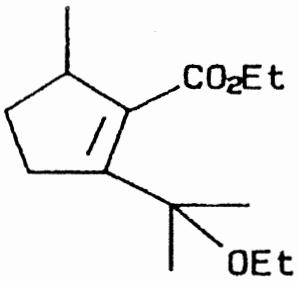


28b



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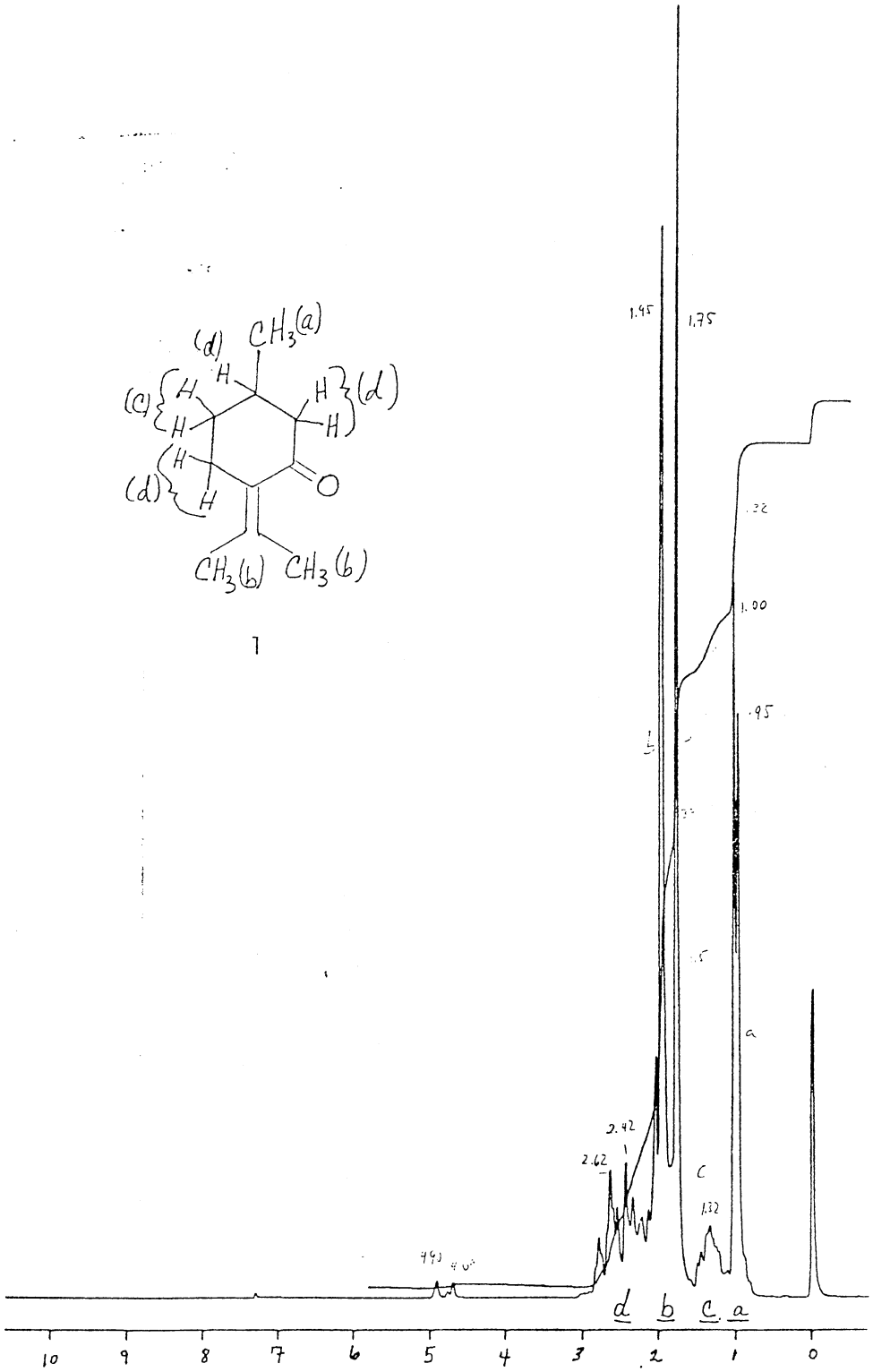
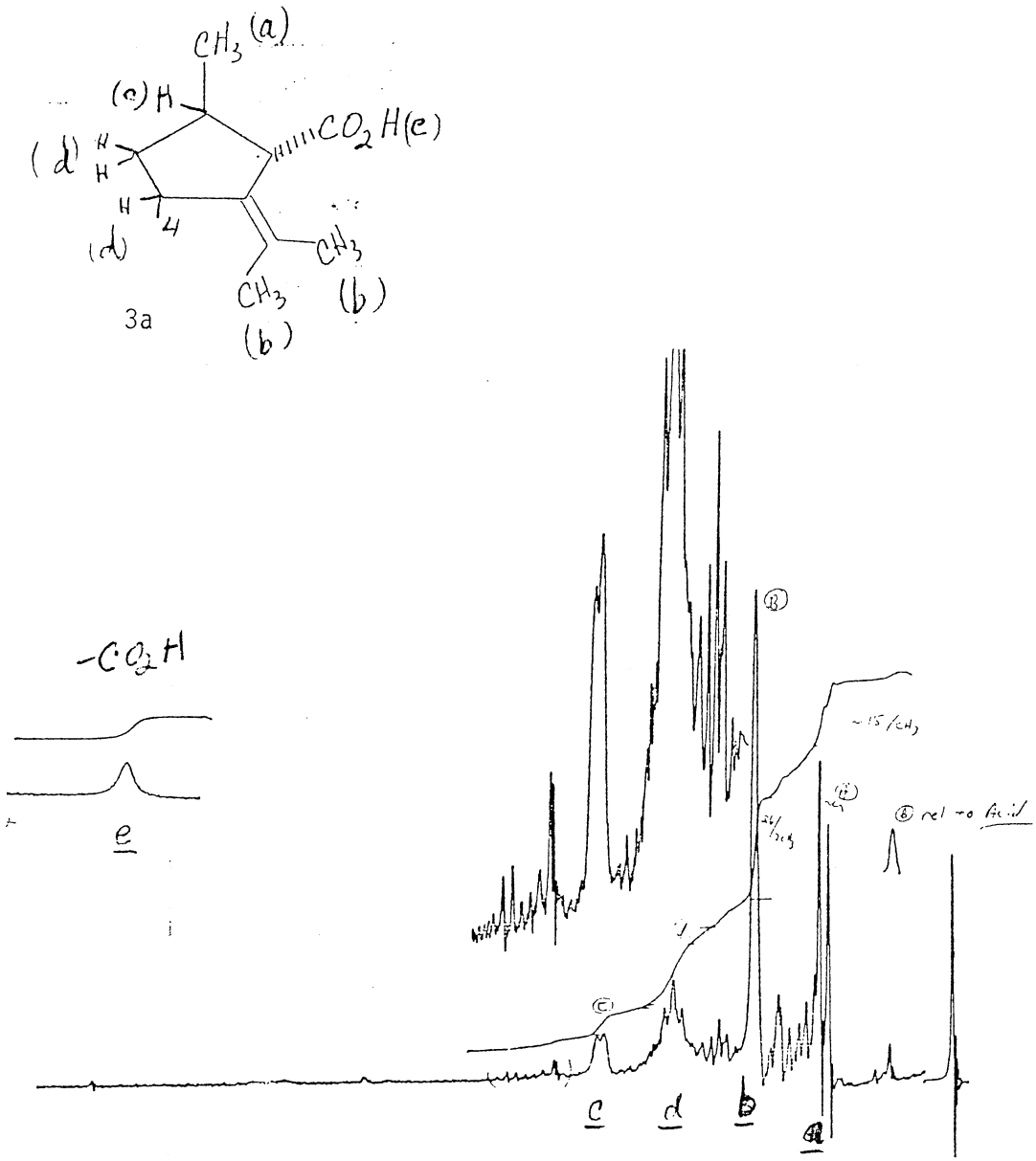
APPENDIX B

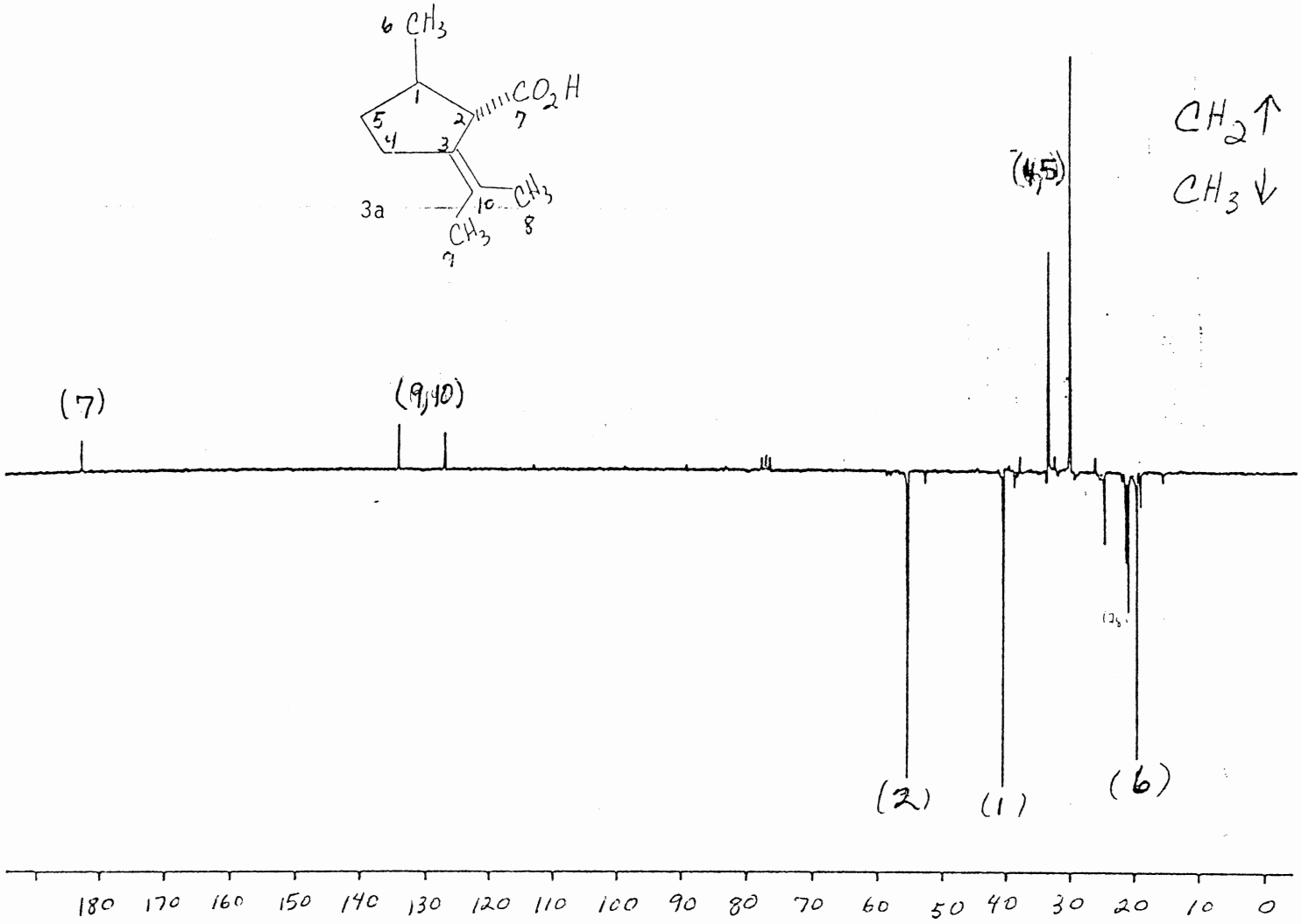
SELECTED SPECTROSCOPIC DATA



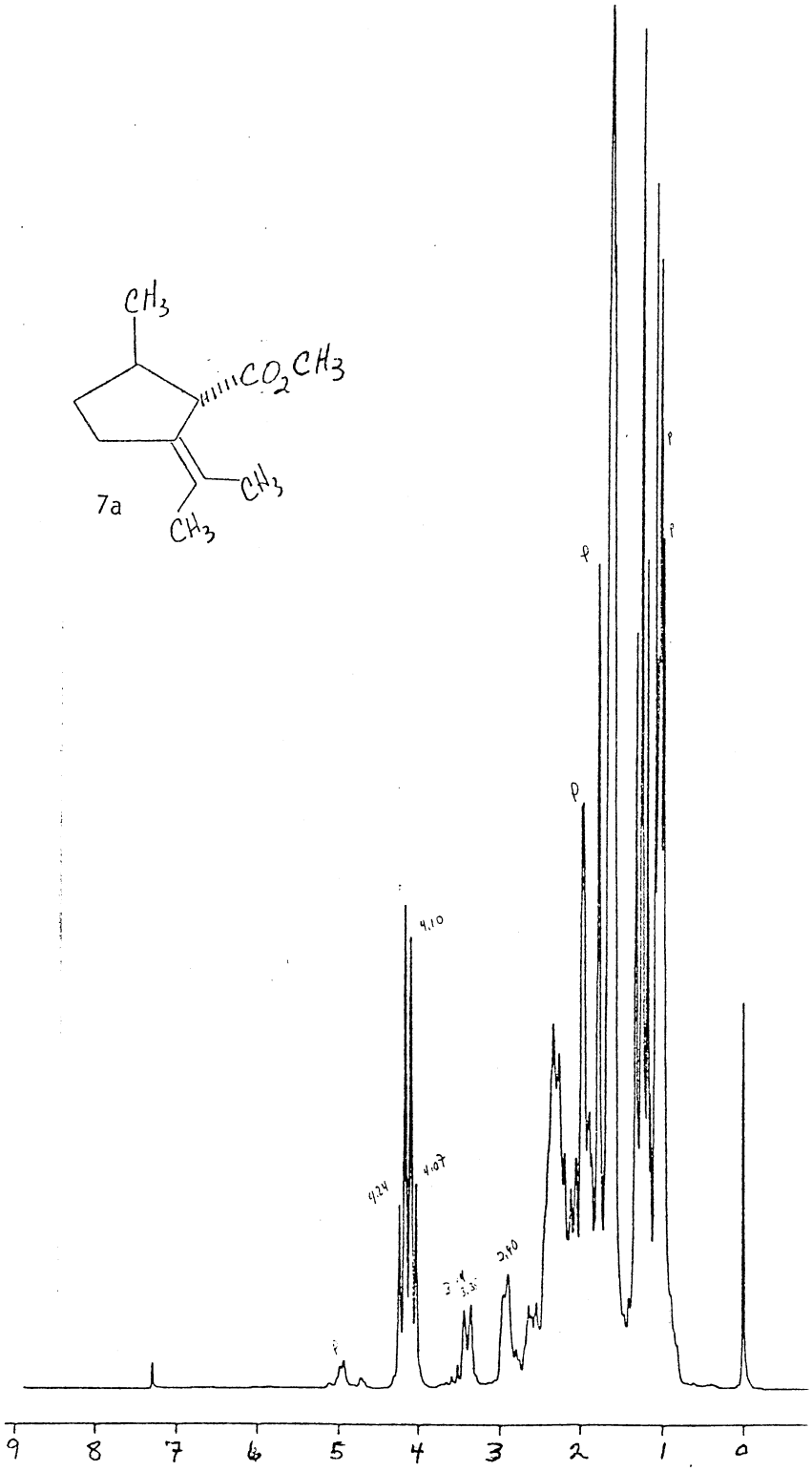
Proton NMR Spectrum of Pulegone (**1**)



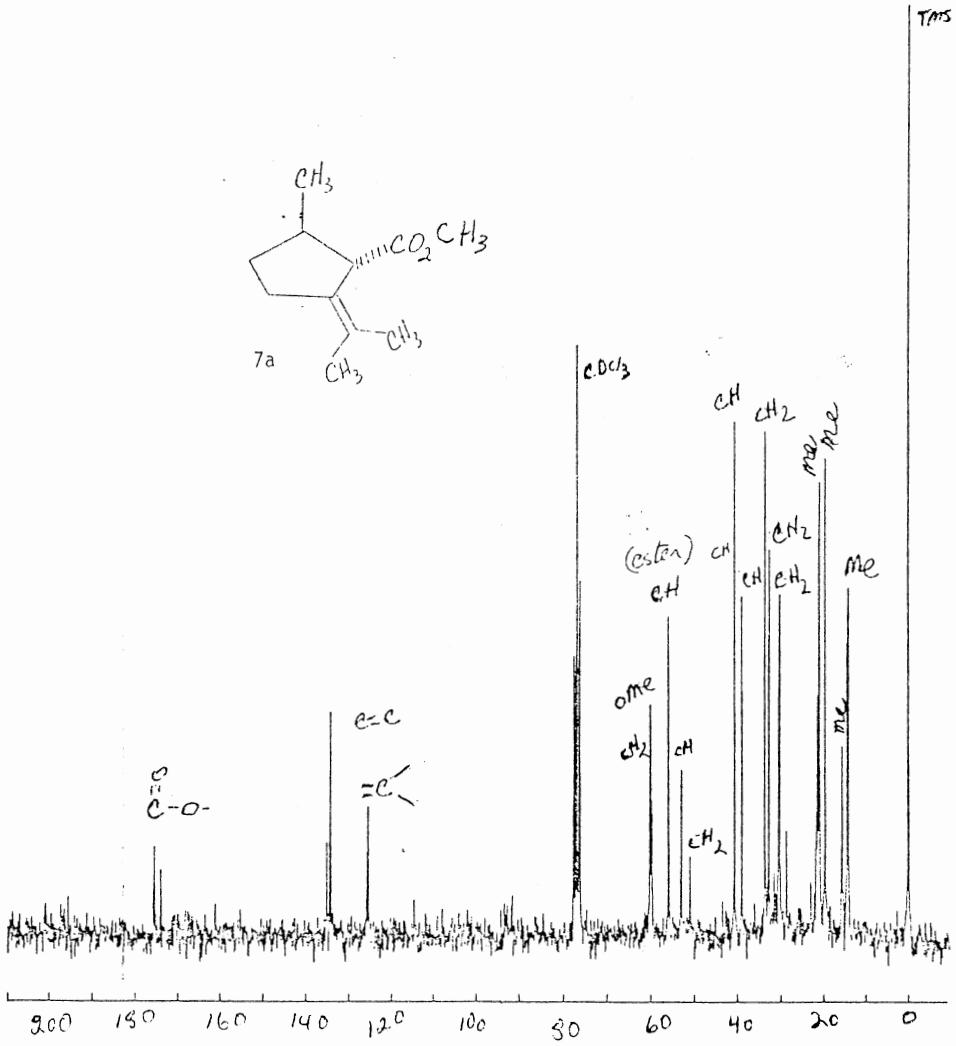
Proton NMR Spectrum of Pulegenic Acid (**3a**)



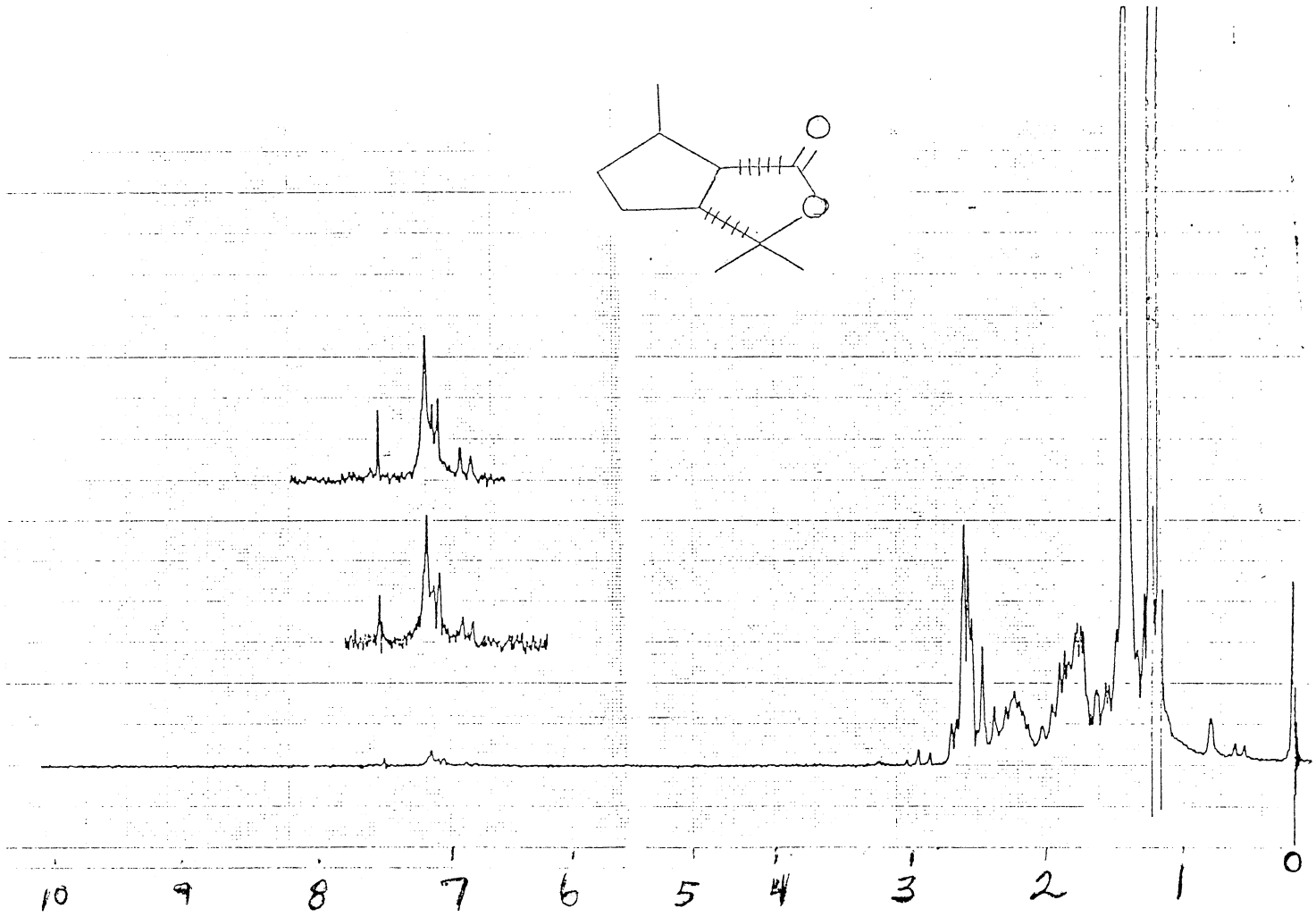
Carbon-13 NMR Spectrum of Pulegenic Acid (**3a**)



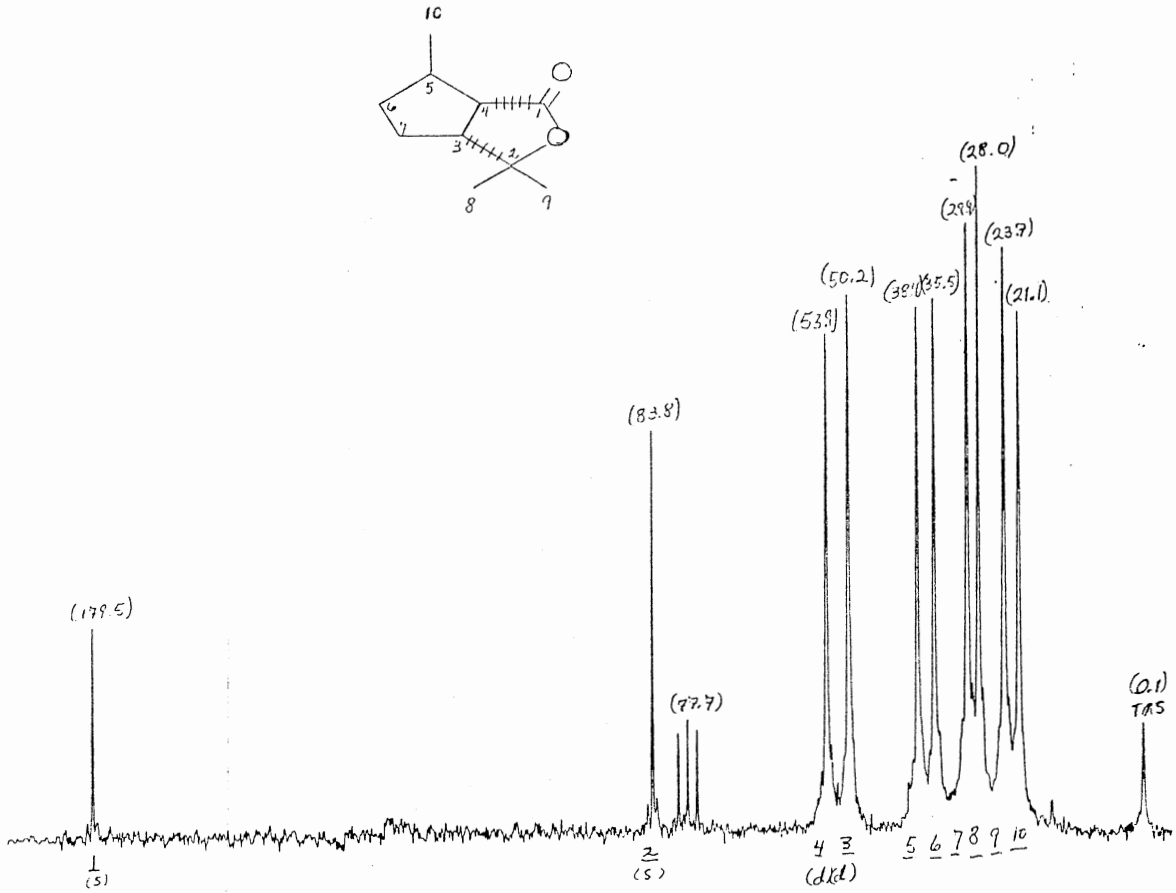
Proton NMR Spectrum of Methyl Pulegenate (**7a**)



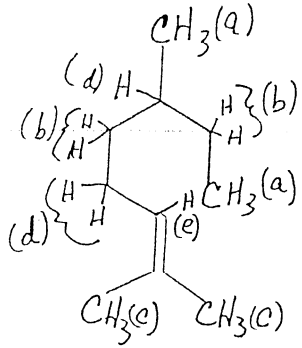
Carbon-13 NMR Spectrum of Methyl Pulegenate (**7a**)



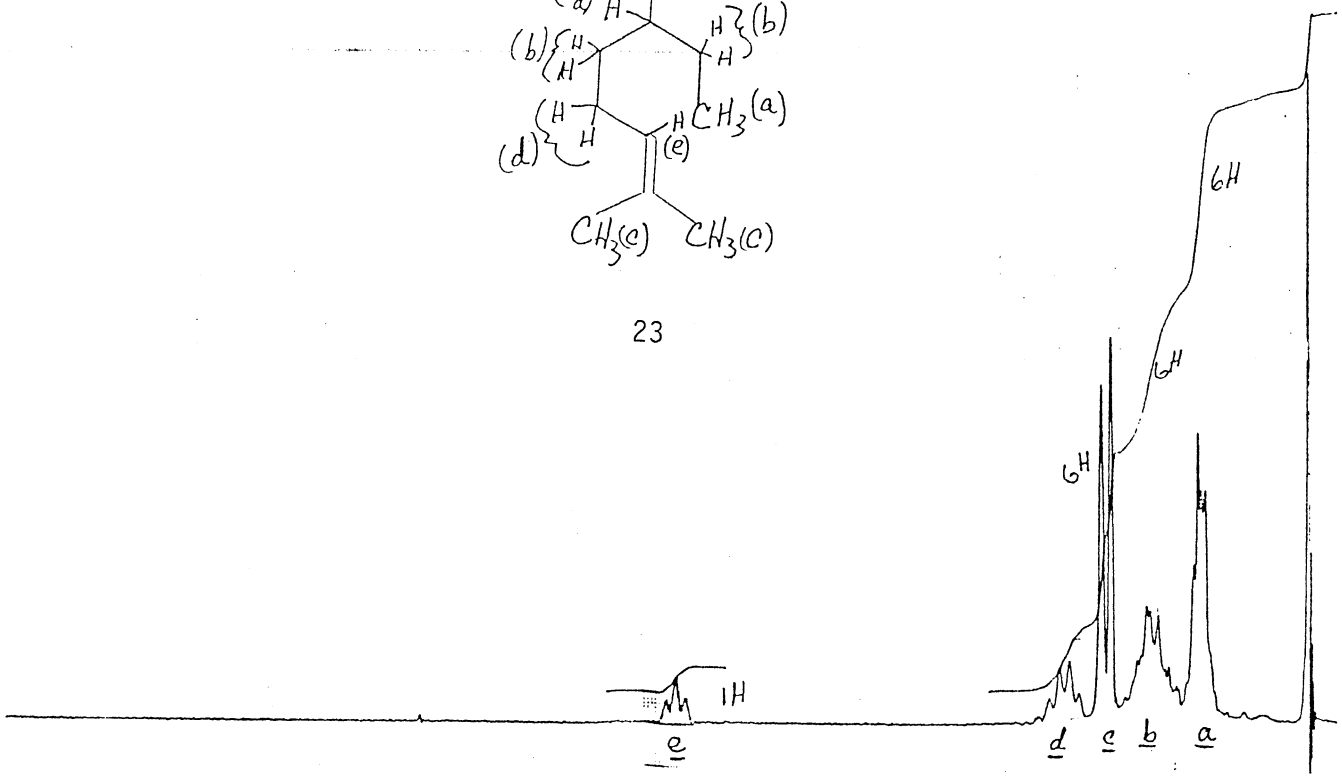
Proton NMR Spectrum of Pulegenic Lactone (**4a**)



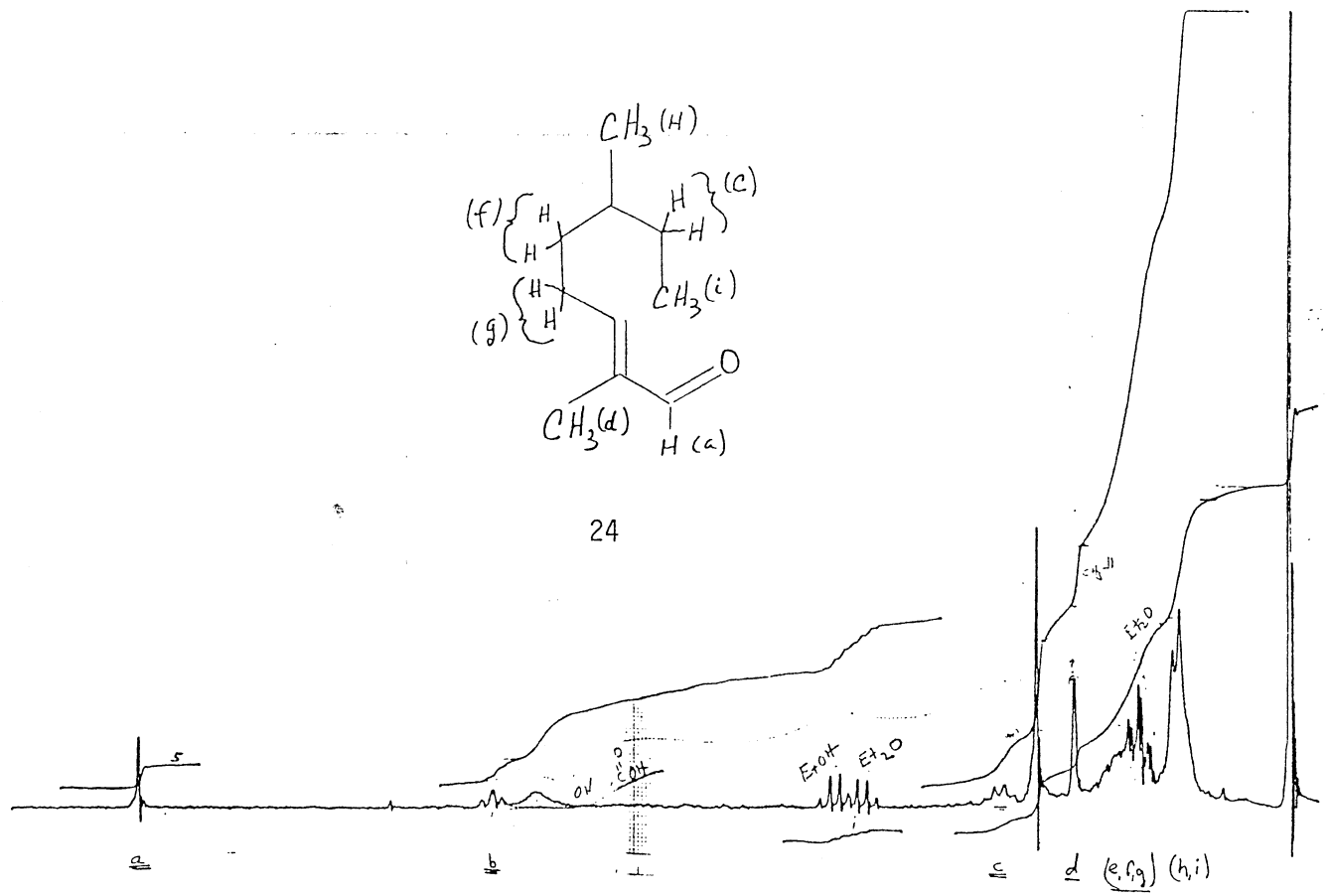
Carbon-13 NMR of Pulegenic Lactone (**4a**)



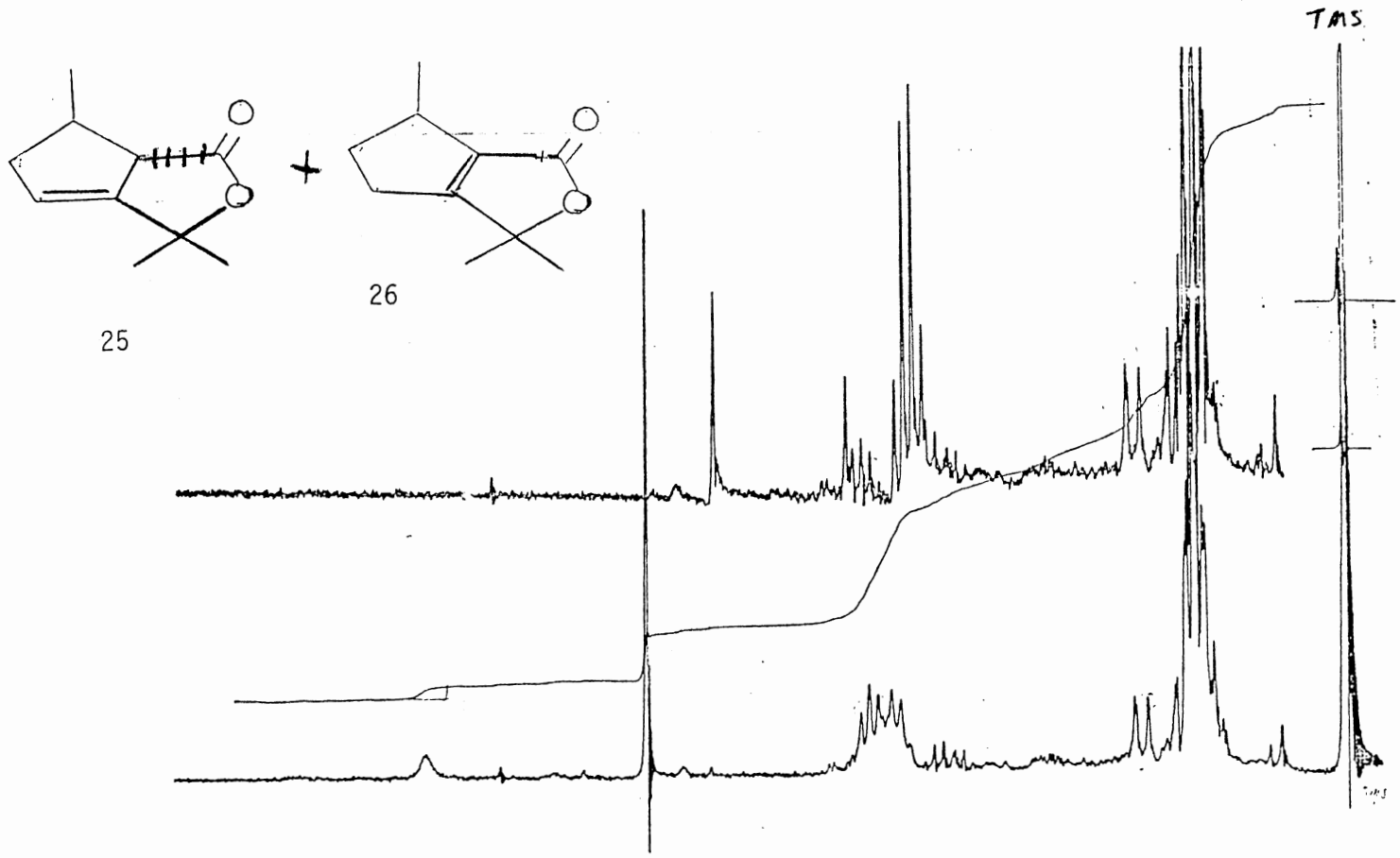
23



Proton NMR Spectrum of **23**



Proton NMR Spectrum of **24**



Proton NMR Spectrum of **25** and **26**

VITA 2

Arnold Richard Taylor, Jr.

Candidate for the Degree of

Doctor of Philosophy

Thesis: A STUDY OF PULEGENIC ACID, ITS ISOMERS, AND ITS CONVERSION TO LACTONES

Major Field: Chemistry

Biographical:

Personal Data: Born in Winfield, Kansas, November 25, 1950, the son of Arnold R. and Irene M. Taylor. Married Alicia L. B. Endicott on January 1, 1972. I have two sons, Evan Andrew and Drew Richard, ages 9 and 5, respectively.

Education: Graduated from Hugo High School, Hugo, Oklahoma, in 1969; received a bachelor of science degree from Oklahoma State University, Stillwater, Oklahoma, in the spring of 1973, with a degree in chemistry. Received a master of science degree from the same institution in the fall of 1974. Completed the requirements for the doctor of philosophy degree in chemistry at Oklahoma State University in the spring of 1987.

Professional Experience: Laboratory Technician at the Reservoir Research Center at Oklahoma State University, 1972-1973. Graduate Teaching Assistant in chemistry department, 1973-1974. December 1974 to present employed at Conoco Inc. in the Analytical Services Section of the Research Services Division. I am a Senior Research Chemist working in the Mass Spectrometry Group. Chairman of the North Central American Chemical Society, 1987. An 11-year member of Toastmasters International.