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Regioselectivity in the Cyclization of Delta, Epsilon-Epoxy Esters

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REGIOSELECTIVITY IN THE CYCLIZATION OF DELTA,EPSILON-EPOXY ESTERS

by

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VITA

The author, William F. Prout, is the son of Franklin S. Prout and Joan (Schaefer) Prout. He was born on October 3, 1955, in Evanston, Illinois.

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TABLE OF CONTENTS

		Page
ACKNOWLEDGEMENTS		ii
VITA		iii
TABLE OF CONTENTS		iv
Chapter		
I.	HISTORICAL INTRODUCTION	1
II.	STATEMENT OF THE PROBLEM	23
III.	RESULTS AND DISCUSSION	24
IV.	EXPERIMENTAL PROCEDURES	38
V.	SUMMARY	56
VI.	SPECTRA	57
VII.	BIBLIOGRAPHY	89

CHAPTER I

HISTORICAL INTRODUCTION

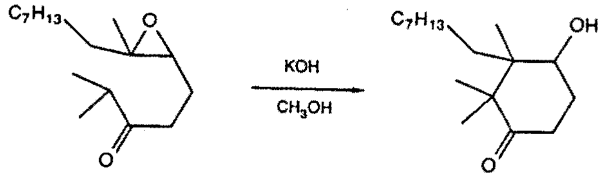
Epoxides are versatile intermediates in organic synthesis[1,2]. These compounds are easily prepared (often with stereochemical control) and very reactive, due in part to the strain on the small ring, withl a large number of reagents. The types of reactions that these compounds can undergo include substitution (for one of the C-O bonds), acid-catalyzed rearrangement (usually to form ketones), base-promoted rearrangement (usually to form allylic alcohols), oxidation, and base or acid-catalyzed intramolecular cyclization. Although there are many examples of these reactions available in the literature[1,2] this discussion will restrict itself to anionic intramolecular cyclizations of epoxides leading to the formation of new carbocycles.

Work with epoxycompounds has led chemists to many applications in organic synthesis. The utility of reagents possessing this functionality has been demonstrated by the by the synthesis of various terpenes, both naturally occurring as well as those possessing novel structures.

EXPOXYKETONES

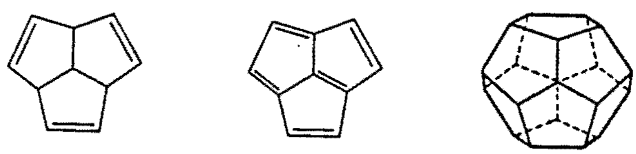
The earliest reported anionic cyclizations of functionalized epoxides involved substrates possessing a carbanionic center stabilized by an adjacent carbonyl group. This type of reaction had been reported as early as 1950.

Barton and Lindsey[3], while attempting to determine the structure of caryophyllene, treated "Treibs' oxido ketone"[4] (1) with potassium hydroxide in methanol and obtained ketoalcohol 2. The formation of this product can be explained by postulating an intramolecular cyclization of the enolate derived from keto-epoxide 1.

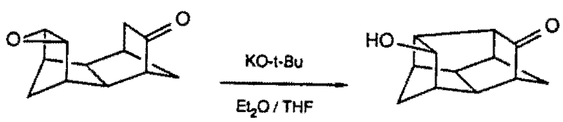


1 2

Woodward, along with his co-workers[5], found another use for the base-promoted cyclization of epoxyketones during an attempted synthesis of triquinacene (tricyclo-[5.2.-1.0^{4,10}]deca-2,5,8-triene) (3), a precursor to acepentalene (4) and possible precursor to dodecahedrane (5).



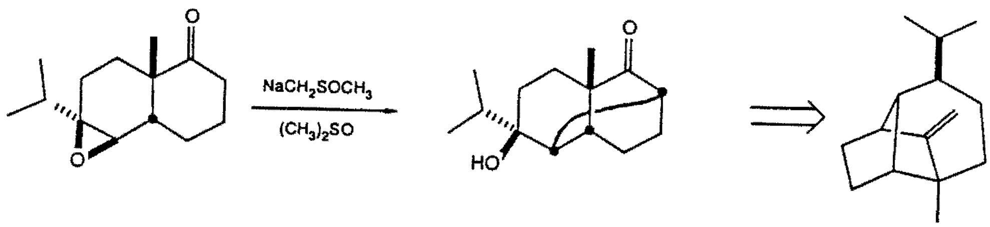
3 4 5



6 7

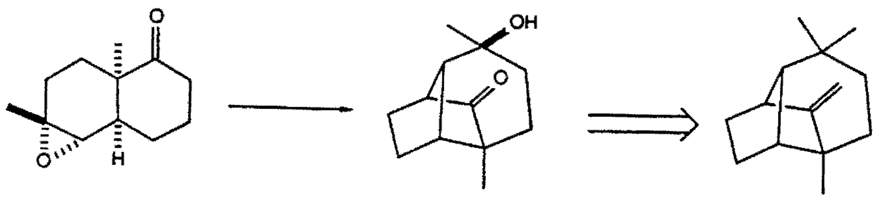
As part of the synthesis, ketone 6 was treated with potassium t-butoxide in ether-tetrahydrofuran to furnish the keto-alcohol 7, which was ultimately converted to triquinacene (3).

McMurray[6] synthesized copacamphene (8) via cyclization of epoxyketone 9 under basic conditions. Ketoalcohol 10 was furnished in excellent yield. This reaction could be carried out using either dimsyl sodium in dimethyl sulfoxide (2 days) or potassium t-butoxide in t-butyl alcohol (7 days). The cyclized product was ultimately carried on to copacamphene (8), a rearrangement product from copaborneol.



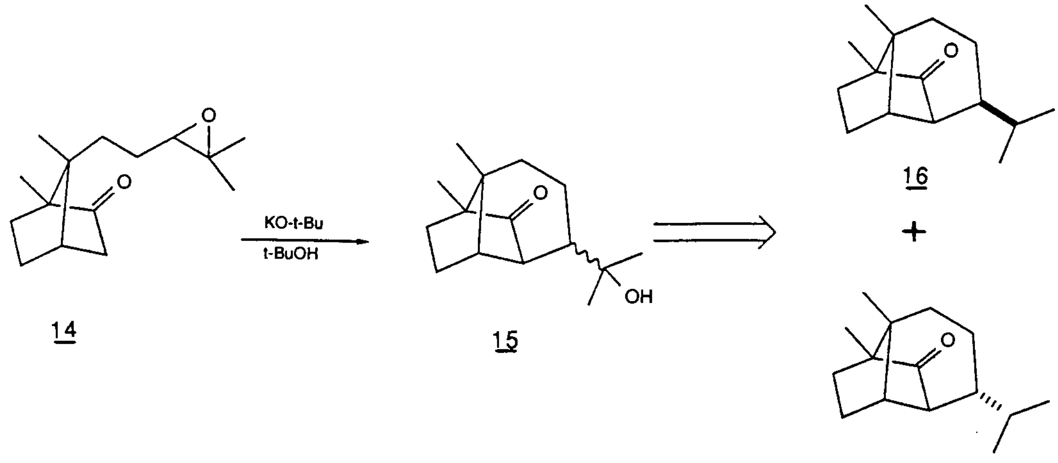
9 10 8

The same methodology was used by McMurry[7] to form the skeleton of longifolene (13). Ketoepoxide 11 was treated with dimsyl sodium in dimethyl sulfoxide for 5 days to furnish alcohol 12. Elaboration of the alcohol to longifolene (13) completed the synthesis.



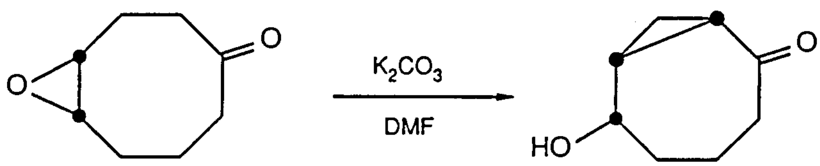
11 12 13

Hodgson, MacSweeney and Money[8] in reporting the synthesis of a series of polycyclic sesquiterpenes treated epoxyketone 14 with potassium *t*-butoxide in refluxing *t*-butyl alcohol to obtain a mixture of isomeric alcohols 15 which were elaborated to form copacamphor (16) and ylangocamphor (17) respectively.



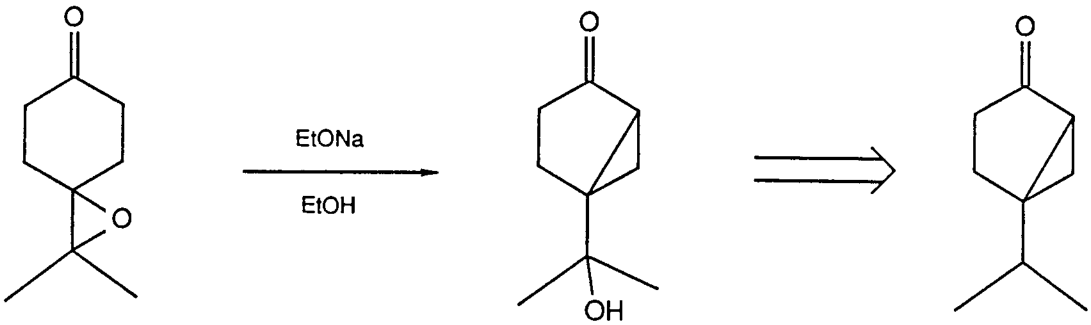
14 15 16 17

In a study of transannular alkylation of enolates Crandall, Huntington and Brunner[9] treated 4,5-epoxycyclooctanone (18) with base to form only one of the possible products: *endo*-6-hydroxybicyclo[5.1.0]octanone (19).



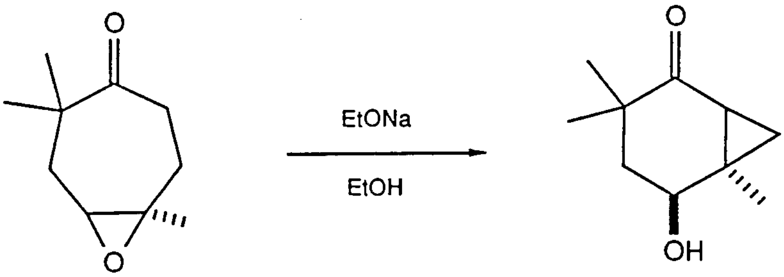
18 19

In 1957 Nelson and Mortimer[10] attempted to synthesize sabina ketone (one of the thujane terpenes). The methods attempted involved the displacement of a tertiary halide by an anion formed alpha to a ketone. All attempts failed. In 1972 Gaoni[11] described the synthesis of sabina ketone starting from keto epoxide 20. This compound was smoothly converted to ketoalcohol 21 as shown. The alcohol was readily transformed to sabina ketone (22) by dehydration followed by hydrogenation.



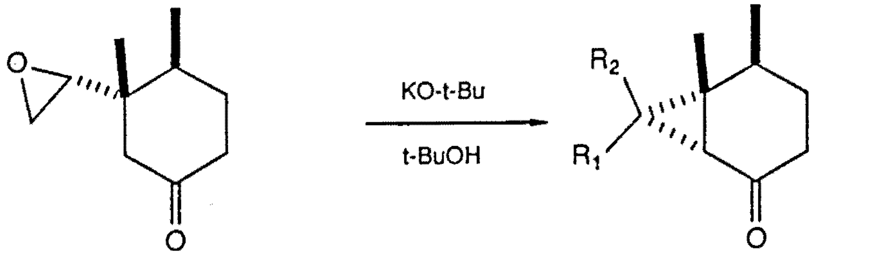
20 21 22

Gaoni, in an accompanying publication[12], reported the cyclization of epoxykarahanaenone (23) to form bicyclo[4.1.0]heptanone 24 as the only product.



23 24

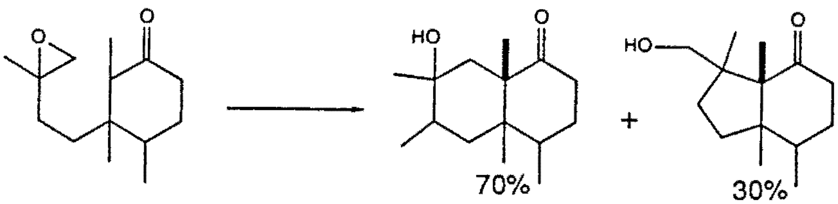
As part of a project to synthesize eremophilone, Ziegler and co-workers[13] carried out the cyclization of epoxy ketone 25. The only product formed after treatment with base was bicyclic alcohol 26, no 4-membered ring being observed.



25 26

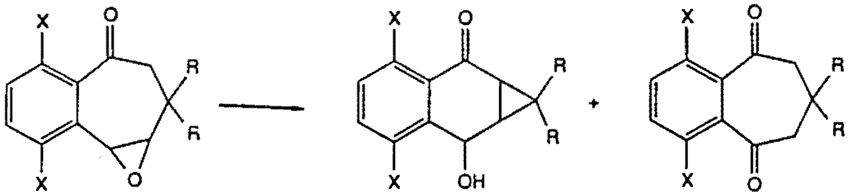
a: $R_1 = CH_2OH$; $R_2 = H$
b: $R_1 = H$; $R_2 = CH_2OH$
SYN / ANTI 2.5:1

Cory and his co-workers[14] carried out an anionic cyclization on keto-epoxide 27, with potassium t-butoxide in t-butyl alcohol, which provided them with a mixture of isomers. The major product was tertiary alcohol 28 and the minor product primary alcohol 29.



27 28 29

Recently a study was conducted comparing the competition between base-promoted cyclization and rearrangement of epoxy carbonyl compounds.[15] Both compounds 30a and 30b when treated with sodium isopropoxide furnished only cyclization products, ketoalcohols 31a and 31b respectively. When epoxyketones 30c and 30d were subjected to the same conditions, diones 32c and 32d were found to be the major products. Evidently, placement of methyl groups in the beta position had caused rearrangement to be favored over cyclization.

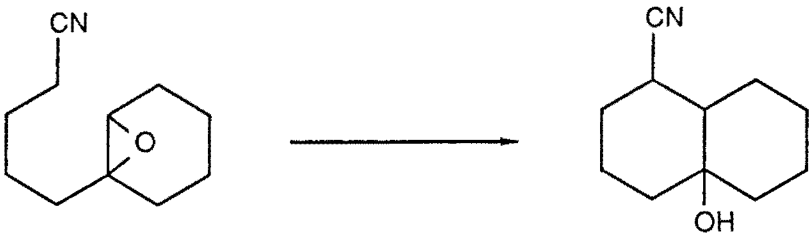


30 31 32

	31	32
a.) X = R = H	88%	---
b.) X = OMe, R = H	89%	---
c.) X = H, R = Me	38%	55%
d.) X =OMe, R = Me	32%	64%

EPOXYNITRILES

Analogous to the behavior of epoxycarbonyl compounds, base-promoted intramolecular cyclization reactions of epoxynitriles have also found a place in organic synthesis. This reaction was introduced into the literature by Stork and co-workers in 1974[16,17]. Epoxynitriles 33 and 35 were treated with base to form bicyclic cyanoalcohols 34 and 36 respectively.



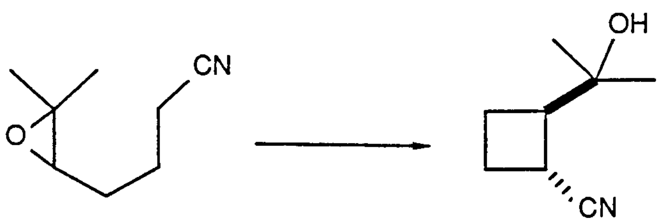
33 34

35 36

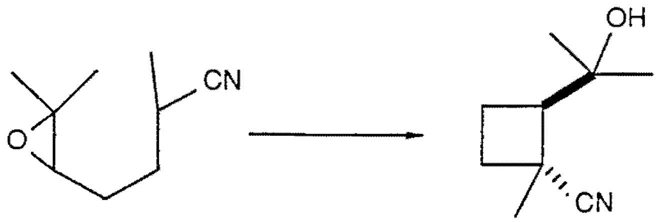
The observation that the 6-membered ring compound 34 was formed faster than its 5-membered ring counterpart 36 is in contrast to the observations of other cyclizations involving SN2 type transition states.[18] This suprising result is only observed when cyclization to afford a 5-membered ring involves attack at the far end of the epoxide. When the proximate end of the epoxide is attacked normal behavior is observed. This was verified by the reaction shown below where cyanoepoxide 37 was cyclized to form cyanoalcohol 38.

37 38

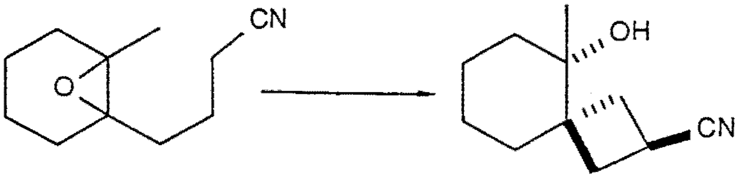
In the second paper, published simultaneously, Stork and Cohen[17] elaborated on these findings by demonstrating that cyclobutanoids 40 and 42 were the only products derived from treatment of epoxides 39 and 41 with potassium hexamethyldisilazane in benzene. Several other systems were also studied including epoxynitrile 43 which underwent cyclization to furnish the bicyclic spiroalcohol 44 shown below.



39 40

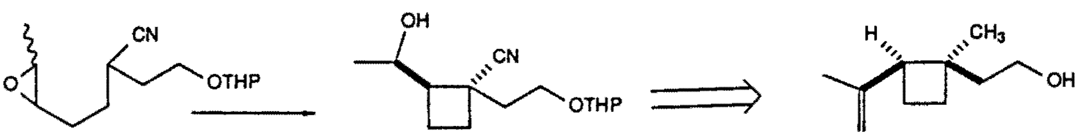


41 42



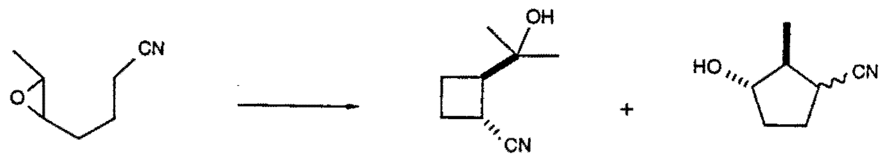
43 44

Other examples demonstrated that with equal substitution only the smaller ring size would be formed whether it be 3-, 4-, 5-, or 6-membered. The only exception was that the three membered ring would always form regardless of epoxide substitution. These findings led to the total synthesis of (±)-grandisol[17] (47), one of the four components of the sex attractant of the boll weevil. The key step in the synthesis involved the cyclization of epoxide 45 to the cyclobutyl alcohol 46. This compound was then manipulated through several steps to transform it into (±)-grandisol (47).



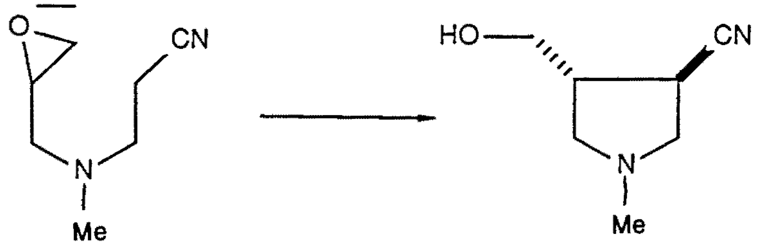
45 46 47

The work of Stork and co-workers stimulated further investigations in this area. One such examination was that by Lallemand and Onaga who showed that Stork's generalization that a 4-membered ring would always be formed in preference to 5-membered rings was valid only when the epoxide possessed a cis configuration[19]. This was demonstrated by the reaction of trans-epoxynitrile 48 with base to give a mixture of both 4-membered and 5-membered ring products (49 and 50 respectively). The major product was the cyclopentanoid 50, contrary to predictions using Storks findings. The cyclization of the cis-epoxide, on the other hand, gave only 4-membered ring products.



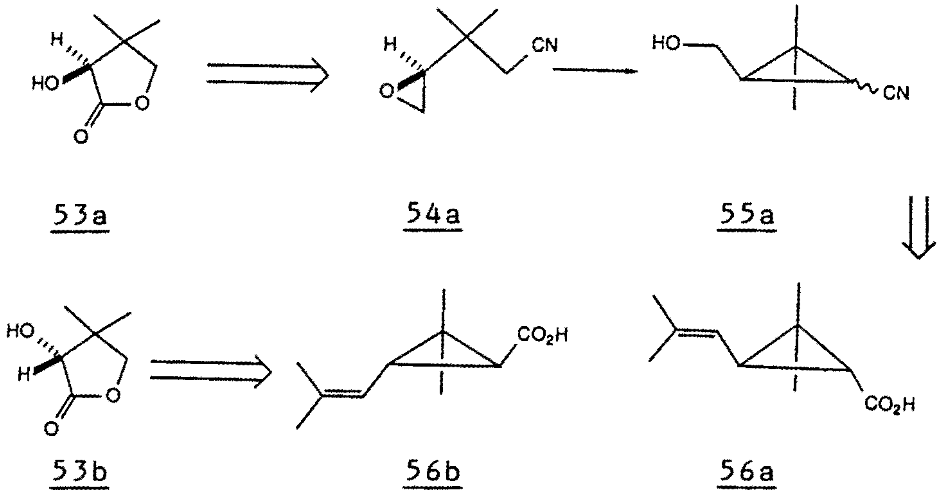
48 49 50

Achini and Oppolzer[20] reported use of the same methodology for the intramolecular cyclization of epoxyaminonitriles. Cyanoepoxide 51 was treated with sodium hexamethyldisilazane to form the 3,4-disubstituted pyrrolidine derivative 52.

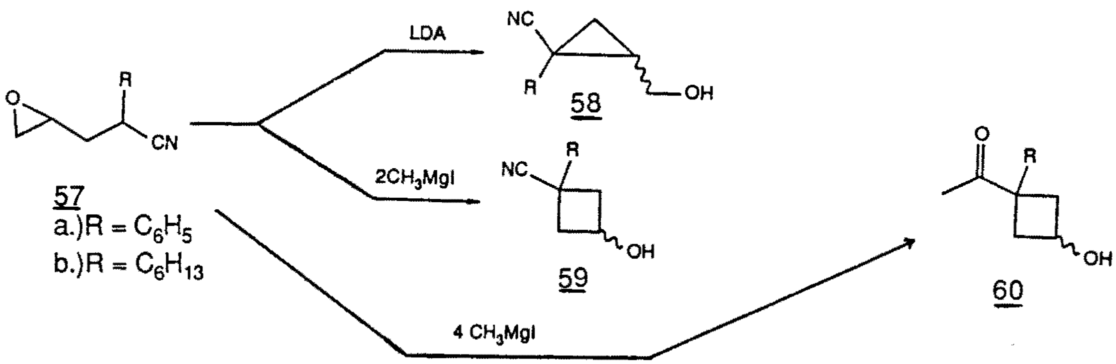


51 52

Matsuo, Mori and Matsui[21] carried out a series of reactions in which they synthesized (+)-trans-chrysanthemic acid (56a) as well as (-)-trans-chrysanthemic acid (56b) separately, utilizing optically active epoxides formed from (2S)-(-)-pantolactone (53a) and (2R)-(+)-pantolactone (53b). The key step involved the cyclization of the epoxynitrile 54 to afford cyclopropane 55. The alcohol was then converted to (+)-*trans*-chrysanthemic acid (56a).



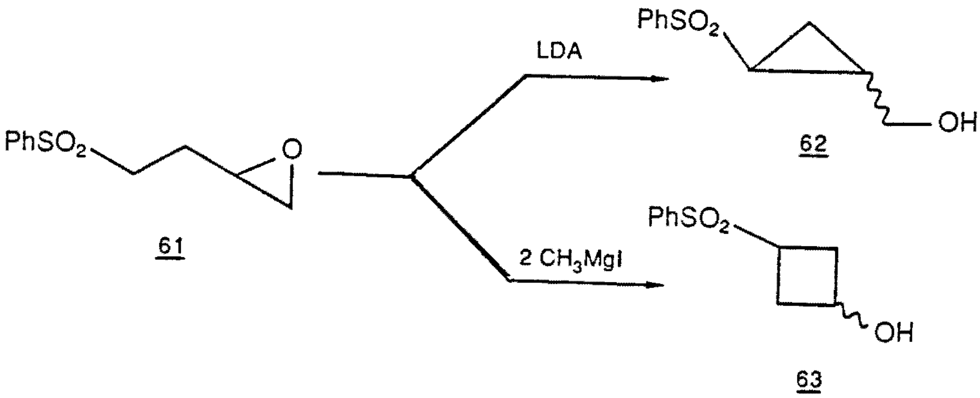
Corbel and Durst[22], while reinvestigating the earlier work of Stork and co-workers, found that a 3,4-epoxynitrile when treated with lithium diisopropylamide furnished only cyclopropanoid products. However, when methylmagnesium iodide was used as the base, 4-membered ring products were obtained, as shown below. For example, when



epoxide 57 was treated with 4 equivalents of methylmagnesium iodide, methyl ketone 60 was formed.

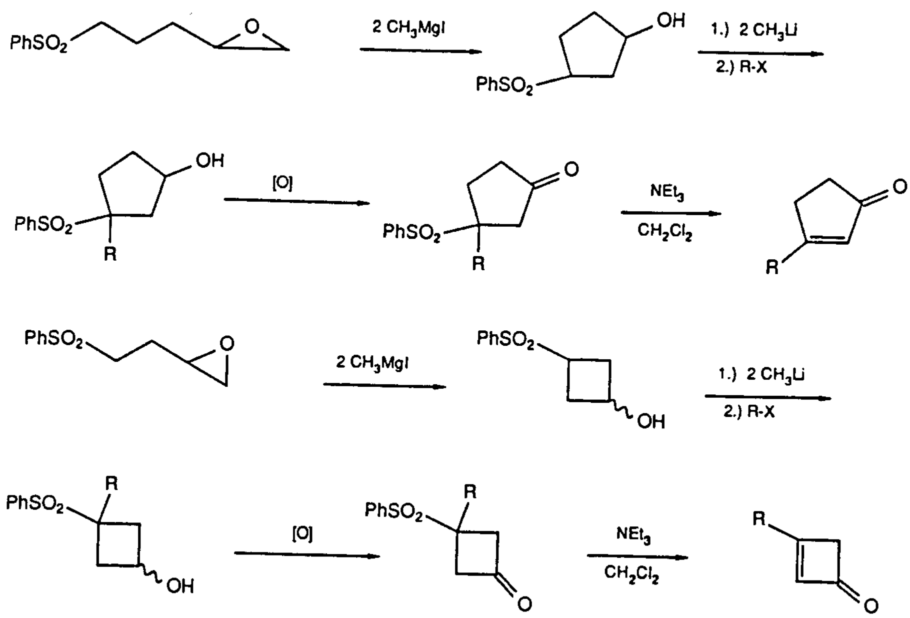
EPOXYSULFONES AND -SULFIDES

Corbel and Durst[22] also explored the use of methylmagnesium iodide for the cyclization of epoxysulfones. Use of two equivalents of this base induced formation of the larger ring size. Lithium diisopropylamide, in contrast, caused the smaller ring to be formed as shown.



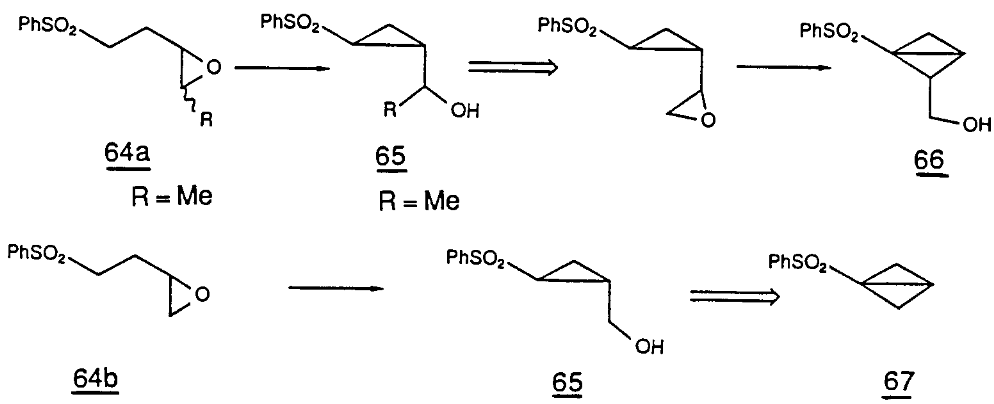
The use of Grignard reagents to promote cyclization of epoxysulfones was also illustrated in multi-step processes involving the formation of cyclobutenones and cyclopentenones. Examples of these reactions are shown in Scheme I below. After initial formation of the ring the sulfone can be alkylated at the alpha position. Subsequent oxidation of the alcohol followed by elimination of the phenylsulfonyl moiety furnishes the 3-substituted cycloalkenones. After initial formation of the ring the sulfone can be alkylated at the alpha position. Subsequent oxidation of the alcohol followed by elimination of the phenylsulfonyl moiety

SCHEME I



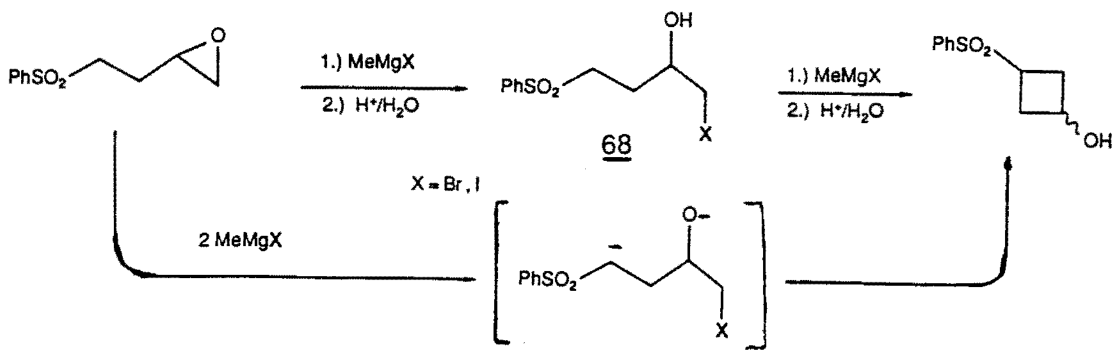
furnishes the 3-substituted cycloalkenones.

Gaoni[24a] described the use of epoxysulfones 64 to form cyclopropanoids 65. Such products, (if R = Me or alkyl), could undergo elimination to form an alkene, which upon subsequent treatment with meta-chloroperbenzoic acid and then an additional equivalent of base (in this case

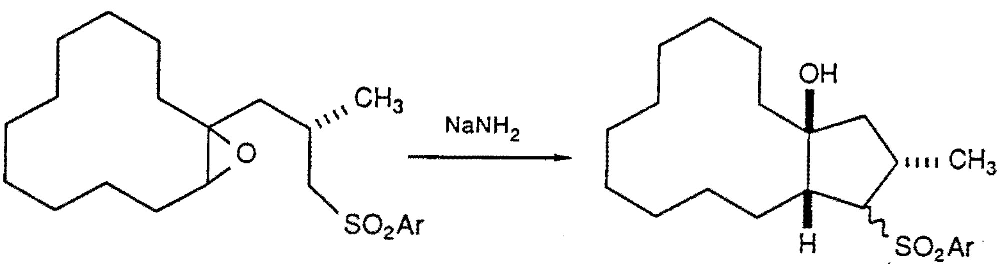


lithium diisopropylamide) furnished bicyclobutane 66. Alternatively the alkoxide initially generated in the cyclization process could be treated with mesyl chloride and then a second equivalent of base to furnish the unsubstituted bicyclobutane[24b] 67 as shown above.

Durst and co-workers have shown that methylmagnesium iodide-induced cyclizations of epoxysulfones do not procede via intramolecular epoxide-ring opening[25]. The first step involves formation of an isolable halohydrin 68 (magnesium bromide can also catalyze this reaction), which when treated with a second equivalent of methylmagnesium iodide will undergo intramolecular cyclization. The mechanism is shown below.



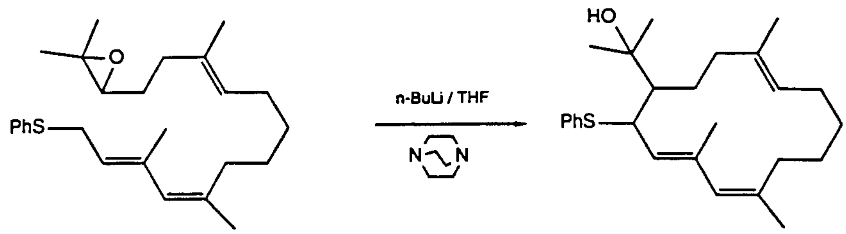
Fischli and co-workers utilized cyclization of an epoxysulfone in a synthesis of muscone[26]. The cycliza-



69 70

tion of epoxysulfone 69 was effected by using sodamide to furnish the bicyclic alcohol 70 as shown.

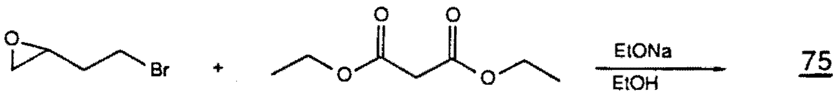
Sulfides have also been used to stabilize the anion for intramolecular cyclizations of epoxides. This method has proven very useful in the synthesis of macrocycles. Kodama and co-workers[27], who used thioethers for base-catalyzed intramolecular cyclization of epoxy compounds, were able to form 14-membered ring macrocyclic compounds. In the key step (see diagram below) the epoxide 71 was cyclized to alcohol 72, a useful precursor to several compounds in the cembrene family.



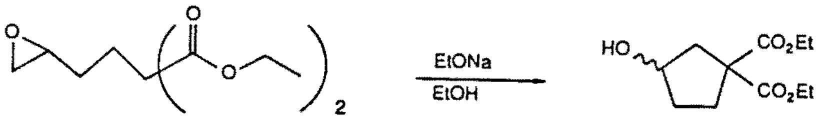
71 72

ACID DERIVATIVES

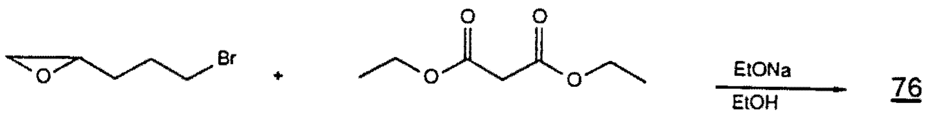
Cruickshank and Fishman[28], while conducting a study involving the alkylation of 4-bromo-1,2-epoxybutane (73) and 5-bromo-1,2-epoxypentane (74) with diethyl sodiomalonate, found unexpected and unknown alcoholic products. These products were the result of a side reaction that occurred following the initial alkylation. Epoxydiesters 75 and 76 underwent base-promoted anionic cyclization to form cyclopentanol 77 and cyclo- pentylmethanol 78a, (the actual product isolated was the bicyclic lactone 78b). The proposed reaction pathway was verified when epoxydiester 75 was isolated from the reaction mixture and subsequently treated with base under the same conditions to furnish cyclopentanol 77.



73



75 77



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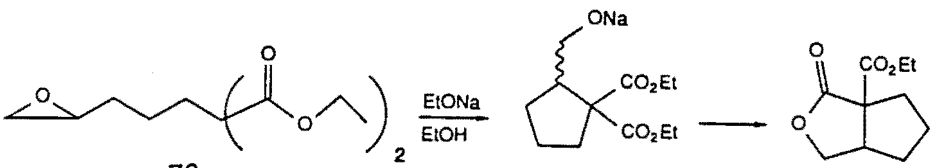
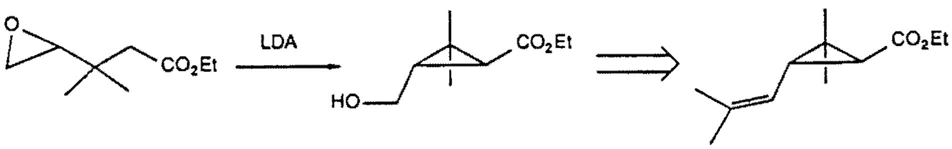


76 78a 78b

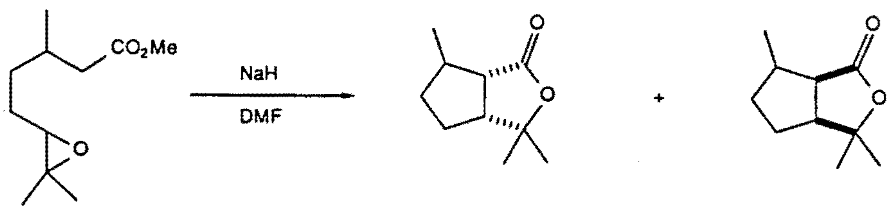
In a study concerning the cyclization of ethyl 4,5-epoxypentanoates, Babler and Tortorello[29] were able to show the preferential formation of 3-membered rings over 4-membered rings no matter how the oxirane ring was substituted. Such reactions were also stereoselective.



79 80 81

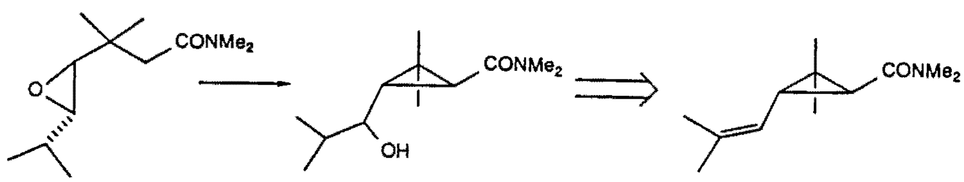
Compound 79 was converted to cyclopropanoid 80 (as shown), which lead to the total synthesis of ethyl trans-chrysanthemate (81).

In another study involving monoterpene epoxides, Wolinsky, Hull and White[30] reported that the epoxide formed from methyl citronellate 82 could be cyclized to form a mixture of lactones 83 and 84 when treated with sodium hydride or potassium t-butoxide in dimethyl formamide.



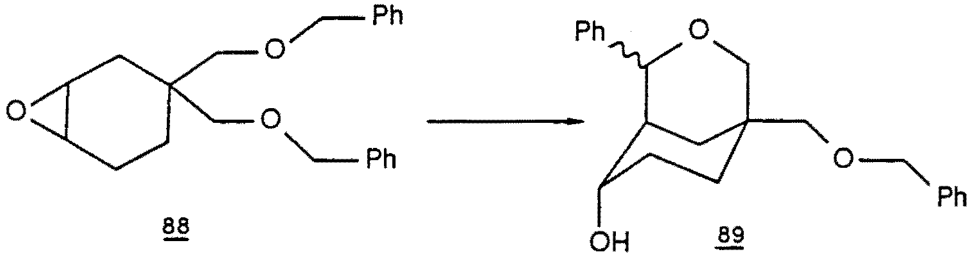
80 83 84

In 1982 Majewski and Snieckus[31] also used intramolecular anionic cyclization of an epoxide as the key step in the synthesis of a pyrethroid. The important step in the synthesis was the cyclization of epoxyamide 85 to provide a 1:3 mixture of cis:trans isomers of cyclopropanoid 86 which, after separation, could be carried on to furnish amide 87, a precursor to trans-pyrethroids.



85 86 87

Williams and Grote[32] performed another stabilized anionic cyclization which involved the selective deprotonation of benzyl ethers with lithio-2,6-dimethylpiperidide to initiate the intramolecular attack at a nearby epoxide. One example is given below. The epoxy ether 88 was cyclized to provide the bicyclic alcohol 89. This transformation was carried out using several examples, resulting in formation of 5-membered as well as 6-membered heterocyclic rings.

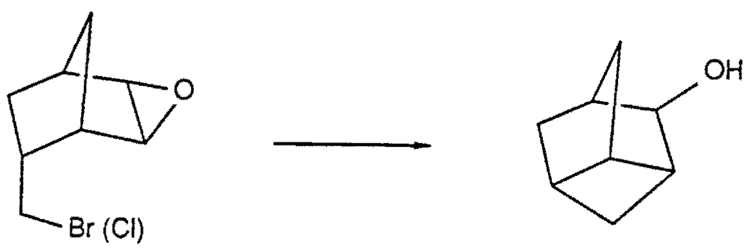


88 89

NON-STABILIZED CYCLIZATIONS

This discussion, until now, has dealt only with intramolecular cyclizations of epoxy carbanions stabilized by an adjacent functional group. The reaction used most often for the formation of the non-stabilized carbanions is the metal-halogen exchange reaction.

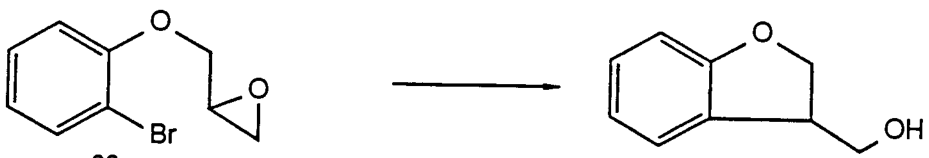
Sauers and co-workers [33] performed some of the early work on these compounds when the need for tricyclo-



90 91

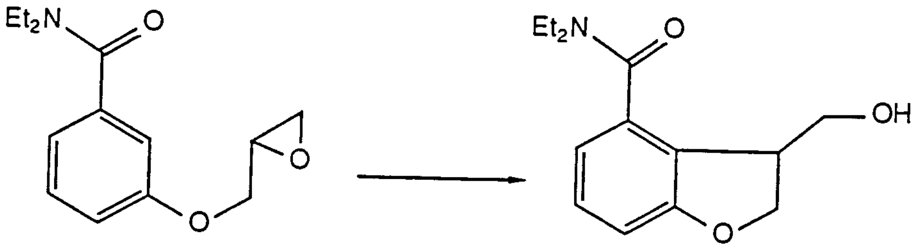
[3.2.1.$0^{3,6}$]octanes arose. They cyclized the haloepoxide 90 using lithium metal in tetrahydrofuran to form the tricyclic alcohol 91.

Bradsher and Reames[34] used metal-halogen exchange to initiate the intramolecular cyclization of epoxide 92 to form bicyclic alcohol 93. An interesting note is that only the smaller ring was formed. This was explained by the fact that incorporation of an aromatic ring increases the rigidity of the molecule. This rigidity appears to inhibit the collinearity of the anion[17] with the C-O bond which must be broken to form the larger 6-membered ring.

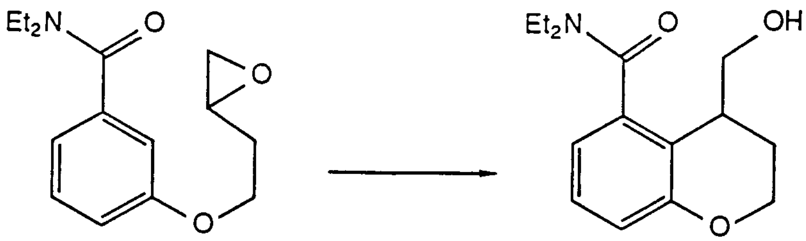


92 93

Similar results were obtained by Shankaran and Snieckus during attempts to cyclize epoxybenzamides[35]



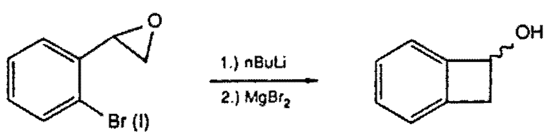
94 95



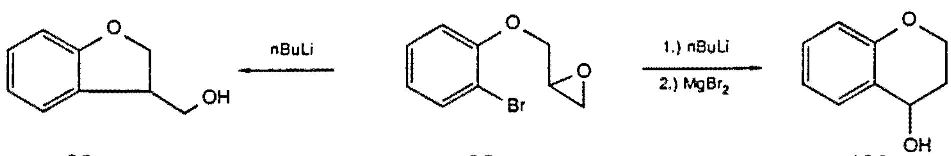
96 97

94 and 96. Benzofuran 95 and benzopyran 97 derivatives were formed after metalation of the aromatic ring. Only exo-tet cyclization was observed. It appears that the geometry of the transition state (with the electron pair and the C-O bond collinear) favors the formation of the smaller ring and it is formed exclusively, (see above).

In another study[36] Dhawan, Gowland and Durst were able to form benzocyclobutanol 99 from epoxide 98. The reaction involved the use of *n*-butyllithium in an exchange with the halide, followed by addition of magnesium bromide. This resulted in a cyclization to the larger ring (absence of magnesium bromide resulted in no ring formation). The regioselectivity in the cyclization of epoxide 92 could be altered to allow the 6-membered ring 100 to be formed by addition of magnesium bromide to the reaction mixture. The reaction pathway (as stated earlier) probably involves initial formation of a halohydrin followed by cyclization rather than a concerted cyclization-ring opening. Further work is being continued to accurately determine the mechanism.

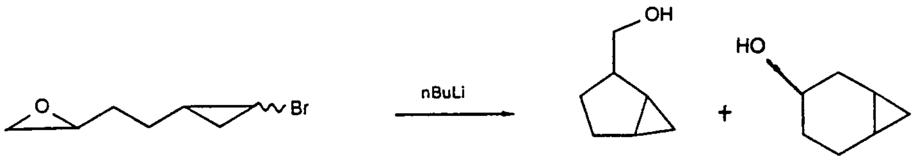


98 99



93 92 100

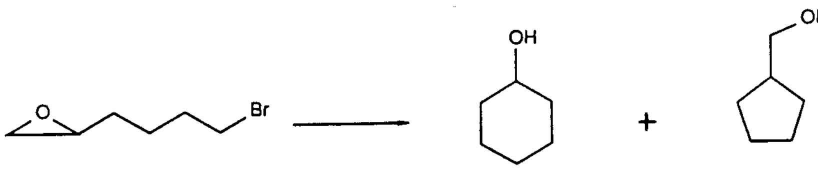
Last, Fretz and Coates discovered a new way to form polycyclic compounds from bromocyclopropyl epoxides[37]. This transformation was effected by treatment of the bromocyclopropyl epoxide 101 with *n*-butyllithium. Subsequently, the intramolecular attack of the cyclopropyl anion at the epoxide ring gave a mixture of bicyclic alcohols 102 and 103.



40% 60%

101 102 103

Recently some very interesting results involving metal-halogen exchange promoted anionic cyclization have been reported. When Erdik[38] treated haloepoxide 104 with excess magnesium in the presence of copper(I) iodide, a 4:1 mixture of cyclohexanol (105) and cyclopentylmethanol (106) were formed. The use of lithium and copper(I) iodide in tetrahydrofuran gave cyclohexanol as the only product[39].



104 105 106

Babler and Bauta[40] have reported conditions which allow for a shift in the regioselectivity in the cyclization of 6-bromo-1,2-epoxyhexane (104) to favor the formation of the smaller ring (106) by using *sec*-butyllithium in an exchange process. These results were confirmed by the work of Cooke and Houpis[41] who also found that addition of Lewis acids in the reaction mixture could dramatically affect the regioselectivity of the reaction, thereby increasing the selectivity to 100:1 in favor of the smaller ring. However, the use of copper(II) bromide favored generation of cyclohexanol (105).

This discussion has illustrated the use of functionalized epoxides for the formation of rings of various sizes, from the smallest to macrocyclic rings of 14 carbons. It has also been shown that due to the interest in these types of compounds a large body of work has been done. The ability to control the regioselectivity in these cyclizations has led to the syntheses of many natural products some of which may not be able to be prepared conveniently by any other means.

CHAPTER II

STATEMENT OF THE PROBLEM

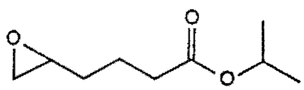
The goal of this work is to prepare delta,epsilon-epoxy esters with varying substitution and to determine their feasibility for base-promoted intramolecular cyclization. The results of these novel epoxy ester cyclizations would also test the rules for ring closure formulated by Baldwin[42]. The resulting products formed will be either 4-membered or 5-membered ring carbocycles. Similar studies have been carried out by Babler and Tortorello on gamma,delta-epoxy esters;[29] by Cruickshank and Fishman on epoxymalonates;[28] and by Wolinsky, Hull and White on methyl epoxycitronellate.[30]

In order to accomplish these novel cyclizations however, the effects of a competing Claisen condensation must be minimized.

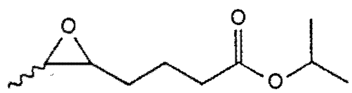
CHAPTER III

RESULTS AND DISCUSSION

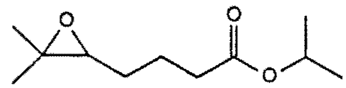
The specific epoxy esters which we plan to use [107, 108 and 109] are shown below. Treatment of these epoxides



107



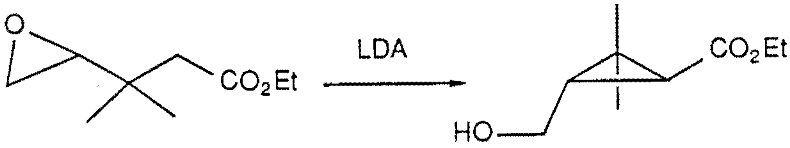
108



109

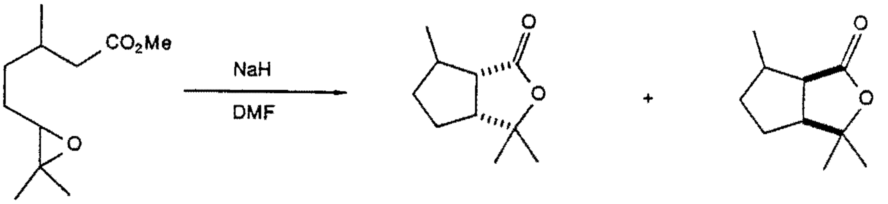
with an appropriate base could result in either cyclobutanoid and/or cyclopentanoid products. The cyclization product resulting from proximate attack would be the 4-membered ring, whereas terminal attack would furnish a 5-membered ring product. The enolate anion formed by treatment of each of these esters with lithium diisopropylamide can also undergo competing intermolecular reactions (e.g., Claisen condensation).

According to results published in the literature, the anions derived from epoxy esters will tend to cyclize so as to form the smaller ring product. In both of the examples published[29,30] to date, the larger ring size was not observed. For example, cyclization of ethyl 4,5-epoxy-3,3-dimethylpentanoate (79) with lithium diisopropylamide furnished onlycyclopropanoid 80[29]. Likewise, methyl



79 80

epoxycitronellate (82) when treated with base gave only cyclopentanoid lactones 83 and 84[30]. These results

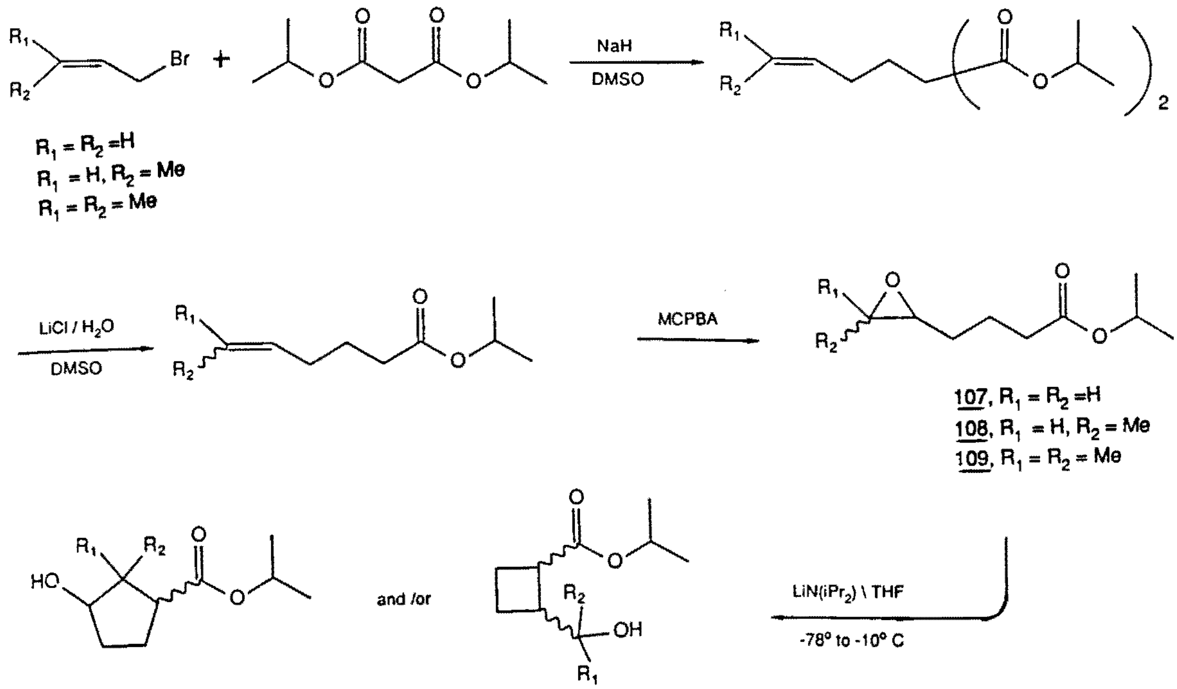


82 83 84

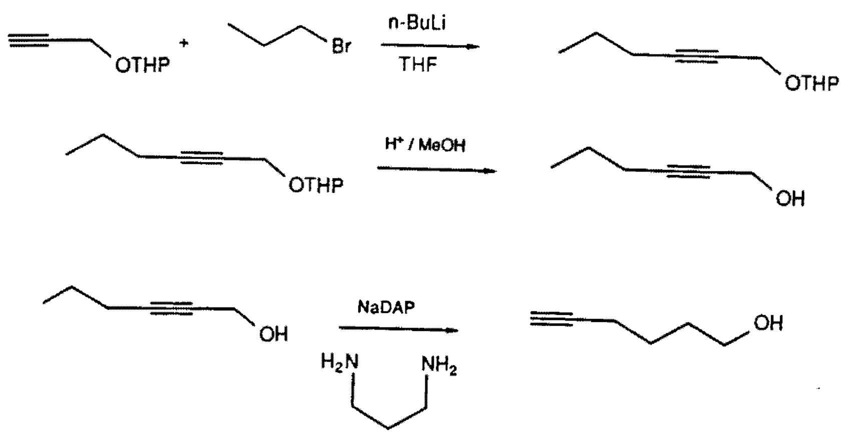
are consistent with the predictions of Baldwin who stated that the exo-tet product would be favored in systems of this type[42].

The preparation of the epoxides will be discussed prior to the discussion of the results. These compounds were prepared from the corresponding unsaturated halides by way of the malonic ester synthesis (the general sequence of reactions is shown in Scheme II). The monoesters were obtained by treating the initially formed malonate esters with lithium chloride in wet dimethyl sulfoxide using the method of Krapcho[43] to effect decarbalkoxylation. The alkenyl esters were subsequently oxidized with m-chloroperbenzoic acid. These epoxides were all able to be purified by vacum distillation (bulb-to-bulb). ^{1}H NMR, ^{13}C NMR and IR spectra were taken and satisfactory elemental or high resolution mass spectra were obtained to verify the assigned structures.

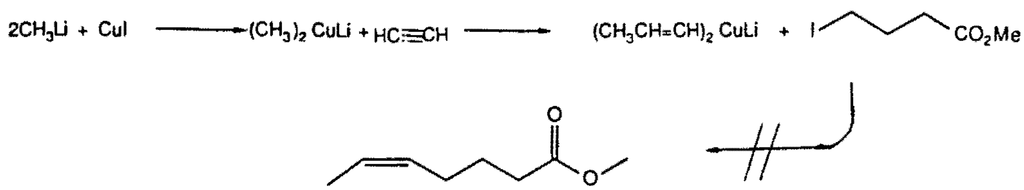
SCHEME II



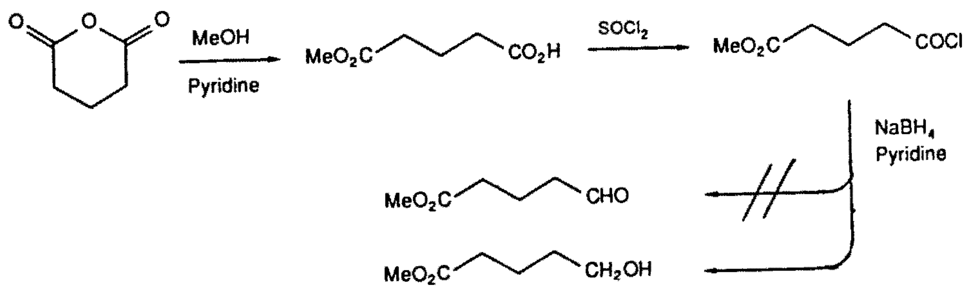
Other methods of formation of the alkenyl esters were attempted. These include formation of 2-hexyn-1-ol and isomerization of it to 5-hexyn-1-ol. Oxidation of the alkynol to 5-hexynoic acid would lead to a compound that



could serve as a building block for the complete series of alkenyl esters. Unfortunately the poor yields in the rearrangement step made this method impractical. Methyl 4-iodobutanoate and 4-iodobutyl acetate were also prepared.



These compunds were used in an attempted coupling reaction with a vinyl cuprate. This also ended in failure. Another route examined involved formation of methyl 5-oxopentanoate for use in a Wittig reaction. Unfortunately the reduction step produced only the alcohol product (as shown). Oxida-tion

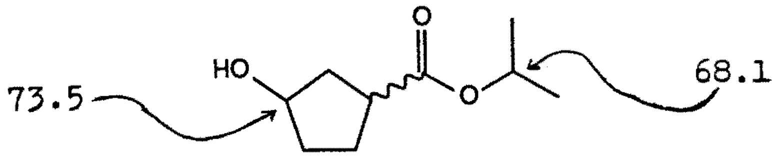


tion of the alcohol was not attempted. Wittig reactions were attempted using methyl 4-iodobutanoate and 4-iodobutyl acetate as well. All of these methods either proved unreliable or resulted in poor yields and were abandoned.

The first of the epoxy esters that we attempted to cyclize was isopropyl 5,6-epoxyhexanoate (<u>107</u>). Initially this compound was treated with lithium diisopropylamide using conditions developed by Babler and Tortorello[29]

(-78° C, external CO_2/acetone cooling, 7h). Unfortunately only starting epoxide was recovered. Subsequent attempts involved prolonged reaction times, and periodic samples were taken to check for formation of possible products. However, after 3 days the reaction was terminated since only starting material could be observed. The reaction was then repeated at a warmer temperature (-10 to -15° C). After 4 days the reaction mixture was subjected to the usual workup and a tan oil was obtained. From this, a colorless oil (0.059 g, 30% based on epoxide) was obtained after distillation, which was identified as isopropyl 3-hydroxycyclopentanecarboxylate (113).

The identification of the cyclized material (113) was based on the analysis of the spectral data. In the ^1H NMR spectrum the multiplet at 4.3-4.5 PPM delta (1H) for the -CH-OH ring proton corresponded very well with the ring proton of methyl 3-hydroxycyclopentanecarboxylate which has been reported to absorb at 4.3 PPM [44]. Also of importance in assigning the structure was the absence of the $-CH_2-OH$ methylene which would be expected if the product contained isopropyl 2-(hydroxymethyl)cyclobutanecarboxylate. This methylene ($C\underline{H}_2OH$) should absorb at about 3.5 PPM based on NMR data for methyl 2-(hydroxymethyl)cyclobutanecarboxylate which has been reported by Shroff and co-workers[45]. The ^{13}C spectrum also showed evidence for a 5-membered ring. Only two peaks corresponding to carbons that are attached to oxygen were found. The first at 68.1 PPM, was assigned to the O-$\underline{C}$H-Me_2 isopropyl carbon and is shifted by only 0.8 PPM from the epoxide which is at

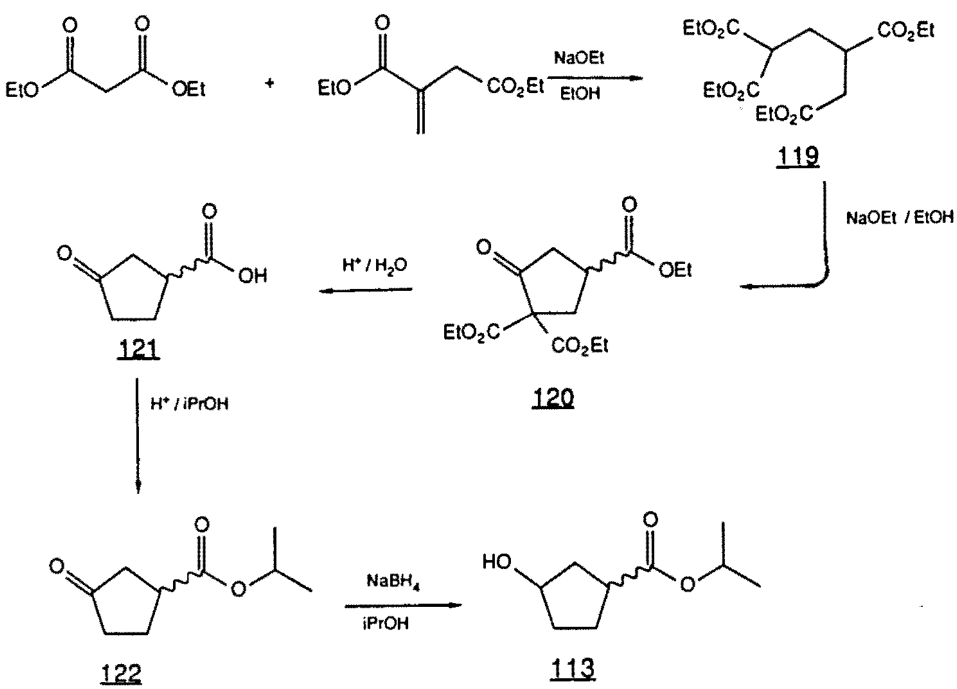


113

67.3 PPM. The other peak is at 73.5 PPM and these peaks correspond to the reference spectra nicely. A coupled spectrum was obtained to verify that the structure was correct. This spectrum (p. 65) showed that the peak at 73.5 PPM was split into a doublet at 74.4 and 72.5 PPM respectively. In the spectrum there was no indication of a triplet which would be indicative of two adjacent H atoms.

Isopropyl 3-hydroxycyclopentanecarboxylate (113) was

SCHEME III

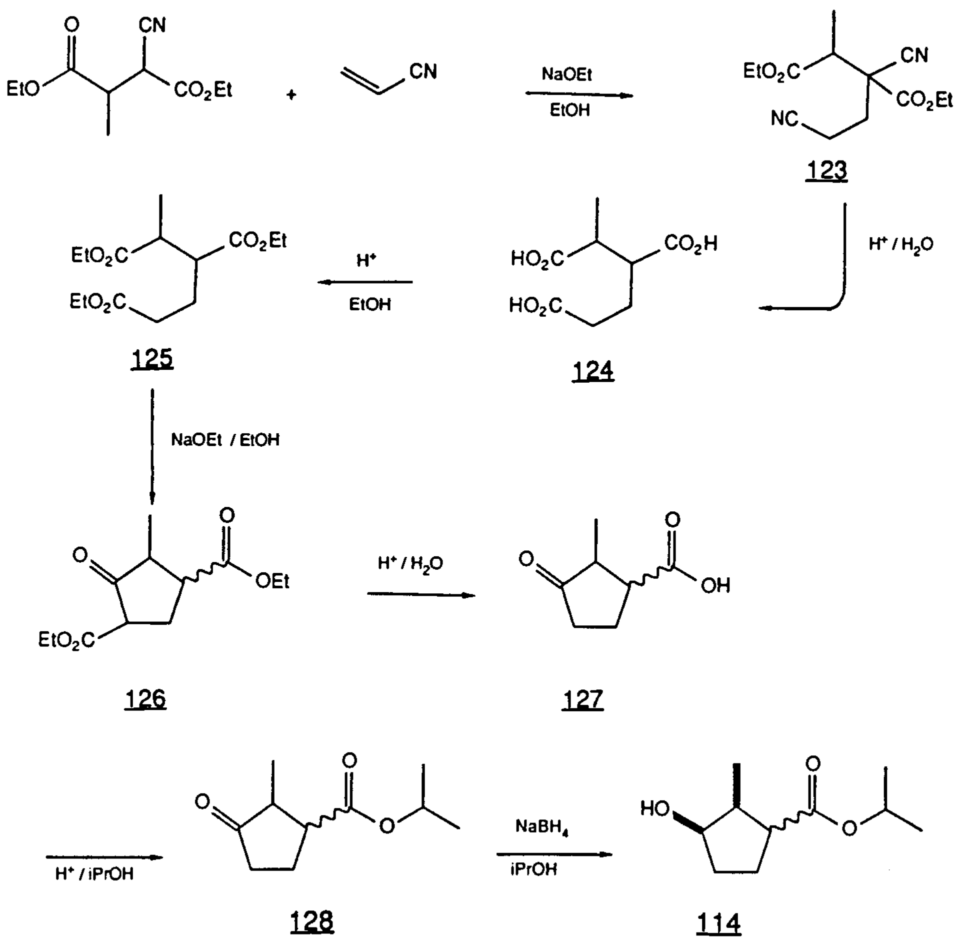


prepared by an independent synthesis starting from diethyl malonate and diethyl itaconate[44] (SCHEME III). This synthesis involved a Michael reaction followed by a Dieckmann condensation to form the cyclopentanoid ring structure. After Fisher esterification and reduction using sodium borohydride the resulting alcohol gave spectra identical to those exhibited by cyclization product 113.

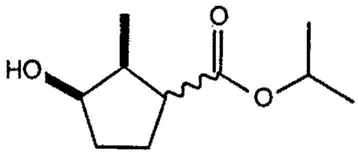
The second compound that we attempted to cyclize was isopropyl 5-6,epoxyheptanoate (108). The reaction conditions were not varied from those described above for the cyclization of epoxy ester (107). This reaction furnished a clear oil which, after column chromatography, was separated into two fractions. The first fraction was determined to be unreacted starting material. The second was identified as a new product: isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate (114) (0.095 g, 48% based on epoxide). It's structure was confirmed by using ^{1}H NMR data (the quartet at 4.0 PPM for the -CH-OH ring proton), spectrum on page 72. The ^{13}C spectrum on page 73, also showed a peak for the -CH-OH ring carbon at 80.11 PPM. This was verified by an attached proton test, (this identifies the carbon atoms with odd or even numbers of H atoms and changes the signs of the peaks), which showed an odd number of protons attached to the carbon.

Isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate (114) was prepared by an independent synthesis starting from diethyl α-cyano-α'-methylsuccinate[46] and acrylonitrile (SCHEME IV). The cyclopentanecarboxylic acid 127 was esterified with isopropyl alcohol to furnish a mixture of keto-esters 128. The ketone was reduced with sodium borohydride to form the alcohol 114 which was compared to the cyclization product. It appeared that there was a difference in the stereochemistry and this was probably due to the cis vs. trans orientation of the methyl group with

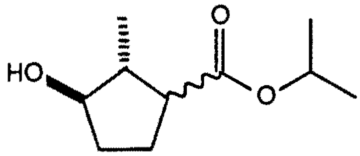
SCHEME IV



relation to the alcohol 114 (as shown below). The ketone 128 was treated with "L-Selectride"[47] to furnish



114c

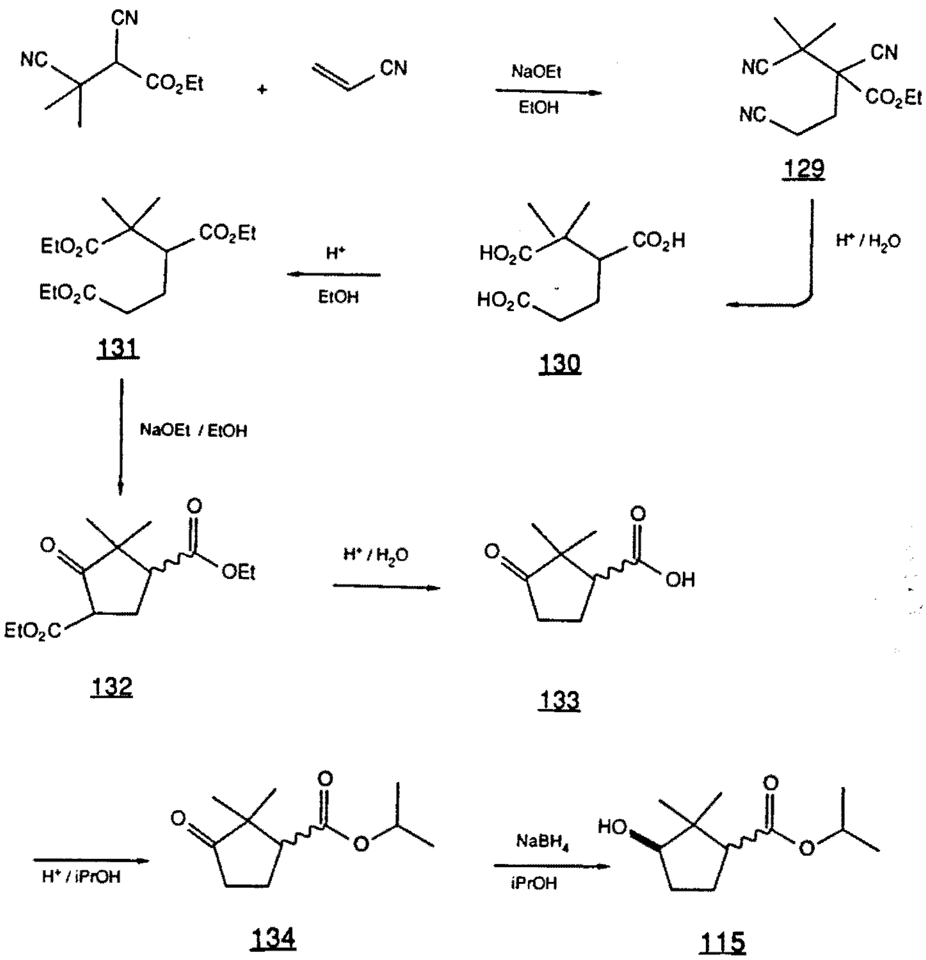


114t

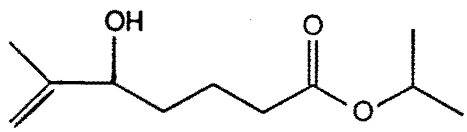
the cis alcohol 114c. The spectra of this compound was still different from the cyclized product leading to the conclusion that the cyclized material possessed a trans arrangement of substituents at the 2 and 3 positions. To verify this conclusion, the cyclization product was oxidized to form ketone 128. This compound had an identical ^{1}H NMR spectrum as the authentic synthesized ketone.

The final epoxy ester that we attempted to cyclize was isopropyl 5-6,epoxy-6-methylheptanoate (109). The first attempts at cyclization of this compound proved unsucessful, furnishing only "tar" and recovered starting material. After an independent synthesis[48], (SCHEME V), of the expected product isopropyl 2,2-dimethyl-3-hydroxy-cyclopentanecarboxylate, (115), the cyclization reaction was repeated allowing most of the starting material to react (>2 weeks). The reaction mixture was analyzed at regular intervals via thin layer chromatography comparing Rf values with those exhibited by the starting material and the expected product 115. After several days a new compound appeared. The Rf of this compound was similar to that of the starting epoxy ester but was different from

SCHEME V



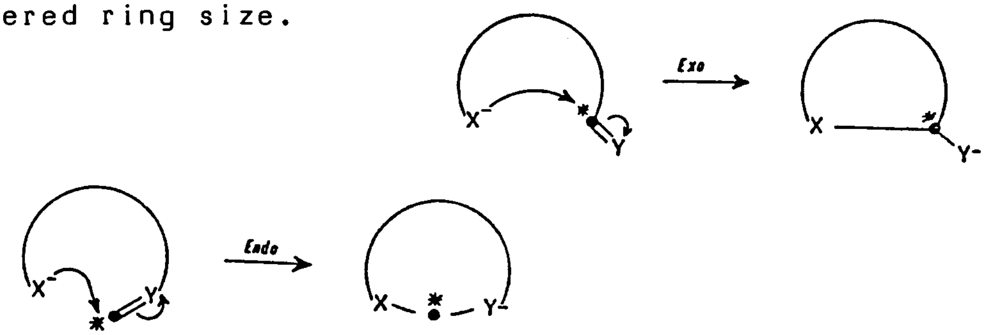
that of the expected product. Upon workup, no cyclized product was obtained. However, a new compound was isolated in about 40% yield and was subsequently identified as isopropyl 5-hydroxy-6-methylhept-6-enoate 135, a rearrangement product.



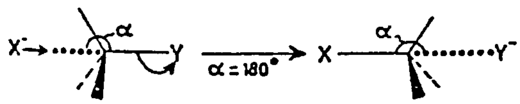
135

The structure of this rearrangement product was deduced by comparison with authentic 2-methyl-2-propen-1-ol with which it has many spectral similarities. The ^1H NMR spectrum exhibited by this compound, the vinyl CH_2 doublet at 4.9 PPM, the allylic CH_2 peaks at 4.1 PPM and the CH_3 singlet at 1.75 PPM correspond very well with the respective peaks shown by 2-methyl-2-propen-1-ol. Satisfactory mass spectral data (p. 47) was also obtained for this compound.

According to the rules for ring closure set forth by Baldwin[42] to predict the products of an intramolecular alkylation, the situation set forth by the cyclization of epoxy esters would favor closure in an exo-tet mode. In our case this would lead to the formation of the smaller 4-membered ring size.

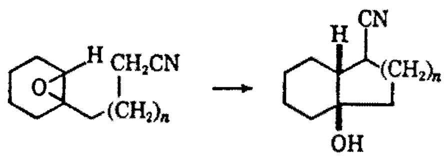


The endo-tet cyclization (leading to 5-membered rings) is disfavored. The basis of Baldwin's rules lies in the stereochemical requirements of the transition state. For clo-



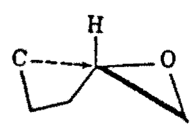
sure at a tetrahedral carbon, the favored pathway is represented by the Walden inversion with the incoming group colinear to the leaving group.

Stork and co-workers in their papers on epoxynitrile cyclization[17] stated that for epoxy compounds like the ones shown below, cyclization is faster for structures with n=2 than when n=1.



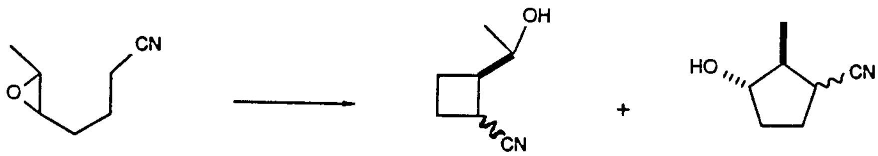
This result is contrary to the results found in classical displacement cyclizations[18] where 5-membered ring formation is faster than the 6-membered ring formation. The reason for this discrepancy appears to be the amount of

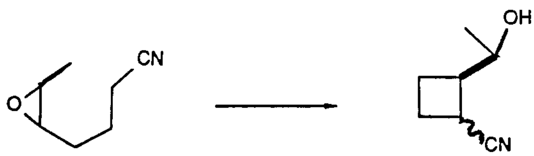
bond distortion that is required for the proper alignment of the carbanion with that of the leaving oxygen. For epoxynitriles this alignment is also easy to achieve in the formation of 4-membered rings. This led Stork to the



conclusion that an epoxy nitrile equally substituted about the oxirane ring will form cyclobutanes preferentially over cyclopentanes.

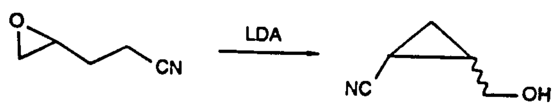
Lallemand and Onaga[19] disputed this claim and have reported cyclization studies using 5,6-epoxy nitriles. If the oxirane ring possessed the cis configuration then





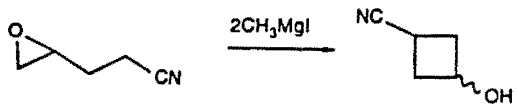
only cyclobutaniod products were formed. However, the corresponding trans stereoisomer afforded a product mixture with the 5-membered ring being favored. It appeared that Stork's observation of preferential cyclobutane formation was a consequence of the cis stereochemistry of the epoxide.

Durst and co-workers[22] found that they could control the ring size generated in intramolecular alkylations by the choice of base used. With a 4,5-epoxy nitrile, Stork had found that only cyclopropanes could be formed using an amide base to initiate the cyclization.



However Durst found, if methylmagnesium iodide was used, then the cyclobutanoid compound was the exclusive product.

This result was explained by the following mechanism. In



the latter reaction the epoxide ring is opened by the Grignard reagent to form an iodo intermediate, and a second equivalent of base is then needed for the ring to close in a subsequent step.

In the case of the epoxy esters reported in this dissertation, no 4-membered ring products were observed. When models were made, the large amount of distortion necessary to form a 4-membered ring was evident. The bond distortion was considerably less for formation of a 5-membered ring. This smaller amount of distortion evidently allowed the cyclopentanoid compounds to be formed preferentially over the cyclobutanoid compounds.

The formation of only one stereoisomer of isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate (both cis and trans epoxide were present in the mixture) was indicative that a methyl group was able to block an attack by the anion from one face of the epoxide. The lack of any cyclization product from the trisubstituted epoxide (109) demonstrates that rearrangement is energetically a better pathway than cyclization because both faces of the epoxide are blocked.

CHAPTER IV

EXPERIMENTAL

General Information

All organic starting materials were obtained from Aldrich Chemical Company except 4-bromo-1-butene and 3-pentyn-1-ol which were purchased from Wiley Organics Company. All inorganic reagents were obtained from Fisher Scientific Company and *n*-butyllithium in hexane was purchased from Aldrich Chemical Co. The *n*-butyllithium concentration was periodically monitored utilizing the method of Eastham and Watson[49]. The solvents were purchased from either Aldrich Chemical Company or Fisher Scientific Company and were used as obtained from the supplier except for: tetrahydrofuran (THF), which was distilled from lithium aluminum hydride as needed and used immediately; diisopropylamine which was distilled from calcium hydride and stored over 4A molecular sieves; dimethyl sulfoxide (DMSO), which was distilled from calcium hydride (under vacuum) and stored over 4A molecular sieves until needed, and petroleum ether (bp 30-60° C) which was distilled through a 40 cm Vigreux column.

Reactions were run under either an argon (when available) or a nitrogen atmosphere except the decarbalkoxylations which were run with an oil bubbler to monitor carbon dioxide evolution.

Combined extracts of crude reaction mixtures were washed with the specified aqueous solutions and subsequently dried over the specified anhydrous inorganic salt, followed by filtration of the drying agent prior to the removal of the solvent at reduced pressure (unless otherwise specified).

Bulb-to-bulb distillation refers to the Kugelrohr short-path distillation (the apparatus used is available from Aldrich Chemical Co.).

Melting points (determined in capillary tubes using a Mel-Temp apparatus) and boiling points are uncorrected.

^{1}H NMR spectra were recorded on a Varian Associates model EM360A spectrometer (60 MHz), a Varian Associates model FT80 spectrometer (80 MHz), or a General Electric model QE-300 and a Varian Associates model VXR 300 spectrometer (300 MHz). ^{13}C NMR spectra were recorded using a Varian Associates model FT80 (20 MHz). For all NMR spectra tetramethylsilane (TMS) was used as an internal standard and chemical shifts were reported downfield from TMS in PPM using the delta scale. Infrared spectra were recorded using a Beckman Acculab I spectrophotometer and only those bands attributable to functional groups have been reported.

Gas-liquid chromatography (GLC) was performed on a Hewlett-Packard model 5750 chromatograph utilizing a 5% OV-17 on Gas Chrom Q (100/120 mesh) column (0.125 in. x 6 ft.). The peak areas were determined by the use of a Hewlett-Packard model 3392 integrator.

Column chromatography was performed on silica gel (230-400 mesh, E. Merck cat# 9385) following the procedure of Still _et al_[50]. Thin-layer chromatography (TLC) was performed on precoated silica gel glass or aluminum plates (Merck cat# 5765 or 5545). Visualization was afforded by using an _o_-methoxybenzaldehyde solution[51] or a molybdophosphoric acid solution[52].

The elemental analyses were performed by Micro-Tech Laboratories, Skokie Illinois. Mas spectra were obtained courtesy of Searle Pharmaceutical Co.

Diisopropyl malonate (_110_). A solution of dimethyl malonate, (66.0 g, 0.50 mol) and _p_-toluenesulfonic acid (4.0 g, 0.02 mol) in dry isopropyl alcohol (300 mL) was heated at reflux for 24 hours at which time 100 mL of alcohol was removed by distillation. After addition of 100 mL of fresh isopropyl alcohol the mixture was once again heated at reflux for 24 hours, followed by distillative removal of 100 mL of solvent. The procedure was repeated until no dimethyl or isopropyl methyl malonate remained. The excess isopropyl alcohol was removed by distillation until only 100 mL remained, after which the solution was cooled and poured into 150 mL of saturated aqueous sodium bicarbonate solution. The product was extracted with ether (3 x 100 mL). The combined extracts were washed in succession with water (2 x 100 mL), brine, and then were dried over magnesium sulfate. Solvent removal followed by distillation furnished 86.5 g (92%) of clear oil: b.p. 28-30° C at 0.4 mm; Lit.[53] b.p. 73-75° C at 2.8 mm; ^1H NMR (CCl_4): 5.0 (septet J=6Hz, 2H, 2 x $-C\underline{H}-(CH_3)_2$), 3.2 (s, 2H, CH_2), 1.25 (d J=6Hz, 12H, 2 x $-CH(C\underline{H}_3)_2$.); IR ($CHCl_3$, 0.2mm): 1100 (C-O), 1720 (C=O) cm^{-1}.

Diisopropyl (3-butenyl)propanedioate (111). Sodium hydride 2.0 g, (41.8 mmol, 50% oil dispersion) was placed in a three-necked, 100 mL round-bottomed flask fitted with a rubber septum, a reflux condenser, and an addition funnel containing diisopropyl malonate, (12.0 g, 63.7 mmol), mixed in an equal volumn of DMSO. The apparatus was purged with argon. Dimethyl sulfoxide (25 mL) was added to the flask, followed by slowly adding the diisopropyl malonate solution to the magnetically stirred suspension. Upon completion of the addition, the reaction mixture was stirred at the ambient temperature until evolution of hydrogen gas, as evidenced by bubbling in the flask, ceased. Through the rubber septum, 4-bromo-1-butene (3.40 g, 25.2 mmol) was added in one portion via syringe. Heat was liberated, and the resulting brownish-yellow solution was stirred at the ambient temperature for 17 hours. At that point aqueous hydrochloric acid (20 mL, 1.2M) was added to the tan, opaque mixture. The resulting turbid solution was transferred to a separatory funnel and extracted with petroleum ether, (3 x 25 mL). The combined extracts were washed once with saturated sodium bicarbonate solution, twice with water and twice with saturated sodium chloride solution. After drying over magnesium sulfate the organic layer was vacuum filtered and the solvent removed using a rotary evaporator. Subsequent fractional distillation furnished 5.34 g of unreacted isopropyl malonate and 5.42 g of the desired product (88% based on 4-bromo-1-butene): b.p. 55° C at 0.1 mm; ^1H NMR ($CDCl_3$): 4.8-6.2 (m, 5H, 2 x -OC<u>H</u>$(CH_3)_2$, -C<u>H</u>=C<u>H</u>$_2$), 3.3 (m, 1H, CH), 1.9-2.3 (m, 4H, 2 x CH_2), 1.25 (d J=6Hz, 12H, 2 x -CH(C<u>H</u>$_3$)$_2$.); IR (liquid film): 1100 (C-O), 1740 (C=O) cm^{-1}; C, H analysis: Carbon: calculated 64.44%, found 64.49%; Hydrogen: calculated 9.15%, found 8.99%.

<u>Isopropyl</u> <u>5-Hexenoate</u> (<u>112</u>). Lithium chloride (2.95 g, 69.6 mmol), diisopropyl (3-butenyl)propanedioate (5.80 g, 23.9 mmol), water (0.86 g, 47.7 mmol) and dimethyl sulfoxide (30 mL) were added to a 50 mL flask equipped with a reflux condenser. The magnetically stirred mixture was heated in an oil bath at 160° C for 72 hours. During this time the homogeneous solution darkened to brown, while small amounts of tan solid precipitated in the flask and gas evolution occurred. The cooled reaction mixture was

transferred to a separatory funnel containing 50 mL of saturated sodium chloride solution. The aqueous solution was extracted with petroleum ether (3 x 25 mL), and the combined extracts were washed with saturated sodium chloride solution. After drying the extracts over magnesium sulfate and solvent removal, the product was vacuum distilled to furnish 3.00 g of monoester (80% based on diester): b.p. 25-30° C at 0.2 mm; ^1H NMR ($CDCl_3$): 5.4-6.2 (m, 1H, -C<u>H</u>=CH_2), 4.8-5.3 (m, 3H, ester, -CH=C<u>H_2</u>) 1.5-2.6 (m, 6H, 3 x CH_2), 1.25 (d J=6.4Hz, 6H, CH(C<u>H_3</u>$)_2$); ^{13}C NMR ($CDCl_3$): 172.40, 137.43, 114.87, 66.92, 33.62, 32.78, 23.96, 21.48; IR ($CHCl_3$, 0.2mm): 1110 (C-O), 1645 (C=C), 1740 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 69.19%, found 69.39%; Hydrogen: calculated 10.32%, found 10.69%.

<u>Isopropyl 5,6-epoxyhexanoate</u> (<u>107</u>). A solution of isopropyl 5-hexenoate (0.5 g, 3.2 mmol), and *m*-chloroperoxybenzoic acid (0.67 g x 82% purity, 3.2 mmol) in 13 mL of benzene was magnetically stirred at the ambient temperature for 48 hours. Slow precipitation of *m*-chlorobenzoic acid from the initially homogeneous solution was observed. The reaction was 90% complete by GLC analysis after 24 hours. The product was isolated from the reaction mixture by adding the slurry to a 10% sodium carbonate solution (15 mL) followed by extraction with ether (3 x 10

mL). The combined organic layers were washed with water, saturated sodium chloride solution and then were dried over magnesium sulfate. Concentration and distillation (bulb-to-bulb) afforded 0.45 g of compound (107) (81% based on alkene): b.p. 40-50° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.1 (pentet J=6.4Hz, 1H, -CH-$(CH_3)_2$), 2.7-3.1 (m, 2H,), 2.2-2.6 (m, 3H,), 1.5-2.1 (m complex, 4H), 1.25 (d J=6.4Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$): 172.46, 67.34, 51.51, 46.57, 34.08, 31.66, 21.65, 21.33; IR (liquid film): 1095 (C-O), 1715 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 62.77%, found 62.64%; Hydrogen: calculated 9.36%, found 9.61%.

Isopropyl 3-Hydroxycyclopentanecarboxylate (113). A 25 mL round-bottomed flask equipped with a magnetic stirrer, septum and pressure equalizing dropping funnel under an argon atmosphere was charged with diisopropylamine (0.35 g, 3.5 mmol) and 15 mL of tetrahydrofuran. This solution was cooled to - 5° C (external ice/acetone bath) for 10 minutes at which time *n*-butyllithium (1.5 mL of a 1.5 M solution in hexane, 2.25 mmol) was added slowly via syringe. This solution was allowed to stir for 20 minutes and then cooled to - 78° C (external CO_2/acetone bath). After 15 minutes epoxide (107) (0.200 g, 1.16 mmol) was slowly added in 5 mL of tetrahydrofuran. The solution subsequently was stirred for 5-10 minutes at - 78° C, then sealed and placed in a freezer maintained at - 10° C for 4 days. Upon removal, the mixture was added to a solution of saturated ammonium chloride (20 mL). The aqueous solution was extracted with ether (3 x 10 mL). The combined extracts were washed in succession with 1.2 M hydrochloric acid solution saturated with sodium chloride (2 x 10 mL), saturated sodium bicarbonate solution, saturated sodium chloride solution and then were dried over magnesium sulfate. Sequential removal of the drying agent and the solvent in vacuo, followed by distillation (bulb-to-bulb) furnished 0.059 g of a clear oil (30%, based on epoxide). This was subsequently identified as isopropyl 3-hydroxycyclopentanecarboxylate (mixture of _cis_ and _trans_): b.p. 60-66° C at 0.2 mm; ^1H NMR ($CDCl_3$): 5.0 (pentet J=6.2 Hz, 1H, -C$\underline{H}$(CH_3)$_2$), 4.4 (m, 1H, -C$\underline{H}$-OH), 3.0 (m, 1H, -C$\underline{H}$-CO_2R), 1.5-2.2 (m, 7H), 1.25 (d J=6.2Hz, 6H, CH(C$\underline{H}_3$)$_2$.); ^{13}C NMR ($CDCl_3$): 175.93, 73.5, 68.1, 67.4, 42.2, 41.8, 39.1 38.6, 35.6, 34.9, 27.7, 27.3, 21.7; IR (liquid film): 1070 (C-O), 1710 (C=O), 3310 (O-H) cm^{-1}. High resolution Mass Spectrum: Calculated for $C_9H_{16}O_3$ 172.1099 g, found 172.1079 g.

Diisopropyl _(4-methyl-3-pentenyl)propanedioate_ (_136_). Using a procedure identical to the preparation of diisopropyl (3-butenyl)propanedioate (_111_), 11.26 g, (68.4 mmol) of crude 5-bromo-2-methyl-2-pentene[54] was converted into the corresponding diester (_136_). Fractional distillation of the crude reaction product furnished 12.54 g of the desired diester product (68% based on 5-bromo-2-methyl-2-pentene): b.p. 78° C at 0.02 mm; ^1H NMR ($CDCl_3$): 5.0 (pentet J=6Hz, 3H, -C<u>H</u>(CH_3)$_2$, vinyl H), 2.9-3.2 (m, 1H, -C<u>H</u>-CO_2R), 1.5-2.1 (m, 10H), 1.25 (d J=6 Hz, 12H, 2 x CH(C<u>H</u>$_3$)$_2$); IR (liquid film): 1105 (C-O), 1740 (C=O) cm^{-1}; C, H analysis: Carbon: calculated 66.64%, found 67.00%; Hydrogen: calculated 9.69%, found 9.89%.

<u>Isopropyl</u> <u>5-methyl-5-heptenoate</u> (<u>137</u>). Using a procedure identical to the preparation of isopropyl 5-hexenoate (<u>112</u>) 12.54 g (46.4 mmol) of diisopropyl (4-methyl-3-pentenyl)propanedioate was converted to the corresponding monoester (<u>137</u>). The crude product was vacuum distilled (bulb-to-bulb) to furnish 7.0 g of product (82% based on diester): b.p. 28-34° C at 0.2 mm; ^1H NMR ($CDCl_3$): 5.0 (pentet J=6 Hz, 2H, C<u>H</u>(CH_3)$_2$, vinyl H), 1.7-2.5 (m, 6H), 1.7 (s vinyl CH_3), 1.6 (s vinyl CH_3), 1.25 (d J=6 Hz., 6H, CH(C<u>H</u>$_3$)$_2$.); ^{13}C NMR ($CHCl_3$): 172.96, 132.05, 123.51, 67.07, 33.98, 27.27, 25.43, 25.03, 21.66, 17.41; IR ($CHCl_3$, 0.2mm): 1100 (C-O), 1720 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 71.70%, found 71.48%; Hydrogen: calculated 10.94%, found 10.90%.

<u>Isopropyl</u> <u>5-methyl-5,6-epoxyheptanoate</u> (<u>109</u>). Using a procedure identical to the preparation of isopropyl 5,6-epoxyhexanoate (<u>107</u>), 0.300 g, (1.62 mmol) of isopropyl 5-methyl-5-heptenoate (<u>137</u>) was converted to the corresponding epoxide (<u>109</u>). The crude product, purified by

distillation (bulb-to-bulb), afforded 0.250 g of epoxide (109) (77% based on alkene): b.p. 55-60° C at 0.25 mm; ^{1}eH NMR ($CDCl_3$): 5.1 (pentet J=6 Hz, 1H, $-C\underline{H}(CH_3)_2$), 1.5-3.0 (m, 6H), 1.1-1.5 (m, 12H, $-CH(C\underline{H}_3)_2$); ^{13}C NMR ($CHCl_3$): 172.47, 67.33, 63.58, 57.77, 34.09, 28.13, 24.62, 21.87, 21.64, 18.51; IR (liquid film): 1110 (C-O), 1725 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 65.97%, found 65.62%; Hydrogen: calculated 10.07%, found 10.23%.

Attempt to cyclize Isopropyl 5-methyl-5,6-epoxyheptanoate (109). Using a procedure identical to the preparation of isopropyl 3-hydroxycyclopentanecarboxylate (113), 0.37 g, (3.7 mmol) of isopropyl 5-methyl-5,6-epoxyheptanoate (109) was allowed to react for 14 days. The crude product was purified by distillation, (bulb-to-bulb), and the resulting oil (0.242 g) was further purified by column chromatography (1:1 ether/petroleum ether) furnishing 0.147 g of recovered starting epoxide and 0.095 g of clear oil (43% based on consumed starting material). This was subsequently identified as isopropyl 5-hydroxy-6-methylhept-6-enecarboxylate (135) a rearrangement product. ^{1}H NMR ($CDCl_3$): 4.7-5.2 (m, 3H), 3.9-4.1 (m, 1H) 2.1-2.6 (m, 3H), 1.5-1.9 (m, 7H) 1.2 (d J=6 Hz, 6H, $CH(C\underline{H}_3)_2$); ^{13}C NMR ($CHCl_3$): 172.98, 147.03, 110.99, 75.32, 67.49, 34.30, 34.12, 21.82, 20.96, 17.51; IR (liquid film): 1660 (C=C), 1720 (C=O), 3100 ($=CH_2$), 3480 (O-H) cm^{-1}; Mass Spectrum: Low resolution; MH^+ 201 g; High resolution; Calculated for $C_8H_{12}O_2$ (lactone) 140.0837 g, found 140.08346 g.

Diisopropyl (3-pentynyl)propanedioate (116). Using a procedure identical to the preparation of diisopropyl (3-butenyl)propanedioate (111), 4.22 g, (28.7 mmol) of crude 5-bromo-2-pentyne was converted into the corresponding diester (116). Fractional distillation of the crude reaction product furnished 4.7 g of the desired diester product (60% based on 5-bromo-2-pentyne): b.p. 73° C at 0.25 mm; ^1H NMR(CCl_4): 5.0 (pentet J=6 Hz 2H, 2 x -C$\underline{H}$(CH_3)$_2$), 3.3 (m 1H), 1.6-2.3 (m, 7H), 1.25 (d J=6Hz, 12H, 2 x -CH(C$\underline{H}_3$)$_2$); IR ($CHCl_3$, 0.2mm): 1100 (C-O), 1730 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 66.12%, found 65.93%; Hydrogen: calculated 8.72%, found 9.03%.

Diisopropyl (3-pentenyl)propandioate (117). To a 500 mL bottle, (flushed with argon), charged with nickel acetate (1.25 g, 10.5 mmol) and 20 mL of 95% ethanol was added sodium borohydride (0.20 g, 5.29 mmol). Hydrogen was evolved as the green suspension turned to a black precipitate. After the hydrogen evolution had ceased, ethylene diamine (0.66 g, 11.0 mmol) was added followed by alkyne (116) (2.00 g, 7.86 mmol). The bottle was then flushed 3 times with hydrogen, and the reduction was carried out using a Parr shaker. After the pressure drop had ceased the bottle was evacuated and decolorizing carbon (0.25 g) was added. The catalyst and carbon were removed by vacuum filtration, followed by removal of the solvent at reduced pressure. The residue was then added to 100 mL of water and extracted with ether (3 x 20 mL). The combined extracts were washed with water (4 x 25) mL and saturated sodium chloride solution. After drying with magnesium sulfate and removal of the ether the product was distilled, (bulb-to-bulb), to furnish 1.8 g of 117 (89% yield based on alkyne 116): b.p. 58-62° C at 0.5 mm; ^1H NMR ($CDCl_3$): 5.3-5.7 (m 2H, C$\underline{H}$=C$\underline{H}$), 5.1 (pentet J=6.2Hz, 2H, 2 x -C$\underline{H}$(CH_3)$_2$), 3.3 (m, 1H, -C$\underline{H}$-CO_2R), 1.8-2.5 (m, 4H), 1.6 (d J=5Hz., 3H, CH_3), 1.25 (d J=6.2 Hz., 12H, 2 x -CH(C$\underline{H}_3$)$_2$); IR ($CHCl_3$ 0.2mm): 1105 (C-O), 1725 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 65.59%, found 65.20%; Hydrogen: calculated 9.44%, found 9.65%.

Isopropyl 5-heptenoate (118). Using a procedure identical to the preparation of isopropyl 5-hexenoate (112), 2.73 g, (11.0 mmol) of diisopropyl (3-pentenyl)-propanedioate was converted to the corresponding monoester (118). The crude product was vacuum distilled (bulb-to-bulb) to furnish 1.37 g of product (76% based on diester): b.p. 25-30° C at 0.2 mm; ^1H NMR ($CDCl_3$): (mixture of cis and trans) 5.3-5.7 (m 2H, C$\underline{H}$=C$\underline{H}$), 5.1 (pentet J=6Hz, 1H, -C$\underline{H}$(CH_3)$_2$, 1.5-2.6 (m, 9H), 1.2 (d J=6Hz., 6H, -CH(C$\underline{H}_3$)$_2$; ^{13}C NMR ($CHCl_3$): 173.04, 130.18, 129.35, 125.63, 124.61, 67.18, 33.93, 31.79, 31.35, 28.66, 26.06, 24.89, 24.72, 21.67; IR ($CHCl_3$ 0.2mm): 960 (HC=CH) 1110 (C-O), 1735 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 70.55%, found 70.28%; Hydrogen: calculated 10.65%, found 10.80%.

Isopropyl 5,6-epoxyheptanoate (108). Using a procedure identical to the preparation of isopropyl 5,6-epoxyhexanoate (107), 0.380 g (2.23 mmol) of isopropyl 5-heptenoate (118) was converted to the corresponding epoxide (108). The crude product was purified by dis- tillation (bulb-to-bulb), afforded 0.330 g of epoxide (108) (89% based on alkene): b.p. 50-58° C at 1.2 mm; ^1H NMR ($CDCl_3$): (mixture of cis and trans) 4.95 (pentet J=6.2 Hz, 1H, -$C\underline{H}(CH_3)_2$), 2.0-3.1 (m, 4H), 1.4-2.1 (m, 4H), 1.25 (d J=6.2Hz., 9H, 3 x CH_3); ^{13}C NMR ($CHCl_3$): 172.52, 67.34, 58.94(t), 56.27(c), 54.16(t), 52.22(c) 34.09, 31.21, 26.82, 21.77, 21.35, 17.38; IR ($CHCl_3$ 0.2mm): 1110 (C-O), 1720 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 64.49%, found 64.44%; Hydrogen: calculated 9.74%, found 9.53%.

Isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate (114). Using a procedure identical to the preparation of isopropyl 3-hydroxycyclopentanecarboxylate (113), 0.200 g, (1.07 mmol) of isopropyl 5,6-epoxyheptanoate (108) was allowed to react for 4 days. The crude product was purified by distillation, (bulb-to-bulb), and the resulting oil (0.107 g) was further purified by column chromatography (1:1 ether/petroleum ether) furnishing 0.095 g of clear oil (48% based on starting epoxide). The new compound was subsequently identified as isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate: b.p. 53-58° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.0 (septet J=6 Hz, 1H, -C<u>H</u>(CH_3)$_2$, 4.0 (q J=7 Hz, 1H, C<u>H</u>-OH), 3.1 (q J=8 Hz, 1H, C<u>H</u>-CO_2R), 1.7-2.4 (m, 5H), 1.4-1.6 (m, 1H, -OH), 1.25 (d J=6 Hz., 6H, -CH(C<u>H</u>$_3$)$_2$), 0.9 (d J=7 Hz, 3H CH_3); ^{13}C NMR ($CHCl_3$): 80.11, 68.27, 47.04, 45.94, 33.36, 24.57, 22.76, 14.29; IR ($CHCl_3$ 0.2mm): 1110 (C-O), 1730 (C=O), 3450 (OH) cm^{-1}; High resolution Mass Spectrum: Calculated for $C_{10}H_{18}O_3$ 186.1256 g, found 186.1271 g.

<u>Isopropyl</u> <u>3-oxocyclopentanecarboxylate</u> (<u>122</u>). A 50 mL round-bottomed flask was equipped with a condenser and drying tube. The flask was charged with 3-oxocyclopentanecarboxylic acid[44], 0.416 g, (3.24 mmol), isopropanol (30 mL), and <u>p</u>-toluenesulfonic acid, 0.06 g, (0.32 mmol). The mixture was heated at reflux for 24h. The solution was then allowed to cool and potassium carbonate was added. After adding water (30 mL) the solution was extracted with ether (3 x 15 mL). The combined extracts were washed with water (2 x 25 mL), saturated NaCl solution, and dried over $MgSO_4$. Sequential removal of the drying agent and the solvent followed by distillation, (bulb-to-bulb), furnished 0.55 g of a clear oil (91% based on acid): b.p. 45-50° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.1 (pentet J=6.4 Hz, 1H, -C<u>H</u>(CH_3)$_2$), 2.8-3.4 (m, 1H),

1.9-2.6 (m, 6H), 1.3 (d J=6.4 Hz., 6H, $-CH(C\underline{H}_3)_2$); ^{13}C NMR ($CHCl_3$): 215.89, 173.38, 67.90, 40.79, 40.69, 30.90, 26.18, 21.36; IR (liquid film): 1110 (C-O), 1750 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 63.51%, found 63.15%; Hydrogen: calculated 8.29%, found 8.50%.

Isopropyl 2,2-Dimethyl-3-oxocyclopentanecarboxylate (134). Using a procedure identical to the preparation of isopropyl 3-oxocyclopentanecarboxylate (122), 1.00 g, (6.4 mmol) of 2,2-dimethyl-3-oxocyclopentanecarboxylic acid[48] was converted to the corresponding ester (134). The crude product was vacuum distilled (bulb-to-bulb) to furnish 0.89 g of a clear oil (70% based on acid): b.p. 62-64° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.1 (pentet J=6.4 Hz, 1H, $-C\underline{H}(CH_3)_2$), 2.0-3.0 (m, 5H), 1.0-1.5 (m, 12H); ^{13}C NMR ($CHCl_3$): 220.12, 172.05, 67.92, 52.24, 47.95, 35.20, 23.86, 21.92, 21.17, 19.38; IR (liquid film): 1080 (C-O), 1725 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 66.64%, found 66.27%; Hydrogen: calculated 9.15%, found 9.11%.

Isopropyl 2-Methyl-3-oxocyclopentanecarboxylate (128). Using a procedure identical to the preparation of isopropyl 3-oxocyclopentanecarboxylate (122), 1.50 g (10.55 mmol) of 2-methyl-3-oxocyclopentanecarboxylic acid[46] was converted to the corresponding ester (128). The crude product was vacuum distilled, (bulb-to-bulb), to furnish 1.74 g of a clear oil (89% based on acid): b.p.

44-50° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.1 (pentet J=6.4 Hz, 1H, -C<u>H</u>(CH_3)$_2$), 1.8-2.9 (m, 6H), 1.0-1.4 (m, 9H); ^{13}C NMR ($CHCl_3$): 217.56, 173.17, 68.10, 49.15, 47.57, 36.70, 24.28, 21.72, 13.04; IR (liquid film): 1070 (C-O), 1725 (C=O) cm^{-1}. C, H analysis: Carbon: calculated 65.19%, found 64.88%; Hydrogen: calculated 8.75%, found 8.69%.

<u>Reduction of isopropyl 3-oxocyclopentanecarboxylate (122) to form isopropyl 3-hydroxycyclopentanecarboxylate (113)</u>. A 25 mL round-bottomed flask was equipped with a drying tube. The flask was charged with isopropyl 3-oxocyclopentanecarboxylate (<u>122</u>) 0.25 g, (1.47 mmol), isopropanol (15 mL), and sodium borohydride 0.06 g, (1.49 mmol). The mixture was stirred at the ambient temperature for 30 minutes. Aqueous HCl solution (1.2 M, 20 mL) was added and the mixture extracted with ether (3 x 15 mL). The combined extracts were washed with aqueous $NaHCO_3$ solution (1 x 20 mL), water (2 x 15 mL), saturated NaCl solution, and dried over $MgSO_4$. Sequential removal of the drying agent and the solvent followed by distillation, (bulb-to-bulb), furnished 0.19 g of a clear oil (76% based on ketone): b.p. 50-55° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.0 pentet J=6.2Hz, 1H, -C<u>H</u>(CH_3)$_2$), 4.3-4.5 (m, 1H, -C<u>H</u>-OH), 3.0 (m, 1H, -C<u>H</u>-CO_2R), 1.5-2.2 (m, 7H), 1.25 (d J=6.2 Hz, 6H, CH(C<u>H</u>$_3$)$_2$.); ^{13}C NMR ($CDCl_3$): 175.93, 73.5, 68.1, 67.4 42.2, 41.8, 39.1 38.6, 35.6, 34.9, 27.7, 27.3, 21.7; IR (liquid film): 1070 (C-O), 1710 (C=O) cm^{-1}.

Reduction of isopropyl 2,2-Dimethyl-3-oxocyclopentanecarboxylate (134) to form isopropyl 2,2-dimethyl-3-hydroxycyclopentanecarboxylate (115). Using a procedure identical to the reduction of isopropyl 3-oxocyclopentanecarboxylate (122), .150 g (0.76 mmol) of isopropyl 2,2-dimethyl-3-oxocyclopentanecarboxylate was reduced to the corresponding alcohol (115). The crude product was vacuum distilled, (bulb-to-bulb), furnishing 0.13 g of a clear oil (88% based on ketone): b.p. 55-60° C at 0.2 mm;

Reduction of isopropyl 2-methyl-3-oxocyclopentane-ycyclopentanecarboxylate (114). Using a procedure identical to the reduction of isopropyl 3-oxocyclopentanecarboxylate (122), 0.150 g, (0.81 mmol) of isopropyl 2-methyl-3-oxocyclopentanecarboxylate was reduced to the corresponding alcohol (114). The crude product was vacuum distilled, (bulb-to-bulb), furnishing 0.12 g of a clear oil (81% based on ketone): b.p. 53-58° C at 0.2 mm; ^{1}H NMR ($CDCl_3$): 5.0 (septet J=6 Hz, 1H, -C$\underline{H}$(CH_3)$_2$), 4.0 (q J=7 Hz, 1H, C$\underline{H}$-OH), 3.1 (q J=8 Hz, 1H, C$\underline{H}$-CO_2R), 1.7-2.4 (m, 5H), 1.4-1.6 (m, 1H, -OH), 1.25 (d J=6 Hz., 6H, -CH(C$\underline{H}_3$)$_2$), 0.9 (d J=7 Hz, 3H CH_3); ^{13}C NMR ($CHCl_3$): 80.11, 68.27, 47.04, !45.94, 33.36, 24.57, 22.76, 14.29; IR ($CHCl_3$ 0.2mm): 1110 (C-O), 1730 (C=O), 3450 (OH) cm^{-1}.

Chromium Trioxide-Pyridine Oxidation of 113. A solution of 0.050 g, (0.029 mmol), of isopropyl 3-hydroxycyclopentanecarboxylate (113) in 3 mL of pyridine was added to 0.087 g, (0.83 mmol), of chromium trioxide in 3 mL of pyridine. The flask was stoppered, the contents mixed thoroughly and allowed to stand at room temperature overnight. The reaction mixture was poured into water and extracted with ether (3 x10 mL). The combined extracts were washed with aqueous $NaHCO_3$ solution (1 x 20 mL), water (2 x 15 mL), saturated NaCl solution, and dried over $MgSO_4$. Sequential removal of the drying agent and the solvent followed by distillation, (bulb-to-bulb), furnished 0.043 g of ketone 122 (87% based on alcohol): b.p. 50-55° C at 0.2 mm. NMR and IR spectra matched those of the known ketone 122. The preparation is described on page 51.

Chromium Trioxide-Pyridine Oxidation of 114. Using a procedure identical to the oxidation of isopropyl 3-hydroxycyclopentanecarboxylate (113), 0.027 g, (0.146 mmol) of isopropyl 2-methyl-3-hydroxycyclopentanecarboxylate was oxidized to the corresponding ketone (114). The crude product was vacuum distilled, (bulb-to-bulb), furnishing 0.023 g of a clear oil (86% based on alcohol): b.p. 55-60° C at 0.2 mm. NMR and IR spectra matched those of the known ketone 128. The preparation is described on page 52.

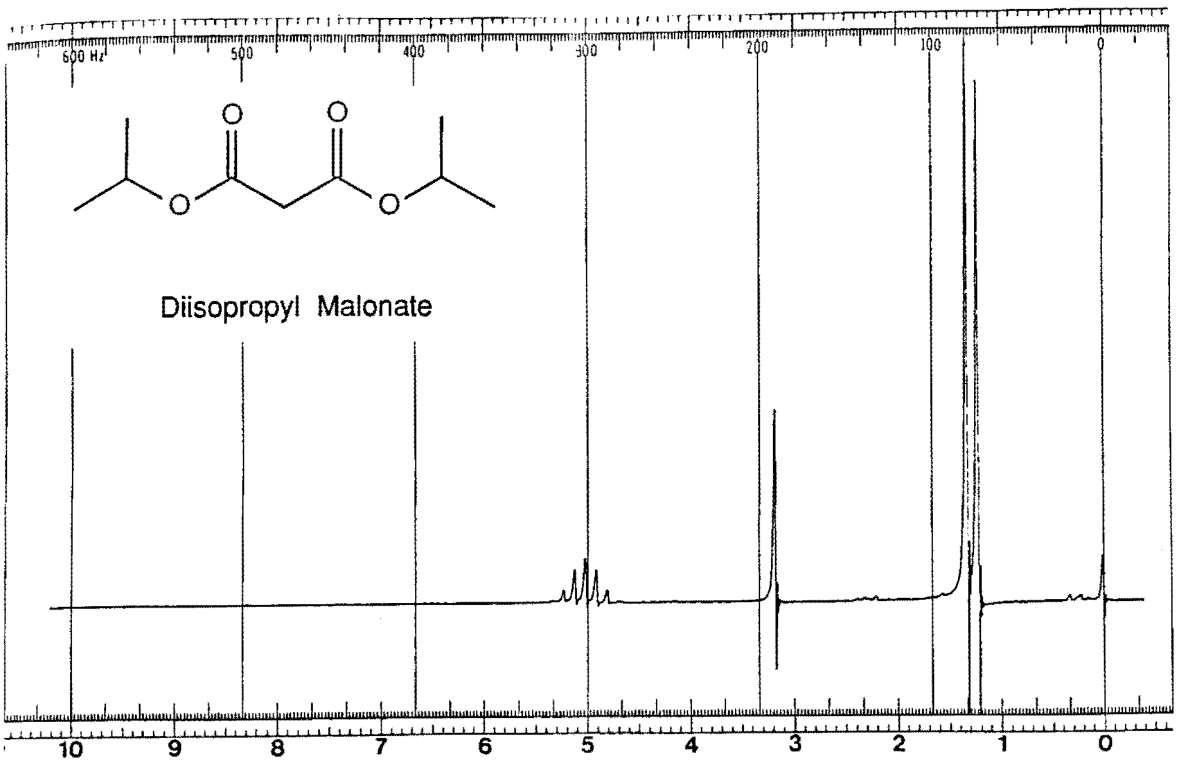
CHAPTER V

SUMMARY

Isopropyl 5,6-epoxyhexanoate (107) and isopropyl 5,6-epoxyheptanoate (108) readily underwent base-induced cyclization to furnish isopropyl 3-hydroxycyclopentanecarboxylate (113) and isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate (114) respectively. This shows the utility of this cyclization reaction for the formation of functionalized cyclopentane ring systems.

However, the disappointing results of isopropyl 5,6-epoxy-6-methylheptanoate (109) which rearranged to form an allylic alcohol (135) show the limitations of the reaction.

SPECTRA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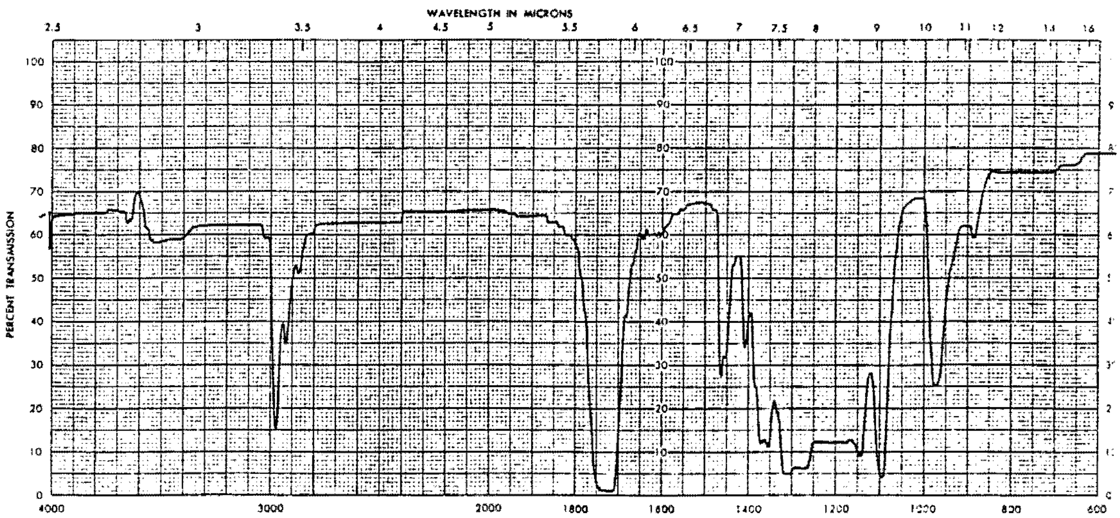
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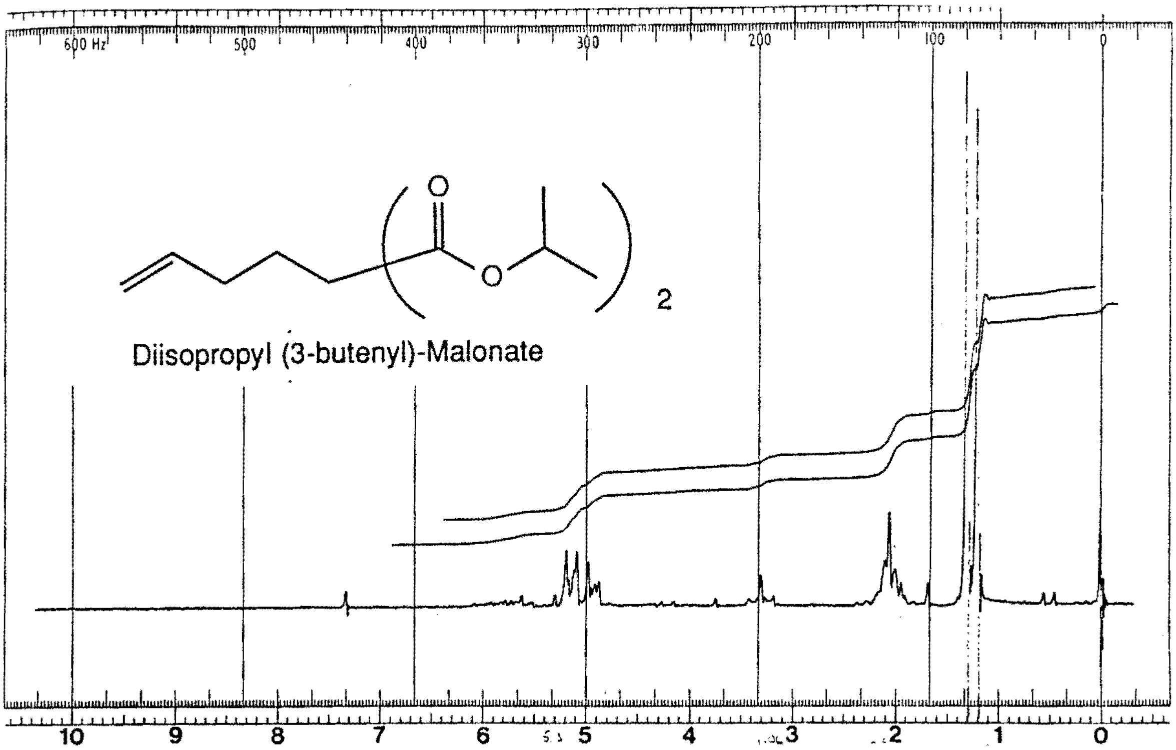
1000
800
600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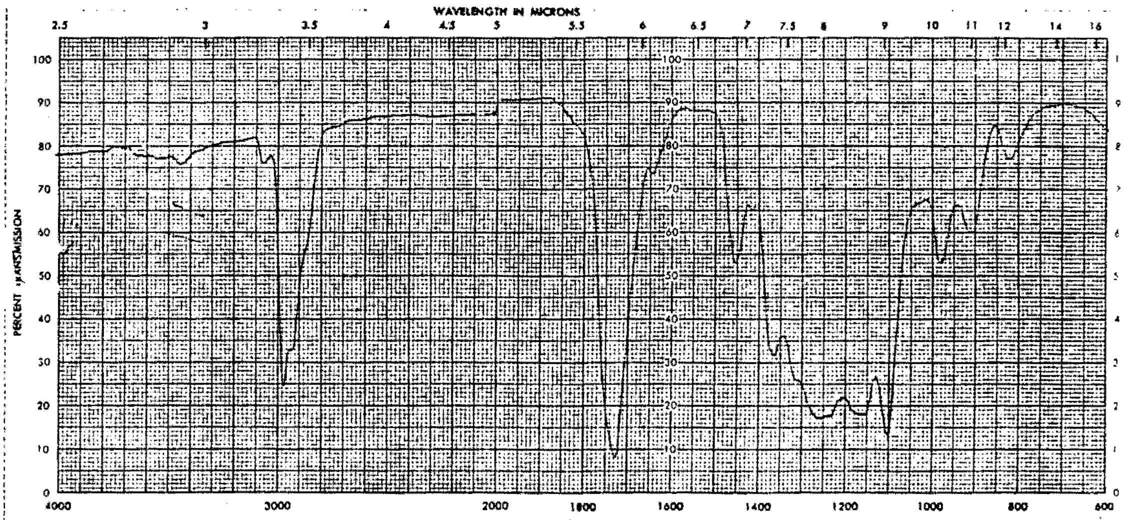
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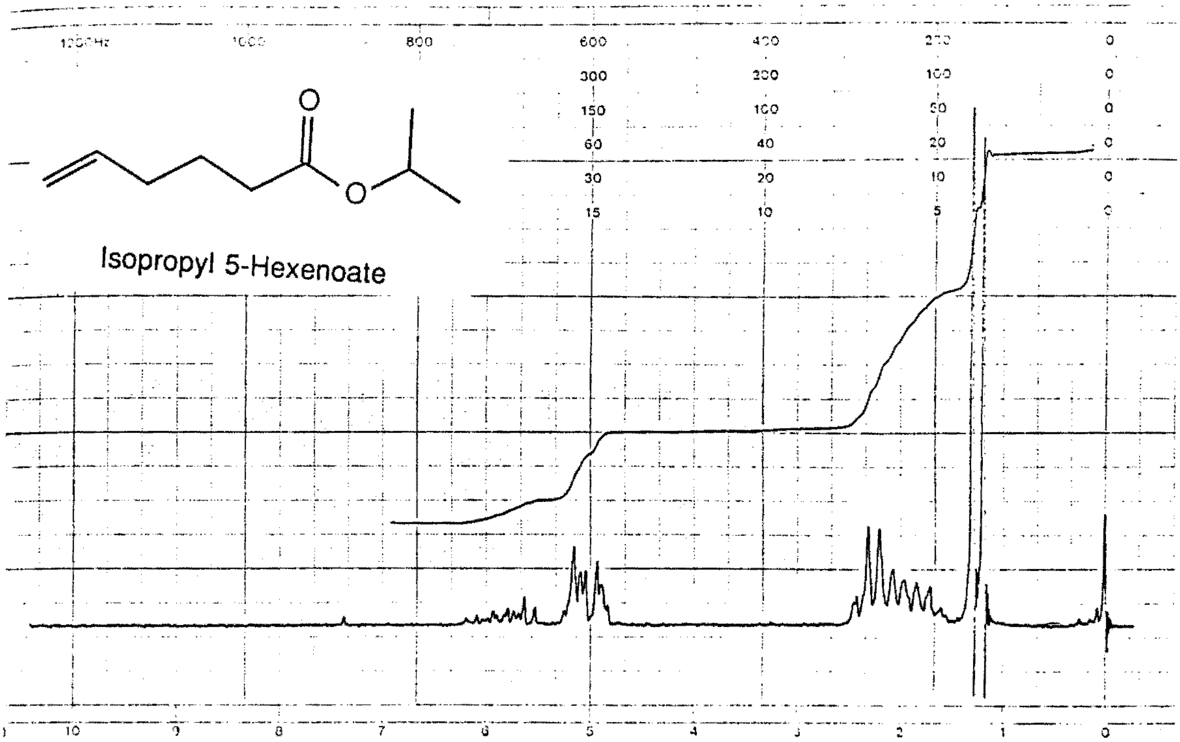

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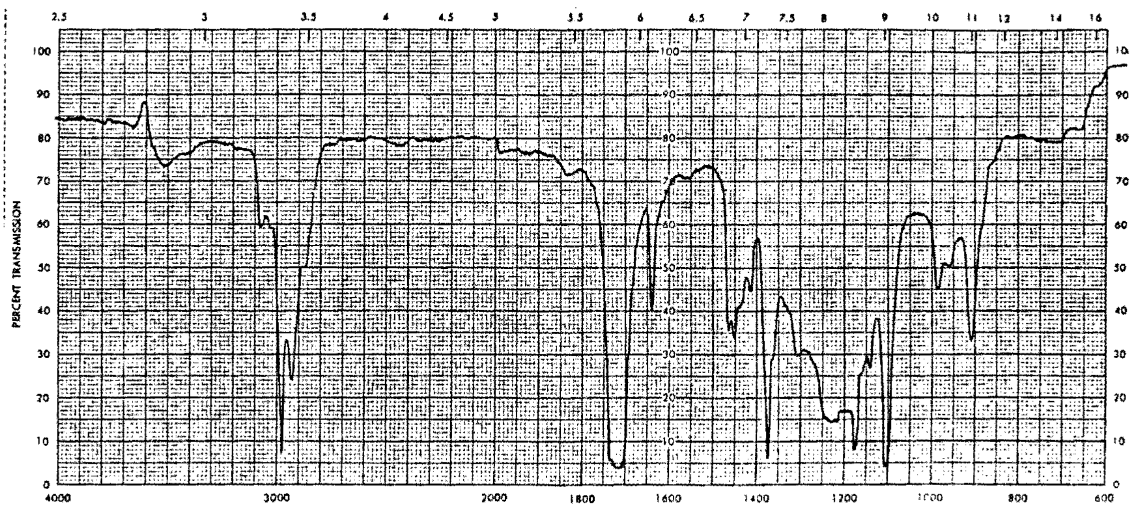
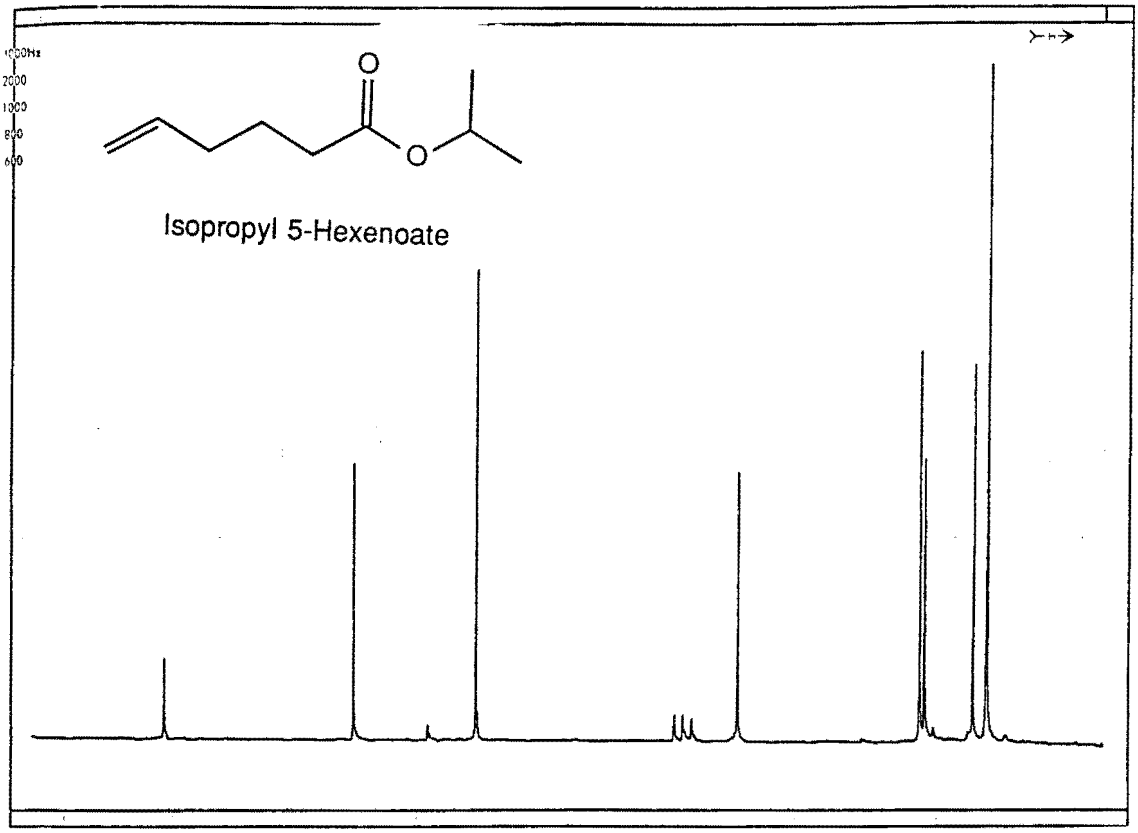
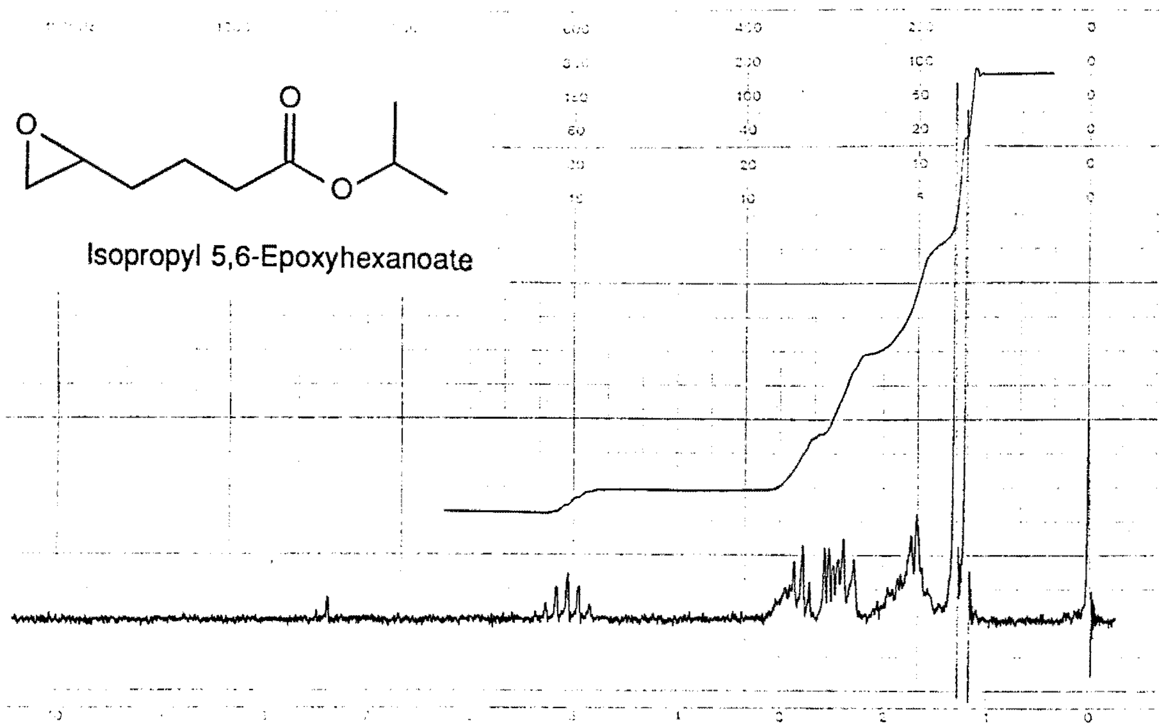
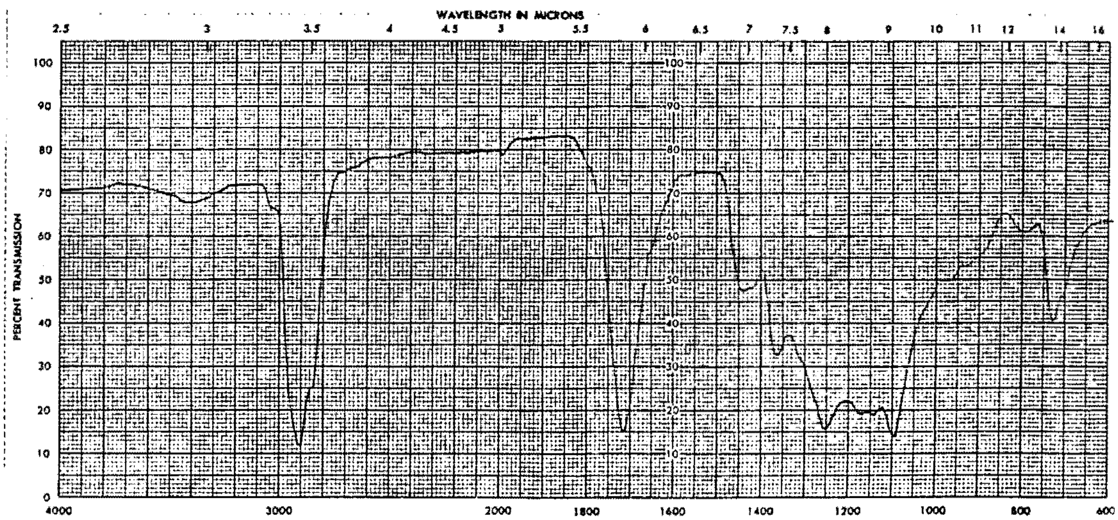
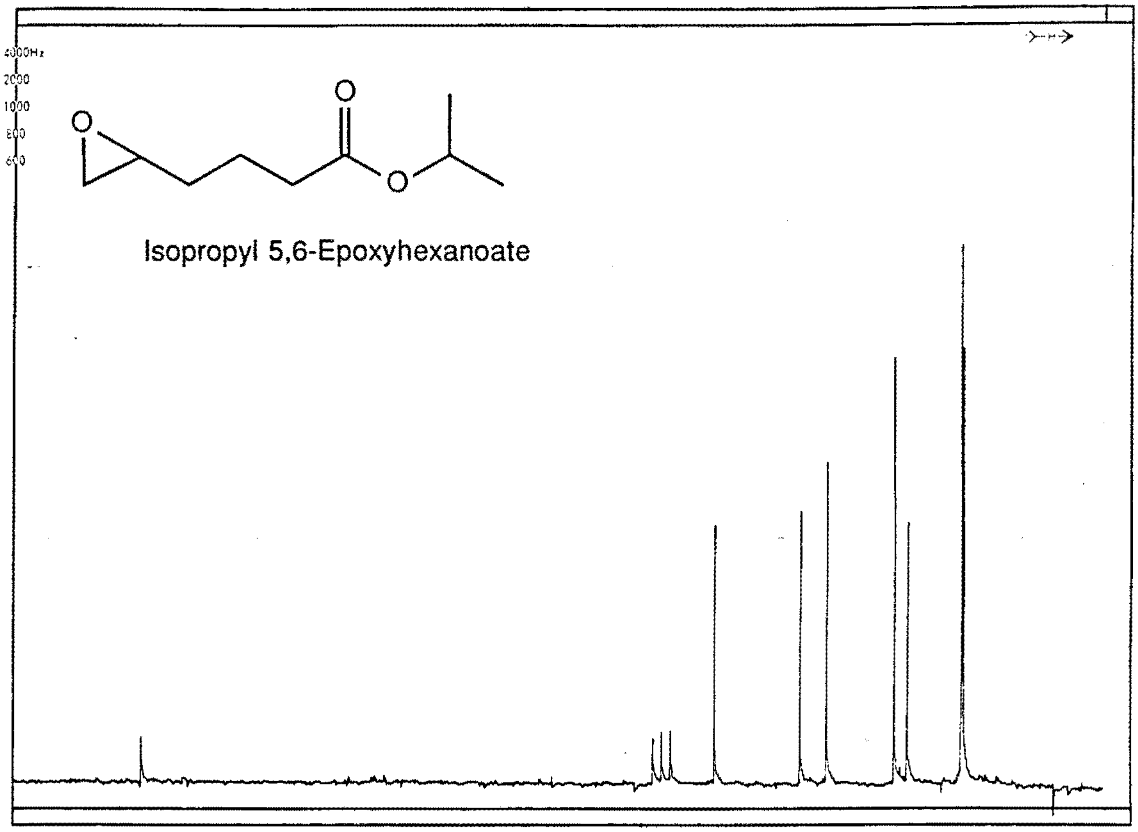



Isopropyl 5-Hexenoate



Isopropyl 5,6-Epoxyhexanoate

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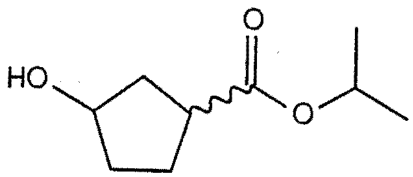
O
O
O
Isopropyl 5,6-Epoxyhexanoate



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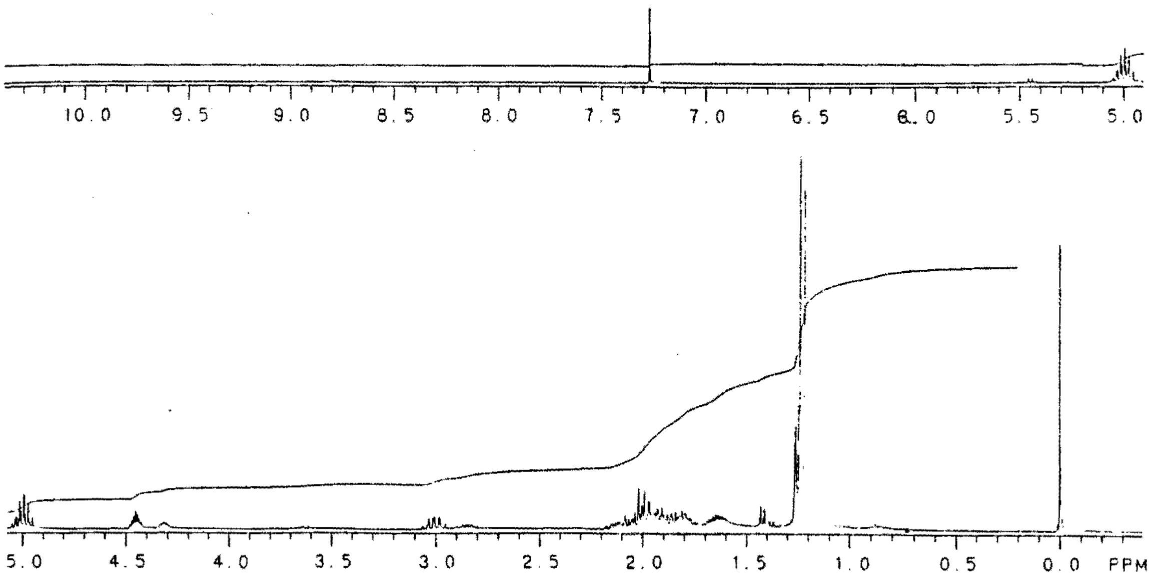
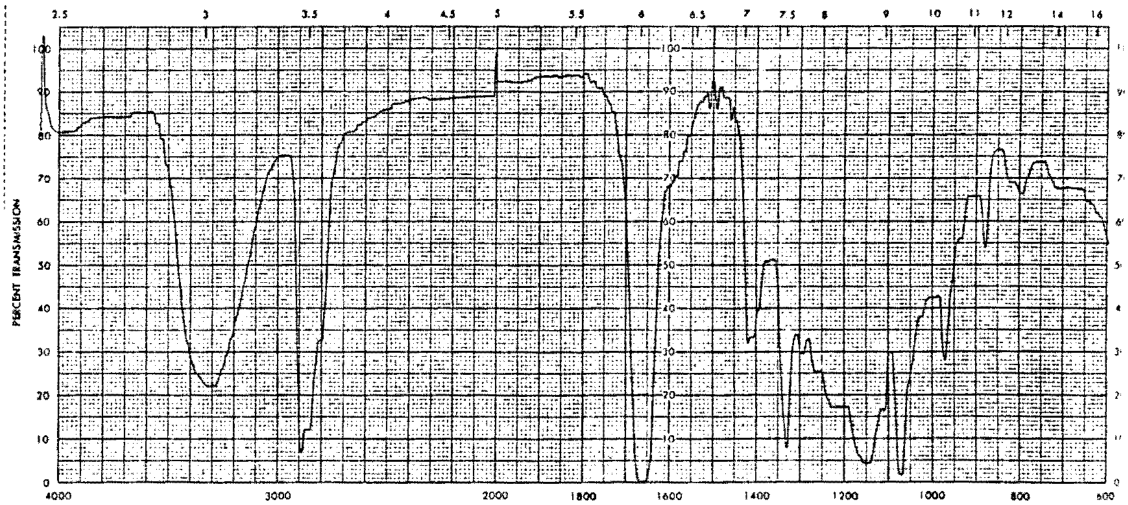
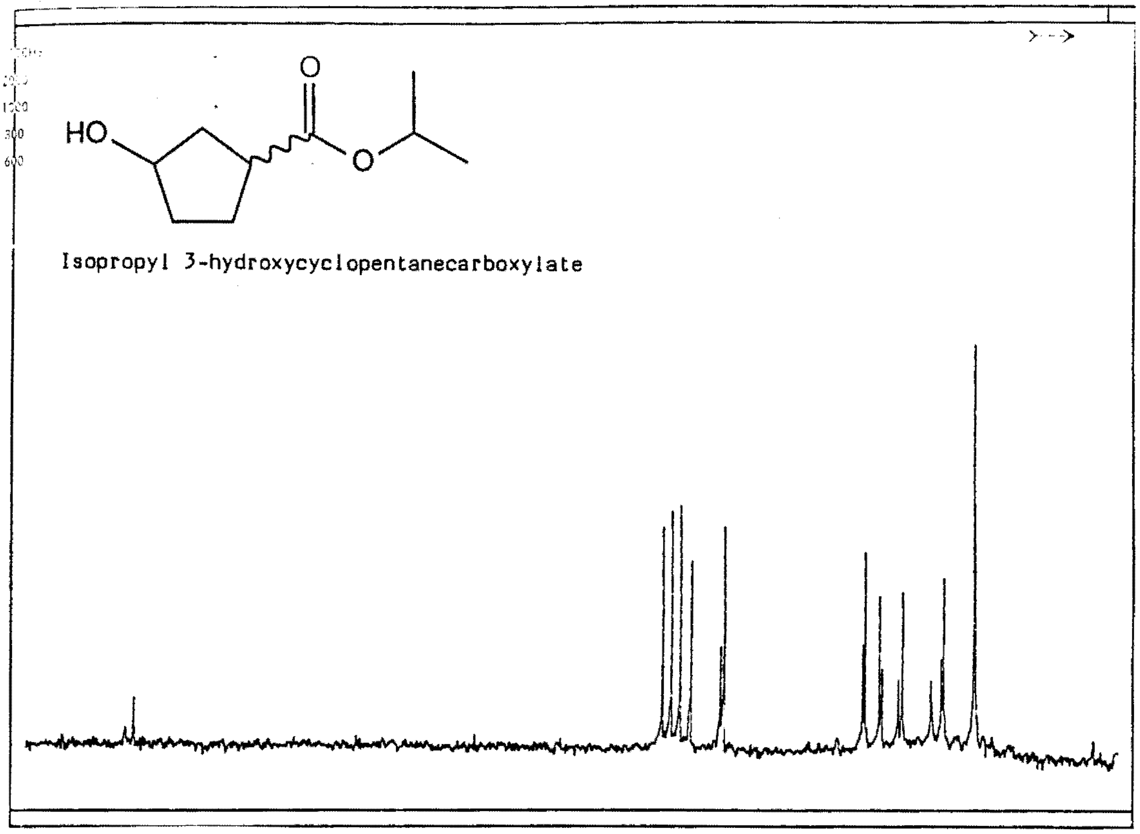
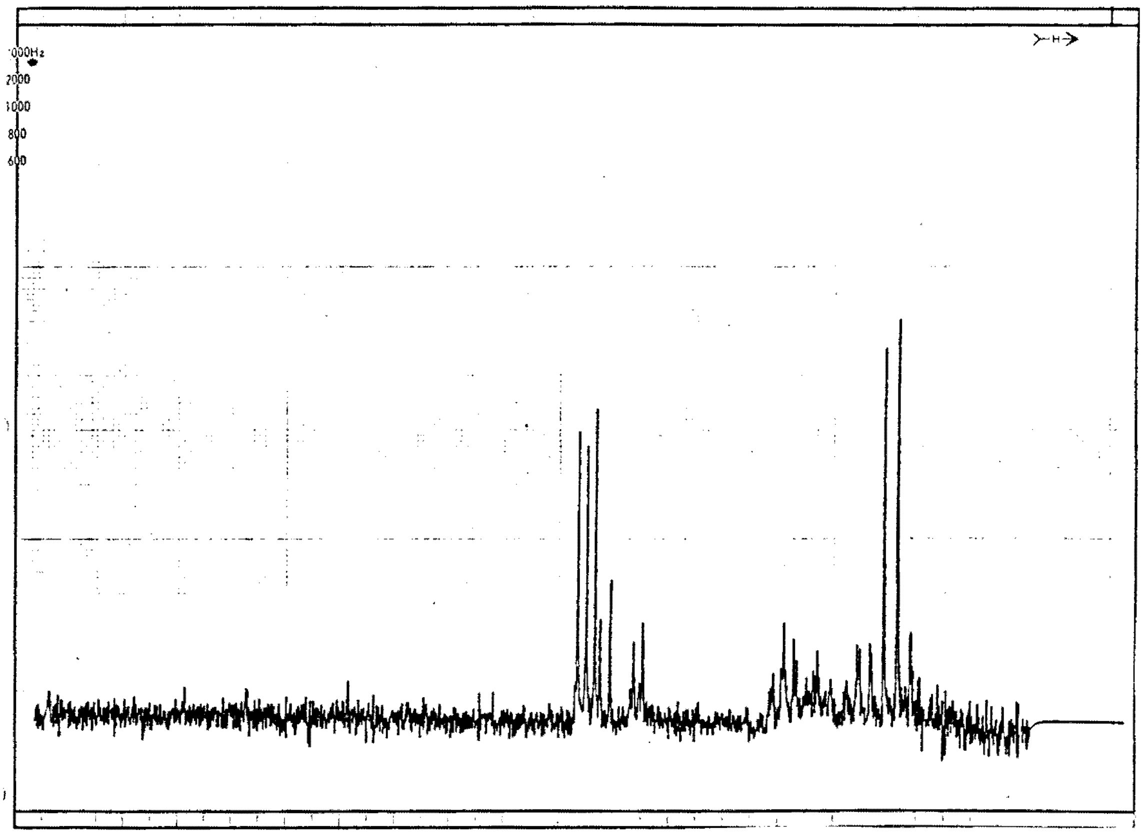
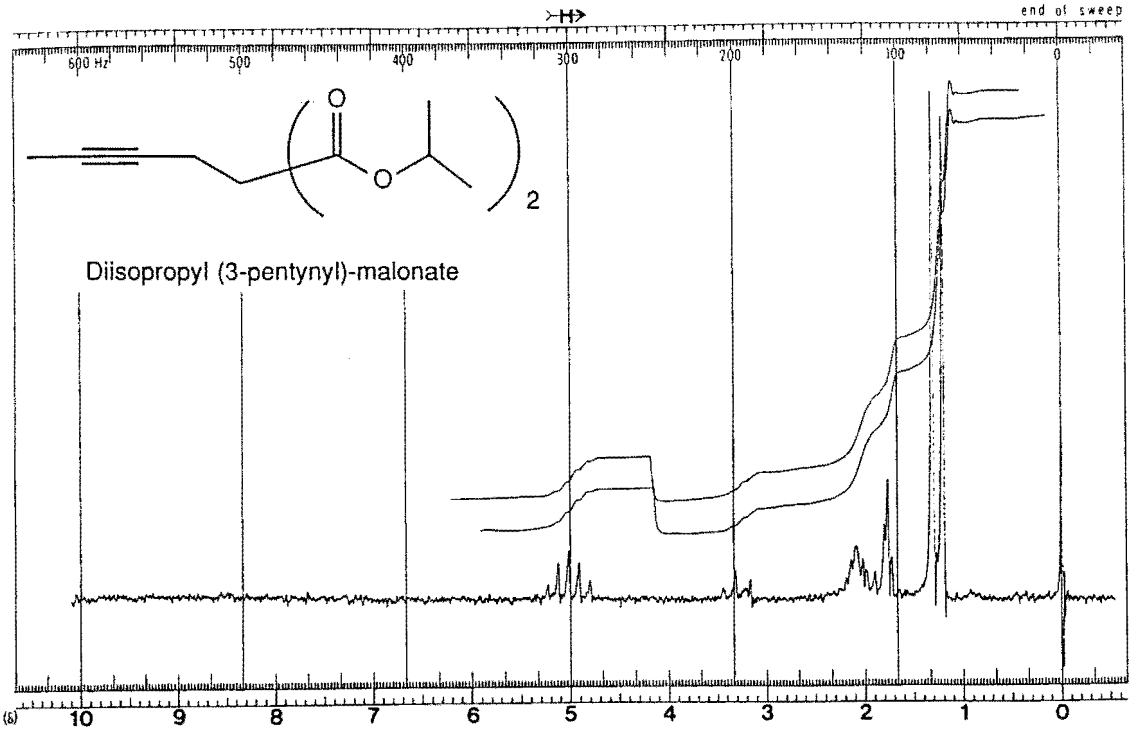






Isopropyl 3-hydroxycyclopentanecarboxylate

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200
100
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(δ)
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9
8
7
6
5
4
3
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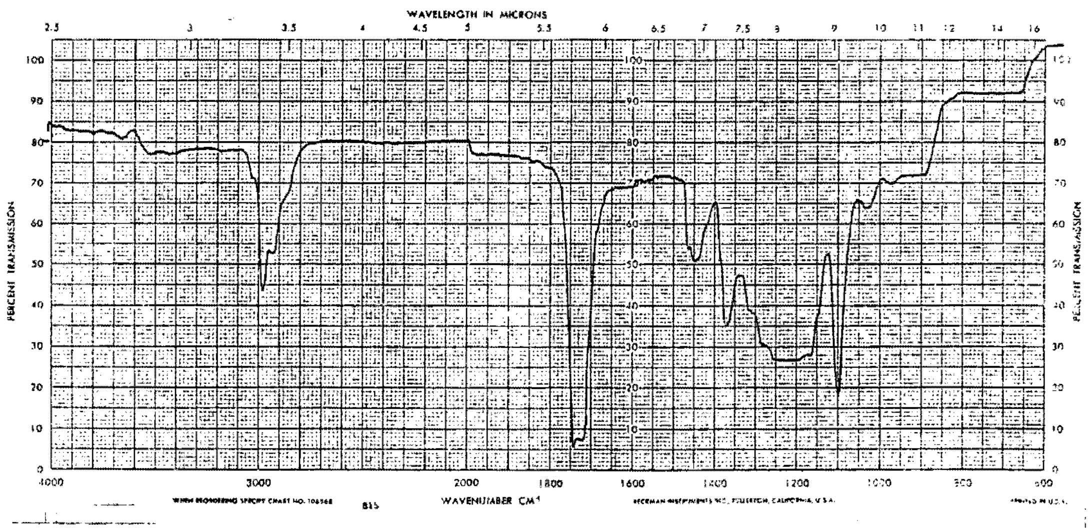
1
0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1800
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1400
1200
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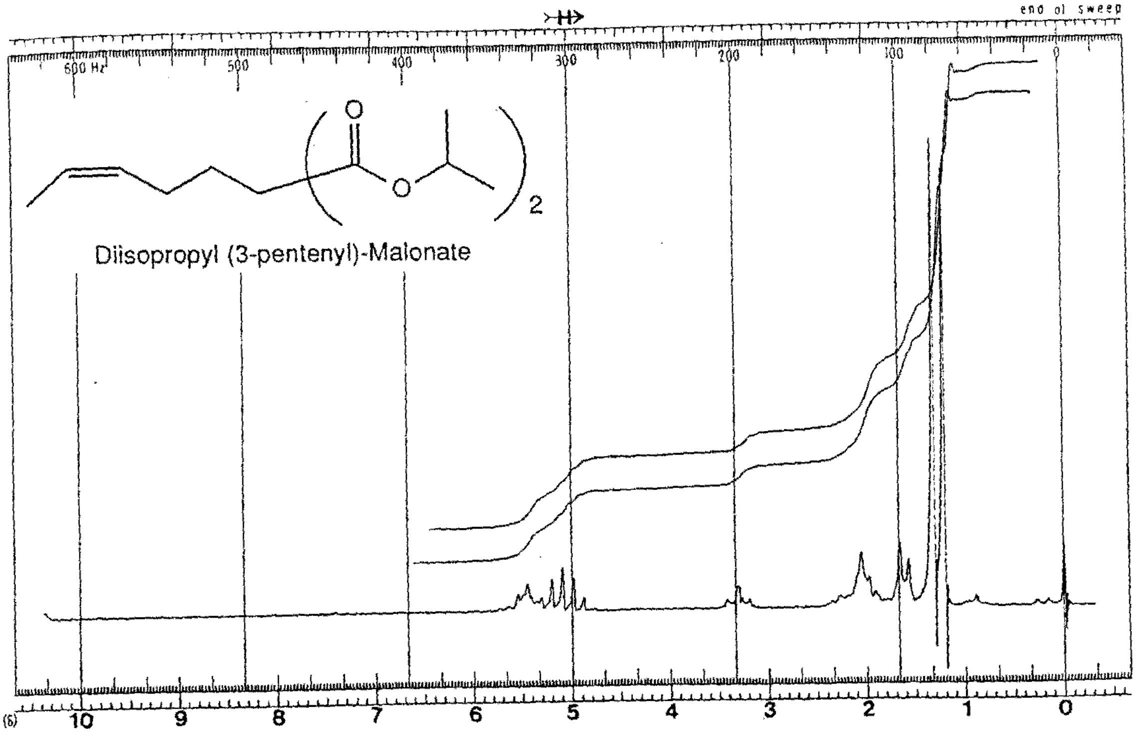

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500
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200
100
0
(δ)
10
9
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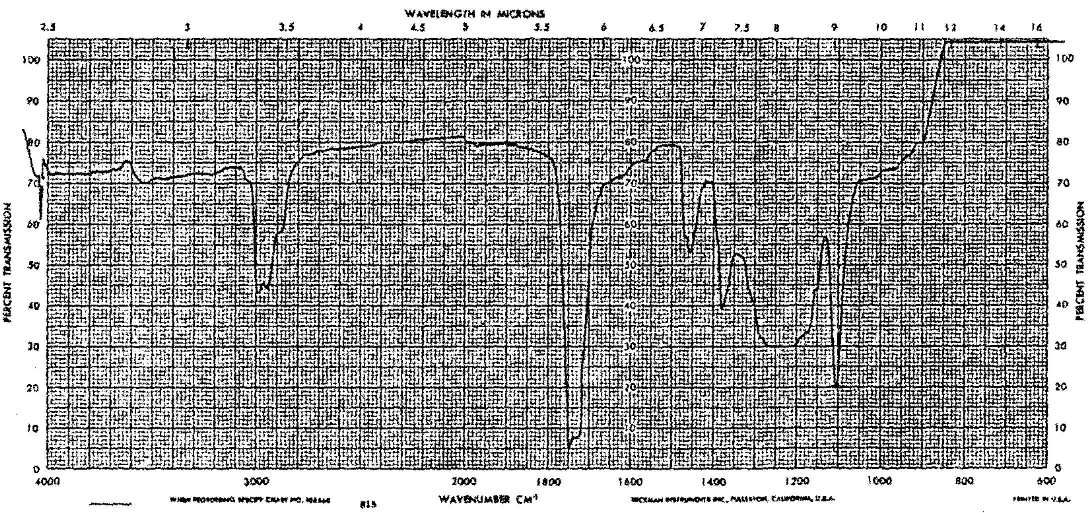

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WAVENUMBER CM⁻¹
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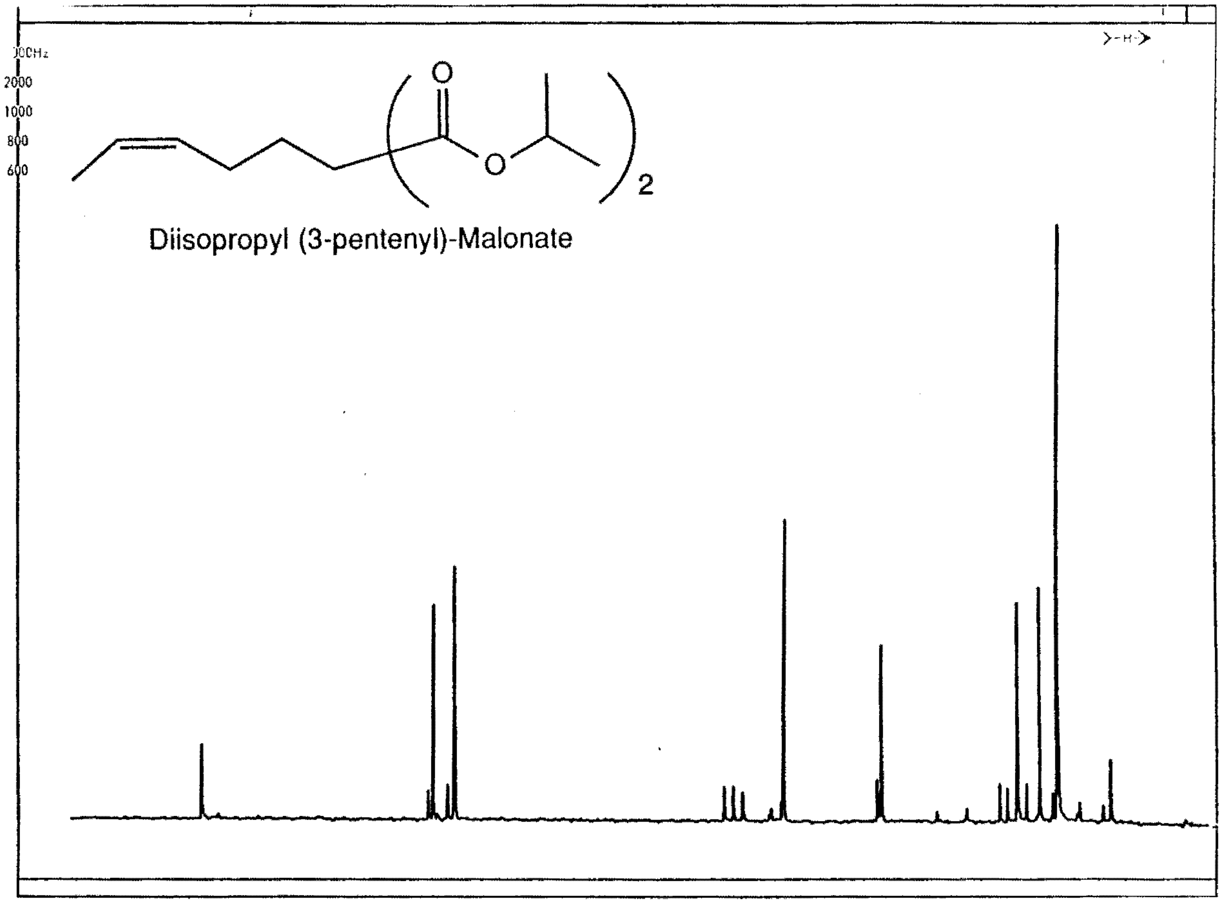
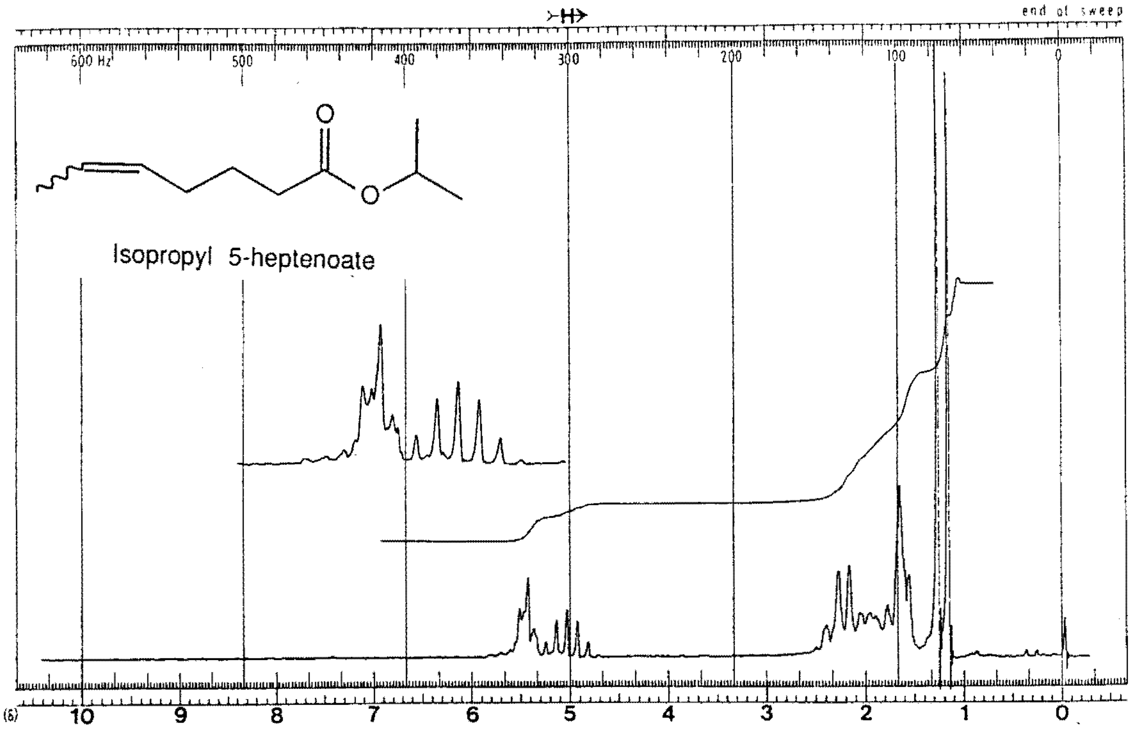


Diisopropyl (3-pentenyl)-Malonate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(δ)
10
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2
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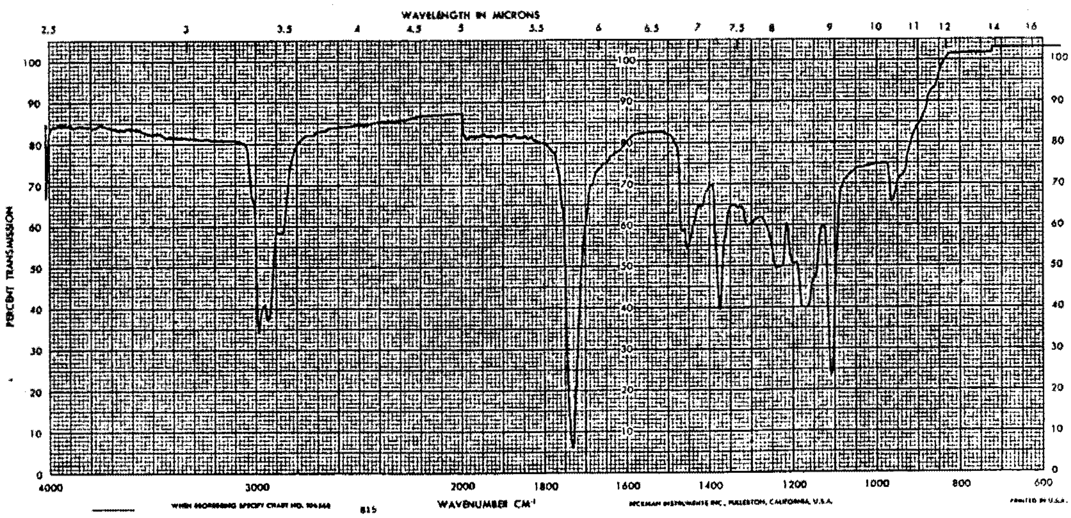
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PERCENT TRANSMISSION
WAVENUMBER CM-1
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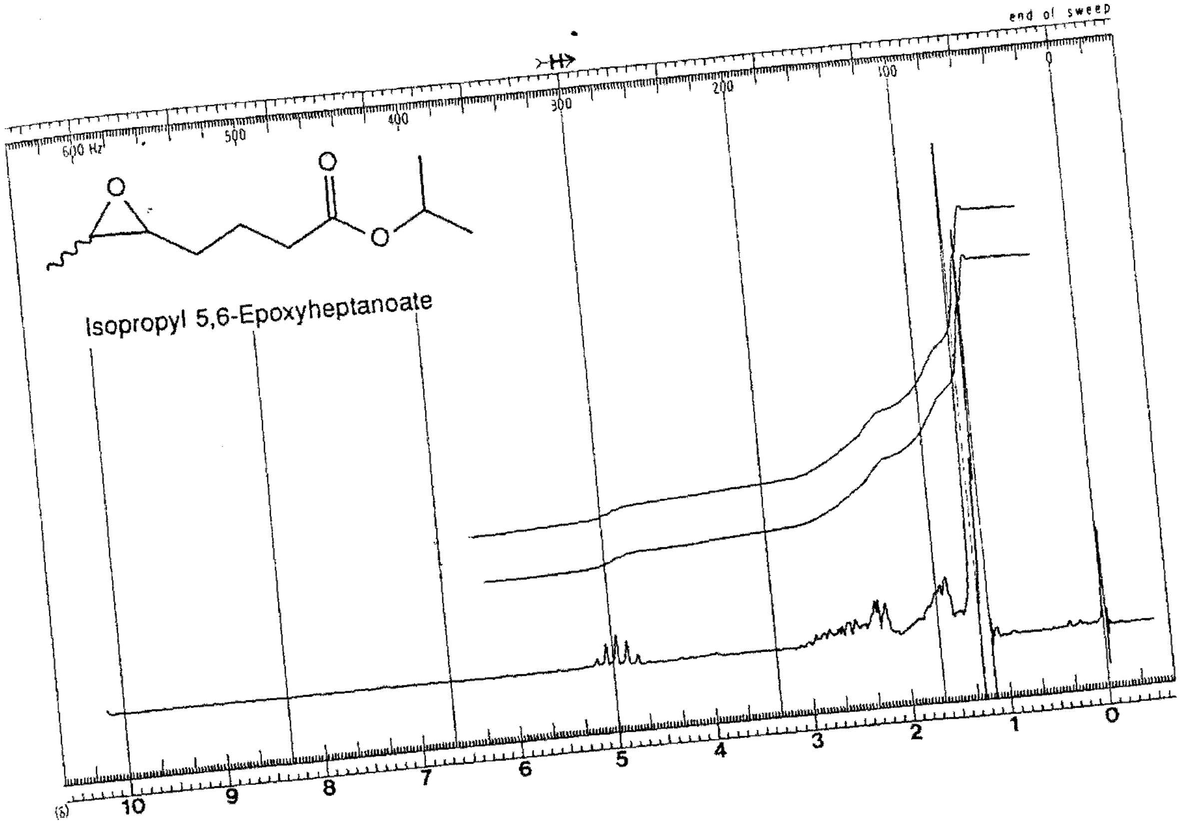
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400
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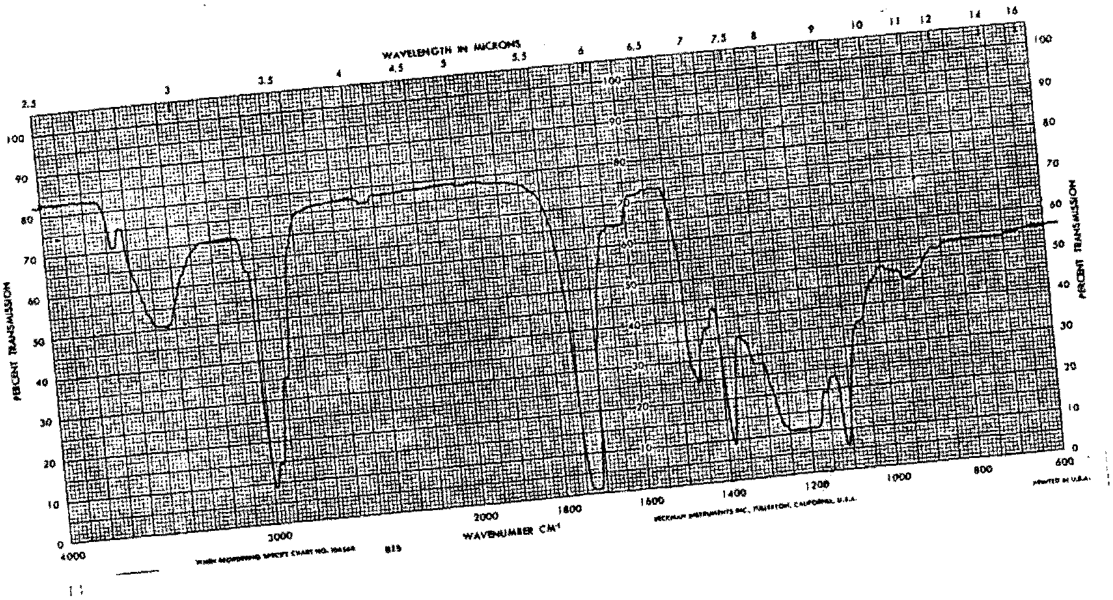
9
8
7
6
5
4
3
2
1
0
(δ)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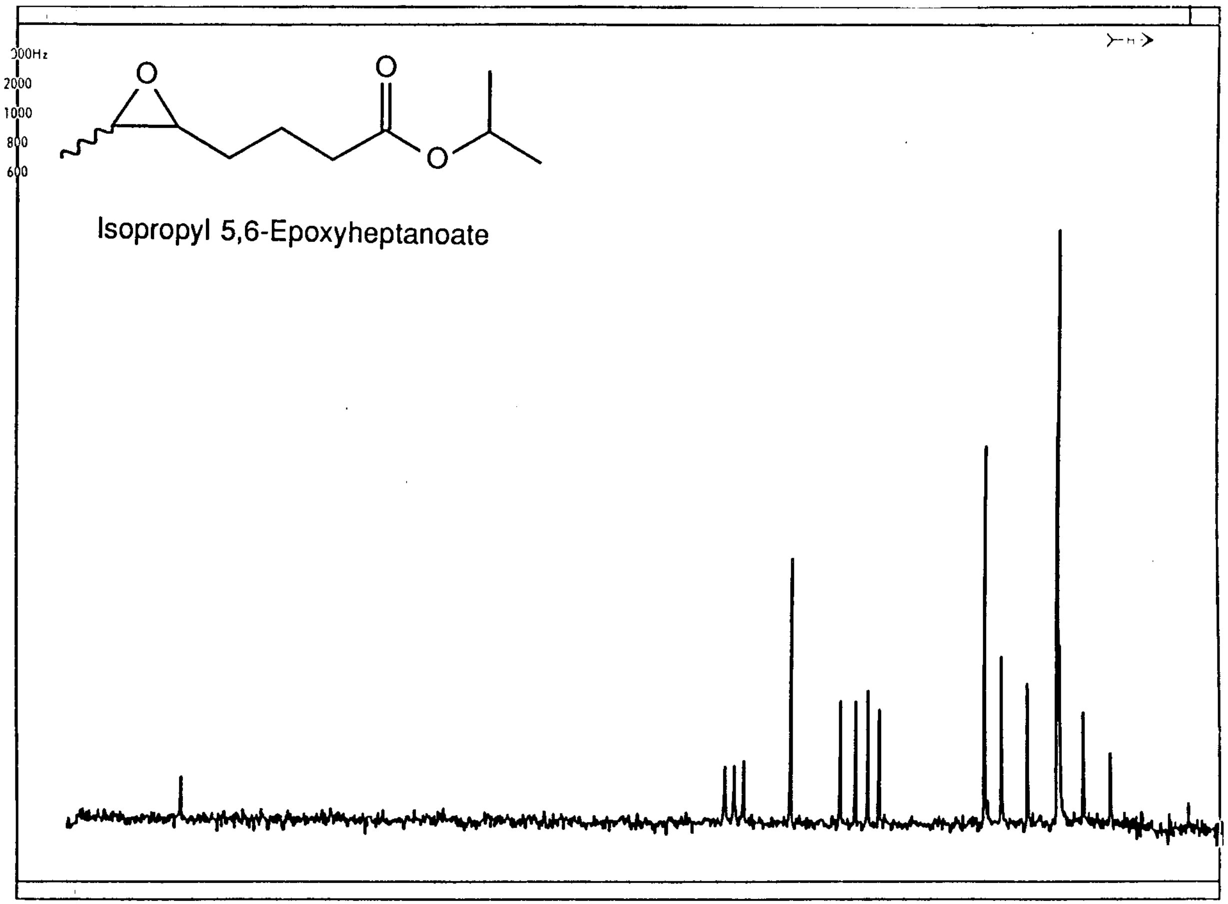
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹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1000
800
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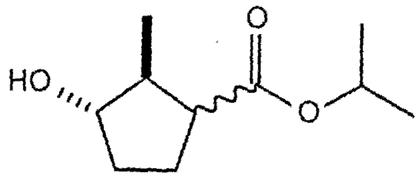
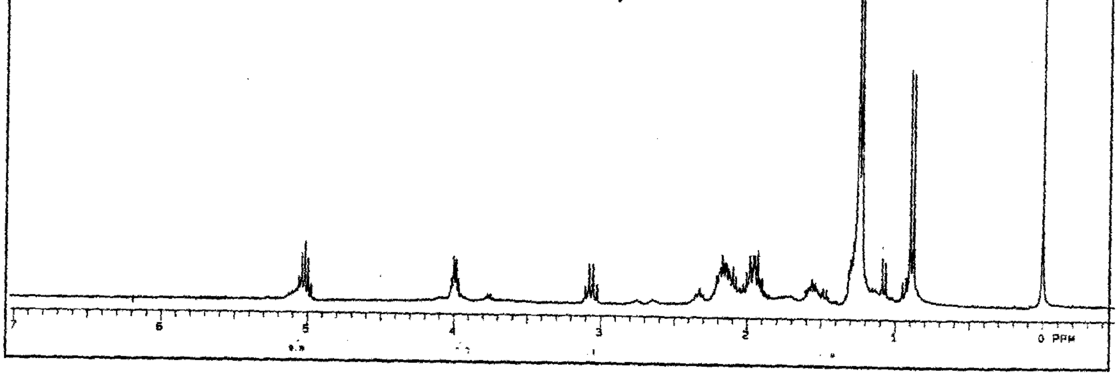
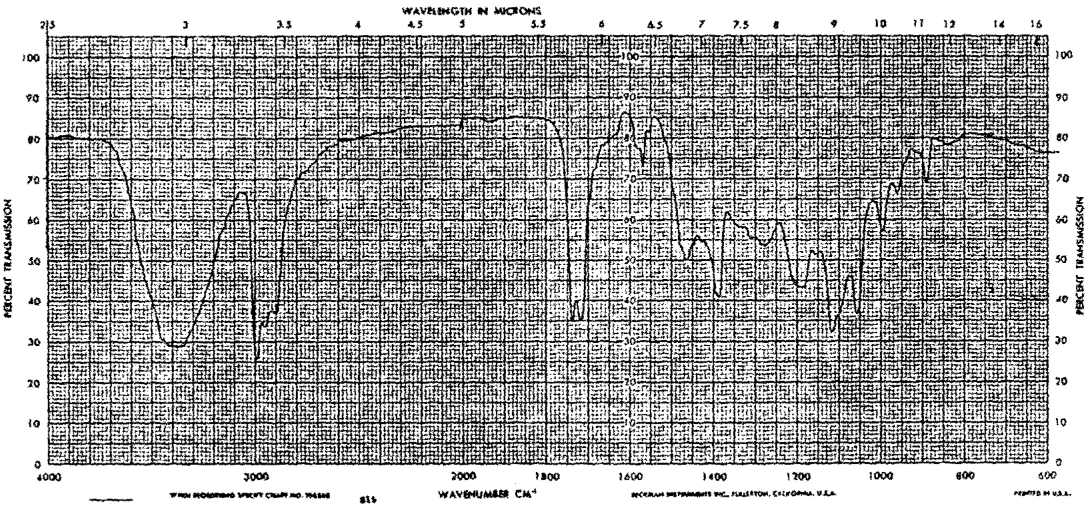
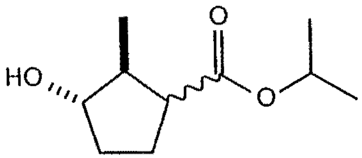


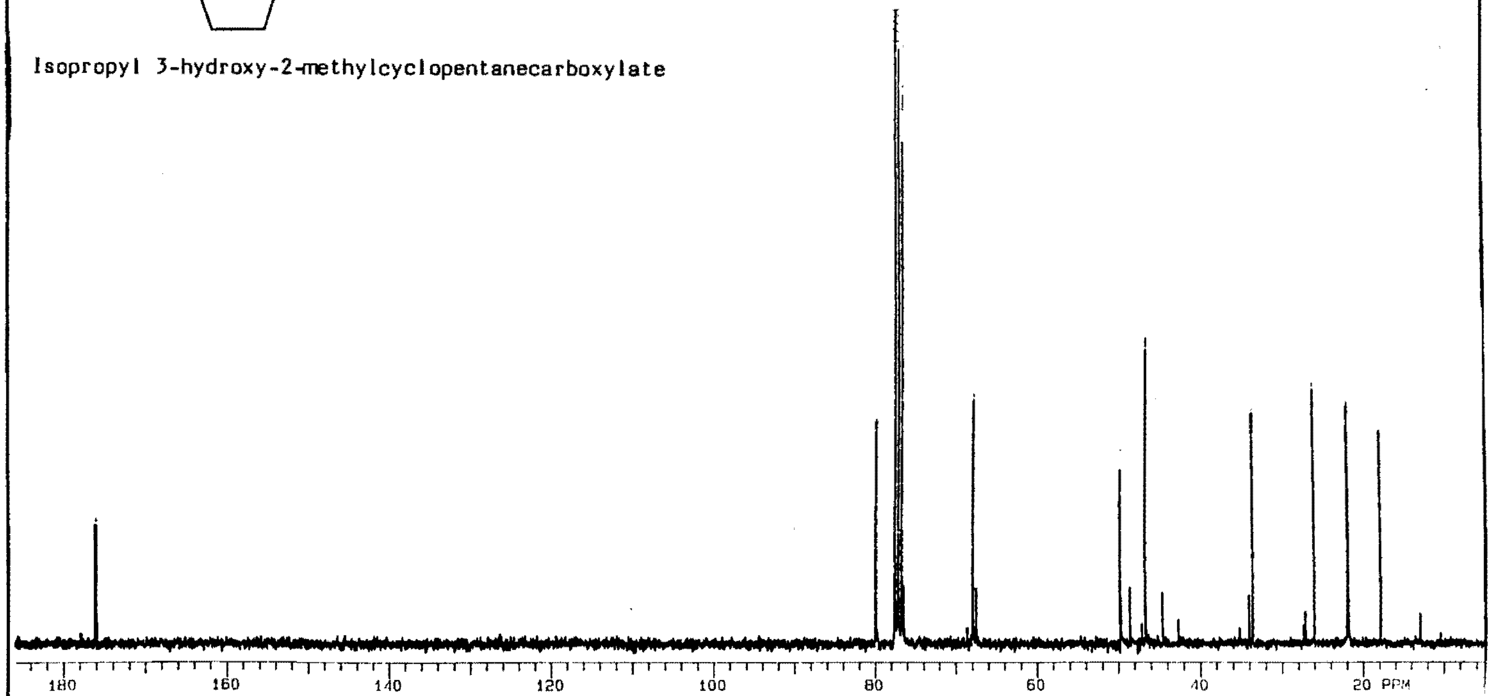
Isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate

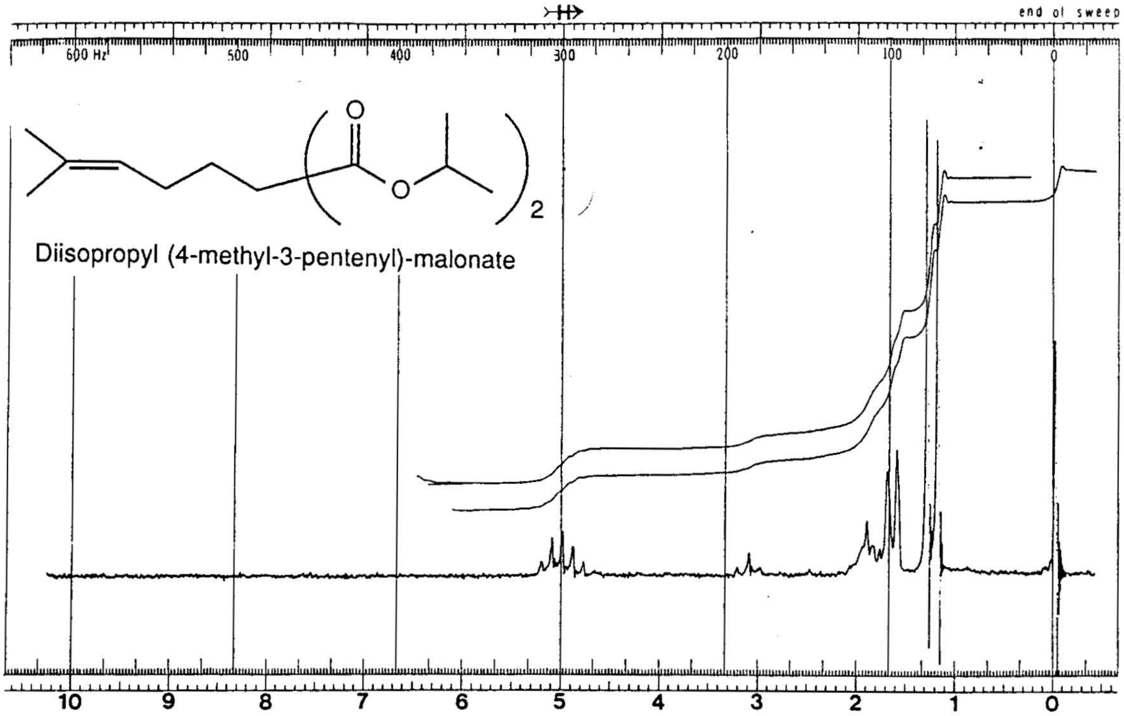






Isopropyl 3-hydroxy-2-methylcyclopentanecarboxylate

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600 Hz
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10
9
8
7
6
5
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3
2
1
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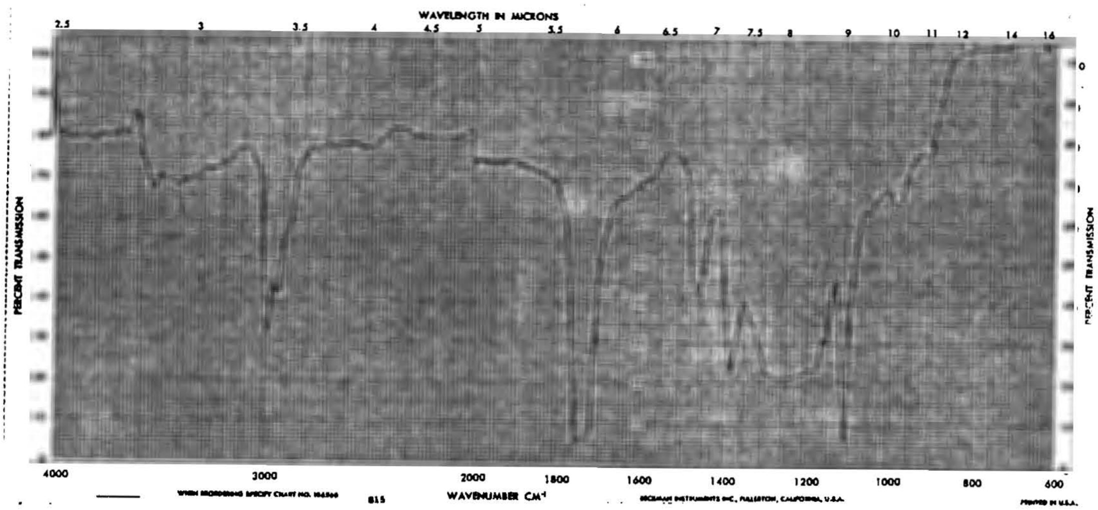
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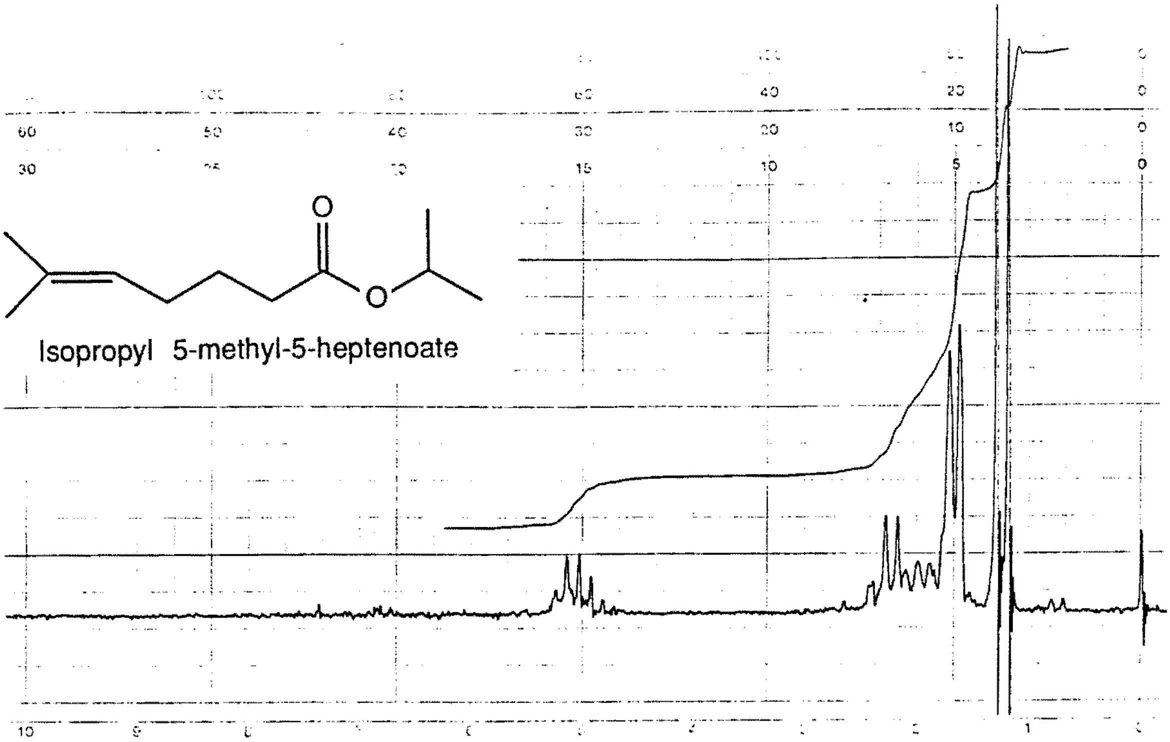
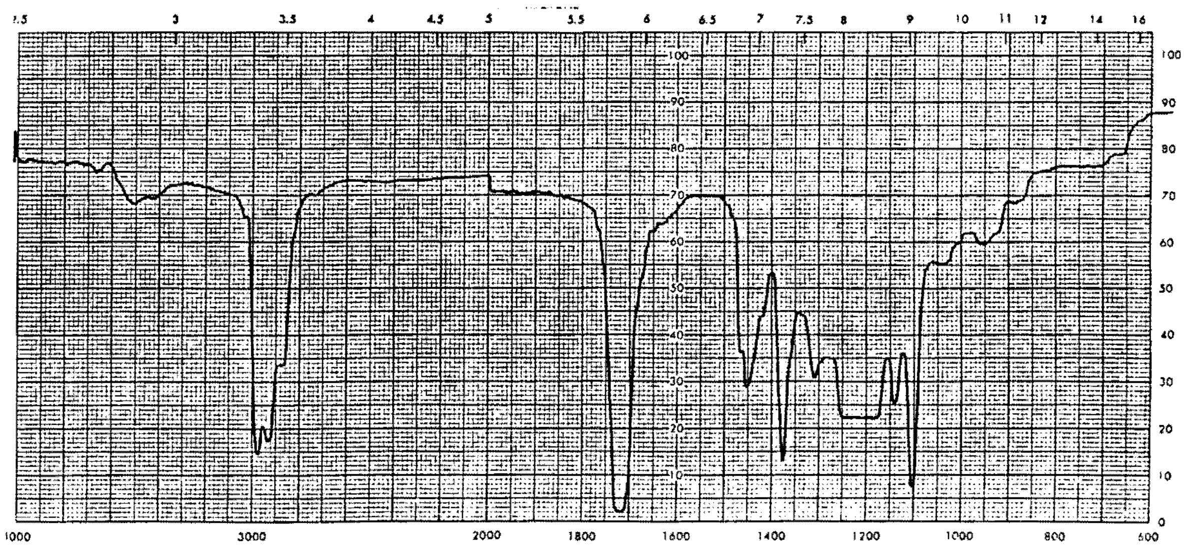
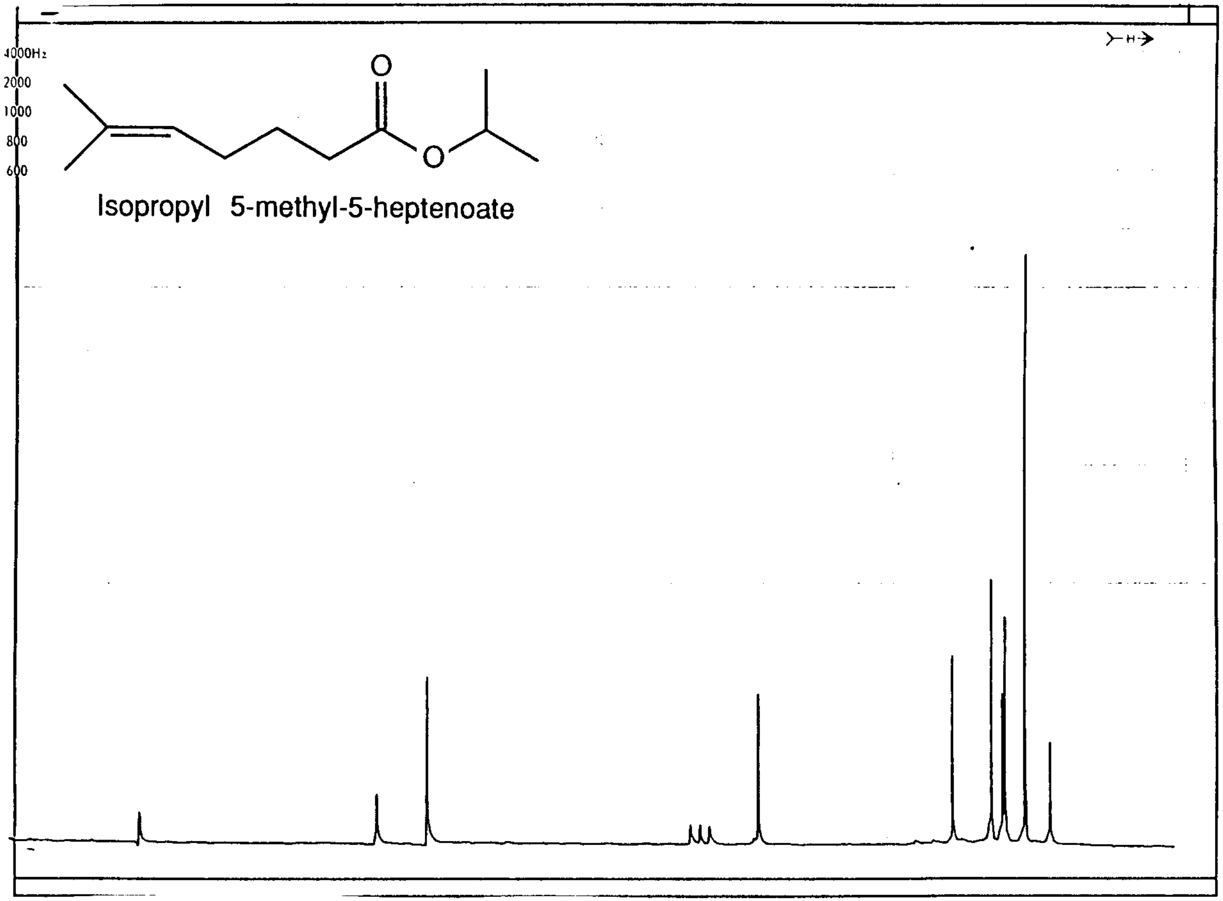
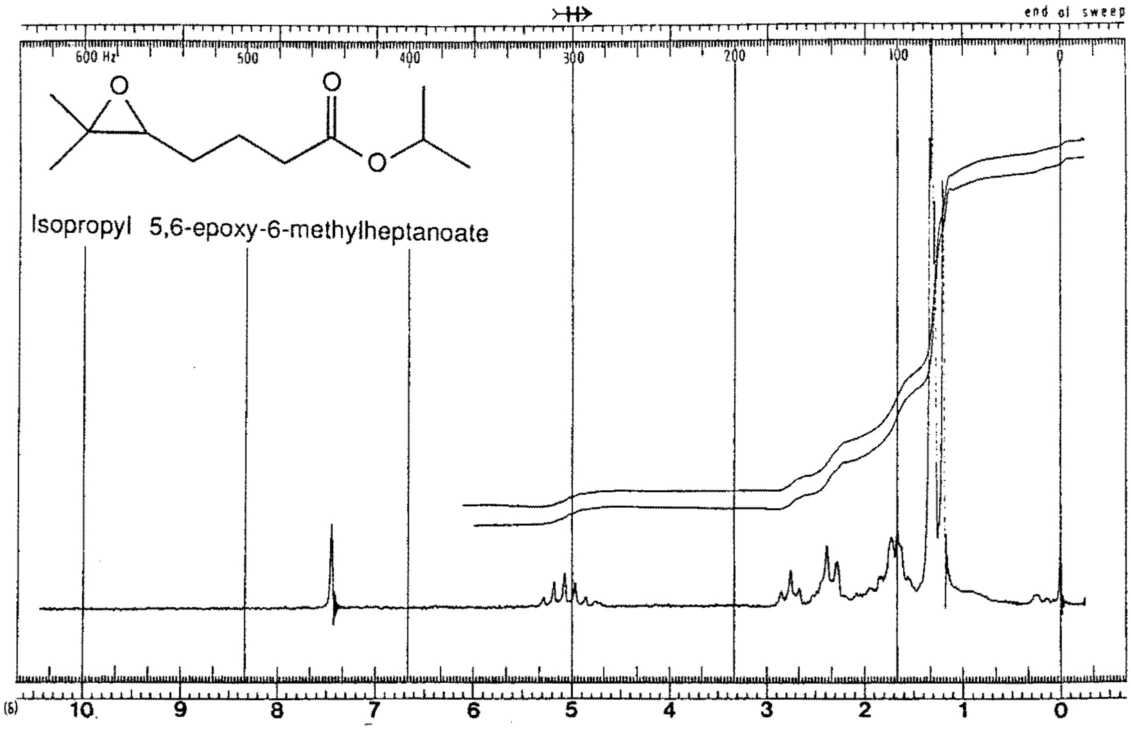
800
600
WAVENUMBER CM⁻¹


Isopropyl 5-methyl-5-heptenoate





Isopropyl 5-methyl-5-heptenoate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600 Hz
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(δ)
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8
7
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5
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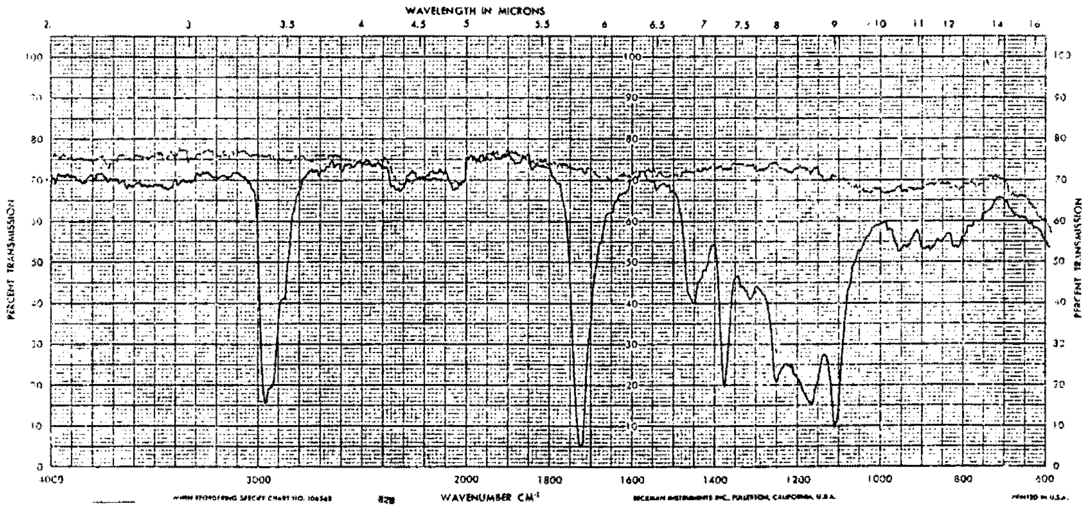
3
2
1
0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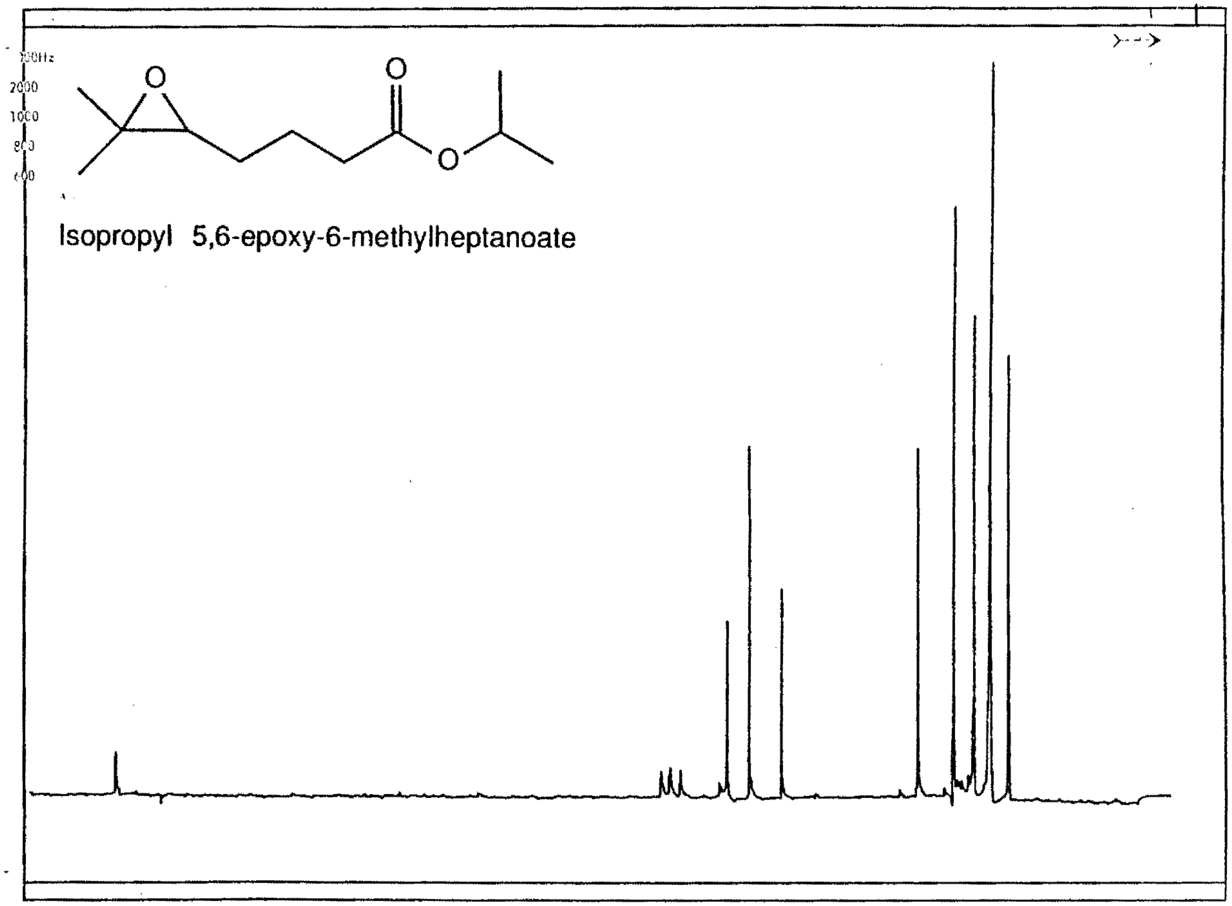
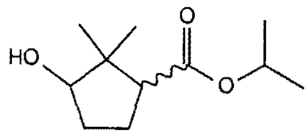


Isopropyl 5,6-epoxy-6-methylheptanoate



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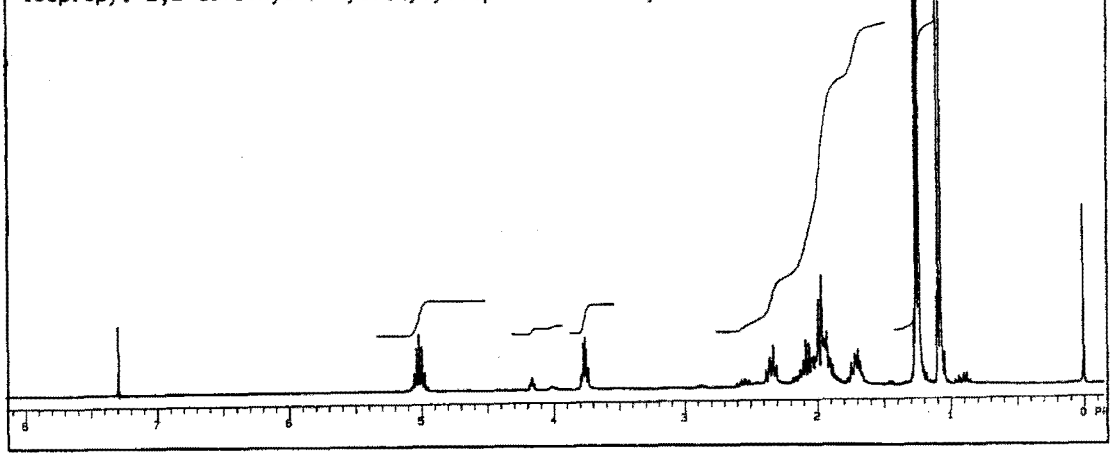

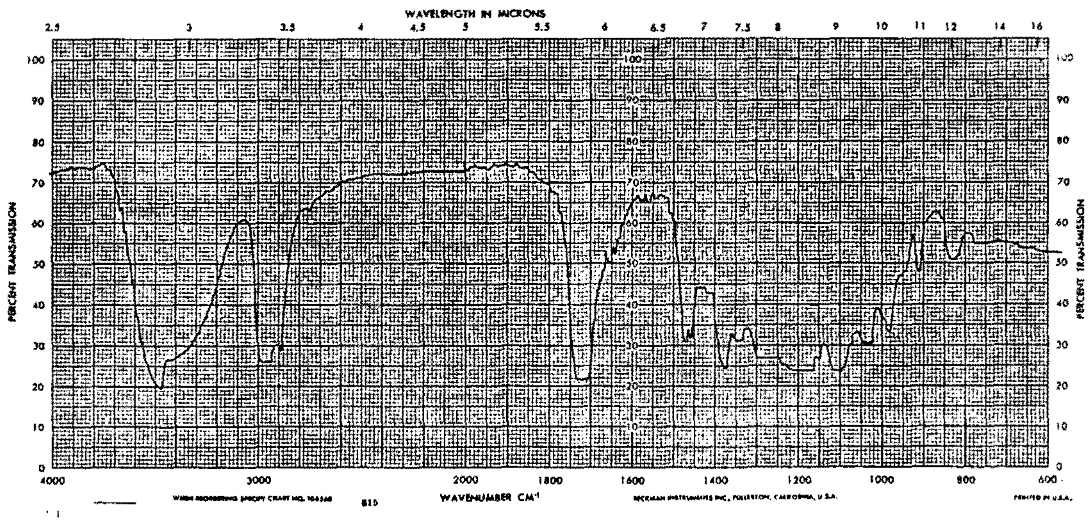

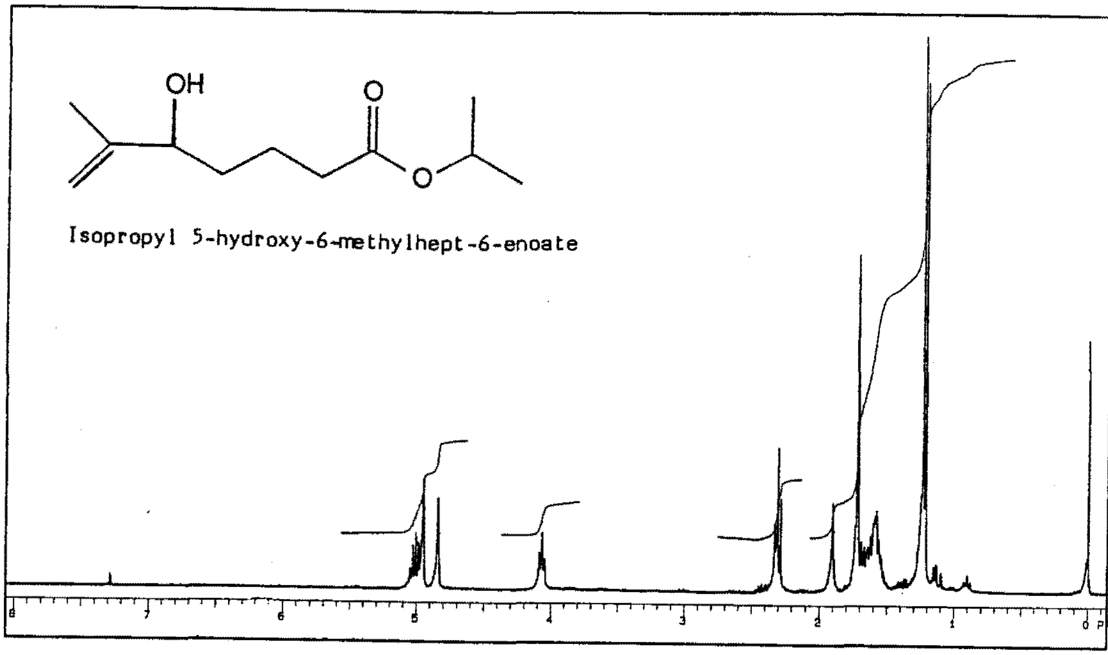
OH
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O
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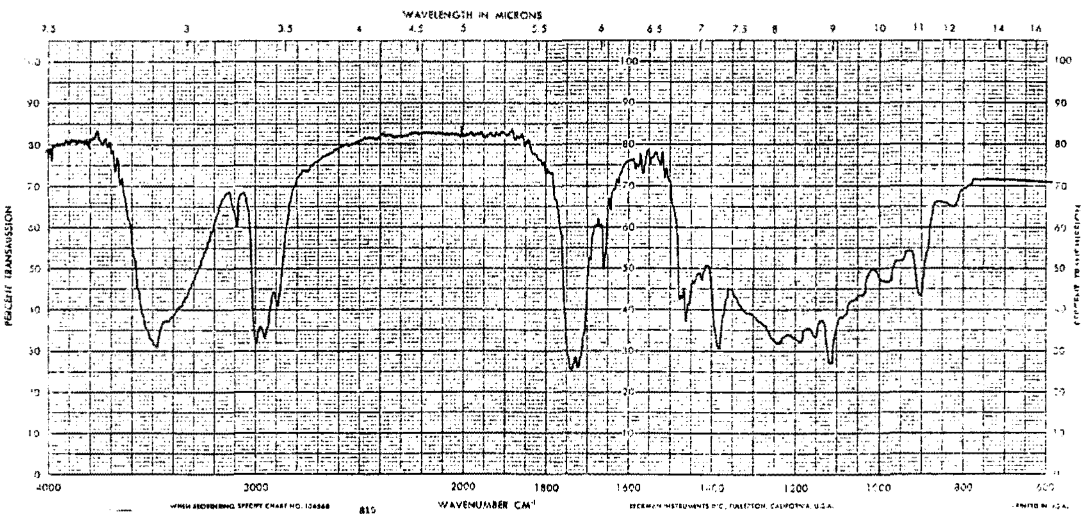
8
7
6
5
4
3
2
1
0 PPM


WAVELENGTH IN MICRONS
PERCENT TRANSMISSION
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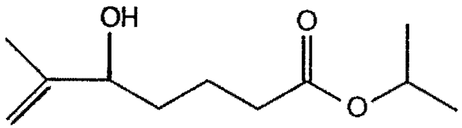
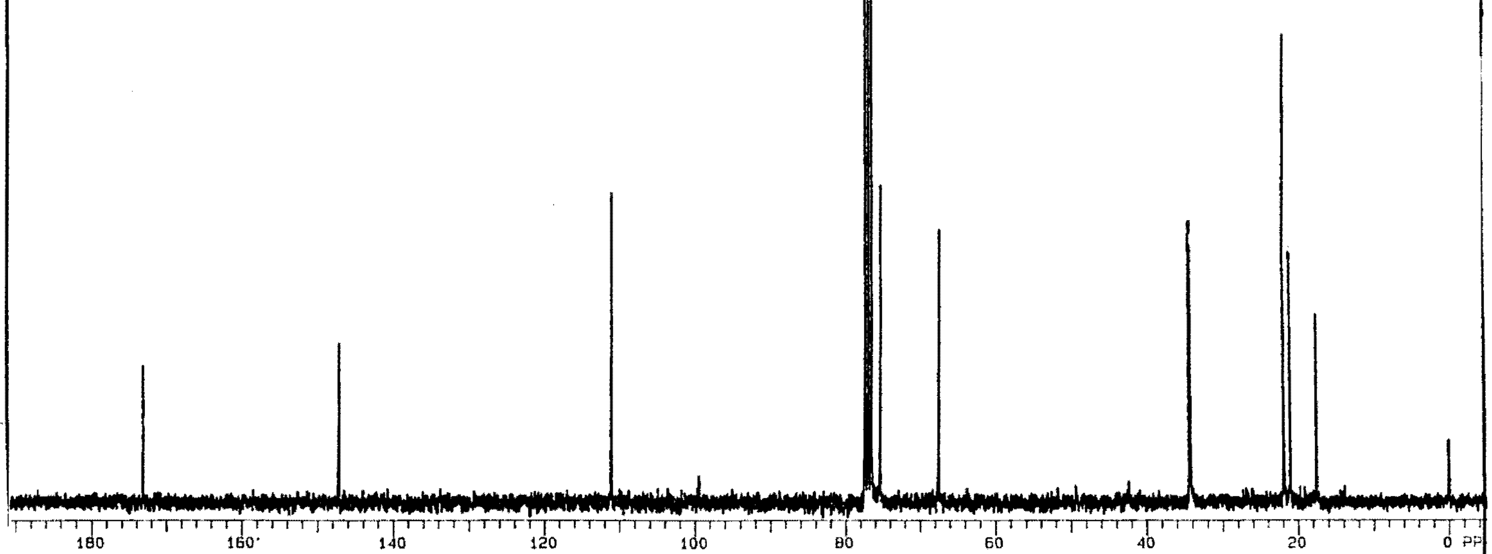
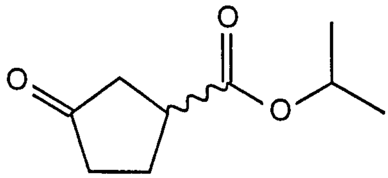
2000
1800
1600
1200
800
WAVENUMBER CM⁻¹

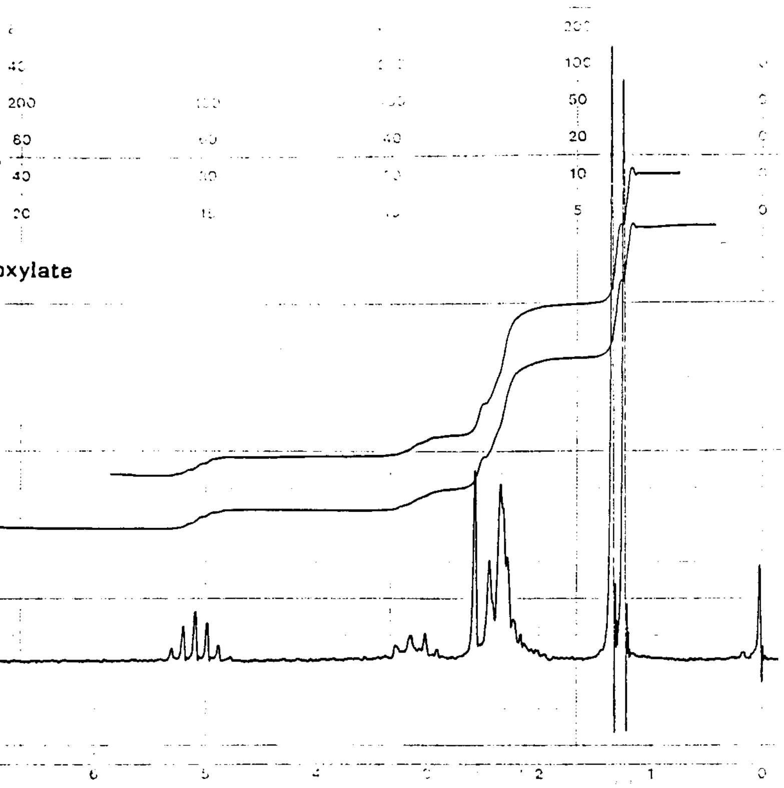


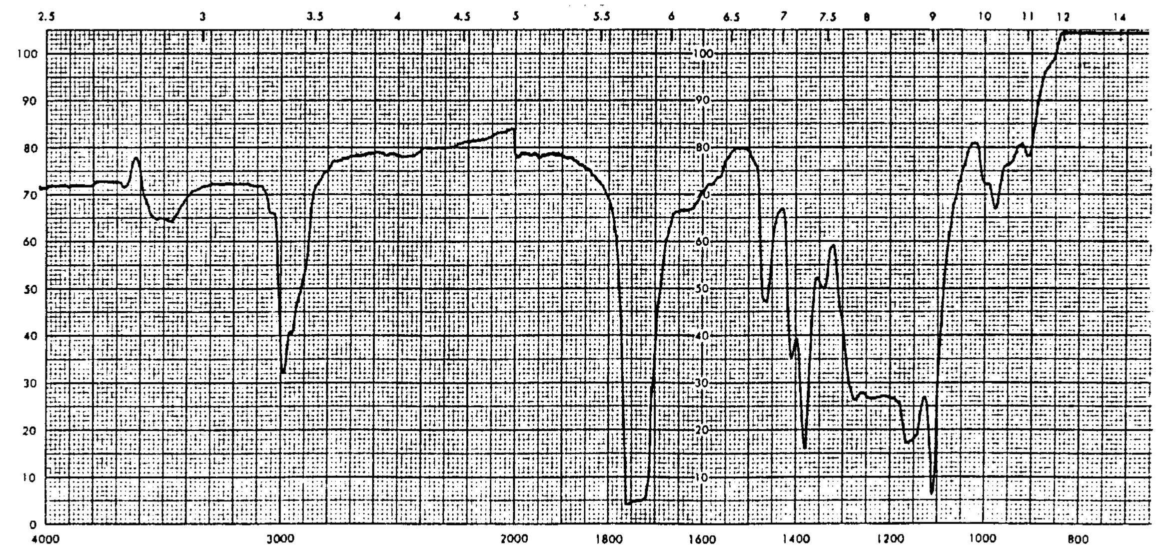
Isopropyl 5-hydroxy-6-methylhept-6-enoate

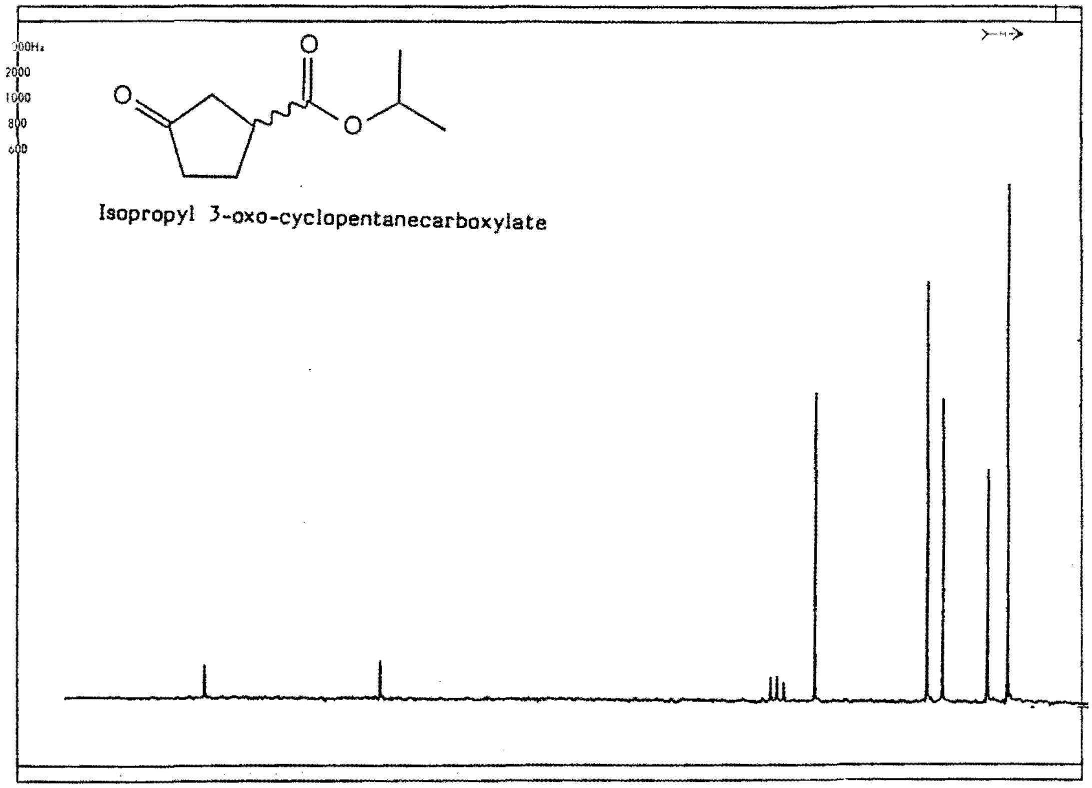




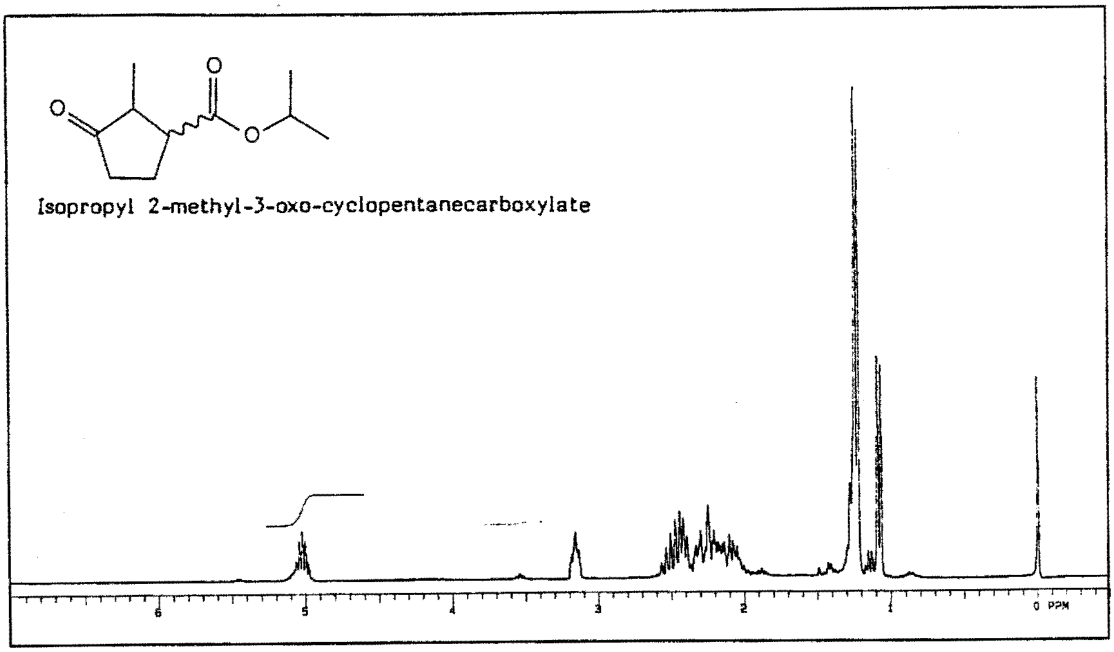
Isopropyl 3-oxo-cyclopentanecarboxylate

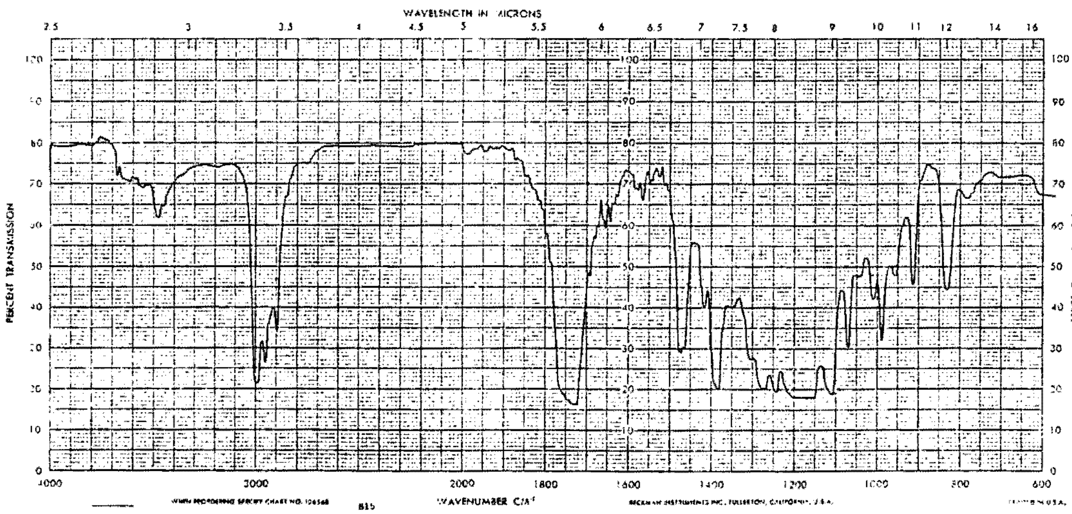






Isopropyl 3-oxo-cyclopentanecarboxylate


Isopropyl 2-methyl-3-oxo-cyclopentanecarboxylate
6
5
4
3
2
1
0 PPM


WAVELENGTH IN MICRONS
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
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1800
1600
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1200
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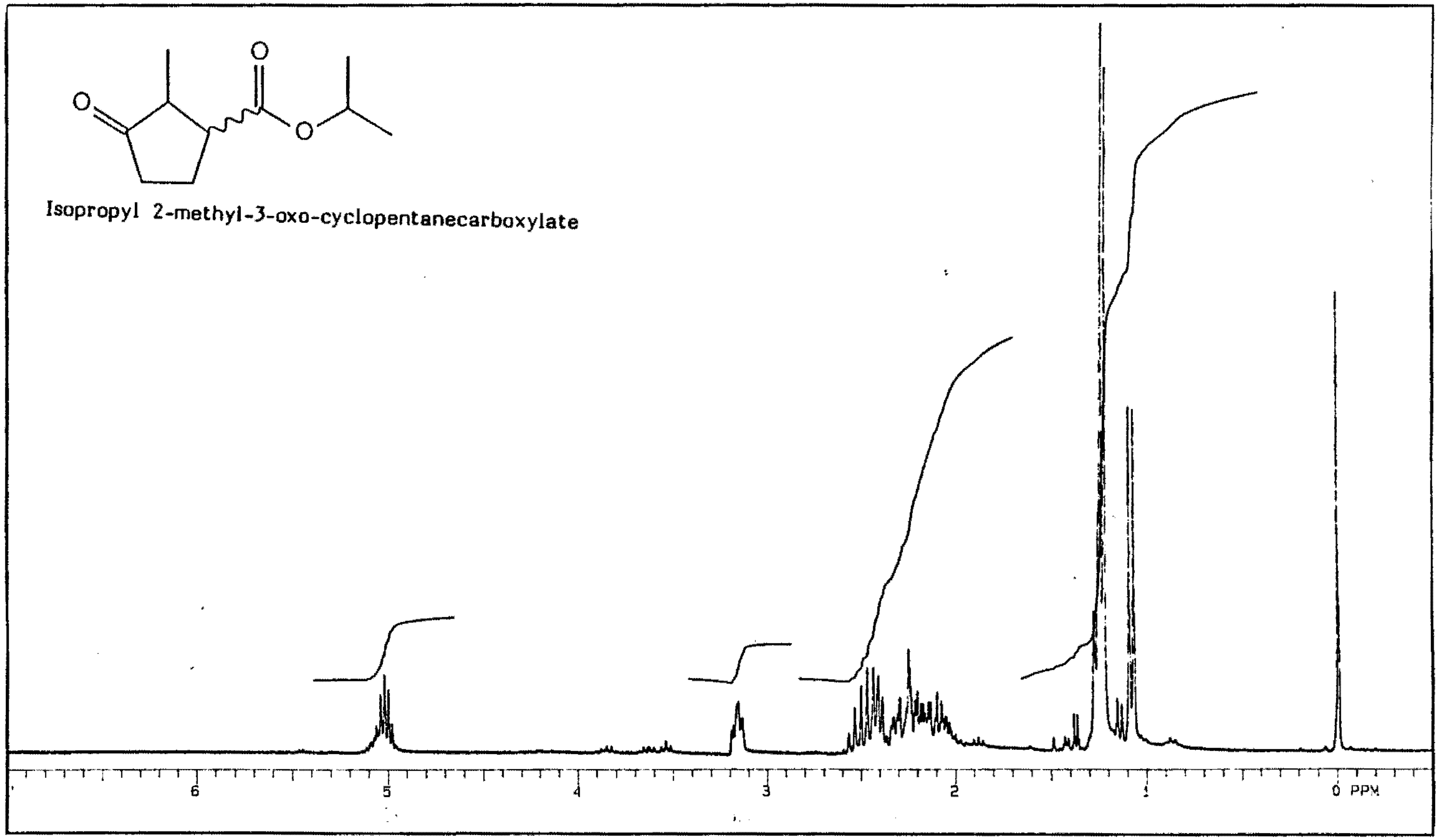
600


Isopropyl 2-methyl-3-oxo-cyclopentanecarboxylate
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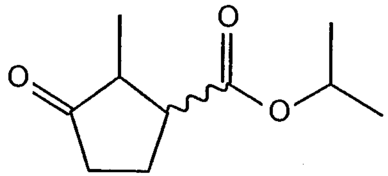
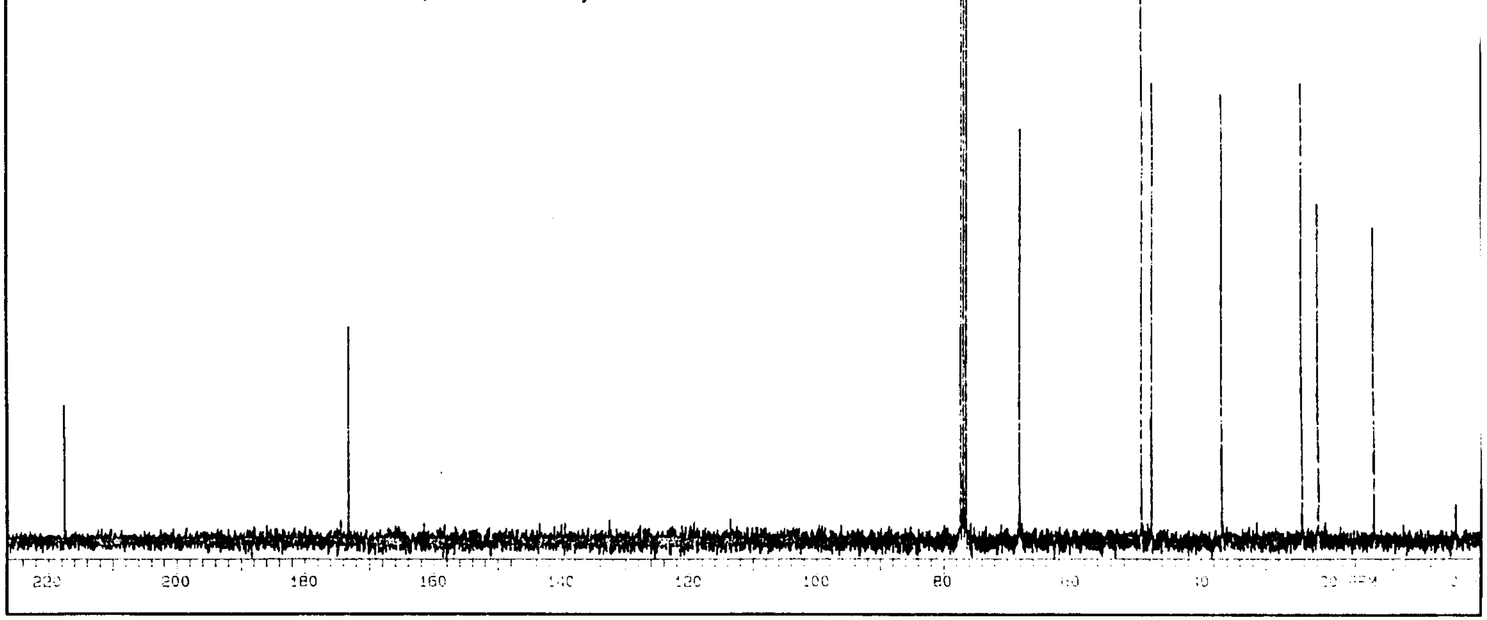
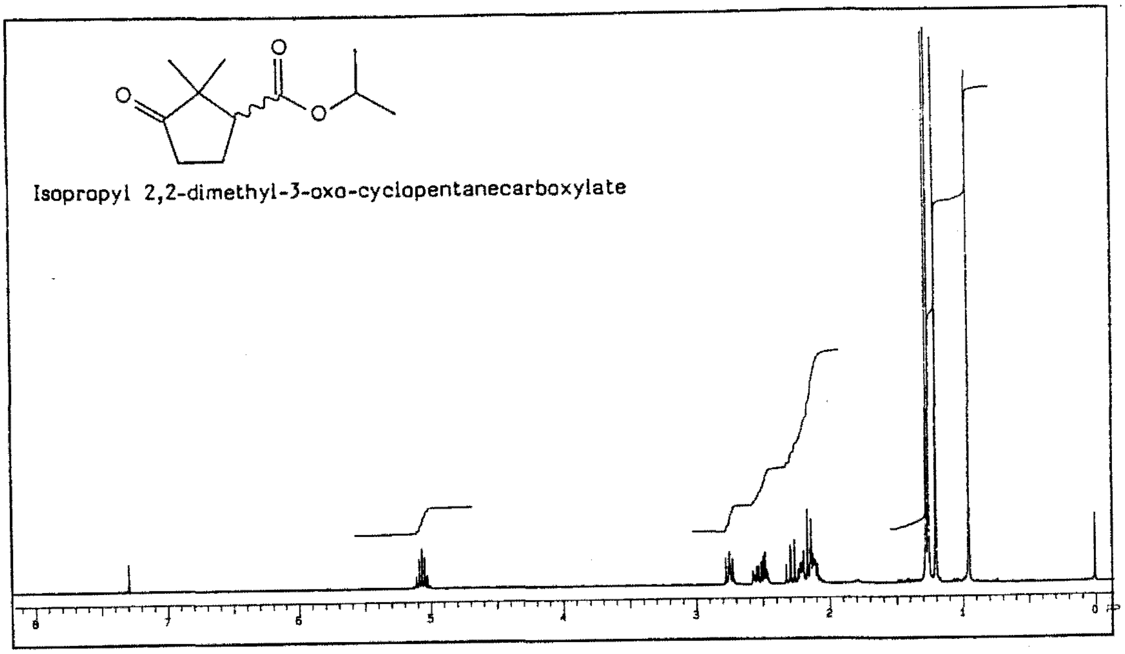
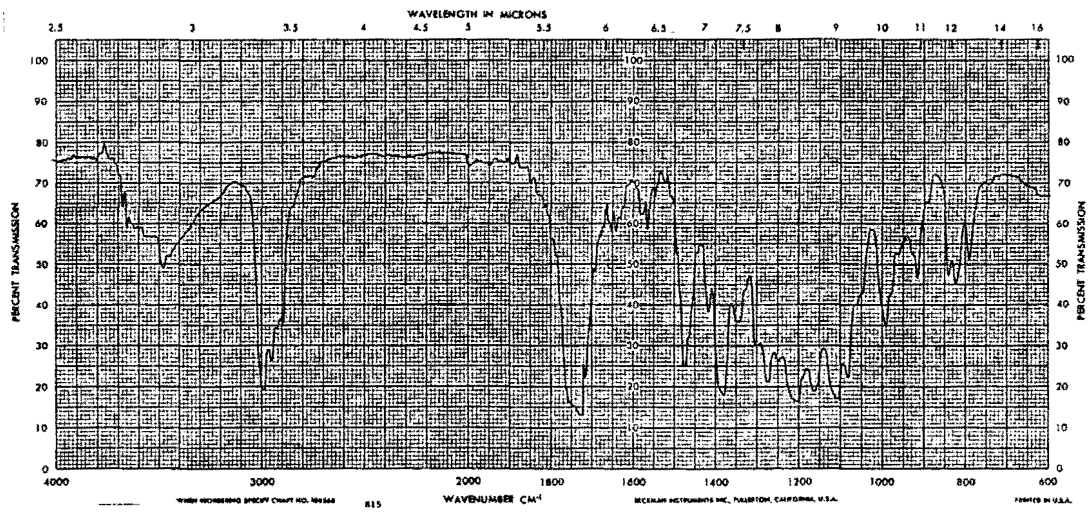
0 PPM

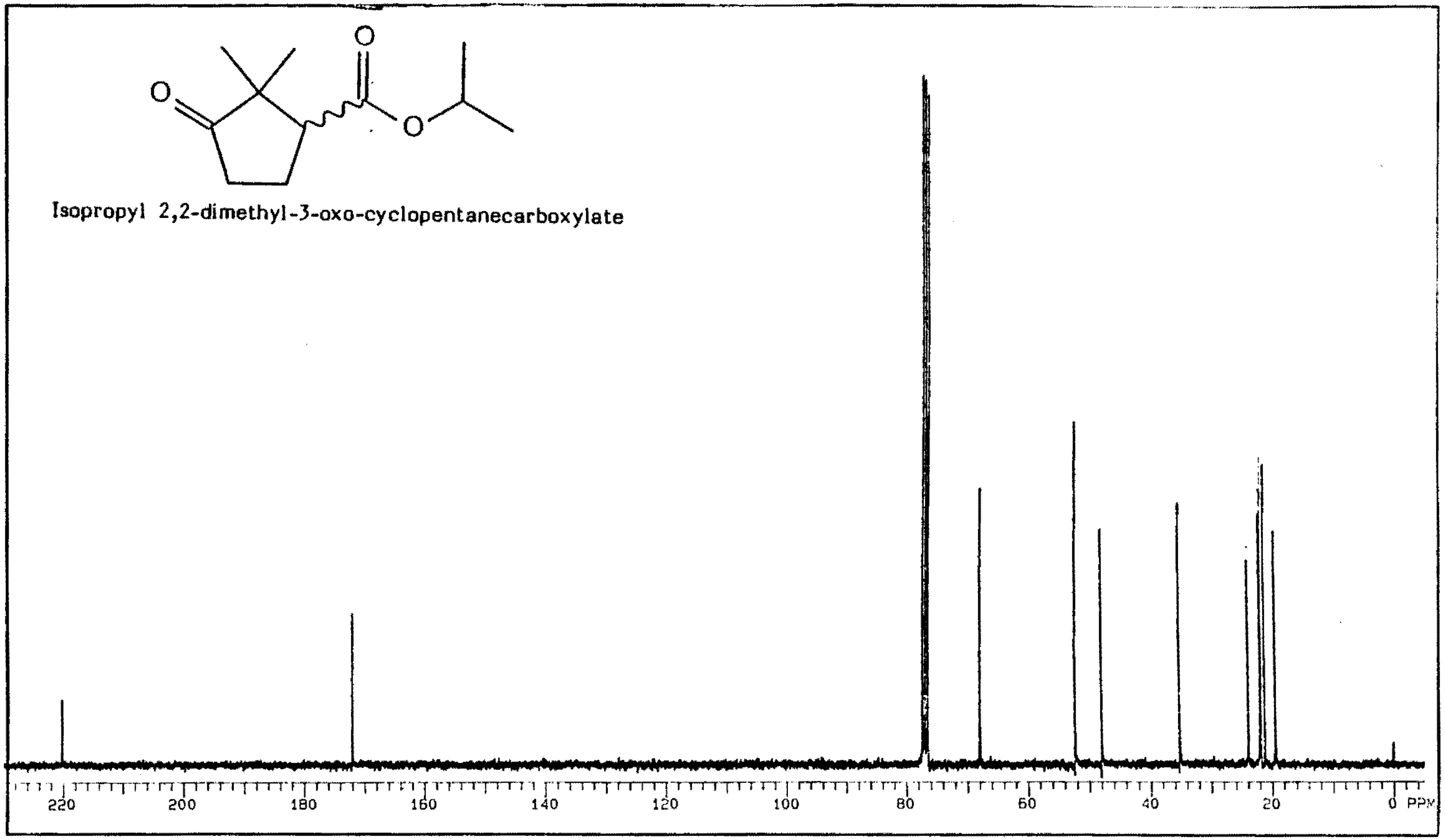


Isopropyl 2,2-dimethyl-3-oxo-cyclopentanecarboxylate




Isopropyl 2,2-dimethyl-3-oxo-cyclopentanecarboxylate
8
7
6
5
4
3
2
1
0


WAVELENGTH IN MICRONS
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
4000
3000
2000
1800
1600
1400
1200
1000
800
600



Isopropyl 2,2-dimethyl-3-oxo-cyclopentanecarboxylate

CHAPTER VII

BIBLIOGRAPHY

1. J.G. Smith, Synthesis, 1984, 269.

2. See reference no. 1 and references therein.

3. D.H.R. Barton and A.S. Lindsey, J. Chem. Soc., (1951), 2988.

4. W. Treibs, Chem. Ber. 1947, 80, 56.

5. R.B. Woodward, T. Fukunaga and R.C. Kelly, J. Am. Chem. Soc, 1964, 86, 3162.

6. J.E. McMurray, Tetrahedron Lett., 1970, 3731.

7. J.E. McMurray and S.J. Isser, J. Am. Chem. Soc., 1972, 94, 7132.

8. G.L. Hodgson, D.F. MacSweeney and T. Money, Tetrahedron Lett., 1972, 3686.

9. J.K. Crandall, R.D. Huntington and G.L. Brunner, J. Org. Chem., 1972, 37, 2911.

10. N.A. Nelson and G.A. Mortimer, J. Org. Chem., 1957, 22, 1146.

11. Y. Gaoni, Tetrahedron, 1972, 28, 5525.

12. Y. Gaoni, Tetrahedron, 1972, 28, 5533.

13. F.E. Ziegler, G.R. Reid, W.L. Studt and P.A. Wender, J. Org. Chem., 1977, 42, 1991.

14. R.M. Cory, D.M. Chan, F.R. McLaren, M.H. Rasmussen and R.M. Renneboog, Tetrahedron Lett., 1979, 4133.

15. Z. Kotkowska-Machnik and J. Zakrzewski, Tetrahedron Lett., 1980, 21, 2091.

16. G. Stork, L.D. Cama and D.R. Coulson, J. Am. Chem. Soc., 1974, 96, 5268.

17. G. Stork and J.F. Cohen, J. Am. Chem. Soc., 1974, 96, 5270.

18. A.C. Knipe and C.J. Stirling, J. Chem. Soc., B, 1968, 67.

19. J.Y. Lallemand and M. Onaga, Tetrahedron Lett., 1975, 585.

20. R. Achini and W. Oppolzer, Tetrahedron Lett., 1975, 369.

21. T. Matsuo , K. Mori and M. Matsui, Tetrahedron Lett., 1976, 1979.

22. B. Corbel and T. Durst, J. Org. Chem., 1976, 41, 3648.

23. B. Corbel, J.M. Decesare and T. Durst, Can. J. Chem., 1978, 56, 505.

24. Y. Gaoni, Tetrahedron Lett., 1976, 503; Y. Gaoni, ibid., 1981, 22, 4339.

25. J.M. Decesare, B. Corbel, T. Durst and J.F. Blount, Can. J. Chem., 1981, 59, 1415.

26. A. Fischli, Q. Branca and J. Daly, Helv. Chim. Acta., 1976, 59, 2443.

27. M. Kodama, Y. Matsuki and S. Ito, Tetrahedron Lett., 1975, 3065; ibid., 1976, 1121; ibid., 1981, 22, 4275.

28. P.A. Cruickshank and M. Fishman, J. Org. Chem., 1969, 34, 4060.

29. J.H. Babler and A.J. Tortorello, J. Org. Chem., 1976, 41, 885.

30. J. Wolinski, P. Hull and E.M. White, Tetrahedron, 1976, 32, 1335.

31. M. Majewski and V. Snieckus, Tetrahedron Lett., 1982, 23, 1343.

32. D.R. Williams and J. Grote, J. Org. Chem., 1983, 48, 134.

33. R.R. Sauers, R.A. Parent and S.B. Damle, J. Am. Chem. Soc., 1966, 88, 2257.

34. C.K. Bradsher and D.C. Reames, J. Org. Chem., 1978, 43, 3800.

35. K. Shankaran and V. Snieckus, J. Org. Chem., 1984, 49, 5022.

36. K.L. Dhawan, B.D. Gowland, and T. Durst, J. Org. Chem., 1980, 45, 922.

37. L.A. Last, E.R. Fretz and R.M. Coates, J. Org. Chem., 1982, 47, 3211.

38. E. Erdik, Chem. Abstr., 1980, 93, 25962y.

39. E. Erdik, Chim. Acta. Turc., 1981, 9, 253.

40. J.H. Babler and W. Bauta, Tetrahedron Lett., 1984, 25, 4323.

41. M.P. Cooke and I.N. Houpis, Tetrahedron Lett., 1985, 26, 3643.

42. J.E. Baldwin, J. Chem. Soc. Chem. Comm., 1976, 734.

43. A.P. Krapcho, Synthesis, 1982, 805, 893.

44. H.K. Hall, Macromolecules, 1971, 4, 139.

45. C.C. Shroff, W.S. Stewart, S.J. Uhm and J.W. Wheeler, J. Org. Chem., 1971, 36, 3356.

46. M.S. Newman and J.L. McPherson, J. Org. Chem., 1954, 19, 1717.

47. Trademark of Aldrich Chemical Co.

48. (a) G. Stork and F.H Clarke J. Am. Chem. Soc., 1961, 83, 3114; (b) C.S. Gibson, K.V. Hariharan and J. Simonsen, J. Chem. Soc, 1927, 3009.

49. S.C. Watson and J.F. Eastham, J. Organometalic Chem., 1967, 9, 165.

50. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923.

51. E. Stahl and U. Kaltenbach, J. Chromatog., 1961, 5, 351.

52. D. Kritchevsky and M.C. Kirk, Arch. Biochem. Biophys., 1952, 35, 346.

53. U.S. Patent No. 2,337,858; cf. Chem. Abstr., 1944, 32971.

54. S. Hiranuma, M. Shibata and T. Hudlicky, J. Org. Chem., 1983 48, 5321.

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The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the dissertation is now given final approval by the committee with reference to content and form.

The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

3/14/88
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