THE KINETICALLY CONTROLLED ENOLIZATION OF α,β-UNSATURATED KETONES AND ITS SYNTHETIC UTILITY

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ROSS ALBERT LEE
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This is to certify that the

thesis entitled

THE KINETICALLY CONTROLLED ENOLIZATION OF
α,β -UNSATURATED KETONES AND ITS SYNTHETIC UTILITY

presented by

ROSS ALBERT LEE

has been accepted towards fulfillment
of the requirements for

Ph. D degree in Chemistry

William Reusch
Major professor

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O-7639

ABSTRACT

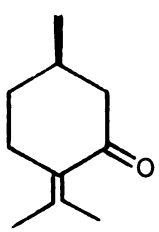
THE KINETICALLY CONTROLLED ENOLIZATION OF
α,β-UNSATURATED KETONES AND ITS SYNTHETIC UTILITY

By

Ross Albert Lee

The enolization of α,β-unsaturated ketones under conditions of kinetic control was shown to involve preferential α'-proton abstraction regardless of the degree of alkyl substitution at the α'- and γ-sites. A general method for the irreversible formation of α'-dienolate bases was developed using the strong base lithium isopropylcyclohexylamide in tetrahydrofuran solution.

Selective methylation of the α'-dienolate bases derived from pulegone (1) and 5,5-dimethylcyclohex-2-enone (3) gave the α'-methyl derivatives 2 and 4, respectively, in good yield.



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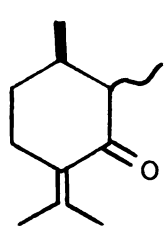

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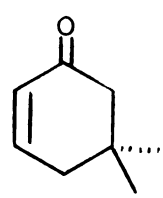

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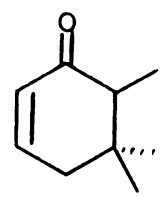
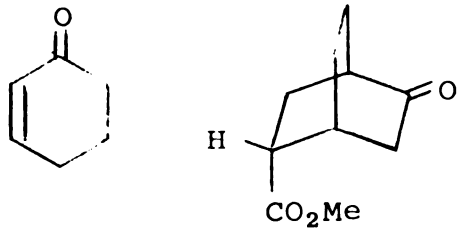
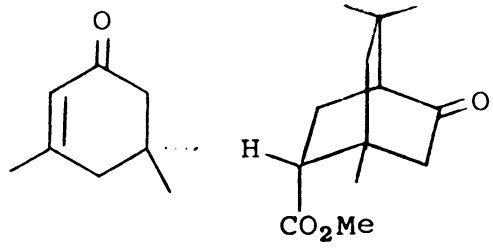


4

Bicyclo[2,2,2]octanones 5 and 6 were synthesized stereoselectively, in high yield (90%), by the reaction of methyl acrylate with the cross-conjugated dienolate bases derived from cyclohex-2-enone (7) and isophorone (8) respectively.



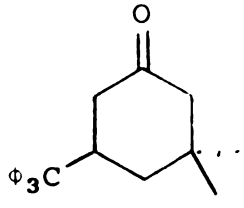
7 5

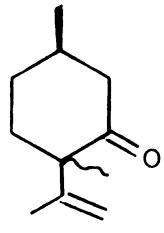


8 6

A sequential Michael mechanism is favored over a Diels-Alder cycloaddition in rationalizing this useful reaction.

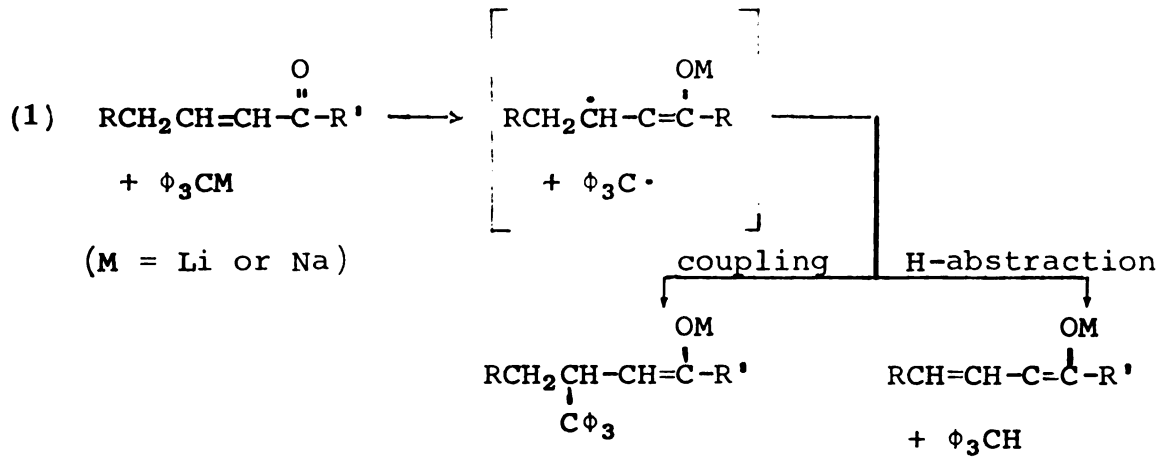
Anomalous results were obtained when tritylllithium was used instead of the amide base. These reactions gave either coupling products (e.g. 9) or products derived from α-alkylation of the fully conjugated dienolate anion formed by γ-proton abstraction (e.g. 10). These unexpected results





9 10

were explained by an electron transfer mechanism (equation 1).


(1)
RCH2CH=CH-C(=O)-R'
+ Φ3CM
(M = Li or Na)
RCH2ĊH-C=C(OM)-R
+ Φ3C·
coupling
H-abstraction
RCH2CH(CΦ3)-CH=C(OM)-R'
RCH=CH-C=C(OM)-R'
+ Φ3CH

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Submitted to
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1973

To Cheryl

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Special thanks are extended to my parents, for their understanding and moral support over the years and for making this opportunity possible. Thanks are also extended to Cheryl McAndrews, above all for her love and moral support, but also for conducting most of the experimental work in the pulegone studies.

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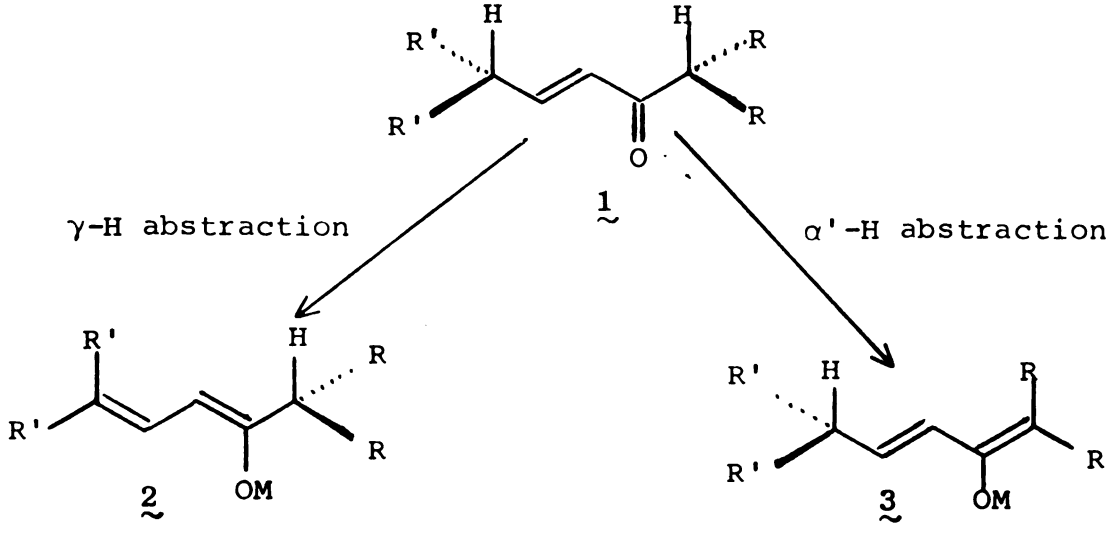
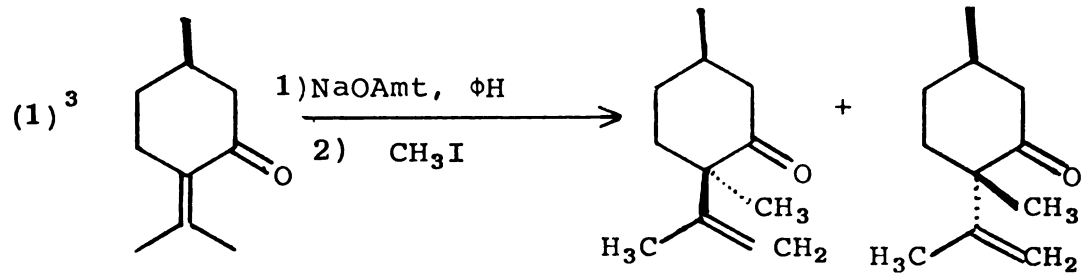
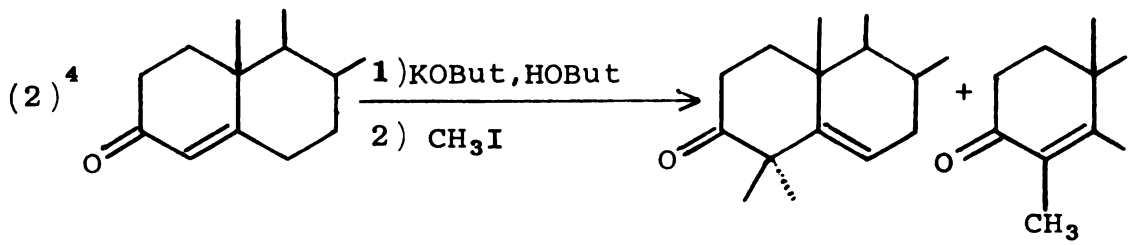
INTRODUCTION

The powerful synthetic utility of carbon-carbon bond formation by alkylation of enolate anions is well established.[1,2] In the case of α,β-unsaturated ketones, having the general structure 1, two types of proton abstraction giving rise to enolate anions 2 or 3 are clearly possible:



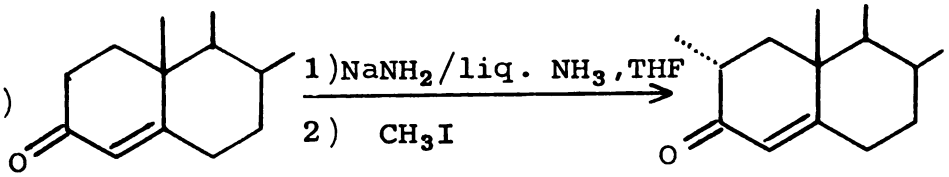
There is abundant evidence indicating that the fully conjugated enolate anion 2, resulting from γ-proton abstraction, undergoes alkylation at the α-carbon atom.[1,2] The majority of these alkylation reactions are reported to give mono and dialkylated β,γ-unsaturated ketones as well as the conjugated monoalkylation products (e.g. equations 1 and 2).



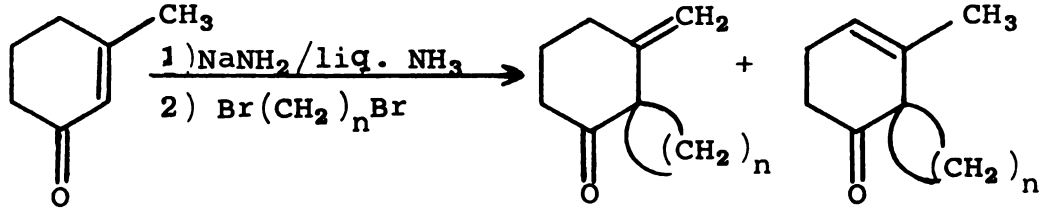


Reports of products derived from the cross-conjugated enolate anion 3, obtained by selective abstraction of an α'-proton, are exceedingly rare. Indeed, Conia reported in 1963[2] that "the only known case of α'-alkylation of an α,β-unsaturated ketone that can undergo tautomerism" was his own observation[5] of α'-allylation of 2-allylcyclohex-2-enone. Two reports of α'-alkylated products derived from enolates formed by the action of sodium amide on α,β-unsaturated ketones are questionable. In 1924 Haller and Ramart[6] described an α'-methylation of pulegone, using sodium amide in ether as the base, and noted that the alleged α'-methyl derivative was levorotatory. This contrasts with our

observation (discussed later) that the major isomer of the α'-methylation of pulegone is dextrorotatory. A patent issued to Schering Corporation[7] describes the 2α-methylation of testosterone, using sodium amide in a liquid ammonia-tetrahydrofuran solvent mixture followed by reaction with methyl iodide (no yields were reported in the abstract) (equation 3). This however, contrasts with the work of

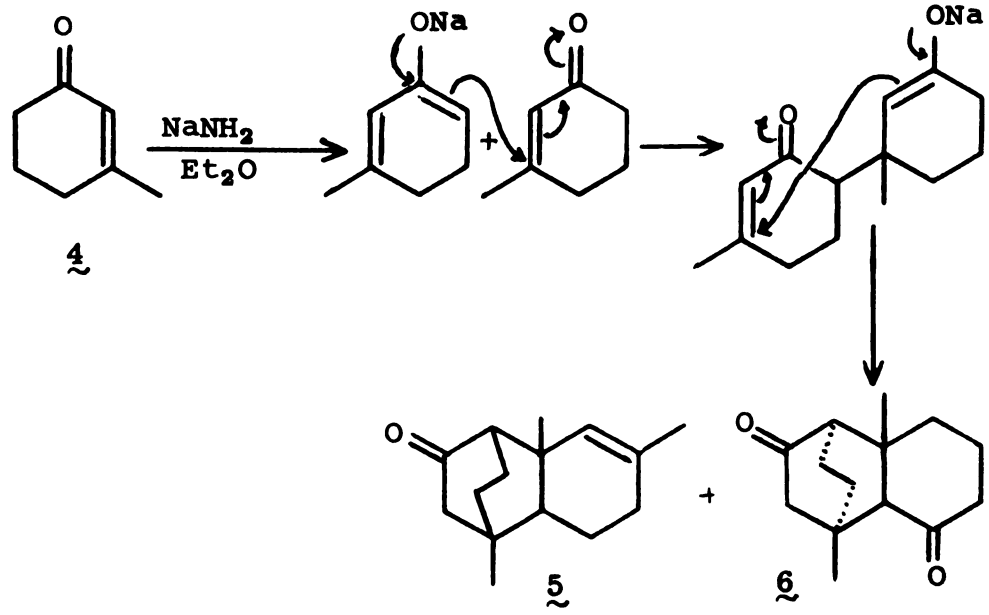
(3) 

Newman et al.[8] in which the same base (sodium amide in liquid ammonia, no tetrahydrofuran cosolvent) was instrumental in effecting cyclobisalkylation of 3-methylcyclohex-2-enone via enolates derived from γ-proton abstraction (equation 4). The homogeneity of the reaction medium may well be a significant factor here.

(4) 

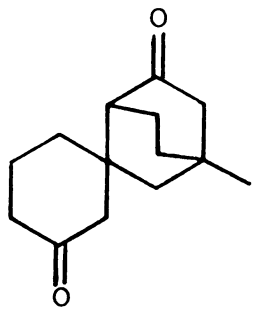
Reports of sequential Michael additions in which an α,β-unsaturated ketone acts both as an enolate acceptor and an enolate donor generated by abstraction of an α'-proton further illustrate the powerful synthetic potential of these intermediate enolate anions. In 1920 Ruzicka[9] proposed structures 5 and 6 for the ketonic dimers formed from base treatment of 3-methylcyclohex-2-enone. Similar structures were also proposed for the dimers obtained from isophorone, and 3,5-dimethylcyclohex-2-enone.

(5)



4 5 6

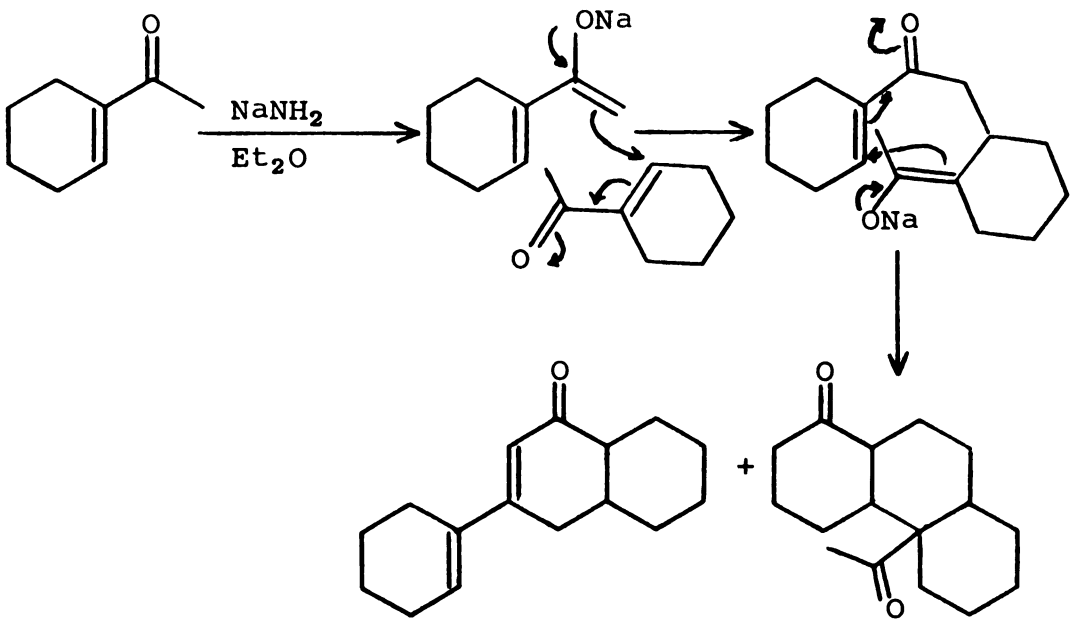
These structures were, however, later refuted by Büchi et al.;[10] and the dimeric product obtained from the reaction of 3-methylcyclohex-2-enone was shown to have structure 7, derived by an initial γ-proton abstraction.



7

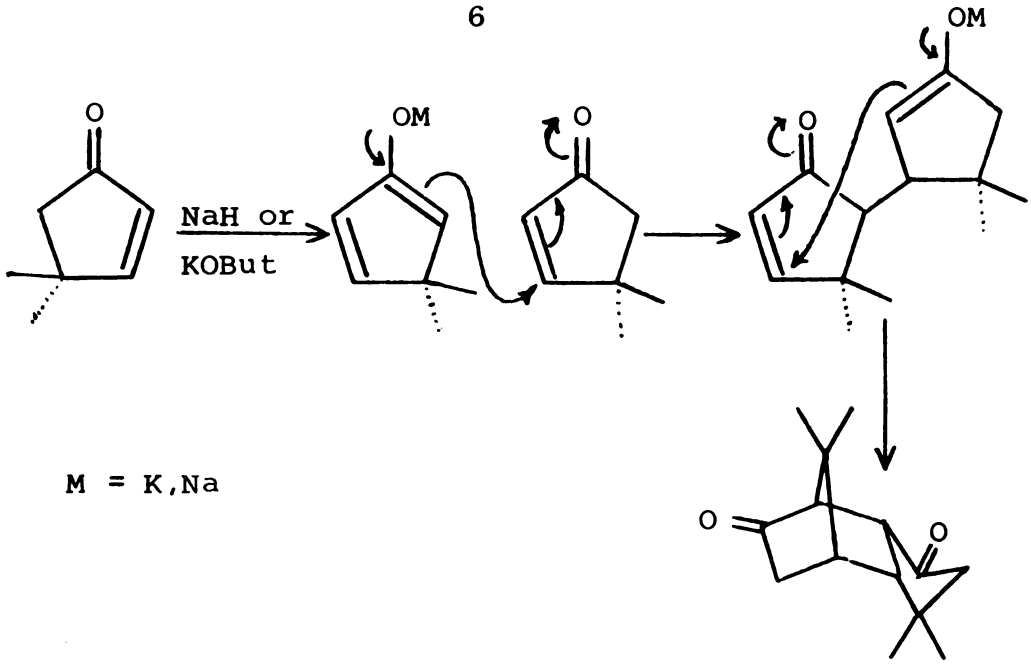
On the other hand, Jones and Koch[11] reported that base catalyzed dimerization of acetylcyclohexene proceeded via α'-proton abstraction, when a suspension of sodium amide in ether was used as the base (equation 6).

(6)



More recently catalysis of a "thermal" double Michael addition by base[12,13] has been explained by the same type of α'-proton abstraction followed by sequential Michael additions of the α'-enolate anion. Bellamy[14] has invoked a similar mechanism to account for the tricyclic dimer obtained by base treatment of 4,4-dimethylcyclopent-2-enone (equation 7).

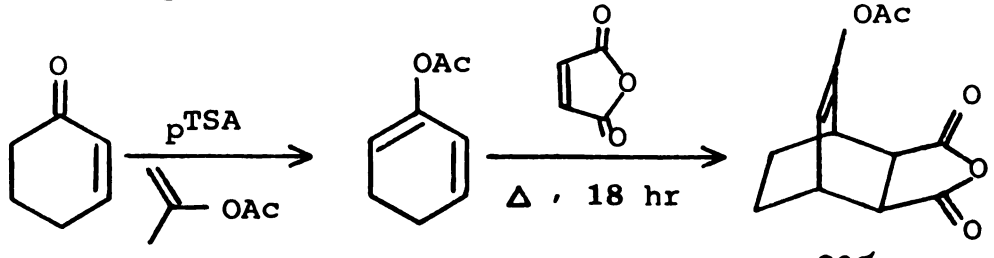
(7)



M = K,Na

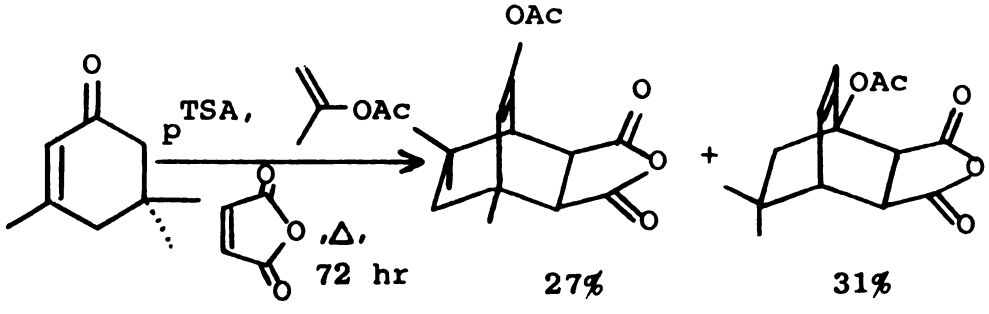
The formation and isolation of stable enol derivatives of α,β-unsaturated ketones has been widely studied.[15,16,17,18] In many cases these derivatives have been formed in situ and trapped by subsequent Diels-Alder cycloaddition reactions. As expected, steric hindrance reduces the effectiveness of this approach (cf. equations 8 and 9).

(8)



80%

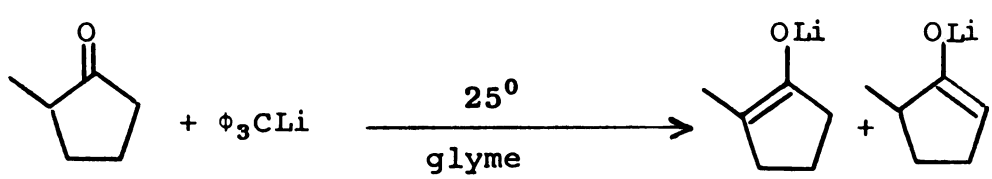
(9)



27% 31%

Nevertheless, these reactions offer a potentially useful means of preparing substituted bicyclo[2,2,2]octane systems.

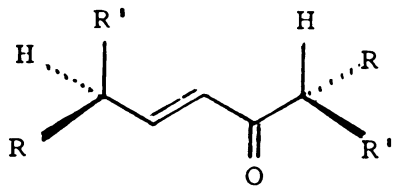
In the case of unsymmetrically substituted saturated ketones, factors influencing the formation of the two possible enolate bases have been carefully studied.[20] Selectivity of enolate alkylations has traditionally been achieved by the use of activating or blocking groups at the less substituted, α-position. Alternatively, it has been found that under equilibrating conditions, in which some proton donor (e.g. protic solvent or unionized ketone) is present, an abundance of the more highly substituted enolate anion is observed. Under kinetically controlled conditions, in which the ketone is added slowly to an excess of strong base in an aprotic solvent, the less substituted enolate anion predominates (equation 10).[1,20]

(10) 

Reaction Conditions	Composition	
Ketone added to excess base (kinetic control)	28%	72%
Excess ketone added to base (equilibrium)	99%	6%

From these results it seems reasonable to assume that under equilibrating conditions, enolization of α,β-unsaturated

ketones (e.g. 1) leads predominantly to a fully conjugated resonance stabilized anion (e.g. 2).



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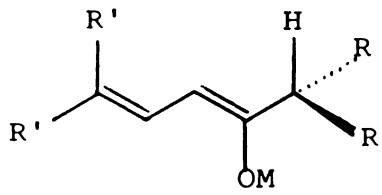
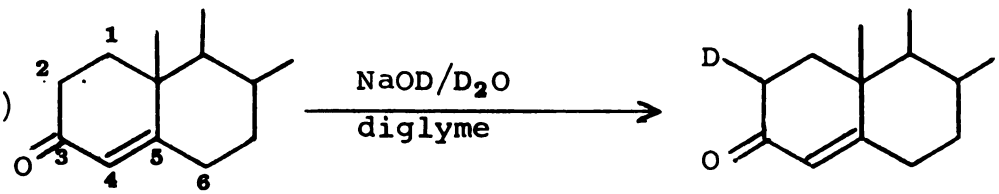


2

However, surprisingly little work seems to have been directed at elucidating the nature of those enolate anions derived from α,β-unsaturated ketones under non-equilibrating or rate controlled reaction conditions. In 1964, Ringold and Malhotra observed[21] that the base catalyzed deuterium exchange of testosterone with sodium deuteroxide in diglyme led to the specific incorporation of one atom of deuterium at C-2 (equation 11):

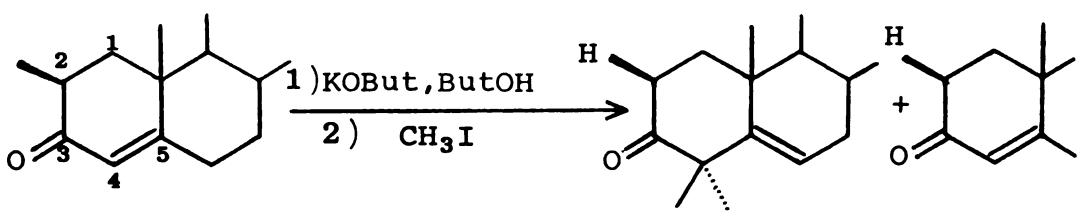
(11)



a similar result was noted in the weak acid catalyzed enolization of testosterone with deuterioacetic acid. These results were interpreted as an indication that kinetically controlled enolization of α,β-unsaturated ketones of this

kind involves preferential α'-proton abstraction. Further support for this view derived from the fact that potassium t-butoxide induced methylation of 2β-deuterioandrost-4-ene-3,17-dione gave both 4,4-dimethylandrost-5-ene-3,17-dione and recovered starting material free of deuterium (equation 12). No investigation, however, was made of the applicability

(12)

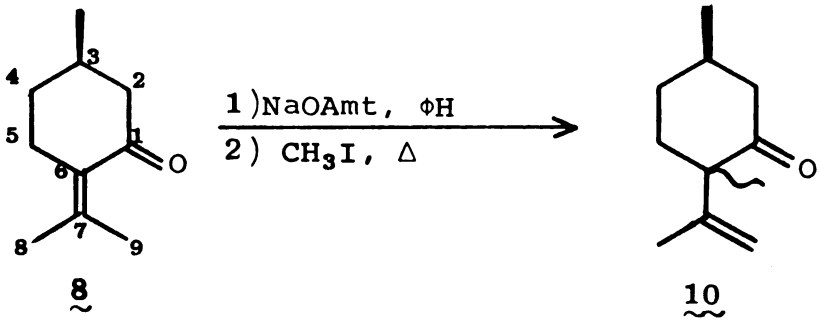


of this interpretation to other substrates or of the effect of substituents at the α'-carbon atom in the determination of the kinetically controlled enolate. Furthermore, no attempt was made to generate irreversibly the kinetically controlled enolate by the slow addition of enone to an excess of strong base in an aprotic solvent. If this should prove to be a general method for selectively generating the cross-conjugated dienolate bases of α,β-unsaturated ketones, then these should be valuable synthetic intermediates which might undergo selective alkylation or Michael addition reactions. Indeed, the latter might offer a versatile alternative to Diels-Alder cycloaddition. An investigation of these possibilities is reported in this dissertation.

RESULTS AND DISCUSSION

The methylation of pulegone (8) under thermodynamically controlled conditions is known to give a mixture of methylisopulegones (10) arising from abstraction of a γ-proton (equation 13)[3]. It was found that the slow addition

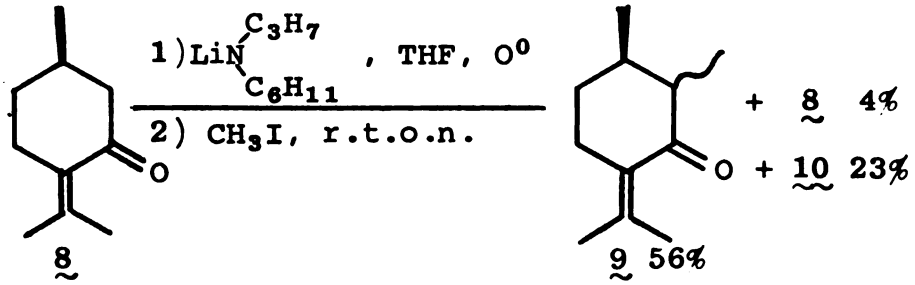
(13)



8 10

of pulegone to an excess of lithium isopropylcyclohexylamide in tetrahydrofuran at 0° (kinetically controlled conditions) followed by methylation with methyl iodide at room temperature gave, as the major product, a mixture of methylpulegones arising from predominate abstraction of an α'-proton (equation 14). Product 9 proved to be an

(14)



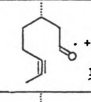
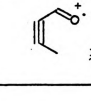
equilibrium mixture of epimers since the relative amounts were unchanged after refluxing the product mixture in methanolic potassium hydroxide.

Using the terpene pulegone, it was shown by mass spectrometric analysis of the products obtained from base catalyzed deuterium exchange that the rate of proton abstraction at the α'-carbon atom is greater than at either of the two γ-carbon atoms. The major fragment ions observed in the mass spectra of the various pulegone samples used in this study are shown in Table I.

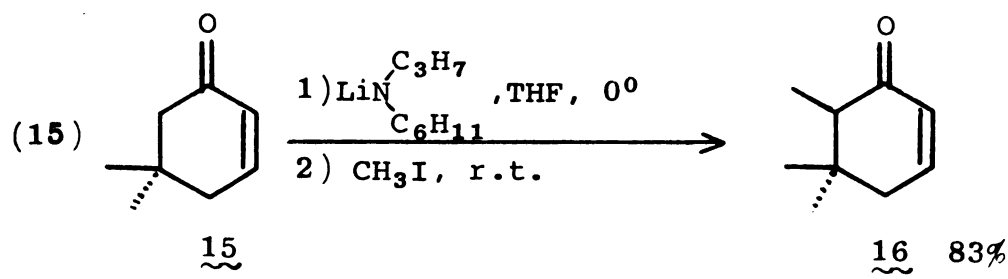
After only fifteen minutes of treatment with a heavy water solution of sodium deuteroxide, a sample of pulegone proved to have the composition 5.5% d_1, 54% d_2, 28% d_3, 8% d_4 and 3% d_5. The loss of only fifteen mass units (no M-16, M-17, or M-18 fragment ions) in forming fragment ions 12, 13, and 14, together with the shift of the base peak from m/e 81 to m/e 82 (identical to the shift observed for d_7,d_8-pulegone (prepared by exhaustive exchange) but not for C-9 d_3-pulegone (prepared according to the procedure of Coleman[22])) indicates that the α'-methylene group has experienced rapid and complete proton exchange while the γ-methyl groups are largely unaffected. These results are in agreement with those obtained by Malhotra and Ringold[21] for testosterone.

In order to determine whether the kinetically favored conjugate base formed from α,β-unsaturated ketones usually involves preferential α'-proton abstraction, other substrates

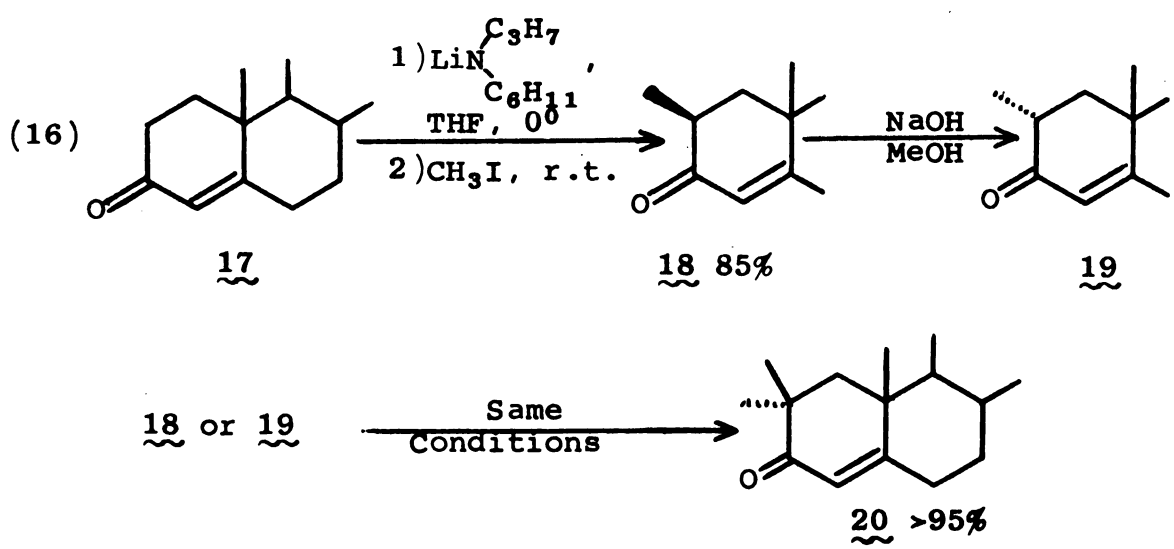
Table I. Mass spectral data for base catalyzed deuterium exchange.

Fragment Ion	Pulegone m/e (rel intensity)	NaOD/D_2O,15 min m/e (rel intensity)	NaOD/D_2O, 1 day m/e (rel intensity)	d_7,d_8-Pulegone m/e (rel intensity)	C-9d_3-Pulegone[22] m/e (rel intensity)
 11	152(54)	153(5) 154(48),155(29) 156(4), 157(3)	154(7) 155(19),156(18) 157(16),158(8)	157(6),158(21) 159(43),160(46)	155(90),156(42)
 12	137(23	139(20),140(5)	139(10),140(12) 141(10)	141(12) 142(21),143(5)	137(20) 140(27)
 13	109(48)	111(45),112(21)	111(25),112(39) 113(30)	114(28),113(14)	109(24) 112(56)
Base Peak	81(100)	82(100)	82(100)	82(100)	81(100)
 14	67(68)	67(49), 68(45)	67(42),68(65) 69(72)	70(40), 69(25)	67(53) 70(71)

of varying structural characteristics were also investigated. 5,5-Dimethylcyclohex-2-enone (15) was chosen since the degree of steric hindrance at the α'- and γ-positions should be similar and both types of proton abstraction would lead to homoannular dienolates. Methylation of this compound under the same conditions described for pulegone gave the α'-methyl derivative 16 in high yield (equation 15).

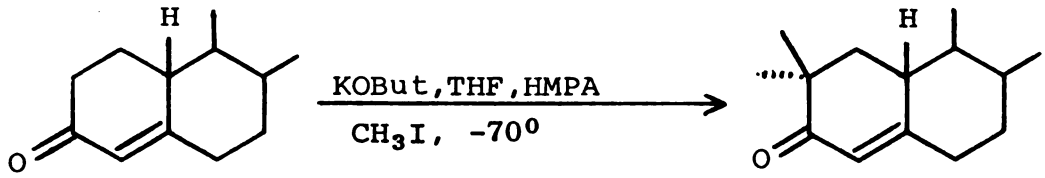


In a separate study on the methylation of steroids, conducted by Patel in this laboratory, the following results were obtained with 3-cholest-4-enone (17) and 2-methyl-3-cholest-4-enones (18 and 19) (equation 16).



The α'-methylation of 19-nortestosterone has recently been described by the Roussel group[23] in France. The addition of potassium t-butoxide to a solution of the enone in tetrahydrofuran containing methyl iodide and hexamethylphosphorus triamide presumably allows trapping of the α'-enolate before equilibration can occur (equation 17).

(17)



"good yield"

In a study of sequential Michael additions (discussed later) the α'-dienolate anions of both cyclohexenone and isophorone were generated in high yield (> 90%) under similar conditions.

The degree of alkyl substitution and steric hindrance to approach at the α'-carbon atom are clearly different in these substrates. In pulegone and isophorone, for example, the α'-carbon atom is secondary and at least one γ-carbon atom is primary. In both 2α- and 2β-methylcholest-4-en-3-one the α'-carbon atom is tertiary while the γ-carbon atom is secondary. In isophorone, steric hindrance to approach is greater at the α'-carbon atom (neopentyl) than at the C-3 methyl γ-position. While both homoannular and heteroannular dienolate anions are possible in the case of cholest-4-ene-3-one and isophorone, only homoannular dienolate anions are possible

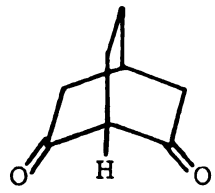
for 5,5-dimethylcyclohex-2-enone and cyclohex-2-enone. Thus, while in the case of saturated ketones, alkyl substitution at the site of proton abstraction is a major factor in determining which of two different enolate anions will be formed most rapidly, it appears that α'-proton abstraction is favored in the generation of dienolate anions from α,β-unsaturated ketones under non-equilibrating conditions, regardless of the degree of alkyl substitution at the different sites.

It has been assumed in this argument that the products of alkylation reflect the composition of the initially formed enolate anion mixture. If this were not the case, then equilibration of enolate anions would be taking place either prior to or during alkylation. Four arguments indicate that this is not happening. First, the slow addition of ketone to an excess of strong base in an aprotic medium under oxygen and moisture-free conditions makes equilibration prior to alkylation highly unlikely. The effectiveness of this procedure has been well established in the case of saturated ketones.[2,20] Second, if equilibration were taking place during alkylation then the rate of proton exchange would have to exceed the rate of alkylation. However, Stork[24] and House[20,25] have shown that lithium enolates are particularly slow to equilibrate <u>via</u> proton exchange with unionized ketone. Indeed, House[20] reported that even when as much as 20 mole percent excess of ketone is present lithium enolates take 30 minutes or more to come to equilibrium. Third,

the use of a large excess of a reactive alkylating agent increases the rate of the alkylation reaction making equilibration during alkylation even more unlikely. Again, House[25] has found that cases in which the thermodynamically more stable enolate is 1.7-2.3 times more reactive toward alkyl halides than the less stable, rate favored enolate anion, give, under similar conditions, the product derived from the latter (> 75 %). Finally, the fact that these results are in agreement with those of the deuterium exchange experiments[21] and that no α'-alkylated products had been observed under conditions in which equilibration is allowed suggests that the initial assumption is valid.

In the case of unsymmetrically substituted ketones, the increased rate of proton abstraction at the less substituted carbon atom has been attributed to inductive effects,[26] steric effects[27,28,29] and stereoelectronic control.[30] An argument based on inductive effects must necessarily assume a transition state resembling ketone. Such a transition state would be characterized by a low degree of carbon-carbon double bond formation but sufficient C_α-H bond breaking to produce a significant negative charge on the α-carbon atom. Alkyl substituents generally destabilize carbanions. Studies by Swain and Rosenberg[31] suggest that the stronger the base the shorter the C_α-H bond is stretched and the closer the transition state resembles ketone. Nevertheless, some carbon-carbon double bond character must be present in the transition state for proton abstraction, since

stereoelectonic factors requiring that the breaking C-H bond be perpendicular to the carbonyl group are well established, especially in the case of bicyclic ketones (e.g. 21).[32]



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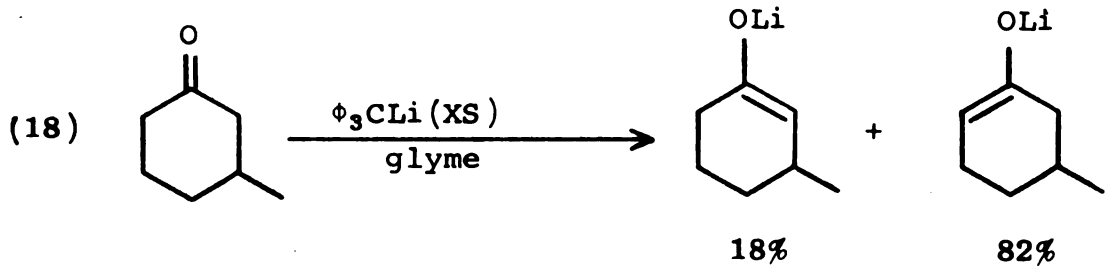
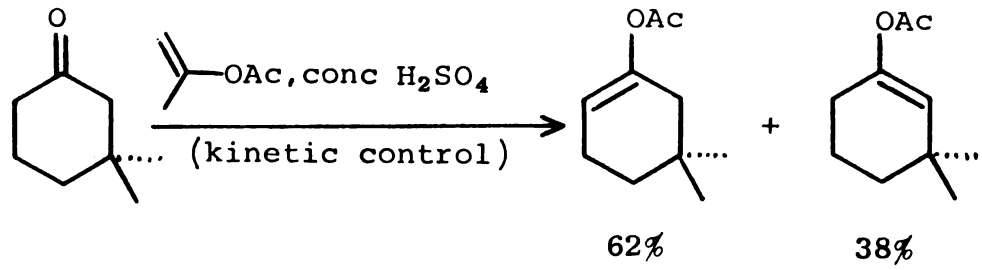
While stereoelectronic factors alone have been used to account for the results obtained with unsymmetrical acyclic ketones[30] they do not explain the results obtained in cases such as 2-methylcyclohexanone or 2-methylcyclopentanone. Steric factors may, in fact, be the largest single contributing factor influencing the rate of base catalyzed enolization, as the results of Antony and Maloney[28] (equation 18)

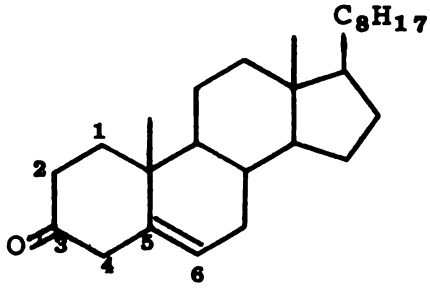


and Champagne et al.[33] (equation 19) suggest.

(19) 

These factors, alone or in combination, will not explain the increased rate of α'-proton abstraction over γ-proton abstraction in the α,β-unsaturated ketone substrates studied here.

Ringold and Malhotra[21] attributed the preferential α'-proton abstraction they observed in the testosterone series to a ketone-like transition state, in which the inductive effect of the carbonyl group increased the acidity at C-2 relative to C-6. They also suggested that stereoelectronic control, favoring abstraction of those protons whose C-H bonds are perpendicular to the carbonyl group (C-2β or C-6β), would afford greater resonance stabilization to the proton adjacent to the carbonyl group (C-2β). The increased acidity of Δ_5-3-ketones (e.g. 22) relative to Δ_4-3-ketones (e.g. 23) was cited as corroborating evidence. While the



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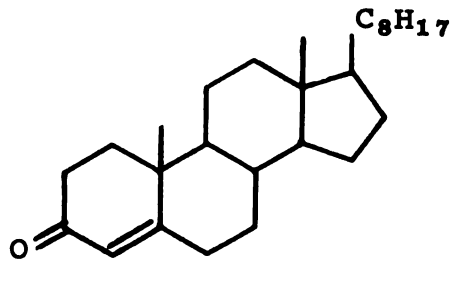
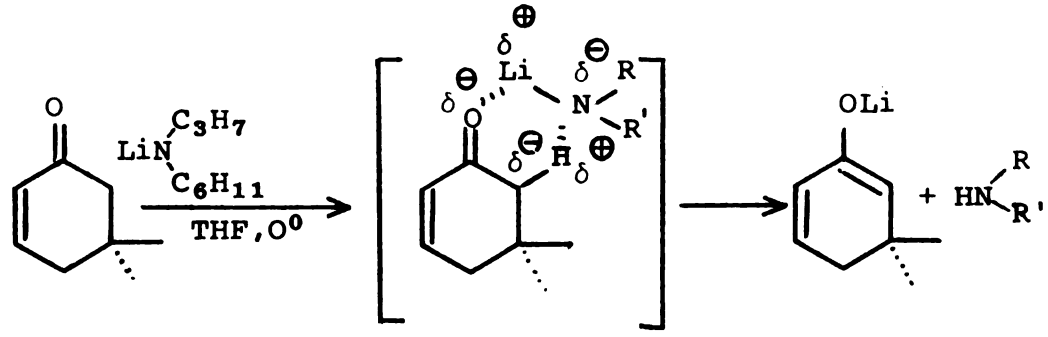


23

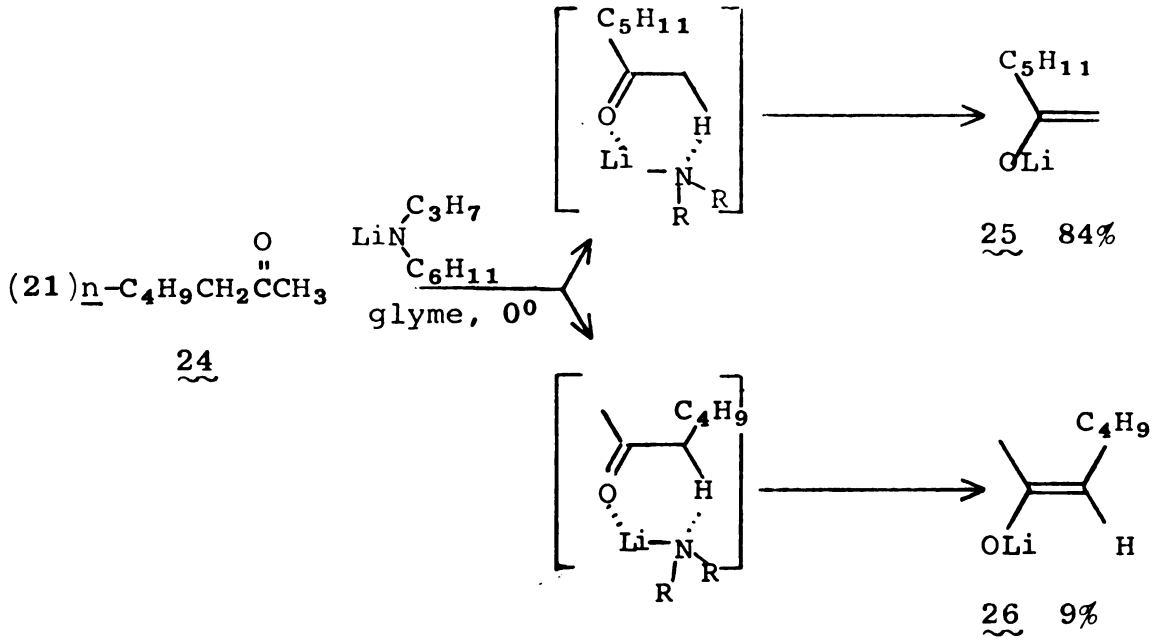
inductive effect of the carbonyl group may be a significant factor, the argument for enhanced resonance stabilization at the α'-position is not convincing. Perhaps the most reasonable assumption that can be made concerning the nature of the transition state for α'- or γ-proton abstraction is that their resemblence to the product dienolate anions is not sufficient for this to be a dominant factor. Furthermore, it may be that some factor other than an inductive effect or steric hindrance is favoring α'-proton abstraction.

Two rationalizations for the regiospecific α'-effect noted above will be considered here, one concerning a cyclic transition state and the other derived from the principle of least motion. The essence of the first proposal is that a six-membered cyclic transition state similar to that shown in equation 20 would necessarily favor α'-proton abstraction.

(20)

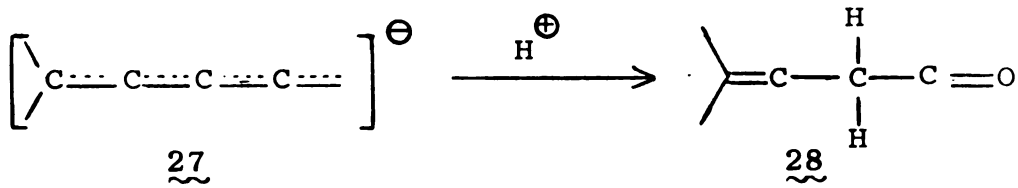


Such a transition state has been proposed[1] to account for the formation of the less stable cis-enolate 26 in the kinetically controlled enolization of 24 (equation 21). However, we would expect the stability of such a metal-oxygen

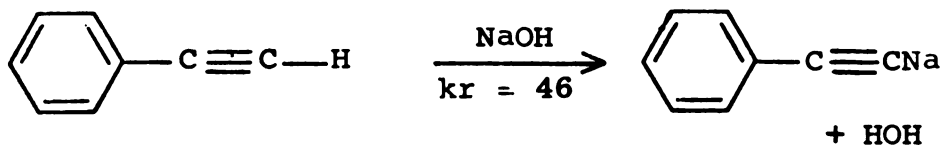


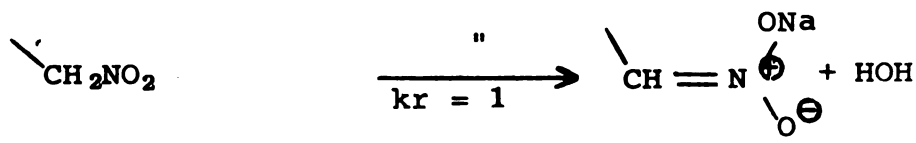
coordinated transition state to be sensitive to cation and solvent variations. Since specific α'-proton abstraction has been observed with lithium ($LiNR_2$), sodium (NaOD), and potassium (KOBut)[21] bases in solvents such as tetrahydrofuran, deuterium oxide/diglyme,[21] deuterium oxide/dioxane, t-butanol,[21] and tetrahydrofuran containing tetramethylethylene diamine (in studies performed by Patel), this proposal loses some of its appeal. Certainly, the specific solvating properties of tetramethylethylene diamine for $Li^{\oplus}$ should be evident if a six-membered cyclic transition state were involved in the proton transfer, however, the results were identical to those obtained with tetrahydrofuran alone. The second proposal is based upon the principle of least motion.[34,35] This principle was originally enunciated by

Rice and Teller[34] and was shown to have semi-quantitative and qualitative application to problems in organic chemistry by Hine.[35] According to this principle "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."[34] Hine applied this principle to explain the kinetically favored α-protonation of mesomeric carbanions such as 27 (equation 22) (and by microscopic reversibility the increased rate of proton abstraction of Δ_5-3-ketones) and the increased rate of proton abstraction of phenylacetylene (pK_a = 21) over nitroethane (pK_a = 10) (equations 23 and 24).

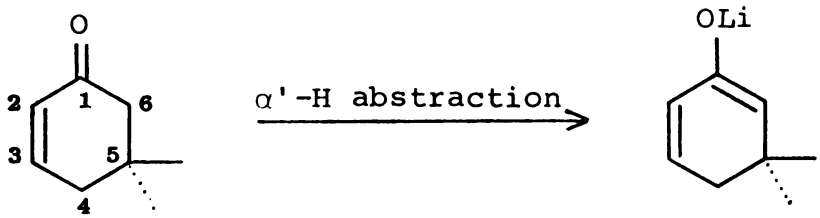
(22) 

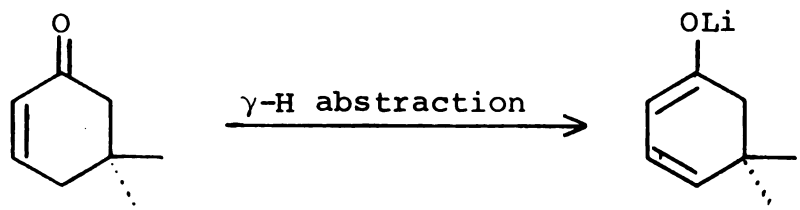
27 28

(23) 

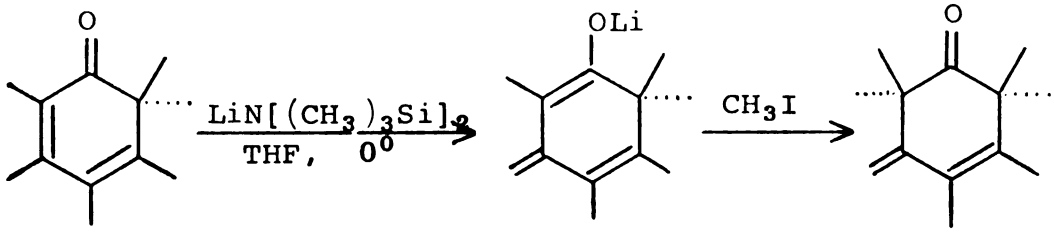
(24) 

In the last two cases little change in molecular motion was anticipated for reaction 23, while several changes in bond distances and bond angles was anticipated for reaction 24. Essentially identical reasoning leads to the prediction that for α,β-unsaturated ketones α'-proton abstraction will be favored energetically over γ-proton abstraction (equations 25 and 26).

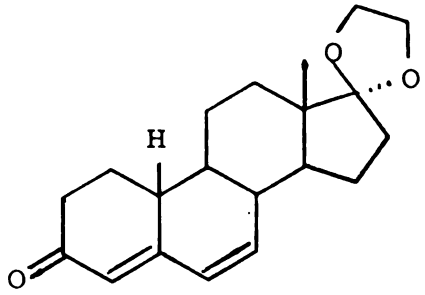
(25) 

(26) 

In equation 25 bond reorganization must occur at C6-C1 and the carbonyl group while in equation 26 bond reorganization must involve C4-C3, C3-C2, C2-C1 and the carbonyl group. Thus, assuming the transition state characterized previously, the activation energy for α'-proton abstraction should be less than for γ-proton abstraction. A recent report of preferential γ-proton abstraction over ε-proton abstraction in the kinetically controlled enolization of an α,β,γ,δ-cyclohexadienone by Hart et al.[36] could be explained by the same principle (equation 27). A steric hindrance effect

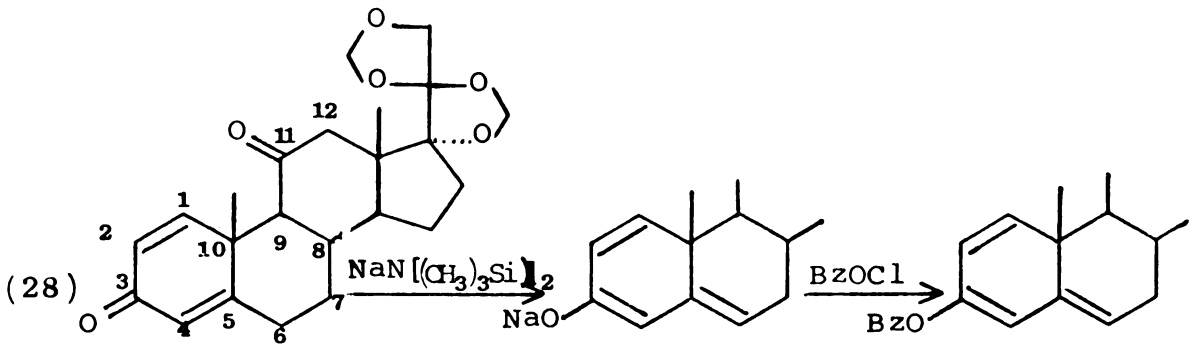
(27) 

might also be important in this case. Investigations into other systems, where for example, α'-proton and γ-proton abstraction may compete with ε-proton abstraction (e.g. 29), could further corroborate this principle and perhaps be



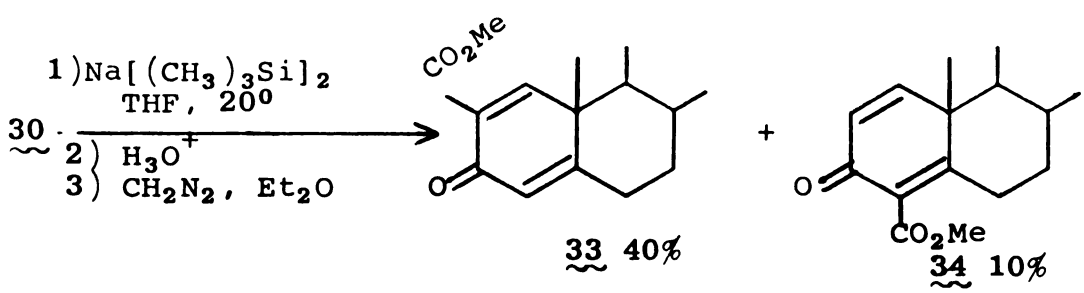
29

synthetically useful. An apparent contradiction to the application of this principle is found in the report of Barton et al.[37] that the kinetically controlled enolization of 30 yielded the $\Delta_{1,3,5}$ trienolate anion 31 (equation 28). The isomeric $\Delta_{9,11}$ enolate anion was found to be thermodynamically favored over 31. However, a concurrent report by Tanabe and Crowe[38] indicates that products from both enolate

(28) 

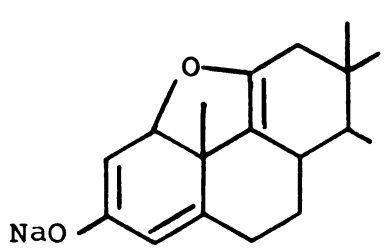
30 31 32 >80%

bases (e.g. 33 and 34) were formed when an enolate anion mixture derived from reaction of 30 with the same base in tetrahydrofuran was quenched with carbon dioxide and subsequently treated with diazomethane (equation 29).

(29) 

33 40% + 34 10%

The formation of 33 was explained as arising from the carbonation of enolate anion 35. The formation of 35 (or other

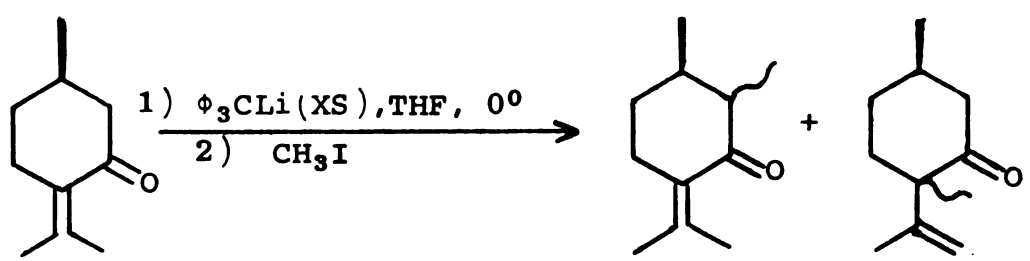


35

possible cyclo-enolates) must require greater bond reorganization in the transition state than the formation of 31. Thus, the principle of least motion may be consistent with the observations cited in this case.

The strong base trityllithium (pKa of ϕ_3CH = 33) has been widely used to effect the irreversible formation of the conjugate bases of ketones and esters, a particularly good example being the previously noted unsymmetrically substituted ketones. Anomalous results were obtained, however, with α,β-unsaturated ketone substrates. When pulegone was added slowly to an excess of trityllithium in cold (0°) tetrahydrofuran solution and the resulting dienolate anion mixture was quenched by reaction with methyl iodide, the major product proved to be the stereoisomers of the methylisopulegones (equation 30). The predominance of α-methyla-

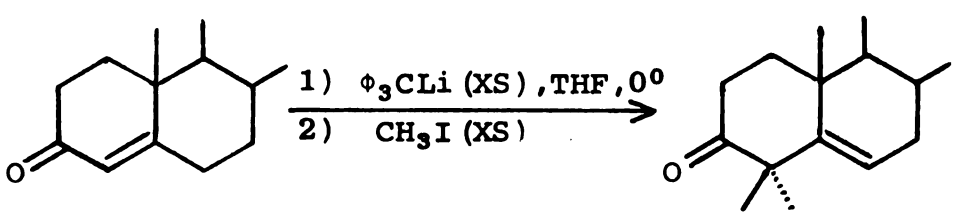
(30)



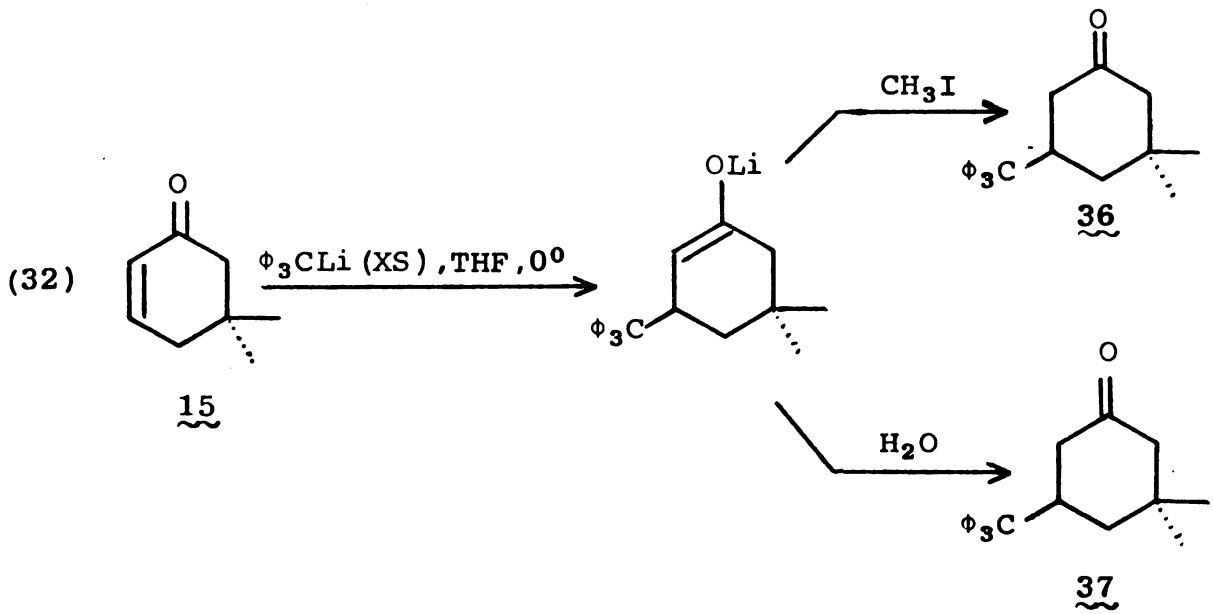
8 9 20% 10 61%

tion under conditions that favored rate-controlled formation of the cross-conjugated dienolate ion was unexpected and inconsistent with the results obtained using the 2°-amide base. As argued earlier equilibration of the conjugate bases prior

to alkylation seemed highly unlikely. Furthermore, if equilibration were occurring during the alkylation step, this would require a significant enhancement of the rate of proton transfer and/or a decrease in the rate of alkylation for the trityllithium reaction compared with the 2^0-amide reaction. The possibility that the 2^0-amine necessarily present in the latter alkylation reactions was causing such rate changes was eliminated by the observation that addition of one equivalent of isopropylcyclohexyl amine to the trityllithium reaction prior to the alkylation step failed to alter the course of the methylation. In a parallel study by Patel, the trityllithium promoted methylation of cholest-4-ene-3-one, again yielded products derived from the more stable γ-dienolate anion (equation 31). However, when the

(31) 

reaction was applied to 5,5-dimethylcyclohex-2-enone (15), quite a different transformation was noted (equation 32).

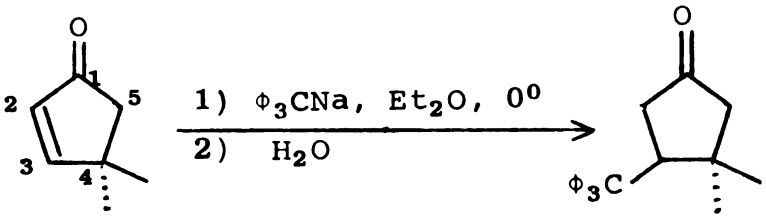


Conjugate addition reactions of tritylllithium or tritylsodium to unsaturated carbonyl systems are rare, as are other conjugate additions of alkyllithiums not catalyzed by copper. Michael and Saffer[39] reported the conjugate addition of tritylsodium to cinnamate esters and benzalacetopheonone but not to methyl crotonate (γ-proton abstraction was reported in this case). However, McPhee and Lindstrom,[40] observed conjugate additions of tritylsodium to methyl acrylate and ethyl crotonate, irrespective of the mode of addition. This striking disagreement has remained unresolved until now. In the course of this study the reaction of tritylllithium with ethyl crotonate (38) was observed to proceed in the manner reported by McPhee and Lindstrom (equation 33).

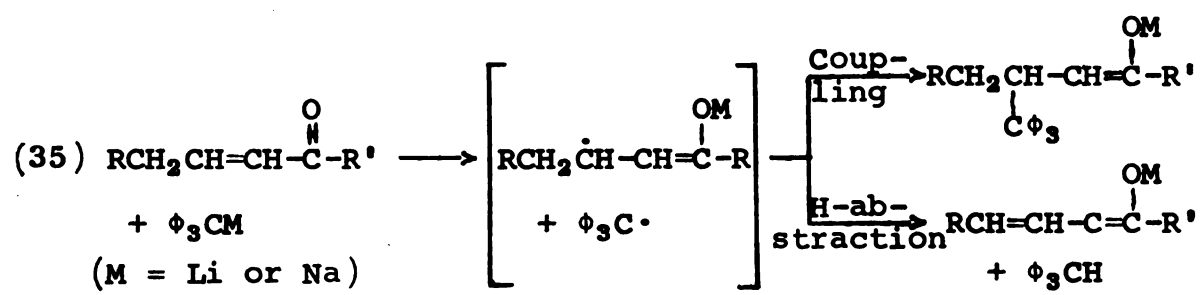
(33) $CH_3CH{=}CHCO_2C_2H_5$ (38) $\xrightarrow[THF,\ -23^0]{\Phi_3CLi}$ $\Phi_3CCH(CH_3)CH_2CO_2C_2H_5$ (39)

(39) $\xrightarrow[EtOH]{KOH}$ $\Phi_3CCH(CH_3)CH_2CO_2H$ (40) 65%

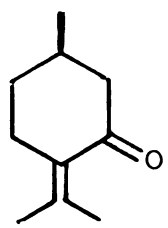
A similar conjugate addition of tritylsodium to 4,4-dimethylcyclopent-2-enone (equation 34) was reported by

(34) 

Bellamy.[14] This unexpected result was rationalized by a steric hindrance effect of the 4,4-dimethyl group. The dipole-dipole interaction of the enone and trityllithium was suggested as the governing factor in orienting the trityl anion on the C-3 side of the gem-dimethyl group in the ground state description of reactants. In order for proton abstraction to occur at the acidic protons at C-5, migration of the trityl anion past the gem-dimethyl group is required; this energy barrier was deemed sufficient to make a Michael addition of the trityl anion to the enone predominate. This argument, however, is theoretically unsound, and a more plausible mechanism that accounts for both the formation of the γ-dienolate conjugate base and the infrequently observed conjugate addition products from the reactions of α,β-unsaturated ketones with trityl bases is shown in equation 35. An initial electron transfer generates

(35) 

a ketyl intermediate which immediately reacts with the accompanying triphenylmethyl radical. The resulting enolate anions, when alkylated or protonated, then lead to the observed products. Whether coupling products or products derived from γ-hydrogen abstraction are obtained appears to be a consequence of the degree of alkyl substitution at the β-carbon atom. Thus pulegone (8) and cholest-4-en-3-one (17), in which the intermediate radical anion



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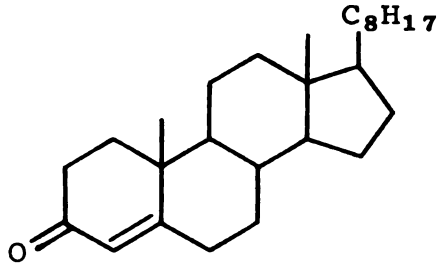

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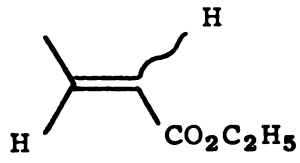
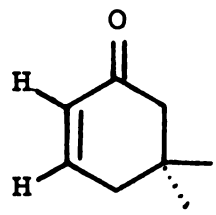
would be tertiary at the β-carbon atom, give products derived from γ-hydrogen abstraction while with ethyl crotonate (38) and 5,5-dimethylcyclohex-2-enone (15), in which the



38

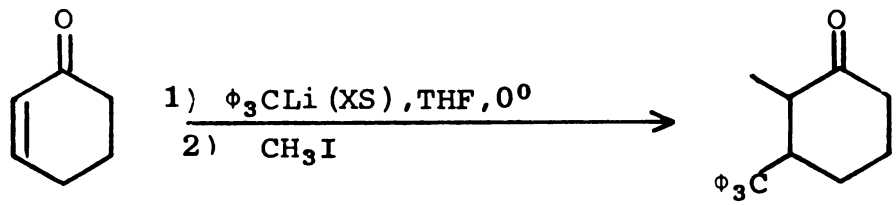


15

corresponding intermediate would be secondary at the

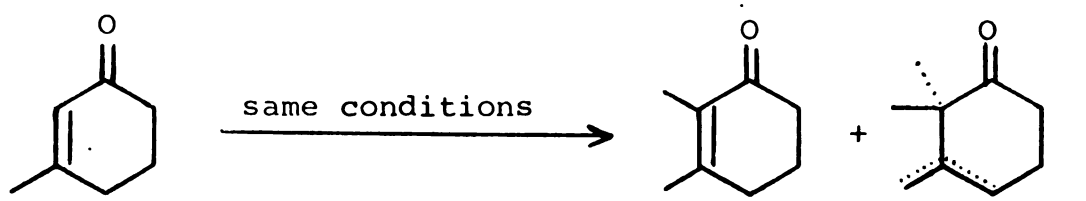
β-carbon atom, coupling products are observed. In support of this argument, only coupling products were obtained when the reaction was applied to cyclohex-2-enone (41), while 3-methylcyclohex-2-enone (43) gave products derived from γ-hydrogen abstraction (no coupling products were observed in this case) (equations 36 and 37). The results obtained

(36)



41 42 60%

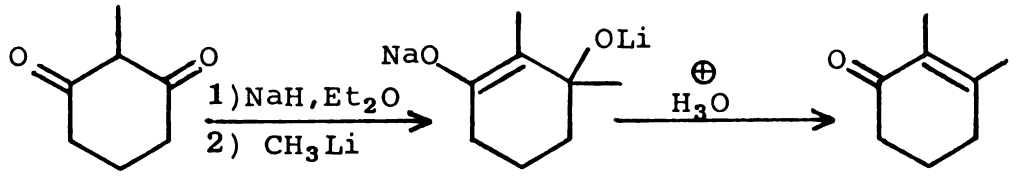
(37)



43 44 23% 45 20%

in the case of cyclohex-2-enone clearly rule out the steric hindrance effect suggested by Bellamy.[14] In summary, it appears that coupling is the preferred reaction but when steric hindrance is sufficient, and an abstractable γ-hydrogen atom is present, dienolate anion formation becomes the predominant reaction.

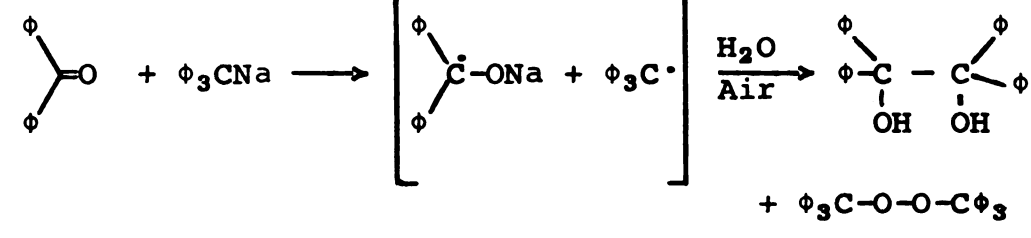
In the course of determining the structure of 44, a product of reaction 37, a novel "single pot" synthesis from 2-methylcyclohexane-1,3-dione (46) was developed. (Equation 38.)

(38) 

46 44 60%

While reactions of carboxylic acid salts with methyllithium to give methylketones are well known,[42] apparently no vinylgous analogs have been reported. An equivalent transformation involving mono-enol ethers of 1,3-cyclohexanediones has been reported;[43] however, the above scheme is particularly attractive for its directness and ease of work-up. The use of metal enolates as protective groups appears to be a general and versatile synthetic procedure.[44]

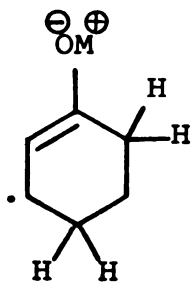
Electron transfer reactions involving the trityl anion and unsaturated electron acceptors are well documented. Schlenk, in 1928, reported[45] the formation of a pinacol from the reaction of tritylsodium with benzophenone (equation 39).

(39) 

In 1964, Russell et al.[46] conducted an electron spin resonance study of radical anions produced by electron transfer from tritylsodium (produced reversibly from triphenylmethane

and sodium ethoxide) to nitrobenzene, m-dinitrobenzene and azobenzene.

In an effort to support the mechanism proposed in equation 35 further, direct evidence for the intermediate ketyl was sought. When 5,5-dimethylcyclohex-2-enone (15) was added to an argon blanketed tetrahydrofuran solution of trityllithium, held at -78° in the resonance cavity of an E-4 Varian ESR Spectrometer, the characteristic signal pattern of the triphenylmethyl radical appeared. This persisted up to 0°, but vanished at 25°. No other resonance signals were observed (Figure 1). The absence of any resonance signal from the ketyl 47 was, however, not unexpected. Russell and Stevenson[47] have noted that when



47

enolizable α'- or γ-protons are present in α,β-unsaturated ketones, the resulting ketyls are so short-lived that detection by electron spin resonance spectroscopy is unsuccessful.

Another, relatively recent, instrumental method for the detection of paramagnetic intermediates is derived from the principle of chemically induced dynamic nuclear polarization (CIDNP).[48,49] According to this principle, enhanced

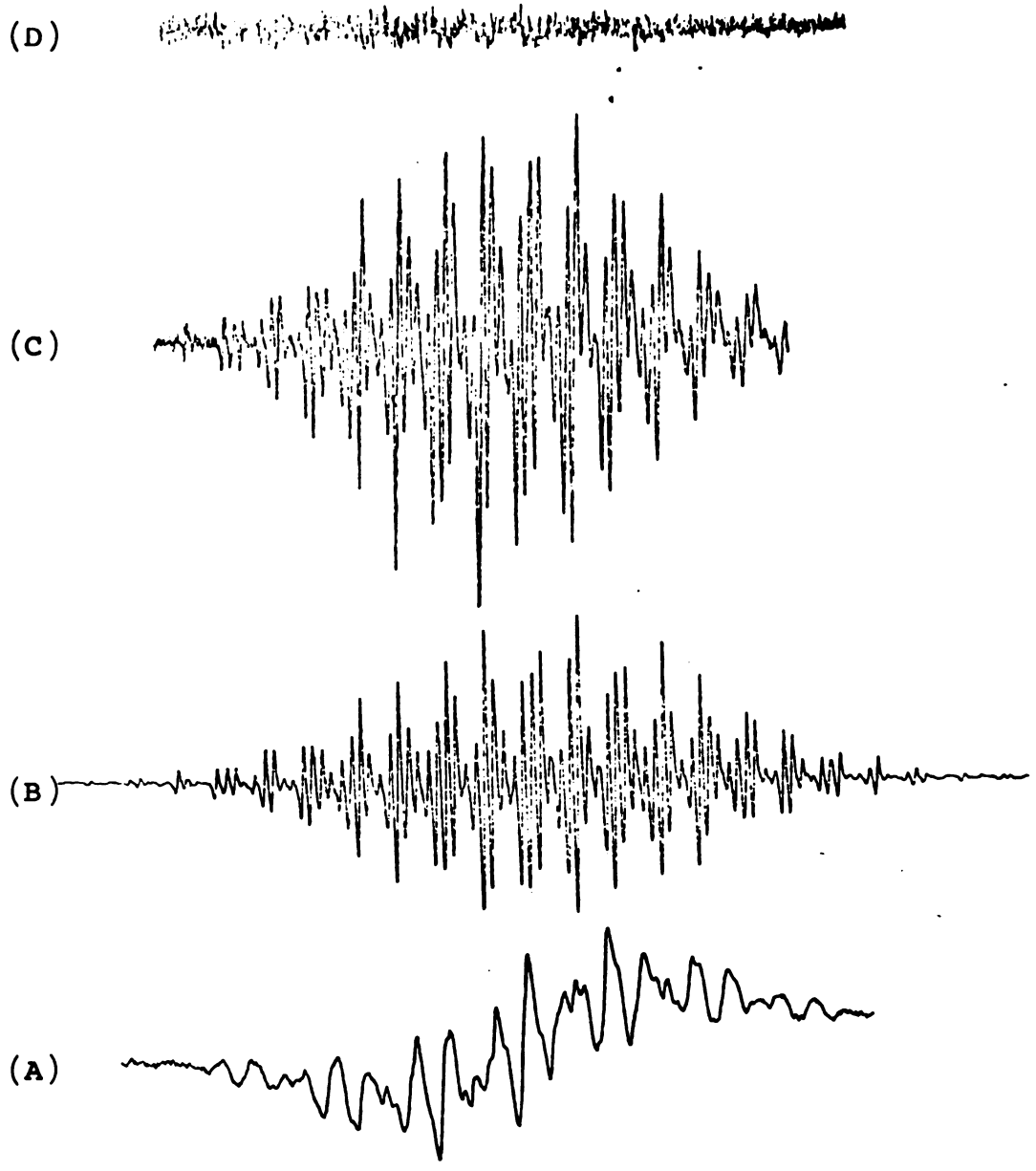
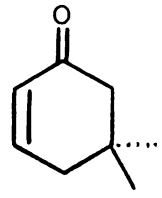


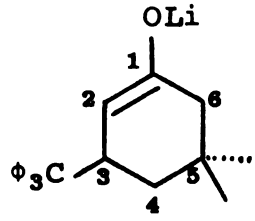
Figure 1. ESR traces of tritylllithium solution, (A) before addition of enone, -78°, (B) immediately after addition, -78°, (C) increased amplitude, 0°, (D) increased amplitude, 25°.

absorption and/or emission of r.f. radiation may be observed in the nmr spectrum of a reaction mixture, as a result of overpopulation of certain nuclear energy levels in compounds derived from radical intermediates produced during the reaction. When a solution of the enone 15 in tetrahydrofuran



15

was added to a cold (-90°) solution of tritylllithium in an nmr tube, the low temperature nmr spectrum showed no enhanced absorption or emission in the region of the C-3 proton or trityl group of 48. However, in one experiment strong



48

emission from the solvent (THF) was observed immediately following the addition of enone 15 to a cold tritylllithium solution. A puzzling weak emission was also noted prior to the enone addition (Fig. 2). Analogous experiments were conducted with cholest-4-ene-3-one, a substrate which does

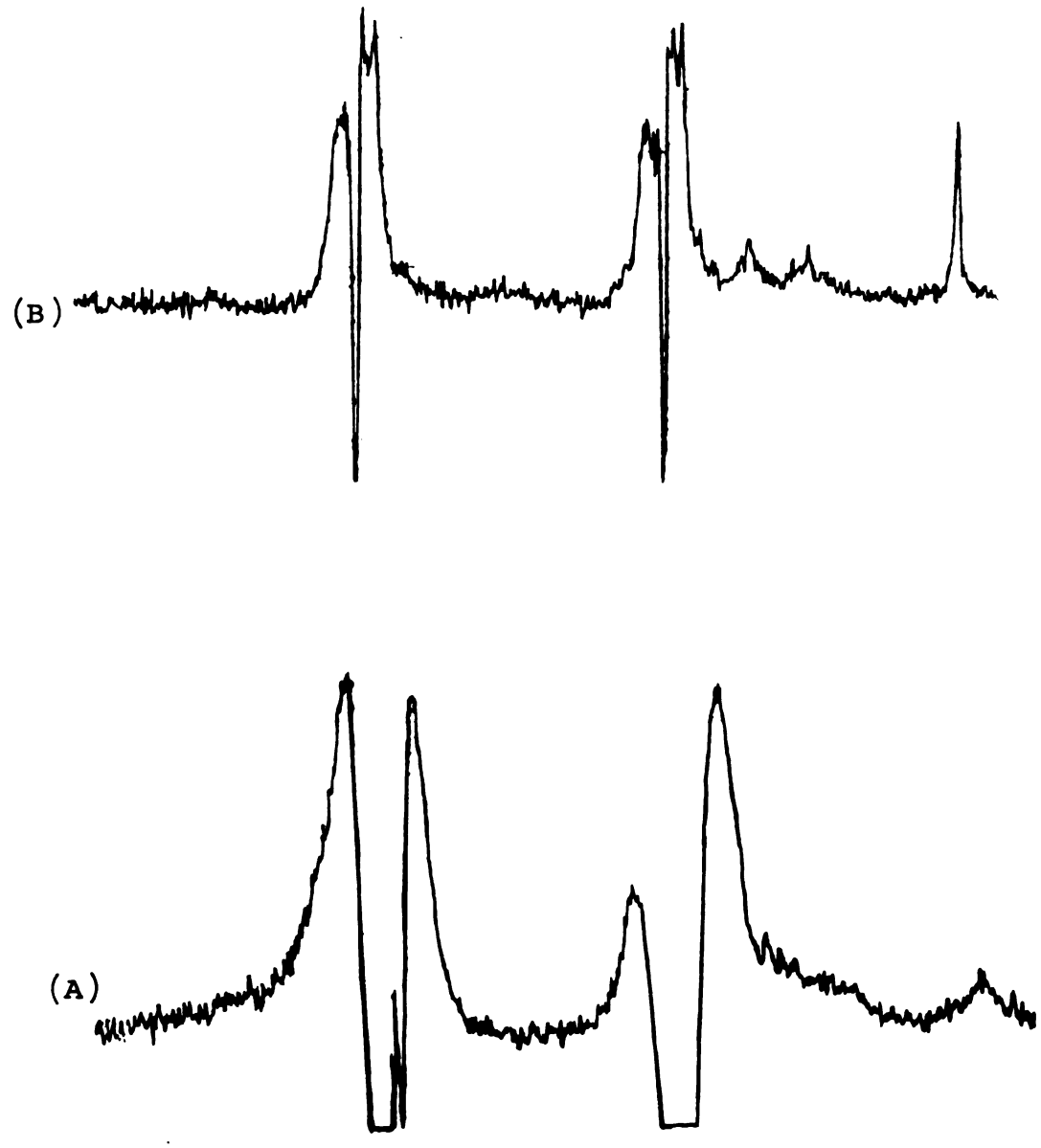
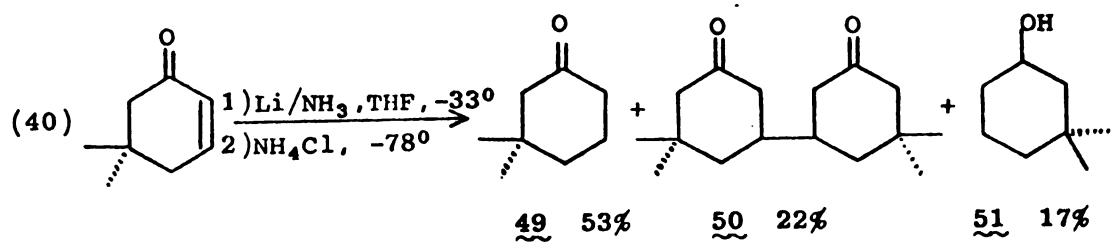


Figure 2. (A) 60Hz Nmr spectrum of tritylllithium in tetrahydrofuran immediately after addition of enone 15, (B) same solution and temperature just prior to addition of 15.

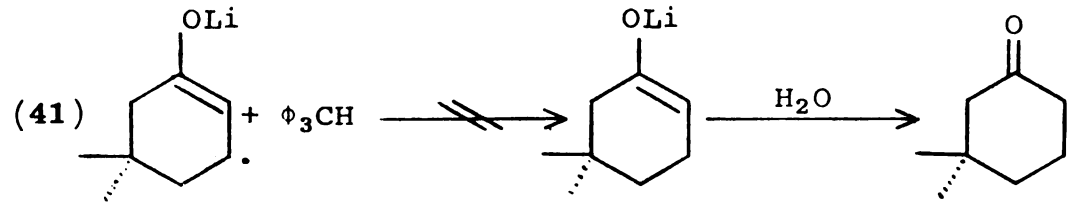
not yield coupling products with tritylllithium. In this case, no enhanced absorption or emission was observed in the region of the methine proton in triphenylmethane.

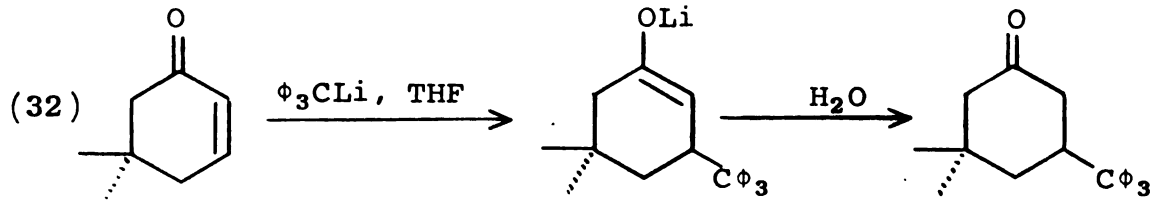
Attempts to trap ketyl intermediates have been unsuccessful. Reductions of α,β-unsaturated ketones with solutions of lithium in liquid ammonia are generally believed to proceed via ketyl intermediates.[1] It was found that lithium in ammonia reduction of enone 15 gave a substantial amount of the dihydrodimer 50 (equation 40).



Similar reductive dimerizations have been reported by House et al.,[50] and it has been suggested[51] that such dimerizations proceed via reaction of an intermediate ketyl with unreduced enone. However, when the reaction of 15 with tritylllithium was carried out in the presence of a large excess of the enone no dimer (50) was obtained.

An attempt to use excess triphenylmethane as a hydrogen-atom trap to reduce the ketyl (equation 41) also failed. The coupling reaction (32) was unchanged and no 3,3-dimethylcyclohexanone could be detected among the products.

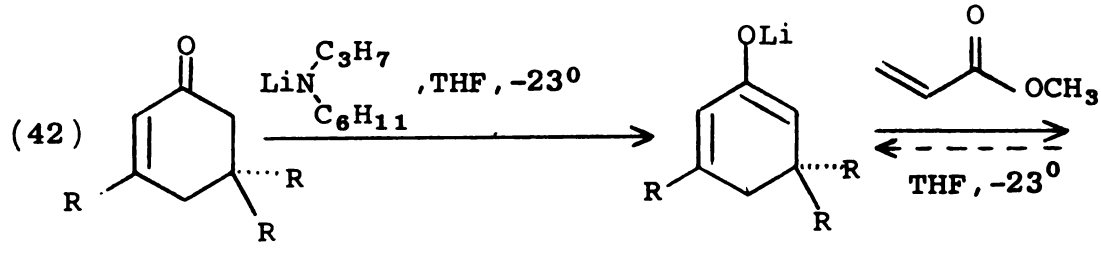


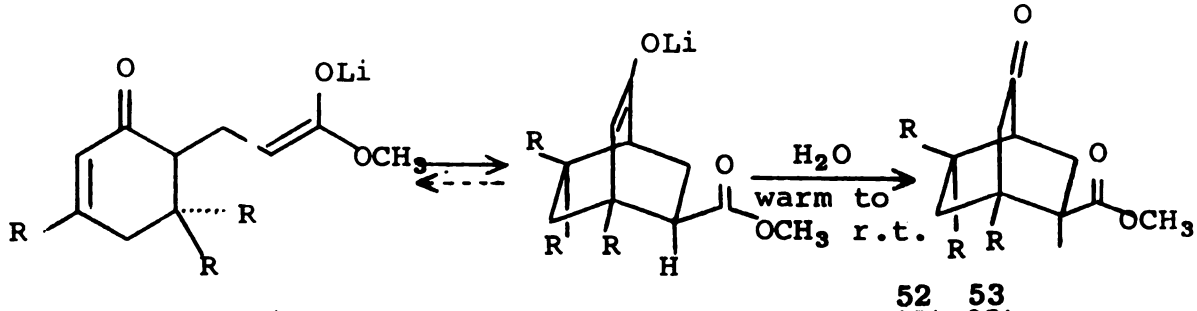


A possible explanation of these results is that the proposed ketyl intermediate and the trityl radical react with each other very rapidly, either by coupling or γ-hydrogen abstraction. The presence of lithium cation in a solvent such as tetrahydrofuran may well be a significant factor in determining this rate, inasmuch as House et al.[50] have observed that added $Li^{\oplus}$ significantly shortens the lifetime of ketyls prepared by electrolysis of α,β-unsaturated ketones by promoting coupling and hydrogen abstraction reactions. A small amount of ketyl may, however, escape the solvent cage and would be rapidly destroyed, either by reaction with solvent or another paramagnetic species. The remaining triphenylmethyl radical may then give rise to the observed esr spectrum.

With a method for the selective generation of α'-dienolate anions from α,β-unsaturated ketones in hand, the

intriguing possibility of sequential Michael reactions of these intermediates with unsaturated carbonyl compounds was explored. The addition of methyl acrylate to the cross-conjugated dienolate bases derived from cyclohex-2-enone and isophorone led to the bicyclo-[2,2,2]octan-2-ones 52 and 53, respectively, in high yield (equation 42). The

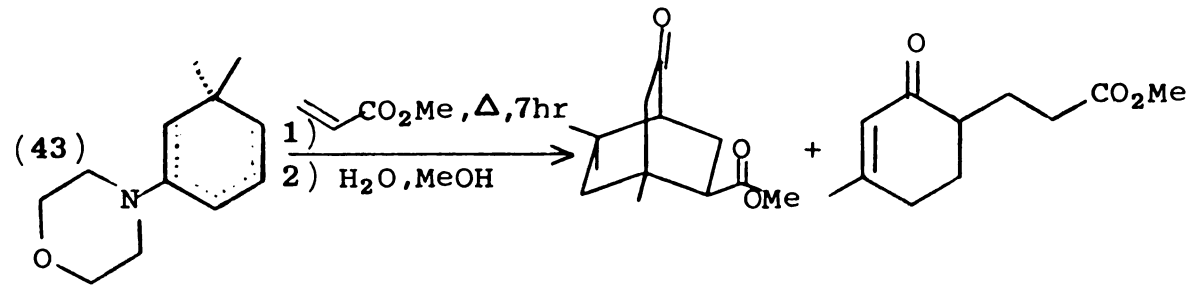




52, R = H, 90%; 53, R = CH_3, 98%

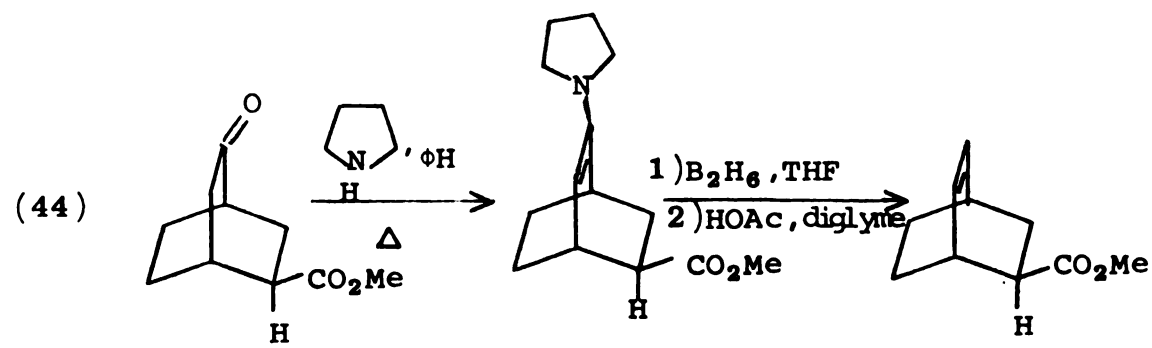
reactions were observed to be highly stereoselective, giving rise in each case to a single diastereomer as evidenced by sharp melting points [52 (2,4 DNP) 139-140°, 53 53-54° (lit.[17] 54-55.5°)] chromatographic homogeneity (glpc, tlc), and sharp carbomethoxy singlets in the nmr spectra (52, δ 3.69; 53, δ 3.70). The nmr spectrum of 53 proved identical to that reported for this compound by H. Nozaki et al.[17]

These workers prepared 53 by the reaction of methyl acrylate with the cross-conjugated dienamine of isophorone (equation 43).



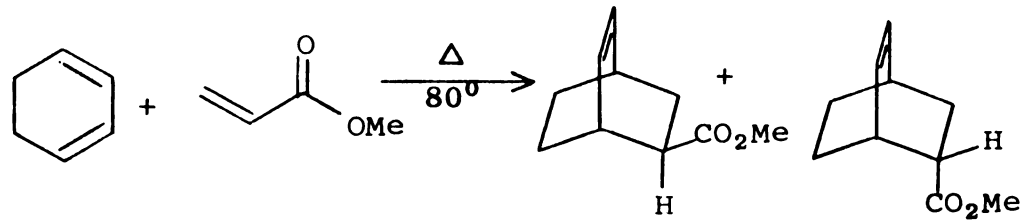
54 53 29% 55 23%

The configuration of the carbomethoxy function at C-5 in 52 was demonstrated by two distinct chemical approaches. In the first, keto-ester 52 was converted to the ene-ester 57 by the general method of Lewis and Pearce[53] (equation 44).



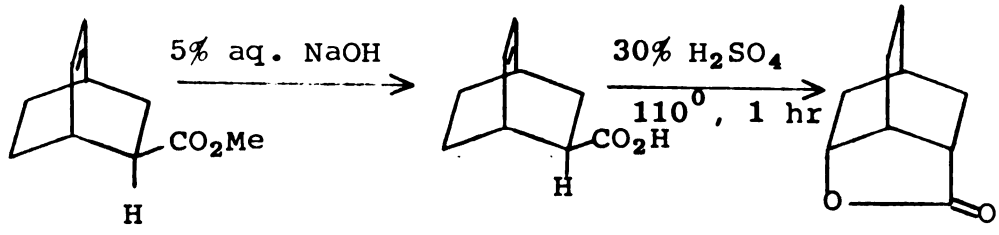
52 56 57

Product 57 proved to be identical (glpc, ir, nmr) with the major isomer formed in the Diels-Alder cycloaddition of methyl acrylate with 1,3-cyclohexadiene (equation 45).

(45) 

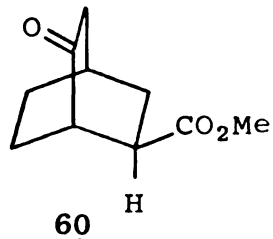
9.6 : 0.4

The major product of reaction 45 was reported[54] to be the endo-isomer, and this was further established by conversion of the ene-ester 57 to the known endo-ene-acid 58, mp 54-55° (lit.[55] 56-57°), and subsequent lactonization (equation 46).

(46) 

57 58 59

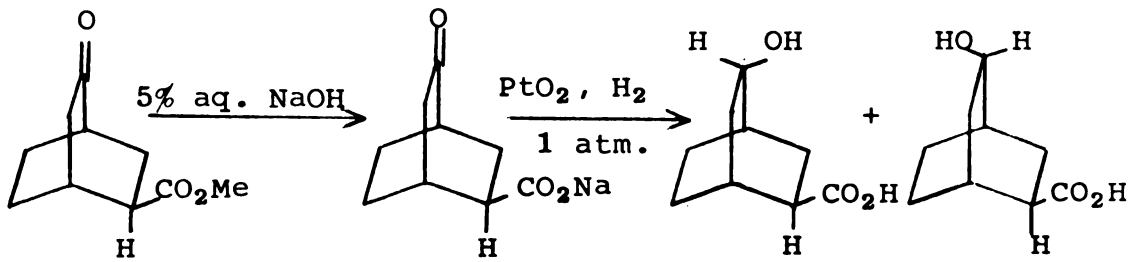
The melting point of the stereoisomeric exo-ene-acid is 46-47°. While this approach established the bicyclo[2,2,2]-octane skeleton in 52, and showed the stereochemistry of the C-5 carboxyl function, it did not permit exclusion of the isomeric structure 60. In the second approach, keto-ester 52 was saponified to the keto-carboxylate 61, which



60

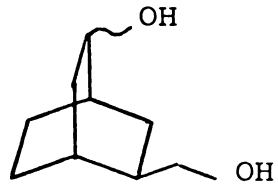
was then reduced by catalytic hydrogenation to give, in 80% yield, a mixture containing 89% syn-hydroxy-acid 62 and 11% of the anti-isomer 63 (equation 47). A similar stereoselec-

(47)



52 61 62 71% 63 9%

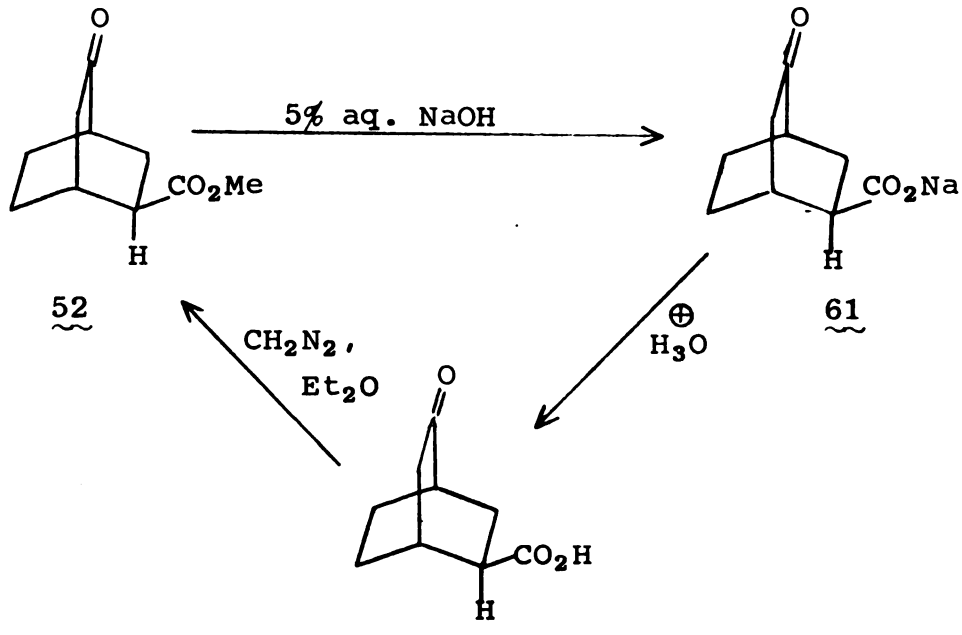
tive reduction of sodium cyclohexan-1-one-4-carboxylate has been reported by Plattner et al.[56] In contrast, sodium borohydride reduction of 52 gave a 50:50 mixture of the hydroxy-esters and a small amount of a compound tentatively identified as the diol 64. The absence of epimerization at C-5 during saponification was demonstrated by methylation



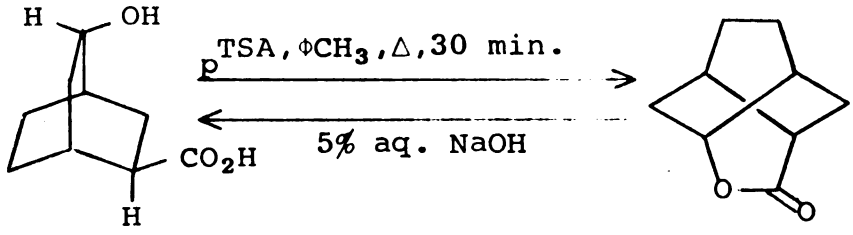
64

(CH_2N_2) of the resulting carboxylic acid (equation 48).

(48)

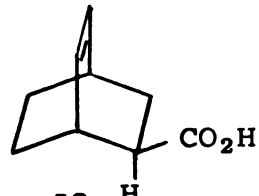


Lactonization of the syn-hydroxy-acid 62 was accomplished in refluxing toluene containing para-toluenesulfonic acid (equation 49). Attempts to effect this conversion with acetic anhydride or dicyclohexylcarbodiimide and pyridine were unsuccessful. The absence of skeletal rearrangement



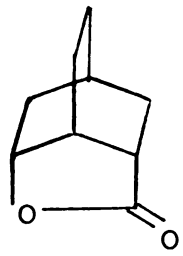
62 66

in the lactonization was shown by saponification of lactone 66 to the starting hydroxy-acid 62. A lactone alleged to be 66 was prepared by Storm and Koshland[57] by reaction of ene-acid 58 with 75% sulfuric acid (24 hr). The properties



58

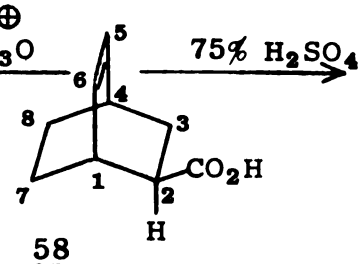
characterizing the lactone prepared here by reaction 49 (ir 1750 cm^{-1}, mp 204.5-205.5°) are clearly different, however, from those (ir 1735 cm^{-1}, mp 229-230°) reported by these workers and while a compound absorbing at this frequency (1735 cm^{-1}) in the ir was noted in the reaction (46) giving 59 it was not identical to 66 by glpc analysis. This discrepancy strongly suggests that the structural assignment



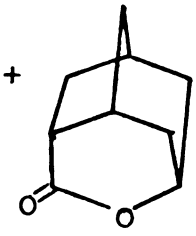
59

in the earlier work is incorrect. Very recently, Moriarty and Adams[58] also contested the assignments made by Storm and Koshland, and showed that acid induced lactonization of 58 does not yield 66, but gives instead the bicyclo[3,2,1]-octyl δ-lactone 67 (equation 50).

(50) 66 ⟵ $\overset{\oplus}{H_3O}$ // 75% H_2SO_4 ⟶ 59 +



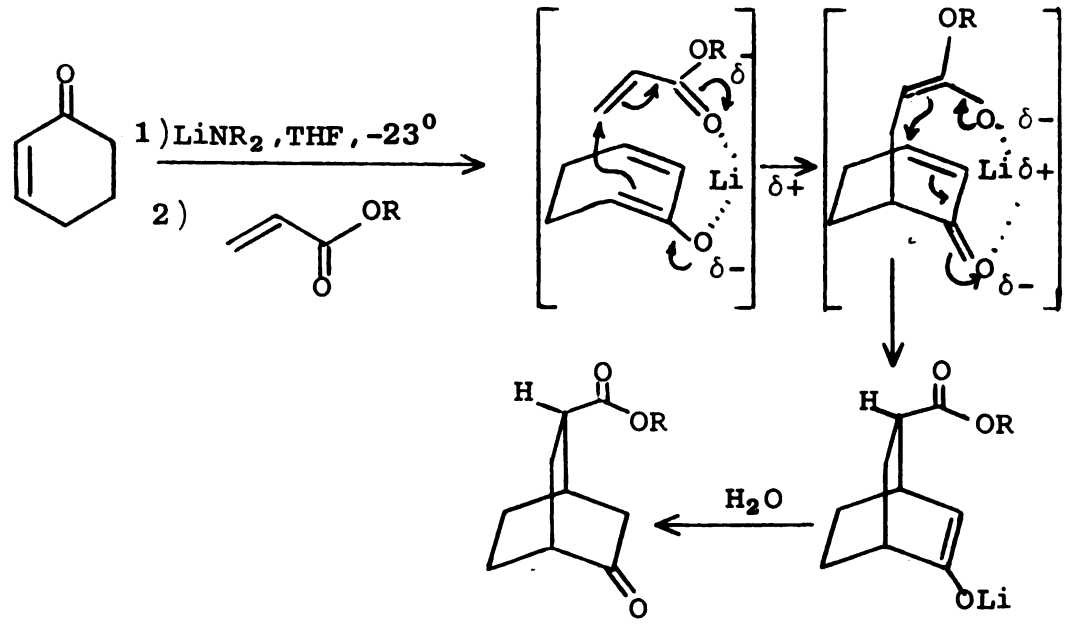
58
or C-2 epimer



The mechanism of the cyclization involving cross-conjugated dienolate bases and Michael acceptors has not been rigorously defined. A Diels-Alder cycloaddition is clearly possible; however, in view of the very high yields observed under exceptionally mild conditions with substrates of varying steric hindrance, a path involving sequential Michael additions seems more favorable.

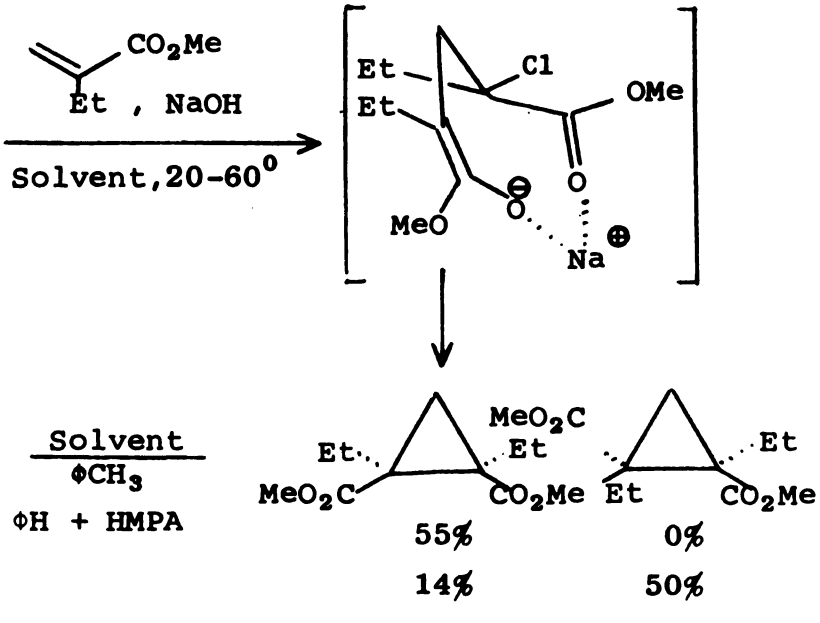
The observed stereochemistry could be rationalized in such a mechanism by a metal-oxygen coordinated transition state, such as that shown in equation 51. A similar effect

(51)

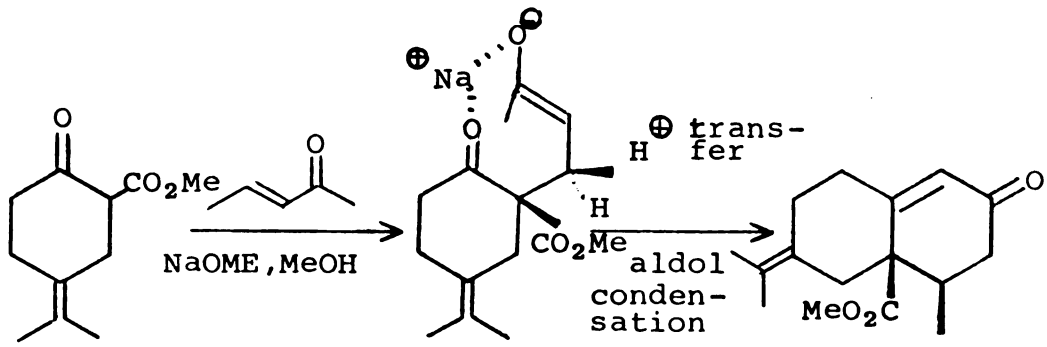


has been invoked[1] to explain the observed stereochemistry in certain other Michael reactions (equations 52 and 53).

(52) Et-C(H)(Cl)-CO_2Me



(53)



The large product dependency on solvent observed in reaction 52 suggests that an investigation of different solvent systems in the reaction of cross-conjugated dienolate bases with Michael acceptors may well prove worthwhile in further elucidating the mechanism.

EXPERIMENTAL

General

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian T-60 high resolution spectrometer; low temperature nmr spectra were recorded on a Varian A56/60 high resolution spectrometer; tetramethylsilane was used as an internal standard in all cases. Electron spin resonance spectra were obtained with a Varian E-4 spectrometer. Ultraviolet spectra were recorded on a Unicam SP-800 spectrophotometer. Mass spectra were obtained with an Hitachi RMU-6 mass spectrometer.

Melting points were taken on either the Hoover-Thomas apparatus (capillary tubes) or on a hot-stage microscope and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter.

Gas-liquid phase chromatographic analyses (glpc) were conducted with either a Varian 1200 flame ionization gas chromatograph or an Aerograph A-90P3 thermal conductivity instrument.

Micro-analyses were performed by either Spang Microanalytical Labs, Ann Arbor, Michigan or Chemalytics, Inc., Tempe, Arizona.

In reactions involving moisture and oxygen sensitive reagents the reaction flask was flame-dried under argon.

Methylation of Pulegone (8) Using Lithium Isopropylcyclohexylamide (LiICA) as the Base

To a solution of 55.6 mg of durene (internal standard) in 12 ml dry (distilled from a benzophenone ketyl solution) tetrahydrofuran (THF) was added 0.23 ml (1.45 mmoles) of isopropylcyclohexyl amine (ICA). The stirred solution was cooled (0^0) while 0.6 ml of 2.2M (1.32 mmoles) n-butyllithium in hexane was added under an argon atmosphere. After the reaction was stirred at 0^0 for 25 minutes, 188 mg (1.23 mmoles) of pulegone was slowly added and the resulting solution of the conjugate base was held at 0^0 for one hour. Rapid addition of 0.8 ml (12.8 mmoles) of methyl iodide completed the reaction, and the resulting mixture was allowed to warm to room temperature while it was stirred. After it had stood overnight, the reaction was worked-up by the addition of water and ether, the aqueous phase was extracted several times. The combined ether extracts were washed twice with five percent hydrochloric acid and once each with dilute sodium bicarbonate and saturated sodium sulfate solutions. Gas chromatographic analysis (20% SE-30, 163^0) of the dried ($MgSO_4$) concentrated (reduced pressure) extracts showed 56% methylpulegones (9), (45% major, 11% minor) and 23% methylisopulegones (10), (17% major, 6% minor). Analytical samples (preparative glpc) gave the following spectral data:

Methylpulegones (9):

(a) Major ir (liquid film) 1675 cm^{-1}, 1620 cm^{-1}; nmr (CCl_4) δ1.87 (s, 3H, vinyl $\underline{CH_3}$), 1.75 (s, 3H, vinyl $\underline{CH_3}$), 1.05 (d, 6H, J 7Hz, C-2 HC$\underline{CH_3}$, C-3 HC$\underline{CH_3}$), 3.0-1.2 (m, 6H); nmr (benzene) δ2.20 (s, 3H, vinyl $\underline{CH_3}$), 1.48 (s, 3H, vinyl $\underline{CH_3}$), 1.16 (d, 3H, J 6Hz, C-2 HC$\underline{CH_3}$), 0.82 (d, 3H, J 6Hz, C-3 HC$\underline{CH_3}$), 2.6-1.0 (m, 6H); mass spectrum (70 eV) m/e (rel intensity) 166(100), 167(17), 95(92); calcd for $C_{11}H_{18}O$: P + 1(167) = 0.122P(166). A sample of 56.2 mg of the pure major isomer of methylpulegone obtained by auto-annular vacuum spinning band distillation (Nester/Faust Auto Annular Teflon Spinning Band Distillation Column) had bp 125-128° (14-18 mm), $[\alpha]_D$ = (+)57.30 (0.562 g/100 ml chloroform).

(b) Minor Mass spectrum (70 eV) m/e (rel intensity) 166(66), 167(8), 95(100); P + 1(167) = 0.121P(166). Calcd. for $C_{11}H_{18}O$: P + 1(167) = 0.125P(166).

Methylisopulegones (10)[3]:

(a) Major ir (liquid film) 1703 cm^{-1}, 1643 cm^{-1}; nmr (CCl_4) δ4.87 (d, 2H, J 7Hz, vinyl protons), 1.68 (s, 3H, vinyl $\underline{CH_3}$), 1.10(s, 3H, C-6 C-$\underline{CH_3}$), 0.96 (d, 3H, J 5Hz; C-3 HC$\underline{CH_3}$), 2.75-1.0 (m, 7H); mass spectrum (70 eV) m/e (rel intensity) 166(14),

(b) Minor ir (liquid film) 1705 cm^{-1}, 1640 cm^{-1}; nmr (CCl_4) δ4.85 (d, 2H, J 10.0Hz, vinyl protons), 1.68 (s,

3H, vinyl $\underline{CH_3}$), 1.05 (d, 3H, J 6Hz, C-3 HC$\underline{CH_3}$), 1.01 (s, 3H, C-6 C$\underline{CH_3}$), 2.6-1.2 (m, 7H); mass spectrum (70 eV) m/e (rel intensity) 166(24), 123(100).

Attempted Epimerization of the Methylated Pulegone Mixture

The crude mixture of methylpulegones (9) and methylisopulegones (10) was dissolved in methanol and a small amount of solid potassium hydroxide added. The solution was refluxed for one hour, cooled to 25° and stirred at this temperature for one hour. The methanol was removed under reduced pressure, the residue neutralized with 6N HCl and the aqueous solution extracted twice with ether. The combined ether extracts were washed once each with water and saturated sodium sulfate solution and dried over $MgSO_4$. Gas chromatographic analysis (15% SE-30, 125°) of the concentrated solution (reduced pressure) showed identical ratios of products as found in the original mixture.

Base Catalyzed Deuterium Exchange of Pulegone (8)

To 10 ml of deuterium oxide under dry nitrogen at 0° was added 100 mg of sodium peroxide and 1.0 g of pulegone. Dioxane (20 ml) was added to the stirred solution to achieve homogeneity, and the mixture was held at 0° for 15 minutes. A small aliquot was removed and the recovered pulegone, collected by preparative glpc (15% SE-30, 125°), was subjected to mass spectroscopic analysis (see Table I). The remaining

solution was warmed to 25° and stirred for one day, following which a second sample of pulegone was obtained in the same manner (see Table I). The remaining solution was extracted with pentane and the combined extracts evaporated under reduced pressure. Deuterium oxide, sodium peroxide and dioxane were then added to the residue, and the resulting mixture was stirred at room temperature for one week. A third sample of pulegone collected at this time proved to be mainly a mixture of d_7- and d_8-pulegone (see Table I).

5,5-Dimethylcyclohex-2-enone (15)

This compound was prepared by the general method of Gannon and House.[43] 3-Methoxy-5,5-dimethylcyclohex-2-enone (15.4 g, 100.0 mmoles) in 16 ml of ether was added slowly (1 hr) to a solution of 2.0 g (52.5 mmoles) lithium aluminum hydride (LAH) in 60 ml of anhydrous ether. The mixture was refluxed for 30 min and cooled to 0°. Water (5 ml) was added cautiously to the stirred mixture, and after 10 minutes at 25°, the resulting mixture was poured into 200 ml of cold, ten percent sulfuric acid. The combined organic extracts from these ether extractions of the aqueous mixture were washed once each with water and saturated sodium bicarbonate solution and then dried over $MgSO_4$. The ether was removed from the extract solution by distillation through a 20 cm vigreaux column. Distillation of the residue through the same column afforded 10.05 g (84%) 15, bp 48.0-48.5° (3.0 mm) [lit.[60] 77-78° (18 mm)]; ir (liquid film) 1675 cm^{-1};

nmr (CCl_4) δ6.80 (dt, 1H, $J_{3,2}$ 10Hz, $J_{3,4,a,e}$ 4Hz, H3), 5.90 (dt, 1H, $J_{2,3}$ 10.0Hz, $J_{2,4a,e}$ 2Hz, H2), 2.16 (bs, 4H, H2a,e, H4a,e), 1.03 (s, 6H, $C(CH_3)_2$).

5,5,6-Trimethylcyclohex-2-enone (16)

To a solution of 1.6 mmoles LiICA, prepared from 0.281 ml (248 mg, 1.76 mmoles) ICA and 0.729 ml of 2.2M n-butyllithium in hexane in tne same manner described for pulegone (8), in THF at 0° under a nitrogen atmosphere and containing 48.7 mg durene (internal standard), was added, over a period of 10 min, 187 mg (1.51 mmoles) enone 15. The reaction mixture was stirred under nitrogen at 0° for 1 hr, 15 min, and then quenched by rapid addition of excess methyl iodide. The mixture was allowed to warm to 25° and was then stirred at this temperature overnight. Water and ether were added, the aqueous solution was extracted three times, and the combined extracts were washed twice with 1N hydrochloric acid, and once each with water, dilute sodium bicarbonate and saturated sodium sulfate solutions. Glpc analysis (20% SE-30, 145°) of the dry ($MgSO_4$), concentrated (reduced pressure) solution showed a mixture of 16 (83%), 15 (10%) and an impurity (5%) present in the starting material (15). An analytical sample of 5,5,6-trimethylcyclohex-2-enone (16) obtained by preparative glpc exhibited the following properties: λ_{max}(EtOH) 227 nm (ε8850) [lit.[61] λ_{max} 227.5 nm (ε 5950)]; ir (liquid film) 1680 cm^{-1}; nmr (CCl_4) δ6.72 (dt, 1H, $J_{3,2}$ 10.0Hz, $J_{3,4a,e}$ 4Hz, H3), 5.95 (dt, 1H, $J_{2,3}$ 10.0Hz,

$J_{2\ 4a,e}$ 2Hz, H2), 2.22 (m, 3H, H4a,e, H6), 1.07, 0.88 (6H, C-5 $C(CH_3)_2$), 1.00 (d, 3H, J 6.5Hz, C-6 $HC\underline{CH_3}$); mass spectrum (70 eV) m/e (rel intensity) 138(24), 139(3.0), 68(100); P + 1(13a) = 0.12P(138); calcd for $C_9H_{14}O$: P + 1(139) = 0.099P(138).

Methylation of Pulegone (8) Using Triphenylmethyllithium as the Base

(a) To 2.02 g (8.3 mmoles) of triphenylmethane in dry THF at 0° under nitrogen, was added 3.2 ml of 2.39M n-butyllithium in hexane to the stirred mixture. The resulting red solution was warmed to room temperature and stirred for one hour, before being cooled to 0° again. A solution of durene (internal standard) in dry THF was added followed by the dropwise addition of pulegone (8) (1 ml, 6.12 mmoles) over a 10 min period. After the orange reaction mixture was stirred at 0° for 1 hr, methyl iodide (0.572 ml, 9.2 mmoles) was added and the mixture was refluxed overnight. The residue remaining after the solvent (THF) was removed under reduced pressure, was added to ice water and extracted with ether. The combined extracts were washed once each with aqueous ammonium chloride and water and dried over $MgSO_4$. Gas chromatographic analysis of the concentrated ether solution showed 20% methylpulegones (9) (14% major, 6% minor) and 61% methylisopulegones (10) (48% major, 13% minor).

(b) The same procedure as in (a) was followed with the exception that 1.25 equivalents of tetramethylethylene-

diamine (TMEDA) was added to the THF solution of triphenylmethane. Glpc analysis showed a mixture containing 9 (5%) and 10 (68%) (52% major, 16% minor).

(c) The same procedures as in (a) was followed except that 1.25 equivalents of ICA was added immediately preceding the addition of methyl iodide. Glpc analysis of the final mixture showed 9 (14%) and 10 (68%) (54% major, 14% minor).

3-Triphenylmethyl-2,5,5-trimethylcyclohexanone (36)

Enone 15 (1.2 g, 10.0 mmoles) was added slowly to a stirred cold (0°) solution of 12.31 mmoles of triphenylmethyllithium in dry THF [prepared from 5.15 ml of 2.39M n-butyllithium and 3.27 g (13.4 mmoles) triphenylmethane as described in the previous section] maintained under an argon atmosphere, and containing 304 mg durene as an internal standard. After the mixture was stirred for one hour at 0°; methyl iodide (1.4 ml, 22.4 mmoles) was added and the solution kept at reflux overnight. Water and ether were added to the cooled mixture, and the aqueous solution was extracted and the combined extracts washed once each with water and saturated sodium sulfate solution. After removal of the solvents from the dried extracts under reduced pressure, the residue was mixed with ether to afford 949 mg of a white solid, mp 191-197°. Recrystallization from ethyl acetate and sublimation gave colorless crystals of 36,

mp 204.5-207°; ir 1700 cm^{-1}; nmr (CCl_4) δ7.34 (m, 15H, $-C\phi_3$), 3.67 (bt, 1H, $J_{3,2a}$, $J_{3,4a}$ 11Hz, H3), 1.92 (m, 4H, H2a, H2e, H6a,e), 1.18 (s, 3H, C-5 $\underline{CH_3}$), 0.92 (s, 3H, C-5 $\underline{CH_3}$), 0.92 (m, 1H, H4a), 0.67 (d, 3H, J 6Hz, C-2 $\underline{CH_3}$); the mass spectrum did not show a parent ion, highest m/e (70 eV) was 243 (ϕ_3C +).

Anal. Calcd. for $C_{28}H_{30}O$: C, 87.91; H, 7.91.

Found: C, 87.91; H, 7.75.

Glpc analysis (5% SE-30, 200°) of the remainder of the 949 mg of white solid showed 65.4% 36, 24.8% 37, and 10% of an unidentified impurity. Glpc analysis of the filtrate residue containing the internal standard showed 2.26 g 36, and 235 mg 37. The total yield of 36 was 75%.

3-Triphenylmethyl-5,5-dimethylcyclohexanone (37)

Freshly distilled enone 15 was added to a stirred solution of 0.66 mmoles of triphenylmethyllithium in THF (prepared in the usual manner) at 0° under argon. After the mixture was stirred for 5 min at this temperature, water and ether were added and the aqueous solution extracted. The combined extracts were washed twice with water, once with saturated sodium sulfate solution and dried ($MgSO_4$). After removal of the solvent under reduced pressure, ether was added to afford 61 mg of 37, mp 225-230°. The filtrate residue was subjected to preparative thick layer chromatography (silica gel, methylene chloride) and gave 45 mg

additional 37, mp 223-229° (total 106 mg, 77%). An analytical sample obtained by recrystallization from ethyl acetate had mp 230.5-232°; ir 1704 cm^{-1}; nmr (100 mHz, $CDCl_3$) δ7.34 (bs, 15H, $-C\phi_3$), 3.78 (tt, 1H, $J_{3,4a}$, $J_{3,2a}$ 12.5Hz, $J_{3,4e}$, $J_{3,2e}$ 2.5Hz, H3), 2.57 (dd, 1H, $J_{2e,2a}$ 12.5Hz, $J_{2e,3}$ 2.5Hz, H2e), 2.07 and 1.88 (ABq, 2H, J 13.5Hz, H6a,e), 1.84 (dd, 1H, $J_{4e,4a}$ 12.5Hz, $J_{4e,3}$ 2.5Hz, H4e), 1.56 (t, 1H, $J_{2a,2e}$, $J_{2a,3}$ 12.5Hz, H2a), 1.17 (s, 3H, C-5 CH_3), 0.94 (s, 3H, C-5 CH_3), 0.95 (t, 1H, $J_{4a,e}$, $J_{4a,3}$ 12.5Hz, H4a); mass spectrum (70 eV) showed no parent ion; 60% of the total ion current consisted of m/e 243 (ϕ_3C +).

Anal. Calcd. for $C_{27}H_{28}O$: C, 88.00; H, 7.66.
Found: C, 88.02; H, 7.87.

3-(1,1,1-Triphenylmethyl)-butanoic Acid (40)

Ethyl crotonate (38) (319 mg, 2.8 mmoles) was added slowly to a stirred solution of 3.92 mmoles of triphenylmethyllithium (prepared in the usual way) in 12 ml of dry THF at -23° (Dry Ice, CCl_4) under argon. After the mixture was stirred at this temperature for 25 min it was extracted with ether and the combined extracts washed and dried. Glpc analysis (5% SE-30, 220°) of the concentrated solution showed one major peak at longer retention time than triphenylmethane and no ethyl crotonate. The viscous residue (1.4 g) obtained after removal of solvent was saponified with refluxing 10% ethanolic potassium hydroxide.

After removal of the solvent under reduced pressure, the residue was washed three times with ether and then acidified with 6N hydrochloric acid. Extraction with methylene chloride and chloroform, however, afforded only 10 mg of the acid 40. The previously obtained ether extracts were combined, methylene chloride and 6N hydrochloric acid were added and the acidic aqueous solution was extracted with methylene chloride. The combined extracts were washed twice with water, once with saturated sodium sulfate solution, dried ($MgSO_4$) and concentrated to leave 1.0 g of residue which yielded 389 mg of crude, solid acid 40 after mixing with ether. An analytical sample was obtained by recrystallization of a small amount of this from aqueous methanol and had mp 219-220° (lit.[40] 213.5-215.5°); ir 3000 cm^{-1}, 1700 cm^{-1}; nmr ($CDCl_3$) δ7.34 (m, 15H, $-C\phi_3$), 4.02 (m, 1H, H3), 2.84 (bd, 1H, $J_{2g,a}$ 15Hz, H2 gauche to H3), 1.55 (dd, 1H, $J_{2a,g}$ 15Hz, $J_{2a,3}$ 11Hz, H2 anti to H3), 0.95 (d, 3H, J 6Hz, C-3 CH_3).

A portion (117 mg) of the ethereal filtrate residue (542 mg) was subjected to preparative thick layer chromatography (silica gel, methylene chloride) and yielded 35 mg of acid 40. The total yield of 40 is 575 mg (65%).

3-Triphenylmethyl-2-methylcyclohexanone (42)

To a cooled (0°) stirred solution of 2.37 mmoles triphenylmethyllithium, containing 82 mg of durene (internal standard) was added, under an argon atmosphere 185 mg (1.93

mmoles) of cyclohex-2-enone in dry THF. The mixture was stirred at 0° for 1 hr followed by the addition of 1 ml (2.28 g, 16.0 mmoles) of methyl iodide. After the mixture was warmed to 25° and stirred for 2 hrs, it was diluted with water and ether. The aqueous solution was extracted three times, and the combined extracts were washed twice with water, once with saturated sodium sulfate solution and finally dried over $MgSO_4$. Glpc analysis (20% SE-30, 140°) showe no volatile products. Preparative thick layer chromatography (silica gel, methylene chloride) of 174 mg of the residue (1.1 g) remaining after removal of the solvent afforded 63 mg (60%) of ketone 42. An analytical sample obtained by recrystallization from ethyl acetate and aqueous ethanol had mp 162-164°; ir (KBr) 1705 cm^{-1}; nmr ($CDCl_3$) δ7.34 (m, 15H, - $C\phi_3$), 3.67 (m, 1H, H3), 2.75-1.90 (m, 3H, C-2 methine and C-6 methylene protons), 1.80-1.20 (m, 4H, C-4, C-5 methylene protons), 1.16 (d, 3H, J 7Hz, C-2 CH_3).

Anal. Calcd. for $C_{26}H_{26}O$: C, 88.09; H, 7.39.
Found: C, 87.94; H, 7.33.

Methylation of 3-Methylcyclohex-2-enone (43) Using Triphenylmethyllithium as the Base

To a cooled (0°) solution of 2.0 mmoles triphenylmethyllithium in dry THF under argon was added slowly 172 mg (1.56 mmoles) of freshly distilled 3-methylcyclohexenone (43). After 20 min at 0°, methyl iodide was added (1 ml, 16.0 mmoles) and the mixture was allowed to warm to 25° and

was stirred at this temperature for 4 hr. Water and ether were added and the aqueous solution was extracted in the usual manner. Glpc analysis (4% QF-1, 150°; 5% SE-30, 70°) of the concentrated solution showed at least 8 components: recovered 3-methylcyclohex-2-enone (43) (9%), 2,3-dimethylcyclohex-2-enone (44) (23%), 2,2,3-trimethylcyclohex-3-enone (45i) and 2,2-dimethyl-3-methylenecyclohexanone (45ii) (20% of a 50:50 mixture by nmr and glc analysis. Inseparable on 4% QF-1 and only partially resolved on 5% SE-30) and four minor unidentified compounds of approximately equal abundance (total 11%). Temperature programmed glpc analysis (up to 250°) showed the absence of any material at longer retention times than triphenylmethane. A sample of the mixture of double bond isomers 45i and 45ii obtained by preparative glpc was examined by: ir (liquid film) 1715 cm^{-1}, 1630 cm^{-1}, 885 cm^{-1} ($=CH_2$); nmr (CCl_4) (a) 2,2,3-trimethylcyclohex-3-enone δ5.5(1H, m, C-4 vinyl proton), 2.4 (m, 4H, C-5, C-6 methylene protons), 1.7 (bs, 3H, C-3 $\underline{CH_3}$), 1.23 [s, 3H, C-2 $C(CH_3)_2$], 1.13 [s, 3H, C-2 $C(CH_3)_2$]; (b) 2,2-dimethyl-3-methylenecyclohexanone δ4.8 (bs, 2H, C-3 $=CH_2$), 2.4 (m, 4H, C-4, C-6 methylene protons), 1.7 (m, 2H, C-5 methylene protons), 1.23 [s, 3H, C-2 $C(CH_3)_2$], 1.13 [s, 3H, C-2 $C(CH_3)_2$]; mass spectrum (70 eV) m/e (rel intensity) 138 (37), 139(4.0), 96(93), 81(100), 67(82); P + 1(139) = 0.12P (138). Calcd. for $C_9H_{14}O$: P + 1(139) = 0.10P(138).

A sample of 2,3-dimethylcyclohex-2-enone (44) obtained by preparative glpc had identical glpc retention time

(4% QF-1, 5% SE-30) and identical ir and nmr spectra as a sample prepared independently from 2-methylcyclohexane-1,3-dione.

2,3-Dimethylcyclohex-2-enone (44)

To a stirred solution of 2-methylcyclohexane-1,3-dione in 100 ml of anhydrous ether maintained at room temperature under argon, was added 44 mmoles of sodium hydride (from 2.0 g of 52.8% oil dispersion after washing with pentane). After it had stirred at 25° for 2 hr, the heterogeneous mixture was refluxed for one hour, cooled to 25° and treated with 25 ml of 2.3M methyllithium in ether (57.5 mmoles). Evolution of gas suggests that enolate salt formation with sodium hydride may not have been complete. The reaction mixture was stirred at room temperature overnight then quenched with saturated ammonium sulfate solution and extracted with ether. The combined ether extracts were washed three times with dilute sodium carbonate solution and once each with water and saturated sodium sulfate solution and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure left 2.3 g of crude 2,3-dimethylcyclohex-2-enone 44 (60%). Distillation through a short-path still afforded 1.7 g colorless 44, bp 95° (15 mm) [lit.[59] 90-96° (14 mm)]; ir 1665 cm^{-1}, 1630 cm^{-1}; nmr (CCl_4) (essentially identical to undistilled material) δ2.3 (m, 4H, C-4, C-6 methylene protons), 2.0 (m, 2H, C-5 methylene protons), 1.88 (s, 3H, C-3 vinyl $\underline{CH_3}$), 1.67 (s, 3H, C-2 vinyl $\underline{CH_3}$).

Electron Spin Resonance Study of Reaction 32

A 3mm o.d. esr tube was modified by removing a one inch piece from the top and sealing an equivalent length of 7 mm o.d. tubing in its place. A rubber septum was affixed to the tube and an argon atmosphere maintained over the contents via inlet and outlet syringe needles. The tube was cooled to -78 ± 3° in the cavity of a Varian E-4 spectrometer by means of a Varian Variable Temperature Controller containing a Dry Ice-acetone slurry in the Dewar flask. A solution of triphenylmethyllithium (0.2 ml of 1M ϕ_3CLi in THF prepared in the usual way) was introduced and scan A, Fig. 1 recorded. Enone 15 (1 drop) was then added and scan B, Fig. 1 recorded. Scans C and D were obtained by successively warming this solution to 0° and 25°.

Low-Temperature NMR Studies

A trityllithium solution (0.4 ml of 0.25M ϕ_3CLi in THF) was introduced along with a small amount of TMS into a conventional nmr tube previously dried, flushed with argon (15-20 min) and equipped with a rubber septum. The contents were then cooled to a specified temperature (±3°) in the probe of a Varian A56/60 spectrometer by means of a Varian Variable Temperature Controller containing liquid nitrogen in the Dewar flask. A THF solution of the enone (60-70 mg/ml) was cooled to -78° in a previously dried and argon flushed container equipped with a rubber septum. After the nmr

spectrum of the initial triphenylmethyllithium solution was scanned, the cold solution of the enone was added (~ 0.2 ml) and the spectrum immediately scanned (3-5 sec), starting at the region of interest with a sweep rate of 100 sec. Repeated scans of the solution were made at several temperatures between -90° and 20°.

Lithium in Ammonia Reduction of 5,5-Dimethylcyclohex-2-enone (15)

Liquid ammonia (50 ml) was distilled into a 100 ml three-necked flask equipped with a magnetic stirrer and a Dry Ice condenser. Lithium (0.4 cm ribbon, 3.4 mmoles) was added and the resulting dark blue solution was stirred at reflux (-33°) for 5 min. A solution of enone 15 (212 mg, 1.7 mmoles) in 3 ml of dry THF was then added over a period of 5 min. After it was stirred at -33° for 2 hr the mixture was cooled to -78° and solid ammonium chloride was added. The Dry Ice condenser was replaced with a water condenser and the ammonia was allowed to evaporate overnight. Water and ether were added to the residue; the aqueous solution was extracted; and the combined extracts were washed twice with water, once with saturated sodium sulfate and dried over $MgSO_4$. Removal of the solvents under reduced pressure left 250 mg of an oil from which 33 mg of dimer 50 crystallized, mp 141-145°. Recrystallization from a pentane and methylene chloride solution afforded an analytical sample that had mp 148-149°; ir 1700 cm^{-1}; nmr (CCl_4) δ2.05 (s, 4H,

H2a,e H2'a,e), 2.44 t 1.17 (m, 10H, H4a,e, H4'a,e, H5, H5', H6a,e, H6'a,e), 1.08 (s, 6H, C-3, 3' -$\underline{CH_3}$), 0.87 (s, 6H, C-3, 3'-$\underline{CH_3}$); mass spectrum (70 eV) m/e (rel. intensity) 250(8), 125(100).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47.

Found: C, 76.67; H, 10.52.

The mother liquor was subjected to glpc analysis (4% QF-1, 110°) and proved to be a mixture of 3,3-dimethylcyclohexanol (51) (17%) containing an impurity present (5%) in the starting enone 15, 3,3-dimethylcyclohexan-1-one (49) (53%) and dimer 50 (12%).

An analytical sample (preparative glpc) of 3,3-dimethylcyclohexan-1-one (49) was characterized by ir (liquid film) 1713 cm^{-1} and nmr (CCl_4) δ2.06 (s, 2H, H2a,e), 2.4-1.4 (m, 6H, C-4,5,6 methylene protons), 1.0 (s, 6H, C-3 gem-dimethyl).

5-endo-Carbomethoxybicyclo[2,2,2]octan-2-one (52)

To a stirred solution of 21 ml of ICA (18.6 g, 0.132 moles) in dry THF at -23° (Dry Ice and CCl_4), under argon, was added 55 ml of 2.2M n-butyllithium in hexane (0.121 moles); and the resulting mixture was stirred for 20 min. Cyclohex-2-enone (10g) was added to this solution over a 15 min period and the solution was stirred at -23° for 50 min. Methyl acrylate (11.3 g, 0.132 mmoles) was then added over a 15 min period, and the resulting solution was stirred at -23° for 2 hr. Water and ether were added to the reaction mixture and the aqueous solution was extracted. The

combined extracts were washed four times with 1N hydrochloric acid and once each with water and saturated sodium sulfate and then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 17.8 g (90%) of keto-ester 52, which proved to be homogeneous by glpc (4% QF-1, 180°) and tlc (silica gel, 1:1 ether/hexane). A short path distillation afforded 10.4 g of clear colorless 52, bp 100-104° (0.65-0.75 mm); ir (liquid film) 1725 cm^{-1}, 1735 cm^{-1}; nmr (CCl_4) (essentially identical to undistilled material) δ 3.69 (s, 3H, $-CO_2\underline{CH_3}$), 2.8-1.8 (m, 11H, methine and methylene protons); mass spectrum (70 eV) m/e (rel intensity) 182(30), 96(100).

A 2,4-dinitrophenylhydrazone derivative of 52, mp 139-140°, was prepared.

Anal. Calc. for $C_{16}H_{18}N_4O_6$: C, 53.03; H, 5.01; N, 15.46.
Found: C, 53.03; H, 5.01; N, 15.43.

8-Carbomethoxy-4,6,6-trimethylbicyclo[2,2,2]octan-2-one

To a stirred solution of LiICA (1.6 mmoles)[prepared as described in the previous section from 246 mg (1.74 mmoles) of ICA and 0.85 ml of 1.9M n-butyllithium (1.6 mmoles)] in dry tetrahydrofuran at -23° under argon was added 210 mg (1.5 mmoles) isophorone in 5 ml of dry THF over a period of 10 min. The mixture was stirred at -23° for 50 min, then methyl acrylate (150 mg, 1.7 mmoles) was added in 4 ml of dry THF over a period of 10 min and the resulting solution

was stirred at -23°, under argon for 3.5 hr. Water and ether were added to the reaction mixture and the aqueous solution was extracted. The combined extracts were washed three times with 1N hydrochloric acid and once each with water and saturated sodium sulfate solution and then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 330 mg of the keto-ester 53 (98%) as a pale yellow oil, which was homogeneous by glpc (4% QF-1, 150°) and tlc (silica gel, 1:1 ether hexane) and exhibited the following properties: ir (liquid film) 1725 cm^{-1}, 1735 cm^{-1}; nmr (CCl_4) δ3.70 (s, 3H, $-CO_2CH_3$), 2.87-1.46 (m, 6H, C-1, C-3, C-7, C-8 methylene and methine protons), 1.30 (bs, 2H, C-5 methylene), 1.10 (s, 3H, C-6 methyl endo to carbonyl), 0.94 (s, 6H, C-6 methyl exo to carbonyl and C-4 methyl); mass spectrum (70 eV) m/e (rel intensity) 224(6)P, 123(100).

A small sample which was collected by glpc crystallized on cooling (Dry Ice) and had mp 53-54° (lit.[17] 54.5-55.5°). Using one of these crystals as a "seed", the remaining material was crystallized from hexane, mp 53.5-54.5°.

5-endo-Carbomethoxybicyclo[2,2,2]oct-2-ene (57)

(a) From 5-endo-carbomethoxybicyclo[2,2,2]octan-2-one (52):- To a solution of pyrrolidine (190 mg, 2.7 mmoles) in 10 ml of dry benzene was added keto-ester 52 (416 mg, 2.2 mmoles) and the solution was then refluxed under nitrogen overnight with a Dean-Stark water trap containing molecular sieves (4A). Glpc analysis (5% SE-30, 180°) of the

benzene solution showed greater than 90% conversion to the enamine 56. The benzene and pyrrolidine were removed under reduced pressure and an ir that was taken of the crude enamine showed λ_{max} at 1620 cm^{-1}. Without further characterization the crude enamine was dissolved in 10 ml of dry THF and 2.5 ml of 1.29M diborane in THF (3.2 mmoles) was added and the solution was stirred under argon at room temperature for 3 hr. Glacial acetic acid (1.5 ml) was added and the mixture then refluxed for 1 hr. Tlc analysis (silica gel, 1:1 ether/hexane) showed no keto-ester and no components at higher R_f values. The THF was removed under reduced pressure, diglyme (10 ml) and glacial acetic acid (1 ml) were added and the mixture was refluxed for 45 min. After cooling to 25^0, it was stirred overnight at this temperature, then the reaction mixture was diluted with water and the aqueous solution was extracted with ether. The combined extracts were washed four times with water and once with saturated sodium bicarbonate solution and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a residue (5 ml) containing diglyme and acetic acid. Pentane and water were added; the aqueous solution was extracted with pentane and the combined extracts were washed four times with water (until neutral), once with saturated sodium sulfate solution and finally dried over $MgSO_4$. Removal of the pentane under reduced pressure left a residue (1.5 ml), glpc analysis (5% SE-30, 120^0) of which showed diglyme and 5-endo-carbomethoxybicyclo[2,2,2]oct-2-ene(57)

(> 90%). Column chromatographic separation (30 g silica gel, eluting with 1:4 ether/hexane) gave 60 mg of sweet-smelling 57, which had ir (liquid film) 1735 cm^{-1}; nmr (CCl_4) δ6.21 (m, 2H, H2, H3), 3.60 (s, 3H, $-CO_2\underline{CH_3}$), 2.91 (m, 1H, H5), 2.57 (m, 2H, H1, H4), 1.76-1.1 (m, 6H, C-6,7,8 methylene protons).

(b) From Diels-Alder reaction of 1,3-cyclohexadiene and methyl acrylate: 1,3-Cyclohexadiene (900 mg, 11.25 mmoles) was added to 4 ml of methyl acrylate and the resulting mixture was refluxed for 36 hr. Excess methyl acrylate was then distilled off and the viscous residue was extracted with ether. The combined extracts were dried over $MgSO_4$ followed by the removal of ether under reduced pressure to give 752 mg sweet smelling oil (40%). Glpc analysis (4% QF-1, 155°) of this showed two peaks in the ratio of 0.4:9.6. The major peak was increased in amplitude upon addition of 57 prepared as in (a). The ir spectrum of the oil was identical to that reported for 57. The nmr spectrum was essentially identical with the exception of a new carbomethoxy peak at δ3.63 which was approximately 5% of the peak at δ3.60 (from 57).

Bicyclo[2,2,2]oct-2-ene-5-endo-carboxylic Acid (58)

To 43 mg (0.259 mmoles) of ene-ester 57 (prepared in the manner described for (a) above) was added 3 ml of five percent aqueous sodium hydroxide and the solution stirred

for 4 hr at room temperature (until homogeneous). After acidification with 6N hydrochloric acid, the solution was saturated with ammonium sulfate and extracted four times with chloroform. After washing the combined extracts with water and saturated sodium sulfate solution and drying over magnesium sulfate the solvent was removed under reduced pressure to give 31 mg (82%) solid, mp 44-48°. Recrystallization (3X) from pentane at -78° afforded ene-acid 58, mp 54-55° (lit.[55] 56-57°).

6-Hydroxybicyclo[2,2,2]octan-2-carboxylic Acid γ-Lactone (59)

The procedure of Wagner et al.[52] was followed. To 23 mg (0.151 mmoles) of the ene-acid 58 was added 2 ml of 30% aqueous sulfuric acid and the mixture was refluxed at 110° for 1 hr. The cooled mixture was then poured into ice water and extracted four times with chloroform. The combined chloroform extracts were washed with 10% aqueous sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 18 mg of lactone 59 contaminated with a minor (~ 20%) impurity (glpc analysis, 4% QF-1, 100°). Recrystallization from hexane gave 59, mp 208-210° (lit.[62] 207-208°); ir ($CHCl_3$) 1765 cm^{-1} and a small absorption at 1735 cm^{-1} (impurity); mass spectrum (70eV) m/e (rel intensity) 152(3), 108(18), 66(100).

Syn-5-Hydroxybicyclo[2,2,2]octan-2-carboxylic Acid (62)

The keto-ester 52 (875 mg, 4.8 mmoles) was added to a solution of 5% aqueous sodium hydroxide and stirred at room temperature for 20 min (until homogeneous). Platinum oxide (170 mg, 82%) was then added and the solution was hydrogenated at room temperature and atmospheric pressure for 2 days (theoretical uptake of hydrogen). After filtering off the catalyst through a celite mat, the solution was acidified with 2N hydrochloric acid, saturated with ammonium sulfate and extracted four times with chloroform. After the combined extracts were washed with saturated sodium sulfate solution they were dried with $MgSO_4$ and the solvent was removed under reduced pressure to give 650 mg of white solid. Glpc analysis (4% QF-1, 155°) of the methyl esters of this material (prepared by treatment with methanolic diazomethane) showed 89% of syn-methyl-5-hydroxybicyclo-[2,2,2]octan-2-carboxylate and 11% of anti-methyl-5-hydroxy-bicyclo[2,2,2]octan-2-carboxylate. An analytical sample of syn-5-hydroxybicyclo[2,2,2]octan-2-carboxylic acid was obtained by recrystallization of the white solid from ethyl acetate and had mp 143-144°; ir (KBr) 3350 cm^{-1}, 1700 cm^{-1}; nmr ($CDCl_3$) δ7.27 (concentration dependent) (bs, 2H, -OH), 3.87 (m, 1H, H5), 2.85 to 1.33 (m, 11H, C-1, 2,3,4,6,7,8 methine and methylene protons); mass spectrum (70 eV) m/e (rel intensity) 170(5), 152(85), 80(100).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29.
Found : C, 63.63; H, 8.22.

5-Hydroxybicyclo[2,2,2]octan-2-carboxylic Acid δ-Lactone(66)

To a solution of 10 ml of toluene containing a small amount of para-toluenesulfonic acid was added 100 mg (0.59 mmoles) of hydroxy-acid 62 and the resulting mixture was refluxed 30 min with a Dean-Stark water trap containing molecular sieves (4A). Ether was added to the cooled solution and the organic mixture was washed with cold (3°) five percent sodium bicarbonate and saturated sodium sulfate solutions and dried over $MgSO_4$. Removal of the solvents under reduced pressure left 91 mg of a solid residue. Preparative thick layer chromatography of this afforded 35 mg of the lactone 66 (40%). Crystallization from petroleum ether and hexane gave colorless crystals, mp 204.5-205.5°; ir ($CHCl_3$) 1750 cm^{-1}; nmr (CCl_4) δ4.79 (m, 1H, H5), 2.80 (m, 1H, H2), 2.18 (m, 2H, H1, H4), 1.75 (m, 8H, C-3,6,7,8 methylene protons); mass spectrum (70 eV) m/e (rel intensity) 152(10), 66(100), 80(86).

Saponification with 5% aqueous sodium hydroxide gave hydroxy-acid 62, mp 139-140°; mass spectrum (70 eV) identical to 62 prepared above.

Sodium Borohydride Reduction of Keto-ester 52

To a stirred solution of 4.5 g (24.8 mmoles) of keto-ester 52 in 50 ml of methanol at 0°, was added 2.2 g (58 mmoles) sodium borohydride and the mixture held at 0° for 2.5 hr. After the removal of methanol under reduced

pressure, water and ether were added and the aqueous solution was extracted twice with ether. The combined ether extracts were washed once each with 1N hydrochloric acid, water, and saturated sodium sulfate solution and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure left 3.75 g (82%) of colorless oil. Glpc analysis of this material (4% QF-1, 150°) showed two peaks of approximately equal area, with the same retention times as those of the hydroxy-ester mixture previously prepared by treatment of hydroxy-acids 62 and 63 with methanolic diazomethane. Tlc analysis (silica gel, ether) showed two components at R_f 0.8 and R_f 0.3. Preparative thick layer chromatography of 164 mg of the crude oil gave 80 mg of a mixture of the epimeric alcohols (R_f 0.8) in ~ 50:50 ratio as determined by nmr and glpc and which exhibited the folowing characteristics: ir (liquid film) 1730 cm^{-1}, 3360 cm^{-1}; nmr (CCl_4) δ3.8 (m, 1H, $\underline{H}\dot{C}OH$), 3.70, 3.64 (s, 3H, $-CO_2\underline{CH_3}$), 2.9-1.0 (m, 12H, methine and methylene protons, -OH); mass spectrum (70 eV) m/e (rel intensity) 184(3), 166(11), 80(100).

From the lower R_f fraction (R_f 0.3) was obtained 14 mg of oil having the following characteristics: ir 3350 cm^{-1}, (very strong), essentially transparent in the 1730 cm^{-1} carbonyl region; nmr ($CDCl_3$) δ4.1-3.3 (bm, 3H, $\underline{H}\dot{C}OH$, $-CH_2OH$), 2.2 (concentration dependent) (bs, 2H, -OH), 2.0-1.3 (bm,

11H, methine and methylene protons); mass spectrum (70 eV) m|e (rel intensity) 156(3), 138(33), 79(100). These data are most consistent with structure 64.

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REFERENCES

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APPENDIX

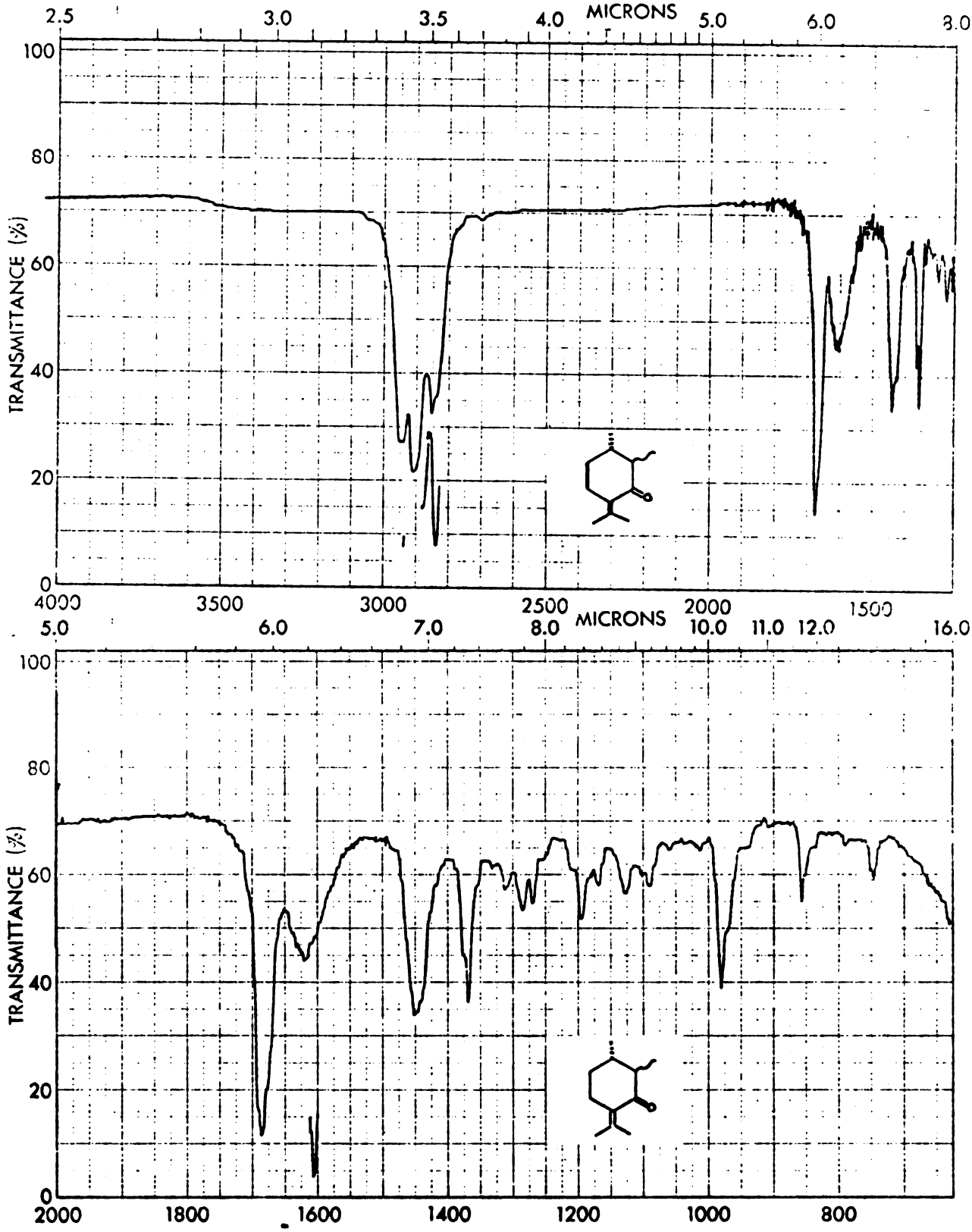


Figure 3. Infrared spectrum of methylpulegone (9, major isomer).

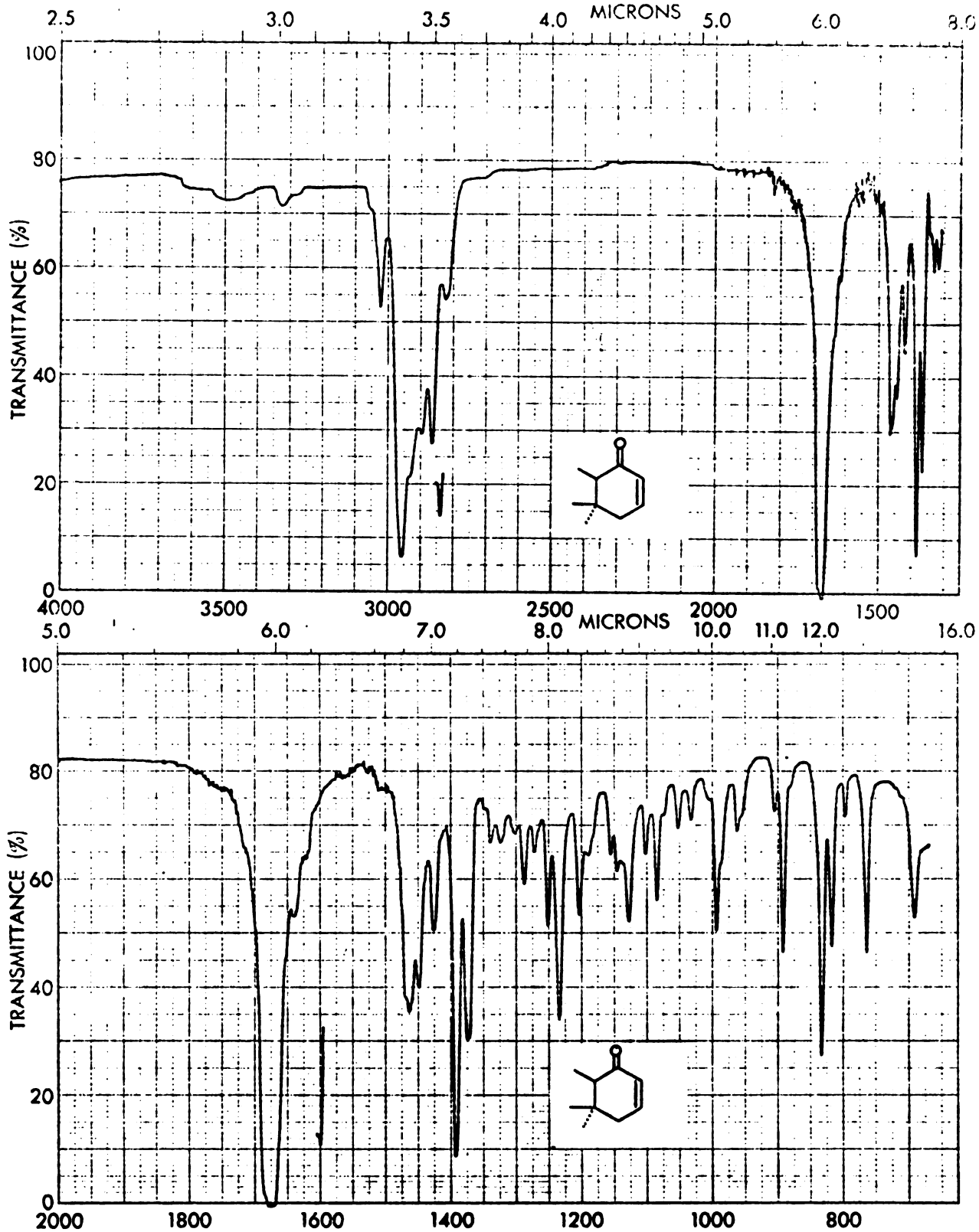


Figure 4. Infrared spectrum of 5,5,6-trimethylcyclohex-2-enone (16).

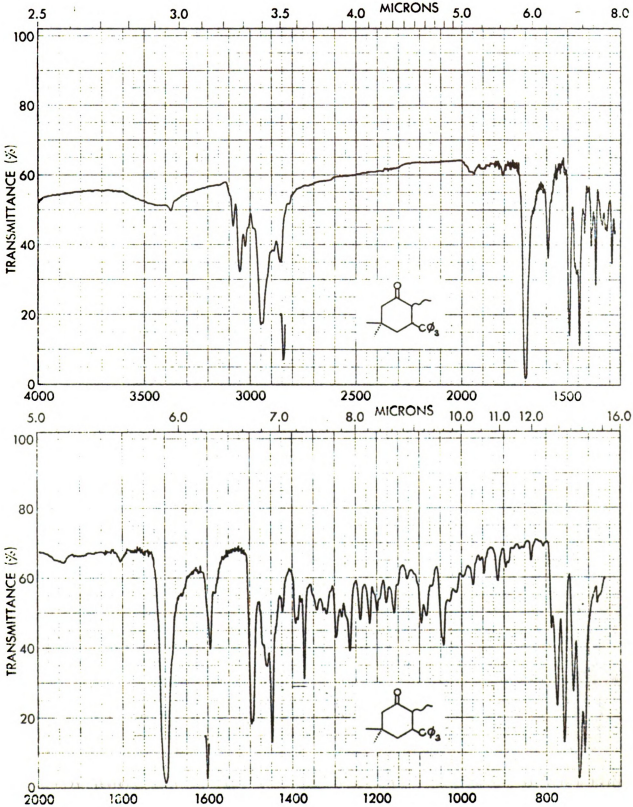


Figure 5. Infrared spectrum of 3-triphenylmethyl-2,5,5-trimethylcyclohexanone (36).

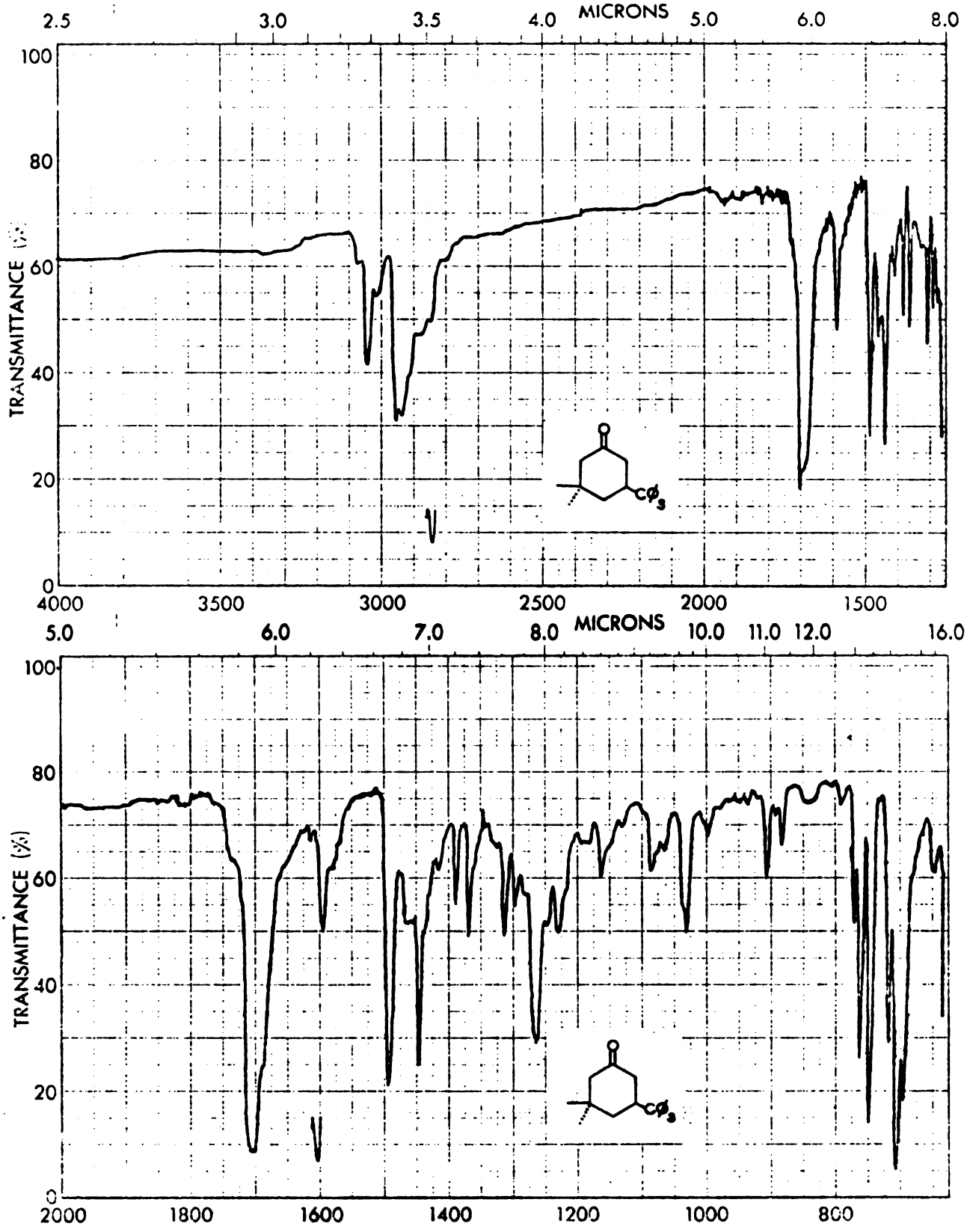


Figure 6. Infrared spectrum of 3-triphenylmethyl-5,5-dimethylcyclohexanone (37).

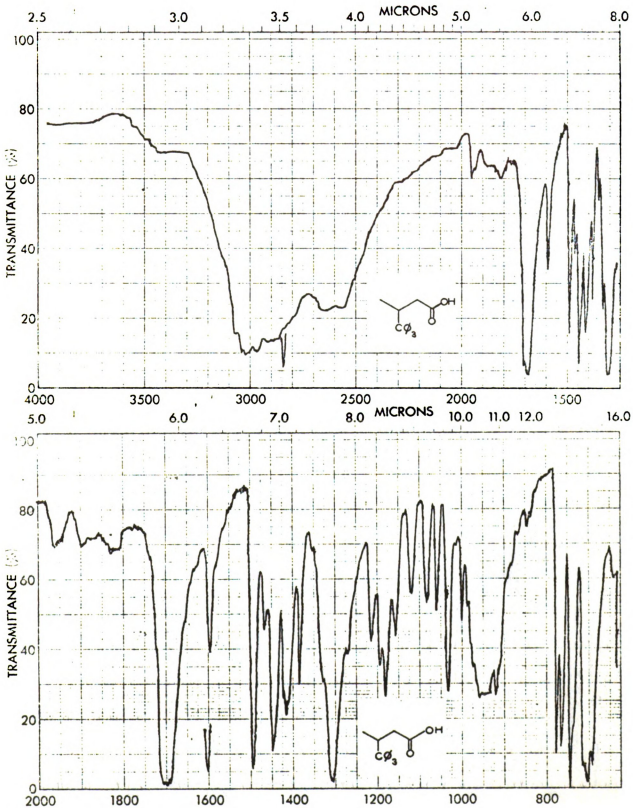


Figure 7. Infrared spectrum of 3-(1,1,1-triphenylmethyl)-butanoic acid (40)

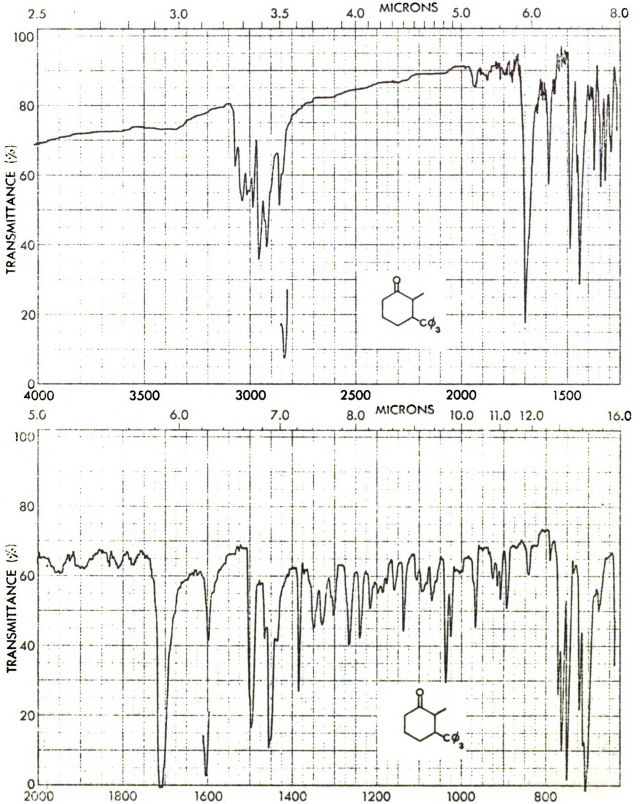


Figure 8. Infrared spectrum of 3-triphenylmethyl-2-methyl-cyclohexanone (42).

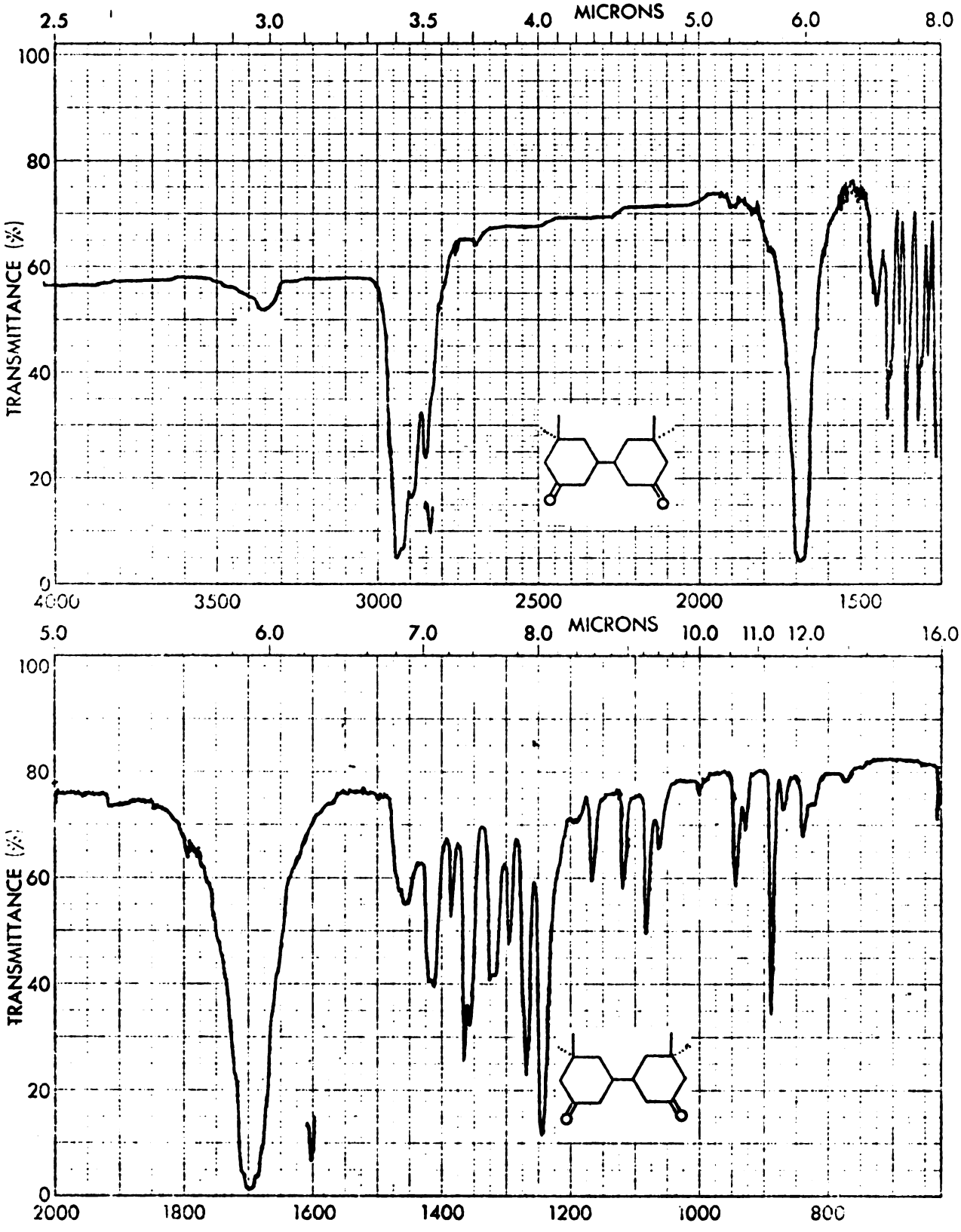


Figure 9. Infrared spectrum of the dihydrodimer (50).

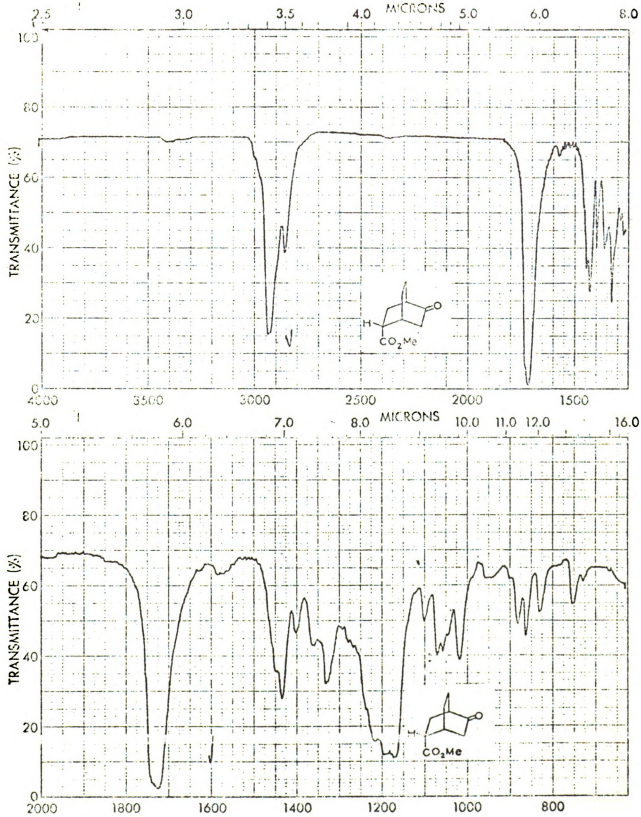


Figure 10. Infrared spectrum of 5-endo-carbomethoxybicyclo-[2,2,2]octan-2-one (52).

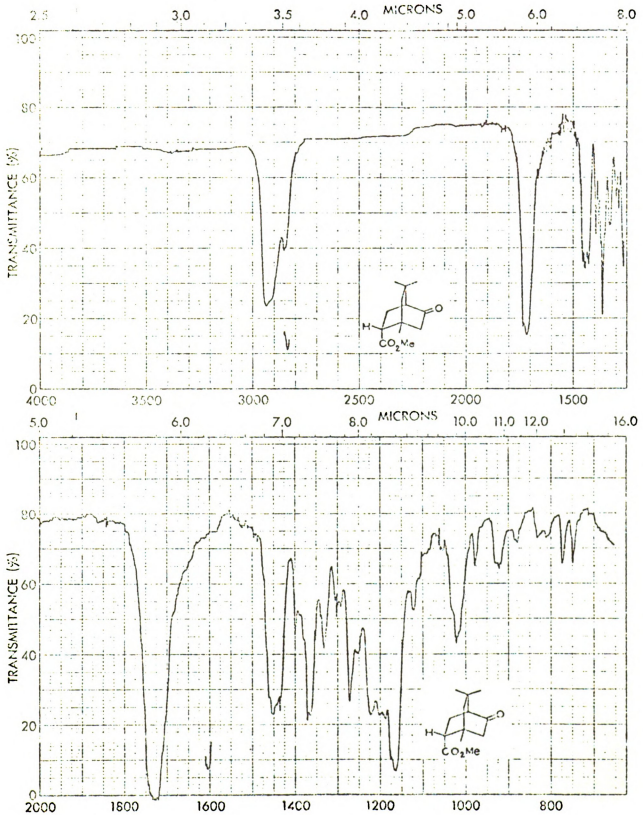


Figure 11. Infrared spectrum of 8-carbomethoxy-4,6,6-trimethylbicyclo[2,2,2]octan-2-one (53).

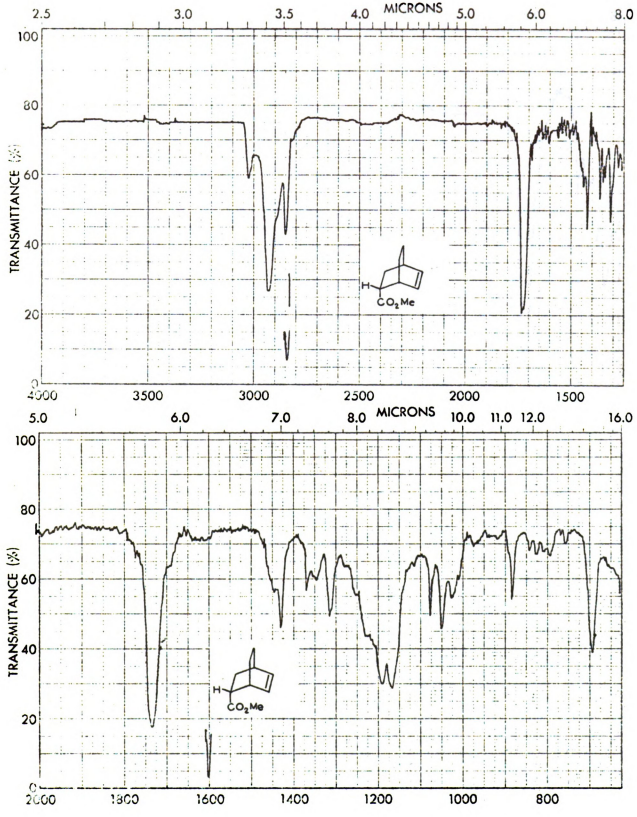


Figure 12. Infrared spectrum of 5-endo-carbomethoxybicyclo-[2,2,2]oct-5-ene (57).

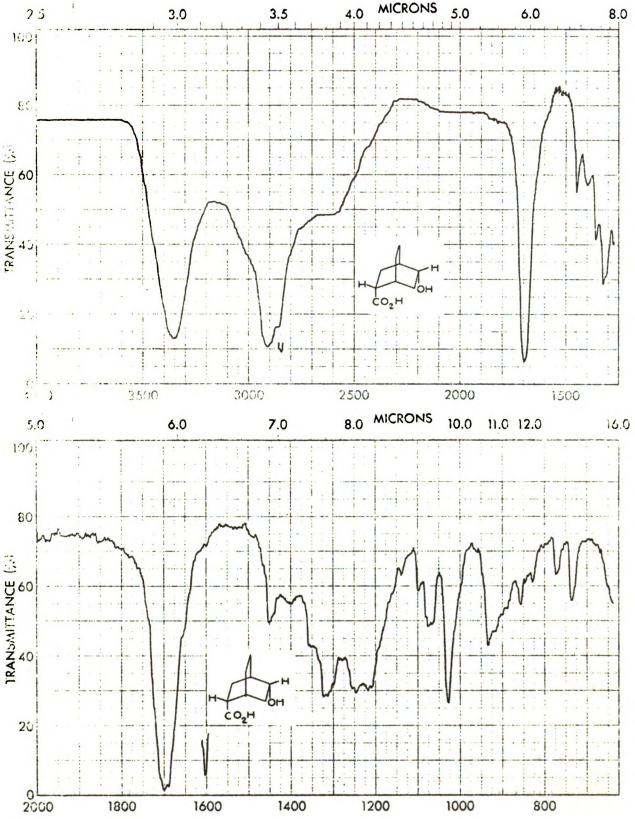


Figure 13. Infrared spectrum of syn-5-hydroxybicyclo-[2,2,2]octan-2-carboxylic acid (62).

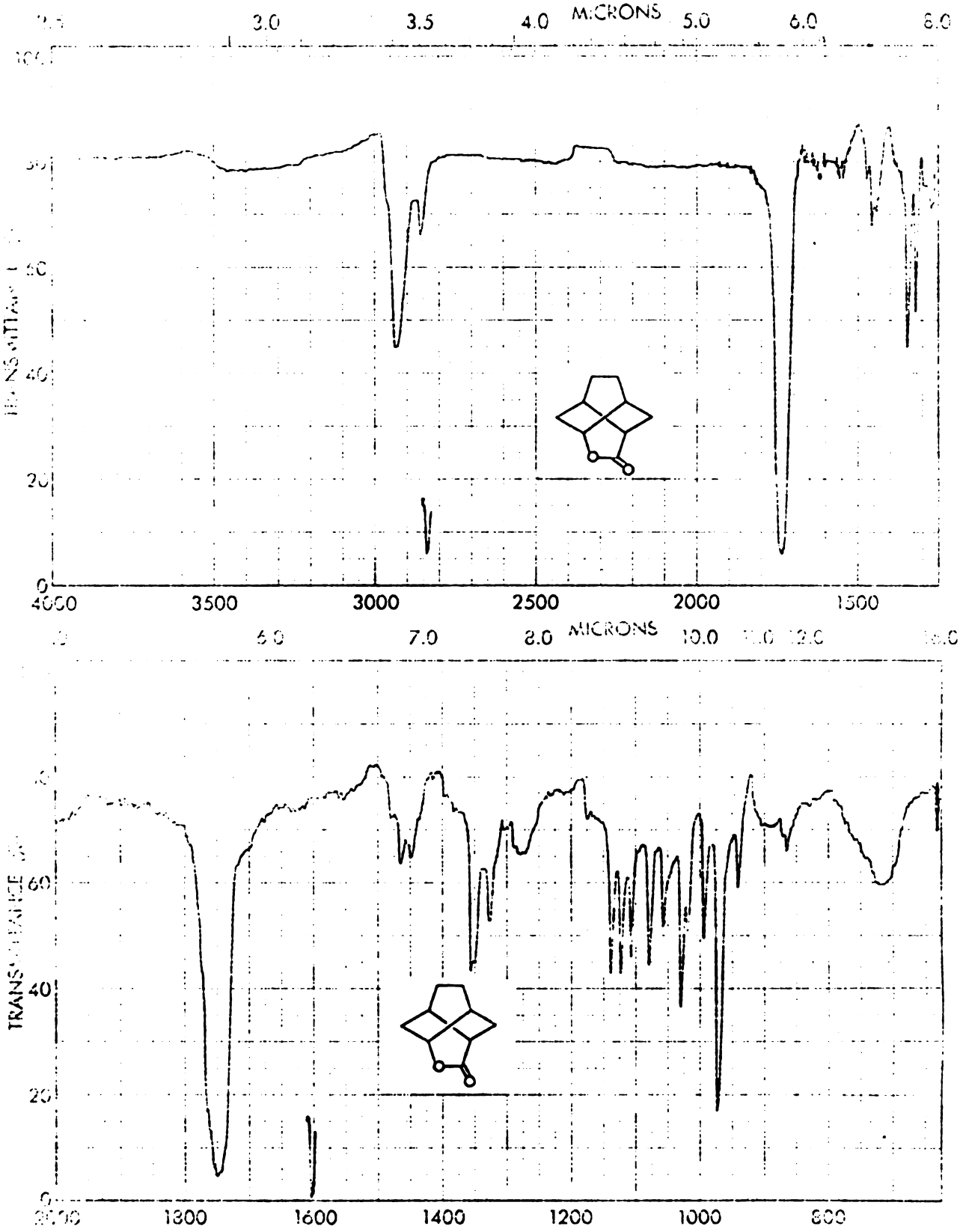


Figure 14. Infrared spectrum of syn-5-hydroxybicyclo-[2,2,2]octan-2-carboxylic acid, δ-lactone (66)

Figure 15. (A) Nmr spectrum of methylpulegone (9, major isomer) in CCl_4. (B) Same spectrum taken with benzene as the solvent

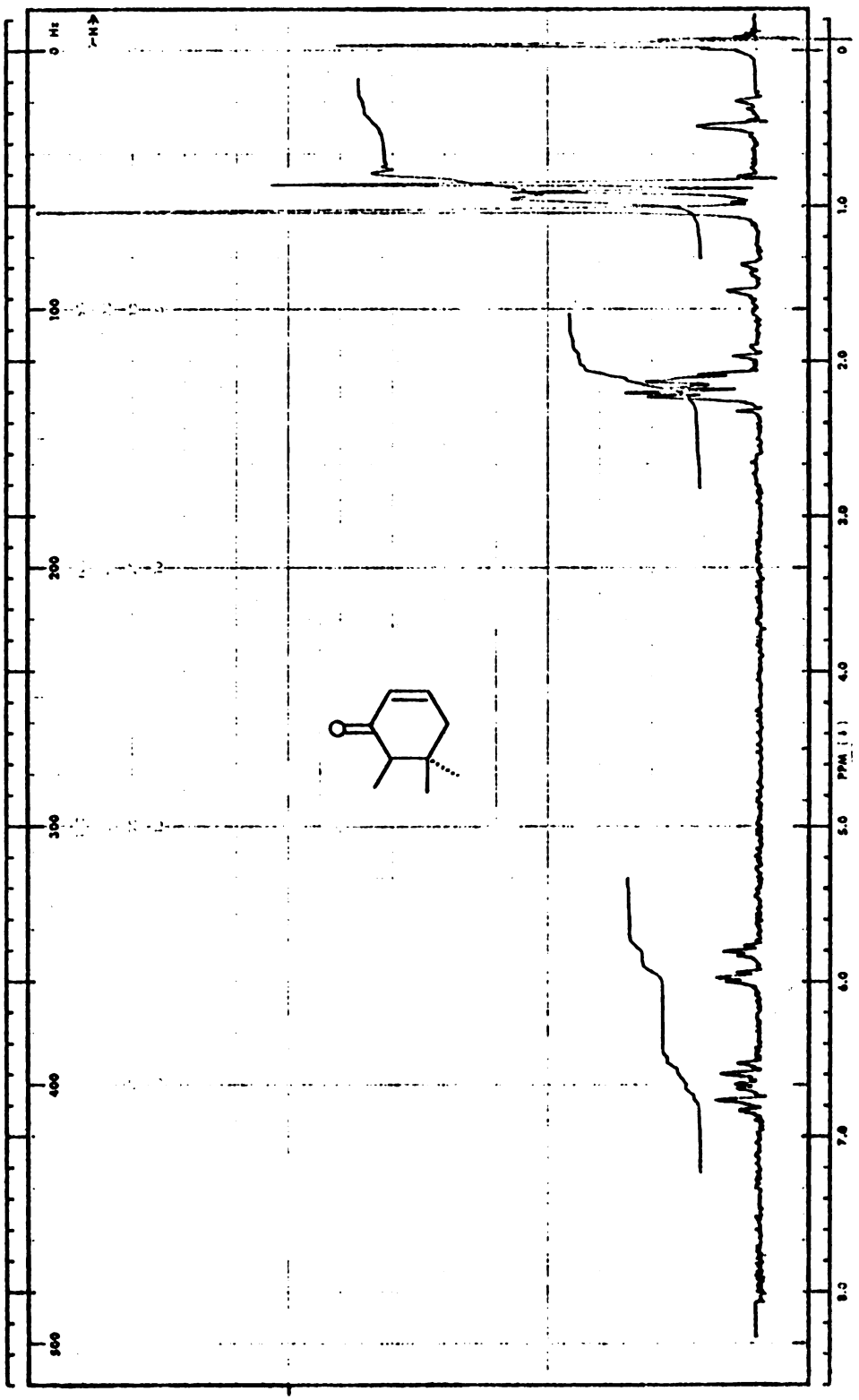


Figure 16. Nmr spectrum of 5,5,6-trimethylcyclohex-2-enone (16) (CCl_4).

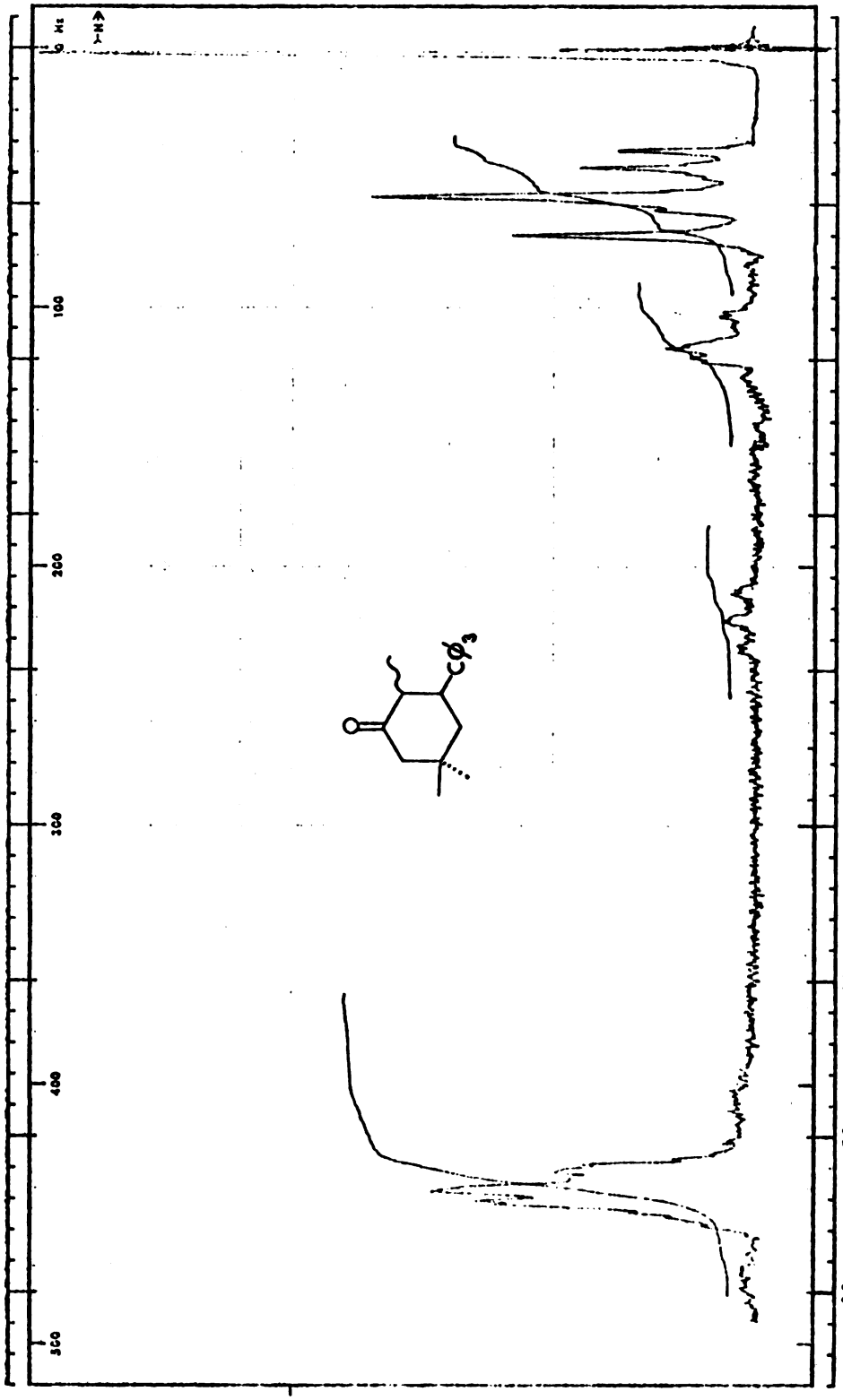


Figure 17. Nmr spectrum of 3-triphenylmethyl-2,5,5-trimethylcyclohexanone (36) (CCl_4).

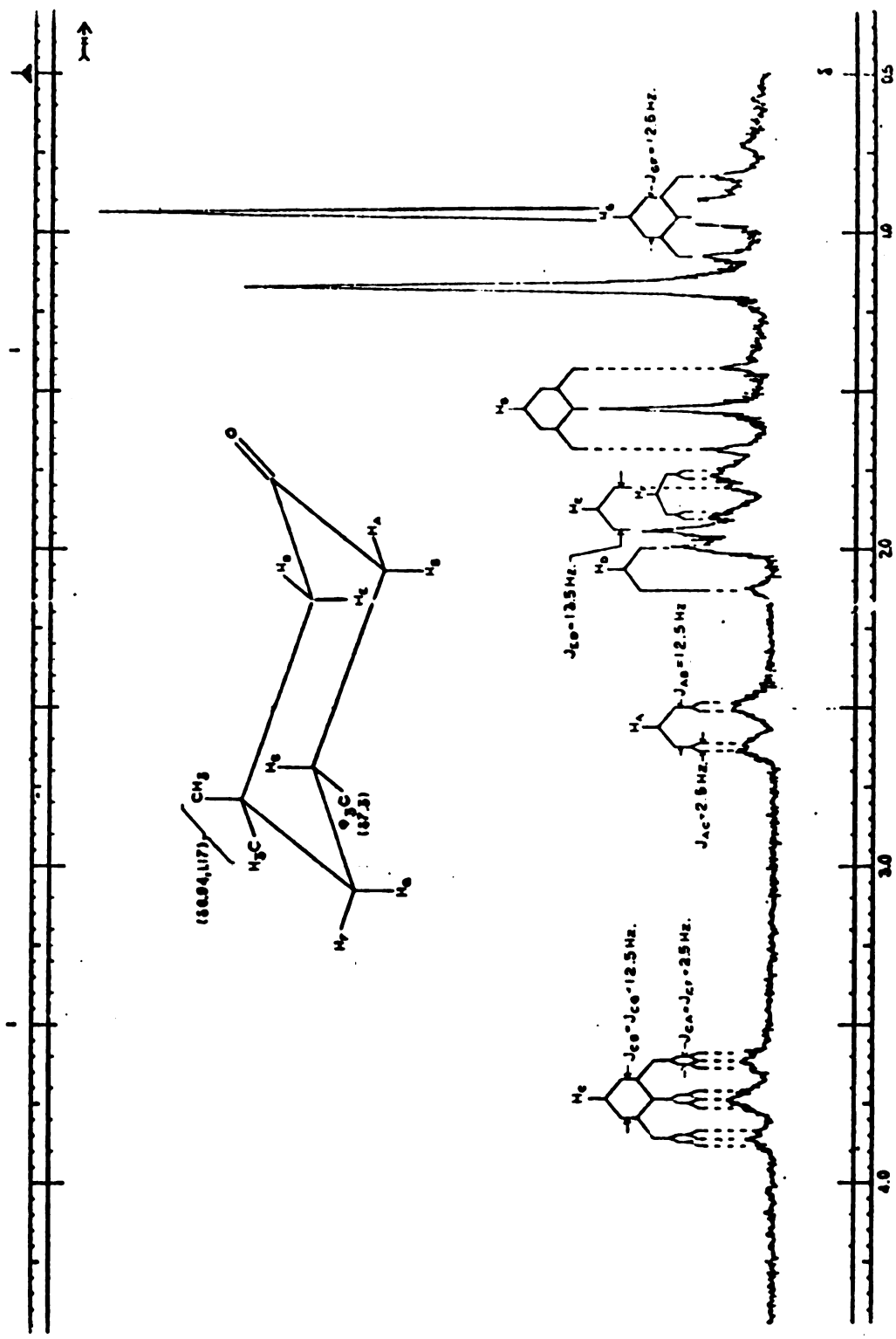


Figure 18. Nmr spectrum (100MHz) of 3-triphenylmethyl-5,5-dimethylcyclohexanone (37) ($CDCl_3$).

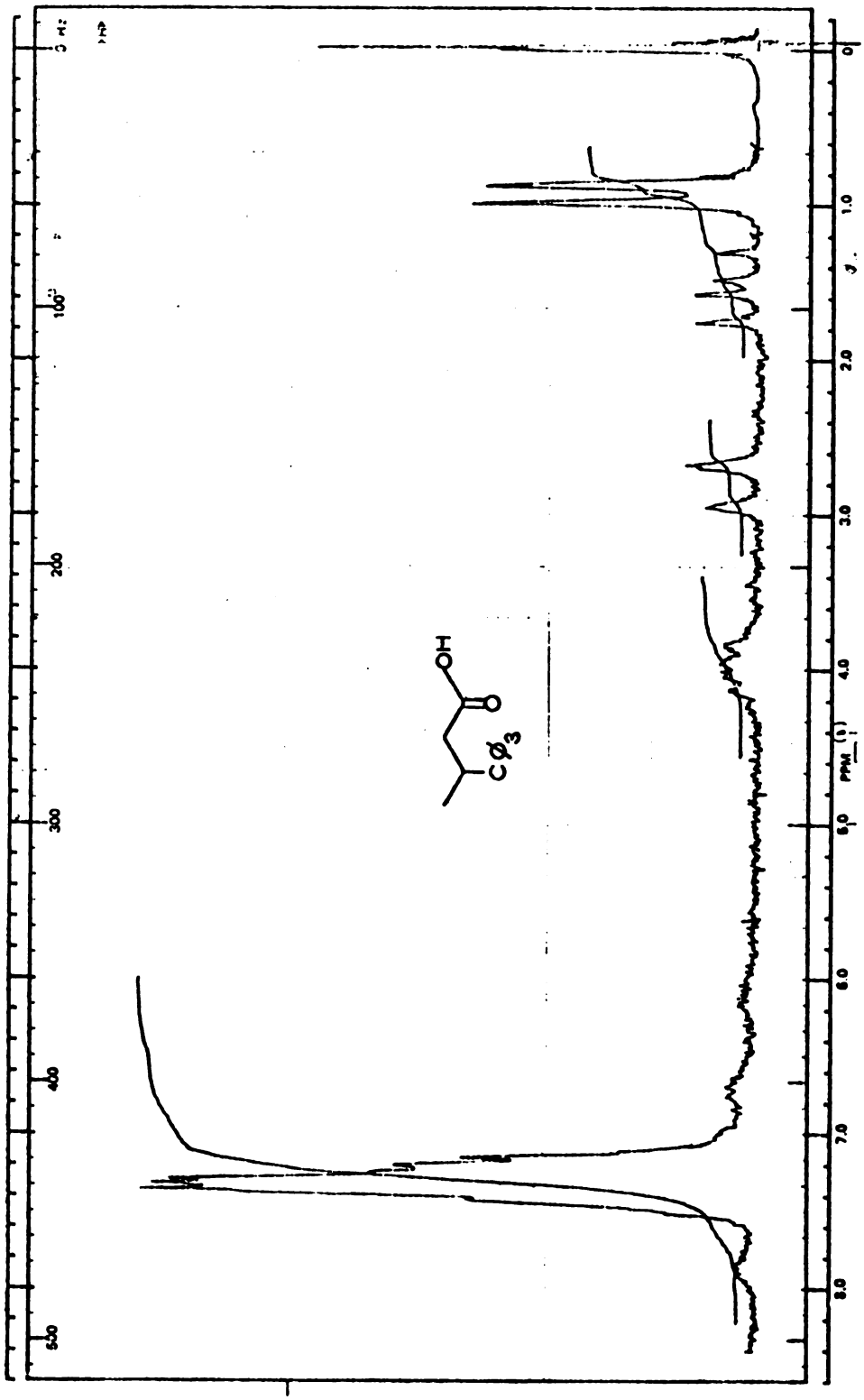


Figure 19. Nmr spectrum of 3-(1,1,1-triphenylmethyl)-butanoic acid (40) ($CDCl_3$).

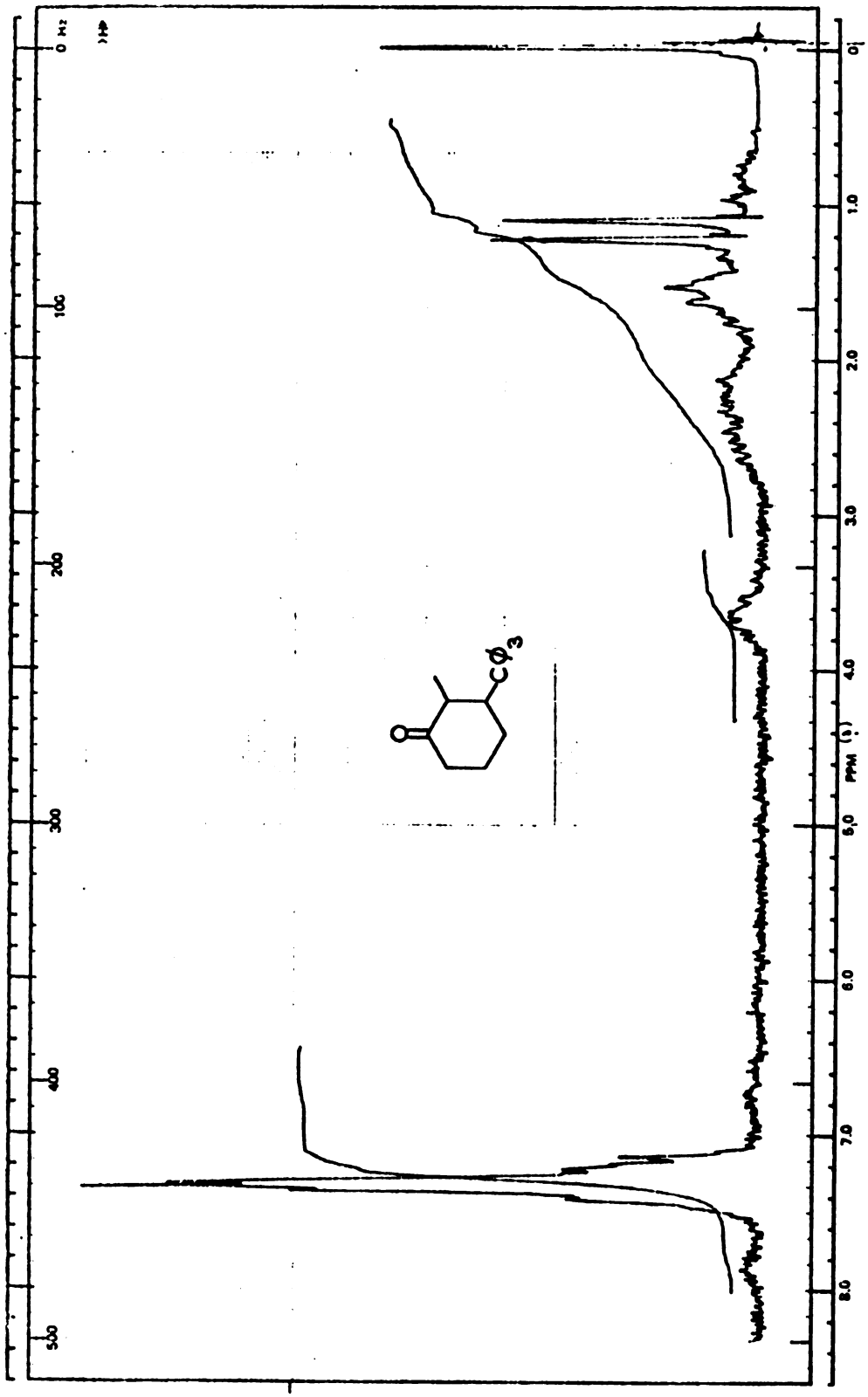


Figure 20. Nmr spectrum of 3-triphenylmethyl-2-methylcyclohexanone (42)($CDCl_3$).

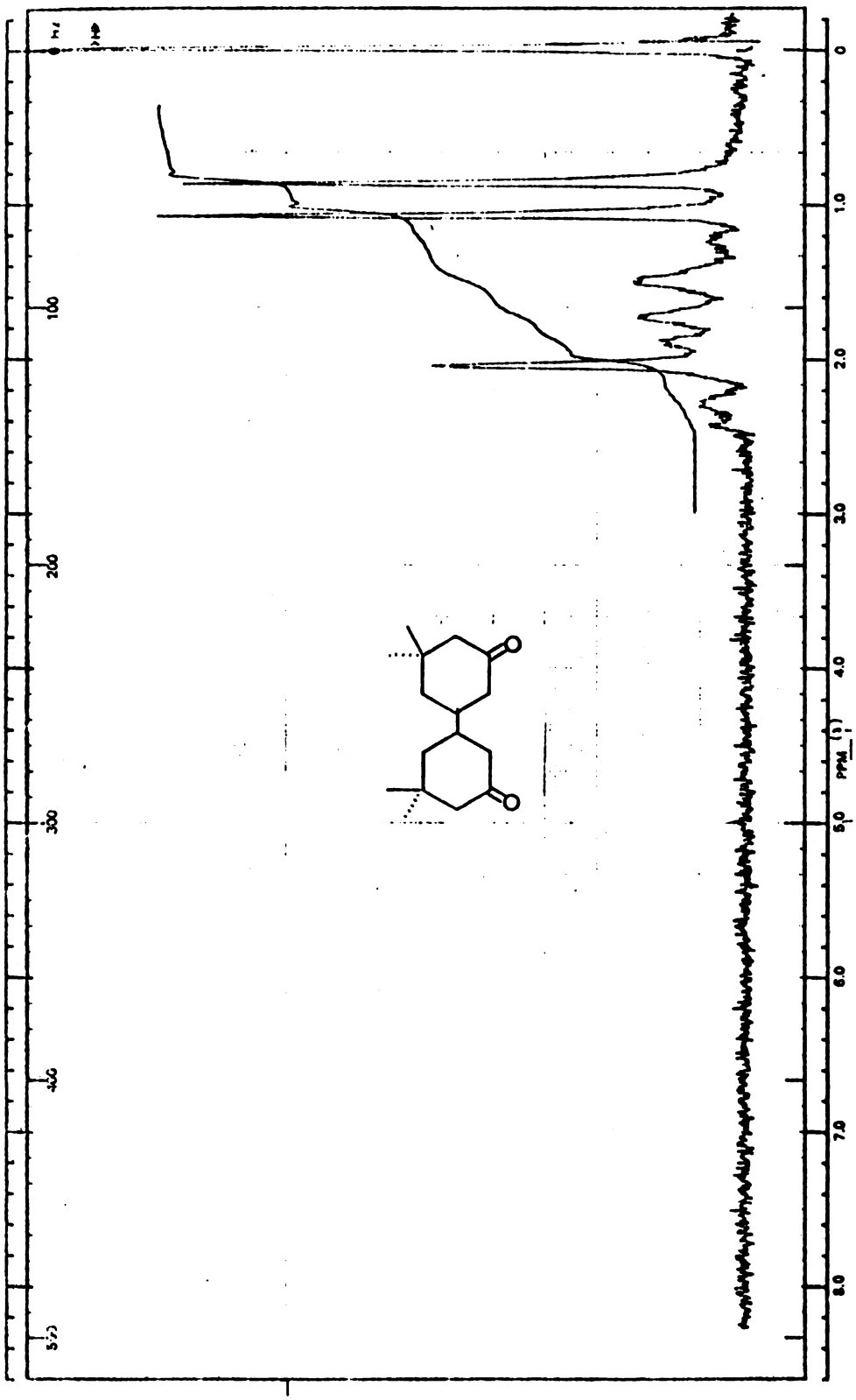


Figure 21. Nmr spectrum of the dihydrodimer (50) of 5,5-dimethylcyclohex-2-enone (CCl_4).

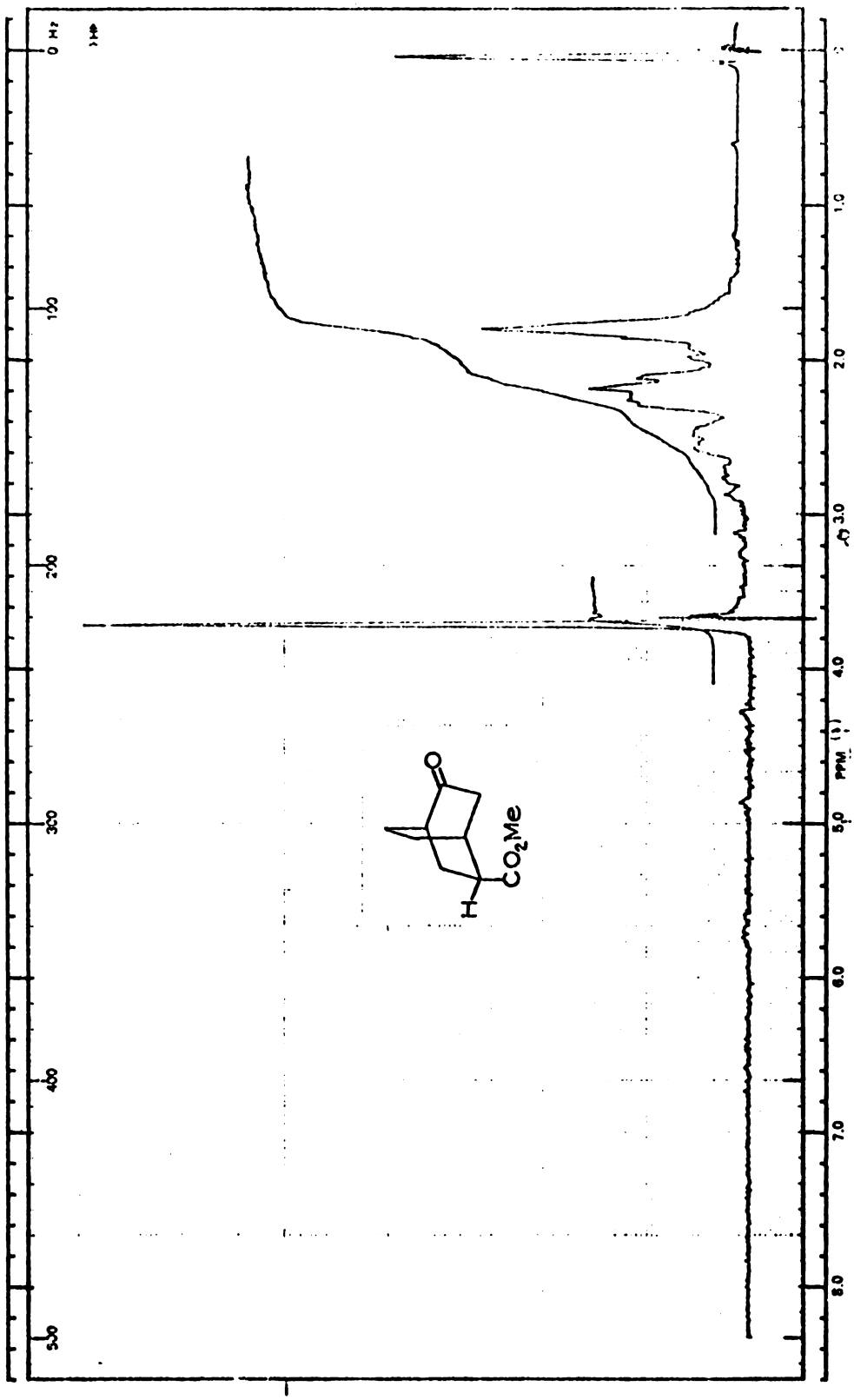


Figure 22. Nmr spectrum of 5-endo-carbomethoxybicyclo[2,2,2]octan-2-one (52) (CCl_4).

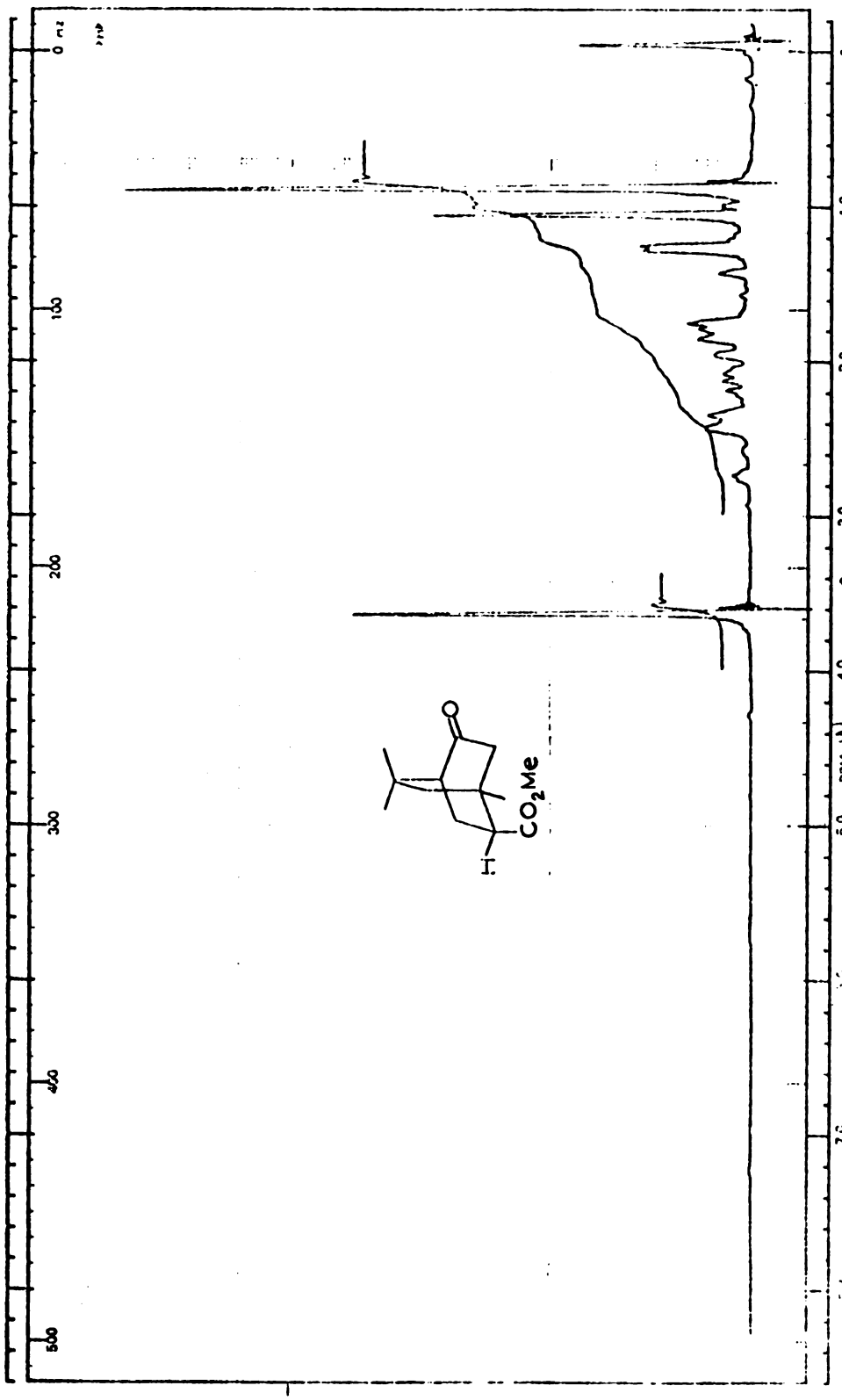
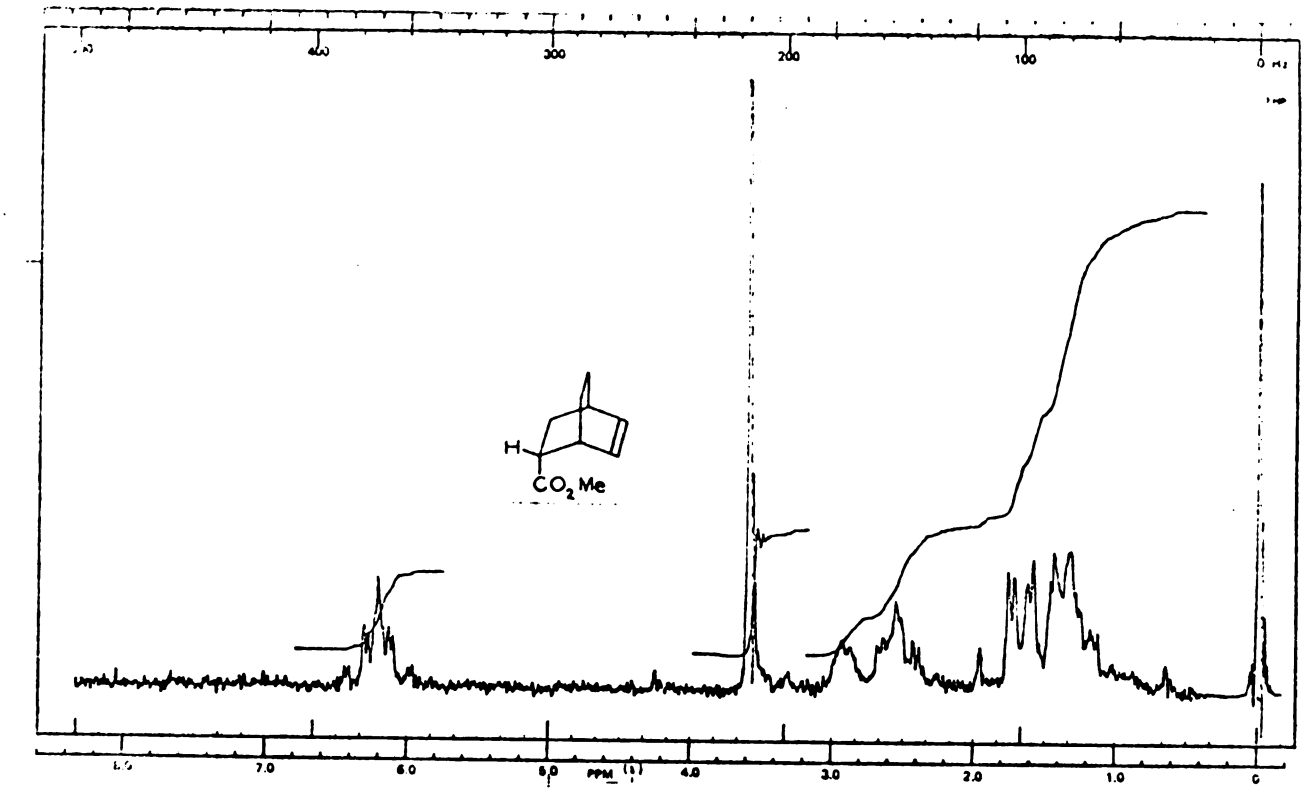
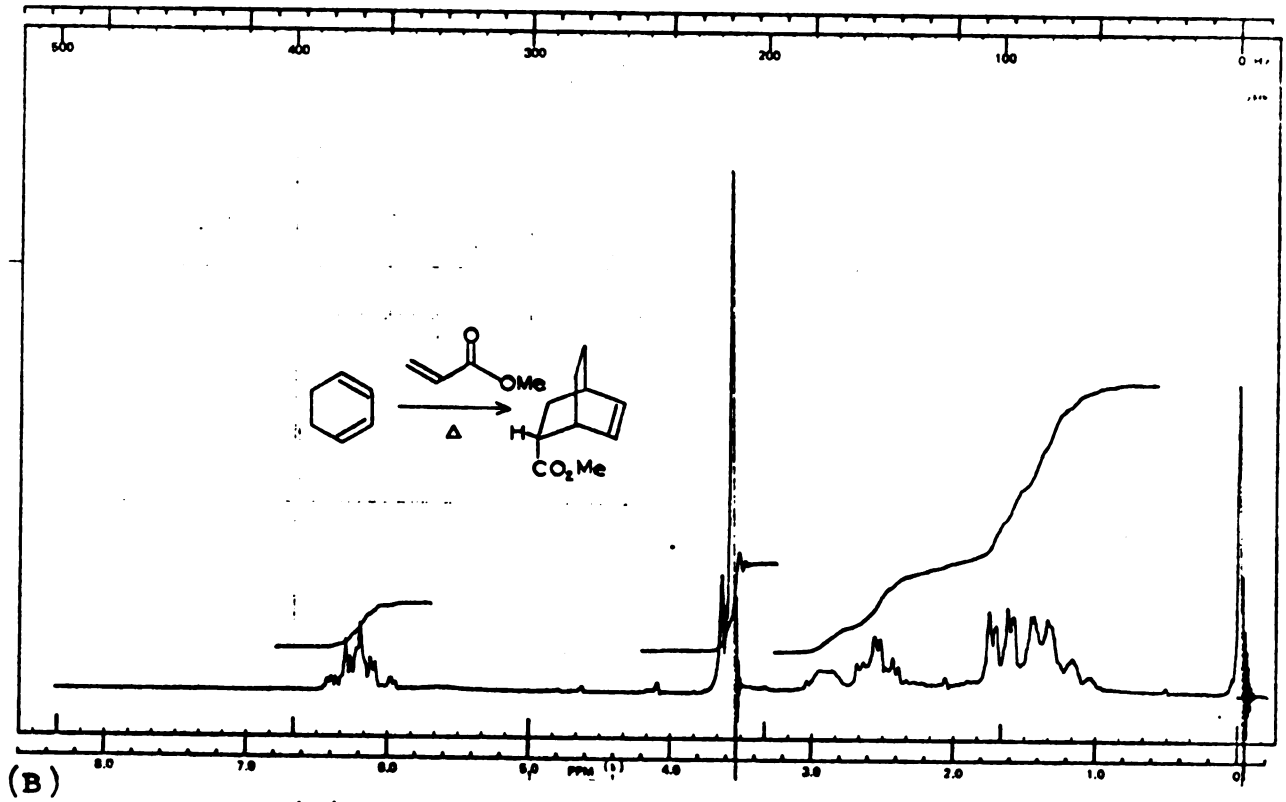


Figure 23. Nmr spectrum of 8-carbomethoxy-4,6,6-trimethylbicyclo[2,2,2]-octan-2-one (53) (CCl_4).



(A)



(B)

Figure 24. (A) Nmr spectrum of 5-endo-carbomethoxybicyclo-[2,2,2]oct-2-ene (57) prepared from 52 (CCl_4). (B) Nmr spectrum of 5-endo-carbomethoxybicyclo-[2,2,2]oct-2-ene (57) prepared by Diels-Alder reaction.

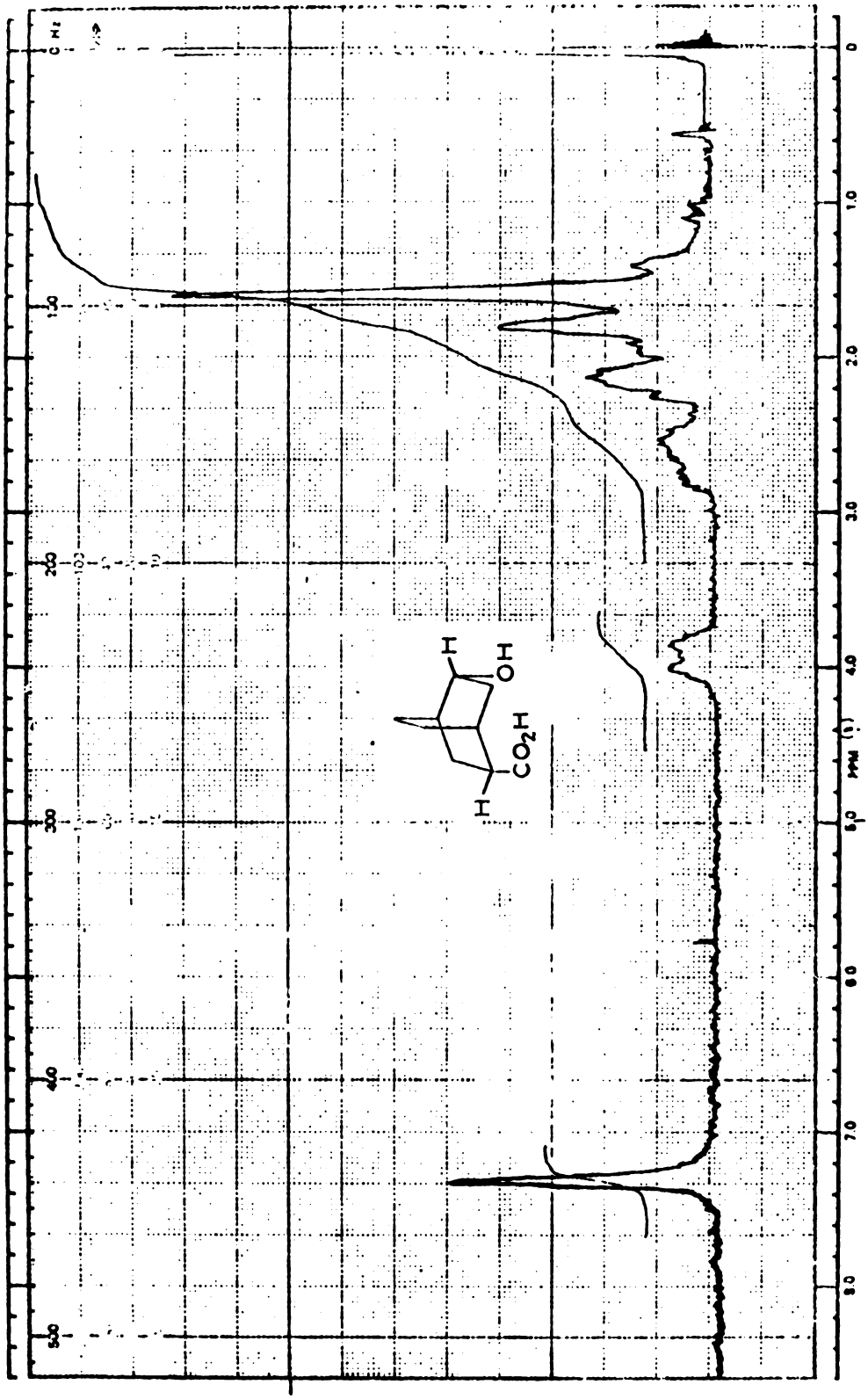


Figure 25. Nmr spectrum of **syn**-5-hydroxybicyclo[2,2,2]octan-2-carboxylic acid (62) ($CDCl_3$).

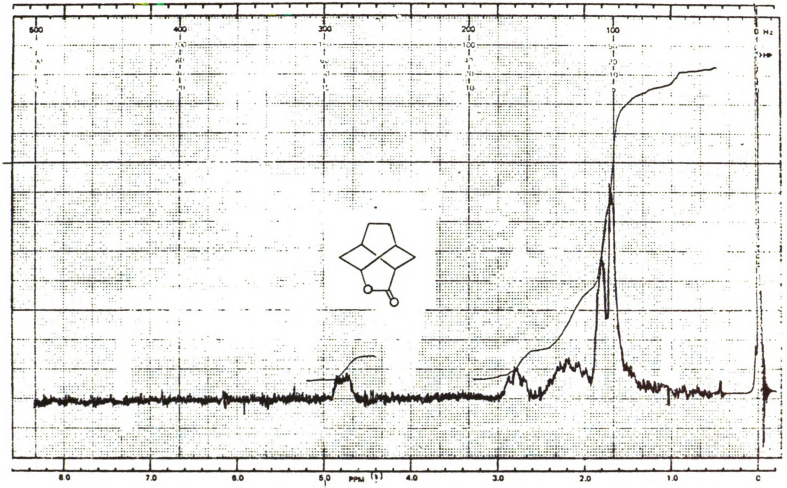


Figure 26. Nmr spectrum of syn-5-hydroxybicyclo[2,2,2]octan-2-carboxylic acid, δ-lactone (66) (CCl_4).