ABSTRACT

PART I

SYNTHESIS AND PHOTOCHEMISTRY OF CYCLOHEXADIENONE EPOXIDES

PART II

ACID-CATALYZED REARRANGEMENTS OF

CYCLOHEXADIENONE EPOXIDES

PART III

DIELS-ALDER REACTIONS OF A DIHYDROBENZOPENTALENE

AND THE SYNTHESIS OF HIGHLY-STRAINED QUADRICYCLANES

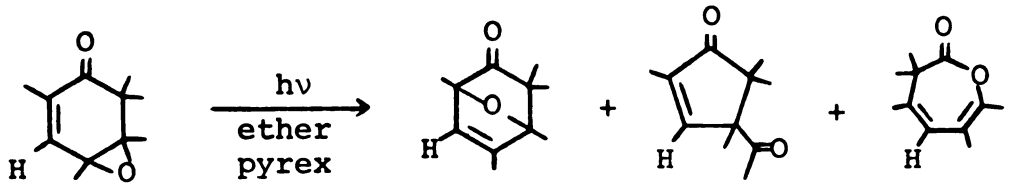
PART IV

MISCELLANEOUS

By

Cheng-Tai Peng

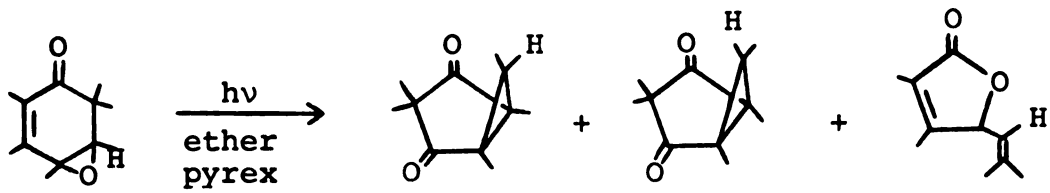
The photochemistry of cyclohexadienone epoxides, 34, 35 and 36, is described in Part I of this thesis. The irradiation of 4,5-epoxy-2,4,5,6,6-pentamethyl-2-cyclohexenone (34) in ether through a Pyrex filter gave 1,3,3,4,5-pentamethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-one (37, 25%), 4-acetyl-2,4,5,5-tetramethyl-2-cyclopentenone (38, 44%), and 3,3,4,6,7-pentamethyl-2(3H)-oxepinone (39, 30%).



34 → 37 (25%) + 38 (45%) + 39 (30%)

A new epoxyketone photorearrangement leading from 34 to 39 involving a cyclopropanone-aldehyde intermediate was proposed. Separated irradiation of 37 and 38 did not give any 39, eliminating 37 and 38 as reaction intermediates. Deuterium-labeling experiments support the proposed mechanism for the photorearrangement of 34.

The irradiation of 4,5-epoxy-2,3,4,6,6-pentamethyl-2-cyclohexenone (35) in ether through a Pyrex filter afforded anti-1,3,3,5,6-pentamethylbicyclo[3.1.0]hexan-2,4-dione (49, 62%), syn-1,3,3,5,6-pentamethylbicyclo-[3.1.0]hexan-2,4-dione (50, 11%) and lactone (51, 27%).

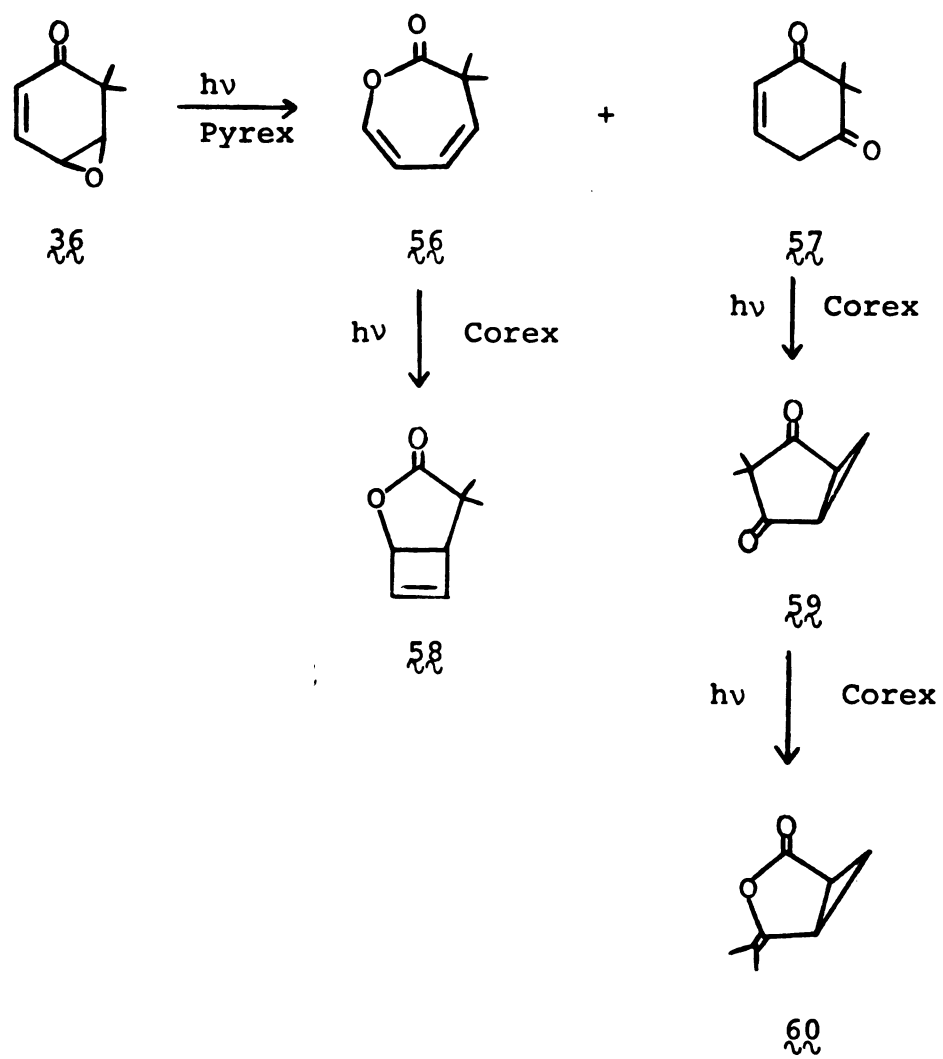


35 → 49 (62%) + 50 (11%) + 51 (27%)

Deuterium-labeling experiments were consistent with the proposed mechanisms for the photorearrangement of 35.

The irradiation of 4,5-epoxy-6,6-dimethyl-2-cyclohexenone (36) in ether through pyrex gave 3,3-dimethyl-2(3H)-

oxepinone (56, 86%) and 6,6-dimethyl-2-cyclohexen-1,5-dione (57, 14%). Each of these photoproducts underwent further photoisomerization through a Corex filter. Compound 56 rearranged to a single photoisomer, 2,2-dimethyl-4-oxa-bicyclo[3.2.0]hept-6-en-3-one (58) and compound 57 rearranged to 3,3-dimethyl-bicyclo[3.1.0]hexan-2,4-dione (59) which was also photolabile and rearranged further to 2-cis-(1'-hydroxy-2'-methyl-1'-propenyl)-cyclopropanecarboxylic acid-γ-lactone (60).

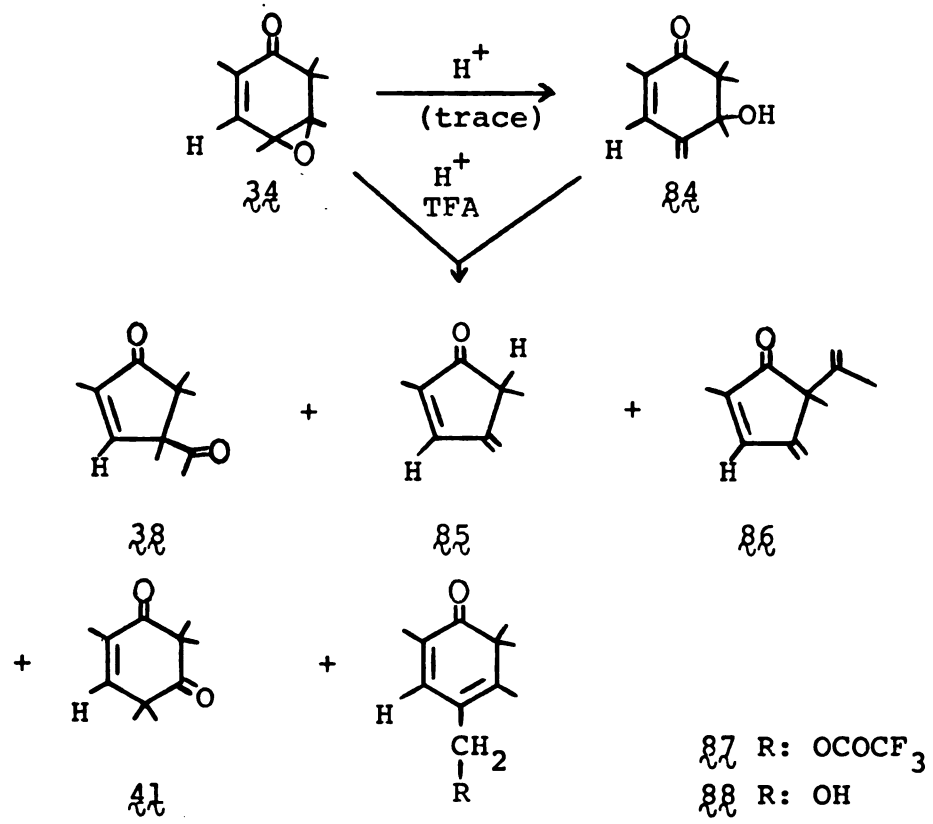


36 56 57 58 59 60

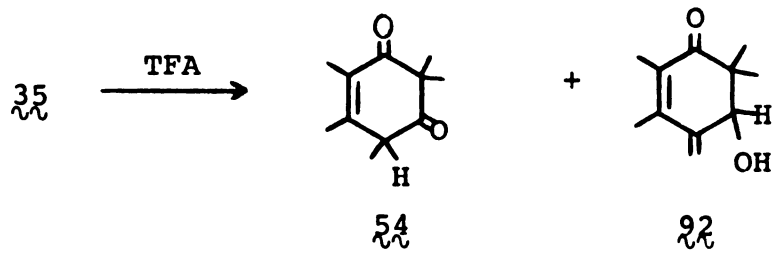
The photoisomerization of 36 could be sensitized (acetophenone, benzophenone) and quenched (trans-1,3,5-hexatriene, but not piperylene). The formation of 56 from 36 is presumed to be the same as that proposed for the formation of 39 from 34 which involves a cyclopropanone-aldehyde intermediate. In an attempt to trap the cyclopropanone, compound 36 was irradiated in methanol at room temperature and at -78°, only 56 and 57 were formed, in about the same ratio as in ether. However, after irradiation of 36 in tetrahydrofuran at -105°, a weak band at 1815 cm^{-1} was observed. When the solution was warmed to room temperature, the band at 1815 cm^{-1}, which may be attributed to the cyclopropanone carbonyl, gradually disappeared.

The acid-catalyzed rearrangement of cyclohexadienone epoxides, 34, 35 and 36, was studied in Part II of this thesis. In trace acid, epoxide 34 rearranged quantitatively to 5-hydroxy-4-methylene-2,5,6,6-tetramethyl-2-cyclohexenone (84). In neat trifluoroacetic acid (TFA), compound 34 rearranged to 4-methylene-2,5-dimethyl-2-cyclopentenone (85, 4%), 5-isopropenyl-4-methylene-2,5-dimethyl-2-cyclopentenone (86, 20%), 2,4,4,6,6-pentamethyl-2-cyclohexen-1,5-dione (41, 10%), 4-acetyl-2,4,5,5-tetramethyl-2-cyclopentenone (38, 8%), 4-trifluoroacetoxymethyl-2,5,6,6-tetramethyl-2,4-cyclohexadienone (87, 52%) and 4-hydroxymethyl-2,5,6,6-tetramethyl-2,4-cyclohexadienone (88, 6%). When 84 was treated with TFA, the same products were obtained and the product ratios were almost the same. On

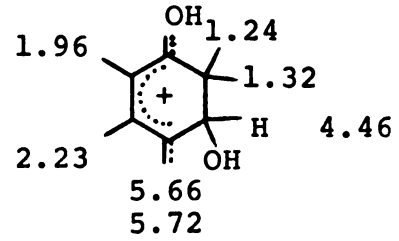
longer treatment with TFA, 86 was dealkylated to 85 and acetone. Saponification of 87 gave 88 in quantitative yield. Deuterium-labeling experiments support the proposed mechanism.



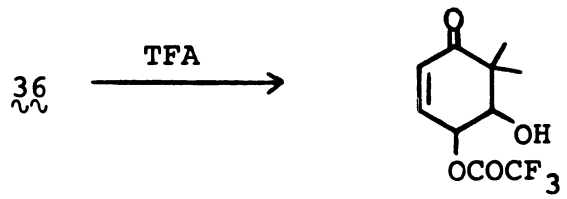
Rearrangement of epoxyketone 35 in TFA at room temperature gave 2,3,4,6,6-pentamethyl-2-cyclohexen-1,5-dione (54, 60%) and 4-methylene-5-hydroxy-2,3,6,6-tetramethyl-2-cyclohexenone (92, 40%).



In contrast to compound 84, 92 underwent no further rearrangement on treatment with TFA and this was attributed to preferential protonation at the carbonyl oxygen to give the highly delocalized cation 7.

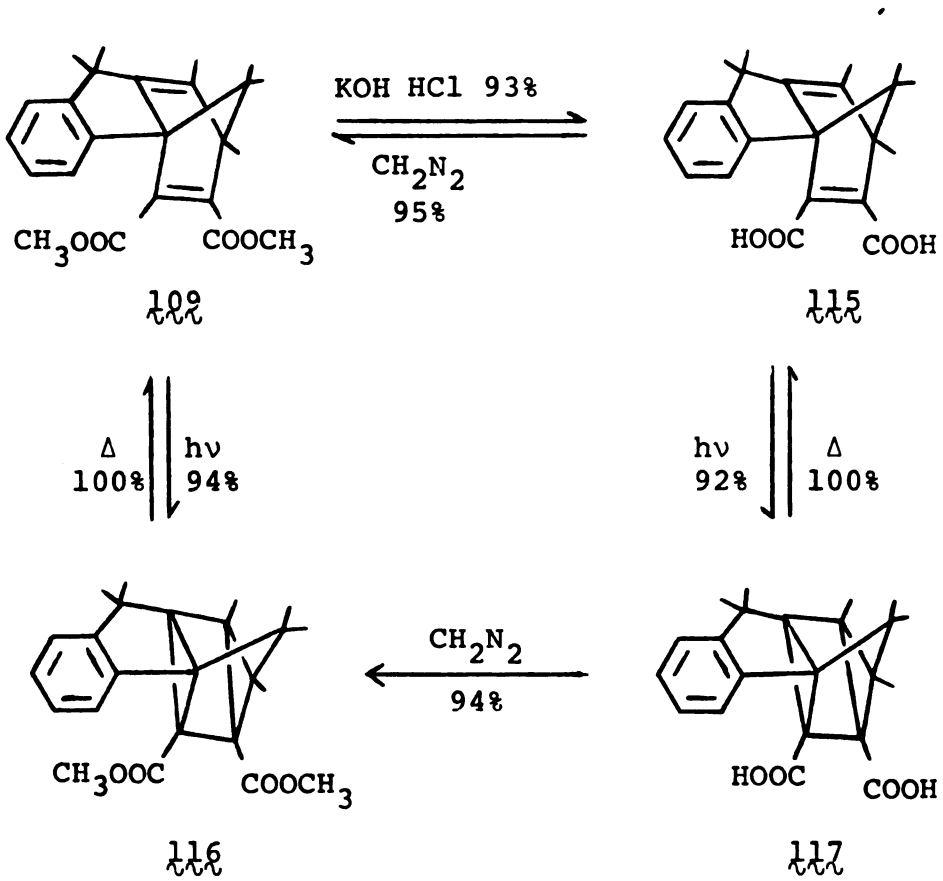


Treatment of the epoxyenone 36 in TFA gave the trifluoroacetate 98 (95%).



Prolonged treatment of 36 with TFA did not bring about any carbocation skeletal rearrangement.

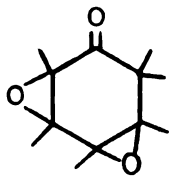
In Part III of this thesis, Diels-Alder reactions of a dihydrobenzopentalene 103, in particular with acetylenic dienophiles, and the synthesis of highly-strained quadricyclanes were studied. The highly substituted benzodihydropentalene 103 gave Diels-Alder adducts with dimethylacetylene dicarboxylate, diethyl azodicarboxylate, 3,6-dimethylbenzyne and 2-butyne. Irradiation of 109 and 115 in ether through vycor gave a good conversion to quadricyclane derivatives of 116 and 117, respectively.



Some miscellaneous results are described in Part IV of this thesis.

In Part IV (1), a new alkylation reagent - high surface sodium (HSS) was described to generate enolates which can then be alkylated. In the cases of hexamethyl-2,4-cyclohexadienone, alkylation occurred *via* a cross - rather than a fully conjugated to give a single product. Methylation *via* the addition of 2-tetralone to HSS proceeded smoothly to yield solely the 1-alkylated derivative.

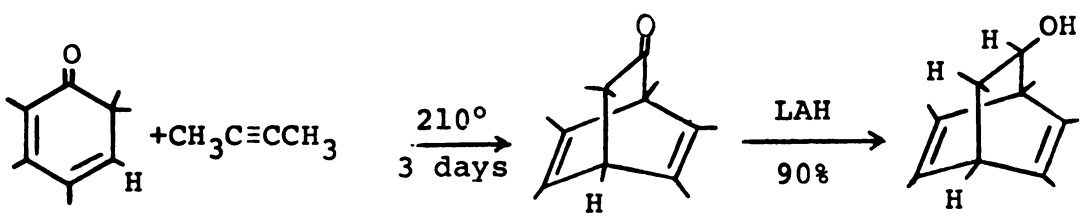
In Part IV (2), the synthesis of the diepoxy ketone 132 is described.



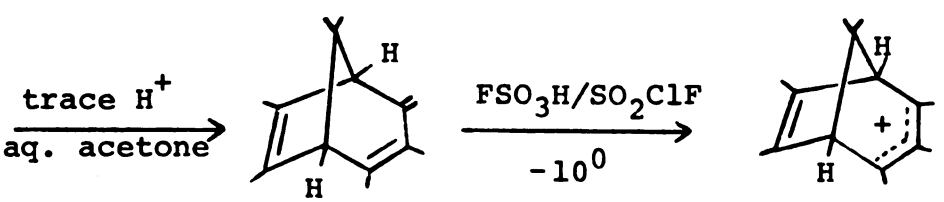
132

Attempts to rearrange 132 by photolysis and by acid are also described.

In Part IV (3), the synthesis of bicyclo[3.2.1]octadienyl carbocation 140 is described. The Diels-Alder



32 137 138



139 140

addition of 2-butyne to pentamethyldienone 32 gave 1,2,3,-5,6,8,8-heptamethyl-bicyclo[2.2.2]octa-2,5-dien-7-one (137, 93%). Reduction of 137 with lithium aluminum hydride gave 1,3,3,5,6,7,8-heptamethyl-bicyclo[2.2.2]octa-5,7-dien-2-ol (138, 90%). Treatment of 138 with a trace of acid in

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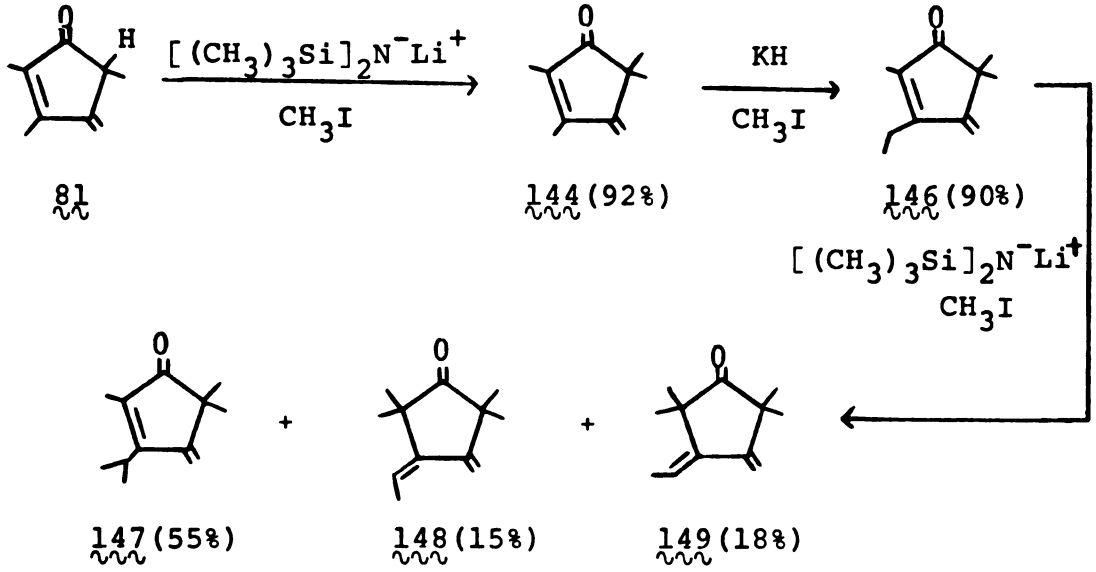
acetone caused it to dehydrate with rearrangement to give 2-methylene-3,4,6,7,8,8-hexamethylbicyclo[3.2.1]octa-3,6-diene (139, 41%). When 139 was treated at -78° with FSO_3H/SO_2ClF, the stable carbocation, heptamethylbicyclo[3.2.1]-octa-3,6-dien-2-yl cation (140) was obtained.

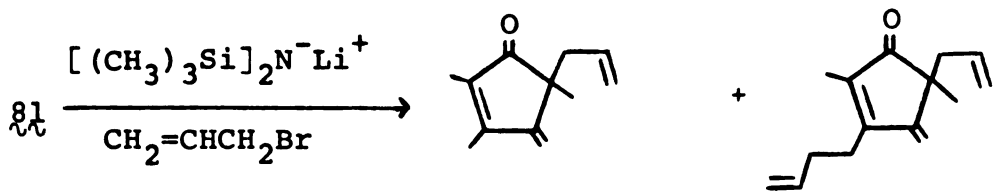
In Part IV (4), alkylation studies with 4-methylene-2,3,5-trimethyl-2-cyclopentenone (81) are described. Alkylation of 81 with methyl iodide gave 4-methylene-2,3,5,5-tetramethyl-2-cyclopentenone (144, 92%) and alkylation of



81 144(92%) 146(90%)

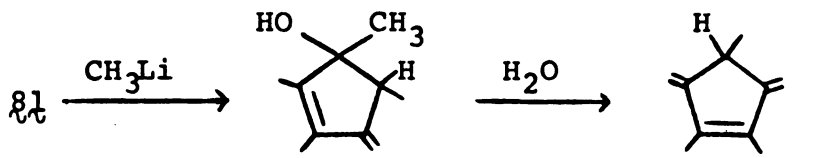
147(55%) 148(15%) 149(18%)

144 gave 4-methylene-3-ethyl-2,5,5-trimethyl-2-cyclopentenone (146, 90%). Further alkylation of 146 gave 147 (55%), 148 (15%) and 149 (18%). Alkylation of 81 with allyl bromide gave 150 (66%) and 151 (20%).



150 (66%) + 151 (20%)

Treatment of 81 with methyllithium followed by dehydration gave the triene 153 in 40% yield.



152 → 153 (40%)

PART I

SYNTHESIS AND PHOTOCHEMISTRY OF CYCLOHEXADIENONE EPOXIDES

PART II

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PART IV

MISCELLANEOUS

By

Cheng-Tai Peng

A DISSERTATION

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in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1977

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(2) 4,5-EPOXY-2,3,4,6,6-PENTAMETHYL-2-CYCLOHEXENONE

(3) 4,5-EPOXY-6,6-DIMETHYL-2-CYCLOHEXENONE

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PART IV

MISCELLANEOUS

(1) A NEW ALKYLATION REAGENT - HIGH SURFACE SODIUM

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PART I

SYNTHESIS AND PHOTOCHEMISTRY OF CYCLOHEXADIENONE EPOXIDES

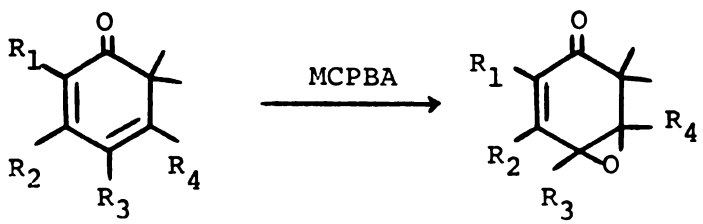
(1) 4,5-EPOXY-2,4,5,6,6-PENTAMETHYL-2-CYCLOHEXENONE

(2) 4,5-EPOXY-2,3,4,6,6-PENTAMETHYL-2-CYCLOHEXENONE

(3) 4,5-EPOXY-6,6-DIMETHYL-2-CYCLOHEXENONE

INTRODUCTION

The preparation of γ,δ-epoxyenones from conjugated dienones can be carried out by a number of methods.[1] The most common peracids used to convert dienones to epoxides have been perbenzoic acid,[2] monoperphthalic acid[3] and m-chloroperbenzoic acid.[4] m-Chloroperbenzoic acid is the most convenient oxidizing agent. It is commercially available, and it reacts at a somewhat faster rate than perbenzoic acid, and is ideally suited for epoxidations of the cyclohexadienone system.[5]



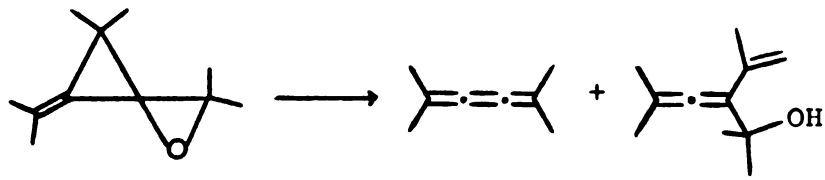
R_1	R_2	R_3	R_4	Ref.
Me	Me	Me	Me	5
H	Me	Me	H	23
Me	H	Me	Me	This work
Me	Me	Me	H	This work
H	H	H	H	This work

Preferential oxidation of the γ,δ-double bond over the α,β-double bond in conjugated dienones is a reflection of the electrophilic nature of organic peracids. Epoxidation reactions proceed by electrophilic attack of the peracid upon the double bond; thus the rate of epoxidation is very sensitive to the electron density at the olefinic site.[6] In 2,4-cyclohexadienones, the γ,δ-double bond has a greater electron density than the α,β-double bond and selectivity is easily achieved.

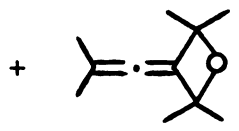
Among the synthetic uses of the epoxidation products, the photochemistry and the acid-catalyzed rearrangements are of special interest.[5,7] They provide an unusual array of structures from a single type of starting material. Moreover, those compounds will routinely be screened for antibiotic activities (for example, the antibiotics Magnamycin A, cirramycin A, chalcomycin, and neutramycin contain mainly the γ,δ-epoxy enone functional group).

The first part of my thesis deals mainly with the photochemistry of γ,δ-epoxyenones. As we know, the unusual ground state reactivity of oxiranes toward nucleophilic attack has long been recognized and exploited. Only in recent years, however, has the excited-state chemistry of these inherently strained substrates been extensively explored and the potential synthetic utility of the photoreactions received attention. Here a brief survey of the photochemistry of oxiranes pertinent to the present study will be presented.

The photochemical reactions of oxiranes lacking an aromatic chromophore have been studied. Irradiation of this type of compound results in decomposition,[8,9] isomerization[10] and carbene formation.[11] The mechanisms of photomolecular decomposition and isomerization are simple, but the carbene formation is more complicated. For example, irradiation of a benzene solution of the oxaspiropentane derivative 1 affords the cumulene 2, an allenic alcohol 3 and allenic oxetane 4. The oxetane 4 was shown to be a secondary product resulting from cycloaddition of 2 to acetone.

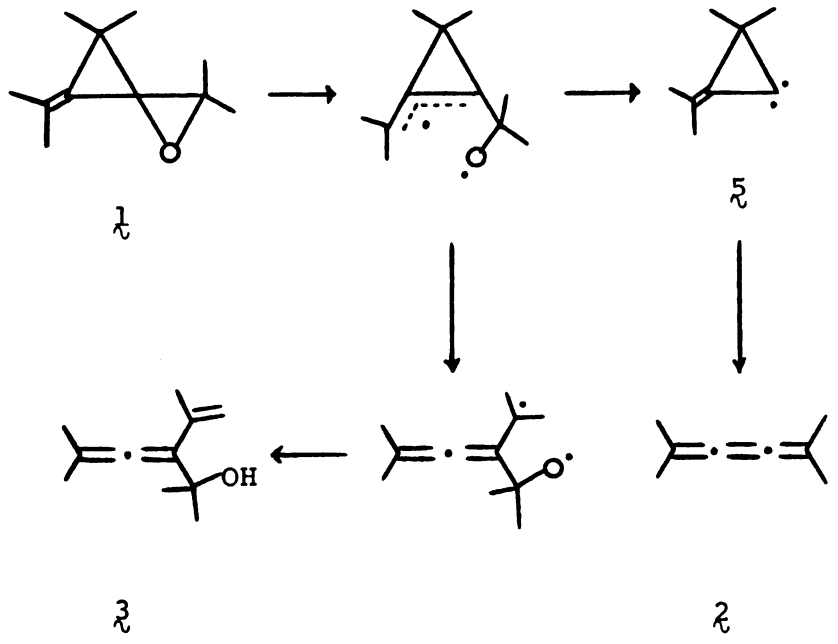


1 2 3

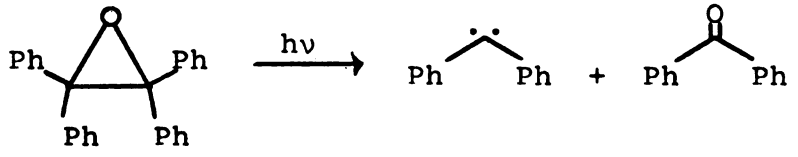


4

The cyclopropyl carbene 5 was proposed to rationalize the formation of 2.



Aryloxiranes have been shown to undergo photofragmentation in solution to give arylcarbenes and carbonyl compounds.[12] For example, photolysis of tetraphenyloxirane[13] in methanol/benzene gave benzhydryl methyl ether in quantitative yield. Benzophenone, tetraphenylethylene (a primary photoproduct), and diphenyl carbene are observable upon irradiation of tetraphenyloxirane in a rigid glass at 77°K.



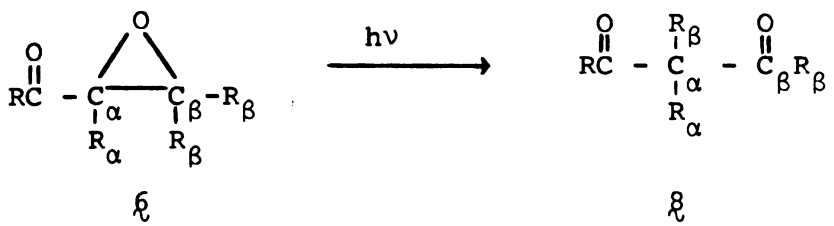
Several other phenyl-substituted oxiranes have been found to add methanol photochemically.[14]

The photochemistry of epoxyketones has been reviewed.[15] It is generally accepted that the n,π*-excited state is the chemically significant excited state involved in the photochemical transformations of this class of ketones.

In this introduction, a brief review of the photochemistry of α,β- and β,γ-epoxy ketones and α,β-unsaturated γ,δ-epoxyketones are presented in order to set the various possibilities for the photochemical behavior of 34, 35, and 36 in perspective.

A. The Photochemistry of α,β-Epoxyketones.

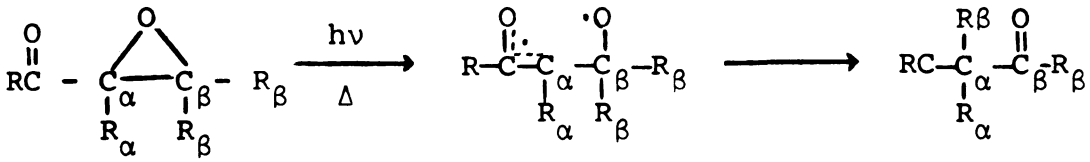
The photoisomerization of an α,β-epoxy ketones usually proceeds via a 1,2-alkyl or hydrogen migration to give a β-diketone 8.



6

R, R_α, R_β = H, alkyl or aryl

The most rational mechanism for this reaction is that they proceed via homolysis of the C_α-O bond. The carbonyl group can then stabilize the radical at C_α as shown in structure 7. Concurrently or at a later stage an R group migrates from C_β to C_α, forming a carbonyl group at C_β.



6 7 8

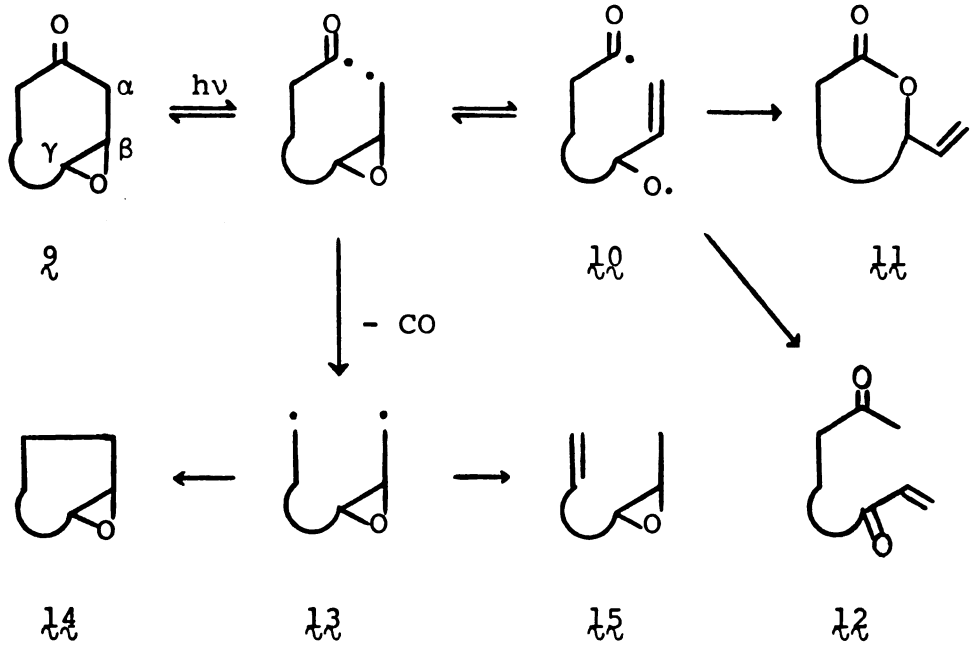
The usual migratory order for different R groups at C_β is H > alkyl > aryl.[15(a-c),26]

B. The Photochemistry of β,γ-Epoxyketones.

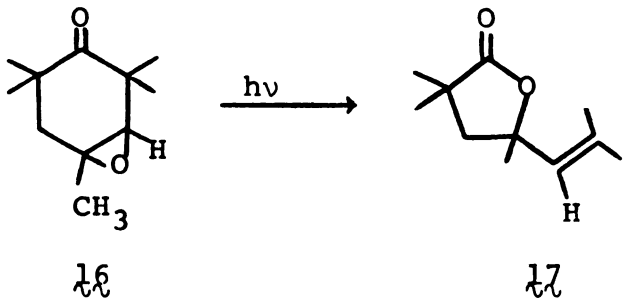
Irradiation of a β,γ-epoxy cyclic ketone 9 initially leads to Norrish type I bond cleavage with formation of a diradical which undergoes subsequent epoxide ring opening to give an acyl-alkoxy radical 10. This then undergoes ring closure to give a lactone 11 and/or hydrogen transfer to afford an aldehyde 12. If the formation of both of these products is structurally precluded, then decarbonylation occurs to give a biradical (13) which undergoes disproportion and/or ring closure to afford

stable products. These are illustrated in Scheme 1.[17]

Scheme 1



If the hydrogen at the γ-carbon in the β,γ-epoxyketone moiety of 9 is replaced by an alkyl substituent, then the formation of aldehyde 12 is precluded. For example, irradiation of epoxy ketone 16 gives lactone 17 as the only major reaction product.[17]

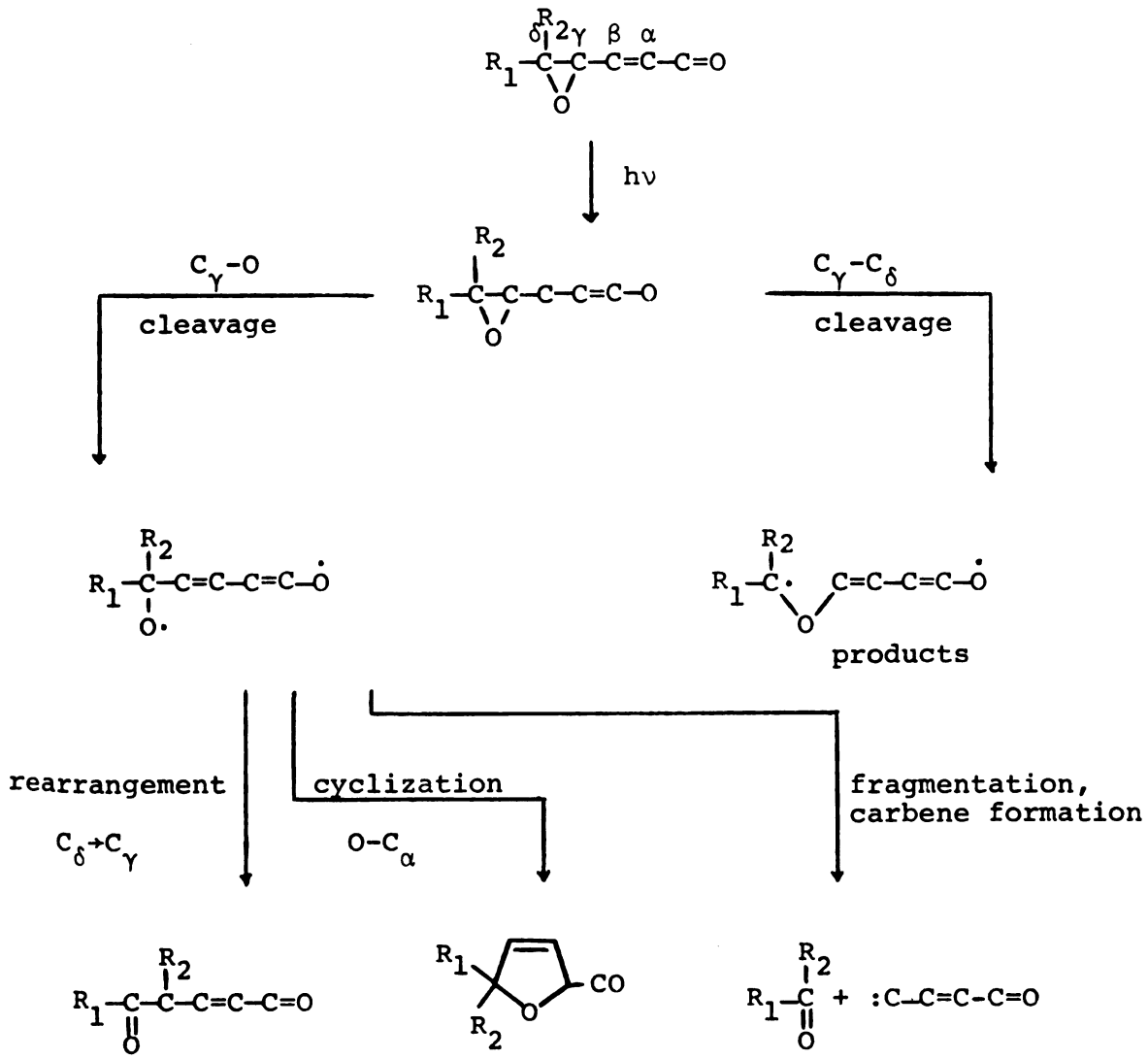


16 17

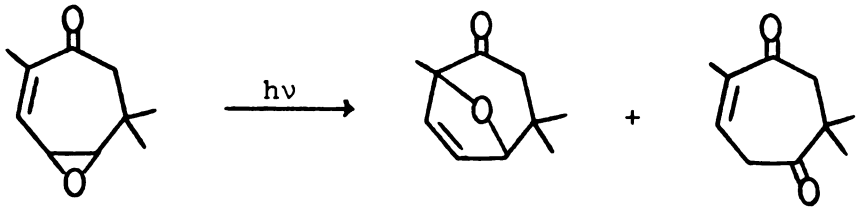
C. The Photochemistry of α,β-Unsaturated γ,δ-Epoxyketones.

A mechanistic scheme which rationalizes all previous results on the photochemistry of α,β-unsaturated γ,δ-epoxyketones was proposed by Hart.[18]

Scheme 2

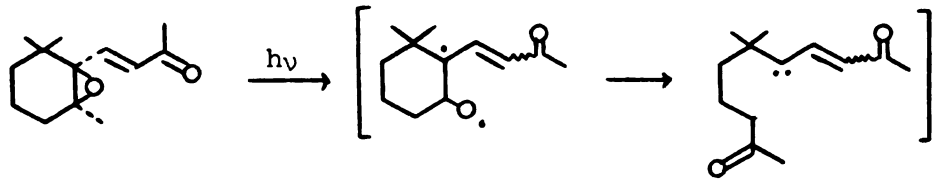


The more common reaction path involves C_γ-O bond cleavage at initial step. Three different types of subsequent reactions have been observed. These are migration of a group from C_δ to C_γ[7,19(a-c)] cyclization at C_α, or fragmentation to a carbene.[21] For example, photocyclization at C_α and $C_\delta \rightarrow C_\gamma$ hydrogen migration in the irradiation[20] of eucarvone 18 gave 19 and 20, respectively.



18 19 20

The irradiation[22] of trans-β-ionone 21 was interpreted in terms of a carbene intermediate formed by fragmentation of the C_γ-C_δ bond following C_γ-O bond cleavage.



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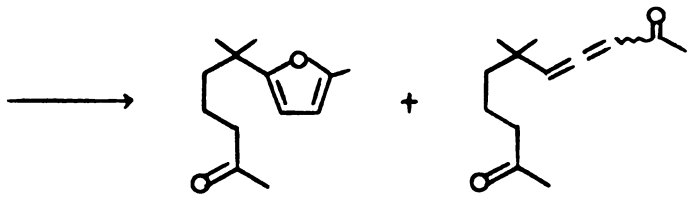
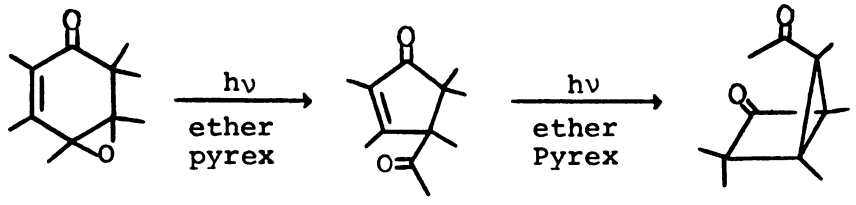


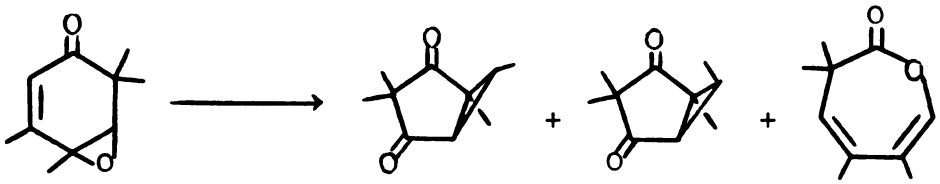
22 23

Very recently, the photochemistry of hexamethyl-2,4-cyclohexadienone-4,5-epoxide (24) was reported.[7] Irradiation of 24 gave 2,3,4,5,5-pentamethyl-4-acetyl-2-cyclopentenone (25) which then photoisomerized to endo-5-acetyl-1,3,3,4,5-pentamethylbicyclo[2.1.0]pentan-2-one (26).



24 25 26

Finally, the remarkable formation of 28, 29 and 30 from 4,5-epoxy-3,4,6,6-tetramethyl-2-cyclohexenone 27 was recently reported.[18,23]

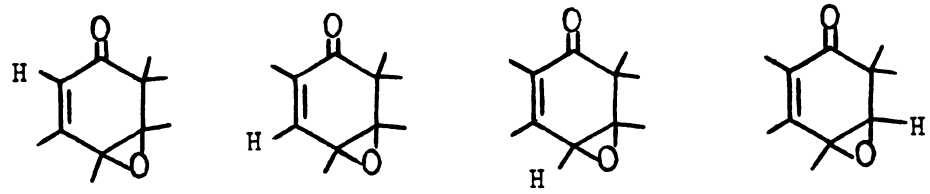


27 28 29 30

The proposed intermediate leading to products 28 and 29 was not isolated and the new fragmentation mechanism leading to product 30 was open to some question. Therefore a systematic study of epoxy enones was undertaken as part one of my thesis to further investigate these new photoreactions.

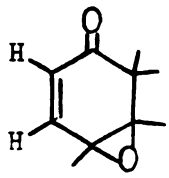
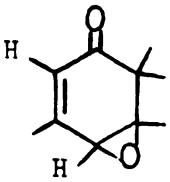
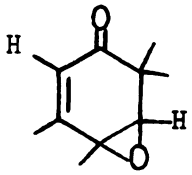
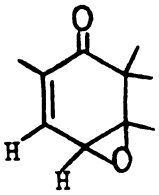
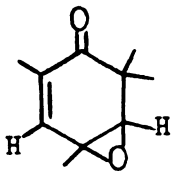
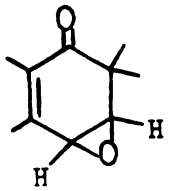
It is clear from the results on 24 and 27 that the replacement of H for CH_3 in certain positions can profoundly affect the photochemical results. Consequently, it would be desirable to study all possible substitutions systematically.

<u>One hydrogen</u>

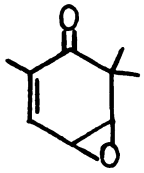
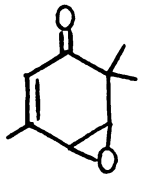
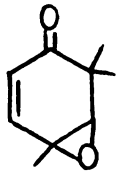
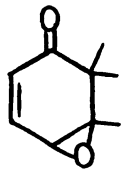


34 35

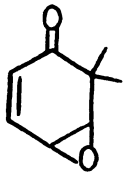
Two hydrogens

Three hydrogens

Four hydrogens

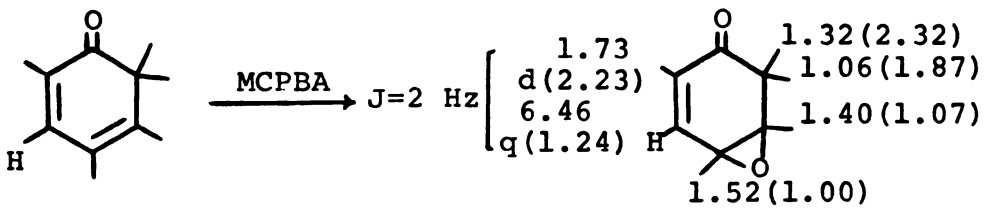


Naturally not all of these compounds are readily accessible synthetically. In this thesis the results obtained with two compounds containing only one hydrogen (34) and (35) are described. The compound with all four hydrogens (36) was also studied. These examples were selected for two reasons; the precursors for their synthesis[16,30] were known and the latter compound particularly with all hydrogens in the positions of interest could be compared with the already studied fully methylated compound.

RESULTS AND DISCUSSION

1. Photochemistry of 4,5-Epoxy-2,4,5,6,6-pentamethyl-2-cyclohexanone (34)

The epoxyenone 34 has not been previously described. It was synthesized in good yield from the corresponding dienone 31[16] and m-chloroperbenzoic acid.



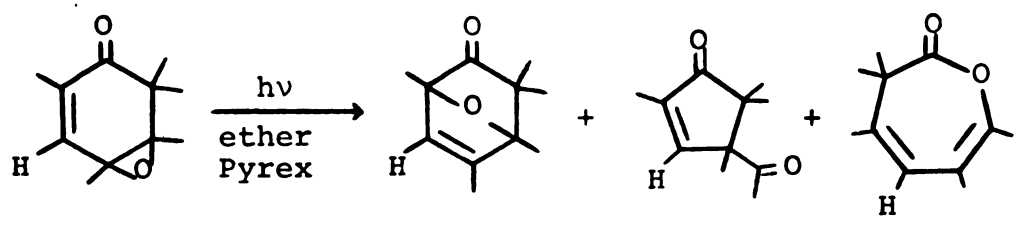
31 34

Compound 34 was assigned the structure shown on the basis of the following spectral data and chemical transformations. The molecular formula $C_{11}H_{16}O_2$ was confirmed by the mass spectrum (parent peak m/e 180) and elemental analysis. The ir spectrum showed a strong absorption at 1680 cm^{-1} for a conjugated C=O, and the uv spectrum was also consistent with conjugation, having a λ_{max} at 250 nm. The nmr spectrum is indicated on the structure (NOTE: Figures in parentheses are the relative shifts with Eu shift reagent). All of the data show that 34 has a double bond in the α,β-position, and that the epoxide ring is in the γ,δ-position. The europium shift data

were also consistent with this structure.

A. Product Structures

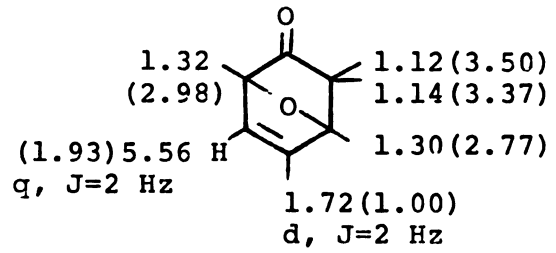
The irradiation of 34 (0.01 M in ether) through a pyrex filter was followed by vapor phase chromatography (vpc). As the peak due to 34 decreased in intensity, three new peaks appeared which were assigned to compounds with the structures 37, 38 and 39. After one hour, the peak due



34 37 (25%) 38 (44%) 39 (30%)

to 38 diminished in area in favor of a new peak which was assigned to the structure 40. After two hours, the peak due to 38 had disappeared, and the peak due to 40 was fully developed.

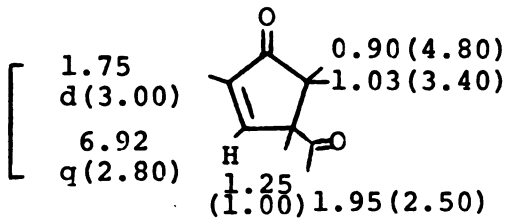
Compound 37 was assigned the structure shown, on the basis of the following spectral data.



37

The molecular formula $C_{11}H_{16}O_2$ was confirmed by the compound's mass spectrum (parent peak m/e 180) and elemental analysis. The ir spectrum of this clear oil showed a strong carbonyl absorption at 1740 cm^{-1} (five-numbered ring ketone) and its ultraviolet spectrum had maxima at 207 nm (ε 950) in methanol. The nmr spectrum is summarized on the structure.

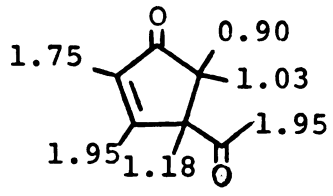
Compound 38 was assigned the structure shown.



38

The molecular formula $C_{11}H_{16}O_2$ was confirmed by the mass spectrum (parent peak m/e 180) and elemental analysis. The nmr signals (see structure) were nearly identical to those of the permethyl diketone 25. The shift reagent appeared

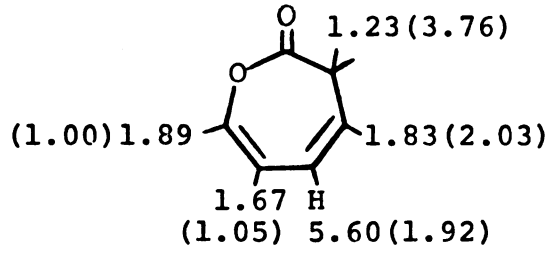
to coordinate primarily at the cyclopentenone carbonyl group. The base peak in the mass spectrum of 38 appeared



25

at M-42 (loss of CH_2=C=O) and the next most intense peak (rel. intensity 62) was at M-57 (loss of CH_2=C=O and CH_3). All spectroscopic data were nearly identical to those of the known compound 25.[5]

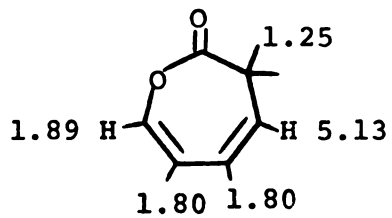
Compound 39 was assigned the structure shown.



39

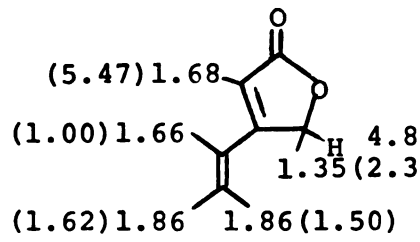
The molecular formula $C_{11}H_{16}O_2$ was confirmed by the mass spectrum (parent peak m/e 180) and elemental analysis. The presence of two equivalent gem-dimethyl signals as revealed by its nmr spectrum suggested that 39 possessed a plane of symmetry or readily passed through such a

conformation. The gem-dimethyl signal could not be separated even by using shift reagent. Besides this, the nmr spectrum showed two homoallylically coupled methyl groups at δ1.67 and 1.89, and one vinyl methyl group as a doublet at δ1.83. The vinyl proton appeared as a multiplet at δ5.60. Decoupling at the vinyl proton using a 100 MHz nmr instrument caused the methyl signal at δ1.83 to become a sharp singlet. The uv spectrum of 39 showed a maximum at 248 nm (ε 10,570), similar to the uv maximum at 248 nm (log ε 3.87) reported for 1,3-cycloheptadiene by Pesch and Friess.[24] The ir spectrum of 39 had an intense carbonyl absorption at 1750 cm^{-1} which showed that there was no conjugation between the carbonyl group and the diene moiety. All of the spectroscopic data were similar to those of the known compounds 30[23] and 56.[31]



30

Compound 40 was assigned the structure shown.



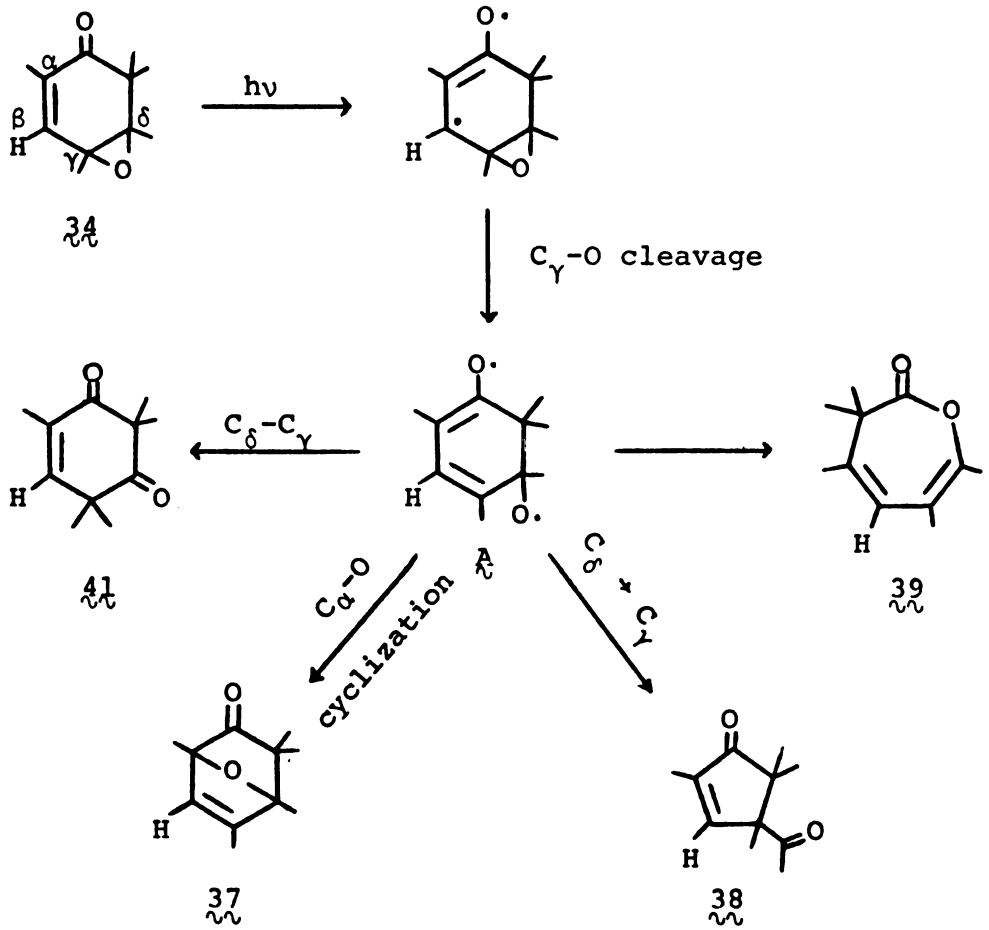
40

The molecular formula $C_{11}H_{16}O_2$ was confirmed by its mass spectrum (parent peak m/e 180) and elemental analysis. Compound 40 showed infrared absorption bands at 1760 ($\nu_{C=O}$) and 1662 ($\nu_{C=C}$) cm^{-1} and uv maxima at 222 nm (ε 7640) and at 263 nm (ε 6250) which indicated that 40 is a Δ'-butenolide with extended conjugation. In spite of the extended conjugation, compound 40 exhibited a normal uv maximum. The reason for this is attributed to the non-planarity between the butenolide group and the exo-cyclic double bond.[7,25] The nmr spectrum of 40 consisted of four vinyl methyl group signals at δ1.66, 1.86 (which showed homoallylic coupling between them) and 1.68, one methyl signal as doublet at δ1.35 and one proton at δ4.85 as quartet. Decoupling the proton at δ4.85 caused the peak at δ1.35 to sharpen to a singlet. The shift reagent data were also consistent with the structure. Also the spectroscopic data were similar to those of the closely related permethylated butenolide.[7]

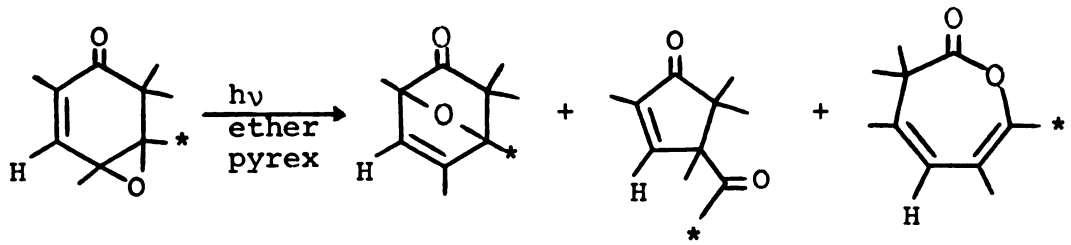
B. Mechanism

The primary products from the photolysis of 34 through a pyrex filter were 37, 38 and 39. The photoisomerization may occur by the initial cleavage of the C_γ-O bond followed by C_α-O cyclization to give 37, or followed by alkyl rearrangement from $C_\delta \rightarrow C_\gamma$ to give 38. Preferred ring contraction over methyl migration (to give 41) is consistent with the usual order of migratory aptitudes observed in the photorearrangement of an α,β-epoxyketone to a β-diketone.[15(a-c),26]

Scheme 3



Consistent with this scheme, irradiation of labeled 34* (*=CD_3 in place of CH_3) gave 37* and 38*.



34* 37* 38* 39*

The mechanisms leading from 34* to 37* or from 34* to 38* are fairly obvious, as this type of photorearrangement has been reported in literature.[7,20]

Irradiation of 34* also gave 39* and the mechanism leading from 34* to 39* is unusual. There are at least three plausible mechanisms to account for the formation of 39 as shown in Scheme 4.

Mechanism a involves the initial formation of 37 (an observed reaction product). Further irradiation of 37 might cause α-cleavage followed by bond reorganization as shown, to give 39. This mechanism was eliminated on two grounds. Beginning with 34* one should obtain 39 labeled at C-6 (42) whereas in fact the label appeared at C-3 (39*). Furthermore, separate irradiation of 37 under the same conditions used to transform 34 to 39 (in part) did not produce any 39.

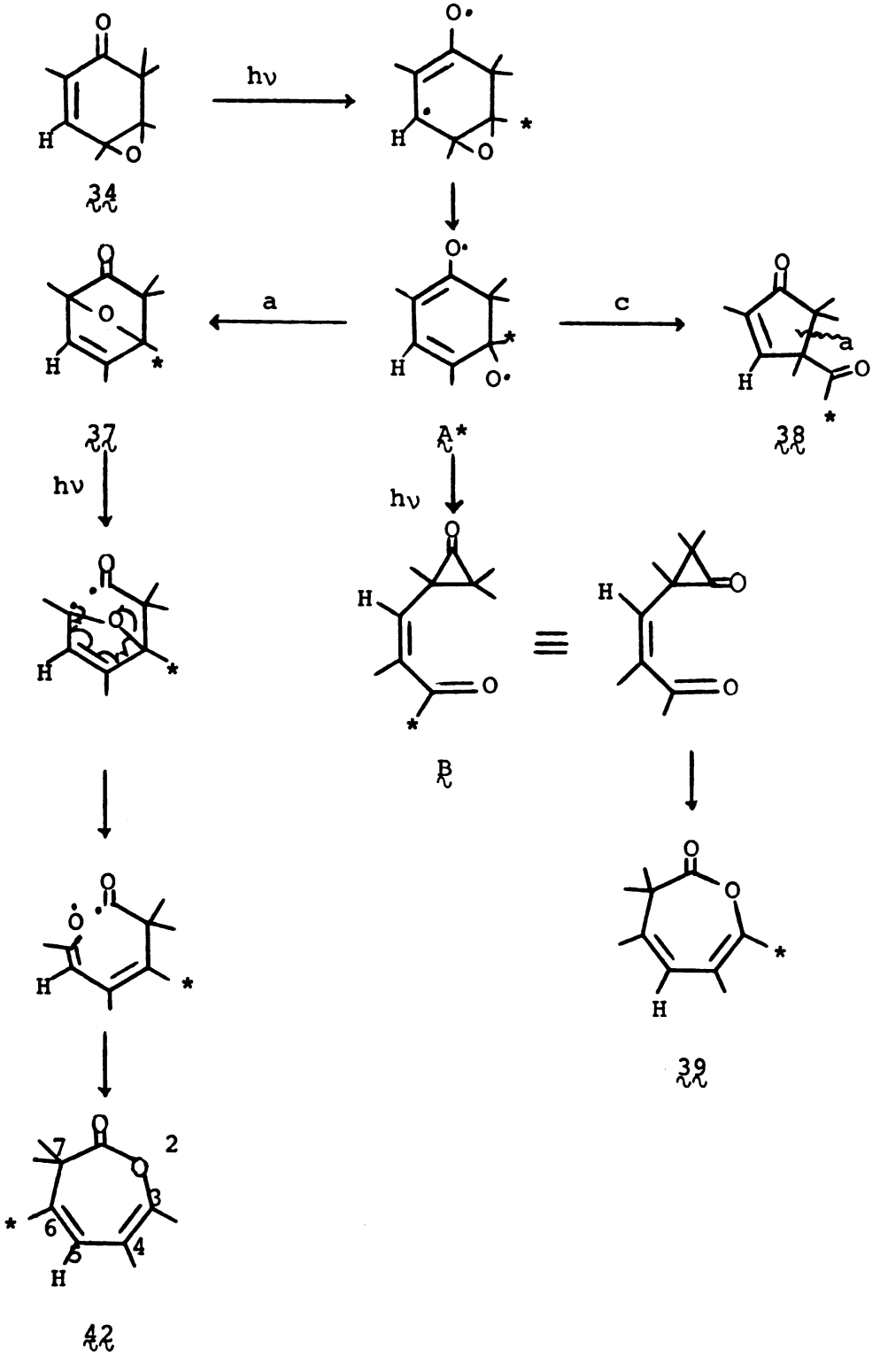
In mechanism b the initial intermediate A undergoes

C_δ-C_ε bond cleavage (as in the mechanism for the formation of 38) but instead of a 1,2-shift, a 1,4-shift is proposed, leading to the cyclopropanone-aldehyde intermediate B. A six-electron electrocyclic reaction of B would give 39. This scheme is entirely consistent with the observed labeling results (see Scheme 4).

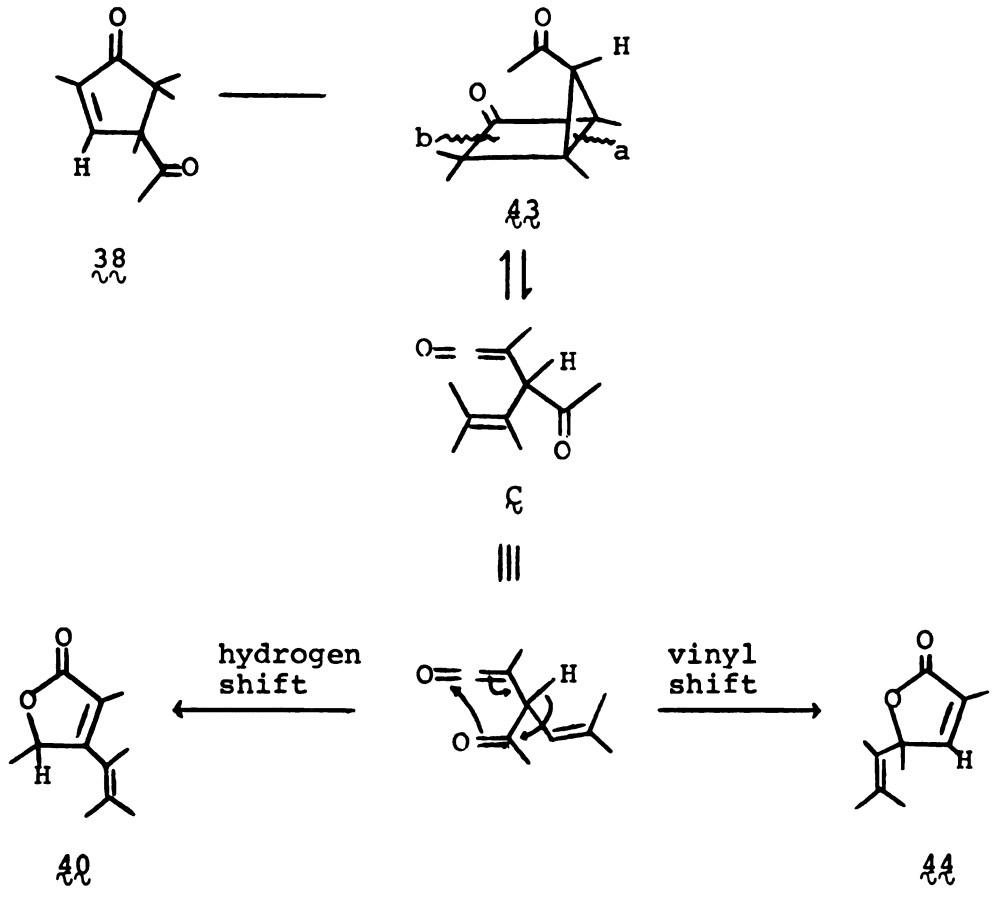
A third alternative mechanism is c in which 39 is produced from 38 via the same cyclopropanone-aldehyde intermediate proposed in mechanism b. Although the labeling result is consistent with this mechanism, it was ruled out by a control experiment. Direct irradiation of 38 under the same conditions used to convert 34 to 39 (in part) gave exclusively 40 (and 40^* from 38^*). Consequently mechanism c is also eliminated, and the only one of the proposed three which fits the data is b.

The quantitative photoisomerization of 38 to 40 can be regarded as proceeding via the initial oxa-di-π-methane photorearrangement product 43,[37] which is thermolabile (Scheme 5). Homolysis of bonds a and b of compound 43 can give ketene C as an intermediate, from which 40 can be formed by ring closure with a hydrogen migration. Vinyl migration might also occur, leading to 44; this possibility cannot be excluded, since trace amounts of minor products could not be isolated. A similar mechanism in closely related photoreactions has been reported by Davis,[27] Burkinshaw and Matsuura.[28,29] For example, the

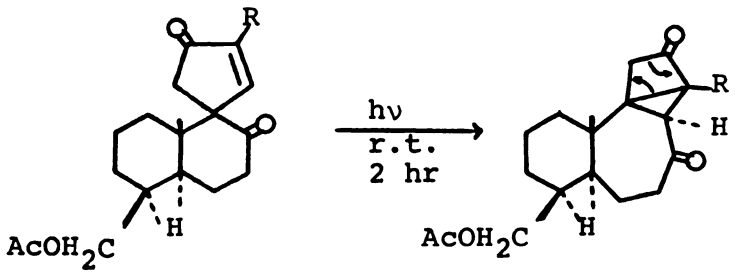
Scheme 4



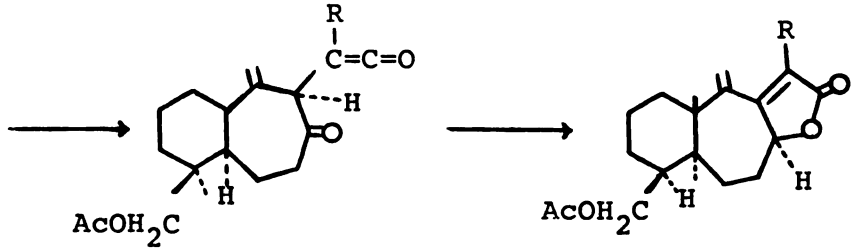
Scheme 5



spirodiketone 45 rearranged photochemically to an intermediate 46 which rearranged directly to 48 at room temperature within 2 hours. No vinyl migration product from the intermediate 47 was isolated.



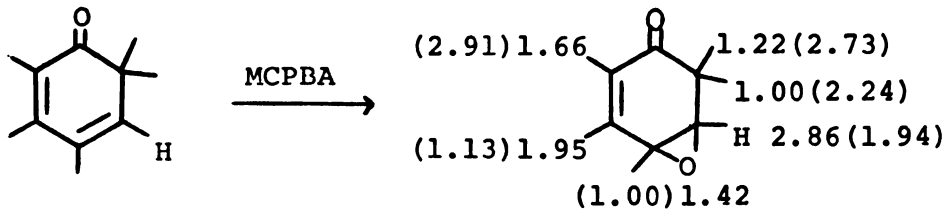
45 46



47 48

2. Photochemistry of 4,5-Epoxy-2,3,4,6,6-pentamethyl-2-cyclohexenone (35)

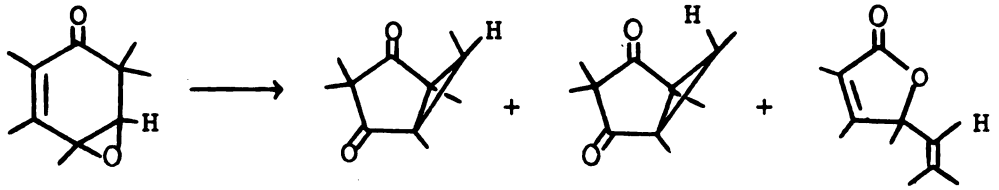
The epoxyenone 35 has not been previously described. It was synthesized in good yield from the corresponding dienone 32[16] and m-chloroperbenzoic acid. Its infrared and ultraviolet spectra showed that the carbonyl group was still conjugated with a double bond [$\nu_{C=O}$ 1657 cm^{-1}, λ_{max} (methanol) 255 nm (ε 8460), 325 nm (ε 270)] and the nmr spectrum with europium shift data was also consistent with epoxidation having occurred solely at the γ,δ double bond.



32 35

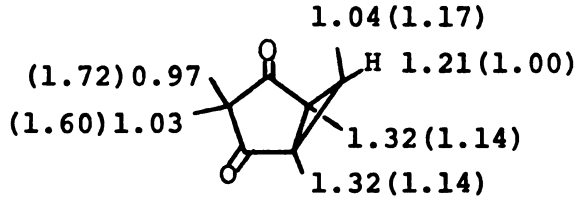
A. Product Structures

Irradiation of 35 (0.01 M in ether) through pyrex for 2 hr gave three photoproducts



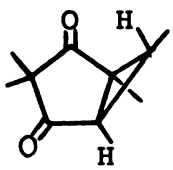
35 49(62%) 50(11%) 51(27%)

Compound 49 was assigned the structure shown on the basis of the following spectral data. The molecular formula

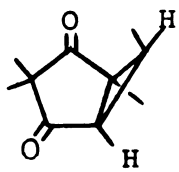


49

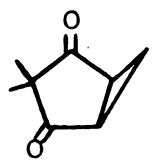
$C_{11}H_{16}O_2$ was confirmed by the mass spectrum (parent peak m/e 180) and elemental analysis. The infrared spectrum had carbonyl peaks at 1700 and 1738 cm^{-1}. These two ir absorption bands may originate from coupling between the two carbonyl groups. This kind of coupling is well documented.[7,17,18] The uv spectrum possessed only end absorption and the ir spectrum lacked any olefinic hydrogen absorption. In the nmr spectrum, all methyl signals appeared at or above δ1.32. These spectroscopic data indicate that 49 must be a saturated compound. The structural and stereochemical assignments are based on the 100 MHz nmr spectrum (CCl_4): δ0.97 (s, 3H), 1.03 (s, 3H), 1.04 (d, 3H, J = 5 Hz), 1.17-1.25 (q, 1H, J = 5 Hz), 1.32 (s, 6H). Decoupling by irradiation at δ1.21 caused the peak at δ1.04 to sharpen to a singlet. The europium shift data showed that the two methyls at δ1.32 were equivalent, as required by the plane of symmetry. Also, in comparison with the shift data for 50 (vide infra) the stereochemistry at C-6 is clear. The mass spectrum of 49 showed a base peak at m/e 110 corresponding to the loss of a $(CH_3)_2C{=}C{=}O$ moiety. The spectral data of 49 were similar to those of the closely related compounds 28, 29 and 59[18,23,36]



28

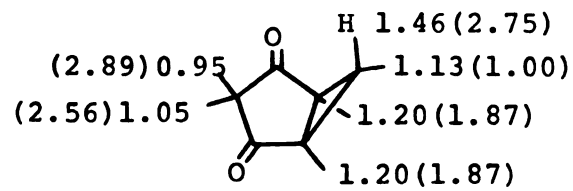


29



59

Compound 50 was assigned the structure shown.

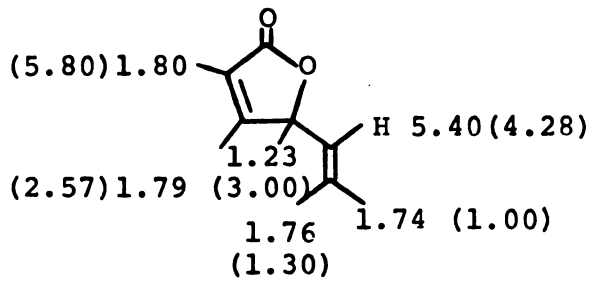


50

The molecular formula $C_{11}H_{16}O_2$ was confirmed by the mass spectrum (parent peak m/e 180) and the elemental analysis. The mass spectrum showed a base peak at m/e 110 corresponding to the loss of $(CH_3)_2C{=}C{=}O$ moiety. The ir spectrum showed two coupled carbonyl absorption peaks at 1741 and 1701 cm^{-1}. The uv spectrum again showed only end absorption. These data strongly suggest that 50 is a stereoisomer of 49. The 100 MHz nmr (CCl_4) showed peaks at δ0.95 (s, 3H), 1.05 (s, 3H), 1.13 (d, 3H, J = 5 Hz), 1.20 (s, 6H), 1.30-1.60 (q, 1H, J = 5 Hz). Decoupling by irradiating the multiplet at δ1.46 caused the methyl group

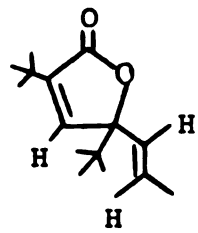
at δ1.13 to sharpen to a singlet. The europium shift data are consistent with the assignment of exo geometry to the C-6 methyl group.

Compound 51 was assigned the structure shown primarily by its spectral properties. The molecular formula was



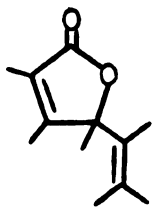
51

confirmed by the compound's mass spectrum (parent peak m/e 180) and elemental analysis. Strong carbonyl absorption at 1741 cm^{-1} and a uv λ_{max} 225 nm (in methanol) were consistent with the presence of a Δ'-butenolide moiety. These data are similar to those reported for 52 and 53.[7,24,25]



ir(C=O): 1748 cm^{-1}
uv(EtOH): λ_{max} 218 nm (ε 7250)
NMR: -CH=CH- δ5.65 to δ5.68

52



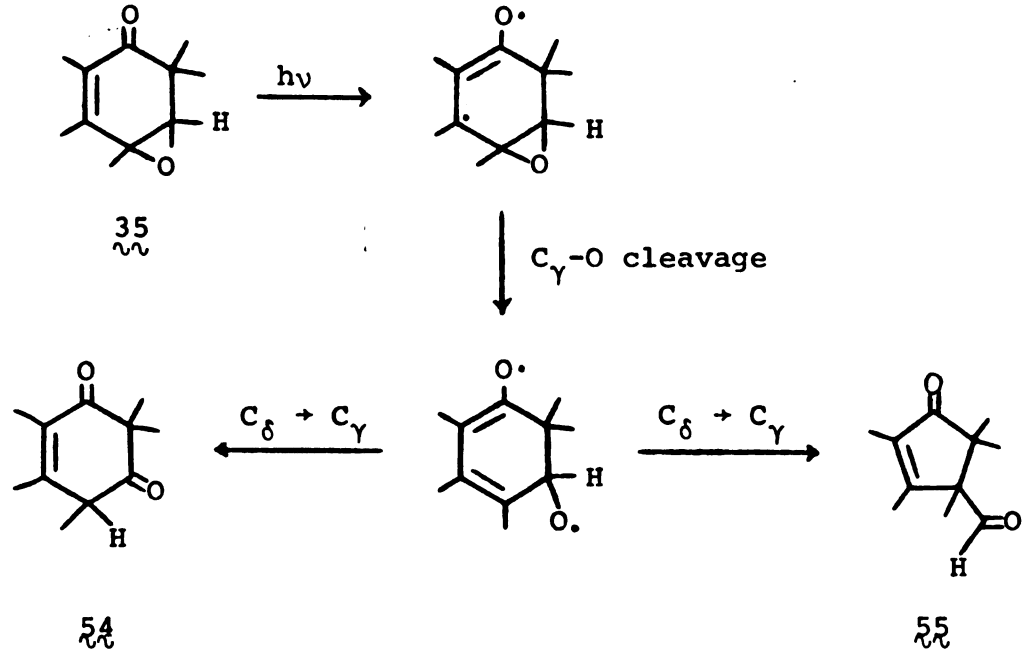
ir(C=O): 1745 cm^{-1}
uv(MeOH): λ_{max} 230 nm (ε 3100)

53

The nmr spectrum of 51 ($CDCl_3$) showed a singlet at δ1.23 (3H), four vinyl methyl signals from δ1.75-1.80 and one vinyl proton signal at δ5.40 as a multiplet. Decoupling by irradiation at the vinyl methyl signals caused the vinyl proton signal at δ5.40 to sharpen to a singlet. This showed that the vinyl proton is coupled to one of the methyl groups. The europium shift data are consistent with the assigned structure.

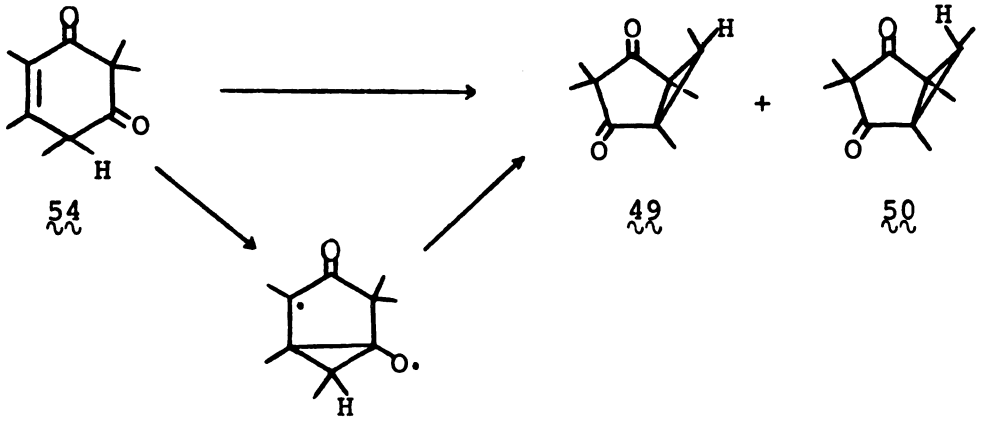
B. Mechanism

It is clear that 49 and 50 do not arise directly from the irradiation of 35, but are formed from the photoisomerization of primary photoproduct 54. Irradiation of epoxyketones generally leads to β-diketones. The formation of 54 occurs by cleavage of the C_γ-O bond and hydrogen



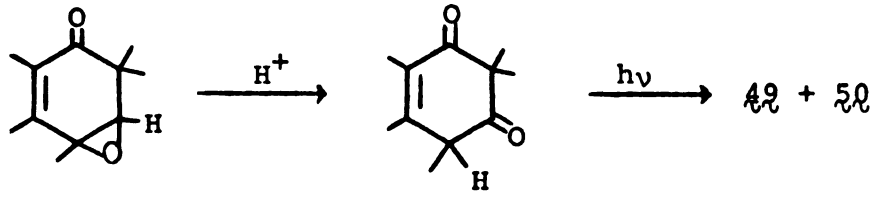
migration over ring constraction is consistent with the usual migratory aptitudes observed in the photochemistry of α,β-epoxyketones.[15(a-c),26]

The photoisomerization of 54 to 49 and 50 is an oxa-di-π-methane rearrangement.[37]



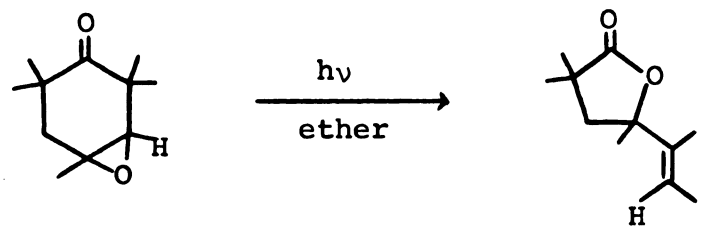
54 49 50

Though no evidence could be obtained for the formation of 54 during the course of the irradiation of 35, there is strong evidence that it is an intermediate in the process. Compound 54 was isolated from the acid-catalyzed rearrangement of 35. Irradiation of 54 under the same reaction conditions used to irradiate 35 gave 49 and 50 in the same ratio.



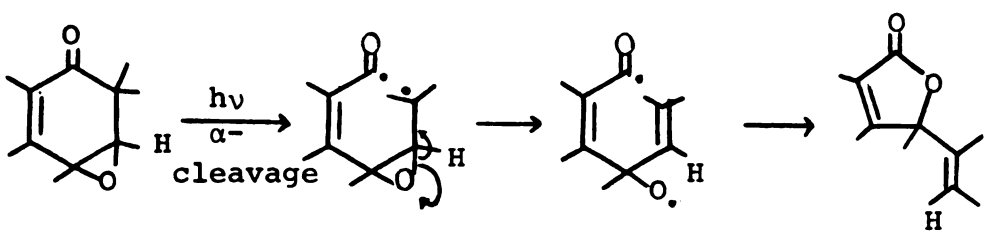
35 54

Concerning the mechanism for the formation of 51, Murray found[17] in a study of closely related compounds that irradiation of epoxyketone 16 in ether gave lactone



16 17

17 as an only reaction product (see Introduction). A similar mechanism could operate with 35

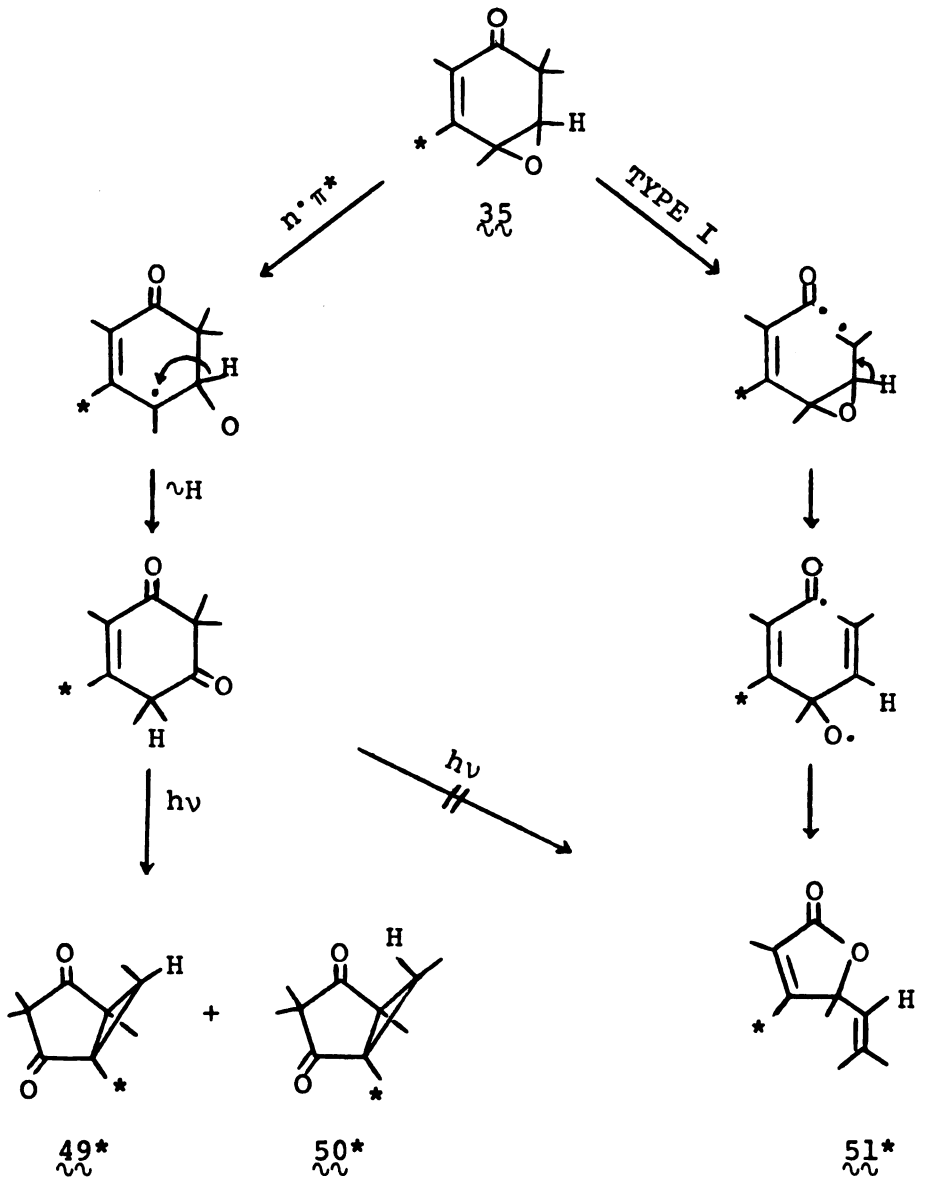


35 51

This suggests that there is a competition between C_γ-O cleavage and Norrish-Type I cleavage in the irradiation of 35.

Labeling experiments were done with trideuterioepoxyketone 35 to test these mechanisms (Scheme 6).

Scheme 6

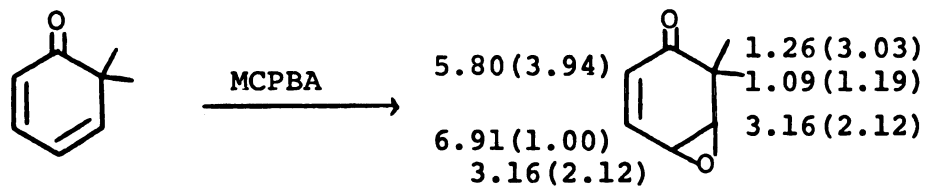


The mechanisms leading from 35* to 49* and 50* are straightforward but the mechanism leading from 35* to 51* is new. The possibility that 54* was an intermediate in the formation of 51* was eliminated by direct irradiation of 54*. Only 49* and 50* were formed in the ratio of 85:15.

The direct formation of 51 from 35 represents a new, previously unobserved mechanism in the photochemistry of α,β-unsaturated γ,δ-epoxy ketones.

3. The Photoisomerization of 4,5-Epoxy-6,6-dimethyl-2-cyclohexenone (36).

The epoxyenone 36 has not been previously described. It was obtained as colorless liquid in high yield from the corresponding dienone 33.[30] The structure of 36 was established by its spectral properties and chemical transformations.

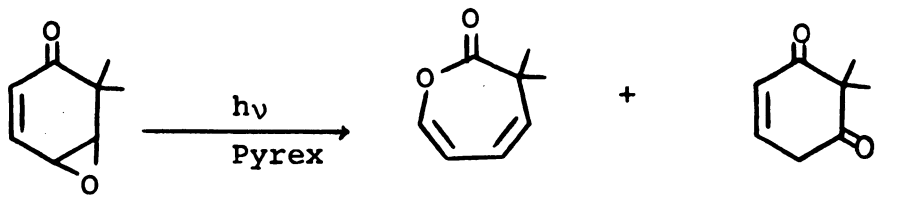


33 36

Its infrared and ultraviolet spectra showed that the carbonyl group was still conjugated with a double bond [$\nu_{C=O}$ 1680 cm^{-1},

λ_{max} (methanol) 235 nm], and the nmr spectrum was also consistent epoxidation having occurred at γ,δ double bond.

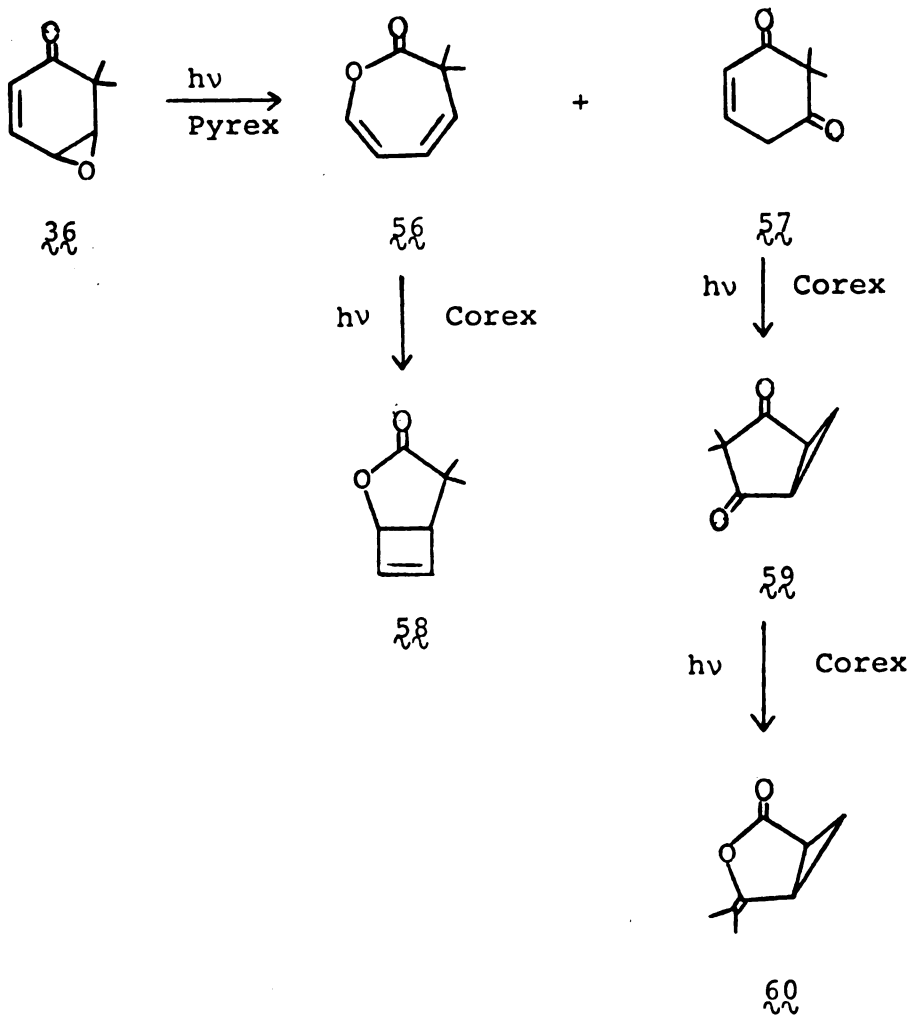
Irradiation of 36 (0.01 M in ether) through pyrex gave two photoproducts to which the structures 56 and 57 were assigned.



36 56 (86%) 57 (14%)

Each of these photoproducts underwent further photoisomerization slowly through pyrex but more rapidly when irradiated through a corex filter. Compound 56 rearranged to 58 and compound 57 rearranged to 59 which was also photolabile and rearranged further to 60 (Scheme 7).

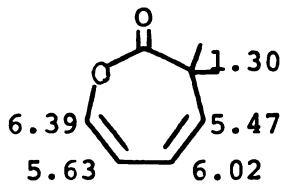
Scheme 7



36 56 57 58 59 60

A. Product Structures

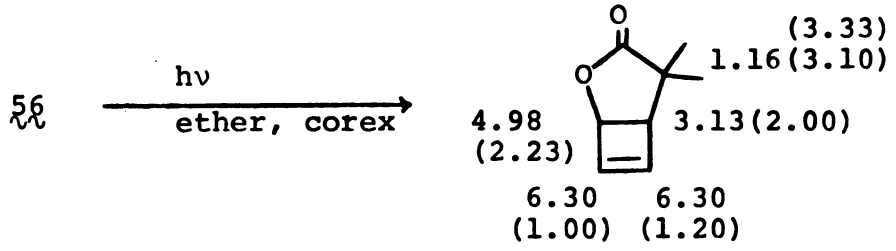
The nmr, ir, uv and mass spectral data of 56 were identical to those reported in the literature.[31-34] In



56

the literature, enol lactone 56 was obtained by both direct and the dye sensitized photooxygenation of 6,6-dimethylfulvene.

The linearly conjugated diene moiety in 56 becomes clear from the product obtained by further irradiation of 56. Irradiation of 56 (0.03 M in ether, corex) gave a single photoisomer to which the structure 58 was assigned.[35]

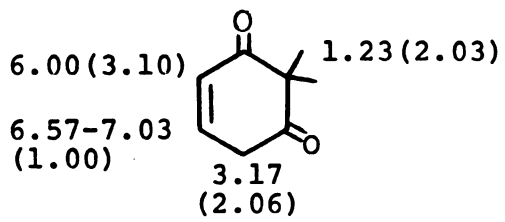


58

The carbonyl band at 1770 cm^{-1} showed that 58 was a γ-lactone. The europium shift data of compound 58 showed that the gem-methyl groups were not identical. The nmr spectrum of 58 showed only two vinyl protons the methine hydrogens are easily identified since the one adjacent to

the oxygen atom is deshielded relative to the other.

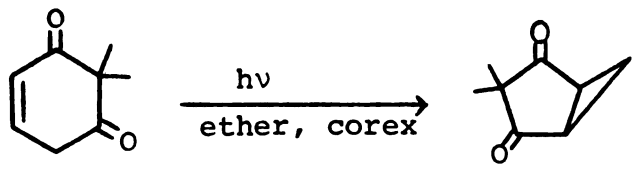
The structure of 57 was assigned on the basis of its spectral data and chemical transformations. The molecular



57

formula $C_8H_{10}O_2$ was confirmed by the mass spectrum (parent peak m/e 138) and elemental analysis. The diketone showed two carbonyl absorptions at 1720 and 1675 cm^{-1}, and a uv maximum absorption (methanol) at 228 nm indicating the presence of one conjugated and one non-conjugated carbonyl group in a six-membered ring. The nmr spectrum of 57 showed a sharp singlet for the gem-methyl groups at δ1.23, which indicated that 57 possessed a plane of symmetry. The nmr spectrum also showed two vinyl protons coupled to one another at C-2 and C-3 and two methylene protons at δ3.17. Europium shift data were consistent with the assigned structure.

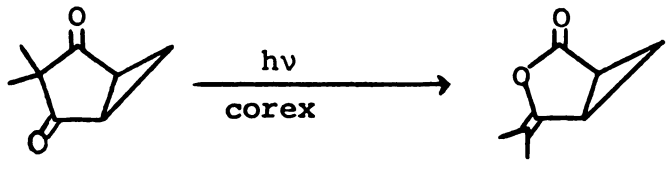
Irradiation of 57 (0.03 M in ether, corex) gave the known photoisomer 59. The compound assigned structure 59 showed two coupled carbonyl bands, at 1750(w) and 1710(s) cm^{-1}. The uv spectrum showed only one absorption.



57 59

The mass spectrum had an M^+ peak at m/e 138. The nmr spectrum was consistent with the literature report.[36]

Irradiation of compound 59 (0.02 M in ether, corex; or in benzene, pyrex) gave the known lactone 60.[36] The ir spectrum of 60 showed a strong carbonyl band at 1795 cm^{-1} which is typical of enol lactone absorption. The uv spectrum showed only end absorption. The nmr spectrum showed two methyl group signals at δ1.70 and 1.74, two methylene protons at δ0.80-1.50 and two methine protons as multiplets at δ2.23 and 2.65.

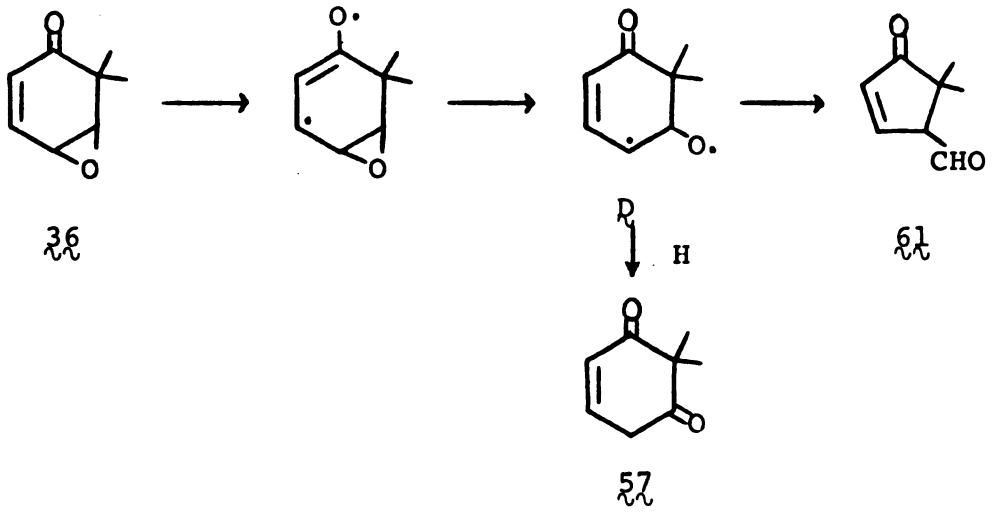


59 60

B. Mechanism

The formation of 57 from 36 undoubtedly occurred by cleavage of the C_γ-O bond to give intermediate D and followed by hydrogen migration from C_δ to C_γ.

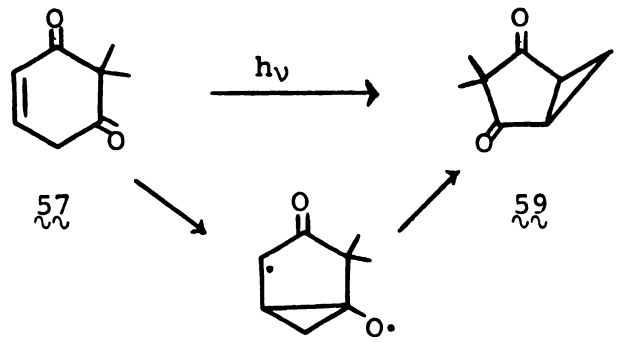
Scheme 8



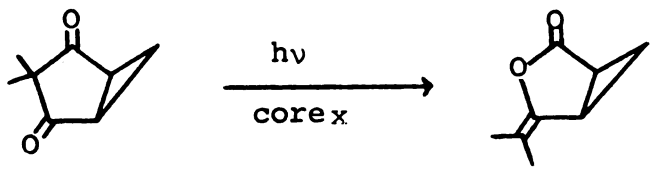
36 61 57

The preferential hydrogen migration to give 57 rather the alkyl group migration to give 61 is consistent with the usual order of migratory aptitude observed for the photochemical rearrangement of α,β-epoxy ketones to β-diketones.[15(a-c),26]

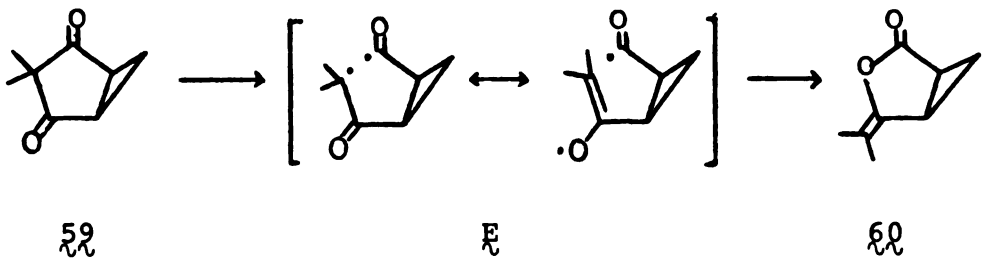
The formation of compound 59 proceeds via an oxa-di-π-methane rearrangement of 57[37].



The photochemical rearrangement of non-enolizable β-diketones is known[36] to give enol lactones with an exocyclic double bond.



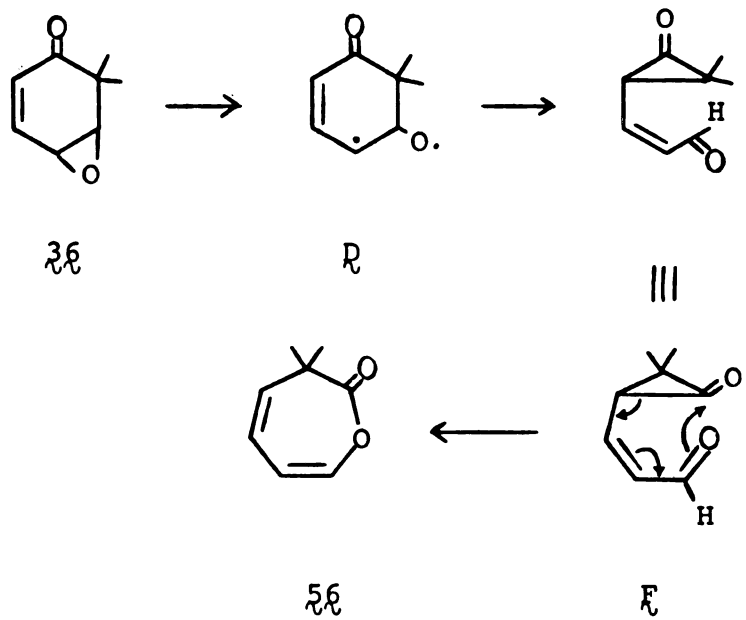
The mechanism for the formation of the enol lactone is as follows:



Photoexcitation of 59 leads to Type I cleavage to give diradical E, which recyclizes to the enol lactone 60.

The mechanism for the formation of compound 56 from 36 is presumed to be the same as that proposed (Scheme 4) for the formation of 39 from 34. It is outlined again in Scheme 9.

Scheme 9



36 D III

56 F

Compound 56 is formed from intermediate D through fragmentation of a C-C bond and the formation of cyclopropanone intermediate F. Subsequent electrocyclic rearrangement of F would lead directly to 56.

Since the yield of 56 from 36 was high, an effort was made to detect the formation of cyclopropanone intermediate F. The low temperature irradiation of 36 was carried out using acetone-d_6 as solvent at -78°, and the reaction was

monitored by nmr. After 4 hr irradiation, besides the strong product peaks [56: δ1.30(s), 5.47-6.39(m); 57: δ1.23(s), 3.17(q), 5.80-7.03(m)], an α,β-unsaturated aldehyde peak corresponding to intermediate F appeared at δ9.7 as multiplet. When the solution was allowed to remain at the same temperature for a longer time, the aldehyde proton signal gradually decreased in intensity. Also, if the solution was warmed up to room temperature, the signal due to the aldehyde proton slowly disappeared.

Low temperature infrared spectroscopy is another useful technique for studying molecules which are unstable at a higher temperature.

Murray[41] used 2-methyltetrahydrofuran as a matrix for the low temperature detection of dimethylketene, and Hart and Love[42] reported the observation of a ketene in a pentane matrix at -196°. Chapman[43] et al. have reported the observation of ketene at low temperatures in an ether-methanol glass and in an EPA (ether-pentane-alcohol) glass.

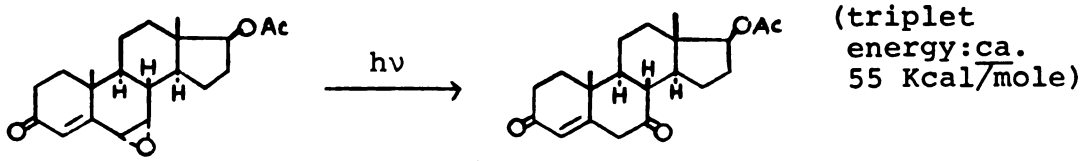
A low temperature study of the photolysis of 70 was carried out in an attempt to observe the intermediate cyclopropanone derivative. A solution of 70 in tetrahydrofuran was irradiated for short intervals at -105°C in a sodium chloride cavity cell. The infrared spectrum showed a carbonyl absorption at 1815 cm^{-1}. The intensity of the carbonyl absorption of 70 decreased after the irradiation was stopped. The absorption at 1815 cm^{-1} is attributed to the formation of cyclopropanone F. Cyclopropanone

itself and its derivatives have now been prepared and show infrared bands in the region 1813-1850 cm^{-1} depending on the substituents on the ring.[38]

The low temperature nmr and ir observations in this study are consistent with the mechanism in which cyclopropanone intermediate F was proposed, during the conversion 36 to 56.

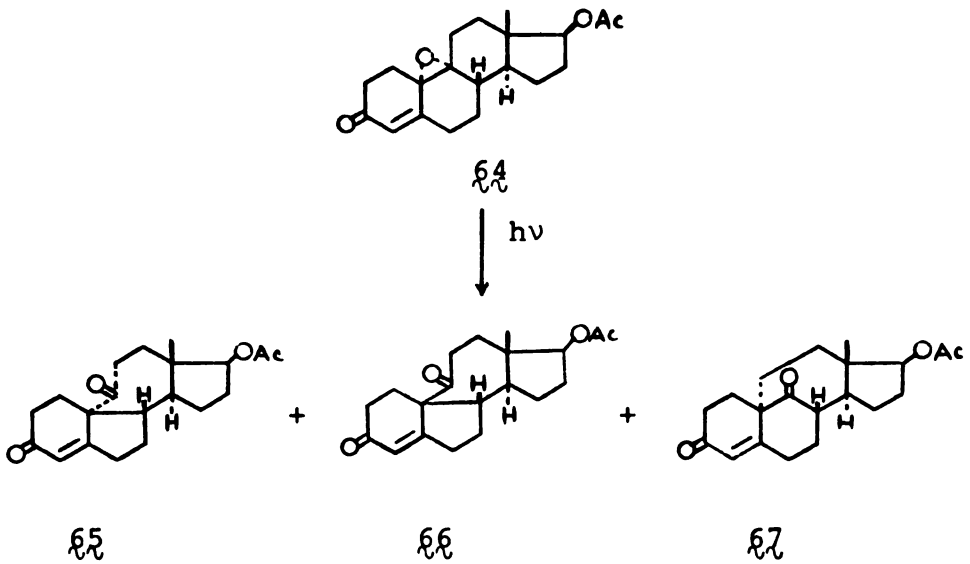
It was reported that cyclopropanones[38-40] can be trapped by reaction with methanol or ethanol to form a hemiketal. However, when the irradiation of compound 36 was carried out using methanol-d_4 as solvent at -78° (the reaction was monitored by nmr and GC) identical results were obtained as in other solvents. The inability to trap the cyclopropanone intermediate F with methanol indicates that the intramolecular rearrangement to 56 must be very fast with respect to the intermolecular addition of methanol.

Some experiments were performed to determine whether the conversion of 36 to 56 and 57 was a singlet or triplet state reaction. Jeger *et al.*[19c] noted in 1968 that α,β-unsaturated-γ,δ-epoxyketone 62 isomerized almost exclusively to the diketone 63 upon triplet sensitization (using acetophenone in benzene).



62 63

Later, Jeger and Schaffner reported[19a] that irradiation of 64 using triplet sensitization gave products 65, 66 and 67.



64

65 66 67

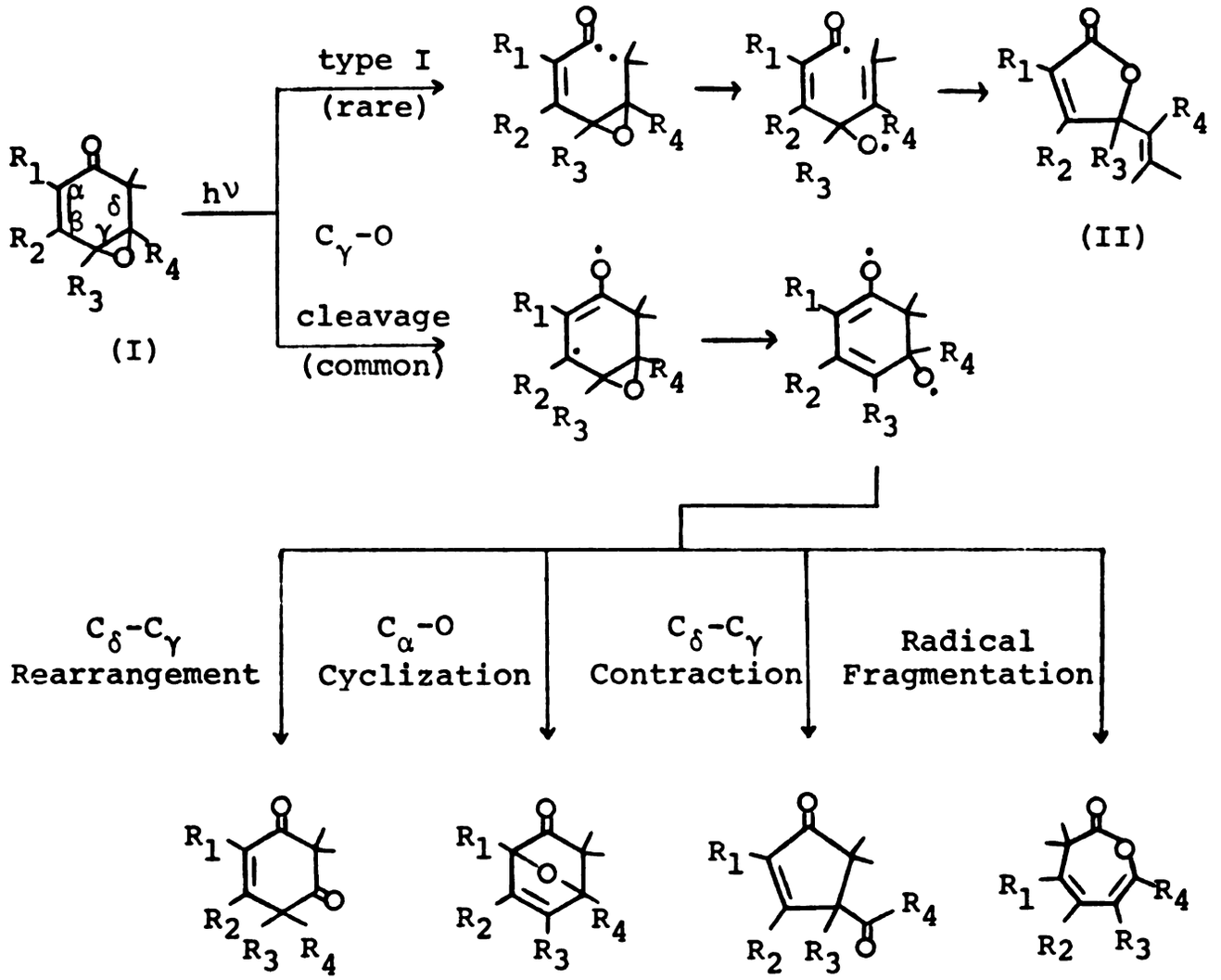
The photoisomerization of 36 can be sensitized by acetophenone and benzophenone and the triplet conversion is not affected by the addition of piperylene (which often acts efficiently as a triplet quencher). But, the reaction could be efficiently quenched by trans-1,3,5-hexatriene

(E_T = 47 Kcal/mole). The results suggest that the photoisomerization of 36 occur <u>via</u> a triplet with a triplet energy of about 50-60 Kcal/mole.

In summary, a mechanistic scheme which rationalizes all previous results on the photochemistry of cyclohexadienone epoxides is proposed. Following initial excitation (Scheme 10), either C_γ-O or α-bond cleavage occurs, the former path being by far the more common. The latter path leads to a diradical which undergoes subsequent epoxide ring opening to give an acyl-alkoxy radical; this then undergoes ring closure to give a lactone. Four different types of subsequent reactions have been observed for the intermediate produced by C_γ-O cleavage. These are migration of a group from C_δ to C_γ, ring contraction, cyclization at C_α, and fragmentation of an R group from C_δ.

It is clear in the comparison of the results from 34 with 24, or 36 with 27, respectively, that the replacement of H for CH_3 in the C-3 or C-2 and C-3 positions of permethylated dienone epoxide 24 has only a modest effect on the photochemical results. From the results on 34, 35, 27 and 36, it is logical to conclude that the replacement of H for CH_3 in the C-2 and C-5 positions, especially in C-5 position, profoundly effects the photochemical results.

Scheme 10



Cpd/yield				
24	----	----	90%	----
34	----	25%	45%	30%
35	73%[a]	----	----	27%[c]
27	78%[b]	----	----	22%
26	14%	----	----	86%

a. Intermediate 54 forms products 49 (62%) and 50 (11%).
b. Intermediate forms products 28 (34%) and 29 (44%)
c. Yield of (II).

EXPERIMENTAL

General Procedures (These apply to all parts of the thesis).

Analytical gas chromatography (vpc) was carried out on a Varian Aerograph Model 1400 (flame ionization detector), and preparative vpc was performed with a Varian Aerograph Auto Model 700 instrument (thermal conductivity detector).

The nmr spectra were obtained on a Varian Associates T-60 spectrometer, usually in CCl_4 using tetramethylsilane (TMS) as an internal standard. Decoupling experiments were done on an HA-100 spectrometer. Carbocation spectra were obtained on an A56-60 spectrometer equipped with a variable temperature probe. The solvent was FSO_3H/SO_2ClF (ca.1:4), sometimes with CD_2Cl_2; either $(CH_3)_4NBF_4$ (δ3.13) or CH_2Cl_2 (δ5.30) was used as an internal standard. The temperature control was calibrated with a methanol standard sample and is accurate to ±0.5°. Low temperature nmr spectra were obtained on an A56-60 spectrometer. The nmr spectra were recorded in units of delta. Numbers placed next to protons in structures in the discussion section refer to chemical shifts of these protons. Numbers in brackets beside chemical shifts in the discussion section are "europium shift numbers" obtained by adding small increments of tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)Eu(III) to the CCl_4 solution being investigated. After each addition the nmr spectrum was scanned

and the new frequency of each absorption was recorded. The shift for each absorption is the difference between the frequency of the shifted absorption and the original one. Shift numbers are the ratios obtained by dividing the shift of each signal in the spectrum by the shift of the least shifted signal.

Infrared spectra were obtained on a Unicam SP-200 spectrometer except for the low temperature study in which a Perkin-Elmer 237 grating spectrophotometer was used.

Ultraviolet-visible spectra were obtained with a Unicam-800 spectrometer. Mass spectra were obtained from a Hitachi-Perkin Elmer RMU-6 operated by Mrs. Lorraine Guile. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan, and by Clark Microanalytical Laboratories, Urbana, Illinois.

General Photolysis Procedures

Solutions of the compounds to be irradiated were placed in septum-capped Pyrex tubes or nmr tubes and purged of oxygen by bubbling dry, oxygen-free nitrogen through them for 30 minutes prior to photolysis. Irradiations were carried out with a 450 watt Hanovia Type L medium pressure mercury vapor lamp with the appropriate filter. The tubes

were fastened to an immersion well apparatus which was immersed in water at ambient temperature. Alternatively, a Rayonet Photochemical Chamber Reactor or Type RS Preparative Photochemical Reactor was used. Photolyses were monitored by withdrawing small (< 1 μl) aliquots and injecting them into a Varian Aerograph Series 1400 analytical gas chromatograph.

1. Synthesis of 4,5-Epoxy-2,4,5,6,6-pentamethyl-2-cyclohexenone (34)

To a solution of 2.10 g (12.8 mmole) of 2,4,5,6,6-pentamethyl-2,4-cyclodienone (31)[16] in 40 ml of methylene chloride was added, at 0°C, a solution of 2.20 g (12.8 mmol) of m-chloroperbenzoic acid in 60 ml of methylene chloride. The mixture was stirred at room temperature for 2 hours (nmr monitoring showed complete reaction). During this time, a white precipitate formed and the precipitate was removed by filtration. The solvent was removed by rotary evaporation, petroleum ether (bp 30-60°C) was added, the filtrate was washed three times with 15% aqueous sodium sulfite, water and saturated sodium chloride solution, dried ($MgSO_4$) and evaporated to give 2.24 g (97.4%) of light yellow oil. The crude product was chromatographed on florisil (mesh 60-200) using ether: hexane (1 : 10) as eluent, to give colorless epoxide 34. Compound 34 was subjected to preparative vpc (10' x 0.25 in column, 20%

SE-30 on chromosorb W, AW-DMCS 80/100 mesh, 180°, 60 ml/min He, retention time 18 min), 60% of compound 34 remained and 40% of 34 was converted to alcohol due to thermal oxirane ring opening. Compound 34 had ir (neat) 3000 (s), 1680 (s), 1550 (w), 1480 (s), 1400 (s), 1380 (m), 1278 (m), 1200 (w), 1130 (m), 1100 (s), 1080 (m), 1060 (m), 1003 (m), 978 (m), 900 (s), 848 (m), 780 (w), 740 (m) cm^{-1}; uv (methanol) λ_{max} 208 nm (ε 3200), 250 (9560) 320 (500); nmr (CCl_4) see structure, δ1.06 (s, 3H), 1.33 (s, 3 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 1.73 (d, 3 H, J = 2 Hz), 6.46 (q, 1 H, J = 2 Hz); mass spectrum (70 eV) m/e (rel intensity) 180 (9), 165 (18), 137 (100), 112 (40), 110 (20), 109 (18), 97 (10), 69 (35), 67 (36).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.33; H, 9.02

2. Synthesis of 5-Trideuteromethyl-4,5-epoxy-2,4,6,6-tetramethyl-2-cyclohexenone (34*)

One gram of 2,4,5,6,6-pentamethylcyclohexa-2,4-dienone (31) was added to a solution of 0.30 g of potassium t-butoxide in dimethyl sulfoxide-d_6.[48] The solution became deep red immediately and remained so. The mixture was stirred at room temperature for 5 hr (nmr monitoring showed complete reaction). The red-brown solution was poured into 300 ml of methylene chloride and washed with ice water (three 50-ml portions). After being dried, the

solution was evaported to an oil, which was purified by distillation, then further purified by vpc (5′ x 0.25 in. column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 148°, 60 ml/min He, retention time 2 min). The nmr spectrum was consistent with the structure of 5-trideuteromethyl-2,4,6,6-tetramethyl-2,4-cyclohexadienone. It consisted of three signals at δ1.12, δ1.81 and δ6.60 with relative areas 6:6:1, assigned respectively to the gem-dimethyls, the allylic methyls at C-2, C-4, and the C-3 vinyl proton.

To a solution containing 120 mg (0.73 mmole) of 2,4,6,6-tetramethyl-5-methyl-d_3-2,4-cyclohexadienone in 2 ml of methylene chloride was added a solution of 148 mg (0.86 mmol) of m-chloroperbenzoic acid in 2 ml of methylene chloride. The mixture was stirred at room temperature for 2 hours, and workup was as described for the preparation of 34. The epoxidation product 34* had an nmr spectrum identical with that of 34 except that the signal at δ1.40 was absent.

3. Irradiation of 4,5-epoxy-2,4,5,6,6-pentamethyl-2-cyclohexenone (34)

A degassed solution of 100 mg (0.55 mmole) of 34 in 50 ml of anhydrous ether was irradiated through pyrex with a 450 W Hanovia lamp. The photolysis was followed by vpc, and was complete in about 1 hr. Analytical vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, AW-DMCS

80/100, 178°C, 30 ml/min N_2) showed three components: 37 (retention time 1 min), 38 (7 min) and 39 (9 min). Preparative vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 120°, 60 ml/min He) gave pure 37 (25%; retention time 8 min), 38 (45%; 25 min), and 39 (30%; 40 min).

For 1,3,3,4,5-pentamethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-one (37): ir (neat) 3000 (s), 1740 (s), 1640 (w), 1470 (m), 1450 (m), 1392 (m), 1300 (w), 1220 (m), 1200 (m), 1180 (m), 1100 (s), 1020 (w), 1000 (s), 900 (w), 860 (w), 810 (s) cm^{-1}; uv (MeOH) λ_{max} 207 nm (ε 950) with a shoulder) 280 (ε 100); nmr (CCl_4) δ1.12 (s, 3 H), 1.14 (s, 3 H), 1.30 (s, 3 H), 1.32 (s, 3 H), 1.72 (d, 3 H, J = 2 Hz), 5.56 (q, 1 H, J = 2 Hz); mass spectrum (70 eV) m/e (rel intensity) 180 (14), 165 (5), 152 (5), 140 (100), 139 (42), 138 (35), 137 (75), 124 (20), 122 (76), 121 (83), 111 (11), 110 (84), 108 (15), 95 (40), 94 (62), 92 (15), 82 (64), 77 (77), 69 (12), 67 (25), 59 (60), 55 (20), 54 (68), 53 (31), 52 (10), 51 (15).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.34; H, 8.96

For 4-acetyl-2,4,5,5-tetramethyl-2-cyclopentenone (38): ir (CCl_4) 3000 (s), 1710 (s), 1660 (w), 1480 (w), 1460 (w), 1400 (w), 1373 (m), 1305 (w), 1300 (w), 1192 (w), 1160 (m), 1050 (m), 990 (m), 890 (m) cm^{-1}; uv (cyclohexane) λ_{max} 265 (ε 7000); nmr (CCl_4), δ0.90 (s, 3 H), 1.03 (s, 3 H), 1.25 (s, 3 H), 1.75 (d, 3 H, J = 1.0 Hz),

1.95 (s, 3 H), 6.92 (q, 1 H, J = 1 Hz); mass spectrum (70 eV) m/e (rel intensity) 180 (6), 162 (5), 144 (5), 139 (26, 138 (100, 137 (35), 123 (62), 109 (43), 93 (7), 91 (7), 81 (8), 71 (10), 77 (9), 69 (8), 67 (60), 55 (15).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.14; H, 8.91

For 3,3,4,6,7-pentamethyl-2(3H)-oxepinone (39): ir (neat) 3000 (s), 1750 (s), 1660 (m), 1460 (m), 1400 (m), 1340 (w), 1280 (w), 1260 (w), 1200 (m), 1150 (m), 1120 (w), 1100 (w), 1040 (w), 950 (w), 880 (w) cm^{-1}; uv (MeOH) λ_{max} 212 nm (ε 2700), 250 (10,570); nmr (100 MHz) (CCl_4) δ1.23 (s, 6 H), 1.67 (broad singlet, 3 H), 1.83 (doublet, 3 H, J = 2 Hz), 1.89 (broad singlet, 3 H), 5.60 (m, 1 H), decoupling at δ5.60 caused the doublet at δ1.83 to become a singlet; mass spectrum (70 eV) m/e (rel intensity) 180 (61), 165 (7), 138 (30), 137 (98), 109 (100), 108 (71), 93 (75), 91 (32, 97 (34), 67 (50), 65 (20), 55 (15), 53 (20).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.21; H, 9.09

4. Irradiation of 34*

The conditions and workup procedure were as for the unlabeled material. From 34* the resulting 37* had an nmr spectrum identical with that of 37 except the signal at δ1.30 was absent. The spectrum of the resulting 38* was

identical with that of 38 except that the singlet at δ1.95 was absent. The resulting 39* was identical with that of 39 except that the signal at δ1.89 was absent and the peak at δ1.67 sharpened to a singlet.

5. Irradiation of 4-Acetyl-2,4,5,5-tetramethyl-2-cyclopentenone (38)

A degassed solution of 50 mg (0.28 mmole) of 38 in 25 ml of anhydrous ether was irradiated through pyrex with a 450 W Hanovia lamp at room temperature. The photolysis was followed by vpc, and was complete in about 40 minutes. Analytical vpc (5' x 0.125 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 150°C, 30 ml/min N_2) showed two components with retention times of 3.5 and 19 min respectively, in a ratio of 1:6. Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 120°, 60 ml/min He) allowed collection of the major product 40 with a retention time of 52.5 min. For 40: ir (neat) 3000 (m), 1760 (s), 1662 (m), 1460 (m), 1396 (m), 1360 (w), 1330 (m), 1200 (w), 1120 (m), 1080 (m), 1040 (w), 940 (w) cm^{-1}; uv (MeOH) λ_{max} 222 (ε 7640), 263 (6250); nmr (CCl_4) δ1.35 (d, 3 H, J = 6 Hz), 1.66 (s, 3 H), 1.68 (s, 3 H), 1.86 (homoallylic coupling, 6 H), 4.85 (q, 1 H, J = 6 Hz); mass spectrum (70 eV) m/e (rel intensity) 180 (60), 165 (4), 137 (100), 138 (30), 123 (10), 110 (17), 109 (85), 108 (50), 93 (50), 91 (20), 77 (20), 67 (40)

55 (10), 53 (14).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95

Found: C, 73.33; H, 8.86

6. Irradiation of 1,3,3,4,5-Pentamethyl-7-oxabicyclo-[2.2.1]hept-5-en-2-one (37)

A degassed solution of 37 (25 mg, 0.14 mmole) in 10 ml of anhydrous ether was irradiated through pyrex with a 450 W Hanovia Type L lamp the reaction was followed by nmr. After 1 hour, the nmr spectrum showed no change and compound 37 was recovered.

7. Synthesis of 4,5-Epoxy-2,3,4,6,6-pentamethyl-2-cyclohexenone (35)

To a solution of 1.20 g (7.32 mmole) of 2,3,4,6,6-pentamethyl-2,4-cyclohexadienone 32^{16} in 20 ml of methylene chloride was added, at 0°C, a solution of 1.42 g (8.61 mmole) of m-chloroperbenzoic acid in 20 ml of methylene chloride. The mixture was stirred at room temperature for 3 hours (nmr monitoring showed complete reaction at this time). m-Chlorobenzoic acid was removed by filtration, and the solvent was removed by rotary evaporation. Petroleum ether (bp 30-60°C) was added, the filtrate was washed with aqueous sodium bicarbonate and saturated sodium chloride solution, dried ($MgSO_4$) and evaporated to give 1.20 g (91%) of 35 as a light oil. The crude product

was chromatographed on florisil (mesh 60-200) using ether:hexane (1:5) as eluent, to give pure epoxide 35. Ir (neat) 3000 (s), 1674 (s), 1616 (m), 1480 (m), 1390 (m), 1320 (m), 1260 (m), 1090 (m), 1050 (m), 918 (m); uv (MeOH) λ_{max} 210 nm (ϵ 2970), 255 (8460), 325 (270); nmr (CCl_4) see structure, the peaks at δ1.66 and 1.95 were broadened, but all other methyl groups were sharp singlets at δ1.00, 1.22 and 1.42; one proton appeared as singlet at δ2.86; mass spectrum (70 eV) m/e (rel intensity) 180 (50), 165 (35), 164 (15), 151 (26), 137 (100), 135 (52), 123 (34), 121 (31), 119 (25), 112 (35), 110 (55), 95 (20), 91 (20), 83 (15), 81 (30), 69 (24), 67 (50), 55 (26), 53 (30).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.24; H, 8.92

8. Synthesis of 3-Trideuteromethyl-4,5-epoxy-2,4,6,6-tetramethyl-2-cyclohexenone (35*)

To a solution containing 500 mg (2.77 mmole) of 35 in 10 ml of dimethyl sulfoxide-d_6 was added with stirring and under N_2, 310 mg (2.77 mmole) of potassium t-butoxide.[23] The mixture was stirred at room temperature for 1 hour, then quenched with ice-water and extracted with ether. Organic layers were dried ($MgSO_4$) and the solution was evaporated to give a nearly quantitative yield of 35*. The nmr spectrum was identical to that of the starting

material, except that the signal at δ1.95 had disappeared.

9. Irradiation of 4,5-Epoxy-2,3,4,6,6-pentamethyl-2-cyclohexenone (35)

A degassed solution of 100 mg (0.55 mmole) of 35 in 30 ml of anhydrous ether was irradiated through pyrex with a 450 W Hanovia lamp at room temperature for 2 hours. The photolysis was followed by vpc. Analytical vpc (5' x 0.125 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 160°C, 30 ml/min N_2) showed three components: 49 (62% retention time 2.5 min), 50 (11%, 5 min) and 51 (27%, 25 min). Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 140°, 60 ml/min He) gave pure 49 (retention time 18 min), 50 (31 min) and 51 (over 1 hr). Further purification of 51 with vpc (5' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 180°, 60 ml/min He) gave pure 51 (retention time 12 min).

For 49 (anti-1,3,3,5,6-pentamethylbicyclo[3.1.0]hexan-2,4-dione): ir (KBr) 3000 (m), 1700 (s), 1462 (m), 1380 (m), 1360 (w), 1300 (m), 1205 (m), 1110 (w), 1090 (w), 1040 (m), 845 (m) cm^{-1}; uv (MeOH) λ_{max} 215 nm (ε 2610); nmr (CCl_4) δ0.97 (s, 3 H), 1.03 (s, 3 H), 1.04 (d, 3 H, J = 5 Hz), 1.21 (q, 1 H, J = 5 Hz), 1.32 (s, 6 H); decoupling at δ1.06-1.27 caused the doublet at δ1.04 to sharpen to a singlet; mass spectrum (70 eV) m/e (rel intensity) 180 (42), 165 (20), 163 (10), 137 (60), 120 (11), 110 (100), 109 (22),

105 (15), 95 (25), 82 (22), 79 (13), 67 (80).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.29; H, 8.97

For 50 (syn-1,3,3,5,6-pentamethylbicyclo[3.1.0]hexan-2,4-dione): ir (neat) 3000 (m), 1742 (w), 1701 (s), 1470 (m), 1398 (m), 1295 (m), 1101 (w), 1080 (m), 1040 (w), 845 (w) cm^{-1}; uv (MeOH) λ_{max} 215 nm (ϵ 1870); nmr (CCl_4) δ0.95 (s, 3 H), 1.05 (s, 3 H), 1.13 (d, 3 H, J = 5 Hz), 1.20 (s, 6 H), 1.46 (q, 1 H, J = 5 Hz); decoupling at δ1.46 caused the methyl signal at δ1.13 to sharpen to a singlet; mass spectrum (70 eV) m/e (rel intensity) 180 (53), 165 (20), 162 (9), 138 (20), 137 (60), 121 (13), 120 (25), 110 (100), 109 (27), 105 (10), 95 (25), 82 (25), 81 (15), 67 (88), 55 (7), 54 (7).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.11; H, 8.98

For 51: ir (neat) 2985 (m), 1741 (s), 1680 (m), 1448 (m), 1382 (m), 1325 (m), 1281 (m), 1180 (w), 1140 (w), 1100 (m), 1005 (m), 760 (m) cm^{-1}; uv (MeOH) λ_{max} 225 nm (ϵ 7150); nmr ($CDCl_3$) δ1.23 (s, 3 H), 1.74 (broad s, 3 H), 1.76 (s, 3 H), 1.79 (s, 3 H), 1.80 (s, 3 H), 5.40 (m, 1 H), decoupling at δ1.74-1.80 caused the vinyl proton at δ5.40 to sharpen to a singlet; mass spectrum (70 eV) m/e (rel intensity) 180 (60), 165 (92), 137 (30), 135 (80), 125 (20), 119 (25), 112 (21), 110 (35), 105 (20), 97 (100), 91 (19),

69 (65), 68 (25), 55 (40), 54 (40), 53 (30).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.11; H, 9.02

10. Irradiation of 3-Trideuteromethyl-4,5-epoxy-2,4,6,6-tetramethyl-2-cyclohexenone (35*)

The conditions and workup procedure were as described for the unlabeled material. From 35* the resulting 49* had an nmr spectrum identical with that of 49 except that the signal at δ1.32 (s, 6 H) was reduced to half its area (s, 3 H). The spectrum of the resulting 50* was identical with that of 50 except that the signal at δ1.20 (s, 6 H) was reduced to half its area (s, 3 H). The spectrum of the resulting 51* was identical with that of 51 except that signal at δ1.79 was absent.

11. Irradiation of 2,3,4,6,6-Pentamethyl-2-cyclohexen-1,5-dione (54)

A degassed solution of 54 (50 mg, 0.27 mmole) in 25 ml of anhydrous ether was irradiated through pyrex with a 450 W Hanovia lamp. The photolysis, followed by vpc and nmr was complete in about 1 hour. Analytical vpc (5' x 0.125 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 160°, 30 ml/min N_2) showed two components: 49 (85%, retention time 2.5 min) and 50 (15%, 5 min). Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS

80/100, 140° 60 ml/min He) gave pure 49 and 50 in the same ratio.

12. Irradiation of 54*

The conditions and workup procedure were as described for the unlabeled material. From 54* (labeled with CD_3 at C-3) the resulting 49* and 50* were identical with the products obtained from the irradiation of labeled 35*. The product ratio was nearly the same.

13. Synthesis of 4,5-Epoxy-6,6-dimethyl-2-cyclohexenone (36)

To a solution of 2.5 g (0.02 mole) of 6,6-dimethyl-2,4-cyclohexadienone[30] (33) in 20 ml of methylene chloride was added, at 0°C, a solution of 3.54 g (0.02 mole) of m-chloroperbenzoic acid in 20 ml of methylene chloride. The mixture was stirred at room temperature for 8 hr, precipitated m-chlorobenzoic acid was removed by filtration, and the solvent was removed by rotary evaporation. Petroleum ether (bp 30-60°) was added, the filtrate was washed with aqueous sodium bicarbonate and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 2.37 g of a light yellow oil (86%). The crude product was chromatographed on florisil (mesh 60-200) using ether:hexane (1:10) as eluent, to give 36. Analytical vpc (5' x 0.125 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100,

130°, 30 ml/min N_2) showed retention time 3 min; preparative vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80-100, 100°, 60 ml/min He, retention time 22 min) gave 4,5-epoxy-6,6-dimethyl-2-cyclohexenone 36: ir (neat) 3000 (s), 1680 (s), 1480 (m), 1385 (m), 1380 (w), 1295 (m), 1250 (m), 1225 (w), 1180 (m), 1118 (s), 1065 (m), 940 (m), 860 (m), 830 (s) cm^{-1}; uv (MeOH) λ_{max} 235 nm (ε 35,370) 280 (4080); nmr (CCl_4) δ1.09 (s, 3 H), 1.26 (s, 3 H), 3.20-3.39 (m, 2 H), 5.66-5.92 (d, 1 H), 6.75-7.06 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 138 (7), 123 (10), 122 (29), 109 (45), 95 (44), 82 (100), 79 (60), 77 (30), 70 (20), 67 (20), 55 (40), 54 (25).

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30.
Found: C, 69.54; H, 7.26.

14. Irradiation of 4,5-Epoxy-6,6-dimethyl-2-cyclohexenone (36)

Typical procedure: A degassed solution of vpc collected compound 36 (100 mg, 0.73 mmole) in 50 ml of anhydrous ether was irradiated through pyrex with a 450 W Hanovia lamp at room temperature. The photolysis, followed by vpc and nmr, was complete in 7 hr. Analytical vpc (5' x 0.125 in column, 10% Carbowax on chromosorb W, AW-DMCS 80/100, 109° 30 ml/min N_2) showed two components 56 (85%, retention time 17 min) and 57 (14%, 24 min). Preparative vpc (6' x 0.25 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 105°, 60 ml/min He) gave the pure compounds

56 and 57.

Compound 56 (3,3-dimethyl-2(3H)-oxepinone): ir (neat) 1740 cm^{-1} ($\nu_{C=O}$), 1640 and 1603 cm^{-1} ($\nu_{C=C}$); uv (ethanol) λ_{max} 243 nm (ε 6460); nmr (CCl_4) (60 MHz) δ1.30 (s, 6 H) and multiplets between δ5.47 and 6.39. The nmr spectrum (in CCl_4) (100 MHz) showed four sets of vinyl protons at δ5.47, 5.63, 6.02 and 6.39 ($J_{1,2}$ = 6.7 Hz, $J_{2,3}$ = 6.2 Hz, $J_{3,4}$ = 10.2 Hz, respectively). The mass spectrum (70 eV) m/e (rel intensity) 138 (12) 109 (1.5), 95 (100), 81 (5.2), 79 (6), 77 (4.2), 68 (1.9), 67 (19), 66 (1.4), 65 (4.5), 55 (3), 52 (1.4), 50 (2), 43 (1.5), 42 (1.6), 40 (45), 39 (30), 38 (2.5). All spectral data were identical to the literature report.[31-35]

Compound 57 (6,6-dimethyl-2-cyclohexen-1,5-dione): ir (neat) 2990 (m), 1720 (s), 1675 (s), 1640 (w), 1530 (m), 1385 (m), 1340 (w), 1300 (m), 1170 (w), 830 (m) cm^{-1}; uv (MeOH) λ_{max} 228 nm (ε 7,000); nmr (CCl_4) δ1.23 (s, 6 H), 3.17 (br, 2 H), 5.80-6.20 (m, 1 H) and 6.57-7.03 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 138 (42), 123 (1), 110 (12), 95 (22), 77 (4), 70 (100), 68 (55).

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30
Found: C, 69.60; H, 7.39

Identical results were obtained as when carbon tetrachloride, benzene, methanol, t-butyl alcohol or acetone were used as the solvent for irradiation of compound 36 through a pyrex filter.

Irradiation of compound 36 using a uranyl glass filter gave an almost quantitative yield of 56; no 57 was isolated.

15. Irradiation of compound 36 using a corex filter or 254 nm light (Rayonet Merry-go-round Model MGR-100, 115 volt, 50/60 Hz AC 5 RPM)

The irradiation of an 0.01 M solution of 36 in ether under these conditions, monitored by vpc, gave compounds 56 and 57 in a ratio of 7:1 after 2 hr of irradiation. Further irradiation for 7 hr, followed by vpc (5' x 0.125 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 125°, 30 ml/min N_2) gave four products (% retention time): 56 (38, 6 min), 58 (46, 9.5 min), 59 (12, 17 min), and 60 (4, 30 min).

For known compound 58 (2,2-dimethyl-4-oxa-bicyclo [3.2.0]-hept-6-en-3-one)[35]: ir (neat) 2980 (m), 2940 (w), 1770 (s), 1540 (m), 1390 (w), 1360 (m), 1350 (w), 1300 (w), 1270 (m), 1170 (m), 1140 (s), 1095 (s), 1015 (s), 970 (m), 930 (w), 910 (w), 860 (m), 800 (s) cm^{-1}; uv (MeOH) λ_{max} 220 nm (ε 235); nmr (CCl_4) δ1.16 (s, 6 H, europium shift showed that the two methyl groups are not identical), 3.13 (m, 1 H), 4.98 (m, 1 H), 6.30 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 138 (1.5), 123 (2), 110 (15), 109 (36), 95 (100), 93 (10), 91 (11), 83 (12), 81 (33), 79 (66), 77 (35), 67 (28), 53 (22), 51 (11).

For known compound 59 (3,3-dimethyl-bicyclo[3.1.0]-hexane-2,4-dione): ir (neat) 3001 (w), 1750 (w), 1710 (s), 1480 (m), 1400 (w), 1307 (w), 1290 (m), 1241 (w), 1190 (m), 1160 (w), 1010 (m), 900 (m) cm^{-1}; uv (ethanol) λ_{max} 215 nm (ε 550), 280 (190); nmr (CCl_4) δ1.04 (s, 6 H), 1.07 (m, 1 H), 1.55 (m, 1 H), 2.50 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 138 (47), 123 (9), 110 (21), 109 (16), 97 (17), 95 (70), 93 (6), 91 (7), 83 (6), 82 (10), 81 (15), 79 (24), 77 (8), 70 (100), 69 (19), 68 (69), 67 (55). All spectral data were identical to the literature report.[36]

For known compound 60 (2-cis-(1'-hydroxy-2'-methyl-1'-propenyl)-cyclopropanecarboxylic acid-γ-lactone): ir (neat) 3100 (m), 1795 (s), 1720 (s), 1680 (w), 1480 (w), 1380 (w), 1238 (w), 1210 (m), 1150 (m), 1050 (m), 1100 (m) cm^{-1}; uv (methanol) showed end absorption; nmr (CCl_4) δ0.85-1.50 (m, 2 H), 1.70 (s, 3 H), 1.74 (s, 3 H), 2.23 (m, 1 H), 2.65 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 138 (50), 123 (18), 110 (15), 109 (20), 96 (18), 95 (80), 79 (35), 77 (25), 70 (100), 68 (80), 67 (62). All spectral data were identical to the literature report.[36]

16. Irradiation of 36 at low temperature

A. A degassed solution of compound 36 (25 mg) in 0.5 ml of acetone-d_6 was irradiated through pyrex with a 450

W Hanovia lamp at -78°. The photolysis was followed by nmr (Varian associate A56-60) at that temperature and by vpc. After 4 hr irradiation, besides the strong product signals of 56 and 57 [56: δ1.30 (s), 5.47-6.39 (m) and 57: δ1.23 (s), 3.17 (q), 6.0-7.03 (m)], an aldehyde proton peak at δ9.7 was observed. When the solution stood at the same temperature for 3 hr, the intensity of the aldehyde proton signal gradually decreased. Following a similar separate irradiation, the solution was warmed slowly (8 hr) to room temperature, and the signal due to the aldehyde proton disappeared. Replacement of the acetone by methanol-d_4 gave identical results.

B. The Technology of Low Temperature Infrared Spectroscopy

The apparatus consisted of a lead block (designed to hold liquid nitrogen) into which a sodium chloride cavity cell (0.2 mm path length) could be set via a hole suitably drilled in the block. The metal block was insulated by a close fitting styrofoam box. When the reservoir was filled with liquid nitrogen, the cell was cooled to an equilibrium temperature of -100°±10°C. Icing of the cavity cell windows was minimized by passing a vigorous stream of very dry nitrogen over the cell windows throughout the experiment.

A solution of 20 mg of 36 in 0.1 ml of tetrahydrofuran

was sealed in the cavity inside the styrofoam block and cooled to -105° with liquid nitrogen. A parallel beam of radiation from a 1000-watt Hanovia mercury lamp was filtered through pyrex and diverted into the cavity cell. Examination of the ir spectrum after irradiation for 10 min indicated a decrease in the intensity of the carbonyl absorption at 1680 cm^{-1} due to 36 and the appearance of a sharp intense absorption at 1740 and 1720 cm^{-1}, which were attributed to the formation of photoproducts. Most important, a weak peak appeared at 1815 cm^{-1} which was attributed to a cyclopropanone. When the solution was warmed to room temperature, the band at 1815 cm^{-1} gradually disappeared.

17. Irradiation of 3,3-Dimethyl-2(3H)-oxepinone (56)[35]

A degassed solution containing 60 mg of 56 in 15 ml of anhydrous ether was irradiated through Corex with a 450 W Hanovia lamp. The photolysis was followed by analytical vpc (5' x 0.125 in column, 10% Carbowax on chromosorb W, AW-DMCS 80/100, 100° 30 ml/min N_2). As the reaction proceeded, the peak with a retention time 12 min (corresponding to 56) decreased in intensity; and the peak (ret. time 15 min) due to 58 appeared. After 20 hr irradiation, preparative vpc (6' x 0.25 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 105°, 60 ml/min He) allowed collection of the single photoproduct

58. The nmr (CCl_4) of 58 showed δ1.16 (s), 3.13 (m), 4.98 (m), 6.30 (m).

18. Irradiation of 6,6-Dimethyl-2-cyclohexen-1,5-dione (57)

A degassed solution containing 40 mg of compound 57 in 10 ml of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp, the photolysis was followed by analytical vpc (5' x 0.125 in column, 10% Carbowax on chromosorb W, AM-DMCS 80/100, 100°, 30 ml/min N_2). As the reaction proceeded, the peak with a retention time of 29 min (corresponding to 57) decreased in intensity and the peak due to the product 59 appeared at 39 min. After the complete reaction (2 hr), preparative vpc (5' x 0.25 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 125°, 60 ml/min He) allowed collection of the single photoproduct 59 in 95%. The nmr spectrum of 59 showed δ1.04 (s, 6 H), 1.07 (m, 1 H), 1.55 (s, 1 H), 2.50 (m, 2 H) and the ir spectrum showed a strong carbonyl absorption at 1710 cm^{-1}.

19. Irradiation of 3,3-Dimethyl-bicyclo[3.1.0]-hexane-2,4-dione (59)

A degassed solution containing 35 mg of compound 59 in 10 ml of anhydrous ether was irradiated through Corex or 30 mg of compound 59 in 10 ml benzene was irradiated through pyrex with a 450-W Hanovia lamp. The photolysis

was followed by nmr (benzene-d_6) and analytical vpc (5' x 0.125 in column, 10% carbowax on chromosorb W, AW-DMCS 80/100, 153°, 30 ml/min N_2). The reaction was complete within 2 hr with the pyrex filter. As the reaction proceeded, the peak with a retention time 18 min (corresponding to 59) decreased in intensity and the product peak 60 with a retention time 23 min appeared. The preparative vpc (6' x 0.25 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 105°, 60 ml/min He) allowed collection of the single photoproduct in 90%. The ir spectrum of 60 showed enol lactone absorption at 1720 and 1795 cm^{-1} and the nmr (CCl_4) showed δ0.85-1.50 (m, 2 H), 1.70 (s, 3 H), 1.74 (s, 3 H), 2.23 (m, 1 H), 2.65 (m, 1 H).

20. Sensitization and Quenching Studies

A. Solvent Purification

a. Benzene: Analytical grade benzene was purified by stirring it over concentrated sulfuric acid several times for several days until the acid no longer turned yellow. It was then washed with 10% sodium hydroxide solution, water, and sodium chloride solution, respectively, and dried over anhydrous calcium hydride, after drying, the benzene was distilled from potassium, and the middle fraction was retained.

b. Methanol. Reagent grade methanol was distilled from magnesium turnings and only the middle fraction was

retained.

c. Acetophenone (ACP). Acetophenone was distilled under reduced pressure and vpc analysis showed no appreciable impurities.

d. Benzophenone. Reagent grade benzophenone was recrystallized twice from ethanol.

e. Trans-1.3.5-hexatriene. Aldrich Chemical Company trans-1,3,5-hexatriene was used as purchased.

f. Piperylene. Aldrich Chemical Company piperylene was used as purchased.

h. Hexamethylbenzene (HMB) was purified by recrystallization from ethanol.

B. Photolysis

The following solutions were prepared:

Run 1: 0.02 M solution of epoxyenone 36 was prepared by adding 110 mg of epoxyenone 36 and 64 mg of hexamethylbenzene (HMB) in 40 ml of benzene.

1. Sensitization solution (3 M): 3.6 g of acetophenone was dissolved in 10 ml of 0.02 M epoxyenone (36) solution.

2. Quenching solution (2.6 M): 1 g of trans-1,3,5-hexatriene was dissolved in 5 ml of 0.02 M epoxyenone (36) solution.

3. Blank solution: 0.02 M of epoxyenone (36) solution.

Run 2: 0.02 M solution of epoxyenone 36 was prepared by adding 110 mg of 36 and 64 mg of HMB in 40 ml of methanol.

1. Sensitization solution (2 M): 3.5 g of benzophenone

was dissolved in 10 ml of 0.02 M of epoxyenone (36) solution.

2. Quenching solution (5 M): 3.4 g of piperylene was dissolved in 10 ml of 0.02 M of epoxyenone (36) solution.

3. Blank solution: 0.02 M of epoxyenone (36) solution.

Aliquots (2.8 ml) of each above solution were placed in 13 x 100 mm pyrex tubes using a 5 ml syringe with a six inch needle. The tubes had previously been constricted about 2 cm from the top, so that they could be easily sealed after being degassed by five freeze-thaw cycles ($p<0.005$ torr), by using liquid nitrogen. The samples were irradiated in parallel using a water bath immersed merry-go-round apparatus to insure that all the samples received the same amount of incident light and that the temperature remained constant. A 450 W Hanovia lamp was used as light source, and Pyrex was used as filter.

After 7 hr irradiation, the products were identified by careful comparison of the vpc retention time with those of authentic samples in each case. For Run 1: In acetophenone solution, the analytical vpc (5' x 0.125 in column, 10% carbowax on chromosorb W, AW-DMCS 80/100, 155°, 30 ml/min N_2) showed a peak with a retention time 8 min (corresponding to 56). In trans-1,3,5-hexatriene solution, the analytical vpc (5' x 0.125 in column, 10% carbowax on chromosorb, AM-DMCS 80/100, 150°, 30 ml/min N_2) showed two peaks with retention time of 8.5 min (corresponding to 56,

10%) and 10.5 min (corresponding to 36, in 90%). In blank solution, the analytical vpc in the same condition as described above except the column temperature at 156° showed a peak with a retention time of 8.5 min (corresponding to the compound 56). For Run 2: Analytical vpc (5' x 0.125 in column, 5% SE-30 on chromosorb W, AW-DMCS 80/100, 131°, 30 ml/min N_2) showed a retention time 2 min (corresponding to the product 56) in sensitization, quenching and blank solutions.

PART II

ACID-CATALYZED REARRANGEMENTS OF CYCLOHEXADIENONE EPOXIDES

(1) 4,5-EPOXY-2,4,5,6,6-PENTAMETHYL-2-CYCLOHEXENONE

(2) 4,5-EPOXY-2,3,4,6,6-PENTAMETHYL-2-CYCLOHEXENONE

(3) 4,5-EPOXY-6,6-DIMETHYL-2-CYCLOHEXENONE

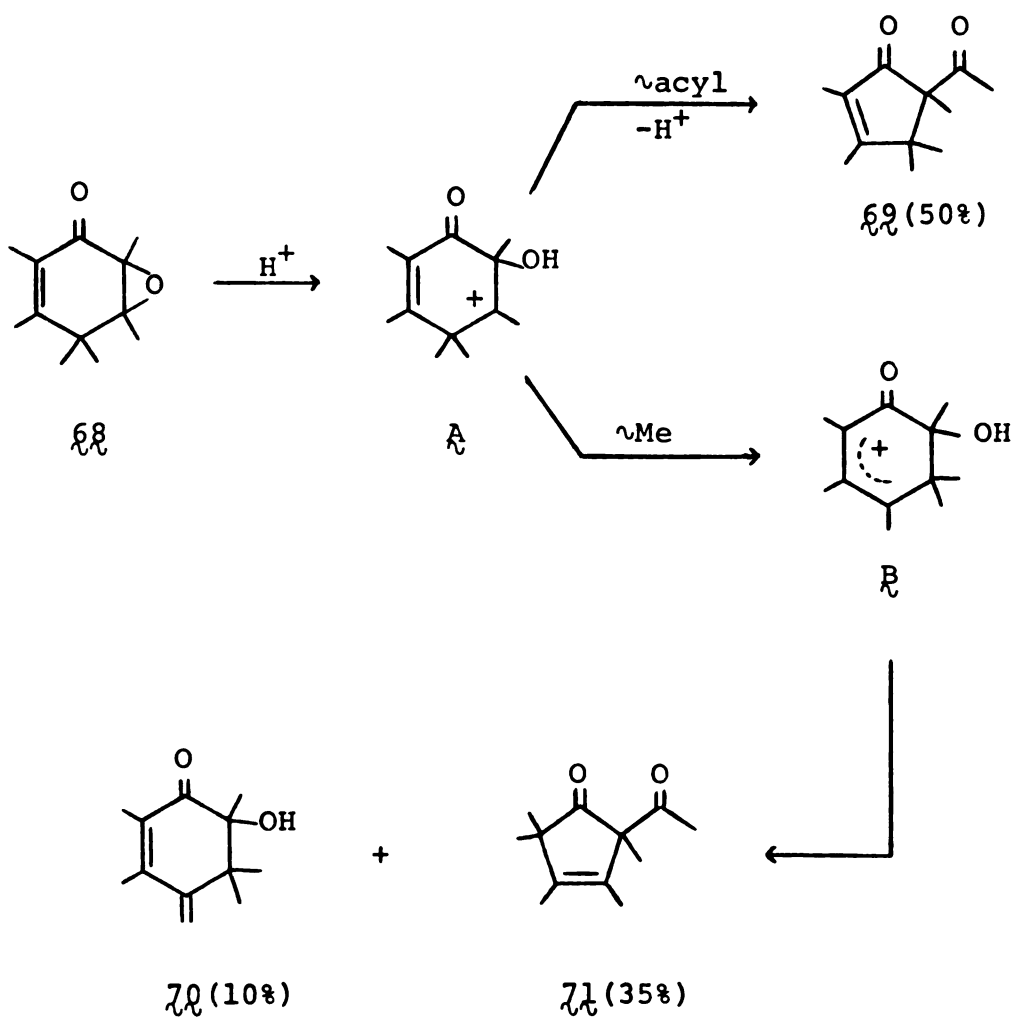
INTRODUCTION

The acid-catalyzed rearrangements of epoxides are of special interest since they provide a simple means of converting olefins to carbonyl compounds.[6e,44] The major product formed from the rearrangement of an epoxide is governed by two main factors. These are the direction of ring opening and the relative migratory aptitude of different substituents.

The direction of ring opening in acid-catalyzed rearrangement is governed by the stability of the carbocation which would be formed. The expected sequence is aryl, allyl > tertiary > secondary > primary. Thus in the presence of aluminum trichloride, trimethylethylene oxide rearranges to methyl isopropyl ketone, isobutylene oxide gives mainly isobutyraldehyde,[45] and indene oxide gives 2-indanone.[46]

Once the ring opens, the structure of the product depends on which group migrates. The relative migratory aptitude of different substituents is, in general, vinyl > acyl > H > ethyl > methyl.[5,44] In a recent study[5] it was shown that acyl and methyl migration may compete on an approximately equal basis. Thus on treatment with trifluoroacetic acid (TFA), 68 rearranged (Scheme 11) to nearly equal amounts of 69 and (70 + 71). Following protonation, ring opening of 68 occurs in such a manner as to place the positive charge remote from the carbonyl group, giving

Scheme 11



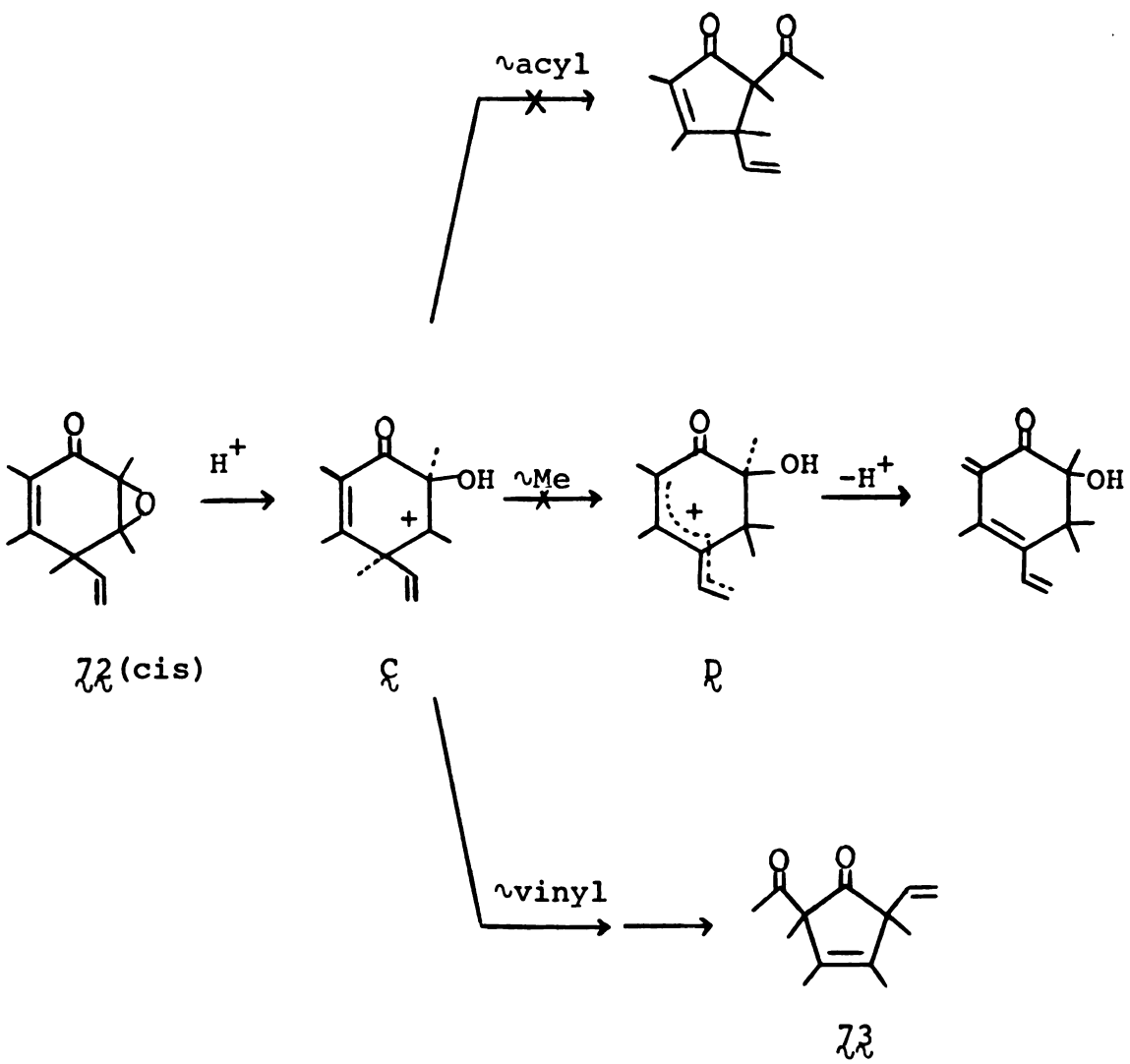
68 A 69 (50%) B 70 (10%) 71 (35%)

ion A. Acyl migration and proton loss affords the major product 69. Methyl migration competes effectively, giving the allylic ion B, which may either lose a proton to give 70 or rearrange by a more complex process, eventually to

give 71.

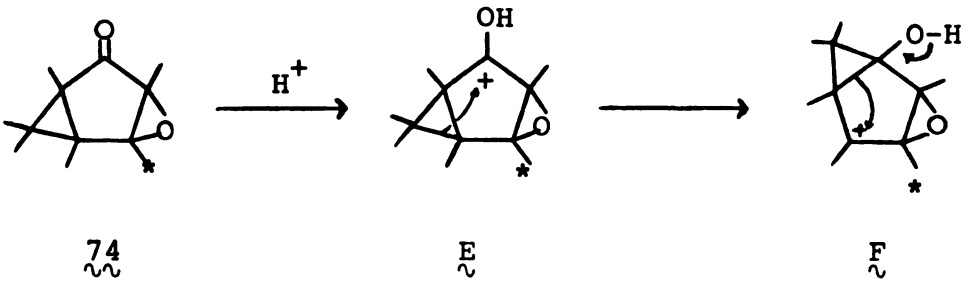
The α,β-epoxy ketone 72 rearranged in acid exclusively by vinyl migration, in preference to either acyl or methyl migration.[47].

Scheme 12

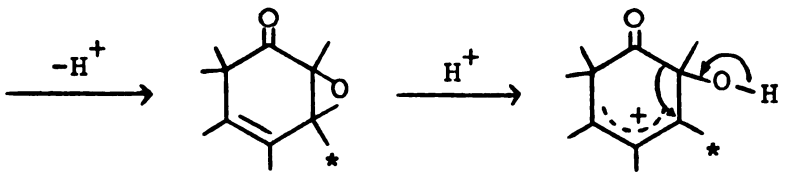


Although the acid-catalyzed rearrangement of epoxyketones is generally initiated by protonation of the epoxy oxygen atom, a competitive protonation of the carbonyl oxygen has been found in the acid catalyzed rearrangement of 74.[48]

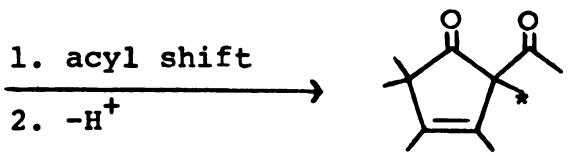
Scheme 13



74 E F

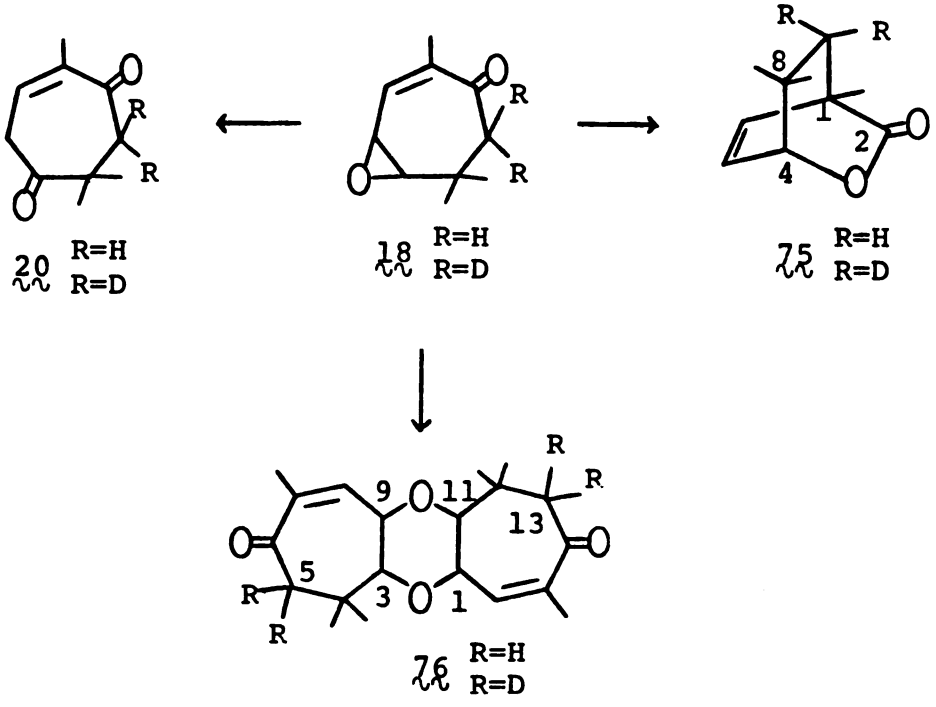


G



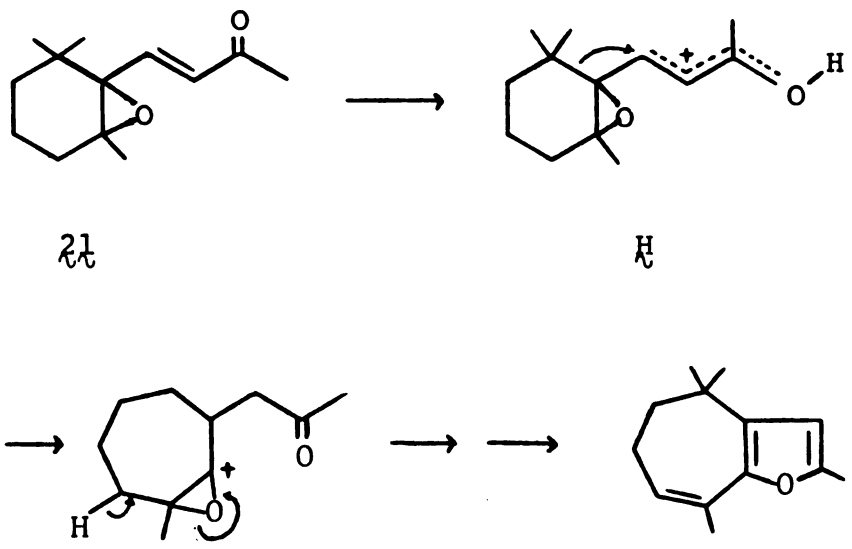
71*

Although the acid-catalyzed rearrangement of α,β-epoxyketones has been extensively studied, only recently have the vinylogous α,β-unsaturated-γ,δ-epoxyketones been reported.[20] In the case of eucarvone γ,δ-epoxide[20] 18, in the presence of BF_3, dimerization (to give 76) competes with hydrogen migration (to give 20) and alkyl shift (to give 75).



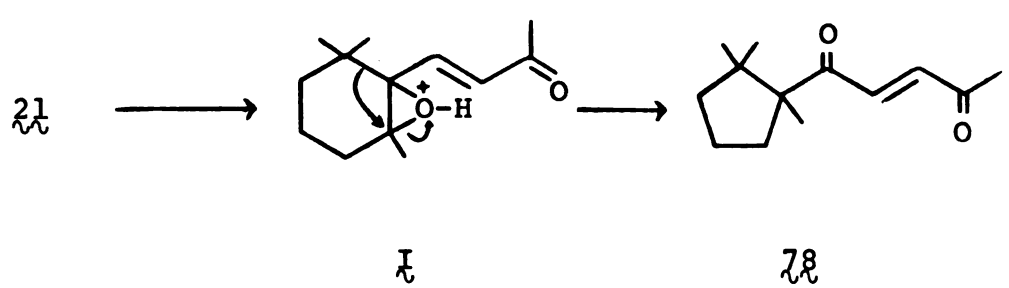
The remarkable formation of 77 and 78 from 21 has been interpreted as resulting from ring expansion (intermediate H) and contraction (intermediate I).[49,50]

Scheme 14



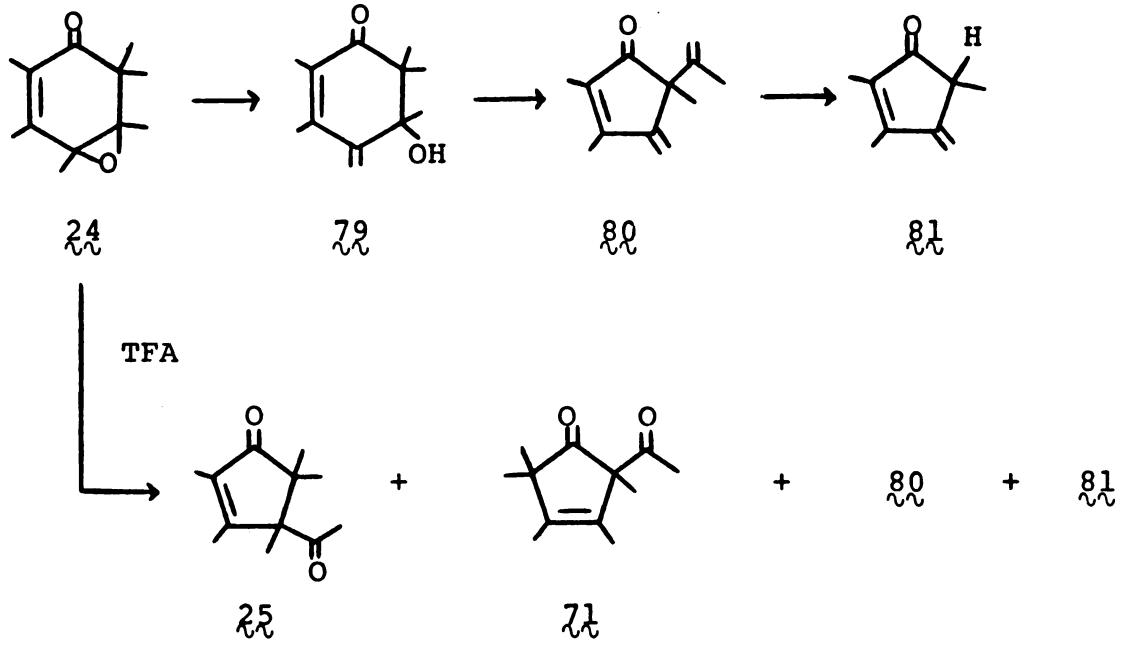
21 H

Scheme 15



21 I 78

The acid-catalyzed rearrangement of epoxyenone 24 has been reported.[5] Compound 24 rearranged quantitatively in aqueous acid to 79. In neat TFA, 79 rearranged to 80 which, on longer treatment with TFA, was dealkylated to 81 and acetone.

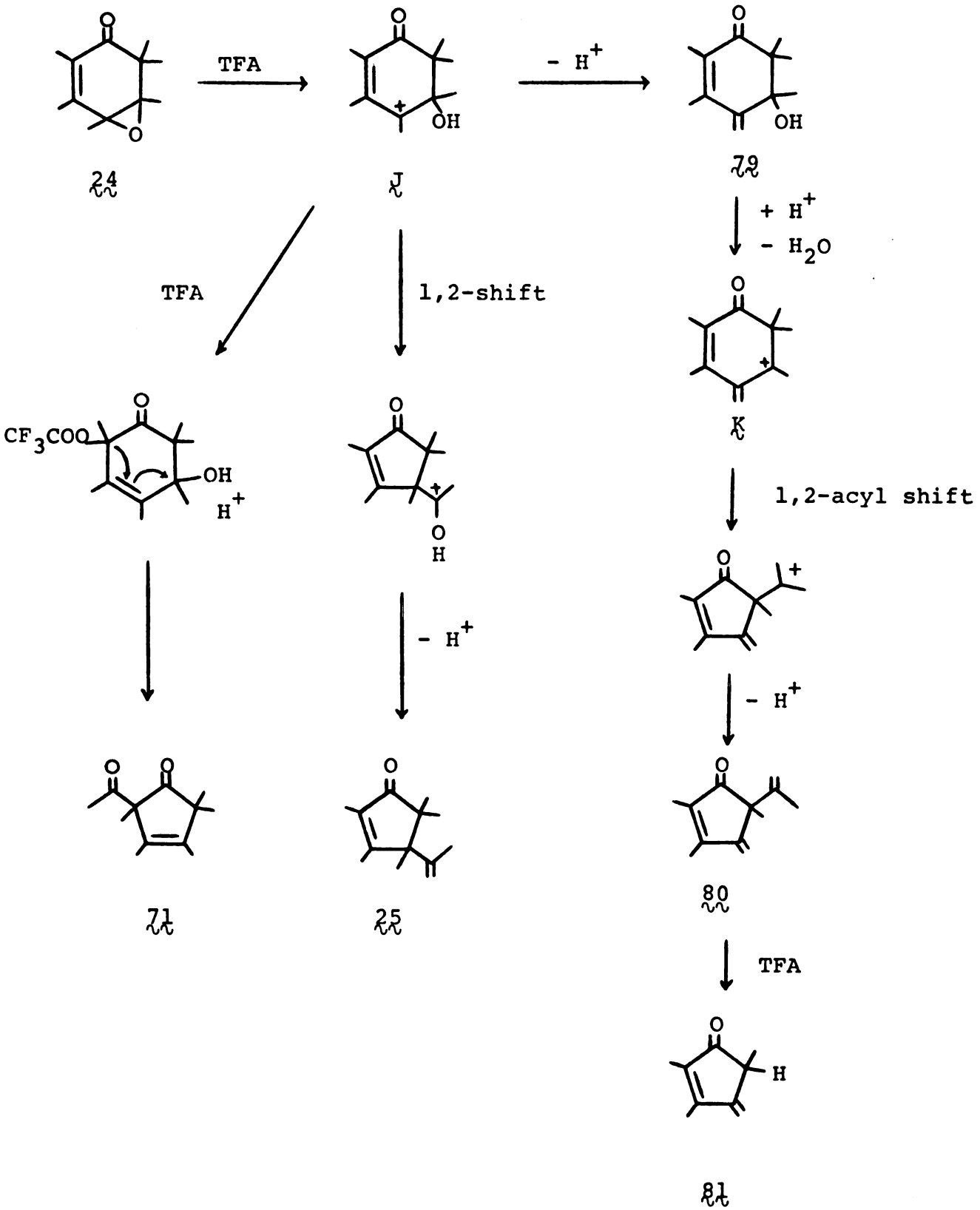


24 79 80 81

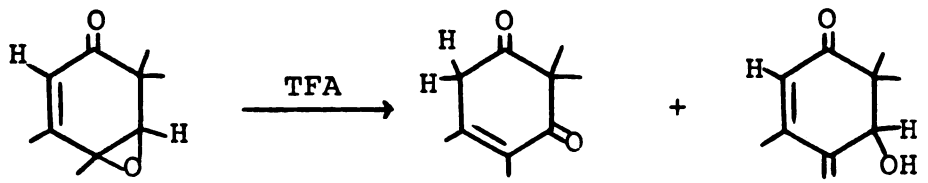
25 71

However, when 24 was treated directly with neat TFA there was found, in addition to 80 and 81, a small yield of 71 and a larger amount of 25. Scheme 16 describes the mechanisms for these rearrangements. The intermediate J can collapse to 79 by losing a proton. In neat trifluoro-acetic acid, the same intermediate may rearrange by a 1,2-alkyl shift to give 25, or following nucleophilic attack, ring contraction may occur to give 71. The major product 81 arises from protonation of 79 followed by a 1,2-acyl shift and deprotonation. Product 81 is formed by dealkylation of 80.

Scheme 16


TFA
- H+
OH
24
J
79
+ H+
- H2O
TFA
1,2-shift
CF3COO
OH
H+
K
1,2-acyl shift
O
H
- H+
- H+
71
25
80
TFA
H
81

It was also reported that treatment of 27 with TFA gave 82 and 83.



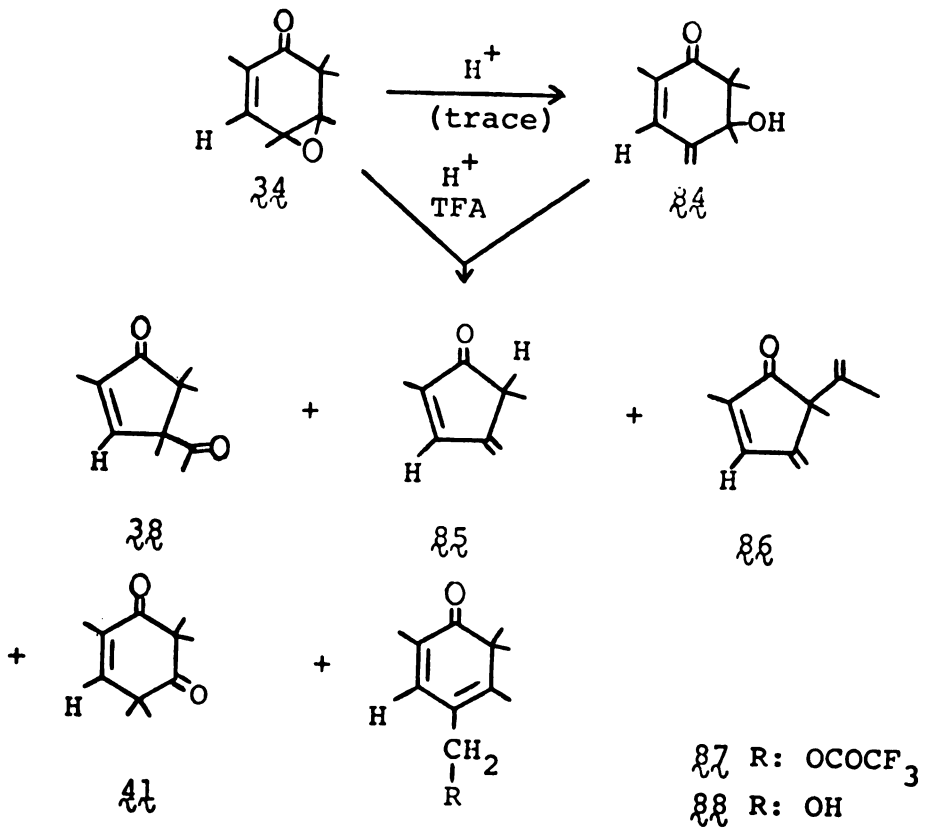
27 82 83

The manner in which the various methyl groups in 68, 72, 24 or 27 may determine the mode of the acid-catalyzed rearrangements of cyclohexadienone epoxides remains to be further studied. Moreover, vinyllog of an α,β-epoxyketone can be synthetically useful in this type of reaction to make variously substituted cyclopentenones. Such compounds, and polyoxygenated compounds which can be prepared from them, are expected to possess useful pharmaceutical activity.

In Part II of the thesis the acid-catalyzed rearrangements of 34, 35 and 36, the same epoxyketones whose photochemistry was studied in Part I of the thesis, will be described.

1. Acid-catalyzed Rearrangement of 4,5-Epoxy-2,4,5,6,6-Pentamethyl-2-cyclohexenone (34)

Compound 34 was sensitive to small amounts of acid. Column chromatography on alumina or gas chromatography using an SE-30 column resulted in nearly quantitative rearrangement to the hydroxyketone 84. When 34 was treated



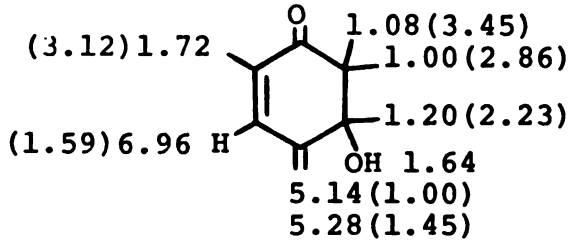
directly with neat TFA for 30 min, a small yield of 38, 41, 85, 88 a mild amount of 86, and a large amount of 87

were obtained. When 84 was treated with TFA, the same products were obtained and the product ratios were almost the same. On the longer treatment with TFA, compound 86 was dealkylated to 85 and acetone. Saponification of compound 87 gave 88 in quantitative yield.

In the following sections evidence for each structure will be presented, followed by mechanism and deuterium labeling experiments which support the mechanism.

A. Product Structures

The structure of 84 was assigned, based on its spectral properties and further rearrangement in strong acid. The molecular formula $C_{11}H_{16}O_2$ was confirmed by the mass

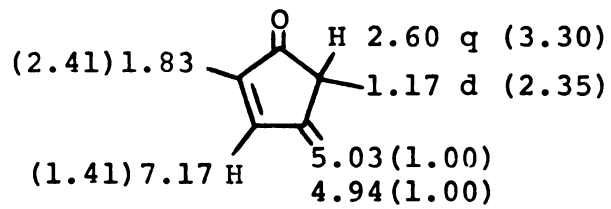


84

spectrum (parent peak m/e 180) and elemental analysis. The infrared spectrum of 84 showed a carbonyl band at 1670 cm^{-1} which indicated conjugation with two double bonds, a hydroxy group band at 3500 cm^{-1}, and a terminal methylene group band at 950 and 930 cm^{-1}. The uv λ_{max} 273 nm (ε16,430)

supported conjugation of the carbonyl group with both double bonds. The nmr and europium shift data were consistent with the structure. The hydroxyl proton signal disappeared when 84 was shaken with deuterium oxide.

The product assigned structure 85 corresponded in analysis not only to the loss of water from epoxyenone 34,

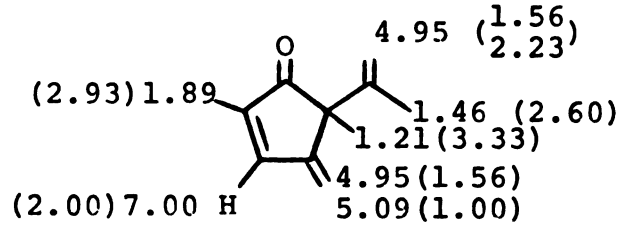


85

but also to the loss of a C_3H_4 fragment. The ir spectrum showed a carbonyl absorption at 1710 cm^{-1}, strong carbon-carbon double bond absorptions at 1540 and 1615 cm^{-1}, and a strong terminal methylene band at 915 cm^{-1}. The uv spectrum showed a λ_{max} at 275 nm (ε 10,800). The ir and uv spectra were consistent with a cyclopentenone moiety.[5] The nmr spectrum showed three vinyl protons, one allylic methyl and a $>CHCH_3$ moiety. The nmr chemical shifts and europium shift data were consistent with structure 85.

The product assigned structure 86 corresponded in analysis to loss of water from the epoxyenone 34. The ir spectrum was very similar to that of 85 ($\nu_{C=O}$ 1710,

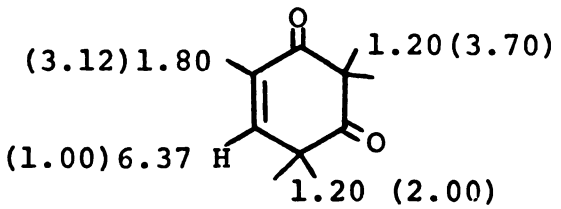
$\nu_{C=CH_2}$ 915 cm^{-1}), as was the uv spectrum showed a λ_{max} 273 nm (ε 9800). The nmr spectrum showed five vinyl protons, and two allylic methyl groups as well as one sharp aliphatic methyl singlet. The nmr chemical shifts and



86

europium shift data were consistent with structure 86.

Compound 41 was assigned the structure shown, based on

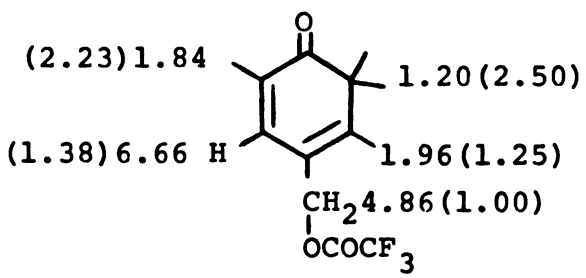


41

its spectral properties. The molecular formula $C_{11}H_{16}O_2$ was confirmed by the mass spectrum (parent peak m/e 180) and elemental analysis. In the ir spectrum, the diketone 41 showed two carbonyl absorptions at 1720 and 1682 cm^{-1}. The uv spectrum showed a λ_{max} at 253 nm, and these data

indicate that there is one conjugated and another non-conjugated carbonyl group in a six-membered ring. The nmr spectrum showed an aliphatic singlet for 12 H which is due to two sets of gem-methyl groups. Homoallylic coupling was observed between the allylic methyl and a vinyl proton. Europium shift reagent showed that the two sets of gem-methyl groups were not identical.

Compound 87 was assigned its structure based on the

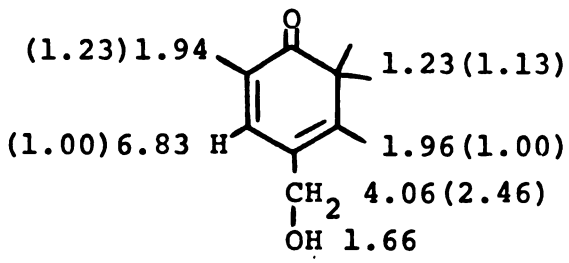


87

following data, and on its subsequent reaction. The molecular formula $C_{13}H_{15}O_3F_3$ was confirmed by the mass spectrum (parent peak m/e 276). The ir spectrum showed two strong carbonyl absorptions at 1780 cm^{-1} ($\nu_{O-\overset{O}{\overset{\|}{C}}-CF_3}$) and 1660 cm^{-1} ($\nu_{C=O}$, dienone). The uv spectrum showed a λ_{max} 309 nm (ϵ 4,890) consistent with a dienone chromophore. The nmr spectrum showed a gem-dimethyl group, two allylic methyl groups, a methylene group and a vinyl proton. The nmr and europium shift data were consistent with the structure. An alternative structure which was considered

and discarded on the basis of labeling results will be described later.

The structure of compound 88 is based on its spectral



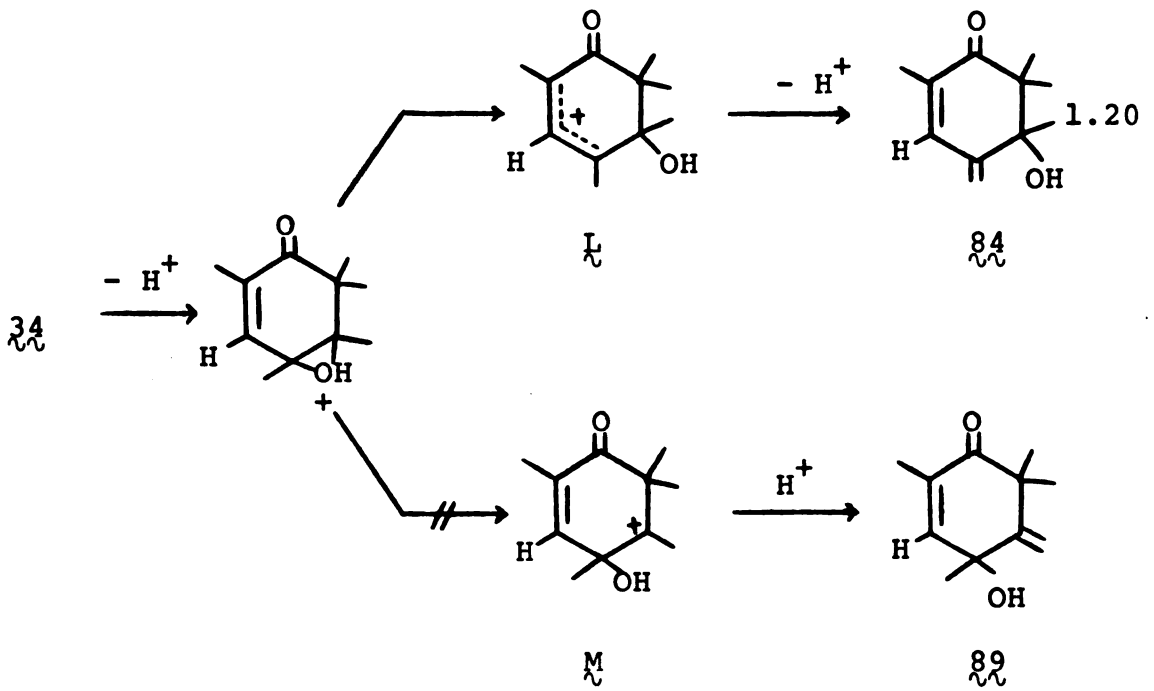
88

properties. That it was isomeric with 34 was shown by the mass spectrum (parent peak m/e 180). The ir spectrum showed a broad hydroxyl band at 3100-3700 cm^{-1} and a strong carbonyl absorption at 1658 cm^{-1}. The uv spectrum showed a λ_{max} at 310 nm (ε 4,040). The ir and uv spectra were consistent with a dienone chromophore.

B. Mechanism

Alcohol 84 is undoubtedly formed from 34 by proton loss from the intermediate cation L (Scheme 17). The alternative epoxide ring opening mode to give M would lead to structure 89, which is also reasonably consistent with the observed nmr spectrum. However, this structure was conclusively eliminated by a labeling experiment.

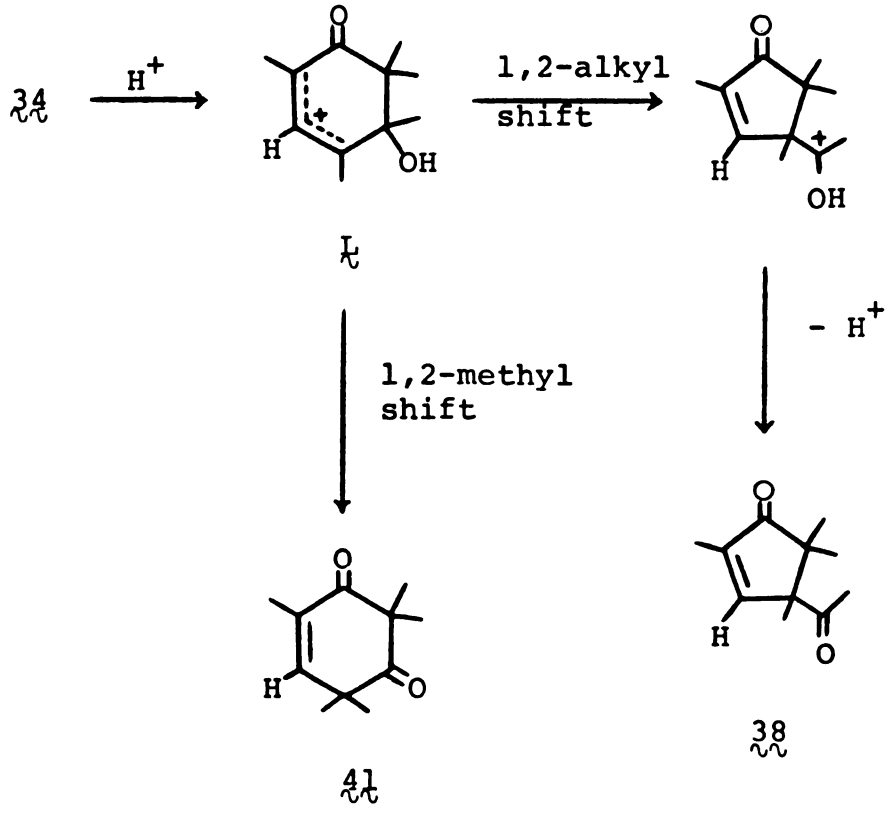
Scheme 17



Preparation of 84 from 34, containing a CD_3 group at C-5, gave 84-d_3, lacking methyl signal at δ1.20. Had the hydroxy ketone been 89, the product would have lacked the vinyl proton signals.

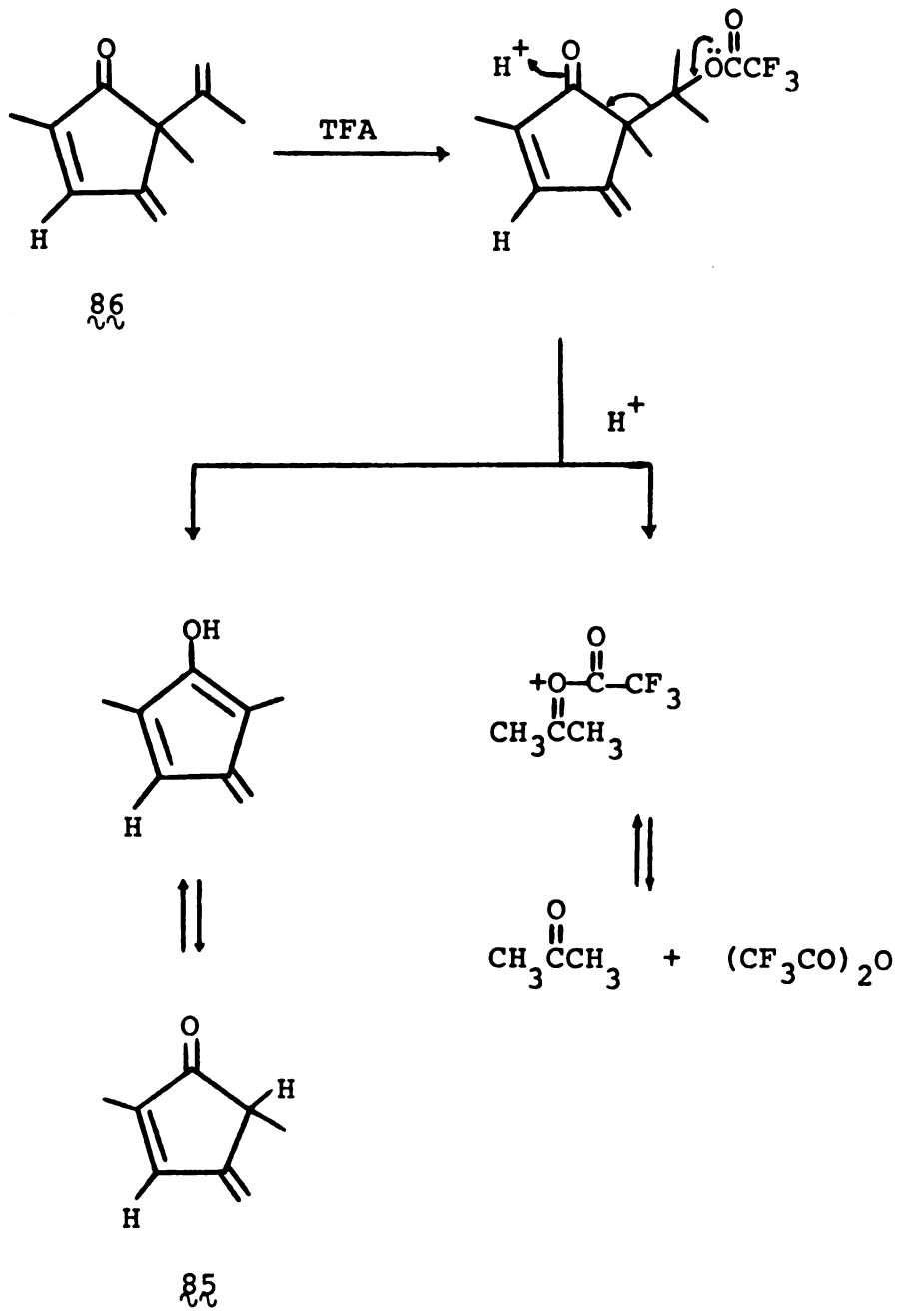
Scheme 18 gave plausible mechanisms for the formation of 38 and 41 from 34.

Scheme 18



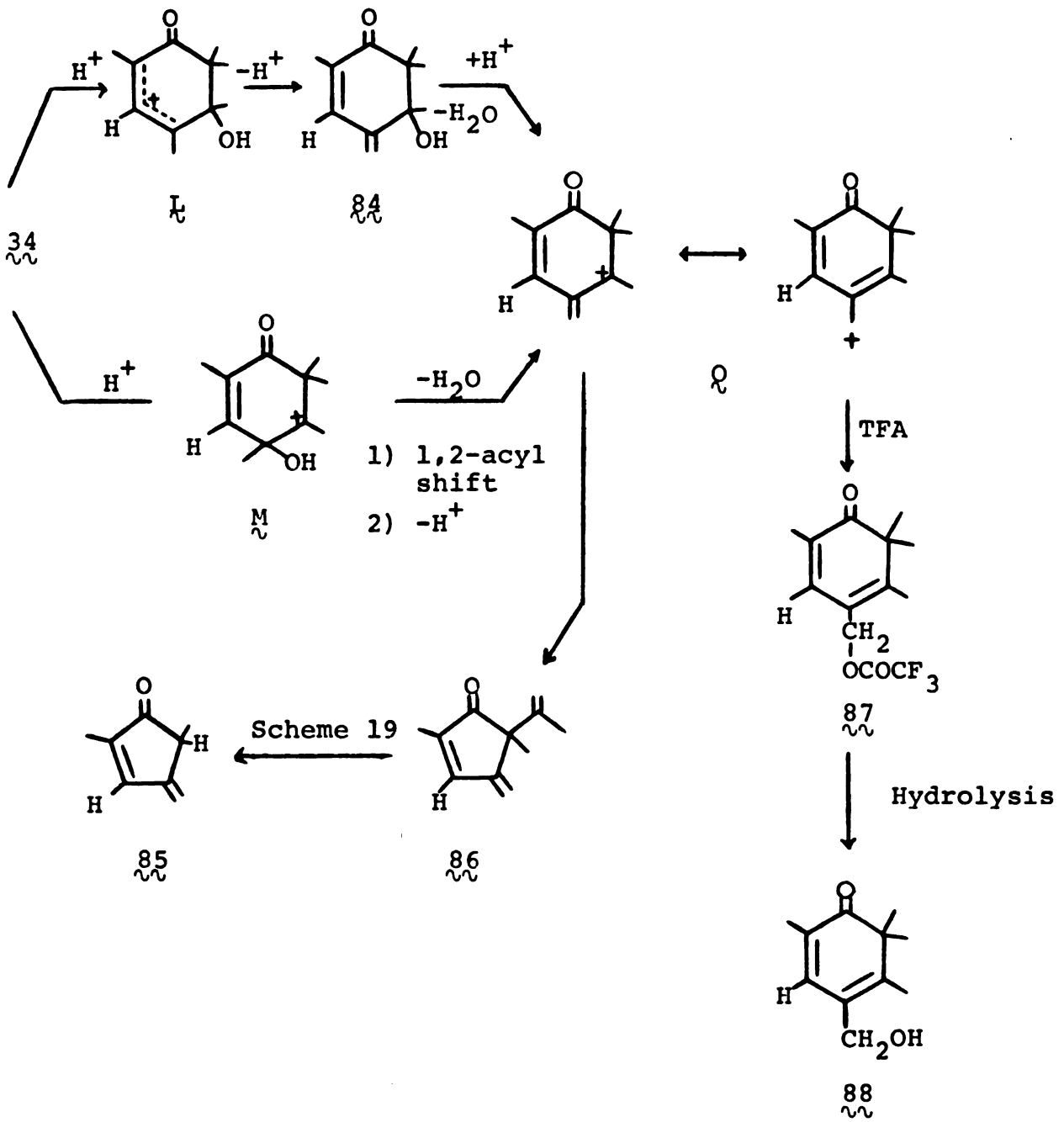
Scheme 19 gives a plausible mechanism for the formation of 85 from 86. When the reaction was carried out in an nmr tube, the appearance of the sharp singlet due to acetone was observed.

Scheme 19



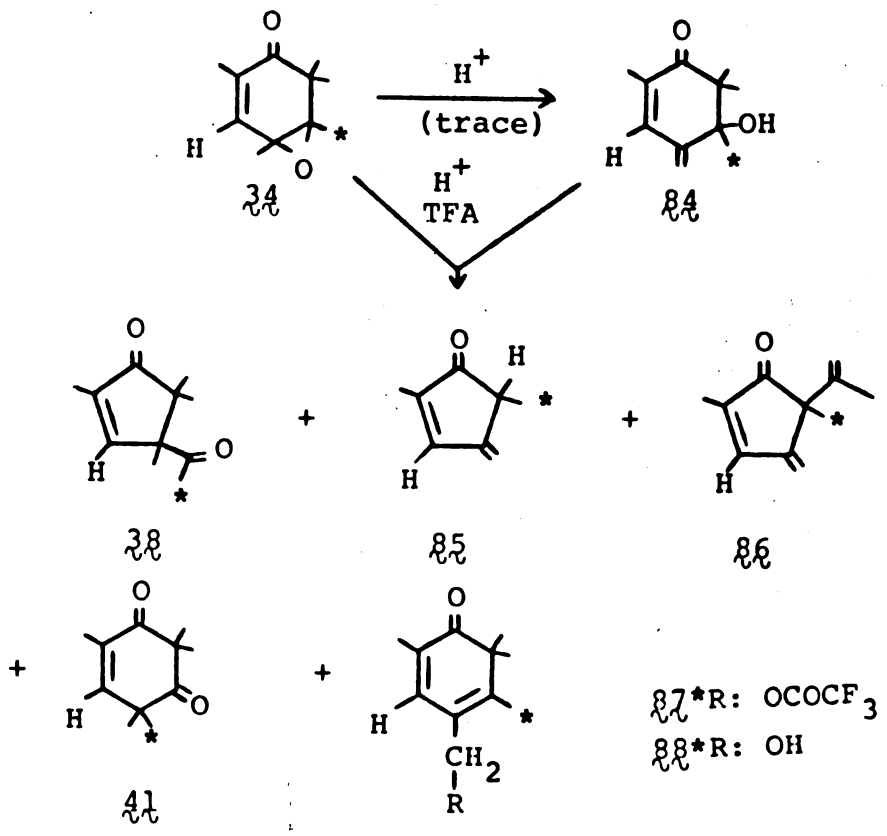
The possible routes to 86 and 87 are shown in Scheme 20.

Scheme 20



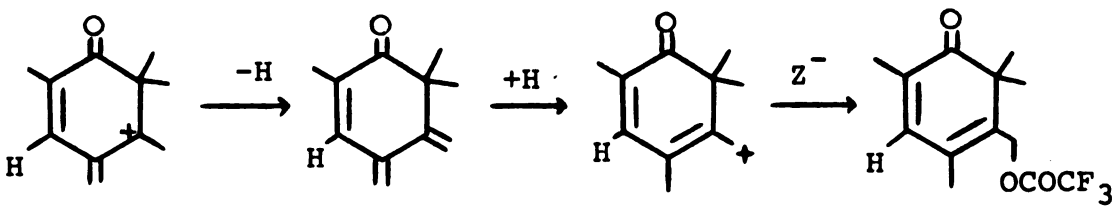
Independent treatment of 87 with a solution of potassium carbonate in methanol gave a quantitative yield of 88. Scheme 20 also represents the mechanisms by which the various products are obtained from alcohol 84.

The expected labeling results (based on Scheme 17-20) are as follows.



The actual results were consistent with these expectations (see Experimental for details of the nmr spectra of the labeled products).

Scheme 21

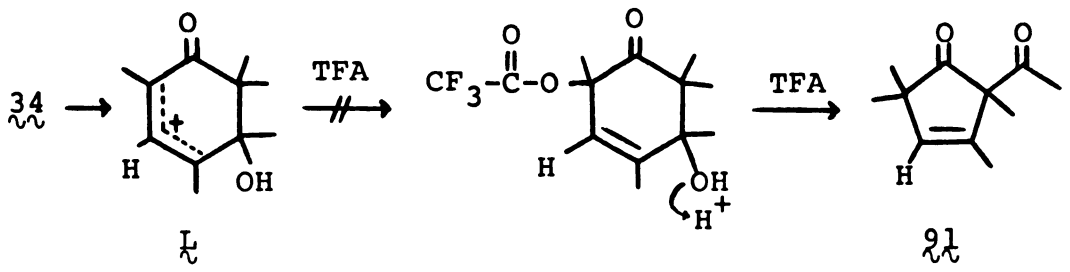


N Q 90

An alternative reaction path from intermediate N to give Q could lead to a product with structure 90 (Scheme 21). Although the nmr, ir and uv spectra for the product assigned structure 87 are also reasonably consistent with structure 90, this structure (and the mechanism in Scheme 21) is definitely excluded by the labeling experiment.

A product with structure 91, which could be formed from nucleophilic attack at the carbon alpha to the carbonyl group followed by ring contraction (corresponding to the formation of 25 from 24), was not observed. This may be due to the higher activation energy associated with the formation of a secondary carbonium ion (note the H-atom at C-3).

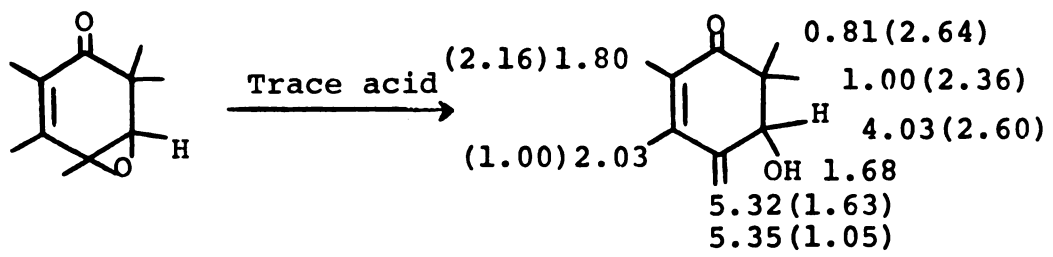
Scheme 22



L 91

2. Acid-catalyzed Rearrangement of 4,5-Epoxy-2,3,4,6,6-pentamethyl-2-cyclohexenone (35)

Although the epoxy enone 35 could be purified by chromatography over florisil, it was sensitive to heat or small amounts of acid. Chromatography on alumina, treatment with a little aqueous acid or subjection to gas chromatography resulted in nearly quantitative rearrangement to a hydroxy ketone assigned structure 92. The compound 92 shows a $\nu_{C=O}$ at 1660 cm^{-1} consistent with a conjugated carbonyl group in a six-membered ring. The presence of a hydroxyl group was clear from the ν_{O-H} at 3500 cm^{-1}.

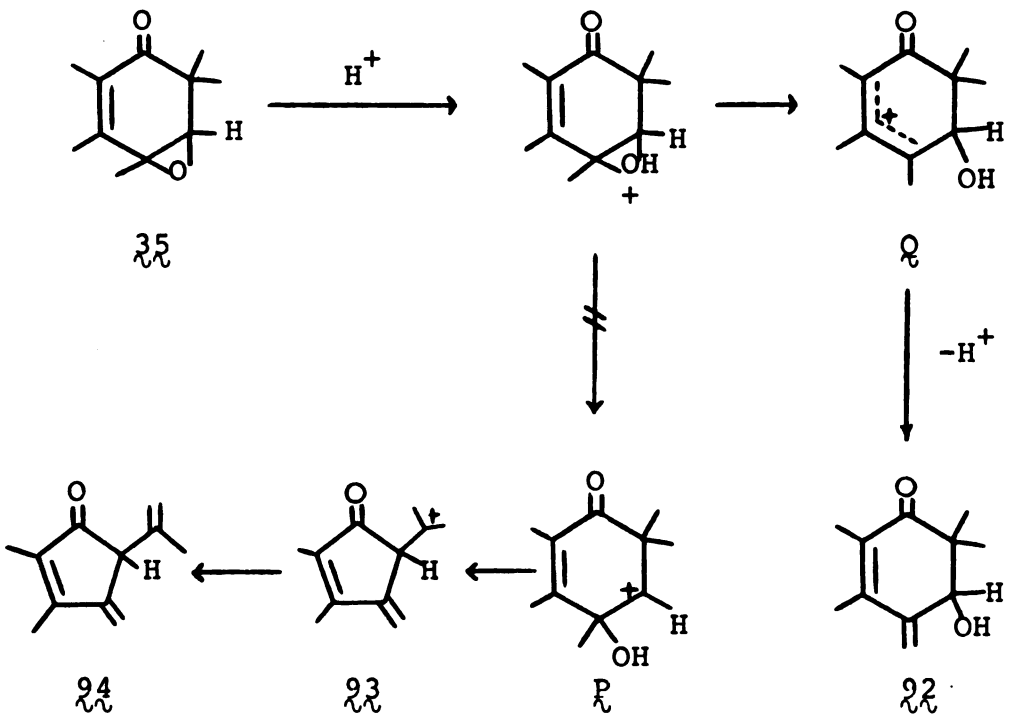


35 92

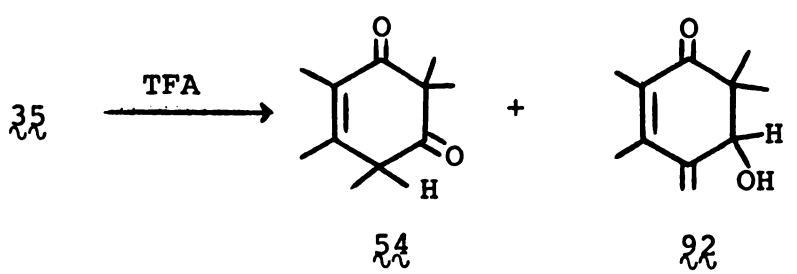
The nmr spectrum of 92 showed two vinyl protons (δ5.32, 5.35), two gem-dimethyls as singlets (δ0.81, 1.00) and two allylic methyl groups (mutually coupled at δ1.80, 2.03). Moreover, the ir spectrum showed a terminal methylene group (960, 930 cm^{-1}) and the uv maximum at 275 nm (ε 14,430) suggested that both double bonds were linearly conjugated with the carbonyl group. Compound 92 is undoubtedly from 35 by proton loss from the intermediate cation Q (Scheme 23). The alternative ring-opening to give P, possibly followed by a 1,2-acyl shift, would lead to structure 94 which is inconsistent with the observed spectra. Ion Q is preferred over P because it is tertiary and allylic. The formation of 92 is analogous to the formation of 84 from 34 via L (Scheme 17).

Treatment of 35 with neat TFA at room temperature for 40 minutes gave two isomers of the starting epoxy

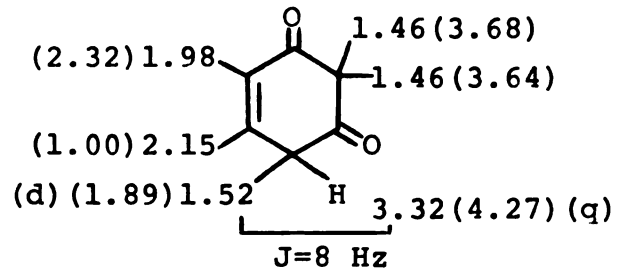
Scheme 23



enone. The structure of one product was 92, already identified. The other product structure 54 was based



primarily on its spectral properties. The diketone 54 showed two carbonyl absorptions in the ir spectrum at 1720 and 1665 cm^{-1}, and strong uv absorption at 243 nm, indicating one conjugated and another non-conjugated carbonyl group in a six-membered ring. The nmr spectrum (in $CDCl_3$) showed two mutually coupled vinyl methyl groups (δ1.98, 2.15), a gem-methyl group (with non-equivalent methyls, as shown by Eu-shift reagent) and a >CH(CH_3) group.



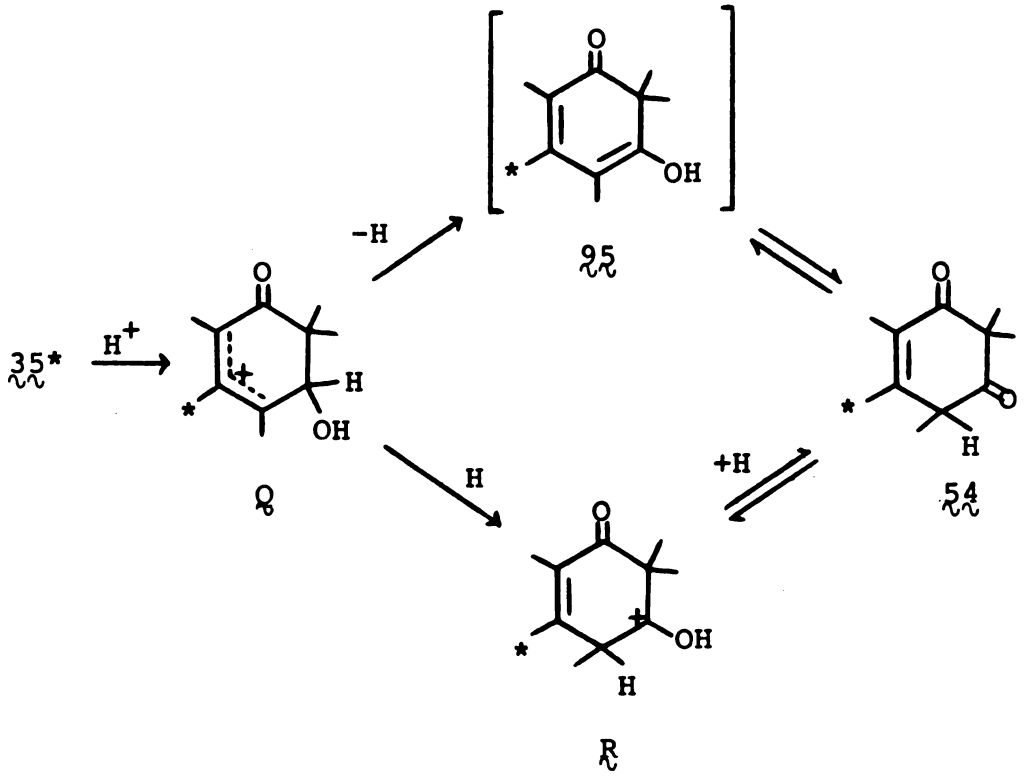
54

A labeling experiment was performed to establish unequivocally the nmr assignments of 92 and 54. Treatment of 35 with DMSO-d_6 and potassium t-butoxide gave 35* whose nmr spectrum was identical with that of 35 except that the peak at δ1.95 was absent (labeled at C-3). Treatment of 35* with neat TFA at room temperature for 40 minutes gave 92* whose nmr spectrum lacked the signals at δ2.03 and 54* whose nmr spectrum lacked the signal at δ2.15. These results showed that there are no skeletal rearrangements occurring during the acid rearrangement

of 35*.

Possible mechanisms for the formation of 54 are shown in Scheme 24.

Scheme 24

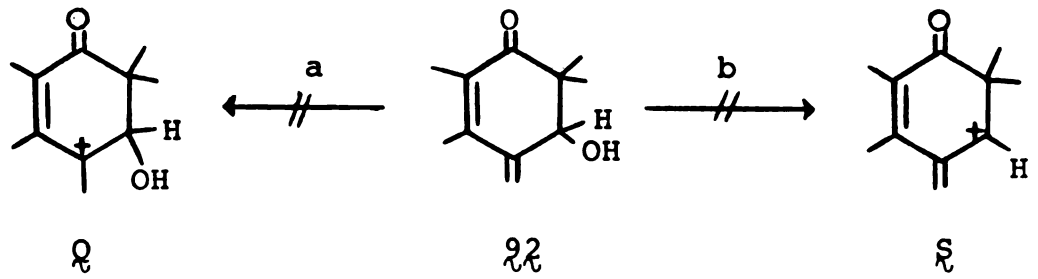


The intermediate cation Q can lose a proton to give 95 which, however, was not isolated. Its rapid keto-enol tautomerism accounts for the formation of 54. An alternative process (preferred reaction pathway) involves a hydride shift and then deprotonation to give product 54. In the ir spectrum of 54 one could see, in addition to the carbonyl bands, other bands due to ν_{O-H} 3500 (w), and

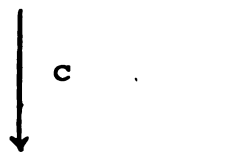
1640 (broad) due to the enol form. Presumably intermediate 95 and product 54 are in equilibrium, and the keto form seems the more stable. Obviously in TFA, 95, R and product 54 should be in equilibrium

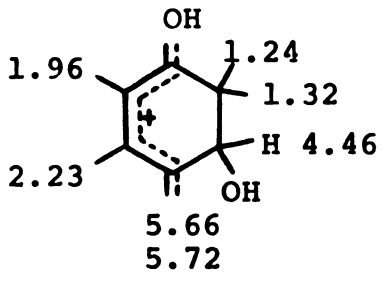
In contrast to 79 and 84, which on protonation rearranged further, compound 92 underwent no further rearrangement on treatment with neat TFA under similar conditions.

Scheme 25



Q 92 S





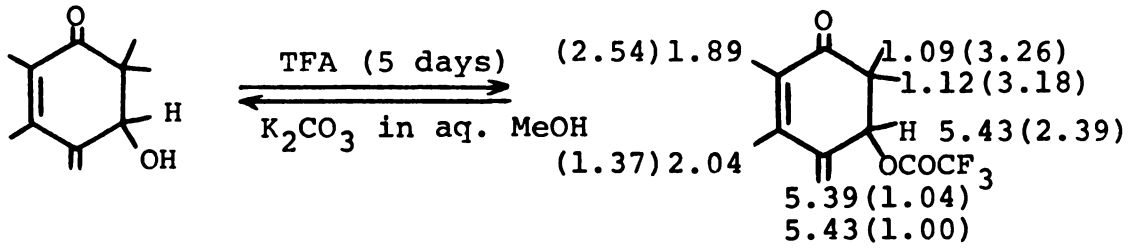
T

There are three possible positions for the protonation of 92 (Scheme 25). Pathway a can be eliminated on the basis that if the allylic cation Q is formed, it should give 92 and 54 on quenching. But 92 did not rearrange to 54 on treatment with acid. The reaction was repeated on 92*. No trace of 54* was found.

Pathway b can be eliminated on the basis of the nmr spectrum of 92 in acid. The nmr spectrum of 92 in neat TFA showed gem-methyls at δ1.24 and 1.32 where each appeared as a singlet, two allylically coupled methyl groups at δ1.96 and 2.23, two vinyl protons at δ5.66 and 5.72, and one proton at δ4.46 (C-5). The nmr of 92* in neat TFA showed exactly the same chemical shifts except that the signal at δ2.23 had disappeared. If carbocation S were formed, it would be difficult to understand why the proton at C-5 should not be strongly deshielded. Examination of the nmr spectrum of 92 in 80% H_2SO_4 (δ4,52), D_2SO_4 (δ4.52) or even 98% D_2SO_4 (δ5.33) showed that the proton at C-5 is not strongly deshielded. Also, if S were formed, why would it not undergo a 1,2-acyl shift similar to that of compound 79?

It is concluded that protonation of 92 occurs via path c to give the cation T. This highly stabilized cation may simply be incapable of rearranging under the prescribed experimental conditions, and is converted back to starting material 92 on quenching. Solutions of 92 in TFA or in 80% H_2SO_4, D_2SO_4 or concentrated D_2SO_4 aqueous solution,

on quenching, gave back the starting material.



92 96

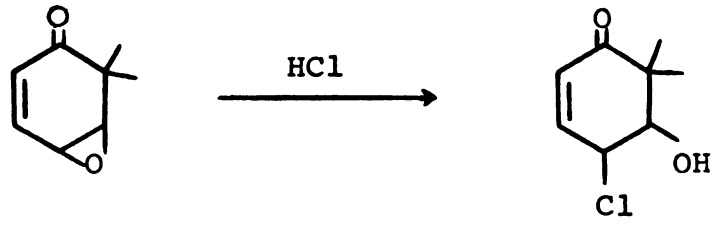
Prolonged treatment of 92 in TFA (over 5 days) converted it in part (60%) to 96, through esterification, and 40% of unreacted 92 was recovered. The experiment was repeated with 92*, and showed no skeletal change in the recovered product. The facile removal of the trifluoroacetyl group was demonstrated by converting 96 to 92 in a 7% solution of potassium carbonate in aqueous methanol at room temperature for 4 hr.

A new and previously unobserved protonation path, namely at the carbonyl oxygen, appears to operate on the acid treatment of 92. This pathway gives the highly delocalized cation T.

3. Acid-catalyzed Rearrangement of 4,5-Epoxy-6,6-epoxy-6,6-dimethyl-cyclohexen-2-one (36)

Treatment of enone epoxide 36 with dilute aqueous hydrochloric acid or with hydrogen chloride gas (in

ether) leads to the formation of 4-chloro-5-hydroxy-6,6-dimethylcyclohexen-2-one (97) in 98% yield.

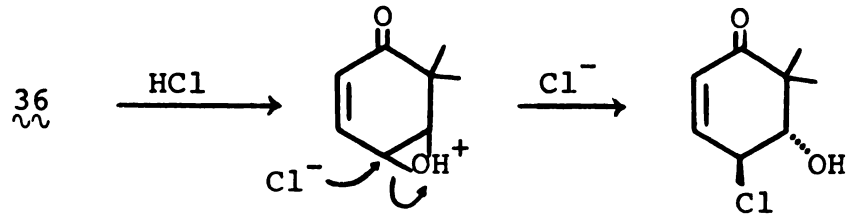


96 97

The halohydrin structure was established primarily from its spectral properties. The molecular formula $C_8H_{11}O_2Cl$ was confirmed by the mass spectrum (parent peak m/e 176) and elemental analysis. The ir spectrum showed a broad hydroxyl absorption at 3100-3800 cm^{-1} and a carbonyl absorption at 1685 cm^{-1} typical of a conjugated enone. The uv spectrum showed a λ_{max} at 240 nm which substantiated the presence of the conjugated enone moiety. The mass spectrum showed a monochloro fragmentation pattern, showing that the hydroxyl group had not been replaced by a second chlorine atom. The nmr spectrum showed two methyl groups at δ1.00 and 1.20 as singlets, two vinyl protons at δ5.80 and 6.60 and two methine protons at δ3.65 and 4.57. The large coupling constant for the methine protons (J = 8 Hz) implies a trans geometry and hence a trans relationship between the chloro and hydroxyl groups.

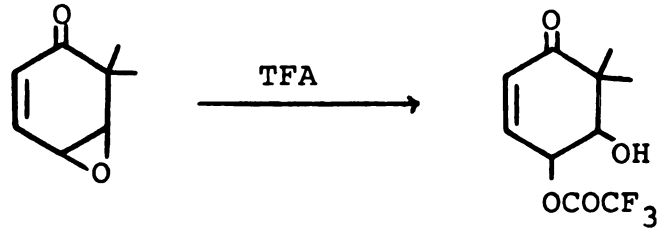
A plausible mechanistic route to 97 is shown in Scheme 26. Chloride ion displaces at the allylic and also less

Scheme 26



crowded carbon to give the trans-chlorohydrin.

Treatment of the epoxyenone 36 with TFA gave the trifluoroacetate 98.[51] The structure of 98 was established



36 98

primarily by its spectral properties. The molecular formula $C_{10}H_{11}O_4F_3$ was confirmed by the mass spectrum (parent peak m/e 252). The ir spectrum showed a strong broad hydroxyl group absorption at 3010-3800 cm^{-1} and a strong carbonyl absorptions at 1780 cm^{-1} for the trifluoro ester moiety and at 1680 cm^{-1} for the conjugated enone carbonyl. The uv spectrum had an absorption maximum at 240 nm confirming the conjugated enone moiety. The nmr spectrum showed two methyl groups as a singlet at δ1.03, two vinyl protons δ5.40-6.04 and 6.40-6.60 as multiplets

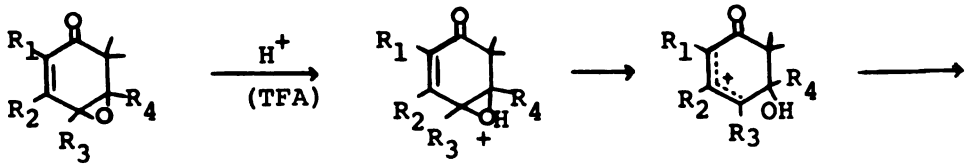
and two methine protons at δ3.74-3.92 and 4.40-5.20 with a coupling constant 8 Hz. The large coupling constant indicates that the hydroxyl and trifluoroacetate groups are trans to each other.

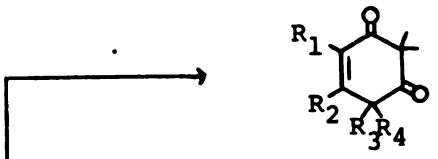
Prolonged treatment of 36 with TFA did not bring about any carbocation skeletal rearrangement.

In summary, in neat trifluoroacetic acid, the vinylogs of α,β-epoxyketones rearrange initially to allylic cations. The intermediate cations may rearrange by a 1,2-hydride shift, a 1,2-methyl shift, a 1,2-alkyl shift (ring contraction), or may be attacked by solvent.

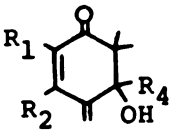
In the comparison of the results from 35 with 27, it is obvious that the replacement of H for CH_3 in the C-2 position has no effect on the acid-catalyzed rearrangement result. However, the replacement of H for CH_3 in the C-3 and C-4 positions significantly effects the acid-catalyzed rearrangements.

Scheme 27

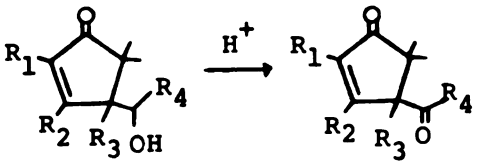




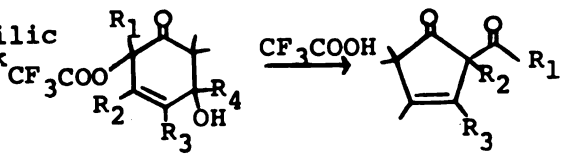
deprotonation



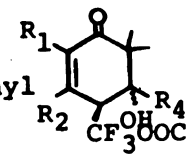
$C_\delta \rightarrow C_\gamma$



nucleophilic attack at C_α to carbonyl group



nucleophilic attack at C_γ to carbonyl group



Compound/yield				
24	34	35	27	36
--	10%	60%	53%	--
a	b			
(79)	(84)	40%	47%	--
67%	82%			
27%	8%	--	--	--
6%	--	--	--	--
--	--	--	--	95%

a. 79 forms 89 (97%).

b. 84 forms 85 (4%), 86 (20%) 41 (10%), 38 (8%), 87 (52%) 88 (6%).

EXPERIMENTAL

1. Acid-catalyzed Rearrangement of 4,5-Epoxy-2,4,5,6,6-pentamethyl-2-cyclohexenone (34) in Trifluoroacetic acid

A solution of 400 mg (2.22 mmol) of 34 in 4 ml of ice-cold trifluoroacetic acid was stirred at 0° for 25 min, then at room temperature for 30 min. The reaction was then quenched by pouring the mixture into ice and saturated sodium bicarbonate solution. The products were extracted with ether, and the combined ether layers were washed successively with saturated sodium bicarbonate solution, water, saturated sodium chloride solution and dried ($MgSO_4$). Evaporation of the solvent left a light yellow liquid, which was analyzed by vpc (10' x 0.125 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 143°, 30 ml/min N_2). Products (%, retention time) were observed: 85 (4%, 8 min), 86 (20%, 18 min), 41 (10%, 22 min), 38 (8%, 30 min), 87 (52%, 58 min), 88 (6%, 67 min). The experiment was repeated on a larger scale to isolate all the products.

For 4-methylene-2,5-dimethyl-2-cyclopentenone (85): ir (neat) 3010 (m), 2960 (w), 2925 (w), 1710 (s), 1640 (m), 1615 (w), 1460 (m), 1395 (m), 1340 (w), 1300 (w), 1200 (w), 1180 (w), 1160 (w), 1030 (w), 990 (m), 915 (s) cm^{-1}; uv (cyclohexane) λ_{max} 275 nm (ϵ 10,800); nmr (CCl_4)

δ1.17 (d, 3 H, J = 7.5 Hz), 1.83 (broad, 3 H), 2.60 (q, 1 H, J = 7.5 Hz), 4.94 (s, 1 H), 5.03 (s, 1 H), 7.17 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 122 (4), 121 (18), 100 (56), 107 (15), 94 (100), 93 (40), 80 (20), 79 (100), 78 (50), 68 (25), 67 (14), 66 (22).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25
Found: C, 78.63; H, 8.39

For 5-isopropenyl-4-methylene-2,5-dimethyl-2-cyclopentenone (86), this product was obtained as white plates which melt at room temperature: ir (neat) 3000 (s), 2965 (w), 1710 (s), 1645 (m), 1610 (w), 1455 (s), 1385 (m), 1340 (w), 1295 (w), 1200 (w), 1150 (w), 1105 (w), 1030 (w), 985 (w), 950 (w), 915 (s) cm^{-1}; uv (cyclohexane) λ_{max} 225 nm (ε 9800), 273 (4450); nmr (CCl_4) see structure; the band at δ1.46 was a doublet, J = 1 Hz, that at δ1.89 was broadened, that at δ7.26 was a multiplet, that at δ4.95 was a multiplet (3 vinyl protons) and that at δ5.09 was a broaden singlet, and the peak at δ1.21 was a sharp singlet; mass spectrum (70 eV) m/e (rel intensity) 162 (65), 147 (35), 134 (89), 133 (21), 119 (100), 118 (25), 105 (32), 91 (70), 77 (35), 65 (20).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70
Found: C, 81.26; H, 8.71

For 2,4,4,6,6-pentamethyl-2-cyclohexen-1,5-dione (41): ir (neat) 3006 (s), 1720 (s), 1682 (s), 1490 (m), 1480 (w), 1400 (m), 1380 (w), 1310 (m), 1260 (w), 1180 (w),

1070 (m), 910 (w), 890 (m) cm^{-1}; uv (cyclohexane) λ_{max} 253 nm (ϵ 7200); nmr (CCl_4) δ1.20 (s, 12 H), 1.80 (d, 3 H, J = 0.8 Hz), 6.37 (q, 1 H, J = 0.8 Hz); mass spectrum (70 eV) m/e (rel intensity) 180 (60), 165 (e), 163 (4), 137 (45), 79 (10), 67 (30).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.49; H, 8.60

For 4-trifluoroacetoxymethyl-2,5,6,6-tetramethyl-2,4-cyclohexadienone (87): ir (CCl_4) 3000 (s), 2900 (s), 1780 (s), 1660 (s), 1600 (m), 1480 (m), 1460 (m), 1395 (m), 1385 (m), 1230 (s), 1180 (m), 1145 (m), 1242 (w), 1010 (w), 905 (w), 820 (s) cm^{-1}; uv (cyclohexane) λ_{max} 223 nm (ϵ 1700), 309 (4900) and uv (CCl_4) showed λ_{max} at 317 nm; nmr (CCl_4) δ1.20 (s, 6 H), 1.84 (d, 3 H, J = 0.5 Hz), 1.96 (s, 3 H), 4.86 (s, 2 H), 6.66 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 276 (20), 185 (1), 162 (77), 147 (58), 134 (28), 119 (100), 105 (25), 91 (52), 79 (20), 77 (30), 69 (42).

The mass spectrum of same sample compound changed after a few hours. The parent peak at m/e 276 diminished in intensity and the peak at m/e 180 increased suddenly. At the same time, the sample changed color from yellowish to dark. The mass spectral pattern of the later sample was similar to that of 87. The nmr spectrum also changed; a new set of peaks appeared at δ1.23, 1.93, 4.06 and 6.83 corresponding to 87. These data show that 87 was not

stable, and no attempt was made to do the elemental analysis.

For 4-hydroxymethyl-2,5,6,6-tetramethyl-2,4-cyclohexadienone (88): ir (neat) 3510 (br., m), 3500 (w), 3000 (s), 2910 (m), 1658 (s), 1600 (w), 1583 (w), 1460 (w), 1380 (m), 1305 (m), 1280 (w), 1270 (m), 1210 (w), 1180 (m), 1140 (w), 1010 (m), 1000 (m), 890 (m), 820 (s), 815 (s) cm^{-1}; uv (cyclohexane) λ_{max} 223 (ϵ 2300), 310 (4100) and uv (CCl_4) λ_{max} shifted to 315 nm; nmr (CCl_4) δ1.23 (s, 6 H), 1.96 (s, 3 H), 1.94 (d, 3 H, J = 1 Hz), 4.06 (s, 2 H), 6.83 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 180 (52), 165 (38), 149 (20), 147 (49), 137 (44), 136 (12), 135 (80), 123 (20), 122 (98), 119 (100), 109 (20), 107 (43), 105 (40), 93 (24), 91 (62), 79 (40), 77 (43), 65 (23).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.72; H, 8.93

2. Acid-catalyzed Rearrangement of 5-isopropenyl-4-methylene-2,5-dimethyl-2-cyclopentenone (86) in Trifluoroacetic acid

A solution of 86 (80 mg, 0.5 mmol) in 1 ml of trifluoroacetic acid was allowed to stand at room temperature for 4 hrs, the reaction being monitored by analytical vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 100°, 30 ml/min N_2). The product, compound 85, showed

a retention time of 7 min, whereas the starting compound 86 showed a retention time of 16 min. During the reaction, a sharp singlet appeared at δ2.33 due to acetone in trifluoroacetic acid. In the vpc, the peak due to 86 diminished and the peak due to 85 increased. The reaction was quenched by pouring it into ice and saturated sodium bicarbonate solution. The mixture was extracted with ether, and the ether extract was worked up as in the rearrangement of 34 to give 75 mg (98%) of 85.

3. Saponification of 4-Trifluoroacetoxymethyl-2,5,6,6-tetramethyl-2,4-cyclohexadienone (87)

A solution of 87 (80 mg, 0.29 mmol) in 7% potassium carbonate in aqueous methanol (volume ratio of water to methanol was 2 to 7) was stirred at room temperature for 4 hrs. The mixture was poured into ice-water and extracted with ether, the combined ether extracts were washed with water, saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent gave 50 mg of 88 (96%). The residue, analyzed by vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 160°, 30 ml/min N_2), showed that all of 87 was consumed, the sole product was 88. The nmr spectrum also showed that the transformation of 87 to 88 was complete.

4. Synthesis of 5-Hydroxy-4-methylene-2,5,6,6-tetramethyl-2-cyclohexenone (84)

Compound 34 (0.5 g, 2.7 mmol) was chromatographed on aluminum oxide (Brockmann Activity, Grade 1) using methanol as the eluent, to give 0.5 g (100%) of 84 as a colorless oil. The residue was subjected to analytical vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 170°, 30 ml/min N_2). There was only one peak, corresponding to 84 (retention time 6.3 min). Preparative vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 143°, 60 ml/min He, ret. time 36 min) gave the pure hydroxy ketone 84: ir (neat) 3500 (s), 2995 (s), 1670 (s), 1458 (m), 1382 (w), 1305 (w), 1260 (w), 1200 (m), 1140 (m), 1050 (m), 1005 (m), 950 (m), 930 (m), 805 (w), 780 (m) cm^{-1}; uv (methanol) λ_{max} 223 nm (ε 4200), 270 (16,400); mass spectrum (70 eV) m/e (rel intensity) 180 (59), 165 (100), 147 (18), 137 (90), 123 (45), 119 (45), 109 (23), 107 (19), 95 (37), 91 (46), 77 (35), 67 (40), 66 (37); nmr (CCl_4) δ1.00 (s, 3 H), 1.08 (s, 3 H), 1.64 (s, 1 H), 1.72 (d, 3 H, J = 1 Hz), 5.14 (s, 1 H), 5.28 (s, 1 H), 6.96 (q, 1 H, J = 1 Hz).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.14; H, 8.92

Compound 84 could be also obtained by treating 34 with TFA for a shorter period of time (less than 30 min). Also,

subjecting to vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 120°, 60 ml/min He) gave 80% of the hydroxy ketone 84.

5. Acid-catalyzed Rearrangement of 5-Hydroxy-4-methylene-2,5,6,6-tetramethyl-2-cyclohexenone (84) in Trifluoroacetic acid

A solution of 84 (400 mg, 2.22 mmol) in 4 ml of ice cold trifluoroacetic acid was stirred at 0° for 25 min, then at room temperature for 30 min, and then was quenched and worked up as described for the rearrangement of 34 in TFA. The crude product was analyzed by vpc (10' x 0.125 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 143°, 30 ml/min N_2) and gave compounds 85, 86, 41, 38, 87, and 88 in approximately the same ratio as from 34.

6. Acid-catalyzed Rearrangement of 5-Trideuteromethyl-, 4,5-epoxy-2,4,6,6-tetramethyl-2-cyclohexenone (34*)

The experimental and workup procedures were as described for the treatment of 34 with trifluoroacetic acid. The nmr spectra of the rearrangement products: 85* had an nmr spectrum identical with that of 85 except that the signal at δ1.17 disappeared; 86* had an nmr spectrum identical with that of 86 except that signal at δ1.21 disappeared; 38* had an nmr spectrum identical with that of 38 except that signal at δ1.95 disappeared; 41* had an nmr spectrum identical with that of 41 except that the intensity of the

peak at δ1.20 was reduced from 12 H to 9 H; 87* had an nmr spectrum identical with that of 87 except that the signal at δ1.96 disappeared; 88* had an nmr spectrum identical with that of 88 except that the signal at δ1.96 disappeared; 84* had an nmr spectrum identical with that of 84 except that the signal at δ1.20 disappeared.

7. Acid-catalyzed Rearrangement of 84*

The procedure and workup were as described for the treatment of 84 with TFA, and the same products were obtained as in the rearrangement of 34* in TFA.

8. Acid-catalyzed Rearrangement of 4,5-Epoxy-2,3,4,6,6-pentamethyl-2-cyclohexenone (35)

A solution of 35 (300 mg, 1.66 mmol) in 3 ml of TFA, prepared at 0°, was allowed to stir for 40 min (monitoring by nmr) at room temperature, then poured into a cold sodium bicarbonate solution and extracted several times with ether. The combined ether extracts were washed successively with saturated sodium bicarbonate solution or 30% potassium hydroxide solution, water and saturated sodium chloride solution, and dried ($MgSO_4$). Solvent removal left 291 mg of a light yellow oil. The residue was subjected to analytical vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 150°, 30 ml/min N_2), and showed two peaks corresponding to 54 (60%, retention time

8.5 min) and 92 (40%, 16 min). Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 180°, 60 ml/min He) gave 2,3,4,6,6-pentamethyl-2-cyclohexen-1,5-dione (54): ir (neat) 3500 (w), 3010 (s), 2980 (m), 1720 (s), 1665 (s), 1640 (m), 1480 (m), 1400 (m), 1345 (m), 1180 (m), 1040 (m) cm^{-1}; uv (methanol) λ_{max} 210 nm (ε 3370, shoulder), 243 (5620); nmr ($CDCl_3$) δ1.46 (s, 6 H), 1.52 (d, 3 H, J = 8 Hz), 1.98 (br., 3 H), 2.15 (br., 3 H), 3.32 (q, 1 H, J = 8 Hz); mass spectrum (70 eV) m/e (rel intensity) 180 (55), 165 (10), 137 (18), 110 (100), 109 (20), 95 (20), 82 (25), 67 (76).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.33; H, 9.01

For 4-methylene-5-hydroxy-2,3,6,6-tetramethyl-2-cyclohexenone (92): ir (neat) 3502 (s), 3000 (s), 2960 (s), 2900 (s), 1660 (s), 1600 (m), 1480 (m), 1400 (s), 1300 (m), 1220 (m), 1125 (m), 1115 (m), 1070 (s), 923 (s) cm^{-1}; uv (methanol) λ_{max} 208 nm (ε 3680), 275 (14,430); nmr (CCl_4) δ0.81 (s, 3 H), 1.00 (s, 3 H), 1.80 (br., 3 H), 2.03 (br., 3 H), 4.03 (s, 1 H), 5.32 (s, 1 H), 5.35 (s, 1 H); mass spectrum (70 eV) m/e (rel intensity) 180 (63), 175 (23), 151 (21), 135 (100), 122 (30), 121 (30), 120 (21), 119 (45), 110 (10), 109 (25), 91 (24), 80 (35), 79 (34), 78 (28), 67 (20).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.23; H, 8.96

9. Acid-catalyzed Rearrangement of 35*

The procedure and workup procedure were as described for the treatment of 35 with TFA. The rearrangement product 92* had an nmr spectrum identical with that of 92 except that the signal at δ2.03 disappeared. The other product, 54*, had an nmr spectrum identical with that of 54 except that the signal δ2.15 was absent.

10. Acid-catalyzed Rearrangement of 4-Methylene-5-hydroxy-2,3,6,6-tetramethyl-2-cyclohexenone (92)

A. With TFA for 5 hr

A solution of 92 (0.25 g, 1.38 mmol) in 3 ml of ice-cold TFA was stirred at room temperature for 5 hr. The reaction was monitored by nmr. The nmr spectrum of 92, which remained constant with time, in neat TFA (methylene chloride as internal standard) showed peaks at δ1.24 (s, 3 H), 1.32 (s, 3 H), 1.96 (s, 3 H), 2.23 (s, 3 H), 4.46 (s, 1 H), 5.66 (s, 1 H), 5.72 (s, 1 H). The reaction mixture was quenched by pouring it into ice and saturated sodium bicarbonate solution. The product was extracted with ether, and combined ether layers were washed successively with saturated sodium bicarbonate solution, water and saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent left 0.25 g of unrearranged compound 92 (by nmr).

B. With TFA for 5 days

A solution of 92 (250 mg, 1.39 mmol) in 3 ml of TFA was stirred at room temperature for 5 days and worked up as described in (A) to leave 0.31 g of yellowish liquid. One product was the starting material (40%), and the other product, which was analyzed by preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 190°, 60 ml/min He), gave trifluoroacetyl derivative 96 (ret time 23 min): ir (CCl_4) 3000 (m), 1780 (s), 1679 (s), 1600 (w), 1480 (w), 1400 (w), 1240 (s), 1180 (s), 1160 (s), 1040 (w) cm^{-1}; uv (methanol) λ_{max} 210 nm (ε 7200), 272 (16,200); nmr (CCl_4) see structure; the peaks at δ1.89 (3 H) and 2.04 (3 H) showed homoallylic coupling, whereas the other methyl groups were singlets at δ1.09 and 1.12. There were also three vinyl hydrogens at δ5.39, 5.34 and 5.43; mass spectrum (70 eV) m/e (rel intensity) 276 (38), 171 (25), 163 (100), 147 (40), 135 (59), 134 (34), 128 (30), 119 (78), 112 (30), 107 (28), 105 (45), 91 (55).

Anal. Calcd for $C_{13}H_{15}O_3F_3$: C, 56.65; H, 5.47

Found: C, 56.61; H, 5.56

C. With 80% H_2SO_4 or D_2SO_4

About 0.5 ml of CCl_4 containing 40 mg of 92 was placed in an nmr tube. Under a nitrogen atmosphere, 1 ml of 80% D_2SO_4 (or H_2SO_4) was added. The contents were then mixed using a "supermixer" (Matheson Scientific, No. 601-0005)

to give a brownish yellow solution of 92 and then the CCl_4 was removed by a pipette. In another experiment, neat 92 (40 mg) was placed in an nmr tube, and 1 ml of 80% D_2SO_4 was added under a nitrogen atmosphere. The contents were mixed. In each case, the nmr spectrum (for 80% H_2SO_4 using CH_2Cl_2 as internal standard and 80% D_2SO_4 using $(CH_3)_4N^+BF_4^-$ as internal standard) showed peaks at δ1.32 (s, 6 H), 2.00 (s, 3 H), 2.32 (s, 3 H), 4.52 (s, 1 H), 5.76 (s, 1 H), 5.91 (s, 1 H). The mixture was poured into ice cold saturated sodium bicarbonate solution and extracted with ether. Workup as in (A) gave 40 mg of unreacted 92.

D. With Concentrated D_2SO_4

The procedure and workup were as described in (C). The nmr spectrum of carbocation [$(CH_3)_4N^+BF_4^-$ as internal standard] showed δ1.74 (s, 6 H), 2.37 (s, 3 H), 5.33 (s, 1 H), 7.40 (s, 1 H), 7.63 (s, 1 H). The mixture was quenched by pouring into ice water and the starting material 92 was recovered.

11. Acid-catalyzed Rearrangement of 92*

The procedure and workup were as described for the treatment of 92 with TFA. The nmr spectrum of the carbocation 92* was identical with that of 92 except that the signal at δ2.03 had disappeared. On prolonged treatment

of 92* (over 5 days) the ester 96* was formed; it had an nmr spectrum identical with that of 96 except that the signal at δ2.04 had disappeared.

12. Saponification of Trifluoroacetyl Derivative 96

Compound 96 (380 mg, 1.38 mmol) was hydrolyzed by stirring it with 14 ml of a 7% solution of potassium carbonate in methanol for 4 hr. The reaction mixture was poured into water and the organic product was extracted with ether. The combined ether layers were washed successively with water, saturated sodium chloride solution and then dried ($MgSO_4$). Evaporation of solvent left 240 mg of a light yellow liquid whose nmr and ir spectra were identical with those of 92.

13. Saponification of 96*

The procedure and workup were as described for treatment of 96 with aqueous methanol. The product had an nmr spectrum identical with that compound 92*.

14. Acid-catalyzed Rearrangement of 4,5-Epoxy-6,6-dimethylcyclohexen-2-one (36) in Hydrochloric Acid

A solution of 100 mg of 36 in 5 ml of ether was shaken with 5 ml of 3% hydrochloric acid, and left at room temperature for 4 hr. The ether layer was then washed with

aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated the solvent to give 123 mg (98%) of 97. Analytical vpc (5' x 0.125 in column, 5% FFAP on chromosorb W, AW-DMCS 80/100, 156°, 30 ml/min N_2) showed one peak with a retention time of 3.5 min. Preparative vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 150°, 60 ml/min He, ret time 20 min) gave only one pure product, trans-4-chloro-5-hydroxy-6,6-dimethyl-cyclohexen-2-one (97): ir (neat) 3100-3800 (br.), 3010 (m), 2950 (m), 1685 (s), 1480 (m), 1380 (w), 1360 (w), 1300 (m), 1260 (w), 1220 (w), 1185 (w), 1140 (m), 1100 (s), 1070 (s), 1010 (w), 1000 (w), 875 (s), 840 (s), 800 (s) cm^{-1}; uv (methanol) λ_{max} 240 nm (ε 1500); nmr (CCl_4) δ1.00 (s, 3 H), 1.20 (s, 3 H), 3.65 (d, 1 H, J = 8 Hz), 4.57 (m, 1 H), 5.80 (m, 1 H), 6.60 (m, 1 H); mass spectrum (70 eV) m/e (rel intensity) 176 (6), 175 (2), 174 (18), 139 (7), 122 (11), 104 (29), 102 (85), 95 (10), 91 (10), 79 (20), 77 (18), 72 (100), 70 (15).

Anal. Calcd for $C_8H_{11}O_2Cl$: C, 55.17; H, 6.32
Found: C, 55.06; H, 6.32

15. Acid-catalyzed Rearrangement of 36 in Hydrogen Chloride

Compound 36 (100 mg, 0.72 mmol) in 3 ml ether was placed in a 25-ml flask and cooled to 0° in an ice bath. Hydrogen chloride gas was passed slowly into the ether solution for 30 min. The solution was washed with aqueous sodium

bicarbonate and dried ($MgSO_4$), and evaporated to give 120 mg (95%) of 97.

16. Acid-catalyzed Rearrangement of 36 in Trifluoroacetic Acid

A solution containing 100 mg of 36 in 2 ml of carbon tetrachloride was added to 8 ml of TFA under nitrogen. The mixture was stirred at room temperature and the reaction was monitored by nmr. It was complete in a half hour. The mixture was quenched with cold saturated sodium bicarbonate solution and extracted several times with ether. The combined ether extracts were washed successively with saturated sodium bicarbonate solution, water and saturated sodium chloride, and dried ($MgSO_4$). After solvent removal there remained 120 mg (95%) of a light yellow oil. The crude product was subjected to vpc (5' x 0.125 in column, 5% FFAP chromosorb W, AW-DMCS 80/100, 155°, 30 ml/min N_2). There was one peak, with a retention time of 3.5 min. Preparative vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 150°, 60 ml/min He, ret time 11 min) gave pure hydroxy trifluoroacetate 98: ir (neat) 3010-3800 (br.), 3000 (w), 2950 (w), 1780 (s), 1680 (s), 1475 (w), 1400 (m), 1380 (m), 1230 (m), 1160 (m), 1080 (w), 960 (m) cm^{-1}; uv (methanol) λ_{max} 240 nm (ε 2900); nmr (CCl_4) δ1.03 (s, 6 H), 1.66 (br. 1 H), 2.61 (s, 1 H), 3.83 (d, 1 H, J = 8 Hz), 4.40-5.20 (m, 1 H), 5.40-6.04 (m, 1 H), 6.40-6.60 (m, 1 H); mass spectrum

(70 eV) m/e (rel intensity) 252 (4), 225 (2), 196 (2), 180 (9), 156 (6), 138 (31), 122 (9), 109 (21), 95 (19), 93 (12), 91 (10), 86 (23), 85 (34), 84 (100), 83 (33), 82 (30), 72 (90), 68 (57).

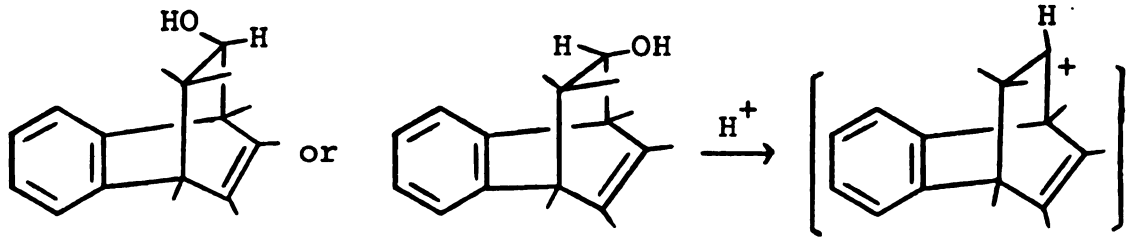
Anal. Calcd for $C_{10}H_{11}O_4F_3$: C, 47.63; H, 4.40

Found: C, 47.82; H, 4.36

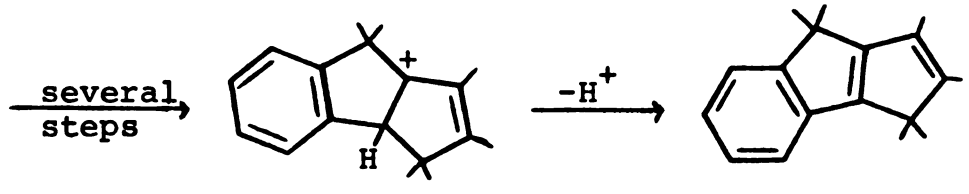
PART III

DIELS-ALDER REACTIONS OF A DIHYDROBENZOPENTALENE AND THE SYNTHESIS OF HIGHLY-STRAINED QUADRICYCLANES

An unexpected, profound, but facile rearrangement of a highly methyl-substituted bicyclo[2.2.2]-2-octyl system was reported by Hart. Either of the epimeric alcohols 99 or 100 rearranged on dehydration with strong acid to the benzodihydropentalene 103.[52,53]



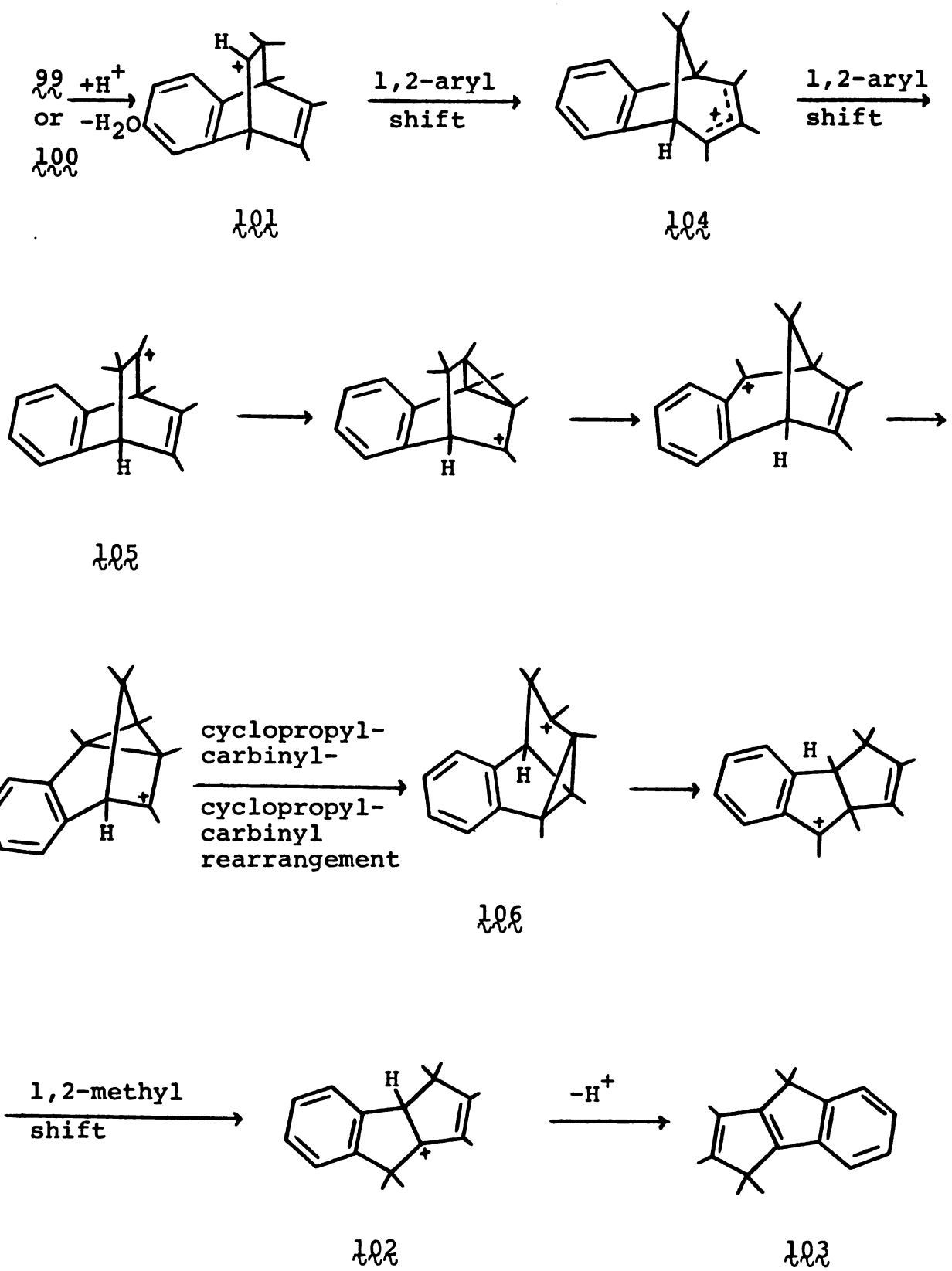
99 100 101



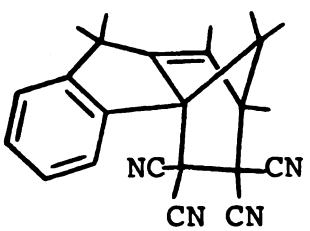
102 103

A plausible mechanism analogous to those postulated for the rearrangement of other bicyclo[3.2.1]octadienyl cations is shown in Scheme 28. The key step is a cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement.[54-57]

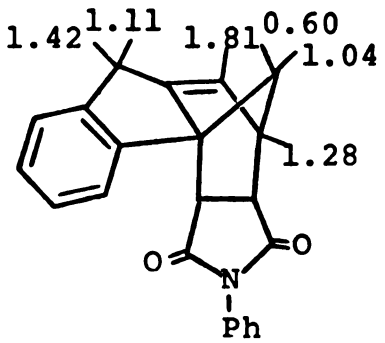
Scheme 28


99
or
100
+H+
-H2O
1,2-aryl
shift
1,2-aryl
shift
101
104
105
cyclopropyl-
carbinyl-
cyclopropyl-
carbinyl
rearrangement
106
1,2-methyl
shift
-H+
102
103

The structure of 103 was deduced from its spectral properties and chemical transformations. Compound 103 is hydrogenated preferentially at the central double bond, and forms Diels-Alder adducts 107 and 108 with tetracyanoethylene and N-phenylmaleimide, respectively.



107



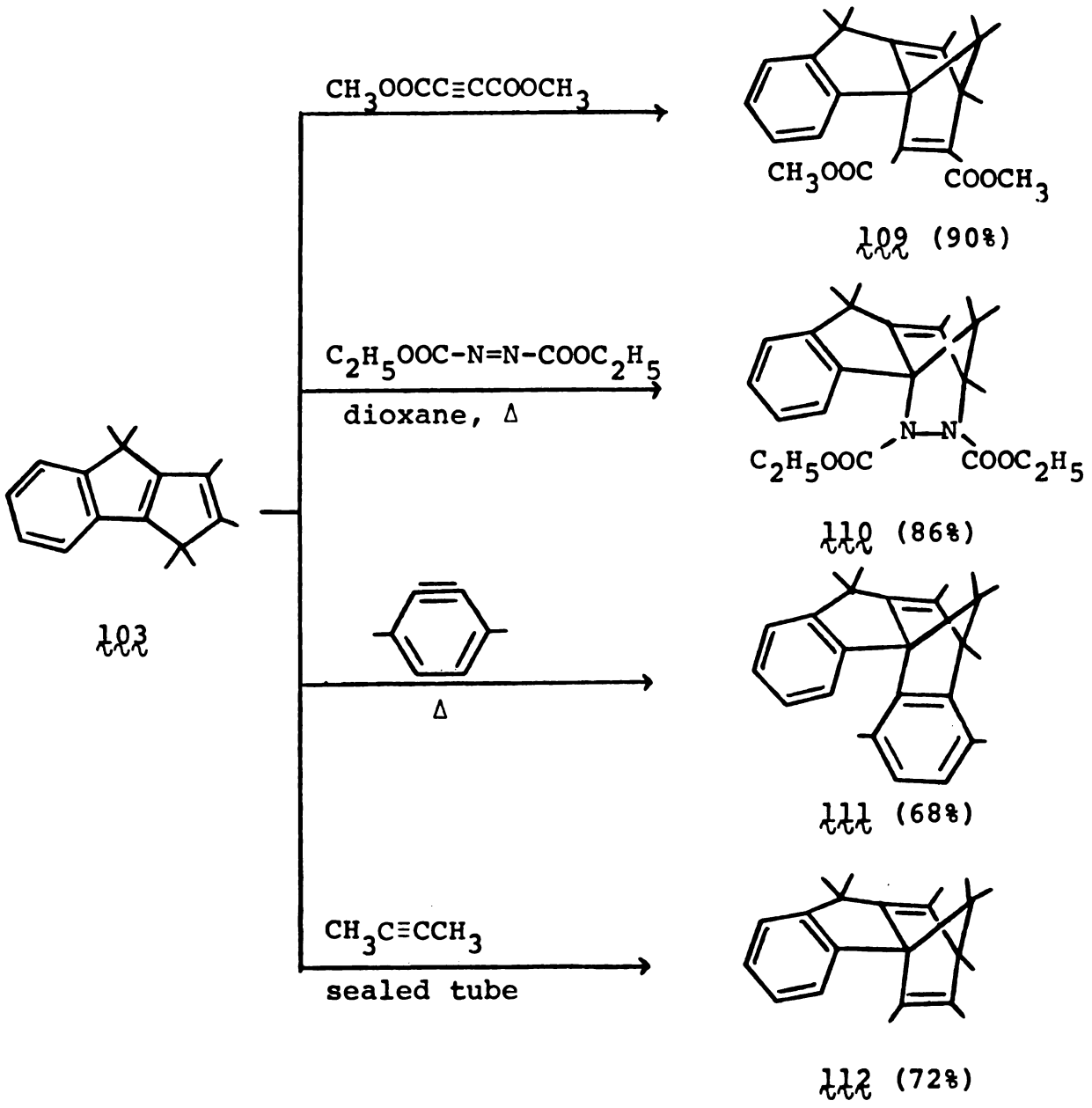
108

It was of interest to further explore the reactions of 103, and in particular to study its reactions with acetylenic dienophiles to see if strained norbornadienes could be formed in this way (bridged from C-1 to C-2 by three carbon atoms), and if so, whether they could be converted to quadricyclanes on irradiation. Results of this study form Part III of the thesis.

RESULTS AND DISCUSSION

1. Structures of the Diels-Alder Adducts

The highly substituted benzodihydropentalene 103 gave Diels-Alder adducts with dimethyl acetylenedicarboxylate,[58] diethyl azodicarboxylate,[59] 3,6-dimethylbenzene,[60] and 2-butyne.[54]



103

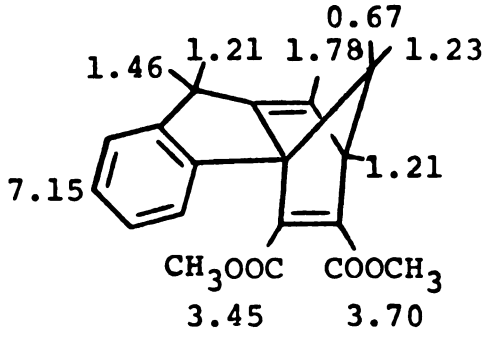
109 (90%)

110 (86%)

111 (68%)

112 (72%)

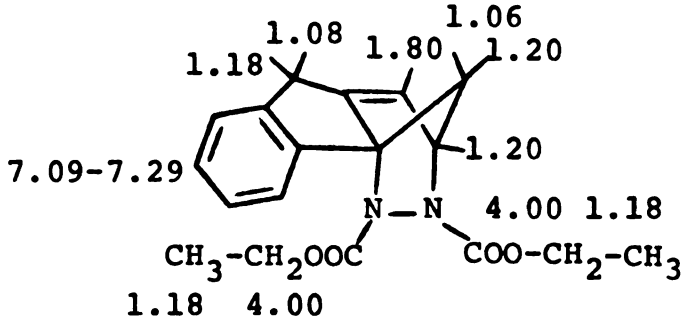
Compound 109 was assigned the structure shown:



109

The molecular formula $C_{24}H_{28}O_4$ was confirmed by the mass spectrum (parent peak m/e 380) and elemental analysis. The ir spectrum of 109 showed carbonyl absorption at 1703 cm^{-1}, consistent with the presence of α,β-unsaturated ester groups. Compound 109 had a simple benzenoid uv spectrum. The nmr spectrum showed four aliphatic methyl singlets, one allylic methyl singlet, two methoxyl singlets and four aromatic protons. The nmr assignment is based on model compound 108 and chemical transformations.

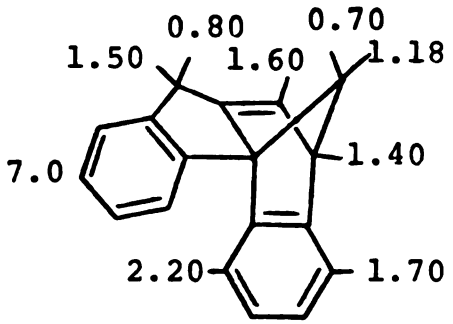
Compound 110 was assigned the structure shown:



110

The molecular formula $C_{24}H_{32}N_2O_4$ was confirmed by the mass spectrum (parent peak m/e 412) and elemental analysis. The ir spectrum of 110 showed a broad, strong carbonyl absorption peak between 1690-1740 cm^{-1} and the uv spectrum showed only a benzenoid chromophore. The nmr spectrum showed four aliphatic methyl singlets, one allylic methyl singlet, four aromatic protons as multiplet as well as methyl triplets, and methylene quartets for the ethyl groups. The nmr assignment is based on model compound 108.

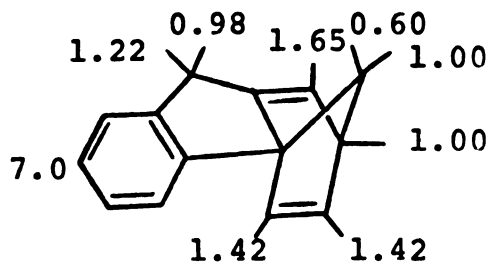
Compound 111 was assigned the structure shown:



111

The mass spectrum showed a parent peak at m/e 342. The uv spectrum showed a benzenoid chromophore. The nmr spectrum showed five aliphatic methyl singlets and three allylic or aromatic methyl singlets. The nmr assignment is based on model compound 108.

Compound 112 was assigned the structure shown.

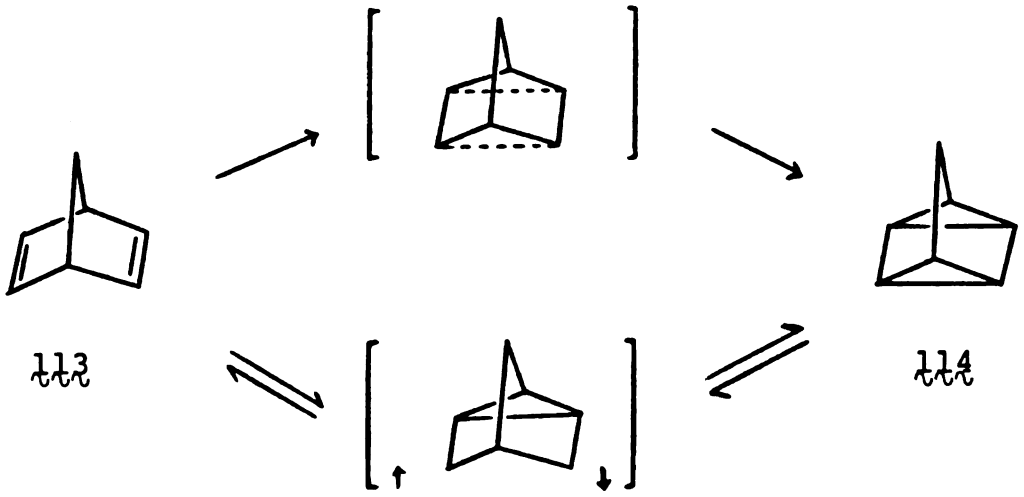


112

The molecular formula $C_{22}H_{28}$ was confirmed by the mass spectrum (parent peak m/e 292) and elemental analysis. The uv spectrum showed a simple benzenoid chromophore. The nmr spectrum showed five aliphatic methyl singlets, two allylic methyl singlets and four aromatic protons. The nmr assignment was also based on the model compound 108.

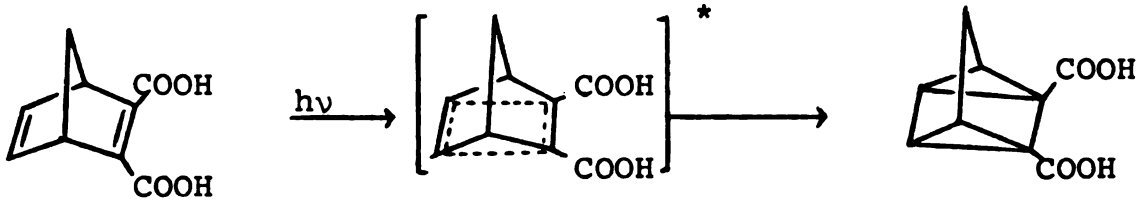
2. Quadricyclane Synthesis[61]

The well-known photoisomerization of norbornadienes to quadricyclanes was originally reported by Cristol and Snell.[62] This intramolecular cycloaddition reaction (113 → 114) has been studied in detail. The conversion 113 → 114 can be accomplished either by direct or sensitized excitation. The photoproduct 114 is surprisingly stable thermally ($t_{1/2}$ = 14 hr at 140°), the $2\sigma \rightarrow 2\pi$ opening 114 → 113 being "forbidden" by the Woodward-Hoffmann rules. The rate of reaction 114 → 113 is dramatically

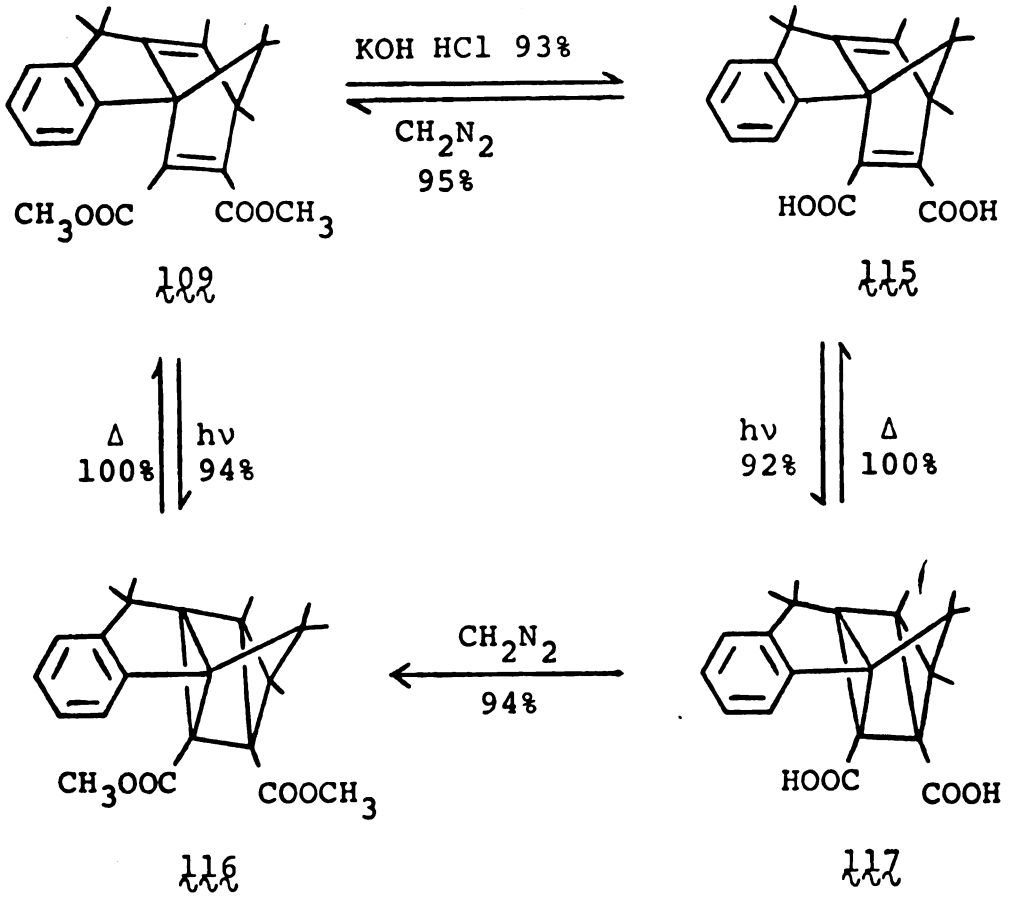


113 114

increased ($t_{1/2}$ = 45 min at -26°) by coordination with a metal, making the isomerization an "allowed" process. The bicycloheptadiene carboxylic acid[62] has been converted to the quadricyclane isomer without a sensitizer.

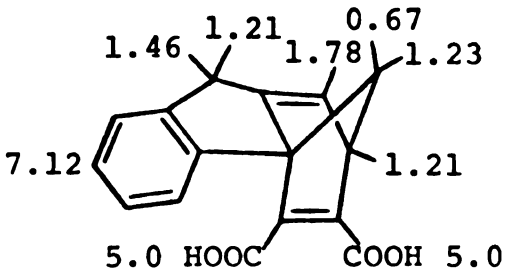


Although numerous publications have been devoted to this one-step synthesis of quadricyclane derivatives, relatively little is known about the synthesis of related highly strained and substituted systems.



The synthesis of 117 originated with 109. Saponification of 109 yielded the di-acid 115. The structure of 115 was substantiated in several ways. Esterification of 115 with diazomethane proceeded smoothly to give back 109. Photoisomerization of 115 gave a quadricyclane diacid 117.

Compound 115 was assigned the structure shown. The molecular formula $C_{22}H_{24}O_4$ was confirmed by the mass spectrum (parent peak m/e 352) and elemental analysis. The ir spectrum of 115 showed carbonyl absorptions at

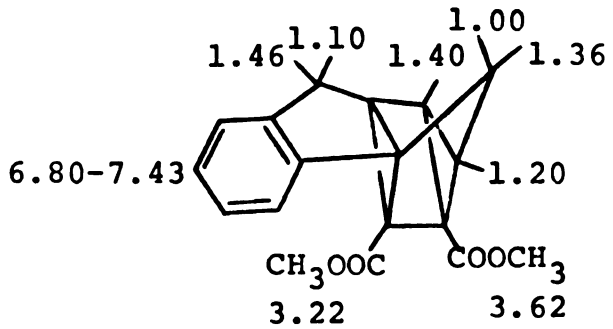


115

1690 and 1682 cm^{-1} which are consistent with the presence of α,β-unsaturated acid groups. The uv spectrum showed a simple benzenoid chromophore. The nmr spectrum showed five aliphatic methyl singlets, one allylic methyl singlet, four aromatic protons as a multiplet, and two carboxylic acid protons.

Irradiation of an ether solution of compound 109 through vycor gave a good conversion to 116. The photolysis product was more stable thermally than similar previously reported quadricyclane derivatives.

Although 116 is stable at room temperature, it slowly reverts to the starting diene 109 at a higher temperature. At 170°, the half-life of the isomerization is 30 min. The quadricyclane could be recrystallized from cyclohexane without thermal isomerization. Compound 116 was assigned the structure shown. The molecular formula $C_{24}H_{28}O_4$ was confirmed by the mass spectrum and elemental analysis. The ir spectrum showed a carbonyl absorption at 1700 cm^{-1}. The uv spectrum showed the benzenoid chromophore. The nmr

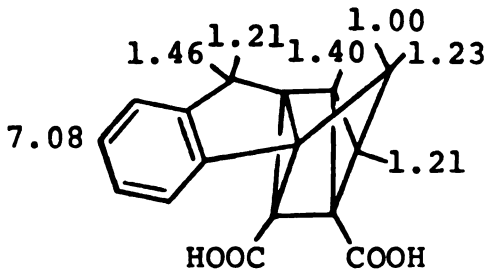


116

spectrum showed six aliphatic methyl singlets and two methoxy singlets.

Irradiation of an ether solution of 115 through vycor filter gave a good conversion to 117. The photolysis product was less stable thermally than ester 116. Compound 117 slowly reverts to the starting diene 115 at room temperature, the half-life of the isomerization being about one month. At 89°, the half-life of the isomerization is 30 min.

The structure of 117 was proved by spectral properties and chemical transformation. Upon treatment with diazomethane, compound 117 was converted to 116 in nearly quantitative yield. The molecular formula $C_{22}H_{24}O_4$ was confirmed by its mass spectrum (parent peak m/e 352) and elemental analysis. The ir spectrum of 117 showed carbonyl absorption at 1700 cm^{-1}. The uv spectrum showed a simple benzenoid chromophore. The nmr spectrum showed six



117

aliphatic methyl singlets.

The cycle of photochemical and thermal isomerizations clearly establishes the structural relationships between the four compounds.

In summary, highly strained dihydropentalene 103 underwent Diels-Alder reactions with tetracyanoethylene, N-phenylmaleimide, dimethyl acetylenedicarboxylate, diethyl azodicarboxylate, 1,4-dimethylbenzene and 2-butyne easily.

Structural distortions of the basic skeleton caused by substitution have practically no influence on the results of the photochemical reaction. Highly strained norbornadiene derivatives substituted by several large groups such as 109 and 115 are still very effectively converted to the tetracyclic systems.

EXPERIMENTAL

1. Diels-Alder Adducts of the Dihydrobenzopentalene (103)

A. With Dimethyl Acetylenedicarboxylate

To a solution of 2.4 g (0.01 mol) of dihydropentalene 103 in 50 ml of xylene was added 1.4 g (0.01 mol) of dimethyl acetylenedicarboxylate. The mixture was allowed to stand for 10 hr, then cooled and evaporated. The crystalline solid was filtered and recrystallized from ethanol to give 3.39 g (90%) of 109 as a white solid, mp 106-107°; ir (Nujol) 2900 (s), 1703 (br, s), 1603 (s), 1406 (s), 1380 (s), 1340 (w), 1300 (w), 1280 (w), 1230 (m), 1140 (m), 1080 (m), 1050 (w), 1000 (w), 950 (w), 900 (w), 850 (m) cm^{-1}; uv (ethanol) λ_{max} 228 nm (ε 15,850), 250 (5900); nmr ($CDCl_3$) δ0.67 (s, 3 H), 1.21 (s, 6 H), 1.23 (s, 3 H), 1.46 (s, 3 H), 1.78 (s, 3 H). 3.45 (s, 3 H), 3.70 (s, 3 H), 7.15 (m, 4 H); mass spectrum (70 eV) m/e (rel intensity) 380 (4), 365 (43), 349 (4), 333 (100), 307 (39), 289 (56), 274 (14), 259 (18), 231 (6), 215 (4), 202 (4), 191 (4), 178 (6), 159 (6), 73 (18).

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42
Found: C, 75.63; H, 7.27

B. With Diethyl Azodicarboxylate

The dihydrobenzopentalene 103 (0.5 g) in 10 ml of dioxane was refluxed with 0.34 g of diethyl azodicarboxylate for 35 hr. The solution was evaporated to an oil which crystallized on chilling. The crude product was recrystallized from cyclohexane to yield 0.66 g (85%) of 110 as a pale yellowish solid, mp 106-107°. The adduct had the following characteristics: ir (Nujol) 3300 (s), 2950 (s), 1690-1740 (br, s), 1610 (m), 1595 (w), 1520 (m), 1480 (s), 1380 (s), 1320 (s), 1220 (s), 1180 (w), 1110 (m), 1080 (s), 1002 (w), 890 (s), 880 (s) cm^{-1}; uv (ethanol) λ_{max} 210 nm (ε 10,730), 220 (10,000), 228 (11,000), 236 (13,200), 244 (11,800), 310 (18,200); nmr ($CDCl_4$) δ1.06 (s, 3 H), 1.08 (s, 3 H), 1.18 (t, 6 H), 1.20 (s, 6 H), 1.80 (s, 6 H), 4.00 (q, 4 H), 7.09-7.29 (m, 4 H); mass spectrum (70 eV) m/e (rel intensity) 412 (52), 397 (3), 367 (2), 339 (5), 324 (7), 309 (5), 293 (7), 279 (5), 253 (9), 236 (100), 221 (82), 208 (27), 207 (69), 195 (22), 194 (23), 193 (22), 192 (17), 178 (20), 165 (22), 128 (10), 118 (13), 116 (15), 104 (8), 86 (12), 71 (10).

Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79
Found: C, 69.88; H, 7.69; N, 6.77

C. With 3,6-Dimethylbenzyne

3,6-Dimethylbenzyne was generated by Friedman's method. A mixture of 0.734 g (3.5 mmol) of 3,6-dimethylbenzene-

diazonium carboxylate hydrochloride 0.83 g (3.5 mmol) of dihydropentalene 103 and 0.8 ml of propylene oxide which was added last, in 10 ml of ethylene chloride was warmed up gradually while stirring was continued. As gas evolution started, the temperature was controlled so that no vigorous foaming took place. Ten minutes after gas formation started, the solution became clear and it was heated at reflux for one hr. Removal of solvent from the reaction mixture left a brown liquid which was redissolved in ether and the ethereal solution was washed with dilute aqueous sodium hydroxide three times then with water two times and was dried ($MgSO_4$). Evaporation of the solvent yielded a yellow oil 111 (68%). Purification was effected by preparative vpc (5' x 0.25 in column, 3% SE-30 on chromosorb W, AW-DMCS 80/100, 195°, 60 ml/min He, ret time 7 min). Ir (CCl_4) 2890 (s), 1480 (w), 1450 (s), 1380 (m), 1360 (m), 1305 (w), 1290 (w), 1120 (m), 1095 (m), 1030 (w), 1020 (w), 940 (w), 800 (m), 760 (m), 680 (m) cm^{-1}; uv (cyclohexane) λ_{max} 225 nm (ε 1800); nmr ($CDCl_3$), see structure; mass spectrum (70 eV) m/e (rel intensity) 342 (31), 328 (10), 327 (39), 312 (10), 300 (30), 299 (100), 298 (15), 285 (24), 284 (22), 282 (12), 271 (30), 270 (15), 267 (20), 257 (22), 253 (18), 252 (16), 243 (17), 239 (23), 228 (11), 171 (35), 164 (20), 156 (32), 141 (34), 133 (50), 126 (42), 114 (15), 101 (10), 89 (10).

D. With 2-Butyne

A solution of 0.5 g of dihydropentalene 103 in three times its volume of 2-butyne was heated in a sealed tube at 200° for four and a half days. Evaporation of the volatiles left a residue which was purified through preparative vpc (5' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 150°, 60 ml/min He, ret time 25 min) to give pure 112 (72%) as a colorless liquid: ir (neat) 2992 (s), 1620 (w), 1598 (w), 1434 (s), 1380 (s), 1360 (m), 1280 (m), 1260 (w), 1120 (w), 1080 (w), 1029 (m), 1000 (w), 970 (w), 880 (m), 675 (s) cm^{-1}; uv (ethanol) λ_{max} 290 nm (ε 3240); nmr (CCl_4), see structure; mass spectrum (70 eV) m/e (rel intensity) 292 (100), 277 (63), 262 (10), 249 (30), 235 (50), 221 (44), 207 (40), 193 (25), 171 (20), 165 (20), 157 (20), 141 (20), 129 (29), 121 (20), 115 (20).

Anal. Calcd for $C_{22}H_{28}$: C, 90.35; H, 9.65

Found: C, 90.57; H, 9.74

2. Saponification of the Diels-Alder Adduct 109

Typically, the ester 109 (0.8 g, 2.2 mmol) was saponified by refluxing for 8 hr with 47 ml of 8% ethanolic potassium hydroxide solution. The mixture was then poured into 50 ml of water to dissolve the salt residue. Upon acidification of the alkaline solution with 25% dilute hydrochloric acid, 0.245 g (94%) of the acid 115 was obtained. Recrystallization from cyclohexane gave product

melting at 242-243°; ir (Nujol) 2900 (s), 2650 (w), 2550 (w), 1690 (s), 1682 (s), 1620 (w), 1480 (s), 1420 (m), 1380 (m), 1300 (m), 1220 (w), 1160 (m), 1120 (w), 1020 (w), 940 (m), 780 (m) cm^{-1}; uv (ethanol) λ_{max} 215 nm (ε 14,150), 250 (4580); nmr ($CDCl_3$), see structure; mass spectrum (70 eV) m/e (rel intensity) 352 (1), 337 (19), 334 (48), 319 (100), 293 (92), 275 (41), 260 (10), 247 (17), 232 (12), 215 (24), 202 (24), 189 (21), 178 (20), 165 (18), 99 (30), 84 (41).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.97; H, 6.86

Found: C, 75.12; H, 7.19

3. Photoisomerization of Diene Diacid 115 to Quadricyclane Diacid 117

A solution containing 0.354 g (1 mmol) of 115 in 130 ml of ether was degassed and irradiated through a vycor filter (Hanovia 450-W lamp). After one and one-half hr, the ether was removed in vacuo to leave yellow crystals (92%) which nmr showed to be mainly one product. The solid was recrystallized from a mixture of carbon tetrachloride-cyclohexane. Ir (Nujol) 2890 (s), 2630 (w), 2580 (w), 1700 (s) 1680 (s), 1600 (m), 1450 (s), 1382 (s), 1300 (m), 1150 (m), 1005 (w), 920 (w), 750 (m) cm^{-1}; uv (ethanol) λ_{max} 217 nm (ε 18,300), 249 (9800); nmr ($CDCl_3$), see structure; mass spectrum (70 eV) m/e (rel intensity) 352 (1), 337 (5), 334 (20), 319 (100), 293 (99), 260 (45), 247 (54), 232

(62), 215 (25), 202 (24), 189 (15), 178 (20), 165 (16).

Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86

Found: C, 75.12; H, 7.10

The quadricyclane diacid 117 did not have a definite melting point. The solid begins to soften at 86°, the exact temperature depending upon the rate of heating. This mp behavior is in striking contrast with the diene diacid 115 which melts at 242-243°.

4. Photoisomerization of Diene Diester 109 to Quadricyclane Dicarboxylate 116

A solution containing 0.358 g (1 mmol) of diester 109 in 130 ml of ether was degassed and irradiated through a vycor filter. After two and one-half hr, the ether was removed in vacuo to leave yellow crystals (94%). An nmr spectrum showed only one product and the solid was recrystallized from cyclohexane and acetone. Ir (Nujol) 2900 (s), 1720 (s), 1700 (s), 1460 (s), 1380 (s), 1300 (w), 1200 (w), 1180 (w), 1120 (w), 1040 (m), 940 (m) cm^{-1}; uv (ethanol) λ_{max} 234 nm (ε 19,700), 268 (5830), 275 (4850); nmr ($CDCl_3$), see structure; mass spectrum (70 eV) m/e (rel intensity) 380 (6), 365 (7), 349 (6), 333 (67), 321 (57), 307 (100), 289 (58), 274 (47), 261 (30), 247 (59), 231 (50), 233 (25), 215 (45), 202 (38), 189 (37), 178 (43), 165 (26).

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42

Found: C, 75.74; H, 7.43

5. Isomerization of Quadricyclane Diacid 117 to Diene Diacid 115

Twenty-five milligrams of 117 dissolved in 1 ml of carbon tetrachloride was heated at reflux in a sealed nmr tube in an oil bath at 89°. The reaction was followed by nmr. As peaks due to 117 decreased in intensity, a new set of peaks corresponding to 115 appeared. After 1 hr, the peaks of 115 were fully developed. The nmr and ir spectra of residue were identical with those of an authentic sample prepared by saponification of 109.

6. Isomerization of Quadricyclane Diester 116 to Diene Diester 109

Twenty-five milligrams of 116 dissolved in 1 ml of carbon tetrachloride was heated at reflux in a sealed nmr tube in an oil bath at 170°. The reaction was followed by nmr. After 1 hr, the reaction was complete. The nmr and ir spectra of residue were identical with those of authentic sample 109.

7. Esterification of Quadricyclane Diacid 117 to Quadricyclane Diester 116

Treatment of the quadricyclane diacid 117 with diazomethane gave the dimethyl ester in excellent yield. A typical preparation is described. To a 100-ml Erlenmeyer

flask cooled in an ice bath and containing 1.76 g (5 mmol) of 117 dissolved in 45 ml of absolute methyl alcohol was added an ethereal solution of diazomethane in small portions until gas evolution ceased and the solution acquired a pale yellow color. The solvent and excess reagent were evaporated and the residue was recrystallized from cyclohexane and acetone to give 1.80 g (94%) of white crystals. The nmr and ir spectra were identical with those of authentic sample of 116.

8. Esterification of Diene Diacid 115 to Diene Diester 109

The same procedure used to convert 116 to 117 was followed for 115, to give 109 in 95% yield. The nmr and ir spectra were identical with those of authentic sample 109.

PART IV

MISCELLANEOUS

(1) A NEW ALKYLATION REAGENT - HIGH SURFACE SODIUM

(2) SYNTHESIS OF POTENTIAL CARCINOGENIC DIEPOXIDES

(3) THE EFFECT OF METHYL GROUPS AT A BRIDGE-HEAD POSITION ON THE COMPETING CARBONIUM ION REARRANGEMENT OF THE BICYCLO[3.2.1]OCTA-3,6-DIEN-2-YL SYSTEM

(4) ALKYLATION STUDIES WITH 4-METHYLENE-2,3,5-TRIMETHYL -2-CYCLOPENTENONE

(1) A NEW ALKYLATION REAGENT - HIGH SURFACE SODIUM

INTRODUCTION

The term High Surface Sodium (HSS)[63] is applied to films of sodium approaching colloidal dimensions, spread over inert solids of high surface area. Sodium in this form is advantageous for the preparation of finely divided metals, for the purification of hydrocarbons and ethers, and for the preparation of inorganic and organic sodium derivatives. In this part of the thesis, the use of HSS to generate ketone enolates which can then be alkylated is described.

The ease and simplicity of generating HSS make it desirable to prepare the sodium in this form at the point of use. Although it seems likely that conditions could be developed for storing HSS without appreciable loss of activity, this has not yet been done.

The preparation of HSS is accomplished simply by mixing molten sodium with suitable inert solid materials having very large surface areas. Many substances may be used as sodium carriers, e.g., salt, carbon, ceramic materials like aluminum oxide. At a temperature above its melting point (97.5°), sodium spontaneously coats the solid materials.

The effective surface area of the solid carrier determines the amount of sodium which can be absorbed. Salt

may carry 2 to 10% sodium; soda ash, 10% sodium; alumina, 20 to 25% sodium; and activated or colloidal carbons over 30% sodium. Within these concentrations a free flowing solid is obtained, whereas above these concentrations the mixture becomes a pasty mass. This free flowing characteristic can be maintained at a temperature up to the boiling point of sodium (883°C) depending, of course, on the temperature stability of the carrier. This important feature permits HSS to be handled in fluidized and other moving solid systems.

Typical Applications of High Surface Sodium

1. Reduction of Metal Salts and Oxides to Colloidal Metals.

Many metal salts and oxides react with sodium adsorbed on an inert carrier smoothly, rapidly and at relatively low temperatures. The metals produced are of colloidal dimensions, hence, extremely reactive. They are usually pyrophoric when exposed to the air. Metal compounds which have been reduced by HSS systems include nickel chloride, copper chloride, lead chloride, chloroplatinic acid, silicon tetrachloride, titanium tetrachloride, zirconium tetrachloride, iron oxide, zinc oxide and metal soaps such as nickel oleate.

2. Preparation of Catalysts for Hydrogenation.

Nickel and platinum catalysts prepared by HSS techniques are comparable with Raney Nickel and Adams platinum catalyst in the hardening of olive oil. The result shows that finely divided nickel prepared by HSS reduction of nickel oleate produced faster hardening of olive oil than either Raney Nickel or nickel catalyst produced by thermal decomposition of the nickel formate.

3. Reduction of Metal Oxides.

Zinc oxide, iron oxide, copper oxide, nickel oxide are reducible by sodium.

4. Hydrocarbon Refining

The reduction of sulfur in certain petroleum naphthas to less than 0.001% were made by HSS.

5. Ether Refining.

HSS is especially effective in removing water, alcohols, acids, aldehydes, ketones, and peroxides quantitatively from ethers. Diethyl ether, 1,2-diethoxyethane, and tetrahydrofuran have been purified in the vapor phase over HSS on soda ash.

6. Formation of Sodium Hydride.

Sodium hydride with a particle size below 10 microns can be conveniently prepared in *situ* from HSS and hydrogen.

7. Preparation of Organosodium Derivatives.

Many important sodium derivatives, difficult to prepare by classic methods, have been made commercially feasible through the use of sodium dispersions. For example, sodium in this form has proven useful in metalation reactions, Claisen condensation, Wurtz type reaction, reductions, catalytical polymerization and the preparation of alcohol-free aldoxides. Compounds more specifically illustrating the versatility of sodium dispersions are phenylsodium, amylsodium, sodium anilide, sodioacetoacetic ester and sodio-malonic ester.

8. Isomerization

High surface sodium is effective for isomerization of alkenes. In contrast to acid-catalyzed isomerizations, no skeletal rearrangements occur. The results indicate some stereo-selectivity. Thus 1-butene is isomerized initially to about equal amounts of *cis*- and *trans*-2-butene; eventually the thermodynamic equilibrium mixture rich in the *trans*-isomer is obtained. The catalyst was used to effect almost quantitative conversion of methylenecyclo-butane to 1-methylcyclobutene.

RESULTS AND DISCUSSION

The application of HSS in organic synthesis was limited to the alkylation of ketones. Such alkylations, when carried out in solution using conventional strong bases, often suffer from low to modest yields, lack of regiospecificity, considerable dialkylation and other problems which clearly limit synthetic utility. It was the hope that the reaction would be regiospecific and limited to monoalkylation using HSS, where the reactions might occur on a surface instead of in solution.

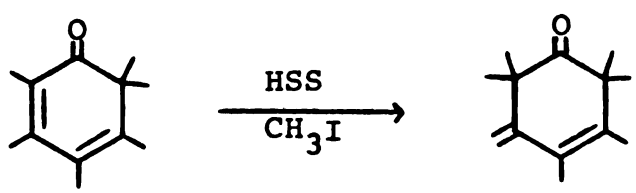
HSS can be prepared[66] readily in glass equipment employing a rugged sweep-type stirrer. This apparatus has proved satisfactory for a wide variety of preparations. A typical procedure for the preparation of 20% sodium on charcoal is illustrated below:

1. Place 2.8 g of dry charcoal in the reaction flask and displace the air with dry nitrogen. Adjust the stirrer speed to 100-300 RPM for expanding the charcoal to approximately twice its settled volumn, and heat the flask contents to about 125°.
2. Add 0.69 g of sodium in 5 to 50 mg pieces through the charging port. As soon as the sodium has melted, stir somewhat more rapidly for about 5 min, then cool to room temperature.
3. Check the reactivity of the HSS by exposing a small sample to air. HSS on charcoal become

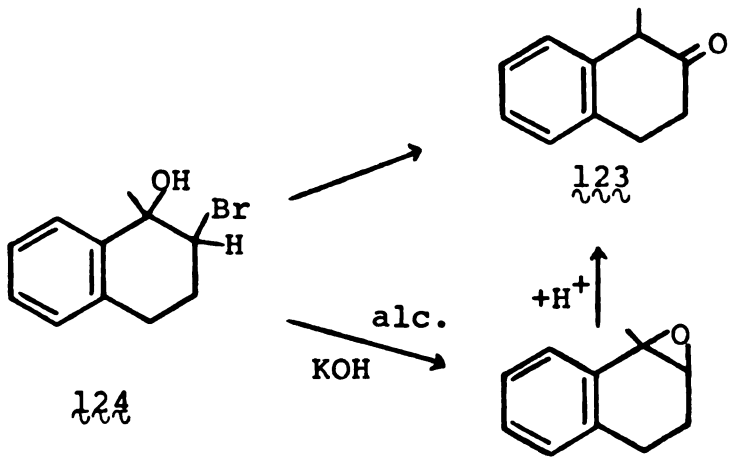
heated to redness due to the oxidation of both sodium and charcoal.

4. Subsequent reactions of HSS may now be started. Add 50 ml of a previously dried solvent (hexane, cyclohexane, THF, benzene) to the flask. A solution containing 25 mmoles of the appropriate ketone in 10 ml of benzene was added with stirring. The reaction mixture, after being heated for 5 min at reflux, was cooled to room temperature and 3.55 g (25 mmol) of methyl iodide was added. The reaction mixture was refluxed for 2 hr, then allowed to come to room temperature. Workup consisted of addition to 95% ethanol, extraction with ether, and drying over $MgSO_4$.

In the case of hexamethyl-2,4-cyclohexadienone, alkylation occurred *via* a cross - rather than a fully - conjugated enolated anion, to give a single product 118. Unreacted hexamethyl-2,4-cyclohexadienone (50%) was also recovered. The product was identified by comparison of its ir and nmr spectra with those of an authentic sample.[67]



118



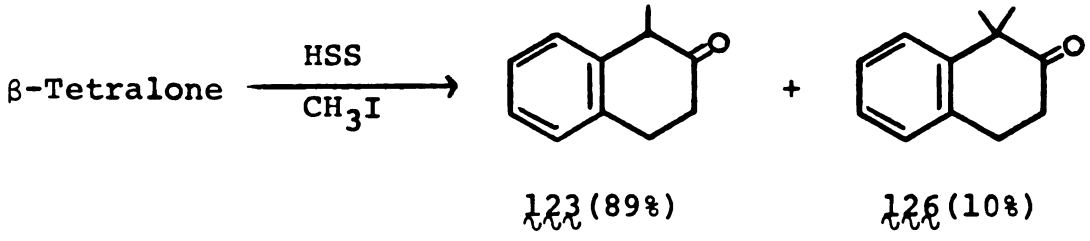
123

124

Monoalkylation of β-tetralone is a key step in the synthesis of natural products such as (±) callitrisic acid,[72] dehydroabietic acid,[73] and resin acid.[74] A rather long route has been reported[75,76] to accomplish the monoalkylation of β-tetralones in 80% yield.

The conventional use of alkoxide and methyl iodide on 2-tetralone gave largely the dimethyltetralone,[70] though monoalkylation product had been previously reported to form low yield (58%).[71] Methylation via the addition of 2-tetralone to HSS proceeded smoothly to yield solely the 1-alkylated derivatives. Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 148°, 60 ml/min He) gave 89% of the monoalkylation product (123, ret time 30 min) and 10% of the dialkylation product (119, 41 min). 1-Methyl-2-tetralone was identified by the comparison of its ir (neat, $\nu_{C=O}$ 1710 cm^{-1}) with that of the literature report.[71,75,76] The mass spectrum showed a parent peak at m/e 160, and the nmr spectrum

(CCl_4) showed a doublet at δ1.36 (J = 7 Hz) for the 1-methyl substituent. 1,1-Dimethyl-2-tetralone was identified by the comparison of its mass, nmr, and ir spectra with those of an authentic sample.

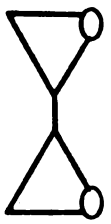


123 (89%) 126 (10%)

Research on the application of high surface sodium to the alkylation reaction is at an initial stage. It might be interesting to use sodium chloride (40-80 mesh) as the solid carrier in order to increase the sodium efficiency for forming enolate and reduce the possibility of chemical reduction of the ketone (using only 2-10% sodium). This support showed also reduced sample loss in the workup process. Also, it might be interesting to compare the alkylation result with that of high dispersion sodium[65] or alkali metalgraphite intercalation compounds.[77]

(2) SYNTHESIS OF POTENTIAL CARCINOGENIC DIEPOXIDES

A number of epoxides have been shown to be carcinogenic.[78] Simple examples include 127, 128, and 129.

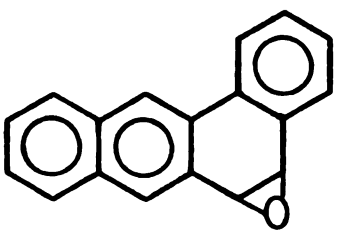


127

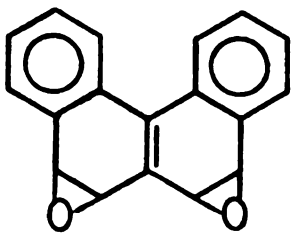
128

129

A series of arene oxides such as 130 and 131, and other oxidized arene metabolites are also carcinogenic.[79]

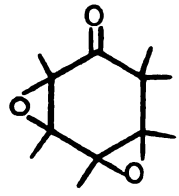


130



131

In this part of the thesis, I describe the synthesis of the diepoxy ketone 132. The monoepoxide (24) had been previously prepared. Attempts to rearrange 132 by photolysis and by acid are also described.

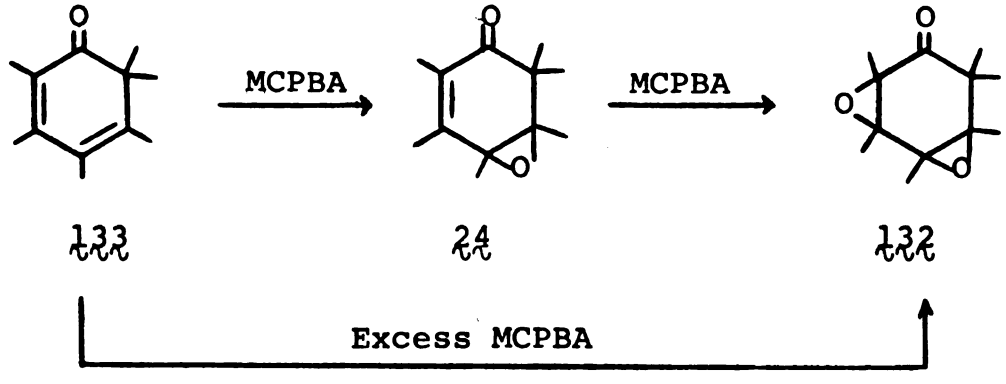


132

RESULTS AND DISCUSSION

The reaction of α,β-unsaturated ketones with peracids[6e] usually does not lead to epoxidation of the double bond. Although exceptions to this generality are known, they are not common.[80]

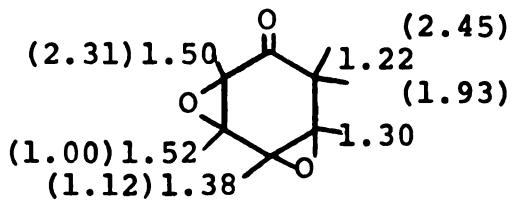
Treatment of 133 with m-chloroperbenzoic acid in benzene afforded the monoepoxide 24. Further treatment of 24 with m-chloroperbenzoic acid gave a single diepoxide 132. Compound 132 could also be obtained directly from



133 24 132

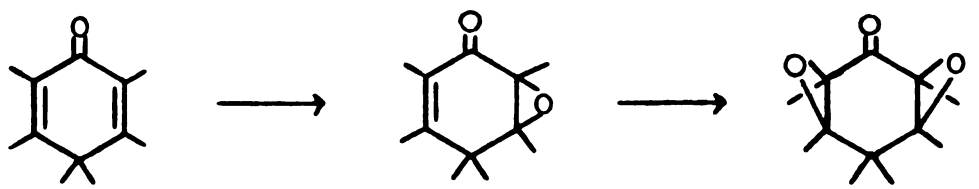
133 by using excess oxidant.

The gross structure of 132 was established by its spectral properties. The molecular formula $C_{12}H_{18}O_3$ was confirmed by the compound's mass spectrum (parent peak



132

m/e 210) and microanalysis. The ir spectrum showed a carbonyl absorption at 1710 cm^{-1}. The uv spectrum showed only end absorption. The nmr spectrum showed that all methyl signals appeared at or above δ1.52. These spectroscopic data indicate that 132 must be a saturated compound. The stereochemical assignment is not completely certain yet. However, it should be pointed out that the epoxidation of 134 gives only the cis-diepoxide.[81]



134 68

Diepoxide prepared from 133* in which the C-3 methyl was replaced by a CD_3 group lacked the singlet at δ1.52. Diepoxide prepared from 133** in which both the C-3 and C-5 methyls were replaced by CD_3 groups lacked the singlets at δ1.52 and 1.30. Thus the nmr assignments shown on the structure are correct.

Irradiation of 132 under a variety of conditions led only to recovered starting material. Treatment of 132 with TFA resulted in an interesting molecular rearrangement to form two isomeric products. However, additional work is necessary before the structures can be unambiguously characterized.

The method described here is probably generally applicable to the synthesis of diepoxides with different substituents in the cyclohexadienone system.

EXPERIMENTAL

1. Synthesis of 2,3,4,5-Diepoxy-2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (132)

An ice-cold solution of 9.6 g (0.05 mol) of m-chloroperbenzoic acid in 150 ml of carbon tetrachloride was added slowly to a solution of the monoepoxide 24 (4.85 g, 0.025 mol) in 50 ml of carbon tetrachloride. Reaction was allowed to warm to room temperature and stirred for 1 hr. The nmr monitoring showed complete reaction at this time. The solvent was removed by rotary evaporation, petroleum ether (b.p. 30-60°) was added, and the m-chlorobenzoic acid was removed by filtration. The filtrate was washed with aqueous sodium bicarbonate, and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 4.90 g of diepoxide 132 in 96% yield. The same product could be obtained directly from dienone using an excess (three or four fold) of oxidant. The crude product can be purified by fractional distillation (b.p. 82°/10^{-3} mm Hg) or by vpc (10' x 0.25 in column, 10% FFAP on chromosorb W, 80/100). Ir (neat) 3001 (m), 1710 (s), 1480 (m), 1400 (m), 1145 (w), 1122 (w), 1103 (m), 1080 (m), 940 (w), 890 (w), 870 (m), 830 (w), 800 (w), 780 (w) cm^{-1}; uv (cyclohexane) showed only end absorption; nmr (CCl_4) δ1.22 (s, 6 H), 1.30 (s, 3 H), 1.38 (s, 3 H), 1.50 (s, 3 H), 1.52 (s, 3 H); mass spectrum (70 eV) m/e

(rel intensity) 210 (5), 195 (3), 182 (5), 167 (45), 153 (85), 139 (47), 111 (24), 99 (41), 97 (40), 86 (20), 81 (25), 71 (11), 69 (40), 55 (24).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63
Found: C, 68.48; H, 8.54

2. Synthesis of 2,3:4,5-Diepoxy-3-trideuteromethyl-2,4,5,6,6-hexamethyl-2,4-cyclohexadienone (132*)

An ice-cold solution of 1.92 g (0.01 mol) of MCPBA in 30 ml of carbon tetrachloride was added slowly to a solution of 3-trideuteromethyl-2,4,5,6,6-pentamethyl-2,4-cyclohexadienone (0.97 g, 0.005 mol) in 10 ml of carbon tetrachloride and stirred at room temperature for 10 hr, and worked up as described for the corresponding compound 132.[48] The epoxidation product 132* had an nmr spectrum identical with that of 132 except that the signal at δ1.30 had disappeared.[48]

3. Synthesis of 2,3:4,5-Diepoxy-3,5-bis-trideuteromethyl-2,4,6,6-tetramethyl-2,4-cyclohexadienone (132**)

The procedure was as described for the corresponding 132.[48] The product had an nmr spectrum identical with that of 132 except that the signals at δ1.30 and 1.52 had disappeared.

4. Irradiation of Diepoxide 132

Irradiation of a 0.01 M solution of 132 in ether through pyrex or quartz for 10-15 hr with a 450 W Hanovia lamp, gave only unchanged starting material.

5. Acid-catalyzed Rearrangement of Diepoxide 132

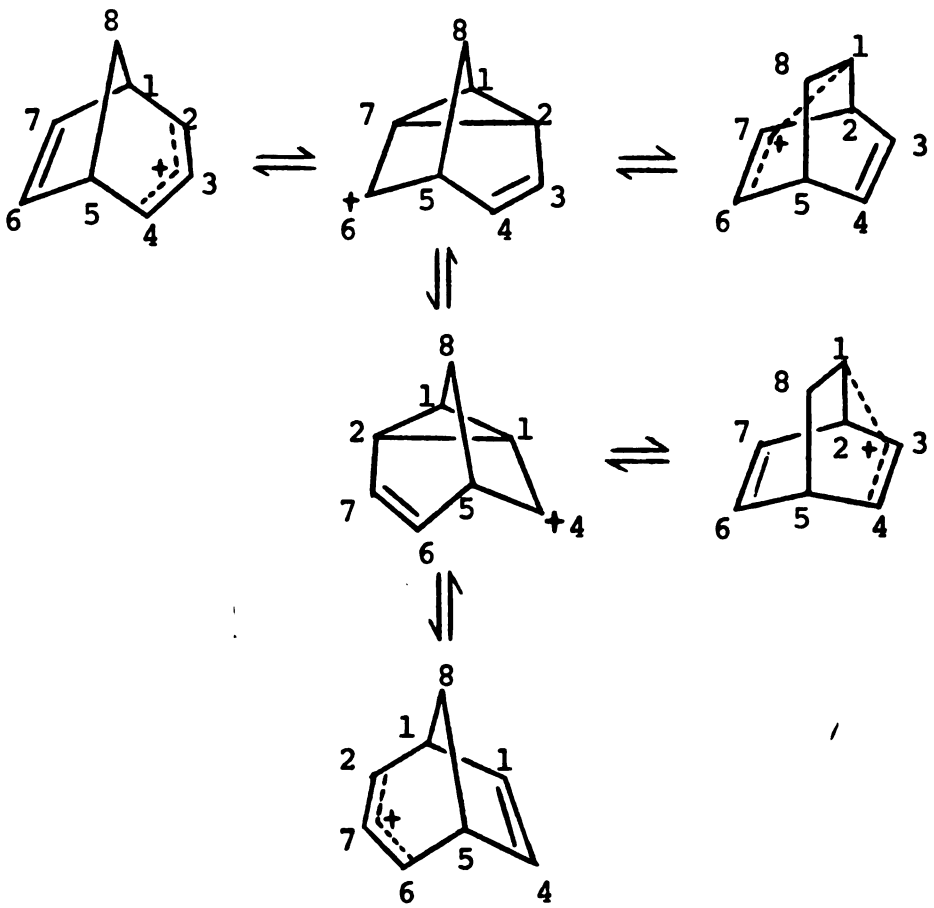
A solution of the diepoxide 132 (100 mg, 0.48 mmol) in 3 ml of TFA, prepared at 0°, was allowed to stir for 15 min at room temperature (monitoring by nmr) then poured into a cold sodium bicarbonate solution and extracted several times with ether. The combined ether extracts were washed successively with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, and dried ($MgSO_4$). After solvent removal there remained 95 mg of a light yellow oil. The residue, when subjected to preparative vpc (5' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 60 ml/min He, 150°), gave two compounds with retention times of 4 min (40%), 132a, and 8 min (60%) 132b, respectively. For 132a: ir (neat) 3500 (w), 3000 (s), 2980 (s), 2905 (m), 1738 (s), 1718 (s), 1685 (m), 1460 (m), 1395 (s), 1365 (s), 1305 (m), 1270 (m), 1203 (m), 1160 (m), 1135 (m), 1100 (w), 1058 (m) cm^{-1}; uv (methanol) λ_{max} 215 nm (ε 2100), 250 (1050); nmr (CCl_4) δ1.06 (s, 3 H), 1.09 (s, 3 H), 1.20 (s, 3 H), 1.32 (s, 3 H), 1.83 (s, 3 H), 2.03 (s, 3 H); mass spectrum (70 eV) m/e (rel intensity) 210 (5), 195 (5), 167 (32),

154 (10), 153 (90), 139 (10), 125 (20), 109 (4), 97 (7), 81 (15), 69 (10). For 132b: ir (neat) 3350 (m), 2960 (s), 2905 (m), 1705 (s), 1660 (m), 1650 (s), 1400 (s), 1350 (m), 1180 (m), 1100 (m), 1030 (m), 790 (s), 760 (m) cm^{-1}; uv (methanol) λ_{max} 223 nm (ε 1610), 276 (2030); nmr (CCl_4) δ1.06 (s, 3 H), 1.09 (s, 3 H), 1.29 (s, 3 H), 1.60 (s, 3 H), 2.00 (s, 3 H), 2.17 (s, 3 H); mass spectrum (70 eV) m/e (rel intensity) 210 (10), 195 (1), 167 (52), 137 (12), 125 (50), 113 (10), 99 (40), 97 (38), 69 (28). Neither product was fully characterized.

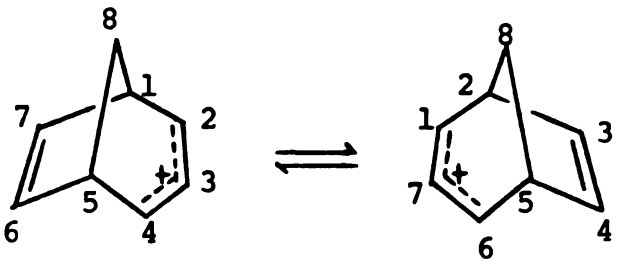
(3) THE EFFECT OF METHYL GROUPS AT A BRIDGE-HEAD POSITION ON THE COMPETING CARBONIUM ION REARRANGEMENT OF THE BICYCLO[3.2.1]OCTA-3,6-DIEN-2-YL SYSTEM

Recently, Kuzuya and Hart[54-57] observed degenerate rearrangements of the nonamethyl bicyclo[3.2.1]octa-3,6-dien-2-yl cation 135. In strong acid, cation 135 undergoes three distinct types of rearrangements. They are listed in order of increasing activation energy.

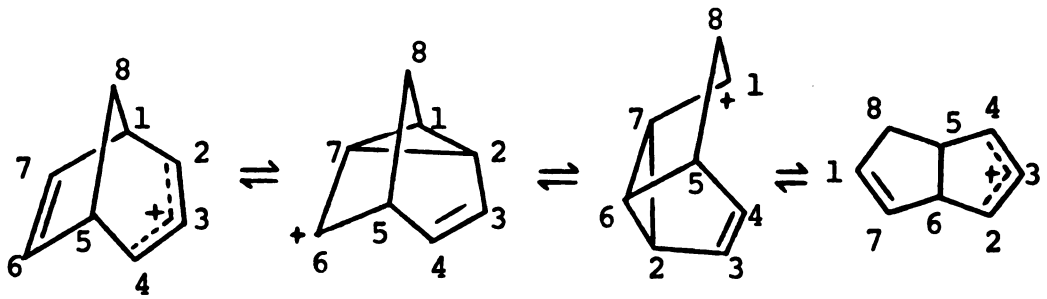
(a) Circumambulation



(b) 1,2-Bridge Shift



(c) 1,3-Cyclopropylcarbinyl Shift

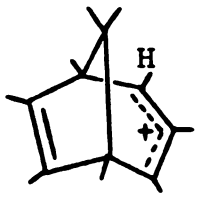


The fastest of these ($k_{-80°}$ 31.1 sec^{-1}, $\Delta F^{\neq}$ 10.2 kcal/mole, $\Delta S^{\neq}$ -14.5 eu/mole, $\Delta H^{\neq}$ 7.4 kcal/mole) was detected by changes in the nmr spectrum between -100° and -50° in FSO_3H/SO_2ClF. It equilibrates the two methyls at C-8 and methyls at C-2,3,4,6, and 7 but leaves the methyls at C-1 and 5 unique. A circumambulation mechanism accounts for the results. The slower degenerate rearrangement of 135 ($\Delta H^{\neq}$ > 7.4, but <17.8 kcal/mole) was concealed from nmr detection but was established by deuterium labeling experiments. It equilibrates the two methyls at C-8 and all the methyls at C-1 through C-7. A 1,2-bridge shift accounts

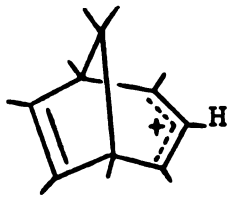
for the results. In the slowest process, carbocation 135 (which in FSO_3H/SO_2ClF undergoes rapid degenerate rearrangements below -60°) rearranges irreversibly above -60° to the nonamethylbicyclo[3.3.0]octa-3,6-dien-2-yl cation. A 1,3-cyclopropylcarbinyl shift accounts for the results.

Kuzuya and Hart also found that ion 136 rearranged to ion 136a below -50° by circumambulation mechanism, and not

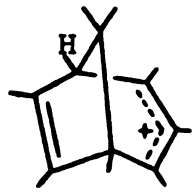
135



136



136a



136b

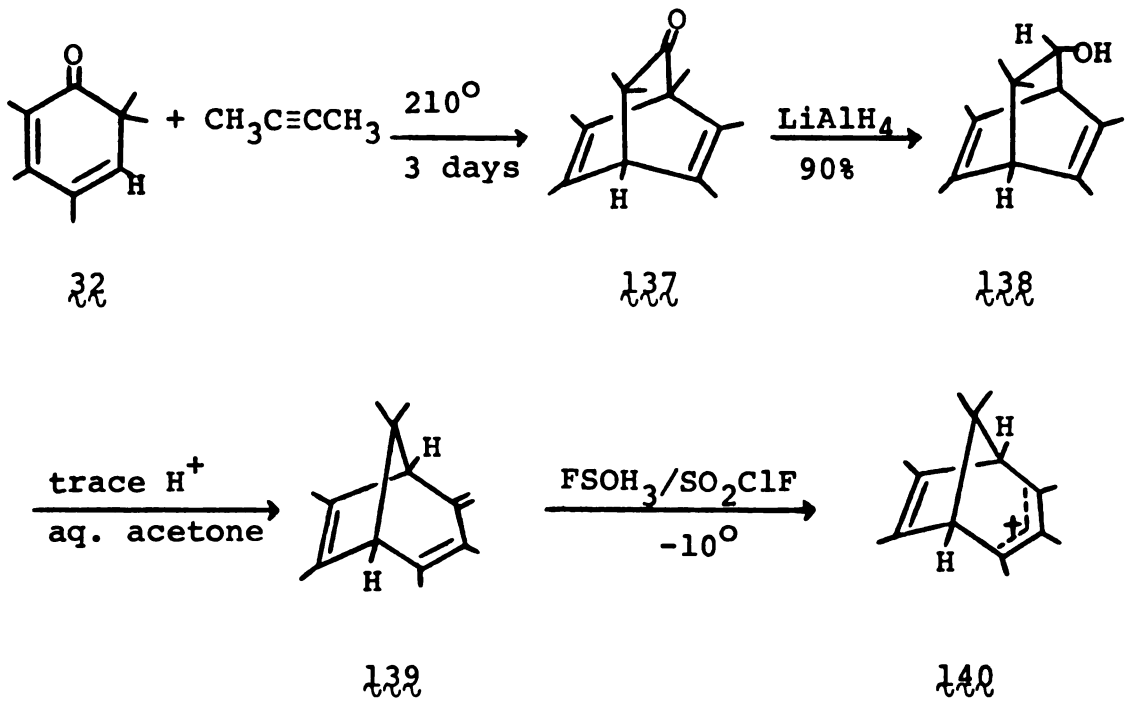
by successive 1,2-bridge shift, as proved by deuterium labeling experiments. Only at higher temperatures do the 1,2-bridge shifts (observed by deuterium scrambling) occur. Again, the slowest reaction was a 1,3-cyclopropylcarbinyl shift. Similarly, circumambulation (nmr observed) of 136b occurred faster than 1,2-bridge shifts and the slowest reaction was a 1,3-cyclopropylcarbinyl shift.

Even though C-1 and C-5 remain unique in the circumambulation mechanism, positive charge develops at these carbons in various steps of the mechanism. This was clearly observed by Hart and Kuzuya in their study of ion 136b. It was therefore desirable to prepare and study the rearrangements of the ion with hydrogens at both

bridgehead positions, and methyl groups at every other position. A preliminary study of this system is described here.

RESULTS AND DISCUSSION

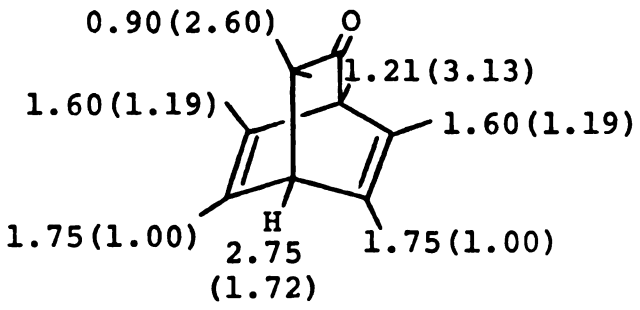
The scheme used to synthesize ion 140 is summarized below.



32 137 138

139 140

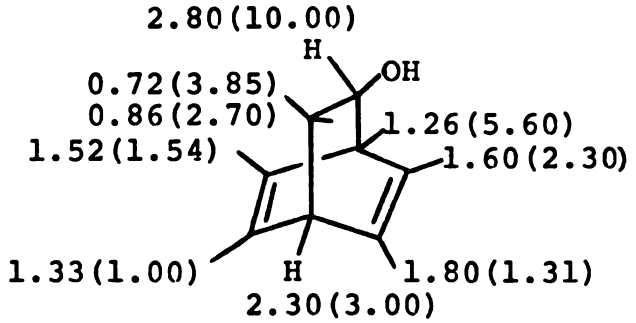
The Diels-Alder addition of 2-butyne to the pentamethyldienone 32 gave adduct 137 in 93% yield. Compound 137 was assigned the structure shown on the basis of its spectral properties and chemical transformations. The molecular formula $C_{15}H_{22}O$ was confirmed by the mass spectrum (parent peak m/e 218) and elemental analysis.



137

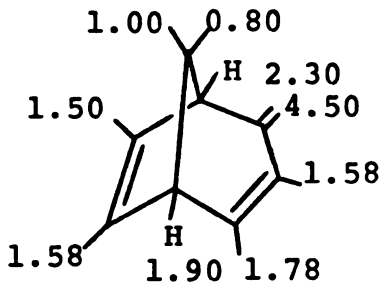
The ir spectrum of 137 had a strong band at 1690 cm^{-1} and the uv spectrum showed a λ_{max} at 218 nm (ε 1700) consistent with bicyclo[2.2.2]octadienone system. The nmr spectrum is consistent with the C_s symmetry and showed a gem-dimethyl group at δ0.90, a bridgehead methyl group at δ1.21, four allylic methyl groups at δ1.60 and 1.75, and a single bridgehead proton at δ2.75. The europium shift data were also consistent with the structure.

Reduction of 137 with lithium aluminum hydride gave alcohol 138. The structure of 138 is based on spectral properties and chemical transformations. The ir spectrum showed a broad hydroxyl group absorption at 3200-3700 cm^{-1}. The nmr spectrum showed that the three highest field methyl proton peaks were sharp singlets, as were the two protons at δ2.30 and 2.80. The signals at δ1.52, 1.60, 1.80, and 1.83 showed homoallylic coupling and the europium shift data clearly delineated the correct nmr assignments.

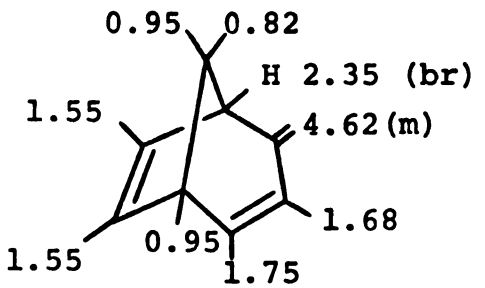


138

Treatment of 138 with a trace of acid in acetone caused it to dehydrate with rearrangement to give triene 139. The structure of 139 follows from its spectral properties. The two highest field gem-dimethyl peaks



139

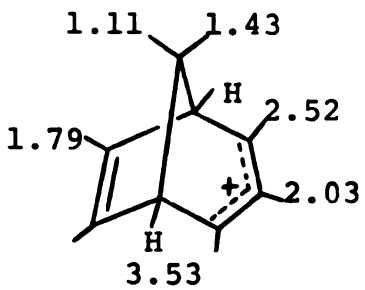


141

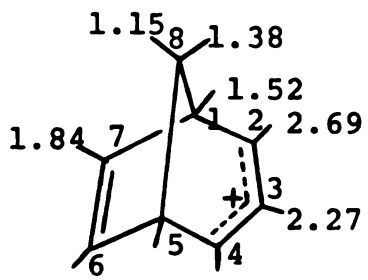
were sharp singlets and the peaks at δ1.50, 1.58, and 1.78 showed homoallylic coupling; other peaks were singlets or were split as shown on the structure. The nmr spectrum of 141 is shown for comparison, and the close agreement in chemical shifts is apparent.

When 139 was treated at -78° with FSO_3H/SO_2ClF, the

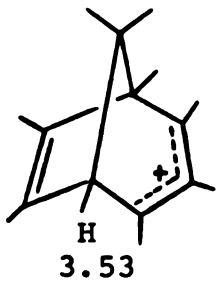
stable carbocation 140 was obtained. The nmr spectrum is consistent with the C_s symmetry. It had two 6-proton singlets, one 2-proton singlet, and three 3-proton singlets, assigned as shown on the structure. The only arbitrary feature of the assignment is at C-6, where we can not say with certainty whether the lowest field methyl is <u>syn</u>- or <u>anti</u> to the positively charged bridge. The nmr spectrum of carbocations 135 and 136b are shown for comparison.



140



135



136b

Carbocation 140 does not undergo either circumambulatory rearrangement or 1,2-bridge shifts at -78°. Indeed, the nmr spectrum did not change until the temperature was raised to -10°. Above -10°, the changes occurred which appeared to be irreversible; however, insufficient material was on hand to investigate the reaction further.

EXPERIMENTAL

1. Synthesis of 1,2,3,5,6,8,8-Heptamethyl-bicyclo[2.2.2] octa-2,5-dien-7-one (137)

A mixture of 1 g of 2,4,5,6,6-pentamethyl-2,4-cyclohexadienone (4.58 mmol) and an equal volume of 2-butyne were heated in a thick-walled sealed glass tube at 203° for 3 days. Excess 2-butyne was allowed to evaporate from the cooled reaction mixture, and the viscous residue was chromatographed over silica gel (<230 mesh) using methylene chloride as the eluent, to give 1.03 g of 137 (93% yield) as a pale yellow oil. Analytical vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 162°, 30 ml/min N_2) showed a retention time of 5 min. Preparative vpc gave pure 137: ir (neat) 2905 (s), 2895 (s), 1690 (s), 1440 (s), 1370 (s), 1350 (w), 1300 (w), 1240 (w), 1200 (w), 1145 (m), 1060 (m), 1020 (m), 1003 (s), 870 (m) cm^{-1}; uv (ethanol) λ_{max} 218 nm (ε 1630), 245 (shoulder, 390); nmr (CCl_4) δ0.90 (s, 6 H), 1.21 (s, 3 H), 1.60 (broad s, homoallylic coupling, 6 H), 1.75 (broad s, 6 H), 2.75 (s, 1 H); mass spectrum (70 eV) m/e (rel intensity) 218 (10), 203 (13), 175 (11), 160 (3), 149 (53), 148 (100), 134 (45), 133 (85), 119 (20), 117 (20), 115 (18), 105 (32), 91 (42), 77 (27).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.15; H, 10.16
Found: C, 82.16; H, 10.18

2. Synthesis of 1,3,3,5,6,7,8-Heptamethyl-bicyclo[2.2.2] octa-5,7-dien-2-ol (138)

To a suspension of 0.57 g of $LiAlH_4$ in 25 ml of anhydrous ether, there was added 1 g of 137 in 25 ml of anhydrous ether. The mixture was stirred for 8 hr at room temperature. Excess hydride was destroyed by adding water, the ether layer and extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$). The solvent was evaporated to give 138 as a pale yellow oil in virtually quantitative yield. The crude product was chromotographed over silica gel using pentane:ether (5:1) as eluent to give a colorless oil (138). Analytical vpc (5' x 0.125 in column, 20% FFAP on chromosorb W, 150°, 30 ml/min He) gave two peaks. The retention time of 138 was 7 min. Preparative vpc (10' x 0.25 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 140°, 60 ml/min He) showed the retention time of 138 was 20 min. Another peak, retention time 30 min, was identified as due to pentamethylbenzene (82% yield) due to a thermal fragmentation reaction.

For 138: ir 3500 (s), 3000 (s), 2950 (s), 1490 (w), 1460 (s), 1400 (w), 1390 (w), 1130 (w), 1250 (s), 1100 (w) cm^{-1}; uv (ethanol) λ_{max} 215 nm (ε 2860); nmr (CCl_4) δ0.72 (s, 3 H), 0.80 (s, 3 H), 1.26 (s, 3 H), 1.52 (broad singlet, 3 H), 1.57 (broad singlet, 3 H), 1.60 (broad singlet, 3 H), 1.66 (broad singlet, 3 H), 1.77 (broad singlet, 3 H), 2.29 (s, 1 H), 2.77 (s, 1 H), 2.80 (broad,

1 H, exchanged with D_2O); mass spectrum (70 eV) m/e (rel intensity) 220 (1), 202 (10), 187 (23), 172 (8), 149 (20), 148 (90), 133 (100), 119 (9), 107 (8), 105 (10), 91 (15), 77 (8).

Since purification through chromatography was accompanied by the formation of pentamethylbenzene, no attempt was made to perform an elemental analysis.

3. Synthesis of 2-Methylene-3,4,6,7,8,8-hexamethylbicyclo [3.2.1]octa-3,6-diene (139)

A solution of 138 (50 mg, 17.85 mmole) in 0.5 ml of 0.1% hydrochloric acid diluted with 1 ml of acetone was allowed to stand for 15 hr at room temperature. The mixture was diluted with water and extracted with methylene chloride. The combined extracts were washed with 5% sodium bicarbonate, water and dried (Na_2SO_4). Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, 160°, 60 ml/min He, ret time 1.5 min) gave 139 (41%) as a colorless oil: ir (neat) 3025 (w), 2900 (s), 1638 (s), 1605 (s), 1485 (m), 1468 (s), 1420 (w), 1398 (s), 1390 (s), 1342 (w), 1320 (m), 1310 (w), 1276 (m), 1260 (w), 1178 (w), 1158 (m), 1100 (w), 980 (w), 898 (s), 798 (m) cm^{-1}; uv (ethanol) λ_{max} 212 nm (ε 3960), 246 (8680); nmr (CCl_4) δ0.80 (s, 3 H), 1.00 (s, 3 H), 1.50 (broad singlet, 3 H), 1.58 (broad singlet, 6 H), 1.73 (broad singlet, 3 H), 1.80 (s, 1 H), 2.26 (s, 1 H): mass spectrum (70 eV) m/e (rel

intensity) 202 (57), 187 (100), 172 (32), 157 (15), 145 (30), 133 (15), 119 (10), 105 (10), 91 (12), 77 (10), 44 (40).

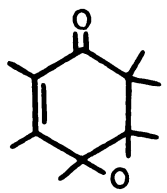
Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96
Found: C, 88.90; H, 11.03

4. Synthesis of Heptamethylbicyclo[3.2.1]octa-3,6-dien-2-yl cation (140)

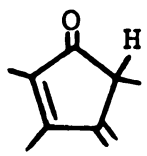
Approximately 50 μℓ of FSO_3H was placed in a 5 mm-diameter nmr tube, cooled to -78°, and approximately 200 μℓ of SO_2ClF was condensed above the acid. A CD_2Cl_2 solution containing 30 mg of the precursor of compound 139 was placed in the tube above the SO_2ClF layer and allowed to stand at -78° for 5 min. The contents of the nmr tube were then mixed using a "supermixer" (Matheson Scientific, Cat. No. 60100-05) to give a purple solution of cation 140. For its nmr spectrum see structure. Carbocation ion spectra were obtained on a Varian Associate A50-60 equipped with a variable temperature probe. The temperature control was calibrated with a methanol standard sample. The carbocation 140 was held at -78° for several hours with no change in the spectrum. When the solution was warmed to -10°, the nmr spectra still remained the same, but above -10°, the nmr spectrum became complicated immediately. The solution was cooled to -78° and quenched at that temperature with excess sodium bicarbonate in methanol. There was not enough sample for analysis of the products.

(4) ALKYLATION STUDIES WITH 4-METHYLENE-2,3,5-TRIMETHYL-2-CYCLOPENTENONE

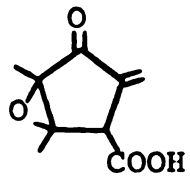
The acid-catalyzed rearrangement of epoxyketone 24 can be useful for the synthesis of cyclopentenones, some of which might serve as precursors to certain antibiotic compounds[82] and prostaglandins. Therefore, it was of considerable interest to study the reactions of the dienone 81.



24

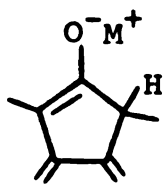


81

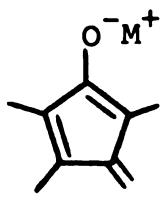


142

This compound could form two different enolates:



143a



143b

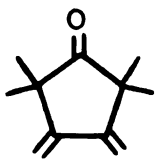
Each of these enolates has extended conjugation, and it is not clear a priori which would be formed preferentially, nor is it readily predictable when each of these enolates would react with an alkylating agent.

This final portion of the thesis presents a preliminary

study of alkylation reactions in this system.

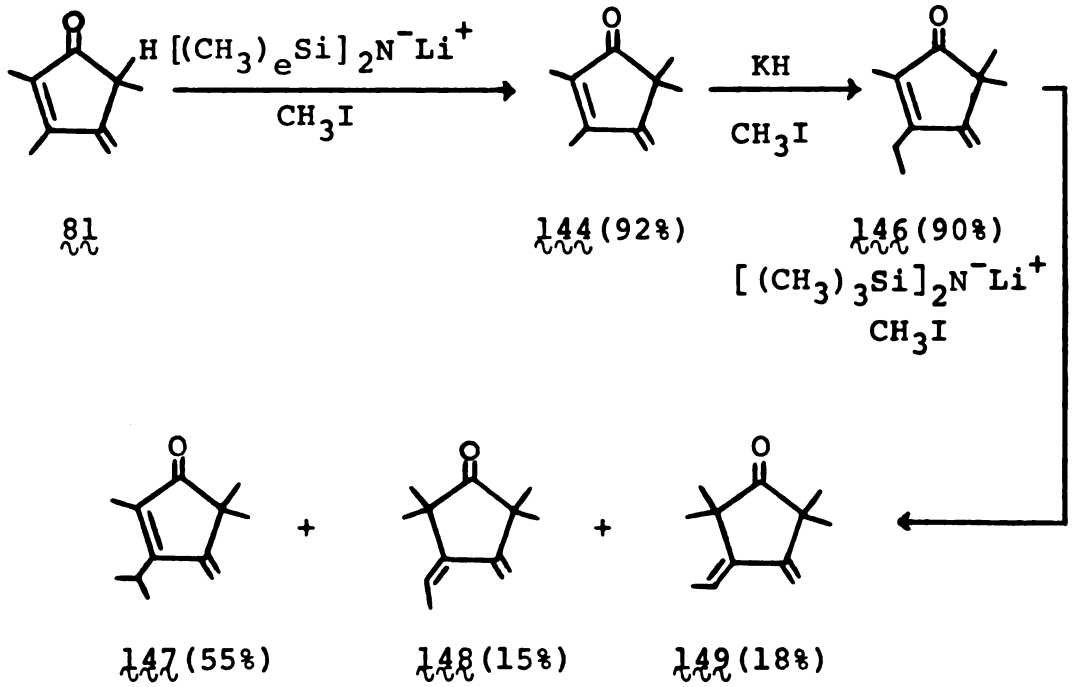
RESULTS AND DISCUSSION

A tetrahydrofuran (THF) solution of 81 was added at 0° to base prepared by adding hexamethyldisilazane to a solution of n-butyllithium. After 1 hr, excess methyl iodide was added, and the mixture was stirred for 8 hr at room temperature, then worked up to give a 92% yield of 144. Alkylation of 144 following the same procedure or using potassium hydride as the base gave methylation product 146 in approximately 90%. Expected alkylation at α-position



145

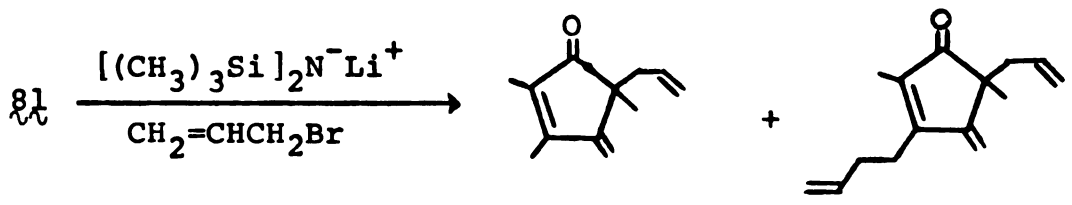
leading to exocyclic diene 145 was not observed. The unexpected but facile alkylation at the γ-position may be a consequence of steric control. Further methylation of 146 by the same procedure gave 147 as the major product, and 148 and 149 as minor products.



81 144(92%) 146(90%)

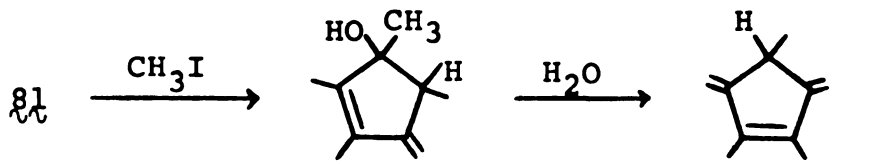
147(55%) 148(15%) 149(18%)

Alkylation of 81 at the position also occurred with allyl bromide. Two products, 150 and 151 were obtained (in 66% and 20% yield respectively) on treatment of 81 with lithium hexamethyldisilazane and an excess of allyl bromide.



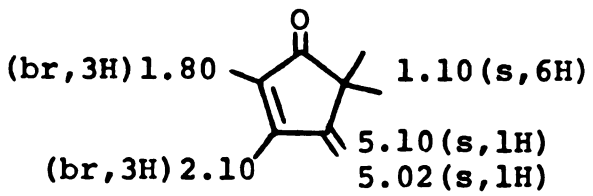
150(66%) 151(20%)

Treatment of 81 with methyllithium followed by dehydration gave the triene 153 in 40% yield. There was no evidence for the formation of tetramethylfulvene in this reaction.



152 153 (40%)

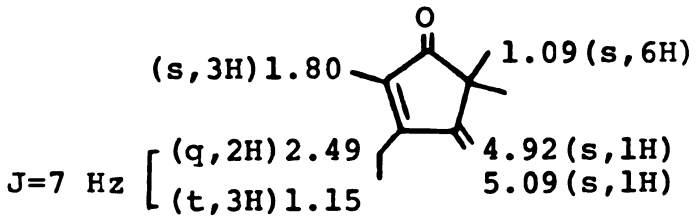
Compound 144 was assigned the structure shown:



144

The molecular formula $C_{10}H_{14}O$ was confirmed by the mass spectrum (parent peak m/e 150) and elemental analysis. The ir spectrum of 144 showed a strong carbonyl absorption at 1701 cm^{-1} and its uv spectrum had a maxima at 275 nm (ε 15,000) in ethanol. The nmr spectrum is summarized on the structure.

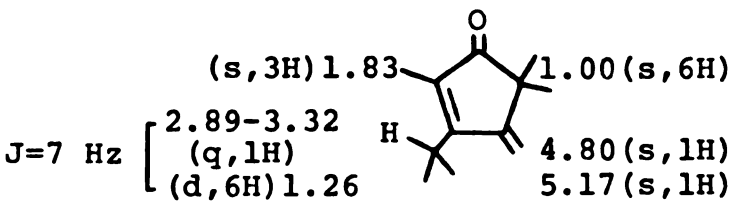
Compound 146 was assigned the structure shown. The molecular weight was confirmed by the mass spectrum (parent peak m/e 164). The ir spectrum of 146 showed a strong



146

carbonyl absorption at 1701 cm^{-1} (cyclopentenone) and its uv spectrum had maxima at 275 nm (ε 15,200) in ethanol. The nmr spectrum is summarized on the structure.

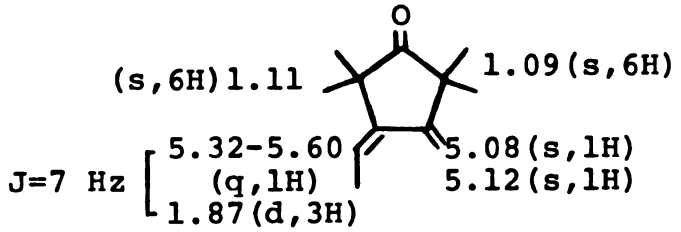
Compound 147 was assigned the structure shown



147

The molecular formula $C_{12}H_{18}O$ was confirmed by the mass spectrum (parent peak m/e 178) and elemental analysis. The ir spectrum of 147 showed a strong carbonyl absorption at 1701 cm^{-1} (cyclopentenone) and its uv spectrum had maxima at 275 nm (ε 19,200) in ethanol. The nmr spectrum is summarized on the structure.

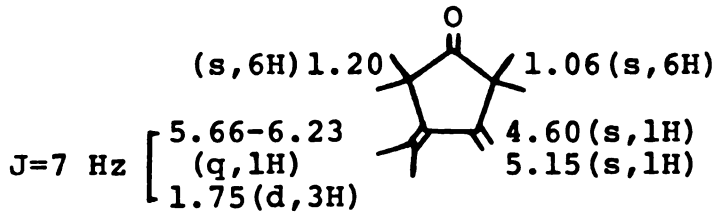
Compound 148 was assigned the structure shown. The molecular weight was confirmed by the mass spectrum (parent peak m/e 178). The nmr spectrum is summarized on the



148

structure. The stereochemical assignment is based on the nmr magnetically anisotropy effect.

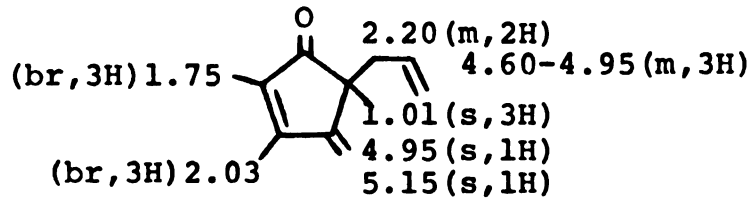
Compound 149 was assigned the structure shown



149

The molecular weight was confirmed by the mass spectrum (parent peak m/e 178). The nmr spectrum is summarized on the structure. The stereochemical assignment is based on the nmr magnetically anisotropy effect.

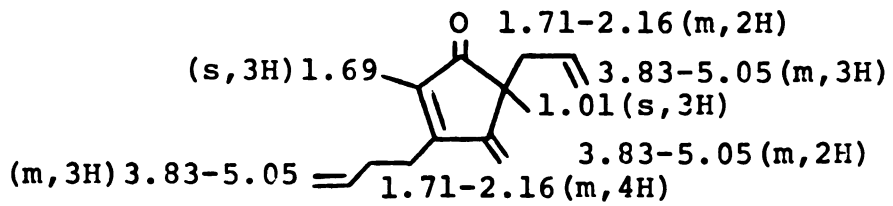
Compound 150 was assigned the structure shown



150

The molecular formula $C_{12}H_{16}O$ was confirmed by the mass spectrum (parent peak m/e 176) and elemental analysis. The ir spectrum of 150 showed a strong carbonyl absorption at 1693 cm^{-1} (cyclopentenone) and its uv spectrum had maxima at 278 nm (ε 21,000) in ethanol. The nmr spectrum is summarized on the structure.

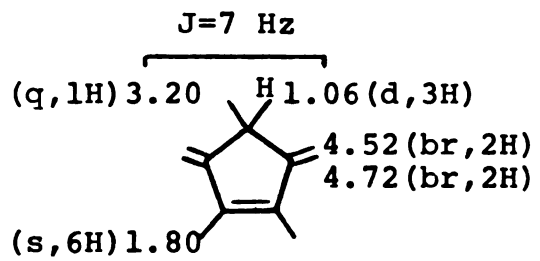
Compound 151 was assigned the structure shown



151

The molecular formula $C_{15}H_{20}O$ was confirmed by the mass spectrum (parent peak m/e 216) and elemental analysis. The ir spectrum of 151 showed a strong carbonyl absorption at 1698 cm^{-1} (cyclopentenone) and its uv spectrum showed a maxima 278 nm (ε 16,800) in ethanol. The nmr spectrum is summarized on the structure.

Compound 153 was assigned the structure shown



153

The molecular weight was confirmed by the mass spectrum (parent peak m/e 134). The ir spectrum of 153 showed a strong carbon-carbon double bond absorption at 1620 cm^{-1} and its uv spectrum had maxima at 277 nm (ε 6000) in ethanol. The nmr spectrum is summarized on the structure.

EXPERIMENTAL

1. Alkylation of 4-Methylene-2,3,5-trimethyl-2-cyclopentenone (81)

A tetrahydrofuran (THF) solution of 81 (400 mg, 2.94 mmol) was added at 0° to base prepared by adding hexamethyldisilozane (550 mg, 3.4 mmol) to a solution of n-butyllithium (2 ml of 2.06 M in hexane + 10 ml of THF). After a half hour, methyl iodide (450 mg, 3.1 mmol in 2 ml THF) was added, and the mixture was stirred for 7 hr at room temperature. The reaction mixture was poured onto cracked ice and extracted with ether. Evaporation of the solvent left 4.07 mg (92%) of a light yellow oil which, when subjected to analytical vpc (5' x 0.125 in column, 20% SE-30 on chromosorb W, AW-DMCS 80/100, 30 ml/min N_2, 150°) showed one peak corresponding to 144 (retention time 2 min). Preparative vpc (10' x 0.25 in column, 10% FFAP on chromosorb W, AM-DMCS 80/100, 60 ml/min He, 140°, ret time 4 min) gave pure 4-methylene-2,3,5,5-tetramethyl-2-cyclopentenone (144): ir (neat) 2900 (s), 2820 (s), 2720 (m), 1701 (s), 1620 (s), 1500 (m), 1380 (m), 1300 (m),

1180 (s), 1100 (s), 880 (s), 860 (s) cm^{-1}; uv (ethanol) λ_{max} 208 nm (ε 7050), 217 (15,000); nmr (CCl_4) δ1.10 (s, 6 H), 1.80 (homoallylic coupling, 3 H), 2.10 (homoallylic coupling, 3 H), 5.02 (s, 1 H), 5.10 (s, 1 H); mass spectrum (70 eV) m/e (rel intensity) 150 (42), 135 (15), 122 (27), 107 (100), 105 (14), 91 (45), 79 (30), 65 (17).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39
Found: C, 80.00; H, 9.36

The same methylation procedure, but with an excess of methyl iodide (600 mg) being used, gave a mixture of compounds 144 (70%) and 145 (30%).

2. Alkylation of 4-Methylene-2,3,5,5-tetramethyl-2-cyclopentenone (144)

A. The same methylation procedure was followed for the alkylation of 144. Preparative vpc (10' x 0.25 in column, 10% FFAP on chromosorb W, AW-DMCS 80/100, 140°, 60 ml/min He, ret time 13 min) gave 4-methylene-3-ethyl-2,5,5-trimethyl-2-cyclopentenone (146): ir (CCl_4) 2950 (s), 2859 (m), 1701 (s), 1640 (m), 1420 (m), 1350 (m), 1295 (w), 1250 (m), 1005 (m), 900 (s) cm^{-1}; uv (ethanol) λ_{max} 208 nm (ε 7100), 275 (15,200); nmr (CCl_4) δ1.09 (s, 6 H), 1.15 (t, 3 H, J = 7 Hz), 2.49 (q, 2 H, J = 7 Hz), 1.80 (s, 3 H); mass spectrum (70 eV) m/e (rel intensity) 164 (100), 149 (42), 136 (35), 135 (63), 121 (74), 107 (60), 105 (20), 93 (52), 79 (40), 78 (10), 77 (38).

B. A weighed sample of potassium hydride dispersion (4 g, 0.02 mol, 20% excess) was placed in a flask equipped with a magnetic stirring bar, condenser, and injection port capped with a rubber sleeve stopper. The apparatus was purged with nitrogen and connected through traps to a gas-measuring device. The oil was removed with pentane. To the dry potassium hydride was added 20 ml of THF and a solution of 142 (2.46 g) in 10 ml of THF at 0°. After a half hour, methyl iodide (2.5 g in 2 ml of THF) was added and the mixture was stirred for 7 hr at room temperature. Worked up as described for Experiment 1 gave 2.4 g (90%) of 146.

C. The same methylation procedures, but with an excess of methyl iodide (600 mg) being used, gave a mixture of 146 and 147.

3. Alkylation of 4-Methylene-3-ethyl-2,5,5-trimethyl-2-cyclopentenone (146)

The same procedure as described in Experiment 1 was followed for the alkylation of 146. Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb W, AW-DMCS 80/100, 140°, 60 ml/min He), gave 149 (15%), 148 (18%), and 147 (55%) with retention times 7, 10, and 16, min, respectively.

For 147: ir (neat) 3000 (m), 2900 (m), 1701 (s), 1640 (w), 1605 (m), 1475 (s), 1385 (s), 1260 (m), 1210 (w), 1090 (m), 1060 (s), 1010 (w), 900 (w), 800 (w) cm^{-1}; uv

(ethanol) λ_{max} 275 nm (ε 19,200); nmr (CCl_4) δ1.00 (s, 6 H), 1.26 (d, 6 H, J = 7 Hz), 1.83 (s, 3 H), 2.89-3.32 (q, 1 H, J = 7 Hz), 4.80 (s, 1 H), 5.17 (s, 1 H); mass spectrum (70 eV) m/e (rel intensity) 178 (100), 164 (27), 163 (77), 149 (20), 148 (12), 136 (30), 135 (9), 121 (27), 119 (12), 105 (52), 103 (39), 93 (25), 91 (31), 81 (25), 79 (20), 77 (35), 67 (17).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18
Found: C, 80.61; H, 10.27

The small amounts of 148 and 147 isolated were only sufficient for mass and nmr spectra. For 148: nmr (CCl_4) δ1.09 (s, 6 H), 1.11 (s, 6 H), 1.87 (d, 3 H, J = 7 Hz), 5.08 (s, 1 H), 5.12 (s, 1 H), 5.32-5.60 (q, 1 H, J = 7 Hz); mass spectrum (70 eV) m/e (rel intensity) 178 (64), 163 (8), 135 (100), 121 (41), 119 (19), 107 (62), 93 (35), 79 (30), 77 (33). For 149: nmr (CCl_4) δ1.06 (s, 6 H), 1.20 (s, 6 H), 1.75 (d, 3 H, J = 7 Hz), 4.60 (s, 1 H), 5.15 (s, 1 H), 5.66-6.23 (q, 1 H, J = 7 Hz); mass spectrum (70 eV) m/e (rel intensity) 178 (62), 150 (11), 135 (100), 121 (43), 119 (15), 108 (20), 107 (59), 105 (15), 93 (31), 91 (25), 78 (28).

4. Alkylation of 81 with Allyl Bromide

The same procedure as described in Experiment 1, except that allyl bromide was the alkylating reagent, was followed. Preparative vpc (10' x 0.25 in column, 20% FFAP on chromosorb

W, AM-DMCS 80/100, 150°, 60 ml/min He) gave pure 150 (66%) and 151 (20%).

For 150: ir (neat) 2903 (m), 1693 (s), 1613 (m), 1606 (m), 1450 (w), 1433 (w), 1397 (m), 1321 (w), 1285 (w), 1211 (w), 1022 (m), 1003 (w), 910 (s), 903 (m) cm^{-1}; uv (95% ethanol) λ_{max} 208 nm (ε 420), 278 (21,000); nmr (CCl_4) δ1.01 (s, 3 H), 1.75 (s, homoallylic coupling, 3 H), 2.03 (s, homoallylic coupling, 3 H), 2.20 (m, 2 H), 4.60-4.95 (m, 4 H), 5.15 (s, 2 H); mass spectrum (70 eV) m/e (rel intensity) 176 (100), 119 (23), 107 (65), 105 (43), 91 (74), 79 (38), 77 (30), 65 (20), 53 (29).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15
Found: C, 81.54; H, 9.08

For compound 151: ir (neat) 3000 cm^{-1} (m), 1698 (s), 1630 (w), 1618 (m), 1460 (w), 1440 (w), 1400 (w), 1380 (w), 1320 (w), 1260 (w), 1105 (w), 920 (s), 900 (m) cm^{-1}; uv (ethanol) λ_{max} 213 nm (ε 6000), 278 (16,800); nmr (CCl_4) δ1.01 (s, 3 H), 1.69 (s, 3 H), 1.71-2.16 (m, 6 H), 3.83-5.05 (m, 6 H); mass spectrum (70 eV) m/e (rel intensity) 216 (27), 201 (32), 188 (22), 176 (23), 175 (100), 174 (45), 173 (32), 161 (32), 159 (33), 147 (90), 131 (40), 119 (60), 105 (25), 91 (63), 77 (32).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32
Found: C, 83.41; H, 9.39

5. Treatment of Compound 81 with Methyl Lithium

To a 50-ml three necked flask equipped with a condenser, serum cap, magnetic stirrer and nitrogen gas inlet was added 1.5 g (0.011 mmol) of compound 81 in 20 ml of anhydrous ether. The solution was cooled to approximately 0°. There was added, by means of a syringe, 8 ml (excess amount) 1.50 M solution of methyllithium in ether. The reaction mixture was stirred under nitrogen at room temperature for 2 hr., then quenched with saturated NH_4Cl solution and extracted with ether. The ether extracts were combined, washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was subjected to preparative vpc (10' x 0.25 in column, 20% Carbowax on chromosorb W, AW-DMCS 80/100, 140°, 60 ml/min He, ret time 14 min) to give pure 153 in 40% yield. For 153: ir (neat) 3400 (w), 2900 (s), 1620 (s), 1450 (s), 1380 (s), 1020 (w), 960 (s); uv (ethanol) λ_{max} 277 nm (ϵ 6000); nmr (CCl_4) δ1.06 (d, 3 H, J = 7 Hz), 1.80 (s, 6 H), 2.70-3.20 (q, 1 H, J = 7 Hz), 4.52 (br s, 2 H), 4.72 (br s, 2 H); mass spectrum (70 eV) m/e (rel intensity) 134 (50), 120 (10), 119 (100), 103 (6), 91 (25), 74 (12).

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