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Part I Photochemical Deconjugation Reactions Of 3-alkyl-2-cyclohexenones Part Ii Biradicals In 2+2 Photocycloaddition Reactions Of 2-cyclopentenone

Andreas Rudolph

PART I

PHOTOCHEMICAL DECONJUGATION REACTIONS

OF 3-ALKYL-2-CYCLOHEXENONES

PART II

BIRADICALS IN 2 + 2 PHOTOCYCLOADDITION

REACTIONS OF 2-CYCLOPENTENONE

by

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ABSTRACT

PART I

Ultraviolet irradiation of 3-methyl-2-cyclohexenones leads to the formation of the deconjugated exocyclic isomers in low quantum yields. The reaction proceeds *via* the triplet excited state of the enone but the mechanism has not been determined satisfactorily. Part I of this thesis describes evidence for acid catalysis of the reaction. The presence of small quantities of carboxylic acid greatly enhances the quantum yield of the deconjugation reaction. Kinetic studies measuring deconjugation quantum yields of 3,5,5-trimethyl-2-cyclohexenone (isophorone) in benzene in the presence of various amounts of acetic acid lead to the proposal of the intermediacy of a *trans*-enone which is derived from relaxation of the enone triplet excited state. Protonation of the *trans*-enone by acid present leads to the formation of a tertiary carbocation in the 3-position of the enone which can lose a proton in the 2-position to regenerate starting material or lose a proton in the 1-position of the side chain to form the exocyclic isomer. The proposal of the intermediacy of a carbocation was supported by the detection of products derived from addition of the conjugate base of the acid to the carbocation. In addition, the presence of 10 % methanol in the irradiation mixture led to the formation of products derived from addition of the alcohol to the carbocation. From the kinetic data obtained the lifetime of the *trans*-enone was determined to be at least 1 μs.

The presence of alkenes in the reaction mixture led to a decrease in the quantum yield of the deconjugation reaction; instead products derived from 2+2 cycloaddition between the enone and the alkene were observed.

Contrary to literature reports it was found that the deconjugation reaction proceeds not only for 3-methyl substituted 2-cyclohexenones but also for 3-ethyl-5,5-dimethyl-2-cyclohexenone. Irradiation of the latter compound led to the formation of two geometrical isomers of the exocyclic deconjugated isomer. No deconjugation products were found in the irradiation of 3-isopropyl substituted 2-cyclohexenones which was believed to be due to steric hindrance to formation of the *trans*-enone. Acid catalysis was also found in the deconjugation reaction of *R*-10-methyl-$\Delta^{1,9}$-2-octalone, a bicyclic cyclohexenone.

PART II

Irradiation of 2-cyclopentenone in the presence of alkenes leads to the formation of cyclobutane ring containing 2 + 2 cycloadducts. The reaction proceeds *via* the triplet excited state of the enone which is quenched by the alkene to give an intermediate triplet 1,4-biradical. This can either undergo fission to regenerate starting materials or close to give cycloadducts. The intermediate biradicals in the photocycloaddition reaction between 2-cyclopentenone and 1,6-heptadiene and vinylcyclopropane, respectively, contain radical centres which are able to undergo radical rearrangement which leads to the formation of isomeric products. The rate constants for the respective radical rearrangement reactions are known and allow the use of the rearrangement reaction as a clock for the lifetime of the 1,4-biradical.

No products derived from rearrangement of the intermediate biradical of the reaction between 2-cyclopentenone and 1,6-heptadiene were observed. Irradiation of the enone with vinylcyclopropane, however, led to the detection of products derived from radical rearrangement of the intermediate biradical in addition to 2+2

cycloadducts. From the product distribution the lifetime of the triplet 1,4-biradical intermediate in this reaction was estimated to be 20 - 50 ns.

It was also demonstrated that the initial bond formation between the alkene and the enone was at both the α- and the β-position of the enone since products derived from rearrangement of both regioisomeric biradicals were observed.

The intermediacy of triplet exciplexes in the photochemical 2 + 2 cycloaddition reaction between cyclic enones and alkenes has been proposed to explain rate and regiochemical outcome of the reaction; however, this theory fails in an increasing number of cases. An alternative mechanism has been proposed which is based on the different fates of each of the possible intermediate biradicals. To test this mechanism the independent generation of each biradical was necessary in order to be able to determine its fate. A number of differently substituted diketones based on the bicyclo[3.3.]octane system were synthesized. It was hoped that these would undergo a photochemical decarbonylation reaction generating the desired biradicals; however, only the cyano substituted diketones underwent the expected reaction. This led to the determination of the partitioning ratio for cleavage and closure of the intermediate triplet 1,4-biradicals implicated in the 2+2 photocycloaddition reaction between cyclopentenone and acrylonitrile. The results suggest that the cycloaddition reaction regiochemistry is indeed determined by the fates of the biradical intermediates rather than their relative rates of formation.

It was also found that the regiochemical outcome of that reaction is in disagreement with the exciplex theory because the major cycloadducts formed have head-to-tail regiochemistry.

This thesis is dedicated to my loving family

Annette, Stephanie and Valerie

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CHAPTER 1

INTRODUCTION

1.1 Photochemistry of Cyclic Enones

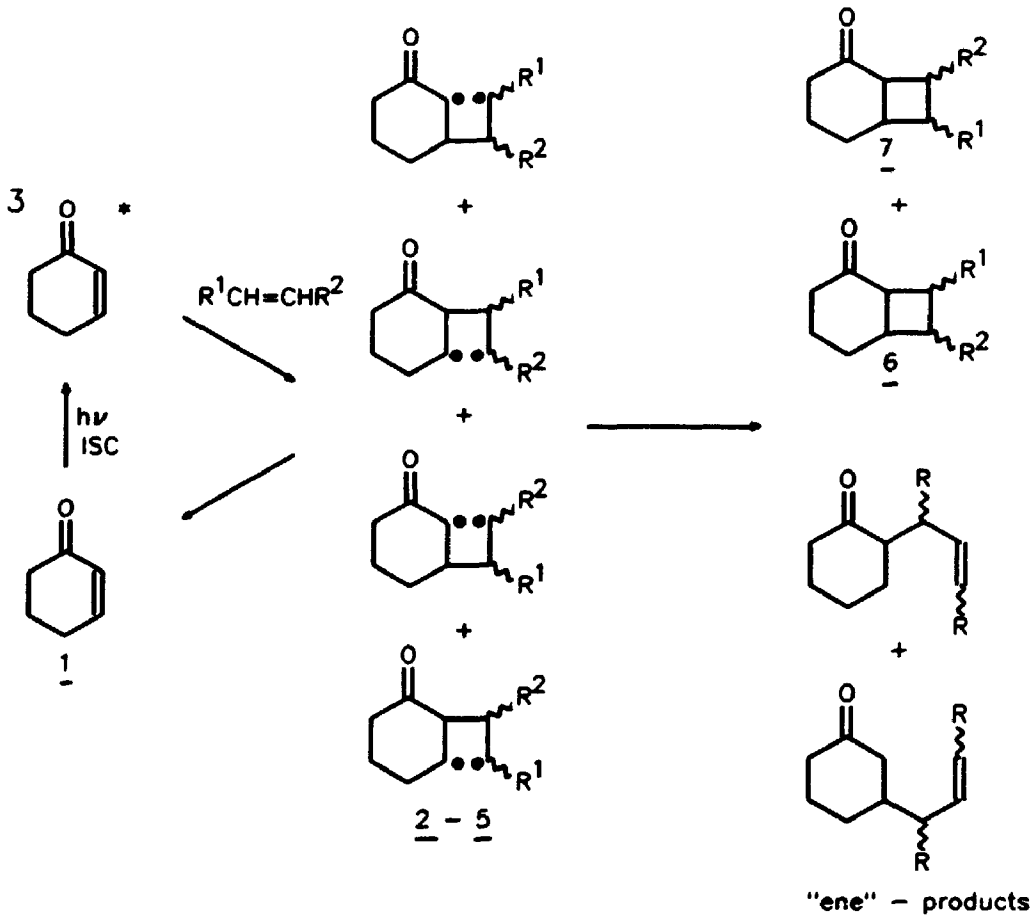
2-Cyclohexenones undergo a wide variety of reactions upon irradiation with ultraviolet light depending on the conditions and possible reaction partners present.[1]

The most common pathways are [2 + 2] cycloaddition reactions with alkenes[2] and the lumiketone rearrangement.[3] The former has been shown to proceed *via* the triplet excited state of an enone such as 2-cyclohexenone **1** which reacts with an olefin to give one or more triplet 1,4-biradical intermediates **2**-**5**. In the case of unsymmetrically substituted olefins up to four biradical structures are possible as shown in SCHEME 1. These can undergo reversion to starting enone and alkene or they can collapse to give the cyclobutane products **6** and **7**. Alternatively, they can undergo an intramolecular disproportionation reaction to yield so-called ene products.

In the absence of olefins in the reaction mixture photodimerization of the enone can be observed. This is the reaction of an enone (here represented by **1**) in its triplet excited state with a molecule of ground state enone, the double bond of which serves as an alkene to give a biradical as shown in SCHEME 2. Biradical formation can be followed by ring closure to give the cyclobutane ring containing dimers of the enone which could be head-to-head (**8**) or head-to-tail oriented (**9**).

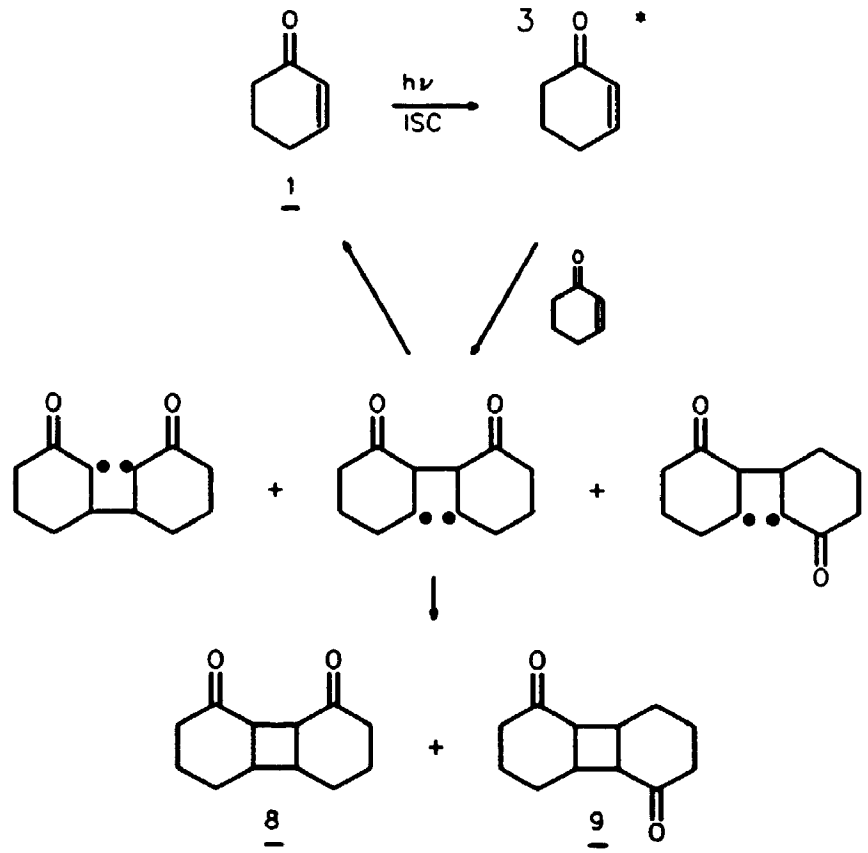
The lumiketone rearrangement is a characteristic photochemical reaction of 4,4-disubstituted 2-cyclohexenones such as such as 4,4-dimethyl-2-cyclohexenone **10** (R,R' = Me).[1,4] The reaction involves the triplet excited state of the enone which undergoes twisting about the carbon-carbon double bond followed by rearrangement

to give the bicyclo[3.1.0]hexanone products 11 and 12 accompanied by 3-substituted 2-cyclopentenones (13) as shown in SCHEME 3.

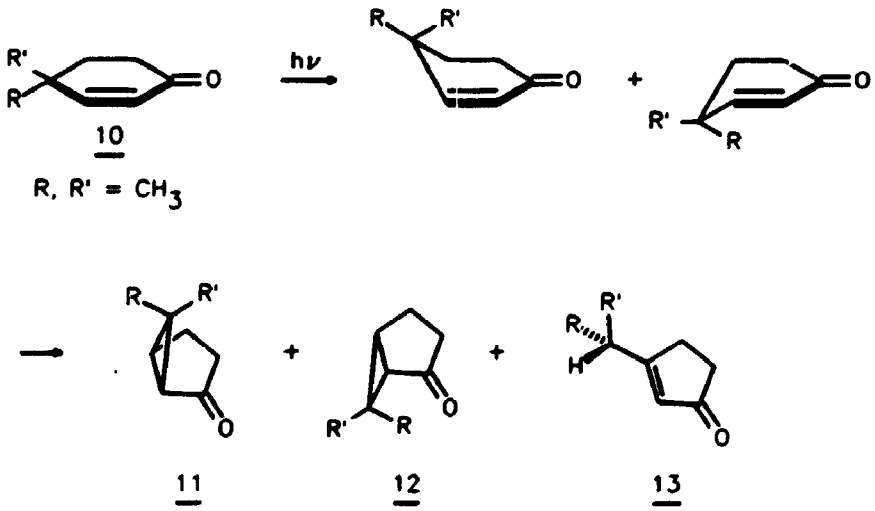


SCHEME 1

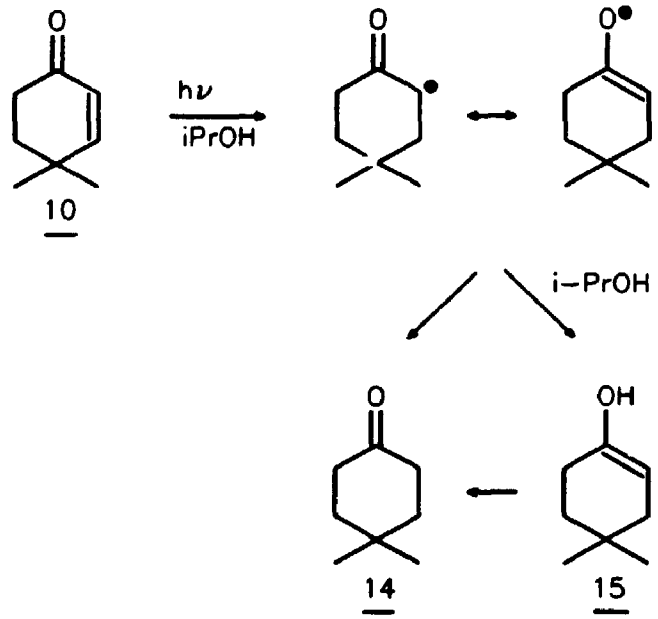
Photoreduction competes with the above described reactions. This also proceeds *via* the triplet excited state of the enone such as 10 which abstracts a hydrogen from a suitable donor to give the resonance stabilized radical *α* to the carbonyl carbon. A second hydrogen abstraction gives the cyclohexanone product 14, most likely *via* the corresponding enol 15, as shown in SCHEME 4.[5]



SCHEME 2



SCHEME 3



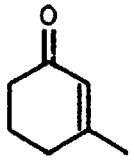
SCHEME 4

1.2 The Photochemical Deconjugation Reaction of 3-Methyl-2-cyclohexenones

Another photochemical reaction of 2-cyclohexenones, specific to those substituted with a methyl group in the 3-position, appeared in the literature in the 1960's. In his PhD thesis Jennings[6] reported that 3,5,5-trimethyl-2-cyclohexenone (isophorone) **16** gave a low yield of the exocyclic β,γ-unsaturated isomer, 5,5-dimethyl-3-methylenecyclohexanone **17**, upon irradiation with ultraviolet light. The product isomerized slowly back to starting material upon standing in the dark.

16 17

In 1968 Dauben et al.[4c] reported a study of the photochemical reactivity of a large group of differently substituted 2-cyclohexenones. They found that the deconjugation reaction to the exocyclic isomer proceeded only if the substituent in the 3-position was a methyl group as in 3-methyl-2-cyclohexenone **18**[7], **16** and 3,4,4-trimethyl-2-cyclohexenone **19**.



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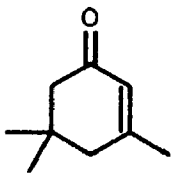

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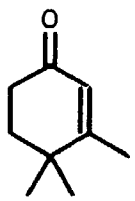
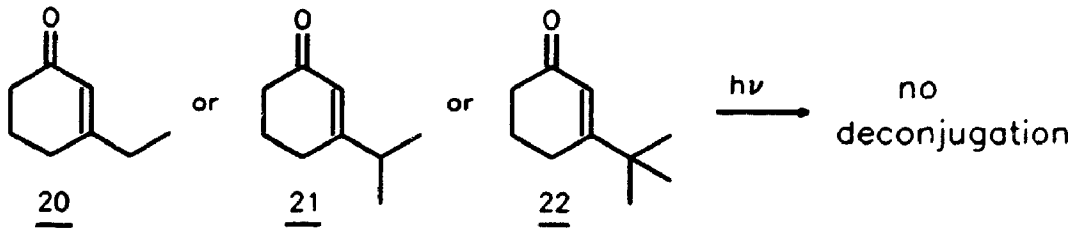


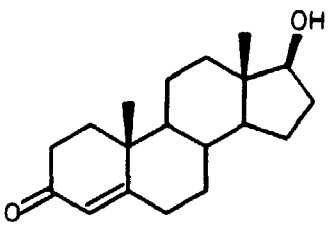
19

2-Cyclohexenones with other alkyl substituents in the 3-position such as 3-ethyl-2-cyclohexenone **20**, 3-isopropyl-2-cyclohexenone **21** or 3-*t*-butyl-2-cyclohexenone **22** did not show the deconjugation reaction but instead dimerized upon irradiation with ultra-violet light.[4c]



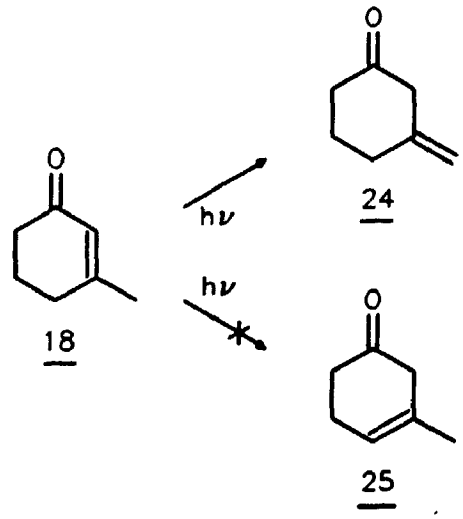
20 21 22

The only exception found by Dauben et al. to this rule was 10-*α*-testosterone **23** which deconjugated to the *β*,*γ*-unsaturated isomer. This reaction has also been described by Schaffner et al..[3]



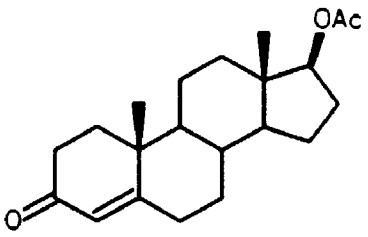
23

As summarized in SCHEME 5, in all cases where deconjugation was observed only the exocyclic isomer (i.e. **24** from **18**) was formed; there were no indications of any endocyclic 3-cyclohexenones such as **25** present after irradiation.

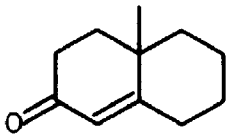


SCHEME 5

In 1969 Schaffner et al.[4d] reported the results of an investigation of the photochemistry of O-acetyl testosterone **26** and 10-methyl-$\Delta^{1,9}$-2-octalone **27**, two more complex 2-cyclohexenones.



26

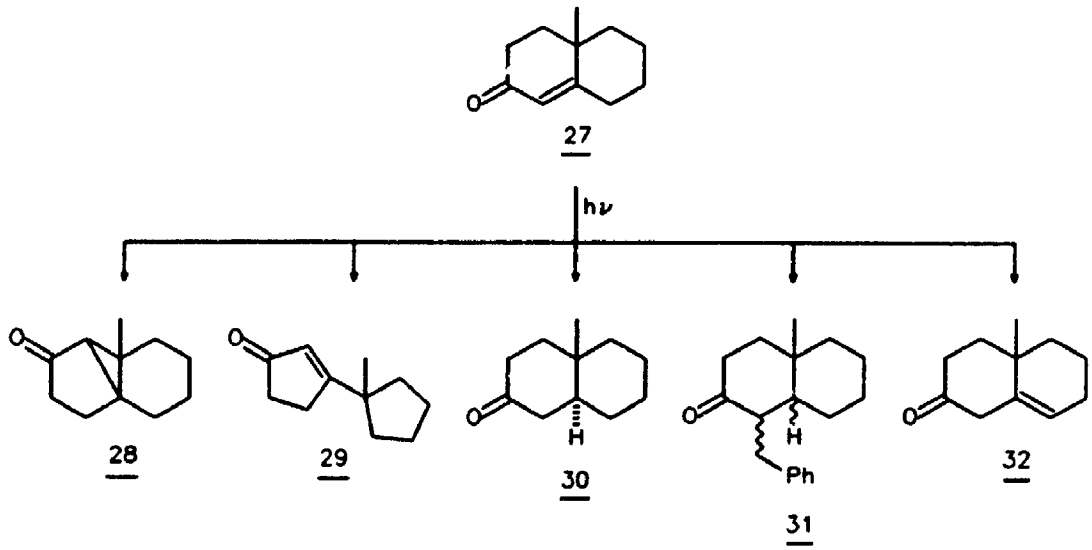


27

They found a dramatic solvent effect on the product distribution. Direct irradiation of **27** at $\lambda > 300$ nm gave the following results. In *t*-butanol the main product was a cyclopropyl ring-containing derivative **28** which arose from lumiketone rearrangement (80 %) accompanied by *ca.* 5 % cyclopentenone product **29** (also by the lumiketone pathway). A further component of the product mixture (11 %) was the deconjugated isomer **32** and 3 % of the photoreduced product **30** was also found. In isopropanol, a better hydrogen atom donor solvent, photoreduction was the main reaction (35 %) and the two lumiketone rearrangement products **28** and **29** were suppressed to 31 % and *ca.* 2 %, respectively. In toluene the major product was **31** which stems from solvent addition, a radical process (40 %), with photoreduction accounting for 19 % of the products; only small amounts of lumiketone and deconjugation reaction products (< 3 %) were obtained. In benzene the photodeconjugation reaction was the dominant process (45 %), products of lumiketone rearrangement were reduced to 14 % and products of photoreduction were suppressed to 6 %. SCHEME 6 illustrates the products from the irradiations of **27**.

The results of the irradiation of testosterone **26** were not quantified since the irradiation products could only be analyzed qualitatively by thin layer chromatography whereas the octalone products could be analyzed more quantitatively by gas chromatography. However, the qualitative results obtained by thin layer

chromatography supported the findings in the octalone experiments in that analogous products were formed.



SCHEME 6

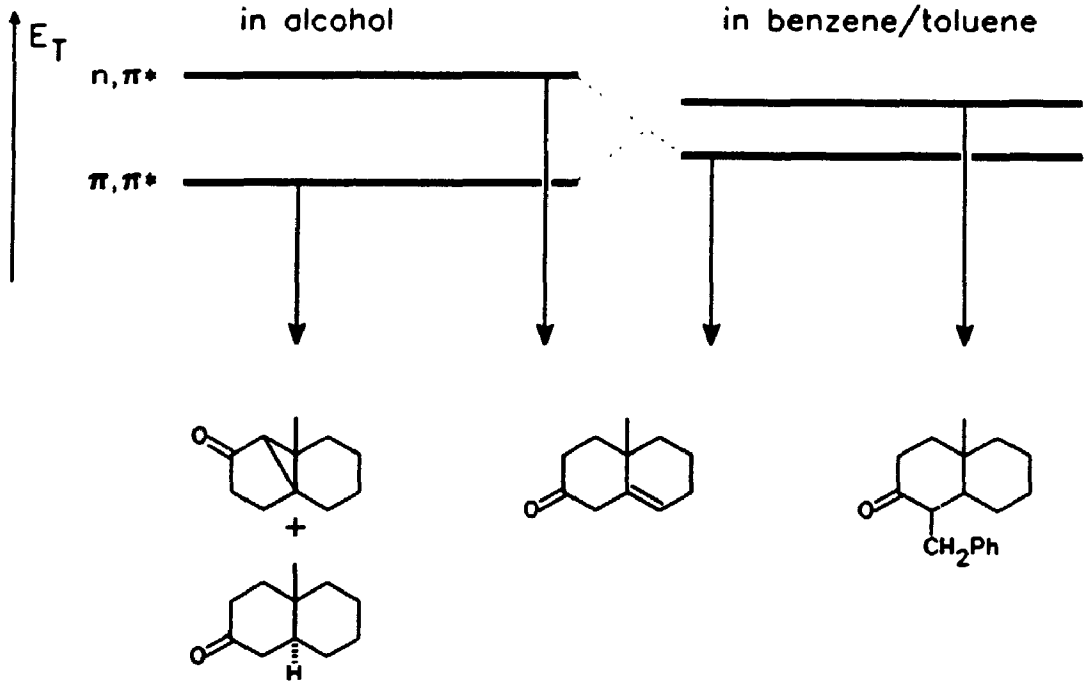
Indirect excitation (sensitization) of the enones with suitable triplet sensitizers (i.e. acetophenone) gave the same product distributions whereas the presence of a triplet quencher (eg. 2,5-dimethyl-2,4-hexadiene) led to no product formation. These findings indicate that the observed photoreactions proceed *via* a triplet excited state of **26** and **27**. Stern-Volmer experiments with a variety of quenchers led to more differentiated results when the reactions of **27** were investigated. Addition of naphthalene to an irradiation mixture in benzene did not inhibit the photodeconjugation reaction whereas in toluene the solvent addition process was quenched by its presence. The triplet energy of **27** was initially estimated to be similar to the known triplet energies of the testosterone derivative **26** ($E_{T(\pi,\pi^*)}$ = 73.3 kcal/mole, $E_{T(n,\pi^*)}$ = 74.4 kcal/mole).[9]

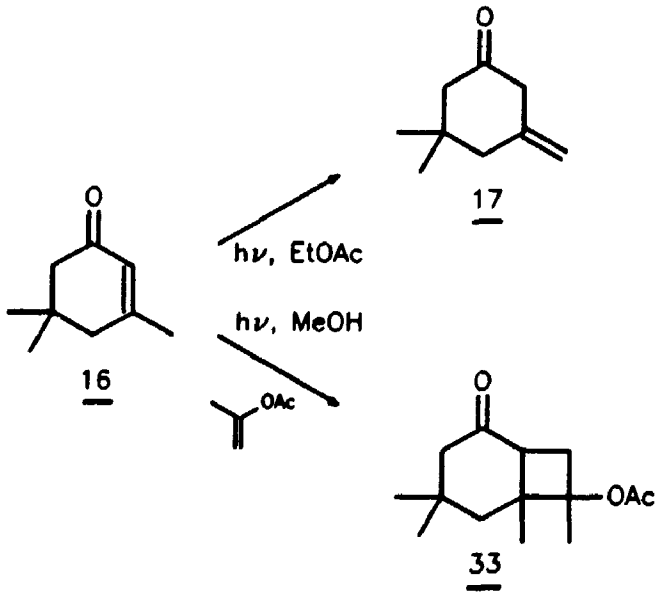
However, the fact that all observed photoreactions of **27** (lumiketone rearrangement, photoreduction, solvent addition and photodeconjugation) were quenched by 2,5-dimethyl-2,4-hexadiene (E_T = 58 kcal/mole)[10] and *trans*-stilbene ($E_T \approx 50$ kcal/mole)[11] but only the first three by naphthalene (E_T = 61 kcal/mole)[12] led to the conclusion that the observed reactions proceeded from two different triplet excited states of the octalone. From the quenching studies the energy of the triplet state responsible for the photodeconjugation reaction was estimated to be 58-61 kcal/mole; thus an energy transfer from this triplet to naphthalene would be endothermic and therefore naphthalene would not quench the deconjugation.

As for the nature of the triplet states involved, Schaffner concluded that in polar solvents the π,π^* triplet has a lower energy than the n,π^* triplet. Changing to a nonpolar solvent would lower the energy of the n,π^* state and increase the energy of the π,π^* state slightly so that now the n,π^* state was the lowest triplet. It was suggested that the lumiketone/reduction/solvent addition reactions of **27** proceed from the π,π^* state (and are thus favoured in polar solvents) in contrast to the deconjugation reaction which involves reaction from the n,π^* state (which accounted for the product distribution in nonpolar solvents). This interpretation is summarized in FIGURE 1.

Similar conclusions were drawn by Shiloff and Hunter in 1979[13] based upon their observations of the photochemistry of isophorone **16**. As shown in SCHEME 7 they obtained almost complete conversion to its exocyclic deconjugated isomer **17** upon irradiation in ethyl acetate whereas in methanol in the presence of isopropenyl acetate [2+2] cycloaddition products **33** were formed in good yields and no deconjugation was observed.

FIGURE 1: Energy levels of the triplet excited states of **27**

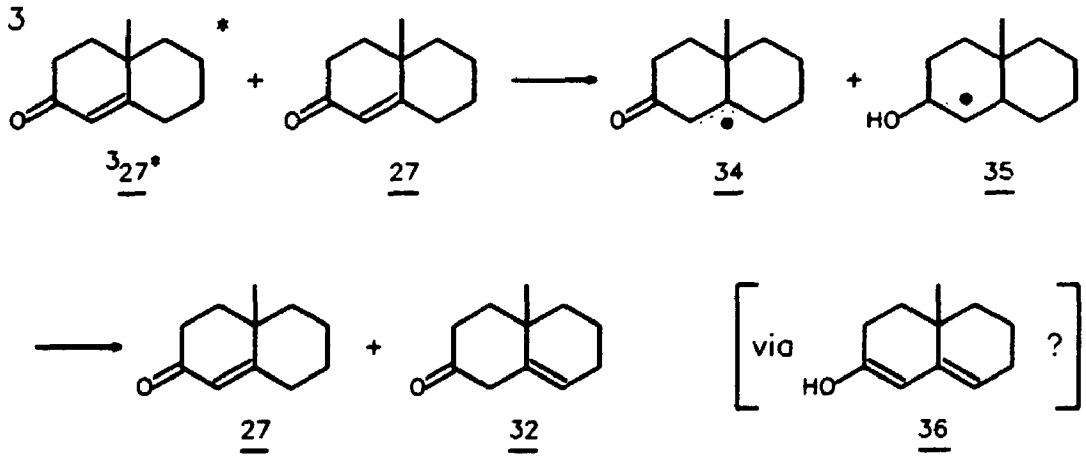




SCHEME 7

This difference in reactivity was attributed to the different triplet excited states involved in the reactions and the effect of solvents on them.[14]

An investigation of the photochemical kinetics of the photodeconjugation reaction of octalone **27** by Schaffner et al.[4d] resulted in the proposal of a bimolecular mechanism. Experiments with varying concentrations of the enone led to the finding that the quantum yield for the deconjugation reaction was a function of the enone concentration (Φ^{-1} linear with $[\mathbf{27}]^{-1}$) which would be expected if the reaction were second order in enone. In view of this result Schaffner postulated the reaction mechanism shown in SCHEME 8. In this mechanism hydrogen abstraction by an excited octalone molecule from a ground state enone leads to two allylic radical intermediates **34** and **35** which disproportionate to give **27** and **32**. The possible intermediacy of the dienol **36** could not be determined. It was considered to be involved as one of the direct products of the disproportionation reaction which would quickly reketonize to give the deconjugated isomer.



^{3}**27*** **27** **34** **35**

27 **32** **36**

SCHEME 8

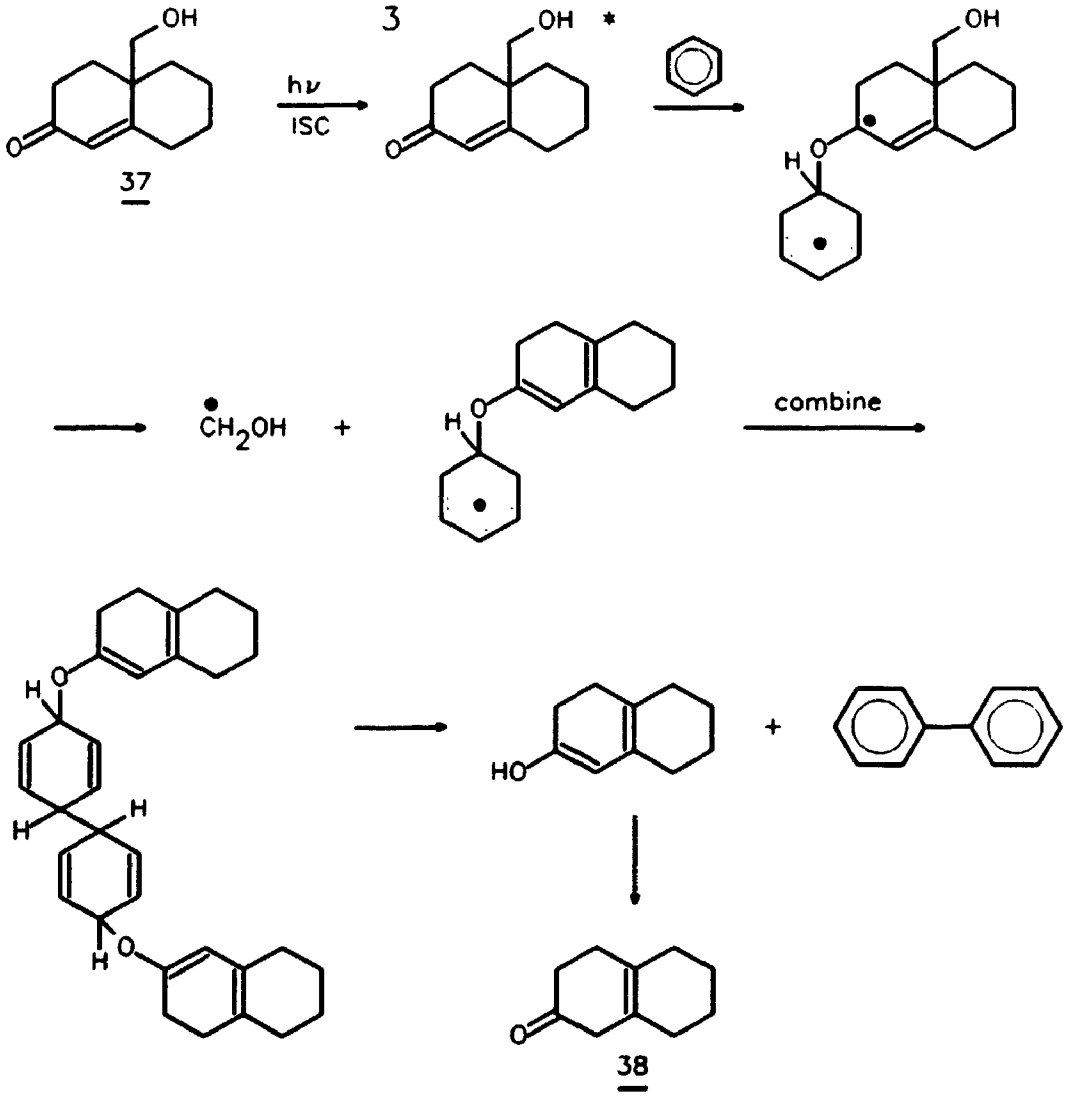
Support for this type of mechanism was also found in the fact that when *t*-butanol-OD was present in the solution deuterium was incorporated into the product and starting material, which points to the involvement of an intermediate suitable for proton exchange such as **35**.

In 1973 Margaretha and Schaffner[15] reinvestigated the photochemical reactions of 10-methyl-$\Delta^{1,9}$-2-octalone **27** discussed in Schaffner's earlier report of 1969.[4d] This new work indicated that the β,γ-unsaturated isomer **32** reconjugates thermally quite readily; under the gas chromatographic conditions employed in the earlier study at least 20 % reversion had in fact taken place. Thus the results and conclusions drawn from the earlier study were cast into doubt and the work had to be repeated. This time proton magnetic resonance spectroscopy was used to determine the quantity of the products in the reaction mixture. The results were used to confirm a bimolecular mechanism involving two radical intermediates and the dienol **36** but convincing evidence for the presence of two triplet excited states leading to the different reactivity in polar and nonpolar solvents was not obtained.

In 1969 Schuster and Brizzolara[16] looked into the photochemistry of the related compound 10-hydroxymethyl-$\Delta^{1,9}$-2-octalone **37** and compared the results obtained with those from Schaffner's work.[4d] Contrary to Schaffner's findings for **27** they found no evidence for two reactive triplet excited states separated by a considerable energy difference in the reactions of **37**.

They concluded that the n,π^* and the π,π^* states are so close in energy that under the reactions conditions they exist in thermal equilibrium. On the other hand they did find evidence that the reaction that leads to the deconjugation of the starting enone is second order in enone. However, their suggested mechanism differs from Schaffner's; it was proposed that the triplet excited enone adds to the solvent

(benzene) to give a radical pair addition product which upon cleavage yields the deconjugated product **38**, as shown in SCHEME 9.



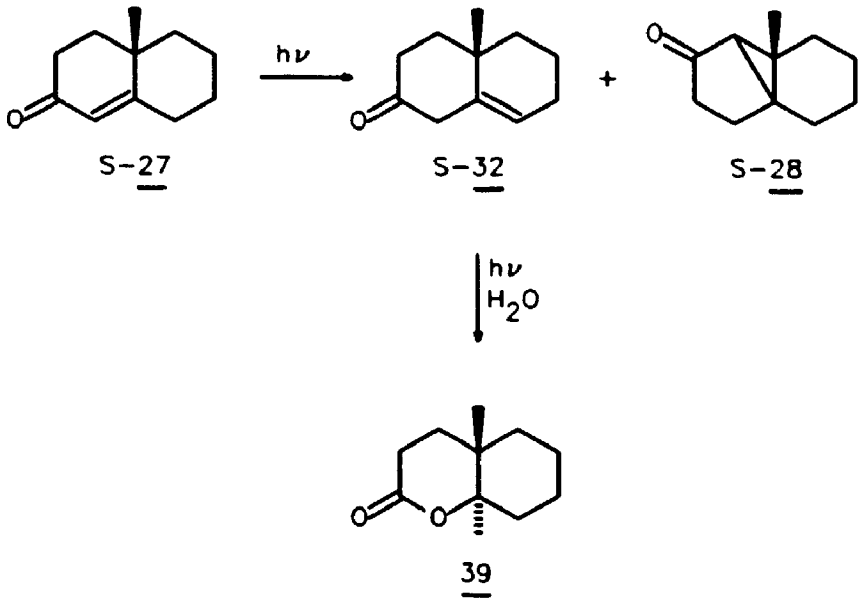
SCHEME 9

Deuterium incorporation studies using benzene-d_6 and the detection of biphenyl gave further support to this proposed mechanism.

The system involved in the the above investigation differs from the other deconjugation reports cited in this chapter in that deconjugation leads primarily to the endocyclic isomer as opposed to the exocyclic isomers; in addition it involves cleavage of a small fragment of the starting material. Consequently the results obtained in this study do not necessarily relate to the findings of earlier work on this subject.

Recently, Scaiano and co-workers[17] published the results of their work on the photochemical behaviour of *R*-10-methyl-$\Delta^{1,9}$-2-octalone in an α-cyclodextrin inclusion complex. Unfortunately their results were ambiguous since they referred in the text to the *R*-isomer of **27** but the illustrations showed the *S*-isomer. Irradiation of the complex in solid state and in aqueous solution led to the following results. In the solid state the ratio of deconjugation product to lumiketone rearrangement product was around 20:1, while in aqueous solution the ratio was similar to that obtained from excitation of the starting material dissolved in polar media and was around 1:8. Under both conditions a new product, **39**, was observed after prolonged irradiation time, resulting from addition of water to give a lactone. Following the irradiation by gas chromatography revealed that **39** is a secondary photoproduct derived from excitation of the deconjugated isomer **32**, as shown in SCHEME 10.

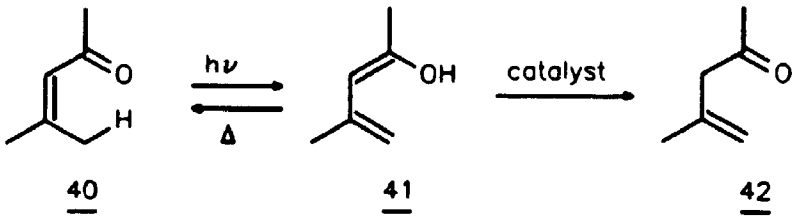
Scaiano et al. concluded that the fact that *S*-**32** was formed even when the starting material is included as a guest in α-cyclodextrin (and had thus very restricted mobility) points strongly to an intramolecular (and therefore unimolecular) process leading to the product observed.



SCHEME 10

In summary it can be said that the mechanism leading to the photochemical formation of the exocyclic β,γ-unsaturated isomer of a 3-alkyl α,β-unsaturated cyclohexenone has not been completely and satisfactory determined. Evidence on important points (i.e. molecularity, excited state(s) involved, solvent dependency, ground state intermediates and substituent effects) is inconclusive and sometimes contradictory.

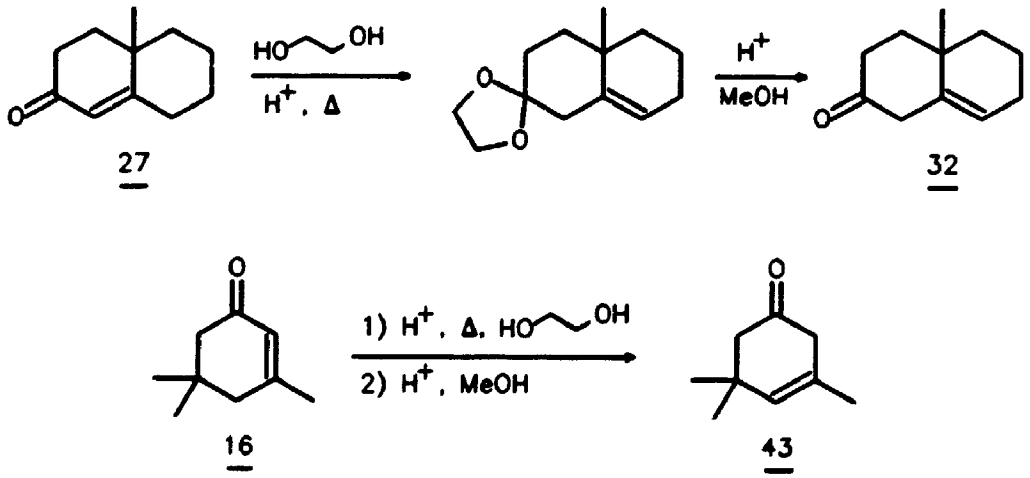
On the other hand the photochemical deconjugation reaction of the corresponding acyclic conjugated enones is a well understood process.[18] It proceeds *via* the S_1 state of an enone (eg. **40**) and involves formation of the dienol **41** by a photochemical 1,5-hydrogen transfer reaction. This is followed by acid or base catalyzed reketonization to the deconjugated isomer **42** as shown in SCHEME 11. Due to the skeletal rigidity of the six membered ring (which cannot change into the *s-cis* conformation) this route is not open to 3-alkyl-2-cyclohexenones.



40 41 42

SCHEME 11

The ground state deconjugation reaction of 3-alkyl-2-cyclohexenones is also known. In 1978 Babler et al.[19] reported details of the preparation of β,β-disubstituted α,β-unsaturated cyclohexenones. They were able to obtain the deconjugation product **32** using Schaffner's octalone **27** by ketalization and subsequent hydrolysis in 59 % overall yield; with **16** they isolated the endocyclic deconjugated isomer **43** and no exocyclic isomer **17** was found, as shown in SCHEME 12.



27 32

16 43

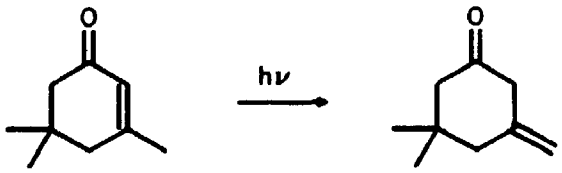
SCHEME 12

CHAPTER 2

ACID CATALYSIS OF THE PHOTOCHEMICAL DECONJUGATION REACTIONS OF 3-ALKYL-2-CYCLOHEXENONES

2.1 Introduction

In the mid 1980's work was undertaken by Lombardo and Weedon[20] to investigate the mechanism of the photodeconjugation reaction of 3-alkyl-2-cyclohexenones. Due to its availability and because it had been the subject of earlier studies of the photochemical deconjugation reaction,[4c,6,13] 3,5,5-trimethyl-2-cyclohexenone (isophorone, **16**) was chosen as the enone in that project. Irradiation in nitrogen purged ethyl acetate with Pyrex filtered light from a medium pressure mercury lamp ($\lambda \geq 313$ nm) resulted in incomplete conversion of **16** to its deconjugated isomer **17**.



16 **17**

This finding was in accordance with the results reported by Shiloff and Hunter.[13]

Short wavelength irradiation of **16** (low pressure mercury lamp, quartz vessel, $\lambda = 254$ nm) in diethyl ether also led to the formation of **17**. At low conversion **17** was formed with approximately zero order kinetics as determined by a plot of reaction

mixture against irradiation time. Changing the solvent to cyclohexane gave the same result. At higher conversions a secondary, unidentified product was seen, probably derived from light absorption by **17**.

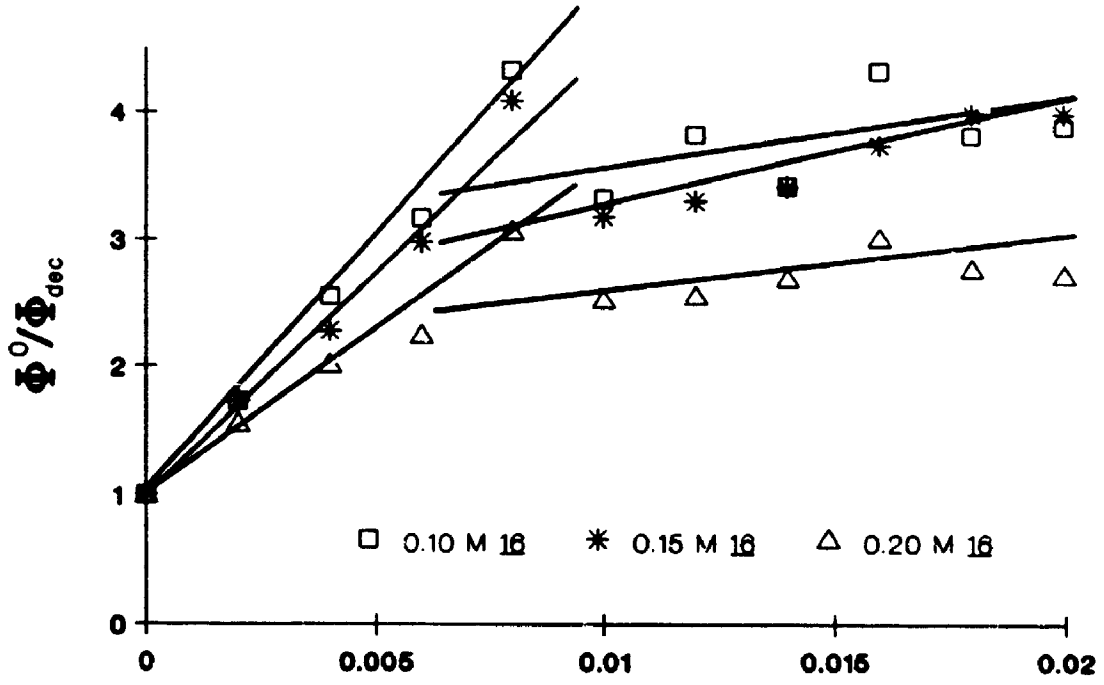
In order to determine the multiplicity of the excited state involved in the photodeconjugation reaction, sensitization and quenching studies were carried out.

Employing benzene both as solvent and as sensitizer, excitation with light of 254 nm initially resulted in rapid conversion of **16** to **17**. At longer irradiation times the rate of conversion of **16** fell as **17** competed with **16** in quenching the excited state of benzene. A number of by-products were observed and attributed to Norrish Type I photochemistry of **17**.

Following calibration of the 254 nm light source to determine its photon flux, the quantum yield for the sensitized formation of **17** was measured at low conversions (to avoid secondary photochemistry) in benzene. The value determined was *ca.* 0.004. Similarly the quantum yield for the disappearance of **16** was found to be *ca.* 0.007. A second experiment gave quantum yields of 0.007 and 0.009, respectively. Quantum yield of formation of **17** in benzene was also determined using longer wavelength light (λ = 313 nm), under which conditions **16** underwent direct excitation. The values obtained varied from 0.027 to 0.039 depending on the concentration of **16**.

Quenching experiments were undertaken at low conversion using 2,5-dimethyl-2,4-hexadiene as quencher in a Merry-Go-Round apparatus. The results were plotted in a Stern-Volmer diagram (quantum yield in the absence of quencher over quantum yield in its presence $[\Phi^0/\Phi^Q]$ against quencher concentration). The graphs obtained for three different isophorone concentrations were not linear but seemed to be made up of two intersecting lines with different slopes (FIGURE 2).

FIGURE 2: Stern-Volmer plot of early quenching experiments[20]



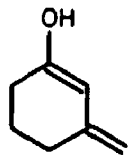
This type of behaviour is symptomatic of the presence of two different excited states leading to the same product. The slope of a straight line in a Stern-Volmer plot is equal to $k_q\tau$ where k_q is the diffusion controlled quenching rate constant and τ the lifetime of the excited state being quenched. Lombardo calculated the lifetimes of the two excited states corresponding to the two straight lines in his Stern-Volmer plot to be as shown in TABLE 1.

Analysis of this data led to the statement[20] that, since the lines corresponding to the shorter τ were of approximately the same gradient, the process being quenched was unimolecular whereas the lines for the longer lived state were not parallel, suggesting that the process being quenched may be bimolecular in nature (reaction of excited state **16** with ground state **16**).

TABLE 1: Earlier quenching studies of the isophorone deconjugation reaction

[16]	τ (s)
0.10 M	4.46×10^{-8}
	3.36×10^{-9}
0.15 M	4.09×10^{-8}
	5.48×10^{-9}
0.20 M	2.65×10^{-8}
	2.30×10^{-9}

Additional results were obtained from deuterium incorporation studies. Irradiation of **16** in diethyl ether containing 10 % (v/v) methanol-OD led, after 10 % conversion, to incorporation of one deuterium into 64 % of **17** and 22 % of **16**. This was interpreted as evidence for the intermediacy of a dienol species such as **44**.



44

In his summary Lombardo came to the conclusion that the photodeconjugation reaction of isophorone proceeds *via* both the singlet and triplet excited state (since the quenching studies pointed to the presence of two excited states) by a polar mechanism (incorporation of deuterium from methanol-OD rather than a hydrogen atom), possibly *via* the dienol **44**.

The purpose of this part of this thesis was to reinvestigate the photodeconjugation reaction of isophorone **16** and to gain further insight into the mechanism of this reaction. To begin, Lombardo's experiments were repeated in order to confirm his results.

2.2 Quantum Yield Determinations

2.2.1 Calibration of the Quantacount Instrument

The quantum yield Φ of a photochemical reaction is a measure of the efficiency of that process and is defined as the ratio of number of events over the number of photons absorbed. Its unit is mole/Einstein (mole/E) but it is usually given in dimensionless form.

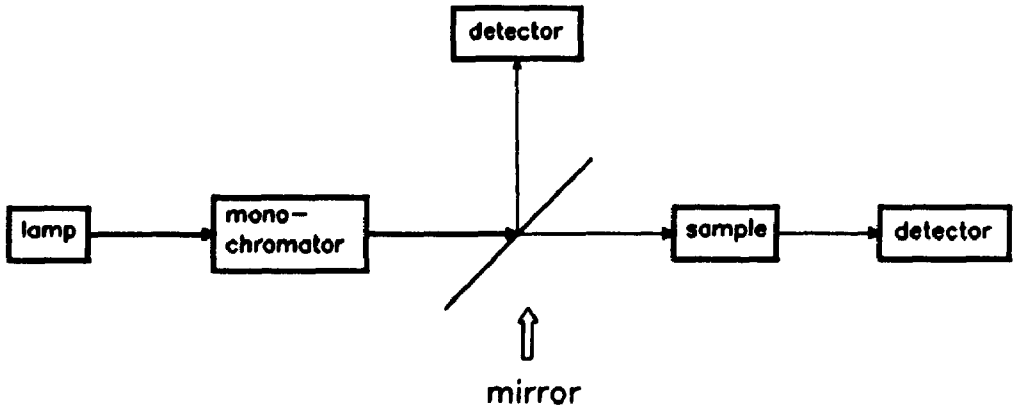
Two general methods are available for the measurement of quantum yields of photochemical reactions. One involves the calibration of a light source with a reaction of known quantum yield (an actinometer). This provides the researcher with a value for the photon flux (E/s) of the light source which can be used to calculate absolute quantum yields if the products of subsequent irradiations are quantified. The advantage of this method is the simple setup of an experiment to determine quantum yields; once the photon flux is known one only has to carry out one irradiation in one vessel for a certain time to come up with a value. A major disadvantage is the fact that the photon flux of a light source is not constant with time; usually over both short and long time spans the lamp output varies. Consequently actinometry has to be performed frequently, making the assumption that the photon flux is constant between determinations.

Another way to determine quantum yields avoids the shortcoming of the above method by parallel irradiation of a number of samples in a Merry-Go-Round apparatus. In this setup the samples are held in a carousel which rotates around a light source to achieve identical illumination of each sample. Product yield determination after irradiation provides relative quantum yields or, if one of the samples is an actinometer, absolute values by comparison. The advantage of this apparatus is that it is not

necessary to know the photon flux of the light source since all the samples are exposed to the same photon dose. A disadvantage is that many samples have to be made up simultaneously and all must possess the same absorbance at all the wavelengths of the lamp output.

The Quantacount instrument, marketed by Photon Technologies International (PTI), provides a convenient method to measure absolute quantum yields by combining the best features of the above methods. This apparatus was used extensively in this work; since it is a specialist instrument and not widely available, it will be briefly described here and is schematically shown in FIGURE 3.

FIGURE 3: The Quantacount instrument (schematic)



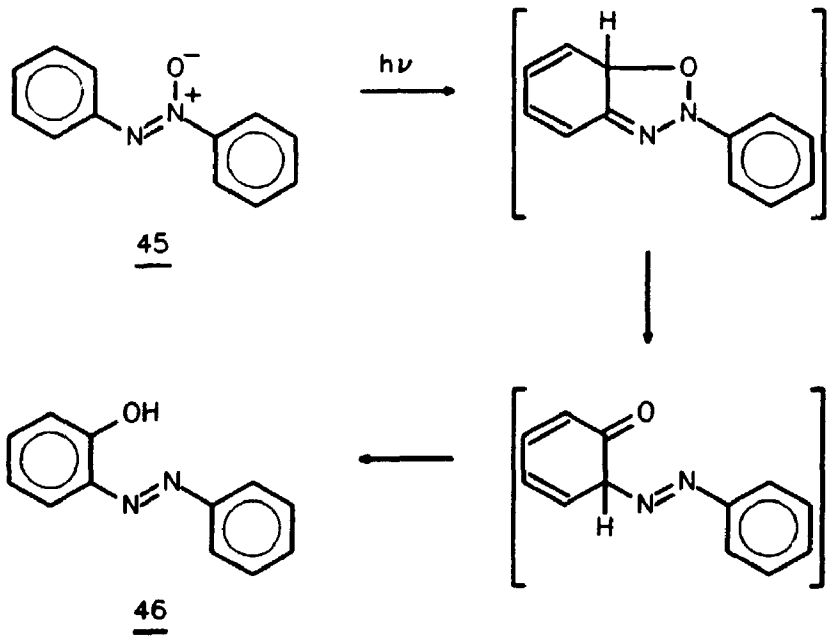
In this apparatus a light source (in this work a 100 W super high pressure mercury arc was used) is focused into a monochromator. The selected wavelengths are then passed to a light splitter. A fraction of the light is deflected into a cuvette containing a solution of a rhodamine dye causing it to fluoresce. The fluorescence intensity is measured by a photon detector mounted behind the cuvette. The non-deflected light travels through the splitter to a cuvette holding a solution of the sample

under investigation. Any unabsorbed light passing through the sample cuvette also impinges upon a cuvette containing rhodamine dye solution and the resulting fluorescence is quantified by a photon detector.

In the absence of a sample the two detectors are electrically balanced; in the presence of the sample the difference between the signals of the two detectors is proportional to the amount of light absorbed by the sample. This signal can be calibrated using an actinometer and integrated electronically with time so as to yield an absolute value for the numbers of photons absorbed by the sample. The advantage of this apparatus is that it automatically corrects for variation in lamp intensity and for incomplete light absorption by the sample. In addition, because the detectors are responding to rhodamine fluorescence, the calibration is independent of the wavelength of the light used for an experiment.

Calibration of the Quantacount apparatus requires an actinometer. This can be any photochemical reaction for which the quantum yield is reliably known. A number of actinometers are frequently used but perhaps the most common one is the ferrioxalate system[21]. This actinometer uses the photoreduction of potassium ferrioxalate to Fe^{2+} and has a number of advantages, such as wide useful spectral range, high sensitivity and reliability. Its main disadvantages are that quite a number of manipulations must be carried out and all of the procedures must be performed in the dark.

Recently Bunce et al.[22] reported the use of the photorearrangement of azoxybenzene **45** to 2-hydroxyazobenzene **46** as an actinometer system, outlined in SCHEME 13.



SCHEME 13

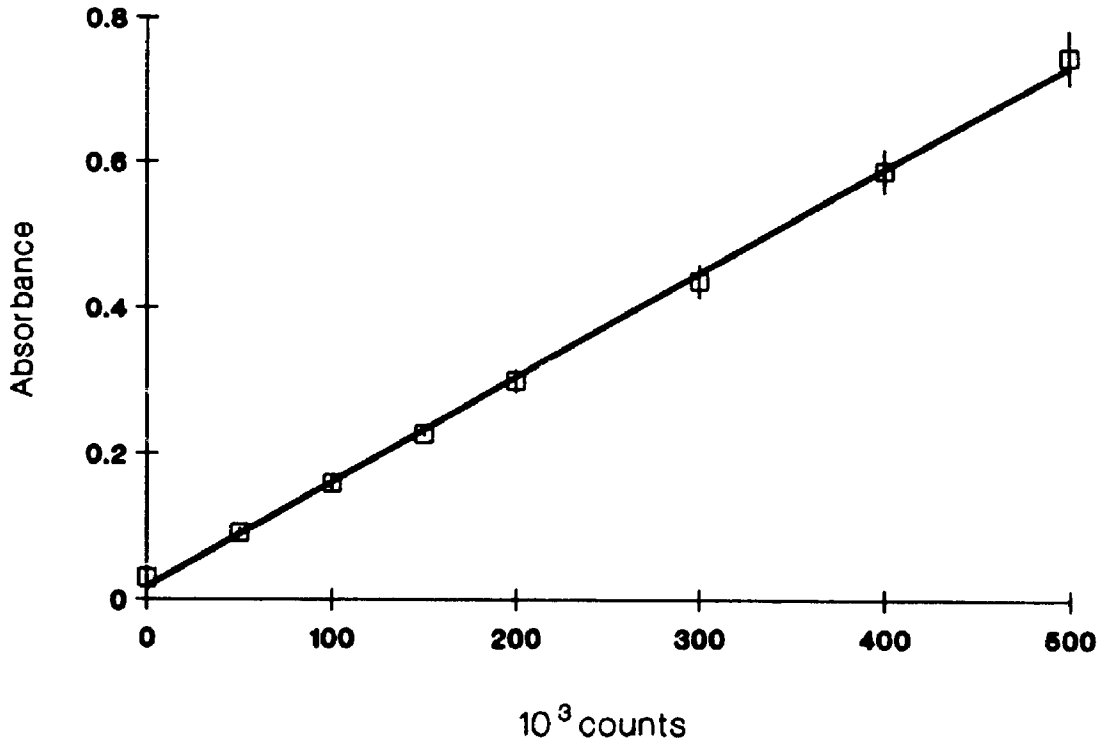
This system was used in this work to calibrate the Quantacount detector because it provided a convenient actinometer which was easy to prepare in subdued light and was stable over a large range of temperature and concentration variations. Irradiation of an ethanolic KOH solution of **45** at 348 nm leads to the formation of the anion of **46** which at low conversions does not absorb in this range but can be monitored at 458 nm where **45** does not absorb.

The calibration sequence involved irradiating an aliquot of a solution of **45** in ethanolic KOH for a given number of counts* in the Quantacount immediately followed by determination of the absorbance of **46** at 458 nm. Repeating this for

* The time integrated detector response of the Quantacount is in "counts", a count being proportional to a photon dose.

different numbers of counts and plotting absorbance vs counts led to a straight line with a slope B of 1.440×10^{-6} Abs/count ± 14 % as shown in FIGURE 4.

FIGURE 4: Quantacount calibration



Using this value in the following equation (EQUATION 1) allows the calculation of the calibration constant I_c, which is the photon flux/count for the Quantacount instrument. The value determined was 2.2373×10^{-11} E/count ± 19 %.

$$I_o = \frac{B \times V}{\epsilon \times \Phi} \qquad \text{Eq. 1}$$

where

$B = 1.44 \times 10^{-6} \pm 14\ \%$ Abs count^{-1}

$V = 3.00 \times 10^{-3}$ l

= volume of solution irradiated

$\epsilon = 7600$ Abs l mole^{-1}

= extinction coefficient of **46** at 458 nm in basic EtOH

$\Phi = 0.025 \pm 5\ \%$ mole Einstein^{-1}

= quantum yield for formation of **46** from **45** at 348 nm

2.2.2 Photochemical Deconjugation Reaction of Isophorone 16

Irradiation of nitrogen purged solutions of **16** in either diethyl ether or cyclohexane in a Pyrex container with light from a medium pressure mercury lamp led to the expected reaction to give the exocyclic deconjugated product **17**.

16 17

The progress of the reaction was monitored by gas chromatography; the formation of a product with a shorter retention time than the starting material was observed. Analysis by gas chromatography coupled mass spectroscopy (gc/ms) revealed that the molecular weight of the product was 138, which is the same as **16**. Proton magnetic resonance spectroscopy indicated that this product was **17**, as it

showed a signal at 4.75 ppm integrating for two protons, assigned to the exocyclic double bonded methylene. This is in accordance with Lombardo's work.[20] The irradiation times, however, were significantly increased compared to Lombardo's work.

Initial deuterium incorporation studies were carried out, which verified the earlier results.[20] Nitrogen purged ether solutions of **16** were irradiated in the presence of methanol-OD (10 % v/v) and were analyzed by gc/ms to determine the deuterium content in **16** and **17**. The results listed in TABLE 2 were obtained.

TABLE 2: Preliminary deuterium incorporation studies

Irradiation time	Deuterium in **17**	Deuterium in **16**
141 h	36 %	2 %
468 h	56 %	22 %

These results resembled Lombardo's findings. However, much longer irradiation times were again found to be necessary. For example, Lombardo had reported irradiation times of around 8 hours to achieve 10 % conversion of **16** to **17** whereas the results of this work showed that at least 136 hours of irradiation time were required to generate 10 % conversion of **16**.

Experiments were then undertaken to determine the quantum yield of the deconjugation, Φ_{dec}, using the Quantacount instrument, using the freeze-pump-thaw technique to remove dissolved oxygen from the solutions. All quantum yield determinations reported in this work were carried out using the same technique; this is briefly described below and in more detail in the experimental section.

A 3.00 ml aliquot of a solution of known concentration of the enone containing a suitable photochemically inert standard was subjected to three freeze-pump-thaw

cycles and then irradiated in the Quantacount at 313 nm for a given number of counts (corresponding to a given number of photons absorbed). The known gc ratio of starting material to standard and the gc ratio of product to standard, determined after the irradiation, were then used to calculate the absolute amount of product formed, which allowed for the calculation of Φ. It was assumed that **16** and **17** were detected with equal efficiency by the gc detector (i.e. that they had identical response ratios); this assumption is reasonable since **16** and **17** are isomers with very similar structures and would be expected to have similar response ratios.

Preliminary calculations using the previously determined value of the quantum yield for deconjugation, Φ_{dec}, of 0.04[20] showed that in order to achieve 5 % conversion of **16** to **17**, 3 ml of a 48 mM solution of **16** in pentane would have to be irradiated in the Quantacount instrument for about 8×10^6 counts.* However, irradiation for 1.723×10^6 counts did not lead to a detectable amount of **17** in the mixture; in order to observe **17** by gc the irradiated solution had to be concentrated. This made accurate quantum yield determination impossible since the standard used (2-methylnonane) is more volatile than both **16** and **17**. Furthermore **17** was known to slowly reconjugate to **16** thermally[4c,13] so that any excessive handling of the irradiated solution could have given erroneous results. A value of Φ_{dec} of 0.04 should have led to about 1 % conversion which would have been easily detected by gas chromatography.

Another set of experiments was carried out, this time in benzene instead of pentane. Irradiation of a 71 mM solution of **16** for about 1.8×10^6 counts gave no detectable amount of **17**. Concentration of the sample allowed the estimation of an

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* Using the value 1 count = 2.373×10^{-11} Einsteins determined as described in Section 2.2.1.

inaccurate value of Φ_{dec} of *ca.* 0.0073 ± 4.6 %, or about one order of magnitude smaller than expected. In order to determine the effect of oxygen on the photodeconjugation reaction an identical sample was irradiated in the Quantacount instrument, but without prior degassing. Again the resulting mixture had to be concentrated in order to see **17** in the gas chromatogram and Φ_{dec} was calculated to be ≈0.0015 ± 18 %, significantly lower than that in the absence of oxygen, thus emphasizing the importance of proper degassing technique. Since molecular oxygen exists as a triplet in its ground state and is known to be an effective triplet quencher[23] (E_T = 22.5 kcal/mole), this result pointed to the involvement of the triplet excited state of **16** in the deconjugation reaction. A more extended irradiation of an identical sample (with degassing) for 7.2 x 10^6 counts led to about 0.3 % conversion to **17** and allowed the calculation of Φ_{dec} without concentration to be 0.0040 ± 22 %, confirming that it is one order of magnitude smaller than Lombardo's value. In another experiment Φ_{dec} was determined for a 148 mM solution of isophorone in benzene in the presence of two standards, 2-methylnonane and the less volatile dodecane. Irradiation for ≈ 1.8 x 10^6 counts gave the results listed in TABLE 3.

TABLE 3: Difference in Φ_{dec} of isophorone with various standards and conditions

Analysis conditions	Φ_{dec} calculated vs 2-methylnonane	Φ_{dec} calculated vs dodecane
direct	0.0181 ± 7.6 %	0.0087 ± 3.6 %
concentrated	0.0098 ± 18 %	0.0066 ± 6.6 %

As can be seen concentration of the irradiated mixture led to a considerable change in Φ_{dec} demonstrating that this was not a reliable way to calculate quantum

yields. It also showed that dodecane was a better standard since it was much less affected by concentration and gave smaller errors in the results due to evaporation loss. The larger values for Φ_{dec} when calculated using 2-methylnonane as a standard are the result of its higher volatility leading to handling losses. A number of Φ_{dec} determinations in benzene with dodecane as standard were performed to verify the above results. These are listed in TABLE 4.

TABLE 4: Φ_{dec} of isophorone in benzene

[16]	Light absorbed (E)	Φ_{dec}
148 mM	4.077×10^{-5}	0.0066 ± 6.6 %
148 mM	1.671×10^{-4}	0.0039 ± 6.6 %
143 mM	4.093×10^{-5}	0.0079 ± 4.3 %
143 mM	8.531×10^{-5}	0.0063 ± 3.3 %
143 mM	2.513×10^{-4}	0.0046 ± 3.0 %
143 mM	2.991×10^{-4}	0.0036 ± 4.6 %
143 mM	4.904×10^{-4}	0.0040 ± 2.7 %
3 mM	7.958×10^{-5}	0.0042 ± 5.8 %
15 mM	1.592×10^{-4}	0.0035 ± 8.1 %
44 mM	1.592×10^{-4}	0.0033 ± 1.8 %
73 mM	1.592×10^{-4}	0.0036 ± 2.0 %
102 mM	1.592×10^{-4}	0.0036 ± 3.4 %
117 mM	1.592×10^{-4}	0.0053 ± 1.6 %
649 mM	1.592×10^{-4}	0.0126 ± 3.3 %

The most important point to note about the quantum yields listed in the above table is that they vary in an irregular manner. The first seven entries in the table are for similar concentrations of **16** and appear to indicate a decrease in Φ_{dec} with higher

photon dose. The second set of seven entries in the table shows evidence of concentration dependence of Φ_{dec} at higher concentrations of **16** under otherwise identical conditions. In all cases the conversion of **16** to **17** was kept well below 5 % so that secondary photochemistry leading to depletion of **17** was avoided.

Values of Φ_{dec} were also determined at similar isophorone concentrations in various solvents. The results are summarized in TABLE 5.

TABLE 5: Φ_{dec} of isophorone in various solvents

Solvent	[16]	Φ_{dec}
Benzene	145 mM	0.0013 ± 6.4 %
Cyclohexane	142 mM	0.0008 ± 25 %
Diethyl ether	127 mM	0.0004 ± 30 %
Acetonitrile	139 mM	0.0009 ± 9.2 %

photon dose = 1.592×10^{-4} E

The variation in quantum yield is dramatic; of even more importance is the observation of a value of Φ_{dec} of 0.0013 in benzene; the values determined before under similar conditions are listed in TABLE 4 and were in the range of 0.0040 - 0.0079. The cause of this decline in Φ_{dec} was sought; one factor which had changed between the Φ_{dec} determinations listed in TABLE 4 and TABLE 5 was the sample of isophorone used. The data in TABLE 4 had been determined using a sample of **16** purified by distillation, while the later data in TABLE 5 were obtained using a newly purified sample of **16** which had also been washed with 5 % aq. sodium bicarbonate prior to distillation.[24a] This fact led to the suspicion that the base wash had removed an acidic impurity in the isophorone and that this impurity might have had some effect on the photochemical deconjugation reaction of isophorone.

2.2.3 Acid Catalysis in the Photochemical Deconjugation Reaction of Isophorone 16

In order to test the possibility that acid catalysis might be important in the photochemical deconjugation reaction of **16**, a series of quantum yield determinations for conversion of **16** to **17** was performed with different concentrations of acid present. Acetic acid (AcOH) was chosen as the acid. This choice was made because AcOH is readily soluble in benzene and it does not absorb light at the irradiation wavelength of 313 nm. The effect of addition of base upon Φ_{dec} was also examined. The bases used were dimethylimidazole (DMI) and triethylamine (NEt_3). These were chosen for their solubility and absorbing properties. The results are given in TABLE 6.

TABLE 6: Φ_{dec} of isophorone with added acid and base

[16]	catalyst	Φ_{dec}
145 mM	-	0.0013 ± 6.8 %
145 mM	1.0 mM AcOH	0.0356 ± 4.6 %
145 mM	1.9 mM NEt_3	0.0016 ± 5.4 %
139 mM	0.8 mM DMI	0.0014 ± 10 %

solvent = benzene, photon dose = 2.046×10^{-4} E

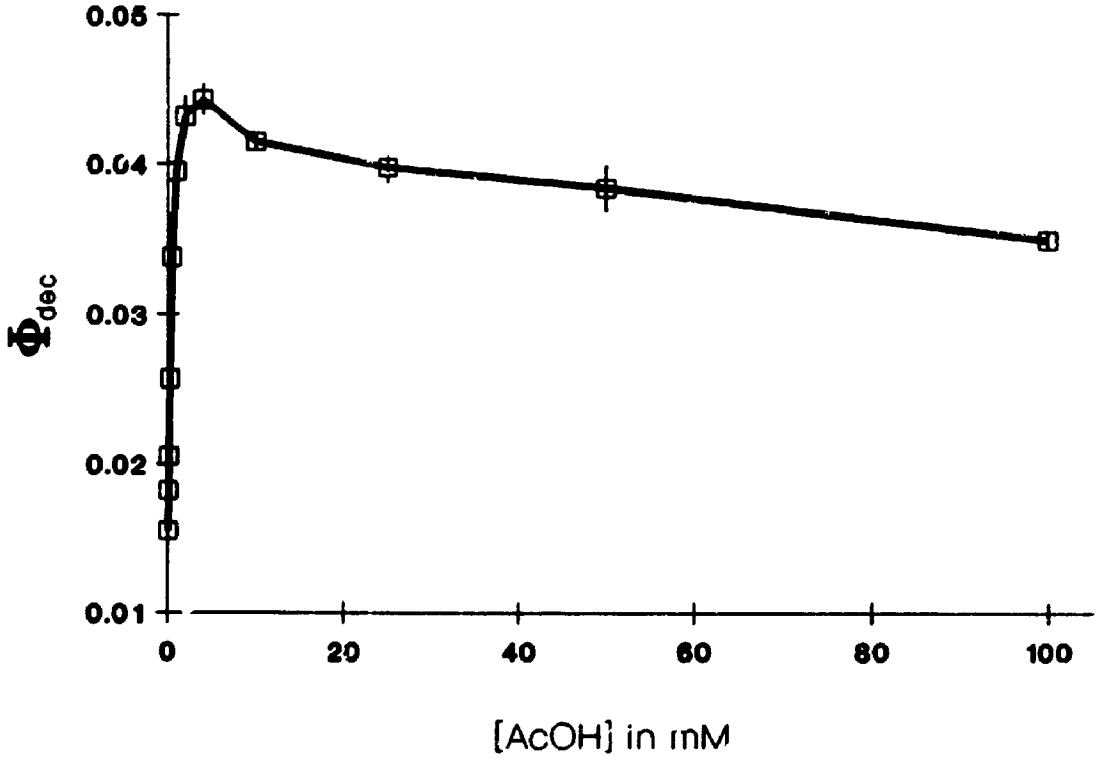
These results show clearly that addition of base to the purified isophorone does not have any effect on the efficiency of deconjugation of **16** to **17** while addition of acid leads to an increase of Φ_{dec} by a factor of over 25. Since the presence of acid appeared to catalyze the photodeconjugation reaction, values of Φ_{dec} at various acid concentrations were determined. The results are summarized in TABLE 7 and plotted as a graph in FIGURE 5.

TABLE 7: Φ_{dec} of isophorone at various concentrations of acetic acid

[AcOH]	Φ_{dec}	[AcOH]	Φ_{dec}
0.10 mM	0.0155 ± 4.8 %	2.0 mM	0.0432 ± 2.9 %
0.12 mM	0.0182 ± 3.3 %	4.0 mM	0.0443 ± 2.3 %
0.15 mM	0.0205 ± 1.3 %	10 mM	0.0415 ± 1.2 %
0.25 mM	0.0257 ± 2.4 %	25 mM	0.0398 ± 1.8 %
0.5 mM	0.0338 ± 1.8 %	50 mM	0.0384 ± 3.9 %
1.0 mM	0.0395 ± 2.6 %	102 mM	0.0350 ± 1.2 %

solvent = benzene, [16] = 145 mM, photon dose = 2.046×10^{-4} E

FIGURE 5: Plot of Φ_{dec} of isophorone vs concentration of acetic acid



The data show that maximum deconjugation efficiency occurs at *ca.* 4 mM AcOH and imply that at zero acid concentration little or no deconjugation should occur. The results also suggest an explanation for the discrepancy observed between the

results reported by Lombardo[20] and those found in this work, namely that isophorone contains an acidic impurity which catalyzes the photodeconjugation with an efficiency which is dependent on the impurity concentration. The data plotted in FIGURE 5 also indicate that at AcOH concentrations greater than 4 mM the value of Φ_{dec} falls. This observation was initially attributed to the fact that acetic acid is known to form hydrogen-bonded dimers in benzene at higher concentrations; consequently the effective acid concentration is lowered.[25] No evidence was found for thermal reconjugation of **17** to **16** during the time frame of an experiment (see Experimental Section).

Since Schaffner had observed evidence of a bimolecular process in the deconjugation of **27**[4d] the effect of the isophorone concentration on Φ_{dec} was also determined with acetic acid present at its optimum concentration of 4.0 mM. The results are given in TABLE 8 and plotted as graph in FIGURE 6.

TABLE 8: Φ_{dec} of isophorone at various concentrations

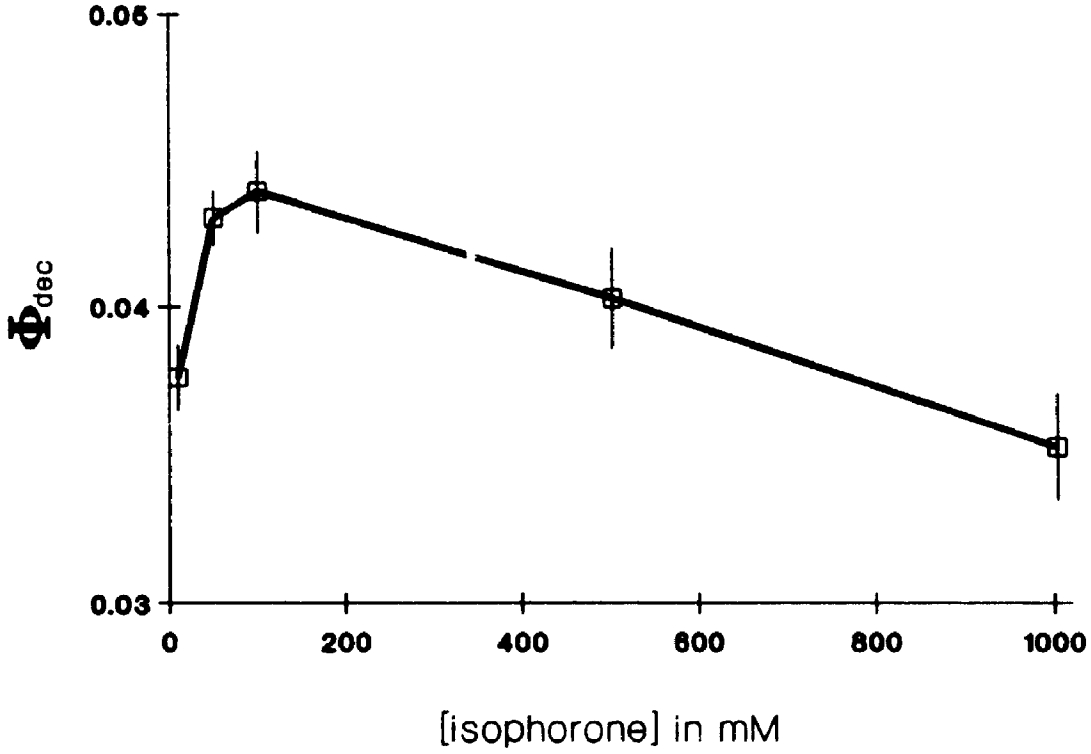
[**16**]	Φ_{dec}
10 mM	0.0376 ± 2.9 %
50 mM	0.0430 ± 2.0 %
100 mM	0.0439 ± 3.1 %
503 mM	0.0403 ± 4.1 %
1005 mM	0.0353 ± 5.0 %

solvent = benzene, [AcOH] = 4 mM, photon dose = 1.137×10^{-4} E

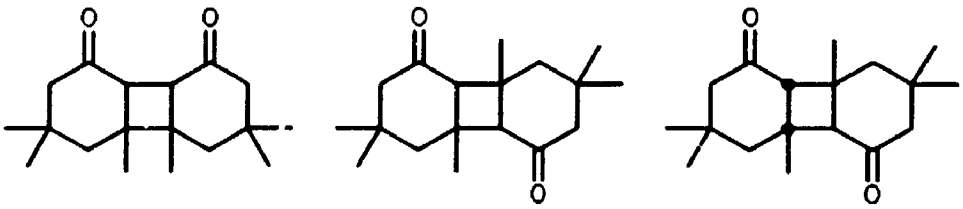
The data show that Φ_{dec} decreases at higher isophorone concentration. This is the reverse of the effect expected if the deconjugation reaction were a bimolecular process second order in **16**. It is tempting at this point to conclude that Schaffner's observations are a consequence of an acidic impurity in his enone sample. Thus as the

enone concentration was raised so was the concentration of the impurity with the consequence that the deconjugation efficiency was also increased.

FIGURE 6: Plot of Φ_{dec} of isophorone at various concentrations



The 20 % decrease in deconjugation quantum yield observed in FIGURE 6 when the isophorone concentration is raised from 0.1 M to 1 M may be due to a self quenching process. The interaction of an isophorone molecule in its triplet excited state with a ground state isophorone molecule is known to result in quenching and photodimerization. For example Chapman and coworkers[27] investigated the photodimerization of **16** and isolated three different dimers **47**, **48** and **49**. They found that the ratio of head-to-head dimer (**47**) to head-to-tail dimer (**48** and **49**) is highly solvent dependent. In nonpolar solvent (cyclohexane) it was 1:4, in polar protic solvents (methanol, 90 % aqueous acetic acid) it was 4:1.

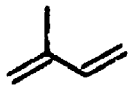


47 48 49

In the qualitative irradiations carried out during the initial stages of this project at least two products at long gc retention times were observed which had the correct mass for dimers of **16**. They accounted for *ca.* 15 % of the products but were not characterized further. In the quantum yield determinations these products were not observed; due to their long retention times and the temperature program used they did not elute from the column.

To determine the effect of moisture in the benzene used on Φ_{dec} of **16**, an experiment was carried out ([**16**] = 126 mM, photon dose = 1.364×10^{-4} E, [AcOH] = 4.2 mM) in dried benzene.[24b] The resulting quantum yield of 0.0478 was in good agreement with values obtained from comparable runs where benzene was not dried so that it was concluded that the effect of moisture in this solvent was negligible.

To determine the multiplicity of the excited state responsible for the acid catalyzed photodeconjugation of **16**, a series of quenching experiments were undertaken. Isoprene, **50**, which has a triplet energy of 60.1 kcal/mole[23],was used as a quencher.



50

The results of this quenching study are given in TABLE 9.

TABLE 9: Quenching of the isophorone deconjugation reaction with isoprene

[50]	Φ_{dec}	Φ^o/Φ_{dec}
0	0.0487 ± 2.9 % (Φ^o)	1.00 ± 2.9 %
8.1 mM	0.0290 ± 3.1 %	1.68 ± 6.0 %
10 mM	0.0262 ± 2.3 %	1.86 ± 5.2 %
20 mM	0.0193 ± 3.3 %	2.52 ± 6.2 %
50 mM	0.0105 ± 3.3 %	4.64 ± 6.2 %
81 mM	0.0072 ± 3.7 %	6.76 ± 6.6 %
101 mM	0.0064 ± 10 %	7.61 ± 13 %

solvent = benzene, [16] = 140 mM, [AcOH] = 4 mM,
photon dose = 1.364 x 10^{-4} E, Φ^0 is Φ_{dec} of 16 for [50] = 0

Using the data from TABLE 9 a Stern-Volmer plot was constructed in which Φ^o/Φ_{dec} (the ratio of quantum yields in the absence and presence of quencher) was plotted against the quencher concentration. This is shown in FIGURE 7 and indicates a linear relationship which, contrary to Lombardo's findings[20], points to the involvement of only one excited state species in the photodeconjugation reaction of 16.

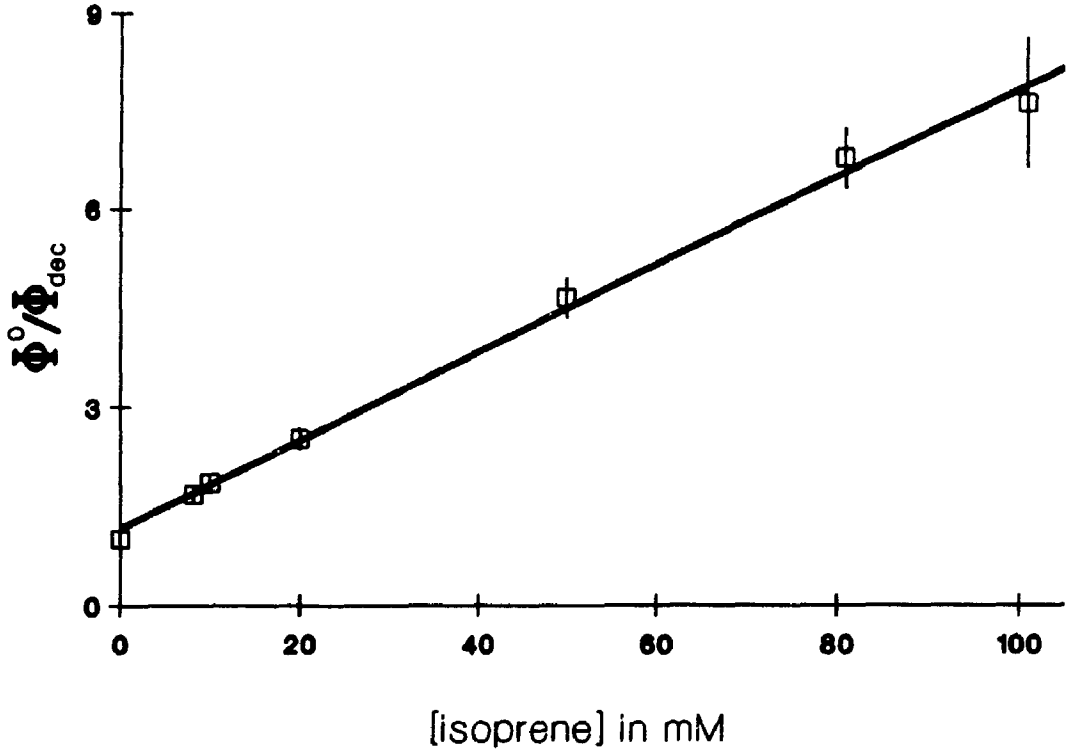
The slope of the line in FIGURE 7 is equal to $k_q\tau$ if the Stern-Volmer equation (EQUATION 2) applies and was determined to be 66.4 ± 3.2 %.

$$\frac{\Phi^o}{\Phi_{dec}} = 1 + k_q\tau[52] \qquad \text{Eq. 2}$$

Using the assumption that the quenching rate constant k_q approaches the diffusion controlled rate constant k_{diff} (1.5 x 10^{10} in benzene[23]) the lifetime τ of the excited species responsible for deconjugation was calculated to be 4.4 ns ± 3.2 %. This value is similar to typical values of cyclohexenone triplet lifetimes (Wagner and

Bucheck[26] reported a triplet lifetime of 3.3 ns for 2-cyclohexenone) and suggests that the excited state responsible for the photodeconjugation of **16** is its lowest triplet.*

FIGURE 7: Stern-Volmer plot of the quenching data



The question of the mechanism of the photodeconjugation of the triplet excited state of isophorone still remained to be answered. From the results given above it is clear that presence of acetic acid increases the deconjugation quantum yield dramatically. Comparison of the UV absorption spectra of **16** in the absence and presence of acetic acid at concentrations sufficient to catalyze deconjugation indicated that a ground state interaction (some kind of complex formation) between the enone

* However, recent data obtained by Schuster and coworkers using flash photolysis and photoacoustic calorimetry resulted in a value of 79 ns for the triplet lifetime of **16**.[144] This also led to the conclusion that the quenching of the triplet excited state of **16** by dienes proceeds slower than the diffusion controlled rate.

and the acid could be excluded because there was no detectable difference between the spectra.

In addition, the lifetime of 4.4 ns, estimated from Stern-Volmer quenching, for the triplet excited state of **16** implicated in the deconjugation reaction was thought to be too short lived to react with the acetic acid at its optimum concentration (4 mM) for deconjugation catalysis. This is because for a 4.4 ns transient to collide and react with a partner at 4 mM concentration a rate constant of the order of 10^{12} $M^{-1}s^{-1}$ would be required, which is two orders of magnitude higher than the diffusion controlled rate constant. Normal triplet decay of **16** would be much more efficient under these conditions.[1]

This necessitates the introduction of a post-triplet excited state species into the mechanism in order to provide an intermediate with a sufficiently long lifetime to be able to react with low concentrations of acetic acid.* A reasonable candidate for this intermediate would be a *trans*-cyclohexenone species.[28]

There is a reasonable literature precedent for a *trans*-cyclohexenone intermediate. Wagner's work on the photodimerization of 2-cyclohexenone led to the suggestion that a twisted triplet excited state was an intermediate in the reaction.[26] This suggestion was partly based on findings by Eaton and Corey who had reported evidence that 2-cyclooctenone **51** and 2-cycloheptenone **52** undergo photochemical *cis*→*trans* isomerization.[29] It was shown that the *trans*-isomers of **51** and **52** were short-lived intermediates which react further to give products of dimerization and addition reactions in the absence of light.

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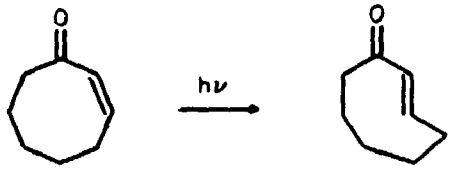
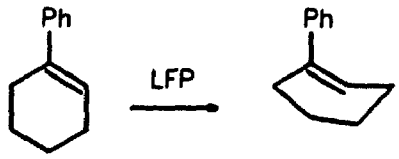
* In fact, if a 79 ns lifetime for the isophorone triplet is assumed, it is just possible that acid could react directly with the triplet if the protonation is diffusion controlled.



51

52

In 1976 Joussot-Dubien et al.[30] reported evidence that *trans*-1-phenylcyclohexene is formed during laser flash photolysis of *cis*-1-phenylcyclohexene **53**. They found that the intermediate was quenched by protons since the rate of its disappearance increased with increasing acidity of the solution. The direct quenching product was a carbocationic species (derived from proton attack with Markovnikov regiochemistry) which reacted with methanol to give an ether.

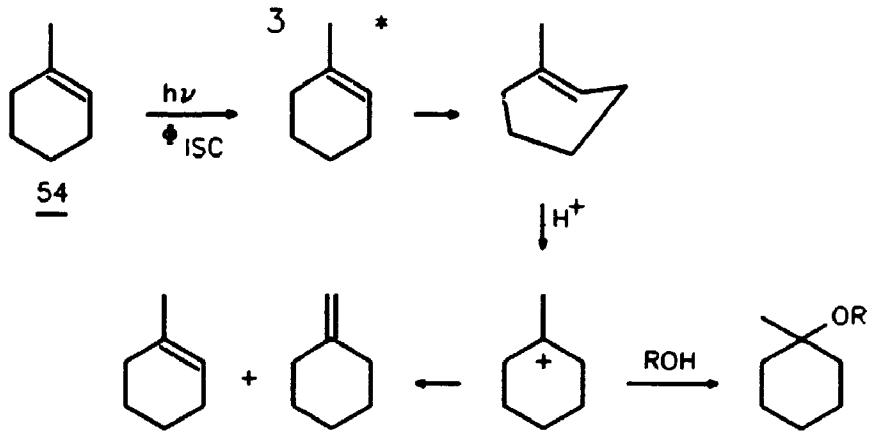


53

Similar *trans*-cyclohexene species had been proposed before.[31] In 1969 Marshall proposed that the products seen in the irradiation of 1-methylcyclohexenes in the presence of alcohols or acids were derived from a common intermediate.[31a] For example the photolysis of 1-methylcyclohexene, **54**, in the presence of acetic acid led to formation of an acetate and a rearranged product with an exocyclic double bond in

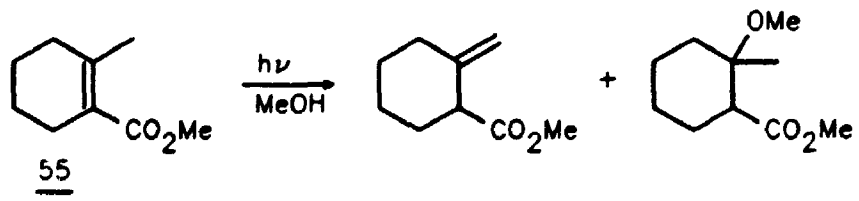
a ratio of 3:2. Marshall proposed a *trans*-cyclohexene species which was quenched by acid to a Markovnikov oriented tertiary cation as an intermediate.

Kropp et al. also investigated the photoreactions of 1-methylcyclohexene.[31b-d] Their results indicated that the *trans* species was derived from the triplet excited state of the alkene and was quenched by protons to give a cation which could undergo proton loss to either revert back to **54** or to the exocyclic isomer. Alternatively the presence of alcohol would give the ether as shown in SCHEME 14.



SCHEME 14

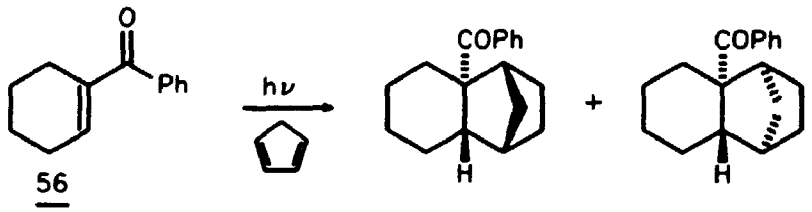
In 1973 Majeti and Gibson reported the photochemical deconjugation of the unsaturated ester **55** in methanol to give a product with an exocyclic double bond and a methanol adduct (SCHEME 15).[31e]



SCHEME 15

Based on the results bv Marshall and Kropp the authors explained the products by protonation of the *trans*-isomer of **55**; in dry acetonitrile, a non-protic solvent, none of the above products were observed.

Similar conclusions were drawn by Schaffner et al. when they investigated the photochemistry of ketone **56**.[31f] The intermediacy of its *trans*-isomer was suggested by its addition reaction to cyclopenta 'iene since the observed Diels-Alder adducts had *trans*-fused rings in their structures, as indicated in SCHEME 16.

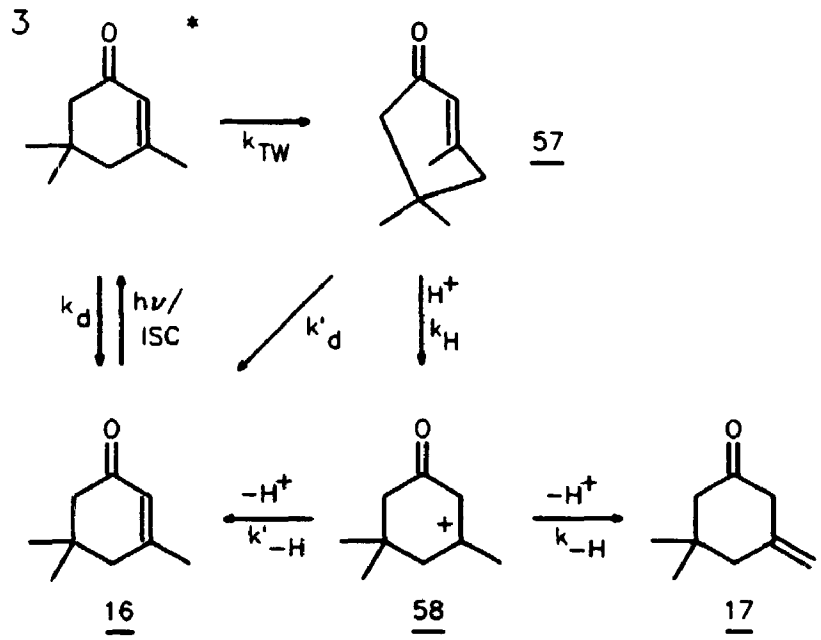


SCHEME 16

If the intermediacy of a *trans*-cyclohexenone intermediate is accepted, then the mechanism of the acid catalyzed photochemical deconjugation reaction of isophorone can be described as shown in SCHEME 17.

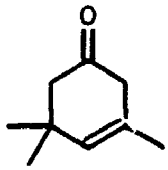
In this scheme, excitation of **16** followed by intersystem crossing yields the twisted triplet excited state. Intersystem crossing then gives the strained, highly reactive ground state *trans*-enone **57**.

In absence of acid this can revert to the ground state of **16**; if acid is present, however, then protonation of the *trans* species with Markovnikov regiochemistry would give the tertiary carbocation **58**. Since the solvent is benzene this would probably exist in a solvent cage with the conjugate base of the acid. Elimination of a proton from **58** could lead either to starting enone **16** or the deconjugated isomer **17**.



SCHEME 17

Inspection of molecular models indicated that **58** was much more likely to lose a proton from the 3-methyl group than from the 4-position because free rotation of the methyl group increases the probability of a favourable conformation for the loss of a proton. Models also showed that the two protons in the 4-position are not coplanar with the empty p-orbital of the cationic centre and twisting would have to be involved to make them available for abstraction. This could explain why none of the endocyclic deconjugated isomer **43** was observed.



43

Kinetic treatment of the mechanism shown in SCHEME 17 gave rise to the following set of equations.

$$\frac{d[^3E]}{dt} = I_a\Phi_{ISC} - (k_d+k_{TW})[^3E] \qquad \text{Eq. 3}$$

$$\frac{d[\underline{57}]}{dt} = k_{TW}[^3E] - (k_H[HOAc]+k_d')[\underline{57}] \qquad \text{Eq. 4}$$

$$\frac{d[\underline{58}]}{dt} = k_H[HOAc][\underline{57}] - (k_{-H}+k'_{-H})[\underline{58}] \qquad \text{Eq. 5}$$

$$\frac{d[17]}{dt} = k_{-H}[\underline{58}] \qquad \text{Eq. 6}$$

Under steady state assumptions ($d[^3E]/dt = 0$, $d[\underline{57}]/dt = 0$, $d[\underline{58}]/dt = 0$) the following equations could be derived:

$$[^3E] = \frac{I_a\Phi_{ISC}}{k_d+k_{TW}} \qquad \text{Eq. 7}$$

$$[\underline{57}] = I_a\Phi_{ISC}\left(\frac{k_{TW}}{k_d+k_{TW}}\right)\left(\frac{1}{k_H[HOAc]+k_d'}\right) \qquad \text{Eq. 8}$$

$$[\underline{58}] = I_a\Phi_{ISC}\left(\frac{k_{TW}}{k_d+k_{TW}}\right)\left(\frac{1}{k_{-H}+k'_{-H}}\right)\left(\frac{k_H[HOAc]}{k_H[HOAc]+k_d'}\right) \qquad \text{Eq. 9}$$

$$\frac{d[17]}{dt} = I_a\Phi_{ISC}\left(\frac{k_{TW}}{k_d+k_{TW}}\right)\left(\frac{k_{-H}}{k_{-H}+k'_{-H}}\right)\left(\frac{k_H[HOAc]}{k_H[HOAc]+k_d'}\right) \qquad \text{Eq. 10}$$

$$\Phi_{dec} = \Phi_{ISC}\left(\frac{k_{TW}}{k_d+k_{TW}}\right)\left(\frac{k_{-H}}{k_{-H}+k'_{-H}}\right)\left(\frac{k_H[HOAc]}{k_H[HOAc]+k_d'}\right) \qquad \text{Eq. 11}$$

Rearrangement of EQUATION 11 yields

$$\frac{1}{\Phi_{dec}} = \frac{1}{\Phi_{ISC}}\left(\frac{k_d+k_{TW}}{k_{TW}}\right)\left(\frac{k_{-H}+k'_{-H}}{k_{-H}}\right)\left(\frac{k_H[HOAc]+k'_d}{k_H[HOAc]}\right) \qquad \text{Eq. 12}$$

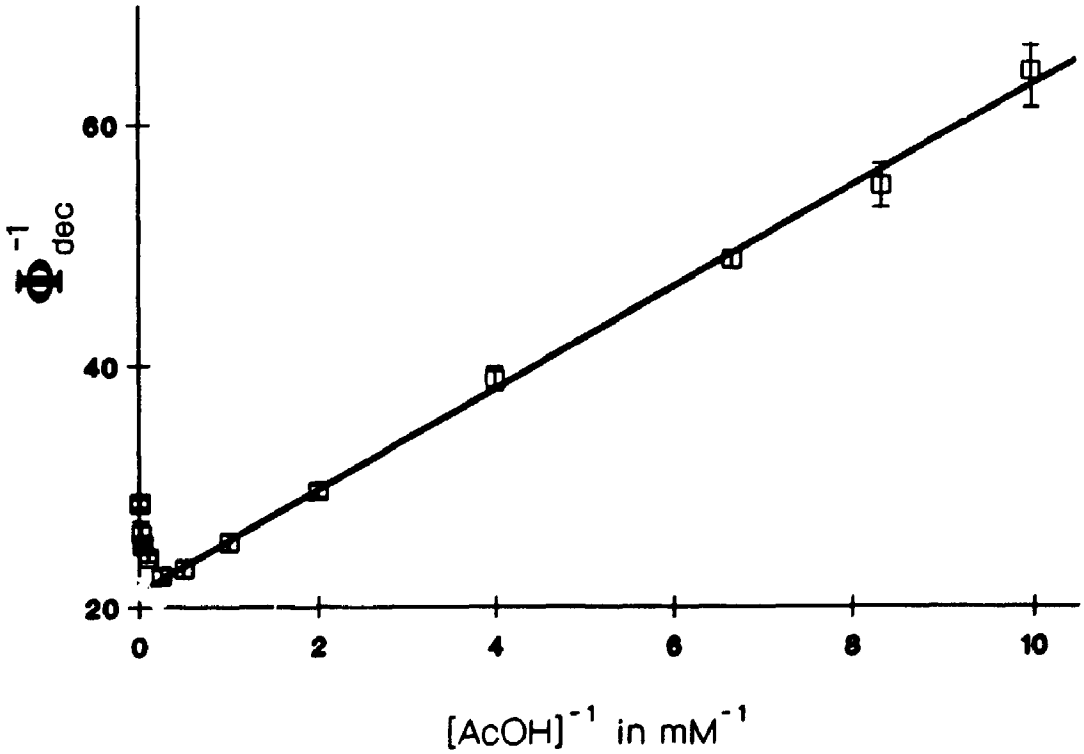
$$= K\left(1 + \frac{k'_d}{k_H[HOAc]}\right)$$

with

$$\frac{1}{K} = \Phi_{ISC}\left(\frac{k_{-H}}{k_{-H}+k'_{-H}}\right)\left(\frac{k_{TW}}{k_d+k_{TW}}\right) \qquad \text{Eq. 13}$$

EQUATION 12 indicates that a plot of Φ_{dec}^{-1} vs $[AcOH]^{-1}$ should result in a straight line. The actual plot of the data is shown in FIGURE 8.

FIGURE 8: Plot of Φ_{dec}^{-1} of isophorone vs $[AcOH]^{-1}$



Inspection of the plot reveals that the straight line fit is good for lower acid concentrations whereas at higher acid concentrations a deviation is observed. This deviation is attributed to the formation of hydrogen bonded dimers of acetic acid which reduces the effective acid concentration.[25] From the straight part of the graph the slope and intercept were used to calculate k_d'/k_H.

$$\text{slope} = K\,\frac{k_d'}{k_H} = 4.2 \pm 5\ \% \qquad \text{Eq. 14}$$

$$\text{intercept} = K = 21.8 \pm 5\ \% \qquad \text{Eq. 15}$$

$$\text{whence} \quad \frac{\text{slope}}{\text{intercept}} = \frac{k_t'}{k_H} \qquad \text{Eq. 16}$$

The value obtained for k_d'/k_H was 1.9×10^{-4} M ± 10 %. The fastest value k_H could reasonably adopt is the rate constant for diffusion (1.5×10^{10} M^{-1} s^{-1} in benzene[23]) and therefore k_d' had to be $\leq \approx 3 \times 10^6$ s^{-1}.* This corresponds to an intermediate with a lifetime of approximately a microsecond or greater, which compares with 9 μs for the lifetime of the transient assigned as *trans*-1-phenylcyclohexene **53**.[30]

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* This result rules out direct reaction of the acid with the triplet of **16** because, if the twisted intermediate is omitted from the mechanism, then $k_d' = k_d$, which leads to wrong values for the triplet lifetime of **16**.

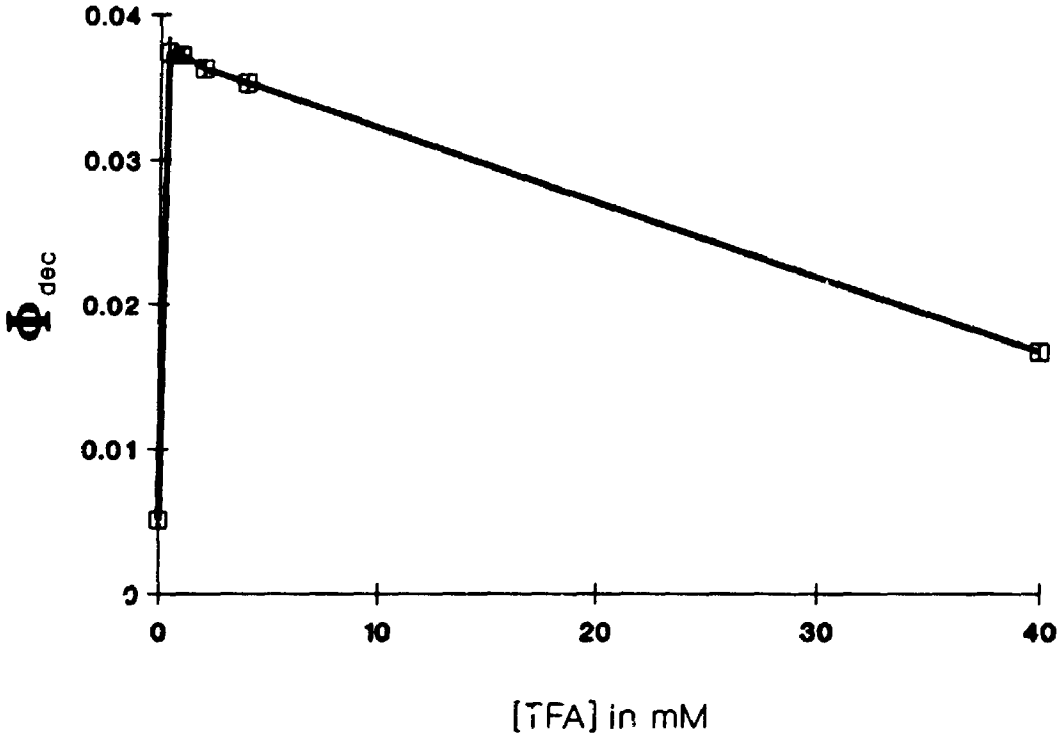
It was decided to study the effect of acids other than acetic acid on the photodeconjugation of **16**. A determination of Φ_{dec} was carried out using acetic acid-COOD. At [**16**] = 140 mM and [acid] = 4.1 mM, Φ_{dec} was 0.0443 ± 2.4 %, a very similar value to that obtained with non-deuterated acetic acid. Propionic acid was also tried and it also catalyzed the reaction (*vide infra*) but since the acids possess very similar pK_a values the effect was not quantified. Aqueous hydrochloric acid was chosen next but the results from these experiments were not useful since the solubility of HCl in benzene is rather low and the data obtained were ambiguous. Ethanesulfonic acid was also tried since it is a much stronger acid than acetic acid but does not absorb in the irradiation region as toluenesulfonic acid would. Unfortunately the purification process for this acid was complicated and unyielding, while its solubility in benzene was found to be low; consequently its use was also abandoned. More success was obtained using trifluoroacetic acid (TFA) which is substantially stronger than acetic acid (pK_a of acetic acid: 4.77, pk_a of TFA: 0.22[32]), does not absorb light at 313 nm and is quite soluble in benzene. A series of experiments to determine Φ_{dec} for **16** in benzene was carried out. The results are shown in TABLE 10 and are plotted in FIGURE 9.

TABLE 10: Φ_{dec} for isophorone with trifluoroacetic acid

[TFA]	Φ_{dec}	[TFA]	Φ_{dec}
0	0.0051 ± 5.4 %	2.0 mM	0.0363 ± 1.4 %
0.4 mM	0.0374 ± 2.6 %	4.0 mM	0.0353 ± 1.8 %
1.0 mM	0.0372 ± 1.0 %	40 mM	0.0167 ± 2.9 %

[**16**] = 140 mM, photon dose = 1.364×10^{-4} E

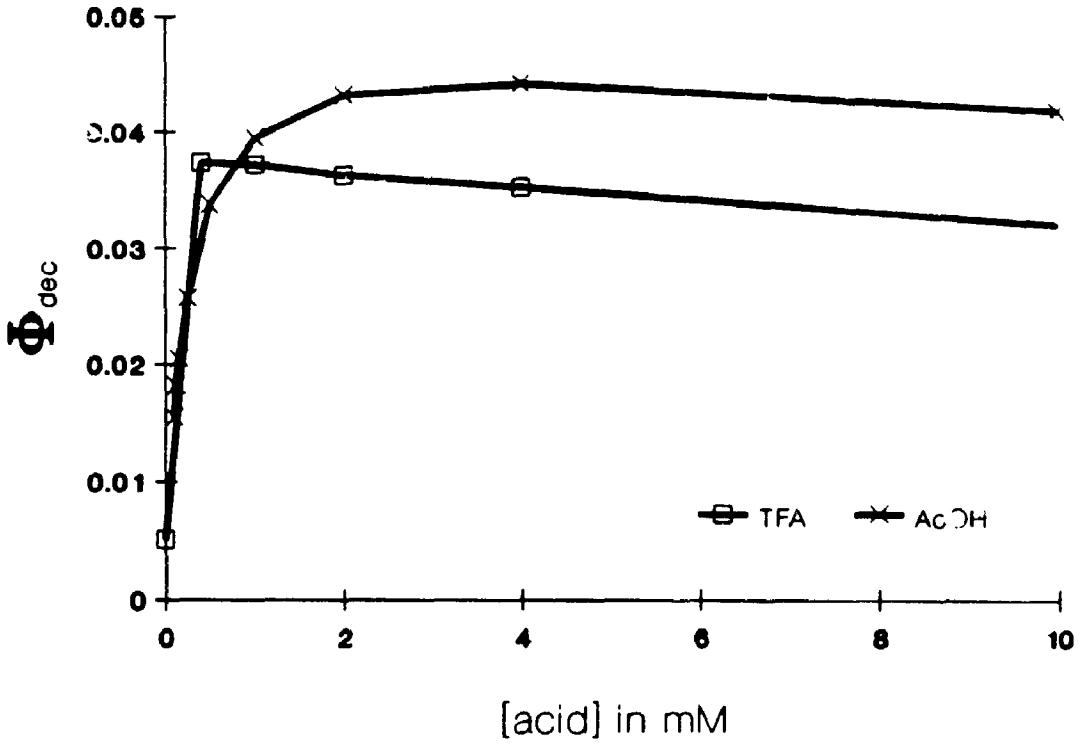
FIGURE 9: Plot of Φ_{dec} of isophorone vs concentration of TFA



Comparison with the results obtained with acetic acid indicated some differences. The acid concentration dependencies of Φ_{dec} of **16** using AcOH and TFA are summarized in FIGURE 10.

In FIGURE 10 it can be seen that the optimum acid concentration for deconjugation is at least one order of magnitude smaller with TFA than with AcOH and that the use of TFA results in a faster rise of Φ_{dec} with increasing concentration of acid. Both observations presumably reflect the lower pK_a of TFA since a stronger acid should protonate the twisted enone **57** faster. The results also imply that the quenching of **57** with acetic acid proceeds more slowly than the rate of diffusion since the use of TFA resulted in a faster increase of Φ_{dec} with acid concentration. This means that the intermediate **57** has a substantially longer lifetime than the limiting value of *ca.* 0.3 μs calculated assuming diffusion limited protonation of **57** by AcOH.

FIGURE 10: Comparison of the effects of acetic acid and TFA on Φ_{dec} of isophorone

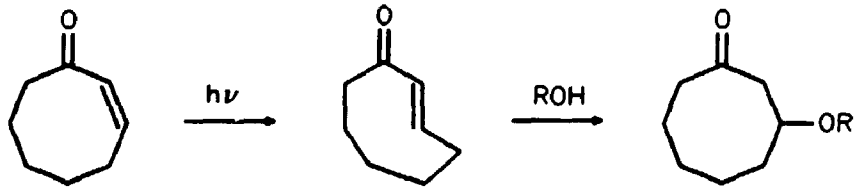


A variety of solvents was also tried for the acid catalyzed photodeconjugation of **16** since the literature data on this subject was not consistent. In the absence of added acid the reaction is reported to proceed in alkane solvents[33a,b] but exceptions are known.[33c] Similarly it is usually reported to fail in alcohols[4d,13,15] but again exceptions are published.[8,33d] The reaction is reported to be efficient in benzene[4d,33a] and ethyl acetate[13] and proceeds in acetonitrile[33a] but not diethyl ether.[33c]

Qualitative irradiations showed that the reaction proceeded most efficiently in benzene (with added acid), but also reasonably in pentane, cyclohexane and diethyl ether (acidic impurity containing sample). It was slower in benzene/methanol 1:1 (v/v, at optimum acid concentration) and acetonitrile (added acid at *ca.* 4 mM) whereas in methanol (added acid) it was almost non existent. These results were difficult to interpret since it is not clear what factors are influencing the success of the

photodeconjugation. Variation of solvent may have an effect on triplet lifetime and energy, stability of intermediate carbocation and effective acid strength. Purity of the solvents may also be an important factor since the reported photodeconjugation of **16** in ethyl acetate could reflect the presence of small amounts of acetic acid in this solvent.[4c]

In order to provide further evidence for the intermediacy of the carbocation **58** experiments were designed and carried out to trap **58** by reaction with nucleophiles. In 1968 Noyori et al. reported the photochemical addition of alcohols to 2-cyclooctenone **51**.[34] Their results indicated that the addition is a ground state reaction between the photochemically formed *trans*-cyclooctenone and the alcohol, since low temperature irradiation of the *cis*-enone led to *cis*→*trans* isomerization; further dark reaction with alcohols gave the products as shown in SCHEME 18.

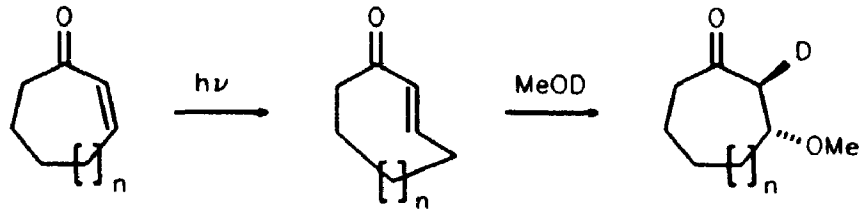


51

SCHEME 18

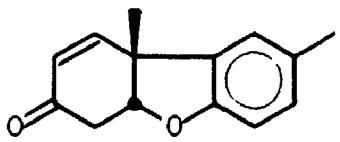
In the late 1970's Hart and coworkers published work on the photoinduced addition of methanol to cyclic 2-enones.[35] In the case of 2-cyclooctenone **51** and 2-cycloheptenone **52** the reactions proceeded smoothly to give the corresponding 3-methoxy alkanones **59** and **60**. In both cases the addition was a ground state reaction to the *trans*-enone which possessed a highly polarized double bond. Studies

with methanol-OD showed that the addition was stereoselective as demonstrated in SCHEME 19.



SCHEME 19

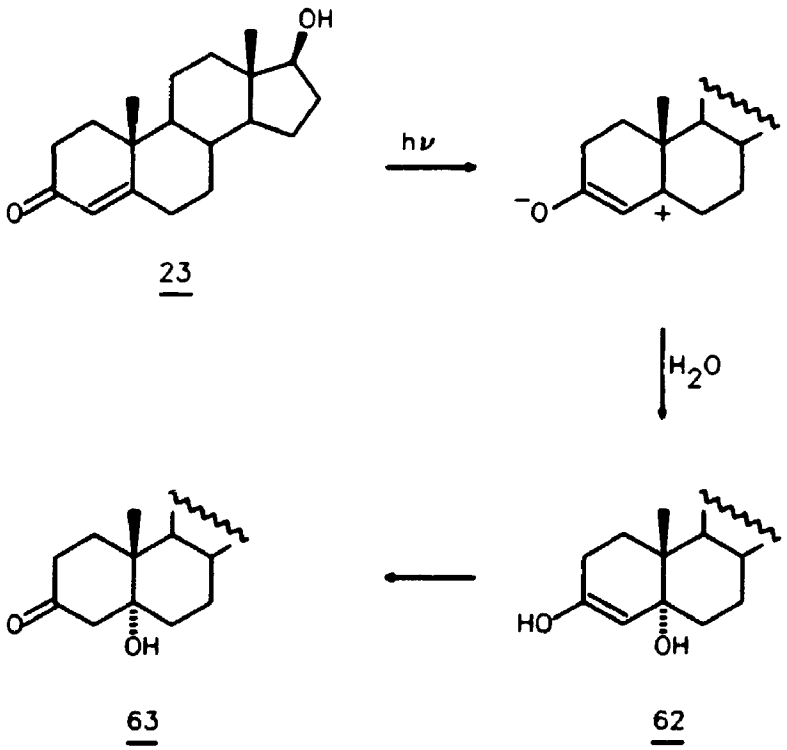
2-Cyclohexenone itself gave only a very poor yield of the photochemically induced solvent addition product. Hart attributed this to the inability of cyclohexenones to isomerize to a reasonably stable *trans* species. The only exception found was Pummerer's ketone **61**, a tricyclic 2-cyclohexenone.[36]



61

With **61** the methanol addition was known to proceed in high yields[37] and Hart concluded that it had to involve either an excited state or an intermediate with a double bond twisted more than 90° to which methanol would add. Other groups reported similar findings when they investigated the photochemical addition of alcohols or water to 2-enones which were part of larger systems such as steroids.[38] Cornell

postulated in the case of water addition to testosterone **23** that the quenching of the excited state, represented as the bipolar species, by the nucleophile water[38b] led to the formation of the hydroxy enol **62** which tautomerized back to the 3-hydroxy ketone **63** as shown in SCHEME 20.

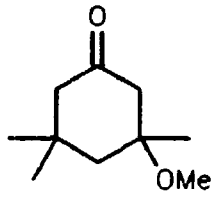


23 62 63

SCHEME 20

In order to test for similar nucleophilic addition products in the photodeconjugation of **16**, an irradiation was performed in a 9:1 (v/v) mixture of benzene and methanol in the presence of acetic acid. Isophorone had already been irradiated in neat methanol without the addition of acid and the deconjugation reaction had been quite inefficient. After addition of acid to the reaction in the mixed solvent deconjugation efficiency was increased but a new product was also seen by gas chromatography with a higher retention time than isophorone or its deconjugated

isomer. It was formed in small amounts only; after 28 hours of irradiation in benzene at 313 nm and 65 % conversion of **16** only 6 % conversion to this product was observed whereas 17 % conversion to **17** was found. Gas chromatography coupled with mass spectroscopy gave a molecular mass for the new compound of 170 corresponding to a 1:1 addition product of **16** (138) and methanol (32). After a large scale preparative irradiation in the same solvent the product was isolated by column chromatography on silica gel followed by preparative gas chromatography. It was analyzed by ^{1}H-nmr spectroscopy and assigned structure **64**.



64

In the ^{1}H-nmr spectrum the olefinic resonance of **16** at 5.79 ppm was no longer visible, while four methyl singlets were observed, one of which was at lower field (3.11 ppm). This is in the correct chemical shift region for a methoxy group.[39] The presence of methyl and methoxy groups at the 3-position had the expected effect of rendering each pair of hydrogens on the 2-, 4- and 6-carbons magnetically non-equivalent. As a result the signals for the protons on the 2- and 4-carbons were split to give pairs of doublets with large coupling constants due to geminal coupling (in each pair one doublet was further split into multiplets due to long range coupling into the methyl groups). The signal for the more remote protons on the 6-carbon did not exhibit geminal coupling but showed some broadening.

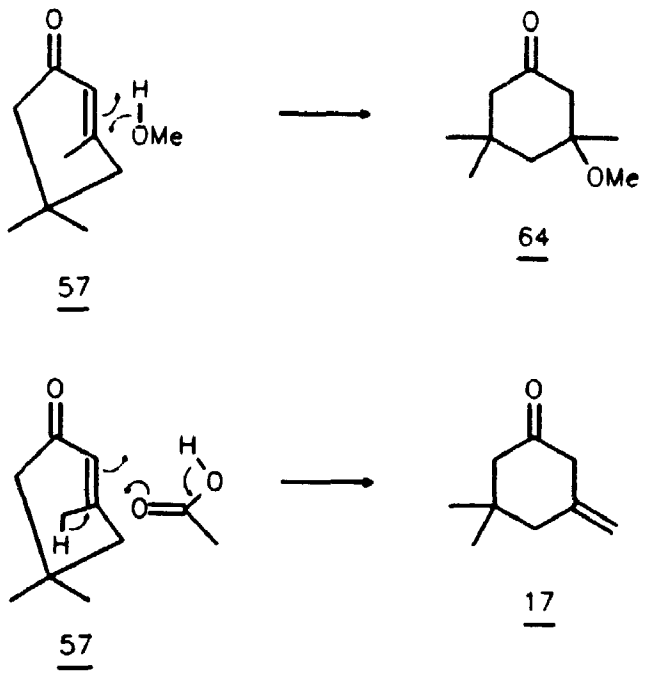
In addition the two methyl groups on the 5-carbon were also non-equivalent and showed up as two singlets integrating for three protons each. In both **16** and **17** these methyl groups were equivalent and gave rise to one singlet integrating to six protons. All spectral evidence thus pointed to the formation of **64** by Markovnikov addition of methanol across the enone double bond.

A parallel reaction utilizing the same reactants and concentrations as above was kept in the dark for the same time and then analyzed by gas chromatography. No signs of formation of **64** were found in this case, confirming that the addition of methanol was the result of isophorone photochemistry.

A similar experiment was undertaken in which **16** was excited in benzene/octanol 1:1 (v/v) in the presence of acetic acid. After 19 hours at 313 nm, a small peak was detected by gas chromatography which gave a molecular ion in the mass spectrometer of 268, corresponding to a 1:1 adduct between isophorone (138) and octanol (130). No further investigation was conducted due to the very small amount of product formed.

The literature reports of the photoaddition of methanol to cyclic 2-enones interpret the reaction in terms of a mechanism involving nucleophilic addition of methanol to a polarized *trans*-enone rather than to a carbocation produced by protonation of a *trans*-enone.[35]

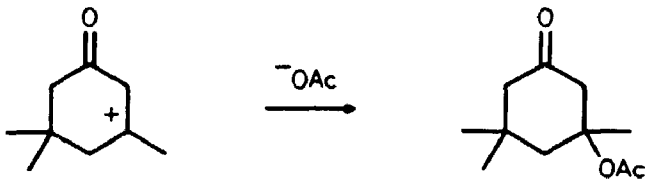
Because the work described in this thesis was performed in non-polar solvents such as benzene where carbocation formation might be expected to be highly endothermic, a different pathway for the formation of the deconjugated isomer and the alcohol addition product was also considered involving a concerted mechanism for both the deconjugation and alcohol addition. This involves the reaction of the *trans*-enone **57** and the acid or alcohol as shown in SCHEME 21.



SCHEME 21

This mechanism seemed to be a viable alternative to the ionic stepwise process even though in the case of the methanol addition an unfavourable four membered transition state would have been required. However, it was found that in the methanol addition reaction the amount of adduct formed depended on the concentration of acid present (as determined by comparison of gc data of the amount of **64** formed). If the proton concentration was low, the efficiency of adduct formation was low, while an increase in acid concentration led to an increase in the efficiency of adduct formation. This result is inconsistent with a concerted mechanism which would have predicted no effect of acid on the addition. In view of these findings the concerted mechanism theory was abandoned.

If, as the above experiments indicated, the carbocation intermediate **58** was trappable by nucleophiles like alcohols, one might also expect to find some products of addition of the acid anion, resulting in the formation of acetate **65**.



58 65

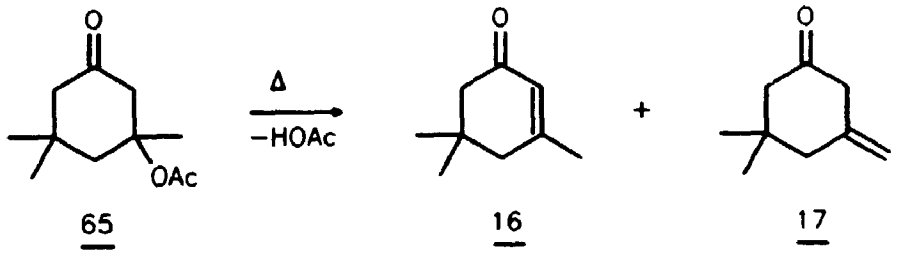
In order to probe for such adducts, experiments were carried out in benzene using **16** (≈ 135 mM) and acetic acid at a concentration optimum for deconjugation (8.7 mM) and also at high concentrations (422 mM). These mixtures were irradiated and the reaction progress followed by gas chromatography. The appearance of a product with a retention time longer than that of isophorone but shorter than those of isophorone dimers was observed (12.94 min vs 7.20 min and ≈ 24 min, respectively). The relative ratios of the products formed are given in TABLE 11 where the new product is referred to as "adduct".

TABLE 11: Relative product ratios in the deconjugation of **16** with different acid concentrations

[AcOH]	**17**	"adduct"	Σ dimers
8.7 mM	1	0.1	0.2
422 mM	1	0.4	0.5

As can be clearly seen the "adduct" formation increased with increasing acid concentration. Gas chromatography coupled with mass spectroscopy gave only a very low response to the "adduct" peak in both electron impact (EI) and chemical ionization (CI) modes and the results obtained could not support a 1:1 adduct between **16** and acetic acid (mass of 198) which is consistent with structure **65**. The weakness of the

molecular ion of **65** in the mass spectrum was attributed to the thermal instability of the adduct. The acetate ion is a reasonable leaving group which in **65** would yield a tertiary carbocation; consequently thermally induced acetic acid elimination in the mass spectrometer (as shown in SCHEME 22), leading to **16** and **17**, is a feasible decomposition pathway.

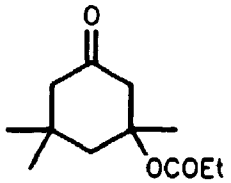


65 16 17

SCHEME 22

The acid used was then switched to propionic acid (Et-COOH). If acid addition occurred, the adduct with propionic acid **66** should have a different retention time (presumably longer) when analyzed by gas chromatography due to its higher molecular weight and lower volatility. Accordingly a reaction was carried out using light of 313 nm wavelength, **16** (133 mM) and propionic acid (389 mM) in benzene. In addition to the known deconjugation and dimerization products, a new peak was observed at a retention time of 14.48 min, which is about 1.5 min longer than that of the product observed in the acetic acid reaction. Mass spectroscopy of the peak indicated a mass of 138 which corresponds to isophorone. The fragmentation pattern was an exact match when compared with a mass spectrum of an authentic sample of **16**; however, an additional fragment with a mass of 74 was also present which corresponds to the mass of propionic acid. This again suggests that a thermally induced elimination reaction of the propionic acid adduct **66** is occurring in the mass

spectrometer. Chemical ionization gave the same result, as did lowering the ionization energy from 70 eV to 30 eV.



66

In order to characterize more fully the structure of this elusive adduct, a large scale preparative irradiation was carried out. Use was made of the fact that **17** slowly reconjugates to **16** by allowing an irradiation mixture to stand for two weeks in a refrigerator. After this time the amount of adduct produced had stayed constant whereas the amount of **17** had dropped sharply and the quantity of the remaining starting material had increased. Further irradiation then produced adduct **66** in up to 44 % gas chromatographic yield. Careful distillations were carried out and the residue obtained was subjected to preparative thin layer chromatography (tlc). A fraction containing **66** (in a *ca.* 2:3 ratio with **16** by gas chromatography) was analyzed by nmr spectroscopy.

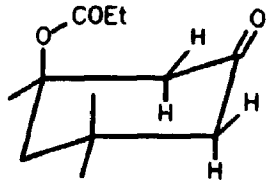
The spectrum obtained showed that the mixture had decomposed (probably induced by acidic impurities in the $CDCl_3$ used) to a mixture of isophorone and propionic acid; the former was identified from its known nmr data, the latter by the presence of a triplet at 1.07 ppm and the corresponding quartet at 2.29 ppm (indicating the ethyl group within propionic acid) and the acid proton resonance at 9.9 ppm.[39] Gas chromatographic analysis of the nmr solution confirmed that the adduct peak had disappeared. The preparative tlc separation was repeated and this

time C_6D_6 was chosen as the nmr solvent since it is much less likely to contain or develop acidic impurities.

The ^{1}H-nmr spectrum of the mixture (**16**:**66** ≈ 3:2) provided evidence for the presence of the proposed propionic acid adduct. Apart from the isophorone peaks, three singlets were observed at 0.73, 0.75 and 1.41 ppm, each one integrating for three protons, corresponding to the methyl groups located at the 5- and 3-carbons. The 5-methyl groups are diastereotopic and thus non-equivalent. Another signal integrating for three protons was observed as a triplet (J = 7.53 Hz) with slightly increased linewidths (*vide infra*) at 0.91 ppm. This corresponded to the methyl group in the side chain of **66** next to the methylene group. The protons of this methylene group were diastereotopic since they are adjacent to the 3-position which is a stereogenic carbon. They appeared, shifted downfield due to the neighbouring ester carbonyl, as two sets of quartets at 1.94 ppm (J = 7.70 Hz) and 1.93 ppm (J = 7.40 Hz), respectively. The line broadening of the adjacent methyl group is therefore due to the signal being a doublet of doublets with very similar coupling constants, leading to the appearance of a triplet with an average coupling constant of 7.53 Hz and broader lines.

Also observed in the ^{1}H-nmr spectrum of **66** were two doublet of triplets at 2.45 and 2.86 ppm, each integrating for one proton. The smaller coupling constant in each of the triplets was 2.3 Hz whereas the larger doublet coupling constants were 14.1 and 15.0 Hz, respectively. A two dimensional ^{1}H-nmr spectrum (2D-HOMOCOR) confirmed that these protons were coupled but indicated that they are not located on the same carbon, since the larger geminal coupling constants were not identical. The HOMOCOR spectrum showed strong coupling into multiplets at ≈ 1.79 and ≈ 1.12 ppm, respectively.[40]

If the synthesized adduct **66** exists in the chair conformation shown below then the chemical shifts of the above signals (2.4[5] and 2.86 ppm) suggest that they corresponded to the two equatorially oriented protons in the α- and α'-positions of the cyclohexanone system.



Their downfield shift is explained by the presence of the neighbouring carbonyl function and the fact that equatorial protons usually appear at lower field than the corresponding axial protons.[39,40] Additionally, the 1,3-equatorial arrangement allows for W-coupling which explains the relative large coupling constant between the equatorial α- and α'-protons of 2.3 Hz.

The ^{13}C-nmr spectrum of the mixture showed, after subtraction of the known isophorone resonances, the required twelve lines for **66**. Multiplicity determinations (APT, DEPT)* confirmed the presence of a ketone carbonyl peak at 207.1 ppm, an ester carbonyl peak at 173.5 ppm and a quaternary carbon next to an oxygen at 84.1 ppm (3-position). Furthermore, four methyl resonances (two very similar) were observed in addition to four methyl[ene] peaks (three shifted downfield due to neighbouring carbonyl carbons) and one other quaternary carbon.

In the FT-infrared spectrum of the mixture the following absorptions could be observed in the carbonyl stretch area: A band at 1670 cm^{-1}, which was derived from

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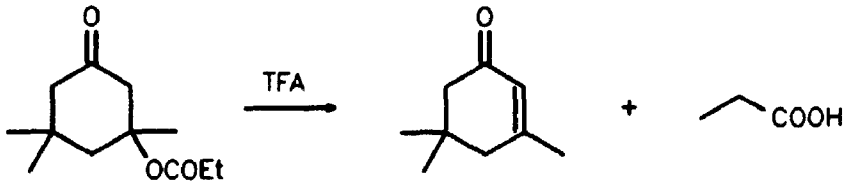
* With these experiments it is possible to distinguish between carbon atoms with different numbers of hydrogen atom substituents (methyl, methylene, methine and quaternary carbons) by examining the phasing of the individual peaks.[40]

16 in addition to bands at 1721 cm^{-1} and 1734 cm^{-1}, which were not present in **16**. The former corresponds to an ester carbonyl stretch and the latter to a typical cyclohexanone carbonyl stretch.[39]

The spectroscopic evidence described for the structure of **66** confirms that it is derived from the addition of propionic acid across the double bond of **16**. Its formation supports the intermediacy of carbocation **58**.

The stability of **66** was examined by adding a small amount of TFA to a solution of **66** and **16** in C_6D_6 (at room temperature) and following the reaction by gas chromatography and nmr spectroscopy. It was shown that the amount of **66** slowly decreased (over ≈ 10 days) while signals for propionic acid as the only new product appeared, as indicated in SCHEME 23. It is likely that this was the reaction that prevented analysis of the mixture in $CDCl_3$.

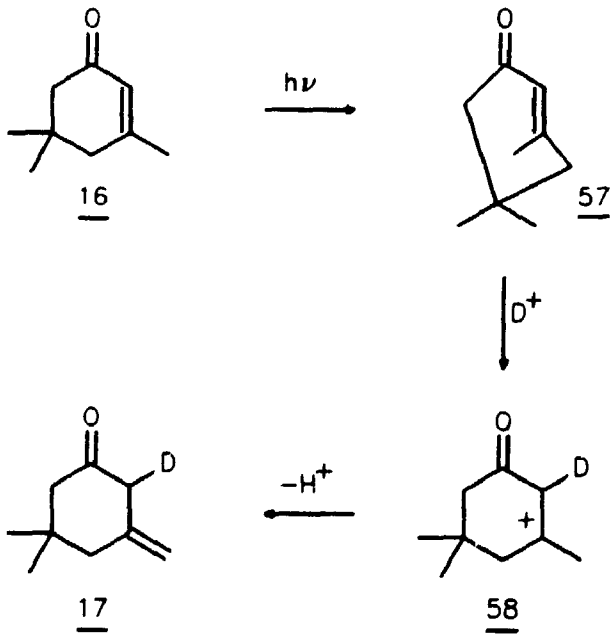


66 **16**

SCHEME 23

A number of deuterium incorporation experiments were carried out in dry benzene (to avoid exchange with residual moisture) in order to find further support for the mechanism. In the first experiment **16** was irradiated with acetic acid-COOD (AcOD, ≈ 5 mM) and the amount of deuterium incorporation into both **16** and **17** was determined by gas chromatography coupled mass spectroscopy. This was done by comparing the intensities of the M + 1 peaks of each of the compounds of interest to

the M + 1 peaks of these compounds present in a control irradiation performed in the presence of AcOH rather than AcOD.[39] The amounts of deuterium incorporation after 30 minutes of irradiation were 0.1 % for **16** and 9 % for **17**. It had been expected that for **17** the incorporation would approach 100 % since the carbocation mechanism assumes deuteration at the 2-position of the twisted enone **57** followed by loss of a proton from the 3-methyl group as shown in SCHEME 24. However, further experiments demonstrated that the low incorporation resulted from exchange of the AcOD with water in the "dry" benzene.



SCHEME 24

When the experiment was repeated, using AcOH or AcOD and a solution of dried benzene and methanol or methanol-OD (9:1 v/v), the results shown in TABLE 12 were obtained.

TABLE 12: Deuterium incorporation studies

Acid	Alcohol	Deuterium in **16**	Deuterium in **17**
AcOD	MeOH	0.2 %	0 %
AcOH	MeOH-d_4	13 %	85 %
AcOD	MeOH-d_4	12 %	86 %

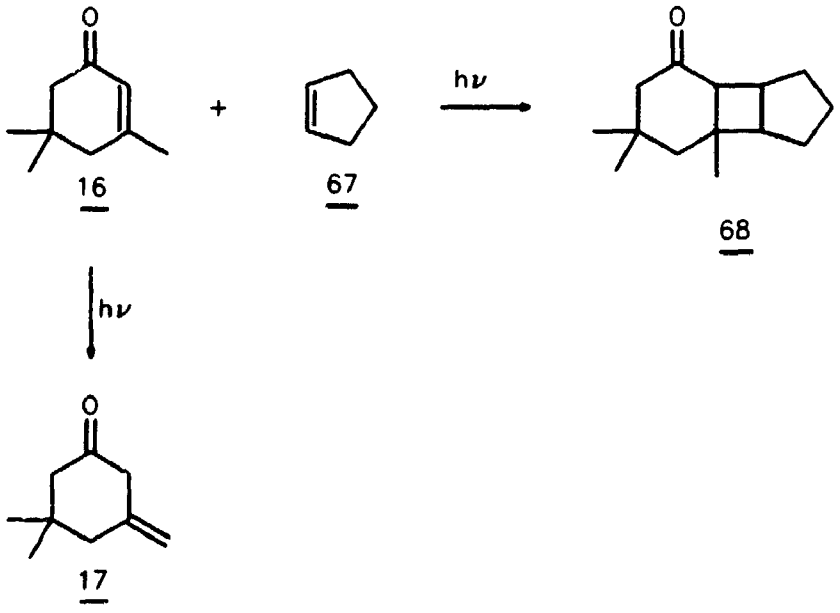
[**16**] ≈ 140 mM, [acid] ≈ 4 mM

As can be clearly seen, the deuterium incorporation found when MeOH was used as a cosolvent was close to non existent, probably due to the fact that the acid deuteron was exchanging rapidly with the methanol and thus not available for protonation. This exchange is also reflected in the numbers from the other two experiments. When the solvent was 9:1 benzene and methanol-OD the amount of deuterium incorporated was independent of whether AcOH or AcOD was used; even with AcOH a large degree of incorporation was achieved, presumably because rapid exchange converted AcOH to AcOD. The results shown in TABLE 12 are consistent with the intermediacy of a carbocation in the formation of **17**; it is assumed at this point that the deuterium incorporation of 86 % rather than 100 % arises from exchange with adventitious water. The small level of deuterium incorporation into **16** suggests that loss of a proton from the 2-position of **58** is slower than from the methyl group, under the assumption that thermal rearrangement of deuterated **17** to **16** is negligible under the conditions employed (earlier experiments have demonstrated that this back-reaction does not occur to a detectable degree in the usual time-frame of a photolysis experiment). This result is consistent with the fact that none of the endocyclic deconjugated isomer is formed in the photodeconjugation reaction. The low deuterium incorporation into **16** also implies that in normal ground state E1 reactions,

where the dominant product is the more substituted, more stable alkene, the products are formed under thermodynamic rather than kinetic control whereas most texts use Hammond Postulate arguments to explain E1 product selectivities and hence imply kinetic control.

^{2}H-Nmr studies were attempted in order to confirm the site of the deuterium incorporation. Unfortunately in the system used (MeOD) the chemical shifts of the signals of interest were too close to the resonance of MeOD. Consequently the position of the deuterium incorporation in **16** and **17** could not be clearly determined using this technique.

The effect of the presence of acetic acid on the photochemical [2 + 2] cycloaddition reaction of isophorone and cyclopentene **67** was also examined as shown in SCHEME 25.



SCHEME 25

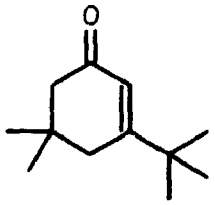
Addition of acetic acid (4 mM) to a mixture of **16** (140 mM) and **67** (1 M) in benzene and irradiation of this mixture improved the yield of the photodeconjugation product **17** dramatically but had only minor effects on the yield of the cycloaddition products **68** when compared with an irradiation carried out without added acid. This result is consistent with a mechanism in which deconjugation occurs from a post-triplet excited state intermediate (such as a ground state *trans*-enone); the acid would then not be expected to change the yield or efficiency of formation of the triplet excited state derived 2+2 cycloaddition product. However, it should be noted that a large difference in deconjugation efficiency would not necessarily lead to a large change in cycloaddition yield if the latter is already much more efficient than the deconjugation.

Thus after three hours of irradiation almost complete conversion of **16** was obtained; the ratios of **68**:**17** were determined by gas chromatography to be 72:1 in the absence of acid and 19:1 in the presence of acid. This indicates that even at optimum acid concentration the cycloaddition proceeds much more efficiently than the deconjugation reaction.

A quantum yield determination confirmed this; using a benzene solution of [**16**] (137 mM) and AcOH (4.1 mM) in the presence of 1 M cyclopentene gave Φ_{dec} = 0.022 ± 11 % and $\Phi_{cycloaddition}$ = 0.39 ± 3.3 %. From this it can be concluded that the presence of cyclopentene leads to a decrease of Φ_{dec} by a factor of two (Φ_{dec} in the absence of alkene under similar conditions was determined to be ≈0.045) which means that **67** quenches the deconjugation reaction by reacting with the triplet excited state of **16**, which is a precursor to the deconjugated product.

2.3 Investigation of the Photochemistry of other 2-Cyclohexenones

The earlier literature reports stated that the photochemical deconjugation reaction of 2-cyclohexenones proceeds only if a methyl group is present in the 3-position. The only exceptions to this rule were large steroid systems and octalones where the cyclohexenone ring was part of a larger multiple ring system.[4c,4d,8,15-17] In view of the findings so far reported in this chapter it could not be rationalized why simple 3-alkyl substituted 2-cyclohexenones such as 3-ethyl- or 3-isopropyl-2-cyclohexenone (**20**, **21**) do not also undergo photodeconjugation.[4c] If the mechanism postulated in Section **2.2.3** is correct, then any 3-alkyl substituted 2-cyclohexenone should yield a deconjugated product by proton loss from the carbocation produced by protonation of a *trans*-enone intermediate. The only exceptions would be those in which no proton is available on the 3-position substituent; for example, in the case of the 3-*t*-butyl substituted 2-cyclohexenone **22** this pathway would not be possible and so no exocyclic deconjugation product should be formed.



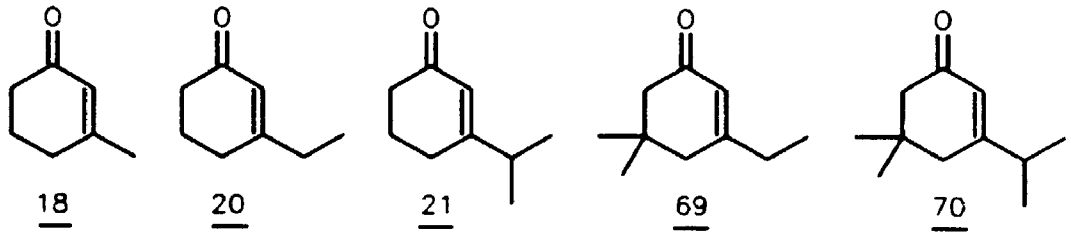
22

In order to investigate the reactivity of 3-alkyl substituted 2-cyclohexenones in general it was decided to synthesize some examples and look for acid catalysis of the photochemical deconjugation reaction. It was also decided to examine the influence of the two methyl substituents in the 5-position of **16**; accordingly the syntheses of

different 3-alkyl substituted 2-cyclohexenones with and without 5,5-dimethyl substitution were undertaken.

2.3.1 Synthesis of 3-Alkyl Substituted 2-Cyclohexenones

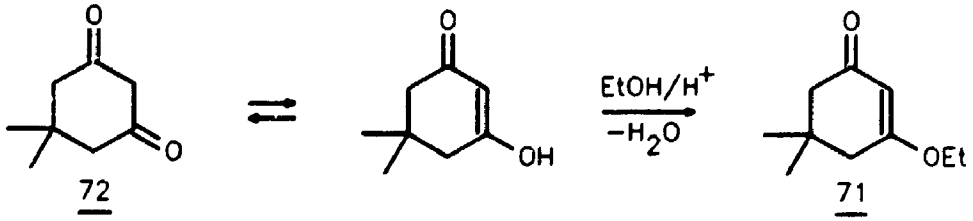
The following compounds were prepared: 3-methyl-2-cyclohexenone **18**, 3-ethyl-2-cyclohexenone **20**, 3-isopropyl-2-cyclohexenone **21**, 3-ethyl-5,5-dimethyl-2-cyclohexenone **69** and 3-isopropyl-5,5-dimethyl-2-cyclohexenone **70**.



The literature procedures for the preparation of the desired compounds involved reaction of an appropriate precursor with the required alkyl Grignard reagent.[41]

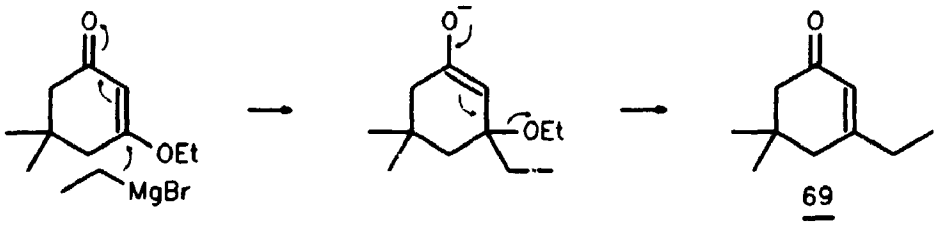
The first precursor examined was 3-ethoxy-5,5-dimethyl-2-cyclohexenone **71**, which was easily prepared by reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **72** and ethanol under Dean-Stark conditions as shown in SCHEME 26.[42]

This compound has been utilized in the synthesis of various 3-substituted 5,5-dimethyl-2-cyclohexenones.[43]



SCHEME 26

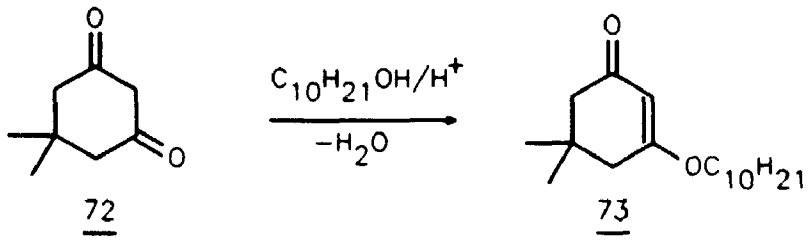
For the preparation of 3-ethyl-5,5-dimethyl-2-cyclohexenone **69**, the enol ether **71** was allowed to react with ethyl magnesium bromide. A mass spectrum of the reaction mixture (gc/ms) implied that the desired reaction (SCHEME 27) had taken place and that **69** had been formed.



SCHEME 27

However, the conversion was far from complete. Use of ethyl magnesium iodide as the Grignard reagent did not improve the yield of **69**. Attempts to separate the product **69** from the precursor **71** by distillation were unsuccessful since their boiling points were too close together. A chromatographic separation might have been successful but was not feasible on the large scale the reaction was carried out. Consequently the precursor was altered by changing the alcohol with which the dimedone was allowed to react. The reasoning behind this tactic was to increase the boiling point of the precursor to facilitate easier separation from the product by distillation.

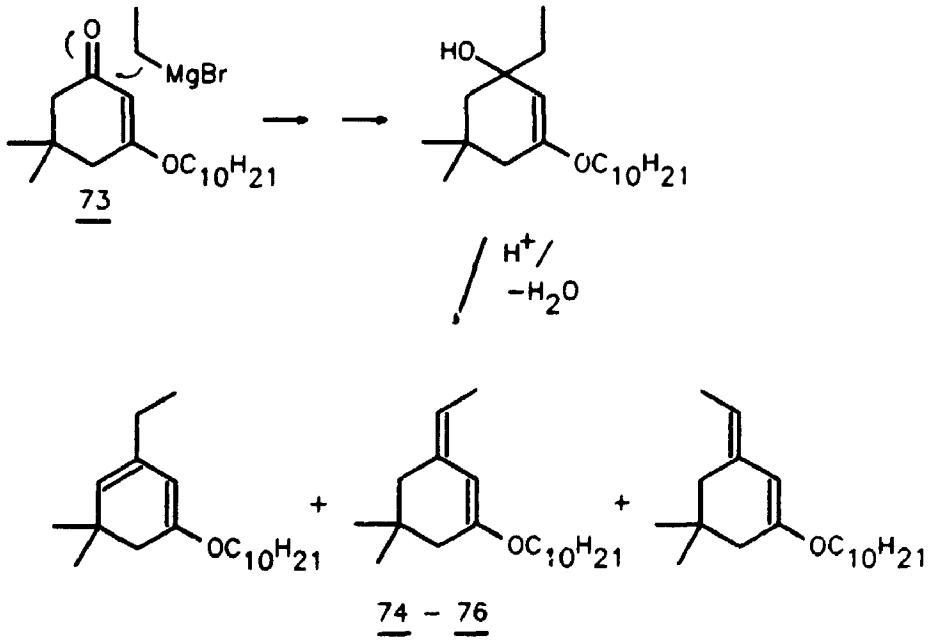
The alcohol chosen was *n*-decanol, which under Dean-Stark conditions was allowed to react with dimedone **72** to give 3-*n*-decyloxy-5,5-dimethyl-2-cyclohexenone **73** in good yields, as shown in SCHEME 28.



72 73

SCHEME 28

Compound **73** was then treated with the ethyl Grignard reagent a: . . this successfully yielded **69** but again the reaction did not go to completion. In addition three new side products were observed with a mass according to gc/ms of 292. These were tentatively assigned structures **74** - **76** which would arise from attack of the Grignard reagent on the carbonyl carbon to give the alcoholate which eliminates during acidic workup as shown in SCHEME 29.



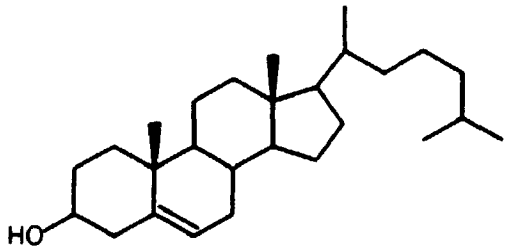
73

74 - 76

SCHEME 29

The main product formed in the reaction was **69**, as indicated by gc/ms, but unfortunately purification by distillation again proved impossible because the by-product of the reaction, *n*-decanol, had a very similar boiling point to **69**. Attempts were made to oxidize the decanol to the corresponding acid with permanganate under mild conditions so as to not destroy the product; this would have allowed easy removal of the acid by a base wash. However, the attempted oxidation resulted in a complex product mixture.

Because of the difficulties encountered using decanol, an alternative alcohol was sought. The next alcohol chosen was cholesterol, **77**.



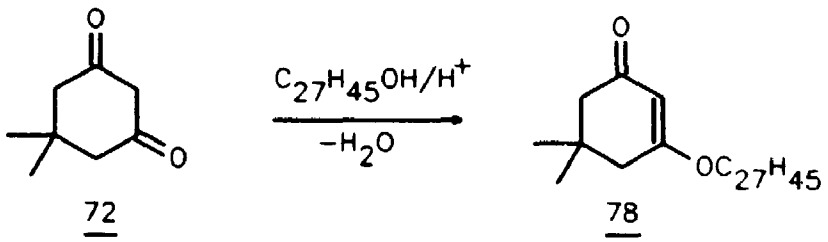
≡ $C_{27}H_{45}OH$

77

Cholesterol is a solid whose boiling point was anticipated to be far higher than that of the desired products **18**, **20**, **21**, **69** or **70**, so that its separation at the end of the reaction would present no difficulties.

Reaction of dimedone with **77** under Dean-Stark conditions gave, after recrystallization, the solid product **78** (SCHEME 30). Due to the very low volatilities of cholesterol and the product the reaction could not be analyzed by gas chromatography but was instead followed by tlc. The structure of the product obtained was confirmed by mass, proton nmr and infrared spectroscopy. The mass spectrum gave the correct mass of 508; in the proton nmr spectrum two olefinic protons were observed at

= 5.4 ppm as expected, and the infrared spectrum showed an absorption at 1684 cm^{-1}, which is in the correct region for an α,β-unsaturated ketone.[39]



72 78

SCHEME 30

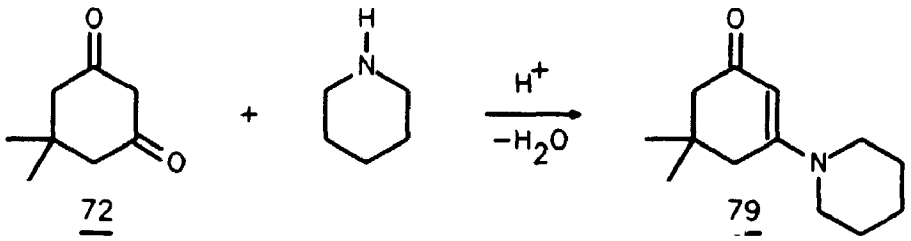
Reaction of **78** with an ethyl Grignard reagent did not lead to a useful yield of the desired 3-ethyl substituted product **69**. Tlc analysis of the reaction mixture indicated formation of cholesterol and the presence of **69** could be inferred by nmr spectroscopy (a signal at 5.9 ppm was observed which is in the right chemical shift range for an enone). However, only very small amounts of **69** appeared to have been formed and so no isolation was attempted.

Since the use of cholesterol did not facilitate the synthesis of **69** in reasonable quantity, another pathway was considered. It has been known for a long time that acyclic enaminones, when reacted with alkyl Grignard reagents, give the corresponding α,β-unsaturated 3-alkyl substituted ketones as shown generally in SCHEME 31.[44]

SCHEME 31

Enaminones derived from cyclohexane-1,3-diones have, on the other hand, been reported not to undergo a similar reaction but are stable under these conditions.[45] Nevertheless the reaction was tried out.

The precursor **79** was prepared from reaction of dimedone and piperidine under Dean-Stark conditions in low yields as shown in SCHEME 32.[43b,46]

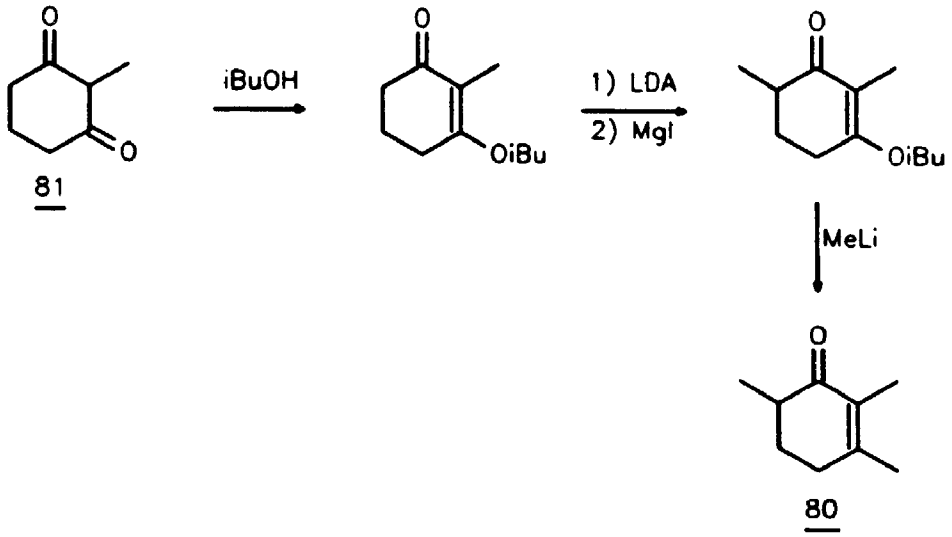


72 79

SCHEME 32

When **79** was allowed to react with an ethyl Grignard reagent no formation of **69** could be detected. Repeated experiments with changed reaction times did not alter the outcome; only starting material was recovered. This might have been due to the fact that the Grignard reagent reacted as a base to form the enolate of **79**, which upon workup gave the starting material.

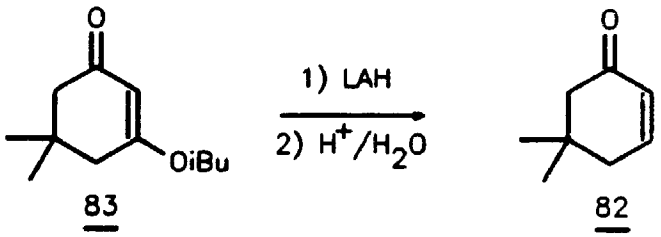
In 1984 Cory et al. reported the use of isobutanol in the synthesis of 2,3,6-trimethyl-2-cyclohexenone **80** from 2-methyl-1,3-cylohexanedione **81**, as outlined in SCHEME 33.[47]



81 80

SCHEME 33

Earlier House and Fischer had published the synthesis of 5,5-dimethyl-2-cyclohexenone **82** employing the reaction of 3-isobutoxy-5,5-dimethyl-2-cylohexenone **83** with LAH, as shown in SCHEME 34.[48]

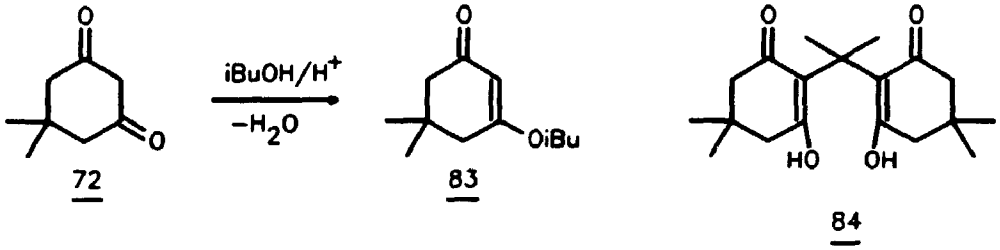


83 82

SCHEME 34

Both of these literature precedents suggested that displacement of the isobutoxy group by a powerful nucleophile proceeds in good yield. Accordingly isobutanol was allowed to react with dimedone under Dean-Stark conditions and gave **83** in good yield as shown in SCHEME 35. An additional peak in the gas chromatogram

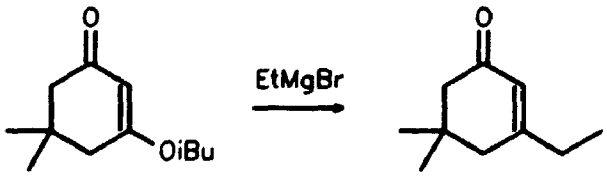
of the reaction mixture was observed at longer retention time. This compound was isolated and identified by nmr spectroscopy as compound **84**. Analysis of the stock dimedone revealed that **84** was already present in it as an impurity. Due to the low solubility of **84** in diethyl ether (as compared with dimedone) it could easily be removed. Presumably **84** is formed by reaction of dimedone with acetone during its preparation or purification.



72 83 84

SCHEME 35

Compound **83** was treated with an ethyl Grignard reagent and gave the desired product **69**, as shown in SCHEME 36.



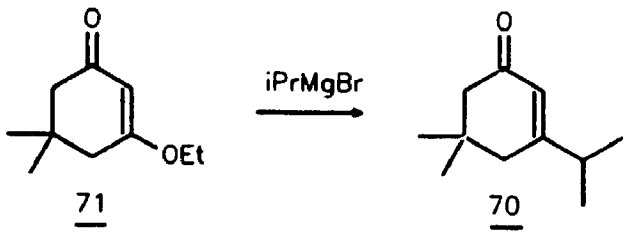
83 69

SCHEME 36

Again the reaction did not go to completion, but this time it was possible to distil the components apart and obtain pure samples of **69**. The structure was confirmed by mass spectroscopy and by the ^{1}H-nmr spectrum. The latter showed a

triplet at 1.10 ppm integrating for three protons which was assigned to the terminal methyl group of the ethyl substituent. A multiplet at 5.88 ppm integrating for one proton was observed and assigned to the olefinic proton.

The preparation of 3-isopropyl-5,5-dimethyl-2-cyclohexenone **70** was achieved by the analogous reaction of **71** with an isopropyl Grignard reagent, as shown in SCHEME 37.

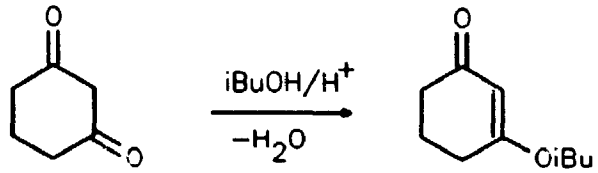


71 **70**

SCHEME 37

Compound **70** could be separated from remaining starting material by column chromatography on silica gel. It was identified by its mass spectrum and by its ^{1}H-nmr spectrum. In the latter the two methyl groups in the isopropyl substituent appeared at 1.10 ppm as a doublet due to coupling with the neighbouring methine proton which was observed as a multiplet at 2.40 ppm. In addition a multiplet at 5.89 ppm integrating for one proton was assigned to the olefinic proton.

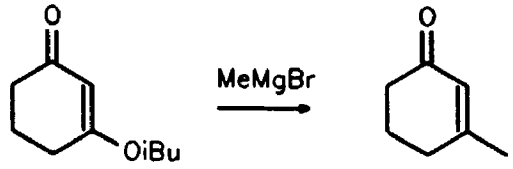
Compounds **18**, **20** and **21** were synthesized using the procedure eventually found acceptable for the preparation of the 5,5-dimethyl substituted enones **69** and **70**.[41a,49] For all three compounds, the precursor 3-isobutoxy-2-cyclohexenone **86** was prepared from 1,3-cyclohexanedione, **85**, as shown in SCHEME 38.



85 86

SCHEME 38

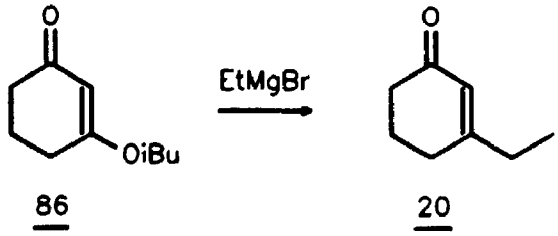
Reaction of **86** with a methyl Grignard reagent (SCHEME 39) gave, after distillation from starting material, **18**, identified by comparison of its mass spectrum and its nmr spectra with published data.[41]



86 18

SCHEME 39

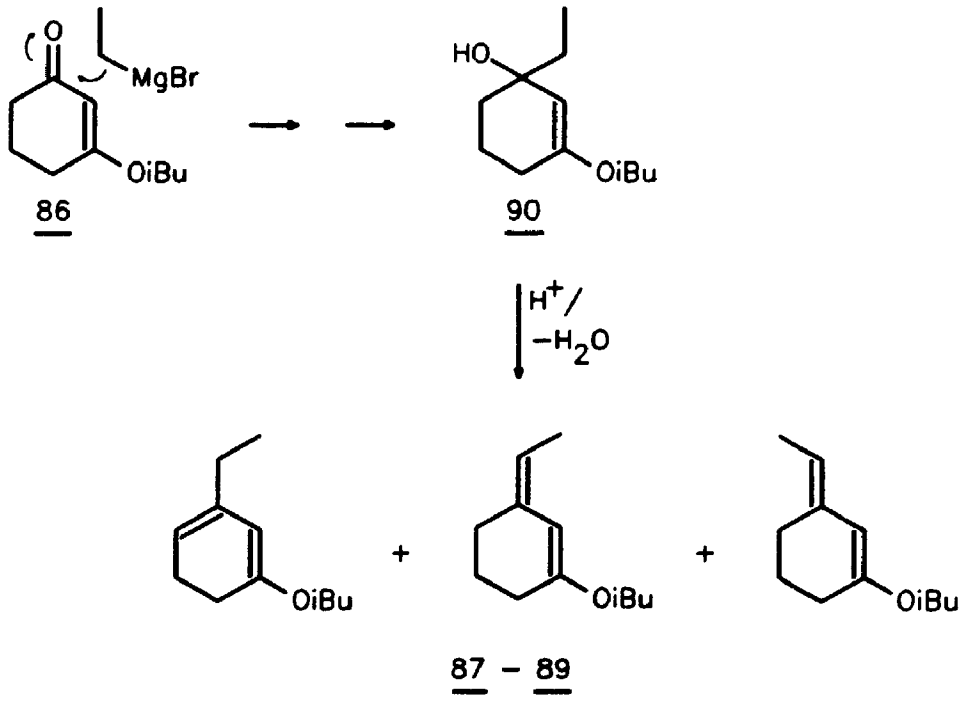
Treatment of **86** with an ethyl Grignard reagent led, after distillation and column chromatography, to the isolation of **20** as shown in SCHEME 40.



86 20

SCHEME 40

In this reaction side products were observed which were believed to be the isomeric dienes **87** - **89**, presumably generated by attack of the Grignard reagent on the carbonyl carbon followed by elimination of water from the intermediate alcohol **90** as outlined in SCHEME 41.

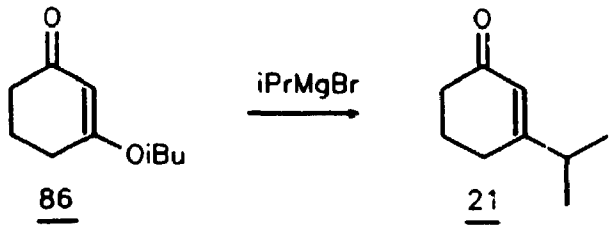


SCHEME 41

The structure of **20** was confirmed by its mass and proton nmr spectra. In the latter the terminal methyl group in the ethyl substituent appeared as a triplet at 1.11 ppm and the olefinic proton was observed as a multiplet at 5.88 ppm.

Reaction of **86** with an isopropyl Grignard reagent resulted, after distillation, in the isolation of **21** (SCHEME 42), which was identified by mass and proton nmr spectroscopy. In its nmr spectrum the two methyl groups of the isopropyl group

appeared as a doublet at 1.11 ppm and the neighbouring methine proton signal was observable as a multiplet at 1.96 ppm. In addition the olefinic proton was observed at 5.88 ppm as a multiplet.



86 21

SCHEME 42

2.3.2 Irradiation of 2-Cyclohexenones 18, 21, 69 and 70[4c]

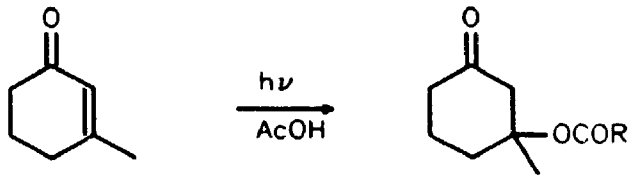
3-Methyl-2-cyclohexenone 18 was irradiated in benzene in the absence and presence of acetic acid. The reaction was followed by gas chromatography and showed the appearance of one new product with a shorter retention time than 18. The relative amount of this product formed was considerably larger in the presence of acid. Mass spectroscopic analysis of the mixture (gc/ms) revealed that the new product had the same mass as 18. In order to positively identify the product as the deconjugated isomer of 18, the irradiation was repeated in benzene-d_6 and the product mixture (58 % conversion of 18 to 24) analyzed by ^{1}H-nmr spectroscopy. After subtraction of the known resonances for 18 the spectrum for the product was obtained. In this spectrum two new olefinic resonances were observed at 4.49 and 4.55 ppm, respectively, each one a multiplet integrating for one proton. The signal for the methyl group of 18 had disappeared as had the olefinic proton signal for the hydrogen in the 2-position. This confirmed that the product formed was the exocyclic deconjugated

isomer 3-methylenecyclohexanone **24**, as previously reported by Dauben and coworkers.[4c]

18 **24**

Comparison of these two irradiations demonstrates that the presence of acetic acid improved the yield dramatically. After six hours the conversion from **18** to **24** was 22 % without added acid and 41 % in the presence of ≈ 2 mM acetic acid. Quantum yields were not determined. The fact that **18** was converted to **24** even in the absence of added acid can be attributed to the presence of acidic impurities in the samples of **18**. This is quite feasible since no base wash of **18** was performed prior to the irradiation and the preparation of **18** involved an acidic aqueous workup.

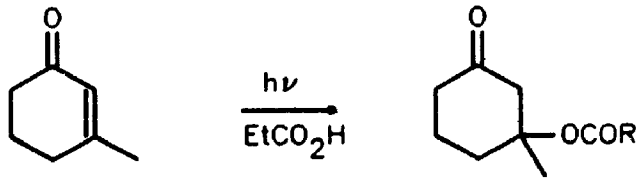
Enone **18** was also irradiated in benzene in the presence of high acid concentrations in order to investigate the possible formation of acid adducts similar to those observed for isophorone, i.e. adducts **65** and **66**. When **18** was irradiated in the presence of ≈ 81 mM acetic acid, a product with a higher retention time than **18** was seen by gas chromatography (in a ratio to **24** of ≈ 1:1); the retention time was shorter than that of the photodimers of **18**[4c] and also shorter than that of adduct **65** formed in the irradiation of isophorone and acetic acid. Attempts to confirm that the adduct had the expected structure **91** (R = Me, SCHEME 43) using gc/ms were unsuccessful, presumably because of the thermal lability of the compound; thus only the molecular ion and fragmentation pattern of **18** could be observed.



18 91 , R = Me

SCHEME 43

As in the analogous isophorone irradiations, the acid was changed to propionic acid. The gc retention time of the presumed adduct peak was increased relative to that observed in the presence of acetic acid. However, the mass spectrum for this peak again corresponded to **18** and no ion corresponding to the expected product **91** (R = Et, SCHEME 44) was observed. However, a fragment with a mass of 74 was observed, which corresponds to propionic acid.



18 91 , R = Et

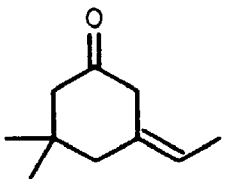
SCHEME 44

No further investigations into the adduct were undertaken, but the similarity between this product and the product from propionic acid addition to isophorone leads to the conclusion that **18** upon irradiation also added acid to give the adduct **91**.

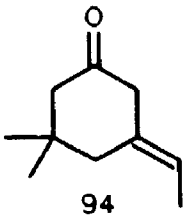
When 3-ethyl-5,5-dimethyl-2-cyclohexenone **69** was irradiated in benzene with and without acetic acid, the formation of three new products was observed by gas chromatography. These were subsequently assigned structure **92** - **94**. Their gc

retention times were shorter than that of **69** and gc/ms revealed that they all had a mass of 152, identical to that of **69**. The product ratio (both with and without added acid) was ≈1:2:3 after 16 hours (**92**:**93**:**94**, short to long retention time) which changed after 56 hours to ≈1:1:1. The presence of acetic acid increased the rate of the reaction; in the absence of added acid the conversion after 56 hours was 35 %, while in the presence of 10 mM acetic acid 94 % of **69** was converted. The product mixture was separated by preparative gas chromatography and analyzed by proton nmr spectroscopy.

A mixture of **93** and **94** was obtained in a ratio of *ca.* 2:1. The ^{1}H-nmr spectrum suggested that the two compounds were isomers since their spectra were very similar in appearance. For each compound a singlet accounting for six protons (two methyl groups at the 5-position) was observed at 0.90 ppm (**93**) and 0.93 ppm (**94**), respectively (assigned by the relative integrals). In addition in each a multiplet at ≈5.3 ppm integrating for one proton indicated the presence of one olefinic proton. Another multiplet was recorded for each compound at 1.58 and 1.54 ppm, respectively, integrating for three protons. From these signals the structures of **93** and **94** could be assigned to be the geometric isomers of 3-ethylidene-5,5-dimethylcyclohexanone. A NOE difference spectrum was recorded.[50] Irradiation at 1.5 ppm (ethylidene methyl groups) led to an increase in intensity of one of the signals for the methylene protons at the 2-position at ≈3 ppm. This identified the methylene signal for the *Z*-isomer **93** since the methylene protons at the 2-position of **93** are closer to the irradiated methyl group. From the relative integrals of the peaks for the methylene groups at the 2-position in the fully coupled spectrum it could be determined that the *E*-isomer **94** was the one present in lesser amount.

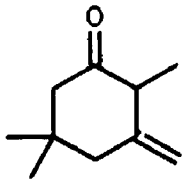


93



94

Product **92** was isolated pure and determined to be 3-methylene-2,5,5-trimethylcyclohexanone from its ^{1}H-nmr spectrum. In the spectrum two singlets (0.80 and 1.03 ppm) integrating to three protons each were assigned to the methyl groups at the 5-position. These methyl groups are non-equivalent due to the chirality of the 2-position which makes them diastereotopic. A doublet (three protons) was seen for the 2-position methyl group at 1.18 ppm, and the methine in the 2-position showed up as a quartet at 2.98 ppm. A multiplet at 4.78 ppm integrating for two protons was assigned to the exocyclic olefinic protons.[39]



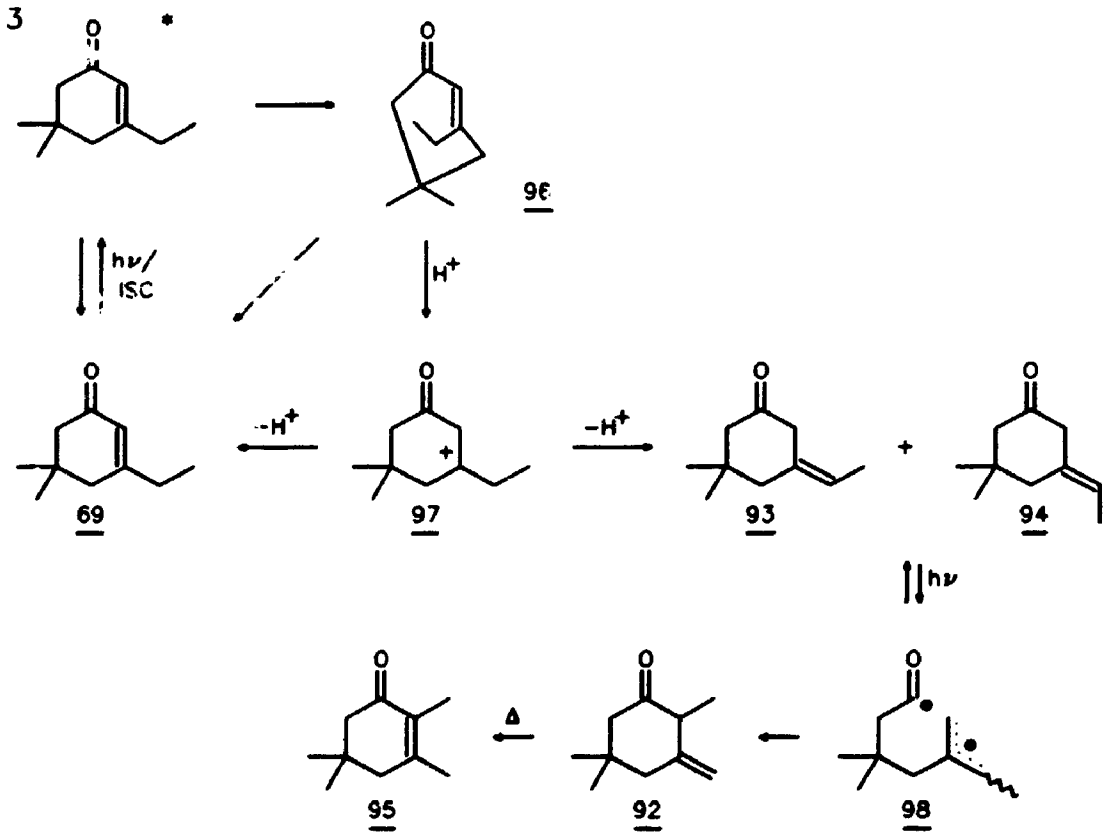
92

After separation of the irradiation mixture another peak was observed by gas chromatography in the fraction containing **92**. Its retention time was longer than those of **92** - **94** but shorter than that of the starting enone **69**. From its proton nmr spectrum it was determined to be 2,3,5,5-tetramethyl-2-cyclohexenone **95**. A singlet at 0.97 ppm accounting for six protons was assigned to the two methyl groups at the 5-position while two multiplets with small coupling constants (< 1 Hz) at 1.74 and

1.87 ppm, each integrating for three protons, were assigned to the methyl groups on the 3- and 2-positions. They were split by long range couplings into each other and into the methylene protons at the 4-position.

This analysis was supported by the fact that the fraction containing **92** showed the presence of a small amount of **95** after standing.

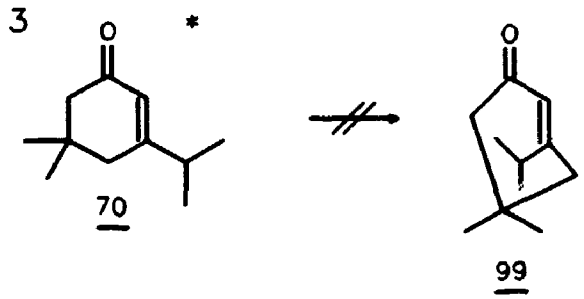
The formation of the compounds **92** - **95** can be explained in terms of the mechanistic model developed for the deconjugation of isophorone and is shown in SCHEME 45.



SCHEME 45

Thus irradiation of **69** and intersystem crossing yields the triplet excited state, which relaxes to the *trans*-enone **96**. Protonation of **96** by acid gives the cation **97** which can lose a proton from either the 2-position (leading back to **69**) or from the side chain methylene group to give both **93** and **94**. Secondary photolysis of either **93** or **94** leads to Norrish Type I cleavage and formation of the biradical **98** which possesses an allylic radical centre.[1,51] Recombination gives either **93** and **94** or, by coupling to the alternative end of the allylic system, **92**. Formation of **95** may arise from reconjugation of **92** catalyzed by adventitious acid present in the solvent ($CDCl_3$) used for recording of the nmr spectra.

Irradiation of 3-isopropyl-5,5-dimethyl-2-cyclohexenone **70** in benzene did not lead to detection of any product; only slow depletion of **70** was observed, presumably due to photodimer formation and/or polymerization. Addition of acetic acid (4 mM) did not change the result. The failure of **70** to undergo deconjugation may arise from the more sterically demanding nature of the isopropyl group. Molecular model studies indicate that in the *trans*-enone the isopropyl group would be brought into close proximity with the 5- and 6-positions as indicated in SCHEME 46.



70 99

SCHEME 46

Consequently it may be postulated that the triplet excited state of **70** is unable to relax to the *trans* enone species **99** and therefore that protonation and deconjugation do not occur.

Removal of the two methyl groups on the 5-position did not change the picture significantly; irradiation of 3-isopropyl-2-cyclohexenone **21** in the presence of acetic acid (≈ 80 mM) led, after extended reaction, to the formation of only small amounts of product as detected by gas chromatography. Gc/ms indicated that these possessed the same mass as **21**; however, the small amounts of product formed made further investigation impossible. The exact nature of these products could not be determined but model studies showed that the steric hindrance in the formation of the *trans*-isomer of **21** was not much less than in the case of **70**.

At this point a comparison of the results obtained in this study regarding the photochemical deconjugation reaction of 3-alkyl substituted 2-cyclohexenones with earlier work is in order. It has been confirmed that isophorone and 3-methyl-2-cyclohexenone undergo photoreactions to yield their respective exocyclic deconjugated isomers as reported by various groups.[4c,6,13] No indication of any formation of endocyclic deconjugated isomers was found, which is also in accordance with the literature data. Dauben reported that only 2-cyclohexenones with a methyl substituent in the 3-position were found to undergo photodeconjugation reactions.[4c] The study described in this thesis indicates that this is not the case since 3-ethyl-2-cyclohexenone **69** undergoes photolysis to its exocyclic deconjugated isomers.

The results from quenching studies carried out in the course of this investigation have confirmed that the triplet excited state of the enone is involved in the mechanism. No indication has been found for the involvement of two triplet excited states as

reported by Shiloff and Hunter for isophorone[13] and Schaffner et al. for the photodeconjugation of octalone **27a**.[4d]

The discovery of acid catalysis of the photodeconjugation reaction leads to a reasonable explanation of the reaction mechanism. From steady state kinetic analysis the intermediacy of a *trans*-enone is proposed which can be protonated by acid to give a carbocation leading either to starting material or to deconjugated product. This is in accordance with literature reports of the photochemical addition of alcohols to seven and eight membered ring enones[28] and of the photoreactions of 1-methylcyclohexenes[31] which also proceed *via trans* species followed by protonation to give carbocations.

The results obtained in this study fit the proposed mechanism. Kinetic analysis shows the need for an intermediate longer lived than the triplet excited state of the enone and derived from it. The intermediacy of a carbocation species is strongly suggested by isolation of alcohol and acid adducts of the enone.

The enone concentration dependency of the deconjugation reaction further indicates that a bimolecular mechanism as proposed by Schaffner et al.[4d,15] and contemplated by Lombardo[20] can be ruled out since the rate of deconjugation reaction did not show the expected increase with increasing enone concentration.

Finally the proposed mechanism can be used to explain some of the contradictory results about the solvent dependency of the photodeconjugation reaction. Since it was found that even small amounts of acid (0.2 mM) present in the photolysis of isophorone led to an increase in the quantum yield of the deconjugation reaction, it can be rationalized that incomplete solvent purification coupled with varying amounts of acidic impurities in the enones led to erroneous results in some of the reports as indicated in Section **2.2.3.** The fact that Shiloff and Hunter observed a high

yield of deconjugated product by irradiating isophorone in ethyl acetate can be explained by the presence of acidic impurities inherent to this solvent.[13] They also did not observe any deconjugation products when they irradiated isophorone in methanol in the presence of an alkene. This can be understood in view of the fact that alkenes react with triplet excited states of enones to form cycloadducts in relatively high quantum yields and therefore compete efficiently with the relaxation of the triplet excited state to the *trans*-enone on the pathway leading to deconjugation. However, in the work described in this thesis it was found that 3-alkyl-2-cyclohexenones do not photodeconjugate in methanol solvent, even in the presence of acid, although deconjugation could be achieved in methanolic benzene (9:1). The failure of the reaction in pure methanol is not understood and requires further investigation.

2.3.3 Irradiation of *R*-10-Methyl-$\Delta^{1,9}$-2-octalone 27a

The earlier investigations dealing with the photochemical deconjugation reaction of **27** had led to contradictory results. Schaffner et al. came to the conclusion that it is a bimolecular process and presumably involved a dienol species as outlined in Section 1.1.[4d,15] However, Scaiano et al. postulated an unimolecular reaction mechanism based on their findings of the photolysis of **27** in *α*-cyclodextrin matrices.[17]

In order to clarify this situation, the photochemistry of **27** was examined to determine if acid catalysis was important in this system. Irradiation of **27a** as received[52] in benzene[4d,15,17] led to the partial conversion to its deconjugated isomer **32a** as shown in SCHEME 47.

27a 32a

SCHEME 47

The product was identified by gc/ms and proton nmr spectroscopy of the mixture. The ^{1}H-nmr spectrum revealed the presence of a multiplet at ≈5.1 ppm integrating to one proton (olefinic proton in **32a**) as well as the appearance of a singlet at 0.84 ppm integrating to three protons which was assigned to the methyl group in **32a**.

These data are in accordance with those previously reported by Schaffner.[4d,15] The ratio of **27a** to **32a** determined by ^{1}H-nmr spectroscopy of the mixture correlated well with the ratio determined by gc; accounting for the error margin in nmr integrations less than 5 % thermal reconjugation of **32a** to **27a** in the gc was observed. This reconjugation had been a problem which Schaffner did not recognize in his initial report[4d] and led to erroneous results causing him to reexamine his findings later.[15]

Addition of acetic acid (≈5 mM) did not change the rate of the photochemical deconjugation reaction. Similarly irradiation of a benzene solution of **27a** in the presence of solid sodium carbonate also did not result in any change in the reaction rate. However, when **27a** was purified by a base wash (sodium hydroxide), irradiation of a benzene solution showed a large decrease in the rate of the deconjugation reaction, while addition of acetic acid resulted in restoration of the rate of isomerization.

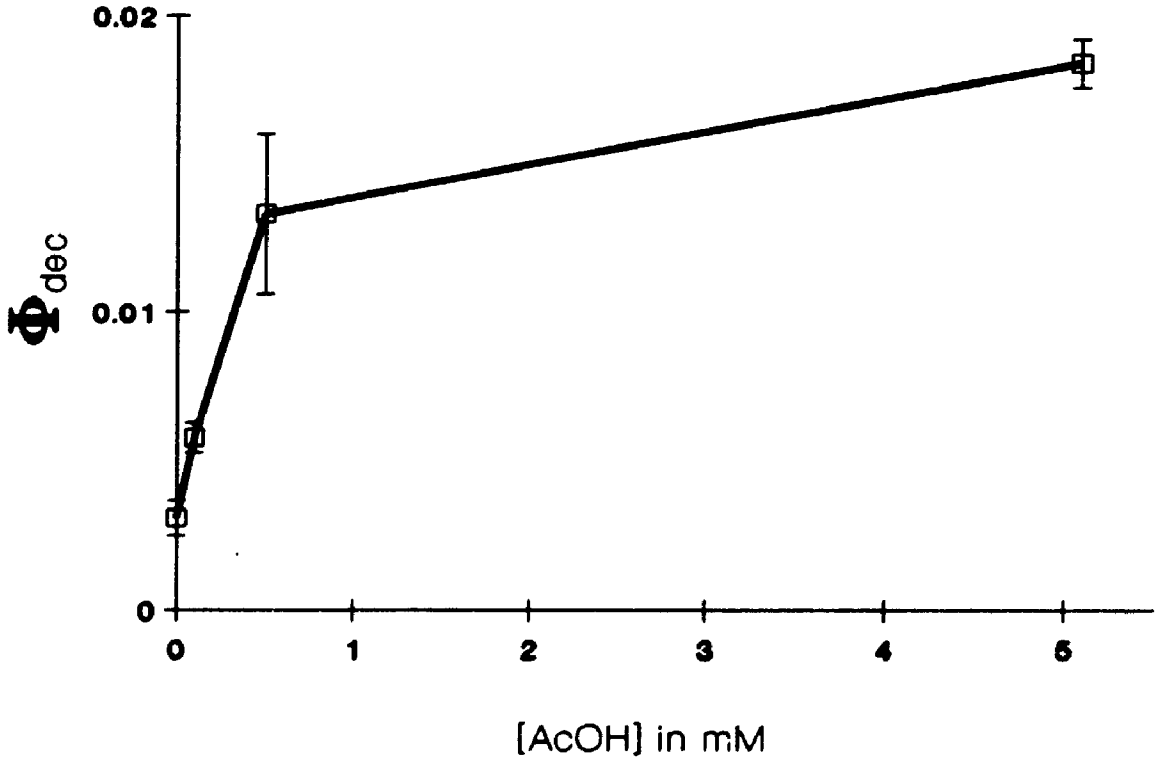
Quantum yield determinations for the photochemical deconjugation of purified (i.e. base washed) **27a** at 313 nm in the presence of various concentrations of acetic acid were carried out and the results are reported in TABLE 13 and illustrated in FIGURE 11.

TABLE 13: Φ_{dec} for *R*-10-methyl-$\Delta^{1,9}$-2-octalone with acetic acid

[AcOH]	Φ_{dec}
0	0.0031 ± 20 %
0.1 mM	0.0058 ± 8.7 %
0.5 mM	0.0133 ± 20 %
5.1 mM	0.0184 ± 4.5 %

[**27a**] = 100 mM, solvent = benzene, photon dose = 1.364×10^{-4} E

FIGURE 11: Plot of Φ_{dec} of **27a** vs concentration of acetic acid



The data shown in TABLE 13 and FIGURE 11 clearly illustrate the acid dependence of the deconjugation reaction of **27a**. The value of Φ_{dec} prior to the base wash of **27a** was determined to be 0.0185 ± 6.2 % indicating that the acid present in the commercial octalone sample used was equivalent to ≈ 5 mM acetic acid. In the light of the results obtained for isophorone and its homologues reported in Sections **2.2.3** and **2.3.2**, it seems probable that the deconjugation reaction may proceed by an analogous mechanism involving the formation of a *trans*-enone species, rather than by a bimolecular reaction as proposed by Schaffner and coworkers.[4d,15] It also seems likely that if **27a** could be obtained totally acid free and irradiated in the absence of any acid, no deconjugation reaction would be observed.

2.4 Conclusion

The work reported in this chapter indicates that the photodeconjugation reaction of simple 3-methyl substituted 2-cyclohexenones (**16** and **18**) is catalyzed by acids such as acetic acid, propionic acid and trifluoroacetic acid. The reaction proceeds *via* the triplet excited state of the enone as was shown by triplet quenching experiments. The results of a steady state kinetic treatment of the dependency of the deconjugation quantum yield upon acid concentration suggest that the triplet excited state relaxes to a *trans*-enone which has a lifetime of > 1 μs. This may be protonated by the acid to give a tertiary carbocation. Loss of a proton then results either in formation of starting material or in production of the exocyclic deconjugated isomer. Contrary to literature reports,[4c] the 3-ethyl analogue of isophorone (**69**) does undergo photodeconjugation to the corresponding exocyclic isomers and this reaction is also acid catalyzed. The 3-isopropyl analogues (**21** and **70**) did not show evidence of any photodeconjugation

reactions, possibly due to steric hindrance in the formation of the *trans*-enone species. The bicyclic 2-cyclohexenone **27a** also undergoes an acid catalyzed photodeconjugation reaction. As the kinetic studies and the proposed mechanism indicate, the photodeconjugation reaction is unimolecular in enone, contrary to earlier literature reports.[4d,20]

CHAPTER 3

EXPERIMENTAL SECTION

3.1 General

^{1}H-Nmr spectra were recorded at 60 MHz in $CDCl_3$ or D_2O on a Varian EM 360 instrument, or at 200 MHz in $CDCl_3$ or C_6D_6 on Varian XL 200 or Varian Gemini 200 instruments. ^{2}H-Nmr spectra were recorded at 92 MHz in C_6H_6 on a Varian XL 300 instrument. ^{13}C-Nmr spectra in $CDCl_3$ or C_6D_6 were recorded on a Varian XL 300 (75 MHz) or a Varian Gemini 200 (50 MHz) instrument. Chemical shifts (δ) are given in ppm downfield from TMS (0.00 ppm). Data for ^{1}H-nmr spectra are reported as follows: δ (multiplicity, coupling constant(s) in Hz, integration). Abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet). Data for ^{13}C-nmr spectra are given as follows: δ (degree of substitution).

Infrared spectra (film or in Nujol) were recorded on a Bruker IFS 32/IBM System 9000 FT-IR instrument.

Ultraviolet absorption spectra in various solvents were obtained on a Shimadzu UV-160 spectrophotometer. Data are reported as follows: λ_{max} in nm (ϵ).

Gas chromatography coupled mass spectroscopy was performed using a Varian 3400 gc equipped with a 30 m DB-5 capillary column attached to a Finnegan MAT 8230 mass spectrometer. Ionization was achieved by electron impact (EI; 25 or 70 eV) or by chemical ionization (isobutane; CI). Data are given as follows: Fragment mass (intensity in %).

Preparative gas chromatography was carried out on a Varian 920 instrument equipped with a packed column (8' x ¼", 10 % SE-30 on Chromosorb W, He carrier).

Analytical gas chromatography was performed on a Varian 2400 gc equipped with a 15 m DB-1 megabore column or a Hewlett-Packard 5880 gc equipped with a 30 m DB-5 capillary column (He carrier). Flame ionization detectors were used.

Quantum yield determinations were carried out using a 3.00 ml of a sample solution which was degassed (unless otherwise stated) by the freeze-pump-thaw technique (three cycles, residual pressure $< 10^{-4}$ mbar). A Photon Technology International (PTI) Quantacount instrument was used for the determinations. The light source used was a 100 W high pressure mercury lamp. The light was passed through a monochromator to obtain light with a wavelength of $\lambda = 313 \pm 2.5$ nm. The irradiated samples contained an internal hydrocarbon standard and were analyzed by repeated injections on the gc. From the ratio of starting material to standard at t_0 and the ratio of product to standard at t_{end} (five injections each) the absolute amount of product formed was calculated assuming an identical response of the gc detector to both compounds. Combination of this with the number of photons absorbed (from the Quantacount calibration) the absolute quantum yield was determined.

Preparative and analytical irradiations were performed at room temperature with a 400 W medium pressure mercury lamp housed in a water cooled Pyrex jacket. The irradiation samples were deoxygenated by passing a stream of dry nitrogen through the solutions prior to irradiation. The solvents used for irradiations were of spectrophotometric grade; dry benzene was obtained by distillation from CaH_2.[24b]

All other solvents were of analytical grade; diethyl ether for Grignard reactions was dried by refluxing over and distilling from sodium metal under nitrogen with benzophenone as indicator. Commercial isophorone **16** (Aldrich) was washed (unless otherwise stated) with 5 % aqueous Na_2CO_3 solution, dried ($MgSO_4$) and distilled under reduced pressure ($bp._{16}$ 108°C). A commercial sample of R-10-methyl-$\Delta^{1,9}$-2-

octalone **27a**[52] was purified (unless otherwise stated) by washing with 5 % aqueous NaOH solution and dried (Na_2SO_4). Commercial isoprene (Aldrich) was washed with 5 % aqueous NaOH solution and water, dried (CaH_2) and distilled under nitrogen (bp. 33-34°C). All other chemicals were used as supplied by Aldrich.

3.2 Preparations of 3-Alkylsubstituted 2-Cyclohexenones

3.2.1 Preparation of 3-Ethoxy-5,5-dimethyl-2-cyclohexenone 71

A solution of 50 g dimedone **72** (0.36 mole), 53.7 g abs. ethanol (1.17 mole) and 1.3 g *p*-toluenesulfonic acid in 400 ml benzene was refluxed with azeotropic removal of water (Dean-Stark trap). After collection of 13 ml of the lower layer (ethanol/water) the reaction was stopped and the solvent removed. The residue was distilled to give 48.2 g (80.3 %) of a colourless liquid ($bp._{1.3}$ 94-96°C) which solidified (mp. 53-54°C, lit. 57-58°C[42a]). ^{1}H-nmr (200 MHz, $CDCl_3$): 1.05 (s, 6 H), 1.34 (t, 7.08 Hz, 3 H), 2.19 (s, 2 H), 2.25 (s, 2 H), 3.88 (q, 7.08 Hz, 2 H), 5.32 (s, 1 H); ms (EI): 168 (M^+, 62), 112 (96), 84 (100), 69 (62), 68 (62)

3.2.2 Preparation of 3-*n*-Decyloxy-5,5-dimethyl-2-cylohexenone 73

A solution of 5 g dimedone **72** (35.7 mmole), 22.1 g *n*-decanol (0.14 mole) and 0.2 g *p*-toluenesulfonic acid in 40 ml benzene was refluxed with azeotropic removal of water (Dean-Stark trap). Benzene and decanol ($bp._{0.3}$ 79-80°C) were removed by distillation under reduced pressure and the residue distilled also under reduced pressure to give 8.3 g (83.0 %) of a slightly yellow liquid ($bp._{0.02}$ 133-137°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 0.88 (t, 6.69 Hz, 3 H), 1.07 (s, 6 H), 1.28 (bs, 16 H), 2.21 (s, 2 H), 2.28 (s, 2 H), 3.83 (t, 6.50 Hz, 2 H), 5.34 (s, 1 H); ms (EI): 280 (M^+, 32), 265 (78), 141 (100), 125 (30)

3.2.3 Preparation of 3-Cholesteryloxy-5,5-dimethyl-2-cyclohexenone 78

A solution of 1 g dimedone 72 (7.1 mmole), 2.6 g cholesterol 77 (6.8 mmole) and 40 mg *p*-toluenesulfonic acid in 40 ml benzene was refluxed with azeotropic removal of water (Dean-Stark trap). After 18 hours no more change was apparent by tlc. The reaction mixture was washed with sat. $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the solvent gave 3.4 g of a black oil. This was dissolved in hot diethyl ether, filtered and treated with hexanes. Crystals were formed and the flask was stored in the freezer overnight to give 793.0 mg (23.2 %) of creamy white crystals (mp. 164-168°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 0.68 (s, 3 H), 0.86 (d, 7.10 Hz, 6 H), 0.92 (d, 6.67 Hz, 3 H), 1.00-2.45 (m, 28 H), 1.03 (s, 3 H), 1.07 (s, 6 H), 2.21 (s, 2 H), 2.25 (s, 2 H), 4.08 (m, 1 H), 5.36 (bs, 2 H); ms (CI): 509 ($M^+ + 1$, 8), 370 (32), 369 (100), 368 (28); IR (nujol): 1684 cm^{-1}

3.2.4 Preparation of 3-(N-Piperidyl)-5,5-dimethyl-2-cyclohexenone 79

A solution of 1.4 g dimedone 72 (10 mmole), 0.85 g piperidine (10 mmole) and 10 mg *p*-toluenesulfonic acid in 50 ml benzene were refluxed with azeotropic removal of water (Dean-Stark trap). After one hour a gc analysis showed none of 72 was left in the reaction mixture. The solution was worked up by washing with sat. $NaHCO_3$ solution and drying (Na_2SO_4). Removal of the solvent gave 650.3 mg of orange crystals. Recrystallization from hexanes (twice) and ethyl acetate (once) yielded 280.0 mg (13.5 %) of yellow crystals (mp. 79-80°C). ^{1}H-nmr (200 MHz, $CDCl_3$)[53]: 1.08 (s, 6 H), 1.50-1.82 (m, 6 H), 2.17 (s, 2 H), 2.24 (s, 2 H), 3.37 (m, 4 H), 5.30 (s, 1 H); ms (EI): 207 (M^+, 100), 192 (36), 179 (36), 164 (89), 124 (46), 123 (72), 83 (56), 82 (36), 67 (48), 55 (36); IR (nujol): 1659 cm^{-1}

3.2.5 Preparation of 3-Isobutoxy-5,5-dimethyl-2-cyclohexenone 83

A solution of 20 g dimedone 72 (0.143 mole, purified by dissolving in diethyl ether, filtering and removal of solvent), 11 g isobutanol (0.149 mole) and 1 g *p*-toluenesulfonic acid in 200 ml benzene was refluxed with azeotropic removal of water (Dean-Stark trap). The reaction was monitored by gc and worked up after three hours by washing with sat. $NaHCO_3$ solution and drying (Na_2SO_4). The solvent was removed to give 42.1 g of a greenish liquid. Distillation yielded 21.3 g (76.1 %) of a colourless liquid ($bp._{0.3}$ 96°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 0.98 (d, 6.71 Hz, 6 H), 1.08 (s, 6 H), 2.04 (m, 1 H), 2.21 (s, 2 H), 2.29 (s, 2 H), 3.60 (d, 6.59 Hz, 2 H), 5.33 (s, 1 H); ms (EI): 196 (M^+, 8), 181 (6), 141 (100), 85 (46), 84 (88), 57 (46); IR (film): 2968, 2974, 1659, 1609 cm^{-1}

These data were in agreement with those reported by House and Fischer.[48b] The impurity 2,2-bis(2-hydroxy-4,4-dimethylcyclohex-1-en-6-onyl)propane 84 present in 72 prior to purification was isolated by crystallization at low temperature as white crystals from the distillation residue of an earlier experiment (mp. > 240°C, subl.). ^{1}H-nmr (200 MHz, $CDCl_3$): 1.07 (s, 12 H), 1.58 (s, 2 H), 1.64 (s, 6 H), 2.23 (s, 4 H), 2.29 (s, 4 H); ^{1}H-nmr (60 MHz, $CDCl_3/D_2O$): 1.05 (s, 12 H), 1.65 (s, 6 H), 2.25 (m, 8 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 26.02 (CH_3), 28.08 (CH_3), 31.54 (C), 32.05 (C), 41.43 (CH_2), 52.93 (CH_2), 119.71 (C), 160.49 (C), 197.58 (C=O); ms (CI): 303 (M^+-17, 30), 288 (22), 287 (100), 231 (6)

3.2.6 Preparation of 3-Isobutoxy-2-cyclohexenone 86

A solution of 40 g 1,3-cyclohexanedione 85 (0.35 mole), 2 g *p*-toluenesulfonic acid and 32 ml isobutanol (0.35 mmole) in 300 ml benzene was refluxed with azeotropic removal of water (Dean-Stark trap). After 2.5 hours the reaction mixture was washed with sat. $NaHCO_3$ solution and sat. NaCl solution and dried (Na_2SO_4).

Removal of solvent led to 74.9 g of a red liquid which gave after distillation 55.2 g (92 %) of a colourless liquid ($bp._{0.2}$ 88-89°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 0.88 (d, 6.69 Hz, 6 H), 1.91 (m, 3 H), 2.25 (m, 2 H), 2.33 (t, 6.25 Hz, 2 H), 5.24 (s, 1 H); ^{13}C-nmr (75 Hz, $CDCl_3$): 18.65 (CH_3), 20.84 (CH_2), 27.28 (CH), 28.56 (CH_2), 36.34 (CH_2), 74.21 (CH_2-O), 103.22 (CH), 177.67 (C-O), 199.15 (C=O); ms (EI): 168 (M^+, 12), 113 (82), 85 (38), 84 (100), 57 (86), 56 (36)

3.2.7 Preparation of 3-Ethyl-5,5-dimethyl-2-cyclohexenone 69

a) from 3-ethoxy-5,5-dimethyl-2-cyclohexenone 71

A Grignard reagent was prepared from 3.6 g Mg (0.15 mmole) and 11.2 g ethyl bromide (0.15 mmole, alternatively 0.15 mmole ethyl iodide were used) in 150 ml dry diethyl ether. To this was added at 0°C a solution of 5 g 71 in 70 ml dry diethyl ether and the mixture was allowed to warm to ≈ 20°C. The mixture was then heated to reflux and the reaction progress monitored by gc. Gc/ms aided in identification of the product peak. After 3.5 hours the ratio 69:71 was constant at 4.5:1 and the reaction was worked up (hydrolysis with ice/dil. HCl, extraction with Et_2O, wash with sat. $NaHCO_3$ solution and drying with $MgSO_4$) to give after solvent removal 4.3 g of a yellow liquid. A distillation did not result in satisfactory separation of the compounds.

b) from 3-decyloxy-5,5-dimethyl-2-cyclohexenone 73

A Grignard reagent was prepared from 0.96 g Mg (40 mmole) and 4.4 g (40 mmole) ethyl bromide in 50 ml dry diethyl ether. To this was added 3 g 73 (10.7 mmole) in 30 ml dry diethyl ether at 0°C. The mixture was then heated to reflux and monitored by gc. Gc analysis after four hours revealed three high retention time (just shorter than 73) side products (74 - 76) and decanol as by-product in a gc ratio of 69:decanol:74:75:76:73 of 1.5:1.7:0.3:1.0:0.7:1. ms (EI) for 74: 292 (M^+, 38), 277 (70), 152 (100), 137 (92); for 75: 292 (M^+, 38), 277 (22), 152 (100), 137 (24);

for **76**: 292 (M^+, 42), 277 (22), 152 (100), 137 (24). These data are consistent with 1-decyloxy-3-ethyl-5,5-dimethyl-1,3-cyclohexadiene and *E*- and *Z*-1-decyloxy-3-ethylidene-5,5-dimethyl-1-cyclohexene, respectively. After 20 hours the reaction was worked up as described in **a)** above; 2.6 g of a greenish liquid were obtained. Compounds **74** - **76** were no longer present in the mixture and the ratio **69**:decanol:**73** was 2.4:2.7:1. The similarity of the boiling points of **69** and decanol did not permit a separation by distillation. Oxidation of decanol with $KMnO_4$/KOH failed to remove it from the mixture; no product ratio change was observed.

c) from 3-cholesteryloxy-5,5-dimethyl-2-cyclohexenone **78** (attempt)

A Grignard reagent was prepared from 1 g Mg (42 mmole) and 4.5 g (42 mmole) ethyl bromide in 30 ml dry diethyl ether. A 10 ml portion of this solution was slowly added to a 0°C cold solution of 4.5 g **78** (8.9 mmole) in 300 ml dry diethyl ether. Yellow crystals precipitated and the reaction was stirred at rt. Reaction progress was monitored by tlc (Et_2O, formation of cholesterol was seen) until no further product change was observed (one hour); the mixture was then heated to reflux for 21 hours, but no further change was observed. Work-up (dil. HCl, sat. $NaHCO_3$, $MgSO_4$, solvent removal) gave 4.33 g of yellow crystals which were separated with pentane into two fractions (soluble [1.8 g] and non-soluble [2.1 g]). ^{1}H-Nmr analysis revealed the latter to be **78**, the former proved to be a mixture of compounds (cholesterol was detected). A signal at 5.9 ppm was present but no isolation was performed.

d) from 3-(N-piperidyl)-5,5-dimethyl-2-cyclohexenone **79** (attempt)

A Grignard reagent was prepared from 24 mg Mg (1 mmole) and 109 mg ethyl bromide (1 mmole) in 10 ml dry diethyl ether. To this was slowly added at rt a solution of 207 mg **79** (1 mmole) in 5 ml dry diethyl ether. The mixture was stirred at rt for one hour (a white precipitate appeared) and worked up (dil. HCl, sat. $NaHCO_3$, $MgSO_4$). Gc

analysis showed formation of a small amount of a product at higher retention time than **79** (unidentified but with a mass of 287) but mainly **79** was recovered and no **69** was detectable.

e) from 3-isobutoxy-5,5-dimethyl-2-cyclohexenone **83**

A Grignard reagent was prepared from 2.4 g Mg (0.1 mole) and 10.9 g ethyl bromide (0.1 mole) in 100 ml dry diethyl ether. To this was added at 0°C a solution of 9.8 g **83** (50 mmole) in 70 ml dry diethyl ether. The reaction was allowed to warm to rt and then refluxed and monitored by gc. After 16 hours no change in the ratio of **69** and **83** was observed and the reaction was worked up (dil. HCl, sat. $NaHCO_3$, $MgSO_4$, solvent removal) to give 6.23 g of a yellow liquid with a ratio **69**:**83** of ≈3:1. This was distilled using a spinning band column to give 3.61 g (48 %) **69** (colourless liquid, $bp._{1.5}$ 66°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 1.04 (s, 6 H), 1.10 (t, 7.3 Hz, 3 H), 2.1-2.3 (m, 6 H), 5.88 (m, 1 H); ms (EI): 152 (M^+, 38), 96 (100); uv (CH_3OH): 237 (13700), 312 (50)

These data were in accordance with literature values.[43a]

3.2.8 Preparation of 3-isopropyl-5,5-dimethyl-2-cyclohexenone **70**

A Grignard reagent was prepared from 2.4 g Mg (0.1 mole) and 8 g isopropyl chloride (0.1 mole) in 100 ml dry diethyl ether. To this was added a solution of 8.4 g **71** (50 mmole) in 50 ml dry diethyl ether at 0°C and the mixture was refluxed. After one hour the reaction was worked up (dil. HCl, sat. NaHCO3, $MgSO_4$, solvent removal) to give 7 g of a yellowish liquid with a ratio of **70**:**71** of 1.1:1. This was separated by column chromatography (125 g silica gel, Et_2O/hexanes 1:1) to give 2.7 g (33 %) of a colourless liquid. ^{1}H-nmr (200 MHz, $CDCi_3$): 1.04 (s, 6 H), 1.10 (d, 6.8 Hz, 6 H), 2.18 (bs, 2 H), 2.22 (s, 2 H), 2.40 (m, 1 H), 5.89 (m, 1 H); ms (EI): 166 (M^+, 66), 110 (100), 95 (82); uv (CH_3OH): 236 (12000), 304 (68)

3.2.9 Preparation of 3-Methyl-2-cyclohexenone 18

A Grignard reagent was prepared from 4.3 g Mg (0.18 mole) and 25.4 g methyl iodide (0.18 mole) in 120 ml dry diethyl ether. To this was added at 0°C a solution of 15 g **86** (89 mmole) in 75 ml dry diethyl ether. The reaction was refluxed and monitored by gc. After three hours **86** had disappeared and the solution was worked up (dil. HCl, sat. NaHCO3, $MgSO_4$, solvent removal) and distilled to give 2.8 g (28.5 %) of a colourless liquid ($bp._{19}$ 90°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 1.81-1.95 (m, 5 H), 2.14-2.27 (m, 4 H), 5.76 (m, 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 22.3 (CH_3), 24.2 (CH_2), 30.7 (CH_2), 36.7 (CH_2), 126.3 (CH), 162.7 (C), 199.4 (C=O); ms (EI): 110 (M^+, 42), 82 (100)

These data were in agreement with those reported in the literature.[41]

3.2.10 Preparation of 3-Ethyl-2-cyclohexenone 20

A Grignard reagent was prepared from 857.3 mg Mg (35.7 mmole) and 5.58 g ethyl iodide (35.8 mmole) in 50 ml dry diethyl ether. At 0°C a solution of 3 g **86** (17.9 mmole) in 20 ml dry diethyl ether was added and the solution was refluxed for two hours. Three side products **87** - **89** were observed at shorter retention times than **20** in small amounts (ratio **87**:**88**:**89**:**20** ≈ 1:7.4:12.4:204.5). ms (EI) for **87**: 136 (M^+, 32), 121 (18), 107 (70), 93 (14), 91 (24), 79 (100), 77 (18); for **88**: 136 (M^+, 78), 121 (38), 107 (100), 93 (40), 91 (40), 79 (88), 77 (24); for **89**: 136 (M^+, 80), 121 (38), 107 (100), 93 (40), 91 (38), 79 (84), 77 (24). These data were consistent with 1-isobutoxy-3-ethyl-1,3-cyclohexanedione and *E*- and *Z*-1-isobutoxy-3-ethylidene-1-cyclohexene, respectively. After work up (dil. HCl, sat. $NaHCO_3$, $MgSO_4$, solvent removal) distillation yielded 2.2 g of a yellow liquid ($bp._{33}$ 96-100°C) which was column chromatographed (100 g silica gel, diethyl ether/hexanes 1:6→1:1 to give 1.63 g (73.6 %) of a colourless liquid. ^{1}H-nmr (200 MHz, $CDCl_3$): 1.11 (t, 7.45 Hz,

3 H), 1.92-2.07 (m, 2 H), 2.18-2.41 (m, 6 H), 5.88 (m, 1 H); ms (EI): 124 (M^+, 50), 96 (100), 67 (44)

3.2.11 Preparation of 3-Isopropyl-2-cyclohexenone 21

A Grignard reagent was prepared from 4.29 g Mg (0.18 mole) and 14.1 g isopropyl chloride (0.18 mole) in 70 ml dry diethyl ether. To tnis was added at 0°C a solution of 15.2 g 86 (90 mmole) in 50 ml dry diethyl ether. The mixture was refluxed for 1.5 hours and worked up (dil. HCl, sat. $NaHCO_3$, $MgSO_4$, solvent removal) and distilled to give 3.15 g (25.2 %) of a colourless liquid ($bp._{0.2-0.3}$ 45-48°C). ^{1}H-nmr (200 MHz, $CDCl_3$): 1.11 (d, 6.8 Hz, 6 H), 1.96 (m, 1 H), 2.1-2.5 (m, 6 H), 5.88 (m,1 H); ms (EI): 138 (M^+, 58), 110 (88), 95 (100), 67 (56); uv (C_6H_6): 333 (41)

3.3 Irradiation of Isophorone 16

3.3.1 Photodeconjugation of 16 Without Added Acid

a) Ultraviolet absorption of 16 (used as received) in various solvents

The absorption characteristics of 16 are given below in TABLE 14.

TABLE 14: Ultraviolet absorption data for isophorone

solvent	λ_{max} (π,π^*)	ϵ_{max}	$\epsilon_{254\ nm}$
MeCN	232.4 nm	13600	1470
pentane	225.6 nm	14000	42
MeOH	235.4 nm	13600	4310

solvent	λ_{max} (n,π^*)	ϵ_{max}	$\epsilon_{313\ nm}$
MeCN	321.4 nm	37	35
pentane	337.0 nm	30	22
MeOH	311.8 nm	50	49
benzene	331.4 nm	37	30

b) Identification of the deconjugated isomer of **16**

Nitrogen purged solutions of **16** (560 mg, not base washed, 100 mM) in cyclohexane and diethyl ether were irradiated and the reaction progress was monitored by gc. The appearance of one new peak at lower retention time (1.82 min vs 2.82 min for **16**) was observed. Removal of the solvent after 138 hours irradiation (in diethyl ether) led to the isolation of a mixture of **16** and 3-methylene-5,5-dimethylcyclohexanone **17** (2:1). ^{1}H-nmr (200 MHz, $CDCl_3$) for **16**: 0.95 (s, 6 H), 1.85 (m, 3 H), 2.09 (m, 4 H), 5.79 (m, 1 H); for **17**: 0.91 (s, 6 H), 2.19 (s, 2 H), 2.22 (s, 2 H), 2.98 (m, 2 H), 4.75 (m, 2 H); ^{1}H-nmr (200 MHz, C_6D_6) for **16**: 0.75 (s, 6 H), 1.43 (m, 3 H), 1.56 (s, 2 H), 2.05 (s, 2 H), 5.90 (m, 1 H); for **17**: 0.66 (s, 6 H), 1.81 (s, 2 H), 1.87 (s, 2 H), 2.70 (m, 2 H), 4.55 (bs, 2 H); ^{13}C-nmr (50 MHz, C_6D_6) for **16**: 23.89 (CH_3), 28.06 (2 CH_3), 33.03 (C), 44.78 (CH_2), 50.88 (CH_2), 126.21 (CH), 158.32 (C), 197.9[illegible] (C=O); ^{13}C-nmr (75 MHz, $CDCl_3$) for **16**: 24.57 (CH_3), 28.34 (2 CH_3), 33.57 (C), 45.31 (CH_2), 50.79 (CH_2), 125.52 (CH), 160.39 (C), 200.02 (C=O); ms (EI) for **16**: 138 (M^+, 70), 82 (100); for **17**: 138 (M^+, 44), 83 (90), 82 (100), 54 (76). At longer retention times at least two small peaks were observed which were attributed to dimers of **16**: ms (EI, sample): 276 (M^+, 2), 259 (8), 139 (100), 138 (76), 123 (39), 82 (59)

No evidence for thermal reconjugation of **17** to **16** was found when the nmr solution was reinjected, good agreement was found between nmr and gc ratios.

c) Preliminary deuterium incorporation studies

A solution of 548.9 mg **16** (not base washed, 4 mmole) and 4 ml MeOD in 40 ml diethyl ether was irradiated and the reaction progress was followed by gc. After 141 hours ≈ 6 % conversion of **16** to **17** was observed; gc/ms analysis (looking at the intensity of the M+1 peak for each compound after subtraction of the amount due to

natural occurrence of deuterium and carbon-13) revealed 36 % deuterium incorporation into **17** and 2 % into **16**. After 468 hours (≈ 24 % conversion to **17**) these figures were 56 % and 22 %, respectively.

d) Quantacount calibration

103.1 mg azoxybenzene **45** (0.52 mmole, recrystallized from EtOH) were dissolved to 50 ml in a solution of 7.2 g KOH in 350 ml 95 % EtOH. A 3.00 ml sample of this solution was irradiated in the Quantacount at 348 nm for a certain number of counts, then a uv spectrum of the solution at 458 nm was performed and its absorbance recorded as shown in TABLE 15.

TABLE 15: Quantacount calibration data

counts	Abs	counts	Abs
0	0.029	20×10^4	0.300
5×10^4	0.091	30×10^4	0.438
10×10^4	0.159	40×10^4	0.590
15×10^4	0.227	50×10^4	0.750

A plot of the data gave a straight line with a slope of 1.440×10^{-6} Abs/count ± 14 % from which the conversion factor I_c was calculated to be 2.2737×10^{-11} E/count ± 19 %.

e) Determination of Φ_{dec} of **16** (sample experiment)

A solution of 991.5 mg **16** (not base washed, 7.2 mmole) and 143.8 mg dodecane in 50.00 ml benzene was prepared; a 3.00 ml sample of this solution (containing 4.304×10^{-4} mmole **16**) was irradiated in the Quantacount. After 3.752×10^6 counts (corresponding to 8.531×10^{-5} E ± 19 %) the solution was analyzed by gc and from the area ratios (**16**/dodecane at t_0 [5.659 ± 1.6 %] and

17/dodecane at t_{end} [7.087×10^{-3} ± 3.3 %]) the absolute amount of 17 present was calculated to be

$$[17] = \left(\frac{7.087 \times 10^{-3}}{5.659}\right) \times (4.304 \times 10^{-4})$$

$$= 5.391 \times 10^{-7} \text{ moles} \pm 3.3\ \%$$

This assumes that the gc detector response was the same for 16 and 17. By combination with the photon dose Φ_{dec} was calculated as follows:

$$\Phi_{dec} = \frac{[17]}{\text{photon dose}}$$

$$= \frac{5.391 \times 10^{-7} \pm 3.3\ \%}{8.531 \times 10^{-5} \pm 19\ \%}$$

$$= 0.0063 \pm 22.3\ \%$$

The quantum yield determination data of the other experiments are listed in TABLE 16 and TABLE 17 below.

TABLE 16: Quantum yield determination data of isophorone deconjugation at various photon doses in benzene (% error in parenthesis)

Light absorbed (E)	16/dodecane (t_0)	17/dodecane (t_{end})	Φ_{dec}
4.077×10^{-5}	8.200 (3.9)	4.960×10^{-3} (2.8)	0.0066 (6.6)[a]
1.671×10^{-4}	8.200 (3.9)	1.217×10^{-2} (3.9)	0.0039 (6.6)[a]
4.093×10^{-5}	5.724 (1.6)	4.347×10^{-3} (2.8)	0.0079 (4.3)[b]
8.531×10^{-5}	5.659 (1.6)	7.087×10^{-3} (2.4)	0.0063 (3.3)[b]
2.513×10^{-4}	5.725 (0.2)	1.529×10^{-2} (2.9)	0.0046 (3.0)[b]
2.991×10^{-4}	5.725 (0.2)	1.732×10^{-2} (3.7)	0.0036 (4.6)[b]
4.904×10^{-4}	5.725 (0.2)	2.609×10^{-2} (1.9)	0.0040 (2.7)[b]

[a] [16] in 3 ml: 4.450×10^{-4} mole [b] [16] in 3 ml: 4.304×10^{-4} mole

TABLE 17: Quantum yield determination data of isophorone deconjugation at various concentrations in benzene (% error in parenthesis)

[16] in 3 ml (mole)	16/dodecane t_0	17/dodecane t_{end}	Φ_{dec}
8.754×10^{-6}	7.306 (1.6)	2.791×10^{-1} (5.6)	0.0042 (5.8)[a]
4.377×10^{-5}	6.891 (2.0)	8.803×10^{-2} (7.8)	0.0035 (8.1)[b]
1.313×10^{-4}	6.814 (0.8)	2.759×10^{-2} (1.6)	0.0033 (1.8)[b]
2.188×10^{-4}	6.911 (0.2)	1.804×10^{-2} (1.9)	0.0036 (2.0)[b]
3.064×10^{-4}	6.903 (1.7)	1.295×10^{-2} (2.6)	0.0036 (3.4)[b]
3.508×10^{-4}	6.773 (0.7)	1.612×10^{-2} (1.4)	0.0053 (1.6)[b]
1.946×10^{-3}	44.60 (0.8)	4.582×10^{-2} (2.7)	0.0126 (3.3)[b]

photon dose: [a] 7.958×10^{-5} E [b] 1.592×10^{-4} E

3.3.2 Photodeconjugation of 16 With Added Acid

a) Determination of Φ_{dec} of 16 (sample experiment)

A 10.00 ml stock solution was prepared by dissolving 1001.1 mg 16 (7.25 mmole) and 116.8 mg dodecane in benzene. A 2.00 ml aliquot of this solution was added to 1.00 ml of a solution of acetic acid in benzene (made by dissolving 5.7 mg acid [0.1 mmole] to 10.00 ml) and 7.00 ml benzene were added to bring the total volume to 10.00 ml. A 3.00 ml aliquot of this solution was then (after freeze-pump-thawing) irradiated in the Quanta-Count for 9×10^6 counts (corresponding to 2.046×10^{-4} E) and analyzed by gc. The value of Φ_{dec} was determined as described above to be 0.0356 ± 4.6 %. All other experiments were carried out in similar fashion varying the amounts of 16 and/or acid (acetic acid and TFA) and solvents.

The data of the other experiments are listed in TABLE 18, TABLE 19 and TABLE 20.

TABLE 18: Quantum yield determination data of isophorone deconjugation at various concentrations of acetic acid in benzene (% error in parenthesis)

[AcOH] (mM)	**16**/dodecane t_0	**17**/dodecane t_{end}	Φ_{dec}
0.10	6.040 (1.1)	4.406×10^{-2} (1.3)	0.0155 (4.8)
0.12	5.760 (0.7)	4.950×10^{-2} (2.8)	0.0182 (3.3)
0.15	5.712 (0.8)	5.530×10^{-1} (0.7)	0.0205 (1.3)
0.25	5.740 (0.4)	6.949×10^{-2} (2.2)	0.0257 (2.4)
0.50	5.705 (1.1)	9.083×10^{-2} (1.3)	0.0338 (1.8)
1.00	5.734 (1.0)	1.069×10^{-1} (2.3)	0.0395 (2.6)
2.00	5.727 (1.0)	1.168×10^{-1} (2.5)	0.0432 (2.9)
4.00	5.664 (0.9)	1.183×10^{-1} (2.0)	0.0443 (2.3)
10.0	5.654 (0.9)	1.107×10^{-1} (0.6)	0.0415 (1.2)
25.0	5.668 (0.5)	1.063×10^{-1} (1.6)	0.0398 (1.8)
50.0	5.638 (3.5)	1.021×10^{-1} (1.0)	0.0384 (3.9)
102.0	6.154 (0.6)	1.016×10^{-2} (0.9)	0.0350 (1.2)

photon dose = 2.046×10^{-4} E, [**16**] in 3 ml: 4.337×10^{-4} mole

TABLE 19: Quantum yield determination data of isophorone deconjugation at various concentrations of TFA in benzene (% error in parenthesis)

[TFA] (mM)	**16**/dodecane t_0	**17**/dodecane t_{end}	Φ_{dec}
0	6.978 (0.8)	1.146×10^{-2} (2.5)	0.0051 (5.4)
0.4	7.017 (0.9)	8.518×10^{-2} (2.0)	0.0374 (2.6)
1.0	6.990 (0.5)	8.428×10^{-2} (0.4)	0.0372 (1.0)
2.0	7.008 (0.6)	8.250×10^{-2} (0.7)	0.0363 (1.4)
4.0	6.944 (1.2)	7.946×10^{-2} (0.7)	0.0353 (1.8)
40.0	6.915 (1.9)	3.738×10^{-2} (0.9)	0.0167 (2.9)

photon dose = 1.364×10^{-4} E, [**16**] in 3 ml: 4.207×10^{-4} mole

TABLE 20: Quantum yield determination data of isophorone deconjugation at various concentrations in benzene (% error in parenthesis)

[16] in 3 ml (mole)	16/dodecane t_0	17/dodecane t_{end}	Φ_{dec}
2.995×10^{-5}	0.398 (1.6)	5.685×10^{-2} (2.4)	0.0376 (2.9)
1.497×10^{-4}	1.992 (1.1)	6.506×10^{-2} (1.6)	0.0430 (2.0)
2.995×10^{-4}	4.030 (0.4)	6.723×10^{-2} (2.9)	0.0439 (3.1)
1.510×10^{-3}	20.73 (2.0)	6.295×10^{-2} (2.0)	0.0403 (4.1)
3.014×10^{-3}	43.20 (2.3)	5.752×10^{-2} (0.9)	0.0353 (5.0)

photon dose = 1.137×10^{-4} E, [AcOH] = 4 mM

Again no evidence for thermal reconjugation of 17 to 16 was found in the usual timeframe of an experiment (< 2 hours) when solutions containing mixtures of 16 and 17 were checked by gas chromatography.

b) Stern-Volmer quenching studies of the photodeconjugation reaction of 16 in the presence of isoprene 50 (sample experiment)

A stock solution (A) of 16 was prepared from 2.4196 g 16 (17.5 mmole), 29.8 mg acetic acid (0.5 mmole) and 358.6 mg dodecane in 25.00 ml in benzene. A stock solution (B) of 50 was prepared from 686.0 mg 50 (10.1 mmole) in 10.00 ml in benzene. A 2.00 ml portion of A and a 1.00 ml portion of B were dissolved to 10.00 ml in benzene and a 3.00 ml aliquot of this solution (containing 4.208×10^{-4} moles 16, 1.192×10^{-5} moles acetic acid and 3.026×10^{-4} moles 50) was irradiated in the Quantacount for 6×10^6 counts (corresponding to 1.364×10^{-4} E). The value of Φ_{dec} was determined as described in 3.3.1 e) to be 0.0064 ± 10 %. Other quantum yields at different concentrations of 50 were determined in an analogous way by irradiating solutions containing different proportions of A and B as shown in TABLE 21.

TABLE 21: Quantum yield determination data of isophorone deconjugation at various concentrations of isoprene in benzene (% error in parenthesis)

[50] (mM)	16/dodecane t_0	17/dodecane t_{end}	Φ_{dec}
0	5.672 (0.4)	8.951×10^{-2} (2.6)	0.0487 (2.9)
8.1	5.701 (2.4)	5.365×10^{-2} (1.2)	0.0290 (3.1)
10	5.580 (1.3)	4.744×10^{-2} (1.4)	0.0262 (2.3)
20	5.694 (1.4)	3.562×10^{-2} (2.3)	0.0193 (3.3)
50	5.626 (1.2)	1.911×10^{-2} (1.2)	0.0105 (3.3)
81	5.648 (0.7)	1.316×10^{-2} (1.9)	0.0072 (3.7)
101	5.632 (1.0)	1.161×10^{-2} (6.1)	0.0064 (10)

photon dose = 1.364×10^{-4} E, [16] in 3 ml: 4.208×10^{-4} mole, [AcOH] = 4 mM

c) Preparation of acetic acid-d_1

Acetic anhydride was purified by distillation with toluene to remove acetic acid impurities as azeotrope.[24c] To a solution of 5.1 g acetic anhydride (50 mmole) in 1.0 g D_2O (50 mmole) was added one drop of a dilute solution of H_2SO_4 in D_2O. The reaction mixture was stirred at rt for two hours, then refluxed for one hour until gc analysis showed total disappearance of anhydride. ^{1}H-Nmr analysis (60 MHz, $CDCl_3$) showed, by integrating the peaks for the methyl group and the acidic proton, that the product was ≈95 % deuterated.

d) Deuterium incorporation studies with AcOD and MeOH/MeOD

Three stock solutions (A - C) were prepared. Solution A: 964.8 mg 16 (7 mmole) and five drops dodecane dissolved to 5.00 ml in dried benzene, solution B: 11.9 mg AcOH (0.2 mmole) dissolved to 5.00 ml in dried benzene, solution C: 12.6 mg AcOD (0.2 mmole) dissolved to 5.00 ml in dried benzene. Four solutions (I - IV) each of total volume to 10 ml in dry benzene were prepared. Solution I: 1 ml

A, 1 ml **B** and 1 ml MeOH (this solution served as a reference), solution **II**: 1 ml **A**, 1 ml **B** and 1 ml MeOH-d_4, solution **III**: 1 ml **A**, 1 ml **C** and 1 ml MeOH, solution **IV**: 1 ml **A**, 1 ml **C** and 1 ml MeOH-d_4. The irradiation of these solutions was followed by gc and gc/ms to give after 22 hours the results shown in TABLE 22 (determined as described in **3.3.1 c)**).

TABLE 22: Deuterium incorporation studies of the photodeconjugation of isophorone

Solution	Deuterium in **16**	Deuterium in **17**
I (reference)	0 %	0 %
II	13 %	85 %
III	0.2 %	0 %
IV	12 %	86 %

^{2}H-Nmr (92 MHz, C_6H_6) studies of the deconjugation of **16** (20.5 mg **16**, 0.2 mg AcOH and 100 μl MeOH-d_4) showed that the resonances of interest (2-position and exocyclic methylene position) were obstructed by the peaks derived from the CD_3- and OD-groups in MeOH-d_4.

3.3.3 Photoaddition of Alcohols to 16

a) Addition of methanol

A solution of 4.87 g **16** (35 mmole), 57.8 mg acetic acid (1 mmole) and 25 ml MeOH in 250 ml benzene containing a standard (2-methylnonane) was irradiated and the reaction progress followed by gc. After 28 hours 65 % conversion of **16** was observed (17 % to **17** and 6 % to a new product [**64**] with a longer retention time than **16**, the rest to higher molecular weight products). The solvent was removed to give 6.35 g of a slightly yellow liquid with a ratio **17**:**16**:**64** of ≈ 3:6:1. A 3.5 g portion of the mixture was separated by column chromatography (silica gel, hexanes/diethyl

ether 3:2) to give three fractions I-III (least polar to most polar). Fraction I (1.15 g) contained **17** and **16** in a 1:8 ratio, fraction II (2.11 g) contained **16** and **64** in a 6:1 ratio and fraction III **16** and **64** in a 1:13 ratio, but was only obtained in very small amounts (0.09 g). No spectroscopic data of **64** could be obtained from fraction III so fraction II was further separated by preparative gc to give 3-methoxy-3,5,5-trimethylcyclohexanone **64** and **16** in a 15:1 ratio. ^{1}H-nmr (200 MHz, C_6D_6): 1.02 (s, 3 H), 1.05 (s, 3 H), 1.21 (s, 3 H), 1.52 (d, 14.7 Hz, 1 H), 1.93 (dm, 14.7 Hz, 1 H), 2.17 (bs, 2 H), 2.25 (d, 13.9 Hz, 1 H), 2.54 (dm, 13.9 Hz, 1 H), 3.11 (s, 3 H); ms (EI): 170 (M^+, 9), 155 (22), 114 (40), 113 (100)

b) Addition of octanol

A benzene solution (10 ml) of 194.1 mg **16** (1.4 mmole), 2.4 mg acetic acid (40 μmole) and 1 ml *n*-octanol was irradiated and monitored by gc. After 19 hours small amounts (< 5 %) of a new product at longer retention time than **16** were observed. ms (EI): 268 (14), 253 (18), 213 (22), 101 (82), 97 (100). No further investigations were conducted.

3.3.4 Photoaddition of Acids to 16

a) Addition of acetic acid

A solution of 190.0 mg **16** (1.38 mmole), 10 μl dodecane and 25 μl acetic acid diluted to 10 ml in benzene was prepared. A 1.00 ml aliquot of this solution was deoxygenated (N_2 purging) and irradiated; reaction progress was followed by gc. After 15 hours 76 % conversion of **16** was recorded (25 % to **17**, 10 % to three dimers [4:5:1] and 9 % to a new product with a retention time between **16** and its dimers, the rest of **16** was converted to higher molecular weight products). The mixture was analyzed by gc/ms. Both EI (lowered to 25 eV) and CI resulted in a mass of 138 for the new peak. ms (EI): 138 (54), 82 (100); ms (CI): 139 (100), 138 (25), 82 (37)

b) Addition of propionic acid

A solution of 950.1 mg **16** (6.9 mmole) and 10 ml propionic acid in 250 ml benzene (containing 2-methylnonane as standard) was irradiated and the progress was followed by gc. After 15 hours 75 % conversion of **16** was observed (43 % to **17**, 13 % to a new peak **66** with a retention time between **16** and its dimers but higher than **65** and ≈ 2 % to dimers). A further sample of **16** (602.5 mg, 4.4 mmole) was added and the reaction continued. After 26 hours conversion of **16** to **17** was 65 % (21 % to **66** and 5 % to dimers). Gc/ms analysis for the new peak gave a mass of 138, but additionally a fragment with a mass of 74 was observed. The solution was then stored at 5°C for two weeks. Conversion to **17** had dropped to 15 %, while **66** remained at 21 % and dimers were also constant at 5 %. The irradiation was resumed and after 32 hours conversion of **16** to **17** was 48 %, to **66** 44 % and to dimers 12 %. Solvent removal in vacuo at 35°C gave 11.48 g of a yellow liquid. The product mixture was subjected to a series of solvent evaporations, starting at 30°C/25 torr through 35°C/6 torr, 32°C/0.9 torr, 25°C/0.2 torr to 60°C/0.1 torr to give 0.92 g of an orange liquid residue. It was distilled in a Kugelrohr apparatus at 120°C/0.6 torr to give 0.49 g of a slightly yellow distillate containing **17**, **16**, **66** and dimers in a ratio of ≈ 1:23:18:1. A sample (80.4 mg) of the mixture was separated by preparative tlc (Et_2O/hexanes 1:1) to give five fractions, the main one (75 mg, intermediate polarity) contained **16** and **66** in a ratio of ≈ 4:3. ^{1}H-nmr (200 MHz, $CDCl_3$) showed only signals for **16** and propionic acid (1.09 [t, 7.55 Hz, 3 H], 2.29 [q, 7.55 Hz, 2 H], 9.9 [bs, 1 H]) in a ratio of ≈ 5:2, indicating decomposition of the mixture within a few hours. Gc analysis of the nmr solution showed only **16** present, and no **66** was detectable. A 103.5 mg sample of the distillate was separated by preparative tlc (Et_2O/hexanes 1:1) to give as the main fraction (64.7 mg, intermediate polarity) a ≈ 1.5:1 mixture of

16 and 3,5,5-trimethylcyclohexanone-3-propionate 66. ^{1}H-nmr (200 MHz, C_6D_6): 0.73 (s, 3 H), 0.75 (s, 3 H), 0.91 (t, 7.5 Hz, 3 H), 1.07-1.18 (m, 2 H), 1.41 (s, 3 H), 1.73-1.84 (m, 2 H), 1.93 (q, 7.5 Hz, 2 H), 2.45 (dt, 15.0, 2.3 Hz, 1 H), 2.86 (dt, 14.1, 2.3 Hz, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): 9.0 (CH_3). 26.9 (CH_3), 27.0 (CH_3), 28.7 (CH_2), 32.8 (CH_3), 34.8 (C), 45.9 (CH_2), 51.6 (CH_2), 53.8 (CH_2), 84.1 (C-O), 173.5 (C=O), 207.1 (C=O); ms (EI): 138 (26), 82 (100), 74 (11); ms (CI): 139 (100), 82 (63), 75 (11); ir (film): 1734, 1721 cm^{-1}

After nmr spectroscopy of the mixture one drop of TFA was added; the reaction was stored at rt and followed by gc. After 142 hours the initial ratio 16:66 of 1.55:1 had changed to 17.5:1, after 237 hours it was 75.5:1. Nmr analysis revealed an increase of 16, disappearance of 66 and formation of propionic acid: ^{1}H-nmr (200 MHz, C_6D_6): 0.86 (t, 7.58 Hz, 3 H), 1.98 (q, 7.58 Hz, 2 H), 12.45 (bs, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): 8.59 (CH_3), 27.35 (CH_2), 182.08 (C=O)

3.3.5 Photodeconjugation of 16 vs Photocycloaddition of 16 and Cyclopentene 67

Mixtures of 16 (140 mM) and 67 (1 M) without and with acetic acid (4 mM) in benzene were irradiated and followed by gc. Cycloadducts 68 were identified by gc/ms and had a longer retention time than 16. A typical ms showed (CI): 207 ($M^+ + 1$, 12), 139 (100), 82 (36). After three hours gc/ms showed almost complete conversion of 16 (> 96 % vs dodecane) in both cases; the ratio of 17:68 was 1:72 without and 1:19 with acid, respectively. Three adducts were observed with a relative ratio of 1:20:16, and this was constant in both irradiations. For a quantum yield determination a solution of 94.4 mg 16 (0.68 mmole), 341.1 mg 67 (5.02 mmole) and 1.2 mg acetic acid (20 μmole) diluted to 5.00 ml in benzene (containing dodecane as internal standard) was prepared and a 3.00 ml aliquot irradiated in the Quantacount for 8×10^6 counts corresponding to 1.819×10^{-4} E. Calculations described in **3.3.1 e)**

(16/dodecane at t_0: 5.302 ± 0.7 %, 17/dodecane at t_{end}: 5.114 x 10^{-2} ± 5.4 %, 68/dodecane at t_{end}: 9.919 x 10^{-1} ± 3.2 %, [16] in 3 ml: 4.104 x 10^{-4} mole, photon dose = 1.891 x 10^{-4} E) resulted in Φ_{dec} = 0.0218 ± 11 % and $\Phi_{cycloaddition}$ (sum of all three adducts) = 0.3911 ± 3.3 %.

3.4 Irradiation of 3-Methyl-2-cyclohexenone 18

a) Identification of the deconjugated isomer of 18

Irradiation of 2.5 ml benzene solutions containing 18 (39.3 mg, 0.36 mmole) and undecane as standard with and without acetic acid (≈ 2 mM) were carried out and followed by gc. After six hours the following conversions of 18 to a new product 24 (shorter retention time than 18) were observed: 22 % without and 41 % with acid. Total conversion of 18 was 51 % and 69 %, respectively; the missing fraction probably arose from conversion to higher molecular weight products. An irradiation of 18 in C_6D_6 led after 21 hours to a mixture of 18 and 3-methylenecyclohexanone 24 in a ≈ 1.9:1 ratio. ^{1}H-nmr (200 MHz, C_6D_6): 1.5-2.2 (m, 6 H), 2.79 (m, 2 H), 4.49 (m, 1 H), 4.55 (m, 1 H); ms (EI): 110 (M^+, 41), 81 (100)

b) Photoaddition of acids

b.I) Addition of acetic acid

A 1.00 ml sample of a solution of 80 mg 18 and 25 µl acetic acid in 5 ml benzene (undecane as standard, 144 mM in 18 and 81 mM in acid) was irradiated and monitored by gc. After 15 hours 76 % of 18 was converted as follows: 15 % to 24, 15 % to dimers (three in a ≈3:22:1 ratio, identified by gc/ms, typical ms [EI]: 220 [M^+, 4], 177 [6], 111 [82], 110 [74], 82 [100]) and 17 % to a product with a retention time higher than 18, shorter than its dimers and shorter than the corresponding peak in a similar irradiation with 16. Gc/ms (EI, EI at 25 eV and CI) gave

for this peak a mass of 110 with the same fragmentation pattern as **18**; no further investigations were carried out.

b.II) Addition of propionic acid

A 1.00 ml sample of a solution of 80 mg **18** and 30 µl propionic acid in 5 ml benzene (undecane as standard, 144 mM in **18**, 81 mM in acid) was irradiated and monitored by gc. After 15 hours 67 % conversion of **18** were observed: 17 % to **24**, 17 % to dimers and 13 % to a new product **91** with a retention time higher than **18**, lower than its dimers, higher than the observed product with acetic acid and lower than **66**. Gc/ms (EI and CI) for this product gave a mass of 110 with a similar fragmentation pattern to **18**, the only difference was a fragment with a mass of 74 (75 by CI) not present in **18** corresponding to the mass of propionic acid.

3.5 Irradiation of 3-Ethyl-5,5-dimethyl-2-cyclohexenone 69

A solution of 236 mg **69** (1.55 mmole) and 6 mg acetic acid (0.1 mmole) in 10 ml benzene was irradiated for 56 hours (94 % conversion of **69** by gc). Three products **92** - **94** were observed (lower retention time than **69**, low→high retention time) in a ratio **92**:**93**:**94** of ≈ 1:2:3 (after 16 h) changing to ≈ 1:1:1 (after 56 h). After solvent removal the mixture was separated by preparative gc.

Fraction I contained 3-methylene-2,5,5-trimethyl-2-cyclohexanone **92**: ^{1}H-nmr (200 MHz, $CDCl_3$): 0.80 (s, 3 H), 1.03 (s, 3 H), 1.18 (d, 6.7 Hz, 3 H), 2.1-2.4 (m, 4 H), 2.98 (q, 6.7 Hz, 1 H), 4.78 (m, 2 H); ms (EI): 152 (M^+, 78), 96 (44), 83 (90), 68 (100). Fraction II contained two *E*/*Z*-isomeric 3-ethylidene-5,5-dimethyl-2-cyclohexanones **93** and **94** in a 2:1 ratio: ^{1}H-nmr (200 MHz, $CDCl_3$) for **93**: 0.90 (s, 6 H), 1.58 (m, 3 H), 2.22 (bs, 4 H), 3.01 (bs, 2 H), 5.2-5.4 (m, 1 H); for **94**: 0.93 (s, 6 H), 1.55 (m, 3 H), 2.18 (m, 4 H), 2.94 (m, 2 H), 5.2-5.4 (m, 1 H); ms (EI) for **93**: 152 (M^+, 84), 96 (50), 83 (81), 68 (100); for **94**: 152 (M^+, 80), 96 (50), 83 (82), 68

(100). NOE difference spectroscopy led, by irradiation at ≈ 1.5 ppm, to an increase of the signal at 3.01 ppm relative to the one at 2.94 ppm. Whence **93** was the *Z*-, **94** the *E*-isomer. Fraction III contained a mixture of **94** and 2,3,5,5-tetramethyl-2-cyclohexenone **95**: ^{1}H-nmr (200 MHz, $CDCl_3$): 0.97 (s, 6 H), 1.74 (m, 3 H), 1.87 (m, 3 H), 2.21 (m, 4 H)

3.6 Irradiation of 3-Isopropyl-5,5-dimethyl-2-cyclohexenone 70

Solutions of 118 mg **70** (0.71 mmole) in 5 ml benzene without and with 1.2 mg acetic acid (0.02 mmole) were irradiated for 78 hours. By gc and gc/ms no deconjugation products could be detected in either solution and the ratio of **70** to standard (tridecane) became smaller only very slowly indicating some depletion of **70**, probably to higher molecular weight polymers and/or dimers.

3.7 Irradiation of 3-Isopropyl-2-cyclohexenone 21

Solutions of 103 mg **21** (0.75 mmole) in 5 ml benzene with and without 2.5 μl acetic acid were irradiated for 6 hours. The conversions of **21** were 15 % without and 22 % with acid, respectively. Small product peaks in the expected retention time range in the gc accounted (total) for only 2 and 10 % of the total area, respectively. Long analysis runs revealed presence of at least three products at very high retention times with masses by gc/ms of 276, attributed to dimers. Gc/ms analysis also showed product peaks at shorter retention time than **21** having a mass of 138 (isomers of **21**) but conversion to these products was less than 1 %. No further investigations were carried out.

3.8 Irradiation of *R*-10-Methyl-$\Delta^{1,9}$-2-octalone 27a

a) Identification of the deconjugated isomer 32a

Nitrogen purged benzene-d_6 solutions (0.5 ml) of **27a** (not purified, 8.1 mg, 50 μmole) with and without added acetic acid (≈ 5 mM) were irradiated and the

progress followed by gc and ^{1}H-nmr. After 10 hours 27 % conversion to *R*-10-methyl-$\Delta^{8,9}$-2-octalone **32a** was observed. ^{1}H-nmr (200 MHz, C_6D_6) for **27a**: 0.74 (s, 3 H), 0.80-1.06 (m, 2 H), 1.08-1.56 (m, 6 H), 1.82-1.96 (m, 2 H), 2.19-2.24 (m, 2 H), 5.76 (s, 1 H); for **32a**: 0.84 (s, 3 H), 0.90-1.50 (m, 6 H), 1.68-1.73 (m, 2 H), 2.10 (m, 2 H), 2.82 (m, 2 H), 5.09 (m, 1 H); ms (EI) for **27a**: 164 (M^+, 76), 136 (66), 122 (100), 121 (60), 107 (68), 93 (36), 79 (52); for **32a**: 164 (M^+, 54), 109 (100), 93 (54), 79 (40)

b) Determination of Φ_{dec} for **27a** (sample experiment)

A 2.00 ml sample of a solution of 410 mg base washed **27a** (2.5 mmole) and tetradecane to 10 ml in benzene was diluted to 5.00 ml; a 3.00 ml aliquot of this solution was degassed (freeze-pump-thaw) and irradiated in the Quantacount for 1.2×10^7 counts corresponding to 2.728×10^{-4} E. Using standard procedures described in **3.3.1 e)** the value of Φ_{dec} of **27a** was calculated to be 0.0031 ± 20 %. Φ_{dec} values in the presence of acetic acid were calculated similarly as shown in TABLE 23.

TABLE 23: Quantum yield determination data of the deconjugation of **27a** at various concentrations of acetic acid in benzene (% error in parenthesis)

[AcOH] (mM)	**27a**/tetradecane t_0	**32a**/tetradecane t_{end}	Φ_{dec}
0	6.198 (0.4)	1.733×10^{-2} (14)	0.0031 (20)
0.1	6.212 (0.6)	3.300×10^{-2} (3.0)	0.0058 (8.7)
0.5	6.196 (1.0)	7.481×10^{-2} (4.7)	0.0133 (20)
5.1	6.202 (0.7)	1.038×10^{-1} (3.4)	0.0184 (4.5)

photon dose = 1.364×10^{-4} E, [**27a**] in 3 ml: 3.000×10^{-4} mole

PART II

BIRADICALS IN 2 + 2 PHOTOCYCLOADDITION

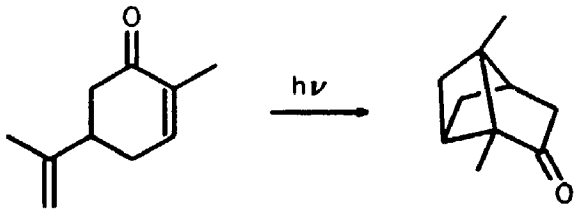
REACTIONS OF 2-CYCLOPENTENONE

CHAPTER 1

INTRODUCTION

1.1 Introduction

The 2+2 photochemical cycloaddition of an alkene to an α,β-unsaturated ketone (enone) has been the subject of many reports over the last 30 years and recently has enjoyed a revival of interest.[1,2] The reaction itself, however, has been known for over 80 years. As early as 1908 examples began to appear in the chemical literature when Ciamician and Silber published their work on the photochemical "rearrangement" of carvone **100**.[54] They noted that **100** was converted to carvone-camphor **101** upon exposure to light as shown in SCHEME 48.

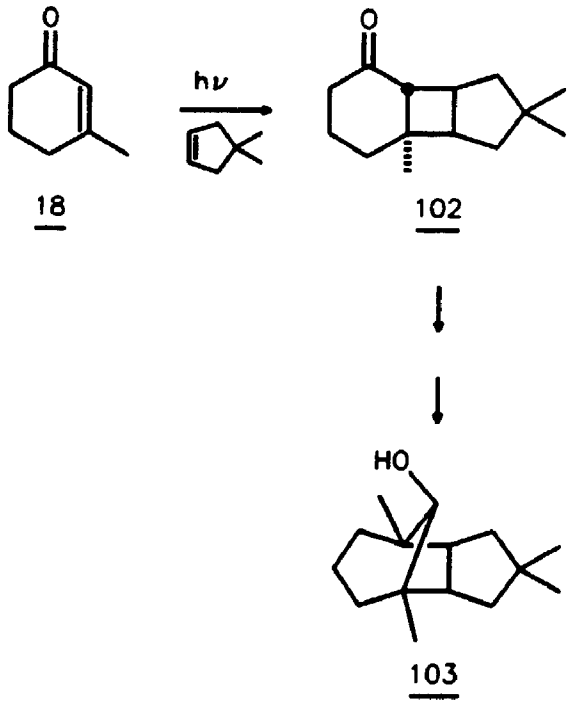


100 **101**

SCHEME 48

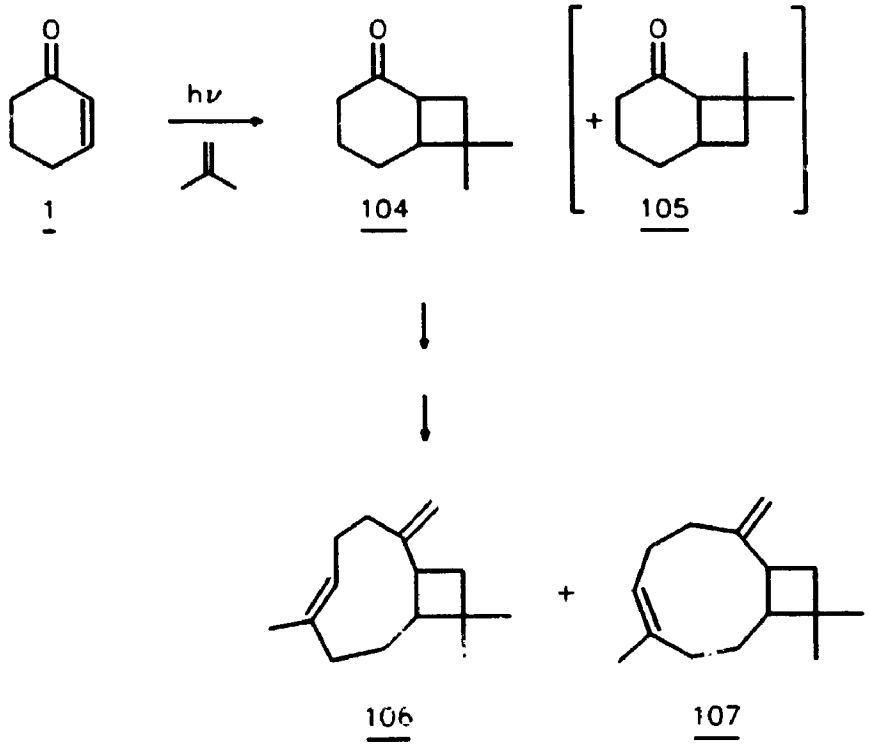
This first example of an intramolecular 2 + 2 photocycloaddition went by largely unnoticed and the reaction did not receive much attention until the 1960's. It was then that the groups of de Mayo, Corey and Eaton among others examined the synthetic potential and the mechanistic details of the 2+2 cycloaddition.

In 1964 Corey and Nozoe illustrated the versatility of the reaction when they reported the total synthesis of α-caryophyllene alcohol **103**.[55] The initial step in the sequence was the 2 + 2 photocycloaddition of 4,4-dimethylcyclopentene to 3-methyl-2-cyclohexenone **18** to give predominantly the adduct **102** which was then converted to **103** as outlined in SCHEME 49.



SCHEME 49

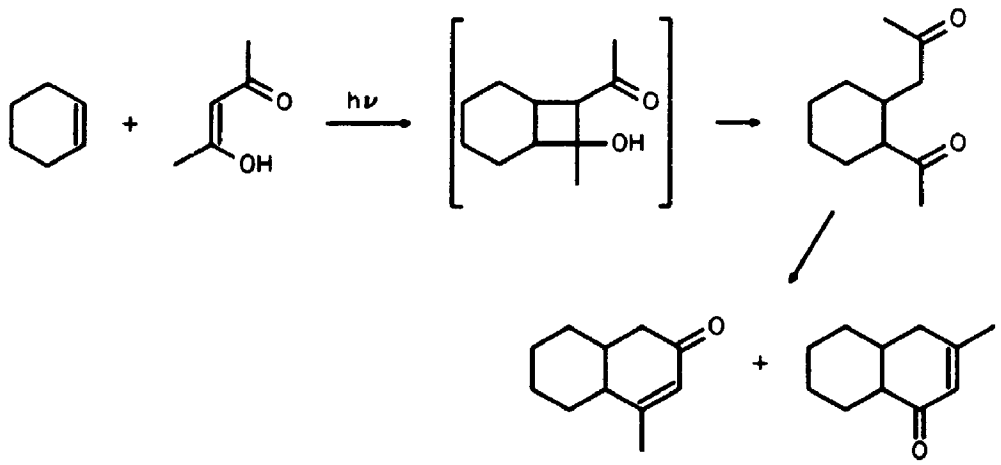
The same year Corey et al. published the more complex total syntheses of *d,l*-caryophyllene **106** and *d,l*-isocaryophyllene **107**.[56] The initial step in both cases was the 2 + 2 photocycloaddition of isobutene to 2-cyclohexenone **1** to give the adduct **104** as the major product, which was then converted to **106** and **107** as illustrated in SCHEME 50.



SCHEME 50

In their paper the authors noted the apparent regiochemical preference of the addition; the other regioisomer **105** was formed in only minor amounts. The reason for this preference can be found in the mechanism of the cycloaddition reaction and will be discussed extensively below.

In 1962 de Mayo reported the first example of a new annelation process.[57] Addition of an alkene to an enolized 1,3-diketone afforded initially the 2+2 cycloadduct which spontaneously underwent a retro-aldol reaction to give a 1,5-diketone. The latter could be cyclized by acid or base catalysis to generate enones, as illustrated in SCHEME 51 for the reaction of cyclohexene with acetylacetone.

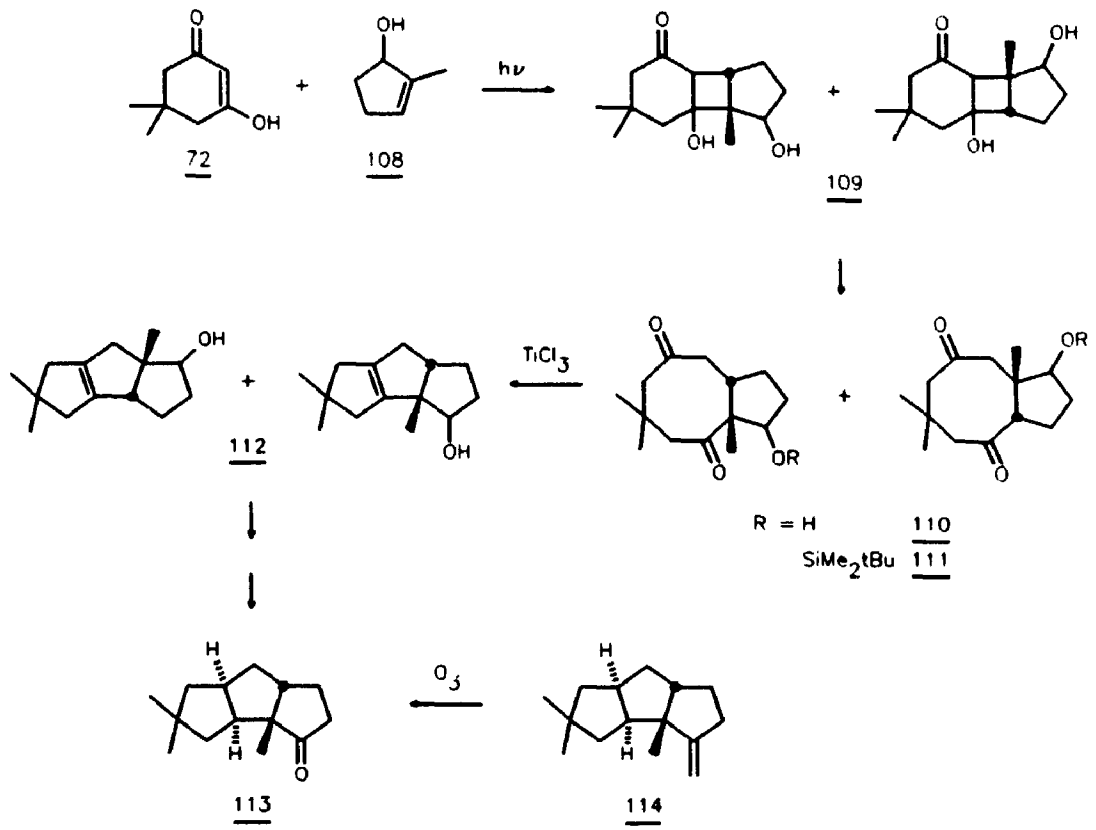


SCHEME 51

The sequence of reactions initiated by the photoaddition of an olefin to an enolized 1,3-diketone has become known as the de Mayo reaction and has proven to be of great synthetic use.

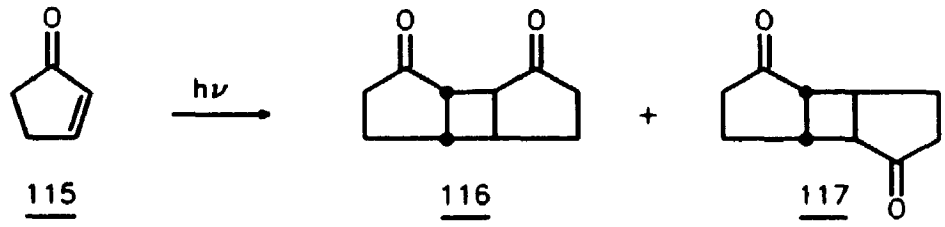
In a recent example of the de Mayo reaction Disanayaka and Weedon reported the formal synthesis of hirsutene **114**, a physiologically active fungal metabolite, which is shown in SCHEME 52.[58] Addition of 2-methyl-2-cyclopentenol **108** to dimedone **72** gave the short-lived 2+2 cycloadducts **109** which spontaneously ring opened to the cyclooctanediones **110**, which proved to be unstable and were thus silylated in situ to yield **111**. Treatment of the mixture with a low valence titanium reagent effected cyclization to **112**; functional group interconversion and separation gave the norketone **113**, a product of ozonolysis of **114**.

In 1962 Eaton published reports on the photochemical dimerization of cyclopentenone **115**.[59] This special case of the 2+2 photocycloaddition involved the addition of an enone serving as an olefin to another enone molecule leading to the formation of the two dimers **116** and **117** as shown in SCHEME 53.



72 108 109 112 110 111 113 114

SCHEME 52



115 116 117

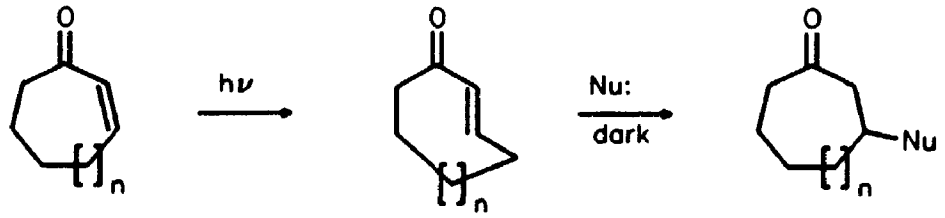
SCHEME 53

1.2 Mechanistic Aspects of the 2+2 Photocycloaddition

When the researchers of the 1960's began to realize the synthetic potential of the enone 2+2 cycloaddition reaction efforts were undertaken to understand the

mechanism by which the reaction proceeded. As de Mayo pointed out in a review in 1971 it was by then well established that the reactive species was a triplet excited enone.[60] In all cases that were discussed the enone was a cyclic one; acyclic enones, because of their inherent flexibility, decay rapidly and efficiently to the ground state from both the singlet and triplet excited state by *cis-trans* isomerization, consequently no cycloaddition reaction occurs because the excited states are not long-lived enough.[2] Enolized acyclic 1,3-diketones can undergo photocycloaddition reaction because intramolecular hydrogen bonding slows the *E/Z*-isomerism.

Larger ring enones such as cycloheptenone **52** and cyclooctenone **51** generally do not undergo photocycloaddition reactions; the flexibility of these rings is great enough to allow them to isomerize to the *trans*-enone. This species is highly reactive and undergoes dark reactions such as addition of nucleophiles (SCHEME 54) as discussed in Part I of this thesis.[29,61]

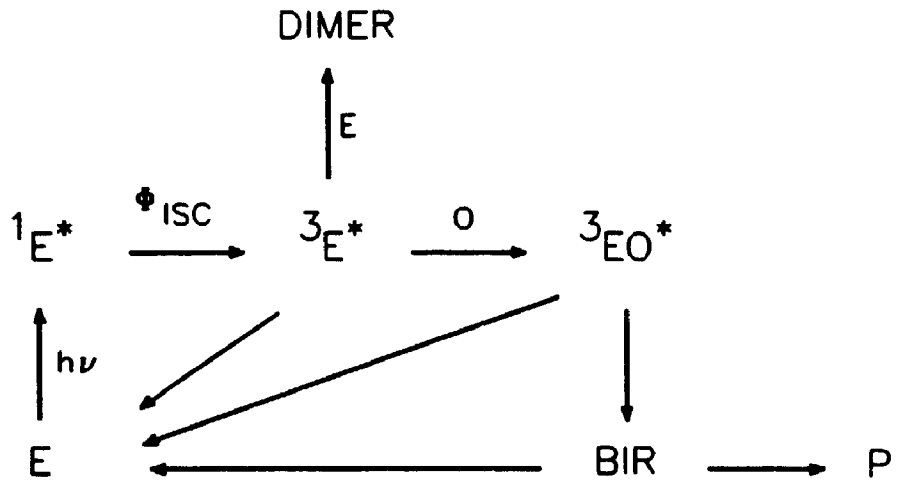


n = 1 **52**
2 **51**

SCHEME 54

In 1964 Corey and co-workers reported an extensive study of the photoreactions of 2-cyclohexenones with various alkenes.[62] During the later 1960's de Mayo's group conducted studies of the reaction mechanism.[63] The work of these

two groups led to the formulation of a proposed mechanism for the photocycloaddition reaction which is shown in SCHEME 55.



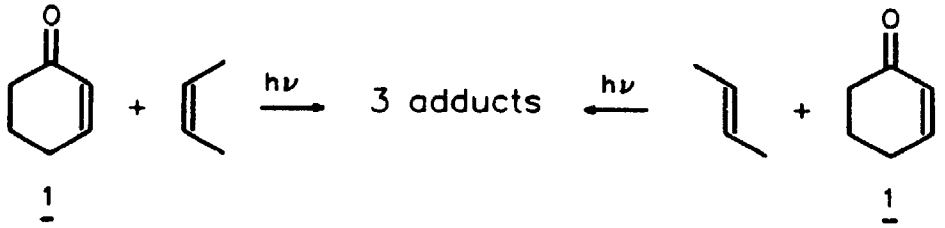
SCHEME 55

In the mechanism illustrated in SCHEME 55 irradiation of an enone E leads to the singlet excited state $^1E^*$ which undergoes intersystem crossing with high efficiency to its triplet excited state $^3E^*$. The triplet excited state reacts with a ground state olefin O to give a so-called "oriented π-complex" or exciplex (from excited complex) $^3EO^*$. In competition with decay to the ground state the exciplex can react to give a triplet biradical intermediate BIR which in turn can partition between cycloaddition product(s) P and the ground state starting materials.

1.2.1 The Triplet 1,4-Biradical Intermediate

There is a substantial body of evidence for the existence of triplet 1,4-biradical intermediates in 2 + 2 photocycloaddition reactions of enones. One of the first pieces

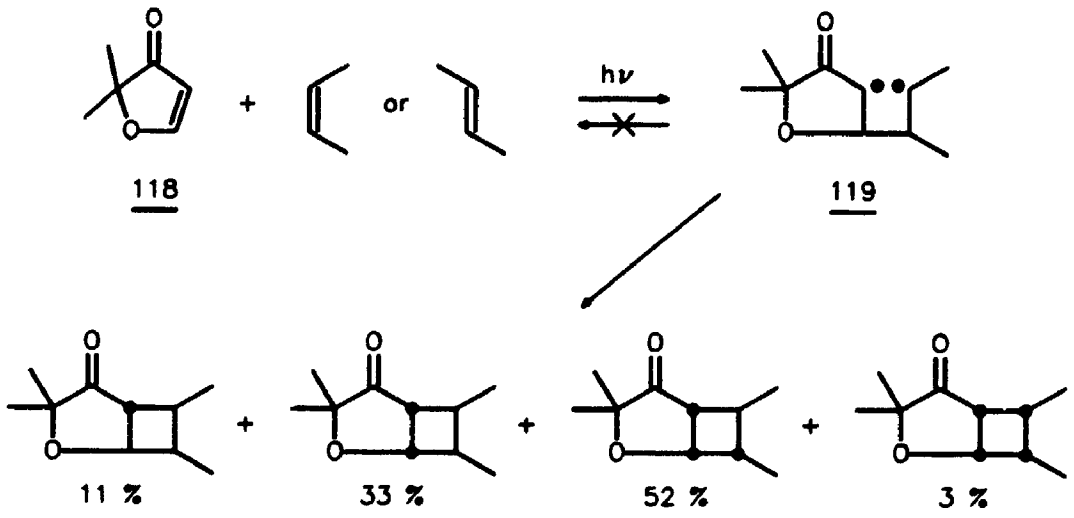
of evidence was obtained by Corey who showed that irradiation of cyclohexenone **1** with either *cis*- or *trans*-2-butene gave a similar uncharacterized mixture of three cycloadducts as shown in SCHEME 56.[62]



1 **1**

SCHEME 56

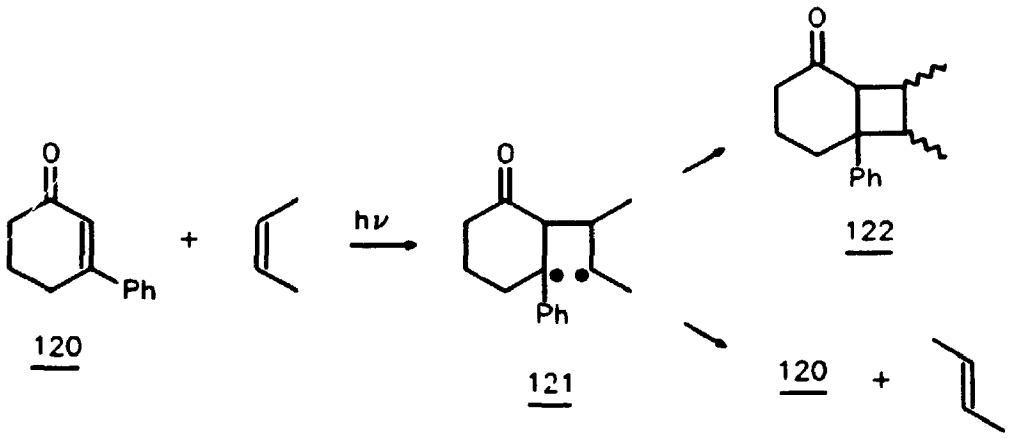
A similar report was published in 1973 by Margaretha who observed similar product mixtures from the irradiation of 4-oxa-5,5-dimethyl-2-cyclopentenone **118** with *cis*- or *trans*-2-butene as shown in SCHEME 57.[64] He suggested that formation of the intermediate biradical **119** allowed for bond rotation and loss of memory of the alkene stereochemistry.



118 **119**

SCHEME 57

Neither Corey nor Margaretha were able to observe isomerized olefin in the reaction mixture; Margaretha explained this by proposing that the biradical largely prefers to ring close rather than to cleave to regenerate ground state enone and isomerized olefin. Olefin isomerization was, however, reported in 1975 by McCullough et al. who examined the photochemistry of 3-phenyl-2-cyclohexenone **120** in the presence of *cis*-2-butene.[65] Besides cycloadducts **122** they observed a large amount of *trans*-2-butene derived from cleavage of the biradical **121** as illustrated in SCHEME 58.

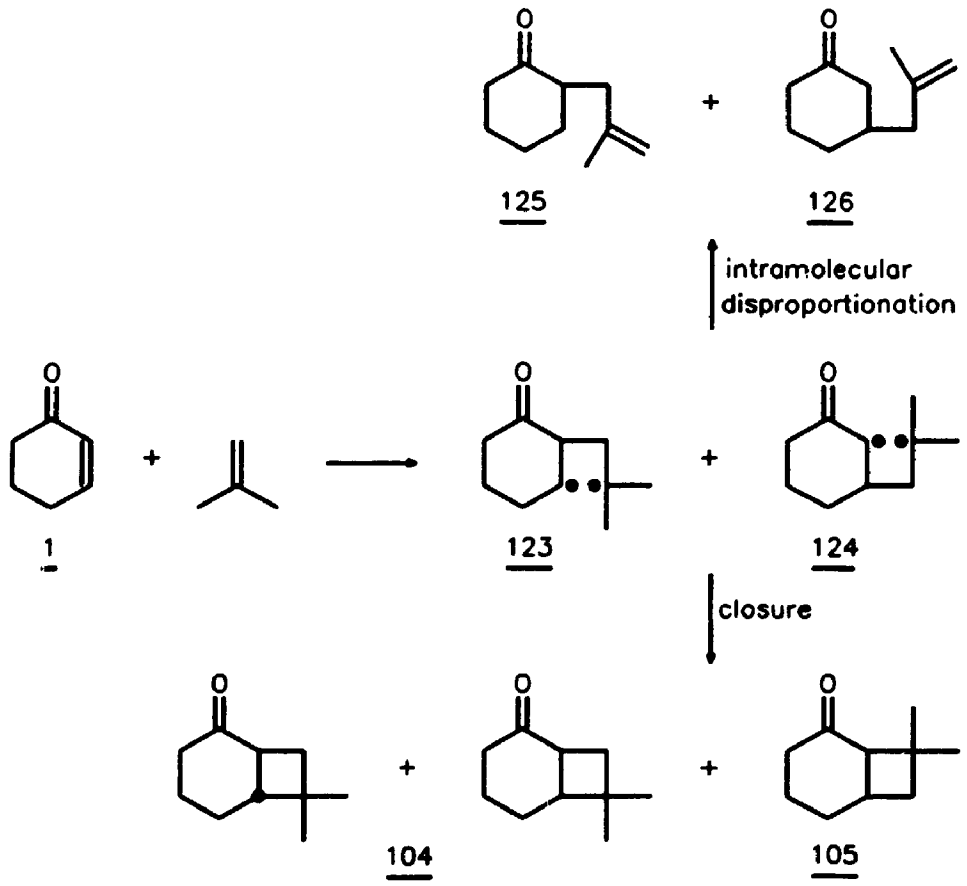


SCHEME 58

Photochemical isomerization of an olefin by biradical formation rather than decay of the olefin excited state is called Schenck isomerization.[66]

Further evidence for the intermediacy of biradicals was provided by Corey and coworkers. They found that irradiation of cyclohexenone **1** in the presence of isobutene gave five identifiable products.[62] The predominant products were 2+2 cycloadducts **104** and **154**. However, the 2- and 3-substituted β-methylallyl cyclohexanones **125** and **126** were also formed. These were presumed to be derived

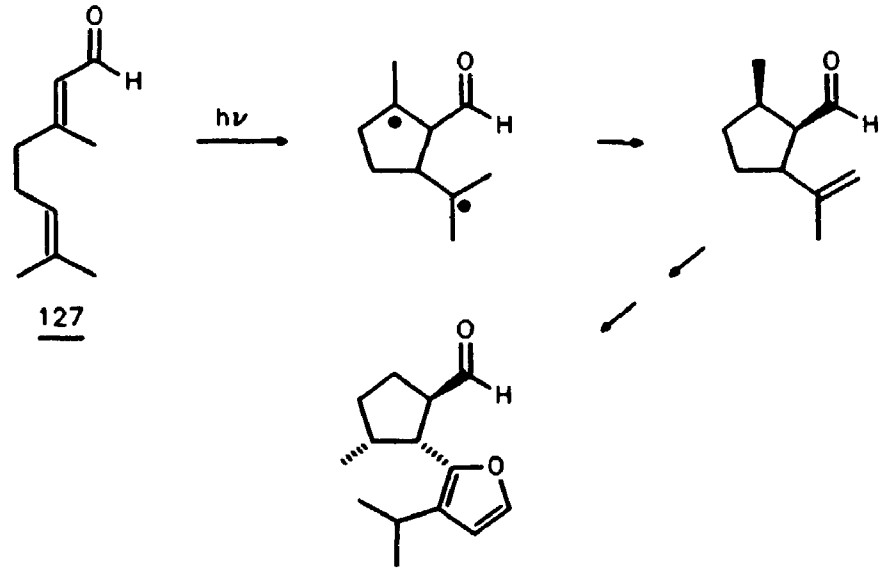
from the intermediate biradicals **123** and **124** by intramolecular disproportionation as shown in SCHEME 59.



SCHEME 59

A similar observation has been made by Cookson et al. in the intramolecular cycloaddition of **127**.[67] In this case the dominant reaction of the biradical was intramolecular abstraction, a fact which was utilized in the synthesis of furopelargone A **128** as shown in SCHEME 60.[68]

This is a rare example of an acyclic enone excited state undergoing a reaction in competition with relaxation by *E*/*Z*-isomerization. Presumably the close proximity of the alkene is responsible; intermolecular examples of this are essentially unknown.



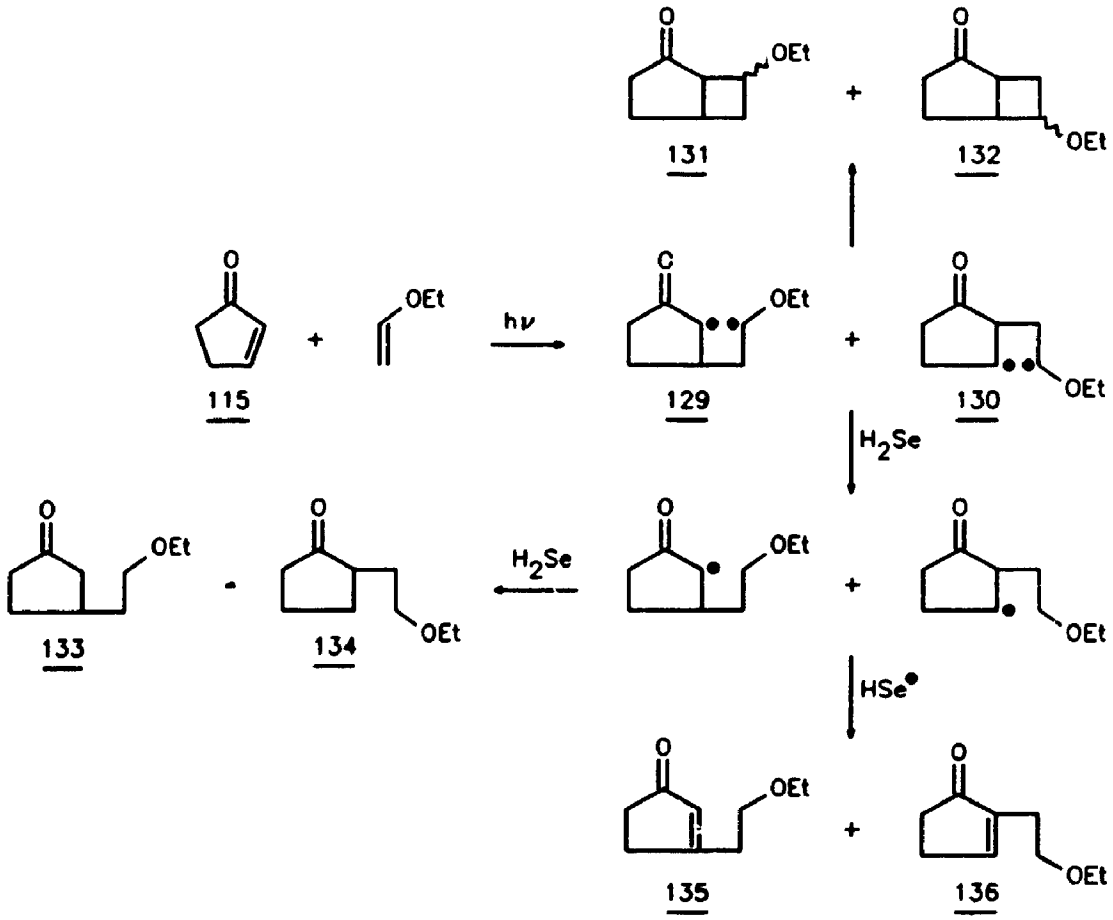
127

128

SCHEME 60

Recently the presence of triplet 1,4-biradicals in the 2 + 2 photocycloaddition reaction has been demonstrated very elegantly by Hastings and Weedon.[69] They were able to trap the biradicals which are intermediates in the photoaddition of 2-cyclopentenone **115** and ethyl vinyl ether as illustrated in SCHEME 61. Addition of hydrogen selenide to a mixture of these compounds quenched cycloadduct formation (i.e. stereoisomers of **131** and **132**) completely; instead four new products (**133** - **136**) were observed stemming from reaction of hydrogen selenide with the intermediate biradicals **129** and **130**.

The two cyclopentanone derivatives **133** and **134** are direct hydrogen abstraction products whereas the cyclopentenone compounds **135** and **136** are derived from disproportionation of the partially trapped biradicals with hydrogen selenyl radical.



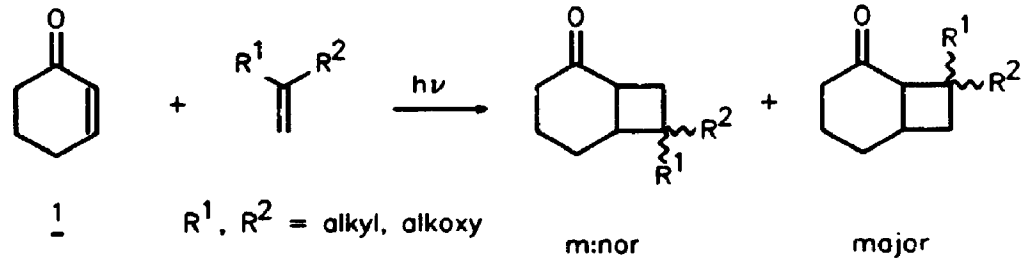
SCHEME 61

Similar results were obtained by trapping the biradicals in the reaction of **115** with cyclopentene **67**.[69]

1.2.2 The Exciplex

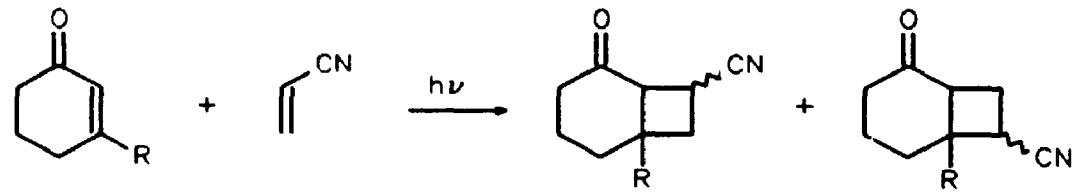
In his initial study of the enone photocycloaddition reaction Corey observed, for most alkenes, a distinct preference in the regiochemistry of the 2 + 2 cycloadducts.[62] Irradiation of cyclohexenone 1 with a variety of olefins bearing electron donating substituents such as isobutene ($R^1 = R^2 = Me$), 1,1-dimethoxy-ethylene ($R^1 = R^2 = OMe$), benzyl vinyl ether ($R^1 = OCH_2Ph$, $R^2 = H$), methyl vinyl ether ($R^1 = OMe$, $R^2 = H$) and vinyl acetate ($R^1 = OCOMe$, $R^2 = H$) led to the identification of the major cycloadduct(s) as the head-to-tail isomer(s) as opposed to the head-to-head isomer(s) as shown in SCHEME 62.

Similar results were obtained by Cantrell et al. when 3-substituted 2-cyclohexenones were irradiated with various electron rich olefins.[70]



SCHEME 62

However, in the case of irradiation of 1 with acrylonitrile 137, an olefin with an electron withdrawing substituent, Corey noticed not only a much "slower" reaction but also assigned the d[illegible] regioisomer to the adduct(s) containing a head-to-head regiochemical arrangement as shown in SCHEME 63.

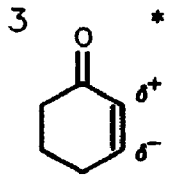


R = H 1 137 major minor

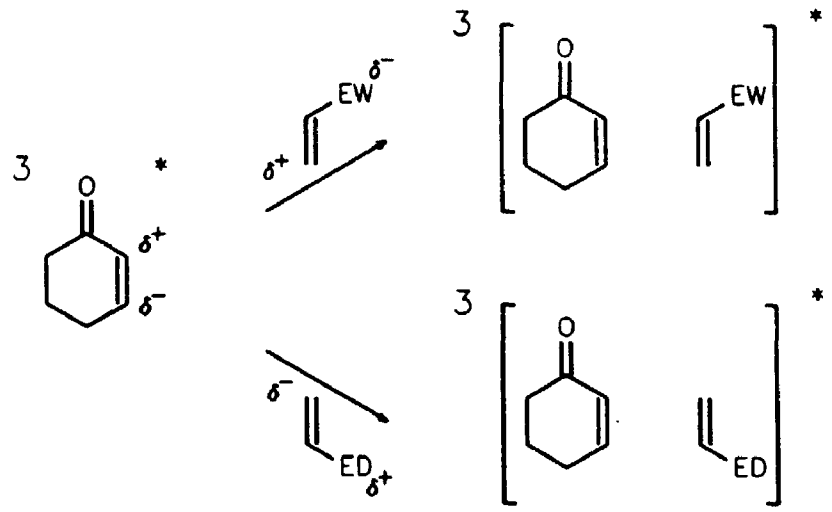
Me 18

SCHEME 63

Again Cantrell saw the same trend upon irradiation of 3-methyl-2-cyclohexenone **18** with acrylonitrile **137**. In order to explain the variation of reaction regiochemistry with alkene structure Corey proposed the intermediacy of a -complex or exciplex. He assumed that the triplet excited state of the enone was of the n,π^* nature. Calculations of electron distribution in the n,π^* state had revealed that the β-carbon carries a substantial partial negative charge whereas the α-carbon is relatively positively polarized as shown in the structure below.[28]



This is the reverse of the charge distribution in the enone in its ground state. Considering the polarization of an olefin bearing either an electron donating (ED) or electron withdrawing (EW) substituent, Corey envisioned an interaction between the excited enone and the olefin in which the relative arrangement was as shown in SCHEME 64, whereby the opposite charges were aligned to allow for maximum attraction.



SCHEME 64

This concept of an exciplex was thus able to provide a convenient explanation for the different regiochemistry observed, since the orientations in the postulated exciplex correlated with the orientation found in the observed products.

Corey's original mechanism was elaborated upon by de Mayo who applied a steady state kinetic treatment to probe the reaction.[60,63] The quantum yield of cycloadduct formation for the addition of alkenes to cyclopentenone was measured as a function of alkene concentration. Extrapolation of the results to infinite alkene concentration yielded a maximum quantum yield of 0.5 for the addition of cyclohexene and lower values for other alkenes. Since the value of intersystem crossing for cyclopentenone was known to be unity, and since the quantum yield at infinite alkene concentration corresponded to interception of all the enone triplet excited states by alkene, the fact that the limiting quantum yields were < 1 required the introduction into the mechanism of routes for decay of the exciplex and biradical intermediates to starting material.

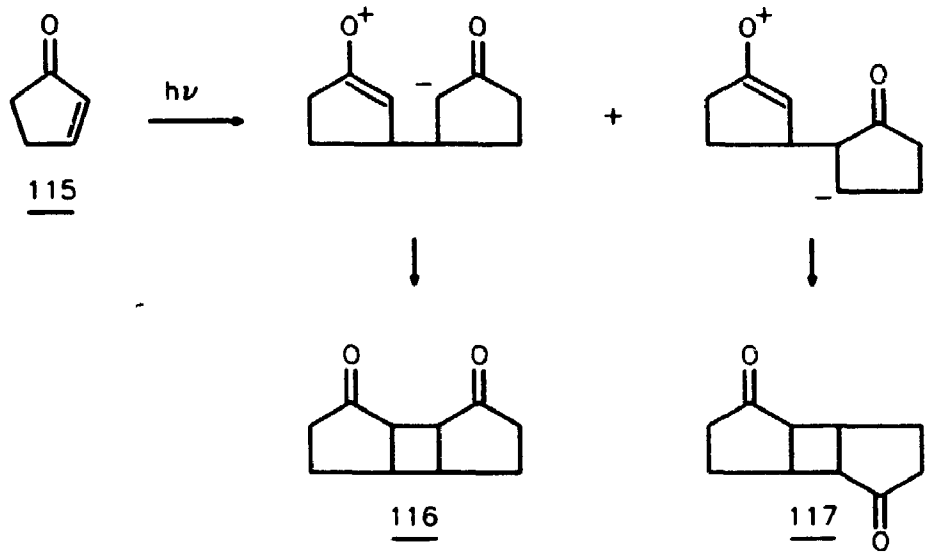
De Mayo's quantum yield measurements also allowed the extraction of values of the rate constants for the reaction of an olefin with a triplet enone.[63] The derived values were in the 10^7 - 10^8 $M^{-1}s^{-1}$ range which is several orders of magnitude higher than the rate constants of the reaction of an olefin with a free radical. This was of some concern since the triplet enone was regarded as a biradical species from the point of view of its chemical reactivity and was expected to react at a similar rate as free radicals. This perceived inconsistency was remedied by the introduction of the exciplex which, it was argued, is formed irreversibly from the triplet enone and the olefin with a rate constant of 8.24×10^8 $lmole^{-1}s^{-1}$ for the reaction of cyclopentenone with cyclohexene and 3.3×10^7 $lmole^{-1}s^{-1}$ for the cyclohexenone-cyclohexene reaction.[63c] Once formed the exciplex apparently had a lifetime of less than 10^{-9} s since it could not be intercepted by triplet quenchers. The contributions of Corey and of de Mayo to the development of the mechanistic model for reaction of enone with alkenes have led to the model involving sequential formation of an exciplex and a biradical, becoming known as the Corey-de Mayo mechanism.

1.2.3 Critical Analysis of the Corey-de Mayo Mechanism

The Corey-de Mayo mechanism has been used extensively as a working model for the rationalization of the regiochemical outcome of many enone-alkene reactions. However, it fails as an explanation in a number of instances. Corey in his original paper pointed out that the mechanism apparently could not be applied to the photodimerization of enones.[62] Eaton had reported that the photodimerization of cyclopentenone yielded two dimers (head-to-head, **116**, and head-to-tail, **117**) in

approximately equal amounts, which does not support the idea of an oriented π-complex based on electrostatic interactions.[59,71]

According to the exciplex theory **116** should have been formed in larger amounts due to the polarization in the ground and excited state enone molecules. Eaton suggested as intermediates the dipolar species shown in SCHEME 65 but pointed out that, if one assumed the dipole moment in the excited enone was that expected for a n,π^* state, **116** should have formed in larger amounts.[61]



SCHEME 65

In 1967 Ruhlen and Leermakers reported the results of a study of the photodimerization of cyclopentenone.[72] They were able to confirm Eaton's results concerning dimer formation but did not resolve the controversy over the excited state involved. It was identified as a triplet excited state (but no mention was made about its nature) and an apparent solvent dependency of the adduct ratio was explained by the fact that a polar solvent would better stabilize the transition state leading to the more polar adduct **116** relative to the transition state leading to **117**. This solvent

dependency (the ratio of **116**:**117** increased slightly when switching to a polar solvent) was also reported earlier by Eaton but considered not to be significant.[71]

In a communication in 1969 Wagner and Bucheck[73] reported that the intersystem quantum yield Φ_{ISC} for cyclopentenone was unity, which was in agreement with results of de Mayo[74] and Ruhlen and Leermakers.[72] When they studied the quantum yield of cyclopentenone dimer formation as a function of enone concentration they found that even at high enone concentration the quantum yield for the dimer formation did not exceed 0.36. They concluded that, since Φ_{ISC} was unity and the triplet did not decay rapidly by other pathways, another major source of inefficiency for the dimer formation had to be present. They identified it as cleavage back to starting material of a possible biradical intermediate, again in accordance to similar suggestions made by de Mayo for the addition of an olefin to an enone.[60]

In a later report the same authors took an in-depth look at the photodimerization of cyclopentenone and cyclohexenone.[26] They came up with a number of interesting observations. From quenching studies lifetimes for the enone triplets were determined to be $\approx 10^{-9}$ and $\approx 3 \times 10^{-9}$ s, respectively. Extensive kinetic analysis, combined with Zimmerman's calculations of charge distribution in n,π^* and π,π^* triplets[28], and comparison with known rate constants of reaction of n,π^* enone triplets in Paterno-Büchi reactions led to the conclusion that the reactive state responsible for the enone photodimerization reaction of enones was the π,π^* triplet.

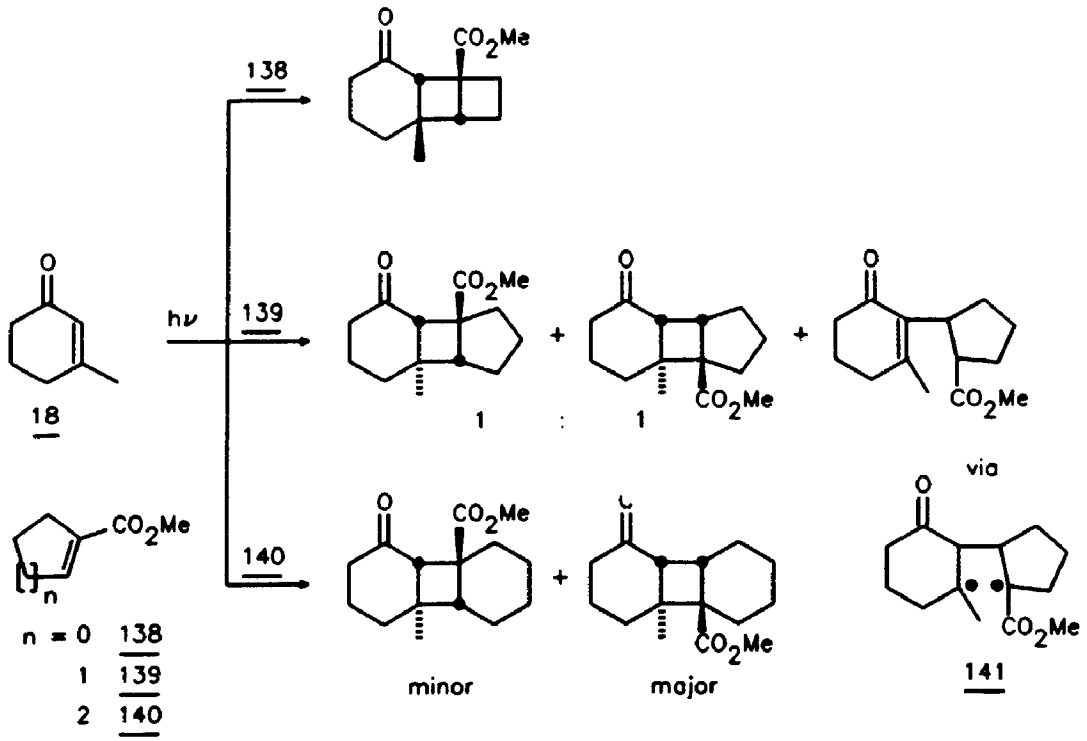
This was in contradiction to Corey's assumption that the n,π^* state was responsible for the 2+2 photocycloaddition reaction.[62] The π,π^* state differs significantly from the n,π^* state with respect to the charge distribution as indicated by the calculations of Zimmerman.[28] These calculations indicate that the relative

polarities of the α- and β-carbons are reversed, the β-carbon being more positive compared to the α-carbon.

Nevertheless Wagner and Bucheck assumed the intermediacy of some kind of charge-transfer complex preceding biradical formation (based primarily on kinetic evidence as pointed out earlier in this chapter) but admitted that this was not a completely satisfactory explanation. Newer calculations of charge distributions in excited states suggest that the polarity of the enone carbon-carbon double bond is also reversed in the π,π^* state, albeit to a lesser degree than in the n,π^* state.[75]

Other evidence which contradicts the predictions of the Corey-de Mayo mechanism has recently been published by Lange and coworkers.[76] They irradiated 3-methyl-2-cyclohexenone **18** in the presence of methyl esters of α,β-unsaturated carboxylic acids where the double bond was part of a ring system of different sizes (**138** - **140**). The results obtained were startling: with the cyclobutene derivative **138** only the head-to-head adduct was observed, the cyclopentene derived system **139** gave a mixture of head-to-head and head-to-tail adducts in about equal amounts, and the cyclohexene **140** yielded the head-to-tail adduct as the dominant product as illustrated in SCHEME 66.

This dependency of the adduct regiochemistry on the ring size of the cyclic alkene could not be explained by the exciplex theory. According to the latter the polarization of the various esters should be very similar and thus the adduct regiochemistry should not differ by much. In the case of the irradiation of **18** with **139** Lange also observed the formation of product **142**, believed to have derived from the intermediate biradical **141** by intramolecular disproportionation.



SCHEME 66

This was not the first piece of evidence to cast doubt on the exciplex theory. Two years earlier Schuster et al. published a paper questioning the necessity of exciplexes as intermediates in the reactions of enones with alkenes.[77] He emphasized that Corey assumed incorrectly that the reactive enone triplet was the n,π^* state whereas in fact it was the π,π^* state as found by Schaffner and others.[1,9] Using the technique of flash photolysis he measured triplet state lifetimes of various cyclic enones at varying alkene concentrations. From these data he was able to determine rate constants for interception of the enone triplet excited state by alkenes of different structure.

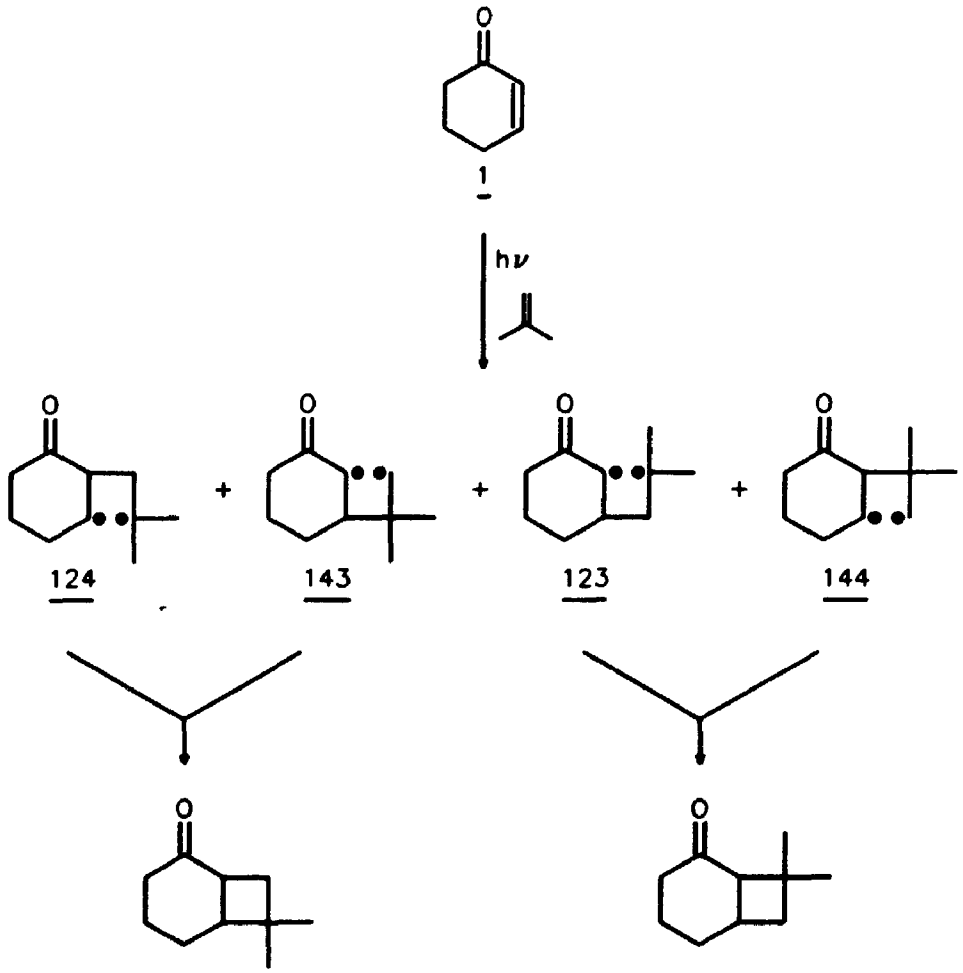
Contrary to the conclusions drawn in Corey's initial report[62] he found that olefins carrying an electron withdrawing substituent, such as acrylonitrile and

α-chloroacrylonitrile, quenched the triplet faster than other alkenes such as cyclopentene. However, the apparent reaction rates did not correlate with the quantum efficiencies of the cycloadditions. For example acrylonitrile quenched the triplet of **18** ≈ 150 times faster than cyclopentene but its quantum yield for addition was ≈ 30 % lower. It should be pointed out that while enone triplet excited states were found to be quenched faster by electron deficient alkenes, this does not necessary mean that they react faster. This is because the triplet energy of acrylonitrile is lower than that of enones, so that the enone triplet could be quenched by energy transfer rather than by reaction in the flash photolysis experiments. This possibility will be discussed later in this thesis.

Schuster's data did not directly exclude an exciplex but it did not *require* it either. This is because the rate of reaction between the enone triplet excited state and an alkene could not be correlated to the observed quantum yield for the formation of cycloadducts and the preference for one or the other regiochemistry in the cycloadduct can be explained by different partitioning of the different biradical intermediates between starting materials and products. His results showed that the quantum yield for triplet capture Φ_{TC} was typically much higher than Φ_{add}, for example for acrylonitrile and **18**, Φ_{TC} was 0.84 and Φ_{add} was 0.14. This discrepancy was easily resolved if one assumed that the biradicals formed in this particular reaction preferred to cleave instead of closing. In addition, no correlation between the rates of alkenes reacting with enone triplets and alkene ionization potentials were found, as one would expect if donor-acceptor complexes influence the rates.[1]

The same concept of biradicals reacting with different rates for closure and cleaving was proposed in 1970 by Bauslaugh.[78] He concluded that in the reaction of cyclohexenone **1** with isobutene, for example, four different biradicals **123**, **124**, **143**

and **144** were possible, each with different stability and each partitioning differently between starting material and product as shown in SCHEME 67. The head-to-head adduct would come from closure of **123** and **144** whereas the head-to-tail isomer would arise from **124** and **143**.

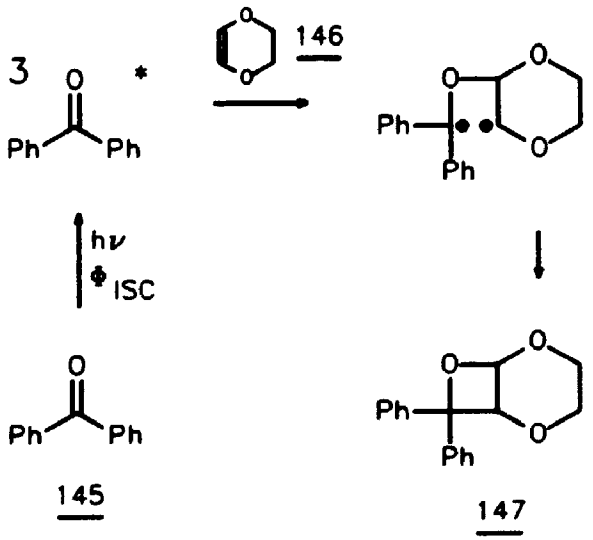


SCHEME 67

Bauslaugh argued, based on previous work by Bartlett[79], that the more stable a biradical was the more would it revert to starting material. For the above reaction this would mean the following: **123** was the most stable biradical (under the assumption that an adjacent carbonyl group stabilizes a radical centre) whereas **144** would be the least likely and therefore the one formed in the least amount. Product

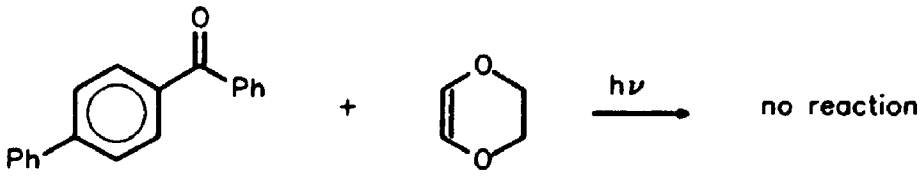
formation would then mainly come from **124** and **143** leading to the observed regiochemical preference for the head-to-tail adduct.[62] As Schuster after him Bauslaugh omitted the exciplex from his reaction mechanism since it was not required to explain the regiochemistry. Regiochemistry in the product(s) could be explained solely by different partitioning of the biradicals, involved which eliminated the need for an activated π-complex prior to biradical formation to account for orientation.

The kinetic argument for the existence of the exciplex was proposed by de Mayo to explain the fact that the rate constants estimated for the reaction of an alkene with a triplet excited enone were extremely high compared with those for the reaction of an alkene with a simple radical.[60,63c] A possible solution to this dilemma can be found in work published by Freilich and Peters in 1985.[80] They investigated the Paterno-Büchi reaction between benzophenone **145** and dioxene **146** utilizing picosecond absorption spectroscopy. Excitation of **145** led to its triplet excited state (after intersystem crossing) which was quenched by **146** to give a 1,4-biradical and finally the adduct **147** as shown in SCHEME 68.



SCHEME 68

The biradical was observed spectroscopically and its lifetime determined, which allowed for the estimation of a rate constant for its disappearance in the order of $6 \times 10^{8}\ s^{-1}$. The half life of the triplet excited state of **145** in the presence of **146** was determined to be in the range of $1 - 2 \times 10^{-10}$ s. The reason that no exciplex was included in the reaction was explained by the fact that the triplet state of another ketone, 4-phenylbenzophenone **148**, was not quenched by **146** over the observation time as indicated in SCHEME 69.



148 **146**

SCHEME 69

Compound **148** showed similar rates to **145** when involved in electron transfer reactions but hydrogen abstraction reactions of **148** were very inefficient compared to **145**.

If exciplexes were involved (which were postulated to be donor-acceptor complexes) the triplet of **148** should react with **146** as fast as **145**, but the biradical formation (leading to ε similar species as in a hydrogen abstraction) was suppressed. This result ruled out the intermediacy of exciplexes in Paterno-Büchi reactions* and also showed that the rate of a triplet excited state reacting with an olefin could be in

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* In contrast to these results, Caldwell has argued for the irreversible formation of triplet exciplexes in Paterno-Büchi reactions using secondary deuterium isotope effect data.[145]

the order of de Mayo's results, eliminating the need for the intermediacy of an exciplex in the 2 + 2 photocycloaddition of enones and alkenes.

If an exciplex intermediate is dispensed with then one must focus on the 1,4-biradical intermediate and its properties in order to explain the regiochemistry of enone cycloaddition reactions. In particular it would be desirable to gain knowledge of the relative ratios of formation of the various possible biradicals and also of their partitioning ratios for closure to product relative to reversion to starting materials.

In their paper of 1977 Loutfy and de Mayo reported that they were able to extract ratios for the biradical partitioning (reversion to starting material relative to product formation) from steady state kinetic studies.[63c] The values for the ratios in the addition of cyclopentene to cyclopentenone and cyclohexenone were 3.35 and 1.78, respectively.

This means that 77 % of the biradicals in the reaction of cyclopentenone with cyclopentene revert to starting material and only 23 % close to product. In the reaction of cyclohexenone with cyclopentene 64 % of the biradicals cleave back to starting materials and 36 % react to cycloadducts.

Unfortunately the authors failed to take into account that there had to be more than one biradical involved, as shown for example by Bauslaugh[78]. This would complicate the kinetic analysis tremendously and make it impossible to obtain partitioning ratios from the kinetic data, as shown by Hastings.[81] This is because each of the possible biradicals (two in each of the above mentioned reactions, four in the case of unsymmetrically substituted olefins) could be expected to be formed with a different rate constant and each would have different partitioning ratios. Furthermore a cycloadduct can be derived from more than one biradical precursor which forbids the use of simple product distribution analysis to yield information about the intermediates.

The question of biradical partitioning will be discussed in Chapter 3 of this part of this thesis. By independent generation of the intermediate biradicals involved in the 2 + 2 photocycloaddition reaction of enones and alkenes, product distribution studies allow the determination of partitioning ratios of individual biradicals. Lifetime measurements of the intermediate biradicals will be subject of Chapter 2. Utilizing the concept of radical clocks, estimations of biradical lifetimes will be made by comparison with reactions with known rate constants.

CHAPTER 2

RADICAL CLOCKS AS PROBES OF 1,4-BIRADICALS IN 2 + 2 PHOTOCYCLOADDITION REACTIONS OF 2-CYCLOPENTENONE WITH ALKENES

2.1 Introduction

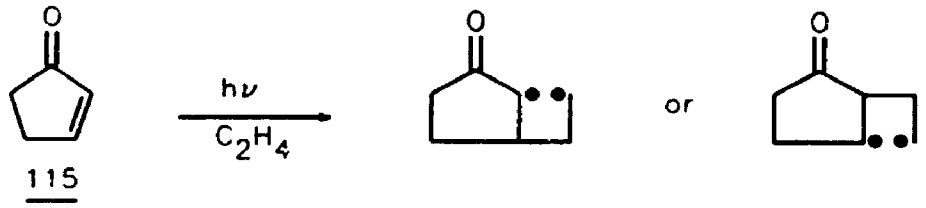
2.1.1 General Aspects

As pointed out in Chapter 1 of this part of this thesis the intermediacy of 1,4-biradical species in the 2 + 2 photocycloaddition reaction of enones with olefins is well established. However, they have not been observed directly (i.e. spectroscopically), although lifetime measurements have been undertaken for the similar biradicals present in the dimerization reaction of enones.[82]

The work described in this chapter was designed to allow an estimate to be made of biradical lifetimes and to determine the site of initial bonding in the cycloaddition reaction of cyclopentenone with alkenes.

The latter question has been controversial for some time and when this work was commenced was still not completely agreed upon. However, since the completion of the work described here, Hastings and Weedon have been able to show that in the photocycloaddition reaction of cyclopentenone with ethyl vinyl ether the initial bond between the enone and the alkene is formed to similar extent to both the α- and the β-positions of the enone carbon-carbon double bond.[69,81] This will be discussed later.

In principle an alkene could bond to an excited enone in either the α- or β-position leading to different biradicals as shown in SCHEME 70 for the addition of ethylene to cyclopentenone 115.



115

SCHEME 70

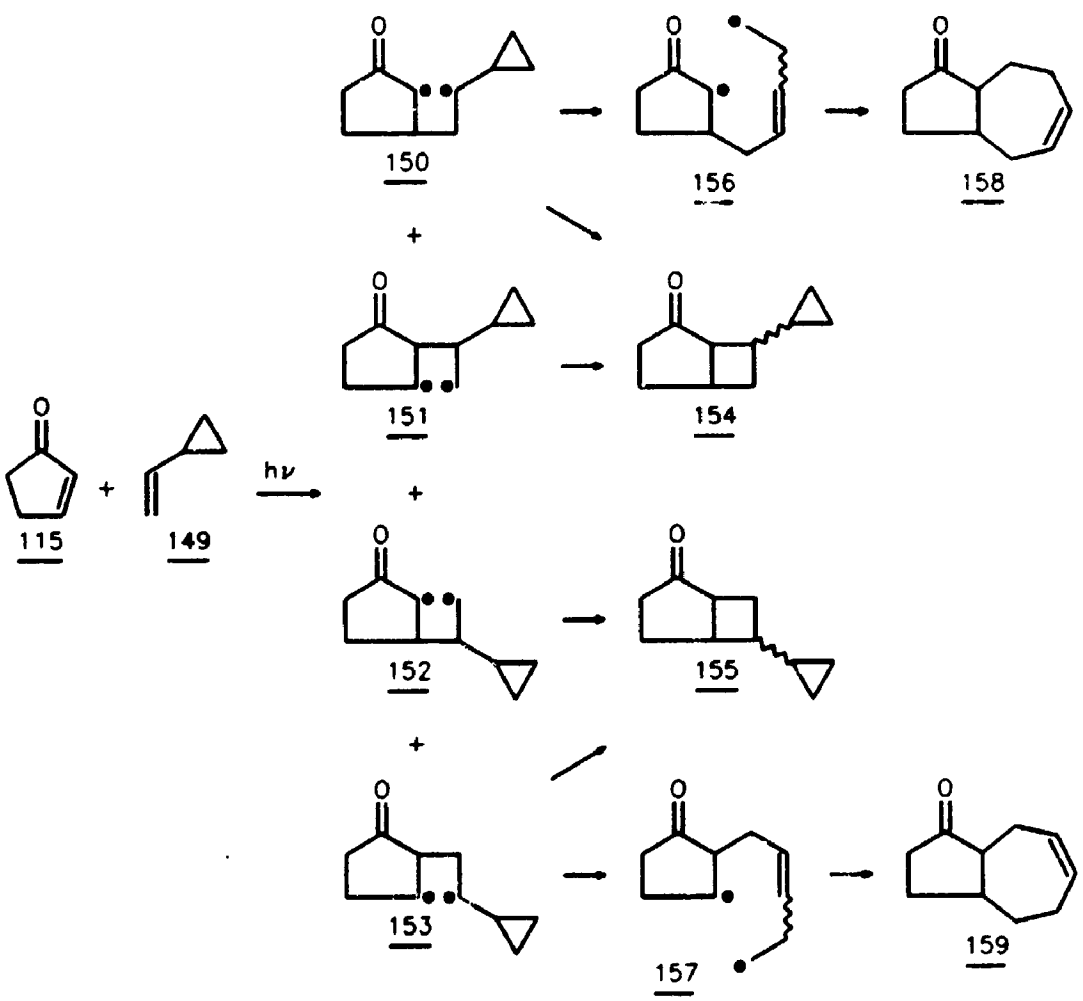
Thus at least two biradical structures are possible and for a non-symmetrical olefin this number rises to four. Examining the products of the cycloaddition does not identify which biradical was involved since one particular product could be derived from more than one biradical precursor.

The approach taken in this work was to perform the 2 + 2 photocycloaddition reaction with **115** and alkenes that lead to biradical intermediates capable not only of back reaction to starting materials or ring closure to cycloadducts but also of rearrangement to new biradicals and alternative products. The rearrangement reaction could then be used to probe the structure of the biradicals and, if the rearrangement rates were known, as a clock to estimate the lifetimes of the initial biradicals. This concept of radical clocks has been utilized by a number of groups. In their reviews of 1980, Griller and Ingold listed thirteen different radical rearrangement reactions with known rate constants for primary radicals.[83] Another fourteen reactions involving other radicals showed the wide variety of reactions available to organic chemists but, as the authors pointed out, the list was far from complete and some types of radicals were not represented. Radical clocks were considered by the authors as a convenient way to measure rate constants of new radical reactions by comparing them to a reaction with a known rate constant (hence the term radical clock). Initial calibration of the clocks was done by electron paramagnetic resonance (epr) spectroscopy, which

allowed determination of the Arrhenius parameters of the observed reaction and thus enabled the use of the clock over a range of temperature, as opposed to only the temperature at which it was calibrated.[83b] The radical clocks chosen as probes for 1,4-biradical intermediates in the 2 + 2 photocycloaddition reactions of **115** were the cyclopropylcarbinyl and the 5-hexen-1-yl radical clocks.

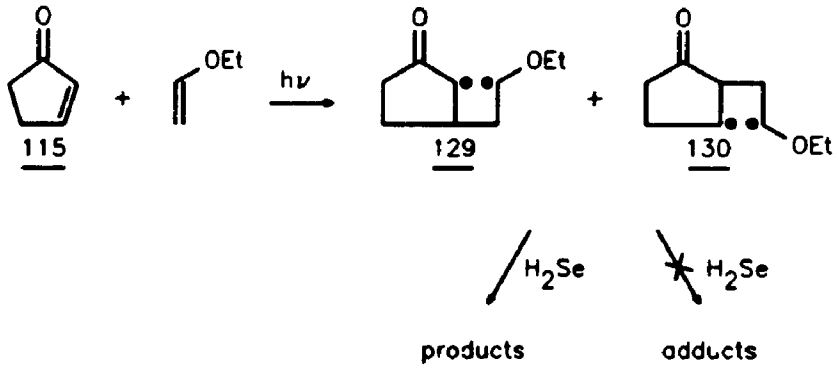
2.1.2 The Cyclopropylcarbinyl Radical Clock

In the reaction of cyclopentenone **115** with vinylcyclopropane **149** up to four biradical intermediates **150** - **153** could be anticipated as outlined in SCHEME 71.



SCHEME 71

Two of them (**151** and **152**) were expected to be present only in minor amounts because they contained primary radical centres. Work subsequently undertaken by Hastings and Weedon[69 81] dealing with the trapping by hydrogen selenide of 1,4-biradical intermediates in the photoaddition of **115** and ethyl vinyl ether confirmed that the biradicals containing primary radical centres were not formed since no trapping products from them could be detected. All products obtained were derived from the biradicals **129** and **130** as shown in SCHEME 72.

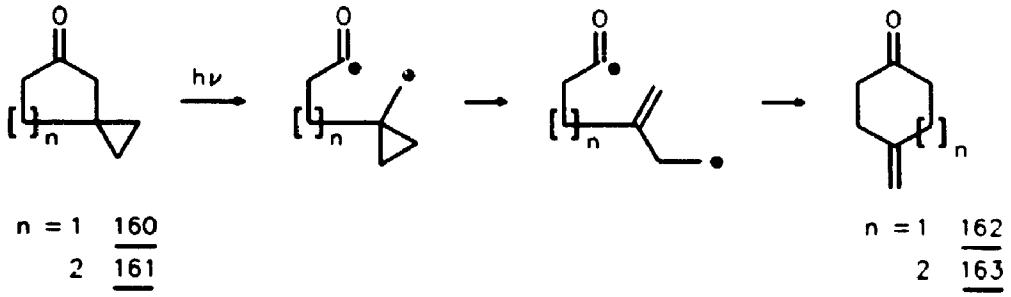


SCHEME 72

Ring closure of **150** and **151** would lead to the head-to-head adducts **154** whereas **152** and **153** would give the head-to-tail adducts **155**. Additionally biradicals **150** and **153** contain a cyclopropylcarbinyl radical centre which could rearrange to the 1,7-biradicals **156** and **157**. Ringclosure of these could then yield the cycloheptene products **158** and **159**, respectively, as shown in SCHEME 71 above.

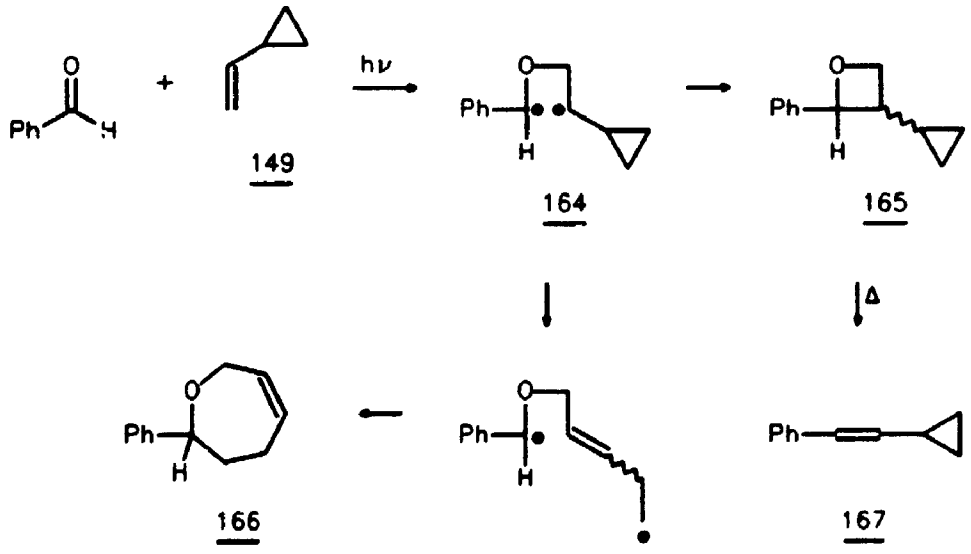
This rearrangement of a cyclopropylcarbinyl radical to a 3-buten-1-yl radical is a well known reaction which had been investigated extensively. In 1972 Nishida et al. reported that the cyclopropylmethyl radical centres generated by photolysis of the spiroalkanones **160** and **161** rearranged to the 3-buten-1-yl radicals. Ring closure then

gave solely the 4-methylene substituted cyclohexanone **162** and cycloheptanone **163**, respectively as shown in SCHEME 73.[84a]



SCHEME 73

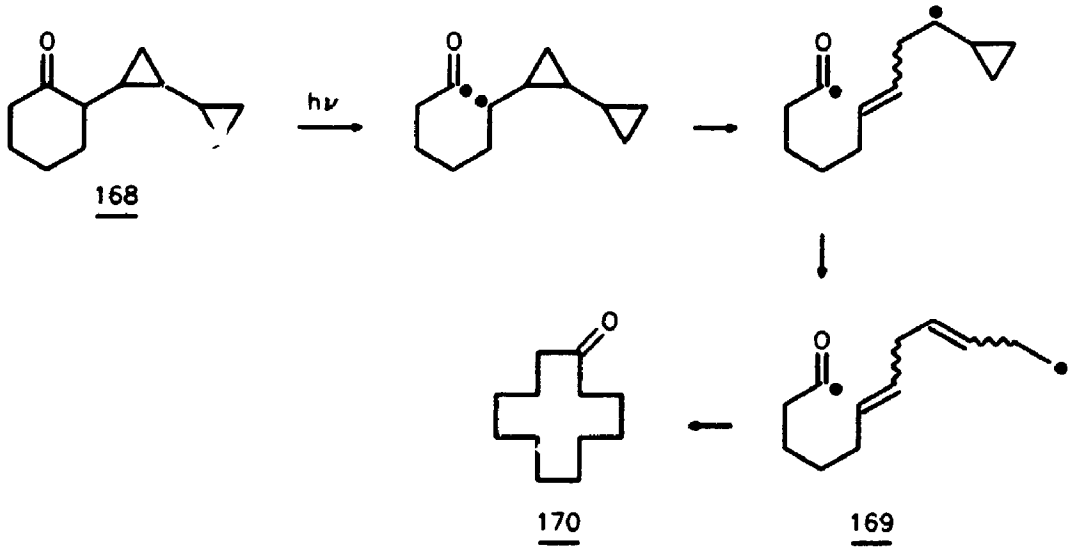
Two years later they were able to report similar results obtained in an investigation of the Paterno-Büchi reaction between aromatic carbonyl compounds and vinylcyclopropane and its derivatives.[84b] For example irradiation of benzaldehyde with vinylcyclopropane **149** at 75°C gave two photoproducts **165** and **166** as well as **167** in a ≈3:1:1 ratio as can be seen in SCHEME 74.



SCHEME 74

Compound **167** was derived by thermal cleavage of **165** whereas **166** could only have come from radical rearrangement of the intermediate biradical **164**.

In 1975 Carlson and Mardis reported that they were able to perform a reaction sequence (which is shown in SCHEME 75) involving two consecutive cylopropylcarbinyl radical to 3-buten-1-yl radical rearrangements.[85] Photolysis and subsequent α-cleavage of 2-(2-cyclopropylcyclopropyl)cyclohexanone **168** led to the first cyclopropylcarbinyl radical, which rearranged to the second cyclopropylcarbinyl radical. This further rearranged to the biradical **169**. Ring closure and catalytic hydrogenation gave the cyclododecanone **170** in 61 % yield.

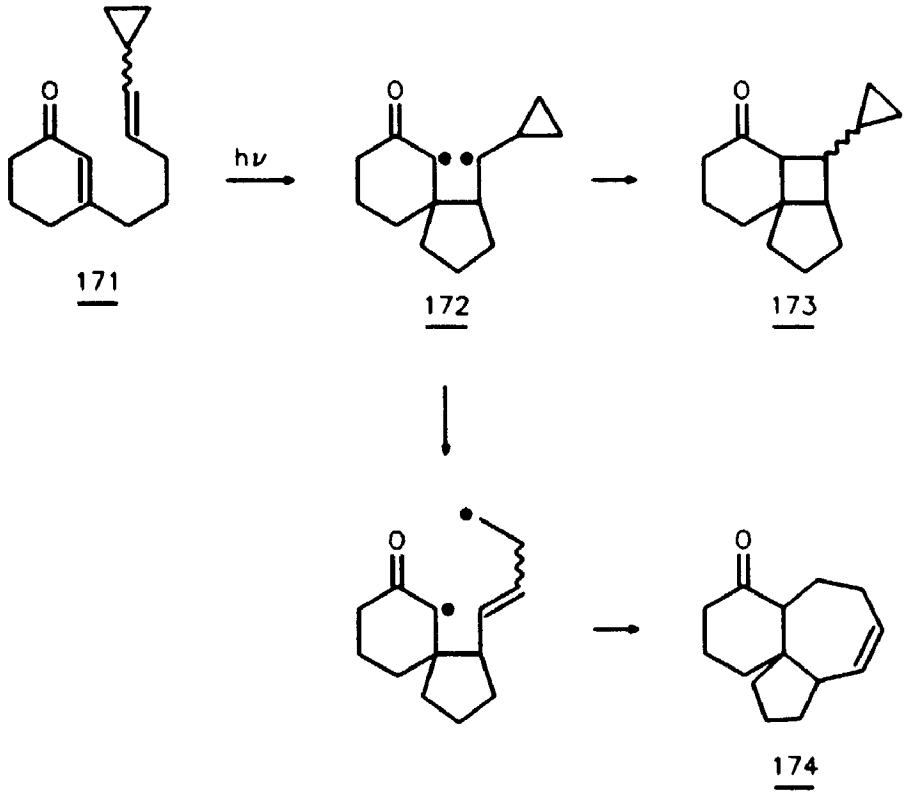


168 170 169

SCHEME 75

Recently Becker et al. have shown that systems such as **171** and **175** undergo intramolecular cycloaddition reactions upon irradiation.[86] Photolysis of compound **171** led to the formation of biradical **172** which either closed to **173** or rearranged to a

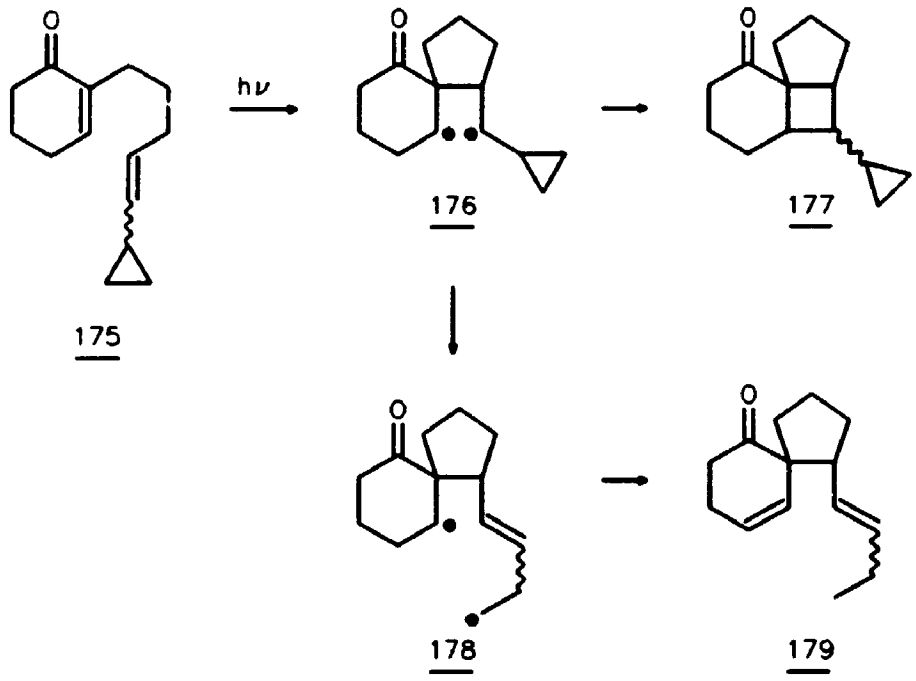
1,7-biradical with subsequent closure to **174** (in a ratio of **173**:**174** of ≈ 6:5) as shown in SCHEME 76.



171 172 173 174

SCHEME 76

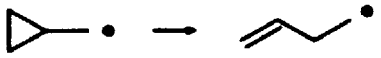
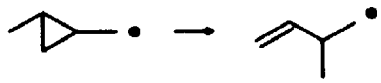
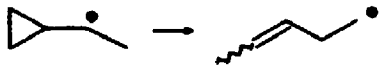
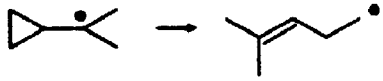
Similarly irradiation of compound **175** led to the formation of biradical **176** which either closed to the cyclobutane product **177** or underwent rearrangement to biradical **178**. Subsequent 1,8-hydrogen abstraction gave the 3-cyclohexenone products **179** as can be seen in SCHEME 77. The observed product ratio **179** to **177** was ≈5:4.[86] The occurrence of the cyclopropylcarbinyl to 3-buten-1-yl radical rearrangement led Becker to postulate that in system **171** the first bond was being formed to the β-carbon of the enone.



SCHEME 77

The rates of the ring opening of the cyclopropylcarbinyl radical have been measured by various groups and the results at room temperature are listed in TABLE 24. As can be seen, the rearrangement reaction is fastest for the parent cyclopropylmethyl radical while methyl substituted radicals were found to ring open somewhat slower, presumably due to an increase in stability of the closed radical. These rates are fast when compared with many other radical rearrangement reactions. For example the 5-hexen-1-yl to cyclopentylmethyl radical rearrangement (*vide infra*) was measured to proceed with a rate constant of $\approx 1 \times 10^5\ s^{-1}$ at 25°C[83a]. This has prompted researchers to use the cyclopropylcarbinyl radical rearrangement as a radical clock in systems that require a fast standard.

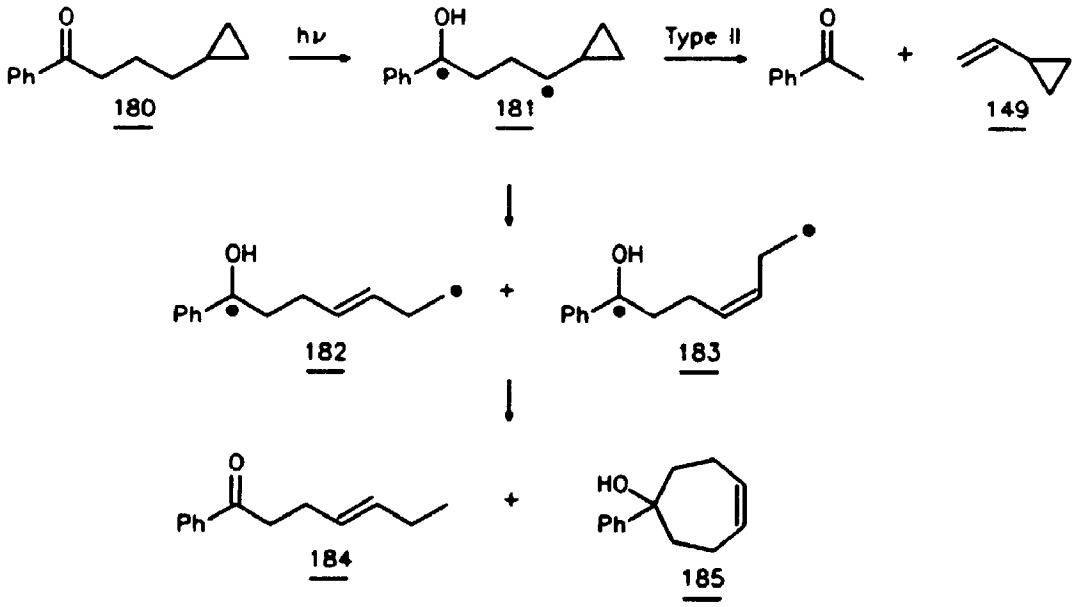
TABLE 24: Rate constants for some cyclopropylcarbinyl radical to 3-buten-1-yl radical rearrangements

Rearrangement	Rate constant (10^8 s^{-1})	Reference
	1.3	87a
	2.1	87b
	1.6	87c
	1.2	87d,e
	1.6	87e
	2.3	87e
	0.2	87c
	0.7	87e
	0.9	87e

The rate constant for the back reaction of the 3-buten-1-yl radical to give the cyclopropylcarbinyl radical has been determined to be 4.9×10^3 s^{-1}; this is considerably slower than the ring opening reaction so that in the absence of competing reactions a cyclopropylcarbinyl radical will ring open practically irreversibly.[87f]

In 1981 Wagner and coworkers reported the use of the cyclopropylcarbinyl radical clock to estimate the rates with which some 1,4-biradicals, generated by Norrish Type II reactions, reacted to products.[88] Irradiation of ketone **180** led to biradical **181**, which could either undergo normal Type II chemistry (i.e. β-cleavage) to give acetophenone and vinylcyclopropane **149**, or rearrange to **182** and **183**, which in turn could give **184** or **185** as shown in SCHEME 78. The results (the authors

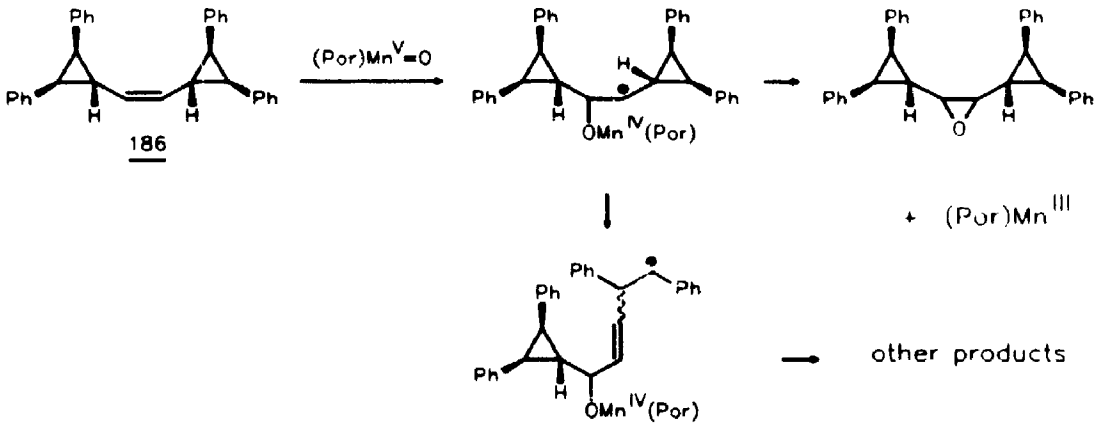
concluded that **181** underwent 38 - 50 % rearrangement) led to the postulate that **181** underwent β-cleavage with a rate constant of 2 - 3 x 10^7 s^{-1}, based on an estimated rearrangement rate for **181** of 2 x 10^7 s^{-1}.



SCHEME 78

In 1988 Castellino and Bruice reported on the intermediates in the metalloporphyrin catalyzed epoxidation of olefins with pentafluoroiodosobenzene.[87c] This reaction was believed to proceed *via* a radical cation intermediate and the authors used a modified cyclopropylcarbinyl radical to 3-buten-1-yl radical rearrangement to extract a rate constant for the conversion of the cation radical to the epoxide. Reaction of alkene **186** allowed for rearrangement of the radical centre to give alternative products as outlined in SCHEME 79. The rate constant for the ring opening of a cyclopropylalkyl radical with two *trans*-phenyl groups on the cyclopropyl ring has been determined to be $\geq$ 2 x 10^{10} s^{-1}. This is about 1000 times faster than for an unsubstituted system[87c], and the acceleration is explained by differences in ground and transition state energies.[87c] With this clock or hand and the amount of product derived

from ring opening seen (5 - 16 %), the rate constant for epoxide formation was estimated to be 1 - 2 x 10^{11} s^{-1} which is not unreasonable for the reaction of a system such as the one shown.



$$(Por)Mn^{III} \xrightarrow{C_6F_5IO} (Por)Mn^{V}=O$$

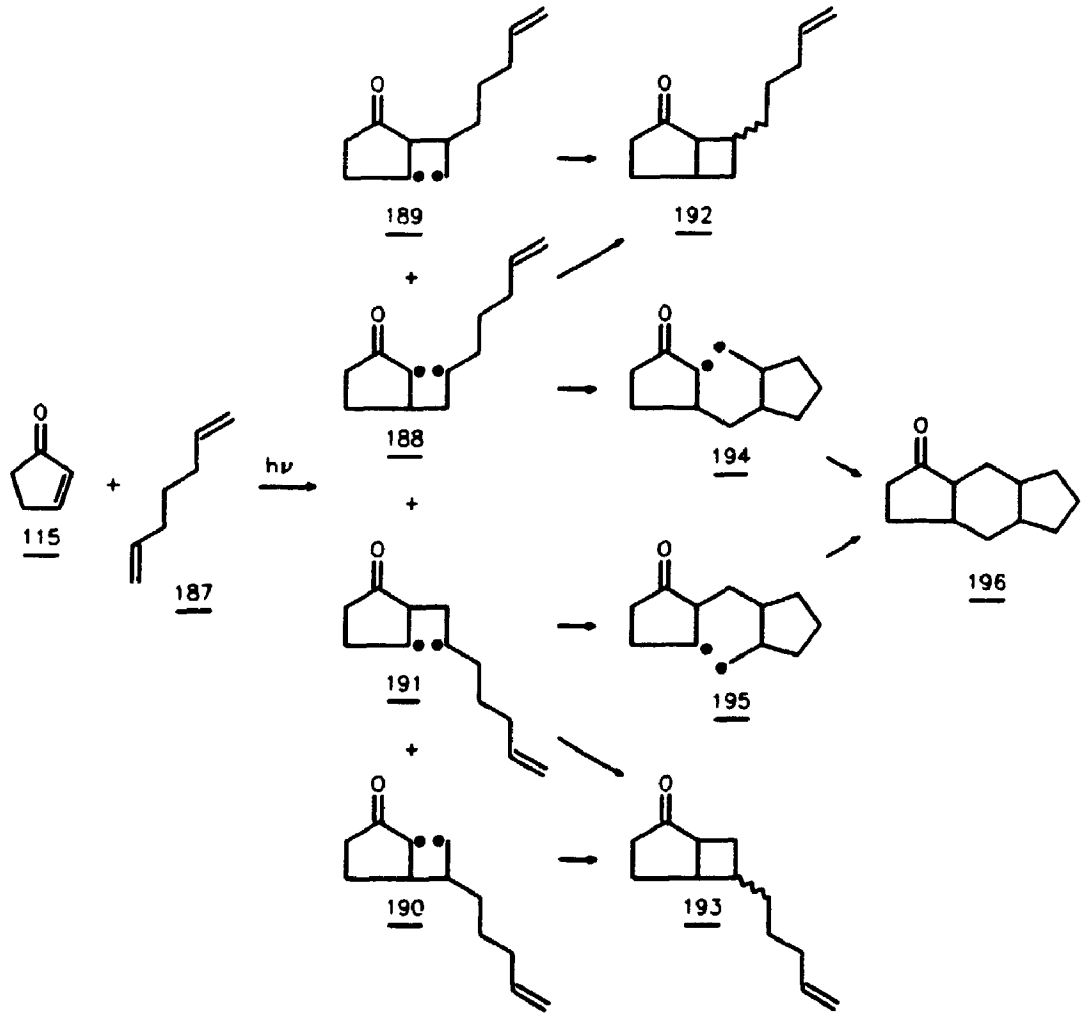
SCHEME 79

In 1989 Becker and coworkers used system **171** to estimate the rate of cyclobutane formation from the photochemically produced biradical **172**.[86a] Since both **173** and **174** (as shown in SCHEME 76 above) were observed in similar amounts the authors concluded that the rates of biradical closure and radical rearrangement were of the same order; this led to the conclusion that **173** was formed from **172** with a rate constant of $\approx 10^8$ s^{-1}.

2.1.3 The 5-Hexen-1-yl Radical Clock

In the photochemical reaction of cyclopentenone **115** with 1,6-heptadiene **187** the four triplet 1,4-biradicals **188** - **191** are potential intermediates. As in the case of

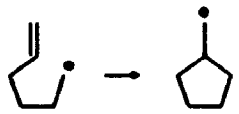
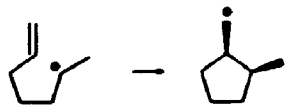
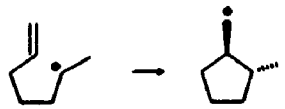
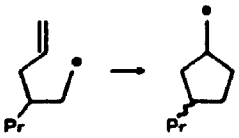
the reaction of **115** with vinylcyclopropane the two biradicals containing primary radical centres (ie. **189** and **190**) were considered likely to be formed only in very small amounts or not at all; this supposition has subsequently being confirmed by Hastings and Weedon using hydrogen selenide to trap the intermediate biradicals found in the photochemical reaction of **115** with ethyl vinyl ether.[69,81] Ring closure of **188** and **189** would give the 2 + 2 adducts **192** whereas closure of **190** and **191** would lead to **193**. On the other hand **188** and **191** contain a 5-hexen-1-yl radical which could rearrange to **194** and **195**, respectively. These 1,6-biradicals could then close to give **196** as shown in SCHEME 80.



SCHEME 80

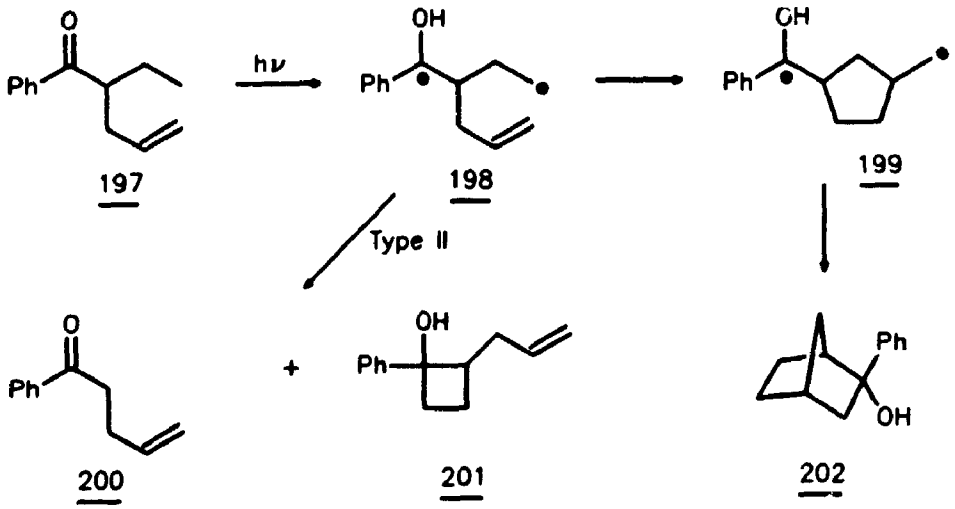
The 5-hexen-1-yl radical to cyclopentylmethyl radical rearrangement is a well known process. The rate of this rearrangement and the rates for rearrangement of methyl substituted derivatives have been measured by Ingold and co-workers and are listed in TABLE 25.

TABLE 25: Rate constants for some 5-hexen-1-yl radical to cyclopentylmethyl radical rearrangements

Rearrangement	Rate constant (10^5 s^{-1})	Reference
	1.0	83a
	2.5	89a
	1.0	89b
	0.3	89b
	5.0	89c

Wagner et al. also utilized the 5-hexen-1-yl radical clock to investigate the kinetics of ketones undergoing Norrish Type II reactions.[88] Irradiation of the ketone **197** induced intramolecular hydrogen abstraction and led to biradical **198** which could undergo radical rearrangement to **199**. Biradical **198** could also undergo normal Type II chemistry to give **200** and **201** whereas **199** could cyclize to **202** as shown in SCHEME 81. Combination of the product ratio (products from **198** and **199** were observed in a 24:1 ratio) with the estimated quantum efficiency for Type II reaction

of **197** (40 %) and the estimated value of the rate constant for rearrangement of **198** to **199** ($\approx 3.6 \times 10^5$ s^{-1}) allowed the calculation of the rate constant for reaction of **198** to **200** and **201**. The value derived was *ca.* 2.2×10^7 s^{-1} which is very similar to that obtained with the cyclopropylcarbinyl radical clock.[88]



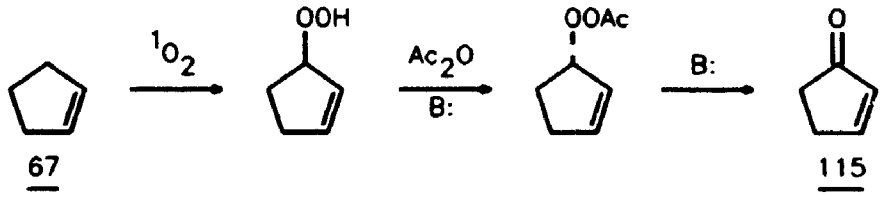
SCHEME 81

2.2 Photocycloaddition of Vinylcyclopropane 149 and Cyclopentenone 115

2.2.1 Preparation of Cyclopentenone 115

Various methods for the preparation of cyclopentenone, **115**, have been published in the literature.[90] Most involve a number of steps and the reported overall yields are not high. The majority of the methods are based on cyclopentanone or cyclopentadiene as the starting material. The procedures include elimination of hydrogen chloride from 2-chlorocyclopentanone[90a], acid catalyzed elimination of cyclopentenediols[90b] and reaction of silyl enol ethers of cyclopentanone with palladium(II)/benzoquinone[90c] or triphenylmethyl cation.[90d]

For this work 2-cyclopentenone was prepared by a one-pot method first described by Mihelich and Eickhoff which was modified by using a different sensitizer and a more effective dry ice condenser.[90e] In this procedure irradiation of a solution of cyclopentene **67** in the presence of oxygen, tetratolylporphyrin (TTP) as sensitizer, acetic anhydride, pyridine and 4-(N,N-dimethylamino)pyridine with Pyrex and water filtered light results in generation of singlet oxygen which reacts with the olefin by an ene-reaction to give an allylic hydroperoxide. Acetylation and Grob cleavage then gives **115** as shown in SCHEME 82.



SCHEME 82

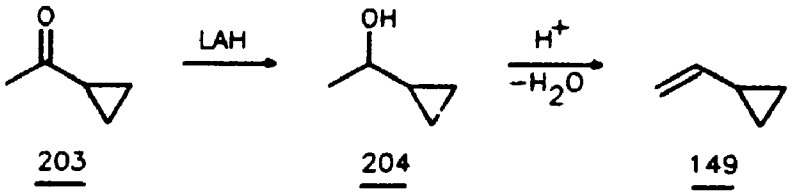
Unfortunately the workup proved to be difficult since the excess anhydride could be removed only after a large number of base washes This resulted in a decreased yield due to the partial solubility of **115** in water. Extraction with saturated aqueous $CuSO_4$-solutions did not facilitate removal of TTP so in later runs these were abandoned and the TTP was removed in the final distillation step. The highest yield obtained was 55 % compared with 71 % reported in the literature.[90e] The product was easily identified by nmr and mass spectroscopy by comparison with the literature data.[39,91]

Since it later proved to be crucial to know the chemical shifts of the α- and the β-olefinic protons of 2-cyclopentenones (*vide infra*), their positions in **115** were

determined. Both appeared as doublets of triplets at 7.76 and 6.21 ppm. Due to resonance in the enone system the β-carbon bears a partially positive charge with the consequence that the β-proton is less shielded and appears at lower field. This is in accordance with the reported data for cyclohexenone[39]. The ^{13}C-nmr data for cyclopentenone showed a similar trend.[91a] It was thus concluded that the olefinic α-proton of **115** has a chemical shift of 6.21 ppm and the corresponding β-proton a shift of 7.76 ppm which is in agreement with literature assignments.[91b] The coupling constants observed supported this assignment. The vicinal coupling between the α- and β-protons was determined to be 5.67 Hz. The β-proton was coupled into the adjacent methylene group with a coupling constant of 2.75 Hz whereas the α-proton was coupled into the same methylene group with an allylic coupling constant of 2.17 Hz.

2.2.2 Preparation of Vinylcyclopropane 149

A number of procedures for the preparation of vinylcyclopropane have been described in the chemical literature. In 1949 van Volkenburgh et al. published a synthesis of **149** which started from cyclopropyl methyl ketone **203**.[32] The ketone was reduced to the alcohol **204** with lithium aluminum hydride; acid catalyzed dehydration then gave **149** in 39 % yield as outlined in SCHEME 83.

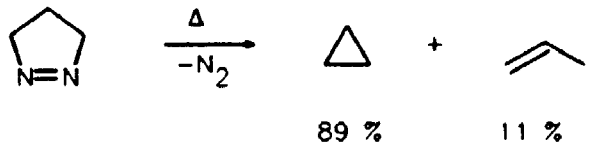


203 204 149

SCHEME 83

In 1952 Slabey improved the dehydration step by passing alcohol **204** through a column of alumina at 265 - 300°C.[93] He was able to increase the yield of **149** to ≈ 54 % and then further purified it by azeotropic distillation with ethanol.

In the mid 1960's Crawford and coworkers reported the thermal decomposition of 1-pyrazolines. Heating of 1-pyrazoline and its derivatives resulted in formation of cyclopropane products and small amounts of olefinic material as shown for 1-pyrazoline in SCHEME 84.[94a]



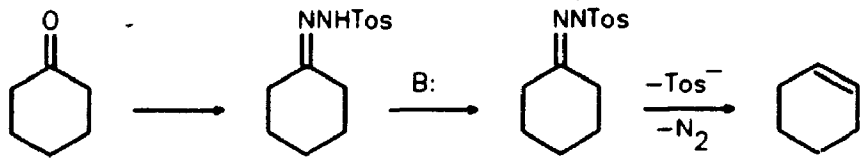
SCHEME 84

The authors concluded that the intermediate leading to the products is a biradicaloid species generated by homolytic C-N bond cleavage. They were able to extend this synthetic principle to the preparation of **149**.[94b] Thermal decomposition of 3-vinyl-1-pyrazoline **205** led to the formation of **149** and cyclopentene **67** in a 99:1 ratio (no absolute yields were given). Again the reaction was presumed to proceed *via* a biradical with one of the radical centres being an allylic system. Ring closure then gave either **149** or **67** as shown in SCHEME 85.

SCHEME 85

Variable temperature studies indicated that the optimum yield of **149** was obtained at ≈ 128°C; at higher temperatures the fraction of **67** increased dramatically (up to 29 % at ≈ 186°C).

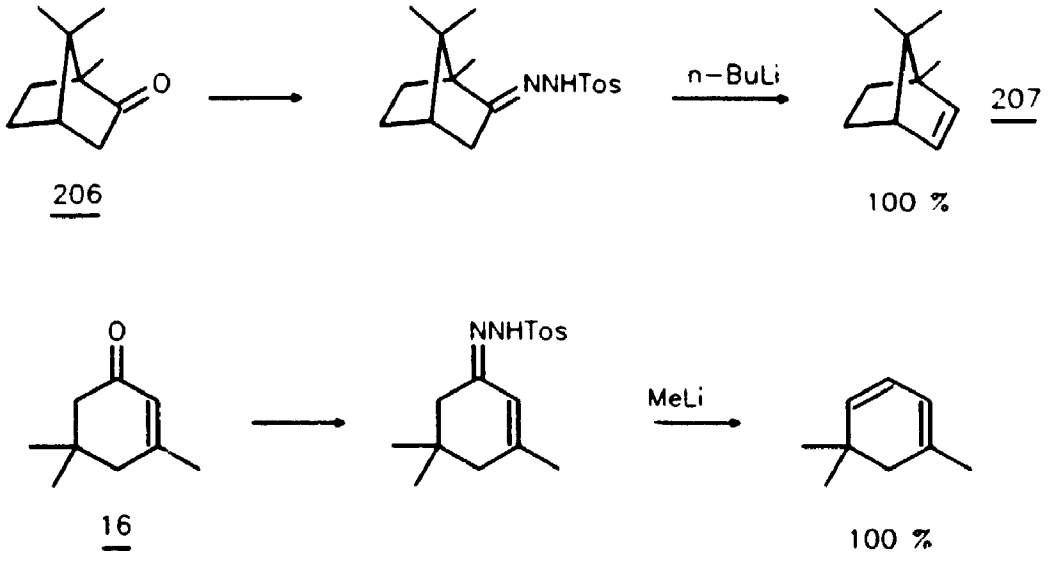
A different approach to the synthesis of **149** was taken by Kirmse and coworkers who utilized the Bamford-Stevens reaction (with sodium amide and hydride).[95] Bamford and Stevens originally found that *p*-toluenesulfonyl hydrazones of simple non-aromatic ketones yielded olefins when treated with strong base.[96] This reaction was shown to proceed by proton abstraction followed by loss of sulfinate and nitrogen concomitant with migration of one of the groups on the *α*-carbon, usually hydrogen, as shown in SCHEME 86 for the case of cyclohexanone which was converted quantitatively to cyclohexene.



100 %

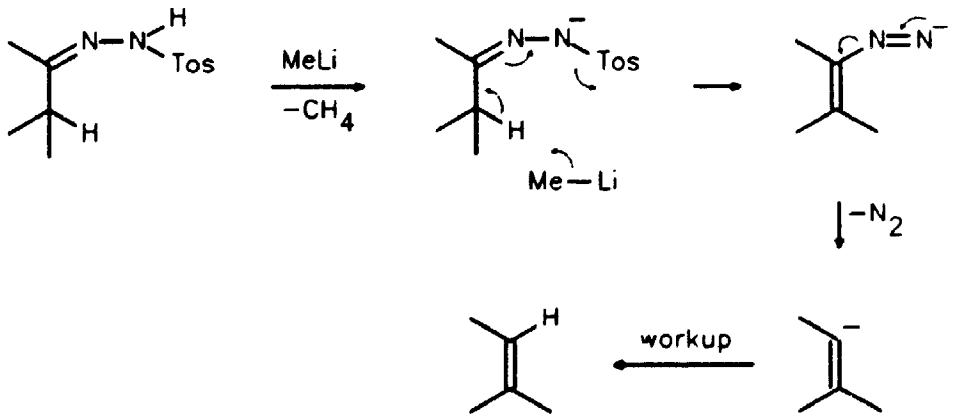
SCHEME 86

The Bamford-Stevens reaction was extensively investigated by the groups of Shapiro and others who adapted the reaction to a variety of substrates and bases (sodium hydride, sodium methoxide, alkyllithium and other).[97] Syntheses such as the preparation of 2-bornene **207** from camphor **206** were practically quantitative and the procedure could also be applied to the preparation of conjugated dienes from enones like isophorone **16** as outlined in SCHEME 87.



SCHEME 87

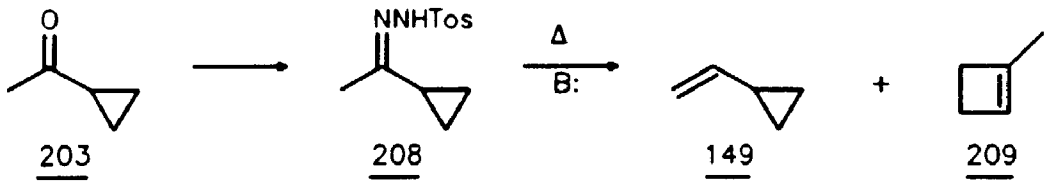
The mechanism, which was proposed to be carbanionic with the base attacking preferentially the most acidic hydrogen on the *α*-carbon of the tosylhydrazone, is shown in SCHEME 88.



SCHEME 88

This synthetic concept was applied by Kirmse et al. to the preparation of **149** *via* the tosylhydrazone **208** of the cyclopropyl methyl ketone **203**.[95] Reaction of **208**

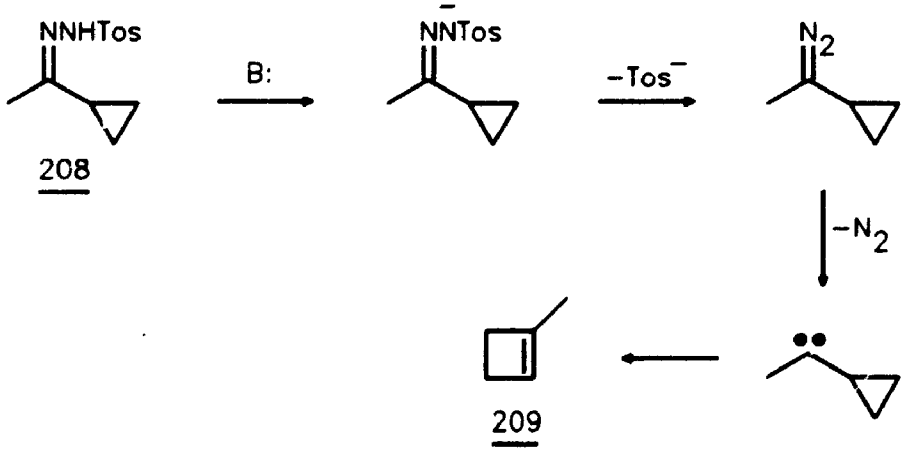
at ≈ 190°C in an inert solvent with sodium hydride gave a 92 % yield of **149**; with sodium amide as the base an 80 % yield of **149** was obtained, contaminated with ≈ 1 % 1-methylcyclobutene **209** as shown in SCHEME 89.



Base = NaH	100 %	–
$NaNH_2$	99 %	1 %
NaOMe	minor	major

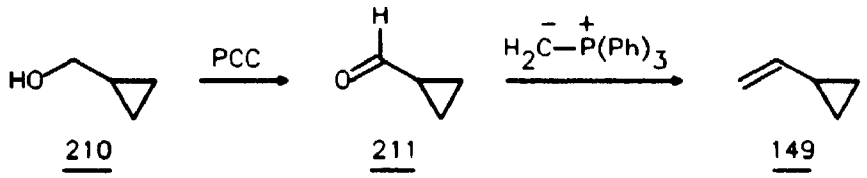
SCHEME 89

Cyclobutene **209** was the major product in the reaction of **208** with sodium methoxide. It was believed to be formed by an alternative carbene mechanism, dominating when alkoxides were used as the base.[95] In this mechanism the intermediate carbene rearranges to the alkene with the endocyclic double bond as can be seen in SCHEME 90.



SCHEME 90

An alternative method for the preparation of vinylcyclopropane was reported by Fischetti and Heck in 1985 and is presented in SCHEME 91.[98] This involved PCC oxidation of the commercially available alcohol **210** to the aldehyde **211**, followed by a Wittig reaction with methylenephosphonium reagent to give **149** in 80 % yield.



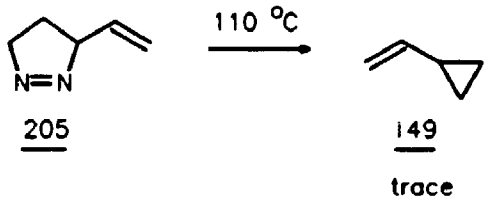
210 211 149

SCHEME 91

Two methods were investigated for the preparation of vinylcyclopropane needed for the work described in this thesis. These were thermal decomposition of 3-vinyl-1-pyrazoline and Bamford-Stevens reaction of the tosylhydrazone of cyclopropyl methyl ketone.

The synthesis of 3-vinyl-1-pyrazoline **205** was carried out according to literature procedure.[94b] Diazomethane was prepared by the method of de Boer and Backer by base treatment of N-methyl-N-nitroso-*p*-toluenesulfonamide (Diazald®).[99] This was added to 1,3-butadiene at -78°C to give, after distillation, **205** which was identified by its ^{1}H-nmr spectrum. In the spectrum the two protons on the 4-carbon appeared as a multiplet at 0.9 - 2.2 ppm, the signal of the proton on the 3-carbon was superimposed upon that of the protons on the 5-carbon as a multiplet at 4.2 - 5.0 ppm and the olefinic methylene protons showed as a multiplet (caused by the overlay of the expected pair of doublets of doublets) at 5.1 - 5.5 ppm. The olefinic methine proton was recorded as an eight line signal (doublet of doublets of doublets with coupling constants of 18, 9 and 7 Hz, respectively) at 6.0 ppm. A solution of **205** in decalin

was heated to 110°C for one hour; a slight vacuum (108 torr) was then applied and a few drops of a smelly, colourless liquid distilled out and were collected. The ^{1}H-nmr spectrum (*vide infra*) indicated the distillate to be pure **149** (as shown in SCHEME 92). However, the conversion was extremely low and this method could not be used to prepare vinylcyclopropane in the amounts required for cycloaddition with **115**.



205 → 149 (trace)

SCHEME 92

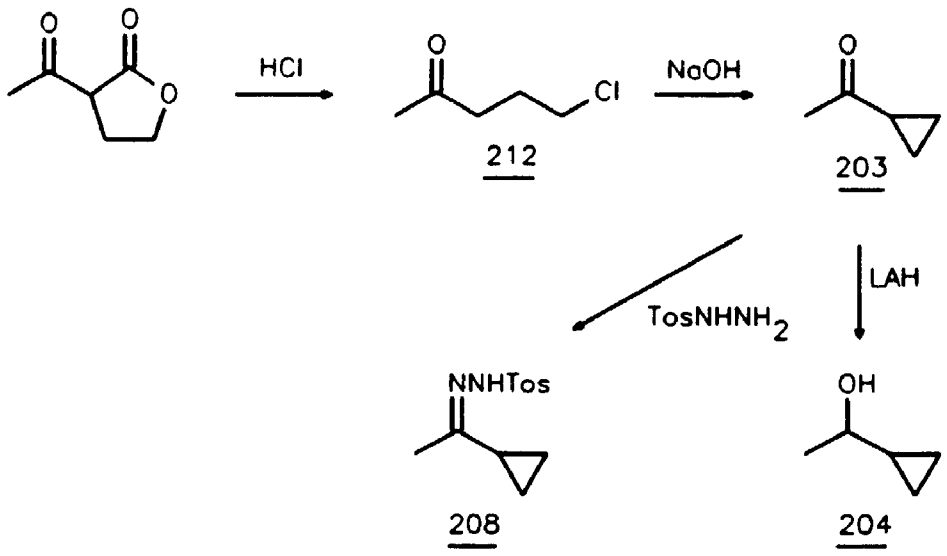
The other route of preparation of vinylcyclopropane was more promising because the reported absolute yields were quite high.[95] Cyclopropyl methyl ketone **203** was prepared according to the procedure described by Cannon and coworkers.[100] This involved acid hydrolysis of α-acetyl-γ-butyrolactone to give 5-chloro-2-pentanone **212** which was identified by its ^{1}H-nmr spectrum. The spectrum showed the presence of two triplets at 3.58 and 2.65 ppm corresponding to the methylene group bearing the chlorine and that situated α to the carbonyl group, respectively. The remaining methylene group appeared at 2.03 ppm as a multiplet and the methyl singlet appeared at 2.17 ppm. Base induced ring closure of **212** led to the formation of **203**. Its ^{1}H-nmr spectrum showed a methyl singlet at 2.24 ppm and a triplet of triplets at 1.95 ppm, corresponding to the cyclopropyl methine proton α to the carbonyl. The other signals were shifted upfield, as expected for cyclopropyl protons[39], and appeared as two sets of multiplets (accounting for two protons each) resembling doublets of triplets rather

than the expected doublets of doublets of doublets at *ca.* 0.9 and 1.0 ppm. In the infrared spectrum a band above 3000 cm^{-1} was observed, characteristic of cyclopropyl compounds, in addition to the carbonyl stretch at 1710 cm^{-1}.[39]

Reaction of **203** with tosylhydrazine in refluxing ethanol led to the formation of the hydrazone **208** obtained as white crystals with a melting point of 121°C (lit.[95] 123°C). Its ^{1}H-nmr spectrum showed the presence of two aromatic doublets at 7.83 and 7.30 ppm in addition to two methyl singlets (one at 2.43 ppm representing the methyl group *a* to the former carbonyl carbon and one at 1.68 ppm for the methyl group on the aromatic ring). Cyclopropyl hydrogen signals were observed as multiplets below 1 ppm while the hydrogen on the nitrogen was not identified.

Ketone **203** was also reduced with lithium aluminum hydride[101] to the alcohol **204** which was identified by its spectral properties. In the ^{1}H-nmr spectrum the signal for the methyl group appeared as a doublet at ≈ 1.24 ppm due to coupling with the methine proton on the neighbouring carbon. The latter was observed as a doublet of quartets at 3.04 ppm. The hydroxyl proton appeared as a broad singlet at 1.73 ppm whereas the cyclopropyl methine came as a multiplet at 0.8 - 1.0 ppm and the cyclopropyl methylenes as multiplets at 0.1 - 0.3 and 0.4 - 0.5 ppm, each integrating for two protons. The infrared spectrum revealed the absence of a carbonyl stretch and the presence of a strong, wide band from 3100 - 3800 cm^{-1} corresponding to the hydroxyl function. A weak band just above 3000 cm^{-1} indicated the presence of the cyclopropyl ring. The preparation and reactions of **203** are shown in SCHEME 93.

The purpose of the reduction of **203** to **204** was to allow subsequent conversion of the hydroxyl function into a better leaving group and attempt an elimination reaction to prepare **149**.[102] Unfortunately it was not possible to convert **204** cleanly to its acetate or tosylate and consequently this route was abandoned.

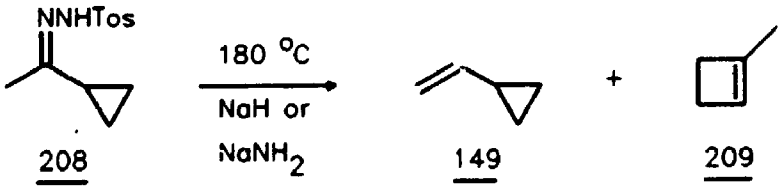


SCHEME 93

The first attempt to obtain vinylcyclopropane by heating the hydrazone **208** in decalin with sodium hydride did not result in any product formation and consequently butyllithium was substituted as the base. However, again no product was formed. In a further attempt a fresh dispersion of sodium hydride was utilized and a trap cooled to -78°C was used to collect the products. The reaction mixture was heated in a nitrogen atmosphere and after one hour at 180°C a small amount of distillate was obtained. Spectroscopic evidence indicated that the product was a mixture of **149** and an unidentified compound; the latter was tentatively assigned as 1-methylcyclobutene **209** based upon literature precedent.[95] The ^{1}H-nmr spectrum of the distillate showed the expected signals for **149**. Two quite symmetrical multiplets, each integrating for two protons, were observed centred at 0.38 and 0.68 ppm, corresponding to the cyclopropyl methylene protons. Another symmetrical ten line signal at 1.38 ppm was assigned to the cyclopropyl methine proton. The olefinic signals were nicely resolved; the methine appeared as a doublet of doublets of doublets at 5.30 ppm with coupling

constants of *ca.* 17, 10 and 8.5 Hz while each o the two methylene protons were recorded as doublet of doublets with coupling constants of *ca.* 17 and 2 Hz (5.04 ppm) and 10 and 2 Hz (4.83 ppm), respectively, with line broadening due to long range allylic coupling. The ^{13}C-nmr spectrum confirmed the identification since all peaks expected for **149** could be assigned: the two equivalent cyclopropyl methylenes gave rise to a signal at 6.67 ppm, the cyclopropyl methine was observed at 14.76 ppm and the olefinic carbons were observed at 111.50 (methylene) and 142.61 ppm (methine). These data are in good agreement with literature values.[103]

Repetition of the experiment increased the fraction of the impurity which was identified by its proton and carbon nmr spectra as 1-methylcyclobutene **209**. In the ^{1}H-nmr spectrum resonances at 1.64 ppm (multiplet integrating for three protons, methyl group), 2.27 and 2.36 ppm (each a multiplet accounting for two protons, ring methylenes) and 5.55 ppm (one proton multiplet, olefinic ring methine) were observed. In the ^{13}C-nmr spectrum the following peaks were assigned: the methyl peak at 16.88 ppm, the methylenes at 26.45 and 32.67 ppm, the quaternary carbon at 146.47 ppm and the olefinic methine carbon at 127.90 ppm. Again these are data in good accordance with published values.[104] At no time was any cyclopentene observed which is known to be a thermal rearrangement product of **149**.[94b] The thermolysis of **208** is shown in SCHEME 94.



SCHEME 94

Since both **149** and **209** have similar boiling points of ≈ 40°C[93,104] separation by distillation was not possible. Also, because of their low volatilities chromatographic separation was also not feasible. Consequently attempts were made to optimize the Bamford-Stevens reaction of **208** induced by sodium hydride as a base. The ratios of **149** to **209** obtained in various experiments was measured by ^{1}H-nmr spectroscopy and are reported in TABLE 26. The results reveal that it was not possible to reproduce Kirmse's finding that none of the cyclobutene **209** is formed when sodium hydride is used as a base.[95]

TABLE 26: Preparation of vinylcyclopropane using sodium hydride

Ratio **149**:**209**	Combined yield	References
no **209**	92 %	Kirmse et al.[95]
4.56:1	50 %	This study
6.69:1	18 %	"
2.57:1	52 %	"
2.70:1	32 %	"
4.00:1	24 %	"
4.88:1	53 %	"

In view of these results the base was changed to sodium amide which was freshly prepared prior to each reaction by reacting sodium metal with liquid ammonia in the presence of ferric nitrate.[105]

The purity of the vinylcyclopropane samples obtained in a series of reactions increased significantly but again Kirmse's results could not be duplicated, as can be seen from the results summarized in TABLE 27.

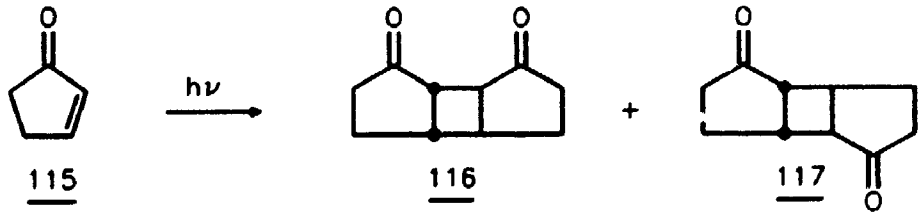
TABLE 27: Preparation of vinylcyclopropane using sodium amide

Ratio 149:209	Combined yield	References
142:1	80 %	Kirmse et al.[95]
7.33:1	67 %	This study
24.0:1	46 %	"
32.3:1	57 %	"
24.0:1	51 %	"

The purity of **149** obtained was, however, judged high enough for use in the 2 + 2 photocycloaddition reaction with cyclopentenone.

2.2.3 Photodimerization of Cyclopentenone 115

In order to be able to recognize dimers of cyclopentenone formed in the irradiations with vinylcyclopropane a separate irradiation was carried out using only **115**. As described in publications by Eaton, Wagner and others, two dimers, **116** and **117**, were observed when a cyclohexane solution of **115** was irradiated as shown in SCHEME 95.[26,59,71-73] The ratio of the two adducts was ≈ 2:1 and from the literature data the more abundant isomer was assigned as the head-to-tail adduct **117**.[71,72] The dimers were identified by gc/ms; no further characterization was carried out since this experiment was only performed to establish gc retention times for the dimers.



115 116 117

SCHEME 95

2.2.4 Irradiation of Cyclopentenone 115 and Vinylcyclopropane 149

A mixture of **115** and **149** in a molar ratio of 1:3 was irradiated in cyclohexane with Pyrex and water filtered light ($\lambda > 300$ nm) and after two hours formation of six products was observed in a ratio of ≈9:4.6:4.7:15:1:4. The products are listed from lower to higher retention times and are designated as compounds **A** - **F**. The last two peaks (ie. compounds **E** and **F**) were identified by gc and gc/ms as dimers of **115**. Coupled gas chromatography/mass spectroscopy indicated molecular weights of 150 for the other four peaks (i.e. compounds **A** - **D**), indicating them to be 1:1 adducts of **115** and **149**.

The solvent was then carefully removed at reduced pressure. It was found to contain still unreacted starting materials; consequently it was irradiated further. After another two hours the solvent was again removed in vacuo and, after addition of more **115**, irradiated further. This procedure was repeated twice more and afterwards the residues, which were identical in composition, were combined to give a mixture of the adducts **A** - **D** in a ≈1.6:1:1.4:3.5 ratio with small amounts of dimers present. A ^{1}H-nmr spectrum of the crude reaction mixture showed peaks in the high field region (< 1 ppm) indicating cyclopropyl hydrogens as well as olefinic signals to lower field (> 5 ppm). The latter signals were expected to be present if radical rearrangement had taken place.

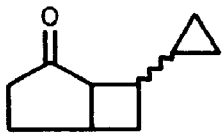
Brief treatment of part of the mixture with a solution of bromine resulted in a large depletion of adduct **A** and a slight depletion of adduct **D**; adducts **B** and **C** were not affected. This indicates that **B** and **C** do not contain any olefinic double bond; they were thus suspected to be the 2+2 cycloadducts of **115** and **149**.

Preparative tlc allowed for removal of the dimers and partial separation of the adducts into two fractions. The more polar fraction (I) contained mainly **B** and **C** whereas fraction II (containing mostly **A** and **D**) was slightly less polar.

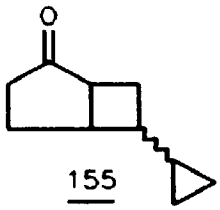
A ^{1}H-nmr spectrum of fraction I revealed the presence of cyclopropyl protons in the range of 0.1 - 0.5 ppm and signals in the chemical shift range of 1.5 - 2.8 ppm (which appeared as a large multiplet) consistent with the presence of saturated cyclobutane and cyclopentanone structures. Only small signals were observed in the olefinic region; this is consistent with compounds **B** and **C** being 2 + 2 cycloadducts (as indicated in the bromine test above) if the weak olefinic signals are attributed to impurities due to imperfect separation of **A** and **D** from **B** and **C**. Further preparative gas chromatography of the mixture of **B** and **C** present in fraction I yielded three new fractions. These were analyzed by ^{1}H-nmr spectroscopy.

The first of the three fractions contained mainly compounds with cyclopropyl protons and only traces of compounds possessing olefinic signals; the second fraction contained only compounds with cyclopropyl protons and no olefinic material while the third (and minor) fraction contained almost exclusively material with olefinic protons. Comparison of these spectra with the ^{1}H-nmr spectrum of fraction I showed that all peaks recorded there were accounted for in the three fractions obtained by preparative gc.

From the spectral data it was concluded that compounds **B** and **C** present in fraction I were predominantly stereo- and regioisomers of 2 + 2 photocycloadducts **154** and **155** contaminated with small amounts of material containing olefinic hydrogens (compounds **A** and **D**) as shown below.



154



155

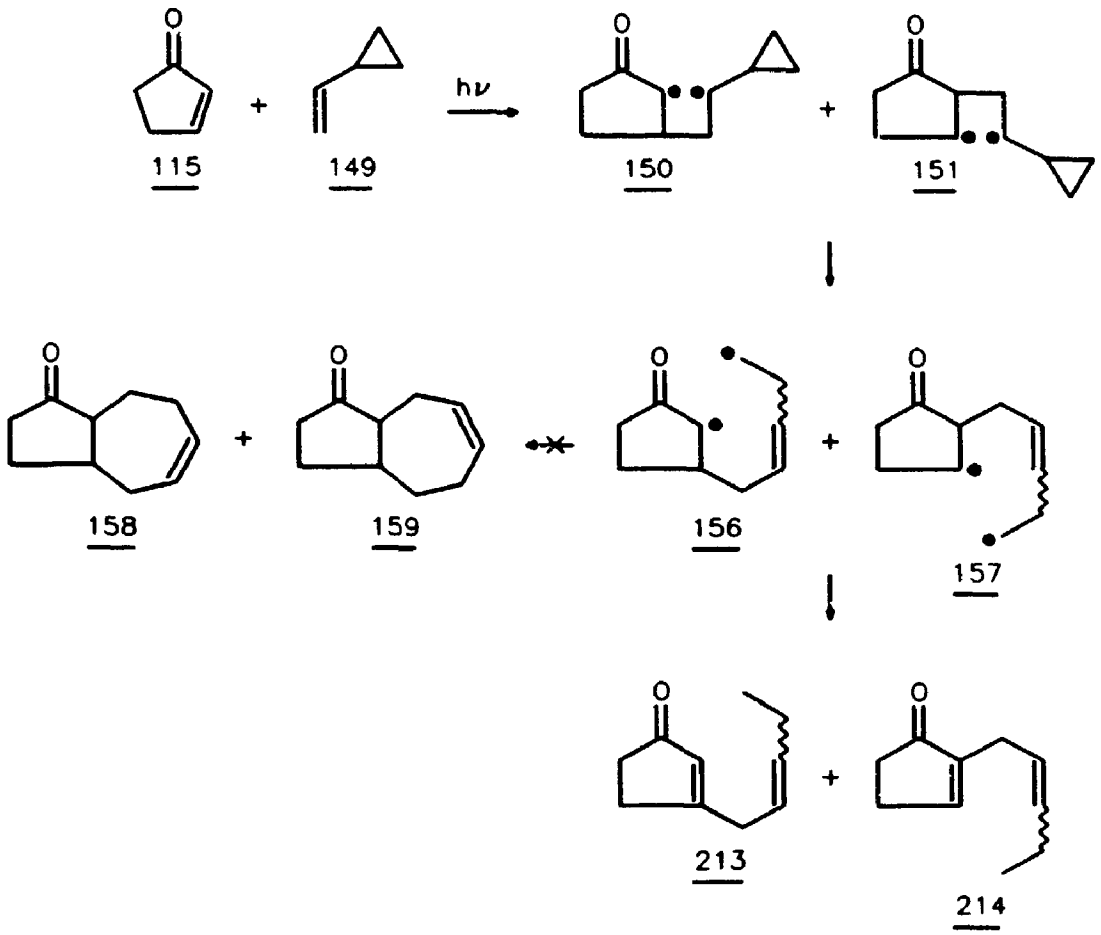
Because of the small amount of material available no further investigations into the stereo- and regiochemistry of compounds **B** and **C** were carried out. The mass spectra obtained for the separated 2+2 adducts matched those obtained from the original irradiation mixture; the weak molecular ions observed (≈8 %) are explained by efficient ring cleavage of the cyclobutane ring leading to an intense (100 %) fragment at 68, which is the mass of vinylcyclopropane. The low intensity (22 %) of the fragment peak with a mass of 82, which is the mass of cyclopentenone (**115**), indicates further fragmentation of this fragment, indicative by the presence of an intense (78 %) peak at 53 which is also present in the mass spectrum of cyclopentenone. This fragmentation pattern was not observed in compounds **A** and **D**.

The ^{1}H-nmr spectrum of fraction II (containing compounds **A** and **D**) showed the absence of cyclopropyl proton resonances and the presence of olefinic signals at ≈5.5 ppm indicative of non-conjugated 1,2-disubstituted double bonds[39]. Such signals were expected if compounds **A** and **D** were products such as **158** and **159** which could be derived from rearrangement of the biradicals **150** and **153** to biradicals **156** and **157**. However, in addition to these olefinic resonances, signals were observed at ≈6 and ≈7.5 ppm, in the chemical shift range characteristic of the α- and β-protons of cyclopentenones.[39,91a] Since all starting materials had been removed the source of these signals could not be **115** but had to be the products **A** and **D**.

Fraction II was separated by preparative gas chromatography into three fractions (II.I - II.III) which were analyzed by analytical gc. Fraction II.I (shortest retention time) proved to be essentially compound **A**, fraction II.III (longest retention time) was almost exclusively compound **D** whereas fraction II.II was obtained in only trace amounts and contained two compounds different from compounds **A** and **D**. ^{1}H-Nmr spectroscopy of II.I showed the presence of a triplet at ≈0.9 ppm integrating for three protons which pointed to the methyl portion of an ethyl group. Olefinic signals were seen at 6.05 ppm (narrow multiplet) and two more multiplets at 5.30 and 5.45 ppm, respectively. Each of the olefinic multiplets accounted for one proton, a finding which was not in agreement of the anticipated cycloheptene structures **158** or **159**. These ^{1}H-nmr data along with the fact that the mass spectrum of this fraction indicated that compound **A** was an isomer of the 2+2 adducts led to the conclusion that the structure of compound **A** was either **213** or **214**. These compounds could be formed as shown in SCHEME 96 below by intramolecular disproportionation of biradicals **156** and **157** rather than the expected closure to **158** and **159**.

Comparison of the chemical shift of the olefinic enone proton of compound **A** with those of **115** suggested that it was in the α-position (see discussion in section 2.2.1) and consequently that the side chain had become attached to the β-position of the enone as shown in structure **213**.

This assignment was further supported by the fact that the signal for the enone proton of compound **A** was a narrow multiplet indicating only small (long range) couplings whereas if it were the β-proton one would expect larger couplings due to vicinal coupling to the methylene group in the 4-position of the enone ring. A two dimensional ^{1}H-nmr spectrum of compound **A** yielded the expected coupling relationships for structure **213**.



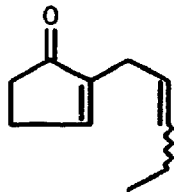
SCHEME 96

Thus the side chain methyl group was found to be coupled into a multiplet (accounting for two protons) at ≈2 ppm. This methylene (the 4'-position of the side chain) was further coupled into the olefinic region by vicinal and allylic couplings. A multiplet (two protons) at ≈3 ppm was assigned to the methylene in the 1'-position of the side chain, while the remaining two methylene groups of the cyclopentenone ring were observed as multiplets at ≈2.1 and ≈2.4 ppm, respectively.

Due to the extensive couplings of the side chain olefinic protons and their close chemical shift it was not possible to determine the stereochemistry about the double

bond from the ^{1}H-nmr spectra or decoupling experiments. However, with the help of two dimensional J-resolved spectroscopy this problem was solved.[40,50] In this technique the spectrum is recorded in one dimension and the couplings of each signal appear in the other dimension. Using this technique it was possible to extract from the olefinic region evidence for a doublet with a coupling constant of ≈ 8 - 9 Hz. This small value suggests that the double bond in **213** possesses *cis*-stereochemistry since vicinal *trans* couplings are usually in the range of 12 ppm or larger.[39,91a]

Fraction II.III containing mainly compound D was also analyzed by ^{1}H-nmr spectroscopy and was assigned structure **214**.

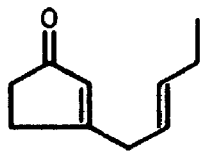


214

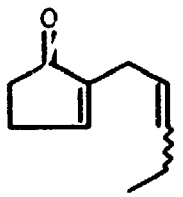
Thus a methyl group at 0.96 ppm was observed as a triplet suggesting that it was part of an ethyl group. Multiplets (accounting for two protons each) were observed at 2.05, 2.43, 2.58, 2.88 and 5.50 ppm. The last multiplet is at the chemical shift expected for the side chain olefinic protons. Another multiplet (one proton) was seen at 7.29 ppm. The chemical shift of this signal indicates it to be the olefinic hydrogen in the β-position of the cyclopentenone ring, as established in section **2.2.1**, and consequently establishes the position of the 2-pentenyl substituent as being in the α-position of the enone. Two dimensional ^{1}H-nmr spectroscopy confirmed the analysis; the methyl group was coupled into the two proton multiplet at 2.05 ppm which in turn showed couplings to the olefinic signal at 5.5 ppm. That latter coupled into the signal

at 2.88 ppm which allowed the assignment of this signal as the methylene group in the 1'-position of the side chain. As was the case for **213** the signal of the aliphatic region shifted to lowest field was derived from the methylene group with two double bonds as neighbours. Because of the very close chemical shift of the side chain olefinic protons (which gave rise to a single multiplet) combined with the small amount of fraction **II.III** obtained, no determination of the stereochemistry about the side chain double bond could be made. Thus compound **D** could only be identified as a single geometric isomer of **214**.

Fraction **II.II**, which was obtained in only minute amounts, showed in its ^{1}H-nmr spectrum the presence of two cyclopentenone olefinic signals at ≈6.15 and ≈7.65 ppm. The chemical shifts of these were not identical to the corresponding signals in compounds **A** and **D**. Other olefinic multiplets at ≈5.4 ppm were recorded as well as multiplets in the aliphatic region and resonances for the methyl parts of ethyl groups. It was thus deduced that because of the similarities in the spectra of fraction **II.II** to compounds **A** and **D** it was likely that fraction **II.II** was a mixture of *trans*-**213** and the alternative stereoisomer of **214**. No further investigation of these compounds was carried out.



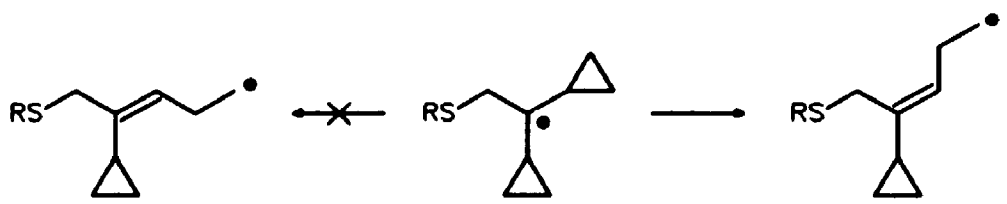
trans-213



214

The fact that the *cis*-isomer of **213** was formed in higher amounts than the *trans*-isomer requires some comment. Molecular model studies show that biradical **156**

can only acquire a conformation favourable for intramolecular hydrogen transfer if its double bond is *cis*-substituted. Additional support for the regioselectivity observed comes from results published by Griller et al. who investigated the rearrangements of sulfur substituted cyclopropylalkyl radicals to substituted 3-buten-1-yl radicals as shown in SCHEME 97.[106] They found a remarkable regioselectivity in that only the *Z*-isomer of the rearranged radical was observed and none of the *E*-isomer, which they explained by assuming that the cyclopropylcarbinyl radical reacts from its most probable conformation characterized by the least steric interactions and the maximized overlap between the cyclopropyl ring orbitals and the unpaired electron.



R = alkyl, aryl

SCHEME 97

2.3 Photocycloaddition of 1,6-Heptadiene 187 and Cyclopentenone 115

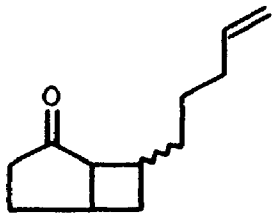
Irradiation of a cyclohexane solution of **187** and **115** (molar ratio ≈3:1) with Pyrax and water filtered light afforded a mixture of five products in a ratio of ≈ 1:6.2:6.9:2.2:1.5 (in order of increasing retention time). Gas chromatography/mass spectroscopy showed the first three to be 1:1 adducts of **187** and **115** (molecular ion mass of 178) whereas the last two had a mass of 164, indicating that they were

dimers of **115**. The latter assignment was supported by comparison with the products of the irradiation of **115** in the absence of olefin (see section **2.2.3**). A ^{1}H-nmr spectrum of the mixture following removal of unreacted **187** revealed the presence of many signals in the 1 - 3 ppm region as well as a pair of olefinic multiplets at ≈4.9 and ≈5.7 ppm in a ratio of 2:1; since no more **187** was present these had to be derived from adducts with a terminal double bond still intact. The chemical shifts recorded in the olefinic region were typical for terminal alkenes with the methylene protons appearing almost 1 ppm towards lower field than the methine signals.[39]

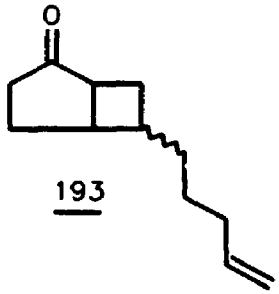
Separation of the product mixture by preparative tlc allowed removal of the dimers of **115** and the isolation of a fraction which gc analysis indicated to be a mixture of the three adducts in a ratio of ≈1:5:2. In addition a fraction containing mainly one adduct was isolated; the gc retention time was identical with that of the component with the longest retention time in the mixture containing three adducts. Thus, in the original mixture, which gc indicated to be a mixture of three adducts, the component with the longest retention time is in act a mixture of two adducts with different mobilities on silica gel. The ^{1}H-nmr spectra of both fractions confirmed that the adducts present contained terminal double bonds (as noted above). This conclusion was supported by their mass spectra; efficient allylic fragmentation was observed as judged by the appearance of a fragment corresponding to M^+-41. This pattern is typical of carbon chains with a terminal double bond[39], and suggests strongly that all four adducts are cyclobutane products derived from 2+2 cycloaddition of the enone to one terminus of the diene **187**. Thus the four adducts are two pairs of diastereomers possessing structures **192** and **193** as shown below.

The olefinic region of the ^{1}H-nmr spectrum of the fraction containing a single adduct could be analyzed partially. The lower field portion exhibited for the double

bond methine a ten line signal derived from its coupling to the neighbouring aliphatic methylene group and each of the vicinal olefinic protons. This doublet of doublets of triplets was reduced to a symmetrical ten line signal due to overlap of some of the signals. The following coupling constants could be extracted: 6.68 Hz (to the aliphatic methylene group protons), 10.20 Hz (to the *cis* olefinic proton) and 17.02 Hz (to the *trans* olefinic proton). The signal due to the olefinic methylene protons was insufficiently resolved for coupling constants to be extracted.

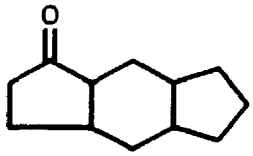


192



193

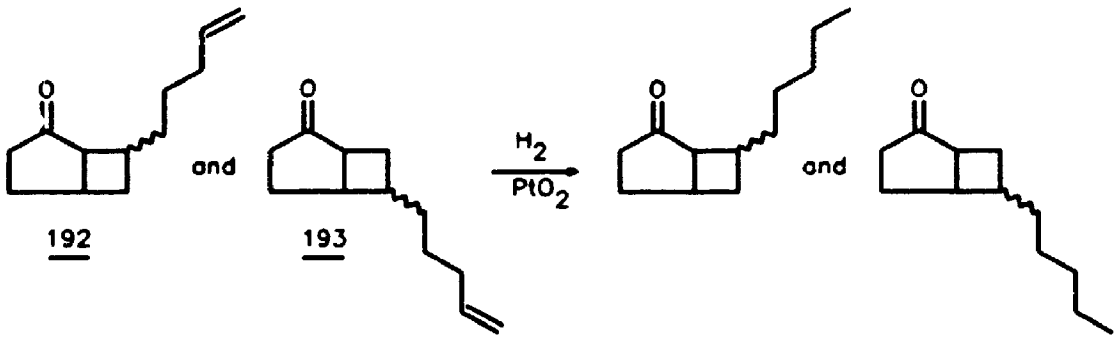
No evidence was found for formation of products derived from radical rearrangement of the intermediate 1,4-biradical such as the tricyclic compound **196**.



196

However, it was realized that traces of stereoisomers of **196** could be present undetected in the fraction containing three of the adducts **192** and **193** if they

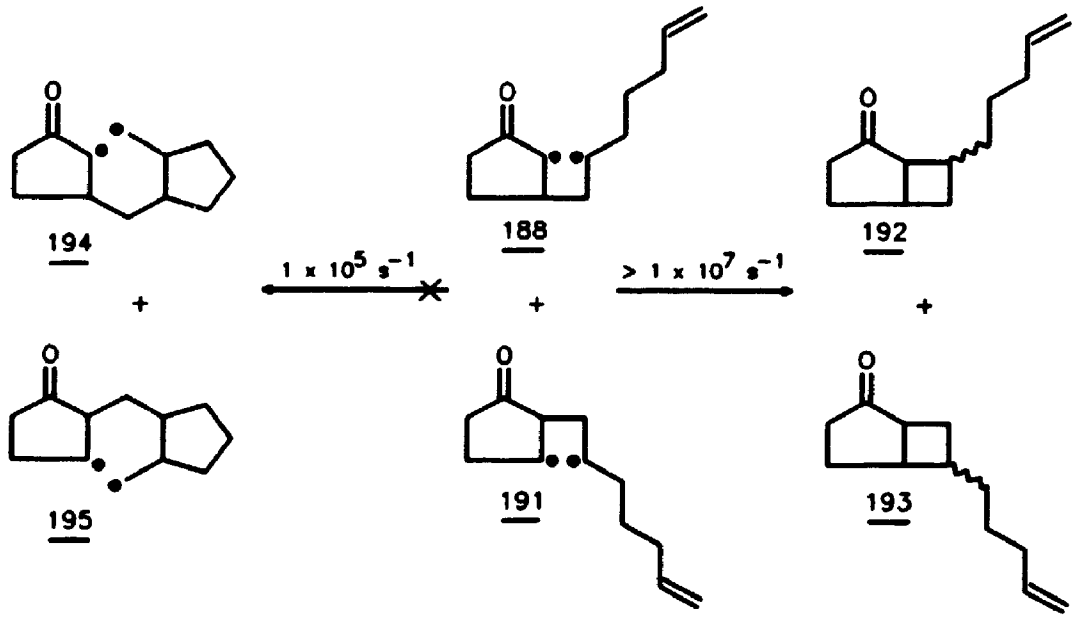
possessed similar gc retention times and mobility on silica gel. Traces of **196** would also not be detected in the ^{1}H-nmr spectra of the adducts since the signals would be obscured by those of **192** and **193**. In order to detect isomers of **196**, the fractions containing the partially separated adducts as well as the original irradiation mixture were hydrogenated with hydrogen gas and platinum(IV) oxide as a catalyst. Gc analysis indicated that the peaks due to the 1:1 adducts had all been completely replaced by peaks with slightly longer retention times. In addition the peaks due to the dimers of **115** resent in the crude reaction mixture were not affected by the hydrogenation process. Gc/ms analysis of the hydrogenated adducts indicated that they possessed masses of 180, two mass units higher than the original adducts as expected if one double bond per adduct had been hydrogenated as shown in SCHEME 98. ^{1}H-Nmr spectra of the hydrogenated mixture also indicated that the olefinic signals had disappeared completely. Most importantly, the gc and gc/ms of the hydrogenated adducts or reaction mixture showed no evidence for the presence of unchanged species with masses of 178; this conclusively demonstrates that no radical rearrangement products with structure **196** were formed.



SCHEME 98

2.4 Discussion of Results

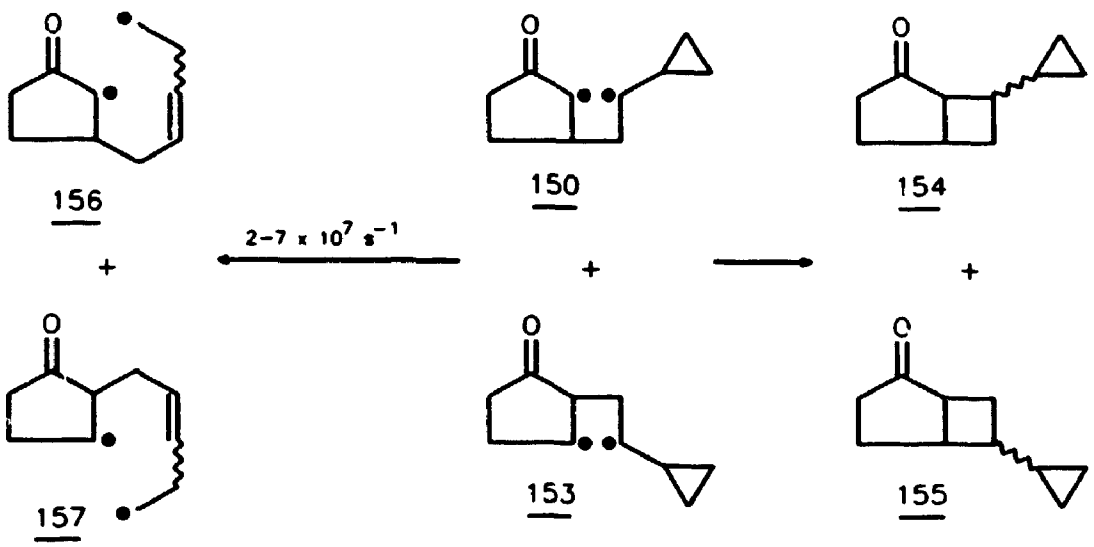
Since no evidence was found for biradical rearrangement in the reaction of cyclopentenone with 1,6-heptadiene it was concluded that the lifetime of the 1,4-biradical intermediates were too short to allow time for such a reaction to occur. The rate constant for rearrangement of a 1-methyl-5-hexen-1-yl radical to a (2-methylcyclopentyl)methyl radical has been determined to be *ca.* 1×10^5 s^{-1}.[89b] If it is assumed that 1 % rearrangement products could have been detected, then the 1,4-biradical must close to **192** and **193** with a rate constant of at least 1×10^7 s^{-1}. Consequently it can be concluded that the biradicals **188** and **191** shown in SCHEME 99 possess a lifetime of 10^{-7} s or less.



SCHEME 99

On the other hand when cyclopentenone was irradiated in the presence of vinylcyclopropane not only were 2+2 cycloadducts **154** and **155** observed but also

comparable amounts of products **213** and **214** were obtained in a ratio of cycloadducts to rearranged products of ≈ 1:2.6. Products **213** and **214** are presumably derived from rearrangement of the primary biradicals **150** and **153** (as shown in SCHEME 100) to **156** and **157** and subsequent intramolecular disproportionation.

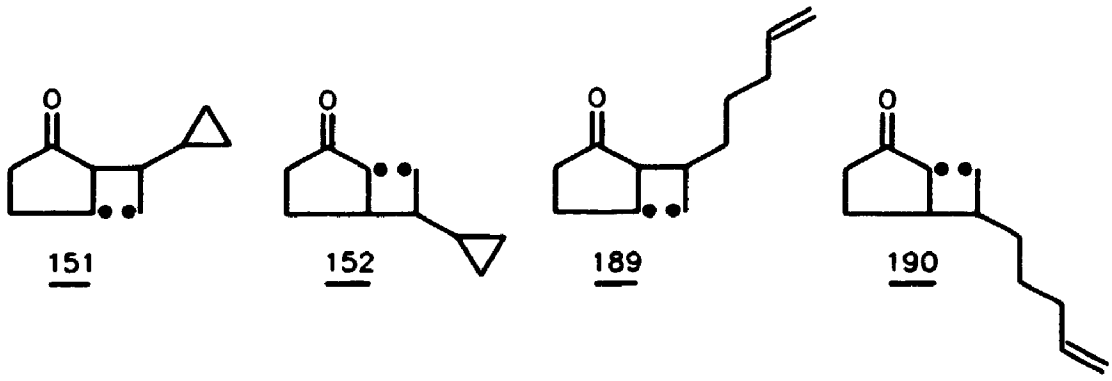


SCHEME 100

The rate constant for ring opening of the cyclopropylmethyl radical to the 3-buten-1-yl radical has been determined[87a-d] to be *ca.* 1 - 2 x 10^8 s^{-1}. However, methyl substitution on the radical centre slows this down by about one order of magnitude to *ca.* 2 - 7 x 10^7 s^{-1}.[87c,e] If radicals **150** and **153** open to **156** and **157** at similar rates then the sum of their rate constants for formation of the 2 + 2 adducts **154** and **155**, respectively, plus the sum of their rate constants for reversion to the starting materials has to be comparable with the rate constant for rearrangement. Hence the lifetimes of **150** and **153** have to be of the order of *ca.* 20 - 50 ns.[107] This

value compares favourably with data obtained by Caldwell and Schuster* for the lifetimes of the biradical intermediates in the photodimerization reaction of cyclopentenone which were measured by photoacoustic calorimetry to be ≈ 37 ns.[82b]

The estimated biradical lifetimes are based on the assumption that none of the 2 + 2 cycloadducts are derived from the biradicals containing a primary radical centre, ie. **151**,**152**,**189** and **190**.



151 **152** **189** **190**

As already pointed out above, Hastings and Weedon have subsequently shown that this assumption is valid when they investigated the photocycloaddition reaction of **115** with ethyl vinyl ether.[69,81] Trapping of the intermediate biradicals with hydrogen selenide did not lead to any products derived from primary radical containing biradicals. Earlier support for this assumption came from the fact that it is known that simple alkyl radicals react regioselectively with non-symmetrical alkenes. The major product is always derived from attack at the less substituted end of the double bond leading to the radical centre at the more highly substituted carbon as indicated in SCHEME 101.[108]

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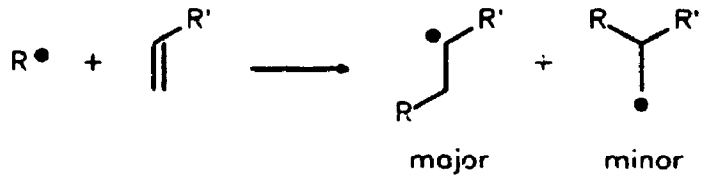
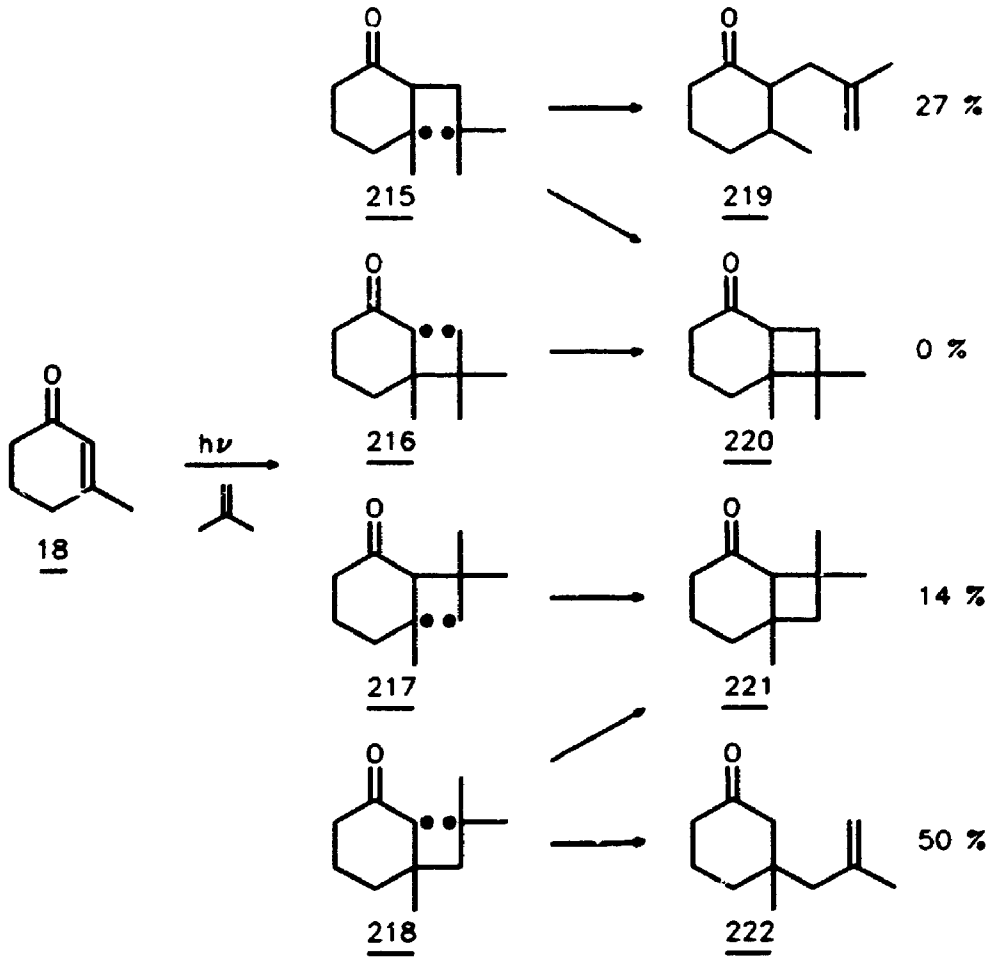
* Recently Schuster and coworkers were able to measure lifetimes of triplet biradicals implicated in the photocycloaddition of enones and alkenes, using photoacoustic calorimetry.[144] The values ranged from 20 to 600 ns.



SCHEME 101

Simple alkyl radicals, however, are not necessarily perfect models for the triplet excited state of an enone. Better evidence for the initial regiochemistry of addition of an enone to an alkene could be found in the observed products of photoaddition between cyclohexenones and 2-methylpropene.

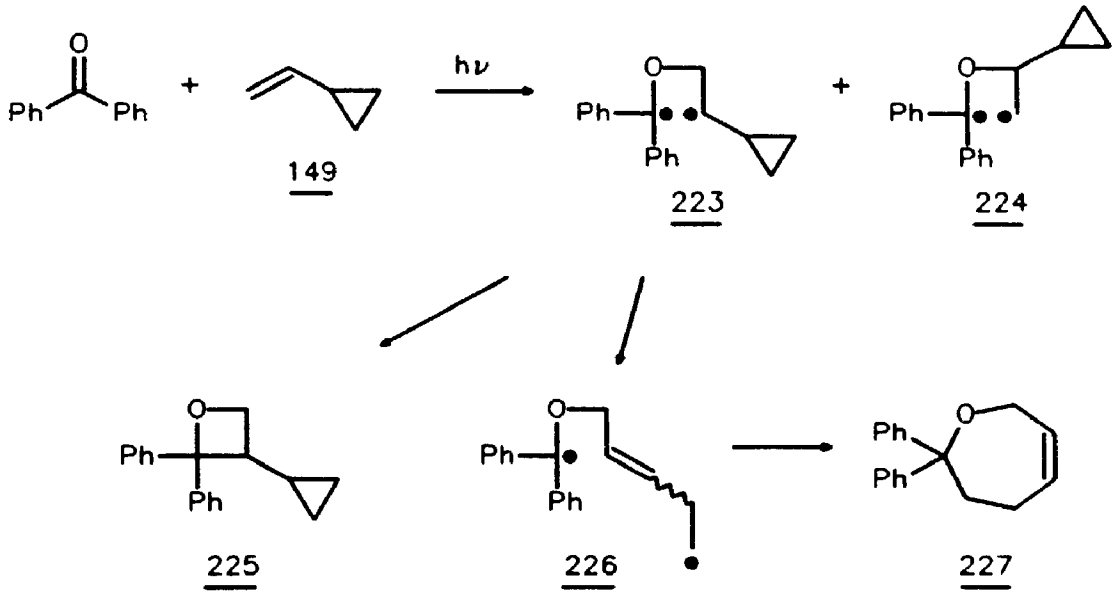


SCHEME 102

For example the photochemical reaction of 3-methylcyclohexenone **18** with 2-methylpropene has been reported to give not only 2+2 cycloadducts but also considerable amounts of products derived from disproportionation of the intermediate biradicals.[70] The products and yields are given in SCHEME 102. Products **219** - **222** can, in principle, be derived from the four biradicals **215** - **218**. Of these, compound **219** most come exclusively from biradical **215** while compound **222** must come exclusively from biradical **218**. Of the isolated products at most 14 % (ie. **221**) could have their origin in a biradical resulting from addition of the enone triplet to the more substituted end of the alkene (ie. primary radical containing biradical **217**). However, a weakness of this argument is that substantial quantities of biradicals **216** and **217** (containing primary radical centres) may in fact be formed, but they revert preferentially to starting materials rather than proceeding to products.

Evidence that triplet excited states of ketones add regioselectively to mono-substituted alkenes to yield biradicals which do not contain primary radicals has been obtained by Nishida et al. who investigated the Paterno-Büchi reaction of aromatic carbonyl compounds with vinylcyclopropanes. Only products derived from the biradical formed by addition of the excited ketone to the less substituted end of the alkene were obtained as shown in for the reaction between benzophenone **145** and vinylcyclopropane **149** in SCHEME 103.[84b]

The biradicals **223** and **224** are possible intermediates; however, only products derived from **223** were formed, either by ring closure to **225** or, after rearrangement to **226**, by ring closure to **227**. The fact that these workers observed products of closure of **226** rather than products resulting from intramolecular disproportionation, such as those reported in this thesis, can be explained by the absence of a suitable abstractable hydrogen adjacent to the ketyl radical centre in **226**.

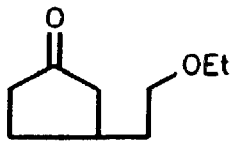


SCHEME 103

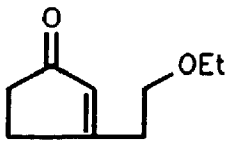
The estimated lifetime for the triplet 1,4-biradical intermediate in the photocycloaddition of cyclopentenone with vinylcyclopropane of 20 - 50 ns is towards the lower end of the range of lifetimes reported for other triplet 1,4-biradicals such as those generated in the Norrish Type II reaction or the Paterno-Büchi reaction.[80,109] These values range from ≈ 1 ns to over 2000 ns. However, they are not ideal models for the biradicals formed in the 2 + 2 cycloaddition reaction since both in the Paterno-Büchi reaction and in the Norrish Type II reaction one of the radical centres is stabilized by an oxygen function (see also footnote on page 185).

An important conclusion which can be drawn from the work described here is derived from the fact that similar quantities of **213** and **214** are formed in the reaction of cyclopentenone and vinylcyclopropane. This indicates that initial bond formation between the triplet of **115** and the olefin occurs to a similar extent at both the α- and the β-position of the enone.

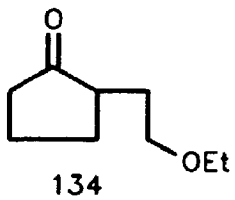
This is in accordance with subsequent work by Hastings and Weedon who have found that initial bond formation occurs at both α- and β-positions of the enone in the irradiation of **115** with ethyl vinyl ether.[69,81] Trapping of the biradicals in that reaction allowed the isolation of products **133** and **135** in similar quantities to compounds **134** and **136** which demonstrates that the initial bond forming step is not regioselective.



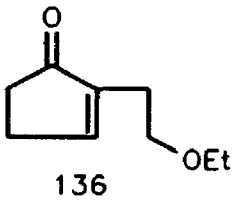
133



135

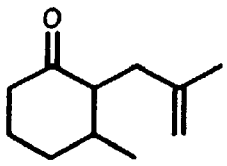


134



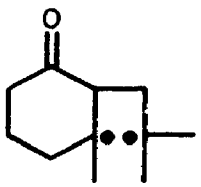
136

For cyclohexenones the same conclusion can be inferred from the nature of the products found in the reaction of **18** with 2-methylpropene.[62,70] The products of hydrogen abstraction, **219** and **222**, could only have been formed from biradicals **215** and **218**, respectively, indicating that the initial site of bonding occurs at both enone double bond positions.

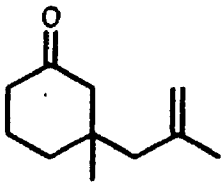


219

only from

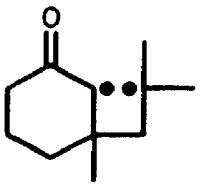


215



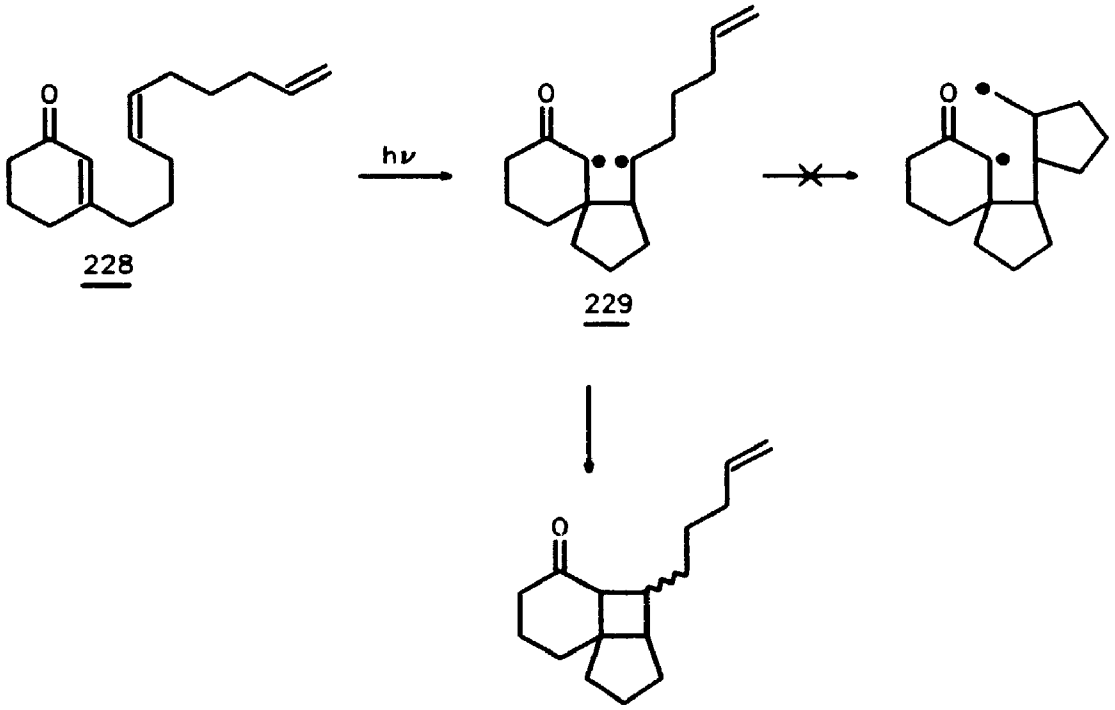
222

only from



218

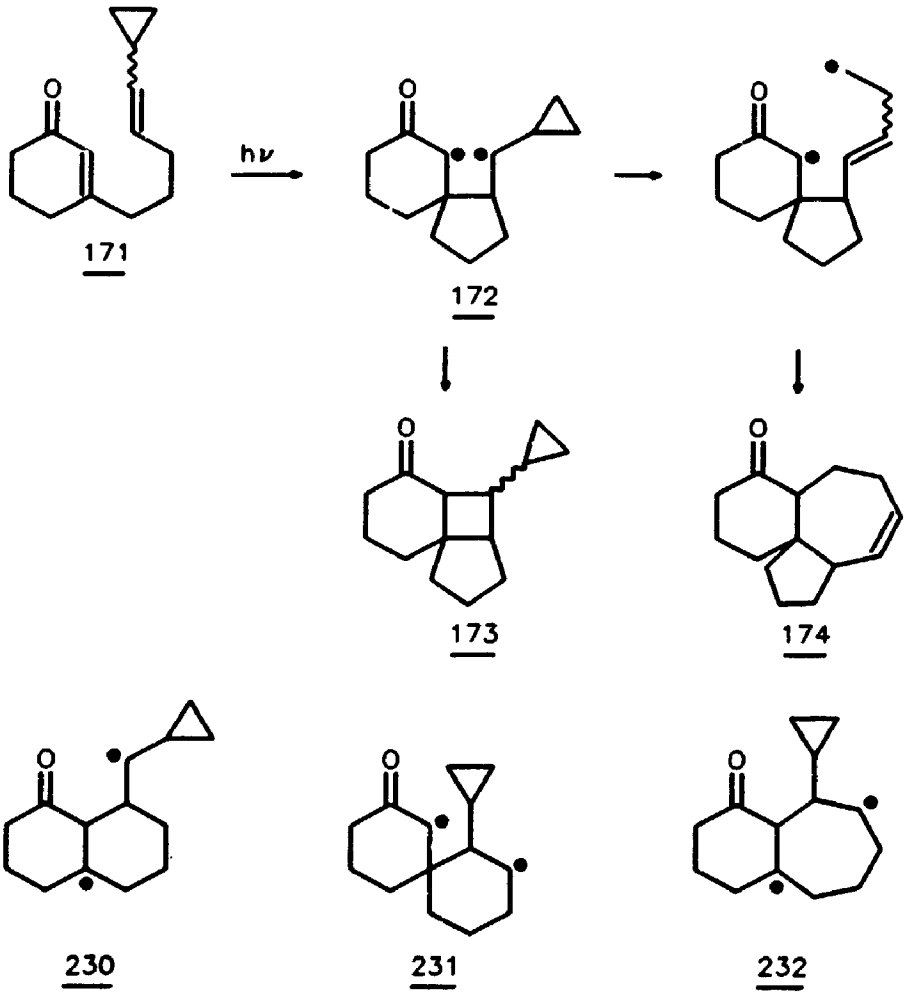
The results reported in this thesis for the photochemical reactions of cyclopentenone with 1,6-heptadiene and vinylcyclopropane are similar to those reported by Becker's group for cyclohexenones possessing 1,6-heptadiene or vinylcyclopropane substituents.[86] For example, irradiation of compound **228** only gave 2 + 2 cycloadducts and no products derived from rearrangement of biradical **229** were observed as shown in SCHEME 104, which is in accordance with the results presented in this thesis.



SCHEME 104

Similarly irradiation of compound **171** gave a mixture of **173**, the intramolecular 2 + 2 cycloadduct, and **174**, the product derived from biradical rearrangement of **172** as can be seen in SCHEME 105.[86a] No hydrogen abstraction products were observed

which was most likely due to the absence of an abstractable hydrogen on the 3-position of the cyclohexanone ring of **172**.

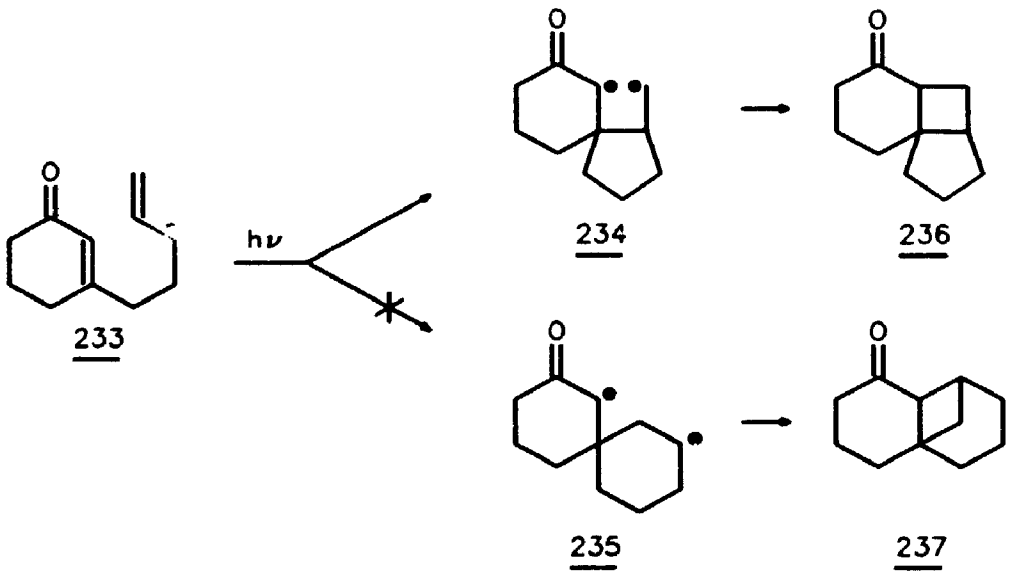


SCHEME 105

Becker concluded that in this reaction, and possibly generally in enone photocycloaddition reactions, the initial bond formation between the enone part and the alkene part occurred exclusively at the β-carbon of the enone system, a result in sharp contrast to the work described in this thesis; however, **171** was not a good

probe of the site of initial bonding since the "rule of five" would predict that only the biradical **172** would have been formed and none of the other possible biradicals **230** - **232**.

The "rule of five" frequently explains the regiochemical outcome of intramolecular enone cycloadditions.[2,110] This general rule predicts that the major regioisomeric product formed is that obtained from closure of the biradical intermediate in which a five membered ring has been formed. This is illustrated in SCHEME 106; irradiation of **233** led to **236** (*via* **234**) rather than to **237**, a reflection of the fact that **235** does not contain a five membered ring.[2]



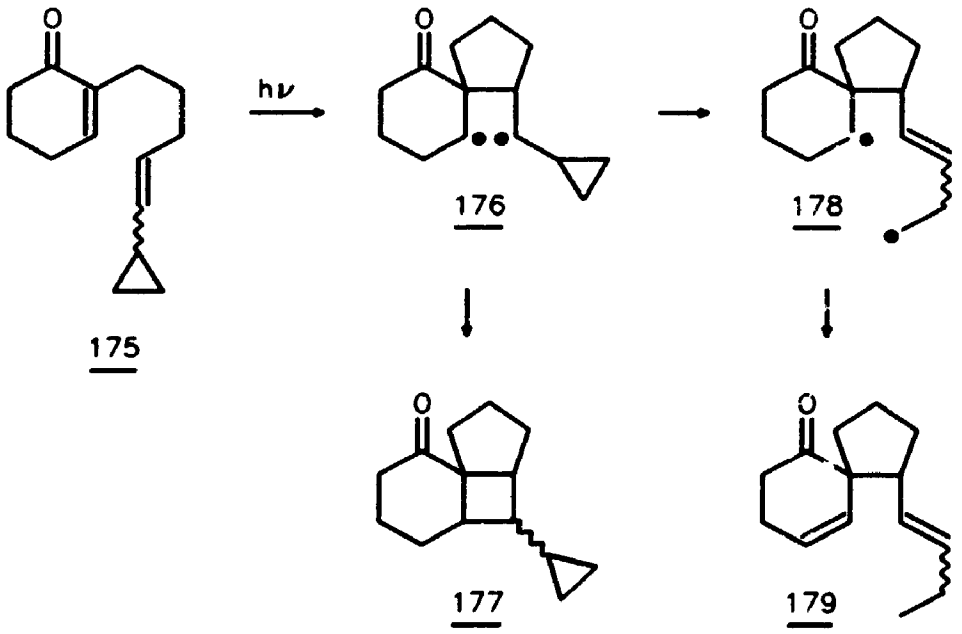
SCHEME 106

For Becker's compound **171** biradicals **230** - **232** would violate the "rule of five" whereas **172** does not; consequently, sole formation of products from biradical **172** is expected. From this it follows that Becker's claim that initial bond formation occurs exclusively and generally to the β-carbon of the enone[86a] is overstated. In fact,

in later publications Becker found evidence that in other structures initial bond formation occurs preferentially to the α-carbon of the enone.[86b,c]

Thus in the case of compound **175** Becker obtained, apart from 2+2 cycloadducts **177**, products **179**, derived from intramolecular disproportionation in the rearranged biradical **178**.[86c] As indicated in SCHEME 107 these must be derived from a biradical produced from bonding to the α-carbon of the enone.

It is also interesting to note that no ring closure products containing cycloheptene rings were found. This is in agreement with the findings reported in this thesis that intramolecular hydrogen abstraction is a viable alternative to ring closure to cycloheptene rings for rearranged biradicals, if a suitable hydrogen atom is accessible.



SCHEME 107

2.5 Conclusions

Two important conclusions about the mechanism of enone photocycloaddition with olefins can be drawn from the work reported in this thesis. Firstly, the formation of a product mixture containing both the rearranged adducts **213** and **214** from the photochemical reaction of vinylcyclopropane and cyclopentenone is good evidence that initial bonding between the enone and the alkene occurs to both the α- and β-positions of the enone. Secondly, formation of the rearranged products **213** and **214** in addition to comparable quantities of the 2 + 2 adducts **154** and **155** suggests that cyclopropane ring opening in the initially formed biradicals **150** and **153** occurs at a similar rate to their ring closure to cyclobutane ring containing adducts. Using the known rate of the ring opening reaction as a clock it was possible to estimate the lifetime of the initial triplet 1,4-biradicals to be *ca.* 20 - 50 ns.

CHAPTER 3

INDEPENDENT GENERATION OF THE TRIPLET 1,4-BIRADICAL INTERMEDIATES IN THE 2 + 2 PHOTOCYCLOADDITION REACTIONS OF 2-CYCLOPENTENONE WITH ALKENES

3.1 Introduction

3.1.1 General Aspects

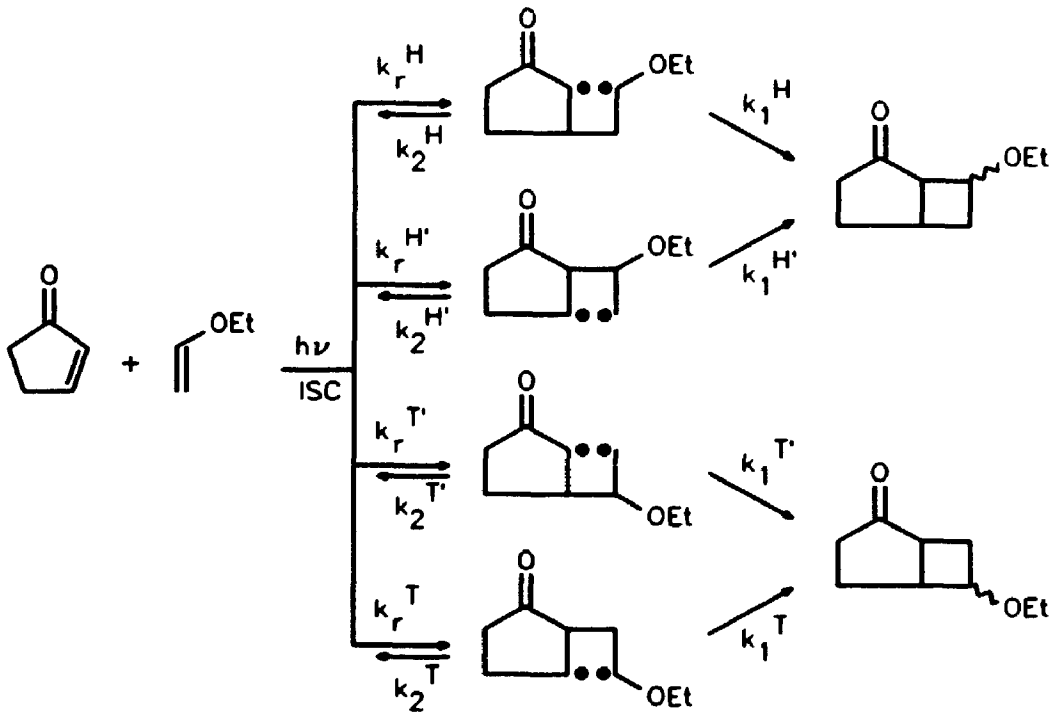
As explained in Chapter 1 of this part of this thesis, for many years exciplex formation in the 2 + 2 photocycloaddition reactions of enones with olefins has been discussed and used to explain the reaction regiochemistry;[60,62,63,66] however, recently doubts have been expressed about exciplex intermediacy in the reaction.[1,76-78,80,81] If exciplexes are not involved then an alternative explanation of the reaction regiochemistry has to be sought.

In 1970 Bauslaugh suggested an alternative to the exciplex as the origin of the regiochemistry, as described by the Corey-de Mayo mechanism.[78] He proposed that the regiochemical outcome of the cycloaddition reaction could depend on the fates of the various different biradicals which could be involved. These could have different rates of formation and could either cleave to give back the starting materials (rate constant k_2) or collapse to the cyclobutane adducts (rate constant k_1). This partitioning of the biradicals could then be responsible for the observed regiochemistry since different biradicals could have a different partitioning ratio ρ defined in EQUATION 17.

$$\rho = \frac{k_1}{k_1 + k_2} \qquad \text{Eq. 17}$$

If then, for example, the biradical(s) leading to head-to-head adduct(s) had a low ρ and the biradical(s) leading to head-to-tail adduct(s) had a high ρ then the observed regiochemistry would be predominantly head-to-tail if the biradicals were formed in comparable amounts.

The kinetic scheme for a simple 2 + 2 cycloaddition of a non-symmetrical olefin to an excited state enone involving four biradicals becomes quite complicated if all possible reaction pathways are considered. This is shown for the reaction of cyclopentenone with ethyl vinyl ether in SCHEME 108.[69,81]



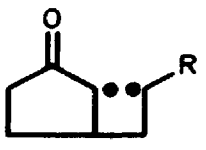
SCHEME 108

Inspection of this scheme indicates that simple product analysis or quantum yield measurement cannot allow separation of the parameters ρ and the relative rates of formation of each possible biradical. As already mentioned a number of times,

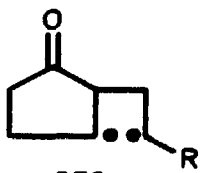
Hastings and Weedon were able to measure the relative rates of formation of the biradicals in their systems by trapping them with hydrogen selenide. They also demonstrated that the biradicals containing a primary radical centre are formed in negligible amounts.[69,81] Even if the latter is taken into account there are still too many unknowns to separate values of ρ for the remaining biradicals and hence determine whether biradical partitioning (i.e. ρ for each biradical) is the factor which determines the reaction regiochemistry.

One way out of this dilemma would be to generate each of the desired biradicals by an independent route and monitor their fates. Measurement of the amount of cycloadduct formed as well as the amount of collapse of each biradical to enone plus alkene would allow the estimation of values of ρ for each biradical. Comparison of the values of ρ for each possible biradical with the actual distribution of regioisomers in a photochemical cycloaddition reaction would then allow an estimate to be made of the amount of each biradical formed and hence their relative rates of formation. Ultimately this would demonstrate whether the reaction regiochemistry is governed by biradical partitioning or, as the exciplex theory suggests, by the relative rates of formation of the various possible intermediate biradicals.

This chapter deals with the investigation into the independent generation of the 1,4-biradicals **238** and **239** implicated as intermediates in the 2 + 2 photocycloaddition reactions of 2-cyclopentenone **115** with a variety of monosubstituted alkenes.



238

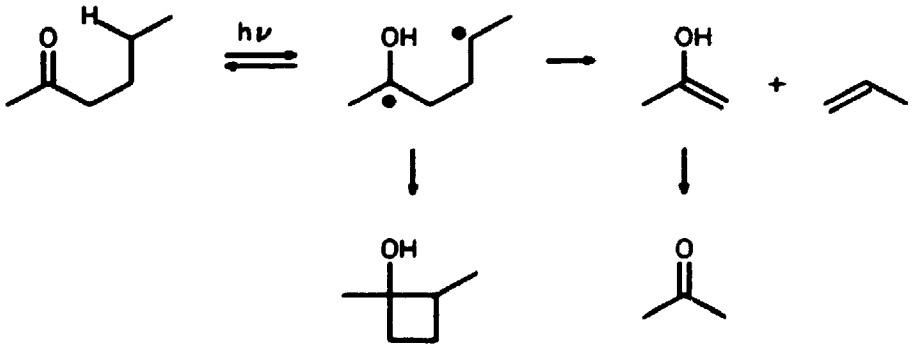


239

3.1.2 Generation of 1,4-Biradicals

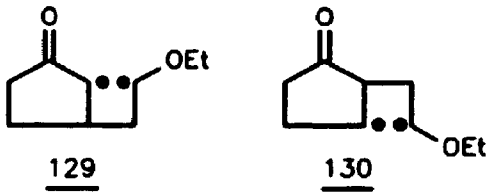
A number of ways are known for the generation of 1,4-biradicals. Two of the more common methods will be discussed here. These are the Norrish Type II reaction and the photoextrusion of smaller molecules, such as nitrogen or carbon monoxide, from cyclic systems. Extrusion of carbon monoxide is often a secondary process in the Norrish Type I reaction.

The Norrish Type II reaction is a well known process and has been reviewed extensively in the past.[111] In this reaction, excitation of a ketone results in the intramolecular abstraction of an appropriately oriented hydrogen by the carbonyl oxygen. Normally this means that a 1,5-hydrogen transfer occurs from the γ-position to the carbonyl oxygen to generate a 1,4-biradical. The 1,4-biradical can undergo back hydrogen transfer to yield the starting material or it can undergo homolytic cleavage of the bond between the α- and β-carbon to give an enol and an olefin. Alternatively the biradical can undergo ring closure to a cyclobutanol derivative as shown in SCHEME 109.



SCHEME 109

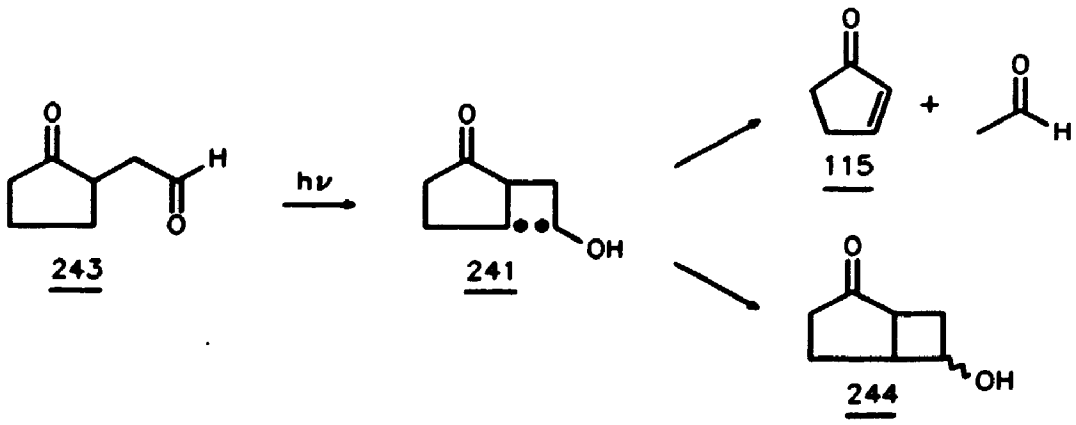
The Norrish Type II reaction can be used to generate models of the 1,4-biradicals implicated in the reactions of cyclic enones with alkoxy-substituted alkenes. This possibility has been examined by Hastings and Weedon who used the biradicals **240** and **241** as models for the biradicals **129** and **130** present in the photocycloaddition of cyclopentenone **115** and ethyl vinyl ether.[81]



129 130

The biradicals **240** and **241** were generated by Norrish Type II photochemistry of the cyclopentanone aldehydes **242** and **243**, respectively.

Photolysis of **243** led to **241** which collapsed to the isolated products. These were cyclopentenone **115** and acetaldehyde, resulting from the scission of the 1,4-biradical, and cyclobutanols **244** which arise from ring closure as illustrated in SCHEME 110.

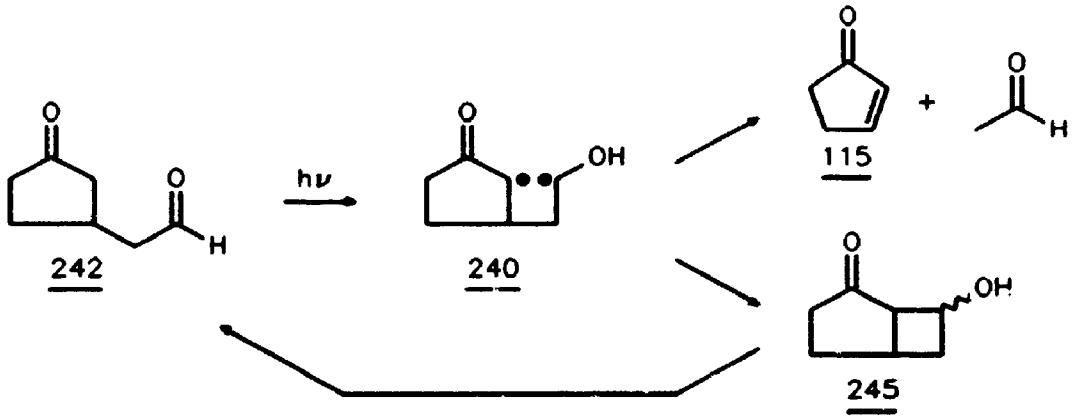


243 241 115 244

SCHEME 110

The ratio of cyclopentenone **115** to **244** allowed determination of the partitioning ratio ρ^T for **241**. This was calculated to be 0.29 indicating that biradical **241** closed to cyclobutanol products with an efficiency of ≈ 29 %.

Photolysis of **242** led to **240** which either fell apart to **115** and acetaldehyde or closed to cyclobutanols **245** as shown in SCHEME 111. Unfortunately **245** underwent very efficiently a retro-aldol reaction back to **242** so that it could not be quantified. This problem was overcome by irradiation in the presence of methanol-d_4, which led to deuterium incorporation into **242** upon retro-aldol reaction. Low conversions and mass spectroscopy allowed for quantification of deuterated **242** which had to be derived from biradical **240**.



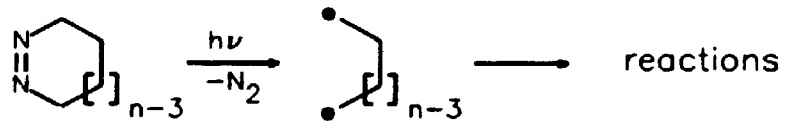
SCHEME 111

The partitioning ratio ρ^H for **240** was determined to be 0.23 indicating that it closed to cyclobutanols a little less efficiently than **241**.

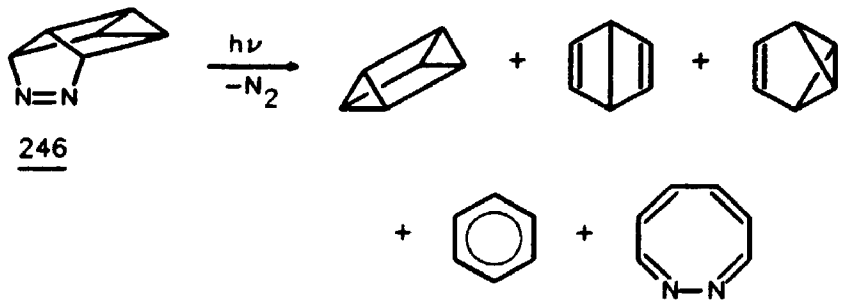
If biradicals **240** and **241** are good models for the biradicals **129** and **130** implicated as intermediates in the reaction of cyclopentenone with ethyl vinyl ether, then this result implies that both biradicals close to products with similar efficiency and

therefore that the regioselectivity (i.e. preferential formation of head-to-tail products) must be derived from faster formation of biradical **130**.

The photoextrusion of nitrogen from cyclic azenes to yield 1,n-biradicals has been reviewed.[112a] The mechanism by which the reaction proceeds is not completely known; however, there is some indication that more than one mechanism is possible. The key step is homolytic cleavage of both carbon-nitrogen bonds (either in parallel or stepwise) to give a 1,n-biradical which can then undergo a variety of reactions.[112a]



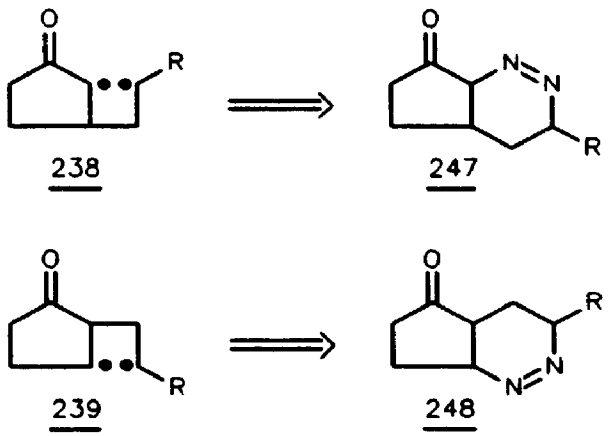
An interesting example was published in 1973 when Katz and Acton irradiated compound **246**.[112b] This lost nitrogen and gave the isomers of benzene shown in SCHEME 112. A side product was 1,2-diazacyclooctatetraene, which is probably derived from the initial biradical formed by cleavage of one of the two carbon-nitrogen bonds.



246

SCHEME 112

This route could be used to generate the 1,4-biradicals **238** and **239** implicated as intermediates in the reaction of cyclic enones with alkenes. However, in order to generate **238** and **239** one would have to synthesize compounds **247** and **248**.

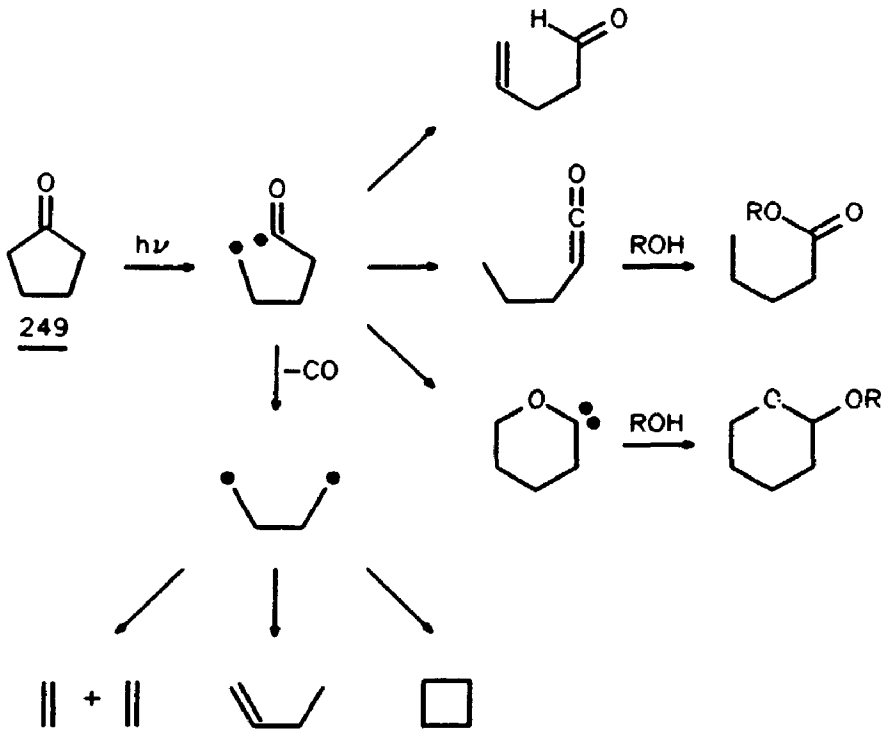


238 247

239 248

A possible route for this has been shown in principle by Kjell and Sheridan[113] who reported that they were able to generate similar compounds by oxidation of the appropriate cyclic hydrazines obtained by a lengthy synthesis; however, the synthetic effort involved would be considerable. In addition the route would not be adaptable for the variety of R-substituents which one would wish to examine. Consequently, this approach was not pursued in the work described in this thesis.

A more attractive route to 1,4-biradicals involves the photoextrusion of carbon monoxide from carbonyl compounds. This is a well reviewed reaction.[112a,114] It is known to proceed *via* a biradical derived from sequential cleavage of the bonds between the carbonyl carbon and its α-carbons. The first α-cleavage, which is the first step in the Norrish Type I reaction[114c], can proceed from both the singlet and the triplet excited state of the ketone and thus leads to either a singlet or triplet biradical.[112a] Once this biradical has been formed it can undergo a variety of secondary reactions, as demonstrated for the photolysis of cyclopentanone **249** shown in SCHEME 113.[112a,114a,c]

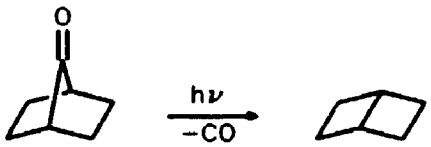


SCHEME 113

Intramolecular hydrogen transfer from the γ-carbon to the carbonyl radical centre leads to an aldehyde, while hydrogen transfer from the α-carbon to the δ-carbon radical centre gives a ketene which is usually trapped by protic solvents as an ester.

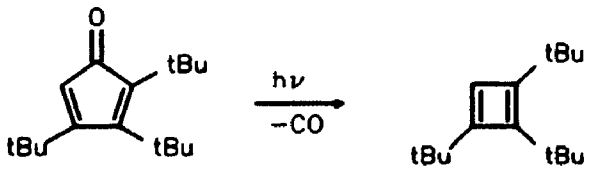
Attack of the δ-carbon radical centre on the carbonyl oxygen results in formation of a ring expanded ether carbene, also usually trapped by protic solvents as an acetal. The process of interest for this thesis was another decay reaction, the loss of carbon monoxide (decarbonylation). This brings about a 1,4-biradical which can either disproportionate to an alkene, ring close to the cyclobutane or cleave to two alkenes.

The photoextrusion of carbon monoxide has been widely used to generate biradicals which collapse to a number of novel, high energy compounds, hard to prepare by "conventional" chemistry. In 1974 Givens et al. reported on the synthesis of bicyclo[2.2.0]octane by photochemical extrusion of carbon monoxide from ketone **250**.[115a]



250

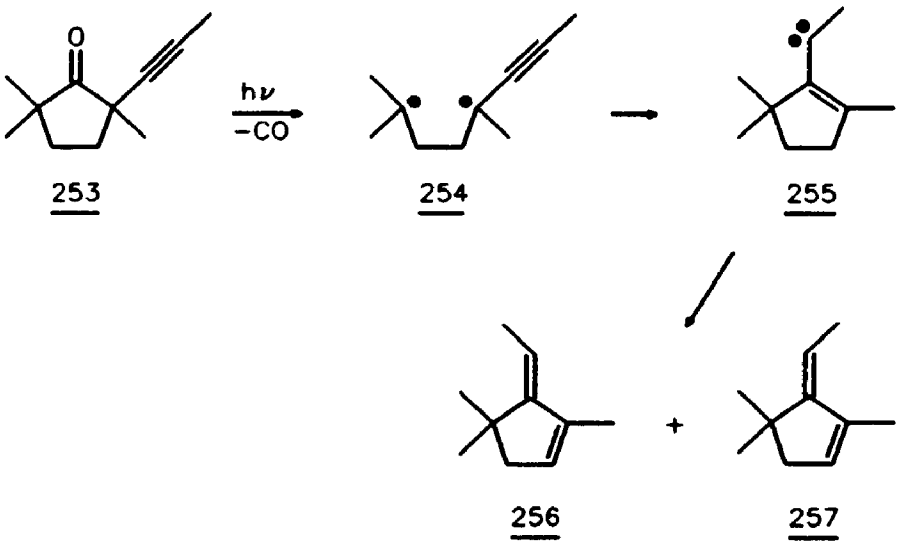
Maier and Alzérreca were able to prepare cyclobutadiene **252** in an argon matrix by decarbonylation of cyclopentadienone **251**.[115b]



251 **252**

In 1987 Rudolph and coworkers reported the photodecarbonylation of the 1-propynyl substituted cyclopentanone **253** to the biradical **254**.[115c] This underwent cleavage and 1,4-ring closure reactions as well as 1,5-ring closure to the vinyl carbene **255** which rearranged to the dienes **256** and **257** as illustrated in SCHEME 114.

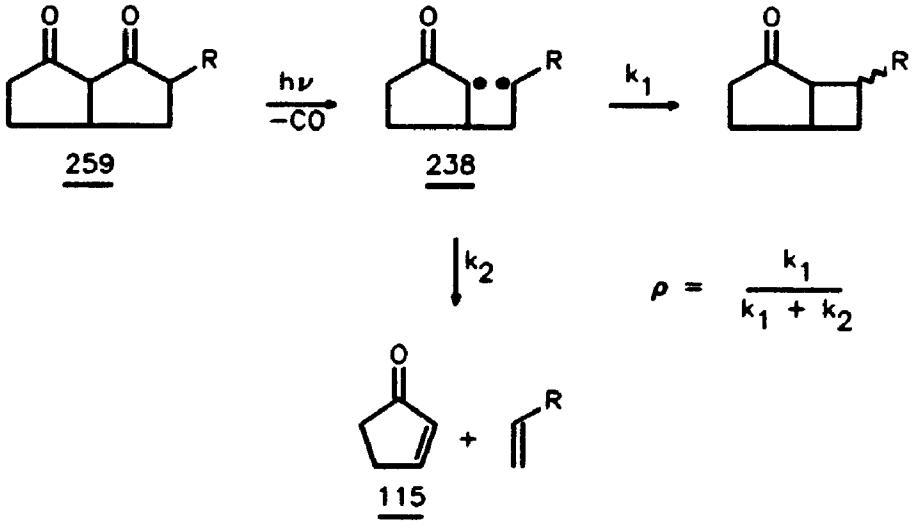
This was the first example of an all carbon skeleton undergoing this type of reaction.



253 254 255 256 257

SCHEME 114

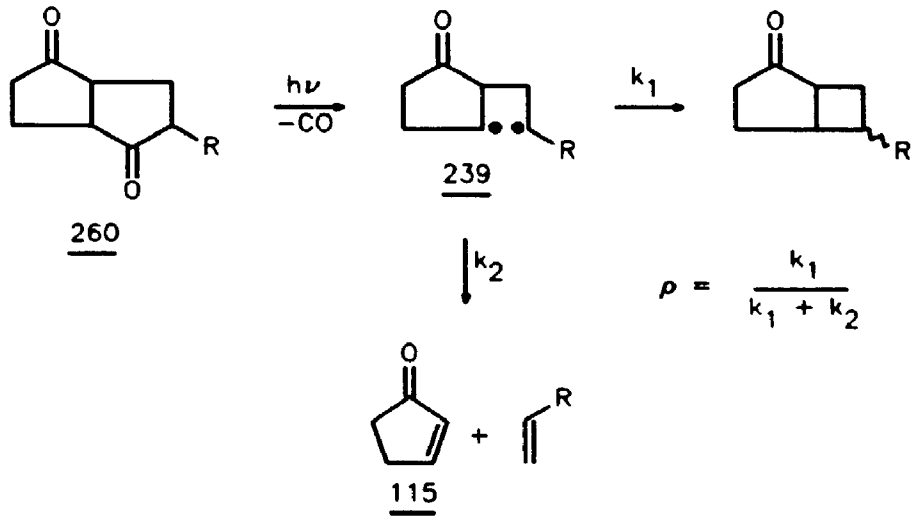
In order to utilize this reaction for the preparation of the 1,4-biradicals in the 2 + 2 photocycloaddition reaction of cyclic enones with alkenes the proper precursors had to be designed.[81] To generate biradical **238** by this route diketone **259** would have to be synthesized (see SCHEME 115) whereas the regioisomeric biradical **239** would have diketone **260** as its precursor (see SCHEME 116).



259 238 115

$$\rho = \frac{k_1}{k_1 + k_2}$$

SCHEME 115



SCHEME 116

Biradicals **238** and **239** were then expected to either cleave to cyclopentenone **115** and olefin or ring close to cyclobutanes in an identical manner to their behaviour when generated by cycloaddition. The amount of **115** and cyclobutanes produced from **259** and **260** could then be quantified and used to determine ρ for each of the biradicals.

In planning this project it was realized that the biradical formed by α-cleavage would have a number of fates dependent on a number of variables such as the nature of the R-substituent, temperature and photolysis conditions.[112a,114c] It was expected that some of these decay processes would be favoured over loss of carbon monoxide. This was not considered to be of grave consequence as long as some 1,4-biradicals were formed. Even if only 1 % of the Type I biradicals underwent decarbonylation this would likely yield sufficient cyclopentenone and cyclobutane products to allow measurement of ρ values. Consequently it was decided to synthesize diketones **259** and **260** with a variety of R-substituents such as electron withdrawing groups (eg. cyano), electron donating groups (eg. alkoxy) as well as hydrogen and alkyl groups.

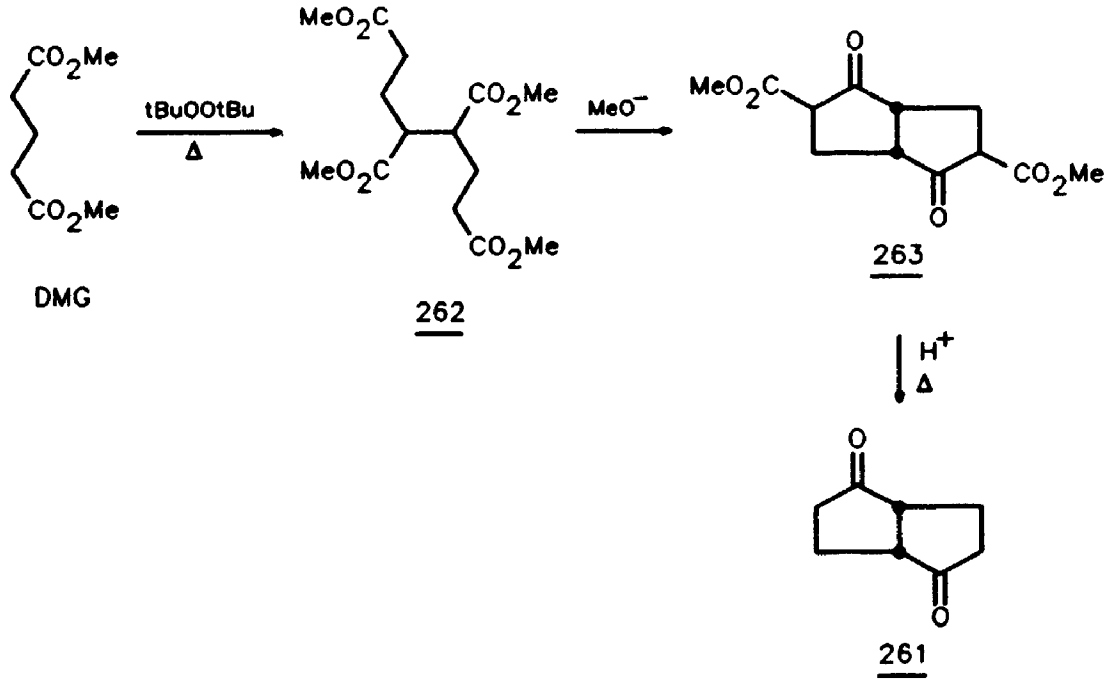
3.2 Preparations and Photolyses of Bicyclo[3.3.0]octane-2,6-dione 261 and its 3-Substituted Derivatives

3.2.1 Preparation of Bicyclo[3.3.0]octane-2,6-dione 261

For the synthesis of **261** the procedure of Hagedorn and Farnum was followed.[116] This route commences with free radical coupling of dimethylglutarate (DMG) which leads to the tetraester **262**. This reaction proceeded only in low yield (≈ 11 %) but large amounts of unreacted DMG were recovered; the yield based on reacted DMG was ≈ 78 %. Compound **262** was a low melting white solid which was formed as a mixture of diastereomers (*d,l* and *meso*). It was identified by comparison of its spectral data (nmr and mass spectroscopy) with the reported values.[116] In the ^{13}C-nmr spectrum four carbonyl resonances were observed in addition to two methine peaks and four methylene signals, which indicated the presence of two stereoisomers. However, only two methyl peaks were seen; this is most likely due to isochronicity of the individual signals because of the distance of the methyl groups from the chiral centres. Base catalyzed double Dieckmann cyclization of **262** led to 3,7-bis(methoxycarbonyl)bicyclo[3.3.0]octane-2,6-dione **263**, a beige solid. Excluding optical isomers only one isomer of **263** appeared to have been formed. It was expected that because of strain the two five membered rings would be *cis*-fused, eliminating one source of isomerism. In addition, nmr spectroscopy (both proton and carbon) revealed that the double β-ketoester system in **263** was completely enolized. This removes two of the chiral centres in **263** and explains why only a single isomer was observed. The ^{1}H-nmr spectrum showed only four groups of signals indicating a symmetrical molecule. The signals observed were a methyl singlet (≈ 3.7 ppm), multiplets at ≈ 3.4 ppm (bridgehead methine) and ≈ 2.7 ppm (ring methylenes) as well as a broad

singlet at ≈ 10.3 ppm; this extremely low field signal was assigned to the quite acidic enol protons.[39] The ^{13}C-nmr spectrum supported the analysis. Six signals were observed and confirmed the symmetry of the molecule. The chemical shifts and multiplicities of the signals were in accordance with known values for enolized β-ketoesters.[39] Most significant the centre carbon of the 1,3-dicarbonyl system was shifted to very low field (≈ 99 ppm); an APT experiment[50] indicated that it did not bear any hydrogen. No trace of non- or half enolized material was found as indicated by the absence of a tertiary carbon signal at ≈ 60 ppm which would be the expected shift for the centre carbon of a non-enolized 1,3-dicarbonyl system.[39]

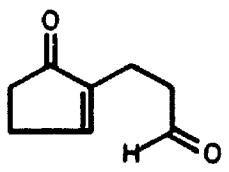
Acidic ester hydrolysis of **263** followed by decarboxylation gave **261** which was purified by sublimation. It was identified by mass and nmr spectroscopy. The latter indicated a symmetrical structure with only four resonances in the ^{13}C-nmr spectrum and was in agreement with the literature data.[116,117] The synthesis of **261** is illustrated in SCHEME 117.



SCHEME 117

3.2.2 Photolysis of Bicyclo[3.3.0]octane-2,6-dione 261

It was expected that photolysis of **261** would result in Norrish Type I cleavage and decarbonylation to give one of the 1,4-biradicals implicated in the addition of ethylene to cyclopentenone. Accordingly the photochemistry of **261** was examined. When a benzene solution of **261** was irradiated through Pyrex with a medium pressure Hg-lamp (water filtered) formation of one product at a slightly longer retention time than **261** was observed by gas chromatography. Under these conditions most of the light absorbed by **261** would have been at 313 nm. The same product was seen when a benzene solution of **261** was irradiated in quartz with shorter wavelength light (λ = 254 nm). Under these conditions the solvent would have absorbed the light and sensitized **261** into its triplet excited state. No formation of cyclopentenone **115** was observed in either experiment. Inspection of the irradiation mixtures using coupled gas chromatography/mass spectroscopy indicated that the product possessed a mass of 138 and was an isomer of **261**. The ^{1}H-nmr spectrum of a mixture generated by irradiation in benzene-d_6 revealed the presence of a triplet at ≈9.2 ppm pointing to an aldehyde as the product. Larger scale irradiations allowed for separation (by column chromatography) of unreacted **261** and of the product; the latter was identified from its nmr spectroscopic data as aldehyde **264**.



264

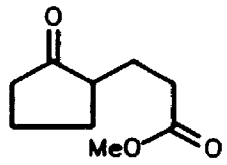
Thus in the ^{1}H-nmr spectrum ($CDCl_3$) a triplet at ≈ 9.7 ppm was assigned to the aldehyde proton, its multiplicity due to the methylene neighbour. A symmetrical seven line signal centred at ≈ 7.3 ppm (overlapping doublet of doublets of triplets) was seen for the olefinic proton in the β-position of the cyclopentenone ring. Its chemical shift is consistent with the data presented in Chapter 2 of this part of this thesis. The ^{13}C-nmr spectrum confirmed the identification of **264**; all the expected peaks were present with the correct multiplicities. Characteristic were two carbonyl peaks and two olefinic carbon resonances.

The exclusive formation of aldehyde **264** suggests that the initial α-cleavage proceeded as expected to give the more stable biradical **265** rather than the alternative biradical **266**.[114c] However, biradical **265** evidently did not undergo decarbonylation to **267** but instead decayed by intramolecular hydrogen transfer to **264**.

Hydrogen transfer to give the ketene **268** would also have been possible, but ketenes are unstable species and would not survive long enough to be detected. Irradiation of solutions of **261** containing an inert standard indicated that this might be another mode of decay for **265** since the sum of the areas of **261** and **264** did not remain constant but decreased slowly, even though no other product was seen by gas chroma ,graphy; however, polymeric products (from a ketene) would not have been detected by this analysis method.

Since ketenes usually are trapped by reaction with nucleophiles solutions of **261** were irradiated in 9:1 benzene/methanol mixtures. Gc analysis showed the appearance of small amounts of a new product **269** at higher retention times than **261** in a ratio of **264**:**269** of ≈ 11:1. Mass spectral analysis allowed observation of a weak molecular ion of mass 170, indicative of a 1:1 adduct of **261** and methanol. Larger scale

experiments allowed the isolation of **269**; ^{1}H-nmr spectroscopic analysis showed the presence of a singlet integrating tc three protons at ≈3.6 ppm, characteristic of the methyl group of methyl esters.[39] Compound **269** was thus identified as the ester **269**.



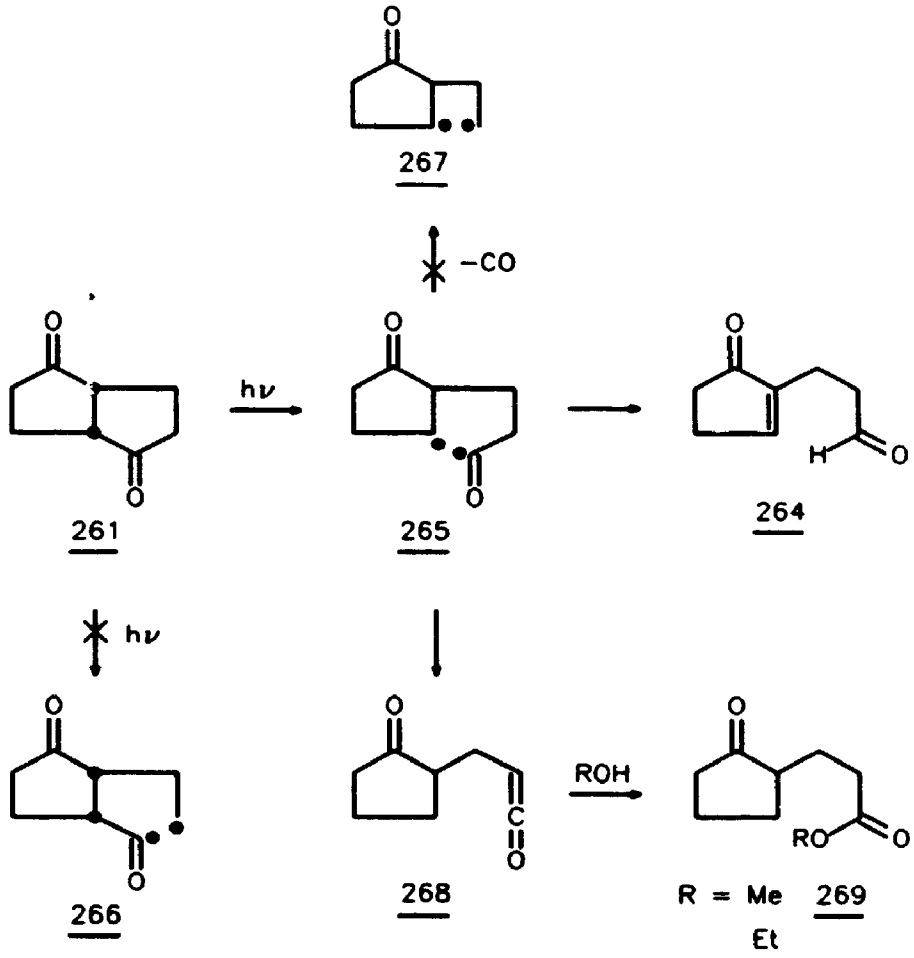
269

This was confirmed by changing the alcohol to ethanol; this resulted in the formation of a product with higher retention time and a mass of 184.

The formation of **264** and **269** as the sole products of the photolysis of diketone **261** suggests that decarbonylation of **265** is a relatively slow process, presumably because decarbonylation would result in the formation of a primary radical centre as shown in structure **267**.

In order to increase the chances of decarbonylation an irradiation of **261** was performed at higher temperature (benzene/ethanol 9:1, Pyrex filtered light, 70°C). However, this led to the same result. No decarbonylation was observed even though it is known that higher temperatures favour this reaction pathway.[114c]

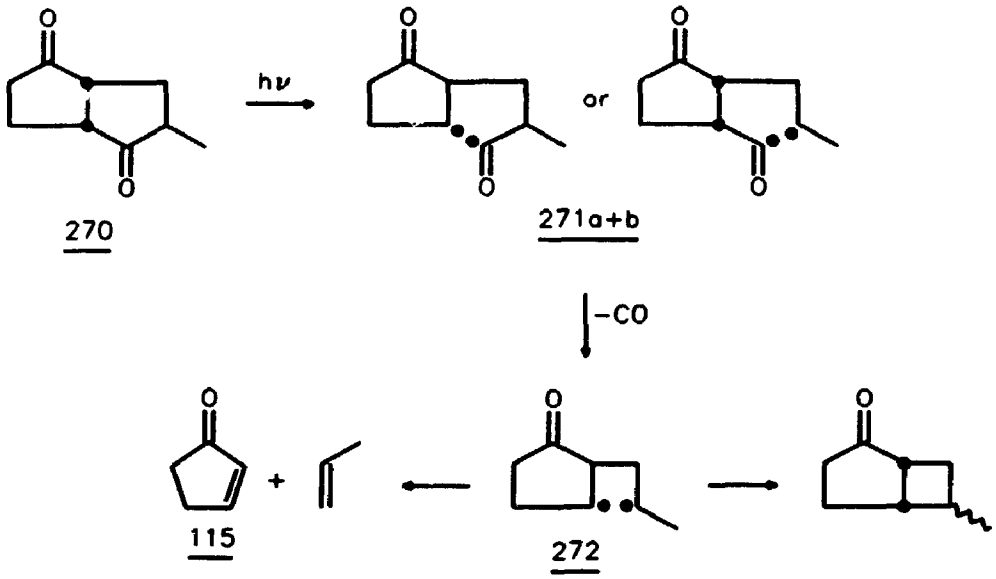
The results obtained by photolysis of **261** and some of the interpretations are summarized in SCHEME 118.



SCHEME 118

3.2.3 Preparation of 3-Methylbicyclo[3.3.0]octane-2,6-dione 270

It was hoped that the presence of the methyl group in **270** would accelerate decarbonylation of the Type I biradicals **271a + b** to yield the biradical **272** implicated in the photocycloaddition reaction of cyclopentenone and propene as shown in SCHEME 119.



SCHEME 119

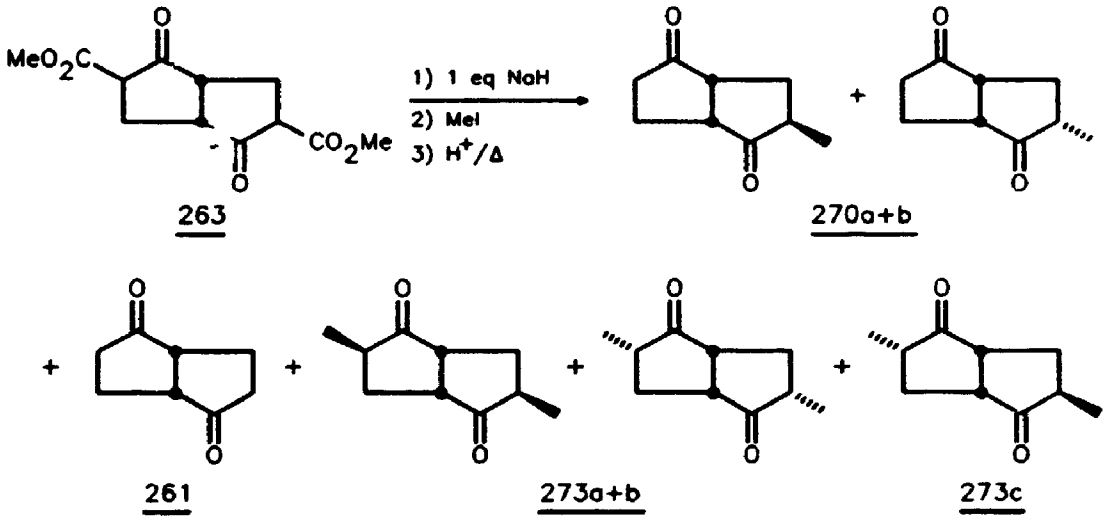
Accordingly the diketone **270** was prepared. Two methods for the preparation of **270** were examined. The first was based on the observation that the precursor of **261**, the bis(β-ketoester) **263**, had two quite acidic hydrogens, which were expected to be easily abstracted by base to form a bis-enolate system. It was hoped that reaction of **263** with one equivalent of base would generate an enolate which would be quenched with methyl iodide to ultimately lead to **270**.

When the bis(β-ketoester) **263** was allowed to react with *ca.* one equivalent of sodium hydride followed by a large excess of methyl iodide, slightly reddish crystals were obtained. As was the case for **263** the products could not be eluted from a gc column due to their high polarity, so that the success of the reaction had to be determined by hydrolysis and decarboxylation of the bis(β-ketoester) to the corresponding diketone.

It was anticipated that monomethylation of **263** would give two stereoisomers of **270** in which the new methyl group was *cis* or *trans* to the ring fusion hydrogens.

Because of greater steric interactions between the methyl group and the opposite five membered ring in the *cis* isomer, the *trans* isomer was expected to be the dominant product on both kinetic and thermodynamic grounds.

After workup six products were observed by gas chromatography in a ratio of ≈ 28:12:8:1:1:1 (in order of increasing retention time); the first eluted product was identified as starting material **261** by comparison with an authentic sample. Mass spectroscopy on the mixture suggested that the second two products eluted were monomethylated diketones (presumably **270a+b**) and that the last three products eluted were dimethylated diketones (presumably **273a-c**) as illustrated in SCHEME 120.



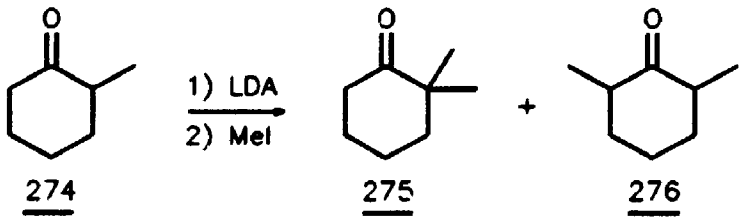
SCHEME 120

The six diketones were separated by column chromatography which allowed the isolation of a ≈ 5.5:1 mixture of stereoisomers of **270a+b** in 98 % purity. The ^{1}H-nmr spectrum of this mixture showed the existence of two doublets at ≈ 0.8 ppm in a ≈ 5:1 ratio, the sum of which integrated to three hydrogens when compared with

the rest of the spectrum. The ^{13}C-nmr spectrum of this mixture showed seven signals in the aliphatic region with the right multiplicity (by APT) for **270**; each signal was accompanied by a much smaller neighbour corresponding to the minor isomer. Only two equally intense carbonyl peaks were observed; the carbonyl peaks of the minor isomer could not be detected.

A ≈2:1 mixture of two of the isomers of **273a-c** was also be obtained. The ^{1}H-nmr spectrum of this mixture showed three doublets in the methyl region. Two were of equal intensity and integrated to *ca.* half the amount of the major doublet. It was thus concluded that the minor of these two isomers was non-symmetrical (i.e. **273c**) and consequently gave two different methyl group signals. The major isomer is therefore one of the symmetrical dimethyldiketones **273a + b**; no further investigations into the structures of the dimethyldiketones was carried out.

The second approach to the preparation of **270** utilized the fact that reaction of a non-symmetrical ketone with a hindered base at low temperatures leads to the kinetically favoured enolate with high regioselectivity.[118] This is illustrated for the alkylation of ketone **274** in SCHEME 121.



274 275 276

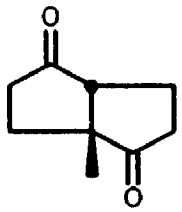
1 : 20

SCHEME 121

Reaction of **274** with lithium diisopropylamide (LDA) has been reported to give a mixture of the regioisomeric enolates which were then alkylated with excess methyliodide to give a ≈20:1 mixture of the products **275** and **276**.[118]

It was therefore anticipated that reaction of **261** with one equivalent of LDA and subsequent treatment with methyl iodide at -78°C would generate the target compound. However, in the event seven products were formed; the ratio obtained was ≈3:4:2:5:1:3:2 in order of increasing retention times.

Analysis by coupled gas chromatography/mass spectroscopy identified six of these as the compounds **261**, **270a+b** and **273a-c** formed in the reaction of **263** with base and methyl iodide. The extra product (the third eluted species in the mixture) possessed the same mass as **270** and was tentatively assigned as **277**, derived from the thermodynamically favoured enolate.



277

Since this method of preparing **270** did not show a clear advantage over the first procedure examined it was not investigated further.

3.2.4 Photolysis of 3-Methylbicyclo[3.3.0]octane-2,6-dione 270

Irradiation with Pyrex and water filtered light of a benzene-d_6/methanol-d_4 (9:1) solution of methyl diketone **270** (mixture of two stereoisomers in a 1.19:1 ratio, in order of increasing gc retention times) did not lead to any cyclopentenone formation

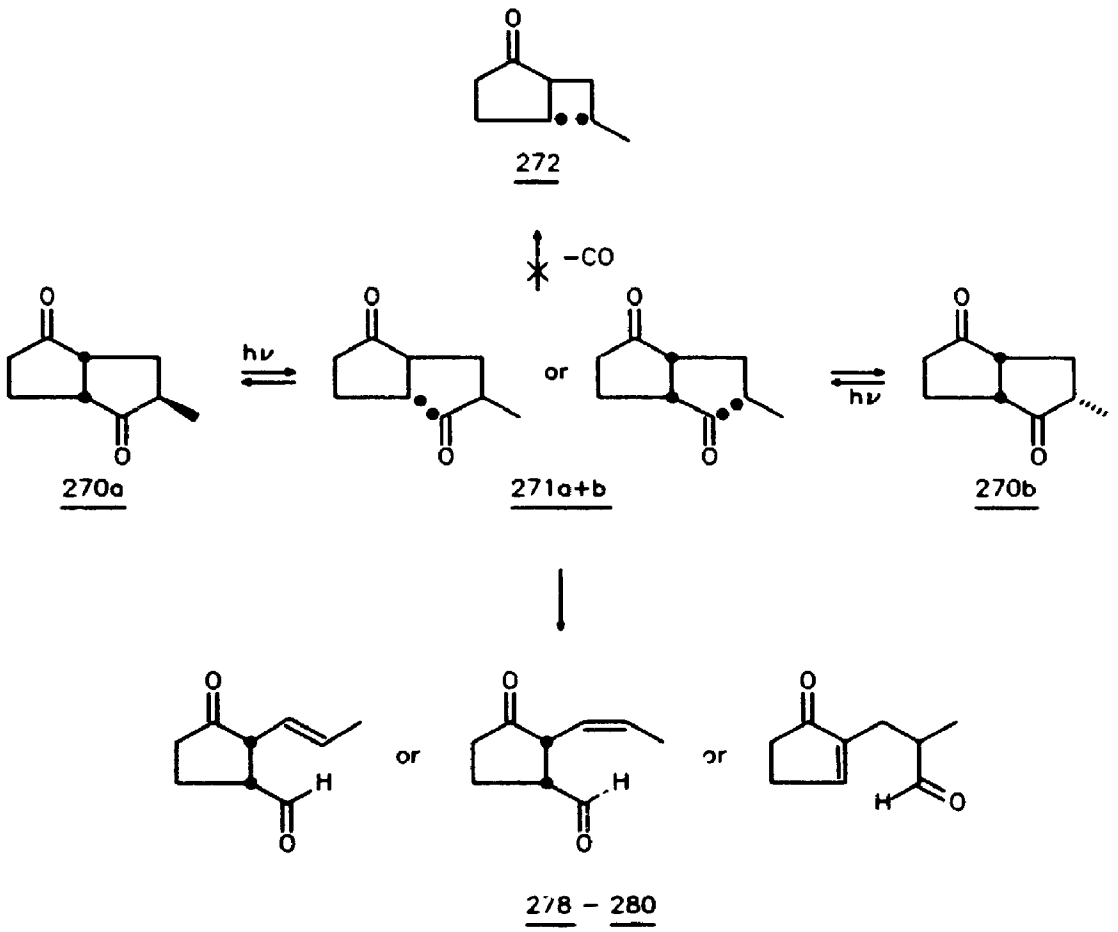
detectable by gc. In the beginning stages of the irradiation the only visible change was an alteration of the ratio of the isomers (from 1.19:1 to 0.97:1 after six hours). This trend continued but after 10 hours a new product was observed with a slightly shorter retention time than both isomers of **270**. It grew larger with time and after 35 hours the ratio of this new product to the isomers of **270** was 0.33:0.55:1, respectively.

^{1}H-Nmr and mass spectral analysis at this stage suggested that a similar reaction to that obtained in the photolysis of the unsubstituted diketone **261** had taken place. Thus gc/ms gave a mass of 152 for the new product, which is the same as that of **270**.

In the ^{1}H-nmr spectrum a doublet at ≈9.3 ppm and multiplets in the olefinic region pointed to the formation of at least one aldehyde with the structures **278** - **280**. However, because of the small amount of product obtained and the number of signals for olefinic protons the structure of the product(s) could not be determined. A ^{13}C-nmr spectrum confirmed the general conclusion by exhibiting signals in the olefinic region.

Since none of these products corresponded to cyclopentenone or the closure products of the desired biradical **272** they were not examined further.

It was therefore concluded that no decarbonylation of the primary Norrish Type I biradicals **271a+b** had taken place; instead α-cleavage of **270** had resulted in epimerization at the 3-position while extended irradiation allowed the observation of aldehyde products formed by intramolecular disproportionation of the Norrish Type I biradical as shown in SCHEME 122.

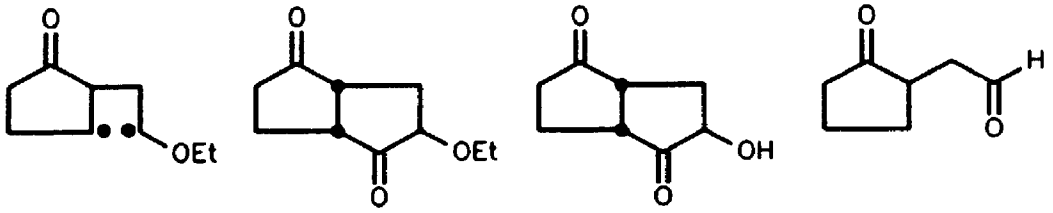


SCHEME 122

3.2.5 Preparation of 3-Ethoxybicyclo[3.3.0]octane-2,6-dione 281 and 3-Hydroxybicyclo[3.3.0]octane-2,6-dione 282

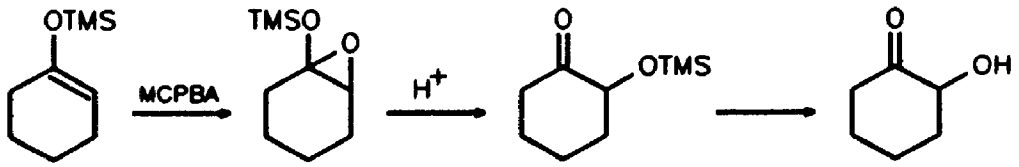
Biradical 130 is one of the intermediates implicated in the photocycloaddition reaction of cyclopentenone with ethyl vinyl ether. It was hoped that this would be generated by photolysis of diketone 281 and that the presence of an ethoxy group would stabilize the adjacent radical centre sufficiently to promote decarbonylation of the initially produced Norrish Type I biradical. Accordingly the preparation of 281 was

carried out. In addition a route was sought for the preparation of **282** in order to allow comparison with the results obtained by Hastings and Weedon for the photolysis of compound **243** as shown earlier in this chapter.[69,81]



130 281 282 243

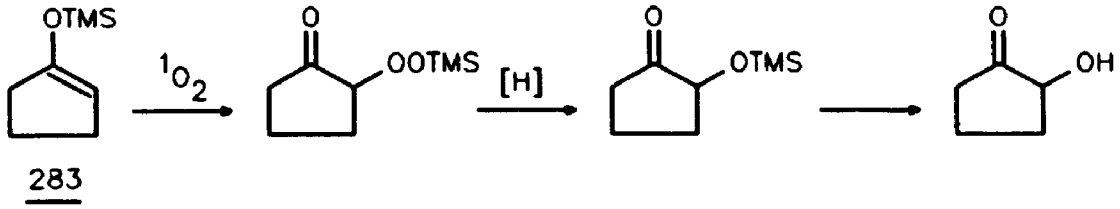
Hydroxylation of a ketone in the α-position is a reaction that can be carried out in a number of ways. The groups of Rubottom and others have examined procedures for the hydroxylation of silyl enol ethers of carbonyl compounds.[119a-d] For example, treatment of the silyl enol ether of cyclohexanone with *m*-chloroperbenzoic acid (MCPBA) led to the isolation of 2-hydroxycyclohexanone in 64 % yield. The reaction was believed to proceed by acid catalyzed 1,4-silyl rearrangement in a siloxyoxiran to yield an α-siloxyketone which was hydrolysed to the product as shown in SCHEME 123.[119a]



SCHEME 123

In 1979 Friedrich and Lutz reported the preparation of 2-hydroxy-cyclopentanone. Reaction of the silyl enol ether **283** with singlet oxygen (generated

by sensitized irradiation) led to the formation of a silylperoxy ketone which could be reduced to a siloxy ketone and subsequently hydrolysed to the product as illustrated in SCHEME 124.[120]

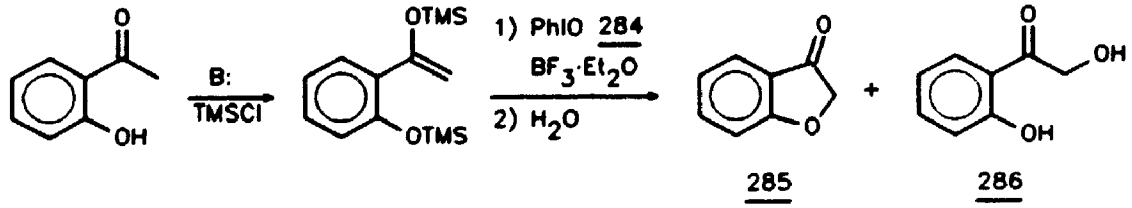


283

SCHEME 124

Another way to prepare *α*-hydroxyketones has been reported by Moriarty and coworkers.[121] Treatment of the silyl enol ether of an aryl methyl ketone with iodosobenzene **284** in the presence of boron trifluoride etherate yielded, after aqueous work-up, the corresponding aryl hydroxymethyl ketone. The mechanism was thought to involve an iodosobenzene-boron trifluoride complex which added to the substrate resulting in an *umpolung* of the enolate anion.

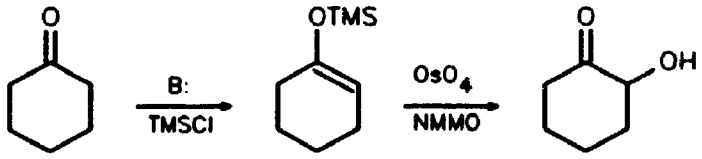
This procedure was used by the authors for the convenient preparation of 3-coumaranone **285** and 2,2'-dihydroxyacetophenone **286** from *o*-hydroxyacetophenone as shown in SCHEME 125.[121c]



285 286

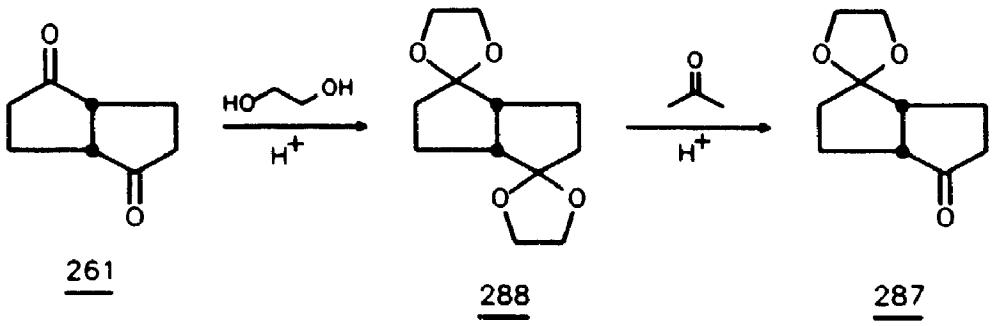
SCHEME 125

In 1981 McCormick et al. published a further method for the preparation of *α*-hydroxyketones. Again the precursor was the silyl enol ether, but the oxidizing agent used was osmium tetroxide in the presence of N-methylmorpholine-N-oxide. This is illustrated for the preparation of 2-hydroxycyclohexanone from the ketone *via* its silyl enol ether in SCHEME 126; the reaction was found to proceed in 89 % yield.[122]



SCHEME 126

It was decided to attempt the synthesis of **282** by oxidation of the appropriate silyl enol ether with MCPBA or iodosobenzene/boron trifluoride. Since the initial precursor used was a diketone but only one hydroxyl group was to be introduced, the partial protection of **261** had to be undertaken. Reaction of **261** with ethylene glycol[123] in the presence of acid led to a mixture of the mono- and diprotected species **287** and **288**. These were separable by column chromatography; however, the amount of the desired product **287** was disappointingly low. The yield was improved by changing the procedure. Total protection of **261** to give **288** was achieved in quantitative yields; partial deprotection by refluxing in acetone was a slow and easily monitored reaction which could be stopped when optimum amounts of **287** had been formed as shown in SCHEME 127.[123]

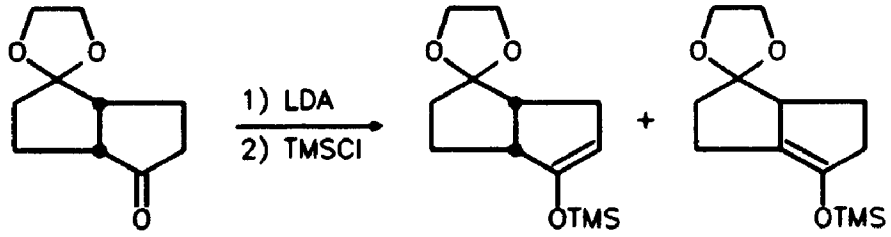


261 288 287

SCHEME 127

Ketals **287** and **288** were identified by their mass, ^{1}H- and ^{13}C-nmr spectra; the protons of the 1,3-dioxolane ring appeared as expected at ≈3.8 ppm[39], while in the ^{13}C-nmr spectrum the carbon bearing the protecting group had a characteristic chemical shift of ≈120 ppm.[39]

In order to prepare the silyl enol ether of **289** with the correct regiochemistry the kinetically favoured enolate of **287** was prepared by reaction with LDA at -78°C and immediately quenched with trimethylsilyl chloride (TMSCl).[118,124] The product was isolated as two isomers in a ≈15:1 ratio in high yield. The major product was the desired silyl enol ether **289** and the minor product was tentatively assigned as the isomer **290** as illustrated in SCHEME 128.



287 289 290

SCHEME 128

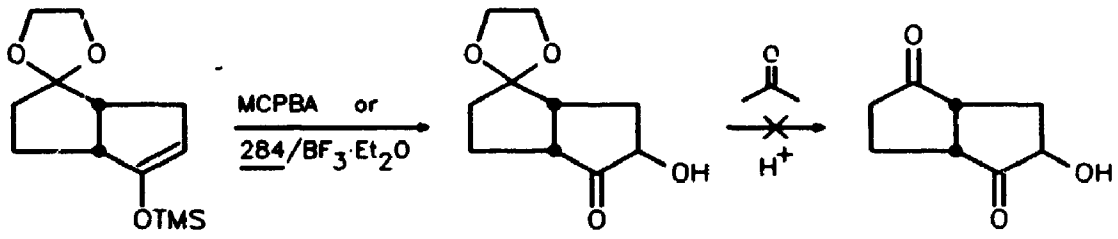
Ether **289** was identified from its nmr spectra; the ^{1}H-nmr spectrum exhibited a characteristic singlet accounting for the nine protons of the TMS-group at ≈0.15 ppm and the olefinic hydrogen appeared as a doublet of doublets at ≈4.5 ppm. In the ^{13}C-nmr spectrum a large methyl signal appeared at ≈0 ppm and the two olefinic carbons at ≈101 ppm and ≈155 ppm had the correct multiplicities (methine and quaternary carbon, respectively) for **289**. The corresponding carbons in compound **290** would both be quaternary.[39] Analysis of the mass spectrum confirmed the identification of **289**; besides the molecular ion at 254 mass units a large peak at 73 mass units was observed corresponding to the TMS-fragment.

With enol ether **289** on hand, preparation of the hydroxydiketone **282** was attempted. Reaction of **289** with MCPBA led to the successful formation of **291** but in low yields. The product was identified by nmr and mass spectroscopy. In the ^{1}H-nmr spectrum the characteristic signal for the methylene protons in the 1,3-dioxolane ring and the methine proton adjacent to the hydroxy group were superimposed as a multiplet at ≈4.2 ppm. The hydroxy proton could not be detected but may have been masked by the multiplet of the 1,3-dioxolane protons. The ^{13}C-nmr spectrum showed the presence of all required resonances with the correct multiplicities; in particular the methine bearing the hydroxyl substituent was observed at ≈74 ppm. The mass spectrum showed the expected molecular ion with a mass of 198. The spectroscopic data indicated that the hydroxyketone **291** was formed as a single diastereomer; however, the configuration of the hydroxy group relative to the ring fusion hydrogens was not assignable.

Attempts to remove the ethylene glycol protecting group from **291** using *p*-toluenesulfonic acid in acetone led to the disappearance of **291** but did not lead to any detectable amounts of **282**. In the ^{1}H-nmr spectrum of the product mixture no

signal corresponding to the methine proton adjacent to the hydroxy group could be observed. The ^{13}C-nmr spectrum showed a low intensity signal at ≈ 74 ppm which is were the methine bearing the hydroxy group was expected. Because of the small amount of product obtained and difficulty in purification the synthesis was abandoned. It was suspected that *α*-hydroxyketone **282** might be too unstable under the reactions conditions employed.

When **289** was allowed to react with iodosobenzene/boron trifluoride etherate the same result was obtained. The hydroxyketone **291** was formed but only unidentified mixtures resulted when deprotection was attempted. Both attempts to synthesize **282** are summarized in SCHEME 129.



289 291 282

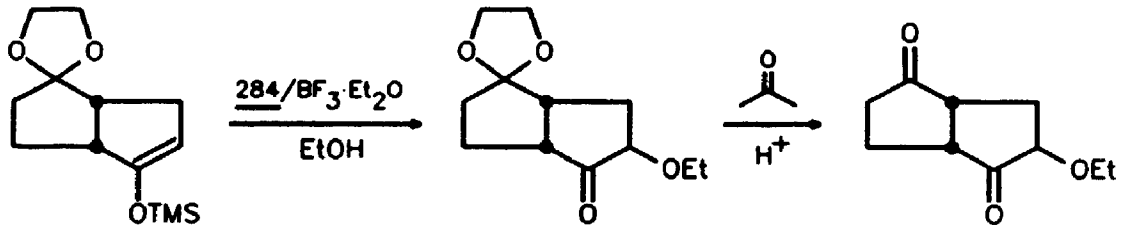
SCHEME 129

At this point it was decided to focus the efforts on the synthesis of *α*-ethoxydiketone **281**. It was hoped that the ethoxy substituent would be more stable than the hydroxy group of **282**.

The preparation of **281** was carried out in an analogous manner to the attempted synthesis of **282** *via* oxidation of the silyl enol ether **289**.

Compound **289** was treated with iodosobenzene[125] **284**/boron trifluoride etherate and then with ethanol rather than water, as proposed by Moriarty and coworkers.[121c-e,126] After separation from the by-product (iodobenzene) this gave **292** which was identified by its mass spectrum which showed the expected molecular ion peak at 226 mass units.

Acid catalyzed deprotection of **292** with acetone allowed isolation of the desired compound **281** (as shown in SCHEME 130) which was identified by its mass and nmr spectra.



289 292 281

SCHEME 130

As with the methyl substituted diketone **270**, the ethoxy diketone **281** was found to exist as two stereoisomers in a ≈1:2 ratio. In the ^{1}H-nmr spectrum two triplets for the terminal methyl groups of the ethoxy side chain were observed; the methylenes of the ethoxy group exhibited a more complicated pattern since the two hydrogens on each methylene are diastereotopic. Consequently each methylene hydrogen showed a separate signal (doublet of quartets due to coupling to the geminal hydrogen and the neighbouring methyl group) so that a total of four resonances could

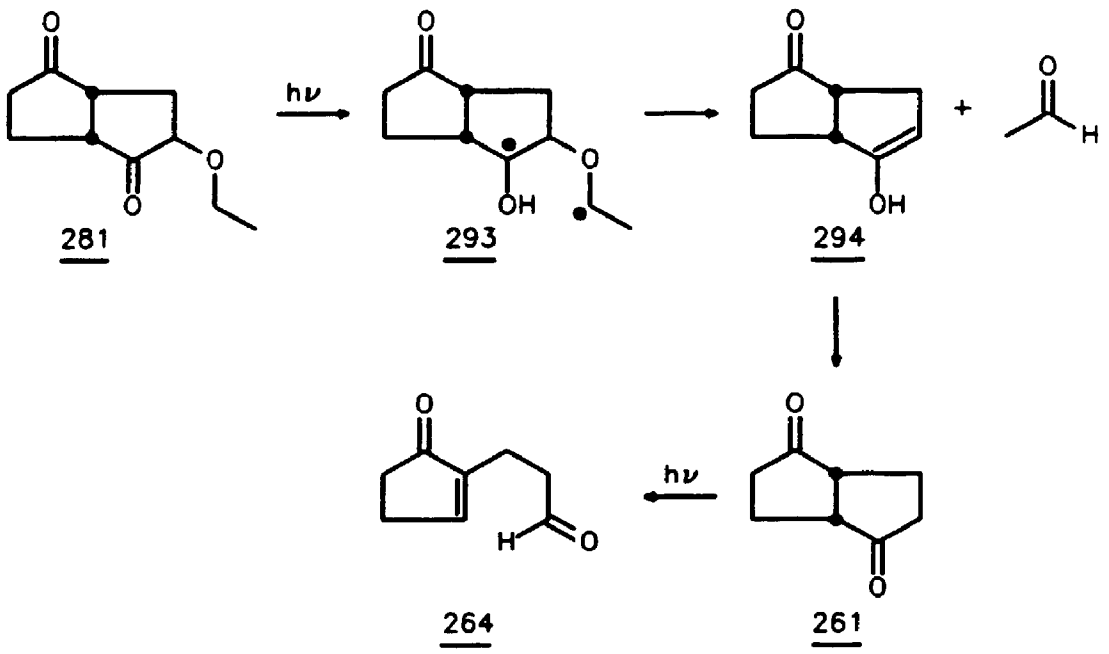
be seen. Different geminal coupling constants and the integrations allowed the assignment of these methylene signals to the major and minor isomer.

In the case of the major isomer (presumed to be the one with the ethoxy group in a *trans* arrangement to the other cyclopentanone ring) the α-hydrogen on the carbon bearing the substituent was observable as a doublet of doublets, the corresponding signal of the minor isomer could not be resolved and no assignment of the stereochemistry of the isomers was possible on the basis of the ^{1}H-nmr spectrum. The ^{13}C-nmr spectrum provided supporting evidence for the existence of two stereoisomers of **281** since for all resonances there existed a smaller peak with similar shift and multiplicity; the methine carbon bearing the ethoxy group was visible at the expected chemical shift of ≈80 ppm.

3.2.6 Photolysis of 3-Ethoxybicyclo[3.3.0]octane-2,6-dione 281

When the ethoxy diketone **281** was irradiated in benzene-d_6 no formation of cyclopentenone **115** or adducts **132** could be detected by gc or gc/ms comparison with authentic samples. Instead a product was formed with a retention time identical with that of the parent diketone **261**; co-injection with an authentic sample of **261** confirmed that it was the major product of the photolysis and this was supported by mass spectral analysis.

This finding suggested that after excitation **281** underwent a Norrish Type II reaction leading to biradical **293**, which either reverted to **281** or cleaved to acetaldehyde and enol **294** which would ultimately generate **261** as illustrated in SCHEME 131.[111b]



SCHEME 131

This conclusion was confirmed by further inspection of the reaction mixture which revealed the presence of acetaldehyde when a sample was co-injected on the gc with an authentic sample. In addition, gc analysis showed the presence of aldehyde **264** which is derived from secondary photochemistry of **261**. The ^{1}H-nmr spectrum of the irradiated mixture also indicated the presence of **264** since the characteristic seven line resonance at ≈ 6.5 ppm and the triplet in the aldehyde region at ≈ 9.2 ppm were observed. A quartet in the same region (at ≈ 9.1 ppm) was assigned to acetaldehyde while its methyl group was observed as a doublet at ≈ 1.35 ppm.[39]

During the photolysis a change in the ratio of diastereomers of **281** was observed. This could be derived from faster Norrish Type II cleavage of one of the diastereomers but could also originate from α-cleavage and recombination rather than decarbonylation. Repetition of the irradiation in the presence of an inert standard showed that the former is the correct explanation since the absolute amount of the

major diastereomer of **281** was observed to decline more rapidly than the growth in the amount of the minor diastereomer. This suggests that one diastereomer undergoes Type II reaction much faster than the other and reflects the fact that the Norrish Type II reaction of cyclic ketones has strict stereoelectronic requirements.[111a]

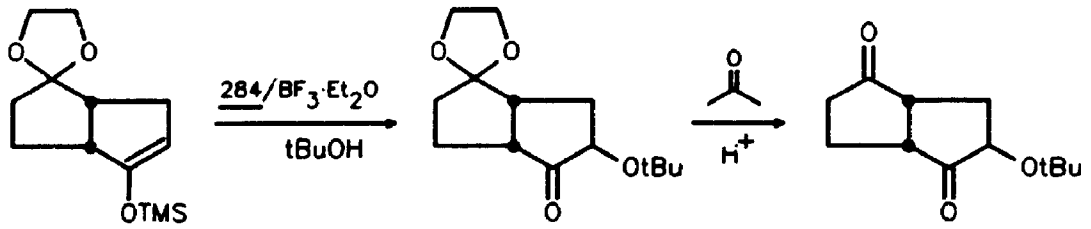
3.2.7 Preparation of 3-*t*-Butoxybicyclo[3.3.0]octane-2,6-dione 295

The failure of **281** to undergo Type I cleavage and photodecarbonylation to the desired biradical **130** was due to the presence of an abstractable γ-hydrogen on the ethoxy group. It was anticipated that removal of this abstractable hydrogen would suppress Norrish Type II reactions and allow for *α*-cleavage. Thus the synthesis of the *α*-*t*-butyl ketone **295** was carried out since this compound does not possess the γ-hydrogen necessary to interfere with Type I cleavage.

Compound **295** was prepared using a modification of the procedure found successful for the synthesis of **281**. *t*-Butanol was substituted for ethanol in the reaction and a higher temperature (0°C rather than -78°C) was used since *t*-butanol, even in a mixture with dichloromethane, could not be used at -78°C due to its high melting point. After reaction and separation by column chromatography **296**, the ketal protected precursor of **295**, was obtained and identified by its mass (molecular ion of 254 mass units, characteristic *t*-butyl fragment at 57 mass units) and ^{1}H-nmr spectra. The latter exhibited two intense singlets at ≈ 1.2 ppm and ≈ 1.3 ppm in a ≈ 1:1 ratio, characteristic of compounds containing the *t*-butoxy moiety and suggesting the existence of two diastereomers.

Deprotection with *p*-toluenesulfonic acid in acetone gave, after preparative gc separation, the desired diketone **295** which was identified by its mass (molecular ion

of 210 mass units, an intense fragment of 57 mass units corresponding to the *t*-butyl group), and nmr spectra. The ^{1}H-nmr spectrum again showed the existence of two stereoisomers in a ≈ 1:1 ratio by the presence of two large singlets (at ≈ 1 ppm) accounting for nine protons each (*t*-butoxy methyl groups). The ^{13}C-nmr spectrum confirmed the identification with the correct number and multiplicities of resonances; the isomers exhibited slight chemical shift differences but no stereochemical assignment was possible. The synthesis of **295** is summarized in SCHEME 132.



289 **296** **295**

SCHEME 132

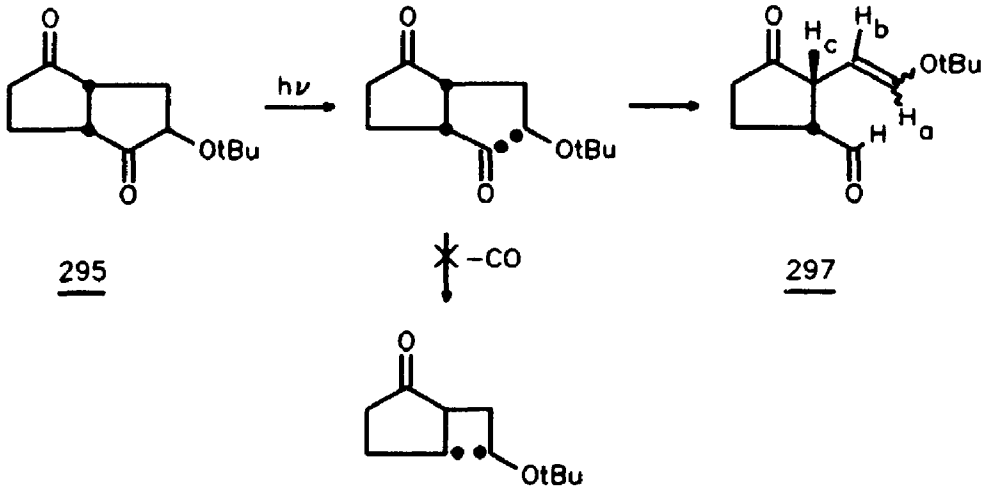
3.2.8 Photolysis of 3-*t*-Butylbicyclo[3.3.0]octane-2,6-dione 295

Irradiation of a solution of **295** led to no detectable photodecarbonylation products (cyclopentenone and cycloadduct) when the reaction was monitored by gc. In addition, no other products appeared to be formed. However, after 15 hours the mixture was analyzed by ^{1}H-nmr spectroscopy and this revealed that a reaction had indeed taken place but that the products had retention times identical to the starting materials and could therefore not be observed by gc. Thus in addition to the *t*-butoxy

signals of **295** two new singlets at ≈ 1 ppm were observed. The ratio of the areas of these new singlets to the *t*-butoxy resonances of the isomers of **295** was ≈ 1:1 1:4:2.5 (from low to high field) with the centre two being the peaks for **295**. This indicated that not only did the ratio of the isomers of **295** change (from ≈ 1:1 to ≈ 3:1) but also that ≈ 20 % conversion had occurred. Because of the low conversion and the magnitude of the ratio change the latter probably arises from epimerization by Norrish Type I cleavage and recombination rather than from faster rate of reaction of one of the two isomers of **295**.

The presence of olefinic resonances and aldehyde peaks in the ^{1}H-nmr spectrum of the product mixture suggested that *α*-cleavage had taken place and had been followed by intramolecular hydrogen transfer. From the multiplicities and chemical shifts of the signals it was concluded that the bond from the carbonyl carbon to the *α*-carbon bearing the substituent had broken and not the bond from the carbonyl carbon to the second five membered ring. The latter process would have resulted in formation of a 2-substituted cyclopentenone (similar to that obtained in the photolysis of **261**) but the multiplicities and shifts for the olefinic signals (*vide infra*) did not support this. Rather the nmr spectrum indicated the formation of diastereomers of **297**. Thus in each the aldehyde proton showed as a doublet at ≈ 9.3 and ≈ 9.5 ppm, respectively. The olefinic protons on the carbon bearing the *t*-butoxy substituent (H_a) were observed as doublets of doublets (coupled to H_b and allylicly to H_c) at ≈ 6.0 and ≈ 6.3 ppm, whereas the other olefinic protons (H_b) came as doublets of doublets (coupled to H_a and H_c) at ≈ 4.6 and ≈ 5.0 ppm. Integration of the above signals in the ^{1}H-nmr spectrum of the irradiation mixture allowed for the assignment of the peaks to one or the other geometrical isomer of **297**. The larger olefinic vicinal coupling constant $^3J_{ab}$ in the minor isomer (≈ 12 Hz vs ≈ 6.3 Hz) enabled the identification of

it as the *trans* compound.[39] The photolysis of compound **295** is illustrated in SCHEME 133.

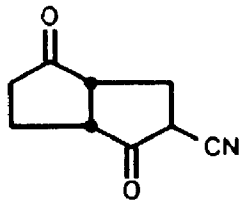


SCHEME 133

3.2.9 Preparation of 3-Cyanobicyclo[3.3.0]octane-2,6-dione 298

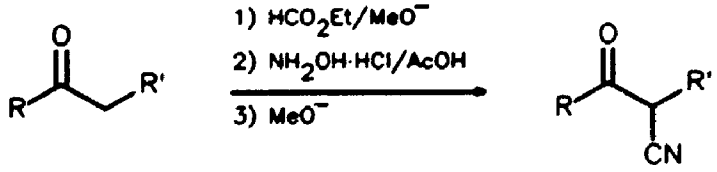
Since photolyses of the diketones **261**, **270**, **281** and **295** with neutral or electron donating substituents in the *α*-position did not result in any photodecarbonylation reaction, a compound with an electron withdrawing substituent was designed. Groups like carbonyl functions were considered but dismissed due to the fact that the part of the molecule where the photochemistry was supposed to happen would be a 1,3-dicarbonyl compound and thus highly likely to exist in its enolized form to a considerable extent. This would not have been a good substrate since the photochemical properties would be significantly different than those of a normal ketone.[18]

A cyano group in the α-position to a ketone on the other hand was not expected to lead to a large amount of enolization.[127] The synthesis of **298** was therefore investigated. Decarbonylation of this diketone would yield one of the biradicals implicated in the 2 + 2 cycloaddition reaction of cyclopentenone with acrylonitrile.



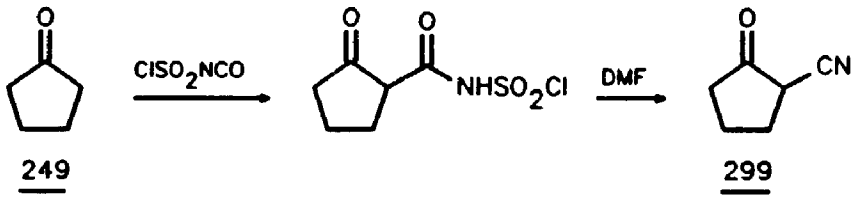
298

A number of methods have been described in the literature for the introduction of a cyano group into the α-position of a ketone.[128] Elnagdi et al. reviewed some of the syntheses in 1984 but most of the reactions cited started from precursors already containing a cyano function.[128a] A standard procedure used for many years to synthesize α-cyano ketones from ketones has been the method developed by Johnson.[128b-d] This involves a three step procedure illustrated in SCHEME 134. Unfortunately this route demands acid catalysis in the second step. This could cause problems for the synthesis of **298** because it could result in premature removal of the ketal protecting group in the substrate **287**.



SCHEME 134

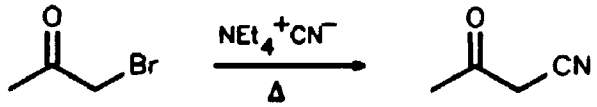
In 1973 Rasmussen and Hassner reported the preparation of the 2-cyano substituted cyclopentanone **299** from cyclopentanone **249** in 54 % yield using chlorosulfonyl isocyanate followed by treatment with DMF in a one-pot reaction as shown in SCHEME 135.[128e]



249 299

SCHEME 135

Five years later Simchen and coworkers reported that they were able to convert ketones such as α-bromo acetone into the corresponding α-cyano ketones by reaction with tetraethylammonium cyanide at elevated temperatures; however, their yields were rather low.[128f]

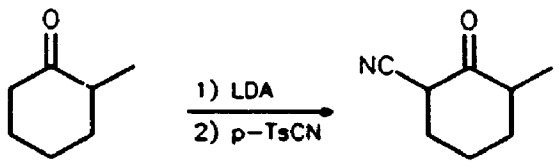


33 %

In the early 1980's Rodriguez et al. discovered that enolates react with benzylthiocyanate (BTC) to give α-cyano ketones albeit in low yields; for instance with cyclopentanone and cyclohexanone the yields were 20 and 35 %, respectively.[128g]

A report of great interest to the work described here appeared in 1981. Kahne and Collum reported the introduction of a cyano function into unsymmetrically

substituted ketones with *p*-toluenesulfonyl cyanide (*p*-TsCN) *via* the kinetically favoured enolate as demonstrated in the reaction of **274**.[128h]

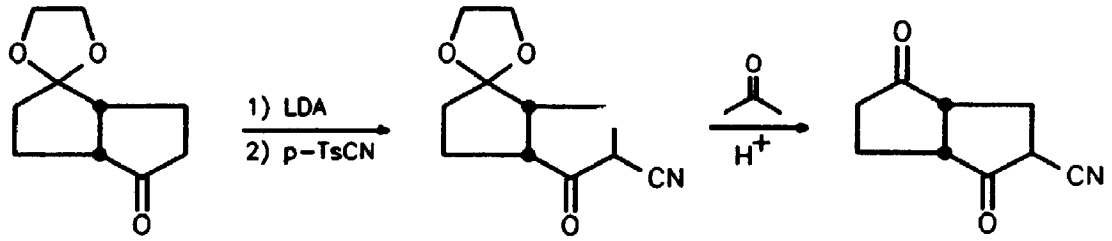


274

The monoprotected diketone **287** was an ideal candidate to test this pathway. In the event, reaction of **287** with lithium diisopropyl amide (LDA) at -78°C followed by addition of the enolate to *p*-TsCN gave a mixture of stereoisomers of **300** in ratio of ≈ 5:3 as determined by comparison of the intensities of the carbonyl peaks in the ^{13}C-nmr spectrum. It was assumed that the major isomer would be the one with the cyano substituent *trans* to the other ring. Compound **300** was identified by mass and nmr spectroscopy of the mixture of diastereomers. In the ^{13}C-nmr spectrum two cyano resonances in the region of ≈ 120 ppm could be observed but not all of the remaining expected signals for both isomers could be seen, probably due to isochronicity. The ^{1}H-nmr spectrum showed the methine proton between the carbonyl and the cyano carbons as doublet of doublets in the major isomer and as triplet (i.e. doublet of doublets with similar coupling constants) of doublets in the minor isomer. The appearance of the extra splitting in the minor isomer is most likely due to long range coupling into the α'-proton.

When compound **300** was deprotected with *p*-toluenesulfonic acid in acetone a mixture of two stereoisomers of **298** was obtained in a ratio of ≈ 5:3 as determined by ^{13}C-nmr spectroscopy. The purity was ≈ 98 %. Both the ^{1}H-nmr and the ^{13}C-nmr spectra showed the disappearance of the 1,3-dioxolane function and in the ^{13}C-nmr

spectrum two carbonyl peaks for each isomer were observed; in addition, the correct number and expected multiplicities for two isomers of **298** were present. In the ^{1}H-nmr spectrum for one of the isomers, the proton between the carbonyl and cyano carbons was resolved to be a triplet of doublets. Mass spectral analysis supported the structure by showing the correct mass (molecular ion of 163) for **298**. The synthesis of compound **298** is summarized in SCHEME 136.



287 300 298

SCHEME 136

In both compounds **298** and **300** no evidence for enolization of the α-cyano ketone system was found; the ^{1}H-nmr spectrum did not exhibit a low field enol proton as was seen for **263**, and the ^{13}C-nmr spectrum lacked the expected peaks for an enolized compound. The fact that two distinct stereoisomers of both **298** and **300** were observed confirmed the analysis; enolization would have required planarity of the system and thus allowed for the observation of only one stereoisomer.

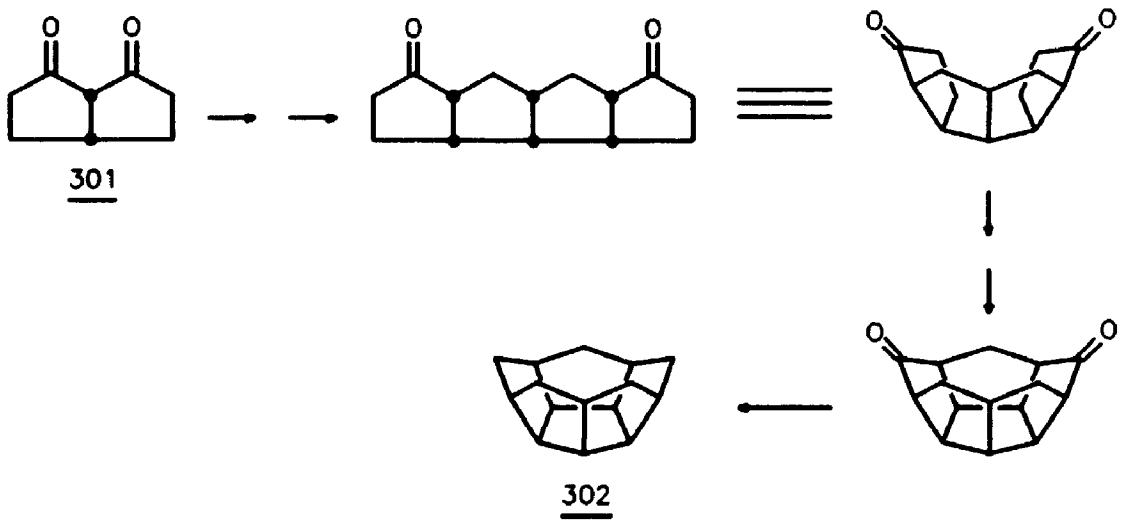
Amazingly, given the precedents of diketones **261**, **270**, **281** and **295**, the photolysis of **298** led successfully to decarbonylation products. For clarity of discussion, the photochemistry of cyano diketone **298** will be discussed in Section 3.5 along with that of its isomer 3-cyanobicyclo[3.3.0]octane-2,8-dione.

3.3 Preparations and Photolyses of Bicyclo[3.3.0]octane-2,8-dione 301 and its 3-Substituted Derivatives

In parallel with the syntheses of the 3-substituted bicyclo[3.3.0]octane-2,6-diones, some of the corresponding 3-substituted bicyclo[3.3.0]octane-2,8-diones were prepared and photolysed. The results are described in this section.

3.3.1 Preparation of Bicyclo[3.3.0]octane-2,8-dione 301

In the 1970's Eaton and his group worked on the synthesis of large hemispheric hydrocarbons like peristylane 302.[129] They envisioned the stepwise construction of this molecule as shown in SCHEME 137 and the key starting material was diketone 301.

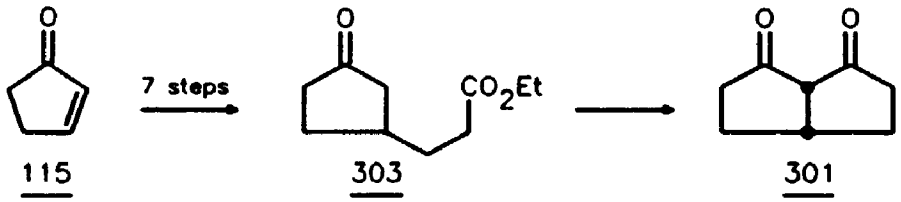


301 302

SCHEME 137

The preparation of 301 had been previously described by Stetter et al.[130] who reported an eight step synthesis with only 17 % overall yield starting from

cyclopentenone **115** as illustrated in SCHEME 138. The last step was the Claisen condensation of **303** to give **301**.



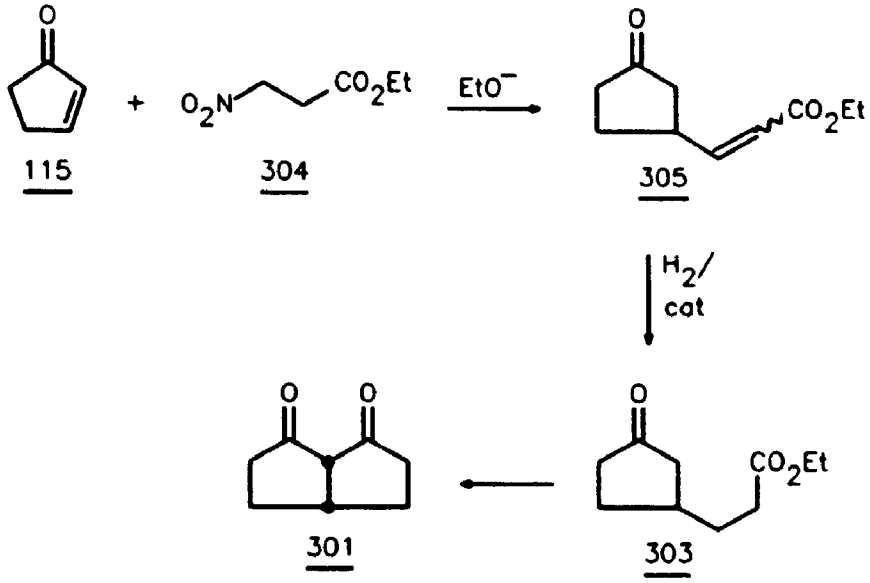
115 303 301

SCHEME 138

Eaton was able to improve the overall yield of formation of the methyl ester analogue of **303** to ≈50 % by reacting **115** with an appropriate lithium cuprate; however, this sequence for the preparation of **301** still involved seven steps.[129]

In 1984 a new synthesis of **301** was reported by Duthaler and Maienfisch.[131] This also proceeded *via* Claisen condensation of **303** but the latter compound was now prepared more conveniently by Michael addition of ethyl 3-nitropropionate **304** to **115** and hydrogenation of the adduct. This two step route proceeded in a yield of 52 % and is shown in SCHEME 139.

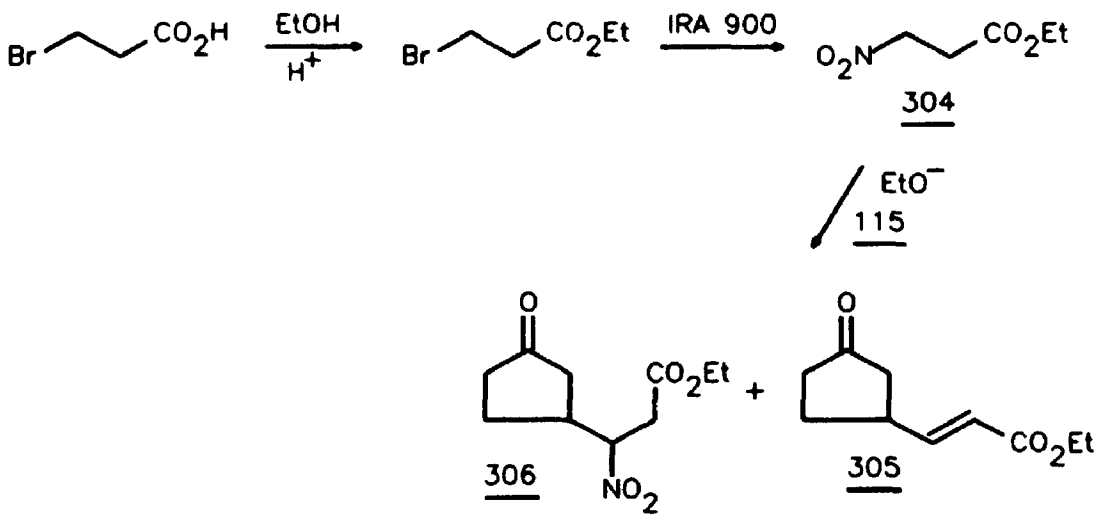
The Duthaler and Maienfisch route was the one employed in the preparation of **301** needed for the work described in this thesis. Propionate **304** was prepared by a two step synthesis from commercially available 3-bromopropionic acid. The latter was esterified by standard procedure with ethanol to give 3-bromopropionic acid ethyl ester in 63 % yield. The ester was converted to **304** by stirring in dry benzene in the presence of nitrite charged Amberlite® IRA 900 ion exchange resin[81]. The sample of **304** obtained was identified by mass and ^{1}H-nmr spectroscopy. Exchange of the bromo substituent with the nitro group led to a downfield shift of the methylene signals on the adjacent carbon from 3.45 ppm in the bromoester to 4.58 ppm in **304**.



SCHEME 139

Treatment of **304** with strong base resulted in anion formation at the 3-position and addition of this to **115** led to compound **305**.[132] Gc analysis of the product mixture showed large amounts (≈ 33 %) of two impurities in a ≈ 1:1 ratio which were identified, after the mixture was separated by column chromatography, by mass and nmr spectroscopy as two diastereomers of **306**. These appear to be the precursors of **305** since, when the reaction was monitored by gc, initially only **306** was observed but **305** grew in progressively at the expense of **306**. The reaction sequence is illustrated in SCHEME 140.

Compound **305** was identified by its mass (molecular ion peak of 182 mass units) and nmr spectra. The ^{1}H-nmr spectrum showed, besides the expected peaks for the ethylester function, two doublets of doublets for the two olefinic hydrogens. From these a vicinal coupling constant of ≈ 16 Hz could be extracted which strongly suggested that the double bond was *trans* substituted.



SCHEME 140

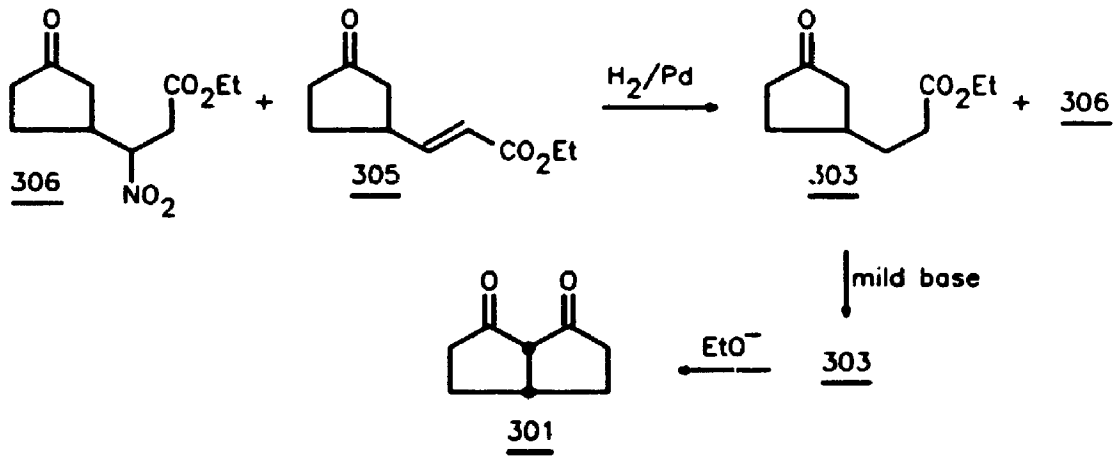
In the ^{13}C-nmr spectrum two olefinic resonances with the correct multiplicities were observed. The mixture of stereoisomers of **306** was also identified by mass ([molecular ion + 1]-peak at 230 mass units using chemical ionization) and nmr spectroscopy. The ^{1}H-nmr spectrum showed two sets of signals for the ethyl ester function, the absence of olefinic resonances and the presence of a multiplet at ≈4.8 ppm, assigned to the protons on the carbons bearing the nitro groups. In the ^{13}C-nmr spectrum the carbon with the nitro group showed up at ≈87 ppm with the correct multiplicity as determined by an APT experiment.

Since **305** was prone to decomposition and the chromatographic separation from **306** yielded only small amounts of pure material, it was decided to hydrogenate the mixture of both. Tests showed that **305** could be hydrogenated smoothly to **303** whereas **306** was inert under the same conditions.[131,132]

The mass spectrum of **303** showed that its mass was two units higher than that of **305** and the nmr spectra supported the analysis by the disappearance of the

olefinic signals. After a mixture of **305** and **306** was hydrogenated it was possible to extract the isomers of **306** into aqueous base leaving **303** in the organic phase. This was made possible by the presence of the acidic hydrogen on the carbon bearing the nitro group of **306** which is about ten orders of magnitude more acidic than the proton *α* to the carbonyl of the ester function.[127]

Claisen condensation of **303**, catalyzed by sodium ethoxide, was followed by pH-controlled workup (utilizing potassium dihydrogenphosphate as buffer) since **301** has an acidic hydrogen between the two carbonyl groups and deprotonation could have led to ring cleavages. This gave the desired product as yellow crystals which were recrystallized from diethyl ether to yield white crystals as shown in SCHEME 141.[131,132]



SCHEME 141

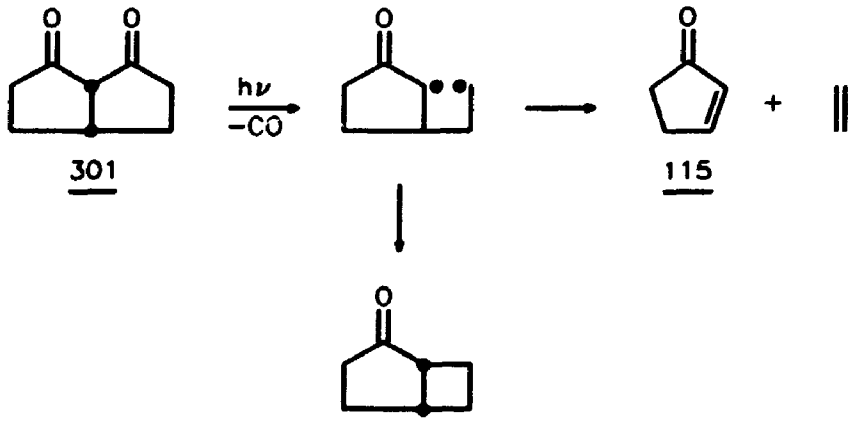
Mass spectroscopy showed the right mass (138) and nmr analysis confirmed the formation of **301**. The ^{1}H-nmr spectrum exhibited a doublet for the proton between the carbonyl groups and multiplets for the other protons, confirming a symmetrical

molecule. The ^{13}C-nmr spectrum confirmed this by displaying five lines with the correct multiplicities. The spectral data observed were in accordance with the literature.[131] A two dimensional heteronuclear correlation spectrum (HETCOR) allowed the assignment of the multiplets in ^{1}H-nmr spectrum by their coupling to ^{13}C-nmr resonances.

In all the nmr spectra no evidence for enolization was found. This is probably due to the fact that enolization would require a change in hybridization of the carbon α to both carbonyls from sp^3 to sp^2. This would force a planar arrangement which would be of higher energy for the fused ring system.

3.3.2 Photolysis of Bicyclo[3.3.0]octane-2,8-dione 301

Norrish Type I cleavage of **301** followed by decarbonylation would yield one of the biradicals implicated in the cycloaddition reaction between cyclopentenone and ethylene. This could then collapse to adducts or cleave to enone and alkene as illustrated in SCHEME 142.



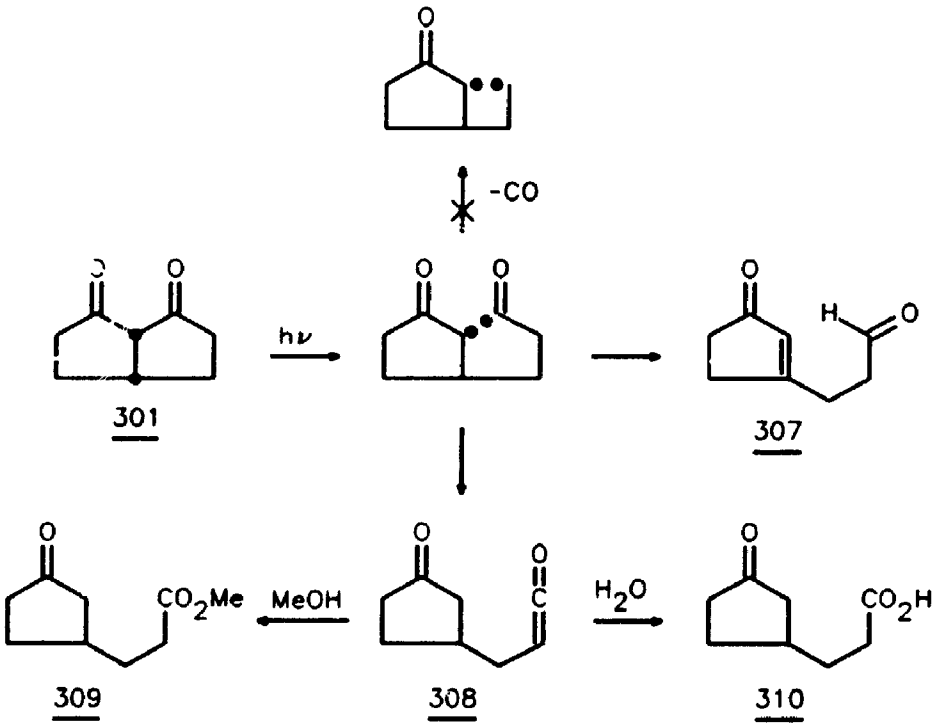
SCHEME 142

A benzene-d_6 solution of **301** was irradiated at room temperature with a medium pressure Hg-lamp in a Pyrex vessel.[132] After 23 hours ≈ 75 % conversion to a product with a slightly shorter retention time than **301** was observed. Additionally ≈ 5 % of a product with a longer retention time than **301** was seen; no formation of cyclopentenone was detected. Coupled gas chromatography/mass spectral analysis of the mixture showed that the major product had a mass identical to that of **301** whereas the minor product had gained mass 18 mass units. No indication for formation of any decarbonylation product was found.

Nmr spectroscopy of the irradiation mixture allowed the identification of the major product as aldehyde **307**. The presence of a triplet in the ^{1}H-nmr spectrum at ≈ 9.15 ppm and a multiplet at ≈ 5.63 ppm pointed to a 3-substituted cyclopentenone with an aldehyde in the side chain; as discussed in Section **2.2.1** the proton in the 2-position of cyclopentenones appears at a chemical shift of *ca.* 6.2 ppm.[91b] The ^{13}C-nmr spectrum confirmed the assignment; two carbonyl groups and two olefinic resonances were observed as expected.

These results were in accordance with the results of photolyses of **301** previously performed in our laboratory.[81]

When the irradiation was carried out in benzene/methanol 1:1,[132] the minor product observed by coupled gas chromatography/mass spectroscopy in the reaction performed in benzene-d_6 was not detected; instead a new product was formed with a mass of 170. This is suggestive of methanol quenching of the ketene **308** to give the methyl ester **309**. The minor product of the irradiation performed in benzene-d_6 was thus tentatively assigned as the acid **310** produced by adventitious water quenching of **308**. A summary of the photochemistry of **301** is shown in SCHEME 143.



SCHEME 143

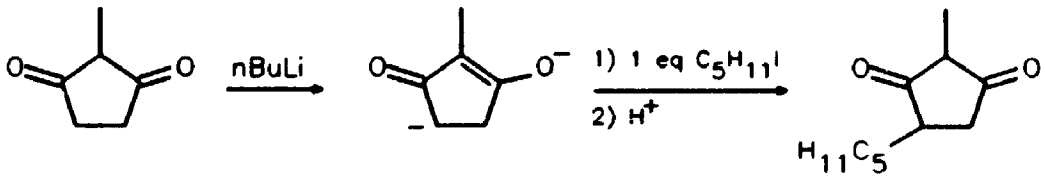
3.3.3 Preparation of 3-Methylbicyclo[3.3.0]octane-2,8-dione 311

Since in the bicyclo[3.3.0]octane-2,6-dione system the only substituent leading to decarbonylation products was the cyano group (*vide infra*) only this substituent was targeted for introduction into the bicyclo[3.3.0]octane-2,8-dione system. However, the reagent *p*-toluenesulfonyl cyanide (*p*-TsCN) utilized in the preparation of 3-cyanobicyclo[3.3.0]octane-2,6-dione **298** from diketone **261** was expensive and consequently it was decided to study the reactivity of diketone **301** with a cheaper electrophile, methyl iodide, before attempting to prepare the cyano derivative of **301** by reacting **301** with *p*-TsCN.

Alkylation of a 1,3-diketone at the less acidic α-positions presents a special problem because the central α-position flanked by two carbonyl groups is *ca.* ten orders of magnitude more acidic. Consequently normal alkylation procedures using base and electrophiles lead to substitution at the central carbon.

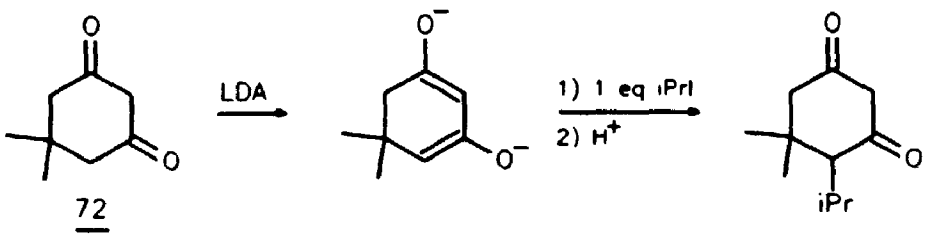
An elegant solution to this problem is the use of a dianionic species.[133] This involves treatment of a 1,3-diketone with two equivalents of a base strong enough to abstract a proton from the more acidic α-position and additionally a proton from one of the less acidic α-positions. Addition of one equivalent of the desired electrophile would result in preferential reaction with the more basic, more nucleophilic enolate site.

An example of this approach was published by Mellor and Pattenden in 1979 who were able to alkylate 2-methylcyclopentane-1,3-dione using the dianion generated by reaction with *n*-butyllithium. This yielded the product in 71 % yield as shown in SCHEME 144.[133b]



SCHEME 144

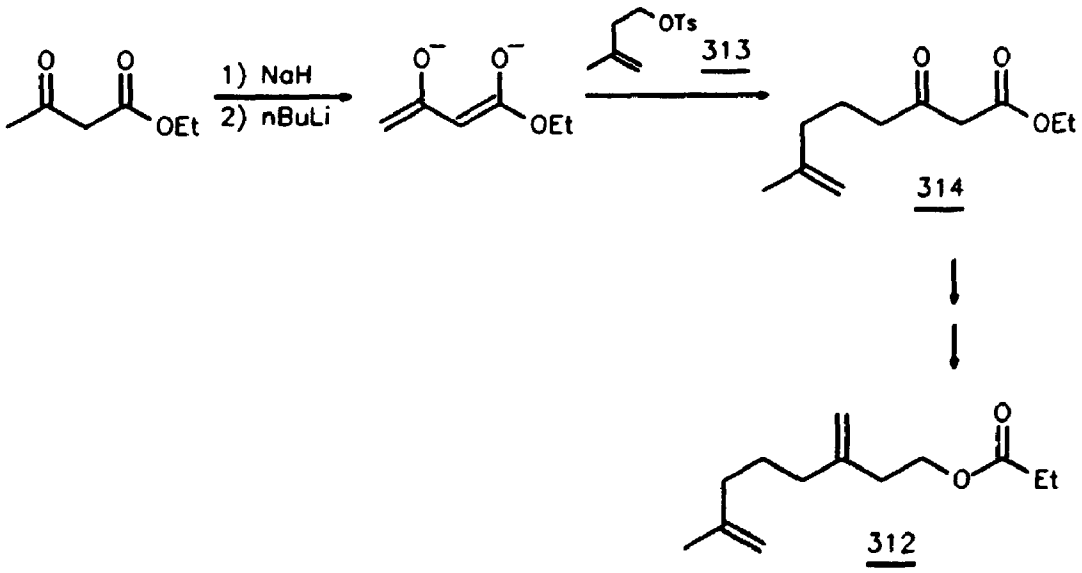
Similarly Harwood et al. reported in 1986 that they were able to alkylate dimedone **72** *via* its dianion to give the isopropyl substituted product in 78 % yield as illustrated in SCHEME 145.[133e]



72

SCHEME 145

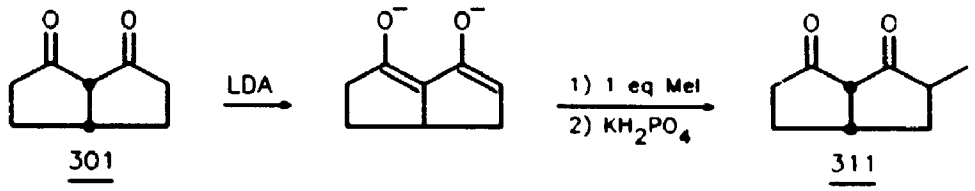
The same year Lombardo and Weedon published a synthesis for the insect pheromone **312**. This preparation involved the reaction of the dianion of ethyl acetoacetate with the tosylate **313** to generate β-ketoester **314** which was ultimately converted to **312** as shown in SCHEME 146.[133f]



SCHEME 146

This alkylation sequence was applied to diketone **301** using methyl iodide as the electrophile. Reaction of **301** with four equivalents of lithium diisopropyl amide (LDA) at -78°C in the presence of HMPA (to prevent O-alkylation[133g]) followed by addition

of one equivalent of methyl iodide led, after pH-controlled workup and chromatographic separation, to **311** (SCHEME 147) which was identified by its mass and nmr spectra.[132]



301 311

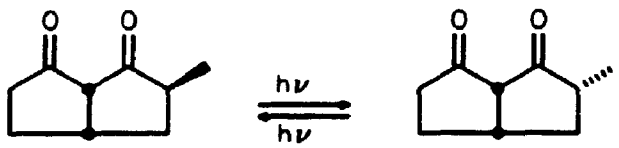
SCHEME 147

The spectroscopic data indicated that the product was a single stereoisomer of the monomethylketone **311** but it was not possible to determine the stereochemistry. The ^{1}H-nmr spectrum showed the methyl group as a doublet, proving that it was introduced correctly into the 3-position and not the 1-position. In addition, the doublet attributed to the central hydrogen between the carbonyl groups was visible. The ^{13}C-nmr spectrum exhibited nine peaks with expected multiplicities confirming that the desired product had been produced since substitution at the 3-position destroyed the symmetry present in **301**.

3.3.4 Photolysis of 3-Methylbicyclo[3.3.0]octane-2,8-dione 311

Since it was on hand **311** was irradiated in benzene to examine its photochemistry. After 18 hours ≈ 30 % conversion to two products (ratio ≈ 9:1) was observed. Coupled gas chromatography/mass spectroscopy studies of the product mixture showed that the major product (with a retention time slightly shorter than **311**) had the same mass as the starting material and a similar fragmentation pattern whereas the minor product (shorter retention time than **311**) also had the same mass

but a different fragmentation pattern. No indication of products derived from decarbonylation reactions was found, as shown in SCHEME 148. It was tentatively concluded that the major product stemmed from epimerization of **311** while the minor product might be derived from *α*-cleavage followed by hydrogen abstraction to give an aldehyde, as observed in the photolysis of **301**. Since the diketone **311** showed no evidence of decarbonylation and formation of the biradicals implicated in cycloaddition of cyclopentenone with propene, the photolysis products of **311** were not examined further.



311 311

no decarbonylation

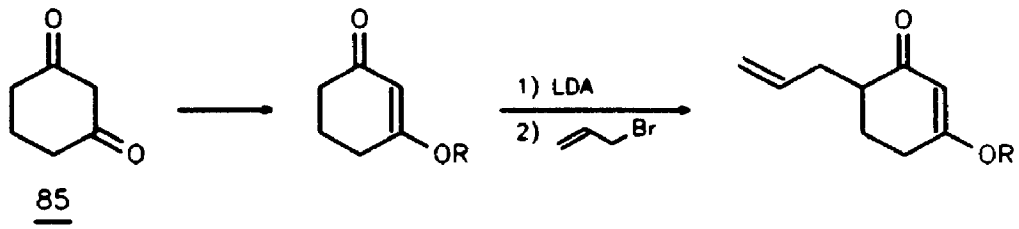
SCHEME 148

3.3.5 Preparation of 3-Cyanobicyclo[3.3.0]octane-2,8-dione 315

Since the methylation of the dianion of **301** in the 3-position was successful, attempts were made to introduce the cyano group into the same position using *p*-toluenesulfonyl cyanide (*p*-TsCN) as the electrophile. As described above for bicyclo[3.3.0]octane-2,6-dione **261** (Section 3.2.9) *p*-TsCN reacts with enolates to give the corresponding cyano compounds.[128h] Unfortunately reaction of **301** with lithium diisopropyl amide (LDA) followed by treatment with *p*-TsCN did not lead to any

formation of **315**; in addition to unreacted **301**, a number of unidentified side-products were recovered and a minor amount of *p*-toluenedisulfide was isolated and identified from the product mixture.[134]

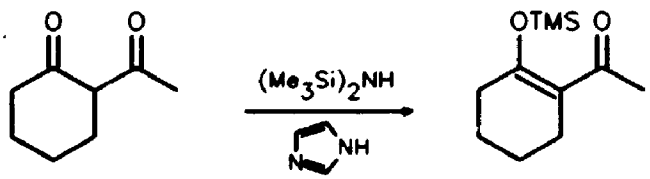
Several unsuccessful repetitions of the reaction resulted in this pathway for the preparation of **315** being abandoned and a different route was sought. In 1973 Stork and Danheiser reported that they were able to alkylate an enol ether of 1,3-cyclohexanedione **85** exclusively in the 6-position by treatment with lithium diisopropyl amide (LDA) followed by allylbromide as illustrated in SCHEME 149.[135]



85

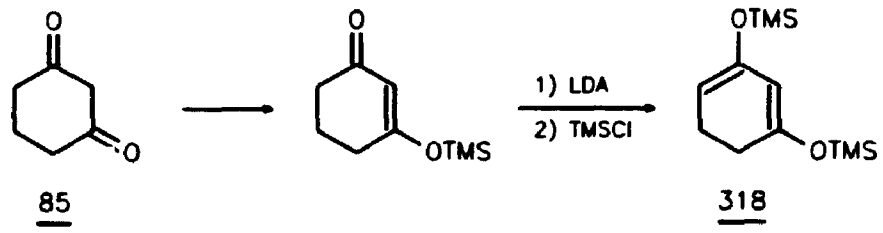
SCHEME 149

Torkelson and Ainsworth have reported a more comprehensive study of the chemistry of silyl enol ethers of 1,3-dicarbonyl compounds which they obtained by reaction of the 1,3-diketones with hexamethyldisilizane and imidazole.[136a,b] This reagent produces the desired compounds in very high yields (generally > 90 %) as shown for the preparation of **316** from **317**.



317 **316**

It was also shown that these silyl enol ethers could be deprotonated with lithium diisopropyl amide at low temperatures and then coupled with electrophiles.[136b] For example the silyl enol ether derived from **85** reacted with lithium diisopropyl amide followed by trimethylsilyl chloride to give **318**, the product of O-silylation, as shown in SCHEME 150.



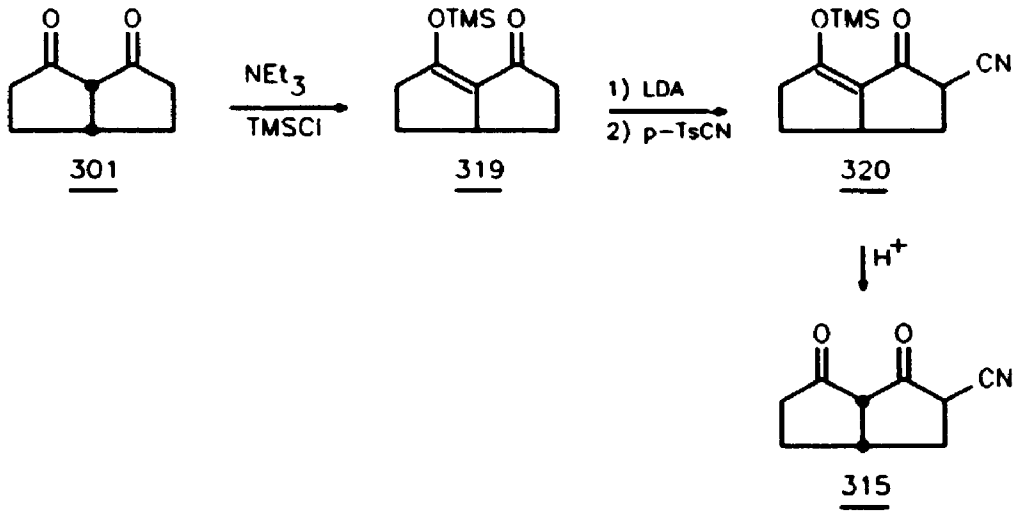
85 **318**

SCHEME 150

Similar results were obtained by the groups of Chan[136c] and Yamamoto.[136d] Encouraged by those reports it was decided to prepare the silyl enol ether **319** from diketone **301** and then react it with lithium diisopropyl amide followed by *p*-TsCN in order to generate **320**. Since silyl enol ethers are very susceptible to acid, mild hydrolysis of **320** should lead to **315** as illustrated in SCHEME 151.[124]

Unfortunately **319** was rather difficult to prepare. Treatment of a benzene solution of **301** with triethylamine followed by trimethylsilyl chloride resulted in formation of the insoluble amine hydrochloride; nmr analysis of the filtrate indicated the presence of **319** (≈ 54 %), diketone **301** (≈ 39 %) and a bis(trimethylsilyl) ether (≈ 7 %). Thus in the ^{1}H-nmr spectrum a singlet for the trimethylsilyl function of **319** was observed at 0.18 ppm and in the ^{13}C-nmr spectrum the expected nine lines with the correct multiplicities were seen. The presence of bis(trimethylsilyl) ether as the other product was based on the presence of a second singlet at ≈ 0 ppm in the ^{1}H-nmr

spectrum (but no other additional peaks) and a second peak in the 0 ppm region of the ^{13}C-nmr spectrum. Coupled gas chromatography/mass spectroscopy supported these conclusions.

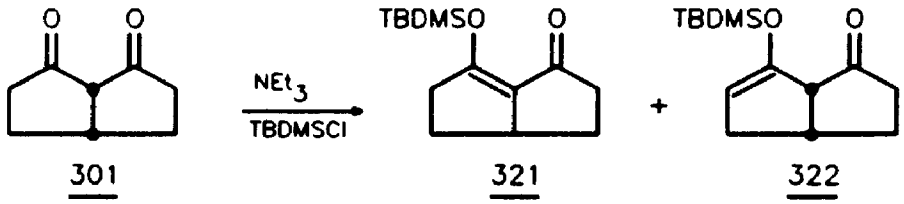


301 319 320 315

SCHEME 151

Repetitions of the reaction failed to increase the yield of **319** significantly, and it was concluded that this was because the silyl enol ether was extremely susceptible to hydrolysis. For example, exposure of **319** to laboratory air or non-dried dichloromethane resulted in rapid formation of diketone **301**. Attempts to generate **319** by reaction of **301** with hexamethyldisilizane and imidazole were not more successful and consequently the preparation of a more stable silyl enol ether of **301** was considered.

It has been reported that *t*-butyldimethylsilyl (TBDMS) enol ethers are more stable than their trimethylsilyl analogues, especially with respect to hydrolysis by acid or moisture.[137] This protecting group is also easily removed by reaction with fluoride ions.[123] Accordingly, the TBDMS enol ether, compound **321**, was prepared by reaction of **301** with TBDMSCl and triethylamine in benzene as shown in SCHEME 152.



301 321 322

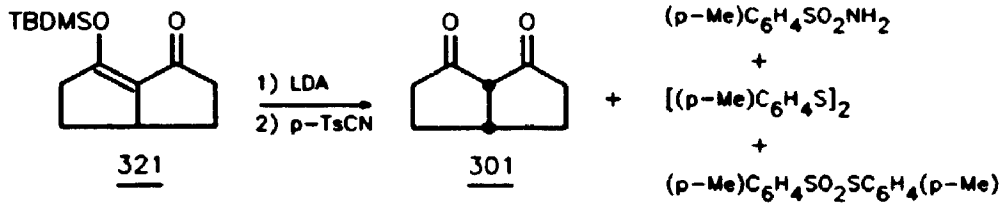
SCHEME 152

The enol ether **321** was isolated contaminated with *ca.* 10 % of **301** but because it was much more stable than **319** separation from **301** was possible by chromatography.

The structure of enol ether **321** was confirmed by inspection of the mass and nmr spectra. In the ^{1}H- and ^{13}C-nmr spectra the two methyl groups directly bonded to the silicon were not equivalent, possibly because of slow rotation about the oxygen-silicon bond The ^{1}H-nmr spectrum also exhibited a large singlet accounting for the nine (equivalent) protons of the *t*-butyl group and the ^{13}C-nmr spectrum showed the correct number of resonances with appropriate multiplicities; these included characteristic peaks for the olefinic carbons. The latter clearly showed that **321** had been formed and not its isomer **322** which was found as a by-product (≈ 30 %) in a preliminary run of the synthesis. Isomer **322** could easily be detected in a mixture because of the presence of two additional olefinic resonances in a ^{13}C-nmr spectrum; the APT spectrum indicated that one of these carbons was bonded to a hydrogen atom. The two enol ethers could not be separated by chromatography but fortunately later runs of the synthesis showed that **322** was not formed in significant amounts (< 0.5 %).

When enol ether **321** was treated with lithium diisopropyl amide followed by *p*-TsCN no indication of formation of the desired cyano compound was observed. The

products were mainly unidentified but coupled gas chromatography/mass spectroscopy showed the presence of **321**, **301** and species resulting from decomposition of *p*-TsCN, such as *p*-toluenesulfonamide, *p*-toluenedisulfide and *p*-tolyl *p*-toluenethiosulfonate as illustrated in SCHEME 153.[134,138]

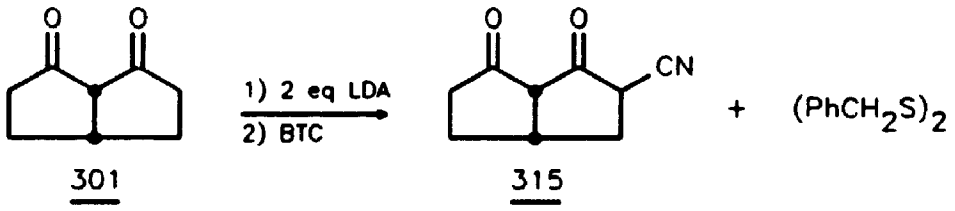


321 301

SCHEME 153

In repetitions of the experiment small amounts of product were observed which had the correct mass for the desired cyano silyl enol ether and its hydrolysis product **315**; however, the yields were so low that separation was not attempted.

Because of the difficulties encountered, the preparation of **315** by cyanation of the dianion of diketone **301** was attempted again. This time, reactior. of **301** with two equivalents of lithium diisopropyl amide followed by *p*-TsCN resulted in a mixture which by coupled gas chromatography/mass spectroscopy contained a small amount of desired product (≈8 %); the main products were derived from decomposition of *p*-TsCN. Since the cause of the problems in the reaction appeared to be the *p*-TsCN, an alternative cyanation reagent was examined. Use of benzylthiocyanate (BTC[128g]) in place of *p*-TsCN yielded a mixture of benzyldisulfide[134], unreacted **301** and the desired product **315** (SCHEME 154).



301 315

SCHEME 154

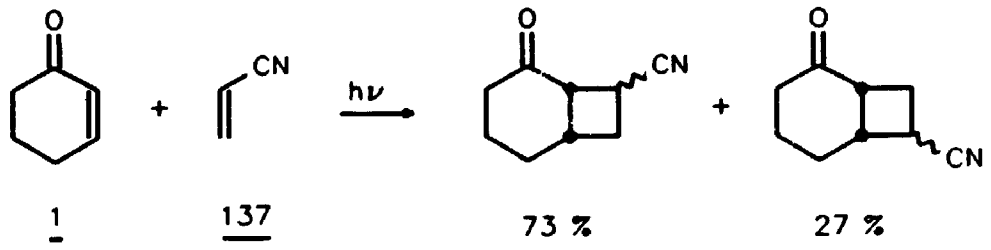
Purification and sublimation gave **315** which was identified by its mass and nmr spectra. The ^{13}C-nmr spectrum showed that the cyanodiketone isolated was a mixture of two stereoisomers present in a ratio of ≈3:2. The incorporation of a cyano group was confirmed by the presence of two signals at ≈ 115 ppm; in addition, four carbonyl resonances were observed and at higher field the correct number of signals with appropriate multiplicities were observed for the sp^3-carbons. No indication for enolization of the *α*-cyano ketone system was found.

3.4 Preparation and Assignment of the Regiochemistry of the 2 + 2 Cycloadducts 323 - 326 of Cyclopentenone 115 and Acrylonitrile 137

The first example for the 2 + 2 photocycloaddition between a cyclic enone and acrylonitrile appeared in the literature in the 1960's. In their much cited paper of 1964, Corey and coworkers dedicated a relatively small part of their work to the 2 + 2 cycloaddition reaction between 2-cyclohexenone **1** and acrylonitrile **137**.[62] They observed four isomeric cycloadducts (all *cis*-fused at the 6:4 ring junction) and concluded that the dominant mode of addition involved formation of the head-to-head isomers as indicated in SCHEME 155. They noted a large amount of polymeric material

building up in the reaction vessel and reported that the reaction was relatively slow compared with other alkenes. Their assignment of the ring fusion stereochemistry was based on the fact that under basic conditions none of the products isomerized as would be expected for a *trans*-fused ring fusion.

The 60 MHz ^{1}H-nmr spectra of the cycloadducts were used to assign their regiochemistry and based upon these assignments they concluded that the two major products (49 and 24 %) were the head-to-head regioisomers and the two minor products (15 and 12 %) were the head-to-tail regioisomers. Unfortunately no nmr data were reported by the authors so that the correctness of their assignments cannot be assessed.[62]

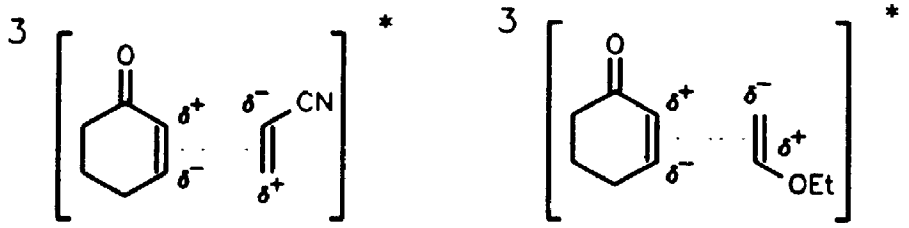


1 137 73 % 27 %

SCHEME 155

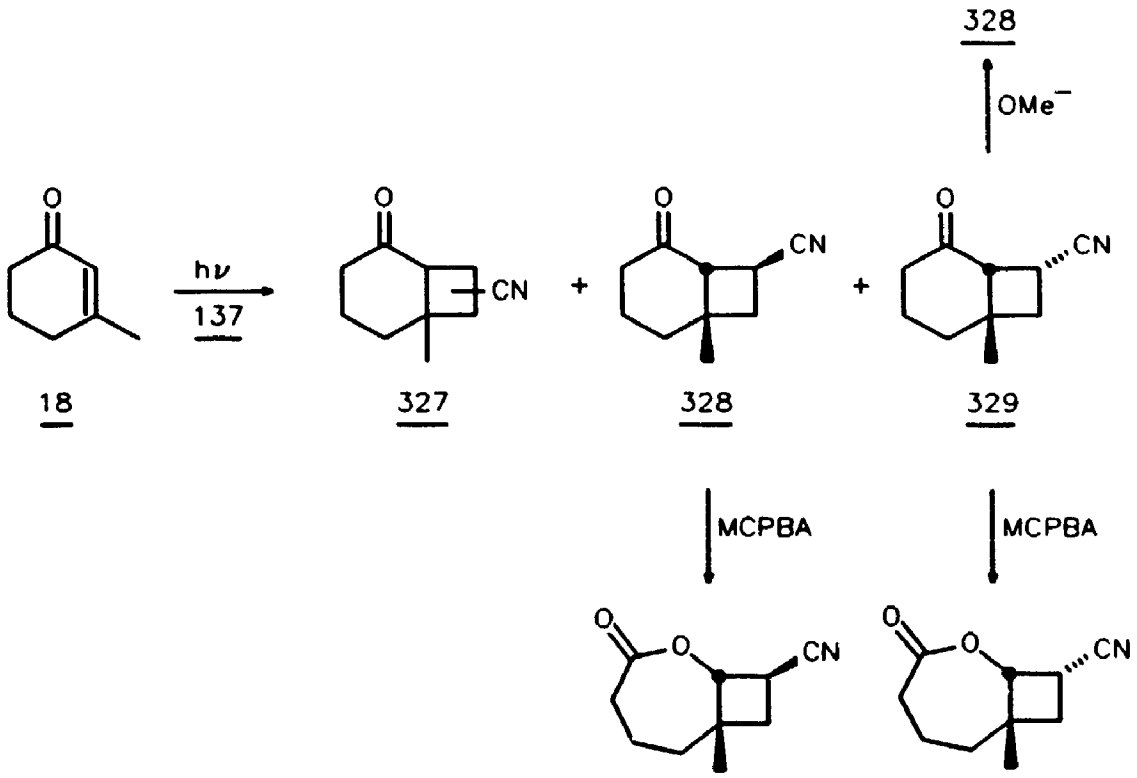
This regiochemical assignment was partly responsible for the development of the exciplex theory, since the polarity of the double bond in **137** is opposite to the polarity of the double bond in ethyl vinyl ether. These polarizations nicely explain the differing regiochemistry of addition of these two alkenes if it is assumed that they align with the polarized enone triplet excited state as shown in FIGURE 12.

FIGURE 12: Exciplexes between cyclohexenone and acrylonitrile and between cyclohexenone and ethyl vinyl ether



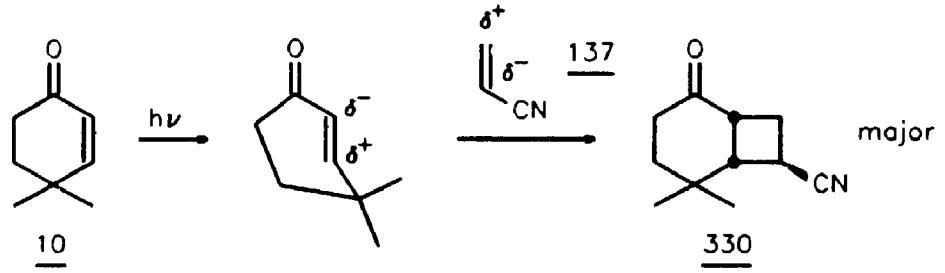
In 1968 Cantrell et al. published their work on the photocycloaddition reactions of 3-substituted 2-cyclohexenones.[70] They investigated the reaction between **137** and 3-methylcyclohexenone **18** and found that the addition proceeded surprisingly efficiently. In fact **137** reacted more efficiently with **18** than the other olefins studied (more than 13 times more efficiently than isobutene, more than 7.5 times more efficiently than cyclopentene and almost four times more efficiently than ethyl vinyl ether). This is in stark contrast to Corey's results.[62] The reaction between **137** and **18** led to the formation of three isomeric cycloadducts **327** - **329**. The assignment of the stereo- and regiochemistry of the main products was made by analysis of the ^{1}H-nmr spectra of the adducts and indicated that the head-to-head regioisomers dominated over the head-to-tail isomers in a ≈5:1 ratio.

Cantrell and coworkers were able to convert adduct **329** into its isomer **328** by treatment with sodium methoxide. Corey et al. did not see an analogous isomerization in the adducts between cyclohexenone and **137**; however, they used a different technique for epimerization (passing through alumina).[6] Cantrell's group also oxidized adducts **328** and **329** with *m*-chloroperbenzoic acid (MCPBA) to give the corresponding lactones in order to make the nmr analysis and regiochemical assignment more secure as illustrated in SCHEME 156.



SCHEME 156

Cantrell's results support Corey's findings that the preferred regiochemistry of the 2 + 2 cycloaddition is head-to-head when an olefin bearing an electron withdrawing group is used. Recently Kunwar et al. published a report of the photocycloaddition reaction of 4,4-dimethyl-2-cyclohexenone **10** with acrylonitrile **137**.[139] Using one and two dimensional nmr techniques they concluded that the major isomer formed is the head-to-tail isomer **330** shown in SCHEME 157. This result contradicts Corey's[62] and Cantrell's[70] findings and was explained by addition of the alkene to the ground state *trans*-isomer of **10** which would be polarized as illustrated in SCHEME 157.[139]



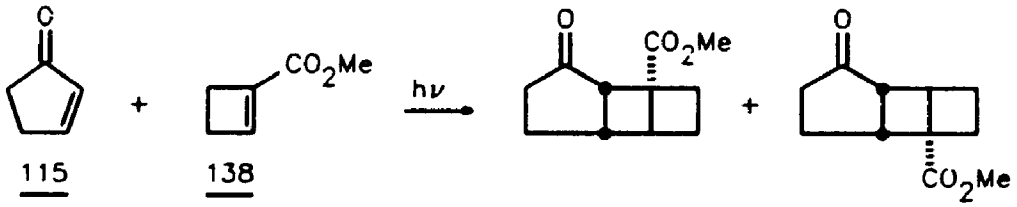
10 330

SCHEME 157

In his review Schuster considered the possibility of energy transfer between triplet enone and **137** (*vide infra*) but the product distribution in terms of regiochemistry (especially in the cyclopentenone case) was not discussed.[1]

Electron withdrawing substituents other than cyano groups on the alkene have been investigated by a number of groups.[2,76,140] The most frequently examined systems have been esters of acrylic acid.

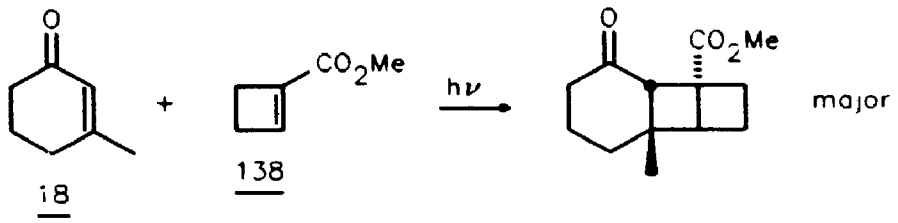
Wender and Lechleiter irradiated **115** with the cyclobutene **138** and found a preference for the head-to-tail adduct as shown in SCHEME 158.[140a]



115 138 29 % 71 %

SCHEME 158

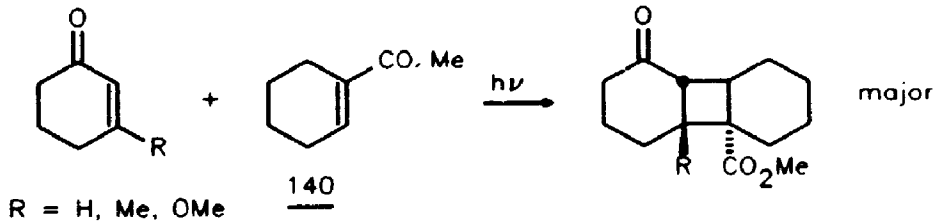
Wender and Hubbs showed that **138** added photochemically to 3-methyl-2-cyclohexenone **18** to give the head-to-head isomer as the major product as illustrated in SCHEME 159.[140b]



18 138

SCHEME 159

Recently Tada and Nieda published their results of the photocycloaddition reaction of 3-substituted 2-cyclohexenones with methylcyclohexene-1-carboxylate **140**.[140c] They found that the major products formed were the head-to-tail adducts as illustrated in SCHEME 160.

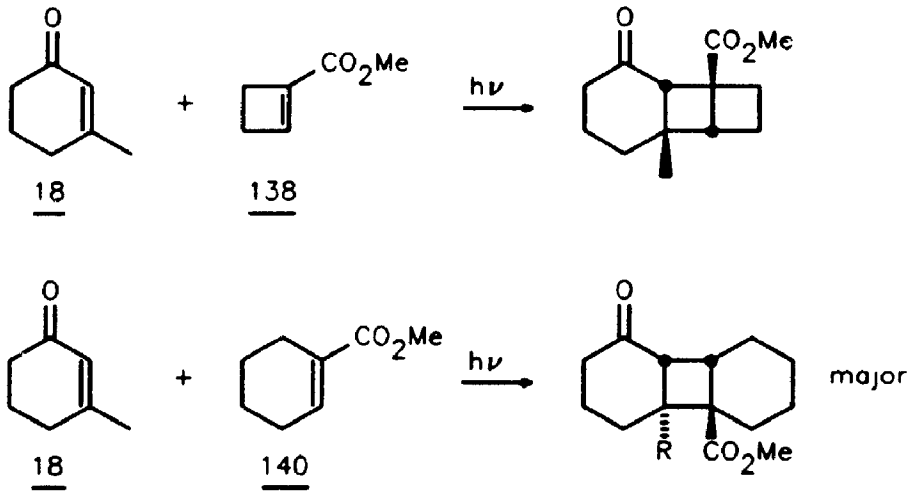


R = H, Me, OMe 140

SCHEME 160

Wender's[140b] and Tada's[140c] results support the findings by Lange et al. who published a report on the influence of the ring size of various cycloalkene-1-carboxylates on the regiochemical outcome of the 2 + 2 photocycloaddition reaction with 3-methylcyclohexenone **18**, as discussed earlier.[76] However, Lange's group reported that the products obtained in their reactions had different stereochemistry (as shown in SCHEME 161) than those reported by Wender and Tada. They observed for the reaction with cyclobutene carboxylate **138** a *cisoid* configuration with respect to

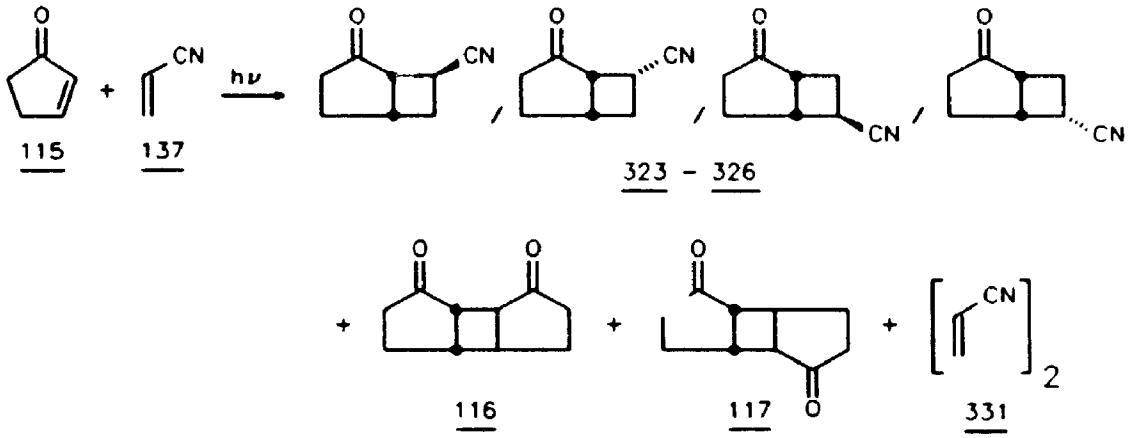
the arrangement at the central cyclobutane ring[76] whereas Wender reported a *transoid* configuration in their product.[140b] Lange also observed different stereochemistry in the irradiation of **18** with cyclohexene carboxylate **140** in comparison with Tada's results.[140c]



SCHEME 161

In the work described in this thesis it was necessary to isolate and identify the cycloadducts formed from photochemical reaction between **115** and **137** in order to be able to recognize them as possible products in the irradiations of the cyanodiketones **298** and **315**. Accordingly a benzene solution of cyclopentenone was irradiated in the presence of a five fold excess of acrylonitrile. As the reaction progressed the formation of a large amount of polymeric material was observed (most likely polyacrylonitrile from polymerization of **137**, along with the formation of seven products as observed by gas chromatography. Coupled gas chromatography/mass spectroscopic analysis showed that the last two (i.e. least volatile) products were dimers of **115** (**116** and **117**) and this was confirmed by comparison with authentic samples of the dimers obtained from earlier experiments. The first product (i.e. that

with the shortest gc retention time) had a mass of 106 which led to its preliminary identification as **331**, a dimer of **137** (*vide infra*). The other four products **323** - **326** were found to have a mass of 135 which is consistent with their being stereo- and regioisomeric 1:1 adducts of **115** and **137** as illustrated in SCHEME 162.



SCHEME 162

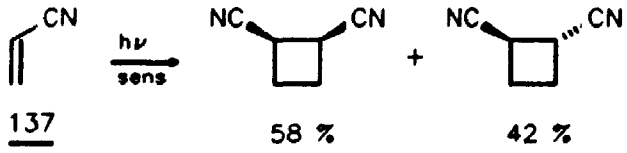
The ratio (in order of increasing retention time) of adducts **323**:**324**:**325**:**326** was ≈ 1.77:1.11:2.74:1. The mass spectral fragmentation patterns of **323** and **326** showed a resemblance; this was also true for the pair of adducts **324** and **325**. However, there were significant differences between the fragmentation patterns of the two pairs. For example **324** and **325** both had a large (100 %) fragment at 82 mass units whereas this signal was small for **323** and **326**. The latter pair also exhibited a much smaller amount of a fragment of 54 mass units than the former pair. These findings hinted that **324** and **325** might be diastereomers which are regioisomers of **323** and **326**.

The mixture of seven products was separated by chromatography into five fractions (I - V) each containing two or three of the products as shown in TABLE 28.

TABLE 28: Product distribution after partial separation of the adduct mixture

	Composition in %						
Fraction	**323**	**324**	**325**	**326**	**331**	**117**	**116**
I	79				21		
II	69	31					
III		41	53				6
IV		2	97			1	
V			56	34		10	

Analysis of the ^{1}H-nmr spectra of these mixtures was not very useful since all signals were essentially overlaying multiplets between 1 and 3 ppm. The ^{13}C-nmr spectra, on the other hand, allowed the assignment of all peaks to the various products since the signals for the dimers **116** and **117** were known and subtraction led to the adduct signals. It was possible to confirm that **331** was in fact a 2+2 dimer of **137** since it only had three resonances, one methylene, one methine and one nitrile. In 1968 Hosaka and Wakamatsu described the (triplet sensitized) photodimerization of **137** which gave a 58:42 mixture of *cis*- and *trans*-1,2-dicyanocyclobutane believed to proceed *via* a biradical intermediate as shown in SCHEME 163.[141a]



137 58 % 42 %

SCHEME 163

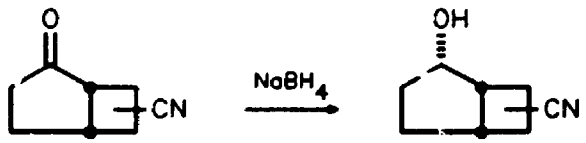
No further investigations of the regio- and stereochemistry of dimer **331** were carried out; however, the ^{1}H-nmr and ^{13}C-nmr chemical shifts of product **331** were in very good agreement with published data for 1,2-dicyanocyclobutane.[141b,c]

The ^{13}C-nmr analysis also confirmed that **323** - **326** were 2 + 2 cycloadducts of **115** and **137** since the expected number of peaks were present with the appropriate multiplicities. Unfortunately was it not possible to assign regiochemistry to **323** - **326** from the nmr spectra obtained since the important cyclobutane resonances could not be isolated from the remaining signals. The ^{13}C-nmr spectra were also not sufficiently different to allow unambiguous assignment. However, as with the mass spectral fragmentation patterns of **323** - **326**, the ^{13}C-nmr spectra did suggest a pairing of regioisomers. For example **323** and **326** both exhibited their lowest field methine signal at 47.4 and 46.2 ppm, respectively, whereas **324** and **325** had theirs at 42.0 and 41.8 ppm, respectively. Similarly the carbonyl resonances of **323** and **326** appeared at slightly lower field than those of **324** and **325**.

In order to confirm the regiochemical pairing, attempts were made to epimerize the samples of partially separated adducts using bases such as proton sponge (1,8-bis[dimethylamino]naphthalene) and also with sodium methoxide. This was done by analogy with the isomerizations reported by Cantrell et al. for adducts of **18** with **137**.[70] It was hoped that if **323** and **326** were diastereomers, regioisomeric with **324** and **325**, then the action of base would interconvert **323** with **326**, and **324** with **325**. In the event, no reaction occurred when proton sponge was used while methoxide appeared to yield products of methanolysis of the nitrile groups, as judged by gc/ms.

The alcoholysis of nitriles is a known reaction and is usually performed in acidic media although the base catalyzed reaction has also been reported.[142]

As an alternative to the isomerization of the adducts with base as a probe of regiochemistry, reduction of the carbonyl groups of the adducts was attempted. It was anticipated that reduction of the carbonyl group to an alcohol function would generate a methine visible in the ^{1}H-nmr spectrum whose coupling pattern could be used to garner information about the position of the cyano group. Literature precedents indicate that a carbonyl group can be reduced to an alcohol function in the presence of a cyano group.[142] Sodium borohydride in ethanol is the reagent of choice since lithium aluminum hydride is known to attack nitriles also. Reduction of adduct **323** (contaminated with the dimer of **137**) to the corresponding alcohol with this reagent was therefore attempted. Gas chromatographic analysis of the reaction mixture obtained showed the total disappearance of **323** and formation of one single new product with a longer retention time which was still contaminated with **331**. Chromatographic separation increased the purity of the product to > 98 %. It was identified by mass and nmr spectroscopy as one isomer of the alcohol **332**.



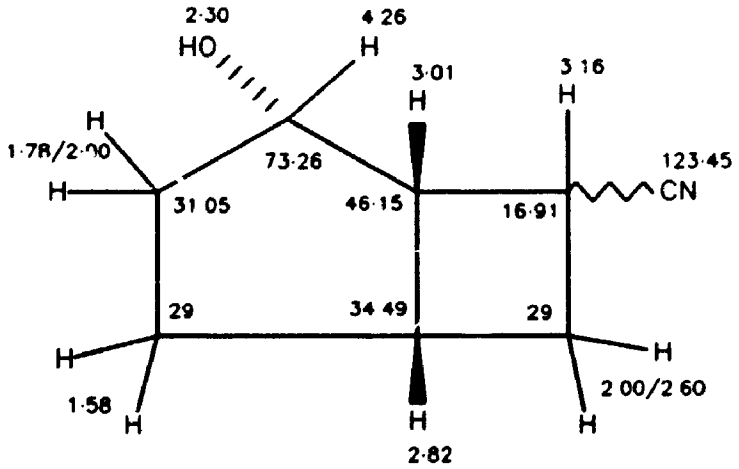
323 **332**

The mass spectrum of **332** indicated a molecular ion with a mass of 137, confirming the addition of two hydrogens to **323**, while the ^{13}C-nmr spectrum showed the disappearance of the carbonyl peak which was replaced with a resonance at ≈ 73 ppm. This is in the correct range for carbons bearing a hydroxyl group[39]; the peak also possessed the expected methine multiplicity. The nitrile signal was still present at ≈ 123 ppm. The fact that only one single stereoisomer of **332** was formed by

reduction of the carbonyl group can be explained if the borohydride attacks the carbonyl exclusively from the less hindered face of **323** leading to the stereochemical arrangement shown in structure **332**.

The ^{1}H-nmr spectrum of **332** showed a dramatic change when compared to that of **323**. Instead overlapping multiplets, signals due to single protons could be resolved, especially in the lower field region of the spectrum. The signals due to single protons were observed at 2.60, 2.82, 3.01, 3.16 and 4.26 ppm whereas three multiplets at 1.56, 1.78 and 2.00 ppm accounted for two, one and two protons each, respectively. The hydroxyl proton was recorded as a broad singlet at 2.30 ppm. This dispersion allowed the assignment of head-to-head regiochemistry to **332**, and ultimately to **323**, by two dimensional nmr spectroscopy combined with decoupling experiments. The final assignment of structure **332** along with the proton and carbon chemical shift assignments (in ppm) is shown in FIGURE 13 and is followed by the discussion of the spectroscopic analysis.

FIGURE 13: Nmr assignment of alcohol **332**



332

The lowest field multiplet (4 26 ppm) in the ^{1}H-nmr spectrum of **332** was assigned to the proton on the carbon bearing the hydroxyl function since this would be expected to be most deshielded.[39] This was confirmed by a HETCOR experiment which showed that this proton was attached to the lowest field methine carbon (≈ 73 ppm) which from its chemical shift must be that attached to the hydroxyl group. Also of interest was the observation that the second lowest proton signal at 3.16 ppm was connected to the most upshifted methine at ≈ 17 ppm. The other carbon-hydrogen correlations were less significant and basically showed that the single proton signals at 3.16, 3.01 and 2.82 ppm were derived from methine groups whereas the single proton signal at 2.60 ppm and the higher field multiplets were part of methylene groups.

A HOMOCOR experiment revealed that the proton at 4.26 ppm was coupled into the methylene proton multiplets at 1.78 and 2.00 ppm as well as to the methine signal at 3.01 ppm. Thus the single proton signal at 1.78 ppm and one of the two protons appearing at 2.00 ppm were determined to be attached the methylene carbon adjacent to that bearing the hydroxyl group (the HETCOR confirmed that these were both bonded to a methylene carbon at ≈ 29 ppm); the coupling between the proton at 4.26 ppm and that at 3.01 ppm indicates that the latter is at the ring junction adjacent to the hydroxyl bearing carbon. The signal at 3.16 ppm was also found to couple into the two proton multiplet at 2.00 ppm in addition to the single proton signals at 3.01 and 2.60 ppm. Other couplings were observed between the signals at 2.82 ppm, 2.60 and 2.00 ppm and extensively between the highfield multiplets.

The proton at 4.26 ppm was a six line signal derived from partial overlapping of a doublet of doublets of doublets; this is the expected coupling pattern for this proton in the reduction product of both of the possible regioisomeric 2 + 2 adducts.

Selective decoupling of this proton led to changes in the multiplets at 1.78 and 2.00 ppm as well as in the signal at 3.01 ppm. This decoupling experiment confirmed the assignment of the protons on the carbons adjacent to the alcohol substituted carbon obtained from the two dimensional ^{1}H-^{1}H correlated spectrum. The fully coupled signal at 3.01 ppm was a four line resonance with significant line broadening indicating that it was a doublet of doublets of doublets (with similar coupling constants causing the appearance of a quartet). After irradiation at 4.26 ppm the signal at 3.01 ppm changed into a triplet, again with significantly broadened lines.

Selective decoupling of the signal at 3.01 ppm gave the following result. The six line signal at 4.26 ppm was reduced to a four line signal (doublet of doublets), the signal at 3.16 ppm was completely altered (*vide infra*) and a small change in appearance was observed in the signals at 2.82, 2.60 and 2.00 ppm.

Using coarser rules for calculation of proton chemical shifts[39] it was proposed at this stage that the signal at 3.16 ppm was the proton on the methine carbon bearing the cyano group. Starting with the chemical shift of an unsubstituted cyclobutane of $\approx$ 2.0 ppm[39] and taking into account that according to the modified Shoolery rules[39] a cyano group on a methine leads to a downfield shift of $\approx$ 1.2 ppm, then this predicts that the proton adjacent to the cyano group should appear at 3.2 ppm. Cantrell and coworkers determined the chemical shift of the proton adjacent to the cyano group in the two cycloadducts **327** and **328** to be 3.42 ppm and 3.17 ppm, respectively.[70]

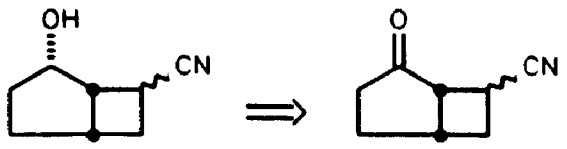
Various calculation methods for carbon chemical shifts show that a cyano substituent induces only a small change in shift of the substituent bearing carbon.[39] This is reflected in the chemical shift of the carbon bearing the cyano substituent in compounds such as acetonitrile (1.3 ppm), propionitrile (10.6 ppm), 2-cyanopropane (22.4 ppm), cyanocyclohexane (28.3 ppm) and cyanocyclobutane (22.0 ppm).[39,91a,c]

These shifts differ only slightly from those of the non-substituted hydrocarbons; in addition, Kunwar and coworkers have shown that the carbon bearing the cyano group in the cycloadduct **330** between 4,4-dimethylcyclohexenone and acrylonitrile was the highest field signal (22.8 ppm) of all carbons in that compound.[139]

The HETCOR experiment ruled out the other possibility that the proton adjacent to the cyano group was the signal at 2.82 ppm because this correlated with the methine at ≈34 ppm which is too low field shifted to be the cyano bearing methine carbon. All other proton signals were either already assigned or the HETCOR experiment showed that they were bonded to a methylene carbon.

The signal for the proton at 3.16 ppm was a solvable sixteen line doublet of doublets of doublets with coupling constants of ≈10, 7, 5 and 1 Hz. In both possible regioisomeric alcohols this pattern would be expected for the proton adjacent to the cyano substituent (three couplings to the vicinal neighbours and one small coupling diagonally across the cyclobutane ring); however, the HOMOCOR experiment clearly showed that the signal at 3.16 ppm was coupled strongly into the proton adjacent to the alcohol carbon at 3.01 ppm and hardly at all into the other methine hydrogen at 2.82 ppm which had to be the proton on the other ring junction. On the other hand this proton was coupled to the signals at 2.60 and 2.00 ppm which were assigned to be the two protons on the cyclobutane methylene.

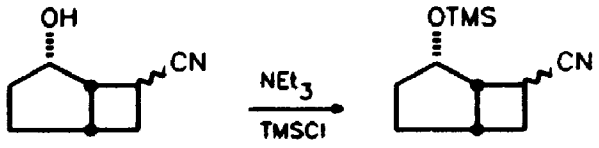
Thus it was concluded that **332** was a single stereoisomer of a reduced adduct **323** with head-to-head regiochemistry. No stereochemical analysis regarding the position of the cyano group was carried out.



332 323

At this point it was hoped that base catalyzed epimerization of the cyano group of **332** would lead to the identification of its stereoisomer and hence the assignment of the other regioisomeric pair of stereoisomers of the cycloadducts. However, treatment of **332** with proton sponge in refluxing benzene did not lead to any detectable reaction after 19 hours. It was suspected that the relatively acidic hydroxyl proton interfered with the isomerization attempt by being more readily abstracted than the much less acidic proton adjacent to the cyano group.

Protection of the alcohol function with trimethylsilyl chloride was carried out and led to the formation of a new product with a slightly longer retention time than **332** when analyzed by gas chromatography. Its mass spectrum gave a mass of 209 mass units confirming its identity as silyl ether **333**.



332 333

When **333** was heated in benzene with proton sponge for 19 hours no change in the composition of the mixture was detected; addition of triethylamine and continued heating for additional 21 hours also induced no change. At this point it was

decided not to pursue the isomerization pathway any further but rather to analyze spectroscopically the fractions II - V containing the other adducts.

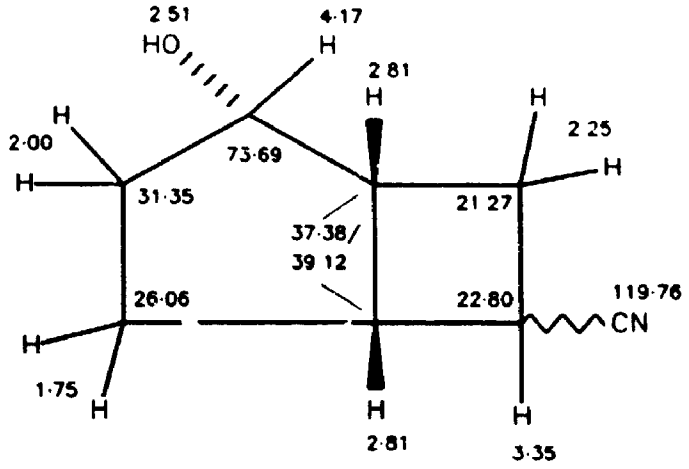
Fraction II (containing adducts **323** and **324** in a ≈ 7:3 ratio) was reduced with sodium borohydride. Coupled gas chromatography/mass spectral analysis of the product mixture showed two products with the correct mass in a ≈ 7:3 ratio, although the order of elution was reversed. Co-injection with an authentic sample of **332** obtained from reduction of **32**[illegible] in fraction I proved that alcohol **334** (from **324**) eluted first.

Chromatography allowed concentration of **334** in the mixture to ≈ 44 % but further structural identification was not possible because of the contamination by **332**. Isomerization of the products was attempted with proton sponge but again did not lead to any new products detectable by gas chromatography nor any change in the ratio of the alcohols.

Fraction IV (containing adduct **325** in ≈ 97 % purity) was also reduced with sodium borohydride to give one alcohol **335** in > 99 % purity. Again it was argued that attack of the borohydride from the less hindered side of the carbonyl group would lead to preferential formation of one stereoisomer of the alcohol. The alcohol was identified by its mass spectrum as well as by nmr analysis which allowed the determination of the regiochemistry as head-to-tail.

The final assignment for the structure of **335** with the proton and carbon chemical shift assignments (in ppm) is shown in FIGURE 14 and is followed by the discussion of the spectroscopic analysis.

FIGURE 14: Nmr assignment of alcohol **335**



335

The ^{13}C-nmr spectrum showed the correct number of signals each possessing the expected multiplicities for the product. The characteristic peaks for the nitrile carbon (≈ 120 ppm) and methine carbon bearing the hydroxyl group (≈ 74 ppm) were observed. The ^{1}H-nmr spectrum exhibited drastically improved dispersion of the signals when compared with the spectrum of **325**. The higher field hydrogens came as two close multiplets, each accounting for two hydrogens, at 1.75 and 2.00 ppm. Further downfield a multiplet (two hydrogens) at 2.25 and a broad singlet (hydroxyl proton) at 2.51 ppm were observed. Then followed multiplets at 2.81 (two hydrogens), 3.35 and 4.17 ppm (one hydrogen each). The latter signal was a six line multiplet, which was assigned to the methine proton on the carbon bearing the hydroxyl group. This was supported by a HETCOR spectrum which showed that it was attached to the lowest field methine carbon.

The HETCOR spectrum also revealed that the two hydrogens at 2.81 ppm were connected to two different methine carbons. The highest field methine carbon at

≈ 23 ppm was assigned to that bearing the cyano group and was connected to the proton at 3.35 ppm. The other correlations were of lesser significance.

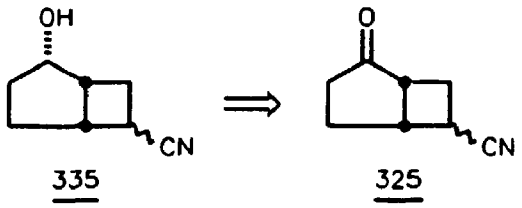
A HOMOCOR experiment showed that the proton at 4.17 ppm was strongly coupled into the two proton multiplets at 2.00 and 2.81 ppm. The former was identified by HETCOR spectroscopy to be a methylene group and was thus assigned to the group adjacent to the former carbonyl carbon. Since the two protons at 2.81 ppm were connected to two different methine carbons they were identified as the protons on the ring junction carbons.

The HOMOCOR spectrum further demonstrated that these protons were coupled to the signal at 3.35 ppm as well as to the two proton multiplets at 1.75 and 2.25 ppm. The coupling of the latter to the signal at 3.35 ppm allowed the assignment of the methylene group in the cyclobutane ring whereas the former showed coupling into the methylenes at 2.00 ppm and was thus determined to be the remaining methylene group in the cyclopentanol ring.

The problem that had to be overcome was the apparent isochronicity of the protons on the ring junction. Without resolving these signals a regiochemical assignment would not be possible since any decoupling experiments would be inconclusive. However, when the multiplet at 2.81 ppm was expanded it could be seen that it was composed of two overlaying multiplets, one to lower field having triplet-like substructure and one to higher field having broad singlet substructures.

Irradiation at the frequency of the signal at 4.17 ppm led to a change in the lower multiplet whereas irradiation at 3.35 ppm led to a change of the higher multiplet. This was only explainable if the lower signal was close to the hydroxyl bearing carbon and the upper signal close to the cyano bearing carbon. This led to the conclusion that

335 is the alcohol derived from reduction of adduct **325** with head-to-tail regiochemistry.



335 325

Compound **335** was converted to its silyl ether **336** by reaction with trimethylsilyl chloride which was identified by its mass spectrum. Epimerization of the cyano group of **336** was attempted by refluxing in benzene with proton sponge and, subsequently, triethylamine. After 76 hours the only observable change was a moderate degree of deprotection (≈ 20 % by gas chromatography) to regenerate **335**. Using more drastic conditions (sodium hydride in benzene at low temperature for one hour) did not lead to any reaction at all, while heating in dimethyl formamide (≈ 100°C) with sodium hydride for two hours resulted in complete conversion to **335**.

Since the attempted epimerization of **323** and **325** and their derivatives was unsuccessful it was conjectured that this could be due to the fact that they already existed as the more stable stereoisomers so that any isomerization would be endothermic. Another explanation could be that the stereoisomers at the alcohol and silyl ether stage had identical gas chromatographic retention times and thus were not detected. To test this hypotheses fraction III (containing **324** and **325** in a ≈44:56 ratio) was reduced with sodium borohydride. Gas chromatographic analysis of the product showed only one peak; however, the ^{13}C-nmr spectrum (which was easier to analyze than the ^{1}H-nmr spectrum since known resonances could be more easily

identified and subtracted) clearly revealed that two isomeric products had been formed. Consequently alcohols **334** and **335** had identical retention times which meant that in the attempted epimerization reactions no change would have been detected by gas chromatography. Therefore the mixture of **334** and **335** was treated with triethylamine in refluxing benzene and the reaction progress was monitored by ^{13}C-nmr spectroscopy. After 19 hours the ^{13}C-nmr spectra of the mixture was compared with that of the original mixture. Since ^{13}C-nmr spectra can only be integrated with difficulty due to the different relaxation properties of differently substituted nuclei[39] the intensities of similar nuclei in each compound were used for quantitative comparison. This resulted in the ratios shown in TABLE 29.

TABLE 29: Ratios of intensities of similar carbon nuclei

Nuclei in **335**/**334** (shift in ppm)	Ratio before isomerization	Ratio after isomerization
highest field methylene (21.26/20.68)	1.560	1.514
highest field methine (24.74/22.78)	0.795	0.739
Σ of other two highfield methines (37.35+39.12/38.29+41.92)	1.098	1.242
lowest field methine (CH-OH) (73.69/73.27)	1.191	1.162

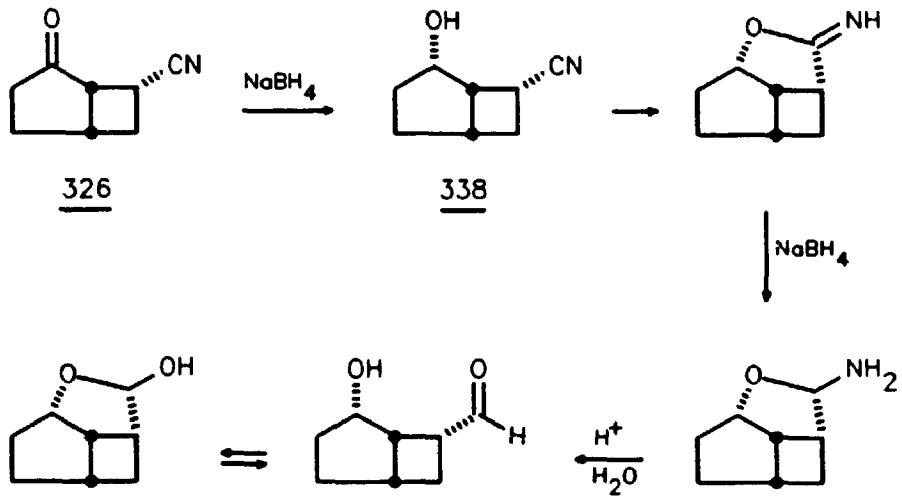
As can be seen the numbers before and after isomerization are, within the relatively large error margins inherent to this method, identical and therefore no isomerization to each other, or to other species, had occurred.

The mixture of **334** and **335** was converted to their silyl ethers by treatment with trimethylsilyl chloride. A gas chromatogram of the reaction mixture showed

disappearance of the alcohols and formation of two products in a ≈4:5 ratio. The major product was identified by comparison with known data for **336** and nmr spectroscopy allowed the assignment of the minor product as silyl ether **337**, but no further regiochemical assignment was possible. The ^{1}H-nmr spectrum exhibited one large singlet at ≈0 ppm indicative of the trimethylsilyl function and revealed that the two signals for the products were isochronous. The broad singlet of the hydroxyl group had disappeared but no assignment of the other peaks to one or the other isomer could be made. In the ^{13}C-nmr spectrum two peaks at ≈0 ppm were observed for the trimethylsilyl groups in addition to the appropriate number and multiplicities of peaks for the two isomers but no assignment to a specific silyl ether was possible. The silyl ether mixture was refluxed in benzene containing triethylamine. Gas chromatographic analysis after 17 hours showed no change in the ratio of **336** and **337** and no other new product formation. Addition of sodium hydride also did not lead to any change.

The only adduct not yet reduced to the corresponding alcohol was **326**. Fraction V (containing **325** and **326** in a 56:34 ratio in addition to 10 % dimer **117**) was treated in the usual manner with sodium borohydride. This resulted in a relatively complex product mixture as determined by gas chromatography. The major product (≈80 %) was identified by comparison of coupled gas chromatography/mass spectroscopy data as alcohol **335** derived from adduct **325**. Of the other peaks none could be identified by coupled gas chromatography/mass spectroscopy as the expected reduction product of **326**. In contrast to the reductions carried out so far with the fractions containing **323** - **325** (which had been very clean reactions without any by-products being formed) the reduction of fraction V gave ≈20 % other products. In particular one product peak (≈6 %) was of interest; the mass spectrum indicated that its mass was 140 and its fragmentation pattern showed peaks at 123 (-17) and 112

(-28) mass units. These data pointed to an alcohol and/or carbonyl compound. It was hypothesized that if reduction of **326** yielded **338** then this might close to a cyclic imine which on further reduction would produce the species obtained in 6 % yield. For this to occur **326** would have to be the endo head-to-head isomer adduct as indicated in SCHEME 164.



SCHEME 164

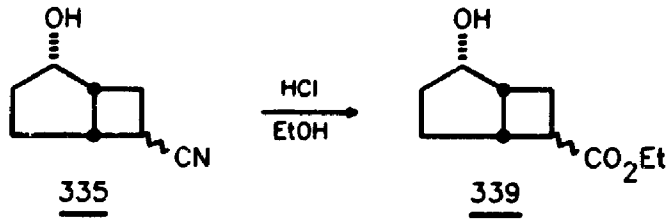
Because of lack of material and time constraints further examination of the reduction product of **326** was not undertaken. Instead a different method of identifying the adducts by chemical alteration was tried out. This used the fact that nitriles undergo acid catalyzed alcoholysis to the corresponding esters by reaction in alcohol with aqueous acid (Pinner synthesis).[142]

$$R-CN \xrightarrow[R'OH]{H^+/H_2O} R-COOR'$$

Since the α protons of esters are more acidic than the α protons of nitriles it was envisioned that conversion of an adduct into the corresponding ester would lead to a compound which could be easier to epimerize in order to identify the pairs of diastereomers present in the mixture of **323** - **326**.

When adduct **325** was treated with 1 M HCl in ethanol, formation of a new product (≈ 67 %) with longer retention time was observed. Coupled gas chromatography/mass spectroscopic analysis showed that the product had a mass of 209 mass units (27 mass units higher than the expected ester). No further attempts at identification of this product were made.

Next alcoholysis of the corresponding alcohol **335** was investigated. Reaction with 1 M HCl in ethanol led to 45 % conversion to a single new product which was identified by its mass spectrum as the desired ester **339**. In the mass spectrum this showed a small molecular ion peak in electron impact mode due to very efficient fragmentation to a species with a mass of 101 (loss of 73 mass units, correlated to the ester function COOEt); in chemical ionization mode the molecular ion-peak at 185 mass units was more pronounced.

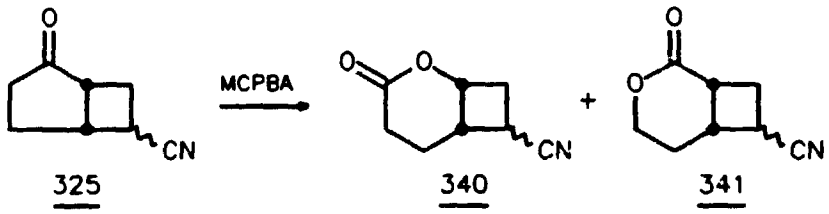


335 339

Ester **339** (in a 45:55 mixture with precursor **335**) was refluxed in benzene with triethylamine and the reaction progress was followed by gas chromatography. After 120 hours no new products were observed; the only result was a change in ratio of **339**:**335** to ≈35:65 indicating slow hydrolysis.

Due to time constraints and dwindling resources, the isomerization pathway was finally abandoned. One last approach for chemical alteration of the adducts was investigated. This used the fact that Cantrell had shown that enone-acrylonitrile cycloadducts can be oxidized to lactones with retention of stereochemistry using *m*-chloroperbenzoic acid to effect a Baeyer-Villiger oxidation.[70] It was hoped that the lactones produced from **323** - **326** would possess more dispersion of the signals in their ^{1}H-nmr spectra which would allow assignment of regiochemistry in all four isomers. Accordingly **325** was subjected to Baeyer-Villiger oxidation conditions.[142] After reflux with *m*-chloroperbenzoic acid in methylene chloride and work-up a single product (by gas chromatography) was obtained in high purity (longer retention time than **325**). It could be identified by mass spectroscopy as the expected lactone due to its mass of 151 mass units (16 mass units higher than **325**, corresponding to the addition of one oxygen atom). However, the ^{13}C-nmr spectrum revealed that there were two products present since twice as many peaks as predicted were recorded. At first it was thought that epimerization at any of the methine carbons could have led to stereoisomers but closer inspection and an APT experiment showed that two structural isomers had been obtained. These were the expected lactone **340** with the oxygen inserted between carbonyl and ring junction methine carbons and its isomer **341** in which oxygen insertion had occurred on the other side of the carbonyl carbon as shown in SCHEME 165. This was confirmed by identification of the two lowfield carbons (at ≈70 ppm) adjacent to the ring oxygen. The APT spectrum clearly showed

that the larger peak came from a methine (**340**) whereas the smaller one was due to a methylene (**341**). All other resonances were in the expected chemical shift region and were observed with the correct multiplicities. From the intensities of the carbonyl peaks a ratio for **340**:**341** of ≈3:1 was estimated.



325 340 341

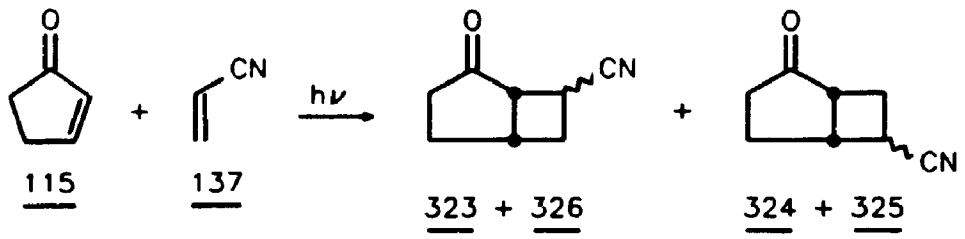
SCHEME 16.

The analysis of the ^{1}H-nmr spectrum proved to be more difficult. In chloroform three signals were observed in the lowfield region between 4 and 5 ppm. These were assigned to the protons on the carbons adjacent to the ring oxygens of each isomer as these would be expected to appear shifted downfield. Two of the signals were doublet of doublets of doublets with the same integration ratio whereas the third was a multiplet (quartet-like at first glance but with splitting and underlying peaks) with an integration ratio to each of the former of ≈2.85:1. This led to the identification of this last signal as the proton on the ring junction neighbouring the ring oxygen in lactone **340**, whereas the former pair of signals was assigned to be the two methylene protons adjacent to the ring oxygen in lactone **341**. A multiplet accounting for two protons of the minor isomer was observed at ≈3.4 ppm, all other resonances formed an unresolvable multiplet at 2.1 - 3.2 ppm.

When the solvent was changed to benzene dramatic changes in chemical shifts were observed. Signals for all protons were shifted upfield by approximately 1 ppm.

In addition, the signal assigned to the proton on the carbon attached to the ring oxygen of **340**, which in chloroform was quartet-like, appeared in benzene as a complex and unresolvable multiplet with at least ten lines. This pattern was expected for the oxidation product of a head-to-tail adduct because the proton on the ring junction carbon adjacent to the ring oxygen has three vicinal neighbouring protons, resulting in three large coupling constants, and one proton diagonally across the four membered ring, resulting in a small coupling constant. This result indicates that **340** (and hence its precursor **325**) indeed possessed head-to-tail regiochemistry since the complexity of the high field proton in question could only be explained by this regiochemical arrangement. The hydrogen adjacent to the ring oxygen of the lactone derived from the head-to-head adduct (i.e. **323**) would exhibit a simpler signal since it only has two vicinal neighbouring hydrogens. Unfortunately due to time constraints this route for determination of regiochemistry determination could not be extended to the other adducts.

To summarize, the results of the 2+2 photocycloaddition reaction between cyclopentenone and acrylonitrile yields four cycloadducts **323** - **326** which comprise two regioisomeric pairs of stereoisomers. Assignment of the regiochemistry was successful for adducts **323** (head-to-head) and **325** (head-to-tail). The remaining two adducts could not be definitely identified but the similarities between the mass and the ^{13}C-nmr spectra of **323** and **326**, and **324** and **325**, strongly suggest that **324** is a stereoisomer of **325** and **326** is a stereoisomer of **323**, as indicated in SCHEME 166. Further evidence for this assignment was obtained by the reduction of adduct **326** which led to a by-product apparently derived from cyclization of the new hydroxyl onto the cyano function, which is only possible for the endo stereoisomer of the head-to-head adducts, i.e. **326**.



SCHEME 166

To determine the regioselectivity of the photochemical reaction between cyclopentenone and acrylonitrile a small scale cycloaddition reaction was carried out and the ratio of the regioisomers determined by multiple gc injections and comparison to an inert internal standard at low conversion to minimize disturbance from secondary photochemistry of the adducts. The results are shown in TABLE 30 in relative area ratios to tetradecane (= 1):

TABLE 30: Relative areas of cycloadducts vs standard

Adduct	Ratio to standard
323	1.81 ± 3.6 %
324	1.07 ± 5.4 %
325	3.29 ± 1.2 %
326	1.14 ± 3.3 %

From these data the ratio of the head-to-head isomers (**323**:**326**) was calculated tc be 1.59:1 ± 6.9 %, the ratio of the head-to-tail isomers (**324**:**325**) was determined to be 0.32:1 ± 6.6 % and the ratio of the head-to-tail to the head-to-head regioisomers was calculated to be 1.48:1 ± 5.7 %. This result confirms that the head-to-tail isomers are formed in larger amounts, in contrast to the results of Corey's and Cantrell's work. They reported that in the irradiation of cyclohexenones with

acrylonitrile the dominant product regiochemistry is the head-to-head.[62,70] In addition, the findings presented in this thesis contradict the exciplex theory which predicts that the major adducts would be head-to-head oriented due the alignment of the dipole moments of the excited enone and **137**. Changing the enone from cyclohexenone to **115** should not alter the excited state dipole moment drastically so according to the exciplex theory **115** and **137** should add preferentially head-to-head.

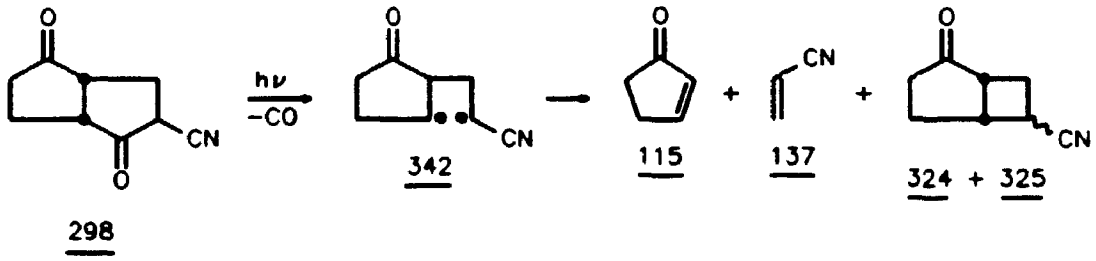
As will be shown below, the regiochemical assignment was confirmed by the results of photolysis of the cyano substituted diones **298** and **315**; in each case loss of carbon monoxide followed by closure of the biradical yields the expected pair of cycloadducts, **324** and **325**, and **323** and **326**, respectively.

3.5 Photolysis of 3-Cyanobicyclo[3.3.0]octane-2,6-dione 298

A benzene-d_6 solution of **298** was irradiated with light of wavelength 254 nm in order to sensitize formation of the triplet excited state of the diketone. The main product observed by gc had a retention time shorter than that of **298** and by coupled gas chromatography/mass spectroscopy the same mass. ^{1}H-Nmr analysis of the reaction mixture showed the presence of two resonances in the lowfield part of the spectrum (8 - 9 ppm) which led to the conclusion that the species observed by gc was a mixture of aldehydes derived from α-cleavage of **298** followed by intramolecular hydrogen abstraction.

Also observed by gc was the appearance of a minor product possessing a shorter retention time than **298**. By comparison with known retention time data and by mass as well as ^{1}H-nmr spectroscopy it was identified as 2-cyclopentenone **115**. This finding indicates that the diketone had undergone α-cleavage followed by

decarbonylation and that cleavage of the resultant 1,4-biradical **342** had taken place as shown in SCHEME 167.



SCHEME 167

Since **115** was found to have been formed the reaction mixture was also scanned for 2 + 2 cycloadducts **324** and **325**. Gas chromatographic co-injection with authentic adduct mixtures along with coupled gas chromatography/mass spectroscopic analysis led to the identification of two adducts in the mixture which were assigned to be the head-to-tail cycloadducts **324** and **325** based on the gas chromatographic data. One of them could be resolved by coupled gas chromatography/mass spectroscopy and exhibited a fragmentation pattern similar to the mass spectrum previously observed for **326**. In particular, ions with large intensities at 82, 55 and 54 mass units were observed; as described in Section 3.4. This pattern is characteristic for the two adducts assigned head-to-ta.. ·giochemistry and is not observed for the head-to-head regioisomers **323** and **326**. No evidence was found for the presence of regioisomeric adducts **323** or **326**. The product of fragmentation of **342**, acrylonitrile **137**, could not be observed due to its high volatility which resulted in a gc retention time too short to be distinguished from that of the solvent.

This result confirms the assignment of **324** and **325** as the head-to-tail adducts in the mixture of **323** - **326** since only **324** and **325** could have resulted from

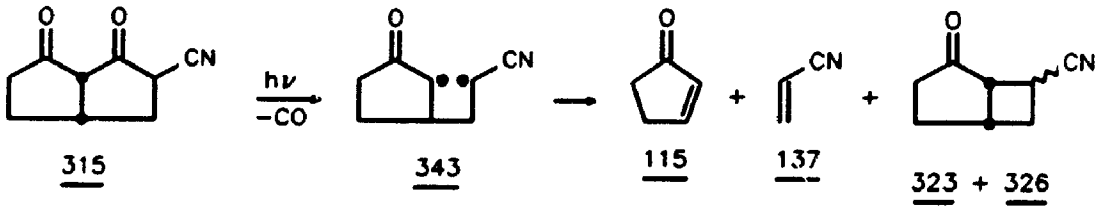
photolysis of diketone **298**. The amount of **115** formed relative to the amount of the adducts **324** and **325** was determined by comparison of the peak areas in the gc of the photolysis mixture. The uncalibrated ratio of areas was 0.83:1 with a statistical error of 24 % determined by multiple injections. This large error is due to the small amounts of adducts formed in the irradiation of **298**; the adducts made up only 5 % of the mixture since the main pathway for photolysis led to the aldehyde(s) which comprised *ca.* 40 % of the product mixture. The average ratio of cycloadducts (**324**:**325**) was 0.36:1 with an error of 45 % which compares favourably with the ratio **324**:**325** of 0.32:1 obtained in cycloaddition reaction of **115** with **137**. Again, the large error results from the small amounts of the compounds in the mixture.

Direct photolysis of **298** at 313 nm did not lead to very conclusive results; since the reaction was performed at relatively low concentrations of **298** it was difficult to obtain good integration values by gas chromatography. Both cyclopentenone **115** and cycloadducts **324** and **325** were found but only one data point for the ratio of **115** to the sum of the adducts could be obtained. The ratio obtained was 0.43:1 while the ratio **324**:**325** was 0.21:1. Due to shortage in the supply of **298** (which was found to decompose rapidly to **261**) no further investigations into the long wavelength irradiation were carried out. It was, however, concluded that no drastic change in the photochemical properties of **298** occurred with the change in mode of excitation from sensitized to direct irradiation.

3.6 Photolysis of 3-Cyanobicyclo[3.3.0]octane-2,8-dione 315

Sensitized irradiation using short wavelength light of a ≈ 10 mM solution of diketone **315** in benzene led to a mixture of compounds, one of which was identified

by gc and gc/ms comparison as cyclopentenone **115**. This was evidence for a decarbonylation reaction leading to 1,4-biradical **343** followed by cleavage to **115**. As in the photolysis of **298**, acrylonitrile **137**, the other cleavage product, could not be observed due to its short retention time. After 36 min (≈ 15 % conversion of **315**, the reaction mixture contained ≈ 1.8 % of **115**) product peaks could be integrated by gc that were identified by comparison with authentic samples as 2 + 2 cycloadducts **323** and **326** (totalling ≈ 0.6 % of the mixture). Coupled gas chromatography/mass spectroscopic analysis of the reaction mixture confirmed the initial assignment by exhibiting fragmentation patterns for the compounds that were very similar to the fragmentation patterns observed for **323** and **326** generated by addition of **137** to **115**. As pointed out in Section 3.4, these were significantly different from the fragmentation patterns of **324** and **325** in that they possessed characteristically low intensities for the 82 and 54 fragments. No evidence was found for formation of the isomeric adducts **324** and **325**. This confirmed the identity of **323** and **326** as the 2 + 2 adducts with head-to-tail regiochemistry in the cycloaddition of **115** with **137** since only these products could be derived from photolysis of diketone **315** as shown in SCHEME 168.



315 → 343 → 115 + 137 + 323 + 326

SCHEME 168

The uncalibrated gas chromatography area ratios of **115** to the sum of **323** and **326** calculated at different reaction times as well as the **323**:**326** area ratios are listed in TABLE 31 below:

TABLE 31: Ratios of gc areas of products in the photolysis of **315**

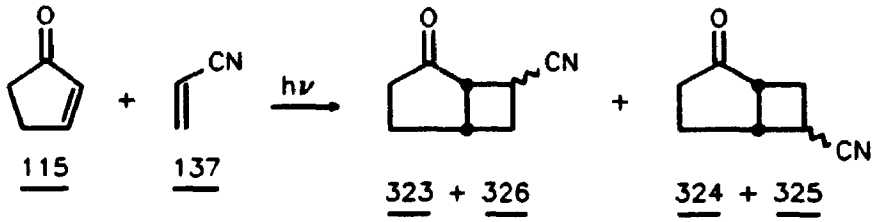
Reaction time	Ratio **115**:Σadducts	Ratio **323**:**326**	Comments
36 min	2.98:1	2.09:1	single injection
48 min	2.96:1 ± 7.7 %	2.06:1 ± 14.2 %	five injections
60 min	2.80:1 ± 6.3 %	2.00:1 ± 7.3 %	"
84 min	2.74:1 ± 10.4 %	2.02:1 ± 7.5 %	"
2 hours	2.53:1	1.88:1	single injection
3 hours	2.56:1	1.78:1	"
5 hours	2.61:1	1.67:1	"
8 hours	2.56:1	1.73:1	"

From this data it can be seen that the **115**:adduct area ratio decreased with increasing reaction time which was probably due to the fact that as the concentration of **115** increased it began to be sensitized by benzene and underwent secondary photochemistry leading to its depletion relative to the adducts. Therefore the gas chromatography area ratio calculated at 48 min was considered the closest to the actual value. The area ratio of the two adducts, which compares with a value of 1.59 ± 6.9 % obtained in the cycloaddition reaction of **115** and **137**, stayed constant over the time with reliable data, the apparent change at two hours and later could be superficial due to the data gathering technique with only one injection per time data point.

As with the corresponding photolysis of **298**, the long wavelength irradiation (direct excitation) of **315** did not give very satisfactory results since under these conditions it proved difficult to obtain good gas chromatography integration values due to low concentrations of the products. After two hours gc analysis indicated the formation of **115**, **323** and **326** and the area ratio **115**:adducts was determined to be 2.47:1 ± 10.3 %, and the ratio **323**:**326** was 2.22:1 ± 2.9 %. These numbers are similar to those obtained for the sensitized irradiation and it was concluded that the photochemical outcome of the reaction did not change drastically with the mode of excitation.

3.7 Discussion of Results and Conclusions

The outcome of the 2+2 cycloaddition between cyclopentenone **115** and acrylonitrile **137** was surprising. Based upon the results by Corey obtained in the photoaddition reaction of cyclohexenone with acrylonitrile[62] it had been expected that the head-to-head regioisomers would predominate. In fact, the head-to-tail isomers **324** and **325** were formed in larger amounts than the head-to-head isomers **323** and **326** as indicated in SCHEME 169. A ratio of 1.48:1 for (**324**+**325**):(**323**+**326**) was calculated during a photolysis experiment as shown above.



SCHEME 169

One explanation for the "wrong" outcome of the cycloaddition in question could, of course, be that exciplexes do not exist and that the alignment of reactant dipoles is not responsible for the regiochemistry. Instead the reaction regiochemistry could be governed by the partitioning ratio ρ of each of the 1,4-biradicals involved, as pointed out in the introduction to this chapter. This will be dealt with later but first another aspect of the cycloaddition reaction between cyclopentenone **115** and acrylonitrile **137** has to be discussed.

As mentioned earlier, irradiation of **137** in the presence of triplet sensitizers such as benzophenone and acetophenone leads to dimerization and the formation of stereoisomers of 1,2-dicyanocyclobutane. This was demonstrated by Hosaka and Wakamatsu as early as 1968.[141a]

These workers estimated the triplet energy (E_T) of **137** to be *ca.* 62 kcal/mole based on the observation that sensitizers with triplet energies of 68.5 and 73.6 kcal/mole (i.e. benzophenone and acetophenone, respectively) and 4-phenylbenzophenone (E_T = 62.8 kcal/mole) sensitized the reaction successfully whereas naphthalene (E_T = 60.9 kcal/mole) and other triplet sensitizers with even lower triplet energies did not.

Recently Lavilla and Goodman measured the triplet energy for **137** using photoacoustic calorimetry[143] and obtained a value of 58 ± 4 kcal/mole.* Cyclic enones have triplet energies which are higher than that of acrylonitrile (≈ 65-68 kcal/mole for cyclohexenone and > 70 kcal/mole for cyclopentenone[1,26,82a]); this raises the possibility of triplet energy transfer between an excited enone and ground state **137**. As pointed out earlier a reaction product in the photocycloaddition

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* This is the energy for the relaxed (twisted) triplet of **137**. Wong determined the energies for the planar triplets of maleo- and fumaronitrile to be 59 ± 2 kcal/mole.[146]

between **115** and **137** was found that was identified by mass and nmr spectroscopy as a dimer of **137**. Its amount was low (a ratio of it to the sum of adducts and dimers of **115** of ≈ 1:80 was obtained) but its formation could be explained by energy transfer from the excited enone to the alkene and subsequent reaction of the excited alkene with ground state alkene. If such energy transfer is occurring and leads to dimerization of **137**, then it could also be possible for cycloadducts **323** - **326** to be formed by interaction of excited alkene with ground state enone. This possibility was addressed by Schuster et al. who irradiated various enones (among them **115**) in neat acrylonitrile and found only traces of alkene dimers thus ruling out a sensitization of **137** by triplet enone.[1,77] On the other hand irradiation of **115** and **137** with benzophenone under conditions that the sensitizer absorbed > 97 % of the light only dimers of **137** were found and no adducts, which led the workers to conclude that triplet energy transfer from triplet **115** to **137** was very inefficient compared to formation of triplet biradicals en route to cycloadducts.[1,77]

The concept of enones sensitizing **137** is currently under investigation in our laboratory but no conclusive results have been obtained so far. For the purpose of the work described in this thesis it is of secondary importance because even if **137** was the excited species in the cycloaddition to **115** the reaction would still have proceeded *via* the same biradical intermediates.

In order to calculate the partitioning ratios ρ for biradicals **342** and **343** which were produced in the photolyses of **298** and **315**, respectively, it was necessary to determine the ratio of the products of radical fission to the products of radical closure. The latter were the corresponding adducts and the former **115** and **137**. The alkene could not be quantified by gc due to its volatility but using the amount **115** would give the desired results since it is formed in a 1:1 ratio with **137**.

As described above the area ratios of the gc peaks of **115** to the sum of the gc peaks of the adducts could be determined but different response factors in gc analysis did not allow these values to be used directly for calculation of product ratios. The gas chromatograph was therefore calibrated with five solutions containing known mass (and mole) ratios of **115** and adducts **323** and **324** (with the assumption that the response factors for the adducts would be similar and thus this solution was representative). The results of the calibration are shown in TABLE 32:

TABLE 32: Results of the gc calibration

115 vs	Excitation	gc ratio	mole ratio
Σ HH adducts (**323**, **326**)	sensitized	2.96	3.67
"	direct	2.47	3.08
Σ HT adducts (**324**, **325**)	sensitized	0.83	1.09
"	direct	0.43	0.60

In order to interpret these results it was decided that the ratios derived from sensitized irradiation* were more reliable due to the larger number of individual data points and these are therefore used in the following discussion. It is also assumed, as pointed out in the beginning of this chapter, that only the two biradicals **342** and **343** participated in the cycloaddition reaction and that no biradicals with primary radical centres were involved. This is supported by the results obtained by Hastings and Weedon.[69,81]

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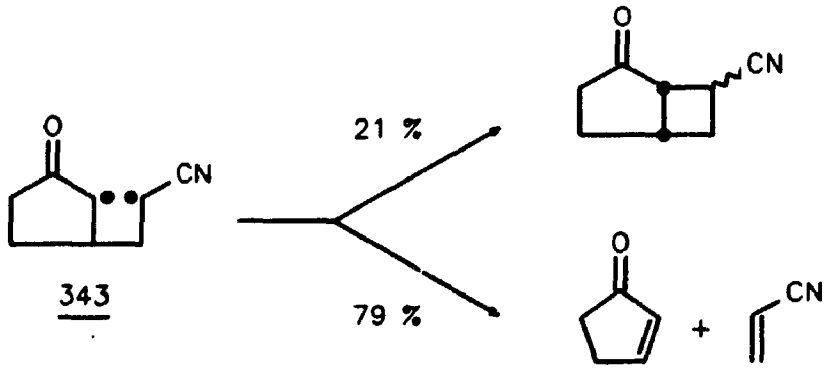
* Taking into account the ratio of triplet to singlet lifetime of benzene (≈ 100:1) and its quantum yield for intersystem crossing (0.56 in benzene) it was concluded that the diketones **298** and **315** were sensitized almost exclusively into their triplet excited states by benzene and that little or no singlet energy transfer took place.[147] It is also known that α-cleavage, the first step in photodecarbonylation, proceeds much faster from the triplet state of a ketone than from its singlet state.[110] In addition, similar product ratios were observed for direct and sensitized irradiations.

From the mole ratios in TABLE 32, which are eqivalent to the relative rates of reaction of each biradical (k_2^H/k_1^H for **343** and k_2^T/k_1^T for **342** where the k's are defined as shown in SCHEME 116 and 117, respectively), the partitioning ratios ρ of the biradicals in the cycloaddition of **115** and **137** could be calculated using EQUATION 18.

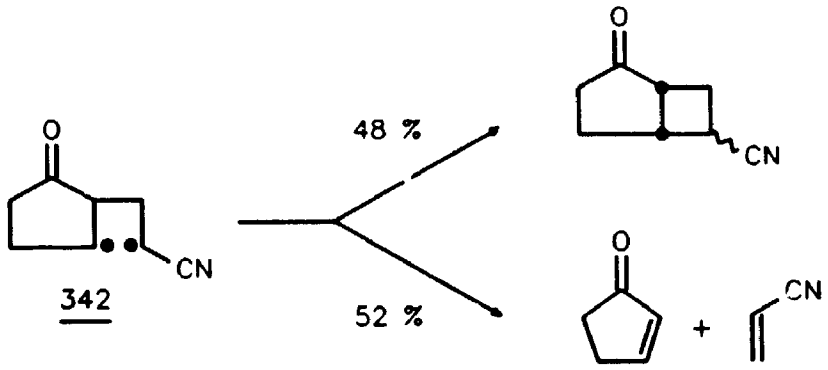
$$\rho^H = \frac{k_1^H}{k_1^H + k_2^H} = \left(1 + \frac{k_2^H}{k_1^H}\right)^{-1} \quad \text{for } \mathbf{343}$$

$$\rho^T = \frac{k_1^T}{k_1^T + k_2^T} = \left(1 + \frac{k_2^T}{k_1^T}\right)^{-1} \quad \text{for } \mathbf{342} \qquad \text{Eq. 18}$$

Biradical **343**, derived from photolysis of diketone **315** and leading to the head-to-head adducts with $k_2^H/k_1^H = 3.67$, had a partitioning ratio ρ^H of 0.21 ± 7.7 %, which meant that it preferred to cleave back to enone and alkene 3.67 times faster than it proceeded to cycloadducts. In other words, once formed, 79 % of **343** reverted and only 21 % gave products.



The analysis for biradical **342**, derived from photolysis of diketone **298** and leading to the head-to-tail adducts with $k_2^T/k_1^T = 1.09$, yields a partitioning ratio ρ^T of 0.48 ± 24 %, meaning that it cleaved to enone and alkene and proceeded to adducts with nearly identical rates (52 vs 48 %) as shown below.



From combination of the calculated ρ's with the known ratio of head-to-tail vs head-to-head adducts (Φ_T/Φ_H) obtained in the addition of acrylonitrile to cyclopentenone (1.48:1) the relative rate of formation for each biradical (k_r^H/k_r^T), and therefore its share in the cycloaddition reaction, could be calculated utilizing EQUATION 19.

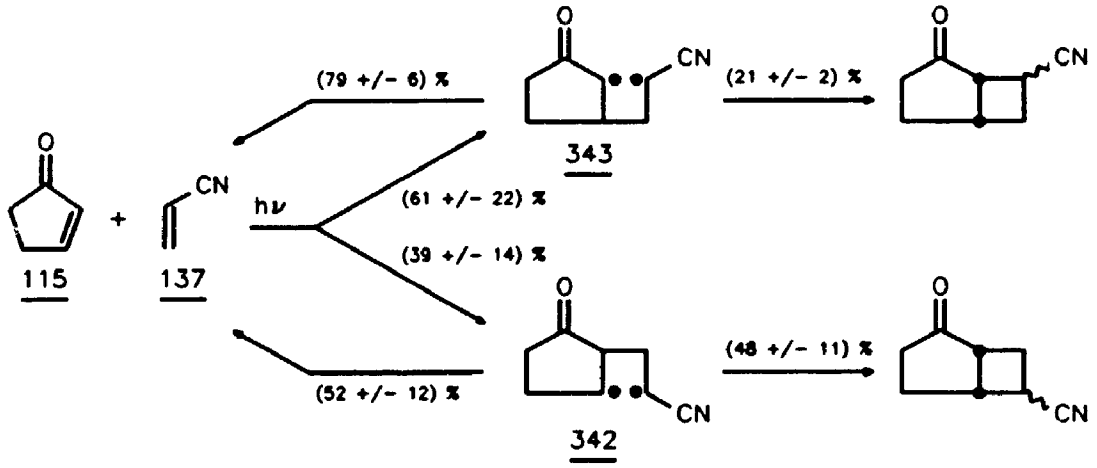
$$\frac{k_r^H}{k_r^T} = \frac{\rho^T}{\rho^H} \times \left(\frac{\Phi_T}{\Phi_H}\right)^{-1}$$

$$= \frac{0.48}{0.21} \times (1.48)^{-1} \qquad \text{Eq. 19}$$

$$= 1.54$$

Error propagation on the obtained value gave an uncertainty of ≈37 %. Knowing the relative rates of formation of **342** and **343**, the kinetic scheme for the

photoaddition of acrylonitrile to cyclopentenone can be completed as shown in SCHEME 170.

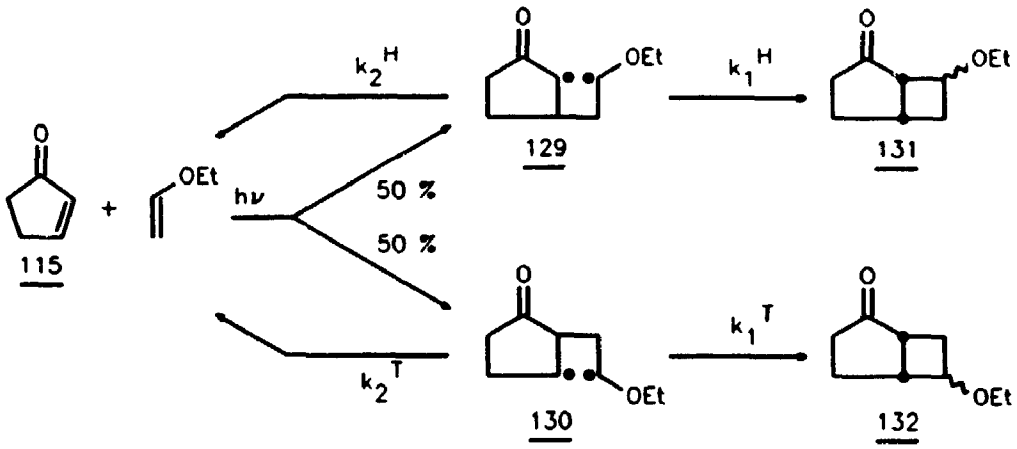


SCHEME 170

From this scheme it can be seen that **343**, the biradical leading to the head-to-head adducts, is formed faster than **342** but prefers to cleave back to starting material to a higher degree resulting in an observed overall head-to-tail regiochemistry. This confirms the fact that one cannot use the product distribution of a photochemical reaction to gather information about the relative amounts of intermediates formed if these are able to partition between starting material and product.

The results obtained in this study can be compared with the results obtained by Hastings and Weedon when they investigated the 2 + 2 photocycloaddition reaction between cyclopentenone **115** and ethyl vinyl ether.[69,81] As mentioned in the introduction to Chapter 1 of this part of this thesis, these workers were able to trap the biradicals implicated in this photocycloaddition reaction with hydrogen selenide. From a product distribution study Hastings and Weedon concluded that, firstly,

biradicals containing a primary radical centre do not play a role in the cycloaddition reaction, and secondly, biradicals **129** and **130** are formed in a 1:1 ratio. When the reaction was carried out in the absence of hydrogen selenide, 2 + 2 cycloadducts **131** and **132** were obtained in a 1:2.64 ratio, as illustrated in SCHEME 171.



$$\rho^H = k_1^H/(k_1^H+k_2^H)$$

$$\rho^T = k_1^T/(k_1^T+k_2^T)$$

$$\rho^T/\rho^H = 2.64$$

SCHEME 171

Combination of this ratio with the ratio of the biradicals present (obtained from trapping studies) allowed the calculation of the ratio of the individual partitioning ratios of the biradicals (ρ^T/ρ^H). The value obtained (2.64) illustrates that the head-to-tail biradical **130** closes to cycloadducts to a higher degree than the head-to-head biradical **129**. This finding supports the results described in this thesis in that it is not the rate of formation of the intermediate biradicals that governs the regiochemical outcome of the photochemical cycloaddition reaction (as the exciplex theory assumes); instead the partitioning of the biradicals is responsible for the observed regiochemistry.

In summary the 2 + 2 photocycloaddition reaction between cyclopentenone **115** and acrylonitrile **137** leads to the formation of four cycloadducts in a regioisomeric ratio of HT/HH = 1.48. This is in disagreement with the predicted selectivity if an exciplex intermediate is assumed to govern the reaction regiochemistry.[62,70] The results, however, can be explained without the need for an exciplex. Independent generation of the biradicals **342** and **343** implicated as intermediates in the reaction resulted in different partitioning ratios ρ for each biradical (ρ^{H} = 0.21 for **343** and ρ^{T} = 0.48 for **342**). It was shown that the observed regiochemistry was due to the relatively large difference in ρ, leading to the result that the major biradical is not the precursor for the major products.

The work for the future is already carved out and under way in our laboratory and will include an investigation of Corey's original cycloaddition reactions between cyclohexenone and acrylonitrile.[62] Modern analysis methods such as high field proton and carbon nmr spectroscopy, which were not available at the time Corey undertook his research, will be utilized to determine whether Corey correctly interpreted his results, which are based on nmr assignments. Since the exciplex is no longer needed to explain the outcome of a cycloaddition reaction, biradical partitioning should be used to interpret the results of the work to come.

What has not been addressed in this thesis is the question as to why structurally similar biradicals choose to react differently. The preferred conformations of the biradicals are expected to be part of the answer but there is still a lot of work to be undertaken to understand what factors govern the partitioning ratio for each biradical.

CHAPTER 4

EXPERIMENTAL SECTION

4.1 General

^{1}H-Nmr spectra were recorded at 60 MHz in $CDCl_3$ on a Varian EM 360 instrument or at 200 MHz spectra in $CDCl_3$ or C_6D_6 on Varian XL 200 or Varian Gemini 200 instruments. For ^{13}C-nmr spectra in $CDCl_3$ or C_6D_6 Varian XL 300 (75 MHz) or Varian Gemini 200 (50 MHz) instruments were used. Chemical shifts (δ) are given in ppm downfield from TMS (0.00 ppm). Data for ^{1}H-nmr are reported as follows: δ (multiplicity, coupling constant(s) in Hz, integration). Abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet). Data for ^{13}C-nmr are given as follows: δ (degree of substitution).

Infrared spectra (film or in Nujol) were recorded on a Bruker IFS 32/IBM System 9000 FT-instrument.

Ultraviolet spectra in various solvents were obtained on a Shimadzu UV-160 spectrophotometer. Data are reported as follows: λ_{max} in nm (ϵ).

Gas chromatography coupled mass spectroscopy was performed on a Varian 3400 gc with a 30 m DB-5 capillary column attached to a Finnegan MAT 8230 mass spectrometer. Ionization was achieved by electron impact (EI, 70 or 25 eV) or by chemical ionization (CI) with isobutane. Data are given as follows: Fragment mass (intensity in %).

Preparative gas chromatography was carried out on a Varian 920 instrument equipped with a packed column (8' x ¼", 5 % or 10 % SE-30 on Chromosorb W, He carrier).

Analytical gas chromatography was performed on a Varian 1400 gc equipped with a 15 m DB-1 megabore column or Hewlett-Packard 5830 or 5880 gc equipped with 30 m DB-5 capillary columns (H_2 carrier). Flame ionization detectors were used.

Unless otherwise stated preparative and analytical irradiations were performed at room temperature with a medium pressure mercury lamp in a water cooled Pyrex housing. For short wavelength irradiations a Rayonet apparatus (The Southern New England Ultraviolet Co.) equipped with tubes emitting mainly light with λ = 254 nm was employed. The samples were deoxygenated by passing a stream of dry nitrogen through the solutions prior to irradiation. The solvents used for irradiations were of spectrophotometric grade; anhydrous THF and diethyl ether were prepared by refluxing over sodium and distillation under nitrogen atmosphere; DMSO, diisopropylamine, borontrifluoride etherate and trimethylsilyl chloride were purified according to literature procedures.[24]

4.2 Preparation of 2-Cyclopentenone 115

A solution of 2 g cyclopentene **67** (30 mmole), 3.1 g acetic anhydride (30 mmole), 72 mg 4-(N,N-dimethylamino)pyridine (0.6 mmole), 1.2 g pyridine (15 mmole) and 3.1 mg TTP (4.6 μmole) in 50 ml dichloromethane was irradiated in a vessel equipped with a dry ice condenser while an oxygen stream passed through the solution. The reaction was followed by gc and worked up after 10 hours by diluting with diethyl ether, washing with 1 N HCl (organic phase turned from red to green) and sat. $NaHCO_3$ solution (organic phase turned red). After drying ($MgSO_4$) the solvents were evaporated and the residue distilled to obtain 1.34 g (55 %) of a colourless liquid ($bp._{21}$ 61°C). ^{1}H-Nmr (200 MHz, $CDCl_3$): 2.37 (m, 2 H), 2.72 (m, 2 H), 6.21 (dt, 5.67, 2.17, 1 H), 7.76 (dt, 5.67, 2.75, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 28.62 (CH_2), 33.62

(CH_2), 134.01 (CH), 164.91 (CH), 210.42 (C=O); ms (EI): 82 (M^+, 100), 54 (55), 53 (48); uv (cyclohexane): 304 (19), 316 (24), 330 (26), 347 (19), 362 (8)

4.3 Preparation of Vinylcyclopropane 149

4.3.1 Preparation of Diazomethane

This reaction was carried out in a glass apparatus with smooth joints. A solution of 44 g N-methyl-N-nitroso-*p*-toluenesulfonamide (Diazald®, 0.21 mole) in 400 ml diethyl ether was slowly added at 70°C to a solution of 12 g KOH (0.21 mole) in 130 ml of a mixture of diethyl ether, triethylene glycol and water (4:7:1 by volume). The distilling diazomethane was collected in a 2 l flask containing diethyl ether at 0°C. Portions of the diazomethane solution (5.00 ml) were titrated as follows (sample experiment): After addition of 1.2129 g benzoic acid (9.94 mmole) the solution was titrated with 0.502 N NaOH solution to a methyl orange endpoint. It was found that 18.3 ml of the base solution was needed which calculated to 9.18 mmole acid remaining in the solution. Consequently 0.76 mmole of acid was consumed by the diazomethane present in 5.00 ml. It was calculated that a total of 0.12 mole diazomethane (5.2 g, 60 %) was collected.

4.3.2 Preparation of 3-Vinyl-1-pyrazoline 205

The above prepared solution of diazomethane in diethyl ether containing 5.2 g (0.12 mole) was stirred at -78°C and ≈ 16 g 1,3-butadiene (≈0.3 mole) were added. The reaction was allowed to warm up to room temperature overnight and excess diazomethane (yellow colour) was destroyed by addition of a diethyl ether solution of acetic acid. After washing with sat. $NaHCO_3$ solution and drying ($MgSO_4$) the solvent was evaporated and the residue distilled to give 4.9 g (41 %) of a colourless liquid ($bp._{50}$ 70°C). ^{1}H-Nmr (60 MHz, $CDCl_3$): 0.9 - 2.2 (m, 2 H), 4.2 - 5.0 (m, 3 H), 5.1 - 5.5 (m, 2 H), 6.0 (ddd, 18.0, 9.0, 7.0, 1 H)

4.3.3 Preparation of 5-Chloro-2-pentanone 212

A mixture of 23.7 ml conc. HCl and 27.7 ml water was added to 20.2 g α-acetyl-γ-butyrolactone. Gas formation (CO_2) began immediately and the reaction mixture was heated up to ≈ 90°C; the effervescence subsided and the solution turned black. When distillation started (bp. ≈ 106°C), the distillate separated into two phases. After ≈ 45 ml had distilled 24 ml water were added to the stillpot and ≈ 15 ml more distillate were collected. At this point the organic phase in the stillpot had disappeared. The distillate was extracted with diethyl ether and the combined organic phases were dried with $MgSO_4$. Removal of the solvent gave 15.9 g (84 %) of a yellowish liquid. ^{1}H-Nmr (200 MHz, $CDCl_3$): 2.03 (m, 2 H), 2.17 (s, 3 H), 2.65 (t, 7.00, 2 H), 3.58 (t, 6.32, 2 H)

4.3.4 Preparation of Cyclopropylmethylketone 203

A mixture of 27.3 g **212** (0.23 mole), 13.6 g NaOH (0.34 mole) and 13.6 ml water was refluxed for one hour. Water (28 ml) was added and reflux was continued for another hour. The mixture was then distilled (two phases) until no organic phase remained in the stillpot. The aqueous layer of the distillate was saturated with K_2CO_3 and the phases separated. The aqueous phase was extracted with diethyl ether and the organic phases were combined and dried ($MgSO_4$). The solvent was distilled off to give 22.2 g of a colourless liquid. By ^{1}H-nmr the product contained ≈ 18 % diethyl ether so that the actual yield of **203** was ≈ 18 g (≈ 95 %). ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.89 (m, 2 H), 1.00 (m, 2 H), 1.95 (tt, 7.5, 4.5, 1 H), 2.24 (s, 3 H); ir (film): 3040, 2960, 1710 cm^{-1}

4.3.5 Preparation of 1-Cyclopropylethanol 204

Solid $LiAlH_4$ (2.1 g, 55 mmole) was suspended in 250 ml dry diethyl ether. A solution of 14.6 g **203** (0.17 mole) was added dropwise and the mixture stirred at

room temperature for two hours. It was quenched with water and 10 % H_2SO_4 and the phases separated. The aqueous layer was extracted with diethyl ether; the combined organic phases were washed with sat. $NaHCO_3$ solution and dried ($MgSO_4$). Solvent removal gave 14.1 g (94 %) of a colourless liquid. ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.1 - 0.3 (m, 2 H), 0.4 - 0.5 (m, 2 H), 0.8 - 1.0 (m, 1 H), 1.24 (d, 6.23, 3 H), 1.73 (bs, 1 H, disappeared after addition of D_2O), 3.04 (dt, 8.27, 6.23, 1 H); ir (film): 3120 - 3860, 3100, 3030, 2950 cm^{-1}

4.3.6 Preparation of Cyclopropylmethylketone Tosylhydrazone 208

A solution of 7.1 g **203** (85 mmole) and 15.8 g *p*-toluenesulfonyl hydrazine (85 mmole) in 200 ml ethanol was refluxed for one hour and then stored at 5°C overnight. White crystals had formed and were filtered off; the mother liquor was concentrated and cooled to obtain more crystals. This procedure was repeated once more; all crystals were combined and dried in vacuo to give a total yield of white crystals of 19.2 g (90 %, mp. 121°C, lit.[95] 123°C). ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.6 - 0.8 (m, 4 H), 0.8 - 1.05 (m, 1 H), 1.68 (s, 3 H), 2.43 (s, 3 H), 7.30 (d, 8.20, 2 H), 7,83 (d, 8.20, 2 H)

4.3.7 Preparation of Vinylcyclopropane 149

a) from 3-vinyl-1-pyrazoline **205**

A solution of 1.04 g **205** in 20 ml decalin was heated to 110°C for one hour, then a slight vacuum was applied (108 torr) and heating continued for another hour. A very small amount of a smelly, colourless liquid distilled off (due to high volatility and low yield no mass was determined) which by ^{1}H-nmr (*vide infra*) proved to be **149**.

b) from cyclopropylmethylketone tosylhydrazone **208**

b.I) with *n*-butyllithium

Tosylhydrazone **208** (1.99 g, 7.9 mmole) was suspended in 50 ml decalin. A solution of *n*-butyllithium in hexane (17.2 mmole, 8.2 ml of a 2.1 M solution) was added at O°C and the stirred mixture was slowly heated to ≈ 110°C. A small amount (≈ 0.2 g) of a colourless liquid distilled off but ^{1}H-nmr examination showed that it was hexane. No **149** was detected.

b.II) with sodium hydride (sample experiment)

Tosylhydrazone **208** (15 g, 60 mmole) and 20 g of a ≈ 50 % dispersion of sodium hydride in mineral oil (≈ 10 g NaH, ≈ 416 mmole) were suspended in 250 ml decalin. The mixture was heated up, N_2-evolution was visible and at an oil bath temperature of ≈ 190°C the reaction turned dark and distillation started. After the distillation stopped 2.11 g (52 %) of a volatile, colourless liquid was obtained in the dry ice/acetone cooled receiver. ^{1}H-Nmr analysis (*vide infra*) showed the product to be a 72:28 mixture of **149** and 1-methylcyclobutene **209**.

b.III) with sodium amide (sample experiment)

Ammonia (≈ 200 ml) was condensed into a flask equipped with a dry ice condenser. To it was added 6.6 g Na (0.29 mole) and 0.6 g $Fe(NO_3)_3$ which caused a greyish colour. Decalin (200 ml) was added, the dry ice condenser was removed and the mixture allowed to warm to room temperature to evaporate the excess ammonia. Tosylhydrazone **208** (10 g, 40 mmole) was added. The system was then set up for distillation and heated to ≈ 190°C. A colourless liquid (still containing ammonia) was obtained in the dry ice/acetone cooled receiver and redistilled to give 1.38 g (51 %) of a colourless liquid which was stored in the freezer (bp. ≈ 40°C). ^{1}H-Nmr analysis showed it to be a 96:4 mixture of compounds **149** and **209**. Compound **149**: ^{1}H-Nmr

(200 MHz, $CDCl_3$): 0.38 (m, 2 H), 0.68 (m, 2 H), 1.38 (m, 1 H), 4.83 (dd, 9.8, 2.0, 1 H), 5.04 (dd, 16.8, 2.0, 1 H), 5.30 (ddd, 16.8, 9.8, 8.4, 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 6.67 (2 CH_2), 14.76 (CH), 111.5 (CH_2), 142.61 (CH); ir (film): 3100, 3020, 2950 cm^{-1}; Compound **209**: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.64 (m, 3 H), 2.27 (m, 2 H), 2.36 (m, 2 H), 5.55 (m, 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 16.88 (CH_3), 26.24 (CH_2), 32.67 (CH_2), 127.90 (CH), 146.47 (C)

4.4 Dimerization of 2-Cyclopentenone 115

a) in cyclohexane

A solution of 43.3 mg **115** (0.53 mmole) in 4 ml cyclohexane was irradiated at room temperature with a medium pressure Hg-lamp for five hours (> 90 % conversion). Two product peaks were seen by gc (ratio 1.9:1, shorter retention time first) and identified by ms as dimers **117** and **116**. The solvent was taken off to give 117 mg of a colourless liquid. Dimer **116**: ms (EI): 164 (M^+, 100), 82 (86), 79 (100), 54 (73); dimer **117**: ms (EI): 164 (M^+, 82), 82 (100), 79 (83), 54 (70)

b) in benzene

A solution of 47.6 mg **115** (0.58 mmole) in 1 ml benzene was irradiated at room temperature with a medium pressure Hg-lamp. After nine hours (≈50 % conversion of **115**) two products were observed by gc in a ≈4.2:1 ratio. They were identified by gc/ms as dimers **117** and **116**, respectively (ms see above). No further separation was carried out but the mixture was analyzed by ^{13}C-nmr (50 MHz, $CDCl_3$): Dimer **117**: 27.94 (CH_2), 36.02 (CH_2), 37.21 (CH), 49.35 (CH), 219.59 (C=O); dimer **116**: 27.29 (CH_2), 35.54 (CH_2), 40.03 (CH), 44.86 (CH), 218.36 (C=O)

4.5 Irradiation of 2-Cyclopentenone 115 With Alkenes

4.5.1 Irradiation of 115 With 1,6-Heptadiene 187

A solution of 974 mg 187 (10 mmole) and 295 mg 115 (3.6 mmole) in 60 ml cyclohexane was irradiated with a medium pressure Hg-lamp. After three hours five products were observed in a ≈ 1:6.2:6.9:2.2:1.8 ratio (in order of increasing retention time). Gc/ms showed masses of 178 for the first three and 164 for the last two, which had the same retention time as the products from the irradiation of 115 without olefin and were thus identified as dimers of 115. The solvent was distilled off at 32°C/130 torr to give 179 mg of a colourless liquid. The distillate containing the starting materials was further irradiated for two hours and then distilled off at 36°C/140 torr to give 104 mg of a colourless liquid. The distillate still contained 115 and 187 and was irradiated for two more hours, then distilled off at 34°C/136 torr to give 61 mg of a colourless liquid. All three distillation residues contained the same five products in similar ratios and were combined. ^{1}H-Nmr spectroscopy showed signals at 1 - 3 ppm as well as multiplets at ≈4.9 and ≈5.7 ppm, the latter in a ratio of 2:1. The products were separated by preparative tlc (three runs diethyl ether/hexanes 1:6) to give three fractions (in order of increasing polarity): One containing dimers of 115, one containing three adducts in a ≈ 1:5:2 ratio and one containing one adduct with the same retention time by gc as the third adduct in the mixed fraction. Gc/ms showed that all adducts had similar fragmentation patterns and ^{1}H-nmr experiments confirmed that they were all 2+2 adducts (192 and 193) of 115 and 187. No evidence for a product (i.e. 196) derived from rearrangement of the intermediate 1,4-biradical was seen. Typical data for adducts 192/193: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.2 - 1.6 (m, 7 H), 1.8 - 2.8 (m, 8 H), 4.9 (m, 2 H), 5.75 (ddt, 17.02, 10.20, 6.68, 1 H); ms (EI): 178 (M^+, 6), 137 (5), 83 (100), 67 (42), 55 (60), 54 (44)

A sample of the adduct mixture (203 mg) was hydrogenated in 10 ml methanol with hydrogen over 7.1 mg PtO_2. After one hour 25 ml hydrogen had been taken up and the catalyst was filtered off. Gc analysis showed that all the adduct peaks had shifted to slightly longer retention times (eg. from 9.20 to 9.54 min). The dimers of **115** did not exhibit any change under the same hydrogenation conditions. ^{1}H-Nmr analysis of the hydrogenated adduct mixture showed the total disappearance of the olefinic resonances; typical ms (EI): 180 (M^+, 12), 83 (100), 55 (48)

4.5.2 Irradiation of 115 With Vinylcyclopropane 149

A solution of 556 mg **115** (6.8 mmole) and 1.38 g **149** (20 mmole) in 40 ml cyclohexane was irradiated with a medium pressure Hg-lamp. After two hours the solvent and unreacted starting material were distilled off at 34°C/135 torr and the distillate was irradiated for a further two hours, after which the procedure was repeated. Then 20[illegible] mg **115** (2.5 mmole) were added and the irradiation continued for three hours. Solvent and starting material removal was repeated and irradiation continued for four more hours after which all residues were combined to give 1.18 g of a slightly yellow liquid. Gc analysis showed, besides small amounts of **115**-dimers (identified by comparison with an authentic dimer sample), four products **A** - **D** in a ≈ 1.6:1:1.4:3.5 ratio (in order of increasing retention times). Gc/ms analysis showed that they were 1:1 adducts of **115** and **149** (M^+ = 150). ^{1}H-Nmr studies of the mixture revealed resonances in the cyclopropyl region (< 1 ppm) as well as saturated alkyl protons and olefinic signals (> 5 ppm).

Treatment of a small sample of the product mixture with bromine in carbon tetrachloride resulted in large depletion of the first adduct peak (compound **A**) and smaller depletion of the last peak (compound **D**) whereas the centre two peaks (compounds **B** and **C**) were not affected.

Preparative tlc of the product mixture allowed separation into three product containing fractions: Fraction II (containing mainly compounds **A** and **D**), fraction I (containing mostly compounds **B** and **C**) and the dimers of **115** (in order of increasing polarity). Fraction I was further separated by preparative gc into three fractions with the last one, obtained only in minute amounts, containing mainly compounds **A** and **D**, due to incomplete separation of the adduct mixture by tlc. The other two fractions were both identified as mixtures of stereo- and regioisomers of the 2 + 2 adducts (**154** and **155**) of **115** and **149** by ^{1}H-nmr spectroscopy due to the absence of any olefinic resonances and the presence of cyclopropyl resonances (0.1 - 0.5 ppm) as well as saturated cyclobutane and cyclopentanone signals at 1.5 - 2.8 ppm. Typical ms (EI): 150 (M^+, 8), 121 (16), 82 (22), 79 (28), 68 (100), 67 (56), 53 (78)

The ^{1}H-nmr spectrum of fraction II showed the absence of cyclopropyl signals and, apart from saturated resonances, olefinic peaks at ≈5.5, 6.0 and 7.5 ppm. Preparative gc separation gave three fractions: Fraction II.I (containing almost exclusively compound **A**), fraction II.II (small amount, containing two products different from compounds **A** and **D**) and fraction II.III which contained mainly compound **D** (in order of increasing retention time). Fraction II.I (compound **A**) was identified as 3-(*cis*-2-pentenyl)-2-cyclopentenone (*cis*-**213**). ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.94 (t, 7.44, 3 H), 1.96 (m, 2 H), 2.11 (m, 2 H), 2.40 (m, 2 H), 2.85 (m, 2 H), 5.30 (m, 1 H), 5.45 (m, 1 H, both olefinic protons coupling to each other with a coupling constant of ≈8 - 9 Hz), 6.05 (m, 1 H); ms (EI): 150 (M^+, 2), 91 (20), 82 (100), 79 (38), 69 (60), 53 (36)

Fraction II.III (compound **D**) was identified as a single geometric isomer of 2-(2-pentenyl)-2-cyclopentenone **214**. ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.99 (t, 7.46, 3 H),

2.05 (m, 2 H), 2.43 (m, 2 H), 2.58 (m, 2 H), 2.88 (m, 2 H), 5.50 (m, 2 H), 7.29 (m, 1 H); ms (EI): 150 (M^+, 44), 91 (36), 83 (100), 79 (57), 67 (21)

Fraction II.II was identified as a ≈1:1 mixture of the remaining geometrical isomers of **214** and **213** (*trans*-**213**) and was not further separated. ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.93 (t, 7.52, 3 H), 0.96 (t, 7.39, 3 H), 1.9 - 2.2 (m, 2 x 4 H), 2.3 - 2.9 (m, 2 x 4 H), 5.2 - 5.6 (m, 2 x 2 H), 6.15 (m, 1 H), 7.65 (m, 1 H)

4.5.3 Irradiation of 115 With Acrylonitrile 137

a) determination of the regiochemistry of the adducts

A solution of 5 g **115** (61 mmole) and 16.2 g **137** (305 mmole) in 200 ml benzene was irradiated at room temperature in Pyrex with a medium pressure Hg-lamp. The reaction was followed by gc and showed the formation of seven products in a ratio (in order of increasing retention time) of ≈1:17.9:11.2:27.2:10.1:3.0:1 after 115 hours of irradiation (≈95 % conversion of **115**) as well as polymer formation (polyacrylonitrile). The first product (compound **331**) had a mass of 106 and was tentatively assigned to be a dimer of **137**, the second to fifth products (compounds **323** - **326**) were identified as 1:1 adducts of **115** and **137** (by gc/ms) and the last two as dimers of **115** (**117** and **116** by gc/ms and comparison with known retention time data). The solvent and excess **137** were taken off in vacuo to give 4.5 g of an orange liquid which was separated by column chromatography (330 g silica gel, diethyl ether/cyclohexane 2:1 to give five fractions I - V as shown in TABLE 33.

TABLE 33: Distribution of cycloaddition/dimerization products after separation

		Composition in %						
Fraction	Mass (mg)	**323**	**324**	**325**	**326**	**331**	**117**	**116**
I	183.2	79				21		
II	922.0	69	31					
III	402.8		41	53				6
IV	266.0		2	97			1	
V	1218.8			56	34		10	

^{13}C-Nmr (50 MHz, $CDCl_3$) analysis of all fractions allowed assignments of the resonances to the individual components of the mixtures. Adduct **323**: 22.83 (CH), 26.52 (CH_2), 29.91 (CH_2), 33.53 (CH), 36.47 (CH_2), 47.41 (CH), 121.09 (C≡N), 217.12 (C=O); adduct **324**: 24.61 (CH), 26.14 (CH_2), 26.28 (CH_2), 35.76 (CH_2), 41.18 (CH), 42.04 (CH), 121.06 (C≡N), 219.10 (C=O); adduct **325**: 23.34 (CH_2), 23.70 (CH), 26.12 (CH_2), 35.46 (CH), 36.23 (CH_2), 41.77 (CH), 119.38 (C≡N), 218.30 (C=O); adduct **326**: 20.63 (CH), 26.95 (CH_2), 29.52 (CH_2), 33.64 (CH), 36.42 (CH_2), 46.16 (CH), 118.45 (C≡N), 216.56 (C=O); dimer **331**: 24.76 (CH_2), 26.58 (CH), 118.66 (C≡N); dimer **117**: 27.96 (CH_2), 36.04 (CH_2), 37.23 (CH), 49.37 (CH), 219.51 (C=O); dimer **116**: 27.29 (CH_2), 35.54 (CH_2), 40.03 (CH), 44.86 (CH), 218.36 (C=O); ^{1}H-nmr (200 MHz, $CDCl_3$): all fractions exhibited unresolvable multiplets between 1 and 3 ppm; ms (EI): adduct **323**: 135 (M^+, 52), 107 (24), 106 (34), 82 (26), 81 (35), 80 (36), 79 (44), 66 (33), 55 (100), 54 (50); adduct **324**: 135 (M^+, 50), 107 (18), 106 (22), 82 (100), 81 (38), 80 (43), 79 (40), 66 (55), 55 (81), 54 (99); adduct **325**: 135 (M^+, 50), 107 (10), 106 (24), 82 (100), 81 (40), 80 (38), 79 (43), 66 (51), 55 (91), 54 (98); adduct **326**: 135 (M^+, 30), 107 (15), 106 (13), 82 (10), 81 (17), 80 (17), 79 (22), 66 (13), 55 (100), 54 (23); dimer **117**: 164 (M^+, 95), 83 (53), 82 (100), 81 (47), 80 (62), 79 (84), 54 (56); dimer **116**: 164 (91), 83

(35), 82 (98), 81 (38), 80 (76), 79 (100), 54 (54); ms (CI): dimer **331**: 107 ($M^+ + 1$, 100), 79 (16)

A small portion of fraction I was refluxed in benzene under nitrogen with proton sponge and the reaction was followed by gc. After 42 hours no product derived from adduct **323** was observed.

Another small portion of fraction I was stirred under nitrogen at room temperature in methanol containing a small amount of sodium methoxide. After four hours the reaction was quenched with dry ice/sat. KH_2PO_4 solution and worked up (extraction into diethyl ether, drying with $MgSO_4$) to give a yellow liquid which showed five major products in a ratio (in order of increasing retention time) ≈4.4:15.8:1:53.1:5.0. The first was identified from known data as dimer **331**, the fourth as adduct **323**. The others were tentatively assigned to be (in order of increasing retention time) 1-cyanocyclobutane-2-methylcarboxylate: ms (CI): 140 ($M^+ + 1$, 100), 108 (20), 80 (38), 79 (20); cyclobutane-1,2-bis(methylcarboxylate): ms (CI): 173 ($M^+ + 1$, 55), 141 (100), 140 (51), 113 (69), 112 (40), 108 (19), 81 (29), 71 (30); methylester of adduct **323**: ms (CI): 169 ($M^+ + 1$, 74), 168 (47), 137 (100), 109 (48), 81 (51)

A small portion of fraction IV was treated similarly but after workup no product formation could be detected by gc.

For the reduction of adduct **323** 46.6 mg of fraction I (containing ≈35 mg adduct **323**, ≈0.26 mmole) dissolved in abs. ethanol were added to a suspension of 15.0 mg 98 % $NaBH_4$ (0.39 mmole) in abs. ethanol. The reaction was stirred at room temperature for 30 min, quenched with water, made slightly acidic with dil. HCl and concentrated in vacuo. The aqueous residue was extracted with diethyl ether, the combined organic phases dried ($MgSO_4$) and the solvent removed to give 36.4 mg of

a colourless liquid (containing dimer **331** and a single new product in a ≈ 1:4 ratio) which was flash chromatographed on silica gel (diethyl ether/hexanes 1:1) to give 15.3 mg of a colourless liquid **332**. Dimer **331**: ^{1}H-nmr (200 MHz, $CDCl_3$): 2.45 (m, 4 H), 3.45 (m, 2 H); alcohol **332**: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.42 - 1.68 (m, 2 H), 1.70 - 1.86 (m, 1 H), 1.90 - 2.10 (m, 2 H), 2.30 (bs, 1 H), 2.52 - 2.68 (m, 1 H), 2.74 - 2.90 (m, 1 H), 3.01 (m, 1 H), 3.16 (dddd, 9.97, 6.99, 4.92, 0.90, 1 H), 4.26 (m, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 16.91 (CH), 29.14 (CH_2), 29.25 (CH_2), 31.05 (CH_2), 34.49 (CH), 46.15 (CH), 73.26 (CH), 123.45 (C≡N); ms (CI): 138 ($M^+ + 1$, 100), 120 (18), 84 (38), 83 (87)

Alcohol **332** (≈ 5 mg) was refluxed under nitrogen in benzene with proton sponge. After 19 hours no change in the ratio of the alcohol to the base was detected.

The remainder of alcohol **332** (≈ 10 mg) was stirred under nitrogen at room temperature in benzene with ≈ 0.5 ml triethylamine and ≈ 1 ml TMSCl. After one hour the mixture was filtered and the filtrate concentrated in vacuo to give silyl ether **333** as a colourless liquid. Ms (CI): 210 ($M^+ + 1$, 76), 194 (99), 167 (47), 75 (100), 73 (73)

Silyl ether **333** was refluxed under nitrogen in benzene with proton sponge for 19 hours, then triethylamine was added and reflux continued for another 21 hours. Gc monitoring showed no change in the reaction mixture.

An abs. ethanol solution of 87.9 mg of fraction II (total of 0.65 mmole adducts in a **323**:**324** ratio of ≈ 7:3 was added to an ethanol suspension of 31.0 mg 98 % $NaBH_4$ (0.8 mmole). After 30 min stirring at room temperature the reaction was made slightly acidic with dil. HCl and extracted with dichloromethane. After drying ($MgSO_4$) and solvent removal a colourless liquid (65.4 mg, 73 %) was obtained. Gc/ms analysis showed two peaks with a mass of 137 in a ≈ 3:7 ratio, co-injection with an authentic

sample showed the major one to be alcohol **332**. Flash chromatography (silica gel, diethyl ether/hexanes 1:3) gave separation into pure alcohol **332** and a mixture with a ratio of alcohols **332**:**334** of ≈44:56. Alcohol **334**: ms (CI): 138 ($M^+ + 1$, 100), 120 (14), 84 (83), 83 (72)

The mixture was refluxed under nitrogen with proton sponge for 22 hours in benzene after which no change in the ratio of alcohols **332** and **334** was detected and no new products appeared.

Fraction IV (74.9 mg, containing 0.54 mmole adduct **325**) was reduced in abs. ethanol with 38.3 mg 98 % $NaBH_4$ (0.99 mmole). After 30 min stirring at room temperature the reaction was quenched with water and, after making it slightly acidic with dil. HCl, extracted into dichloromethane. Drying ($MgSO_4$) and solvent removal gave a colourless liquid (70.1 mg, 95 %) which was identified as alcohol **335**: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.6 - 1.9 (m, 2 H), 1.9 - 2.1 (m, 2 H), 2.2 - 2.3 (m, 2 H), 2.51 (bs, 1 H), 2.71 - 2.91 (m, 2 H), 3.35 (m, 1 H), 4.17 (m, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 21.27 (CH_2), 22.80 (CH), 26.06 (CH_2), 31.35 (CH_2), 37.38 (CH), 39.12 (CH), 73.69 (CH), 119.76 (C≡N); ms (CI): 138 (M^+, 30), 120 (95), 84 (100), 83 (82), 67 (74)

Alcohol **335** (≈35 mg) was stirred at room temperature under nitrogen with TMSCl/triethylamine for 15 min, then filtered and concentrated to give a white solid (one compound by gc with a longer retention time than alcohol **335**) identified as silyl ether **336**. Ms (CI): 210 ($M^+ + 1$, 100), 195 (84), 194 (100), 74 (100), 73 (100)

A sample of silyl ether **336** was refluxed under nitrogen in benzene with proton sponge. After three hours triethylamine was added and after 76 hours the reaction was stopped. No new product was detectable but ≈ 20 % (by gc) of alcohol **335** had been formed.

Treatment of silyl ether **336** with a small amount of sodium hydride in benzene at ≈5°C for one hour led after workup (quenching with sat. KH_2PO_4 solution, extraction with benzene, drying with $MgSO_4$) to a colourless liquid containing exclusively starting material as determined by gc.

A sample of silyl ether **336** was heated in DMF with a small amount of sodium hydride for two hours and then worked up by quenching with sat. KH_2PO_4 solution, extraction into benzene and drying ($MgSO_4$) to give a colourless liquid which consisted solely of alcohol **335** as determined by gc.

Reduction of fraction III (203.8 mg, ≈1.45 mmole, with a ratio of adducts **324**:**325** of ≈44:56) was accomplished in abs. ethanol with 97.2 mg 98 % $NaBH_4$ (2.51 mmole) at room temperature followed by workup (quenching with water, slightly acidifying with dil. HCl, removal of the ethanol, extraction into dichloromethane, drying with $MgSO_4$ and removal of the solvent) which gave a colourless liquid (199.4 mg, ≈100 %) which gave one peak in the gc but two compounds were observed by ^{13}C-nmr spectroscopy. By comparison with known data one was identified as alcohol **335**, the other was assigned to be alcohol **334**: ^{13}C-nmr (50 MHz, $CDCl_3$): 20.68 (CH_2), 24.74 (CH), 28.82 (CH_2), 31.10 (CH_2), 38.29 (CH), 41.92 (CH), 73.27 (CH), 122.93 (C≡N)

The mixture of alcohols was refluxed in benzene with triethylamine for 19 hours and then analyzed by ^{13}C-nmr. The ratios of similar nuclei were compared as shown in TABLE 34.

TABLE 34: ^{13}C-Nmr data of the epimerization attempt of alcohols **334** and **335**

Nuclei in **335**/**334** (shift in ppm)	Ratio before isomerization	Ratio after isomerization
21.26/20.68	1.560	1.514
24.74/22.78	0.795	0.739
(37.35+39.12)/(38.29+41.92)	1.098	1.242
73.69/73.27	1.191	1.162

No change and thus no isomerization had taken place. All of the above mixture (≈200 mg, ≈1.45 mmole) was stirred at room temperature in benzene with 0.5 ml triethylamine and 1 ml TMSCl for 20 min, then repeatedly filtered and concentrated to give a slightly pinkish liquid (186.2 mg, ≈60 %) with two compounds in a ≈4:5 gc ratio (in order of increasing retention time). The major product was identified from known gc data as silyl ether **336**, the minor one was assigned to be silyl ether **337**. Mixture: ^{1}H-nmr (200 MHz, $CDCl_3$): -0.03 (s, 18 H), 1.4 - 2.9 (m, 17 H), 3.25 (m, 1 H), 3.95 - 4.16 (m, 2 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 0.43 (3 CH_3), 0.49 (3 CH_3), 21.64 (CH_2), 22.12 (CH_2), 23.45 (2 CH), 25.34 (CH_2), 26.46 (CH_2), 29.24 (CH_2), 32.41 (CH_2), 37.64 (CH), 39.15 (CH), 40.09 (CH), 42.32 (CH), 74.42 (CH), 74.66 (CH), 120.37 (C≡N), 123.68 (C≡N)

A sample of the silylether mixture (100.5 mg) was refluxed in benzene with 0.5 ml triethylamine for 17 hours. Gc analysis showed no change. A small amount of sodium hydride was added and reflux continued for one hour, then the reaction was quenched with sat. KH_2PO_4 solution, extracted into dichloromethane and dried ($MgSO_4$). Removal of the solvent led to the recovery of the unchanged starting mixture (74.5 mg, 74 %).

Fraction V (257.5 mg, with a compound ratio **325**:**326**:**117** of ≈56:44:10) was stirred at room temperature for 30 min in abs. ethanol with 111.5 mg 98 %

$NaBH_4$ (2.9 mmole). It was worked up by addition of water, slightly acidifying with dil. HCl, removing the ethanol and extracting into dichloromethane. Drying ($MgSO_4$) and solvent removal gave a yellowish liquid (221.8 mg). The main product (as determined by gc/ms) was alcohol **335** (≈80 %), the second largest (≈6 %, shortest retention time) showed the following ms (EI): 140 (M^+, 1.5), 123 (0.9), 112 (1), 79 (38), 66 (100); ms (CI): 141 ($M^+ + 1$, 4), 123 (35), 79 (36), 66 (100)

Fraction IV (12.2 mg, 97 % adduct **325**) was stirred at room temperature in 1 M ethanolic HCl and the reaction was followed by gc. After 24 hours it was worked up (diluting with water, neutralizing with sat. $NaHCO_3$ solution, extraction into dichloromethane, drying with $MgSO_4$) and analyzed by gc/ms which showed adduct **325** and a new product (higher retention time) in a ≈1:2 ratio. Ms (EI) of new product: 209 (M^+, 4), 164 (60), 136 (68), 84 (59), 69 (53), 55 (54), 49 (100)

A sample of alcohol **335** (≈20 mg, ≈0.15 mmole) was stirred at room temperature in 1 M ethanolic HCl for 37 hours, then neutralized with sat. $NaHCO_3$ solution, extracted into dichloromethane and dried ($MgSO_4$). Gc/ms analysis showed formation of one new product (≈45 %) which was identified as ester **339**: ms (EI): 184 (M^+, 0.1), 101 (66), 73 (86), 67 (70), 66 (100), 55 (81); ms (CI): 185 ($M^+ + 1$, 19), 167 ([illegible]), 101 (100), 73 (35), 67 (43), 66 (44)

All of the above ester/alcohol mixture was refluxed in benzene with triethylamine. After 120 hours only a ratio change from 45:55 to ≈35:65 was observed and the reaction was stopped.

The oxidation of alcohol **335** was carried out by refluxing 19.0 mg of fraction IV (≈0.14 mmole alcohol) in dichloromethane with 42.6 mg 85 % MCPBA (0.21 mmole). After four hours the reaction was stopped, washed with sat. $NaHCO_3$ solution and dried ($MgSO_4$) to give after solvent removal 19.9 mg (≈94 %) of a

colourless liquid (one peak in > 98 % purity by gc). Ms (EI): 151 (M^+, 11), 123 (89), 98 (100), 80 (88), 70 (89), 68 (80), 67 (61), 55 (99), 53 (66); ms (CI): 152 ($M^+ + 1$, 100)

Nmr spectroscopy showed the presence of two isomeric lactones in a ratio of ≈ 2.5-3:1. The major one was assigned to be lactone **340**, the minor one lactone **341**. ^{1}H-Nmr (200 MHz, $CDCl_3$): 2.1 - 3.2 (m, **340**: 8 H, **341**: 5 H), 3.27 - 3.50 (m, **341**: 2 H), 4.35 (ddd, 11.71, 7.59, 3.97, **341**: 1 H), 4.63 (ddd, 11.71, 6.21, 3.71, **341**: 1 H), 4.82 - 4.96 (m, **340**: 1 H); ^{1}H-nmr (200 MHz, C_6D_6): 1.0 - 2.0 (m, **340**: 8 H, **341**: 5 H), 2.08 - 2.22 (m, **341**: 2 H), 3.38 (ddd, 11.58, 8.16, 3.09, **341**: 1 H), 3.66 - 3.78 (m, **340**: 1 H), 3.83 (ddd, 11.58, 6.75, 3.01, **341**: 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$): lactone **340**: 19.45 (CH), 20.78 (CH_2), 28.60 (CH_2), 34.52 (CH_2), 35.52 (CH), 70.31 (CH), 118.53 (C≡N), 169.65 (C=O); lactone **341**: 23.23 (CH), 24.75 (CH_2), 29.[illegible] (CH_2), 33.42 (CH), 33.61 (CH), 67.18 (CH_2), 118.65 (C≡N), 171.53 (C=O); ms (EI): 151 (M^+, 10), 123 (89), 98 (99), 80 (88), 70 (89), 68 (79), 55 (100); ms (CI): 152 ($M^+ + 1$, 100), 123 (9), 98 (8), 80 (7), 70 (8)

b) determination of the relative rates of formation of the adducts

A solution of 66.0 mg cyclopentenone **115** (0.8 mmole) and 849.8 mg acrylonitrile **137** (16.0 mmole) in 5 ml benzene containing a drop of tetradecane was prepared. A ≈ 1 ml aliquot of this solution was irradiated in a Pyrex nmr-tube with a medium pressure Hg-lamp. After 30 min the reaction was analyzed for the adducts and the area ratio of each adduct relative to tetradecane determined by five injections on the gc. The results for adducts **323**, **324**, **325** and **326** were (errors in % in parenthesis) 1.811 (3.6), 1.069 (5.4), 3.285 (1.2) and 1.138 (3.3), respectively.

4.6 Preparation of Iodosobenzene 284

At 30°C a solution of peracetic acid in acetic acid (24.7 ml of a 32 % solution by weight, 118 mmole) were slowly added to 5.5 ml iodobenzene (49 mmole). After addition the mixture was stirred for 30 min, then cooled to 0°C for 30 min leading to crystallization. The crystals were filtered off, washed with cold water and airdried (mp. 156-158°C, lit. 158-159°C dec.[125a]). The yield of the intermediate acetate $(PhIOCOCH_3)^+(CH_3COO)^-$ was 13.11 g (83 %). To the acetate was added 3 N aqueous NaOH (65 ml) under stirring resulting in a yellow suspension. The crystals were filtered off, suspended in water and re-filtered. After airdrying the product was suspended in chloroform , filtered and dried to give yellow crystals (8.56 g, 95.5 %, 79.4 % overall, mp. 214-216°C, lit. 210°C expl.[125a]).

4.7 Preparation of Bicyclo[3.3.0]octane-2,6-dione 261 and its Derivatives

4.7.1 Preparation of Tetraester 262

Dimethylglutarate (DMG, 465 g, 2.9 mole) was heated under nitrogen to reflux for 15 min and then allowed to cool to 175°C (measured internally). To the DMG was slowly added a mixture of 35 g DMG (0.22 mole) and 60 g *t*-butylperoxide (0.41 mole). Gas effervescence started and the reaction mixture darkened. After the addition was completed (*ca.* 100 min) the reaction was kept at ≈ 175°C until gas evolution ceased (*ca.* 30 min) and then cooled followed by vacuum distillation. DMG (419 g, 2.6 mole) was distilled off at ≈ 115°C/27 torr; additional DMG (6.2 g, 39 mmole) was obtained at ≈ 68°C/0.9 torr. Tetraester 262 was distilled as a yellow liquid ($bp._{0.3}$ 165-175°C, 98 % purity by gc, mixture of two stereoisomers in a 47.5:52.5 ratio by gc) which solidified on standing to give white crystals (mp. 49-54°C). The yield was 55.5 g (0.17 mole), 78 % based on DMG consumed. ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.7 - 1.9 (m, 8 H), 2.1 - 2.3 (m, 8 H), 2.6 - 2.7 (m, 4 H),

3.55 (s, 6 H), 3.56 (s, 6 H), 3.58 (s, 6 H), 3.59 (s, 6 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 23.48 (CH_2), 24.66 (CH_2), 30.86 (CH_2), 31.16 (CH_2), 45.25 (CH), 46.39 (CH), 51.18 (2 CH_3), 51.48 (2 CH_3), 172.44 (C=O), 172.57 (C=O), 173.09 (C=O), 173.52 (C=O)

4.7.2 Preparation of 3,7-Bis(methoxycarbonyl)bicyclo[3.3.0]octane-2.6-dione 263

Sodium methoxide, prepared from 10.1 g sodium (0.44 mole) and methanol under nitrogen, was suspended in dry DMSO and a dry DMSO solution of tetraester 262 (32.3 g, 0.1 mole) was added. The reaction mixture darkened and was heated to ≈80°C for one hour. After cooling to below 30°C 80 ml halfconcentrated HCl was slowly added resulting in precipitation. The mixture was poured into ice water and filtered. The crystals were washed with cold water and cold water/methanol 1:1, airdried and finally vacuum dried to give colourless crystals (18.0 g, 70 %, mp. 95-96°C, subl.). ^{1}H-Nmr (200 MHz, $CDCl_3$): 2.7 (m, 4 H), 3.38 (m, 2 H), 3.72 (s, 6 H), 10.33 (bs, 2 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 29.27 (CH_2), 43.46 (CH), 51.28 (CH_3), 98.80 (C), 170.23 (C=O), 175.30 (C=O); ms (EI): 254 (M^+, 86), 222 (84), 190 (64), 162 (47), 141 (48), 109 (100), 108 (58)

4.7.3 Preparation of Bicyclo[3.3.0]octane-2,6-dione 261

Compound 263 (15.0 g, 59 mmole) was heated in 60 ml halfconcentrated HCl to ≈70°C for 90 min, cooled to room temperature, saturated with NaCl and extracted with chloroform. The combined organic layers were washed with sat. $NaHCO_3$ solution and dried with Na_2SO_4. Removal of the solvent gave a red liquid (16.7 g) which solidified. Sublimation (40°C, 0.1 torr) gave dione 261 (7.13 g, 87.5 %) as colourless crystals (mp. 45-46°C, lit. 45-46°C[116]). ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.9 - 2.4 (m, 8 H), 2.85 (m, 2 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 23.23 (CH_2), 37.80 (CH_2), 49.73 (CH),

221.00 (C=O); uv (MeOH): 207.8 (274), 255.0 (134), 292.4 (42); uv (C_6H_6): 281.4 (46), 294.0 (46), 303.6 (49), 314.4 (40)

4.7.4 Preparation of 3-Methylbicyclo[3.3.0]octane-2,6-dione 270

a) by methylation of compound **263**

To a stirred suspension of 215.4 mg of a sodium hydride dispersion in mineral oil (4.5 mmole) in dry THF under nitrogen a dry THF solution of 1.15 g compound **263** (4.5 mmole) was added. After addition the mixture was heated to 50°C for one hour, then cooled to -78°C and 2.5 ml methyl iodide (5.7 g, 40 mmole) was added. The mixture was allowed to warm to room temperature and stirred for 45 min. Water was added and the organic solvent and excess methyl iodide taken off in vacuo. The residue was extracted with diethyl ether and the combined extracts washed with sat. $Na_2S_2O_3$ solution and dried ($MgSO_4$). Solvent removal gave reddish crystals (742.2 mg, fraction **A**). Hydrolysis/decarboxylation of *ca.* 10 % of the product with halfconcentrated HCl to determine the success of the reaction gave a colourless liquid (21.1 mg). Gc/ms analysis showed six compounds in approximately the following ratio (in order of increasing retention times, M^+ in parenthesis): 28(138):12(152):8(152):1(166):1(166):1(166). The first compound was identified by comparison with known gc data as bis(*β*-ketoester) **263**.

The remainder of fraction **A** was re-methylated with 109.6 mg of the above sodium hydride dispersion (2.3 mmole) and 3.2 g methyl iodide (23 mmole) following the same procedure. Similar workup gave a slightly red liquid (439.3 mg) which was hydrolyzed/decarboxylated with halfconcentrated HCl to give a colourless liquid (310.3 mg, fraction **B**). Gc/ms analysis of fraction **B** showed the presence of the same six compounds in a ≈26:14:9:1:1:1 ratio. Fraction **B** was separated by column

chromatography (40 g silica gel, diethyl ether/hexanes 1:3) to give two product containing fractions, **B.I** and **B.II**, the latter more polar.

Fraction **B.I** (49.9 mg) proved to be a ≈2:1 mixture of two stereoisomers of 3,7-dimethylbicyclo[3.3.0]octane-2,6-dione **270** as determined by gc and ^{1}H-nmr. ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.02 (d, 6.95, 3 H, minor isomer), 1.06 (d, 6.91, 3 H, minor isomer), 1.09 (d, 6.69, 6 H, major isomer), 1.2 - 1.55, 1.65 - 2, 2.4 - 2.5, 2.8 (m, total of 16 H); ms (EI, sample): 166 (M^+, 100), 152 (36), 123 (38), 97 (65), 81 (86), 67 (60)

Fraction **B.II** (46.7 mg) was a ≈5.5:1 mixture of the two stereoisomers of compound **273** as determined by gc and ^{1}H-nmr. ^{1}H-Nmr (200 MHz, C_6D_6): 0.81 (d, 6.92, 3 H, minor isomer), 0.82 (d, 6.82, 3 H, major isomer), 1.0 - 1.2, 1.3 - 1.6, 1.7 - 1.9, 2.0 - 2.25 (m, total of 18 H); major isomer: ^{13}C-nmr (50 MHz, C_6D_6): 14.17 (CH_3), 23.46 (CH_2), 32.37 (CH_2), 37.18 (CH_2), 43.08 (CH), 47.06 (CH), 48.67 (CH), 219.20 (C=O), 220.34 (C=O); ms (EI): 152 (M^+, 100), 97 (50), 83 (54), 82 (46), 67 (40); minor isomer: ^{13}C-nmr (50 MHz, C_6D_6): 14.67 (CH_3), 22.25 (CH_2), 31.43 (CH_2), 36.35 (CH_2), 43.60 (CH), 46.98 (CH), 48.80 (CH), no carbonyls resolved; ms (EI): 152 (M^+, 100), 97 (52), 83 (51), 82 (49), 67 (44)

b) by methylation of dione **261**

A dry THF solution of LDA was prepared from 149.9 mg diisopropylamine (1.48 mmole) and 0.58 ml of a 2.58 M solution of *n*-butyllithium in hexane (1.49 mmole). After 10 min stirring at -20°C a dry THF solution of dione **261** (204.7 mg, 1.48 mmole) was added dropwise. After warming to room temperature methyl iodide (0.6 ml, 1.37 g, 9.6 mmole) was added at once and the mixture stirred for 10 min, then quenched with water and extracted with diethyl ether. The combined organic phases were washed with 5 % HCl, sat. $NaHCO_3$ solution and dried ($MgSO_4$).

Solvent removal gave a yellow liquid (170.7 mg), a mixture of seven compounds in a ratio of ≈3:4:2:5:1:3:2 (as determined by gc, in order of increasing retention times). All six compounds from the above described preparation of dione **270** were present, the additional one (#3) showed ms (EI): 152 (M^+, 68), 97 (100), 67 (42)

4.7.5 Preparation of Bicyclo[3.3.0]octane-2,6-dione Bis(ethylene ketal) 288

A solution of dione **261** (11.4 g, 83 mmole) and ethyleneglycol (7.5 g, 121 mmole) in 200 ml benzene was refluxed with a few crystals of *p*-toluenesulfonic acid. The reaction was monitored by gc; after five hours dione **261** was completely converted to one product. The mixture was washed with water and sat. $NaHCO_3$ solution and dried ($MgSO_4$); solvent removal gave a slightly yellow liquid (18.6 g, 99.5 %). ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.5 - 2.0 (m, 8 H), 2.36 (m, 2 H), 3.78 - 3.88 (m, 8 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 23.79 (CH_2), 34.69 (CH_2), 47.87 (CH), 64.14 (CH_2), 65.14 (CH_2), 119.24 (C); ms (EI): 226 (M^+, 38), 181 (24), 165 (26), 99 (100)

4.7.6 Preparation of Bicyclo[3.3.0]octane-2,6-dione Monoethylene Ketal 287

A solution of diketal **288** (9.17 g, 41 mmole) and a few crystals of *p*-toluenesulfonic acid in 200 ml acetone was refluxed and the progress monitored by gc. After five hours optimum conversion to monoketal **287** was seen and the reaction stopped by evaporating the acetone in vacuo. The residue was taken up in dichloromethane, washed with sat. $NaHCO_3$ solution and dried ($MgSO_4$) to give 8.77 g of a yellow liquid containing dione **261**, monoketal **287** and diketal **288** in a ≈1:14:5 ratio. It was column chromatographed (240 g silica gel, diethyl ether/hexanes 1:4) to give three fractions I - III (in order of increasing polarity). Fraction I (4.95 g, yellow liquid) was a ≈1.6:1 mixture of dione **261** and monoketal **287**, fraction II (2.75 g, 37 %, yellow liquid) was monoketal **287** and fraction III (0.65 g, yellow liquid) was a ≈3:1 mixture of monoketal **287** and diketal **288**. Monoketal **287**: ^{1}H-nmr (200 MHz,

$CDCl_3$): 1.4 - 1.9 (m, 6 H), 2.0 - 2.1 (m, 2 H), 2.4 - 2.6 (m, 2 H), 3.69 - 3.81 (m, 4 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 21.43 (CH_2), 24.92 (CH_2), 34.58 (CH_2), 38.13 (CH_2), 47.11 (CH), 49.51 (CH), 64.57 (CH_2), 65.06 (CH_2), 118.62 (C), 222.88 (C=O); ms (EI): 182 (M^+, 10), 100 (90), 99 (100), 86 (50)

4.7.7 Preparation of 2-Trimethylsiloxybicyclo[3.3.0]oct-2-en-6-one Ethyleneketal 289

At 0°C a LDA solution in dry THF was prepared from 122.2 mg diisopropylamine (1.21 mmole) and 490 μl of a 2.45 M solution of *n*-butyllithium in hexane (1.20 mmole). To it was slowly added a dry THF solution of monoketal **287** (218.9 mg, 1.20 mmole) and after five minutes stirring 250 μl trimethylsilyl chloride (TMSCl) were added. After warming to room temperature the reaction was worked up by addition of pentane, washing with cold sat. $NaHCO_3$ solution and drying (Na_2SO_4). Solvent removal in vacuo gave a reddish liquid (273.5 mg, by gc > 98 % purity). Gc analysis showed two products in a ≈15:1 ratio. Silyl ketal **289**: ^{1}H-nmr (200 MHz, $CDCl_3$): 0.15 (s, 9 H), 1.55 - 1.75 (m, 4 H), 2.2 - 2.35 (m, 2 H), 2.36 - 2.52 (m, 1 H), 2.9 - 3.04 (m, 1 H), 3.74 - 3.96 (m, 4 H), 4.48 (dd, 3.89, 2.24, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 0.04 (3 CH_3), 25.99 (CH_2), 29.93 (CH_2), 32.56 (CH_2), 45.12 (CH), 48.38 (CH), 63.82 (CH_2), 65.06 (CH_2), 101.31 (CH), 119.49 (C), 154.85 (C); ms (EI): 254 (M^+, 20), 226 (14), 209 (90), 99 (48), 73 (100); silyl ketal **290**: ms (EI): 254 (M^+, 18), 182 (40), 167 (58), 73 (100)

4.7.8 Attempted Preparation of 3-Hydroxybicyclo[3.3.0]octane-2,6-dione 282

a) with MCPBA

To a stirred solution of silyl ketal **289** (790.8 mg, 2.7 mmole) in dichloromethane over solid $NaHCO_3$ was added a dichloromethane solution of 85 % MCPBA (606.3 mg, 3.0 mmole). Gc showed disappearance of silyl ketal **289**. The mixture was washed with Na_2SO_3 solution, sat. $NaHCO_3$ solution and dried. Gc/ms

analysis showed several products one of which had the correct mass for hydroxy ketal **291** (198). After solvent removal the residue (552.4 mg of a yellow viscous liquid) was separated by column chromatography (60 g silica gel, diethyl ether/hexanes 1:3) to give a fraction (156.5 mg, highest polarity) containing hydroxy ketal **291** in ≈ 63 % purity (as determined by gc). ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.5 - 2.1 (m, 4 H), 2.2 - 2.4 (m, 2 H), 2.6 - 2.8 (m, 2 H), 3.80 - 3.94 (m, 4 H), 4.17 - 4.29 (m, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 25.52 (CH_2), 29.00 (CH_2), 35.38 (CH_2), 42.61 (CH), 46.12 (CH), 64.46 (CH_2), 64.88 (CH_2), 73.38 (CH), 117.40 (C), 220.86 (C=O); ms (EI): 198 (M^+, 6), 100 (32), 99 (100), 86 (22)

Hydroxy ketal **291** was dissolved in acetone and stirred with a few crystals of *p*-toluenesulfonic acid. After 47 hours the reaction was heated to reflux for five hours; hydroxy ketal **291** was converted to an unidentified mixture; due to lack of the expected ^{1}H-nmr signal for the *α*-proton adjacent to the hydroxyl group and small mass obtained (< 5 mg) the attempt to prepare hydroxy diketone **282** was stopped.

b) with iodosobenzene/BF_3•Et_2O

To a slurry of iodosobenzene **284** (727.8 mg, 3.3 mmole) in diethyl ether at 0°C was added 750 µl BF_3•Et_2O (866 mg, 6.1 mmole) and silyl ketal **289** (760.3 mg, 3.0 mmole). The mixture was stirred at 0°C for two hours, then at room temperature for three hours. It was neutralized with solid $NaHCO_3$ and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and the solvent removed to give a yellow liquid (847.4 mg). The product mixture was separated by column chromatography (85 g silica gel, diethyl ether/cyclohexane 1:1) to give a fraction (113 mg) containing hydroxy ketal **291** in ≈ 80 % purity (as determined by gc).

It was again tried to deprotect hydroxy ketal **291** by refluxing in acetone with added *p*-toluenesulfonic acid but again only unidentified products were obtained; nmr and gc/ms did not detect any hydroxy diketone **282** formed.

4.7.9 Preparation of 3-Ethoxybicyclo[3.3.0]octane-2,6-dione 281

To a slurry of iodosobenzene **284** (152 mg, 0.69 mmole) in abs. ethanol under nitrogen was added 154 µl $BF_3 \bullet Et_2O$ (178 mg, 1.25 mmole). The solution went clear and was cooled to -78°C. Silyl ketal **289** (179 mg, 0.70 mmole) was added and the mixture stirred for 30 min in the cold, then warmed to room temperature and stirred for additional 20 min. The solvent was removed and water added to the residue. The reaction was neutralized with sat. $NaHCO_3$ solution, extracted with dichloromethane and the combined organic extracts dried with $MgSO_4$. Removal of the solvent gave an orange liquid (155 mg). Preliminary nmr analysis showed the presence of iodobenzene (peaks at $\delta > 7$ ppm in the ^{1}H-nmr, $\delta > 120$ ppm in the ^{13}C-nmr). Gc/ms analysis showed a large amount of iodobenzene (M^+ of 204) and a peak with M^+ of 226 corresponding to ethoxy ketal **292**.

The product mixture was separated by preparative TLC, the bands containing ethoxy ketal **292** (59 mg) combined and refluxed in acetone with a few crystals of *p*-toluenesulfonic acid. The reaction was followed by gc and after four hours a few ml of water were added. After 50 hours disappearance of ethoxy ketal **292** to two products (> 80 %) was observed and the reaction stopped. Acetone was removed in vacuo, the residue dissolved in diethyl ether, washed with sat. $NaHCO_3$ solution and dried ($MgSO_4$). Solvent removal gave a colourless liquid (46 mg) which was separated by preparative TLC to give a ≈ 1:2 mixture of two stereoisomers of ethoxy diketone **281** (9.2 mg, purity ≈ 80 %) eluting closely together on the gc. Major isomer: ^{1}H-nmr (200 MHz, C_6D_6): 0.93 (t, 7.02, 3 H), 1.3 - 2.2 (m, 8 H), 3.13 (dd, 5.29, 4.48, 1 H),

3.16 (dq, 9.26, 7.02, 1 H), 3.44 (dq, 9.26, 7.02, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): 15.17 (CH_3), 23.32 (CH_2), 31.19 (CH_2), 36.41 (CH_2), 45.62 (CH), 46.65 (CH), 65.05 (CH_2), 79.51 (CH), 214.66 (C=O), 216.98 (C=O); ms (EI): 182 (M^+, 1.8), 154 (20), 138 (4), 110 (3), 72 (100); minor isomer: ^{1}H-nmr (200 MHz, C_6D_6): 1.05 (t, 7.01, 3 H), 1.3 - 2.2 (m, 8 H), 3.15 - 3.25 (m, 1 H), 3.22 (dq, 9.10, 7.01, 1 H), 3.70 (dq, 9.10, 7.01, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): 15.43 (CH_3), 22.87 (CH_2), 30.67 (CH_2), 37.06 (CH_2), 44.88 (CH), 49.04 (CH), 65.99 (CH_2), 80.33 (CH), 215.86 (C=O), 217.93 (C=O); ms (EI): 182 (M^+, 1.7), 154 (20), 138 (4), 110 (4), 72 (100)

4.7.10 Preparation of 3-*t*-Butoxybicyclo[3.3.0]octane-2,6-dione 295

To a slurry of iodosobenzene **284** (1004 mg, 4.6 mmole) in a mixture of *t*-butanol and dichloromethane (1:1 v/v) was added at 0°C 1 ml BF_3•Et_2O (1.15 g, 8.1 mmole) and a dichloromethane solution of silyl ketal **289** (1004 mg, 4.0 mmole). The reaction was stirred at 0°C for one hour, warmed up to room temperature, neutralized with sat. $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts gave, after drying ($MgSO_4$) and solvent removal, a yellow liquid (1146 mg). Gc/ms analysis showed peaks corresponding to iodobenzene and two isomers of *t*-butoxy ketal **296** (with almost identical retention times). The mixture was separated by column chromatography (110 g silica gel, diethyl ether/cyclohexane 2:3) to give a ≈1:1 mixture (195 mg) of two stereoisomers of *t*-butoxy ketal **296**. ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.13 (s, 9 H), 1.33 (s, 9 H), 1.5 - 2.7 (m, 16 H), 3.7 - 4.1 (m, 10 H); ms (EI): 254 (M^+, 9), 198 (30), 197 (27), 170 (24), 153 (25), 141 (37), 127 (46), 100 (49), 99 (82), 57 (100)

t-Butoxy ketal **296** was refluxed in acetone with a catalytic amount of *p*-toluenesulfonic acid for 17 hours after which gc indicated disappearance of the starting material and formation of two products at shorter retention times in a ≈5:1

ratio. After workup (removal of acetone, dissolving in dichloromethane, washing with sat. $NaHCO_3$ solution, drying with $MgSO_4$, removal of solvent) a yellow liquid (97 mg) was obtained which was separated by preparative gc to give a colourless liquid (28 mg) containing the two products in a ≈1:1 ratio in ≈95 % purity. They were identified as stereoisomers of *t*-butoxy diketone **295**. ^{1}H-Nmr (200 MHz, C_6D_6): 1.01 (s, 9 H), 1.05 (s, 9 H), 1.3 - 2.3 (m, 15 H), 2.36 (ddd, 12.98, 8.08, 1.85, 1 H), 3.41 - 3.55 (m, 2 H); ^{13}C-nmr (50 MHz, C_6D_6): 22.90 (CH_2), 23.13 (CH_2), 28.15 (3 CH_3), 28.19 (3 CH_3), 32.83 (2 CH_2), 36.58 (CH_2), 36.97 (CH_2), 44.62 (CH), 44.91 (CH), 46.06 (CH), 46.28 (CH), 73.95 (2 CH), 74.81 (C), 75.03 (C), 215.34 (C=O), 216.64 (C=O), 217.07 (C=O), 218.11 (C=O); ms (EI, sample): 210 (M^+, 0.5), 182 (12), 139 (16), 126 (15), 97 (19), 83 (74), 57 (100); ms (CI, sample): 211 ($M^+ + 1$, 11), 182 (18), 155 (81), 139 (41), 126 (27), 97 (23), 83 (100)

4.7.11 Preparation of 3-Cyanobicyclo[3.3.0]octane-2,6-dione 298

At 0°C a LDA solution in dry THF was prepared from 132.6 mg diisopropylamine (1.31 mmole) and 525 µl of a 2.45 M solution of *n*-butyllithium in hexane (1.29 mmole). To it was added a dry THF solution of monoketal **287** (203.2 mg, 1.12 mmole) and after 10 min of stirring the mixture was transferred *via* syringe to a -78°C cold solution of *p*-toluenesulfonyl cyanide (430.2 mg, 95 %, 2.26 mmole). A precipitate appeared and 0.5 ml conc. aqueous ammonia solution was added. After warming to room temperature the now clear reaction mixture was acidified with 10 % HCl and extracted with dichloromethane. The combined organic phases were washed with sat. $NaHCO_3$ solution and dried ($MgSO_4$). Removal of the solvent gave a slightly yellowish liquid (331.0 mg). Gc/ms analysis indicated formation of cyano ketal **300**. The mixture which was column chromatographed (25 g silica gel, diethyl ether/hexanes 1:1) to give a colourless liquid (24.1 mg) analyzed to be two

stereoisomers of cyano ketal **300** in a ≈5:3 ratio (in ≈95 % purity as determined by gc, both isomers had the same retention time). Major isomer: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.6 - 1.8 (m, 2 H), 1.9 - 2.2 (3 H), 2.4 - 2.6 (m, 1 H), 2.7 - 2.9 (m, 2 H), 3.52 (dd, 11.45, 9.21, 1 H), 3.8 - 4.0 (m, 4 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 25.18 (CH_2), 25.98 (CH_2), 35.04 (CH_2), 38.35 (CH), 45.10 (2 CH), 64.84 (2 CH_2), 116.86, 117.15 (CH_2, C≡N), 209.97 (C=O); minor isomer: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.6 - 1.8 (m, 2 H), 1.9 - 2.2 (3 H), 2.4 - 2.6 (m, 1 H), 2.7 - 2.9 (m, 2 H), 3.39 (td, 9.18, 1.02, 1 H), 3.8 - 4.0 (m, 4 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 23.82 (CH_2), 26.37 (CH_2), 33.33 (CH_2), 39.19 (CH), 48.13 (CH), 48.18 (CH), 64.98 (2 CH_2), 116.60, 117.36 (CH_2, C≡N), 208.41 (C=O); both isomers: ms (EI): 207 (M^+, 4), 179 (10), 151 (20), 135 (18), 123 (22), 107 (33) 106 (34), 100 (100), 99 (49), 86 (66); ms (CI): 208 ($M^+ + 1$, 100), 100 (50), 99 (21), 86 (29)

The mixture of isomers of cyano ketal **300** was refluxed in acetone with a few crystals of *p*-toluenesulfonic acid and a few drops of water for 24 hours after which gc analysis showed disappearance of the starting material and appearance of one new peak. The reaction was stopped, sat. $NaHCO_3$ solution added and the acetone removed in vacuo. The residual aqueous layer was made acidic and extracted with dichloromethane to give, after drying ($MgSO_4$) and solvent removal, a colourless liquid (11.5 mg) identified as two stereoisomers of cyano diketone **298** (in ≈98 % purity, ≈5:3 ratio as determined by ^{13}C-nmr). Mixture of both isomers: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.9 - 2.5 (m, 12 H), 2.6 - 2.8 (m, 2 H), 2.9 - 3.2 (m, 3 H), 3.46 (td, 9.64, 0.96, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 22.62 (CH_2), 23.17 (CH_2), 27.35 (CH_2), 28.16 (CH_2), 29.68 (CH_2), 37.18 (CH_2), 37.27 (CH_2), 38.52 (CH_2), 39.11 (CH), 46.80 (CH), 47.51 (CH), 48.22 (CH), 115.51 (C≡N), 115.55 (C≡N), 206.45 (C=O), 208.44

(C=O), 216.24 (C=O), 217.51 (C=O); ms (EI): 163 (M^+, 98), 135 (32), 107 (36), 106 (37), 86 (45), 84 (74), 82 (62), 80 (52), 79 (65), 66 (66), 55 (71), 54 (100)

4.8 Preparation of Bicyclo[3.3.0]octane-2,8-dione 301 and its Derivatives

4.8.1 Preparation of 3-Bromopropionic Acid Ethylester

A solution of 3-bromopropionic acid (100.4 g, 0.66 mole) and *p*-toluenesulfonic acid (2 g) in 1 l abs. ethanol was refluxed until gc analysis showed > 96 % conversion of the carboxylic acid. The reaction was worked up by diluting with diethyl ether, washing with sat. $NaHCO_3$ solution and water and drying with $MgSO_4$ to give, after solvent removal, a yellow liquid (82.1 g) which was distilled in vacuo to give the ester as a colourless liquid (75.2 g, 63 %, $bp._{91}$ 35-36°C). ^{1}H-Nmr (60 MHz, $CDCl_3$): 1.20 (t, 6.5, 3 H), 2.78 (t, 6.3, 2 H), 3.45 (t, 6.3, 2 H), 4.03 (q, 6.5, 2 H); ms (EI): 182 (M^+, 8), 180 (M^+, 8), 154 (97), 152 (100), 137 (42), 135 (43), 109 (39), 107 (44), 73 (38)

4.8.2 Preparation of the Amberlite® IRA 900 Resin

The resin (Aldrich, ≈ 150 g) was placed in a large column and washed with 1 l of a 1 M $NaNO_2$ solution, 600 ml water, 500 ml abs. ethanol and 500 ml benzene. The aqueous washes were tested with $AgNO_3$ solution for the presence of bromide ions which gave negative results after the nitrite wash was completed. The resin was dried under oilpump vacuum at 40°C and stored until use.

4.8.3 Preparation of 3-Nitropropionic Acid Ethylester 304

A solution of 3-bromopropionic acid ethylester (18.6 g, 0.1 mole) in ≈ 250 ml dry benzene was stirred with nitrite charged IRA 900 resin (100 g) at room temperature and the progress monitored by gc. After four hours the reaction was stopped, the resin filtered off and the solvent evaporated to give a yellow liquid (13.92 g). It was distilled under reduced pressure to afford ester 304 (8.02 g, 53 %)

as a colourless liquid (bp.$_{0.8}$ 76°C). ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.20 (t, 7.15, 3 H), 2.90 (t, 6.09, 2 H), 4.12 (q, 7.15, 2 H), 4.58 (t, 6.09, 2 H); ms (EI): 147 (M^+, 0.4), 102 (42), 73 (38), 55 (100)

4.8.4 Preparation of 3-(*trans*-2-Ethoxycarbonylethenyl)cyclopentanone 305

Under nitrogen a suspension of potassium *t*-butoxide (0.93 g, 8.3 mmole) in dry THF was added over 30 min to a -10°C cold solution of ester **304** (1.34 g, 9.7 mmole) in dry THF resulting in a yellow solution which was stirred at ≈-5°C for 15 min. A solution of cyclopentenone **115** (0.91 g, 11.1 mmole) in dry THF was added over five min and the bright yellow mixture was allowed to warm up to room temperature slowly (≈40 min). Abs. ethanol (2 ml) was added and after 15 min a sample was worked up (addition of 5 % HCl, extraction with diethyl ether, wash with sat. $NaHCO_3$ solution and drying with $MgSO_4$). It showed two products at longer retention times than ester **304**. Following the reaction by working up small samples as described above a new product was seen growing in with a retention time shorter than the initial products. After ≈21 hours no more change was observed, the ratio of the three products was ≈4:1:1. Gc/ms showed correct mass for the major product for compound **305** (182) and for the minor products masses of 229 each. The reaction was worked up as above to give a yellow oil (1.89 g).

The oil was separated by column chromatography (200 g silica gel, diethyl ether/hexanes 1:3) to give two fractions. The first fraction (267.3 mg, least polar) was identified as compound **305**: ^{1}H-nmr (200 MHz, C_6D_6): 0.99 (t, 7.12, 3 H), 1.3 - 2.1 (m, 7 H), 4.04 (q, 7.12, 2 H), 5.68 (dd, 15.64, 1.25, 1 H), 6.76 (dd, 15.64, 7.37, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 14.33 (CH_3), 28.99 (CH_2), 38.05 (CH_2), 39.44 (CH), 43.85 (CH_2), 60.66 (CH_2), 121.63 (CH), 150.01 (CH), 166.83 (C=O), 217.77 (C=O); ms (EI): 182 (M^+, 30), 153 (40), 137 (44), 109 (66), 81 (100)

The second fraction (269.5 mg, most polar) was identified as a ≈ 1:1 mixture of two stereoisomers of nitro compounds **306**: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.18 (t, 7.15, 3 H), 1.19 (t, 7.14, 3 H), 1.5 - 2.4 (m, 14 H), 2.71 (m, 2 H), 3.08 (dd, 4.57, 10.28, 1 H), 3.17 (dd, 4.59, 10.28, 1 H), 4.03 (q, 7.14, 2 H), 4.10 (q, 7.15, 2 H), 4.76 - 4.89 (m, 2 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 14.33 (2 CH_3), 26.28 (CH_2), 26.55 (CH_2), 35.82 (CH_2), 36.46 (CH_2), 38.37 (CH_2), 38.61 (CH_2), 40.35 (CH), 40.42 (CH), 41.48 (CH_2), 41.93 (CH_2), 61.75 (2 CH_2), 86.99 (CH), 97.09 (CH), 169.52 (C=O), 169.58 (C=O), 215.44 (C=O), 215.49 (C=O); ms (CI, sample): 230 ($M^+ + 1$, 10), 183 (100), 148 (36), 137 (44), 109 (86), 83 (56)

4.8.5 Preparation of 3-(2-Ethoxycarbonylethyl)cyclopentanone 307

A ≈ 4:1 mixture of compounds **305** and **306** (the latter as two stereoisomers in a ≈ 1:1 ratio, 19.95 g) was hydrogenated in 200 ml abs. ethanol with hydrogen gas using 10 % palladium on carbon as catalyst. After gc tests showed the disappearance of compound **305** and formation of a new product with shorter retention time than compound **305** the reaction was stopped (nitro compounds **306** did not undergo any change and the ratio new product:**306** was ≈ 4:1). The catalyst was filtered off and the solvent replaced with diethyl ether. After 20 washes with 0.5 % NaOH the amount of nitro compounds **306** present was greatly reduced (≈ 1 %) but ≈ 5 % of compound **305** had been formed. The mixture was hydrogenated (H_2/5 % Pd on $BaSO_4$) to give after workup (filtering, solvent removal) ester **307** in > 97 purity as a colourless liquid. ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.25 (t, 7.14, 3 H), 1.7 - 1.9 (m, 4 H), 2.1 - 2.5 (m, 7 H), 4.13 (q, 7.14, 2 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 14.70 (CH_3), 29.74 (CH_2), 31.06 (CH_2), 33.15 (CH_2), 37.14 (CH), 38.96 (CH_2), 45.34 (CH_2), 60.95 (CH_2), 173.21 (C=O), 218.92 (C=O); ms (CI): 185 ($M^+ + 1$, 63), 167 (61), 139 (100), 96 (32), 83 (28)

4.8.6 Preparation of Bicyclo[3.3.0]octane-2,8-dione 301

At 0°C ester 307 (1.89 g, 10.3 mmole) dissolved in dry diethyl ether was added dropwise under nitrogen to a suspension of sodium ethoxide (2.59 g, 38.1 mmole) over 30 min; a thick, creamy precipitate was formed. After four hours the reaction was quenched with sat. KH_2PO_4 solution, extracted with dichloromethane and the combined organic layers washed with sat. $(NH_4)_2SO_4$ solution and dried ($MgSO_4$). Solvent removal gave an orange solid (1.42 g) which was recrystallized from diethyl ether to give white crystals (1.17 g, 82 %, mp. 56.5-57.5°C, lit. 63-64°C[129b]). ^{1}H-Nmr (200 MHz, $CDCl_3$): 1.8 (m, 2 H), 2.1 - 2.4 (m, 6 H), 3.01 (d, ≈ 10, 1 H), 3.1 - 3.3 (m, 1 H); ^{1}H-nmr (200 MHz, C_6D_6): 1.1 (m, 2 H), 1.43 (m, 2 H), 1.6 - 2.0 (m, 4 H), 2.33 (m, 1 H), 2.59 (d, 8.24, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 26.01 (CH_2), 37.72 (CH_2), 39.25 (CH), 63.17 (CH), 208.98 (C=O); ^{13}C-nmr (75 MHz, C_6D_6): 25.77 (CH_2), 37.51 (CH_2), 39.19 (CH), 62.87 (CH), 207.72 (C=O); ms (EI): 138 (M^+, 100), 109 (44), 55 (75); uv (MeOH): 219.4 (951), 249.4 (127), 261.6 (138), 304.2 (167); uv (C_6H_6):284.4 (105), 295.0 (125), 304.6 (147), 316.0 (140), 328.0 (83)

4.8.7 Preparation of 3-Methylbicyclo[3.3.0]octane-2,8-dione 311

A LDA solution, prepared in dry THF under nitrogen at 0°C from 1.18 g diisopropylamine (11.6 mmole) and 5.8 ml of a 2.04 M solution of *n*-butyllithium in hexane (11.8 mmole), was stirred for an hour and then cooled to -78°C. A dry THF solution of diketone 301 (399.6 mg, 2.9 mmole) was added dropwise over five min followed by addition of HMPA (≈ 2 ml). After one hour stirring in the cold methyl iodide (400 mg, 2.8 mmole) was added and the reaction allowed to warm up to room temperature over an hour. The reaction was quenched with 3 ml water, diluted with dichloromethane and washed with four 25 ml portions of 10 % KH_2PO_4 solution. The aqueous washes were back-extracted with dichloromethane and the combined organic

extracts washed with sat. NaCl solution and dried ($MgSO_4$). Gc/ms analysis showed, apart from HMPA, a new product **311** with longer retention time than diketone **301** with a mass of 152 in a ratio **313**:**304** of ≈5:3. The mixture was column chromatographed (210 g silica gel, diethyl ether/cyclohexane 2:1) to give methyl diketone **311** as a yellow liquid (139.1 mg) in > 98 % purity (as determined by gc) as one stereoisomer. ^{1}H-Nmr (200 MHz, C_6D_6): 0.85 (d, 6.94, 3 H), 0.9 - 1.1 (m, 2 H), 1.3 - 1.5 (m, 2 H), 1.6 - 2.0 (m, 3 H), 2.16 (m, 1 H), 2.56 (d, 8.69, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): 14.41 (CH_3), 26.68 (CH_2), 34.51 (CH_2), 36.39 (CH), 39.31 (CH_2), 41.41 (CH), 62.46 (CH), 207.92 (C=O), 209.29 (C=O); ms (EI): 152 (M^+, 100), 109 (52), 82 (60), 68 (58)

4.8.8 Preparation of 3-Cyanobicyclo[3.3.0]octane-2,8-dione 315

a) *via* the TMS enolether of diketone **301** (attempt)

To a benzene solution of diketone **301** (101.6 mg, 0.74 mmole) was added under nitrogen triethylamine (91 mg, 0.9 mmole). After 10 min stirring a benzene solution of freshly distilled TMSCl (87 mg, 0.8 mmole) was added and the cloudy mixture was stirred for 15 min, then filtered and the solvent removed to give a colourless liquid (138.5 mg). Gc/ms analysis showed incomplete formation of one new product (**319**) with very similar retention time to diketone **301**, nmr showed additional formation of bis(trimethylsilyl)ether in a nmr-ratio **319**:**301**:bis(TMS)ether of ≈54:39:7. Compound **319** was identified as 2-trimethylsiloxybicyclo[3.3.0]oct-1-en-8-one. ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.18 (s, 9 H), 1.3 - 1.8 (m, 2 H), 2.0 - 2.4 (m, 5 H), 2.70 (dddd, 17.05, 11.28, 7.44, 2.67, 1 H), 3.0 - 3.3 (m, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 0.40 (3 CH_3), 31.04 (CH_2), 31.39 (CH_2), 40.19 (CH_2), 44.36 (CH_2), 46.27 (CH), 119.05 (C), 158.80 (C), 208.83 (C=O); ms (EI): 210 (M^+, 38), 195 (100), 73

(81); bis(TMS)ether: ^{1}H-nmr (200 MHz, $CDCl_3$): -0.04 (s, 18 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 1.74 (6 CH_3)

Tests showed instability of enol ether **319** towards moisture (decomposition to diketone **301**) so separation was not possible. Higher yields than described above could not be achieved in other trials.

Under nitrogen a hexamethyldisilazane solution (≈ 4 ml, ≈ 3.1 mg, ≈ 20 mmole) of diketone **301** (103.5 mg, 0.75 mmole) and imidazole (3.6 mg, 50 μmole) was heated to reflux. After two hours the reaction was cooled to room temperature and the solvent taken off to give an orange liquid which contained (by nmr) enol ether **319** and diketone **301** in a ≈ 46:54 ratio. No separation was attempted and no higher yield was obtained in other runs.

b) *via* the TBDMS enolether of diketone **301** (attempt)

To a benzene solution of diketone **301** (498.4 mg, 3.6 mmole) was added under nitrogen a benzene solution of TBDMSCl (622.5 mg, 4.1 mmole) and triethylamine (1.16 g, 11.5 mmole). The mixture was stirred at room temperature and the progress monitored by gc. After 41 hours ≈ 95 % conversion of diketone **301** to one product was observed and the reaction worked up by filtering off the amine hydrochloride and removing the solvent to give a dark liquid (898.0 mg). Gc/ms analysis showed that the desired product had been formed. The crude mixture was flash chromatographed on silica gel (diethyl ether/hexanes 1:1) to give a light yellow liquid (668.4 mg, 73 %) which solidified upon cooling (mp. ≈ 20°C) and was identified as 2-(dimethyl-*t*-butylsiloxy)bicyclo[3.3.0]oct-1-en-8-one **321**. ^{1}H-Nmr (200 MHz, C_6D_6): 0.23 (s, 3 H), 0.39 (s, 3 H), 0.95 (s, 9 H), 1.0 - 1.3 (m, 2 H), 1.6 - 1.8 (m, 2 H), 2.0 - 2.3 (m, 3 H), 2.49 (dddd, 16.92, 11.18, 7.44, 2.73, 1 H), 2.85 - 3.05 (m, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): -5.35 (CH_3), -3.84 (CH_3), 18.51 (C), 25.69 (3 CH_3), 31.32 (CH_2),

31.46 (CH_2), 40.50 (CH_2), 44.49 (CH_2), 46.86 (CH), 119.50 (C), 157.96 (C), 196.89 (C=O); ms (CI): 253 ($M^+ + 1$, 59), 237 (6), 195 (100)

In an earlier experiment (utilizing the same conditions as described above) ≈30 % of 2-(dimethyl-*t*-butylsiloxy)bicyclo[3.3.0]oct-2-en-8-one **322** could be detected by nmr and gc. It could not be separated from **321**. ^{1}H-Nmr (200 MHz, $CDCl_3$): 0.10 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H), 2.59 (dddd, 15.60, 7.97, 2.25, 2.25, 1 H), 1.3 - 1.7 (m, 2 H), 2.0 - 2.5 (m, 4 H), 2.95 - 3.05 (m, 1 H), 4.62 (dd, 4.68, 2.32, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): -4.99 (CH_3), -4.80 (CH_3), 18.11 (C), 25.58 (3 CH_3), 37.19 (CH), 58.51 (CH), 103.34 (CH), 150.34 (C), 215.59 (C=O), the rest of the signals could not be assigned; ms (CI): 253 ($M^+ + 1$, 80), 237 (27), 195 (100), 167 (64)

At 0°C under nitrogen a LDA solution in dry THF was prepared from 47 mg diisopropylamine (0.46 mmole) and 230 µl of a 2.04 M solution of *n*-butyllithium in hexane (0.47 mmole). It was stirred for 10 min, then cooled to -78°C and a dry THF solution of enol ether **321** (101.2 mg, 0.40 mmole) was added. After stirring for five min the mixture was transferred *via* syringe to a -78°C cold suspension of *p*-TsCN (145.3 mg, 0.80 mmole) in dry THF immediately followed by addition of aq. ammonia (≈1 ml). The reaction was allowed to warm to room temperature, quenched with water/10 % KH_2PO_4 and extracted with dichloromethane. Gc/ms indicated no formation of desired product but a large number of peaks some of which could be identified by comparison with known data.[134] *p*-$TsNH_2$: ms (EI): 171 (M^+, 37), 155 (28), 107 (30), 91 (100), 65 (45); *p*-toluenedisulfide: ms (EI): 246 (M^+, 72), 123 (100); *p*-tolyl *p*-toluenethiosulfonate: ms (EI): 278 (M^+, 43), 155 (24), 139 (100), 123 (45), 91 (80), 65 (36)

In one run of this synthesis small amounts of product having the right mass for the cyano silyl enol ether and cyano diketone **315** were identified by gc/ms (*vide infra*) but no separation was attempted.

c) *via* the dianion of diketone **301** with *p*-TsCN (attempt)

At room temperature a LDA solution in dry THF was prepared from 75.8 mg diisopropylamine (0.75 mmole) and 350 µl of a 2.04 M solution of *n*-butyllithium in hexane (0.71 mmole). It was stirred for 25 min and then cooled to -78°C followed by addition of a dry THF solution of diketone **301** (50.2 mg, 0.36 mmole). After stirring for one hour in the cold the mixture was transferred *via* syringe to a -78°C cold dry THF solution of *p*-TsCN (136.6 mg, 0.75 mmole) immediately followed by addition of aq. sat. KH_2PO_4 solution (≈ 1.5 ml). A precipitate occurred and the reaction was warmed to room temperature. The mixture was extracted with dichloromethane and the combined organic extracts dried with $MgSO_4$. Removal of the solvent gave an orange liquid (243.9 mg). Gc/ms analysis showed ≈ 8 % of a product having the correct mass for cyano diketone **315** (*vide infra*) but an isolation attempt (column chromatography) failed.

d) *via* the dianion of diketone **301** with benzylthiocyanate (BTC)

At room temperature a LDA solution in dry THF was prepared from 375.4 mg diisopropylamine (3.7 mmole) and 2.3 ml of a 1.63 M solution of *n*-butyllithium in hexane (3.7 mmole). After 15 min the solution was cooled to -78°C and a dry THF solution of diketone **301** (252.0 mg, 1.83 mmole) was added. After one hour the mixture was transferred *via* syringe to a -78°C cold solution of BTC (539.1 mg, 3.6 mmole) and sat. aq. KH_2PO_4 solution (≈ 2 ml) was added. After warming to room temperature it was worked up (extraction with dichloromethane, drying with $MgSO_4$ and solvent removal) to give a yellow liquid (1063.4 mg) containing BTC, diketone

301, cyano diketone **315** and benzyldisulfide in a ≈ 7:1.5:1:5 ratio. Further evacuation reduced the mass of products to 804.4 mg in a ≈5:1.1:1:3.5 ratio. The product mixture was heated in oilpump vacuum to give a dark yellow liquid (452.5 mg) containing the four compounds in a ≈0.7:0.7:1:4 ratio. This mixture was separated by flash chromatography on silica gel (diethyl ether/hexanes 1:1) to give two fractions; fraction I (50.3 mg, yellow liquid, less polar) and fraction II (42.5 mg, yellow liquid, more polar). Fraction I proved to be a mixture of diketone **301** and cyano diketone **315** in a ≈1:1 ratio, fraction II was cyano diketone **315** in ≈90 % purity (one peak in gc, by ^{1}H-nmr a mixture of two stereoisomers). Fraction I was separated by preparative tlc (2 elutions with diethyl ether/hexanes 9:1) to give cyano diketone **315** (5.0 mg) in ≈97 % purity. BTC: ms (EI): 149 (M^+, 5), 121 (3), 91 (100); benzyldisulfide: ms (EI): 246 (M^+, 7), 182 (7), 123 (3), 91 (100); cyano diketone **315**: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.5 - 2.9 (m, 5 H), 3.0 - 3.7 (m, 2 H); ^{13}C-nmr (75 MHz, $CDCl_3$): 24.61 (CH_2), 26.05 (CH_2), 30.94 (CH_2), 31.35 (CH_2), 35.38 (CH_2), 37.19 (CH), 37.43 (CH), 38.10 (CH), 38.87 (CH_2), 40.61 (CH), 61.14 (CH), 61.57 (CH), 115.74 (C≡N), 115.97 (C≡N), 197.05 (C=O), 197.56 (C=O), 206.52 (C=O), 206.72 (C=O); ms (EI): 163 (M^+, 100), 109 (63), 79 (46), 68 (92)

4.9 Photolysis of Bicyclo[3.3.0]octane-2,6-dione 261 and its Derivatives

4.9.1 Photolysis of 261

a) in benzene at λ > 300 nm

A solution of diketone **261** (20 mg, 0.14 mmole) in ≈1 ml benzene was irradiated in a Pyrex nmr-tube at room temperature with a medium pressure Hg-lamp with tetradecane as standard. After 12 hours ≈69 % conversion to one product (slightly longer retention time) was observed which had the same mass (138) by gc/ms as dione **261**.

b) in benzene at λ = 254 nm

A solution of diketone **261** (20 mg, 0.14 mmole) in ≈1 ml benzene was irradiated in a quartz nmr-tube at room temperature in the Rayonet reactor at 254 nm with tetradecane as standard. The same result as in the experiment described above was obtained, no additional product was detected.

c) in benzene/methanol at $\lambda > 300$ nm

A solution of dione **261** (291.2 mg, 2.1 mmole) in 10 ml benzene/methanol 9:1 was irradiated with a medium pressure Hg-lamp at room temperature. After 159 hours ≈60 % conversion of dione **261** to two products (ratio ≈ 11:1) was observed. The first was identical to the product from irradiation of dione **261** in the absence of methanol, the second had a longer retention time and a mass by gc/ms of 170. The solvents were removed to give a colourless liquid (376.6 mg) which was column chromatographed (150 g silica gel, diethyl ether/hexanes 1:1) to give three fractions I - III (in order of increasing polarity) with fraction II containing starting material.

Fraction I (19.3 mg) was identified as 2-(2-methoxycarbonylethyl)-cyclopentanone **269**: ^{1}H-nmr (200 MHz, $CDCl_3$): 1.3 - 2.4 (m, 10 H), 3.2 - 3.5 (m, 1 H), 3.63 (s, 3 H); ms (EI): 170 (M^+, 15), 139 (38), 138 (92), 110 (100), 67 (71), 55 (95)

Fraction III (77.6 mg) was identified as 2-(3-propanalyl)cyclopent-2-enone **264**: ^{1}H-nmr (200 MHz, $CDCl_3$): 2.25 - 2.32 (m, 2 H), 2.35 - 2.52 (m, 4 H), 2.52 - 2.62 (m, 2 H), 7.27 (ddt, 2.62, 1.31. 1.31, 1 H), 9.66 (t, 1.32, 1 H); ^{13}C-nmr (50 MHz, $CDCl_3$): 17.89 (CH_2), 26.70 (CH_2), 34.70 (CH_2), 41.77 (CH_2), 144.78 (C), 159.36 (CH), 202.08 (CH=O), 210.20 (C=O); ms (EI): 138 (M^+, 23), 110 (100), 109 (36), 67 (78)

d) in benzene/ethanol at $\lambda > 300$ nm at higher temperature

A solution of diketone **261** (37.6 mg, 0.27 mmole) in ≈ 2 ml benzene/ethanol 1:1 was irradiated in a sealed Pyrex nmr-tube at 67-70°C with dodecane as standard. After 10 hours ≈ 40 % conversion of dione **261** to two products in a ratio of ≈ 7:1 was observed. The first was identified as aldehyde **264**, the second had a longer retention time than ester **269** and was tentatively assigned to be 2-(2-ethoxycarbonylethyl)cyclopentanone: ms (EI): 184 (M^+, 12), 139 (70), 138 (100), 110 (38), 55 (99)

4.9.2 Photolysis of 3-Methylbicyclo[3.3.0]octane-2,6-dione 270

A solution of methyl diketone **270** (30 mg, two stereoisomers in a 1.19:1 ratio [in order of increasing retention time], 0.2 mmole) in ≈ 2 ml benzene-d_6/methanol-d_4 9:1 was irradiated at room temperature with a medium pressure Hg-lamp. After six hours the only observed result was the ratio change to 0.97:1, after 10 hours a new product at slightly shorter retention time than dione **270** was observed, after 35 hours the ratio of the new product to the isomers of dione **270** was 0.33:0.55:1. Gc/ms showed a mass of 152 for the product (M^+, 100), the ^{1}H-nmr spectrum (200 MHz, C_6D_6) of the mixture exhibited signals at 9.27 (m) and 6.70 - 6.85 ppm (m). The ^{13}C-nmr spectrum (50 MHz, C_6D_6) had peaks at 99, 157 and 161 ppm; due to the small amount and time constraint no further investigations were carried out since no decarbonylation products were detected.

4.9.3. Photolysis of 3-Ethoxybicyclo[3.3.0]octane-2,6-dione 281

A solution of ethoxy diketone **281** (9.2 mg, mixture of stereoisomers in a ≈ 1:2.5 ratio, 50 μmole) in ≈ 1 ml benzene-d_6 was irradiated in a Pyrex nmr-tube at room temperature with a medium pressure Hg-lamp. After seven hours (≈ 60 %

conversion of dione **281**) the gc ratio had changed to ≈ 1:0.9 and formation of a product (≈ 24 %) at shorter retention time than dione **281** was observed.

Comparison with an inert standard showed that mainly the isomer of dione **281** present in larger amounts at the start reacted whereas the minor isomer decreased only slowly; after seven hours 26 % of the minor isomer had disappeared but 75 % of the major isomer had reacted. Gc/ms and co-injecti ⁻ with an authentic sample confirmed that the product was diketone **261**; a small amount of its photolysis product aldehyde **264** (≈ 6 %) was also observed by gc. No other products were detected until a low temperature gc (35°C isothermal) allowed the identification (by co-injection with an authentic sample) of acetaldehyde (≈ 4 %) having a shorter retention time than the solvent.

A ^{1}H-nmr spectrum (200 MHz, C_6D_6) of the mixture showed the following characteristic product peaks: 1.36 (d, 2.85, methyl group of acetaldehyde), 6.48 (m, olefinic proton of aldehyde **264**), 9.13 (q, 2.85, aldehyde proton of acetaldehyde), 9.23 (t, 1.33, aldehyde proton of compound **264**)

4.9.4 Photolysis of 3-*t*-Butoxybicyclo[3.3.0]octane-2,6-dione 295

A solution of dione **295** (28 mg, 0.13 mmole, 1.13:1 ratio of stereoisomers) was irradiated in 1 ml benzene-d_6 in a Pyrex nmr-tube at room temperature with a medium pressure Hg-lamp. After nine hours the only apparent result was ratio change to 1.98:1, the temperature was raised to 70°C and after 15 hours (ratio 1.9:1) the mixture was analyzed by ^{1}H-nmr. New peaks were observed and confirmed that products had been formed with retention times identical to those of the isomers of dione **295**. Four methyl singlets (of *t*-butyl groups) were recorded at 0.97, 1.02, 1.06 and 1.07 ppm with a relative ratio of ≈ 2.5:4:11:1, the centre two were identified by comparison with known data as the methyl groups of the stereoisomers of dione **295**.

Therefore during irradiation the ratio of these isomers changed to ≈ 1:3 and ≈ 20 % conversion to two products had occurred.

Since the products did not separate by gc no gc/ms analysis could be performed. They were identified by ^{1}H-nmr spectroscopy of the irradiation mixture as geometrical isomers of 2-(2-*t*-butoxyethenyl)cyclopentanone-3-aldehyde **297**. Major isomer (*cis*-**297**): ^{1}H-nmr (200 MHz, C_6D_6): 0.97 (s, 9 H), 4.59 (dd, 7.21, 6.28, 1 H), 6.02 (dd, 6.28, 1.55, 1 H), 9.48 (d, 1.67, 1 H), other resonances not attributable; minor isomer (*trans*-**297**): ^{1}H-nmr (200 MHz, C_6D_6): 1.07 (s, 9 H), 4.96 (dd, 12.05, 8.67, 1 H), 6.34 (dd, 12.05, 1.14, 1 H), 9.32 (d, 2.18, 1 H)

4.9.5 Photolysis of 3-Cyanobicyclo[3.3.0]octane-2,6-dione 315

a) in benzene at λ = 254 nm

A solution of cyano diketone **315** in ≈ 1 ml benzene-d_6 (10 mg, ≈ 60 mM) was irradiated at room temperature in a quartz nmr-tube in the Rayonet reactor. After 75 min a ^{1}H-nmr spectrum (200 MHz, C_6D_6) showed the presence of triplets at 8.84 ppm (0.71 Hz) and 9.06 ppm (0.97 Hz) as well as numerous signals between 4.5 and 6 ppm. The reaction was followed by gc which showed formation of a main product [shorter retention time than dione **315**, ms (EI): 163 (M^+, 80), 135 (100), 107 (50), 106 (60), 79 (84), 67 (74), 66 (77); ≈ 40 %] as well as a peak at short retention time and other product peaks.

Injections after two, three, five and nine hours allowed the identification of cyclopentenone **115** and cycloadducts **324** and **325** (total area after nine hours ≈ 11 %) by comparison with authentic samples, no other adducts were found. The area ratio of **115**:(**324** + **325**) was 0.95:1 after two hours with an average over the whole reaction (five injections) of 0.83:1 ± 23.8 %. The area ratio of **324**:**325** was 0.22:1 after two hours with an average over the whole reaction (five injections) of

0.36:1 ± 45.4 %. Adduct **325** could be resolved after nine hours by gc/ms. ms (EI): cyclopentenone **115**: 82 (M^+, 100), 54 (43), 53 (43); adduct **325**: 135 (M^+, 66), 107 (19), 106 (33), 82 (100), 81 (42), 80 (52), 79 (77), 66 (56), 55 (91), 54 (99)

b) in benzene at $\lambda > 300$ nm

A benzene solution of dione **315** in ≈ 1 ml benzene (6.5 mg, ≈ 40 mM) was irradiated in a nmr-tube with a medium pressure Hg-lamp at room temperature. The reaction was followed by gc and after two hours formation of cyclopentenone **115** could be detected (by comparison with known gc data). After four hours peaks correlating to cycloadducts **324** and **325** were observed, continued irradiation did not allow integration of the peak of adduct **324** since diketone **261**, a decomposition product of dione **315**, obscured it due to its retention time being too close to that of adduct **324**. The area ratio **115**:(**324**+**325**) after four hours was 0.43:1 and the area ratio **324**:**325** was 0.21:1.

4.10. Photolysis of Bicyclo[3.3.0]octane-2,8-dione 301 and its Derivatives

4.10.1 Photolysis of 301

a) in benzene at $\lambda > 300$ nm

A solution of dione **301** (30.0 mg, 0.2 mmole) in 1 ml benzene-d_6 was irradiated in a Pyrex nmr-tube at room temperature with a medium pressure Hg-lamp and monitored by gc. After 23 hours ≈ 80 % conversion of dione **301** to two products (ratio ≈ 15:1, the major product had a retention time slightly shorter, the minor product longer than that of dione **301**) was observed. Gc/ms analysis showed masses of 138 (major product) and 156 (minor product). Nmr analysis allowed the identification of the major product as 3-(3-propanalyl)cyclopent-2-enone **307**: ^{1}H-nmr (200 MHz, C_6D_6): 1.7 - 1.8 (m, 4 H), 1.9 - 2.0 (m, 4 H), 5.63 (m, 1 H), 9.15 (t, 0.93, 1 H); ^{13}C-nmr (50 MHz, C_6D_6): 25.26 (CH_2), 31.23 (CH_2), 35.18 (CH_2), 40.62 (CH_2), 129.49 (CH),

178.93 (C), 198.89 (CH=O), 207.65 (C=O); ms (EI): 138 (M^+, 24), 110 (100), 81 (54), 68 (44), 67 (46), 53 (50); minor product (tentatively assigned to be 3-(ethyl-2-carboxylic acid)cyclopentanone **310**: ms (EI): 156 (M^+, 6), 138 (11), 110 (14), 96 (50), 83 (100), 55 (69)

b) in benzene/methanol at $\lambda > 300$ nm

A solution of dione **301** (17.6 mg, 0.13 mmole) in 1 ml benzene/methanol (9:1 v/v) was irradiated in a Pyrex nmr-tube at room temperature with a medium pressure Hg-lamp, followed by gc. After 89 hours about 20 % conversion to one product (by gc) was observed. Gc/ms analysis revealed the presence of two products with almost identical retention times, the first (and major) one being aldehyde **307**, the second one with a mass of 170; no acid **310** was detected. The new minor product was tentatively assigned to be 3-(2-methoxycarbonylethyl)cyclopentanone **309**: ms (CI): 171 ($M^+ + 1$, 71), 142 (27), 139 (40), 129 (100), 97 (66), 74 (51), 69 (99)

4.10.2 Photolysis of 3-Methylbicyclo[3.3.0]octane-2,8-dione 311

A solution of dione **311** (139.1 mg, 0.9 mmole) in 1 ml benzene-d_6 was irradiated at room temperature in a Pyrex nmr-tube with a medium pressure Hg-lamp. The reaction was monitored by gc and after 18 hours ≈ 30 % conversion of dione **311** to essentially two products (ratio ≈ 9:1, the major had a slightly shorter retention time than that of dione **311**, the minor even shorter. Gc/ms analysis showed that both peaks had the same mass as dione **311**, the major product also had very similar fragmentation pattern to dione **311** and was assigned to be its stereoisomer. Ms (EI): 152 (M^+, 9), 124 (100), 109 (42), 95 (38), 81 (61), 67 (51), 53 (38); starting isomer of dione **311**: ms (EI): 152 (M^+, 7), 124 (100), 109 (47), 95 (45), 81 (85), 67 (78), 53 63); the minor product was tentatively assigned to be a compound derived from

α-cleavage of dione **311** and hydrogen abstraction: ms (EI): 152 (M^+, 58), 137 (75), 134 (83), 123 (99), 109 (94), 95 (100), 92 (74), 81 (79), 67 (74), 55 (77)

4.10.3 Photolysis of 3-Cyanobicyclo[3.3.0]octane-2,8-dione 315

a) in benzene at λ = 254 nm

A solution of cyano diketone **315** in 1 ml benzene (≈ 1.6 mg, ≈ 10 mM) was irradiated at room temperature in a quartz nmr-tube in the Rayonet reactor. After 36 min (≈ 15 % conversion of dione **315**) product peaks for cyclopentenone **115** and cycloadducts **323** and **326** were identified by comparison with known gc data and by gc/ms. No indication for formation of adducts **324** or **325** was found. Ms (EI): cyclopentenone **115** (≈ 1.8 % of the irradiation mixture): 82 (M^+, 100), 54 (54), 53 (48); adduct **323** (≈ 0.4 % of the irradiation mixture): 135 (M^+, 50), 107 (23), 106 (29), 82 (28), 81 (34), 80 (39), 79 (45), 66 (35), 55 (100), 54 (60); adduct **326** (≈ 0.2 % of the irradiation mixture): 135 (M^+, 27), 107 (10), 106 (11), 82 (15), 81 (20), 80 (16), 79 (21), 66 (17), 55 (100), 54 (28)

The reaction was followed by gc and the area ratio **115**:(**323**+**326**) was calculated after 48, 60 and 84 min by five injections each to be 2.96:1 ± 7.7 %, 2.80:1 ± 6.3 % and 2.74:1 ± 10.4 %, respectively. The area ratio **323**:**326** was calculated for the same time data points to be 2.06:1 ± 14.2 %, 2.00:1 ± 7.3 % and 2.02:1 ± 7.5 %, respectively. The area ratios **115**:(**323**+**326**) and **323**:**326** (in parenthesis) at 36 min, two, three, five and eight hours were determined by single injections. The values obtained were 2.98:1 (2.09:1), 2.53:1 (1.88:1), 2.56:1 (1.78:1), 2.61:1 (1.67:1) and 2.56:1 (2.56:1), respectively.

b) in benzene at λ > 300 nm

A solution of dione **315** in ≈ 1 ml benzene-d_6 (≈ 5 mg, ≈ 30 mM) was irradiated in a nmr-tube at room temperature with a medium pressure Hg-lamp. The progress of

the reaction was monitored by gc. After two hours (≈ 50 % conversion of dione **315**) formation of two main products at shorter (mass of product: 164, ≈ 11 % of the mixture) and slightly longer (mass of product: 182, ≈ 28 % of the mixture) retention times than dione **315** was observed. These products were not identified.

Peaks correlating to cyclopentenone **115** (mass of 82, ≈ 4.6 % of the mixture) and cycloadducts **323** and **326** (masses of 135, ≈ 1.2 and ≈ 0.6 % of the mixture) were identified by gc/ms which gave similar results to the findings described above.

The area ratios were calculated from the average of two gc injections to be 2.47:1 ± 10.3 % for **115**:(**323** + **326**) and 2.22:1 ± 2.9 % for **323**:**326**. No indication for formation of the regioisomeric adducts **324** and **325** was found.

4.11 Calibration of the Gas Chromatograph for Cyclopentenone 115 and the Cycloadducts of the Photoreaction between 115 and Acrylonitrile 137

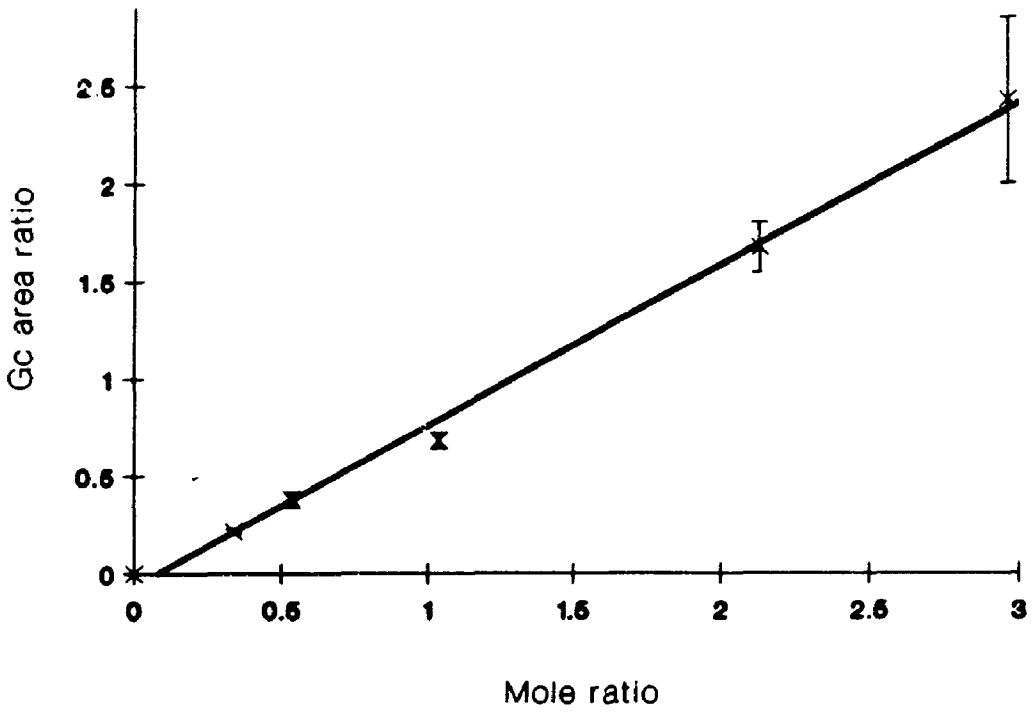
Five solutions (I - V) were prepared in ≈ 5 ml benzene from **115** and fraction II of the cycloaddition experiment between **115** and **137** (Section **4.5.3a**, containing adducts **323** and **324** in a ≈ 7:3 ratio). Samples of these solutions were injected five times each on the gas chromatograph to obtain an average value for the gc area ratio **115**:Σadducts as outlined in TABLE 35.

TABLE 35: Calibration of the gas chromatograph

Solution	**115**	Adducts	Mole ratio	Gc area ratio
I	15.5 mg	75.7 mg	0.337 ± 3.8 %	0.216 ± 6.0 %
II	48.4 mg	146.8 mg	0.535 ± 0.8 %	0.382 ± 9.5 %
III	39.1 mg	62.0 mg	1.038 ± 0.7 %	0.684 ± 5.7 %
IV	74.8 mg	57.7 mg	2.134 ± 0.2 %	1 675 ± 7.7 %
V	116.7 mg	64.8 mg	2.965 ± 0.1 %	2.424 ± 17.5 %

Plotting gc area ratios as a function of mole ratios including the point (0;0) led to a straight line with a slope of 0.824 ± 10 %, an intercept of -0.067 ± 15 % and a correlation coefficient γ of 0.99801, as shown in FIGURE 15.

FIGURE 15: Plot of the gc calibration data



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