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Synthesis and Photochemical reactions of 6-alkenyl-3-phenylcyclohex-2-enones.

by

Stephen Anthony Bradley

A Thesis Presented to the University of Dublin

for the award of Ph.D.

Prepared under the supervision of Dr. M. Jeffares, Chemistry Department, Dublin Institute of Technology, Kevin Street, and Prof. T. B. H. McMurry, Chemistry Department, Trinity College Dublin.

Declaration

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Abstract

The synthesis and photochemical reactions of a series of molecules containing both the 3-phenylcylohexenone moiety and an C-6 substituted alkenyl side chain (2-propenyl, 3-butenyl and 4-pentenyl) are described. The C-6 position was further substituted with a carbomethoxy group to generate a conformational control factor.

A synthetic strategy involving a three-step sequence was employed. This involved alkylation of a β-ketoester with a halogenated substituent, followed by Michael addition, with phenyl vinyl ketone prior to ring closure to the cyclohexenone. Cyclohexenone derivatives containing a pyrimidine ring were also investigated. In this case results suggested a thermodynamically controlled reaction with pka dependency in the Michael addition step.

The photocycloaddition reactions of substituted 6-alkenyl-3-phenylcyclohexenones were found to be regiochemically controlled. In the case of a 3-carbon chain and a C-6 carbomethoxy substituent, parallel photoadducts were formed. It was found that a competitive photoreaction was established between closure to the target molecule, methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate, and hydrogen abstraction affording the βγ enone, methyl 9-oxo-2-phenylbicyclo[4.3.1]non-2-ene-5-carboxylate. Photolysis of 3-phenyl-(2-propenyl)cyclohex-2-en-1-one afforded the βγ enone, 2-phenylbicyclo[4.3.1]non-2-en-9-one exclusively. This indicated that the carbomethoxy group had a stereoselective effect.

When the alkenyl group is a 4- and 5-carbon chain cross photoadducts were formed exclusively affording methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate and methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate respectively. These results suggest that biradical conformations are a factor in determining the regiochemistry of intramolecular [2+2] photochemical cycloaddition reactions.

Acknowledgements

Firstly, I would like to express my thanks to my supervisors Dr. Mark Jeffares, Prof. T. Brian. H. McMurry for the guidance, encouragement and extreme patience over the past few years and throughout the course of this study. I would also like to say that I am entirely grateful to Prof. T. Brian. H. McMurry for his financial support. I would also like to thank Dr. Mark Jeffares for his generous offers of beer money every Christmas. To this day I do not know why I refused.

I wish to thank Dr. Noel Russell and the Dublin Institute of Technology for allowing me the use of department facilities and instrumentation in order to carry out this study. I would also like to thank all of the technical staff in the school of chemistry at Dublin Institute of Technology Kevin St., for their assistance over the years. I would especially like to thank Sean McGee for his speedy NMRs.

I would like to Dr. John O'Brian Chemistry Department, Trinity College Dublin for NMR analysis and Dr. Sylvia Draper also Chemistry Department, Trinity College Dublin. for X-ray analysis. I would also like to thank Dr. Niall Geraghty, University College Galway, for his molecular modelling analysis

I would like to express my sincere thanks to Dr. John Cassidy and Dr Ellish O'Donoghue for their continuous support and encouragement to "hurry up and finish". I would also like to thank Dr. Noreen Hanley formally Dublin Institute of Technology and now at University College Limerick, for her help and written profanities and of course her singing which was "fantastic".

I am also grateful to the VEC in Dundalk for financial support, and the Dublin Institute of Technology for SRD and Seed funding grants.

Finally I wish to thank all my family and friends for their endless patience and support over the past number of years. I would like say a special mention to Julie my long time friend whom I knew before I started and is now very dear to me.

Abbreviations

$CDCl_3$	Deuterated Chloroform
2D	Two-Dimensional
DBU	1,8-diazabicylo[5.4.0]undecane
DEPT	Distortionless Enhancement by Polarisation Transfer
DMF	N,N-dimethyformamide
DMSO	Dimethysulfoxide
d_6-DMSO	Deuterated Dimethysulfoxide
DQFCOSY	Double Quantum Filter Correlated spectroscopy
^{13}C NMR	Carbon Nuclear Magnetic Resonance
$CaCl_2$	Calcium Chloride
COSY	Correlated Spectroscopy
FN	Fumaronitrile
GC	Gas Chromatography
GC-MS	Gas Chromatography Mass Spectrometry
HCL	Hydrochloric acid
HETCOR	Heteronuclear Correlation
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
^1H NMR	Proton Nuclear Molecular Resonance
IR	Infrared
KOH	Potassium Hydroxide
MeOH	Methanol
$MgSO_4$	Magnesium Sulfate
MN	Maleonitrile
m/z	Mass to charge ratio
NaH	Sodium hydride
NaI	Sodium Iodide
$NaOCH_3$	Sodium Methoxide
$NaOC_2H_5$	Sodium ethoxide
NOE	Nuclear Overhauser Effect/Enhancement
P_2O_5	Phosphorous pentoxide

Pd/C	Palladium carbon
Rf	Distance travelled with respect to solvent front
t-BuOK	Potassium *t*-butoxide
TsCl	Toluene p-sulfonyl chloride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TOCSY	Total Correlation Spectroscopy
UV	Ultraviolet Light

Table of Contents

Chapter 1

		page no.
1.0	Introduction	1
1.1	The Corey-de Mayo Reaction Mechanism	3
1.2.	The "Bauslaugh-Schuster-Weedon Biradical Mechanism for enone-alkene Photocycloaddition"	6
1.3.	Regioselectivity of [2+2] intramolecular photoaddition	11
1.4.	Stereoselectivity of [2+2] intramolecular photoaddition	18
1.5.	Intramolecular [2+2] photocycloaddition of 3-phenyl-cycloalkenones tethered with an olefinic chain	22
1.6.	Bibliography	26

Chapter 2

2.0.	Introduction		31
2.1	Results and Discussion		
	2.11.	Synthesis of 6-(substituted)-3-phenylcyclohex-2-en-1- ones	33
	2.12	Synthesis of 6-(disubstituted)-3-phenylcyclohex-2-en-1-ones	42
	2.121.	Synthesis of substituted β-ketoesters [127-130]	42
	2.122.	Synthesis of diketoesters [131-134]	46
	2.123.	Synthesis of methyl 2-oxo-4-phenyl-1-(2-propenyl)-cyclohex-3-ene-1-carboxylate [136]	50
	2.124.	Synthesis 6-phenyl-(2-propenyl)cyclohex-2-en-1-one [135]	59
	2.125.	Synthesis of methyl 2-oxo-1-(3-butenyl)-4-phenyl-cyclohex-3-ene-1-carboxylate [140] and methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138]	70
	2.13	Synthesis of compounds containing the 3-phenylcyclohex-2-en-1-one moiety and a pyrimidine ring	73

2.2 Conclusion 96
2.3 Experimental 97
2.4 Bibliography 115

Chapter 3

3.0. Introduction 117
3.1. Conformations of the cyclohexenone ring 120
3.2 Results
3.21. Photolysis of methyl 2-oxo-4-phenyl-1-(2-propenyl)-cyclohex-3-ene-1-carboxylate [136] 121
3.22. Photolysis of 6-phenyl-(2-propenyl)cyclohex-2-en-1-one [135] 140
3.23 Identification of methyl 9-oxo-2-phenylbicyclo[4.3.1]non-2-ene-5-carboxylate [191] 145
3.24 Photolysis of 3-phenyl-6-(5-uracilyl)cyclohex-2-en-1-one [147] 149
3.25 Photolysis of methyl 2-oxo-4-phenyl-1-(3-butenyl)cyclohex-3-ene-1-carboxylate [137] 150
3.26 Photolysis of methyl 2-oxo-1-(4-pentenyl)-4-phenyl-cyclohex-3-ene-1-carboxylate [138] 173

3.3. Discussion
3.31 The excited state of 3-phenylcyclohex-2-en-1-one [225] 196
3.32. Regioselectivity of the photocycloadditions of substituted 3-phenylcyclohex-2-en-1-ones tethered to a 3-carbon chain 197
3.33. Regioselectivity of the photocycloadditions of substituted 3-phenylcyclohex-2-en-1-ones tethered to a 4- and 5-carbon chain 201

3.4. Conclusion 204
3.5. Experimental 205
3.6. Bibliography 211

Appendix

4.0 Nomenclature of the photoproducts 214

4.1 X-ray: Crystal structure determination 221

4.12 Crystal data and structure refinement for methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136] 222

4.13 Crystal data and structure refinement for methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] 228

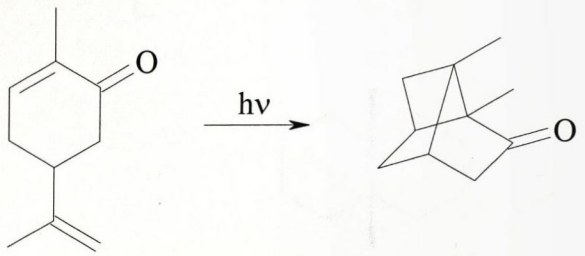
4.14 Crystal data and structure refinement for methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] 234

4.3 Bibliography 240

Chapter 1

1.0 Introduction

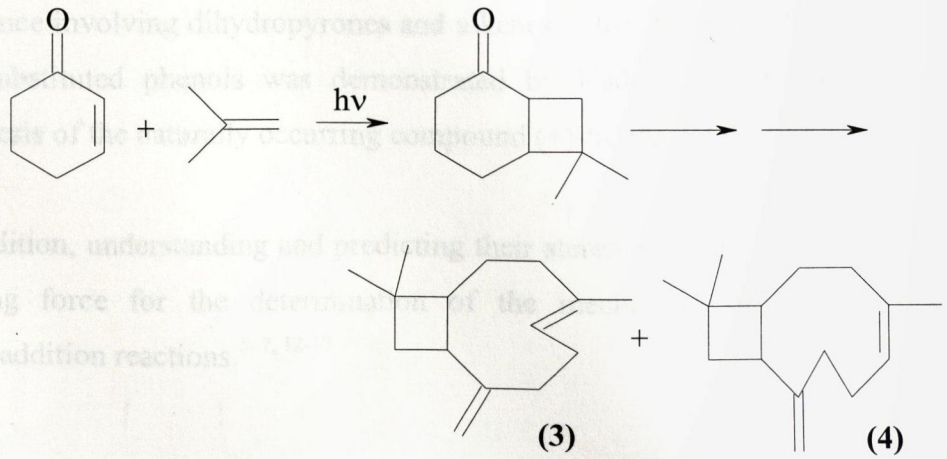
The [2+2] enone-olefin photoaddition reactions have been studied extensively from a synthetic and mechanistic point of view for some time. Despite its early discovery in 1908 when Ciamician and Silber [1] reported the intramolecular photoreaction of carvone [1] to carvone-camphor [2] (Scheme 1.1), it was not until 1957 with Buchi's reinvestigation of the isomerisation reaction that its potential for carbon-carbon bond synthesis emerged. [2]



(1) **(2)**

Scheme 1.1

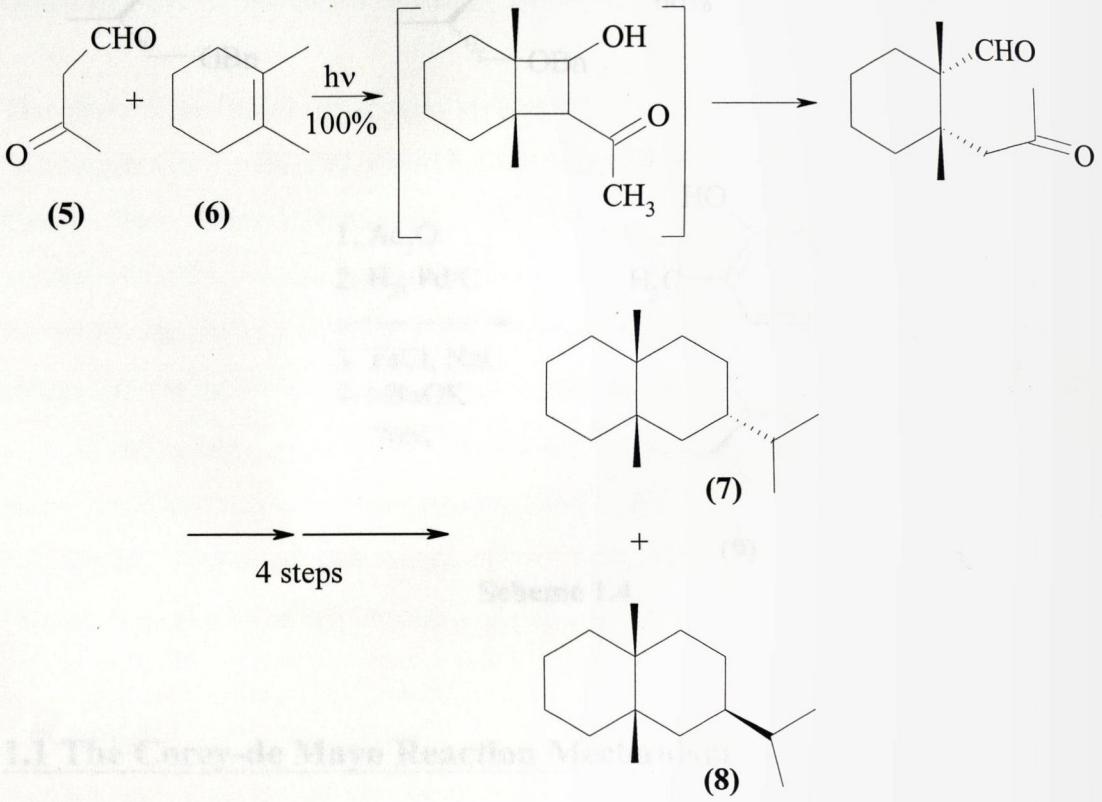
In 1964 Corey's synthesis of caryophyllene [3] and isocaryophyllene [3] [4] (Scheme 1.2) indicated its synthetic utility for natural products containing a cyclobutane ring,[4] while the inclusion of the cyclobutane ring has allowed other natural products to be synthesised by cleavage and rearrangement reactions of the photoadducts.[5-8]



(3) **(4)**

Scheme 1.2

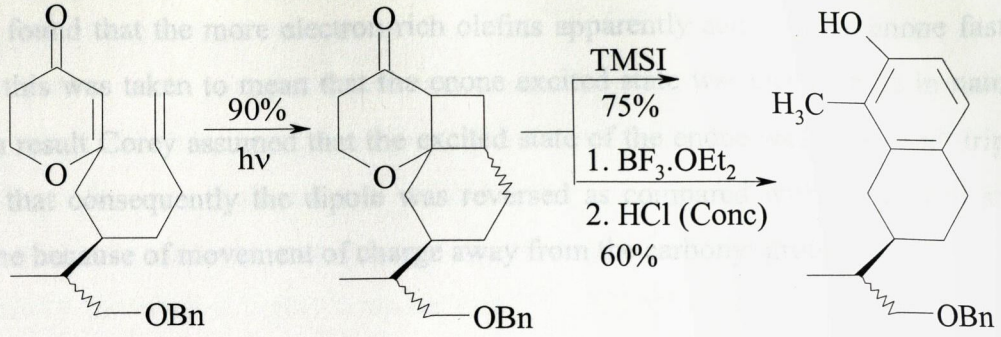
For example, the efficient synthesis of valerane [7] and isovalerane [8] involves the highly stereoselective formation of the cyclobutane-cyclohexane ring junction on the irradiation of enolised formylacetone [5] and 1,2-dimethylcyclohexene [6] (Scheme 1.3). [9]

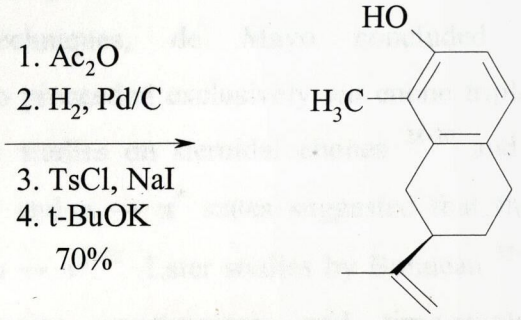


Scheme 1.3

The use of a synthetic sequence "photoaddition-fragmentation-aromatic annulation" sequence involving dihydropyrones and alkenes [10] for the regioselective synthesis of polysubstituted phenols was demonstrated by Haddad and Salman in the first synthesis of the naturally occurring compound (+)-ligudentatol [9] (Scheme 1.4).[11]

In addition, understanding and predicting their stereo and regioselectivity has been a driving force for the determination of the mechanism of [2+2] enone-olefin photoaddition reactions.[5, 7, 12-17]



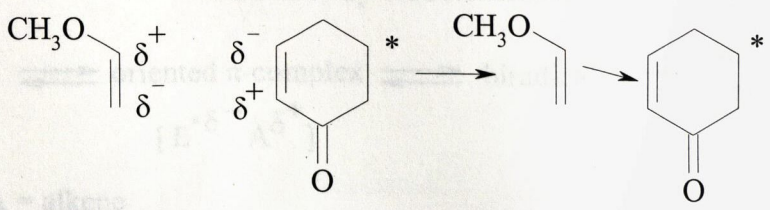


(9)

Scheme 1.4

1.1 The Corey-de Mayo Reaction Mechanism

In 1964 [18] Corey proposed that the first step in the [2+2] photocycloaddition of enones to alkenes involved the initial excitation of the ground state enone to the $n \rightarrow \pi^*$ singlet state followed by intersystem crossing to the $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ triplet state. The excited state enone interacted with the ground-state alkene to form what he called an "oriented π complex" or exciplex [10] (Scheme 1.5).



(10)

Scheme 1.5

The origin of the complex was based on "relative rate factors" experiments where it was found that the more electron-rich olefins apparently added to the enone fastest and this was taken to mean that the enone excited state was electrophilic in nature. As a result Corey assumed that the excited state of the enone was an $n \rightarrow \pi^*$ triplet and that consequently the dipole was reversed as compared with the ground state enone because of movement of charge away from the carbonyl group.

The photodimerisation of simple enones using triplet sensitisation and quenching techniques confirmed that photodimers occurred *via* the lowest enone triplet.[19-25] Using the same techniques, de Mayo concluded that enone-alkene photocycloadditions also proceeded exclusively *via* enone triplet excited states,[26,27] However, spectroscopic studies on steroidal enones [28-30] and calculations of the energy of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ states suggested that the excited state is a $\pi \rightarrow \pi^*$ rather than an $n \rightarrow \pi^*$.[31] Later studies by Bonneau [32-35] and Schuster [36-38] using transient absorption spectroscopy and time-resolved photoaccoustic calorimetry confirmed that enone-alkene photoaddition reactions occurred *via* a twisted excited $\pi \rightarrow \pi^*$ triplet state and not a polarised $n \rightarrow \pi^*$ triplet state.

The exciplex [10] was believed to be the deciding factor in determining the regiochemistry of the photoproducts and the concept was successful in explaining the regiochemistry in most cases. However the collapse of the exciplex to 1,4-biradicals followed by spin inversion and ring closure was introduced (Scheme 1.6) to explain the loss of alkene stereochemistry in the photoaddition of cyclohexenone to *cis* and *trans*-2-butenes, and in some cases the formation of disproportionation products.[18] The complete Corey mechanism is shown in Scheme 1.6.

The Corey Mechanism

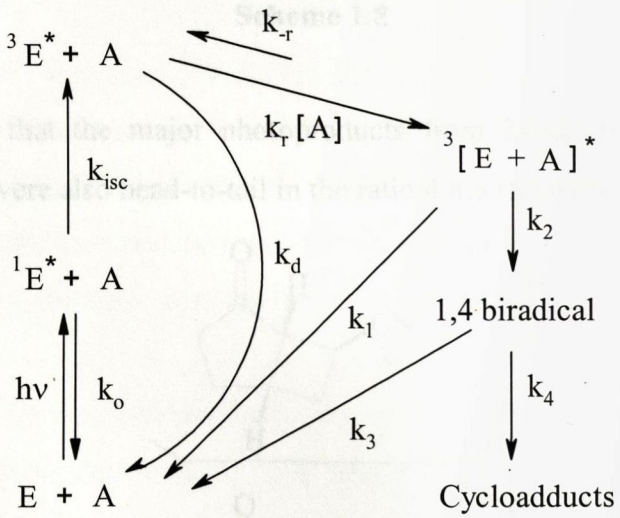
$$E^* + A \rightleftharpoons \underset{[E^{*\delta-}A^{\delta+}]}{\text{oriented } \pi\text{-complex}} \rightleftharpoons \text{biradical} \longrightarrow \text{cycloaddition product}$$

E = enone, A = alkene

Scheme 1.6

De Mayo's photocycloaddition reactions of cyclopentenone and cyclohexenone afforded quantum yields no greater than 0.50.[22,23,26,39] This implied that the reaction intermediate could partition between reversion to ground-state starting material and progress to products, an option Corey did not consider. This partition was further confirmed by increased quantum yields for the photoaddition of cyclopentenone to both cyclopentene and cyclohexane at a lower reaction temperature [27] since fission is generally favoured at higher temperatures.[40-42] In further studies on quantum yield dependency on temperature and alkene concentration, as well as quenching reactions by 2,5-dimethyl-2,4-hexadiene, Loufty and de Mayo concluded that in enone cycloaddition, a triplet exciplex formed irreversibly and collapsed to one or more biradicals.[44] In addition, the biradicals can either cyclise or revert to ground state starting materials. This reversion represents the main source of inefficiency in the cycloaddition. Corey's original hypothesis was expanded by de Mayo to include these findings (Scheme 1.7).

The Corey-de Mayo Mechanism

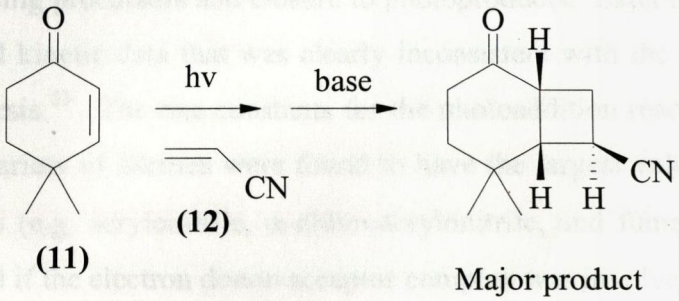


E = enone, A = alkene .

Scheme 1.7

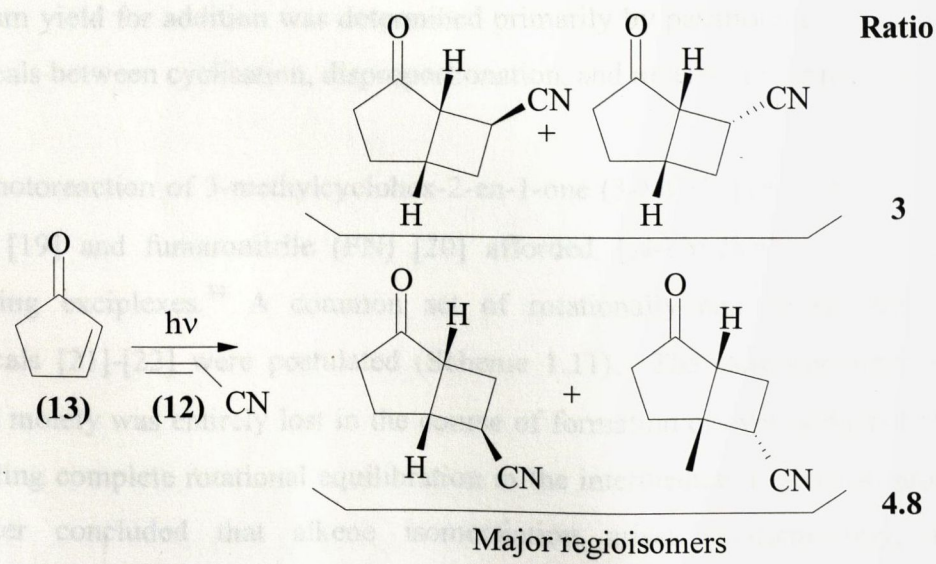
1.2 The "Bauslaugh-Schuster-Weedon Biradical Mechanism for Enone-Alkene Photocycloadditions"

Corey's exciplex hypothesis was successful in explaining why the major regioisomer in [2+2] intermolecular photocycloaddition reactions of electron-rich alkenes to enones was predominantly head-to-tail,[45,46] while the major regioiosmer in electron deficient alkenes was predominately head-to-head.[46-48] However, there are cases in the literature where Corey's exciplex hypothesis breaks down. It has been established by Rao and co-workers that the major photoproduct from the photoaddition of 4,4-dimethylcyclohexenone [11] and acrylonitrile [12] had a head-to-tail structure (Scheme 1.8).[49]



Scheme 1.8

Weeden reported that the major photoproducts from 2-cyclopentenone [13] and acrylonitrile [12] were also head-to-tail in the ratio 4.8:3 (Scheme 1.9). [50]



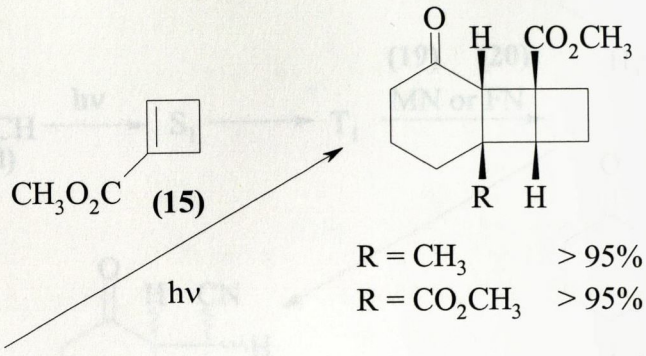
Scheme 1.9

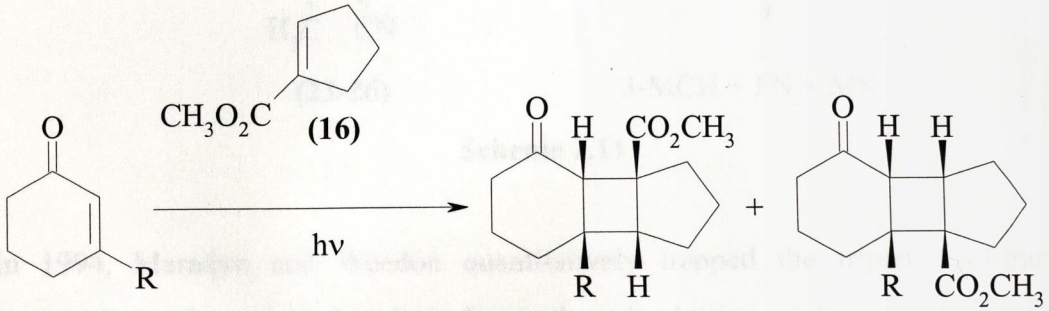
Photoaddition studies by Lange on 3-substituted cyclohexenones [14] and a series of cycloalkene esters [15-17] resulted in a progressive change in regiochemistry from head-to-head to head-to-tail as the ring size increased from cyclobutene to cyclohexene (Scheme 1.10).[51] This would suggest that the regiochemistry of the photoadducts becomes less predictable when more substituents on the alkene are present indicating a more complex reaction mechanism than one guided by electrostatic alignment.

It was Bauslaugh who first proposed by that 1,4-biradicals could be invoked to explain the regiochemistry of the photoadducts without using an exciplex.[52] He suggested that biradical stability was the deciding factor in the competition between reversion to starting precursors and closure to photoproducts. Later Schuster and co-workers reported kinetic data that was clearly inconsistent with the Corey-de Mayo exciplex hypothesis.[53] The rate constants for the photoaddition reactions of a series of enones to a variety of alkenes were found to have the largest values for electron-deficient alkenes (e.g. acrylonitrile, α-chloroacrylonitrile, and fumaronitrile). This was not expected if the electron donor-acceptor complex was involved.

The involvement of exciplexes of different polarity depending on the electron-donor properties of the alkene could not be excluded. Furthermore the efficiency of triplet capture was much higher than the quantum yield for photoaddition indicating that the quantum yield for addition was determined primarily by partitioning of one or more biradicals between cyclisation, disproportionation, and reversion to starting material.

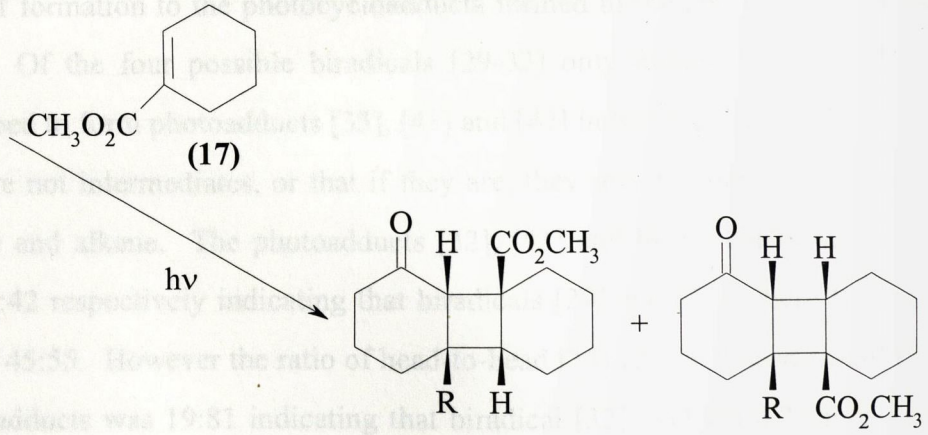
The photoreaction of 3-methylcyclohex-2-en-1-one (3-MCH) [18] with maleonitrile (MN) [19] and fumaronitrile (FN) [20] afforded 1,4-biradicals directly without involving exciplexes.[54] A common set of rotationally equilibrated triplet 1,4-biradicals [21]-[22] were postulated (Scheme 1.11). The stereochemistry on the alkene moiety was entirely lost in the course of formation of cycloadducts [23]-[26] indicating complete rotational equilibration in the intermediate triplet 1,4 biradicals. Schuster concluded that alkene isomersiation arises predominantly, if not exclusively, from reversion of 1,4-biradicals [21] and [22] to starting material.





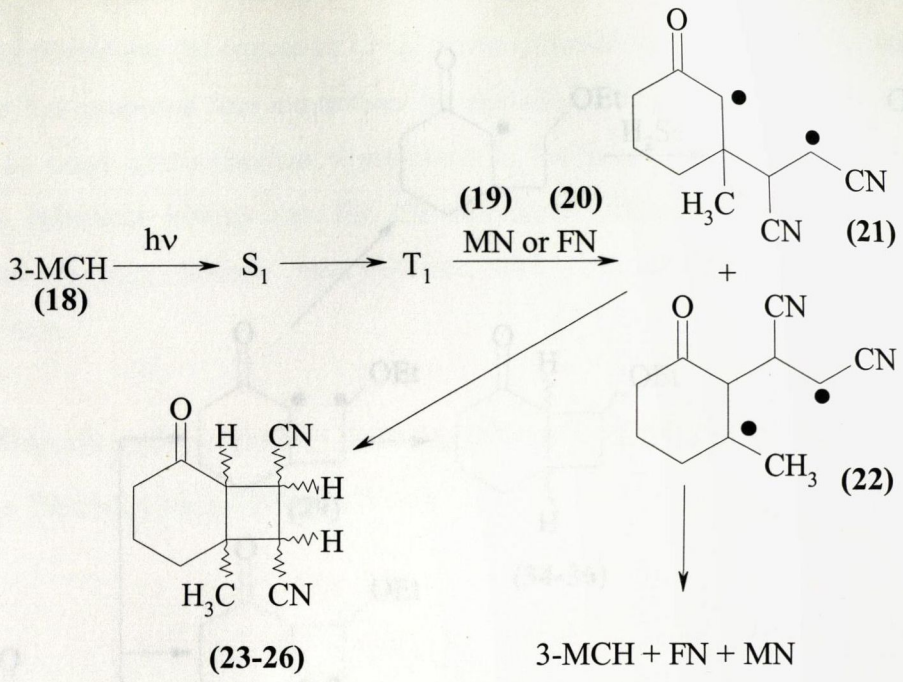
$R = CH_3$ 50% 50%
$R = CO_2CH_3$ 60% 40%

(14)



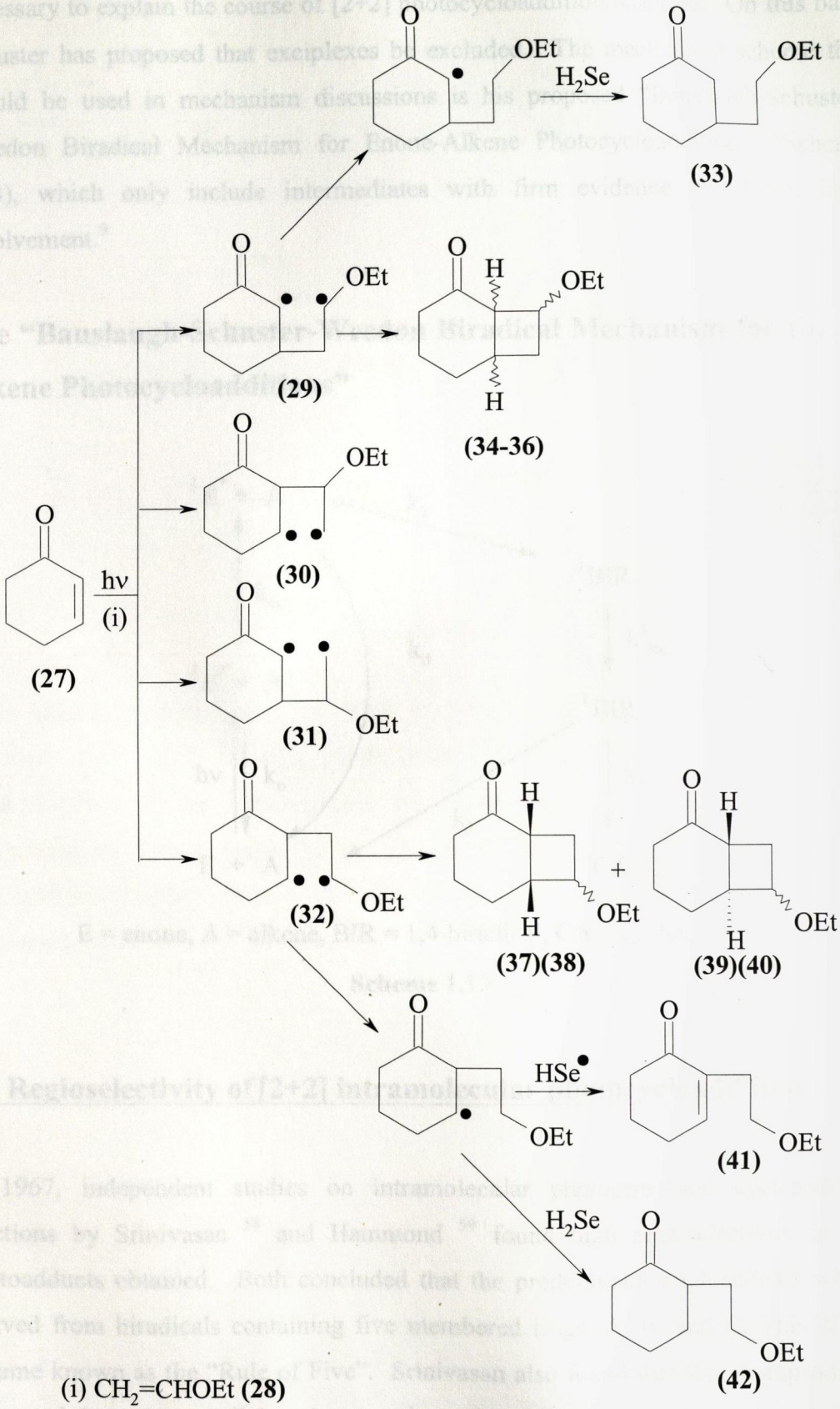
$R = CH_3$ 11% 89%
$R = CO_2CH_3$ < 5% 95%

Scheme 1.10



Scheme 1.11

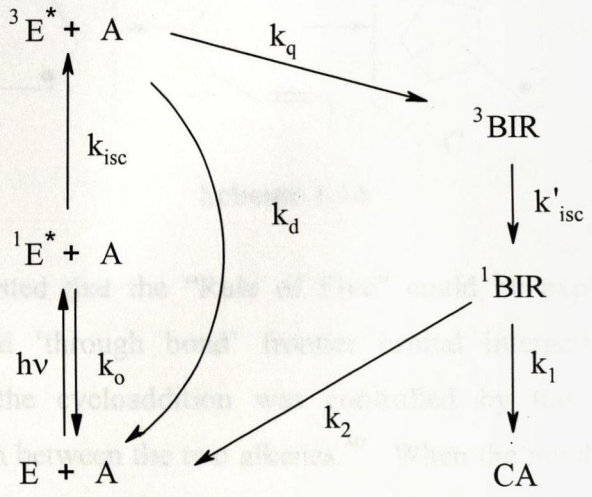
In 1994, Maradyn and Weedon quantitatively trapped the triplet 1,4-biradical intermediates formed in the photochemical cycloaddition of 2-cyclohexenone [27] with ethyl vinyl ether [28] using hydrogen selenide (Scheme 1.12) and compared their rate of formation to the photocycloadducts formed in the absence of hydrogen selenide.[55] Of the four possible biradicals [29-32] only biradicals [29] and [32] where trapped to form photoadducts [33], [41] and [42] indicating that biradicals [30] and [31] are not intermediates, or that if they are, they revert completely to ground state enone and alkene. The photoadducts [32], [41] and [42] were formed in the ratio 45:13:42 respectively indicating that biradicals [29] and [32] where formed in the ratio of 45:55. However the ratio of head-to-head [34]-[36] and head-to-tail [37]-[39] photoadducts was 19:81 indicating that biradical [32] cyclised 4.2 times faster than biradical [29] or that biradical [29] has a greater tendency to revert to starting precursors rather than proceeding to photoproducts. Weeden concluded that the regiochemistry was determined by how biradicals partition between fragmentation to give ground state starting materials and ring closure to give products. Their rate of formation was not implicated. Weedon's conclusions were in direct conflict with the evidence postulated for the existence of exciplexes. Similar results were found in photochemical studies on 2-cyclopentenone.[56,57]


O
OEt
H2Se
(33)
(29)
H
(34-36)
(30)
hν
(i)
(27)
(31)
(32)
+
(37)(38)
(39)(40)
HSe
(41)
(42)
(i) CH2=CHOEt (28)

Scheme 1.12

There is no evidence requiring exciplex precursors to biradicals, and they are not necessary to explain the course of [2+2] photocycloaddition reactions. On this basis Schuster has proposed that exciplexes be excluded. The mechanistic scheme that should be used in mechanism discussions is his proposed "Bauslaugh-Schuster-Weedon Biradical Mechanism for Enone-Alkene Photocycloadditions" (Scheme 1.13), which only include intermediates with firm evidence to support their involvement.[9]

The "Bauslaugh-Schuster-Weedon Biradical Mechanism for Enone-Alkene Photocycloadditions"

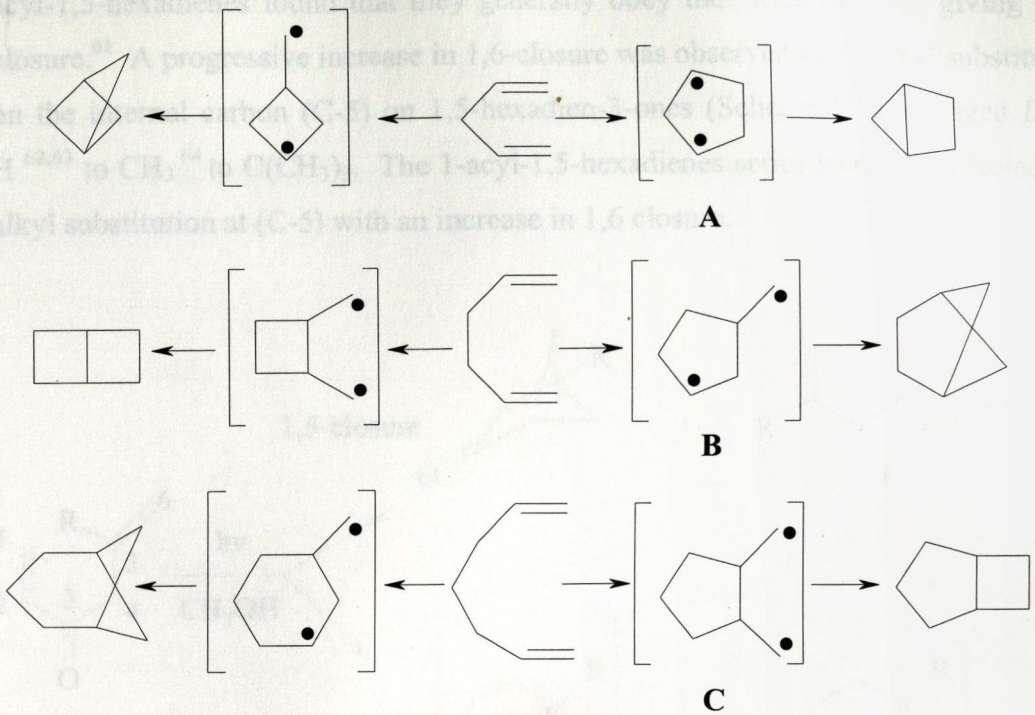


E = enone, A = alkene, BIR = 1,4-biradical, CA = cycloadducts

Scheme 1.13

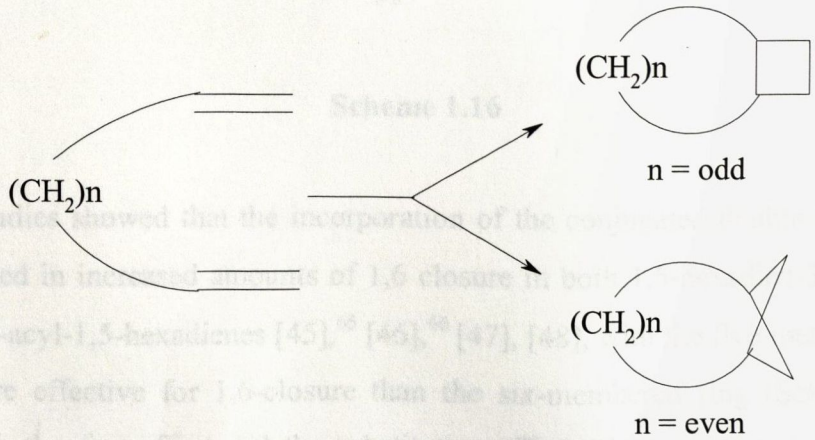
1.3 Regioselectivity of [2+2] intramolecular photocycloaddition

In 1967, independent studies on intramolecular photosensitised cycloaddition reactions by Srinivasan [58] and Hammond [59] found high regioselectivity in the photoadducts obtained. Both concluded that the predominant photoadducts where derived from biradicals containing five membered rings, A, B, and C. This effect became known as the "Rule of Five". Srinivasan also found that the photoproducts alternated between parallel and cross-photoadducts as the number of methylene groups in the diene increased from 1 to 3 (Scheme 1.14).



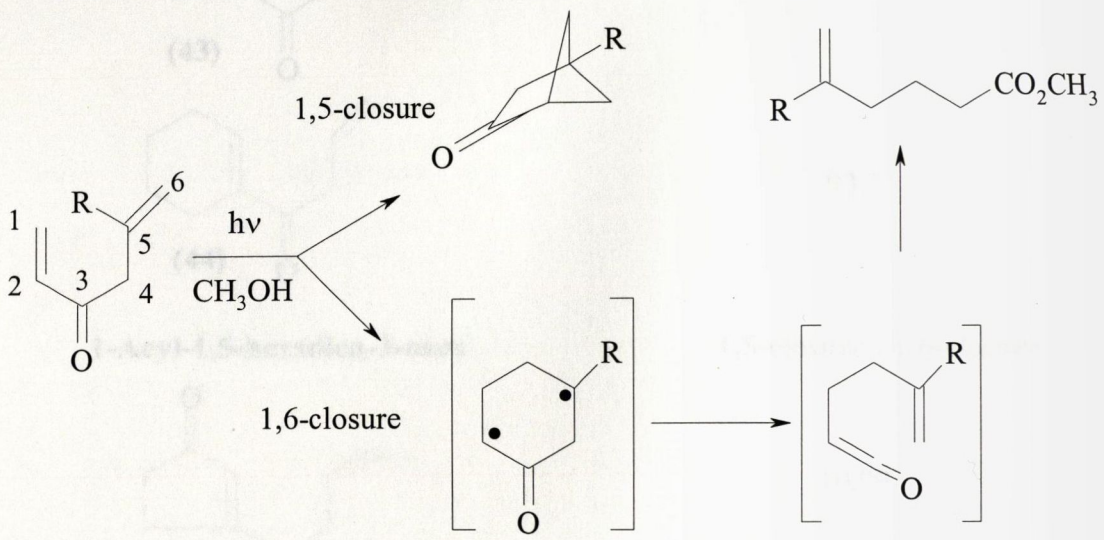
Scheme 1.14

Later Gleiter suggested that the "Rule of Five" could be explained on basis of 'through space' and 'through bond' frontier orbital interactions, and that the regiochemistry of the cycloaddition was controlled by the number of atoms comprising the chain between the two alkenes.[60] When the number was even, cross cycloaddition occurs, while if the number is odd, parallel cycloaddition occurs (Scheme 1.15).



Scheme 1.15

Wolff and Agosta's photochemical studies on a series of 1,5-hexadien-3-ones and 1-acyl-1,5-hexadienes found that they generally obey the "Rule of Five" giving 1,5-closure.[61] A progressive increase in 1,6-closure was observed as the alkyl substituent on the internal carbon (C-5) on 1,5-hexadien-3-ones (Scheme 1.16) changed from H [62,63] to CH_3 [64] to $C(CH_3)_3$. The 1-acyl-1,5-hexadienes series were also affected by alkyl substitution at (C-5) with an increase in 1,6 closure.

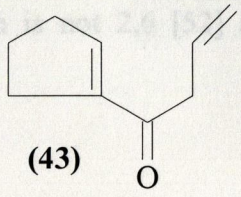
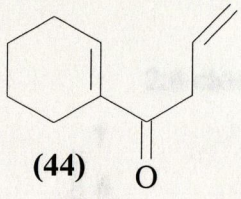


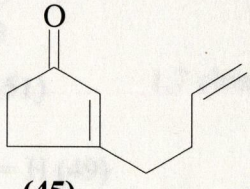
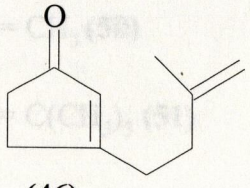
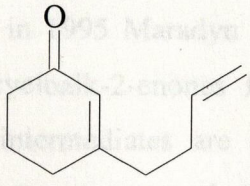
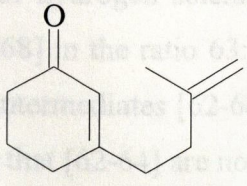
	1,5-closure : 1,6-closure
1. R = H	only 1,5 closure
2. R = CH_3	61:39
3. R = $C(CH_3)_3$	10:90

Scheme 1.16

Further studies showed that the incorporation of the conjugated double bond into a ring resulted in increased amounts of 1,6 closure in both 1,5-hexadien-3-ones [43]-[44] and 1-acyl-1,5-hexadienes [45],[65] [46],[66] [47], [48], with the five-membered ring being more effective for 1,6-closure than the six-membered ring (Scheme 1.17). When both the ring effect and the substitution effect where present the result was additive [46]-[48]. Agosta concluded that partitioning between 1,5- and 1,6-closure was sterically controlled and possibly due to radical stability. Similar photochemical

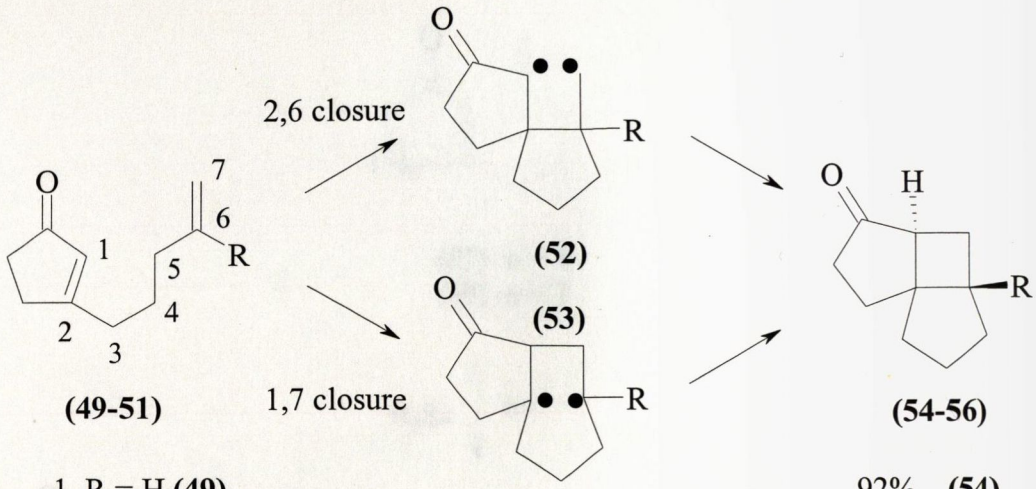
studies on 2-acyl-hexadienes afforded adducts in agreement with the rule of five with no significant deviations due to substitution and ring effects.[66]

1,5-hexadien-3-ones	1,5-closure : 1,6-closure
 **(43)**	43:**57**
 **(44)**	**93**:7

1-Acyl-1,5-hexadien-3-ones	1,5-closure : 1,6-closure
 **(45)**	10:**90**
 **(46)**	**only 1,6**
 **(47)**	**74**:26
 **(48)**	13:**87**

Scheme 1.17

Later, while studying regiochemical control in intramolecular photochemical reactions of a series of 1,6-heptadienes, Agosta found that the regiochemical outcome was also substitution dependent.[67] However, 1,6-hexadienes [49]-[51] were unaffected by substitution affording exclusively straight adducts [54]-[56] as predicted by the "rule of five" (Scheme 1.18). Agosta suggested that the initial cyclisation is not 2,6 [52] as predicted but rather 1,7 [53] giving a more stable biradical.



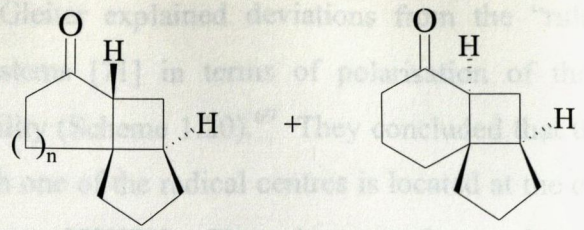
1. R = H **(49)** 92% **(54)**

2. R = CH_3 **(50)** 93% **(55)**

3. R = $C(CH_3)_3$ **(51)** 92% **(56)**

Scheme 1.18

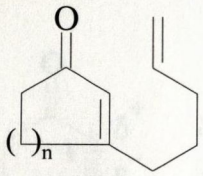
However, in 1995 Maradyn and Weedon's biradical trapping studies on two 3-(4-pentenyl)cycloalk-2-enones found direct evidence that only five-membered ring biradical intermediates are involved in the photocycloaddition of 1,6 and 1,7-heptadiene type compounds (Scheme 1.19).[68] The irradiation of [57] and [58] in the presence of hydrogen selenide afforded the racemic diasteroisomeric spiroketones [67] and [68] in the ratio 63:37 and [69] and [70] in ratio 91:9. Of the five possible biradical intermediates [62-66] only [65] and [66] are trapped by hydrogen selenide indicating that [62-64] are not intermediates or revert exclusively to ground state at a rate too fast to be trapped by hydrogen selenide. The biradical [66] also reverts exclusively to starting material, as the stereochemistry will not allow closure to a cycloadduct.



(59) n = 1
(60) n = 2

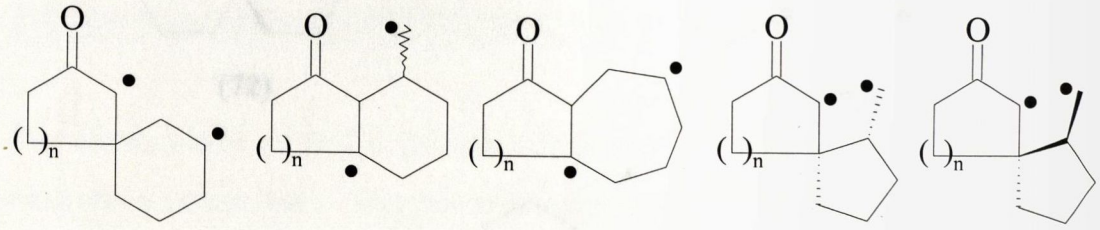
(61)

hν

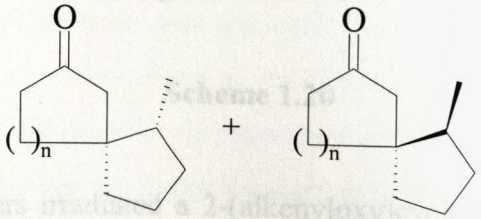


(57) n = 1
(58) n = 2

H_2Se hν



(62) **(63)** **(64)** **(65)** **(66)**

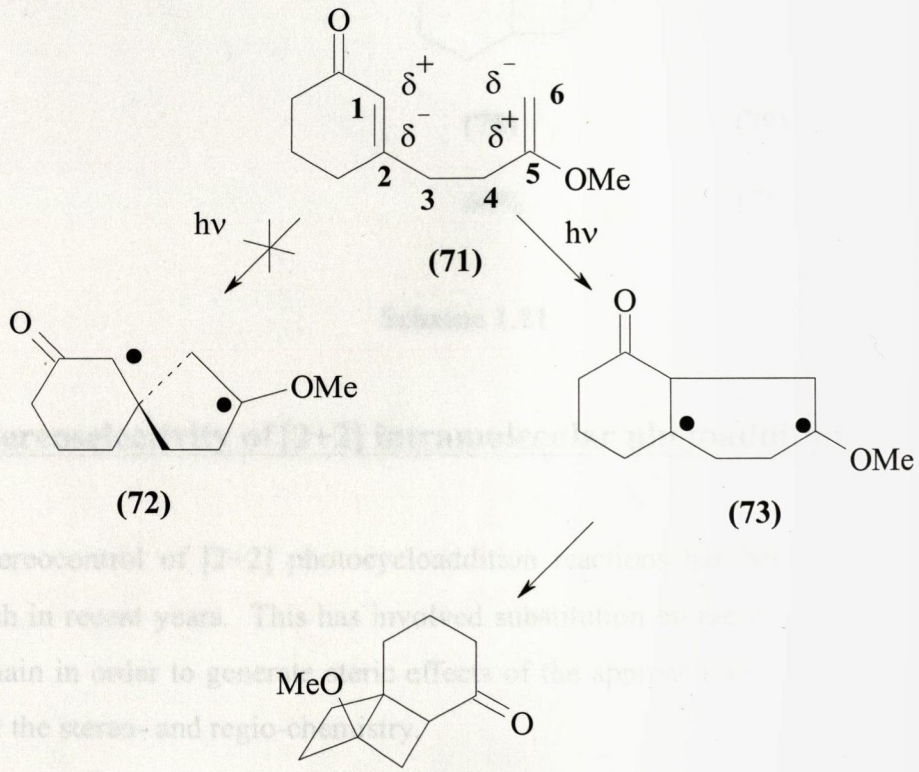


(67) n = 1
(69) n = 2

(68) n = 1
(70) n = 2

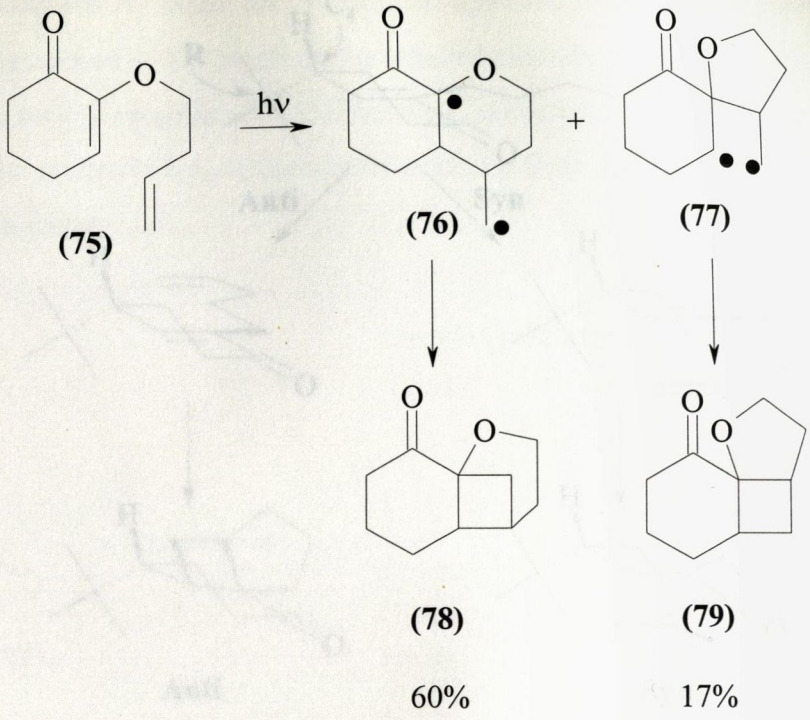
Scheme 1.19

Fischer and Gleiter explained deviations from the "rule of five" in 1-acyl-1,5-hexadiene systems [71] in terms of polarisation of the two double bonds and biradical stability (Scheme 1.20).[69] They concluded that the preferred biradicals are those in which one of the radical centres is located at the carbon atom substituted by the alkoxy group [72][73]. There is no preference between C-1 and C-2 for the second radical centre. The five membered ring radical [72] should be more stable. However, polarisation prefers [73] to [72] affording the straight photoadduct [74] exclusively *via* 1,6-closure.



Scheme 1.20

Tamaura and co-workers irradiated a 2-(alkenyloxy)cyclohexenone [75] and found that the major adduct was formed *via* cross-closure [78] instead of the anticipated parallel closure adduct [79] (Scheme 1.21).[70] This was again explained on basis of the greater stability of the six-membered biradical intermediate [76] compared to the five-membered biradical intermediate [77].

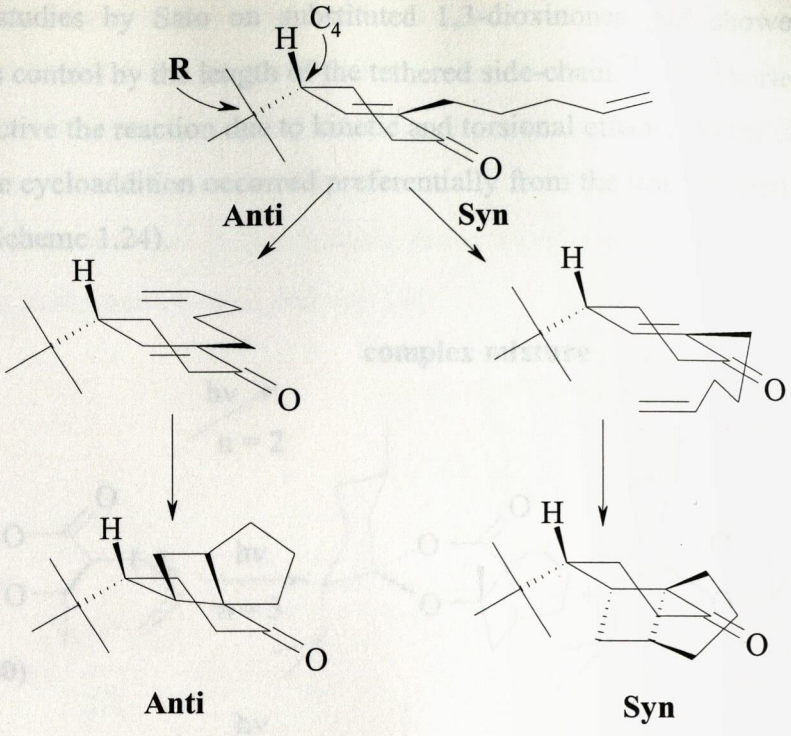


Scheme 1.21

1.4 Stereoselectivity of [2+2] intramolecular photoaddition

The stereocontrol of [2+2] photocycloaddition reactions has been area of intense research in recent years. This has involved substitution on the ring and the tethered side-chain in order to generate steric effects of the approaching reactants and hence control the stereo- and regio-chemistry.

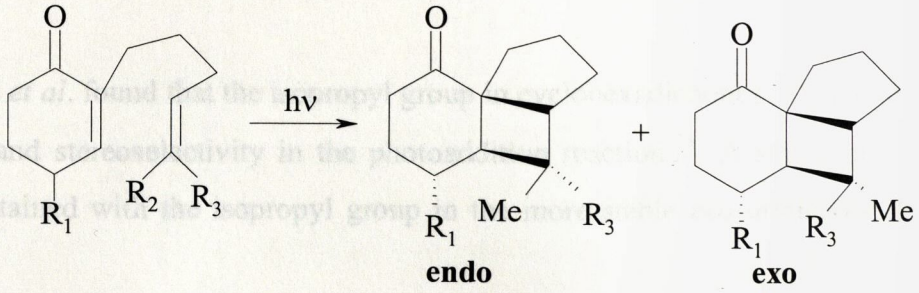
Irradiation studies by Becker *et al.* on cyclohexenones with tethered alkenes showed that the ratio of *anti*/*syn* isomers was sterically controlled.[71] The regiochemistry gave exclusively parallel photoadducts as predicted. The mode of approach of the alkene was determined by the size of the substituent on C-4 with a *t*-butyl group affording the *anti* isomer as the major product indicating approach from the least hindered side (Scheme 1.22). A mixture of *endo* and *exo* steroisomers where formed when the reactive centres on the olefin were substituted (Scheme 1.23). Becker concluded that the *endo*:*exo* ratio of photoadducts was also sterically controlled by the bulkiness of the C-4 substituent and substitution on the olefinic tethered chain.



Anti **Syn**

	Anti : Syn
1. R = Bu^t	2.3:1
2. R = Me	1.4:1

Scheme 1.22

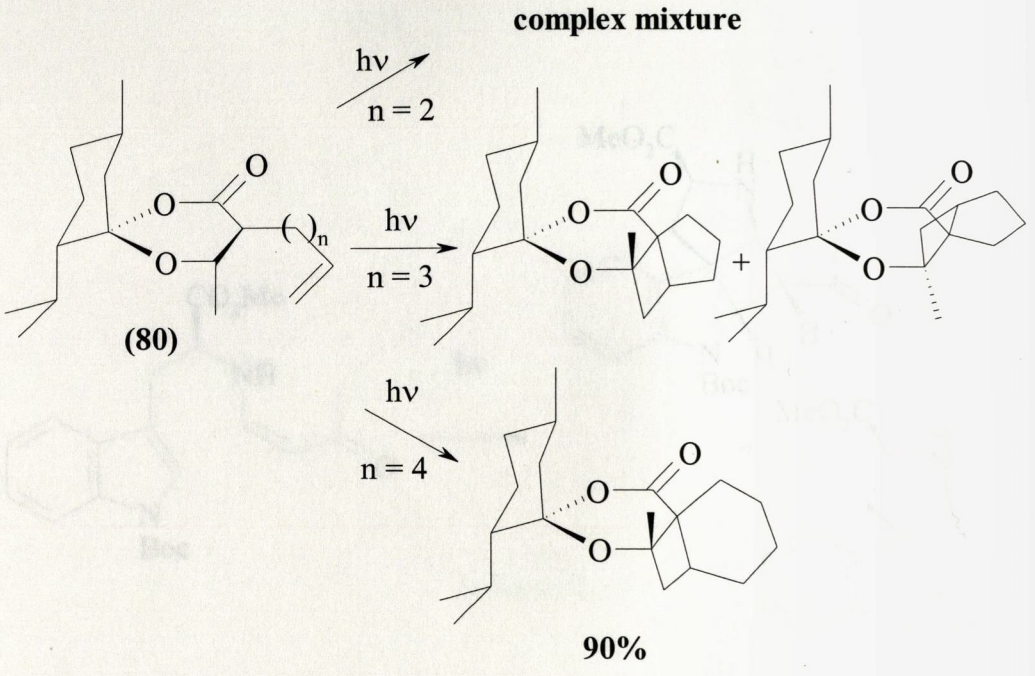


endo **exo**

	ratio endo : exo
1. R_1 = Me; R_2 = H; R_3 = Bu^t	4:1
2. R_1 = H; R_2 = Me; R_3 = Bu^t	1.8:1
3. R_1 = Me; R_2 = H; R_3 = H	35:1
4. R_1 = H; R_2 = Me; R_3 = H	8:1

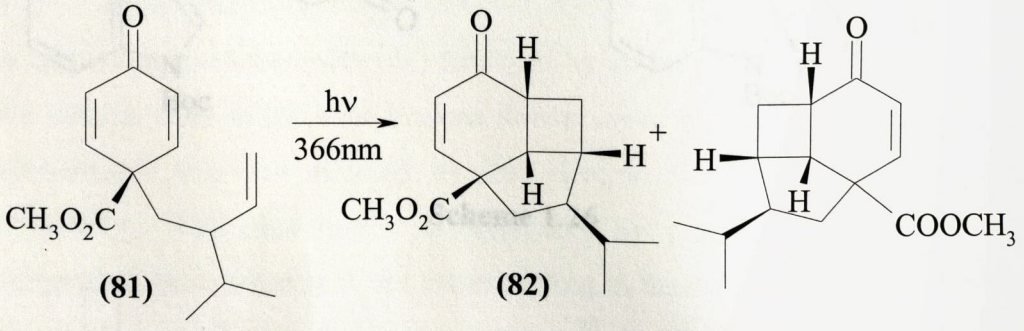
Scheme 1.23

Irradiation studies by Sato on substituted 1,3-dioxinones [80] showed that the reaction was control by the length of the tethered side-chain.[72] The shorter the tether the less selective the reaction due to kinetic and torsional effects. As the chain length increased the cycloaddition occurred preferentially from the less hindered side of the molecule (Scheme 1.24).



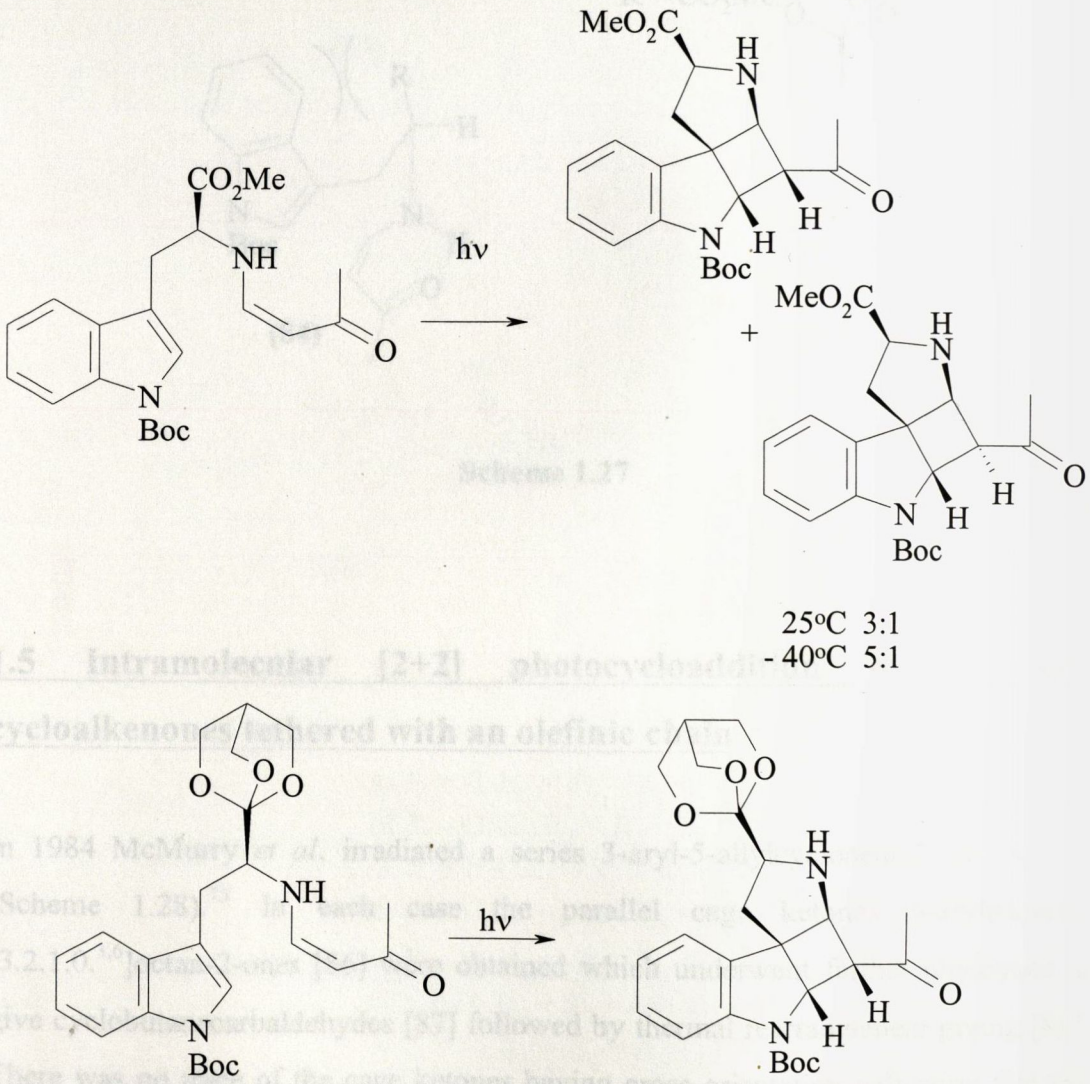
Scheme 1.24

Schultz *et al.* found that the isopropyl group in cyclohexadienones [81] controlled the regio- and stereoselectivity in the photoaddition reaction.[73] A single product [82] was obtained with the isopropyl group in the more stable *exo* orientation (Scheme 1.25)

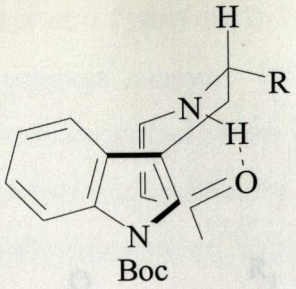


Scheme 1.25

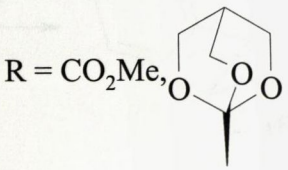
The irradiation of vinylogous amide-tethered tryptophan derivatives showed that the bulkier the substituent on the stereocentre of the tether, the greater the selectivity (Scheme 1.26).[74] Examination of the transition state structures [83] [84] (Scheme 1.27) indicates that the preferred orientation is that in which the substituent is in the pseudo-equatorial position [83] affording fewer steric interactions than when the substituent is in the pseudo-axial position [84].

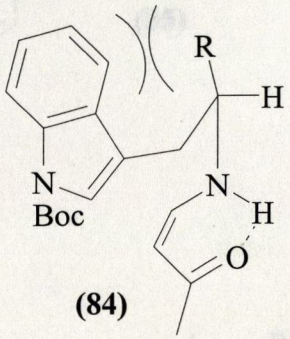


Scheme 1.26



(83)



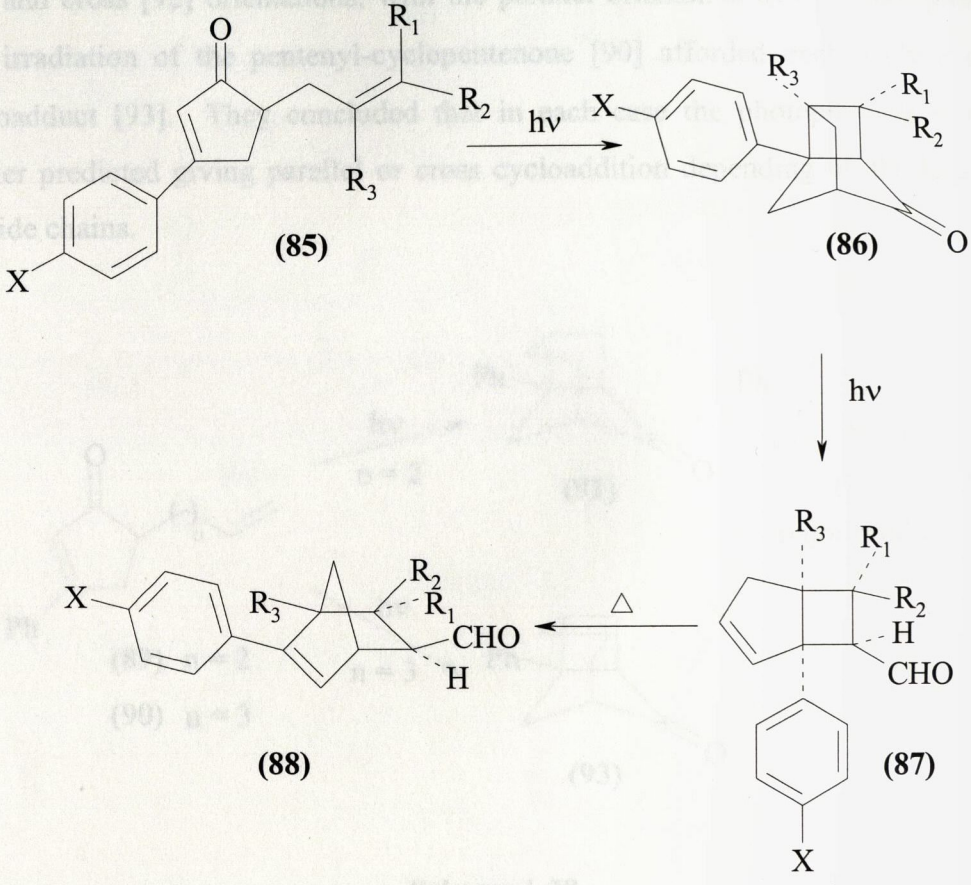


(84)

Scheme 1.27

1.5 Intramolecular [2+2] photocycloaddition of 3-phenyl-cycloalkenones tethered with an olefinic chain

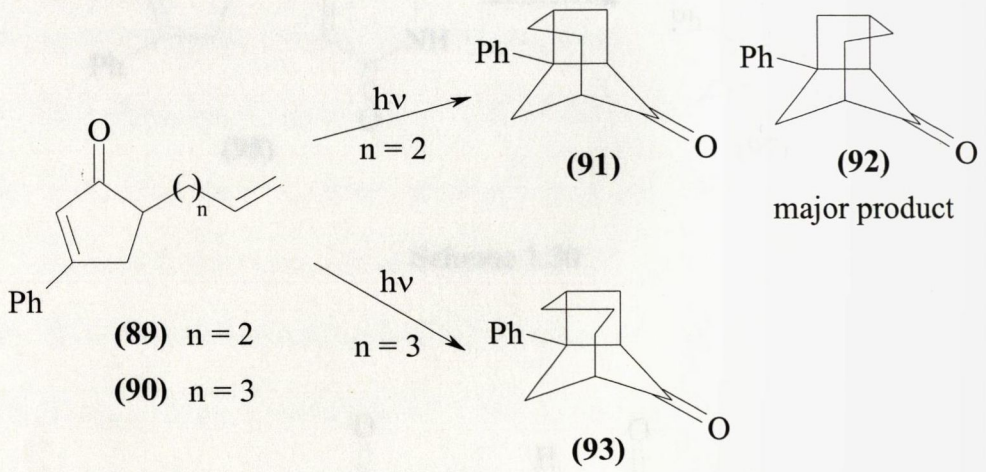
In 1984 McMurry *et al.* irradiated a series 3-aryl-5-allylcyclopent-2-enones [85] (Scheme 1.28).[75] In each case the parallel cage ketones 6-aryltricyclo-[3.2.1.0.^{3,6}]octan-2-ones [86] were obtained which underwent further photoylsis to give cyclobutanecarbaldehydes [87] followed by thermal rearrangement giving [88]. There was no trace of the cage ketones having cross orientation indicating that the regiochemistry was not affected by the electron density changes on the ene functionality. This was further demonstrated by placing a methoxy or cyano substituent at the 4-position of the aromatic ring in the 5-(3-phenylprop-2-enyl) side chain attached to a 3-phenylcyclopent-2-enone.[76] In all instances the regiochemistry was unaffected.



a) X = H, $R_1 = R_2 = R_3 = H$
b) X = OMe, $R_1 = R_2 = R_3 = H$
c) X = CN, $R_1 = R_2 = R_3 = H$
d) X = H, R_1 = Me, $R_2 = R_3 = H$
e) X = H, $R_1 = R_3 = H$, R_2 = Me
f) X = H, $R_1 = R_2$ = Me, $R_3 = H$
g) X = H, $R_1 = R_2 = H$, R_3 = Me

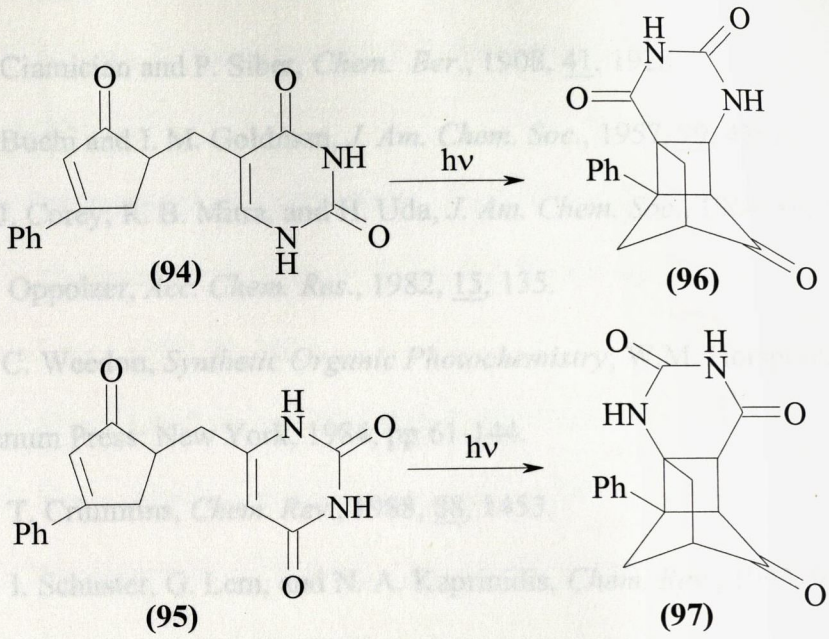
Scheme 1.28

Irradiation studies of 5-(but-3-enyl)-3-phenylcyclopent-2-enone [89] and 5-(pent-4-enyl)-3-phenylcyclopent-2-enone [90] were examined to determine if the regioselectivity was controlled by the length of the side chain (Scheme 1.29).[77] The irradiation of butenyl-cyclopentenone [89] afforded two photoadducts with parallel [91] and cross [92] orientations, with the parallel orientation as the major product. The irradiation of the pentenyl-cyclopentenone [90] afforded exclusively a cross photoadduct [93]. They concluded that in each case the photoproducts were as Gleiter predicted giving parallel or cross cycloaddition depending on the length of the side chains.

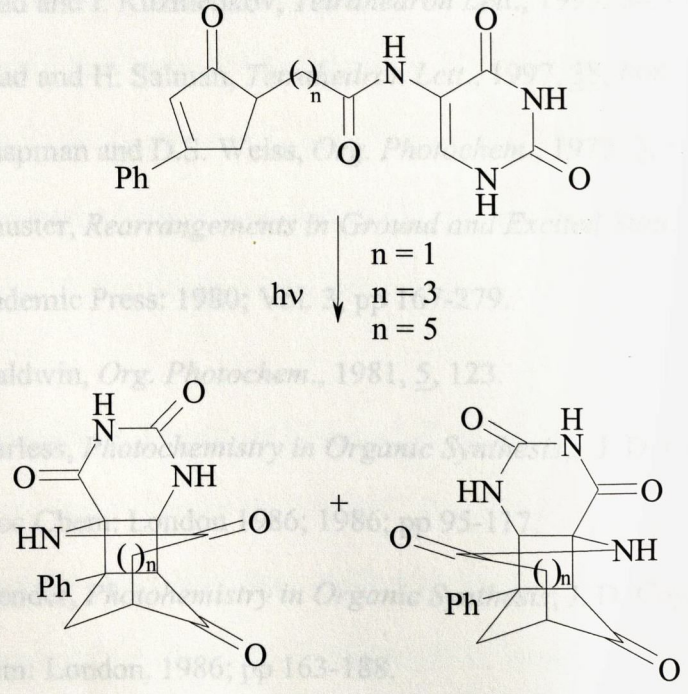


Scheme 1.29

In 1986 Clements and McMurry incorporated the aromatic "double bonds" of 1-naphthylmethyl, 2-naphthylmethyl and 9-phenaphthylmethyl substituents into cycloaddition products with no regiochemical effects affording parallel photoproducts.[78] This was followed by the incorporation of the alkene into a uracil ring. In both cases where the alkene was 5-methyluracil [94] and 6-methyluracil [95] the reaction gave parallel cycloaddition products [96] and [97] in high yield (Scheme 1.30).[79] The length of the tethered chain was increased by Kerley but photochemical reactions afforded compounds which were too insoluble, in some cases, too unstable to be identified by spectroscopic techniques.[80] It was unclear whether one, two, or more photoadducts were formed (Scheme 1.31).



Scheme 1.30



Scheme 1.31

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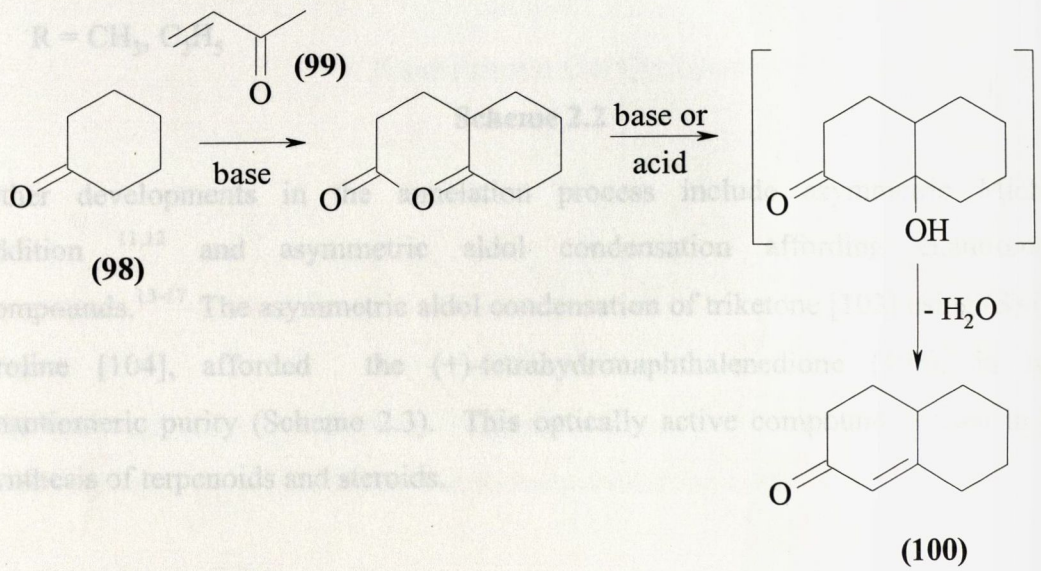
Chapter 2

2.0 Introduction

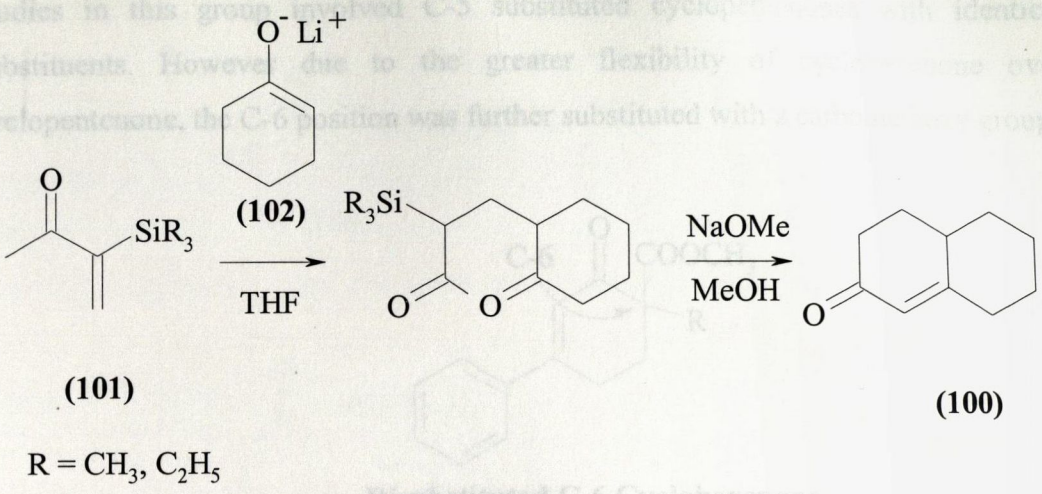
The biological importance of natural compounds containing the cyclohexenone ring and its derivatives has led to intense research over the years. There are several synthetic routes to cyclohexenones with the most common *via* the aldol condensation.[1] The classical Robinson Annelation reaction (Scheme 2.1) involves a base-catalysed Michael addition of an active methylene group of a cyclohexanone [98] to methyl vinyl ketone [99] followed by base or acid catalysed aldol condensation to give $\Delta^{1,9}$-2-octalone [100] containing the cyclohexenone ring.[2]



Scheme 2.1

The annelation process is successfully employed to form six membered cyclohexenone systems.[3-5] However, a major problem of the reaction is the low yields caused by polymerisation of the α, β-unsaturated ketones. This has led to modifications on the methods of introducing the vinyl ketone, for example, the *in situ* preparation of the unsaturated ketone from its corresponding Mannich base.[6-9] Decombe showed that β-chloroketones could replace the α, β-unsaturated ketones in his preparation of substituted cyclohexenones [10] while, Stork and Ganem introduced α-trialkylsilyl ketone [101] as a substitute for methyl vinyl ketone [99] in the synthesis of $\Delta^{1,9}$-2-octalone [100] giving higher yields under the same reaction conditions (Scheme 2.2).[11] The silyl ketone adds to the lithium enolate [102], which then undergoes condensation with elimination of the silyl group to give the octalone

[100] in 80% overall yield, as compared to the < 5% yield obtained using methyl vinyl ketone (Scheme 2.1).



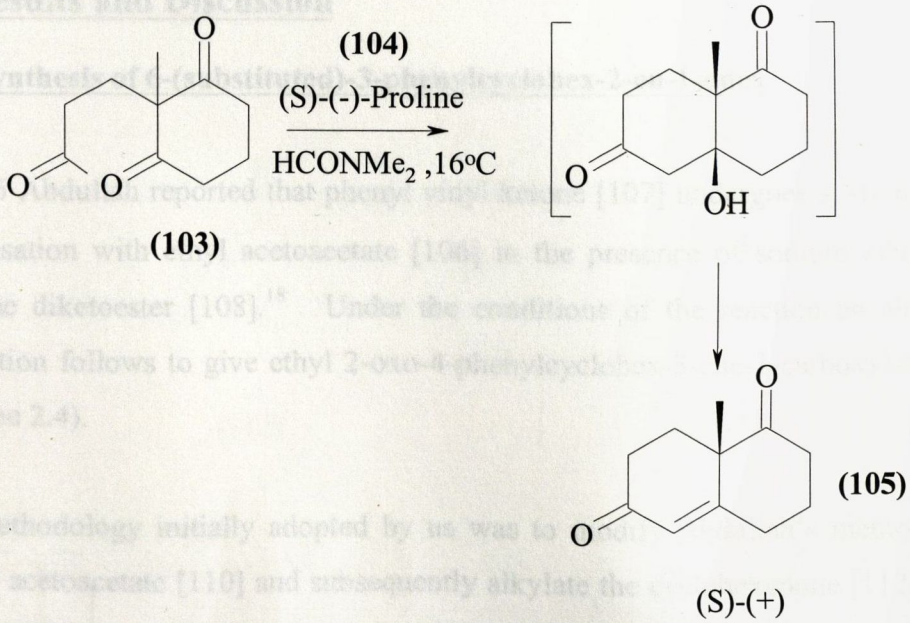
(101)

$R = CH_3, C_2H_5$

(100)

Scheme 2.2

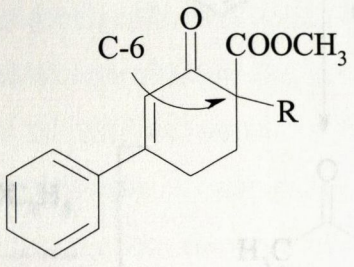
Other developments in the annelation process include asymmetric Michael addition [11,12] and asymmetric aldol condensation affording enantiomeric compounds.[13-17] The asymmetric aldol condensation of triketone [103] using (S)-(−)-proline [104], afforded the (+)-tetrahydronaphthalenedione [105], in high enantiomeric purity (Scheme 2.3). This optically active compound is used in the synthesis of terpenoids and steroids.



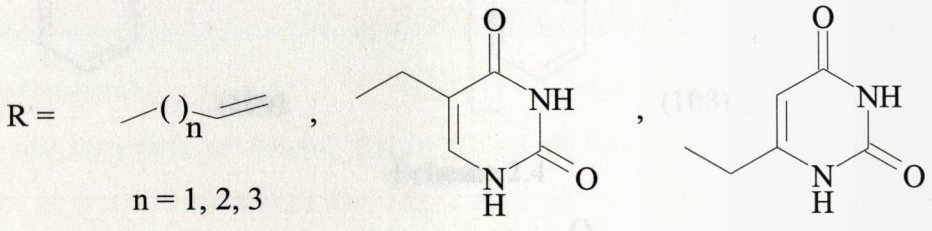
(103)

Scheme 2.3

We investigated the synthesis of a series of C-6 substituted cyclohexenones (see below) with the intention of studying their photochemical potential. Similar enone studies in this group involved C-5 substituted cyclopentenones with identical substituents. However due to the greater flexibility of cyclohexenone over cyclopentenone, the C-6 position was further substituted with a carbomethoxy group.



Disubstituted C-6 Cyclohexenone



The carbomethoxy group was deemed necessary in order to generate a conformational control factor, so that photocycloaddition could occur.

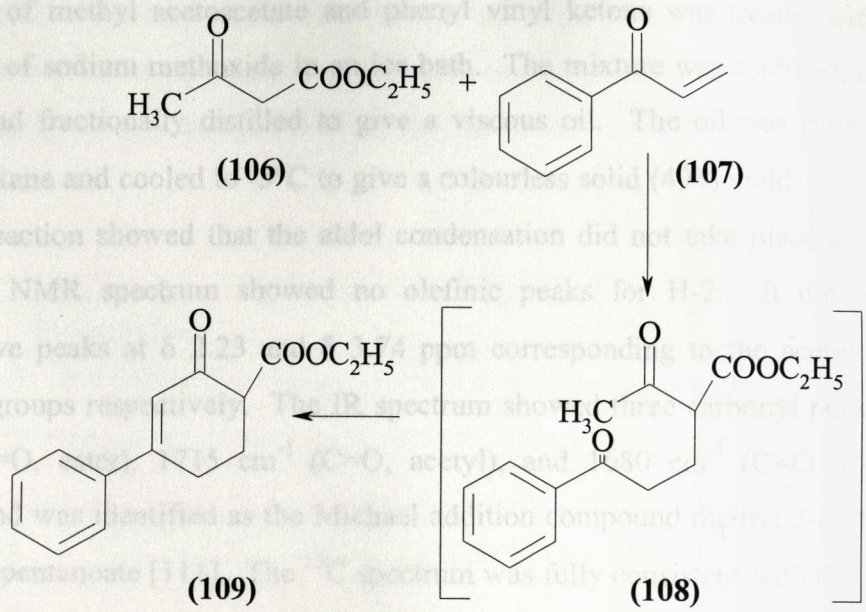
2.1 Results and Discussion

2.11 Synthesis of 6-(substituted)-3-phenylcyclohex-2-en-1-ones

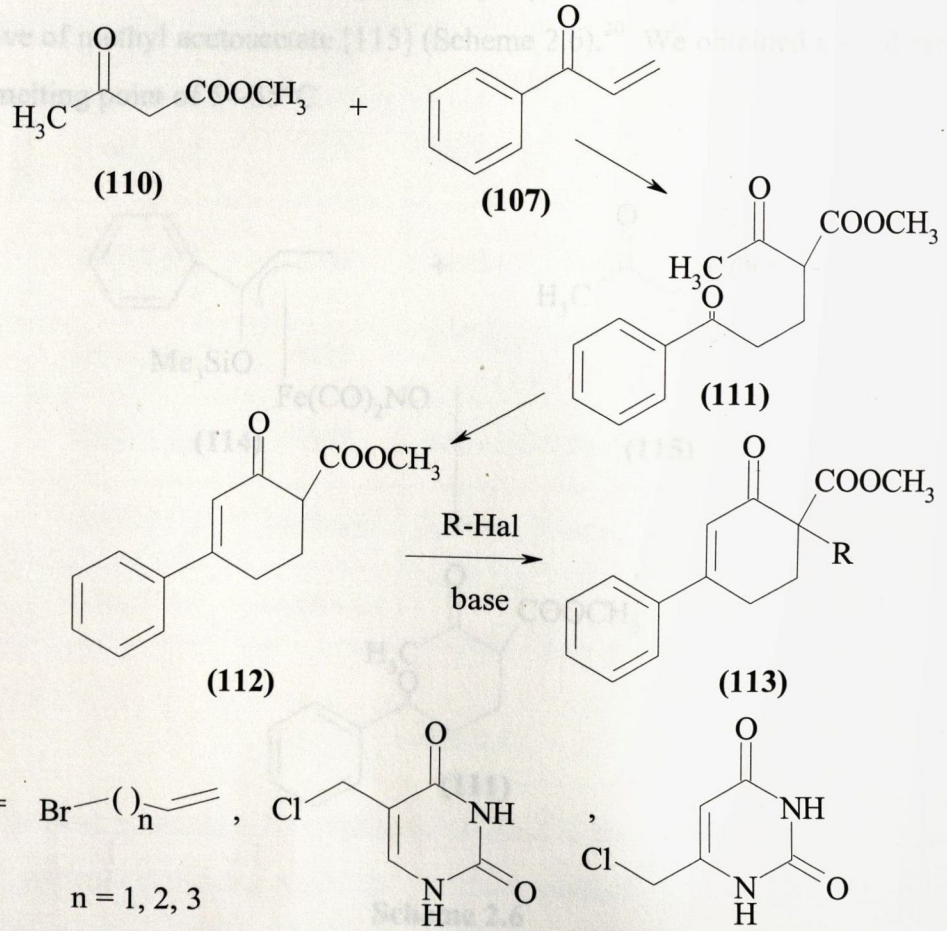
In 1935 Abdullah reported that phenyl vinyl ketone [107] undergoes a Michael type condensation with ethyl acetoacetate [106] in the presence of sodium ethoxide to give the diketoester [108].[18] Under the conditions of the reaction an aldol-type cyclisation follows to give ethyl 2-oxo-4-phenylcyclohex-3-ene-1-carboxylate [109] (Scheme 2.4).

The methodology initially adopted by us was to modify Abdullah's method using methyl acetoacetate [110] and subsequently alkylate the cyclohexenone [112] with a halo-compound to give 6-(disubstituted)-3-phenylcyclohex-2-en-1-ones [113]

(Scheme 2.5). It was decided to prepare the methyl ester [112] instead of the ethyl ester [109] as it would make NMR interpretation easier.

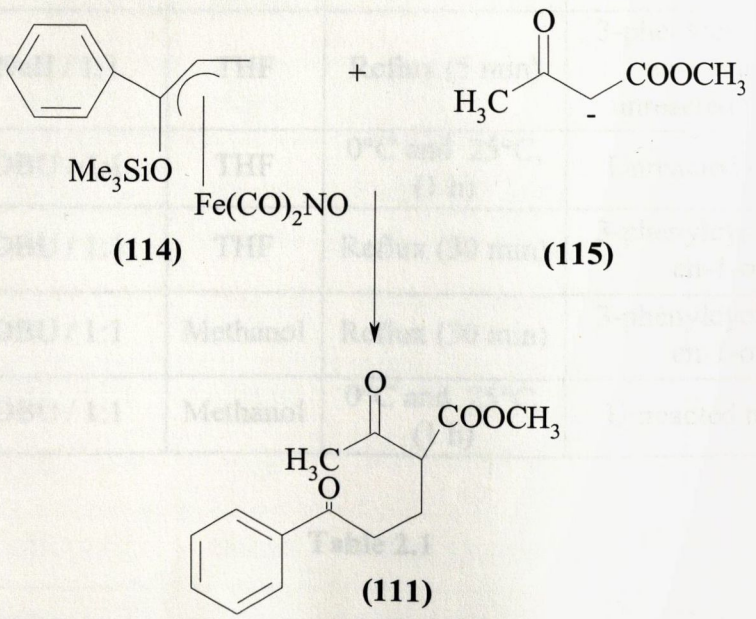


Scheme 2.4



Scheme 2.5

Phenyl vinyl ketone [107] was synthesised by pyrolysis of dimethylamino-propiophenone hydrochloride and isolated by vacuum distillation.[19] The compound was redistilled and stored at 0°C over a few crystals of hydroquinone. An equimolar mixture of methyl acetoacetate and phenyl vinyl ketone was treated with a 1 % solution of sodium methoxide in an ice bath. The mixture was acidified, extracted, dried, and fractionally distilled to give a viscous oil. The oil was triturated with ether/hexane and cooled to -5°C to give a colourless solid (49% yield). The analysis of the reaction showed that the aldol condensation did not take place as expected. The ^{1}H NMR spectrum showed no olefinic peaks for H-2. It did show two distinctive peaks at δ 2.23 and δ 3.74 ppm corresponding to the acetyl and ester methyl groups respectively. The IR spectrum showed three carbonyl peaks at 1745 cm^{-1} (C=O, ester), 1715 cm^{-1} (C=O, acetyl), and 1680 cm^{-1} (C=O, C-5). The compound was identified as the Michael addition compound methyl 2-acetyl-5-oxo-5-phenylpentanoate [111]. The ^{13}C spectrum was fully consistent with this structure. Otsuji and co-workers reported the synthesis of this compound as an oil by the reaction of a (R^3-1-trimethylsiloxyallyl)$Fe(CO)_2NO$ complex [114] and the sodio derivative of methyl acetoacetate [115] (Scheme 2.6).[20] We obtained a solid product with a melting point of 54-55°C.



Scheme 2.6

We attempted to cyclise methyl 2-acetyl-5-oxo-5-phenylpentanoate [111] using a range of reagents and conditions (Table 2.1). However, in each case we obtained ring closure but with concomitant loss of the ester group to give 3-phenylcyclohex-2-en-1-one [116] (Scheme 2.7). The loss of the ester group must involve attack of hydroxide or methoxide anion on the ester carbonyl resulting in cleavage. The hydroxide anion can be formed from the molecule of water generated in the ring closure step.

Expt no.	Base/ Reactant:base	Solvent	Temp	Product
1.	$NaOCH_3$ / 10:1	THF	0°C and 25°C, (1 h)	Unreacted material
2.	$NaOCH_3$ /10:1	THF	25°C (12 h)	Unreacted material
3.	$NaOCH_3$ / 10:1	THF	Reflux (1 h)	3-phenylcyclohex-2-en-1-one
4.	$NaOCH_3$ / 10:1	THF	30°C (12 h)	3-phenylcyclohex-2-en-1-one and unreacted material
5.	NaH / 1:1	THF	0°C and 25°C, (1h)	unreacted material
6.	NaH / 1:1	THF	Reflux (30 min)	3-phenylcyclohex-2-en-1-one
7.	NaH / 1:1	THF	Reflux (5 min)	3-phenylcyclohex-2-en-1-one and unreacted material
8.	DBU / 1:1	THF	0°C and 25°C, (1 h)	Unreacted material
9.	DBU / 1:1	THF	Reflux (30 min)	3-phenylcyclohex-2-en-1-one
10.	DBU / 1:1	Methanol	Reflux (30 min)	3-phenylcyclohex-2-en-1-one
11.	DBU / 1:1	Methanol	0°C and 25°C, (1 h)	Unreacted material

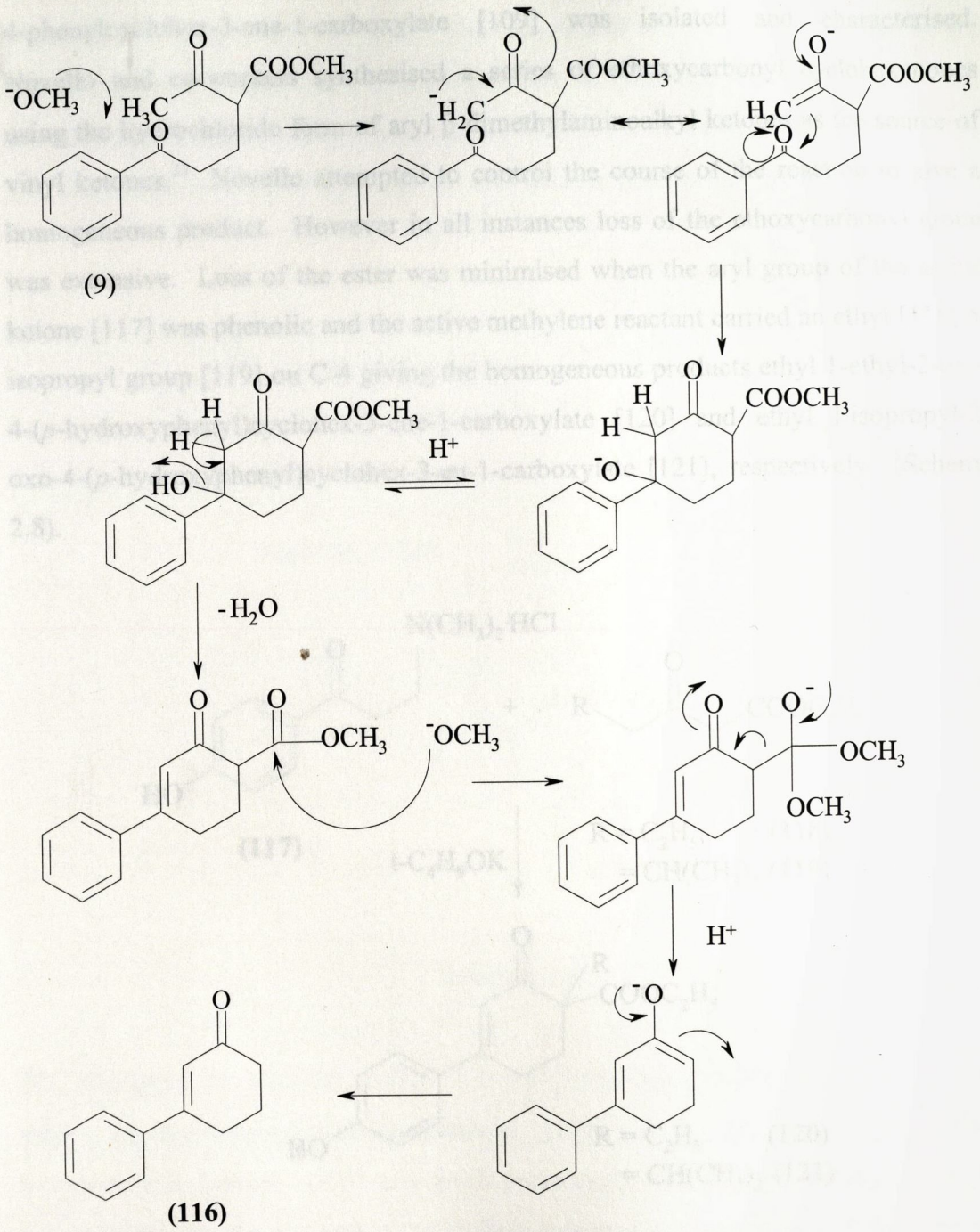
Table 2.1

It was decided to attempt the synthesis of ethyl 2-oxo-4-phenylcyclohex-2-ene-1-carboxylate [109] following Abdullah's original method (Scheme 2.4). The product was distilled as a viscous oil in 45% yield. The ^1H NMR spectrum showed no

olefinic peak for H-2. It did show an acetyl CH_3 at δ 2.20 ppm. The ester CH_2 appeared as a quartet at δ 4.10 ppm (J = 7.1 Hz) and the CH_3 as a triplet at δ 1.18 ppm (J = 7.1 Hz). The IR spectrum showed three carbonyl peaks at 1739 cm^{-1} (C=O, ester), 1716 cm^{-1} (C=O, acetyl), and 1685 cm^{-1} (C=O, C-5). The compound was identified as ethyl 2-acetyl-5-oxo-5-phenylpentanoate [108]. Abdullah reported that cyclisation occurred under these conditions to give the cyclohexenone [109] (Scheme 2.4). The diketoester ester [108] was not expected. It was attempted to induce ring closure to give the desired cyclohexenone [109] using a range of reagents and conditions similar to Table 2.1 (Table 2.2). The result was the same as before ring closure but with concomitant loss of the ester group to give 3-phenylcyclohex-2-en-1-one [116].

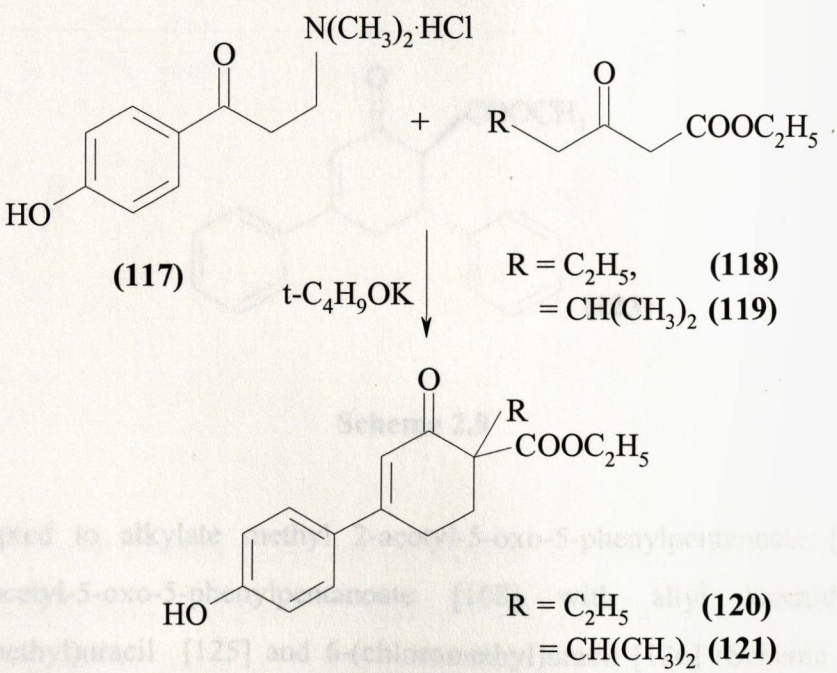
Expt no.	Base/ Reactant:base	Solvent	Temp	Product
1.	$NaOC_2H_5$ / 10:1	ethanol	0°C and 25°C, (1 h)	Unreacted material
2.	$NaOC_2H_5$/ 10:1	ethanol	25°C (12 h)	Unreacted material
3.	$NaOC_2H_5$/ 10:1	ethanol	Reflux (1 h)	3-phenylcyclohex-2-en-1-one
4.	$NaOC_2H_5$/ 10:1	ethanol	30°C (12 h)	3-phenylcyclohex-2-en-1-one and unreacted material
5.	NaH / 1:1	ethanol	0°C and 25°C, (1 h)	unreacted material
6.	NaH / 1:1	ethanol	Reflux (30 min)	3-phenylcyclohex-2-en-1-one
7.	NaH / 1:1	ethanol	Reflux (5 min)	3-phenylcyclohex-2-en-1-one and unreacted material
8.	DBU / 1:1	ethanol	0°C and 25°C, (1 h)	Unreacted material
9.	DBU / 1:1	THF	0°C and 25°C (1 h)	Unreacted material
10.	DBU / 1:1	ethanol	Reflux (30 min)	3-phenylcyclohex-2-en-1-one
11.	DBU / 1:1	THF	Reflux (30 min)	3-phenylcyclohex-2-en-1-one

Table 2.2



Scheme 2.7

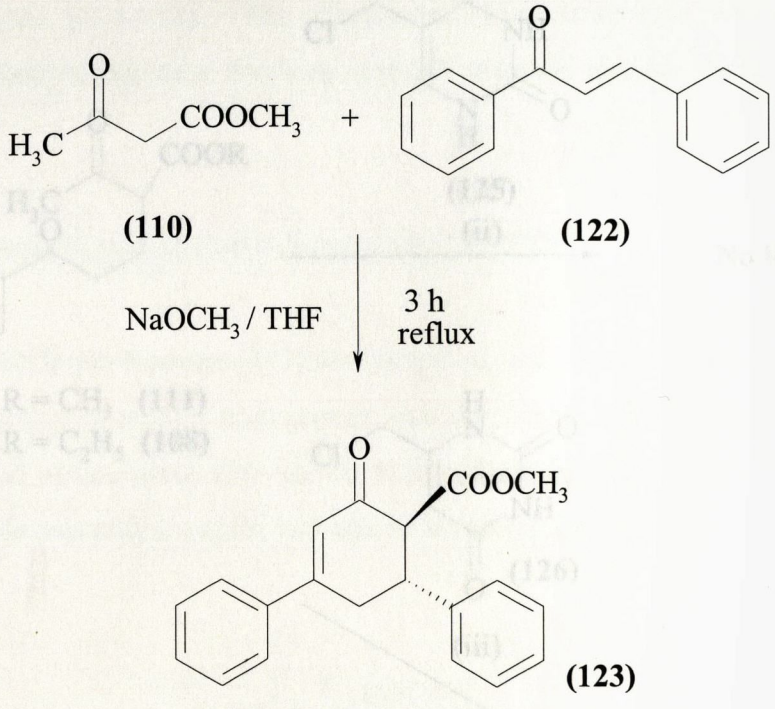
Despite the apparent ease of synthesis of cyclohexenones by this method, very little work has been done on the synthesis of 6-alkoxycarbonyl-3-phenylcyclohexenones.[18] To our knowledge there are no reports in the literature since 1935 when ethyl 2-oxo-4-phenylcyclohex-3-ene-1-carboxylate [109] was isolated and characterised. Novello and co-workers synthesised a series of ethoxycarbonyl cyclohexenones using the hydrochloride form of aryl β-dimethylaminoalkyl ketones as the source of vinyl ketones.[21] Novello attempted to control the course of the reaction to give a homogeneous product. However in all instances loss of the ethoxycarbonyl group was extensive. Loss of the ester was minimised when the aryl group of the amino ketone [117] was phenolic and the active methylene reactant carried an ethyl [118] or isopropyl group [119] on C-4 giving the homogeneous products ethyl 1-ethyl-2-oxo-4-(*p*-hydroxyphenyl)cyclohex-3-ene-1-carboxylate [120] and ethyl 1-isopropyl-2-oxo-4-(*p*-hydroxyphenyl)cyclohex-3-en-1-carboxylate [121], respectively (Scheme 2.8).



Scheme 2.8

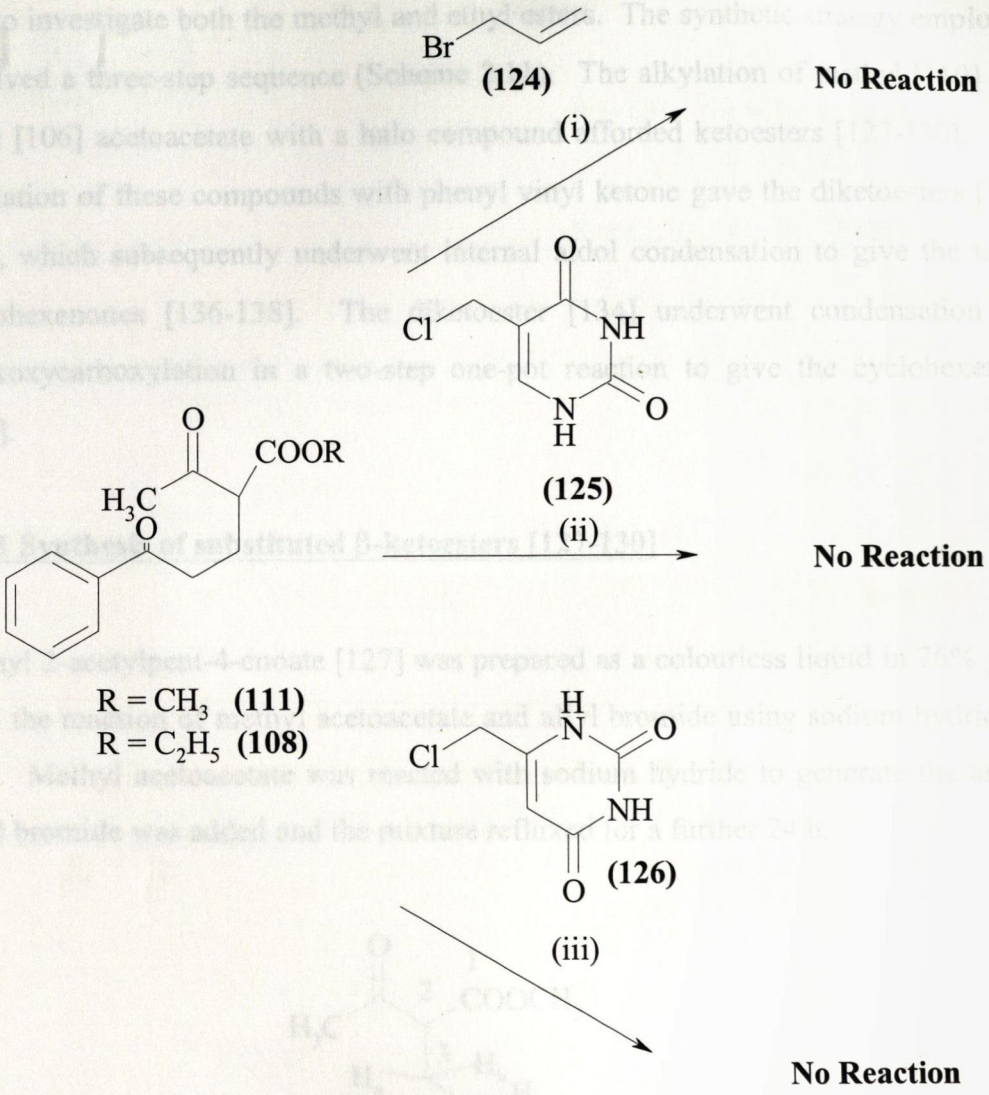
We have postulated that the ethyl and isopropyl groups inhibit the approach of the butoxide anion and therefore prevent dealkoxycarboxylation of the ethoxycarbonyl group. This would imply that steric factors are involved in the attack on the ester

carbonyl. Further evidence is seen in the base-catalysed synthesis of methyl 4,6-diphenyl-2-oxocyclohex-3-ene-1-carboxylate [123] using methyl acetoacetate [110] and benzalacetophenone [122] (Scheme 2.9). The compound was synthesised over a period of 3 h at 66°C in 70% yield. The presence of the bulky phenyl group in the 6-position prevented the attack of the methoxide or hydroxide anion. The compound was identified by spectroscopic techniques. The ^{1}H NMR showed the presence of the H-3 olefinic peak at δ 5.53 ppm and the methyl ester peak at δ 3.33 ppm.



Scheme 2.9

We attempted to alkylate methyl 2-acetyl-5-oxo-5-phenylpentanoate [111] and ethyl 2-acetyl-5-oxo-5-phenylpentanoate [108] with allyl bromide [124], 5-(chloromethyl)uracil [125] and 6-(chloromethyl)uracil [126] (Scheme 2.10). It was believed that the addition of the olefinic substituent would have a steric effect on the ester preventing dealkoxycarboxylation during cyclisation. However due to the susceptibility of the diketoester to ring closure and decarboxylation at elevated temperatures under basic conditions, all reactions were carried out at room temperature. However, no alkylation was detected by TLC during the course of these reactions and the diketoesters [111] and [108] were recovered.



Reagents: (i) allyl bromide [124] and (a) NaH in THF or (b) NaOR in ROH; (ii) 5-(chloromethyl)uracil [125] and (a) NaH in DMF, (b) ammonium acetate in DMF or (c) diisopropylethylamine in DMF; (iii) 6-(chloromethyl)uracil [126] and (a) NaH in DMF, (b) ammonium acetate in DMF or (c) diisopropylethylamine in DMF.

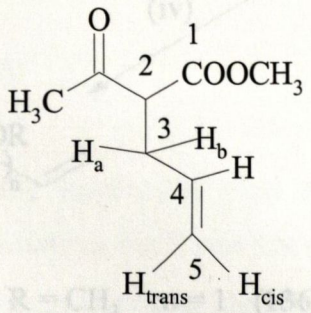
Scheme 2.10

2.12 Synthesis of 6-(disubstituted)-3-phenylcyclohex-2-en-1-ones

Due to the failure of the above methods it was decided to use a different approach and to investigate both the methyl and ethyl esters. The synthetic strategy employed involved a three-step sequence (Scheme 2.11). The alkylation of methyl [110] and ethyl [106] acetoacetate with a halo compound afforded ketoesters [127-130]. The alkylation of these compounds with phenyl vinyl ketone gave the diketoesters [131-134], which subsequently underwent internal aldol condensation to give the target cyclohexenones [136-138]. The diketoester [134] underwent condensation and dealkoxycarboxylation in a two-step one-pot reaction to give the cyclohexenone [135].

2.121 Synthesis of substituted β-ketoesters [127-130]

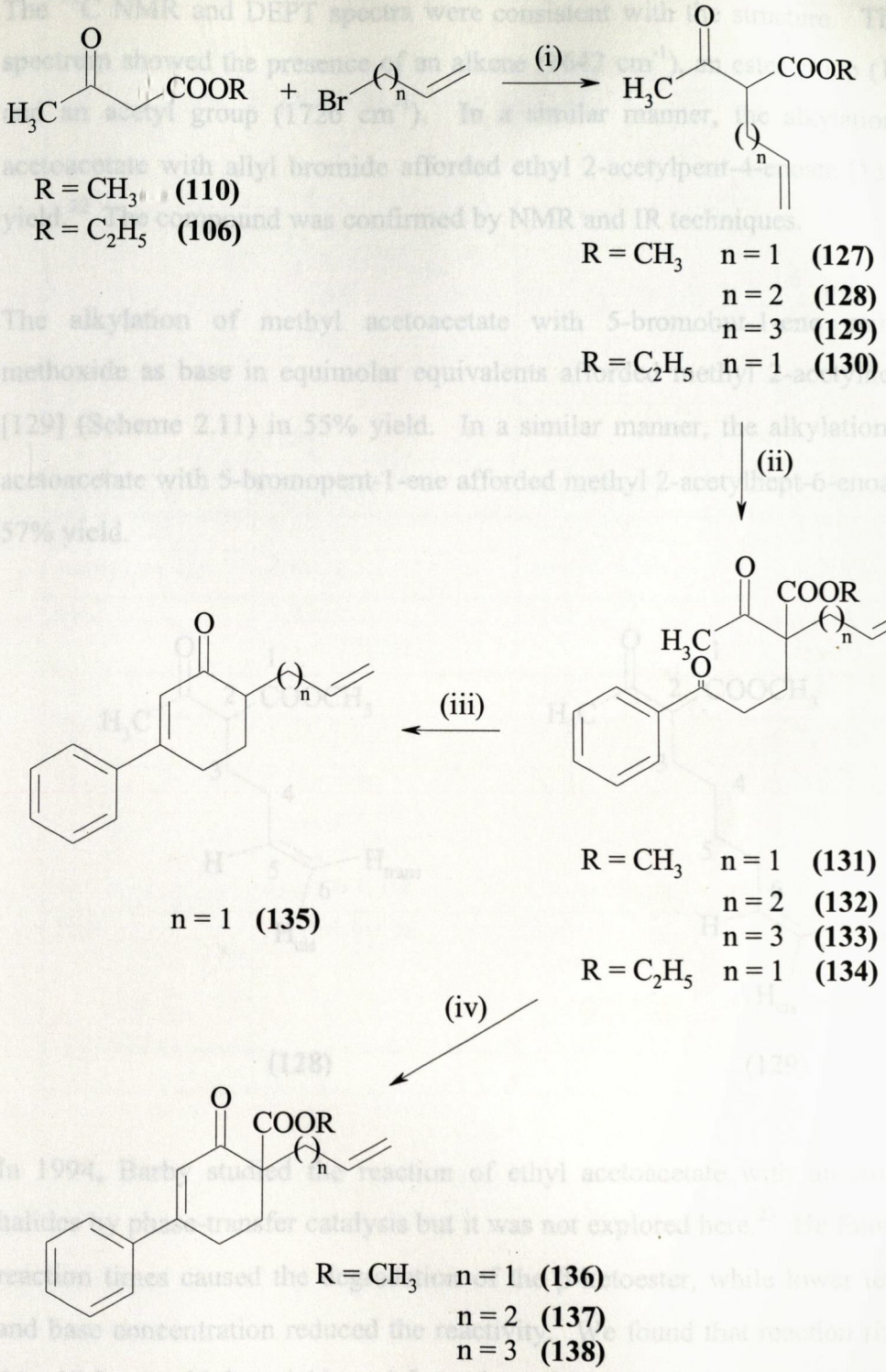
Methyl 2-acetylpent-4-enoate [127] was prepared as a colourless liquid in 76% yield from the reaction of methyl acetoacetate and allyl bromide using sodium hydride as base. Methyl acetoacetate was reacted with sodium hydride to generate the anion. Allyl bromide was added and the mixture refluxed for a further 24 h.



(127)

The compound was fully characterised by spectroscopic techniques. The ^{1}H NMR spectrum showed several distinctive peaks, namely:

1. The olefinic splitting pattern of H-4 at δ 5.65 ppm was observed as a double, double, triplet ($J_{4,5trans}$ = 17.1, $J_{4,5cis}$ = 10.1, $J_{4,3}$ = 7.0 Hz).
2. The triplet at δ 3.47 ppm corresponded to the hydrogen on the stereogenic carbon at C-2. There was no difference in coupling constants between the 2-H and the two 3-Hs ($J_{2,3Ha}$ = $J_{2,3Hb}$ = 7.4 Hz).

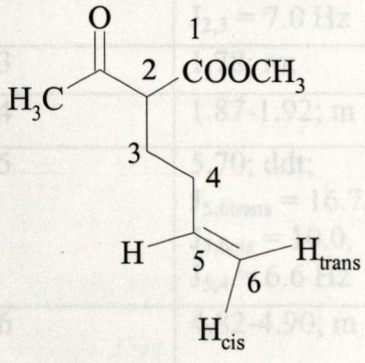


Reagents: (i), R = CH_3, C_2H_5, n = 1, NaH in THF; R = CH_3, n = 2, 3, $NaOCH_3$ in methanol; (ii) $PhCOCH{=}CH_2$; R = CH_3, $NaOCH_3$ in methanol; R = C_2H_5, $NaOC_2H_5$ in ethanol; (iii) NaH in THF; (iv) DBU in methanol.

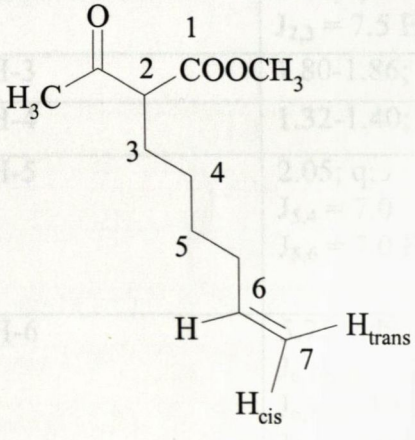
Scheme 2.11

The ^{13}C NMR and DEPT spectra were consistent with the structure. The infrared spectrum showed the presence of an alkene (1642 cm^{-1}), an ester group (1745 cm^{-1}) and an acetyl group (1726 cm^{-1}). In a similar manner, the alkylation of ethyl acetoacetate with allyl bromide afforded ethyl 2-acetylpent-4-enoate [130] in 68% yield.[22] The compound was confirmed by NMR and IR techniques.

The alkylation of methyl acetoacetate with 5-bromobut-1-ene using sodium methoxide as base in equimolar equivalents afforded methyl 2-acetylhex-5-enoate [129] (Scheme 2.11) in 55% yield. In a similar manner, the alkylation of methyl acetoacetate with 5-bromopent-1-ene afforded methyl 2-acetylhept-6-enoate [129] in 57% yield.

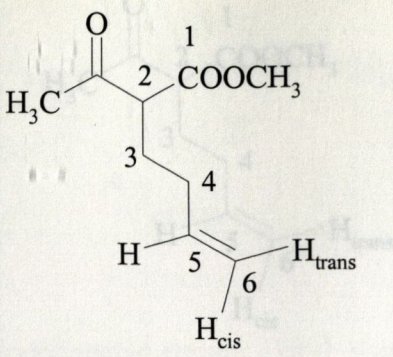


(128)

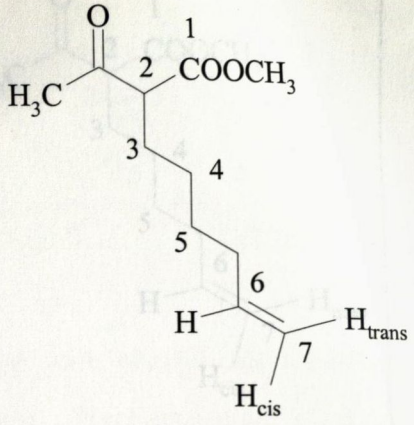


(129)

In 1994, Barby studied the reaction of ethyl acetoacetate with unsaturated alkyl halides by phase-transfer catalysis but it was not explored here.[23] He found that long reaction times caused the degradation of the β-ketoester, while lower temperatures and base concentration reduced the reactivity. We found that reaction times of less than 10 h gave higher yields and fewer impurities with sodium methoxide than with the stronger base, sodium hydride. Both alkylations were stopped after 7 h and worked up to give colourless liquids by fractional distillation under reduced pressure. The compounds were identified by ^{1}H NMR (Table 2.3), ^{13}C NMR (Table 2.4), DEPT, 2-D COSY, and IR spectra.



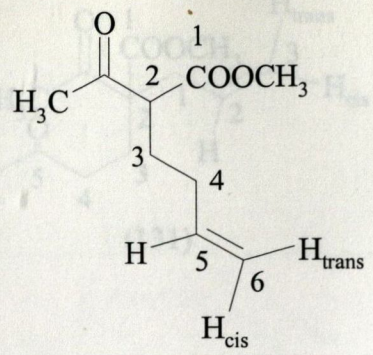
[128]



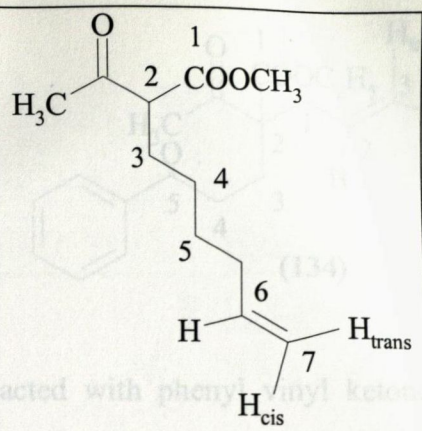
[129]

Hydrogen	δ_H (ppm)	Hydrogen	δ_H (ppm)
ester -CH_3	3.57; s	ester -CH_3	3.71; s
acetyl -CH_3	2.06; s	acetyl -CH_3	2.20; s
H-2	3.33; t; $J_{2,3}$ = 7.0 Hz	H-2	3.41; t; $J_{2,3}$ = 7.5 Hz
H-3	1.78; m;	H-3	1.80-1.86; m
H-4	1.87-1.92; m	H-4	1.32-1.40; m
H-5	5.70; ddt; $J_{5,6trans}$ = 16.7, $J_{5,6cis}$ = 10.0, $J_{5,4}$ = 6.6 Hz	H-5	2.05; q; $J_{5,4}$ = 7.0 $J_{5,6}$ = 7.0 Hz
H-6	4.82-4.90; m	H-6	5.75; ddt; $J_{6,7trans}$ = 17.0, $J_{6,7cis}$ =10.3, $J_{6,5}$ = 6.6 Hz
		H-7	4.90-5.02; m

Table 2.3



[128]



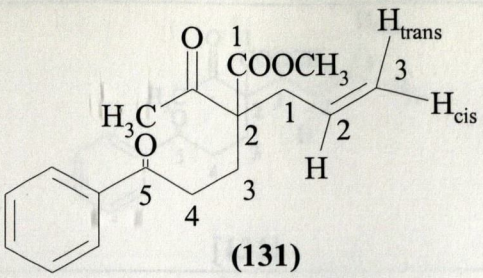
[129]

Carbon	δ_C (ppm)	Carbon	δ_C (ppm)
C-1	169.7	C-1	170.1
C-2	58.1	C-2	59.4
C-3	26.7	C-3	27.5
C-4	30.4	C-4	26.5
C-5	136.6	C-5	33.2
C-6	115.4	C-6	137.6
		C-7	114.9
acetyl C=O	202.3	acetyl C=O	202.8
ester -CH_3	51.8	ester -CH_3	52.2
acetyl -CH_3	28.5	acetyl -CH_3	28.6

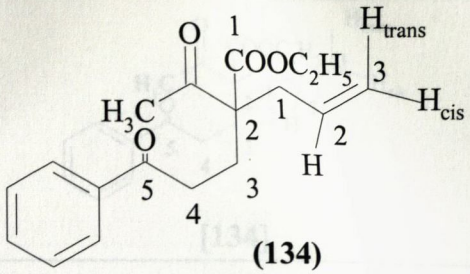
Table 2.4

2.122 Synthesis of diketoesters [131-134]

A mixture of methyl 2-acetylpent-4-enoate [127] and phenyl vinyl ketone was treated with a catalytic amount of sodium methoxide in methanol. The mixture was stirred in an ice bath for 1 h. The reaction was worked up and the solvent removed by rotary evaporator under reduced pressure leaving a viscous brown oil. The oil was fractionally distilled under vacuum to give a viscous yellow oil in 53% yield. The compound was identified by spectroscopic techniques as methyl 2-acetyl-5-oxo-5-phenyl-2-(2-propenyl)pentanoate [134] (Tables 2.5 and 2.6).



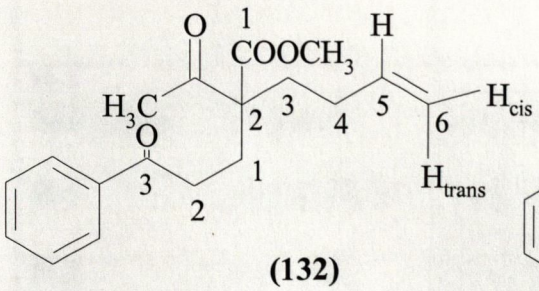
(131)



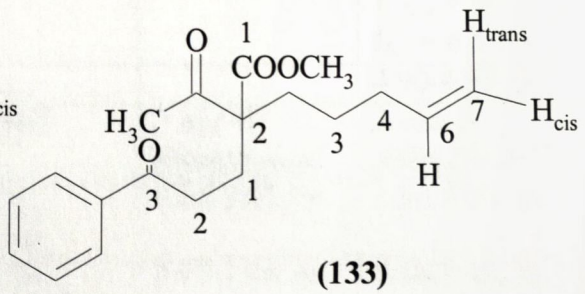
(134)

Ethyl 2-acetylpent-4-enoate [130] was reacted with phenyl vinyl ketone, with a catalytic amount of sodium ethoxide in ethanol. Fractional distillation afforded a viscous yellow oil. The oil was dissolved in hexane/ether (9:1) and cooled to -40°C to give a colourless precipitate (m.p. 48-49°C; 53%), which was filtered off at -40°C. The compound was identified by spectroscopic techniques as ethyl 2-acetyl-5-oxo-2-(2-propenyl)-5-phenylpentanoate [134] (Tables 2.5 and 2.6).

The Michael addition step was repeated with β-ketoesters [128] and [129] (Scheme 2.11) to give methyl 2-acetyl-2-(3-oxo-3-phenylpropyl)hex-5-enoate [132] and methyl 2-acetyl-2-(3-oxo-3-phenylpropyl)hept-6-enoate [133], respectively. Both diketoesters were isolated as viscous oils and identified by spectroscopic techniques (Tables 2.5 and 2.6).

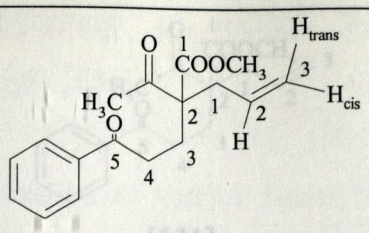


(132)

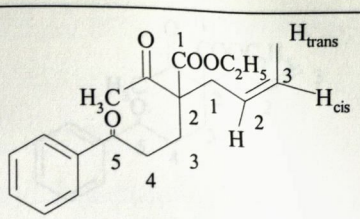


(133)

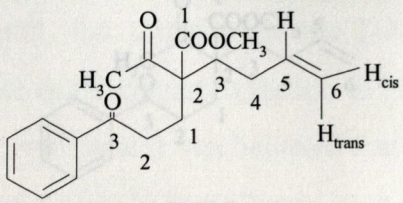
Analysis of the ^{1}H NMR data (Tables 2.5) shows several consistent signals. The ester and acetyl in diketoesters [128-130] remain steady at ≈ δ 3.66 ppm and ≈ δ 2.11 ppm, respectively, while the CH of the olefinic tethered chain shows consistent coupling constants in all esters of $J_{trans} \approx 17$ Hz, $J_{cis} \approx 11$ Hz and the vicinal coupling of the methylene group of ≈ 7 Hz. The ^{13}C NMR data are shown in Table 2.6 and are assigned on the basis of NMR techniques and calculated values. [24]



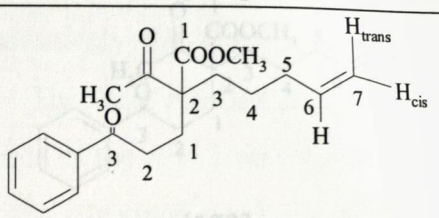
[131]



[134]



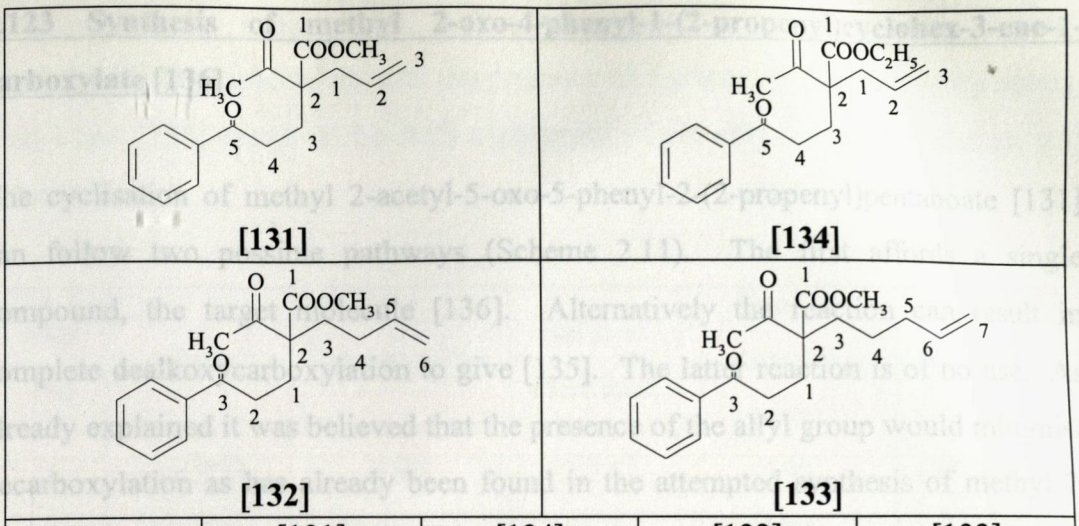
[132]



[133]

	[131]	[134]	[132]	[133]
Hydrogen	δ_H (ppm)	δ_H (ppm)	δ_H (ppm)	δ_H (ppm)
ester -CH_3	3.66; s	1.25; t J = 7.2 Hz	3.67; s	3.67; s
ester -CH_2		4.18; q J = 7.2 Hz		
acetyl -CH_3	2.11; s	2.17; s	2.11; s	2.11; s
H-3	2.22-2.29; m	2.23-2.33; m	1.90-1.94; m	1.82-1.86; m
H-4	2.79-2.89; m	2.82-2.93; m	2.15-2.20; m	1.14-1.28; m
H-5			5.60; ddt; $J_{5,6trans}$ =17.0, $J_{5,6cis}$ = 10.5, $J_{5,4}$ = 6.7 Hz	2.02-2.06; m
H-6			5.01-5.09; m	5.60; ddt; $J_{6,7trans}$ =16.5, $J_{6,7cis}$ = 10.5, $J_{6,5}$ = 6.5 Hz
H-7				4.90-4.98; m
Side-chain	*propenyl*	*propenyl*	*3-oxo-3-phenylpropyl*	*3-oxo-3-phenylpropyl*
H-1	2.60-2.63; m	2.65; d; J = 7 Hz	2.23-2.32; m	2.20-2.30; m
H-2	5.60; ddt; $J_{2,3trans}$=17.2, $J_{2,3cis}$ = 9.9, $J_{2,1}$ = 7.3 Hz	5.61; ddt; $J_{2,3trans}$=17.0, $J_{2,3cis}$ = 10.5, $J_{2,1}$ = 7.1 Hz	2.77-2.86; m	2.78-2.80; m
H-3	5.01-5.11; m	5.06-5.72; m		
Ph-m Ph-p	7.24-7.48; m	7.39-7.57; m	7.38-7.55; m	7.36-7.40; m
Ph-o	7.84-7.88; m	7.89-7.93; m	7.84-7.90; m	7.86-7.88; m

Table 2.5



[131] **[134]**

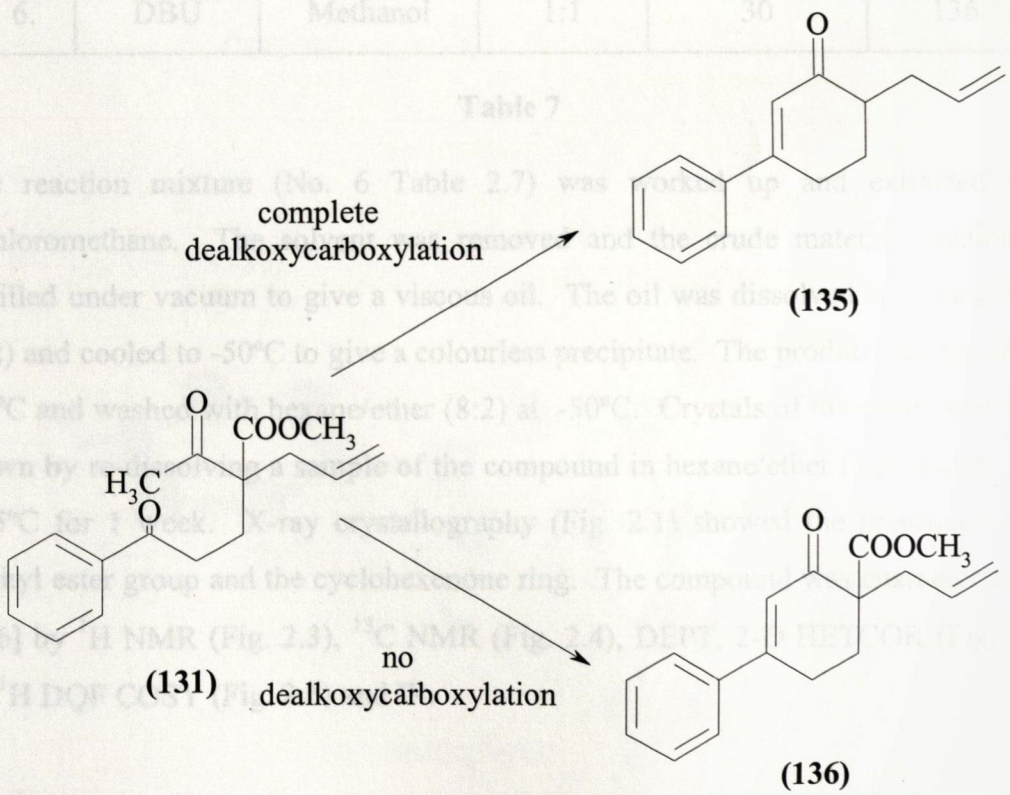
[132] **[133]**

	[131]	[134]	[132]	[133]
Carbon	δ_C (ppm)	δ_C (ppm)	δ_C (ppm)	δ_C (ppm)
acetyl C=O	202.4	204.7	205.1	202.7
acetyl -CH_3	26.6	26.8	26.7	26.6
ester -CH_3	52.1	13.9	52	52
ester -CH_2		61.4		
C-1	172	171.7	172.6	172.4
C-2	62.3	62.5	62.3	62.4
C-3	25.7	25.9	34.4	31.6
C-4	32.9	33.1	30.4	23
C-5	198.6	198.8	130.4	33.5
C-6			117	137.5
C-7				115
Side-chain	*propenyl*	*propenyl*	*3-oxo-3-phenylpropyl*	*3-oxo-3-phenylpropyl*
C-1-	36.7	36.8	25.7	25.7
C-2-	127.8	133.1	32.8	33.1
C-3-	119	119.2	198.6	198.5
Ph-ipso	136.4	136.6	136.4	136.4
Ph-o	127.8	128	127.8	127.7
Ph-m	128.4	128.6	128.4	128.3
Ph-p	131.9	132	131.9	132.8

Table 2.6

2.123 Synthesis of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]

The cyclisation of methyl 2-acetyl-5-oxo-5-phenyl-2-(2-propenyl)pentanoate [131] can follow two possible pathways (Scheme 2.11). The first affords a single compound, the target molecule [136]. Alternatively the reaction can result in complete dealkoxycarboxylation to give [135]. The latter reaction is of no use. As already explained it was believed that the presence of the allyl group would minimise decarboxylation as has already been found in the attempted synthesis of methyl 2-oxo-4-phenylcyclohex-3-ene-1-carboxylate [112] (Scheme 2.4). Of course the reaction can give rise to a mixture of [135] and [136].



Scheme 2.12

A series of experiments was conducted to obtain the target molecule. The reaction conditions were optimised to find the minimum temperature and time combined with a suitable solvent and base to give a homogenous product (Table 2.7). All

experiments were followed by TLC and stopped after all the starting material reacted. All experiments showed the presence of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135] except in the sixth experiment where only the target molecule was detected.

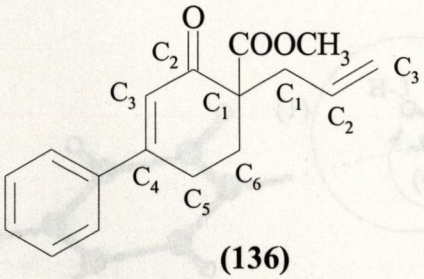
Expt. No.	Base	Solvent/reflux	Ratio of ester:base	Time of Reaction (min)	Product(s)
1.	$NaOCH_3$	THF	2.2:1	180	135 + 136
2.	$NaOCH_3$	Methanol	6.1:1	180	135 + 136
3.	$NaOCH_3$	Methanol	6.1:1	120	135 + 136
4.	$NaOCH_3$	Methanol	1:1	30	135 + 136
5.	DBU	THF	1:1	180	135 + 136
6.	DBU	Methanol	1:1	30	136

Table 7

The reaction mixture (No. 6 Table 2.7) was worked up and extracted with dichloromethane. The solvent was removed and the crude material fractionally distilled under vacuum to give a viscous oil. The oil was dissolved in hexane/ether (8:2) and cooled to -50°C to give a colourless precipitate. The product was filtered at -50°C and washed with hexane/ether (8:2) at -50°C. Crystals of the compound were grown by re-dissolving a sample of the compound in hexane/ether (8:2) and cooling to 5°C for 1 week. X-ray crystallography (Fig. 2.1) showed the presence of the methyl ester group and the cyclohexenone ring. The compound was characterised as [136] by ^{1}H NMR (Fig. 2.3), ^{13}C NMR (Fig. 2.4), DEPT, 2-D HETCOR (Fig. 2.5), ^{1}H-^{1}H DQF COSY (Fig. 2.6) and IR.

The ^{1}H NMR (Fig. 2.3) identified the olefinic peaks of H-3 at δ 6.67 ppm and the characteristic allyl spitting patterns for H-2-propenyl (ddt) and H-3-propenyl (m) at δ 5.80 and δ 5.12-5.17 ppm respectively. The IR spectrum showed three distinctive peaks 1640, 1671, and 1728 cm^{-1} corresponding to the enone alkene, enone carbonyl, and the ester carbonyl respectively. The 2-D HETCOR (Fig. 2.5) spectrum identified six protons corresponding to three methylene groups. The Carbon peak at δ 29.4

ppm showed correlation to protons in the region δ 2.07-2.63 and δ 2.57-2.63 ppm, while the Carbon peak at δ 25.3 ppm showed correlation to protons in the region δ 2.74-2.81 and δ 2.90-2.99 ppm. The methylene carbon at δ 38.4 ppm showed correlation to two protons in the region δ 2.57-2.63 and δ 2.74-2.81ppm. This carbon was identified as C-1-propenyl from the 2-D ^{1}H-^{1}H DQFCOSY (Fig. 2.6), which showed coupling between these protons and the olefinic protons on the tethered carbon chain. The analysis of the spectrum indicated that H-1a-propenyl (δ 2.74-2.81 ppm) is further downfield than H-1b-propenyl (δ 2.57-2.63 ppm). This is due to the position of the H-1a-propenyl, which is oriented to experience an additional deshielding effect of the carbonyl group in the ring.



(136)

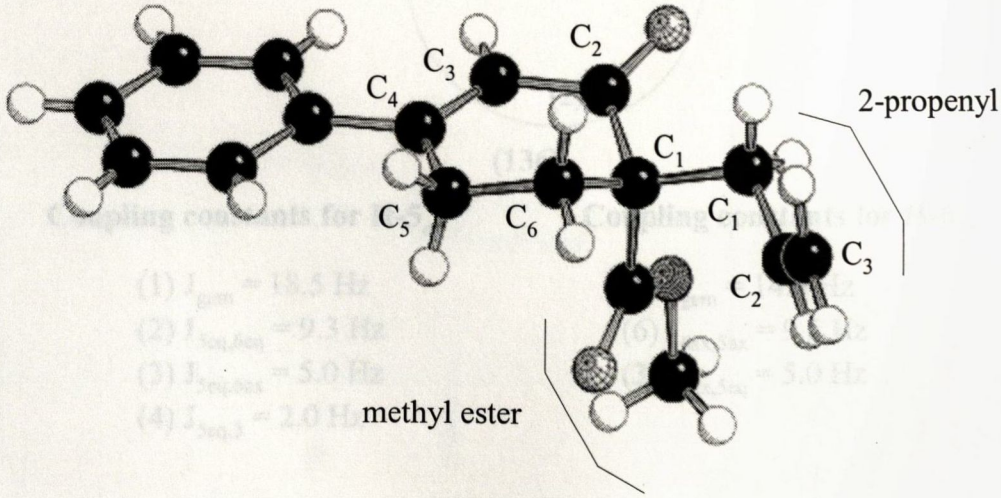
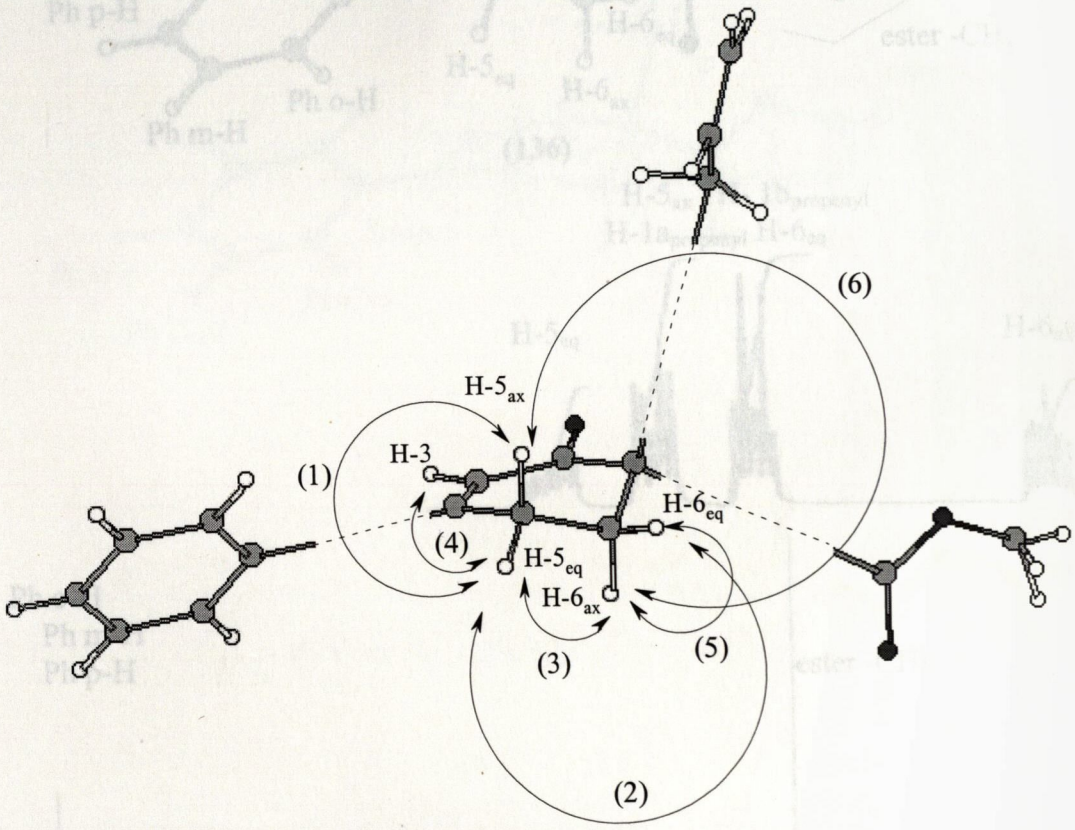


Fig. 2.1

The 2-D ^{1}H-^{1}H DQFCOSY (Fig. 2.6) showed long range coupling between H-3 and H-5_{eq}, J = 2 Hz (δ 2.94 ppm). Therefore H-5_{ax} is located at δ 2.74-2.81 ppm (Fig. 2.5). The protons H-6_{ax} and H-6_{eq} were assigned based on coupling constants analysis (Fig. 2.2). The remaining proton and carbon peaks were assigned by comparison to the corresponding β-ketoester [127] and diketoester [131] (Tables 2.5 and 2.6) and are summarised in Table 2.8.



(136)

Coupling constants for H-5_{eq}

(1) J_{gem} = 18.5 Hz
(2) $J_{5eq,6eq}$ = 9.3 Hz
(3) $J_{5eq,6ax}$ = 5.0 Hz
(4) $J_{5eq,3}$ = 2.0 Hz

Coupling constants for H-6_{ax}

(5) J_{gem} = 14.0 Hz
(6) $J_{6ax,5ax}$ = 9.5 Hz
(3) $J_{6ax,5eq}$ = 5.0 Hz

Fig. 2.2

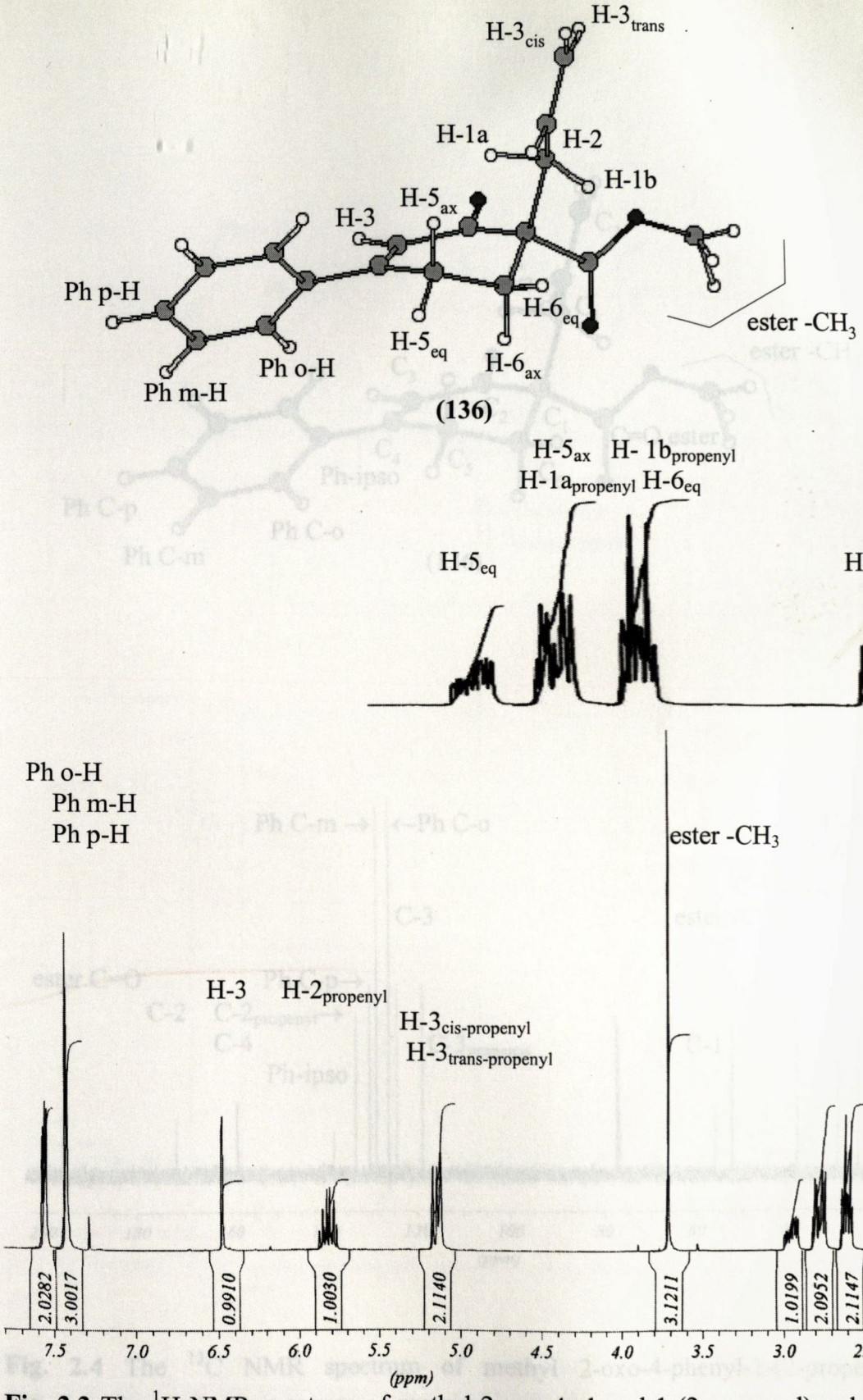
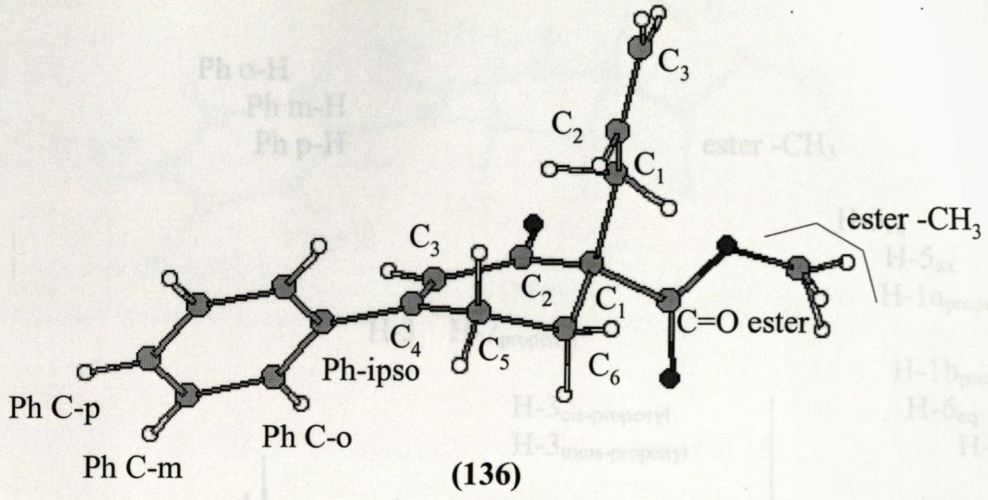


Fig. 2.3 The ^{1}H NMR spectrum of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136].



(136)

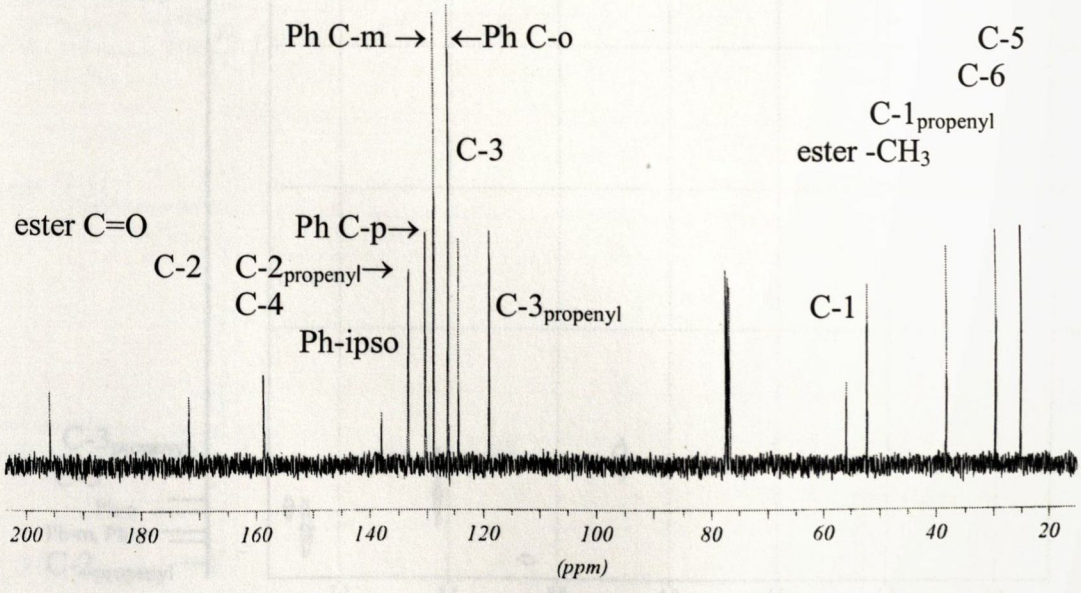


Fig. 2.4 The ^{13}C NMR spectrum of methyl 2-oxo-4-phenyl-1-(2-propenyl)-cyclohex-3-ene-1-carboxylate [136].

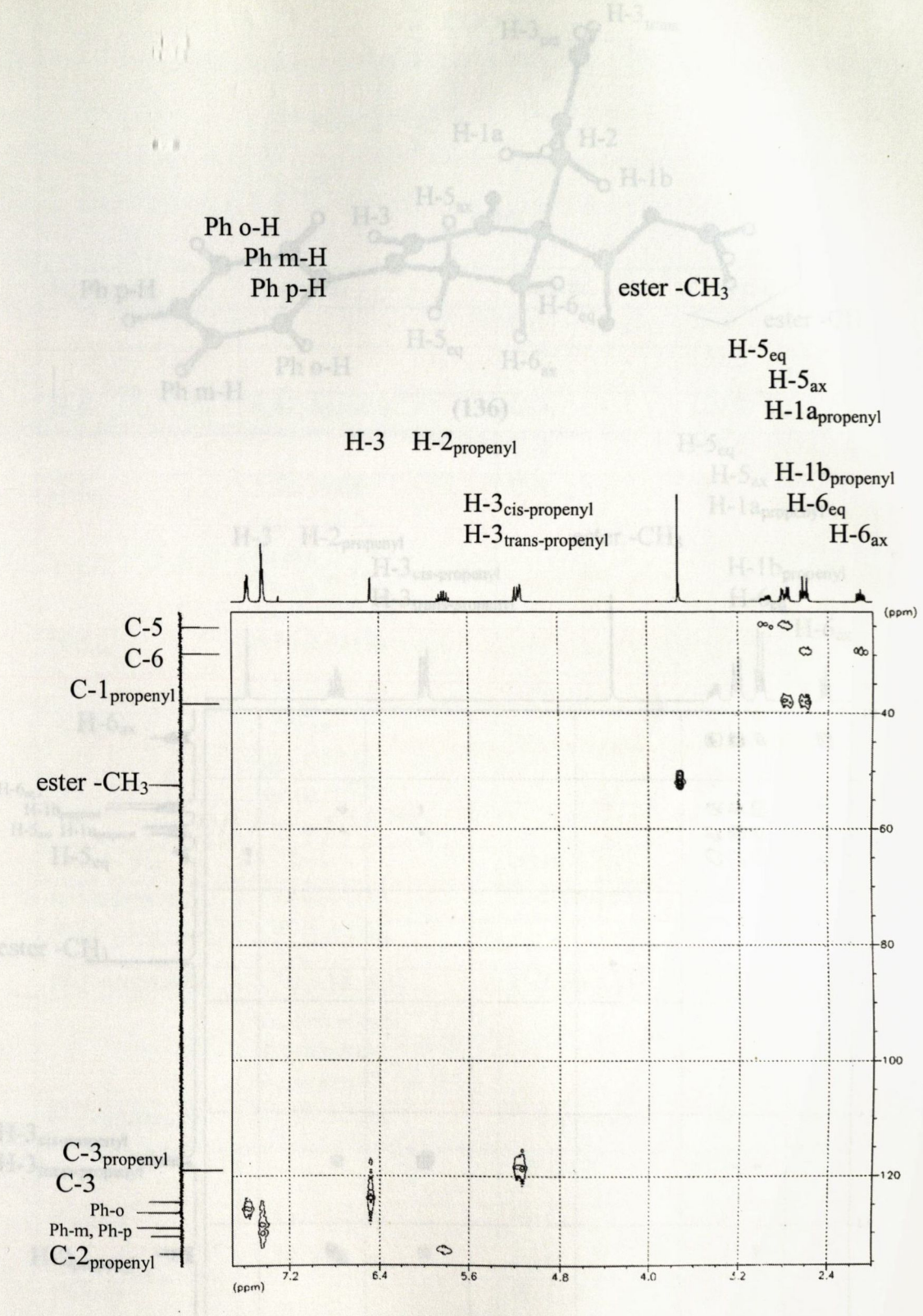


Fig. 2.5 The ^{1}H-^{13}C HETCOR NMR spectrum of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136].

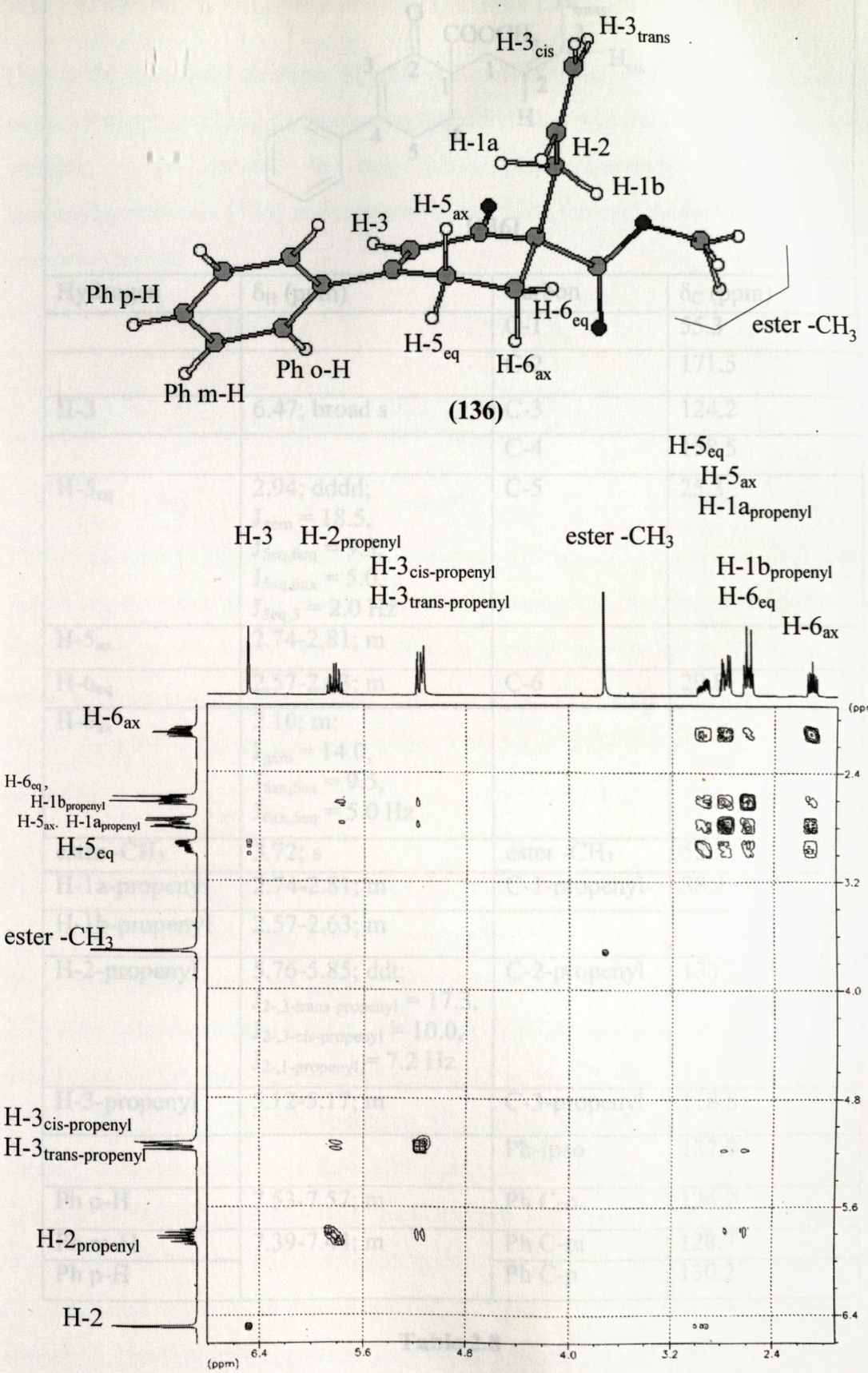
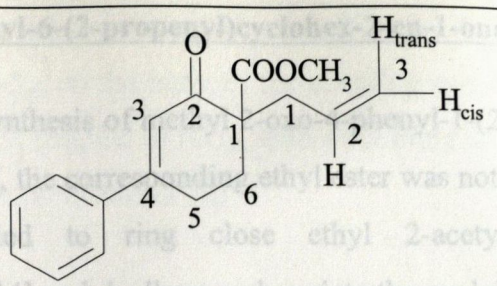


Fig. 2.6 The ^{1}H-^{1}H DQF COSY spectrum of methyl 2-oxo-4-phenyl-1-(2-propenyl)-cyclohex-3-ene-1-carboxylate [136].



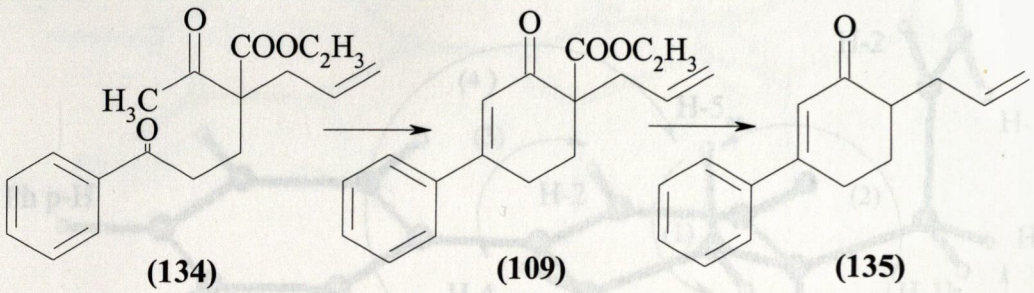
[136]

Hydrogen	δ_H (ppm)	Carbon	δ_C (ppm)
		C-1	55.3
		C-2	171.5
H-3	6.47; broad s	C-3	124.2
		C-4	158.5
H-5_{eq}	2.94; dddd; J_{gem} = 18.5, $J_{5eq,6eq}$ = 9.3, $J_{5eq,6ax}$ = 5.0, $J_{5eq,3}$ = 2.0 Hz	C-5	25.3
H-5_{ax}	2.74-2.81; m		
H-6_{eq}	2.57-2.63; m	C-6	29.8
H-6_{ax}	2.10; m; J_{gem} = 14.0, $J_{6ax,5ax}$ = 9.5, $J_{6ax,5eq}$ = 5.0 Hz		
ester -CH_3	3.72; s	ester -CH_3	52.3
H-1a-propenyl	2.74-2.81; m	C-1-propenyl	38.4
H-1b-propenyl	2.57-2.63; m		
H-2-propenyl	5.76-5.85; ddt; $J_{2-,3\text{-trans-propenyl}}$ = 17.3, $J_{2-,3\text{-cis-propenyl}}$ = 10.0, $J_{2-,1\text{-propenyl}}$ = 7.2 Hz	C-2-propenyl	133.2
H-3-propenyl	5.12-5.17; m	C-3-propenyl	118.8
		Ph-ipso	137.9
Ph o-H	7.53-7.57; m	Ph C-o	126.2
Ph m-H	7.39-7.44; m	Ph C-m	128.7
Ph p-H		Ph C-p	130.2

Table 2.8

2.124 Synthesis 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135]

Due to the successful synthesis of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136], the corresponding ethyl ester was not required (as explained earlier). We decided to ring close ethyl 2-acetyl-5-oxo-5-phenyl-2-(2-propenyl)pentanoate [134] and dealkoxycarboxylate the cyclohexenone in a two step one-pot reaction.

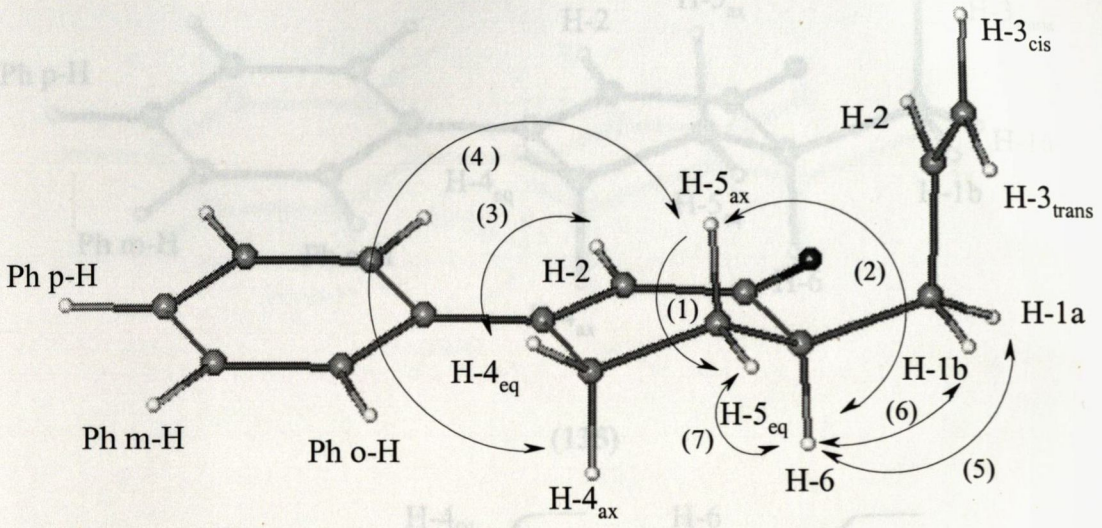


(134) **(109)** **(135)**

The diketoester [131] was treated with sodium hydride and refluxed in THF for 1 h. Following the work up the crude material was fractionally distilled *in vacuo* to give a viscous yellow oil, which was dissolved in acetone and cooled to -75°C to give a colourless precipitate. The product was filtered at -75°C and washed with acetone at -75°C to give a colourless powder in 70% yield with a sharp melting point of 48-49°C.

The ^{1}H NMR (Fig. 2.8) showed the olefinic peaks of H-2 (δ 6.43 ppm), H-2-propenyl (δ 5.80-5.99 ppm) and H-3-propenyl (δ 5.07-5.14 ppm). The irradiation of the phenyl ortho-hydrogens gave an nOe difference at H-2 and in the region δ 2.78-2.79 ppm, which can only be H-4_{eq} (Fig. 2.9). The identification of H-4_{eq} was further confirmed by the long range coupling to H-2 in the ^{1}H-^{1}H TOCSY spectrum (Fig. 2.10). The ^{1}H-^{1}H TOCSY spectrum (Fig. 2.10) showed that H-2-propenyl was coupled to H-1a-propenyl (δ 2.68-2.77 ppm) and H-1b-propenyl (δ 2.18-2.30 ppm). The 2-D HETCOR spectrum (Fig. 2.11) showed both regions correlated to the same carbon at δ 33.7 ppm. The decoupled spectrum (Fig. 2.12) showed that irradiation of H-2-propenyl resulted in simplification of signals for H-1a-propenyl and H-1b-propenyl. The H-6 proton was assigned to δ 2.39-2.45 ppm and was correlated to the carbon at δ 45 ppm (Fig. 2.11). Further analysis of the HETCOR (Fig. 2.11) showed it was difficult to assign the protons of H-4_{ax}, H-5_{eq}, and H-5_{ax} as their corresponding

carbons (δ 27.36 and 27.43 ppm) were very close (Fig. 2.13). The region δ 1.84-1.93 ppm was assigned to H-5_{ax} on the basis of the coupling constants of H-6 and H-5_{ax}, which showed that H-6 is coupled to H-5_{ax} with a coupling constant of 11.5 Hz. The coupling constants are summarised in Fig. 2.7.

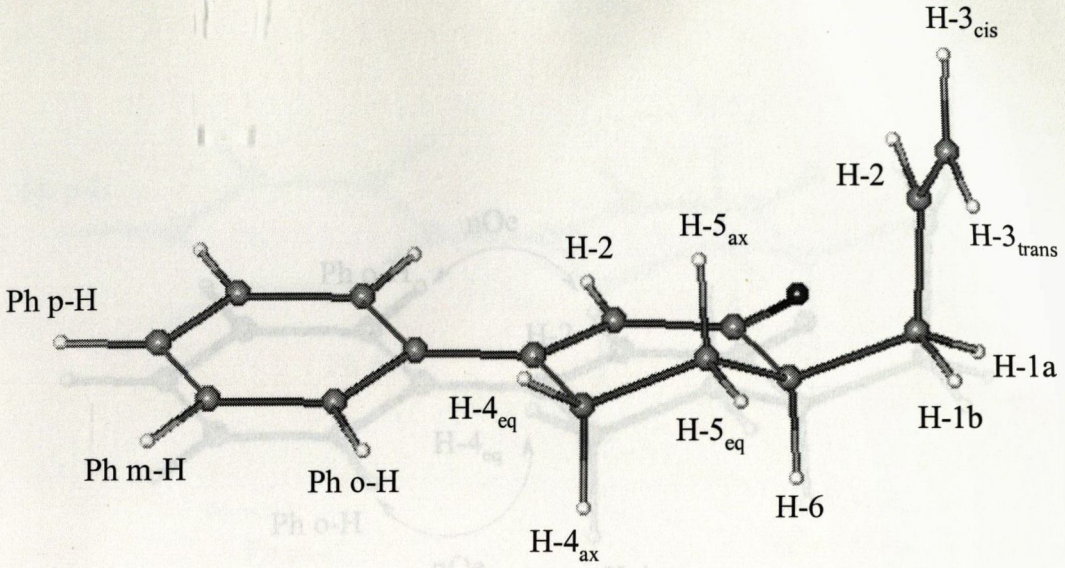


(135)

Coupling constants for H-5_{ax}	**Coupling constants for H-6**
(1) J_{gem} = 13.5 Hz	(2) $J_{6,5ax}$ = 11.5 Hz
(2) $J_{5ax,6}$ = 11.4 Hz	(5) $J_{6,1a-}$ = 8.8 Hz
(3) $J_{5ax,4ax}$ = 9.3 Hz	(6) $J_{6,1b-}$ = 4.4 Hz
(4) $J_{5ax,4eq}$ = 5.3 Hz	(7) $J_{6,5eq}$ = 4.5 Hz

Fig. 2.7

The decoupled spectrum (Fig. 2.14) showed that irradiation of H-6 resulted in the simplification of the signal of H-5_{ax} (δ 1.84-1.93 ppm), H-1b-propenyl, H-5_{eq} (δ 2.18-2.30 ppm) and H-1a-propenyl (δ 2.68-2.77 ppm). There was no simplification of the signal for the region δ 2.78-2.89 ppm indicating that H-4_{ax} resonates in this region. Further confirmation comes from the decoupling of H-5_{ax} (Fig. 2.14) (δ 1.84-1.93 ppm), which showed peak simplification at H-6 (δ 2.42 ppm), H-5_{eq} (δ 2.18-2.30 ppm) and H-4_{ax} and H-4_{eq} (δ 2.78-2.89 ppm). The remaining signals where assigned from analysis of the 2-D HETCOR expanded for the region δ 5.0-7.6 ppm (Fig. 2.15) and comparison to β-ketoesters [127-130] and diketoesters [131-134]. The hydrogen and carbon peaks are summarised in Table 2.9



(135)

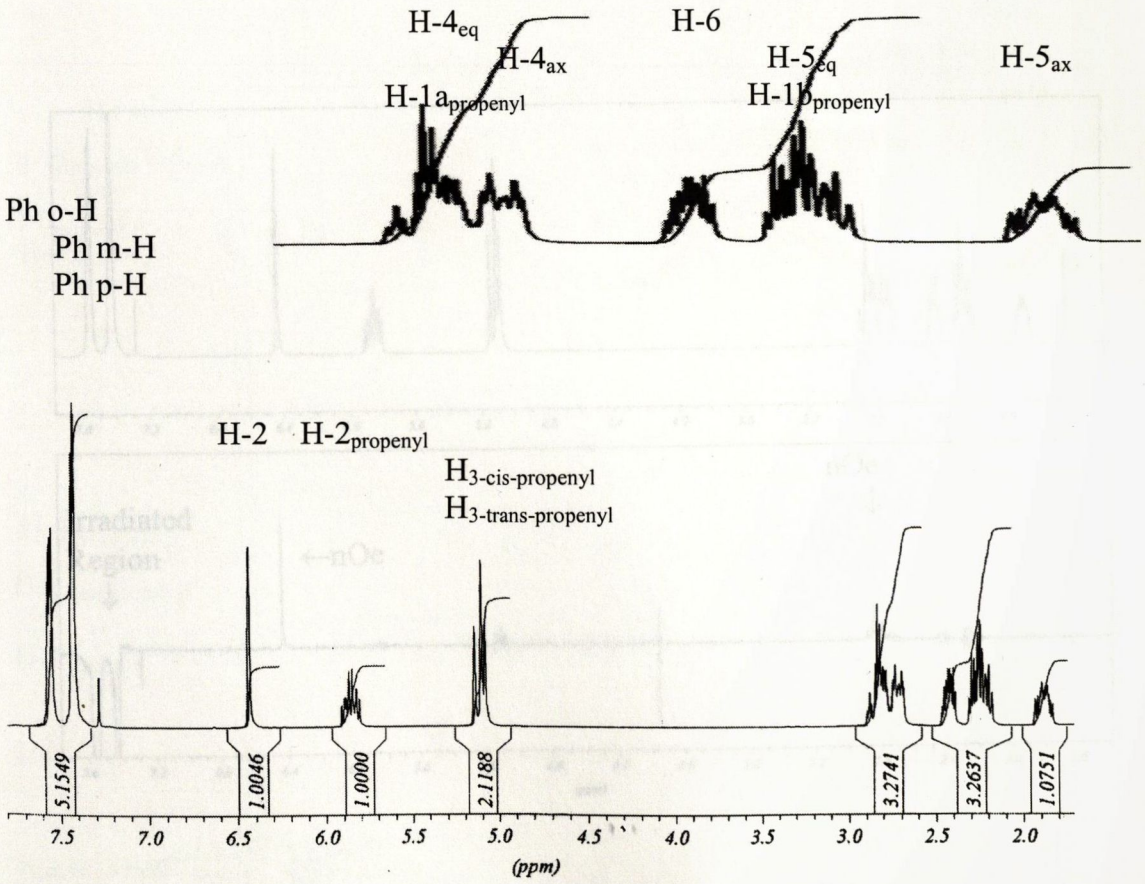
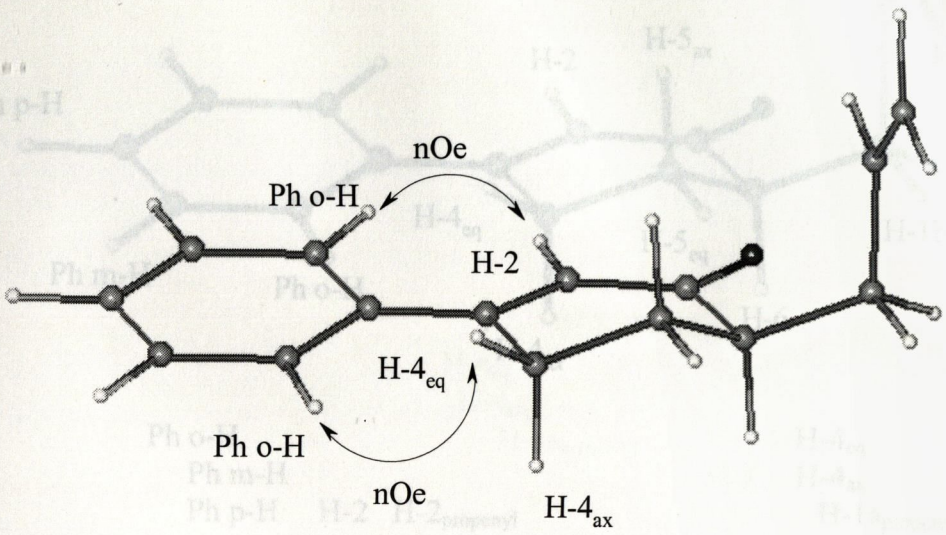


Fig. 2.8 The ^{1}H NMR spectrum of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135].



(135)

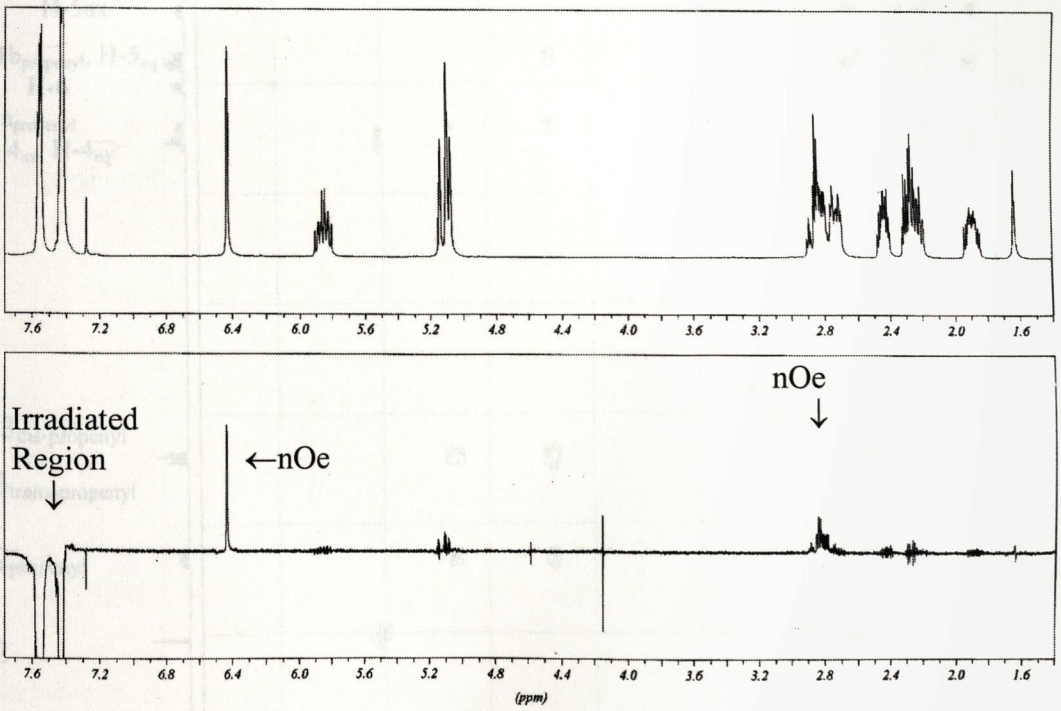


Fig. 2.9 The nOe difference spectrum of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135] for the irradiation of the ortho-hydrogens.

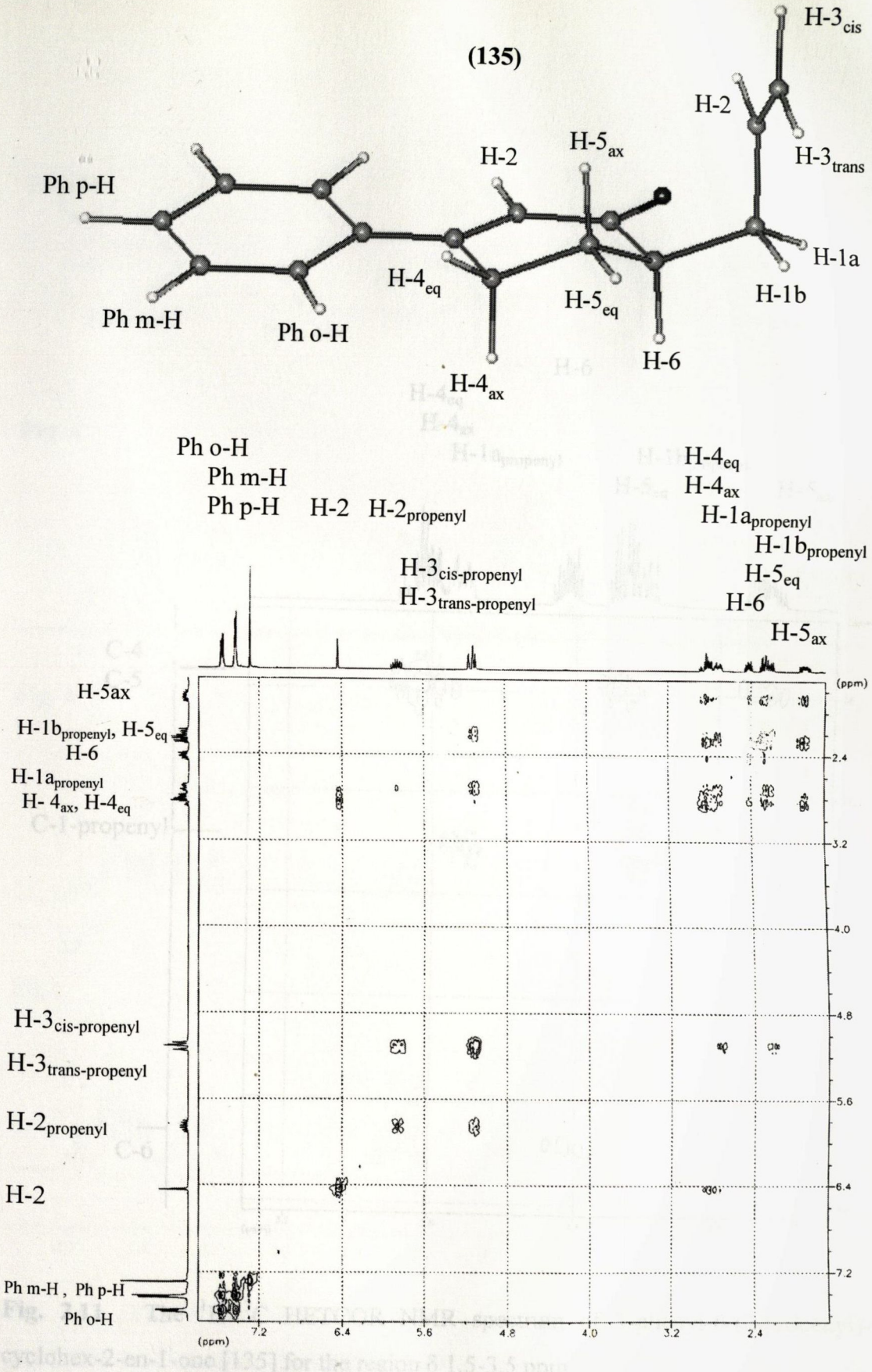


Fig. 2.10 The ^{1}H-^{1}H TOCSY spectrum of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135].

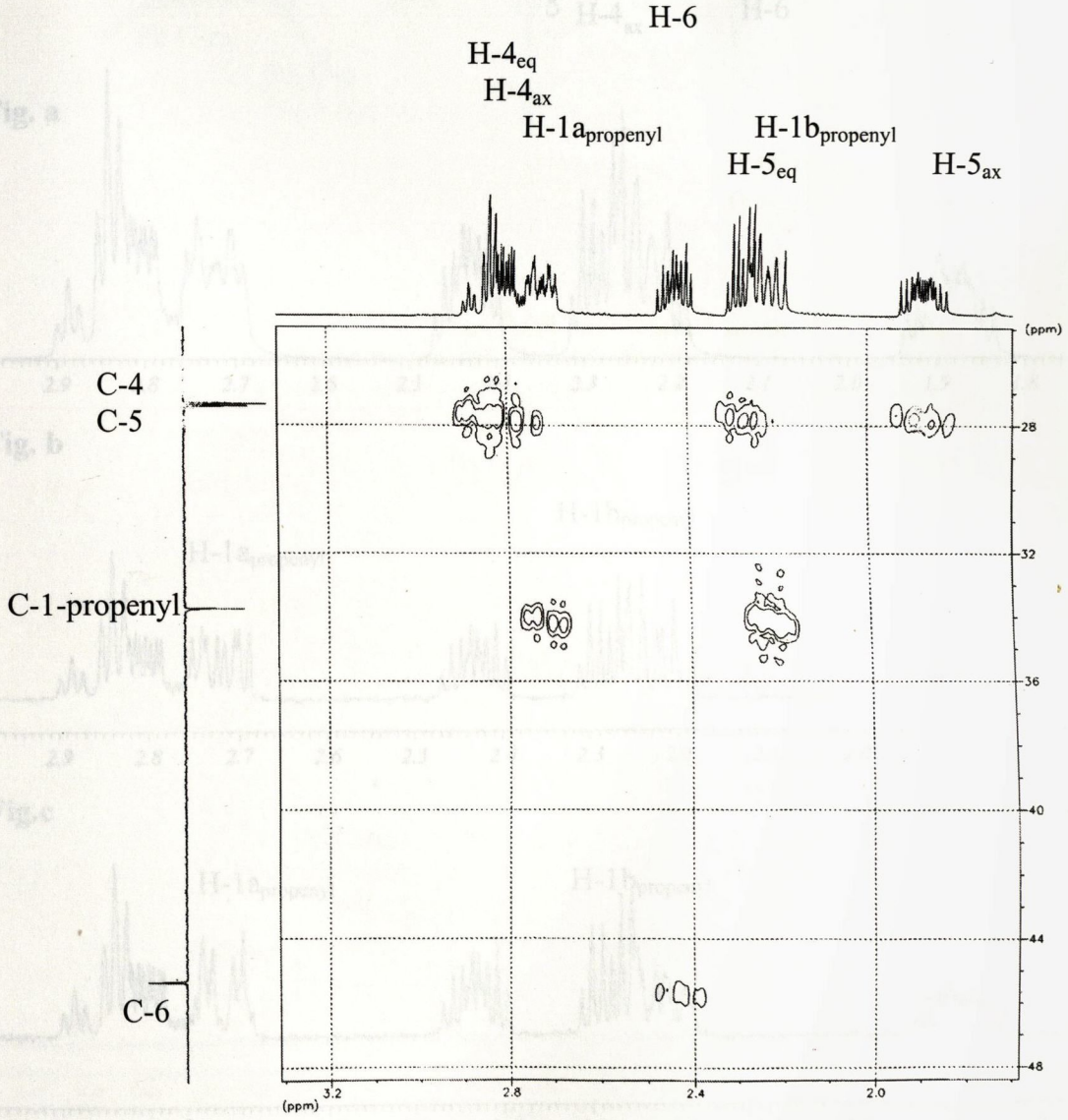


Fig. 2.11 The ^{1}H-^{13}C HETCOR NMR spectrum of 3-phenyl-6-(2-propenyl)-cyclohex-2-en-1-one [135] for the region δ 1.5-3.5 ppm.

(135)

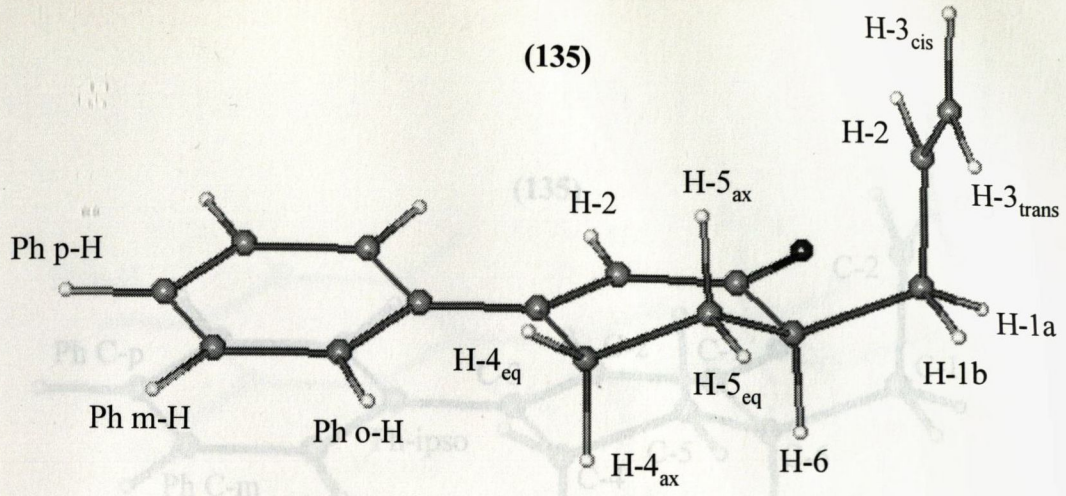


Fig. a

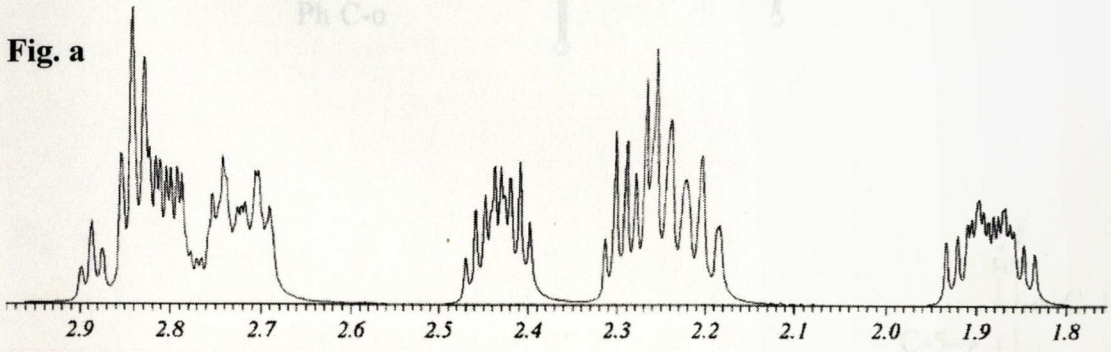


Fig. b

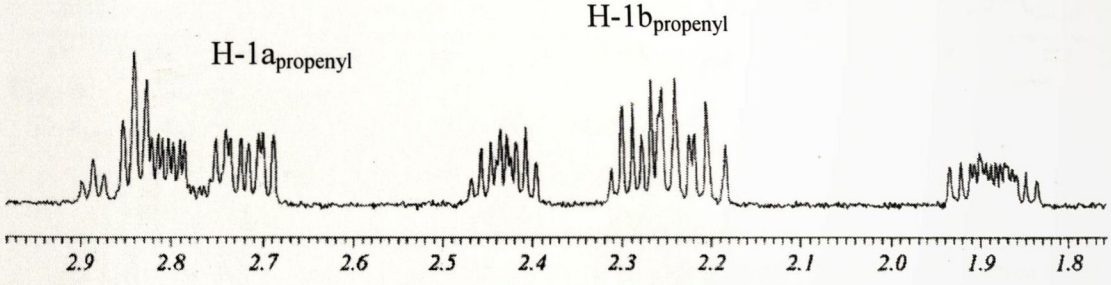


Fig.c

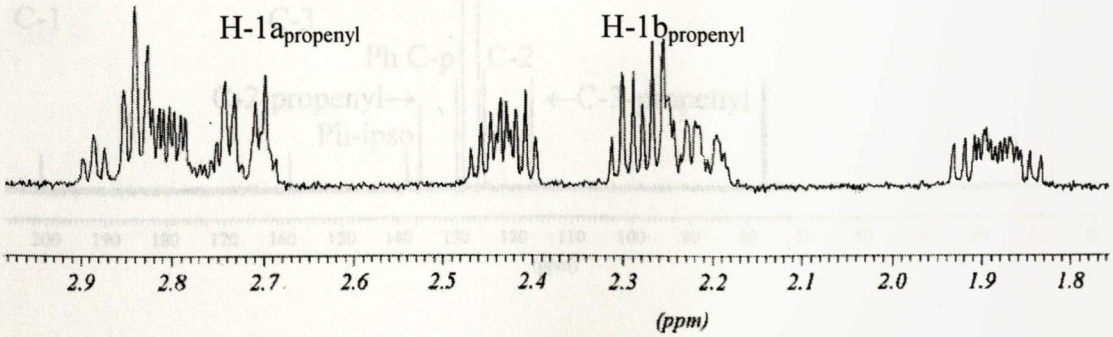
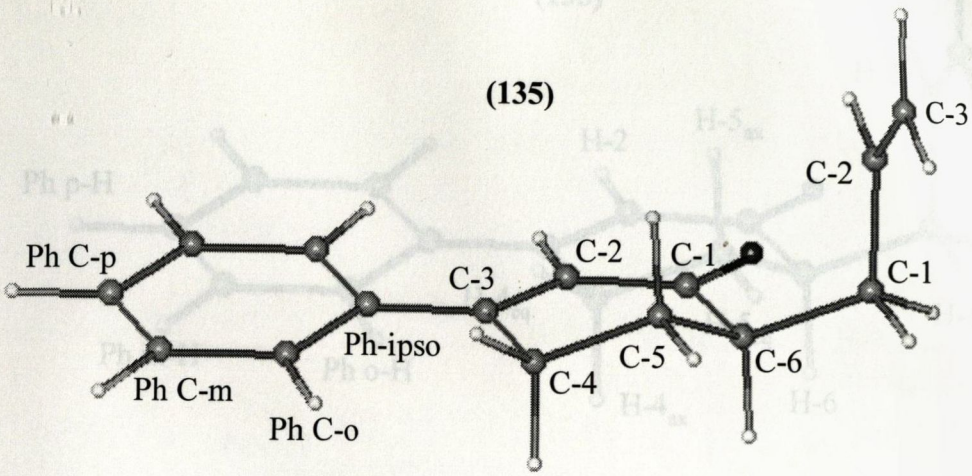
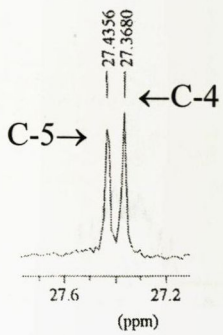


Fig. 2.12 The ^{1}H decoupled spectra of 3-phenyl-6-(2-propenyl)cyclohex-2-ene-1-one [135] showing peak simplification for H-1a-propenyl and H-1b-propenyl. **Fig. a**: reference NMR. **Fig. b**: decoupled at H-3-propenyl. **Fig. c**: decoupled at H-2-propenyl.





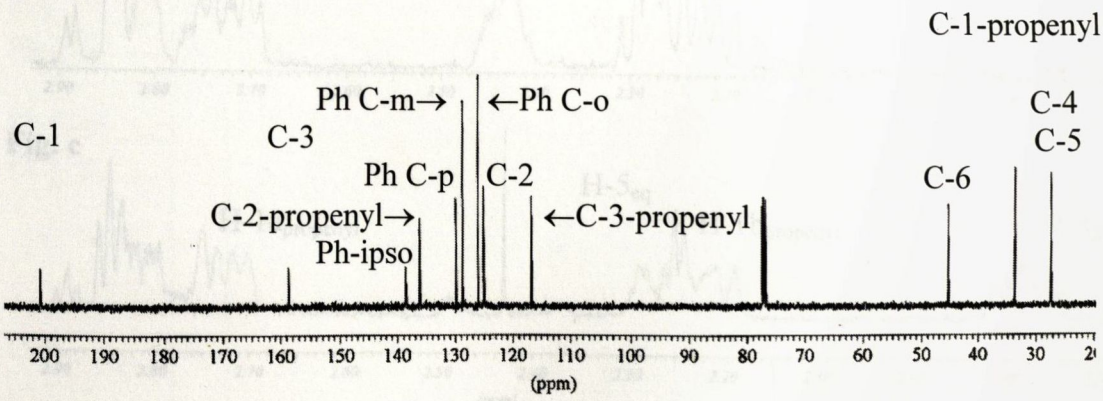


Fig. 2.13 The ^{13}C NMR spectrum of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135].

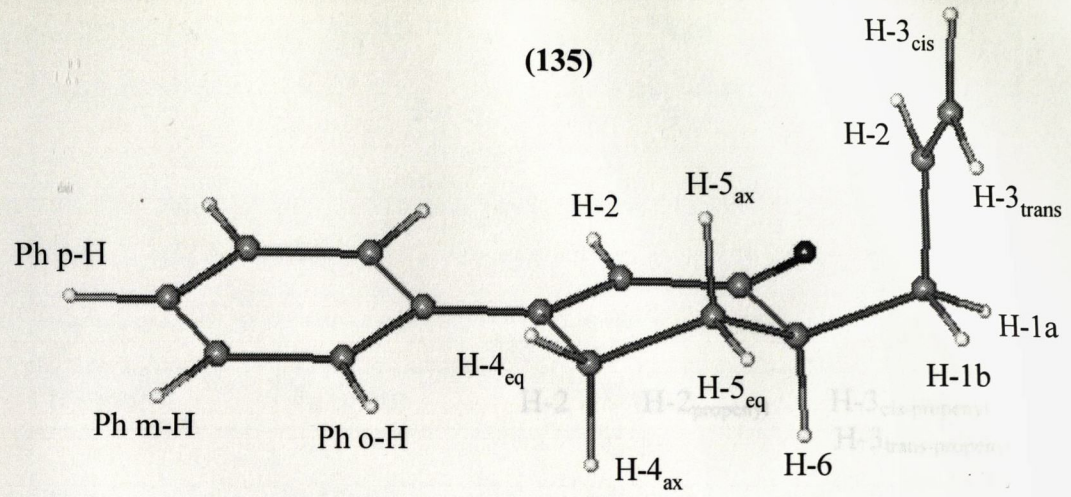


Fig. a

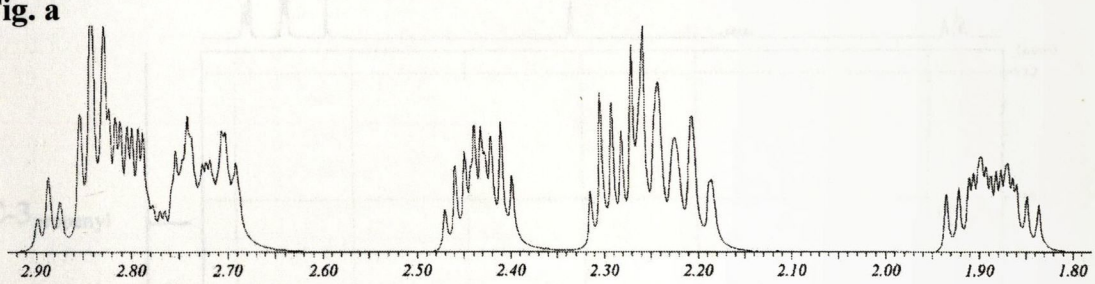


Fig. b

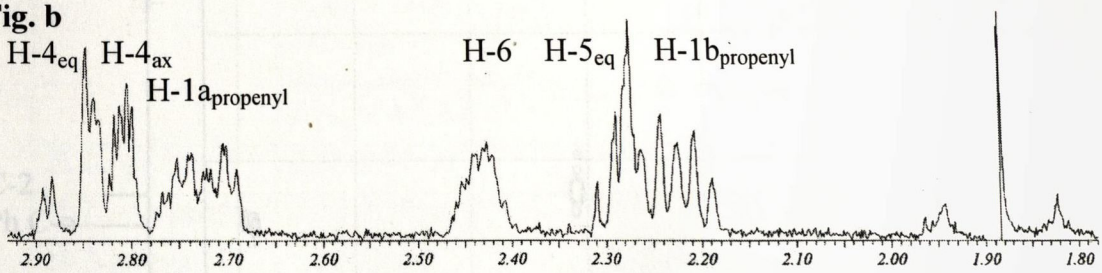


Fig. c

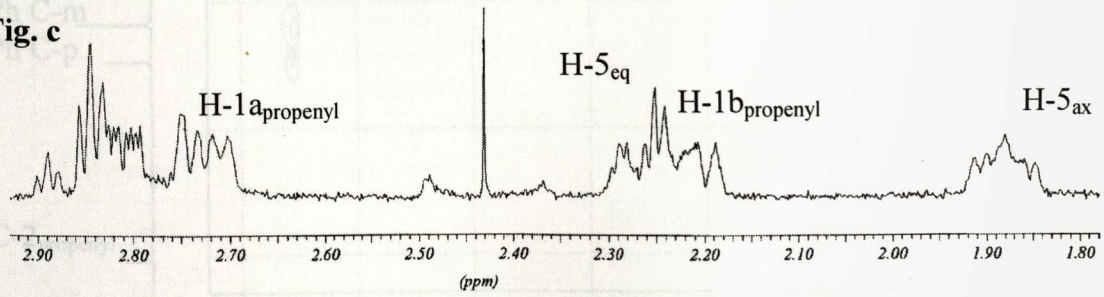


Fig. 2.14 The ^{1}H decoupled spectra of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135] showing peak simplification. **Fig. a**: reference NMR. **Fig b**: decoupled at $H\text{-}5_{ax}$. **Fig c**: decoupled at H-6.

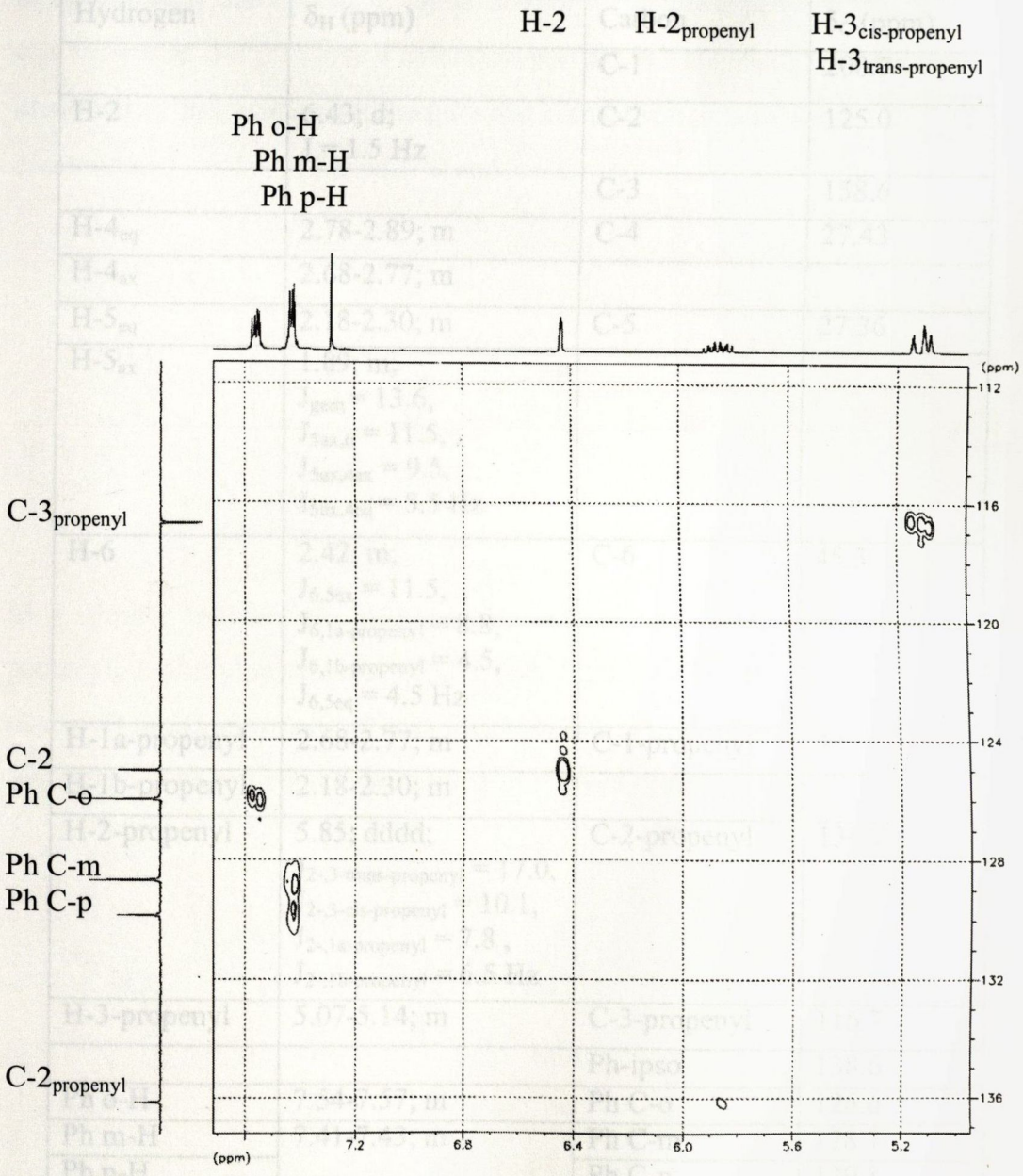
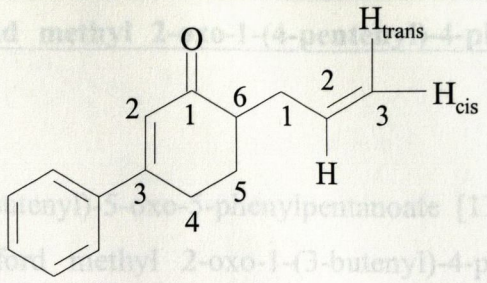


Fig. 2.15 The ^{1}H-^{13}C HETCOR NMR spectrum of 3-phenyl-6-(2-propenyl)-cyclohex-2-en-1-one [135] for the region δ 5.0-7.6 ppm.



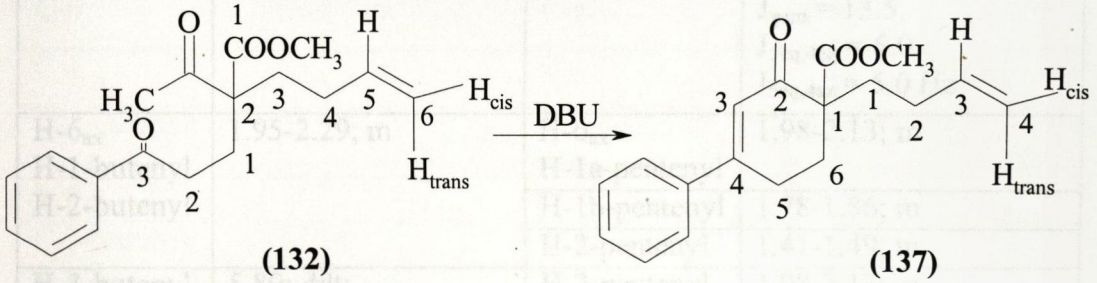
[135]

Hydrogen	δ_H (ppm)	Carbon	δ_C (ppm)
		C-1	200.7
H-2	6.43; d; J = 1.5 Hz	C-2	125.0
		C-3	158.6
$H\text{-}4_{eq}$	2.78-2.89; m	C-4	27.43
$H\text{-}4_{ax}$	2.68-2.77; m		
$H\text{-}5_{eq}$	2.18-2.30; m	C-5	27.36
$H\text{-}5_{ax}$	1.89; m; J_{gem} = 13.6, $J_{5ax,6}$ = 11.5, $J_{5ax,4ax}$ = 9.5, $J_{5ax,4eq}$ = 5.5 Hz		
H-6	2.42; m; $J_{6,5ax}$ = 11.5, $J_{6,1a\text{-propenyl}}$ = 8.8, $J_{6,1b\text{-propenyl}}$ = 4.5, $J_{6,5eq}$ = 4.5 Hz	C-6	45.3
H-1a-propenyl	2.68-2.77; m	C-1-propenyl	33.7
H-1b-propenyl	2.18-2.30; m		
H-2-propenyl	5.85; dddd; $J_{2\text{-},3\text{-trans-propenyl}}$ = 17.0, $J_{2\text{-},3\text{-cis-propenyl}}$ = 10.1, $J_{2\text{-},1a\text{-propenyl}}$ = 7.8 , $J_{2\text{-},1b\text{-propenyl}}$ = 6.5 Hz	C-2-propenyl	136.1
H-3-propenyl	5.07-5.14; m	C-3-propenyl	116.7
		Ph-ipso	138.6
Ph o-H	7.54-7.57; m	Ph C-o	126.6
Ph m-H	7.41-7.43; m	Ph C-m	128.7
Ph p-H		Ph C-p	129.8

Table 2.9

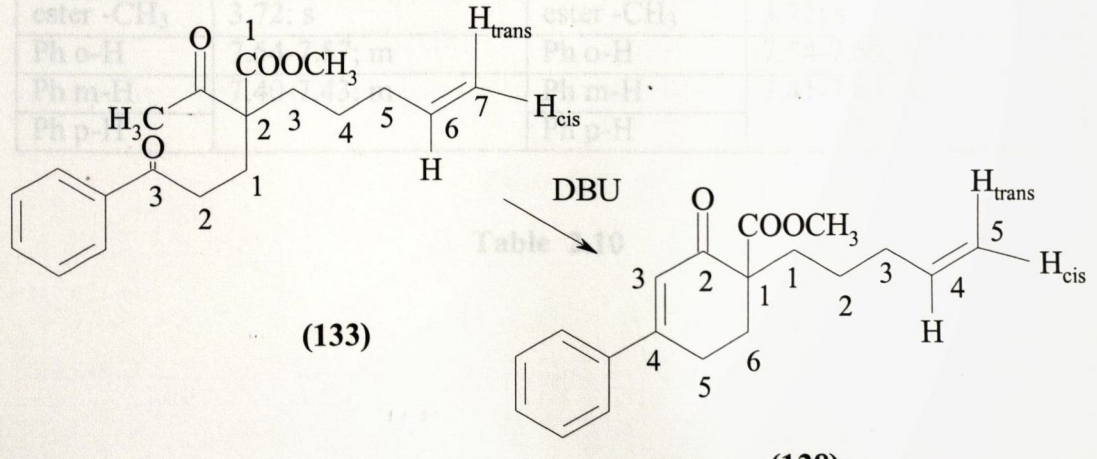
2.125 Synthesis of methyl 2-oxo-1-(3-butenyl)-4-phenylcyclohex-3-ene-1-carboxylate [137] and methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138]

Methyl 2-acetyl-2-(3-butenyl)-5-oxo-5-phenylpentanoate [132] was cyclised using DBU as base to afford methyl 2-oxo-1-(3-butenyl)-4-phenylcyclohex-3-ene-1-carboxylate [137]. The reaction was worked up as before and the distillate dissolved in hexane/ether and cooled to -50°C to give a colourless precipitate. The product was filtered at -50°C to give a colourless powder in 52% yield. The compound was identified by spectroscopic techniques and comparison to β-ketoesters [127-130] and diketoesters [131-134] (Tables 2.10 and 2.11).

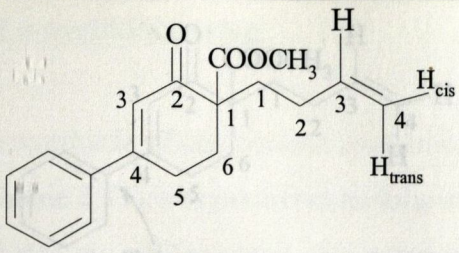


(132) **(137)**

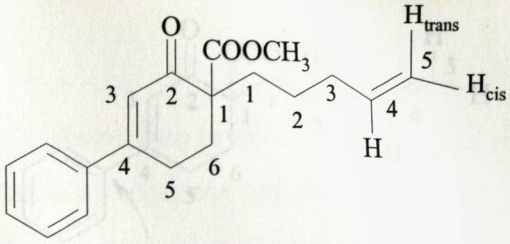
In a similar manner, the condensation reaction of methyl 2-acetyl-5-oxo-2-(4-pentenyl)-5-phenylpentanoate [133] with DBU afforded methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138] as a colourless powder in 50% yield. The compound was fully characterised (Tables 2.10 and 2.11).



(133) **(138)**



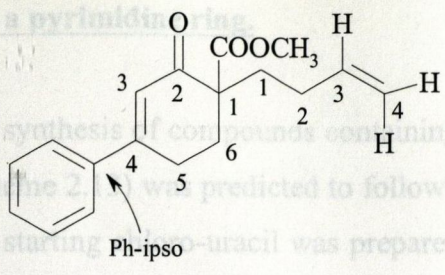
[137]



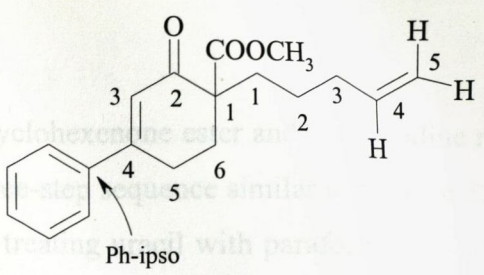
[138]

Hydrogen	δ_H (ppm)	Hydrogen	δ_H (ppm)
H-3	6.45; s	H-3	6.46; s
H-5_{eq}	2.90-2.99; m	H-5_{eq}	2.91-2.99; m
H-5_{ax}	2.75-2.81; m	H-5_{ax}	2.76; dt J_{gem} = 18.5, $J_{4ax,5ax}$ = 5.0, $J_{4ax,5eq}$ = 5.0 Hz
H-6_{eq}	2.58-2.64; m	H-6_{eq}	2.64; dt; J_{gem} = 13.5, $J_{5eq,4eq}$ = 5.0, $J_{5eq,4az}$ = 5.0 Hz
H-6_{ax} H-1-butenyl H-2-butenyl	1.95-2.29; m	H-6_{ax} H-1a-pentenyl	1.98-2.13; m
		H-1b-pentenyl	1.78-1.86; m
		H-2-pentenyl	1.41-1.49; m
H-3-butenyl	5.80; ddt; $J_{3-,4\text{-trans-butenyl}}$ = 17.1, $J_{3-,4\text{-cis-butenyl}}$ = 10.0, $J_{3-,2\text{-butenyl}}$ = 7.0 Hz	H-3-pentenyl	1.98-2.13; m
		H-4-pentenyl	5.81; ddt; $J_{4-,5\text{-trans-pentenyl}}$ = 17.0, $J_{4-,5\text{-cis-pentenyl}}$ = 10.0, $J_{4-,3\text{-pentenyl}}$ = 6.7 Hz
H-4_{cis} and H-$4_{trans\text{-butenyl}}$	5.04-5.10; m	H-5_{cis} and H-$5_{trans\text{-pentenyl}}$	4.96-5.06; m
ester -CH_3	3.72; s	ester -CH_3	3.73; s
Ph o-H	7.54-7.57; m	Ph o-H	7.54-7.59; m
Ph m-H	7.40-7.43; m	Ph m-H	7.41-7.43; m
Ph p-H		Ph p-H	

Table 2.10



[137]



[138]

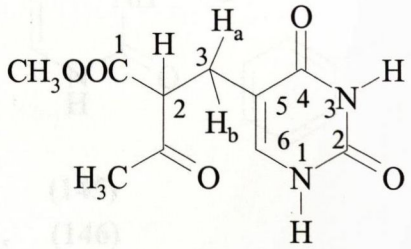
Carbon	δ_C (ppm)	Carbon	δ_C (ppm)
C-2	171.0	C-2	172.0
C-3	124.3	C-3	124.3
C-4	158.2	C-4	158.1
C-5	25.3	C-5	25.4
C-6	29.9	C-6	29.9
C-1	55.7	C-1	56.1
C-1-butenyl	33.1	C-1-pentenyl	33.3
C-2-butenyl	36.4	C-2-pentenyl	23.9
C-3-butenyl	137.4	C-3-pentenyl	33.9
C-4-butenyl	115.1	C-4-pentenyl	138.0
		C-5-pentenyl	114.8
ester -CH_3	52.3	ester -CH_3	52.3
ester C=O	195.4	ester C=O	196.1
Ph-ipso	138.0	Ph-ipso	138.1
Ph C-o	126.1	Ph C-o	126.0
Ph C-m	128.7	Ph C-m	128.7
Ph C-p	130.1	Ph C-p	130.1

Table 2.11

2.13 Synthesis of compounds containing the 3-phenylcyclohex-2-en-1-one moiety and a pyrimidine ring.

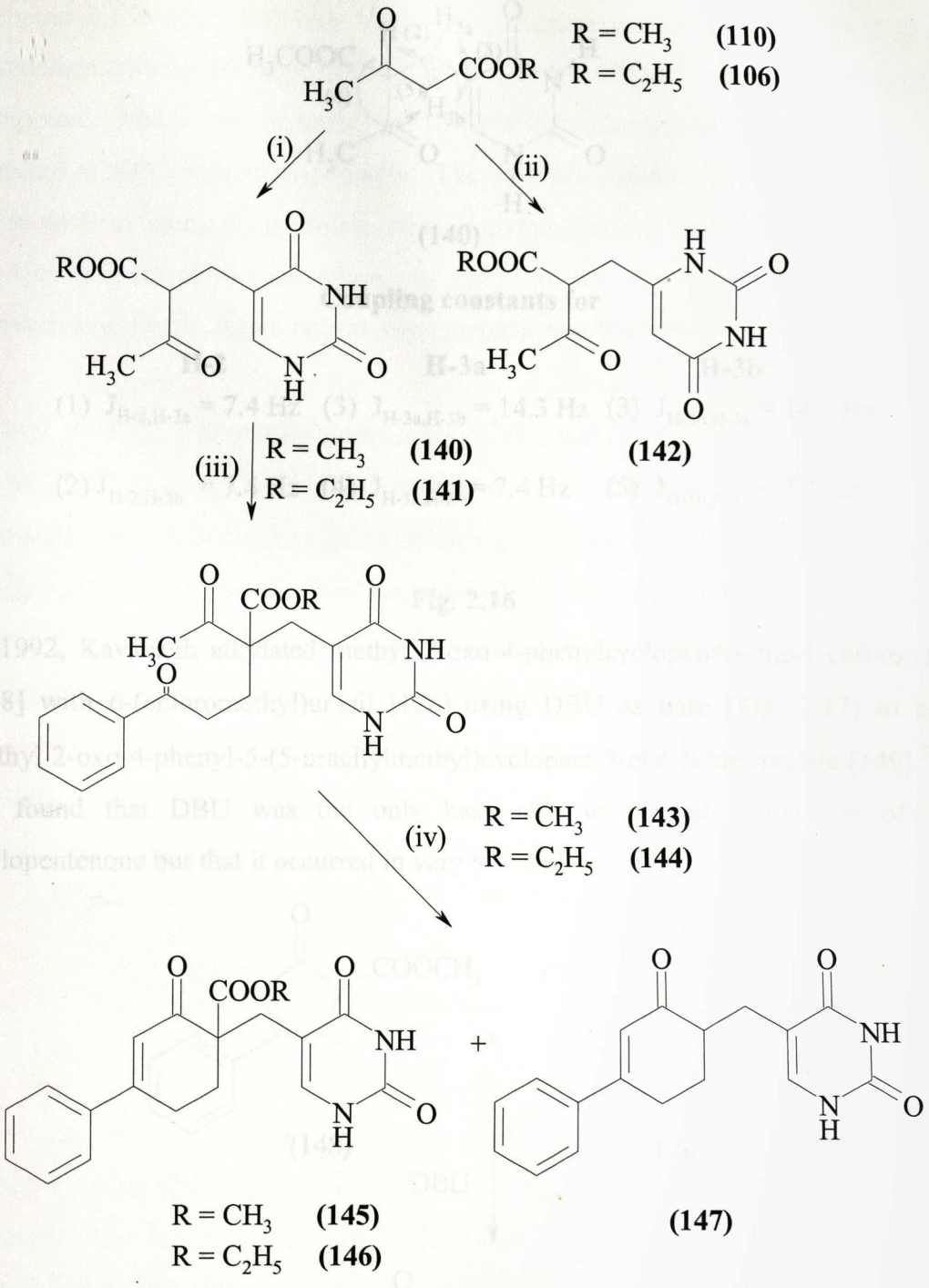
The synthesis of compounds containing a cyclohexenone ester and a pyrimidine ring (Scheme 2.13) was predicted to follow a three-step sequence similar to Scheme 2.11. The starting chloro-uracil was prepared by treating uracil with paraformaldehyde in aqueous KOH to give 5-(hydroxymethyl)uracil [139].[25] This was reacted with concentrated hydrochloric acid to give 5-(chloromethyl)uracil [125] as a colourless powder in 72% yield.[26] 6-(chloromethyl)uracil [126] was available commercially (Aldrich Chemical Co.).

Methyl acetoacetate [110] was alkylated with 5-(chloromethyl)uracil [125] at room temperature under nitrogen using NaH as base. Dimethylformamide was used as solvent, as the starting chloride was insoluble in other potential solvents. The mixture was worked up to give a brown oil. The oil was dissolved in methanol and cooled to 5°C overnight to give a colourless precipitate in 76% yield. The compound was identified by spectroscopic techniques as methyl 2-acetyl-3-(5-uracilyl) propanoate [140]. The ^{1}H NMR showed the characteristic peaks of the acetyl -CH_3 at δ 2.15 ppm and the ester -CH_3 at δ 3.65 ppm. Also present were the uracil peaks of NH-1 doublet at δ 10.76 ppm and NH-3 broad singlet at δ 11.27 ppm.



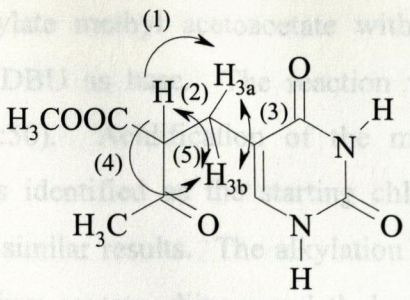
(140)

The C-3 methylene group resonated in the region δ 2.60 and δ 2.69 ppm giving two double doublets corresponding to H-3b and H-3a respectively. The hydrogen, H-2, located at the chiral carbon, C-2, should display a dd. However a distorted triplet was observed due to very similar coupling constants between H-3a and H-2 ($J_{H\text{-}3a,H\text{-}2}$ = 7.4 Hz) and H-3b and H-2 ($J_{H\text{-}3b,H\text{-}2}$ = 7.4 Hz) (Fig. 2.16). The ^{13}C NMR was consistent with the structure [140].



Reagents: (i) 5-(chloromethyl)uracil [125], NaH in DMF; (ii) 6-(chloromethyl)uracil [126], (iii) $PhCOCH{=}CH_2$ [10]; R = CH_3, $NaOCH_3$ in methanol; R = C_2H_5, $NaOC_2H_5$ in ethanol; (iv) $PhCOCH{=}CH_2$ [107]; $NaOCH_3$ in DMF, DBU in DMF

Scheme 2.13



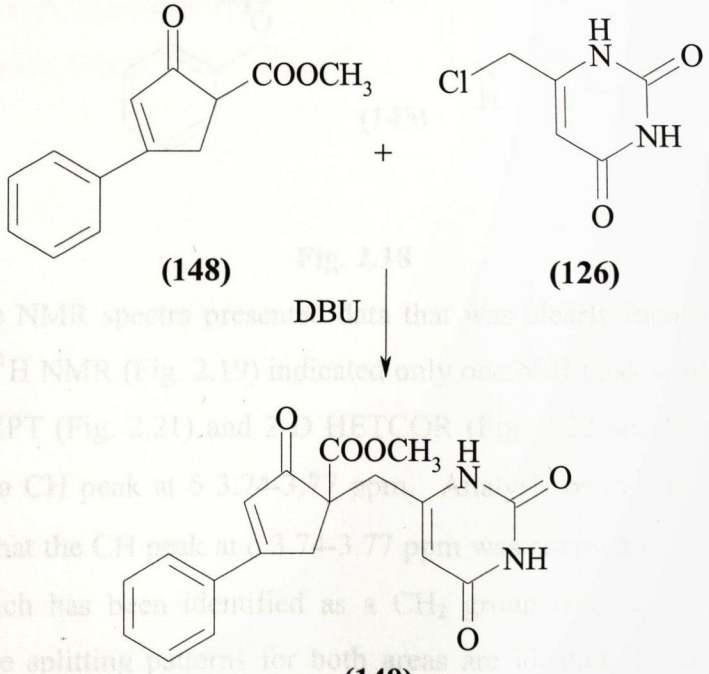
(140)

Coupling constants for

H-2	H-3a	H-3b
(1) $J_{H-2,H-3a}$ = 7.4 Hz	(3) $J_{H-3a,H-3b}$ = 14.3 Hz	(3) $J_{H-3b,H-3a}$ = 14.1 Hz
(2) $J_{H-2,H-3b}$ = 7.4 Hz	(4) $J_{H-3a,H-2}$ = 7.4 Hz	(5) $J_{H-3b,H-2}$ = 7.4 Hz

Fig. 2.16

In 1992, Kavanagh alkylated methyl 2-oxo-4-phenylcyclopent-3-ene-1-carboxylate [148] with 6-(chloromethyl)uracil [126] using DBU as base (Fig. 2.17) to give methyl 2-oxo-4-phenyl-5-(5-uracilylmethyl)cyclopent-3-ene-1-carboxylate [149].[26,27] He found that DBU was the only base able to promote alkylation of the cyclopentenone but that it occurred in very low yield.



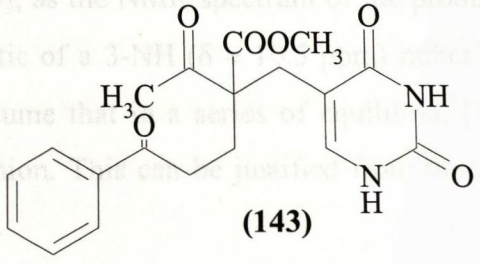
(148) **(126)**

(149)

Fig. 2.17

We attempted to alkylate methyl acetoacetate with 6-(choromethyl)uracil [126] (Scheme 2.13) using DBU as base. The reaction was followed by TLC (ethyl acetate/acetonitrile 50:50). Acidification of the mixture afforded a colourless compound, which was identified as the starting chlorouracil. The reaction was repeated at 50°C with similar results. The alkylation step was repeated using other bases such as ammonium acetate, diisopropylethylamine, and sodium hydride. A catalytic amount of sodium iodide was added to increase the reactivity of the halo derivative of uracil. Again only starting material was recovered.

Methyl 2-acetyl-3-(5-uracilyl)propanoate [140] was alkylated with phenyl vinyl ketone [107] to give a colourless compound. The product was recrystallised from methanol/acetonitrile (5:2) to give a colourless powder mp. 158-160°C. The product predicted from our knowledge of previous alkylations of this type (Scheme 2.11) is methyl 2-acetyl-5-oxo-5-phenyl-2-(5-uracilylmethyl)pentanoate [143] (Scheme 2.13) (Fig. 2.18).



(143)

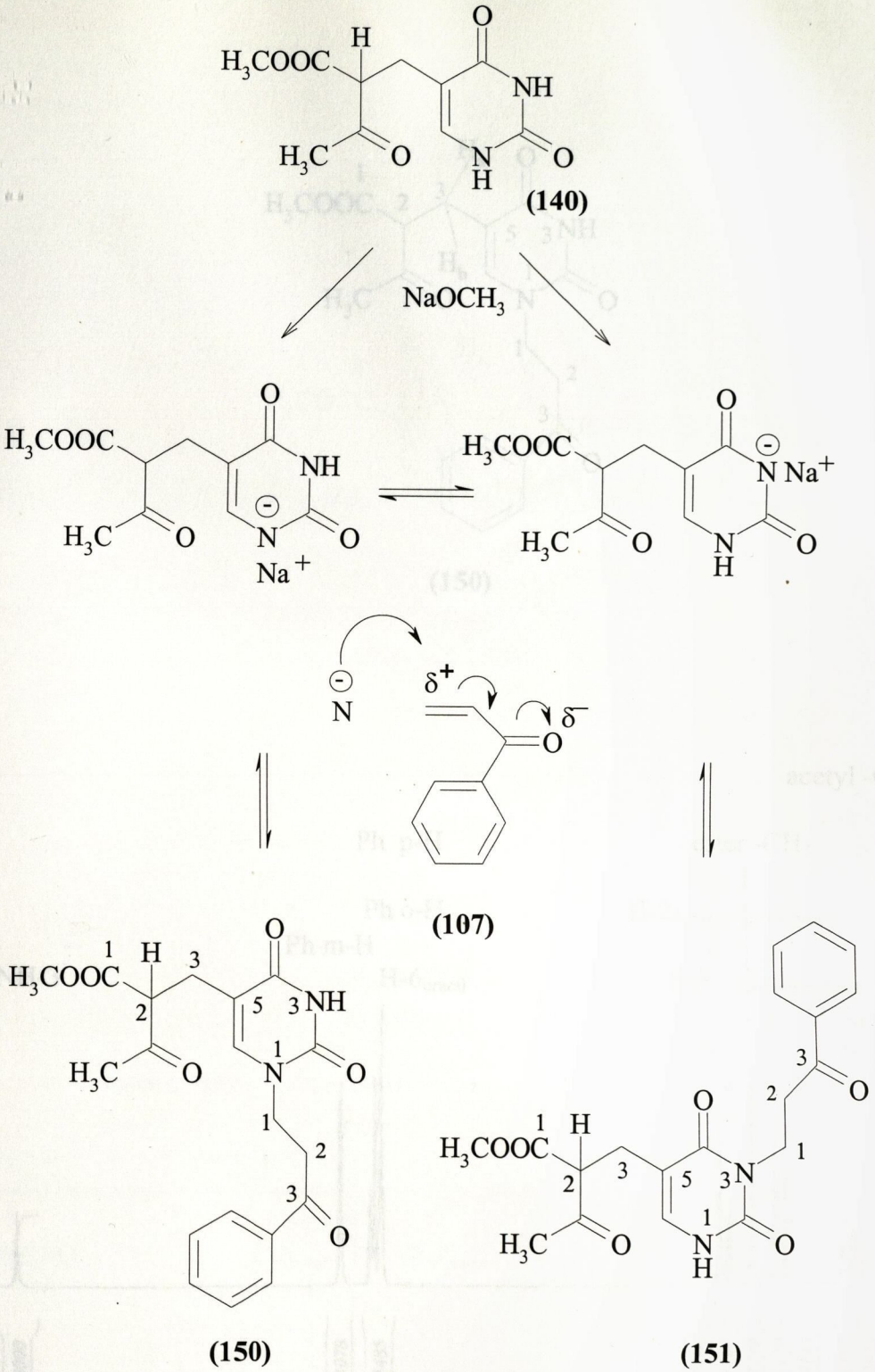
Fig. 2.18

Analysis of the NMR spectra presented data that was clearly inconsistent with this structure. The ^{1}H NMR (Fig. 2.19) indicated only one N-H peak while the ^{13}C NMR (Fig. 2.20), DEPT (Fig. 2.21) and 2-D HETCOR (Fig. 2.22 and Fig. 2.23) showed the present of a CH peak at δ 3.74-3.77 ppm. Analysis of the ^{1}H-^{1}H COSY (Fig. 2.24) showed that the CH peak at δ 3.74-3.77 ppm was coupled to the region δ 2.44-2.61 ppm, which has been identified as a CH_2 group (Fig. 2.22 and Fig. 2.23). Analyses of the splitting patterns for both areas are identical to the H-3a double-doublet, H-3b double-doublet and the H-2 triplet from methyl 2-acetyl-3-(5-uracilyl)-propanoate [140]. This suggested that the alklyation did not take place at the C-2

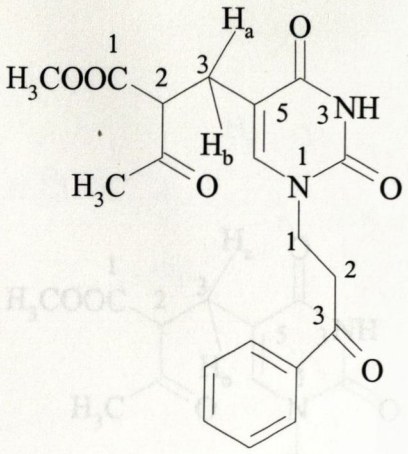
position on methyl 2-acetyl-3-(5-uracilyl)propanoate [140] (Scheme 2.13) but at the N-1 uracil position affording methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]-uracilyl}propanoate [150] (Scheme 2.14).

Re-examination of the region δ 2.44-2.61 ppm and its coupling constants indicated two doublet-doublets at δ 2.48 (J_{gem} = 14.0, $J_{H\text{-}3a,H\text{-}2}$ = 7.5 Hz) and δ 2.58 (J_{gem} = 14.0, $J_{H\text{-}3b,H\text{-}2}$ = 6.5 Hz) ppm corresponding to H-3b and H-3a respectively. The H-2 triplet at δ 3.75 ppm afforded coupling constants of $J_{H\text{-}2,H\text{-}3a} = J_{H\text{-}2,H\text{-}3b}$ = 7.3 Hz. Analysis of the ^{1}H-^{1}H COSY spectrum and identical splitting patterns enabled us to identify the two triplets at δ 3.29 and δ 3.85 ppm as the H-1 and H-2 on the 3-oxo-3-phenylpropyl side chain respectively.

We have to consider that the uracil derivative [151] would be the major product of the reaction (Scheme 2.14). The N-3 hydrogen is more acidic than the N-1 hydrogen and any equilibrium involving the N-anions would favour the N-3 anion. This should result in the subsequent formation of [151] rather than [150]. However, we prefer the structure [150], as the NMR spectrum of the product shows a NH peak at δ 11.3 ppm, characteristic of a 3-NH (δ ≈ 10.5 ppm) rather than a 1-NH (δ ≈ 11.0 ppm). We can only assume that in a series of equilibria, [151] reverts to a larger extent to the uracil 3-anion. This can be justified from the relative pKa of the two NHs



Scheme 2.14



(150)

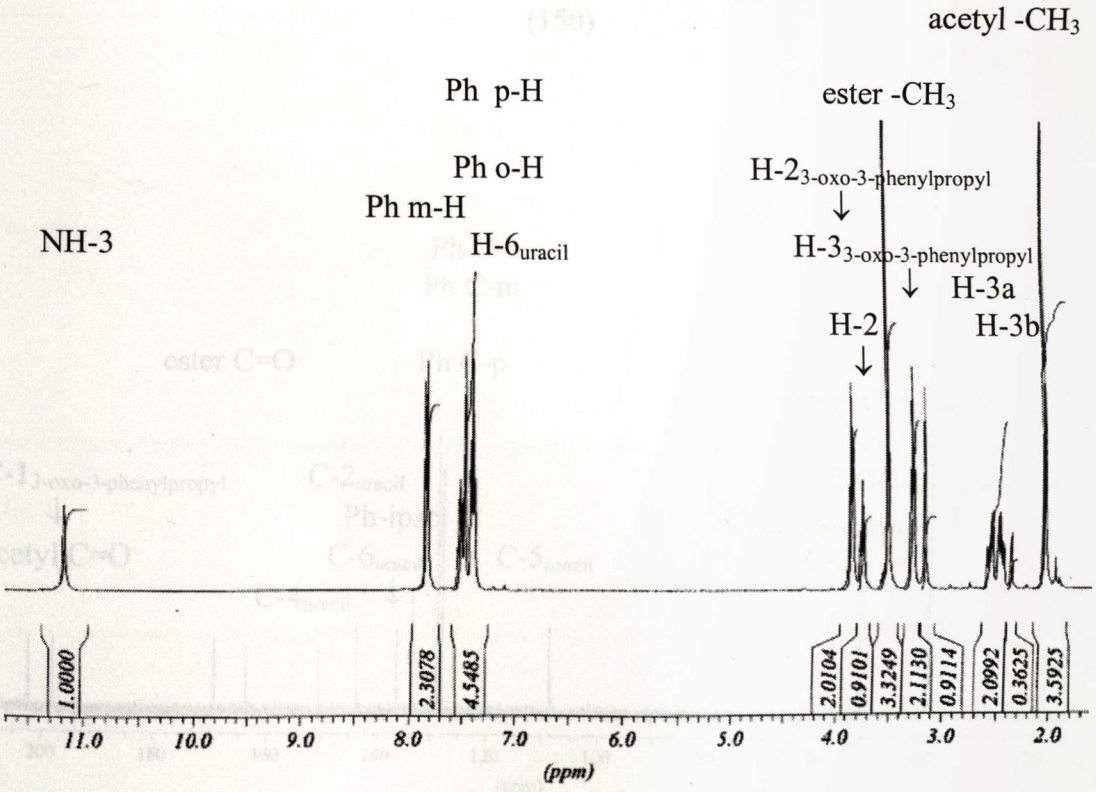
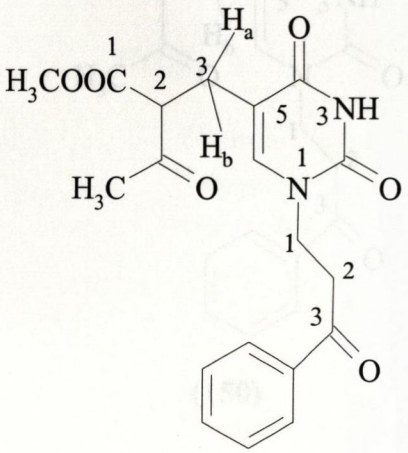


Fig. 2.19 The ^{1}H NMR spectrum of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenyl-propyl)]uracilyl}propanoate [150].



(150)

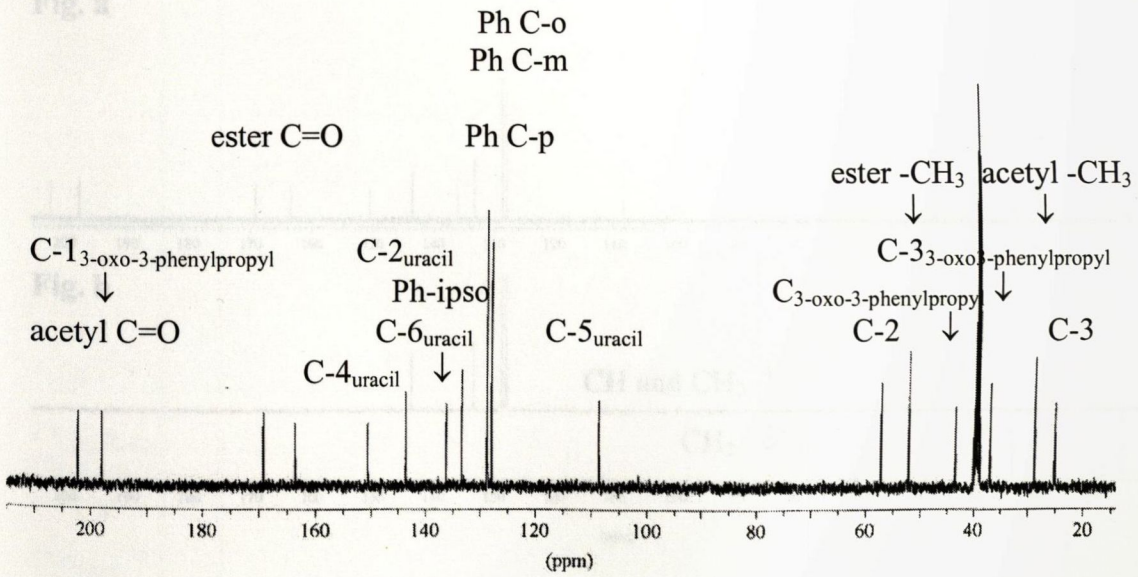
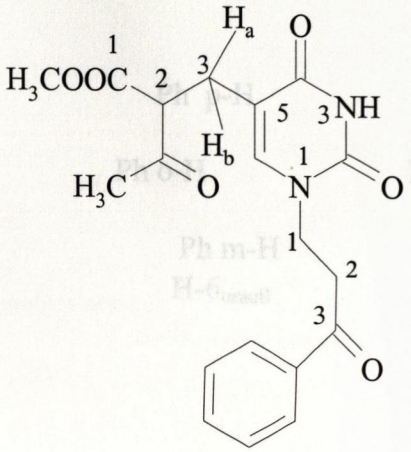


Fig. 2.20 The ^{13}C NMR spectrum of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenyl-propyl)]uracilyl}propanoate [150].



(150)

Fig. a

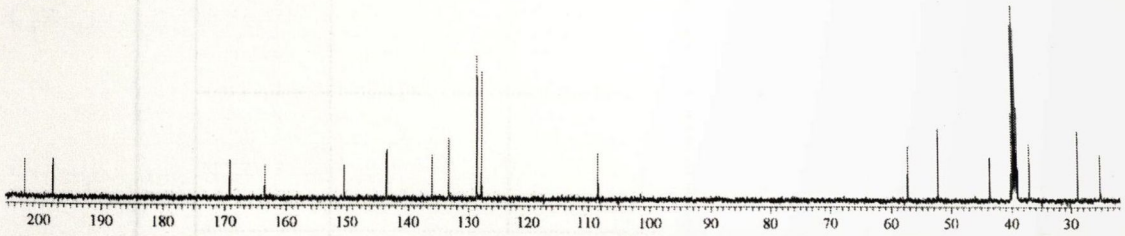


Fig. b

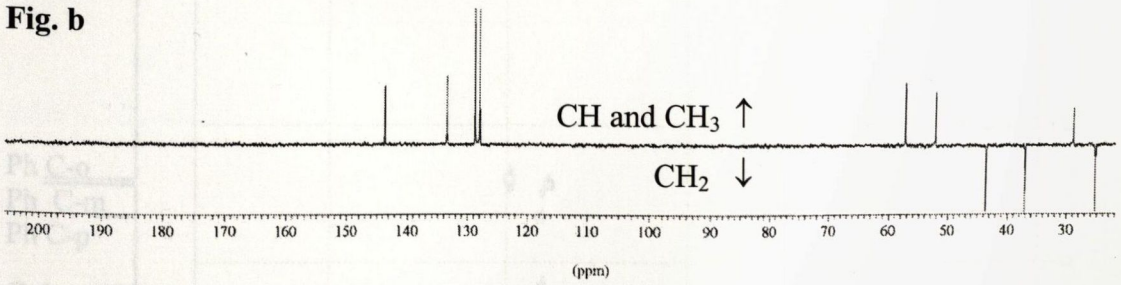


Fig. 2.21 The 1-D DEPT spectrum of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenyl-propyl)]uracilyl}propanoate [150]. **Fig. a** The complete carbon spectrum. **Fig. b** All protonated carbons with CH and CH_3 pointing up and CH_2 pointing down.

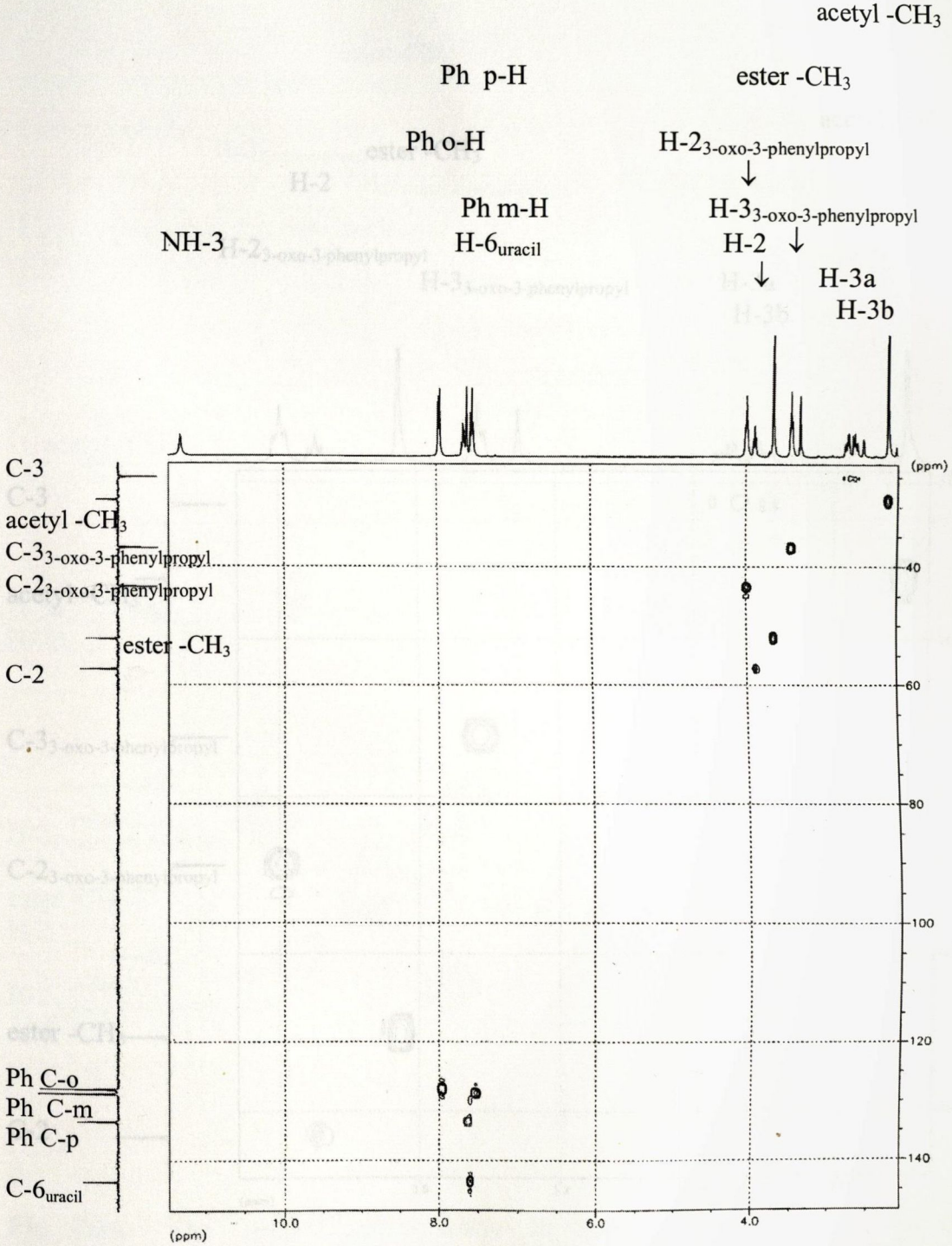


Fig. 2.22 The ^{1}H-^{13}C HETCOR NMR spectrum of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150].

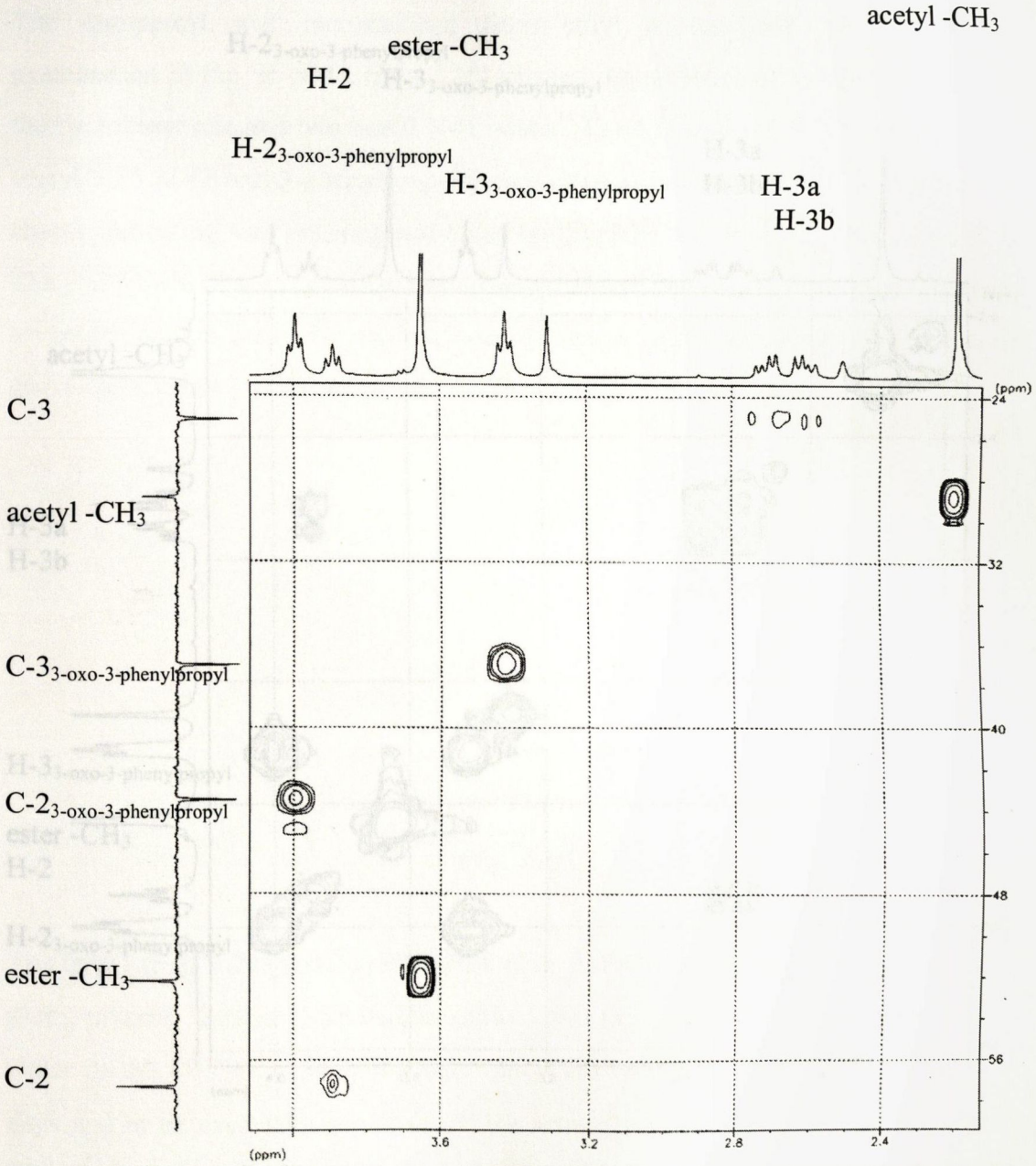


Fig. 2.23 The ^{1}H-^{13}C HETCOR NMR spectrum of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150] expended for the region δ 2.2-3.9 ppm.

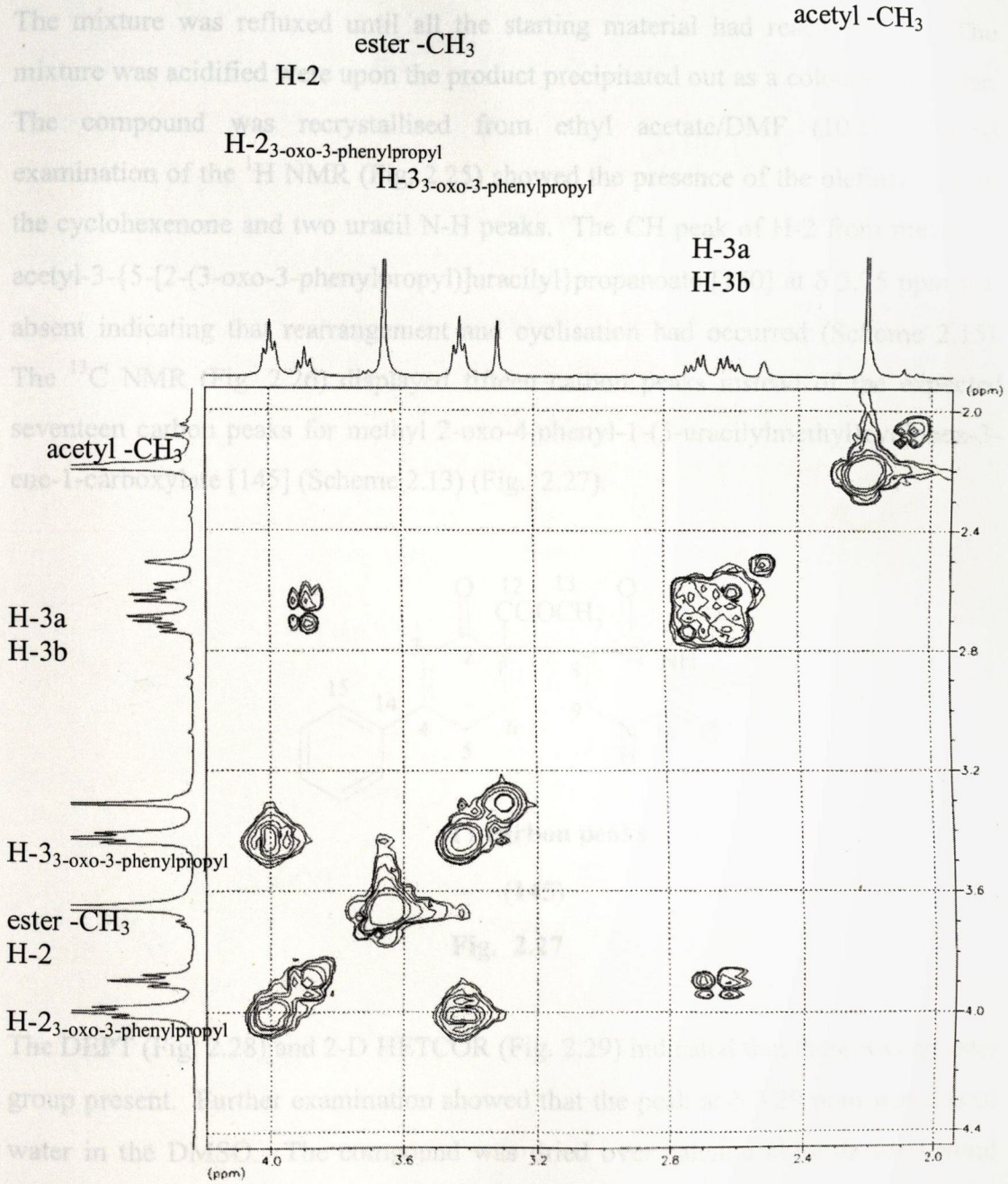
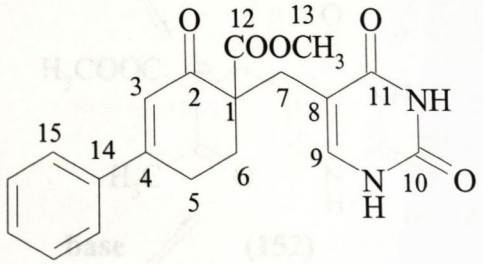


Fig. 2.24. The ^{1}H-^{1}H COSY spectrum of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150].

We attempted to induce rearrangement and cyclisation of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150] in a two step one-pot reaction using a catalytic amount of sodium methoxide in DMF at 60°C (Scheme 2.15). The reaction was followed by TLC. However the temperature was not high enough and starting material was recovered. It was found that no reaction occurred below 140°C. The mixture was refluxed until all the starting material had reacted (1 h). The mixture was acidified were upon the product precipitated out as a colourless powder. The compound was recrystallised from ethyl acetate/DMF (10:1). Initial examination of the ^{1}H NMR (Fig. 2.25) showed the presence of the olefinic peak of the cyclohexenone and two uracil N-H peaks. The CH peak of H-2 from methyl 2-acetyl-3-{5-[2-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150] at δ 3.75 ppm was absent indicating that rearrangement and cyclisation had occurred (Scheme 2.15). The ^{13}C NMR (Fig. 2.26) displayed fifteen carbon peaks instead of the expected seventeen carbon peaks for methyl 2-oxo-4-phenyl-1-(5-uracilylmethyl)cyclohex-3-ene-1-carboxylate [145] (Scheme 2.13) (Fig. 2.27).



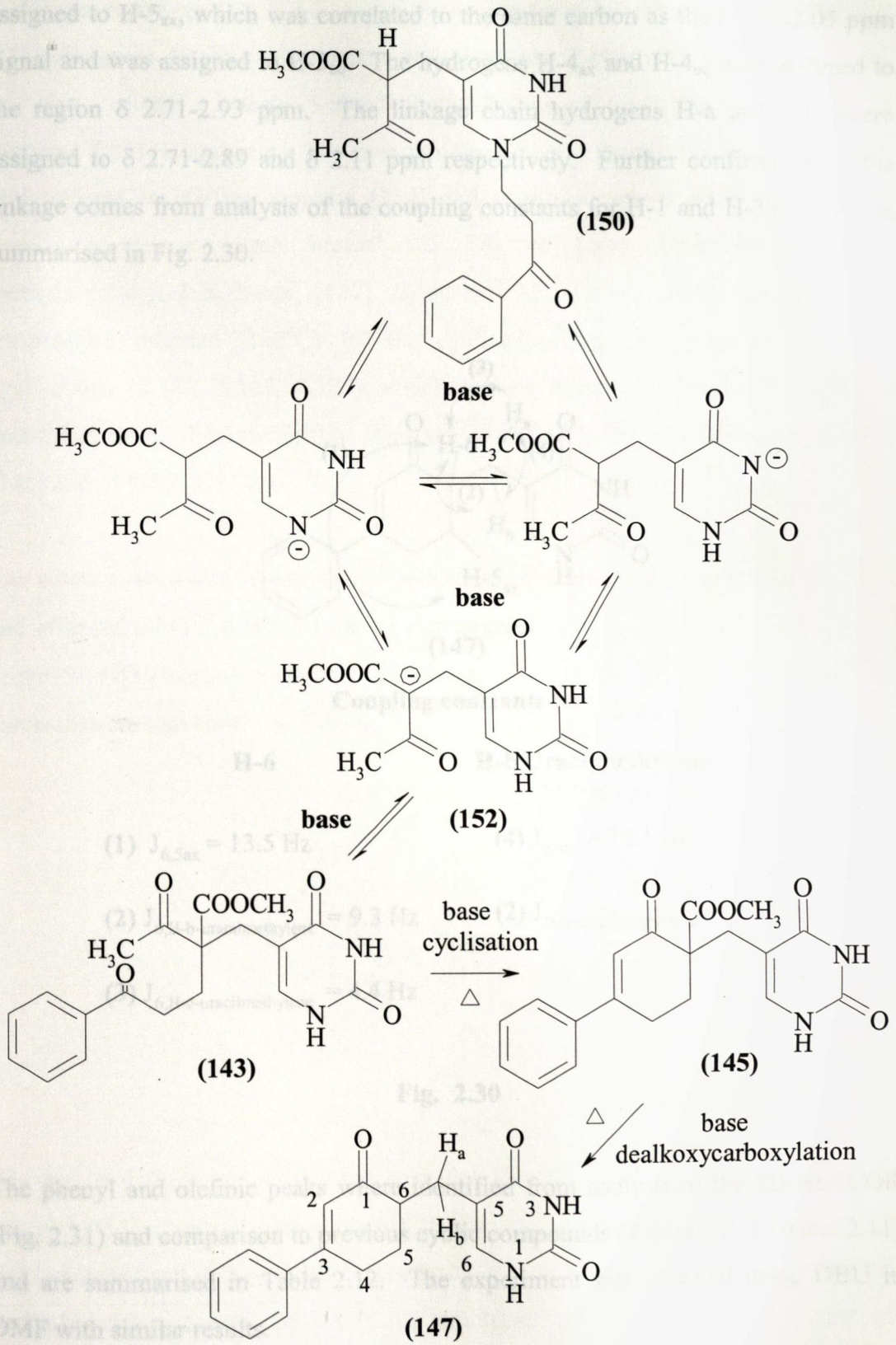
17 carbon peaks

(145)

Fig. 2.27

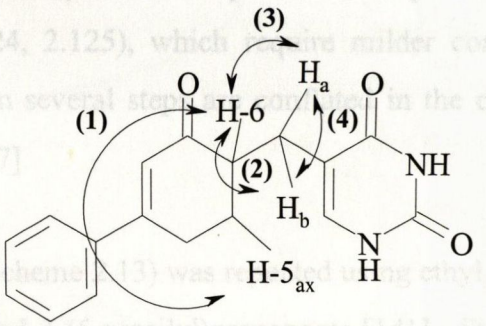
The DEPT (Fig. 2.28) and 2-D HETCOR (Fig. 2.29) indicated that there was no ester group present. Further examination showed that the peak at δ 3.29 ppm was due to water in the DMSO. The compound was dried over calcium chloride for several days and in an oven *in vacuo* at 40 °C for several hours. The ^{1}H NMR (Fig. 2.25) still showed the presence of water but in a smaller amount. The sensitivity of the cyclisation reaction to temperature was apparent as the compound had undergone dealkoxycarboxylation to give 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one [147] (Scheme 2.15). The ddd CH peak at δ 2.59 ppm (Fig. 2.25) has been identified

as H-6. H-6 is coupled to thee two protons of the bridging methylene group, and to the axial proton. The coupling to the 5_{eq} hydrogen is not observed, as the dihedral angle is nearly 90°



Scheme 2.15

The CH_2 groups of C-5, C-6 from the cyclohexenone [147] and the CH_2 from the linkage chain where identified by comparison to previous substituted cyclohexenones [136]-[138] (Tables 2.8, 2.10 and 2.11). The multiplet at δ 1.63-1.70 ppm was assigned to H-5_{ax}, which was correlated to the same carbon as the δ 2.02-2.05 ppm signal and was assigned to H-5_{eq}. The hydrogens H-4_{ax} and H-4_{eq} were assigned to the region δ 2.71-2.93 ppm. The linkage chain hydrogens H-a and H-b where assigned to δ 2.71-2.89 and δ 2.11 ppm respectively. Further confirmation of the linkage comes from analysis of the coupling constants for H-1 and H-3b, which are summarised in Fig. 2.30.



(147)

Coupling constants for

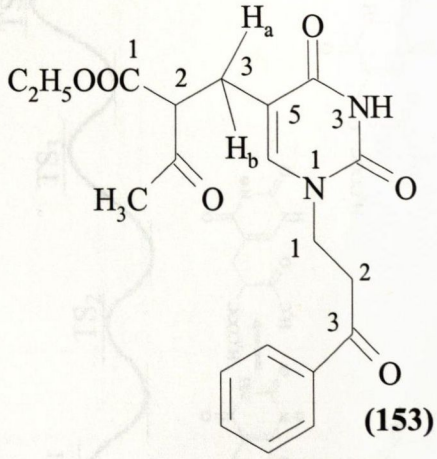
H-6	**H-b Uracilmethylene**
(1) $J_{6,5ax}$ = 13.5 Hz	**(4)** J_{gem} = 14.1 Hz
(2) $J_{6,H\text{-}b\text{-}uracilmethylene}$ = 9.3 Hz	**(2)** $J_{H\text{-}b\text{-}uracilmethylene,6}$ = 9.0 Hz
(3) $J_{6,H\text{-}a\text{-}uracilmethylene}$ = 4.4 Hz	

Fig. 2.30

The phenyl and olefinic peaks where identified from analysis of the 2D-HETCOR (Fig. 2.31) and comparison to previous cyclic compounds (Tables 2.8, 2.10 and 2.11) and are summarised in Table 2.12. The experiment was repeated using DBU in DMF with similar results.

The reaction mechanism (Scheme 2.15) can be explained by an energy profile diagram (Diagram. A). The base removes the 3-oxo-3-phenylpropyl group *via* transition state TS_1 generating a tautomeric equilibrium, which subsequently undergoes rearrangement (TS_3) to give the resonance stabilised anion [152] (Scheme 2.15) (Diagram A). This anion reacts with the 3-oxo-3-phenylpropyl group in [150] to give methyl 2-acetyl-5-oxo-5-phenyl-2-(5-uracilylmethyl)pentanoate [143] (Scheme 2.15) (Diagram A). However this compound is thermodynamically unstable with respect to starting material [150] and therefore reverts back unless it can overcome the activation barrier *via* TS_5 to form 3-phenyl-6-(5-uracilyl-methyl)cyclohex-2-en-1-one [147] (Diagram A). This explains the necessary temperature increase (140°C) for the cyclisation step as compared to similar cyclisations (2.123, 2.124, 2.125), which require milder conditions. It should be noted that in the diagram several steps are conflated in the conversion of [143] to [145] and of [145] to [147].

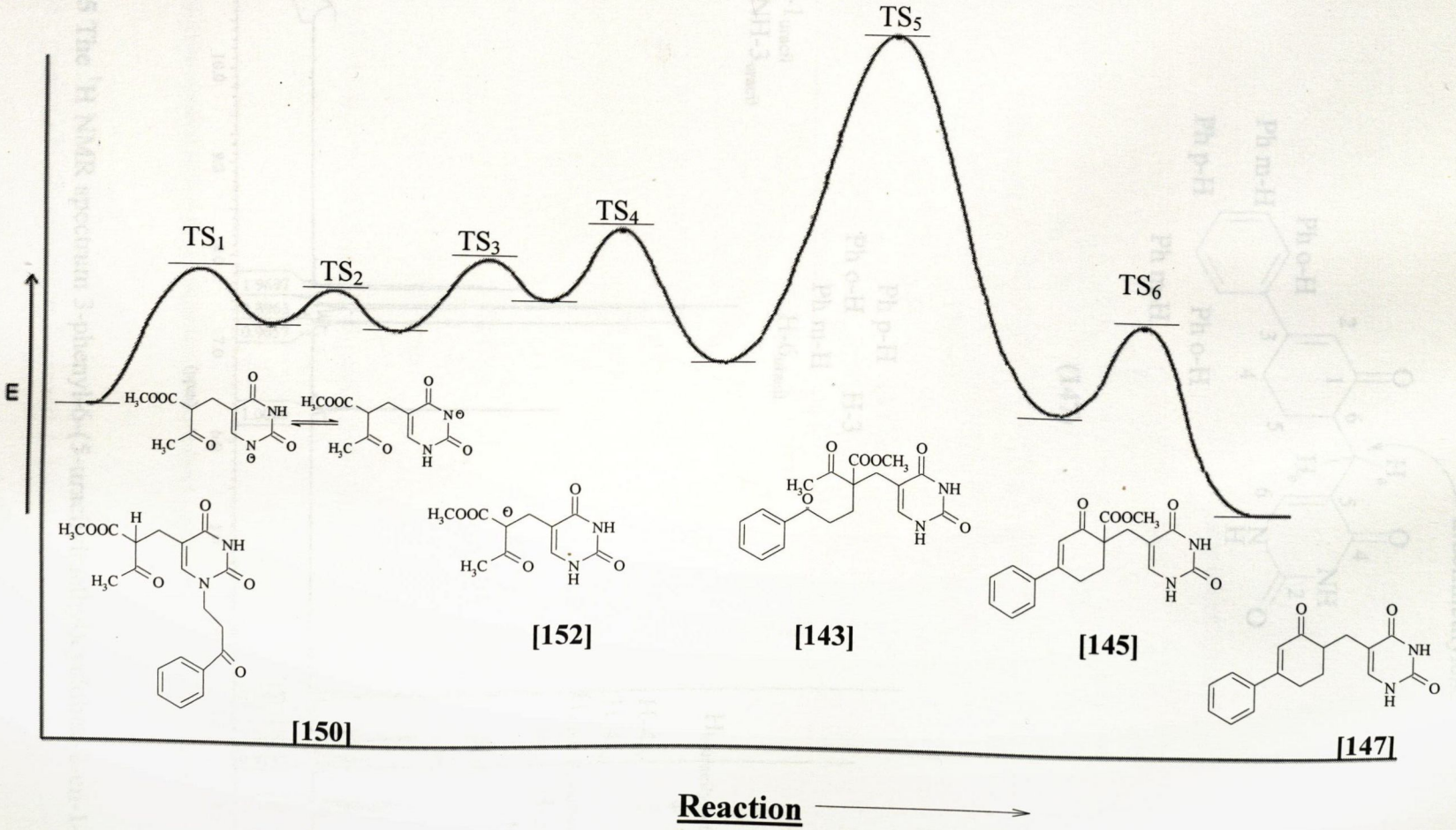
The reaction sequence (Scheme 2.13) was repeated using ethyl acetoacetate in Step 1 and afforded ethyl 2-acetyl-3-(5-uracilyl)propanoate [141]. Step 2 afforded ethyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [153] by a similar mechanism to that shown in Scheme 2.14.

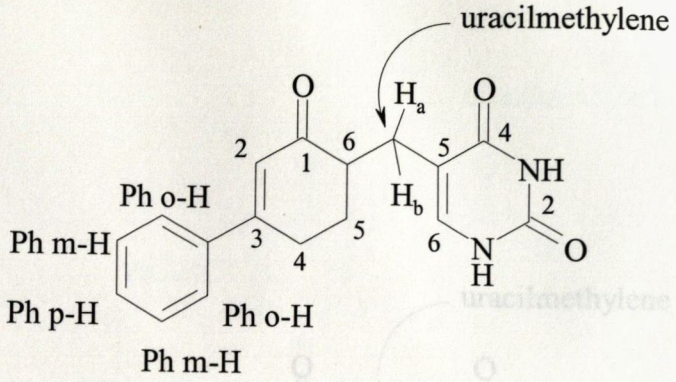


(153)

The rearrangement and cyclisation step was identical to the reaction of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150] (Scheme 2.14) with concomitant loss of the carboethoxy group to give 3-phenyl-6-(5-uracilyl-methyl)cyclohex-2-en-1-one [147]. All structures were identified by spectroscopic techniques.

(Diagram. A)





(147)

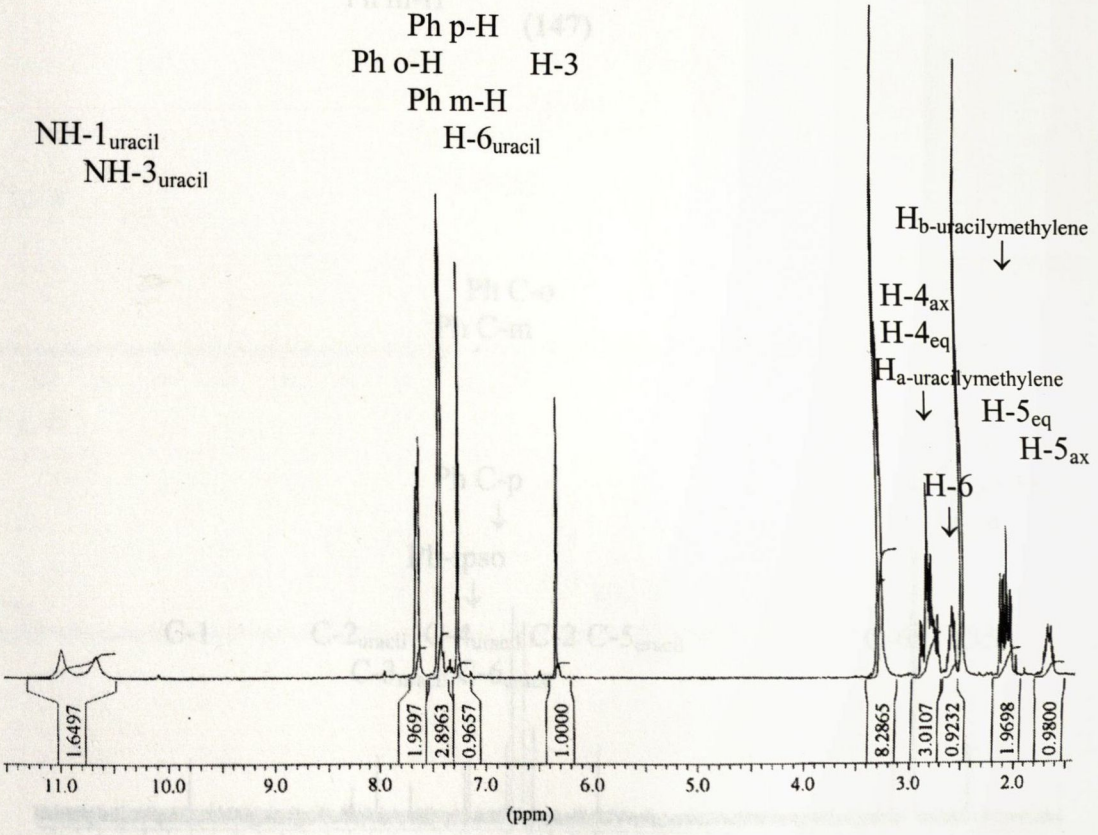
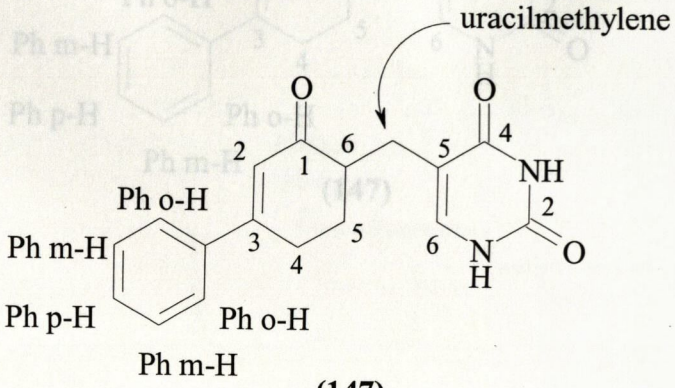


Fig. 2.25 The ^{1}H NMR spectrum 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one [147].



(147)

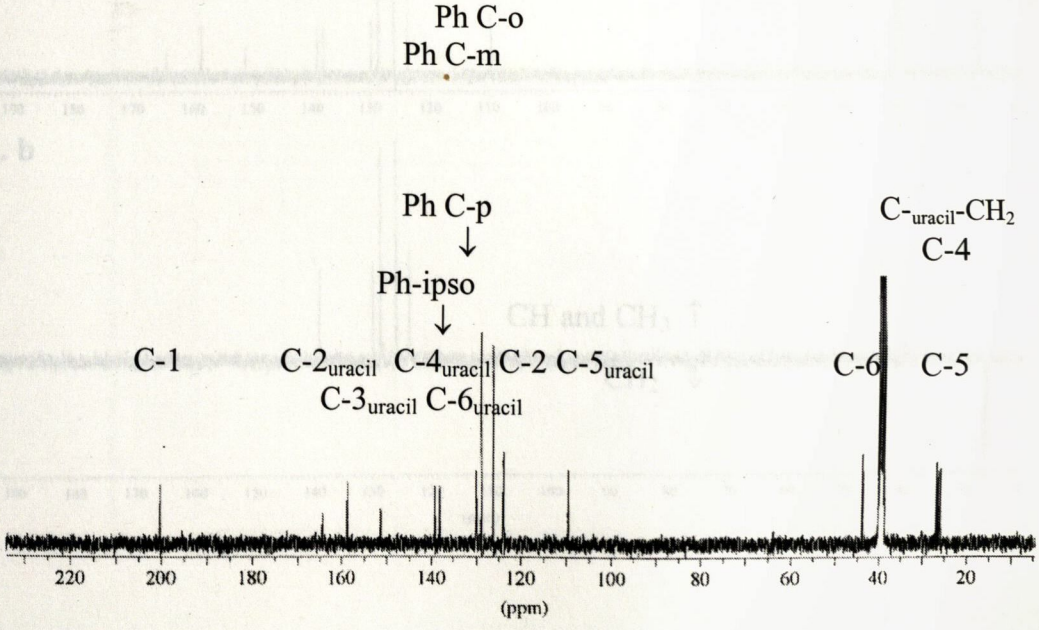
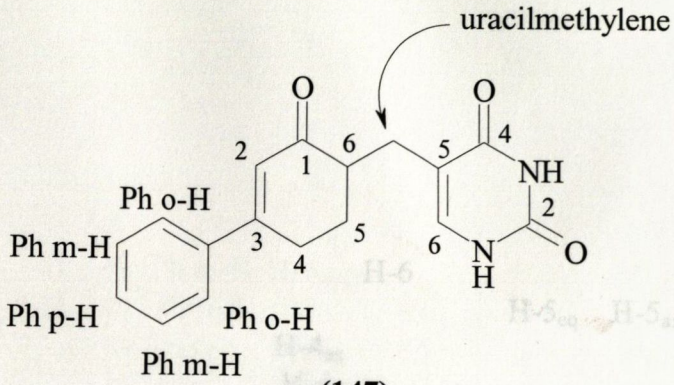


Fig. 2.26 The ^{13}C NMR spectrum 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-one [147].



(147)

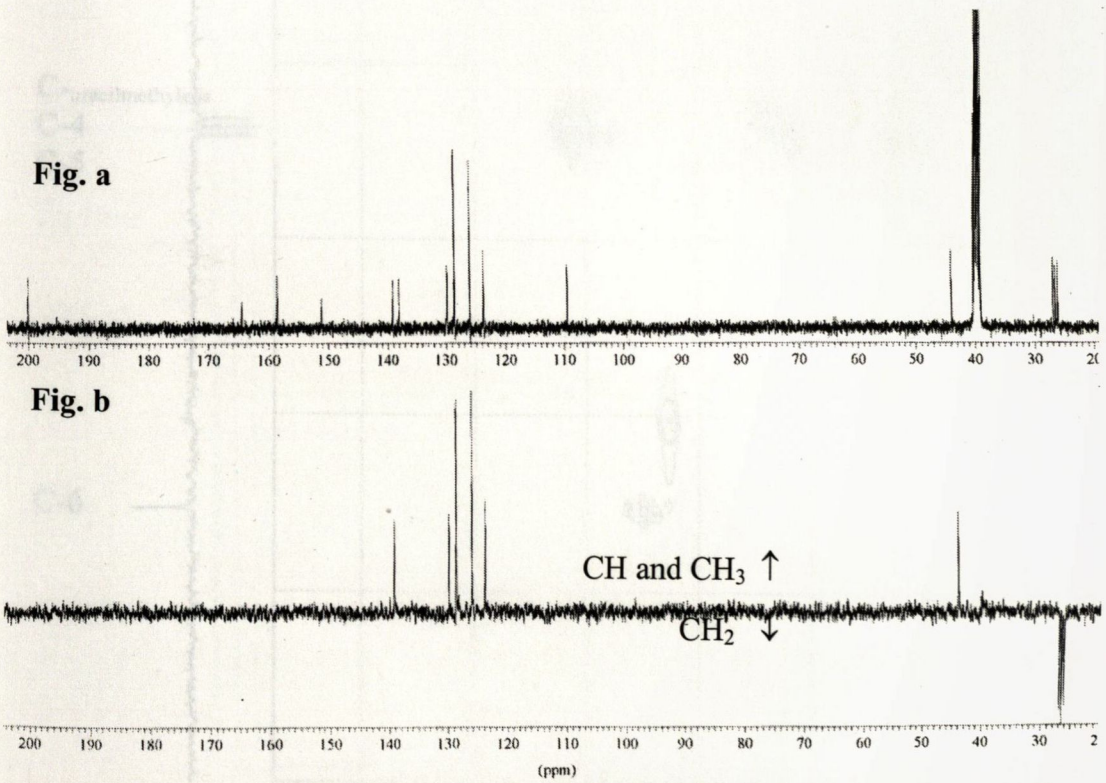


Fig. 2.28 The DEPT ^{13}C NMR spectrum of 3-phenyl-6-(5-uracilylmethyl)-cyclohex-2-en-1-one [147]. **Fig. a** The complete carbon spectrum. **Fig. b** All protonated carbons with CH and CH_3 pointing up and CH_2 pointing down.

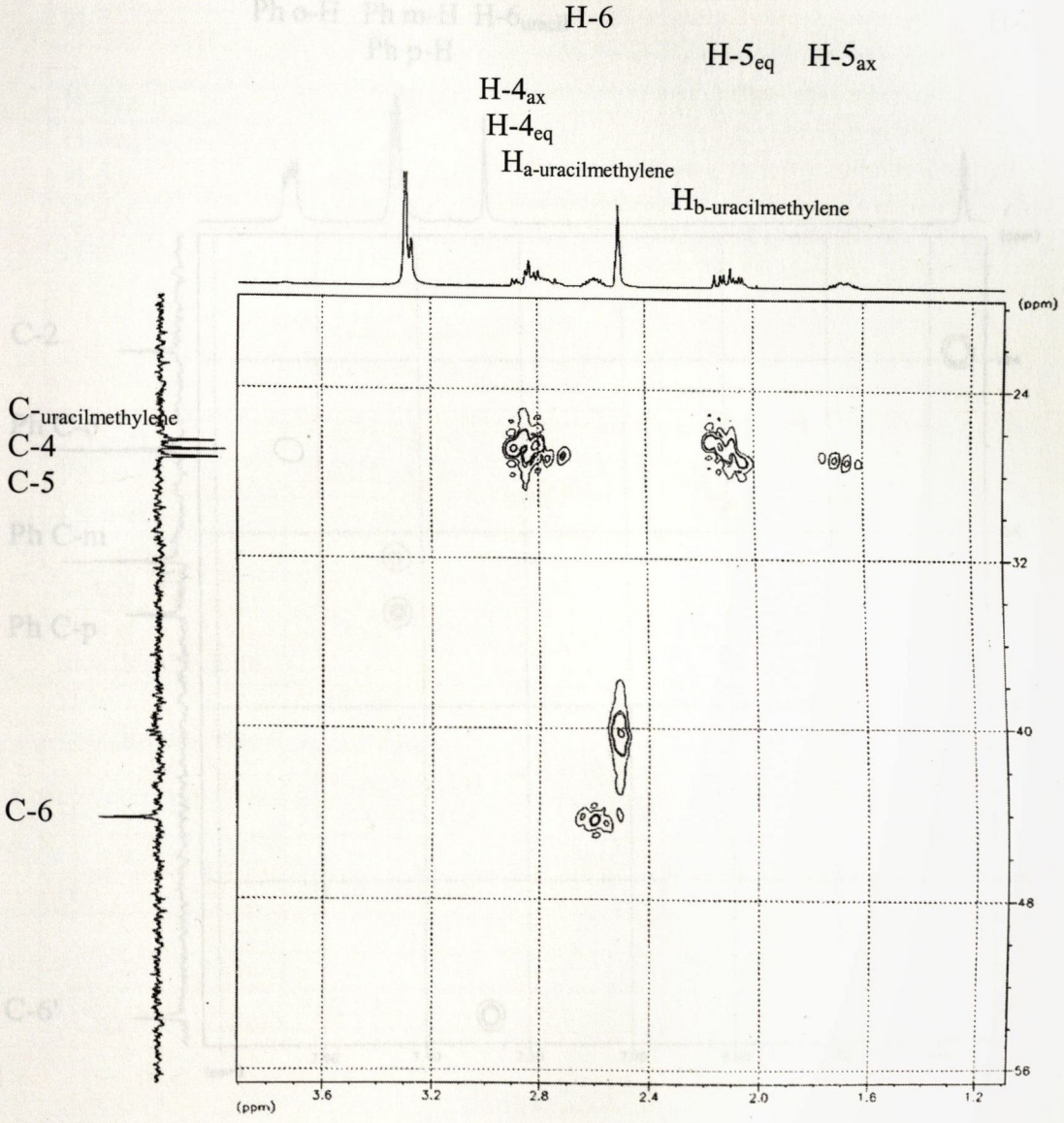


Fig. 2.29 The ^{1}H-^{13}C HETCOR of 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one [147] expanded for the region δ 1.1-3.7 ppm.

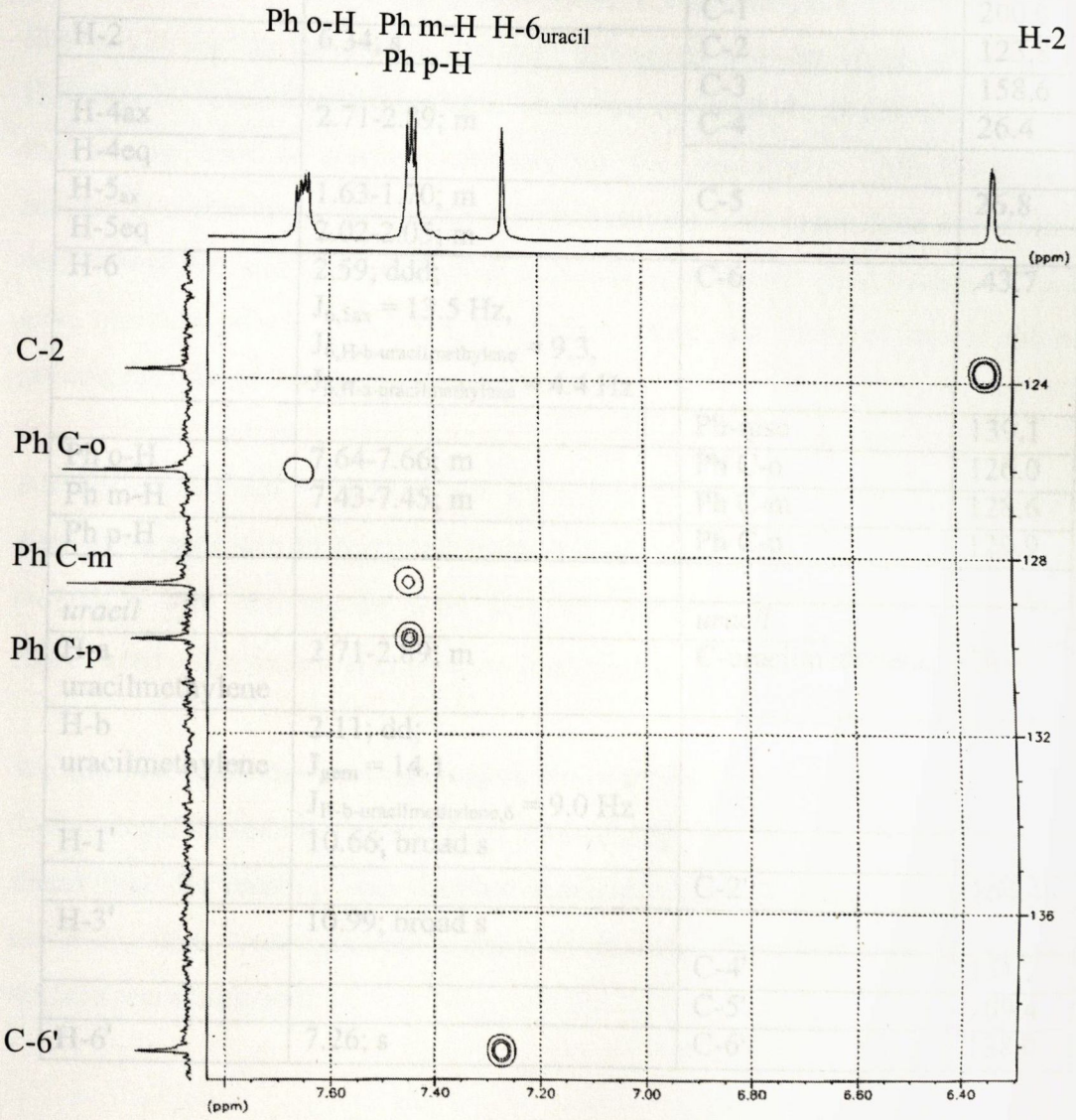
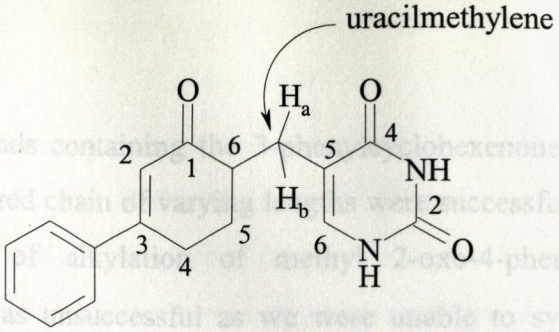


Fig. 2.31 The ^{1}H-^{13}C HETCOR of 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one [147] expanded for the region δ 6.30-7.50 ppm.



[147]

Hydrogen	δ_H	Carbon	δ_C
		C-1	200.0
H-2	6.34; s	C-2	123.8
		C-3	158.6
H-4ax	2.71-2.89; m	C-4	26.4
H-4eq			
$H\text{-}5_{ax}$	1.63-1.70; m	C-5	26.8
H-5eq	2.02-2.05; m		
H-6	2.59; ddd; $J_{6,5ax} = 13.5$ Hz, $J_{6,H\text{-}b\text{-}uracilmethylene} = 9.3$, $J_{6,H\text{-}a\text{-}uracilmethylene} = 4.4$ Hz	C-6	43.7
		Ph-ipso	139.1
Ph o-H	7.64-7.66; m	Ph C-o	126.0
Ph m-H	7.43-7.45; m	Ph C-m	128.6
Ph p-H		Ph C-p	129.9
uracil		*uracil*	
H-a uracilmethylene	2.71-2.89; m	C-uracilmethylene	26.0
H-b uracilmethylene	2.11; dd; $J_{gem} = 14.1$, $J_{H\text{-}b\text{-}uracilmethylene,6} = 9.0$ Hz		
H-1'	10.66; broad s		
		C-2'	164.4
H-3'	10.99; broad s		
		C-4'	151.2
		C-5'	109.4
H-6'	7.26; s	C-6'	138.0

Table 2.12

2.2 Conclusion

Substituted compounds containing the 3-phenylcyclohexenone moiety and an all-carbon olefinic tethered chain of varying lengths were successfully synthesised. The classical approach of alkylation of methyl 2-oxo-4-phenylcyclohex-3-ene-1-carboxylate [112] was unsuccessful as we were unable to synthesise the starting cyclohexenone. We found that the methyl ester group at the C-6 position of the cyclohexenone moiety was highly susceptible to base catalysed decarboxylation and this would explain the lack of literature references to these types of compounds. However by reversal of the synthetic steps, we were able to obtain the compounds that we required as starting materials for the photolysis. Alkylation of the acetoacetate ester to introduce the appropriate alkenyl side chain gave intermediates, which were then subjected to Michael additions using phenyl vinyl ketone. This step gave products, which would then be cyclised using base, without loss of the ester groups, the ester groups being more hindered.

All cyclohexenones containing all alkenyl side-chains where purified using an alternative approach to recrystallisation termed "low temperature recrystallisation" (<-50°C). The compounds were isolated quickly and in high purity, which represented a convenient alternative to flash chromatography.

We did not enjoy the same success in the synthesis of compounds containing the 3-phenylcyclohexenone moiety, a pyrimidine ring, and a methyl ester group. We found that the reaction was thermodynamically controlled and that the extreme conditions that were required to force cyclisation, were too extreme to prevent dealkoxycarboxylation.

2.3 Experimental

Nuclear magnetic resonance spectra were recorded on a 200MHz Varian, Gemini 2000, or a 300MHz Bruker MSL 300 or a 400Mhz Brucker DPX machines. All spectra were run as solutions in deuterated chloroform and deuterated dimethyl sulfoxide. All deuterated solvents were obtained from the Aldrih Chemical Co. in sealed 5 and 10ml vials.

Infrared spectra were carried out on a Perkin Elmer Paragon 1600 FT-IR or a Perkin Elmer Paragon 1000 FT-IR as neat liquids or in Flurolobe or nujol mulls.

Ultraviolet spectra were recorded from spectroscopic grade methanolic or ethanolic solutions using a Shimadzu UV-60 spectrophotometer.

Melting points were recorded using an Electrothermal 9100 melting point apparatus and are uncorrected.

TLCs were carried out using Kieselgel $60F_{254}$ silica plates. Flash chromatography was performed in the manner of Still and co-workers [28] using Kieselgel 60 (0.040-0.063mm) silica gel.

All solvents were fractionally distilled and dried prior to use and stored over Linde Type 4A molecular sieve or sodium wire. Sodium hydride (80% dispersion in oil) was washed with hexane and dried under nitrogen prior to use. Phenyl vinyl ketone was prepared according to Vogel [25] and used within 30 minutes of preparation.

Microanalysis was carried out by the 'Chemical Services Unit Microanalysis Lab' in U.C.D. Belfield.

Methyl 2-acetyl-5-oxo-5-phenylpentanoate [111] [20]

Methyl acetoacetate (15.53g; 133.8mmol) and sodium methoxide (0.4g, 7.4mmol) were dissolved in THF (20ml) at 0°C. Phenyl vinyl ketone (17.65g, 133mmol) was added and the mixture was stirred for 1 h. The mixture was acidified with dilute hydrochloric acid (1M, 10ml) and extracted with ether (3x30ml). The ethereal extract was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. The oil was distilled (bp. 178-184°C/2mbar) to give a viscous yellow oil. The oil was dissolved in ether/hexane, (60:40) (50ml) and cooled to -5°C to precipitate the product. The product was filtered and dried in a desiccator ($CaCl_2$) to give a colourless powder (16.46g; 49%) mp. 54-55°C: [Found: C: 67.85; H: 6.37. $C_{14}H_{16}O_4$ requires C: 67.73; H: 6.50 %].

δ_H ($CDCl_3$; 300MHz)

2.28 (3H; s; acetyl -CH_3), 2.25-2.32 (2H; m; H-3), 3.05 (2H; t; $J_{4,3}$ = 7.0 Hz; H-4) 3.65 (1H; t; $J_{2,3}$ = 7.0 Hz; H-2), 3.74 (3H; s; ester -CH_3), 7.43-7.53 (3H; m; Ph m- and p-H) and 7.87-7.95 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 75MHz)

22.2 (C-3), 29.1 (acetyl -CH_3), 35.5 (C-4), 52.4 (ester -CH_3), 58.1 (C-2), 128.0 (Ph C-o), 128.6 (Ph C-m), 133.2 (Ph C-p), 136.4 (Ph-ipso), 170.0 (ester C-1), 198.9 (C-5), and 202.8 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1684 (5-CO), 1715 (acetyl C=O), 1745.0 (ester C=O).

Ethyl 2-acetyl-5-oxo-5-phenylpentanoate [108] [18]

Sodium ethoxide (from 0.2g sodium in 20ml ethanol) was added slowly to a stirring mixture of ethyl acetoacetate (11.5g, 8.7mmol) and phenyl vinyl ketone (11.5g, 8.7mmol) at 0°C. The mixture was stirred for 1 h, acidified with dilute hydrochloric acid (1M, 10ml) and extracted with ether (3x30ml). The combined ether layers were dried ($MgSO_4$). Following removal of the solvent, the mixture was fractionally distilled to give a viscous yellow oil (10.2g, 44.7%); bp.168-170°C/2.5mbar.

δ_H ($CDCl_3$; 200MHz)

1.18 (3H; t; J = 7.1 Hz; ester -CH_3), 2.16-2.22 (2H; m; H-3), 2.20 (3H; s; acetyl -CH_3), 2.96 (2H; t; $J_{4,3}$ = 7.0 Hz; H-4), 3.56 (1H; t; $J_{2,3}$ = 7.0 Hz; H-2), 4.06-4.17 (2H; q; J = 7.1 Hz; ester -CH_2), 7.34-7.48 (3H; m; Ph m- and p-H) and 7.84-7.86 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 200MHz)

13.7 (ester -CH_3), 21.9 (C-3), 28.8 (acetyl -CH_3), 35.2 (C-4), 58.0 (C-2), 61.1 (ester -CH_2), 127.8 (Ph C-o), 128.0 (Ph C-m), 133.0 (Ph C-p), 136.4 (Ph-ipso), 169.43 (C-1), 198.8 (C-5) and 202.8 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1685 (5-CO), 1716 (acetyl C=O), 1739 (ester C=O).

Methyl 4,6-diphenyl-2-oxocyclohex-3-ene-1-carboxylate [123]

Sodium methoxide (0.5g 9mmol) was added slowly to a stirring mixture of methyl acetoacetate (5.57g, 48mmol) and benzalacetophenone [29] (10g, 48mmol) in THF (60mls). The mixture was refluxed for 3 h. The mixture was then acidified with aqueous hydrochloric acid (1M, 20ml) and extracted with dichloromethane (3x30ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a cream compound. The compound was washed with acetone (10ml) and recrystallised from ethyl acetate to give a colourless compound (10.28g, 70%) mp. 179-180 °C

δ_H (DMSO; 200MHz)

2.25-2.46 (2H; m; H-5_{eq} and H-5_{ax}), 3.33 (3H; s; ester -CH_3), 3.67 (1H; td; $J_{6ax,5ax}$ = $J_{6ax,2ax}$ = 12.4, $J_{6ax,5eq}$ = 3.6 Hz; H-6_{ax}), 4.08 (1H; d; $J_{2ax,6ax}$ = 12.4 Hz; H-1_{ax}), 5.53 (1H; s; H-3), 7.03-7.42 (10H; m; Ph m-, p-H and Ph o-H).

δ_C (DMSO; 200MHz)

42.4 (C-5), 46.4 (C-1), 51.8 (ester -CH_3), 75.8 (C-6), 124.9 (C-3), 127.2 (Ph o-C, 4-phenyl), 127.7 (Ph o-C, 6-phenyl), 128.4 (Ph m-C), 128.9 (Ph p-C), 143.1 (Ph-ipso), 148.2 (C-4), 169.9 (C-2) and 205.1 (ester -C=O).

Methyl 2-acetylpent-4-enoate [127]

Sodium hydride (2g, 83.3mmol) was added slowly to a solution of methyl acetoacetate (9.66g, 83.2mmol) in dry THF (300ml) at 0°C under nitrogen. The mixture was refluxed to generate the anion and cooled to room temperature. Allyl bromide (10g, 83.3mmol) was added over a period of 10 min and the mixture refluxed for 24 h. The solvent was distilled off and the residue acidified with dilute hydrochloric acid (1M, 100ml) and extracted with dichloromethane (3x50ml). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was fractionally distilled to give a colourless oil (9.87g, 76%), bp. 60-62°C/3.0mbar: [Found: C: 61.40; H: 7.62. $C_8H_{12}O_3$ requires C: 61.56; H: 7.74%].

δ_H ($CDCl_3$; 200MHz)

2.15 (3H; s; acetyl -CH_3), 2.50 (2H; m; H-3), 3.47 (1H; t; $J_{2,3}$ = 7.4 Hz; H-2) 3.64 (3H; s; ester -CH_3), 4.92-5.0 (2H; m; H-5_{trans} and H-5_{cis}); 5.65 (1H; ddt; $J_{4,5trans}$ = 17.1, $J_{4,5cis}$ = 10.1, $J_{4,3}$ = 7.0 Hz; H-4).

δ_C ($CDCl_3$; 50 MHz)

28.9 (acetyl -CH_3), 31.9 (C-3), 52.2 (ester -CH_3), 58.8 (C-2), 117.3 (C-5), 134.1 (C-4), 169.6 (ester C=O), 202.3 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1642 (C=C), 1716.2 (acetyl C=O), 1745.0 (ester C=O).

Ethyl 2-acetylpent-4-enoate [130] [22]

Sodium hydride (3.82g, 159mmol) was added slowly to a solution of ethyl acetoacetate (20g, 153mmol) in dry THF (200ml) under nitrogen at 0°C. The mixture was refluxed to generate the corresponding anion. Allyl bromide (18.62g, 153mmol) was added over a period of 10 min and the mixture was refluxed for 12 h. The mixture was acidified with dilute hydrochloric acid (1M; 30ml) and extracted with ether (3×100ml). The combined ether layers were dried ($MgSO_4$). Following removal of the solvent *in vacuo*, the residue was fractionally distilled to give a colourless oil (17.74g, 68%); bp. 62-64 °C/3.5mbar.

δ_H ($CDCl_3$; 200MHz)

1.27 (3H; t; J = 7.0 Hz; ester -CH_3), 2.24 (3H; s; acetyl -CH_3), 2.59 (2H; t; $J_{3,2}$ = 7.0 Hz; H-3), 3.53 (1H; t; $J_{2,3}$ = 7.4 Hz; H-2), 4.20 (2H; q; J = 7.1 Hz; ester -CH_2), 5.02-5.14 (2H; m; H-5_{trans} and H-5_{cis}); 5.70 (1H; ddt; $J_{4,5trans}$ = 17.0, $J_{4,5cis}$ = 10.0, $J_{4,3}$ = 7.0 Hz; H-4).

δ_C ($CDCl_3$; 50MHz)

13.7 (ester -CH_3), 28.8 (acetyl -CH_3), 31.8 (C-3), 58.9 (C-2), 61.1 (ester -CH_2), 117.2 (C-5), 134.1 (C-4), 169.6 (ester C=O), 202.3 (acetyl C=O).

ν_{max}/cm^{-1} (in Fluorolube)

1644 (C=C), 1721 (acetyl C=O), 1746 (ester C=O).

Methyl 2-acetylhex-5-enoate [128]

Methyl acetoacetate (8.59g, 74mmol) was added to a sodium methoxide solution (1.75g sodium (76mmol) in 100ml of methanol) and refluxed to generate the anion. The mixture was cooled to room temperature. 4-Bromo-1-butene (10g, 74mmol) was added over a period of 10 min and the mixture was refluxed for 7 h. The experiment was worked up in the same manner as methyl 2-acetylpent-4-enoate [30]. Fractional distillation gave a colourless oil (6.92g, 55%) bp. 67-69°C/0.5mmbar: [Found: C: 63.53; H: 8.20. $C_9H_{14}O_3$ requires C: 63.51; H: 8.29%].

δ_H ($CDCl_3$; 400MHz)

1.78 (2H; m; H-3), 1.87-1.92 (2H; m; H-4), 2.06 (3H; s; acetyl -CH_3), 3.33 (1H; t; $J_{2,3}$ = 7 Hz; H-2) 3.57 (3H; s; ester -CH_3), 4.82-4.90 (2H; m; H-6_{trans} and H-6_{cis}); 5.70 (1H; ddt; $J_{5,6trans}$ = 16.7, $J_{5,6cis}$ = 10.0, $J_{5,4}$ = 6,6 Hz; H-5)

δ_C ($CDCl_3$; 80 MHz)

26.7 (C-3), 28.5 (acetyl -CH_3), 30.4 (C-4), 51.8 (ester -CH_3), 58.1 (C-2), 115.4 (C-6), 136.6 (C-5), 169.7 (C-1), 202.3 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1641 (C=C), 1717 (acetyl C=O), 1741 (ester C=O).

Methyl 2-acetylhept-6-enoate [129]

Methyl acetoacetate (9.24g, 70mmol) was added to a sodium methoxide solution (1.66g sodium (72mmol) in 100ml of methanol) and refluxed to generate the anion. The mixture was cooled to room temperature. 5-Bromo-1-pentene (10g, 67mmol) was added over a period of 10 min and the mixture was refluxed for 8 h. The experiment was worked up in the same manner giving methyl 2-acetylpent-4-enoate [127]. Fractional distillation gave a colourless oil (7.05g, 57%) bp. 85-87°C/6.0 mbar: [Found: C: 65.09; H, 8.66. $C_{10}H_{16}O_3$ requires C: 65.23; H: 8.75%].

δ_H ($CDCl_3$; 400MHz)

1.32-1.40 (2H; m; H-4), 1.80-1.86 (2H; m; H-3), 2.05 (2H; q; $J_{5,6}$ = 7.0 Hz, $J_{5,4}$ = 7.0 Hz; H-5), 2.20 (3H; s; acetyl -CH_3), 3.41 (3H; t; $J_{2,3}$ = 7.5 Hz; H-2), 3.71 (3H; s; ester -CH_3), 4.90-5.02 (2H; m; H-7_{trans} and H-7_{cis}), 5.75 (1H; ddt; $J_{6,7trans}$ = 17.0, $J_{6,7cis}$ = 10.3, $J_{6,5}$ = 6.6 Hz; H-6).

δ_C ($CDCl_3$; 80MHz)

26.5 (C-4), 27.5 (C-3), 28.6 (acetyl -CH_3), 33.2 (C-5), 52.2 (ester -CH_3), 59.4 (C-2), 114.9 (C-7), 137.6 (C-6), 170.1 (C-1), 202.8 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1641 (C=C), 1717 (acetyl C=O), 1744 (ester C=O).

Methyl 2-acetyl-5-oxo-5-phenyl-2-(2-propenyl)pentanoate [131]

Sodium methoxide (from 0.2g (12mmol) in 10ml methanol) was added slowly to a stirring mixture of methyl 2-acetylpent-4-enoate [127] (4g, 25.6mmol) and phenyl vinyl ketone (3.38g, 25.6mmol) at 0°C. The mixture was stirred for 1 h, in an ice bath. The mixture was then acidified with aqueous hydrochloric acid (1M, 20ml) and extracted with dichloromethane (3x30ml). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was fractionally distilled to give a viscous yellow oil (3.91g, 53%); bp. 162-164°C/0.3mbar [Found: C: 70.68; H: 7.15. $C_{17}H_{20}O_4$ requires C: 70.81; H: 6.99%].

δ_H ($CDCl_3$; 200MHz)

2.11 (3H; s; acetyl -CH_3), 2.22-2.29 (2H; m; H-3), 2.60-2.63 (2H; broad doublet; H-1-propenyl), 2.79-2.89 (2H; m; H-4), 3.66 (3H; s; ester -CH_3), 5.01-5.11 (1H; m; H-$3_{trans\text{-}propenyl}$ and H-$3_{cis\text{-}propenyl}$), 5.60 (1H; ddt; $J_{2\text{-}propenyl,3\text{-}trans\text{-}propenyl}$ = 17.2, $J_{2\text{-}propenyl,3\text{-}cis\text{-}propenyl}$ = 9.9, $J_{2\text{-}propenyl,1\text{-}propenyl}$ = 7.3 Hz; H-2 propenyl), 7.347.48 (3H; m; Ph m- and p-H), 7.84-7.88 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 50MHz)

25.7 (C-3), 26.6 (acetyl -CH_3), 32.9 (C-4), 36.7 (propenyl C-1), 52.1 (ester -CH_3), 62.3 (C-2), 119 (propenyl C-3), 127.8 (propenyl C-2), 127.8 (Ph C-o), 128.4 (Ph C-m), 131.9 (Ph C-p), 136.4 (Ph-ipso), 172 (C-1), 198.6 (C-5) and 202.4 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1686 (5-CO), 1712 (C=O acetyl), and 1741.1 (C=O ester).

Ethyl 2-acetyl-5-oxo-2-(2-propenyl)-5-phenylpentanoate [134]

Sodium ethoxide (0.05g (2mmol) in 10ml ethanol,) was added slowly to a stirring mixture of ethyl 2-acetylpent-4-enoate [130] (12.87g, 75.7mmol) and phenyl vinyl ketone (10g, 75.7mmol) at 0°C. The mixture was stirred for 1 h, in an ice bath. The mixture was then acidified with aqueous hydrochloric acid (1M, 20ml) and extracted with dichloromethane (3x30ml). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was fractionally distilled to give a viscous yellow oil (13.57g, bp. 172-176°C /0.7mbar). The oil was dissolved in hexane/ether (9:1, 20ml) and cooled to -40°C to give a colourless precipitate. The product was washed with hexane/ether (9:1, at -40°C) and air-dried. The product was further dried in a desiccator ($CaCl_2$) *in vacuo* to give a colourless compound (10.99g, 53%) mp. 48-49°C: [Found: C: 71.41; H: 7.29. $C_{18}H_{22}O_4$ requires C: 71.50; H: 7.33%].

δ_H ($CDCl_3$; 200MHz)

1.25 (3H; t; J = 7.2 Hz; ester -CH_3), 2.17 (3H; s; acetyl -CH_3), 2.23-2.33 (2H; m; H-3), 2.65 (2H; d; J = 7.2 Hz; H-1 propenyl), 2.82-2.93 (2H; m; H-4), 4.20 (2H; q; J = 7.2 Hz; ester -CH_2), 5.06-5.15 (2H; m; H-$3_{trans\text{-}propenyl}$ and H-$3_{cis\text{-}propenyl}$), 5.62 (1H;

ddt; $J_{2\text{-propenyl,3-trans-propenyl}} = 17.0$, $J_{2\text{-propenyl,3-cis-propenyl}} = 10.5$, $J_{2\text{-propenyl,1-propenyl}} = 7.1$ Hz; H-2 propenyl), 7.39-7.57 (m; 3 H; Ph m- and p-H) and 7.89-7.93 (m; 2 H; Ph o-H).

δ_C ($CDCl_3$; 50MHz)

13.9 (ester -CH_3), 25.9 (C-3), 26.8 (acetyl -CH_3), 33.1 (C-4), 36.8 (propenyl C-1), 61.4 (ester -CH_2), 62.5 (C-2), 119.2 (propenyl C-3), 128 (Ph C-o), 128.6 (Ph C-m), 132 (Ph C-p), 133.1 (propenyl C-2), 136.6 (Ph-ipso), 171.7 (C-1), 198.8 (C-5) and 204.7 (acetyl C=O).

ν_{max}/cm^{-1} (nujol)

1686 (5-CO), 1712 (acetyl C=O), and 1737 (ester C=O).

Methyl 2-acetyl-(3-oxo-3-phenylpropyl)hex-5-enoate [132]

Sodium methoxide (from 0.2g in 10ml methanol, 12mmol) was added slowly to a stirring mixture of methyl 2-acetylhex-4-enoate [128] (12.8g, 75.7mmol) and phenyl vinyl ketone (10g, 75.7mmol) at 0°C. The mixture was stirred for 1 h, in an ice bath. The mixture was then acidified with aqueous hydrochloric acid (1M; 20ml) and extracted with dichloromethane (3x30ml). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was fractionally distilled to give a viscous yellow oil (11.62g, 51%) bp. 170-172°C /0.5mbar [Found: C: 71.38; H: 7.39. $C_{18}H_{22}O_4$ requires C: 71.50; H: 7.33%]

δ_H ($CDCl_3$; 200MHz)

1.90-1.94 (2H; m; H-3), 2.11 (3H; s; acetyl -CH_3), 2.15-2.20 (2H; m; H-4), 2.23-2.32 (2H; m; H-1 3-oxo-3-phenylpropyl), 2.77-2.86 (2H; m; H-2 3-oxo-3-phenylpropyl), 3.67 (3H; s; ester -CH_3), 5.01-5.09 (1H; m; H-6_{trans} and H-6_{cis}), 5.60 (1H; ddt; $J_{5,6\text{-trans}} = 17.0$, $J_{5,6\text{-cis}} = 10.5$, $J_{5,3} = 6.7$ Hz; H-5 3-oxo-3-phenylpropyl), 7.38-7.55 (3H; m; Ph m- and p-H), 7.84-7.90 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 50MHz)

25.7 (3-oxo-3-phenylpropyl C-1), 26.7 (acetyl -CH_3), 34.4 (C-3), 30.4 (C-4), 32.4 (3-oxo-3-phenylpropyl C-2), 52.0 (ester -CH_3), 62.3 (C-2), 117 (C-6), 127.8 (Ph C-o), 130.4 (C-5), 128.4 (Ph C-m), 131.9 (Ph C-p), 136.6 (Ph-ipso), 130.4 (3-oxo-3-

phenylpropyl C-3), 172.6 (C-1), 198.6 (3-oxo-3-phenylpropyl C-3) and 205.1 (acetyl C=O).

ν_{max}/cm^{-1} (neat)

1686 (5-CO), 1712 (C=O acetyl), and 1741.1 (C=O ester).

Methyl 2-acetyl-2-(3-oxo-3-phenylpropyl)hept-6-enoate [133]

Sodium methoxide (0.2g in 10ml methanol, 12mmol) was added slowly to a stirring mixture of methyl 2-acetylpent-4-enoate [129] (4g, 25.6mmol) and phenyl vinyl ketone (3.38g, 25.6mmol) at 0°C. The mixture was stirred for 1 h, in an ice bath. The mixture was then acidified with aqueous hydrochloric acid (1M, 20ml) and extracted with dichloromethane (3x30ml). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was fractionally distilled to give a viscous yellow oil (3.91g, 53%) bp. 162-164°C /0.3mbar [Found: C: 70.68; H: 7.15. $C_{17}H_{20}O_4$ requires C: 70.81; H: 6.99%]

δ_H ($CDCl_3$; 200MHz)

1.14-1.28 (2H; m; H-4), 1.82-1.86 (2H; m; H-3), 2.02-2.06 (2H; m; H-5), 2.11 (3H; s; acetyl -CH_3), 2.20-2.30 (2H; m; H-1 3-oxo-3-phenylpropyl), 2.78-2.80 (2H; m; H-2 3-oxo-3-phenylpropyl), 3.67 (3H; s; ester -CH_3), 4.90-4.98 (1H; m; H-7_{trans} and H-7_{cis}), 5.60 (1H; ddt; $J_{6,7\text{-trans}}$ = 16.5, $J_{6,7\text{-cis}}$ = 10.5, $J_{6,5}$ = 6.5 Hz; H-6), 7.36-7.40 (2H; m; Ph m-H), 7.47-7.49 (1H; Ph p-H), 7.86-7.88 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 50MHz)

23.0 (C-4), 25.7 (3-oxo-3-phenylpropyl C-1), 26.6 (acetyl -CH_3), 31.6 (C-3), 33.1 (3-oxo-3-phenylpropyl C-2), 33.5 (C-5), 52.0 (ester -CH_3), 62.4 (C-2), 115.0 (C-7), 127.7 (Ph C-o), 128.3 (Ph C-m), 132.8 (Ph C-p), 136.4 (Ph-ipso), 137.5 (C-6), 172.4 (C-1), 198.5 (3-oxo-3-phenylpropyl C-3) and 202.7 (acetyl -CH_3).

ν_{max}/cm^{-1} (neat)

1686 (5-CO), 1712 (C=O acetyl), and 1741.1 (C=O ester),

Methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]

A mixture of methyl 2-acetyl-5-oxo-5-phenyl-2-(2-propenyl)pentanoate [134] (6.29g, 21.8mmol) and DBU (3.32g, 21.8mmol) in methanol (50ml) was refluxed for 30mins. The mixture was acidified with aqueous hydrochloric acid (30ml, 1M) and extracted with dichloromethane (3 x 50ml). The combined organic layers were washed first with dilute HCL (50ml) and then with deionised water (50ml). The organic layer was dried ($MgSO_4$) and refluxed *in vacuo* to give a yellow oil (4.02g). The oil was fractionally distilled to give a viscous yellow oil (2.53g, bp. 162-165°C/2mbar). The oil was dissolved in hexane/ether (8:2, 20ml) and cooled to -50°C to give a white precipitate. The product was washed with hexane/ether (8:2, at -50°C) and air-dried. The product was further dried in a desiccator ($CaCl_2$) *in vacuo* to give a colourless compound (2.95g, 47%, 65-66°C) [Found: C: 75.58; H: 6.56. $C_{17}H_{18}O_3$ requires C: 75.55; H: 6.67%].

δ_H ($CDCl_3$; 400MHz)

2.10 (1H; m; J_{gem} = 14.0, $J_{6ax,5ax}$ = 9.5, $J_{6ax,5eq}$ = 5.0 Hz; H-6_{ax}), 2.57-2.63 (2H; m; H-6_{eq}, H-1b propenyl), 2.74-2.81 (2H; m; H-5_{ax}, H-1a propenyl), 2.94 (1H; dddd; J_{gem} = 18.5, $J_{5eq,6eq}$ = 9.3, $J_{5eq,6ax}$ = 5.0, $J_{5eq,3}$ = 2.0 Hz; H-5_{eq}). 3.72 (3H; s; ester -CH_3), 5.12-5.17 (2H; m; H-$3_{trans\text{-}propenyl}$ and H-$3_{cis\text{-}propenyl}$), 5.80 (1H; ddt; $J_{2\text{-}propenyl,3\text{-}trans\text{-}propenyl}$ = 17.3, $J_{2\text{-}propenyl,3\text{-}cis\text{-}propenyl}$ = 10.0, $J_{2\text{-}propenyl,1\text{-}propenyl}$ = 7.2 Hz; H-2 propenyl), 6.47 (1H; broad s; H-3), 7.39-7.44 (3H; m; Ph m and p-H), 7.53-7.57 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 80MHz)

25.3 (C-5), 29.8 (C-9), 38.4 (propenyl C-1), 52.3 (ester -CH_3), 55.3 (C-1), 118.8 (C-3 propenyl), 124.2 (C-3), 126.2 (Ph C-o), 128.7 (Ph C-m), 130.2 (Ph C-p), 133.2 (propenyl C-2), 137.9 (Ph-ipso), 158.5 (C-4), 171.5 (C-2), 195 (ester C=O).

ν_{max}/cm^{-1} (neat)

1640 (C=C), 1671 (enone C=O), 1728 (ester C=O).

3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135]

A mixture of ethyl 2-acetyl-5-oxo-5-phenyl-2-(2-propenyl)-pentanoate [134] (10g, 33.1mmol) and NaH (0.85g, 35.4mmol) in THF (50ml) was refluxed for 1 h. The mixture was acidified with aqueous hydrochloric acid (50ml, 1M) and extracted with dichloromethane (3 x 50ml). The combined organic layers were washed first with aqueous hydrochloric acid (50ml) and then with deionised water (50ml). The organic layer was dried ($MgSO_4$) and refluxed *in vacuo* to give a yellow oil. The oil was fractionally distilled to give a viscous yellow oil (2.53g, bp. 165-170°C/ 0.8mbar). The oil was dissolved in acetone (30ml) and cooled to -75°C to give a colourless precipitate. The product was washed with acetone (10ml at -75°C) and air-dried. The product was further dried in a desiccator ($CaCl_2$) *in vacuo* to give a colourless compound (4.96g, 70%, 48.6-49°C) [Found: C: 84.73; H: 7.56. $C_{15}H_{16}O$ requires C: 84.87; H: 7.60%]

δ_H ($CDCl_3$; 80MHz)

1.89 (1H; m; J_{gem} = 13.6, $J_{5ax,6}$ = 11.5, $J_{5ax,4ax}$ = 9.5, $J_{5ax,4eq}$ = 5.5 Hz; H-5_{ax}), 2.18-2.30 (2H; m; H-5_{eq}, H-1b-propenyl), 2.42 (1H; m; $J_{6,5ax}$ = 11.5, $J_{6,1a\text{-propenyl}}$ = 8.8, $J_{6,1b\text{-propenyl}}$ = 4.5, $J_{6,5eq}$ = 4.5 Hz; H-6), 2.68-2.77 (2H; m; H-4_{ax}, H-1a propenyl), 2.78-2.89 (1H; m; H-4_{eq}), 5.07-5.14 (2H; m; H-$3_{trans\text{-propenyl}}$ and H-$3_{cis\text{-propenyl}}$), 5.85 (1H; dddd; $J_{2\text{-propenyl},3\text{-trans-propenyl}}$ = 17.0, $J_{2\text{-propenyl},3\text{-cis-propenyl}}$ = 10.1, $J_{2\text{-propenyl},1a\text{-propenyl}}$ = 7.8, $J_{2\text{-propenyl},1b\text{-propenyl}}$ = 6.5 Hz; H-2 propenyl), 6.43 (1H; partially resolved doublet; J = 1.5 Hz; H-2), 7.41-7.43 (3H; m; Ph m and p-H), 7.54-7.57 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 80MHz)

27.43 (C-4), 27.36 (C-5), 33.7 (propenyl C-1), 45.3 (C-6), 116.7 (propenyl C-3), 125.0 (C-2), 126.6 (Ph C-o), 128.7 (Ph C-m), 129.8 (Ph C-p), 136.1 (propenyl C-2), 138.6 (Ph-ipso), 158.6 (C-3), and 200.7 (C-1).

ν_{max}/cm^{-1} (neat)

1649,1651 (allyl and enone C=C), 1669 (enone C=O).

Methyl 2-oxo-4-phenyl-1-(3-butenyl)cyclohex-3-ene-1-carboxylate [137]

A mixture of methyl 2-acetyl-(3-oxo-3-phenylpropyl)hex-5-enoate [132] (6g, 19.8mmol) and DBU (3.01g, 19.8mmol) in methanol (50ml) was refluxed for 30mins. The mixture was acidified with aqueous hydrochloric acid (30ml, 1M) and extracted with dichloromethane (3 x 50ml). The combined organic layers were washed first with aqueous hydrochloric acid (50ml) and then with deionised water (50ml). The organic layer was dried ($MgSO_4$) and refluxed *in vacuo* to give a yellow oil. The oil was fractionally distilled to give a viscous yellow oil (3.75g, bp. 184-189°C/0.6mbar). The oil was dissolved in hexane/ether (8:2, 20ml) and cooled to -50°C to give a white precipitate. The product was washed with hexane/ether (8:2, at -50°C) and air-dried. The product was further dried in a desiccator ($CaCl_2$) *in vacuo* to give a colourless compound (2.93g, 52%, 67-68°C) [Found: C: 76.08; H: 7.15. $C_{18}H_{20}O_3$ requires C: 76.03; H: 7.09%].

δ_H ($CDCl_3$; 400MHz)

1.95-2.29 (5H; m; H-1 butenyl, H-2 butenyl, H-6_{ax}), 2.58-2.64 (1H; m; H-6_{eq}), 2.75-2.81 (1H; m; H-5_{ax}), 2.90-2.99 (1H; m, H-5_{eq}), 3.72 (3H; s; ester -CH_3) 5.04-5.10 (2H; m; H-$4_{transbutenyl}$ and H-$4_{cis\text{-}butenyl}$), 5.80 (1H; ddt; $J_{3\text{-}butenyl,4\text{-}trans\text{-}butenyl}$ = 17.1, $J_{3\text{-}butenyl,4\text{-}cis\text{-}butenyl}$ = 10.0, $J_{3\text{-}butenyl,2\text{-}butenyl}$ = 7.0 Hz; H-3 butenyl), 6.45 (1H; broad s; H-3), 7.40-7.43 (3H; m; Ph m and p-H), 7.54-7.57 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 80MHz)

25.3 (C-5), 29.9 (C-6), 33.1 (butenyl C-1), 36.4 (butenyl C-2), 52.3 (ester -CH_3), 55.7 (C-1), 115.1 (butenyl C-4), 124.3 (C-3), 126.1 (Ph C-o), 128.7 (Ph C-m), 130.1 (Ph C-p), 137.4 (butenyl C-3), 138.0 (Ph-ipso), 158.2 (C-4), 171.0 (C-2), 195.4 (ester C=O)

ν_{max}/cm^{-1} (neat)

1638 (C=C), 1664.8 (enone C=O), 1723.5 (ester C=O).

Methyl 2-oxo-4-phenyl-1-(4-pentenyl)cyclohex-3-ene-1-carboxylate [138]

A mixture of methyl 2-acetyl-2-(3-oxo-3-phenylpropyl)hept-6-enoate [133] (7.2g, 22.7mmol) and DBU (3.46g, 22.7mmol) in methanol (50ml) was refluxed for 30mins. The mixture was acidified with aqueous hydrochloric acid (30ml, 1M) and

extracted with dichloromethane (3 x 50ml). The combined organic layers were washed first with aqueous hydrochloric acid (50ml) and then with deionised water (50ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. The oil was fractionally distilled to give a viscous yellow oil (3.75g, bp. 184-189°C/0.6mbar). The oil was dissolved in hexane/ether (8:2, 20ml) and cooled to -50°C to give a white precipitate. The product was washed with hexane/ether (8:2, at -50°C) and air-dried. The product was further dried in a desiccator ($CaCl_2$) *in vacuo* to give a colourless compound (3.39g, 50%, 70-72°C) [Found: C: 76.38; H: 7.50. $C_{19}H_{22}O_3$ requires C: 76.48; H: 7.43%].

δ_H ($CDCl_3$; 400MHz)

1.41-1.49 (2H; m; H-2 pentenyl) 1.78-1.86 (1H; m; H-1b-pentenyl) 1.98-2.13 (4H; m; H-6_{ax}, H-3 pentenyl, H-1a-pentenyl), 2.64 (1H; dt; J_{gem}=13.5, $J_{6eq,5eq}$ = 5.0, $J_{6eq,5ax}$ = 5.0 Hz; H-6_{eq}), 2.76 (1H; dt; J_{gem}=18.5, $J_{5ax,6ax}$ = 5.0, $J_{5ax,6eq}$ = 5.0 Hz; H-5_{ax}) 2.91-2.99 (1H; m; H-5_{eq}), 3.72 (3H; s; ester -CH_3) 4.96-5.06 (2H; m; H-$5_{trans\text{-}pentenyl}$ and H-$5_{cis\text{-}pentenyl}$), 5.81 (1H; ddt; $J_{5\text{-}pentenyl,4\text{-}trans\text{-}pentenyl}$ = 17.0, $J_{4\text{-}pentenyl,5\text{-}cis\text{-}pentenyl}$ = 10.0, $J_{4\text{-}pentenyl,3\text{-}pentenyl}$ = 6.7 Hz; H-4 pentenyl), 6.46 (1H; broad s; H-3), 7.41-7.43 (3H; m; Ph m and p-H), 7.54-7.59 (2H; m; Ph o-H).

δ_C ($CDCl_3$; 80MHz)

23.9 (pentenyl C-2), 25.4 (C-3), 29.9 (C-6), 33.3 (pentenyl C-1), 33.9 (pentenyl C-3), 52.3 (ester -CH_3), 56.1 (C-1), 114.8 (pentenyl C-5), 124.3 (C-3), 126.0 (Ph C-o), 128.7 (Ph C-m), 130.1 (Ph C-p), 138.0 (pentenyl C-4), 138.1 (Ph-ipso), 158.1 (C-4), 172.0 (C-2), 196.1 (ester C=O).

ν_{max}/cm^{-1} (neat)

1638 (C=C), 1664.8 (enone C=O), 1723.5 (ester C=O).

5-(hydroxymethyl)uracil [139] [25]

Uracil (4.65g, 41.5mmol) and paraformaldehyde (1.57g) were added to a solution of potassium hydroxide (1.6g) in deionised water (65ml). The solution was heated (oil bath at 50-60°C) with stirring for 72 h. The cloudy mixture was cooled and filtered. The clear filtrate was acidified with concentrated hydrochloric acid and set aside

overnight at 5°C. The resulting precipitate was filtered off and dried in a *vac* oven (60°C/1mbar) to give a colourless solid (4.302g, 73%):

δ_H (DMSO: 200MHz)

4.06 (3H; broad s; CH_2 and OH), 7.25 (1H; d; J = 0.2 Hz; H-6), 10.73 (1H; distorted d; NH-1), 11.04 (1H; s; NH-3).

δ_C (DMSO: 40MHz)

55.8 (CH_2), 112.8 (C-5), 138.4 (C-6), 151.5 (C-2), and 164.03 (C-4).

λ_{max}

(pH 2) 261nm; lit [24] (pH 2) 261nm, λ_{max} (pH 12) 286nm; lit [24] (pH 12) 285.5nm.

5-(chloromethyl)uracil [125] [26]

5-(hydroxymethyl)uracil [139] (10g, 71.4mmol) was dissolved in concentrated hydrochloric acid (60ml). The mixture was stirred at room temperature for 90 min. A colourless precipitate was collected and washed with concentrated hydrochloric acid (10ml). The product was dried *in vacuo* in a desiccator (P_2O_5). Further drying in a desiccator over $CaCl_2$ gave a colourless powder (8.09g, 72%): The compound was used without any further purification.

δ_H (DMSO; 200MHz)

4.39 (2H; s; $-CH_2Cl$), 7.73 (1H; d; J = 6 Hz; H-6), 11.0 (1H; partially resolved d; NH-1) and 11.27 (1H; s; NH-3).

δ_C (DMSO; 40MHz)

39.6 ($-CH_2Cl$), 109.1 (C-5), 142.7 (C-6), 151.3 (C-2), and 163.2 (C-4).

Methyl 2-acetyl-3-(5-uracilyl)propanoate [140]

Methyl acetoacetate (1.50g, 12.9mmol) was dissolved in dry DMF (20ml). Sodium hydride (0.168g, 7mmol) was added and the mixture was stirred until all the sodium hydride had dissolved. 5-(chloromethyl)uracil [125] (1g; 12.5mmol) was added and the mixture left stirring overnight at room temperature under nitrogen. The whitish

suspension was acidified with aqueous hydrochloric acid (30ml; 1M). The solution was extracted with dichloromethane (3x30ml). The combined organic layers were dried ($MgSO_4$) and reduced *in vacuo* to an oil. The oil was dissolved in methanol (20ml) and the solution was set aside overnight at 5°C to give a colourless precipitate. The solid was filtered off and the filtrate was cooled to 5°C for a further 24 h to precipitate more of the compound. The latter step was repeated several times to obtain the maximum yield. All samples were washed with methanol (10ml), dried in a desiccator ($CaCl_2$) and combined to give a colourless powder (1.15g, 76%, mp. 190-191°C).

δ_H (DMSO; 300MHz)

2.15 (3H; s; acetyl -CH_3), 2.60 (2H; dd; $J_{H\text{-}3b,H\text{-}3a}$ = 14.1, $J_{H\text{-}3b,H\text{-}2}$ = 7.4 Hz; H-3b), 2.69 (2H; dd; $J_{H\text{-}3a,H\text{-}3b}$ = 14.3, $J_{H\text{-}3a,H\text{-}2}$ = 7.4 Hz; H-3a), 3.65 (3H; s; ester -CH_3), 3.91 (1H; t; $J_{H\text{-}2,H\text{-}3a}$ = $J_{H\text{-}2,H\text{-}3b}$ = 7.4 Hz; H-2), 7.26 (1H; d; J = 5.5 Hz; uracil H-6), 10.76 (1H; distorted d; uracil NH-1), 11.27 (1H; broad s; uracil NH-3),

δ_C (DMSO; 60MHz)

25.0 (C-3), 29.0 (acetyl -CH_3), 52.2 (ester -CH_3), 57.2 (C-2), 108.0 (uracil C-5), 139.5 (uracil C-6), 151.2 (uracil C-2), 164.3 (uracil C-4), 169.4 (ester C=O) and 202.6 (acetyl C=O).

Ethyl 2-acetyl-3-(5-uracilyl)propanoate [141]

Ethyl acetoacetate (1.65g, 12.5mmol) was dissolved in dry DMF (20ml). Sodium hydride (0.3g, 12.5mmol) was added and the mixture stirred until all the sodium hydride had dissolved. 5-(Chloromethyl)uracil [125] (2g, 12.5mmol) was added and the mixture left stirring overnight at room temperature under nitrogen. The mixture was acidified with aqueous hydrochloric acid (20ml; 1M) and extracted with dichloromethane (3x50ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to a brown oil. The oil was dissolved in dry ethanol (40ml) and set aside overnight at 5°C. The colourless precipitate was filtered off and dried in a desiccator ($CaCl_2$) to give a colourless powder (1.59g, 49%, mp 145-146°C):

δ_H (DMSO; 200MHz)

1.12 (3 H; t; J = 7.0 Hz; ester -CH_3), 2.14 (3 H; s; acetyl -CH_3), 2.53-2.64 (1 H; m; H-3a and H-3b), 3.84 (2 H; t; $J_{H\text{-}2,H\text{-}3a} = J_{H\text{-}2,H\text{-}3b}$ = 6.5 Hz; H-2), 4.06 (2 H; q; J = 7.0 Hz; ester -CH_2), 7.20 (1 H; d; J = 6.0 Hz; uracil H-6), 10.71 (1 H; d; J = 5.2 Hz; uracil NH-1), and 11.10 (1 H; broaden s; uracil NH-3).

δ_C (DMSO; 40MHz)

13.8 (ester -CH_3), 24.9 (C-3), 28.8 (acetyl -CH_3), 57.3 (C-2), 60.8 (ester -CH_2), 108.0 (uracil C-5), 139.6 (uracil C-6), 151.2 (uracil C-2), 164.3 (uracil C-4), 169.0 (ester C=O), and 202.7 (acetyl C=O).

Methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150]

Sodium methoxide was added (0.05g in 5ml DMF) to a mixture of methyl 2-acetyl-3-(5-uracilyl)propanoate [140] (1g, 4.1mmol) and phenyl vinyl ketone (0.55g, 4.1mmol) in dry DMF (20ml) at 0°C. The mixture was stirred for 1 h then poured into aqueous hydrochloric acid (100ml; 1M). The cloudy suspension was set aside overnight at 5°C. The colourless product was filtered off, washed with deionised water (100ml), methanol (10ml) and acetone (20ml) and then recrystallised from methanol/acetonitrile (5:1). The product was dried in a desiccator ($CaCl_2$) under reduced pressure to give a colourless powder (0.75g, 49%, mp. 158-160°C).

δ_H (DMSO; 400MHz)

2.06 (3H; s; acetyl -CH_3), 2.48 (dd; 1H; J_{gem} = 14.0, $J_{H\text{-}3b,H\text{-}2}$ = 7.5 Hz; H-3b), 2.58 (dd; 1H; J_{gem} = 14.0, $J_{H\text{-}3a,H\text{-}2}$ = 6.5 Hz; H-3a), 3.29 (2H; t; $J_{H\text{-}1\text{-}3\text{-}oxo\text{-}3\text{-}phenylpropyl,H\text{-}2\text{-}3\text{-}oxo\text{-}3\text{-}phenylpropyl}$ = 6.5 Hz; H-1 3-oxo-3-phenylpropyl), 3.52 (3H; s; ester -CH_3), 3.75 (t; 1 H; $J_{H\text{-}2,H\text{-}3b} = J_{H\text{-}2,H\text{-}3a}$ = 7.3 Hz; H-2), 3.85 (2H; t; $J_{H\text{-}2\text{-}3\text{-}oxo\text{-}3\text{-}phenylpropyl,H\text{-}3\text{-}3\text{-}oxo\text{-}3\text{-}phenypropyl}$ = 6.3 Hz; H-2 3-oxo-3-phenylpropyl), 7.37-7.53 (2H; m; Ph m-H), 7.59 (1H; s; uracil H-6), 7.62-7.66 (2H; m; Ph p-H), 7.95-7.97 (1H; m; Ph o-H) and 11.3 (1H; broad s; uracil NH-3).

δ_C (DMSO; 80MHz)

25.1 (C-3), 28.9 (acetyl -CH_3), 37.0 (3-oxo-3-phenylpropyl C-1), 43.4 (3-oxo-3-phenylpropyl C-2), 52.2 (ester -CH_3), 57.2 (C-2), 108.5 (uracil C-5), 127.8 (Ph C-o),

128.6 (Ph C-m), 133.3 (Ph C-p), 136.1 (Ph-ipso), 143.4 (uracil C-6), 150.5 (uracil C-2), 163.6 (uracil C-4), 169.2 (ester C=O), 197.9 (3-oxo-3-phenylpropyl C-3) and 202.3 (acetyl C=O).

3-Phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one [147]

A mixture of methyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [150] (2g; 0.5mmol) and sodium methoxide (0.01g) in dry DMF (20ml) was refluxed (2h) under nitrogen. The mixture was cooled and poured into aqueous hydrochloric acid (100ml; 1M). The cloudy suspension was set aside overnight at 5°C. The colourless product was filtered off, washed with water (100ml) followed by methanol (10ml). The compound was recrystallised from ethyl acetate/DMF (10:1) and dried in a desiccator ($CaCl_2$) under reduced pressure to give a colourless powder, mp.151-153°C (0.54g, 28%).

δ_H (DMSO; 400MHz)

1.63-1.70 (1H; m; H-5_{ax}), 2.02-2.05 (1H; m; H-5_{eq}), 2.11 (1H; dd; J_{gem} = 14.1, $J_{H\text{-}b\text{-}uracilmethylene,6}$ = 9.0 Hz; H-b uracilmethylene), 2.59 (1H; ddd; $J_{6,5ax}$ = 13.5 Hz, $J_{6,H\text{-}b\text{-}uracilmethylene}$ = 9.3, $J_{6,H\text{-}a\text{-}uracilmethylene}$ = 4.4 Hz; H-6), 2.71-2.89 (3H; m; H-4_{eq}, H-4_{ax}, H-a uracilmethylene) 6.34 (1H; s; H-2), 7.26 (1H; s; uracil H-6), 7.43-7.45 (3H; m; Ph m- and p-H), 7.64-7.66 (2H; m; Ph o-H), 10.66 (1H; broad s; uracil H-1), 10.99 (1H; broad s; uracil H-3).

δ_C (DMSO; 80MHz)

26.0 (C-uracilmethylene), 26.4 (C-4), 26.8 (C-5), 43.7 (C-6), 109.4 (uracil C-5), 123.8 (C-2), 126.0 (Ph C-o), 128.6 (Ph C-m), 129.9 (Ph C-p), 138.0 (uracil C-6), 139.1 (Ph-ipso), 151.2 (uracil C-4), 158.6 (C-3), 164.4 (uracil C-2) and 200.0 (C-1).

ν_{max}/cm^{-1} (neat)

1644 (C=C enone), 1671 (enone C=O), 1728 (C=C uracil).

Ethyl 2-acetyl-3-{5-[1-(3-oxo-3-phenylpropyl)]uracilyl}propanoate [153]

To a mixture of ethyl 2-acetyl-3-(5-uracilyl)propanoate [141] (1g; 3.9mmol) and phenyl vinyl ketone (0.55g; 4.2mmol) in dry DMF (20ml) was added sodium

ethoxide (1ml of 1% solution) at 0°C. The mixture was stirred for 1 h then poured into aqueous hydrochloric acid (100ml; 1M). The cloudy suspension was set aside overnight at 4°C. The colourless product was filtered off and washed with deionised water (100ml). The product was dried in a desiccator under reduced pressure to give a colourless powder (0.32g; 21%).

δ_H (DMSO; 200MHz)

1.09-1.16 (3H; t; J = 7.0 Hz; ester -CH_3), 2.16 (3H; s; acetyl -CH_3), 2.55-2.70 (2H; m; H-3a and H-3b), 2.86 (2 H; t; $J_{\text{H-1-3-oxo-3-phenylpropyl,H-2-3-oxo-3-phenylpropyl}}$ = 5.8 Hz; H-1 3-oxo-3-phenylpropyl), 3.84 (t; 1 H; $J_{\text{H-2,H-3b}} = J_{\text{H-2,H-3a}}$ = 7.2 Hz; H-2), 4.08-4.15 (4H; m; H-2 3-oxo-3-phenylpropyl and ester -CH_2), 7.49-7.67 (4H; m; Ph m-H, Ph p-H and uracil H-6,), 7.89-7.94 (2H; m; Ph o-H), 11.33 (1H; d; J = 10.6 Hz; uracil H-3).

δ_C (DMSO; 200MHz)

13.8 (ester -CH_3), 25.1 (uracil -CH_2), 28.9 (acetyl -CH_3), 37.0 (C-3), 43.4 (C-4), 60.9 (C-2), 108.6 (uracil C-5), 128.0 (Ph C-o), 128.8 (Ph C-m), 133.5 (Ph C-p), 136.2 (Ph-ipso), 143.6 (uracil C-6), 150.7 (uracil C-2), 163.8 (uracil C-4), 168.9 (ester C=O), 198.1 (C-5) and 202.6 (acetyl C=O).

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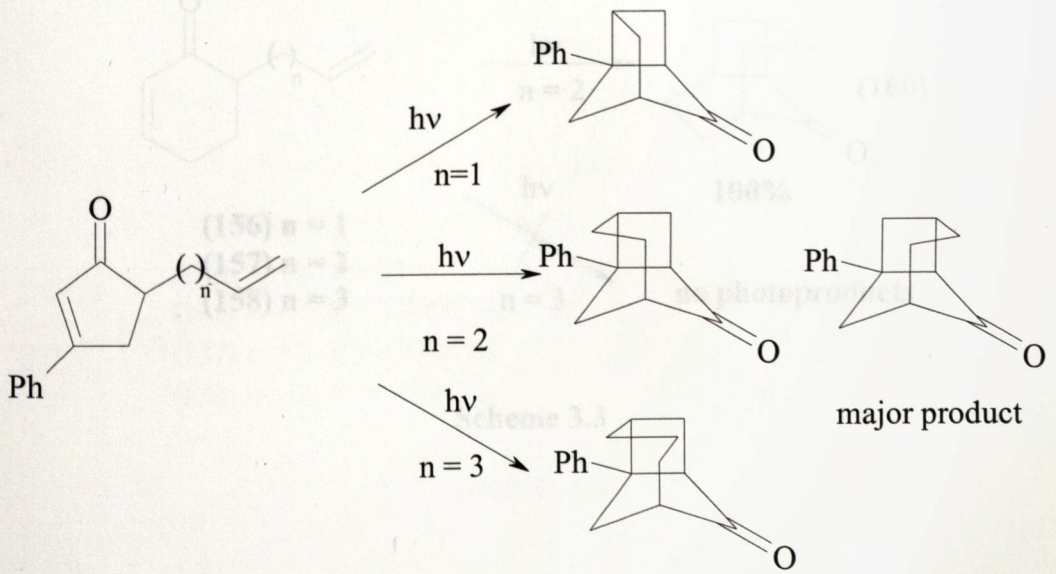
Chapter 3

Chapter 3

3.0 Introduction

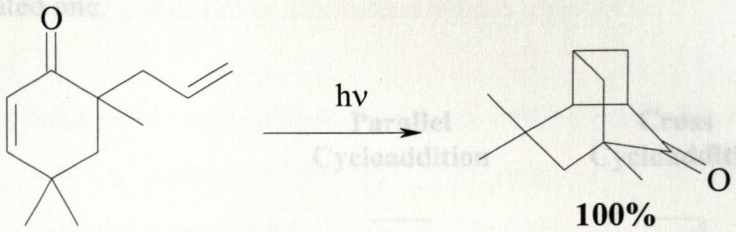
The photochemical [2+2] cycloaddition reactions of alkenes to α,β unsaturated cyclic carbonyl compounds have been of interest for many years. Intermolecular cycloaddition reactions have been widely investigated, however the lack of regiochemical control in enone cycloaddition has been a limiting factor in its synthetic applications. Several factors have been employed to influence the regioselectivity namely reaction conditions and the structural framework of the reagents.[1-4] Adjustments of the reaction conditions include change of solvent, temperature, and concentration while structural framework adjustments include both substitution on the ene and enone functionality with electron withdrawing or donating groups. In addition, ring size and substitution on other positions of the enone ring and alkene have been shown to influenced the regiochemistry.

Despite these adjustments the regiochemical control of [2+2] intermolecular reactions is in general quite poor. This has led to intense interest in [2+2] intramolecular reactions where regioselectivity is high because of geometrical constraints. McMurry and co-workers [5,6] reported that the regiochemistry was predictable in a series of substituted cyclopentenones with photoadducts alternating between parallel and cross-products as the number of atoms between the double bonds increased (Scheme 3.1).



Scheme 3.1

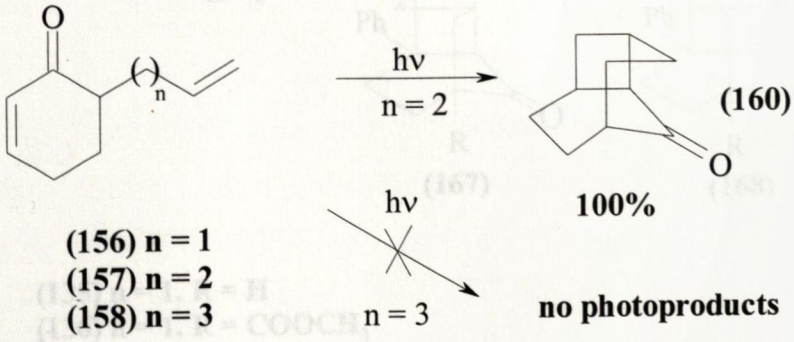
Margartha and co-workers showed that 6-allyl-6-methyl-4-dimethycyclohex-2-en-1-one [154] gave exclusively the parallel photoproduct [155] (Scheme 3.2).[7] Lakshmi and Rao studied a series of 6-(ω-alkenyl)-cyclohex-2-en-1-ones [156-158] (Scheme 3.3) and found that 6-allyl-cyclohex-2-en-1-one [156] afforded the cross photoadduct [159] exclusively.[8] A cross photoproduct [160] was also obtained from 6-(3-butenyl)-cyclohex-2-en-1-one [157], while 6-(3-pentenyl)cyclohex-2-en-1-one [158] did not undergo cycloaddition even after prolonged irradiation.



100%

(154) **(155)**

Scheme 3.2



(159)

100%

(160)

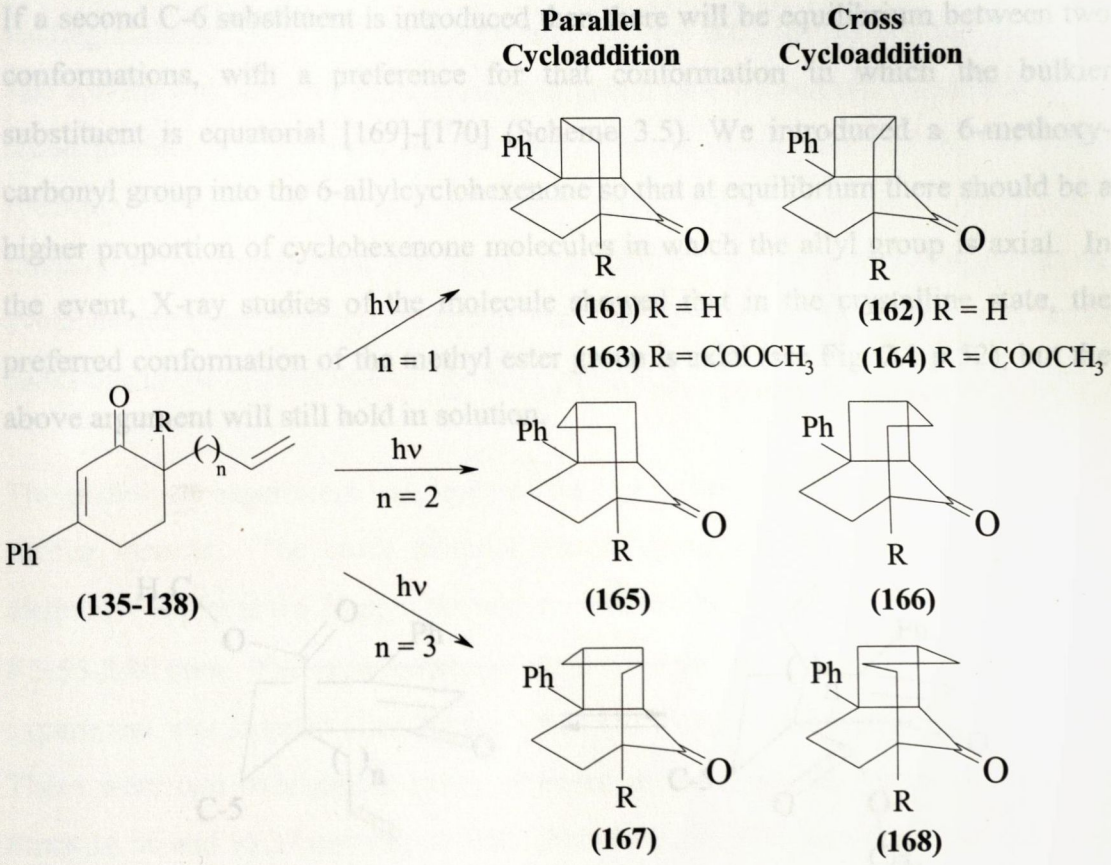
100%

(156) n = 1
(157) n = 2
(158) n = 3

no photoproducts

Scheme 3.3

A series of compounds containing the 3-phenylcyclohex-2-en-1-one moiety tethered with an all carbon chain of varying length [135]-[138] (Scheme 3.4) was irradiated to study the photochemical reactions of 3-phenylcyclohexenones. There are two possible photoadducts for each photochemical reaction resulting from parallel and cross cycloaddition (Scheme 3.4). It was hoped that the preorganisation of the molecule using the methyl ester group would establish that the reacting double bonds were in close proximity for [2+2] cycloaddition to occur and the side chain would adopt specific conformation and hence control the regiochemistry. The situation is a more complicated one.



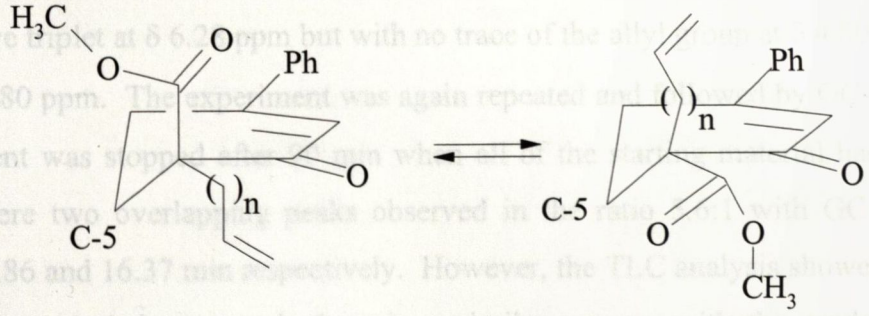
(135) n = 1, R = H
(136) n = 1, R = $COOCH_3$
(137) n = 2, R = $COOCH_3$
(138) n = 3, R =$COOCH_3$

Scheme 3.4

3.1 Conformations of the cyclohexenone ring

Excluding all other factors the intramolecular photocycloaddition of substituted cyclic enones with all carbon chains is dependent on the chromophores being in close proximity to each other. In the case of 6-substutited cyclohexenones [8] the ideal conformation for minimum separation is for the chain to be in an axial position. The cyclohexenone ring in the ground state has all carbons in a planar configuration except for C-5 (Scheme 3.5).[9] However if there is a single C-6 substituent, this can adopt either an axial or equatorial conformation with a preference for the latter.

If a second C-6 substituent is introduced then there will be equilibrium between two conformations, with a preference for that conformation in which the bulkier substituent is equatorial [169]-[170] (Scheme 3.5). We introduced a 6-methoxy-carbonyl group into the 6-allylcyclohexenone so that at equilibrium there should be a higher proportion of cyclohexenone molecules in which the allyl group is axial. In the event, X-ray studies of the molecule showed that in the crystalline state, the preferred conformation of the methyl ester group is axial (see Fig. 2.1 p 52), but the above argument will still hold in solution.



n = 1, 2, 3

(169) (170)

Scheme 3.5

3.2 Results

3.21 Photolysis of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]

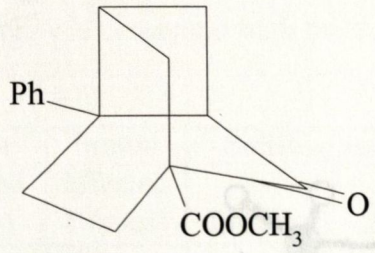
A solution of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136] (2.0g) in acetonitrile (450ml) was irradiated for 12 h and followed by TLC, (hexane/ether 8:2). The TLC showed a single spot after 1 h, which appeared to be starting material. Further observations using a different elution system (ether/pet ether 8:2) showed it to be a new spot with a slightly different rf value than that of the starting material, (rf = 0.65 for the product and rf = 0.60 for the starting material). The solvent was removed under vacuum to give a dark viscous oil. A sample of the crude product was analysed by ^{1}H NMR. Initial examination of the ^{1}H NMR spectrum showed a signal at δ 6.28 ppm corresponding to olefinic hydrogen(s). Initially we presumed that the signal was due to the olefinic hydrogen in the cyclohexenone and that cycloaddition was not complete. There were also small peaks due to the hydrogens from the allyl group at δ 4.80-5.20 and δ 5.55-5.80 ppm.

The photolysis experiment was repeated for 12 h. The solution was worked up in a similar manner. The crude material was analysed by ^{1}H NMR and showed a distinctive triplet at δ 6.28 ppm but with no trace of the allyl group at δ 4.80-5.20 and δ 5.55-5.80 ppm. The experiment was again repeated and followed by GC-MS. The experiment was stopped after 90 min when all of the starting material had reacted. There were two overlapping peaks observed in the ratio 5.6:1 with GC retention times 16.86 and 16.37 min respectively. However, the TLC analysis showed a single spot. The solution was worked up in a similar manner with the crude material affording similar ^{1}H NMR results. The crude material was purified by flash chromatography (hexane/ether 9:1) to give a colourless oil. The ^{1}H NMR of the oil was similar to the crude material.

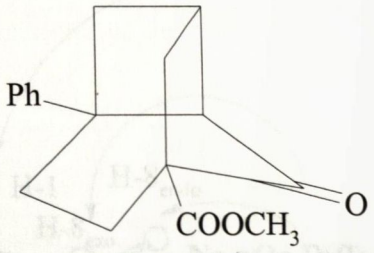
The minor component was isolated by dissolving the oil in hexane/ether 9:1 and cooling to -50°C to give a colourless compound. The compound was filtered, washed with hexane/ether (9:1) at -50°C, and dried *in vacuo* in a desiccator to afford

a colourless powder (38 mg) of melting point 136-137°C. The cooling process was repeated several times on the filtrate, to afford a further 51mg of photoproduct (total mass after drying 78mg, 3.9%). A sample of the compound was analysed by GC-MS. It possessed a retention time of 16.37 min corresponding to the minor photoproduct. This photoproduct was analysed by NMR techniques.

The ^{1}H NMR spectrum (Fig. 3.2 and 3.3) indicated the presence of eighteen hydrogens and the notable absence of any olefinic peaks from the starting material in the region δ 5-7 ppm. The ^{13}C NMR spectrum (Fig. 3.4) displayed fourteen peaks as expected. The 1-D DEPT (Fig. 3.5) showed the presence of five quaternary peaks, four -CH_2 peaks and a further six protonated peaks consisting of five CH peaks and one CH_3 peak as confirmed by the 2-D HETCOR spectrum (Fig. 3.6). There are two possible photoproducts for the photolysis of the methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136], parallel [163] and cross-adducts [164]. In our assignment of the NMR peaks below [163], and other photoproducts some of the *exo* and *endo* assignments may appear ambiguous, but agree with the established nomenclature (see Appendix).



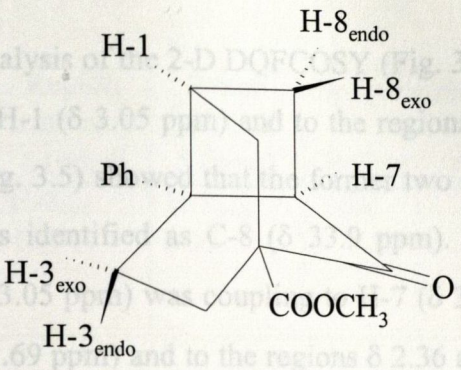
(163)



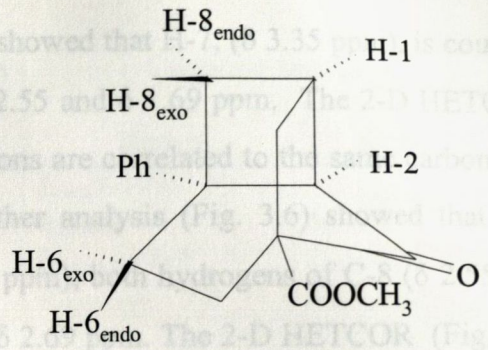
(164)

Analysis of the nOe difference spectrum (Fig. 3.7) for the irradiation of the phenyl ortho hydrogens showed enhancement of peaks at δ 3.35 (+ 2.31), δ 3.05 (+ 2.00), δ 1.73-1.78 (+ 0.40) and δ 1.88 ppm (+ 0.38). Analysis of the 2-D HETCOR (Fig. 3.6) identified these regions as a CH (δ 3.35 ppm), a CH (δ 3.05 ppm) and a CH_2 (δ 1.73-1.78 and δ 1.88 ppm). If the photoproduct has the structure [163] then the CH peak at δ 3.35 ppm is identified as H-7 as it is further downfield than H-1 due to the additive effects of the phenyl and carbonyl group. If the structure is [164] this CH

peak at δ 3.35 ppm is identified as H-2. Therefore the CH peak at δ 3.05 ppm was assigned to H-1 for both [163] and [164].

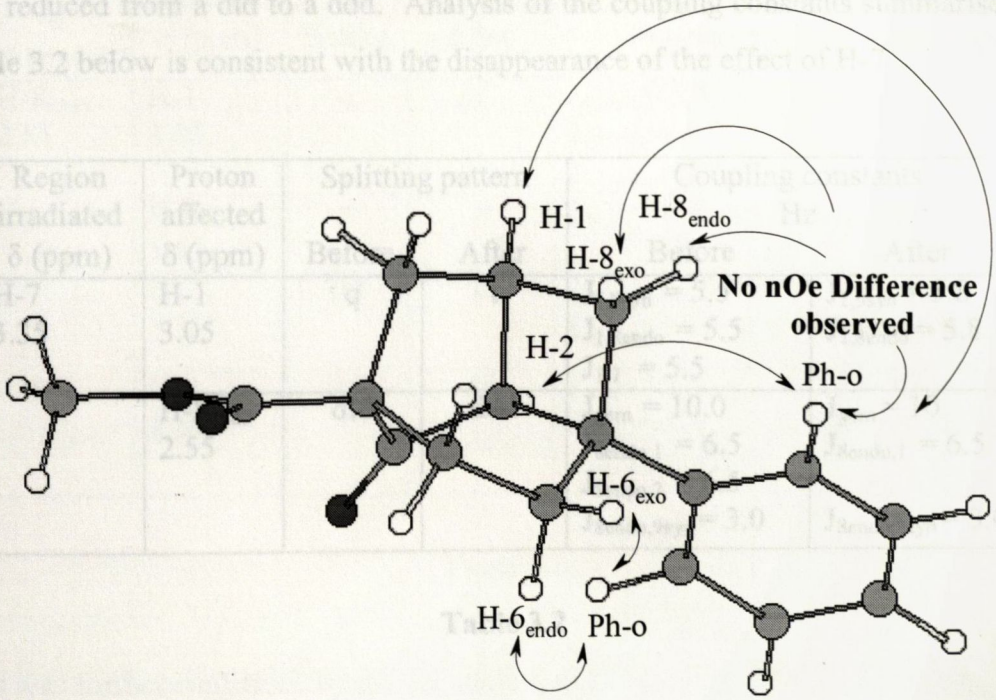


(163)



(164)

If we consider structure [163] then the CH_2 (δ 1.73-1.78 and δ 1.88 ppm) can only be C-3 as C-8 is too far away to experience an nOe for both hydrogens. The hydrogens on C-3 were identified as H-3_{exo} (δ 1.73-1.78 ppm) is closer to the o-H than H-3_{endo} (δ 1.88 ppm) and therefore experience a larger nOe. With [164] this CH_2 is C-6. The orientation of the phenyl group in relation to H-1 in structure [164] suggests that because of the large nOe for H-1 (δ 3.05 ppm) of + 2.00 there should also be an nOe for the H-8_{endo} but this is not the case (Fig. 3.1).



(164)

Fig 3.1

This suggests that photoproduct cannot be [164]. The photoproduct was identified as the parallel photoproduct methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] (see Appendix).

Analysis of the 2-D DQFCOSY (Fig. 3.8) showed that H-7, (δ 3.35 ppm), is coupled to H-1 (δ 3.05 ppm) and to the regions δ 2.55 and δ 1.69 ppm. The 2-D HETCOR (Fig. 3.5) showed that the former two regions are correlated to the same carbon and was identified as C-8 (δ 33.9 ppm). Further analysis (Fig. 3.6) showed that H-1 (δ 3.05 ppm) was coupling to H-7 (δ 3.35 ppm), both hydrogens of C-8 (δ 2.55 and δ 1.69 ppm) and to the regions δ 2.36 and δ 2.69 ppm. The 2-D HETCOR (Fig. 3.6) showed that the latter two regions are correlated to the same carbon and was identified as C-9 (δ 35.2 ppm).

The C-8 hydrogens where identified by analysis of the coupling constants. The 2-D DQFCOSY (Fig. 3.8) demonstrates that H-7 (δ 3.35 ppm) showed a vicinal splitting with H-8_{endo} (δ 2.55 ppm) (J = 6.5 Hz) and by long range coupling to H-1 (δ 3.05 ppm) (J = 5.5 Hz). This was confirmed in the decoupling spectrum for the irradiation of H-7 (Fig. 3.9b) where H-1 was reduced from a 'quartet' to a 'triplet' and H-8_{endo} was reduced from a dtd to a ddd. Analysis of the coupling constants summarised in Table 3.2 below is consistent with the disappearance of the effect of H-7.

Region irradiated δ (ppm)	Proton affected δ (ppm)	Splitting pattern		Coupling constants Hz	
		Before	After	Before	After
H-7 3.35	H-1 3.05	q	t	$J_{1,9syn}$ = 5.5 $J_{1,8endo}$ = 5.5 $J_{1,7}$ = 5.5	$J_{1,9syn}$ = 5.8 $J_{1,8endo}$ = 5.8
	H-8_{endo} 2.55	dtd	ddd	J_{gem} = 10.0 $J_{8endo,1}$ = 6.5 $J_{8endo,7}$ = 6.5 $J_{8endo,9syn}$ = 3.0	J_{gem} = 10 $J_{8endo,1}$ = 6.5 $J_{8endo,9syn}$ = 3.0

Table 3.2

The absence of any measured coupling constant in the decoupling experiments between H-7 and H-8_{exo} (δ 1.69 ppm) is indicative of a dihedral angle of ≈ 90°. This is further confirmed by examination of the decoupling spectrum of H-8_{exo} (Fig.

3.10c), which shows only a reduction in the splitting pattern of H-8_{endo} (Table 3.3). There is also no coupling between H-8_{exo} and H-1, (Fig. 3.10c) again due to a dihedral angle of ≈ 90°.

Region irradiated δ (ppm)	Proton affected δ (ppm)	Splitting pattern		Coupling constants Hz	
		Before	After	Before	After
H-8_{exo} 1.69	H-8_{endo} 2.55	dtd	td	J_{gem} = 10.0 $J_{8endo,1}$ = 6.5 $J_{8endo,7}$ = 6.5 $J_{8endo,9syn}$ = 3.0	$J_{8endo,1}$ = 7.0 $J_{8endo,7}$ = 7.0 $J_{8endo,9syn}$ = 2.7

Table 3.3

The C-9 hydrogens were identified by analysis of the decoupled spectrum of H-8_{endo} (δ 2.55 ppm) (Fig. 3.10b). A reduction in the splitting patterns of H-8_{exo} (δ 1.69 ppm), H-1 (δ 3.05 ppm), H-7 (δ 3.35 ppm) and the region δ 2.36 ppm were observed (Table 3.4). This region was assigned to H-9_{syn} due to the symmetry requirement for W-coupling.

Region irradiated δ (ppm)	Proton affected δ (ppm)	Splitting pattern		Coupling constants Hz	
		Before	After	Before	After
H-8_{endo} 2.55	H-1 3.05	q	t	$J_{1,9syn}$ = 5.5 $J_{1,8endo}$ = 5.5 $J_{1,7endo}$ = 5.5	$J_{1,9syn}$ = 5.5 $J_{1,7endo}$ = 5.5
	H-8_{exo} 1.69	d	s	J_{gem} = 10.0	
	H-7 3.35	dd	d	$J_{7endo,8endo}$ = 6.5 $J_{7endo,1}$ = 5.5	$J_{7endo,1}$ = 5.5
	H-9_{syn} 2.36	ddd	dd	J_{gem} = 12.5 $J_{9syn,1}$ = 5.5 $J_{9syn\ 8endo}$ = 3.0	J_{gem} = 12.5 $J_{9syn,1}$ = 5.5

Table 3.4

This was further confirmed by the decoupling of H-9_{anti} (Fig. 3.9d), which resulted in the reduction of the splitting patterns for H-9_{syn} (δ 2.36 ppm) and H-4_{endo} (δ 2.55 ppm) (Table 3.5). The 2-D HETCOR (Fig. 3.5) identified H-9_{anti} at δ 2.69 ppm.

Region irradiated δ (ppm)	Proton affected δ (ppm)	Splitting pattern Before	Splitting pattern After	Coupling constants Hz Before	Coupling constants Hz After
H-9_{anti} 2.69	H-9_{syn} 2.36	ddd	dd	J_{gem}= 12.5 $J_{9syn,1}$= 5.5 $J_{9syn\ 8endo}$ = 3.0	$J_{9syn,1}$= 5.5 $J_{9syn\ 8endo}$ = 3.0
	H-4_{endo} 2.19-2.30	m	m		

Table 3.5

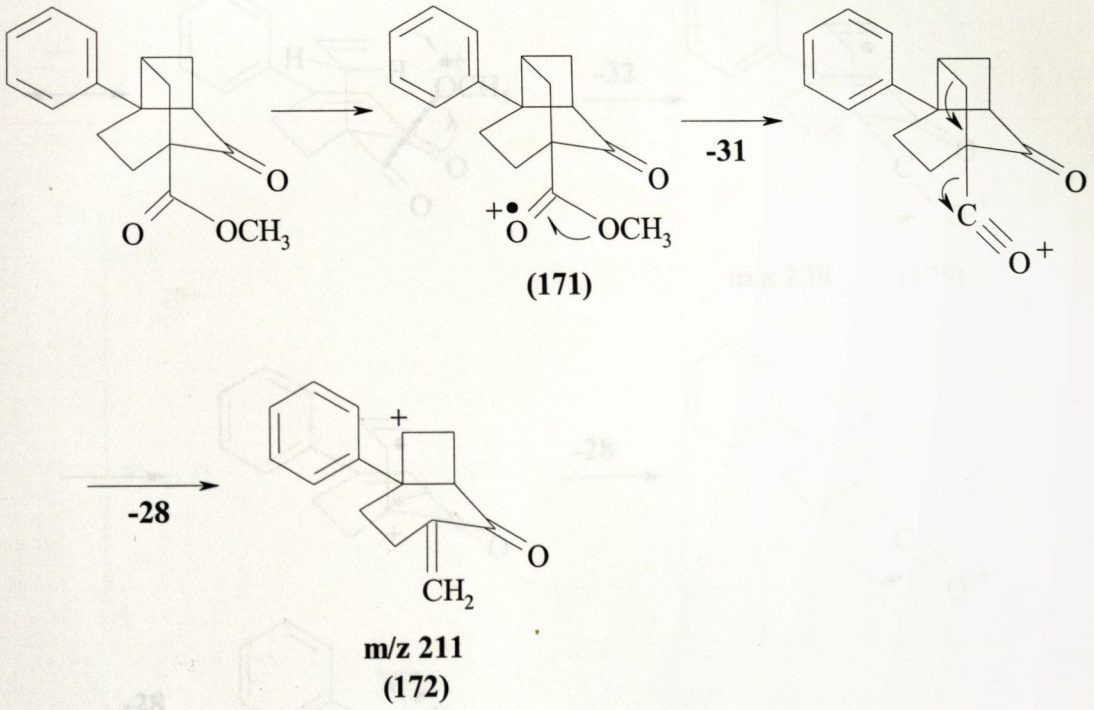
The decoupling of H-1 (δ 3.05 ppm) (Fig. 3.9c) resulted in the reduction of the splitting patterns for H-8_{endo} (δ 2.55), H-9_{syn} (δ 2.36), and H-7 (δ 3.35 ppm) (Table 3.6). Analysis of the decoupled spectra of H-7 (Fig. 3.9a) and H-8_{endo} (Fig. 3.10b), showed that H-1 was reduced from a quartet to triplet. This implied that $J_{1,8endo}$ = $J_{1,9syn}$ = $J_{1,7}$ = 5.5 Hz giving a splitting pattern of a quartet. The absence of any measured coupling constant in the decoupling experiments between H-9_{anti} and H-1 (Fig. 3.9b) (δ 1.69 ppm) is indicative of a dihedral angle of ≈ 90°.

Region irradiated δ (ppm)	Proton affected δ (ppm)	Splitting pattern Before	Splitting pattern After	Coupling constants Hz Before	Coupling constants Hz After
H-1 3.05	H-7 3.35	q	d	$J_{7,8endo}$ = 5.5 $J_{7,1}$ = 5.5	$J_{7,8endo}$ = 5.5
	H-8_{endo} 2.55	dtd	ddd	J_{gem} = 10.0 $J_{8endo,1}$ = 6.5 $J_{8endo,7}$ = 6.5 $J_{8endo,9syn}$ = 3.0	J_{gem} = 10 $J_{8endo,7}$ = 6.5 $J_{8endo,9syn}$ = 3.0
	H-9_{syn} 2.36	ddd	dd	J_{gem} = 12.5 $J_{9syn,1}$ = 5.5 $J_{9syn\ 8endo}$ = 3.0	J_{gem} = 12.5 $J_{9syn\ 8endo}$ = 3.0

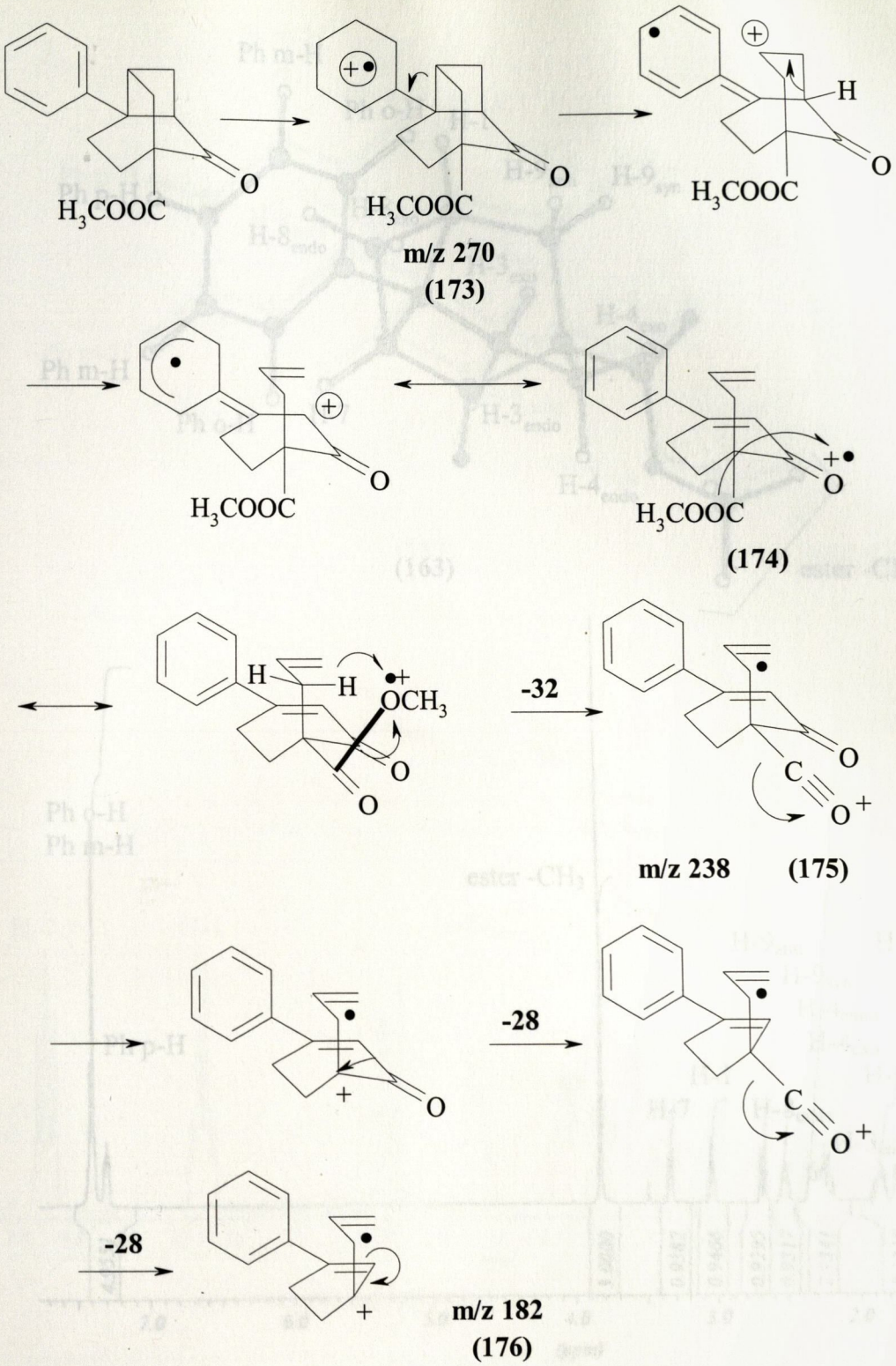
Table 3.6

The remaining two hydrogens in the region δ 2.19-2.30 ppm were correlated to the same carbon at δ 31.0 ppm and were assigned to C-4. The 2-D DQFCOSY (Fig. 3.8) identified H-8_{endo} further downfield than H-8_{exo} as it showed long range coupling to H-9_{syn}. The remaining hydrogen and carbon assignments are summarised in Tables 3.7 and 3.8 respectively.

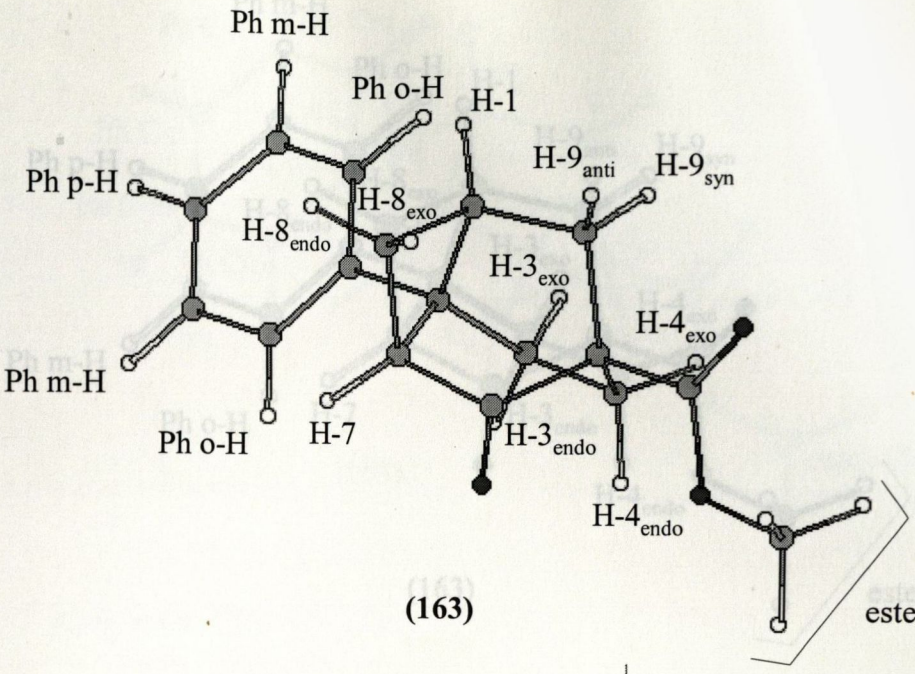
The photoproduct was further analysed by mass spectrometry. There are two concerted mechanisms involved with the generation of the radical cation in the mass spectrum. The first mechanism (Scheme 3.6) involves loss of an electron from the carbonyl group on the methyl ester [171] resulting in loss of the ester group affording an ion of m/z = 211 ($M^{+\cdot}$ -59) [172]. The second and most favourable involves the loss of an electron from the phenyl group which afforded a molecular ion, $M^{+\cdot}$, m/z = 270 [173] (Scheme 3.7). Molecular rearrangement affords the starting enone with the radical cation centred on the carbonyl group of the ring [174]. The radical cation undergoes further rearrangement with loss of -$HOCH_3$ to give the ion m/z = 238, ($M^{+\cdot}$ -32) [175]. Further loss of the two carbonyl groups affords the base peak m/z = 182 (100%) ($M^{+\cdot}$ -88) [176].



Scheme 3.6



Scheme 3.7



(163)

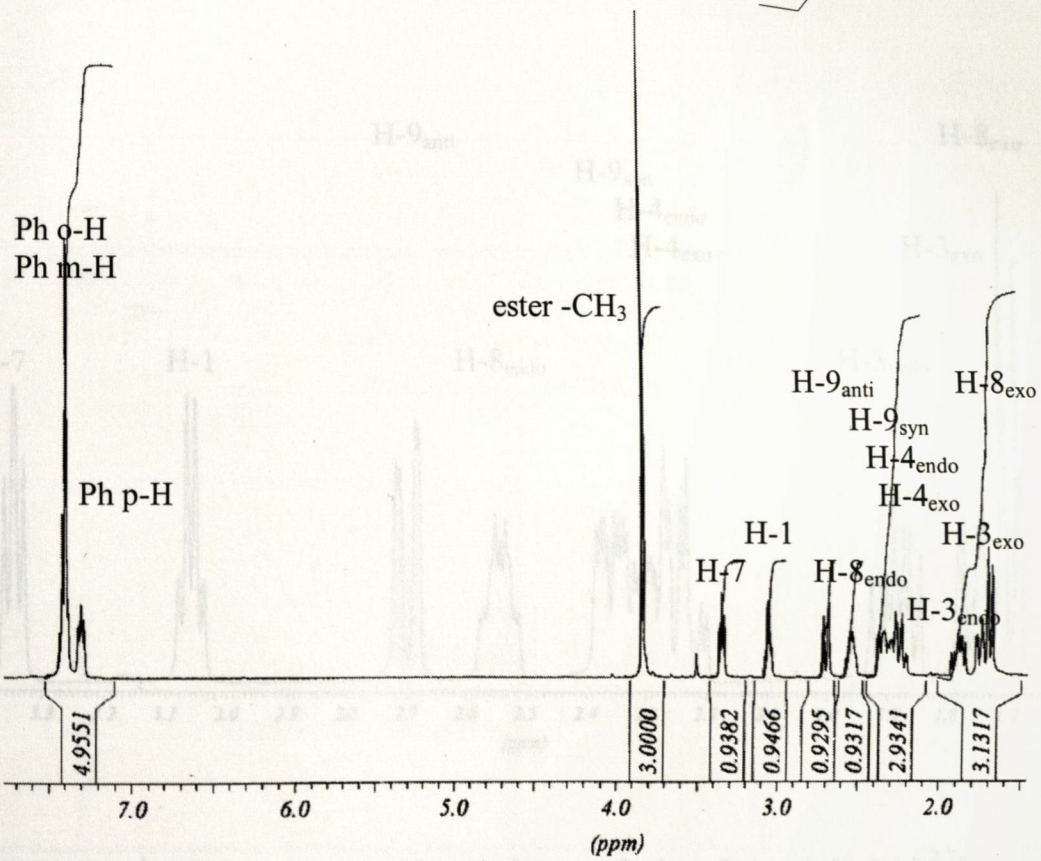
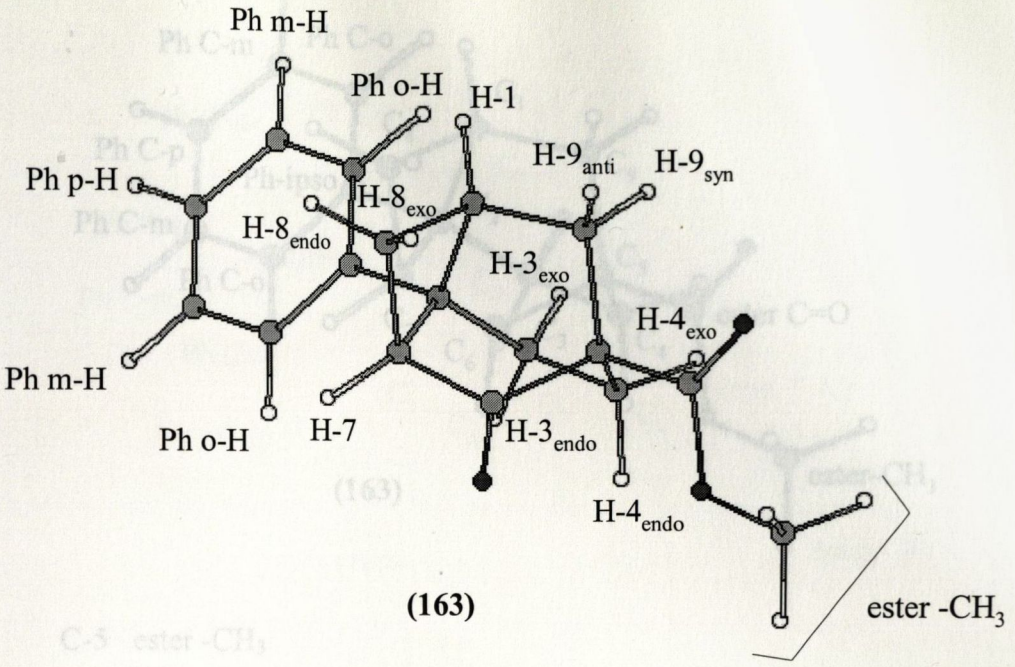


Fig. 3.2 The ^{1}H NMR spectrum of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163].



(163)

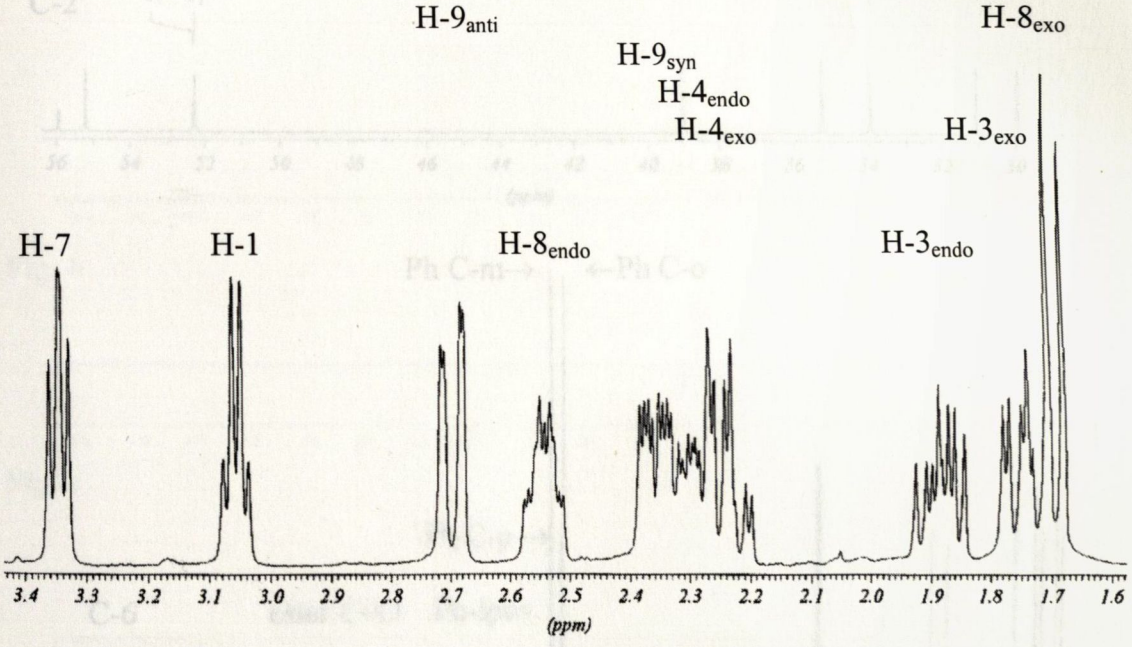
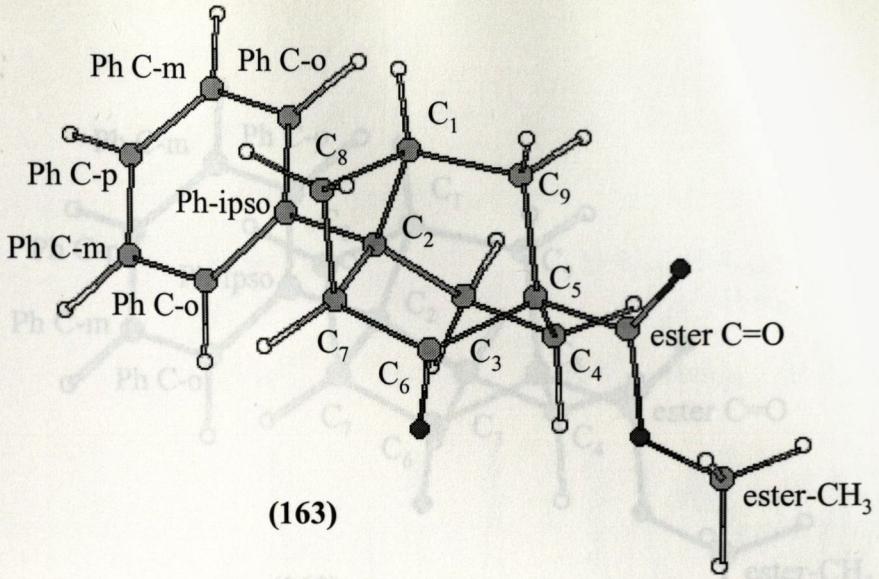


Fig. 3.3 The ^{1}H NMR spectrum of methyl 6-oxo-2-phenyltricyclo[3.3.1.0^{2,7}]nonane-5-carboxylate [163] expanded in the region δ 1.7-3.4 ppm.



(163)

C-5 ester -CH_3

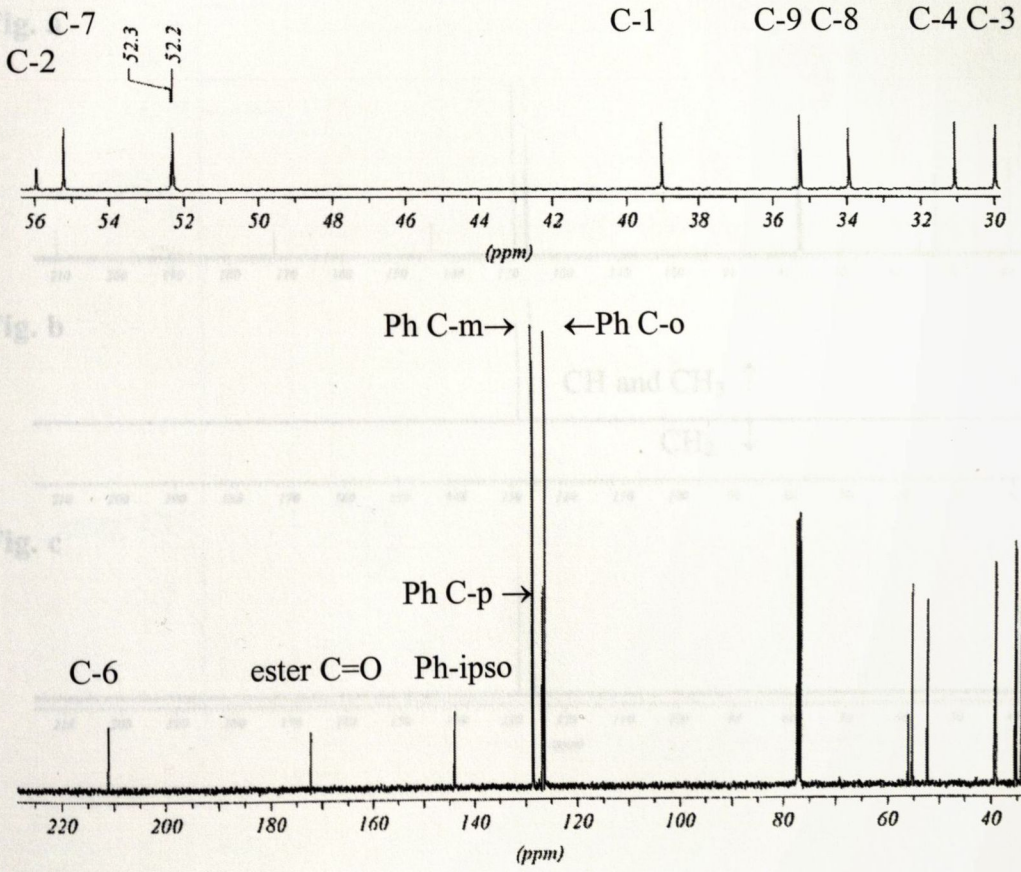
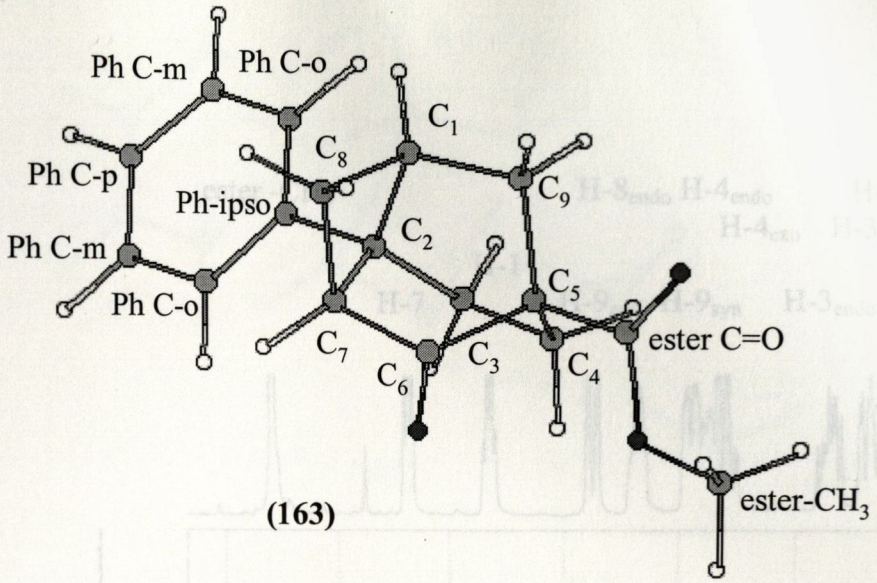


Fig. 3.4 The ^{13}C NMR spectrum of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]-nonane-5-carboxylate [163].



(163)

Fig. a

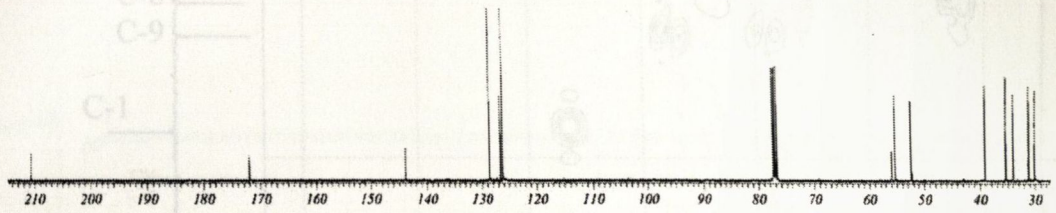


Fig. b

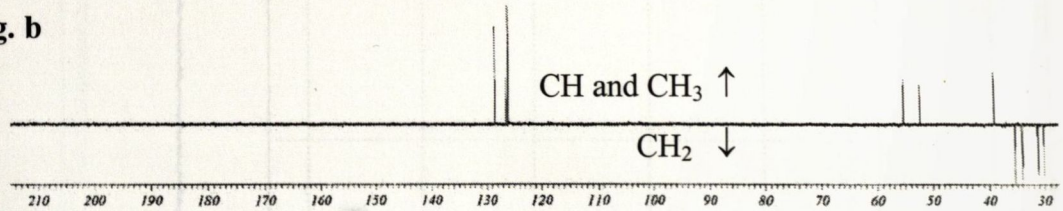


Fig. c

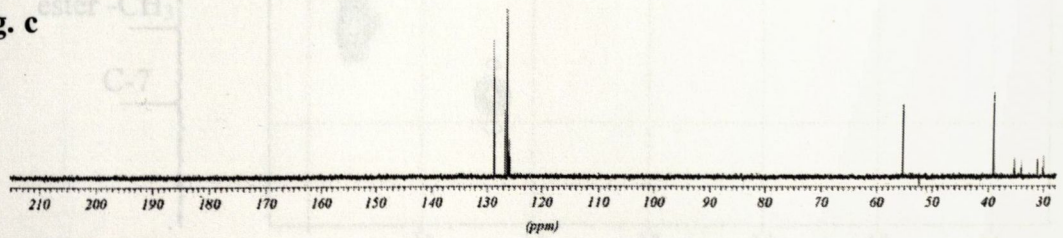


Fig. 3.5 The 1-D DEPT spectrum of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]-nonane-5-carboxylate [163]. **Fig. a** All carbon peaks. **Fig. b** All protonated carbon peaks with CH's and CH_3's pointing up and CH_2's pointing down. **Fig. c** All CH's and CH_3's carbon peaks.

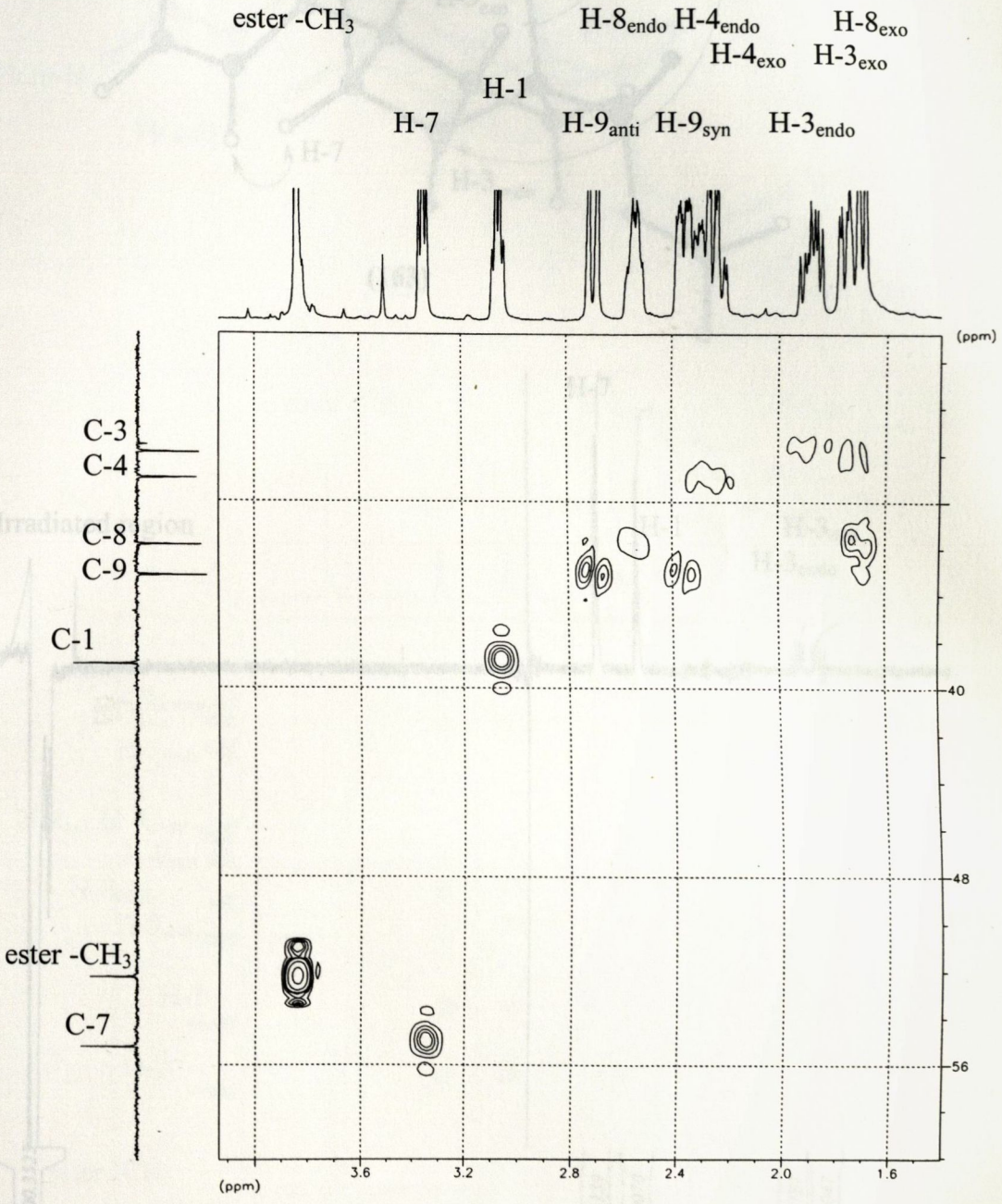
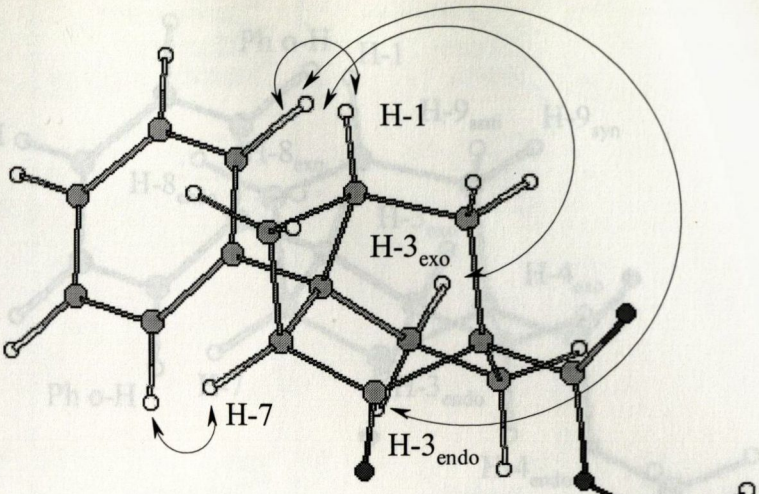


Fig. 3.6 The 2-D HETCOR spectrum of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]-nonane-5-carboxylate [163] expanded in the region δ 1.5-3.8 ppm.



(163)

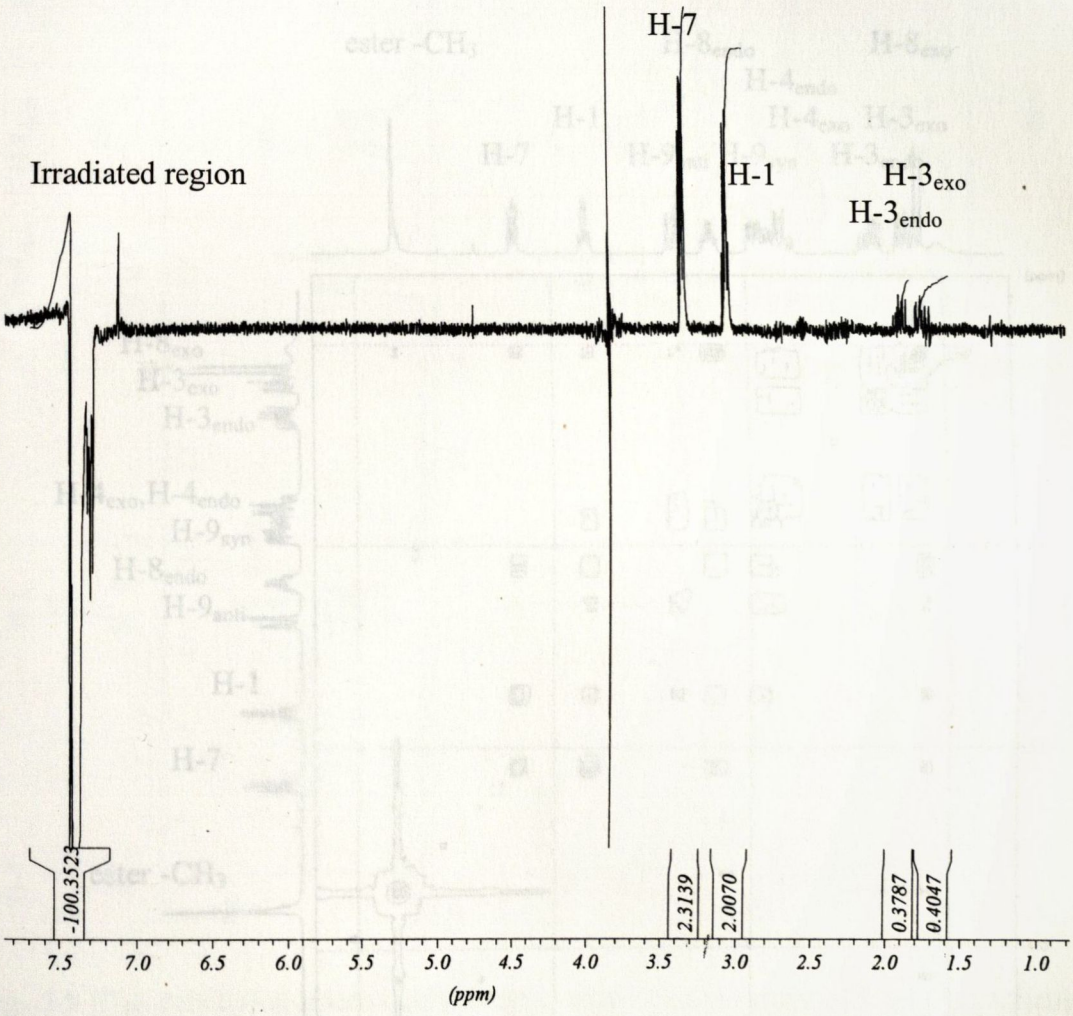


Fig. 3.7 The nOe difference spectrum of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]-nonane-5-carboxylate [163] for the irradiation of the ortho hydrogens.

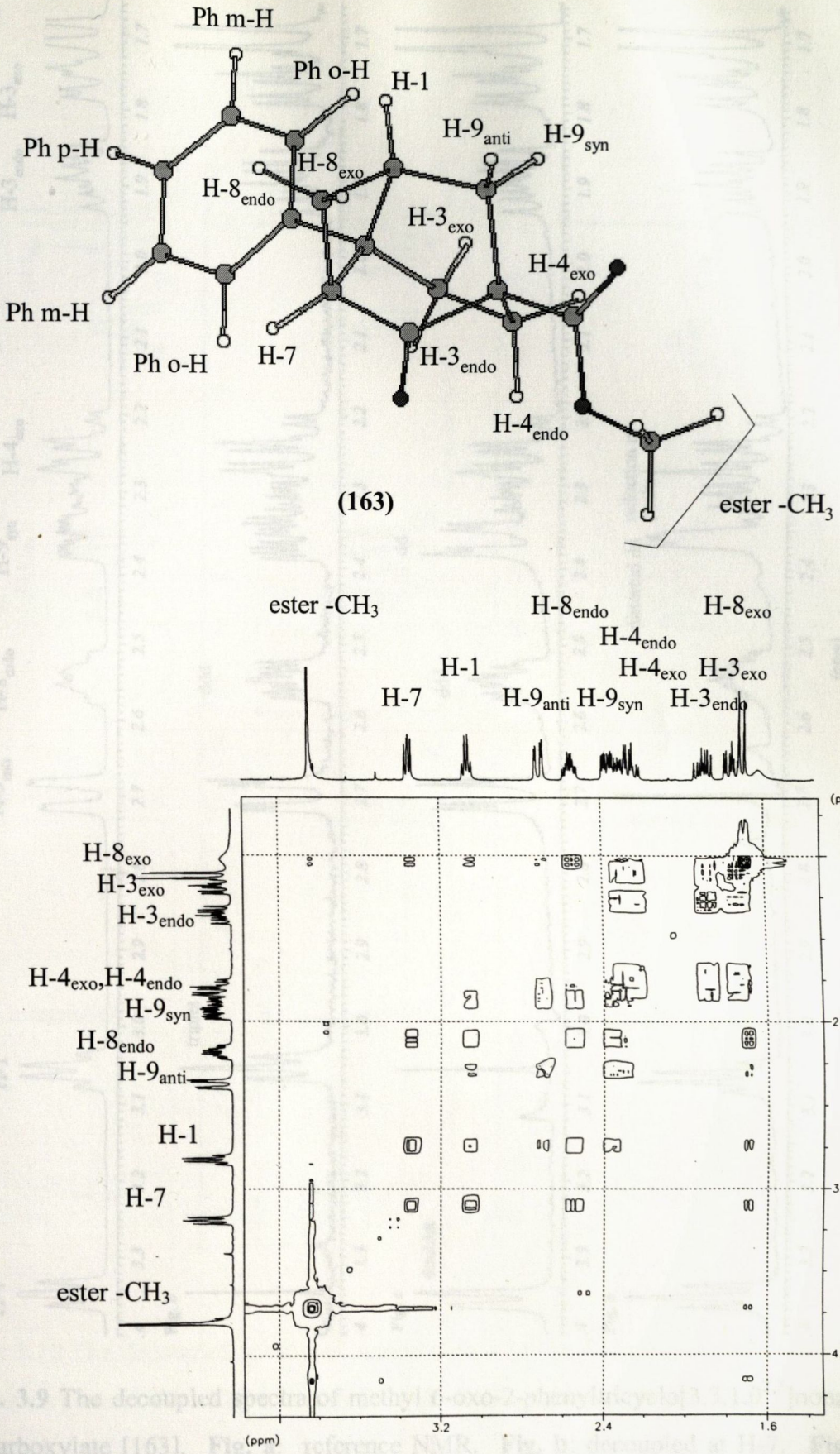


Fig. 3.8 The 2-D DQFCOSY spectrum of methyl 6-oxo-2-phenyltricyclo-[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163]

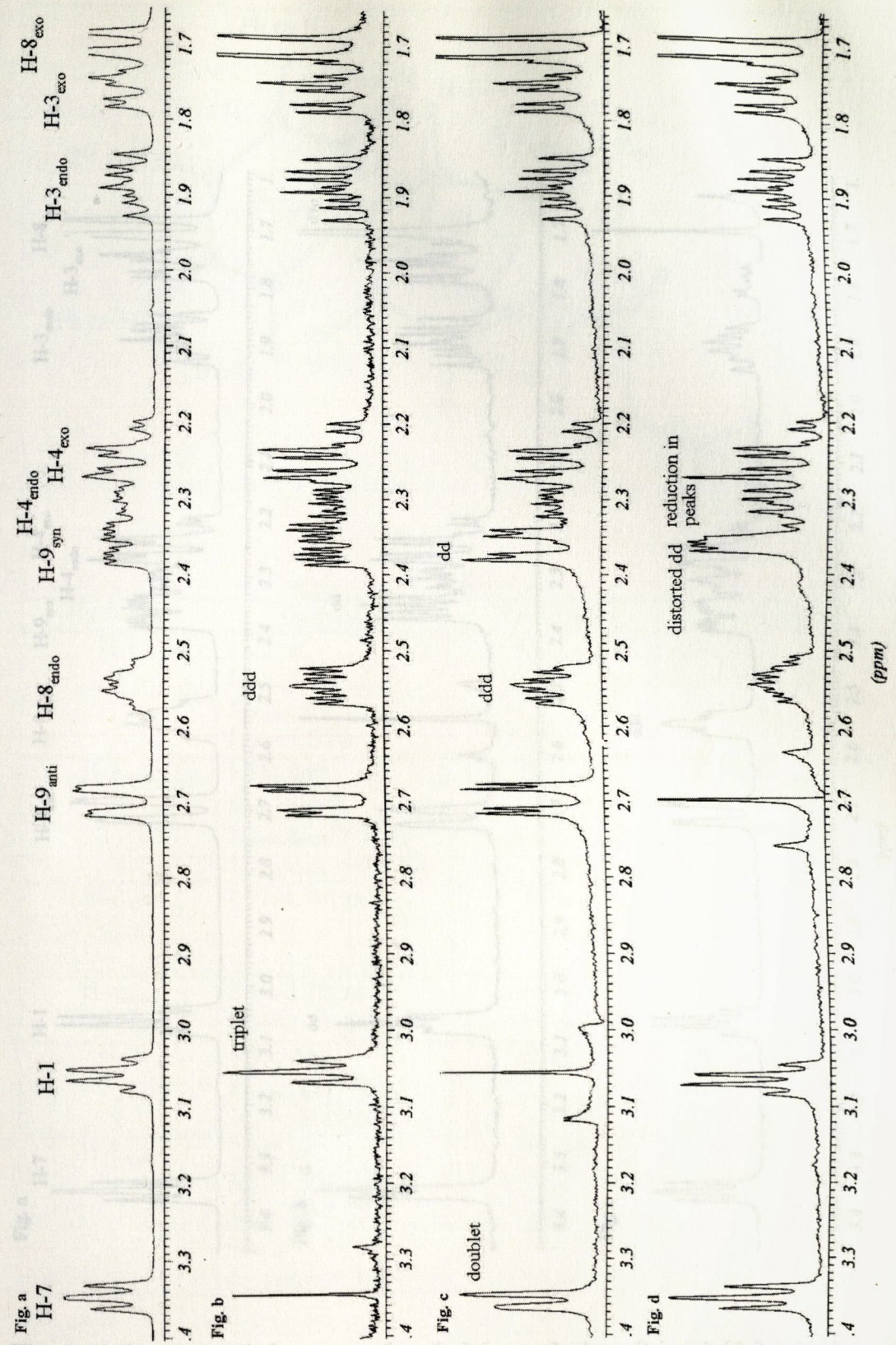


Fig. 3.9 The decoupled spectra of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163]. **Fig. a**: reference NMR. **Fig. b**: decoupled at H-7. **Fig. c**: decoupled at H-1. **Fig. d**: decoupled at H-9_{anti}.

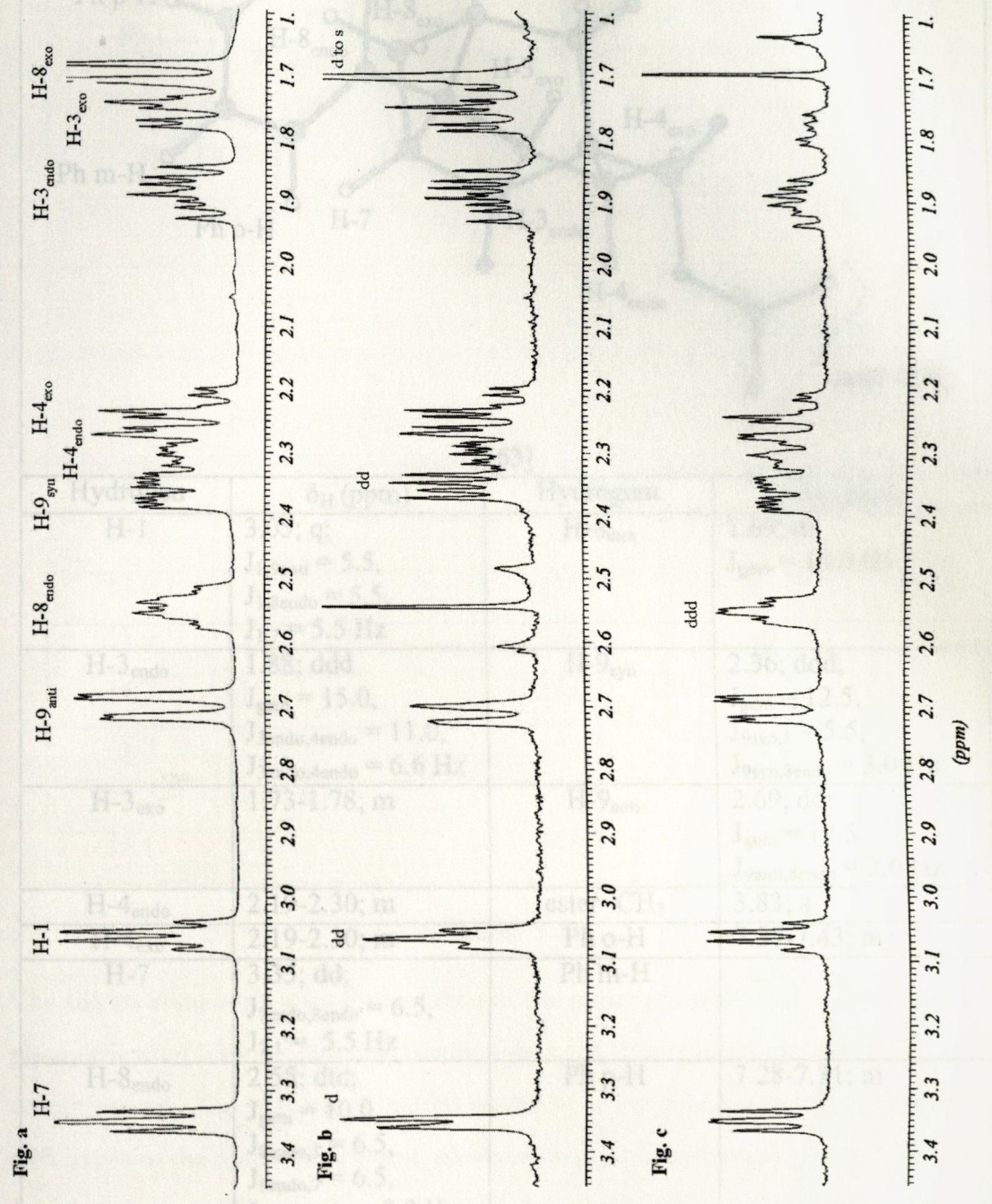
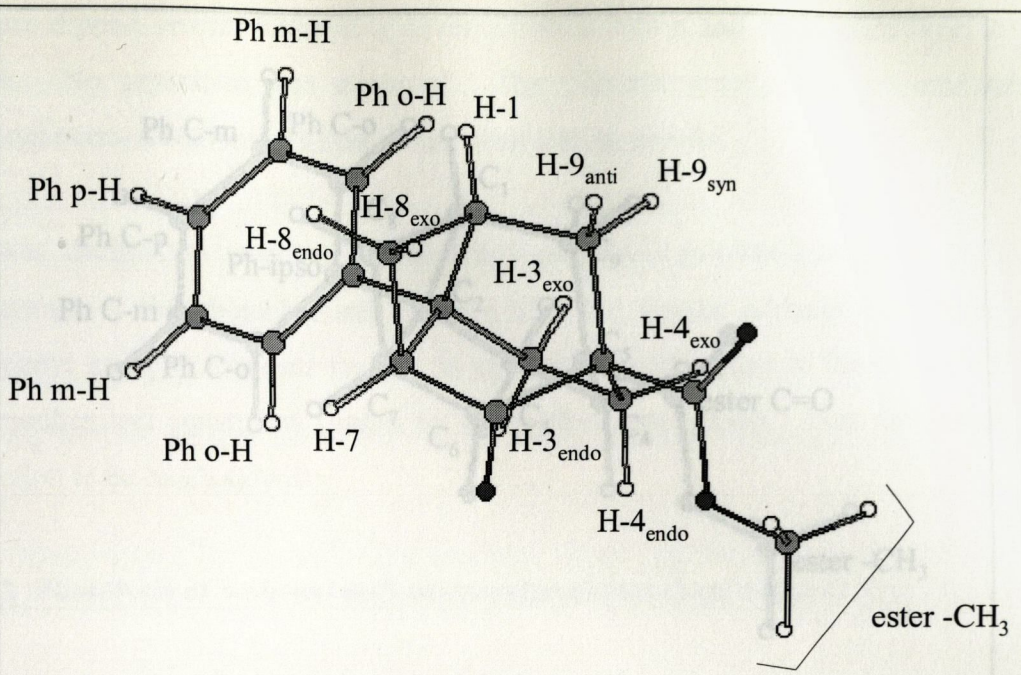


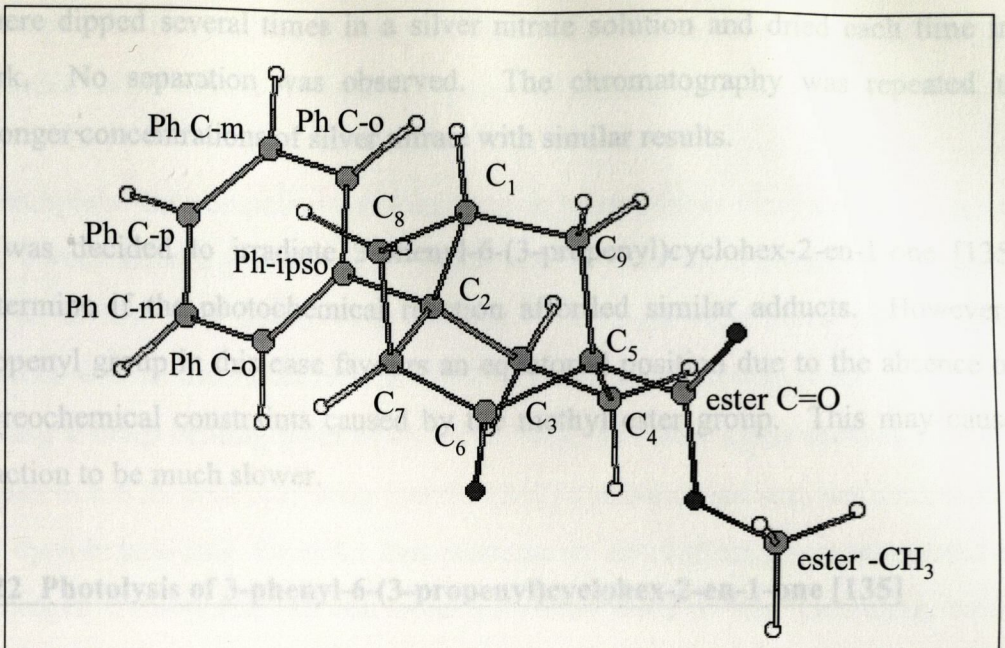
Fig. 3.10 The decoupled spectra of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163]. **Fig. a** reference NMR. **Fig. b** decoupled at H-8_{endo}. **Fig. c** decoupled at H-8_{exo}.



[163]

Hydrogen	δ_H (ppm)	Hydrogem	δ_H (ppm)
H-1	3.05; q; $J_{1,9anti}$ = 5.5, $J_{1,8endo}$ = 5.5, $J_{1,7}$ = 5.5 Hz	$H\text{-}8_{exo}$	1.69; d; J_{gem} = 10.0 Hz
$H\text{-}3_{endo}$	1.88; ddd J_{gem} = 15.0, $J_{3endo,4endo}$ = 11.0, $J_{3endo,4endo}$ = 6.6 Hz	$H\text{-}9_{syn}$	2.36; ddd; J_{gem} = 12.5, $J_{9syn,1}$ = 5.5, $J_{9syn,8endo}$ = 3.0 Hz
$H\text{-}3_{exo}$	1.73-1.78; m	$H\text{-}9_{anti}$	2.69; dd; J_{gem} = 12.5, $J_{9anti,4endo}$ = 2.0 Hz
$H\text{-}4_{endo}$	2.19-2.30; m	ester $-CH_3$	3,83; s
$H\text{-}4_{exo}$	2.19-2.30; m	Ph o-H	7.37-7.43; m
H-7	3.35; dd; $J_{7endo,8endo}$ = 6.5, $J_{7,1}$ = 5.5 Hz	Ph m-H	
$H\text{-}8_{endo}$	2.55; dtd; J_{gem} = 10.0, $J_{8endo,1}$ = 6.5, $J_{8endo,7}$ = 6.5, $J_{8endo,9anti}$ = 3.0 Hz	Ph p-H	7.28-7.31; m

Table 3.7



[163]

Carbon	δ_C (ppm)	Carbon	δ_C (ppm)
29.9	C-3	55.9	C-2
31.0	C-4	126.2	Ph C-o
33.9	C-8	126.6	Ph C-m
35.2	C-9	128.6	Ph C-p
38.9	C-1	143.9	Ph-ipso
52.2	ester $-CH_3$	172.0	ester C=O
55.1	C-7	210.8	C-6

Table 3.8

The filtrate remaining after the isolation of the minor photoproduct, methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163], was concentrated *in vacuo* to a colourless oil. The analysis of the oil by NMR techniques indicated that there was still traces of the minor component, methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163], present. However, the peaks due to this could easily be recognised.

At this stage we were unable to identify the structure of the major photoproduct, though there was a distinctive triplet in its ^{1}H NMR spectrum at δ 6.29 ppm, corresponding to an olefinic proton. We attempted to separate the two photoproducts by TLC using silver nitrate, which has an affinity for double bonds. The TLC plates

where dipped several times in a silver nitrate solution and dried each time in the dark. No separation was observed. The chromatography was repeated using stronger concentrations of silver nitrate with similar results.

It was decided to irradiate 3-phenyl-6-(3-propenyl)cyclohex-2-en-1-one [135] to determine if the photochemical reaction afforded similar adducts. However, the propenyl group in this case favours an equatorial position due to the absence of the stereochemical constraints caused by the methyl ester group. This may cause the reaction to be much slower.

3.22 Photolysis of 3-phenyl-6-(3-propenyl)cyclohex-2-en-1-one [135]

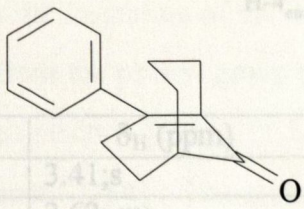
A solution of 3-phenyl-6-(3-propenyl)cyclohex-2-en-1-one [135] (1.743g) was irradiated in acetonitrile (450ml). The reaction was followed by GC-MS. The starting cyclohexenone had a GC retention time of 15.28 min. Only one other peak corresponding to a photoproduct appeared with a retention time of 15.47 min. The peak purity analysis over the entire range of the latter peak showed that the mass spectrum did not change significantly. This suggested that there was only a single photoproduct. The reaction was stopped after 2 h when all of the starting material had reacted. The solvent was removed *in vacuo* to give a dark viscous oil. A sample of the crude was analysed by ^{1}H NMR and a distinctive triplet at δ 6.27-6.30 ppm was observed. This suggested that the photochemical reaction did not give any of the predicted tricyclic compounds [161] and [162] (Scheme 3.4) as expected.

The oil was purified by flash chromatography (hexane/ether 9:1). The fractions containing a single spot as seen by TLC (hexane/ether 8:2) were combined and analyised by GC-MS. A single peak of retention time 15.47 min was observed. The fractions were concentrated to dryness to give an off white solid which was further purified by trituration with hexane/ether (9:1) to give a colourless compound (34mg). The filtrate was cooled to -50°C to precipitate out more of the product giving a combined mass of 185mg. The solid material was dried in a desiccator overnight under reduced pressure but changed from a solid state to an oily residue. It was

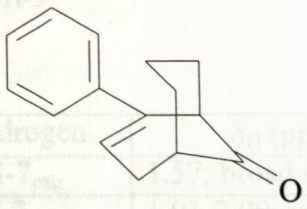
attempted to recrystallise the oily residue from hexane/ether 9:1 at -50°C but this afforded an off white semi-solid compound of melting point 42-48°C.

A sample of the compound was dissolved in hexane/ether (9:1) and set aside at 5°C for 1 week affording needle-like crystals. The crystals were filtered and immediately began to lose their shape. The crystals were re-grown, filtered and immediately washed with hexane/ether (9:1) at -50°C. A melting point was obtained immediately giving a sharp melting point of 40-41°C. The ^{1}H NMR again showed a distinctive triplet at δ 6.29 ppm indicating that the [2+2] cycloaddition was not completed with no cyclobutane ring formed. The presence of an olefinic group suggested that a hydrogen transfer reaction had occurred. This leads to four structures, two from parallel addition [177] and [178] and two from cross addition [179] and [180] (Scheme 3.8). However according to Bredt's Rule [12], a double bond cannot by placed with one terminus at the bridgehead of a bridged ring system unless the rings are large enough to accommodate the double bond without excessive strain, thereby eliminating structures [177] and [179].

Parallel cycloaddition

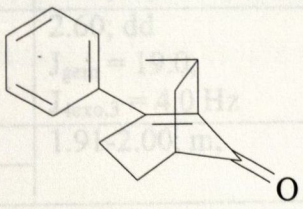


(177)

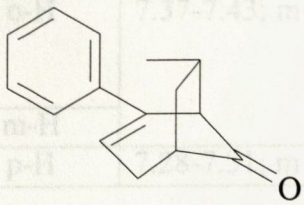


(178)

Cross cycloaddition



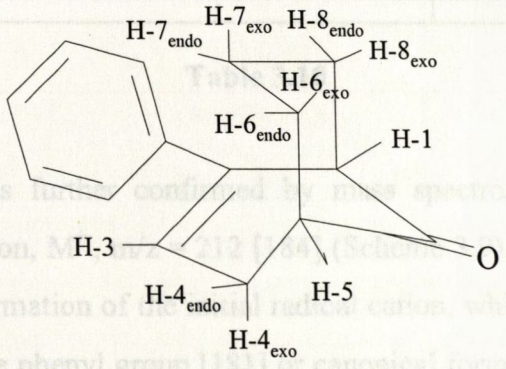
(179)



(180)

Scheme 3.8

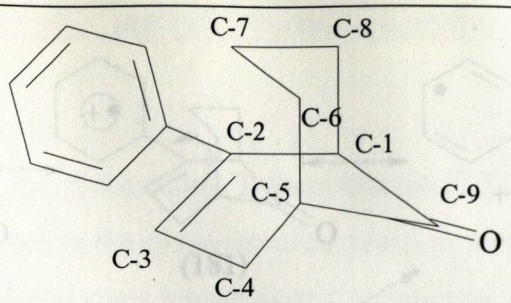
The ^{1}H NMR spectrum indicated the presence of sixteen hydrogens, while the ^{13}C NMR spectrum displayed fourteen peaks. The 1-D DEPT showed the presence of three quaternary peaks, four -CH_2 peaks and a further six protonated peaks as confirmed by the 2-D HETCOR spectrum. The 2-D HETCOR showed that there was no peak corresponding to a CH_3, therefore eliminating the cross product [180]. This left structure [178] as the only candidate and was identified as 2-phenyl-bicyclo[3.3.1]non-2-en-9-one [178]. The CH peak at δ 3.41 ppm was identified as H-1 as it is further downfield than H-5 due to the additive effects of the phenyl, olefinic and carbonyl groups. Therefore the CH peak at δ 2.62 ppm was assigned to H-5. The methylene protons of C-6, C-7, C-8 were identified by comparison to methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] (Table 3.7) and are summarised in Table 3.9. The remaining hydrogens are summarised in Table 3.9 with carbon assignments in Table 3.10.



[178]

Hydrogen	δ_H (ppm)	Hydrogen	δ_H (ppm)
H-1	3.41;s	H-7_{exo}	1.57; broad singlet
H-5	2.62; m;	H-7_{endo}	1.91-2.00; m;
H-3	6.31; t; $J_{3,4exo}$ = 3.5, $J_{3,4endo}$ = 3.5 Hz	H-8_{exo}	
H-4_{endo}	2.89; m;	H-8_{endo}	
H-4_{exo}	2.60; dd J_{gem} = 19.0, $J_{4exo,3}$ = 4.0 Hz	Ph o-H	7.37-7.43; m
H-6_{exo}	1.91-2.00; m;	Ph m-H	
H-6_{endo}		Ph p-H	7.28-7.31; m

Table 3.9

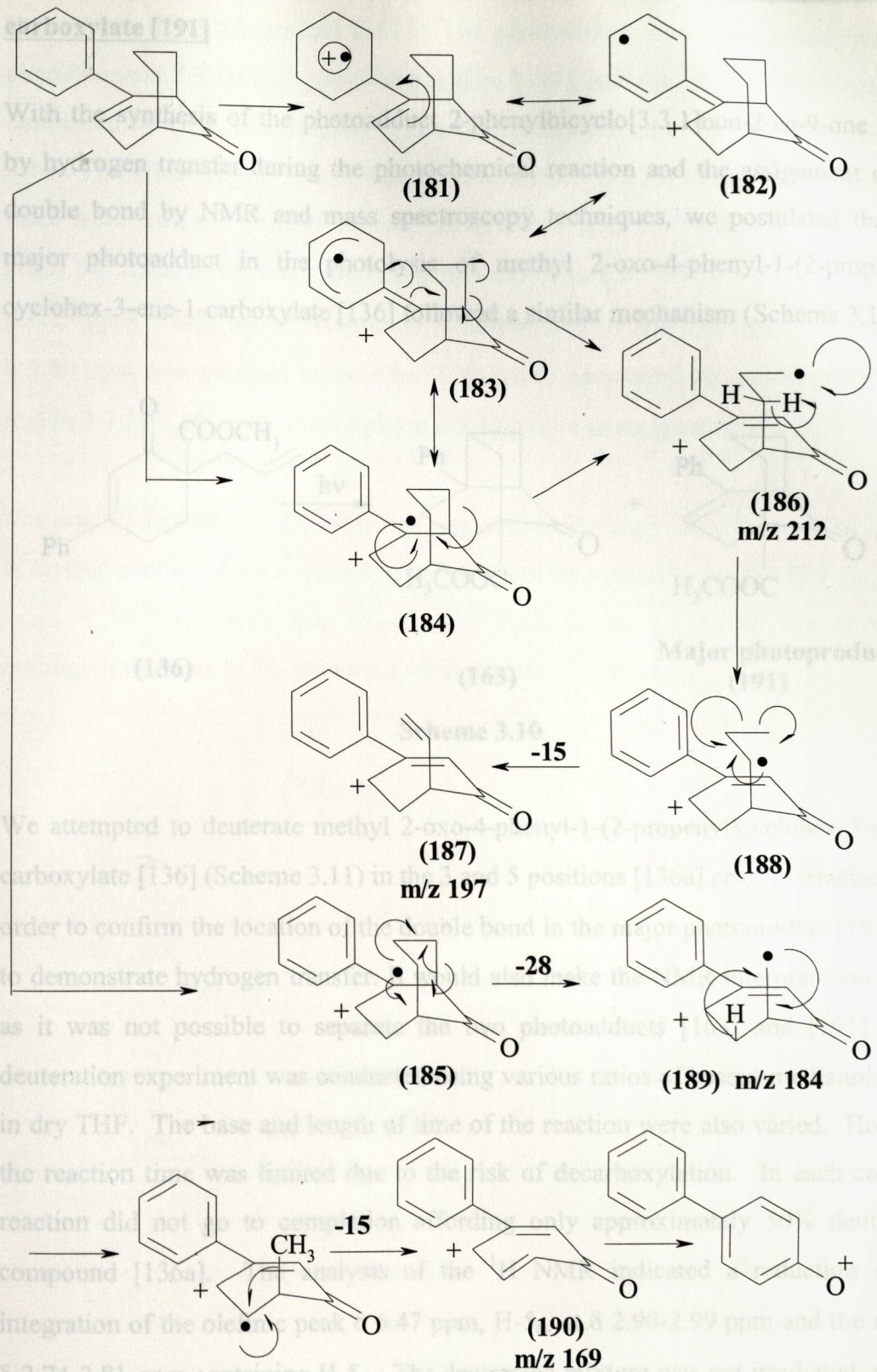


[178]

Carbon	δ_C (ppm)	Carbon	δ_C (ppm)
17.1	C-7	125.7	C-3
32.5	C-6	127.5, 128.4,	Ph C-o, Ph C-m,
35.7	C-4	137.1	Ph C-p
36.8	C-8		
44.4	C-5	139.2	Ph-ipso
49.9	C-1	215.8	C-9
125.6	C-2		

Table 3.10

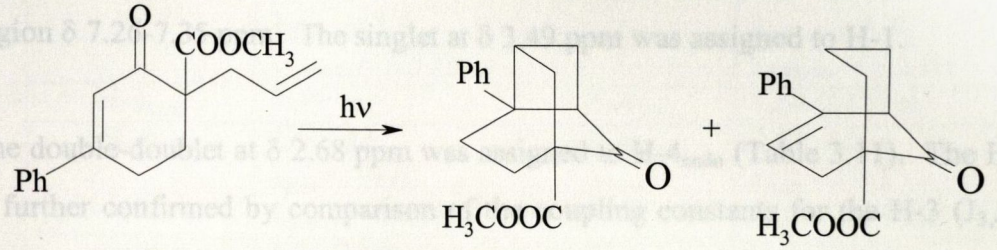
The photoproduct was further confirmed by mass spectroscopy. The compound afforded a molecular ion, $M^{+\cdot}$, m/z = 212 [184] (Scheme 3.9) as the base peak. This is explained on the formation of the initial radical cation, which can involve the loss of an electron from the phenyl group [181] or canonical forms [182] and [183] or by loss of an alkene electron [185] with both pathways affording the same radical cation after rearrangement [184]. The molecule rearranges further with lose of a methyl group to give the ion m/z = 197 [187]. The radical cation formed by lose of the electron from the alkene [185] can rearrange by a different mechanism [186] with lose of $CH_2{=}CH_2$, (-28), affording the ion of m/z = 184 [189]. This radical cation undergoes α-cleavage to give the ion m/z = 169 [190].


(181)
(182)
(183)
(184)
(186)
m/z 212
-15
(187)
m/z 197
(188)
-28
(185)
(189) m/z 184
-15
(190)
m/z 169

Scheme 3.9

3.23 Identification of methyl 9-oxo-2-phenylbicyclo[3.3.1]non-2-ene-5-carboxylate [191]

With the synthesis of the photoadduct 2-phenylbicyclo[3.3.1]non-2-en-9-one [180] by hydrogen transfer during the photochemical reaction and the assignment of the double bond by NMR and mass spectroscopy techniques, we postulated that the major photoadduct in the photolysis of methyl 2-oxo-4-phenyl-1-(2-propenyl)-cyclohex-3-ene-1-carboxylate [136] followed a similar mechanism (Scheme 3.10)



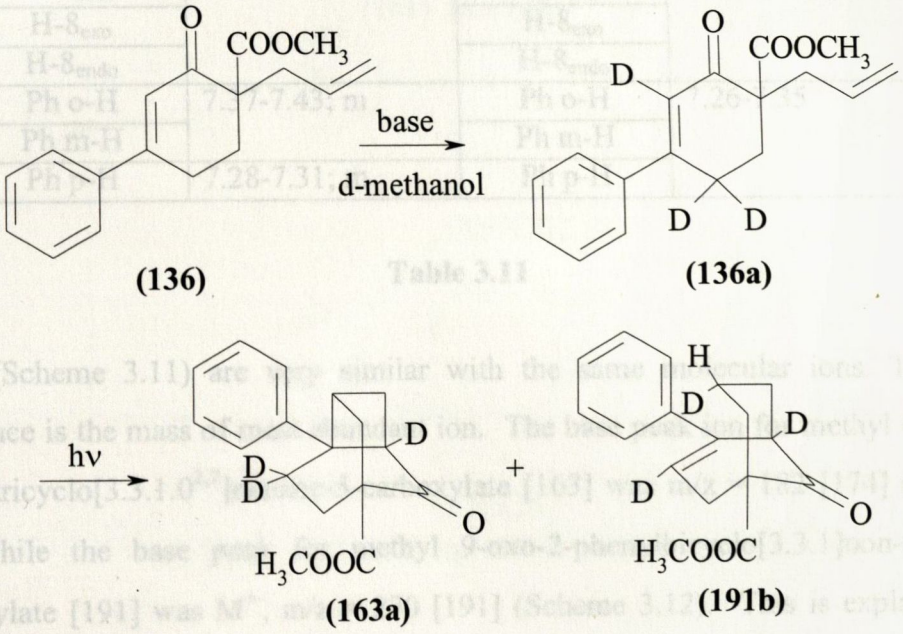
(136) **(163)** **Major photoproduct (191)**

Scheme 3.10

We attempted to deuterate methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136] (Scheme 3.11) in the 3 and 5 positions [136a] prior to irradiation in order to confirm the location of the double bond in the major photoproduct [191] and to demonstrate hydrogen transfer. It would also make the NMR interpretation easier as it was not possible to separate the two photoadducts [163] and [191]. The deuteration experiment was conducted using various ratios of base:d-methanol:enone in dry THF. The base and length of time of the reaction were also varied. However the reaction time was limited due to the risk of decarboxylation. In each case the reaction did not go to completion affording only approximately 50% deuterated compound [136a]. The analysis of the ^{1}H NMR indicated a reduction in the integration of the olefinic peak δ 6.47 ppm, H-5_{ax} at δ 2.90-2.99 ppm and the region δ 2.74-2.81 ppm containing H-5_{eq}. The deuterated mixture was not irradiated, as this would give a mixture of four photoproducts.

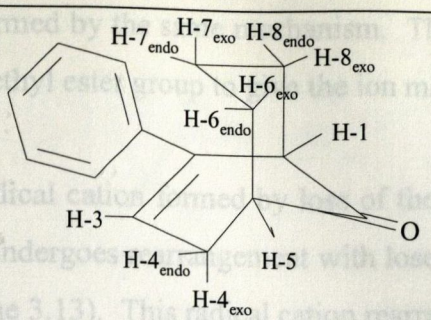
However, in the light of the other photoylsis carried out we were able to assign a structure to this photoproduct [191]. The photoadduct would be methyl 9-oxo-2-phenylbicyclo[3.3.1]non-2-ene-5-carboxylate [191] and that the structure could be confirmed by mass spectrometry and a partial identification by ^{1}H NMR (Scheme 3.11). The NMR peaks were compared with those of [178] (Table 3.11). Although there were traces of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] the main peaks were identified by comparison of the H-3 olefinic triplet at δ 6.29 ppm, which has an integration corresponding to one hydrogen. The peak at δ 3.80 ppm was assigned to the ester -CH_3 while the phenyl group was assigned to region δ 7.26-7.35 ppm. The singlet at δ 3.49 ppm was assigned to H-1.

The double-doublet at δ 2.68 ppm was assigned to H-4_{endo} (Table 3.11). The H-4_{endo} is further confirmed by comparison of the coupling constants for the H-3 ($J_{3,4endo}$ = $J_{3,4exo}$ = 3.8 Hz) and H-4_{endo} ($J_{4endo,4exo}$ = 19.2, $J_{4endo,3}$ = 3.8 Hz). The remaining hydrogens resonate in the region δ 1.64-2.45 ppm (Table 3.11).

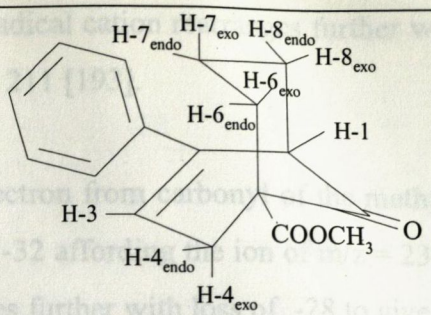


Scheme 3.11

The photoproduct was further confirmed by mass spectroscopy. The mass spectrum of the two photoproducts, methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] and methyl 9-oxo-2-phenylbicyclo[3.3.1]non-2-ene-5-carboxylate



[178]



[191]

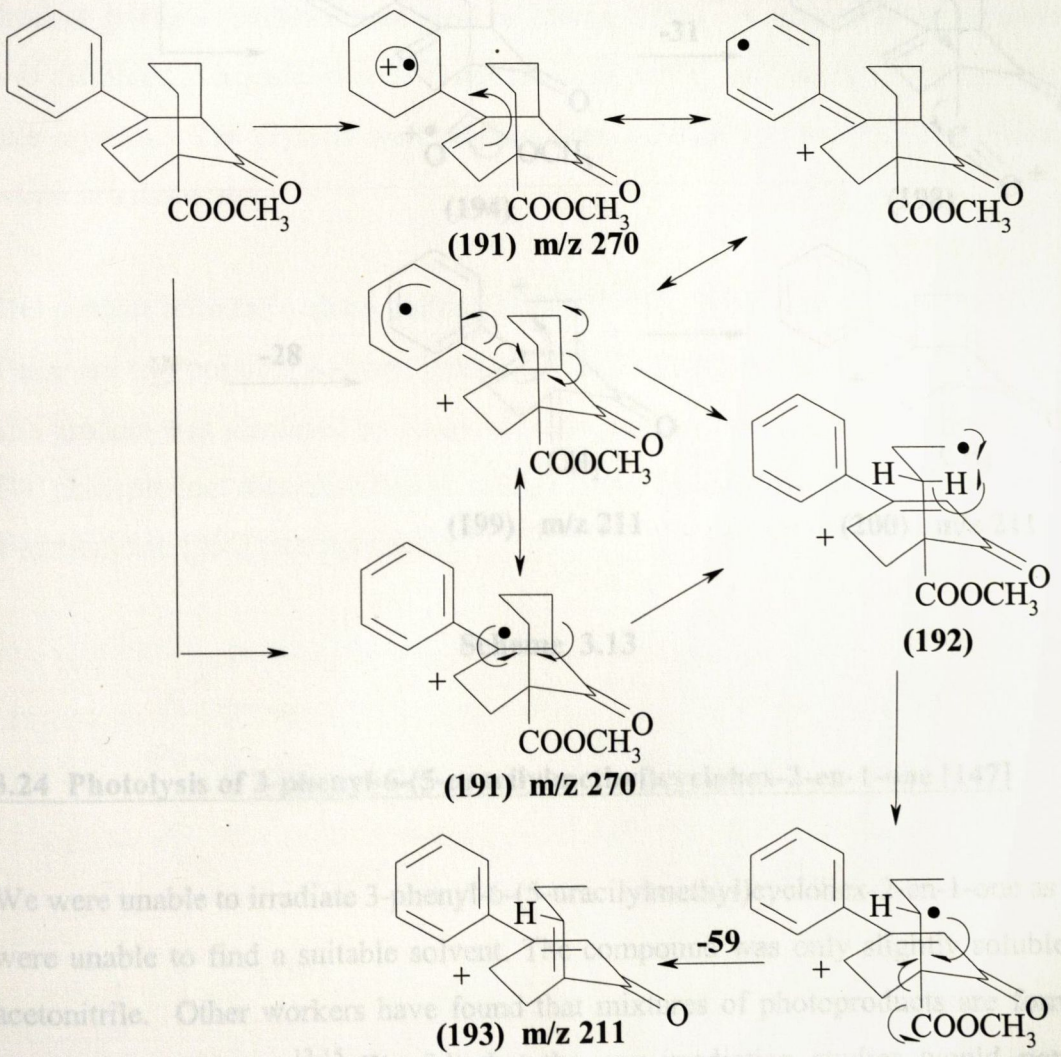
Hydrogen	δ_H (ppm)	Hydrogen	δ_H (ppm)
H-1	3.41;s	H-1	3.49; s
H-5	2.62; m;	ester -CH_3	3.80; s
H-3	6.31; t; $J_{3,4exo}$ = 3.5, $J_{3,4endo}$ = 3.5 Hz	H-3	6.27-6.31; t $J_{3,4exo}$ = 3.8, $J_{3,4endo}$ = 3.6 Hz
H-4_{endo}	2.89; m;	H-4_{endo}	1.64-2.45; m
H-4_{exo}	2.60; dd J_{gem} = 19.0, $J_{4exo,3}$ = 4.0 Hz	H-4_{exo}	2.68; dd; J_{gem} = 19.2, $J_{4exo,3}$ = 3.8 Hz
H-6_{exo}	1.91-2.00; m;	H-6_{exo}	1.64-2.45;m
H-6_{endo}		H-6_{endo}	
H-7_{exo}	1.57; broad singlet	H-7_{exo}	
H-7_{endo}	1.91-2.00; m;	H-7_{endo}	
H-8_{exo}		H-8_{exo}	
H-8_{endo}		H-8_{endo}	
Ph o-H	7.37-7.43; m	Ph o-H	7.26-7.35
Ph m-H		Ph m-H	
Ph p-H	7.28-7.31; m	Ph p-H	

Table 3.11

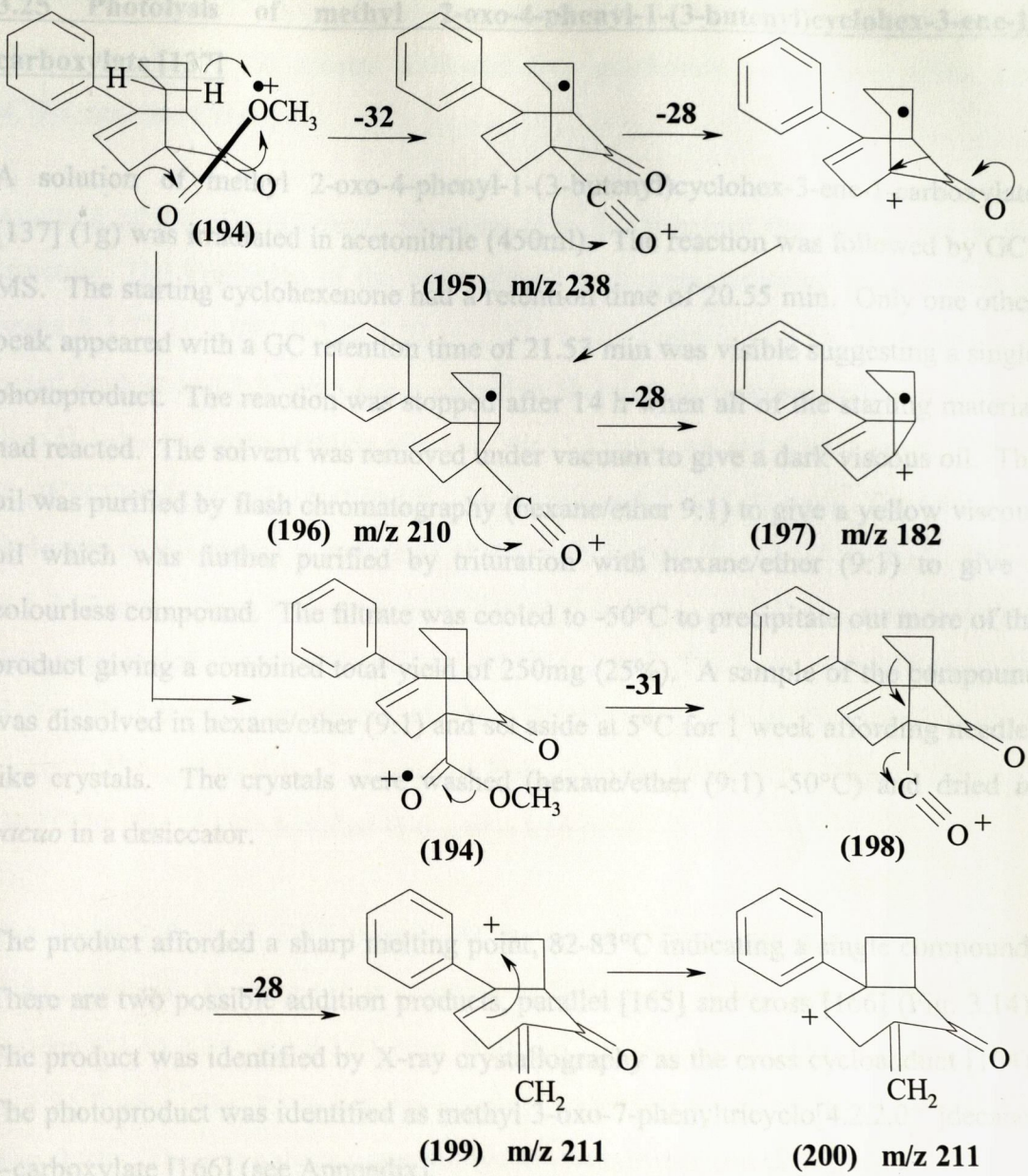
[178] (Scheme 3.11) are very similar with the same molecular ions. The only difference is the mass of most abundant ion. The base peak ion for methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] was m/z = 182 [174] (Scheme 3.6) while the base peak for methyl 9-oxo-2-phenylbicyclo[3.3.1]non-2-ene-5-carboxylate [191] was $M^{+\cdot}$, m/z = 270 [191] (Scheme 3.12). This is explained on basis of radical cation stability, which can involve the loss of an electron from the phenyl group [191] or loss of an alkene electron [191] with both pathways affording the same radical cation after rearrangement [192]. This is also the case for 2-phenyl-bicyclo[3.3.1]non-2-en-9-one [178] (Scheme 3.9) where the base peak ion m/z = 212

was formed by the same mechanism. The radical cation rearranges further with loss of a methyl ester group to give the ion m/z = 211 [193].

The radical cation formed by loss of the electron from carbonyl of the methyl ester [194] undergoes rearrangement with lose of -32 affording the ion of m/z = 238 [195] (Scheme 3.13). This radical cation rearranges further with loss of -28 to give the ion m/z = 210 [196]. A further loss of a carbonyl group -28 affords the ion m/z = 182 [197]. The radical cation formed by loss of the electron from carbonyl of the methyl ester [194] can rearrange by a different mechanism (Scheme 3.13) with loss of -31 [198] and -28 affording the ion of m/z = 211 [199] which rearranges to a more stable cation [200]



Scheme 3.12



Scheme 3.13

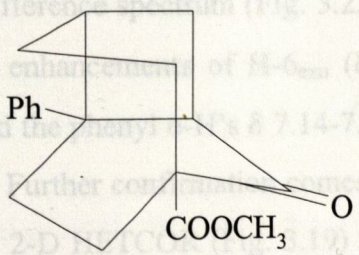
3.24 Photolysis of 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one [147]

We were unable to irradiate 3-phenyl-6-(5-uracilylmethyl)cyclohex-2-en-1-one as we were unable to find a suitable solvent. The compound was only slightly soluble in acetonitrile. Other workers have found that mixtures of photoproducts are formed from related systems.[13-15] We felt that the any irradiation studies would not be productive.

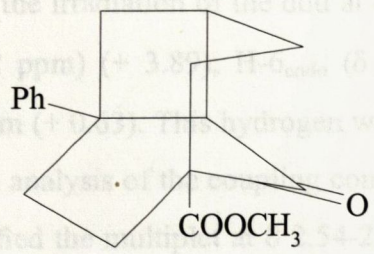
3.25 Photolysis of methyl 2-oxo-4-phenyl-1-(3-butenyl)cyclohex-3-ene-1-carboxylate [137]

A solution of methyl 2-oxo-4-phenyl-1-(3-butenyl)cyclohex-3-ene-1-carboxylate [137] (1g) was irradiated in acetonitrile (450ml). The reaction was followed by GC-MS. The starting cyclohexenone had a retention time of 20.55 min. Only one other peak appeared with a GC retention time of 21.53 min was visible suggesting a single photoproduct. The reaction was stopped after 14 h when all of the starting material had reacted. The solvent was removed under vacuum to give a dark viscous oil. The oil was purified by flash chromatography (hexane/ether 9:1) to give a yellow viscous oil which was further purified by trituration with hexane/ether (9:1) to give a colourless compound. The filtrate was cooled to -50°C to precipitate out more of the product giving a combined total yield of 250mg (25%). A sample of the compound was dissolved in hexane/ether (9:1) and set aside at 5°C for 1 week affording needle-like crystals. The crystals were washed (hexane/ether (9:1) -50°C) and dried *in vacuo* in a desiccator.

The product afforded a sharp melting point, 82-83°C indicating a single compound. There are two possible addition products, parallel [165] and cross [166] (Fig. 3.14). The product was identified by X-ray crystallography as the cross cycloadduct [164]. The photoproduct was identified as methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] (see Appendix).



(165)



(166)

A sample of the compound was analysed by NMR techniques. Initial examination of ^{1}H NMR (Fig. 3.15 and 3.16) indicated the presence of twenty hydrogens, while the

^{13}C NMR (Fig. 3.17) displayed sixteen peaks. The 1-D DEPT (Fig. 3.18) and 2-D HETCOR (Fig. 3.19) spectra indicated five quaternary peaks, five -CHs, five $-CH_2$s, and one CH_3 peak.

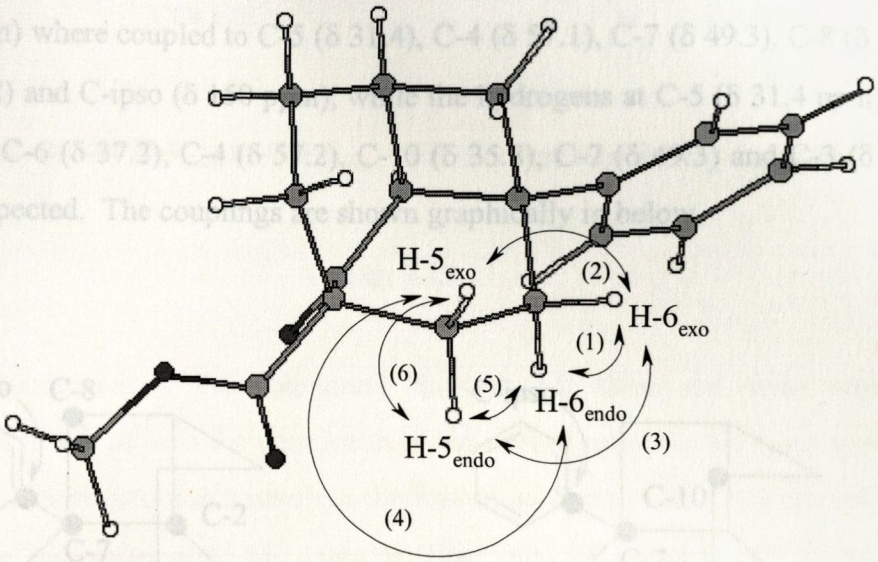
Analysis of the nOe difference spectrum (Fig. 3.20) helped the assignment of the structure. The irradiation of the ortho-phenyl hydrogens indicated enhancement of peaks δ 1.72 (+ 1.08), δ 2.92-3.03 (+ 0.57, + 1.04) and δ 3.30 (+ 2.48) ppm. The broad doublet at δ 3.30 ppm was assigned to H-2 as it is expected further downfield than H-1 due to the deshielding effects of the C-3 carbonyl and phenyl group. The 2-D HETCOR (Fig. 3.19) identified H-1 in the region δ 2.92-3.03 ppm. The remaining hydrogen in this region is correlated to the same carbon (Fig. 3.19) as the hydrogen at δ 2.33 ppm. These hydrogens were identified as $H\text{-}8_{endo}$ and $H\text{-}8_{exo}$ respectively as they are coupled to each other and to H-1 (Fig. 3.21). The large nOe difference for H-2 and H-1 suggests an orientation where the ortho hydrogen on the phenyl group is closer to $H\text{-}6_{exo}$ than $H\text{-}6_{endo}$. Therefore $H\text{-}6_{endo}$ was assigned to δ 1.72 ppm. The 2-D HETCOR (Fig. 3.19) identified $H\text{-}6_{exo}$ at δ 1.86 ppm.

The $^1H\text{-}^1H$ 2-D DQFCOSY (Fig. 3.21) showed that $H\text{-}6_{exo}$ was coupled strongly to $H\text{-}6_{endo}$, weakly by long range coupling to $H\text{-}8_{endo}$ (δ 2.92-3.03 ppm) and to the regions δ 2.54-2.64 and δ 2.81 ppm. Both regions are correlated to the same carbon at δ 31.5 ppm (Fig. 3.19) and are coupled to each other and to $H\text{-}6_{endo}$ and $H\text{-}6_{exo}$ (Fig. 3.21). There is only one possibility with both hydrogens belonging to C-5.

The nOe difference spectrum (Fig. 3.22) for the irradiation of the ddd at δ 2.81 ppm resulted in enhancements of $H\text{-}6_{exo}$ (δ 1.72 ppm) (+ 3.89), $H\text{-}6_{endo}$ (δ 1.86 ppm) (+ 2.34) and the phenyl o-H's δ 7.14-7.22 ppm (+ 0.63). This hydrogen was assigned to $H\text{-}5_{endo}$. Further confirmation comes from analysis of the coupling constants (Fig. 3.11). The 2-D HETCOR (Fig. 3.19) identified the multiplet at δ 2.54-2.64 ppm as $H\text{-}5_{exo}$.

Irradiation of the methyl ester at δ 3.81 ppm (Fig. 3.23) resulted in enhancements of $H\text{-}5_{endo}$ (δ 2.81 ppm) (+ 0.12) and the ddd at δ 2.54-2.56 ppm (+ 0.02), which was assigned to $H\text{-}10_{syn}$. The 2-D HETCOR (Fig. 3.19) identified $H\text{-}10_{anti}$ in the region

δ 2.43 ppm. Analysis of the ^{1}H-^{1}H 2-D DQFCOSY (Fig. 3.21) showed that H-10_{anti} is coupled strongly to H-10_{syn} and to the regions δ 1.89-1.96 and δ 2.07-2.16 ppm. Both regions are correlated to the same carbon δ 24.7 ppm (Fig. 3.19), which is due to C-9.



(166)

Coupling constants for H-6_{exo}
(1) J_{gem} = 13.6 Hz
(2) $J_{6exo,5exo}$ = 13.6 Hz
(3) $J_{6exo,5endo}$ = 6.0 Hz

Coupling constants for H-6_{endo}
(1) J_{gem} = 14.0 Hz
(4) $J_{6endo,5exo}$ = 4.8 Hz
(5) $J_{6endo,5endo}$ = 3.3 Hz

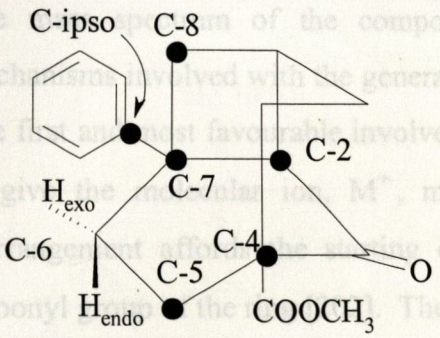
Coupling constants for H-5_{endo}
(6) J_{gem} = 14.6 Hz
(3) $J_{5endo,6exo}$ = 6.0 Hz
(5) $J_{5endo,6endo}$ = 3.0 Hz

Fig. 3.11

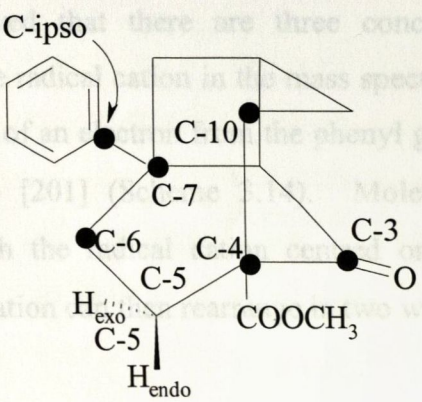
The irradiation of H-10_{anti} (Fig. 3.24) resulted in enhancements of H-1 (δ 2.92-3.03 ppm) (+ 8.49), and the multiplet at δ 1.89-1.96 ppm, which has been assigned to H-9_{anti}. This was further confirmed by the irradiation H-9_{anti} (Fig. 3.25), which resulted in enhancements of H-2 (δ 3.30 ppm) (+ 0.71), H-1 (δ 2.92-3.03 ppm) (+ 7.38) and H-10_{anti} (δ 2.43 ppm) (+ 1.47).

The multiplet at δ 2.07-2.16 ppm was identified from the 2-D HETCOR (Fig. 3.19) as H-9_{syn}. The ^{1}H-^{1}H 2-D DQFCOSY (Fig. 3.21) showed that H-9_{anti} is coupled strongly to H-9_{syn}, H-10_{anti} and H-10_{syn} as expected.

The quaternary carbons C-3, C-4, C-7 and C-ipso where identified by HMBC experiments. The analysis (Fig. 3.26 and 3.27) showed that the hydrogens on C-6 (δ 37.2 ppm) where coupled to C-5 (δ 31.4), C-4 (δ 57.1), C-7 (δ 49.3), C-8 (δ 37.8), C-2 (δ 51.2) and C-ipso (δ 150 ppm), while the hydrogens at C-5 (δ 31.4 ppm) were coupled to C-6 (δ 37.2), C-4 (δ 57.2), C-10 (δ 35.8), C-7 (δ 49.3) and C-3 (δ 173.7 ppm) as expected. The couplings are shown graphically in below.



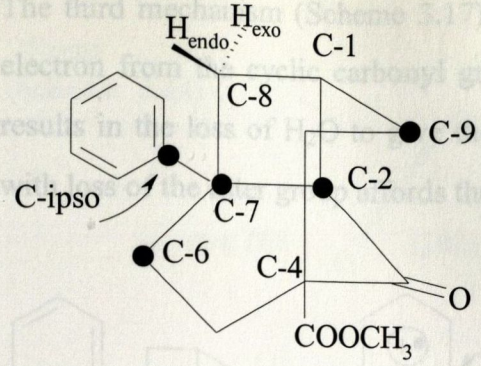
CH-C couplings for H-6_{endo} and H-6_{exo}

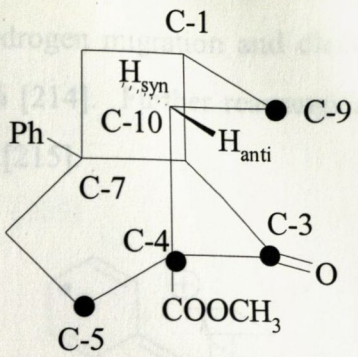


CH-C couplings for H-5_{endo} and H-5_{exo}

Fig. 3.12

The quaternary carbons C-4 and C-7 where further confirmed by examination of the couplings associated with the hydrogens on C-8 (δ 37.8) and C-10 (δ 35.8 ppm). The HMBC spectra (Fig. 3.26 and 3.27) showed that the hydrogens on C-8 (δ 37.8) are coupled to C-1 (δ 29.3), C-7 (δ 49.3), C-9 (δ 24.7), C-6 (δ 37.2) and C-ipso (δ 150 ppm), while the hydrogens on C-10 (δ 35.8 ppm) are coupled to C-9 (δ 24.7), C-4 (δ 57.1), C-1 (δ 29.3), C-3 (δ 173.7) and C-5 (δ 31.4 ppm). The couplings are shown in Fig. 3.13. The remaining hydrogen and carbon assignments are summarised in Tables 3.12 and 3.13 respectively.





CH-C couplings for H-8_{endo} and H-8_{exo} **CH-C couplings for H-10_{syn} and H-10_{anti}**

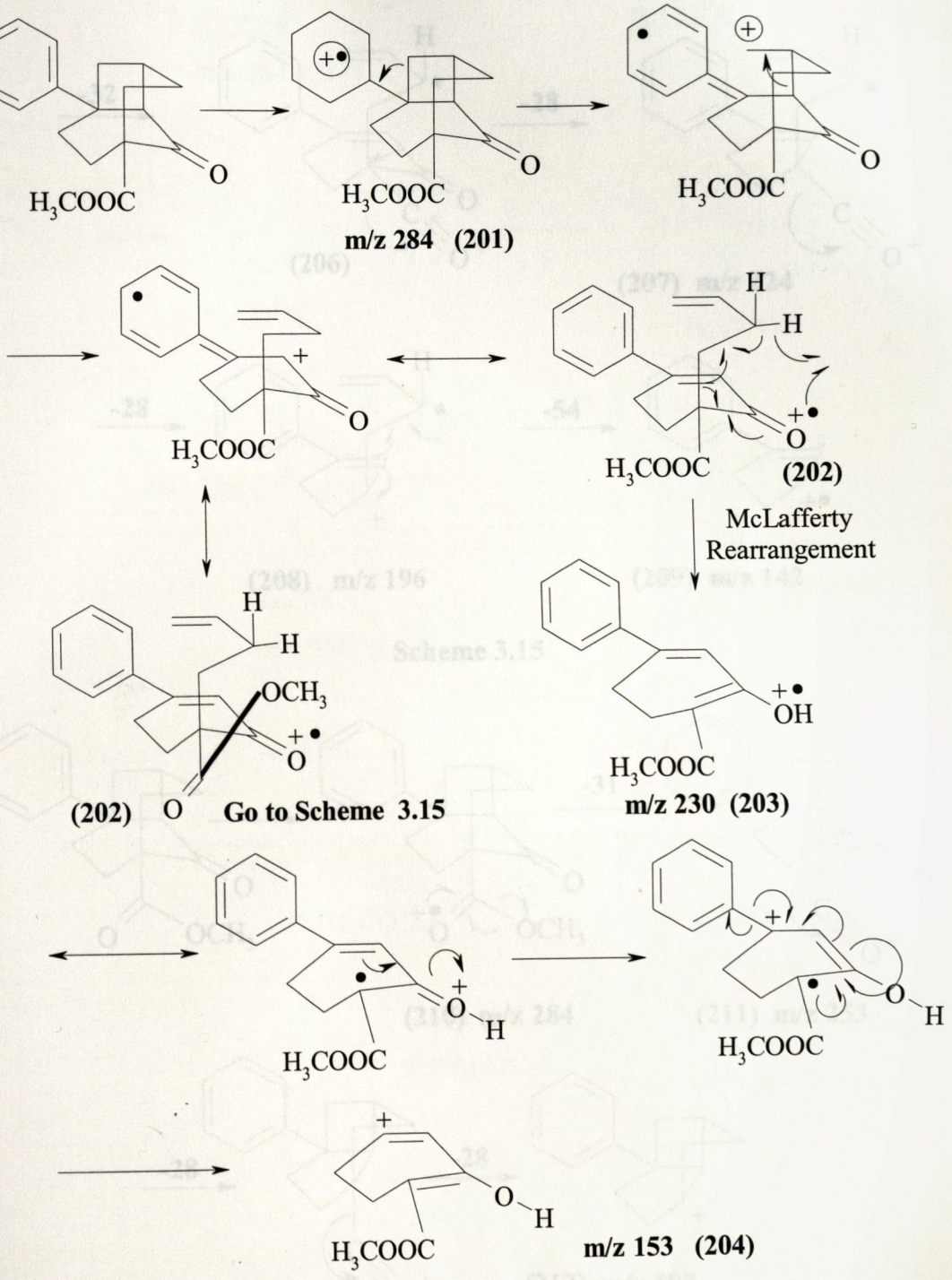
Fig. 3.13

The mass spectrum of the compound showed that there are three concerted mechanisms involved with the generation of the radical cation in the mass spectrum. The first and most favourable involves the loss of an electron from the phenyl group to give the molecular ion, $M^{+\cdot}$, m/z = 284 [201] (Scheme 3.14). Molecular rearrangement affords the starting enone with the radical cation centred on the carbonyl group of the ring [202]. The radical cation can then rearrange in two ways:

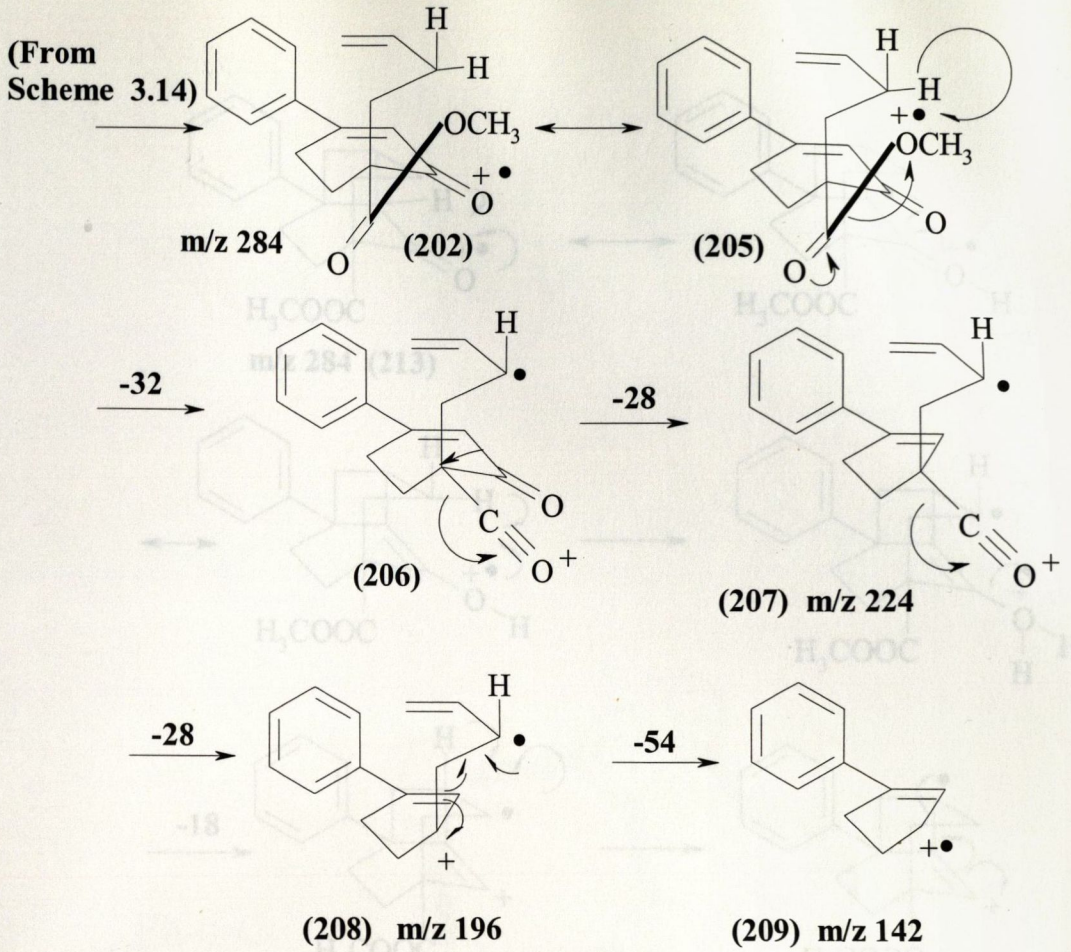
1) McLafferty rearrangement with loss of -52 to give the ion m/z = 230 [203] with subsequently loss of the phenyl group to give the base peak m/z = 153 [204]
2) Electron migration from the ester group [205] resulting in hydrogen abstraction and loss of -$HOCH_3$, -32 [206] (Scheme 3.15). Further loss of a carbonyl groups afforded the ion peak m/z = 224 [207]. The loss of second carbonyl group gave the radical cation m/z = 196 [208], which can rearrange with the loss of -54 to give the ion m/z = 142 [209].

The second mechanism (Scheme 3.16) for the generation of the radical cation involves the loss of an electron from the carbonyl group on the methyl ester [210] resulting in the lose of -21 affording a ion of m/z = 253 [211]. Further rearrangements with loss of two carbonyl groups afforded the radical cation m/z = 197 [212].

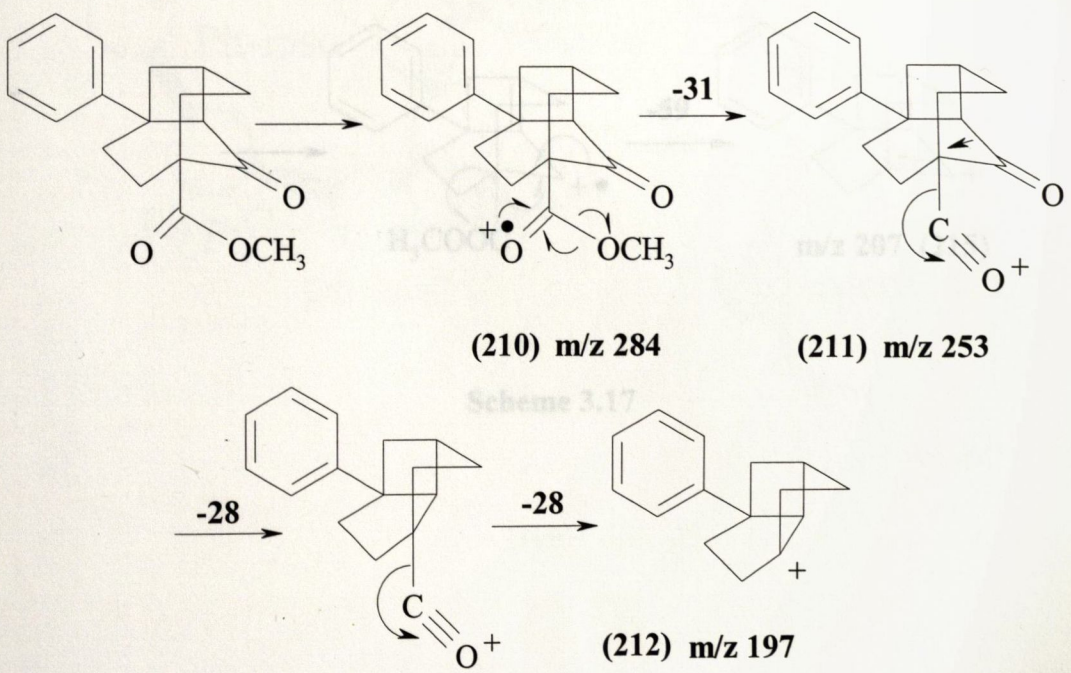
The third mechanism (Scheme 3.17) for radical cation generation is the loss of an electron from the cyclic carbonyl group [213]. Hydrogen migration and cleavage results in the loss of H_2O to give the ion m/z = 266 [214]. Further rearrangement with loss of the ester group affords the ion m/z = 207 [215].



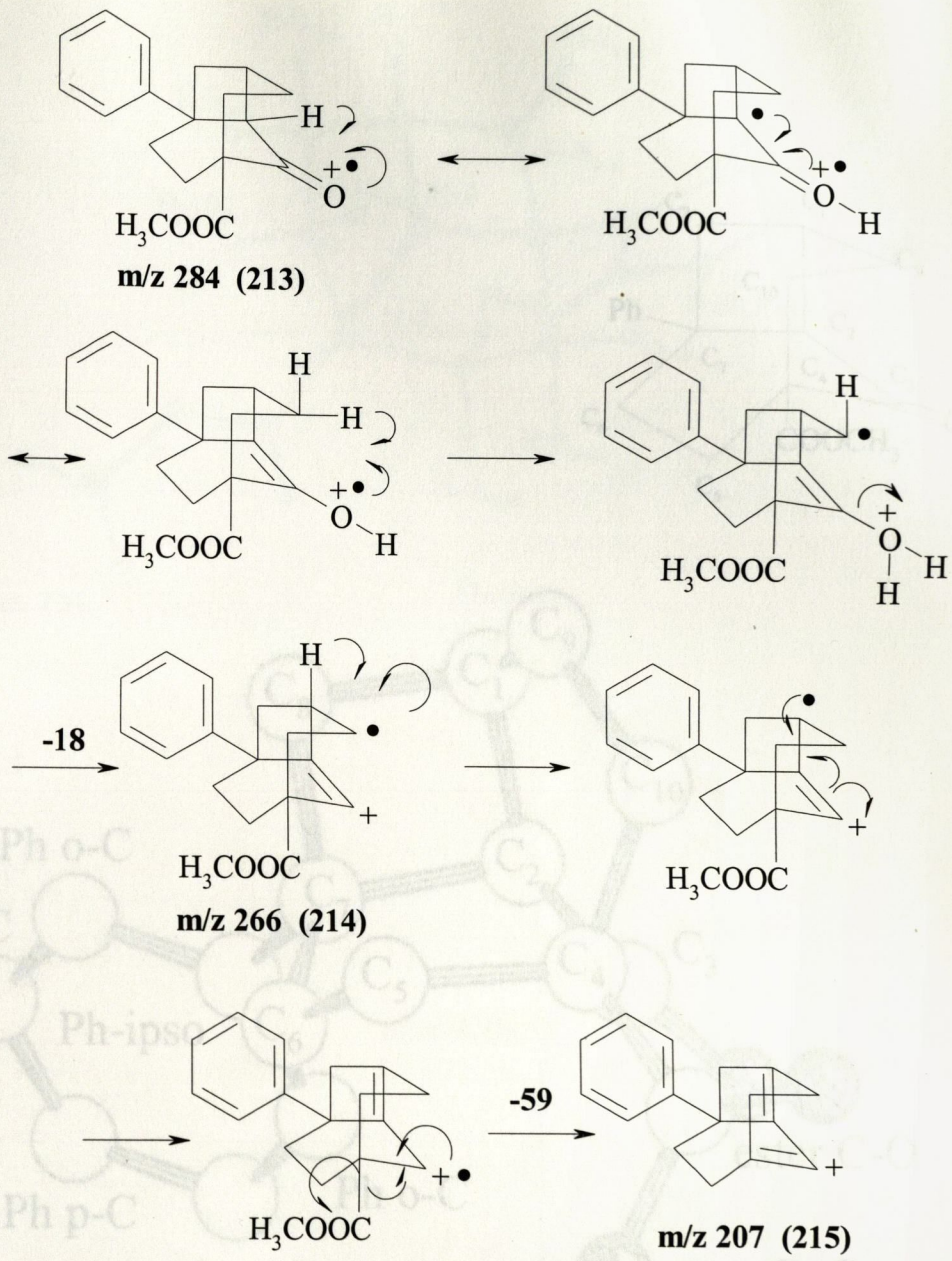
Scheme 3.14



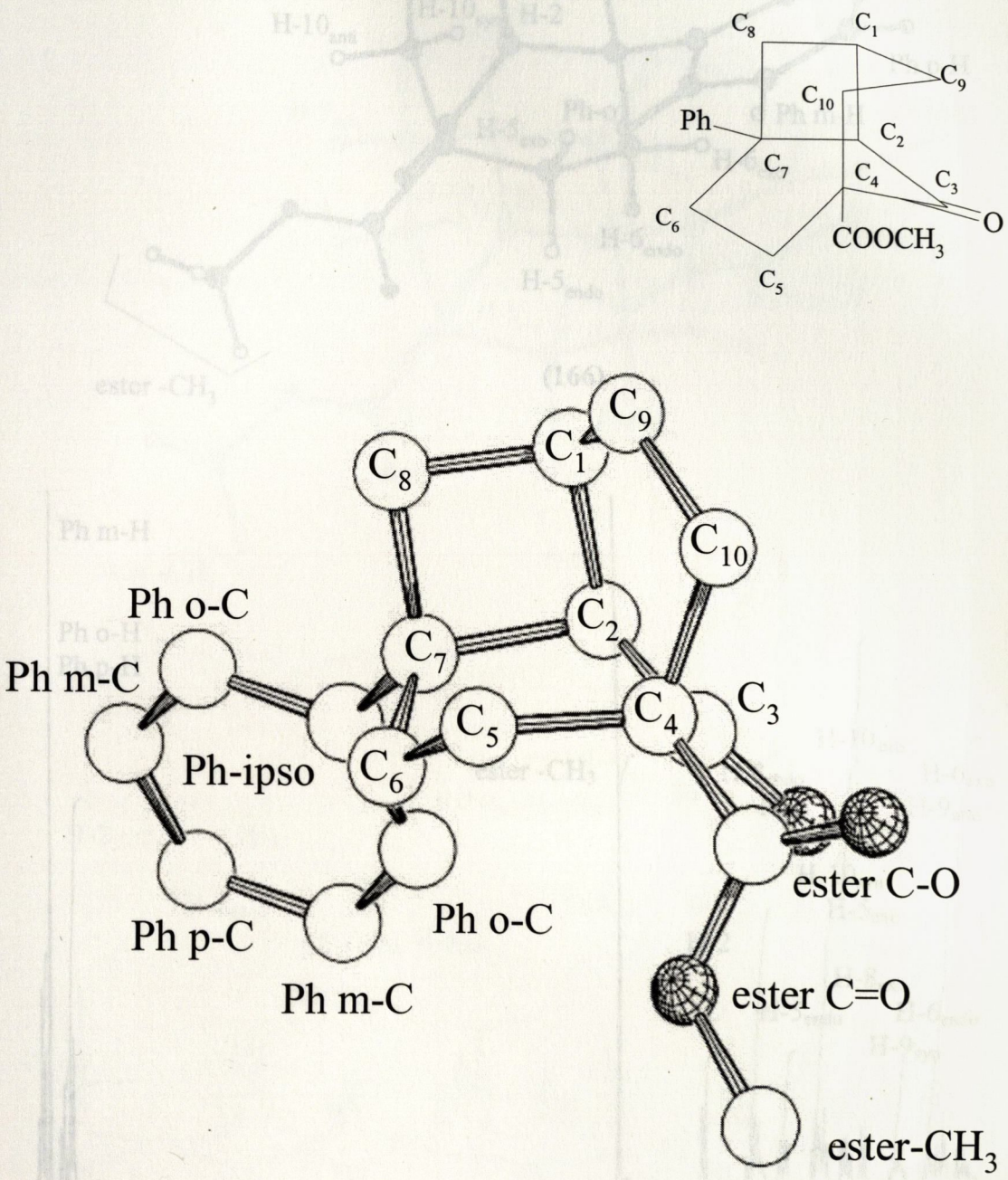
Scheme 3.15



Scheme 3.16

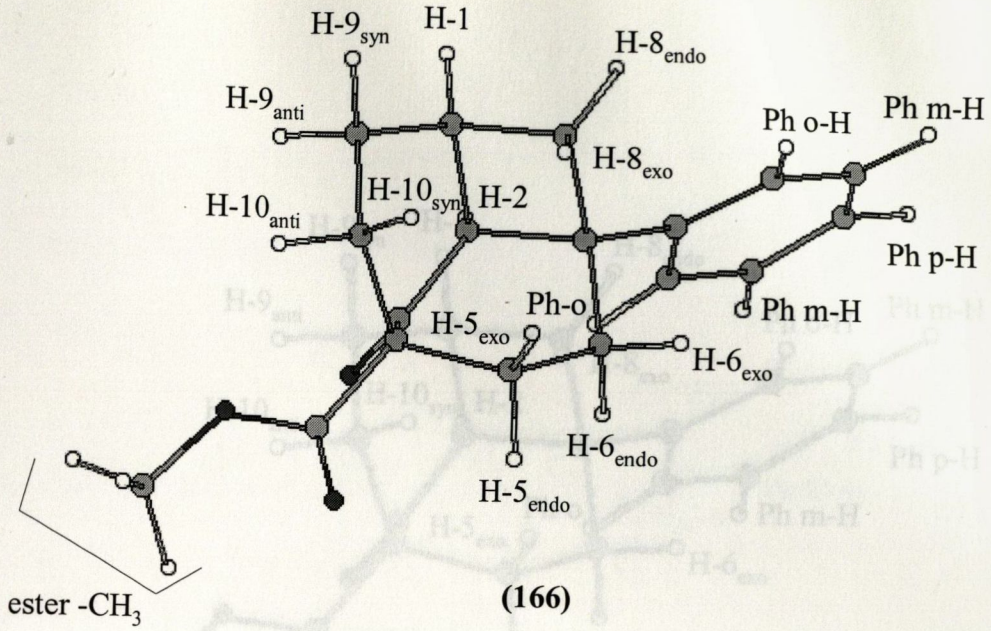

H
O
H3COOC
m/z 284 (213)
H
H
O
H
H3COOC
H
H
O
H
H
H3COOC
-18
H
H3COOC
m/z 266 (214)
-59
H3COOC
m/z 207 (215)

Scheme 3.17



(166)

Fig. 3.14 The X-ray crystallography of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166].



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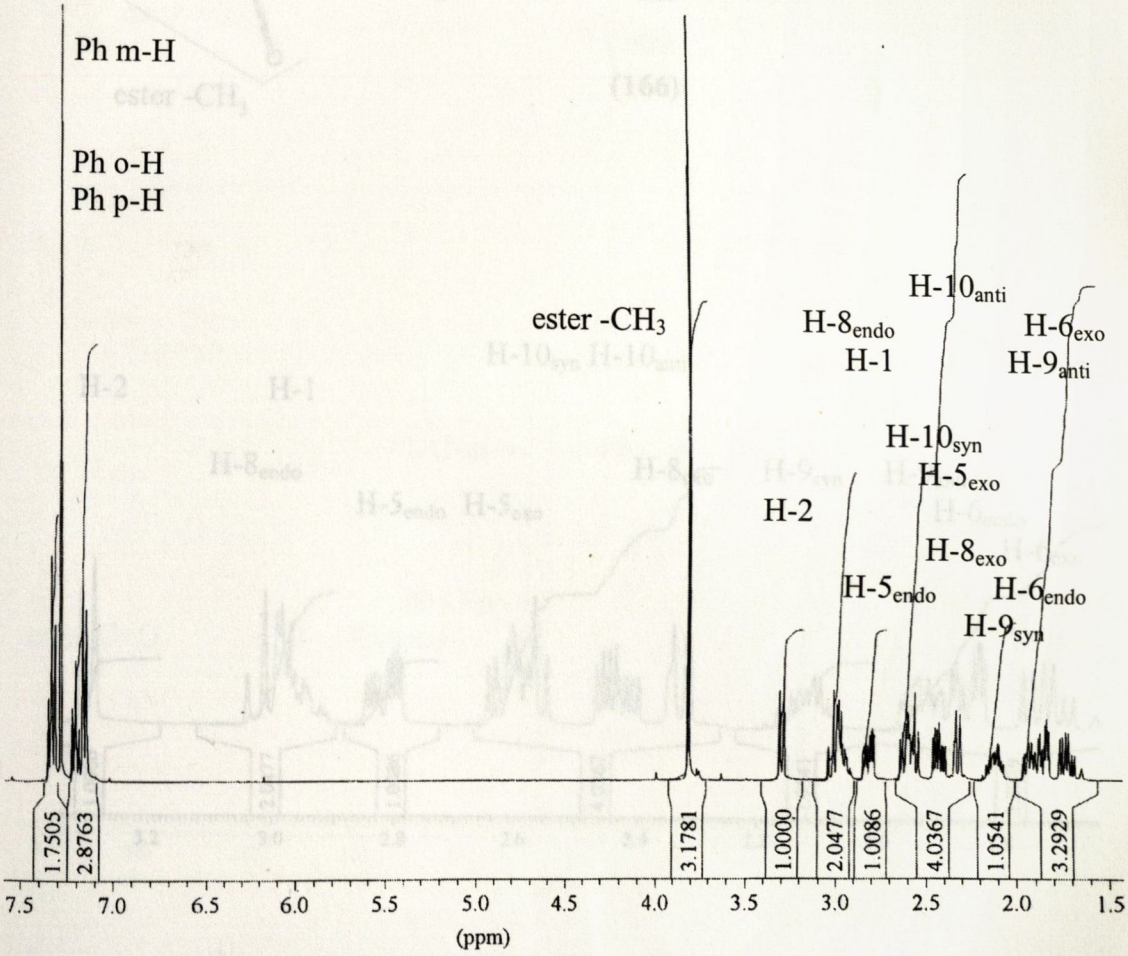
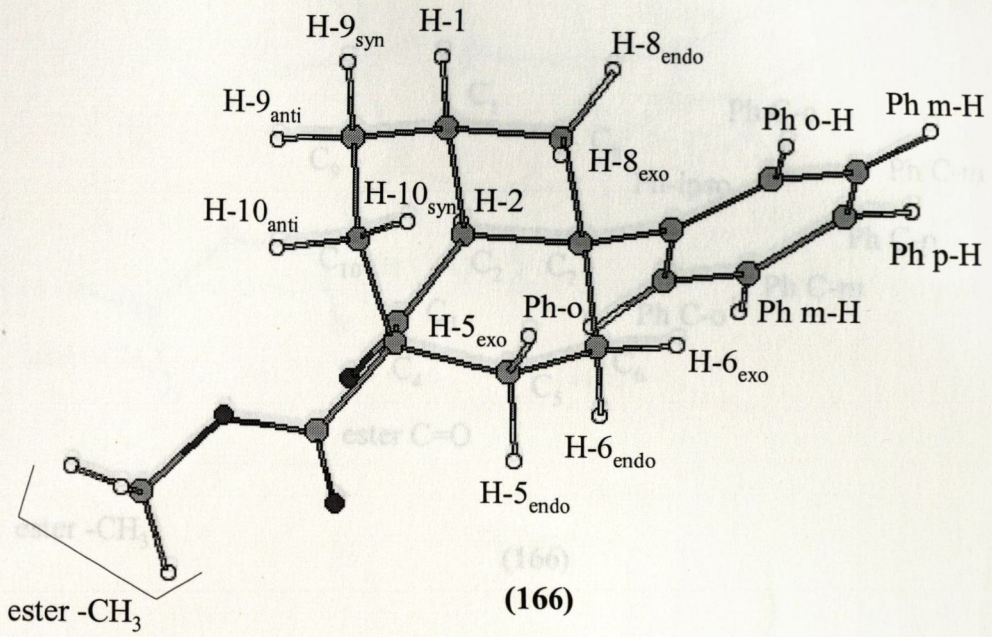


Fig. 3.15 The ^{1}H NMR spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166].



(166)

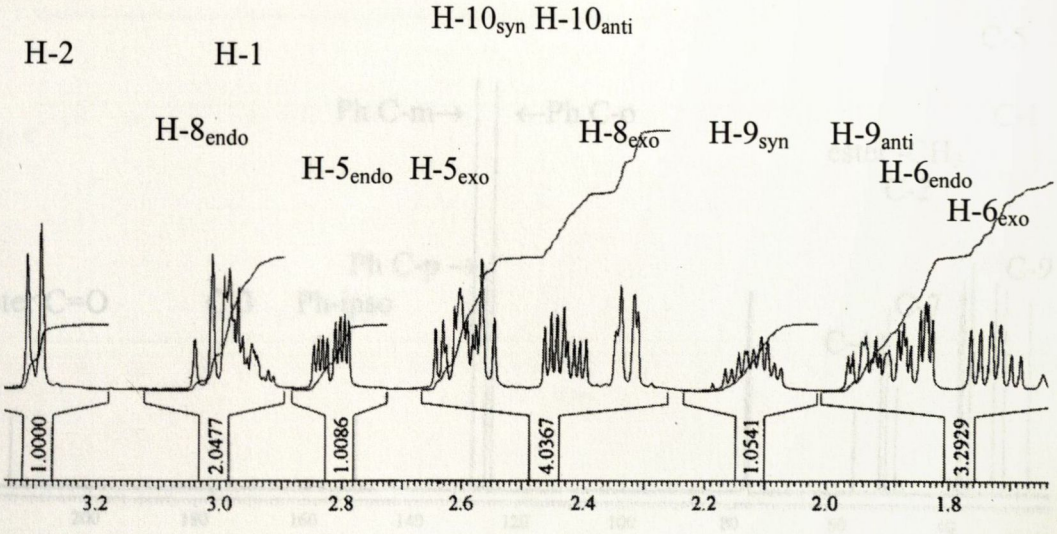
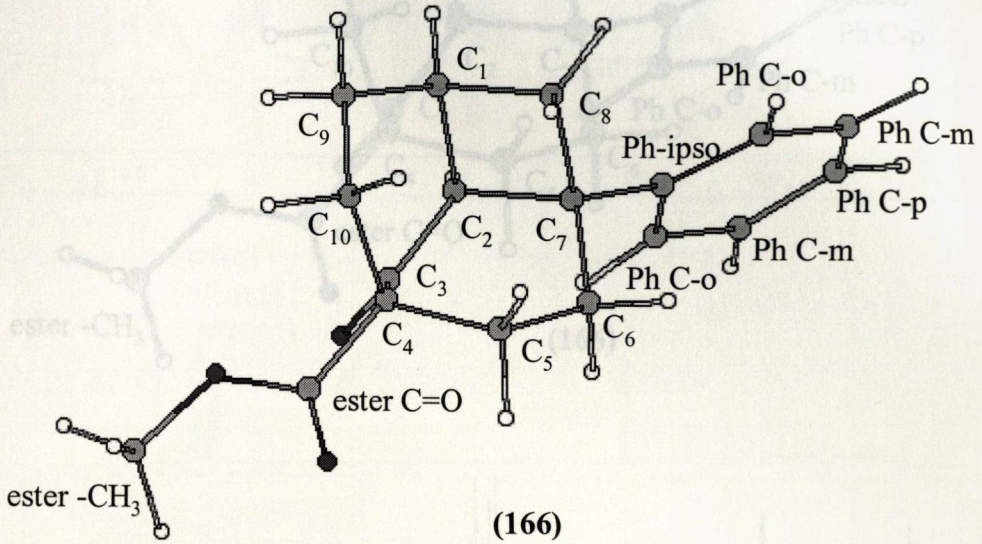


Fig. 3.16 The ^{1}H NMR spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166]expanded for the region δ 1.6-3.34 ppm.



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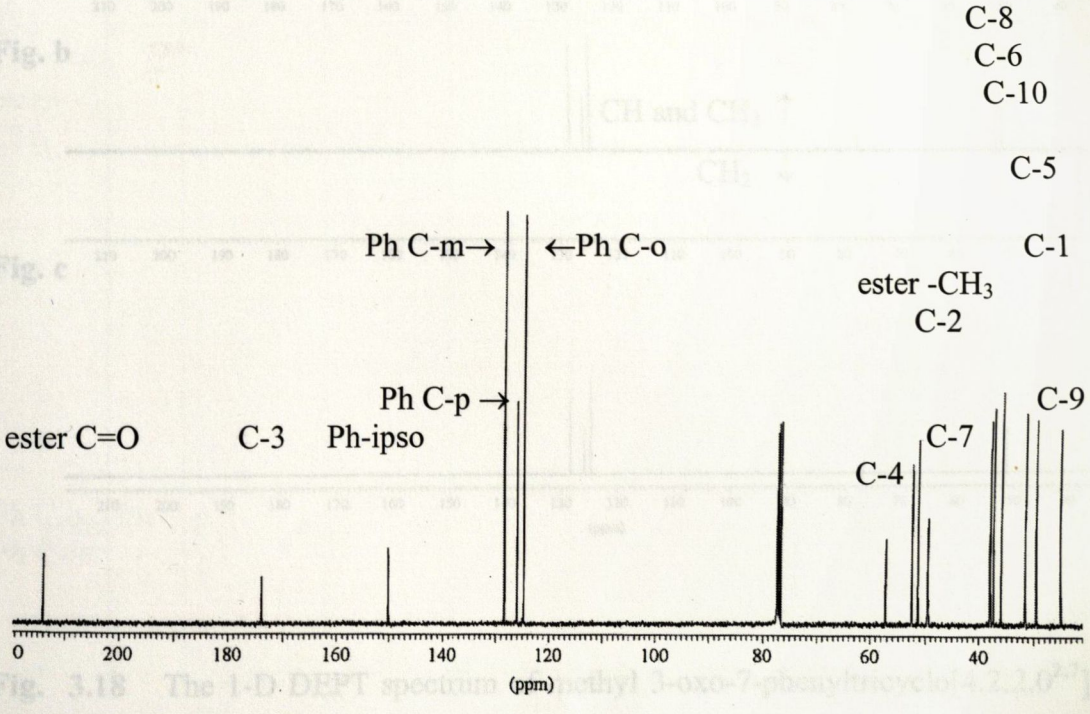
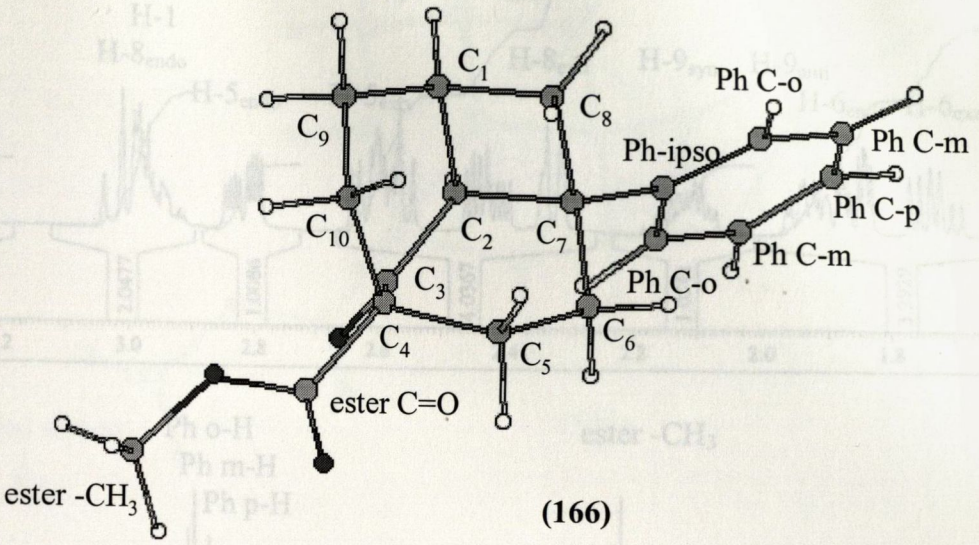


Fig. 3.17 The ^{13}C NMR spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.0^{2,7}]-decane-4-carboxylate [166].



(166)

Fig. a

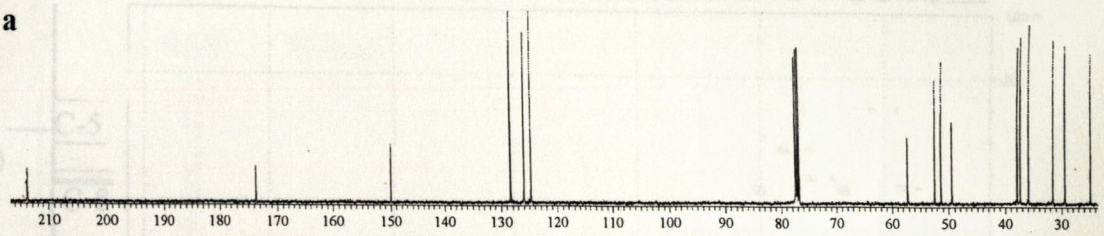


Fig. b

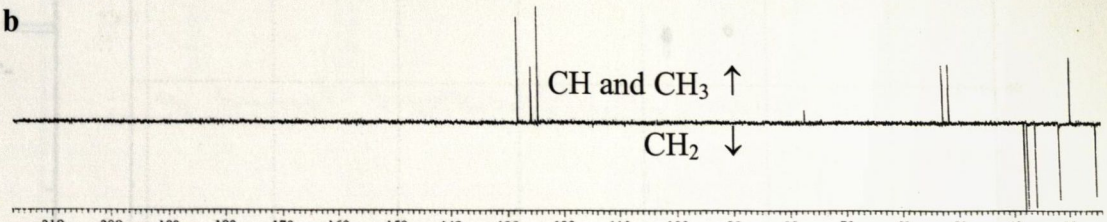


Fig. c

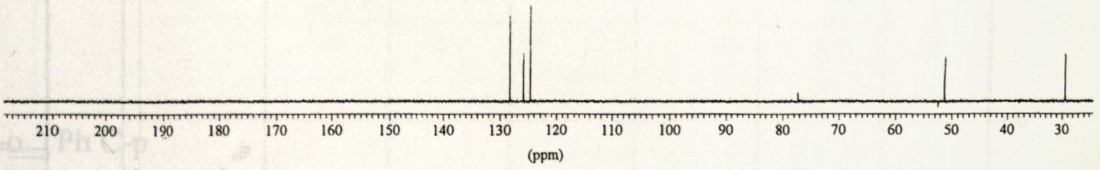


Fig. 3.18 The 1-D DEPT spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166]. **Fig. a** All carbon peaks. **Fig. b** All protonated carbon peaks with CH's and CH_3's pointing up and CH_2's pointing down. **Fig. c** All CH's and CH_3's carbon peaks.

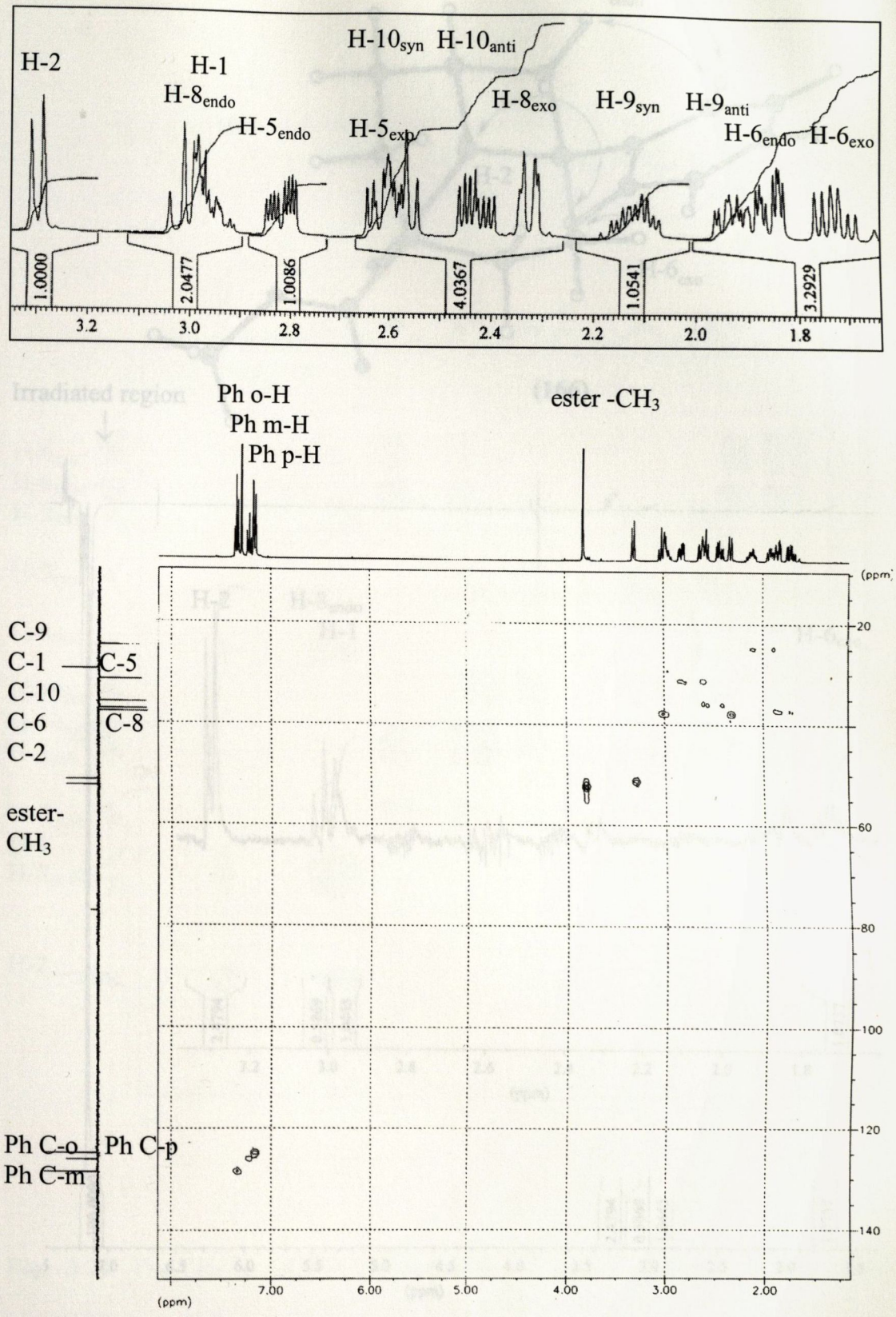


Fig. 3.19 The ^{1}H-^{13}C HETCOR NMR spectrum of methyl 3-oxo-7-phenyltricyclo-[4.2.2.0^{2,7}]decane-4-carboxylate [166].

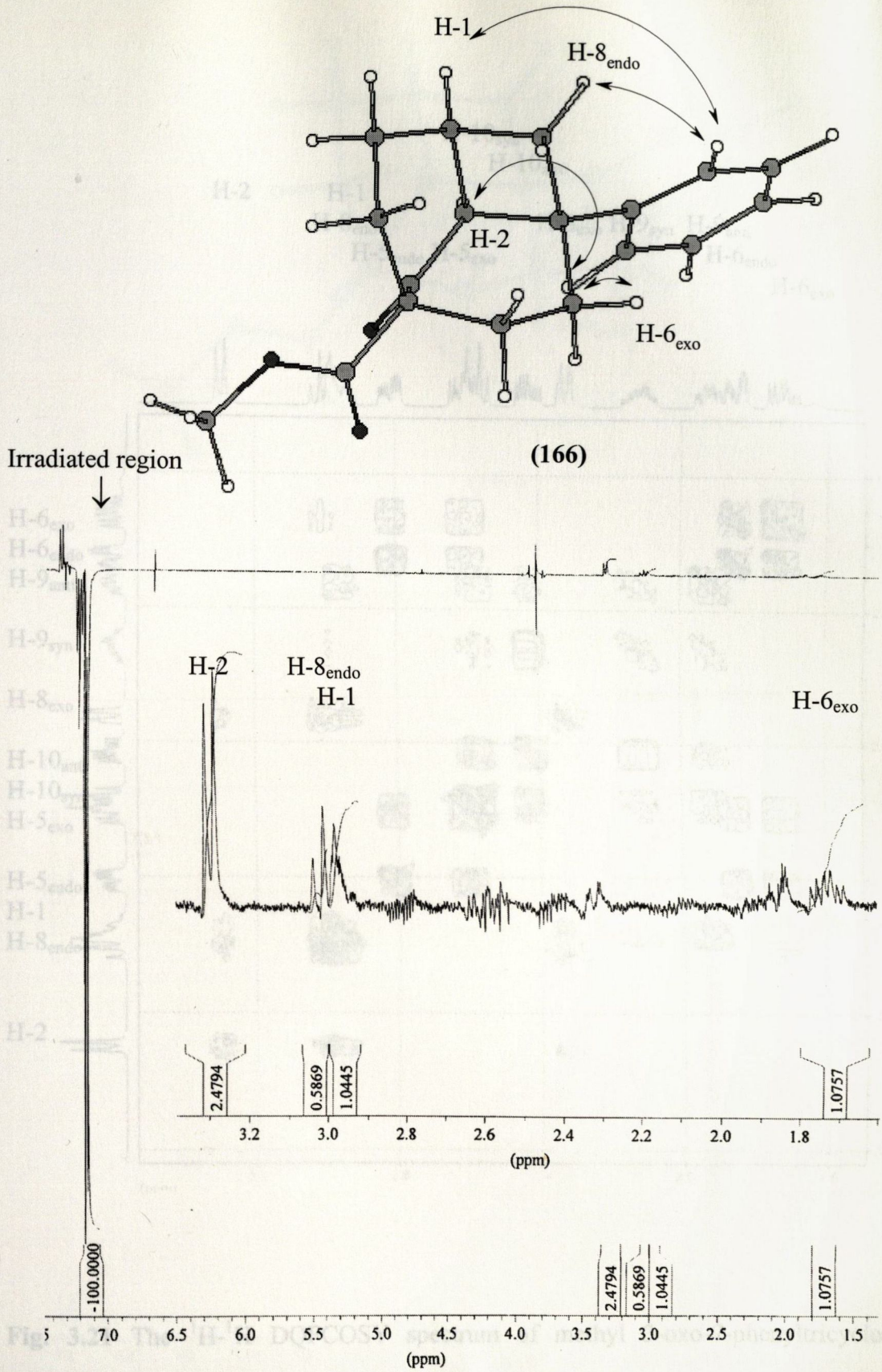


Fig. 3.20 The nOe difference spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166] for the irradiation of ortho Hydrogens on the phenyl ring.

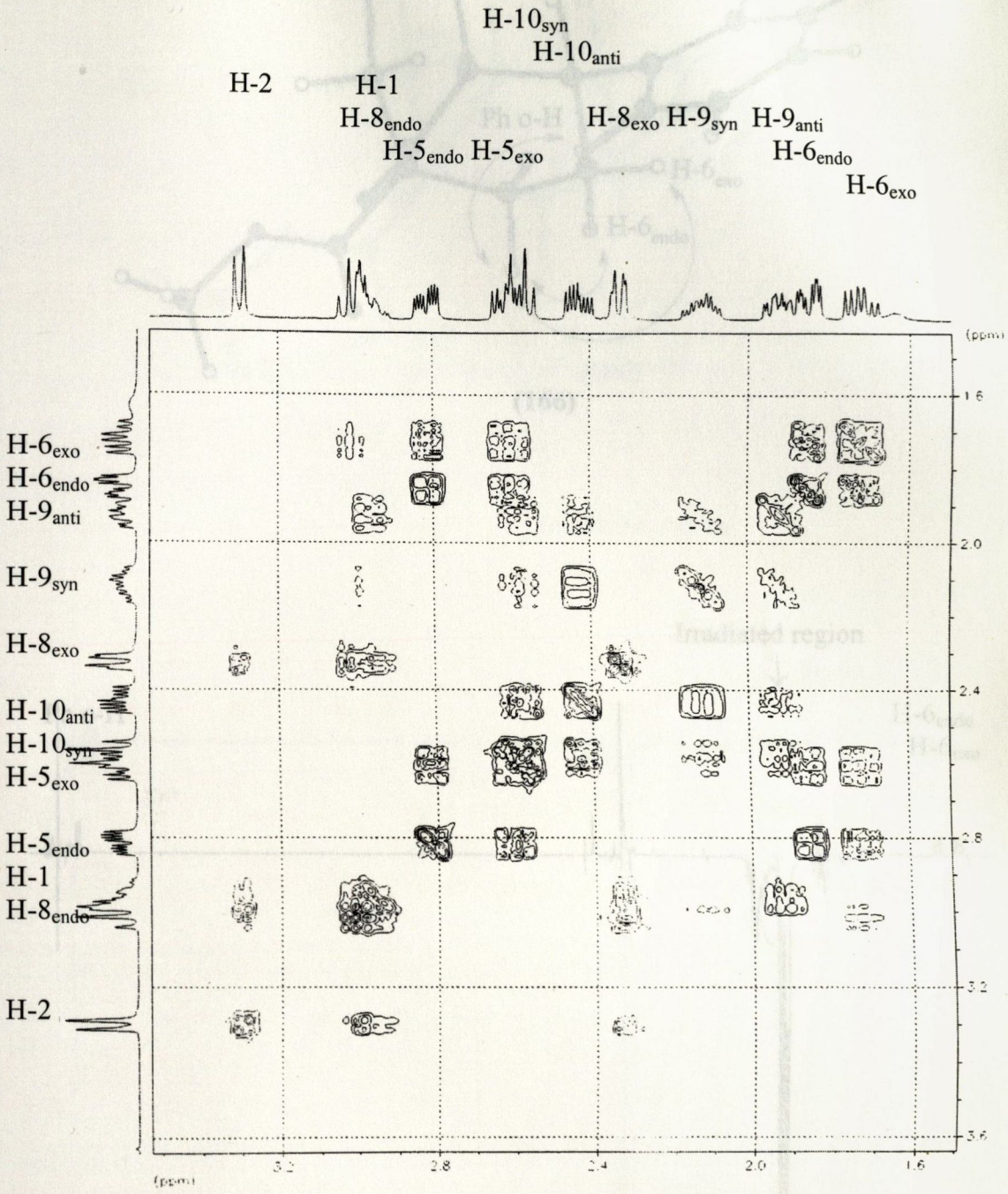
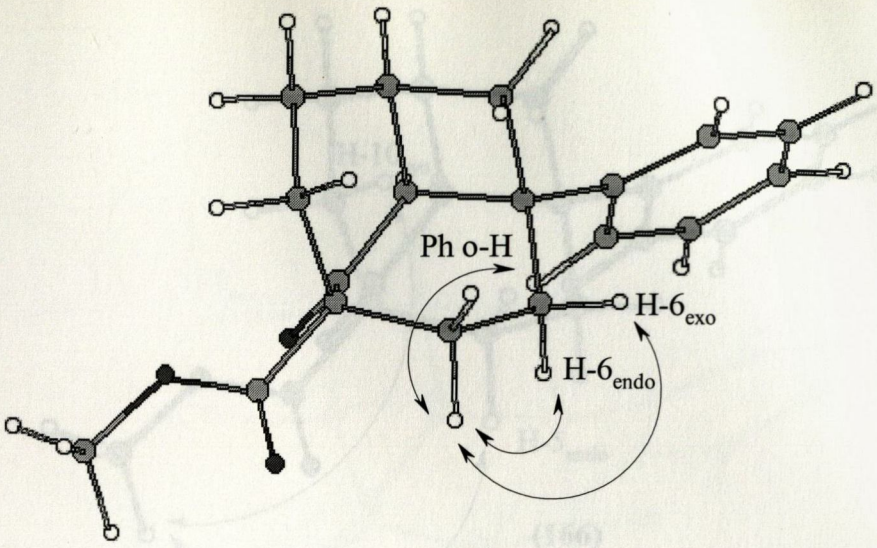


Fig. 3.21 The ^{1}H-^{1}H DQFCOSY spectrum of methyl 3-oxo-7-phenyltricyclo-[4.2.2.0^{2,7}]decane-4-carboxylate [166].



(166)

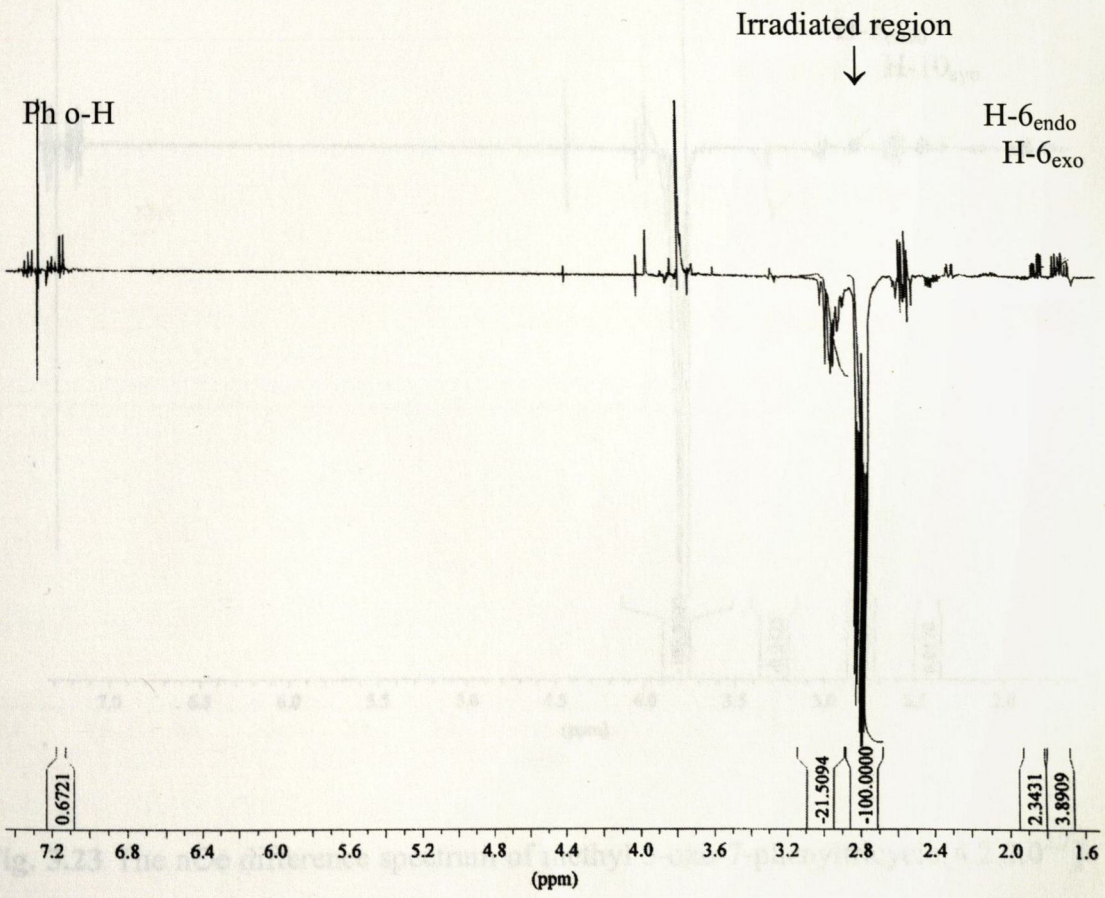
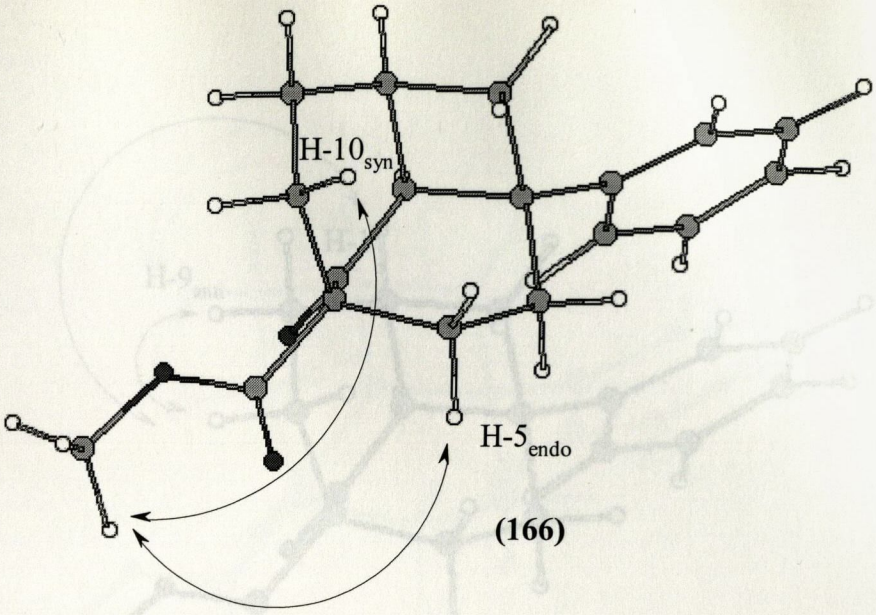


Fig. 3.22 The nOe difference spectrum methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166] for the irradiation of H-5_{endo}.



(166)

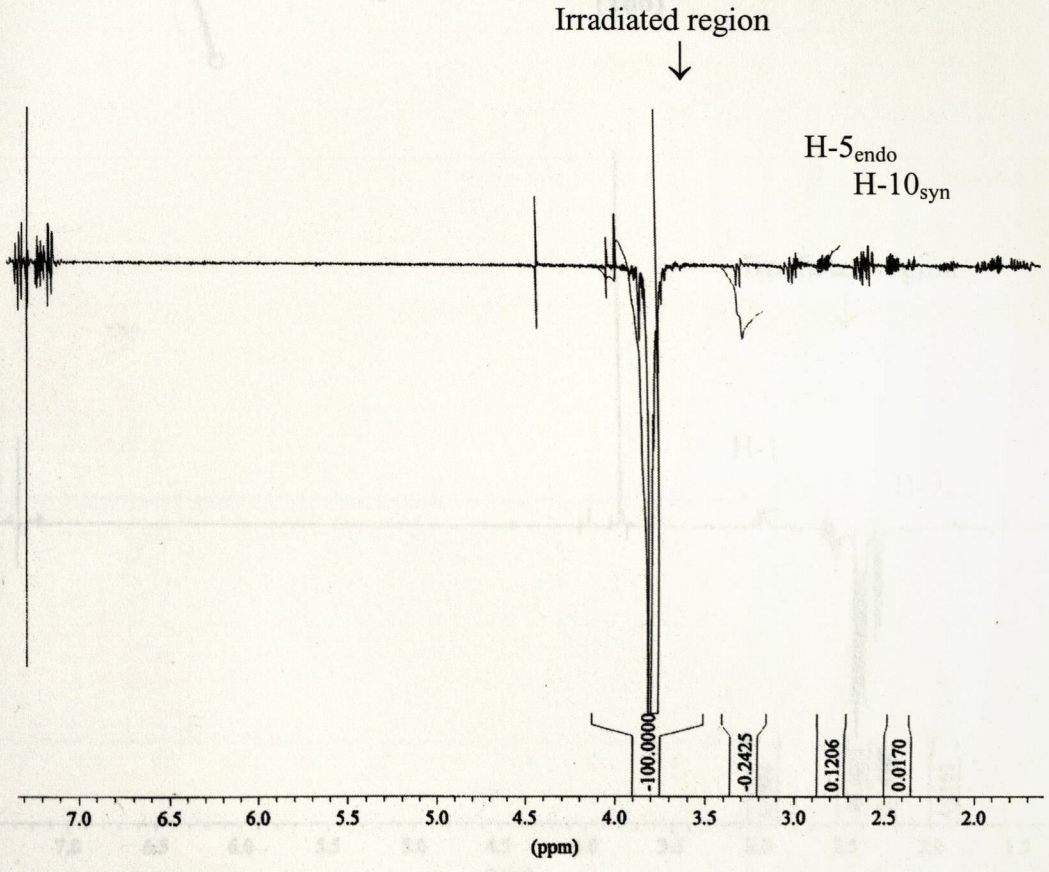
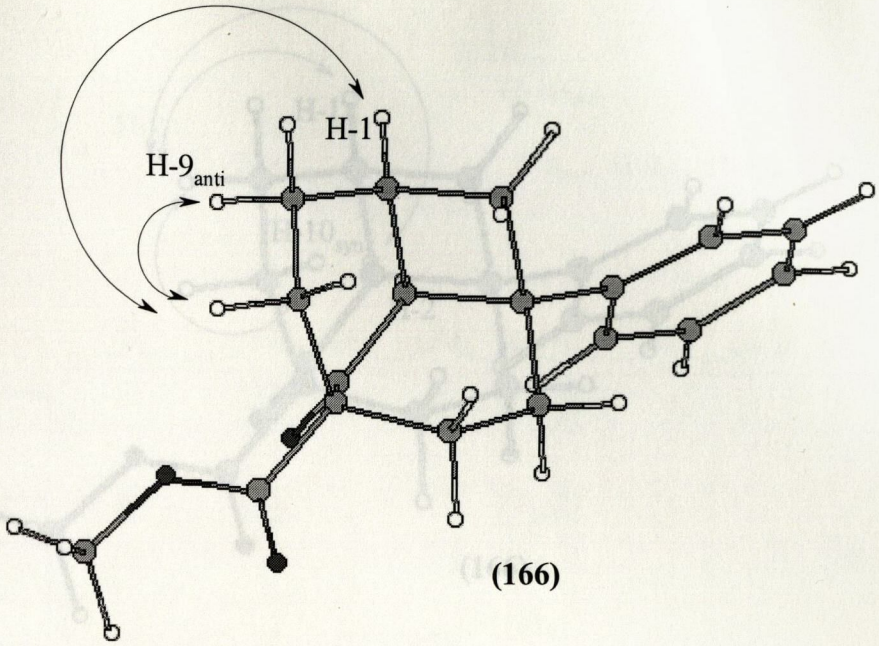


Fig. 3.23 The nOe difference spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166] for the irradiation of the ester -CH_3.



(166)

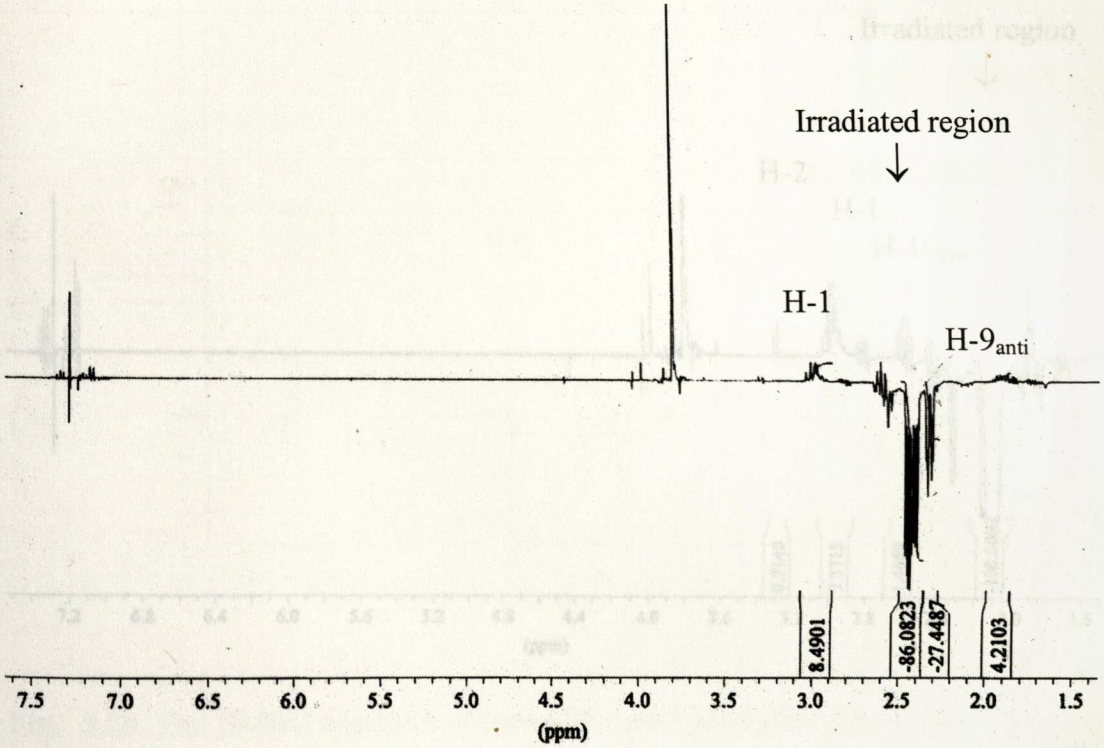
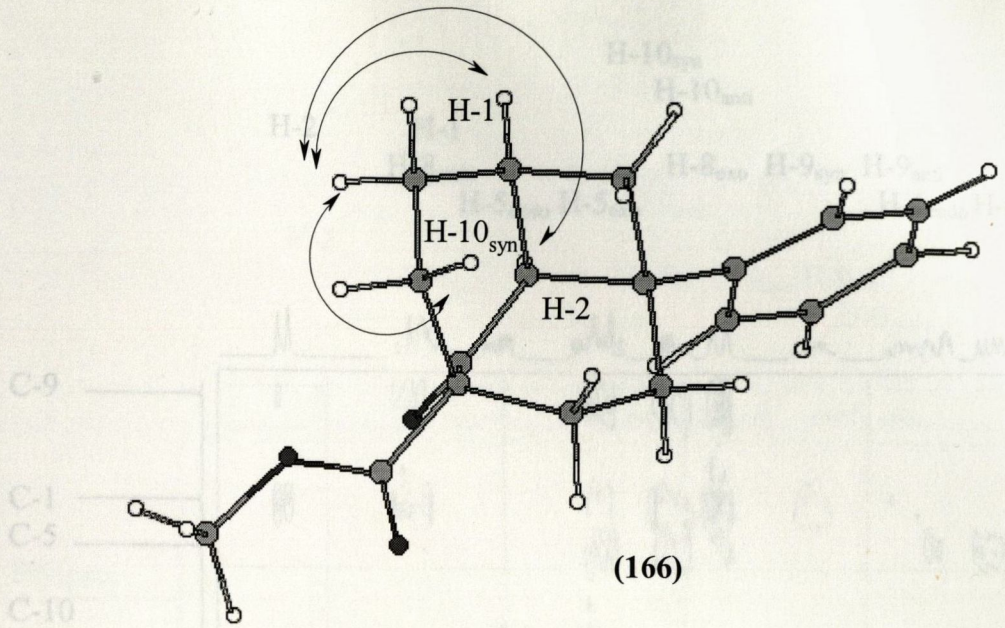


Fig. 3.24 The nOe difference spectrum methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166] for the irradiation of H-10_{anti}.



(166)

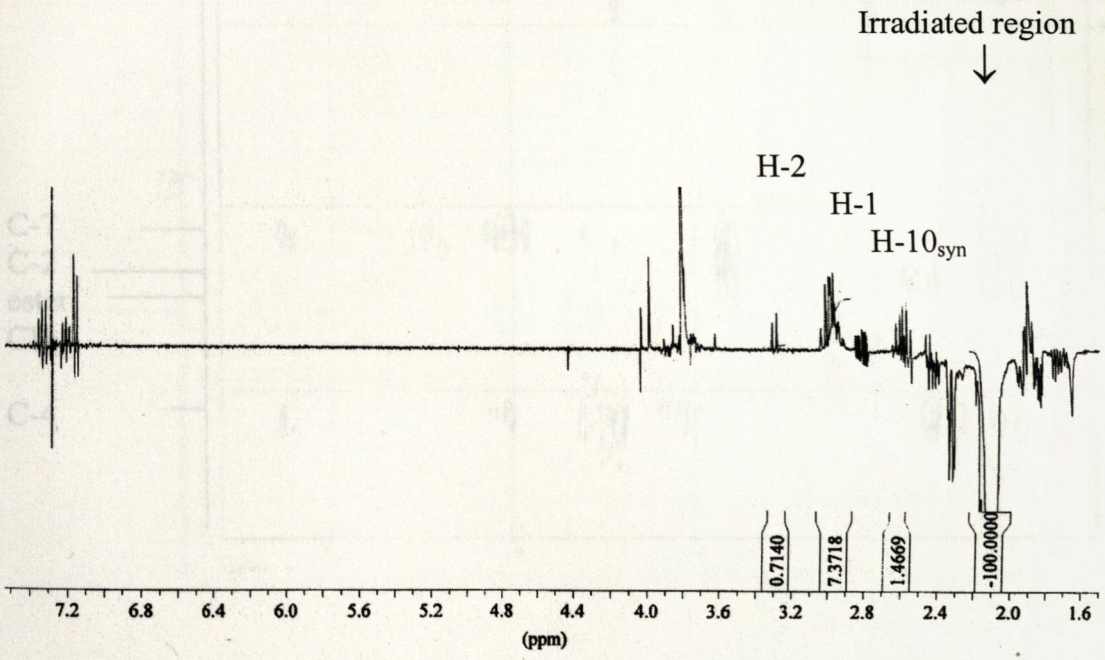


Fig. 3.25 The nOe difference spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166] for the irradiation of H-9_{anti}.

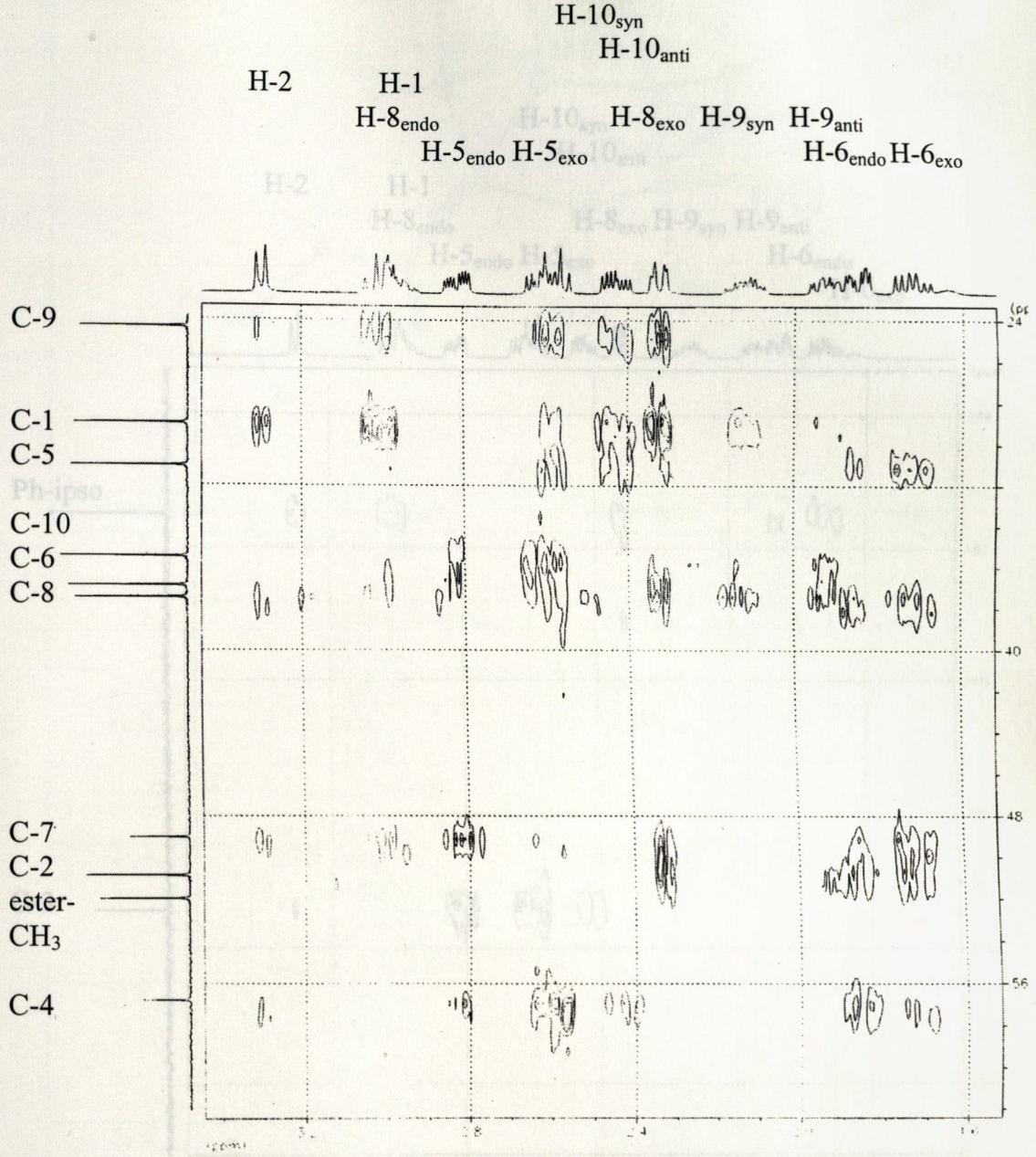


Fig. 3.26 The HMBC spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] for the region δ 24-60 ppm.

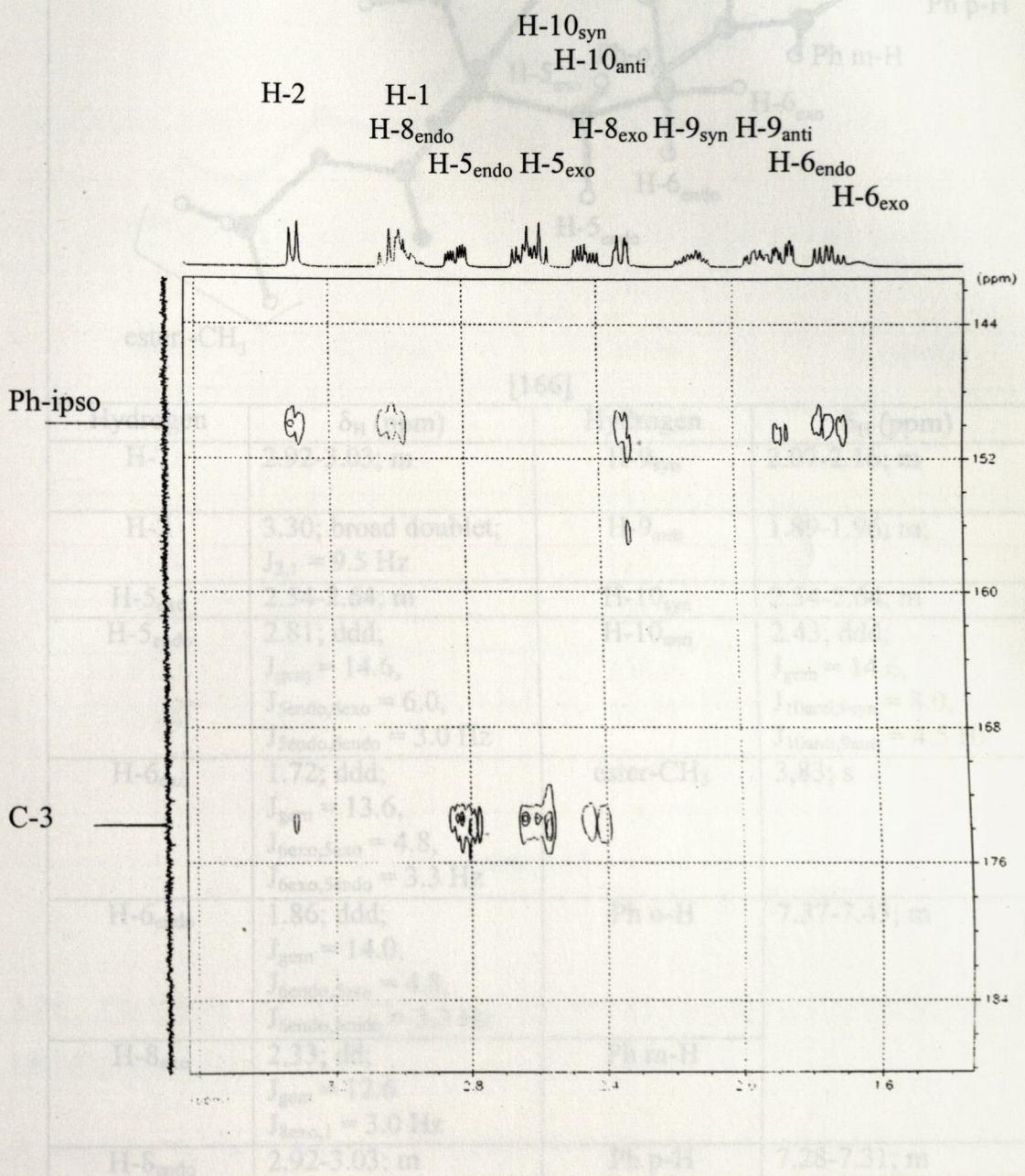
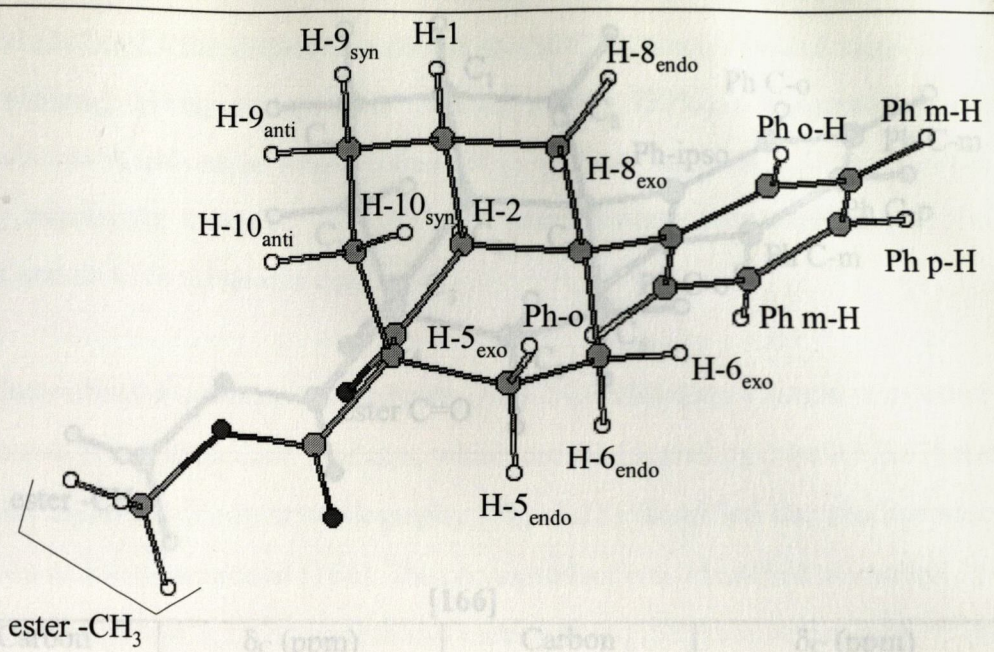


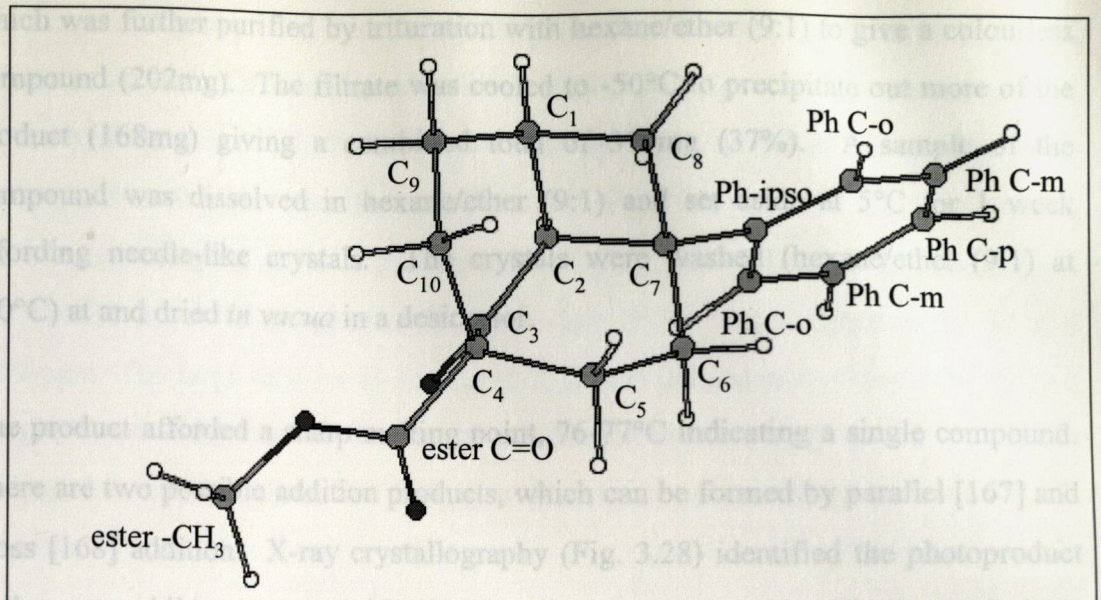
Fig. 3.27 The HMBC spectrum of methyl 3-oxo-7-phenyltricyclo[4.2.2.0^{2,7}]decane-4-carboxylate [166] for the region δ 140-190 ppm.



[166]

Hydrogen	δ_H (ppm)	Hydrogen	δ_H (ppm)
H-1	2.92-3.03; m	$H\text{-}9_{syn}$	2.07-2.16; m
H-2	3.30; broad doublet; $J_{2,1}$ = 9.5 Hz	$H\text{-}9_{anti}$	1.89-1.96; m;
$H\text{-}5_{exo}$	2.54-2.64; m	$H\text{-}10_{syn}$	2.54-2.64; m
$H\text{-}5_{endo}$	2.81; ddd; J_{gem} = 14.6, $J_{5endo,6exo}$ = 6.0, $J_{5endo,6endo}$ = 3.0 Hz	$H\text{-}10_{anti}$	2.43; ddd; J_{gem} = 14.6, $J_{10anti,9syn}$ = 8.0, $J_{10anti,9anti}$ = 4.5 Hz
$H\text{-}6_{exo}$	1.72; ddd; J_{gem} = 13.6, $J_{6exo,5exo}$ = 4.8, $J_{6exo,5endo}$ = 3.3 Hz	ester-CH_3	3,83; s
$H\text{-}6_{endo}$	1.86; ddd; J_{gem} = 14.0, $J_{6endo,5exo}$ = 4.8, $J_{6endo,5endo}$ = 3.3 Hz	Ph o-H	7.37-7.43; m
$H\text{-}8_{exo}$	2.33; dd; J_{gem} = 12.6 $J_{8exo,1}$ = 3.0 Hz	Ph m-H	
$H\text{-}8_{endo}$	2.92-3.03; m	Ph p-H	7.28-7.31; m

Table 3.12



[166]

Carbon	δ_C (ppm)	Carbon	δ_C (ppm)
24.7	C-9	52.3	ester -CH_3
29.3	C-1	57.1	C-4
31.4	C-5	124.7	Ph C-o
35.8	C-10	125.9	Ph C-p
37.2	C-6	128.3	Ph C-m
37.8	C-8	150.0	Ph-ipso
49.3	C-7	173.7	C-3
51.2	C-2	213.9	ester C=O

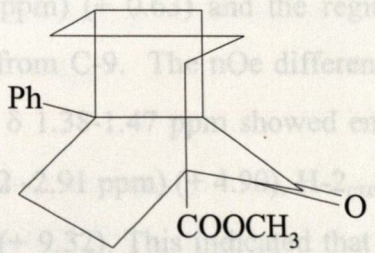
Table 3.13

3.26 Photolysis of methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-2-ene-1-carboxylate [135]

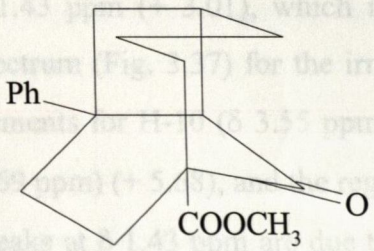
A solution of methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-2-ene-1-carboxylate [135] (1g) in acetonitrile (450ml) was irradiated. The reaction was followed by GC-MS. The starting cyclohexenone had GC retention time of 24.77 min. Only one other peak appeared with GC retention time of 26.06 min suggesting a single photoproduct. The reaction was stopped after 17 h when all of the starting material had reacted. The solvent was removed *in vacuo* to give a dark viscous oil. The oil was purified by flash chromatography (hexane/ether 9:1) to give a yellow viscous oil

which was further purified by trituration with hexane/ether (9:1) to give a colourless compound (202mg). The filtrate was cooled to -50°C to precipitate out more of the product (168mg) giving a combined total of 370mg (37%). A sample of the compound was dissolved in hexane/ether (9:1) and set aside at 5°C for 1 week affording needle-like crystals. The crystals were washed (hexane/ether (9:1) at -50°C) at and dried *in vacuo* in a desiccator.

The product afforded a sharp melting point, 76-77°C indicating a single compound. There are two possible addition products, which can be formed by parallel [167] and cross [168] addition. X-ray crystallography (Fig. 3.28) identified the photoproduct as the cross addition compound [168]. The photoproduct was identified as methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] (see Appendix).



(167)



(168)

The ^{1}H NMR spectrum (Fig. 3.29 and 3.30) indicated the presence of twenty-two hydrogens, while the ^{13}C NMR spectrum (Fig. 3.31) displayed seventeen peaks as expected. The 1-D DEPT spectrum (Fig. 3.32) showed the presence of five quaternary peaks, six CH_2s and a further six protonated peaks consisting of five CH peaks and one CH_3 peak as confirmed by the 2-D HETCOR spectrum (Fig. 3.33 and 3.39).

Analysis of the nOe difference spectrum (Fig. 3.35) for the irradiation of the phenyl ortho hydrogens indicated an enhancement of peaks at δ 3.55 (+ 3.14), δ 2.50-2.57 (+ 1.95) and the region δ 1.73-1.88 ppm (+ 0.73). The 2-D HETCOR (Fig. 3.39) identified the dd at δ 3.55 ppm as a CH. This CH was assigned to H-10 as it is expected further downfield than H-1 due to the additive effects of the phenyl and

C-11 carbonyl group. The remaining CH peak (Fig. 3.39) at δ 2.82 -2.91 ppm was identified as H-1. Examination of the 2-D HETCOR (Fig. 3.39) showed correlation of the hydrogen at δ 2.50-2.57 ppm and the hydrogen at δ 2.69 ppm to the same carbon at δ 28.9 ppm. The ^{1}H-^{1}H DQFCOSY (Fig. 3.38) showed that both regions are strongly coupled to H-1, therefore identifying this CH_2 as C-2. The region δ 2.50-2.57 ppm was assigned to H-2_{endo}, while H-2_{exo} was assigned to the dd at δ 2.69 ppm. The large nOe for H-10 and H-2_{endo} and the absence of any nOe for H-1 suggested an orientation where the ortho-hydrogen on the phenyl group is closer to H-4_{endo} than H-4_{exo}. Therefore H-4_{endo} was assigned to the region between δ 1.73-1.88 ppm.

Analysis of the nOe difference spectrum (Fig. 3.36) for the irradiation of the H-1 (δ 2.82-2.91 ppm) showed enhancements for H-10 (δ 3.55 ppm) (+ 6.42), H-2_{endo} (δ 2.50-2.57 ppm) (+ 0.63) and the region δ 1.43 ppm (+ 3.01), which is due to a hydrogen from C-9. The nOe difference spectrum (Fig. 3.37) for the irradiation of the region δ 1.38-1.47 ppm showed enhancements for H-10 (δ 3.55 ppm) (+ 2.16), H-1 (δ 2.82 -2.91 ppm) (+ 4.90), H-2_{exo} (δ 2.69 ppm) (+ 5.68), and the region δ 1.73-1.88 ppm (+ 9.32). This indicated that the peaks at δ 1.43 ppm are due to H-9_{exo} as H-9_{endo} would not display any enhancements for H-10. The 2-D HETCOR (Fig. 3.39) showed correlation of H-9_{exo} and another hydrogen in the region δ 1.73-1.88 ppm to the same carbon at δ 29 ppm and this was assigned to H-9_{endo}. The ^{1}H-^{1}H DQFCOSY (Fig. 3.38) showed that H-1 is coupled strongly to H-10, H-2_{endo}, H-2_{exo}, H-9_{endo}, and H-9_{exo} as expected.

The decoupled spectrum for the double irradiation of H-1 (Fig. 3.39) showed that H-10 has been reduced from a doublet to a singlet, while H-9_{exo} has been reduced from a tt to a td. There were also peak reductions for H-2_{endo} (δ 2.50-2.57 ppm), H-2_{exo} (δ 2.69 ppm) and the region δ 1.73-1.88 ppm which contains H-9_{endo}. The decoupling of H-10 (Fig. 3.40) showed only peak reductions for H-1 as expected.

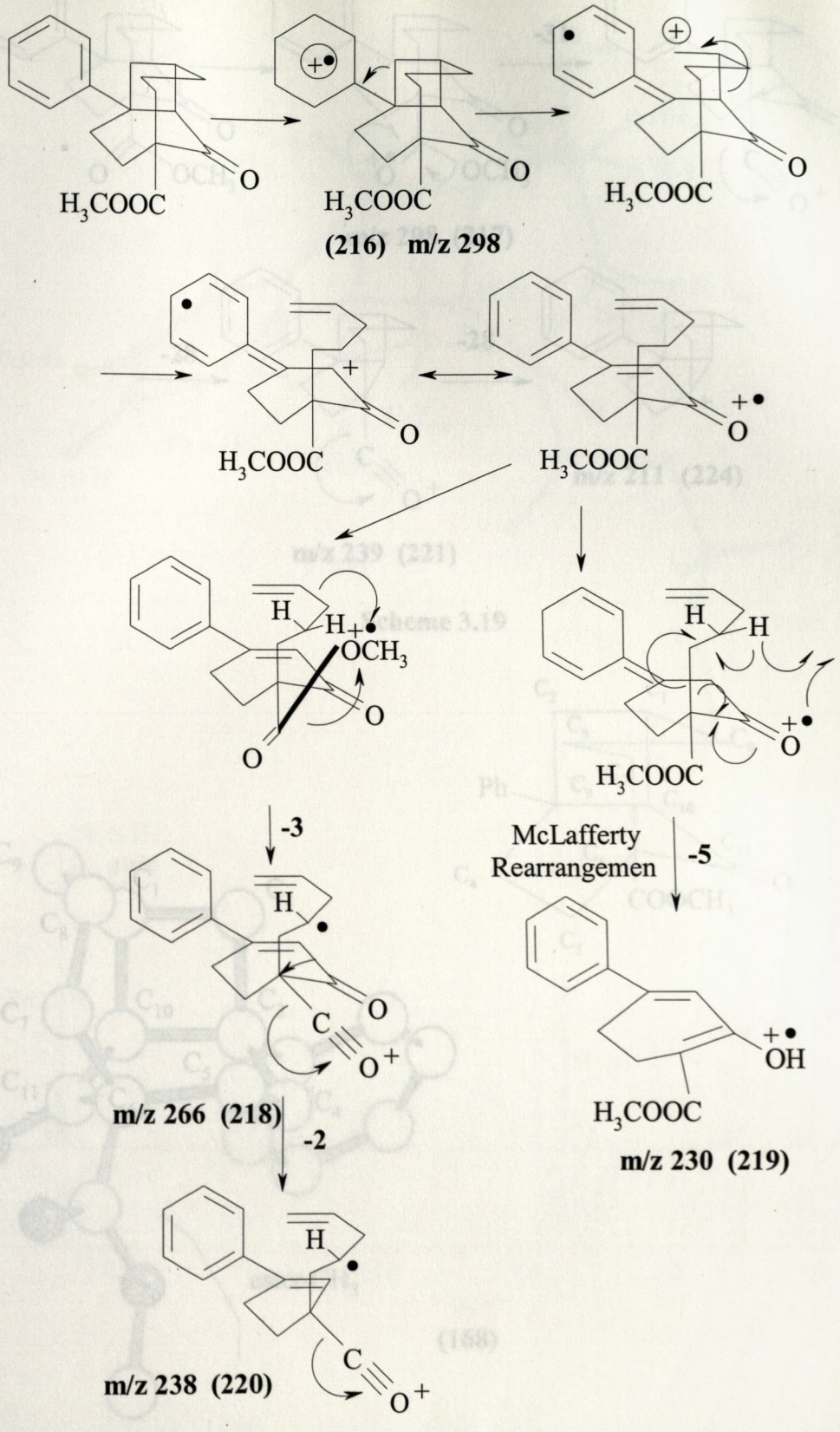
The decoupled spectrum of H-9_{exo} (Fig. 3.41) showed peak reduction for H-1 and the region δ 1.73-1.88 ppm containing H-9_{endo}. No other region was affected indicating that both H-8_{endo} and H-8_{exo} resonate in this region. This is further confirmed from

analysis of the ^{1}H-^{1}H DQFCOSY spectrum, which showed that H-9_{exo} is coupled strongly to H-1 and to the region δ 1.73-1.88 ppm. It has already been established that H-9_{endo} resonates in this region. However there is no coupling to any other region indicating that H-8_{endo} and H-8_{exo} also resonate in this region.

The nOe difference spectrum (Fig. 3.42) for the irradiation of the region δ 2.05 ppm indicated enhancements for H-2_{exo} δ 2.69 ppm (+ 4.20), δ 1.73-1.88 ppm (+ 15.20) and the region δ 2.05 ppm (+ 3.04). This irradiated area has been assigned to H-5_{endo} as H-4_{endo} and H-7_{endo} are too far away to cause such a large effect on H-2_{exo}. The 2-D HETCOR (Fig. 34) identified H-5_{exo} in the region δ 1.73-1.88 ppm. The large nOe at δ 1.73-1.88 ppm (+ 15.20) has been attributed to H-9_{endo} and H-8_{endo}. The remaining hydrogen in the region δ 2.59 ppm has been assigned to H-7_{endo}. The 2-D HETCOR (Fig. 3.34) identified H-7_{exo} in the region δ 2.10-2.16 ppm. There are two hydrogens resonating in the region δ 2.10-2.16 ppm. The remaining hydrogen was assigned to H-4_{exo}.

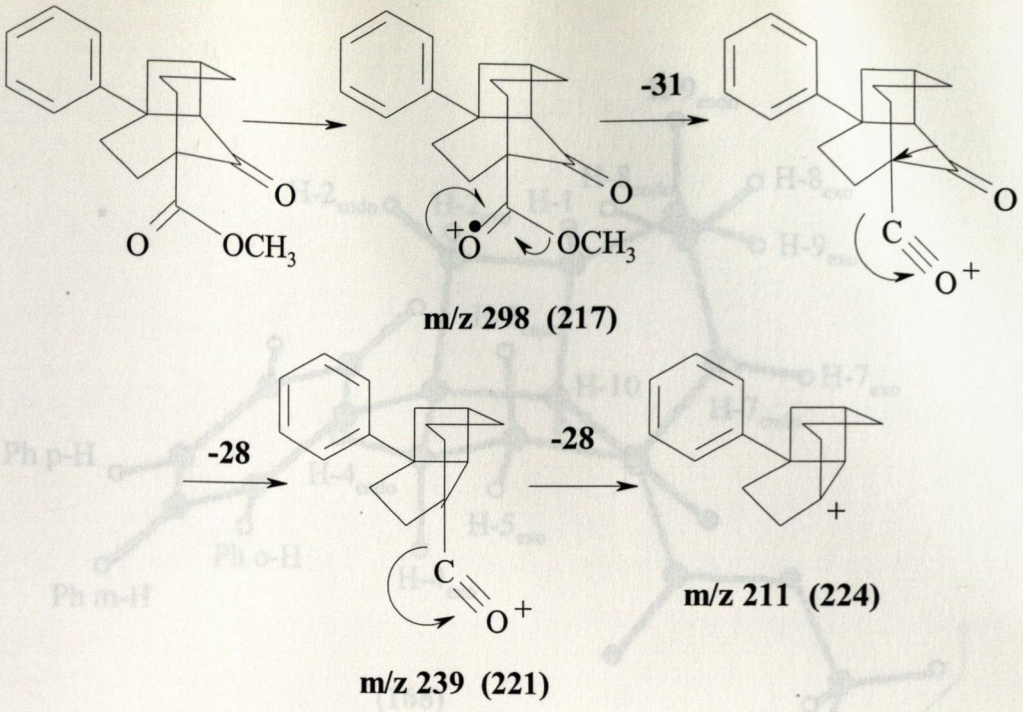
The quaternary carbons C-3 and C-6 where identified by analysis of the HMBC (Fig. 3.43 and 3.44). There is strong coupling between the hydrogens on C-2, Ph C-o, C-10 and C-4 to the carbon peak at δ 43.6 ppm and this was assigned to C-3. The carbon peak at δ 58.2 ppm was assigned to C-6 as it is coupled to the hydrogens on C-10, C-5 and C-7. The remaining hydrogens and carbon peaks are summarised in Table 3.14 and 3.15 respectively.

The mass spectrum of the compound showed similar fragmentation mechanisms as those of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [166] and methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [163] involving the generation of the radical cations [216] (Scheme 3.18) and [217] (Scheme 3.19). Both reaction mechanism afforded the molecular ion, $M^{+\cdot}$, m/z = 284. Molecular rearrangement in both mechanisms afforded the principal ions m/z = 266 [218] (Scheme 3.18), 238 [220] (Scheme 3.19), 239 [221] (Scheme 3.17), 230 [219] (Scheme 3.18), 211 [222] (Scheme 3.19). The base peak was at m/z = 230 [219].

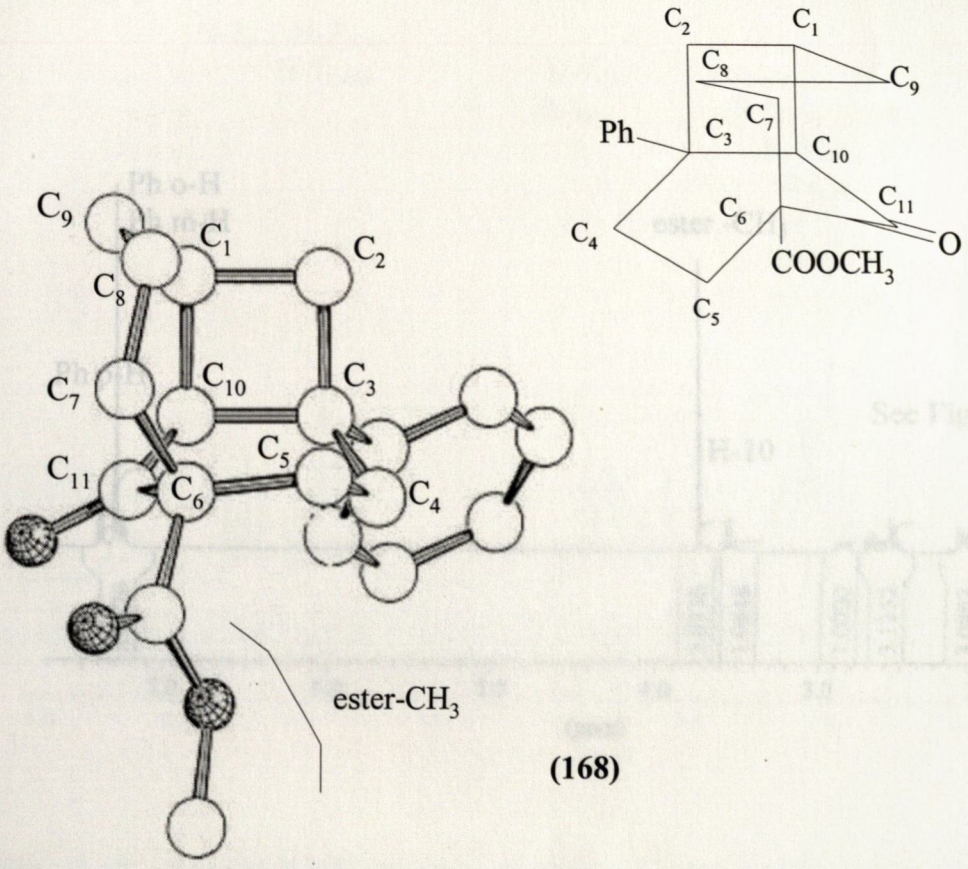


H3COOC
O
(216) m/z 298
H
H
OCH3
-3
McLafferty
Rearrangemen
-5
C
O+
OH
m/z 266 (218)
-2
m/z 230 (219)
m/z 238 (220)

Scheme 3.18

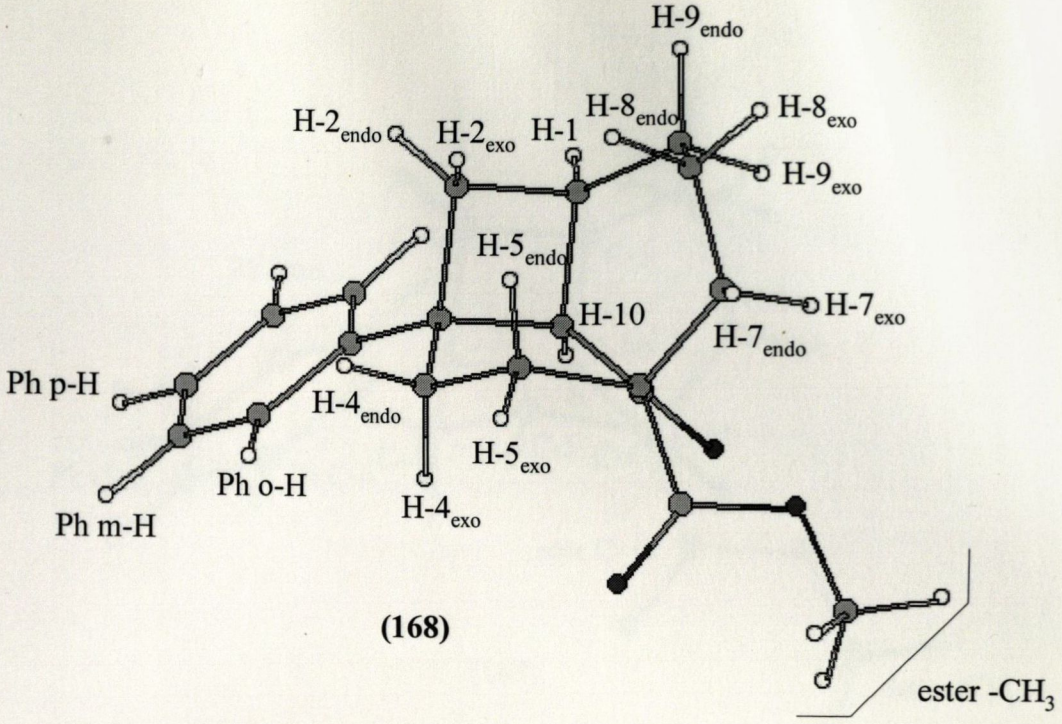


Scheme 3.19



(168)

Fig. 3.28 The X-ray crystallography of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168].



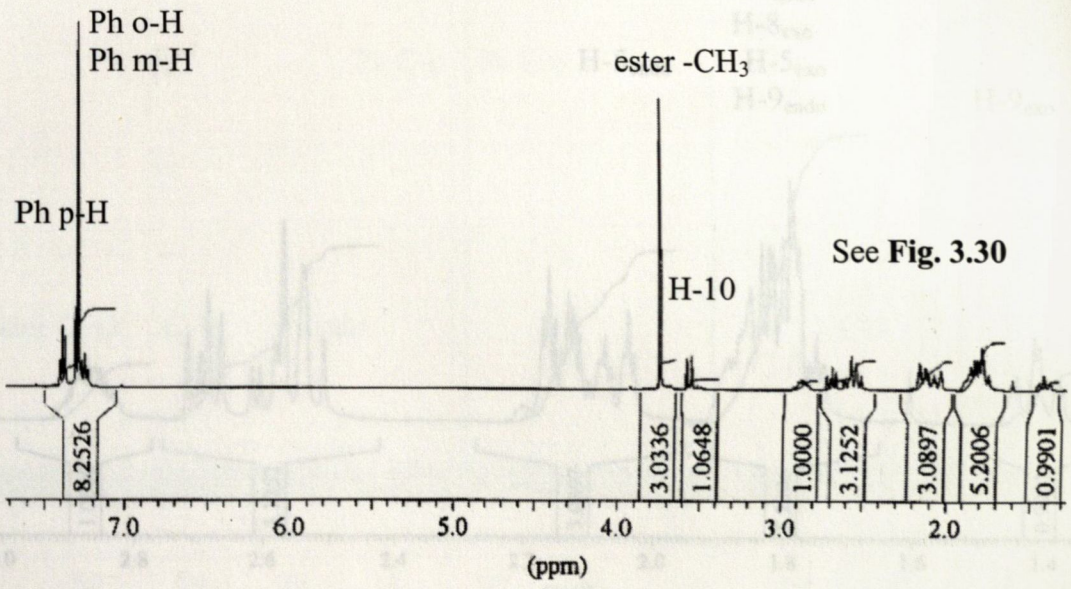


Fig. 3.29 The ^{1}H NMR spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168].

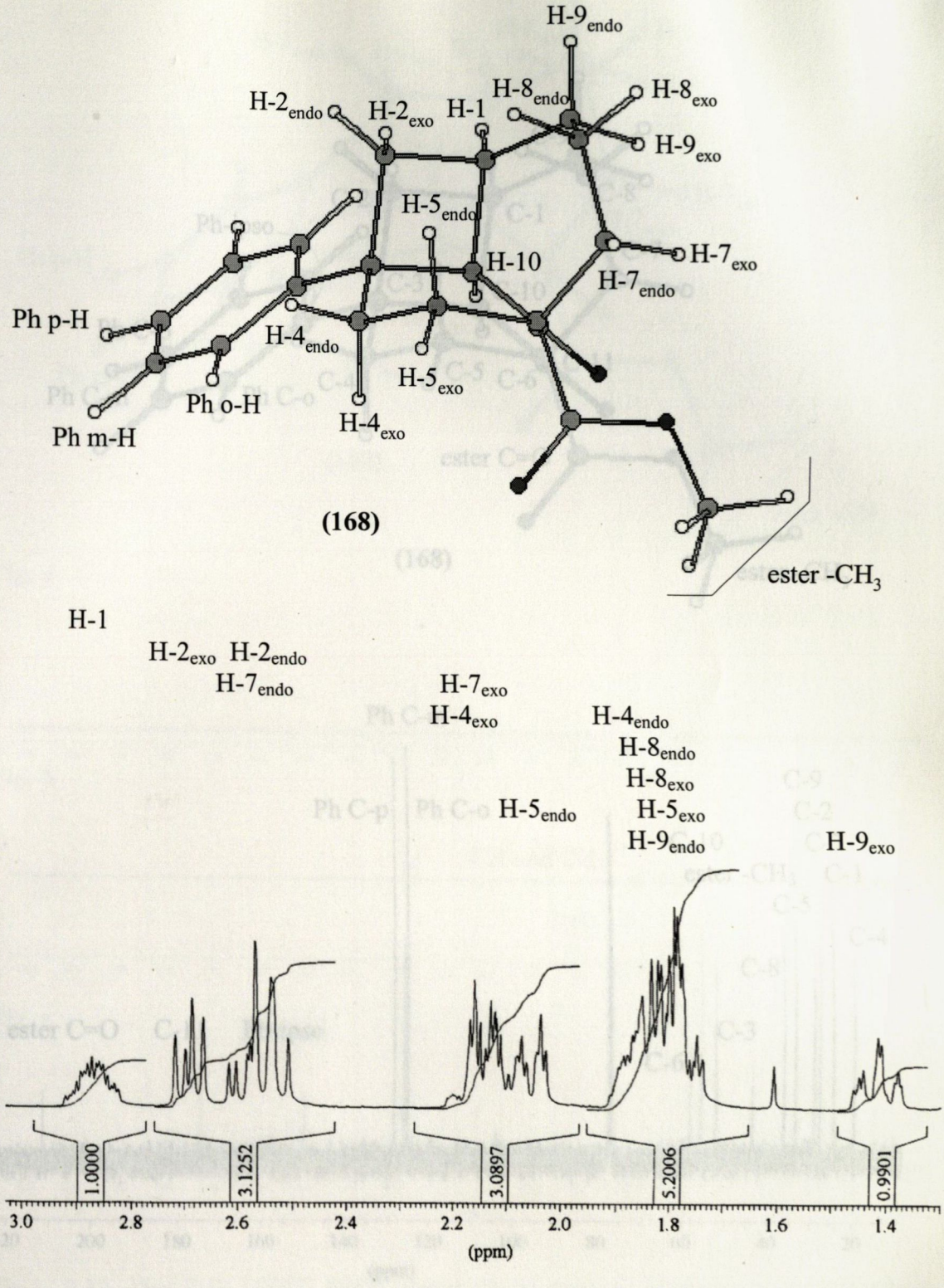
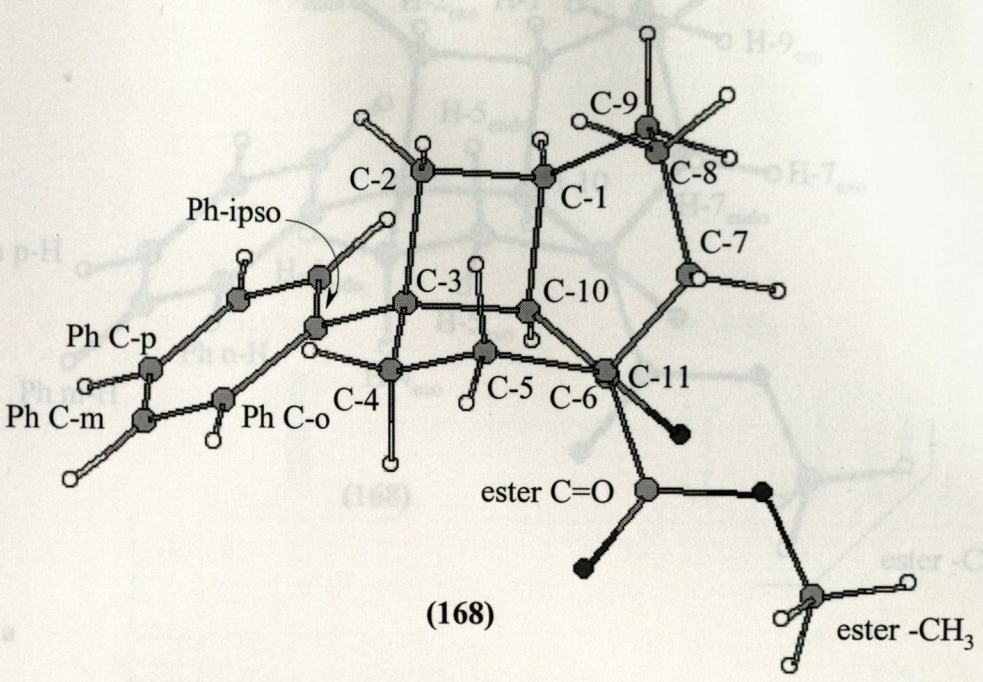


Fig. 3.30 The ^{1}H NMR spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168] expanded for the region δ 1.3-3.0 ppm.



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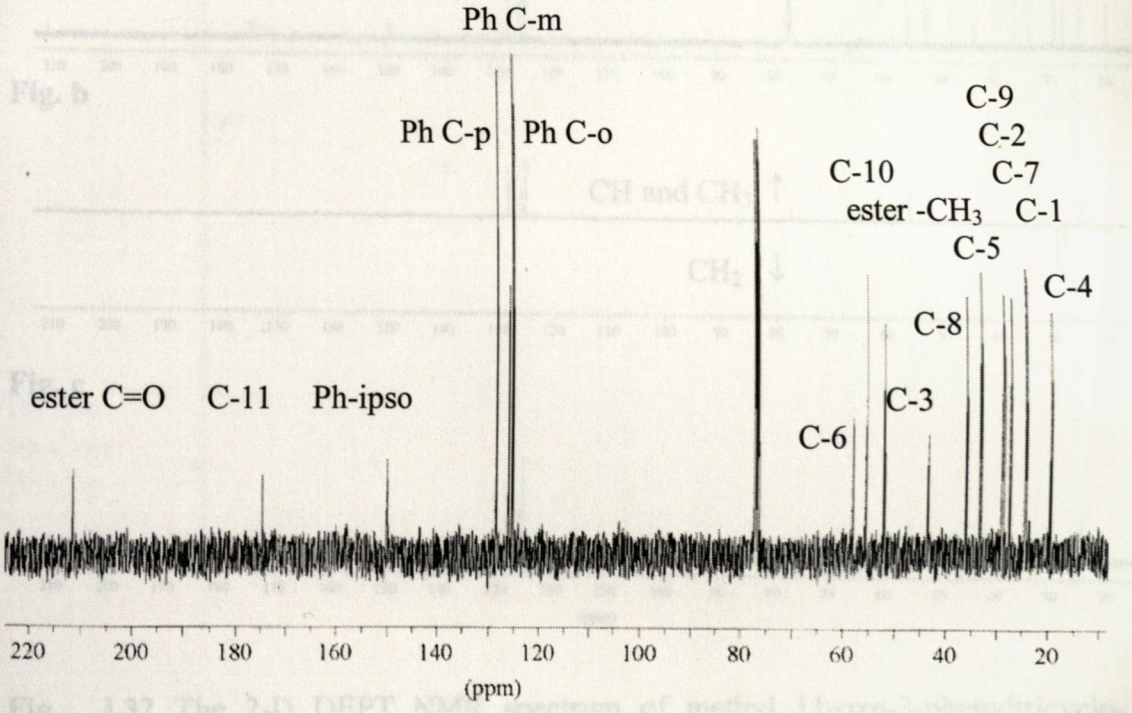
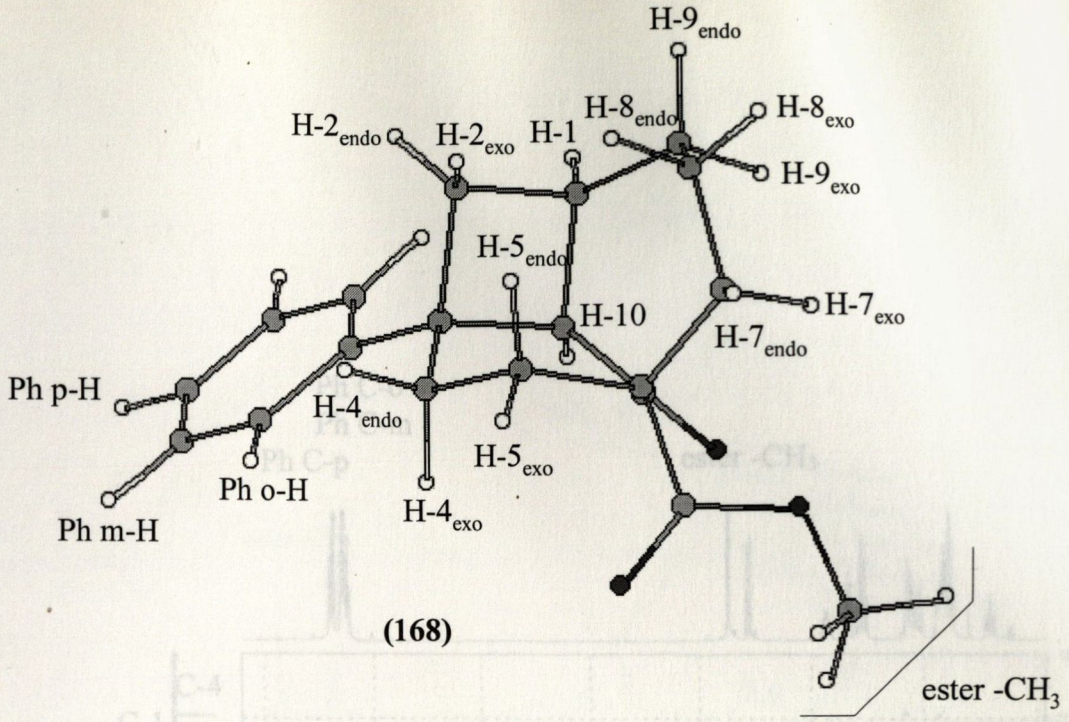


Fig. 3.31 The ^{13}C NMR spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168].



(168)

Fig. a

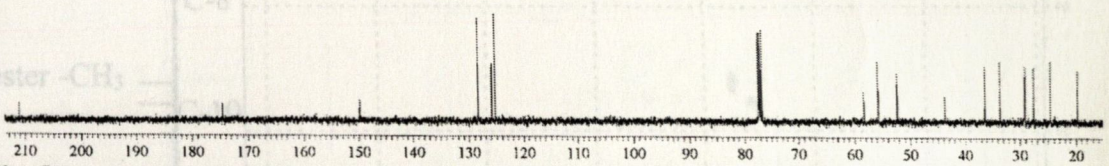


Fig. b

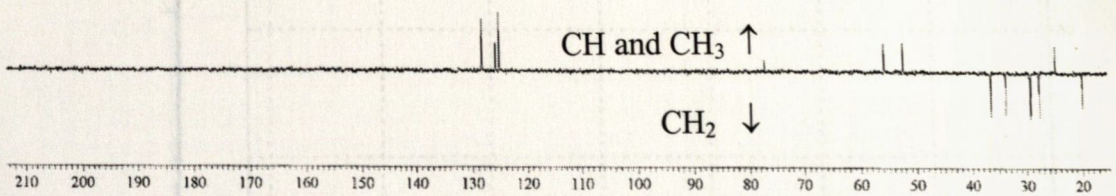


Fig. c

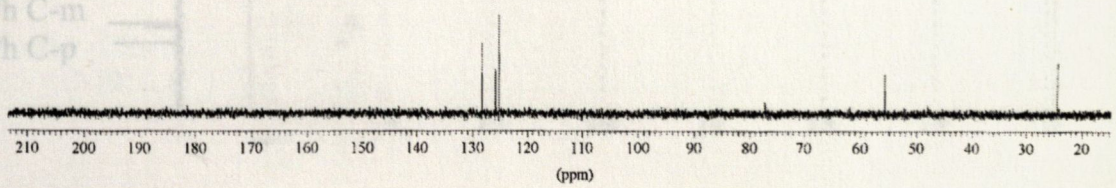


Fig. 3.32 The 2-D DEPT NMR spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168]. **Fig. a** All carbon peaks. **Fig. b** All protonated carbon peaks with CH's and CH_3's pointing up and CH_2's pointing down. **Fig. c** All CH's and CH_3's carbon peaks.

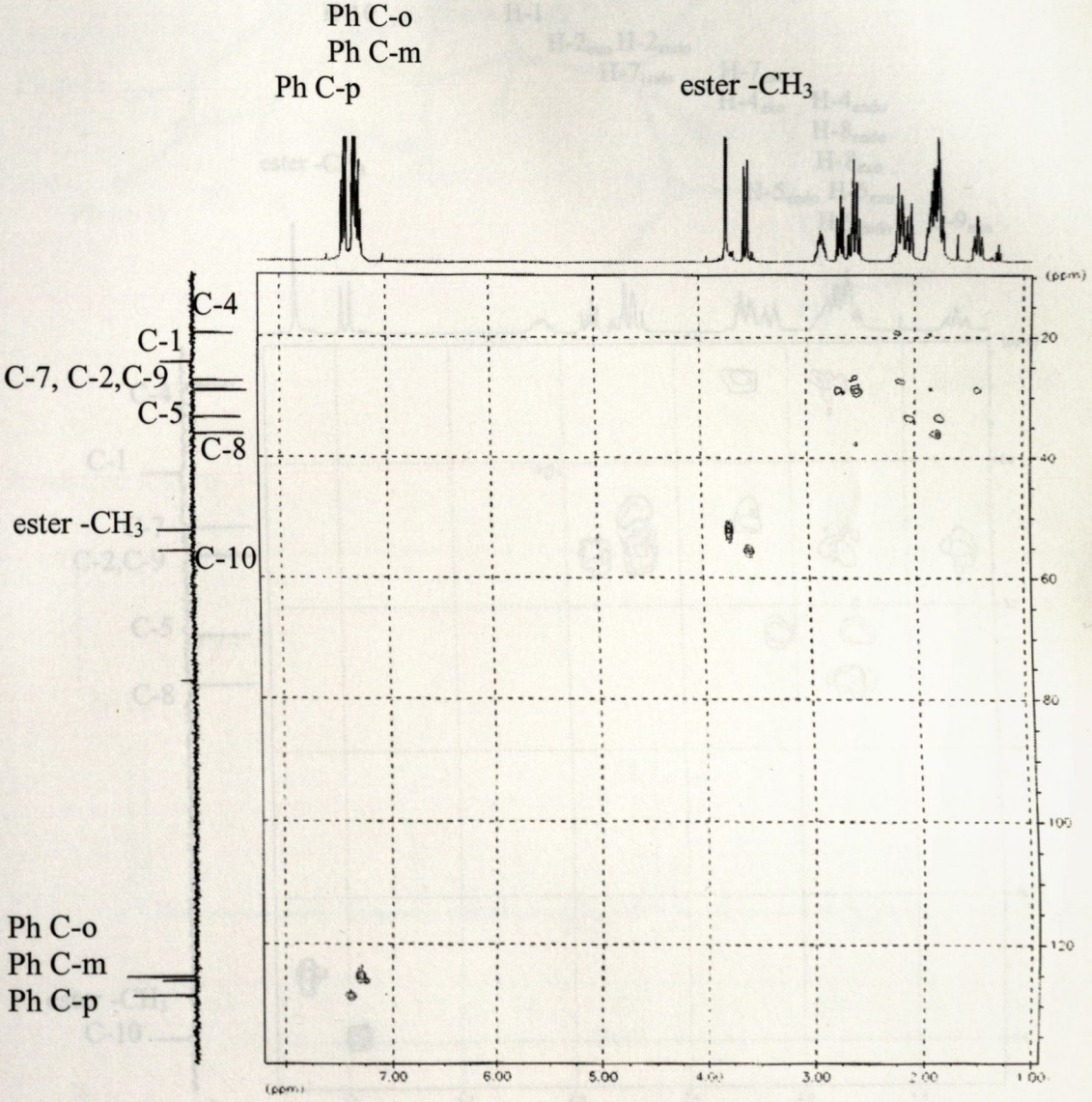


Fig. 3.33 The 2-D HETCOR NMR spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168].

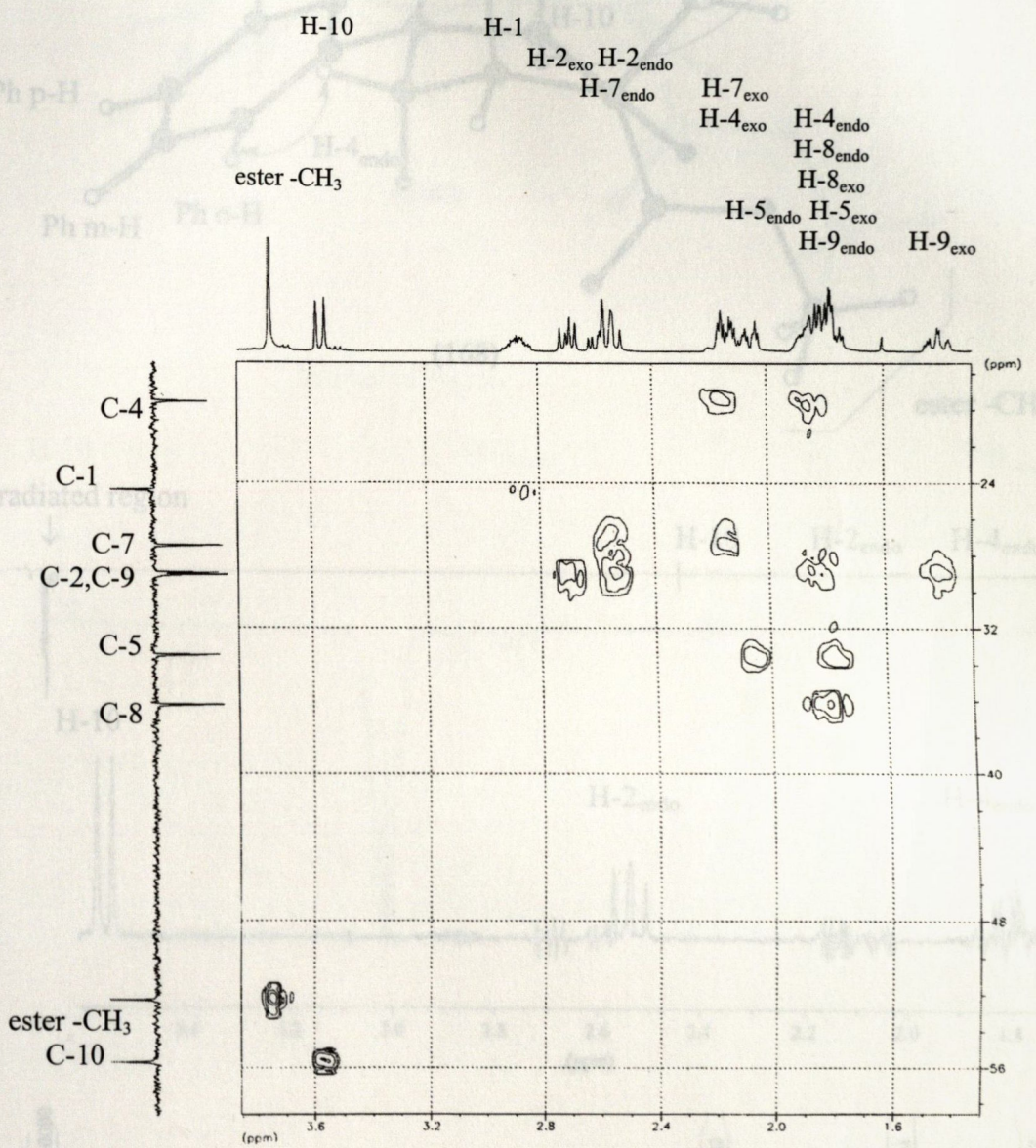
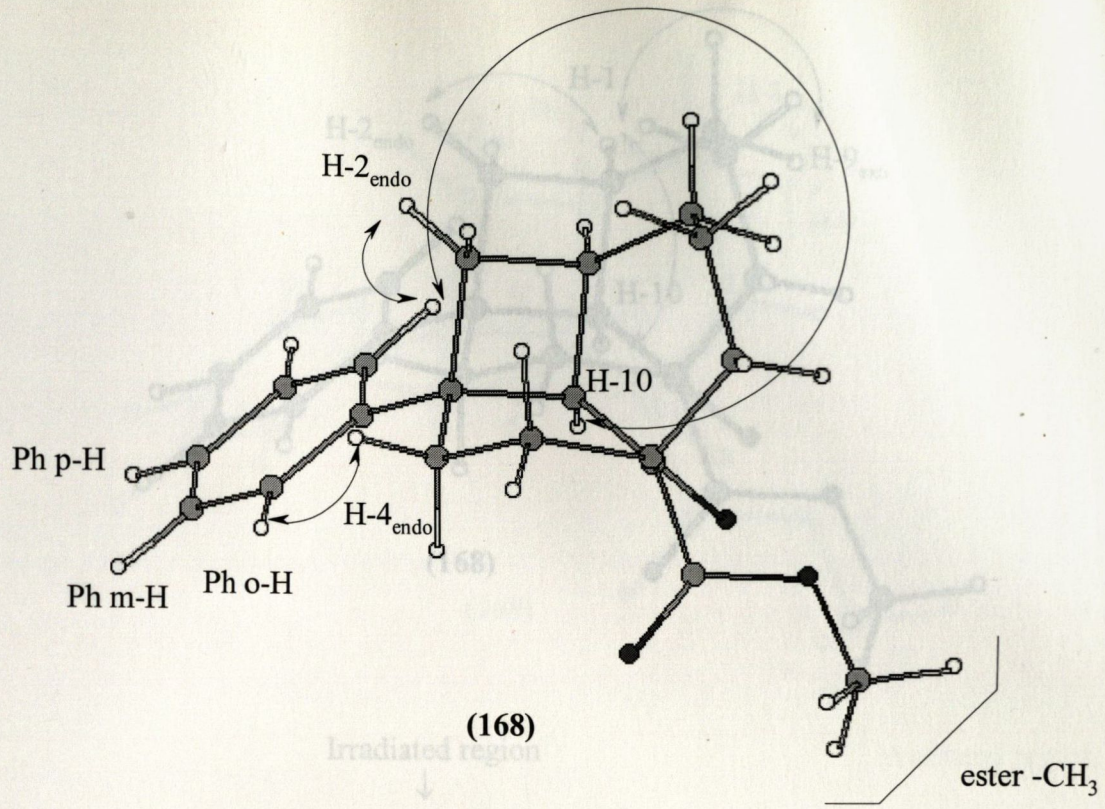


Fig. 3.34 The 2-D HETCOR NMR spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] expanded in the region δ 1.5-3.7 ppm.



(168)

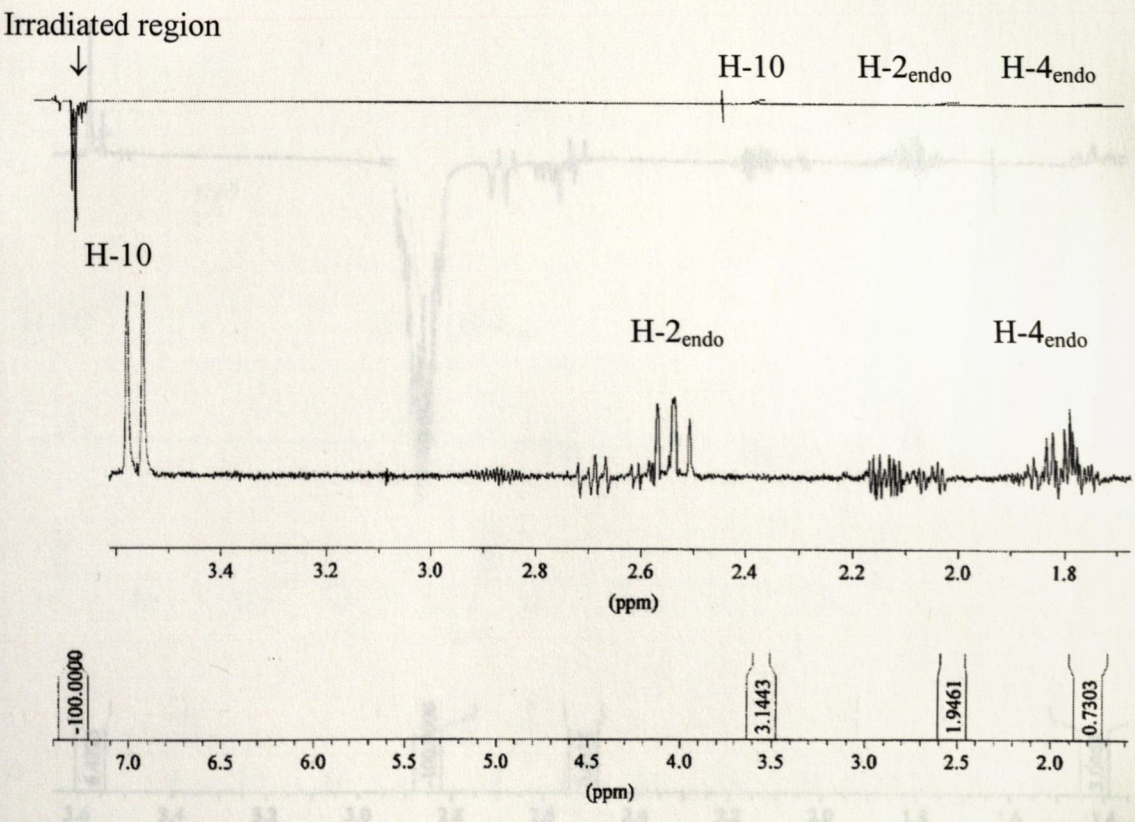
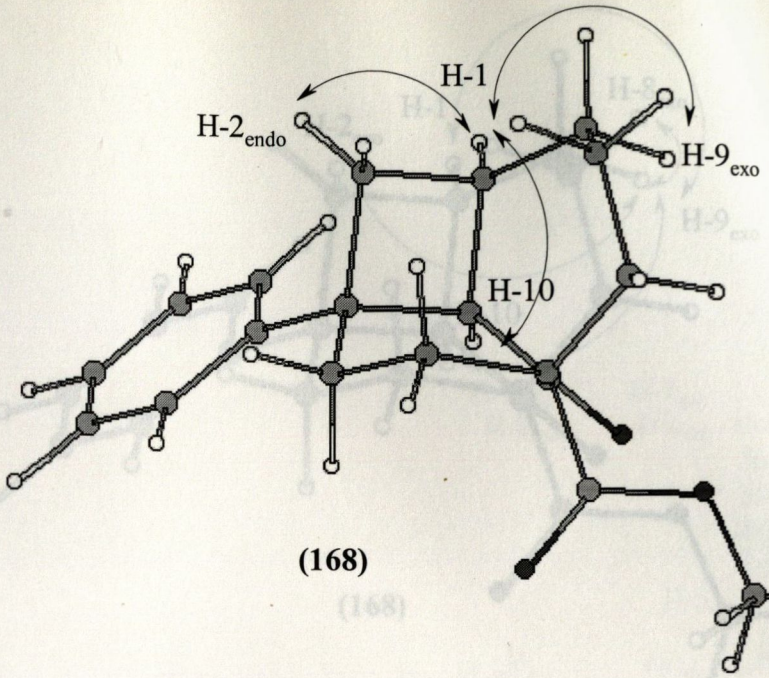


Fig. 3.35 The nOe difference spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] for the irradiation of the ortho hydrogens.



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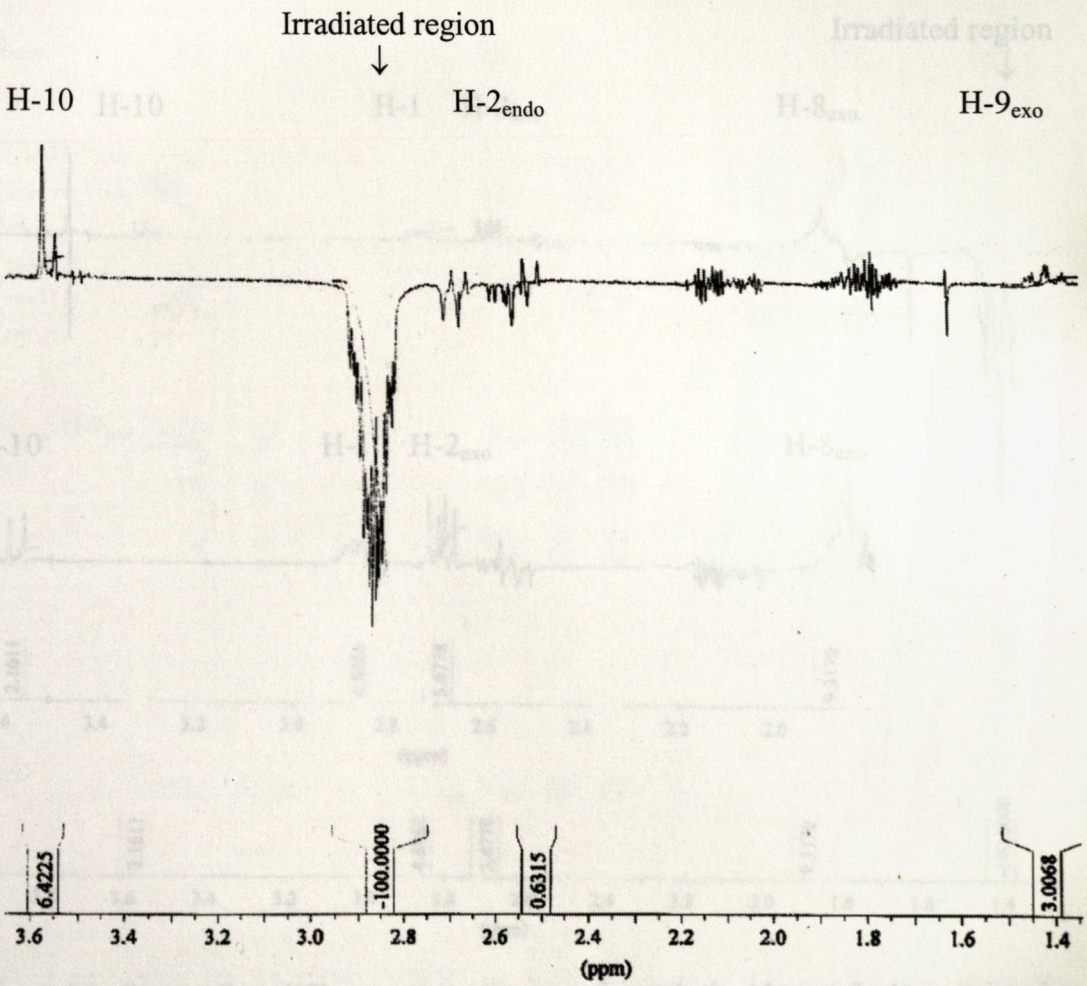
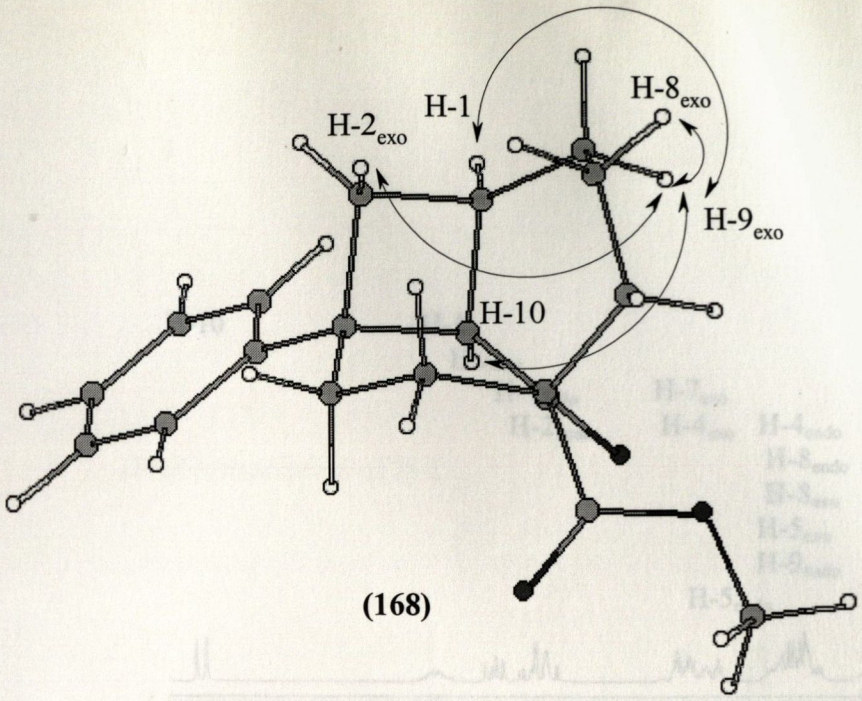


Fig. 3.36 The nOe difference spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] for the irradiation of the H-1.



(168)

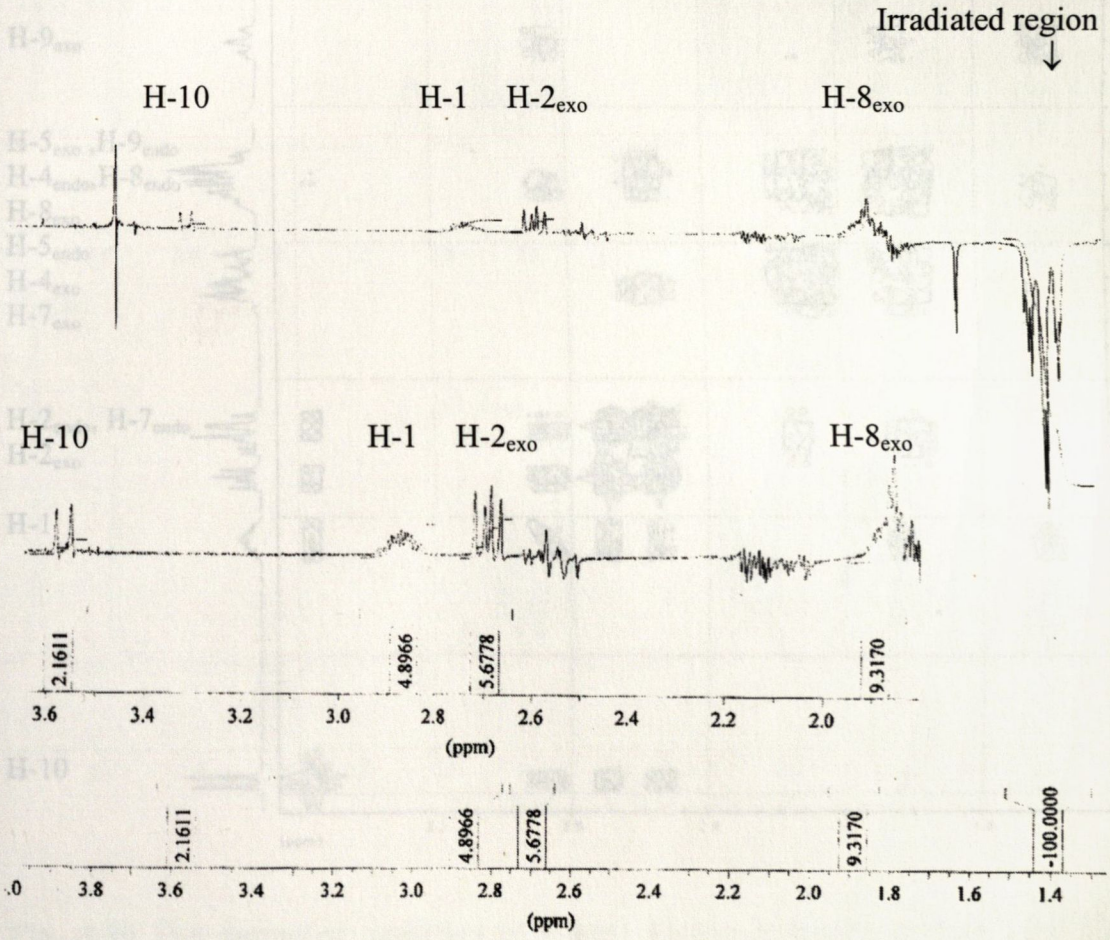


Fig. 3.37 The nOe difference spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] for the irradiation of the H-9_{exo}.

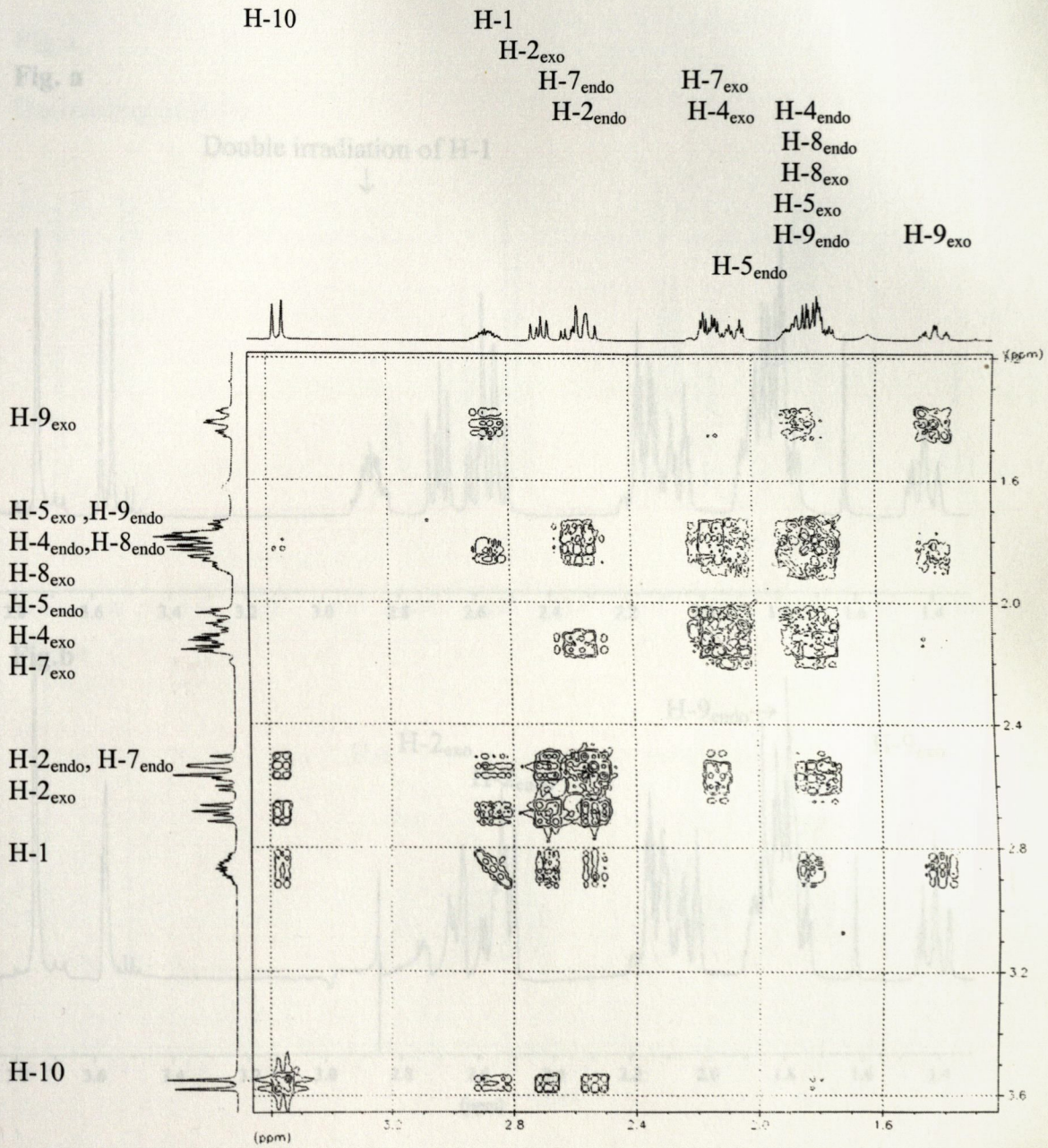


Fig. 3.38 The ^{1}H-^{1}H DQF COSY spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168].

Fig. a

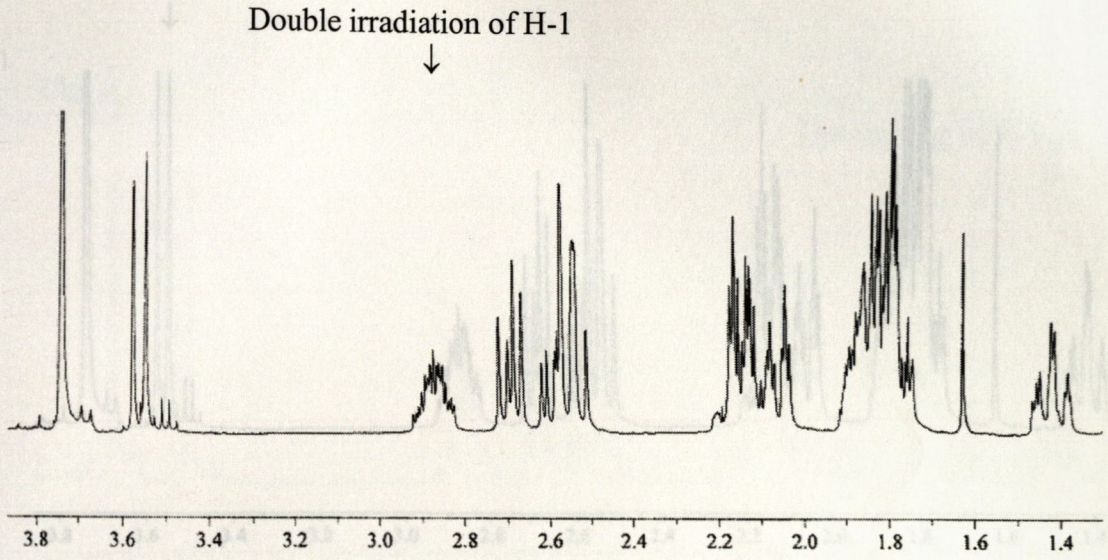


Fig.b

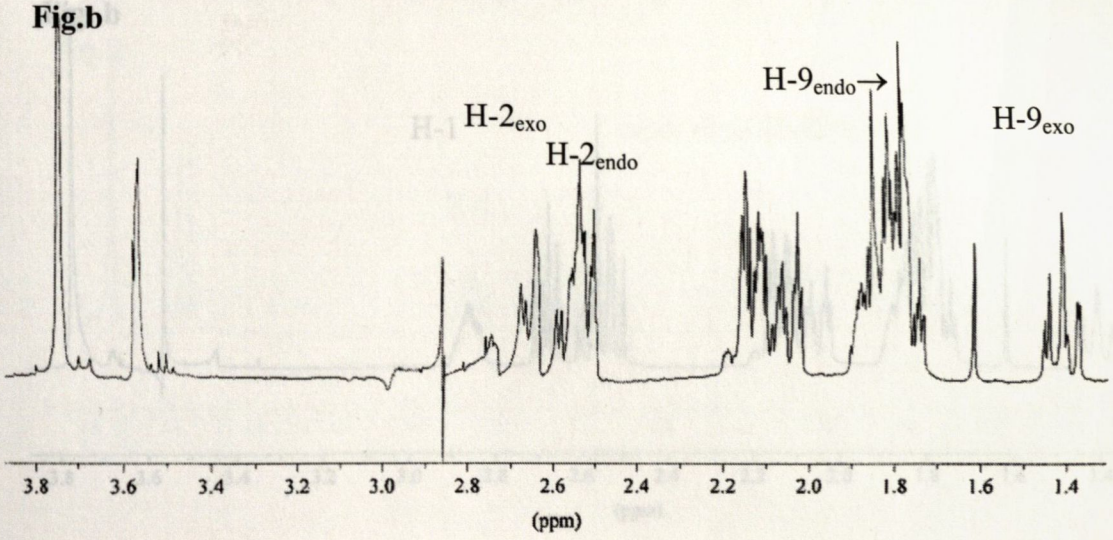


Fig. 3.39 The decoupled spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168] for the decoupling of H-1. **Fig.a** The original NMR. **Fig. b** The NMR spectrum with peak simplification.

Fig.a

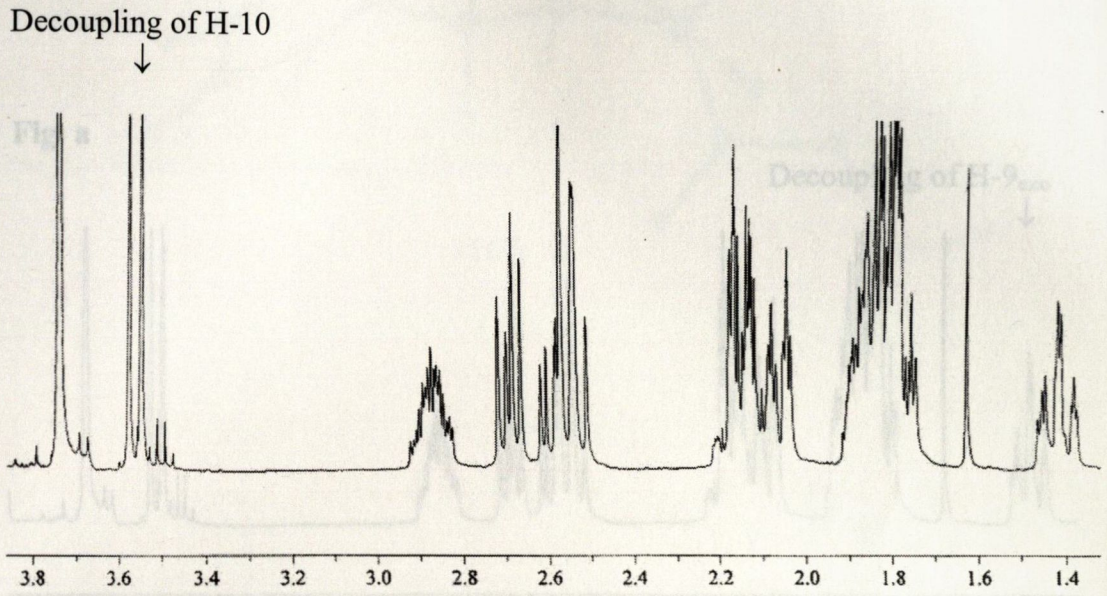


Fig. b

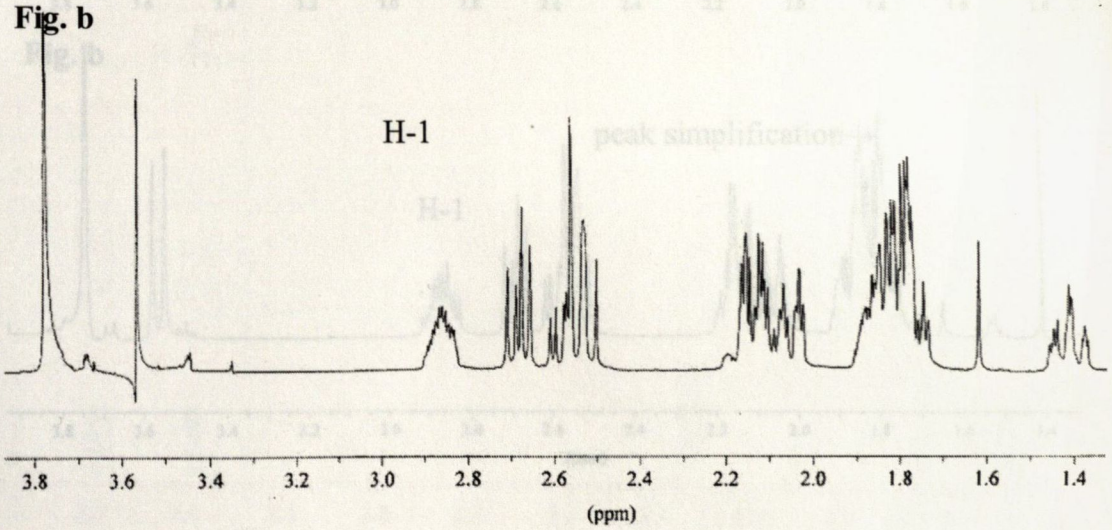


Fig. 3.40 The decoupled spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168] for the decoupling of H-10. **Fig. a** The original NMR. **Fig. b** The NMR with peak simplification.

Fig. a

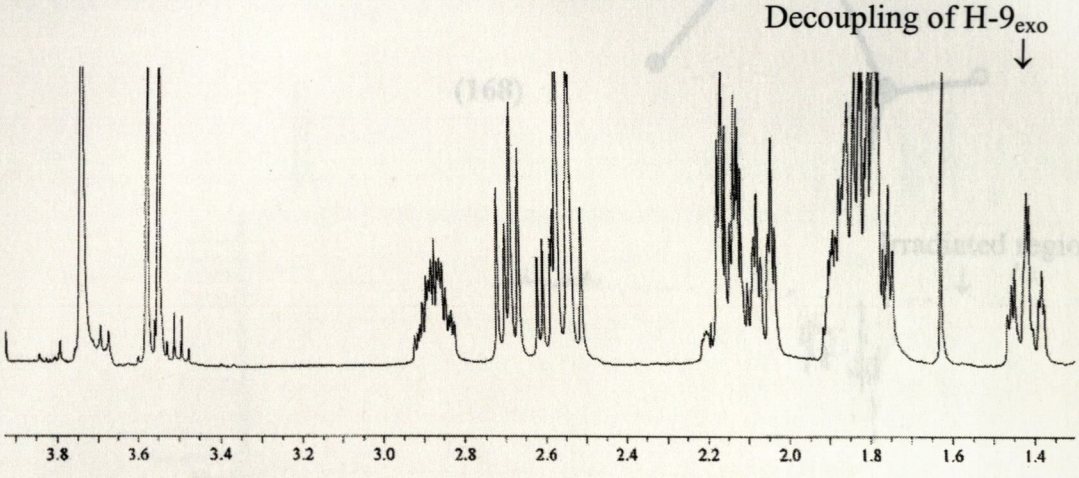


Fig. b

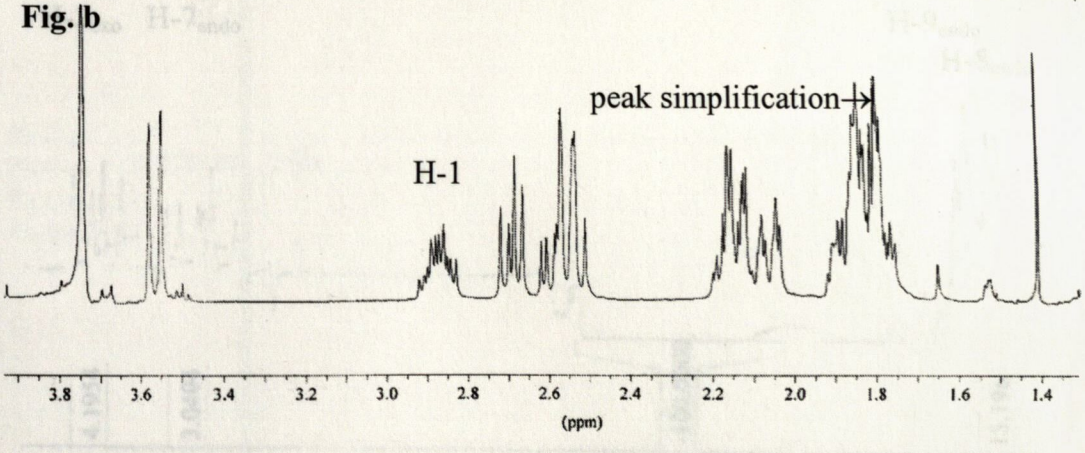
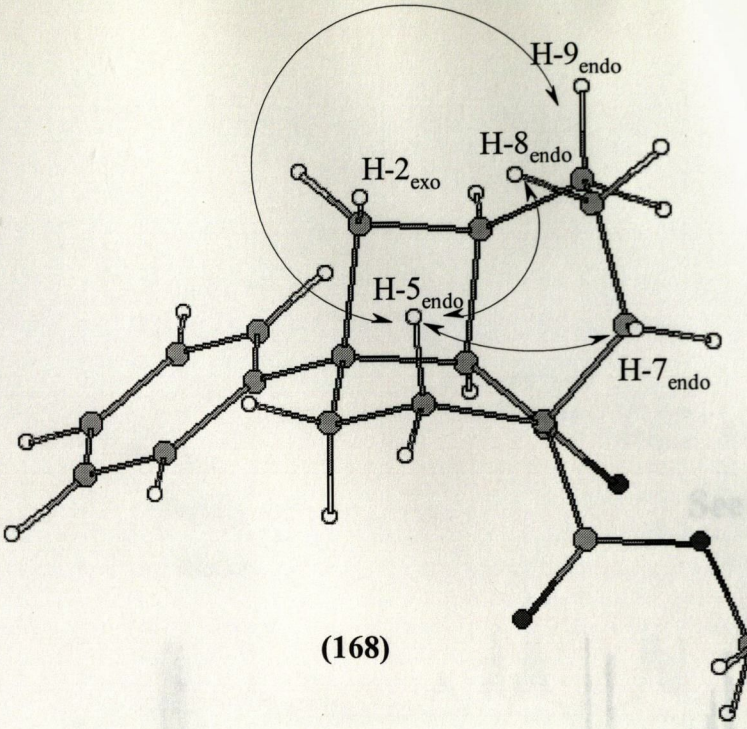


Fig. 3.41 The decoupled spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168] for the decoupling of H-9_{exo}. **Fig. a** The original NMR. **Fig. b** The NMR with peak simplification.



(168)

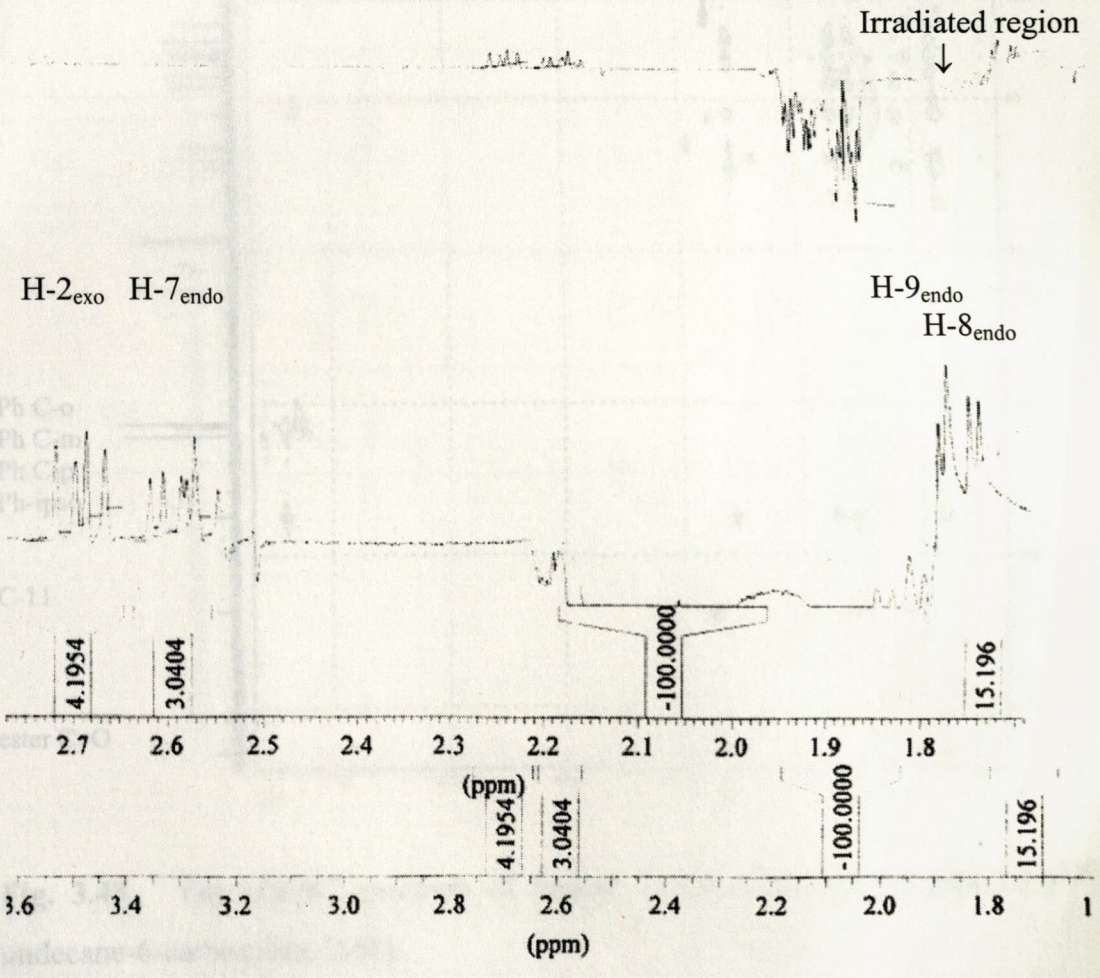


Fig. 3.42 The nOe difference spectrum of methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] for the irradiation of H-5_{endo}.

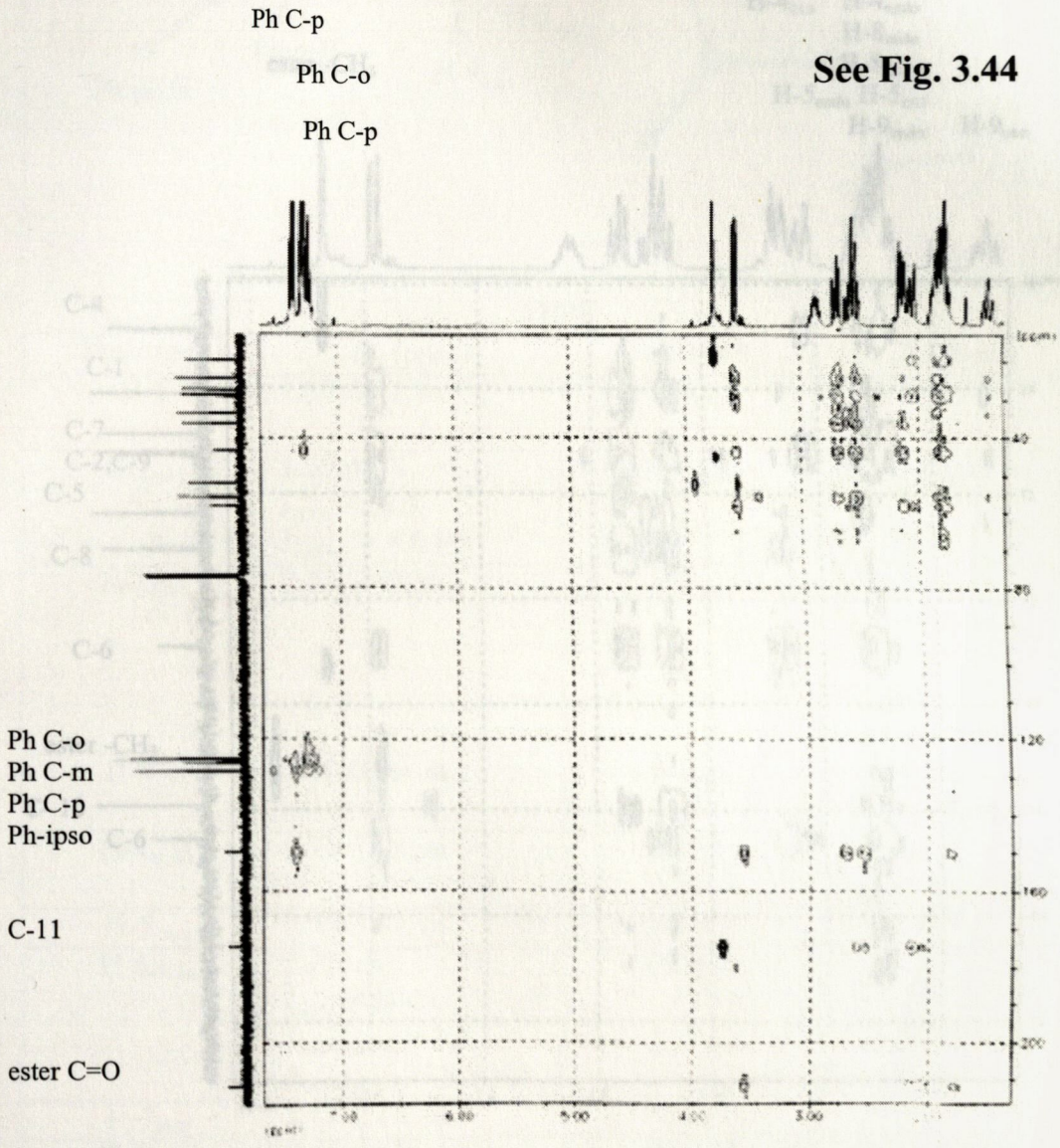


Fig. 3.43 The HMBC spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.0^{3,10}]-undecane-6-carboxylate [168].

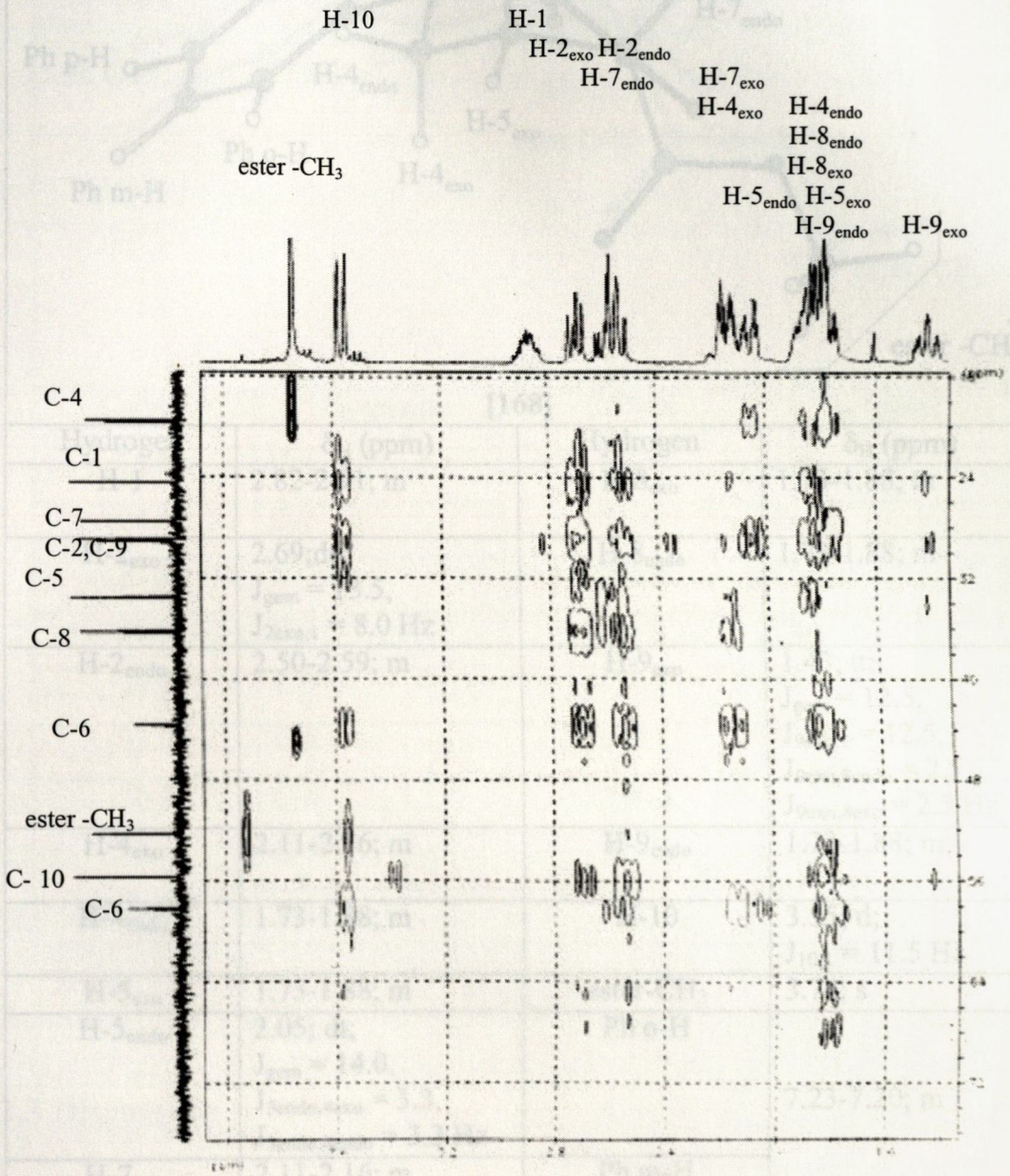
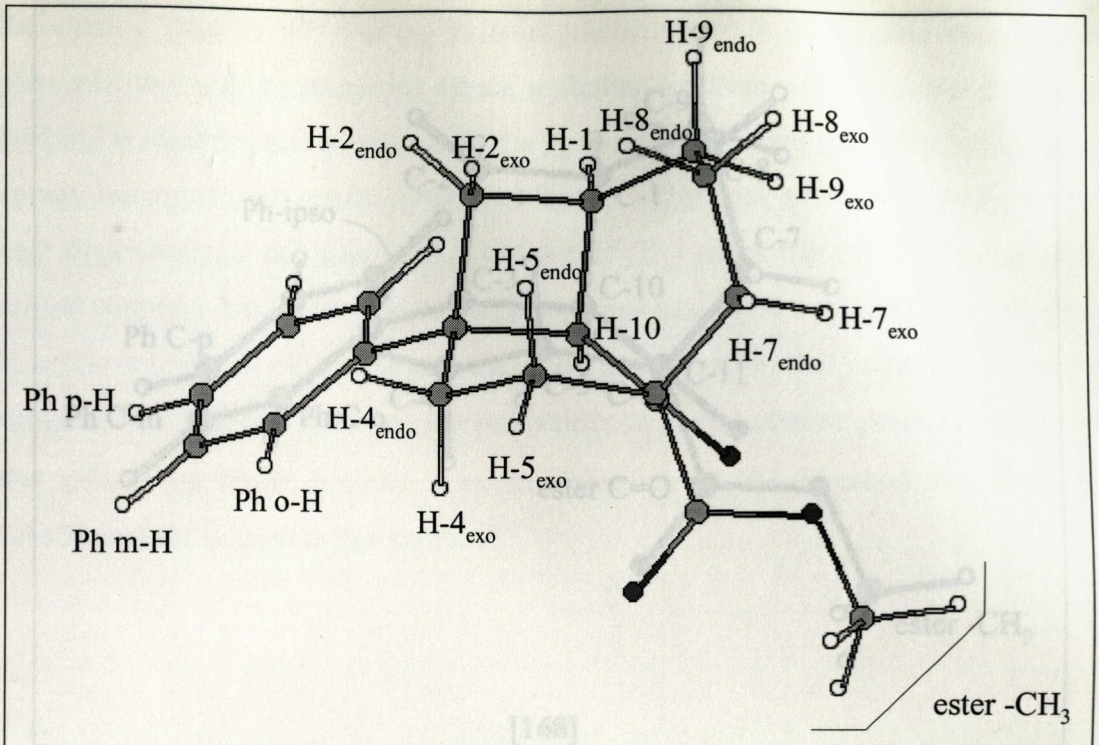


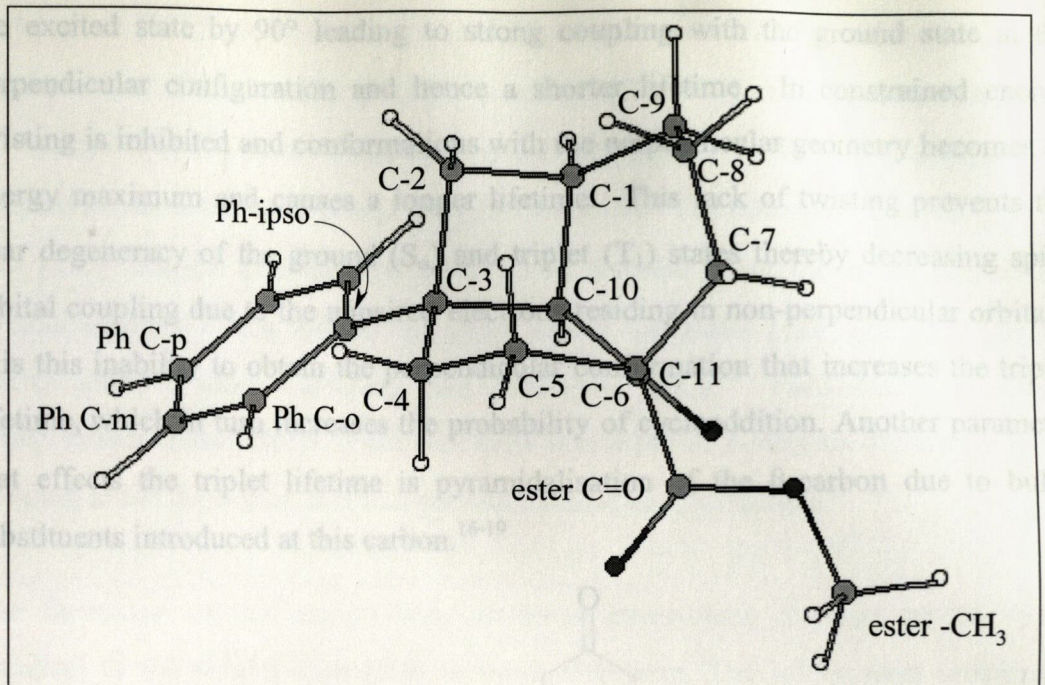
Fig. 3.44 The HMBC spectrum of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168] expanded in the region δ 12-75 ppm.



[168]

Hydrogen	δ_H (ppm)	Hydrogen	δ_H (ppm)
H-1	2.82-2.91; m	$H\text{-}8_{exo}$	1.73-1.88; m
$H\text{-}2_{exo}$	2.69;dd; J_{gem} = 13.5, $J_{2exo,1}$ = 8.0 Hz	$H\text{-}8_{endo}$	1.73-1.88; m
$H\text{-}2_{endo}$	2.50-2.59; m	$H\text{-}9_{exo}$	1.43; tt; J_{gem} = 12.5, $J_{9exo,1}$ = 12.5, $J_{9exo,8endo}$ = 2.5, $J_{9exo,8exo}$ = 2.5 Hz
$H\text{-}4_{exo}$	2.11-2.16; m	$H\text{-}9_{endo}$	1.73-1.88; m;
$H\text{-}4_{endo}$	1.73-1.88; m	H-10	3.55; d; $J_{10,1}$ = 11.5 Hz
$H\text{-}5_{exo}$	1.73-1.88; m	ester-CH_3	3.74; s
$H\text{-}5_{endo}$	2.05; dt; J_{gem} = 14.0, $J_{5endo,4exo}$ = 3.3, $J_{5endo,4endo}$ = 3.3 Hz	Ph o-H	7.23-7.20; m
$H\text{-}7_{exo}$	2.11-2.16; m	Ph m-H	
$H\text{-}7_{endo}$	2.61-2.570;dd; J_{gem} = 13.0, $J_{7endo,8exo}$ = 5.5 Hz	Ph p-H	7.36-7.30; m

Table 3.14



[168]

Carbon	δ_C (ppm)	Carbon	δ_C (ppm)
19.5	C-4	55.6	C-10
24.4	C-1	58.6	C-6
27.4	C-7	125.2	Ph C-o
28.9	C-2	125.9	Ph C-m
29.0	C-9	128.4	Ph C-p
33.4	C-5	149.8	Ph-ipso
36.2	C-8	174.6	C-11
43.6	C-3	211.3	ester C=O
52.2	ester -CH_3		

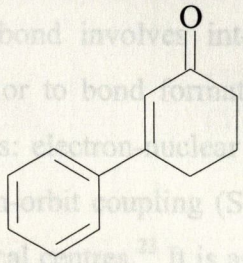
Table 3.15

3.3 Discussion

3.31 The excited state of 3-phenylcyclohex-2-en-1-one [225]

The lifetimes of the triplet states of cyclic enones fall into two categories those of flexible enones whose triplets are short lived due to relaxation by twisting around the C=C bond and those of constrained enones whose triplets are less twisted and are longer lived. In flexible enones the orthogonal triplet state is accessible by twisting in

the excited state by 90° leading to strong coupling with the ground state at the perpendicular configuration and hence a shorter lifetime. In constrained enones twisting is inhibited and conformations with the perpendicular geometry becomes an energy maximum and causes a longer lifetime. This lack of twisting prevents the near degeneracy of the ground (S_o) and triplet (T_1) states thereby decreasing spin-orbital coupling due to the unpaired electrons residing in non-perpendicular orbitals. It is this inability to obtain the perpendicular conformation that increases the triplet lifetime, which in turn increases the probability of cycloaddition. Another parameter that effects the triplet lifetime is pyramidalisation of the β-carbon due to bulky substituents introduced at this carbon.[16-19]



[223]

It has been suggested by Schuster that the triplet lifetime of 3-phenylcyclohexenone [225] resembles that of a styrene more than a cyclohexenone.[14] Furthermore the triplet states of styrene and its derivatives reside only in a perpendicular conformation, except when the olefinic is confined to a small ring affording a planar conformation.[18] By analogy there is limited twisting in 3-phenylcyclohexenone [223] thereby confining the triplet state to planarity. It was suggested by Kelly that the long lifetime was due to the phenyl group conjugating with the excited state species, and inhibit twisting.[21] In addition twisting in the excited state will bring the bulky phenyl group into closer proximity with 4-and 5-methylene groups causing 1,3-interactions.

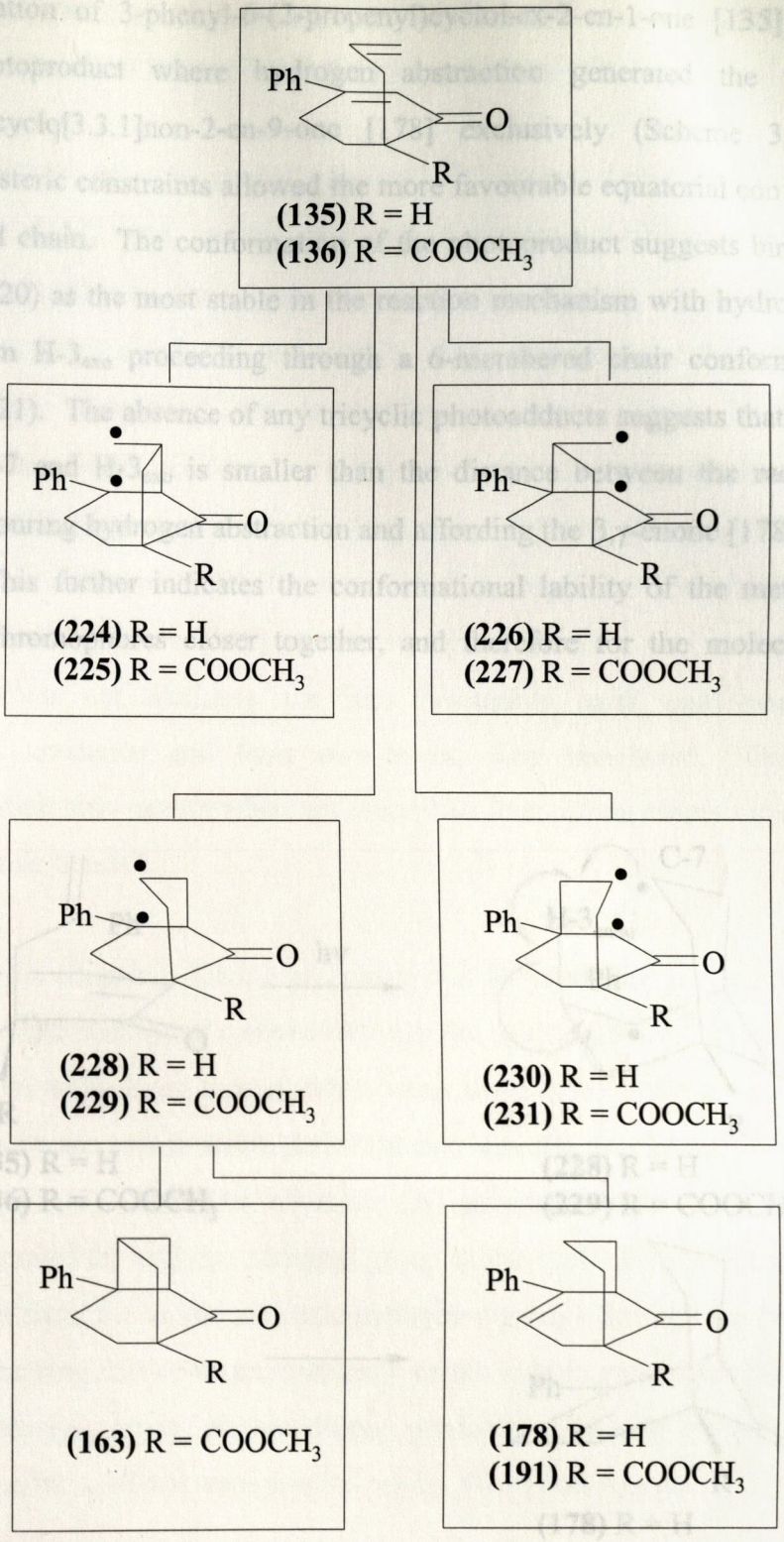
3.32 Regioselectivity of the photocycloadditions of substituted 3-phenylcyclo hex-2-en-1-ones tethered to a 3-carbon chain

The regiochemistry of [2+2] intramolecular photocycloaddition reaction of cyclohexenones tethered with an all carbon chain is determined by the partitioning of the triplet 1,4-biradicals between closure to give products and fragmentation to give starting material. The conformation of methyl 2-oxo-4-phenylcyclohex-3-ene-1-

carboxylate [136] that best suits cycloaddition is one were the tethered chain is in an axial position. There are four possible biradicals [224-231] in the photocycloaddition of methyl 2-oxo-4-phenylcyclohex-3-ene-1-carboxylate [136] and 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135] (Scheme 3.20). The photoproducts [163], [178] and [189] suggest that the first bond to be formed is on the α-position of the cyclohexenones. This affords the more stable biradicals [228] and [229] as the phenyl group is more stabilising than a carbonyl group.[22] Furthermore the phenyl group causes steric effects which will slow formation of biradicals formed by initial bonding at the β-position and will prevent cycloadduct formation.[17]

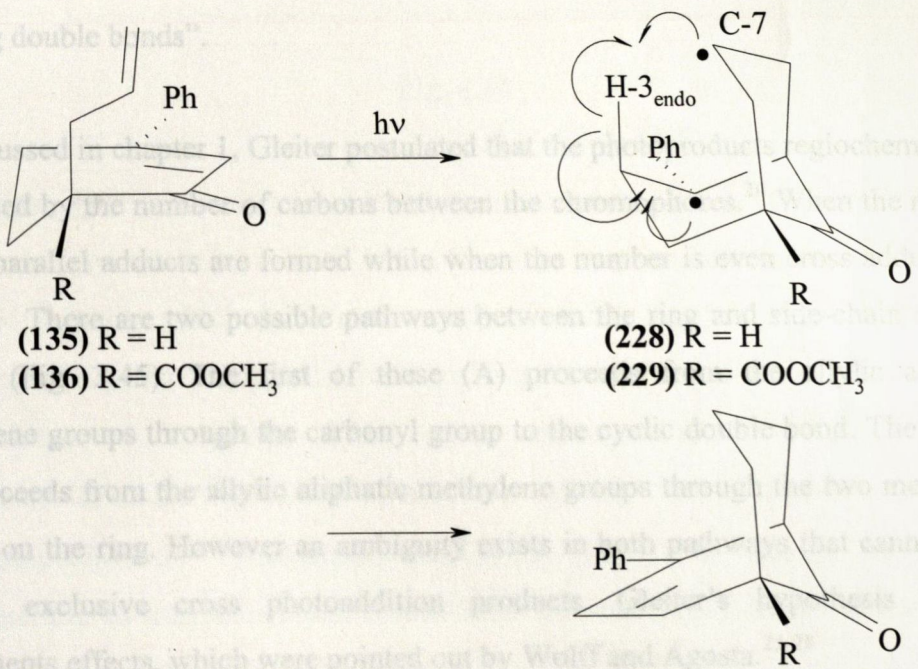
The formation of the second bond involves intersystem crossing of the triplet biradical to the singlet state prior to bond formation. The intersystem crossing is determined by three mechanisms: electron-nuclear hyperfine coupling (HFC), spin-lattice relaxation (SLR) and spin-orbit coupling (SOC) which in turn is determined by the distance between the radical centres.[23] It is assumed that spin-orbit coupling is the more dominant mechanism involved in ring closure.

Dr. N.W.A Geraghty has provided data from a molecular modelling analysis of methyl 2-oxo-4-phenylcyclohex-3-ene-1-carboxylate [136] using a Monte Carlo search technique in conjunction with a MM force field. A series of low energy structures were identified, which were further refined by semiempirical AM1 calculations. When the lower energy structure (in this case $\Delta H°_f$ = -68.5kcal/mol) has a relatively short inter-radical distance (in this case 3.16Å) and the singly occupied orbitals are orientated for maximum overlap, ring closure is favourable. However the distance between C-7 and H-3_{endo} is only 2.54 Å and H-3_{endo} is orientated in such a way that hydrogen transfer to C-7 can occur *via* a six-membered chair conformation [228] (Scheme 3.21). The biradical [228] will undergo ring closure to form methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] but because of the favourable geometry for hydrogen abstraction, the α,β-unsaturated enone undergoes photochemical deconjugation to give the β,γ-enone, methyl 9-oxo-2-phenylbicyclo[3.3.1]non-2-ene-5-carboxylate [191], as the major product.


Ph
O
R
(135) R = H
(136) R = COOCH3
(224) R = H
(225) R = COOCH3
(226) R = H
(227) R = COOCH3
(228) R = H
(229) R = COOCH3
(230) R = H
(231) R = COOCH3
(163) R = COOCH3
(178) R = H
(191) R = COOCH3

Scheme 3.20

The irradiation of 3-phenyl-6-(2-propenyl)cyclohex-2-en-1-one [135] afforded a single photoproduct where hydrogen abstraction generated the photoadduct 2-phenylbicyclo[3.3.1]non-2-en-9-one [178] exclusively (Scheme 3.20). The absence of steric constraints allowed the more favourable equatorial conformation of the tethered chain. The conformation of the photoproduct suggests biradical [228] (Scheme 3.20) as the most stable in the reaction mechanism with hydrogen transfer to C-7 from H-3_{exo} proceeding through a 6-membered chair conformation [228] (Scheme 3.21). The absence of any tricyclic photoadducts suggests that the distance between C-7 and H-3_{exo} is smaller than the distance between the radical centres thereby favouring hydrogen abstraction and affording the β,γ-enone [178] as the only product. This further indicates the conformational lability of the methyl ester to bring the chromophores closer together, and therefore for the molecule to react faster.



(135) R = H
(136) R = $COOCH_3$

(228) R = H
(229) R = $COOCH_3$

(178) R = H
(191) R = $COOCH_3$

Scheme 3.21

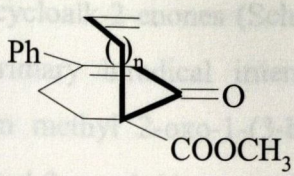
3.33 Regioselectivity of the photocycloadditions of substituted 3-phenyl-cyclohex-2-en-1-ones tethered to a 4-and 5-carbon chain

The irradiation of the methyl 2-oxo-1-(3-butenyl)-4-phenylcyclohex-3-ene-1-carboxylate [137] and methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138] was regiochemically controlled in both cases affording cross photoadducts [166] and [168] respectively. The importance of the methyl ester is evident when comparing the irradiation of methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138] which afforded photoproduct [168] to the irradiation of 6-(4-pentenyl)cyclohex-3-en-1-one [8] [158] (Scheme 3.3) where no photoproducts where obtained. Lakshmi and Rao suggested that the failure of the cyclohexenone derivative [158] to undergo photoaddition was due to the bulky pentenyl group not attaining the less favourable axial conformation. From literature [2,7] evidence and their own work, they concluded, "that cross-ring photoannelation only occurs when not more than four carbon atoms separate the two reacting double bonds".

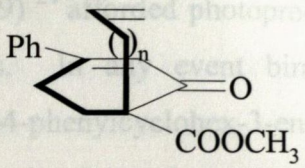
As discussed in chapter 1, Gleiter postulated that the photoproducts regiochemistry is controlled by the number of carbons between the chromophores.[24] When the number is odd parallel adducts are formed while when the number is even cross adducts are formed. There are two possible pathways between the ring and side-chain olefinic groups (Fig. 3.45). The first of these (A) proceeds from the allylic aliphatic methylene groups through the carbonyl group to the cyclic double bond. The second (B) proceeds from the allylic aliphatic methylene groups through the two methylene groups on the ring. However an ambiguity exists in both pathways that cannot fully explain exclusive cross photoaddition products. Gleiter's hypothesis ignores substituents effects, which were pointed out by Wolff and Agosta.[25-28]

There are four possible biradical intermediates in the each photochemical reaction (Scheme 3.22) with the most stable biradicals [232]-[235] being benzylic in nature. The benzylic biradicals are further subdivided into two groups [232], [233] and [234]-[235] where a secondary radical is more stable than a primary radical.

However the regiochemistry of the photoproducts indicates that biradicals [232], [233] are involved.



(A)



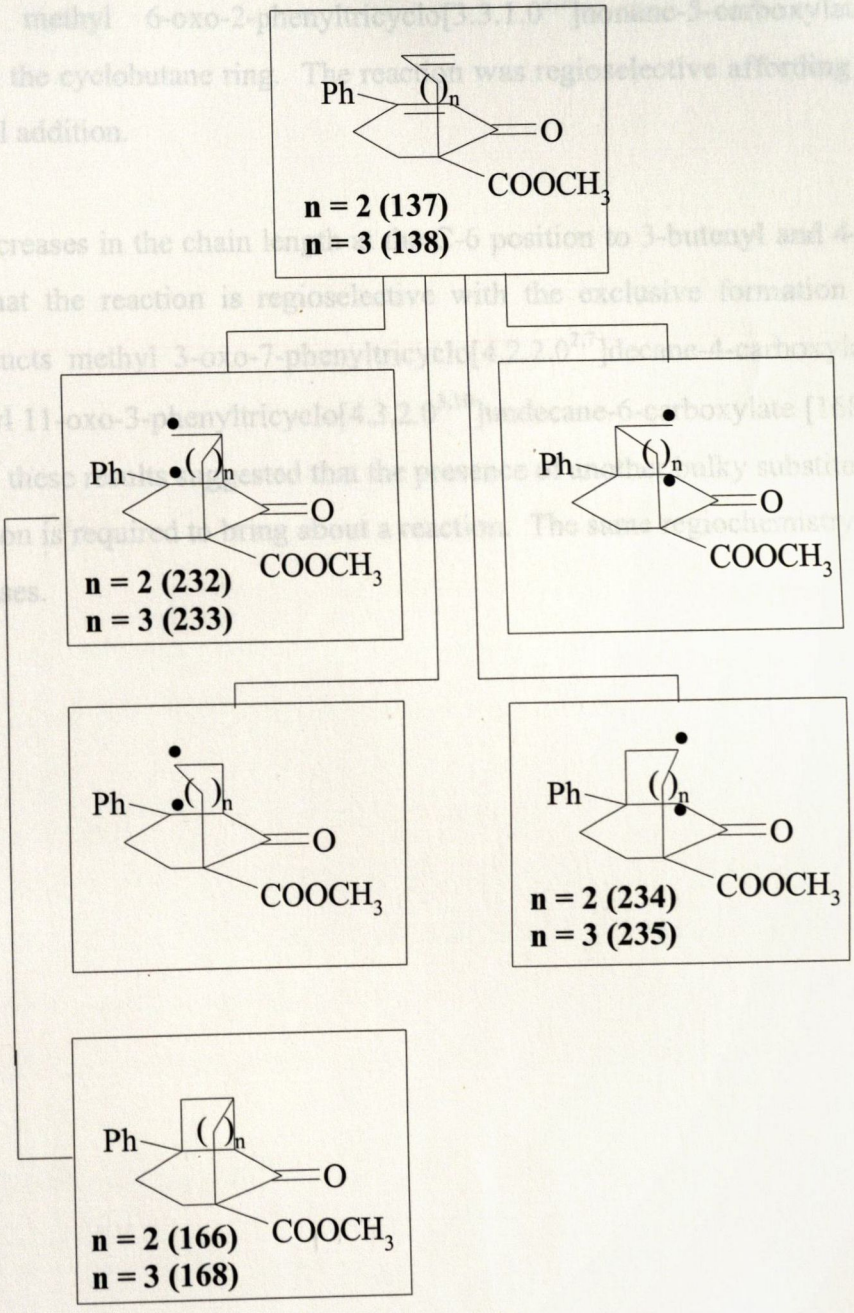
(B)

Number of methylene in the side chain	Number of carbons separating the double bonds.	
	Path **(A)**	Path **(B)**
n = 3 (40)	4	5
n = 4 (41)	5	6

Fig. 4.45

The formation of the second bond is determined again by spin-orbit coupling which is dependent on the inter-radical distance and an angular orientation of the singly occupied orbitals, which facilitates overlap. Dreiding models suggests that both biradicals [232] and [234] will have a sufficiently short inter-radical distances for cycloaddition to occur. The cross photoproducts methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] and methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] were formed *via* six and seven membered transition states respectively (Scheme 3.22). The absence of any photoproducts resulting from a hydrogen abstraction mechanism further confirms the involvement of biradicals [232] and [233], as biradicals [234] and [235] will have the correct geometry for hydrogen abstraction to be competitive. Furthermore closure *via* biradicals [234] and [235] would involve, high energy, eight and nine membered transition states respectively (Scheme 3.22).

However it should be mentioned that Geraghty ignores biradicals with a primary radical component as the energy of these is to high to warrant adequate stability. This would imply that biradicals [234] and [235] are the most favourable intermediates. In contrast Maradyn and Weedon's biradical trapping studies on two 3-(4-pentenyl)cycloalk-2-enones (Scheme 1.19) [29] afforded photoproducts that were formed *via* primary biradical intermediates. In any event biradical trapping experiments on methyl 2-oxo-1-(3-butenyl)-4-phenylcyclohex-3-ene-1-carboxylate [137] and methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138] would determine conclusively which biradicals are involved.



Scheme 3.22

3.4 Conclusion

The structures and regiochemistry of the photoproducts generated in the [2+2] photocycloaddition of 6-alkenyl-3-phenylcyclohex-2-en-1-ones have been determined by NMR and X-ray studies. The results indicate that the 3-phenyl-cyclohex-2-en-1-ones moiety substituted in the C-6 position with 2-propenyl is subject to hydrogen abstraction affording the β,γ-enone, 2-phenylbicyclo[3.3.1]non-2-en-9-one [178] exclusively, a process never before seen in these types of compounds. Further substitution at the C-6 position with a carbomethoxy group showed that hydrogen abstraction is competitive with ring closure to the target molecule, methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] containing the cyclobutane ring. The reaction was regioselective affording products *via* parallel addition.

Further increases in the chain length at the C-6 position to 3-butenyl and 4-pentenyl showed that the reaction is regioselective with the exclusive formation of cross photoproducts methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] and methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168]. In the latter case these results suggested that the presence of another bulky substituent at the C-6 position is required to bring about a reaction. The same regiochemistry is shown in both cases.

3.4 Experimental

All experimental parameters in Chapter 2 apply.

Photochemical reactions were carried out using an 'Applied Photophysics' 400W medium pressure mercury lamp and pyrex glass filter. Acetonitrile was dried and distilled over Calcium hydride prior to use. Solutions were de-oxygenated by bubbling nitrogen through the solution prior to irradiation and during the course of the experiment.

Photolysis of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]

A solution of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136] (2.0g) in acetonitrile (450ml) was irradiated for 1 h 30min and followed by GC-MS. The solvent was removed *in vacuo* to give a viscous oil. The oil was purified by flash chromatography (hexane/ether 9:1) to give a colourless oil. The oil was further purified by dissolving by dissolving in hexane/ether 9:1 and cooling to -50°C to give a colourless compound. The compound was filtered and washed with hexane/ether 9:1 at -50°C. The filtrate was cooled to -50°C several times affording a further 51mg of methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] (total mass 88mg). The product was dried in a desiccator *in vacuo* to give a colourless powder (78mg, 3.9%) of melting point 136-137°C. [Found C: 75.40; H: 6.63. $C_{14}H_{16}O_4$ requires C: 75.53; H: 6.71 %].

δ_H ($CDCl_3$; 400MHz)

1.69 (1H; d; J_{gem} = 10.0 Hz; H-8_{exo}), 1.73-1.78 (1H; m; H-3_{exo}), 1.88 (1H; ddd: J_{gem} = 15.0, $J_{3endo,4endo}$ = 11.0, $J_{3endo,4endo}$ = 6.6 Hz; H-3_{endo}), 2.19-2.30 (2H; m; H-4_{endo}, H-4_{exo}), 2.36 (1H; ddd; J_{gem} = 12.5, $J_{9syn,1}$ = 5.5, $J_{9syn,8endo}$ = 3.0 Hz; H-9_{syn}), 2.55 (1H; dtd; J_{gem} = 10.0, $J_{8endo,1}$ = 6.5, $J_{8endo,7}$ = 6.5, $J_{8endo,9anti}$ = 3.0 Hz; H-8_{endo}) 2.69 (1H; dd; J_{gem} = 12.5, $J_{9anti,4endo}$ = 2.0 Hz; H-9_{anti}), 3.05 (1H; q; $J_{1,9anti}$ = 5.5, $J_{1,8endo}$ = 5.5, $J_{1,7}$ = 5.5 Hz; H-1), 3.35 (1H; dd; $J_{7,8endo}$ = 6.5, $J_{7,1}$ = 5.5 Hz; H-7) 3.83 (3H; s; ester -CH_3), 7.37-7.43 (4H; m; Ph o-H, m-H), 7.28-7.31 (1H; m; Ph p-H).

δ_C ($CDCl_3$; 80MHz)

29.9 (C-3), 31.0 (C-4), 33.9 (C-8), 35.2 (C-9), 38.9 (C-1), 52.2 (ester -CH_3), 55.1 (C-7), 55.9 (C-2), 126.2 (Ph C-o), 126.6 (Ph C-m), 128.6 (Ph C-p), 143.9 (Ph-ipso), 172.0 (ester C=O), 210.8 (C-6).

M/Z

270 ($M^{+\cdot}$), 238, 211, 182 (100%).

The major photoproduct from the photoylsis of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]

The filtrate after the extraction of methyl 2-phenyltricyclo[3.3.1.$0^{2,7}$]octan-2-one-5-carboxylate [163] was removed *in vacuo* to a colourless oil. The oil could not be purified completely. The photoproduct was identified as methyl 9-oxo-2-phenylbicyclo[3.3.1]non-2-ene-5-carboxylate [191] by comparative ^{1}H-NMR techniques and mass spectroscopy.

δ_H ($CDCl_3$; 400MHz)

1.64-2.45 (7H; m; H-4_{endo}, H-6_{exo}, H-6_{endo}, H-7_{exo}, H-7_{endo}, H-8_{exo}, H-8_{endo}), 2.68 (1H; dd; J_{gem} = 19.2, $J_{4exo,3}$ = 3.8 Hz; H-4_{exo}), 3.49 (1H; s; H-1), 3.80 (3H; s; ester -CH_3) 6.27-6.31(1H; t; $J_{3,4exo}$ = 3.8, $J_{3,4endo}$ = 3.6 Hz; H-3) 7.26-7.35 (5H; m; Ph o-H. m-H, p-H)

M/Z

270 ($M^{+\cdot}$), 238, 211, 210, 182 (100%).

Photolysis of 3-phenyl-1-(2-propenyl)cyclohex-2-en-1-one [135]

A solution of 3-phenyl-1-(2-propenyl)cyclohex-2-en-1-one [135] (1.74g) in acetonitrile (450ml) was irradiated for 2 h and followed by GC-MS. The solvent was removed *in vacuo* to give a viscous oil. The oil was purified by flash chromatography (hexane/ether 9:1) to give an off white solid which was further purified by trituration with hexane/ether (9:1) to give a colourless compound (34mg). The filtrate was cooled to -50°C to precipitated out more of the product giving a combined total of 185mg (10.6%). The solid material was dried *in vacuo* in a desiccator overnight but changed from a solid state to an oily residue. It was attempted to recrystallise the oily residue from hexane/ether 9:1 at -50°C but this afforded an off white semi-solid compound of melting point 42-48°C.

δ_H ($CDCl_3$; 400MHz)

1.57 (1H; broad singlet; H-7_{exo}), 1.91-2.00 (5H; m; H-6_{exo}, H-6_{endo}, H-7_{endo}, H-8_{exo} and H-8_{endo}), 2.60 (1H; dd J_{gem} = 19.0, $J_{4exo,3}$ = 4.0 Hz; H-4_{exo}), 2.62 (1H; m; H-5),

2.89 (1H; m; H-4_{endo}), 3.41 (1H; s; H-1), 6.31(1H; t; $J_{3,4exo}$ = 3.5, $J_{3,4endo}$ = 3.5 Hz; H-3), 7.28-7.31 (1H; m; Ph p-H), 7.37-7.43 (1H; m; Ph o-H, m-H).

δ_C ($CDCl_3$; 80MHz)

17.1 (C-7), 32.5 (C-6), 35.7 (C-4), 36.8 (C-8), 44.4 (C-5), 49.9 (C-1), 125.6 (C-2) 125.7 (C-3), 127.5 (Ph C-o), 128.4 (Ph C-m) 137.1 (Ph-p) 139.2 (Ph-ipso), 215.8 (C-9)

M/Z

212 ($M^{+\cdot}$)(100%), 197, 184, 169.

Attempted Crystal growing of 2-phenylbicyclo[3.3.1]non-2-en-9-one [178].

A sample of the compound was dissolved in hexane/ether (9:1) and set aside at 5°C for 1 week affording needle-like crystals. The crystals were filtered and immediately began to lose cohesion. The crystals were re-grown, filtered and immediately washed with hexane/ether (9:1) at -50°C. A melting point was obtained (m.p. 40-41°C).

Photolysis of methyl 2-oxo-4-phenyl-1-(3-butenyl)cyclohex-3-ene-1-carboxylate [137]

A solution of methyl 2-oxo-4-phenyl-1-(3-butenyl)cyclohex-3-ene-1-carboxylate [137] (1g) in acetonitrile (450ml) was irradiated. The reaction was followed by GC-MS and stopped after 14 h. The solvent was removed *in vacuo* to give a dark viscous oil. The oil was purified by flash chromatography (hexane/ether 9:1) to give a viscous yellow oil which was further purified by trituration with hexane/ether (9:1) to give a colourless compound. The filtrate was cooled to -50°C to precipitated out more of the product giving a combined total of 266mg. The solid material was dried *in vacuo* in a desiccator to afford methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] as a colourless powder (250mg; 40%; 82-83°C) (Found: C: 75.95; H: 7.00. $C_{14}H_{16}O_4$ requires C: 76.03; H: 7.09 %).

δ_H ($CDCl_3$; 400MHz)

1.72 (1H; ddd; J_{gem} = 13.6, $J_{6exo,5exo}$ = 4.8, $J_{6exo,5endo}$ = 3.3 Hz; H-6_{exo}) 1.86 (1H; ddd; J_{gem} = 14.0, $J_{6endo,5exo}$ = 4.8, $J_{6endo,5endo}$ = 3.3 Hz; H-6_{endo}), 1.89-1.96 (1H; m; H-9_{anti}), 2.07-2.16 (1H; m; H-9_{syn}), 2.33 (1H; dd; J_{gem} = 12.6, $J_{8exo,1}$ = 3.0 Hz; H-8_{exo}), 2.43 (1H; ddd; J_{gem} = 14.6, $J_{10anti,9syn}$ = 8.0, $J_{10anti,9anti}$ = 4.5 Hz; H-10_{anti}), 2.54-2.64 (2H; m; H-5_{exo} and H-10_{syn}), 2.81 (1H; ddd; J_{gem} = 14.6, $J_{5endo,6exo}$ = 6.0, $J_{5endo,6endo}$ = 3.0 Hz; H-5_{endo}), 2.92-3.03 (2H; m; H-1 and H-8_{endo}), 3.30 (1H; broad doublet; $J_{2endo,1}$ = 9.5 Hz; H-2_{endo}), 3.83 (3H; s; ester -CH_3), 7.28-7.31 (1H; m; Ph p-H), 7.37-7.43 (4Hz; m; Ph o-H, m-H).

δ_C ($CDCl_3$; 80MHz)

24.7 (C-9), 29.3 (C-1), 31.4 (C-5), 35.8 (C-10), 37.2 (C-6), 37.8 (C-8), 49.3 (C-7), 51.2 (C-2), 52.3 (ester -CH_3), 57.1 (C-4), 124.7 (Ph C-o), 125.9 (Ph C-p), 128.3 (Ph C-m), 150.0 (Ph-ipso), 173.7 (C-3), 213.9 (ester C=O).

M/Z

284 ($M^{+\cdot}$), 253, 230, 224, 197, 196, 153 (100%), 142.

Crystal growing of methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166].

A sample of the compound was dissolved in hexane/ether (9:1) and set aside at 5°C for 1 week affording needle-like crystals. The crystals were washed (hexane/ether (9:1) -50°C) and dried *in vacuo* in a desiccator.

Photolysis of methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [135].

A solution of methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-2-ene-1-carboxylate [138] (1g) in acetonitrile (450ml) was irradiated for 17 h. The reaction was followed by GC-MS. The solvent was removed *in vacuo* to give a dark viscous oil. The oil was purified by flash chromatography (hexane/ether 9:1) to give a yellow viscous oil which was further purified by trituration with hexane/ether (9:1) to give a colourless compound (202mg). The filtrate was cooled to -50°C to precipitated out more the product (168mg) giving a combined total of 383mg. The solid material was dried *in*

vacuo in a desiccator to afford methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] as a colourless powder (271mg; 34%; m.p. 76-77°C) [Found C: 76.40; H: 7.39. $C_{19}H_{22}O_3$ requires C: 76.48; H: 7.43].

δ_H ($CDCl_3$; 400MHz)

1.43 (1H; tt; J_{gem} = 12.5, $J_{9exo,1}$ = 12.5, $J_{9exo,8endo}$ = 2.5, $J_{9exo,8exo}$ = 2.5 Hz; H-9_{exo}), 1.73-1.88 (5H; m; H-5_{exo}, H-4_{endo}, H-9_{endo}, H-8_{endo} and H-8_{exo}), 2.05 (1H; dt; J_{gem} = 14.0, $J_{5endo,4exo}$ = 3.3, $J_{5endo,4endo}$ = 3.3 Hz; H-5_{endo}), 2.11-2.16 (2H; m; H-4_{exo} and H-7_{exo}), 2.50-2.59 (1H; m; H-2_{endo}), 2.570-2.61 (1H; dd; J_{gem} = 13.0, $J_{7endo,8exo}$ = 5.5 Hz; H-7_{endo}), 2.69 (1H; dd; J_{gem} = 13.5, $J_{2exo,1}$ = 8.0 Hz; H-2_{exo}), 2.82-2.91 (1H; m; H-1), 3.55 (1H; d; $J_{10,1}$ = 11.5 Hz; H-10), 3.74 (3H; s; ester -CH_3), 7.23-7.20 (4H; m; Ph o-H, m-H), 7.36-7.30 (1H; m; Ph p-H),.

δ_C ($CDCl_3$; 80MHz)

19.5 (C-4), 24.4 (C-1), 27.4 (C-7), 28.9 (C-2), 29.0 (C-9), 33.4 (C-5), 36.2 (C-8), 43.6 (C-3), 52.2 (ester -CH_3), 55.6 (C-10), 58.6 (C-6), 125.2 (Ph C-o), 125.9 (Ph C-m), 128.4 (Ph C-p), 149.8 (Ph-ipso), 174.6 (C-11), 211.3 (ester C=O).

M/Z

298 ($M^{+\cdot}$), 266, 230 (100%), 239, 238, 211.

Crystal growing of methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168]

A sample of the compound was dissolved in hexane/ether (9:1) and set aside at 5°C for 1 week affording needle-like crystals. The crystals were washed (hexane/ether (9:1) at -50°C) at and dried *in vacuo* in a desiccator.

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Appendix

4.0 Nomenclature of the photoproducts

A selection of the relevant rules in accordance with I.U.P.A.C. guidelines are list below for the convenience of assigning tricyclic compound nomenclature.[1,2] The rules for bicyclic systems are discussed and extrapolated to tricyclic systems. The assignment of bicyclic compounds [180] and [191] in Chapter 3 is more straightforward and will not be discussed.

Rules for polycyclic systems

Rule A32.13 [1]

The word "cyclo" is followed by brackets containing in decreasing order numbers indicating the number of carbon atoms in

1) The two branches of the main chain
2) The main bridge
3) The secondary bridges

Rule A32.22 [1]

The location of the other or so-called secondary bridges is shown by subscripts following the number indicating the number of carbon atoms in the said bridges.

Rule A32.31 [1]

When there is a choice, the following criteria are considered in turn until a decision is made.

a) The main ring shall contain as many carbon atoms as possible, two of which must serve as bridgeheads for the main bridge
b) The main bridge shall be as large as possible
c) The main ring shall be divided as symmetrically as possible by the main bridge
d) The subscripts locating the other bridges shall be as small as possible

Rule A31.2 [1]

Applies to bicyclic systems:

The system is numbered commencing with one of the bridge-heads, numbering proceeding by the longest possible path to the second bridgehead, numbering is the continued from this atom by the longer unnumbered path back to the first bridgehead and is completed by the shortest path from the atom next to the first bridgehead. *When after applying this rule a choice in numbering remains unsaturation is given the lowest numbers.*

R-4.1 [2]

The starting point and direction of numbering of a compound are chosen so as to give lowest locants to the following structural features (if present) considered successively in the order listed until a decision is reached.

(a) Fixed numbering (naphthalene, etc.)

(b) Heteroatoms in heterocycles

(c) Indicated hydrogen

(d) Principal group named as suffix

(e) Heteroatoms in an acyclic parent structure

(f) Unsaturation (ene/yne)

(g) Substituents named as prefixes.

Endo, exo, syn and **anti**

The system used by *Chemical Abstracts* to distinguish between *exo* and *endo* hydrogens in bridged polycyclic systems has been applied to these compounds.[3,4] Descriptors of the relative orientation of groups attached to non-bridgehead atoms in a bicyclo[x, y, z]alkane ($x \geq y \geq z > 0$) (Fig. 4.1). If the group is oriented towards the highest numbered bridges (z bridge, Fig. 4.1) it is given the description *exo*; if it is orientated away from the highest numbered bridge it is given the description *endo*. If the group is attached to the highest numbered bridge and is oriented towards the lowest numbered bridge (x bridge, Fig. 4.1) it is given the description *syn*: if the group is oriented away from the lowest numbered bridge it is given the description *anti*.

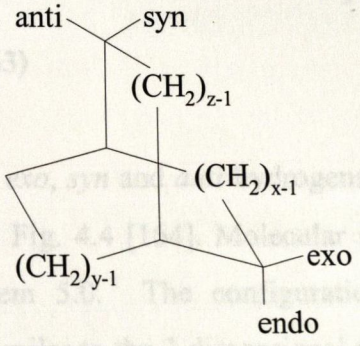


Fig. 4.1

A more simplistic approach is one where *exo* hydrogens are placed *cis* with respect to the shorter bridge (z-bridge) and *endo* hydrogens are placed *trans* to this bridge (Fig. 4.2).[5]

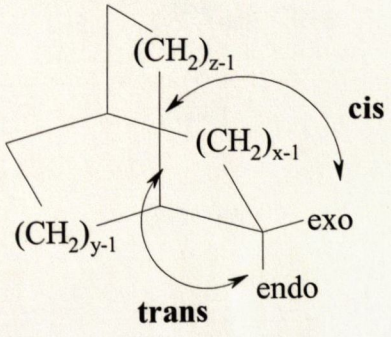
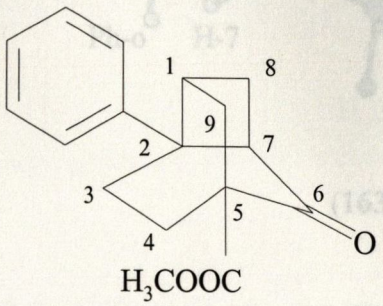
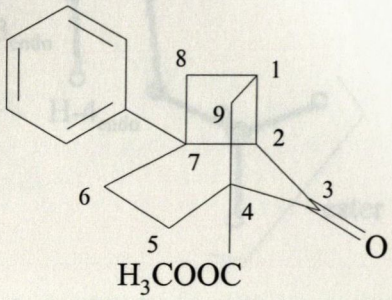


Fig. 4.2

The irradiation of methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136] afforded a photoproduct, which has two possible configurations [164] both have been named as methyl 6-oxo-2-phenyltricyclo[3.3.1.$0^{2,7}$]nonane-5-carboxylate [163] and methyl 3-oxo-7-phenyltricyclo[4.2.1.$0^{2,7}$]nonane-4-carboxylate [164].

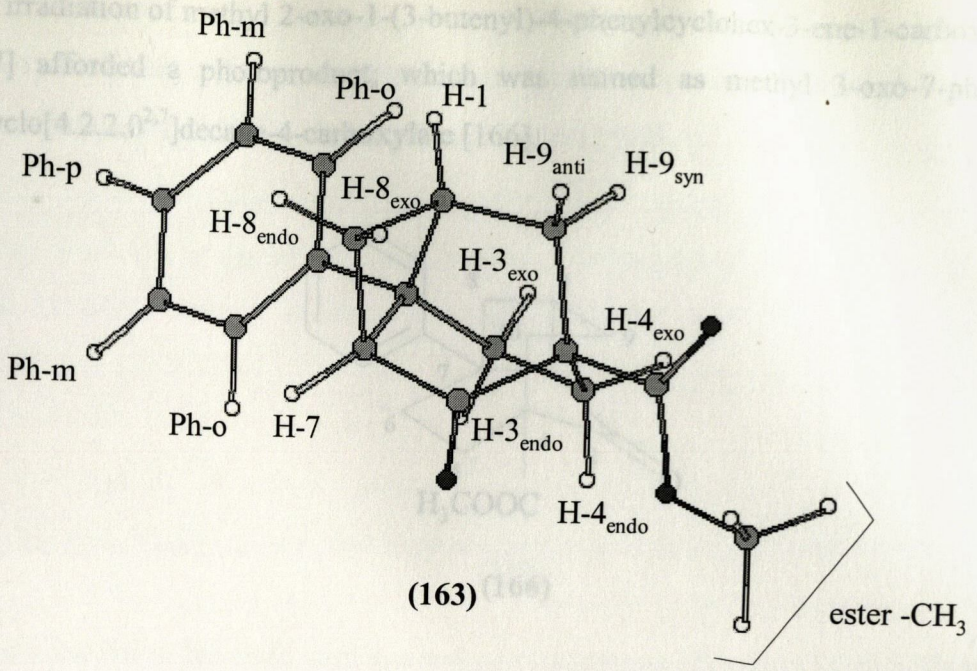


(163)



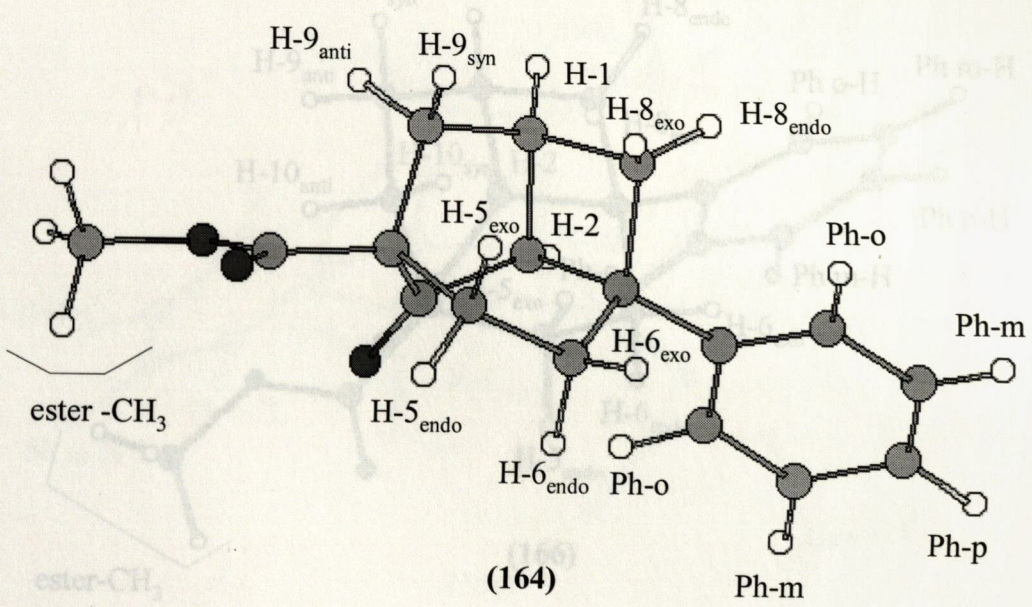
(164)

The assignment of the *endo*, *exo*, *syn* and *anti* hydrogens for both configurations are shown in Fig. 4.3 [163] and Fig. 4.4 [164]. Molecular modelling calculations were carried out using Hyperchem 5.0. The configuration was configured so that 3-dimensional display was similar to the 2-dimensional structures. However the 3-D structure did not fully show the geometry of the molecule. The structure was rotated for better visualisation.



(163)

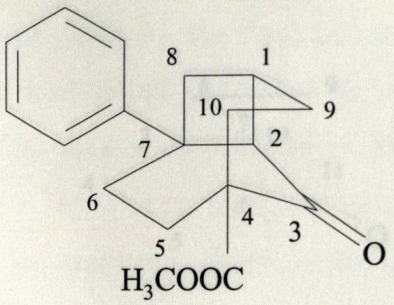
Fig. 4.3



(164)

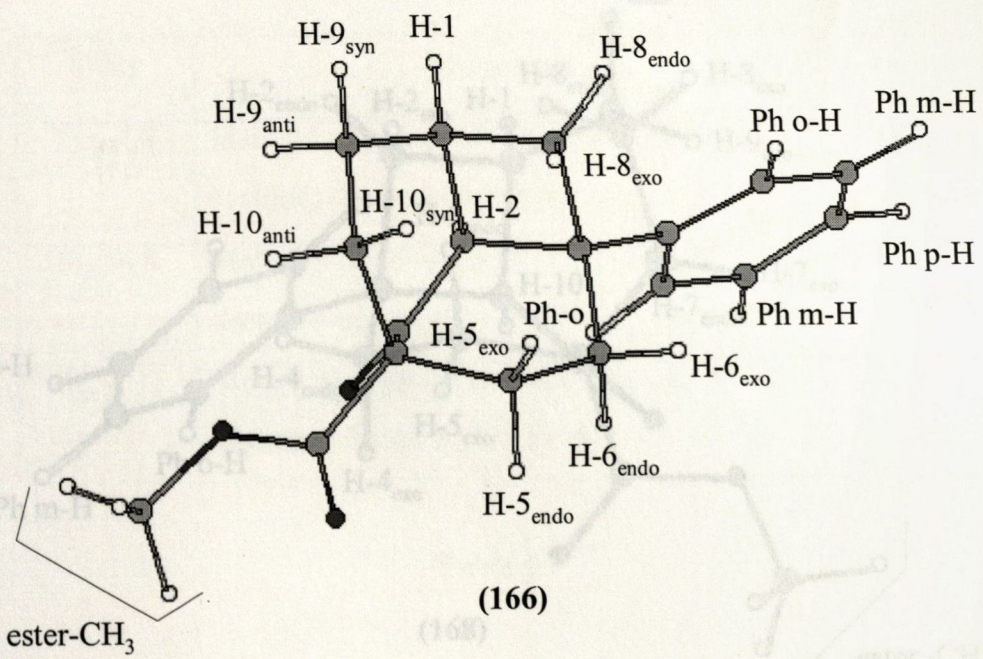
Fig. 4.4

The irradiation of methyl 2-oxo-1-(3-butenyl)-4-phenylcyclohex-3-ene-1-carboxylate [137] afforded a photoproduct, which was named as methyl 3-oxo-7-phenyl-tricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166].



(166)

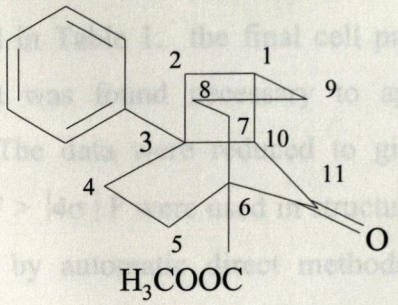
The assignment of the *endo*, *exo*, *syn* and *anti* hydrogens for methyl 3-oxo-7-phenyl-tricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166] are shown in Fig. 4.5.



(166)

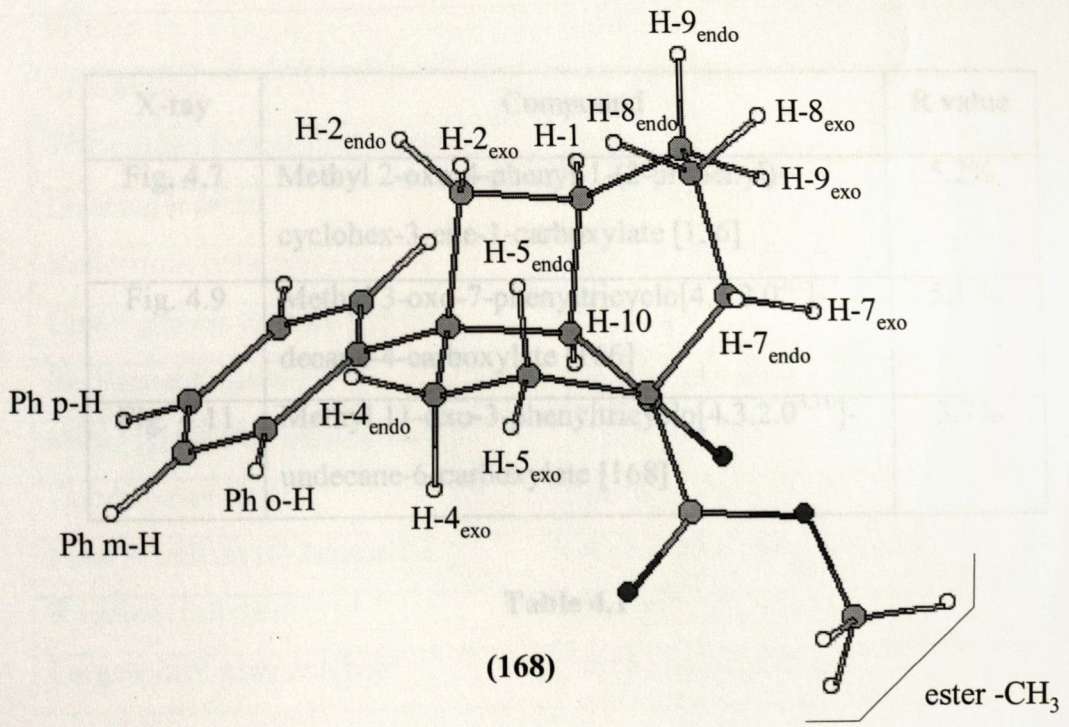
Fig. 4.5

The irradiation of methyl 2-oxo-1-(4-pentenyl)-4-phenylcyclohex-3-ene-1-carboxylate [138] afforded a photoproduct, which was named as methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168].



(168)

The assignment of the *endo*, *exo*, *syn* and *anti* hydrogens of methyl 11-oxo-3-phenyl-tricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168] have been assigned in Fig. 4.6



(168)

Fig. 4.6

4.1 X-ray: Crystal structure determination

Data were collected on an Enraf-Nonius CAD-4 diffractometer (MO radiation, graphite monochrometer) ω-2θ scans 20°C. The crystal data and experimental parameters are summarised in Table 1. the final cell parameters were determined using Celdim routine. It was found necessary to apply decay or absorption corrections to the data. The data were reduced to give the number of unique reflections and those with $F > |4\sigma|F$ were used in structure solution and refinement. The structure was solved by automatic direct methods using SHELX-86.[6] The structure was refined by full-matrix least-squares analysis on F^2 with SHELXS-86.[7] The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were all treated the same and were located from subsequent difference Fourier maps and refined with individual temperature factors. This gave a final R value which is different for each structure (Table 4.1)

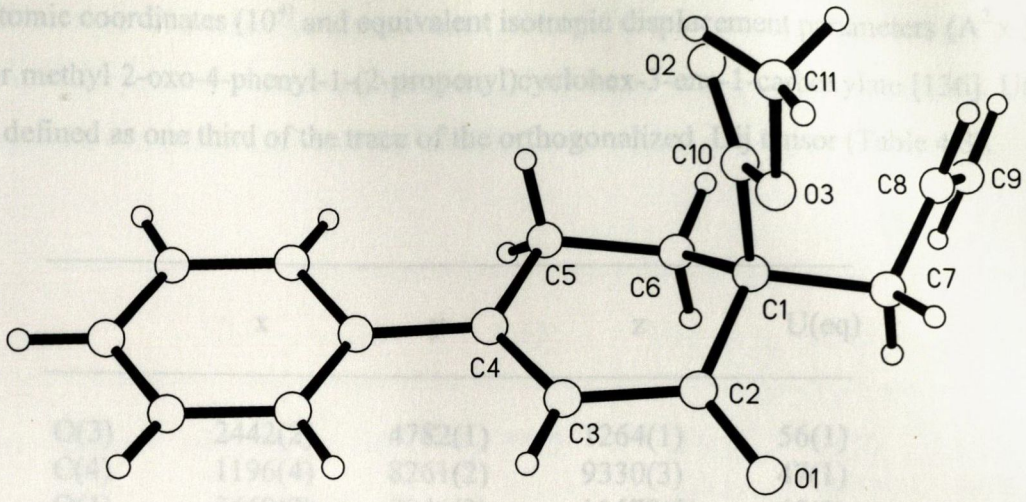
X-ray	Compound	R value
Fig. 4.7	Methyl 2-oxo-4-phenyl-1-(2-propenyl)-cyclohex-3-ene-1-carboxylate [136]	5.2%
Fig. 4.9	Methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]-decane-4-carboxylate [166]	5.1 %
Fig. 4.11	Methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168]	3.7%

Table 4.1

4.12 Crystal data and structure refinement for methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]

Empirical formula	$C_{17}H_{18}O_3$
Formula weight	270.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic
Unit cell dimensions	a = 6.121(6) Å α = 80.995(17) °
	b = 10.219(3) Å β = 83.01(3) °
	c = 12.1028(18) Å χ= 82.18(5)°
Volume	736.9(8) A^3
Z,	2
Calculated density	1.218 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	288
Crystal size	? x ? x ? mm
Theta range for data collection	1.71 to 25.06 °.
Limiting indices	0<=h<=7, -11<=k<=11, -13<=l<=13
Reflections collected / unique	2843 / 2583 [R(int) = 0.0176]
Completeness to theta= 25.06	98.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2583 / 0 / 253
Goodness-of-fit on F^2	1.003
Final R indices [I>2sigma(I)]	R_1 = 0.0525, wR_2 = 0.1036
R indices (all data)	R_1 = 0.1290, wR_2 = 0.1297
Largest diff. peak and hole	0.114 and -0.172 $e.A^{-3}$

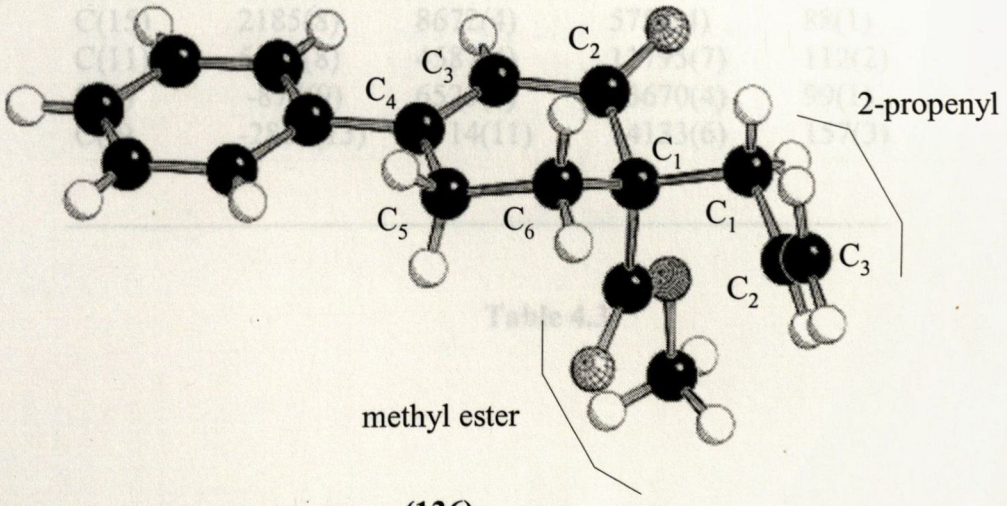
Table 4.2



(136)

Fig. 4.7

The structure was adjusted to best display its conformation. The numbering was simplified for the purpose of spectroscopic identification and nomenclature (Fig. 4.8). All crystal data refer to Fig. 4.7



(136)

Fig. 4.8

Atomic Types, Coordinates and Thermal Parameters

Atomic coordinates ($10^{4)}$ and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor (Table 4.3).

	x	y	z	U(eq)
O(3)	2442(2)	4782(1)	1264(1)	56(1)
C(4)	1196(4)	8261(2)	9330(3)	47(1)
O(1)	3469(3)	9046(2)	11678(2)	65(1)
C(2)	2449(4)	8443(2)	11163(3)	49(1)
O(3)	4174(3)	5903(2)	11824(2)	85(1)
C(3)	2606(4)	8657(2)	9945(3)	49(1)
C(12)	1525(4)	8434(2)	8088(3)	50(1)
O(2)	1227(3)	5133(2)	11432(2)	84(1)
C(5)	-781(4)	7626(3)	9915(3)	53(1)
C(6)	-1175(4)	7690(3)	11165(3)	53(1)
C(10)	2078(4)	6027(2)	11639(2)	51(1)
C(1)	946(4)	7421(2)	11750(2)	47(1)
C(13)	3364(5)	8941(3)	7491(3)	63(1)
C(17)	35(6)	8031(3)	7476(3)	2(1)
C(7)	487(6)	7533(4)	13016(3)	66(1)
C(14)	3697(7)	9055(4)	6350(4)	82(1)
C(16)	374(7)	8159(4)	6320(4)	91(1)
C(15)	2185(8)	8672(4)	5753(4)	88(1)
C(11)	5424(8)	4587(4)	11795(7)	112(2)
C(8)	-873(9)	6523(6)	13670(4)	99(1)
C(9)	-2822(13)	6714(11)	14133(6)	157(3)

Table 4.3

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3) for methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136]. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12] (Table 4.4).

	U11	U22	U33	U23	U13	U12
C(4)	37(1)	30(1)	76(2)	-11(1)	-8(1)	-2(1)
O(1)	63(1)	57(1)	87(2)	-22(1)	-21(1)	-22(1)
C(2)	37(1)	34(1)	80(2)	-18(1)	-13(2)	-2(1)
O(3)	49(1)	43(1)	167(2)	-23(1)	-31(1)	2(1)
C(3)	38(2)	36(1)	76(2)	-11(1)	-8(2)	-10(1)
C(12)	48(2)	34(1)	70(2)	-8(1)	-11(2)	-5(1)
O(2)	75(2)	46(1)	141(2)	-30(1)	-32(1)	-9(1)
C(5)	36(2)	51(2)	76(2)	-9(2)	-14(2)	-10(1)
C(6)	38(2)	46(2)	78(2)	-12(2)	-3(2)	-10(1)
C(10)	46(2)	40(2)	71(2)	-11(1)	-8(1)	-9(1)
C(1)	41(1)	39(1)	62(2)	-15(1)	-6(1)	-6(1)
C(13)	62(2)	57(2)	73(3)	-11(2)	-2(2)	-18(2)
C(17)	63(2)	78(2)	80(3)	-14(2)	-14(2)	-18(2)
C(7)	65(2)	63(2)	73(2)	-22(2)	-4(2)	-11(2)
C(14)	88(3)	83(2)	76(3)	-11(2)	7(2)	-23(2)
C(16)	89(3)	108(3)	88(3)	-21(2)	-28(3)	-25(2)
C(15)	104(3)	90(3)	69(3)	-14(2)	-7(3)	-11(2)
C(11)	68(3)	50(2)	219(7)	-24(3)	-38(4)	14(2)
C(8)	115(4)	116(4)	73(3)	-25(3)	8(3)	-40(3)
C(9)	132(5)	236(9)	118(5)	-44(5)	23(4)	-89(6)

Table 4.4

Molecular Geometry

Bond lengths [Å] and angles [°] for methyl 2-oxo-4-phenyl-1-(2-propenyl)cyclohex-3-ene-1-carboxylate [136] (Table 4.5)

C(4)-C(3)	1.345(4)
C(4)-C(12)	1.478(4)
C(4)-C(5)	1.499(4)
O(1)-C(2)	1.216(3)
C(2)-C(3)	1.449(4)
C(2)-C(1)	1.520(4)
O(3)-C(10)	1.315(3)
O(3)-C(11)	1.457(4)
C(12)-C(13)	1.379(4)
C(12)-C(17)	1.383(4)
O(2)-C(10)	1.184(3)
C(5)-C(6)	1.513(4)
C(6)-C(1)	1.526(4)
C(10)-C(1)	1.516(3)
C(1)-C(7)	1.543(4)
C(13)-C(14)	1.360(5)
C(17)-C(16)	1.378(5)
C(7)-C(8)	1.484(5)
C(14)-C(15)	1.371(5)
C(16)-C(15)	1.355(5)
C(8)-C(9)	1.258(8)
C(3)-C(4)-C(12)	122.1(3)
C(3)-C(4)-C(5)	119.4(3)
C(12)-C(4)-C(5)	118.5(2)
O(1)-C(2)-C(3)	121.6(2)
O(1)-C(2)-C(1)	122.4(3)
C(3)-C(2)-C(1)	116.1(2)
C(10)-O(3)-C(11)	116.9(3)
C(4)-C(3)-C(2)	124.6(3)
C(13)-C(12)-C(17)	117.0(3)
C(13)-C(12)-C(4)	122.0(3)
C(17)-C(12)-C(4)	120.9(3)
C(4)-C(5)-C(6)	114.5(2)
C(5)-C(6)-C(1)	113.5(2)
O(2)-C(10)-O(3)	122.6(2)
O(2)-C(10)-C(1)	125.9(3)
O(3)-C(10)-C(1)	111.5(2)
C(10)-C(1)-C(2)	109.6(2)
C(10)-C(1)-C(6)	110.3(2)
C(2)-C(1)-C(6)	106.7(2)
C(10)-C(1)-C(7)	107.6(2)
C(2)-C(1)-C(7)	110.5(2)

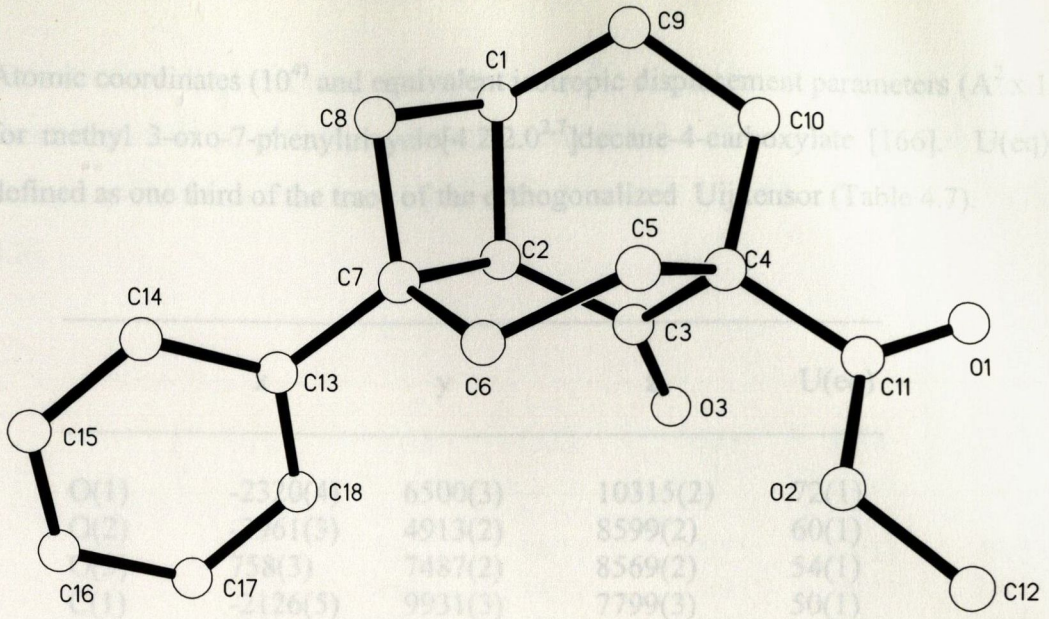
C(6)-C(1)-C(7)	112.1(3)
C(14)-C(13)-C(12)	121.8(4)
C(16)-C(17)-C(12)	120.9(4)
C(8)-C(7)-C(1)	114.3(3)
C(13)-C(14)-C(15)	120.5(4)
C(15)-C(16)-C(17)	120.9(4)
C(16)-C(15)-C(14)	118.9(5)
C(9)-C(8)-C(7)	127.7(7)

Table 4.5

4.13 Crystal data and structure refinement for methyl 3-oxo-7-phenyltricyclo-[4.2.2.$0^{2,7}$]decane-4-carboxylate [166]

Empirical formula	$C_{18}H_{20}O_3$
Formula weight	284.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic
Unit cell dimensions	a = 6.6572(9)Å α = 102.795(8)°
	b = 9.8399(8)Å β = 99.112(11)°
	c = 12.3209(15)Å χ= 105.356(9)°
Volume	738.47(15)A^3
Z,	2
Calculated density	1.279 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	304
Crystal size	0.60 x 0.40 x 0.40 mm
Theta range for data collection	1.74 to 24.97 °
Limiting indices	0<=h<=7, -10<=k<=10, -13<=l<=13
Reflections collected / unique	2763 / 2529 [R(int) = 0.0325]
Completeness to theta= 24.97	97.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2529 / 0 / 270
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R_1 = 0.0507, wR_2 = 0.0959
R indices (all data)	R_1 = 0.1283, wR_2 = 0.1173
Largest diff. peak and hole	0.165 and -0.156 $e.A^{-3}$

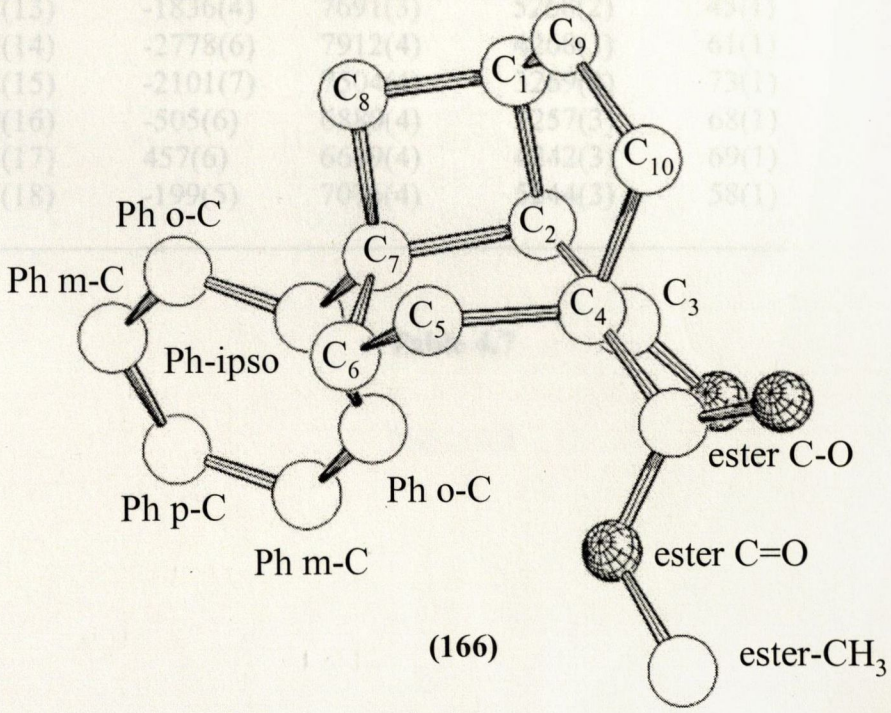
Table 4.6



(166)

Fig. 4.9

The structure was adjusted to best display its conformation. The numbering simplified for the purpose of spectroscopic identification and nomenclature (Fig. 4.10). All crystal data refer to Fig. 4.9



(166)

Fig. 4.10

Atomic Types, Coordinates and Thermal Parameters

Atomic coordinates ($10^{4)}$ and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166]. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor (Table 4.7).

	x	y	z	U(eq)
O(1)	-2320(4)	6500(3)	10315(2)	72(1)
O(2)	-2961(3)	4913(2)	8599(2)	60(1)
O(3)	758(3)	7487(2)	8569(2)	54(1)
C(1)	-2126(5)	9931(3)	7799(3)	50(1)
C(2)	-915(5)	8787(3)	7491(2)	41(1)
C(3)	-820(4)	7821(3)	8250(2)	38(1)
C(4)	-2901(4)	7316(3)	8621(2)	38(1)
C(5)	-4835(4)	6683(3)	7569(2)	44(1)
C(6)	-4167(5)	6579(3)	6430(3)	45(1)
C(7)	-2655(4)	8013(3)	6341(2)	41(1)
C(8)	-3528(6)	9346(4)	6577(3)	57(1)
C(9)	-3293(6)	9857(4)	8780(3)	55(1)
C(10)	-3023(6)	8732(3)	9417(3)	51(1)
C(11)	-2699(4)	6226(3)	9295(3)	47(1)
C(12)	-2800(8)	3775(5)	9143(5)	78(1)
C(13)	-1836(4)	7691(3)	5268(2)	45(1)
C(14)	-2778(6)	7912(4)	4268(3)	61(1)
C(15)	-2101(7)	7504(4)	3269(3)	73(1)
C(16)	-505(6)	6880(4)	3257(3)	68(1)
C(17)	457(6)	6669(4)	4242(3)	69(1)
C(18)	-199(5)	7076(4)	5244(3)	58(1)

Table 4.7

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3) for methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166]. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12] (Table 4.8).

	U11	U22	U33	U23	U13	U12
O(1)	90(2)	95(2)	54(1)	32(1)	27(1)	49(2)
O(2)	74(2)	45(1)	74(1)	28(1)	26(1)	26(1)
O(3)	44(1)	67(1)	63(1)	25(1)	19(1)	26(1)
C(1)	61(2)	34(2)	57(2)	12(1)	21(2)	17(2)
C(2)	39(2)	38(2)	47(2)	12(1)	17(1)	9(1)
C(3)	37(2)	39(2)	34(2)	0(1)	7(1)	13(1)
C(4)	37(2)	40(2)	42(2)	13(1)	16(1)	16(1)
C(5)	37(2)	37(2)	60(2)	14(1)	14(2)	14(1)
C(6)	41(2)	43(2)	49(2)	8(1)	7(2)	12(1)
C(7)	42(2)	39(2)	46(2)	13(1)	10(1)	15(1)
C(8)	58(2)	56(2)	67(2)	26(2)	16(2)	27(2)
C(9)	66(2)	44(2)	63(2)	11(2)	25(2)	28(2)
C(10)	56(2)	47(2)	55(2)	10(2)	26(2)	20(2)
C(11)	44(2)	54(2)	54(2)	20(2)	22(2)	22(1)
C(12)	72(3)	68(3)	126(4)	64(3)	33(3)	37(2)
C(13)	53(2)	44(2)	38(2)	14(1)	12(1)	13(1)
C(14)	66(2)	70(2)	50(2)	25(2)	9(2)	22(2)
C(15)	85(3)	82(3)	45(2)	30(2)	8(2)	9(2)
C(16)	82(3)	65(2)	54(2)	15(2)	30(2)	10(2)
C(17)	76(3)	76(2)	59(2)	14(2)	28(2)	28(2)
C(18)	65(2)	72(2)	46(2)	16(2)	18(2)	32(2)

Table 4.8

Molecular Geometry

Bond lengths [Å] and angles [°] for methyl 3-oxo-7-phenyltricyclo[4.2.2.$0^{2,7}$]decane-4-carboxylate [166]. (Table 4.9).

O(1)-C(11)	1.196(3)
O(2)-C(11)	1.333(3)
O(2)-C(12)	1.445(4)
O(3)-C(3)	1.215(3)
C(1)-C(8)	1.534(4)
C(1)-C(9)	1.542(4)
C(1)-C(2)	1.565(4)
C(2)-C(3)	1.479(4)
C(2)-C(7)	1.570(4)
C(3)-C(4)	1.520(4)
C(4)-C(11)	1.514(4)
C(4)-C(10)	1.546(4)
C(4)-C(5)	1.554(4)
C(5)-C(6)	1.527(4)
C(6)-C(7)	1.539(4)
C(7)-C(13)	1.510(4)
C(7)-C(8)	1.559(4)
C(9)-C(10)	1.523(4)
C(13)-C(14)	1.380(4)
C(13)-C(18)	1.380(4)
C(14)-C(15)	1.391(5)
C(15)-C(16)	1.361(5)
C(16)-C(17)	1.365(5)
C(17)-C(18)	1.385(4)
C(11)-O(2)-C(12)	116.2(3)
C(8)-C(1)-C(9)	116.8(3)
C(8)-C(1)-C(2)	89.4(2)
C(9)-C(1)-C(2)	117.8(2)
C(3)-C(2)-C(1)	116.3(2)
C(3)-C(2)-C(7)	113.0(2)
C(1)-C(2)-C(7)	89.3(2)
O(3)-C(3)-C(2)	124.1(3)
O(3)-C(3)-C(4)	123.1(2)
C(2)-C(3)-C(4)	112.8(2)
C(11)-C(4)-C(3)	108.3(2)
C(11)-C(4)-C(10)	109.9(2)
C(3)-C(4)-C(10)	103.7(2)
C(11)-C(4)-C(5)	113.0(2)
C(3)-C(4)-C(5)	110.6(2)
C(10)-C(4)-C(5)	110.9(2)
C(6)-C(5)-C(4)	113.1(2)
C(5)-C(6)-C(7)	114.8(2)

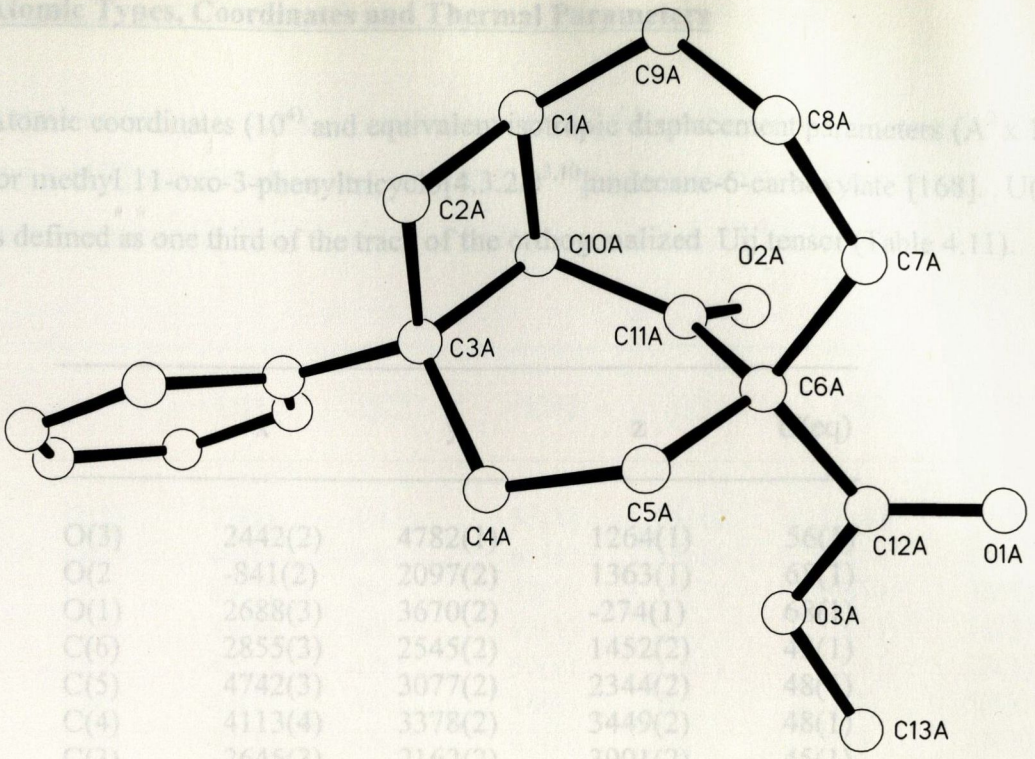
C(13)-C(7)-C(6)	108.9(2)
C(13)-C(7)-C(8)	117.8(2)
C(6)-C(7)-C(8)	114.3(2)
C(13)-C(7)-C(2)	116.4(2)
C(6)-C(7)-C(2)	109.8(2)
C(8)-C(7)-C(2)	88.4(2)
C(1)-C(8)-C(7)	90.9(2)
C(10)-C(9)-C(1)	116.2(2)
C(9)-C(10)-C(4)	112.4(2)
O(1)-C(11)-O(2)	124.0(3)
O(1)-C(11)-C(4)	125.0(3)
O(2)-C(11)-C(4)	111.0(2)
C(14)-C(13)-C(18)	118.0(3)
C(14)-C(13)-C(7)	121.4(3)
C(18)-C(13)-C(7)	120.5(3)
C(13)-C(14)-C(15)	120.4(3)
C(16)-C(15)-C(14)	120.8(4)
C(15)-C(16)-C(17)	119.5(4)
C(16)-C(17)-C(18)	120.2(4)
C(13)-C(18)-C(17)	121.1(3)

Table 4.9

4.14 Crystal data and structure refinement for methyl 11-oxo-3-phenyl-tricyclo[4.3.2.0^{3,10}]undecane-6-carboxylate [168]

Empirical formula	$C_{19}H_{22}O_3$
Formula weight	298.37
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, p-1
Unit cell dimensions	a = 6.6266(7) Å α = 90.769(8)°
	b = 10.1023(10) Å β = 96.613(10)°
	c = 12.3043(11) Å χ=103.792(8)°
Volume	793.91(14) A^3
Z,	2
Calculated density	1.248 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	320
Crystal size	0.30 x 0.20 x 0.20 mm
Theta range for data collection	1.67 to 21.97 °.
Limiting indices	0<=h<=6, -10<=k<=10, -12<=l<=12
Reflections collected / unique	2133 / 1926 [R(int) = 0.0183]
Completeness to theta= 21.97	100 %
Absorption correction	none
Max. and min. transmission	0.9836 and 0.9755
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1926 / 0 / 287
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R_1 = 0.0373, wR_2 = 0.0919
R indices (all data)	R_1 = 0.0523, wR_2 = 0.1003
Largest diff. peak and hole	0.157 and -0.134 $e.A^{-3}$

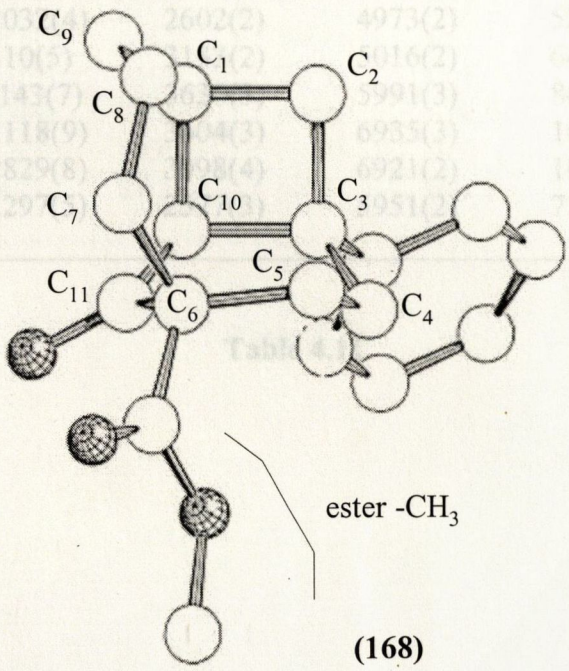
Table 4.10



(168)

Fig. 4.11

The structure was adjusted to best display its conformation. The numbering simplified for the purpose of spectroscopic identification and nomenclature (Fig. 4.12). All crystal data refer to Fig. 4.11.



(168)

Fig. 4.12

Atomic Types, Coordinates and Thermal Parameters

Atomic coordinates ($10^{4)}$ and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168]. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor (Table 4.11).

	x	y	z	U(eq)
O(3)	2442(2)	4782(1)	1264(1)	56(1)
O(2	-841(2)	2097(2)	1363(1)	68(1)
O(1)	2688(3)	3670(2)	-274(1)	68(1)
C(6)	2855(3)	2545(2)	1452(2)	42(1)
C(5)	4742(3)	3077(2)	2344(2)	48(1)
C(4)	4113(4)	3378(2)	3449(2)	48(1)
C(3)	2645(3)	2162(2)	3901(2)	45(1)
C(2)	3392(5)	816(3)	3927(2)	65(1)
C(1)	1519(4)	118(2)	3101(2)	61(1)
C(9)	1823(6)	-615(3)	2066(3)	82(1)
C(8)	3522(6)	104(3)	1390(3)	81(1)
C(7)	3143(5)	1325(2)	767(2)	62(1)
C(11)	781(3)	2070(2)	1921(2)	44(1)
C(10)	791(3)	480(2)	3022(2)	45(1)
C(12)	2639(3)	3693(2)	695(2)	46(1)
C(13)	2398(5)	6003(3)	665(3)	64(1)
C(14)	2032(4)	2602(2)	4973(2)	52(1)
C(15)	310(5)	3133(2)	5016(2)	64(1)
C(16)	-143(7)	3630(3)	5991(3)	86(1)
C(17)	1118(9)	3604(3)	6935(3)	102(1)
C(18)	2829(8)	3098(4)	6921(2)	103(1)
C(19)	3297(5)	2577(3)	5951(2)	77(1)

Table 4.11

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3) for methyl 11-oxo-3-phenyltricyclo-[4.3.2.$0^{3,10}$]undecane-6-carboxylate [168]. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12] (Table 4.12).

	U11	U22	U33	U23	U13	U12
O(3)	77(1)	47(1)	51(1)	11(1)	16(1)	24(1)
O(2)	46(1)	94(1)	61(1)	15(1)	0(1)	11(1)
O(1)	89(1)	80(1)	42(1)	10(1)	15(1)	32(1)
C(6)	44(1)	40(1)	43(1)	2(1)	10(1)	11(1)
C(5)	42(1)	47(1)	57(1)	10(1)	11(1)	12(1)
C(4)	44(1)	51(1)	46(1)	3(1)	-1(1)	5(1)
C(3)	48(1)	45(1)	43(1)	6(1)	3(1)	11(1)
C(2)	74(2)	60(2)	69(2)	24(1)	17(2)	30(1)
C(1)	79(2)	38(1)	66(2)	7(1)	25(1)	6(1)
C(9)	125(3)	40(1)	86(2)	5(1)	48(2)	17(2)
C(8)	121(3)	45(2)	91(2)	4(2)	54(2)	28(2)
C(7)	78(2)	49(1)	66(2)	0(1)	35(2)	14(1)
C(11)	44(1)	43(1)	44(1)	-2(1)	5(1)	9(1)
C(10)	42(1)	46(1)	47(1)	1(1)	10(1)	5(1)
C(12)	44(1)	52(1)	44(1)	2(1)	0(1)	12(1)
C(13)	67(2)	51(1)	79(2)	23(1)	13(2)	19(1)
C(14)	63(2)	45(1)	40(1)	7(1)	6(1)	-1(1)
C(15)	90(2)	56(2)	50(2)	4(1)	18(1)	21(1)
C(16)	128(3)	58(2)	73(2)	-3(1)	48(2)	11(2)
C(17)	145(4)	73(2)	64(2)	-15(2)	45(2)	-36(2)
C(18)	122(3)	109(3)	38(2)	2(2)	-3(2)	-42(2)
C(19)	76(2)	87(2)	52(2)	9(1)	-2(1)	-8(2)

Table 4.12

Molecular Geometry

Bond lengths [Å] and angles [°] for methyl 11-oxo-3-phenyltricyclo[4.3.2.$0^{3,10}$]-undecane-6-carboxylate [168] (Table 4.13).

O(3)-C(12)	1.337(2)
O(3)-C(13)	1.449(3)
O(2)-C(11)	1.213(2)
O(1)-C(12)	1.195(2)
C(6)-C(12)	1.520(3)
C(6)-C(11)	1.526(3)
C(6)-C(7)	1.545(3)
C(6)-C(5)	1.550(3)
C(5)-C(4)	1.515(3)
C(4)-C(3)	1.529(3)
C(3)-C(14)	1.516(3)
C(3)-C(2)	1.554(3)
C(3)-C(10)	1.557(3)
C(2)-C(1)	1.531(4)
C(1)-C(9)	1.522(3)
C(1)-C(10)	1.564(3)
C(9)-C(8)	1.526(4)
C(8)-C(7)	1.518(4)
C(11)-C(10)	1.487(3)
C(14)-C(15)	1.378(3)
C(14)-C(19)	1.390(3)
C(15)-C(16)	1.386(4)
C(16)-C(17)	1.355(5)
C(17)-C(18)	1.352(5)
C(18)-C(19)	1.394(5)
C(12)-O(3)-C(13)	117.04(18)
C(12)-C(6)-C(11)	107.22(16)
C(12)-C(6)-C(7)	108.90(17)
C(11)-C(6)-C(7)	106.80(18)
C(12)-C(6)-C(5)	108.91(16)
C(11)-C(6)-C(5)	113.17(16)
C(7)-C(6)-C(5)	111.67(19)
C(4)-C(5)-C(6)	113.58(18)
C(5)-C(4)-C(3)	113.79(19)
C(14)-C(3)-C(4)	109.11(17)
C(14)-C(3)-C(2)	115.08(18)
C(4)-C(3)-C(2)	115.42(19)
C(14)-C(3)-C(10)	115.47(17)
C(4)-C(3)-C(10)	111.32(16)
C(2)-C(3)-C(10)	89.44(16)
C(1)-C(2)-C(3)	90.89(18)

C(9)-C(1)-C(2)	121.0(3)
C(9)-C(1)-C(10)	120.0(2)
C(2)-C(1)-C(10)	90.02(16)
C(1)-C(9)-C(8)	118.3(2)
C(7)-C(8)-C(9)	117.2(3)
C(8)-C(7)-C(6)	116.8(2)
O(2)-C(11)-C(10)	121.55(19)
O(2)-C(11)-C(6)	119.53(18)
C(10)-C(11)-C(6)	118.74(18)
C(11)-C(10)-C(3)	116.69(17)
C(11)-C(10)-C(1)	114.82(17)
C(3)-C(10)-C(1)	89.55(16)
O(1)-C(12)-O(3)	123.2(2)
O(1)-C(12)-C(6)	126.11(19)
O(3)-C(12)-C(6)	110.62(17)
C(15)-C(14)-C(19)	117.2(3)
C(15)-C(14)-C(3)	122.2(2)
C(19)-C(14)-C(3)	120.4(2)
C(14)-C(15)-C(16)	121.7(3)
C(17)-C(16)-C(15)	120.2(4)
C(18)-C(17)-C(16)	119.7(3)
C(17)-C(18)-C(19)	121.0(3)
C(14)-C(19)-C(18)	120.2(4)

Table 4.13

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