SYNTHESIS AND REARRANGEMENTS OF SOME TETRA- AND PENTACYCLIC CAGE COMPOUNDS

THESIS SUBMITTED TO
THE COCHIN UNIVERSITY OF SCIENCE AND TECHNOLOGY
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY UNDER THE FACULTY OF SCIENCE

BY

UMA SUDHIR

UNDER THE SUPERVISION OF

DR. MANGALAM S. NAIR

ORGANIC CHEMISTRY DIVISION
REGIONAL RESEARCH LABORATORY (CSIR)
TRIVANDRUM-695 019, KERALA, INDIA

MARCH, 2001

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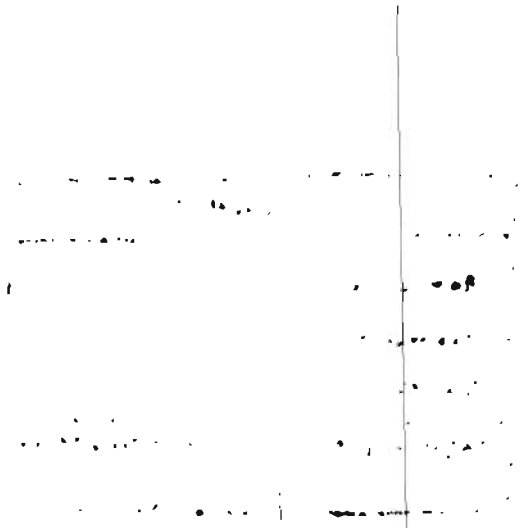
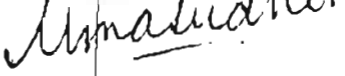


For

Dr. V. Kesavan

DECLARATION

I hereby declare that the thesis entitled **"Synthesis and Rearrangements of some Tetra- and Pentacyclic Cage Compounds"** embodies the results of the investigations carried out by me at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum, under the supervision of **Dr. Mangalam S. Nair** and the same has not been submitted elsewhere for a degree.



Uma Sudhir

March, 2001

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Trivandrum
March, 2001

Uma Sudhir

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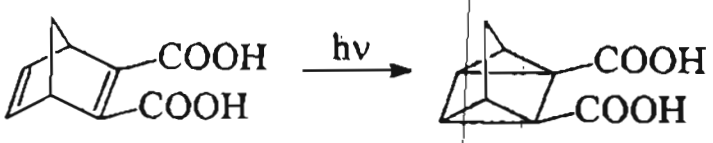
ABBREVIATIONS

AIBN	:	2,2'-azobisisobutyronitrile
Ac	:	acetyl
aq.	:	aqueous
Bu	:	butyl
CAN	:	ammonium cerium(IV) nitrate
cat.	:	catalytic
CPD	:	cyclopentadiene
d	:	day(s)
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	:	distortionless enhancement by polarization transfer
EDA	:	ethyl diazoacetate
eq.	:	equivalents
Et	:	ethyl
h	:	hour(s)
HMPA	:	hexamethylphosphoric triamide
HOMO	:	highest occupied molecular orbital
HRMS	:	high resolution mass spectrum
Hz	:	hertz
IR	:	infrared
J	:	coupling constant
LAH	:	lithium aluminium hydride
LHMDS	:	lithium hexamethyldisilazide
LUMO	:	lowest unoccupied molecular orbital
M^+	:	molecular ion
Me	:	methyl
m.p.	:	melting point
Ms	:	methanesulphonyl (mesyl)
mts	:	minutes
NBS	:	*N*-bromosuccinimide
nm	:	nanometre
NMR	:	nuclear magnetic resonance
o	:	*ortho*
p	:	*para*
PCUD	:	pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione
psi	:	pounds per square inch
Ph	:	phenyl
PPA	:	polyphosphoric acid
Pr	:	propyl
PTSA	:	*p*-toluenesulphonic acid
Py	:	pyridine
RT	:	room temperature
Tf	:	triflouromethanesulphonyl (triflyl)
THF	:	tetrahydrofuran
tlc	:	thin layer chromatography
TMS	:	tetramethylsilane
Ts	:	*p*-toluenesulphonyl (tosyl)

CHAPTER 1 – INTRODUCTION
POLYCYCLIC CAGE COMPOUNDS

For the past three to four decades, many synthetic organic chemists around the world have been enchanted with the synthesis and chemistry of novel strained polycarbocyclic 'cage' compounds.[1] Many compounds of this class possess unusual symmetry properties. Their inherent beauty coupled with structural and chemical features render such 'cage' compounds unique among complex organic compounds. Apart from their aesthetic appeal, study of their rearrangements provide an insight into the pathways that carbonium ions, carbanions and radicals follow under strained circumstances.[2]

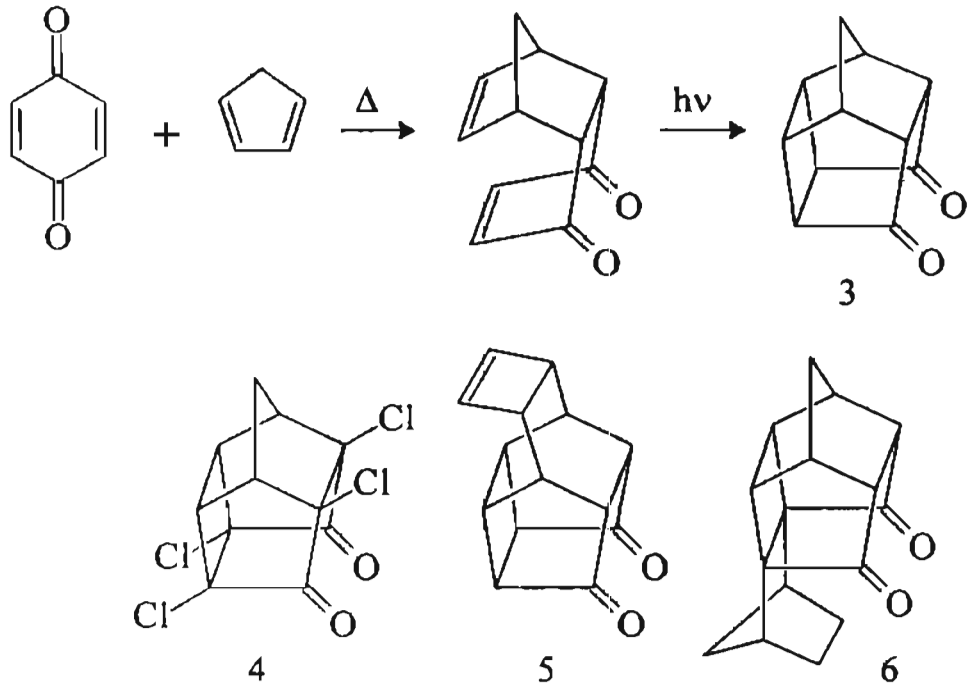
The use of light for the construction of strained rings was first illustrated by Cristol and Snell in 1954.[3] They showed that irradiation of bicyclo[2.2.1]heptadiene-2,3-dicarboxylic acid **1** resulted in an intramolecular [π2s + π2s] cycloaddition leading to the highly strained product tetracyclo[2.2.1.$0^{2,6}$.$0^{3,5}$]heptane-2,3-dicarboxylic acid **2** as shown below (Scheme I). Thus, photochemical [2 + 2] addition was identified as an easy route to these strained systems and the synthetic strategy for obtaining polycylic cage compounds was greatly simplified.



1 2

Scheme I

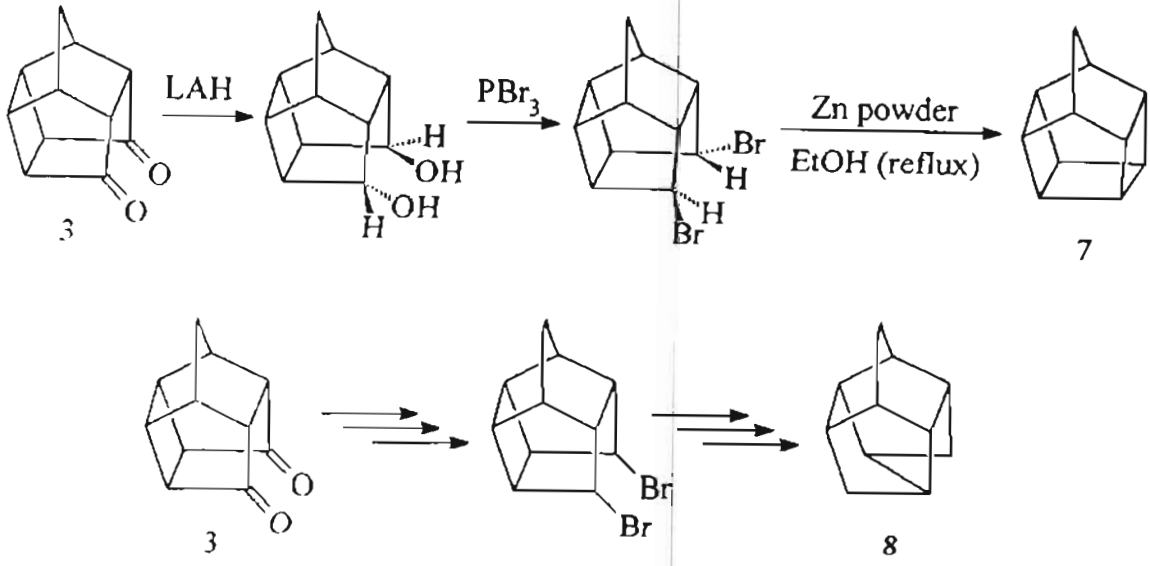
Cookson *et al.* in 1964 were the first to exploit this report.[4] Using the Diels-Alder cycloaddition method, they synthesised a large number of compounds in which the olefinic bonds were spatially oriented in such a manner that [2+2] photocycloaddition was allowed. The simplicity of their approach is best exemplified by the synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione (hereafter abbreviated as PCUD) **3**. The synthesis of the compounds **4**, **5** and **6** (among others) were also carried out by them in both solution and solid phases (Scheme II).



Scheme II

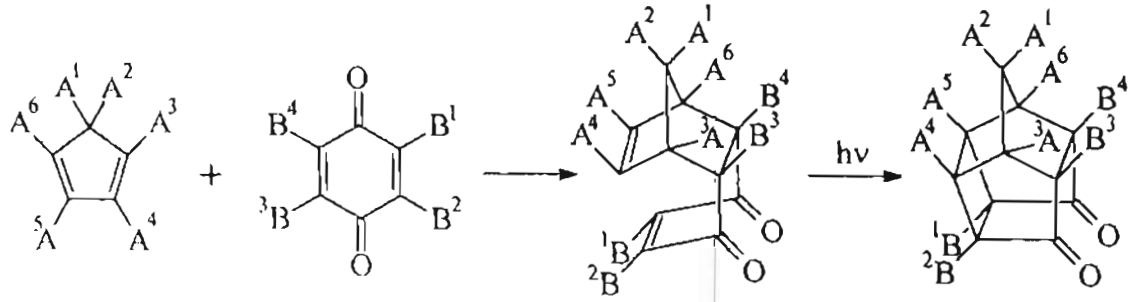
1.1 Synthesis of Substituted Pentacyclic Undecanes and Further Transformations:

One of the earliest and most interesting transformations carried out on **3** was by Underwood and Ramamoorthy in 1970. Their conversion of **3** to the highly symmetrical compounds homopentaprismane **7**[5] and trishomocubane **8**[6] (Scheme III) was carried out through reaction schemes which were the epitome of economy. Their work led to a flurry of activity in studies related to synthesis of and rearrangements involving substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione framework.

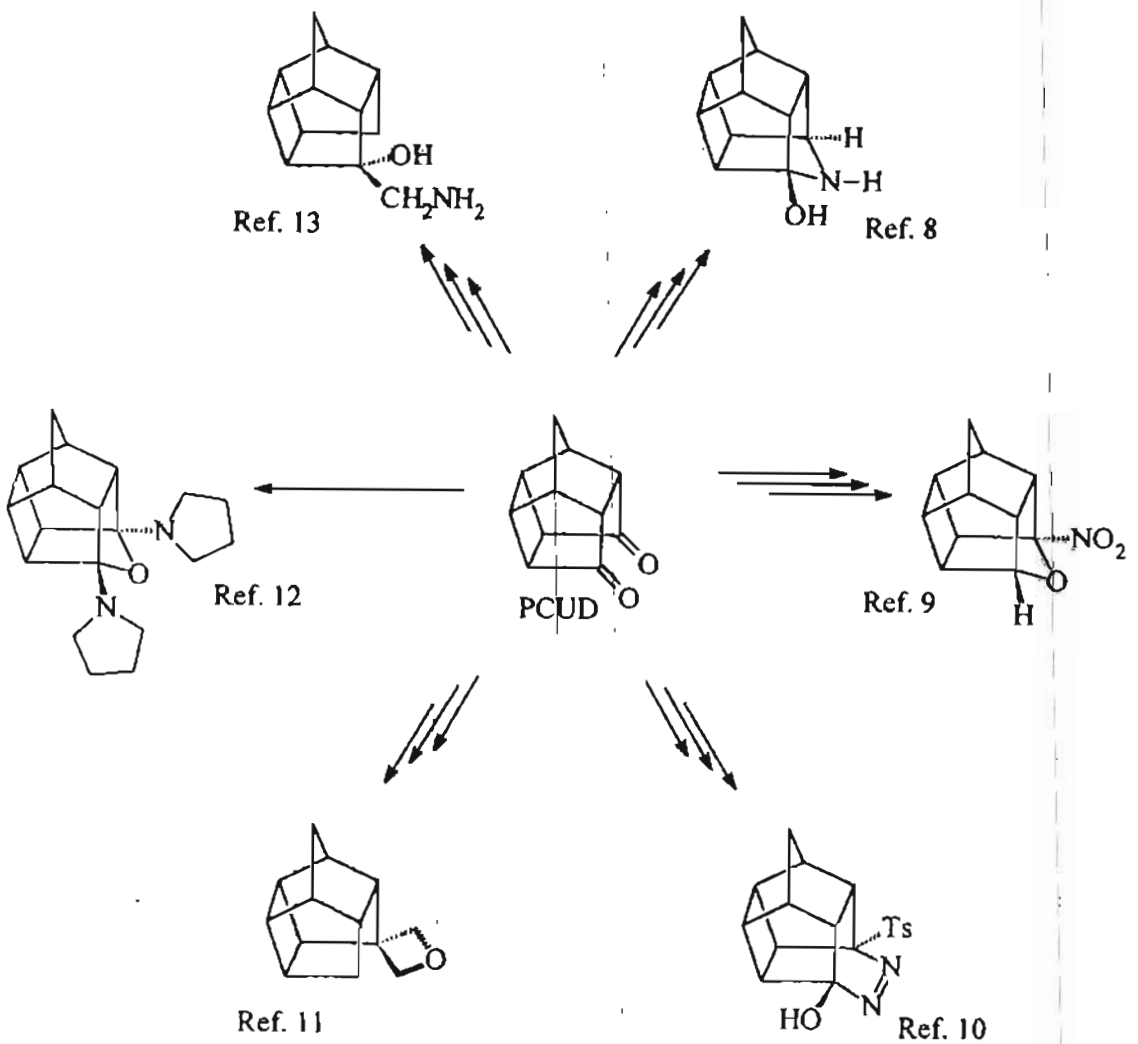


Scheme III

The field of synthesis of non-natural products now saw an explosive growth with a large number of derivatives of PCUD being prepared, especially by the groups led by Marchand and Mehta. The most popular techniques were to either start with appropriately substituted precursors for the Diels-Alder reactions, as extensively elaborated by Mehta *et al.*[7] (Scheme IV), or to use classical chemical methods to modify the functional groups on the PCUD skeleton, as exemplified by Marchand *et al.*[8-13] (Scheme V). Several interesting aspects of the work carried out by Marchand's group are elaborated in the introduction of Chapters 2, 3 and 4, and therefore, only briefly mentioned here.

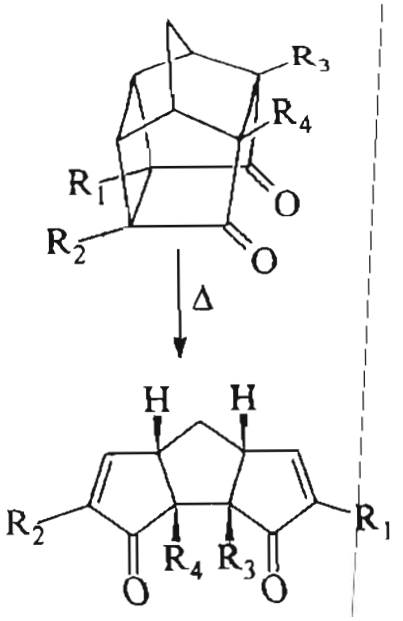


Scheme IV



Scheme V

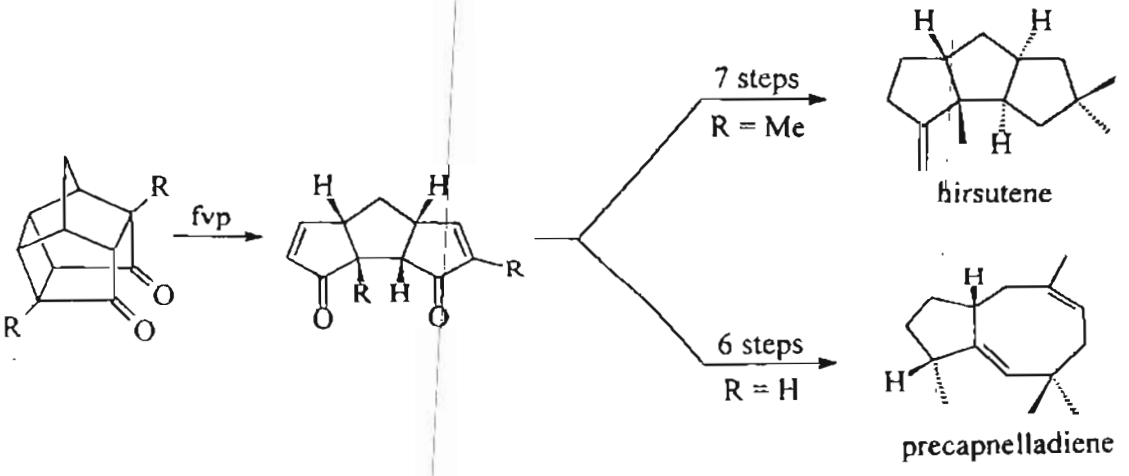
The discovery by Mehta *et al.*[14] that PCUD can be smoothly converted to the triquinane skeleton by flash vacuum pyrolysis provided them the impetus to synthesise many substituted PCUDs. This technique was used to obtain important synthetic intermediates *en route* to the natural products hirsutene, coriolin, $\Delta^{9(12)}$-capnellene, precapnelladiene and ikarugamycin (Scheme VI).[7]



$R_1=R_2=R_3=R_4=H$
$R_1=R_2=CH_3$, $R_3=R_4=H$
$R_1=R_2=Cl$, $R_3=R_4=H$
$R_1=R_4=CH_3$, $R_2=R_3=H$
$R_1=R_4=Cl$, $R_2=R_3=H$
$R_1=R_4=Br$, $R_2=R_3=H$
$R_1=R_3=Cl$, $R_2=R_4=OCH_3$
$R_1=R_4=Cl$, $R_2=R_3=OCH_3$
$R_1=R_2=R_3=R_4=Cl$
$R_1=R_2=R_3=R_4=Br$

Scheme VI

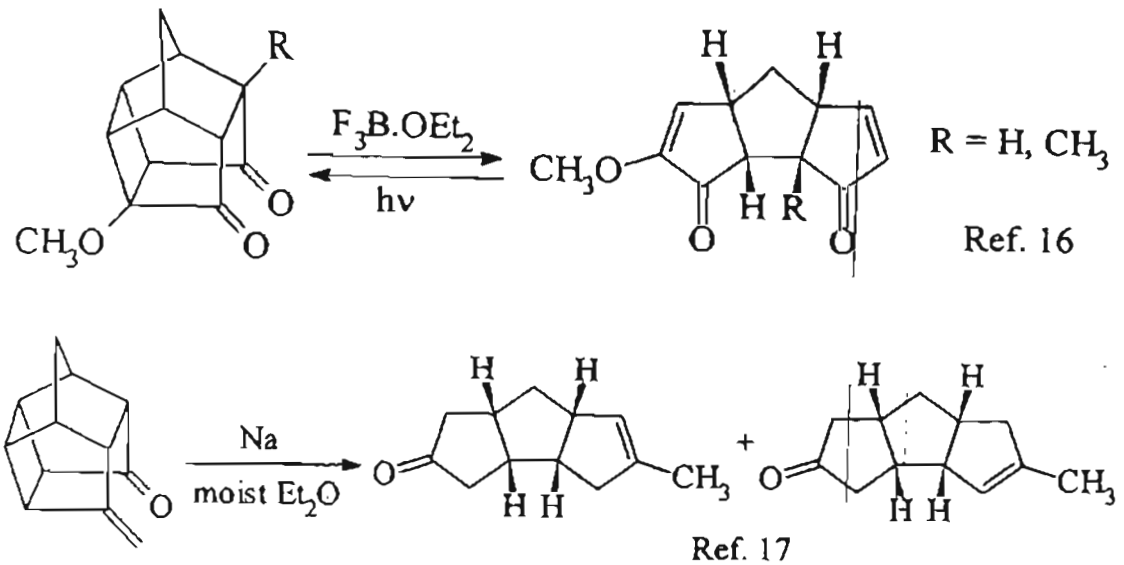
Mehta *et al.* further elaborated these intermediates to prepare hirsutene and precapnelladiene also.[15a,b] The regiospecificity and stereospecificity of the thermal and photochemical reactions leading to PCUD derivatives was exploited in the synthetic scheme in order to obtain the required placement of the various groups (Scheme VII).



Scheme VII

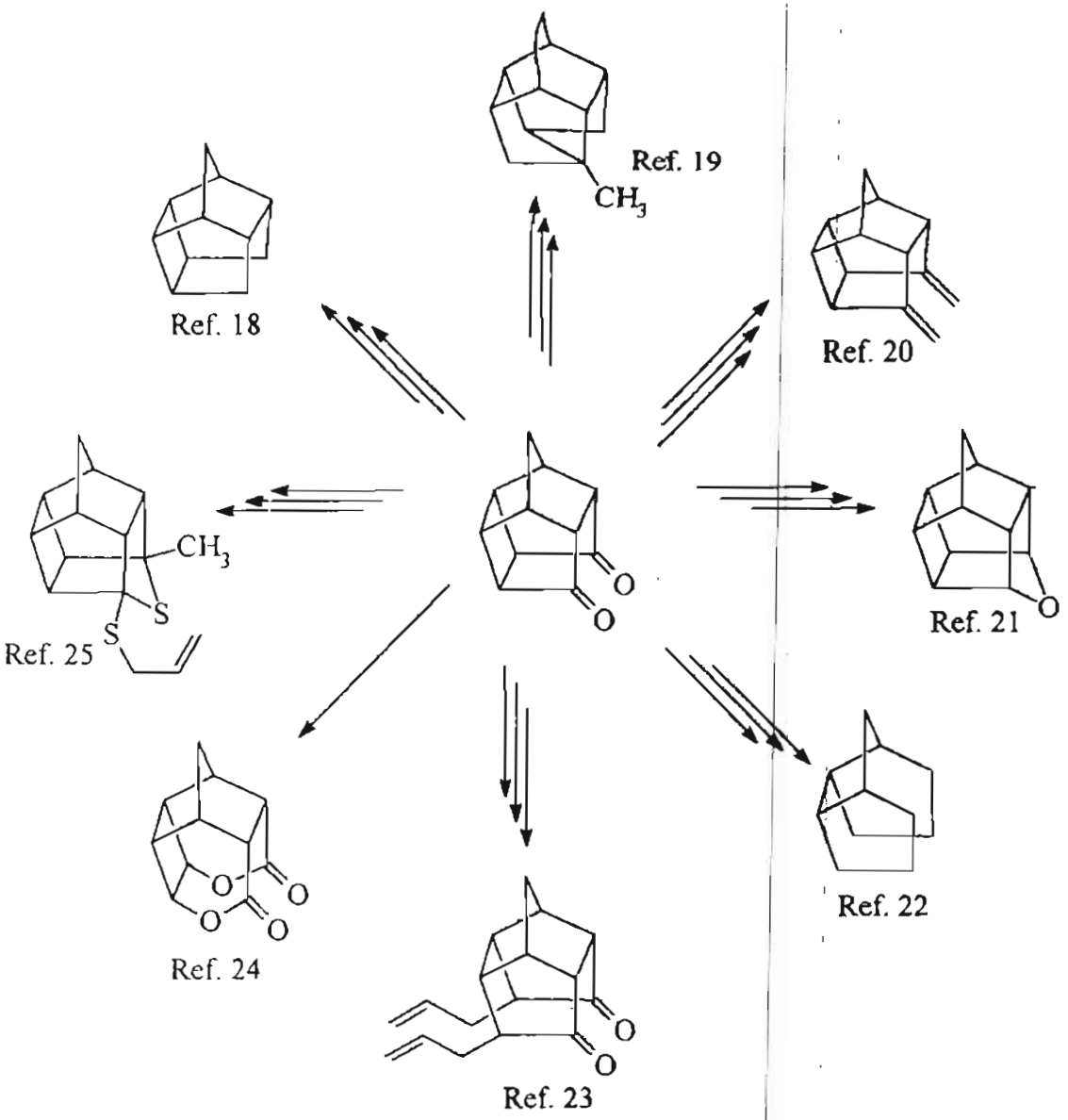
Apart from the flash vacuum pyrolysis technique for the cleavage of the strained cyclobutane ring in the pentacyclic cage, Mehta and co-workers also developed acid and base catalysis methodologies for the same.[16,17] These methods are

complementary to each other and open up many vistas for the future as they lead to differentially functionalised tricyclopentanoids (Scheme VIII).



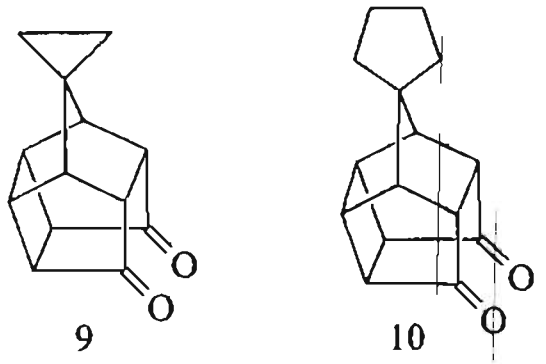
Scheme VIII

Organic chemists went on to display their ingenuity and versatility and synthesised a large number of substituted PCUDs and novel cage systems by manipulations using a variety of synthetic procedures. Some of the fascinating conversions are depicted in scheme IX.[18-25] Details of these transformations could not be included as it would necessitate extensive number of pages. Of note is a recent report in which the group led by Kotha[23] synthesised various allylated derivatives of cage compounds *via* the fragmentation methodology, the allyl group being useful for subsequent synthetic transformations.



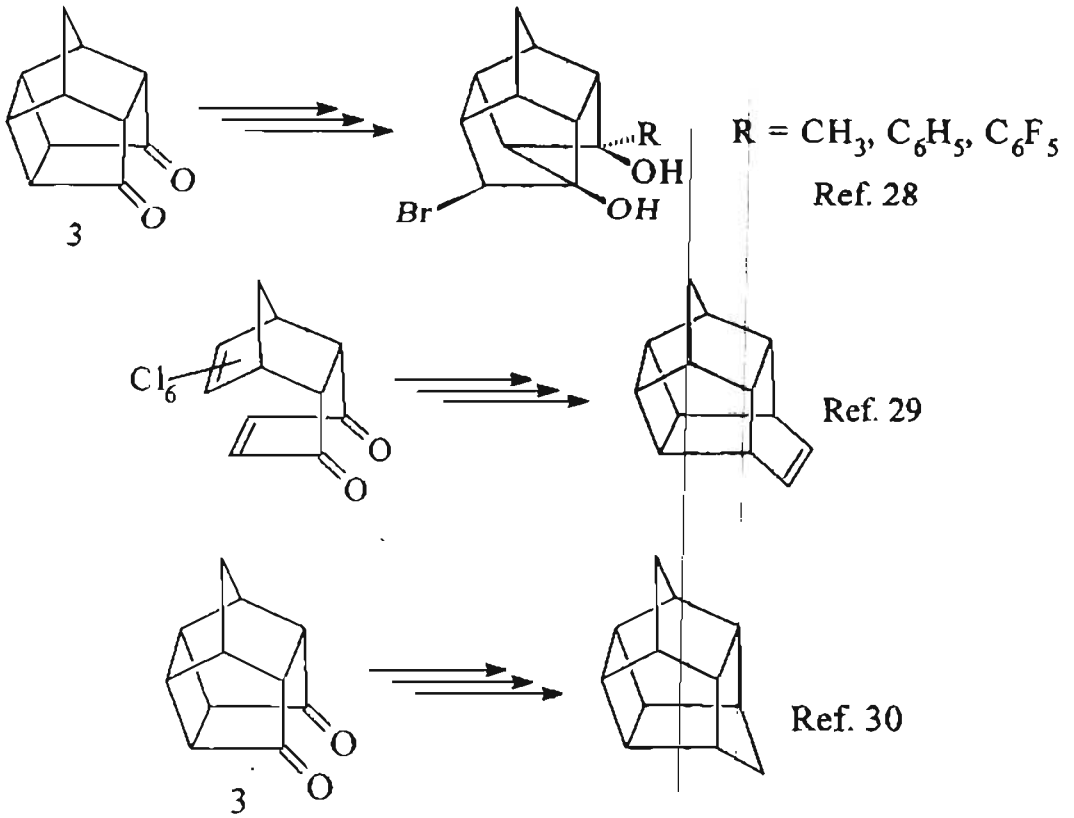
Scheme IX

Two other interesting compounds with the basic PCUD skeleton was synthesised by Singh and co-workers. These compounds **9**[26] and **10**[27] (Scheme X) had an additional ring, three- or five- membered, on the bridging methylene group on the norbornyl portion of the cage. These groups were introduced by first incorporating them on to cyclopentadiene itself.

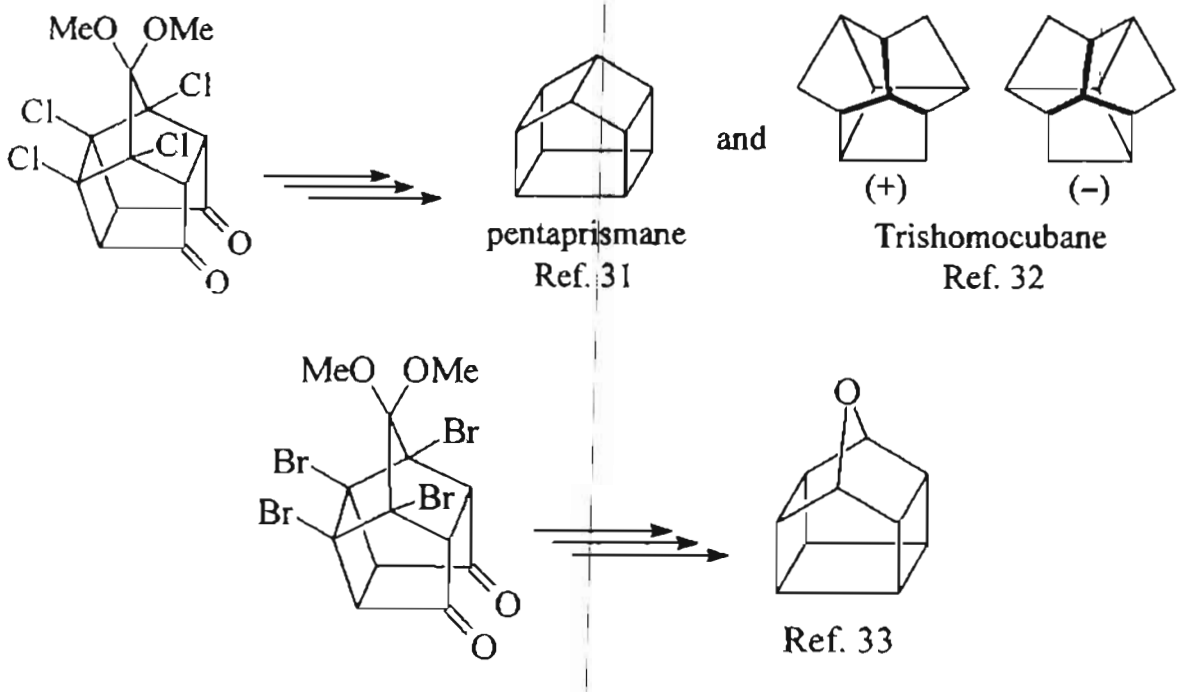


Scheme X

The standard techniques used for manipulating functional groups continue to be used for the preparation of many fascinating molecules starting from PCUD's or PCUD derivatives as shown in scheme XI. These molecules are fascinating on their own with the incredible strain inherent in some of them, as well as their aesthetic appeal arising from symmetry properties.[28-33] Of these, the most note-worthy is the synthesis of pentaprismane by Eaton.[31]

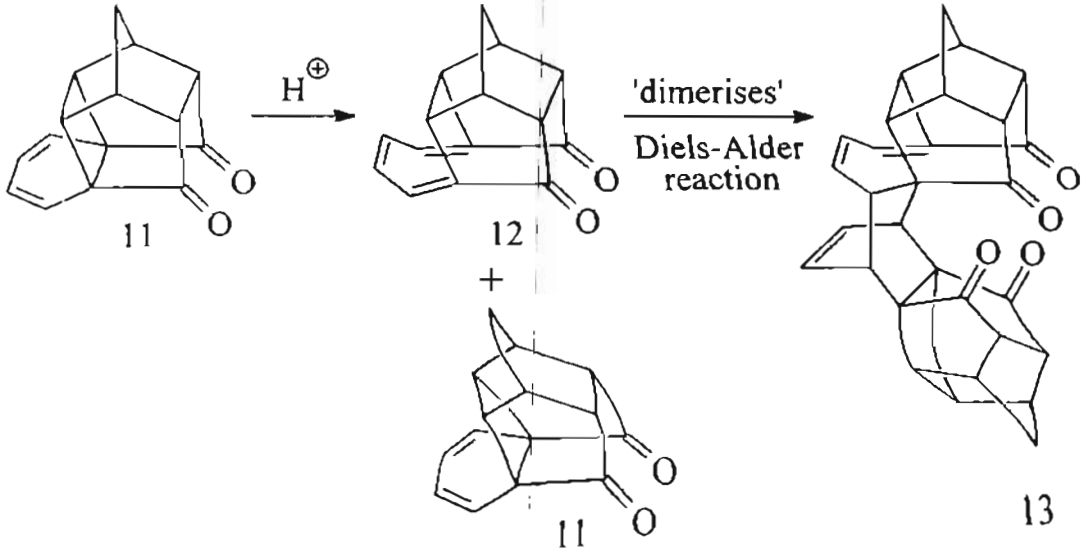


Scheme XI



Scheme XI (contd.)

The synthesis of multicage systems like **13** through an unusual dimerisation of a PCUD derivative has also been reported by Mehta *et al.*[34] In the presence of acid, the hexacyclic propellane **11** smoothly rearranges to pentacyclic triene **12** which undergoes Diels-Alder reaction with another molecule of the hexacyclic diene **11** to give **13** as shown in scheme XII.

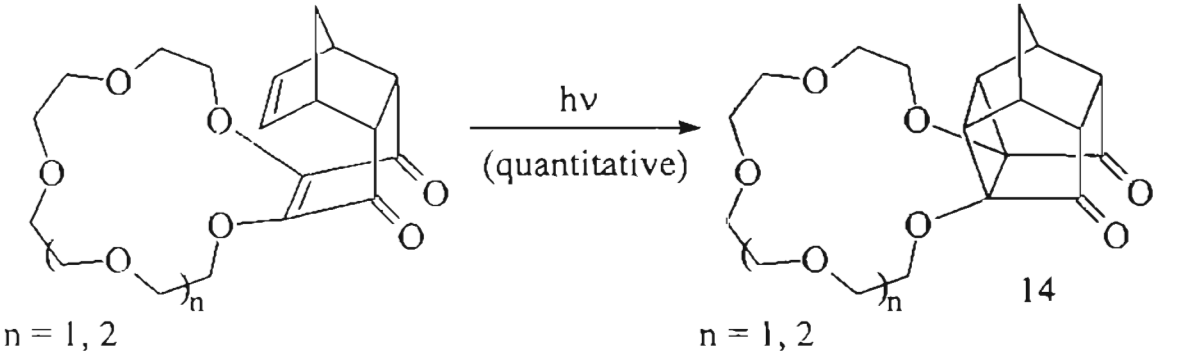


Scheme XII

1.2 Comparative Studies Using PCUD Derivatives:

Suggested uses of such cage compounds are as far reaching as medicinal applications and application as novel explosive substances. Potential medicinal applications are suggested for polycyclic compounds containing polar substituents where the combination of a hydrophobic core surrounded by hydrophilic groups render them unusual properties at cell interphases. The hydrophobicity of the hydrocarbon core allows the molecule to cross the blood-brain barrier and also cross the cell-membranes while the polar groups increase the solubility of the compound under physiological conditions.[35] This leads to the compound having more *in vivo* stability and such drugs can remain active and effective for a longer period. Another potential medicinal application that is envisaged utilises the cavity within the polycyclic cage to transport pharmacological agents across cell-membranes.

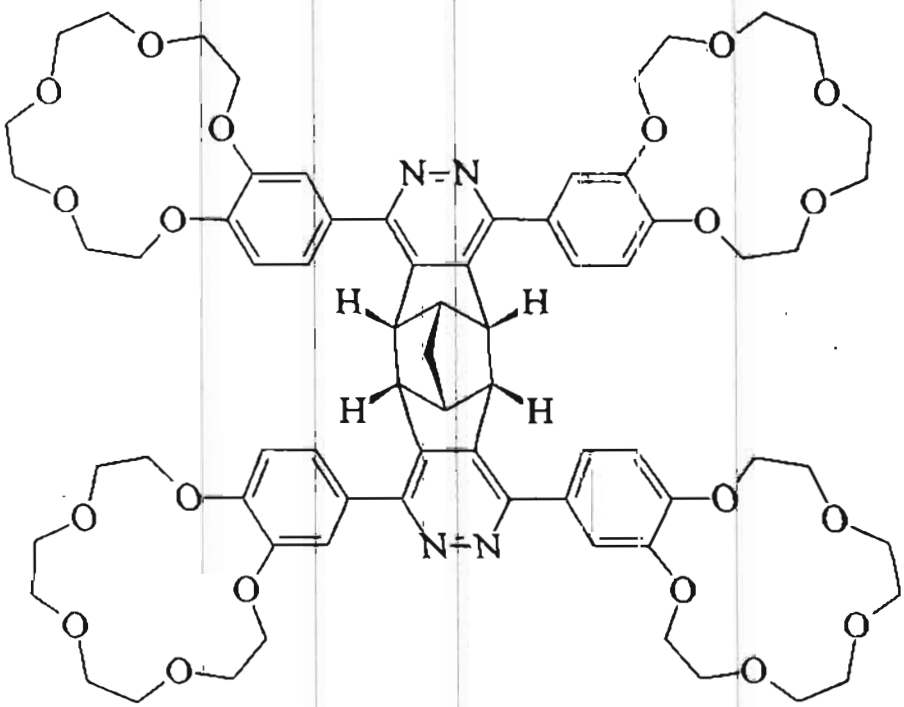
Kanematsu and co-workers have reported the linking of a crown-ether moiety to the PCUD cage in order to study the viability of a new type of ditopic host molecule **14** for amines bearing electron-donating aromatic rings such as dopamine and tryptamine (Scheme XIII).[36] It is anticipated that there will be double interaction *via* ion-binding and charge transfer complex formation. This mimics the non-covalent binding of specific substrates as seen in allosteric enzymes.



Scheme XIII

In addition to the work reported above, many other groups have been working in this area and have synthesised a number of compounds incorporating a crown-ether moiety or aza-crown ether moiety with the cage framework.[37-39] The cage framework

is used not only to fix the orientations of the crown or aza-crown ether in order to increase the affinity of these molecules for small polar entities (Scheme XIV),



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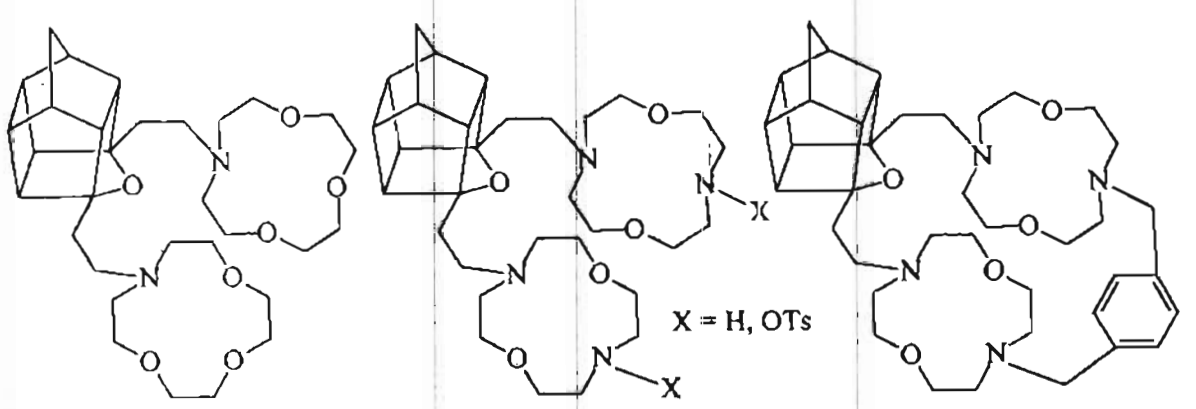
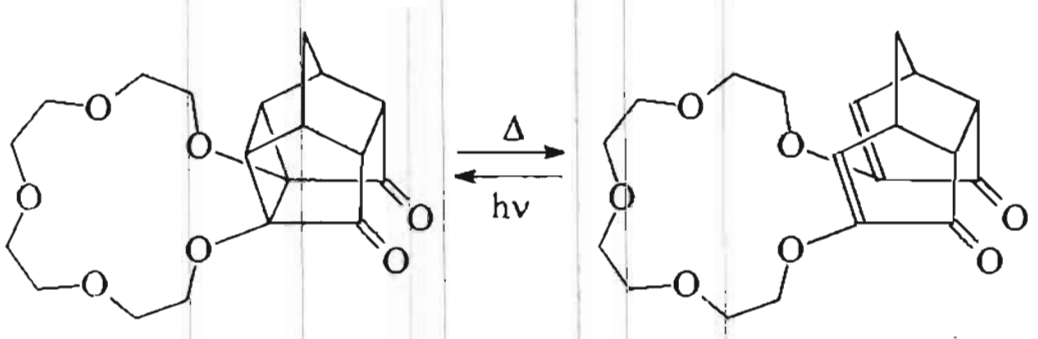


Ref. 38

Scheme XIV

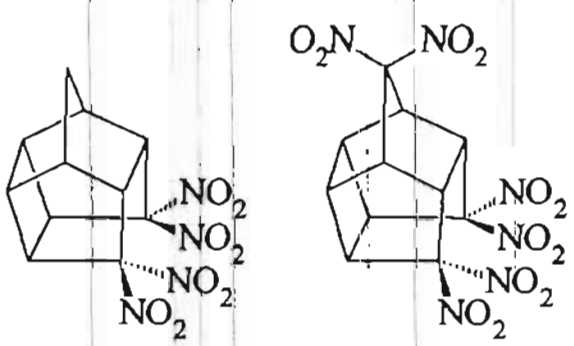
but it is also used to change the cavity size of the ether (Scheme XV). The binding ability of these molecules along with their selectivities have been studied.



Ref. 39

Scheme XV

PCUDs substituted with nitro- groups are of interest as new strained energetic materials.[40] Strain in these compounds can arise from deformations of the carbon framework that is associated with the norbornyl moiety and the cyclobutane ring as well as from the nonbonded interactions between the *endo* nitro groups. Additionally these compounds are of theoretical interest, and the cumulative effects of increasing stability and the chemical reactivity of carbocyclic cage systems have been probed through the studies of the physical and chemical properties of compounds with increasing number of nitro- substituents as in compounds **15** and **16** (Scheme XVI).[40b]

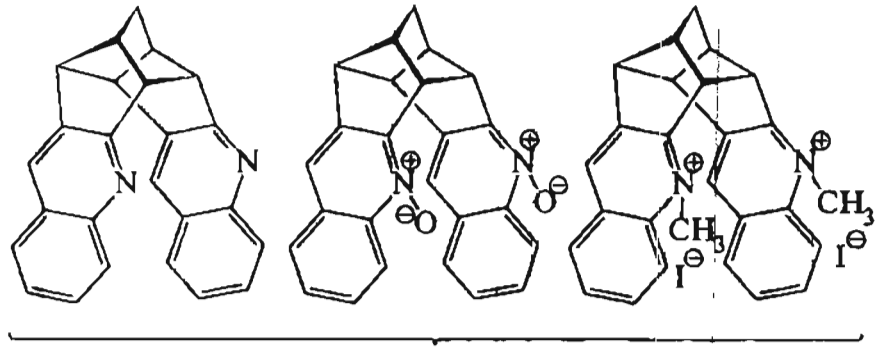


15 16

Scheme XVI

Groups led by Thummel and Marchand have been working on 'cleft' molecules such as **17**, **18** and **19** where a polyaza cavity is formed. These are synthesised through a Friedlander condensation between cage diketones and aromatic ortho-aminoaldehydes. The shape of the cavity of these 'cleft' molecules depend on the ring size of the cage diketones.[41-45] As the carbonyl groups in PCUDs are oriented in a parallel fashion, it leads to the construction of a *syn*-orthocyclophane as depicted in scheme XVII. The X-ray diffraction studies on these compounds reveal that a water

molecule is incorporated in the 'cleft'. This water molecule is hydrogen bonded to the nitrogen atoms and forms an additional bridge between the heteroaromatic rings causing them to cant slightly towards one another. A number of derivatives have been prepared in order to study the complexing ability of these compounds by varying the nature of the heteroaromatic portion of the 'cleft' molecule thereby changing the electron density of the system.[41] The juxtaposition of two aromatic rings close to one another is possible in these cases because of the rigidity of the cage framework.



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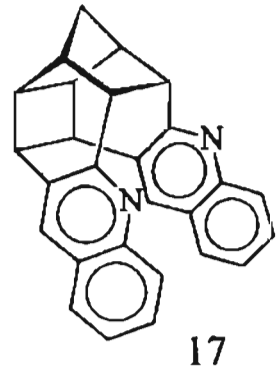

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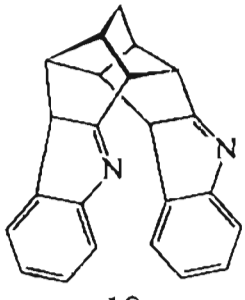
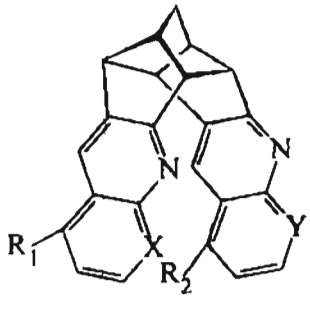


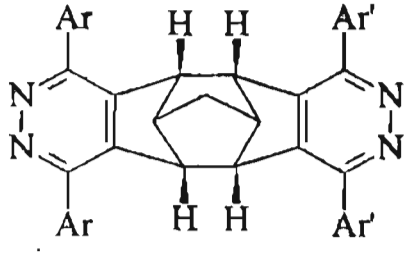
18

Ref. 43



X = Y = CH, $R_1 = R_2 = H$
X = Y = N, $R_1 = R_2 = H$
X = CH, Y = N, $R_1 = R_2 = H$
X = Y = $COCH_3$, $R_1 = R_2 = H$
X = $COCH_3$, Y = CH, $R_1 = OCH_3$, $R_2 = H$
X = Y = $COCH_3$, $R_1 = R_2 = OCH_3$

Ref. 44



Ar = Ar' = 2-pyridyl
Ar = Ar' = Ph
Ar = 2-pyridyl, Ar' = Ph

19

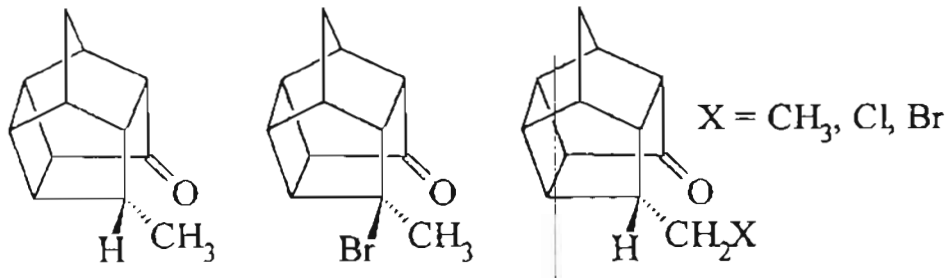
Ref. 45

Scheme XVII

1.3 PCUD Derivatives in Probing the Driving Forces in Reactions:

The strained multiple ring system in PCUD also has other advantages. Because of the rigidity, the substituent groups are held in fixed orientations and this enforced proximity can lead to unexpected effects during the course of reactions or in the physical properties of the compounds. The steric strain during the course of a reaction can also be studied by using appropriately chosen PCUDs.

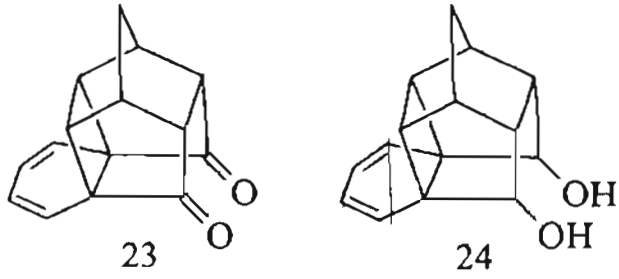
Sauers *et al.* synthesised pentacycloundecanones **20**, **21** and **22** to study hydrogen atom abstraction by photoexcited carbonyl groups (Scheme XVIII).[46] An analysis of these structures by force field calculations emphasised the proximity of the hydrogen atoms to the carbonyl group. However, these compounds were found to be inert to irradiation at 300 nm confirming the importance of stereoelectronic barriers towards hydrogen atom abstraction in the realm perpendicular to the carbonyl plane as predicted by theoretical models.



20 21 22

Scheme XVIII

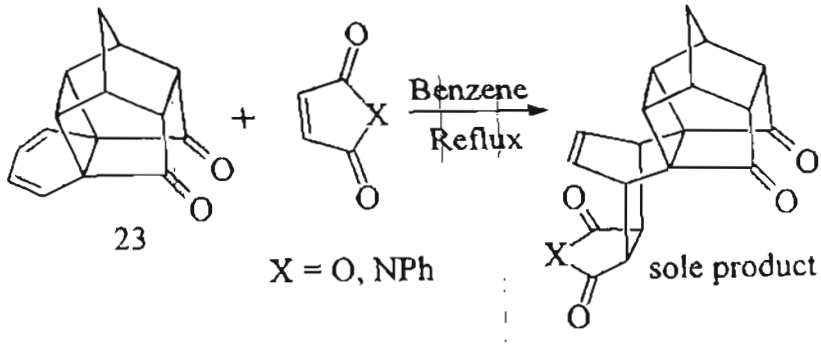
Pandey and co-workers have studied the π-facial stereoselectivity in Diels-Alder reactions of hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane-10,12-diene-2,8-dione **23** and the corresponding diol **24** (formed by the sodium borohydride reduction) (Scheme XIX).[47] Reaction with acrylonitrile, ethyl acrylate and diethyl maleate gave products arising from the addition of the dienophile away from the cyclobutane face, even though rates were slower in the reaction with the diol. This indicates that the carbonyls are not the key directing factor for the π-facial selectivity. The nonreactivity of 2-chloroacrylonitrile and [*E*]-1,2-dichloroethylene with **23** and **24** indicates the development of considerable steric repulsion between the hydrogens on the diene and the C-Cl bond in the dienophile in the transition state.



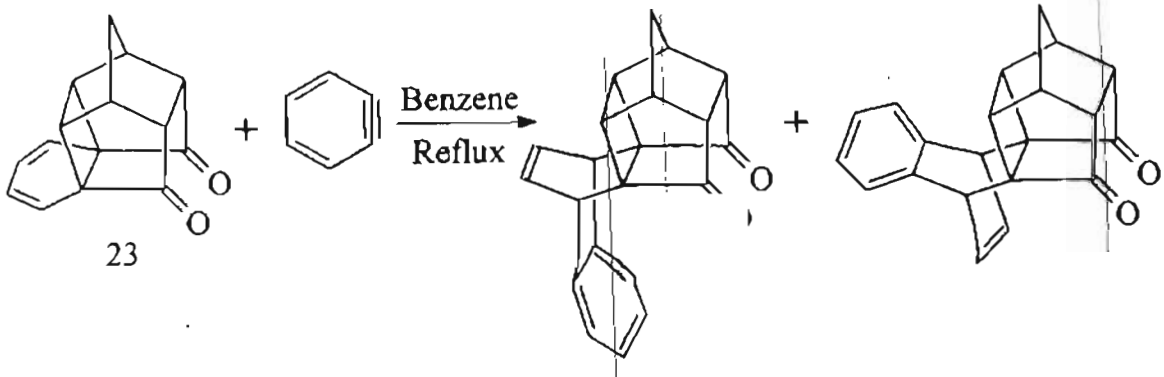
23 24

Scheme XIX

A similar study was carried out by the group led by Coxon and Steel in which they concluded that olefinic dienophiles reacts with the diene hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane-10,12-diene-2,8-dione **23** with exclusive attack on the carbonyl-bearing face of the diene while the dienophiles like benzyne, acetylenes and azo compounds lead to mixed selectivity as seen in scheme XX.[48] The lack of selectivity in the latter cases is attributed to the higher reactivity of these dienophiles as well as a balancing effect of steric factors and non-bonding interactions with the carbonyl groups.



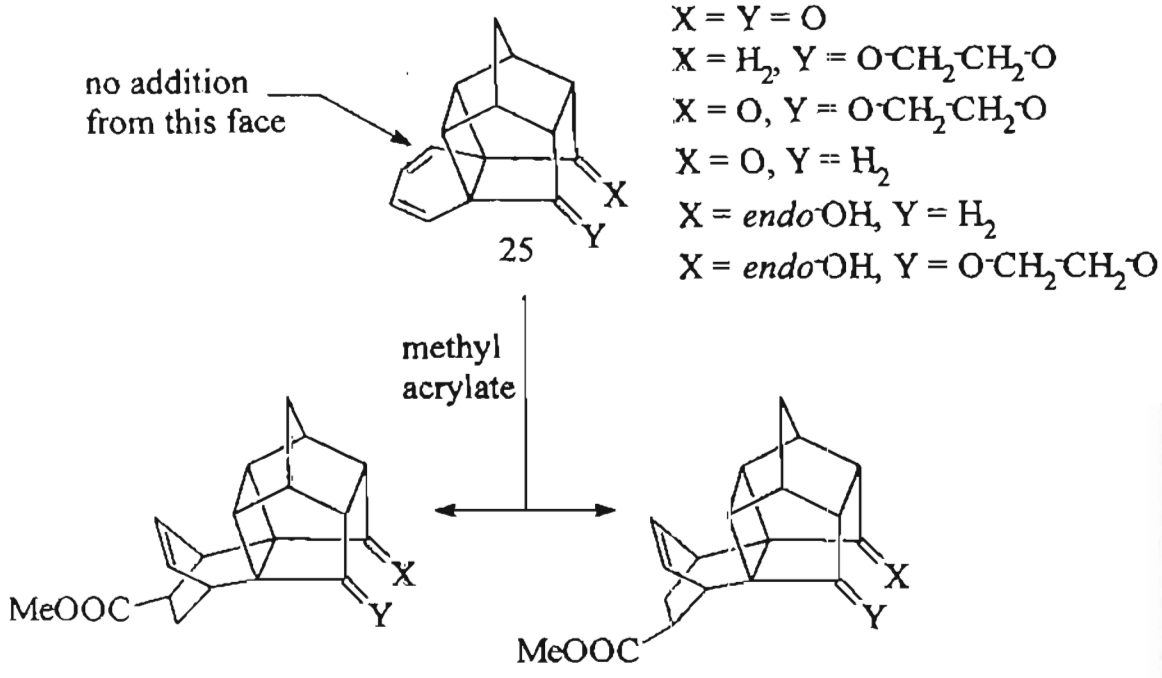
23 X = O, NPh sole product



23

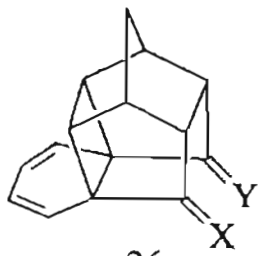
Scheme XX

The diastereofacial selectivity in the addition of methyl acrylate to various unsymmetrical derivatives of the hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane **25** has also been reported.[49] The study reveals that there is high π-facial selectivity with no addition taking place from the cyclobutane face while there is only a moderate level of regioselectivity (Scheme XXI). This has been further studied using theoretical models and the moderate level of regioselectivity has been attributed to the small energy differences in the balance of electrostatic and steric factors.

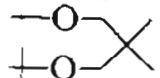
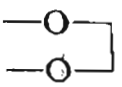


Scheme XXI

Mehta and Uma have studied the diastereofacial control in the addition of singlet oxygen, dimethyl acetylenedicarboxylate and maleic anhydride on other derivatives of hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane **26** (Scheme XXII) and found that the addition of DMAD and singlet oxygen is preferred from the cyclobutane face in the presence of distal protecting groups.[50] They propose that this reflects the effect of subtle variations in the positioning of the oxygen atoms on the extent of repulsive interactions.

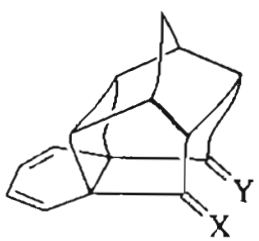


26

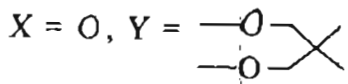
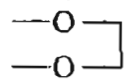
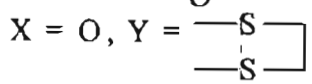
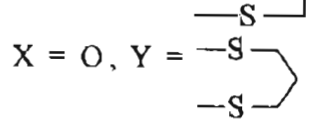
X = Y = O
X = H_2, Y = O-CH_2-CH_2-O
X = O, Y = O-CH_2-CH_2-O
X = O, Y = 
X = O, Y = $(OMe)_2$
X = Y = 

Scheme XXII

The same investigators have extended this study and investigated the stereodirecting influence of distal protecting groups to many more derivatives of **26** (Scheme XXIII).[51] They concluded that in the addition to the cyclobutane face by singlet oxygen, *N*-phenyl-1,2,4-triazolinedione (PTAD), dimethyl acetylenedicarboxylate (DMAD), maleic anhydride (MA) and *N*-methylmaleimide (NMM), the predominant directing effect may be the unfavourable nonbonded interactions between the heteroatoms and the filled orbitals in the dienophiles. The selection of the dienophiles was done so as to encompass the following intrinsic factors, *viz.*, (i) MA and NMM have two olefinic protons to induce a steric bias, (ii) DMAD has a filled π-orbital and (iii) singlet oxygen and PTAD are heterodienophiles with filled *n*-orbitals.

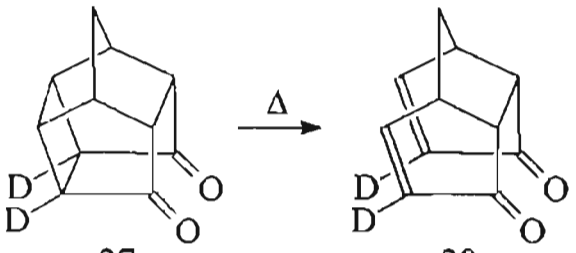


26

X = Y = O
X = H_2, Y = O-CH_2-CH_2-O
X = O, Y = O-CH_2-CH_2-O
X = O, Y = 
X = O, Y = $(OMe)_2$
X = Y = 
X = O, Y = 
X = O, Y = 

Scheme XXIII

Other comparitive studies look into the cycloreversion of PCUD derivatives to give tricyclic derivatives. The group led by Kanematsu has studied the thermal [2 + 2]cycloreversion of **27** to **28** and observed that the increased rate for the –OMe substituted compound is due to the capto-dative substituent effects of the –OMe group and to through-bond interactions (Scheme XXIV).[52]



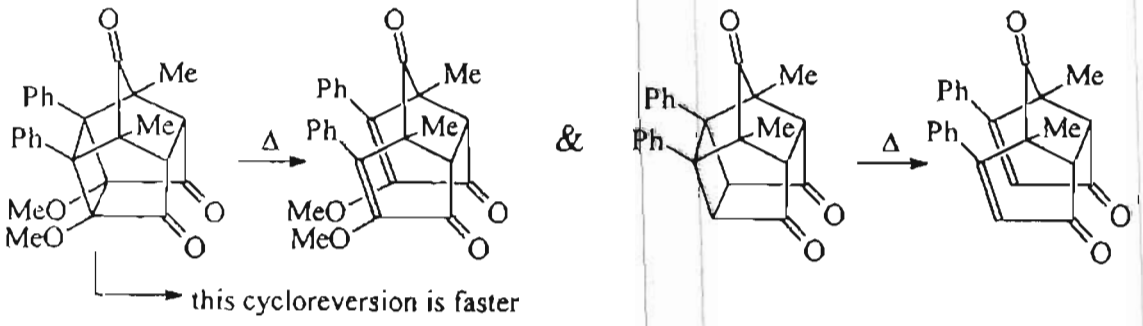
27 28

(fastest when D = OMe)

Temperatures - D = OMe, 85 °C
D = Me, 249 °C
D = H, 261 °C

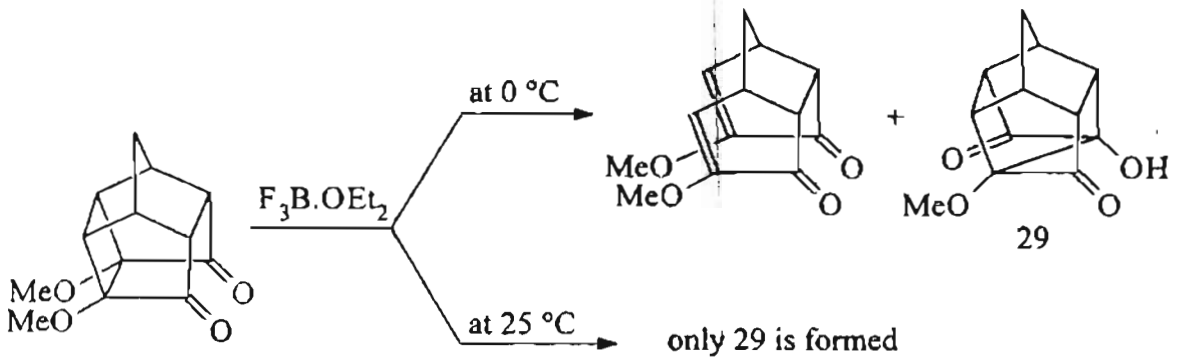
Scheme XXIV

The effect of the methoxy group in dramatically increasing the rate of the reaction is attributed to the enhanced through-bond interaction between the lone-pair electrons, thus leading to the lengthening of the cyclobutane C-C bond which facilitates the bond cleavage.[52] This is again seen in the two examples depicted below in scheme XXV.



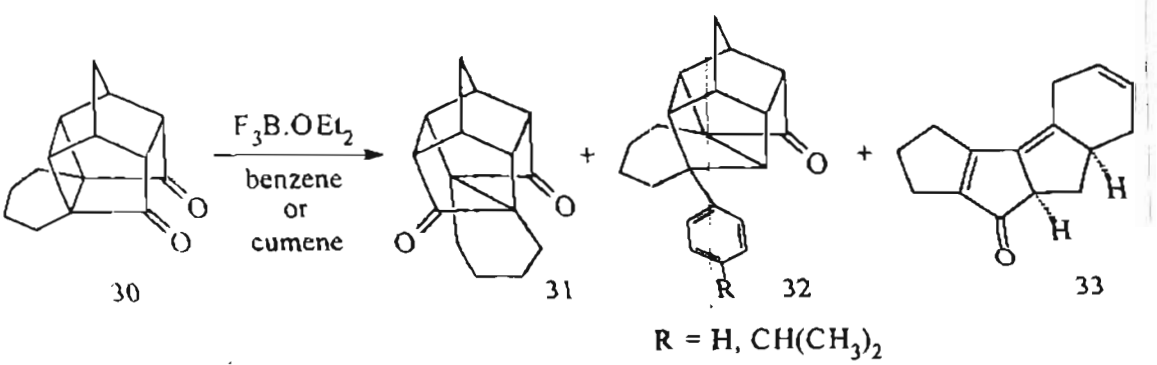
Scheme XXV

A related study by Kanematsu *et al.* of the acid-catalysed cycloreversion revealed the competitive rearrangement which also takes place.[53] At higher temperatures, the rearranged trishomocubane derivative **29** is obtained exclusively as shown in scheme XXVI. This difference in product distribution is attributed to the formation of the thermodynamically more stable trishomocubane derivative at higher temperatures.



Scheme XXVI

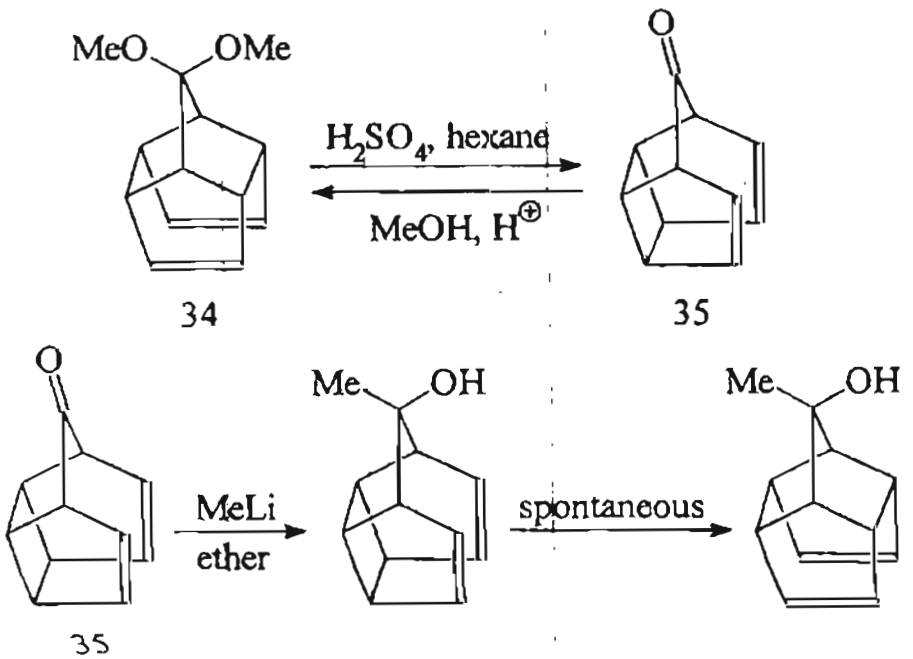
Mehta and co-workers have reported the formation of novel polyquinanes from a caged propellane system **30** under Lewis acid catalysed conditions.[54] The formation of the hexacyclic[4.3.3]propellane **31** in scheme XXVII could be rationalised in terms of a Cargill-type rearrangement in which the driving force for the reaction is the ring expansion of the cyclobutylcarbinyl cation. The second product **32** was formed by tandem reduction and dehydration; when the reaction was carried out in cumene, that was incorporated into the product with no change in the product distribution implying that the source of hydrogen atoms is internal. The formation of the last product **33** is probably *via* a fragmentation-recyclisation pathway. This report once again emphasises the special forces acting upon the cage systems which leads to unexpected products.



Scheme XXVII

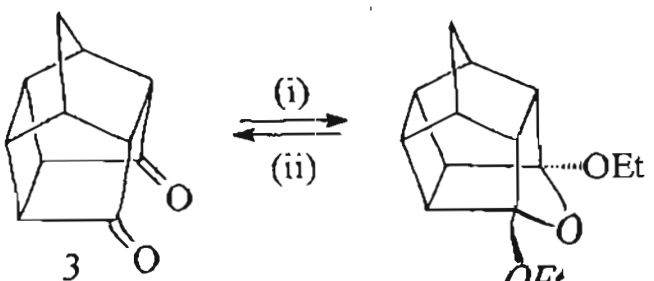
Eaton and Yip have reported a fascinating study into the interconversion of tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undeca-2,6-diene **34** and tetracyclo[7.2.0.0^{4,11}.$0^{6,10}$]undeca-2,7-diene **35** ring systems (Scheme XXVIII).[55] They report that the first ever isolation

of the [7.2.0.$0^{4,11}$.$0^{6,10}$] ring system which is seen in **35** was possible due to the change in the hybridisation of the bridging carbon from sp^3 to sp^2. This paper reveals the often subtle effects that govern the formation and reactions of polycyclic cage compounds.



Scheme XXVIII

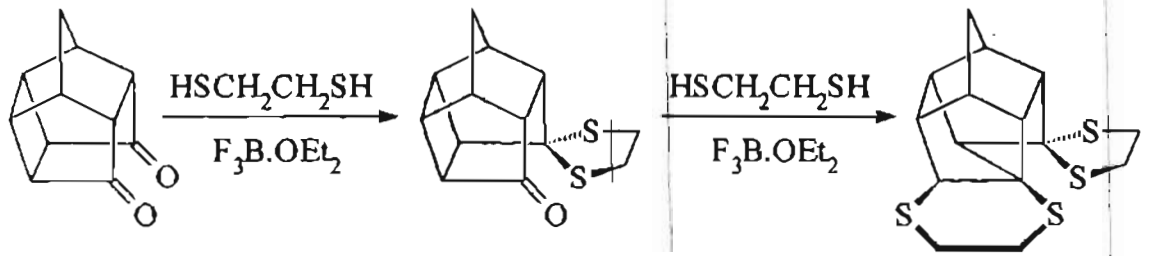
Kotha and Chakraborty have described a protection and deprotection methodology for PCUD **3** which is unique in the usage of tetrachlorosilane (TCS) as a reagent in both the steps under slightly different conditions (Scheme XXIX).[56] This protection strategy is only possible due to the nature of the orientation of the carbonyl groups in PCUD.



(i) TCS / EtOH
(ii) TCS, NaI

Scheme XXIX

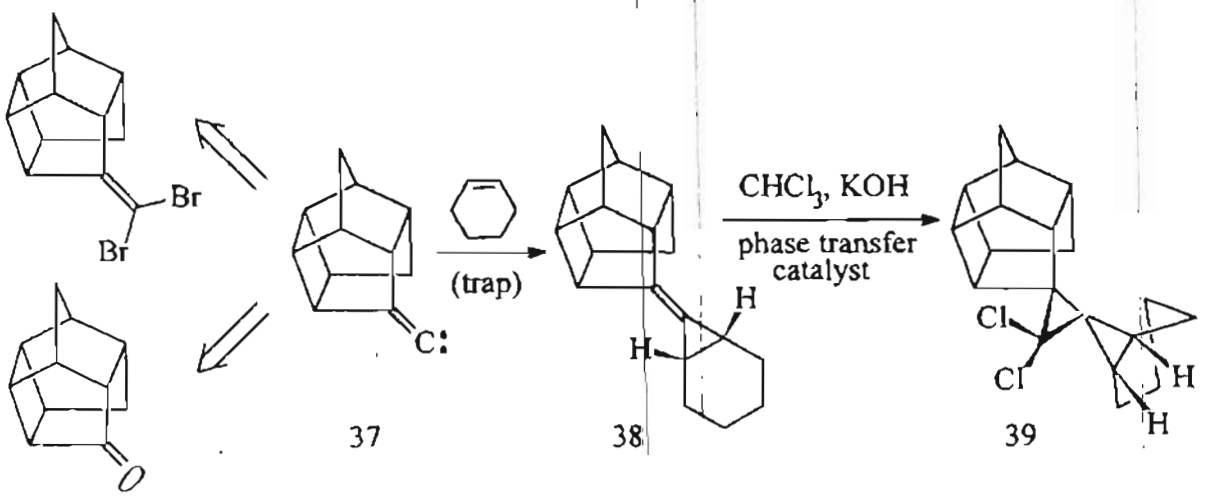
Mlinaric-Majerski and co-workers have reported another thermodynamic rearrangement of the PCUD skeleton 3 on reaction with ethanedithiol in the presence of a Lewis acid (Scheme XXX).[57] The relief of steric strain is proposed to be the driving force for the formation of the product **36** which is a trishomocubane derivative, the parent hydrocarbon having been shown to be the pentacyclic $C_{11}H_{14}$ 'stabilomer'.



3 36

Scheme XXX

Another unexpected result is seen in the case of a caged cyclopentylidenecarbene **37** which contains diastereotopically differentiated π-faces. This vinylidenecarbene is trapped by the addition of cyclohexene from the more highly sterically congested *endo* face of the π-system in the carbene.[58] The cycloadduct **38** was further reacted with dichlorocarbene and the resulting product **39** was established by X-ray crystal studies (Scheme XXXI). Marchand *et al.*, who made the above observation, have not been able to explain this stereopreference.



37 38 39

Scheme XXXI

In the preceding pages, a very brief attempt has been made to convey the magic of polycyclic cage compounds and their myriad uses and applications. Even this manages to convey the vast potential of the field and the many areas and courses that remain to be charted. The work carried out during this Ph. D. programme is an attempt to explore and explain some of the complexities of polycyclic cage compounds. In each of the chapters that follow, a brief introduction outlines the area in which work has been carried out and the rationale behind the selection of that particular problem.

1.4 References:

1. Marchand, A. P. *Advances in Theoretically Interesting Molecules*, Thummel, R. P., Ed., JAI : Greenwich, CT, **1989** Vol. 1, 357-399, and the references cited therein.
2. Marchand, A. P. *Aldrichimica Acta* **1995**, *28*, 95-104, and the references cited therein.
3. Cristol, S. J.; Snell, R. L. *J. Am. Chem. Soc.* **1954**, *76*, 5000-5000.
4. Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062-3075.
5. Underwood, G. R.; Ramamoorthy, B. *J. Chem. Soc., Chem. Commun.* **1970**, 12-14.
6. Underwood, G. R.; Ramamoorthy, B. *Tetrahedron Lett.* **1970**, 4125-4127.
7. Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543-4559.
8. Marchand, A. P.; Dave, P. R.; Satyanarayana, N.; Arney, Jr., B. E. *J. Org. Chem.* **1988**, *53*, 1088-1092.
9. Marchand, A. P.; Arney, Jr., B. E.; Dave, P. R.; Satyanarayana, N.; Watson, W. H.; Nagl, A. *J. Org. Chem.* **1988**, *53*, 2644-2647.
10. Marchand, A. P.; Reddy, G. M.; Watson, W. H.; Kashyap, R. P.; Nagl, A. *J. Org. Chem.* **1991**, *56*, 277-282.

11. Marchand, A. P.; Vidyasagar, V.; Ren, C.-L.; Sherrod, M. J.; Watson, W. H.; Krawiec, M. *Tetrahedron Lett.* **1992**, *33*, 3983-3986.
12. Bott, S. G.; Marchand, A. P.; Kumar, K. A.; Vidyanand, D.; Xing, D.; Watson, W. H.; Kashyap, R. P.; Sachleben, R. A. *Journal of Chemical Crystallography* **1995**, *25*, 633-640.
13. Marchand, A. P.; Aavula, B. R.; Bott, S. G. *Tetrahedron* **1998**, *54*, 5105-5118.
14. Mehta, G.; Reddy, A. V.; Srikrishna, A. *Tetrahedron Lett.* **1979**, 4863-4866.
15. a) Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756-757.
    b) Mehta, G.; Murty, A. N. *J. Chem. Soc., Chem. Commun.* **1984**, 1058-1060.
16. Mehta, G.; Reddy, D. S.; Reddy, A. V. *Tetrahedron Lett.* **1984**, *25*, 2275-2278.
17. Mehta, G.; Rao, K. S.; Marchand, A. P.; Kaya, R. *J. Org. Chem.* **1984**, *49*, 3848-3852.
18. Marchand, A. P.; Chou, T.-C.; Ekstrand, J. D.; van der Helm, D. *J. Org. Chem.* **1976**, *41*, 1438-1444.
19. Dekker, T. G.; Oliver, D. W.; Venter, A. *Tetrahedron Lett.* **1980**, *21*, 3101-3104.
20. Shen, K.-w.; Kuebler, N. A. *Tetrahedron Lett.* **1973**, 2145-2148.
21. Sasaki, T.; Eguchi, S.; Kiriyama, T.; Hiroaki, O. *Tetrahedron* **1974**, *30*, 2707-2712.
22. Marchand, A. P.; Chou, T.-C.; Barfield, M. *Tetrahedron Lett.* **1975**, 3359-3362.
23. Kotha, S.; Manivannan, E.; Sreenivasachary, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2845-2848.
24. Surapaneni, C. R.; Gilardi, R. *J. Org. Chem.* **1986**, *51*, 2382-2385.
25. Marchand, A. P.; Kaya, R.; Muchmore, S. W.; van der Helm, D. *J. Org. Chem.* **1986**, *51*, 825-829.
26. Singh, V. K.; Raju, B. N. S.; Deota, P. T. *Synth. Commun.* **1986**, *16*, 1731-1735.
27. Singh, V. K.; Deota, P. T.; Raju, B. N. S. *Synth. Commun.* **1987**, *17*, 593-599.
28. Aleksandrov, A. M.; Bourne, S. A.; Krawiec, M.; Pehk, T. J.; Petrenko, A. E.; Watson, W. H. *Tetrahedron* **1994**, *50*, 8597-8602.

29. Chow, T. J.; Chao, Y.-S. *Synth. Commun.* **1988**, *18*, 1875-1881.
30. Marchand, A. P.; Wu, A.-h. *J. Org. Chem.* **1986**, *51*, 1897-1900.
31. Eaton, P. E.; Or, Y. S.; Branca, S. J.; Shankar, B. K. R. *Tetrahedron* **1986**, *42*, 1621-1631.
32. Fessner, W.-D.; Prinzbach, H. *Tetrahedron* **1986**, *42*, 1797-1803.
33. Hirao, K.-i.; Kajikawa, Y.; Yonemitsu, O. *Heterocycles* **1982**, *17*, 63-66.
34. Mehta, G.; Singh, V.; Srikrishna, A.; Cameron, T. S.; Chan, C. *Tetrahedron Lett.* **1979**, 4595-4598.
35. Schwab, R. S.; England, Jr., A. C.; Poskanzer, D. C.; Young, R. R. *J. Am Med. Assoc.* **1969**, *208*, 1168-1170.
36. Hayakawa, K.; Kido, K.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 511-519.
37. Marchand, A. P.; Reddy, G. M.; Zaragoza, F.; Bartsch, R. A.; Eley, M. D. *Tetrahedron Lett.* **1993**, *34*, 5377-5380.
38. Marchand, A. P.; McKim, A. S.; Kumar, K. A. *Tetrahedron* **1998**, *54*, 13421-13426.
39. Hayakawa, K.; Naito, R.; Kanematsu, K. *Heterocycles* **1988**, *27*, 2293-2296.
40. a) Marchand, A. P.; Arney, Jr., B. E.; Dave, P. R. *J. Org. Chem.* **1988**, *53*, 443-446.
    b) Marchand, A. P.; Dave, P. R.; Rajapaksa, D.; Arney, Jr., B. E.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. *J. Org. Chem.* **1989**, *54*, 1769-1771.
41. Thummel, R. P.; Lim, J.-L. *Tetrahedron Lett.* **1987**, 28, 3319-3322.
42. Marchand, A. P.; Annapurna P.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. *Tetrahedron Lett.* **1988**, *29*, 6681-6684.
43. Thummel, R. P.; Hegde, V. *J. Org. Chem.* **1989**, *54*, 1720-1725.
44. Lim, J.-L.; Chirayil, S.; Thummel, R. P. *J. Org. Chem.* **1991**, *56*, 1492-1500.
45. Haddadin, M. J.; Wang, Y.; Frenkel, S.; Bott, S. G.; Yang, L.; Braterman, P. S.; Carvallo, C.; Marchand, A. P.; Watson, W. H.; Kashyap, R. P.; Krawiec, M.; Bourne, S. A. *Heterocycles* **1994**, *37*, 869-882.
46. Sauers, R. R.; Scimone, A.; Sharns, H. *J. Org. Chem.* **1988**, *53*, 6084-6089.

47. Pandey, B.; Zope, U. R.; Ayyangar, N. R. *Synth. Commun.* **1989**, *19*, 585-596.
48. Coxon, J. M.; O'Connell, M. J.; Steel, P. J. *J. Org. Chem.* **1987**, *52*, 4726-4732.
49. Coxon, J. M.; Fong, S. T.; Lundie, K.; McDonald, D. Q.; Steel, P. J.; Marchand, A. P.; Zaragoza, F.; Zope, U. R.; Rajagopal, D.; Bott, S. G.; Watson, W. H.; Kashyap, R. P. *Tetrahedron* **1994**, *50*, 13037-13048.
50. Mehta, G.; Uma, R. *Tetrahedron Lett.* **1995**, *36*, 4873-4876.
51. Mehta, G.; Uma, R. *J. Org. Chem.* **2000**, *65*, 1685-1696.
52. Okamoto, Y.; Kanematsu, K.; Fujiyoshi, T.; Osawa, E. *Tetrahedron Lett.* **1983**, *24*, 5645-5648.
53. Okamoto, Y.; Senokuchi, K.; Kanematsu, K. *Chem. Pharm. Bull.* **1985**, *33*, 3074-3076.
54. Mehta, G.; Srikrishna, A.; Rao, K. S.; Reddy, K. R.; Acharya, K. A.; Puranik, V. G.; Tavale, S. S.; Row, T. N. G. *J. Org. Chem.* **1987**, *52*, 457-460.
55. Eaton, P. E.; Yip, Y. C. *Synlett* **1993**, 73-74.
56. Kotha, S.; Chakraborty, K. *Ind. J. Chem.* **2000**, *39B*, 382-383.
57. Mlinaric-Majerski, K.; Veljkovic, J.; Marchand, A. P.; Ganguly, B. *Tetrahedron* **1998**, *54*, 11381-11386.
58. Marchand, A. P.; Kumar, K. A.; Rajagopal, D.; Eckrich, R.; Bott, S. G. *Tetrahedron Lett.* **1996**, *37*, 467-470.

CHAPTER 2 – THE SYNTHESIS OF VARIOUS TETRA- AND PENTACYCLIC CAGE COMPOUNDS

The synthesis and exploration of the chemistry of novel polycyclic cage compounds have been the aim of many research groups for several decades. A few prominent examples have already been discussed in the introductory chapter. This chapter focuses on the synthesis of tetracyclo- and pentacyclo- cage compounds and rearrangements that take place due to the presence of different functional groups on the skeleton leading to novel and unanticipated products.

Rigid cage molecules have proved to be valuable substrates for the study of organic reaction mechanisms. Compounds of this type have marked advantages over conformationally mobile molecules. As reaction centres in rigid molecules are fixed with respect to the remainder of the molecular skeleton, perturbations due to conformational changes are effectively diminished or removed in such systems. This greatly simplifies the understanding of many reaction mechanisms and permits analysis of structure-reactivity relationships.

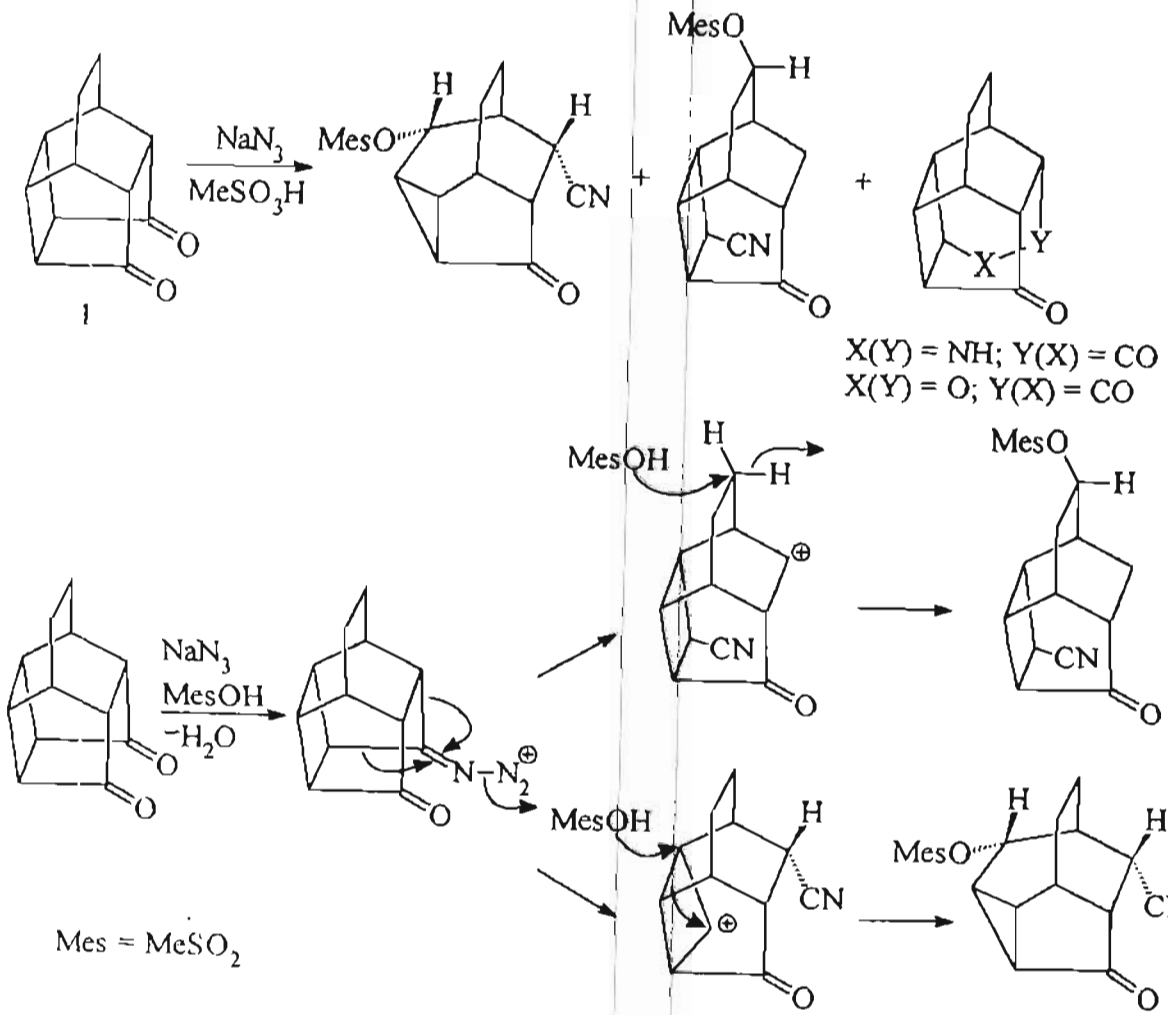
Apart from mechanistic studies, synthetic organic chemists have also taken advantage of the potential interaction between two reactive centres in conformationally restricted molecules to synthesise polycyclic compounds of great rigidity and often of high symmetry. Such compounds often result from transannular ring closure. Also, molecular rearrangements in polycyclic cage compounds occur in highly unexpected fashion because of the proximity effects leading to unusual products.

2.1 Introduction:

As has been elaborated in the first chapter of this thesis, a great many derivatives of pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione, commonly called Cookson's dione (abbreviated as PCUD) have been prepared. All these compounds,

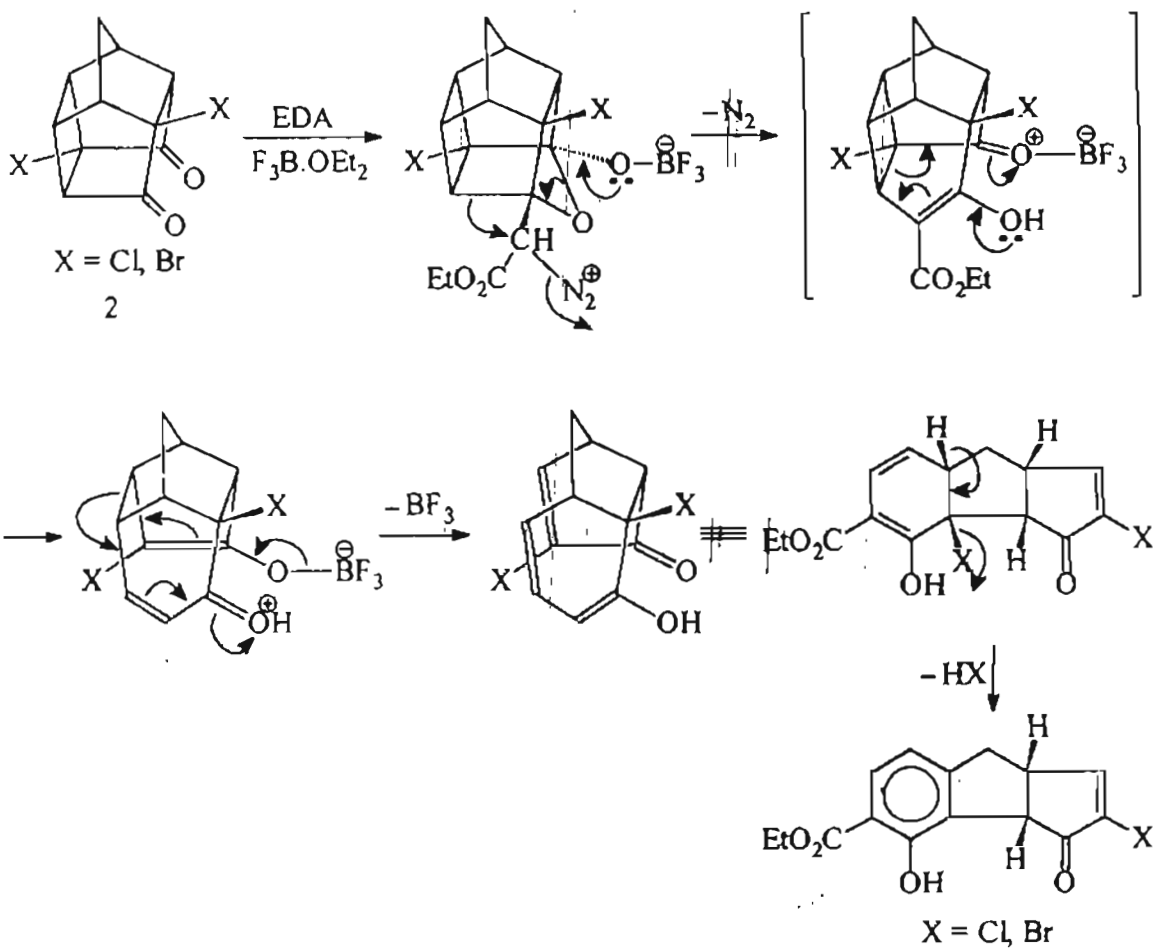
and products formed by the further reactions and rearrangements, have been put to use in divers fields such as solar energy utilisation, natural product synthesis and the synthesis of high energy compounds. It is interesting to note the importance of the exact placing of various substituents in affecting further reactions. A few examples that are significantly important are delineated below.

Mehta and co-workers[1] have reported an unusual [6,2] type of intramolecular hydride shift in a bicyclo[2.2.2]octane system **1** during their study of carbonium ion rearrangements of a pentacyclic dione initiated *via* a Schmidt fragmentation reaction. This fascinating rearrangement and the array of products obtained are depicted in scheme *I*.



Scheme I

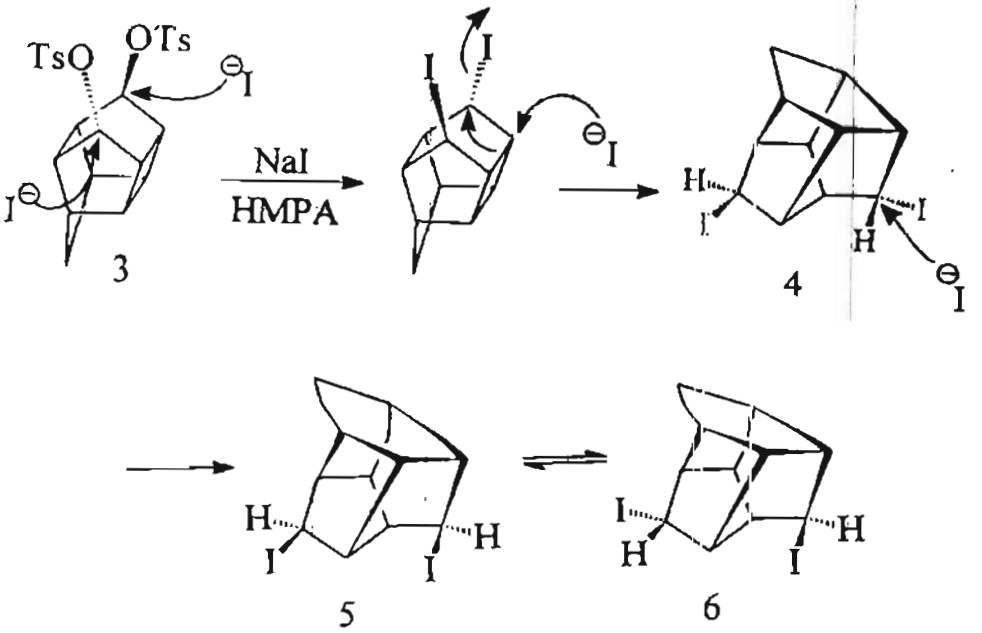
Another example of the effect of strategically placed substituents on further reactions of polycyclic cage compounds is illustrated in scheme II. It was anticipated by Marchand *et al.* that the presence of the halogen atom adjacent to the reaction site would lead to regiospecific ketone homologation by EDA-$F_3B.OEt_2$ leading to the higher homologue.[2] However, it was observed that when α-halo ketone **2** was employed as substrate in the homologation reaction, the presence of the halogen atom effectively suppresses migration of the terminus to which it is attached.



Scheme II

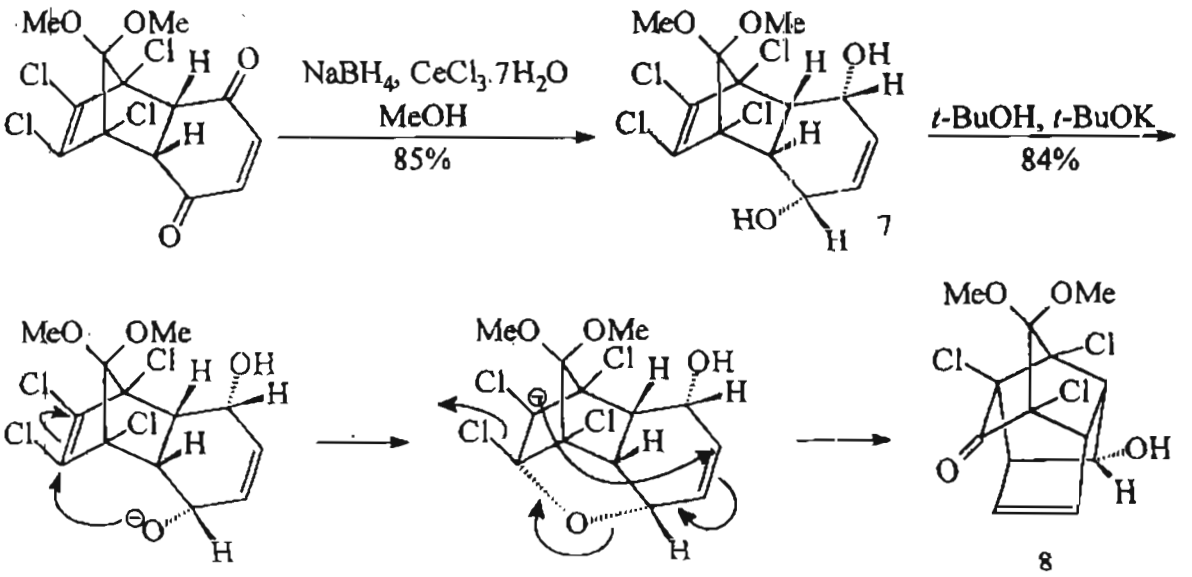
A survey of the literature also revealed some other fascinating rearrangements that have taken place in these constrained systems which deserve special mention. As early as 1976, Marchand *et al.*[3] have reported the transformation of a pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane system **3** into a trishomocubane skeleton as

shown in scheme III. The (*anti, anti*) product **4** is not isolated, instead, under the reaction conditions, an equilibrium mixture of **5** and **6** which are diastereomers are formed as shown in scheme III.



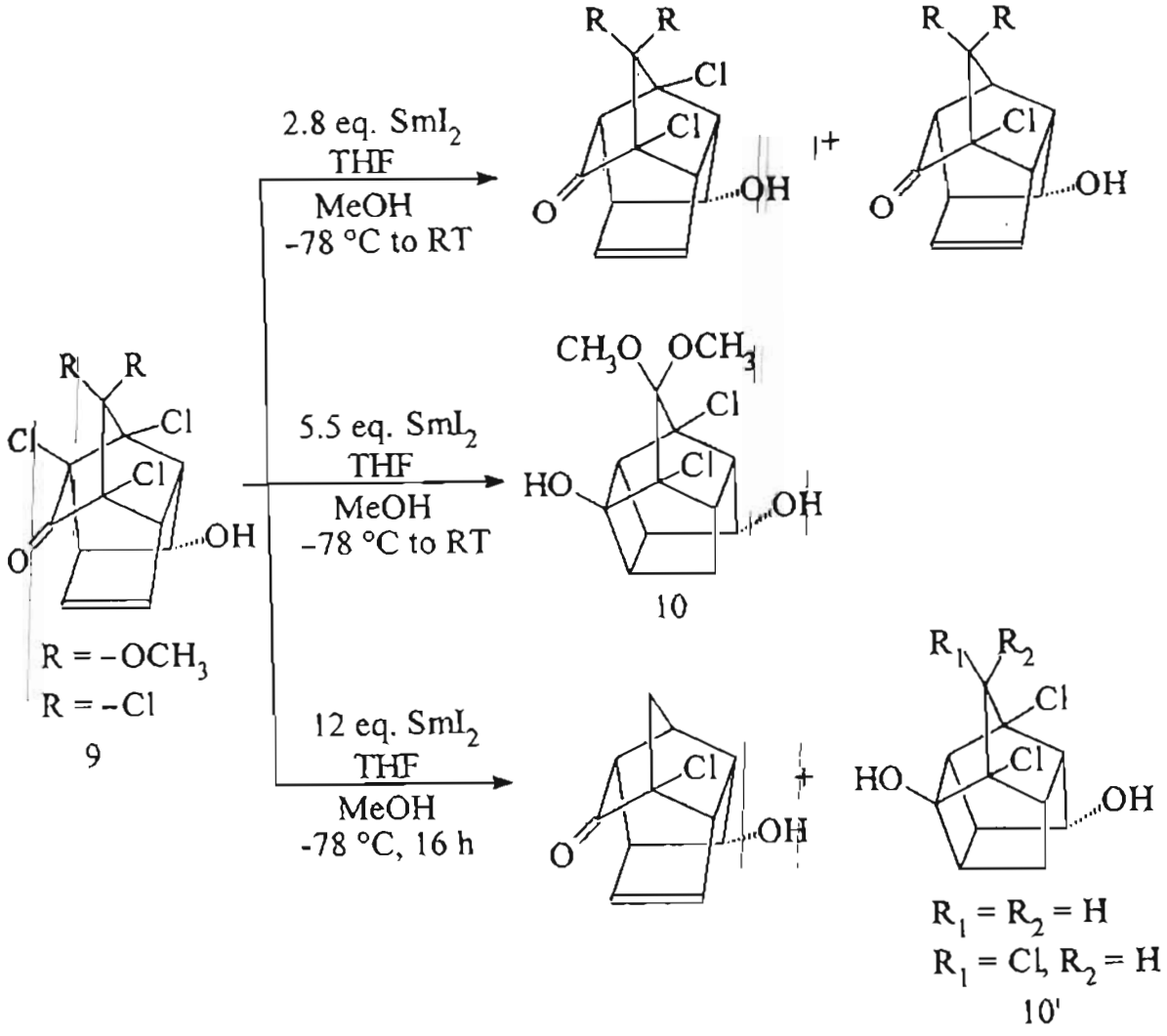
Scheme III

Suri[4] has reported the first entry into the tetracyclo[$5.3.1.0^{2,6}.0^{4,8}$] system ***8*** *via* a base-promoted eliminative cyclisation of **7** as shown in scheme IV.



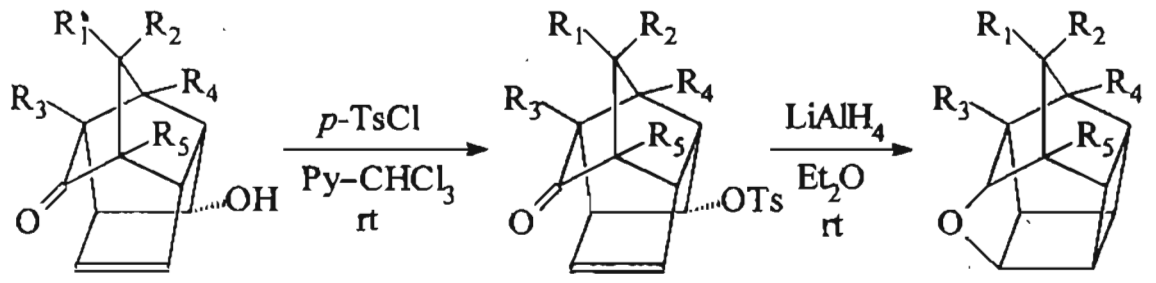
Scheme IV

Further, he has reported a nonphotochemical approach[5] to the synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}] system **10** and **10'** from the tetracyclic compound **9** using samarium(II) iodide mediated reductive cyclisation as shown in scheme V.



Scheme V

Starting from the tetracyclic system **11**, he has also synthesised novel oxa-cage compounds **12** as shown in scheme VI.[6]

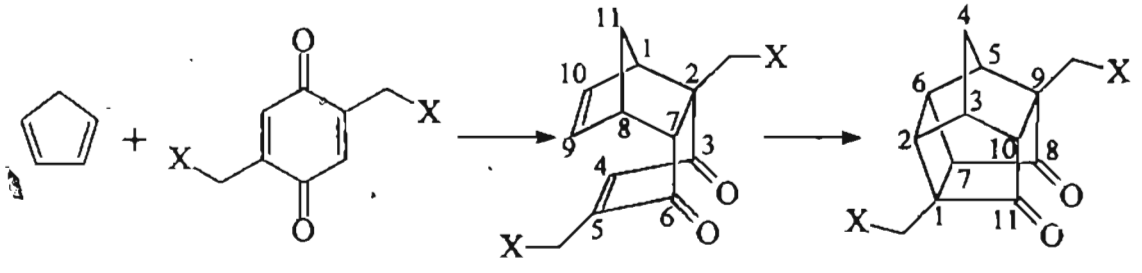


11 12

R_1, R_2 = OCH_3, Cl; R_3, R_4 = H, Cl; R_5 = Cl

Scheme VI

Various derivatives of Cookson's dione have been synthesised and have found applications in fields as diverse as medicinal chemistry[7] and in the probing of molecular mechanics.[8] As the first part of this research programme, it was decided to prepare some 1,9- derivatives of PCUD*. The advantages of having substitutions in these positions are numerous. For example, starting from a symmetrically substituted quinone **13**, reaction with cyclopentadiene followed by [2 + 2] cycloaddition would lead to a molecule **14** which has disymmetric faces (Scheme VII).



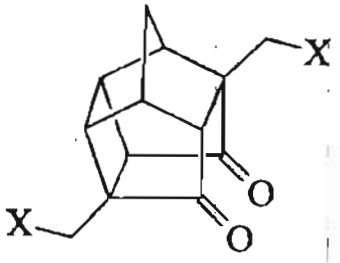
13 14

Scheme VII

Flash vacuum pyrolysis of **14** would lead to substituted triquinanes of use in natural product synthesis. Further reactions on this dione could also reveal the role of the cage skeleton in directing the course of such reactions. Specifically, it could be used to study the difference in approaches from various faces of the cage and the role of the substituents and keto groups in directing the course of the reaction. Radical

* All new compounds have been named using von Baeyer rules for the nomenclature of polycyclic compounds. The nomenclature has been confirmed by the Chemical Abstracts Service in the case of each new ring structure. The numbering has been depicted clearly for each new ring system.

initiated rearrangements could be triggered from different sites leading to new compounds. Therefore, the synthesis of substituted PCUDs appeared to be a worthwhile exercise. The proposed substituents at the 1 and 9 positions being polar groups amenable to further reactions and transformations, it was felt that these compounds **15, 16, 17 and 18** (Scheme VIII) would not only be a synthetic challenge, but also provide new biologically active molecules.



X = Br - **15**
Cl - **16**
OAc - **17**
Ph - **18**

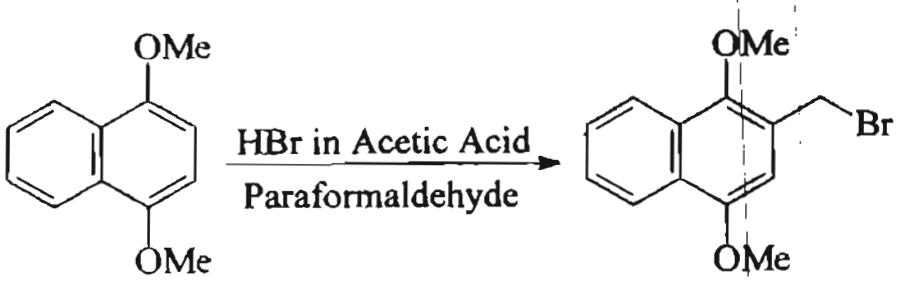
Scheme VIII

2.2 Results and Discussion:

2.2.1 Synthesis of the Required Tricyclic Precursors:

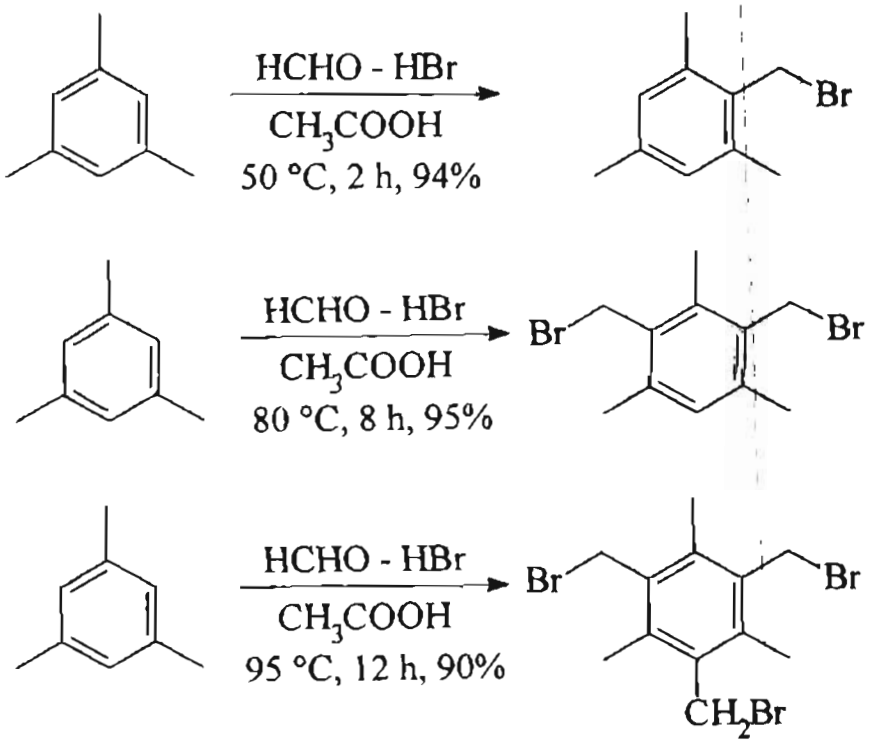
The first requirement was the preparation of the tricyclic precursors which *could* lead to various functionalised pentacyclic compounds through a [2 + 2] photocycloaddition. This in turn necessiated Diels-Alder additions between the *corresponding* functionalised quinones and cyclopentadiene.

Therefore, the immediate target was 2,5-bis(bromomethyl)-1,4-quinone **21** which could be prepared starting from hydroquinone dimethyl ether **19** through bis(bromomethylation). A search of the literature on bromomethylation of aromatic systems revealed a report from Gates[9] which described the mono(bromomethylation) of naphthaquinol dimethyl ether using paraformaldehyde and hydrobromic acid (Scheme *IX*).



Scheme IX

van der Made *et al.*[10] carried this work further by carrying out the facile mono-, bis- and trisbromomethylation of mesitylene using paraformaldehyde and a solution of hydrobromic acid in glacial acetic acid at varying temperatures (Scheme X).

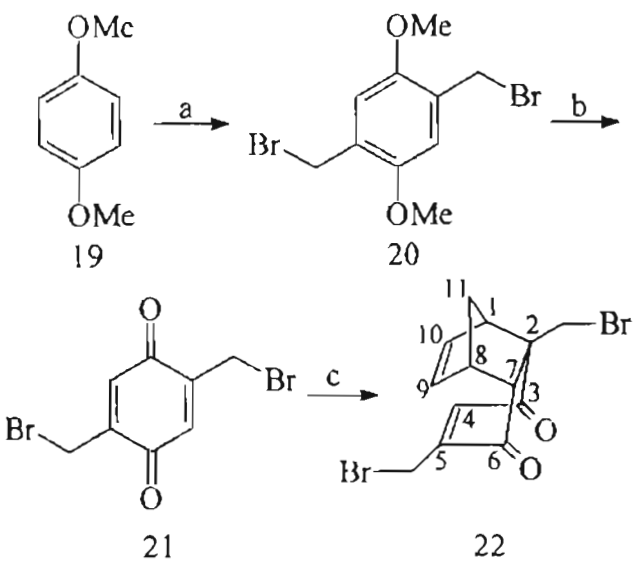


Scheme X

This procedure was adapted for the synthesis of 2,5-bis(bromomethyl)-1,4-quinol dimethyl ether **20**. Accordingly, hydroquinone dimethyl ether **19** in glacial acetic acid solvent was treated with paraformaldehyde and a solution of hydrobromic acid in galcial acetic acid. However, it was found that using the high temperatures required by the reported procedure gave rise to large number of unwanted side products. To our delight, it was observed that sonication speeded up the reaction and

*the expected product **20** could be obtained in 65% yield after purification by* crystallisation from dichloromethane-petroleum ether (Scheme XI). The product was obtained as off-white powdery crystals with a m.p. of 203-205 °C. The ^{1}H NMR spectrum showed two aromatic protons at δ 6.86; four protons of the two bromomethyl groups at δ 4.53 and the six methyl ether protons at δ 3.86, thus confirming the structure.

This compound **20** was readily oxidised to the corresponding quinone **21** using nitric acid in acetic acid (Scheme XI).[11] The quinone **21** (m.p. 122-124 °C) was obtained in 42% yield and was found to be identical to that reported in literature. The ^{1}H NMR spectrum showed two protons at δ 6.87 and the four protons of the bromomethyl groups at δ 4.19. The IR spectrum showed a strong absorption due to the quinone carbonyl group at 1675 cm^{-1}.



a) 3 eq. paraformaldehyde, 3 eq. 33% HBr in glacial acetic acid, glacial acetic acid, sonication, 1 h, 65%. b) conc. nitric acid, glacial acetic acid, RT, 1 h, 42%. c) cyclopentadiene, dry benzene, ~10 °C-RT, 15 h, 88%.

Scheme XI

The quinone **21** was reacted with freshly cracked cyclopentadiene in dry benzene (Scheme XI). After addition of the cyclopentadiene at low temperature (~ 10 °C), the reaction mixture was further stirred at room temperature for fifteen hours which gave the required Diels-Alder adduct 2,5-bis(bromomethyl)tricyclo [6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione **22** in 88% yield as bright yellow diamond shaped crystals (m.p. 110-112 °C). The product was identified on the basis of its spectra. The IR spectrum showed strong carbonyl stretch at 1675 cm^{-1} and a weaker

one at 1657 cm^{-1}, this being indicative of an α,β-unsaturated carbonyl system. The ^1H NMR spectrum (Fig. 1) showed the olefinic protons at δ 6.72 as a singlet and as a multiplet between δ 6.14-6.07. The protons on the allylic bromomethyl group appeared as ½ ABq signals at δ 4.28 (J = 11.5 Hz) and δ 4.03 (J = 11.5 Hz). The proton on C-7 appeared downfield as a doublet at δ 4.06 (J = 9.2 Hz). The proton on C-1 was observed as a multiplet signal between δ 3.51-3.49. The protons on the bromomethyl group at C-2 appeared as a multiplet between δ 3.30-3.23. The protons on C-8 appeared as a multiplet between δ 3.14-3.13. The two protons on the norbornyl bridge were seen as a singlet at δ 1.61. The ^{13}C NMR spectrum (Fig. 2) showed carbonyl carbons at δ 199.7 and 196.3, and the olefinic carbons at δ 148.8, 140.1, 136.7 and 136.4. The quartenary carbon bearing the bromomethyl group gave a signal at δ 59.9, the norbornyl bridge carbon was seen at δ 25.3 and the other saturated carbons gave signals between δ 55.9 and δ 39.9 supporting the assigned structure **22**.

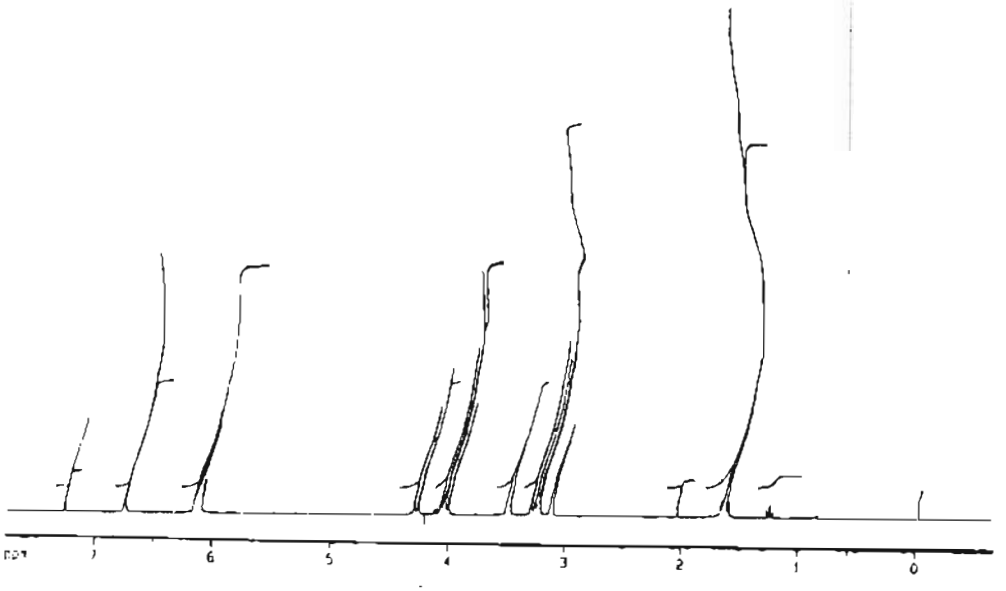


Figure 1: ^1H NMR Spectrum of 22

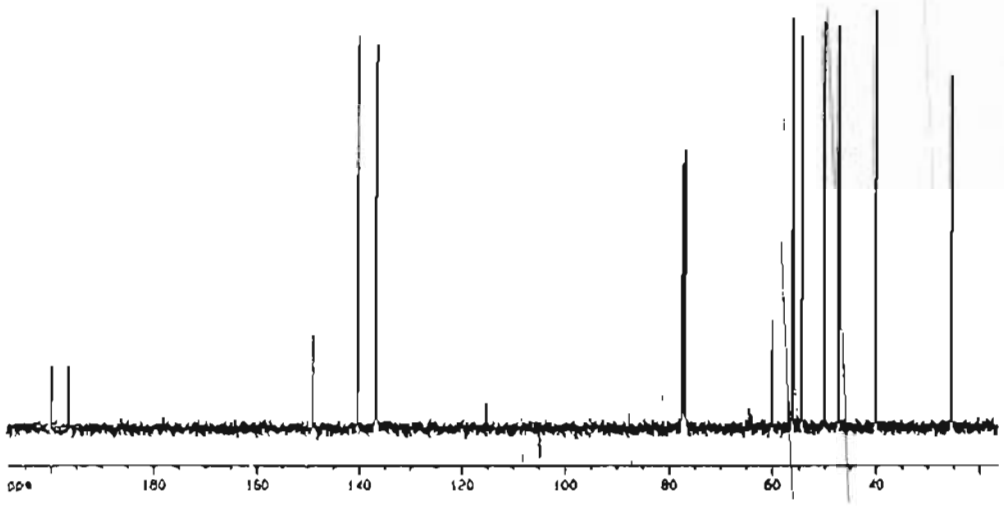
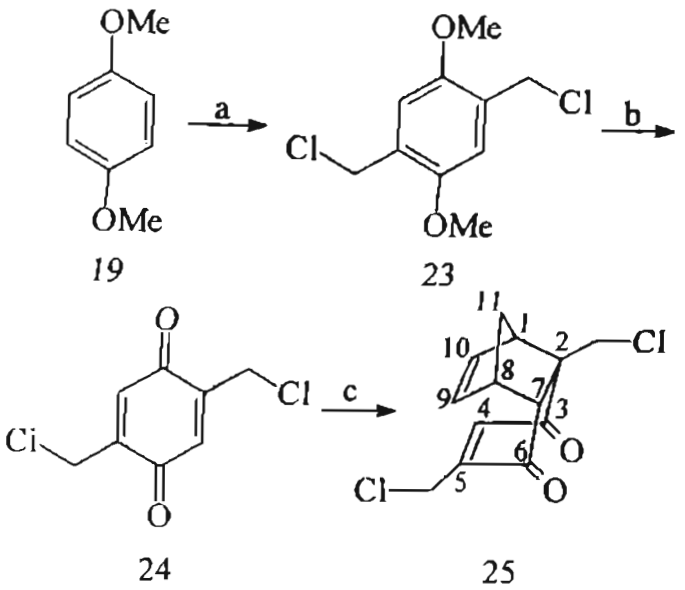


Figure 2: ^{13}C NMR Spectrum of 22

In order to obtain the 2,5-bis(chloromethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **25**, the above procedure was varied slightly. The bis(chloromethylation) of hydroquinone dimethyl ether **19** was successfully carried out using paraformaldehyde and concentrated hydrochloric acid in glacial acetic acid under sonication conditions (Scheme XII). The ^1H NMR spectrum of **23** showed the aryl protons at δ 6.64, the chloromethyl protons at δ 4.63 and the methyl ether protons at δ 3.69.

The 2,5-bis(chloromethyl)-1,4-quinol dimethyl ether **23** was also oxidised using nitric acid in glacial acetic acid (Scheme XII). The IR spectrum of 2,5-bis(chloromethyl)-1,4-quinone **24** showed a strong carbonyl peak at 1660 cm^{-1}. The ^1H NMR showed only two signals, one at δ 6.96 for the two ring protons and one at δ 4.43 for the four protons in the two chloromethyl groups.



a) paraformaldehyde (3 eq.), conc. HCl, glacial acetic acid, sonication, 1 h, 63%.
b) conc. nitric acid, glacial acetic acid, 0 °C-RT, 1 h, 26%.
c) cyclopentadiene (2 eq.), dry benzene, 0 °C-RT, 20 h, 87%.

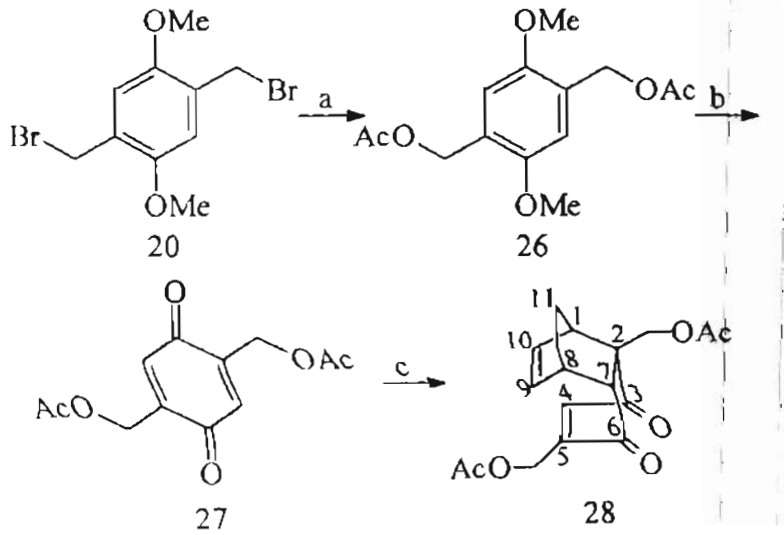
Scheme XII

*The quinone **24** was reacted with cyclopentadiene in benzene to give the required tricyclic precursor 2,5-bis(chloromethyl)tricyclo[6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione **25** (Scheme XII). The structure of the Diels-Alder adduct **25** was assigned* on the basis of spectral data. The IR spectrum showed a strong stretch at 1670 cm^{-1} and a smaller one at 1625 cm^{-1} indicative of an α,β-unsaturated carbonyl group, a peak at 3020 cm^{-1} was indicative of the olefinic groups. The ^{1}H NMR spectrum showed a signal at δ 6.82 for the olefinic proton adjacent to the carbonyl group and another signal at δ 6.12 for the olefinic protons on the norbornyl ring. The allylic chloromethyl protons resonated as a multiplet overlapping with the signal of the proton at C-7 between δ 4.38-4.19. The chloromethyl protons on the norbornyl ring appeared as a multiplet between δ 3.50-3.42. The norbornyl bridgehead protons on C-1 and C-8 showed up upfield as a multiplet between δ 3.25-3.23 and as a singlet at δ 3.12. The protons on the norbornyl bridge appeared as a singlet signal upfield at δ 1.64. The ^{13}C NMR spectrum showed the carbonyl carbons at δ 199.3 and 196.8 and the olefinic carbons at δ 148.6, 140.1, 136.9 and 136.4. The other aliphatic carbons appeared between δ 60.1 to 39.6 with the quarternary carbon C-2 appearing at δ 60.1.

The 2,5-bis(acetoxymethyl)tricyclo[6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione **28** was prepared in three steps starting from the 2,5-bis(bromomethyl)-1,4-quinol

dimethyl ether **20**. Treatment of **20** with sodium acetate in glacial acetic acid resulted in the 2,5-bis(acetoxymethyl)-1,4-quinol dimethyl ether **26** (Scheme XIII) which was identified on the basis of its spectral data. Its IR spectrum showed the presence of a strong absorption at 1736 cm^{-1} indicative of an ester functionality. The ^1H NMR spectrum showed four signals, all of them singlets as expected. The two aromatic protons appeared as a signal at δ 6.89, the four methylene protons were seen at δ 5.13, the six protons on the two methyl ether groups could be observed at δ 3.82 and the six protons on the two acetoxy groups appeared at δ 2.10.

This compound **26** was oxidised using ceric ammonium nitrate in a 3:1 mixture of acetonitrile and water (Scheme XIII). The quinone **27** was identified as 2,5-bis(acetoxymethyl)-1,4-quinone on the basis of spectral analysis. The IR spectrum clearly showed two strong absorptions, one at 1748 cm^{-1} due to the acetoxy carbonyl group and one at 1645 cm^{-1} due to the quinone carbonyl. The ^1H NMR spectrum showed only three signals, one at δ 6.67 due to the two protons on the quinone ring, one at δ 4.98 due to the four methylene protons and one at δ 2.17 due to the six protons on the acetoxy groups.



a) NaOAc (2.5 eq.), glacial acetic acid, 80 °C, 5 h, 84%. b) CAN (5 eq.), acetonitrile-water (3:1), 1 h, 0 °C-RT, 68%. c) cyclopentadiene dry benzene, 0 °C-RT, 3 d, 98%.

Scheme XIII

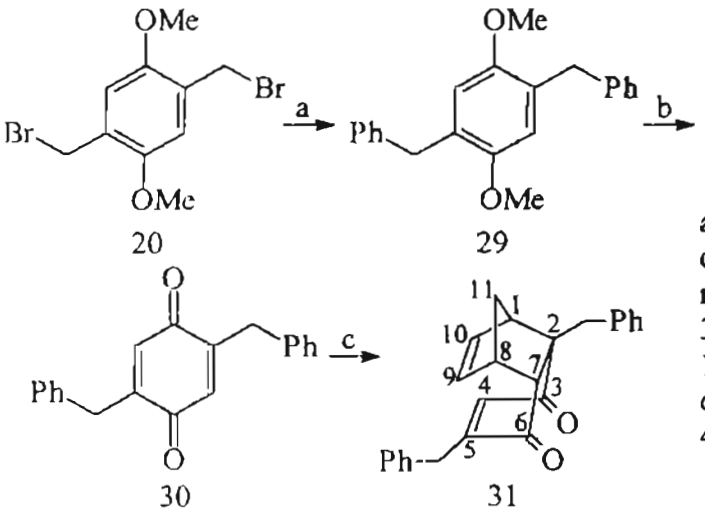
The quinone 27 thus obtained was treated with freshly cracked cyclopentadiene and the Diels-Alder adduct **28** was obtained (Scheme XIII). The product was identified as the required tricyclic dione using various spectral techniques. In the IR

spectrum, the acetoxy carbonyl absorption could be easily identified as the one at 1742 cm^{-1}. The absorption due to the α,β-unsaturated carbonyl group could be clearly seen as a strong peak at 1669 cm^{-1} and a smaller one at 1626 cm^{-1}. In the ^1H NMR spectrum, the olefinic protons gave signals as two singlets, one at δ 6.54 for one proton and another at δ 6.09 for two protons. The allylic methylene appeared as a quartet at δ 4.86 (J = 15.7 Hz), while the other acetoxy methylene appeared as ½ABq signals at δ 4.51 (J = 10.6 Hz) and δ 4.16 (J = 10.6 Hz). The protons attached to the three tertiary carbons on the norbornyl ring appeared at δ 3.49 as a singlet, at δ 3.17 also as a singlet and at δ 3.08 as a doublet with J = 3.8 Hz. The methyl groups on the two acetoxy moieties appeared as two singlets at δ 2.13 and 1.97, the one appearing downfield being attributed to the allylic acetoxymethyl group. The two protons on the norbornyl bridge carbon appeared as a multiplet between δ 1.68-1.56. The ^{13}C NMR spectrum was also in agreement with the proposed structure showing the two carbonyl carbons on the tricyclic system appearing at δ 199.7 and 197.7, the acetoxy carbonyls at δ 170.2 and 169.7. The olefinic carbons gave signals at δ 148.0, 137.5, 136.9 and 135,9 with the fully substituted olefinic carbon appearing the most downfield. The other carbon signals appeared between δ 71.4 and 20.7.

The 2,5-bis(benzyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **31** was prepared starting from 2,5-bis(bromomethyl)-1,4-quinol dimethyl ether **20**. Treatment of the bis(bromomethyl) compound **20** with activiated Montmorillonite K 10 clay in refluxing benzene for eighteen hours led to the 2,5-bis(benzyl)-1,4-quinol dimethyl ether **29** (Scheme XIV). Examination of the ^1H NMR spectrum of **29** clearly indicated the presence of ten aromatic protons as a multiplet between δ 7.28-7.14 showing that both the bromines had been replaced by phenyl groups. The two other aromatic protons appeared separately as a singlet at δ 6.62. The four protons on the two methylene groups appeared as a singlet at δ 3.94 and the six protons on the two methoxy groups also appeared as a singlet at δ 3.68.

This compound **29** was oxidised to 2,5-bis(benzyl)-1,4-quinone **30** using ceric ammonium nitrate in 3:1 acetonitrile-water mixture (Scheme XIV). The IR spectrum of the quinone **30** clearly indicated the presence of carbonyl group by the strong

absorption at 1650 cm^{-1}. The ^{1}H NMR spectrum showed the aromatic protons on the two phenyls as a multiplet between δ 7.27-7.09 and the other two aromatic protons as a singlet at δ 6.28. The four protons on the two methylene groups also appeared as a singlet at δ 3.64.



a) activated Montmorillonite K 10 clay (50% by weight), dry benzene, reflux, 18 h, 66%. b) 4 eq. CAN, 3:1 acetonitrile-water, 0 °C-RT, 1 h, 52%. c) cyclopentadiene, dry benzene, ~10 °C-RT, 4 d, 68%.

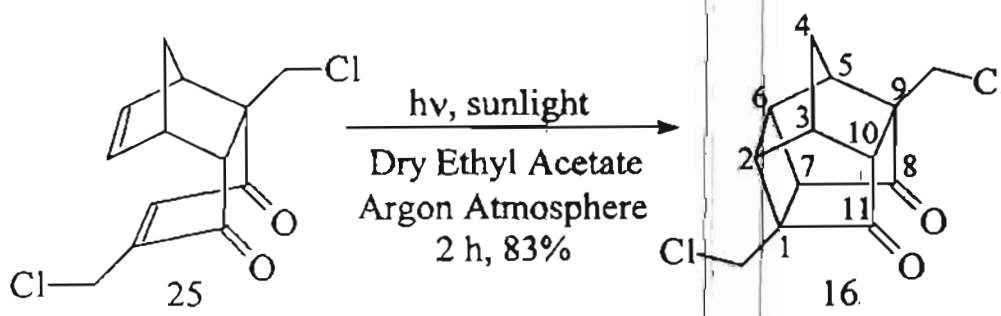
Scheme XIV

The quinone **30** was treated with freshly cracked cyclopentadiene whereupon the expected Diels-Alder adduct **31** was obtained (Scheme XIV). The spectra of this tricyclic adduct displayed various characteristics expected of it. Its IR spectrum showed the expected absorptions at 1655 (strong) and 1619 (weak) cm^{-1} indicating the presence of an α,β-unsaturated carbonyl group. The aromatic protons in the ^{1}H NMR spectrum showed up between δ 7.26-7.16 (6 protons), 6.98-6.96 (2 protons) and 6.75-6.73 (2 protons) as a series of multiplets. The olefinic protons showed up separately as a multiplet between δ 6.10-6.08, a singlet at δ 6.03 and another multiplet between δ 5.87-5.85. The four protons on the two benzyl methylene groups and the norbornyl ring protons showed up as an overlapping multiplet between δ 3.52-3.15 and a doublet at δ 2.68 (J = 12.9 Hz). The norbornyl bridge methylene protons appeared as ½ABq *signals centred at δ 1.77 and δ 1.58 (J = 9.1 Hz). The ^{13}C NMR spectrum showed* signals due to the two carbonyl carbons at δ 202.9 and 198.9. The olefinic carbons on the tricyclic ring system appeared at δ 152.8 (disubstituted olefinic carbon), 140.4, 138.1 and 135.4. The twelve carbons of the two benzene rings showed six signals

between δ 129.5 and δ 126.6. The quarternary carbon on the tricyclic ring appeared at δ 59.7 and the rest of the carbons gave signals upfield between δ 54.5 and δ 35.2.

2.2.2 Photolysis of the Tricyclic Precursors:

The photolysis of the Diels-Alder adducts were carried out by exposing a 1% weight / volume solution of it in dry degassed ethyl acetate to sunlight for about two hours. The products were identified using the usual spectral and analytical methods.



Scheme XV

Specifically, photolysis of the 2,5-bis(chloromethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **25** was carried out by irradiating with sunlight for two hours in dry degassed ethyl acetate (Scheme XV). The crystalline product obtained, *viz.*, 1,9-bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **16** (m.p. 88-90 °C) was characterised using spectroscopic methods. Its IR spectrum showed the carbonyl stretches at 1757 and 1738 cm^{-1}. The characteristic splitting pattern of the norbornyl protons in the ^{1}H NMR spectrum (Fig. 3) of cage compounds was clearly discernable through the signals at δ 2.27 and 1.95 (ABq, J = 11.7 Hz). There were no signals which could be assigned to olefinic protons. The four protons on the two chloromethyl groups overlapped to give a multiplet between δ 3.77-3.51. The six protons on the tertiary carbon atoms on the pentacyclic ring showed up as multiplets between δ 3.23-3.17 (two protons), δ 3.03-2.99 (two protons) and δ 2.82-2.79, and a doublet at δ 2.62 (J = 3.4 Hz). The ^{13}C NMR spectrum (Fig. 4) confirmed the structure by showing the carbonyl carbons at δ 208.9 and 208.1 and all other signals upfield between δ 62.8 and 34.9.

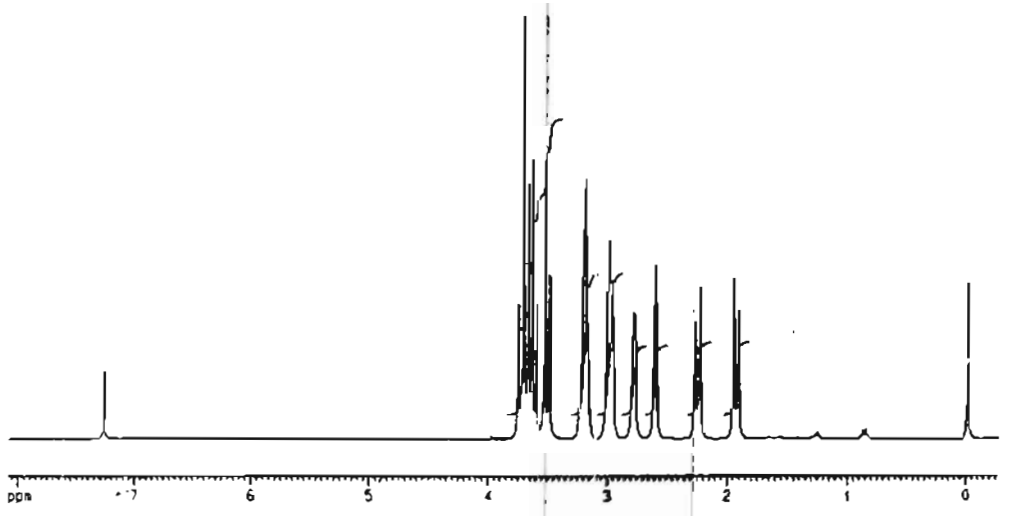


Figure 3: ^{1}H NMR Spectrum of 16

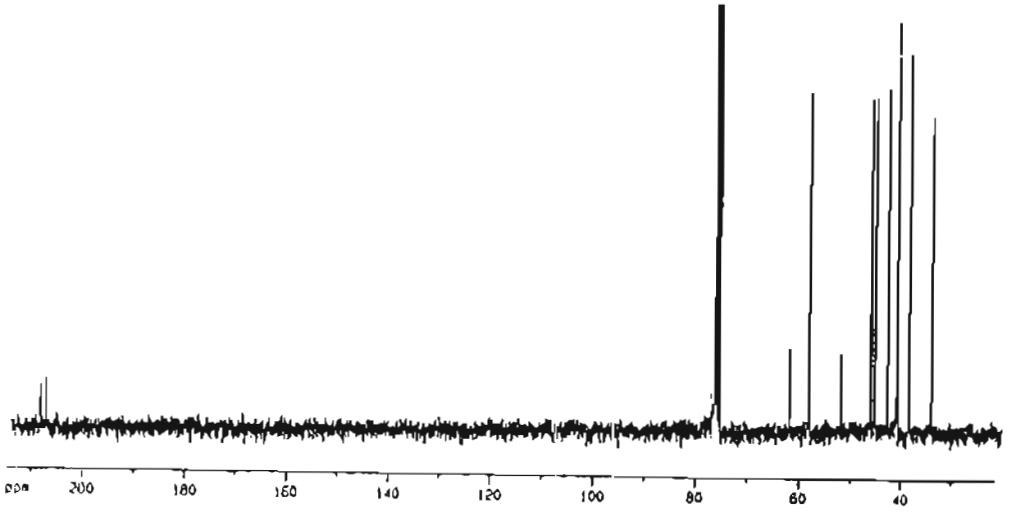
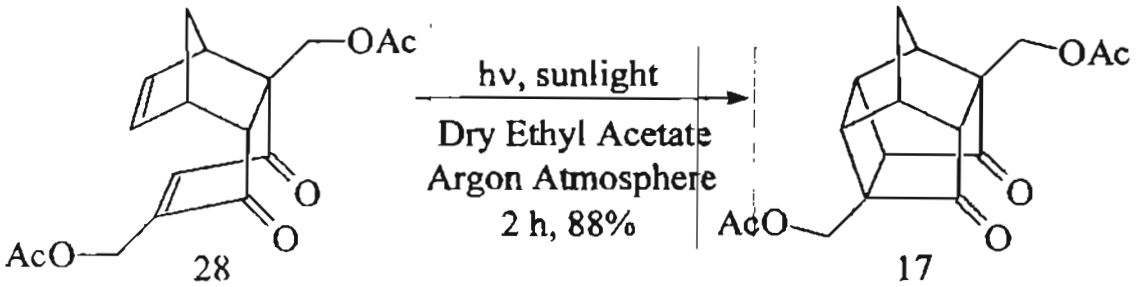
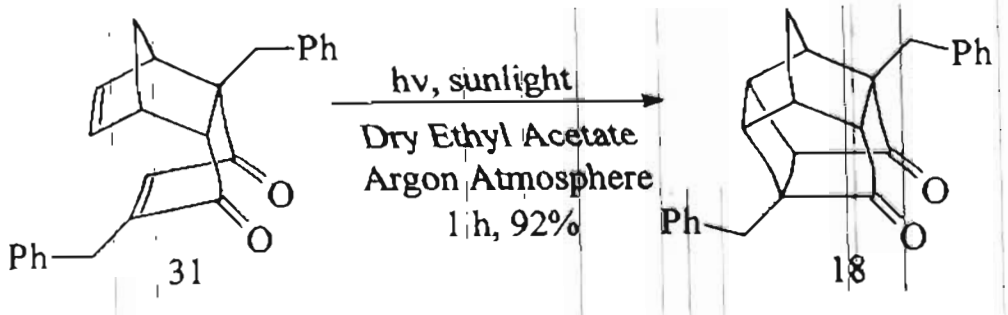


Figure 4: ^{13}C NMR Spectrum of 16



Scheme XVI

The compound 2,5-bis(acetoxymethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **28** was subjected to photolysis by exposing a degassed solution of the compound in dry ethyl acetate to sunlight for two hours (Scheme XVI). The product **17** was easily identified as the expected pentacyclic product 1,9-bis(acetoxymethyl) pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione on the basis of spectral analysis. Its IR spectrum showed a very strong, broad absorption consisting of overlapping peaks at 1762, 1741 and 1725 cm^{-1}. The ^{1}H NMR spectrum showed protons of the acetoxy bearing methylene groups as a combined multiplet between δ 4.24-4.08. The six protons on the tertiary carbons on the pentacyclic ring gave separate signals: a multiplet between δ 3.19-3.14, another between δ 3.09-3.05, a broad singlet at δ 2.95, doublets at δ 2.83 (J = 5.1 Hz), δ 2.72 (J = 6.4 Hz) and δ 2.49 (J = 2.6 Hz). The methylene protons on the norbornyl bridge appeared as characteristic ½ABq signals at δ 2.17 and δ 1.89 (J = 11.6 Hz). The six protons of the two acetoxy groups appeared as a singlet at δ 2.08. The ^{13}C NMR spectrum also supported the proposed structure with the two carbonyls on the pentacyclic ring appearing at δ 209.5 and 208.4 and the two acetoxy carbonyls overlapped to give a single signal at δ 170.6. There were no signals in the olefinic region and all other carbons appeared upfield between δ 61.3 and δ 20.8.

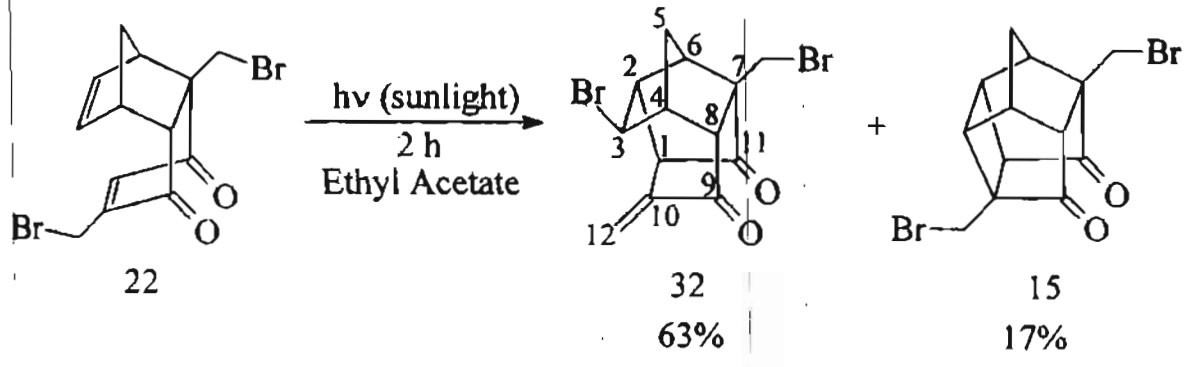


Scheme XVII

The photolysis of the bis(benzyl)tricyclic compound **31** gave the expected pentacyclic compound **18** in high yield (92%) (Scheme XVII) and the compound was readily characterised by its spectral data. Its IR spectrum showed a carbonyl absorption at 1750 cm^{-1} due to the strained ring ketones. The ^1H NMR spectrum showed ten aromatic protons as a multiplet between δ 7.23-7.13. The methylene protons on the norbornyl ring appeared as ½ABq signals at δ 1.77 and 1.65 with a *J* value of 11.2 Hz. The ^{13}C NMR spectrum showed the two carbonyl signals at δ 213.1 and 212.0. The twelve aromatic signals overlapped to give six signals between δ 137.2 and 126.4. The other eleven carbons on the pentacyclic ring and benzyl methylenes appeared upfield between δ 63.2 and 34.9. Thus, the compound was identified as 1,9-bis(benzyl) pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **18**.

Interestingly, the photolysis of the tricyclic precursor **22** to the bis-bromomethyl compound **15** took a totally new turn. The reaction mixture after two hours of irradiation showed a new UV active compound as the major product along with a minor amount of a non-UV compound (Scheme XVIII). After chromatographic separation, the major compound was found to be present in 63% yield and was crystallised from ethyl acetate-petroleum ether as white crystals. Following extensive delibration on the spectral data, the product was assigned the structure **32**. The spectral characteristics which lend credibility to this surmise are described below. The high resolution mass spectrum gave a value of 359.9184 for the compound which is the same as the starting material. This indicated that the compound had been formed by a rearrangement. The IR spectrum showed absorptions at 1715 and 1613 cm^{-1} and the ^1H NMR spectrum (Fig. 5) showed signals at δ 6.21 and 5.49. This indicated an

enone having an exocyclic double bond. A singlet at δ 4.41 could be attributed to the proton on C-1 which would appear downfield since it is α to both the double bond and a carbonyl group. The protons which appeared as ½ABq signals at δ 3.56 and 3.28 with a J value of 10.6 Hz were attributable to the bromomethyl moiety. The norbornyl bridge protons appeared as ½ABq signals at δ 2.81 and 1.98 with a J value of 11.9 Hz. The ^{13}C NMR spectrum (Fig. 6) showed signals at δ 205.0 and 194.7 for the carbonyls and at δ 141.5 and 124.8 for the exocyclic double bond. The DEPT spectrum also supported the assigned structure. The structure of this unexpected compound received final confirmation by single crystal X-ray analysis (Fig. 7).



22 32 63% 15 17%

Scheme XVIII

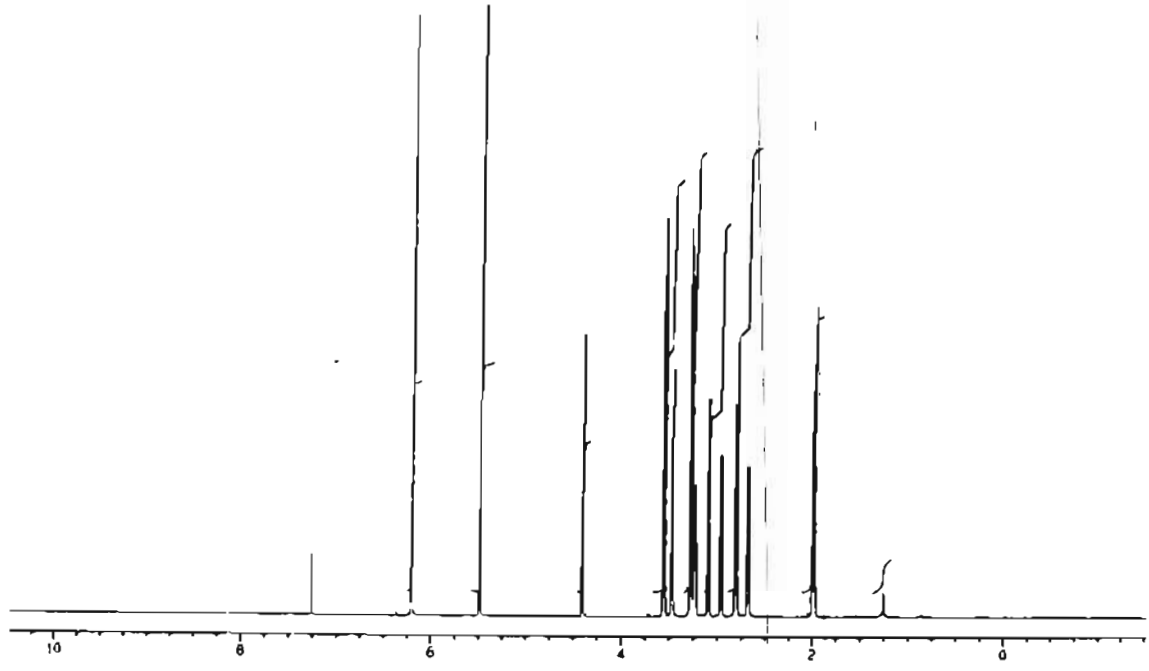


Figure 5: ^1H NMR Spectrum of 32

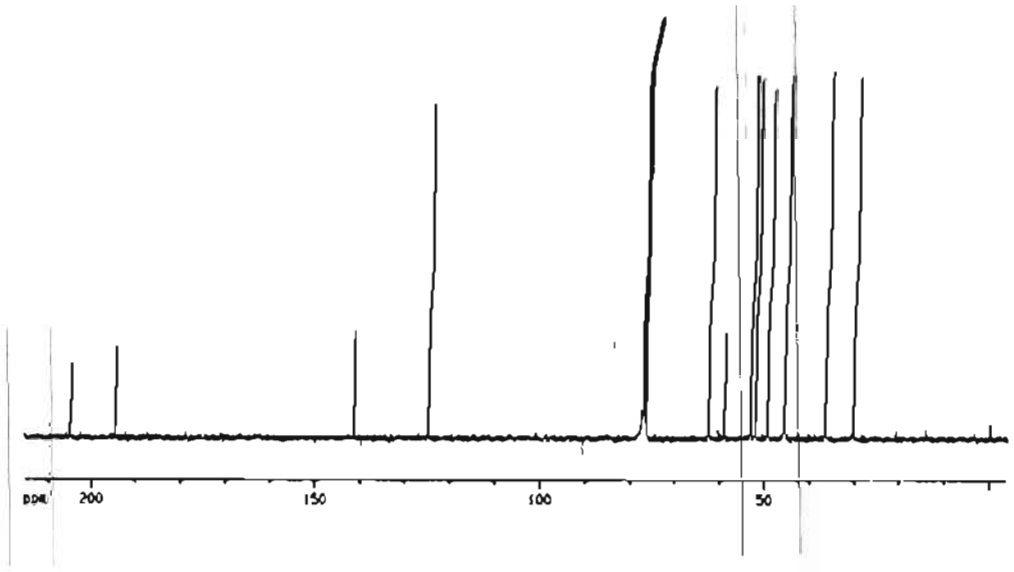


Figure 6: ^{13}C NMR Spectrum of 32

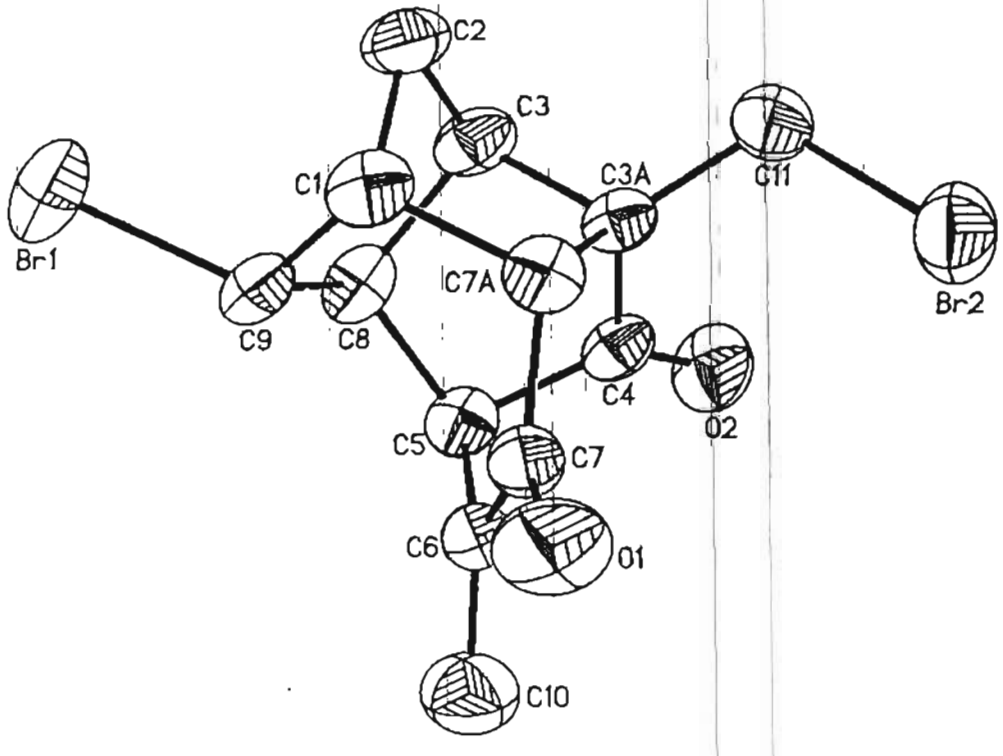
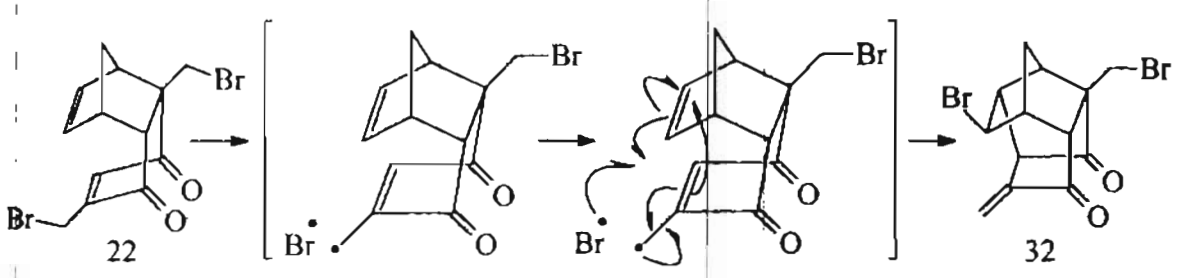


Figure 7: X-ray Crystal Structure of 32

The reaction mechanism proposed for the formation of this compound, *viz.*, 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **32** (Scheme XIX) envisages the initial cleavage of the allylic carbon-bromine bond in the compound **22** to give a bromine radical which is held within the solvent cage itself. Reorganisation of the radical within the polycyclic framework followed by final bromine radical recapture gives the tetracyclic enone **32** as the rearranged product.

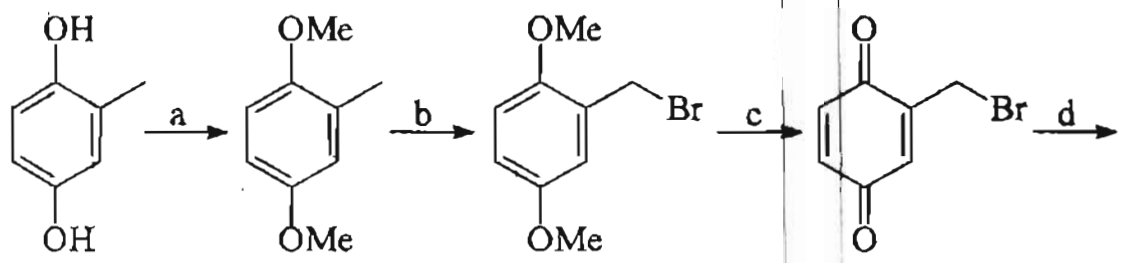


Scheme XIX

The minor product was readily identified as 1,9-bis(bromomethyl)pentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **15** and was obtained in 17% yield (Scheme XVIII) as white crystals with a melting point of 95-96 °C. Its IR spectrum showed strong absorption due to carbonyl at 1755 cm^{-1}. The ^{1}H NMR spectrum showed no signals in the olefinic region and the norbonyl bridge protons were observable as ½ABq signals at δ 2.25 and δ 1.94 with a *J* value of 11.7 Hz. The two bromomethyl groups appeared as two separate ½ABq signals: one at δ 3.63 and δ 3.47 with a *J* value of 10.8 Hz and the other at δ 3.55 and δ 3.35 with a *J* value of 10.9 Hz. Two protons each on the pentacyclic ring system appeared as multiplets between δ 3.21-3.18 and δ 3.04-2.98. Another proton appeared as a multiplet between δ 2.78-2.76 and one as a doublet at δ 2.62 with a *J* value of 4.3 Hz. The ^{13}C NMR spectrum showed two signals corresponding to the carbonyl carbons at δ 208.9 and 207.9 and all other signals were between δ 62.6 and 29.7 confirming the absence of olefinic groups.

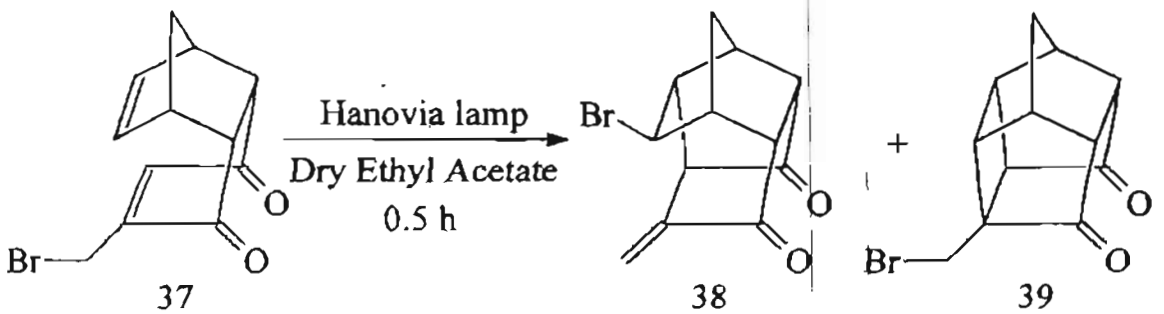
2.2.3 Synthesis and Photolysis of 5-(Bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione:

Since this anomalous behaviour had been exhibited only by the tricyclic precursor having a bromomethyl substituent in the 5 position, it was sought to prepare 5-(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **37** and study its photolysis in order to propose a general reactivity trend. The synthesis started with commercially available toluquinol **33** which was O-methylated using a standard procedure[12] involving heating toluquinol in an aqueous solution of sodium hydroxide with dimethyl sulphate (Scheme XX). This furnished 2,5-dimethoxytoluene **34** as a viscous liquid which was easily identified on the basis of its spectra. The ^{1}H NMR spectrum showed the presence of three aromatic protons as a singlet at δ 6.64, the protons on the two methoxy groups appeared as separate singlets at δ 3.69 and 3.68 while the protons on the methyl group appeared at δ 2.20 as a singlet.



33 34 35 36

a) dimethylsulphate (5 eq.), NaOH(aq.) (8 eq.), 0 °C-RT, then 50-60 °C, 2.5 d, 97%. b) NBS (1 eq.), AIBN (cat.), carbon tetrachloride, reflux, 1 h, 61%. c) CAN (4 eq.), acetonitrile-water (3:1), 0 °C-RT, 1 h, 36%.
d) cyclopentadiene (2 eq.), dry benzene, 0 °C-RT, 2 d, 62%



37 38 39

Scheme XX

The methyl group on the compound **34** was brominated using NBS with AIBN as the initiator (Scheme XX). The product **35** was easily identified as 2-(bromomethyl)-1,4-quinol dimethyl ether on the basis of its ^{1}H NMR spectrum which now showed the aromatic protons as three separate signals at δ 6.93, 6.80 and 6.74. Also was seen a signal at δ 4.55 which integrated for two protons. This signal was downfield of the signals due to the protons on the two methoxy groups at δ 3.86 and 3.73 indicating the successful bromination of the methyl in the starting material.

The compound **35** was oxidised using CAN in acetonitrile-water to give 2-(bromomethyl)-1,4-quinone **36** (Scheme XX) whose identity was confirmed on the basis of its spectra. Its IR spectrum showed a strong absorption at 1678 cm^{-1} indicating a quinone carbonyl stretch. The ^{1}H NMR spectrum showed the presence of only five protons indicating the loss of the methoxy protons. The signals appeared at δ 6.90, 6.82 and 6.72 for the ring protons and the protons on the bromomethyl group appeared as a singlet at δ 4.28.

The Diels-Alder reaction of **36** with freshly cracked cyclopentadiene gave the required adduct 4-(bromomethyl)tricyclo[6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione **37** (Scheme XX). Its IR spectrum showed a strong absorption at 1662 cm^{-1} and a smaller one at 1621 cm^{-1} due to α,β-unsaturated carbonyl group. The ^{1}H NMR spectrum showed the signals due to the three olefinic protons as two singlets at δ 6.68 (one proton) and δ 6.09 (two protons). Since the olefinic region integrated for only three protons, it was clear that the required Diels-Alder adduct with the bromomethyl group on the olefin had been formed by addition of the cyclopentadiene to the unsubstituted double bond in the quinone. The protons on the bromomethyl group appeared as a doublet of a doublet at δ 4.12 and the norbornyl methylene protons appeared as another doublet of a doublet at δ 1.50. The ^{13}C NMR spectrum likewise supported the proposed structure. The carbonyl carbons gave signals at δ 198.9 and 197.1. The olefinic carbons appeared at δ 149.5, 140.0, 135.4 and 135.1. The signal at δ 149.5 was due to a quarternary carbon and could be assigned to the carbon bearing the bromomethyl group. The HRMS value of 265.9934 was in agreement with the required molecular formula $C_{12}H_{11}O_2Br$ for the compound **37**.

The photolysis of the compound **37** could not be carried out under the usual conditions (Scheme XX). On exposure to sunlight, the reaction mixture was seen to turn black in colour and extensive decomposition of the starting material was observed. Therefore, the degassed reaction mixture was irradiated for ½ hour using a Hanovia medium pressure Hg vapour lamp in a quartz immersion well. This yielded the products **38** and **39** after chromatography, albeit in fairly low yields.

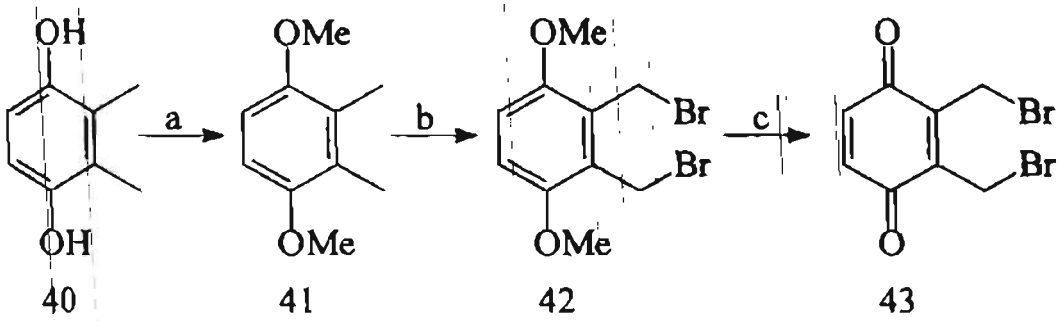
The compound **38** was easily identified as 3-bromotetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione (numbering is the same as in compound **32**) on the basis of its spectra and comparison with the spectra of compound **32**. The IR spectrum showed a strong absorption at 1748 cm^{-1} and a weaker one at 1702 cm^{-1} indicative of the presence of both a carbonyl group and an α,β-unsaturated carbonyl. The ^1H NMR showed two singlets at δ 6.17 and 5.44 for the protons on the exocyclic double bond. The sharp singlet at δ 4.39 could be attributed to the proton on C-1 as in the case of compound **32**, the signal appearing down-field since it is adjacent to both a double bond and a carbonyl group. The ^{13}C NMR spectrum supported the assigned structure by showing the signals due to the carbonyl carbons at δ 211.1 and 197.3 and the olefinic carbons at δ 149.4 and 120.8. All other signals appeared upfield between δ 51.8 and 38.6.

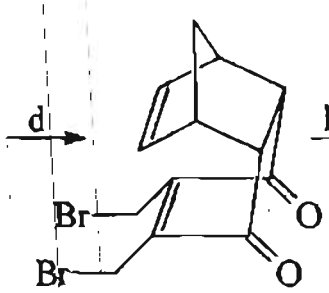
The cycloadduct **39** was also readily identified by means of its spectral data. Its IR spectrum showed strong absorption peaks at 1748 and 1717 cm^{-1} due to the carbonyl groups. The ^1H NMR spectrum showed no signals in the olefinic region, all the protons gave signals between δ 3.62 and 1.95. Of these, the ½ABq signals at δ 3.62 and 3.45 were attributed to the protons on the bromomethyl group. The norbornyl bridge protons appeared as the characteristic ½ABq signals at δ 2.08 and 1.95. The ^{13}C NMR spectrum confirmed the absence of double bonds. The only signals down-field of $CDCl_3$ were the two signals due to the carbonyl carbons at δ 210.3 and 209.1. The other signals appeared up-field between δ 55.3 and 30.5. Thus, the compound **39** could be assigned the structure of 1-(bromomethyl)pentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione.

2.2.4 Synthesis and Attempted Photolysis of 4,5-Bis(bromomethyl)tricyclo [6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione:

After studying the photolysis pathway of 5-(bromomethyl)tricyclo[6.2.1.$0^{2,7}$] undec-4,9-diene-3,6-dione **37**, further confirmation of the role of the allylic bromomethyl group in spearheading the rearrangement was sought. The next derivative prepared was the 4,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **44**. Synthesis started from the commercially available 2,3-dimethyl-1,4-quinol **40** which was O-methylated using the same procedure as before using a solution of dimethyl sulphate in aqueous sodium hydroxide (Scheme XXI).[12] The 2,3-dimethyl-1,4-quinol dimethyl ether **41** formed was identified by its proton NMR which showed the two aromatic protons at δ 6.61, the six methoxy protons as a singlet at δ 3.76 and the six methyl protons as another singlet at δ 2.15.

The two methyl groups in the compound **41** were brominated using *N*-bromosuccinimide with AIBN acting as the catalytic initiator (Scheme XXI). The ^{1}H NMR spectrum of the product **42** clearly showed that the two methyl groups had been replaced by two bromomethyl groups since the signal at δ 2.15 in the starting material had disappeared and another had appeared downfield at δ 4.67 as a singlet integrating for only four protons. The two aromatic protons were seen as a singlet at δ 6.75 and the six methoxy protons were seen as another singlet at δ 3.77.





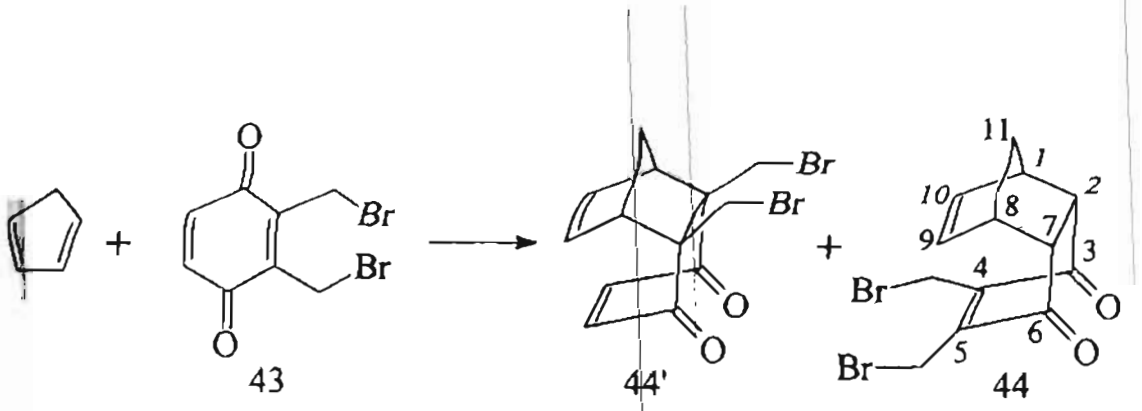
intractable mixture

a) dimethyl sulphate (5 eq.) NaOH (10 eq.), 0 °C-RT, then 70 °C, 4 d, 75%. b) NBS (2.5 eq.), AIBN (cat.), dry benzene, reflux, 3 h, 76%. c) CAN, acetonitrile-water (3:1), 0 °C-RT, 1 h, 78%. d) CPD (3 eq.), dry benzene, 0 °C-RT 2 d, 94%.

Scheme XXI

The 2,3-bis(bromomethyl)-1,4-hydroquinone dimethyl ether **42** was oxidised to the corresponding 2,3-bis(bromomethyl)-1,4-quinone **43** using ceric ammonium nitrate in a 3:1 solution of acetonitrile and water (Scheme XXI). The quinone **43** showed the absence of methoxy protons in its proton NMR spectrum. The two aromatic protons appeared as a singlet at δ 6.88 and the four methylene protons appeared as another singlet at δ 4.39.

The quinone **43** was reacted with freshly cracked cyclopentadiene in order to obtain the required tricyclic photolysis precursor (Scheme XXI). In the reaction of this quinone with cyclopentadiene, there exists the possibility of diene adding to either of the sides of the quinone leading to two products **44** and / or **44'** as shown in scheme XXII.



43 44' 44

Scheme XXII

However, the only product obtained in the reaction was identified as the required compound 4,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **44** on the basis of its spectral data. The IR spectrum as expected showed the presence of an α,β-unsaturated carbonyl moiety with a strong absorption at 1663 associated with a weaker one at 1613 cm^{-1}. The ^1H NMR spectrum (Fig. 8) was much simplified due to the symmetric nature of the compound, the two olefinic protons appeared together as a singlet at δ 6.11, the four methylene protons on the bromomethyl groups showed up at δ 4.29 as a doublet of a doublet (J_1 = 27.3 Hz, J_2 = 9.6 Hz). The two protons on the norbornyl ring α to the ketones (on C-2 and C-7) appeared as a singlet at δ 3.59 and the two protons α to the double bond (on C-1 and C-8) appeared as a singlet at δ 3.37. The methylene protons on the norbornyl bridge appeared as a doublet of a doublet at δ 1.52 (J_1 = 24.8 Hz, J_2 = 8.7 Hz). The ^{13}C NMR spectrum (Fig. 9) showed only 7 signals with equivalent carbons appearing at the same place. The two carbonyl carbons were seen at δ 196.2, the two disubstituted olefinic carbons at δ 146.5, the other two olefinic carbons at δ 135.3, the bromomethyl carbons at δ 49.2, the four tertiary carbons on the norbornyl ring at δ 49.9 and 48.6 and the norbornyl methylene at δ 20.8. Since the ^1H NMR spectrum showed only two olefinic protons, it seemed obvious that the diene had added to the less hindered side of the quinone to give the required tricyclic adduct. Further confirmation was given by the DEPT-135 spectrum which showed only one signal at δ 135.3 in the olefinic region indicating that the other olefinic carbons were substituted with the bromomethyl groups.

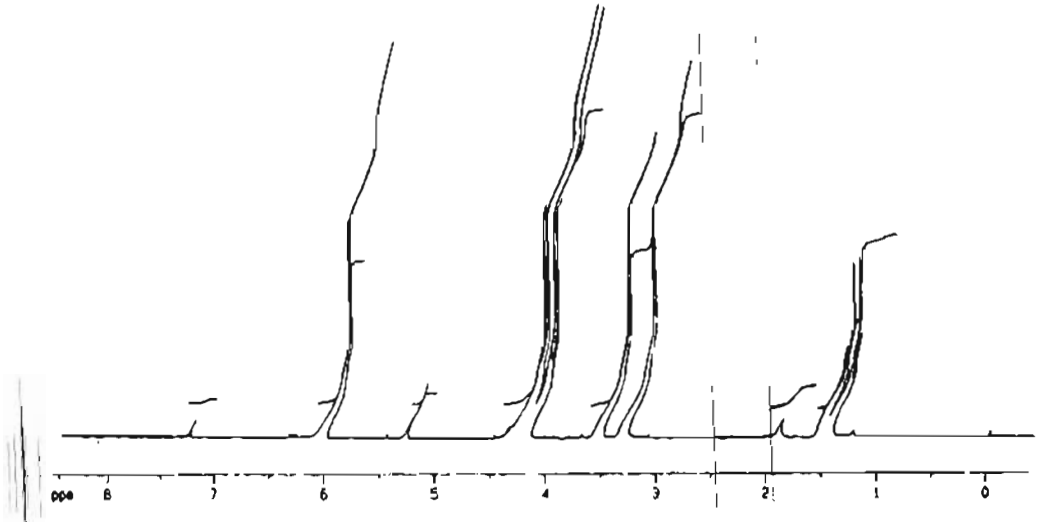


Figure 8: ^{1}H NMR Spectrum of 44

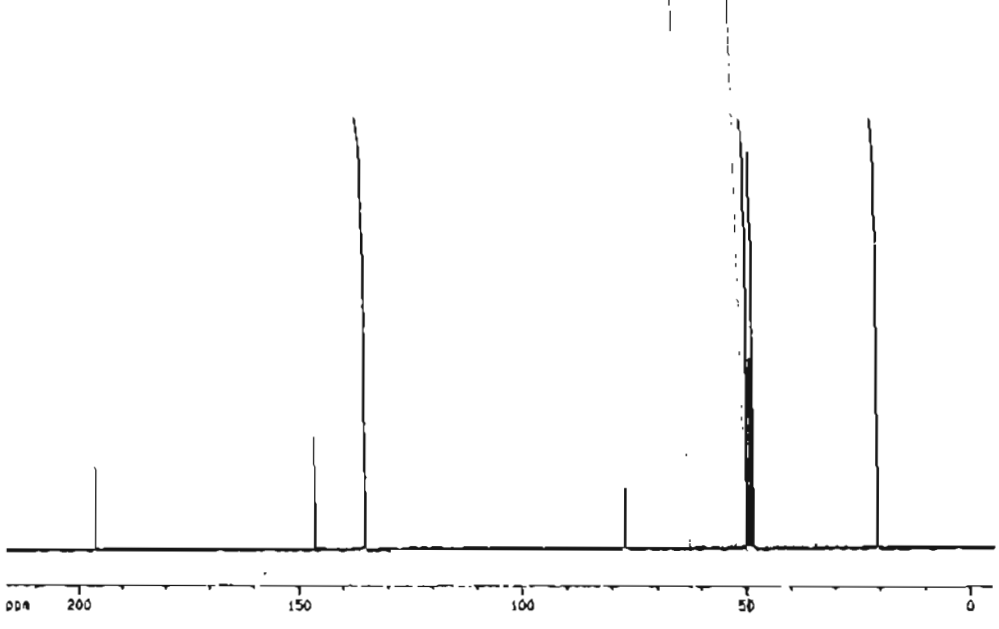


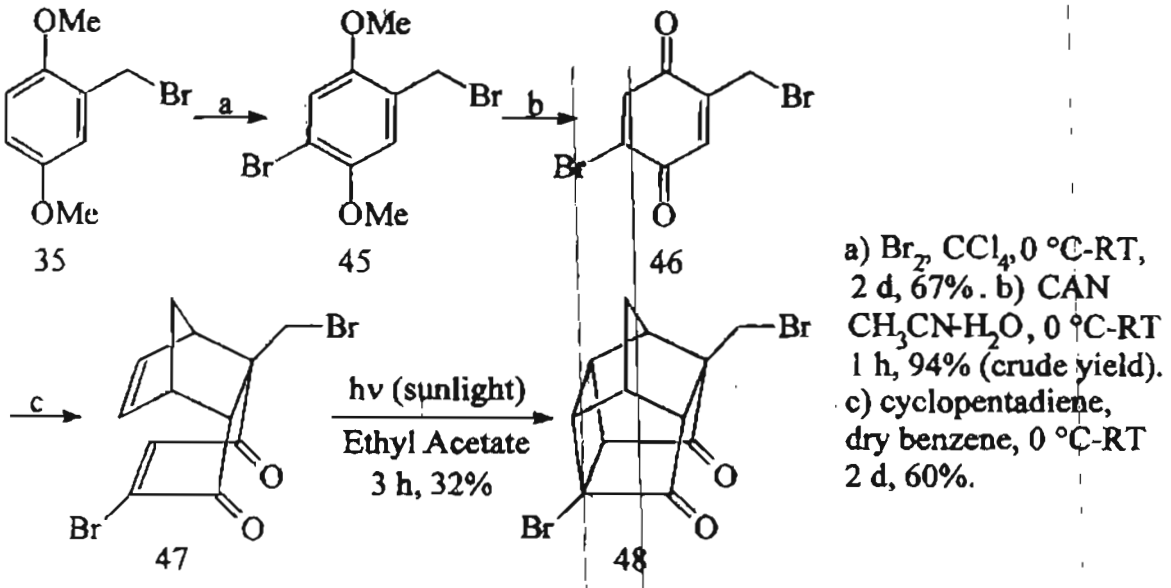
Figure 9: ^{13}C NMR Spectrum of 44

It is probable that the other isomer **44'** did not form due to steric hindrance caused by the two bromomethyl groups to the addition of cyclopentadiene to the tetra-substituted double bond in the quinone **43**.

However, on photolysis of this Diels-Alder adduct **44** under standard reaction conditions (Scheme XXI), the reaction mixture was seen to turn black and led to an intractable mixture not amenable to separation by column chromatography. Indubitably, the two reactive allylic bromines had both formed radicals under the reaction conditions and then given rise to cascade reactions leading to a large number of products.

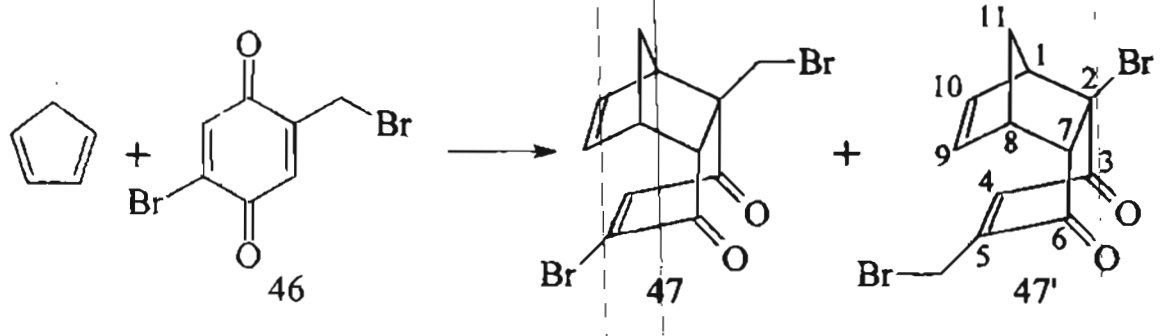
2.2.5 Synthesis and Photolysis of 5-Bromo-2-(bromomethyl)tricyclo [6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione:

In continuation of the earlier studies, the synthesis of another derivative **47'** with the required bromomethyl group on C-5 of the double bond of the tricyclic enone was attempted using a synthetic sequence starting from the 2-(bromomethyl)-1,4-hydroquinone dimethyl ether **35** prepared earlier. This compound **35** was treated with a solution of molecular bromine in carbon tetrachloride which resulted in ring bromination and gave rise to 2-bromo-5-(bromomethyl)-1,4-hydroquinone dimethyl ether **45** (Scheme XXIII). This was characterised in the following manner: in the proton NMR spectrum, two protons showed up separately in the aromatic region at δ 7.08 and δ 6.89 indicating that they were no longer equivalent, the six methoxy protons appeared as two singlets at δ 3.85 and δ 3.84, and the methylene protons appeared at δ 4.51 as a singlet.



Scheme XXIII

The quinol dimethyl ether **45** was oxidised to the quinone **46** using CAN in acetonitrile-water (Scheme XXIII). But 2-bromo-5-(bromomethyl)-1,4-quinone **46** proved to be unstable and could not be purified by column chromatography. Hence the crude product was treated with freshly cracked cyclopentadiene in order to obtain the Diels-Alder adduct (Scheme XXIII). The reaction of this unsymmetric quinone with cyclopentadiene was expected to give rise to two products **47** and **47'** as shown in scheme XXIV.



Scheme XXIV

The Diels-Alder reaction however, gave rise to only one product in moderate yield, and this was identified as the compound **47** by comparision of its spectral data with that of 2,5-bis(bromomethyl)tricyclo[6.2.1.02,7]undec-4,9-diene-3,6-dione **22**. Its IR spectrum showed the expected absorptions due to the α,β-unsaturated dione system at 1688 and 1676 cm^{-1}. The ^1H NMR spectrum (Fig. 10) showed one olefinic

proton α to the carbonyl group as a singlet at δ 7.27 and the other two as a doublet of a doublet at δ 6.14 (J_1 = 7.2 Hz, J_2 = 2.5 Hz). The other protons on the norbornyl system appeared as doublet at δ 4.04 (J = 9.6 Hz), a singlet at δ 3.53, another singlet at δ 3.15 and the methylene protons on the norbornyl bridge appeared at δ 1.65 as a singlet. The protons on the bromomethyl group appeared upfield as a multiplet between δ 3.35-3.29. The absence of the signal downfield indicated that the bromomethyl group was not present on an olefinic carbon. The ^{13}C NMR spectrum (Fig. 11) supported this structure showing the carbonyls at δ 197.1 and 190.7, the four olefinic carbons at δ 144.3, 143.8, 137.3 and 136.3. The other signals came upfield between δ 60.2 and 39.9.

This Diels-Alder adduct 5-bromo-2-(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **47** under standard photolysis reaction conditions (Scheme XXIII) underwent the expected [2 + 2] cycloaddition to give the pentacyclic product **48** which was characterised in the following manner. Its IR spectrum showed the carbonyl absorptions as two peaks at 1746 and 1744 cm^{-1}. The proton NMR spectrum (Fig. 10) showed all the signals between δ 3.54 and 1.92 indicating the total absence of olefinic groups. The protons on the bromomethyl group appeared as ½ABq signals at δ 3.54 and 3.38. The norbornyl methylene protons also appeared as ½ABq signals at δ 2.23 and 1.92. The ^{13}C NMR spectrum (Fig. 11) showed two carbonyls at δ 205.9 and 202.0 and the other signals appeared upfield between δ 62.2 and 29.6 confirming the absence of olefinic groups. The HRMS value of 343.9043 also supported the required molecular formula of $C_{12}H_{10}O_2Br_2$. Thus, the cycloadduct was identified as 1-bromo-9-(bromomethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **48**.

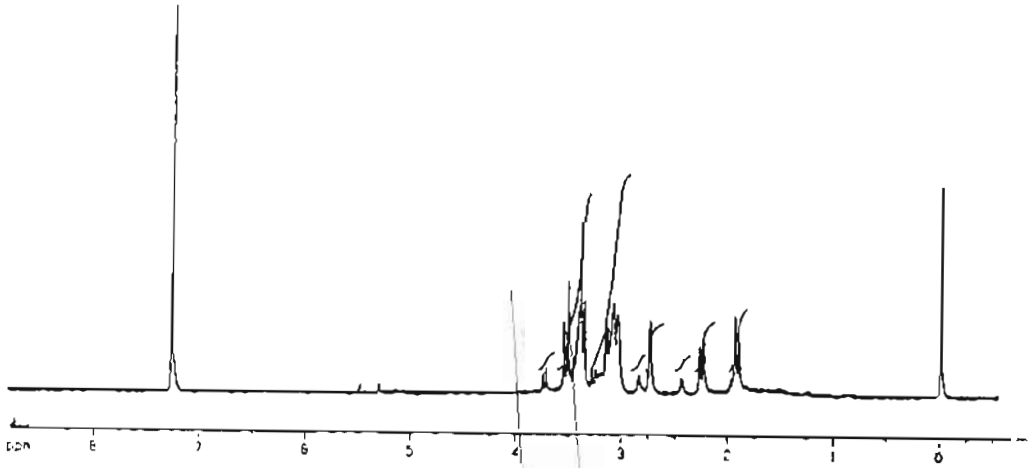


Figure 10: ^{1}H NMR Spectrum of 48

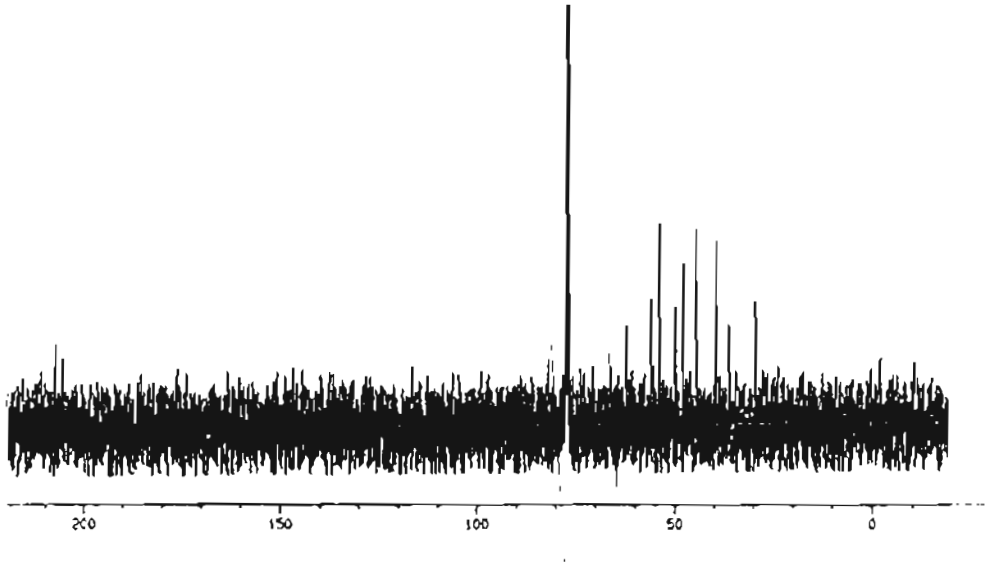


Figure 11: ^{13}C NMR Spectrum of 48

In order to account for the total absence of the expected product **47'** in the Diels-Alder addition, various studies were carried out. The calculation of molecular orbital coefficients using the PC SPARTAN Graphical Interface Package[13] allowed the rationalisation of the formation of a single product (Fig. 12).

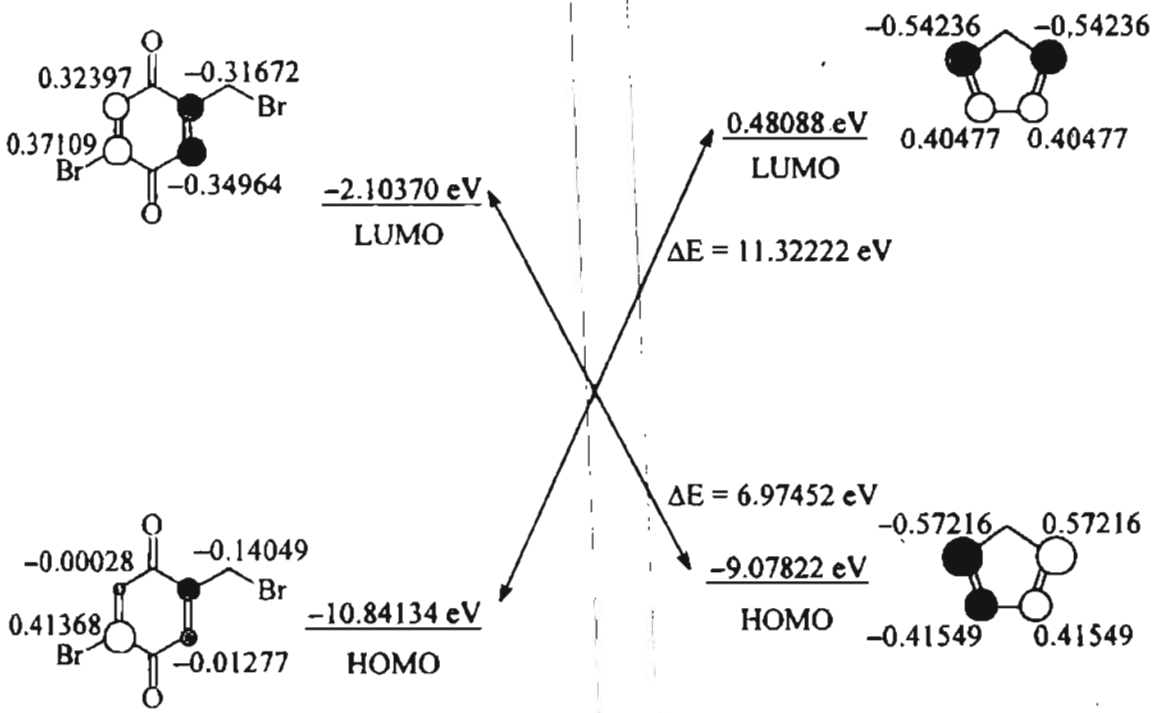


Figure 12

As the figure shows, the signs of the orbital coefficients of the reacting carbon centres show the interaction between HOMO of the diene and LUMO of the dienophile is not possible in spite of the favourable energy difference. In the interaction of the LUMO of the diene with the HOMO of the dienophile too, the signs of the orbital coefficients allow addition from only one side of the quinone since the signs of the orbital coefficients are not compatible on the other side. Thus, an inverse electron demand Diels-Alder pathway is followed and a single product **47** is obtained from this reaction.

Thus we have succeeded in preparing several novel substituted PCUDs and also in unravelling the mechanism of a radical rearrangement which develops an

alternate route to tetracyclic compounds. In the next two chapters, further reactions and rearrangements of the compounds prepared have been explored.

2.3 Experimental:

General Experimental Details:

All melting points are uncorrected and were determined on a Meltemp II hot stage melting point apparatus. Ultrasonication was carried out using Julabo sonicator. The IR spectra were taken on Nicolet (Impact 400D FT-IR) spectrophotometer or Bomem MB-Series FT-IR spectrophotometer. NMR spectra were recorded on Brüker-300 MHz or 500 MHz NMR spectrometer. NMR spectra were obtained using chloroform-d_1 or a 7:3 mixture of $CDCl_3$ and CCl_4 as solvent unless otherwise mentioned. Chemical shifts are given in δ-scale with tetramethyl silane as internal standard. Abbreviations used in ^1H NMR are: s – singlet, d – doublet, dd – doublet of a doublet, brs – broad singlet, q – quartet and m – multiplet.

Analytical thin layer chromatography (tlc) was performed on glass plates coated with silica gel (Merck) containing 13% calcium sulphate as binder. Column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether (60-80 °C) and ethyl acetate for elution unless otherwise specified. The solvents were removed (under reduced pressure where necessary) using Heidolph or Buchi rotary evaporator. All solvents were distilled prior to use and reactions requiring dry conditions were carried out using dry solvents which were dried according to the literature procedure.[14]

Extraction of the reaction mixtures were done with the appropriate organic solvents, the extraction was repeated with fresh solvent at least three times before the organic layers were combined. Washing of the combined organic layer was also repeated three times in each case (distilled water, saturated sodium bicarbonate solution, brine, etc. as required by the procedure). Reactions conducted in an ice-water bath imply a temperature range of 5-10 °C.

Bromomethylation of hydroquinone dimethyl ether **19** to give **20**:

The hydroquinone dimethyl ether **19** (5.04 g, 36.5 mmol) and 3.41 g (0.11 mol, 3 eq.) of paraformaldehyde were taken in 100 ml of glacial acetic acid in a 250 ml flask. Hydrobromic acid in glacial acetic acid (20 ml of a 33% w/v solution, 0.11 mol, 3 eq.) was added to this and then the reaction mixture was sonicated for one hour. The reaction was worked up by pouring into ~ 100 ml of a mixture of ice and water. The precipitate was filtered out and washed with water and then dried. Crystallisation from dichloromethane-petroleum ether gave 5.16 g (65% yield) of the bis(bromomethylated) product **20**.

m.p. (°C)	:	203-205 (Lit. 200-202).[11]
FT-IR (KBr, ν_{max}/cm^{-1})	:	2960, 1510, 1460, 1400, 1320, 1230, 1035, 885, 725.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 6.86 (s, 2H), 4.53 (s, 4H), 3.86 (s, 6H).

Oxidation of the 2,5-bis(bromomethyl)-1,4-hydroquinone dimethyl ether **20** to give **21**:

2,5-Bis(bromomethyl)-1,4-hydroquinone dimethyl ether **20** (3.02 g, 9.3 mmol) was taken in a round-bottomed flask. 60 ml of glacial acetic acid was added and the solution was cooled in an ice-water bath. Nitric acid (38 ml) was slowly added to the above solution and then the reaction mixture was left stirring to come to room temperature. After one hour, all the starting material was seen to have dissolved and the solution was an intense yellow colour. It was worked up by pouring into ~ 100 ml of a mixture of ice and water. The solid precipitate was filtered out and dried. Column chromatography on silica gel gave 1.21 g of the quinone. This was recrystallised from dichloromethane-petroleum ether to give 1.16 g (42% yield) of bright yellow crystals of the quinone **21**.

m.p. (°C)	:	122-124 (Lit. 123-126).[11]
FT-IR (KBr, ν_{max}/cm^{-1})	:	1675, 1440, 1355, 1255, 1205, 1180, 940, 920, 910.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 6.87 (s, 2H), 4.19 (s, 4H).

Preparation of 2,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **22** from **21**:

A solution of 2,5-bisbromomethyl-1,4-benzoquinone **21** (0.85g, 2.9 mmol) in dry benzene (20 ml) was cooled in an ice-water bath (~ 10 °C) and freshly cracked cyclopentadiene (0.50 ml, 6.1 mmol, 2 eq.) was added drop by drop. The reaction mixture was left stirring at room temperature for 15 hours, tlc then indicated that the starting material had been completely consumed. The reaction was worked up by removing the solvent under reduced pressure and the residue was purified by silica gel column chromatography using 5% ethyl acetate in petroleum ether as the eluent which afforded the Diels-Alder adduct **22** as a pale yellow solid (0.92 g, 88% yield). This was recrystallised from CH_2Cl_2-petroleum ether mixture giving pale yellow diamond shaped crystals of **22**.

m.p. (°C)	:	110-112.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3036, 2982, 1675, 1657, 1538, 1331, 1237.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.72 (s, 1H), 6.14-6.07 (m, 2H), 4.28 (½ABq, J = 11.5 Hz, 1H), 4.06 (d, J = 9.2 Hz, 2H), 4.03 (½ABq, J = 11.5 Hz, 1H), 3.51-3.49 (m, 1H), 3.30-3.23 (m, 2H), 3.14-3.13 (m, 1H), 1.61 (s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 199.7, 196.3, 148.8, 140.1, 136.7, 136.4, 59.9, 55.9, 54.2, 49.9, 47.2, 39.9, 25.3.
C / H Analysis	:	Calculated for $C_{13}H_{12}O_2Br_2$ C: 43.37, H: 3.36. Found C: 43.70, H: 3.32.
UV (CH_2Cl_2, λ_{max})	:	243 nm.

Chloromethylation of hydroquinone dimethyl ether **19** to give **23**:

The hydroquinone dimethyl ether **19** (10.11 g, 73.2 mmol) was taken in 100 ml of glacial acetic acid along with 7.25 g (0.24 mol, 3 eq.) of paraformaldehyde in a 250 ml round-bottomed flask. This was sonicated for five minutes to dissolve the hydroquinone dimethyl ether and 25 ml of concentrated hydrochloric acid was added and then the reaction mixture was sonicated for one hour. The reaction mixture was

worked up by pouring into ~ 100 ml of ice-cold water. The precipitate was filtered and dried (initially using filter paper and then by using $CaCl_2$ in a desiccator). The crude product was crystallised from a mixture of dichloromethane and petroleum ether to give 10.75 g (63% yield) of the analytically pure sample of **23** (off-white powdery crystals).

m.p. (°C)	:	163-165 (Lit. 164 °C).[15]
FT-IR (KBr, ν_{max}/cm^{-1})	:	3748, 2945, 1513, 1463, 1406, 1212, 1037, 680.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.64 (s, 2H), 4.63 (s, 4H), 3.69 (s, 6H).

Oxidation of 2,5-bis(chloromethyl)-1,4-hydroquinone dimethyl ether **23** to give **24**:

The 2,5-bis(chloromethyl)-1,4-hydroquinone dimethyl ether **23** (6.01 g, 25.6 mmol) was taken in 50 ml of glacial acetic acid and the reaction mixture was cooled in a mixture of ice-water. To the cooled solution was added 75 ml of concentrated nitric acid. The reaction mixture was allowed to attain room temperature and further stirred for one hour. It was worked up by pouring the reaction mixture slowly into ~ 100 ml of a mixture of ice and water. The product was removed by suction filtration and dried. The crude material was purified on a silica gel column (packed and eluted with 5 % ethyl acetate in petroleum ether). The pure product **24** was obtained in 26% yield after crystallisation from dichloromethane-petroleum ether as bright yellow crystals.

m.p. (°C)	:	98-100 (Lit. 97-99 °C).[16]
FT-IR (KBr, ν_{max}/cm^{-1})	:	2984, 2947, 1660, 1415, 1335, 1225, 1100, 940, 780, 665.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.96 (s, 2H), 4.43 (s, 4H).

Diels-Alder reaction of 2,5-bis(chloromethyl)-1,4-quinone with **24** cyclopentadiene to give **25**:

The quinone **24** (0.64 g, 3.2 mmol) was dissolved in dry benzene and the solution was cooled in an ice-water bath. Cyclopentadiene (0.60 ml, 7.3 mmol, 2 eq.) was added slowly to this solution drop-by-drop. The reaction mixture was left stirring at room temperature for 20 hours. It was worked up by removing benzene under reduced

pressure and then purified on a silica-gel column. The compound was recrystallised from dichloromethane-petroleum ether and gave light yellow coloured crystals (0.74 g, 87% yield) of the Diels-Alder adduct 2,5-bis(chloromethyl)tricyclo[6.2.1.$0^{2,7}$] undec-4,9-diene-3,6-dione **25**.

m.p. (°C)	:	118-120.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3020, 2982, 1670, 1625, 1432, 1334, 1279, 1241, 1073, 708.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.82 (s, 1H), 6.12 (s, 2H), 4.38-4.19 (m, 3H,), 3.50-3.42 (m, 2H), 3.25-3.23 (m, 1H), 3.12 (s, 1H), 1.64 (s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 199.3, 196.8, 148.6, 140.1, 136.9, 136.4, 60.1, 55.0, 53.1, 51.8, 49.8, 47.2, 39.6.
UV (CH_2Cl_2, λ_{max})	:	239 nm.

Acetoxymethylation of 2,5-bis(bromomethyl)-1,4-hydroquinone dimethyl ether **20** to give **26**:

2,5-Bis(bromomethyl)-1,4-hydroquinone dimethyl ether **20** (5.56 g, 17.2 mmol) was taken in a round-bottomed flask along with 3.64 g (44.5 mmol, 2.5 eq.) of sodium acetate and 160 ml of glacial acetic acid. This was heated at 80 °C for 5 hours. At the end of this period, the glacial acetic acid was removed under reduced pressure on the rotary evaporator and the residue diluted with ~ 100 ml of distilled water and extracted with dichloromethane. The combined dichloromethane extracts were washed successively with distilled water, saturated sodium bicarbonate solution, distilled water and brine, and finally dried over anhydrous sodium sulphate. The dichloromethane was removed and the crude product was crystallised from dichloromethane-petroleum ether to give 4.05g (84% yield) of off-white crystals of **26.**

m.p. (°C)	:	117-120 (Lit. 122-123 °C).[17]
FT-IR (KBr, ν_{max}/cm^{-1})	:	2995, 2946, 1736, 1511, 1468, 1377, 1247, 1216, 1030, 860.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.89 (s, 2H), 5.13 (s, 4H), 3.82 (s, 6H),

2.10 (s, 6H).

Oxidation of 2,5-bis(acetoxymethyl)-1,4-hydroquinone dimethyl ether **26** to give **27**:

2,5-Bis(acetoxymethyl)-1,4-hydroquinone dimethyl ether **26** (2.07 g, 7.3 mmol) was taken in a round-bottomed flask with 80 ml of a 3:1 mixture of acetonitrile-water. The reaction mixture was cooled in an ice-water bath and 20.28 g (36.9 mmol, 5 eq.) of ceric ammonium nitrate was added slowly to it. The reaction mixture was allowed to come to room temperature after the addition was completed and then left stirring for one hour. It was worked up by adding ~ 100 ml of distilled water and extracting into dichloromethane. The dichloromethane layer was washed with distilled water and dried with brine and anhydrous sodium sulphate. Dichloromethane was removed on the rotary evaporator and the crude material was purified on a silica-gel column. Elution with 30% ethyl acetate in petroleum ether gave the product. This was crystallised from dichloromethane-petroleum ether to give bright yellow crystals of the quinone **27** (1.26 g, 68% yield).

m.p. (°C)	:	133-137 (Lit. 132-134 °C).[11]
FT-IR (KBr, ν_{max}/cm^{-1})	:	1748, 1645, 1426, 1365, 1322, 1268, 1219, 1036, 927.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.67 (s, 2H), 4.98 (s, 4H), 2.17 (s, 6H).

Diels-Alder Reaction of 2,5-bis(acetoxymethyl)-1,4-quinone **27** with cyclopentadiene to give **28**:

The quinone **27** (0.81 g, 3.2 mmol) was taken in a round-bottomed flask and dissolved in 50 ml of dry benzene. The reaction mixture was cooled in an ice-water bath and 0.32 ml of freshly cracked cyclopentadiene was added drop-by-drop to it. The reaction mixture was left stirring for a day and further 0.30 ml of cyclopentadiene was added after cooling the reaction mixture in an ice-water bath. After another twenty-four hours, the starting material was still present in the reaction mixture as indicated by the tlc, so another 0.36 ml of cyclopentadiene (11.9 mmol, 3.5 eq. total) was added as before and stirred at room temperature for further twenty-four hours. At the end of this time, the reaction mixture was worked up by removing the solvent and the

product purified on a silica-gel column. Crystallisation from dichloromethane-petroleum ether gave 1.001 g of the Diels-Alder adduct **28** in the form of light yellow crystals (98% yield).

m.p. (°C) : 116-117.

FT-IR (KBr, ν_{max}/cm^{-1}) : 3055, 2982, 1742, 1669, 1626, 1371, 1225, 1030, 921, 884.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.54 (s, 1H), 6.09 (s, 2H), 4.86 (q, J = 15.7 Hz, 2H), 4.51 (½ABq, J = 10.6 Hz, 1H), 4.16 (½ABq, J = 10.6 Hz, 1H), 3.49 (s, 1H), 3.17 (s, 1H), 3.08 (d, J = 3.8 Hz, 1H), 2.13 (s, 3H), 1.97 (s, 3H), 1.68-1.56 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) : 199.7, 197.7, 170.2, 169.7, 148.0, 137.5, 136.9, 135.9, 71.4, 59.6 (2C), 57.0, 53.9, 50.9, 49.6, 47.1, 20.7.

UV (CH_2Cl_2, λ_{max}) : 240 nm.

Friedel-Crafts reaction of 2,5-bis(bromomethyl)-1,4-hydroquinone dimethyl ether **20** to give 2,5-bis(benzyl)1,4-hydroquinone dimethyl ether **29**:

2,5-Bis(bromomethyl)-1,4-hydroquinone dimethyl ether **20** (3.25 g, 10.0 mmol) was taken in a dry round-bottomed flask along with Montmorillonite K 10 clay (1.70 g, activated by heating at 85 °C for 2 hours). To this was added 100 ml of dry benzene and the reaction mixture was refluxed for 18 hours. At the end of this period, tlc showed that all the starting material had been consumed. The reaction was worked up by filtering out the clay using Whatman grade 1 filter paper, and then benzene was removed on a rotavapor under reduced pressure. The crude product was purified on a silica-gel column and the compound crystallised from dichloromethane-petroleum ether. The product **29** was obtained in 66% yield (2.10 g).

m.p. (°C) : 97-100 (Lit. 100-102 °C).[18]

FT-IR (KBr, ν_{max}/cm^{-1}) : 3030, 2937, 1495, 1451, 1401, 1220, 1039, 696.

^1H NMR (300 MHz, $CDCl_3$) : δ 7.28-7.14 (m, 10H), 6.62 (s, 2H), 3.94 (s,

4H), 3.68 (s, 6H).

Oxidation of 2,5-bis(benzyl)-1,4-hydroquinone dimethyl ether **29** to give **30**:

2,5-Bis(benzyl)-1,4-hydroquinone dimethyl ether **29** (150 mg, 0.5 mmol) was taken in a round-bottomed flask along with 10 ml of a 3:1 solution of acetonitrile-water and the mixture was cooled in ice-water bath. Ceric ammonium nitrate (1.17 g, 2.1 mmol, 4 eq.) was added slowly to this cooled solution and then the reaction mixture was left stirring at room temperature for 1 hour at which time tlc indicated the absence of starting material. The reaction mixture was worked up by removing the acetonitrile on the rotavapor under reduced pressure and the reaction mixture was diluted with water and extracted with dichloromethane. The combined dichloromethane layer was washed with distilled water and brine; and dried over anhydrous sodium sulphate. After evaporation, the crude product was purified on a silica-gel column and crystallised from dichloromethane-petroleum ether to give 71 mg (52% yield) of the quinone **30**.

m.p. (°C)	:	134-136 (Lit. 136 °C).[19]
FT-IR (KBr, ν_{max}/cm^{-1})	:	3025, 1650, 1614, 1493, 1450, 1304, 1231, 1091, 896.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 7.27-7.09 (m, 10H), 6.28 (s, 2H), 3.64 (s, 4H).

Diels-Alder reaction of 2,5-bis(benzyl)-1,4-quinone **30** with cyclopentadiene to give **31**:

The quinone **30** (0.07 g, 0.25 mmol) prepared in the earlier step was taken in a round-bottomed flask and dissolved in 10 ml of dry benzene. This solution was cooled in an ice-water bath and then 0.04 ml of cyclopentadiene was added to the solution drop-by-drop. After the addition was complete, the reaction mixture was left stirring at room temperature for two days. Since some starting material remained unreacted, the reaction mixture was again cooled in ice and 0.04 ml of cyclopentadiene (total 0.08 ml, 0.97 mmol, 4 eq.) was added. The reaction mixture was further left stirring for 2 days whereupon the tlc indicated complete consumption of the starting material. The

reaction was worked up by removing the benzene under reduced presuure on a rotavapor and the crude product was purified on a silica-gel column. The material thus obtained was crystallised from dichloromethane-petroleum ether to give the light-yellow crystals of the product **31** (0.06 g, 68% yield).

m.p. (°C)	:	125-128.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3033, 2979, 1655, 1619, 1487, 1451, 1332, 1242, 686.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 7.26-7.16 (m, 6H), 6.98-6.96 (m, 2H), 6.75-6.73 (m, 2H), 6.10-6.08 (m, 1H), 6.03 (s, 1H), 5.87-5.85 (m, 1H), 3.52-3.15 (m, 6H), 2.68 (d, J = 12.9 Hz, 1H), 1.77 (½ABq, J = 9.1 Hz, 1H), 1.58 (½ABq, J = 9.1 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 202.9, 198.9, 152.8, 140.4, 138.1, 135.4, 129.5 (2C), 128.9 (2C), 128.6 (2C), 128.5 (2C), 126.9 (2C), 126.6 (2C), 59.7, 54.5, 53.7, 49.5, 46.7 (2C), 35.2.
UV (CH_2Cl_2, λ_{max})	:	239 nm.

Photolysis of 2,5-bis(chloromethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **25** to give **16**:

The Diels-Alder adduct **25** (0.74 g, 2.7 mmol) was taken in a clean and dry round-bottomed flask and dissolved in 80 ml of dry ethyl acetate. The round-bottomed flask was closed with a septum and the solution was degassed by passing argon gas through it for five minutes. The round-bottomed flask was connected to a balloon containing argon gas and then exposed to sunlight for 2 hours. At the end of this period, the UV active starting material absent and a non-UV active product had formed. The reaction was worked up by removing the solvent under reduced pressure on a rotavapor and the crude material was purified by column chromatography on silica-gel. The pure product was crystallised from a mixture of dichloromethane and petroleum ether to give off-white crystals of **16** (0.61 g, 83% yield).

m.p. (°C)	:	88-90.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2970, 1757, 1738, 1430, 1284, 1146, 1100, 732.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 3.77-3.51 (m, 4H), 3.23-3.17 (m, 2H), 3.03-2.99 (m, 2H), 2.82-2.79 (m, 1H), 2.62 (d, J = 3.4 Hz, 1H), 2.27 (½ABq, J = 11.7 Hz, 1H), 1.95 (½ABq, J = 11.7 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 208.9, 208.1, 62.8, 58.9, 52.6, 46.9, 46.2, 43.7, 41.9, 41.7, 41.5, 39.3, 34.9.
C / H Analysis	:	Calculated for $C_{13}H_{12}O_2Cl_2$ C: 57.58, H: 4.46. Found C: 57.74, H: 4.45.

Photolysis of 2,5-bis(acetoxymethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **28** to give **17**:

2,5-Bis(acetoxymethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **28** was dissolved in dry ethyl acetate [0.85 g (2.7 mmol) in 160 ml] and the solution was degassed with argon. The round-bottomed flask was fitted with a balloon containing argon and then exposed to bright sun-light for 2 hours. At the end of this period, tlc showed the absence of starting material. The reaction was therefore worked up by removing the solvent on the rotavapor under vacuum and the residue was purified on a silica gel column. The pure compound **17** thus obtained was crystallised from dichloromethane-petroleum ether (0.76 g, 88% yield).

m.p. (°C)	:	117-119.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2995, 2964, 1762, 1741, 1725, 1443, 1383, 1249, 1225, 1036, 976.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 4.24-4.08 (m, 4H), 3.19-3.14 (m, 1H), 3.09-3.05 (m, 1H), δ 2.95 (brs, 1H), 2.83 (d, J = 5.1 Hz, 1H), 2.72 (d, J = 6.4 Hz, 1H), 2.49 (d, J = 2.6 Hz, 1H), 2.17 (½ABq, J = 11.6 Hz, 1H), 2.08 (s, 6 H), 1.89 (½ABq, J = 11.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 209.5, 208.4, 170.6 (2C), 61.3, 61.1, 61.0, 57.8 (2C), 50.9, 46.5, 45.5, 43.7, 41.4, 39.6, 35.5, 20.8.
C/H Analysis	:	Calculated for $C_{17}H_{18}O_6$ C: 64.14, H: 5.70. Found C: 64.33, H: 5.69.

Photolysis of 2,5-bis(benzyl)tricyclo[6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione **31** to give **18**:

The Diels-Alder adduct **31** (60 mg, 0.17 mmol) was dissolved in dry ethyl acetate (10 ml) and degassed with argon. The reaction vessel was fitted with an argon-filled balloon and kept in direct sunlight for 1 hour. When the reaction was seen to be complete on tlc, it was worked up by removing the solvent on the rotavapor. The crude product was purified on a silica-gel column using 5% ethyl acetate in petroleum ether as the eluent and the pure compound **18** thus obtained was crystallised from a mixture of dichloromethane and petroleum ether (54 mg, 92% yield).

m.p. (°C)	:	121-123.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3030, 2975, 1750, 1480, 1431, 1231, 1140, 1100, 910, 680.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 7.23-7.13 (m, 10H), 3.06 (dd, J_1 = 28.3 Hz, J_2 = 14.2 Hz, 2H), 2.88-2.74 (m, 3H), 2.67-2.62 (m, 2H), 2.54-2.50 (m, 2H), 2.44 (d, J = 2.7 Hz, 1H), 1.77 (½ABq, J = 11.2 Hz, 1H), 1.65 (½ABq, J = 11.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	213.1, 212.0, 137.2 (2C), 130.4 (2C), 129.8 (2C), 128.3 (2C), 128.2 (2C), 126.4 (2C), 63.2, 60.9, 52.9, 47.9, 47.4, 43.9, 41.9, 39.6, 36.9, 35.1, 34.9.
HRMS (M^+)	:	354.1368, $C_{25}H_{22}O_2$ requires 354.1619.

Procedure for the photolysis of 2,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **22**:

The Diels-Alder adduct **22** (0.48 g, 1.3 mmol) was dissolved in 100 ml of dry ethyl acetate, degassed with argon gas and exposed to bright sunlight for two hours. At the end of this period tlc showed the complete consumption of starting material along with the formation of two products. The reaction was worked up by removing the solvent and the residue was separated using silica gel column chromatography. Elution of the column with 10% ethyl acetate in petroleum ether afforded **32** (0.30 g, 53%), *which crystallised from ethyl acetate-petroleum ether as white crystals. Further* elution of the column gave **15** (0.08 g, 17% yield) which crystallised from ethyl acetate-petroleum ether as pure white crystals.

Spectral Data for **32**:

m.p. (°C)	:	136-137.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2989, 1762, 1715, 1613, 1465, 1283, 1175, 960.
^{1}H NMR (500 MHz, $CDCl_3$)	:	*δ 6.21 (s, 1H), 5.49 (s, 1H), 4.41 (s, 1H),* 3.56 (½ABq, *J* = 10.6 Hz, 1H), 3.47 (d, *J* = 8.8 Hz, 1H), 3.28 (½ABq, *J* = 10.6 Hz, 1H), 3.25-3.22 (m, 1H), 3.09 (d, *J* = 4.9 Hz, 1H), 2.97-2.96 (m, 1H), 2.81 (½ABq, J = 11.9 Hz, 1H), 2.68 (d, *J* = 5.5 Hz, 1H), 1.98 (½ABq, *J* = 11.9 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 205.0, 194.7, 141.5, 124.8, 62.6, 59.1, *53.2, 52.2, 49.5, 45.8, 45.6, 36.6, 30.3.*
HRMS (M^+)	:	*359.9184, $C_{13}H_{12}O_2Br_2$ requires 359.9183.*
UV (CH_2Cl_2, λ_{max})	:	*230, 251* and 309 nm.

Crystal data for **32** (Fig. 7):

$C_{13}H_{12}Br_2O_2$, colourless crystalline solid, 0.33 x 0.20 x 0.12 mm., monoclinic, Space group : $P2_1/c$. *Unit cell dimensions : a = 14.2893(2) Å alpha = 90°; b = 13.5780(1) Å*

beta = 96.556(1)°; c = 12.9552(2) Å gamma = 90°. R indices (all data) : R1 = 0.0996, wR2 = 0.0847, Volume = 2497.13(6) $Å^3$, Z = 8. Density(calculated) = 1.915 Mg/m^3. F(000) = 1408. Absorption coefficient = 6.478 mm^{-1}.

Spectral Data for **15**:

m.p. (°C) : 95-96.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2975, 2874, 1755, 1431, 1236, 1142, 1101, 912, 730.

^1H NMR (300 MHz, $CDCl_3$) : δ 3.63 (½ABq, *J* = 10.8 Hz, 1H), 3.55 (½ABq, *J* = 10.9 Hz, 1H), 3.47 (½ABq, J = 10.8 Hz, 1H), 3.35 (½ABq, *J* = 10.9 Hz, 1H), 3.21-3.18 (m, 2H), 3.04-2.98 (m, 2H), 2.78-2.76 (m, 1H), 2.62 (d, *J* = 4.3 Hz, 1H), 2.25 (½ABq, *J* = 11.7 Hz, 1H), 1.94 (½ABq, *J* = 11.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 208.9, 207.9, 62.6, 60.3, 52.7, 48.0, 47.4, 43.9, 42.9, 39.5, 34.9, 30.0, 29.7.

HRMS (M^+) : 359.9184, $C_{13}H_{12}O_2Br_2$ requires 359.9183.

*O-Methylation of toluquinol **33** to give **34**:*

Toluquinol **33** *(5.27 g, 42.5 mmol) was taken in a solution of sodium hydroxide in distilled water (14.29 g, 357.4 mmol, 8 eq., in 50 ml of water) and* argon gas was passed through this solution for five minutes. The round-bottomed flask was fitted with a reflux condensor and the mixture was cooled in an ice-water bath. Dimethyl sulphate (21 ml, 0.22 mol, 5 eq.) was added to this solution slowly, taking care to ensure that the temperature did not go above ~10 °C. After the addition was complete, the reaction mixture was allowed to come to room temperature and then immersed in an oil-bath maintained at 50-60 °C. It was then stirred at this temperature for 2½ days. At the end of this period, the product could be observed as an oily layer on top of the aqueous layer. The reaction was worked up by diluting the aqueous layer with cold distilled water and then extracting with ether. The ether layer was washed with

distilled water and brine, and dried over anhydrous sodium sulphate. The crude material was purified on a silica-gel column using 2% ethyl acetate in petroleum ether to give **34** as a clear colourless oily liquid (6.28 g, 97% yield).

FT-IR (KBr, ν_{max}/cm^{-1}) : 2950, 2918, 1510, 1493, 1467, 1232, 1090, 786.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.64 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 2.20 (s, 3H).

Side-chain bromination of toluquinol dimethyl ether **34** using NBS to give **35**:

2-Methyl-1,4-hydroquinone dimethyl ether **34** (6.05 g, 39.8 mmol) was taken in 50 ml of dry carbon tetrachloride in a round-bottomed flask fitted with a reflux condensor and a calcium chloride guard-tube and 3.63 g *N*-bromosuccinimide was added. The reaction vessel was immersed in an oil-bath maintained at 85 °C and then a catalytic amount of AIBN was added. The reaction mixture was refluxed for ½ hour and then a further aliquot of NBS (3.59 g, total 7.22 g, 40.6 mmol, 1 eq.) and a catalytic amount of AIBN was added. The reaction mixture was again refluxed for ½ hour. At the end of this period, the starting material was seen to have been completely consumed on the tlc and the NBS which had been denser and found at the bottom of the reaction mixture was seen to have been completely converted into succinimide which is lighter than carbon tetrachloride and hence floated on top of the solution. The reaction was worked up by filtering out the solid succinimide and the carbon tetrachloride was removed on the rotavapor under reduced pressure. The crude product was purified on a neutral alumina column to give the product **35** as an off-white solid which was crystallised from dichloromethane-petroleum ether (5.64 g, 61% yield).

m.p. (°C) : 155-157.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2957, 2644, 1509, 1463, 1404, 1320, 1220, 1040, 877, 715, 663, 553.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.93 (s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 4.55 (s, 2H), 3.86 (s, 3H), 3.73 (s, 3H).

Oxidation of 2-(bromomethyl)-1,4-hydroquinone dimethyl ether **35** using CAN to give **36**:

2-Bromomethyl-1,4-hydroquinone dimethyl ether **35** (1.00 g, 4.3 mmol) was taken along with 10 ml of a 3:1 acetonitrile-water mixture and cooled in ice. Then 10.04 g (18.3 mmol, 4 eq.) of ceric ammonium nitrate was added to this solution slowly with stirring and the reaction mixture was left stirring at room temperature for one hour. At the end of this period, the reaction mixture was worked up by removing the acetonitrile on the rotavapor under reduced pressure. The reaction mixture was then diluted with distilled water and extracted with dichloromethane. The dichloromethane layer was washed with distilled water and brine. The organic layer was thoroughly dried over anyhydrous sodium sulphate and the dicholomethane removed by evaporation. The crude material was purified on silica-gel column and crystallised from dichloromethane-petroleum ether *to give* **36** *as yellow crystals (0.31 g, 36% yield).*

m.p. (°C)	:	128-130.
FT-IR (KBr, ν_{max}/cm^{-1})	:	1678, 1455, 1335, 1265, 1208, 1177, 930, 915, 775.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.90 (s, 1H), 6.82 (s, 1H), 6.72 (s, 1H), 4.28 (s, 2H).

Diels-Alder reaction of 2-(bromomethyl)-1,4-quinone **36** with cyclopentadiene to give **37**:

The quinone **36** (0.30 g, 1.5 mmol) prepared in the earlier step was taken in a dry round-bottomed flask and dissolved in 20 ml of dry benzene. This solution was cooled in an ice-water bath and then freshly cracked cyclopentadiene (0.25 ml, 3.0 mmol, 2 eq.) was added drop-by-drop using the syringe-septum technique. The reaction mixture was allowed to attain room temperature and further stirred for two days. The reaction was worked up by removing the solvent under vacuum on the rotavapor. The crude product obtained was purified on a silica-gel column by eluting with 5% ethyl acetate in petroleum ether to give *0.25 g of the product* **37** *after crystallisation from* dichloromethane-petroleum ether (62% yield).

(m, 2H), 2.56-2.53 (m, 1H), 1.97-1.93 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 211.1, 197.3, 149.4, 120.8, 51.8, 50.7, 47.5, 45.7, 45.3, 41.3, 39.2, 38.6.

HRMS (M^+) : 265.9945, $C_{12}H_{11}O_2Br$ requires 265.9942.

Spectral data for **39**:

FT-IR(KBr, ν_{max}/cm^{-1}) : 2982, 1748, 1717, 1663, 1535, 1456, 1420, 1371, 1243, 1109, 1037, 732.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.62 (½ABq, J = 10.8 Hz, 1H), 3.45 (½ABq, J = 10.8 Hz, 1H), 3.17 (s, 2H), 2.94 (brs, 2H), 2.85-2.72 (m, 2H), 2.64-2.63 (m, 1H), 2.08 (½ABq, J = 11.3 Hz, 1H), 1.95 (½ABq, J = 11.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 210.3, 209.1, 55.3, 55.1, 52.4, 48.2, 44.1, 43.6 (2C), 40.8, 36.4, 30.5.

HRMS (M^+) : 265.9939, $C_{12}H_{11}O_2Br$ requires 265.9942.

O-methylation of 2,3-dimethyl-1,4-quinol **40** to give **41**:

Commercially available 2,3-dimethyl-1,4-quinol **40** (1.04 g, 7.5 mmol) was dissolved in an aqueous solution of sodium hydroxide (3.08 g , 77.0 mmol, 10 eq. in 20 ml of distilled water) and argon gas was bubbled through this solution for approximately five minutes. Then the solution was cooled in an ice-water bath and 4.0 ml of dimethyl sulphate (41.9 mmol, 5 eq.) was added drop-by-drop taking care to keep the temperature of the reaction mixture below 10 °C. After the addition was complete the reaction mixture was stirred with heating at 70 °C for 4 days. The reaction was worked up by diluting with distilled water and extracting with diethyl ether. The combined ether layers were washed with distilled water and brine, and dried over anhydrous sodium sulphate. The ether was removed by evaporation and the crude product obtained was purified on a silica-gel column to give the pure product **41** as a colourless viscous liquid (0.93 g, 75% yield).

FT-IR (KBr, ν_{max}/cm^{-1}) : 2958, 2910, 1486, 1462, 1255, 1091, 793.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.61 (s, 2H), 3.76 (s, 6H), 2.15 (s, 6H).

Side-chain bromination of 2,3-dimethyl-1,4-hydroquinone dimethyl ether **41** using NBS to give **42**:

2,3-Dimethyl-1,4-hydroquinone dimethyl ether **41** (0.86 g, 5.2 mmol) was dissolved in 30 ml of dry benzene. *N*-Bromosuccinimide (2.50 g, 14.0 mmol, 2.5 eq.) was added to this in three equal lots along with a catalytic amount of AIBN each. The reaction mixture was refluxed for an hour after each addition. After three hours, when the tlc indicated the absence of starting material, the solvent was removed and the crude product was purified on a silica gel column to give 1.28 g of the product **42** after crystallisation from dichloromethane-petroleum ether (76% yield).

m.p. (°C) : 148-151 (Lit. 152.2 °C).[20]

FT-IR (KBr, ν_{max}/cm^{-1}) : 2968, 2831, 1588, 1487, 1462, 1448, 1436, 1267, 1215, 1158, 1052, 952, 808, 714.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.75 (s, 2H), 4.67 (s, 4H), 3.77 (s, 6H).

Oxidation of 2,3-bis(bromomethyl)-1,4-hydroquinone dimethyl ether **42** using CAN to give **43**:

2,3-Bis(bromomethyl)-1,4-hydroquinone dimethyl ether **42** (0.26 g, 0.8 mmol) was taken in 10 ml of a 3:1 solution of acetonitrile in water and cooled in an ice-water bath. Ceric ammonium nitrate (2.03 g, 3.7 mmol, 4.5 eq.) was added slowly to this solution and the reaction mixture was allowed to attain room temperature and further stirred for 1.5 hours. Acetonitrile was removed under reduced pressure on the rotavapor and the residue diluted with distilled water and the product was extracted with dichloromethane. The combined dichloromethane extract was washed with distilled water and brine. Final drying was carried out using anhydrous sodium sulphate and the solvent was removed. The crude material was purified on a silica-gel column and the product **43** was crystallised from dichloromethane-petroleum ether (0.18 g, 78% yield).

m.p. (°C) : 159-161.

FT-IR (KBr, ν_{max}/cm^{-1}) : 1677, 1450, 1270, 1210, 1165, 938, 924, 910, 769.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.88 (s, 2H), 4.39 (s, 4H).

Diels-Alder reaction of 2,3-bis(bromomethyl)-1,4-quinone **43** with cyclopentadiene to give **44**:

2,3-Bis(bromomethyl)-1,4-quinone **43** (0.18 g, 0.6 mmol) was dissolved in 20 ml of dry benzene and the solution was cooled in an ice-water bath. Freshly cracked cyclopentadiene (0.15 ml, 1.8 mmol, 3 eq.) was added to this cooled solution drop-by-drop using syringe-septum technique. Then the reaction mixture was left stirring at room temperature for two days whereupon tlc indicated the absence of starting material. The reaction was worked up by removing the solvent and the crude product was purified on a silica-gel column. Pure compound was crystallised from dichloromethane-petroleum ether to give the tricyclic compound **44** as pale yellow crystals (0.21 g, 94% yield).

m.p. (°C) : 106-108.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2987, 1663, 1613, 1445, 1420, 1264, 1076, 708.

^1H NMR (300 MHz, $CDCl_3$) : δ 6.11 (s, 2H), 4.29 (dd, J_1 = 27.3 Hz, J_2 = 9.6 Hz, 4H), 3.59 (s, 2H), 3.37 (s, 2H), 1.52 (dd, J_1 = 24.8 Hz, J_2 = 8.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 196.2 (2C), 146.5 (2C), 135.3 (2C), 49.9 (2C), 49.2 (2C), 48.6 (2C), 20.8.

Attempted photolysis of 4,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **44**

The Diels-Alder adduct **44** (0.16 g, 0.4 mmol) prepared in the previous step was taken in 20 ml of dry ethyl acetate and the solution was degassed. The round-bottomed flask was fitted with an argon-filled balloon and exposed to sunlight. However, on exposure to sunlight, the reaction mixture turned black and the crude proved to be an intractable mixture.

Ring Bromination of 2-(bromomethyl)-1,4-hydroquinone dimethyl ether **35** using bromine in carbon tetrachloride to give **45**:

2-(Bromomethyl)-1,4-hydroquinone dimethyl ether **35** (0.39 g, 1.4 mmol), was taken in a dry round-bottomed flask along with 10 ml of dry carbon tetrachloride and the mixture was cooled in an ice-water bath. A solution of bromine in carbon tetrachloride (40% v/v bromine in carbon tetrachloride, 0.18 ml, 1.4 mmol, 1 eq.) was slowly added to this solution and the reaction mixture was left stirring for two days at room temperature. At the end of this period, the reaction mixture was worked up by removing the solvent on the rotavapor under reduced pressure and then the crude material was purified by column chromatography on silica gel. The pure product **45** was crystallised from a mixture of dichloromethane-petroleum ether (0.29 g, 67% yield).

m.p. (°C)	:	92-94.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2958, 2836, 1498, 1462, 1383, 1298, 1030, 787.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 7.08 (s, 1H), 6.89 (s, 1H), 4.51 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H).

Oxidation of 2-bromo-5-(bromomethyl)-1,4-hydroquinone dimethyl ether **45** using CAN to give **46**:

2-Bromo-5-(bromomethyl)-1,4-hydroquinone **45** prepared in the previous reaction (0.40 g, 1.3 mmol) was taken in a solution of acetonitrile in water (3:1, 20 ml) and the mixture was cooled in an ice-water bath. Ceric ammonium nitrate (2.92 g, 5.3 mmol, 4 eq.) was added in small portions to this cold mixture with constant stirring. After the addition was complete, the reaction mixture was left stirring at room temperature for 1 hour. The reaction was worked up by removing the acetonitrile on the rotavapor and then diluting the reaction mixture with distilled water. This was extracted with dichloromethane and the combined dichloromethane layer was washed with distilled water and brine; and dried over anhydrous sodium sulphate to give 0.34 g of the crude product on removal of solvent. Since an earlier attempt to purify the product had led

to decomposition on the column, the crude product was used as such for the next reaction. The crude yield of **46** was 94%.

Diels-Alder reaction of 2-bromo-5-(bromomethyl)-1,4-quinone **46** with cyclopentadiene to give **47**:

The crude quinone **46** prepared in the earlier step (0.42 g, 1.5 mmol) was taken in a round-bottomed flask and dissolved in 30 ml of dry benzene. This was cooled in an ice-water bath and 0.4 ml of freshly cracked cyclopentadiene (0.32 g, 4.9 mmol, 3 eq.) was added and the reaction mixture left stirring at room temperature for 2 days. The reaction was worked up by removing the solvent under reduced pressure and the product was purified on a silica gel column to get 0.31 g of adduct **47** (60% yield).

m.p. (°C) : 108-111.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2980, 2880, 1688, 1676, 1588, 1251, 1189, 920, 646.

^1H NMR (300 MHz, $CDCl_3$) : δ 7.27 (s, 1H), 6.14 (dd, J_1 = 7.2 Hz, J_2 = 2.5 Hz, 2H), 4.04 (d, J = 9.6 Hz, 1H), 3.53 (s, 1H), 3.35-3.29 (m, 2H), 3.15 (s, 1H), 1.65 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 197.1, 190.7, 144.3, 143.8, 137.3, 136.3, 60.2, 55.2, 54.2, 50.1, 47.1, 39.9.

UV (CH_2Cl_2, λ_{max}) : 270 nm.

Photolysis of 5-bromo-2-(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **47** to give **48**:

The Diels-Alder adduct **47** (0.12 g, 0.3 mmol) prepared in the previous step was taken in a round-bottomed flask and dissolved in 15 ml of dry ethyl acetate. The reaction mixture was purged with argon and the round-bottomed flask was fitted with an argon-filled balloon. This set-up was exposed to sunlight for three hours and worked up by removing the solvent under reduced pressure. The crude material was purified on a silica gel column and further crystallised from a mixture of chloroform and petroleum ether to give 37 mg of the product **48** (32% yield).

m.p. (°C)	:	98-100.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2980, 1746, 1744, 1270, 1080, 995, 860.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 3.54 (½ABq, J = 11.1 Hz, 1H), 3.49-3.41 (m, 2H), 3.38 (½ABq, J = 11.0 Hz, 1H), 3.15 (dd, J_1 = 6.5 Hz, J_2 = 1.8 Hz, 1H), 3.07 (dd, J_1 = 14.9 Hz, J_2 = 3.1 Hz, 2H), 2.75-2.73 (m, 1H), 2.23 (½ABq, J = 11.8 Hz, 1H), 1.92 (½ABq, J = 11.9 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 205.9, 202.0, 62.2, 56.1, 53.9, 50.0, 47.9, 44.6, 39.5, 39.4, 36.3, 29.6.
HRMS (M^+)	:	343.9043, $C_{12}H_{10}O_2Br_2$ requires 343.9047.

2.4 References:

1. Mehta, G.; Singh, V.; Pandey, P. N.; Cameron, T. S.; Gardner, P. A. *J. Chem. Soc., Chem. Commun.* **1982**, 217-218.
2. Marchand, A. P.; Reddy, G. M.; Watson, W. H.; Nagl, A. *J. Org. Chem.* **1988**, *53*, 5969-5971.
3. Marchand, A. P.; Chou, T.-C.; Ekstrand, J. D.; van der Helm, D. *J. Org. Chem.* **1976**, *41*, 1438-1444.
4. Suri, S. C. *Tetrahedron Lett.* **1990**, *31*, 3695-3698.
5. Suri, S. C.; Hardcastle, K. I. *J. Org. Chem.* **1992**, *57*, 6357-6360.
6. Suri, S. C. *J. Org. Chem.* **1993**, *58*, 4153-4154.
7. Marchand, A. P. *Aldrichimica Acta* **1995**, *28*, 95-104, and the references cited therein.
8. Coxon, J. M.; O'Connell, M. J.; Steel, P. J. *Aust. J. Chem.* **1986**, *39*, 1537-1557.
9. Gates, M. *J. Org. Chem.* **1982**, *47*, 578-582.
10. van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262-1263.
11. Witiak, D. T.; Loper, J. T.; Ananthan, S.; Almerico, A. M.; Verhoef, V. L.; Filppi, J. A. *J. Med. Chem.* **1989**, *32*, 1636-1642.

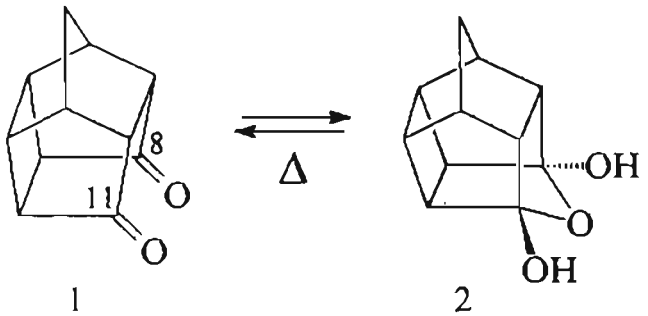
12. Vogel's Textbook of Practical Organic Chemistry, Fourth Edition, The English Language Book Society and Longman, **1978**.
13. PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Orbital Models by Wavefunction Inc. 18401 Von Karman, Suite 370, Irvine, California 92612, USA.
14. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd Edition, Pergamon Press, **1988**.
15. Wood, J. H.; Gibson, R. E. *J. Am. Chem. Soc.* **1949**, *71*, 393-395.
16. von Schill, G. *Justus Liebigs Annalen der Chemie* **1966**, *691*, 79-87.
17. Hunt, S. E.; Lindsey, A. S. *J. Chem. Soc.* **1962**, 4550-4557.
18. Lal, J. *J. Ind. Chem. Soc.* **1935**, *12*, 616.
19. Buchta, E.; Egger, H. *Chem. Ber.* **1957**, *90*, 2748-2759.
20. von Horner, L.; Subramaniam, P. V.; Eiben, K. *Justus Liebigs Annalen der Chemie* **1968**, *714*, 91-111.

CHAPTER 3 – THE CHEMISTRY OF TETRA- AND PENTACYCLIC CAGE COMPOUNDS

In the previous chapter, the syntheses of some substituted cage compounds were discussed in detail. In addition to preparing these fascinating molecules, study of their chemistry would be invaluable in understanding molecular mechanics. Cage compounds are enigmatic in the sense that a large number of their properties are contrary to expected wisdom. The observed thermal stability of these polycyclic hydrocarbons and their calculated strain energies seem paradoxical. However, this thermal stability is merely caused by the inability of the cage molecule to undergo bond reorganisation reactions in a concerted fashion in the ground state. Many groups around the world have been synthesising functionalised cage compounds for further study. Often, surprising results are obtained on carrying out routine chemical transformations on functional groups which are in hindered or strained positions on cage molecules. With this in mind, a study of the chemistry of some tetra- and pentacyclic compounds have been made. Once again, the literature survey revealed several interesting reports, some of which are given in the following introduction.

3.1 Introduction:

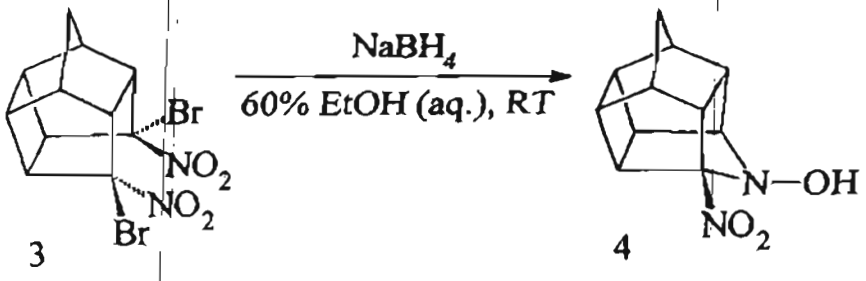
The spatial proximity between the C-8 and C-11 carbons in the PCUD system is known to lead to extensive transannular interactions between endo substituent groups on these carbons.[1] For example, PCUD 1 slowly gets converted to the hydrate 2 on storage at room temperature for longer periods (Scheme I).



1 2

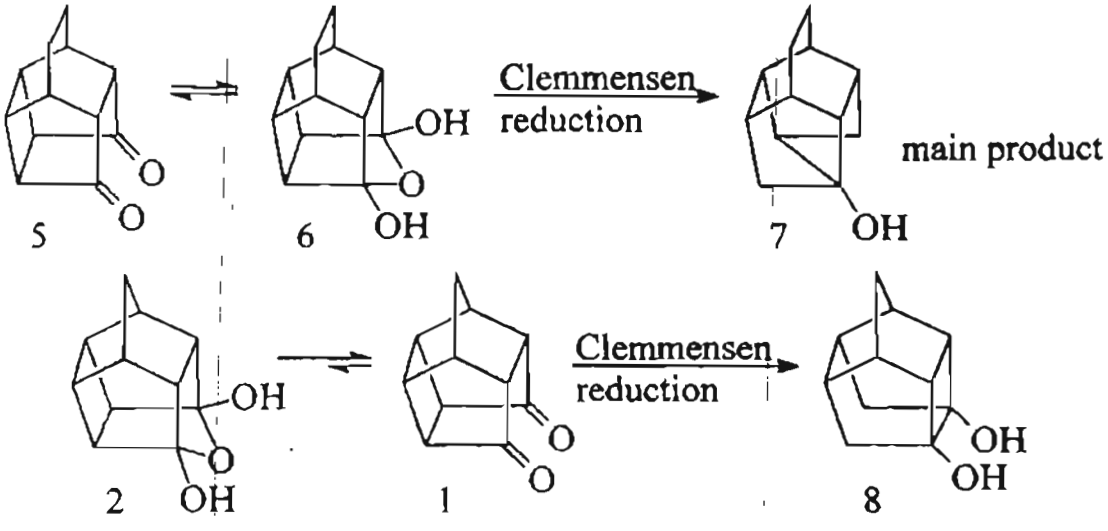
Scheme I

Marchand *et al.* have exploited this proximity effect in the synthesis of many new compounds. For example, the nitrated compound **3** on reduction with sodium borohydride led to the nitrated aza-hexacyclododecane **4** as shown in scheme II.[2]



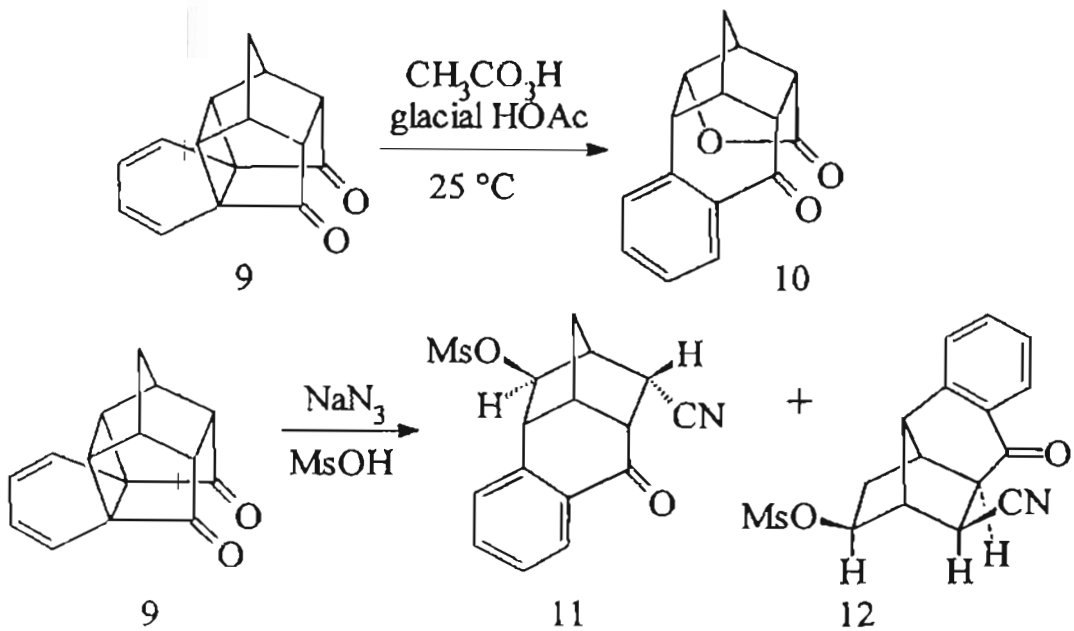
Scheme II

The Clemmensen reduction of pentacyclic systems is found to be dependent on the size of the rings (Scheme III). This has been attributed to the influence of hydrate formation. In the case of the pentacyclododecane system **5** which hydrates readily on exposure to air, it is proposed that the hydrate **6** reacts under the reaction conditions giving rise to a tertiary alcohol **7** as the main product. However, it is different for the pentacyclic undecane system **1** which hydrates comparatively slowly at room temperature. Therefore, it is the diketone **1** which undergoes reaction under Clemmensen conditions where cyclobutane ring cleavage is followed by pinacol formation to give **8**. This pioneering work has been carried out by Martins and co-workers.[3]



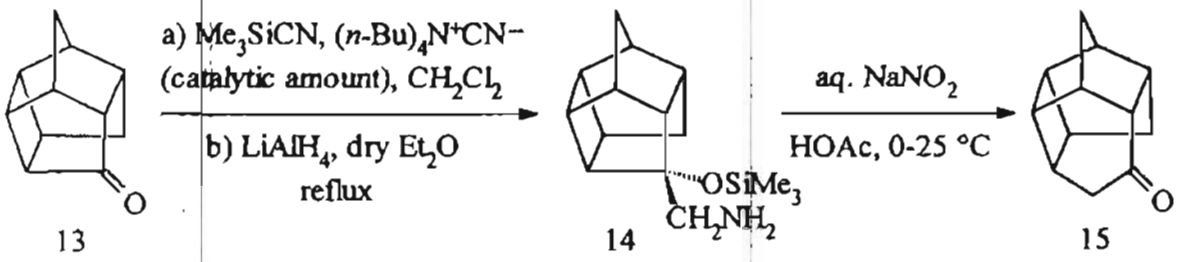
Scheme III

The conjugated diene **9** obtained in two steps from naphthaquinone and cyclopentadiene is so constrained by the nature of the pentacyclic cage that it reacts in an unusual manner with acids and bases.[4] The Baeyer-Villiger oxidation of **9** using peracetic acid affords an extensively rearranged product **10**. Treatment of **9** with NaN_3-MsOH also takes an interesting route and gives rise to the total break-up of the pentacyclic framework leading to novel compounds **11** and **12** as shown in scheme IV.



Scheme IV

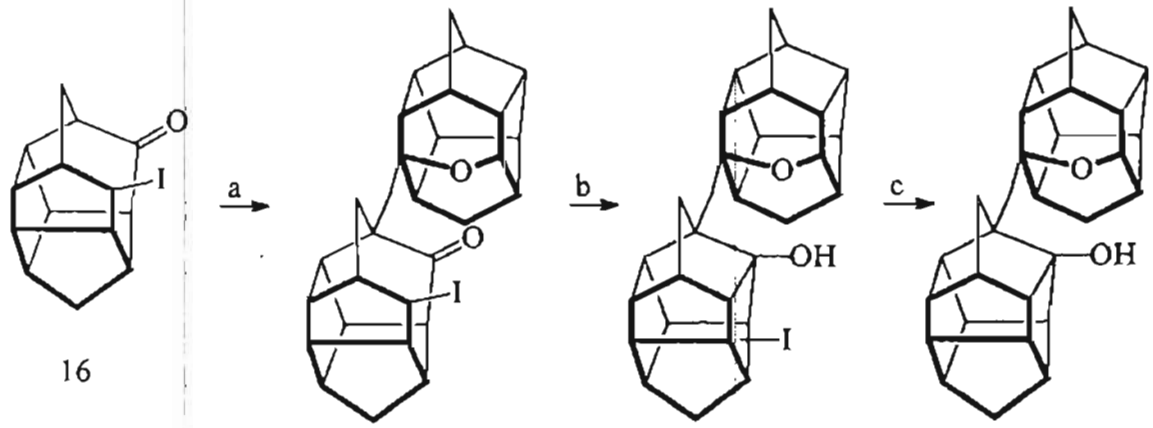
A fascinating Tieffenau-Demjanov ring expansion of the pentacyclic ketone **13** leading to the novel compound **15** has been carried out by Marchand *et al.* (Scheme V).[5] Reaction methodology involved treating **13** with trimethylsilyl cyanide in the presence of a catalytic amount of tetra-*n*-butylammonium cyanide followed by reduction with lithium aluminium hydride to give the amino alcohol derivative **14**. This was ring-expanded using nitrous acid which caused desilylation and deamination along with concomitant ring expansion giving **15**. The chemistry of **15** has been further explored extensively by the authors.



13 14 15

Scheme V

A study by Chow and Wu[6] discusses the unprecedented substitution by a polycyclic system **16** giving rise to a complex molecule **17** consisting of two cage compounds linked by a carbon-carbon bond (Scheme VI). The formation of this condensation product must have proceeded by the initial nucleophilic attack of the anion of one molecule on the carbonyl carbon of another molecule of the same species. The resulting oxide would add across the molecule to form an oxa bridge. If LHMDS is used as base, product **17** undergoes further transformation to give an isomer **18** with a hydroxyl group instead of the carbonyl. During the rearrangement, the iodine moves to an unknown position on the cage. Prolonged reaction with LHMDS at room temperature gives a dehalogenated product **19**.



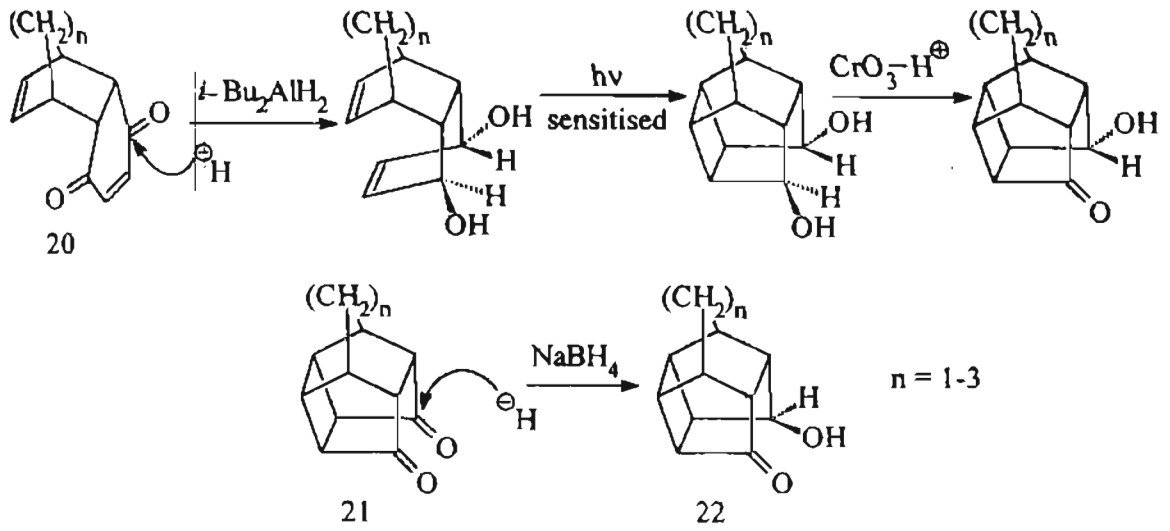
16 17 18 19

a) *t*-BuOK / BuLi, – 40 °C or LHMDS b) LHMDS, 0 °C c) LHMDS, RT

Scheme VI

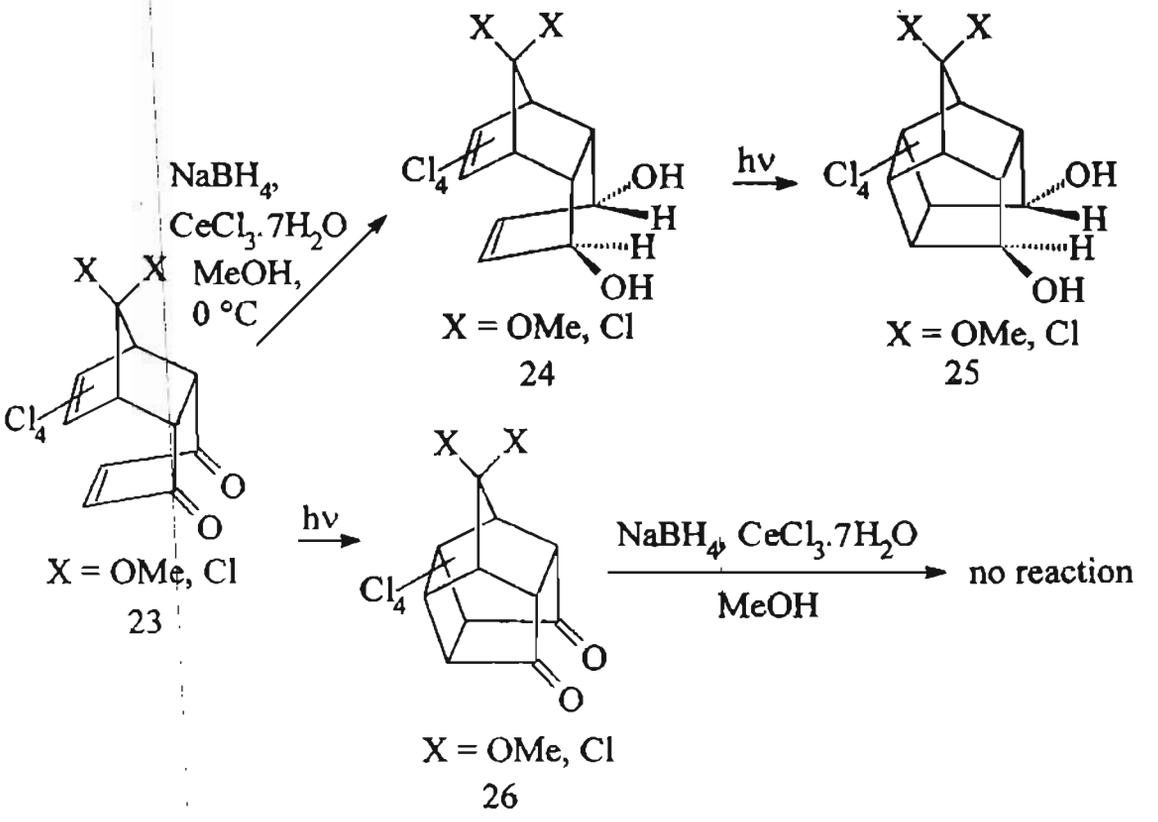
Craze and Watt[7] have utilised the differences in the nature of hydride transfer in a tricyclic and a pentacyclic system to obtain functionalised pentacyclic alcohols (Scheme VII). The delivery of the hydride to the tricyclic system **20** takes place from

the less hindered *exo*-face of the enedione function, and the transformations that follow were carried out in order to confirm this. In the case of the sodium borohydride reduction of the pentacyclic diketone **21**, delivery of hydride occurs from the less hindered outside face of the cage dione to give **22**.



Scheme VII

However, in the highly substituted norbornyl systems such reductions do not take place. Marchand and co-workers[8] have studied the stereoselective reductions of enediones using the Luche reagent, *i.e.*, sodium borohydride in combination with ceric chloride (Scheme VIII). The tricyclic enedione **23** was reduced smoothly to the *exo,exo*-diol **24** which underwent photocyclisation to give the pentacycle **25** with the same configuration. The stereochemistry was established conclusively as this pentacycle failed to undergo dehydration to the hexacyclic ether. In stark contrast to this, the corresponding cage diketone **26** was inert to the same reagent. This failure has been attributed to the steric effect of the nearby bridgehead C-Cl bonds which would impede the approach of the reagent to the *exo* faces of the carbonyl groups in these cage compounds.



Scheme VIII

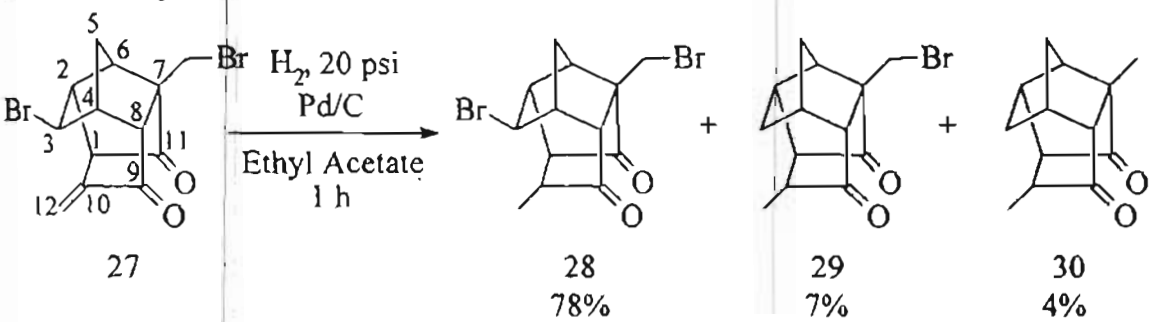
Taking a cue from the above reports, we made an effort to make new multifunctional polycyclic compounds and study the general chemistry of the polycyclic compounds prepared in the previous chapter. Even though we confined ourselves to well-known reactions, some unexpected results were obtained and a number of new compounds synthesised.

3.2 Results and Discussion:

3.2.1 Catalytic Hydrogenation:

The first reaction explored was the catalytic hydrogenation of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **27** using palladium on carbon as the catalyst at twenty psi hydrogen gas pressure for one hour. The reaction gave three products **28**, **29** and **30**. The major product **28** obtained was

easily identified as the expected product of catalytic hydrogenation of the double bond. This showed two carbonyl absorptions in the IR spectrum at 1755 and 1715 cm^{-1}. The proton NMR spectrum (Fig. 1) showed the complete absence of olefinic protons and contained a doublet at δ 1.16 which integrated for three protons implying the presence of a methyl group where the splitting could be attributed to the presence of the proton on C-10. The ^{13}C NMR spectrum (Fig. 2) showed only two signals downfield of $CDCl_3$ due to the carbonyls at δ 207.9. All other carbons gave signals between δ 64.9 and 15.0, of which it was possible to assign the signal at δ 57.4 to the quarternary carbon at C-7 and the signal at δ 15.0 to the methyl carbon. Thus the product **28** was identified as 3-bromo-7-(bromomethyl)-10-methyltetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione.



27 | 28 78% | 29 7% | 30 4%

Scheme IX

The second product **29** was formed by hydrogenolysis of the secondary bromine to give a methylene group in addition to the reduction of the double bond. The IR spectrum could confirm the presence of the carbonyl group by the strong stretch centered at 1751 cm^{-1}. The ^{1}H NMR spectrum confirmed the absence of olefinic protons and also the presence of a doublet at δ 1.36 which could be attributed to the methyl at C-10 as in the earlier product. On integration, the total number of protons were found to be fifteen indicating the further addition on one more proton. The ^{13}C NMR spectrum which showed thirteen peaks and the DEPT-135 spectrum which indicated the presence of three methylene groups at δ 38.9, 31.7 and 30.9 suggested that the bromine at C-3 had been hydrogenolysed leading to an extra methylene group in this product. This identified the product as 7-(bromomethyl)-10-methyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **29**.

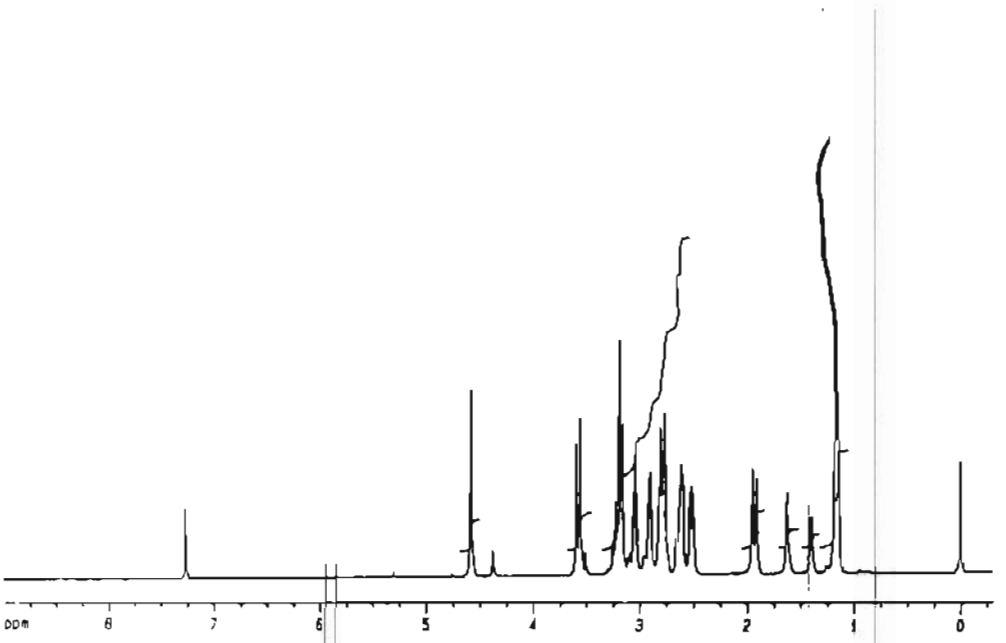


Figure 1: ^{1}H NMR Spectrum of 28

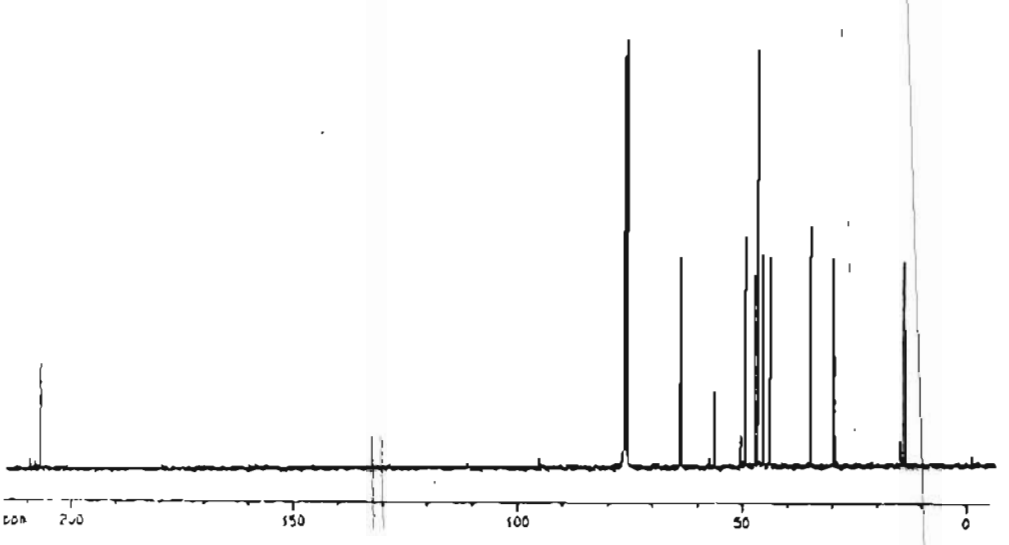


Figure 2: ^{13}C NMR Spectrum of 28

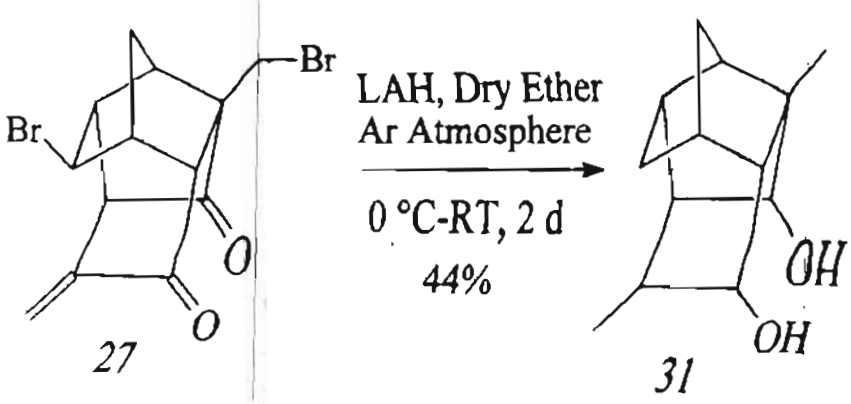
The compound **30** to be eluted out of the silica gel column in 4% yield showed the carbonyl group absorptions at 1757 and 1726 cm^{-1}. Its ^1H NMR spectrum once again showed no olefinic protons. It showed two methyl groups as singlets at δ 1.60 and 1.55 and all other protons appeared between δ 4.43 and 1.97 where individual assignments were not possible. The ^{13}C NMR spectrum showed only two downfield signals at δ 218.8 and 207.4 which were due to the two carbonyls, and all other signals came upfield between δ 60.5 and 24.3. The DEPT-90 confirmed the presence of two methyl groups and the DEPT-135 showed only two methylenes. Thus the structure **30** was proposed which had the double bond reduced and had also lost both the bromines to give 7,10-dimethyltetracyclo[$5.3.1.0^{2,6}.0^{4,8}$]undec-9,11-dione.

3.2.2 Reductions Using Lithium Aluminium Hydride:

The reductions of the tetracyclic and pentacyclic systems with lithium aluminium hydride was explored in order to obtain the respective diols. It was thought to be of interest to explore this field in order to prepare derivatives of the novel compounds prepared thus far.

The lithium aluminium hydride reduction of 3-bromo-7-(bromomethyl) tetracyclo[$5.3.1.0^{2,6}.0^{4,8}$]undeca-10(12)-ene-9,11-dione **27** led to a single product in moderate yield after purification (Scheme X). It showed a broad absorption in its IR spectrum at 3407 cm^{-1} indicating the presence of hydroxyl groups and there were no peaks in the carbonyl region indicating that both the keto- groups had been reduced to secondary alcohols. The ^1H NMR spectrum showed the absence of signals in the olefinic region leading to the conclusion that the double bond too had been reduced by the LAH reagent which added hydride in a 1,4-fashion to the enone of the starting material. The spectrum also showed the presence of two methyl groups, one which overlapped with one half of the characteristic ½ABq signals due to the norbornyl methylene group and appeared as a multiplet between δ 1.24-1.21 and the other appeared as a singlet at δ 1.09. The other ½ABq signal appeared at δ 0.99 with a coupling constant of 10.8 Hz. The ^{13}C NMR spectrum showed the signals due to the secondary alcohols at δ 76.3 and 72.9 and all other signals appeared between δ 53.7

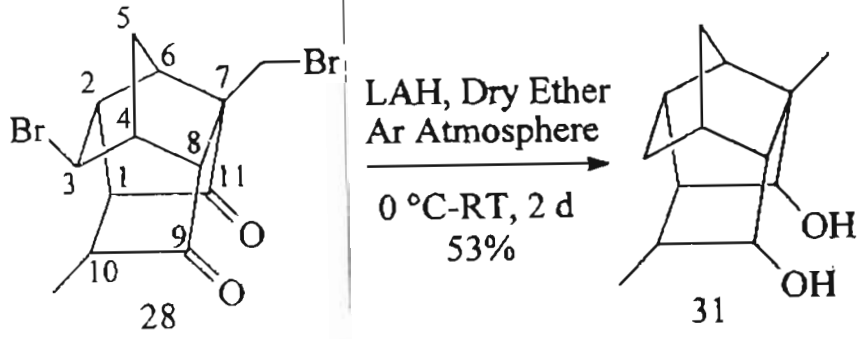
and 21.8 indicating the absence of other functionalities. The two signals at δ 22.4 and 21.8 could be attributed to the two methyl carbons. The product **31** was thus identified as 7,10-dimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-9,11-diol.



27 31

Scheme X

The product obtained upon the lithium hydride reduction of 3-bromo-7-bromomethyl)-10-methyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **28** proved to be identical with the product of the LAH reduction of **27**. All spectral details matched within the limits of instrumental error and comparison of melting points clinched the identity of this product as **31** (Scheme XI).

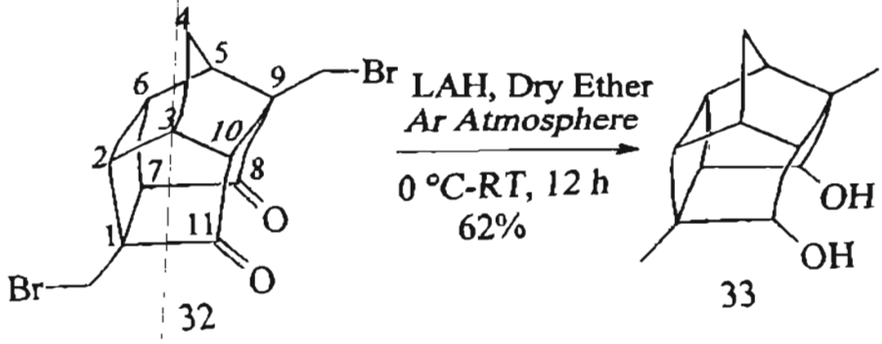


28 31

Scheme XI

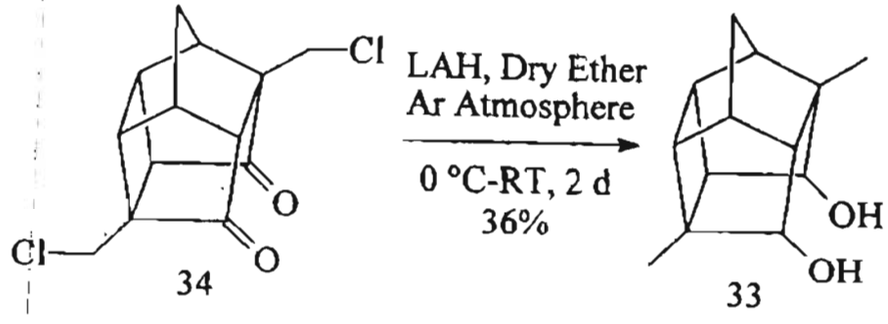
Next, the lithium aluminium hydride reduction of 1,9-bis(bromomethyl) pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **32** was carried out (Scheme XII). Once again a single product **33** was obtained. It showed as expected the broad peak at 3483 cm^{-1} in the IR spectrum indicating the presence of hydroxyl group. The absence of carbonyl absorption peaks indicated that both the carbonyl groups had been reduced by LAH. However, the ^{1}H NMR spectrum showed the presence of eighteen protons, including two methyl signals as singlets at δ 1.19 and 1.07 leading to the conclusion that both the halogens had been removed by the reagent. The protons on

the two hydroxyl groups were seen as a broad signal at δ 5.39. The norbornyl bridge methylene protons were seen as ½ABq signals centered at δ *1.62 and 0.97. All other* protons appeared between δ 3.47 and 1.79 and separate assignments were not possible. The ^{13}C NMR spectrum showed the signals due to the two hydroxyl-bearing carbons at δ 77.1 and 76.6 and all other signals were upfield between δ 53.7 and 21.7. Thus the compound was identified as 1,9-dimethylpentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-diol **33**.



Scheme XII

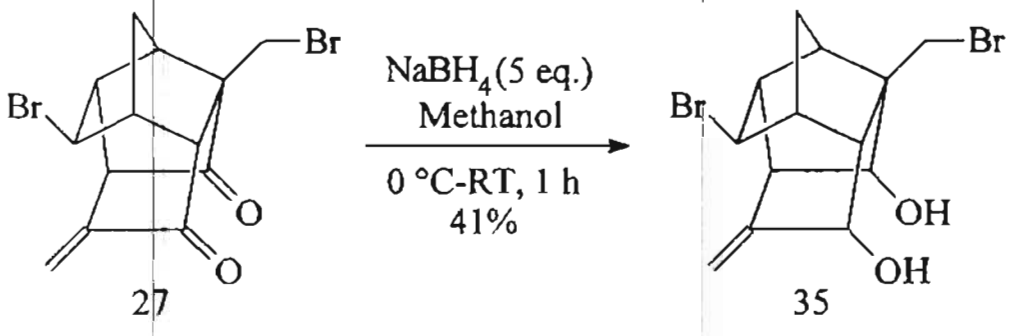
When lithium aluminium hydride reduction of 1,9-bis(chloromethyl)pentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **34** (Scheme XIII) was carried out, the spectral data of the product obtained was found to be similar to the product of the previous reaction. Since all the spectral values of the two products matched within the limits of instrumental error, it seemed safe to conclude that the same product had been formed in both cases. It was further confirmed by comparison of melting points that this product was **33** itself.



Scheme XIII

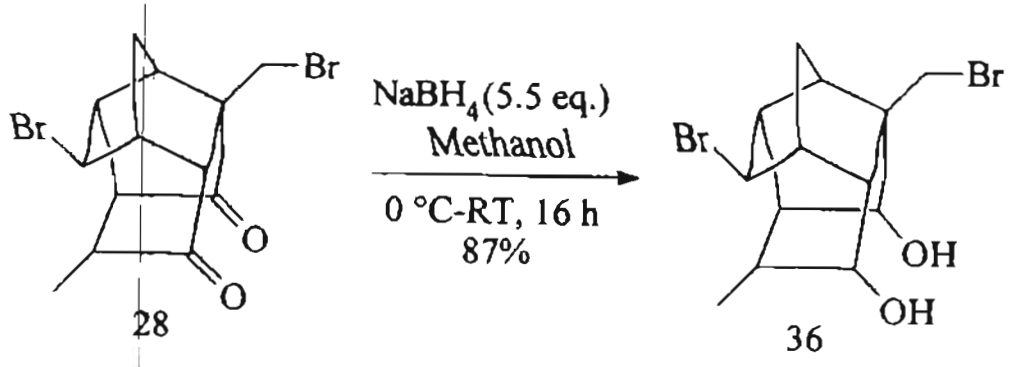
3.2.3 Reductions Using Sodium Borohydride:

Thus when it was found that the reduction conditions using lithium aluminum hydride were too strong, it was necessary to look at alternate methods in order to keep the halogens intact. Accordingly, the reductions of these tetracyclic and pentacyclic systems with sodium borohydride was explored. These reactions were carried out in distilled methanol and gave the expected products with the ketone groups in the starting materials getting reduced to secondary alcohols in all the cases.



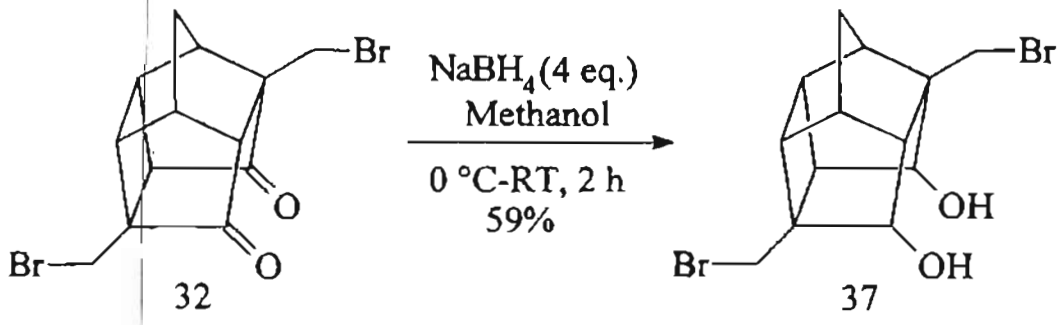
Scheme XIV

The product formed by the sodium borohydride reduction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **27** was seen to be the compound **35** on the basis of its spectra. In the IR spectrum a strong broad absorption at 3407 cm^{-1} for the hydroxyl groups was observed. The ^1H NMR spectrum showed the exocyclic double bond protons as two singlets at δ 5.33 and 5.07. The protons on the bromomethyl group appeared as ½ABq signals at δ 3.59 and 3.35. Half of the characteristic ABq signal usually exhibited by the norbornyl bridge protons was overlapped by other signals whereas the other half of it was visible at δ 1.64 with a coupling constant of 11.3 Hz. The ^{13}C NMR spectrum showed the carbons of the exocyclic double bond at δ 150.2 and 112.8 and two signals due to carbons bearing hydroxyl groups at δ 72.1 and 67.6. Of these, the signal at δ 72.1 could be attributed to the hydroxyl bearing carbon α to the double bond. All other signals were observed upfield between δ 55.1 and 33.6. The product was thus identified as 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-diol **35**.



Scheme XV

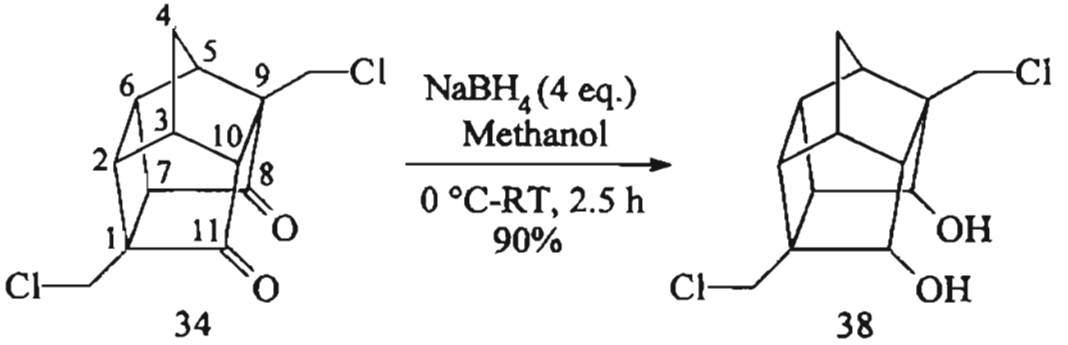
Sodium borohydride reduction of 3-bromo-7-(bromomethyl)-10-methyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **28** also proceeded uneventfully leading to the corresponding diol **36** (Scheme XV). The IR spectrum showed the presence of a hydroxyl absorption at 3444 cm^{-1}. The ^{1}H NMR spectrum showed eighteen protons of which the following could be unambiguosly assigned: the ½ABq signals at δ 3.55 and 3.31 were due to the protons on the bromomethyl group; the methyl group on C-10 appeared as a doublet at δ 1.29; and the hydroxyl protons showed up as a broad overlapping signal between δ 2.26-2.21. Half of the ABq signals due to the norbornyl bridge protons was seen at δ 2.36 with coupling constant of 11.3 Hz, while the other signal was submerged in the multiplet between δ 1.61-1.51. The ^{13}C NMR spectrum showed the hydroxyl-bearing carbons at δ 72.2 and 72.1 and all other signals appeared upfield between δ 57.7 and 19.4. Thus the compound was identified as 3-bromo-7-(bromomethyl)-10-methyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-diol **36**.



Scheme XVI

The product formed upon the sodium borohydride reduction of 1,9-bis(bromomethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **32** was identified as **37** on the basis of its spectral data. Its IR spectrum revealed the broad absorption at

3183 cm^{-1} which indicated that the starting material had been reduced to the alcohol. The ^1H NMR spectrum showed up the norbornyl methylene protons as the characteristic ½ABq signals at δ 1.66 and 1.11 with a coupling constant of 11.2 Hz. The other ½ABq signals at δ 3.65 and 3.41 could be attributed to the protons on one bromomethyl group. The protons on the other bromomethyl group overlapped with the signal due to another proton and appeared as a multiplet between δ 3.79-3.76. The ^{13}C NMR spectrum showed two signals at δ 72.8 and 72.7 which could be attributed to the carbons bearing the hydroxyl groups. All other signals appeared upfield between δ 52.3 and 32.8 and this was in accord for the structure proposed as **37**, i.e., 1,9-bis(bromomethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-diol.

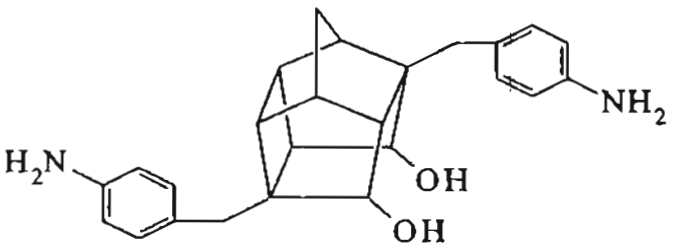


Scheme XVII

The reduction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **34** with sodium borohydride proceeded without trouble (Scheme XVII) and the product was easily identified as **38**. Salient features of the spectral data included the prominent broad stretch for the hydroxy group at 3170 cm^{-1} in the IR spectrum and two broad singlets centered at δ 5.30 and 5.07 corresponding to the two hydroxy protons in the ^1H NMR spectrum. The norbornyl protons appeared as the characteristic ½ABq signals at δ 1.67 and 1.12 and all other protons appeared as overlapping signals between δ 4.00 and 2.02 and could not be assigned to separate protons with any certainty. The ^{13}C NMR spectrum showed the signals due to the two carbons bearing hydroxyl groups at δ 71.9 with all other signals appearing upfield between δ 52.9 and 32.9. Thus the product was identified as 1,9-bis(chloromethyl) pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-diol **38**.

3.2.4 Nitration Reaction:

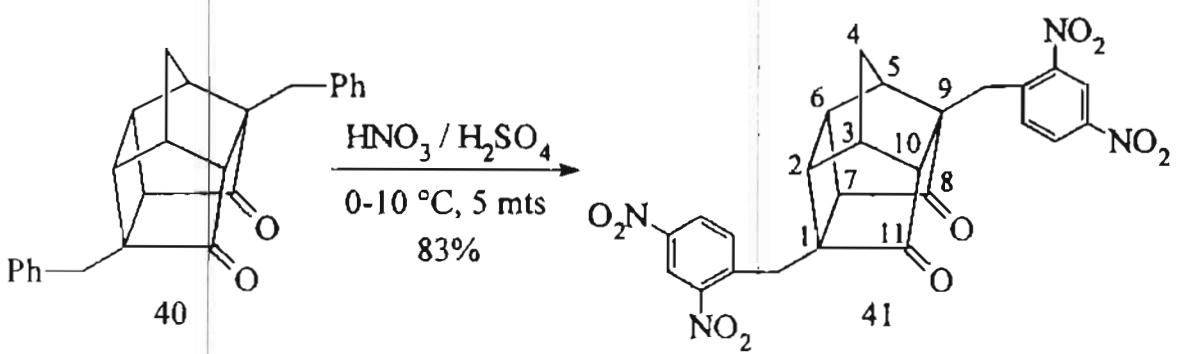
With a long term view of synthesising cage compounds containing both amino- and hydroxy- functions such as **39**, which may serve as DNA binding compounds, efforts were initiated towards its synthesis.



39

Scheme XVIII

It was envisaged that nitration of the aromatic rings of 1,9-bis(benzyl) pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **40** followed by reduction of the nitro groups would lead to amino groups on the benzene ring. Due to the rigid nature of the pentacyclic system, this would give rise to a compound with polar groups on the outside of a hydrocarbon cage. It is known that the biological activity of amantadine (1-aminoadamantane) is due to the hydrophobicity of the hydrocarbon cage which allows it to cross the blood-brain barrier while the amino group is protonated at physiological pH.[9] The nitration of **40** was carried out using a nitrating mixture of nitric acid in sulphuric acid (Scheme XIX).



40 41

Scheme XIX

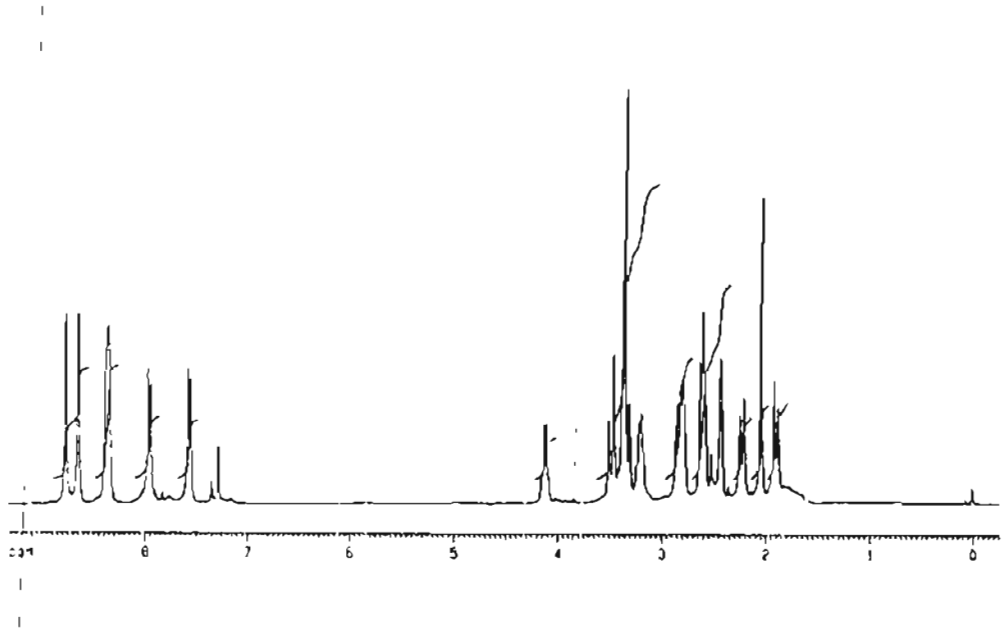


Figure 3: ^{1}H NMR Spectrum of 41

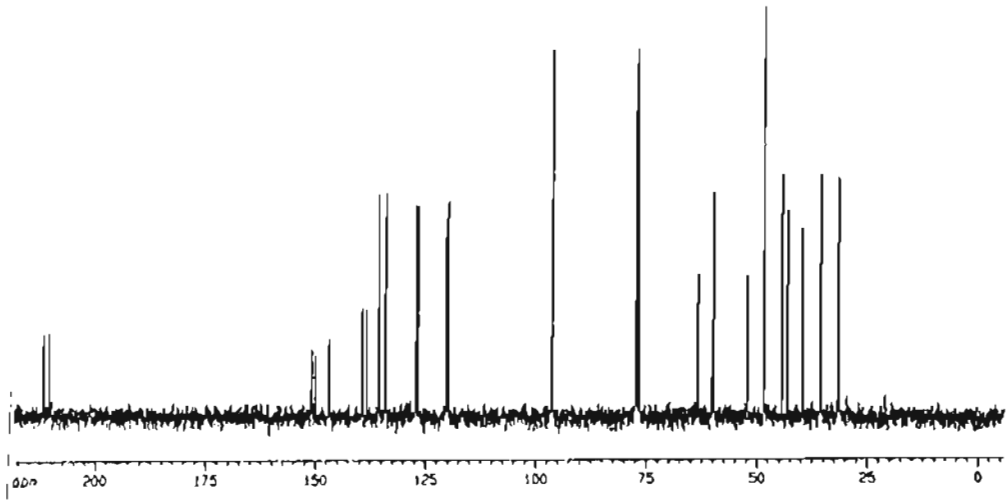


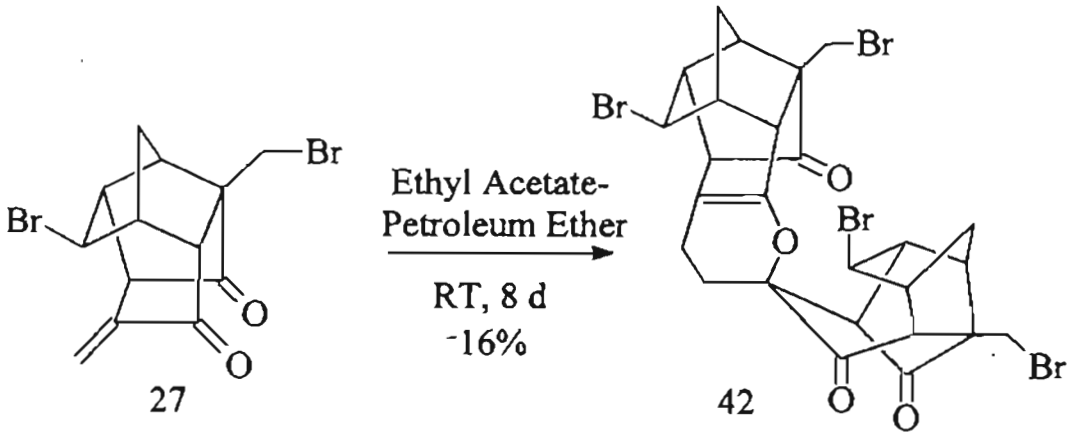
Figure 4: ^{13}C NMR Spectrum of 41

Even low temperatures and short reaction times resulted in the tetranitrated product **41** which was easily identified on the basis of its spectra. The IR spectrum clearly showed the presence of nitro- function and carbonyl groups with a strong absorptions at 1526 and 1751 cm^{-1} respectively. The proton NMR spectrum (Fig. 3) showed the aromatic protons as two singlets at δ 8.76 and 8.63 (one proton each); a broad singlet at δ 8.35 (two protons); and two doublets at δ 7.94 and 7.55 (one proton each). This indicated that each phenyl group had been bisnitrated at *ortho* and *para* positions. The other protons appeared upfield between δ 4.11 and δ 1.89 with the norbornyl methylene protons appearing as ½ABq signals at δ 2.22 and 1.89 with a coupling constant of 11.7 Hz. The ^{13}C NMR spectrum (Fig. 4) showed the two carbonyls at δ 211.6 and 210.4 and the twelve aromatic protons between δ 150.7 and 119.7. Of these, the six signals which were more deshielded were seen to be quarternary carbons suggesting that each phenyl had two nitro- groups substituted on it. This too led credence to the structure as 1,9-bis(*o*,*p*-dinitrophenylmethyl) pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **41** with bisnitration of each aromatic ring. The other signals were shielded and appeared between δ 63.3 and 31.4. Since only the tetra-nitrated compound **41** could be obtained, further plans to reduce these to the amines were abandoned.

3.2.5 Diels-Alder Reactions:

After the synthesis of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$] undeca-10(12)-ene-9,11-dione **27** another very interesting observation was made. It was seen that on keeping the compound **27** for crystallisation, a second compound **42** was formed when the crystals were not separated out quickly. With longer crystallisation times, this second more polar compound increased but **27** did not get completely converted to the second compound. Due to the difference in polarity, it was easily separated by column chromatography. This compound **42** (nomenclature and numbering is shown in scheme XXI) was deduced to be a dimer of the rearranged product on the basis of the high resolution mass spectrum which gave an M^+ peak at 720 (molecular ion). Careful perusal of the ^1H and ^{13}C NMR spectra as well as the IR

spectra indicated the following, *viz.*, a) the IR spectrum indicated the presence of a tetrasubstituted alkene group by a medium absorption at 1669 cm^{-1} and also strong absorptions at 1763 and 1729 cm^{-1} indicated that strained-ring carbonyl groups were present. b) the proton NMR spectrum (Fig. 5) showed a total absence of olefinic protons, indicating that the double bonds were involved in the dimerisation. Whereas the starting material **27** had a clearly discernable peak at δ 4.41 that had been attributed to the proton on C-1, this compound showed two protons in the same region with similar chemical shifts as two singlets at δ 4.39 and 4.29. The ^{13}C NMR spectrum (Fig. 6) and the DEPT studies were the most thought-provoking, it showed: a) the presence of three carbonyl groups by signals at δ 203.1 and 201.9 (two carbons), b) signals at δ 147.5 and 104.7 which indicated a tetra-substituted double bond, and c) a signal at δ 83.3 which pointed to a tertiary carbon perhaps attached to an oxygen functionality. The UV spectrum indicated the absence of an enone moiety. These inferences were put together to hypothesise that the dimerisation had taken place *via* a Diels-Alder reaction between two molecules of **27** with the double bond of one molecule acting as the dienophile and the enone moiety of another acting as the hetero-diene.



Scheme XX

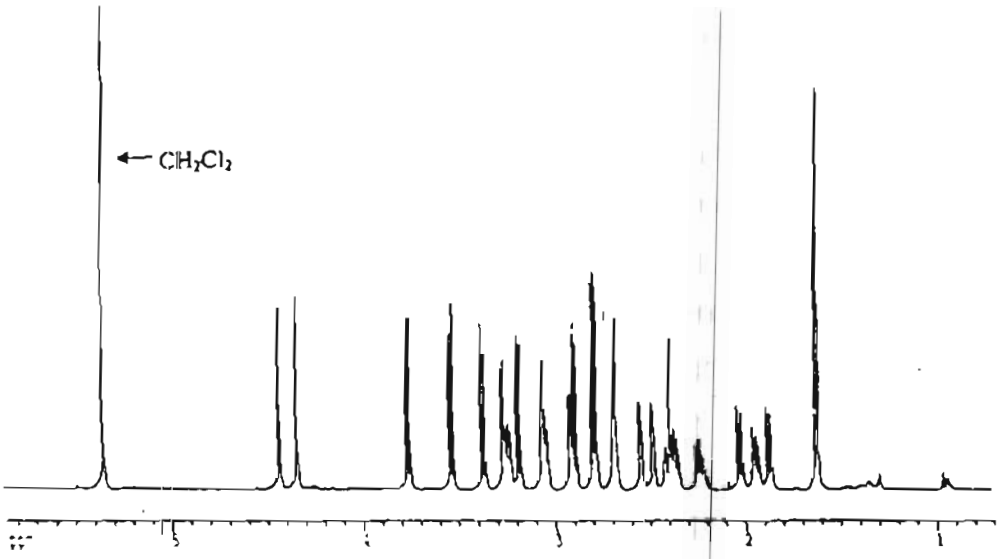


Figure 5: ^{1}H NMR Spectrum of 42

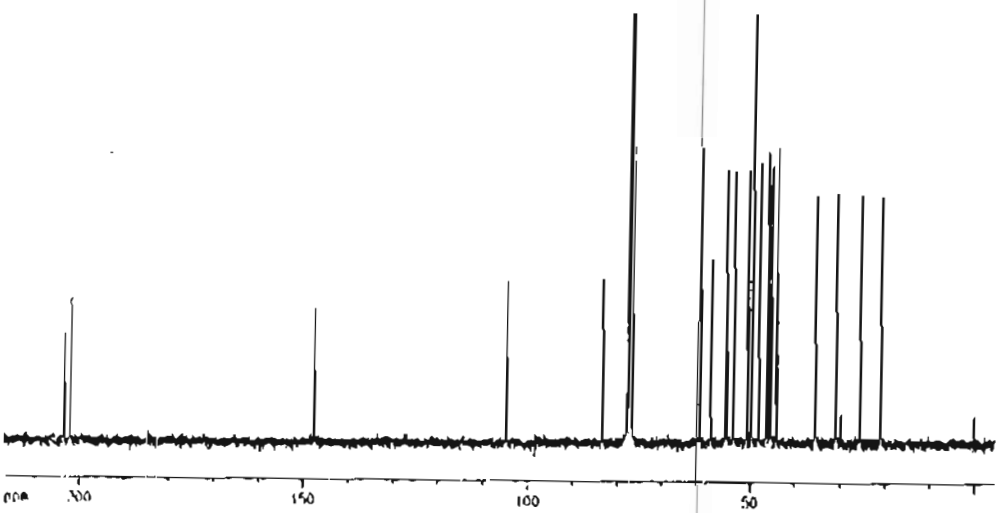
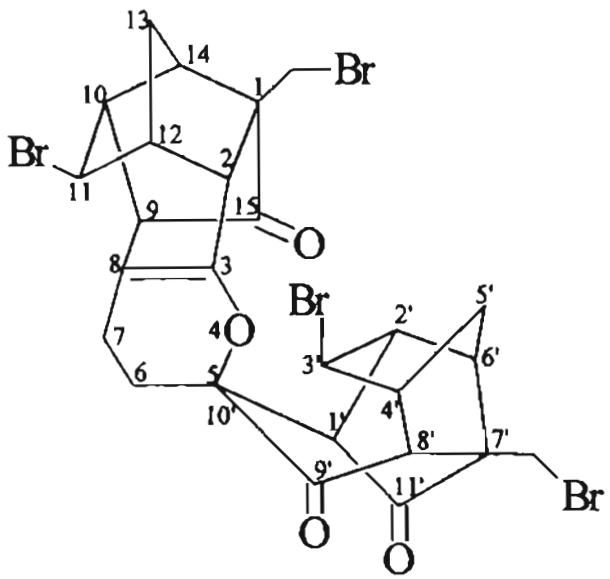


Figure 6: ^{13}C NMR Spectrum of 42

The structure received final confirmation through single crystal X-ray analysis (Fig. 7 and 8). The crystal structure showed the presence of a solvent molecule (dichloromethane) trapped within the lattice. After obtaining this compound by chance rather than by design, it was thought desirable to optimise the conditions under which it would be formed from the monomer. Since the reaction involved a hetero-Diels-Alder reaction, it was thought it would be facilitated by the presence of Lewis acids. However, various reaction conditions tried (using catalysts like PTSA, $SnCl_4$, etc.) did not lead to the formation of even trace amounts of the dimer. Elevated temperatures too did not do the trick, in fact, it was observed that the dimer on heating to its melting point cleanly dissociated to give back 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **27**. The formation of the dimer was found to proceed only on keeping in saturated solutions of a mixture of ethyl acetate and petroleum ether over a period of a few days, even then, total conversion did not take place (Scheme XX).



42

Spiro[11-bromo-1-(bromomethyl)-4-oxapentacyclo[7.5.1.$0^{2,12}$.$0^{3,8}$.$0^{10,14}$]pentadec-3(8)-ene-15-one-5,10'-3'-bromo-7'-(bromomethyl)tetracyclo[5.3.1.$0^{2',6'}$.$0^{4',8'}$]undec-9',11'-dione]

Scheme XXI

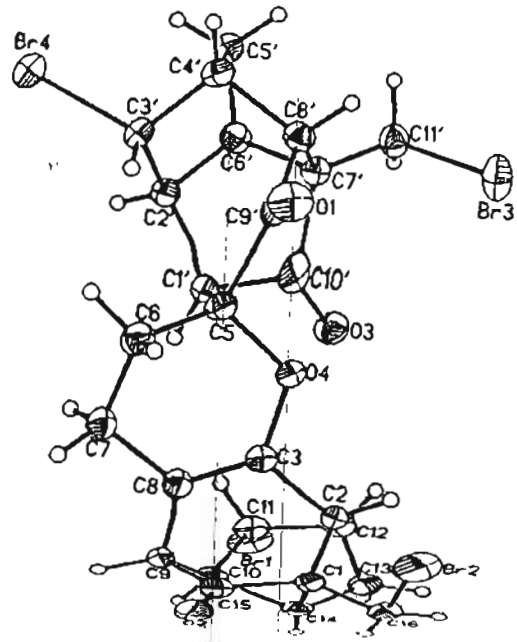


Figure 7: X-ray Crystal Structure of 42

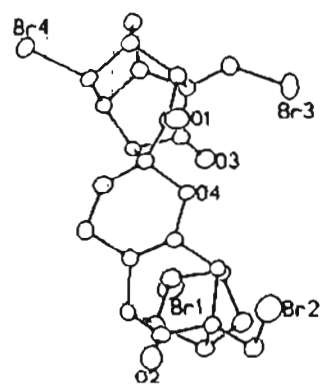
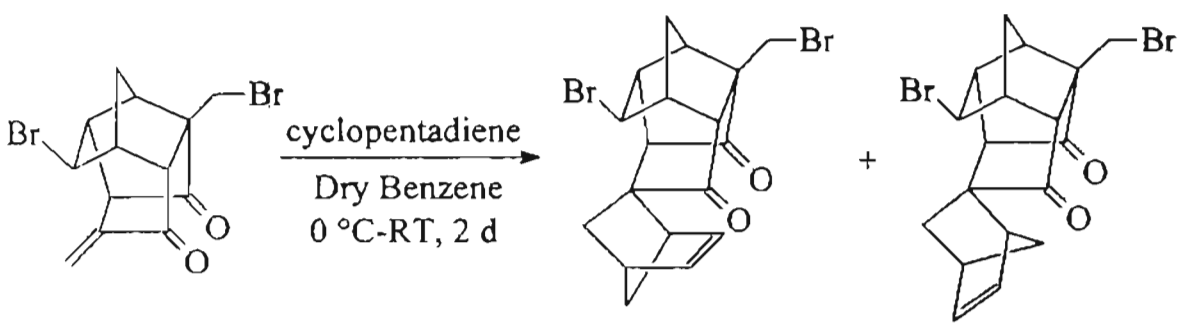


Figure 8: X-ray Crystal Structure showing the Presence of Trapped Solvent Molecule (*Dichloromethane*)

After having observed the ability of the enone moiety in **27** to act as a hetero-diene in a Diels-Alder fashion, it was sought to exploit this facet of the fascinating molecule. However, reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$] undeca-10(12)-ene-9,11-dione **27** with 2,5-bis(bromomethyl)-1,4-quinone did not proceed to the adduct even in a sealed tube under argon atmosphere in toluene. Prolonged reaction times only led to extensive decomposition of the quinone.

The next attempt was to check the efficacy of the double bond in **27** to act as a dienophile in Diels-Alder reactions with other dienes. Reaction with freshly cracked cyclopentadiene proceeded smoothly to give two adducts (Scheme XXII) which were separated by column chromatography and characterised. Both the compounds indicated the addition of one equivalent of cyclopentadiene to **27**, and the formation of two products was attributed to the addition of cyclopentadiene from two faces of the double bond leading to two different diastereomers. However, spectral data could not distinguish between the two isomers **43** and **44** (nomenclature and numbering is shown in scheme XXIII).

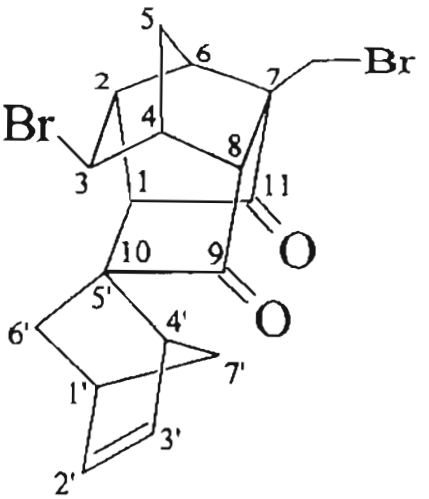


27 — 43 (26%) + 44 (29%)

Scheme XXII

The less polar compound **43** showed strong carbonyl absorptions at 1757 and 1701 cm^{-1} in the IR spectrum. Its ^1H NMR spectrum showed two olefinic protons as a multiplet between δ 6.33-6.26. The proton on C-1 appeared downfield as a singlet at δ 4.43. The other protons on the rings appeared as multiplets and exact assignments were not possible. The ^{13}C NMR spectral data also supported the proposed structure with carbonyls appearing downfield at δ 213.2 and 206.9. The olefinic carbons

appeared at δ 138.9 and 135.6 and it could be discerned from DEPT studies that these signals belonged to a disubstituted double bond. The quarternary carbons at C-7 and the spiro-carbon C-10,5' were seen at δ 58.0 and 61.8 respectively. The HRMS value of 423.9662 also confirmed the addition of one equivalent of cyclopentadiene to **27** leading to the Diels-Alder adduct **43**.



43 & 44

Spiro[3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione-10,5'-bicyclo[2.2.1]hept-2'-ene]

Scheme XXIII

The second compound **44** showed very similar characteristics in its spectra. The carbonyl stretches in the IR spectrum showed up as a broad, strong peak at 1738 cm^{-1}. The ^{1}H NMR spectrum showed the olefinic protons as two separate multiplets between δ 6.39-6.36 and 5.83-5.80. The proton on C-1 showed up as a singlet at δ 4.53, while the other protons appeared as various signals at the upfield region between δ 3.68 to δ 1.43. The ^{13}C NMR spectrum of the second compound was very similar to that of the first with eighteen signals ranging from δ 211.1 to δ 31.2. The two carbonyls gave signals at δ 211.1 and 207.2 and the disubstituted double bond carbons could be seen at δ 139.2 and 132.6. The quarternary carbon at C-7 and the spiro-carbon C-10,5' appeared at δ 58.0 and 60.6 respectively. All other carbons on the rings appeared between δ 63.4 and 31.2. All the above data together is

suggestive of a compound of structure **44**. However, in each case the structural depiction as **43** and **44** are interchangeable.

Thus we have explored some of the elementary chemistry of tetracyclic and pentacyclic compounds and found that the constrained polycyclic ring system gives us unexpected results even in these cases. The synthesis of these derivatives is hoped to be of future use in clinical tests since the biological activity of PCUDs substituted with polar groups is well known.

3.3 Experimental:

For general experimental details, see Chapter 2, page number 60.

Catalytic hydrogenation of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$] undeca-10(12)-ene-9,11-dione **27** to give **28, 29 and 30**:

The compound **27** (0.21 g, 0.6 mmol) was dissolved in 10 ml of dry ethyl acetate taken in a hydrogenation vessel and a catalytic amount (~ 40 mg) of 5% palladium on carbon was added to this solution. The set-up was flushed with hydrogen gas thrice. Then hydrogen gas was filled in the reaction vessel to a pressure of 20 psi and the reaction mixture was agitated at this pressure for one hour. Examination of the tlc at the end of this time period showed complete consumption of the starting material along with the formation of three products. The reaction was worked up by filtering out the catalyst and removing the solvent under reduced pressure on the rotavapor. The crude reaction mixture was separated into the three component products by column chromatography on silica gel. Elution with 7% ethyl acetate in petroleum ether gave the first product 3-bromo-7-(bromomethyl)-10-methyltetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **28** [165 mg (78% yield)]. Subsequent elution with 10% ethyl acetate in petroleum ether gave 7-(bromomethyl)-10-methyltetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **29** [11 mg (7% yield)]. This was followed by elution with 15% ethyl acetate in petroleum ether which gave 7,10-dimethyltetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **30** [6 mg (4% yield)].

*Spectral data for **28**:*

m.p. (°C)	:	131-133.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2982, 1755, 1715, 1465, 1243, 1148, 1067, 872, 778, 670, 636.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 4.57 (s, 1H), 3.57 (d, J = 10.4 Hz, 1H), 3.24-3.16 (m, 2H), 3.04 (d, J = 4.7 Hz, 1H), 2.91 (brs, 1H), 2.81-2.77 (m, 2H), 2.66-2.59 (m, 1H), 2.51 (dd, J_1 = 8.7 Hz, J_2 = 3.2 Hz, 1H), 1.93 (d, J = 11.7, 1H), 1.16 (d, J = 7.4 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 207.9 (2C), 64.9, 57.4, 50.4, 48.5, 47.7 (2C), 46.5, 44.9, 35.9, 30.9, 15.0.
HRMS (M^+ + 1)	:	360.9439, $C_{13}H_{14}O_2Br_2$ requires 359.9361.

Spectral data for **29**:

m.p. (°C)	:	113-115.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2968, 1751, 1730, 1470, 1420, 1270, 1239, 1145, 1108.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 3.47 (½ABq, J = 10.4 Hz, 1H), 3.20 (½ABq, J = 10.4 Hz, 1H), 2.93 (brs, 1H), 2.85-2.81 (m, 1H), 2.73 (brs, 1H), 2.64-2.57 (m, 2H), 2.51 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 1.81-1.71 (m, 3H), 1.58-1.51 (m, 1H), 1.36 (d, J = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 211.9, 211.7, 64.3, 59.4, 51.6, 47.6, 47.3, 42.5, 38.9, 32.8, 31.7, 30.9, 15.8.
HRMS (M^+)	:	282.0225, $C_{13}H_{15}BrO_2$ requires 282.0255.

Spectral data for **30**:

m.p. (°C)	:	89-91.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2980, 1757, 1726, 1470, 1426, 1370, 1276, 1245, 1145, 1089, 1045, 733, 646.

^1H NMR (300 MHz, $CDCl_3$) : δ 4.43 (s, 1H), 3.69 (d, J = 10.4 Hz, 1H), 3.19-3.13 (m, 2H), 2.97 (brs, 1H), 2.76-2.70 (m, 2H), 2.51-2.49 (m, 1H), 2.38 (s, 1H), 1.97 (d, J = 11.7 Hz, 1H), 1.60 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 218.8, 207.4, 60.5, 58.3, 54.8, 52.6, 52.1, 49.9, 49.7 (2C), 46.2, 44.0, 35.3, 30.5, 24.3.

HRMS (M^+) : 204.1185, $C_{13}H_{16}O_2$ requires 204.1150.

Reduction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **27** with lithium aluminium hydride to give **31**:

The compound **27** (44 mg, 0.1 mmol) was taken in a dry pear-shaped flask and dissolved in 5 ml of dry ether. In a dry round-bottomed flask flushed with argon, lithium aluminium hydride was placed (24 mg, 0.6 mmol, 6 eq.) and dry ether (5 ml) was added. This was cooled in an ice-water bath and then the solution of the compound **27** in dry ether was added to this using the syringe-septum technique. The reaction mixture was then left stirring at room temperature for two days under argon and later worked up by adding a few drops of water to destroy the excess lithium aluminium hydride. The white precipitate was filtered off and ether was removed to get the crude product. This was purified on a silica gel column to give 10 mg (44% yield) of the product **31**.

m.p. (°C) : 66-68.

FT-IR (KBr, ν_{max}/cm^{-1}) : 3407, 2952, 2871, 1452, 1253, 1079, 1054, 1029.

^1H NMR (300 MHz, $CDCl_3$) : δ 3.50 (d, J = 4.2 Hz, 1H), 3.36 (s, 2H), 2.48-2.41 (m, 1H), 2.31-2.24 (m, 3H), 2.11-2.07 (m, 1H), 1.97 (s, 1H), 1.81 (d, J = 4.0 Hz, 1H), 1.65-1.62 (m, 2H), 1.24-1.21 (m, 4H, $-CH_3$ and ½ABq), 1.09 (s, 3H), 0.99

(½ABq, J = 10.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 76.3, 72.9, 53.7, 52.5, 49.1, 47.8, 45.6, 44.8, 42.1, 35.0, 33.1, 22.4, 21.8.

HRMS (M^+) : 208.1456, $C_{13}H_{20}O_2$ requires 208.1463.

Reduction of 3-bromo-7-(bromomethyl)-10-methyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-9,11-dione **28** with lithium aluminium hydride to give **31**:

The compound **28** (33 mg, 0.1 mmol) was taken in a pear-shaped flask fitted with a septum. Dry ether (5 ml) was added using a syringe and the compound dissolved in it. 22 mg of lithium aluminium hydride (0.6 mmol, 6 eq.) was taken in a round-bottomed flask along with 5 ml of dry ether and the flask was fitted with a balloon filled with argon. The solution of **28** was added to the suspension of LAH after cooling it in ice and then the reaction mixture was left stirring under argon at room temperature for two days. It was worked up by destroying the excess LAH with a few drops of water. The resultant white precipitate was removed by filtration and ether removed to give the crude product. This was purified on a silica gel column to give 9 mg (53% yield) of the product **31** which was identical in all respects to the product **31** obtained in the previous reaction.

Reduction of 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **32** with lithium aluminium hydride to give **33**:

The compound **32** (85 mg, 0.2 mmol) was dissolved in 10 ml of dry ether taken in a pear-shaped flask. This solution was added *via* a syringe to a cooled solution of lithium aluminium hydride (45 mg, 1.2 mmol, 6 eq.) in 5 ml of dry ether. After the addition was completed, the reaction mixture was left stirring under argon at room temperature for twelve hours. It was worked up by adding a few drops of water to destroy the excess lithium aluminium hydride and the white precipitate that resulted was removed using Whatman 1 filter paper. Ether was removed and the crude obtained was purified on a silica gel column to give 27 mg (62% yield) of the product **33**.

m.p. (°C) : 54-57.

FT-IR (KBr, ν_{max}/cm^{-1})	:	3183, 2946, 2865, 1446, 1240, 1104, 1066.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 5.39 (brs, 2H), 3.47 (d, J = 4.2 Hz, 1H), 3.33 (d, J = 2.8 Hz, 1H), 2.43-2.38 (m, 1H), 2.25-2.22 (m, 2H), 2.08-2.04 (m, 1H), 1.85 (s, 1H), 1.79 (d, J = 4.3 Hz, 1H), 1.62 (½ABq, J = 10.6 Hz, 1H), 1.19 (s, 3H), 1.07 (s, 3H), 0.97 (½ABq, J = 10.7 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 77.1, 76.6, 53.7, 49.0, 47.7, 45.5, 44.7, 42.2, 41.9, 34.9, 33.1, 22.3, 21.7.
C / H Analysis	:	Calculated for $C_{13}H_{18}O_2$ C: 75.69%, H: 8.80%. Found C: 75.32%, H: 8.45%.

Reduction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **34** with lithium aluminium hydride to give **33**:

The compound **34** (40 mg, 0.15 mmol) was weighed into a pear-shaped flask and dissolved in 5 ml of dry ether. Lithium aluminium hydride (25 mg, 0.7 mmol, 4.5 eq.) was taken in a round-bottomed flask along with 5 ml of dry ether and this was cooled in ice. After adding the solution of compound **34** using a syringe to the suspension of LAH, the flask was fitted with a balloon filled with argon and the reaction mixture was left stirring at room temperature for two days. At the end of this period, the excess LAH was destroyed by adding a few drops of water to the reaction mixture. The white precipitate was removed and ether removed from the filtrate to give the crude product. This was purified on a silica gel column using 20% ethyl acetate-petroleum ether as eluent and gave 11 mg (36% yield) of the product which proved to be identical to the product **33**. Spectral data and melting points of the two compounds agreed within the limits of experimental error (m.p. 54-56 °C).

Sodium borohydride reduction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$] *undeca-10(12)-ene-9,11-dione* **27** *to give* **35**:

The compound **27** (38 mg, 0.1 mmol) was taken in a round-bottomed flask and dissolved in 10 ml of distilled methanol. This solution was cooled in an ice bath and

an excess of sodium borohydride (20 mg, 0.5 mmol, 5 eq.) was added to it. The reaction mixture was allowed to attain room temperature and further stirred for 1 hour. The reaction was worked up by removing the methanol under reduced pressure and the residue was diluted with distilled water and then extracted with dichloromethane. The combined organic layer was washed with distilled water and brine and finally dried over anhydrous sodium sulphate. The solvent was removed by distillation and the crude product chromatographed on silica-gel to give the product **35** in 41% yield (16 mg).

m.p. (°C)	:	144-147.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3407, 2971, 2927, 1465, 1265, 1234, 1085, 1010, 724.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 5.33 (s, 1H), 5.07 (s, 1H), 4.69-4.64 (m, 2H), 4.17 (d, J = 6.1 Hz, 1H), 3.59 (½ABq, J = 10.5 Hz, 1H), 3.35 (½ABq, J = 10.5 Hz, 1H), 3.13-3.08 (m, 1H), 2.79-2.75 (m, 1H), 2.69 (s, 1H), 2.34-2.24 (m, 2H), 2.04-1.92 (m, 3H), 1.64 (½ABq, J = 11.3 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 150.2, 112.8, 72.1, 67.6, 55.1, 52.8, 49.6, 49.5, 48.2, 47.9, 43.6, 35.3, 33.6.
C / H Analysis	:	Calculated for $C_{13}H_{16}Br_2O_2$ C: 42.89%, H: 4.43%. Found C: 42.86%, H: 4.43%.

Sodium borohydride reduction of 3-bromo-7-(bromomethyl)-10-methyltetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **28** to give **36**:

3-Bromo-7-(bromomethyl)-10-methyltetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-9,11-dione **28** (33 mg, 0.1 mmol) was taken in a dry round-bottomed flask and dissolved in distilled methanol. The solution was cooled in an ice-water bath. Sodium borohydride (20 mg, 0.5 mmol, 5 eq.) was added to this and the reaction mixture was left stirring at room temperature for 16 hours at which time tlc indicated the absence of starting material. Therefore, the reaction was worked up by removal of methanol on the rotavapor under vacuum and then the residue was extracted with dichloromethane. The combined

organic layer was washed with distilled water and brine, and finally dried over anhydrous sodium sulphate. After removing the dichloromethane on the rotavapor, the residue was loaded on a silica gel column and eluted with 20% ethyl acetate in petroleum ether to give the product as an off-white solid (29 mg, 87% yield). This was crystallised from dichloromethane-petroleum ether to give white crystals of the product **36**.

m.p. (°C)	:	188-189.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3444, 2959, 2934, 2909, 1465, 1412, 1340, 1303, 1209, 1097, 1004, 942.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 4.14 (s, 1H), 4.07-4.03 (m, 1H), 3.55 (½ABq, J = 10.4 Hz, 1H), 3.31 (½ABq, J = 10.4 Hz, 1H), 2.74-2.66 (m, 2H), 2.36 (½ABq, J = 11.3 Hz, 1H), 2.26-2.21 (m, 2H), 2.00 (t, J = 6.5 Hz, 1H), 1.85-1.82 (m, 1H), 1.70-1.69 (m, 1H), 1.61-1.51 (m, 3H), 1.29 (d, J = 6.81 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 72.2, 72.1, 57.7, 51.8, 50.7, 48.6, 48.3, 42.9, 42.7, 39.6, 36.0, 32.9, 19.4.
HRMS (M^+)	:	363.9689, $C_{13}H_{18}Br_2O_2$ requires 363.9673.

Sodium borohydride reduction of 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **32** to give **37**:

The pentacyclic compound **32** (68 mg, 0.2 mmol) was taken in a round-bottomed flask and dissolved in 10 ml of distilled methanol. The solution was cooled in ice and then sodium borohydride (30 mg, 0.8 mmol, 4 eq.) was added to this solution. The reaction mixture was then stirred at room temperature for 2 hours at which time tlc indicated complete consumption of the starting material. The reaction was worked up by removing the methanol under reduced pressure. The residue was diluted with distilled water and extracted with dichloromethane. The organic layer was washed with distilled water and brine and finally dried over anhydrous sodium sulphate. The dichloromethane was then removed and the crude product was purified on a silica gel

column. Elution with 25% ethyl acetate in petroleum ether gave the required product **37** (41 mg, 59% yield).

m.p. (°C) : 150-152.

FT-IR (KBr, ν_{max}/cm^{-1}) : 3183, 2965, 1483, 1458, 1434, 1290, 1234, 1097, 786, 711.

^1H NMR (300 MHz, $CDCl_3$) : δ 4.00 (s, 1H), 3.79-3.76 (m, 3H), 3.71 (d, *J* = 5.6 Hz, 1H), 3.65 (½ABq, *J* = 10.4 Hz, 1H), 3.41 (½ABq, *J* = 10.4 Hz, 1H), 2.55 (s, 2H), 2.43 (d, *J* = 2.6 Hz, 1H), 2.38-2.35 (m, 2H), 2.09 (s, 2H), 1.66 (½ABq, *J* = 11.2 Hz, 1H), 1.11 (½ABq, *J* = 11.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 72.8, 72.7, 52.3, 52.1, 46.9, 44.9, 43.3, 42.0, 41.9, 38.3, 36.6, 34.7, 32.8.

C / H Analysis : Calculated for $C_{13}H_{16}Br_2O_2$ C 42.89%, H 4.43%. Found C 43.39%, H 4.37%.

Sodium borohydride reduction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undeca-8,11-dione **34** to give **38**:

The bis(chloromethyl)pentacyclic derivative **34** (49 mg, 0.2 mmol) taken in a round-bottomed flask was dissolved in 10 ml of distilled methanol and cooled in an ice bath. Sodium borohydride (30 mg, 0.8 mmol, 4 eq.) was added slowly to this solution. After the addition was completed, the reaction mixture was left stirring at room temperature for 2.5 hours. Examination of the tlc at the end of this time period showed the absence of starting material, and the reaction mixture was worked up as before. Removal of the solvent gave the crude product which was purified by chromatography on a silica gel column with 20% ethyl acetate in petroleum ether as the eluent. The product **38** was obtained in 90% yield (45 mg) as a white solid which was crystallised from dichloromethane-petroleum ether.

m.p. (°C) : 149-151.

FT-IR (KBr, ν_{max}/cm^{-1}) : 3170, 2971, 2871, 1489, 1440, 1284, 1234, 1097, 1004, 873.

^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 5.30 (brs, 1H), 5.07 (brs, 1H), 4.00 (s, 1H), 3.84-3.73 (m, 4H), 3.50 (½ABq, J = 11.3 Hz, 1H), 2.57-2.49 (m, 3H), 2.36 (s, 2H), 2.02 (s, 1H), 1.67 (½ABq, J = 11.2 Hz, 1H), 1.12 (½ABq, J = 11.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 71.9 (2C), 52.9, 51.3, 48.0, 47.4, 46.5, 44.1, 42.3, 41.7, 41.3, 35.0, 32.9.
C / H Analysis	:	Calculated for $C_{13}H_{16}O_2Cl_2$ C: 56.74%, H: 5.86%. Got: C: 56.73%, H: 5.43%.

Nitration of 1,9-bis(benzyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **40** to **41**:

The bis(benzyl)pentacyclic compound **40** (36 mg, 0.1 mmol) was taken in a round-bottomed flask and it was cooled in an ice bath. A nitrating mixture of concentrated nitric acid (1.2 ml) and concentrated sulphuric acid (4 ml) was added to the above round-bottomed flask drop-by-drop. After the addition was completed, it was seen that the compound dissolved in the acid within five minutes. It was worked up by adding cold distilled water. The yellow coloured precipitate formed was filtered out and washed thoroughly with distilled water. The precipitate was dissolved in dichloromethane, dried over anhydrous sodium sulphate and the solvent removed. The crude product was purified by column chromatography on silica gel. The product **41** was obtained in 83% yield as a pale yellow solid (45 mg) and crystallised from dichloromethane-petroleum ether mixture.

m.p. (°C)	:	198-201.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3105, 2980, 2874, 1751, 1601, 1526, 1439, 1345, 1264, 1145, 1095, 908, 827, 727.
^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4)	:	δ 8.76 (s, 1H), 8.63 (s, 1H), 8.35 (brs, 2H), 7.94 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 4.11 (q, J = 7.0 Hz, 1H), 3.49-3.45 (m, 1H), 3.35-3.29 (m, 2H), 3.23-3.16 (m, 1H), 2.84-2.78 (m, 2H), 2.62-2.58 (m, 2H), 2.42 (s, 1H), 2.22 (½ABq, J = 11.7 Hz, 1H), 1.89

(½ABq, J = 11.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) : δ 211.6, 210.4, 150.7, 149.8, 146.9, 146.7, 139.2, 138.2, 135.4, 133.9, 127.1, 126.6, 120.3, 119.7, 63.3, 59.8, 52.1, 48.4 (2C), 44.3, 43.0, 39.7, 35.5, 31.6, 31.4.

HRMS (M^+) : 534.1028, $C_{25}H_{18}N_4O_{10}$ requires 534.1023.

Intermolecular Diels-Alder dimerisation of 3-bromo-7-(bromomethyl)tetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **27** to **42**:

The monomer **27** (104 mg) was taken in ~10 ml of a mixture of ethyl acetate and petroleum ether (prepared the solution by dissolving the compound in minimum amount of ethyl acetate and then adding petroleum ether in order to prepare a supersaturated solution). This was left undisturbed for eight days and at the end of this period, tlc examination showed the formation of a considerable amount of a more polar UV-active product. The solvent was removed on the rotavapor under reduced pressure and then the residue was loaded on a silica gel column. Elution with 5% ethyl acetate in petroleum ether gave 75 mg of **27** (i.e., 72% of the starting material was recovered). Further elution with 10% ethyl acetate in petroleum ether gave 17 mg of the dimerised product **42** (16% yield, 59% yield based on the amount of starting material recovered).

m.p. (°C) : 158-160.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2972, 2918, 2844, 1763, 1729, 1669, 1461, 1420, 1373, 1333, 1273, 1246, 1158, 1111, 1044, 729.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 4.39 (s, 1H), 4.29 (s, 1H), 3.71 (d, J = 10.5 Hz, 1H), 3.49 (d, J = 10.5 Hz, 1H), 3.32 (d, J = 10.5 Hz, 1H), 3.23-3.18 (m, 2H), 3.14 (d, J = 10.5 Hz, 1H), 3.02-2.99 (m, 2H), 2.88-2.87 (m, 1H), 2.85 (d, J = 8.9 Hz, 1H), 2.76-2.73 (m, 2H), 2.65-2.63 (m, 2H), 2.50

(d, J = 4.7 Hz, 1H), 2.44 (d, J = 4.7 Hz, 1H), 2.35-2.29 (m, 2H), 2.22-2.18 (m, 1H), 1.98 (d, J = 12.2 Hz, 1H), 1.91-1.88 (m, 1H), 1.83 (d, J = 11.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 203.1, 201.9 (2C), 147.5, 104.7, 83.3, 61.2, 58.7, 55.4, 55.1, 53.7, 53.4, 50.6, 49.6, 48.0, 46.3, 46.0, 45.4, 45.3, 44.1, 35.4, 35.2, 30.8, 30.6, 25.5, 20.9.

HRMS (M^+) : 715.8418, $C_{26}H_{24}O_4Br_4$ requires 715.8408.

UV (CH_2Cl_2, λ_{max}) : 230 and 298 nm.

Crystal data for **42** (Fig. 7 and 8):

$C_{27}H_{26}Br_4Cl_2O_4$ (crystal incorporates one molecule of dichloromethane), colourless cystalline solid, 0.33 × 0.22 × 0.10 mm, monoclinic, space group : $P2_1/c$. Unit cell dimensions : a = 10.7862(2) Å α = 90°; b = 10.8819(1) Å β = 95.8920(10)°; c = 23.8608(3) Å γ = 90°. R indices : R1 = 0.0439, wR2 = 0.0707. Volume = 2785.85(7) Å^3, Z = 4. Density (calculated) = 1.919 Mg/m^3. F(000) = 1576. Absorption coefficient = 6.004 mm^{-1}.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **27** with cyclopentadiene to give **43** and **44**:

The compound **27** (102 mg, 0.3 mmol) was taken in a round-bottomed flask and dissolved in dry benzene. The solution was cooled in an ice-water bath and 0.05 ml of freshly cracked cyclopentadiene was added to this and the reaction was left stirring for a day before checking the tlc. Since some starting material was still present, the solution was again cooled in a ice-water bath and a further aliquot of 0.05 ml of freshly cracked cyclopentadiene (total 0.10 ml, 0.8 g, 1.2 mmol, 4 eq.) was added and the reaction was left stirring at room temperature for another day. The reaction was worked up by removing the solvent and the two products were separated out by column chromatography on a silica gel column. Slow elution with 5% ethyl acetate in

petroleum ether enabled the separation of two products in **43** and **44** in 26% and 29% yields respectively.

Spectral data for **43**:

m.p. (°C)	:	90-92.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3055, 2980, 2924, 2850, 1757, 1701, 1463, 1420, 1264, 1239, 1139, 733.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.33-6.26 (m, 2H), 4.43 (s, 1H), 3.69 (d, J = 10.3 Hz, 1H), 3.17-3.13 (m, 2H), 3.07-3.02 (m, 1H), 2.94 (s, 2H), 2.77-2.68 (m, 2H), 2.47-2.45 (m, 2H), 2.23-2.19 (m, 2H), 1.88 (d, J = 11.7 Hz, 1H), 1.34-1.25 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 213.2, 206.9, 138.9, 135.6, 63.7, 61.8, 58.0, 52.8, 52.7, 52.4, 50.4, 46.4, 45.6, 45.3, 42.5, 40.3, 35.6, 31.4.
HRMS (M^+)	:	423.9662, $C_{18}H_{18}O_2Br_2$ requires 423.9674.

Spectral data for **44**:

m.p. (°C)	:	118-120.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3062, 2968, 1738, 1463, 1420, 1345, 1264, 889, 733.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.39-6.36 (m, 1H), 5.83-5.80 (m, 1H), 4.53 (s, 1H), 3.68 (d, J = 10.3, 1H), 3.21-3.14 (m, 2H), 3.02 (s, 2H), 2.93-2.90 (m, 2H), 2.75-2.69 (m, 2H), 2.49 (s, 1H), 1.90-1.83 (m, 2H), 1.76-1.64 (m, 2H), 1.43 (d, J = 8.9, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 211.1, 207.2, 139.2, 132.6, 63.4, 60.6, 58.0, 53.6, 51.9, 51.1, 50.4, 48.1, 46.2, 45.6, 44.5, 43.9, 35.5, 31.2.

HRMS (M^+) : 423.9613, $C_{18}H_{18}O_2Br_2$ requires 423.9674.

3.4 References:

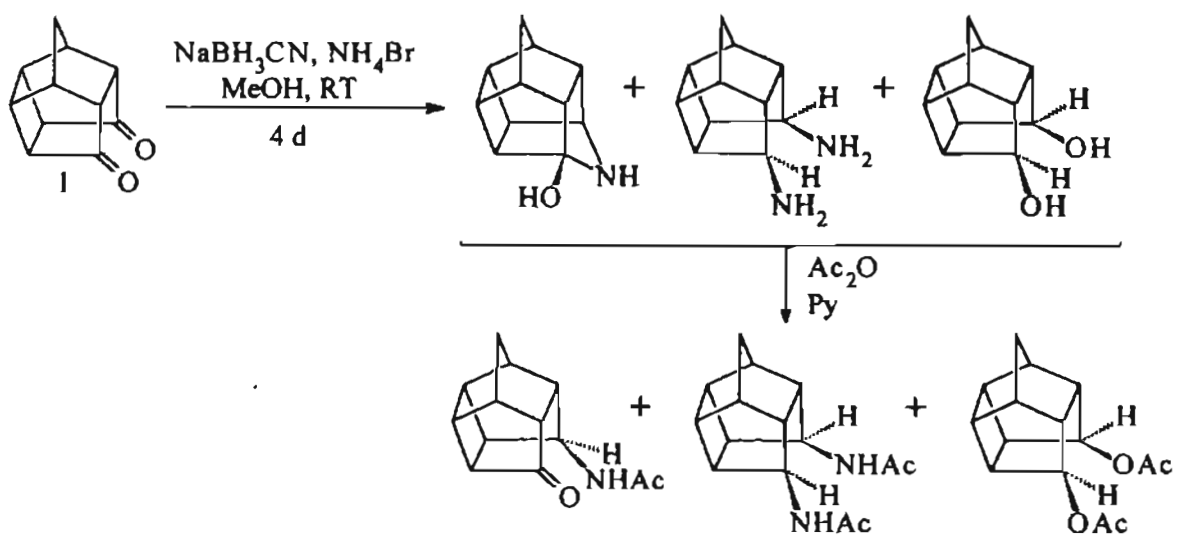
1. Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062-3075.
2. Marchand, A. P.; Arney, Jr., B. E.; Dave, P. R. *J. Org. Chem.* **1988**, *53*, 443-446.
3. Martins, F. J. C.; Viljoen, A. M.; Coetzee, M.; Fourie, L.; Wessels, P. L. *Tetrahedron* **1991**, *47*, 9215-9224.
4. Marchand, A. P.; Chong, H.-S.; Shukla, R.; Sharma, G. V. M.; Kumar, K. A.; Zope, U. R.; Bott, S. G. *Tetrahedron* **1996**, *52*, 13531-13538.
5. Marchand, A. P.; Aavula, B. R.; Bott, S. G. *Tetrahedron* **1998**, *54*, 5105-5118.
6. Chow, T. J.; Wu, T.-K. *J. Org. Chem.* **1991**, *56*, 6833-6835.
7. Craze, G.-A.; Watt, I. *J. Chem. Soc., Perkin Trans. II* **1981**, 175-184.
8. Marchand, A. P.; LaRoe, W. D.; Sharma, G. V. M.; Suri, S. C.; Reddy, D. S. *J. Org. Chem.* **1986**, *51*, 1622-1625.
9. Kruger, H. G. Ph. D. Thesis submitted to the Potchefstroom University for Christian Higher Education, **1996** and the references cited therein.

CHAPTER 4 – REACTIONS AND REARRANGEMENTS OF TETRA- AND PENTACYCLIC CAGE COMPOUNDS WITH PRIMARY AMINES

As has been elaborated in the earlier chapters of this thesis, there has been considerable interest in the synthesis of nitrogen-containing heterocyclic polycycles as they have been proved to be biologically active. Apart from this, introduction of nitro- and amino- groups on the pentacyclic cage system has been studied by Marchand *et al.* especially due to their interest in the development of polynitropolycyclic compounds as high-energy materials. However, reactions of amines with pentacycloundecadiones have not been extensively studied as can be garnered by a survey of the literature. Some of the pertinent studies in this field are given below.

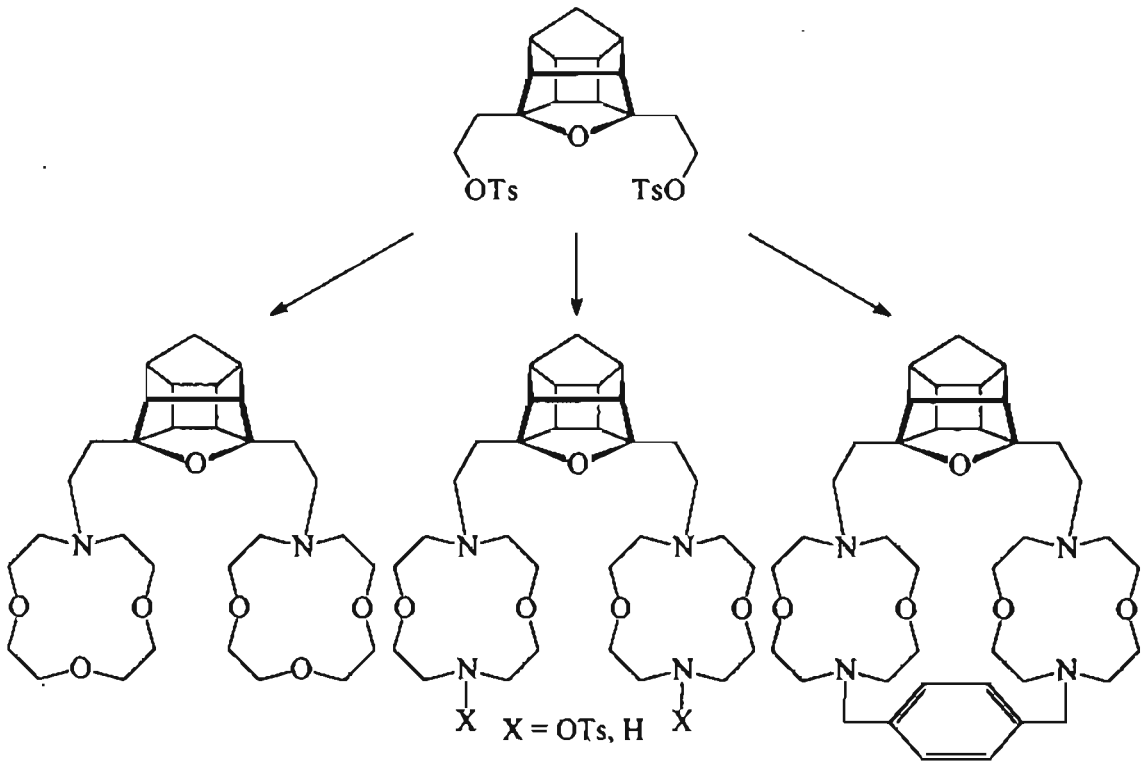
4.1 Introduction:

Marchand *et al.*[1] have reported the reductive amination of the simple pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione (PCUD) **1** to give novel pentacyclic compounds substituted with nitrogen-containing functionalities (Scheme I). These studies were geared towards the synthesis of polynitropolycyclic cage compounds and many nitro compounds were synthesised *via* oxidation of these.



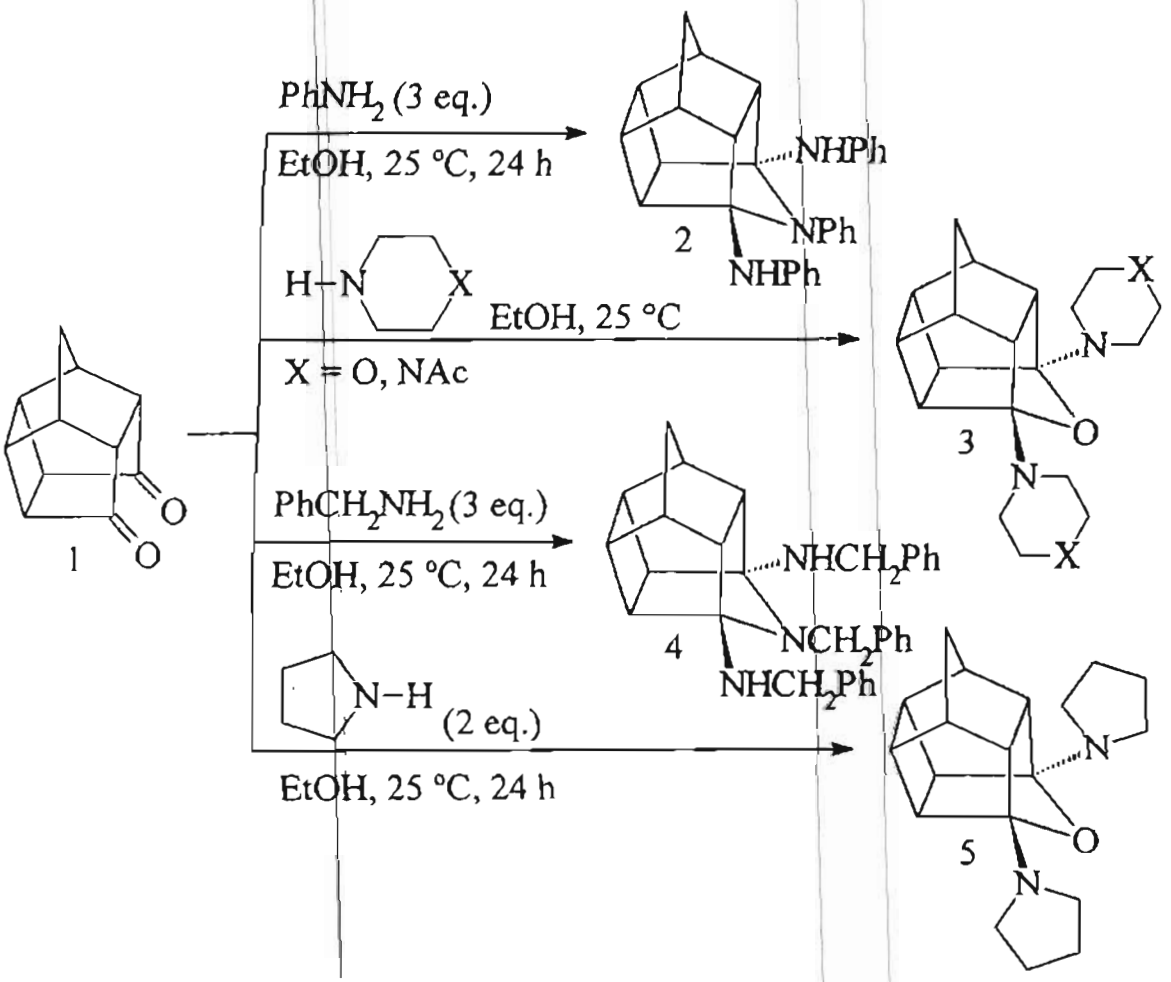
Scheme I

Nitrogen-containing macrocycles tethered to polycyclic cage compounds were also synthesised by Marchand *et al.* (Scheme II) in order to study their effect on the alkali-metal binding abilities.[2] The role of the cage structure in this instance was to anchor the aza-crown ethers in space so as to enhance the rigidity of the cavity formed.



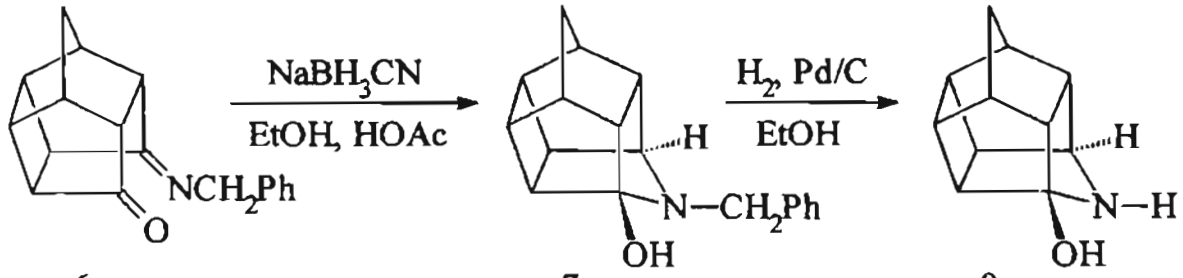
Scheme II

Bott *et al.* have reported the nucleophilic additions of primary and secondary amines to PCUD **1** wherein there is straightforward addition of the amine to the carbonyl carbon followed by intramolecular transannular reactions.[3] This gave rise to novel hexacyclic compounds **2**, **3**, **4** and **5** incorporating hetero-atoms into the ring system as shown in scheme *III*.



Scheme III

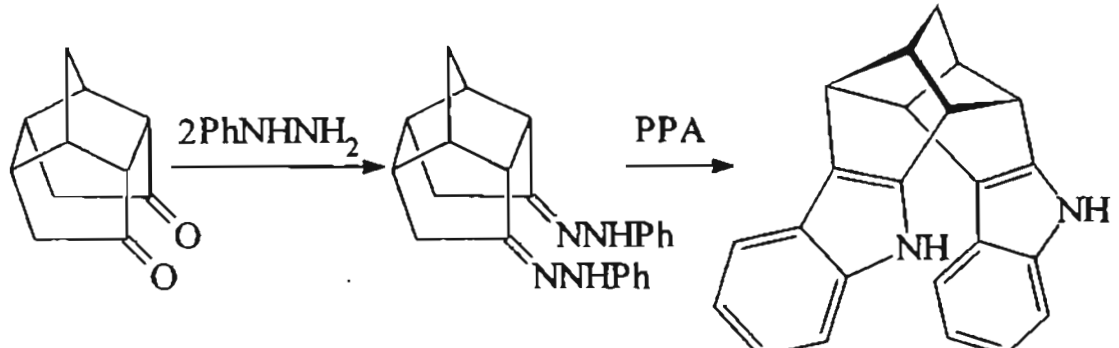
Since sodium cyanoborohydride reduces iminium ions much more rapidly than carbonyl groups, reduction of pentacyclic compound **6** containing an imino group and a ketone was also explored by Marchand *et al.* as a method for the synthesis of novel aza-compounds.[4] The reaction gave rise to hexacyclic compound **7** with a tertiary aza-bridge which on subsequent hydrogenolysis gave rise to the secondary amine bridge in the hexacyclic compound **8** as shown in scheme IV.



6 7 8

Scheme IV

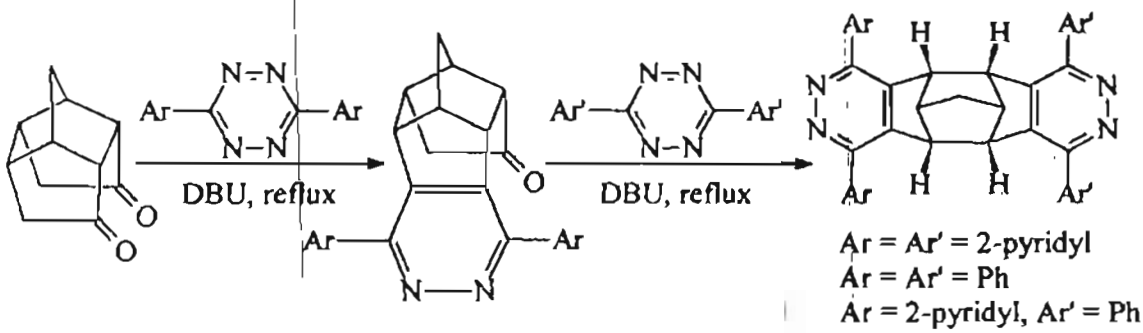
Aromatic systems containing nitrogen have been linked to the polycyclic compounds in order to study the interactions of π-systems through space. For example, UV absorption and hydrogen bonding are found to vary as a function of the planarity of the molecule. As depicted in scheme V, treatment of the diketone **9** with phenylhydrazine led to the corresponding bis(hydrazone) **10** which on treatment with polyphosphoric acid converts into the *syn*-orthocyclophane system **11**.[5] The aromatic proton resonances in **11** are shielded and probably reflect on the interplanar distance between the benzo rings.



9 10 11

Scheme V

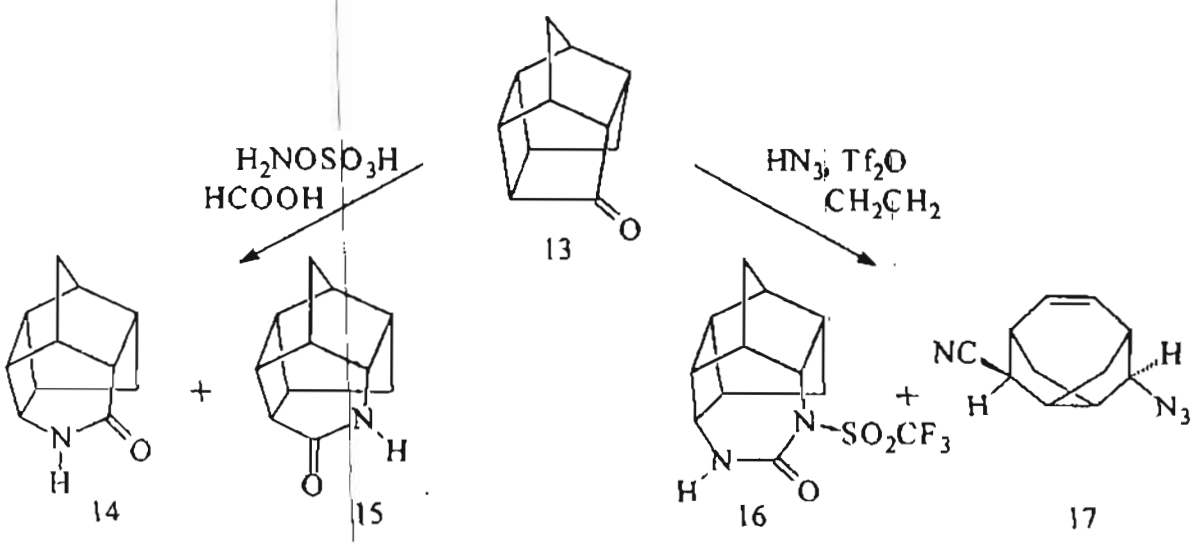
Haddadin et al. have reported the preparation of a large number of 'molecular clefts' of the type **12** by the reaction of 3,6-diaryl-1,2,4,5-tetrazines with the polycyclic diketone **9**.[6] These compounds are of interest as a new class of potential host molecules for the use in host-guest complexation studies such as inclusion phenomena and molecular recognition.



9 12

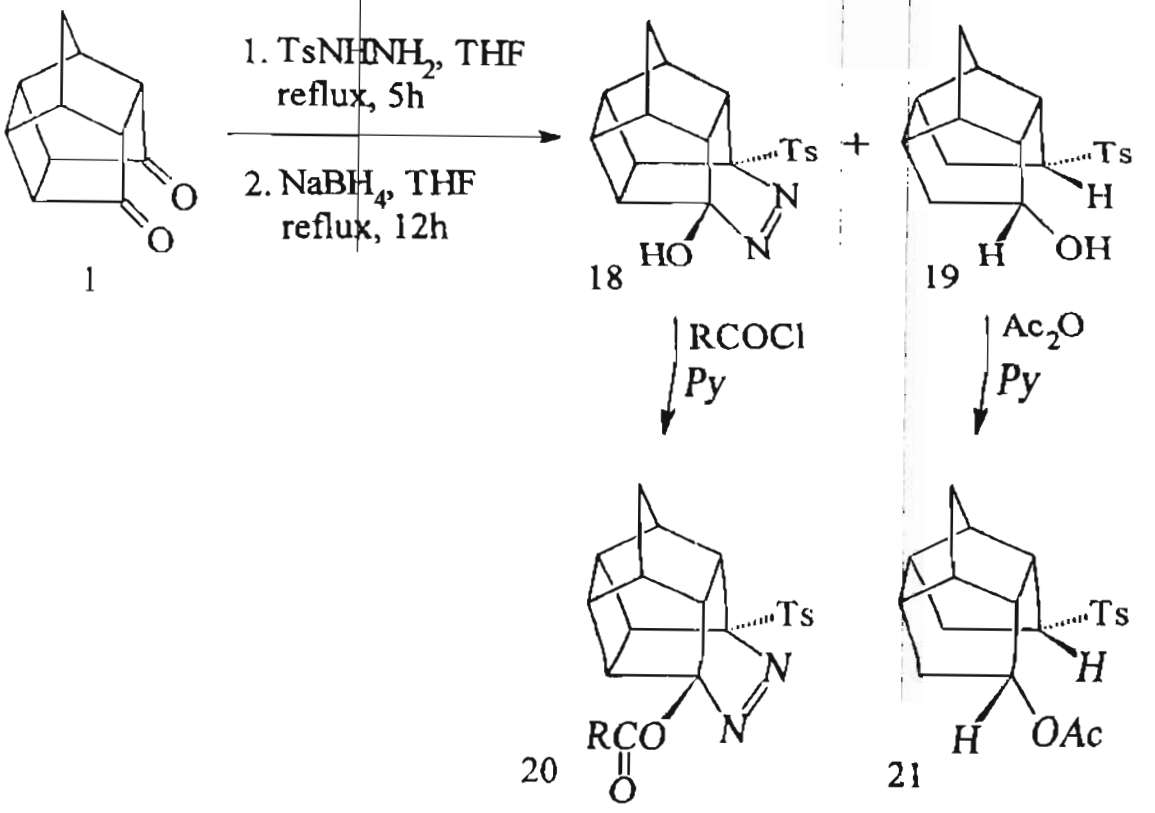
Scheme VI

The Schmidt rearrangement has been used to prepare ring-expanded isomeric lactams **14** and **15** by the treatment of pentacyclic ketone **13** with hydroxylamine-*O*-sulphonic acid in the presence of formic acid. However, attempts to use HN_3-Tf_2O to *effect the Schmidt rearrangement resulted in a 'double Schmidt rearrangement' and concomitant Huisgen* rearrangement leading to compounds such as **16** and **17** shown in scheme VII.[7]



Scheme VII

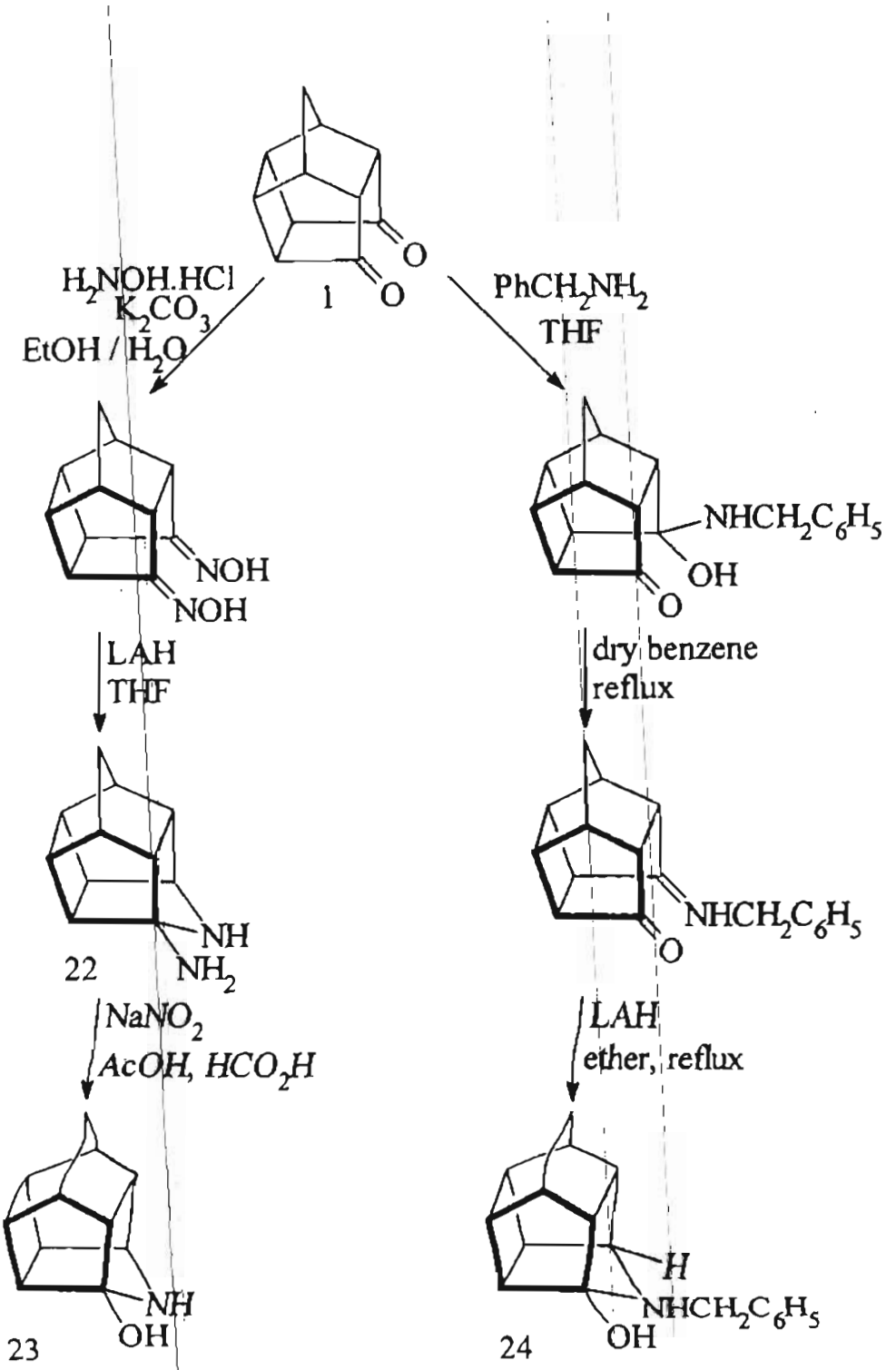
Marchand *et al.* continued their interest in 'roughly spherical cage amines' since they are of interest as analogues of 1-aminoadamantane (amantadine) whose antiviral and anti-Parkinson activities[8] are well known. They proposed the synthesis of amino-substituted PCUDs starting from **1** by reacting it with (*p*-tolylsulphonyl)hydrazine followed by *in situ* reduction with sodium borohydride.[9] This reaction scheme, however, afforded two totally unexpected products: a *hexacyclic azoalkane* ***18*** *and a p-tolylsulphonyl derivative* ***19*** *as shown in scheme* VIII. The structures were establised by further derivatising these products to compounds **20** and **21** and verifying their crystal structure.



1 18 19 20 21

Scheme VIII

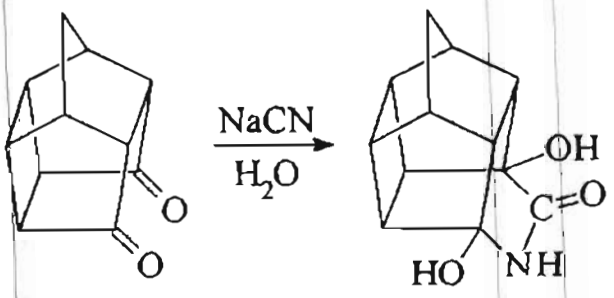
Sasaki and co-workers have carried out extensive studies into the conditions under which transannular cyclisation takes place and have reported the synthesis of *many hexacyclic cages, for example, compounds* **22**, **23** *and* **24**, containing nitrogen as part of the polycyclic framework (Scheme IX). *It is noteworthy that none of these* reactions have affected the pentacyclic framework of the original molecule.[10]



Scheme IX

Kruger *et al.* treated PCUD under Strecker reaction conditions hoping to get intermediate cyanohydrins which would undergo nucleophilic substitution to produce

amino nitriles. However, on treatment with sodium cyanide and water, PCUD **1** unexpectedly produced a δ-lactam **25** as shown in scheme X.[11]



1 25

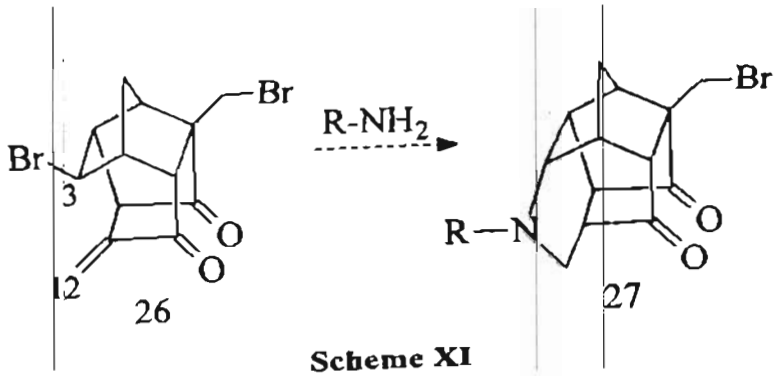
Scheme X

This brief introduction to the variety of cage compounds containing nitrogen functionalities, with nitrogen either as part of the polycyclic framework or as a substituent on the framework, was made with the intention of highlighting the scarcity of work in this area. With their proven biological activity, it would be of more than aesthetic interest to synthesise previously unknown systems of this type.

4.2 Results and Discussion:

4.2.1 Reactions of 3-Bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione with Primary Amines:

In the second chapter of this thesis, the unusual rearrangement of 2,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione to 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione (Chapter 2, Scheme XVIII) was detailed. On obtaining this novel tetracyclic compound (assigned structure number **26** in this chapter), it was thought that its reaction with a primary amine would generate a previously unknown pentacyclic system **27** as shown in scheme XI. These pentacyclic compounds incorporating nitrogen in the ring system would be expected to be physiologically active.



Scheme XI

It was expected that the bromine on C-3 would react in tandem with the double bond of the enone and lead to an aza-bridge between the carbons in the 3 and 12 positions in the original compound leading to **27**.

Accordingly, compound **26** was taken in benzene cooled to ~ 5 °C and a large excess of methylamine was bubbled through the reaction mixture. After stirring for one hour, the tlc of reaction mixture indicated the formation of a single product (Scheme XII). After removal of excess amine and benzene, the product was purified by column chromatography. However, the product of the reaction of **26** with methylamine did not show any of the expected features for **27** in its spectra. On the contrary, the product seemed to contain a lactam ring instead of a tertiary amine. The mass spectrum of the product [with HRMS (M^++1) = 310.0443] clearly indicated the loss of one bromine atom and the addition of one equivalent of amine. Other salient features in the spectral data included (i) signals at δ 5.03 and 4.69 in ^{1}H NMR spectrum (Fig. 1) (one proton each), and δ 145.7 and 109.1 in ^{13}C NMR spectrum (Fig. 2) indicative of an exocyclic methylene group. (ii) signal at δ 209.4 in ^{13}C NMR spectrum and ν_{max} 1708 cm^{-1} in the IR spectrum suggestive of carbonyl group. (iii) signal at δ 2.68 (singlet, 3H) in ^{1}H NMR spectrum and ν_{max} 1681 cm^{-1} in the IR spectrum suggestive of –NCH_3 group and an amide linkage. (iv) the ½ABq signals at δ 2.61 (J = 10.8 Hz) and δ 1.56 (J = 10.8 Hz) which indicate that the strained cage structure is still present making the methylene on the norbornyl bridge appear thus. Consolidating all the information, the structure of the product was proposed as **28** as depicted in scheme XII.

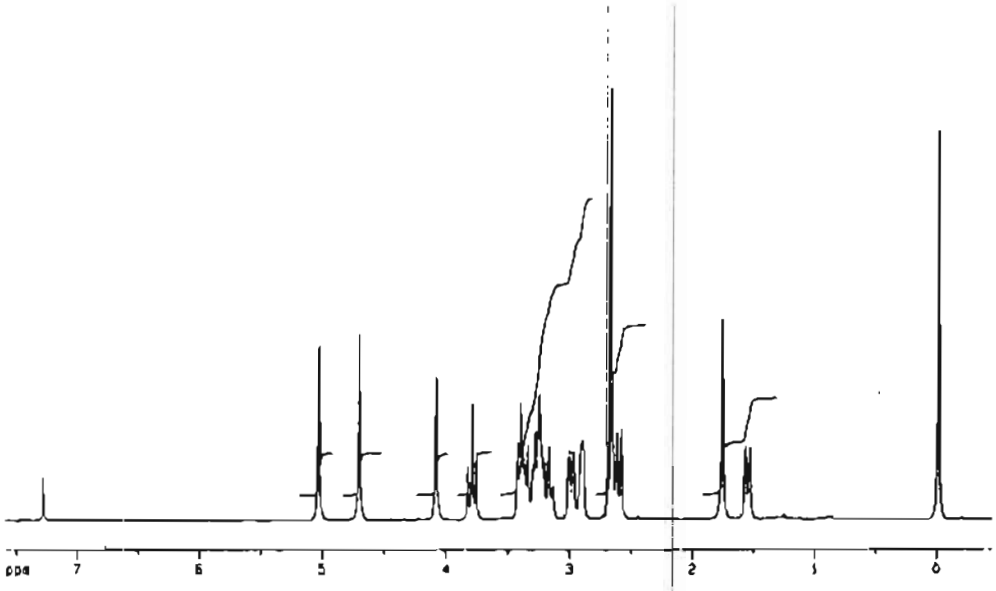


Figure 1: ^{1}H NMR Spectrum of 28

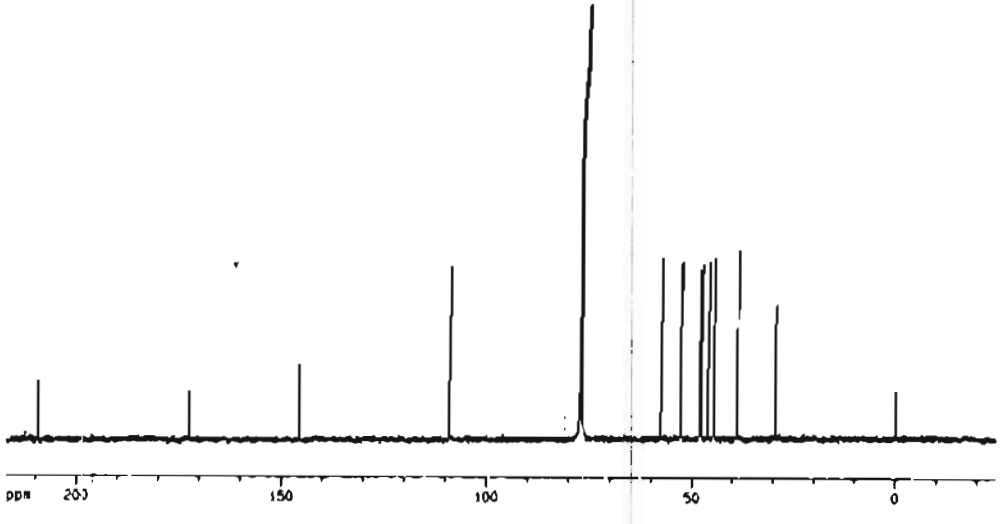
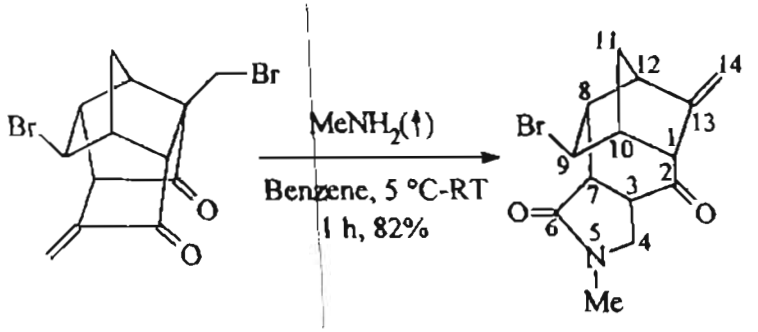


Figure 2: ^{13}C NMR Spectrum of 28



26 28

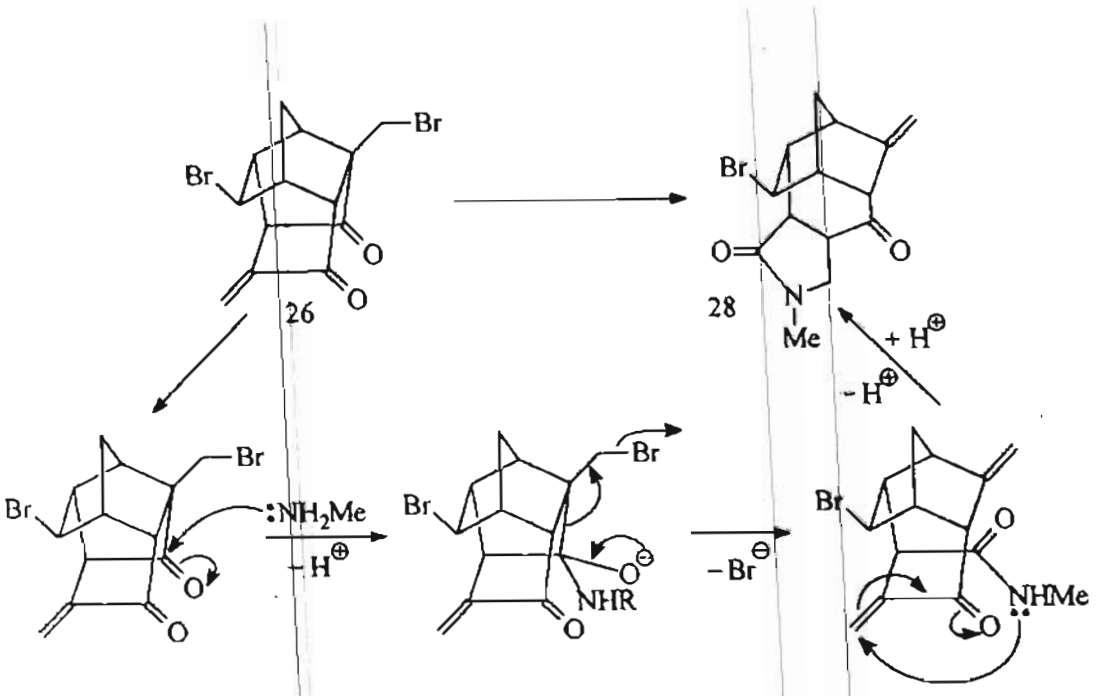
5-Azamethyl-9-bromotetracyclo [8.3.0.0^{3,7}.0^{8,12}]tridec-13(14)-ene-2,6-dione

Scheme XII

This structure also explained the following characteristics, *viz.*, (i) the proton on C-1 appears at δ 4.06 as a singlet since it is adjacent to both a double bond and a carbonyl group and (ii) the proton on C-3 which appears upfield as a triplet at δ 3.79 due to the two adjacent protons on C-4. The other ring protons appeared as various multiplets and individual assignments were not possible.

Mechanistic Outlook:

The mechanism proposed for the formation of this unexpected product **28** is shown in scheme XIII. It invokes the initial addition of the amine to the carbonyl carbon, followed by the halogen being removed as an anion and consequent formation of an exocyclic double bond. The removal of the halogen is probably facilitated by the excess amine present in the medium leading to the formation of an ammonium salt. The lone pair on the nitrogen of the amide then adds to the double bond in a Michael addition fashion. This addition is assumed to be facile due to the proximity of these groups which are pendant on the constrained polycyclic system. Transfer of proton then leads to the polycyclic lactam **28**. This novel ring system contains many functional groups which would be amenable to further transformations: the lactam, the carbonyl, the double bond and also the bromo functionality. With so many polar groups distributed on a hydrocarbon cage system, the molecule is also envisaged to have potential biological applications.

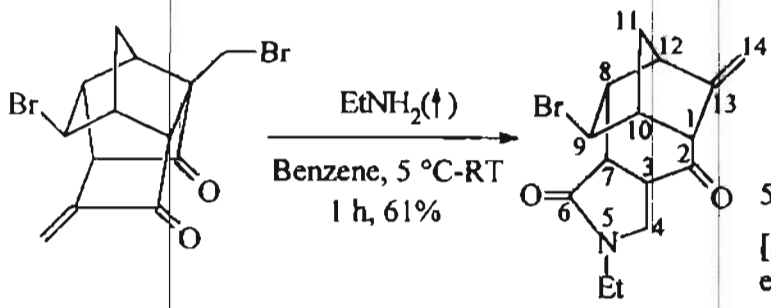


Scheme XIII

The generality of this reaction was confirmed with a number of other primary amines, namely, ethylamine, *n*-butylamine, benzylamine, veratrylamine and homoveratrylamine. In all cases, the homologous lactams were obtained in good to excellent yields and the compounds were fully characterised on the basis of their spectra. The syntheses and salient spectral characteristics of these homologues are discussed in detail in the following pages.

The reaction of **26** with ethylamine was carried out under similar conditions (Scheme XIV) which furnished a single product **29** after chromatographic separation. The IR spectrum of **29** showed a strong absorption at 1700 cm^{-1} indicative of the lactam carbonyl. The proton NMR spectrum showed the protons on the exocyclic double bond as two singlets at δ 4.98 and 4.64. The $-CH_3$ of the lactam ethyl group appeared as expected at δ 0.97 as a triplet. The norbornyl bridge methylene was obvious as ½ABq signals centered at δ 2.54 and 1.49 with a coupling constant of 10.8 Hz. The proton on C-1 appeared as a singlet at δ 4.03 due to the deshielding effect of the adjacent carbonyl group and double bond and the proton on C-3 appeared as a triplet at δ 3.70 with a coupling constant of 10.4 Hz. The ^{13}C NMR spectrum gave ample support to the proposed structure, it showed the carbonyl signal at δ 209.3, the lactam signal at δ 171.7, the exocyclic double bond carbon signals at δ 145.2 and

110.1, and all other signals appeared upfield between δ 56.8 and 10.6. The HRMS value of 323.0519 also lent support to the tetracyclic structure **29**.



5-Azaethyl-9-bromotetracyclo [8.3.0.0^{3,7}.0^{8,12}]tridec-13(14)-ene-2,6-dione

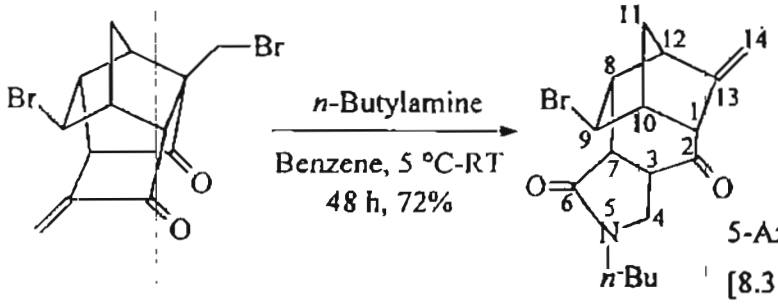
26 29

Scheme XIV

The reaction with *n*-butylamine had to be optimised in order to obtain a maximum yield of the product. In the previous two reactions, a large excess of the amine had been present in the reaction mixture since the gaseous amine had been passed through the solution for ½ hour. On carrying out the reaction of the tetracycle with *n*-butylamine using two equivalents of the amine (one for the formation of the lactam and the other for the removal of the bromine in the form of a salt as required by the reaction mechanism), the reaction was not only found to be sluggish, but also did not go to completion even after long time periods. When the reaction was done with four equivalents of the amine, the reaction was again sluggish. It was finally determined that a large excess of the amine gave reasonable reaction rates with optimum yield. And this practise was followed in the subsequent reactions with other amines too.

The product **30** obtained upon the reaction of *n*-butylamine with **26** (Scheme XV) showed characteristic features in its spectra and the lactam was identified in the following manner: the product showed the characteristic peaks in the IR spectrum due to the two carbonyls as a overlapping peak at 1701 cm^{-1}. The ^{1}H NMR spectrum showed the exocyclic methylene protons as two singlets at δ 5.03 and 4.70. The protons on the *n*-butyl group appeared as (i) a triplet at δ 0.91 and (ii) as two multiplets between δ 1.32-1.25 and δ 1.43-1.36. The protons on C-4 being adjacent to the nitrogen appeared downfield along with the ring protons as overlapping multiplets and could not be clearly distinguished. The proton on C-3 appeared at δ 3.78 as a

triplet and the singlet at δ 4.10 was attributed to the proton on C-1 which appears downfield since it is adjacent to a double bond and a carbonyl group. The norbornyl bridge protons appeared as ½ABq signals at δ 2.61 and 1.55 with a coupling constant of 10.8 Hz. The ring protons appeared as multiplets between δ 3.41 and δ 2.83 and separate assignment was not possible because of complex couplings. The ^{13}C NMR spectrum also lent support to the proposed structure by showing the ring carbonyl signal at δ 209.3, the lactam carbonyl at δ 171.9 and the exocyclic double bond carbons as signals at δ 145.3 and 109.9. All thirteen other carbons gave signals upfield between δ 57.8 and 13.7.



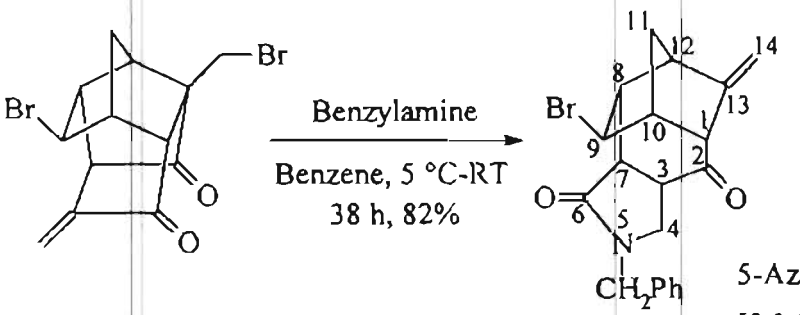
26 *30*

5-Aza-*n*-butyl-9-bromotetracyclo [8.3.0.0^{3,7}.0^{8,12}]tridec-13(14)-*ene-2,6-dione*

Scheme XV

The reaction of **26** with benzylamine (Scheme XVI) was carried out under similar conditions (6 equivalents of benzylamine and a reaction time of 38 hours) to give the expected product **31**. The product formed was easy to characterise by comparing it to the spectra of the products discussed so far. The IR spectrum confirmed the presence of the carbonyl functionalities with peaks at 1694 and 1688 cm^{-1}. The ^{1}H NMR spectrum confirmed the presence of a benzyl group by showing up the aromatic protons as a multiplet between δ 7.32-7.19. The olefinic protons showed up as two singlets at δ 4.85 and 4.51. The proton on C-1 appeared as a singlet at δ 4.09 and the proton at C-3 as a triplet at δ 3.65 (J = 10.6 Hz). The norbornyl bridge methylene protons showed as ½ABq signals at δ 2.61 and 1.55 due to the strained ring system. The ^{13}C NMR spectrum also supported the structure by confirming the presence of the groups proposed: the carbonyl appeared at δ 209.1, the lactam carbonyl at δ 171.9, the olefinic and aromatic carbons appeared between δ 145.1 and 109.8 and all other signals appeared upfield between δ 57.7 and 39.0. The product

was thus thoroughly characterised using usual spectral techniques and further the single-crystal X-ray diffraction technique gave conclusive proof of the tetracyclic lactam structure proposed for these derivatives (Fig. 3).



26 31

5-Azabenzyl-9-bromotetracyclo [8.3.0.0^{3,7}.0^{8,12}]tridec-13(14)-ene-2,6-dione

Scheme XVI

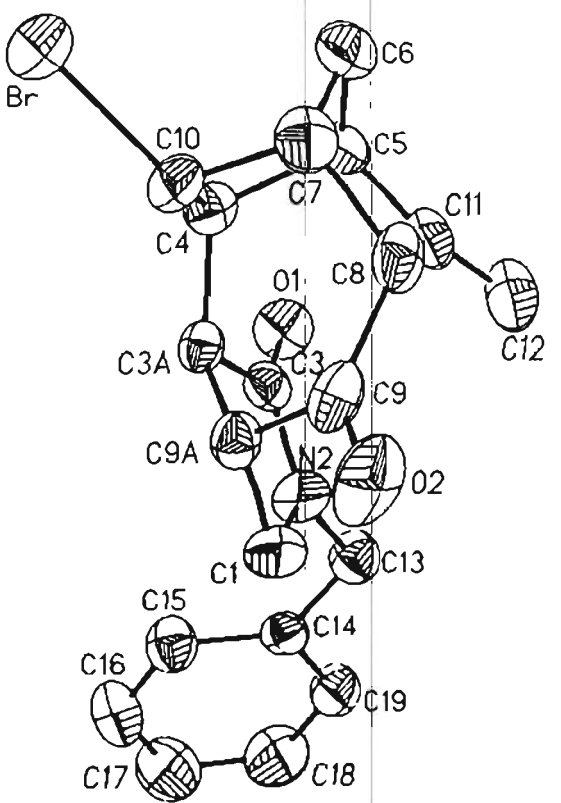
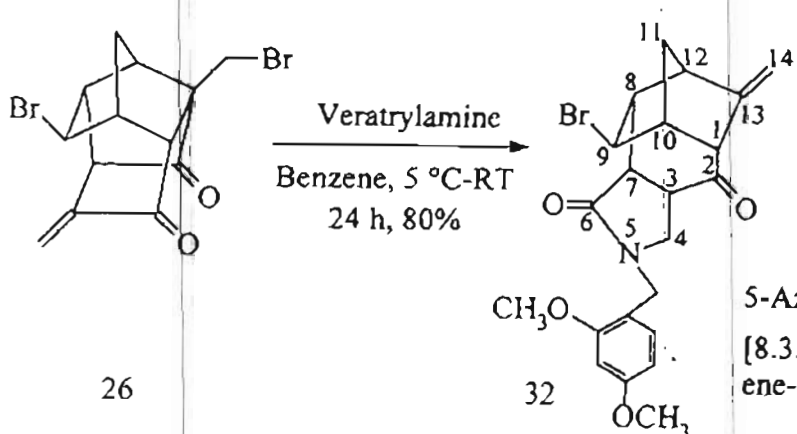


Figure 3: X-ray Crystal Structure of 31

The next derivative **32** was prepared from the reaction between 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** and veratrylamine. The reaction required twenty-four hours at room temperature for completion (Scheme XVII). Once again a single product was seen in the tlc and it was purified by chromatography over silica gel. The IR spectrum of the product showed the carbonyl and lactam carbonyl absorptions overlapping to give a broad peak at 1681 cm^{-1}. Its ^1H NMR spectrum showed the three aromatic protons as a multiplet between δ 6.81-6.73. The two protons on the exocyclic double bond appeared at δ 4.87 and 4.08 as singlets. The benzylic methylene protons appeared as a singlet at δ 4.53. The two methoxy groups showed overlapping signals as a multiplet between δ 3.88-3.83 (six protons). The methylene protons on the norbornyl bridge of the cage system showed up as the characteristic ½ABq signals at δ 2.60 and 1.54 with a coupling constant of 10.7 Hz. The protons on the polycyclic system appeared as multiplet signals between δ 3.41 and 2.87. The ^{13}C NMR spectrum gave further credence to the structural assignment proposed by showing the carbonyl carbon signal at δ 209.1, the lactam carbonyl at δ 171.8 and the olefinic and aromatic carbons between δ 149.1 and δ 109.7. The HRMS value of 445.0865 confirmed that the product had been formed by the addition of one equivalent of the amine to the starting material along with the concomitant loss of one bromine.



26

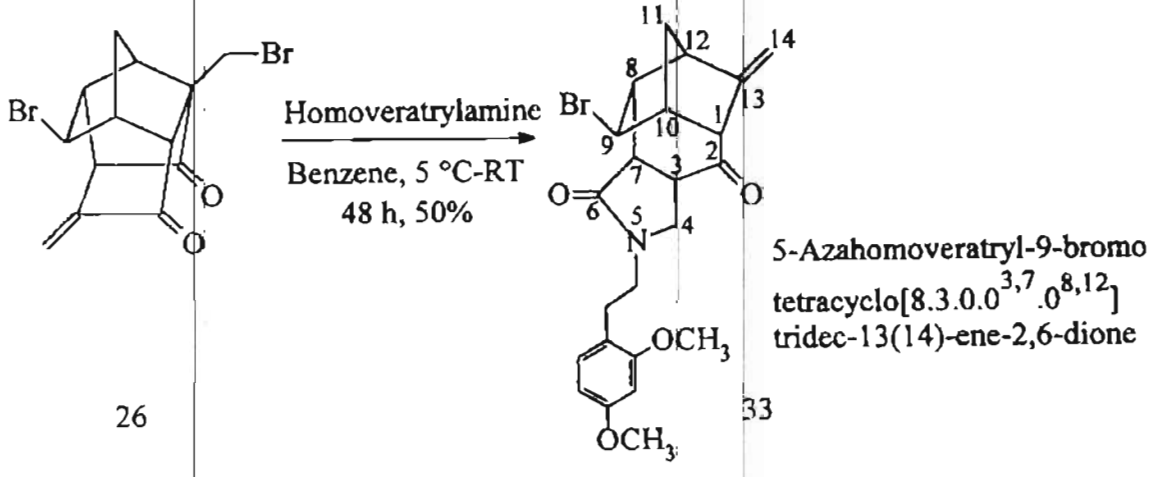
32

5-Azaveratryl-9-bromotetracyclo [8.3.0.$0^{3,7}$.$0^{8,12}$]tridec-13(14)-ene-2,6-dione

Scheme XVII

Reaction of **26** with homoveratrylamine also proceeded well, although much more slowly and provided the expected derivative **33** in 50% yield after

chromatography over silica gel (Scheme XVIII). This was fully characterised using the usual spectral techniques. The IR spectrum of the compound showed the characteristic peak due to both carbonyls as a single strong broad peak at 1694 cm^{-1}. The ^1H NMR spectrum showed the three aromatic protons between δ 6.80 and 6.69 as a multiplet. The olefinic protons showed up as two singlets at δ 5.01 and 4.69. The proton at C-1 showed up as a singlet at δ 4.09 and the proton at C-3 appeared as a triplet at δ 3.68 with a coupling constant of 10.2 Hz. The six methoxy protons showed up as overlapping signals between δ 3.87-3.85. The norbornyl methylene protons showed up as ½ABq signals at δ 2.60 and 1.55 with a *J* value of 10.8 Hz. All other protons showed up as various signals between δ 3.41 and δ 2.70 and separate assignments could not be made due to the complex nature of the splittings. The ^{13}C NMR spectrum showed twenty-three signals and of these, the ones which could be assigned were the signals at δ 209.2 (ring carbonyl), 172.1 (lactam carbonyl) and the signals between δ 149.1 and 109.9 (due to the aromatic and olefinic carbons). The other carbons gave signals upfield between δ 57.8 and 32.6.



26

33

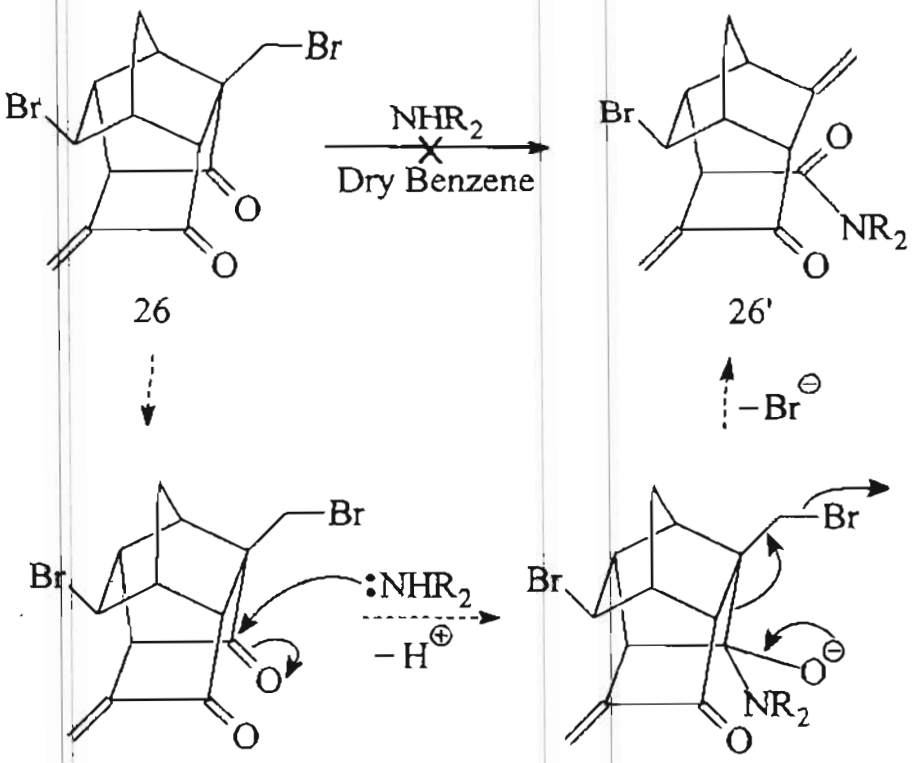
5-Azahomoveratryl-9-bromo tetracyclo[8.3.0.$0^{3,7}$.$0^{8,12}$] tridec-13(14)-ene-2,6-dione

Scheme XVIII

4.2.2 Reactions of 3-Bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione with Secondary Amines:

After investigating the reaction of 3-bromo-7-(bromomethyl)tetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with primary amines and studying the

reaction mechanism proposed, it was thought to be of interest to study the reaction with secondary amines in order to stop the reaction at the amide stage as shown in scheme XIX. The reaction was envisaged to give rise to tricyclic product **26'** with numerous functionalities, namely, a double bond, an enone, an amide linkage and a secondary bromine group. However, this reaction did not proceed at all, and the starting material was recovered unreacted. This may be because the driving force for the former reaction is the formation of the lactam ring which takes the reaction to completion.

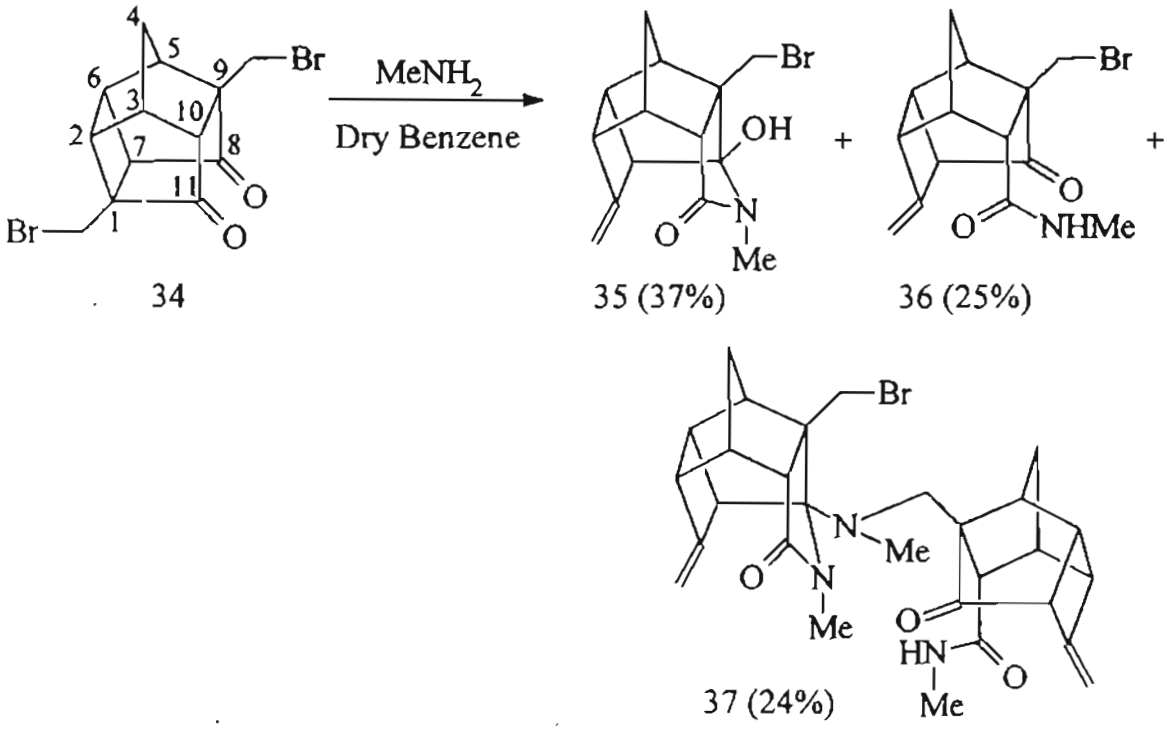


Scheme XIX

4.2.3 Reactions of 1,9-Bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione with Primary Amines:

After investigating the totally novel reaction profile of the rearranged tetracyclic product **26** obtained from the photolysis of 2,5-bis(bromomethyl) tricyclo[6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione with primary amines, it was thought to

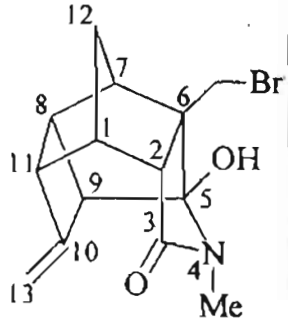
be of interest to study the reactivity pattern of the pentacyclic product of the same reaction *viz.*, 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **34** (synthesis reported in Chapter 2, Scheme XVIII), with the same. Hitherto, all the reactions of the various PCUD derivatives reported have merely led to the reaction of the amine with the proximal ketones leading to the formation of heterocyclic bridges as described in the introduction to this chapter. But, in these molecules with strategically placed bromomethyl groups, it remained to be seen whether it would show reaction profile analogous to that of the tetracyclic product **26**. Therefore, the reaction of 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **34** was carried out with methylamine under the same conditions as before (Scheme XX). However, the tlc of the reaction mixture showed the formation of a number of products in direct contrast to the earlier reactions which had led to the formation of a single product in good yields. These products were seen to be much more polar in nature. Careful chromatographic separation on silica gel using ethyl acetate-petroleum ether and ethyl acetate-methanol led to the isolation of three products **35**, **36** and **37**.



34 35 (37%) 36 (25%) 37 (24%)

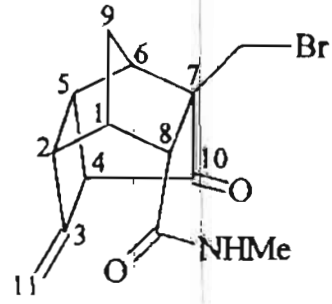
Scheme XX

The first product to be eluted out of the column *viz.*, **35** was obtained in 37% yield and was crystallised from dichloromethane-petroleum ether. It was found to exhibit the following characteristics in its spectra: a) the IR spectrum showed a strong broad peak at 3137 cm^{-1} indicative of a hydroxyl group and another at 1654 cm^{-1} indicative of a carbonyl function. b) the ^1H NMR spectrum (Fig. 4) showed two signals indicative of an exocyclic double bond at δ 4.87 and 4.79; the broad singlet at δ 3.79 was attributed to the hydroxyl proton; the singlet at δ 3.58 which integrated for two protons could be considered the bromomethyl protons' signal; a sharp singlet at δ 2.63 was attributed to the protons on the methyl on the lactam nitrogen; and the ½ABq signals at δ 2.02 and 1.58 readily suggested the presence of norbornyl bridge methylene protons. c) fourteen signals appeared in the ^{13}C NMR spectrum (Fig. 5) where the signal at δ 171.2 could be due to the lactam carbonyl, the signals at δ 143.6 and 108.9 due to the exocyclic double bond, that at δ 101.9 due to the quarternary carbon bearing the hydroxyl group, the other quarternary carbon at C-6 (nomenclature and numbering as shown in scheme XXI) gave a signal at δ 63.1 and all other carbons appeared upfield between δ 60.2 and 24.6. The HRMS value of 310.0437 for $[M^+ + 1]$ supported the proposed structure as a product formed by the addition of one equivalent of the amine and loss of one bromine atom. All the above data put together suggested a structure as depicted for **35**. This was confirmed by single crystal X-ray diffraction studies (Fig. 6).



4-Azamethyl-6-bromomethyl-5-hydroxy pentacyclo[5.4.1.$0^{2,6}$.$0^{5,9}$.$0^{8,11}$]dodec -10(13)-ene-3-one

35



7-Bromomethyl-8-(N-methylcarbamoyl) tetracyclo[4.2.1.$1^{4,7}$.$0^{2,5}$]dec-3(11) -ene-10-one

36

Scheme XXI

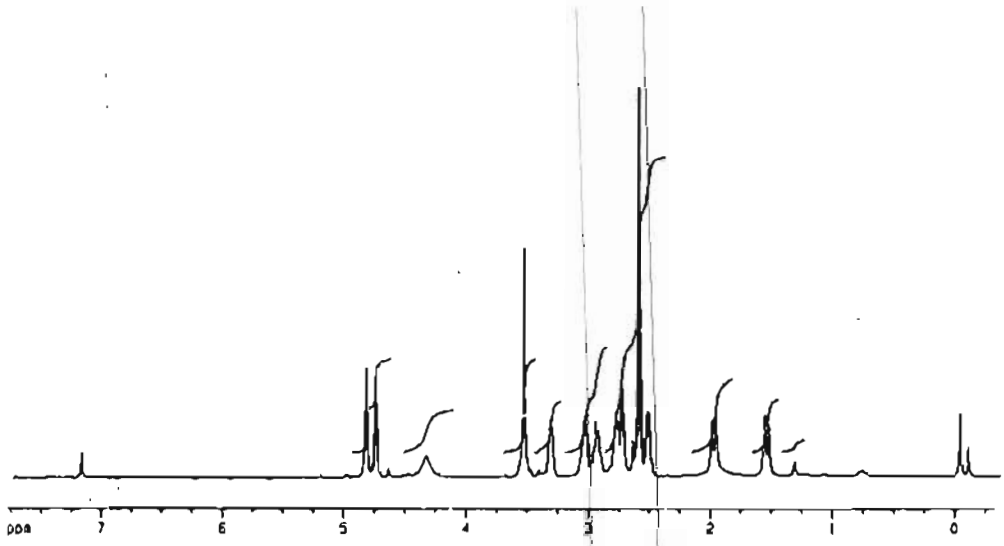


Figure 4: ^{1}H NMR Spectrum of 35

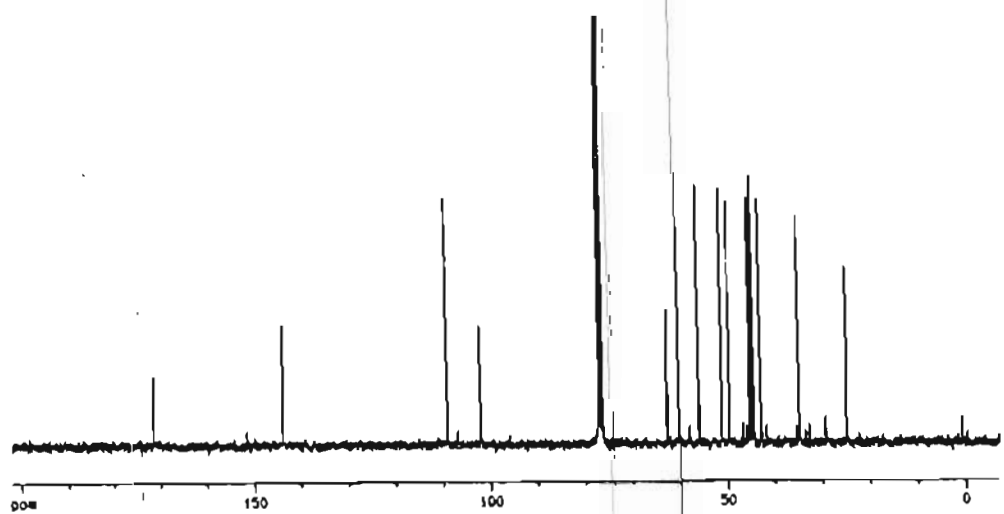


Figure 5: ^{13}C NMR Spectrum of 35

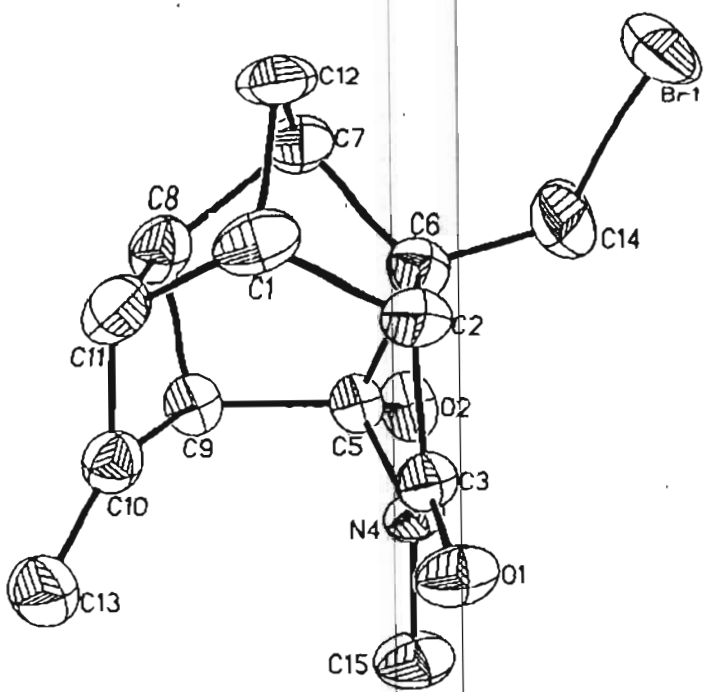
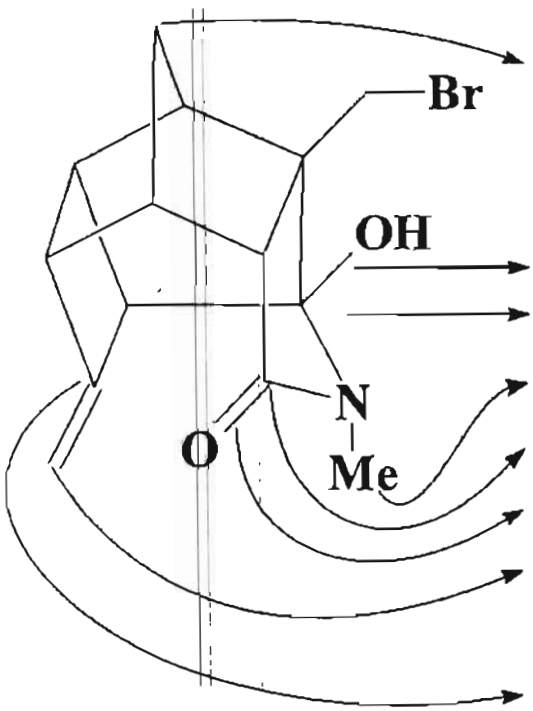


Figure 6: X-ray Crystal Structure of 35



^{1}H NMR ½ABq at δ 2.02 and 1.58

hydroxyl str. at 3137 cm^{-1}

^{13}C NMR at δ 101.9

^{1}H NMR a sharp singlet at δ 2.63

^{13}C NMR at δ 171.2

carbonyl str. at 1654 cm^{-1}

^{13}C NMR at δ 108.9 and
^{1}H NMR at δ 4.87 and 4.79

^{13}C NMR at δ 143.6

HRMS M^++1: 310.0437

Salient Features in the Spectra of **35**

Figure 7

The second product **36** was obtained in 25% yield. It readily crystallised from dichloromethane-petrolem ether. A comparison of its spectra with that of **35** showed some similarities and few dissimilarities. For example, the IR spectrum contained two different carbonyl peaks which were seen at 1651 and 1738 cm^{-1}. These could be attributed to an amide carbonyl and a ring carbonyl group respectively. The ^1H NMR spectrum (Fig. 8) indicated the presence of an exocyclic olefin by giving two signals at δ 5.03 and 4.86 for one proton each. The broad singlet at δ 5.26 indicated a deshielded proton on nitrogen. The protons on the bromomethyl group appeared as ½ABq signals at δ 3.74 and 3.40 with a coupling constant of 10.4 Hz. The three protons attributable to the N-methyl amide group were visible as a doublet at δ 2.53 with a coupling constant of 4.6 Hz. The latter confirmed the secondary nature of the amide group. The protons on the norbornyl bridge methylene showed up as expected as ½ABq signals at δ 1.63 and 1.52 with a coupling constant of 10.4 Hz. The ^{13}C NMR spectrum (Fig. 9) confirmed the presence of a carbonyl group, an amide group and an exocyclic double bond by signals at δ 214.5, 170.7, 146.6 and 111.6 respectively. The quarternary carbon at C-7 (nomenclature and numbering as shown in scheme XXI) appeared at δ 56.8 and all other signals showed up upfield between δ 58.8 and 26.1 as expected. The HRMS value of 310.0386 which was the same as the first compound lent additional support to the compound being identified as **36**.

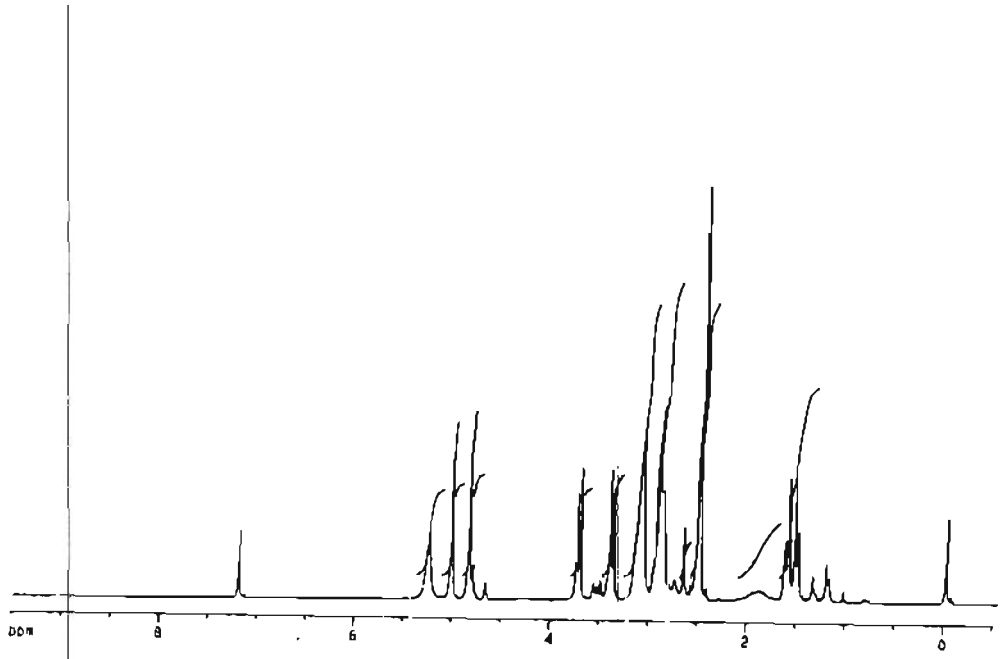


Figure 8: ^{1}H NMR Spectrum of 36

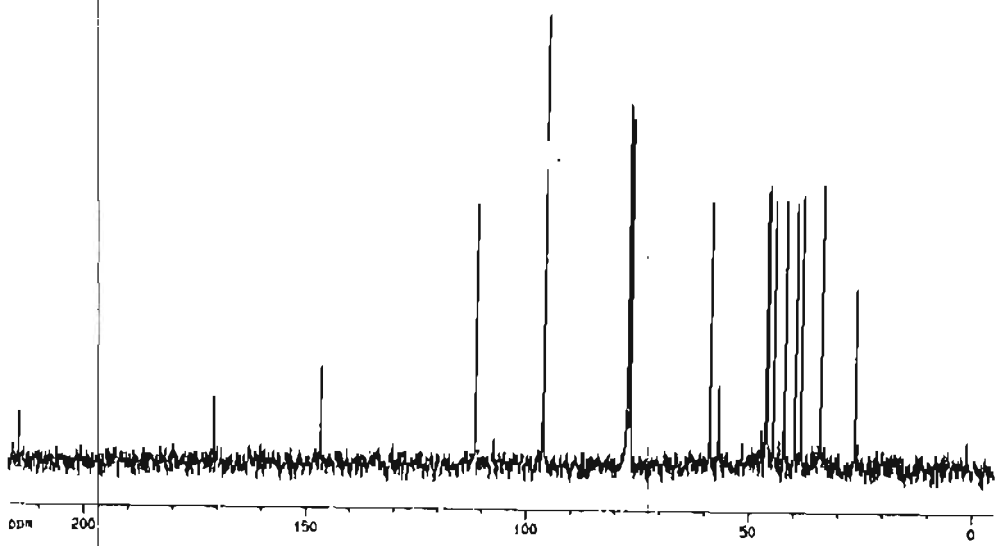


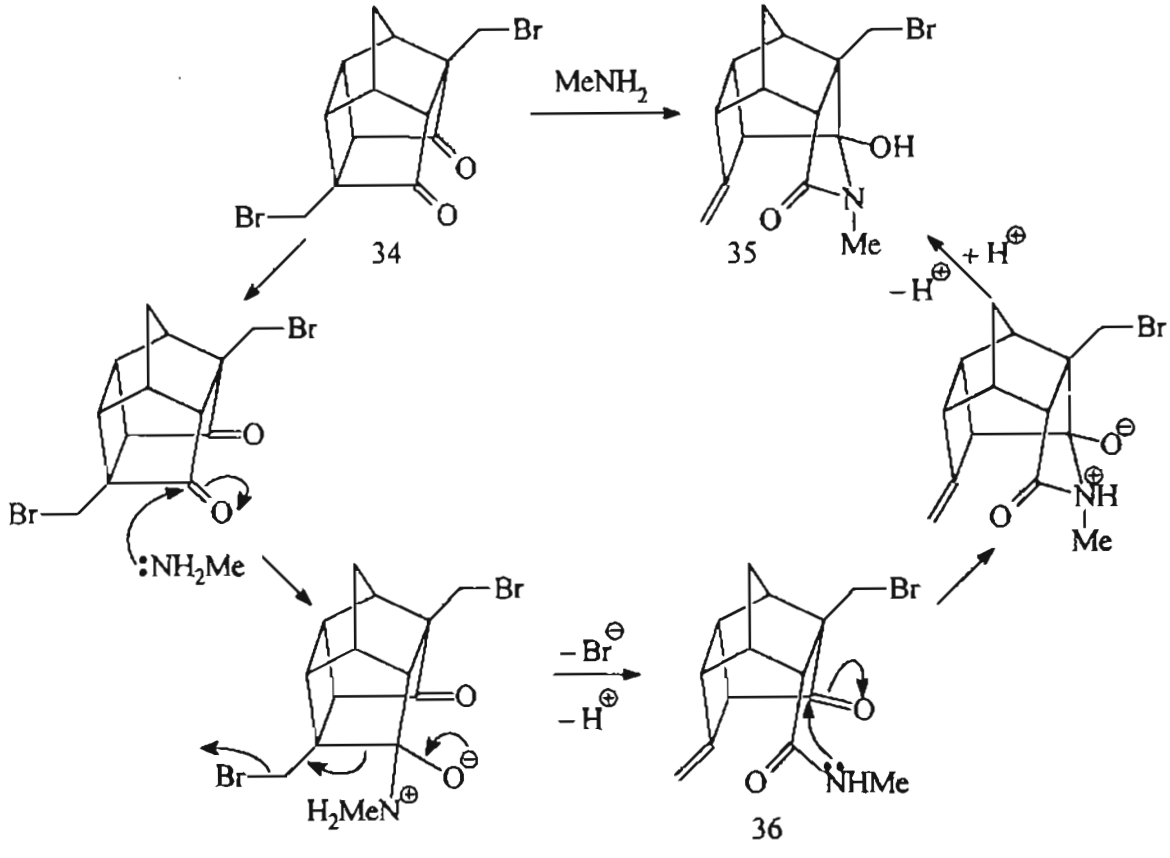
Figure 9: ^{13}C NMR Spectrum of 36

The most polar product 37 formed in this reaction was more difficult to identify. The IR of this compound showed the presence of two types of carbonyl absorptions at 1743 and 1670 cm^{-1}. The proton NMR spectrum showed the presence of thirty-four protons on integration. Of these the signals which could be unambiguously identified were the following: a) four olefinic protons, of which one appeared as a singlet at δ 5.02 and the other three overlapped to give a multiplet between δ 4.94-4.89. b) one set of norbornyl bridge methylene protons which were distinguishable at δ 2.28 and 1.78 as ½ABq signals. c) the methyls on the nitrogens did not give separate signals, but overlapped with two of the ring protons to give a multiplet between δ 3.23-3.13. The ^{13}C NMR spectrum gave a lot more information by revealing the presence of twenty-nine carbon signals, which pointed to the formation of this product from two equivalents of the starting material and three equivalents of the amine. The noteworthy signals were that of a ring carbonyl at δ 209.1; that of a lactam carbonyl at δ 171.8; an amide carbonyl at δ 163.2; four signals due to exocyclic double bonds at δ 151.2, 143.4, 110.6 and 108.8; and the signal at δ 97.1 was attributed to the carbon which is bearing two nitrogen functions. All other signals appeared upfield between δ 65.2 and 29.0. The HRMS value of the product was obtained as 551.1768 which further confirmed the addition of three equivalents of the amine to two of the starting material along with the loss of three bromine atoms. The product was identified as 4-azamethyl-6-bromomethyl-5-(N-(7'-methylamino-8'-(N-methylcarbamoyl)tetracyclo[4.2.1.$1^{4',7'}$.$0^{2',5'}$]dec-3'(11')-ene)-N-methyl) pentacyclo[5.4.1.$0^{2,6}$.$0^{5,9}$.$0^{8,11}$]dodec-10(13)-ene-3-one **37** based on these evidences (the numbering for this compound is depicted in scheme XXIII).

Mechanistic Outlook:

The mechanism proposed for the formation of these totally unexpected *compounds **35** and **36** (Scheme XXII)* envisages the initial addition of one equivalent of the amine to the carbonyl carbon. This leads to the rupture of a five-membered ring followed by formation of an exocyclic double bond and loss of the halogen as shown in scheme XXII. The loss of the halogen is probably facilitated by the excess amine

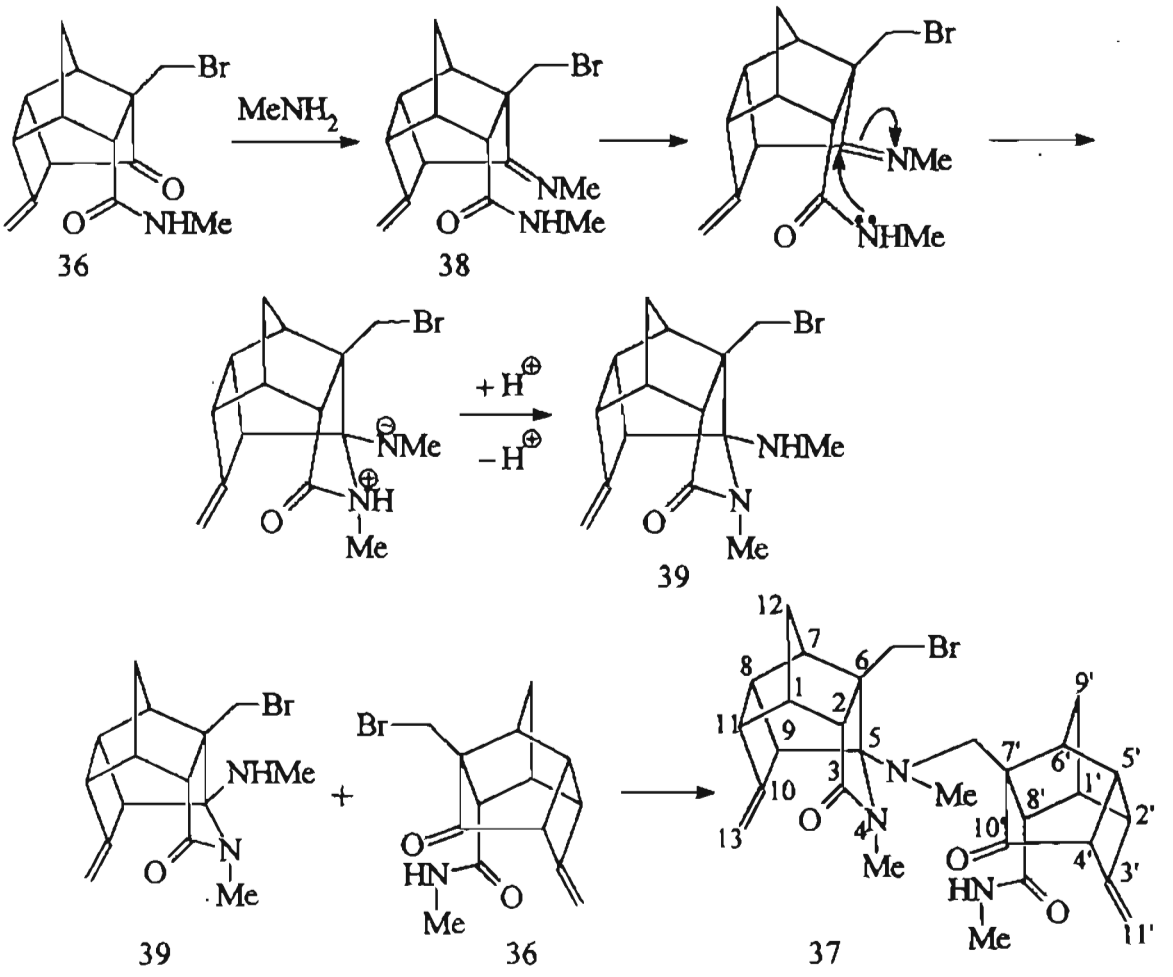
present in the reaction mixture. Thus the product **36** is formed. The amide nitrogen is then able to add to the second carbonyl carbon which is in the proximity due to the ring architecture. Formation of the lactam ring is then followed by proton transfer leading to the generation of a hydroxyl group giving the compound **35**. Thus, starting from a pentacyclic ring with two carbonyl and two bromomethyl groups, we get two products, one with an amide linkage as in **36** and the other with a γ-lactam ring and and hydroxyl group as in **35**. In addition, both resultant compounds **35** and **36** contain an exocyclic double bond and a bromomethyl group. Most surprising however, is the formation of a different exocyclic double bond in these cases.



Scheme XXII

The formation of the last product **37** could be rationalised in the following manner (Scheme XXIII): the ketone group in the product **36** reacts with methylamine to give an imine **38**. The lone pair on the amide nitrogen then adds to the electron deficient imine carbon which is held in proximity due to the cage framework and proton reorganisation forms the intermediate **39**. This intermediate **39** then adds to a

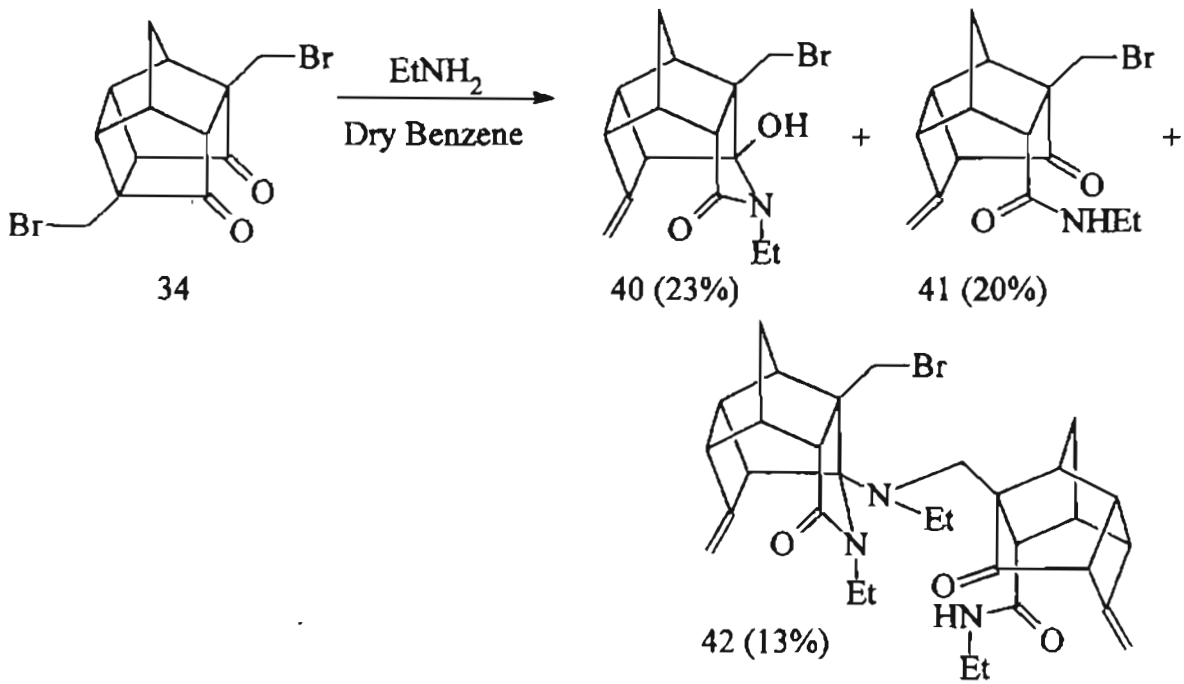
molecule of the product **36** displacing a bromine and gives rise to the product **37**. However, the final confirmation of this compound is possible only through X-ray diffraction studies.



Scheme XXIII

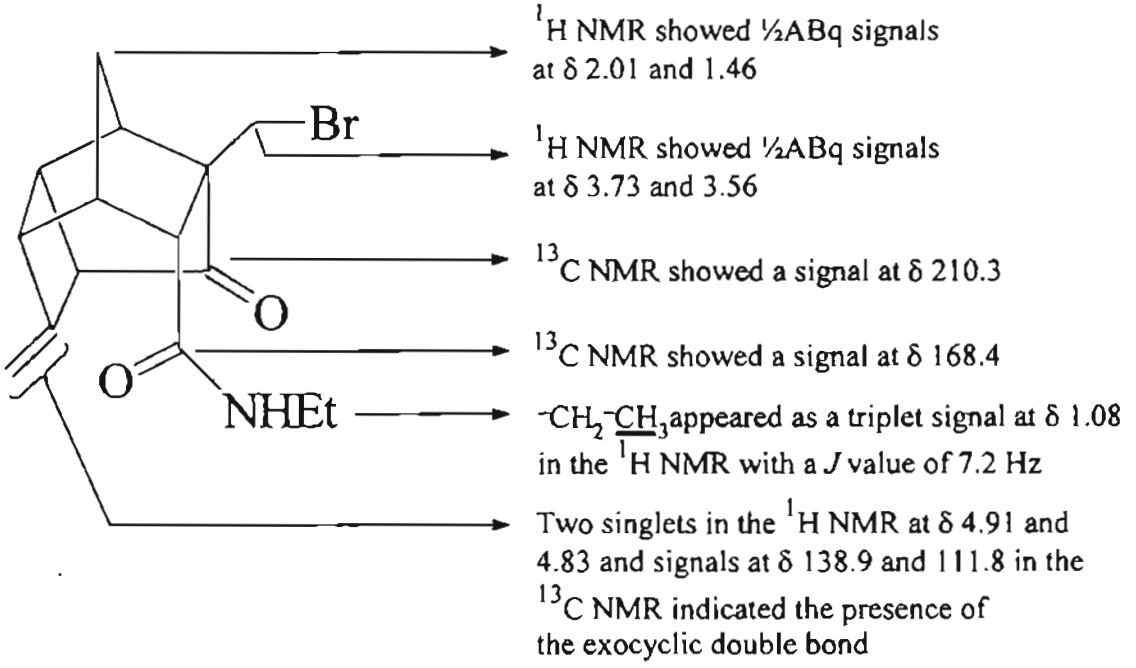
Upon getting so many unexpected compounds on reacting methylamine with 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **34**, we were curious about the generality of this process. Accordingly, the reaction between **34** and ethylamine was investigated. The reaction was carried out under the same conditions as before and the same reaction profile seemed to have resulted with three products to be seen on the tlc of the reaction mixture suggesting a general mode of action (Scheme XXIV). Work-up followed by column chromatography led to the isolation of three products **40**, **41** and **42** homologous to the products of the first reaction.

The products were identified on the basis of their spectral characteristics. The first compound **40** to be isolated was 4-azaethyl-6-bromomethyl-5-hydroxypentacyclo [5.4.1.$0^{2,6}$.$0^{5,9}$.$0^{8,11}$]dodec-10(13)-ene-3-one obtained in 23% yield. This was characterised from the following salient spectral data, *viz.*: a) the IR spectrum of the compound showed a broad absorption at 3074 cm^{-1} indicative of a hydroxy group and a strong absorption at 1651 cm^{-1} due to a lactam carbonyl group. b) the proton NMR spectrum indicated the presence of an exocyclic double bond by the resonances at δ 5.03 and 4.92; the presence of bromomethyl protons which appeared as ½ABq signals at δ 3.75 and 3.69 with a coupling constant of 11.1 Hz; the norbornyl bridge protons which appeared as another ½ABq signal at δ 2.15 and 1.55; and the methyl protons on the azaethyl group which appeared upfield as a multiplet between δ 1.25 and 1.12. c) the ^{13}C NMR spectrum that showed a lactam carbonyl signal at δ 176.6, the exocyclic olefin carbon signals at δ 139.6 and 113.8 and the carbon bearing the hydroxyl group at δ 104.8 and all other signals appeared as expected upfield between δ 55.7 and 16.3. d) the HRMS value of 323.0519 supported the formation of this compound **40** from one equivalent each of the amine and starting material along with the loss of one bromine atom.



Scheme XXIV

*The second product **41** which was isolated from the same reaction mixture was* identified as 7-bromomethyl-8-(N-ethylcarbamoyl)tetracyclo[4.2.1.$1^{4,7}$.$0^{2,5}$]dec-3(11)-ene-10-one. This was done based on its spectral data and comparision with that of compound **40**. The IR spectrum showed strong absorptions at 1695 and 1732 cm^{-1} indicative of two carbonyls, one a lactam and the other a ring ketone. Once again, the proton NMR spectrum confirmed the presence of an exocyclic double bond with singlets at δ 4.91 and 4.83. The bromomethyl group again was observed as ½ABq signals, this time at δ 3.73 and 3.56 with a coupling constant of 10.7 Hz. The norbornyl bridge methylene also appeared as expected as ½ABq signals at δ 2.01 and 1.46 and the methyl on the ethylcarbamoyl function appeared as a triplet at δ 1.08 with a coupling constant of 7.2 Hz. The ^{13}C NMR spectrum gave additional support to the structure proposed by showing the ring carbonyl at δ 210.3, the amide carbonyl at δ 168.4, the olefin carbons at δ 138.9 and 111.8, and all other signals upfield between δ 55.0 and 14.3. The HRMS value of this product, 323.0515, was the same as that of the first product **40** indicating that both have the same molecular formula $C_{15}H_{18}NO_2Br$.



Salient Features in the Spectra of **41**

Figure 10

Characterisation of the final product **42** obtained from the reaction mixture was once again difficult as all spectral data were very complex as found earlier for compound **37**. Its IR spectrum showed two types of carbonyl absorptions at 1632 and 1738 cm^{-1} indicating the presence of an amide group along with a ring ketone. The ^1H NMR spectrum displayed four olefinic protons between δ 5.12 and 4.87 with three of them overlapping to give a multiplet. The protons on the bromomethyl group were seen as ½ABq signals at δ 3.68 and 3.47, only half of the ABq signal which is exhibited by the norbornyl bridge methylene was seen at δ 2.01, the other half had overlapped with the methyl signals which appeared as a multiplet between δ 1.70-1.60. Of the three methyl parts of the ethyl groups attached to nitrogens, two overlapped to give part of the multiplet between δ 1.70 and 1.60 and the third appeared as a triplet at δ 1.18. The ^{13}C NMR spectrum indicated the presence of the following functional groups: ring carbonyl (δ 212.6), lactam carbonyl (δ 171.0), amide carbonyl (δ 163.4), two exocyclic double bonds (δ 148.3, 143.8, 112.0 and 110.2) and the carbon bearing two nitrogen functionalities which was deshielded and appeared at δ 93.9. All other signals appeared upfield between δ 62.7 and 14.1. The structure has been tentatively assigned as 4-azaethyl-6-bromomethyl-5-(*N*-(7'-methylamino-8'-(N-ethylcarbamoyl)tetracyclo[4.2.1.$1^{4',7'}$.$0^{2',5'}$]dec-3'(11')-ene)-N-ethyl)pentacyclo[5.4.1.$0^{2,6}$.$0^{5,9}$.$0^{8,11}$]dodec-10(13)-ene-3-one **42**.

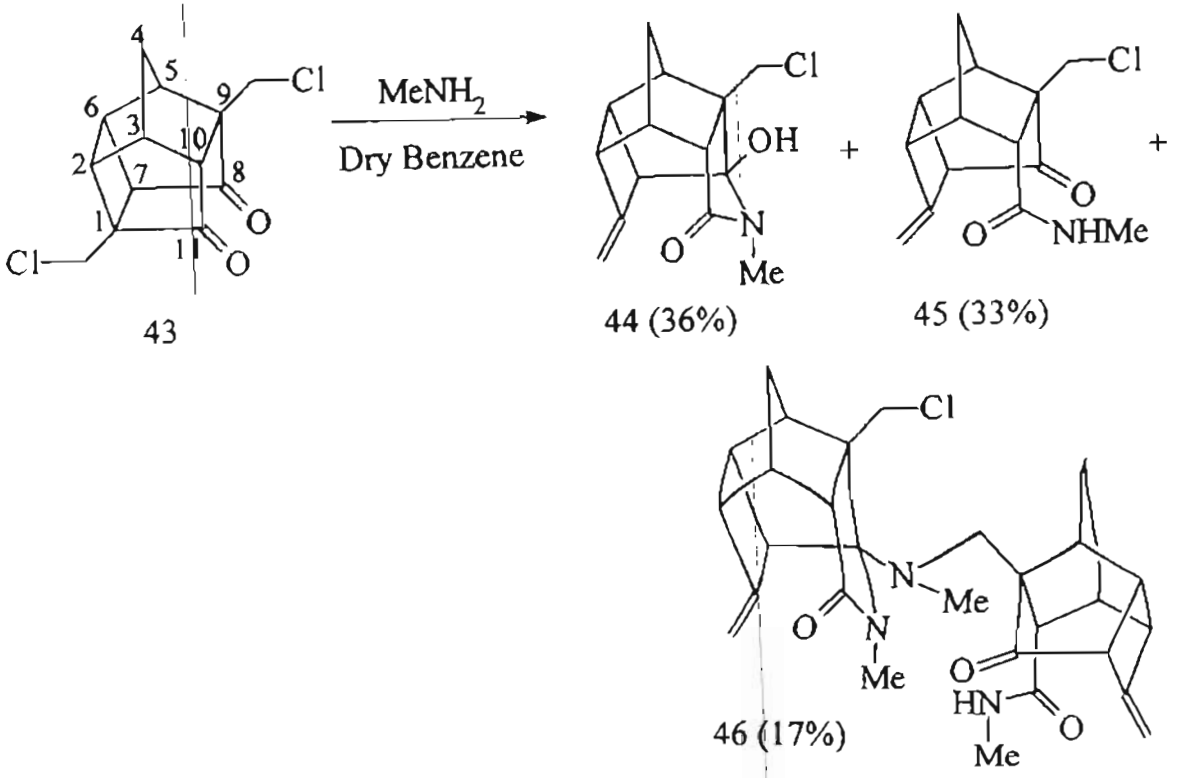
4.2.4 Reactions of 1,9-Bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione with Primary Amines:

The fascinating array of products that were obtained from the reactions of 1,9-bis(bromomethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **34** with two primary amines emboldened us to attempt the same reaction with 1,9-bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **43** (the synthesis of **43** has been outlined in Chapter 2, Scheme XV). The reaction mechanism suggested that the same reaction profile should be seen since the reaction is driven by the nature of the bromide anion as a facile leaving group and the proximity of the two

carbonyl groups in space due to the strained cage form. Since chloride anion too is a good leaving group, we were hopeful of getting the same type of amides and lactams. Thus it was decided to repeat these reactions with the **43** and the same primary amines.

The reaction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **43** with methyl amine gave three products (Scheme XXV). Since the same reaction profile was seen here, a similar mechanism was assumed to operate in this reaction too. Obviously, the prime requirement for this reaction is a good leaving group on the methyl at C-1 which can be eliminated to give an exocyclic double bond at that position and chloro- and bromo- compounds are comparable in this respect.

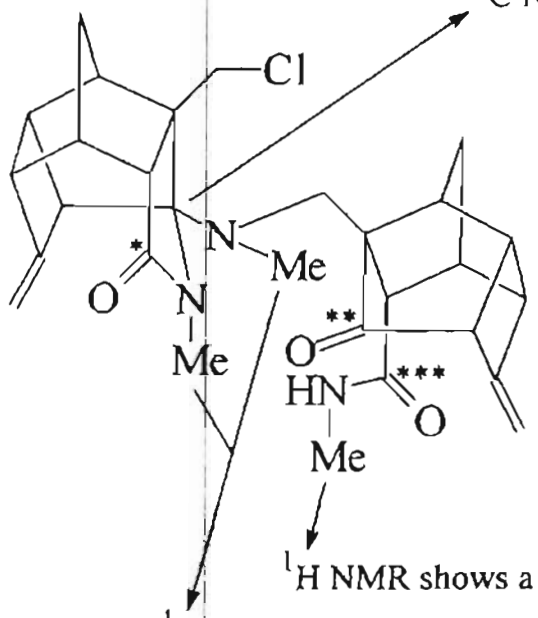
The first compound **44** to be isolated in this reaction was similar to the first product **35** formed between 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}] undeca-8,11-dione **34** and methylamine and exhibited similar features in its spectra. The IR spectrum showed the presence of a hydroxyl group with a broad absorption at 3090 cm^{-1} and also the presence of a carbonyl by a strong absorption at 1651 cm^{-1}. The proton NMR spectrum showed two olefinic protons as two singlets at δ 4.94 and 4.86. The hydroxy proton gave a broad singlet signal at δ 3.98. The chloromethyl group appeared as a singlet at δ 3.77. The methyl on the lactam nitrogen appeared as a sharp singlet at δ 2.70. The norbornyl bridge methylene protons appeared as ½ABq signals at δ 2.03 and 1.87. The ^{13}C NMR spectrum showed the signal for the lactam carbonyl at δ 170.3 and the exocyclic olefin signals at δ 144.9 and 108.0. The quarternary carbon with the hydroxy group appeared at δ 72.5 and all other carbons gave signals upfield between δ 63.1 and 24.3. The HRMS value of 266.0958 for [M^{+}+1] lent support to the structure incorporating one equivalent of the amine along with concomitant loss of one chlorine atom. Thus, **44** was identified as 4-azamethyl-6-chloromethyl-5-hydroxypentacyclo[5.4.1.0^{2,6}.0^{5,9}.0^{8,11}]dodec-10(13)-ene-3-one.



Scheme XXV

The second compound **45** was identified as 7-chloromethyl-8-(N-methylcarbamoyl)tetracyclo[4.2.1.$1^{4,7}$.$0^{2,5}$]dec-3(11)-ene-10-one on the basis of its spectra which exhibited the following salient features: a) its IR spectrum showed the presence of two types of carbonyls by strong absorptions at 1670 and 1732 cm^{-1}. This indicated the presence of an amide carbonyl and a ring ketone respectively. b) the ^{1}H NMR spectrum showed the following signals which were useful in assigning the structure: the singlets at δ 5.03 and 4.80 indicated the protons on an exocyclic methylene; the ½ABq signals at δ 3.80 and 3.58 could be attributed to the protons on the chloromethyl group; the doublet at δ 2.53 with a *J* value of 4.3 Hz indicated the methyl group on the nitrogen which was split due to the secondary nature of the amide; and the ½ABq signals at δ 1.95 and 1.54 could be assigned to the norbornyl bridge methylene protons. c) the ^{13}C NMR spectrum showed 14 signals confirming the addition of one equivalent of the amine to the starting material, of these the signal at δ 212.6 was due to the ring carbonyl, the signal at δ 170.1 was due to the amide carbonyl, the signals at δ 146.6 and 111.4 confirmed the presence of the exocyclic

double bond and all the other signals were seen between δ 58.8 and 26.4. The HRMS value of 265.0932 was also in agreement with the structure proposed for the compound **45**.



^{13}C NMR gave this signal at δ 91.7

IR spectrum showed two -C=O str absorptions at 1732 and 1664 cm^{-1}

^{13}C NMR showed the carbons marked *, **, and *** at δ 172.7, 214.3 and 170.7 respectively

^{13}C NMR showed the olefinic signals at δ 146.5, 144.3, 111.4 and 109.6 due to two exocyclic double bonds

^{1}H NMR shows a doublet at δ 2.57 with J = 4.6 Hz

^{1}H NMR shows two singlets at δ 2.63 and 2.46

Salient Features in the Spectra of **46**

Figure 11

The most polar product **46** obtained upon reacting methylamine with 1,9-bis(chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione was seen to have been formed by the combination of two equivalents of the starting material and three equivalents of the amine with the concomitant loss of three chlorine atoms. Its IR spectrum revealed the presence of amine and carbonyl groups with absorptions at 2965, 1732 and 1664 cm^{-1}. The ^{1}H NMR spectrum (Fig. 12) gave the signal due to the proton on nitrogen at δ 5.31 as a broad singlet. The four olefinic protons appeared as a singlet at δ 5.08 and a multiplet between δ 4.89-4.85. Only one half of the ABq signals of the chloromethyl group were clearly discernable at δ 3.85, the other half being overlapped by the adjoining multiplet. The norbornyl bridge methylene also behaved in a similar manner with one half of the ABq signal appearing at δ 2.01 and the other half showing up as part of a multiplet between δ 1.69-1.55. The three methyl

groups on the nitrogen were observable as two singlets (at δ 2.63 and 2.46) and a doublet (at δ 2.57, J = 4.6 Hz), indicating that the protons of one methyl was being split by the proton on the adjacent nitrogen. This enabled the identification of the nature of the three amines that had been added, the methyls on the tertiary amine and the lactam nitrogen appear as singlets while the methyl on the amide function appears as a doublet since it is a secondary amide moiety. The ^{13}C NMR spectrum (Fig. 13) lent support to the compound being formed by two equivalents of the starting material and three equivalents of the amine by showing twenty-nine signals, and this was also helpful in confirming the nature of the functional groups present. The signal at δ 214.3 indicated the presence of a ring carbonyl, while the signals at δ 172.7 and 170.7 pointed to a lactam and amide carbonyl carbons respectively. The two quarternary signals at δ 146.5 and 144.3 along with the signals at δ 111.4 and 109.6 revealed the presence of two exocyclic double bonds. A quarternary carbon signal at δ 91.7 indicated its downfield shift due to an attached amine functionality along with being adjacent to the lactam nitrogen. All other signals appeared upfield between δ 62.7 and 25.9, and separate assignment of these signals was not possible. But these data was sufficient to highlight the nature of the polar product and the compound was identified as 4-azamethyl-6-chloromethyl-5-(N-(7'-methylamino-8'-(N-methylcarbamoyl) tetracyclo[4.2.1.$1^{4',7'}$.$0^{2',5'}$]dec-3'(11')-ene)-N-methyl)pentacyclo[5.4.1.$0^{2,6}$.$0^{5,9}$.$0^{8,11}$] dodec-10(13)-ene-3-one **46**.

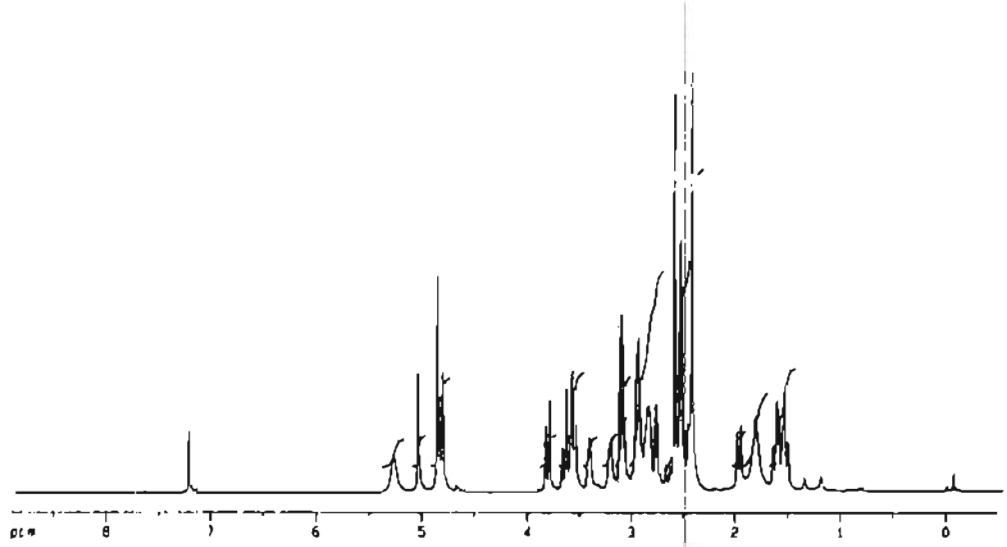


Figure 12: ^{1}H NMR Spectrum of 46

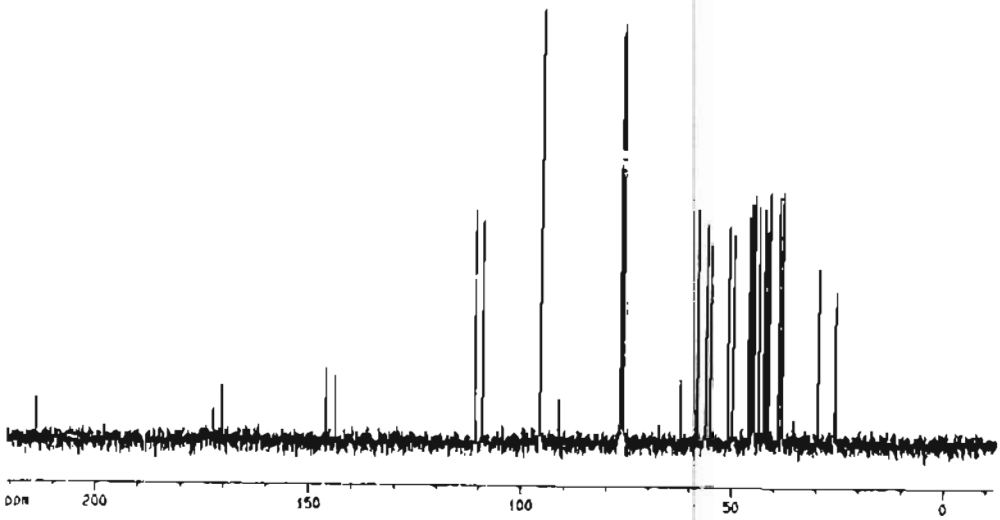
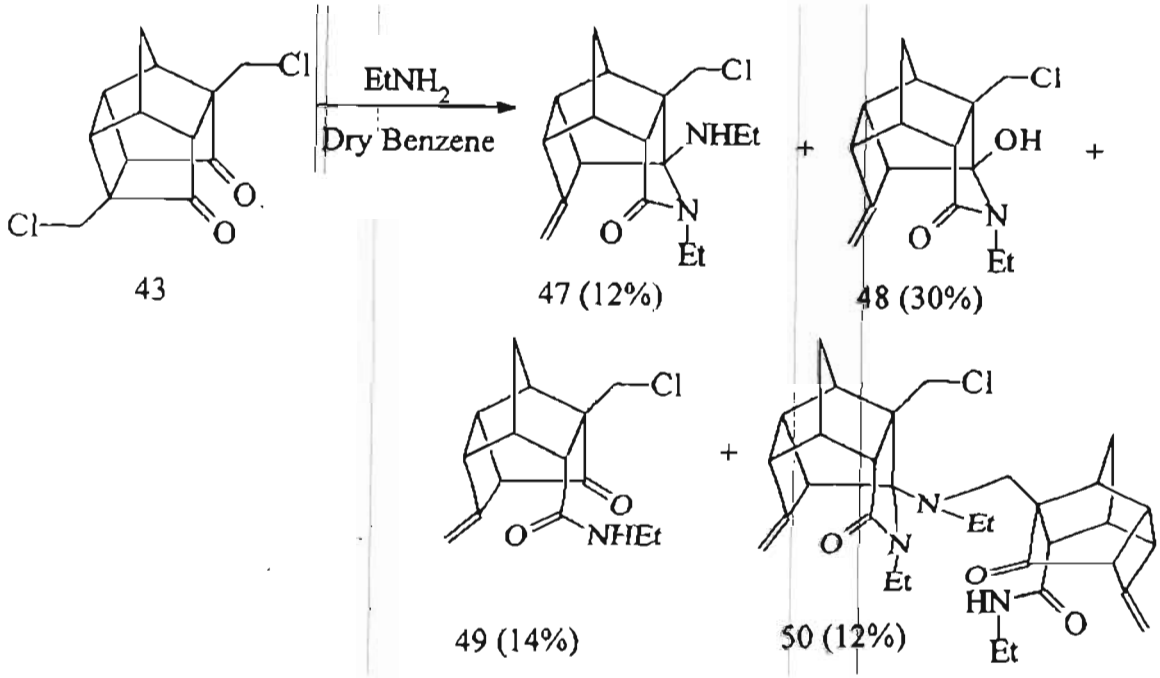


Figure 13: ^{13}C NMR Spectrum of 46

The reaction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **43** with ethylamine (Scheme XXVI) gave rise to a complex reaction mixture from which four products **47**, **48**, **49** and **50** were separated out by column chromatography on silica gel. All products were characterised in a facile manner on the basis of their spectra.

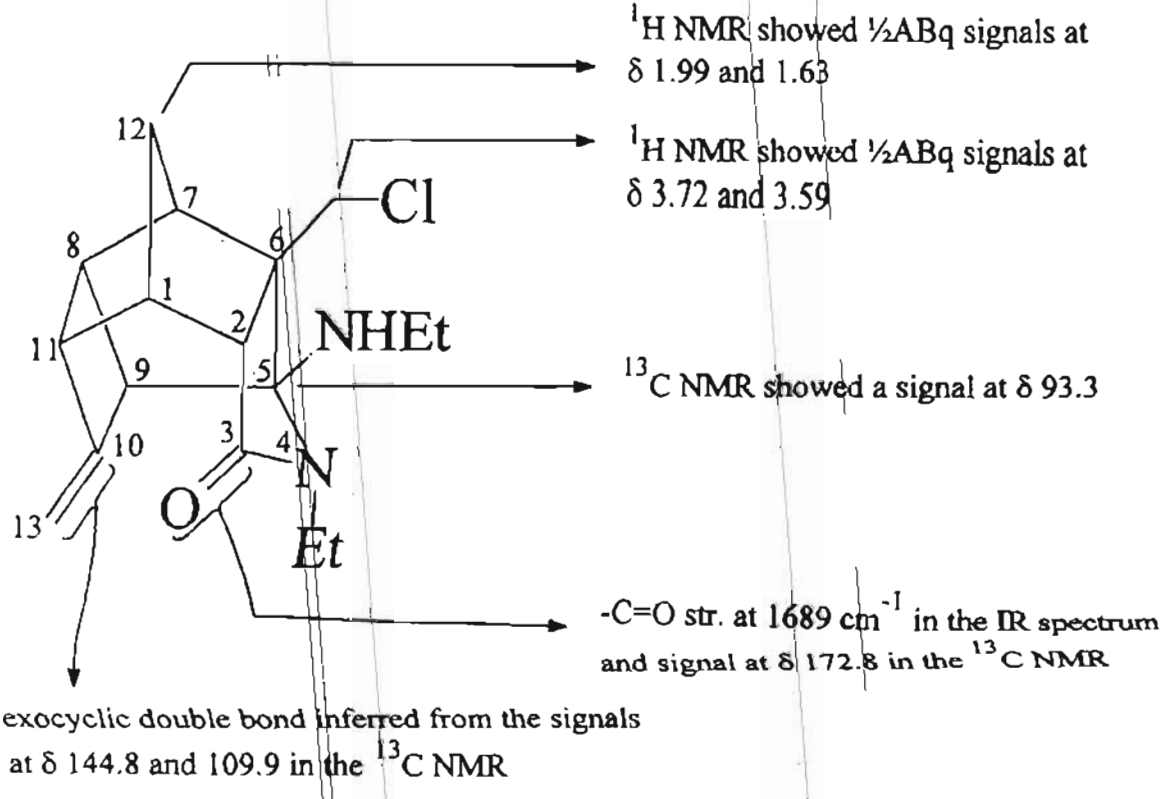


43 47 (12%) 48 (30%) 49 (14%) 50 (12%)

Scheme XXVI

The first product **47** which separated out by the column chromatography showed a peak at 3307 cm^{-1} indicative of N-H linkage and a peak at 1689 cm^{-1} indicating the presence of a C=O stretch in its IR spectrum. The proton NMR spectrum (Fig. 15) gave an integration for twenty-three protons indicating that two equivalents of the amine had added to the starting material. Of these, the signals were assigned as follows: two olefinic protons appeared at δ 4.86-4.85 as a multiplet; the ½ABq signals which showed up at δ 3.72 and 3.59 could be attributed to the protons of the chloromethyl group; the signal at δ 3.14 which appeared as a broad singlet could be attributed to a proton on nitrogen; the two methyl parts of the ethylamine substituents appeared as overlapping multiplets between δ 1.20-1.09; the norbornyl bridge methylene appeared as ½ABq signals at δ 1.99 and 1.63. The ^{13}C NMR spectrum (Fig. 16) confirmed the addition of two equivalents of the amine to the

starting material by showing 17 signals. Of these the signal at δ 172.8 could be attributed to a lactam carbonyl, the signals at δ 144.8 and 109.9 to an exocyclic double bond and the one at δ 93.3 to a quarternary carbon with amine attached. This product **47** is hypothesised to have formed by the addition of ethylamine to **49** to give an imine. The lone pair on the amide nitrogen adds across space to the imine carbon which is electron deficient. Proton rearrangement then gives the product **47** 4-azaethyl-6-chloromethyl-5-(N-ethylamino)pentacyclo[5.4.1.$0^{2,6}$.$0^{5,9}$.$0^{8,11}$]dodec-10(13)-ene-3-one (numbering as shown in Fig. 14). The proposed structure received further confirmation from the HRMS value of 306.1497.



Salient Features in the Spectra of **47**

Figure 14

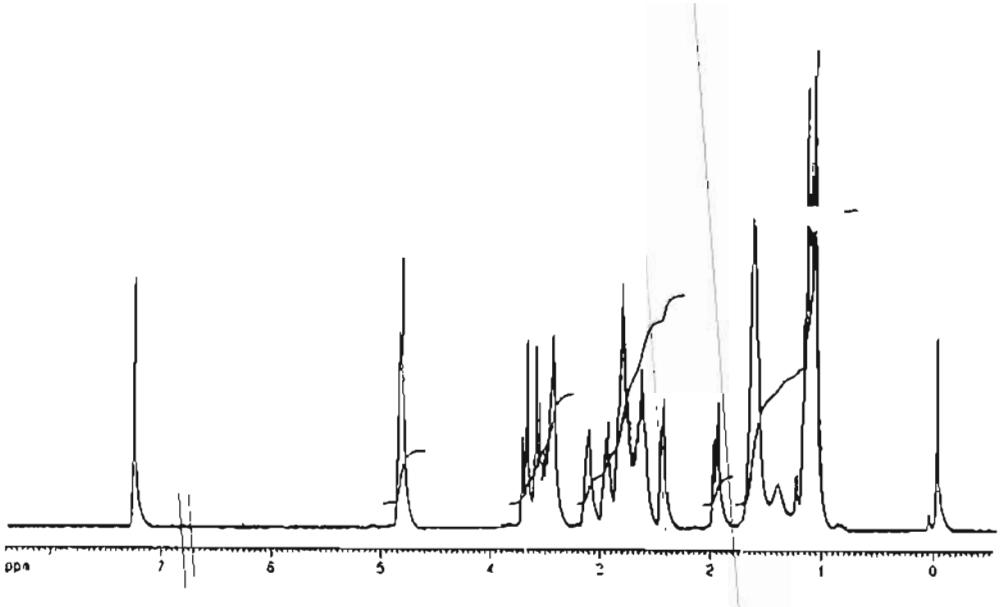


Figure 15: ^{1}H NMR Spectrum of 47

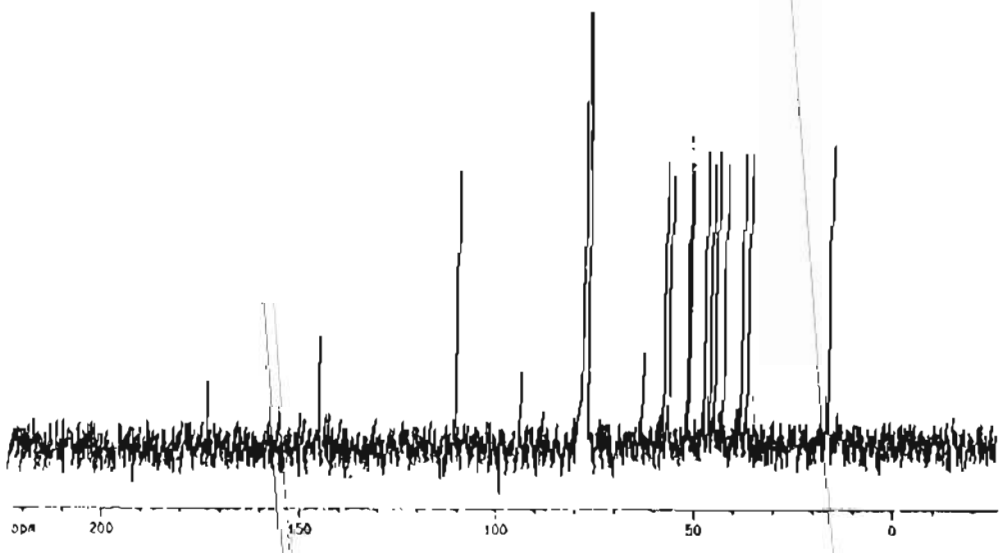


Figure 16: ^{13}C NMR Spectrum of 47

The isolation of the product **47** from this reaction mixture lent weight to the mechanism proposed for the formation of the products **37**, **42**, **46** and **50** since it is similar to the intermediate **39** proposed for the formation of **37** from **34** (Scheme XXIII).

The second compound **48** to be obtained from the reaction mixture had the following characteristics in its spectra: a) the IR spectrum showed a broad absorption at 3089 cm^{-1} indicative of a hydroxyl, and a strong absorption at 1651 cm^{-1} pointed to the presence of an amide carbonyl functionality. b) the ^{1}H NMR showed the olefinic protons at δ 4.87, the chloromethyl protons as ½ABq signals at δ 3.84 and 3.73, the norbornyl bridge protons as another ABq signal at δ 1.98 and 1.67 and the methyl on the azaethyl group between δ 1.19-1.11 as a multiplet. The integration of the spectrum indicated the addition of only one equivalent of the amine to the starting material. c) the ^{13}C NMR showed fifteen signals including a lactam carbonyl at δ 171.3, exocyclic olefin carbons at δ 143.9 and 110.0, a quarternary carbon bearing hydroxyl at δ 103.9 and the most shielded carbon at δ 15.2 suggests the methyl part of the ethyl group on the lactam nitrogen. All other signals appeared between δ 63.3 and 35.3. d) the HRMS value of 279.1021 indicated that the compound had been formed by the addition of one equivalent of the amine to the starting material. All this data was put together to arrive at the structure for the compound **48** as 4-azaethyl-6-chloromethyl-5-hydroxypentacyclo[$5.4.1.0^{2,6}.0^{5,9}.0^{8,11}$]dodec-10(13)-ene-3-one.

The third product **49** formed by the reaction between **43** and ethylamine had the same HRMS value (279.1024) as the second product indicating that had also been formed by the addition of one equivalent of amine to the starting material along with the loss of one chlorine atom. Its IR spectrum showed a stretch due to N-H at 2971 cm^{-1} and also two carbonyl absorptions at 1645 and 1738 cm^{-1}. Of this, the first one could be attributed to an amide carbonyl and the second to a strained ring carbonyl group. The proton NMR spectrum showed signals due to amine proton as a broad singlet at δ 5.21 and the olefinic protons as two singlets at δ 5.06 and 4.86. The chloromethyl protons appeared as ½ABq signals at δ 3.82 and 3.57 with a coupling constant of 11.4 Hz. The norbornyl bridge methylene appeared as another ABq signal at δ 1.62 and 1.52 with a coupling constant of 10.4 Hz. The methyl part of the ethyl

on the amide function appeared as a triplet at δ 0.97 with a coupling constant of 7.3 Hz. All other protons appeared as separate multiplets between δ 3.21 and δ 2.86. The ^{13}C NMR showed fifteen signals, of which the following could be readily identified: the signal at δ 214.3 was due to the ring carbonyl; the signal at δ 169.9 due to the amide carbonyl; the signals at δ 146.4 and 112.0 was due to the exocyclic double bond; the signal at δ 14.1 could be attributed to the methyl part of the ethyl on the amide function; and the signal at δ 57.0 was a quarternary carbon and this could be assigned to C-7 to which the chloromethyl group was attached. All other carbons appeared between δ 58.9 and 34.3 and specific assignments proved to be difficult. Thus the compound was identified as 7-chloromethyl-8-(N-ethylcarbamoyl) tetracyclo[4.2.1.$1^{4,7}$.$0^{2,5}$]dec-3(11)-ene-10-one **49**.

The fourth and most polar product **50** of the reaction between 1,9-bis(chloromethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **43** and ethylamine was seen to be formed by the reaction of two equivalents of the starting material with three equivalents of the amine and the spectra were correspondingly complex. The IR spectrum showed the presence of ring carbonyl and amide carbonyl absorptions at 1735 and 1657 cm^{-1}. The proton NMR showed a lot of overlapping of the signals due to which assignment could only be perfunctory. The olefinic protons appeared as a multiplet between δ 4.95-4.87 and a singlet at δ 4.77. The three methyl parts of the ethyls on the tertiary amine, lactam and amide functions appeared together as a multiplet at δ 1.35-1.20 along with another proton. The ^{13}C NMR showed the following signals which could be assigned with certainty: a signal at δ 215.3 for the ring carbonyl; one at δ 172.3 due to the lactam carbonyl; one at δ 160.8 due to the amide carbonyl; four signals at δ 150.9, 143.4, 111.2 and 109.8 due to the two exocyclic double bonds; one at δ 97.7 due to the carbon which appears downfield due to its being attached to the lactam nitrogen and a tertiary nitrogen; then the three methyl parts of the ethyl groups on the nitrogens gave signals upfield at δ 15.8, 14.2 and 13.8. The HRMS gave an M^+ value of 549.2732, which was in agreement with the rest of the data. Based on this, the structure was deduced as 4-azaethyl-6-chloromethyl-5-(N-(7'-methylamino-8'-(N-ethylcarbamoyl)tetracyclo

[4.2.1.1$^{4',7'}$.0$^{2',5'}$]dec-3'(11')-ene)-N-ethyl)pentacyclo[5.4.1.0^{2,6}.0^{5,9}.0^{8,11}]dodec-10(13)-ene-3-one **50**.

Thus, we have conducted a detailed investigation into the nature of addition of primary amines to substituted tetra- and pentacyclic cage compounds and discovered fascinating new rearrangements giving rise to totally unexpected products. As can be discerned, a lot more studies remain to be conducted in this area and we anticipate rich developments in this field on evaluation of the biological activity of these compounds.

4.3 Experimental:

For general experimental details, see Chapter 2, page number 60.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.0^{2,6}.0^{4,8}]undeca-10(12)-ene-9,11-dione **26** with methylamine to give **28**:

3-Bromo-7-(bromomethyl)tetracyclo[5.3.1.0^{2,6}.0^{4,8}]undeca-10(12)-ene-9,11-dione **26** (58 mg, 0.16 mmol) was dissolved in 15 ml of benzene and after cooling this solution in an ice-water bath (~ 5 °C), methylamine gas (produced by heating a 40% w/v solution of methylamine in water) was passed through it for half an hour. The reaction mixture was left stirring for one hour and tlc examination at the end of this period showed the formation of a single product. The reaction was worked up by removing the solvent and the residue was chromatographed on a silica gel column affording **28** (41 mg, 82% yield) as a white solid. This was recrystallised from CH_2Cl_2-petroleum ether as white needle-like crystals.

m.p. (°C)	:	156-157.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2989, 2881, 1708, 1681, 1506, 1452, 1404, 1290.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 5.03 (s, 1H), 4.69 (s, 1H), 4.06 (s, 1H), 3.79 (t, *J* = 10.5 Hz, 1H), 3.42-3.34 (m, 2H) 3.28-3.17 (m, 3H), 3.02-2.97 (m, 1H), 2.91

(d, J = 4.9 Hz, 1H), 2.68 (s, 3H), 2.61 (½ABq, J = 10.8 Hz, 1H), 1.56 (½ABq, J = 10.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 209.4, 172.3, 145.7, 109.1, 57.7, 52.9, 52.8, 48.3, 47.8, 46.2, 44.8, 44.7, 38.9, 29.6.

HRMS (M^++1) : 310.0443, $C_{14}H_{16}NO_2Br$ requires 309.0364.

UV (CH_2Cl_2, λ_{max}) : 228 nm.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with ethylamine to give **29**:

3-Bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** (49 mg, 0.14 mmol) was taken in a round-bottomed flask and dissolved in 10 ml of dry benzene. This solution was cooled in an ice-water bath and ethylamine gas (ethylamine gas was produced by heating a 70% w/v solution of ethylamine in water on a water bath) was passed through it for ½ hour. After this, stirring was continued at room temperature for a further ½ hour. At the end of this period, tlc showed all the starting material to have been consumed. The reaction was worked up by removing the solvent under vacuum on the rotavapor and then the crude product was purified by column chromatography on silica gel. Elution with 50% ethyl acetate in petroleum ether gave the product **29** (27 mg, 61% yield) as an off-white solid which was recrystallised from dichloromethane-petroleum ether to give white needle-like crystals.

m.p. (°C) : 145-148.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2990, 2960, 1700, 1650, 1525, 1473, 1414, 1281, 911.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.98 (s, 1H), 4.64 (s, 1H), 4.03 (s, 1H), 3.70 (t, J = 10.4 Hz, 1H), 3.33 (t, J = 5.4 Hz, 1H), 3.29-3.19 (m, 3H), 3.14-3.13 (m, 1H), 3.11-3.09 (m, 1H), 3.06-2.99 (m, 2H), 2.84 (d, J = 5.2 Hz, 1H), 2.54 (½ABq, J = 10.8 Hz, 1H), 1.49 (½ABq, J = 10.8 Hz, 1H),

0.97 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 209.3, 171.7, 145.2, 110.1, 56.8, 52.1, 49.2, 47.2, 46.7, 44.9, 44.2, 43.4, 38.0, 36.4, 10.6.

HRMS (M^+) : 323.0519, $C_{15}H_{18}BrNO_2$ requires 323.0521.

UV (CH_2Cl_2, λ_{max}) : 228 nm.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with *n*-butylamine to give **30**:

3-Bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** (65 mg, 0.18 mmol) was taken in a round-bottomed flask and dissolved in dry benzene (10 ml). This solution was cooled in an ice-water bath and then *n*-butylamine (0.38 ml, 0.28 mg, 3.76 mmol, 21 eq.) was added to this solution drop-by-drop. The reaction mixture was stirred at room temperature for two days. At the end of this time, tlc examination showed the reaction to be complete. The reaction was worked up by removing the solvent under reduced pressure on the rotavapor. The crude product was purified by column chromatography on silica gel using 40% ethyl acetate in petroleum ether as the eluent. The product **30** was obtained as a dirty white solid which on recrystallisation from dichloromethane-petroleum ether gave fine white needle-like crystals (46 mg, 72% yield).

m.p. (°C) : 106-108.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2989, 2962, 2928, 2874, 1701, 1499, 1452, 1276, 906.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.03 (s, 1H), 4.70 (s, 1H), 4.10 (s, 1H), 3.78 (t, J = 10.5 Hz, 1H), 3.41-3.34 (m, 3H), 3.32-3.26 (m, 2H), 3.19-3.15 (m, 1H), 3.07-3.02 (m, 1H), 2.91-2.83 (m, 2H), 2.61 (½ABq, J = 10.8 Hz, 1H), 1.55 (½ABq, J = 10.8 Hz, 1H), 1.43-1.36 (m, 2H, -N-CH_2-CH_2-CH_2-CH_3), 1.32-1.25 (m, 2H, -N-CH_2-CH_2-CH_2-CH_3), 0.91 (t, J = 7.2 Hz, 3H, -N-

CH_2-CH_2-CH_2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 209.3, 171.9, 145.3, 109.9, 57.8, 53.1, 50.9, 48.2, 47.8, 46.0, 45.1, 44.6, 42.9, 39.0, 28.7, 20.2, 13.7.
HRMS ($M^+ + 1$)	:	352.0928, $C_{17}H_{22}NO_2Br$ requires 351.0834.
UV (CH_2Cl_2, λ_{max})	:	228 nm.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with benzylamine to give **31**:

The compound **26** (0.11 g, 0.31 mmol) was taken in a dry round-bottomed flask and dissolved in dry benzene (10 ml). The reaction vessel was cooled in an ice-water bath and then benzylamine (0.21 ml, 0.21 g, 1.92 mmol, 6 eq.) was added to the solution slowly using the syringe-septum technique. After the addition was completed, the reaction mixture was left stirring at room temperature for 38 hours. When the tlc was checked after this period the starting material was seen to have been completely consumed, so the reaction mixture was worked up by removing the solvent on the rotavapor under vacuum. The crude residue was purified by passing through a silica gel column, elution with 30% ethyl acetate in petroleum ether gave the product **31** as an off-white solid (97 mg, 82% yield) which was crystallised from dichloromethane-petroleum ether. The crystals were needle-like and white in colour. In order to obtain large crystals for X-ray diffraction studies, these crystals were recrystallised from a solvent mixture consisting of acetone and petroleum ether.

m.p. (°C)	:	155-156.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2982, 2881, 1694, 1688, 1506, 1452, 1290, 919.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 7.32-7.19 (m, 5H), 4.85 (s, 1H), 4.61 (½ABq, J = 14.3 Hz, 1H), 4.51 (s, 1H), 4.09 (s, 1H), 3.95 (½ABq, J = 14.2 Hz, 1H), 3.65 (t, J = 10.6 Hz, 1H), 3.46-3.24 (m, 4H), 3.19-2.87 (m, 3H), 2.61 (½ABq, J = 10.8 Hz, 1H), 1.55 (½ABq, J = 10.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 209.1, 171.9, 145.1, 135.0, 128.9 (2 carbons), 128.7 (2 carbons), 127.9, 109.8, 57.7, 53.1, 50.6, 48.2, 47.7, 47.3, 46.3, 45.1, 44.4, 39.0.
HRMS ($M^+ + 1$)	:	386.0748, $C_{20}H_{20}NO_2Br$ requires 385.0677.
UV (CH_2Cl_2, λ_{max})	:	228 nm.

Crystal data for **31** (Fig. 3):

$C_{20}H_{20}BrNO_2$, colourless crystalline solid, 0.40 x 0.20 x 0.10 mm., monoclinic, space group: $P2_1/n$. Unit cell dimensions: a = 11.1648(2) Å alpha = 90°; b = 6.8268(1) Å beta = 100.6140(10)°; c = 22.6147(3) Å gamma = 90°. R indices (all data): R1 = 0.0703, wR2 = 0.0851, Volume = 1694.20(5) $Å^3$, Z = 4. Density (calculated) = 1.514 Mg/m^3. F(000) = 792. Absorption coefficient = 2.438 mm^{-1}.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with veratrylamine to give **32**:

The compound **26** (69 mg, 0.19 mmol) was taken in a dry round-bottomed flask and dissolved in 15 ml of dry benzene. The reaction vessel was cooled in an ice-water bath and then veratrylamine (0.6 ml, 0.675 g, 4.04 mmol, 21 eq.) was added to this solution drop-by-drop. After the addition was complete, the reaction mixture was left stirring at room temperature for 24 hours. Examination of the tlc now showed the reaction to be complete with total consumption of the starting material. The reaction was worked up by removing the solvent on the rotavapor under reduced pressure. The crude was loaded on a silica gel column and eluted out with 40% ethyl acetate in petroleum ether to give the pure product **32** (68 mg, 80% yield) which was crystallised from dichloromethane-petroleum ether to give fine white crystals.

m.p. (°C)	:	120-122.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2948, 1681, 1600, 1526, 1452, 1270, 1142, 1040, 912.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 6.81-6.73 (m, 3H), 4.87 (s, 1H), 4.53 (s, 2H), 4.08 (s, 1H), 3.88-3.83 (m, 6H), 3.64 (t,

J = 9.3 Hz, 1H), 3.41-3.35 (m, 2H), 3.30-3.28 (m, 1H), 3.17-3.08 (m, 2H), 3.00-2.95 (m, 2H), 2.89-2.87 (m, 1H), 2.60 (½ABq, J = 10.7 Hz, 1H), 1.54 (½ABq, J = 10.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 209.1, 171.8, 149.1, 148.8, 145.1, 128.3, 127.6, 121.3, 112.1, 111.0, 109.7, 57.7, 55.9, 53.0, 50.6, 48.2, 47.7, 47.1, 46.2, 45.1, 44.3, 38.9.

HRMS (M^+) : 445.0865, $C_{22}H_{24}O_4NBr$ requires 445.0889.

UV (CH_2Cl_2, λ_{max}) : 230 nm.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with homoveratrylamine to give **33**:

The compound **26** (70 mg, 0.19 mmol) was taken in a round-bottomed flask and 10 ml of dry benzene was added to this. The solution was cooled in an ice-water bath and then 0.70 ml of homoveratrylamine (0.75 g, 4.15 mmol, 21 eq.) was added with constant stirring using the syringe-septum technique. After the addition was complete, the reaction mixture was left stirring at room temperature for two days. At the end of this time, tlc of the reaction mixture revealed the absence of starting material and so the reaction was worked up by removing the solvent under reduced pressure on the rotavapor. The crude product thus obtained was purified on a silica gel column by elution with 40% ethyl acetate in petroleum ether. The white solid (45 mg, 50% yield) obtained was crystallised from dichloromethane-petroleum ether to give white needle-like crystals of the product **33**.

m.p. (°C) : 98-100.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2948, 2840, 1694, 1593, 1526, 1458, 1270, 1034, 912.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 6.80-6.69 (m, 3H), 5.01 (s, 1H), 4.69 (s, 1H), 4.09 (s, 1H), 3.87-3.85 (m, 6H), 3.68 (t, J = 10.2 Hz, 1H), 3.41-3.26 (m, 4H), 3.15-

3.02 (m, 4H), 2.89 (d, J = 5.2 Hz, 1H), 2.70 (dd, J_1 = 15.6 Hz, J_2 = 8.9 Hz, 2H), 2.60 (½ABq, J = 10.8 Hz, 1H), 1.55 (½ABq, J = 10.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 209.2, 172.1, 149.1, 147.8, 145.3, 130.8, 120.5, 111.7, 111.4, 109.9, 57.8, 55.9 (2 carbons), 52.9, 51.2, 48.2, 47.8, 45.9, 44.9, 44.6, 44.5, 38.9, 32.6.

HRMS (M^+ + 1) : 460.1126, $C_{23}H_{26}NO_4Br$ requires 459.1045.

UV (CH_2Cl_2, λ_{max}) : 229 nm.

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with diisopropylamine:

The compound **26** (21 mg, 0.06 mmol) was taken in 10 ml of dry benzene in a round-bottomed flask and cooled in ice. Diisopropylamine (0.17 ml, 0.12 g, 1.2 mmol, 21 eq.) was added to this solution and the reaction was stirred at room temperature for two weeks. At the end of this period, the starting material **26** was recovered unreacted from the reaction mixture (confirmed by checking the spectral data of the recovered material).

Reaction of 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undeca-10(12)-ene-9,11-dione **26** with diethylamine:

The compound **26** (104 mg, 0.29 mmol) was taken in 10 ml of dry benzene and the solution was cooled in ice. Diethylamine (0.60 ml, 0.42 g, 5.8 mmol, 20 eq.) was added and the reaction mixture was stirred with heating at 50-55 °C for five days. At the end of this period, the starting material was recovered from the reaction mixture.

Reaction of 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **34** with methylamine to give **35**, **36** and **37**:

The compound **34** (84 mg, 0.23 mmol) was taken in 10 ml of dry benzene and the solution was cooled in an ice-water bath. Methylamine gas (produced as described

earlier) was passed through this solution for ½ hour and then the reaction mixture was allowed to come to room temperature and stirred for ½ hour more. After this the reaction was worked up by removing the solvent under reduced pressure on the rotavapor. The crude product mixture was loaded on a silica gel column and then successively eluted with 40%, 50%, 60%, 70%, 80% and 90% ethyl acetate in petroleum ether followed by elution with ethyl acetate and subsequently with 1%, 2%, 5% and 10% methanol in ethyl acetate to give three compounds **35** (27 mg, 37% yield), **36** (18 mg, 25% yield) and **37** (32 mg, 24% yield).

Spectral data for **35**:

m.p. (°C)	:	200-202.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3137, 2962, 2948, 1654, 1431, 1378, 1283, 1263, 1243, 1155, 1088, 1027, 899, 791.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 4.87 (s, 1H), 4.79 (s, 1H), 3.79 (brs, 1H), 3.58 (s, 2H), 3.35 (brs, 1H), 3.07 (brs, 1H), 3.00-2.96 (m, 1H), 2.82-2.77 (m, 2H), 2.63 (s, 3H), 2.56 (d, *J* = 4.9 Hz, 1H), 2.02 (½ABq, *J* = 10.4 Hz, 1H), 1.58 (½ABq, *J* = 10.5 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 171.2, 143.6, 108.9, 101.9, 63.1, 60.2, 55.9, 51.1, 49.5, 45.1, 44.4, 42.8, 34.7, 24.6.
HRMS ($M^+ + 1$)	:	310.0437, $C_{14}H_{16}NO_2Br$ requires 309.0364.

Crystal data for **35** (Fig. 6):

$C_{14}H_{16}BrNO_2$, colourless crystalline solid, 0.30 × 0.24 × 0.20 mm^3, orthorhombic, space group: $P2_12_12_1$. Unit cell dimensions: a = 6.4973(1) Å, α = 90°; b = 12.8707(2) Å, β = 90°; c = 15.6425(3) Å, γ = 90°. *R indices (all data): R1 = 0.0420, wR2 = 0.0857.* Volume = 1308.10(4) $Å^3$, *Z* = 4. Density (calculated) = 1.575 Mg/m^3. F(000) = 632. Absorption coefficient = 3.136 mm^{-1}.

Spectral data for **36**:

m.p. (°C)	:	129-131.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2965, 2865, 1738, 1651, 1538, 1370, 1240, 1109, 885.
^1H NMR (300 MHz, $CDCl_3$ + CCl_4)	:	δ 5.26 (brs, 1H), 5.03 (s, 1H), 4.86 (s, 1H), 3.74 (½ABq, J = 10.4 Hz, 1H), 3.40 (½ABq, J = 10.4 Hz, 1H), 3.15-3.11 (m, 3H), 2.93-2.89 (m, 3H), 2.53 (d, J = 4.6 Hz, 3H), 1.63 (½ABq, J = 10.4 Hz, 1H), 1.52 (½ABq, J = 10.4 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4)	:	δ 214.5, 170.7, 146.6, 111.6, 58.8, 56.8, 46.2, 45.8, 44.5, 41.9, 39.6, 38.3, 33.8, 26.1.
HRMS (M^+ + 1)	:	310.0386, $C_{14}H_{16}BrNO_2$ requires 309.0364.

Spectral data for **37**:

m.p. (°C)	:	109-111.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3444, 3176, 3095, 2983, 2952, 2915, 1743, 1670, 1539, 1508, 1452, 1278, 1147, 1066, 886.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 5.02 (s, 1H), 4.94-4.89 (m, 3H), 3.89-3.79 (m, 4H), 3.74 (d, J = 9.7 Hz, 1H), 3.68-3.63 (m, 1H), 3.46 (d, J = 8.5 Hz, 1H), 3.33 (brs, 2H), 3.23-3.13 (m, 11H), 3.06-3.01 (m, 4H), 2.94 (brs, 2H), 2.82 (d, J = 4.3 Hz, 1H), 2.72 (d, J = 4.8 Hz, 1H), 2.28 (½ABq, J = 10.5 Hz, 1H), 1.78 (½ABq, J = 10.5 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 209.1, 171.8, 163.2, 151.2, 143.4, 110.6, 108.8, 97.1, 65.2, 59.8, 58.3, 51.9, 51.3, 48.7, 47.1, 46.4 (2C), 45.6, 45.4, 44.8, 43.3, 42.7, 42.3, 38.1, 36.3, 30.9, 30.6, 29.3, 29.0.
HRMS (M^+)	:	551.1768, $C_{29}H_{34}BrN_3O_3$ requires 551.1784.

Reaction of 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione with **34** ethylamine to give **40**, **41** and **42**:

The compound **34** (107 mg, 0.29 mmol) was taken in a round-bottomed flask and dissolved in 10 ml of dry benzene. This solution was cooled in an ice-water bath and ethylamine gas was passed through this solution for ½ hour (produced as described earlier). The solution was left stirring at room temperature for a further ½ hour and then worked up by removing the solvent on the rotavapor under vacuum. The residue was loaded on a silica gel column and then eluted successively with increasingly polar solvent mixtures (40%, 50%, 60%, 70%, 80% and 90% ethyl acetate in petroleum ether, ethyl acetate, 1%, 2%, 5% and 10% methanol in ethyl acetate) to give three products **40** (22 mg, 23% yield), **41** (19 mg, 20% yield) and **42** (23 mg, 13% yield).

Spectral data for **40**:

m.p. (°C)	:	231-233.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3349, 3074, 2980, 2874, 1651, 1539, 1414, 1345, 1270, 1133, 1095, 877.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 5.94 (brs, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 3.75 (½ABq, J = 11.1 Hz, 1H), 3.69 (½ABq, J = 11.1 Hz, 1H), 3.39-3.32 (m, 3H), 3.09 (s, 1H), 3.04-2.97 (m, 3H), 2.79 (d, J = 5.3 Hz, 1H), 2.15 (½ABq, J = 10.7 Hz, 1H), 1.55 (½ABq, J = 10.6 Hz, 1H), 1.25-1.12 (m, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 176.6, 139.6, 113.8, 104.8, 55.7, 54.7 (2C), 50.2, 50.0, 47.3, 42.2, 40.6, 38.1, 36.3, 16.3.
HRMS (M^+)	:	323.0519, $C_{15}H_{18}NO_2Br$ requires 323.0521.

Spectral data for **41**:

m.p. (°C)	:	159-161.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3093, 2980, 2868, 1732, 1695, 1414, 1276,

1251, 1139, 883.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.23 (brs, 1H), 4.91 (s, 1H), 4.83 (s, 1H), 3.73 (½ABq, J = 10.7 Hz, 1H), 3.56 (½ABq, J = 10.7 Hz, 1H), 3.31 (brs, 1H), 3.21 (brs, 1H), 3.15-3.08 (m, 3H), 2.93-2.88 (m, 2H), 2.76 (d, J = 4.9 Hz, 1H), 2.01 (½ABq, J = 10.4 Hz, 1H), 1.46 (½ABq, J = 10.3 Hz, 1H), 1.08 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 210.3, 168.4, 138.9, 111.8, 55.0, 54.4, 49.3, 48.7, 41.5, 39.6, 37.3, 35.2, 34.4, 34.1, 14.3.

HRMS (M^+) : 323.0515, $C_{15}H_{18}NO_2Br$ requires 323.0521.

Spectral data for **42**:

m.p. (°C) : 106-109.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2962, 2924, 2850, 1738, 1632, 1557, 1445, 1251, 1089, 1014, 889, 796.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.29 (brs, 1H), 5.12 (s, 1H), 4.93-4.87 (m, 3H), 3.68 (½ABq, J = 10.9 Hz, 1H), 3.59-3.54 (m, 4H), 3.47 (½ABq, J = 10.8 Hz, 1H), 3.37 (brs, 2H), 3.19-3.12 (m, 4H), 3.06-2.99 (m, 5H), 2.89-2.87 (m, 2H), 2.79-2.73 (m, 4H), 2.60 (d, J = 5.3 Hz, 1H), 2.01 (½ABq, J = 10.5 Hz, 1H), 1.70-1.60 (m, 7H), 1.18 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 212.6, 171.0, 163.4, 148.3, 143.8, 112.0, 110.2, 93.9, 62.7, 60.9, 58.8, 56.6, 51.5, 50.4, 46.1, 45.5, 45.4, 44.8, 44.5, 43.3, 43.0, 42.2, 41.9, 39.7, 38.3, 35.5, 34.9, 34.4, 33.9, 15.3 (2C), 14.1.

HRMS (M^+) : 593.2279, $C_{32}H_{40}N_3O_3Br$ requires 593.2253.

Reaction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione 43 with methylamine to give 44, 45 and 46:

The compound 43 (95 mg, 0.35 mmol) was taken in a round-bottomed flask along *with 10 ml of dry benzene. The solution was cooled in an ice-water bath before methylamine gas was passed through it for ½ hour (methylamine gas produced as* described earlier). The reaction mixture was then stirred for ½ hour more and then worked up by removing the solvent under vacuum on a rotavapor. The solid residue was purified on a silica-gel column. Elution with increasingly polar solvent mixtures (40%, 50%, 60%, 70%, 80% and 90% ethyl acetate in petroleum ether, ethyl acetate, 1%, 2%, 5% and 10% methanol in ethyl acetate) led to the isolation of three products **44** (33 mg, 36% yield), **45** (31 mg, 33% yield) and **46** (31 mg 17% yield).

Spectral data for **44**:

m.p. (°C)	:	225-227.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3090, 2968, 1651, 1439, 1376, 1251, 1133, 1020.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 4.94 (s, 1H), 4.86 (s, 1H), 3.98 (brs, 1H), 3.77 (brs, 2H), 3.39 (brs, 1H), 3.15 (brs, 1H), 3.09-3.03 (m, 1H), 2.90-2.85 (m, 2H), 2.70 (s, 3H), 2.64 (d, J = 4.7 Hz, 1H), 2.03 (½ABq, J = 10.8 Hz, 1H), 1.67 (½ABq, J = 10.5 Hz, 1H).
^{13}C NMR (75 MHz, Acetone-d_6)	:	δ 170.3, 144.9, 108.0, 72.5, 63.1, 60.7, 54.9, 51.6, 48.8, 46.6, 45.2, 44.8, 42.8, 24.3.
HRMS (M^+ + 1)	:	266.0958, $C_{14}H_{16}NO_2Cl$ requires 265.0869.

Spectral data for **45**:

m.p. (°C)	:	130-132.
FT-IR (KBr, ν_{max}/cm^{-1})	:	2962, 2868, 1732, 1670, 1539, 1432, 1382, 1258, 1089, 1014, 889, 789, 727.
^{1}H NMR (300 MHz, $CDCl_3$)	:	δ 5.23 (brs, 1H), 5.03 (s, 1H), 4.80 (s, 1H),

3.80 (½ABq, J = 11.2 Hz, 1H), 3.58 (½ABq, J = 11.2 Hz, 1H), 3.10-2.97 (m, 2H), 2.95-2.93 (m, 1H), 2.91-2.83 (m, 3H), 2.53 (d, J = 4.3 Hz, 3H), 1.95 (½ABq, J = 10.4 Hz, 1H), 1.54 (½ABq, J = 10.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 212.6, 170.1, 146.6, 111.4, 58.8, 55.8, 50.4, 46.2, 44.3, 43.1, 39.7, 38.7, 36.1, 26.4.

HRMS (M^+) : 265.0932, $C_{14}H_{16}ClNO_2$ requires 265.0869.

Spectral data for **46**:

m.p. (°C) : 85-88.

FT-IR (KBr, ν_{max}/cm^{-1}) : 3320, 2965, 2871, 1732, 1664, 1539, 1384, 1278, 1147, 1010, 886.

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) : δ 5.31 (brs, 1H), 5.08 (s, 1H), 4.89-4.85 (m, 3H), 3.85 (½ABq, J = 11.3, 1H), 3.71-3.59 (m, 3H), 3.46 (brs, 1H), 3.25 (brs, 1H), 3.15 (brs, 2H), 2.99-2.94 (m, 3H), 2.89-2.88 (m, 2H), 2.82 (brs, 1H), 2.63 (s, 3H), 2.57 (d, J = 4.6, 3H), 2.46 (s, 3H), 2.01 (½ABq, J = 10.7 Hz, 1H), 1.86 (brs, 2H), 1.69-1.55 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) : δ 214.3, 172.7, 170.7, 146.5, 144.3, 111.4, 109.6, 91.7, 62.7, 58.8, 56.8, 56.7, 55.7, 51.5, 50.3, 46.7, 46.1, 45.5, 45.3, 44.3, 44.2, 43.1, 42.4, 41.9, 39.6, 38.8, 30.2, 26.3, 25.9.

HRMS (M^+) : 507.2316, $C_{29}H_{34}ClN_3O_3$ requires 507.2289.

Reaction of 1,9-bis(chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **43** with ethylamine to give **47**, **48**, **49** and **50**:

The compound **43** (112 mg, 0.41 mmol) was taken in a round-bottomed flask and dissolved in 10 ml of dry benzene. This solution was cooled in an ice-water bath and

then ethylamine gas (produced as before) was passed through it for ½ hour. The reaction was then left stirring at room temperature for a further ½ hour. At the end of this period tlc showed complete consumption of the starting material and formation of four products. The reaction was worked up by removing the solvent on a rotavapor under reduced pressure and then the residue was loaded on a silica-gel column and successively eluted with 40%, 50%, 60%, 70%, 80% and 90% ethyl acetate in petroleum ether followed by elution with ethyl acetate to give the first three products **47** (15 mg, 12% yield), **48** (35 mg, 30% yield) and **49** (16 mg, 14% yield). The last product **50** (28 mg, 12% yield) was obtained on further elution with 1%, 2%, 5% and 10% methanol in ethyl acetate.

Spectral data for **47**:

m.p. (°C)	:	158-160.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3307, 2971, 2927, 2871, 1689, 1402, 1346, 1290, 1259, 1141, 879, 792.
^1H NMR (300 MHz, $CDCl_3$)	:	δ 4.86-4.85 (m, 2H), 3.72 (½ABq, J = 11.5 Hz, 1H), 3.59 (½ABq, J = 11.5 Hz, 1H), 3.54-3.47 (m, 2H), 3.14 (brs, 1H), 3.01-2.94 (m, 1H), 2.87-2.76 (m, 4H), 2.69-2.65 (m, 2H), 2.48-2.46 (m, 1H), 1.99 (½ABq, J = 10.2 Hz, 1H), 1.63 (½ABq, J = 10.3 Hz, 1H), 1.20-1.09 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 172.8, 144.8, 109.9, 93.3, 62.5, 57.2, 55.9, 51.3, 50.7, 47.0, 45.5, 44.3, 42.1, 37.7, 35.9, 15.9, 15.4.
HRMS (M^+)	:	306.1497, $C_{17}H_{23}N_2OCl$ requires 306.1498.

Spectral data for **48**:

m.p. (°C)	:	243-245.
FT-IR (KBr, ν_{max}/cm^{-1})	:	3089, 2977, 2927, 1651, 1452, 1415, 1278, 1128, 1097, 879.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.87 (s, 2H), 3.84 (½ABq, J = 11.8 Hz, 1H), 3.73 (½ABq, J = 11.8 Hz, 1H), 3.63-3.56 (m, 1H), 3.43-3.36 (m, 1H), 3.14 (brs, 1H), 3.09-3.05 (m, 1H), 2.88-2.71 (m, 3H), 2.61 (d, J = 5.3 Hz, 1H), 1.98 (½ABq, J = 10.5 Hz, 1H), 1.73 (s, 1H), 1.67 (½ABq, J = 10.5 Hz, 1H), 1.19-1.11 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.3, 143.9, 110.0, 103.9, 63.3, 60.7, 55.7, 51.5, 49.2, 46.1, 45.4, 44.9, 42.8, 35.3, 15.2.

HRMS (M^+) : 279.1021, $C_{15}H_{18}ClNO_2$ requires 279.1026.

Spectral data for **49**:

m.p. (°C) : 98-100.

FT-IR (KBr, ν_{max}/cm^{-1}) : 2971, 2871, 1738, 1645, 1533, 1458, 1278, 1147, 892.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.21 (brs, 1H), 5.06 (s, 1H), 4.86 (s, 1H), 3.82 (½ABq, J = 11.4 Hz, 1H), 3.57 (½ABq, J = 11.4 Hz, 1H), 3.21-3.18 (m, 1H), 3.10 (s, 2H), 3.08-2.95 (m, 4H), 2.86 (brs, 1H), 1.62 (½ABq, J = 10.4 Hz, 1H), 1.52 (½ABq, J = 10.4 Hz, 1H), 0.97 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 214.3, 169.9, 146.4, 112.0, 58.9, 57.0, 46.2, 45.5, 44.1, 43.2, 41.9, 39.8, 38.9, 34.3, 14.1.

HRMS (M^+) : 279.1024, $C_{15}H_{18}ClNO_2$ requires 279.1026.

*Spectral data for **50**:*

m.p. (°C) : *80-83.*

FT-IR (KBr, ν_{max}/cm^{-1}) : 3170, 3102, 3064, 2977, 2934, 1735, 1657, 1439, 1117, 886.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.95-4.87 (m, 3H), 4.77 (s, 1H), 4.13-4.08 (m, 2H), 3.89 (½ABq, J = 11.8 Hz, 1H), 3.84-3.82 (m, 1H), 3.76-3.73 (m, 2H), 3.62 (½ABq, J = 11.9 Hz, 1H), 3.52-3.48 (m, 1H), 3.43-3.40 (m, 2H), 3.36-3.34 (m, 2H), 3.27-3.19 (m, 1H), 3.16-3.09 (m, 1H), 2.99-2.95 (m, 1H), 2.92-2.87 (m, 1H), 2.82-2.78 (m, 2H), 2.65 (d, J = 4.9 Hz, 1H), 2.16 (½ABq, J = 10.5 Hz, 1H), 2.11-2.04 (m, 3H), 1.75 (½ABq, J = 10.5 Hz, 1H), 1.42 (dd, J_1 = 18.4 Hz, J_2 = 8.0 Hz, 2H), 1.35-1.20 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 215.3, 172.3, 160.8, 150.9, 143.4, 111.2, 109.8, 97.7, 65.1, 60.3, 59.7, 57.9, 51.8, 50.9, 48.6, 47.2, 46.5, 46.1, 45.6, 45.3, 44.9, 43.3, 42.6, 42.2, 40.1, 38.1, 37.8, 35.9, 21.0, 15.8, 14.2, 13.8.

HRMS (M^+) : 549.2732, $C_{32}H_{40}ClN_3O_3$ requires 549.2758.

4.4 References:

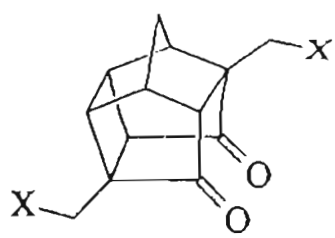
1. Marchand, A. P.; Dave, P. R.; Satyanarayana, N.; Arney, Jr., B. E. *J. Org. Chem.* **1988**, *53*, 1088-1092.
2. Marchand, A. P.; McKim, A. S.; Kumar, K. A. *Tetrahedron* **1998**, *54*, 13421-13426.
3. Bott, S. G.; Marchand, A. P.; Kumar, K. A.; Vidyanand, D.; Xing, D.; Watson, W. H.; Kashyap, R. P.; Sachleben, R. A. *Journal of Chemical Crystallography* **1995**, *25*, 633-640.
4. Marchand, A. P.; Arney, Jr., B. E.; Dave, P. R.;Satyanarayana, N.; Watson, W. H.; Nagl, A. *J. Org. Chem.* **1988**, *53*, 2644-2647.
5. Thummel, R. P.; Hegde, V. *J. Org. Chem.* **1989**, *54*, 1720-1725.

6. Haddadin, M. J.; Wang, Y.; Frenkel, S.; Bott, S. G.; Yang, L.; Braterman, P. S.; Carvallo, C.; Marchand, A. P.; Watson, W. H.; Kashyap, R. P.; Krawiec, M.; Bourne, S. A. *Heterocycles* **1994**, *37*, 869-882.
7. Marchand, A. P.; Sorokin, V. D.; Rajagopal, D.; Bott, S. G. *Heterocycles* **1995**, *40*, 223-230.
8. Schwab, R. S.; England, Jr., A. C.; Poskanzer, D. C.; Young, R. R. *J. Am. Med. Association* **1969**, *208*, 1168-1170.
9. Marchand, A. P.; Reddy, G. M.; Watson, W. H.; Kashyap, R. P.; Nagl, A. *J. Org. Chem.* **1991**, *56*, 277-282.
10. Sasaki, T.; Eguchi, S.; Kiriyama, T.; Hiroaki, O. *Tetrahedron* **1974**, *30*, 2707-2712.
11. Kruger, H. G. Ph. D. Thesis submitted to the Potchefstroom University for Christian Higher Education, **1996**.

Summary

This thesis entitled **"Synthesis and Rearrangements of some Tetra- and Pentacyclic Cage Compounds"** contains the results of the investigations conducted to gain some insight into the nature of polycyclic cage compounds of the type shown below in scheme I. The first chapter consists of a brief review of the earlier work done in this field where prominence has been given to the synthesis of various cage compounds and the studies that have been carried out to probe their reactivity patterns.

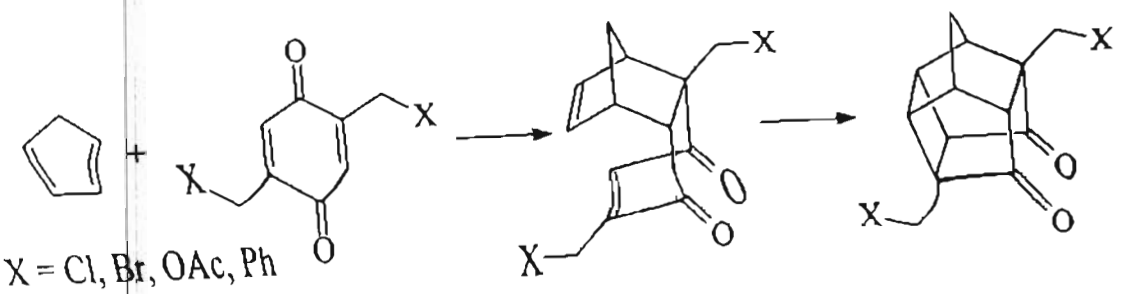
The second chapter deals with the synthesis of a number of derivatives of the pentacyclic undecane skeleton (Scheme I). These substituents were selected because of the potential of such compounds, which have the intrinsic property of a hydrophobic core surrounded by hydrophilic groups, to act as biologically active compounds.



X = Cl -- 1
Br -- 2
OAc -- 3
Ph -- 4

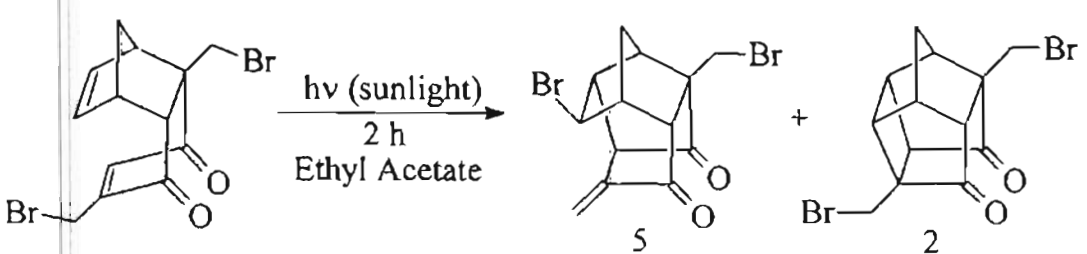
Scheme I

The synthesis of these pentacyclic cage compounds was envisaged to be the outcome of a Diels-Alder reaction between the appropriately substituted quinone and cyclopentadiene. Photolysis of the Diels-Alder adduct was expected to give the required compound by [π2s + π2s] cycloaddition (Scheme II).



Scheme II

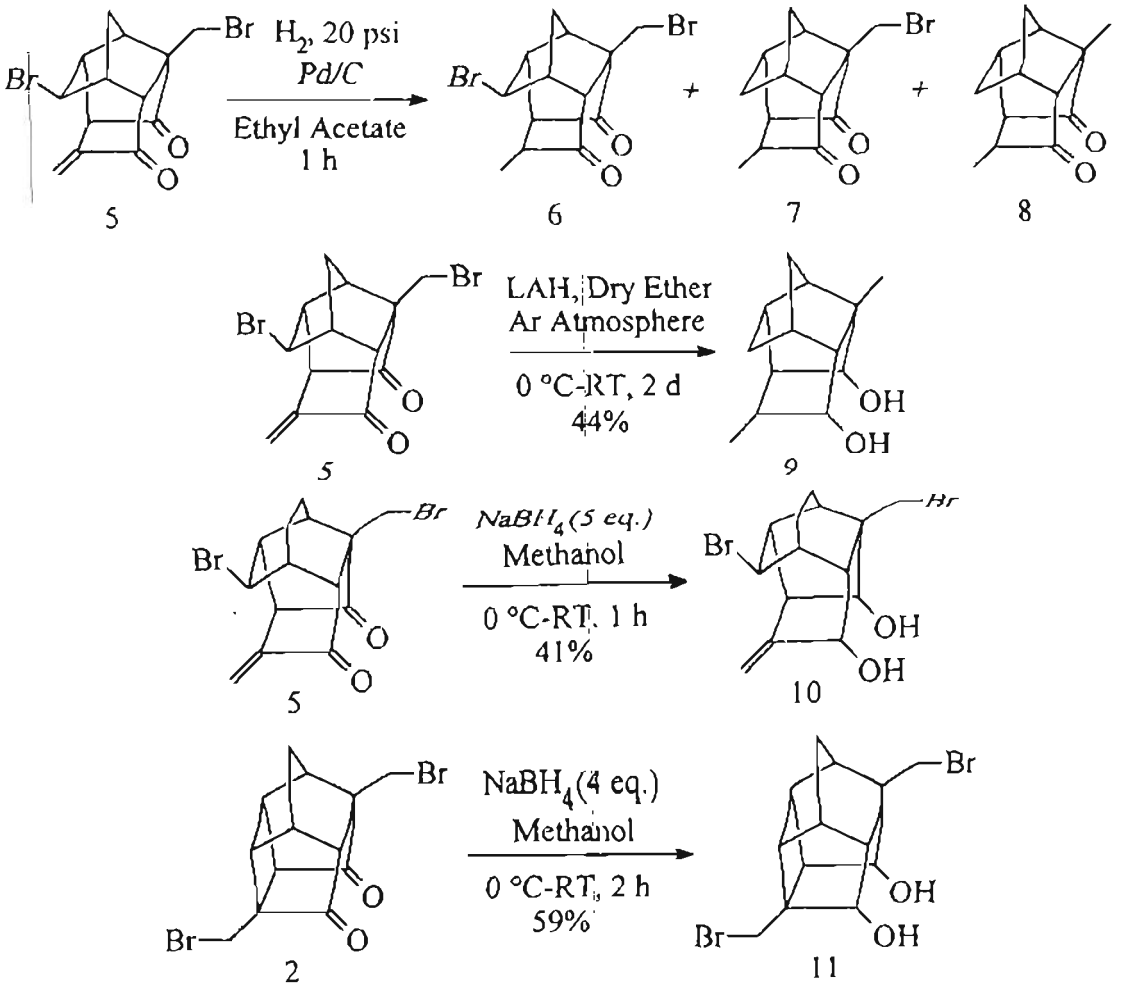
However, it was seen that when X = Br, a very unusual radical initiated rearrangement took place giving a tetracyclic compound **5** as the major product and the expected pentacycle **2** as a minor product (Scheme III). The product **5** is hypothesised to have been formed by the initial cleavage of the allylic carbon-bromine bond to give a bromine radical. Bond reorganisation followed by the recapture of the bromine radical would result in the novel tetracyclic system **5**.



Scheme III

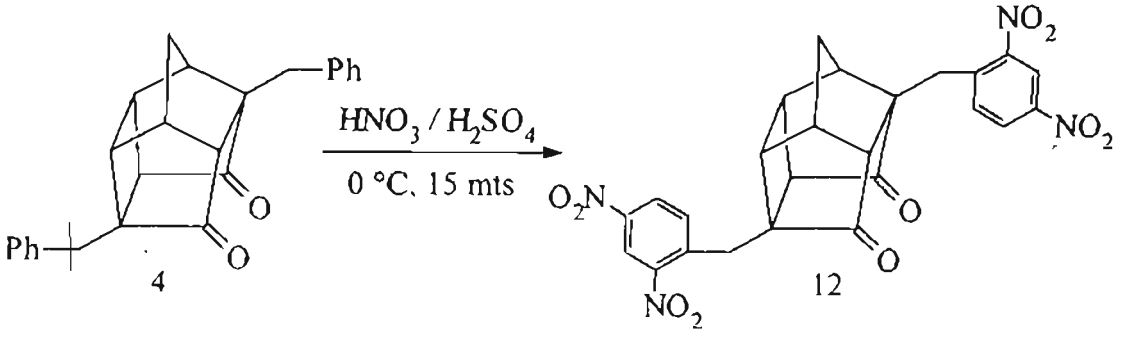
Further work was carried out to establish the role of the bromomethyl group in triggering the rearrangement, and the results have been discussed in detail in the chapter.

The third chapter is a brief look at the reactions of the pentacyclic and tetracyclic compounds prepared thus far to study their chemistry. Reductions using hydrogen with palladium on carbon as the catalyst (which led to the products **6**, **7** and **8** from **5**), lithium aluminium hydride (which led to products such as **9** from **5**) and sodium borohydride (which gave products such as **10** from **5** and **11** from **2**) were carried out and the expected products were obtained (scheme IV).



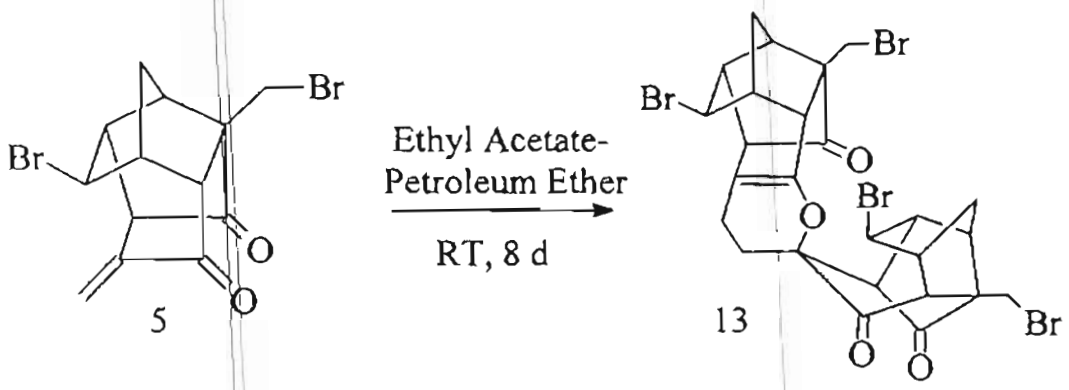
Scheme IV

Nitration of the compound **4** resulted in the formation of the tetranitrated product **12** (Scheme V).



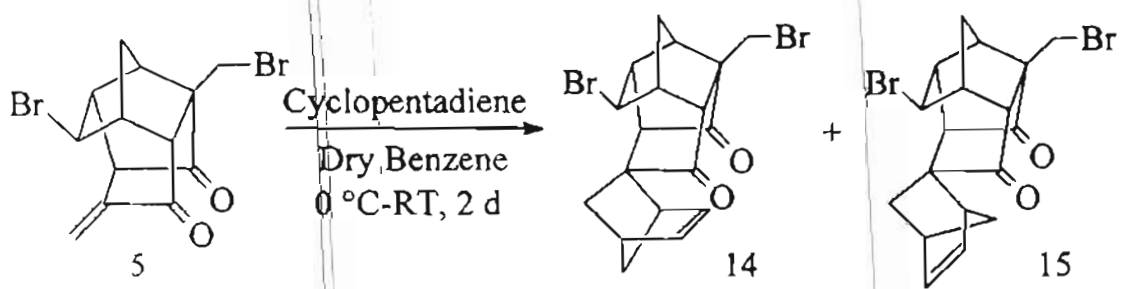
Scheme V

The compound **5** was also seen to undergo dimerisation (Diels-Alder addition between the enone moiety of one molecule and the double bond of another) to give the novel spiro-cage compound **13** as shown in scheme VI.



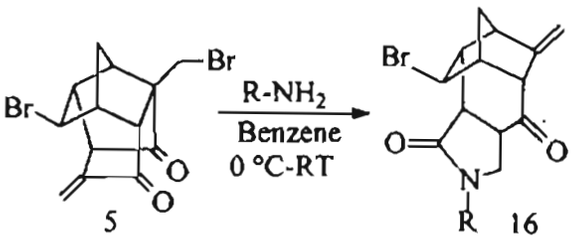
Scheme VI

This led to the investigation into the reaction of **5** with cyclopentadiene which was seen to result in two isomeric spiro-cage products **14** and **15** as shown in scheme VII.



Scheme VII

The fourth chapter deals with the reactions of some of the tetra- and pentacyclic cage compounds with primary amines. The reaction of the tetracyclic compound **5** with primary amines was seen to give a tetracyclic lactam **16** in moderate to good yields (Scheme VIII).

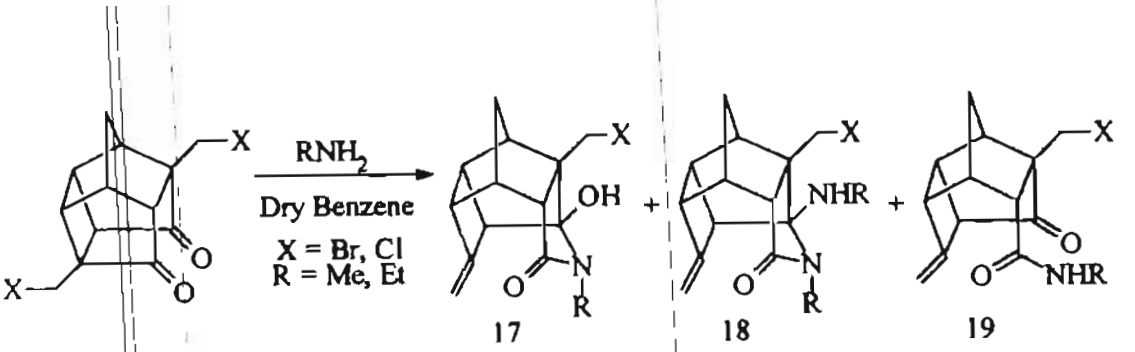


Amine		Time & Yield
R =	Me	1 h, 82%
R =	Et	1 h, 61%
R =	$(CH_2)_3CH_3$	48 h, 72%
R =	CH_2Ph	38 h, 82%
R =	veratryl	24 h, 80%
R =	homoveratryl	48 h, 50%

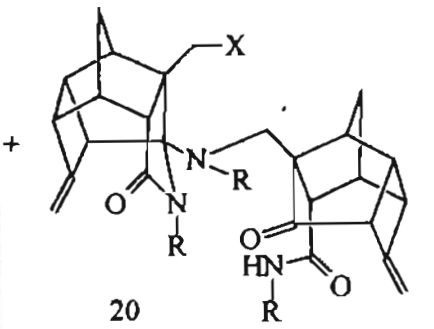
Scheme VIII

The mechanism proposed for the formation of product **16** invokes the initial addition of an amine to the carbonyl carbon, bond reorganisation followed by removal of a halide gives rise to an amide. The lone pair on the nitrogen then adds in a Michael fashion to the enone and transfer of protons leads to the rearranged product **16**.

This was a remarkable departure from the previous reports of amine additions to cage diones and it was thought to be of interest to study the reaction of the pentacyclic compound **2** with primary amines (Scheme IX). Surprisingly, this reaction gave rise to a multitude of products which were separated and identified on the basis of their spectra. The reaction of the bis(chloromethyl) substituted pentacycle **1** too was found to have the same reactivity profile as can be seen in scheme IX. The proposed reaction mechanism envisages an addition of amine to the carbonyl carbon as the first step. The removal of a halide and bond reorganisation gives the compound **19**. The attack of the lone pair of the nitrogen on the electron-deficient carbonyl carbon, which is in the vicinity due to the constrained cage structure, followed by proton rearrangement gives the compound **17**. The compound **18** may be formed by the addition of another mole of amine to compound **19** to give an imine. The lone pair on the amide nitrogen would then add to the imine carbon and proton rearrangement would result in **18**. The last product **20** can be hypothesised to have formed by the addition of **18** and **19** (displacement reaction).



Yield of / Reaction	17	18	19	20
1 + $MeNH_2$	36%	-	33%	17%
1 + $EtNH_2$	30%	12%	14%	12%
2 + $MeNH_2$	37%	-	25%	24%
2 + $EtNH_2$	23%	-	20%	13%



Scheme IX

In conclusion, this work has opened up new routes to novel tetracyclic and pentacyclic cage systems. In addition, it has been possible to elucidate the mechanism of three novel rearrangements. The syntheses of numerous new polycyclic cage compounds have been achieved and it is hoped that this will be of use in the future as biologically active agents. This field of study holds a lot of potential which remains to be exploited in the future.