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STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF TAXANE, A PHOTOCHEMICAL APPROACH

City University of New York PH.D. 1985

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STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF TAXANE. A PHOTOCHEMICAL APPROACH

by

JOHN JOSEPH PERUMATTAM

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1985

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

William F. Berkowitz

9/16/85 date

Chairman of the Examining Committee.

18 September 1985

date

David C. Lorle

Executive Officer.

Supervisory Committee.

The City University of New York

THESIS ABSTRACT

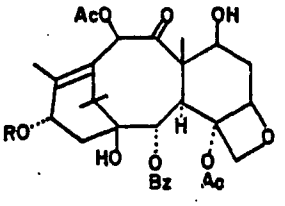
STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF TAXANE. A PHOTOCHEMICAL APPROACH

by

JOHN JOSEPH PERUMATTAM

Adviser: Professor William F. Berkowitz

The de Mayo sequence has been applied to the intermolecular photocycloaddition of various cycloalkenes with homocamphorquinone derivatives to generate a model for the A, B, and C rings of the Taxanes 1.

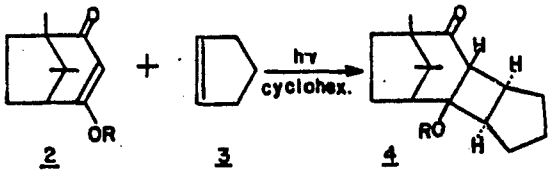


1a: Taxol, R= $C_6H_5CONHCH(C_6H_5)(OH)CHCO-$

1b: Cephalomannine, R= $CH_3CH=C(CH_3)CONHCH(C_6H_5)(OH)CHCO-$

1c: Baccatin III, R=H-

Photoaddition of various cycloalkenes to homocamphorquinone derivatives gave the following results:



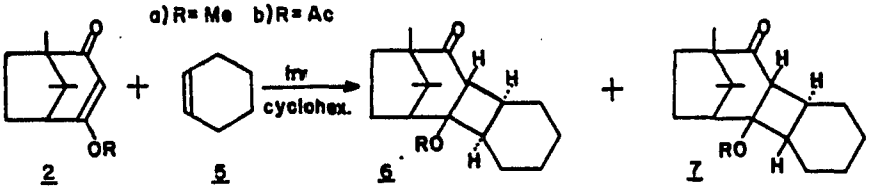
2 3 4

Yields. 4a, 55%; 4b, 50%

6a+7a, 55% (~1/1)

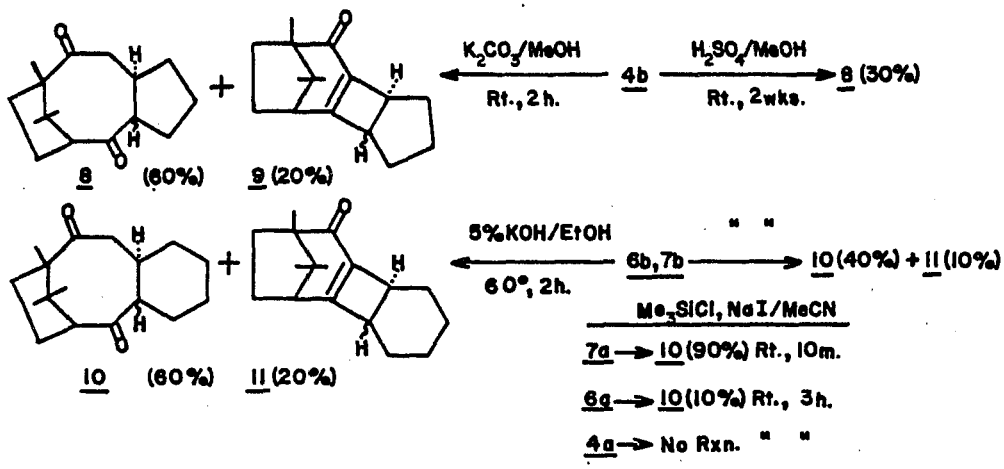
6b+7b, 50% (~1/1)

a) R= Me b) R= Ac

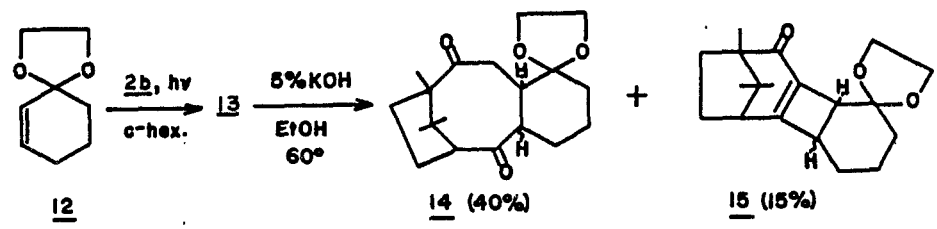


2 5 6 7

Various ring opening reactions of the adducts have been investigated with the following results:



The photoadduct of a ketal also gave two products after hydrolysis:



ACKNOWLEDGEMENTS

I wish to thank Prof. William F. Berkowitz for his help and encouragements.

I also wish to thank Profs. Klaus Grohman, Robert Engel and David C. Locke for their advice and help.

Thanks are due also to fellow friends who made day-to-day life in the laboratory a pleasant as well as educational experience.

Finally, I thank the Department of Chemistry, Queens College, for its financial support.

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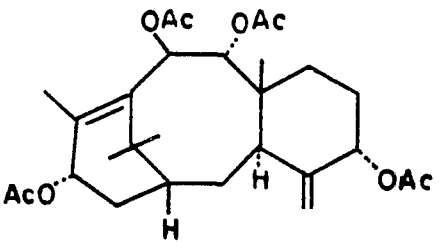
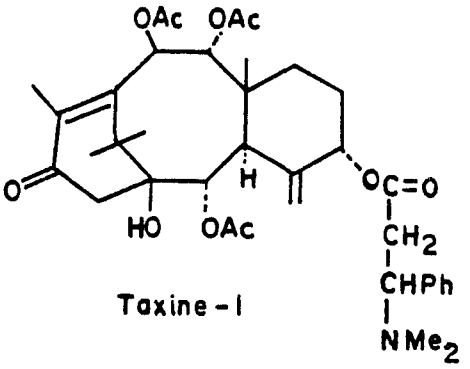
INTRODUCTION

Taxanes[1] are unusually hydroxylated diterpenoids which occur in the plants of the family Taxaceae to which the yew tree (Taxus baccata L.) belongs. Representative members of this class of compounds are shown in Figure 1. Some of its members (Taxol, Cephalomannine) exhibit anti-leukemic and antitumoral activities. A recent review[2] examines the interaction of the novel antimitotic agent, Taxol, with cellular microtubules. Also, in-vitro experiments have shown that less substituted taxane derivatives could also be biologically active[3].

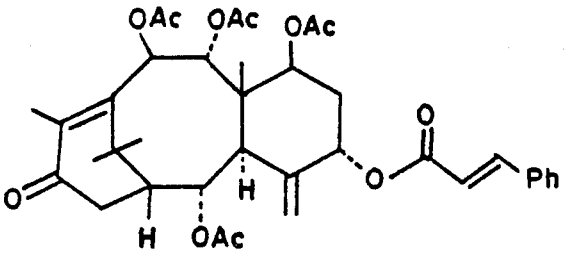
Taxane diterpenes have attracted the attention of synthetic chemists in recent years not only because of their biological activities, but also because of the structural and stereochemical challenges posed by these molecules. The incorporation of a novel methylated tricyclo(9.3.1.$0^{3,8}$)pentadecane skeleton, the presence of a bridgehead double bond[4] (although within the limits of Prelogs extention of Bredt's rule[5]), and the presence of a tertiary hydroxyl group at the A/B ring junction in taxol are some of the novel features of this class of molecules. Hence, various methodologies capable of constructing the basic carbon skeleton (Figure 2) of Taxanes have been developed[6].



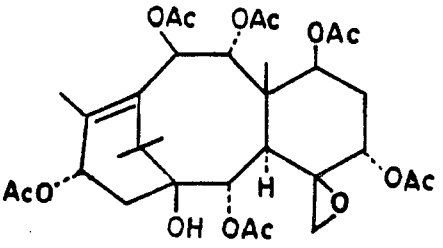
Taxusin



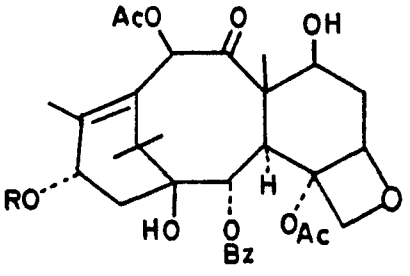
Taxine - I



Taxinin B



1β-Hydroxybaccatin



R= $C_6H_5CONHCH(C_6H_5)CH(OH)CO-$ Taxol

R= $CH_3CH=C(CH_3)CONHCH(C_6H_5)CH(OH)CO-$

Cephalomannine

R= H– Baccatin III

Figure 1

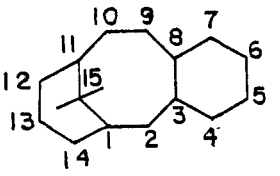
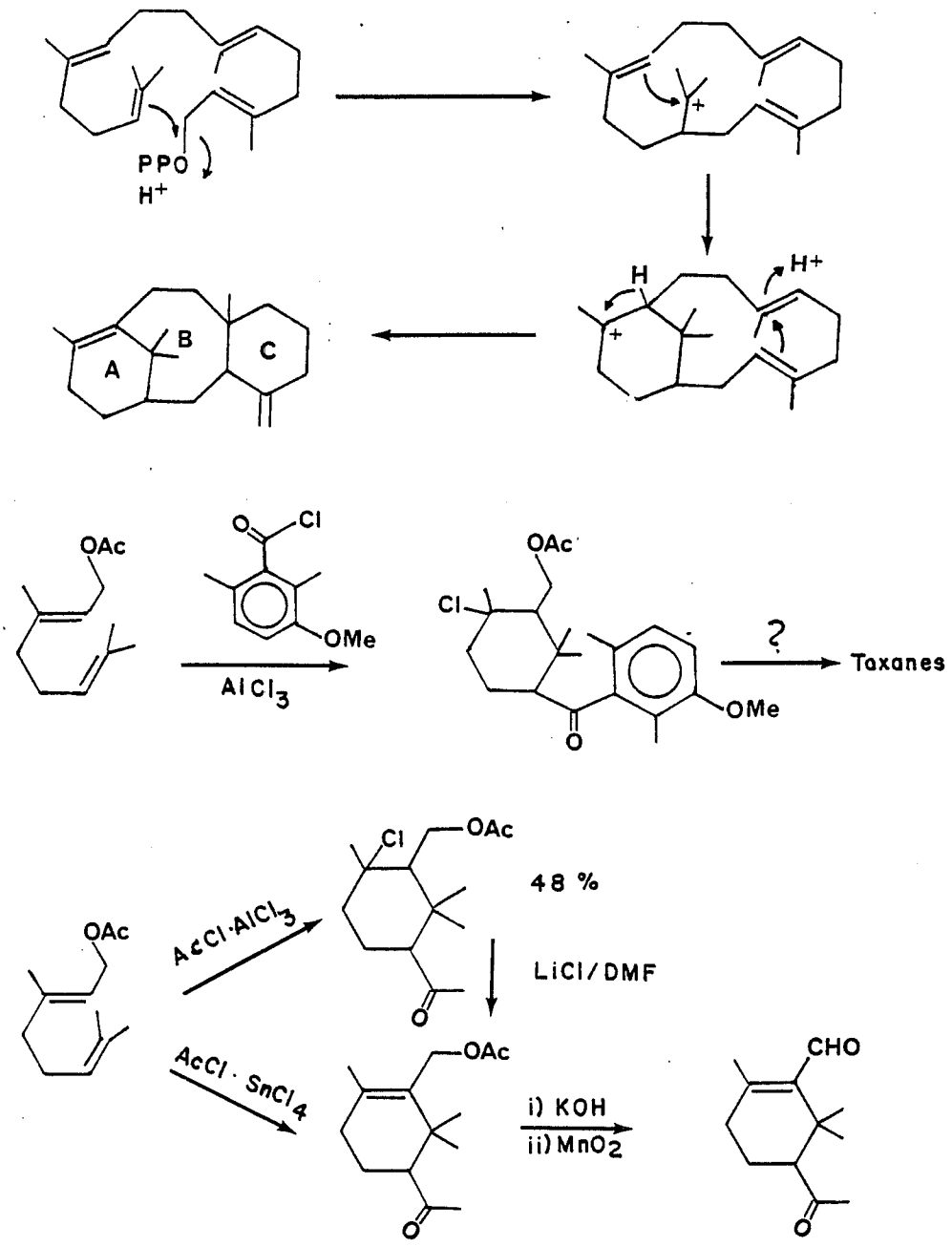


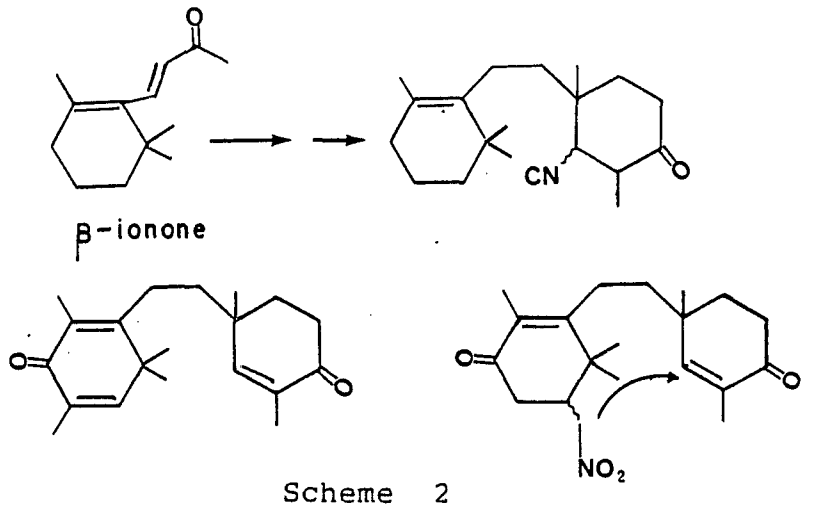
Figure 2

Early synthetic efforts based on biosynthetic pathways were done at the laboratories of S. Kato[7] and Y. Kitahara[8] who investigated the cationic cyclization of geranylgeranic acid derivatives (Scheme 1). Schwartz's group at Florida State University also attempted a biosynthetic pathway using methylgeranylgeranate and the Lucas reagent[6b], but without success. They also attempted an alternate route using bicyclic enone derived from β - ionone (Scheme 2). Various cyclization procedures using derivatized A and C rings were attempted, but without success. Their work showed that generation of the central B ring through C—C bond formation between A and C ring derivatives is not an encouraging strategy in taxane synthesis.

Internal Diels-Alder reaction[6k,6o], enone-olefin (2+2) photocyclization reactions [6q,r], oxy-cope rearrangement[6h], fragmentation reactions[6i], etc. are some of the general methodologies developed in pursuit of taxane synthesis.

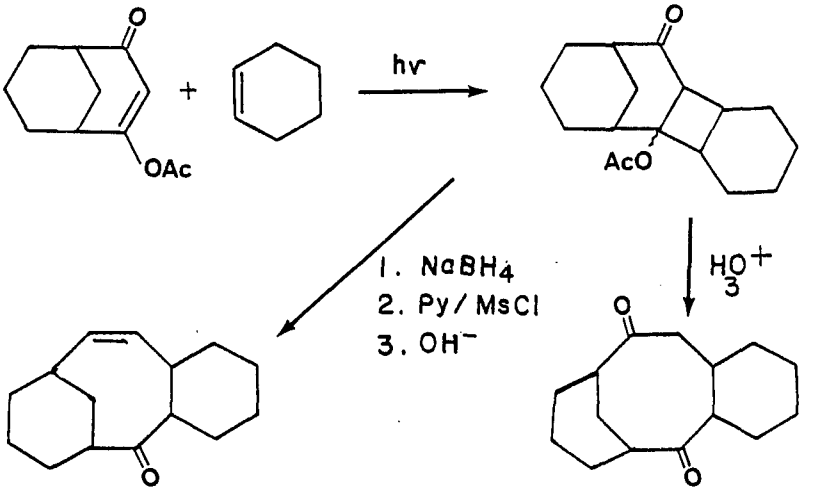

PPO
H+
H
H+
A
B
C
OAc
Cl
OMe
AlCl3
OAc
Cl
?
Taxanes
OMe
OAc
AcCl·AlCl3
Cl
OAc
48 %
LiCl/DMF
AcCl · SnCl4
OAc
i) KOH
ii) MnO2
CHO

Scheme 1



Scheme 2

Our synthetic approach to the taxanes is based on the idea that the photochemical [2+2] cycloaddition of a bicyclo(3.3.1)enone system to a cyclic alkene followed by retro-aldol reaction of the butanol intermediate should provide the tricyclic carbon skeleton of taxanes (Scheme 3).



Scheme 3

Since our work has begun two similar photochemical approaches to the taxanes have been published[6p,6q]. First we will look at the enone-olefin photoaddition reaction in detail and then its utilization in taxane synthesis.

1. Enone Photochemical Cycloaddition in Organic Synthesis

The early investigations of the [2+2] photoreaction were carried out by de Mayo,[9] Corey,[10] and Eaton,[11] who suggested its synthetic potential. Since that time many papers have dealt with the reaction mechanism and its scope and limitations in synthesis, and many examples of its application for the preparation of natural products have appeared. Various aspects of the reaction have already been reviewed[12].

2. The Reaction Mechanism

Generally, photochemical processes are initiated by electromagnetic radiation with wavelengths in the visible and ultraviolet regions of the spectrum (200-700 nm). Light absorption by the molecule results in the promotion of one electron from the bonding π-level to the anti-bonding level. This spectroscopic transition is called a π, π^* transition and, for ethylene, occurs at approximately 180 nm.

When molecules contain an atom with an unshared pair of electrons (oxygen, sulfur, nitrogen), another excitation of an electron is possible, i.e., excitation of one of the nonbonded electron to some higher energy level. A good example are carbonyl compounds which possess a π,π^*-transition of the π-electron as in the case of ethylene. The second transition results from the excitation of one of the non-bonded electrons of the oxygen atom to the antibonding π^* state. This transition is called n,π^* transition. The photocycloaddition of conjugated enones is of interest because either n,π^* or π,π^* states may be involved. In fact, experimental evidence indicates that either or both states may be active under certain conditions. A complicating feature in interpretation of the photocycloaddition reactions of enones is the lack of a definitive means of assigning an appropriate configuration to their lowest excited states. It appears that although the n,π^* state is usually lowest in the singlet manifold, either the n,π^* or π,π^* state may be lowest in the triplet manifold.

If we postulate that the n,π^* state of the enone will behave analogously to the n,π^* states of ketones and that π,π^* states of enones will behave analogously to those of conjugated ethylenes, then we can generate a paradigm for the photocycloaddition reaction of enones (Figure 3). It appears that intersystem crossing is efficient for con-

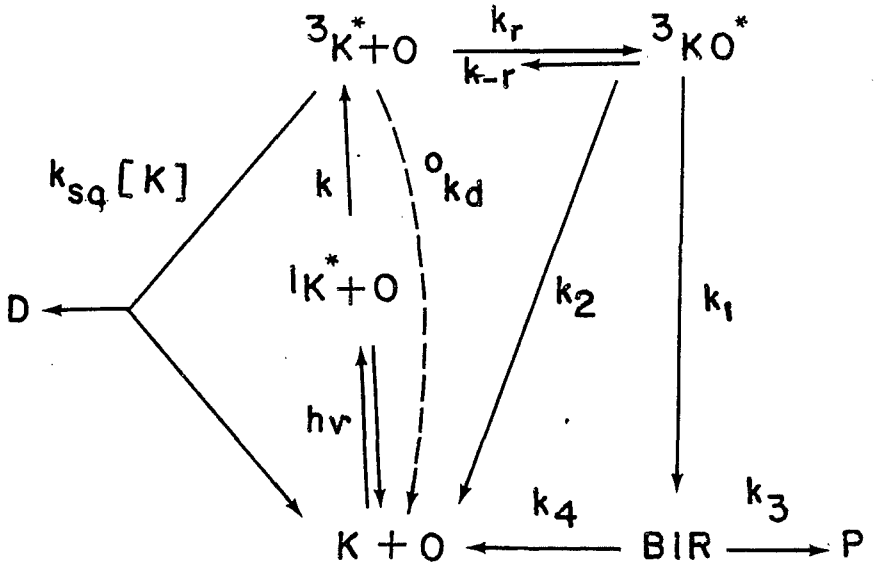
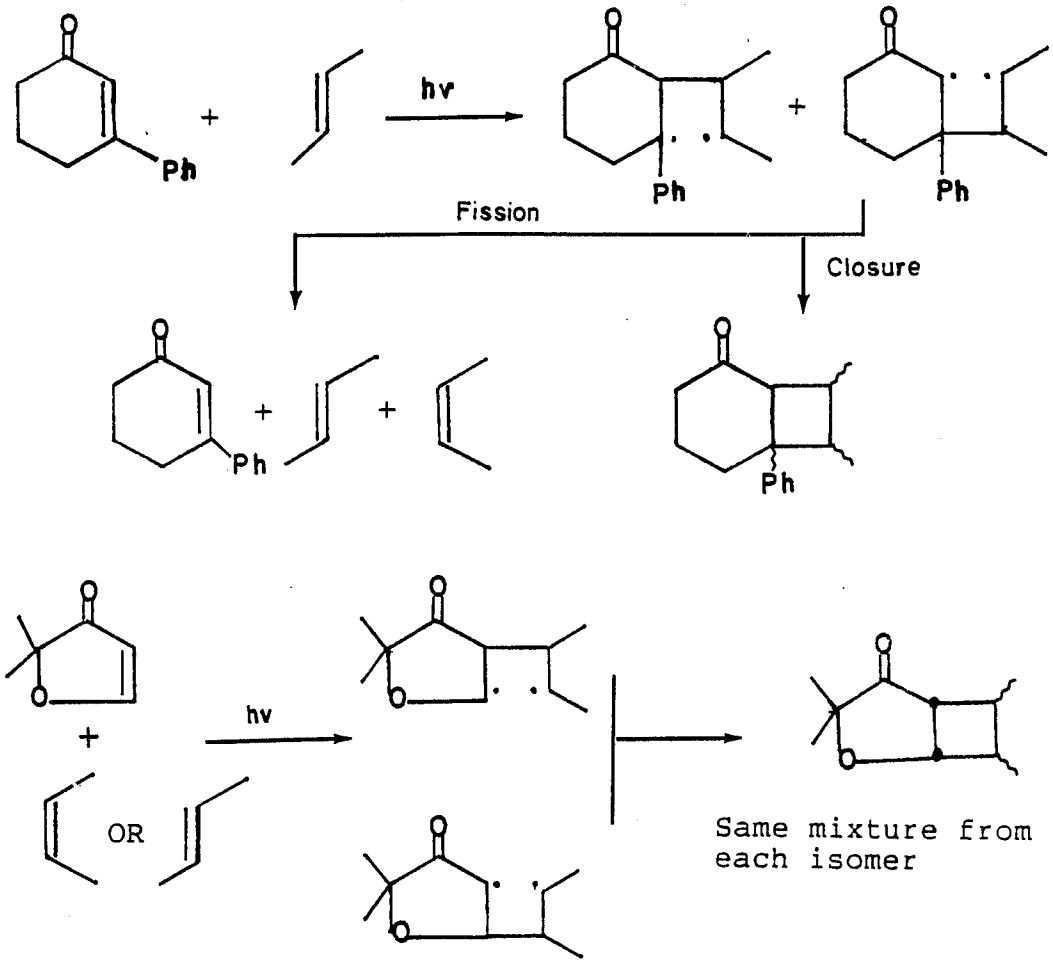


Figure 3. Mechanistic scheme for enone cycloaddition: K, enone; O, olefin; $^1K^*$, singlet excited state of enone; $^3K^*$, triplet excited state of enone; $^3KO^*$, triplet exciplex intermediate; BIR, biradical intermediate; P, enone/alkene adduct; D, dimer adduct.

jugated enones so that T_1 is a likely candidate for the active excited state in photocycloadditions, and the enone (2+2) cycloaddition giving a cyclobutane proceeds through a triplet biradical intermediate. The generally accepted model for enone cycloaddition as originally proposed by Corey[10] and in more detail by de Mayo[13] is shown in Figure 3. The singlet excited state $^1K^*$ of the enone undergoes intersystem crossing to produce a triplet state $^3K^*$. The bimolecular fate of $^3K^*$ includes quenching by ground-state enone molecule and excited complex (exciplex) formation with alkenes. Self-quenching by enone molecules can

lead to dimer formation (which is essentially a special case of enone cycloaddition[14]). The exciplex ($^3KO^*$ in Figure 3) can decay back to the ground-state components or to a triplet biradical intermediate (BIR), which must then undergo spin inversion before closure to give the cyclobutane products, or fission to give back the starting enone and olefin. The evidence for a biradical intermediate in enone cycloaddition is firmly based.

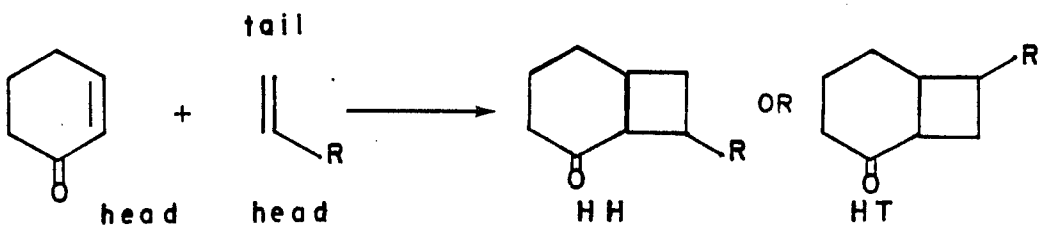


Scheme 4

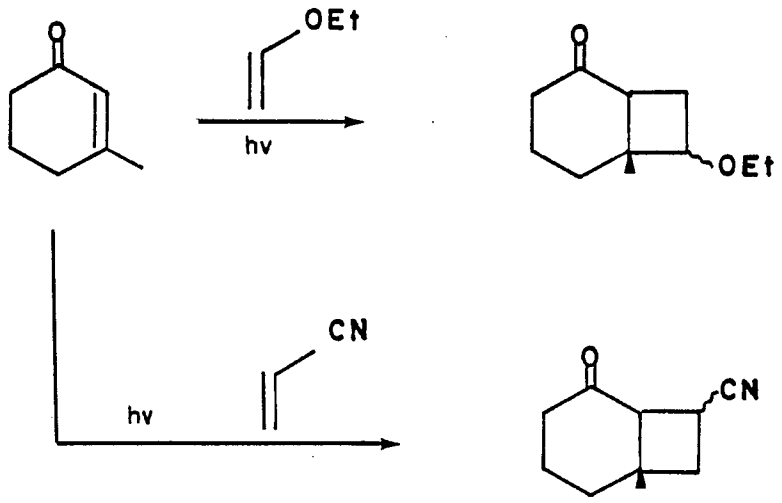
One piece of chemical evidence for the intermediacy of biradicals in these systems is the observation of isomerised unreacted olefin[15], and the formation of similar mixtures of products when starting from either pure cis or pure trans olefin[16] (Scheme 4). The isomerized unreacted olefin is presumed to be formed by fission of the intermediate biradical which has a long enough lifetime to allow rotational equilibration around what was the olefinic double bond. The formation of identical mixtures of cyclobutane isomers from either the cis or trans isomer is similarly explained by rotational equilibration in the intermediate diradical.

3. The Regiochemistry of Enone Cycloaddition

For the synthetic chemist a knowledge of those factors which govern the regiochemistry and stereochemistry of cyclobutane formation is of prime importance in developing a synthetic scheme. The two possible orientations for the addition of an enone to an unsymmetrical alkene are commonly refered to as the head-head (HH) and head-tail (HT) regioisomers respectively, with the "head" of the enone being the carbonyl group and the "head" of the alkene being the more substituted of the alkene carbons.

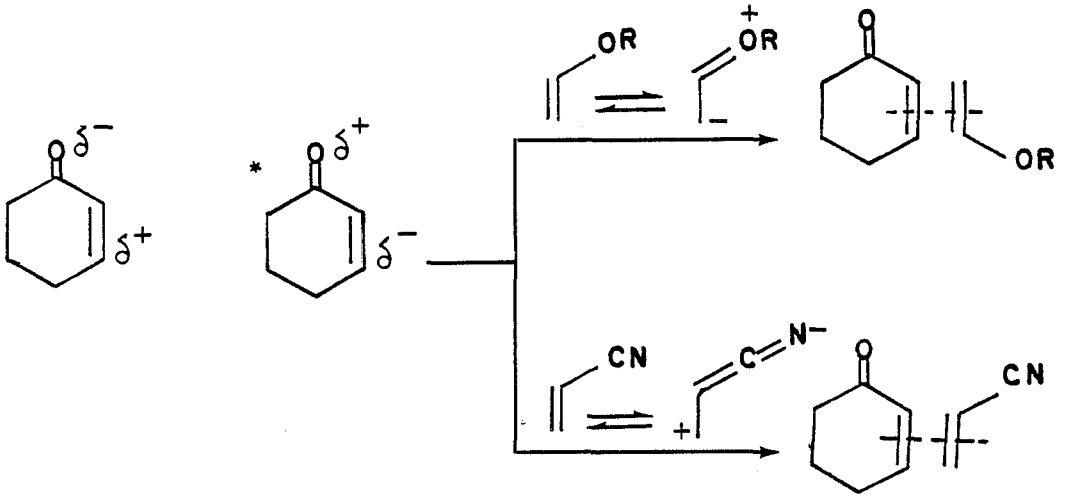


It was demonstrated by Corey[10] that electron-rich alkenes will give rise to a head-to-tail isomer and electron-deficient alkenes will give a head-to-head isomer.



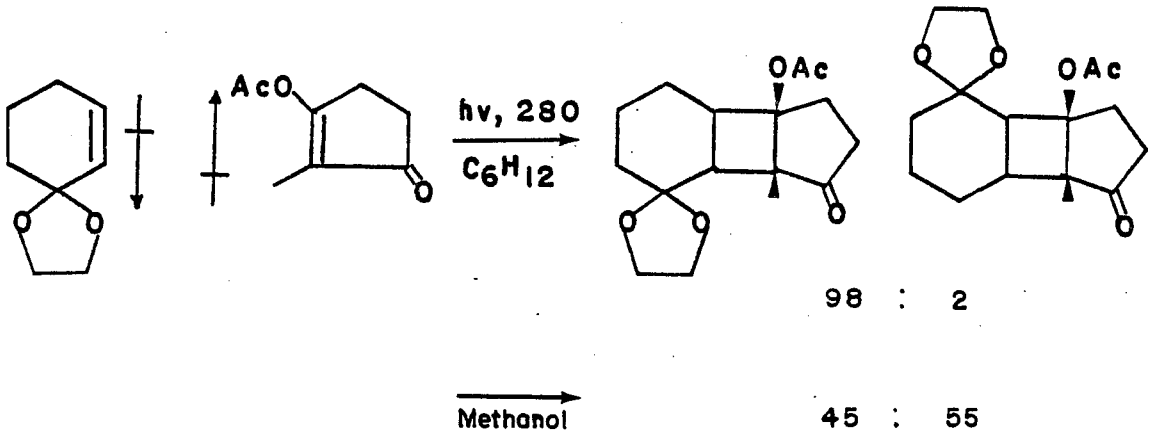
Orientational preferences in the exciplex derive largly from a charge distribution in the excited triplet n, π^* or π, π^*) states which renders C_β somewhat negative relative to C_α, in contrast to the ground state situa-

tion. Several sets of calculations have provided verification of the excited state charge distribution[17]. Corey proposed that the more favorable orientation of the π-complex is that in which the dipole of the alkene is opposed to that of the excited enone (Scheme 5).



Scheme 5

Dipole-dipole interaction of the type postulated by Corey[10] should be subject to solvent effects; this has been treated quantitatively by de Mayo[18] who found that in polar solvents, with their higher dielectric constants, this interaction is decreased, and thus the regiochemistry of cycloaddition is lost. De mayo related the efficiency of the interaction to a function of the dielectric of the medium using an approach originally devised by Kirkwood and Onsager[19] and applied by Berson[20] to the Diels-Alder reaction. It was shown for two systems that the ratio of

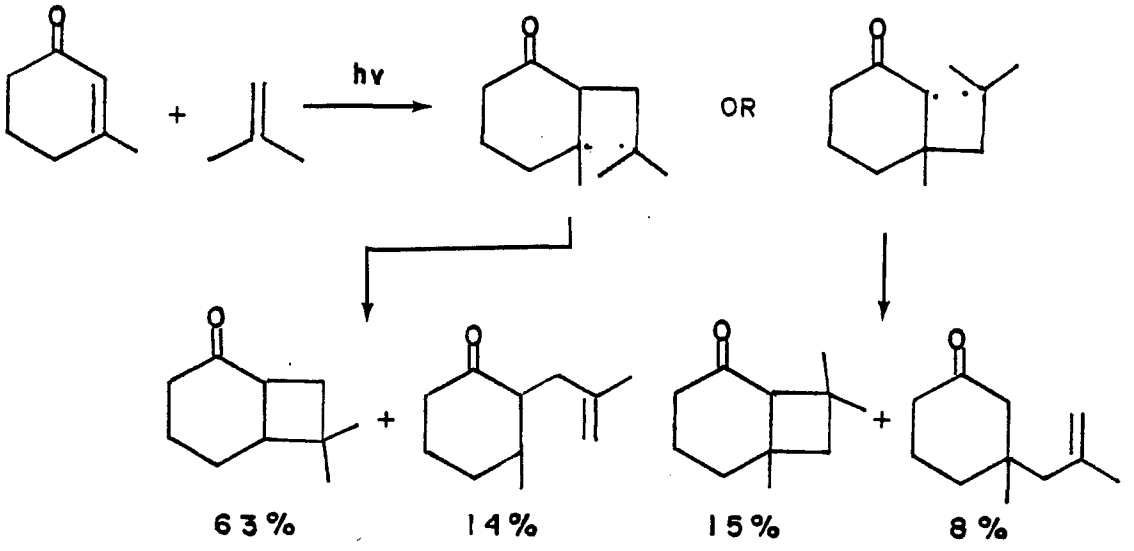


Scheme 6

regioisomeric adducts does correlate with the Kirkwood-Onsager function of dielectric constant.[21]

These studies demonstrate that in order to maximize the proportion of adduct predicted by the Corey rule a nonpolar medium should be used, and conversely enrichment of the isomer with the opposite orientation is expected in a highly polar medium (Scheme 6).

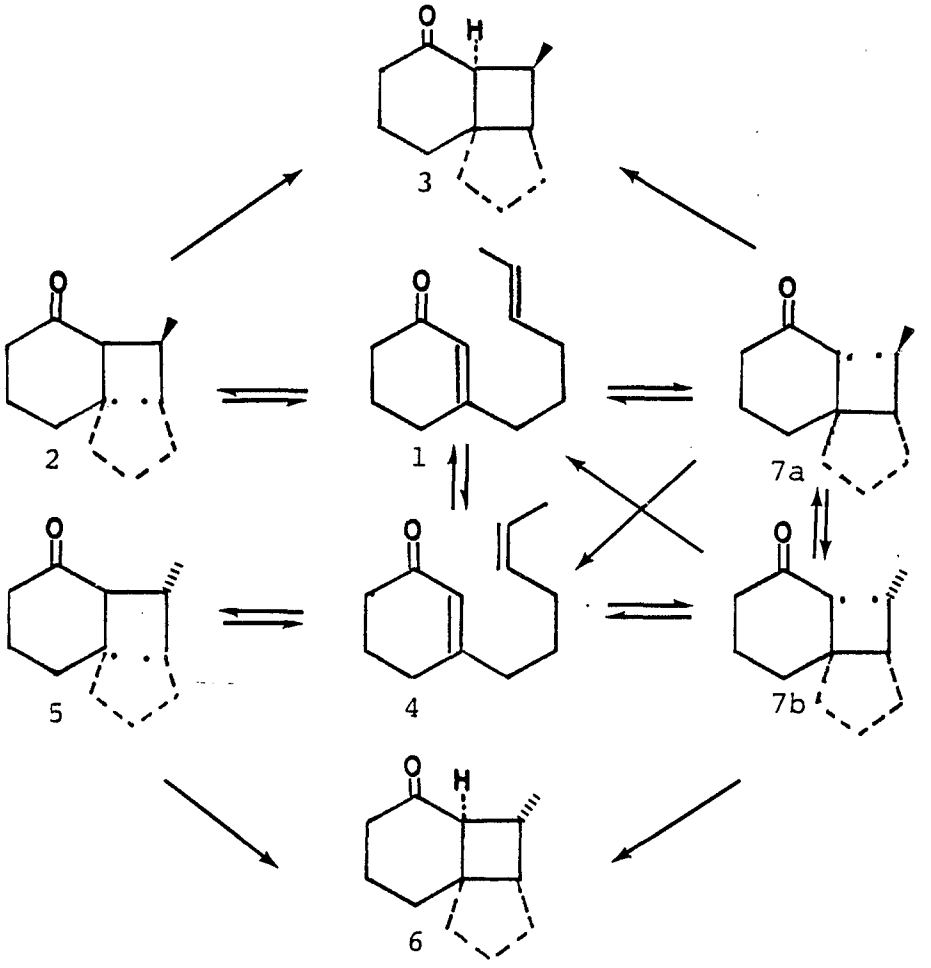
Evidence has been presented to suggest that for simple enones the first bond is formed at the β-position[22] (although some of these results have been shown to be incorrect). The frequent observation of olefinic products which appear to be derived from bonding at either the α-position and β-position indicates that in all probability the initial bonding can be at either position with the



Scheme 7

relative proportion depending upon the the structures of the enone and alkene involved (Scheme 7).[23]

From an investigation[24] of the intramolecular [2 + 2] photocycloaddition of E and Z olefins to cyclohex-2-enone it was concluded that the bond to the β-carbon in the cyclohexene was formed first to give the diradical intermediate (Scheme 8). The approach was based on product analysis. If the photocycloaddition of the E isomer (1) occurs either via concerted mechanism or by the formation of the first bond to C(2) leading to diradical (2), product (3) is to be expected. On the other hand the Z isomer (4) will form the product (6), via a concerted

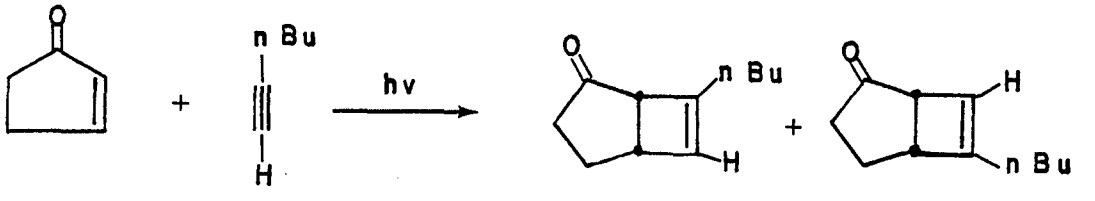


Scheme 8

mechanism or diradical (5), If the first bond is formed to C(3), both (1) and (4) will form the equilibrating diradicals (7a) and (7b) which will leads to a mixture of two stereoisomers (3) and (6). Irradiation of (1) produced, in high yield, a mixture of (3) and (6) in 1:1

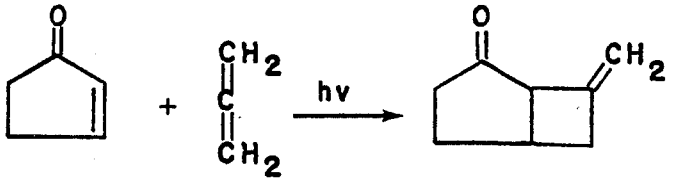
ratio, and precisely the same mixture was formed when (4) was irradiated. This results show that the bond to the β-carbon is formed first during photoaddition reaction.

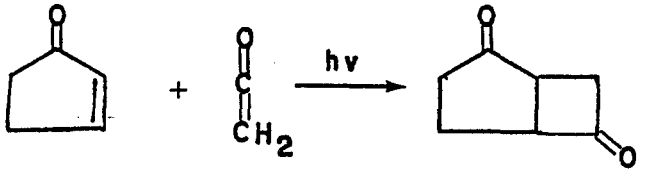
Unsymmetrical alkynes tend to add to enones to give the head-to-head isomer preferentially, a reverse of the comparable enone--alkene cycloadditions.[25] The results of calculations suggest that this is still consistant with the major product arising from the more stable exciplex formed between the ground-state alkynes and π,π^* triplet excited state of the enone. This is supported by the observation of a correlation between the Kirkwood--Onsager function of solvent dielectric and the regioisomeric ratio for alkyne additions; this correlation indicates that the proportion of head-to-head isomer increases at lower solvent polarity where the exciplex effect would be more pronounced.



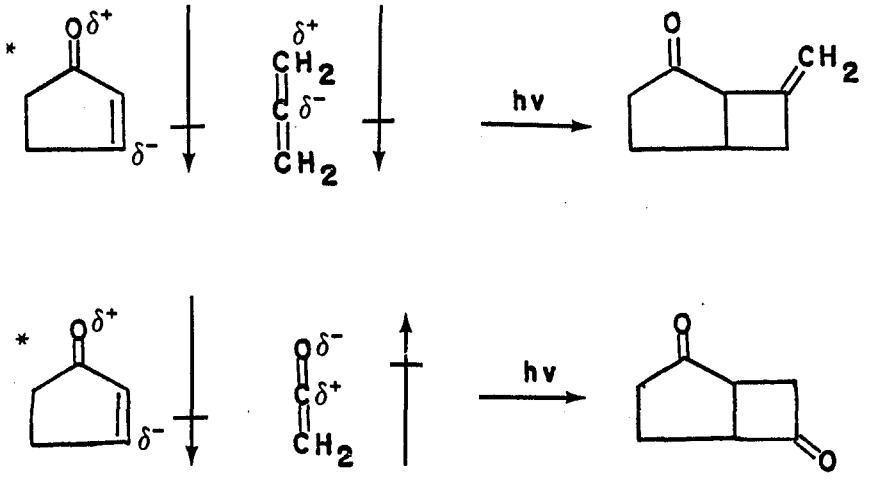
69 : 31. 35%

Allenes[26] and ketenes[27] add to enones with predictable regiochemistry. Allenes add to enones in the opposite regiochemical sense to alkenes, giving the head-to-head adducts with very high selectivity, whilst ketenes have been shown to give the head-to-tail product preferentially.





In the excited state C_β carbon of enone has a larger coefficient in the HOMO. In the LUMO of allene the end carbon carbon has a larger coefficient. If HOMO-LUMO interaction is taken into consideration in photochemical reaction the regiochemistry of the product can be predicted. In the case of ketenes the central carbon has a larger coefficient in the LUMO, thence a reverse regiochemistry is observed. The dipole-dipole orientational preference in the exciplex formation, as predicted by Corey, is also in agreement with the above theory (Scheme 9).



Scheme 9

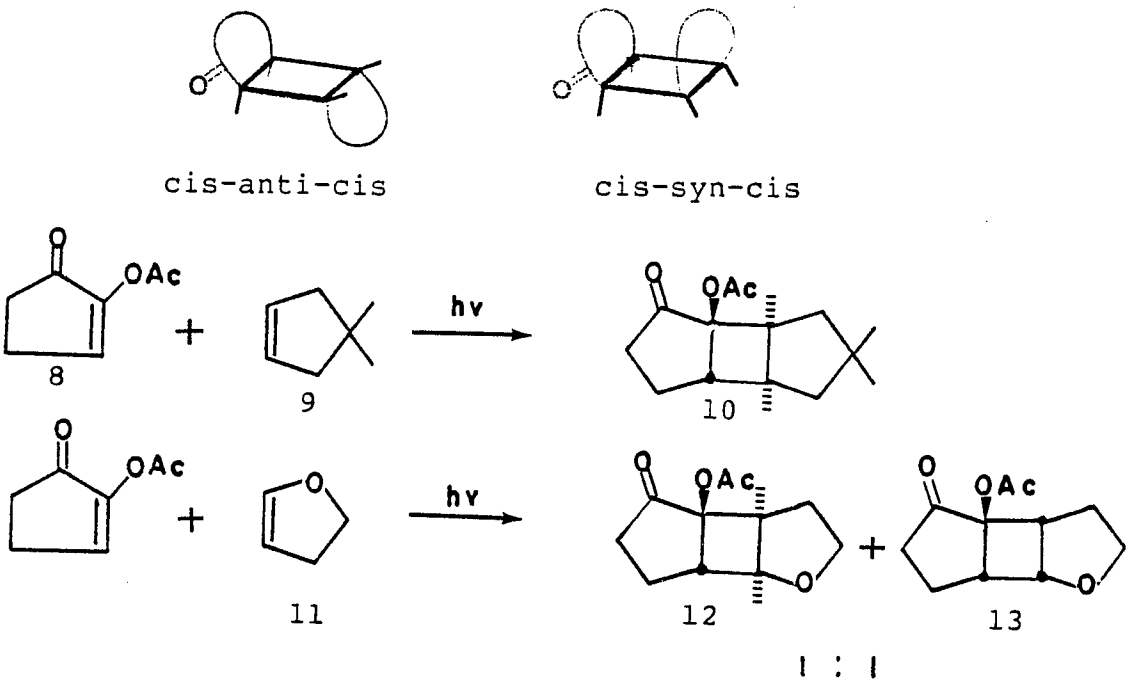
The regiochemical outcome of a number of enone cycloadditions have been altered, and in some cases reversed, by performing the reaction in micellar media.[21]

4. Stereochemistry of Enone Cycloaddition

Cyclobutane ring fusion can be cis or trans on either side; groups Y can be endo, exo or cis, trans to each other. Obviously a large number of isomeric products can arise from cycloaddition reactions; however, usually not all possible products are produced, and it is often

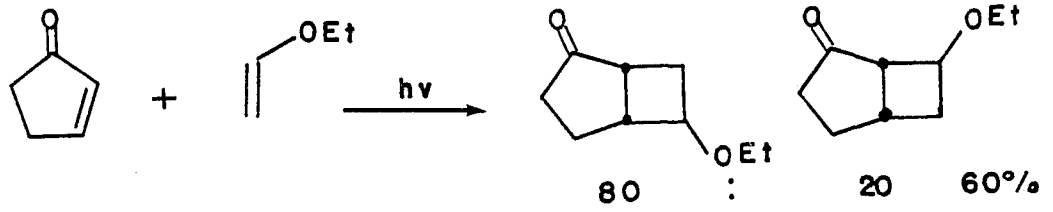
possible to predict the stereochemical outcome of an enone addition. Some generalizations concerning the stereochemistry have been listed below.

The stereochemical disposition around the cyclobutane ring for cis fusion of alkenes will give rise to cis-syn-cis and cis-anti-cis isomerism. There is usually a marked propensity for the anti configuration, although structural features can affect the results. The addition of 2-acetoxycyclopentenone 8 to 4,4-methylcyclopentene 9 leads to nearly exclusive formation of the anti adduct 10, while dihydrofuran 11 gives nearly equal amounts of the syn and anti isomers 12 and 13 (Scheme 10).

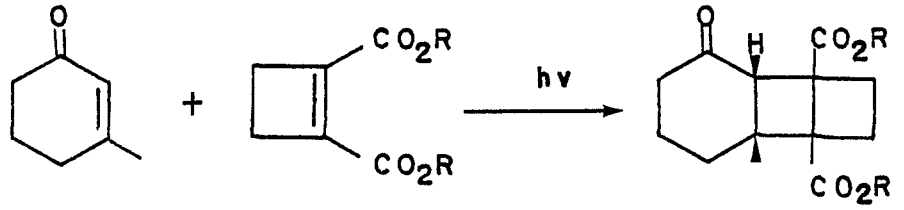


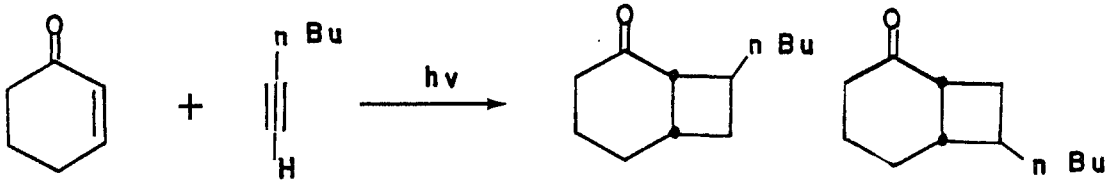
Scheme 10

In the product from addition of cyclopentenone to alkenes, the cyclopentenone-cyclobutane ring fusion is always cis.



Similarly, in the product from the addition of cyclohexenone to alkynes, allenes, and cyclobutenes, the cyclohexanone-cyclobutane ring fusion is always predominantly cis. However, in the product from addition of cyclohexenones to other alkenes, the cyclohexanone ring fusion can be either cis or trans, and both configurations are often observed. For highly electron-rich and electron-deficient alkenes the cis isomer predominates.





88 : 12

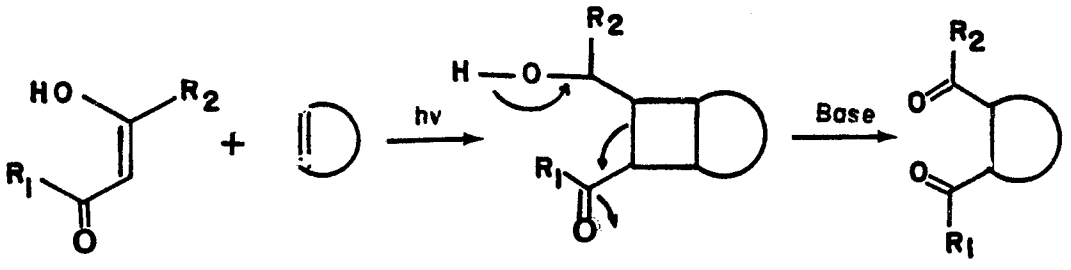
There is also evidence that cyclohexenones possessing charge or radical stabilizing functions at position 3 also give mainly cis-fused products. More rigid cyclohexenones also show a tendency to give cis-fused rings.

In the adducts between enones and 1,2-disubstituted, cyclic alkenes the geometry of the alkene double bond is usually lost, giving a mixture of two isomers. Similarly, addition of a monosubstituted alkene to an enone gives a mixture of adducts in which the sustituent is exo or endo, often in approximately equal amounts.

Enones with non-equivalent double faces usually give as the major product of photoaddition the one arising from the least hindered mode of approach.

5. The de Mayo Reaction

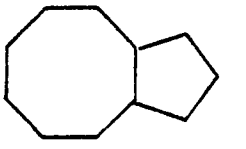
Photochemical [2+2] cycloaddition of an enolized 1,3-diketone to an alkene, followed by retro-aldol reaction of the 2-acylcyclobutanol intermediate to generate a 1,5-diketone is called the de Mayo reaction.



Both inter- and intramolecular variants of the de Mayo reaction have been widely used in synthetic efforts devoted to a large number of natural products.[12]

6. Application of de Mayo Reaction in Organic Synthesis

Bimolecular enone-olefin photoadditions have been applied successfully to the synthesis of a large number of organic compounds. Here we would limit our discussion to the application of the de Mayo reaction in the preparation



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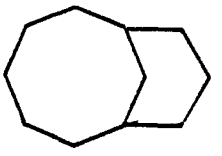

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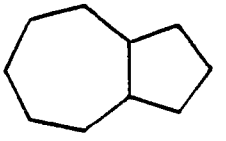

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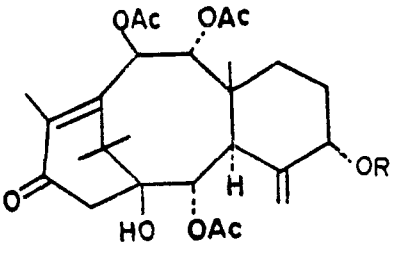

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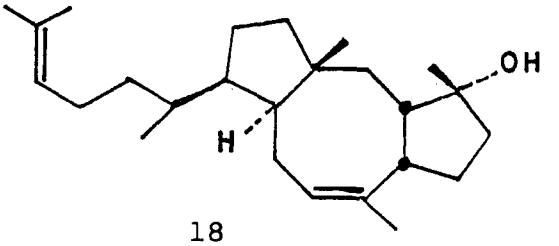

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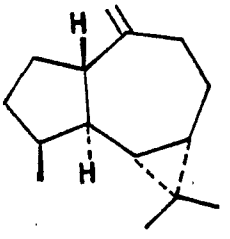

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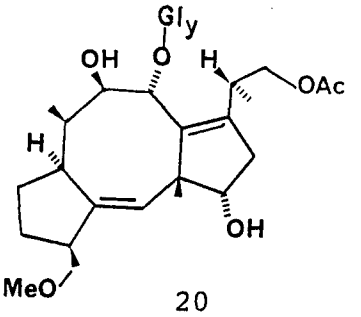
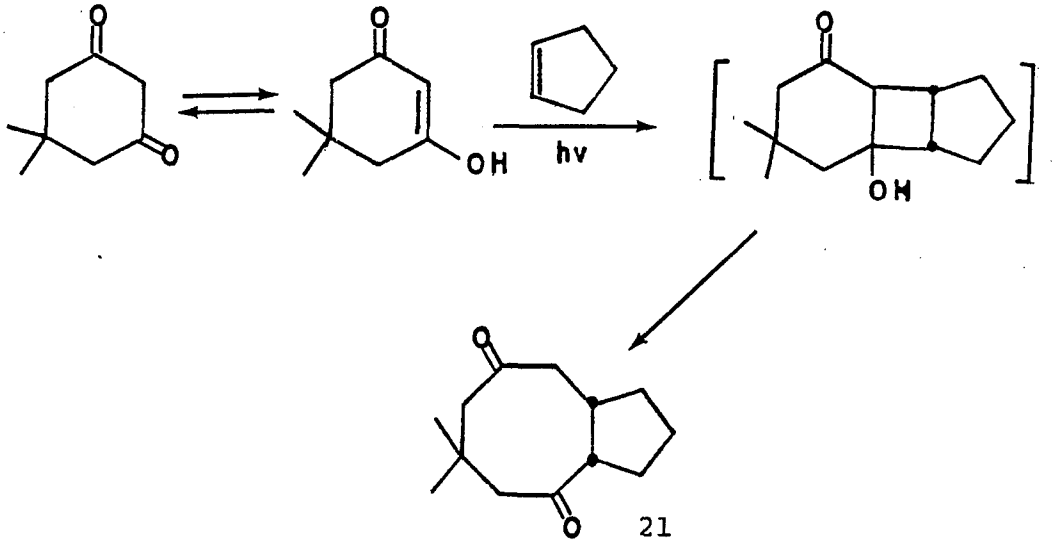


20

Scheme 11

of medium ring compounds (7 and 8-membered rings). The de Mayo reaction has been directed toward the synthesis of the bicyclo[6.3.0]undecane (14), bicyclo[5.3.1]undecane (15), and bicyclo[5.3.0]decane (16) ring systems found in a range of interesting natural products including Taxanes (17),[1] Ophiobolins (18),[28] Arromdendrene (19),[29] fusicossin (20),[30] etc.[31] (Scheme 11).

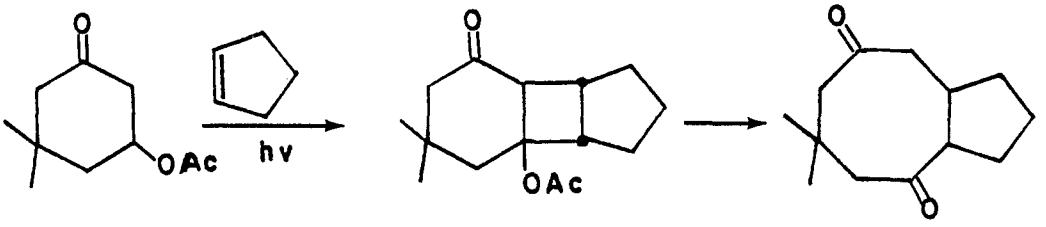
When cyclohexane-1,3-dione (which exists in equilibrium with the corresponding 3-hydroxycyclohex-2-ene-1-one) is irradiated in the presence of an alkene the adduct formation is efficient, and the intermediate undergoes spontaneous retro-aldol opening to a cyclooctanedione 21.



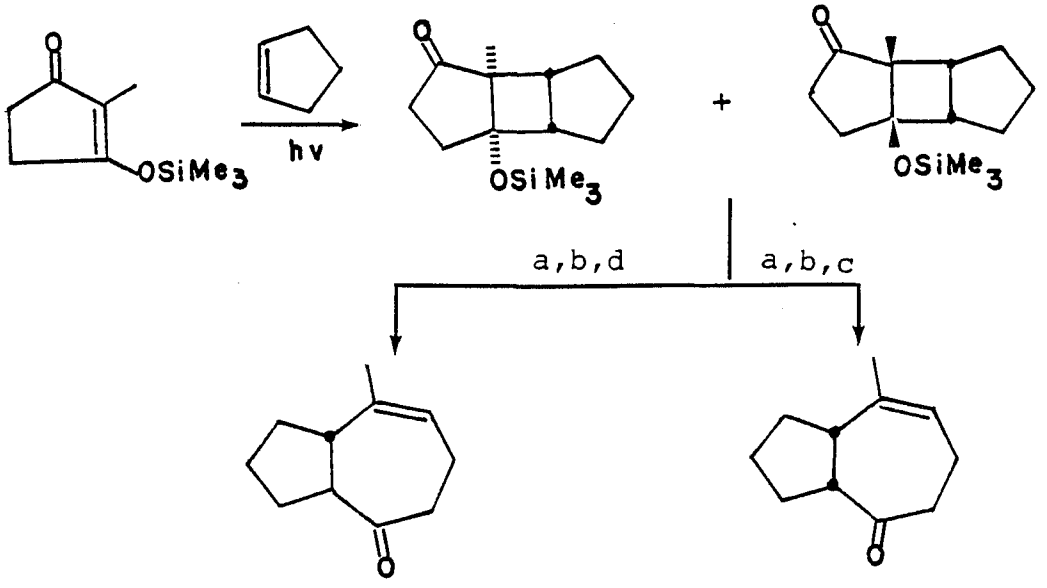
21

Because cycloalkane-1,3-diones are rather insoluble in typical non-polar photochemical solvents, it is fre-

quently advantageous to use the acylated analog; however epimerization of the diketone product then become unavoidable during hydrolysis of the acyl group.



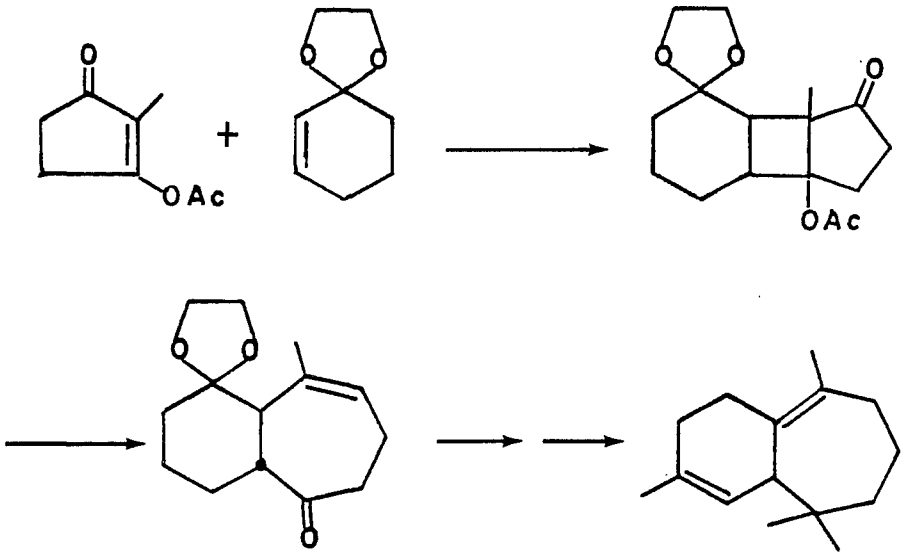
This problem has been overcome by silylating rather than acylating the enol[32] (Scheme 12).



a) LAH, b) MsCl, c) KF, d) base

Scheme 12

The synthesis of β-himachalene 22 makes use of solvent effects upon regiochemistry described in an earlier section,[33] and the recent synthesis of the fungal metabolite hirsutene 23 utilizes the same photoreaction.[34]



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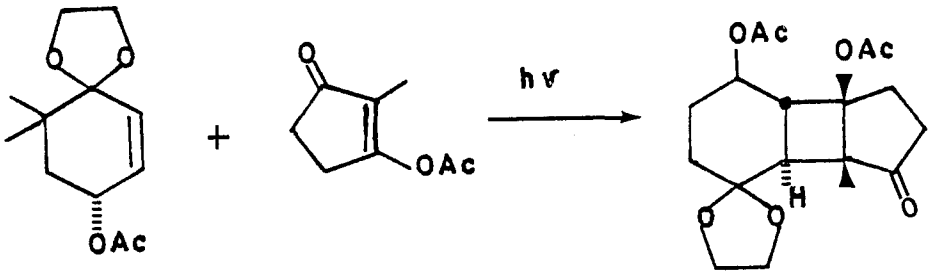
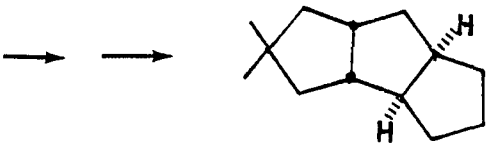
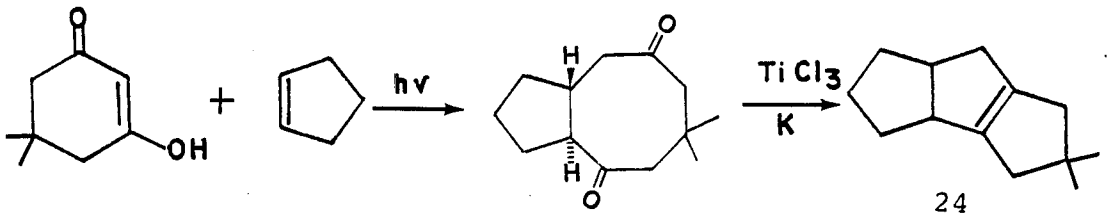




23

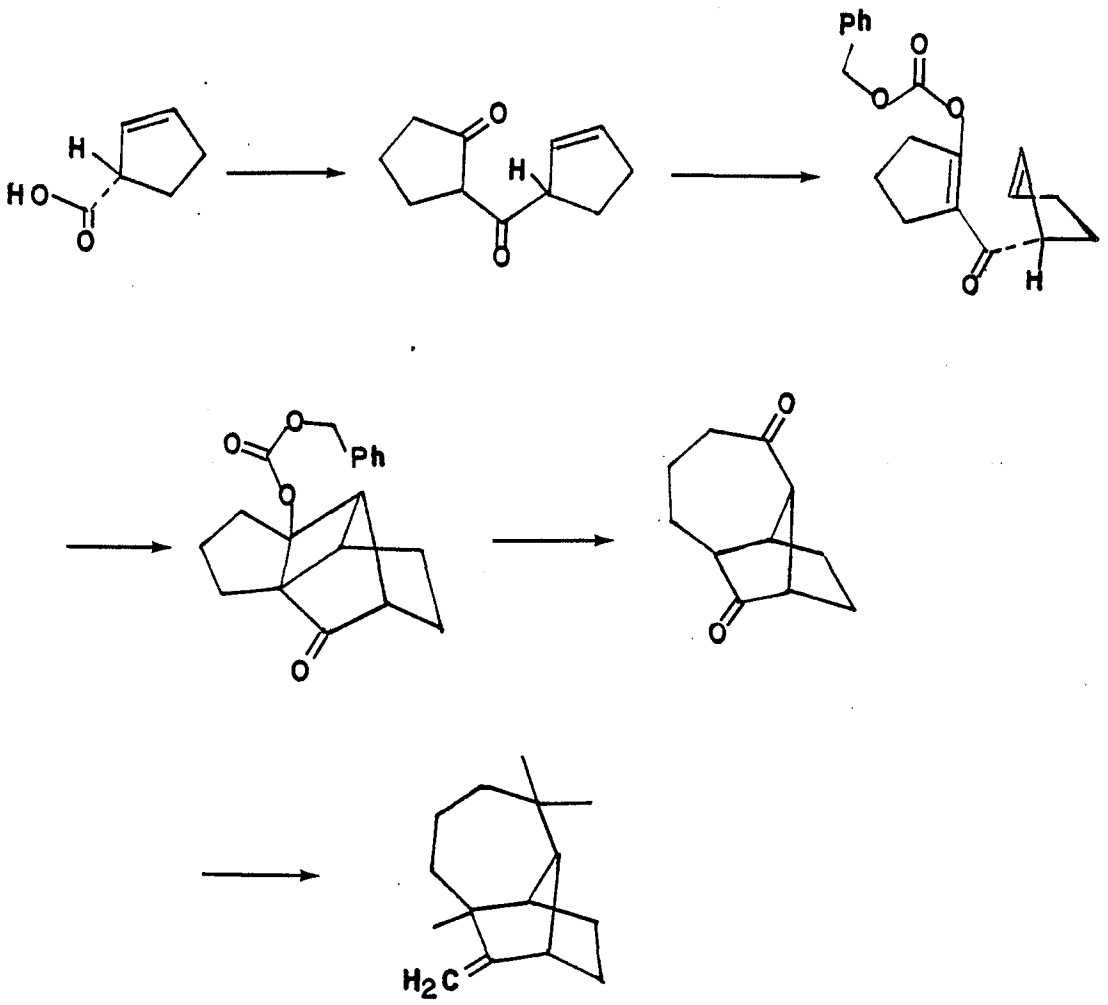
A much shorter route to the hirsutene skeleton (24), also using a de Mayo sequence, is shown below:[35]



24

7. Intramolecular Enone Cycloadditions

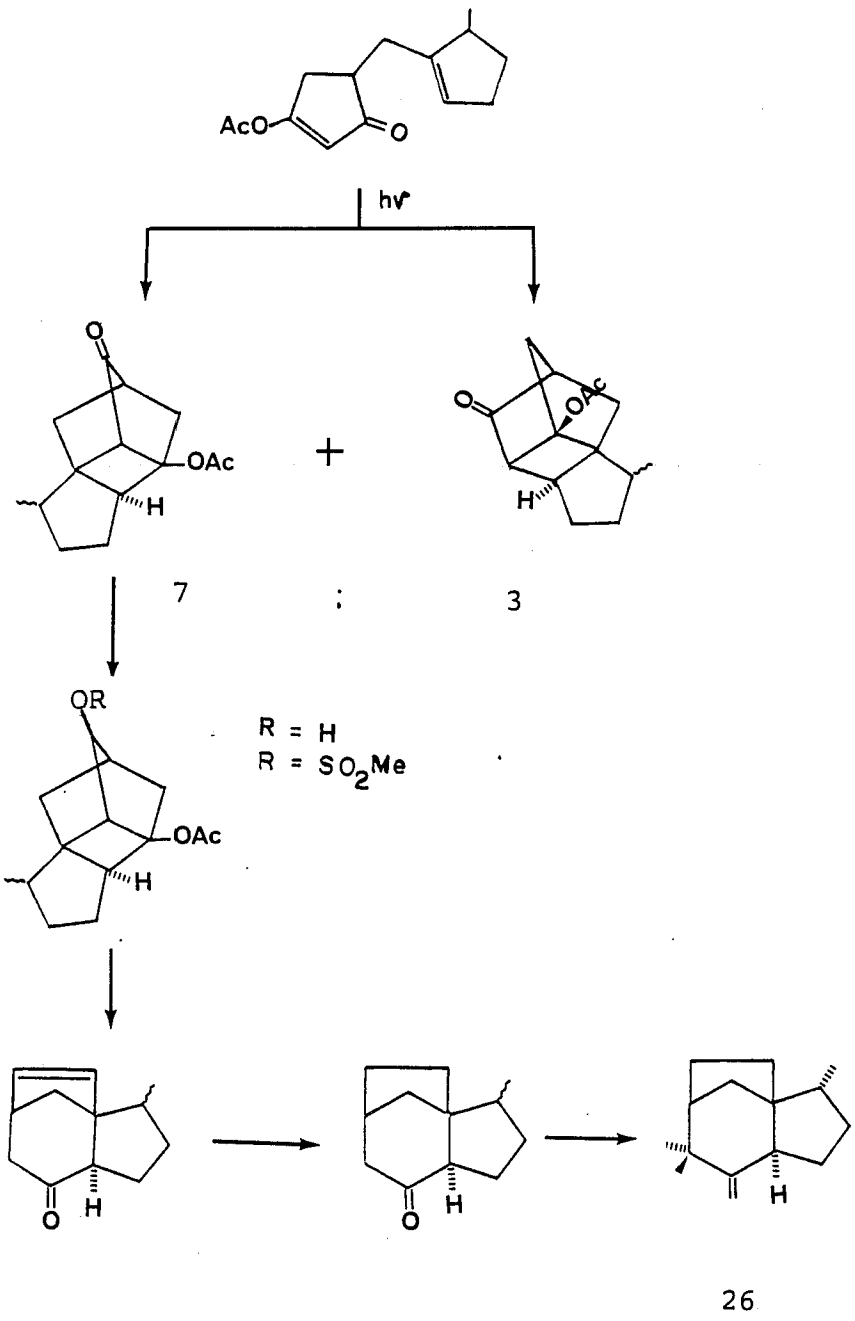
The regiochemistry of the intramolecular addition appears to be quite predictable. Thus in the absence of special constraints, the favored ring system will be that derived from an initial 1,5-addition of the triplet T_1 to form a diradical possessing a five-membered ring (if five-membered ring formation is impossible, a six-membered ring is next favored). This " rule of five", noted first by Srinivasan[36] and Hammond[37] and further established particularly by Wolff and Agosta,[38] depends obviously on entropic factors. Early work on intramolecular enone olefin reactions was done at the laboratories of Corey,[10] Eaton,[11] and de Mayo.[9] Oppolzer[39] and Pattenden[40] demonstrated the synthetic utility of intramolecular [2+2] cycloaddition reactions during synthetic investigations of longifolene (25) and zizaene (26) (Schemes 13 and 14).



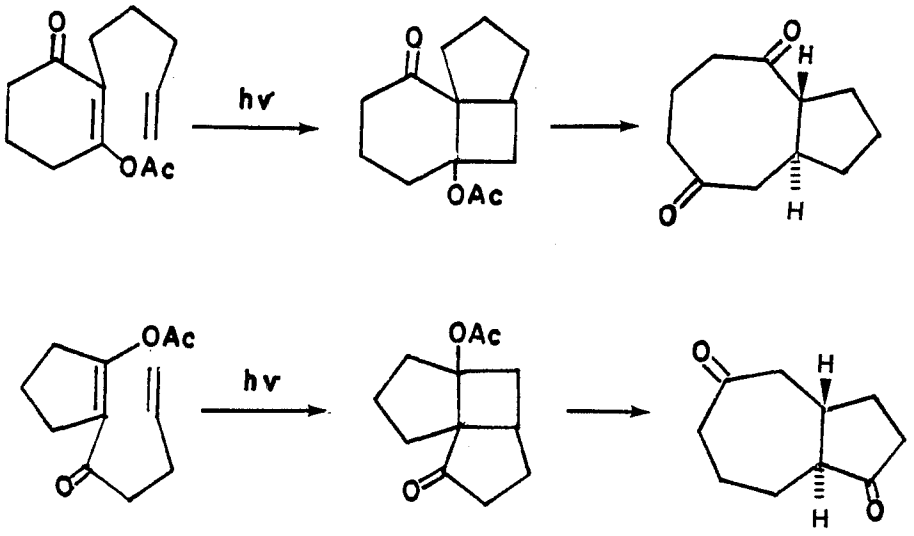
25

Scheme 13

Examples of intramolecular enone cycloaddition obeying the "rule of five" and involving cyclohexane-1,3-dione and cyclopentane 1,3-dione derivatives are shown below[40] (Scheme 15). Hydrolytic cleavage using ethanolic potassium hydroxide gives rise to corresponding diketones.

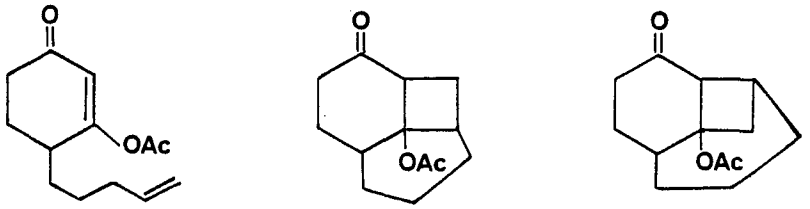


Scheme 14

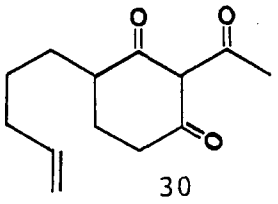


Scheme 15

Irradiation of isomeric enolacetate 27 led to two photoadducts 28 and 29 resulting from intramolecular photoaddition, and to trione 30 produced via photo-Fries rearrangement[31] (Scheme 16).



27 28 29

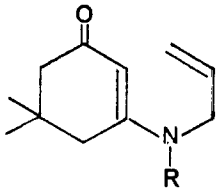


30

Scheme 16

8. Heterocycle Formation

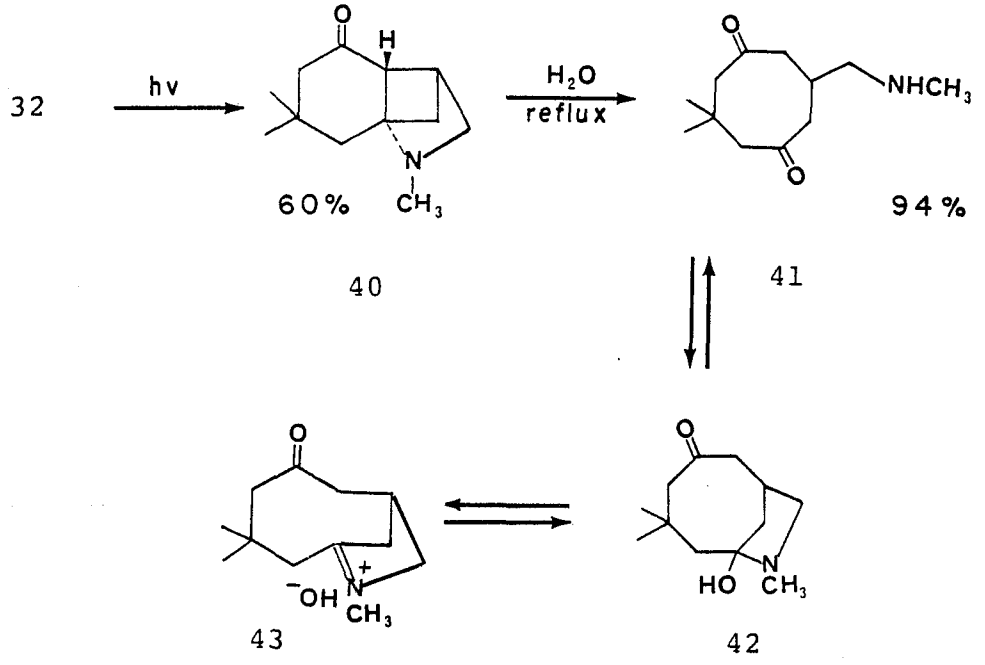
Tamura et al.[41] prepared 2-aza- and 2-oxabicyclo-[2.1.1] hexanes ring systems by photochemical reaction of the corresponding dimedone derivatives. 3-Allylamino-2-cyclohex-1-ones (31-34) were readily obtained from dimedone and the corresponding allylamines (36-39). Acetylation of 31 with acetic anhydride and pyridine gave N-acetyl derivative 35 in 43% yield. The photoadducts were subjected to cleavage reactions to generate 8-membered rings.



31 R = H
32 R = CH_3
33 R = CH_2—CH=CH_2
34 R = C_6H_5
35 R = $COCH_3$

36 R = H
37 R = CH_3
38 R = CH_2—CH=CH_2
39 R = C_6H_5

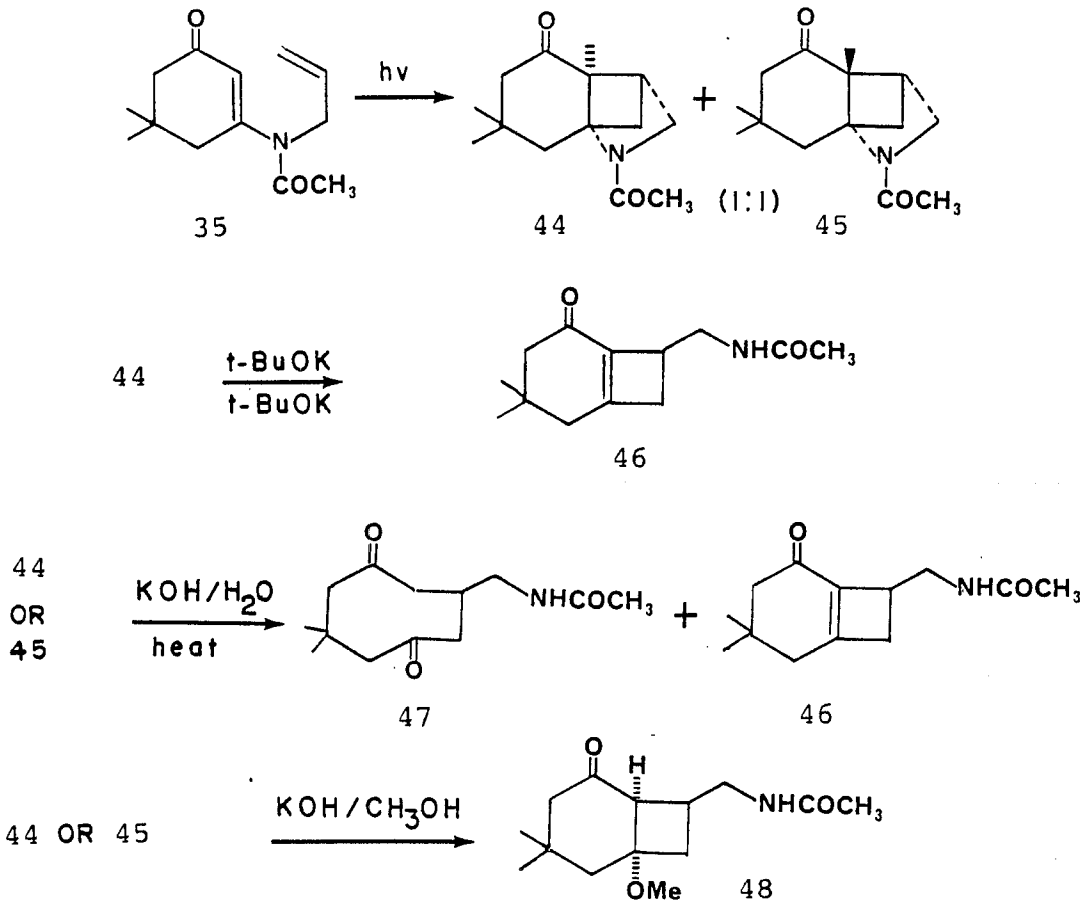
Irradiation of a cyclohexane solution of 32 with a 350-W high-pressure mercury lamp through a Pyrex filter for 10 h resulted in the formation of single photoadduct (Scheme 17) 40 (60%) whose structure was determined by x-ray crystallography. When refluxed in water the photo-



Scheme 17

adduct gave ring opened product 41 in 94% yield. On the basis of the spectral data and chemical evidence the compound 41 was shown to exist as an equillibrium mixture of 41, 42, and 43.

Irradiation of 0.02 M ethereal solution of 35 under similar conditions was found to give two isomeric photo-adducts 44 and 45 (Scheme 18) which were isolated by preparative TLC. The structures were assigned from spectral data. Treatment of 44 with t-butoxide resulted in isomerization to 45 in addition to enone formation (46). Compound 45 remained unchanged under similar conditions. However, heating of 44 or 45 with aqueous potassium



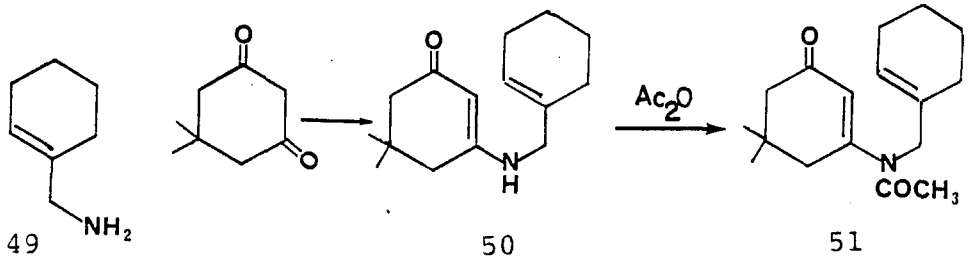
Scheme 18

hydroxide solution gave the same diketo acetate 47 accompanied by enone 46, and treatment with potassium hydroxide in methanol resulted in the formation of the same methanol adduct 48. This is presumably formed through intermediate 46.

These results show that the N-methyl derivative (32) produces exclusively the thermodynamically unstable isomer (trans), while the N-acetyl derivative (35) gives a 1:1

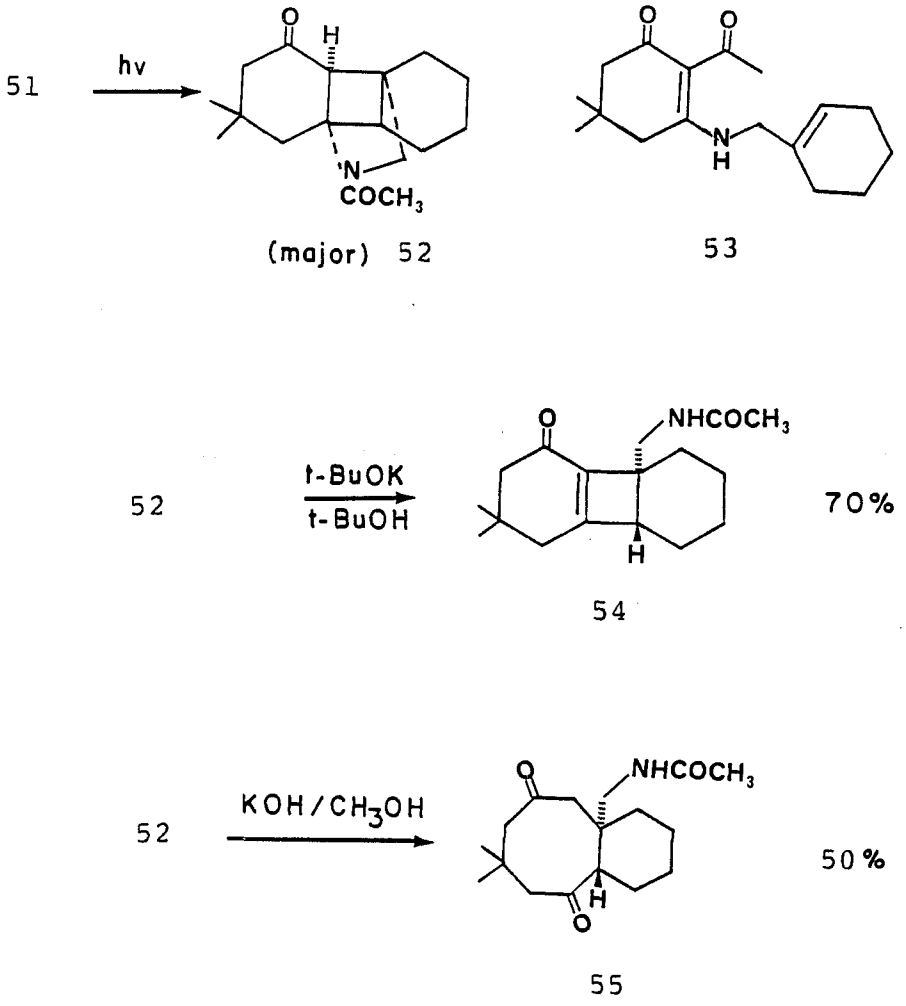
mixture of two possible isomers (44 and 45). It is suggested that the lone-pair electrons of the heteroatom play an important role in deciding the stereochemical course of this cycloaddition reactions.

As an extension to Tamura's procedure, Schell, et al.[42] achieved an intramolecular photochemical cycloaddition of a vinylogous amide 51. The required unsaturated amine 50 was prepared from cyclohexanone cyanohydrin by dehydration and lithium aluminum hydride reduction. Condensation of dimedone and amine 49 produced the vinylogous amide 50, which in turn provided 51 by acetylation.

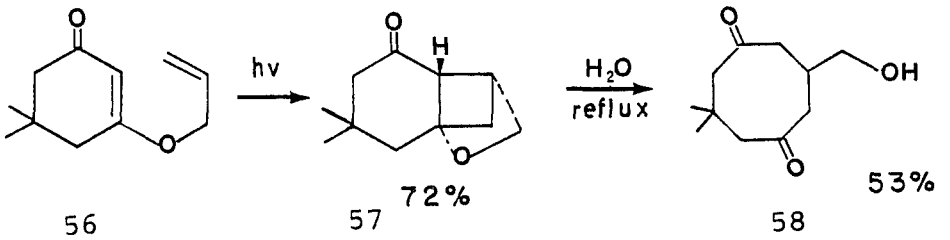


49 50 51

A dilute cyclohexane solution of 51 was irradiated through pyrex for 2 h to afford a mixture of two products, 52 and 53. The structure of 52 was fully defined by x-ray crystallography. Treatment of 52 with refluxing KOH and methanol afforded a diketone 55 in 70% yield, whereas treatment of 52 with potassium tert-butoxide in tert-butyl alcohol provided 54 in in 50% yield.



Irradiation of a cyclohexane solution of 56 led to complete disappearance of the starting material after 10 h and a single photoadduct 57 was formed in 72%. The stereochemistry of 57 was established by comparison with similar compounds (see previous examples). Refluxing 57 with water gave ring opened product 58.

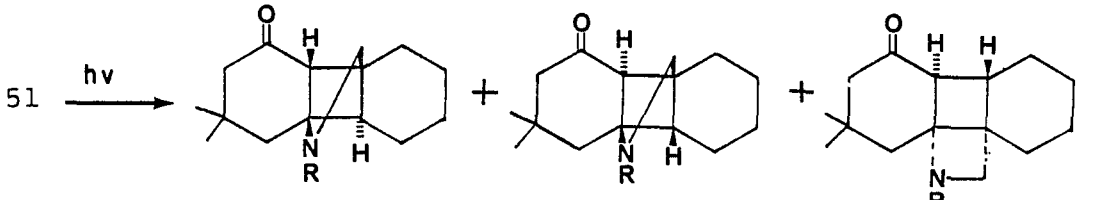


56 57 58

9. Swindell's Approach to Taxanes

Swindell[6p] exploited the above intramolecular (2+2) photocycloaddition of vinylogous imides in his synthetic approach to the Taxanes. He studied the photochemistry of 51 in detail and established several methods for ring cleavage of the photoadducts.

Imide 51 was prepared in 76% yield by phase transfer acetylation of the vinylogous amide 50. Imide 51 was irradiated (Hg arc lamp) in cyclohexane solution through Pyrex to afford the photoadducts 59 (70%), 60 (8%), and 61 (13%). In the previous investigation of the same reaction Schell did not identify the products 60 and 61.



59 R = $COCH_3$ 70%
63 R = CHO 60%

60 8%
64 9%

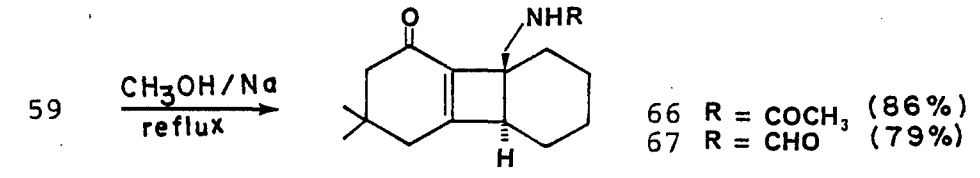
61 13%
65 15%

The stereochemistry of 59 was already established by Schell[42] (x-ray crystallography). Swindell et al. determined the stereochemistry of 60 and 61 also by x-ray crystallogrphy.

Similarly, imide 62, prepared in 78% yield by direct interaction of 50 with acetic formic anhydride in THF, on irradiation gave similar products as those obtained from 51.

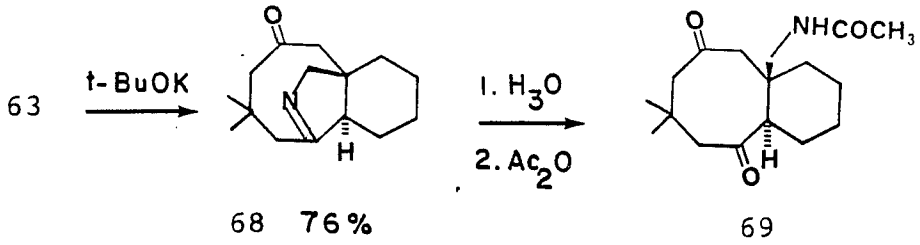
The stereochemical identities of 63, 64, and 65 were assigned by analogy with the firmly established structures of 59, 60, and 61.

Compound 59 on refluxing with methanolic sodium hydroxide, led slowly (24 h) to a known[42] enone 66 in 86 % yield. Likewise, 63 gave the corresponding enone 67 (49%) contaminated with 10% of its cis isomer after treatment with a catalytic amount of t-BuOK in t-BuOH.

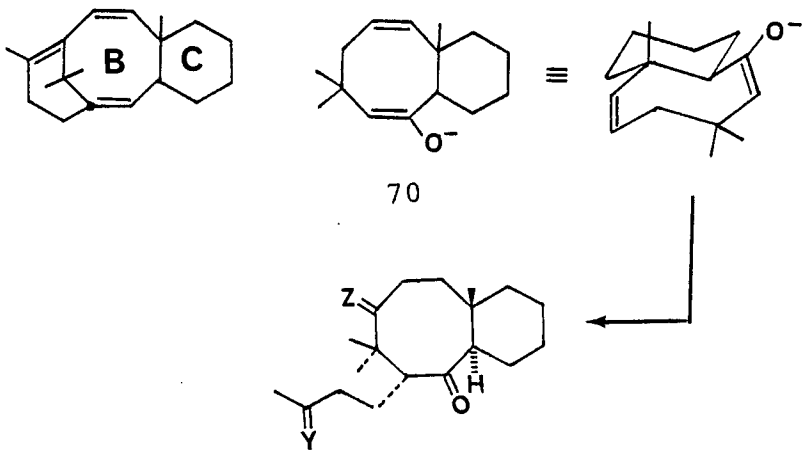


Also, compound 63, by deformylation/fragmentation with t-BuOK, was converted into imine 68, which was transformed

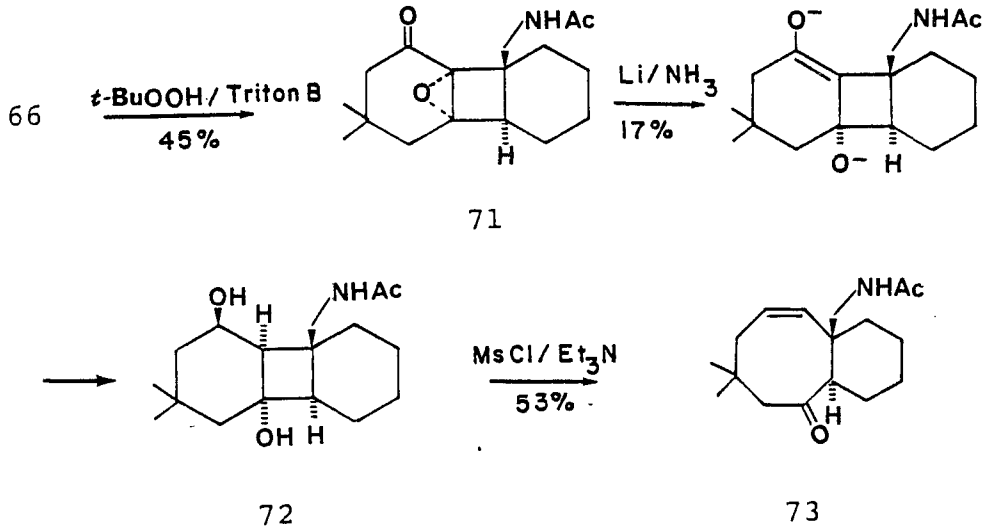
into a known[42] diketone 69 (aqueous acid, then acetic anhydride/pyridine, 43%).



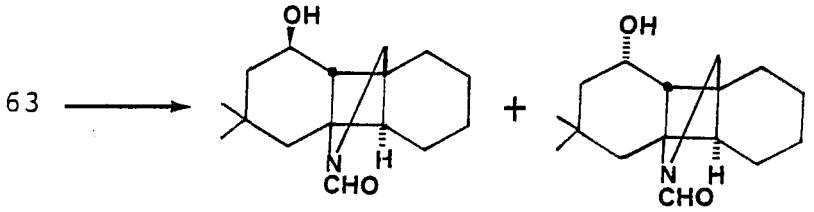
Swindell's approach to the synthesis of Taxanes is based on the assumption that the A ring can be annellated to give a functionalized BC ring intermediate. Molecular mechanics calculations on model compounds showed that the desired enolate 70 possesses a least energy conformation which exposes the α-face to electrophilic attack.



Photoadducts 59 and 63 were chosen as the precursors to 70. First, epoxyketone 71 provided the diol 72 (low yields) upon dissolving metal reduction in presence of a proton source. The mesylate of 72 was then opened by base to give the enone 73.



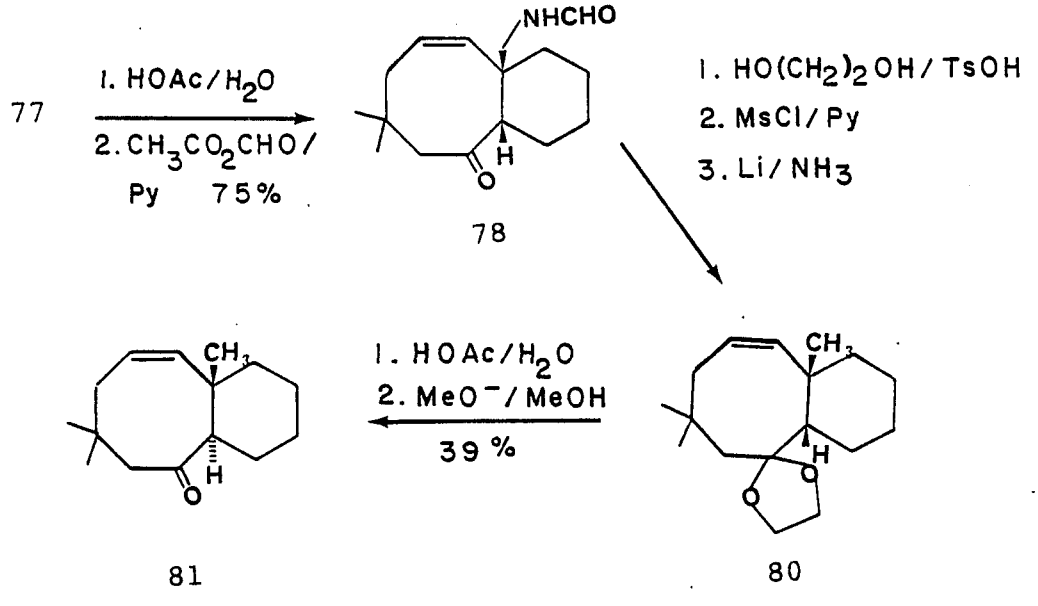
With modest success in the above route a second route to generate 81 was worked out (Scheme 19). The photoadduct 63 was reduced to a mixture of epimeric alcohols 74a and 74b. The mesylate of 74a was transformed into the unstable trans olefinic bridgehead imine 75 by deformylation/fragmentation with one equivalent of methyl lithium. The mesylate of 74b (76) provided the cis olefinic bridgehead imine 77 under the same conditions. Similar chemistry carried out on 59 was not fruitful. Formamidoenone 78, obtained from 77 by treatment of aqueous acetic acid



74a 74b

	74a	74b
$NaBH_4$	30 %	50 %
Li/NH_3	73%	0%
L-Selectride	0%	99%

75 77



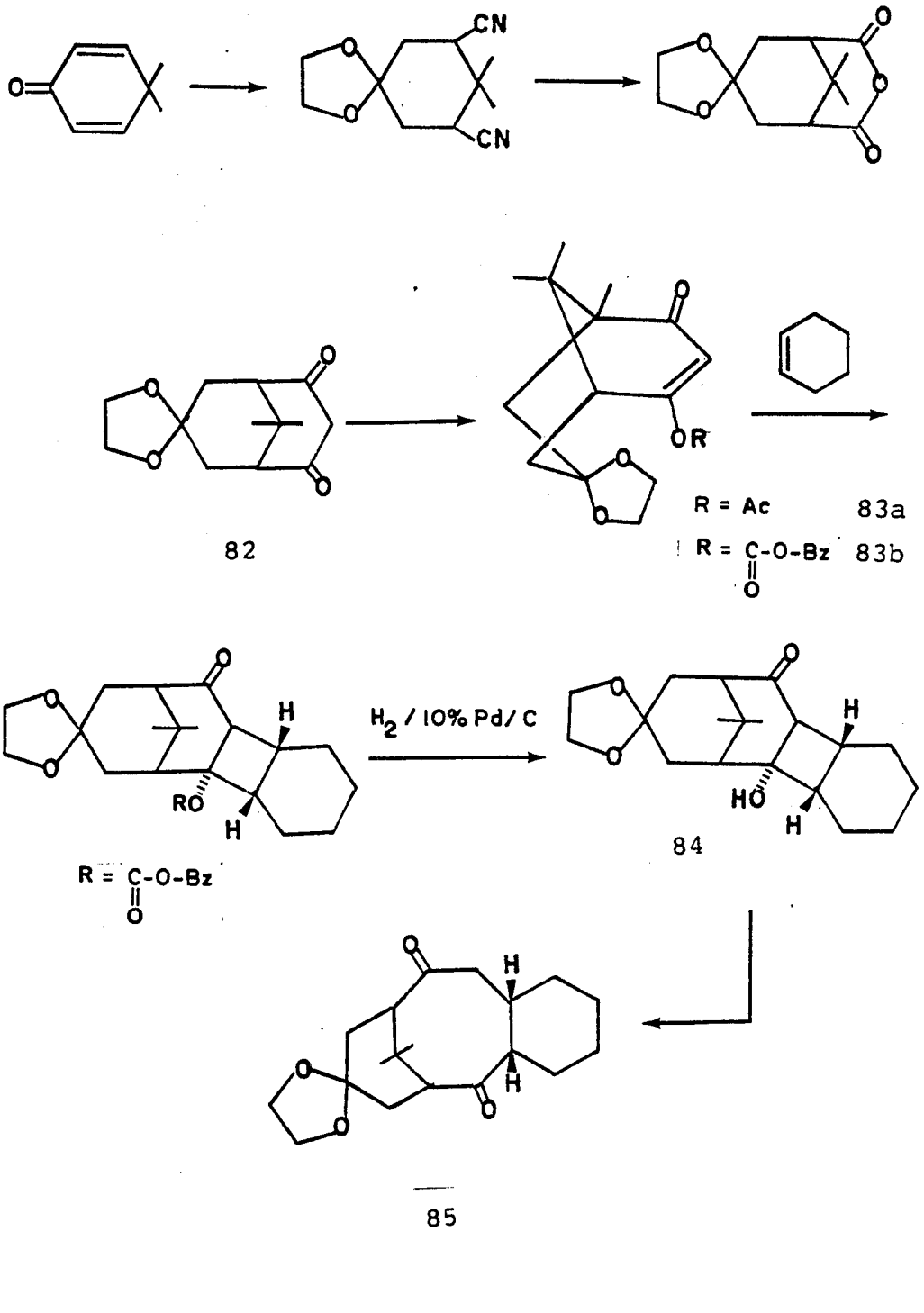
Scheme 19

followed by formylation, was converted to the ketal, then to the isonitrile 79, which gave 80 upon reductive deamination. Finally, ketal removal followed by epimerization led to the desired 81. The overall yield of 81 from 77 in 7 steps was 13%. Construction of the A ring through enolate alkylation of the BC rings of 81 is expected to be reported in the near future.

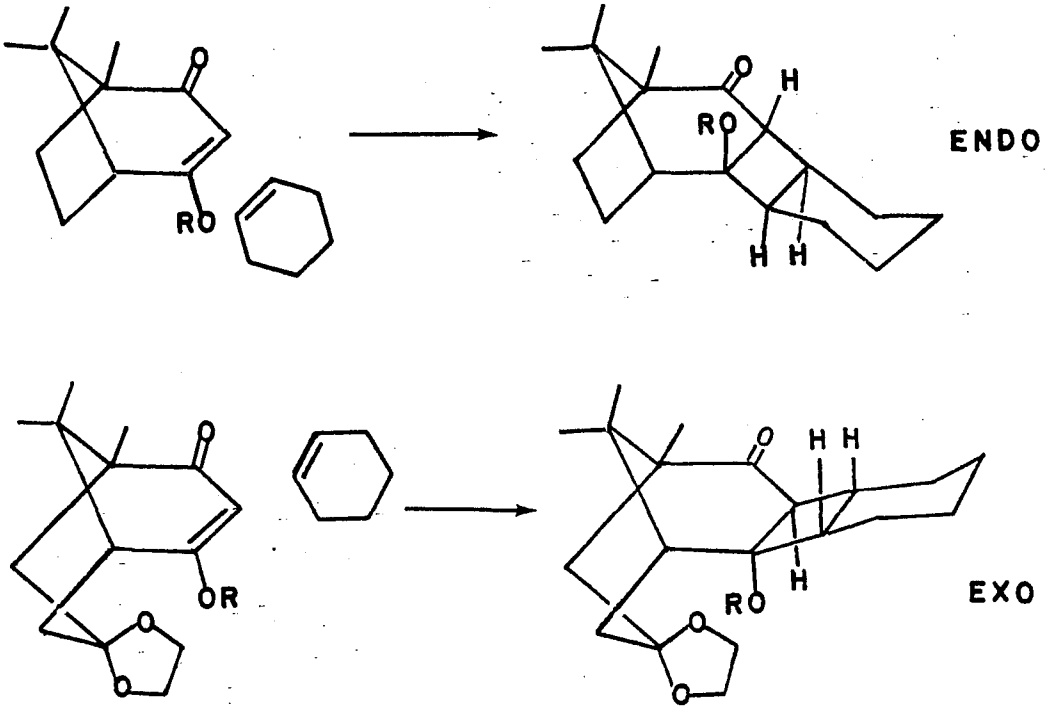
10. Blechert's Approach to Taxanes

As our study was in progress a related synthesis of Taxane was published by West German chemists, Blechert et al.[6q] They prepared a 1,3-diketone intermediate 82 which was then converted into derivatives 83a or 83b. Irradiation of either 83a or 83b with cyclohexene (500 W Hg High-pressure lamp, Pyrex filter) caused formation of a photoadduct. The acetate proved to be less suited for the ring opening reaction, since elimination tookplace more readily giving a cyclobutene. On the other hand, the benzylcarbonate substituent was easily converted quantitatively by hydrogenolysis (H_2,Pd/C) into alcohol 84, which slowly underwent retroaldol cleavage to provide diketone 85. The structure of 85 was proved by X-ray crystallography.

The key step in their reaction sequence is the stereoselective exo attack of the cyclohexene on the

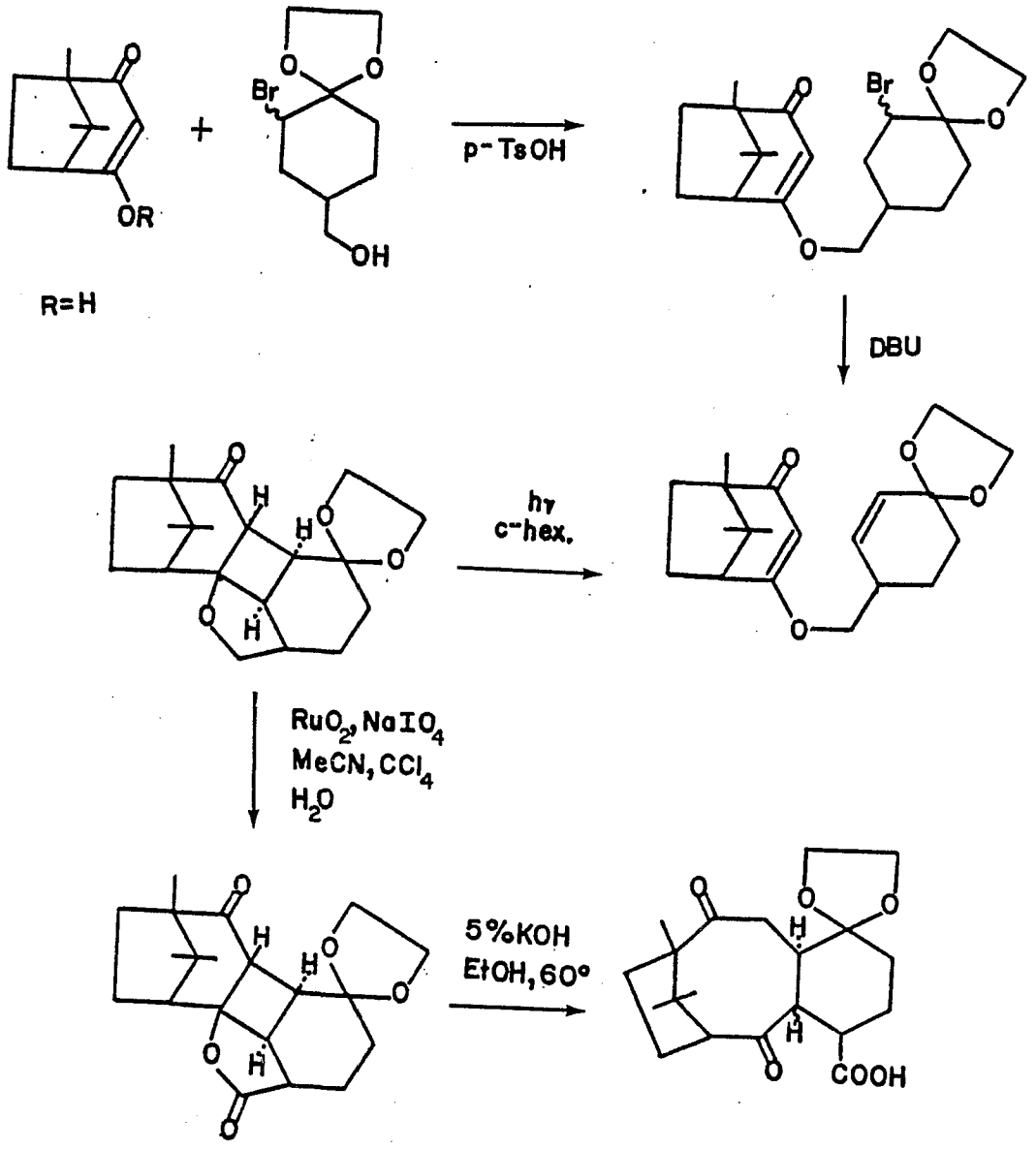

CN
CN
O
O
O
O
O
O
O
O
O
OR
R = Ac
83a
R = C-O-Bz
83b
O
82
H
RO
H
R = C-O-Bz
O
H2 / 10% Pd/ C
H
HO
H
84
H
H
O
O
O
O
85

bicyclo[3.3.1]nonenone. As a directing substituent a ketal was chosen which forced the A ring into a chair conformation in order to diminish interaction with the gem dimethyl group. The ketal provided hindrance to the endo attack and therefore exo product was formed exclusively. In the case of the less flexible 5-membered ring, as in our case, the methyls on the bridging carbon hinder exo attack, and therefore the endo product is formed.



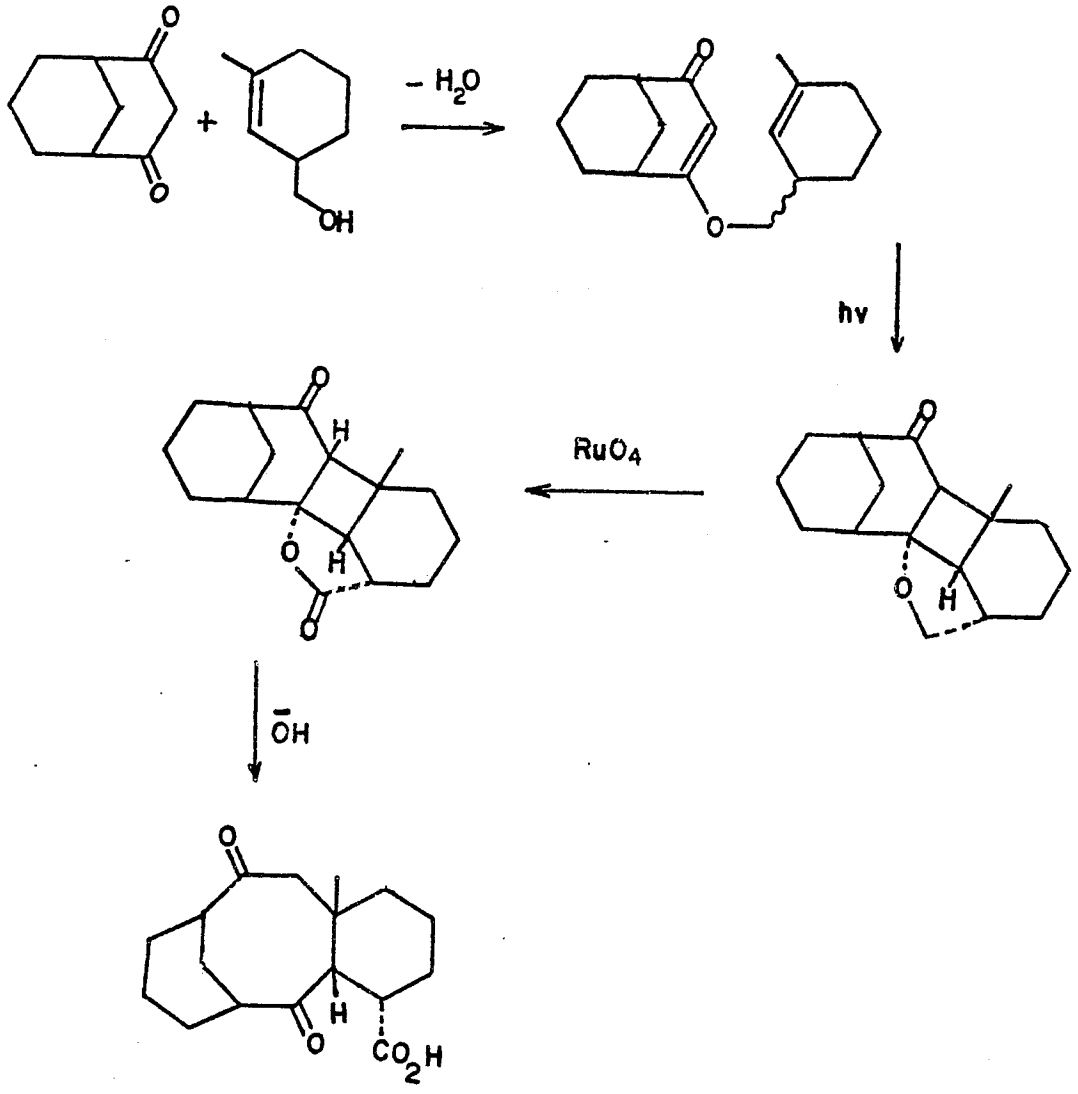
A. Amarasekara [43] in our Laboratory investigated an intramolecular enone-olefine cycloaddition in order to generate a Taxane model (Scheme 20). The hydrofuran ring in the adduct was oxidised to a cyclic lactone using

ruthenium tetroxide. Opening of the lactone with ethanolic potassium hydroxide produced the tricyclic Taxane model.



Scheme 20

A trinortaxane skeleton was synthesised recently by the Japanese group[44] making use of a similar photoaddition reaction (Scheme 21).



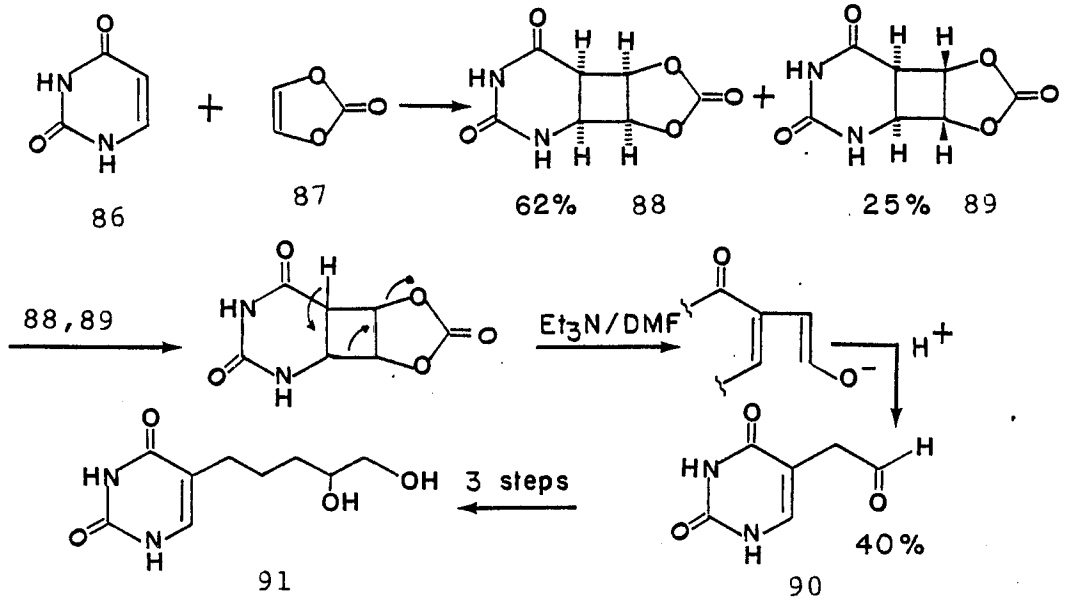
Scheme 21

11. Ring Opening Reactions of Photoadducts[14d]

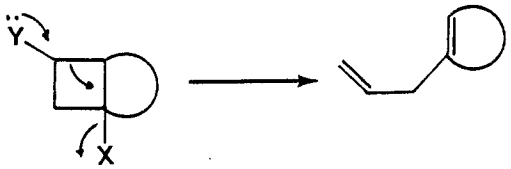
The major impetus in using [2+2] photoreactions in organic synthesis is based on the fact that the cyclobutane ring formed can be cleaved if suitable sustituents are incorporated in the enone or olefin substrates. Thus the cyclobutane ring can presently be cleaved by the different methods outlined below:

(i) Cyclobutane ring opening by base catalyzed elimination:

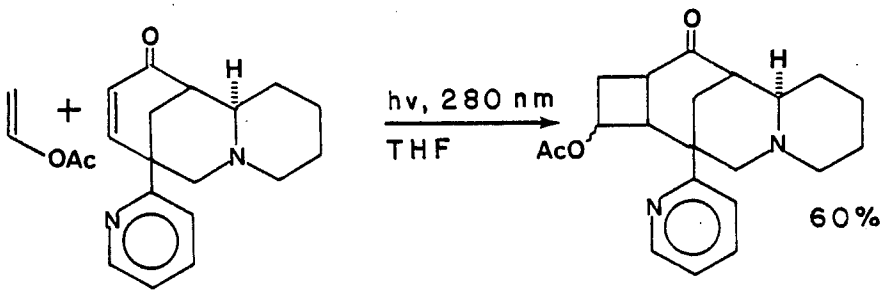
For example[45], irradiation of a solution of uracil (86) and vinylene carbonate (87) gave the two cycloadducts 88 and 89. The synthetic utility of the cycloadduct lay in its conversion to the aldehyde 90 on treatment with triethylamine. The synthesis was completed in three additional steps to give the dihydroxypentyluracil 91, which has been isolated from the DNA of Bacillus subtilis phage SP-15.[45]

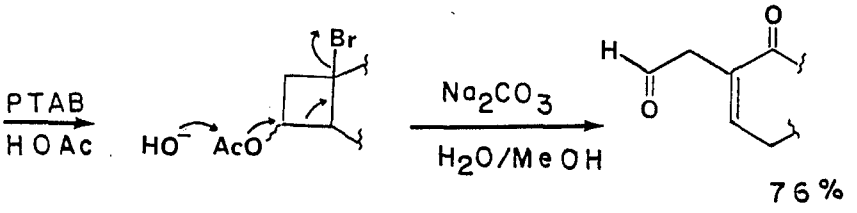


(ii) cyclobutane ring opening by an electron donating substituent and elimination:

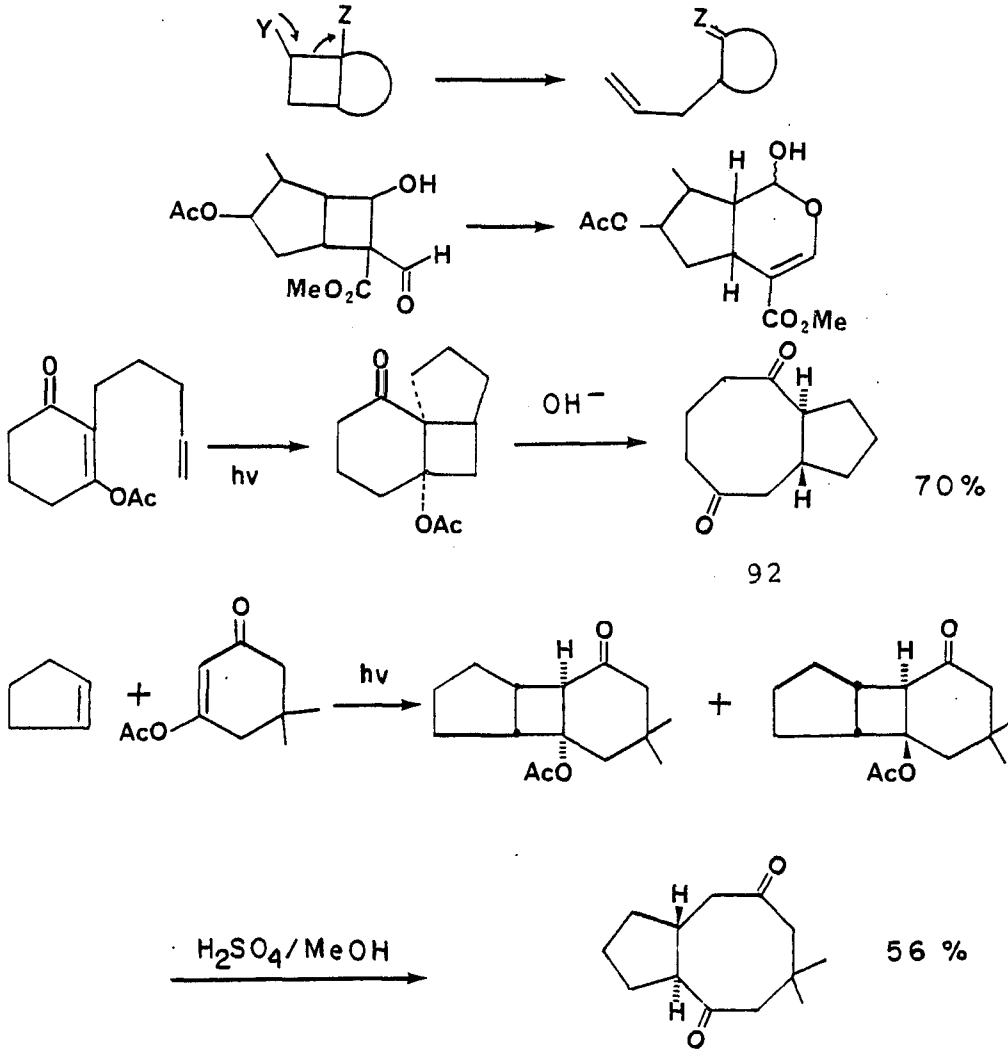


This method has been applied in the total synthesis of ormosanine, piptanthine, and panamine alkaloids.[46]



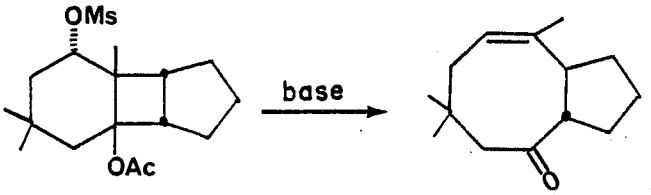


(iii) Cyclobutane ring opening by electron donating and electron accepting substituents: This is the most common method of cyclobutane ring cleavage and is also known as retroaldol cleavage.



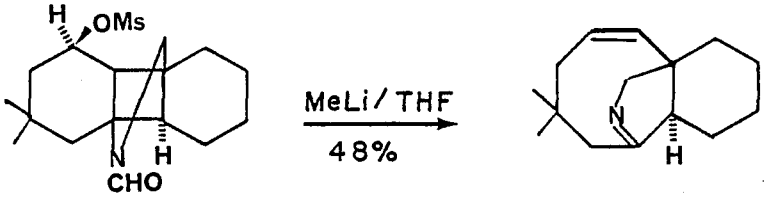
(iv) Grob-type Fragmentation

If the carbonyl group of the photoadduct is reduced to an the alcohol and then converted to a mesylate, a base promoted Grob type fragmentation is possible, forming an olefinic bond.



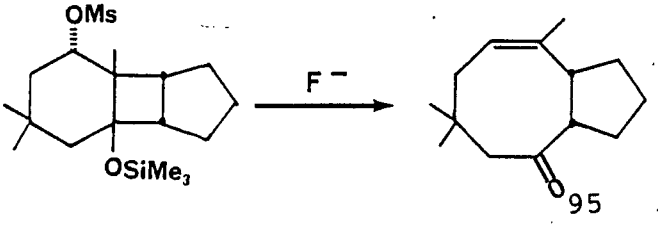
93

Swindell[6p] accomplished a cyclobutane ring cleavage using MeLi on a formamido photoadduct.



94

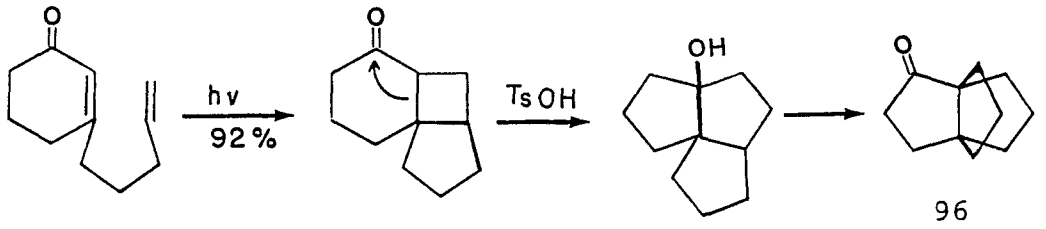
Fluoride ion assisted cleavage has been utilized with an $OSiMe_3$[34] group.



95

(v) Cyclobutane ring expansion

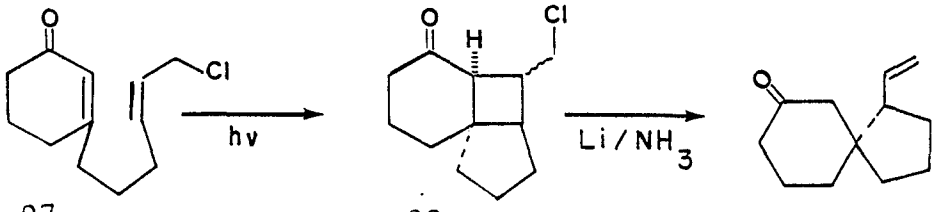
The cyclobutane ring underwent expansion through cationic 1,2 shifts when treated with acid, and provided propellane 96.[47]



96

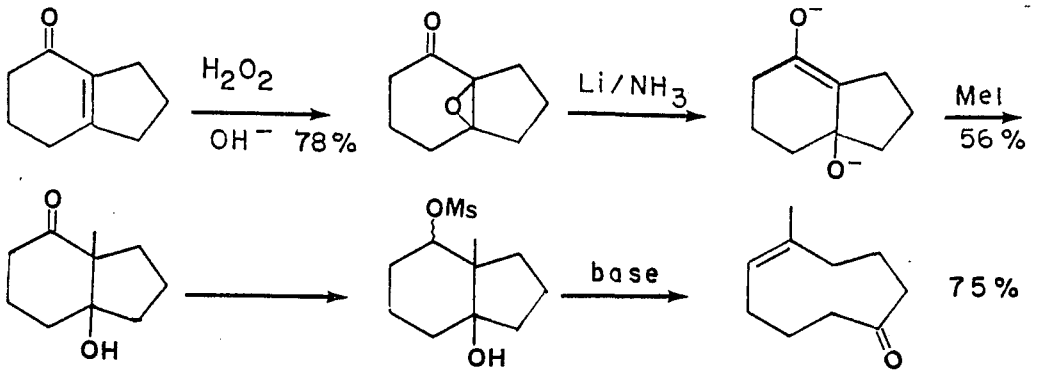
(vi) Reductive Fragmentation

Cycloaddition reaction of 97 (benzene/pyrex) proceeded again regioselectively to give in 95% yield a 4:1 mixture of the C5' epimers of 98. In both isomers, the cyclobutane is cis fused to the five- as well as to the six-membered ring. Hence three out of four chiral centers were assembled in the addition with high steric control. Reductive cleavage led to the spiro ketone 99.[48]

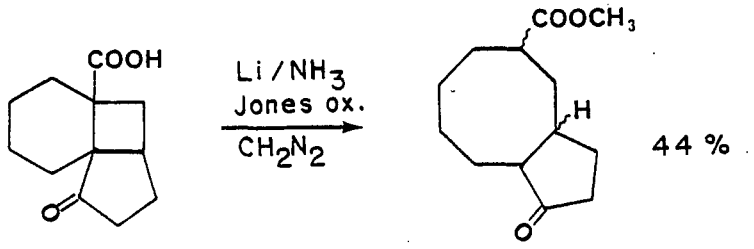


97 98 99

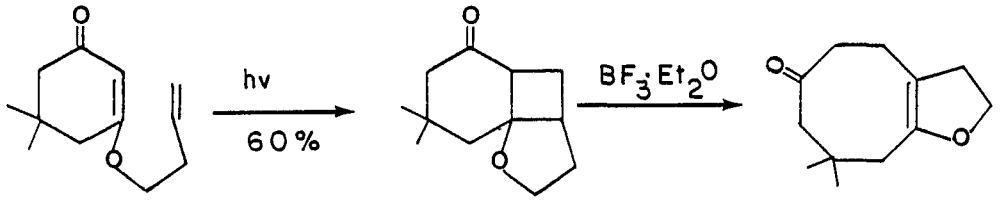
Another variation of the reductive cleavage is the Wharton fragmentation.[49]



Coates[50] accomplished a reductive cleavage of the cyclobutane ring as shown below:



(vii) Fragmentation using boron trifluoride etherate has been used for cyclobutane rings containing an ether linkage.[41,51]



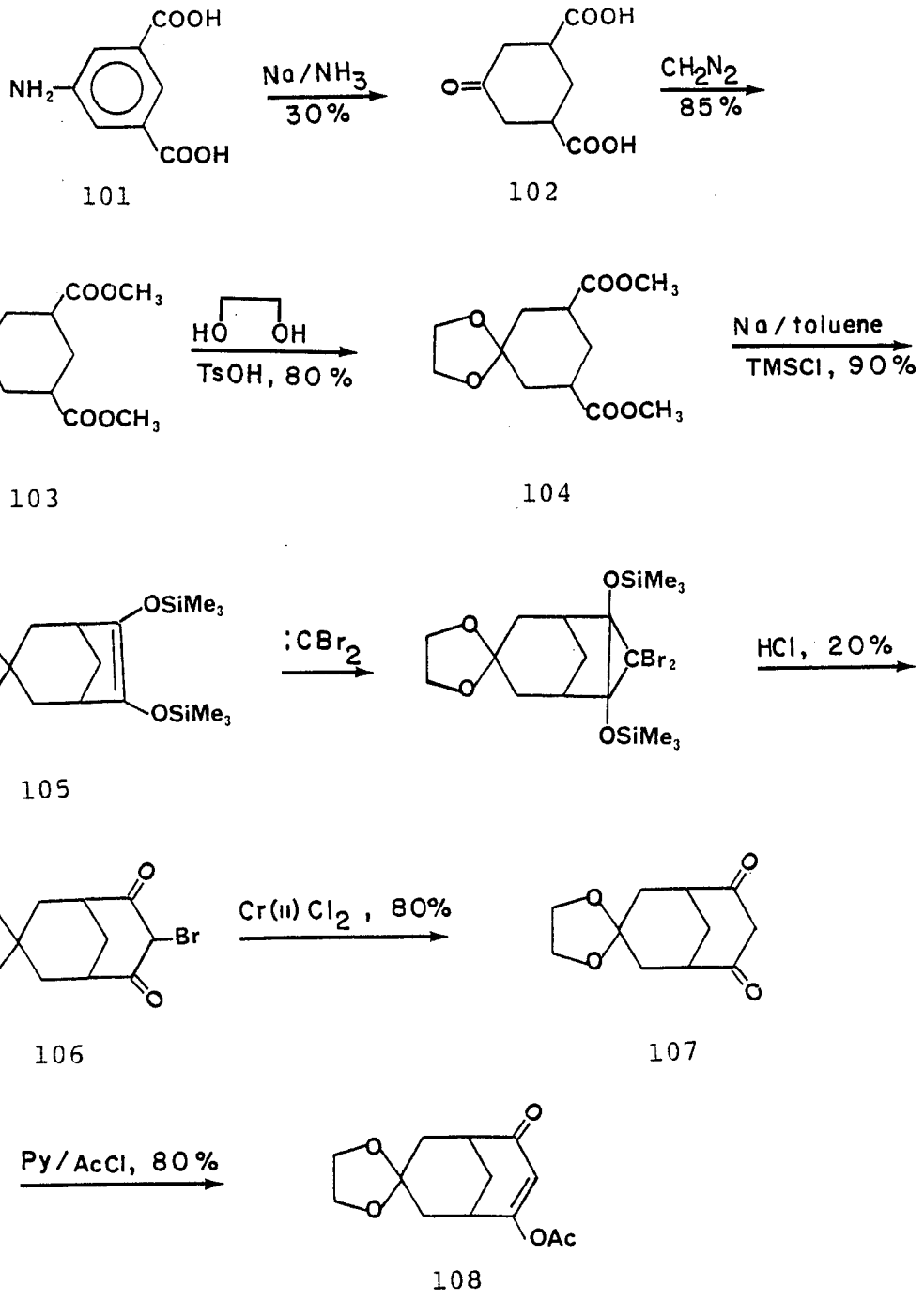
RESULTS AND DISCUSSION

This work can be divided into four parts: i) construction of the tricyclo(3.3.1)nonane system; ii) preparation of homocamphorquinone and its derivatives; iii) enone [2+2] photoaddition reactions; and iv) ring opening reactions of photoadducts.

Part I. Construction of tricyclo(3.3.1)nonane system

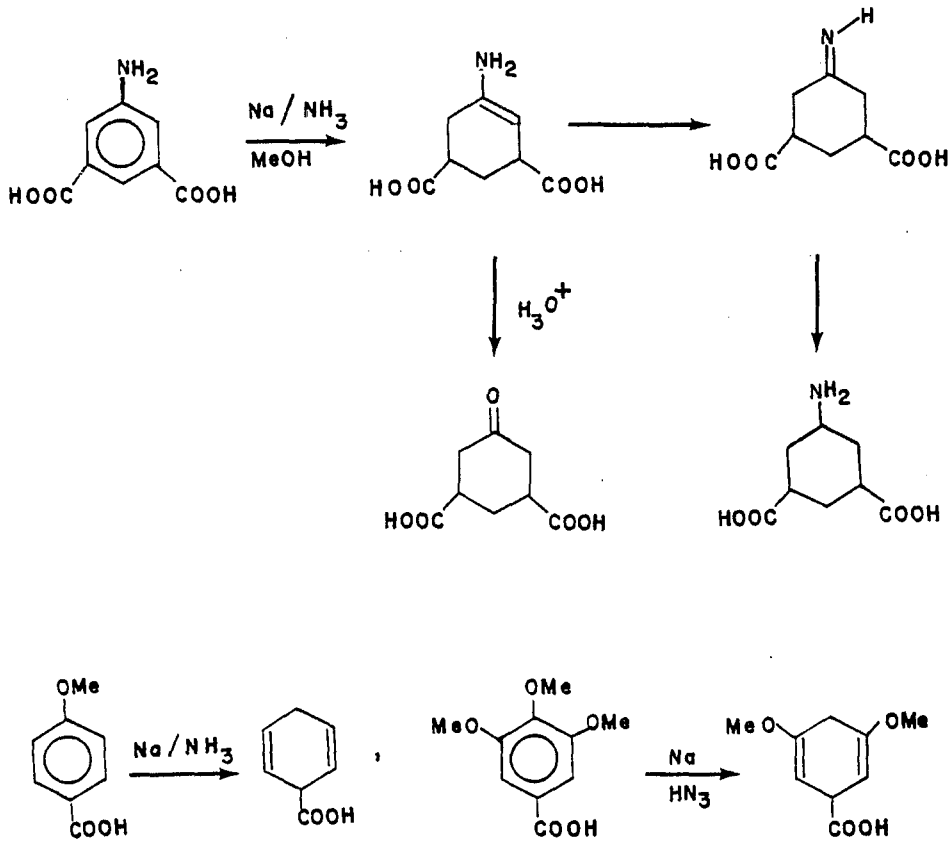
The tricyclo(3.3.1)nonane system was prepared (Scheme 22) according to Hutmacher's procedure.[52] The diketone thus obtained was converted into enol acetate 108. Cylohexane-cis-1,3-dicarboxylic acid 102 was obtained by Na/NH_3 reduction and subsequent hydrolysis of 5-aminoisophthalic acid (101) and then converted into the dimethyl ester 103. Protection of the keto group followed by acyloin condensation[53] gave 105. Dibromocarbene addition followed by hydrolysis afforded a ring expanded bromodiketone 106, and debromination provided a 1,3-diketone 107 which was converted into enolacetate 108.[54]

The Hutmacher procedure suffered many drawbacks. The sodium/ammonia reduction reaction provided only low yields (30-35 %). Attempts to improve the yields by changing the cosolvent, using lithium metal, reverse


COOH
NH2
COOH
Na/NH3
30%
COOH
O=
COOH
CH2N2
85%
101
102
COOCH3
O=
COOCH3
HO OH
TsOH, 80%
COOCH3
COOCH3
Na/toluene
TMSCl, 90%
103
104
OSiMe3
OSiMe3
:CBr2
OSiMe3
CBr2
OSiMe3
HCl, 20%
105
Br
Cr(II) Cl2, 80%
106
107
Py/AcCl, 80%
OAc
108

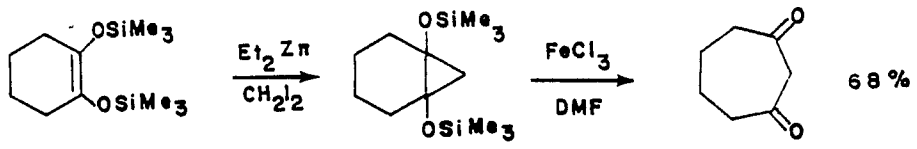
Scheme 22

addition of isophthalic acid, etc. did not give any satisfactory improvement. It is proposed[55] that the low yield is due to the side reaction as shown in Scheme 23. Use of the methoxy group instead of amino would not necessarily improve the yields because para or ortho methoxy acids undergo elimination during reduction (Scheme 23).

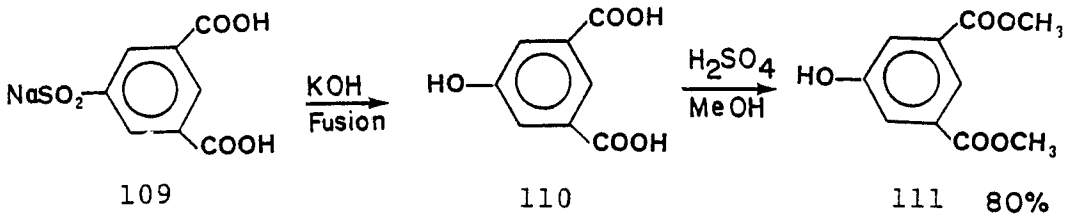


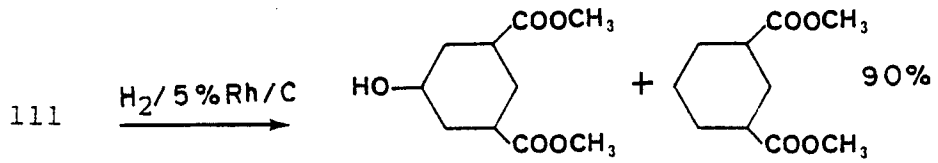
Scheme 23

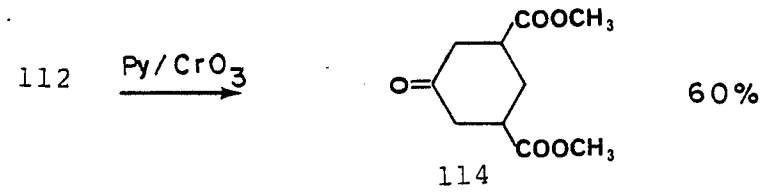
The dibromocarbene addition was another low yield (20 %) reaction. A procedure developed by Ito[56] could be utilized to expand the ene-diol derivative in future works.



An alternate method was worked out to prepare cyclohexane 1,3-dicarboxylic acid as shown in Scheme 24.[57] Alkaline fusion of the monosodium salt of 5-



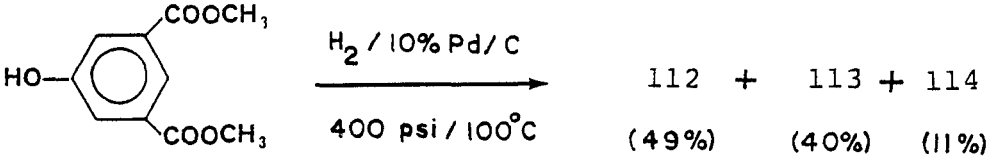




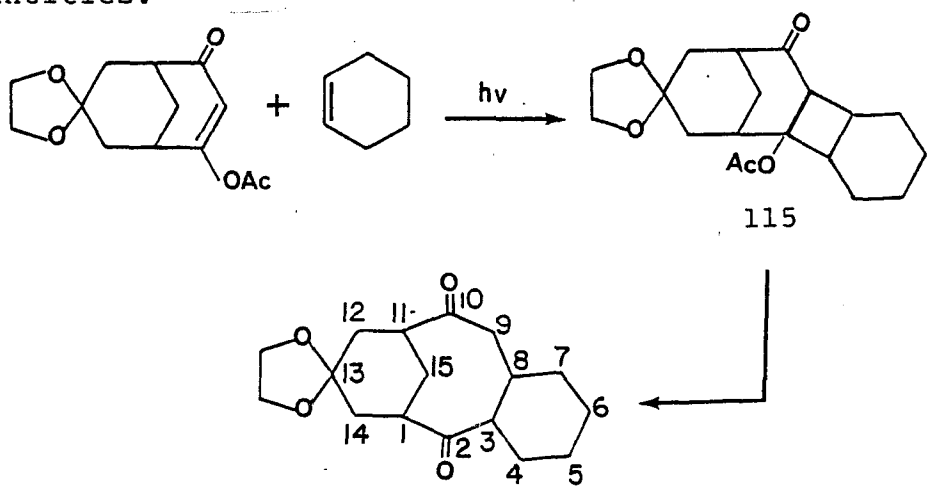
Scheme 24

sulfoisophthalic acid (109) provided 5-hydroxy acid 110 which was converted into dimethyl ester 111 by refluxing in methanol/sulfuric acid. Reduction of 111 using H_2,5% Rh/alumina in ethanol solvent went in only low yield. Compounds 112 and 113 were obtained in a 3 : 5 ratio using H_2, 5% Rh/C and were separated by silica gel chromatography. Compound 112 was then oxidized using chromic acid or pyridiniumdichromate.

About 25 g of hydroxy ester 111 was sent to IFF, Union City, NJ, where Dr. Schreiber performed hydrogenation. The substrate was mixed with 5 parts by weight of 10 % Pd/C catalyst and hydrogenated at 400 psi and at 100° C. We analyzed the mixture by gas chromatography and found it to contain 112 (49 %), 113 (40 %), 114 (11 %). Compounds 112 and 113 were separated by distillation at reduced pressure using a spinning band colum, [bp 64-65° C, 0.05 mm (113), 116-120° C, 0.05 mm (114)]. The residual solid was found to be mainly compound 112.

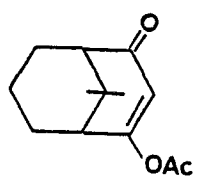


Compound 108 was considered a good enone precursor for [2+2] photochemical reactions with cyclic olefins and for generating the tricylo(9.3.1.$0^{3,8}$)pentadecane system which is the characteristic carbon skeleton of taxanes, except that it was difficult to prepare in large quantities.

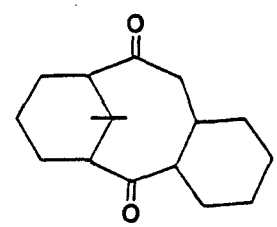


115

In addition, taxane system contains a gem-dimethyl group on the bridging carbon and this might generate significant steric hindrance to the photoaddition reaction. Hence, a new model was employed.



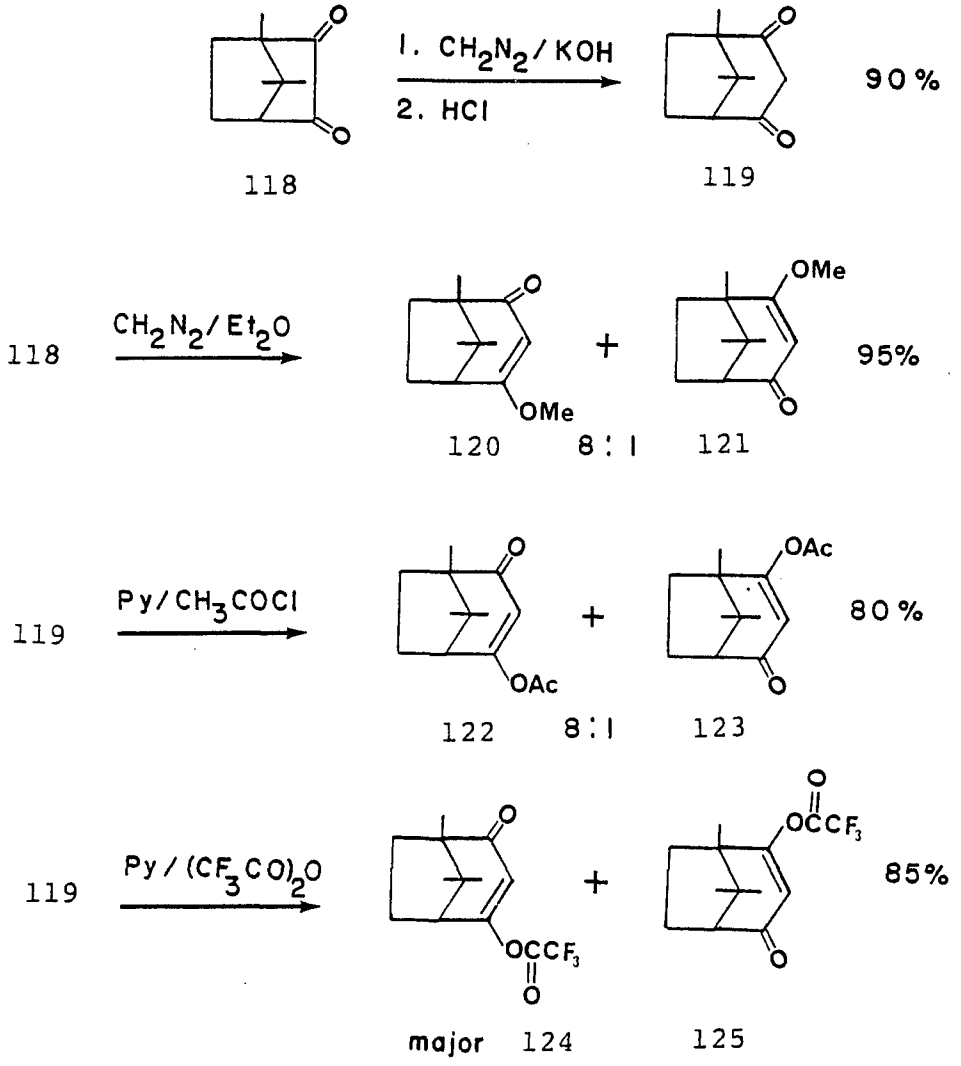
116



117

Part II. 1. Preparation of Homocamphorquinone Derivatives. Model Studies

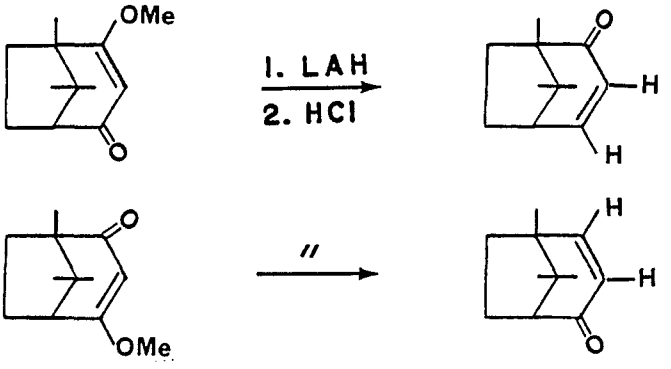
As the bicyclo[3.3.1]nonenones were not easily prepared, the readily available *homocamphorquinone* 119 provided a model for these studies. Ring expansion



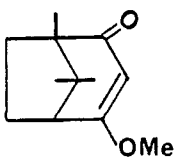
Scheme 25

reactions of commercially available camphorquinone 118 using diazomethane had been shown to afford these compounds in excellent yields (Scheme 25).[58] The 1,3-diketone is trapped by KOH solution (potassium enolate) to avoid further reaction to produce enol ether with excess diazomethane. The isomers of the enol ether were obtained in an 8:1 ratio with excess diazomethane. In addition, acetylation of 119 gave good yields of 122 and 123, in a similar ratio.

We anticipated that the major product possessed the structure 120 (also 122) because of the steric effect of the bridgehead methyl groups. The structural assignments of 120 and 121 were difficult with NMR spectra alone, but were confirmed on the basis of ORD curves and chemical transformations.[58] Lithium aluminum hydride reduction and acid hyrdolysis provided two isomeric enones whose structures were assigned on the basis of the different NMR patterns of the vinylic protons.

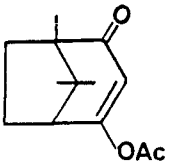


It is interesting to note that the vinylic protons of the enones 120 and 122 showed a substantial differance in chemical shifts (5.1 ppm, 5.7 ppm) due to the electron withdrawing property of the acetate group. The vinylic proton of the trifluoroacetate derivative (124) also showed a large downfield shift (6.0), as expected.



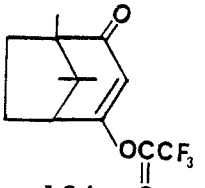
120

(5.1 ppm)



122

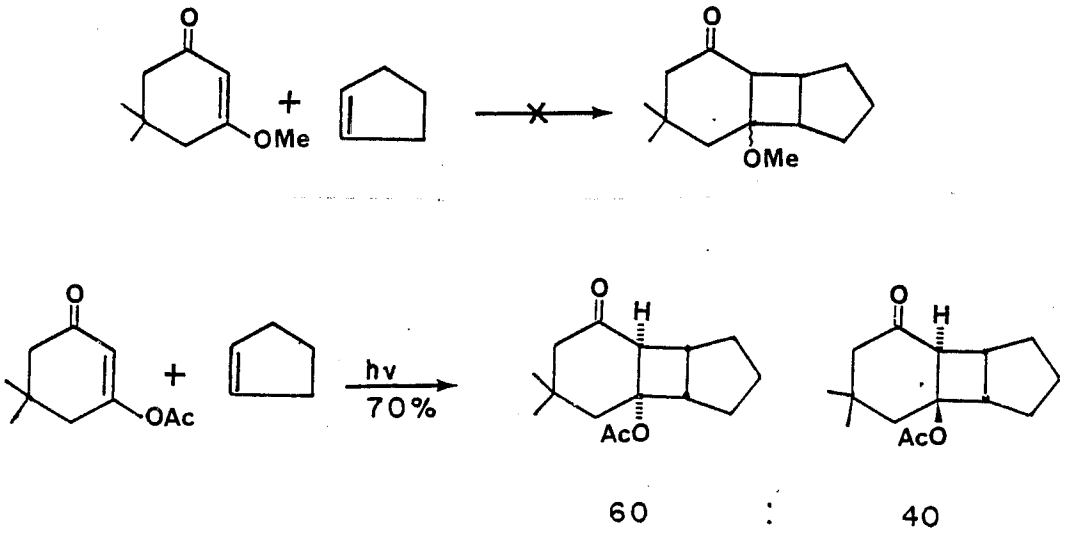
(5.7 ppm)



124

(6.0 ppm)

We hoped this increased electropositive nature of the α carbon might have an influence on the photocycloaddition reaction. This correlation has not been fully investigated so far. However, it is reported that electron-rich olefins react faster than other alkenes with enones. Radical stabilizing substituents in the β-position of the enone also are known to increase the rate of photoaddition. The electronic effects of the β substituent on photoaddition is evident in the reactions of the methyl ether of dimedone, which failed to give any photoadducts with cyclopentene, whereas the acetate derivative did give a photoadduct in good yields.[59]

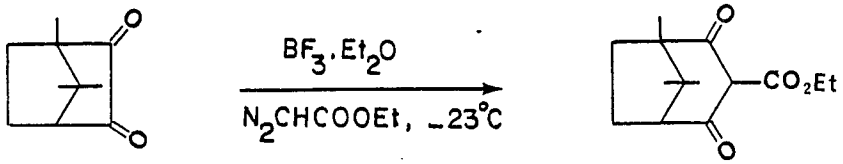


The NMR spectrum of 1,3-diketone 119 also deserves comment. The two unsymmetrical protons situated between the carbonyls appeared as an AB quartet (3.1 ppm, 1H d, J = 18 Hz; 3.6 ppm, 1H d, J = 18 Hz) indicating the presence of the keto form, whereas in dimedone, the 1,3-diketone exists in enol form, as shown by the presence of a vinylic proton (5.1 ppm, 1H) in the NMR spectra.

2. Other Ring Expansion Studies of Camphorquinone

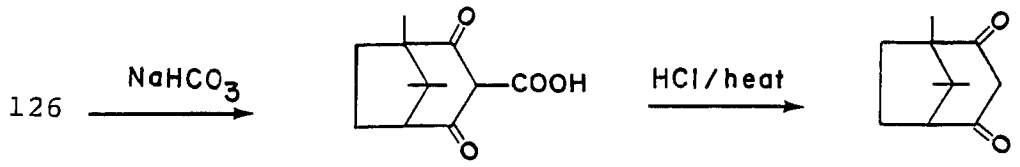
Lewis acid ($BF_3.Et_2o$) catalyzed ring expansion reaction of cyclic ketones with ethyl diazoacetate had been reported in the literature.[60] Treatment of camphorquinone with ethyl diazoacetate in the presence of the borontrifluoride catalyst at various temperatures (20° C, 5° C, 0° C) provided no products. In each case the

evolution of nitrogen was noticed. However, a reaction at -23° C produced a strong UV active spot on examination by TLC, indicative of 1,3-diketone formation. The UV active compound was separated by liquid chromatography and an yellow crystalline compound was obtained in 25% yield. The product isolated showed ethyl protons in the NMR spectra ($-COOCH_2CH_3$, 1.4t, 3H, J=8 Hz,; 4.3 q, 2H, J=8 Hz). Attempts to improve the yield by performing the reaction at much lower temperatures were not rewarding.



118 126

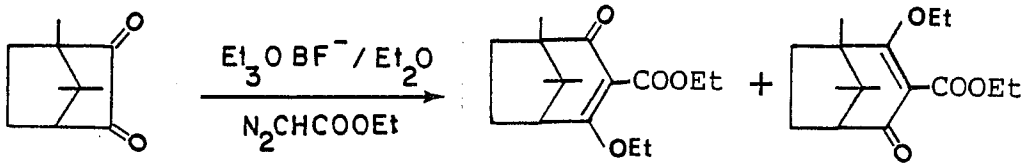
This ester (126) easily underwent hydrolysis in sodium bicarbonate solution and provided a crystalline keto acid 127 (mp 145-146° C) upon acidification. The formation of the acid was monitored first by TLC (a slow-moving spot, with streaks) and later confirmed by IR spectroscopy (3500-3200 cm^{-1}, broad peak).



127 119

The acid 127 underwent decarboxylation upon heating with dilute mineral acids, providing the known homocamphorquinone 119.

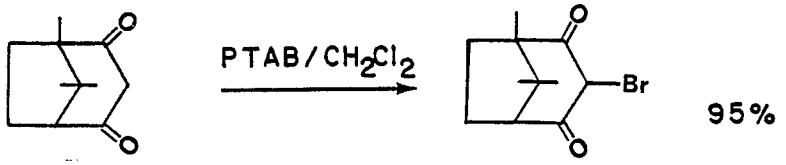
Mock proposed the use of Meerwien's reagent (triethyloxonium fluoroborate) as a catalyst in the ring expansion of ketones with ethyl diazoacetate.[61] Treatment of 118 under Mock's conditions gave a solid showing IR and NMR spectra similar to those of 126, but with an increased ratio of CH_3CH_2 signals to bridge methyl signals. We interpret this as indicating formation of ethyl enol ether 128 (major isomer) and 129. Hydrolysis and decarboxylation of the mixture in refluxing aqueous acetic acid gave 119 as before.



major

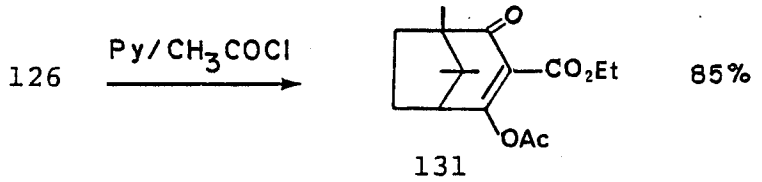
118 128 129

The bromo derivative 130 was prepared by treating homocamphorquinone with phenyltrimethylammonium tribromide (PTAB) in methylene chloride.[62] The product showed a distinctive spot upon TLC examination and the progress of the reaction was thus monitored. Upon isolation, the characteristic methylene peak of the diketone (two doublets) was absent from the NMR spectrum of the product.

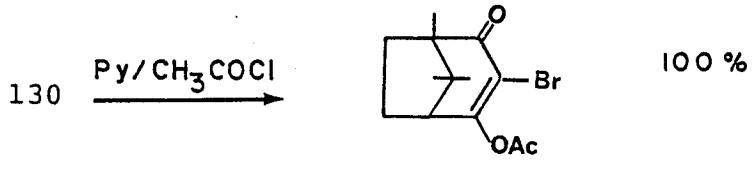


119 130

Both bromo (130) and carboethoxy (126) derivatives of homocamphorquinone were converted into the corresponding enol acetates. The formation of the enol acetate was followed by TLC and the products isolated showed the characteristic peak of the acetate (singlet at 2.1 ppm). Compound 131 was distilled under reduced pressure to give a colorless liquid which gradually turned into a white solid (mp 134-136° C). The bromoacetate 132, obtained in quantitative yield, remained as a colorless liquid. It should be noted that only one isomeric enol acetate was formed in both cases as evidenced by HPLC analysis.



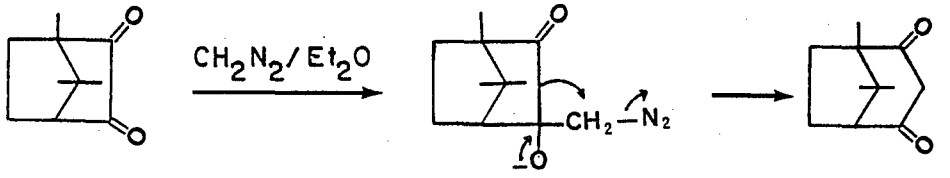
131



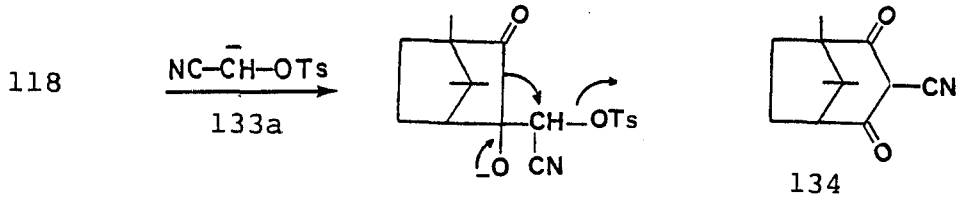
132

Unfortunately no photoadducts were isolated when the above compounds (131 and 132) were subjected to irradiation with cyclopentene.

In order to obtain the cyano derivative, we thought that the anion of cyanomethyl tosylate (133a) might be used as a ring expanding reagent in place of ethyl diazoacetate (or diazomethane).



118 119



118 134

$$NaCN + (CH_2O)_n \longrightarrow NC-CH_2-OH \xrightarrow{TsCl} NC-CH_2\,OTs \quad 60\%$$

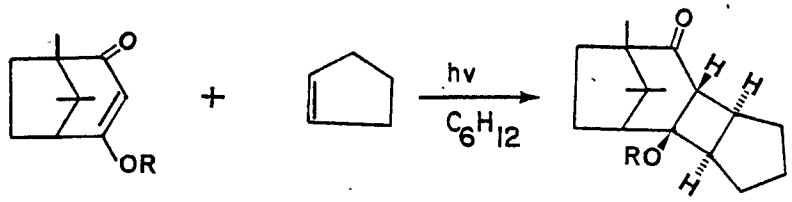
133

Cyanomethyl tosylate (133) was easily prepared by the reaction of sodium cyanide with formaldehyde solution (30% w/w) and subsequent addition of p-toluene sulfonylchloride.[63] The attempted ring expansion reaction was unsuccessful. Cyanomethyl tosylate has been used as an alkylating agent, but never used as a nucleophile.

Treatment of 133 with KH did not result in any evolution of hydrogen, so that evidence for the formation of the anionic intermediate 133a has not been established. Starting material was reisolated in 60% yield after the reaction. Further work in this area is necessary.

Part III. 1. Photoaddition Reactions

The bicyclic enone derivatives are prepared in good amounts (Scheme 25) and the photochemical reactions were carried out. All reactions were run in Pyrex tubes under nitrogen in a Rayonet apparatus using 350 nm lamps.[64] Results of some of these reactions are listed below:

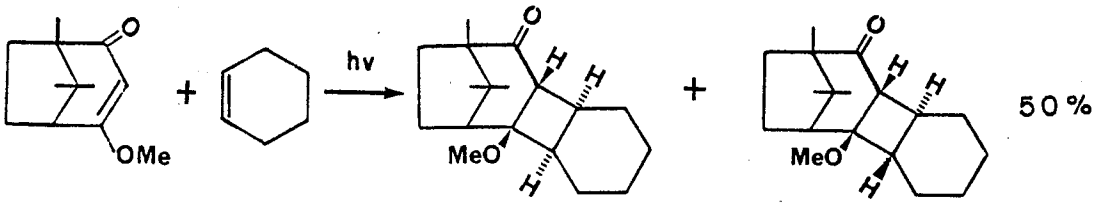


120 R = Me

122 R = Ac

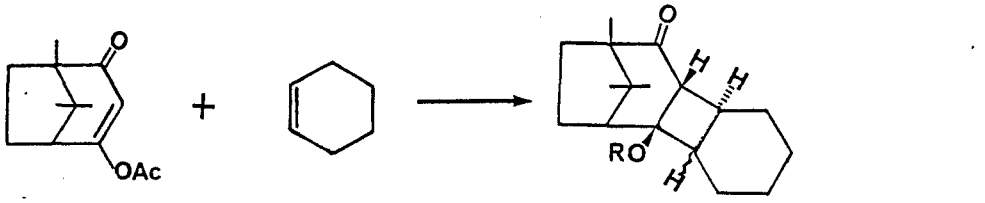
135 R = OMe (50%)

136 R = OAc (55%)



50 %

120 137 138



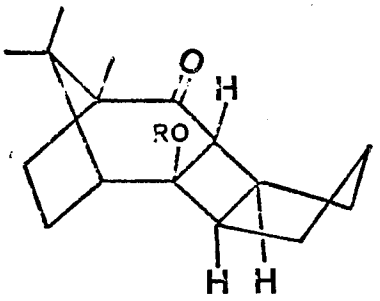
122 139 | mixture R = OAc (55%)

All reactions were conducted in dry cyclohexane. The photoadducts were separated by liquid chromatography and were obtained in crystalline form. Substantial amount of olefin dimer formation[65] rendered separation of the adduct rather difficult. Dimer sometimes amounted to 2-3 times the amount of photoadduct isolated. Utilization of benzene as solvent did not improve the yields of the photoadduct, but only increased reaction times. However, it was observed that dimerization of the olefin was minimized in the benzene medium.

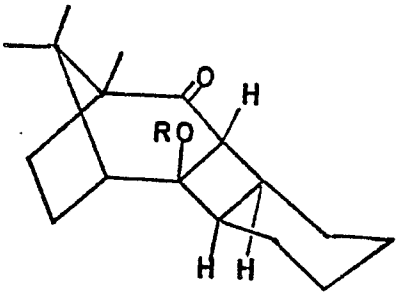
2. Stereochemistry of the Photoadducts

Both cyclopentene adducts 135 and 136 consisted of only one stereoisomer, whereas the cyclohexene adduct with methyl ether 120 was a mixture of two isomers (137, 138). These isomers were separated by preparative liquid chromatography and were obtained pure in a 57:43 ratio. Attempts to separate the isomers of the photoadduct 139, from acetate 122 and cyclohexene, by chromatography was

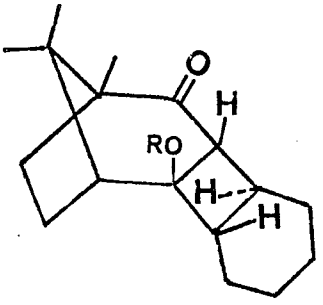
unsuccessful, although one isomer was obtained in 80 % purity by fractional crystallization. Structure determination of these isomers by 400 MHz NMR spectra was attempted, but stereochemical assignment of the protons was difficult due the presence of many overlapping proton signals. The stereochemistries of these adducts were finally determined by X-ray crystallography performed at Hoffmann-La Roche by Dr. J.F.Blount (Figure 4). In all



cis-anti-cis
135 (R = Me)



cis-anti-cis
137 (R = Me)



cis-anti-trans
138 (R = Me)

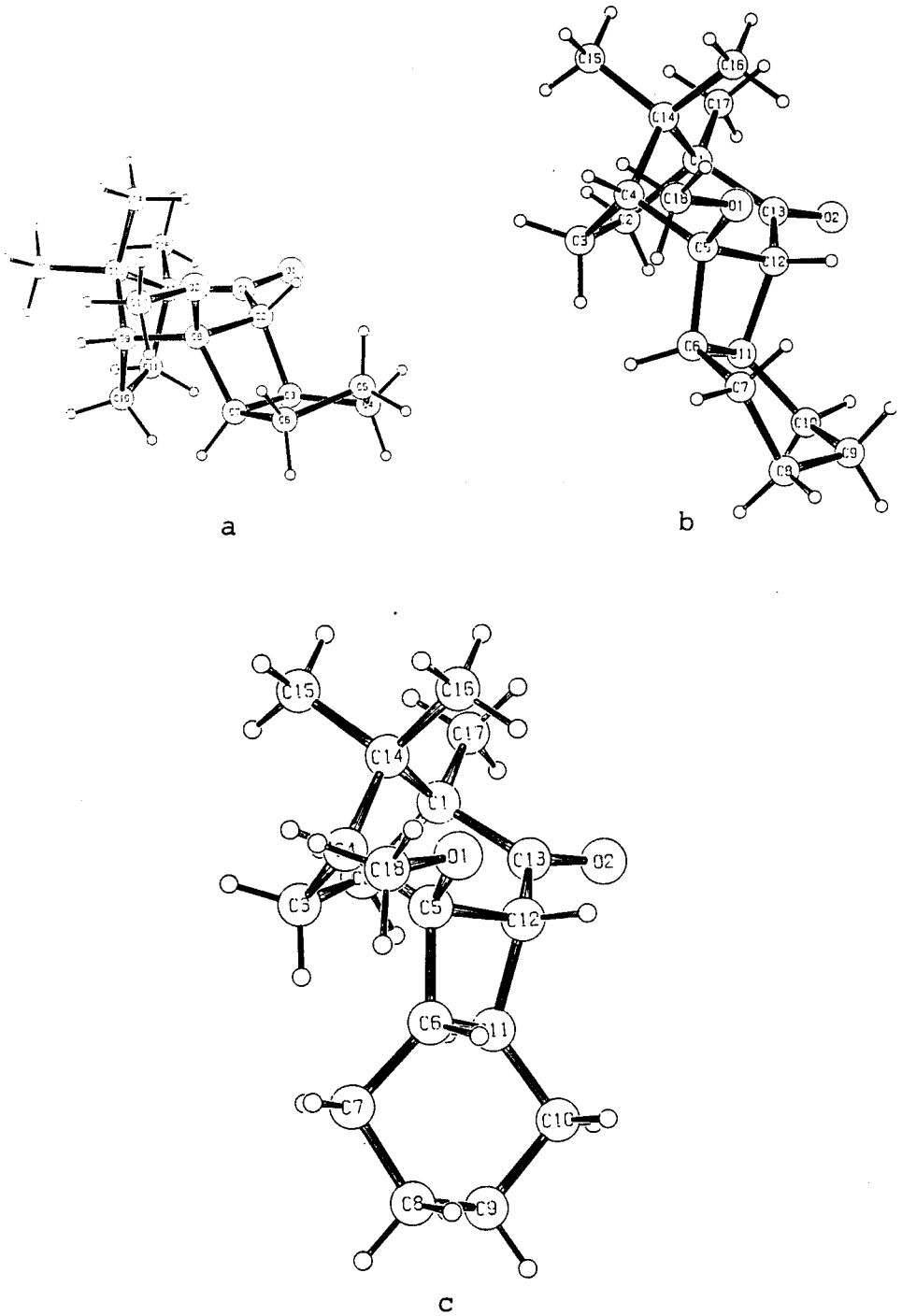
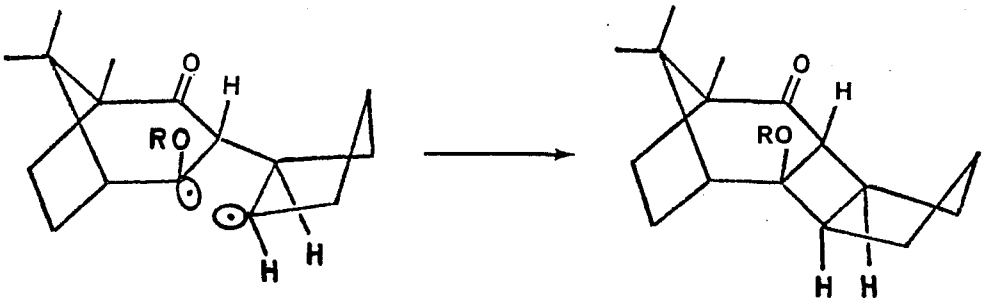
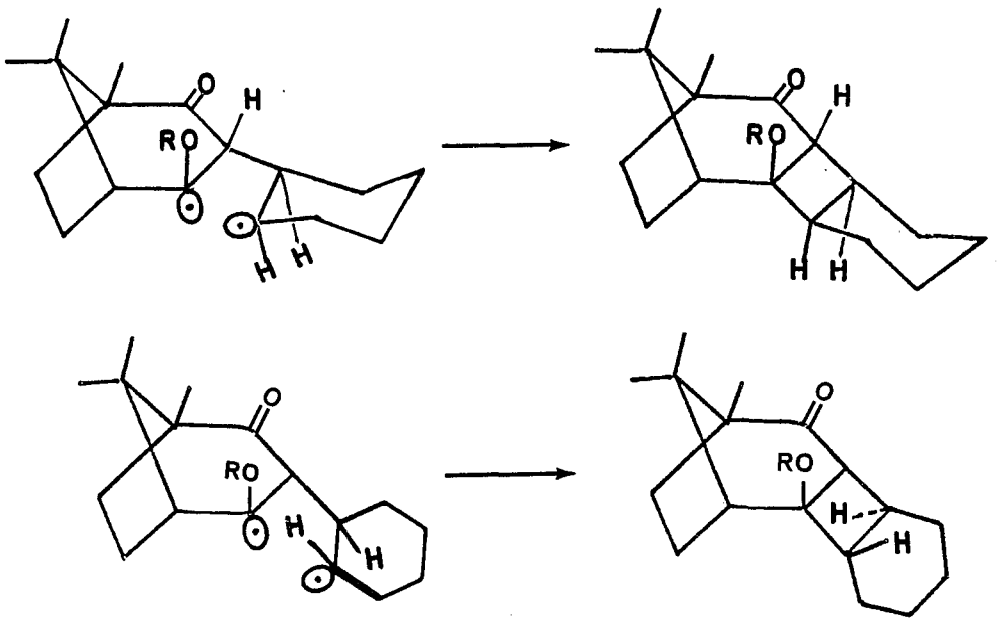


Figure 4. X-ray crysal structures of Compounds a) 135, b) 137, c) 138.

adducts the olefin addition occurred from the endo face of the enone, probably due to hindrance from the gem-dimethyl group. Also, a cis ring fusion on the enone side occurred in all cases. Whereas the cyclopentene adducts proved to be cis,anti,cis, the more flexible cyclohexane ring closed both in cis and trans fashion providing two stereoisomers. (Details of the x-ray crystallographic data are given in appendix i).

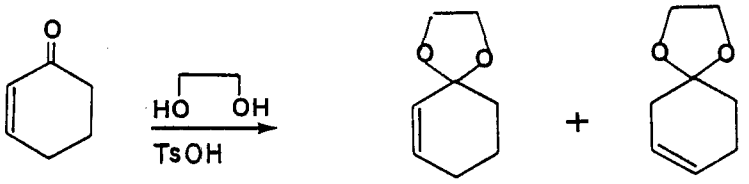
These results are to be contrasted with those of Blechert. Incorporation of a ketal in the A ring forced exo attack by the alkene. Here, the preference appeared to be dictated solely by the bridge gem-dimethyl groups. The intermediate diradicals which lead to the products are shown in Scheme 26. Here the first bond is assumed to be formed at $C\beta$ of enone in contrast to the intramolecular case (Scheme 7), probably due to stabilization of the radical by the oxygen atom.





Scheme 26

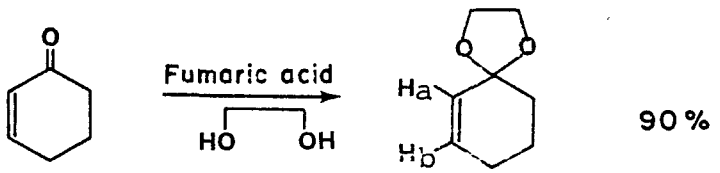
Having achieved some of the photoaddition reactions, we turned our attention to the use of a more functionalized olefin. Cyclohexene ketal 140 was chosen for this purpose. Ketalization of cyclohex-2-en-1-one with ethylene glycol and p-toluenesulfonic acid led to a mixture due to double bond isomerization as reported.[66]



140

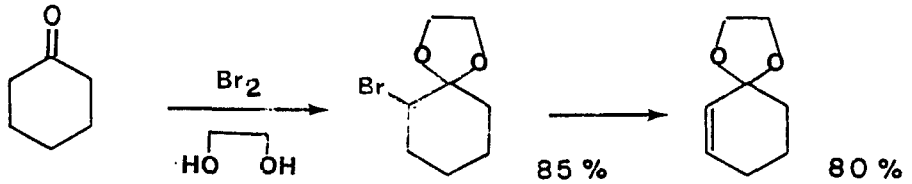
It has been proposed[67] that fumaric acid and weaker acids would diminish isomerization. In fact we were able

to obtain the desired ketal in 90 % yield using fumaric acid as the catalyst. The struture 140 was assigned to this compound based on NMR spectra, protons Ha and Hb could easily be identified by their chemical shifts and coupling constants (Ha, 5.4 ppm dt, J = 10 Hz, 1.5 Hz; Hb, 5.8 ppm dt, J = 10 Hz, 3 Hz). Proton Ha is shifted to high field due to the presence of the ketal.



140

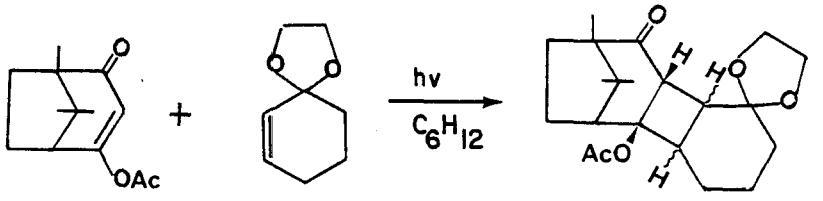
Finally this structural assignment was confirmed by preparing ketal 140 by an alternate route (Garbisch et al.[68]).



141 140

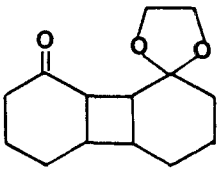
Dipole—dipole interaction in the triplet state exciplex (enone—olefin π complex) controls the regiochemistry in photocycloaddition reactions, as explained earlier. With this idea in mind the photoaddi-

tion reaction of enol acetate 122 with the ketal 140 was carried out in cyclohexane and an adduct 142 was separated in 40 % yield. The structure of the photoadduct was assigned on the basis of spectral data and chemical transformation to a ring opened product. The NMR spectra showed a distinguishable acetate (2.1 ppm), a ketal (4.0 ppm), and three methyls as two singlets (0.95 ppm, 1.00 ppm). IR spectra showed an acetate and ketone absorption at 1720 and 1680 cm^{-1} respectively.

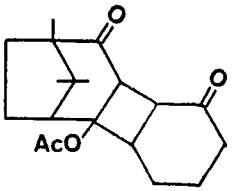


122 140 142

Unless the reaction mixture is scrupulously dried, the ketal hydrolyzes easily to regenerate the enone, which then undergoes a [2+2] addition reaction with unhydrolyzed ketal. Fine crystalline precipitates of this adduct 143 were separated occasionally from the reaction after photolysis. It showed absorption at 1730 cm^{-1} in the IR spectra and a ketal at 3.7 ppm in the NMR spectra, confirming its structure. The ketal of the adduct 142 was also susceptible to hydrolysis on the column during chromatography, and a small amount of the diketone 144 was isolated as a white solid.



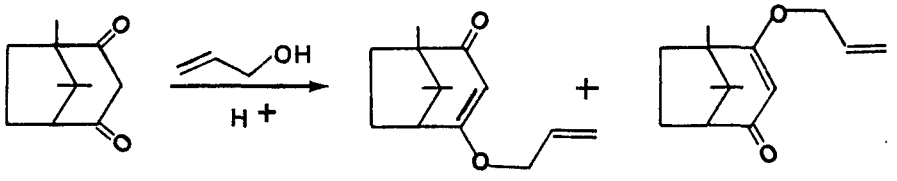
143



144

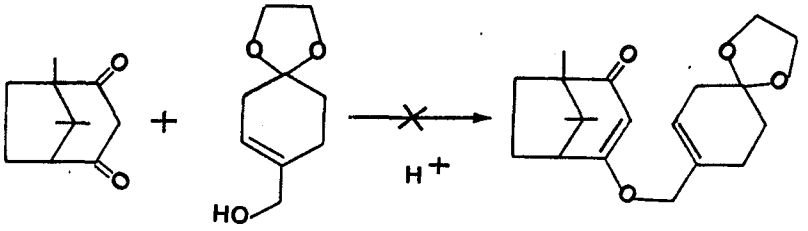
3. Intramolecular Photocycloaddition

The possibility of intramolecular enone—olefin cycloaddition reaction was also investigated. Thus, homocamphorquinone, on refluxing with allyl alcohol and p-toluenesulfonic acid monohydrate in chloroform with a water removing trap, yielded a mixture of isomeric allyl ethers (8:1) in 95 % yield. Here also the structures of the major and minor compounds were assigned by analogy with the firmly established structures of similar compounds (scheme 10). These were separated by silica gel chromatography. Irradiation of the major isomer 145, however, did not produce any photoadducts.

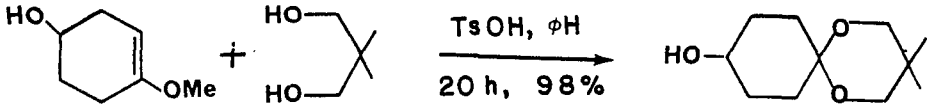


145 146

In another reaction we tried to attach a cyclohexene ketal appendage to the homocamphorquinone, but only intractable products were isolated, probably due to hydrolysis of the ketal and subsequent elimination of alcohol leading to aromatization.

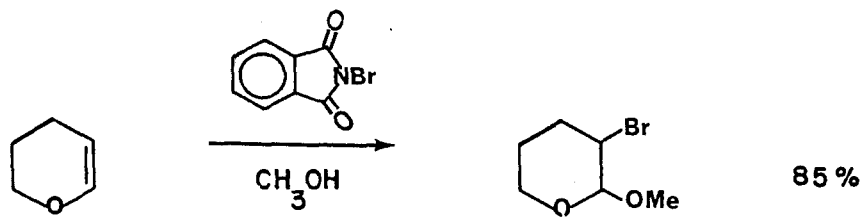


Ketalization of enol ethers can be achieved using the alcohol and an acid catalyst.[67]

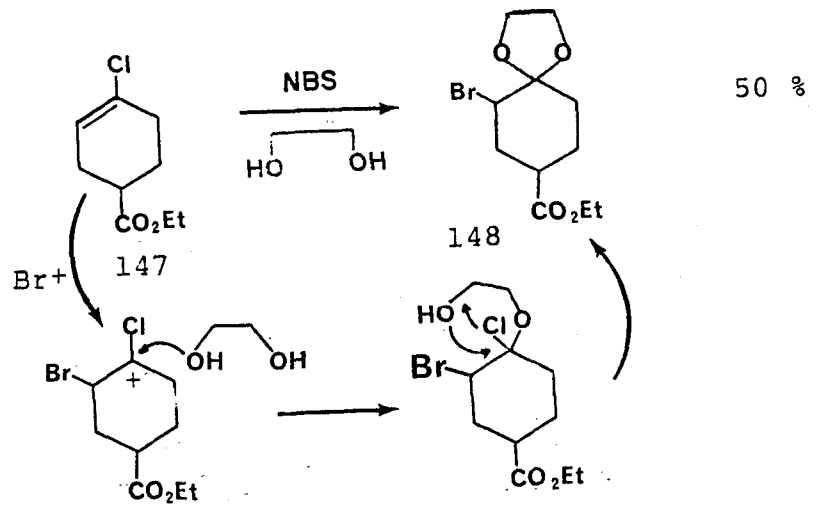


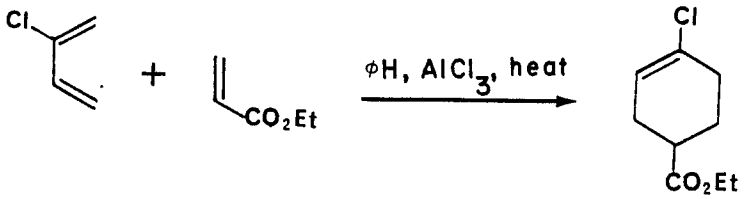
Boron trifluoride etherate also catalyzes this reaction efficiently.[69]

In a related reaction N-bromophthalimide was used to prepare a cyclic bromo ketal as follows:



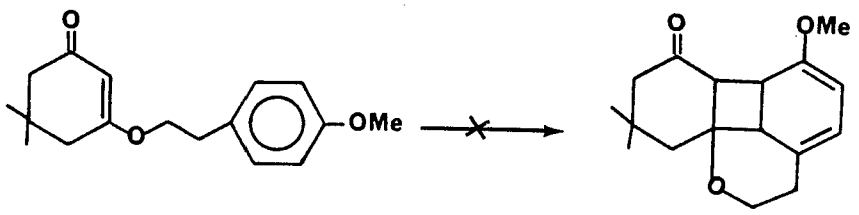
In a similar investigation we achieved brominative ketalization (148) of vinyl chloride 147 using n-bromo-succinimide and ethylene glycol. Bromine and acid catalysed ketalization of 147 with ethylene glycol did not yield any products. The compound 147 was obtained by a Diels-Alder reaction between chloroprene and ethyl acrylate in presence of aluminum chloride.[70] This type of one-step brominative ketalization of vinyl halides has not been reported, and we consider this as a new reaction bearing synthetic potential.





147

An attempt to achieve an intramolecular enone—phenyl photocyclization (rarely found in the literature[71]) was also not rewarding when tried on a model system.

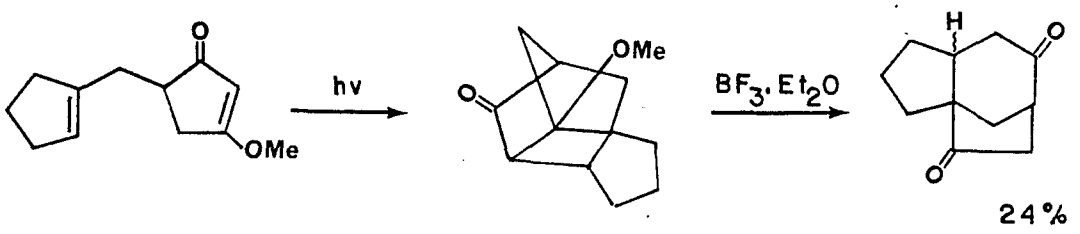


Although we had abandoned this type of photoaddition reaction after a limited investigation, we still hoped that an intramolecular photoaddition reaction and subsequent ring opening would provide a good pathway to generate tricyclic compounds as Taxane models. Later

Mr. Amerasekara in our group successfully carried out an intramolecular photocycloaddition reaction and a subsequent ring opening reaction (Scheme 20).

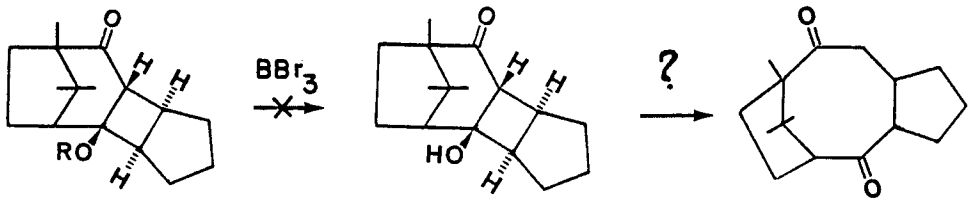
Part IV. Ring Opening Reactions

1. Oppolzer[72] had used boron trifluoride etherate in the ring openings of cyclobutane rings which contain an ether linkage. Treatment of 135, 137, and 138 under Oppolzer's conditions failed to give any products.

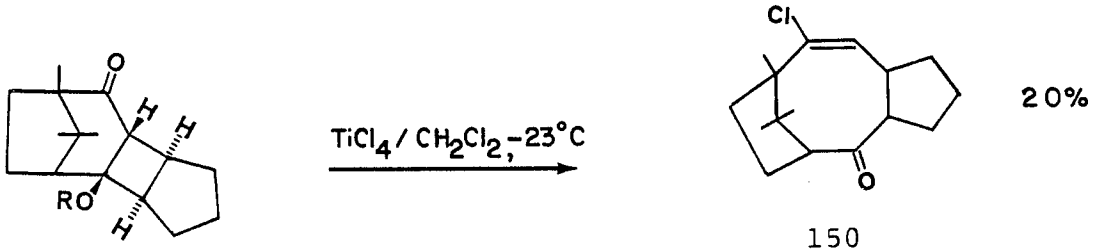


Also these compounds resisted ring opening by mineral acids.

2. Ether cleavage reactions using boron tribromide[73] or titanium tetrachloride were studied in an attempt to generate diketone 149. In each case, however, an olefinic compound was isolated in 20% yield (Scheme 27). The IR spectra showed a ketone absorption at 1730 cm^{-1} and NMR spectra showed the presence of one vinylic proton. Based on this results structures 150 and 151 were assigned.

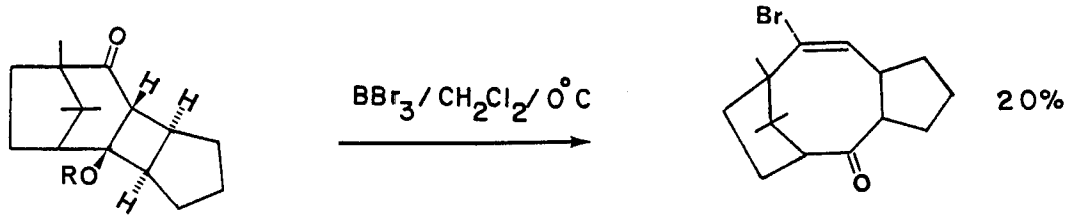


149



20%

150



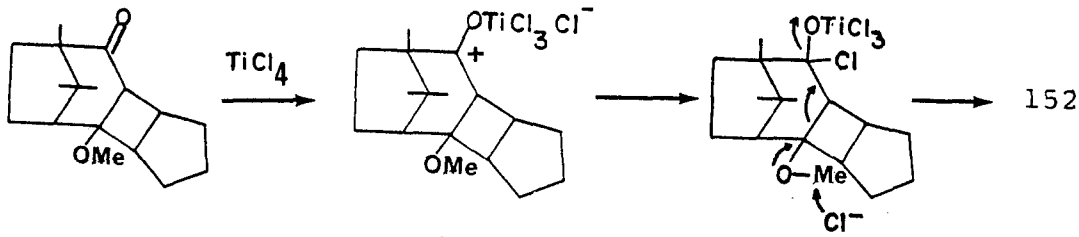
20%

R = OMe 135

151

Scheme 27

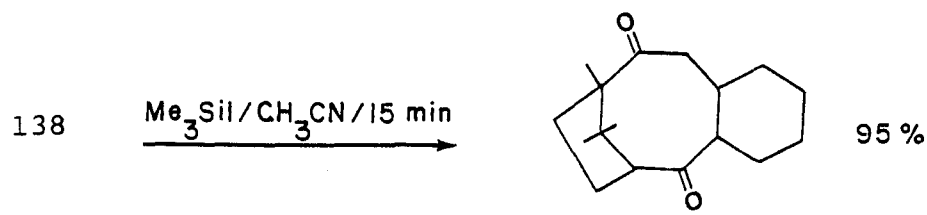
Mass spectral analyses were also in agreement with the above structures. We suggest a mechanism (Scheme 28) which is compatible with the product formed. Since these reactions were done at an earlier stage of the thesis research and were in low yields, we didn't pursue them further. However, we believe that this is an interesting reaction, and future work will help to understand the mechanism and to increase the yields.

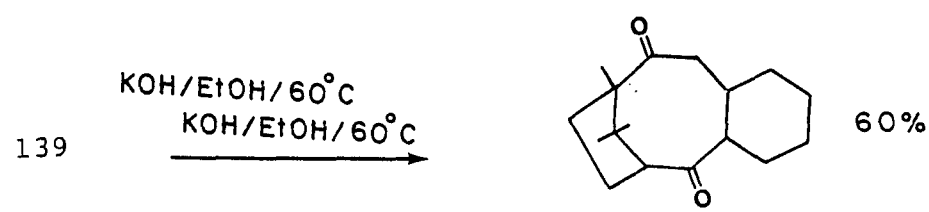


Scheme 28

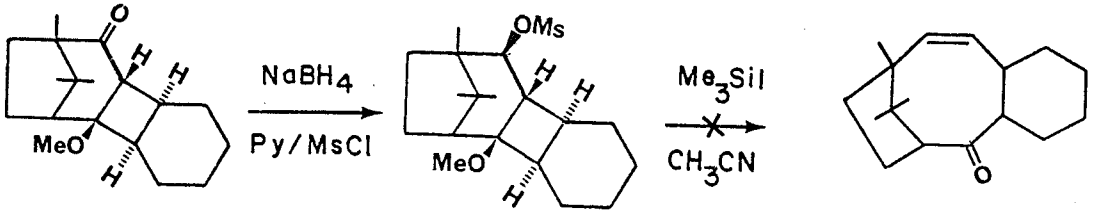
3. Ether Cleavage Using Me_3SiCl/NaI in Acetonitrile

Ether cleavage using trimethylsilyl iodide in acetonitrile, as reported by Olah[74], was applied to the photoadducts 135, 137, and 138. Here compound 138, with a trans cyclobutane ring fusion, underwent ring opening (95 %) in 5 min, whereas 135 and 137 resisted cleavage. This unusual result is best explained in terms of strain in the cyclobutane ring in the adduct 138, compared to that in the cis fused adduct 137. The ring opened compound 152 was identical to the product of base hydrolysis of 139 (mp, IR, NMR).



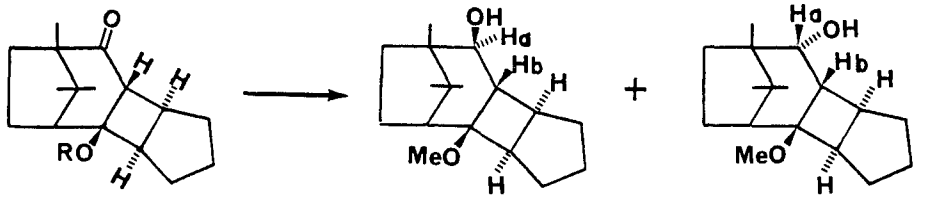


Grob fragmentation using a mesylate 154 derived from 138 was also attempted. No fragmentation occurred with Me_3SiI, suggesting that a trans periplanar relationship between the mesylate and methoxy groups is the overriding factor in the fragmentation reaction, rather than the strain in the cyclobutane ring. It should be noted that the alcohol derived from the sodium



138 154

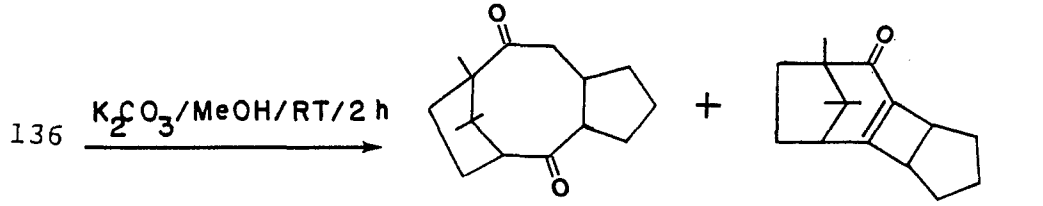
borohydride reduction of the adduct 138 gave an alcohol 153a in 90% yield in which the hydroxyl group was cis to the methoxy group. The α-orientation of the alcohol was expected because the gem-dimethyl hinder exo attack. This stereochemistry was proved by the 200 MHz NMR spectra of the two alcohols (155a and 155b) derived from a similar photoadduct. Here the coupling constant of Ha were compared. In the major alcohol (155a) the dihedral angle between Ha and Hb is 90° and Ha appeared as a singlet (3.75 ppm) whereas in the minor one the angle is zero and Ha appears as a doublet (3.7 ppm, J=8 Hz). Reduction reactions of all similar photoadducts gave a major alcohol bearing this stereochemistry.



155a 90 % 155b 10 %

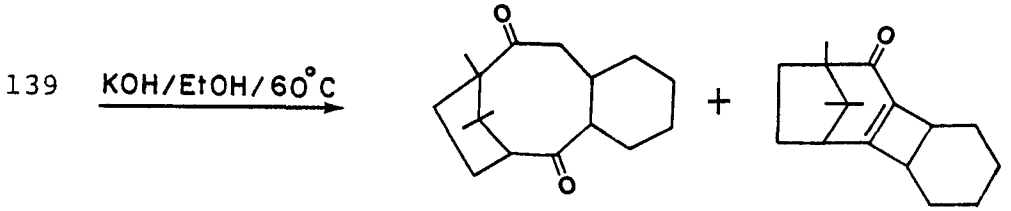
4. Retro-Aldol type Cleavage

The photoadducts with an acetate substituent underwent retro-aldol reaction to give the following results:[75]



156 60% 157 20%

136 H_2SO_4/MeOH/2 weeks 156 30 % + 157 10 %

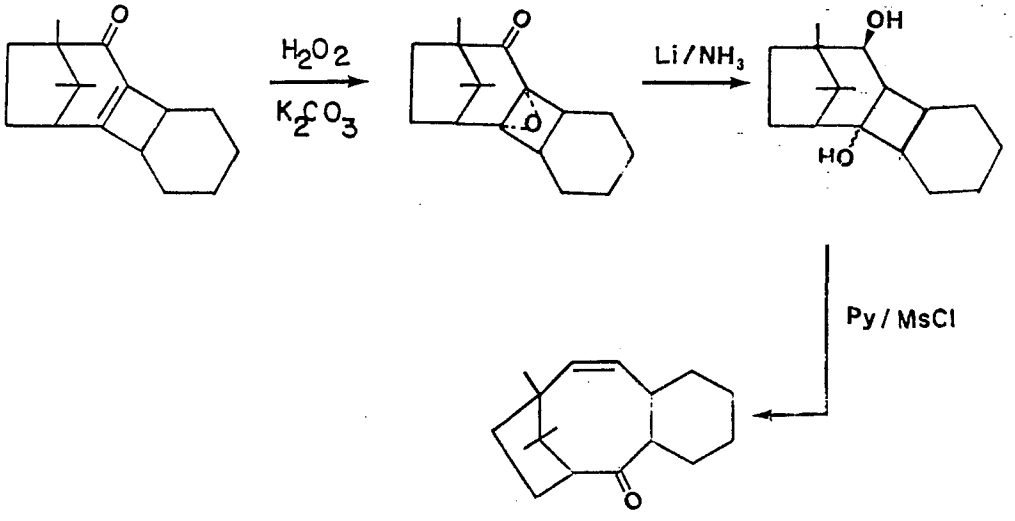


152 60% 158 20%

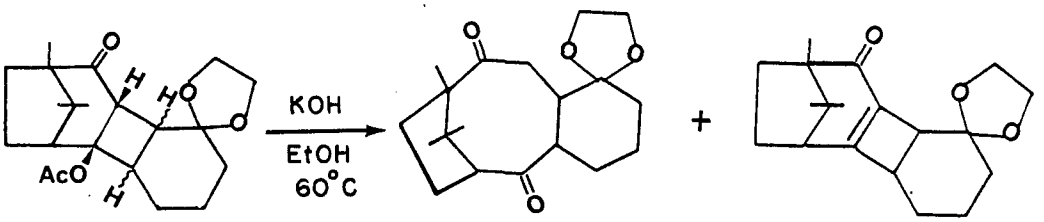
139 H_2SO_4/MeOH/2 days 152 40 % + 158 10 %

All products were isolated in crystalline form and the structures were assigned on the basis of NMR and IR spectra. All compounds gave satisfactory analytical results.

In both acid and base hydrolyses a cis elimination of acetate, though unexpected, occured in significant amounts. However, the enone derived from elimination might be subjected to a Wharton fragmentation[76] reaction to generate the 8-membered ring as demonstrated by Swindell in an attempt at Taxane synthesis.



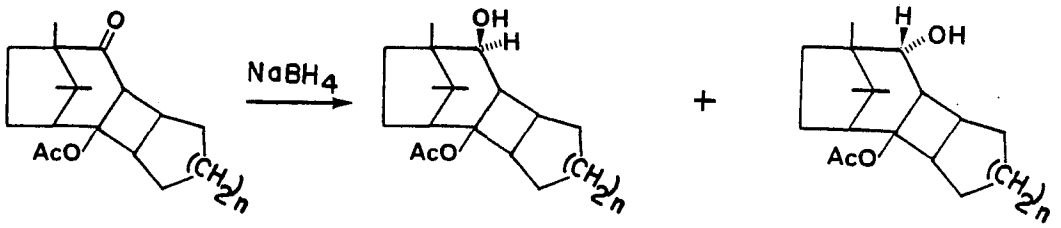
Photoadduct 142 underwent retroaldol reaction when treated with ethanolic KOH. Here also an elimination product was formed in minor amounts.



142 160 (40%) 161 (15%)

5. Grob Fragmentation studies

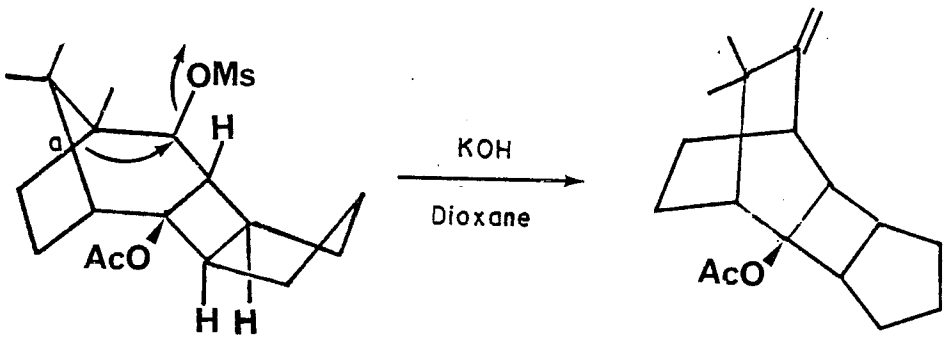
Sodium borohydride reduction of the photoadducts gave the following results:



136	n = 1	162	n = 1	(90%)	164 (10%)
139	n = 2	163	n = 2	(90%)	165 (10%)

As expected the reduction occured from the side opposite to the gem-dimethyl group. The stereochemistry of the alcohol was confirmed by 200 MHz NMR spectra as explained before. The alcohols 162 and 163 were converted

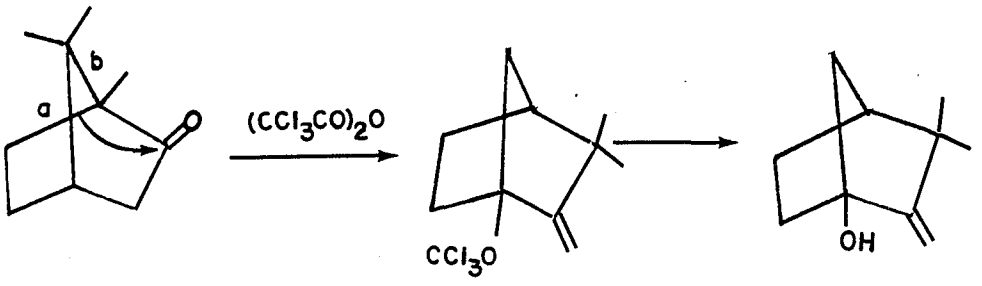
into the corresponding mesylates by treating with triethylamine and methanesulfonyl chloride. The mesylate 166 was refluxed with a dioxane solution of potassium hydroxide whereupon a rearrangement product was isolated



166 167

(80%) with no trace of fragmentation product. This conclusion was reached based on the disappearance of the NMR peaks of the mesylate group and one of the methyl groups, and appearance of two olefinic proton peaks; also, the acetate group remained unreacted (2.1 ppm, singlet) and the IR spectrum showed an absorption at 888 cm^{-1}, characteristic of an exo olefinic group. We attribute the failure of ring opening to the lack of the trans periplanar relationship between the leaving group and the acetate required for Grob fragmentation. In a more flexible system this requirement is not a hindrance to reaction. Also, the mesylate is a good leaving group and

is perfectly oriented to be displaced by the migration of the a bond. Similar rearrangement is common in camphor type molecules, where bond a migrates in preference to bond b.



EXPERIMENTAL

General Procedures. Melting points (uncorrected) were determined in open capillaries in a Thomas--Hoover Uni-melt apparatus. Routine proton spectra were obtained in the indicated solvent on a Varian EM 360 nuclear magnetic resonance (NMR) spectrometer. High field proton spectra were determined on a IBM Bruker WP-200-S4 (200 MHz) instrument. Chemical shifts were reported in ppm downfield from tetramethylsilane. Splitting patterns are designated as s (singlet); d (doublet), t (triplet) q (quartet), and m (multiplet). Coupling constants are given in Hz. Infrared spectra (IR) were recorded on a Perkin-Elmer IR 598 instrument. Ultraviolet (UV) spectra were obtained from solutions in the indicated solvent using Varian Model 635 LC spectrophotometer. Gas liquid chromatography (GLC) were performed with a varian Aerograph 920 thermal conductivity instrument using either by a 10 ft by 1/4 in. column packed with 20 % silicone oil DC 710 on Chromosorb W (60-80 mesh) or by a 10 ft by 1/4 in. column packed with 20% Apiezon L on Chromosorb W. High performance liquid chromatography (HPLC) was conducted using a Waters Associates (Milford, Mass.) system consisting of two 4 mm by 30 cm microporasil silica columns in series, a 6000 SDS pump, U6K injector, and model 401 differential

refractometer. Column Chromatography was carried out on E. Merck silica gel (230-400 mesh) according to the procedure of Clark Still[77]. Preparative LC was performed on E. Merck Art. 7747 silica gel. Some separations were efficiently carried out using Chromatotron apparatus with a rotating plates coated with E. Merk Art. 7749 silica gel. Thin later Chromatography (TLC) were carried out using Macherey-Nagel (MN) silica plates. All photochemical reaction were carried out under nitrogen in pyrex tubes using Rayonett RPR-100 photoreactor with 3000 A lamps. X-ray crystallographic analysis of the photoadducts were performed at Hoffmann La Roche by Prof. J.F. Blount.

Dry solvents were used where required. Tetrahydrofuran was distilled from benzophenone ketyl. Ether and dimethoxyethane were distilled from lithium aluminium hydride. Methylene chloride, acetonitrile, triethylamine (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride with distillation of DMF and DMSO carried out at reduced pressure. All other solvents were dried by appropriate methods[78].

PART I. PREPARATION OF THE BICYCLO[3.3.1]NONANE SYSTEM

Cis-5-Oxo-1,3-Cyclohexanedicarboxylic Acid 102.[52] To a suspension of 4.53 g (0.025 mol) of 5-aminoisophthalic

acid and 20 mL of methanol, 200 mL of ammonia was introduced with Dry Ice-isopropanol cooling. Sodium (3.5 g, 0.15mol) was added in small pieces at -78° C during a period of 15 min. while the reaction mixture was constantly stirred mechanically. The solution became first light green and finally yellow colored. The solution was stirred for an additional 30 min. and 5 g of ammonium chloride was cautiously added in small portions. Ammonia was allowed to evaporate overnight, and the residue was dissolved in a minimum amount of water and acidified with 20% HCl. The aqueous solution was extracted with ethyl acetate (5 times) and the combined extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo to yield 1.4g (30%) of browinsh solid. Crystallization from acetone:ethyl acetate (1:2) furnished powdered white product. mp 178-180° C (lit[52]. 178-182°C).

IR (KBr): 3200-3000, 1705, 1405, 930 cm^{-1}.

NMR (D_2O): 1.53.1 (m, 8H).

In some preparations the crude product was dissolved in ethyl acetate and boiled with activated charcoal to remove colored impurities. Filtration and evaporation of the solvent in vacuo generated colorless solids which were purified by crystallization.

Esterification Using Diazomethane (103). An ethereal solution of diazomethane was prepared from diazald (Aldrich) according to the procedure in Fieser and Fieser[79]. The dicarboxylic acid 102 (500 mg, 2.7 mmol) was added in portions to 50 mL of diazomethane. Evolution of nitrogen was observed. A white precipitate was formed initially which gradually went into solution on stirring at room temperature for 1 h and the solution remained yellowish which indicated the presence of excess of diazomethane. After evaporation of ether, white shining crystals were obtained (490 mg, 85 %). This was further purified by crystallization from ethyl acetate, mp 119-120°C (lit[52]. 120-122°C).

IR ($CHCl_3$) : 1740, 1445, 1360, 1205, 1185 cm^{-1}.

NMR ($CDCl_3$) : 1.7-3.1 (m, 8H), 3.73 (s, 6H).

Esterification Using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and Methyl Iodide in Acetonitrile (103)[80]. Into a dry nitrogen filled flask was introduced a magnetic stirring bar, 500 mg (2.7 mmol) of dicarboxylic acid 102, and 3 mL of dry acetonitrile. To the well stirred solution was added 815 mg (5.36 mmol) of DBU followed by 775 mg (5.46 mmol) of methyl iodide. The reaction mixture was stirred at room temperature for 2 h and at 45°C for 0.5 h. The contents of the flask were cooled and

poured into water and extracted two times with ether. The combined ethereal extracts were dried with magnesium sulfate and concentrated in vacuo to provide 250 mg (43 %) of diester as a white solid which was identical to the compound 103 prepared above using diazomethane (NMR, IR, GLC). Crystallization from ethyl acetate provided colorless crystals, mp 118-120 C(lit[52]. 120-122 C).

IR ($CHCl_3$) : 1740, 1445, 1360, 1205, 1185 cm^{-1}.

NMR ($CDCl_3$) : 1.7-3.1 (m, 8H), 3.73 (s, 6H).

Ketalization of 103. To a solution of diester 105 (2.71 g, 12.66 mmol) in 35 mL of benzene was introduced 0.99 g (13 mmol) of ethylene glycol and 9.65 mg of para-toluene sulfonic acid monohydrate. The mixture was heated under reflux for 6 h in a Dean-Stark apparatus, then cooled, washed with 2 N NaOH solution, water and dried over magnesium sulfate. The benzene was distilled out to provide a solid residue (2.7 mg, 80 %) which was purified by sublimation under reduced pressure (105 C, 0.125 mm), mp 65-66 C (lit[52]. 66-67 C).

IR (KBr) : 1740, 1445, 1360, 1205, 1185, 1085 cm^{-1}.

NMR ($CDCl_3$) : 1.0-2.9 (m, 8H), 3.64 (s, 6H), 3.92 (s, 4H).

Acyloin Condensation (105) . Sodium (0.716 g, 31.0 mmole) was charged into 15 mL of dry toluene in a 50 mL flask equipped with a vibromixer (A.G.fur, Chemie Apparatebau, Zurich, E, No.6215). The flask was heated with an oil bath to 130 C and the vibromixer was set to give a fine suspension of sodium. The sodium suspension was rapidly cooled to 80 C and a solution of 2 g (7.75 mmole) of diester 104 and 4 mL (31.4 mmole) trimethylsilylchloride in 6 mL of toluene was added all at once. The reaction mixture was heated under reflux to 100 C, whereby a sudden reaction occurred which turned the reaction mixture to a violet color. The reaction mixture was refluxed for 2 h, cooled, filtered in the absence of moisture through celite and concentrated in vacuo to afford 3 g of the product as a yellowish oil. This was distilled under reduced pressure to provide 2.4 g (90%) of 105 as a colorless oil.

IR (CCl_4) : 1690, 1430, 1350, 1280 cm^{-1}.
NMR (CCl_4) : 0.17 (s, 18H), 1.16-1.56 and 1.67-2.42 (m, 8H), 3.82 (s, 4H).

Spiro-3-bromobicyclo[3.3.1]nonan-2,4-dione-7,2'-dioxalane (106). To a suspension of 3.17 g (6.0 mmol) of $Ph(CBr_3)Hg$ (Alfa products/Thiokol) in 17 mL of benzene was added 2.4 g (7.0 mmol) of 105 under nitrogen. The

mixture was stirred at 80° C for 2 h. After cooling to 0° C the precipitated phenyl mercuric bromide was filtered out. The oil obtained after evaporation of benzene was taken up in 4 mL of tetrahydrofuran and diluted with 0.75 mL of 1 N HCl and stirred at 30° C for 45 min. The first and second crystallization yielded solids which were phenyl mercuric bromide. A third crystallization provided 400 mg (20%) of 2-bromo-1,3-diketone 106 as white crystals, mp 193-194° C (lit[52]. 194-195° C).

NMR (DMSO) : 1.55-2.28 (m, 6H), 2.78 (br, 2H), 3.75 (s, 4H).

Spirobicyclo[3.3.1]nonan-2,4-dione-7,2'-dioxalane (107). Chromium(II) acetate was prepared according to the literature procedure from chromic chloride hexahydrate[81]. A suspension of freshly prepared Cr(II) acetate dihydrate (from 5.5 g of Cr(III) chloride hexahydrate and Zn) in 5 mL of boiled water was mixed with a solution of 145 mg (0.5 mmol) of 106 in 20 mL of acetone and stirred at 20° C for 16 h. The excess chromium salt was suction filterd and washed twice with 10 mL of acetone. The combined filtrates were extracted twice with 10 mL each of chloroform and ethyl acetate. The combined organic layers, on concentration in vacuo provided 83.5 mg (80%) of diketone which was purified by crystallization (ethanol/

cyclohexane, 1:4) to afford fine crystals of 107, mp 164-166° C (lit[52]. 162-163.5° C).

NMR ($CDCl_3$) : 1.71-2.42 (m, 6H), 2.68- 2.94 (m, 2H), 3.32 (s, 2H), 3.82 (m, 4H).

Preparation of Enolacetate from 1,3-Diketone (108). To a stirred solution of 50 mg (0.238 mmol) of 1,3-diketone 107 in 1 mL of dry chloroform was added 18.8 mg (0.238 mmole) of freshly distilled pyridine. The mixture was stirred for 30 min, then to this solution was introduced 20 mg (0.258 mmol) of freshly distilled acetylchloride, dropwise. This mixture was stirred for 1.5 h at room temperature, then washed with water, dil. HCl, saturated sodium bicarbonate solution, and finally with water. The organic phase was dried with magnesium sulfate and the solvent concentrated in vacuo to provide 55 mg (80%) of enolacetate 108.

IR ($CHCl_3$) : 1770, 1680, 1450, 1360, 1200, 1120 cm^{-1}.
NMR ($CDCl_3$) : 1.3 (s, 2H), 2.0-2.3 (m, 4H), 2.3 (s, 3H), 2.8 (br, 2H), 3.95 (s, 4H), 6.0 (s, 1H).

Compound 103 from 5-Hydroxyisophthalic Acid (110).[57] To a solution of 118 g (0.5 mol) 5-sulfoisophthalic acid monosodium salt (Aldrich) in 400 mL of absolute ethanol was slowly introduced 112 g (2 mol) of potassium

hydroxide in 500 mL of absolute ethanol. The precipitate of tripotassium salt was suction filtered, dried, and collected.

The tripotassium salt was added gradually to a melt of potassium hydroxide pellets (600 g) at 280° C. Gas evolution was noted. The temperature was then held 325° C for 5 h. The resulting solid was mixed with 1.4 L of water, the alkaline mixture was filtered and to the filtrate was added 840 mL of concentrated hydrochloric acid with ice cooling (to pH 2). Filtration of the mixture at room temperature afforded crude 5-hydroxyisophthalic acid as white solid. Several crystallizations from water produced 50 g of 5-hydroxyisophthalic acid 110, mp 300-302° C (lit.[57] 305-306° C).

Dimethyl 5-Hydroxyisophthalate (111). A solution of the above hydrated 5-hydroxyisophthalic acid 110 (40 g, 0.21 mole) in 500 mL of anhydrous methanol containing 5 ml of concentrated sulfuric acid was refluxed for 2 days. After filtration the clear solution was stripped of solvent in vacuo. The residue was taken up in ethyl acetate (400 mL) and the solution was washed free of acid with aqueous sodium bicarbonate. The dried (magnesium sulfate) ethyl acetate solution was concentrated on a rotary evaporator and kept in an open dish until the resulting white crystals of dimethyl 5-hydroxyisophthalate

111 reached a constant weight (37 g, 80 %), mp 160-161°C (lit.[57] mp 162-163°C).

IR (KBr): 3500-3300, 1730, 1710, 1610, 1485, 1350, 1210, 1150 cm^{-1}.

NMR ($CDCl_3$): 3.94 (s, 6H), 7.71-8.12 (m, 3H).

Hydrogenation of Dimethyl 5-Hyrdoxyisophthalate (112). To a suspension of 500 mg 5 % Rh/C catalyst (Englehart Industries, Inc.) in 150 mL absolute ethanol was introduced 1 g (4.76 mmol) of ester and the mixture was hydrogenated at 55 psi until the uptake of hydrogen had stopped (3 h). The reaction mixture was filtered and the solvent was evaporated in vacuo to yield a clear liquid which consisted of two compounds, a hydroxy ester (112) and a hydrogenolysis product (113), in a 3 : 5 ratio. These compounds were separated by column chromatography (hexane/ethyl acetate, 4:1).

Compound 112,[57] IR (CCl_4): 3500-3450, 1735, 1440, 1250, 1165 cm^{-1}.

NMR ($CDCl_3$): 1.2-2.6 (m,10H), 3.7 (s,6H)

Compound 113,[57] IR (CCl_4): 1730, 1450, 1420, 1250, 1180 cm^{-1}.

NMR ($CDCl_3$): 1.2-2.4 (m, 10H), 3.7 (s, 6H).

Oxidation of Methyl 5-Hydroxy-cis-1,3-cyclohexane Dicarboxylate (114). Method a: A solution of finely powdered potassium dichromate (1.59 g, 5.4 mmol) in 8 mL of acetic anhydride was heated to 60° C in a water bath. To this well stirred solution was added 345 mg (1.6 mmol) of alcohol 112 in 2 mL of acetic acid over a period of 5 min. The reaction mixture was kept at 60° C for 15 min, then cooled, diluted with water and extracted several times with ether. The ethereal extract was dried with magnesium sulfate and concentrated in vacuo to provide 250 mg (72 %) of white solids. This was recrystallized from hexane/ethyl acetate (5:1) giving 114, mp 116-117° C (lit.[52] mp 118-120° C).

Oxidation. Method b. Dry pyridine (4 g, 50 mmol) in a round bottom flask was cooled to 0 C and 350 mg (3.5 mmol) of CrO_3 was added slowly with stirring. To this solution 250 mg (1.16 mmol) of alcohol 112 in 2 mL of pyridine added. The reaction mixture was kept at 0° C for 30 min, then warmed to room temperature and stirred for 2 days. The reaction mixture was then diluted with water and extracted with ether. The organic layer was back-washed with water and brine, dried over magnesium sulfate and concentrated in vacuo to provide 150 mg (60%) of ketone 114 as white solids, which was identical (mp, NMR, IR) to the compound prepared by method a.

PART II. PREPARATION OF HOMOCAMPHORQUINONE AND ITS DERIVATIVES

Homocamphorquinone (119).[58] An ethereal solution (220 mL) of diazomethane (3 g, 0.07 mol) prepared from Diazald (Aldrich) was carefully layered over 100 mL of 5 % KOH solution in an Erlenmayer flask. Camphorquinone 118 (3.8 g, 0.022 mol) was added in portions over a period of 5 min with vigorous stirring. Evolution of nitrogen was noted. Stirring was continued for 3 h and the ether layer was allowed to evaporate. The basic aqueous layer was acidified with 12 N HCl with ice cooling. A white precipitate of 1,3-diketone (3.4 g, 93 %) was formed. Crystallization from benzene/petroleum ether (1:1) provided a white solid 119, mp 218-220° C (lit.[58] mp 223-224° C).

IR ($CHCl_3$) : 1720, 1700, 1450, 1370 cm^{-1}.
NMR ($CDCl_3$) : 0.80 (s, 3H) , 0.95 (s, 3H), 1.10 (s, 3H), 1.8-2.1 (m, 4H), 2.5-2.7 (m, 1H), 3.25 (dd, 2H, J = 23 Hz and 18 Hz).

1,8,8-Trimethyl-2-oxo-4-methoxy bicyclo(3.2.1)oct-3-ene (120). To an ethereal solution (240 mL) of diazomethane (3 g, 0.07 mol) at 0° C was added 1.4 g (8.4 mmol) of camphorquinone in small portions; evolution of

nitrogen was noted. After 10 min 1.2 mL of methanol was added and the reaction mixture was kept at 0° C for 3 h, then at room temperature overnight. To the ether layer was added 1 N sulfuric acid dropwise until the excess of diazomethane was removed. The ether layer was washed with 1 N sulfuric acid, water, three times with 3 N NaOH, and finally with brine, dried with magnesium sulfate, and concentrated in vacuo to provide 1.6 g (94 %) of product as a yellowish oil. This product on distillation (bp 146-147° C, 8 mm) yielded 1.54 g of colorless oil . This was a mixture of two isomers 120 and 121 (8 : 1) which were separated by column chromatography using hexane/ ethyl acetate (2:1) as the solvent. Both isomers were purified by crystallization from hexane and were obtained as fine crystals.

Isomer 120, mp 68-69° C (lit.[58] mp 67-69° C).
IR (CCl_4) : 1650, 1600, 1450, 1365, 1275, 1210 cm^{-1}.
NMR (CCl_4) : 0.94 (s, 6H), 0.99 (s, 3H), 1.2-2.0 (m, 4H), 2.3-2.5 (m, 1H), 3.5 (s, 3H), 5.1 (s, 1H).

Isomer 121, mp 52-54° C (lit.[58] 50-52° C).
IR (CCl_4) : 1650, 1600, 1450, 1365, 1275, 1215 cm^{-1}.
NMR (CCl_4) : 0.93 (s, 3H), 0.95 (s, 3H), 1.1 (s, 3H), 1.4-2.2 (m, 4H), 2.3-2.5 (m, 1H), 3.65 (s, 3H), 5.15 (s, 1H).

1,8,8-Trimethyl-2-oxo-4-acetoxy bicyclo(3.2.1)oct-3-ene (122). A solution of 500 mg (2.77 mmol) of diketone 119 was dissolved in 15 mL of dry chloroform and 210 mg (2.77 mmol) of pyridine was added. The mixture was stirred for 15 min and 250 mg (3 mmol) of acetyl chloride was introduced and stirring was continued for 2 h. The reaction mixture was washed with water, dil.HCl, and finally with sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give 550 mg (85 %) of enol acetate as a mixture of two isomers (122 and 123 in a 8 : 1 ratio. The isomers were easily seperated by column chromatography (petroleum ether/ethyl acetate, 4:1) and obtained as colorless viscous liquids.

Isomer 122, IR ($CHCl_3$) : 1760, 1655, 1615, 1430, 1355, 1160 cm^{-1}.

NMR ($CDCl_3$) : 1.05 (s, 6H), 1.15 (s, 3H), 1.8-2.1 (m, 4H), 2.4 (s, 3H), 2.50-2.65 (m, 1H), 5.7 (s, 1H).

Isomer 123, IR ($CHCl_3$) : 1765, 1650, 1610, 1360, 1160 cm^{-1}.

NMR ($CDCl_3$) : 1.05 (s, 3H), 1.15 (s, 3H), 1.2 (s, 3H), 1.8- 2.1 (m, 4H), 2.4 (s, 3H), 2.50-2.65 (m, 1H), 5.7 (s, 1H).

Ring Expansion of Camphorquinone Using Ethyl Diazoacetate (126). a) Boron Trifluoride Etherate as Catalyst. A solution of 200 mg (1.2 mmol) of camphorquinone (118) and 170 mg (1.2 mmol) of boron trifluoride etherate in 5 mL of ether was cooled to -23°C under nitrogen and 136.8 mg (1.2 mmol) of ethyl diazoacetate in 2 mL of ether was added dropwise over a period of 30 min. The reaction mixture was kept at -23° C for 1 h then at room temperature overnight. The presence of a stong UV active product was observed by TLC. The ether layer was washed with sodium chloride several times until neutral, then evaporated to a yellow residue. The residue was dissolved in methylene chloride and the diketone was extracted with sodium bicarbonate. The unreacted camphorquinone remained in the methylene chloride layer and was recovered. The basic solution was acidified with con. HCl and the acidic solution was extracted with methylene chloride. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated in vacuo to provide 60 mg of 126 (yield 20 %) as a yellow solid. (The corresponding acid showed mp 120 C).

NMR ($CDCl_3$) : 1.0 (s, 2 Me), 1.1 (s, Me), 1.4 (t, 3H, J = 8 Hz), 1.7-2.1 (m, 4H), 2.6 (m, 1H), 4.3 (q, 2H, J = 8 Hz).

IR ($CHCl_3$): 1680, 1600, 1220 cm^{-1}.

Preparation of Enol Acetate (131). The above ketoester 126 (437 mg, 1.73 mmol) was dissolved in 7 mL of dry chloroform and 140 µl (1.73 mmol) of pyridine followed by 130 µl (1.9 mmol) of acetyl chloride was added. The reaction mixture was stirred at room temperature overnight. The chloroform layer was washed with dil. HCl, sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo to provide the enol acetate as a yellowish oil (500 mg, 85 %). On distillation under reduced pressure (bp 120° C, 0.025 mm) it afforded a colorless oil which gradually solidified to a white solid 131, mp 134-136° C (hexane ethyl acetate, 9:1).

NMR ($CDCl_3$) : 1.0 (s, 2 Me), 1.1 (s, 1 Me), 1.4 (t, 3H, J = 8 Hz), 1.7-2.1 (m, 4H), 2.25 (s, 3H), 2.6 (m, 1H), 4.3 (q, 2H, J = 8 Hz).

IR ($CHCl_3$): 1690, 1680, 1600, 1460, 1230 cm^{-1}.

b) Triethyloxoniumfluoroborate (Meerwein's Reagent) as Catalyst. Triethyloxoniumfluoroborate was prepared from epichlorohydrin and boron trifluoride[82]. To a solution of camphorquinone (2 g, 12 mmol) in 40 mL of of dry methylene chloride was added 3.8 g (0.02 mol) of triethyloxonium fluoroborate followed by 2.1 mL (0.02 mol) of ethyl diazoacetate dropwise under nitrogen. The reaction

mixture was stirred at room temperature overnight. Appearance of a stong UV active spot was noted on the TLC plate. Saturated sodium bicarbonate (30 mL) was added to the reaction mixture which was then stirred for 30 min. The product was extracted with methylene chloride which was dried over magnesium sulfate and concentrated to a brown viscous liquid. The UV active component was isolated by liquid chromatography (Chromatroton, hexane/ethyl acetate) to afford 110 mg (32 %) of ester as a white solid (128 and 129). This compound without further purification was subjected to decarboxylation.

Decarboxylation. The above ketoesters 128 and 129 (110 mg, 0.39 mmol) were dissolved in 0.5 mL of glacial acetic acid, and a few drops of water was added followed by 0.5 mL of con. HCl. The reaction mixture was refluxed for 3 h, then cooled and extracted with ethyl acetate, washed with sodium bicarbonate, water, brine, and concentrated in vacuo to a brown solid. Recrystallization from benzene/petrolium ether (1:1) provided a white powder which was identical with the diketone 119 previously prepared (mp, NMR).

Preparation of Bromocamphorquinone (130). Method a. A solution of 350 g (1.94 mmol) of homocamphorquinone and 753 mg (2 mmol) of phenyltrimethylammonium tribromide (PTAB) in 5 mL of dry methylene chloride was stirred at

room temperature overnight. The reaction mixture was washed with water, dried, and concentrated in vacuo to provide 500 mg (98 %) of the bromo compound 130 as a brown solid, mp 171-173° C (hexane/ethyl acetate, 5:1).

NMR ($CDCl_3$) : 1.00 (s, 2Me), 1.2 (s, Me), 1.7-2.3 (m, 4H), 2.7-2.9 (m, 1H).

This crude product without further purification was converted into the enolacetate 132 (see below).

Enolacetate of bromohomocamphorquinone (132). To a solution of 450 mg (1.73 mmol) of bromo compound 130 in 5 mL of dry chloroform was added 137 mg (1.73 mmol) of dry pyridine followed by 141 mg (1.8 mmol) of freshly distilled acetyl chloride. The reaction mixture was stirred at room temperature for 15 min whereupon a single UV active spot appeared on TLC. Water was added and the chloroform layer was separated and washed with 6 N HCl and sodium carbonate, and dried over sodium sulfate. Evaporation of the solvent gave 500 mg (98 %) of enol acetate 132 as a colorless liquid. NMR and HPLC showed this to be only one isomer.

NMR ($CDCl_3$) : 1.05 (s, 2Me), 1.2 (s, Me), 1.7-2.4 (m, 4H), 2.35 (s, $OCOCH_3$).

PART III. PHOTOCYCLOADDITION REACTIONS

1,13,13-Trimethyl-9-methoxytetracyclo(8,2,1,$0^{3,9}$,$0^{4,8}$) tridecan-2-one 135. To a solution of compound 120 (320 mg, 1.64 mmol) in 8 mL of dry cyclohexane in a Pyrex photoreaction tube was added 8 g (0.1 mol) of freshly distilled cyclopentene. Dry nitrogen gas was bubbled through the solution with ice cooling to avoid evaporation of volatile cyclopentene. This reaction mixture was irradiated in a Rayonet apparatus. The progress of the cycloaddition was monitored by UV spectrometry. The absorption at 254 nm decreased by 95 % in 19 h. The solvent and excess cyclopentene were removed in vacuo and the crude product (contaminated with various dimers of cyclopentene) gave after column chromatography (hexane/ethyl acetate, 5 : 1), 214 mg (50 %) of photo-adduct 135 as a white solid. Crystallization from hexane provided pure crystals, mp 90-91° C.

IR ($CHCl_3$): 1680, 1460, 1370, 1170, 1160, 1075 cm^{-1}.

NMR ($CDCl_3$) : 0.95 (s, 3H), 1.05 (s, 6H), 1.6-2.5 (m, 13H), 2.7-2.9 (m, 1H), 3.15 (s, 3H).

Analysis: Calculated for $C_{17}H_{26}O_2$: C, 68.17; H, 10.96. Found: C, 68.27; H, 10.87.

X-ray analysis: (see Appendix)

1,13,13-Trimethyl-9-acetoxy-tetracyclo(8,2,1,$0^{3,9}$,$0^{4,8}$) tridecan-2-one (136). A solution of compound 122 (250 mg, 1.13 mmol) in 6 mL of cyclohexane was placed in a Pyrex tube and 6 g (0.075 mol) of freshly distilled cyclopentene was introduced. Dry nitrogen gas was bubbled through the solution for 45 min with ice cooling. The reaction mixture was irradiated until UV absorption of the starting material (236 nm) was diminished by 90 % (23 h). The solvent and excess cyclopentene were removed in vacuo and the crude product, on chromatographic purification, gave 180 mg (55 %) of photoadduct as a white solid. Crystallization from hexane provided compound 136 as fine needles, mp 105-107°C.

IR (CCl_4): 1730, 1695, 1550, 1370, 1230 cm^{-1}.

NMR (CCl_4) : 0.95 (s, 3H), 1.0 (s, 6H), 1.5-2.6 (m, 13H), 2.0 (s, 3H), 3.0-3.2 (m, 1H).

Analysis: Calculated for $C_{18}H_{26}O_3$: C, 74.40; H, 8.95. Found: C, 74.58; H, 8.92.

1,14,14-Trimethyl-10-methoxy -tetracyclo(9,2,1,$0^{3,10}$,$0^{4,9}$) tetradecan-2-one (137, 138). A solution of 300 mg (1.54 mmol) of compound 120 in 6 mL of dry cyclohexane was placed in a Pyrex tube and 6 g (0.073 mol) of freshly distilled cyclohexene was added. Dry nitrogen was bubbled through the solution for 45 min with ice cooling to

minimize evaporation of cyclohexene. The reaction mixture was irradiated until the enol ether peak of the starting material (1650-1600 cm^{-1} in the IR) had diminished by 90 % (32 h). The solution was concentrated in vacuo and the residue, on column chromatography (hexane/ethyl acetate, 9:1), gave 210 mg (50%) photoadduct as a white solid. An NMR spectrum of this mixture showed two OMe peaks of equal intensity (3.0 ppm, 3.1 ppm) indicating the presence of two stereoisomers. These were separated by preparative LC (hex./EtOAc, 9:1) to provide the pure (137 and 138) isomers in a 53:47 ratio. These were recrystallised from hexane to provide 137 and 138 as colorless needles.

Isomer 137, mp 117-118° C.

IR ($CHCl_3$): 1675, 1440, 1070 cm^{-1}.

NMR ($CDCl_3$) : 0.95 (s, 1H), 1.05 (s, 6H), 1.5-2.7 (m, 16H), 3.0 (s, 3H).

Analysis: Calculated for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.91; H, 10.11.

X-ray analysis: See Appendix

Isomer 138, mp 104-105° C.

IR ($CHCl_3$): 1680, 1440, 1075 cm^{-1}.

NMR ($CDCl_3$) : 0.95 (s, 3H), 0.9 (s, 3H), 0.85 (s, 3H), 1.5- 2.3 (m, 15H), 2.4-2.6 (m, 1H), 3.1 (s, 3H).

Analysis: Calculated for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21.
Found: C, 78.31; H, 10.26.
X-ray analysis: See Appendix

1,14,14-Trimethyl-10-acetoxy tetracyclo(9,2,1,$0^{3,10}$,$0^{4,9}$) tetradecan-2-one (139). A solution of compound 122 (300 mg, 1.35 mmol) was dissolved in 6 mL of dry cyclohexane in a Pyrex reaction tube and 8 g (0.09 mol) of cyclohexene was added. Dry nitrogen was bubbled through the solution for 45 min with ice cooling. The mixture was irradiated under nitrgen for 21 h, until the IR absorption of the enol acetate was diminished by 90 %. The solution was concentrated in vacuo to afford a colorless viscous liquid which on chromatographic (hexane/ ethyl acetate, 5:1) purification provided a colorless solid (225 mg, 55 % yield). HPLC and GLC analyses showed the presence two isomers. Efforts to separate the isomers by preparative column chromatography and HPLC were unsuccessful. However, an attempt to separate them by fractional crystallization (hexane) provided one isomer in 80% purity. The isomer mixture gave the following data:

IR (CCl_4): 1720, 1680, 1550, 1370, 1230 cm^{-1}.
NMR (CCl_4) : 0.9 (s, 3H), 0.95 (s, 6H), 2.1 (s, 3H),
Analysis: Calculated for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27.
Found: C, 75.15; H, 9.37.

Ketalization of 2-Cyclohexenone Using Ethylene Glycol and Fumaric Acid (140). To a solution of 5 g (0.052 mol) of 2-cyclohexenone in 260 mL of benzene was added 12.4 g (0.2 mol) of ethylene glycol followed by 392 mg (3.38 mmol) of fumaric acid. This was refluxed in a Dean-Stark apparatus for 63 h. The mixture was cooled and poured onto 100 g of solid anhydrous potassium carbonate and stirred for 15 min. The supernatant solution was transferred to another flask containing 100 g of potassium carbonate, stirred for several minutes, and filtered through a cake of anhydrous potassium carbonate. The filtrate was concentrated in vacuo to give 5.2 g (80 %) of crude product which on distillation under reduced pressure (bp 34% C, 1 mm) afforded pure ketal 140 as a colorless liquid.

IR (CCl_4) : 1645, 1430, 1390, 1340 cm^{-1}.
NMR ($CDCl_3$) : 1.6-2.2 (m, 6H), 3.9 (s, 4H), 5.4 (dt, 1H, J = 10 Hz and 1.5 Hz), 5.8 (dt, 1H, J = 10 Hz and 3 Hz).

Preparation of Ketal 140 by Garbisch's Method. Preparation of Bromoketal 141. To a stirred solution of 20 g (9.2 mol) of cyclohexanone in 250 mL of anhydrous ethylene glycol at room temperature was added a small portion of bromine. The mixture was heated to 60° C whereupon the uptake of bromine started (decolorization).

The temperature was kept at 45-50° C and additon of bromine was continued keeping a faint color of bromine all the time. After the additon of bromine (32 g) was completed a few more drops of bromine were added and the reaction mixture was kept 10° C for 1 h. No further decolorizatoin of bromine was noted. The reaction mixture was added to 50 g of solid sodium carbonate and 200 mL of pentane with stirring. After a few minutes 250 mL of water was added and the pentane layer was separated. The organic layer was washed with water, brine, dried over magnesium sulfate, and evaporated in vacuo to provide 37.6 g (84 %) of crude product as a colorless liquid. The crude product, without further purification, was subjected to dehydrobromination.

Dehydrobromination of Bromoketal (140). To a solution of the above bromoketal in 100 mL of methanol was added 25 g (0.62 mol) of sodium hydroxide. The mixture was refluxed for 20 h, then cooled and poured into 200 mL of aqueous sodium chloride. The product was extracted with two 200 mL portions of pentane. The extracts were combined, dried, and evaporated in vacuo to yield 21.4 g (90 %) of a clear liquid which was purified by distillation through a vigreaux column (bp 80° C, 2 mm).

IR (CCl_4) : 1645, 1430, 1390, 1340 cm^{-1}.

NMR ($CDCl_3$) : 1.6-2.2 (m, 6H), 3.90 (s, 4H), 5.40 (dt, 1H, J = 10, 1.5 Hz), 5.8 (dt, 1H, J = 10, 3 Hz).

Preparation of Ketal Adduct (142). A solution of enol acetate 122 (250 mg, 1.12 mmol) in 5 mL of dry cyclohexane was placed in a Pyrex tube, 3 g (0.02 mol) of ketal 140 was added and the mixture was deoxygenated with bubbling nitrogen for 1 h with ice cooling. Irradiation with 310 nm lamps for 72 h (disappearance of the enol-acetate peak was monitored by IR) and removal of the solvent in vacuo gave a yellow crude product. Unreacted ketal was distilled out at reduced pressure. The colorless, viscous residue, on repeated liquid chromatography (hexane/ethyl acetate, 10:1), gave 130 mg (40 %) of 142 as a white solid.

IR ($CDCl_3$): 1720, 1680 cm^{-1}.
NMR ($CDCl_3$) : 0.95 (s, 3H), 1.00 (s, 6H), 1.5-2.9 (m, 14H), 2.1 (s, 3H), 3.85-4.1 (m, 4H).

PART IV. RING OPENING REACTIONS

1,13,13-Trimethyl-tricyclo(8,2,1,$0^{4,8}$)tridecan-2,9-dione (156). a) Acid Hydrolysis. A solution of 50 mg (1.72 mmol) of photoadduct 136 in 1 mL of methanol containing few drops of sulfuric acid was kept for two weeks at room temperature. The reaction mixture was diluted with water and extracted with ether. The ethereal extract was neutralized with sodium bicarbonate, washed with water, and dried over sodium sulfate. The crude product, after removal of solvent, was purified by liquid chromatography (hexane/ethyl acetate, 4:1) to yield 12.4 g (30 %) of diketone 156 as white crystals. An elimination product (enone) 157 was also identified in about 10 % yield. This was identical to the eliminated product obtained by base hydrolysis (see below).

b) Base Hydrolysis. A solution of photoadduct 136 (50 mg, 1,72 mmol) in 1.5 mL of methanol was mixed with 0.5 mL of saturated potassium carbonate and the mixture was kept at room temperature for 2 h. A strong UV active spot was noticed in the TLC, indicative of an elimination product. The reaction mixture was cooled, methanol was removed in vacuo, and the residue was taken up in a minimum amount of water and extracted several times with ether. The combined ethereal extracts were washed with

water and dried over sodium sulfate. Removal of the solvent gave a yellow oil from which diketone 156 (60 %) and enone 157 (20 %) were separated by liquid chromatography.

Diketone 156. IR ($CHCl_3$) : 1670, 1440, 1100 cm^{-1}.
NMR ($CDCl_3$) : 0.9 (s, 3H), 1.1 (s, 3H), 1.2 (s, 3H), 1.3-2.1 (m, 15H).

Enone 157. IR ($CHCl_3$): 1660, 1630, 1440, 1380 cm^{-1}.
NMR ($CDCl_3$) : 0.8 (s,6H), 0.85 (s, 3H), 1.5-2.1 (m,1H), 2.2-2.4 (m, 1H), 3.3-3.5 (m, 1H).
Analysis: Calculated for C H O: C, 83.43; H, 9.63. Found: C, 83.24; H, 9.60.

1,14,14-Trimethyl Tricyclo(9,2,1,$0^{4,9}$) tetradecan-2,10-dione (152). a) Acid hydrolysis. To a solution of photoadduct 139 (30 mg, 0.098 mmol) in a minimum amount of methanol was added dropwise one mililiter of cold, con. H_2SO_4/MeOH (1:1) solution. The reaction mixture was stirred at room temperature for two weeks. Methanol was removed in vacuo, and the residue was extracted with chloroforom, which was dried with magnesium sulfate, and concentrated in vacuo to yield 30 mg of product as white solid. This was a mixture of ring opened and eliminated products, from which the dione was separated (40%) by column chromatography (hexane/ethyl acetate, 4:1). Crystallization of the dione 152 from hexane/ethyl acetate (15:1) provided fine crystals, mp 80-82° C.

IR ($CHCl_3$) : 1680, 1440, 1360 cm^{-1}.

NMR ($CDCl_3$) : 0.95 (s, 6H), 1.0 (s, 3H), 1.5-2.8 (m, 17H).

b) Base hydrolysis. Photoadduct 139 (30 mg, 0.098) was mixed with 1 ml of 5% KOH/EtOH (1:1) solution. A few drops of THF were added to get a clear solution and the mixture was refluxed at 60° C for 2h, whereupon all the starting material disappeared (TLC). The reaction mixture was poured into water (5 mL), and the product was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo to yield a yellowish liquid which was a mixture of ring opened and elimination products. Liquid chromatographic separation (hexane/ethyl acetate, 4:1) provided 152 (60%) and 158 (20%) as white solids.

Diketone 152, mp 50-52° C, IR ($CHCl_3$): 1680, 1440, 1360 cm^{-1}.

NMR ($CDCl_3$) : 0.95 (s, 6H), 1.0 (s, 3H), 1.5-2.8 (m, 17H).

Analysis: Calculated for $C_{17}H_{26}O_2$: C, 77.86; H, 9.92. Found: C, 78.04; H, 10.00.

Enone 158, IR ($CHCl_3$) : 1660, 1240, 1020 cm^{-1}.

NMR ($CDCl_3$) : 1.0 (s, 3H), 1.1 (s, 3H), 1.2 (s, 3H), 1.4-2.0 (m, 11H), 2.3-2.5 (m, 1H), 3.0-3.2 (m, 1H).

Preparation of Compound 160. To a solution of photoadduct 142 (100 mg, 0.28 mmol) in 1.2 mL of ethanol was introduced 1.2 mL of 5 % KOH solution dropwise. The reaction mixture was stirred at room temperature for 16 h, then heated under reflux at 70° C for 3 h. The reaction mixture was cooled and extracted with ether. The ethereal extract was washed with water, brine, dried over magnesium sulfate, and evaporated in vacuo to yield 96 mg of brown liquid. The crude product was a mixture of ring opened and elimination products (TLC, HPLC) which were separated by liquid chromatography to provide diketone 160 (40 mg, 30 %) and enone 161 (20 mg, 20 %). Both were obtained as colorless solids. Crystallization of diketone 160 (hexane/ethyl acetate) provided fine needles, mp 136-138° C.

Diketone 160, IR ($CHCl_3$) : 1685, 1450, 1380, 1230 cm^{-1}.
NMR ($CDCl_3$) : 1.0 (s, 9H), 1.5-2.0 (m, 10H), 2.1-2.8 (m, 5H), 4.0 (m, 4H).
Analysis : Calculated for $C_{19}H_{28}O_4$: C, 71.22; H, 8.80.
Found : C, 71.13; H, 8.96.

Enone 161, IR ($CHCl_3$): 1660, 1440, 1370 cm^{-1}.
NMR ($CDCl_3$) : 1.0 (s,3H), 1.1 (s,3H), 1.2 (s,3H), 1.7-2.0 (m,12H), 2.5 (m,1H), 4.0 (s,4H).

Fragmentation of Photoadduct 138 with Me_3SiCl/NaI in Acetonitrile (152). Sodium iodide (6 mg, 0.04 mmol) was introduced to one mililiter of dry acetonitrile. To this suspension was added 4.4 mg (0.04 mmol) of freshly distilled trimethylsilylchloride followed by 10 mg (0.036 mmol) of photoadduct 138 in 0.5 mL of acetonitrile. An orange color appeared and the reaction was complete in 15 min (TLC). The reaction was quenched with water and the product extracted with ether. The ether layer was washed with water, sodium thiosulfate, water, brine, and dried over sodium sulfate. Evaporation of ether in vacuo provided 152 (9.2 mg, 95%) as a white solid. This compound was identical to the diketone obtained in retroaldol reaction of the photoadduct (IR, NMR, HPLC). mp 80-82° C.

It should be reminded that isomeric photoadduct 137 resisted cleavage reaction under similar conditions.

Sodium Borohydride Reduction of Photoadduct (162). A solution of photoadduct 136 (46 mg, 0.15 mmol) in 2 mL of methanol was slowly added to a solution of sodium borohydide (11.4 mg, 0,3 mmol) in 1 mL of methanol and 0.25 mL of water at 0-5° C with stirring. The mixture was kept at this temperature for 1 h when TLC showed the reduction to be complete. Methanol was removed in vacuo and the residue was partitioned between water and chloroform. The organic layer was washed with water and brine,

and then dried over sodium sulfate. Evaporation of the solvent in vacuo provided a colorless wax-like product (85 %). The GC and TLC analysis showed that this product contained 90% of one isomeric alcohol.

NMR ($CDCl_3$) : 1.1 (s,3H), 1.2 (s, 3H), 1.25 (s,3H), 1.7-2.4 (m, 13H), 2.0 (s, 3H), 2.6-2.8 (m, 1H), 3.5 (s,1H).

Preparation of Mesylate (166). To a solution of 46 mg (0.15 mmol) of alcohol mixture 162 in 2 mL of methylene chloride was added 0.6 mL of pyridine in 1.2 mL of methylene chloride, with ice cooling. A solution of 176.3 mg (1.54 mmol) of mesyl chloride in 1 mL of methylene chloride was added dropwise over a period of 5 min. The reaction mixture was stirred at room temperature for 30 min giving a light brown solution. This was diluted with methylene chloride and washed several times with water. The organic solution was dried over sodium sulfate and concentrated in vacuo to provide a brown oil which was purified to a clear liquid by silica gel chromatography using hexane/ethyl acetate (4:1) as eluant (50 mg, yield 90%). This product contained 90% of one isomeric mesylate.

NMR ($CDCl_3$) : 1.1 (s, 3H), 1.2 (s,3H), 1.25 (s,3H), 1.7-2.4 (m, 13H), 2.1 (s,3H), 2.4-2.6 (m, 1H), 3.2 (s,3H), 4.7 (d, 1H).

Formation of Compound 167. A solution of mesylate 166 (50 mg, 0.1 mmol) in 20 mL of dioxane was mixed with 300 mg (7.5 mmol) of NaOH in 7 mL of water. The reaction mixture was refluxed at 65-70°C for 1 h. The dioxane was removed in vacuo and the residue was dissolved in water and extracted several times with ether. The combined ethereal layers were dried and evaporated in vacuo to a colorless oil, which was purified by column chromatography to a waxy solid (40 mg, 85%).

IR (CCl_4) : 1730, 1578, 1370, 1250, 1020, 885, 820 cm^{-1}.
NMR (200 MHz, $CDCl_3$) : 1.12 (s, 3H), 1.15 (s, 3H), 1.9 (s, 3H), 1.36-1.86 (m, 7H), 2.2 (m, 2H), 2.3 (m, 2H), 2.5 (m, 2H), 3.23 (m, 2H), 4.61 (s, 1H), 4.65 (s, 1H).

The photoadduct 139 was also subjected to the same sequence of reaction viz. reduction, mesylation, and fragmentation and a similar rearranged product was obtained.

Sodium Borohydride Reduction of Adduct 135. The adduct 135 (50 mg, 0.19 mmol) in methanol (1.5 mL) was added over 5 min to a solution of sodium borohydride (22 mg, 0.58 mmol) in water (0.2 mL) and methanol (1.2 mL) at 0-5°C with stirring. The mixture was kept in the ice bath for 30 min and at room temperature for 1 h. The methanol was evaporated and the residue was taken up in water and extracted several times with methylene chloride. The

organic extract was dried over sodium sulfate and evaporated to give the alcohols (46 mg, 85%) as white solids. The isomeric alcohols (155a and 155b) were separated in HPLC and obtained in an 85:15 ratio. The stereochemistry was determined by the coupling constants of hydrogen on the carbon bearing the hydroxyl group and a hydrogen on the cyclobutane ring (major alcohol, 3.25 ppm, J = 0 Hz; minor alcohol, 3.7 ppm, J = 8 Hz).

Major alcohol 155a, mp 77-78° C.
NMR (200 MHz, $CDCl_3$) : 0.88 (s, 3H), 0.99 (s, 3H), 1.45-2.0 (m, 13H), 2.58 (t, 1H, J = 7 Hz), 3.05 (s, 3H), 3.25 (s, 1H).
Minor alcohol 155b, NMR (200 MHz, $CDCl_3$) : 0.88 (s,3H), 0.90 (s, 3H), 0.93 (s, 3H), 1.45-1.95 (m, 10H), 2.1-2.2 (m, 2H), 2.5 (m, 1H), 3.0 (s, 3H), 3.7 (d, 1H, J = 8Hz).

Bromoketalization of Vinyl Chloride 147 with NBS and Ethylene Glycol (148). Compound 147 was prepared by a Diel Alder reaction according to a known procedure. To a solution of 250 mg (1.55 mmol) of compound 147 in 0.5 mL (8.0 mmol) of ethylene glycol and 1 mL of THF was added 275 mg (1.55 mmol) of NBS with stirring at room temperature. The reaction mixture was stirred at room temperature overnight and at 70-80° C for 30 min. The starting material completely disappeared on TLC (hexane/ethyl acetate, 4:1). The reaction mixture was

cooled and THF was evaporated. Excess methylene chloride was added, washed with water, 5% HCl, water, and dried with sodium sulfate to get a colorless oil. This was purified on column chromatography (hexane/ethyl acetate, 4:1) to yield 150 mg (50%) of 148.

NMR ($CDCl_3$): 1.25 (t, 3H, J = 7 Hz), 1.7-2.5 (m, 8H), 4.1 (s, 4H), 4.2 (q, 2H, J = 7 Hz).

APPENDIX

The structure of your sample JP-40-2 has been determined by a single-crystal X-ray analysis. The R factors are higher than I would have liked, but acceptable; the structure is not in doubt. Four prints of a stereodrawing of the molecule are enclosed, together with tables of the final atomic parameters, bond lengths, bond angles, and selected torsion angles. Your crystals will be returned under separate cover.

The crystals were triclinic, space group $P\bar{1}$, with $a = 7.176(3)$, $b = 10.110(3)$, $c = 11.468(5)$ A, $\alpha = 93.61(3)$, $\beta = 106.69(3)$, $\gamma = 108.37(3)^{\circ}$, and $d_{calcd} = 1.169$ g cm^{-3} for $Z = 2$ ($C_{17}H_{26}O_2$, $M = 262.39$). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.08 x 0.20 x 0.7 mm. A total of 2007 independent reflections were measured for $\theta < 57^{\circ}$, of which 1643 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure [G. Germain, P. Main, and M. M. Woolfson, Acta Cryst. A27, 368 (1971)] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are $R = 0.079$ and $wR = 0.090$ for the 1643 observed reflections. The final difference map has no peaks greater than ± 0.4 e A^{-3}.

Note: Compound JP-40-2 is same as Compound No. 135.

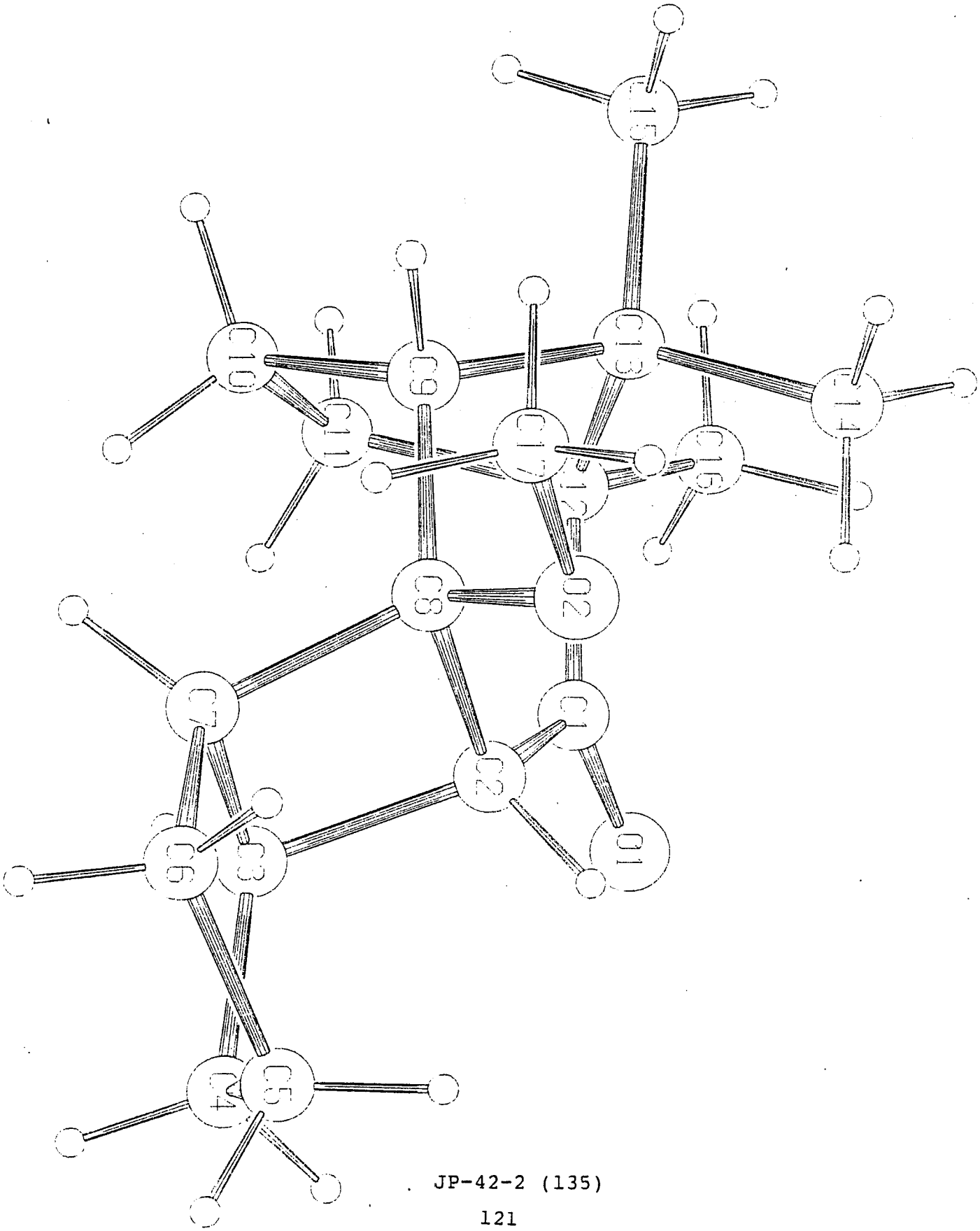

C15
C10
C9
C13
C11
C12
C16
C14
O8
O2
C1
C7
O1
C6
C3
C4
C5

Table I. Final Atomic Parameters for
with Standard Deviations in Parentheses

Atom	X	Y	Z	B
O(1)	0.7634(5)	0.6222(4)	0.1843(3)	*
O(2)	0.3546(4)	0.6386(3)	0.4169(2)	*
C(1)	0.6281(6)	0.6610(5)	0.2042(4)	*
C(2)	0.4759(6)	0.5663(4)	0.2548(3)	*
C(3)	0.2952(6)	0.4399(4)	0.1622(3)	*
C(4)	0.2878(8)	0.2941(5)	0.1906(4)	*
C(5)	0.2274(9)	0.2853(5)	0.3065(5)	*
C(6)	0.0721(8)	0.3631(5)	0.2884(5)	*
C(7)	0.1378(6)	0.4801(4)	0.2158(4)	*
C(8)	0.3136(6)	0.6200(4)	0.2884(3)	*
C(9)	0.3096(6)	0.7558(4)	0.2356(4)	*
C(10)	0.2280(6)	0.7336(5)	0.0934(4)	*
C(11)	0.4159(7)	0.7583(5)	0.0501(4)	*
C(12)	0.6073(6)	0.7998(4)	0.1700(4)	*
C(13)	0.5327(6)	0.8649(4)	0.2656(4)	*
C(14)	0.6794(7)	0.8862(5)	0.3974(4)	*
C(15)	0.5173(8)	1.0096(5)	0.2420(5)	*
C(16)	0.8060(7)	0.8952(5)	0.1515(5)	*
C(17)	0.2106(9)	0.6772(6)	0.4595(5)	*
H(2)	0.551	0.531	0.327	5.0
H(3)	0.274	0.449	0.073	5.0
H(4)A	0.182	0.219	0.121	8.0
H(4)B	0.427	0.284	0.205	8.0
H(5)A	0.351	0.333	0.381	8.0
H(5)B	0.161	0.185	0.314	8.0
H(6)A	-0.071	0.296	0.242	8.0
H(6)B	0.074	0.405	0.371	8.0
H(7)	0.020	0.493	0.152	6.0
H(9)	0.225	0.799	0.270	5.0
H(10)A	0.128	0.635	0.060	6.0
H(10)B	0.158	0.803	0.065	6.0
H(11)A	0.429	0.837	0.000	6.0
H(11)B	0.404	0.670	-0.001	6.0
H(14)A	0.819	0.955	0.405	6.0
H(14)B	0.692	0.794	0.417	6.0
H(14)C	0.623	0.924	0.457	6.0
H(15)A	0.659	1.079	0.253	8.0
H(15)B	0.458	1.044	0.301	8.0
H(15)C	0.425	1.000	0.156	8.0
H(16)A	0.924	0.919	0.230	8.0
H(16)B	0.787	0.984	0.126	8.0
H(16)C	0.837	0.845	0.085	8.0
H(17)A	0.255	0.688	0.552	8.0
H(17)B	0.070	0.602	0.423	8.0
H(17)C	0.205	0.769	0.434	8.0

* Anisotropic thermal parameters are given in Table II

Table II. Final Anisotropic Thermal Parameters for
with Standard Deviations in Parentheses

Atom	$B11 \times 10^4$	$B22 \times 10^4$	$B33 \times 10^4$	$B12 \times 10^4$	$B13 \times 10^4$	$B23 \times 10^4$
O(1)	262(10)	247(6)	265(6)	177(7)	160(6)	62(5)
O(2)	259(9)	181(5)	94(3)	81(5)	62(4)	14(3)
C(1)	158(11)	161(7)	129(5)	87(7)	46(6)	15(4)
C(2)	191(11)	130(6)	108(4)	111(7)	41(6)	29(4)
C(3)	238(12)	118(5)	100(4)	92(7)	40(6)	12(4)
C(4)	399(17)	130(6)	142(6)	123(9)	47(8)	16(5)
C(5)	459(20)	146(7)	150(6)	82(10)	48(9)	46(5)
C(6)	365(17)	156(7)	167(6)	29(9)	118(9)	15(5)
C(7)	205(11)	141(6)	108(4)	77(7)	55(6)	15(4)
C(8)	175(11)	123(5)	84(4)	77(6)	38(5)	7(3)
C(9)	170(11)	125(5)	115(4)	91(6)	52(6)	14(4)
C(10)	212(12)	169(7)	119(5)	107(8)	34(6)	43(5)
C(11)	288(14)	178(7)	109(5)	110(8)	60(7)	45(5)
C(12)	193(11)	142(6)	120(5)	73(7)	60(6)	26(4)
C(13)	225(12)	117(5)	110(4)	70(7)	57(6)	17(4)
C(14)	251(13)	144(6)	126(5)	43(8)	29(7)	5(4)
C(15)	380(17)	134(7)	189(7)	105(9)	115(9)	43(5)
C(16)	253(14)	208(8)	192(7)	63(9)	128(8)	48(6)
C(17)	428(19)	236(9)	140(6)	104(11)	141(9)	10(6)

The anisotropic temperature factor has the form

$$\exp(-(h^2 B11 + k^2 B22 + \ell^2 B33 + 2hkB12 + 2h\ell B13 + 2k\ell B23))$$

Table III. Bond Lengths (A) in
with Standard Deviations in Parentheses

O(1)- C(1)	1.226(7)	C(6)- C(7)	1.520(7)
O(2)- C(8)	1.405(5)	C(7)- C(8)	1.552(5)
O(2)-C(17)	1.406(8)	C(8)- C(9)	1.540(6)
C(1)- C(2)	1.491(6)	C(9)-C(10)	1.542(6)
C(1)-C(12)	1.521(7)	C(9)-C(13)	1.556(5)
C(2)- C(3)	1.561(4)	C(10)-C(11)	1.521(7)
C(2)- C(8)	1.559(7)	C(11)-C(12)	1.560(5)
C(3)- C(4)	1.517(7)	C(12)-C(13)	1.546(7)
C(3)- C(7)	1.573(7)	C(12)-C(16)	1.531(7)
C(4)- C(5)	1.512(8)	C(13)-C(14)	1.530(6)
C(5)- C(6)	1.531(9)	C(13)-C(15)	1.536(7)

Table IV. Bond Angles (°) in
with Standard Deviations in Parentheses

C(8)- O(2)-C(17)	116.0(3)
O(1)- C(1)- C(2)	119.2(4)
O(1)- C(1)-C(12)	120.4(4)
C(2)- C(1)-C(12)	120.3(4)
C(1)- C(2)- C(3)	117.0(3)
C(1)- C(2)- C(8)	119.1(4)
C(3)- C(2)- C(8)	89.6(3)
C(2)- C(3)- C(4)	115.4(3)
C(2)- C(3)- C(7)	89.2(3)
C(4)- C(3)- C(7)	106.9(4)
C(3)- C(4)- C(5)	104.4(4)
C(4)- C(5)- C(6)	103.6(4)
C(5)- C(6)- C(7)	107.4(5)
C(3)- C(7)- C(6)	104.1(4)
C(3)- C(7)- C(8)	89.4(3)
C(6)- C(7)- C(8)	117.6(3)
O(2)- C(8)- C(2)	110.0(3)
O(2)- C(8)- C(7)	114.8(3)
O(2)- C(8)- C(9)	112.4(3)
C(2)- C(8)- C(7)	90.0(3)
C(2)- C(8)- C(9)	110.5(3)
C(7)- C(8)- C(9)	116.8(3)
C(8)- C(9)-C(10)	114.0(3)
C(8)- C(9)-C(13)	111.3(3)
C(10)- C(9)-C(13)	102.1(3)
C(9)-C(10)-C(11)	106.6(3)
C(10)-C(11)-C(12)	105.7(4)
C(1)-C(12)-C(11)	105.7(3)
C(1)-C(12)-C(13)	108.6(4)
C(1)-C(12)-C(16)	110.9(4)
C(11)-C(12)-C(13)	102.6(4)
C(11)-C(12)-C(16)	112.3(4)
C(13)-C(12)-C(16)	115.9(3)
C(9)-C(13)-C(12)	100.6(3)
C(9)-C(13)-C(14)	116.4(4)
C(9)-C(13)-C(15)	108.7(4)
C(12)-C(13)-C(14)	111.7(4)
C(12)-C(13)-C(15)	112.2(4)
C(14)-C(13)-C(15)	107.2(3)

Table V. Torsion Angles (°) in
with Standard Deviations in Parentheses

C(3)- C(4)- C(5)- C(6)	37.1(4)
C(4)- C(5)- C(6)- C(7)	-32.8(4)
C(5)- C(6)- C(7)- C(3)	15.2(4)
C(6)- C(7)- C(3)- C(4)	7.9(4)
C(7)- C(3)- C(4)- C(5)	-28.2(4)
C(2)- C(3)- C(7)- C(8)	10.0(3)
C(3)- C(7)- C(8)- C(2)	-10.0(3)
C(7)- C(8)- C(2)- C(3)	10.1(3)
C(8)- C(2)- C(3)- C(7)	-10.0(3)
C(1)- C(2)- C(8)- C(9)	12.4(4)
C(2)- C(8)- C(9)-C(13)	-48.1(4)
C(8)- C(9)-C(13)-C(12)	76.8(4)
C(9)-C(13)-C(12)- C(1)	-67.4(4)
C(13)-C(12)- C(1)- C(2)	37.3(4)
C(12)- C(1)- C(2)- C(8)	-8.0(5)
C(9)-C(10)-C(11)-C(12)	-1.8(5)
C(10)-C(11)-C(12)-C(13)	-26.6(4)
C(11)-C(12)-C(13)- C(9)	44.2(4)
C(12)-C(13)- C(9)-C(10)	-45.2(4)
C(13)- C(9)-C(10)-C(11)	29.3(5)

The conformation and relative stereochemistry in I are shown in the drawing of I. Compound II crystallizes with two independent molecules in the unit cell. One of these independent molecules has been designated as the "unprimed" molecule and the other as the "primed" molecule. The primed molecules are disordered in the crystal. The disorder involves principally atoms C-9 and C-10 which were resolved as two pairs of half-weight atoms C(9)', C(9)* and C(10)', C(10)*. The conformation of the primed molecule which includes atoms C(9)' and C(10)' is the same as that of the unprimed molecule. Thus the unprimed molecule represents the major conformer in the crystal (ca. 75%) while the primed molecule which includes atoms C(9)* and C(10)* represents the minor conformer. These two conformers are illustrated in the second Figure (major conformer at the top, minor conformer at the bottom).

In Tables III, IV, and V (bond lengths, bond angles, and torsion angles, respectively), four columns of values are presented to the right of the column listing the names of the atoms comprising the bonds or angles. The first of these four columns lists the values in Compound I and the remaining three columns list the values in the two independent molecules of II. Thus, the second column lists the values in one independent molecule of II ("unprimed") and the third column lists the values in the other independent molecule ("primed") for the atoms corresponding to the major conformer. The last column (mostly vacant) lists only those values for the minor conformer (primed molecule) which involve the disordered atoms C(9)* and/or C(10)*.

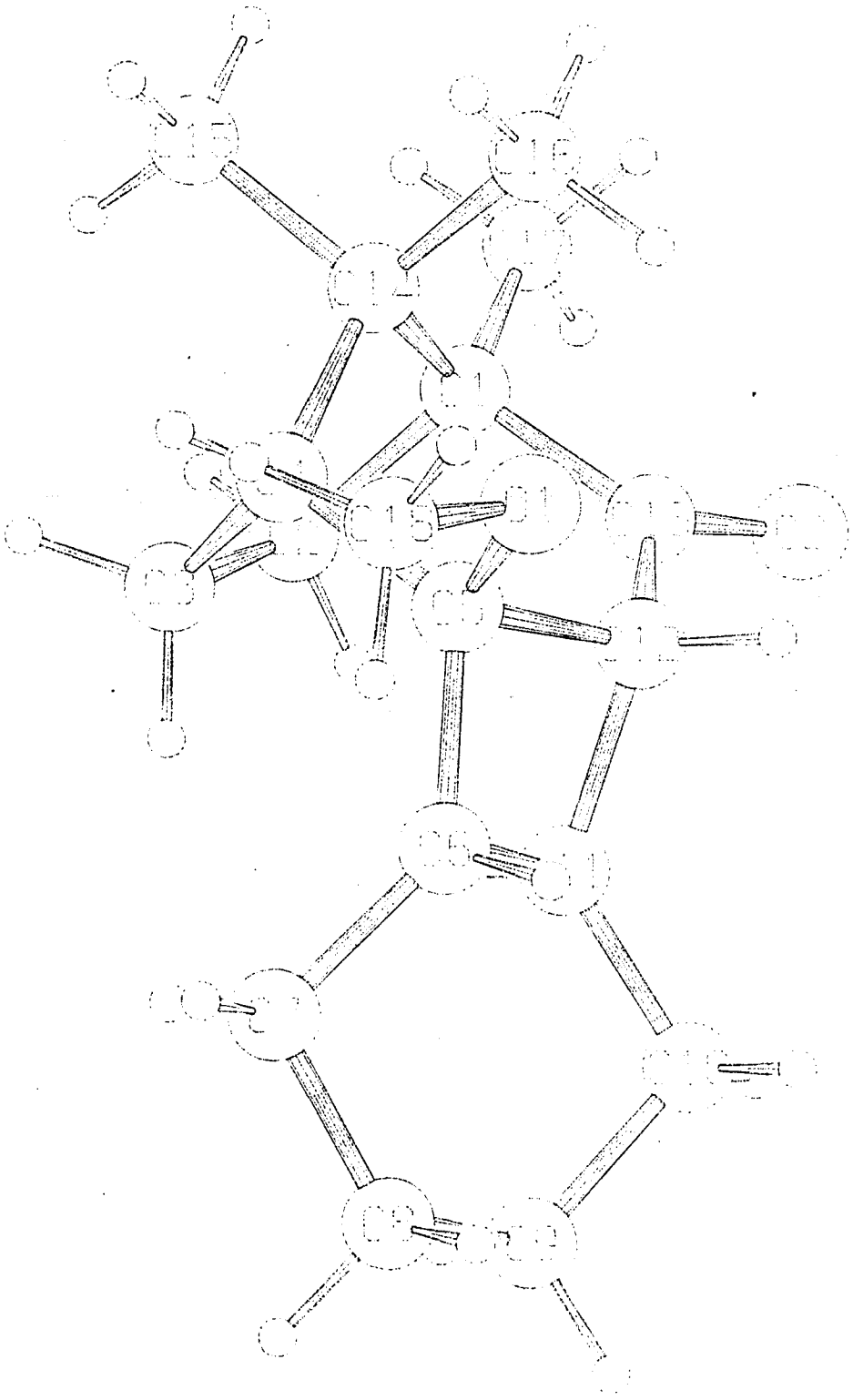
The intensity data for the two compounds were measured on an Enraf-Nonius CAD-4 diffractometer (graphite monochromated Cu Kα radiation, ω-2θ scans). The structures were solved by a multiple-solution procedure [G. Germain, P. Main and M. M. Woolfson, Acta Cryst. A27, 368 (1971)]. Both structures were refined by full-matrix least squares in which the nonhydrogen atoms were refined anisotropically and the hydrogen atoms were held fixed at their calculated positions.

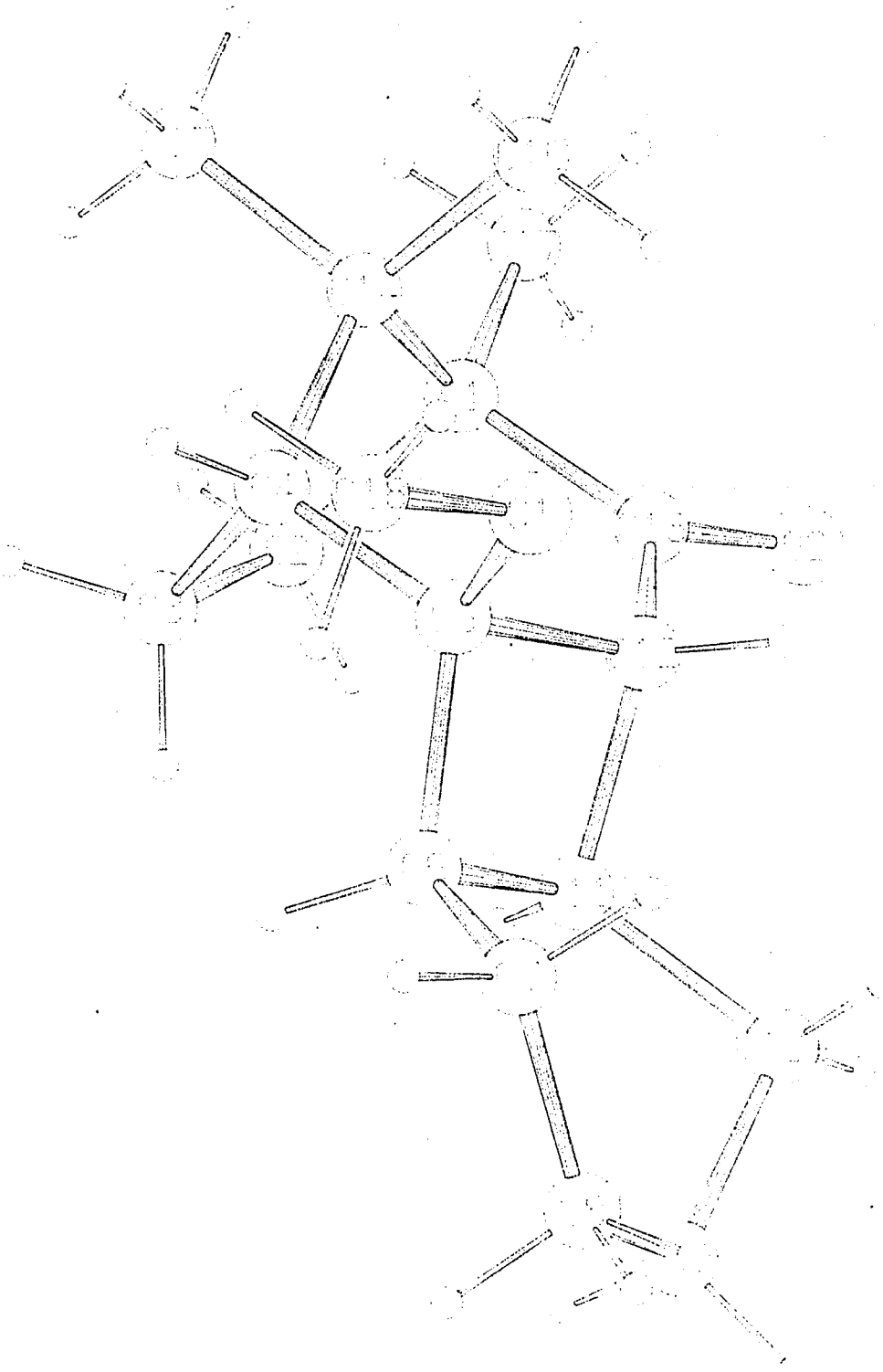
Crystals of I (JP-81-2) are monoclinic, space group $P2_1/c$, with $a = 8.544(4)$, $b = 24.372(5)$, $c = 7.504(4)$ Å, $\beta = 91.55(5)^\circ$, and $d_{calcd} = 1.175$ g cm^{-3} for $Z = 4$ ($C_{18}H_{28}O_2$, $M = 276.42$). The size of the crystal used for data collection was approximately 0.07 x 0.35 x 0.60 mm. A total of 1615 independent reflections were measured for $\theta < 50^\circ$, of which 1252 were considered to be observed [$I > 3\,\sigma(I)$]. The final discrepancy indices are $R = 0.070$ and $wR = 0.086$ for the 1252 observed reflections. The final difference map has no peaks greater than ± 0.3 e Å^{-3}.

Crystals of II (JP-61-1) are triclinic, space group $P\bar{1}$, with $a = 10.892(2)$, $b = 11.137(1)$, $c = 13.712(4)$ Å, $\alpha = 89.95(2)$, $\beta = 70.02(2)$, $\gamma = 88.80(1)^\circ$, and $d_{calcd} = 1.175$ g cm^{-3} for $Z = 4$ ($C_{18}H_{28}O_2$, $M = 276.42$). The size of the crystal used for data col-

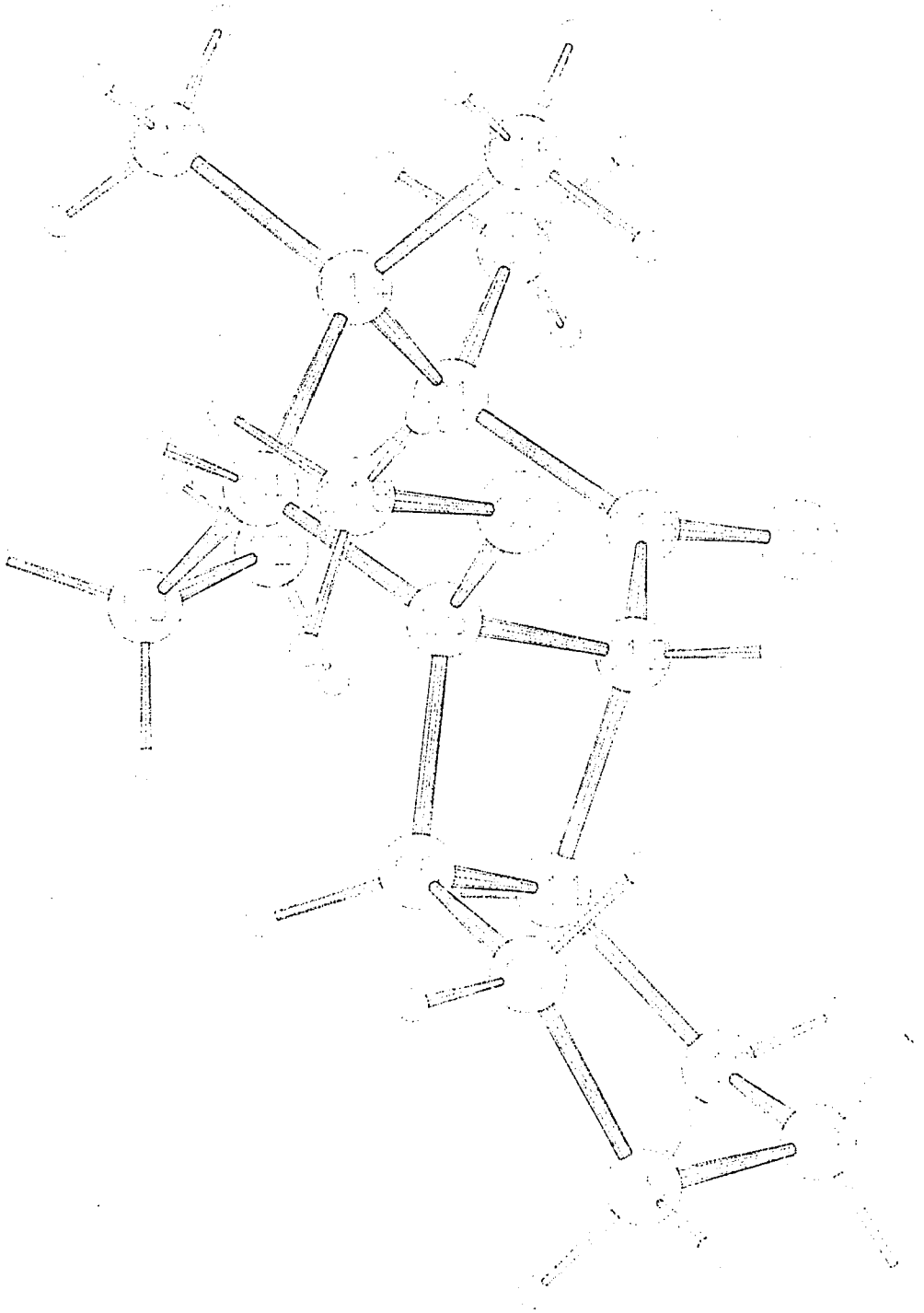
Compound JP-81-2 is same as 138
Compound JP-61-1 is same as 137

lection was approximately 0.20 x 0.20 x 0.7 mm. A total of 4638 independent reflections were measured for $\theta < 60°$, of which 3733 were considered to be observed [$I > 3\,\sigma(I)$]. In order to account for disorder in one of the two independent molecules, atoms C(9)' and C(10)' were each split into two partial atoms [C(9)' and C(9)*, and C(10)' and C(10)*, respectively]. These four partial atoms were assigned fixed occupancy factors of 0.5 and were included on the refinement. The final discrepancy indices are R = 0.058 and wR = 0.072 for the 3733 observed reflections. The final difference map has no peaks greater than ±0.3 e $Å^{-3}$.





II: JP-61-1 (137). Minor conformer



II: JP-61-1 (137). Major conformer

Table I. Final Atomic Parameters for
with Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	*B*
O(1)	0.2369(4)	0.4182(2)	0.8203(5)	*
O(2)	0.4408(5)	0.2513(2)	0.7173(6)	*
C(1)	0.6034(6)	0.3316(2)	0.6926(7)	*
C(2)	0.6283(6)	0.3480(2)	0.4964(7)	*
C(3)	0.5517(6)	0.4043(2)	0.4726(7)	*
C(4)	0.4745(7)	0.4174(2)	0.6509(7)	*
C(5)	0.3048(6)	0.3963(2)	0.6645(7)	*
C(6)	0.1874(6)	0.3944(2)	0.5035(7)	*
C(7)	0.1564(7)	0.4259(2)	0.3316(8)	*
C(8)	0.0271(7)	0.3948(3)	0.2326(8)	*
C(9)	0.0574(7)	0.3331(3)	0.2122(9)	*
C(10)	0.0998(7)	0.3029(2)	0.3860(8)	*
C(11)	0.2321(6)	0.3350(2)	0.4719(7)	*
C(12)	0.2978(6)	0.3331(2)	0.6669(7)	*
C(13)	0.4473(6)	0.3008(2)	0.6973(7)	*
C(14)	0.5850(6)	0.3876(2)	0.7850(7)	*
C(15)	0.7431(7)	0.4191(3)	0.7973(8)	*
C(16)	0.5276(8)	0.3828(3)	0.9772(8)	*
C(17)	0.7325(7)	0.2951(3)	0.7681(8)	*
C(18)	0.1913(8)	0.4737(3)	0.8054(9)	*
H(2)A	0.743	0.351	0.472	5.0
H(2)B	0.578	0.321	0.414	5.0
H(3)A	0.471	0.403	0.374	5.0
H(3)B	0.633	0.433	0.445	5.0
H(4)	0.480	0.458	0.673	4.0
H(6)	0.083	0.392	0.560	5.0
H(7)A	0.122	0.464	0.358	6.0
H(7)B	0.252	0.427	0.259	6.0
H(8)A	0.015	0.411	0.110	7.0
H(8)B	-0.073	0.400	0.297	7.0
H(9)A	-0.038	0.316	0.160	7.0
H(9)B	0.147	0.328	0.130	7.0
H(10)A	0.009	0.302	0.465	6.0
H(10)B	0.135	0.264	0.360	6.0
H(11)	0.322	0.334	0.389	5.0
H(12)	0.216	0.320	0.750	5.0
H(15)A	0.728	0.456	0.850	7.0
H(15)B	0.788	0.423	0.676	7.0
H(15)C	0.819	0.398	0.876	7.0
H(16)A	0.425	0.363	0.976	7.0
H(16)B	0.514	0.420	1.030	7.0
H(16)C	0.606	0.361	1.050	7.0
H(17)A	0.708	0.286	0.895	7.0
H(17)B	0.834	0.315	0.763	7.0
H(17)C	0.735	0.261	0.696	7.0
H(18)A	0.144	0.486	0.920	8.0
H(18)B	0.110	0.477	0.706	8.0
H(18)C	0.283	0.497	0.779	8.0

Table II. Final Anisotropic Thermal Parameters for
with Standard Deviations in Parentheses

Atom	$\beta 11 \times 10^4$	$\beta 22 \times 10^5$	$\beta 33 \times 10^4$	$\beta 12 \times 10^4$	$\beta 13 \times 10^4$	$\beta 23 \times 10^4$
O(1)	169(7)	183(9)	190(9)	5(2)	39(6)	-6(2)
O(2)	172(8)	147(9)	361(12)	3(2)	-32(8)	20(3)
C(1)	94(9)	184(12)	183(13)	3(3)	-29(9)	9(3)
C(2)	97(9)	215(13)	165(13)	-4(3)	4(8)	1(3)
C(3)	115(9)	203(13)	151(12)	-9(3)	9(8)	6(3)
C(4)	185(11)	126(11)	145(12)	-10(3)	-10(9)	-3(3)
C(5)	130(10)	138(11)	131(11)	-8(3)	-3(9)	-2(3)
C(6)	105(9)	153(12)	195(13)	6(3)	6(9)	4(3)
C(7)	135(11)	214(14)	243(15)	3(3)	-31(10)	12(4)
C(8)	140(11)	248(16)	282(17)	0(3)	-62(11)	13(4)
C(9)	160(12)	332(19)	262(17)	-17(4)	-65(11)	-9(5)
C(10)	133(10)	194(13)	279(17)	-10(3)	-9(11)	-13(4)
C(11)	107(9)	136(11)	185(13)	4(3)	-11(9)	-7(3)
C(12)	124(9)	105(10)	188(13)	3(3)	-1(9)	6(3)
C(13)	130(10)	129(12)	166(13)	5(3)	-9(9)	13(3)
C(14)	130(10)	190(12)	141(12)	-12(3)	-20(9)	0(3)
C(15)	179(12)	266(16)	256(16)	-14(3)	-65(11)	-7(4)
C(16)	229(13)	331(17)	132(13)	-6(4)	-30(10)	0(4)
C(17)	144(11)	259(16)	273(17)	8(3)	-56(11)	10(4)
C(18)	260(15)	204(15)	303(18)	14(4)	58(13)	-17(4)

The anisotropic temperature factor has the form

$$\exp[-(h^2\beta 11 + k^2\beta 22 + \ell^2\beta 33 + 2hk\beta 12 + 2h\ell\beta 13 + 2k\ell\beta 23)]$$

Table I. Final Atomic Parameters for
with Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	*B*
O(1)	0.6365(2)	0.9684(1)	0.3669(1)	*
O(2)	0.6758(2)	0.6606(2)	0.5682(2)	*
O(1)'	0.3617(2)	0.4726(2)	0.1355(1)	*
O(2)'	0.4050(3)	0.1546(2)	-0.0783(2)	*
C(1)	0.8376(3)	0.6829(3)	0.3998(2)	*
C(2)	0.8220(3)	0.5937(3)	0.3177(2)	*
C(3)	0.7867(3)	0.6712(2)	0.2376(2)	*
C(4)	0.7774(3)	0.8015(2)	0.2774(2)	*
C(5)	0.6408(2)	0.8415(2)	0.3499(2)	*
C(6)	0.5179(3)	0.7915(2)	0.3307(2)	*
C(7)	0.3997(3)	0.8784(3)	0.3603(3)	*
C(8)	0.2719(3)	0.8164(3)	0.4143(3)	*
C(9)	0.2761(3)	0.7599(4)	0.5141(3)	*
C(10)	0.3781(3)	0.6604(3)	0.4918(3)	*
C(11)	0.5099(3)	0.6955(2)	0.4148(2)	*
C(12)	0.6018(2)	0.7742(2)	0.4536(2)	*
C(13)	0.7034(3)	0.7047(2)	0.4818(2)	*
C(14)	0.8777(3)	0.8005(2)	0.3358(2)	*
C(15)	1.0166(3)	0.7894(3)	0.2557(3)	*
C(16)	0.8744(3)	0.9090(3)	0.4051(2)	*
C(17)	0.9334(3)	0.6351(3)	0.4507(3)	*
C(18)	0.6543(3)	1.0390(3)	0.2770(3)	*
C(1)'	0.2319(3)	0.1591(3)	0.0869(2)	*
C(2)'	0.2649(3)	0.0755(3)	0.1650(3)	*
C(3)'	0.2783(3)	0.1590(3)	0.2504(2)	*
C(4)'	0.2573(3)	0.2886(2)	0.2167(2)	*
C(5)'	0.3835(3)	0.3478(2)	0.1493(2)	*
C(6)'	0.5125(3)	0.3185(2)	0.1721(2)	*
C(7)'	0.6076(3)	0.4198(3)	0.1569(3)	*
C(8)'	0.7470(3)	0.3723(3)	0.1283(3)	*
C(9)'	0.7718(12)	0.3114(9)	0.0186(9)	*
C(10)'	0.6880(14)	0.2092(10)	0.0226(10)	*
C(11)'	0.5537(3)	0.2304(3)	0.0778(2)	*
C(12)'	0.4424(3)	0.2855(2)	0.0429(2)	*
C(13)'	0.3614(3)	0.1979(3)	0.0088(2)	*
C(14)'	0.1640(3)	0.2696(3)	0.1550(2)	*
C(15)'	0.0276(3)	0.2401(3)	0.2318(3)	*
C(16)'	0.1452(3)	0.3747(3)	0.0892(3)	*
C(17)'	0.1496(4)	0.0966(3)	0.0304(3)	*
C(18)'	0.3224(3)	0.5436(3)	0.2281(2)	*
C(9)*	0.7883(8)	0.2622(8)	0.0566(7)	*
C(10)*	0.6958(11)	0.2585(9)	-0.0077(8)	*

Table I (continued) for

Atom	*X*	*Y*	*Z*	*B*
H(2)A	0.906	0.548	0.283	5.0
H(2)B	0.751	0.536	0.351	5.0
H(3)A	0.701	0.647	0.233	5.0
H(3)B	0.856	0.663	0.168	5.0
H(4)	0.807	0.857	0.217	4.0
H(6)	0.539	0.756	0.260	4.0
H(7)A	0.412	0.942	0.408	7.0
H(7)B	0.395	0.917	0.296	7.0
H(8)A	0.259	0.753	0.368	8.0
H(8)B	0.198	0.877	0.431	8.0
H(9)A	0.297	0.823	0.557	8.0
H(9)B	0.189	0.726	0.553	8.0
H(10)A	0.346	0.590	0.463	7.0
H(10)B	0.390	0.637	0.558	7.0
H(11)	0.559	0.621	0.380	4.0
H(12)	0.550	0.828	0.512	4.0
H(15)A	1.036	0.863	0.212	7.0
H(15)B	1.023	0.718	0.210	7.0
H(15)C	1.081	0.780	0.293	7.0
H(16)A	0.897	0.983	0.362	6.0
H(16)B	0.939	0.896	0.441	6.0
H(16)C	0.785	0.919	0.458	6.0
H(17)A	0.901	0.558	0.487	8.0
H(17)B	0.942	0.696	0.502	8.0
H(17)C	1.021	0.620	0.396	8.0
H(18)A	0.650	1.126	0.296	7.0
H(18)B	0.584	1.021	0.248	7.0
H(18)C	0.742	1.019	0.224	7.0
H(2)A'	0.193	0.017	0.195	6.0
H(2)B'	0.349	0.030	0.130	6.0
H(3)A'	0.367	0.149	0.256	6.0
H(3)B'	0.211	0.140	0.319	6.0
H(4)'	0.213	0.340	0.279	4.0
H(6)'	0.496	0.276	0.240	5.0
H(7)A'	0.585	0.467	0.223	6.0
H(7)B'	0.601	0.473	0.100	6.0
H(8)A'	0.755	0.312	0.180	6.0
H(8)B'	0.809	0.439	0.123	6.0
H(9)A'	0.755	0.373	-0.029	8.0
H(9)B'	0.865	0.283	-0.010	8.0
H(10)A'	0.698	0.186	-0.050	8.0
H(10)B'	0.719	0.141	0.056	8.0
H(11)'	0.520	0.151	0.108	6.0
H(12)'	0.479	0.347	-0.012	4.0

Table I (continued) for

Atom	*X*	*Y*	*Z*	*B*
H(15)A'	-0.009	0.311	0.278	7.0
H(15)B'	0.035	0.170	0.275	7.0
H(15)C'	-0.031	0.220	0.192	7.0
H(16)A'	0.105	0.445	0.135	6.0
H(16)B'	0.086	0.351	0.051	6.0
H(16)C'	0.232	0.398	0.038	6.0
H(17)A'	0.200	0.025	-0.009	8.0
H(17)B'	0.130	0.154	-0.019	8.0
H(17)C'	0.066	0.070	0.083	8.0
H(18)A'	0.310	0.629	0.211	6.0
H(18)B'	0.392	0.538	0.261	6.0
H(18)C'	0.239	0.513	0.278	6.0
H(8)A*	0.762	0.351	0.194	6.0
H(8)B*	0.806	0.439	0.094	6.0
H(9)A*	0.780	0.187	0.099	6.0
H(9)B*	0.881	0.270	0.009	6.0
H(10)A*	0.724	0.193	-0.062	6.0
H(10)B*	0.694	0.337	-0.042	6.0
H(11)*	0.542	0.144	0.098	6.0

* Anisotropic thermal parameters are given in Table II

Table II. Final Anisotropic Thermal Parameters for
with Standard Deviations in Parentheses

Atom	$\beta 11 \times 10^4$	$\beta 22 \times 10^4$	$\beta 33 \times 10^4$	$\beta 12 \times 10^4$	$\beta 13 \times 10^4$	$\beta 23 \times 10^4$
O(1)	117(2)	55(2)	57(1)	0(1)	-32(1)	-3(1)
O(2)	157(3)	135(3)	47(2)	4(2)	-27(2)	20(2)
O(1)'	112(2)	57(2)	52(1)	9(1)	-19(1)	-7(1)
O(2)'	208(4)	158(3)	55(2)	-25(3)	-28(2)	-37(2)
C(1)	95(3)	82(3)	60(2)	12(2)	-21(2)	5(2)
C(2)	120(4)	69(3)	66(2)	14(2)	-5(2)	-7(2)
C(3)	101(3)	77(3)	51(2)	-1(2)	-6(2)	-15(2)
C(4)	90(3)	65(2)	38(2)	-10(2)	-12(2)	0(2)
C(5)	84(3)	54(2)	44(2)	-4(2)	-17(2)	-2(2)
C(6)	92(3)	79(3)	50(2)	-1(2)	-22(2)	-9(2)
C(7)	110(4)	116(3)	105(3)	19(3)	-57(3)	-19(3)
C(8)	88(4)	157(4)	118(3)	15(3)	-38(3)	-64(3)
C(9)	94(4)	183(5)	100(3)	-27(3)	5(3)	-49(3)
C(10)	110(4)	132(4)	80(3)	-47(3)	-9(3)	-9(3)
C(11)	85(3)	75(3)	58(2)	-14(2)	-13(2)	-11(2)
C(12)	82(3)	65(2)	38(2)	-2(2)	-12(2)	-5(2)
C(13)	113(3)	68(3)	46(2)	-5(2)	-23(2)	-2(2)
C(14)	78(3)	76(3)	57(2)	-5(2)	-14(2)	-4(2)
C(15)	87(3)	129(4)	83(3)	-10(3)	-13(2)	-4(3)
C(16)	109(4)	98(3)	77(2)	-16(3)	-39(2)	-12(2)
C(17)	135(4)	150(4)	98(3)	41(3)	-44(3)	20(3)
C(18)	175(5)	73(3)	82(3)	7(3)	-55(3)	13(2)
C(1)'	127(4)	87(3)	62(2)	-24(3)	-43(2)	3(2)
C(2)'	154(4)	81(3)	76(2)	-28(3)	-46(3)	12(2)
C(3)'	140(4)	82(3)	55(2)	-17(3)	-34(2)	13(2)
C(4)'	93(3)	78(3)	43(2)	0(2)	-15(2)	-1(2)
C(5)'	90(3)	56(2)	46(2)	5(2)	-17(2)	-5(2)
C(6)'	97(3)	67(3)	62(2)	7(2)	-29(2)	-10(2)
C(7)'	106(4)	87(3)	94(3)	-2(3)	-39(3)	-18(2)
C(8)'	107(4)	107(3)	104(3)	-3(3)	-37(3)	-18(3)
C(9)'	146(13)	126(12)	93(9)	2(10)	13(8)	-16(8)
C(10)'	151(13)	112(13)	89(10)	27(12)	-8(9)	-26(8)
C(11)'	106(4)	69(3)	85(3)	14(2)	-33(3)	-24(2)
C(12)'	96(3)	64(2)	47(2)	4(2)	-13(2)	-7(2)
C(13)'	135(4)	83(3)	55(2)	2(3)	-35(2)	-8(2)
C(14)'	96(3)	94(3)	54(2)	-14(2)	-24(2)	8(2)
C(15)'	102(4)	157(4)	94(3)	-24(3)	-24(3)	17(3)
C(16)'	111(4)	116(3)	80(3)	4(3)	-45(3)	14(2)
C(17)'	188(5)	138(4)	101(3)	-47(4)	-75(3)	-4(3)
C(18)'	143(4)	80(3)	72(2)	19(3)	-25(3)	-22(2)
C(9)*	76(7)	91(8)	69(6)	1(6)	-21(5)	7(5)
C(10)*	67(7)	83(10)	57(6)	-1(7)	-10(6)	-13(6)

The anisotropic temperature factor has the form

$$\exp[-(h^2\beta 11 + k^2\beta 22 + \ell^2\beta 33 + 2hk\beta 12 + 2h\ell\beta 13 + 2k\ell\beta 23)]$$

Table III. Bond Lengths (Å) in
with Standard Deviations in Parentheses

		unprimed	primed	disordered
O(1)- C(5)	1.424(6)	1.430(3)	1.429(3)	
O(1)-C(18)	1.410(8)	1.420(4)	1.428(4)	
O(2)-C(13)	1.216(7)	1.223(3)	1.221(4)	
C(1)- C(2)	1.546(8)	1.557(5)	1.546(5)	
C(1)-C(13)	1.532(7)	1.524(4)	1.522(4)	
C(1)-C(14)	1.541(8)	1.561(4)	1.557(4)	
C(1)-C(17)	1.515(8)	1.527(5)	1.545(6)	
C(2)- C(3)	1.528(8)	1.539(5)	1.543(5)	
C(3)- C(4)	1.541(7)	1.539(4)	1.552(4)	
C(4)- C(5)	1.545(8)	1.537(3)	1.531(3)	
C(4)-C(14)	1.542(7)	1.559(5)	1.546(5)	
C(5)- C(6)	1.550(7)	1.564(4)	1.567(4)	
C(5)-C(12)	1.540(7)	1.536(4)	1.539(3)	
C(6)- C(7)	1.518(8)	1.532(4)	1.513(4)	
C(6)-C(11)	1.518(7)	1.554(4)	1.557(4)	
C(7)- C(8)	1.517(8)	1.516(5)	1.516(5)	
C(8)- C(9)	1.534(10)	1.519(6)	1.584(12)	1.533(9)
C(9)-C(10)	1.532(9)	1.507(5)	1.463(18)	1.550(17)
C(10)-C(11)	1.506(8)	1.522(4)	1.414(14)	1.627(10)
C(11)-C(12)	1.554(7)	1.567(4)	1.562(5)	
C(12)-C(13)	1.513(7)	1.494(4)	1.505(5)	
C(14)-C(15)	1.554(8)	1.538(4)	1.541(4)	
C(14)-C(16)	1.541(8)	1.530(4)	1.530(5)	

Table IV. Bond Angles (°) in
with Standard Deviations in Parentheses

		unprimed	primed	disordered
C(5)- O(1)-C(18)	114.4(4)	114.9(2)	115.2(2)	
C(2)- C(1)-C(13)	106.9(4)	108.0(2)	106.8(3)	
C(2)- C(1)-C(14)	102.6(4)	102.3(2)	103.0(2)	
C(2)- C(1)-C(17)	113.0(4)	112.2(3)	112.5(3)	
C(13)- C(1)-C(14)	109.0(4)	108.1(2)	108.7(2)	
C(13)- C(1)-C(17)	109.2(5)	110.0(2)	110.2(3)	
C(14)- C(1)-C(17)	115.8(4)	115.8(3)	115.1(3)	
C(1)- C(2)- C(3)	105.9(4)	106.0(2)	105.6(2)	
C(2)- C(3)- C(4)	106.1(4)	105.8(2)	105.8(3)	
C(3)- C(4)- C(5)	114.4(4)	114.6(2)	113.7(2)	
C(3)- C(4)-C(14)	101.5(4)	102.5(2)	102.4(2)	
C(5)- C(4)-C(14)	111.0(4)	111.0(2)	111.1(2)	
O(1)- C(5)- C(4)	109.4(4)	110.1(2)	111.1(2)	
O(1)- C(5)- C(6)	112.4(4)	114.5(2)	114.2(2)	
O(1)- C(5)-C(12)	110.4(4)	110.7(2)	109.7(2)	
C(4)- C(5)- C(6)	123.2(4)	119.0(2)	118.4(2)	
C(4)- C(5)-C(12)	111.8(4)	111.4(2)	111.7(2)	
C(6)- C(5)-C(12)	87.5(4)	89.4(2)	89.6(2)	
C(5)- C(6)- C(7)	137.9(5)	114.5(2)	116.6(2)	
C(5)- C(6)-C(11)	89.4(4)	88.1(2)	88.7(2)	
C(7)- C(6)-C(11)	112.8(4)	113.4(2)	111.8(2)	
C(6)- C(7)- C(8)	105.8(5)	112.7(3)	111.4(2)	
C(7)- C(8)- C(9)	114.5(5)	109.3(3)	102.4(5)	118.3(5)
C(8)- C(9)-C(10)	115.0(5)	111.2(3)	113.6(8)	107.0(7)
C(9)-C(10)-C(11)	105.8(5)	113.4(3)	115.0(9)	104.0(7)
C(6)-C(11)-C(10)	111.9(4)	120.4(3)	119.2(7)	113.5(5)
C(6)-C(11)-C(12)	88.1(4)	88.7(2)	89.2(2)	
C(10)-C(11)-C(12)	129.5(5)	118.9(2)	131.3(7)	110.3(5)
C(5)-C(12)-C(11)	88.4(4)	88.6(2)	89.5(2)	
C(5)-C(12)-C(13)	119.3(4)	119.5(2)	119.3(2)	
C(11)-C(12)-C(13)	116.0(4)	114.6(2)	116.4(2)	
O(2)-C(13)- C(1)	122.2(5)	121.0(3)	121.9(3)	
O(2)-C(13)-C(12)	119.6(5)	119.7(2)	119.1(3)	
C(1)-C(13)-C(12)	118.2(5)	119.1(2)	118.9(2)	
C(1)-C(14)- C(4)	101.1(4)	99.9(2)	100.4(2)	
C(1)-C(14)-C(15)	111.4(4)	111.6(2)	112.2(2)	
C(1)-C(14)-C(16)	113.1(5)	112.0(2)	111.9(2)	
C(4)-C(14)-C(15)	108.8(4)	108.9(2)	108.8(2)	
C(4)-C(14)-C(16)	116.3(5)	117.0(2)	116.9(3)	
C(15)-C(14)-C(16)	106.3(5)	107.4(2)	106.8(3)	

Table V. Torsion Angles (°) in
with Standard Deviations in Parentheses

		unprimed	primed	disordered
C(14)- C(1)- C(2)- C(3)	-25.0(5)	-26.8(3)	-26.5(3)	
C(1)- C(2)- C(3)- C(4)	-3.8(5)	-2.2(3)	-2.0(3)	
C(2)- C(3)- C(4)-C(14)	31.0(5)	30.5(2)	29.9(3)	
C(3)- C(4)-C(14)- C(1)	-46.3(5)	-46.6(2)	-45.7(2)	
C(4)-C(14)- C(1)- C(2)	44.2(5)	44.9(2)	44.7(3)	
C(14)- C(4)- C(5)-C(12)	-47.3(6)	-48.0(3)	-47.9(3)	
C(4)- C(5)-C(12)-C(13)	13.4(6)	13.7(3)	12.8(4)	
C(5)-C(12)-C(13)- C(1)	-10.3(7)	-11.0(4)	-9.2(4)	
C(12)-C(13)- C(1)-C(14)	39.4(6)	40.4(4)	38.6(4)	
C(13)- C(1)-C(14)- C(4)	-68.9(5)	-68.9(3)	-68.3(3)	
C(1)-C(14)- C(4)- C(5)	75.6(5)	76.2(2)	76.1(2)	
C(13)- C(1)- C(2)- C(3)	89.6(5)	87.1(3)	88.0(3)	
C(1)- C(2)- C(3)- C(4)	-3.8(5)	-2.2(3)	-2.0(3)	
C(2)- C(3)- C(4)- C(5)	-88.6(5)	-89.9(3)	-90.1(3)	
C(3)- C(4)- C(5)-C(12)	66.8(5)	67.5(3)	67.0(3)	
C(4)- C(5)-C(12)-C(13)	13.4(6)	13.7(3)	12.8(4)	
C(5)-C(12)-C(13)- C(1)	-10.3(7)	-11.0(4)	-9.2(4)	
C(12)-C(13)- C(1)- C(2)	-70.8(6)	-69.6(3)	-71.9(3)	
C(12)- C(5)- C(6)-C(11)	-19.5(4)	-17.4(2)	-13.2(2)	
C(5)- C(6)-C(11)-C(12)	19.3(4)	17.0(2)	13.0(2)	
C(6)-C(11)-C(12)- C(5)	-19.4(4)	-17.3(2)	-13.2(2)	
C(11)-C(12)- C(5)- C(6)	19.0(4)	17.2(2)	13.1(2)	
C(11)- C(6)- C(7)- C(8)	57.6(6)	-39.6(4)	-51.8(4)	
C(6)- C(7)- C(8)- C(9)	-51.1(6)	60.9(4)	65.0(5)	37.4(5)
C(7)- C(8)- C(9)-C(10)	52.2(7)	-65.3(4)	-63.9(10)	24.5(7)
C(8)- C(9)-C(10)-C(11)	-51.7(6)	48.1(4)	48.7(15)	-67.0(7)
C(9)-C(10)-C(11)- C(6)	57.3(6)	-28.5(4)	-32.0(14)	53.0(7)
C(10)-C(11)- C(6)- C(7)	-65.2(6)	24.1(4)	33.2(7)	6.6(6)

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