Amarasekara, Ananda Sarath

STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF TAXANE ALKALOIDS. (I) AN APPROACH TO THE D-RING OF TAXOL. (II) AN INTRAMOLECULAR PHOTOCYCLOADDITION APPROACH TO THE TAXANE SKELETON

City University of New York PH.D. 1985

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BY

ANANDA S.AMARASEKARA

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.

David C. Locke

9/18/85 date

Executive Officer.

Supervisory Committee.

The City University of New York

ABSTRACT

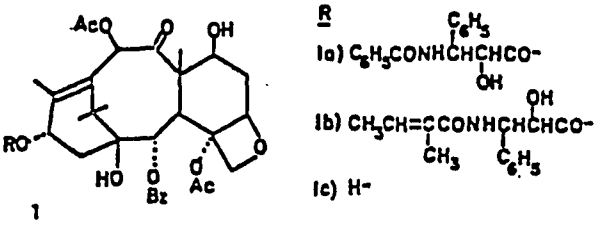
STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF TAXANE ALKALOIDS. [I] AN APPROACH TO THE D RING OF TAXOL. [II] AN INTRAMOLECULAR PHOTOCYCLOADDITION APPROACH TO THE TAXANE SKELETON.

BY

ANANDA S.AMARASEKARA

Adviser: Dr. William F. Berkowitz

Taxol 1a, Cephalomannine 1b and Baccatin III 1c are polyoxygenated diterpenoids isolated from Taxus species.



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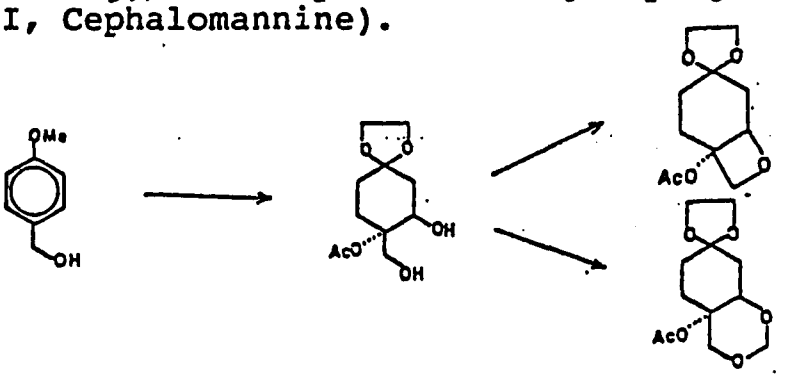
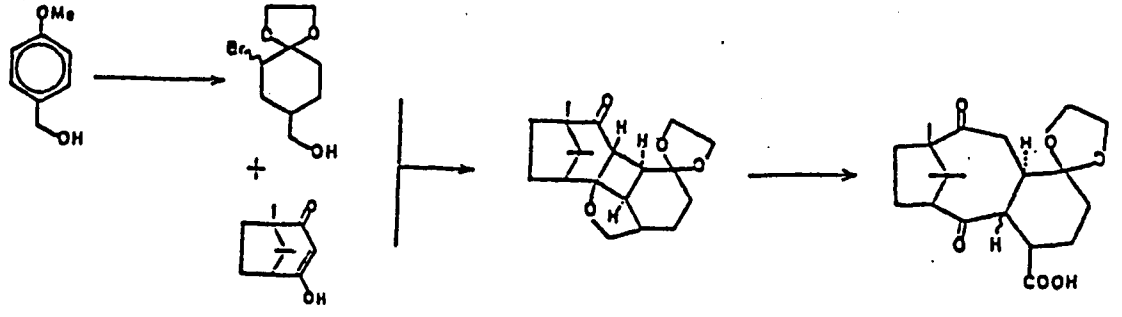
Two key aspects in the synthesis of these compounds have been investigated. In the first phase a method was developed which is applicable to the construction of the Oxetane (D ring)/tertiary acetate grouping of Taxol (Baccatin III, Cephalomannine).



In the second phase model studies have been carried out in development of an intramolecular photocycloaddition approach applicable in the construction of the Taxane skelton.



ACKONOWLEDGEMENTS

The author would like to thank Dr. William F. Berkowitz whose patient, effective instructions and continual support have provided a valuable educational experience and the members of the thesis committee Doctors Engel and Grohman whose encouragement and advice made completion of this work possible.

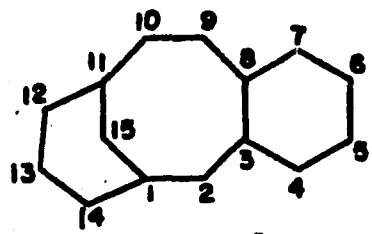
Thanks are also to my fellow gradute students for making the life in the lab enjoyable.

TABLE OF CONTENTS

Chapter. I INTRODUCTION

ISOLATION AND STRUCTURE

Taxanes are a class of diterpenoids isolated from the plants of the family Taxaceae[1-8]. All of these compounds have a common tricyclo [9,3,1,$0^{3,8}$] pentadecane skeleton 1 known as the Taxane skeleton.



1

The common features of this class of compounds are

(1). Oxygen funtionalities at C- 2,5,9 and 10. (The only exception is the C-2 position of Taxusin.)

(2). Bridgehead double bond at C-11/C12.

(3). Gem-dimethyl group at C-15.

(4). Angular methyl group at C-8.

(5). Methyl group at C-2.

Apart from these common features there are other interesting funtionalities, occasionaly found in some of the members of the class such as;

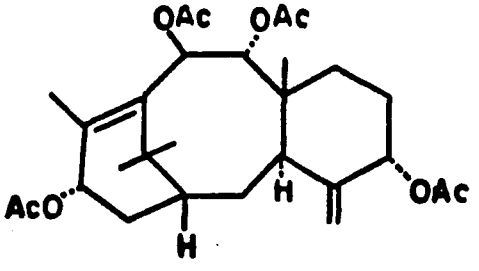
(1). Nitrogen containing side chain in Taxine I, Taxol and Cephalomannine.

(2). Oxetane ring in Taxol, Cephalomannine and Baccatin III.

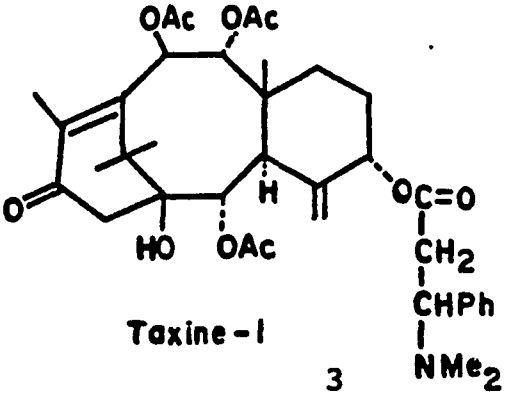
(3). C-1 Angular hydroxyl group in Taxine I, Taxol, Cepholamannine, Baccatin III and 1-β Hydroxybaccatin.

(4). C-4/C-18 epoxide in 1-β Hydroxybaccatin.

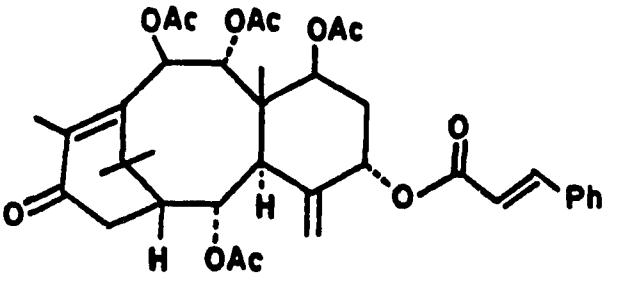
Compound	Plant isolated
(1). Cephalomanine	Taxus Wallichina Zucc and Cephalotaxus Mannii
(2). 1-β Hydroxybaccatin	Taxus Wallichina Zucc.
(3). Taxinin B	Taxus Baccata L and Taxus Brevifolia.
(4). Taxol	Taxus Brevifolia and Taxus Cuspidata.
(5). Taxine I	Taxus Baccata L
(6). Taxusin	Taxus Baccata L
(7). Baccatin	Taxus Baccata L



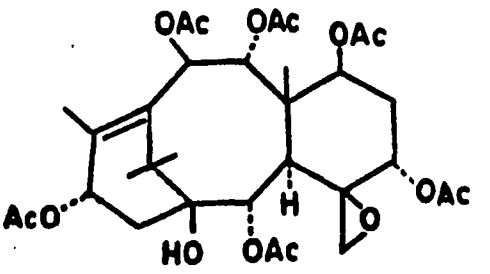
Taxusin 2



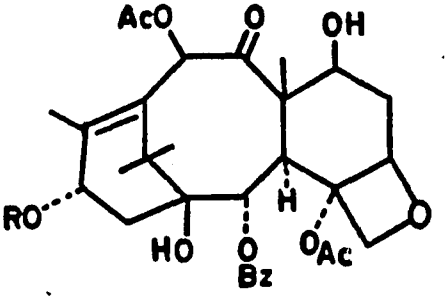
Taxine-I 3



Taxinin B 4



8 1β-Hydroxybaccatin



5 R= $C_6H_5CONHCH(C_6H_5OH)CHCO-$ Taxol

6 R= $CH_3CH{=}C(CH_3)CONHCH(C_6H_5)CHCO-$ Cephalomannine

7 R=H- Baccatin III

Biological Activity

Most of the compounds in this class exhibit promising biological activity against cancer cells, and can be considered as potential chemotheraputic agents.

Taxol shows confirmed activity on L-1210, P-388 and P-1534 leukemias, especially high in the latter two systems, and also shows considerable cytotoxicity in the 9KB assay, ($ED_{50} = 5.5 \times 10^{-5}$)[2].

Taxus Wallichina Zucc. extracts containing Cephalomannine have shown KB and PS antitumor activity[1].

ATTEMPTS TO ASSEMBLE THE TAXANE SKELETON - SYNTHETIC APPROACHES.

The highly funtionalized Taxane class is a considerable challenge. More than a dozen research groups around the world are currently involved in studies on the synthesis of the Taxane system. To date no one has completed a total synthesis of any of the compounds in this class.

Jenkins[15], Sakan[16], Holton[19], Martin[12], Blechert[24] and Inouye[61] have been successful in assembling the basic tricyclo [9,3,1,$0^{3,8}$] pentadecane (Taxane) skeleton. Other groups have concentrated on the A/B - rings or the construction of the 8 - membered B ring.

Model studies can be divided into seven different classes, depending on the key reaction in the approach.

(1). Polyene cyclizations - Biomimetic type.

(2). Anionic oxy-Cope rearrangements.

(3). Intercalation proceses.

(4). Diels-Alder reaction.

(5). Carbonium ion induced fragmentation rearrangements.

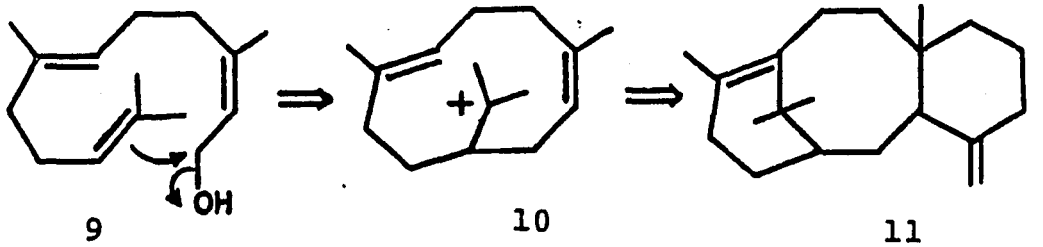
(6). Titanium induced reductive coupling.

(7). Photochemical methods.

(1). Polyene cyclizations - Biomimetic type.

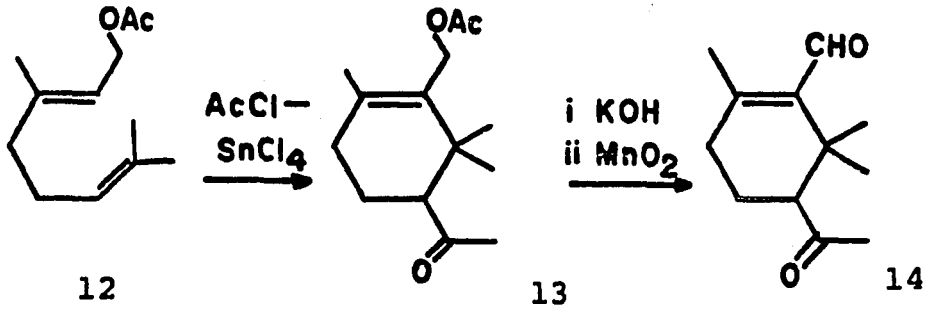
In 1974 Y.Kitahara and coworkers[9] published their results on a biogenetic type of approach, Their plan is outlined in the Scheme I.

Scheme I.



9 10 11

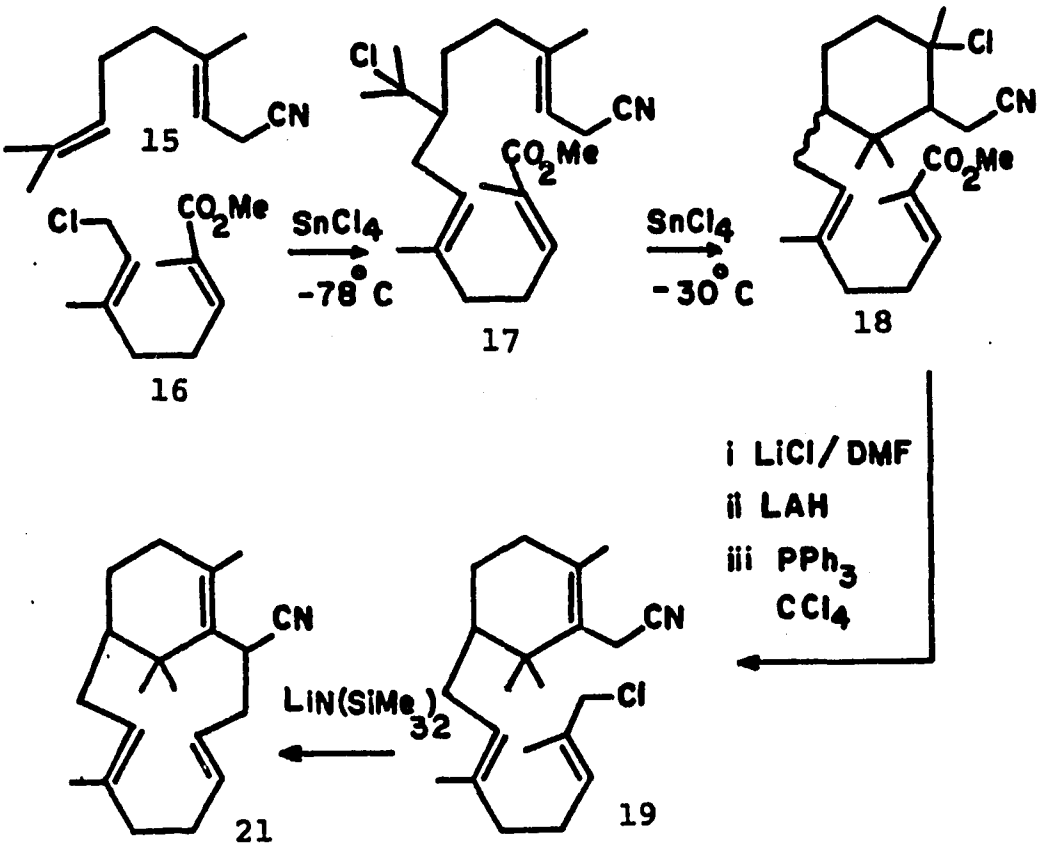
Their model study employed a simpler system, geranyl acetate 12, which was cyclized using AcCl-$SnCl_4$, followed by conversion of the CH_2-OAc group to an aldehyde.



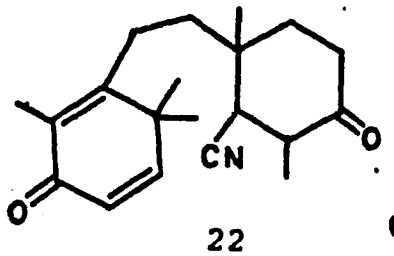
12 13 14

Preparation of a seco-Taxane skeleton 21 was reported by Tadahiro Kato[10] in 1978. Their approach is outlined in the Scheme II.

Scheme II.



A list of unsuccesful attempts to construct the Taxane skeleton by biomimetic type cyclizations has been reported by Chapman[11]. A series of compounds 22-28 were prepared. The ketonitrile 22 was subjected to various reductive cyclization procedures (Li/liq-NH_3, K/liq-NH_3 and Li/TMSCl/THF) without succes. Dienone 23, nitroketone 24, p-nitrobenzoates 25 and 26, and ketoesters 27 and 28 were subjected to anion forming conditions (LDA, KH, K^tBuO and lithium-N-cyclohexylisopropyl amide) but did not cyclize.



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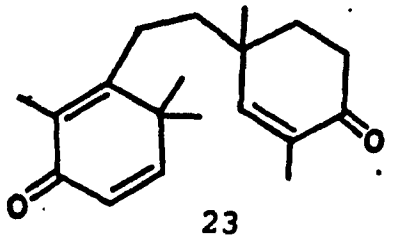

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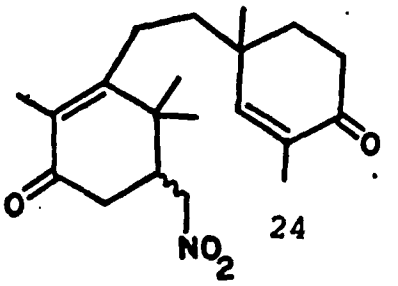

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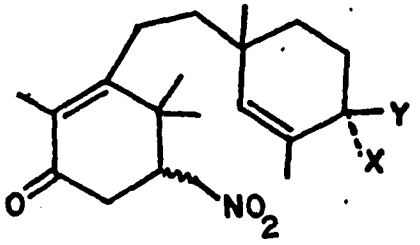
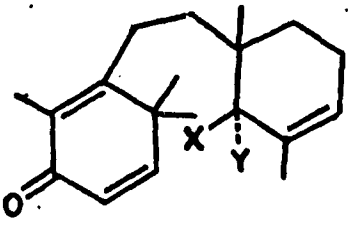


25 X = O_2CPhNO_2, Y = H

26 X = H, Y = O_2CPhNO_2



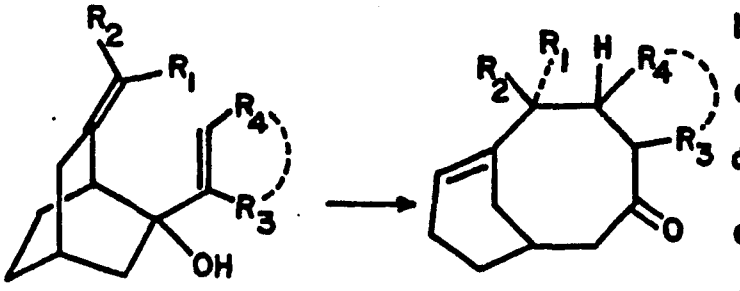
27 X = CH_2CO_2Et, Y = H

28 X = H, Y = CH_2CO_2Et

(2). Anionic oxy-Cope rearrangement.

S.F.Martin et.al.[12] have investigated the possibility of using an anionic oxy-Cope rearrangement to prepare the bicyclo [5,3,1] undeca-7-enes 30 a-f.

They synthesized a series of allyl vinyl carbinols with a common bicyclic framework. These compounds, upon deprotonation with potasium hydride in THF, underwent a facile anionic oxy-Cope rearrangement.



29 30

a. $R_1, R_2, R_3, R_4 = H$

b. $R_1, R_2, R_3 = H$; $R_4 = Me$

c. $R_1, R_2 = H$; $R_3, R_4 = -(CH_2)_4-$

d. $R_1 = Me$; $R_2, R_3, R_4 = H$

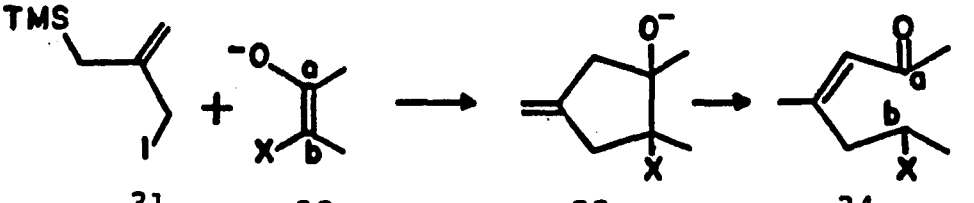
e. $R_1 = OMe$; $R_2, R_3, R_4 = H$

f. $R_1, R_3, R_4 = H$; $R_2 = OMe$

It is interesting to note that compound 30c has the basic Taxane, tricyclo[9,3,1,$0^{3,8}$]pentadecane skeleton.

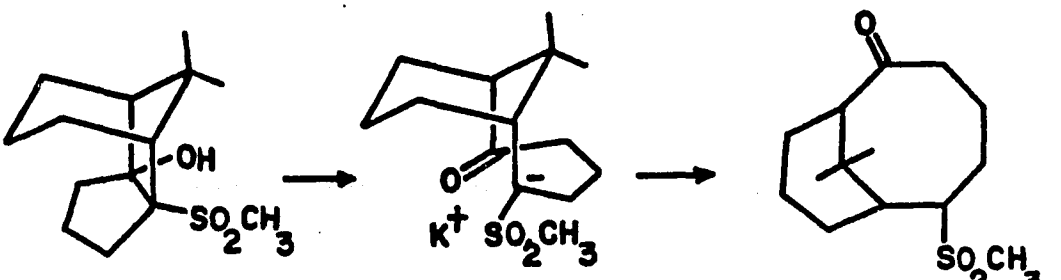
(3). Intercalation processes.

An intercalation process was used by Trost[13] in his approach to the bicyclo[5,3,1]undecyl system. Bifunctional reagents such as 31 offer a unique approach to ring formation. The presence of an electron withdrawing group (X) in 32 induces fragmentation of the initial adduct 33 and thus constitutes a three carbon intercalation between C-a and C-b.



31 32 33 34

Trost prepared 35, which incorporates a gem-dimethyl group to test this reaction. Compound 35 on treatment with KH, in the presence of 18-crown-6, fragmented to give 38.



35 36 38

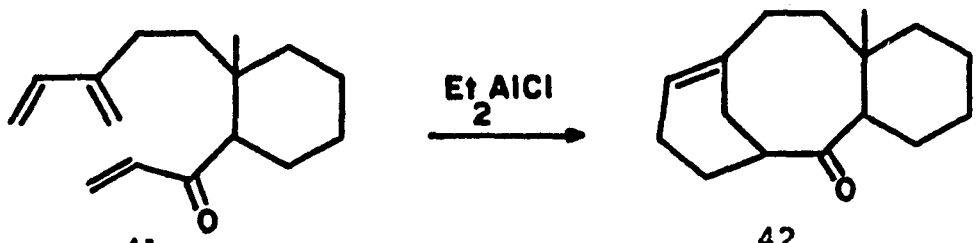
(4). Diels-Alder approach.

Several groups have used the Diels-Alder reaction as the key step in the construction of the Taxane skelton.

The first study was due to K.J.Shea,[14] who tried a diethyl aluminium chloride catalysed cyclization of 39, and showed that one can make the 8 membered B-ring by an intramolecular Diels-Alder reaction.

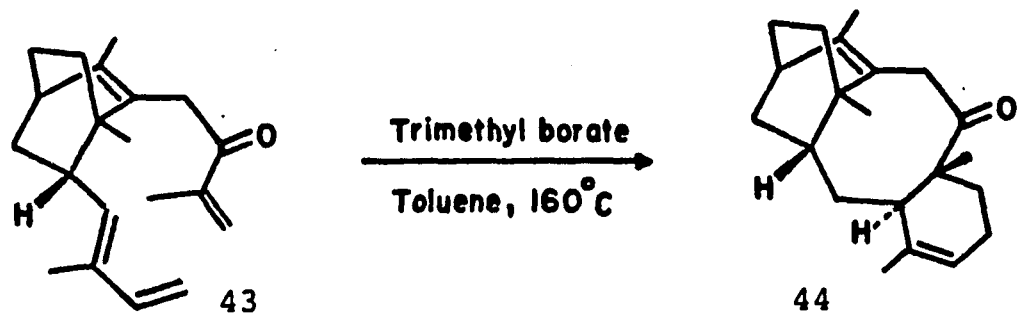
39 40

In 1984 Paul R.Jenkins[15] reported the same reaction on a similar system.



41 42

A more elaborate model for the Taxane system 44 was assembled by Sakan and Cravan[16] as the latest step in the Diels-Alder approach. They used a trimethylborate catylised cyclization procedure.

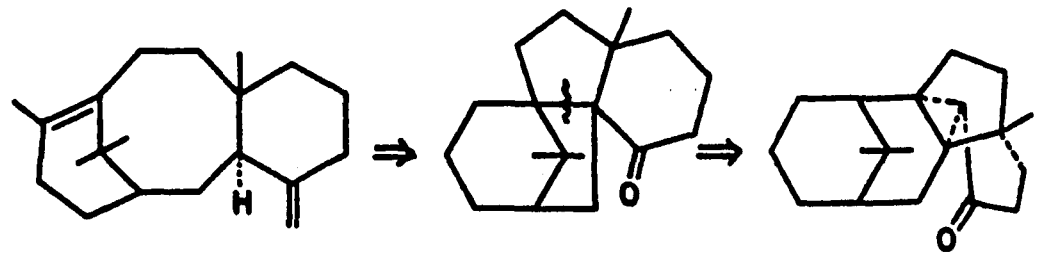


43 44

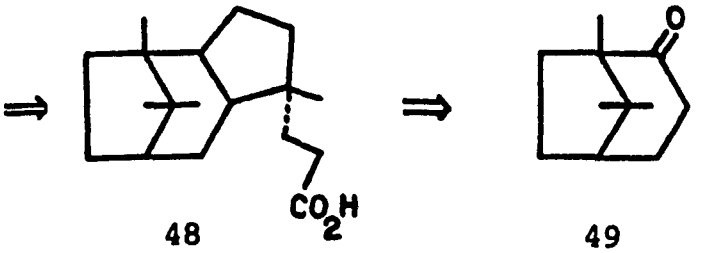
(5). Carbonium ion induced fragmentation rearrangements.

The first studies in this area are due to Inouye[17]. Inouye's strategy is outlined in the Scheme III.

Scheme III.

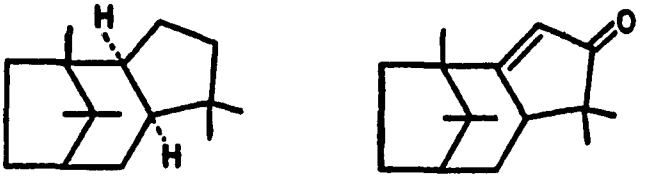


45 46 47



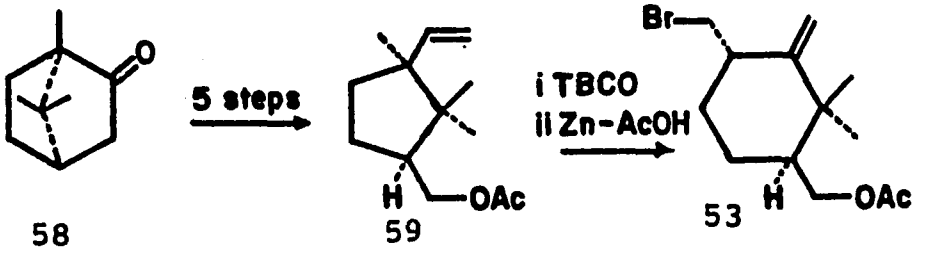
48 49

Inouye has been able to prepare some model compounds for 48 such as 50 and 51, starting from homocamphor 49.



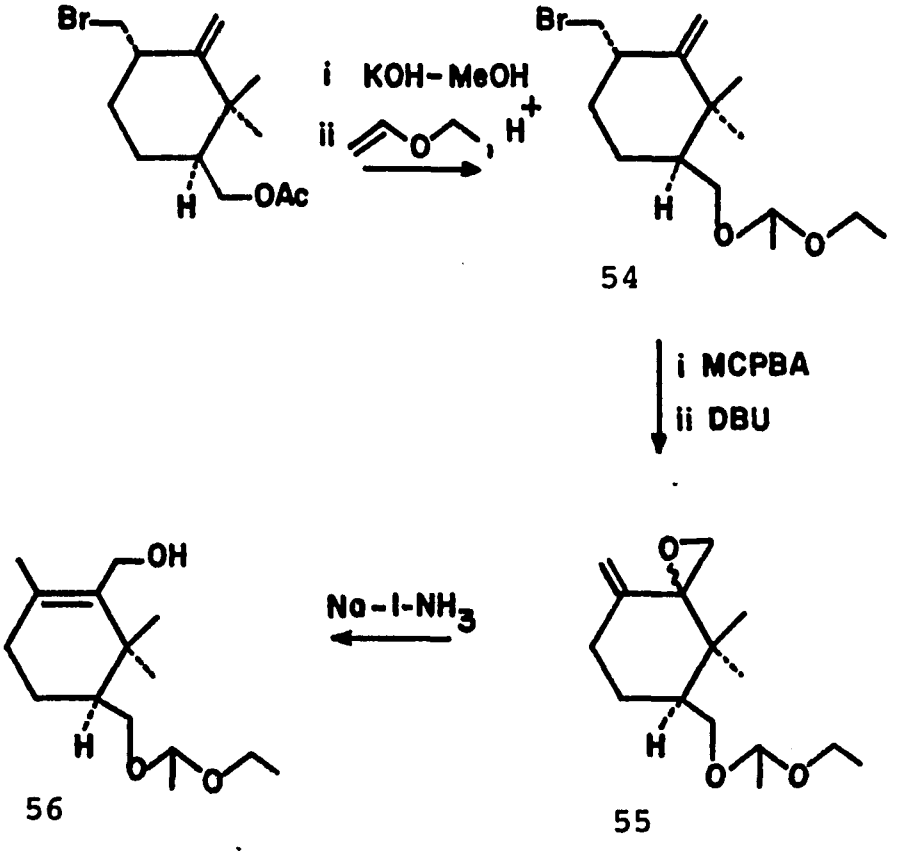
50 51

Isao Kitagawa and coworkers[18] reported a method to synthesis a A-ring building block for the Taxane system. Their approach is dependent on a novel ring enlargement-rearrangement.



58 59 53

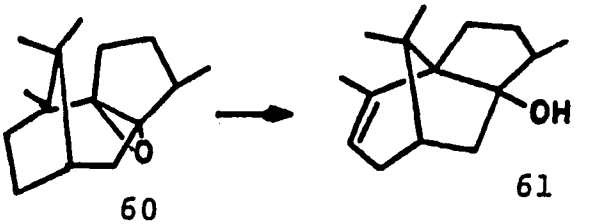
Vinyl cyclopentane derivative 59 was prepared from d-camphor 58 in five steps. Compound 59 on treatment with 2,4,4,6-tetrabromo cyclohexa-2,5-dienone (TBCO) followed by Zn/AcOH gave the ring enlarged compound 53, which could be converted into 56 in five steps.



Transformation 52 - 53 is believed to occur through a bromonium ion induced rearrangement as shown.

Recently, Holton[19] published his results on an elegant rearrangement approach to Taxusin. His starting material was β-patachouline oxide originally made by Buchi[20].

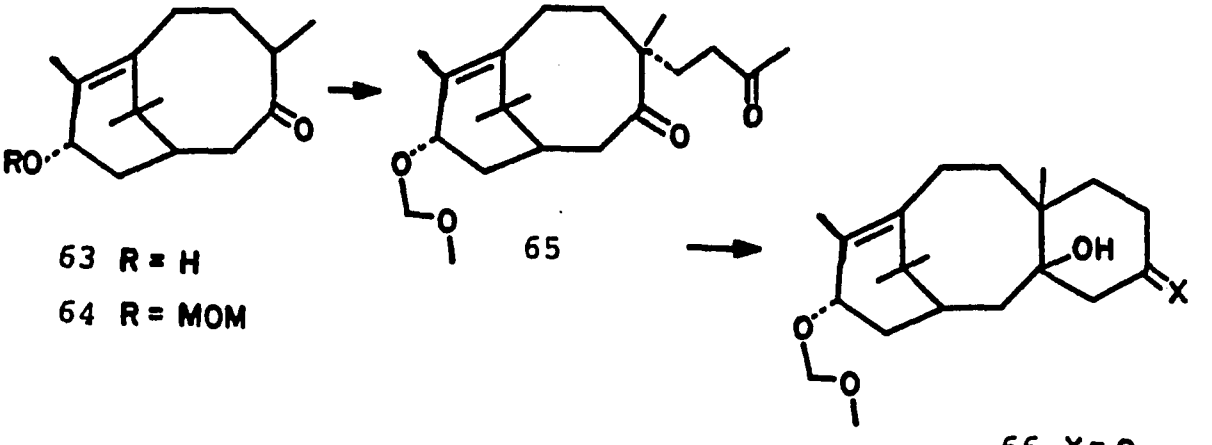
β-Patachouline oxide 60 was converted to a tertiary alcohol 61 using boron triflouride etherate. Epoxidation of 61 using ^{t}BuOOH and Ti(O^{i}Pr)$_4$, gave the unstable epoxide 62, which underwent fragmentation to provide the keto alcohol 63.



60 61

62

The hydroxy ketone 63 was protected as the methoxy methyl ether, then alkylated to give compound 65.
An intramolecular aldol condensation of 65, catalysed by bromomagnesium isopropyl cyclohexylamide (BMICA) gave an unstable β-hydroxy ketoalcohol 66, which was immediately reduced to diol 67.

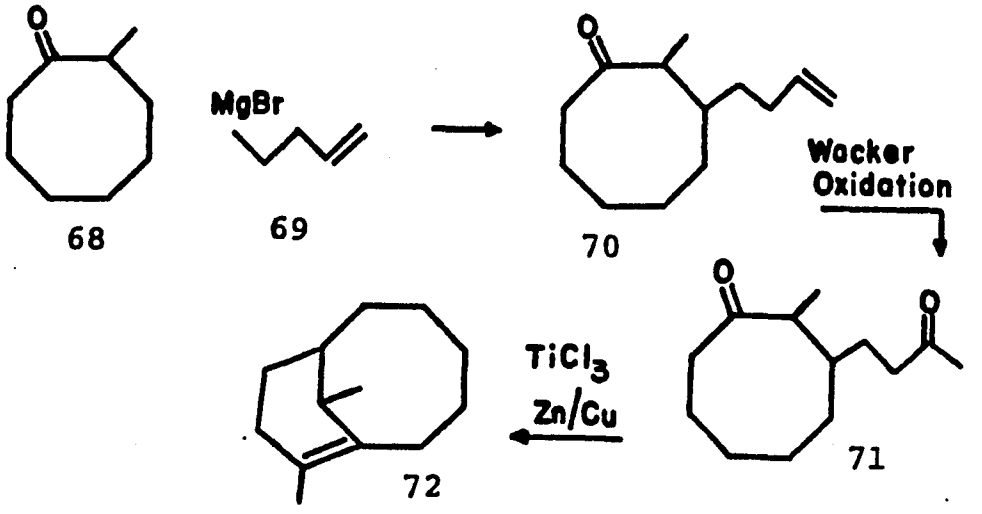


(6). Titanium (III) induced reductive coupling.

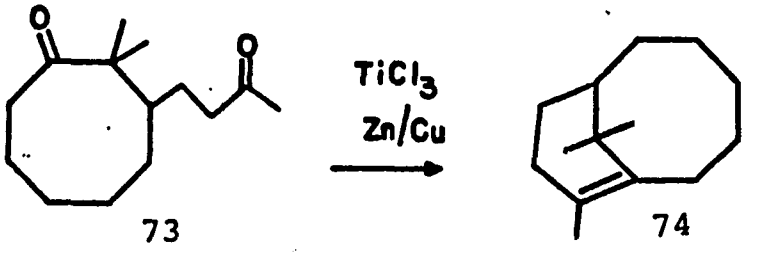
Susan Britcher[21] reported an approach to bicyclo [5,3,1]undec-7-enes using a titanium induced reductive coupling.

The synthesis of 8,11-dimethyl bicyclo[5,3,1]undec-7-ene 72 is shown in the Scheme IV.

Scheme IV.



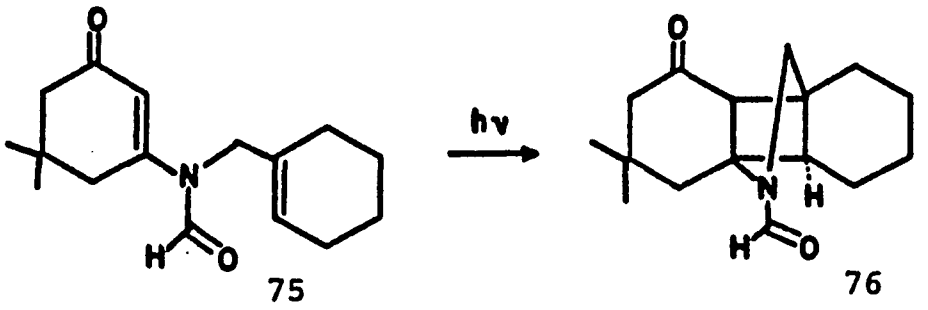
The gem-dimethyl homolog 73 was also subjected to reaction with $TiCl_3$, Zn/Cu, but this compound failed to give the desired product 74.



(7). Photochemical methods.

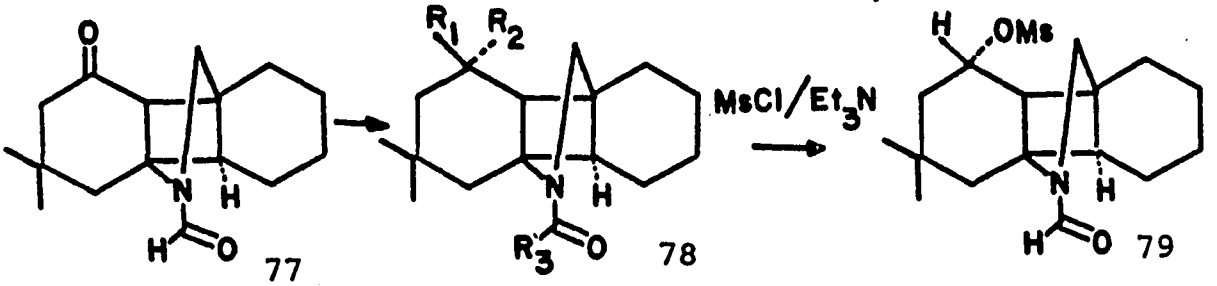
Four photochemical approaches to the Taxane skelton have recently appeared in the literature.

[a]. C.S.Swindell[22,23] prepared 76 by the intramolecular photo cycloaddition of vinylogous imide, first studied by Tamura[24] and Schell[25].



75 76

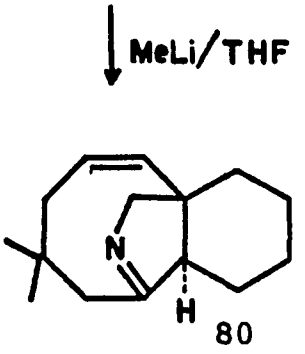
Development of a method to fragment the cyclobutane ring gave a B/C-ring model 82 for the Taxane in ten steps.



77 78 79

R_1= OH R_2,R_3= H

R_1= H R_2= OH R_3=H



80

i HOAc/H_2O

ii CH_3CO_2CHO/py

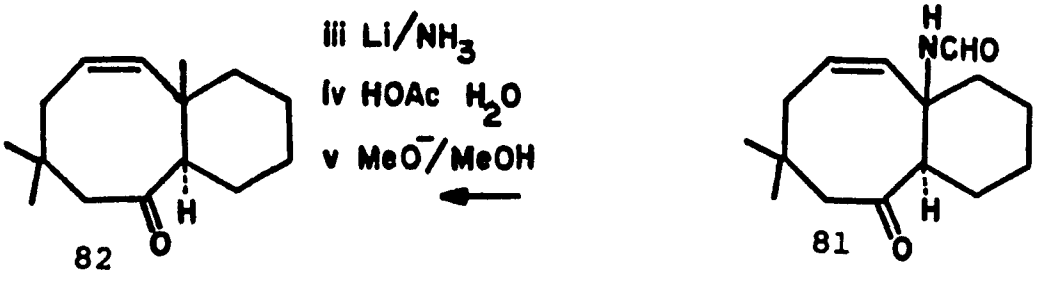
i $HO(CH_2)_2OH$/TsOH

ii MsCl/py

iii Li/NH_3

iv HOAc H_2O

v MeO^-/MeOH

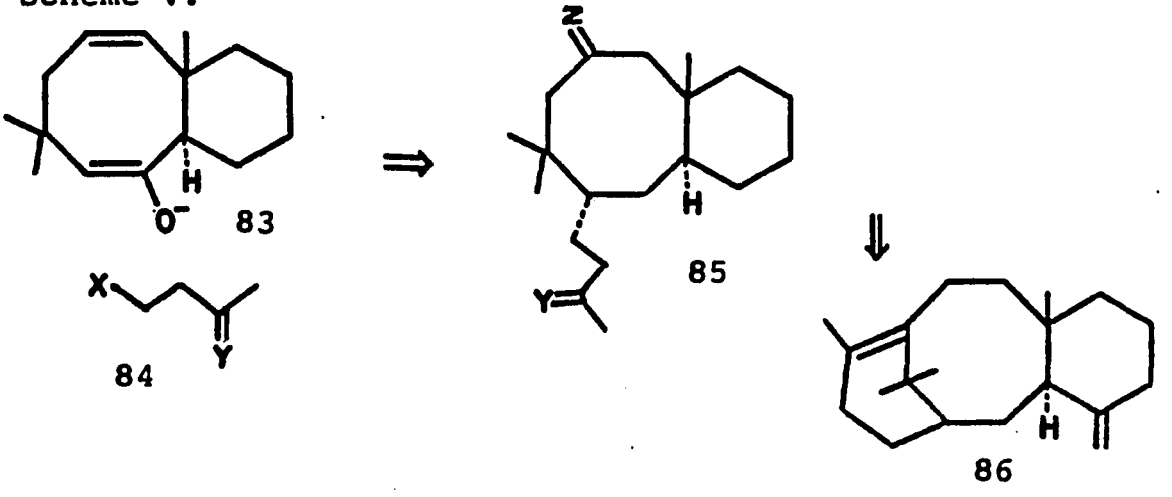


82 81

Stereospecific reductions of 77 were accomplished with various reducing agents, and the resulting α-hydroxy epimer was mesylated and fragmented with MeLi/THF to give the imine 80. Acid hydrolysis and formylation of the amine gave amide 81, which was further converted into 82 bearing an angular methyl group.

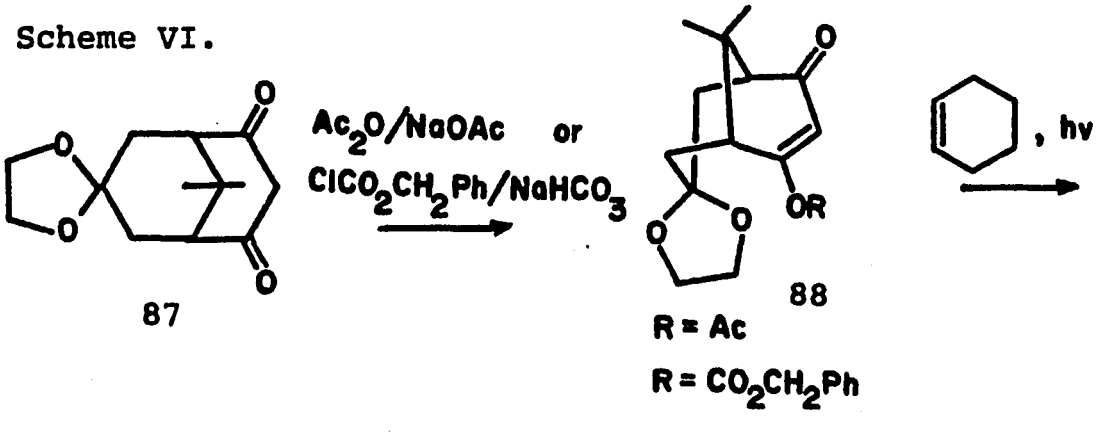
Swindell further proposed a strategy to attach the A'-ring to the B/C-ring synthon 83 as shown in Scheme V.

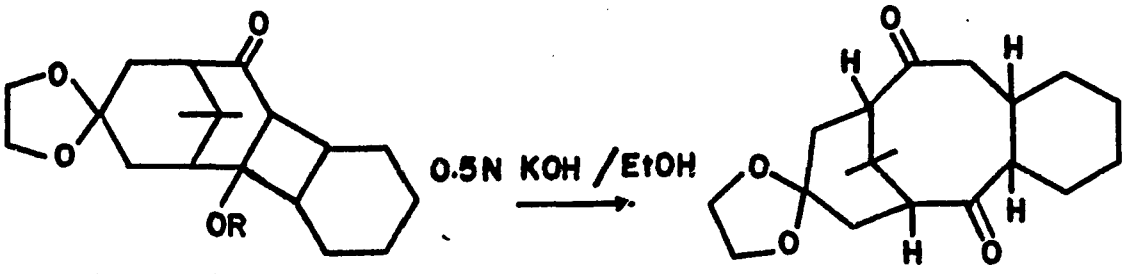
Scheme V.



[b]. The method of Siegfried Blechert et.al.[26] is based on an intermolecular [2+2] photocycloaddition. Their approach is outlined in the Scheme VI.

Scheme VI.





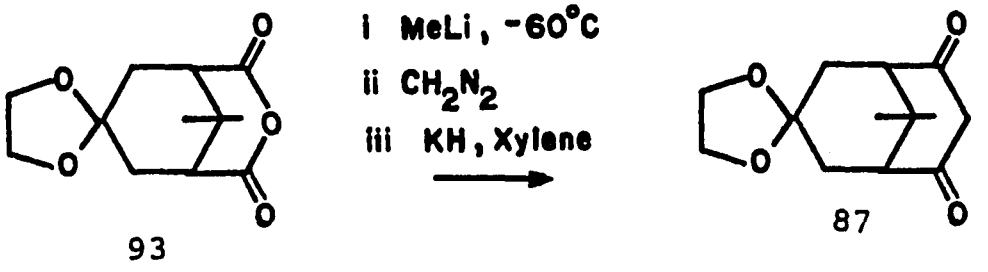
89 R = Ac

90 R = CO_2CH_2Ph

91 R = H

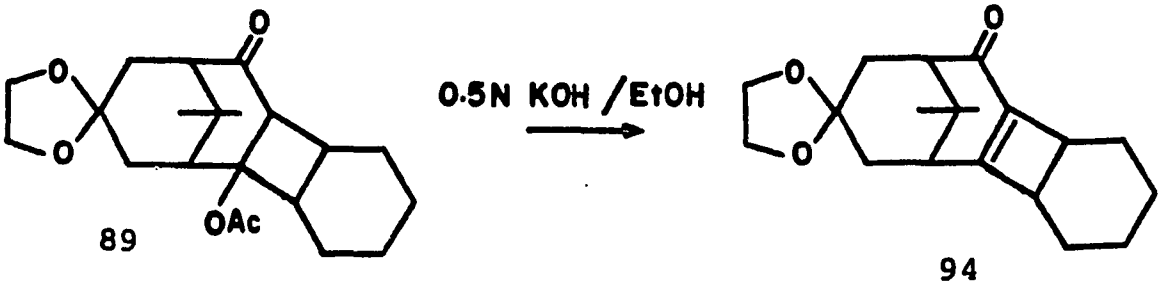
92

The 1,3-diketone 87 was synthesised from the anhydride 93 as shown.



93 87

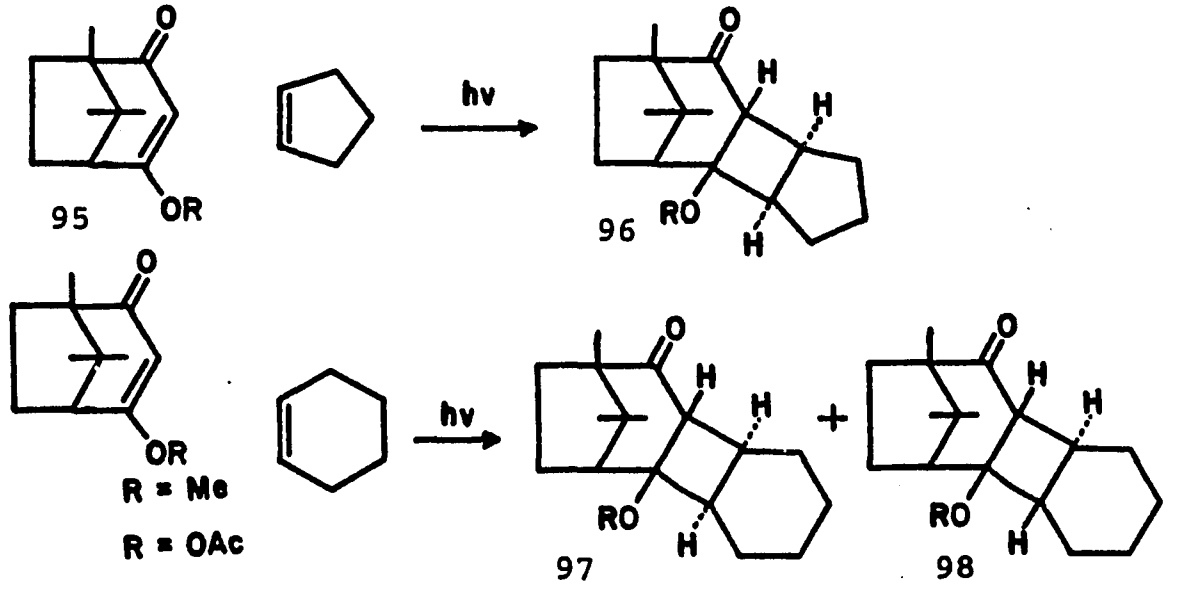
They found that the photoadduct obtained with enol acetate 89 was not suitable for the ring opening reaction, as an elimination took place, forming cyclobutene 94.



89 94

To prevent the elimination reaction they prepared the benzyl carbonate photoadduct 90. The benzyl group was then easily cleaved by hydrogenolysis to give β- keto alcohol 91, which underwent a slow retro-aldol reaction on exposure to ethanolic KOH furnishing the cycloctane dione 92. Further, they established the structure and the configuration of the tricyclic molecule by X-ray crystallography.

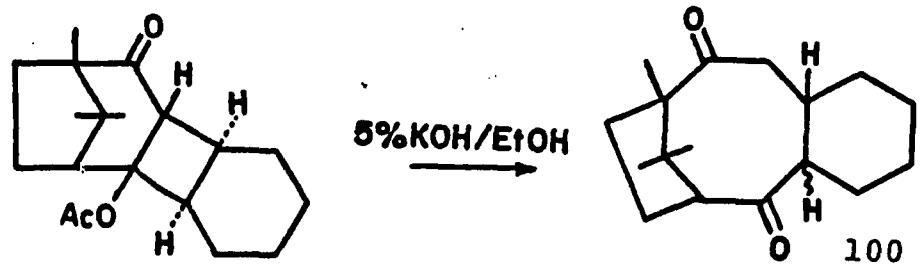
[c]. J.Perumattam[27] in our laboratory has studied the inter-molecular photoadducts formed from homocamphorquinone enol acetate and enol methyl ether with various cycloalkenes. He observed that cyclohexene gives two isomers, 97 and 98, in a 1:1 ratio in 50% total yield, whereas cyclopentene gives only one isomer 96. (These structures were confirmed by single crystal X-ray crystallography, most kindly performed by Dr. J. Blount of Hoffman LaRoche, Nutley, N.J.)



He further studied the ring opening reactions of these photoadducts, the results are outlined in the Scheme VII.

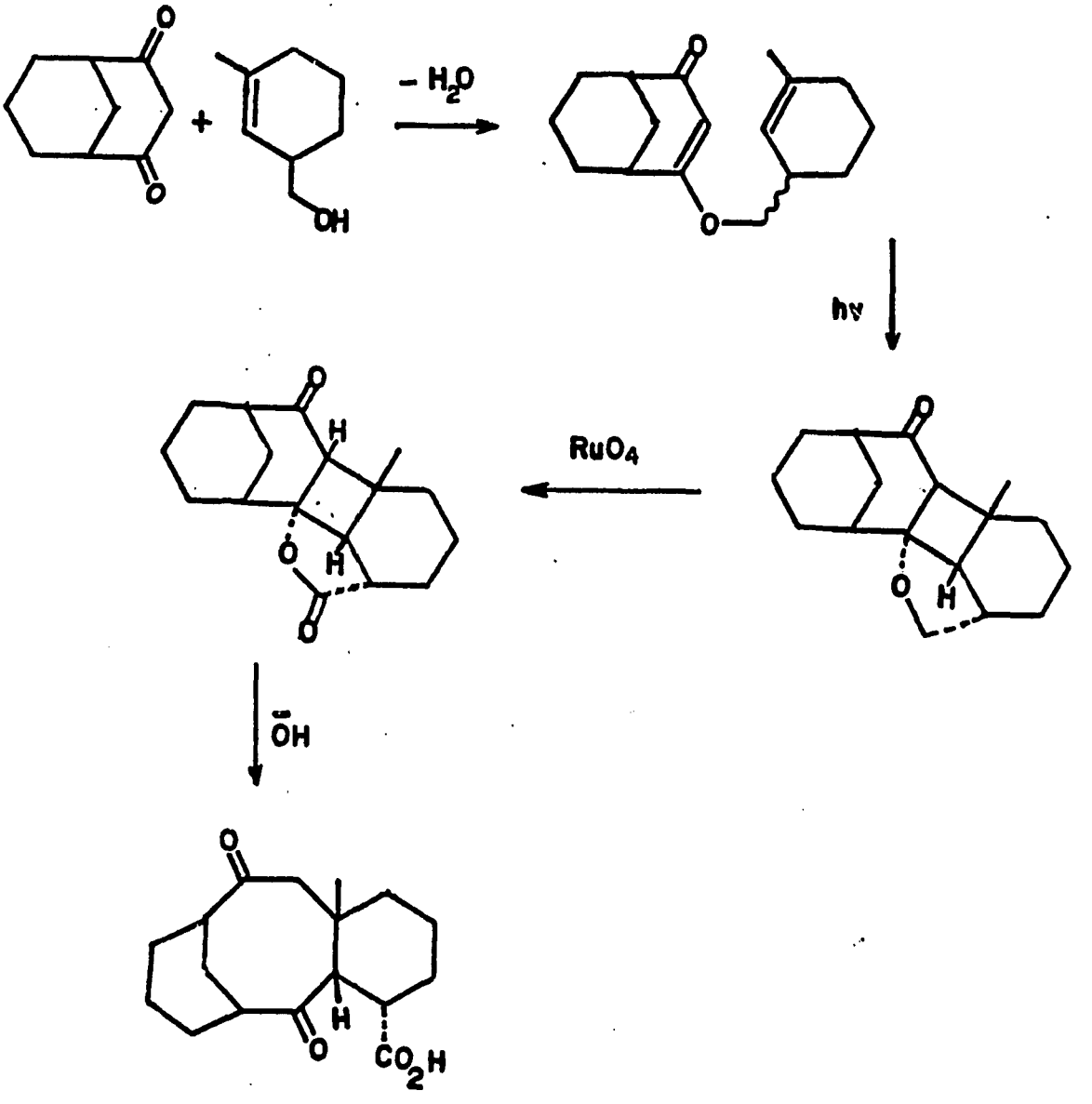
Scheme VII

99

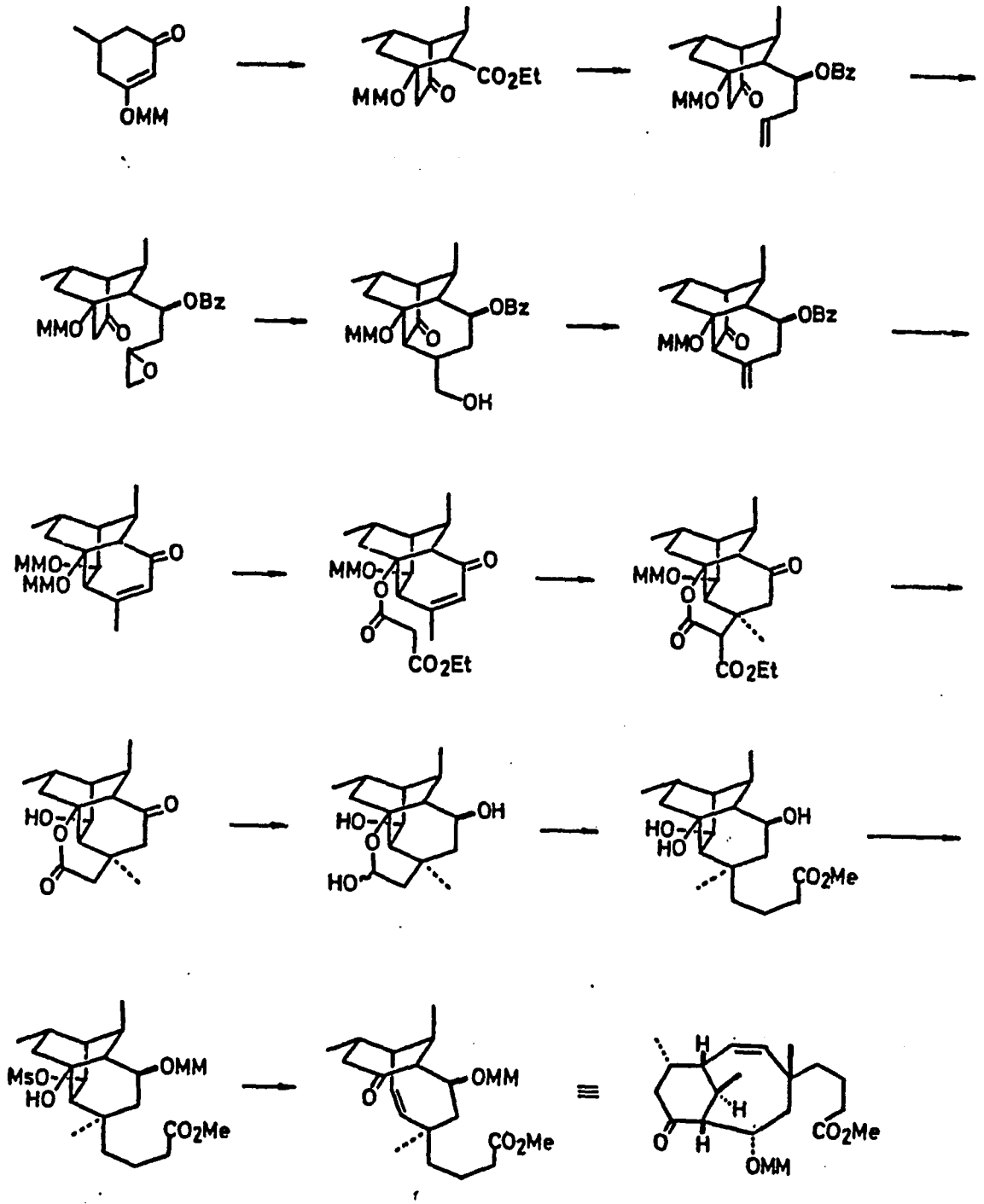


100

[d]. Another photochemical approach appeared in the literature after the experiments of our laboratory were completed. Inouye[61] used an intramolecular photocycloaddition method to construct the Taxane skeleton.



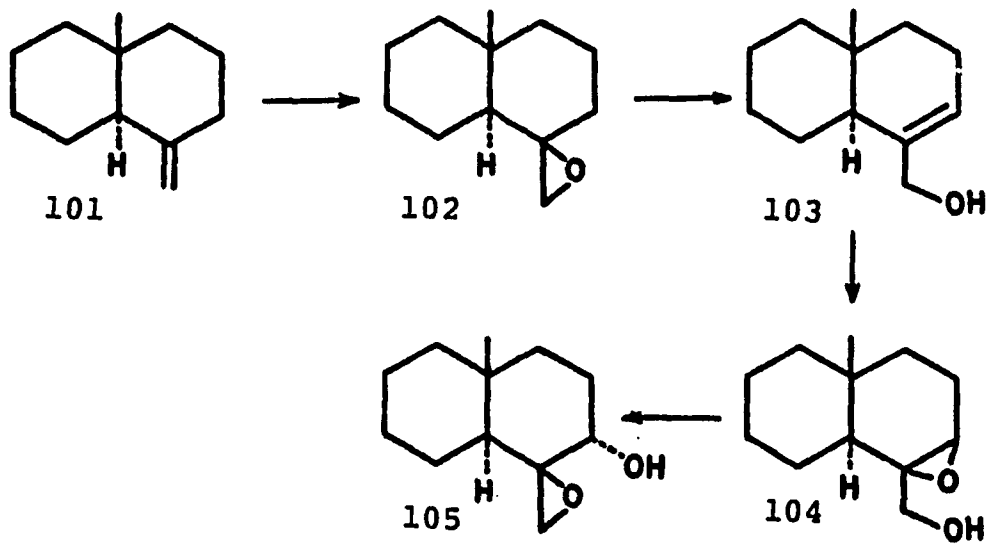
A rather long approach to the basic Taxane skelton was published by Yamada et.al.[63] Their key reaction is a Grob type fragmentation, the reaction pathway is outlined below.



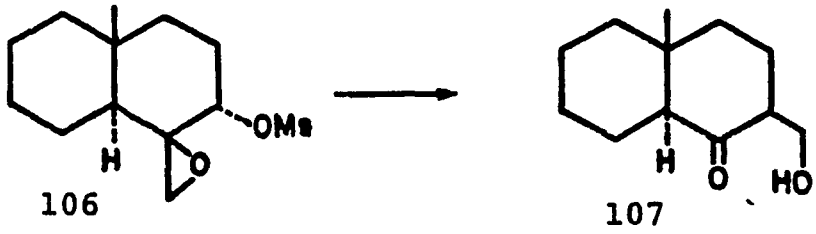
Synthetic approaches to the C/D-ring system of Taxol, Cephalomannine and Baccatin III

Another unusual feature found in Taxol, Cephalomannine and Baccatin III is the oxetane D-ring and the C-4 tertiary acetate.

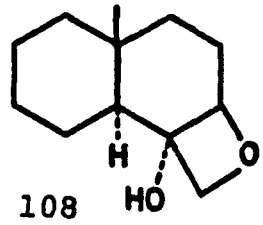
Only one attempt has been reported for the synthesis of this C/D-ring feature.[21] Using 1-methylene-trans-10-methyldecalin as the starting material, the operations shown below were performed. The product 105 mimics the C-ring substituent pattern of the naturally occuring Taxane, β-hydroxybaccatin.



An attempt was made to make the Oxetane D-ring by solvolysis of the epoxy mesylate 106.



106 107



108

However a migration of the methylene group to the 2-position was observed and gave the 2 β-hydroxymethyl - 10-methyl-1-decalone 107 instead of the desired oxetane 108.

Chapter.II RESULTS AND DISCUSSION

This work is divided into four sections.

(1). Studies on the C/D - ring synthon of Taxol, Cephalomannine and Baccatin III.

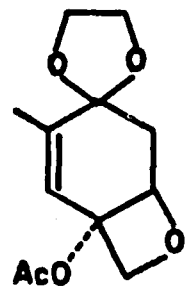
(2). Intramolecular photocycloaddition (model study).

(3). Model studies on A/B/C-ring system of Taxane.

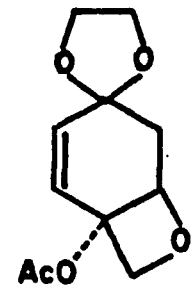
(4). Grob/Bamford-Stevens fragmentation studies on the photoadducts.

(1). Studies on the C/D - ring synthon of Taxol, Cephalomannine and Baccatin III.

The first quarter of the work was directed towards the synthesis of a C/D-ring synthon suitable for Taxol, Cephalomannine and Baccatin III. The original design for this molecule was 109, but later we decided to leave off the methyl group, as in 110, since we would be able to insert it at a later stage.



109

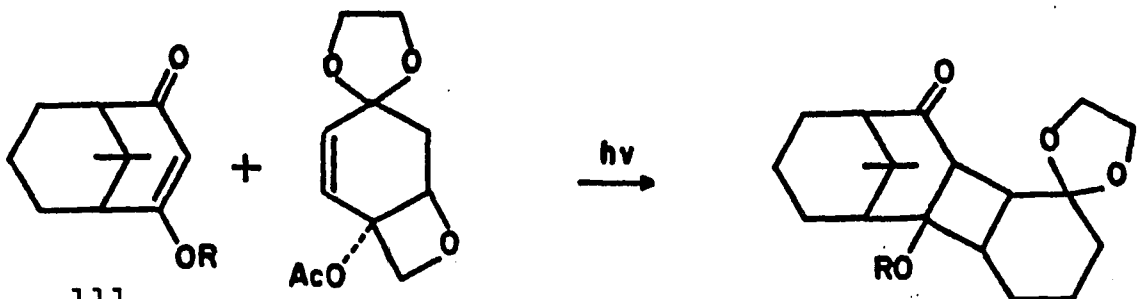


110

This molecule is very attractive because it incorporates all of the C/D-ring funtionalities.

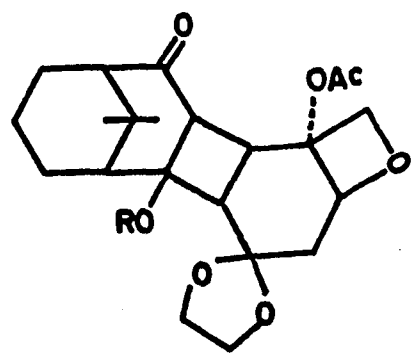
We expected to combine 110 with an A/B-ring synthon using an inter-molecular 2+2 photocycloaddition. The photoadduct should fragment in a deMayo reaction.[29]

It is known[28,29] that the cyclohexenone ketals photoadd to enones with head to head reqiochemistry rater than head to tail. Our strategy is outlined below:



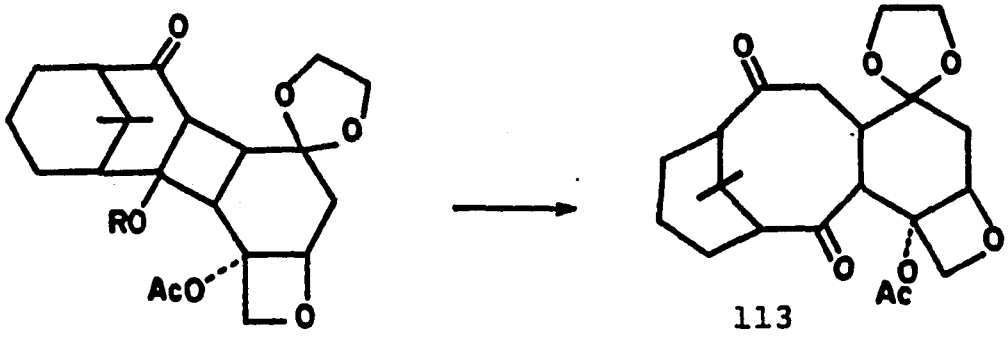
111

112



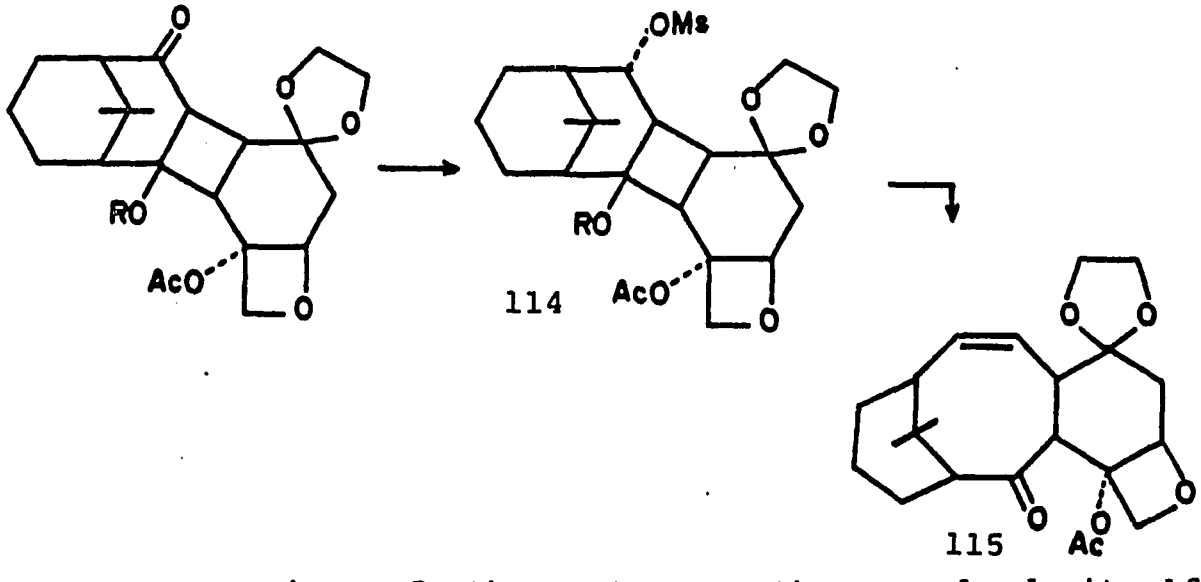
The fragmentation of the cyclobutane ring of the photoadduct was to be accomplished by either retro-aldol or Grob fragmentation reactions[29].

(a). Retro-Aldol opening.



113

(b). Grob fragmentation.

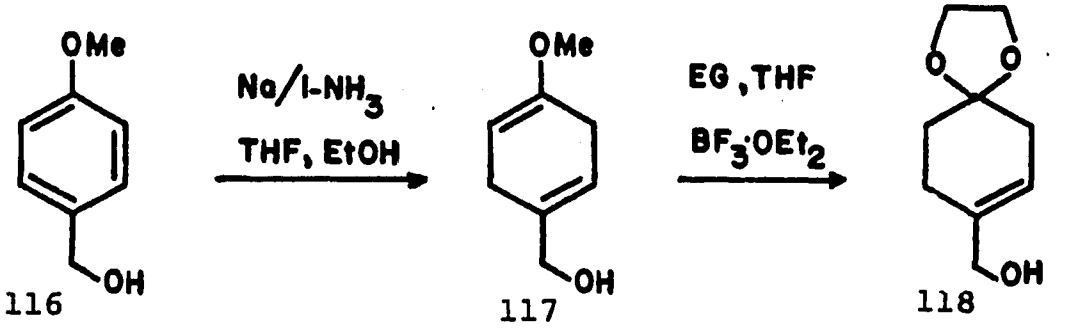


114

115

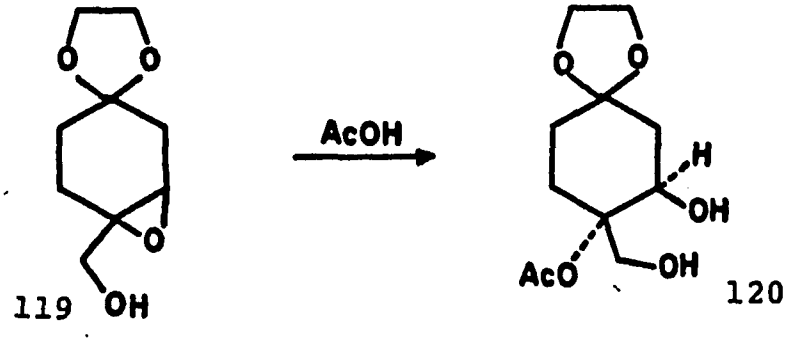
Preparation of the oxetane synthon resolved itself into two operations: [1] formation of the oxetane - tertiary acetate grouping, and [2] introduction of the double bond.

[1] The starting material for the C/D - synthon was chosen to be 4-methoxy benzylalcohol 116. Following the procedure of Ito and coworkers[30], we were able to prepare 118 in large amounts.

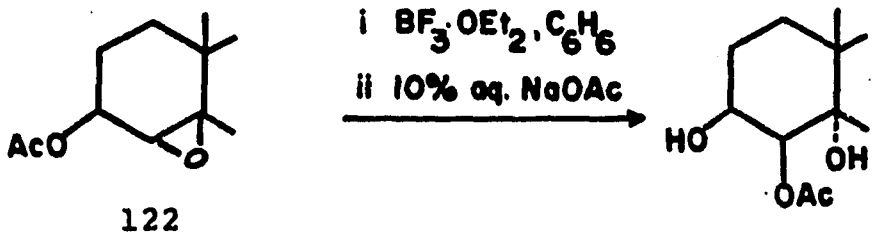


The allyl alcohol 118 was then epoxidized[31] in excellent (93%) yield, using MCPBA in methylene chloride, to give epoxy alcohol 119.

The next step was to open the epoxide to give the 1,3 - diol-acetate 120, the desired oxetane precursor.

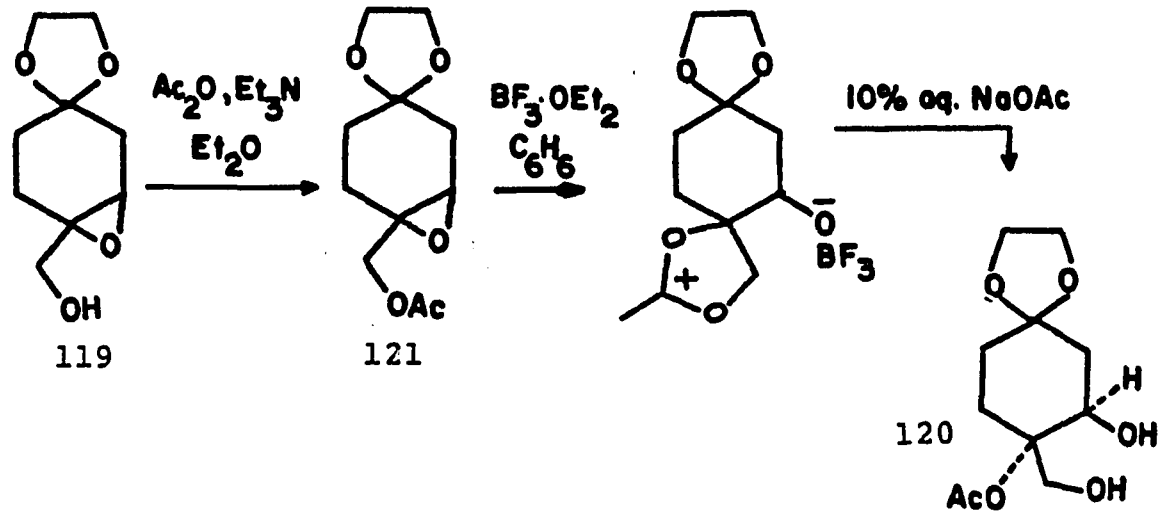


We expected acid catalysis would open the epoxide to give a tertiary carbonium ion which could be captured by acetate ion. This reaction was attempted with glacial acetic acid neat and in different solvents ($CHCl_3$, THF) at different temperatures. However no desired product could be isolated. Decomposition of the starting material and the formation of an aromatic compound were the results. Epoxide ring opening was finally achieved by using one equivalent of acetic acid and a catalytic amount of boron triflouride etherate in CH_2Cl_2 at $-10^{o}C$. After column chromatography the product could only be isolated in a low yield, (22%).



122

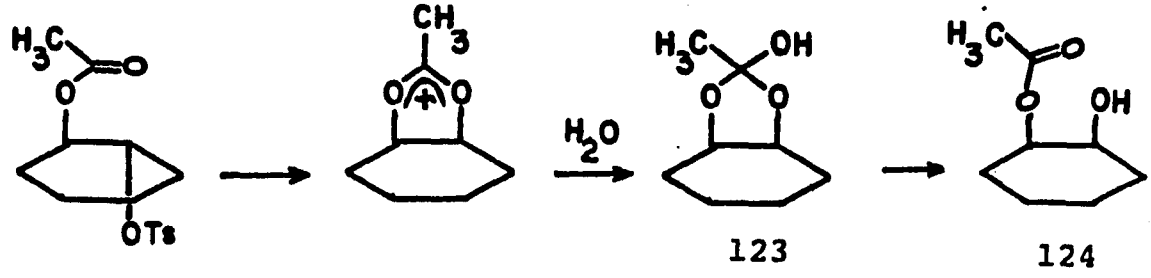
At this point we discovered the work of Coxon et.al.[32], who accomplished a similar rearrangement of epoxy acetate 122 with $BF_3.OEt_2$, via an acetoxonium ion formed by neighbouring group participation in the epoxide ring opening.



119 121 120

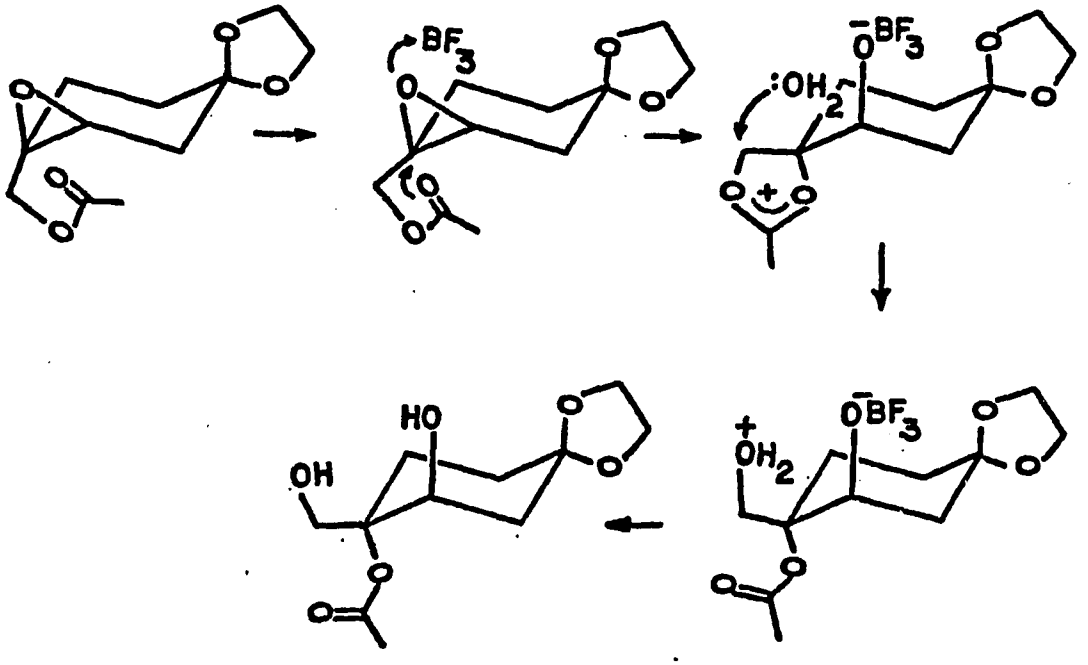
Primary alcohol 119 could be acetylated with acetic anhydride and triethylamine in quantitative yield. The acetate was then treated with one equivelant of $BF_3.OEt_2$ in dry benzene. A boron complex was formed as a pale yellow gelatinous precipate, which was hydrolyzed by adding a 10% aq. solution of NaOAc, giving the acetoxy diol 120 in 85% yield.

It is known that from the work of Winstein[33] that this type of reaction proceeds through an acetoxonium ion. In the case shown in the example, the nucleophilic water molecule attacks on C-3 to give the intermediate 123, which fragments to give the cis hydroxy-acetate 124.



123 124

The probable mechanism for the rearrangement would be:

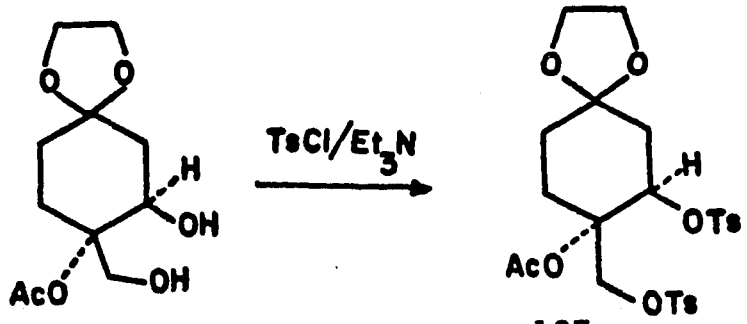


The next step was ring closure of the 1,3-diol. This was first attempted following a one-pot oxetane preparation method developed by Moulines[34], using a consecutive addition of one equivalant each of n-BuLi, TsCl and n-BuLi.

125 126

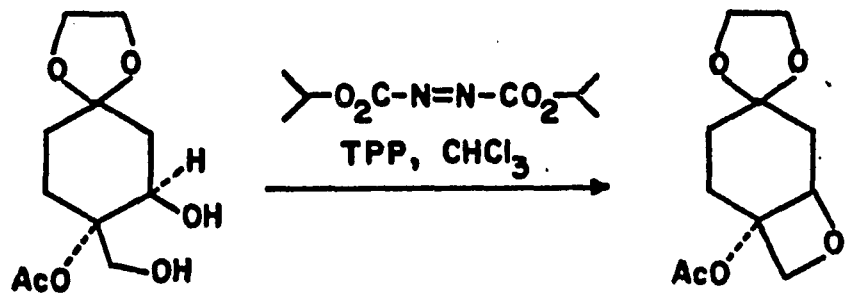
This method was found to be unsuccessful in our system. A mixture of aromatized compounds were found to

be the only products. The next choice was the stepwise tosylation[35] and base induced ring closure of 120.



127

Tosylation was attempted on 120 using one equivalent of TsCl in $CHCl_3$ and Et_3N as the base. The reaction was found to be very slow, and surprisingly the major product isolated after column chromatography was the ditosylate 127.

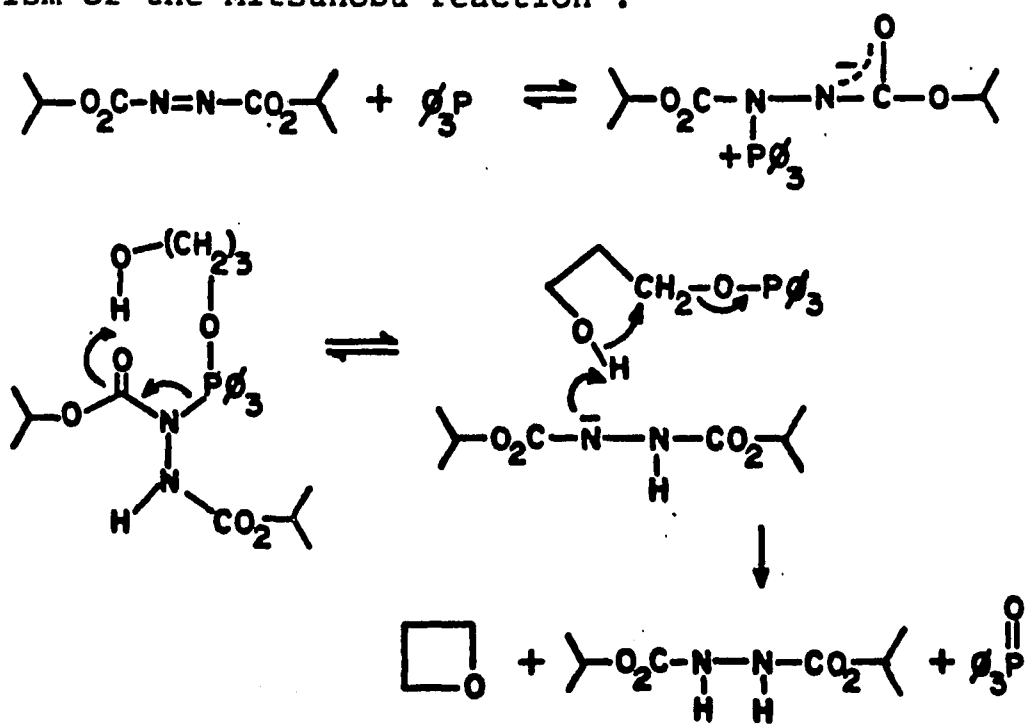


128

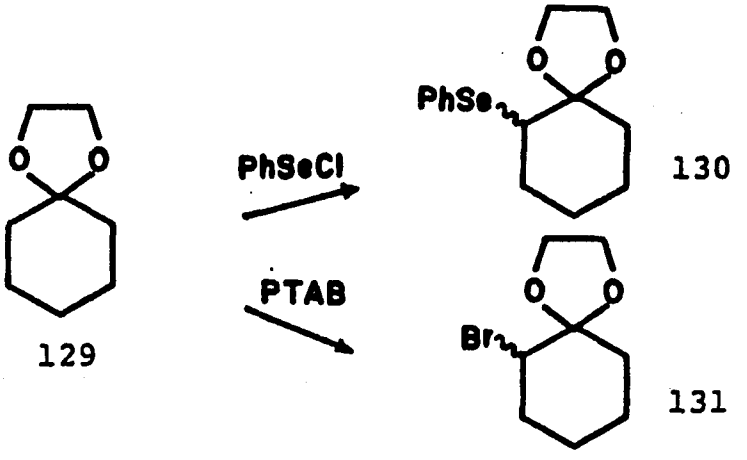
Oxetane 128 was finally formed using the Mitsunobu reaction[36], using triphenylphosphine and diethyl azodicarboxylate in dry $CHCl_3$. The product isolated exhibited the features of the oxetane ring in both the

proton NMR and IR spectra, but never could be purified sufficiently to afford a correct elemental analysis, even after repeated column chromatography, preparative plate TLC or Chromatotron separations. The product and the reaction by-product, dicarbethoxyhydrazine, have very similar chromatographic properties and the hydrazine always contaminated the oxetane. The solution to this difficulty was to replace the diethyl azo-dicarboxylate by diisopropyl azo-dicarboxylate. The reaction was repeated under similar conditions, and gave the pure oxetane 128 in 60% yield after simple flash chromatographic separation. This preparation gave a satisfactory C and H analysis.

Mechanism of the Mitsunobu reaction .



(2). The next challenge was to introduce the double bond to the ketal. Two approaches were tried for this.



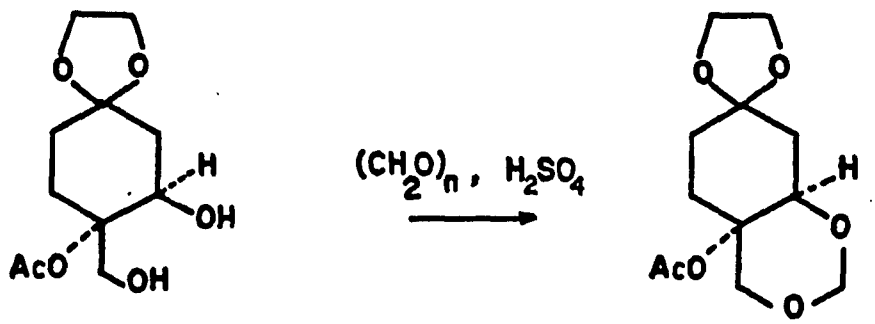
129 130 131

Nicolaou[37] has studied the phenyl selenation α to the ketals. Cyclohexane ketal has been monophenylselenated in 55% yield. Fuchs[38] in his studies on the synthesis of Bruciantin used phenyltrimethylammonium perbromide to brominate α to a cyclohexanone ketal.

We thought of using these ideas to introduce the unsaturation. First choice was bromination α to the ketal using phenyl trimethylammonium-perbromide (PTAB), followed by dehydrobromination.[37] The second approach was phenylselenation followed by H_2O_2 oxidation and deoxyselenation.[39] All the attempts to brominate or phenylselenate α to the ketal in the sensitive oxetane molecule were unsuccesful. Complicated mixtures were found as the reaction products, and the compounds isolated in these reactions showed a breakdown of the oxetane moiety of the molecule (loss of the oxetane CH_2 in the ^1H NMR).

Probably the HBr generated in the bromination reaction and the HCl generated in the selenation reaction destroyed the oxetane ring. After this disappointment we decided to postpone the construction of the oxetane function, and rather protect the 1,3-diol as a methylene dioxy acetal, which could be removed later, and close the ring of the labile oxetane at a later stage.

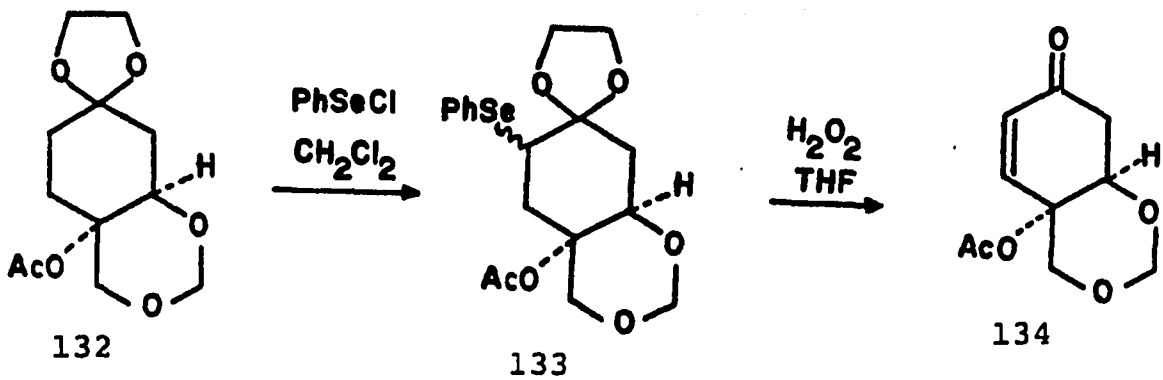
Acetoxy diol 120 was protected using para-formaldehyde and a catylatic amount of conc.H_2SO_4 in methylene chloride.[40] The methylene-dioxy compound 132 was isolated in 67% yield after column chromatography.



132

α- Bromination of 132 gave a complicated mixture. The ^1H NMR of the crude product showed some decomposition of the starting material. α-Phenylselenation of 132 gave more promising results, gave a mixture of three compounds, two major and one minor. The two major compounds were isolated by preparative TLC, following the UV active bands.^1H NMR showed that they were mono-selenated.

Deoxyselenation with hydrogen peroxide was attempted on the crude selenated mixture. A solution of 30% H_2O_2 was added to a cooled (0^oC) solution of the crude selenide 133 in THF and allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 and worked up by washing with aq.$NaHCO_3$.



132 133 134

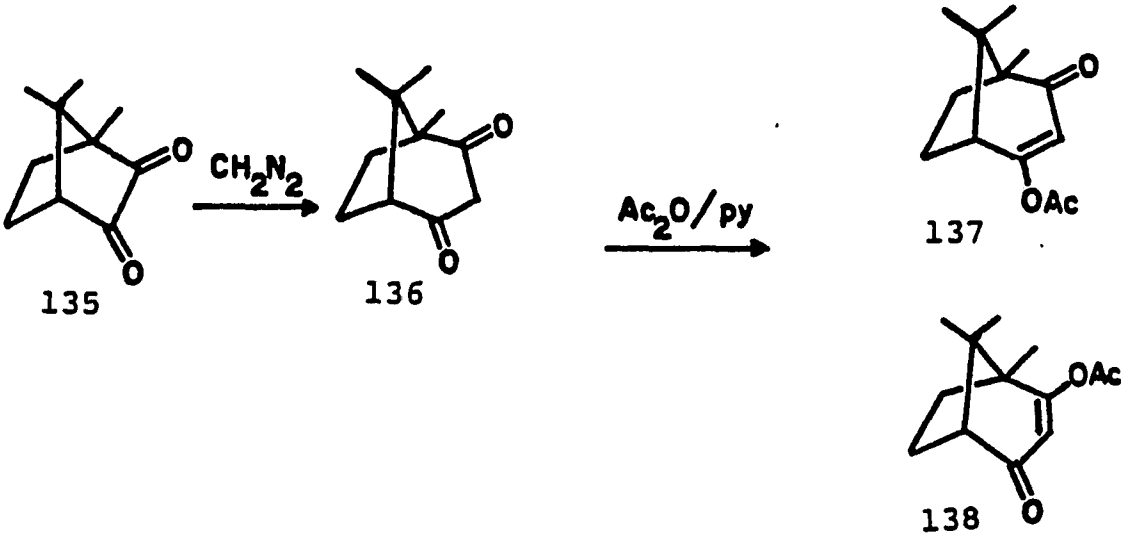
After flash chromatography, the major product of the reaction was isolated in 29% yield, and shown to be cyclohexenone 134 by ^1H, ^{13}C NMR and elemental analysis.

Attempts were made to improve the yield, to prevent the hydrolysis of the ketal, by incorporating a base into the deoxyselenation step. Triethylamine and solid Na_2CO_3 were tried together with hydrogen peroxide, but no improvement in the yield was observed. The unsaturated ketal was never isolated. We concluded that although it was probably formed, it is too unstable and

hydrolysed to the cyclohexenone under the aqueous reaction conditions.

Intermolecular Photocycloaddition Studies with Cyclohexenone 134.

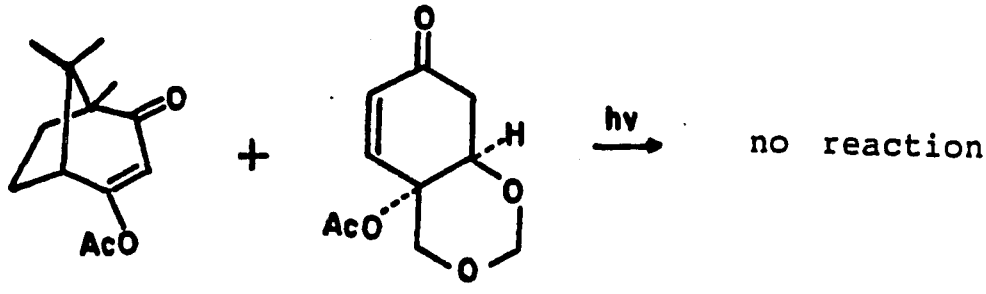
Even though we could not make the C/D -ring synthon as we planned, we thought of testing the intermoleculer photocycloaddition in the enone-enone addition form. The easily accessible A/B - ring model in hand was homocamphorquinone enol acetate 137, which was prepared from the known homocamphorquinone 136.[41]



135 136 137 138

Camphorquinone 135 , on ring expansion with diazomethane, gave homocamphorquinone 136. Acetylation with acetyl chloride and pyridine gave a mixture of enol acetates 137 and 138 in a 8:1 ratio. They were easily separated on the Chromatotron using a silica

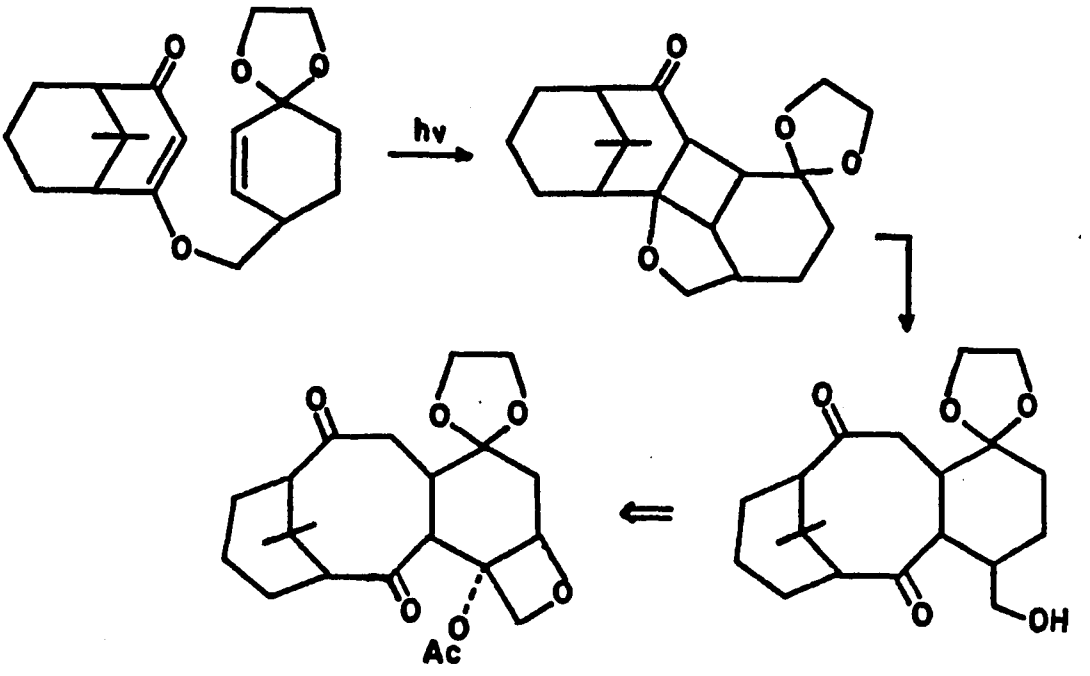
plate and eluting with hexane:EtOAc 4:1. The major enol acetate 137 was chosen for the reaction.



Enone-enone photocycloaddition was attempted by irradiation with 300nm UV light,in Pyrex tube, in a Rayonet apparatus, using as solvents cyclohexane, benzene or a cyclohexane/acetone mixture. One major problem was the insolubility of the cyclohexenone 134 in cyclohexane or benzene. Consequently we had to use very dilute solutions. The reaction was checked by HPLC during the irradiation, looking for the new peaks, but no reaction was observed even after 5 days.

At this point we thought of changing the strategy by postponing elaboration of the D-ring functionality until after the photocycloaddition step, as shown in the Scheme VIII.

Scheme VIII.



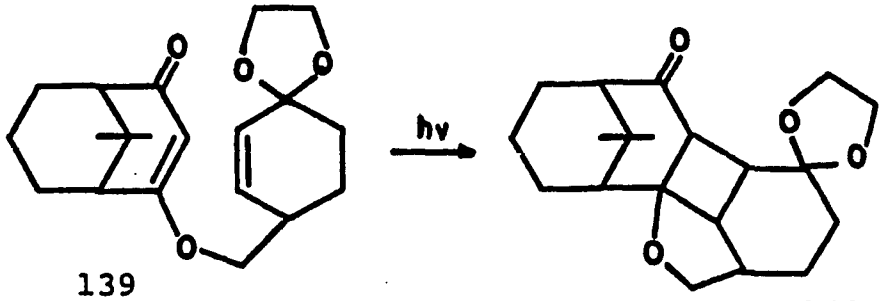
(2). Intramolecular Photocycloaddition Reaction Model Study

Intramolecular photocycloaddition should have several advantages over the intermolecular reaction.

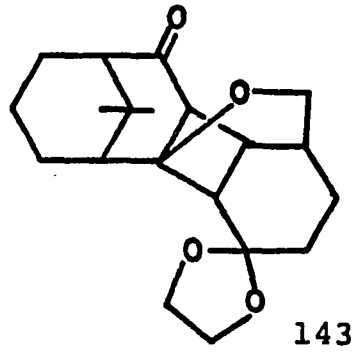
(a). Intermolecular enone-alkene [2+2] photo cycloadditions need a large alkene/enone ratio (examples are known using 30:1 alkene:enone ratio), whereas in the intramolecular reaction the ratio is 1:1.

(b). Intramolecular photocycloadditions can occur in two regiochemical modes, head to head or head to tail. According to the "Rule of five" of Sirinivasan[42] and Hammond[43] and later modified by Agosta,[44] when there is a choice between formation of a five or six membered ring as the bridge ring, the former is preferred. This should solve

the regiochemical problem in our system.

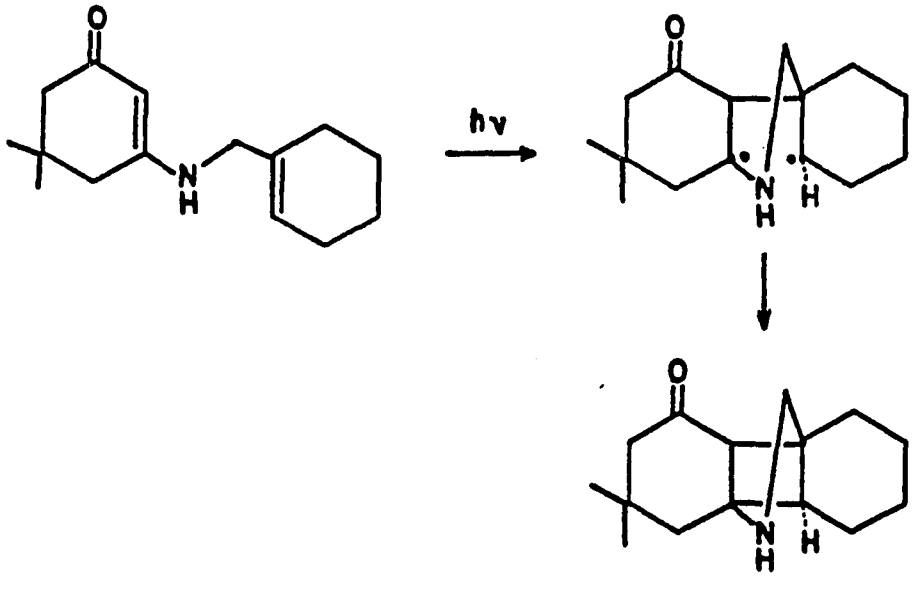


139 142

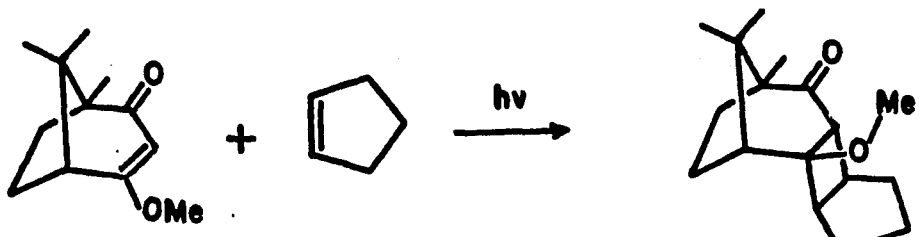


143

Recently a similar intramolecular photocycloaddition was reported in the case of vinylogous imides by Swindell[22].

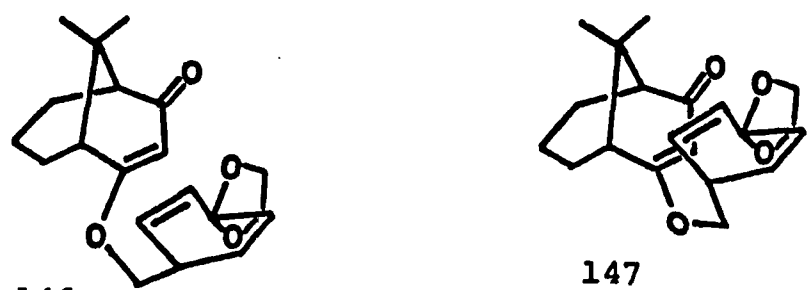


(c). J.Perumattam[27] has shown that in the intermolecular photocycloaddition of homocamphorquinone enol ether 144 and cyclopentene, the cyclopentene approaches from the endo side of the camphorquinone system, to give a cis-anti-cis adduct 145 as shown;



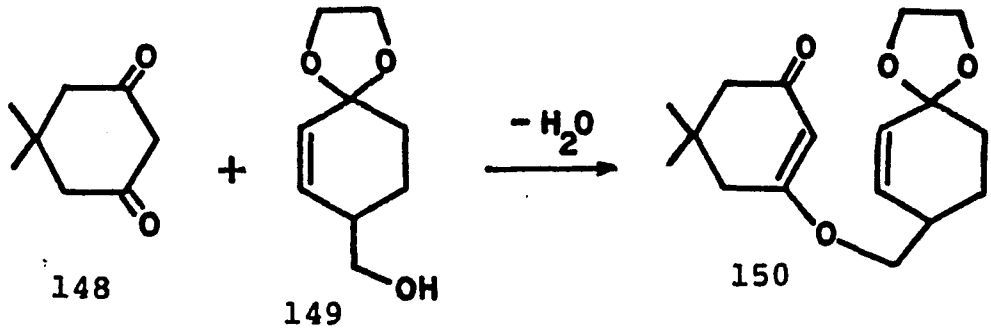
144 145

On the basis of this results we can expect a similar endo approach by the cyclohexene moiety in the intramolecular reaction.



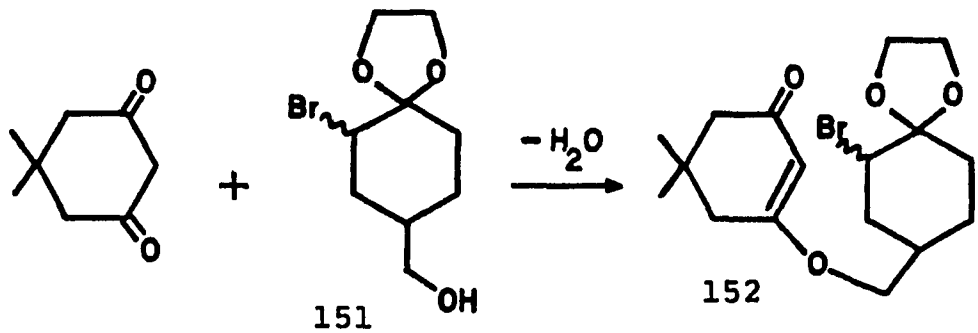
146 147

Before trying the reaction with the homocamphoquinone A/B-ring model synthon we thought of testing the reaction on a simpler system derived from dimedone.



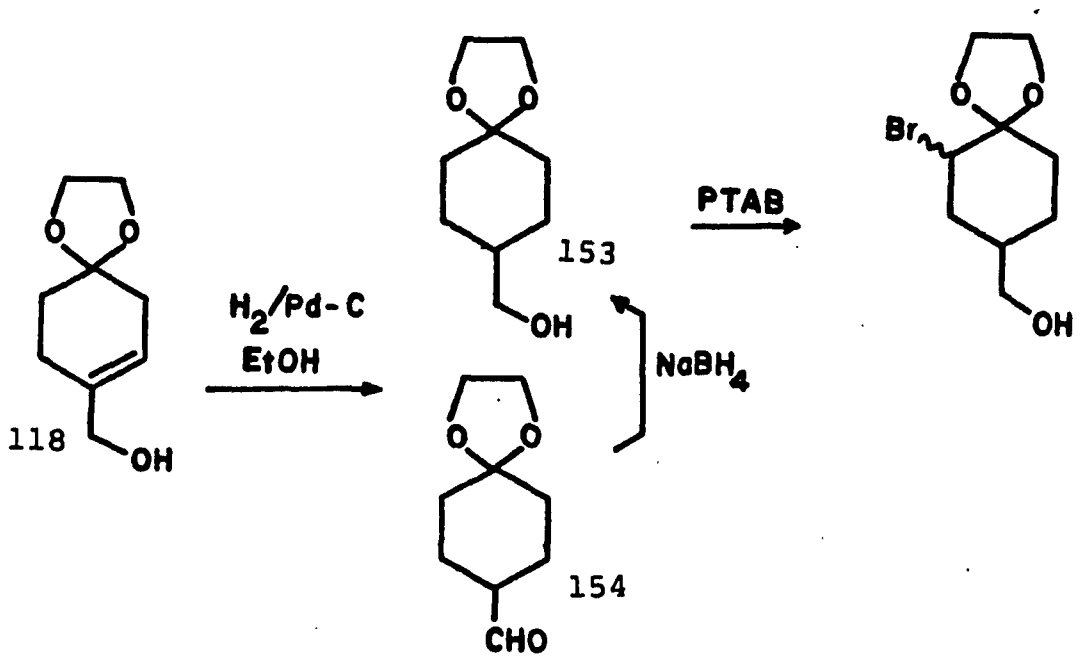
148 149 150

In theory dimedone 148 could be coupled with 149 using acid catalysed etherification, but having had some experience with cyclohexenone ketal compounds like 149 which are highly sensitive to acids, we thought it would be better to couple a precursor of 150 and generate the double bond later by dehydrobromination.



151 152

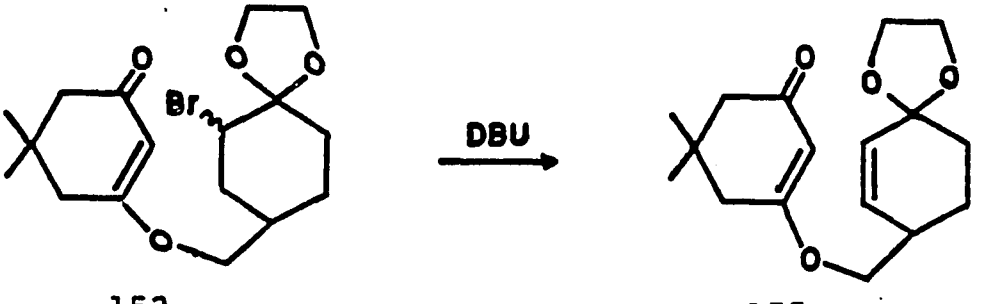
The next challenge was to prepare 151.



We started with the allyl alcohol 118 made previously. This compound was reduced catalytically in ethanol over 5% Pd-C at 30-40 psi of hydrogen, and at room temperature. Surprisingly this reaction gave two compounds (TLC and GLPC). Separation of a small sample by flash chromatography and spectroscopic analysis showed that it was a 3:2 mixture of the desired alcohol 153[60] and an aldehyde 154. The aldehyde 154 could be converted to the alcohol 153 by $NaBH_4$ reduction in methanol at room temperature, giving a quantitative yield of 153 from 154. In later preparations, the crude mixture obtained upon catylatic reduction was treated with $NaBH_4$/MeOH to give a single compound. Alcohol-ketal 153 was brominated α to the ketal using phenyltrimethylammonium perbromide (PTAB) in CH_2Cl_2, in 90% yield. This brominated compound 151 was

found to be a mixture of two compounds. The ^1H NMR of this mixture showed the characteristic features of α brominated ketals. The major compound of this mixture was isolated by flash chromatography and gave a correct elemental analysis. The crude product was assumed to be a mixture of epimeric brominated ketals, and was used directly for further reactions, as theoretically both epimers should dehydro-brominate, assuming a flexible cyclohexane ring.

The bromoketal mixture was coupled with dimedone by dehydration of an equimolar mixture of 148 and 151 in refluxing benzene, using p-toluenesulphonic acid as the catalyst in a Dean—Stark apparatus.

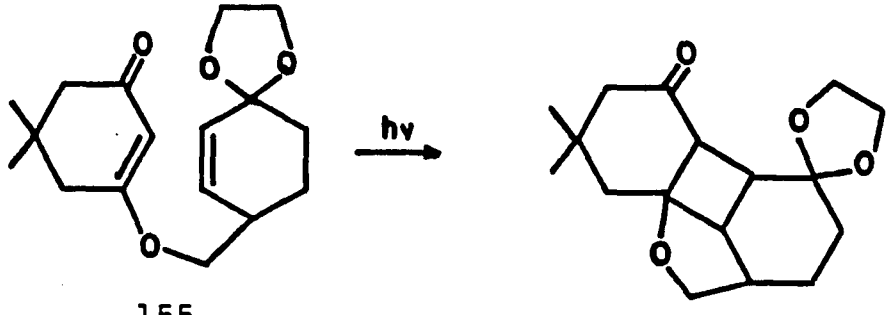


152 155

The crude enol ether 152 was dehydrobrominated without further purification by heating it neat with 1,8-diazabicyclo [5,4,0] undec-7-ene (DBU)[38] at 100-110°C. The

product was purified by passing through a short column of basic alumina.

Compound 155 was found to be unstable and had to be used for the photoreaction as soon as possible. Irradiation was performed in cyclohexane solution, in a Pyrex tube at 300nm in a Rayonet apparatus.

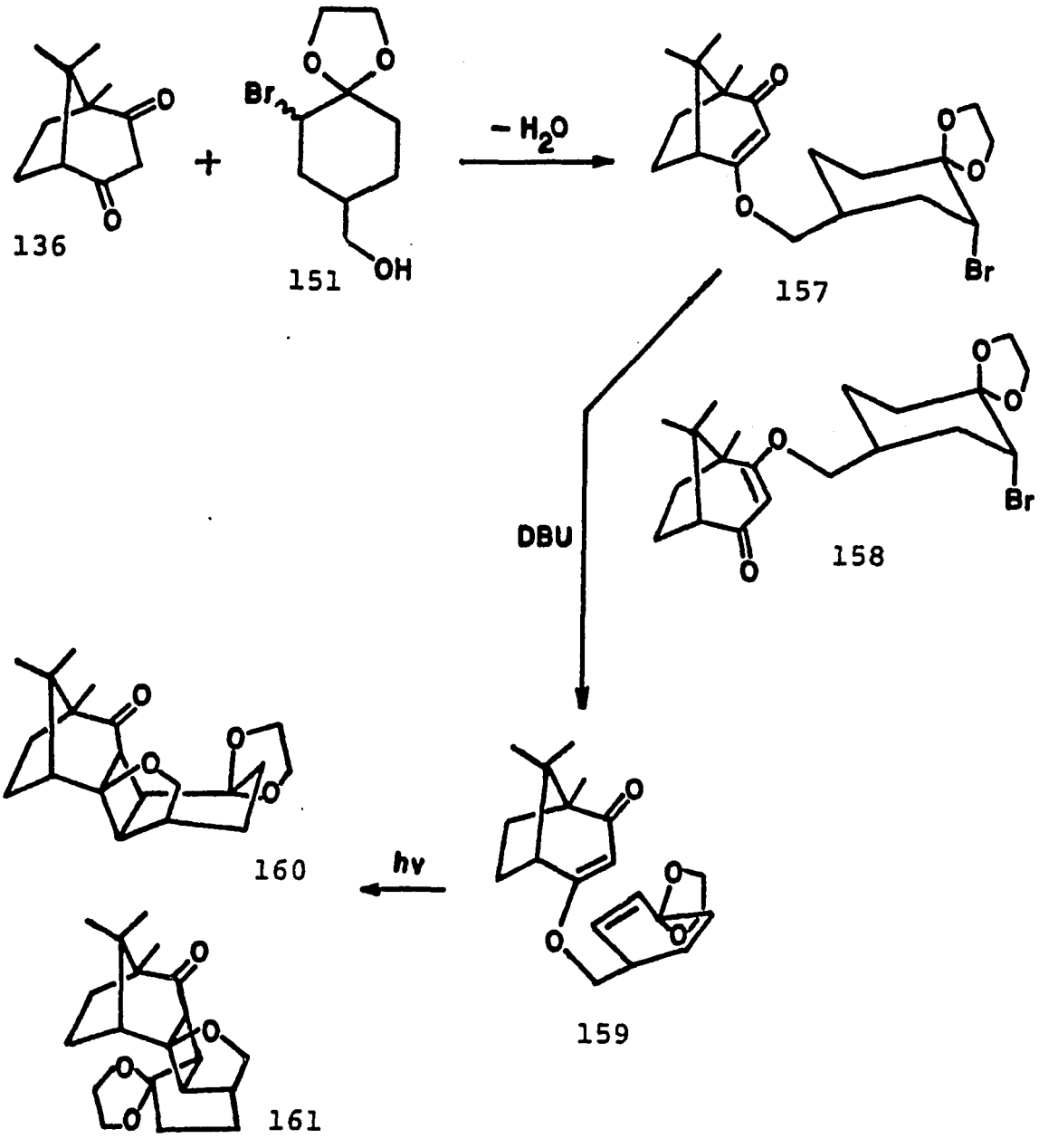


155 156

Photoadduct 156 was isolated as the only product in 58% yield after column chromatography and gave a reasonable IR, ^{1}H NMR and elemental analysis.

(3). Model Studies on the Taxane A/B/C-Ring System.

Having achieved success with the intramolecular photocycloaddition, we tried the reaction sequence on the more elaborate homocamphorquinone system.

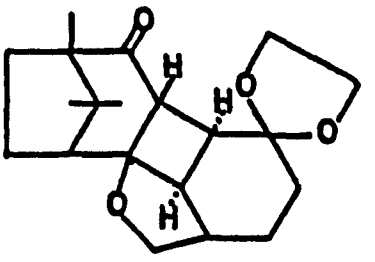


Bromoketal 151 was coupled with homocamphorquinone 136 using p-tolunesulphonic acid catalysis as before. Unlike dimedone, the asymmetric homocamphorquinone gave a mixture of two adducts, 157 and 158 in 19:1 ratio. This can be easily explained in terms of the steric effect of the angular methyl group. The same phenomenon was observed

in the acetylation of homocamphorquinone, which gave a mixture of 137 and 138 in a 8:1 ratio. The major compound 157 was easily separated by column chromatography, and dehydrobrominated with DBU as before to give the coupled alkene-enone 159. This was purified by passing through a short alumina column in chloroform solution, and immediately irradiated at 300nm in cyclohexane solution using a Pyrex tube in a Rayonet apparatus. The reaction was monitored by HPLC, which showed the formation of two new compounds. Evaporation of the solvents and column chromatography gave the two crystalline photoadducts 160 and 161 in 5:1 ratio, after recrystallization from ethyl acetate-hexane.

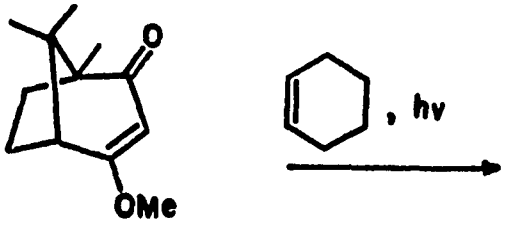
Structure Determination of the Photoadducts 160 and 161.

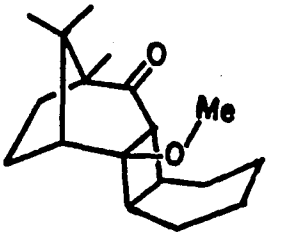
Photoreaction between the alkene and the enone moities makes two new bonds and generates four new chiral centers at C-3,4,9 and 10. Theoretically this reaction should give rise to 2^4=16 isomers. We made molecular models of all of these 16 isomers and we found that only two of the possibilities were reasonable structures. This is in agreemant with the experimental results.



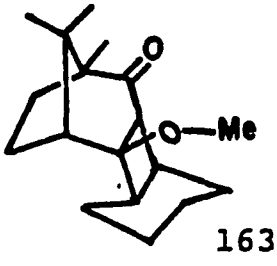
1,14,14, Trimethyl- 5,2'[1,3 dioxolane] 10-8 [oxymethyl-ene] tetracyclo [9,2,1,$0^{3,10}$, $0^{4,9}$] tetradeca 2-one.

The next problem was to tell which was which. This was possible by comparison of the ^{1}H NMR spectra of these two intramolecular photoadducts with the spectra of the two intermolecular isomers 162 and 163 obtained by J.Perumattam[27] in the photocycloaddition between homocamphorquinone methyl ether 144 and cyclohexene. The structures of these compounds have been confirmed by X-ray crystallography.





162



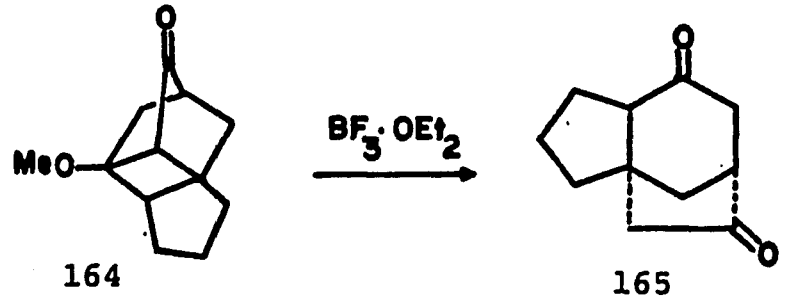
163

The C-3 proton is expected to be furthest down-field and appears as a triplet (J=9.0Hz) at 3.087 in photoadduct 160. A simillar triplet was found at 3.12 in the case of 162, so we concluded that 160 also has the cis-anti-cis stereochemistry. The other isomer has to be the epimer at C-4 and has a cis-anti-trans stereochemistry.

Ring Opening Studies of the Photoadducts

The next step was to open the cyclobutane ring of the photoadduct to give the eight membered B ring of the Taxane model.

(1). A few similar systems have appeared in the literature from the work of W. Oppolzer[45] shown here.

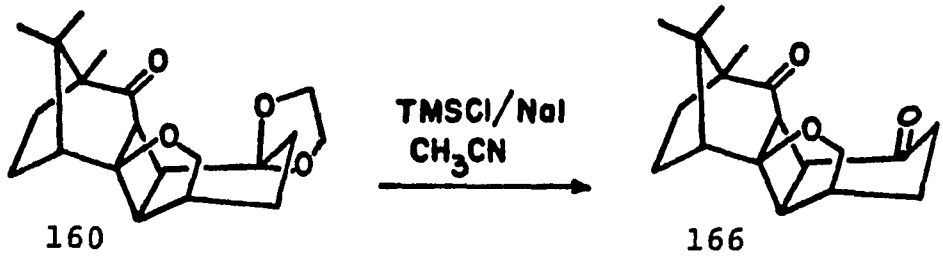


164 165

The first reaction tried was treatment of the major photoadduct 160 with borontriflouride etherate in dry benzene. However, Oppolzer's conditions proved to be

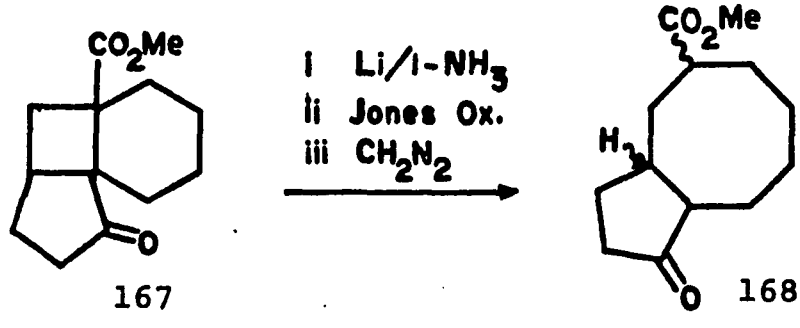
unsatisfactory, and no reaction was observed after 5 days at room temperature.

(2). Trimethylsilyl iodide (TMSCl, NaI, CH_3CN) is known[46] to cleave ethers, so we tried TMSI on photoadduct 160, but without success. TLC analysis of the reaction mixture showed a complicated mixture. The ^1H NMR spectrum of the crude mixture showed the loss of the ketal, but the cyclobutane ring protons remained unchanged. We assume that the major product was 166.



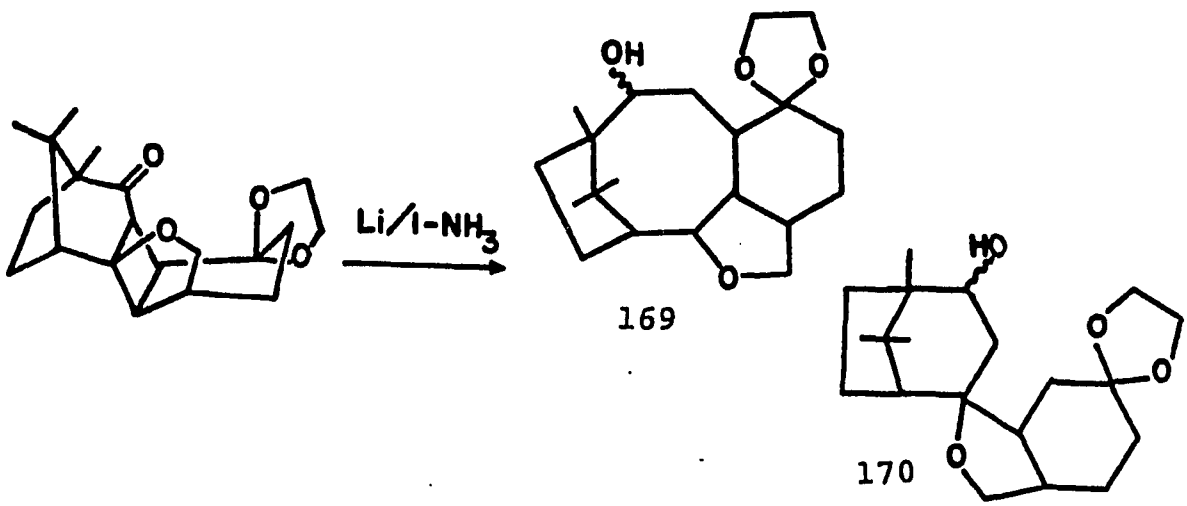
160 166

(3). Coates[47] has used Li-liq.NH_3 for reductive cleavage of the cyclobutane ring. An example is shown here.



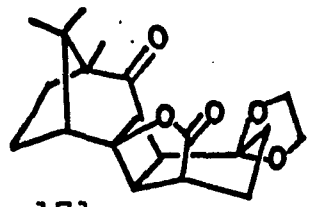
167 168

As the third attempt to construct the B-ring we treated 160 with Li-liq.NH_3 in EtOH. TLC analysis showed one major product, which was purified by column chromatography. ^1H NMR showed the breakdown of the cyclobutane ring, but the tetrahydrofuran methylene signals were still there. IR showed a hydroxyl absorption. We assume that the product was either 169 or 170.



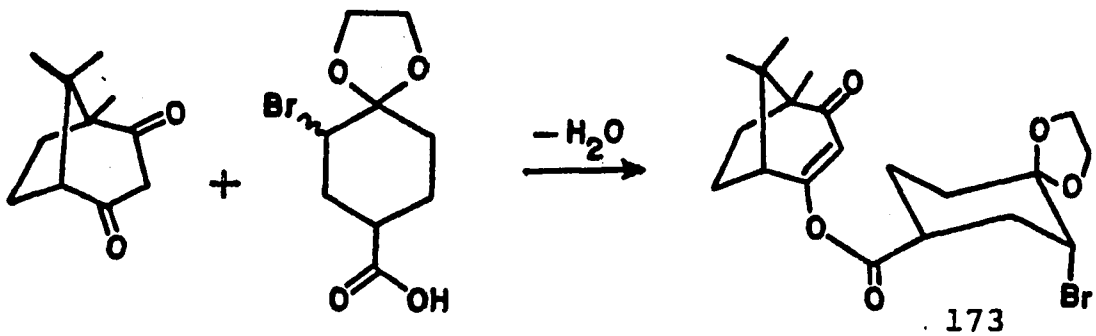
Dehydration of this compound was attempted with DBU/MsCl to prove the structure, however no reaction was observed even after 4 days in refluxing pyridine.

As we found, it is difficult to open the tetrahydro furan ring of the photoadduct to trigger the fragmentation. We thought of making a different photoadduct, such as 171, which has a buytrolactone instead of the tetrahydrofuran ring. Thus we should be able to open the ring by a base and induce the fragmentation.



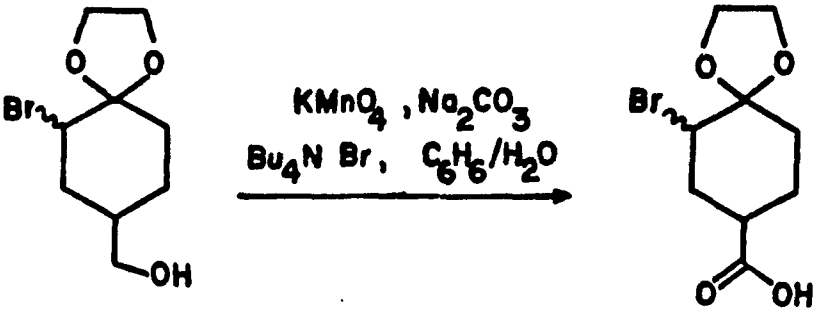
171

Following our previous results, we attempted to synthesis a precursor from bromoketal acid 172 and homocamphorquinone 136.



172 173

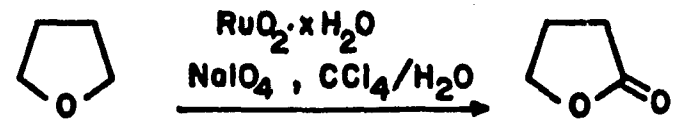
The acid was prepared without any problem by oxidizing the α bromoketal alcohol 151 with $KMnO_4/Na_2CO_3$ in a biphase system of benzene and water using tetrabutyl ammonium bromide as the phase transfer catalyst[48].



Mitsunobu reaction[49] using triphenylphosphine and diethyl azodicarboxylate was chosen as the coupling method. Normal workup gave a complicated reaction mixture. ^1H NMR spectrum of the crude product did not show any enol signals in the alkene region indicating the failure of the coupling process.

At this point Dr. S.Choudry of Hoffman La Roche (Nutley,N.J.) gave us a very useful suggestion. His idea was to use ruthenium tetroxide oxidation to convert the tetrahydrofuran ring of the photoadduct to a butyrolactone, which should give 171 directly from the photoadduct 160.

Rylander[50] first reported the use of RuO_4 for the oxidation of ethers to esters. Later this reaction was tested on various cyclic ethers by A.B.Smith III,[51] who found that the reaction is most suitable for the conversion of tetrahydrofurans to γ-butyrolactones.



174 175

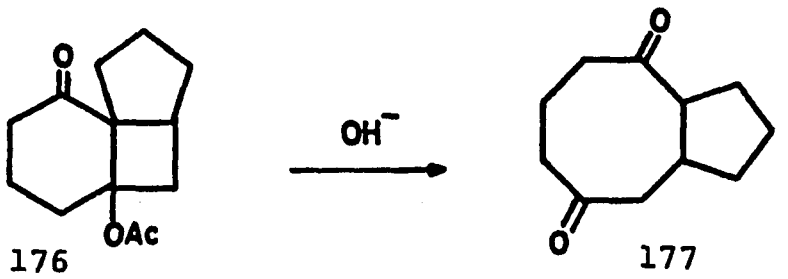
Smith's reaction could be carried out in two ways, either by first converting RuO_2 to RuO_4 using $NaIO_4$ and then using it for the oxidation in a monophase system of CCl_4 (this needs a one equivalant of RuO_2), or by using a catylatic amount of RuO_2 together with one equivalant of $NaIO_4$ in a CCl_4/H_2O biphase system. Recently, Sharpless[52] modified the reaction solvent system by incorporating CH_3CN as a co-solvent. He claimed that CH_3CN acts as a ligand and helps to regenerate RuO_4 faster.

Upon oxidation of photoadduct 160 using the Sharpless modification with $RuO_2.xH_2O$ as the catalyst and one equivalent of $NaIO_4$ in $CCl_4/CH_3CN/H_2O$, one major product was isolated after the flash chromatography. Recrystallization from ethyl acetate-hexane gave 171 in good yield, confirmed by ^1H NMR and elemental analysis.

Having obtained the lactone 171, the next step was to open the cyclobutane ring by base induced retro-aldol reaction.

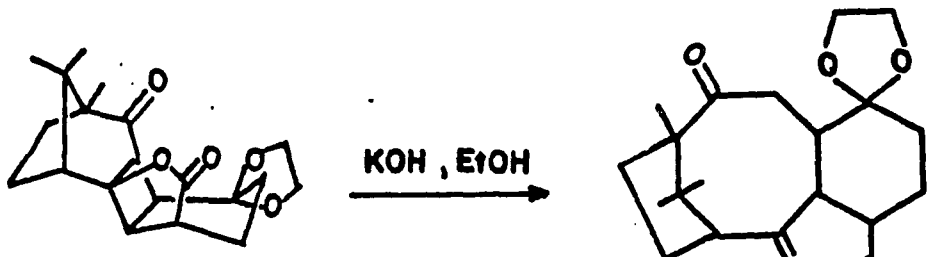
Pattenden[53] and Oppolzer[54] had studied the retro-aldol ring opening reaction on photoadducts such as 176,

that obtained in the intramolecular photo-reaction of 2 substituted - 1,3 cyclohexanedione enolacetate and which was opened by OH^- ions to give a cycloctane-1,5-dione 177.



176 177

We thought that we should be able to open the butyrolactone 171 by OH^-, generating a β-hydroxy ketone which should trigger the retro-aldol type opening of the cyclobutane ring.



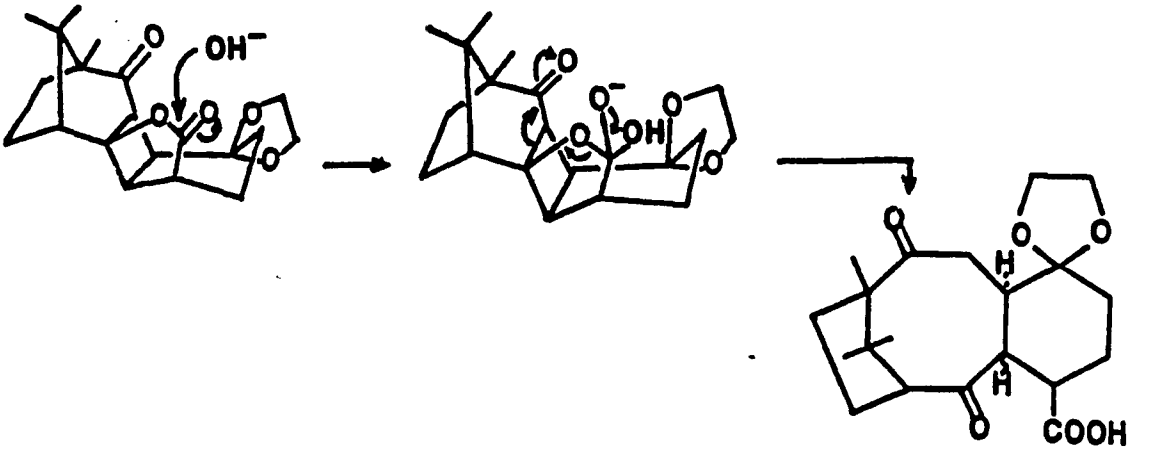
171 178

In fact, lactone 171 on treatment with KOH in refluxing abs. ethanol gave the desired diketo acid 178. This compound showed an acid proton in the NMR at 8.368. The ketal signal remained unchanged at 3.395-3.642, the C-1 proton appears as a triplet at 2.816 (J=10.5Hz), C-9

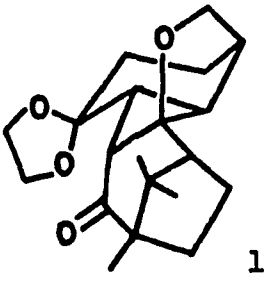
protons give rise to an AB quartet at 2.501 (J_1=6.0Hz, J_2=4.0Hz) . IR spectrum showed two carbonyl absorptions. We can assume that the C-8 proton remains in the configuration after the ring opening, but we are not sure about the configuration of the C-3 proton, as it is next to the C-2 carbonyl group, and there is a possibility of epimerization at C-3 under basic conditions. This C-3 proton appears as doublet of doublets at 3.610 (J_1=6.8Hz, J_2=2.2Hz) in the 200MHz NMR, probably due to the overlapping doublets arising from coupling with the C-4 and C-8 protons. We can assume that the carboxylic group remains in the β configuration. Unfortunately we feel that the NMR data we have is insufficent to reach any firm conclution about the C-3 stereochemistry. Recrstallization of 178 from ethyl acetate gave white needle crystals which afforded a correct elemental analysis.

In any case the stereochemistry of the C-4 carboxylic group does not matter in the long run as we are hoping to convert it to an allyl alcohol to build the oxetane ring.

Mechanisam of the retro-aldol opening.



The minor photoadduct 161 was also subjected to the RuO_4 oxidation, but surprisingly this isomer resisted the oxidation. No reaction was observed even after 5 days at room temperature. The only explanation we could think of is that trans fusion of the cyclohexane/cyclobutane rings at C-4 and C-9 forces the cyclohexane ring into a conformation such that a methylene group of the cyclohexane ring hinders the attack of RuO_4.

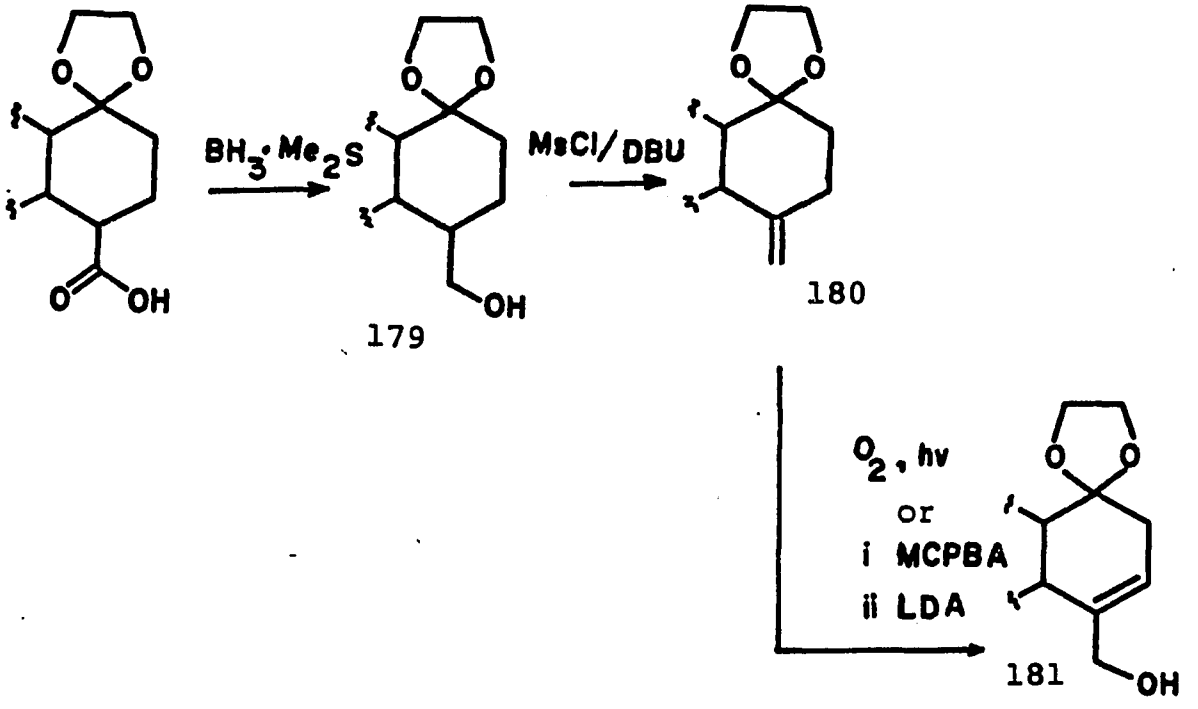


161

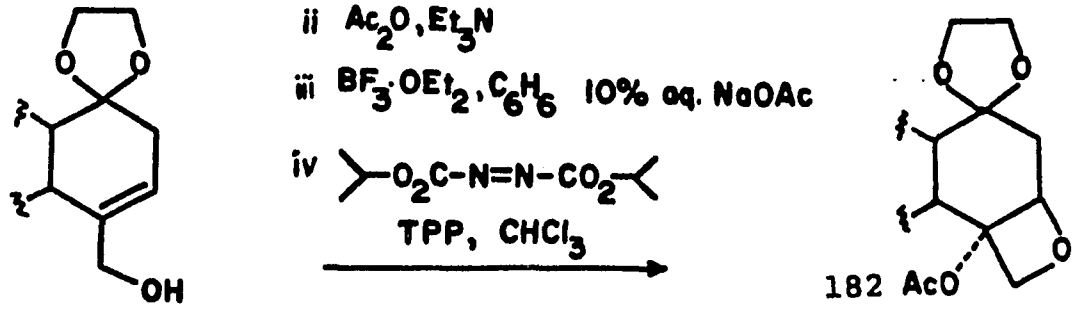
By examining a molecular model it can be shown that the C-6 methylene group blocks approach to the oxidizable methylene at C-15.

Proposed stretagy for construction of the D-ring.

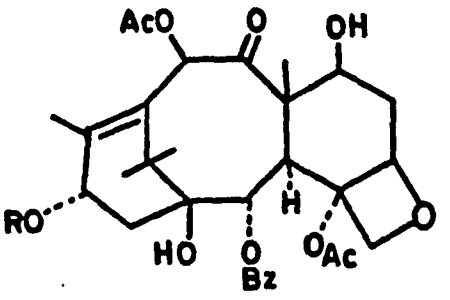
Our model compound 178 has a carboxyl group at C-3, which can be used as a cornerstone for construction of the oxetane D-ring and C-3 tertiary acetate functionality.



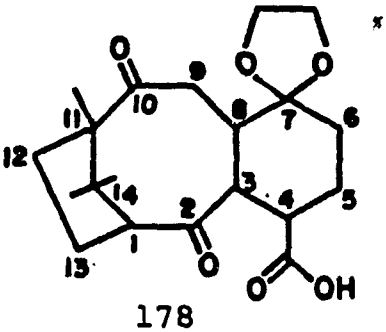
If we can convert it into the allyl alcohol 181, we can apply the sequence we have already developed to convert it to a tertiary acetate-oxetane moiety.



(4). Grob/Bamford-Stevens Fragmentation Studies.



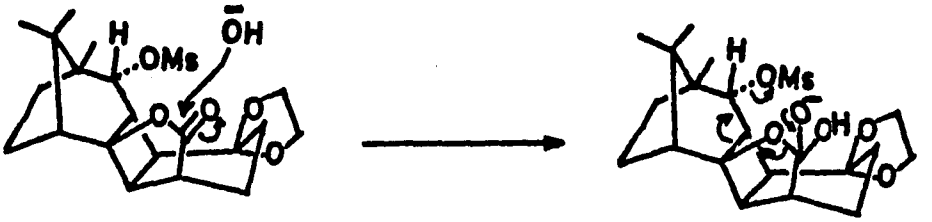
Taxol



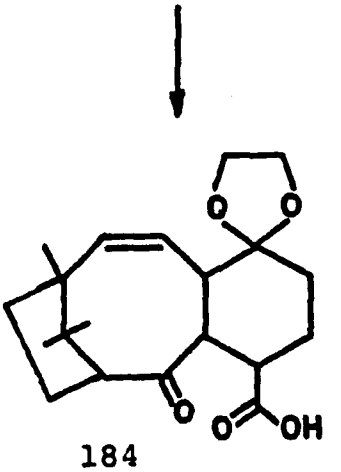
178

The Taxol molecule has a keto group at C-9 and an acetoxy group at C-10. A double bond at C-9,10 would be an appealing precursor to these oxygen funtions. One approach is the Grob fragmentation of the cyclobutane ring, rather than the retro-aldol reaction.

The mechanism would be:



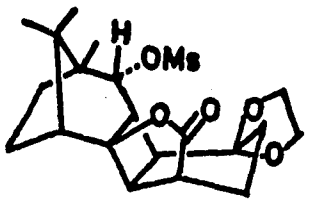
183



184

It would also be possible to introduce a C-9,10 double bond by reduction and dehydration starting with diketone 178, except we are not sure we can reduce the C-10 keto group selectively. In addition, dehydration could give a C-10,11 double bond.

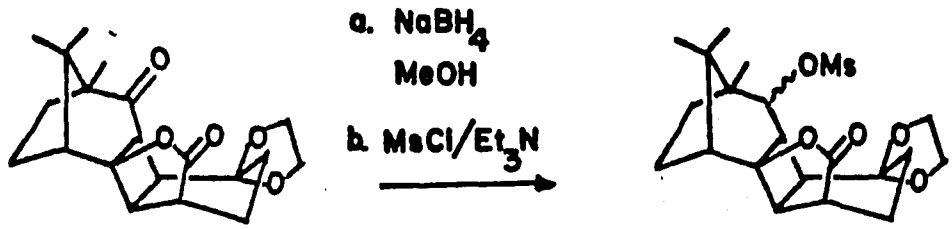
Grob fragmentation reactions have strict stereochemical requirements. In our molecule 183, the breaking C-3——C-10 bond and the leaving mesylate group should be trans and periplaner to each other.



183

The lactone 171 was reduced with sodium borohydride in methanol, giving a single compound (TLC), which was mesylated with MsCl/Et_3N. The mesylate was carefully studied spectroscopically. The C-2 proton under the mesyl group appears as a doublet (J=8.4Hz) and the C-3 proton appears as a doublet of doublets at 3.456 (J_1=8.8Hz, J_2=7.3Hz). The 8.4 Hz coupling constant between the C-2 and C-3 protons is not conclusive enough to decide the correct stereochemistry of the C-2 hydrogen, as an exo or

an endo C-2 hydrogen make similar dihedral angle with the C-3 hydrogen.



Mesylate 185 was subjected to Grob fragmentation by treatment with KOH in refluxing ethanol, but unfortunately the product isolated did not show any alkene signals in the proton NMR. The mesyl group was lost however, and probably was replaced by a hydroxyl group.

185 186

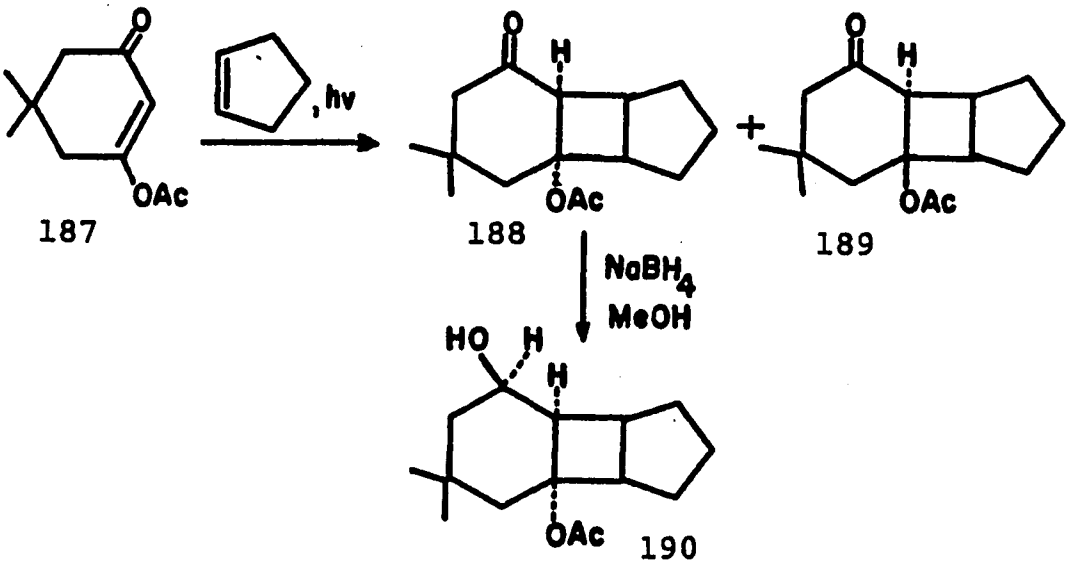
There can be two explanations for the failure of the Grob fragmentation.

(I). Attack of the nucleophilic hydroxyl group at C-2 is

preferred over hydrolysis of the lactone carbonyl. (II). The hydroxyl group attacked the carbonyl of the lactone, but the mesylate was in the wrong stereochemistry for fragmentation. Ultimately the mesylate was lost by displacement by hydroxide.

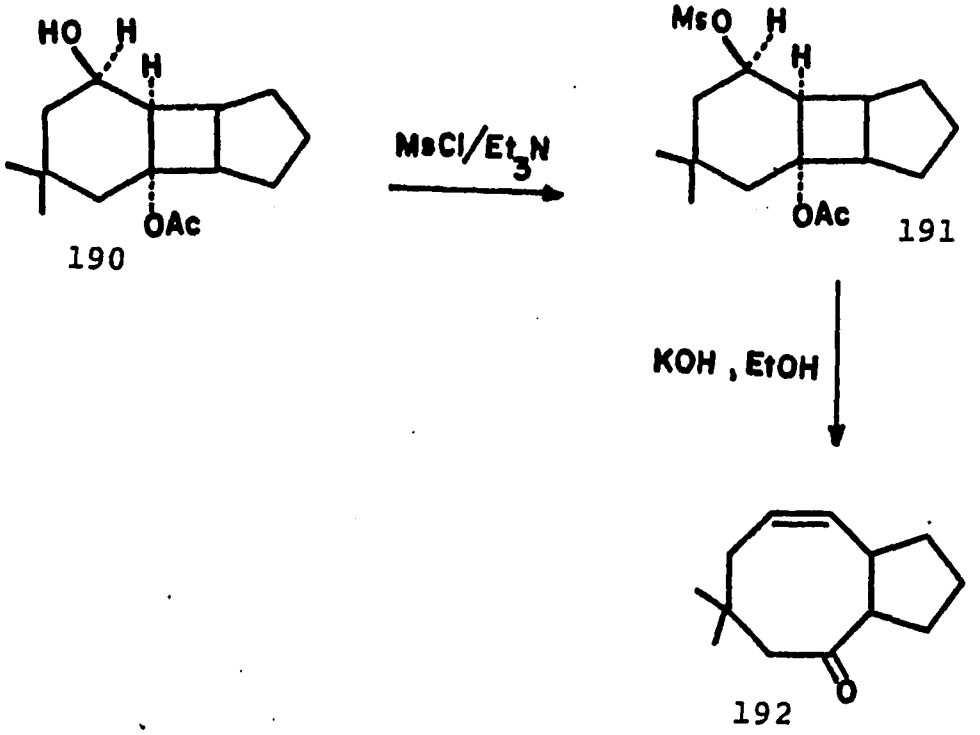
This invited a study of the Grob fragmentation process in a system where the sterochemistry of the leaving group was known without doubt.

After a thorough literature survey we learned that Ikebe and Hishida[55] made alcohol 190.



Dimedone enol acetate 187 was prepared by acetylating dimedone with Ac_2O/Et_3N, then irradiated using cyclopentene as the solvent. Removel of the excess cyclopentene and repeated fractional crystallization from ether gave 188, which was reduced with $NaBH_4$ in methanol

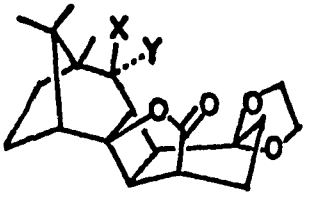
to give the alcohol 190. This alcohol was mesylated using MsCl/ Et_3N to give 191.



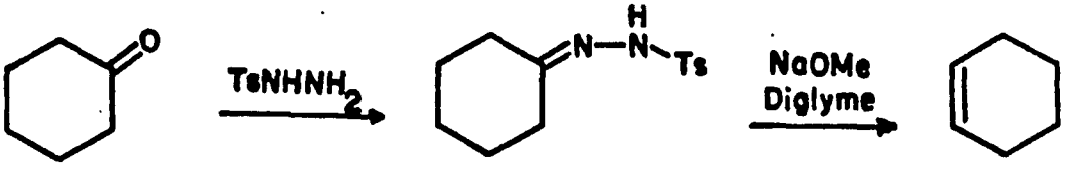
190 191 192

Mesylate 191 was treated with KOH in refluxing abs. EtOH. A single product was formed, ^1H NMR and IR showed it to be 192. This indicates that the sterochemistry of the leaving group is the important factor in determining the succes of the Grob fragmentation. Presumably the epimer of mesylate 191 would give the Grob fragmentation product we desire, but we did not pursue the necessary reduction studies.

On the other hand, if we could induce the fragmentation while C-2 is sp^2 hybridized, stereochemistry would be no problem as in the retro-aldol reaction.

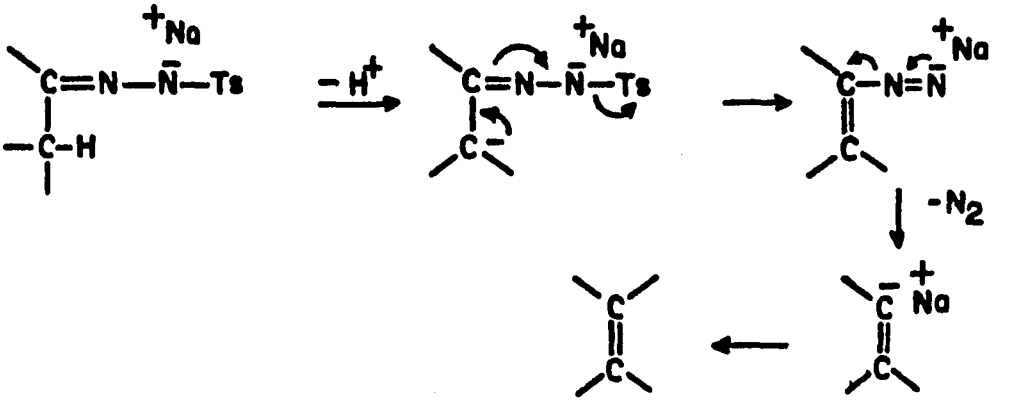


One reaction that might be used here is the Bamford-Stevens reaction[56,57], a general method to convert a carbonyl to an alkene. For example:

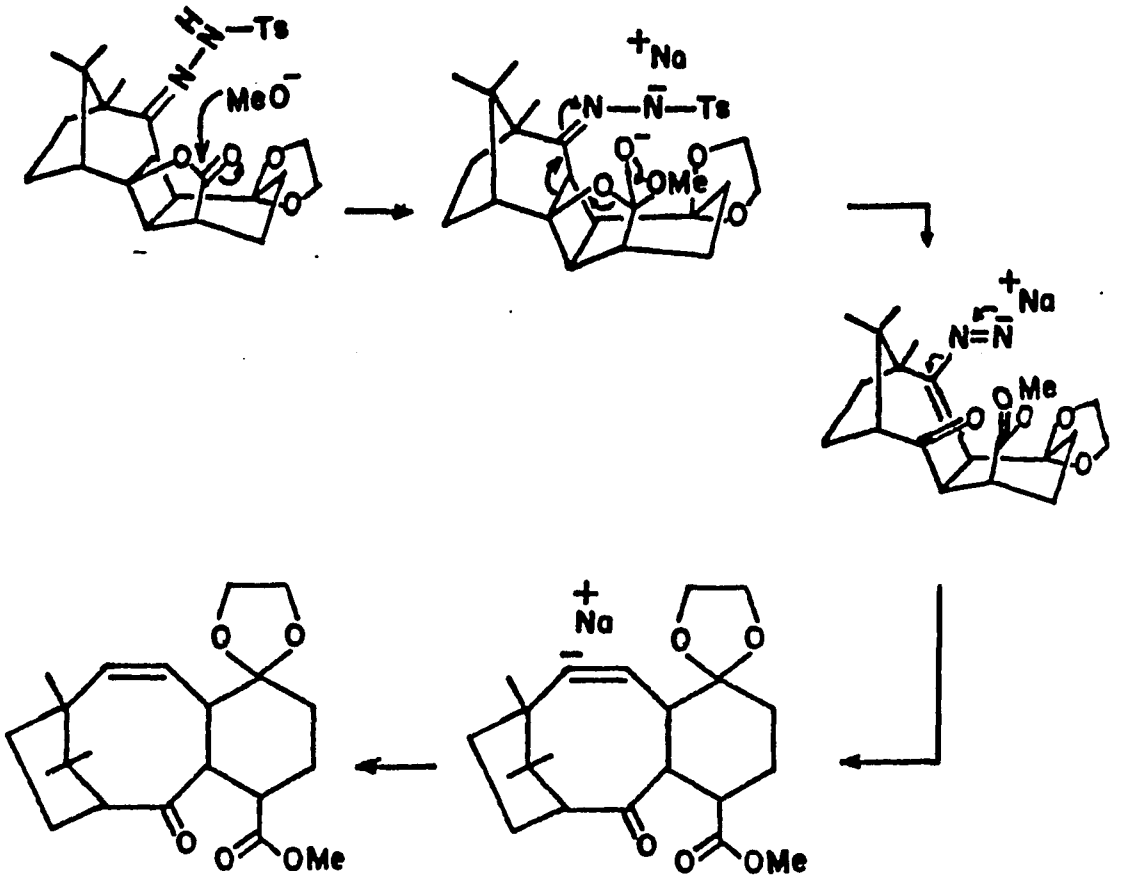


193 194 195

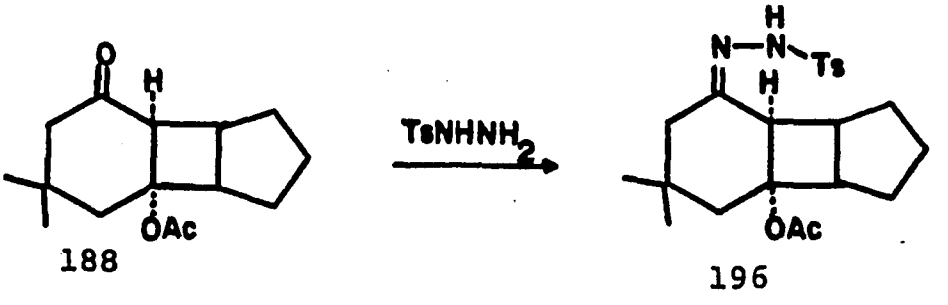
The mechanism [58] is,



Application to our model keto-lactone is shown below:

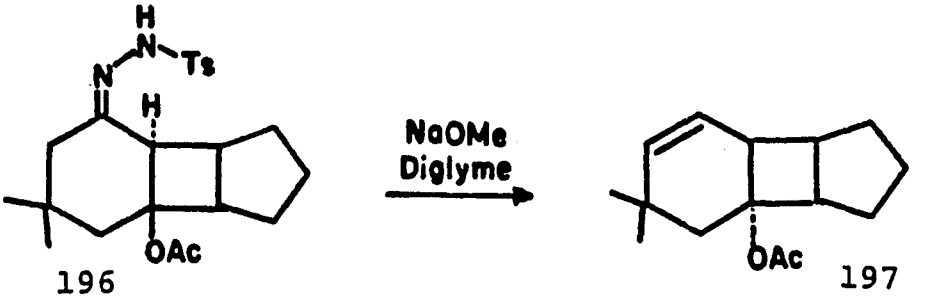


Before trying this new reaction on the lactone 171, we thought it a better idea to try using a simpler system, such as the dimedone-enolacetate/cyclopentene adduct 188.



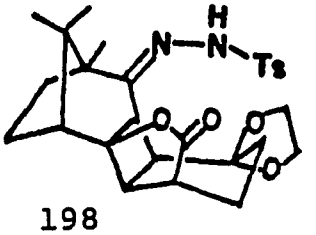
188 196

Tosyl hydrazone 196 was prepared from the photoadduct 188, by treating with tosylhydrazine in abs.ethanol, using powdered molecular sieves as the dehydrating agent. The tosyl hydrazone was then treated with sodium methoxide in refluxing diglyme.



196 197

Aqueous workup gave a single product, which was identified as 197 from ^{1}H NMR and IR. The compound 196 underwent a simple Bamford-Stevens reaction, rather than the fragmentation we wanted.



198

On the other hand, in the Taxane model system 198, there is no hydrogen at C-1 and hydrogen at C-3 is less likely to be eliminated, due to the fact that it would give an exocyclic double bond to a cyclobutane ring.

Next we prepared the tosyl hydrazone 198 by treating the lactone 171 with p-toluenesulfonyl hydrazene in abs. EtOH and using the molecular sieves as the dehydrating agent as before. Then the tosylhydrazone 198 was treated with sodium methoxide in refluxing diglyme, but unfortunately the product isolated after column chromatography did not show any alkene signals in the 200MHz proton NMR, but showed the loss of the tosyl group. Finally we could not identify the product formed in the reaction.

Chapter.III EXPERIMENTAL

Melting points were determined in open capillaries using a Thomas-Hoover Unimelt apparatus and are uncorrected. Routine proton spectra were recorded at 60MHz on a Varien EM360 instrument with TMS as an internl standad. The high field proton NMR spectrums were obtained on a Bruker-IBM WP200SY spectrometer operating at 200.132MHz, using an internal deuterium lock. ^{1}H NMR data is reported in parts per million downfield from TMS (with multiplicity s=singlet, d=doublet,t=triplet, ABq=ABquartet, br=broad and m=multiplet). Infrared spectra were recorded on a Perkin-Elmer IR598 spectrometer, which was calibrated against polystyrene. Absorptions are reported in reciprocal centimeters with intensity in parentheses (s=strong, m=moderate, w=weak, br=broad). Carbon 13 NMR spectra were recorded in a Bruker-IBM WP200SY operating at 50.327MHz, in deuteriochloroform using a deuterium lock, and are reported in ppm down field from TMS.

Silica gel thin layer chromatography was performed using Macherey-Nagel Polygram Sil N-HR/UV254 plates. These were developed in the described solvents, and vizualized by spraying with 10% sulfuric acid in methanol and heating on a hot plate. Preparative thin layer chromatography performed on 20X20cm glass plates coated with silica, (Art

7749,Kieselgel 60PF254,E.Merk) or on a Chromatotron apparatus (Harrison Research, Palo Alto) using silica (Art 7747, Kieselgel 60PF254, E.Merk) plates. Column chromatography separations were carried out in glass columns packed with silica (230-400 mesh, ASTM, E.Merk), under positive air pressure as in the flash chromatographic technique described by Clark Still[59]. Analytical high pressure chromatographic analyses were done using a Waters Associates (Milford, Mass) system consisting of two 4mmX30cm microporasil silica columns in series, a 6000SDS pump, U6K injector and model 401 differential refractometer. Analyses were carried out at a flow rate of 2mL/min using 4:1 hexane:ethylacetate. Gas liquid chromatographic analysis were performed on a Varian - Aerograph 920, thermal conductivity instrument using a column packed with 20% Apiezon-L on Chromasorb W. Photo reactions were carried out in Pyrex tubes using a Rayonet apparatus with 300nm UV lamps. Methylene chloride and chloroform were distilled from phosphorous pentoxide and stored over molecular sieves. Benzene distilled from sodium and spectroscopic grade cyclohexane distilled over calcium hydride were used for the photoreactions. Triethylamine, acetic anhydride, borontriflouride etherate and cyclopentene were distilled before use. Diglyme was distilled over CaH_2 prior to use.

In the workups the solutions were dried over anhydrous Na_2SO_4 and concentrated in a Buchi rotavapor. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennesse.

1-Methoxy,4-(hydroxymethylene),cyclohexa-1,4-diene 117.

4-Methoxy benzyl alcohol 116 (55.0g, 0.400 mmol) was dissolved in THF (150mL),EtOH (500mL) and liquid ammonia (750mL) To this mixture was added sodium (40.0g,1.75 mol) in small portions during a period of 1.0hr, followed rapidly by ammonium chloride (75g, 1.40 mol). The reaction mixture was left overnight for evaporation of ammonia, and the residual solvents were removed under reduced pressure. The residue was dissolved in methylene chloride (1.0L), and the organic layer was washed with water (2X400mL), dried and evaporated to give the crude product. Vacuum distillation afforded 45.2g (81% yield) of 117. (110°C/0.1mmHg). Lit. 120°C/0.1mmHg. This product is shown to be pure by GLPC analyses.

IR (CCl_4) 3600br, 2808m, 1690m, 1658w, 1380s cm^{-1}

^1H NMR (60MHz, $CDCl_3$) δ 5.53(brs,C-5,1H), 4.55(brs,C-2,1H), 4.25(t,J=5.0Hz,D_2O exchangeable,OH,1H), 3.90(t, J=5.0Hz, CH_2-OH,2H), 3.50(s,OMe,3H), 2.69(s,C-3 and C-6,4H).

Spiro [4-hydroxymethylene, 3-cyclohexene, 1,2' [1,3] dioxolane] 118.

To a mixture of enol ether 117 (22.5g,0.160mol) and ethylene glycol (35mL, 0.40mol) in THF (100mL), cooled in an ice bath, was added borontriflouride etherate (3.50mL,0.0280mol) under nitrogen. After stirring for 20min at 0°C, the mixture was poured into cold aqueous saturated $NaHCO_3$ (100mL) and extracted with methylene chloride (3X150mL). The combined organic extracts were washed with water (100mL), dried and concentrated to give the crude product. Vacuum distillation afforded 22.8g(83% yield) of ketal 118 (115°C/0.2mmHg) as a thick oil. Lit. 105°C/0.15mmHg. GLPC showed only one component.
IR (CCl_4) 2920br, 2860m, 1115m, 1058s cm^{-1}
^1H NMR (60MHz, $CDCl_3$) 5.54(brs,C-7,1H), 3.97(s,ketal and CH_2-OH,6H), 2.55(s,D_2O exchangeable, OH,1H), 1.60=2.30(m, remaining 6H).

Spiro [2',4 [1,3] dioxolane,1-hydroxymethylene, [7] oxa bicyclo [4,1,0] heptane] 119.

Ketal alcohol 118 (22.3g, 0.113mol) was dissolved in methylene chloride (100mL) and cooled to 0°C. To this a solution of 85% MCPBA (29.3g 0.123mol) in methylene chloride (250mL) was added during a period of 20min, folloewd by stirring for one hour. A solution of 10%

aqueous NaOH (100mL) was then added and the mixture was extracted with methylene chloride (3X150mL). The combined organic layers were washed with water (100mL), dried and evaporated to give the epoxide 119 as a colorless oil 22.7g, (93% yield).

IR ($CHCl_3$) 2240m, 2038w, 1440m, 1360w cm^{-1}.

^1H NMR (60MHz, $CDCl_3$) δ 3.85(s,ketal,4H), 3.49(s,CH_2-O-,2H), 3.07(t,J=3.0Hz,C-6,1H), 2.78(brs,D_2O exchangeable, OH,1H), 1.95 (d,J=3.0Hz,C-5,2H), 1.25-1.85(m,C-2 and C-3,4H).

Anal.Calcd.for.	$C_9H_{14}O_4$	C 58.05%	H 7.58%
	Found	C 57.98%	H 7.60%

Spiro [2',4 [1,3]dioxolane,1-acetoxymethylene, [7] oxa bicyclo [4,1,0] heptane] 121.

Epoxyalcohol 119 (20.00g, 0.1070mol) was dissolved in ether (300mL) and to this triethylamine (12.06g,0.1170mol) and acetic anhydried (12.00g, 0.117mol) were added. The mixture was stirred at room temperature for 4 days, then poured into 300mL of water and separated. The water layer was extracted with ether (4X200mL) and the combined ether layers were dried and concentrated under reduced pressure to give 24.40g of 121 (100% yield). GLPC showed only one compound.

IR (CCl_4) 2942br, 2880m, 1742s, 1427m, 1364s, 1228br,

1123s, 1068s, 1037s cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) δ 4.10(q,J=11.0Hz,CH_2-OAc,2H), 3.92 (s,ketal,4H), 3.15(t,J=3.0Hz,C-6,1H), 2.10(s,OAc,3H), 1.15-2.00(m,remaining,6H).

^{13}C NMR ($CDCl_3$) δ 169.9, 106.2, 66.5, 64.1, 63.7, 57.2, 55.0, 34.2, 27.3, 22.7, 20.2

Anal.Calcd.for $C_{11}H_{16}O_5$ C 57.88%, H 7.06%.

Found C 57.79%, H 6.99%.

Spiro [2',4 [1,3]dioxolane,1-acetoxymethylene, cis(3-hydroxy, 4-hydroxymethylene) cyclohexane] 120.

Method A:

Epoxy alcohol 119 (230mg, 1.24mmol) was dissolved in 2.00mL of methylene chloride and cooled to -10°C in an ice/salt bath. To this borontriflouride etherate (10 μL) and glacial acetic acid (74mg, 1.236mmol) were added and the solution was stirred under nitrogen for 1.0hr. The mixture was washed with water (5mL), dried and evaporated. The residue was flash chromatographed on silica, eluting with 5% methanol in chloroform and giving 70mg of 120 (22% yield) as a thick oil.

IR ($CHCl_3$) 2950br, 2880m, 1720s, 1235br, 1095s cm^{-1}

^1H NMR (60MHz,$CDCl_3$) δ 4.20(bs,CH_2-O,1H), 3.98(s, ketal,4H), 3.80 (bs,CH_2-O,1H), 3.48(s,D_2O exchangeable,2 OH,2H), 1.20-2.40(m,remaining,7H).

Anal.Clcd.for	$C_{11}H_{18}O_6$	C 53.65%	H 7.37%
	Found	C 54.02%	H 7.39%

Method B:

Epoxy acetate 121 (21.83g,0.09600mol) was suspended in 300mL of dry benzene and to this borontriflouride etherate (11.80g, 0.105mol) was added. A white gelatinous precipitate was formed instantaneously. The mixture was shaken for 2min at room temperature, and to it was added a solution of 10% aq. sodium acetate (250mL) all at once, The mixture was shaken briefly and the layers were separated. The aqueous layer was extracted with ethyl acetate (4X150mL) and the combined organic layers were washed with 250mL of water, dried, and then concentrated to give 20.00g of 120 (85% yield). Spectra of this preparation were identical with those obtained in method A.

Spiro [2',8 [1,3]dioxolane, 1- acetoxy, [3,5]dioxabicyclo [4,4,0] decane] 132.

Acetoxydiol 120 (2.00g, 8.13mmol) was dissolved in dry methylene chloride (50mL). To this was added paraformaldehyde (2.00g, 66.6mmol) and 2 drops of con. sulfuric acid. The mixture was stirred under nitrogen for 4 hrs. Then diluted with 50mL of methylene chloride and washed with 50mL of 10% aq.$NaHCO_3$. The aqueous layer was

back extracted with methylene chloride (3X50mL) and the combined organic layers were washed with water, dried and concentrated to give 2.20g of the crude product. This was flash chromatographed on silica, eluting with 1:1 hexane:EtOAc to give pure 132, 1.40g, (67.0% yield).

IR.(CCl_4) 2970m, 2940m, 2918w, 2880w, 1740s, 1711s, 1453m, 1380m, 1288m, 1253s, 1230s, 1198s, 1189s, 1085s, 1030s cm^{-1}

^1H NMR (60MHz,$CDCl_3$) δ 5.16(s,C-4,2H), 4.85(s,C-2,2H), 4.23 (s,ketal,4H), 2.15(s,OAc,3H), 1.25-2.25(m,remaining 5H).

^{13}C NMR ($CDCl_3$) δ 207.6(C=O), 169.9(C-1), 97.4(C-8), 93.1(C-4), 77.6(ketal), 76.2(C-6), 75.7(ketal), 66.3(C-2), 40.7(C-7), 32.9(C-9), 27.3(C-10), 20.2(acetate CH_3).

Anal.Calcd.for $C_{12}H_{18}O_6$ C 55.80% H 7.02%

Found C 55.59% H 6.88%.

1-Acetoxy,[3,5] dioxabicyclo[4,4,0] deca-9-ene-8-one 134.

Protected diol 132 (454.8mg, 1.763mmol) was dissolved in dry methylene chloride (10mL) and to this phenylselenylchloride (337.6mg, 1.763mmol) was added. The mixture was stirred under nitrogen for 20hrs, diluted with 10mL of methylene chloride, washed with 10% aq.$NaHCO_3$, dried and concentrated to give the crude selenide as a yellow oil (730mg).

To a cooled (0°C) solution of the crude selenide (456.6mg, 1.105mmol) was dissolved in 15mL of THF was added 30% hydrogenperoxide (0.3mL, 2.92mmol). The mixture was stirred for 2 hrs, then dialuted with 10mL of 5% aq. $NaHCO_3$ and extracted with methylene chloride (4X25mL). The combined organic layers were dried and concentrated. The crude product was flash chromatographed on silica, eluting with 2:3 hexane:EtOAc, to give 134 as a colorless thick oil. 108mg, (29% yield).

IR (CCl_4) 3330br, 2406m, 1744s, 1692m, 1238br cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) δ 6.52(d,d,J =10.0Hz,J =2.0Hz, C-10,1H), 6.13(d,J=10.0Hz,C-9,1H), 5.30(s,C-4,2H), 5.06(s,C-2,2H), 2.33-2.96(m, remaining 6H).

^{13}C NMR ($CDCl_3$) δ 143.5(C-10), 131.1(C-9), 94.7(C-4), 64.9(C-2), 38.6(C-7), 21.2(acetate CH_3).

Anal.Calcd.for	$C_{10}H_{12}O_5$	C 52.60%	H 5.70%
	Found	C 52.57%	H 5.63%

Spiro [2',4 [1,3]dioxolane, 1-acetoxy, [7]- oxabicyclo [4,2,0] octane] 128.

In an oven dried three-necked flask was dissolved acetoxydiol 120 (370mg,1.50mmol) in 5mL of dry chloroform, under a nitrogen atmosphere. To this triphenylphosphine (393mg, 1.50mmol) was added. The solution was cooled in an ice bath, and then diisopropyl azodicarboxylate (303mg,

295 μL, 1.50mmol) was added via a syringe during a 10min period. The red color of diisopropyl azodicarboxylate disappeared instantneously during the addition. Stirring was continued for 4hrs at 0°C. The solution was evaporated to dryness, leaving a thick oil which was flash chrmatographed on silica, eluting with 3:2 hexane:EtOAc. The oxetane 128 was obtained as a thick colorless oil, 202mg, (60% yield). Only one component was evident on TLC (silica,3:2 hexane:EtoAc) and HPLC.

IR. ($CHCl_3$) 1727s, 1225br, 1045m, 910s cm^{-1}

^1H NMR (60MHz,$CDCl_3$) δ 4.85(dd,J_1=6.0Hz,J_2= 4.0Hz, C-6,1H), 4.16(ABq,J=3.0Hz,C-8,2H), 3.93(s,ketal,4H), 2.13(s,OAc,3H), 2.00-1.15(m,remaining 6H).

Anal.Calcd.for	$C_{11}H_{16}O_5$	C 57.89%	H 7.07%
	Found	C 57.89%	H 6.88%

Catalytic Reduction of the Allyl Alcohol 118.

Allyl alcohol 118 (20.00g, 0.117mol) was dissolved in 400mL of absolute ethanol and to this 2.00g of 10% Pd-C (Fischer Scientific Co.) was added. The mixture was hydrogenated at 30-40 psi in a Parr apparatus for 10hrs. The catalyst was filtered and the solvent was removed under reduced pressure to give an oil (21.2g). TLC analysis (silica, 1:1 hexane:EtoAc) showed a mixture of

two compounds.

Identification of the components in the mixture.

200mg of the mixture was separated by flash chromatography (silica, 1:1 hexane:EtOAc). Two compounds were isolated and identified as alcohol 153 and aldehyde 154 on the basis of IR and ^{1}H NMR.

Alcohol 153.

IR (CCl_4) 3642m, 3450br, 2940s, 2928s, 2874s, 1444s, 1373s, 1357m, 1332m, 1107s, 1085s, 1033s, 944s, 930s cm^{-1}.

^{1}H NMR (60MHz,$CDCl_3$) δ 3.96(s,ketal and CH_2-O,6H), 3.50(brs,exchangeable with D_2O,OH,1H), 1.20-2.25(m, remaining 9H).

^{13}C NMR ($CDCl_3$) δ 108.2, 66.1, 63.2, 38.2, 33.3, 25.8

Aldehyde 154.

IR (CCl_4) 2890br, 1732s, 2940s, 2870m cm^{-1}.

^{1}H NMR (60MHz,$CDCl_3$) 9.67(s,CHO,1H), 3.95(s,ketal,4H), 1.05-2.32(m,remaining 9H).

Further reduction of the alcohol/aldehyde mixture with sodium borohydride.

The alcohol/aldehyde mixture (20.00g) was dissolved in 300mL of methanol and cooled to 0°C. To this a solution of sodium borohydride (2.50g, 0.0660mol) in 100mL of methanol was added during a period of 15min, and stirring was continued for 2hrs. The mixture was poured into 400mL

of water and extracted with methylene chloride (5X200mL), dried and concentrated to give a colorless oil of 153 (20.05g, 100% yield. Which showed a one component on TLC (silica, 3:2 hexane:EtOAc) and GLPC.

Anal.Calcd.for $C_9H_{16}O_3$ C 62.76% H 9.36%

Found C 62.53% H 9.37%

α-Bromo Ketal Alcohol 151.

Ketal alcohol 153 (4.00g,23.3mmol) was dissolved in 150mL of dry methylene chloride and to this was added phenyl trimethylammonium perbromide (PTAB) (8.74g, 23.3mmol) during a period of 1hr. The mixture was stirred under nitrogen for 2days, then poured into 100mL of 10% aq.$NaHCO_3$ and separated. The sodium bicarbonate layer was extracted with methylenechloride (2X50mL) and the combined organic layers were washed with water (50mL), dried and concentrated to give thick, pale yellow liquid of crude bromide 151, 5.43g, (93% yield).

TLC (silica, 3:2 hexane:EtOAc) and HPLC analysis showed a mixture of two compounds. The major component was separated for analysis by flash chromatography on silica, solvent 3:2 hexane:EtOAc.

IR (CCl_4) 3660br, 2955s, 2900s, 2872s, 1435m, 1332m, 1173m, 1053m cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) δ 4.22(m,ketal and C-2, 5H)

3.515(ABq, J_1=5.0Hz, J_2=5.0Hz,CH_2-O,2H), 2.41-1.20(m, remaining 7H).

Anal.Calcd.for $C_9H_{15}O_3Br$ C 43.05% H 6.02% Br 31.82%

Found C 43.06% H 6.20% Br 31.66%

On the basis of 200MHz ^{1}H NMR of the mixture it was concluded that the product is an epimeric mixture of bromo ketals. The crude mixture was used for further reactions.

Intramolecular photocycloaddition model study

Coupling of Dimedone with α Bromoketal 151.

Bromoketal 151 (410mg,1.63mmol) and dimedone (228mg, 1.63mmol) were dissolved in 50mL of dry benzene and to this 10mg of p-toluenesulphonic acid monohydrate was added. The mixture was refluxed with a Dean-Stark water separator for 24hrs, then washed with 50mL of 10% aq.$NaHCO_3$, dried and concentrated to give a thick brown liquid, 152, 602mg, (99% yield)

^{1}H NMR (60MHz,$CDCl_3$) 5.27(s,C-2,1H), 4.25-3.20 (m,ketal, CH_2-O and CHBr, 7H), 1.04(s,2-Me,6H), 2.30-0.92(m, remaining 11H).

Dehydrobromination of Dimedone- α-Bromoketal coupled product.

Coupled enolether 152 (602mg, 1.61mmol) was dissolved in DBU (1.00mL, 6.69mmol) and heated at 100-110°C under a nitrogen atmosphere for 20hrs, then cooled, dissolved in 50mL of water and extracted with chloroform (4X20mL). The combined organic layers were dried,and concentrated to give a thick brown oil, which was dissolved again in chloroform (50mL) and passed through a short column of basic alumina to remove any unreacted DBU. The alkene-enone 155 was obtained as a pale yellow oil.(406mg,86%).

^{1}H NMR (60MHz,$CDCl_3$) δ 5.90(d,J=10.0Hz,C-3',1H), 5.63 (d, J=10.0 Hz,C-2',1H), 5.25(s,C-2,1H), 4.20-3.65(m,ketal and CH_2-O,6H), 1.03(s,2-Me,6H), 2.40-0.95 (m,remaining 9H). An Elemental analysis was not obtained as the material was too unstable. It was therefore used without further purification.

Intramolecular Photocycloaddition of Alkene-Enone .

Alkene-enone 155 (100mg,0.342mmol) was dissolved in dry cyclohexane (8.0mL),degassed with dry nitrogen for 45 min, then irradiated in a Pyrex tube at 300nm using a Rayonet apparatus. The reaction was monitored by HPLC, and stopped after 3days. The solvent was removed under vacuum and the residue was flash chromatographed on silica. Elution with 2:3 hexane:EtOAc gave 58mg (58%) of the photoadduct 156, mp. 145-147°C.

IR (CCl_4) 2957s, 2864m, 1707s, 1465w, 1449w, 1368w, 1255m, 1236m, 1214m, 1122w, 1105s, 1031s cm^{-1}

^1H NMR (200MHz,$CDCl_3$) δ 4.268(ABq,J_1=7.1Hz,J_2=1.0Hz, C-13,1H), 4.100(ABq,J_1=7.1Hz,J_2=1.0Hz,C-13,1H), 4.02-3.65 (m,ketal,4H), 2.850(d,J=9.2Hz,C-1,1H), 2.551(d,J=9.1Hz,C-2 1H), 2.243(s,C-11,2H), 2.047(s,C-7,1H), 1.902(s,C-9,2H), 1.643(s,C-4,2H), 1.261(t,J=7.2Hz,C-6,1H), 1.045(s,3H) and 0.984(s,3H) C-14, C-15 methyls.

Anal.Calcd.for	$C_{17}H_{24}O_4$	C 69.84%	H 8.27%
	Found	C 69.75%	H 7.82%.

Ring Expansion of Camphorquinone with Diazomethane.

A 5% aq.potasium hydroxide solution (80mL) was added to a cold diazomethane solution.(Prepared according to the Aldrich Chem.Co. DIAZALD procedure, this solution contains 1.0g of CH_2N_2 in 100 mL of abs.ether.) To this was added, finely powderd camphorquinone (2.00g, 0.012mol) during a period of 15min while stirring vigorously at room temperature. Stirring was continued for 3hrs. Ether was then removed on the rotavapor, and the remaining solution was acidified with 12N HCl to pH = 1. A pale yellow solid appeared, and after cooling was filtered. The product was recrystallized from 1:1 petroleum ether(40-60°C):benzene to give pure homocamphorquinone 136, 1.28g (59% yield). mp.222-223°C. lit.223-224°C.

^1H NMR (60Mz,$CDCl_3$) 3.08(ABq,J_1=18.0Hz,J_2=15.0Hz,C-3, 2H), 2.52-1.50(m,remaining 5H), 1.00(s,C-8 2 Me,6H), 0.77(s,C-1 Me,3H).

Coupling of Homocamphorquinone with α-Bromoketal 151.

Homocamphoquinone 136 (1.036g,5.756mmol) and bromoketal 151 (1.445g, 5.756mmol) were dissolved in 100mL of dry benzene and to this 20mg of p-tolunesulfonic acid monohydrate was added. The mixture was refluxed with a Dean-Stark water separator for 24hrs. (The reaction was monitored by TLC on silica,using 8:92 MeOH:$CHCl_3$), then washed with 100mL of 10% aq.$NaHCO_3$. The aqueous layer was back extracted with ethyl acetate (4X100mL), and the combined organic layers were dried and concentrated to give a yellow, gummy product, 2.40g(90% yield). This was flash chromatographed on silica, eluting with 5:95 MeOH:$CHCl_3$ and gave two compounds.

Major 157. 1.70g, (72% yield).

^1H NMR (200MHz,$CDCl_3$) δ 5.113(s,C-3,1H), 4.42-3.56(m, ketal,C-2'and C-7',7H), 2.46-1.20(m,remaining 9H), 1.060 (s,3H), 0.940(s,3H) and 0.931(s,3H) C-1 and C-8 methyl groups.

Minor 158. 0.090g, (4% yield).

^1H NMR (200MHz, $CDCl_3$). δ 5.224(s,C-3.1H), 4.40-3.55(m, ketal,C-2'and C-7',7H), 2.48-1.25(m,remaining 9H), 1.060

(s,3H), 1.162(s,3H), 1.211(s,3H), C-1 and C-8 methyl groups.

Dehydrobromination of the Major Homocamphoquinone Coupled α-Bromoketal 157.

The major compound 157 (1.70g,4.11mmol) was dissolved in DBU (1.80mL,12.3mmol) and heated in an oil bath at 100-110°C under nitrogen for 16hrs. The mixture was then cooled, dissolved in 100mL of water, and extracted with chloroform (5X60mL). The combined organic layers were dried and concentrated to a thick brown oil. Excess DBU was removed by chromatography on a short basic alumina column. Eluting with 500mL of $CHCl_3$ gave pure alkene-enone 159 1.26g, (92% yield).

^1H NMR (200MHz, $CDCl_3$) 5.858(d,J=1.6Hz,C-3',1H), 5.730 (d,J=1.6Hz,C-2',1H), 4.144(s,C-3',1H), 4.40-3.65(m,ketal and C-7',6H), 2.70-1.10(m,remaining 8H), 1.063(s,C-9,3H), 1.037(s,C-10 and C-11,6H).

Intramolecular Photoreaction.

Alkene-enone 159 (1.20g, 3.61mmol) was dissolved in 85mL of dry cyclohexane and degassed with dry nitrogen for 45min, then irradiated in a pyrex tube at 300nm in a Rayonet apparatus. The reaction was monitored by HPLC and was stopped after 15hrs. The solvent was removed under reduced pressure, leaving a thick oil which was flash

chromatographed on silica. Elution with 1:1 hexane:EtOAc gave two compounds. Which were recrystallized from hexane/ethyl acetate.

Major compound, 160 720mg (60% yield), mp.132-133°C.

IR (CCl_4) 2965m, 2932m, 2872w, 1703s, 1391m, 1373m, 1250m, 1115m, 1102s, 1085s, 1030s, 954m cm^{-1}.

^1H NMR (200MHz,$CDCl_3$) δ 4.287(m,C-15,2H), 4.712-4.062 (m,ketal,4H), 3.087(t,J=9.0Hz,C-3,1H), 2.662(d,J=6.5Hz, C-4,1H), 2.55-1.50(m,remaining 11H), 1.000(s,C-16,C-17 and C-18 methyls,9H).

^{13}C NMR ($CDCl_3$) 225.6, 107.8, 74.4, 63.9, 63.6, 50.1, 48.2, 45.5, 41.4, 38.8, 36.0, 31.7, 28.3, 26.6, 25.7, 24.4, 20.9, 13.6

Anal.Calcd.for $C_{20}H_{28}O_4$ C 72.26% H 8.49%

Found C 72.49% H 8.55%

Minor compound, 161 143mg, (12% yield), mp.161-161.5°C.

IR (CCl_4) 2965m, 2940m, 2870w, 1701s, 1373w, 1256m, 1132m, 1112s, 1050s, 1034s cm^{-1}.

^1H NMR (200MHz,$CDCl_3$) δ 4.018(t,J=9.2Hz,C-15,1H), 4.08-3.92 (m,ketal,4H), 3.737(t,J=9.8Hz,C-15,1H), 2.860(t, J=10.4Hz, C-3,1H), 2.52-1.50(m,remaining 12H), 1.019 (s,3H), 0.955 (s,3H), 0.913(s,3H), C-16,17 and 18 methyls.

^{13}C NMR ($CDCl_3$) 212.8, 107.4, 98.5, 86.7, 70.3, 64.1, 57.9, 50.8, 48.0, 43.3, 36.4, 34.2, 31.7, 27.6, 24.0, 23.8, 21.0, 20.5, 13.1

Anal.Calcd.for	$C_{20}H_{28}O_4$	C 72.26%	H 8.49%
	Found	C 72.50%	H 8.48%

RuO_4 Oxidation of the Major Photoadduct 160.

Sodium metaperiodate (582mg, 2.72mmol) and $RuO_2.xH_2O$ (9.1mg) were dissolved in a mixture of 7mL of water, 2mL of acetonitrile and 7mL of carbon tetrachloride. The mixture was stirred for 10min, and a deep green color appeared. The photoadduct 160 (225.7mg, 0.6790mmol) in 10mL of acetonitrile was then added slowly (in 15min), and the color changed to black. Stirring was continued for 20hrs at room temperature. Then the layers were separated and the aqueous layer was extracted with ethylacetate (4X10mL). The combined organic layers were dried and concentrated to give a thick brown oil. This was flash chromatographed on silica, eluting 3:2 hexane:EtOAc and yielded 216mg of lactone 171 (92% yield).mp. 192-193°C.
IR (CCl_4) 2970br, 2870br, 2760w, 1767s, 1729s, 1380w, 1370w, 1232s, 1092s, 1050m, 1010s cm^{-1}.
^1H NMR (200MHz, $CDCl_3$) δ 4.434-3.816(m,ketal,4H), 3.348 (t,J=9.4Hz,C-3,1H), 2.992(d,d,J_1=9.5Hz,J_2=1.3Hz,C-4,1H), 2.638(d,d,J_1=6.6Hz,J_2=4.0Hz,C-8,1H), 2.90-1.10(m,remaining 10H), 1.079(s,3H), 1.062(s,3H), 1.046(s,3H), C-16,C-17 and C-18 methyls.

Anal.Calcd.for	$C_{20}H_{26}O_5$	C 69.34%	H 7.57%
	Found	C 69.37%	H 7.65%

KOH/EtOH Ring opening of the Lactone 171.

Lactone 171 (124.4mg,0.3590mmol) was dissolved in 8.0mL of absolute ethanol and to this potassium hydroxide (250mg, 4.46mmol) was added the mixture was refluxed for 2.0hrs, then cooled and diluted with 50mL of water. The solution was extracted with ether (10mL), and the aqueous layer was acidified with con.HCl to pH=2 and again extracted with ether (4X20mL). The acidic organic extracts were combined, dried and concentrated to give a white solid, which was recrystallized from ethyl acetate to give 178 as white needles 78mg,(60%yield). mp.225-226°C.

IR (CCl_4) 1786s, 1782s, 1725s, 1558br, 1252m, 1006m, 980m cm^{-1}.

^1H NMR (200MHz,$CDCl_3$) δ 8.368(brs,carboxylic acid 1H), 4.395-3.579(m,ketal,4H), 3.456(d,d,J_1=8.8Hz,J_2=7.3Hz,C-3,1H) 2.90-1.10(m,remaining 13H), 1.263(s,6H), 0.868(s,3H), C-16,C-17,and C-18 methyls.

Anal.Calcd.for	$C_{20}H_{28}O_6$	C 65.92%	H 7.74%
	Found	C 66.12%	H 7.76%

Grob-fragmentation/Bamford-Stevens Reaction Model Study.

Acetylation of Dimedone.

Dimedone (10.00g, 0.071mol) was dissolved in 100mL of chloroform and to this pyridine (6.9mL, 0.086mol) and acetic anhydride (8.1mL, 0.086mol) were added. The mixture was stirred at room temperature for 6.0hrs. Then poured into 100mL of water and separated. The organic layer was dried and concentrated to give a pale yellow oil which crystallized slowly upon cooling and afforded 12.20g of 187 (94%yield).

IR (CCl_4) 2920m, 1735s, 1678s, 1588s cm^{-1}.

^1H NMR (60MHz, $CDCl_3$) 5.71(s,C-2,1H), 2.20(s,OAc,3H), 2.43-2.15 (m,C-4 and C-6,4H), 1.12(s,2 Me,6H).

1-Acetoxy,10,10-dimethyl tricyclo[5,4,0,$0^{2,6}$] undeca-8-one. 188 and 189.

A solution of 8.00g(0.0439mol) of dimedone-enol acetate in 80mL of cyclopentene was degassed with dry nitrogen for 20min then irradiated in a pyrex tube for 24hrs, using a 500W mercury lamp. The solvent was removed under reduced pressure and the crude product was crystallized from ether yielding a mixture of 188 and 189. Fractional crystallization from ether gave;

188 4.60g,(42.7%), mp.125.5-126°C, Lit.mp.126-127°C.

IR (CCl_4) 2960s, 2880w, 1736s, 1702s, 1545br, 1370s, 1348m, 1238m, 1206m, 1045m, 1018m cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) 2.10(s,OAc,3H), 3.10-1.45(m, remaining 13H), 1.10(s,3H), 0.95(s,3H),C-12 and C-13 methyl groups.

189 1.80g,(16.7%), mp.118-119.5°C, Lit.mp.117-118°C.

IR (CCl_4) 2960s, 1738s, 1703s, 1370s, 1240br, 1209w, 1020w cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) 2.05(s,OAc,3H), 3.00-1.45 (m, remaining 13H), 1.03(s,3H), 0.90(s,3H) C-12 and C-13 methyl groups.

Sodium Borohydride Reduction of the Major Photoadduct 188.

Photoadduct 188 (1.00g, 4.00mmol) was dissolved in 20mL of methanol and cooled to 0°C. To this $NaBH_4$ (0.10g, 2.6mmol) in 10mL of methanol was added. The mixture was stirred for 1.0hr, then diluted with 100mL of water and extracted with ether (3X40mL). The combined organic layers were dried and concentrated to give the crude alcohol mixture. Repeated fractional crystallition from hexane gave pure alcohol 190, 0.52g, 51% yield. mp.50-52.5°C, Lit.mp.49.5-51.5°C.

IR (CCl_4) 3622br, 1738s, 1704s, 1250w cm^{-1}.

^1H NMR (60MHz, $CDCl_3$) 3.76(m,CH-O,1H), 2.02(s,OAc,3H), 1.02(s,3H), 0.98(s,3H) C-12 and C-13 methyl groups, 2.82-1.25(m, remaining 14H).

Mesylation of the major alcohol 190.

Major alcohol 190 (108mg, 0.428mmol) was dissolved in 5.0mL of chloroform and to this were added triethylamine (48mg, 0.47mmol) and methane sulfonylchloride (54mg, 0.47mmol). The mixture was stirred at room temperature for 4hrs under nitrogen. Then poured into 10mL of water and extracted with chloroform. The organic layers were dried and concentrated to give 110mg,(78% yield) of the crude mesylate 191 as a thick oil. This compound was used for the Grob frgmentation without further purification.

Grob Fragmentation of the Mesylate 191.

Crude mesylate 191 (110mg, 0.333mmol) was dissolved in 8.0mL of absolute ethanol and to this KOH (204mg, 3.58mmol) was added. The solution was refluxed for 2.0hrs, then poured into 20mL of water and extracted with methylene chloride (3X15mL).The combined organic layers were dried and concentrated to give a pale yellow oil. This was flash chromatographed on silica, eluting with 3:2 hexane:EtOAc, and gave cyclooctene 192 as a white powder, (47mg,73%). The anylatical sample was prepared by recrystallization from hexane. mp. 107-108°C.

IR (CCl_4) 2920m, 2860w, 1706s, 1685w, 1040s cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) 5.60(m,C-6 and C-7), 2.05(s,C-5,2H), 1.00 (s,C-12 and C-13 methyls,6H), 2.95-0.85(m, remaining 10H).

Anal.Calcd.for $C_{13}H_{20}O$ C 81.20% H 10.48%

Found C 81.35% H 10.26%

Tosylhydrazone of the Major Photoadduct 188.

Major photoadduct 188 (40.2mg,0.160mmol) was dissolved in 5.0mL of absolute ethanol and to this finely powdered molecular sieves (0.5g, dried in an oven at 120°C for 10hrs) and p-tolunesulfonylhydrazine (31.6mg, 0.17mmol) were added. The mixture was stirred at room temperature under nitrogen for 24hrs. Then filtered and concentrated to give a white crystalline powder. Recrystallization from absolute ethanol gave white needles of 196 (55mg, 82%). mp. 180-181.5°C.

IR (CCl_4) 2960m, 2920m, 1738s, 1420s cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) 7.85(d,J=9.0Hz,aromatic,2H), 7.32 (d,J=9.0Hz,aromatic,2H), 2.43(s,TsMe,3H), 2.00(s,OAc, 3H), 1.00(s,C-10 Me,3H), 0.76(s,C-10 Me,3H), 2.95-1.38(m,remaining 14H).

Anal. Calcd.for $C_{22}H_{30}O_4N_2S$ C 42.72% H 4.89%

Found C 42.50% H 4.92%

Bamford-Stevens Coupled Grob Fragmentation of the Tosylhydrazone-acetate 196.

Tosylhydrazone-acetate 196 (34.6mg,0.0830mmol) was dissolved in 2.0mL of diglyme and to this NaOMe (28mg,

0.52mmol) was added. The mixture was refluxed under a nitrogen atmosphere for 1.5h, then poured into 5.0mL of water and extracted with methylene chloride (5X5mL). The combined organic layers were washed with brine, dried and concentrateed to give a yellow oil, which was flash chromatographed on silica. Elution with 4:1 hexane: EtOAc gave pure alkene-acetate 197 15.1mg,(77% yield) as a thick colorless liquid.

IR (CCl_4) 2950m, 2927m, 2860w, 1735s, 1540br, 1367m, 1244s, 1046m, 1008m, 910m cm^{-1}

^1H NMR (60MHz,$CDCl_3$) 5.80(brs,C-8,1H), 5.60(brs,C-9,1H), 2.03(s,OAc,3H), 3.10-0.95(m,remaining 11H), 1.00(s,C-10 methyl groups 6H).

Anal.Calcd.for	$C_{13}H_{18}O_2$	C 76.88%	H 9.46%
	Found	C 76.60%	H 9.59%

Acetylation of Homocamphorquinone 136.

To a solution of homocamphorquinone 136 (859mg, 4.77mmol) in 50mL of dry chloroform were added pyridine (0.407mL, 5.72mmol) and acetyl chloride (0.463mL,5.72mmol). The mixture was stirred at room temperature for 3.0hrs. Then washed with 5% aq.HCl (25mL) and water (25mL), dried and concentrated to give the crude enol acetate. TLC (silica, 5:1 hexane:EtOAc) showed a mixture of two compounds. Which were separated on the

Chromatotron (silica plate, 4:1 hexane:EtOAc), giving 137 and 138 as colorless oils.

Major compound 137, 630mg, 63% yield.

IR (CCl_4) 1762s, 1655m, 1440m, 1360m cm^{-1}.

^1H NMR (60MHz,$CDCl_3$) 5.68(s,C-3,1H), 2.50-2.72(m,C-5, 1H), 2,36(s,OAc,3H), 1.8-2.2(m,remaining 4H), 1.03(s, C-8 methyl groups 6H), 1.14(s,C-1 Me,3H).

Minor compound 138, 158mg, 16% yield.

IR (CCl_4) 1764s, 1650m, 1360m cm^{-1}

^1H NMR ($CDCl_3$) 5.70(s,C-3,1H), 2.48-2.64(m,C-5,1H), 2.40(s,OAc,3H), 1.8-2.2(m, remaining 4H), 1.05(s,3H), 1.15(s,3H), and 1.21(s,3H) C-1 and C-8 methyl groups.

Oxidation of the α-Bromoketalalcohol 151 to α-Bromoketalacid 172.

Potasium permanganate (139mg,0.880mmol) and tetrabutyl-ammonium bromide (70mg,0.22mmol) were dissolved in 4.0mL of water. To this 2.0mL of benzene was added and the mixture was stirred for 0.5hrs. Then alcohol 151 (110mg,0.438mmol) dissolved in 2.0mL of benzene was added and the mixture was stirred for another 24hrs at room temperature. The mixture was subsequently cooled to 0^oC and reduced with 5mL of saturated aqueous sodium bisulfite after stirring for an additional 15min, the mixture was acidified with con.HCl to pH=2, and extracted with

ethyl acetate (5X10mL). The combined organic layers were washed with water (10mL), dried and concentrated to give the acid 172 as a clear liquid.(96mg, 83%).

IR ($CHCl_3$) 3010br, 1710s, 1445m 1222br cm^{-1}.

^{1}NMR (60MHz, CD_3COCD_3) 10.70(brs,COOH,1H), 4.50-3.98 (m,ketal and C-1,5H), 3.20-0.90(m,remaining 7H).

Preparation of the Lactone mesylate 185.

Lactone 171 (10.0mg,0.029mmol) was dissolved in 2.0mL of methanol and cooled to 0°C, and to this solution was added $NaBH_4$ (5.0mg,0.13mmol). The mixture was stirred at 0°C for 3.0h, then poured into 10mL of water and extracted with methylene chloride (3X10mL). The combined organic layers were dried and concentrated to give the crude alcohol (9.2mg, 91% yield) as a single compound (TLC silica, 4:1 hexane:EtOAc). The alcohol was used without further purification.

The alcohol (9.2mg,0.026mmol) was dissolved in 2.0mL of dry chloroform. To this Et_3N (10 μL,0.10mmol) and MsCl (8 μL,0.10mmol) were added and stirred at room temperature for 6hrs, then diluted with 15mL of $CHCl_3$ and washed with water (2X10mL). The organic layer was dried and concentrated to give the mesylate 185 as a white solid. 8.2mg, 74% yield.

IR (CCl_4) 2940br, 2880w, 1778s, 1318m, 1218w, 1198m, 1107s, 974m, 1030m cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) 4.883(d,J=10.4Hz, C-2,1H), 3.93-3.88(m,ketal,4H), 3.456(d,d,J_1=8.8Hz,J_2=7.3Hz,C-3), 2.882 (d,q, J_1=5.8Hz,J_2=1.4Hz,C-8,1H), 2.268(s,OMs,3H), 2.462-1.530(m,remaining 11H), 1.575(s,3H), 1.371(s,3H) and 1.252(s,3H) C-16,C-17 and C-18 methyl groups.

Preparation of the Lactone tosylhydrazone 198.

To a solution of lactone 171 (15.6mg,0.0450mmol) dissolved in 6.0mL of abs.ethanol were added finely powdered molecular sieve (100mg) and p-tolunesulfonyl hydrazine (8.8mg,0.047mmol). The mixture was stirred under nitrogen at room temperature for 24hrs, then filtered and concentrated to give the tosylhydrazone 198 as a white solid. (20mg, 86%).

IR (CCl_4) 2965m, 2928m, 2878w, 1777s, 1708s, 1450w, 1346br, 1185m, 1170s, 1098m, 1081m, 1023m, 1008m cm^{-1}.

^1H NMR (200MHz, $CDCl_3$) 7.783(d,J=8.1Hz, aromatic, 2H), 7.345(d,J=8.1Hz, aromatic, 2H), 5.720(brs,N-H, 1H), 2.437 (s, tosylmethyl, 3H), 4.40-0.95(m,remaining 17H), 1.056(s, 3H), 1.034(s,3H) and 1.015(s,3H) C-16, C-17 and C-18 methyl groups.

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