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Studies towards the total synthesis of taxol. Synthesis of A-ring intermediate with all the latent functionalities

Rao, Meenakshi Srikumar, Ph.D.

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STUDIES TOWARDS THE TOTAL SYNTHESIS OF TAXOL. SYNTHESIS OF A-RING INTERMEDIATE WITH ALL THE LATENT FUNCTIONALITIES.

BY

MEENAKSHI S. RAO

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

1990

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

8/24/90
Date

William Frost Berkowitz
Chair of Examining Committee

9/25/90
Date

Executive Officer

Dr. Robert Engel

Dr. Richard W. Franck

Supervisory Committee

The City University of New York

ABSTRACT

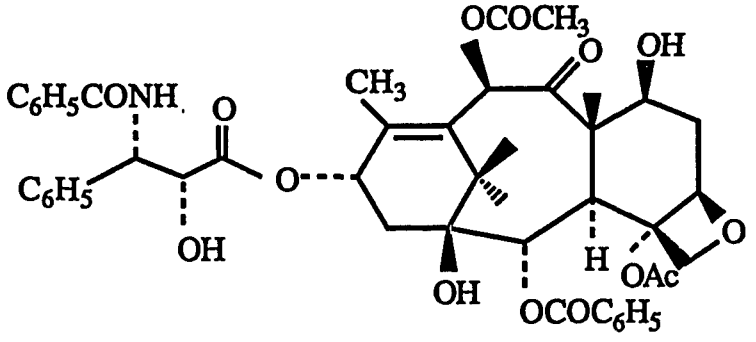
STUDIES TOWARDS THE TOTAL SYNTHESIS OF TAXOL. SYNTHESIS OF A-RING INTERMEDIATE WITH ALL THE LATENT FUNCTIONALITIES.

BY

MEENAKSHI S. RAO

Adviser: Prof. William F. Berkowitz

Taxol (1) belongs to a class of compounds called taxanes, which are diterpenoids isolated from the plants of the family taxaceae. It has potent antileukemic and tumor inhibiting properties.



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Methods for the synthesis of ETHYL 2,6,6-TRIMETHYLCYCLOHEXEN-5-ONE CARBOXYLATE, a key synthon for it's total synthesis were investigated. Robinson anulation was found to be the most effective of these methods, and was applied to obtain this compound.

The allylic alcohol alcohol resulting from the grignard reaction of isobutyraldehyde and vinyl magnesium bromide was oxidized to isopropyl vinyl ketone. Michael addition of diethyl oxalpropionate to this followed by acid catalyzed aldol condensation gave a hydroxy ester, which was dehydrated to give the required compound.

ACKNOWLEDGEMENTS

The ackowledgements section itself would be as big as the thesis if the names of all who contributed in one form or another to the successful completion of this program are listed. However the following few who were perticularly helpful are mentioned below.

My profound thanks are due to Dr. W. F. Berkowitz without whose constant guidance and encouragement this work would not have been completed.

Thanks are to Dr. R. Engel and Dr. R. W. Franck for valuable advices given during the committee meetings. I thank Dr. D. Locke who ran GC/MS's and helped in analysing the samples. I thank Dr. G. Axelrad, Chairman, Chemistry Department, for providing the support. National Institute of Health, whose funding made this project possible is greatfully acknowledged.

Coming to the personal side, first and foremost I thank my husband for being morally very supportive. I thank my mother who spent considerable amount of time here with me, away from her own family, and helped me. In the final moments, while this manuscript was being prepared, my aunt Lalita was of immense help and I thank her for that.

Though the youngest among these my children were very cooperative during this work and my heart goes to them for taking their mother away from them during that time. But I promise, I will make it up.

TO

PADMA,

SUDHI,

GOWRI

GAUTAM

AND

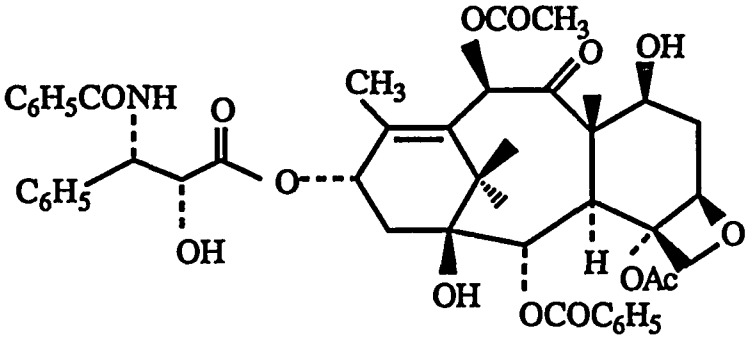
MY PARENTS.

TABLE OF CONTENTS

CHAPTER.1

INTRODUCTION

TAXOL (1) belongs to a class of compounds called TAXANES[1]. Taxanes are diterpenoids isolated from the plants of the family TAXACEAE. Taxol is made up of four rings namely A, B, C and D. Numbering of carbon atoms in taxol is as shown in figure **1**.



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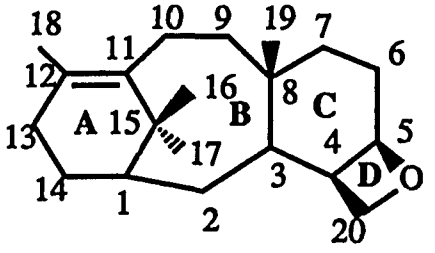


Figure 1.

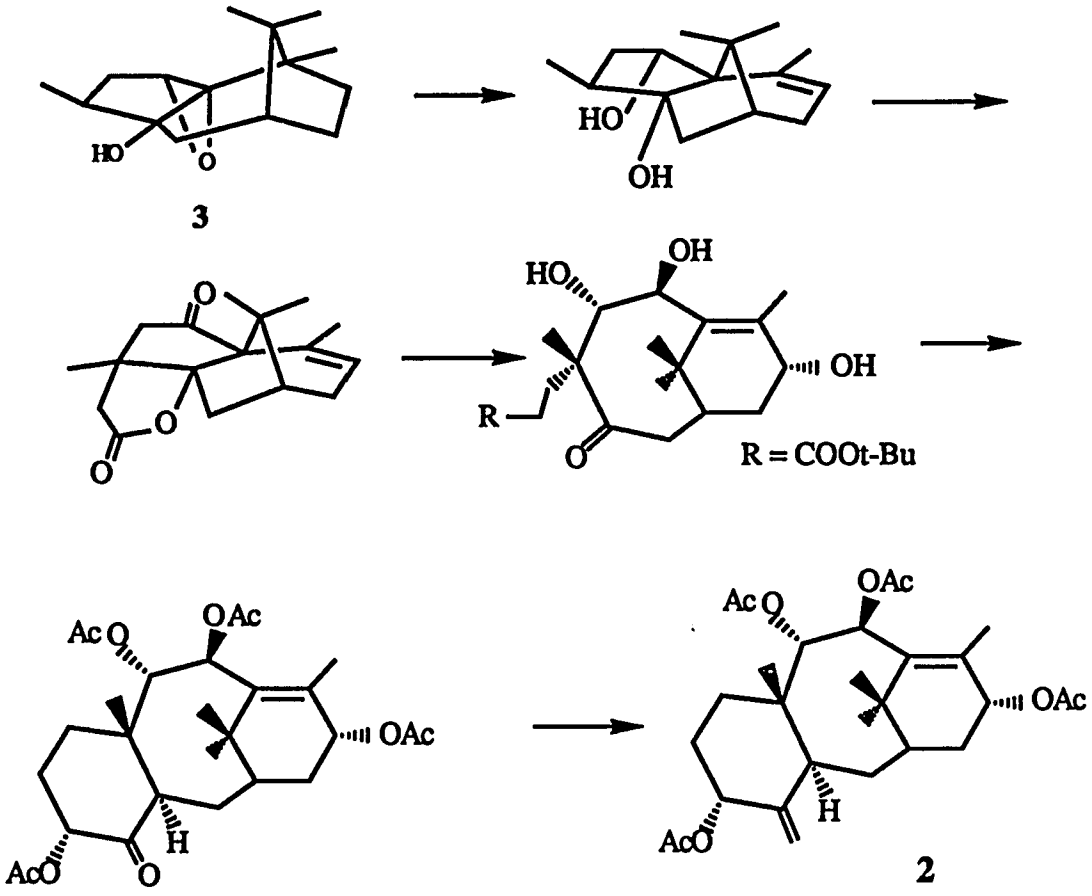
Taxol has potent antileukemic and tumor inhibiting properties. It has been found to be effective against cancerous tumors in mice[2]. It also shows confirmed activity in L-1210, P-388 and P-1534 leukemias[3], being highly active in the latter two systems. Taxol is also highly active as an inhibitor of WM-256 carcinosarcoma, $ED_{50}=5.5 \times 10^{-5}$. Less pure concentrates containing taxol

were also found to be active in Sarcoma 180 and Lewis lung tumors.

Taxol is isolated from the pacific yew trees for the clinical tests. However, it has been calculated that about 2.5 Kg of taxol is obtained from 60,000 Lbs of the bark[4] which requires the sacrifice of approximately 12,000 trees. Environmentalists see this as a threat to the survival of the pacific yew and it's habitat.

Hence there is a lot of activity in the area of its synthesis[5]. However taxane diterpenes in general constitute one of the most synthetically demanding class of compounds as a consequence of both a high level of structural complexity and abundant stereochemical detail. Taxusin (**2**) is the only naturally occuring taxane that has been synthesized to date[6].

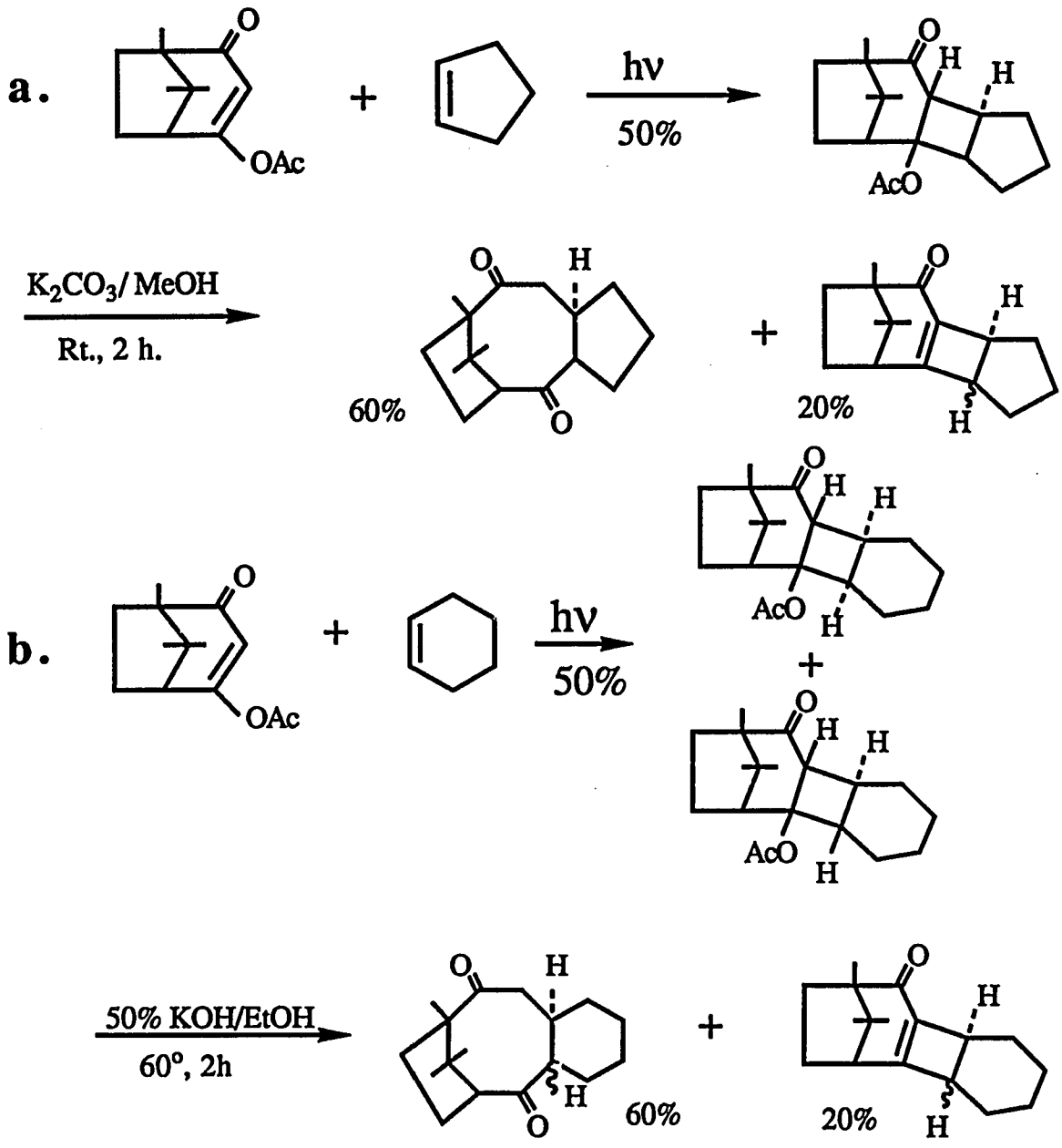
Holton and coworkers accomplished this synthesis starting from β-patchoulene oxide. The vital step in this synthesis is the fragmentation of the bicyclic epoxy alcohol **3** to give the diol. The key steps of the total synthesis are given in **scheme 1.**



SCHEME 1

PLAN OF ACTION :

It has been shown in our laboratories[7] that the deMayo ring closure / retro aldol sequence can be applied to the inter- and intramolecular photocycloaddition of various cycloalkenes and homocamphorquinone derivatives to generate a model for the A, B and C rings of taxanes (**scheme 2**).



SCHEME 2.

Based on the above results it seems very reasonable to assume that the sequence of reactions shown in **part b** of **scheme 2** can be applied to the synthesis of taxol, if proper functional groups are incorporated in the reactants.

The various latent functional groups that we planned to include were as follows :

C-1 angular hydroxyl group,

C-8 angular methyl group,

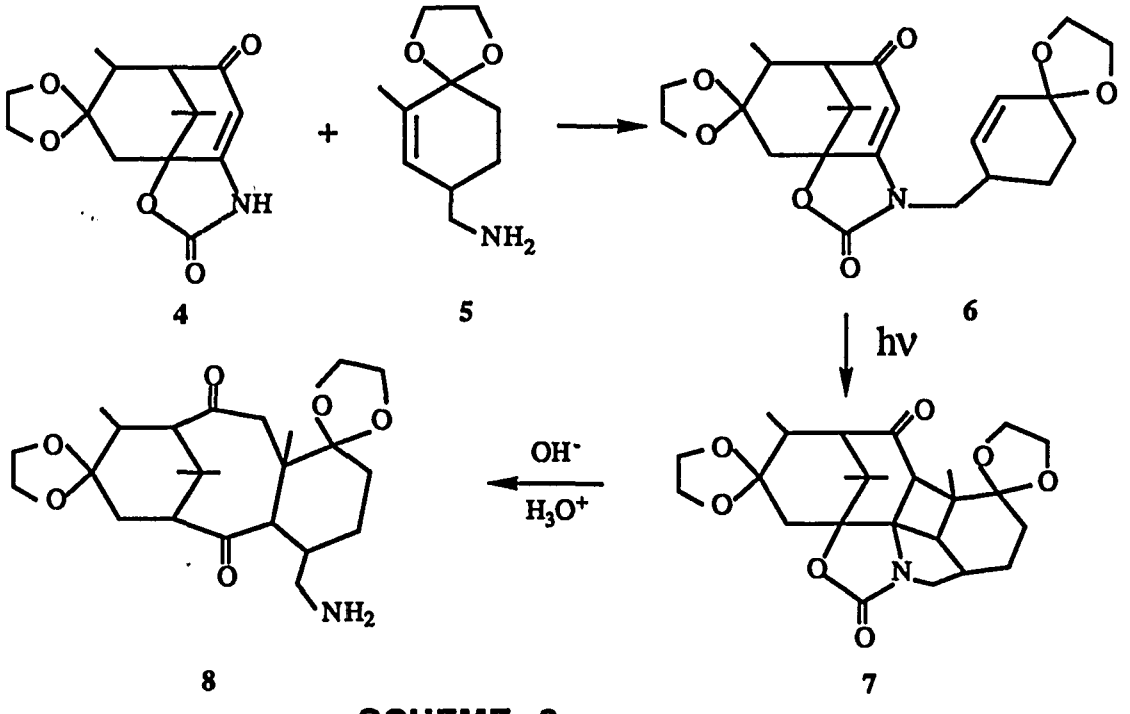
the oxetane / tertiary acetate,

cyclic carbamate moiety and

all the other oxygen functional groups.

Another prerequisite is that photocycloaddition be intramolecular to avoid getting two products.

Then the reaction that we are aiming for will be as shown in **scheme 3.**

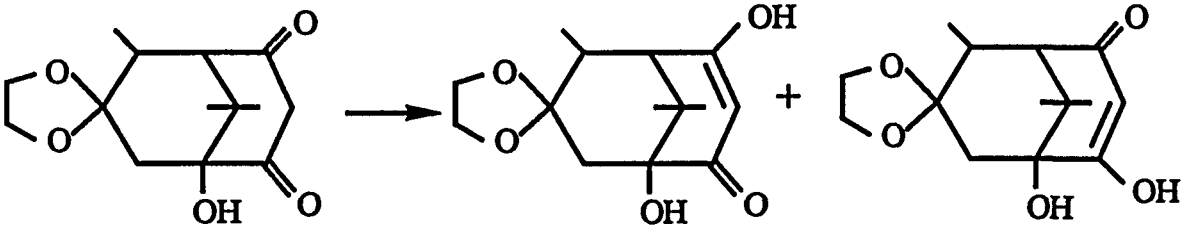


SCHEME 3

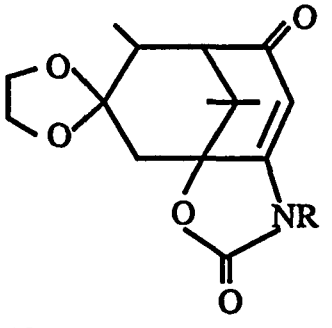
ABOUT SYNTHON 4:

The gem-dimethyl group at C-15 plays an important role in the stereochemistry of the photocycloaddition step. It is the effect of this gem-dimethyl group that endo products were obtained exclusively in the photocycloaddition steps in **scheme 2.** On the contrary, in the absence of the gem-dimethyl group, it has been shown by Inouye[8] and coworkers, that photocycloaddition to bicyclononenone systems occurs from the exo direction.

The cyclic carbamate moiety serves two purposes: **a.** An unsymmetrical 1-hydroxybicyclo (3. 3. 1) nonane-2, 4- dione can enolize in two directions in the manner shown in **scheme 4.** The cyclic carbamate moiety should fix the direction of enolization in the manner that is required for our photocycloaddtion step.



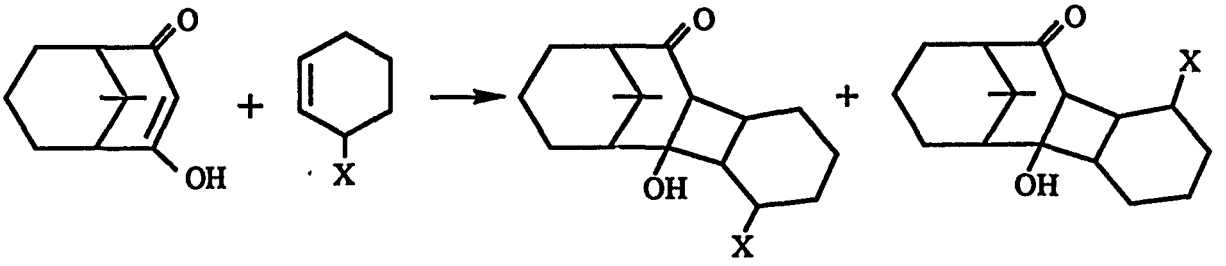
SCHEME 4.



CYCLIC CARBAMATE MOIETY

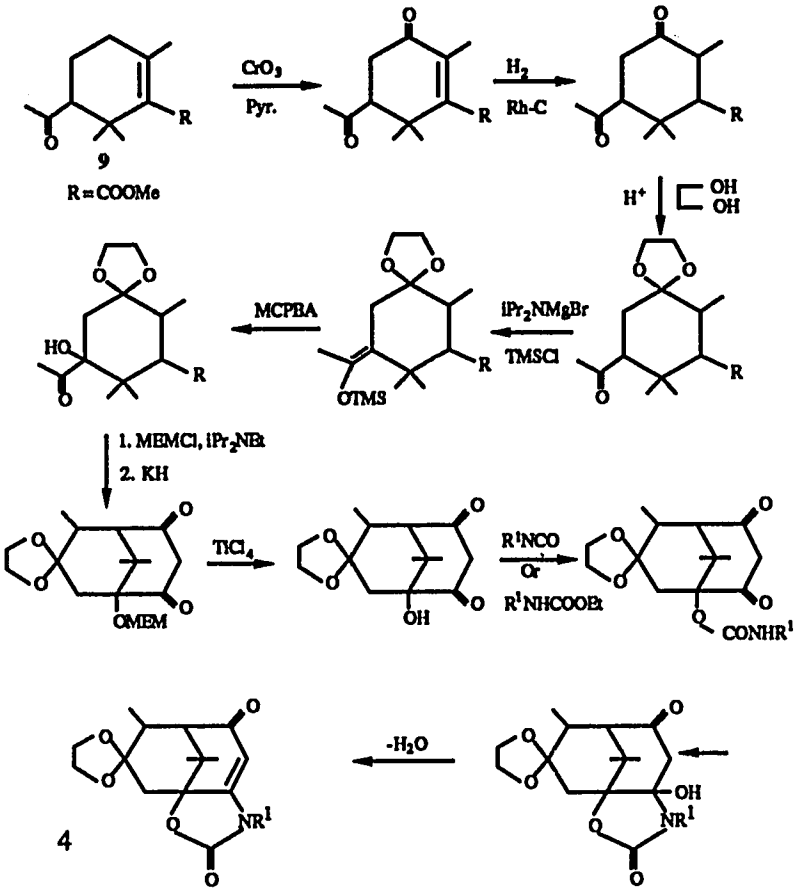
b. Cycloaddtion of an unsymmetrical alkene could give two products,

without considering stereochemistry, as shown in **scheme 5.** But the intramolecular photocycloadditions give primarily one product because they are governed by "the rule of five"[9]. This cyclic carbamate moiety acts as an anchor for intramolecular photocycloaddition of the cyclohexene component as seen in **scheme 3.**



SCHEME 5

The route we initially considered for the synthesis of **4** is shown below (**scheme 6**).



SCHEME 6

The following methods can be thought of as possibilities for making the important starting compound, **9**, of **scheme 6.**

1.Cyclization of geranyl derivatives and other related compounds followed by further modifications.

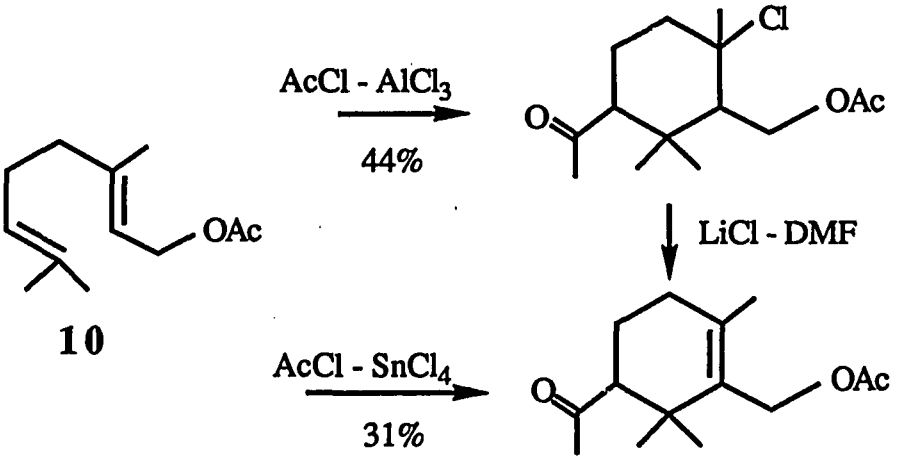
2. Modifications on α- ionone.

3. Acid catalyzed condensation reactions.

4. Robinson annulation reactions.

CYCLIZATION OF GERANYL DERIVATIVES AND OTHER RELATED COMPOUNDS :

A. Kitahara and coworkers[10] have reported a selective C-C bond formation of polyenes with concomitant ring closure. Geranyl acetate and it's analogues were used as polyenes and acetyl, crotonyl and 2,6-dimethyl-3-methoxybenzoyl chlorides as acylating agents. Selective acylation was found to have resulted in moderate yields when the polyenes were treated with $SnCl_4$ or $AlCl_3$ complexes of these acyl chlorides under ice cooling conditions, accompanied by ring closure in all but one case (**table 1**). Reaction of geranyl acetete (**1 0**) with acetyl chloride is shown in **scheme 7.**



SCHEME 7

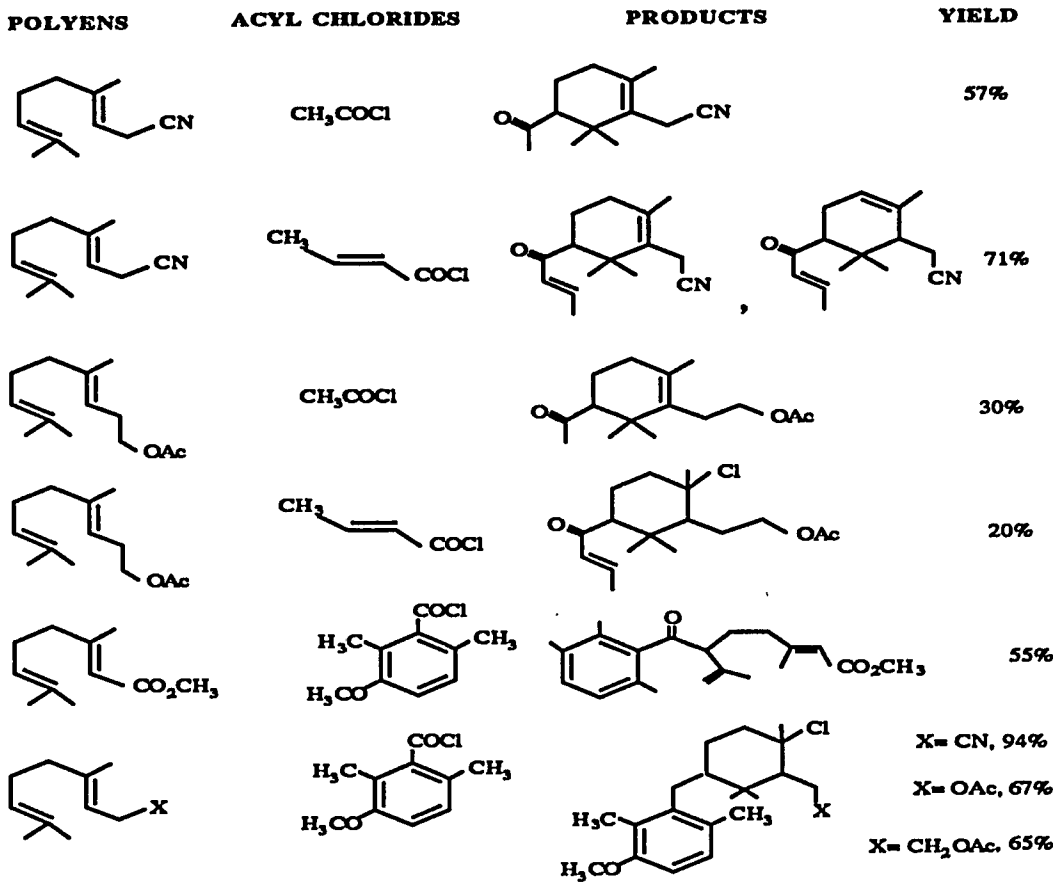
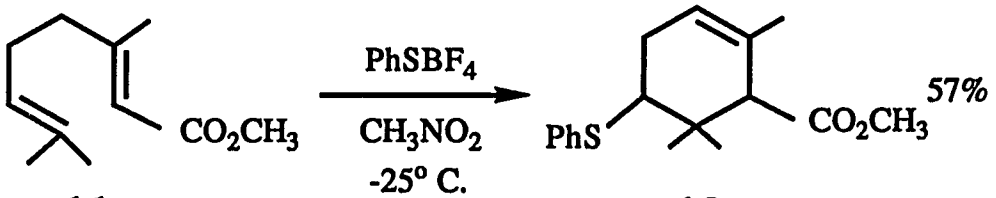


TABLE 1.

B. Geranic acid methyl ester (**11**) was shown to undergo cyclization, by Smit[11] and coworkers, with the cationoid complex, $PhSBF_4$, to give **12** (**scheme 8**).

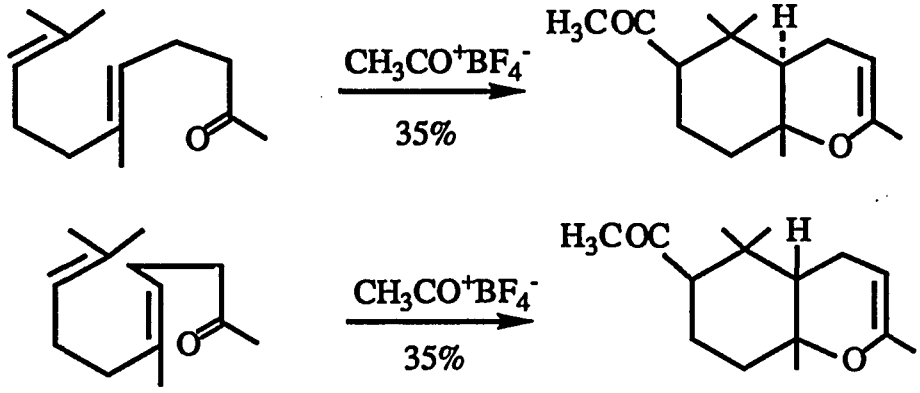


11 **12**

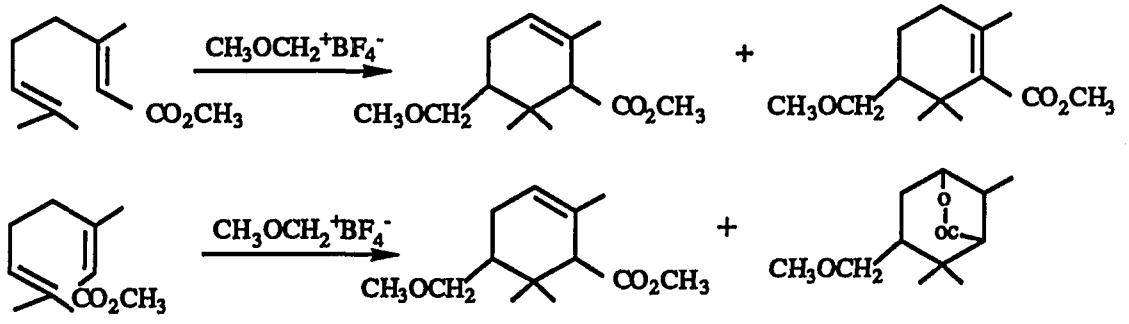
SCHEME 8

They avoided the usual polymerization by conducting the reaction at low temperature. The initial electrophilic attack on the terminal (2,3) double bond, by PhS^+, is followed by ring formation due to nucleophilic participation of the second (6,7) double bond.

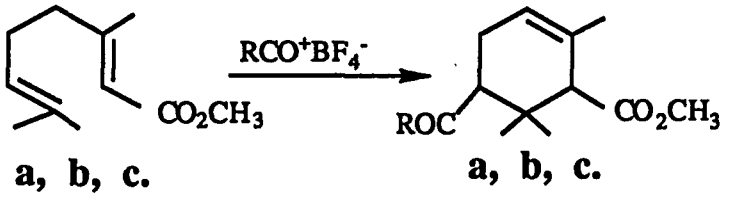
The following cyclizations have been reported by the same group of chemists (**schemes 9, 10 & 11**) :



SCHEME 9



SCHEME 10



a. R = CH_3CH_2- , 20-22 %

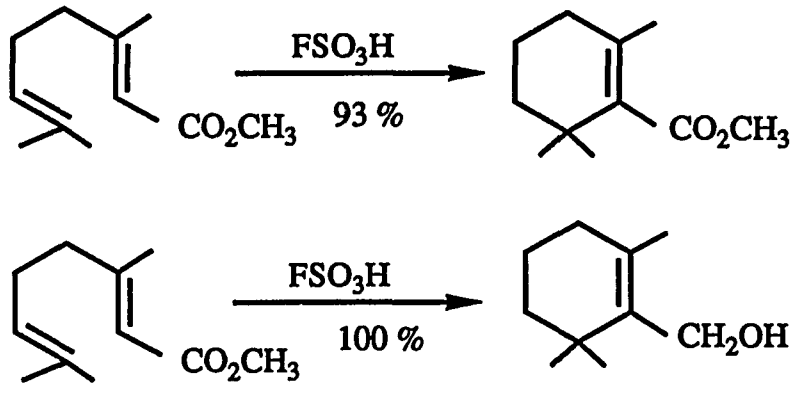
b. R = $(CH_3)_2CH$-, 32%

c. R = $(CH_3)_3CO$-, 56%

SCHEME 11

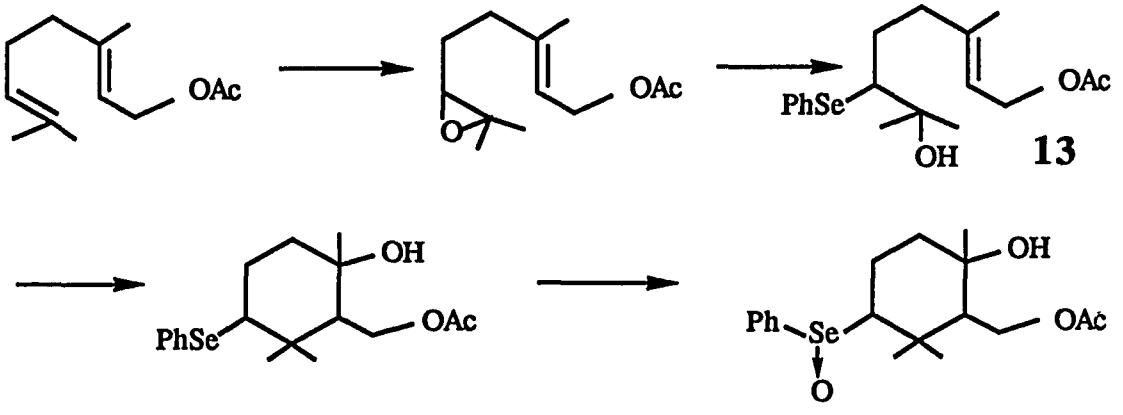
However in the case of **R = Acetyl** group they failed to observe any cyclization.

Also reported are the following cyclizations, by the same workers, in which there were no acylating reagents involved (**scheme 12**).



SCHEME 12

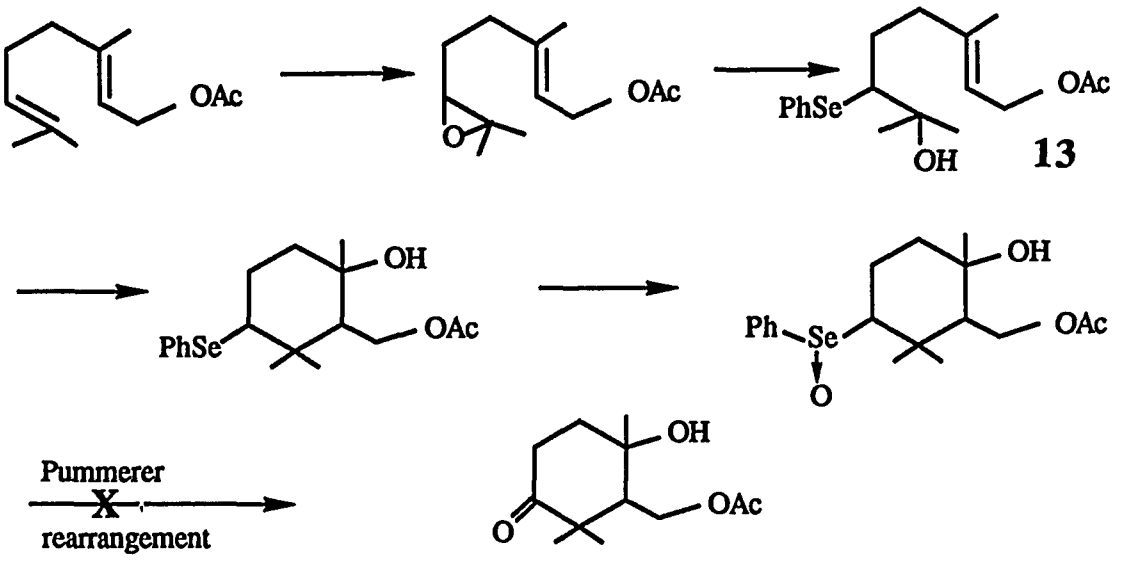
C. Kametani's[12] group in Japan conducted experiments on the cyclization of the olefinic β-hydroxy selenide (**13**) with the following result (**scheme 13**).



SCHEME 13

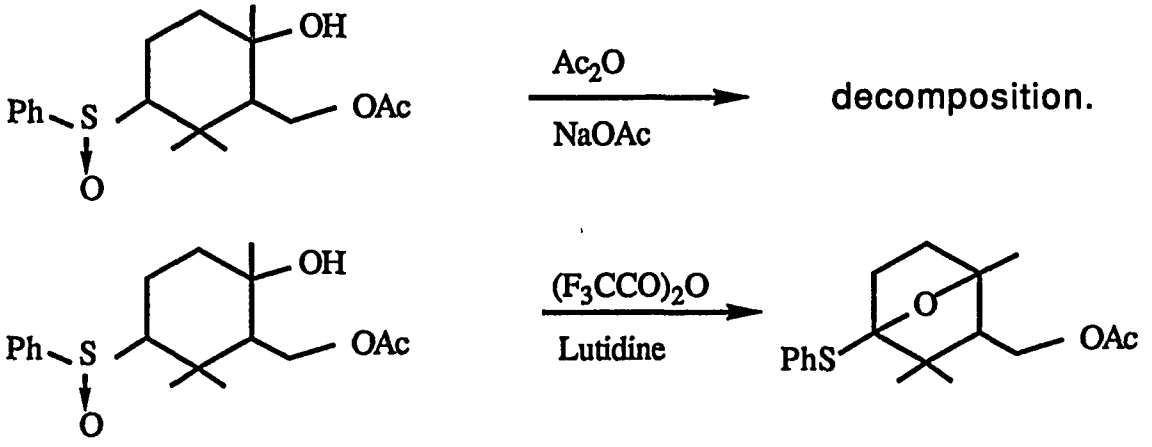
Kamani Subasinghe[13] worked on the above reaction in our laboratories

with the following result (**scheme 14**) :



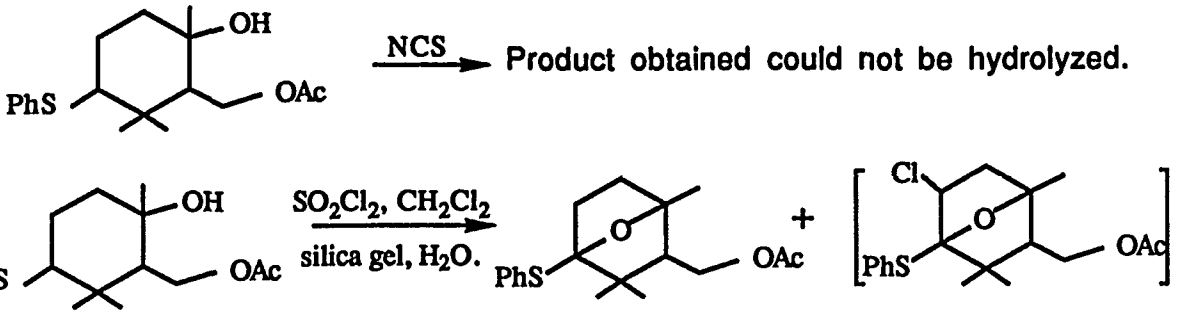
SCHEME 14

Since the Pummerer rearrangement of the selenoxide failed to produce the target cyclohexanone, the sulfoxide analog was prepared by similar route and Pummerer rearrangement was done on that (**scheme 15**).



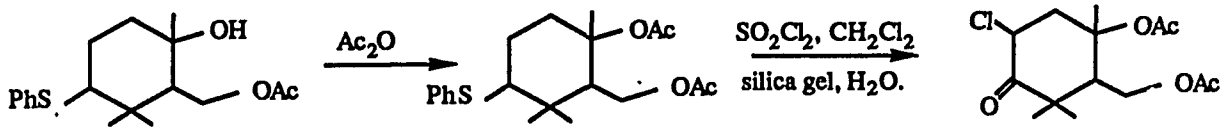
SCHEME 15

Because of the failure of the Pummerer to produce the required compound from both selenoxide and sulfoxide, an alternate route, chlorination and hydrolysis, was tried on the sulfide directly (**scheme 16**).



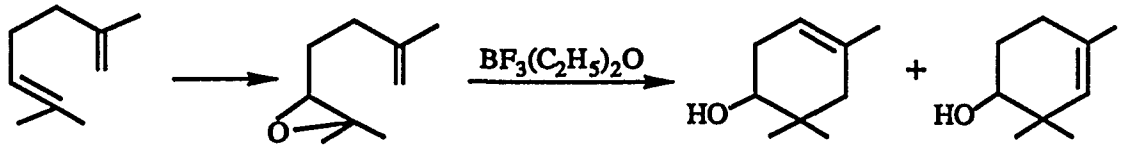
SCHEME 16

The free hydroxyl was then acetylated and the same reaction was repeated only to produce a chlorinated cyclohexanone (**scheme 17**).



SCHEME 17

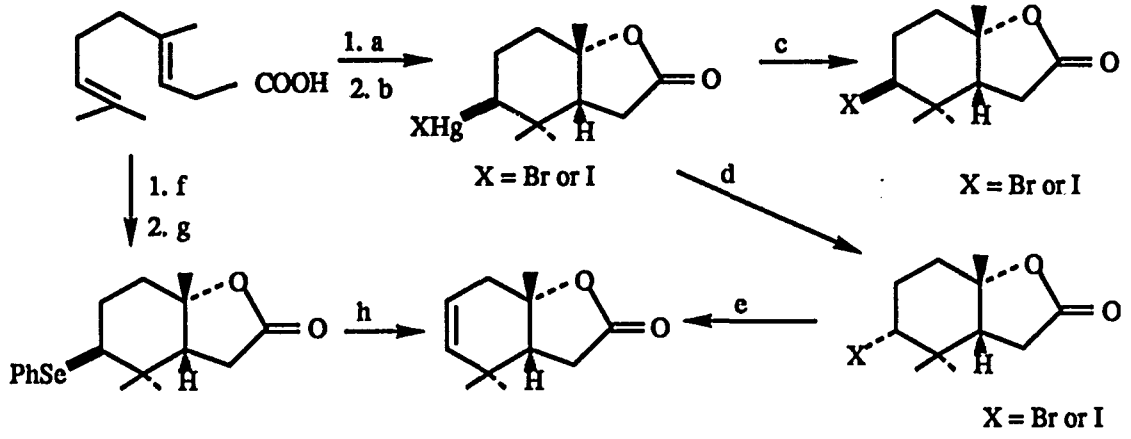
D. Some epoxyolefins undergo acid catalyzed cyclizations to give cyclic compounds. D. J. Goldsmith[14], in 1962, reported that geraniolene monoepoxide reacted in the following manner (**scheme 18**) when treated with boron trifluoride etherate.



SCHEME 18

However, geranyl acetate monoepoxide does not undergo cyclization with either boron trifluoride etherate or p-toluenesulfonic acid[15].

E. Mercuric ion has also been found to initialize cationic cyclization. Rouessac[16] reported the following reaction of homogeranic acid (**scheme 19**).



a = $(CF_3CO_2)Hg$ / NO_2Me / 20°C / 2 h. b = NaX / H_2O / 25°C / 24 h (X = Br or I).

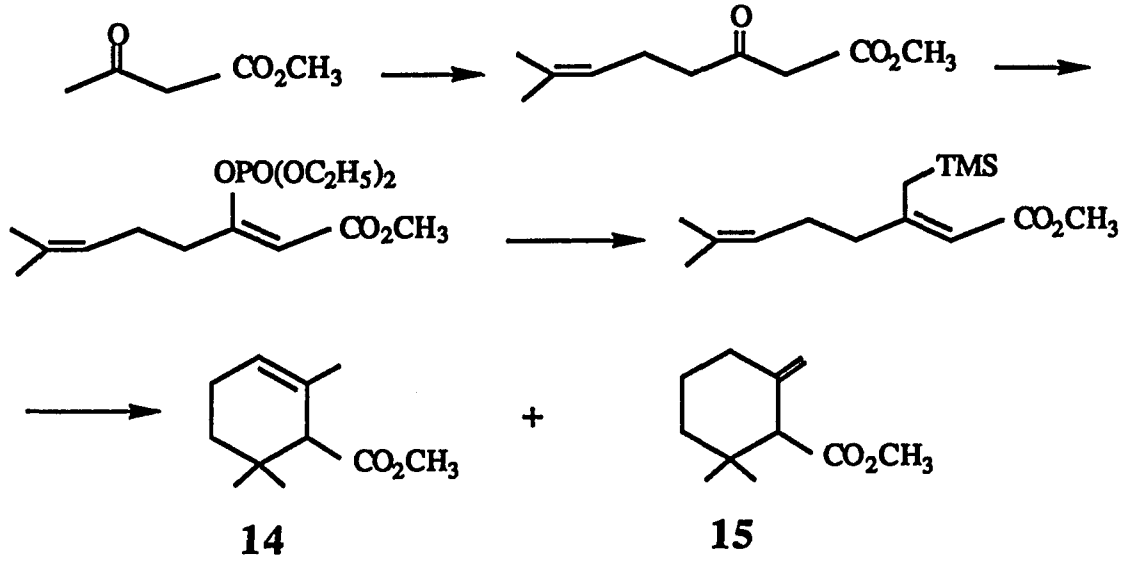
c = LiX_3 / dioxane / O_2 / 3 h. d = X_2 / Pyr / hn /TA /10 min. e = anhy. LiCl / DMF / 50°C / 3h

f = PhSeCl / CH_2Cl_2/ 0°C / 15 min. g = CF_3COOH / CH_2Cl_2 / 20°C / 5 min.

h = $NaIO_4$ / eau (1:1) / 25°C / 20 min.

SCHEME 19

F. Compound **14** and **15** were prepared by Weiler and Armstrong[16] starting from the dianion of methyl acetoacetate (**scheme 20**). However no arrangements were made to introduce an oxygen or a carbon substituent in the C-5 position of **14**.

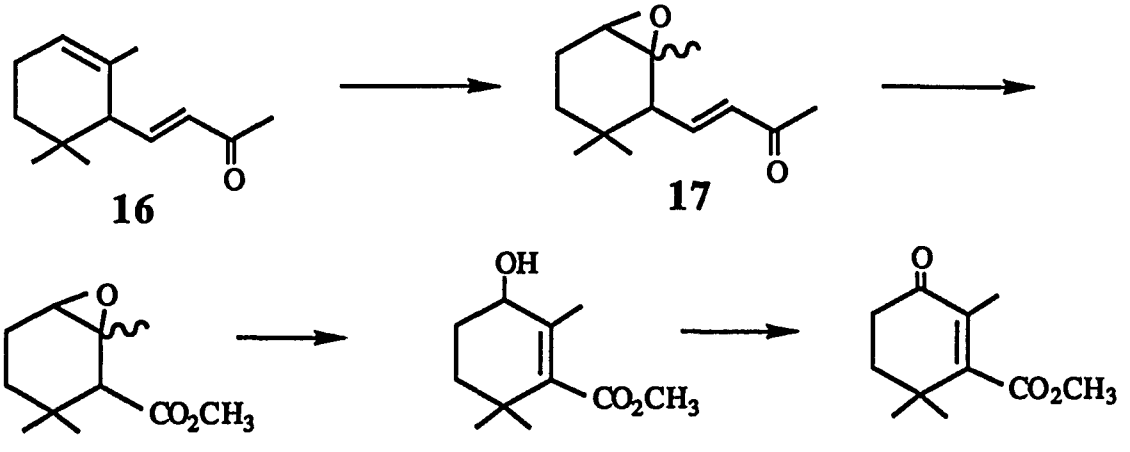


14 15

SCHEME 20

MODIFICATIONS ON α - IONONE.

A compound (**20**) close to our required starting material was synthesized by Brooks and Kennedy[17] starting from α- ionone (**16**) (**scheme 21**) in their studies toward the synthesis of strigol, a potent weed seed germination stimulant. The double bond cleavage was affected by periodate / permanganate oxidation.

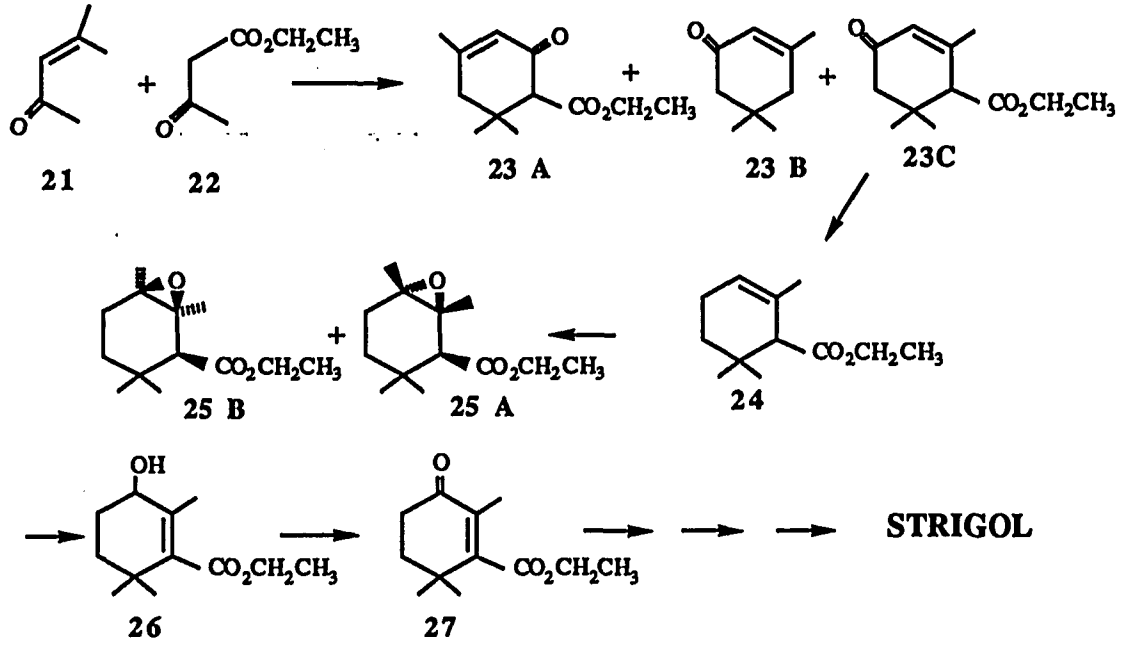


SCHEME 21

Wu and He[18] also prepared the allylic alcohol,19, starting with α-ionone, and using ozone to cleave the double bond.

ACID CATALYZED CONDENSATION REACTIONS :

Acid catalyzed condensation of mesityl oxide (21) and ethylacetoacetate (22) to give ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate (23) as one of the products was utilized by Dailey, Jr[19] on his way to the synthesis of strigol. Compound **23c** in turn was converted to the ethyl ester(24) of the cyclohexenone carboxylate (**scheme 22**).



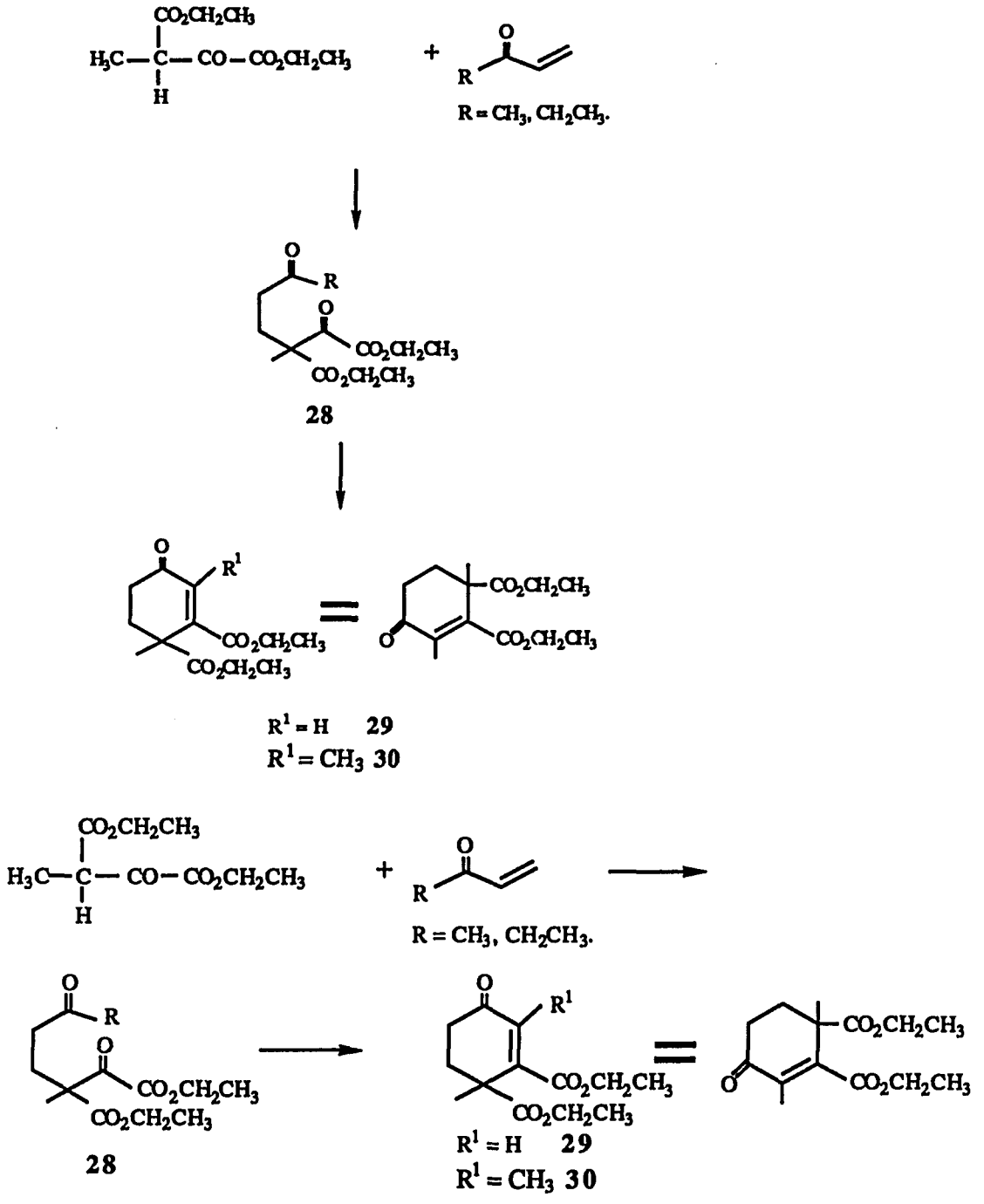
SCHEME 22

Again, however, no simple scheme is applicable to the installation of an appropriate carbon or oxygen function at C-5.

ROBINSON ANNULATION REACTION :

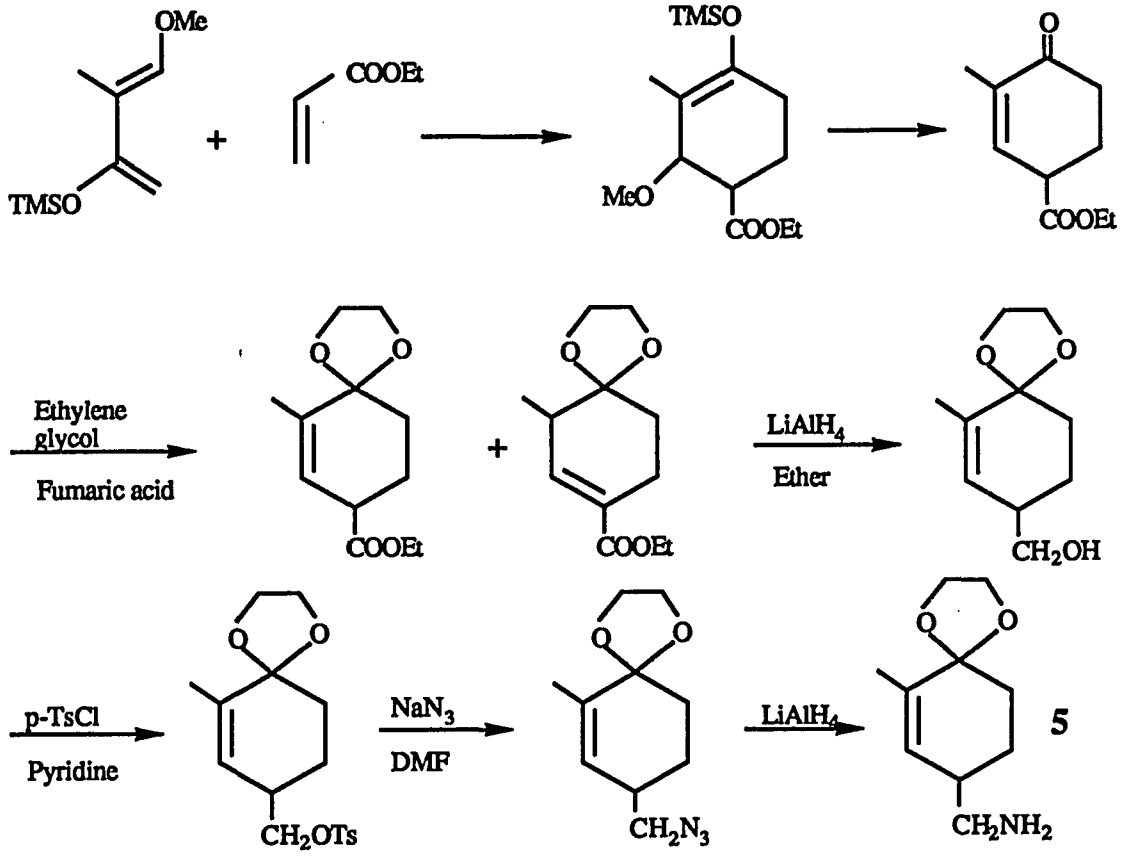
Michael addition between diethyl oxalylpropionate and methyl and ethyl

vinyl ketones followd by acid catalyzed cyclization to give cyclohexenones was reported by D. J. Goldsmith and J. A. Hartman[20] (**scheme 23**).



SCHEME 23.

Synthesis of compound **5** (**of scheme 4**) was pursued by Kamani Subasinghe[13], in our laboratories as shown below:

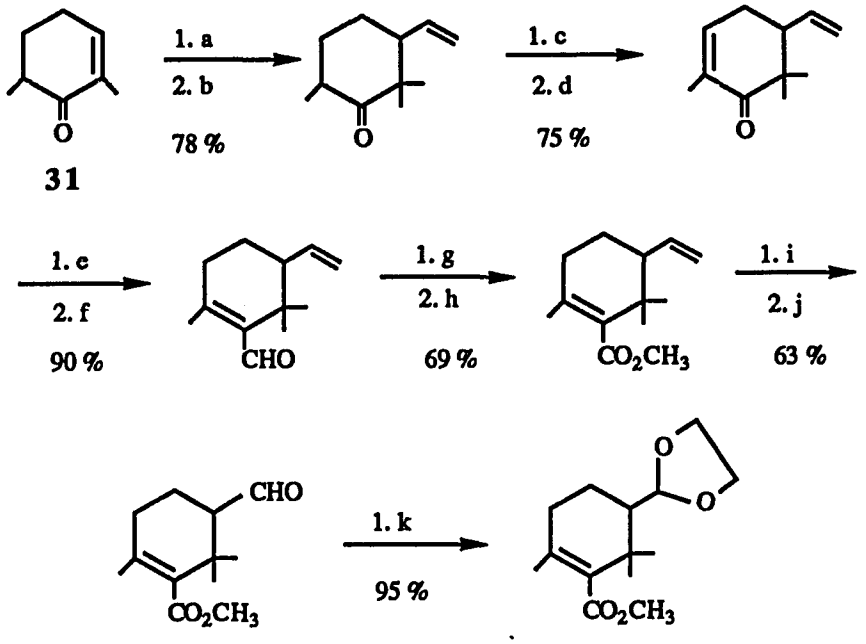


APPROACHES TO THE A-RING OF TAXOL IN LITERATURE:

As mentioned before, several research groups around the world are actively involved in the synthesis of taxol. Some of the routes followed by others in getting the A-ring of taxol are mentioned below.

KENDE and coworkers[21], enroute to the first total synthesis of a racemic taxane triene comprising the full and stereochemically correct carbon

framework of natural taxusin, synthesized the A-ring intermediate in the following fashion, starting from 2,6-dimethylcyclohexenone **31** (**scheme 24**).



a = vinyl magnesium bromide, CuI, ether, THF. b = MeI, HMPA. c = SO_2Cl_2, CCl_4

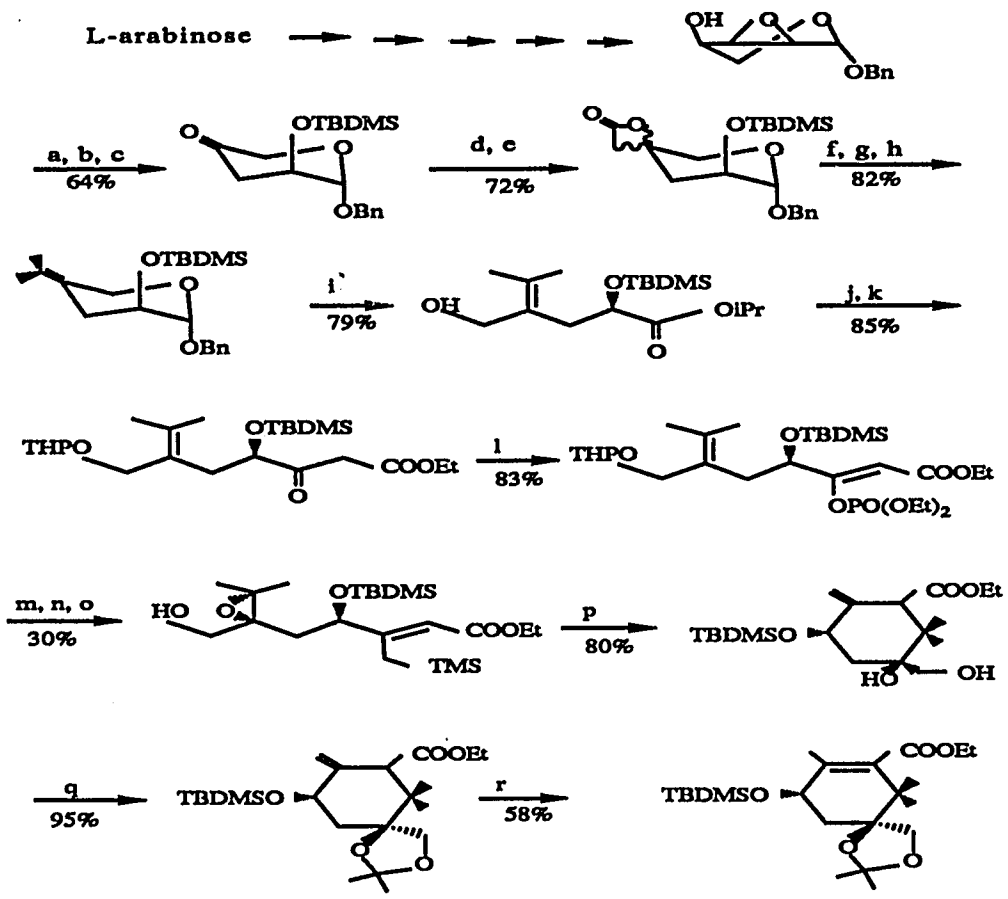
d = LiCl, $LiCO_3$, DMF. e = $Me_3Si\ CH_2Cl$, sec- BuLi. f = 90 % HCOOH.

g = $NaClO_2$, NH_2SO_3H. h = excess CH_2N_2. i = NMO, OsO_4, Me_2CO, H_2O.

j = $NaIO_4$, Me_2CO, H_2O. k = glycol, p-TsOH.

SCHEME 24

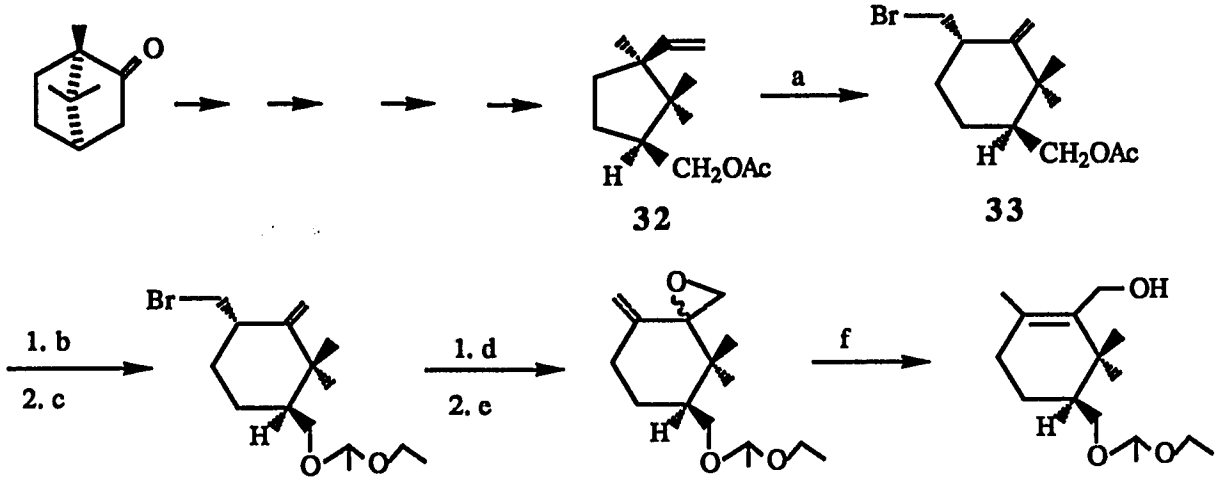
The optically active Taxol A-ring segment was synthesized by **Frejd** and coworkers[22] in the following manner (**SCHEME 25**).



a=DMSO,$(COCl)_2$, NEt_3; b=NaI, acetone, HOAc, NaOAc; c=TBDMS-Cl, imidazole; d=LDA, isobutyric acid; e=$PhSO_2Cl$, pyr; f=Pd-C, H_2, HOAc; g=PDC, Ac_2O, CH_2Cl_2; h=170°C; i=$Ti(OiPr)_4$; j=DHP, pyridinium tosylate; k=$(TMS)_2NLi$, TMEDA, EtOAc; l=KOtBU, $ClPO(OEt)_2$; m=$TMSCH_2MgCl$, 5% $Ni(acac)_2$; n=Pyridinium tosylate, iPrOH, 50°C; o=$Ti(OiPr)_4$, (-)-DET, TBHP, -25°C; p=$BF_3(OEt)_2$, CH_2Cl_2, 0°C, 15 min; q=BF_3OEt_2, acetone, CH_2Cl_2; r=DBU, 185°C, 1h.

SCHEME 25

Ring enlargement of a vinyl cyclopentane derivative **32** was the key step in the synthesis of a chiral 1,1,3-trimethylcyclohexane derivative **33** by **Kitagawa and coworkers[23] (scheme 26).**

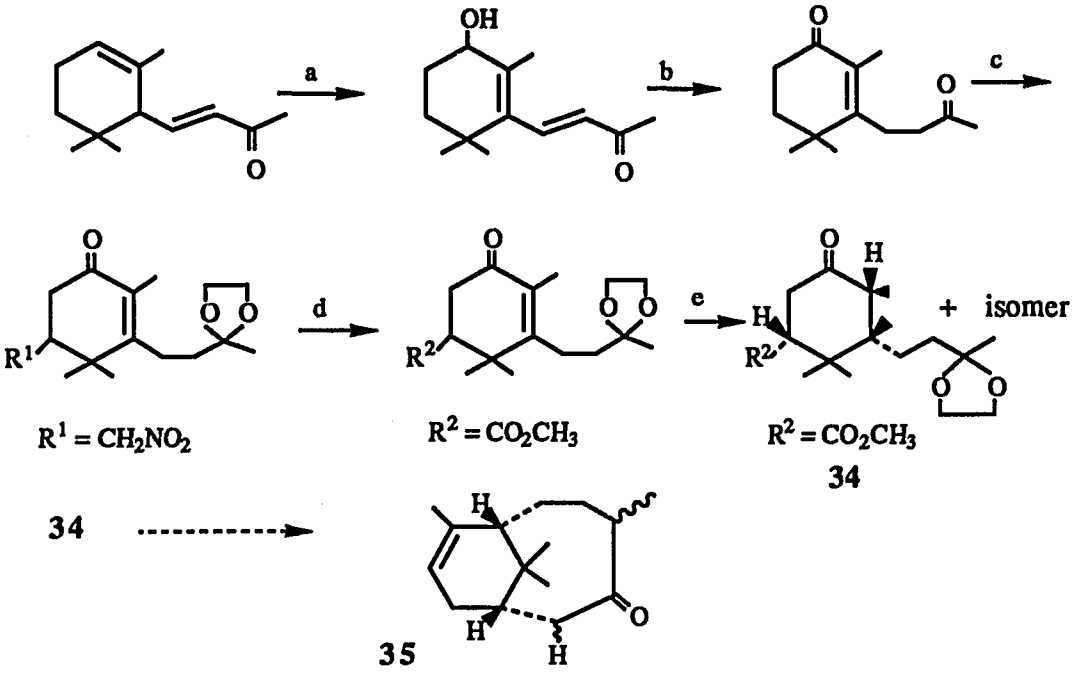


a = TBCO, Zn - AcOH. b = KOH - MeOH. c = ethyl vinyl ether, p - TsOH, H_2O.

d = m - CPBA, CH_2Cl_2. e = DBU. f = Na / liq. ammonia.

SCHEME 26

Enroute to the synthesis of bicyclo (5,3,1) undecenone **35** corresponding to A and B rings in taxane diterpenes **Ohtsuka and Oishi**[24] prepared the A-ring intermediate **34** starting from α-ionone (**scheme 27**).



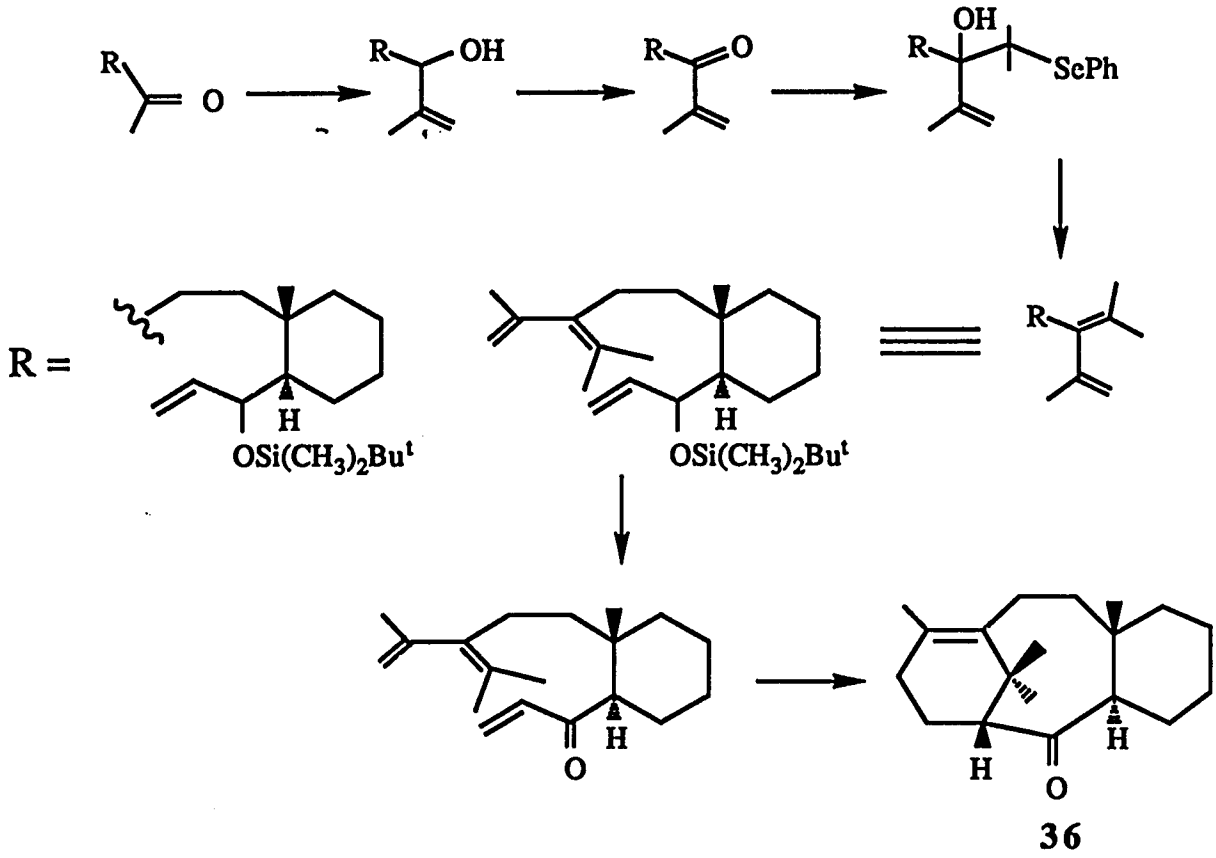
a = m-CPBA / CH_2Cl_2 ; K_2CO_3 / MeOH. b = NaTeH / EtOH ; Jone's reagent.

c = ethylene glycol / TsOH / benzene ; DDQ / benzene ; CH_3NO_2 / i-Pr_2NH / DMSO.

d = MeONa / $TiCl_3$ / $AcONH_4$ / aq. MeOH ; Jone's reagent ; Me_2SO_4 / K_2CO_3 ; ethylene glycol / TsOH / benzene. e = H_2 / Pd - c / AcOEt ; PCC / AcONa / CH_2Cl_2.

SCHEME 27

Formation of both A and B rings simultaneously involving acid catalyzed intramolecular Diels Alder reaction, to get a taxane model compound, 8,12,15,15-tetramethyl tricyclo(9.3.1.0)pentadecane **36** was reported by Jenkins and Bonnert[25] **(scheme 28).**



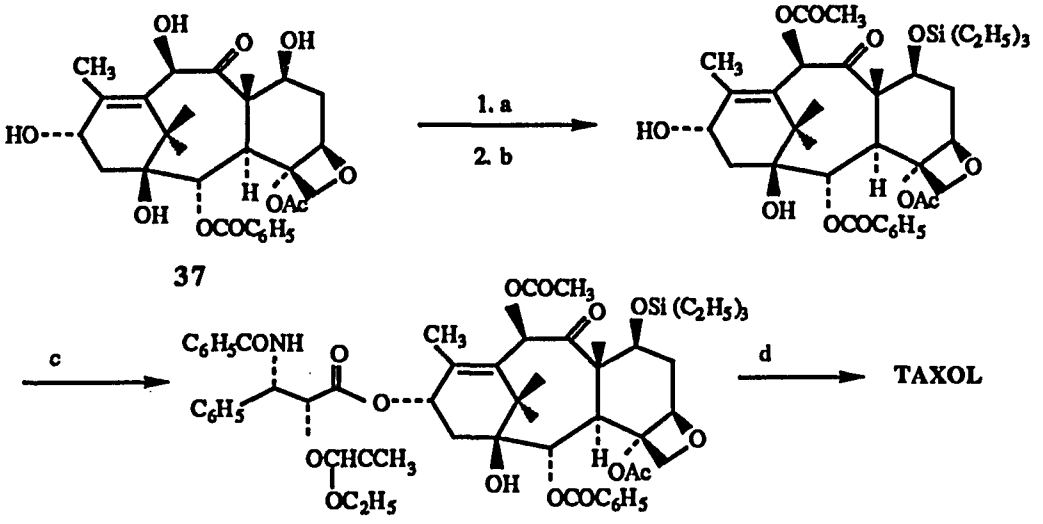
SCHEME 28

PARTIAL SYNTHESIS OF TAXOL :

An alternative approach to the total synthesis of taxol is brought into light by **Green and Voegelein's** group[26].

They reported an effecient partial synthesis of taxol from 10-deacetyl baccatin III **37** which can be readily extracted in high yields from the leaves of

Taxus baccata L[27](**scheme 29**). The side chain amino acid moiety was synthesized starting from phenyl acetylene[28].



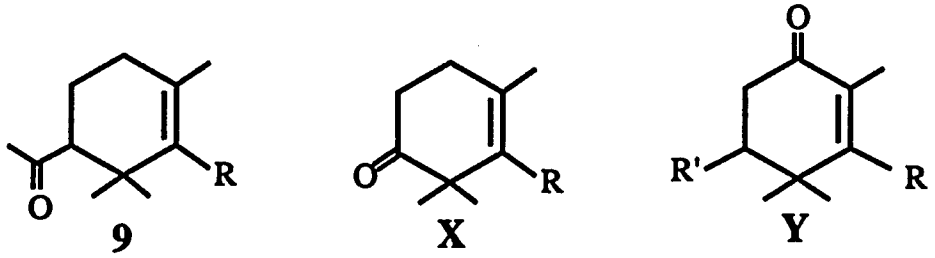
a = $(C_2H_5)_3SiCl$, Pyr. b = CH_3COCl, Pyr. c = (2R, 3S) - N - benzoyl - O - (1-ethoxyethyl) - 3 - phenyl - isoserine, DPC, DMAP, toluene. d = HCl, C_2H_5OH - H_2O.

SCHEME 29

CHAPTER . 2

RESULTS AND DISCUSSION

The target of this work is compound **9** (**scheme 6 , chapter 1**) or a closely related synthon such as **X** or **Y**.



where R = CH_2OAc, $COOC_2H_5$ or $COOCH_3$ and R'= $COOCH_3$ or $COOC_2H_5$

In the previous chapter, routes involving four possible methods of making the above compounds were discussed. However many of them did not result in placing either an oxygen or a carbon functional group at C-5.

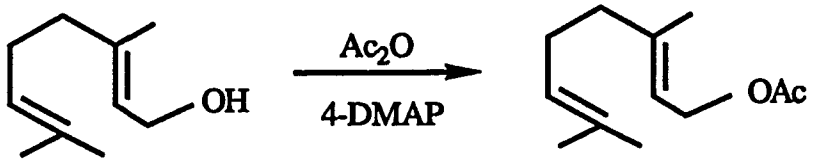
Here, the results of our work in several related categories will be presented. The categories are,

1. Cyclization of geranyl derivatives and other related compounds.
2. Modifications on α–ionone.
3. Acid catalyzed condensation reactions.
4. Robinson annulation reactions.

Cyclization of geranyl derivatives and other related compounds:

We were very attracted by Kitahara's method of Lewis acid catalyzed

cyclization of geranyl acetate **10** and other compounds (**scheme 7, table 1**). They reported a single step conversion of geranyl acetate to synthon 9(R=CH_2OAc) using stannic chloride as Lewis acid[10]. To try out the reaction geranyl acetate **10** was prepared, in quantitative yields, from geraniol using acetic anhydride as the acetylating agent and 4-DMAP (dimethylaminopyridine) as a catalyst (**scheme 30**)[29].



10

SCHEME 30

In our hands cyclization under conditions reported invariably yielded a polymer. The following variations were investigated :

The amount of solvent used was increased three fold and the reaction was repeated only to get the polymer again. NMR of these polymeric products did not show the characteristic -CO-CH_3 absorption in the region δ = 1.9 - 2.4.The two step procedure using $AlCl_3$, which was also done by Kitahara's group[10] was tried. Here too we got a tarry polymeric mixture. Cyclization using $SnCl_4$ was done at -25^oC to see if the reaction would proceed in the desired fashion at lower temperarures, however, the cyclic compound expected was not obtained under this condition either. $AlCl_3$ catalyzed reaction stirred at -78^oC for 1hour and then at -20^oC for 15 minutes also failed to give the required product.

Cyclization using stabilized carbonium ions :

Since the cyclizations using acetylium ion did not give us the required product we thought of using a stabilized carbonium ion which could later be converted to the required functional group.

We chose 1-(phenylthio)-1-chloroethane for this purpose. The carbonium ion **38** is stabilized by the adjacent phenyl thio group.

$$\underset{\mathbf{40}}{Ph\text{-}S\text{-}CHCl\text{-}CH_3} \longrightarrow \underset{\mathbf{38}}{Ph\text{-}S\text{-}C^{+}H\text{-}CH_3} \rightleftharpoons Ph\text{-}S^{+}{=}CH\text{-}CH_3$$

Ethyl phenyl sulfide **39** was prepared starting from thiophenol and bromoethane (**scheme 31**).

$$C_2H_5Br + PhSH \xrightarrow[EtOH]{Na} \underset{\mathbf{39}}{PhSC_2H_5}$$

SCHEME 31

$PhSC_2H_5$ (**39**) :

yield = 85%, NMR (δ) = 7.3 (m) aromatic protons; 2.9 (q) S-C**H**$_2$-C**H**$_3$; 1.3 (t) S-C**H**$_2$-C**H**$_3$.

Chlorination of ethyl phenyl sulfide **39** was achieved as reported by I. Fleming[30] using NCS in carbon tetrachloride (**scheme 32**).

$$PhSC_2H_5 \xrightarrow[CCl_4]{NCS} \underset{\mathbf{40}}{PhSCHClCH_3}$$

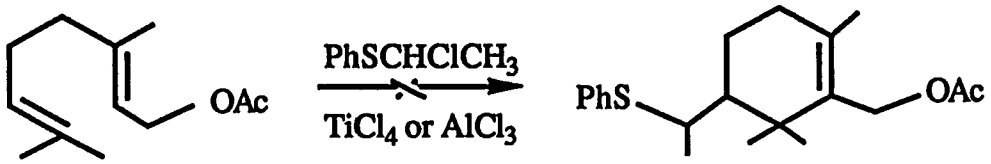
SCHEME 32

Yield = 90%

NMR (δ) = 7.35 (m) aromatic protons; 5.4 (q) S-C**H**Cl-C**H**$_3$; 1.9 (d) C**H**$_3$.

Cyclization reactions of geranyl acetate using 1-(phenylthio)-1-

chloroethane **40** and $AlCl_3$ or $TiCl_4$ also failed to produce the expected cyclic compound **41**. This conclusion was drawn from the fact that the proton NMR's of the product and geranyl acetate were the same.

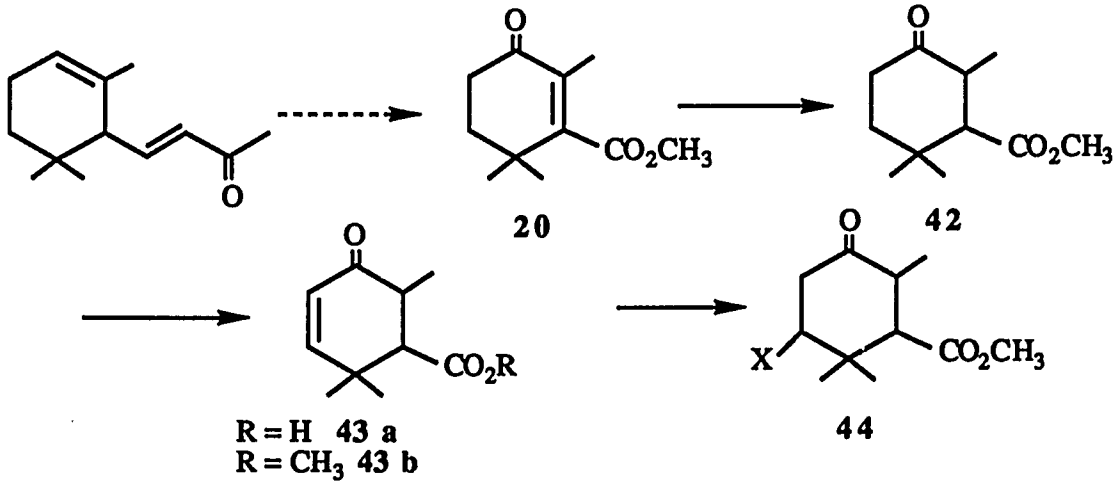


SCHEME 33 **41**

Similar observations were made by Smit and coworkers[11] with the methyl ester of geranic acid.

Modifications on α-ionone:

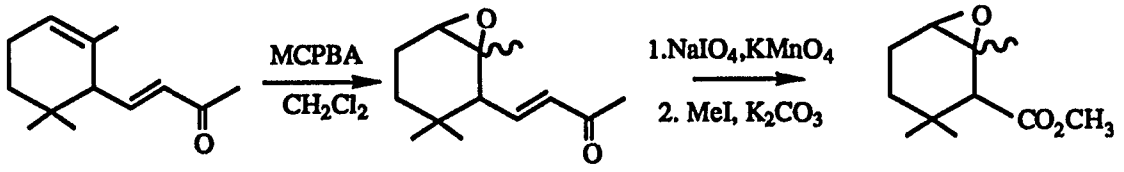
Our initial plan was to make the cyclohexenone ester **20** using known procedures[17], and proceed from there to a C-5 functionalized compound **44** as follows (**scheme 34**):



SCHEME 34

Epoxide **18** was prepared starting from α-ionone[17] as described in

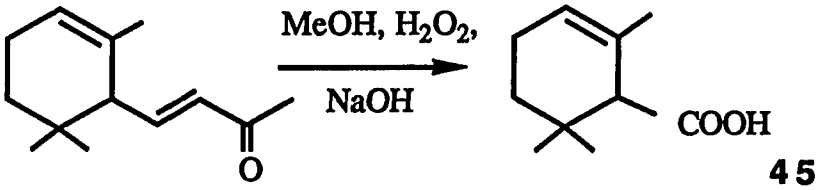
chapter 1.



17 **18**

Yields and spectral data were similar to the literature values. Since large amounts of solvents are used in the enone cleavage step, using the published procedures, it is inconvenient to work with larger amounts of the epoxide. Thus we were led to look for methods of cleaving conjugated double bonds specifically.

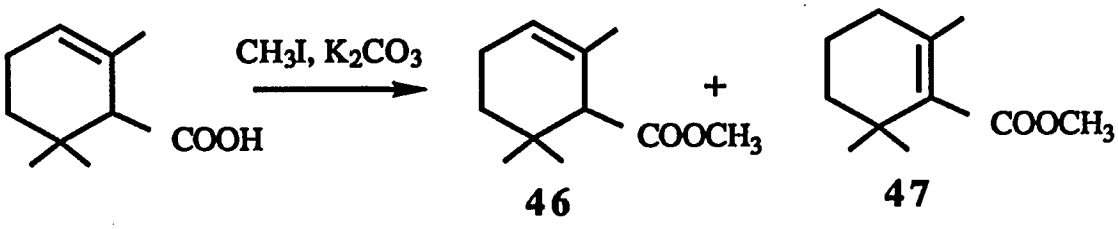
Epoxidation and cleavage of double bonds in α,β-unsaturated ketones was accomplished by Temple[31] using alkaline hydrogen peroxide. When subjected to similar conditions α–ionone gave the acid **45** in 83 % yield **(scheme 35)**.



45

SCHEME 35

This acid **45** was esterified using methyl iodide and potassium carbonate as was done by Brooks[17] **(scheme 21)**. Two ester isomers, a conjugated **47** and an unconjugated **46** were obtained (91% total yield), and were separated partly by fractional distillation **(scheme 36)**.

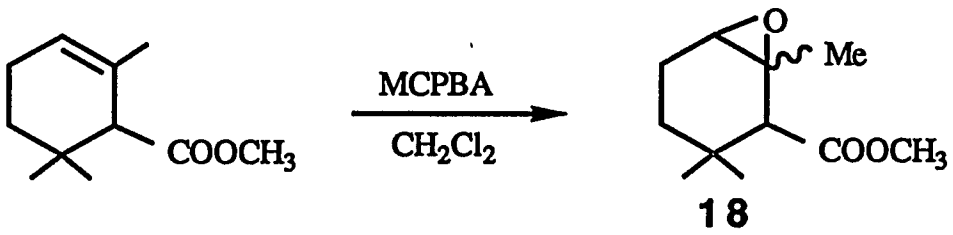


46 47

SCHEME 46

The fraction enriched in **46** was further purified by gas chromatography for identification. NMR of **46** gave the following peaks. δ = 5.6 (br) olefinic proton, 3.7 (s) COO**C**H_3, 1.6 (s) -CH=C-**C**H_3, 0.9 (s) gem dimethyl group. IR showed a strong absorption at 1730 cm^{-1}, which corresponds to the unconjugated ester group (elemental analysis: found C-70.87, H-9.81 and calculated C-71.39, H-9.81).

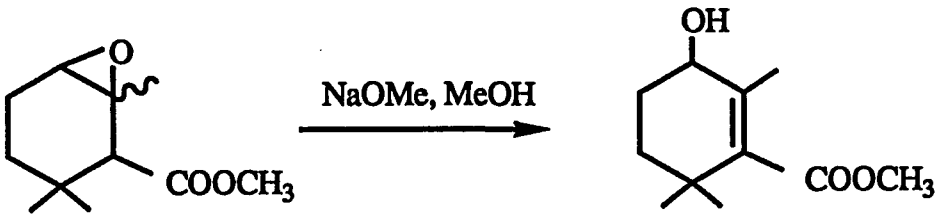
A mixture of epimeric epoxides **18** was obtained by oxidation of the fraction enriched in the unconjugated ester **46** (obtained by distillation) with m-chloroperoxybenzoic acid. Spectral data of **18** were similar to those reported in literature[17], which however was synthesized by a different route.



18

SCHEME 37

Conversion of **18** to the allylic alcohol **19** was accomplished by Brook's[17] procedure using NaOMe.



18 **19**

SCHEME 38

As noted in **scheme 36** esterification of acid **45** gave a mixture of esters **46** and **47**. Since only one of these two isomers can be used for further conversion to the epoxide, we tried to see if only one isomer could be obtained by treating the mixture with acid. The product however remained a mixture of two isomers. Base catalyzed isomerization also gave no enrichment.

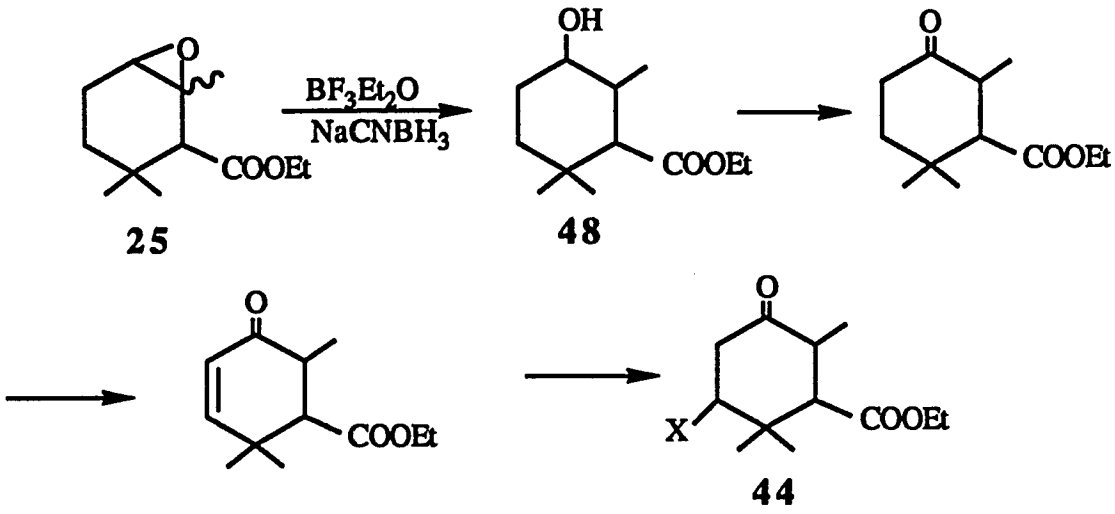
This made us reevaluate our plan of action and consider other ways of getting the required synthon such as acid catalyzed condensation reactions.

Acid catalyzed condensation reactions

Acid catalyzed condensation of mesityl oxide and ethyl acetoacetate gives the following three compounds, **23a**, **23b** and **23c** as was shown by Dailey, Jr[19]. He went on to convert **23c** to cyclohexenone carboxylate **27** as was shown in **scheme 22**.

Double bond transposition and Michael addition as in **scheme 34** (above) should afford the desired intermediate **44**.

Alternatively, to make the synthesis of **44** more efficient than the one presented in **scheme 34**, we attempted to obtain the saturated alcohol **48** directly from epoxides **25**, by reductive opening, as shown in **scheme 39** below. The epoxide mixture **25a** and **25b** was prepared using Dailey's sequence, in 59% yield.

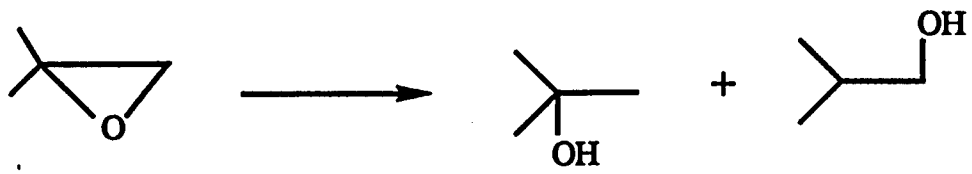


SCHEME 39

Reductive opening of epoxide

Reductive opening of the epoxides to alcohols has been accomplished with a variety of reducing agents[32]. Catalytic hydrogenolysis[33] was a common method in earlier days, but deoxygenation is a common side reaction. Metal hydrides, in particular LAH, are now widely used [34]. With unsymmetrical epoxides the regiochemistry of the reduction results from addition of H^- to the least hindered side, giving the more substituted stable alcohol. However, when mixed hydride reagents (Lewis acid mixed with a metal hydride) are used, a higher percentage of the less substituted alcohol is formed[35].

The following reaction of isobutylene oxide illustrates the above generality[36] **(scheme 40)**.



REAGENT			YIELD
LAH	95 - 98	5 - 2	26%
LAH + $AlCl_3$ (25 : 1)	7 - 5	93 - 95	55%

SCHEME 40

The following results were obtained by Hutchins and coworkers[37] using cyanoborohydride and boron trifluoride etherate: 1-methylcyclohexene epoxide gave 2-methylcyclohexanol and 1-methylcyclohexanol in the ratio 97:3. The overall yield was 87%. Similarly the epoxide of 2-methyl undecene gave 2-methyl-1-undecanol and 2-methyl-2-undecanol in the ratio 95:5, overall yield being 73%. In both the cases, the product ratio was determined by GC.

Based on their results we expected to obtain the desired alcohol **48** from epoxides **25a** and **25b**. However to our disappointment, compound **25** did not undergo reductive opening when treated with boron trifluoride etherate and sodium cyanoborohydride under the conditions reported.

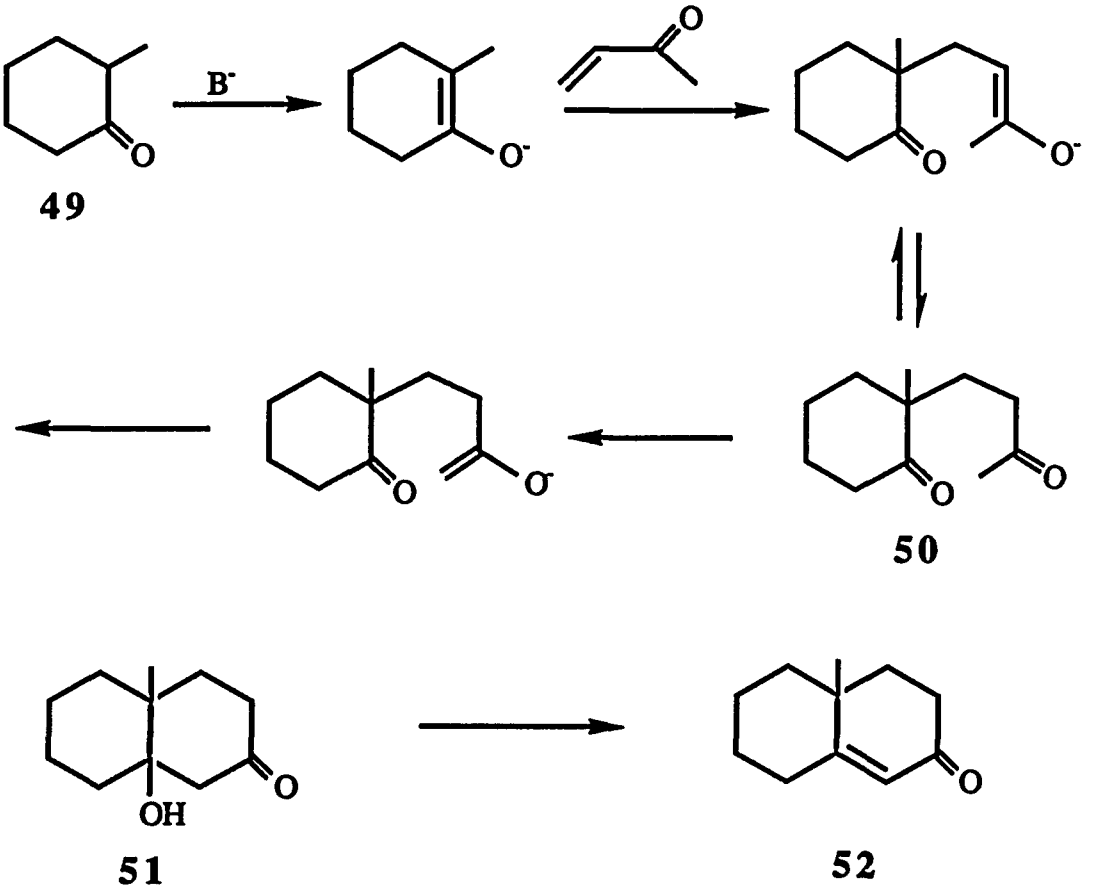
A second attempt was based on the fact that aromatic and cyclopropyl ketones undergo reduction to hydrocarbons by the action of silanes and trifluoroacetic acid[38]. Protonation of the epoxide should afford a tertiary cation which might be reduced by the silane, but this too proved to be futile.

Epoxide **25** can be opened to allylic alcohol **26** and then oxidized to the enone **27**. However since we obtained a mixture of isomers in the first step

(reported above) and failed to convert the epoxide to alcohol **48**, we considered this route synthetically inefficient.

Robinson annulation

Annulation methods (formation of rings) are invaluable to a synthetic organic chemist in the synthesis of complex natural products like steroids, terpenes and alkaloids. Among these, formation of cyclohexenone systems is especially useful. Annulation reagents can be divided into mono-annulation reagents and those which result in several ring segments being added at once. Robinson annulation[39] is a classic example of monoannulation, which involves the base-catalyzed Michael addition[40] of a ketone such as **49** followed by base or acid catalyzed aldol condensation.

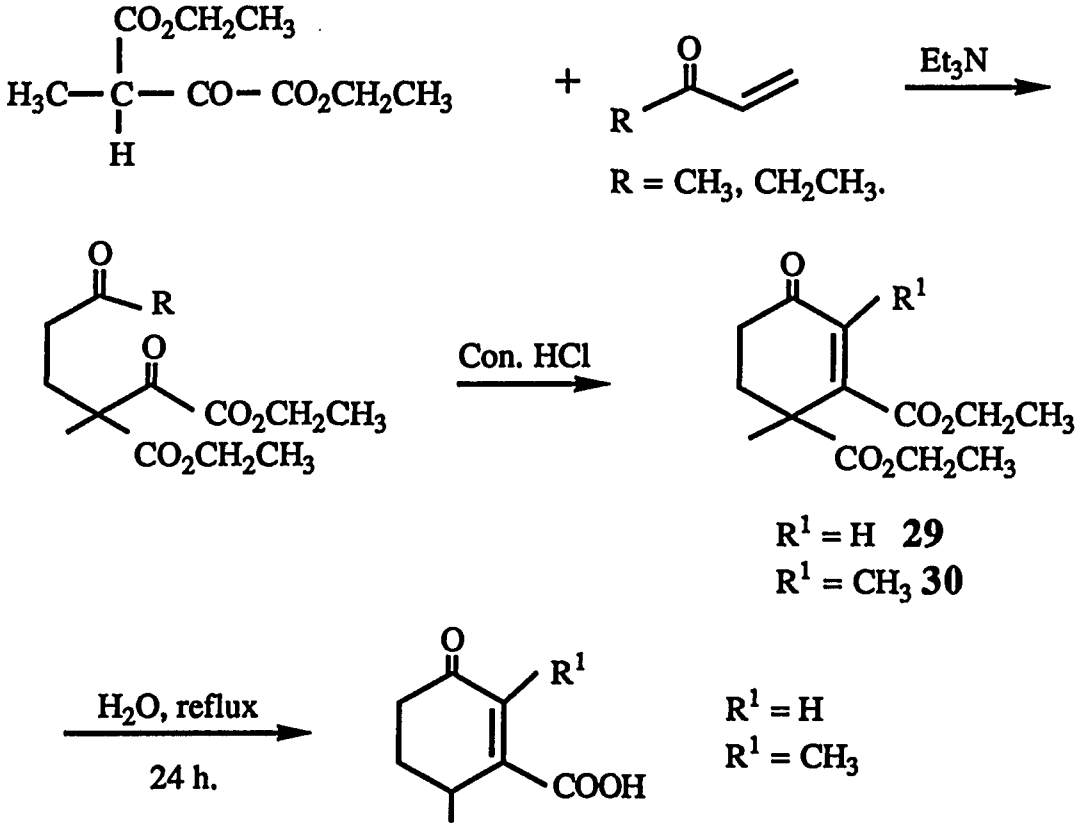


49 **50** **51** **52**

SCHEME 41

By proper adjustment of conditions, the reaction can be used to produce any one of the three possible products, namely the diketone **50**, the ketol **51**, or the enone **52**. Either acid or base treatment converts both the diketone **50** and the ketol **51** into the enone **52**. Robinson annulation gives good yields with acidic compounds such as β–dicarbonyl compounds or β-keto esters.

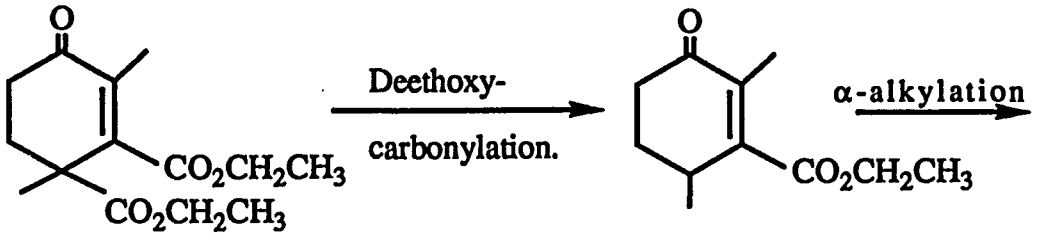
Michael addition between diethyl oxalpropionate[20] and methyl or ethyl vinyl ketone followed by acid catalyzed cyclization gave the cyclohexenone diesters **29** and **30** as was seen chapter I (**scheme 23**).

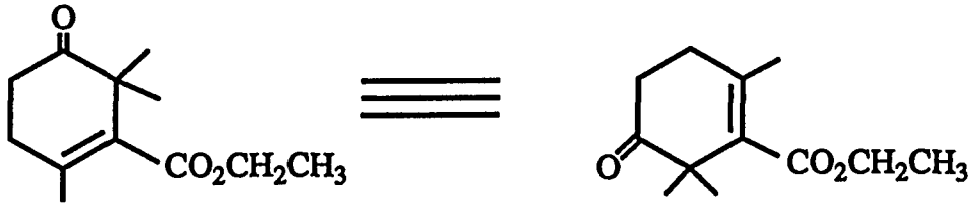


SCHEME 23

Triethylamine was used as a catalyst for Michael addition, and the aldol

condensations of the Michael adducts to cyclohexenone diesters **29** and **30** were accomplished using concentrated hydrochloric acid at room temperature[20]. Following this we planned to decarboxylate the vinylogous β-keto ester and alkylate the resulting enone to give the desired gem-dimethyl target **53** (**scheme 42**).



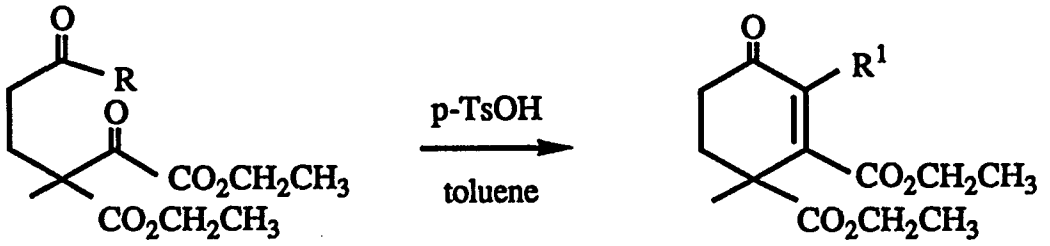


53

SCHEME 42

Aldol condensation

Modification of the harsh cyclization conditions (con. HCl) was of some concern. Accordingly, the Michael adduct **28b** was refluxed in toluene in presence of catalytic amounts of p-toluenesulfonic acid. The product thus obtained had the same spectral (NMR and IR) properties as that of **30**. GC / MS analysis gave the mass of the compound as 266, which confirmed that the Michael adduct had undergone cyclization to give the product **30**. The yield of this reaction was also raised to 85% from 26.5 % during the process.



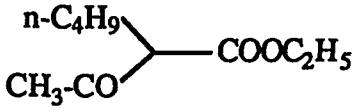
R = CH_3 **28a**
R = C_2H_5 **28b**

R^1 = H **29**, 83 %
R^1 = CH_3 **30**, 85 %

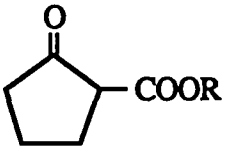
Dealkoxycarboxylation

A. Diethyl diesters

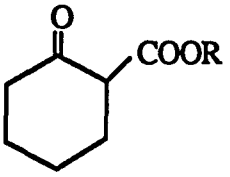
Dealkoxycarbonylation of β-keto esters is well studied[41]. Krapcho reported that β–keto esters undergo dealkoxycarboxylation on being heated in wet DMSO containing sodium chloride to yield the respective ketones in excellent yields, for example **54**, **55** and **56**. Those with no α hydrogens such as **57** and **58** also undergo similar reaction[41] (in particular, those with no α hydrogens require the presence of an added salt).



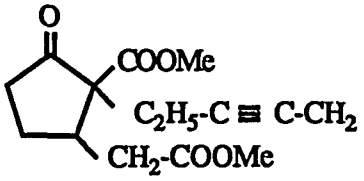
54



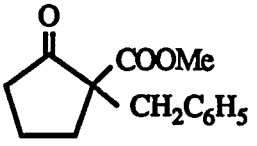
55



56



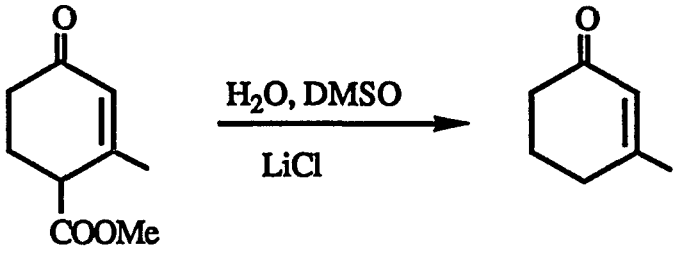
57



58

Similarly in the review article on decarboxylations by Krapcho[41] there is

a mention of the unpublished results of D. A. Seidman at the University of Vermont. Hagemann's ester **59** was demethoxycarbonylated with LiCl in wet DMSO to 3-methyl-2-cyclohexenone **60(scheme 44)**.



59 **60**

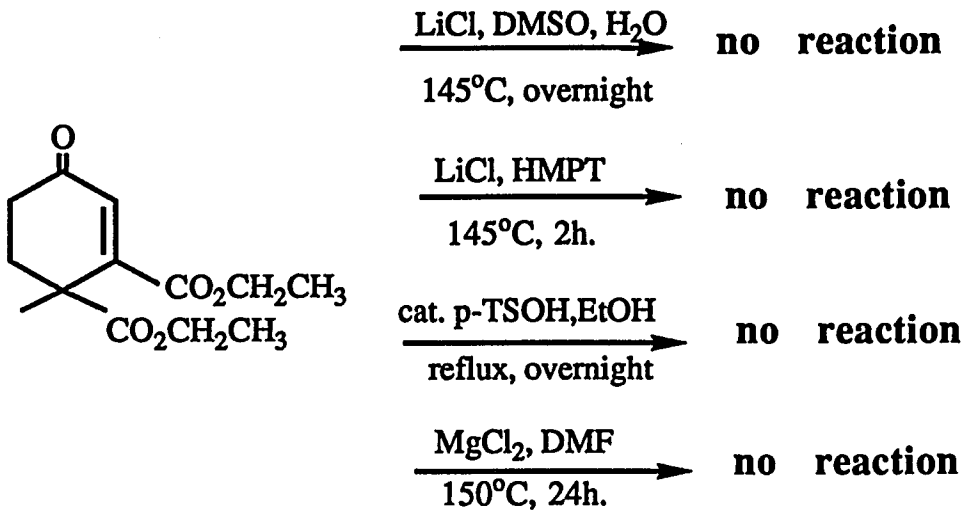
SCHEME 44

Since diethyl diester **30** is a vinylogous β-keto ester with no α hydrogens, we heated this at 140°C overnight in wet DMSO with sodium chloride as the added salt. However no deethoxycarbonylation took place; nor when sodium chloride was replaced by lithium chloride. In fact a series of similar decarbethoxylation conditions in which temperature, time and solvent were varied all failed (by comparison of NMR and IR of the starting material and the product isolated). The reactions done are the following :

Salt	Temperature	Time	Solvent	Result
NaCl	reflux	overnight	wet DMSO	no decarboxylation
LiCl	150°C	3h	wet DMSO	no decarboxylation
LiCl	reflux	5h	wet DMSO	no decarboxylatin
LiCl	reflux	overnight	wet DMF	no decarboxylation
LiCl	reflux	overnight	wet DMSO	no decarboxylation
NaI	162°C	overnight	wet DMF	no decarboxylation
$MgCl_2$	reflux	overnight	wet DMF	no decarboxylation

LiI	200°C	overnight	2,4,6-collidine	acid was formed
NaCN	120°C	4h	HMPA	no decarboxylation
NaOEt	reflux	overnight	EtOH	no decarboxylation

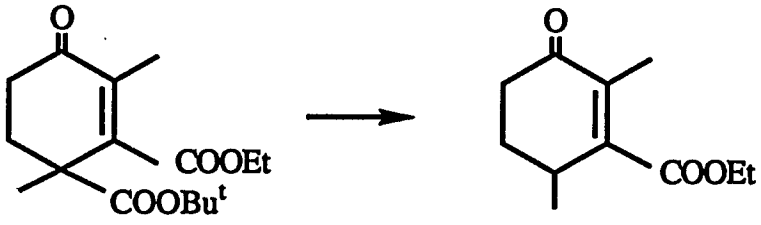
The following decarboxylation reactions on the ketoester **29** (R = H) were also not successful (**scheme 45**).



SCHEME 45

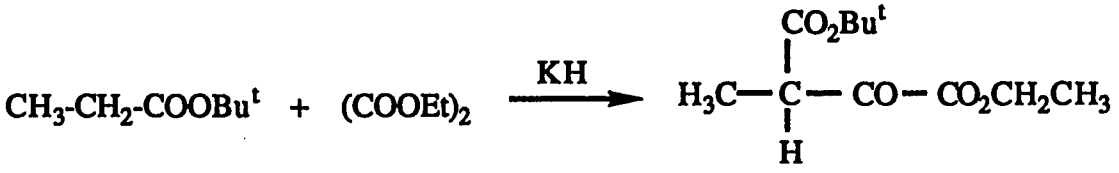
B. Ethyl, t-butyl esters

In order to facilitate decarboxylation, we attempted to differentiate the two ester functions; In particular, to install a t-butyl ester as the group to be lost.



SCHEME 46

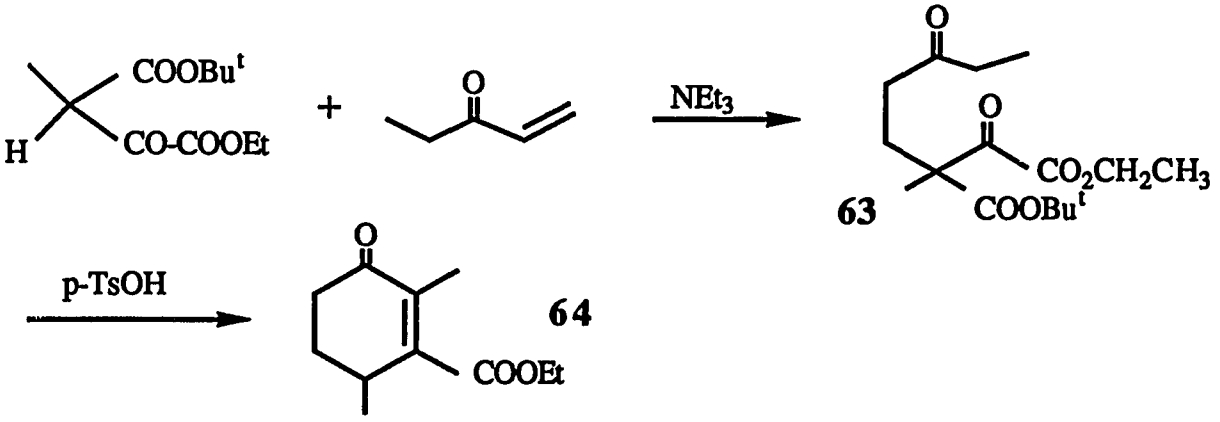
Compound **62** was consequently prepared using diethyloxalate and t-butylpropionate in presence of potassium hydride[42] as base, as shown in the following scheme (**scheme 47**).



SCHEME 47 **62**

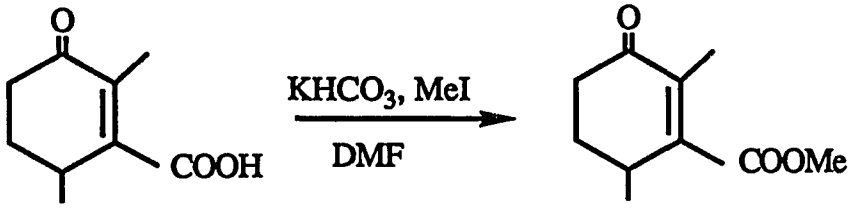
% yield after distillation = 48 %.

Michael addition as before gave the mixed diketodiester **63** in 73 % yield (after distillation). NMR of **63** had a singlet at δ 1.45 and a quartet at δ 4.43. Elemental analysis found for C - 61.25 and H - 8.3 agreed with the caculated values. (C = 61.13 and H = 8.3). Decarboxylation occured readily under aldol condensation coniditions giving **64** (**scheme 48**) in 84% yield (NMR - triplet at 1.25, singlet at 1.90 and a quartet at 4.38 ; GC / MS showed the parent peak at 196 and the splittings were compatible with the structure and elemental analysis gave the following result ; found C - 67.31 %, H - 8.35 %; calculated C - 67.32 %, H - 8.22 %).



SCHEME 48

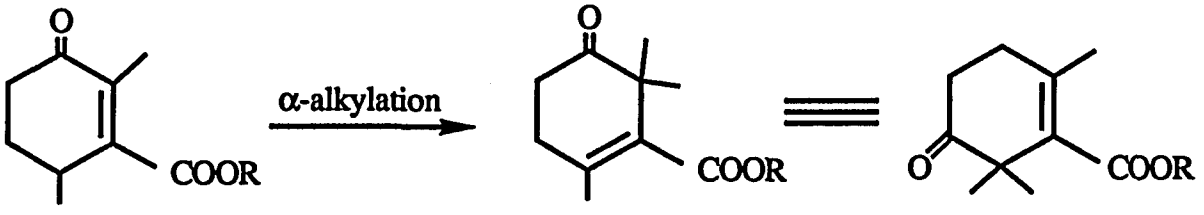
We tried all these methods in order to increase the yield of the corresponding methyl ester obtained by Goldsmith's method[20]. However since the overall yield of the ester **64** from the mixed ester is also low, his method of preparing the acid from the treatment of concentrated HCl on the Michael adduct was adopted. This acid was esterified to get the monoester **65** (yield 98%, NMR - singlet at 1.1, singlet at 1.2, and a singlet at 3.85; GC / MS showed the parent peak at 182) using methyl iodide and potassium carbonate in DMF **(scheme 50).**



SCHEME 50 **65**

Alkylation

As outlined above, α-alkylation on either of the two esters **64** and **65** would afford the target synthon **53** or **66.**

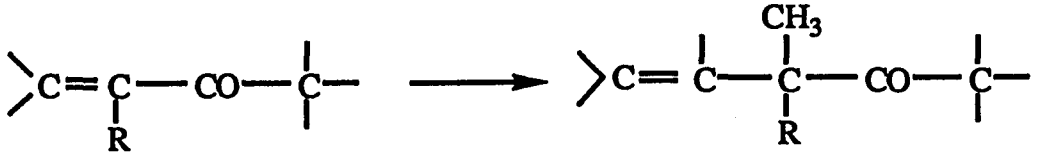


R = Me **65**
R = Et **64**

R = Me **66**
R = Et **53**

It is not unreasonable to expect alkylation at this position, since α,β-

unsaturated ketones are known to undergo alkylation at α rather than at γ[43]. As early as 1926, Kon[44] had shown that some ketones of the type **67** could be alkylated with sodium and methyl iodide in ethyl ether, yielding an α-methyl-β,γ-unsaturated ketone **68**.



R ≠ H

67 **68**

Conia[45] has shown that a number of even unstable unsaturated ketones can be alkylated (mono- and polyalkylated) using sodium tertiary amyloxide in solution and reactive alkylating reagents. His results are summarized in the chart below (**chart 1**). These results are partly confirmed by the works of Woodward et al.,[46], Corey and Burke[47], Bowers and Ringold[48] ,Cooley and coworkers[49f], Sandheimer et al.[50], who worked mostly in the field of keto-steroids. Alkylations were acccomplished most commonly using the system methyl iodide - potassium t-butoxide - t- butyl alcohol (via the thermodynamic enolate). Carbon atoms shown with no hydrogens are quaternary and those shown with hydrogen have one or more hydrogens (**chart 1**).

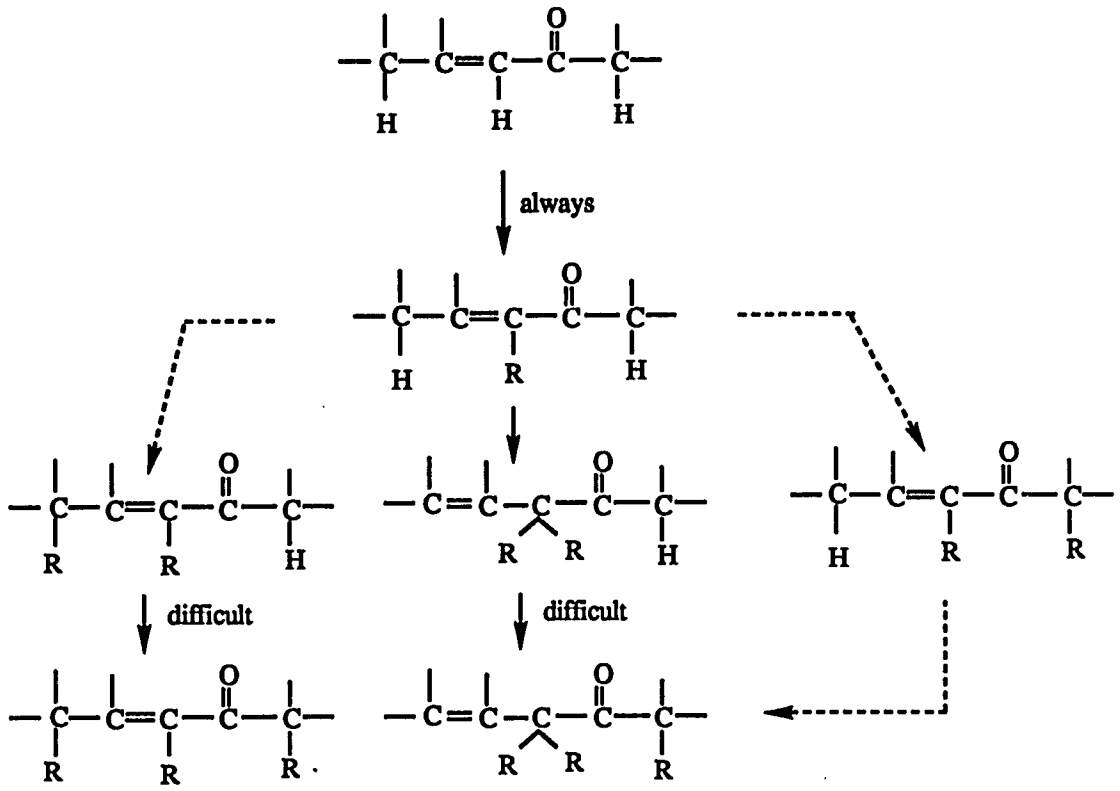
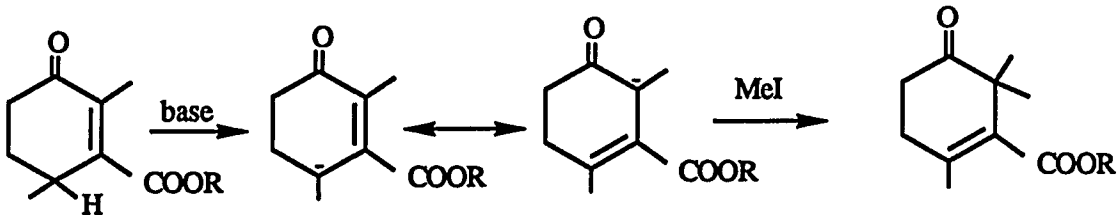


CHART 1

Thus it was expected that the esters **6 4** and **6 5** would form anions when treated with base under thermodynamic conditions, and undergo methylation at the α position giving products as shown below.

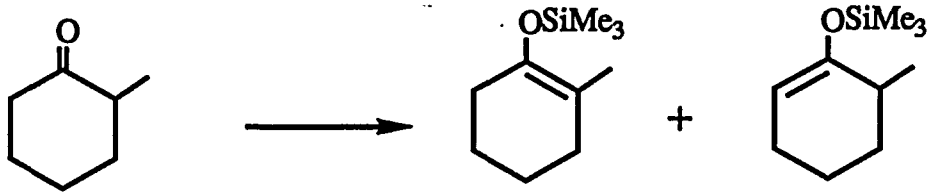


When the ethyl ester **6 4** was treated with three equivalents of potassium t-butoxide in THF and three equivalents of methyl iodide under refluxing conditions for 5 minutes we got an approximately 86% yield of a mixture of compounds. The mixture had two major components and other very minor ones. GC / MS analysis of the sample showed that the two major components had

masses of 224 and 238 respectively, which represent the products of dialkylation and trialkylation. The desired mono alkyl product, which would have a mass of 210 was not observed. Similarly, the use of one equivalent of each of base and methyl iodide, at room temperature for 5 minutes gave a product mixture consisting of four components, with masses of 196 (starting material, 9.7%), 238 (59.5%), 224 (16.8%) and 224 (13.9%).

In order to ensure thermodynamic equilibration, ester **64** was stirred with one equivalent of $KOBu^t$ in THF under nitrogen for 1 1/2 h, then gently warmed for 15 minutes and treated with an equivalent of MeI at room temperature overnight. This too failed to give the monoalkylated product.

Another route for the preparation of the thermodynamic enolates was investigated by Holton and Kraft[51] who found that use of bromomagnesium diisopropylamide (BMDA) in conjunction with trimethylsilyl chloride provided thermodynamic silyl enol ethers regiospecifically. This method gives better yields of themodynamic silyl enol ethers when compared to the other existing methods, as can be seen in the following table (**table 2**) for the preparation of trimethylsilyl enol ethers **70** and **71** from 2-methyl-cyclohaxanone **69** (**scheme 51**).



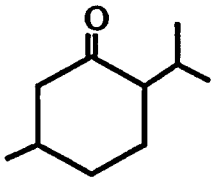
t k

SCHEME 51 **70** **71**

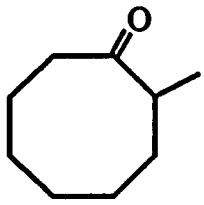
TABLE 2

Reagents	Ratio (t : k)
LDA / DME : TMSCl	1 : 99
NaH / DME : TMSCl	73 : 27
Et_3N / TMSCl / DMF	78 : 22
$(nBu)_4NF$ / $TMSCH_2COOEt$	82 : 18
HMDS / TMSI	90 : 10
KH / THF : TMSCl	67 : 33
BMDA / TMSCl / Et_3N	97 : 3

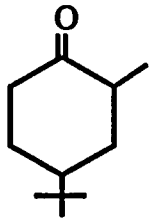
Other compounds **72, 73** and **74** also give similar thermodynamic to kinetic ratios when subjected to Holton's conditions. Yields are also excellent.



72



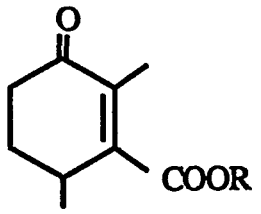
73



74

Considering the excellent regiospecificity of this reaction we planned to use this reagent to get to the thermodynamic enolate of ester **65** and then alkylate it.

BMDA (bromomagnesium diisopropylamide) was prepared according to Holton's procedure and mixed with compound **65**. The alkylating reagent, MeI, along with a base HMPA, was then added and the mixture was stirred for 24 hours. When the reaction mixture was worked up we isolated the starting material.This procedure did not give the alkylated compound when the conditions were varied and the reaction repeated.



65

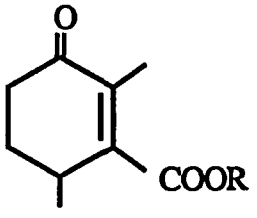
1. Holton's base, 5 min. → 2.HMPA, MeI — **no reaction**

1.Holton's base, 24h. → 2. HMPA, MeI — **no reaction**

1. Holton's base 10 min. → 2. Methyl triflate — **no reaction**

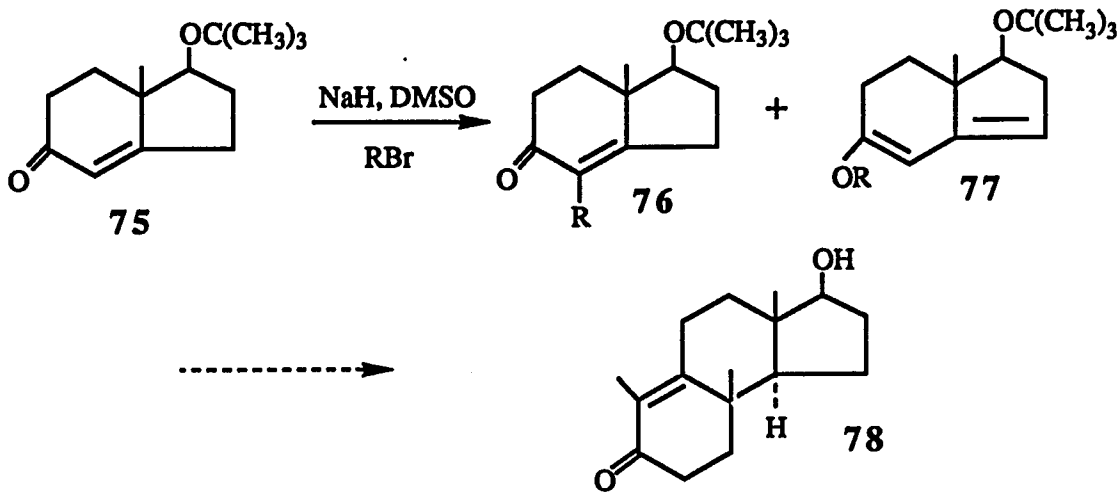
Holton[52]has also discovered another reagent which gives thermodynamic silyl enol ethers. A highly reactive form of zero valent iron, prepared from the reaction of methyl magnesium bromide and ferric chloride was found to deprotonate cyclic unsymmetrical ketones in the presence of TMSCl to give thermodynamic silyl enol ethers regiospecifically. Yields were very good to excellent in the examples cited in their work[52].

We tried to do the alkylation of our ester **65** by first forming the thermodynamic enolate using this reagent. However this too failed to give us the required compound.



Fe (0) → MeI / HMPA — **no alkylation**

Hajos[53] and coworkers used sodium hydride-DMSO-RBr for alkylation of **75** to **76** on their way to the synthesis of an important BCD tricyclic intermediate **78** for the preparation of steroidal compounds (**scheme 52**).

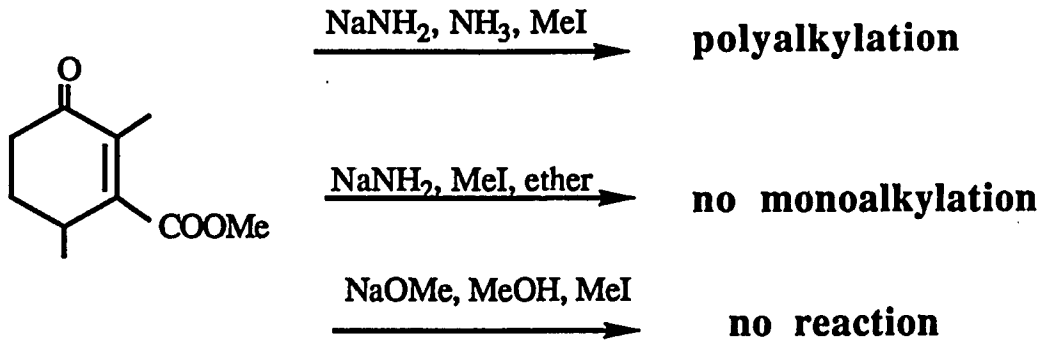


75 76 77 78

SCHEME 52

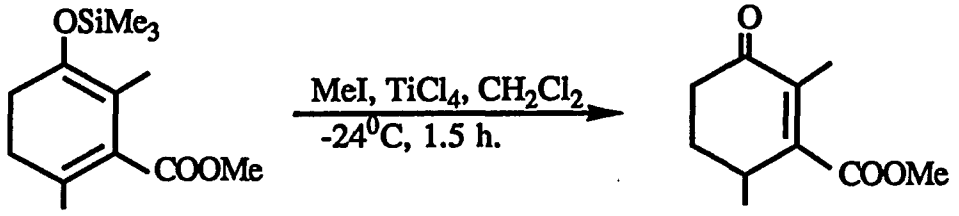
When the reaction was repeated under the same conditions with **65**, except for the use of MeI instead of MeBr, the result was still failure to obtain the monoalkylated product.

Other alkylation reactions tried without success are the following :



Finally, Lewis acid catalyzed alkylation of trimethyl silyl enol ethers was reported by Chan[54] in 1977. Silyl enol ether **79** was prepared by forming the enolate anion of **65** using BMDA and capturing it with TMSCl in presence of triethylamine and HMPA in quantitative yield. Formation of this trimethylsilyl

compound indicates that during alkylation reactions enolate was indeed formed but it was the alkylation step that was not successful. However treatment of our silyl enol ether **79** (see below) with $TiCl_4$ and MeI as the alkylating agent gave back the starting ketoester **65**.

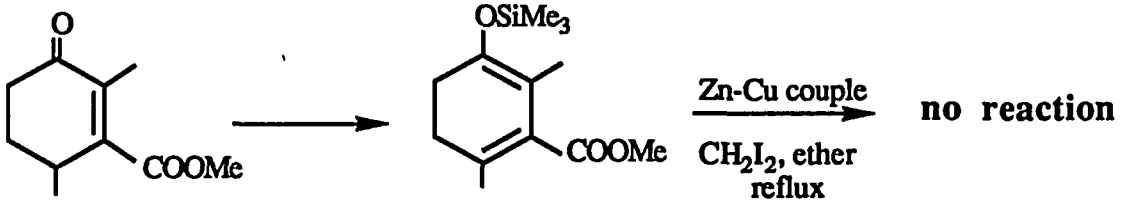


79 **SCHEME 53** **65**

Simmons Smith reaction :

The Simmons Smith reaction is a classic method for the synthesis of cyclopropanes from olefins[55]. Yields, however, depend markedly on the procedure employed and on the structure of the starting olefin. For ketone derived olefins, such as enamines, enol ethers or enol esters the yields are generally low. However, modifications which give improved yields, particularly with functionally substituted olefins, were reported by Conia and coworkers[56].

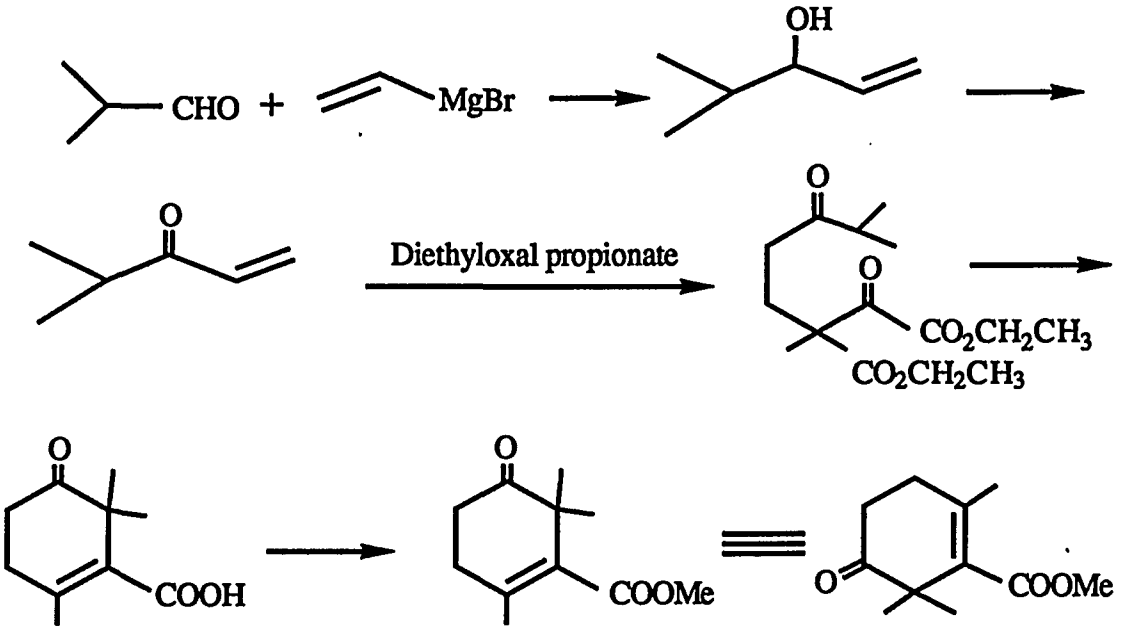
Unfortunately Simmons Smith reaction of **79** using Zn-Cu couple with diiodomethane in refluxing ether, gave no product and starting ketone was reisolated.



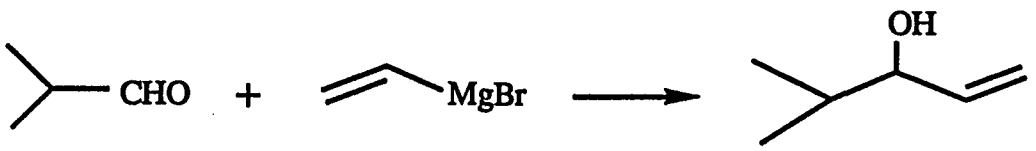
65 **79** **SCHEME 54**

Direct Installation of The Gem Dimethyl (a procedure to avoid methylation)

Having failed to alkylate the esters (**64** and **65**) to get our target synthon we investigated another variation of the Robinson annulation method, which would install the gem dimethyl group in the beginning. This required using isopropyl vinyl ketone (**81**) in the Michael addition step. However since isopropyl vinyl ketone is not a commercially available product, we investigated its preparation starting with the Grignard reaction of isobutyraldehyde and vinyl magnesium bromide. The new scheme then takes the following shape (**scheme 55**).



Grignard reaction between isobutyraldehyde and vinyl magnesium bromide proceeded smoothly to give 1-pentene 4-methyl 3-ol **80** in good yield.

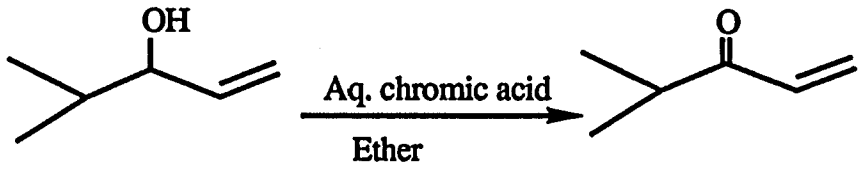


80

Yield = 70 % IR = 3450, 2950 and 1500 cm^{-1}.

NMR = 0.9 (d, 6H), 2.4 (br s, 1H), 5.2 (m, 2H) and 5.8 (m, 1H).

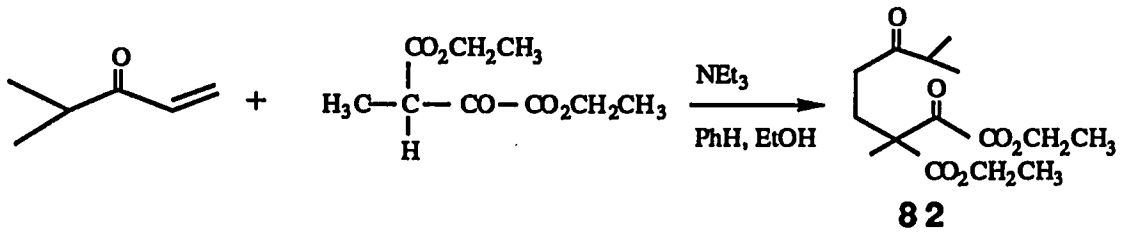
This allylic alcohol **80** was oxidized by aqueous chromic acid as per Brown's[57] procedure to isopropyl vinyl ketone **81**.



80 **81**

Yield = 38 % NMR = 1.2 (d, 6H), 2.7 (br m, 1H) and a complex pattern between 5.7 and 6.5.

Thus prepared, isopropyl vinyl ketone and diethyloxalpropionate underwent Michael addition using previously described conditions to give the Michael adduct **82**.



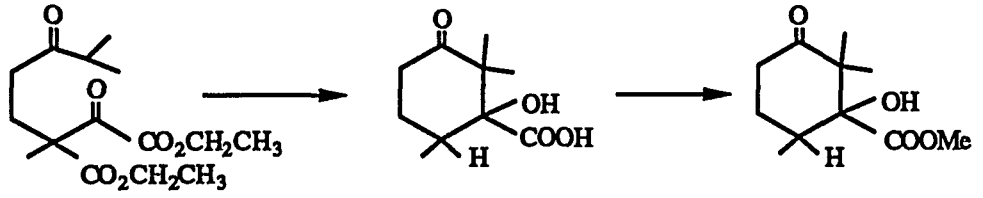
82

Yield = 78 % NMR = 1.0 (d, 6H), 1.4 (tr, 2H), 1.5 (s, 3H), 2.4 (m, 3H), 4.1 (d of q, 4H).

IR = 2960, 1754, 1730, 1715, 1480 cm^{-1}.

This Michael adduct **82** when treated with concentrated HCl, as before,

gave an acid **83** in 46 % yield (m.pt. 163-165^{o}C) that was esterified using MeI and $KHCO_3$. This ester when subjected to GC / MS analysis gave a mass of 214. IR (3514.5-OH, 1732.3-ester carbonyl and 1717.5-keto carbonyl) and NMR (1.0, s; 1.2, s; 3.75, s) confirmed the presence of a cyclohexanone carbonyl, an ester, and a hydroxyl group. This data is consistent with aldol product **84**.

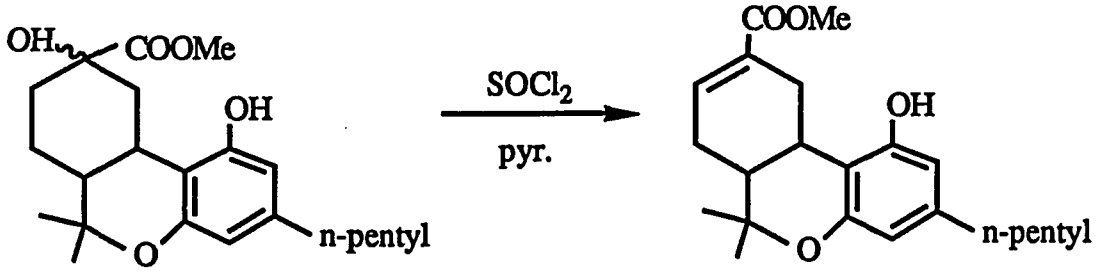


82 **83** **84**

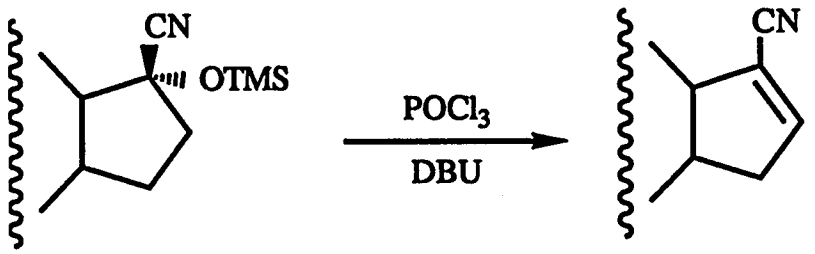
Dehydration of the hydroxy ester

Compound **84** is an α-hydroxy ester. It is difficult to dehydrate such compounds because of the electrophilic carbon to which the hydroxy group is attached. However there are some examples available in literature wherein such a hydroxy group is eliminated.

A. Schwartz[58] used thionyl chloride in pyridine to do the following conversion.



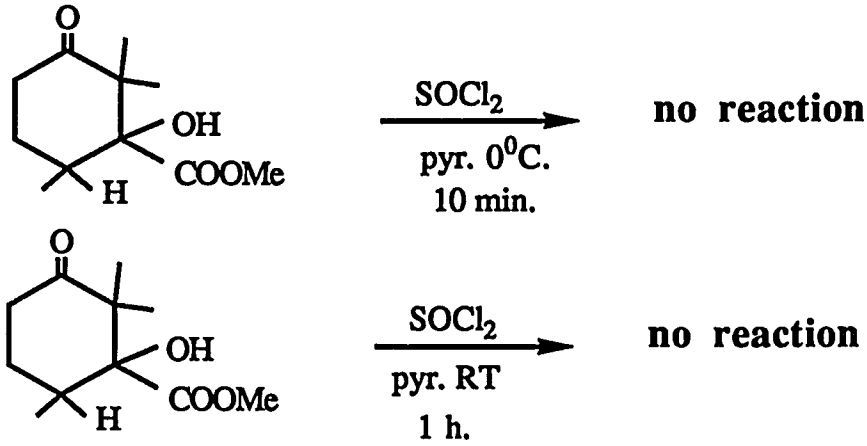
Paquette and coworkers[59] used $POCl_3$ and DBU to get **86** from the α-cyano trimethyl silyl ether **85**.



85 86

Dehydration using $SOCl_2$:

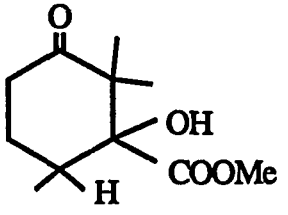
When an ice cold solution of the hydroxy ester **84** in pyridine was treated with thionyl chloride for 10 minutes it did not undergo dehydration, nor when hydroxy ester **84**, pyridine and thionyl chloride were all stirred at room temperature under nitrogen atmosphere for one hour. IR showed a strong hydroxyl absorption implying that the ester did not undergo dehydration.



Dehydration using $POCl_3$ and DBU :

Hydroxy ester **84** decomposed when it was refluxed in pyridine in presence of $POCl_3$ and DBU for 21 h.When the reaction was repeated keeping the temperature below 125^0C. a tarry decomposed material was again obtained. However, when stirred at room temperature overnight, we recovered the starting material. Even at the intermediate temperature of

70^0C. starting material was isolated.



$POCl_3$, pyr., reflux → **decomposed**

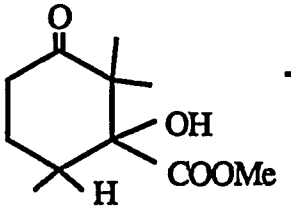
$POCl_3$, pyr., <125^0C. → **decomposed**

$POCl_3$, pyr., RT → **no reaction**

$POCl_3$, pyr., 70^0C. → **no reaction**

Mesylation and dehydration :

When equimolar quantities of the hydroxy ester **84** and methane sulfonyl chloride were treated at ice cold temperature for three hours with a catalytic amount of DBU no reaction took place. The result was the same when the reaction was repeated at room temperature for 24h.



MsCl, DBU, pyr. 0^0C, 3h. → **no reaction**

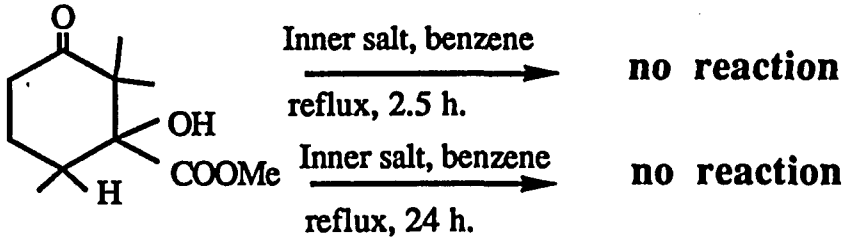
MsCl, DBU, pyr. RT 24h. → **no reaction**

Burgess inner salt method :

(Carboxy sulfamoyl) triethyl ammonium hydroxide inner salt methyl ester reacts with alcohols producing N-carbomethoxy sulfamate esters[60]. Tertiary and secondary alcohols undergo facile thermolytic dehydrations giving olefins.

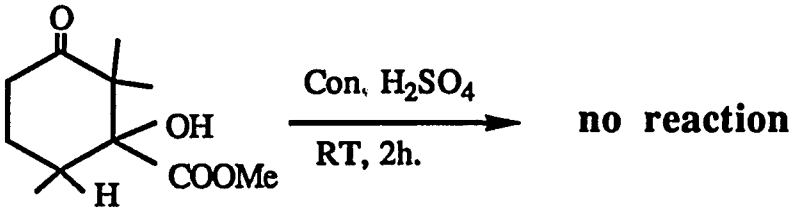
Esters of primary alcohols give urethanes. The point to note is that the formation of this derivative is quite facile even in the presence of severe steric factors, and so this dehydration method was tried.

The inner salt was prepared by the method reported in the literature[60], but when the hydroxy ester **84** was refluxed with the inner salt in benzene for 2.5 hours dehydration did not take place, nor when it was refluxed in benzene overnight.



Sulfuric Acid dehydration :

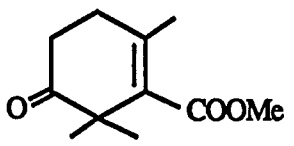
At this point we decided to subject the hydroxy ester to severe conditions, such as concentrated sulfuric acid. When the hydroxy ester was treated with concentrated sulfuric acid at room temperature for 2 hours no dehydration took place.



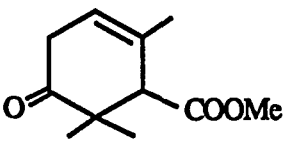
The temperature was then raised to 80^0C and the reaction mixture was stirred for 3 hours. On workup the product showed 7 UV active spots. GC/MS analysis showed 8 peaks, 4 of them in more than 10% amounts each. The masses and the percentage amounts are as follows :

Peaks	Mass	Percentage
1	196	49.5
2	138	12.9
3	138	10.0
4	196	10.5

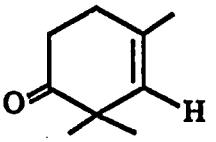
A mass of 196 corresponds to the dehydrated compound **66**, or it's isomer **87**. A mass of 138 corresponds to the dehydrated and demethoxycarbonylated compounds **88** and **89**.



66



87



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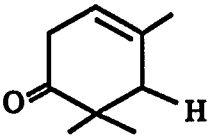

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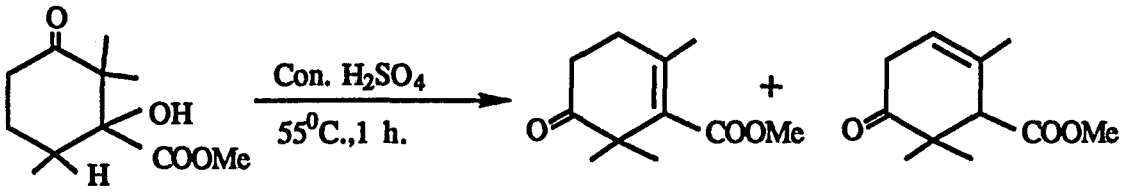
The reaction was then repeated under a variety of conditions in an attempt to delimit the optimum conditions for dehydration.When the reaction was repeated at 75^0C and time stirred reduced to 1 hour 60% of the product formed had a mass of 196.

When the reaction was carried out at 55^0C, for 1 hour, 77% of the product formed was of mass 196.

When the reaction was repeated at 46^0C for 45 minutes, we obtained a mixture of compounds. IR showed hydroxyl absorption, indicating that the dehydration was not complete.Consequently the desired synthon **66** may be obtained by dehydrating the hydroxy ester **84** in concentrated sulfuric acid at 55^0C for one hour.



Pauline Hamilton, in our laboratories, continued the dehydration experiments and also obtained two isomers. 200 MHz NMR showed the presence of olefinic protons which were not detected in 60 MHz NMR. The two isomers were in 5:1 ratio. Double bond isomerization took place when the mixture was subjected to HPLC purification and the minor isomer became the major isomer.

CHAPTER 3

EXPERIMENTAL

Melting points: Thomas Hoover Unimelt apparatus was used to determine the melting points and are uncorrected.

Proton spectra: Routine proton NMR spectra were recorded on a Varian EM 360 nuclear magnetic resonance (NMR) spectrometer using TMS as internal standard in $CDCl_3$, unless otherwise mentioned. Chemical shifts are reported in ppm downfield from TMS with multiplicity designated as **s** for singlet, **d** for doublet, **t** for triplet, **q** for quartet and **dq** for doublet of quartet.

Infrared spectra: Infrared spectra were recorded on a Perkin-Elmer IR 598 instrument.

Gas liquid chromatography: A Varian Aerograph 920 thermal conductivity instrument was used for GC's (column used was either a 10' X 1" column packed with 20% silicone oil DC 710 on Chromosob W (60-80) mesh or a 10' X 1/4" column packed with 20% Apiezon L on Chromosorb W.

Flash column chromatography: Still's procedure was employed to do this and E. Merck silica gel (230-400 mesh) was used.

GC / MS analysis: Dr. D. C. Locke at Queens college performed the GC / MS analyses on a Hewlett Packard 5988A instrument.

Thin layer chromatography: TLC was carried out on Machery-Nagel precoated polygram Sil N/HR UV silica plates.

Solvents: Solvents were dried according to the available methods and the reagents were distilled before using in the reactions.

Elemental analysis: Galbraith Laboratories, Knoxville, TN. performed the elemental analyses.

Preparation of geranyl acetate **10**[29] :

To 46.2g (0.300 mol) of geraniol in a round bottomed flask was added 32.0g (0.315 mol) of acetic anhydride. The mixture was cooled in ice, and a catalytic amount of DMAP (4-dimethylaminopyridine) was added. The mixture was stirred at room temperature for 24 hours, then washed with water and extracted with methylene chloride. Solvent was evaporated under reduced pressure to give geranyl acetate, a colorless oil, in quantitative yield. bp 104-106^{o}C. (6mm). NMR: 1.6 (s, 3H), 1.7 (s, 6H), 1.4 - 2.0 (br, 4H), 2.1 (s, 3H), 4.5 (d, 1H), 5.2 (multiplet, 1H).

Cyclization of geranyl acetate using $SnCl_4$[10] :

To a stirred mixture of 13.4g (0.050 mol) of $SnCl_4$ and 15mL of nitromethane (dried and distilled over P_2O_5) cooled in ice was added a mixture of 10.0g (0.05 mol) of geranyl acetate and 4.5mL (0.05 mol) of acetyl chloride during 20 minutes. Stirring was continued for an additional hour at ice cold temperature, then the mixture was dumped onto ice (25g) and extracted with methylene chloride. The acidic organic layer was washed with saturated aqueous sodium bicarbonate solution, then dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure left only polymer as evidenced by thin layer chromatography.

Cyclization of geranyl acetate using $SnCl_4$ at -25^{o}C :

To a solution of 6.69g (0.025 mol) of $SnCl_4$ in 25mL of nitromethane at -25^{o}C was added 2mL (0.027 mol) of acetyl chloride. This mixture was stirred at -25^{o}C for 5 minutes, then 5.00g (0.025 mol) of geranyl acetate in 25mL of

nitromethane was added all at once. Immediately thereafter an ice cold solution of saturated aqueous sodium bicarbonate was added to the mixture which was then extracted with methylene chloride and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded a polymeric compound.

Cyclization of geranyl acetate using $AlCl_3$ as catalyst :

An equimolar mixture of $AlCl_3$ (0.04 mol) complex of acetyl chloride and geranyl acetate (0.04 mol of each) was stirred in methylene chloride under ice cooling for one hour, then poured into ice cold water. The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution. When the solvent was evaporated the required cyclized compund was not obtained.

Cyclization of geranyl acetate using $AlCl_3$ as catalyst at lower temperature :

Geranyl acetate (1.0 g, 0.0049 mol) was mixed with 400 mg (5.00 mmol) of acetyl chloride in dry methylene chloride. The mixture was cooled to -78^oC and $AlCl_3$ (600 mg, mol) was added. The mixture was stirred for 1.25 h at -78^oC, then the temperature was raised to -20^oC. The mixture was stirred for an additional hour, then poured into ice cold water and extracted with methylene chloride. The organic layer was washed with saturated aqueous sodium bicarbonate, water and dried over anhydrous $MgSO_4$ and solvent evaporated under reduced pressure. None of the desired product was isolated in this case either.

Cyclization of geranyl acetate using BF_3Et_2O and acetonitrile :

Geranyl acetate (500 mg, 2.43 mmol) was dissolved in 20 mL of

methylene chloride and to this was added 1.15 mL (2.50 mmol) of acetonitrile. The mixture was chilled in ice and 0.316 mL (2.50 mmol) of BF_3Et_2O was added with stirring, and the mixture was stirred at ice cold temperature overnight. The usual work up again gave a polymeric compound.

Preparation of ethyl phenyl sulfide **39**:

Freshly cut sodium metal (4.6 g, 0.20 mol) was added to a solution of 22 g (0.20 mol) of thiophenol in 50 mL of absolute ethanol. Bromoethane (21.8 g, 0.20 mol) was added slowly from a separatory funnel (45 min.). The reaction mixture was stirred overnight at room temperature, then quenched with ice and extracted with methylene chloride. The organic layer was washed with 10% aqueous NaOH and water, then dried over Na_2SO_4. Solvent was distilled off at atmospheric pressure. The crude product was distilled to give 85% of pure ethyl phenyl sulfide. bp 96-99^{0}C (7-8 mm) NMR 7.3 (m) aromatic protons; 2.9 (q) S-CH_2-CH_3; 1.3 (t) S-CH_2-CH_3.

Preparation of 1-phenylthioethyl chloride[30] **40** :

A mixture of 1.65 g (12.5 mmol) of 1-phenylthioethane **39** and 1.55 g (12.5 mmol) of N-chlorosuccinimide was stirred in 12.5 mL of CCl_4 at room temperature, under an atmosphere of nitrogen overnight, then filtered. Solvent was evaporated under reduced pressure to give 1-phenylthioethyl chloride in 90% yield. NMR 7.35 (m) aromatic protons; 5.4 (q) S-CHCl-CH_3; 1.9 (d) CH_3

Cyclization of geranyl acetate with 1-phenylthioethyl chloride using $AlCl_3$ as Lewis acid :

To a solution of geranyl acetate (3.92 g, 0.020 mol) in dichloromethane (20 mL) in a three necked flask fitted with a separatory funnel and cooled to -15^{0}C, was added 2.66 g (0.0200 mol) of $AlCl_3$ slowly over a period of 30

minutes. Simultaneously, addition of 3.5 g (0.020 mol) of 1-phenylthioethyl chloride was also started. The mixture was stirred for 2h at -15^{o}C after which it was poured into ice cold aqueous saturated sodium bicarbonate solution. Methylene chloride was added to this and the gelatinous ppt of $Al(OH)_3$ was filtered through a plug of glass wool. The organic layer was separated and washed with water. The product (880 mg after column purification; solvent Hex : CCl_4, 4:1) obtained on evaporation of the solvent under reduced pressure was very much similar to geranyl acetate (by comparison of NMR's).

Cyclization of geranyl acetate with 1-phenylthioethyl chloride using $TiCl_4$ as Lewis acid :

A mixture of 1-phenylthioethyl chloride (5.16 g, 0.030 mol) and $TiCl_4$ (5.7 g, 0.030 mol) in 20 mL of methylene chloride was coolled to -23^{o}C and geranyl acetate (5.9 g, 0.030 mol) in methylene chloride (20 mL) was added dropwise to this. The mixture was further cooled to -73^{o}C and stirred for 2h, then it was warmed upto -10^{o}C and stirred for half an hour after which it was poured into ice cold saturated aqueous sodium bicarbonate solution. Methylene chloride was added to this and the precipitate of TiO_2 was filtered through celite. The organic layer was seperated and washed with brine and water, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give an oil. This was further purified by fractional distillation to give 2.2 g of a purer material. However NMR analysis revealed that this was not the cyclic material that was expected.

4-(2,6,6-trimethyl-2,3-epoxycyclohexyl)-3-buten-2-one 17 from α-ionone[17] :

To a rapidly stirred solution of 10 g (0.052 mol) of α-ionone in 135 mL of dichloromethane at 0°C was added 10.8 g (0.062 mol) of m-chloroperbenzoic acid. The solution was kept below 5°C and the reaction mixture was stirred for 3 hours. The solids were removed by suction filtration and washed with dichloromethane (2 X 5 mL). The filtrate was washed with aqueous 5% Na_2CO_3 (50 mL) and aqueous saturated NaCl (20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give 10.8 g (98 %) of the epoxides **17**.^{1}H NMR = 0.74 (3H, s), 0.90 (3H, s), 1.3-2.1 (5H, m), 2.24 (3H, s), 3.03 (1H, m), 6.10 (1H, d), 6.70 (1H, dd). IR (neat) 2960 (s), 1675 (s), 1620 (m), 1360 (s), 1250 (s) cm^{-1}

2,3-Epoxy-2,6,6-trimethylcyclohexanecarboxylic Acid[17]:

To a solution of 46.5 g (0.216 mol) of sodium metaperiodate in water (1L) was added 0.68 g (0.0044 mol) of potassium permanganate. The solution was stirred at room temperature for 30 min, and then 3.40 g (0.0246 mol) of potassium carbonate, 0.5 L of t-butyl alcohol and 5.0 g (0.12 mol) of **17** were added in succession. The reaction mixture was stirred for 72 hours at room temperature. Ethylene glycol (5.0 mL) was then added to quench any excess periodate, and the solution was stirred for 3 h. The solids were removed by suction filtration and washed with water. The filtrate was concentrated to 500 mL under reduced pressure and extracted with ether (2 X 60 mL). The aqueous layer was acidified to pH 2 with 1N HCl and this was extracted with ethyl acetate (4 X 60 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give 3.0 g (69 %) of the acid as a yellow oil. NMR 0.9 (s, 3H), 1.0 (s, 3H), 1.35 (s, 3H), 1.4-2.1 (m,

4H), 2.35 (s, 1H), 3.1 (br, 1H), 7.5 (br, 1H). IR in CCl_4 3450 (br), 2960 (s), 1725 (s), 1040 (m).

2,6,6-Trimethylcyclohex-2-ene-1-carboxylic Acid **45**[31]:

Hycrogen peroxide (240 mL, 30 %) was added to a stirred solution of 38 g (0.20 mol) of α-ionone in 1L of methanol. The mixture was cooled with an ice bath and 600 mL of 1N NaOH was added dropwise with cooling. After the addition was complete, the reaction mixture was stirred for a further 48 h, keeping the temperature below 10°C. The original volume was reduced to about half by removing the solvent under reduced pressure. Unreacted α-ionone was removed by extraction with ether, and the aqueous layer was acidified with con. H_2SO_4 then was saturated with Na_2SO_4 and extracted thoroughly with ether. The combined ether layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give 27.5 g (83%) of **45**. NMR 1.0 (s, 3H), 1.1 (s, 3H), 1.6 (s, 3H), 1.1-2.2 (m, 4H), 2.1 (s, 1H), 5.55 (br, 1H), 8.15 (br, COOH). IR in CCl_4 3500 (br), 2940 (s), 1705 (s), 1260 (m).

2,6,6-Trimethylcyclohex-2-ene-1-carboxylic Acid methyl ester **46**[17]:

To a stirred solution of 26.0 g (0.195 mol) of anhydrous potassium carbonate in dry acetone (200 mL) was added 39.0 g (0.232 mol) of crude acid **45** and 70.0 g (0.546 mol) of iodomethane. The mixture was stirred overnight at room temperature. The excess acetone and iodomethane were removed under reduced pressure. The solid residue was suspended in 10 % aqueous sodium bicarbonate (200 mL) and extracted with ether. The ether layer was washed with water, brine and dried over anhydrous Na_2SO_4, then filtered and evaporated under reduced pressure to give 38.5 g (91 %) of a mixture of esters

46 and **47**. Distillation of the mixture of esters through a short path still gave a first fraction with bp = 50° C (1 mm). This was subjected to gas chromatographic purification to obtain pure ester **46**. ^{1}H NMR (δ) = 1.0 (s, 6H), 1.1-1.3 (br, 2H), 1.68 (s, 3H), 1.8-2.2 (br, 2H), 2.6 (s, 1H), 3.72 (s, 3H), 5.6 (br, 1H). IR (CCl_4) = 2940 cm^{-1}, 1730 cm^{-1}.

Methyl 2,3-Epoxy-2,6,6-trimethylcyclohexane-1-carboxylate **18**:

To a rapidly stirred solution of **46** (9.1 g, 0.05 mol) in dichloromethane (150 mL) was added 13.0 g (0.078 mol) of m-chloroperoxybenzoic acid at 0°C. The mixture was stirred for 24h at 0°C, and the precipitate was filtered. The organic layer was washed with 5% aqueous Na_2CO_3, and brine, then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 9.1 g (92%) of the epoxide **18**, as a pale yellow oil. ^{1}H NMR 1.0 (s, 3H), 1.1 (s, 3H), 1.45 (s, 3H), 1.6-2.2 (m, 4H), 2.45 (1H, s), 3.1 (t, 1H), 3.85 (s, 3H). IR in CCl_4 2960 (s), 1740 (s), 1150 (s), 1435 (m).

Methyl 3-Hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxylate **19**[17]:

To a stirred solution of sodium methoxide prepared by dissolving 1.0 g (0.043 mol) of sodium metal dissolved in methanol (100 mL) was added, dropwise, 9.0 g (0.050 mol) of **18** in 5 mL of methanol under an atmosphere of nitrogen. The solution was refluxed for 5h, cooled to room temperature and neutralized with 1N HCl. The excess methanol was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with aqueous saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure

to give 7.6 g (85%) of the allylic alcohol **19** ; ^{1}H NMR 1.05 (s, 3H), 1.10 (s, 3H), 1.78 (s, 3H), 2.2 (br s, 1H), 3.75 (s, 3H), 4.2 (m, 1H). IR = 3420 (br), 2960 (s), 1740 (s), 1230 (br), 1060 (m).

Ethyl 4-Oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate **23C** [19] :

A stirred mixture of 104 g (102 mL, 0.8 mol) of ethyl acetoacetate, 82.4 g (96.0 mL, 0.840 mol) of mesityl oxide, 100 mL heptane, 60 mL toluene, and 17.5 g of $ZnCl_2$ (anhydrous) was heated at reflux in a 500 mL round bottomed flask equipped with a Dean-Stark trap and drying tube. After 24h, an additional 2.5 g of $ZnCl_2$ was added and refluxing continued for 40h. After cooling the mixture was washed with water (150 mL), 5% aqueous sodium bicarbonate solution (2 X 100 mL), water (150 mL), and brine (30 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give 120 g (lit 19, yield, 97.9 g) of a mixture of **23A, 23B** and **23C**. Distillation (bp 88-91^{o}C 0.6, mm) provided 56.0 g (34 %) 0f **23C**. Glpc analysis showed the material to be greater than 90% pure.

Ethyl 2,6,6-trimethylcyclohex-2-ene-1-carboxylate **24** [19] :

A mixture of 0.0960 m (20.1 g) of **23C** obtained from the previous reaction, 31.0 mL (0.252 mol) of boron trifluoride etherate and 40 mL (0.25 mol) of triethylsilane was heated at 80-95 ^{o}C for 2h. After cooling, the reaction mixture was partitioned between water (80 mL) and ether (3 X 60 mL). The combined organic layers were washed with 100 mL portions of 10% sodium bicarbonate and brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product which was distilled to give 12.0 g (65 %) of the reduced compound **24**; bp 86 ^{o}C (3.5 mm). ^{1}H NMR: 0.95 (s, 6H),

1.30 (t, 3H), 1.53-2.47 (m, 4H), 1.68 (s, 3H), 2.65 (br s, 1H), 4.25 (q, 2H), 5.67 (br s, 1H).

Ethyl 2,3-Epoxy-2,6,6-trimethylcyclohexane carboxylate **25**[19] :

Unsaturated ester 24 (4.55g, 23.2 mmol), was treated with 6.20 g (34.7 mmol) of m-chloroperoxybenzoic acid in dry dichloromethane for 24h at room temperature. The precipitate which formed was filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous $MgSO_4$. The crude product isolated by evaporation of the solvent under reduced pressure on distillation (bp 96°C, 2.5 mm; lit[19] bp 50-51°C, 0.26 mm) yielded 2.7 g (13.6 mmol, 59 %) of the epoxide **25** as a mixture of two epimeric epoxy compounds which were not separated for future experiments. ^{1}H NMR: 0.93 (s, 3H), 0.97 (s, 3H), 1.3 (t, 3H), 3.05 (br, 1H), 4.25 (q, 2H).

Attempts to prepare Ethyl 3-hydroxy-2,6,6-trimethylcyclohexane-1-carboxylate **48** :

a. Epoxide **25** (400mg, 1.90 mmol), 400 mg (14.0 mmol) of triethylsilane[38] and 220 mg (2.0 mmol) of trifluoroacetic acid were refluxed in dichloromethane overnight. The mixture was cooled and washed with aqueous saturated sodium bicarbonate, water and brine, then the solvent was evaporated under reduced pressure to give 560 mg of a product. This product showed the following IR absorptions (cm^{-1}) : 3690 (w), 3500 (m, br), 1785, 1730, 1705. M^+ peak in GC / MS was 281. Both these (IR and GC / MS) data are inconsistent with the structure of the saturated alcohol **48**. NMR 1.0 (s, 3H),

1.2 (s, 6H), 1.2 (tr, 3H), 1.1-1.9 (m, 7H), 2.1 (s, 1H), 2.4 (s, 1H), 3.3 (br, 1H).

b. When the above experiment was repeated at 0° C, starting material was isolated.

Ethyl 2,6-Diketo-3-carbethoxy-3-methyloctanoate **28b** [20]:

Freshly distilled ethyl vinyl ketone (9.0 mL, 0.075 mol) and diethyloxal-propionate (10.05 g, 0.05 mol) were dissolved in a 1:1 mixture of absolute ethanol (dry) and benzene (dry). Ten drops of triethylamine were added and the solution was heated at reflux overnight. Removal of the solvent in vacuo left 15 g (70 %) of a yellow oil. Distillation (bp 134 - 136 °C /0.06 - 0.09 mm and lit[20] bp 119-129 / 0.03 mm) of this yielded pure **28b**. NMR : 1.03 (tr, 3H), 1.2 (tr, 3H), 1.4 (tr, 3H), 1.5 (s, 3H), 2.0-2.6 (m, 4H), 4.25 (q, 2H) and 4.35 (q, 2H).

3,4-Dicarbethoxy-2,4-dimethyl-2-cyclohexen-1-one **30**[20]:

A mixture of the Michael adduct **28b** (5.72 g, 0.020 mol) in dry toluene and a catalytic amount of p-toluenesulfonic acid was refluxed in a flask equipped with a Dean Stark trap for 48 h. The reaction mixture was then cooled and washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 4.5 g (85 %) of **30**(bp 134°C/1.8 mm and lit[20] bp 109-111°C/0.3 mm). NMR : 1.2 (tr, 3H), 1.3 (tr, 3H), 1.5 (s, 3H), 2.0 (s, 3H), 4.15 (q, 2H), 4.2 (q, 2H). GC / MS: M^+ at 268. IR (in CCl_4) 1730 (s), 1685 (s).

Decarboxylation[41] of the diester **30**:

a. A mixture of **30** (133 mg, .500 mmol), 36 mg (0.60 mmol) of NaCl, 200 mg water, and 5 mL DMSO was stirred at 140°C overnight, then cooled,

poured into water (6 mL) and extracted with pentane. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a compound whose NMR was the same as that of the parent material. The bicarbonate layer was acidified and extracted with pentane which was also dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. No acidic product was isolated.

b. A mixture of the diester **30** (133 mg, 0.500 mmol), 50 mg (0.60 mmol) of LiCl, 200 mg of water and 5 ml of DMSO was stirred at 150°C for 3h, then worked up as before (part **a**). No decarboxylation took place and only starting material was isolated (comparison of the NMR's of the starting material and the isolated product).

c. A mixture of **30** (133 mg, 0.50 mmol), 66.0 mg (0.60 mmol) of LiCl, 200 mg of water and 5 mL of DMSO was stirred at 135°C overnight and then refluxed for a further 5h. Work up as before (part **a**) yielded a product whose NMR and IR were very similar to those of the starting diester **30**.

d. A mixture of the diester **30** (266 mg, 1.0 mmol), 132 mg of LiCl, 55 mg of water and 50 mL of DMSO was heated at 185°C overnight. The mixture was cooled, dumped into water and the product was extracted with ether. The ether layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a product whose NMR was the same as that of the starting material **30**.

e. A mixture of the diester **30** (133 mg, 0.500 mmol), 50 mg (1.2m mol) of LiCl, 2 drops of water in 10 mL of DMSO were stirred at 160°c overnight. The

mixture was cooled and worked up as in part **d**. The product isolated was mostly the starting material **30**.

f. A mixture of the dister **30** (133 mg, 0.500 mmol), 100 mg (1.00 mmol) of NaI, 0.05 mL of water were heated at 162°C for 48 h, in DMF. It was then cooled, poured into water and extracted with carbon tetrachloride. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to again give back most of the starting material (by comparison of NMR and IR spectra).

g. A mixture of the diester **30** (133 mg, 0.0005 mol) and 130 mg of LiI hydrated was heated in 15 mL of 2,4,6-collidine, at 200°C overnight. The reaction mixture was cooled and dumped into cold water, acidified with concentrated hydrochloric acid and extracted with ether (4 X 50 mL). The combined ether layers were washed with saturated sodium bicarbonate, water and brine. This was then dried over anhydrous Na_2SO_4 and solvent evaporated to give traces of starting material. The bicarbonate layer was acidified with concentrated hydrochloric acid (to pH 2) and extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent evaporated to give 30 mg (37%) of 2,6-dimethyl-3-oxocyclohex-2-ene carboxylic acid as a white solid. m.p. = 126 - 128°C (lit[20] m.p. = 124-126°C). NMR : 1.25 (d, 3H), 1.95 (d, 3H), 9.4 (br s). IR (in CCl_4) cm^{-1}: 1675, 1700, 2900 - 3400.

h. A mixture of 268 mg (0.001 mol) of the diester **30** in 5 mL of ethanol was added to a refluxing mixture of sodium ethoxide prepared by dissolving 20 mg of sodium in ethanol, under an atmosphere of nitrogen. This mixture was

refluxed overnight, cooled to room temperature, and neutralized with 1N hydrochloric acid. The excess ethanol was removed under reduced pressure, and the aqueous residue was extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium bicarbonate, water, and brine, then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give only the starting material (comparison of NMR and IR spectra).

Diethyl 2-(3-oxobutyl)-2-methyl-3-oxo butanedioate **28a** [20]:

Freshly distilled methyl vinyl ketone (12.6 mL, 10.5 g, 0.15 mol) and 20.2 g (0.1 mol) of diethyloxalpropionate were dissolved in a 1:1 mixture of dry benzene and absolute ethanol (70 mL of each). Ten drops of triethylamine were added and the solution was heated at reflux overnight. The solvent was removed in vacuo and the residue was distilled to give 24.0 g (88 %) of **28a**, b.p. 133°C/0.6 mm (lit[20] b.p. 110-120°C/0.05 mm). NMR 1.25 (tr, 3H), 1.35 (tr, 3H), 1.4 (s, 3H), 2-2.6 (m, 4H), 2.15 (s, 3H), 4.15 (q, 2H), 4.35 (q, 2H).

Diethyl 1-methyl-4-oxo 2-cyclohexene-1,2-dicarboxylate **29** [20]:

Michael adduct **28a** (24.0 g, 0.088 m) in dry toluene and a catalytic amount of p-toluenesulfonic acid was refluxed in a flask equipped with a Dean Stark trap for 48 h. The reaction mixture was then cooled and washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was distilled to give 82.6 % of the diester **29**, NMR: 1.2 (tr, 3H), 1.3 (tr, 3H), 1.6 (s, 3H), 4.15 (q, 2H), 4.2 (q, 2H), 6.72 (s, 1H).

Decarboxylation of the diester **29**:

a. A mixture of 127 mg (0.005 m) of **29**, 210 mg (0.005 mol) of lithium chloride, 25 mL of DMSO and two drops of water was stirred at

145^{o}C overnight. The reaction mixture was then cooled, dumped into ice water and extracted with pentane (4 X 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give back traces of the starting material (by comparison of the NMR spectra).

b. A mixture of 254 mg (0.01 m) **29**, 0.95 g (0.01 m) $MgCl_2$, and 25 mL of DMF was heated at 150^{o}C overnight, then cooled, dumped into water and extracted with ether. The ether layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, giving a residue which was the same as the starting material (by comparison of NMR spectra).

c. A mixture of ester **29** (623 mg,0.025 mol) in ethanol containing a catalytic amount of p-toluenesulfonic acid was refluxed overnight. The mixture was then cooled, washed with saturated aqueous sodium bicarbonate, water, brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure giving a product which showed the same NMR spectrum as the starting material.

t-Butyl Ehtyloxaloylpropionate **62**:

Potassium hydride (2.6 g, 35 % in mineral oil) was washed with freshly distilled THF under an atmosphere of nitrogen. To this mixture was added a mixture of 3.0 g (0.02 mol) of diethyl oxalate and 2.60 g (0.02 mol) of t-butyl propionate in THF dropwise during 2h. Then the reaction mixture was carefully neutralized with glacial acetic acid and diluted with ice cold water. The organic layer was extracted with ether and the ether layer was washed with sodium

bicarbonate, water and brine respectively. It was then dried over anhydrous sodium sulfate, filtered and solvent evaporated to give the crude product. This on distillation provided 2.5 g (48 %) of the pure mixed ester **62**, b. p. 76^{o}C at 0.6 mm of Hg. NMR δ : 1.4 (s, 3H), 1.5 (s, 9H), 4.4 (q, 2H).

This compound gave a positive ferric chloride test confirming the presence of a β-keto ester group.

O-1Ethyl O-4tButyl 3-methyl-2-oxo-3-(3-oxopentyl)butanedioate **63** :

Ethyl vinyl ketone(2.7 mL), 3.6 g of **62** dissolved in 50 mL of 1: 1 dry benzene and absolute ethyl alcohol, and a catalytic amount of triethylamine were refluxed overnight. The crude product was obtained by removing the solvent under reduced pressure, followed by fractional distillation under reduced pressure.The fraction boiling at 158^{o}C (2.2 mm) which was enriched in **63** was collected(3.6 g). This fraction was further purified by flash column chromatography (hexane : ethyl acetate 2 : 1). NMR δ : 1.45 (s, 9H), 4.43 (q, 2H). Elemental analysis (found) : C - 61.25 %, H - 8.3 % (calculated for $C_{16}H_{26}O_6$: C - 61.13 %, H - 8.34 %).

Ethyl 2,6-dimethyl3-oxocyclohexene carboxylate **64** :

The MIchael adduct **63** (0.01 mol) was refluxed in toluene in presence of a catalytic amount of p-toluenesulfonic acid, overnight. The reaction mixture was cooled and washed with saturated aqueous sodium bicarbonate , water and brine, then dried over anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure to give 1.62 g (84 %) of crude aldol product.This was further purified by flash column chromatography (7:1 hexane:ethyl acetate) to give 630 mg (33%) of pure **64**. NMR δ 1.25 (t, 3H), 1.35 (d, 3H),1.8-2.0 (m, 2H),

2.2-2.6 (m, 3H), 1.9 (s, 3H), 4.38 (q, 2H). GC / MS splitting : 196 (M^+), 181 (loss of CH_3), 168 (loss of CO_2), 151 (loss of OEt), 123 (loss of COOEt). Elemental analysis (found) : C - 67.31 %, H - 8.35 % (calculated for: C - 67.32, H - 8.35).

Methyl 2,6-dimethyl3-oxocyclohexene carboxylate **65** :

a. Treatment of 5.72 g (0.0200 mol) of **28b** with 50 mL of concentrated hydrochloric acid overnight at room temperature was followed by dilution of the mixture with 50 mL of water and heating at reflux overnight. The solution was cooled, made alkaline, and extracted with ether. The aqueous solution was then acidified and extracted with mehtylene chloride. The solvent was then evaporated under reduced pressure to give 1.4 g (41.7 %) of **2,4-Dimethyl-3-carboxycyclohex-2-en-1-one** (m.p. 126-128^{0}C).

b. A mixture of the above acid 4.0 g (0.024 mol), $KHCO_3$ (6.82 g, 0.0480 mol) and MeI (3.0 mL, 0.048 mol) in 50 mL dry DMF was stirred overnight at room temperature, then diluted with water and extracted with ether (3 X 50 mL). The organic layer was washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated to give ester **65** in 97 % (4.2 g) yield. GC / MS analysis gave 182 as the mass of the parent peak. NMR : 1.2 (d, 3H), 1.85 (s, 3H), 1.6-2.5 (m, 5H), 3.85 (s, 3H).

α - Alkylation of the monoester **64** :

a.To 98 mg (0.50 mmol) of **64** in a three necked round bottommed flask equipped with a condenser and a nitrogen inlet tube was added 1.5 mL of 1M $KOBu^t$ (1.5 mmol) solution in THF, followed by (0.70 mL, 1.5 mmol) of methyl iodide which was added with stirring. The mixture was refluxed for 5 min and

precipitated potassium iodide was filtered and washed with ether. The filtrate and washings were combined and the solvent was evaporated under reduced pressure to give a pale yellow oil. This was diluted with ether, washed with 2 mL of 6N HCl, saturated aqueous sodium bicarbonate, water, and brine, then dried over anhydrous magnesium sulfate. This was filtered and the solvent was evaporated under reduced pressure to give 90 mg of the product which was found to be a mixture of dialkylated and trialkylated products (GC / MS : peak 1 - M^+ 224 and peak 2 - M^+ 238). This mixture was not separated and analyzed since the required monoalkylated product was not obtained.

b. Alkylation using one equivalent of $KOBu^t$:

The experiment (**a**) above was repeated, except that the amounts of $KOBu^t$ and MeI used were reduced to one equivalent apiece. The product obtained by this method consisted of four components in the following proportion: starting material - 9.7 %: trimethylated - 59.5 %: dimethylated isomer 1 - 16.8 %: dimethylated isomer 2 - 13.9 %.

c. Alkylation under thermodynamic enolate formation conditions :

To 98 mg (0.5 mmol) of **64** taken in a round bottomed flask set up as before (**a**) was added 0.5 mL of 1M $KOBu^t$ in THF (0.5 mmol). The mixture was stirred at room temperature for 1.5h before the alkylating agent (MeI, 0.5 mmol) was added. The mixture was then refluxed for 5min and worked up as before to again give a mixture of products which did not include the monoalkylated product.

d. Alkylation under thermodynamic enolate formation conditions in t-butanol as solvent :

A mixture of 98 mg (0.5 mmol) of **64**, 6 mL of t-butanol, 0.5 mL 1M $KOBu^t$ (in THF) was stirred under a nitrogen atmosphere for 1.5 h at room temperature, then gently warmed for 15 min (40°C). To this solution was added 0.5 mmol of methyl iodide and the mixture was heated at 80°C for 20 min, then cooled to room temperature and stirred overnight. Precipitated potassium iodide was filtered off and washed with ether. The washings were combined with the filtrate and the solvent was evaporated under reduced pressure to give a very sticky material. This was redissolved in ether, washed with 3 mL of 3N HCl, water, saturated aqueous sodium bicarbonate and brine. The ether solution was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give traces of a product. This product was found to be mainly starting material (71 %) and there was no evidence for the presence of the monoalkylated product (GC / MS analysis).

e. Alkylation using sodium hydride as base and DMSO as solvent [53]:

Sodium hydride (30 mg, 53 % suspension in oil) was washed with pet. ether and dried under nitrogen, then mixed with dry DMSO (10 mL) and stirred at 60°C for one hour. After the mixture was cooled to room temperature, 98 mg (0.050 mmol) of **64** in 5 mL of dry DMSO was added and the mixture was again stirred at room temperature for 1.5h. An equivalent of methyl iodide was then added and stirring was continued for a further 5h. To the reaction mixture 30 mL of saturated NH_4Cl solution was then cautiously added and the product was extracted with ether (30 mL X 4). The combined ether extracts were washed with water, and brine and dried over anhydrous $MgSO_4$. A product mixture (70 mg) showing peaks (GC/MS) corresponding to the mass of the

dialkylation product was obtained, when the solvent was evaporated under reduced pressure.

f. Alkylation of the thermodynamic enolate formed by using bromo magnesium diisopropylamide (BMDA) and methyl iodide as the alkylating agent[51]:

To a solution of 0.09 mL (0.63 mmol) of diisopropyl amine in 10 mL of anhydrous ether under nitrogen at 26°C, was added 0.21mL (0.63 mmol) of a 3.0 M etheral solution of methyl magnesium bromide. The mixture was stirred for 6h at room temperature during which time a white suspension of BMDA was formed. To this suspension was added 96 mg (0.49 mmol) of keto ester **64**, 213 mg (95 µL, 1.5 mmol) methyl iodide, 0.21 mL of triethylamine and 0.04 mL of HMPA. The reaction was monitored by TLC and no change could be observed even after several days of stirring (4 days). NMR of the product (45 mg) was the same as that of the starting keto ester **64**.

g. Alkylation using BMDA and methyl triflate:

A mixture of 0.19 mL (1.3 mmol) of diisopropylamine and 0.42 mL(1.3 mmol of methyl magnesium bromide (3.0 M in ether) was stirred in 25 mL of ether overnight at room temperature. To the white suspension formed was added 182 mg (1.00 mmol) of **64** in 2 mL of ether. After the mixture was stirred for 10 min, 113 µL (1.00 mmol) of methyl triflate was added and stirring was continued for 24 h at room temperature. The reaction mixture was quenched with ice cold water and extracted with ether. The ether layer was washed with water, saturated aqueous sodium bicarbonate, water and brine. The solvent was evaporated under reduced pressure after drying over anhydrous $MgSO_4$

and the starting (150 mg) ester was recovered.

h. Deprotonation and alkylation of **64** using a highly reactive form of Fe (0)[52] :

To an etheral solution of 81 mg (0.50 mmol) of anhydrous ferric chloride in 5 ml of anhydrous ether at 0°C was added 0.50 mL (1.5 mmol) of an etheral solution (3M) of methyl magnesium bromide. The resulting slurry was stirred for 1h at 25°C before the addition of 0.45 mmol of **64** dissolved in 2 mL of ether. After 20 min, 90μL (1.5 mmol) of methyl iodide, then 40 μL of HMPA were added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4. The product obtained (70 mg) on solvent evaporation showed exactly same NMR spectrum as that of the starting material **64**.

i. Alkylation using sodamide as base and liquid ammonia as solvent :

A solution of 182 mg (1.00 mmol) of **65** in 1 mL of ether was added to a refluxing suspension of 117 mg (3.00 mmol) of sodamide in 20 ml of liquid ammonia and the mixture was stirred for 1 h. To this was added 142 mg (3.00 mmol, 62μL) of methyl iodide and the mixture was refluxed for 8 h, then quenched with ammonium chloride (200 mg). Ammonia was allowed to evaporate under nitrogen and the product was extracted with dichloromethane. The organic layer was washed with water, 10 % NH_4Cl and dried over anhydrous $MgSO_4$. When solvent was evaporated under reduced pressure, 90 mg of a product was obtained. On GC / MS analysis most of the product (73 %) was found to be trialkylated (mass = 224) and the rest, starting material. Since

there was no evidence of monoalkylation the mixture was not futher purified.

Preparation of the silyl enol ether **79** :

BMDA was prepared as in **g** above and to this suspension was added a solution of 196 mg (1.00 mmol) in 20 mL of ether. After 15 minutes of stirring, TMSCl (0.40 mL, 3.0 mmol),NEt_3 (0.41 mL, 3.0 mmol) and HMPA (0.08 mL, 0.5 mmol) were added in that order. The mixture was stirred for 60h, then diluted with ether, washed with saturated aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure to give **79** in quantitative yield. NMR 0.1 (s, 9H), 0.8-1.5 (complex pattern, 13 H), 4.0 (q, 2H). GC/MS M^+at 268, M^+-Me at 253, M^+-Et at 239, M^+-OEt at 223, M^+-$SiMe_3$ at 195, M^+-$OSiMe_3$at 179.

Preparation of 4-methyl-1-penten-3-ol **80** :

Vinyl magnesium bromide(0.065 mol, 65 mL, 1M in THF) was slowly added (during 60 min) to an ice cooled solution of 3.6 g (0.05 mol, 4.5 mL) of isobutyraldehyde in 125 mL of anhydrous ether. The mixture was stirred for 2.5h at room temperature, after the addition was complete. The reaction mixture was then acidified with 3N HCl and the organic layer was separated, washed with saturated aqueous sodium bicarbonate , 10% sodium thiosulfate solution, water brine, then dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure afforded 4.55g (70 %) of alcohol **80**. This crude product was further purified by distillation for analysis purposes (bp.126-128^oC at 1atm). NMR : 0.9 (d, 6H), 1.5-2.0 (br, 1H), 2.4 (br s, 1H), 3.8 (tr,1H), 5.2 (m, 2H), 5.8 (m, 1H). IR cm^{-1}: 3450 (s, -OH), 2950 (s, -CH), 1500 (m, C-O).

Isopropyl vinyl ketone **81** from oxidation[57] of **80** using aqueous chromic

acid :

a. Preparation of chromic acid solution : The chromic acid solution was prepared by dissolving 10 g (0.033 mol) of sodium dichromate dihydrate in 30 mL water. Sulfuric acid (97 %, 0.134 mol, 13.6 g, 7.4 mL) was added and the solution was diluted to 50 mL volume to obtain the stock chromic acid solution.

b. Oxidation : To a solution of the vinyl alcohol **80** (980 mg, 10.0 mmol) in 15 mL of ether in a three necked round bottomed flask fitted with a condenser and an adddition funnel was added 6.5 mL of chromic acid stock solution during 15 min. The mixture was stirred at room temperature for 2h and the ether layer was separated. The aqueous layer was futher washed with ether (2 X 5 mL) and the washings were combined with the original ether layer. The combined organic layers were washed with saturated aqueous sodium bicarbonate, water (4 mL), and brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated at atmospheric pressure to give 360 mg (38 %) of the vinyl ketone **81**. NMR 1.2 (d, 6H), 2.7 (m, 1H), complex pattern between 5.7 and 6.5 (3H).

Michael addition of diethyl oxalpropionate and isopropyl vinyl ketone to give the diester **82** :

A mixture of 1.26 g (0.0126 mol) of isopropyl vinyl ketone, 2.1 g (mol) of diethyl oxalpropionate, and 10 drops of triethylamine in 60 mL of 1: 1 ethanol and dry benzene was refluxed overnight. Solvents were distilled off under reduced pressure to give 3.0 g (78 %) of the Michael adduct **82**, bp 162^{o}C (2.7 mm) . NMR : 1.0 (d, 6H), 2.4 (m, 4H), 4.1 (d of q, 4H). IR in cm^{-1}: 2960 (s), 1754 (s), 1730 (s), 1715 (s), 1480 (ms).

Preparation of the hydroxy acid **83** :

The Michael adduct **82** 2.80 g (0.009 mol) was stirred with 30 mL of concentrated HCl overnight, at room temperature. The mixture was diluted with 30 mL of water then refluxed for 24h, cooled, made alkaline with concentrated NH_4OH, and extracted with ether.The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated under reduced pressure to give 952 mg (46 %) of the acid **83** (m.p. 163-165^{0}C). NMR : 0.95 (s, 6H), 0.9-1.2 (m, 3H), 1.4-2.2 (br, 2H), 2.7 (br, 1H), 4.1 (COO**H**).

Esterification of the hydroxy acid to give the hydroxy ester **84** :

A mixture of hydroxy acid **83** (0.0027mol, 546 mg), $KHCO_3$ (0.600g, 0.006 mol) and MeI (852 mg, 0.37 mL, 0.006 mol) in 25 mL of dry DMF was stirred overnight at room tempeature, then diluted with water and extracted with ether. The organic layer was washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the hydroxy ester **84** in quantitative yield. NMR : 0.90 (s, 3H), 0.93 (s, 6H), 1.25 (s, 3H), 3.25 (br, 1H), 3.8 (s, 3H). IR in cm^{-1} : 3514.5 (s, -OH), 1732.3 (s, ester), 1717.5 (s, keto carbonyl). GC / MS analysis revealed it to be a mixture of two epimers : M/e : M^+ 214, M^+-H_2O 196, M^+-COOMe & OH 137.

Dehydration of the hydroxy ester **84** using $POCl_3$ [59]:

a. A mixture of 53 mg (0.25 mmol) of the hydroxy ester **84**, 0.16 mL (1.8 mmol) of $POCl_3$, 0.18 mL (1.2 mmol) DBU and 2.5 mL dry pyridine was heated at reflux temperature for 21h, then cooled and poured into a mixture of 20 mL

cold 5 % HCl and 20 mL of ether. The organic layer was separated and the aqueous layer was washed with ether (2 X 15 mL). The combined organic layers were washed with water and brine, then dried over anhydrous $MgSO_4$. When the solvent was evaporated under reduced pressure a tarry decomposed material was obtained.

b. The above reaction (**a**) was repeated changing only the temperature. The reaction mixture was stirred at room temperature overnight instead of refluxing. The product (32 mg) obtained from this method showed a hydroxyl absorption in the IR, and GC / MS showed the mass of parent ion to be 214, both of which correspond to the starting material.

C. Mesylation and dehydration :

To an ice cooled solution of 107mg (0.500 mmol) of the hydroxy ester **84** in 10 mL of dry dichloromethane was added 69 mg (0.60 mmol) of methanesulfonyl chloride and 152 mg (1.00 mmol, 0.15 mL) of DBU. This mixture was stirred at ice temperature for 3h and then kept at -15^{o}C overnight, and finally poured into a mixture of 3N HCl and ether (40 mL). The two layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with water, saturated sodium bicarbonate solution and brine. The solvent was evaporated under reduced pressure after drying over anhydrous Na_2SO_4, to give 90 mg of product which had the same TLC R_f value and infrared spectrum as that of the starting material.

d. Mesylation and dehydration at room temperature :

The above reaction was repeated at room temperature with identical

results.

e. Dehydration using (carboxysulfomyl)triethylammonium hydroxide inner salt methyl ester ($MeO_2CN^-SO_2N^+Et_3$)[60] :

1. Preparation of the inner salt:

Anhydrous methanol (1.9 g, 0.055 mol) in 2.5 mL of benzene was added dropwise to a solution of chlorosulfonyl isocyanate (6.6 g, 0.05 mol) in 20 mL of benzene in a 50 mL flask fitted with an addition funnel. The mildly exothermic reaction was controlled with a cool water bath. After the addition was complete (30 min) solvent was removed under reduced pressure. The residue, a white solid, was crystallized to give a colorless crystalline solid mp 69^oC. A solution of this of this carbomethoxysulfamoyl chloride (3.47g, 0.0200mol) dissolved in 50 mL of benzene was added dropwise to a solution of triethylamine (4.6 g, 0.045 mol) in 25 mL of benzene in a 250 mL three necked round bottomed flask fitted with a 125 ml addition funnel under a nitrogen atmosphere (over 1.25 h). After the addition was complete, the precipitate of triethylamine hydrochloride was removed by filtration. Solvent was removed from the filtrate under reduced pressure and the residue was crystallized to give 3.7 g (77 %) of the inner salt (m. p. 70 - 72 ^oC lit m. p. 71-72^oC). NMR : 3.66 (s, 3H), 3.3 (q, 6H) and 1.1 (t, 9H).

2. Dehydration using the inner salt :

A mixture of 53 mg (0.25 mmol) of the hydroxy ester **8 4**, 3 mL of benzene and 143 mg (0.600 mmol) of the inner salt from part 1 above, were refluxed for 2.5 h. Water was then added to the mixture and the benzene layer was separated. This was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 50 mg of a compound which was very similar to

the starting material (IR showed the hydroxy absorption, and the R_f values of the starting material and the product were also the same).

This reaction was repeated with the same quantities of starting materials but the period of reflux was increased to 24 h. The result, however, was the same.

f. Dehydration using thionyl chloride in pyridine [58] :

A mixture of hydroxy ester **84** 53 mg (0.25 mmol), 0.7 mL pyridine and 1 mL of thionyl chloride was stirred at room temperature under an atmosphere of nitrogen for 1h, then quenched by pouring into 20 mL of ice water, and extracted with ethyl acetate (3 X 15 mL). The combined organic layers were dried and solvent was evaporated under reduced pressure to give 60 mg of product which showed a strong peak at 3500 cm^{-1} in the IR, indicating that dehydration did not take place. R_f's of both the starting material and the product were the same in TLC confirming that dehydration did not take place.

Dehydration Experiments using Concentrated Sulfuric Acid :

a. A solution of 53 mg (0.25 mmol) of the hydroxy ester **84** in 2 ml of concentrated sulfuric acid was stirred at room temperature for 2h, then carefully poured into a mixture of cold water and dichloromethane (40 mL of 1 : 1 mixture). The organic layer was separated and washed with water, dried over anhydrous $MgSO_4$, concentrated under reduced pressure to give 40 mg of product. This proved to be identical with the starting hydroxy ester by comparison of IR spectra and TLC R_f's.

b. Dehydration at 80°C for 3h :

A solution of 53 mg (0.25 mmol) of the hydroxy ester **84** in 2 ml of

concentrated sulfuric acid was heated at 80°C for 3h, then carefully poured into a mixture of cold water and dichloromethane (40 mL of 1 : 1 mixture). Layers were separated and the aqueous layer was washed twice with dichloromethane (2 X 15 mL). The combined organic layers were washed with water and brine then dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give traces of product whose TLC (hex : EtOAc) showed 7 UV active spots. This mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate to remove any acid component present. It was then analyzed by GC / MS, which revealed the presence of 8 components, 4 of which were very minor. The other 4, that were present were the following :

1. Mass 196, 10.5 %, 2. Mass 196, 49.5 %, 3. Mass 138, 12.9 % and 4. 138, 10.0 % (mass of 196 corresponds to dehydration products).

c. Dehydration at 75°C for 1h :

A solution of 53 mg (0.25 mmol) of the hydroxy ester in 2 mL of concentrated sulfuric acid was stirred at 75°C for 1h, then carefully poured into a mixture of cold water and dichlormethane. The layers were separated and the aqueous layer was further extracted with dichloromethane (2 X 15 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, water and brine, then dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave a product which showed very little IR absorption in the hydroxyl region. GC / MS of this revealed it to be a mixture of 4 components as follows :

1.Mass 196, 55 %, 2. Mass 196, 5.3 %, 3. Mass 142, 25 %, 4. Mass 138, 6.6 %.

d. A mixture of 53 mg (0.25 mmol) of the hydroxy ester **84** in 2 mL of concentrated sufuric acid was stirred at 55^{o}C for 1h, then carefully poured into a mixture of cold water and dichloromethane (20 mL of each). The layers were separated, the aqueous layer was extracted twice with dichloromethane (2 X 15ml). The combined organic layers were worked up as before (**a to c**) to obtain 40 mg of product which again consisted of 4 components whose masses and compositions were as follows:

1. Mass 196, 73.02 %, 2. Mass 196, 4.2 %, 3 & 4 together contributed to 22.6 % of the product.

The IR of the crude product showed peaks at 1772 (m), 1734 (s), and 1684 (s) cm^{-1}. Further purification and assignment of the correct structures to the individual peaks is currently being pursued by Pauline Hamilton in our laboratories.

CHAPTER 4

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