

1971

Synthetic approaches to the eremophilane sesquiterpenes

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Iowa State University

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SESQUITERPENES.

Iowa State University, Ph.D., 1971
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Synthetic approaches to the eremophilane sesquiterpenes

by

Richmond Mullins Starrett

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of/Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State University
Ames, Iowa

1971

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DEDICATION

To my wife, Mary, and to my son, William
whose love, understanding and patience
made the pursuit of this research
a meaningful experience

To my parents, whose love,
guidance, and patience made
this work possible

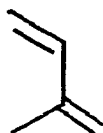
INTRODUCTION

For many centuries, Man has been intrigued with the numerous essential oils which he has been able to extract from various sources within his immediate environment. He has employed these essential oils as poisons to kill his enemies, perfumes to attract and subdue his loves, and for a multitude of other purposes to advance his species.

The essential oils are largely terpenes, which contain, by definition, ten carbon atoms in the basic skeleton. A significant fraction, however, are sesquiterpenes, an ever-expanding group of naturally occurring materials strictly defined as containing fifteen atoms in the basic skeleton. The more popular term sesquiterpenoid, like terpenoid, is generally employed with reference to materials exhibiting a close structural or biogenetic relationship to the sesquiterpenes but not necessarily containing fifteen carbon atoms.

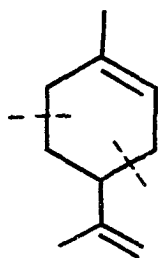
A number of impressive texts have been published which deal, at least in part, with the various sources, isolation techniques, structure elucidation methods, and nomenclature of sesquiterpenes. In this connection, the author recommends the works of Simonsen¹, de Mayo², Pinder³, and Richards and Hendrickson⁴. In all of these texts, the biogenetic origins of the sesquiterpenes are generally discussed in terms of the so-called "isoprene rule", first expounded by Wallach in 1887⁵.

The rule states, in its simplest form, that the carbon skeletons of the sesquiterpenes can be built up by the union of three isoprene ($\overset{1}{\curvearrowright}$) or isopentane ($\overset{1}{\curvearrowright}$) residues. The units

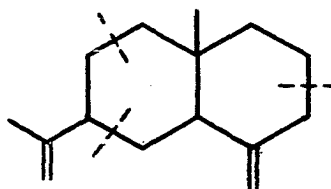


$\overset{1}{\curvearrowright}$

are generally joined in a head to tail fashion; yielding as simple examples the terpene limonene ($\overset{2}{\curvearrowright}$) and the sesquiterpene selinene ($\overset{3}{\curvearrowright}$). It is not to be implied however, that the terpenes

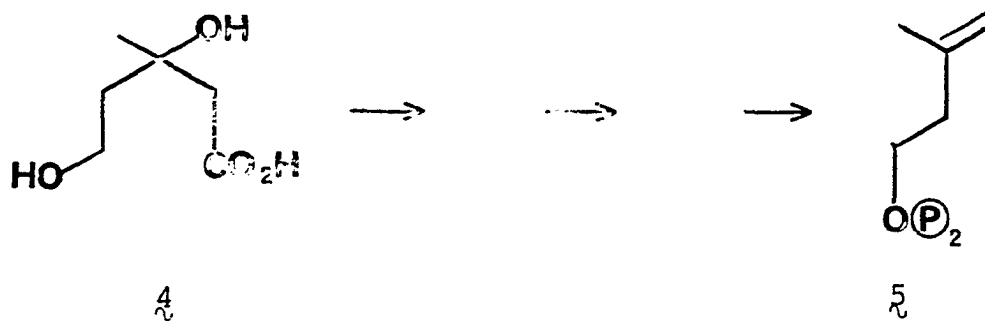


$\overset{2}{\curvearrowright}$



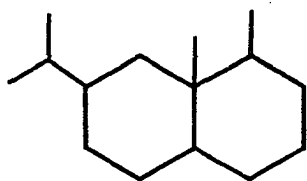
$\overset{3}{\curvearrowright}$

and their derivatives are formed in nature by condensation of "bare" isoprene units. As discussed in length by Richards and Hendrickson⁴, the recognition of the conversion of mevalonate ($\overset{4}{\curvearrowright}$) to Δ^3 -isopentenyl pyrophosphate ($\overset{5}{\curvearrowright}$) was an impressive breakthrough in terpene biosynthetic and biogenetic theory. The resulting pyrophosphate $\overset{5}{\curvearrowright}$ has been appropriately named "biochemical isoprene". Many of the more widely occurring essential



oils have been demonstrated to arise from biochemical isoprene.

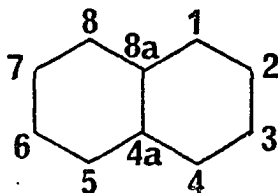
In this connection, one particular class of sesquiterpenes becomes ever more interesting, in that the basic carbon skeleton of this class cannot be accounted for by either a general (head to tail) or a special (head to head) isoprene rule. These are the eremophilane sesquiterpenes⁶, which exhibit a skeleton as shown below, and it is with the attempted stereoselective synthesis of a particular eremophilane sesquiterpene that this work is concerned.



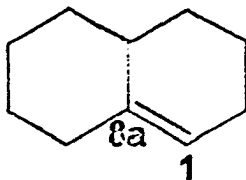
NOMENCLATURE SECTION

In order that this manuscript might assume a form as practical and useful as possible, it was decided to use the nomenclature system currently employed by Chemical Abstracts. Since this system is decidedly more cumbersome than that based on the trivial name "decalin", this section will serve as a brief explanation of Chemical Abstracts nomenclature. For further information, the reader may consult references 7, 8, and 9.

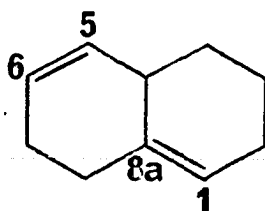
A. Numbering: The numbering system employed in this manuscript is illustrated below.



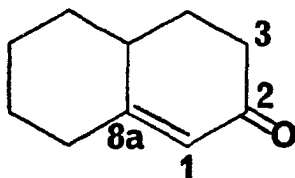
B. Compounds containing an angular methyl group: These materials are named as derivatives of the completely saturated system; 1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene. Note that this name is derived by saturation of each of the five naphthalene double bonds and designation of the added hydrogens by numerical prefixes. The position, as well as the degree of unsaturation, is indicated by the absence of numerical prefixes indicating added hydro-substituents. For example, 2,3,4,4a,5,6,7,8-octahydronaphthalene indicates unsaturation (no added hydrogens) at position 1,8a. The prefix octa- indicates the



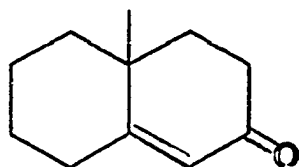
total number of hydrogens which have been added to naphthalene at the indicated positions. Again, 2,3,4,4a,7,8-hexahydro-naphthalene indicates unsaturation between positions 5,6 and 1,8a.



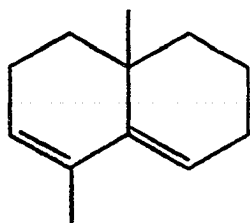
When the compound to be named is a ketone, the use of "indicated hydrogen" becomes necessary. This designation is essential since the carbonyl group occupies only "one-half" of the naphthalene double bond which is "saturated" by addition of the carbonyl. For example, the name 4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone indicates a ketone at position 2 along with the "added or indicated" hydrogen at position 3, as well as unsaturation at position 1,8. Note that the indicated



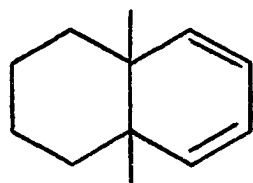
hydrogen is always given the lowest possible number consistent with a chemically correct parent compound. Substituents other than carbonyl are prefixed by numbers indicating their position but do not require the use of indicated hydrogen. A few examples will clarify this system.



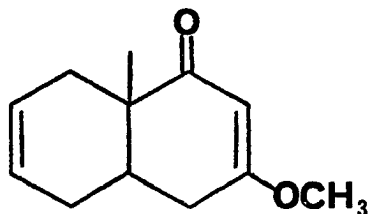
4,4a,5,6,7,8-hexahydro-4a-methyl-
2(3H)-naphthalenone



4a,8-dimethyl-2,3,4,4a,5,6-
hexahydronaphthalene



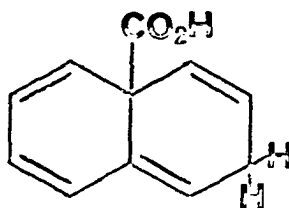
cis-4a,8a-dimethyl-4a,5,6,7,8,8a-
hexahydronaphthalene



3-methoxy-8a-methyl-4a,5,8,8a-
tetrahydro-1(4H)-naphthalenone

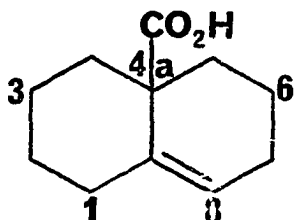
C. Compounds containing an angular carbomethoxy group:

Due to the high oxidation state of the angular substituent, these compounds are named as derivatives of the parent compound shown below.



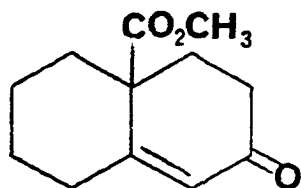
4a(2H)-naphthalenecarboxylic acid

The indicated hydrogen must be located at position 1 since a conventional structure for the unsaturated compound cannot be written with a $-\text{CH}_2-$ group at position 1. The designation of unsaturation, as well as substituent position, is accomplished in the same manner as discussed above. For example,

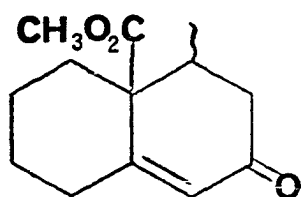


1,3,4,5,6,7-hexahydro-4a(2H)-
naphthalenecarboxylic acid.

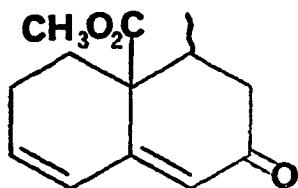
Note that the numbering system in this example is reversed such that the indicated hydrogens may have the lowest possible numbers. It is only when naming compounds with angular substituents more highly oxidized than methyl that this numbering system is employed. A few further examples are:



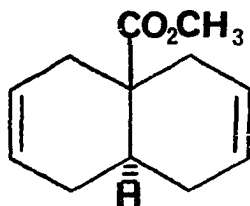
methyl 1,3,4,5,6,7-hexahydro-
7-oxo-4a(2H)-naphthalene-
carboxylate



methyl 1,3,4,5,6,7-hexahydro-
5-methyl-7-oxo-4a(2H)-
naphthalenecarboxylate



methyl 4,5,6,7-tetrahydro-5-
methyl-7-oxo-4a(3H)-naphthalene-
carboxylate



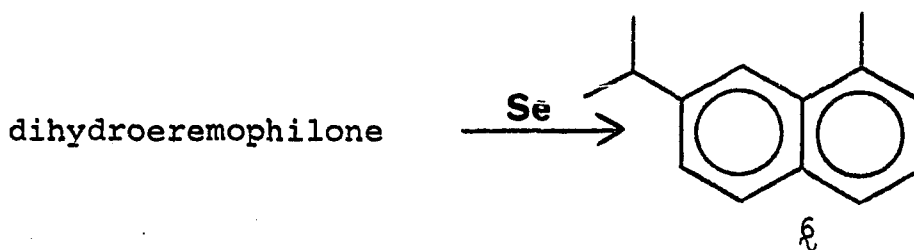
methyl 1,5,8,8a-tetrahydro-
4a(4H)-naphthalenecarboxylate

HISTORICAL SECTION

The Eremophilane Sesquiterpenes

The first isolation of an eremophilane sesquiterpene was reported by A. E. Bradfield, A. R. Penfold, and J. L. Simonsen¹⁰ in 1932. These workers digested the wood oil of Eremophila mitchelli, a studdy shrub prevalent in southern Australia, with an aqueous sodium bisulfite solution and isolated by fractional crystallization and subsequent decomposition of the bisulfite addition compounds, three distinct products. The first of these, a crystalline ketone with molecular formula $C_{15}H_{22}O$ was named eremophilone. The other products were shown to be hydroxyketones and named 2-hydroxy-eremophilone and 2-hydroxy-1,2-dihydroeremophilone.

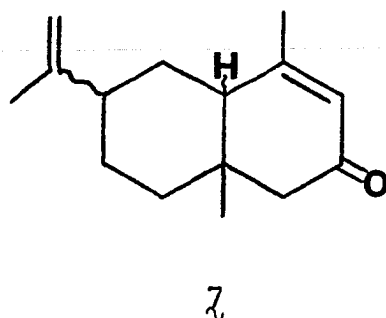
The structure of eremophilone was investigated in detail by Simonsen¹⁰, who found that treatment of dihydroeremophilone with selenium metal gave eudalene (ξ). This experiment established the naphthalene skeleton for eremophilone. In



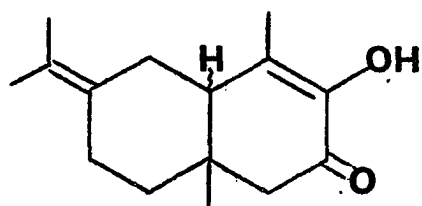
addition, the observation that eremophilone rapidly formed a crystalline hydroxymethylene derivative with base and ethyl formate as well as an oxide upon treatment with alkaline

hydrogen peroxide allowed Simonsen to deduce the presence of a $-\text{CH}_2-\text{CO}-\text{CH}=\text{CH}-$ moiety in the molecule.

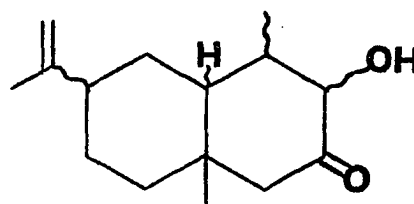
The reduction of eremophilone with sodium in absolute ethanol gave dihydroeremophilol, $\text{C}_{15}\text{H}_{26}\text{O}$, which upon treatment with ozone afforded formaldehyde and a hydroxyketone, $\text{C}_{14}\text{H}_{24}\text{O}_2$. When the hydroxyketone was treated with sodium hypobromite, a carboxylic acid was obtained along with bromoform. These results clearly established the presence of an isopropenyl group in eremophilone and lead Simonsen to propose¹⁰ the following isoprenoid structure ζ for eremophilone.



The two hydroxyketones coisolated with eremophilone were subjected to similar elemental and chemical analysis, and the following structures were proposed¹⁰.



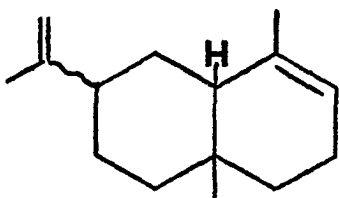
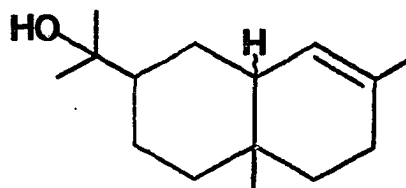
hydroxyeremophilone



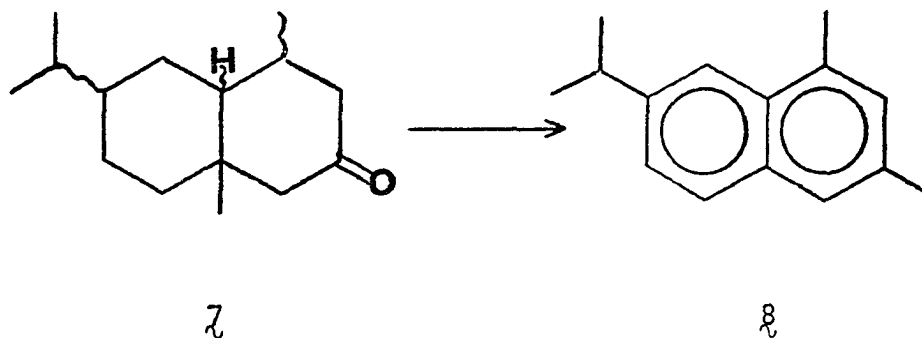
hydroxydihydroeremophilone

In this connection, it may be noted that Simonsen and his coworkers found, early in their investigations, that eremophilone oxide could be rearranged directly to hydroxy-eremophilone. Therefore, any proposed structure for eremophilone had to render itself liable to this rearrangement, the mechanism of which is not fully understood today.

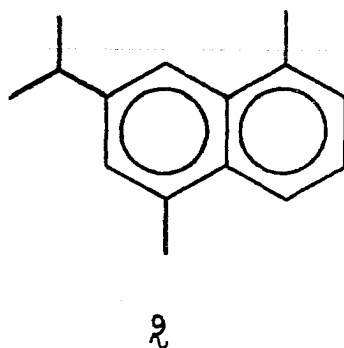
The proposed structure for eremophilone, as well as the coisolation of the two closely related hydroxyketones, suggested to Simonsen that eremophilone might be derived from either α -selinene or α -eudesmol, both known sesquiterpenes.

 α -selinene α -eudesmol.

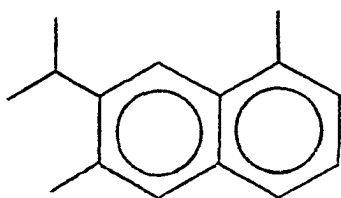
Several years later however, Simonsen and his coworkers^{11,12} described an experiment which involved the treatment of tetrahydroeremophilone with excess methylmagnesium iodide followed by dehydrogenation of the resulting alcohol with selenium metal. The isolated product was tentatively identified¹¹ as 1,3-dimethyl-7-isopropyl-naphthalene (**8**), which was to be expected from the originally proposed structure **7** for eremophilone. However, in the following year Simonsen



reinvestigated¹² the reaction and identified the isolated product as 1,5-dimethyl-7-isopropylnaphthalene (9). This

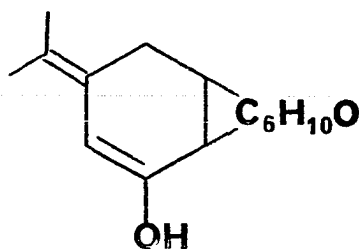
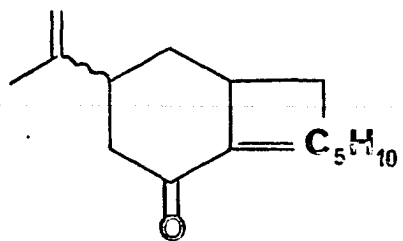


result clearly established that the carbonyl group occupied position 8 in eremophilone. Shortly thereafter, Simonsen et al., reported¹³ that reduction (Na/EtOH) and dehydrogenation (Se) of the hydroxymethylene derivative of tetrahydro-eremophilone gave 1,6-dimethyl-7-isopropylnaphthalene (10). This work completely ruled out all previously considered



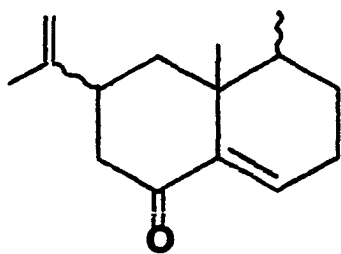
10

structures and prompted Simonsen to propose¹³ the following general structures for eremophilone and hydroxyeremophilone,

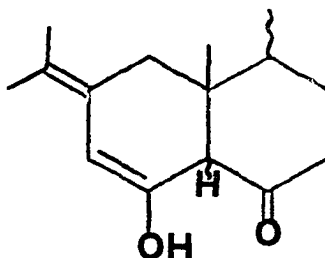


respectively. It remained for Sir Robert Robinson to suggest to Penfold and Simonsen¹⁴ that perhaps the eremophilane sesquiterpenes which they had isolated were exceptions to the well established isoprene rule. In any case Robinson suggested the following structures 11, 12, 13 for eremophilone, hydroxyeremophilone, and hydroxydihydroeremophilone, respectively.

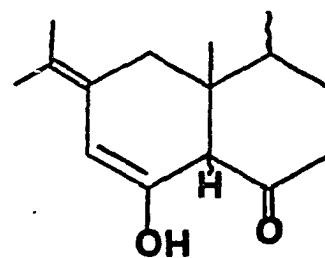
The following structure 12 for hydroxyeremophilone was shown to be at least partially correct by treatment of the corresponding benzoate with ozone, followed by dehydrogenation of the resulting keto acid with selenium metal to yield



11



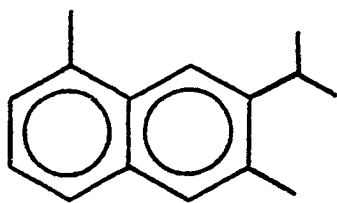
12



13

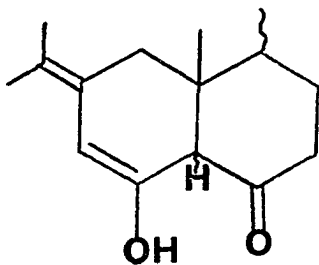
o-xylene. However, oxidation of hydroxyeremophilone with alkaline hydrogen peroxide gave two stereoisomeric hydroxyacids, which was suggestive of a potential 1,2-diketone structure. Also, the reduction (Na/EtOH) product of hydroxyeremophilone gave a positive test with Criegee's Reagent, thus confirming the presence of a glycol, presumably a 1,2-glycol. Since structure 12 could not adequately account for the formation of a 1,2-glycol, further investigation became necessary.

In their last two publications in this area, Simonsen and his coworkers described^{15,16} an experiment which involved treatment of tetrahydroxyeremophilone methyl ether with excess methylmagnesium iodide followed by dehydrogenation with selenium metal. The isolated product was identified as 1,6-dimethyl-7-isopropyl-naphthalene (14), whereas the proposed structure 12 would be expected to yield 1,4-dimethyl-7-isopropyl-naphthalene (15). This lead Simonsen to propose 16 for

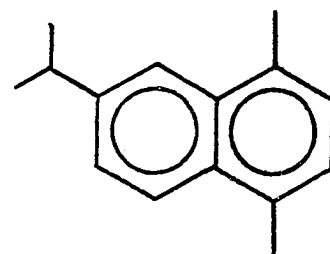


14

isolated



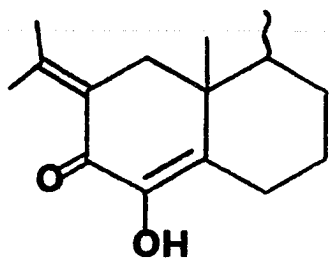
12



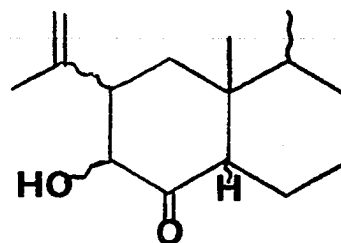
15

expected

hydroxyeremophilone and 17 for hydroxydihydroeremophilone. In addition, Simonsen presented¹⁶ an elaborate scheme to account



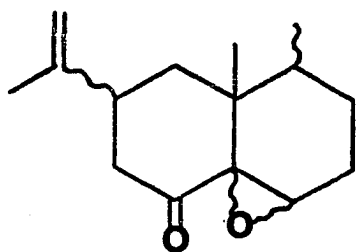
16



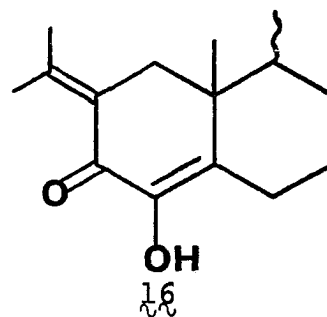
17

for the aforementioned rearrangement of eremophilone oxide to hydroxyeremophilone, now formulated as the transformation

18 + 16.



18

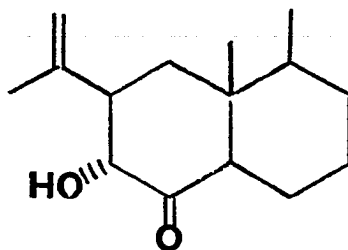


16

In 1953, Geissman¹⁷ confirmed Simonsens' proposed structures by the positive identification of a "phenolic" material isolated in trace amounts during the oxidation of hydroxyeremophilone methyl ether.

With the carbon framework of the three new eremophilane sesquiterpenes finally established, attention was focused on the stereochemistry of the trio.

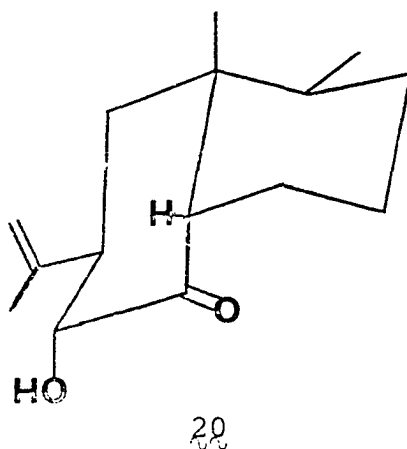
An X-ray diffraction study^{18,19} of natural (+)-hydroxydihydroeremophilone showed the relative stereochemistry of the natural material to be as indicated in 19. The molecule is



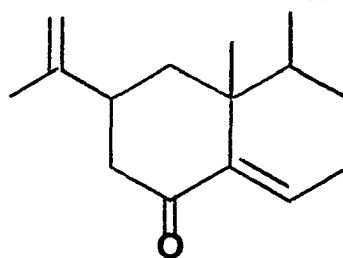
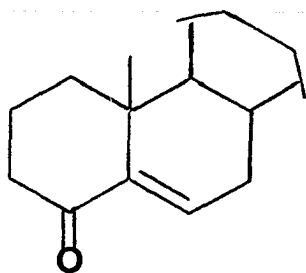
19

arranged in a cis"steroidal" manner, with all the non-angular groups disposed equatorially²⁰. The cis ring fusion is favored since only this conformation allows all the non-angular groups to be equatorial.

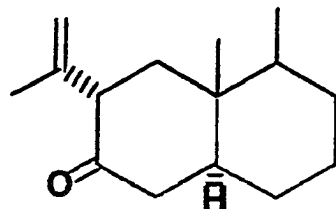
With respect to the stereochemistry of eremophilone itself Klyne²⁰ noted the similarity in the molecular rotations of natural (-)-eremophilone and steroidal 5-en-4-ones, such as



cholest-5-en-4-one (21), and deduced the absolute configuration of (-)-eremophilone to be 22. Shortly thereafter, Djerassi et al., presented²¹ optical rotatory dispersion (ORD) data

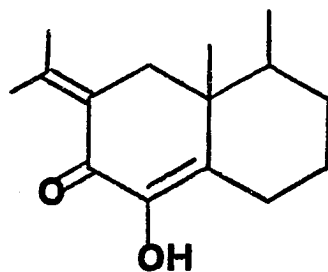


which lead to the opposite assignment. However, later recognition of the fact that the ORD comparisons of eremophilone and its derivatives with reference steroids were invalid due to serious conformational (vida infra) differences between the two series lead Djerassi and his collaborators to reinvestigate^{22,23} the original assignment. In 1960, they presented²³ a stereochemically unambiguous correlation of eremophilone, hydroxyeremophilone, and hydroxydihydroeremophilone with ketone 23,



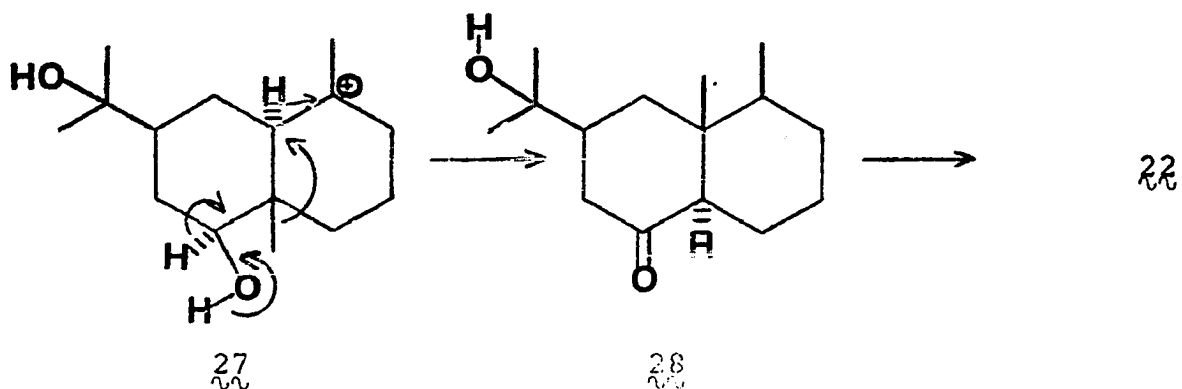
23

of known²³ absolute configuration. This work convincingly proved the absolute configuration of natural (-)-eremophilone to be as originally suggested by Klyne²⁰, namely 22, as well as that of hydroxyeremophilone to be 24.

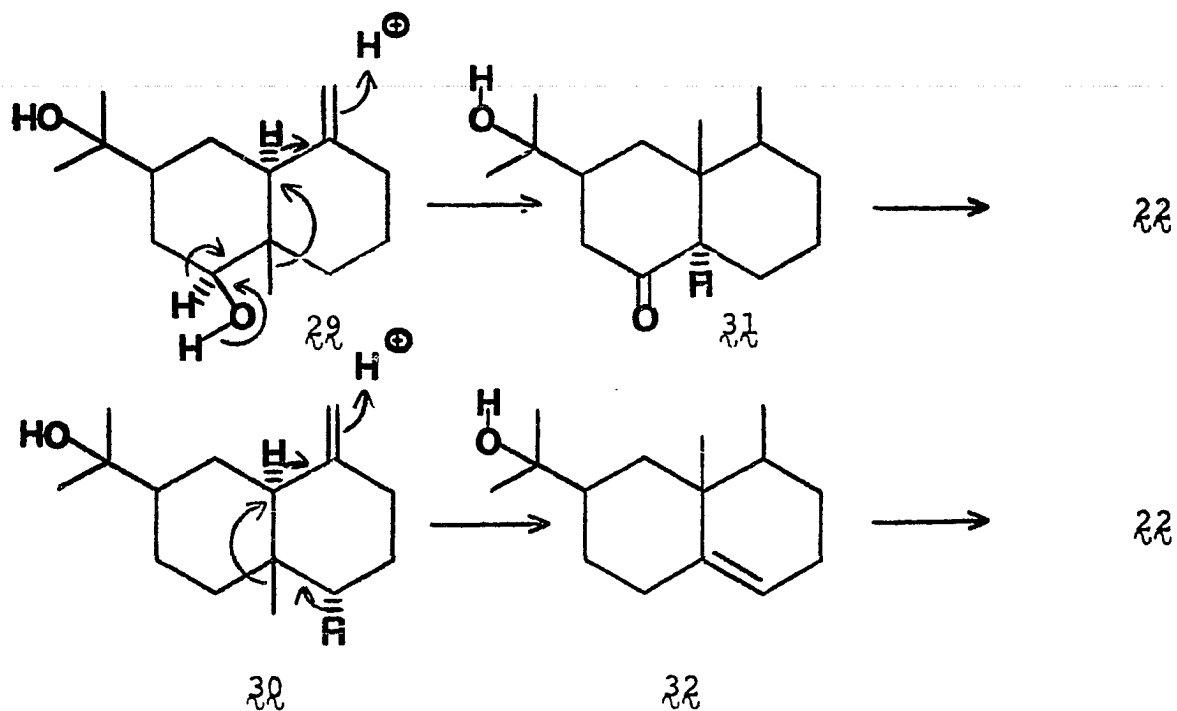


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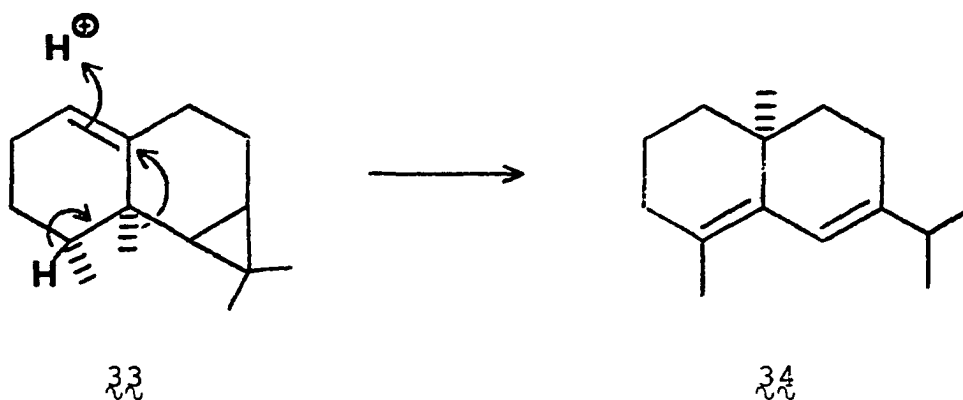
In addition to the above work, Djerassi et al., presented^{22,23} ORD evidence which indicated that the carbonyl-containing ring of eremophilone (22) has a twist-boat conformation. This conformation allows the severe 1,3-diaxial interaction between the isopropenyl and angular methyl groups, which exist when the ring is a chair, to be avoided. It was



collaborators²³ prefer olefinic precursors, such as 29 and 30 .



Buchi et al.,²⁶ has observed a similar methyl migration from calarene (33) to the diene 34 , but did not investigate the reverse reaction.

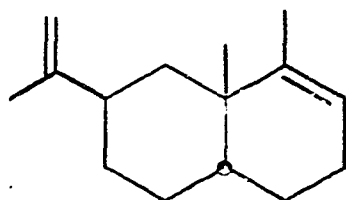


Heathcock and his coworkers^{27,28} have studied the 1,2-methyl migration as a possible synthetic route to the eremophilane sesquiterpenes, but with little success.

To date, no biogenetic studies on eremophilane sesquiterpenes have been reported.

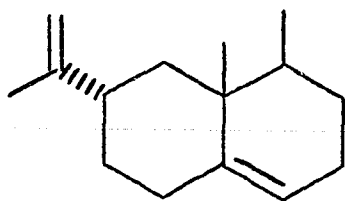
Since the isolation of eremophilone and the related hydroxyketones in 1932, the number of known sesquiterpenes with the eremophilane skeleton has increased rapidly. In order to emphasize the scope of the eremophilane family, a few recently isolated and in some cases recently synthesized eremophilane sesquiterpenes will be briefly discussed.

1. Eremophilene - This eremophilane sesquiterpene has been isolated in the levorotatory form from P. japonicus²⁹, and in the dextrorotatory form from Valeriana officinalis³⁰. Structure 35 has been proposed³⁰ for eremophilene but recent synthetic efforts by Piers and Keziere³¹ appear to render this structure invalid.



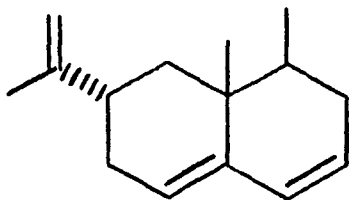
35

2. Valencene - This material was recently isolated from orange peel oil^{32,33}. The proposed³³ structure 36 has been confirmed by total synthesis³⁴.



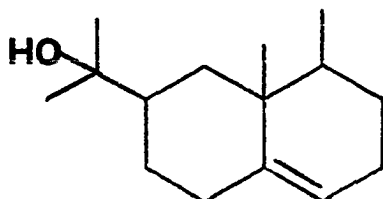
36

3. Nootkatene - Isolated as the major hydrocarbon constituent of Alaska cedar wood³⁵, structure 37 was proposed by MacLeod³³ on the basis of a partial synthesis. Recently, a total synthesis was reported which confirmed the original structure.



37

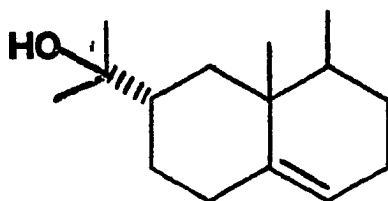
4. Eremoligenol - This material is a levorotatory tertiary alcohol found in numerous plants³⁶. The structure 38 proposed for eremoligenol is of particular interest since it is identical with the hypothetical intermediate derived from methyl



38

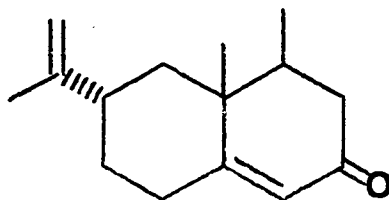
migration of β -eudesmol (30). - The isolation of this material from natural sources lends considerable support to the biogenetic theory expounded by Djerassi²³ and others.

5. Valerianol - This eremophilane sesquiterpene is the C-6 epimer of eremoligenol (38), and may well be the biogenetic precursor of the other C-6 epimeric eremophilane sesquiterpenes (vida infra). The alcohol occurs in *Valeriana officinalis*³⁷, and has been shown^{34,37} to possess structure 39.



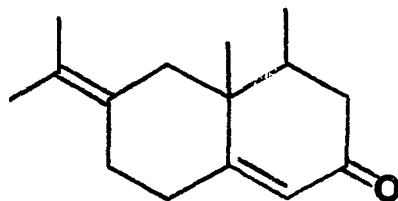
39

6. Nootkatone - This material is a crystalline ketone isolated^{33,38} from grapefruit peel oil and is valued for its contribution to the flavor of grapefruit. Several recent total syntheses^{39,40} have confirmed the structure of nootkatone to be 40.



40

7. α -Vetivone (isonootkatone) - This ketone was originally assigned⁴¹ a hydroazulene-type structure but upon further investigation an eremophilane-type skeleton was proposed^{42,43}. Indeed, a recent total synthesis⁴⁴ of α -vetivone has confirmed its structure as 41.

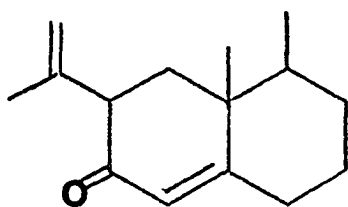


41

In addition, the name isonootkatone has been proposed⁴⁴ to eliminate the suggestion of a vetivane skeleton implied by

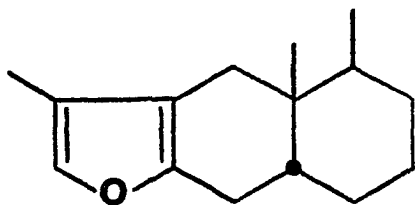
the name α -vetivone.

8. Alloeremophilone - This ketone was recently found to accompany eremophilone (22) in the wood oil of Eremophila mitchelli⁴⁵. A partial synthesis⁴⁶ from hydroxydihydro-eremophilone (19) established the structure of alloeremophilone as 42.

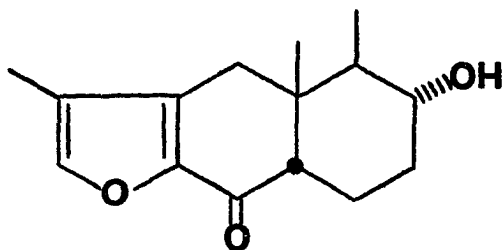


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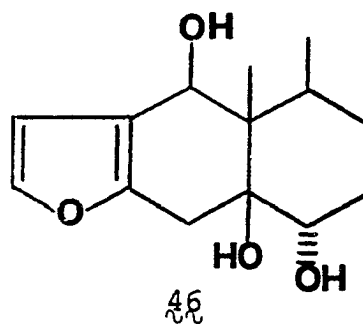
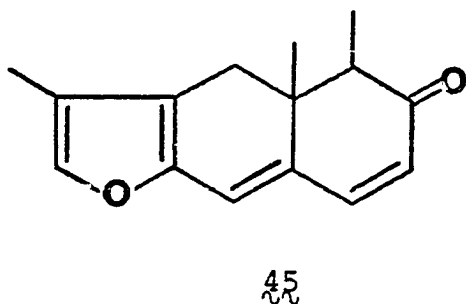
In addition to the above eremophilane sesquiterpenes, the class is extended by the existence of a large group of so-called furano-eremophilanes, exemplified by furanoeremophilane (43) euryopsonol (44), warburgin (45), and euryopsol (46).



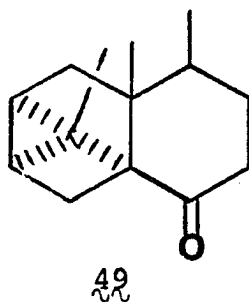
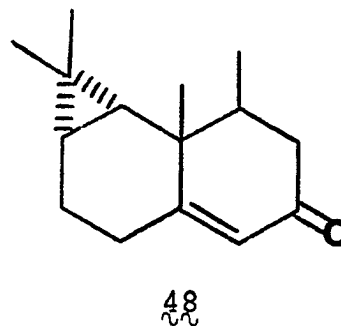
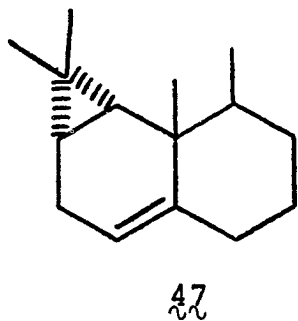
43



44



Also, a large number of eremophilane sesquiterpenes are known in which the C-6 side chain has been transformed into a three-membered ring. Examples of this group include 1,9-aristolene (47) and debione (48), as well as the tetracyclic structure ishwarone (49).

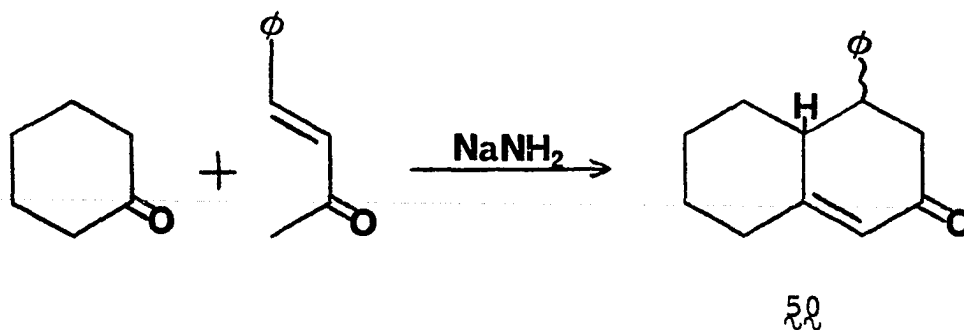


In any event, is it obvious that the eremophilane family of non-isoprenoid sesquiterpenes is exceptionally vast and is growing at a fantastic rate. For an unusually complete tabulation of the existing eremophilane sesquiterpenes, the reader may consult the excellent work by Ourisson.⁴⁶

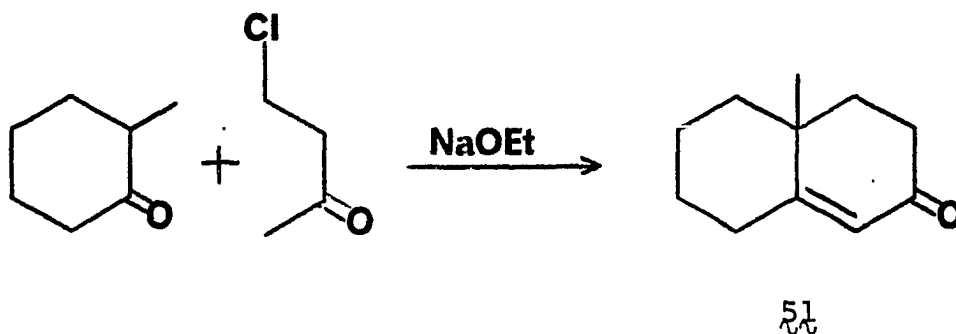
As noted in the above discussion, many of the proposed structures for the eremophilane sesquiterpenes were proven to be either correct or incorrect by a total synthesis. Indeed, the sesquiterpenes of the eremophilane family are ideal challenges for the synthetic chemist. They are not prohibitively large molecules, yet they are of sufficient size and complexity to make a freshman graduate student exert careful consideration before attempting a total synthesis. The justification for such an attempt may be had from a consideration of the literature pertaining to the eremophilane sesquiterpenes, which is noticeably lacking in a synthetic route to eremophilone (22), the first isolated and perhaps most important eremophilane sesquiterpene. In fact, all of the presently available synthetic methods which lead to eremophilane sesquiterpenes of any type are either inapplicable to eremophilone or would be exceedingly lengthy and difficult to execute. We felt therefore, that a thorough investigation aimed at the development of a highly stereoselective (if not stereospecific) synthetic route to eremophilone (22) was a worthy objective. It was toward that end that the present work was directed.

The Robinson Annulation Reaction

The first generally applicable synthetic method for the large scale preparation of the hydronaphthalene ring system was described by Rapson and Robinson⁴⁷ in 1935. Condensation of styryl methyl ketone with cyclohexanone in ether in the presence of sodamide gave the phenyl substituted naphthalenone **50** in 43%. Shortly thereafter, duFeu, McQuillin, and

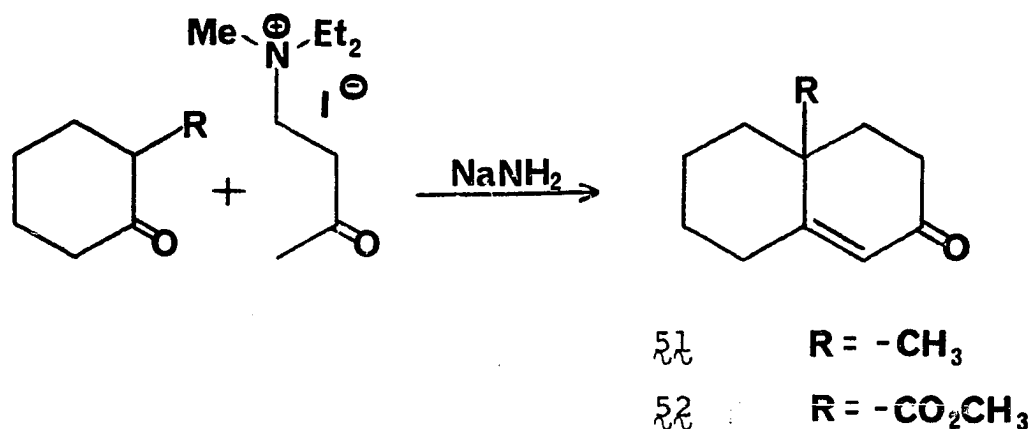


Robinson⁴⁸ reported that the condensation of 2-methylcyclohexanone with 4-chloro-2-butanone in ethanol with sodium ethoxide as the base gave 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (**51**). The yield however, was only 15-20%.



They reasoned that the chlorobutanone suffered rapid elimination of HCl to form methyl vinyl ketone which then reacted with 2-methylcyclohexanone in the same fashion as the unsaturated ketone investigated earlier. The authors felt that the low yield of cyclized product was probably due to polymerization of the methyl vinyl ketone during the rather long reaction times necessary to generate a sufficient concentration of the 2-methylcyclohexanone anion. They therefore investigated the use of other materials which could serve as active precursors for the in situ generation of methyl vinyl ketone.

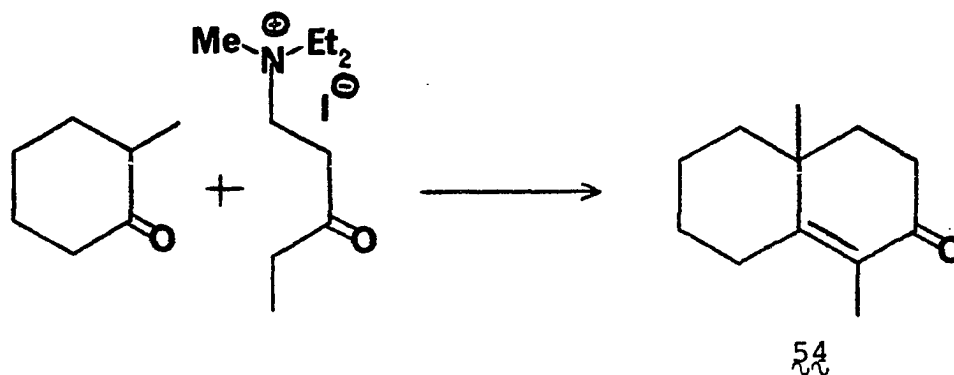
Quaternary ammonium salts, prepared by quaternization of Mannich bases, proved reasonably satisfactory. Thus the reaction, now known as the Robinson annulation reaction⁴⁹, involves condensation of 1-diethylaminobutan-3-one methiodide with 2-methylcyclohexanone in the presence of sodamide. In this manner, the yield of cyclized product 51 was raised to



Hussey et al.,⁵¹ employed potassium t-butoxide in t-butyl alcohol as the base and thereby increased the yield of crude ketone $\overset{51}{\text{R}}_2\text{C}$ to 28%. They also noted that the use of an activated ketone, specifically ethyl 2-oxocyclohexanecarboxylate, allowed the preparation of the naphthalenecarboxylic acid ester $\overset{52}{\text{R}}_2\text{C}$ in 71%, and suggested that this method might be superior in spite of its obvious length.

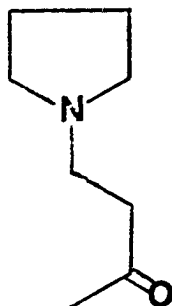
Dauben and his students⁵² used the procedure of Hussey⁵¹, as well as that of Cornforth and Robinson⁵⁰, and adjusted the ratio of methiodide to ketone to 1.9:1. They were thus able to obtain ketone $\overset{51}{\text{R}}_2\text{C}$ from 2-methylcyclohexanone and 1-diethylaminobutan-3-one methiodide in 42%.

Gunstone and Heggie⁵³ employed the Mannich base methiodide precursor for ethyl vinyl ketone, namely 1-diethylaminopentan-3-one methiodide, and obtained ketone $\overset{54}{\text{R}}_2\text{C}$ in 46%.



Yanagita and Yamakawa⁵⁴ attempted to use the Mannich base as the free amine, without solvent, in the presence of metallic sodium and thereby obtained $\overset{54}{\text{R}}_2\text{C}$ in 35% yield. Alternatively, the use of 1-N-piperidinobutan-3-one ($\overset{55}{\text{R}}_2\text{C}$) as the Mannich base

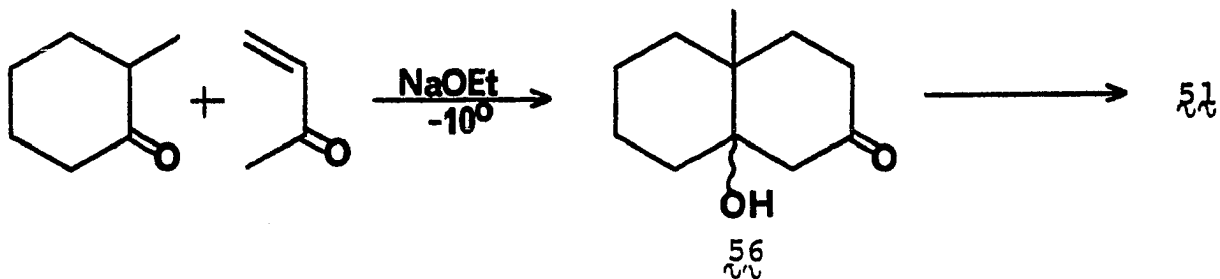
gave ketone 51 in 32%.



55

In addition to the disappointing yields, there were several indications that the cyclic ketones produced in the Robinson annulation reaction were generally obtained in a state of questionable purity 55 .

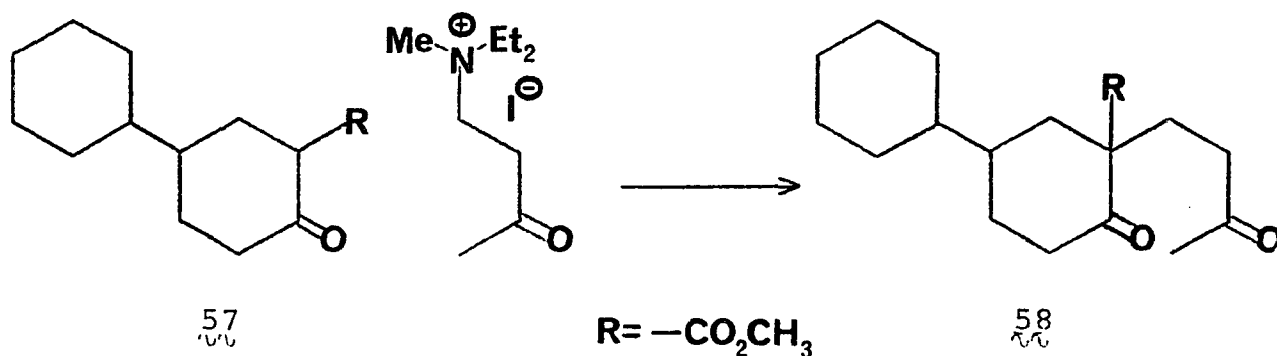
Recently, Marshall and Fanta 56 reported the isolation of the intermediate ketol 56 , in 50-55%, by the reaction of methyl vinyl ketone itself with 2-methylcyclohexanone at -10° in the presence of a catalytic amount of sodium ethoxide, followed by dehydration to yield ketone 51 in a 45% overall



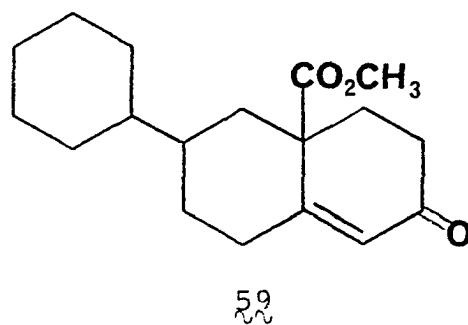
yield. The product isolated was also demonstrated to be exceptionally pure. The use of a catalytic amount of base thus significantly reduced the polymerization of the methyl vinyl ketone which had plagued earlier workers.

Finally, Ross and Levine⁵⁷ have reported the preparation of ketone $\overset{\sim}{\underset{\sim}{51}}$ in a 55.5% yield, the best to date. They employed potassium hydroxide as the base in an ethanol-ether solvent under very well-defined conditions.

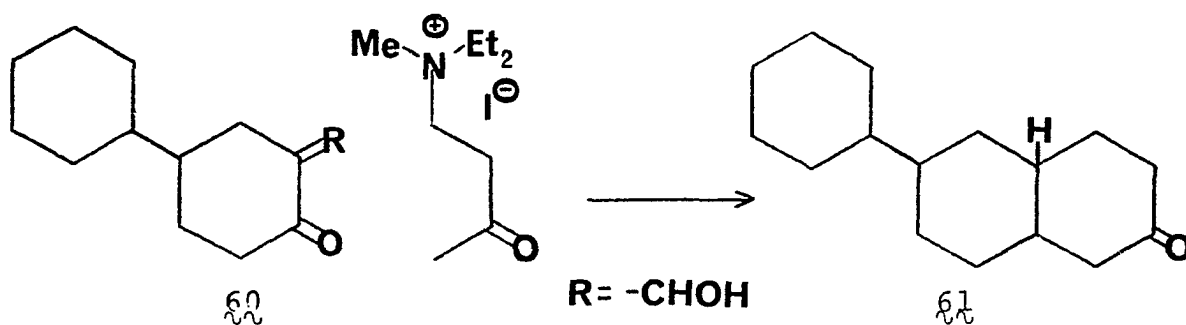
Throughout the above discussion, it has been repeatedly obvious that cyclohexanones activated in the α -position are necessary for the Robinson annulation reaction to proceed in high yield. For example, Shunk and Wilds⁵⁸ condensed β -keto ester $\overset{\sim}{\underset{\sim}{57}}$ with the Mannich base methiodide and isolated the



ester dione $\overset{\sim}{\underset{\sim}{58}}$ in 95% yield. Unfortunately, they were able to effect cyclization to the vinylogous β -keto ester $\overset{\sim}{\underset{\sim}{59}}$ in only 17% by using sodium methoxide in methanol.

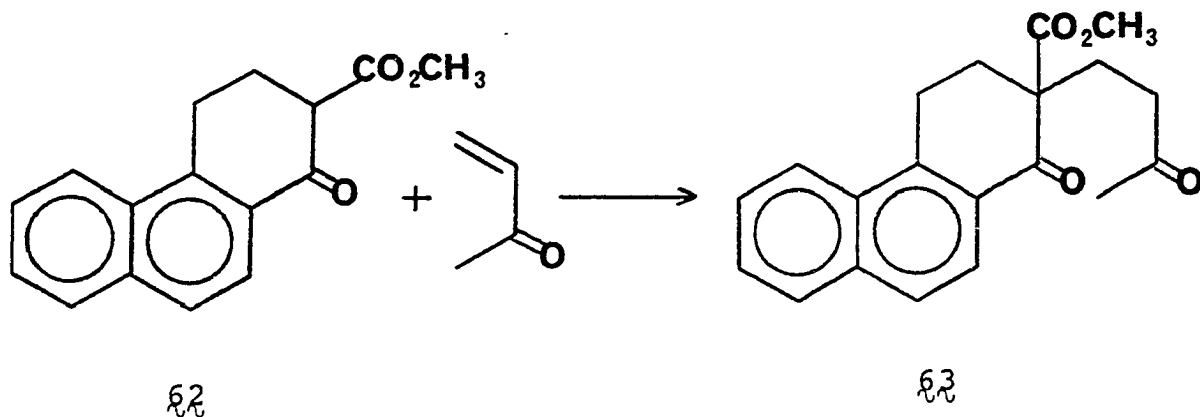


In the same paper, Wilds and Shunk also presented the first example of the use of a hydroxymethylene activating group. Condensation of ketone 60 with the Mannich base methiodide followed by treatment of the product with an aqueous sodium hydroxide solution gave the cyclized product 61 in 65% overall yield.

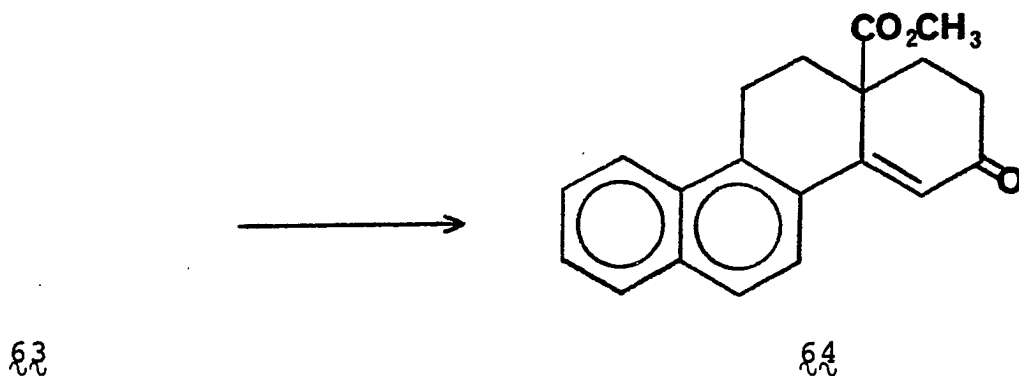


Of course, this procedure gives a product with no angular substituent.

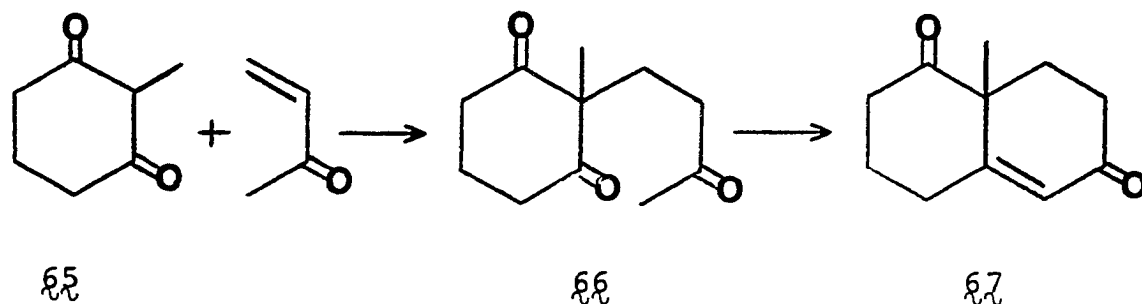
In another series, Wilds and Werth⁵⁹ were able to condense β -keto ester 62 with methyl vinyl ketone itself to obtain ester dione 63 in 93%. Again, the use of a catalytic amount



of base avoided extensive polymerization of the methyl vinyl ketone. In this case, cyclization was effected in 86% yield by treatment of dione **63** with mineral acid.



In addition to the work described above, β -dicarbonyl compounds have been employed as activated ketones in the Robinson annulation reaction. For example, Wendler et al.,⁶⁰ treated 2-methyl-1,3-cyclohexanedione (**65**) with methyl vinyl ketone in the presence of triethylamine giving trione **66** in 45%.

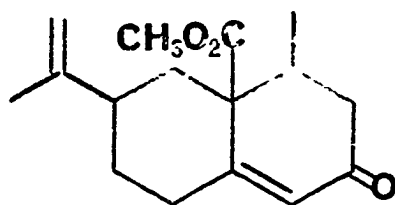


Cyclization was effected with aluminum tri-t-butoxide in 80% yield.

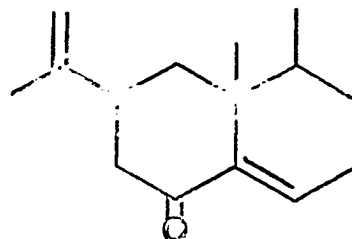
Ramachandran and Newman⁶¹ accomplished the annulation in 64% overall yield by the use of potassium hydroxide in place of the triethylamine, followed by cyclization with pyrrolidine.

After a careful consideration of the work described in this section, we decided that our synthetic objective should be two-fold.

First, we decided to undertake the development of a unique synthetic scheme which would allow preparation of methyl 1,3,4,5,6,7-hexahydro-3-isopropenyl-5-methyl-7-oxo-4a(2H)-naphthalenecarboxylate (**68**) in reasonable yield and stereochemical purity. Such a material would serve as an ideal precursor for eremophilone (**22**). In conjunction, work was initiated which was designed to provide a convenient means for the conversion of the carbomethoxy group in **68** to a methyl group. This work has been completed and summarized⁶².

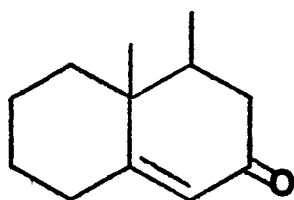


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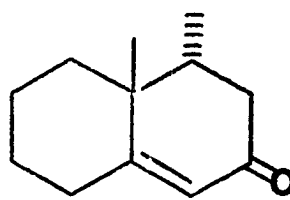


22

Second, we envisioned the development of a simple stereoselective reaction based on the Robinson annulation which would allow preparation of both cis- and trans-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69c and 69t) in high yield.



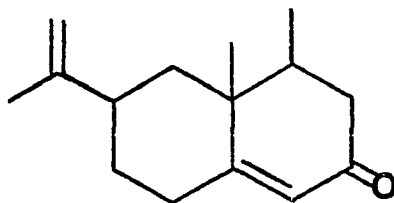
69c



69t

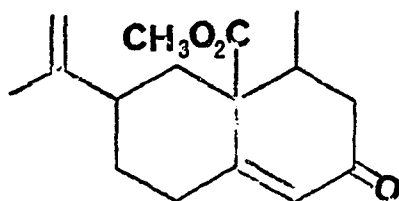
Based on the preceding discussion of the Robinson annulation reaction of unactivated ketones, this at first seemed a formidable undertaking, but the obvious and overwhelming utility of such a stereoselective synthesis provided the necessary impetus. Furthermore, if a highly stereoselective synthesis of 69c and 69t could be achieved, an investigation

of the direct preparation of 4 β ,4 α -dimethyl-4,4 α ,5,6,7,8-hexahydro-6 β -isopropenyl-2(3H)-naphthalenone (70) might be undertaken.

70
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RESULTS AND DISCUSSION

Attempted Preparation of Methyl 1,3,4,5,6,7-hexahydro-3 β -isopropenyl-5 β -methyl-7-oxo-4a(2H)-naphthalenecarboxylate (68)



68

Use of *trans*-3-penten-2-one in the Robinson annulation reaction

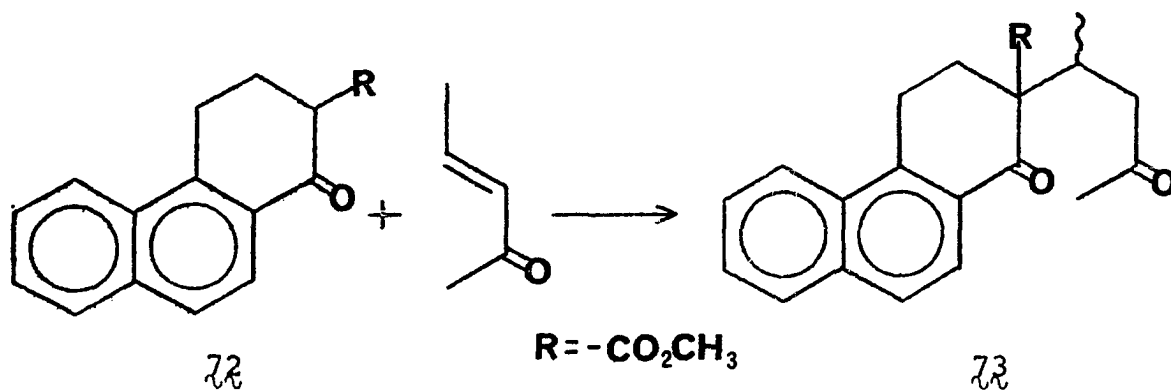
In order that the Robinson annulation reaction could be rendered applicable to a synthesis of compound 68, it became necessary to devise a method for the introduction of a methyl group at position 5 under conditions compatible with the usual Robinson annulation. In addition, it was imperative that this new procedure allow the methyl group to be introduced cis to the angular carbomethoxy group. The cis orientation was essential since the resulting synthetic scheme was to be applied to a synthesis of eremophilone, which is known²³ to have the methyl groups at positions 4 and 4a oriented cis to one another.

A brief literature search suggested that the use of trans-3-penten-2-one (71) in place of methyl vinyl ketone in the published Robinson annulation procedures might allow the

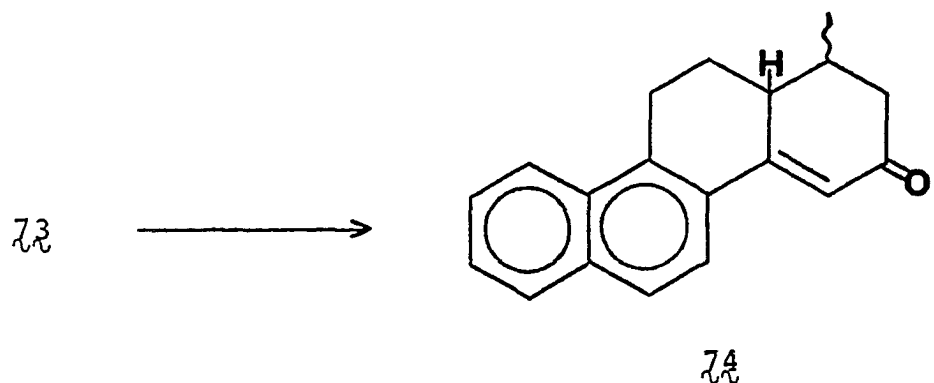


71

introduction of a methyl group at the desired position. For example, in 1946 Wilds and Djerassi⁶³ condensed β -keto ester 72 with trans-3-penten-2-one under the influence of a catalytic

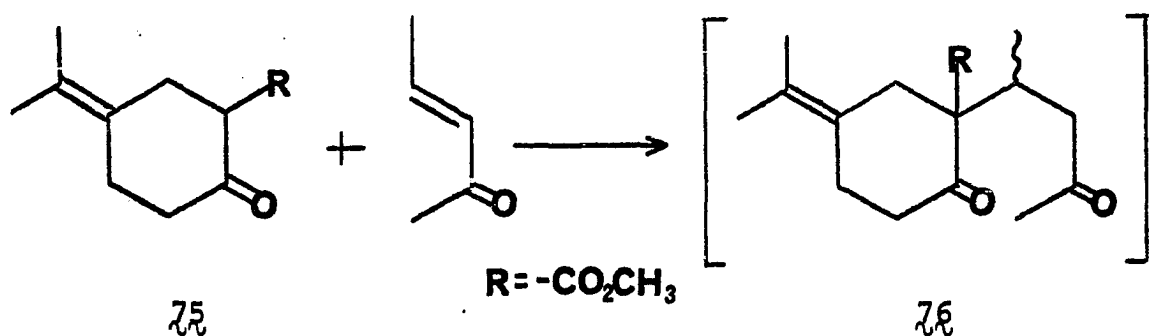


amount of sodium methoxide in methanol and obtained ester dione 73 in 58% yield. Cyclization of dione 73 with an aqueous 5% potassium hydroxide solution gave the α,β -unsaturated ketone 74 in 59% isolated yield. The cyclization conditions were harsh enough to cause elimination of the angular carbomethoxy group, presumably by decarbomethoxylation of the initially

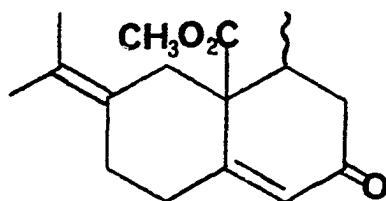


formed vinylogous β -keto ester.

More recently, Marshall et al.,⁴⁴ accomplished the annulation of the cyclic β -keto ester 75 with trans-3-penten-2-one by treatment of an equi-molar mixture of the two with a

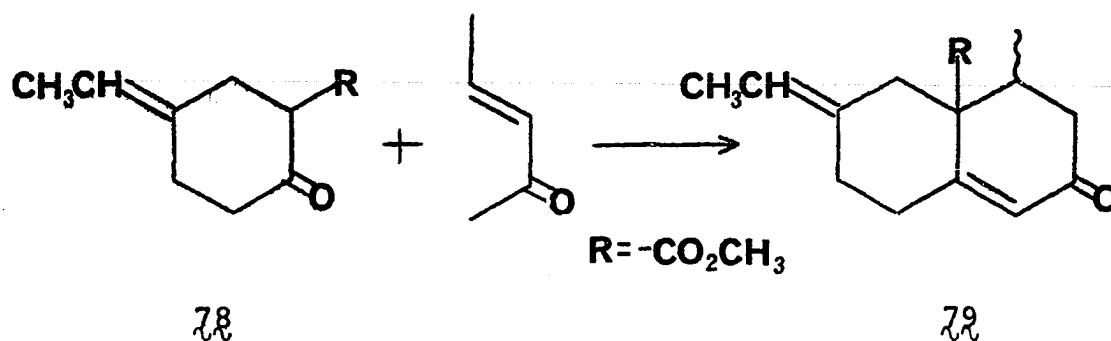


catalytic amount of methanolic sodium methoxide to effect the initial Michael addition. This presumably gave ester dione 76, although this material was not isolated. The annulation was immediately completed by treating the crude reaction mixture with excess methanolic sodium methoxide in order to effect the aldol cyclization and subsequent dehydration affording 77.



77

Using slightly different conditions, Marshall and Ruden⁴⁰ condensed β -keto ester 78 with trans-3-penten-2-one in the



78

79

presence of potassium t-amylate, followed by treatment of the resulting crude ester dione with methanolic sodium methoxide to isolate 79 in a 75% overall yield.

Thus, the use of trans-3-penten-2-one in the Robinson annulation reaction with cyclic β -keto esters seems well documented and appeared to be the method of choice for the introduction of a methyl group into position 5 in 68.

As mentioned earlier, in order that this method for the introduction of the C-4 methyl group be applicable to a

synthesis of eremophilone (22), the procedure must allow introduction of the methyl substituent in a cis stereochemical relationship to the angular carbomethoxy group. With regard to this requirement, Marshall, Faubl, and Warne⁴⁴ have suggested that steric and electronic factors should favor a transition state for the initial Michael addition as depicted in Figure 1.

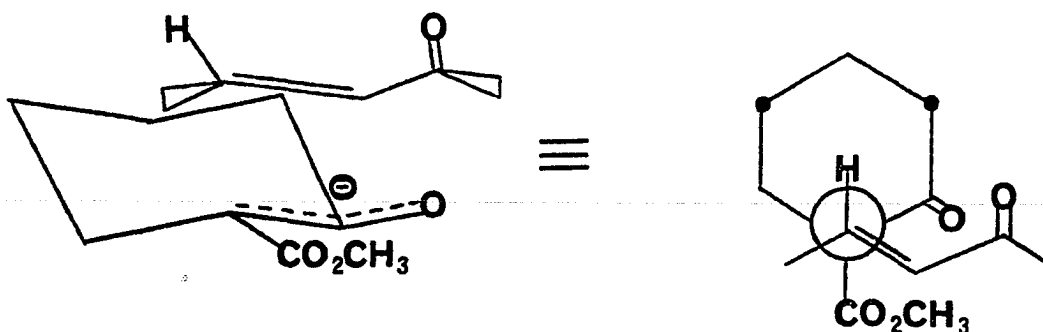
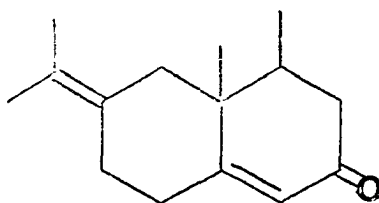


Figure 1. Diagram of the proposed⁴⁴ transition state for annulation of methyl 2-oxocyclohexanecarboxylate with trans-3-penten-2-one

According to this picture, the Michael addition (leading to a dione) would be expected to occur with the α,β -unsaturated ketone oriented above the planar enolate system such that the C-C bond formed would be axial. The unsaturated ketone should be in a cisoid conformation, since in this conformation both methyl groups are directed away from the opposing (1,3-diaxial) hydrogens. This orientation can be shown to lead ultimately

to a cyclized product such as $\lambda\lambda$ and $\lambda\rho$ in which the C-4 methyl is in a cis stereochemical relationship to the angular carbomethoxy group.

Based primarily on considerations of this type, Marshall and his collaborators⁶⁴ assigned the cis configuration to the cyclized product $\lambda\lambda$. This assignment was supported by the subsequent conversion of $\lambda\lambda$ into isonootkatone ($\lambda\lambda$), which is



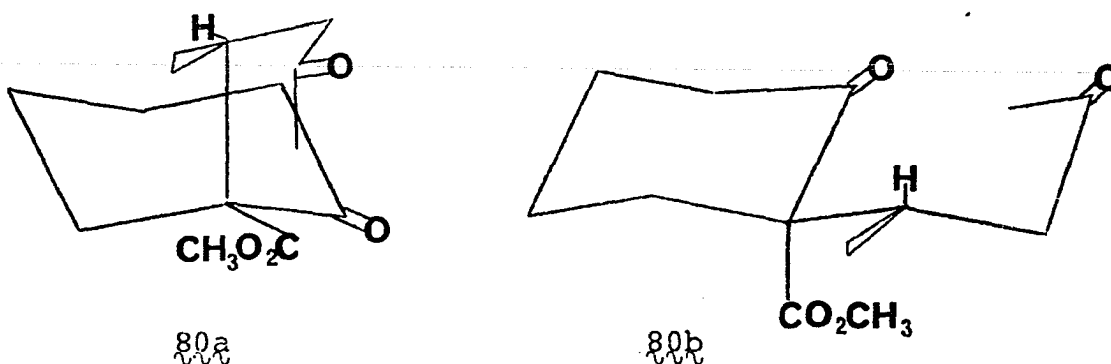
$\lambda\lambda$

known to possess the cis-4,4a-dimethyl stereochemistry. The conversion, which involved reduction of the carbomethoxy group to a methyl group, was accomplished in such a manner that the relative stereochemistry of the two groups remained unaffected.

However, the similar product $\lambda\rho$ was shown⁴⁰ to be a 3:1 mixture of carbomethoxy to methyl cis-trans isomers. In addition, reference⁶⁴ was made to unpublished observations which indicated a solvent dependency for the stereochemical outcome of the Robinson annulation reaction when trans-3-penten-2-one was used. In view of these results, it is quite possible that the product $\lambda\lambda$ was initially produced as a mixture of cis-trans isomers which was unknowingly separated

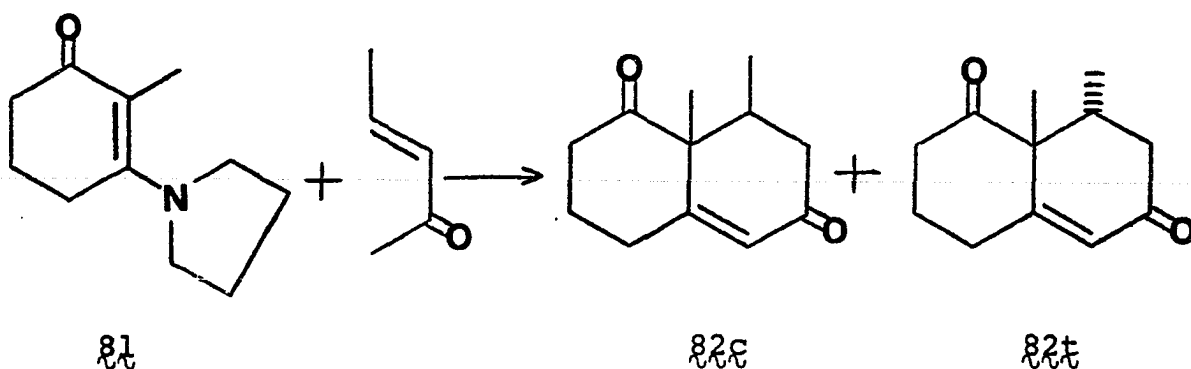
during the subsequent transformations into isonootkatone (41). The results obtained during the current study (*vide infra*) tend to support this conclusion.

At this point, it may be well to consider the stereochemistry of the intermediate dione resulting from the initial Michael addition. If the reaction were to proceed via the transition state depicted in Figure 1, the dione produced can be pictured as 80a or the alternative conformation 80b. In any event, it can easily be shown (by the judicious manipulation of Drieding models) that once the initial Michael addition

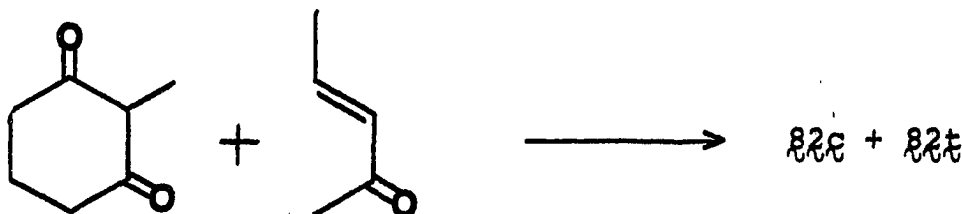


has occurred, the relative stereochemistry between the angular carbomethoxy and the secondary methyl group is determined. The direction (axial or equatorial attack on the carbonyl group of the six-membered ring) of cyclization in the aldol step of the annulation cannot affect the relative stereochemistry of the two groups. Thus, the steric and electronic factors which favor a transition state such as that shown in Figure 1 are those which in fact determine the stereochemistry of the angular carbomethoxy and the secondary methyl groups.

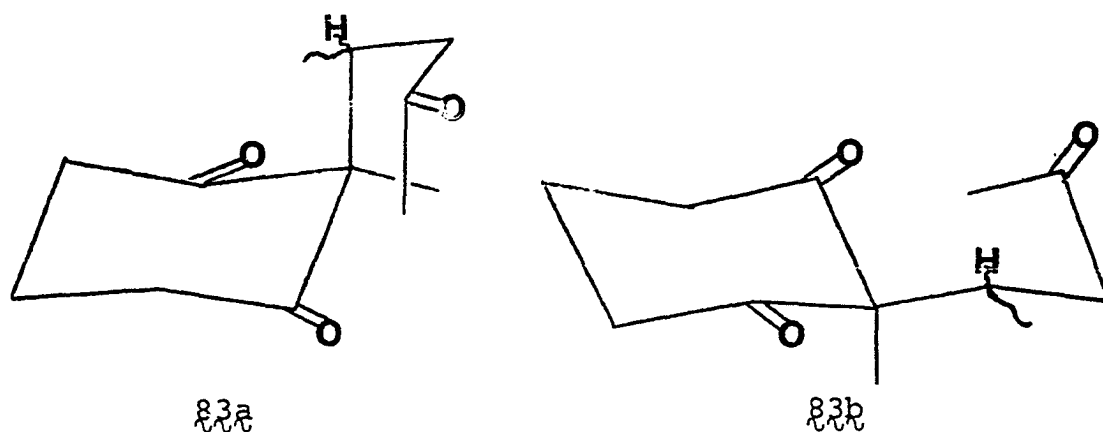
The fact that the relative stereochemistry of the two groups is unaffected by the direction of cyclization in diones such as those discussed above is in direct contrast to the situation prevailing in a similar system studied by previous investigators. For example, Coates and Shaw⁶⁵ found that the pyrrolidine enamine 81 of 2-methyl-1,3-cyclohexanedione upon reaction with trans-3-penten-2-one gave a mixture of the cis- and trans-4,4a-dimethyl naphthalenones (82c) and (82t). The



reaction could be controlled to yield a mixture which contained predominately the trans isomer 82t by the appropriate choice of solvent. Also, Hale and Zalkow⁶⁶ reported that the Robinson annulation of 2-methyl-1,3-cyclohexanedione itself with trans-3-penten-2-one gave a 1:6 mixture of cis and trans naphthalenones 82c and 82t .



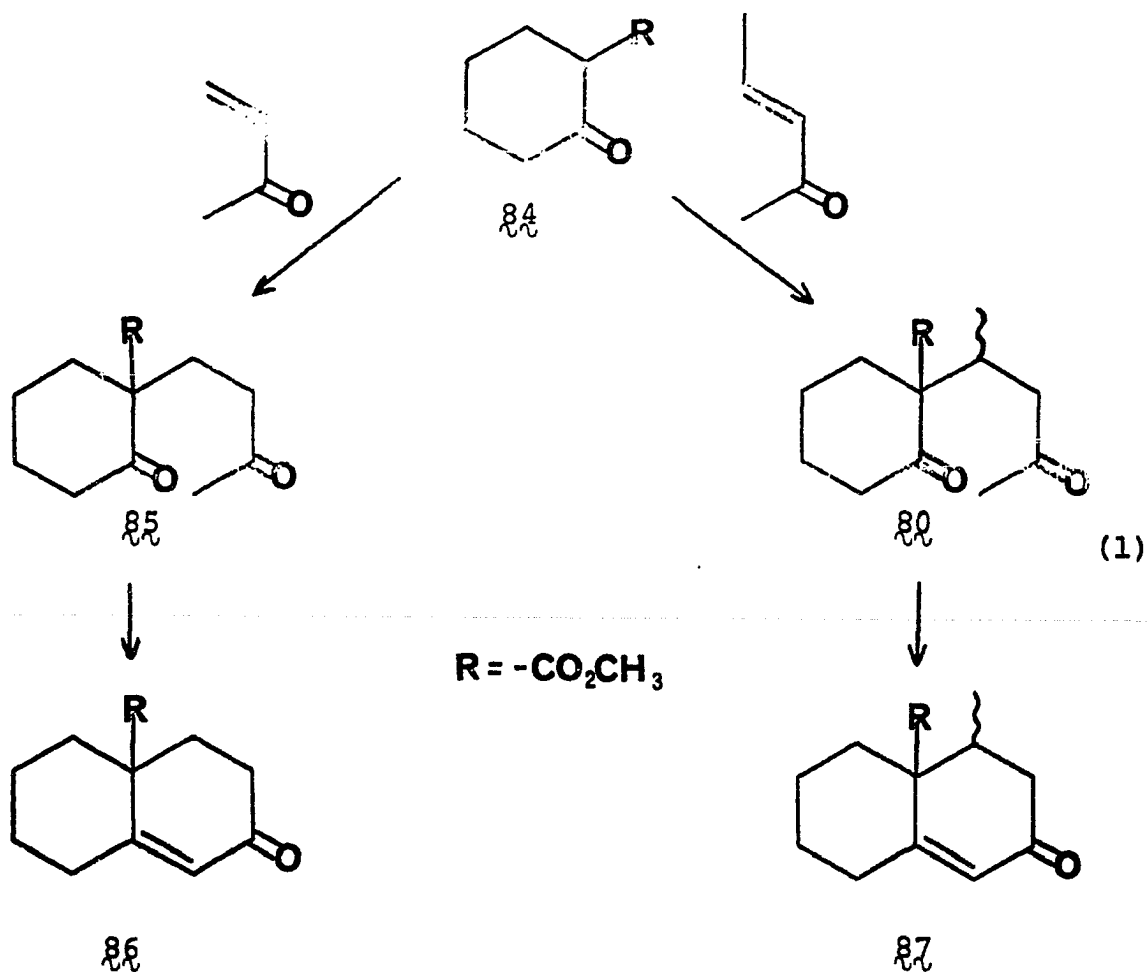
In this system, the intermediate trione 83a or 83b which



results from the initial Michael addition can cyclize to either carbonyl group (depending largely on the solvent) with the stereochemistry of the resulting compound dependent solely on the direction of cyclization. Thus, these results have no bearing on the stereochemistry to be expected from the reaction of trans-3-penten-2-one with β -keto esters such as 75 and 78 .

In order to determine the exact reaction conditions which would allow the preparation of a naphthalenone ring system which contained the required cis stereochemistry, we undertook a study of the reaction sequence shown below, scheme 1.

Condensation of methyl 2-oxocyclohexanecarboxylate (84) with methyl vinyl ketone in the presence of a 0.087N methanolic sodium methoxide solution gave methyl 2-oxo-1-(3'-oxobutyl)-cyclohexane-1-carboxylate (85) in a 58.7% isolated yield. Cyclization was effected by refluxing dione 85 for 27 hours in benzene, containing a trace of pyrrolidine⁶¹, with the



continuous removal of water. This procedure afforded methyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2H)-naphthalenecarboxylate (86) in 95.5% yield from dione 85. An alternative cyclization procedure (see experimental section) which involved the use of a large excess of pyrrolidine was found to yield highly impure

cyclized ketone 85 in very poor yield.

As expected, condensation of methyl 2-oxocyclohexane-carboxylate (84) with trans-3-penten-2-one under conditions similar to those described above gave methyl 2-oxo-1-(4'-oxo-2'-pentyl)-cyclohexane-1-carboxylate (80) in 43.6% isolated yield. However, the Michael addition was noticeably slower in this case. Whereas the alkylation reaction of β -keto ester 84 with methyl vinyl ketone was complete (negative alcoholic ferric chloride test) within three hours, that with trans-3-penten-2-one was complete only after 10.5 hours. This behavior was not unexpected, since attack at the β carbon of the α,β -unsaturated ketone system should be relatively more hindered in trans-3-penten-2-one than in methyl vinyl ketone due to the additional methyl group attached to the β carbon.

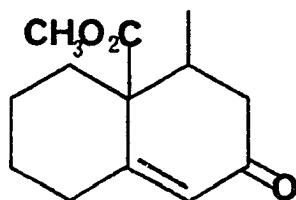
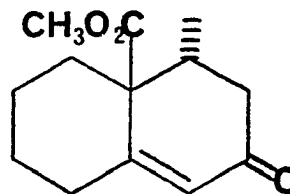
At this point, the similarity between the two reaction systems ended. Numerous attempts to cyclize dione 80 with pyrrolidine in benzene, the method which had been highly successful in the previous system, proved futile. For example, the cyclized product 86 from β -keto ester 84 and methyl vinyl ketone could be obtained in 95.5% yield as described above, whereas identical treatment of dione 80 gave less than 15% cyclization after 200 hours. We can offer no reasonable explanation for this unusual behavior. In fact, an examination of molecular models indicated that the additional methyl group (the only difference between the two systems) should have little if any steric effect on the cyclization step.

We were however, able to effect cyclization by treatment of dione 80 with excess methanolic sodium methoxide, a procedure eventually published by Marshall *et al.*,⁴⁴ in 1967. This procedure afforded methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenecarboxylate (87) in a 71.3% yield from dione 80 . In addition, an experimental procedure was developed whereby it became unnecessary to isolate the intermediate dione 80 . This method involved treatment of methyl 2-oxocyclohexanecarboxylate (84) with *trans*-3-penten-2-one in the presence of a catalytic amount of methanolic sodium methoxide. When a negative alcoholic ferric chloride test was obtained, the reaction mixture was treated with excess base and the formation of the cyclized product 87 was followed via analytical thin layer chromatography. The reader should consult the experimental section for details.

The cyclization reaction ($\text{80} \rightarrow \text{87}$) could be made to proceed at almost any desired rate, but a too rapid addition of the excess base resulted in a considerable amount of polymer formation. The best yield obtained was 88.5% overall; that by addition of the excess base over a 48 hour period.

The methyl substituted naphthalenone 87 was isolated as white, needle-like crystals which, after repeated recrystallization from an ether-hexane solvent, had a melting range of 59.5-60.3°. The material appeared to be homogeneous during extensive examination on three thin layer chromatography

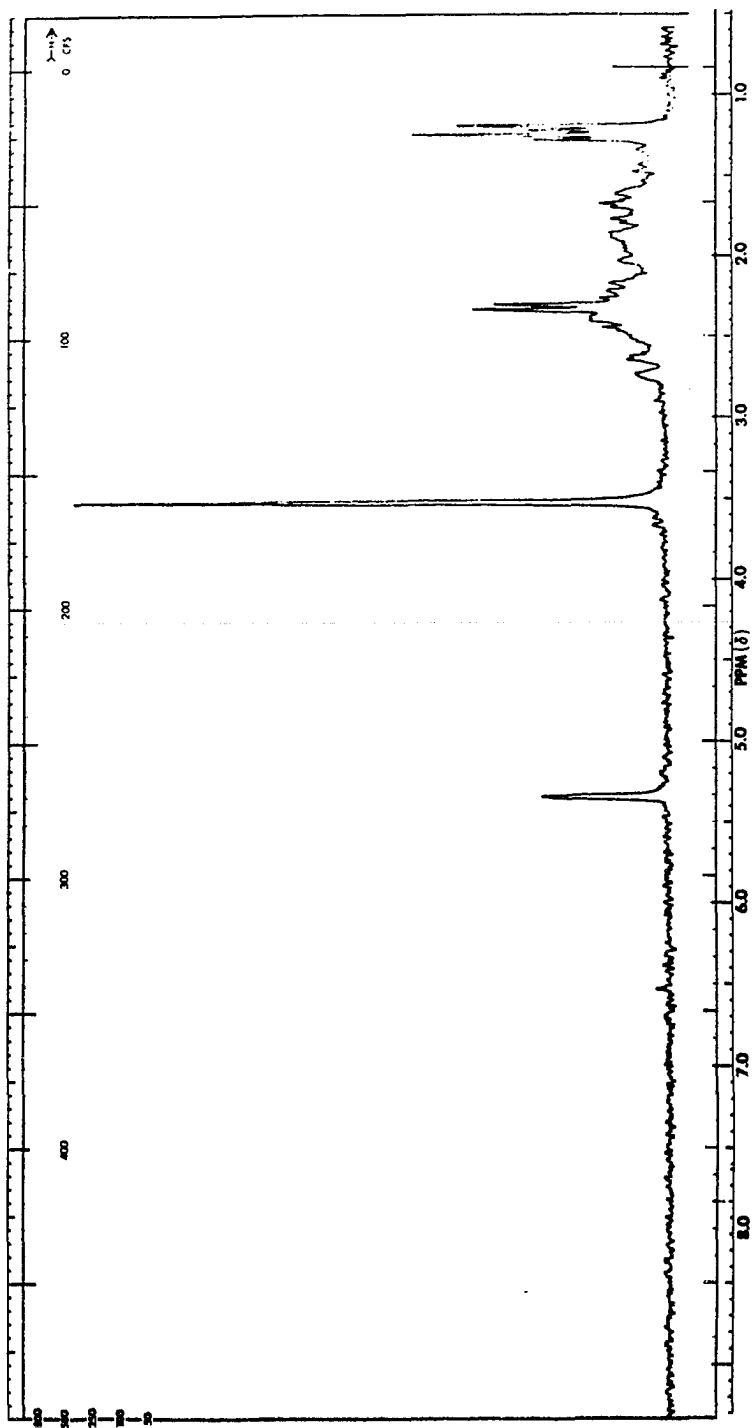
supports and six vapor phase chromatography columns. However, the presence of two major components in the isolated product was evident from the 100 MHz nmr spectrum (Figure 2). The presence of two methyl doublets in the region of 1.0 ppm indicated that the reaction had indeed produced a mixture of cis and trans isomers, namely 87c and 87t .

 87c  87t

Based on the work discussed earlier⁴⁴, the upfield doublet probably corresponds to the cis isomer, 87c , but a definite assignment cannot be made at this point.

Thus, it became painfully apparent that the use of this method for the introduction of the secondary methyl group at position 5 in compound 87 could be expected to produce a mixture of isomeric products. However, from a consideration of the transition state preference depicted in Figure 1, as well as the work of Marshall et al.,⁴⁴ it appeared that the isomeric mixture thus produced would almost certainly contain the desired cis isomer as the major product. Furthermore,

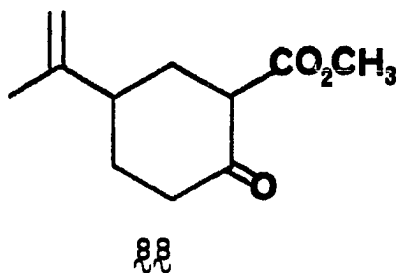
Figure 2. 100 MHz nmr spectrum of methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenone (87); 1000 Hz sweep width



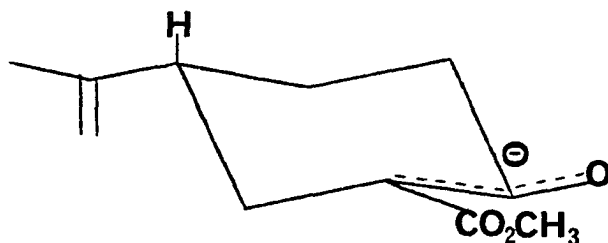
since a considerable amount of effort had already been expended in order to develop the high yield procedure described earlier for the preparation of these compounds, and since a separation of this type of isomeric mixture was not expected to be impossibly difficult, it was decided to continue to rely on this procedure for the introduction of the methyl substituent at position 5.

With a suitable method now available for the introduction of the methyl substituent, it remained only to devise a synthetic scheme whereby a isopropenyl group could be introduced into the molecule at position 3 cis to the angular carbomethoxy group. Such a scheme, if successful, would complete the synthesis of compound 68.

The most obvious method for the introduction of an isopropenyl group into position 3 would be by the use of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (88) in the Robinson annulation. Reaction of this material with trans-3-penten-2-one should afford a molecule with the desired skeleton. However, the requirement of a β orientation for the newly



introduced isopropenyl group necessitated more serious consideration. For example, if the transition state described earlier was reconsidered using β -keto ester **88** as a participant, it became obvious that the most stable conformation for the β -keto ester enolate was that illustrated below. The presence of an equatorial isopropenyl group would be expected to make



this conformation the only reasonable one through which the β -keto ester might undergo a Michael addition. Any other conformation would involve an axial isopropenyl group and hence would be decidedly less stable.

It is possible however, to conceive of approach of the α,β -unsaturated ketone from either the top or bottom side of the enolate system, as depicted in Figure 3. Either direction of approach can be shown to lead to a cis stereochemical relationship between the angular carbomethoxy and secondary methyl groups, but this is not true with respect to the isopropenyl group. Top-side (axial) approach, illustrated by **A**, can be shown to produce an intermediate dione such as **89a**

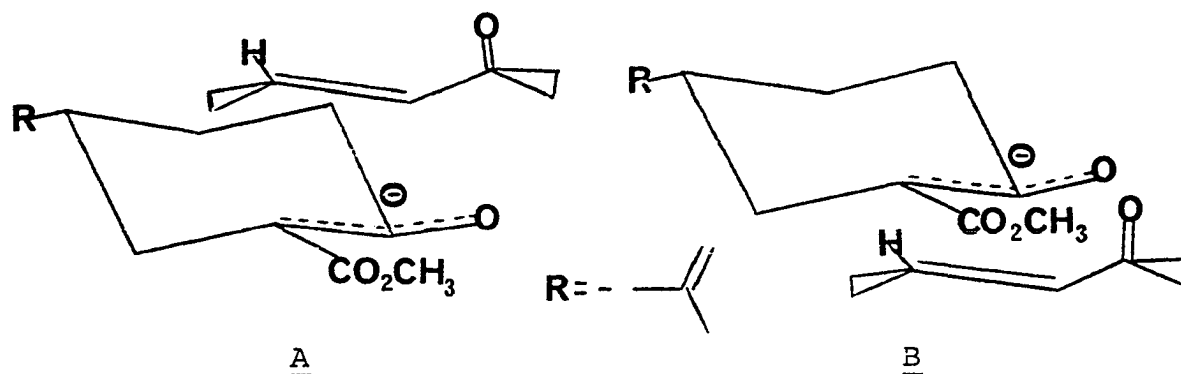
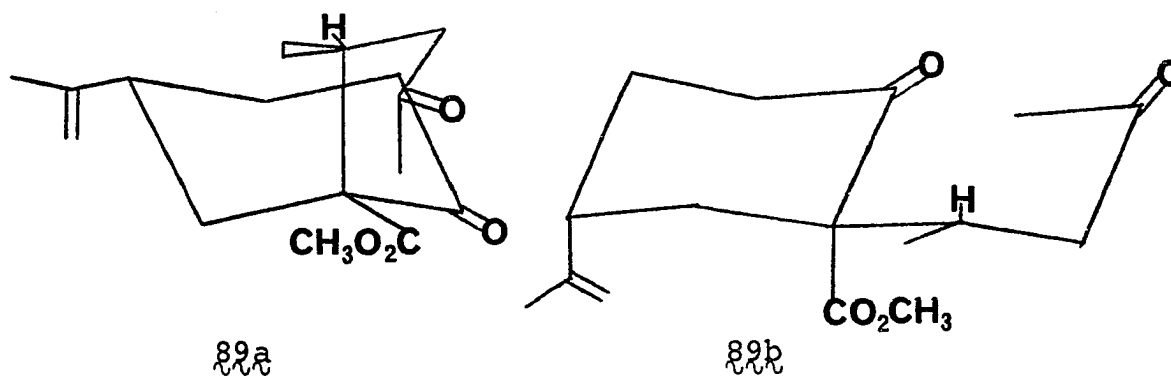
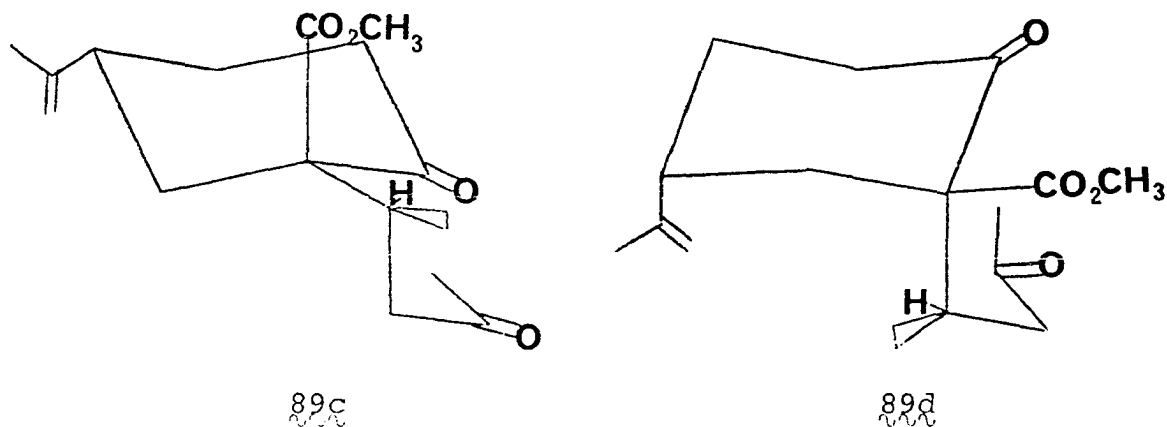


Figure 3. Diagram of the two possible directions of approach of trans-3-penten-2-one to the enolate system

or the alternative $\beta\beta$, in which the carbomethoxy and isopropenyl groups are cis. Bottom-side (equatorial) approach,



illustrated by β , would lead to an intermediate dione such as $\beta\beta$ or $\beta\beta$, in which a trans relationship exists. It would appear then, that the stereochemical outcome of the Robinson annulation of β -keto ester $\beta\beta$ with trans-3-penten-2-one, at least with respect to the isopropenyl and carbomethoxy groups,



is dependent upon the direction of approach of the α,β -unsaturated ketone to the enolate anion.

However, based on general and well accepted stereo-electronic⁶⁷ considerations, the approach of trans-3-penten-2-one to the enolate anion was not anticipated to be an entirely random process. In fact, a definite preference for top-side (axial) approach was expected based on the fact that during the course of the Michael addition, the α carbon of the β -keto ester must experience a change in hybridization from sp^2 to sp^3 . Furthermore, transition state A -Figure 4 which would result from axial approach and bond formation in that direction can be seen to allow continuous overlap along the π system during the rehybridization, whereas transition state B -Figure 4 from equatorial approach and bond formation does not. The fact that orbital overlap can be maintained throughout the entire

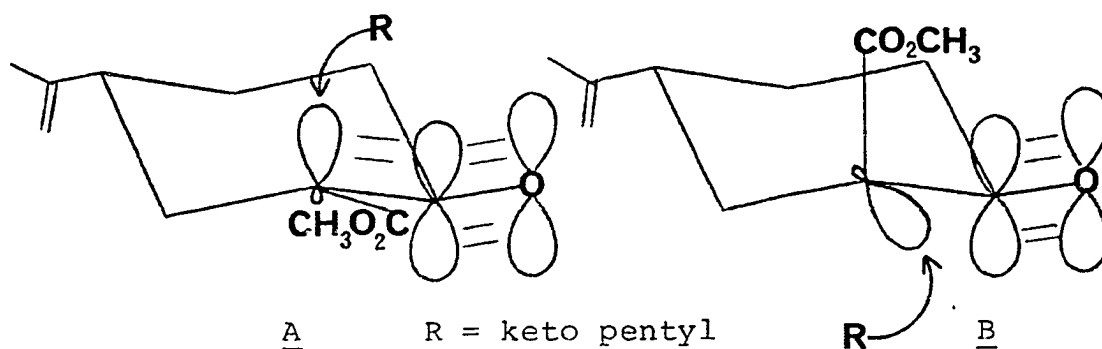
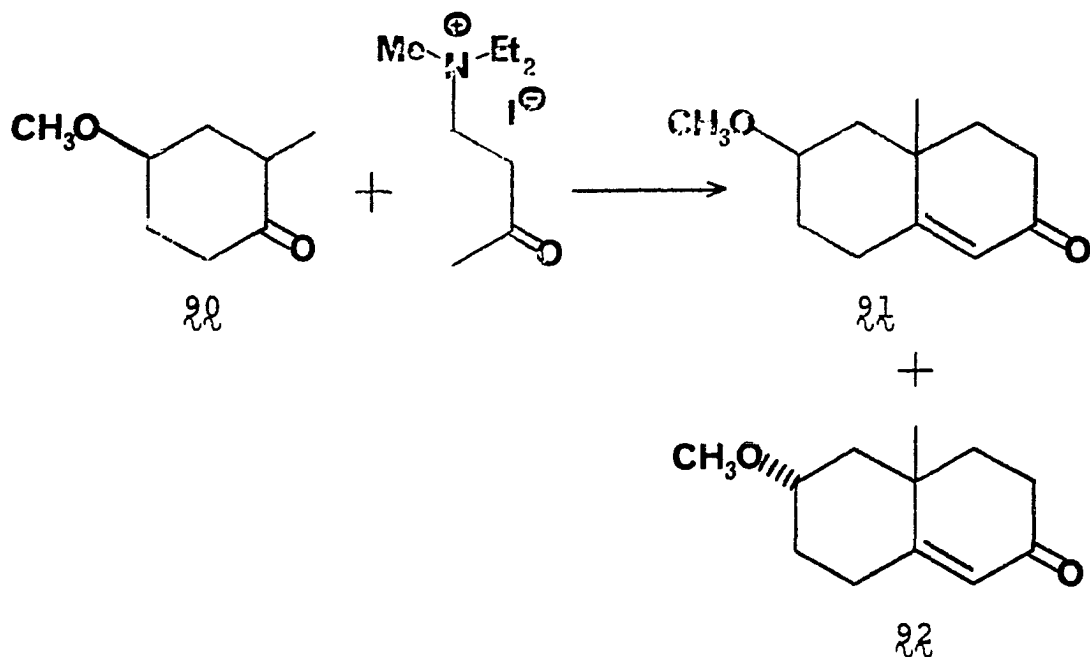


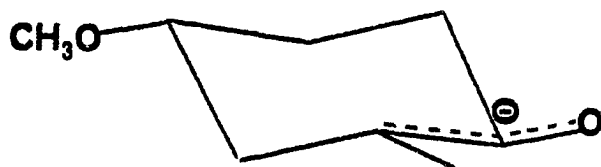
Figure 4. Diagram of the transition states resulting from axial and equatorial introduction of the keto pentyl group

reaction would be expected to strongly favor axial approach of, and bond formation to, the α, β -unsaturated ketone system. This would then lead to an intermediate dione such as 89a and 89b with the desired cis stereochemistry between the isopropenyl and carbomethoxy groups.

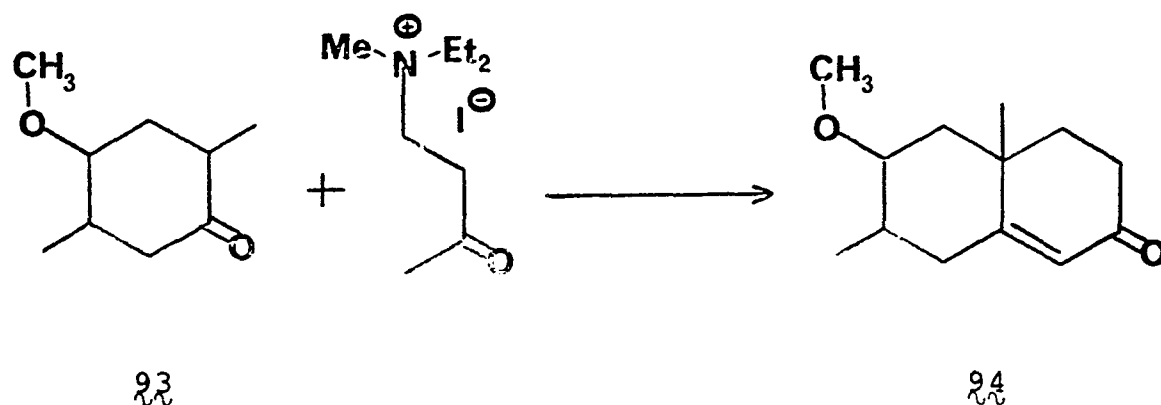
These expectations are supported by results obtained by Stork and Darling⁶⁸, who condensed 2-methyl-4-methoxycyclohexanone (90) with 1-diethylaminobutan-2-one methiodide and isolated naphthalenones 91 and 92 in an 85:15 ratio. In this case, the cis-isomer 91 predominated to the extent of 85%. Stork attributed this result to the axial (top-side) introduction of the keto butyl group while the ketone 90 existed in a



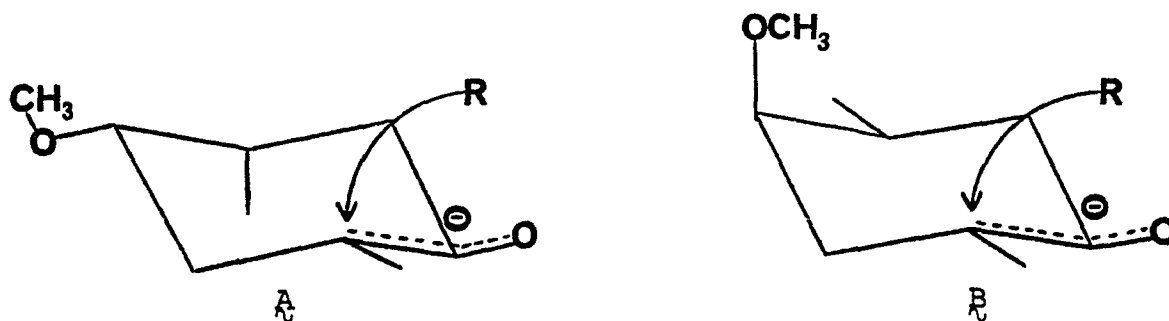
conformation (see below) identical to that suggested for β -keto



ester 88. In addition, Stork and Darling⁶⁸ were able to condense 2,5-dimethyl-4-methoxycyclohexanone (93) with 1-diethylaminobutan-2-one methiodide to isolate the all cis naphthalenone 94 as the sole reaction product. Presumably, ketone 93 reacted by axial introduction of the keto butyl group



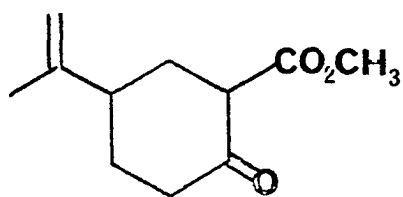
while in conformation A , shown below. The alternative conformation B was considered⁶⁸ unlikely due to the severe steric hinderance imposed on the entering keto butyl group (R) by the axial methoxy group.



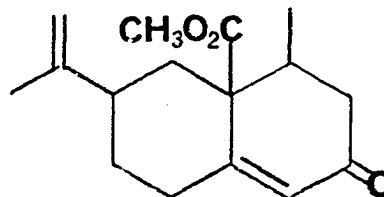
R = keto butyl

A complete analysis in terms of energy factors and ring conformations has also been presented⁶⁹.

Thus there appeared to be sufficient precedent for the expectation that reaction of β -keto ester 88 with trans-3-penten-2-one would yield a product with the desired stereochemistry, namely 89 . We therefore set out to prepare methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (88).



88

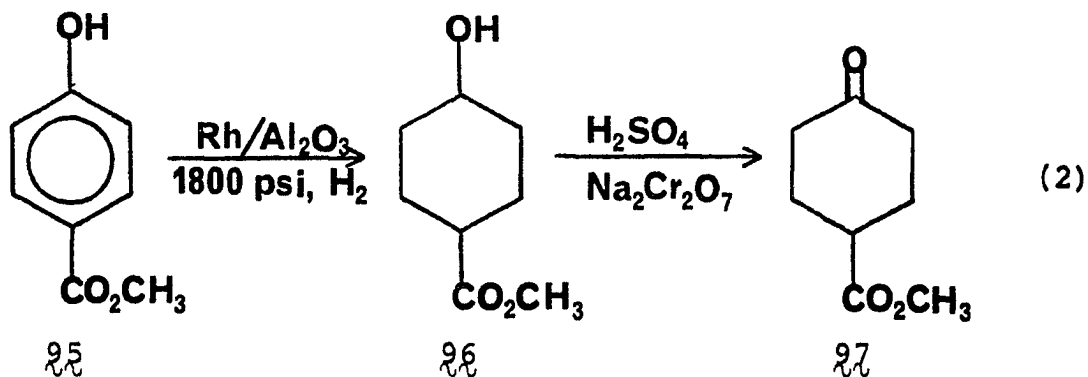


89

Synthesis of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate

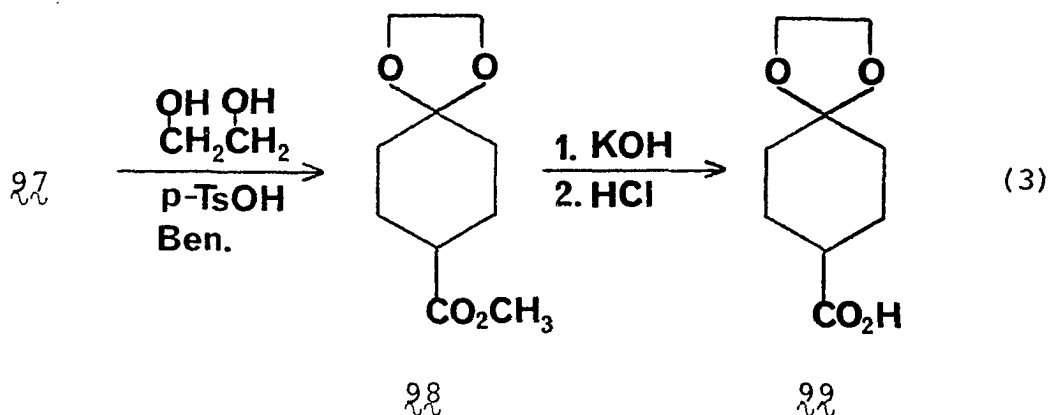
(88)

We began with commercially available methyl *p*-hydroxybenzoate (95), scheme 2. Attempted hydrogenation of 95 over



5% rhodium on alumina proceeded very slowly at 3 atmospheres (less than 15% reduction after 48 hours)⁷⁰. Hydrogenation at 130 atmospheres, however, proceeded rapidly and hydrogen uptake ceased after 48 hours affording 90% of methyl 4-hydroxycyclohexanecarboxylate (96). It was gratifying to find that even

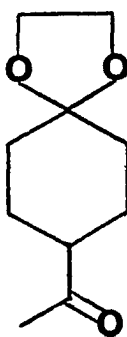
at these high pressures, less than 5% hydrogenolysis (addition of hydrogen across the C-O bond with concomitant loss of water) of **95** to methyl cyclohexanecarboxylate had occurred. The oxidation of alcohol **96** was accomplished by a procedure developed during this work and subsequently shown to be of general utility. (See experimental section) This procedure gave methyl 4-oxocyclohexanecarboxylate (**97**) in a 78% yield. Protection of the carbonyl group was accomplished by treatment of ketone **97** with ethylene glycol and p-toluenesulfonic acid in refluxing benzene with continuous removal of water, scheme 3. This procedure gave methyl 4,4-ethylenedioxycyclohexanecarboxylate (**98**) in nearly quantitative yield. Saponification



of the ester moiety with potassium hydroxide followed by acidification gave 4,4-ethylenedioxycyclohexanecarboxylic acid (**99**) in 96% yield. Considerable difficulty was experienced during the isolation of the acid **99** due to its unexpected

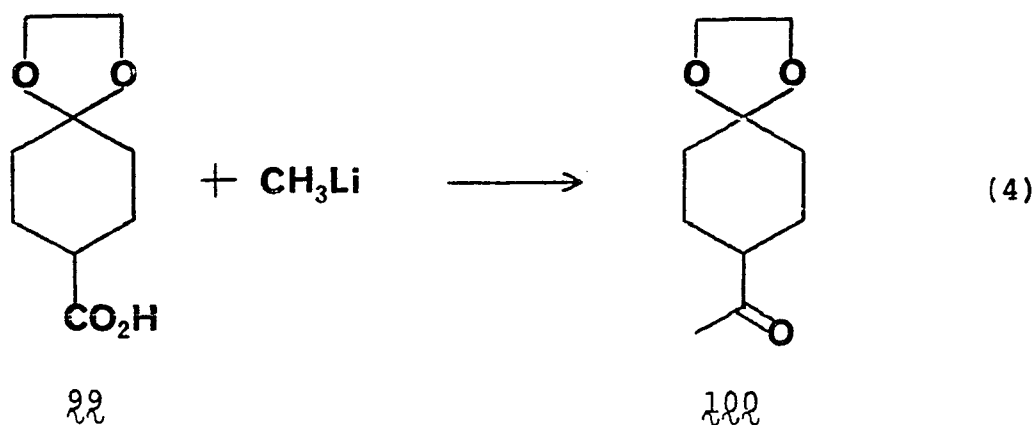
high solubility in water. It was eventually discovered that a 48 hour continuous extraction with benzene would increase the yield of product from 54% to 96%. In addition, crystallization of the acid ketal 99 was virtually impossible until an ether-hexane solution of the compound had been treated with a small amount of activated charcoal.

With the above experimental procedures well established, we proceed to consider three alternative preparations of methyl 4,4-ethylenedioxcyclohexyl ketone (100), which was envisioned as a possible synthetic intermediate for the introduction of an isopropenyl group (Wittig-type reaction).



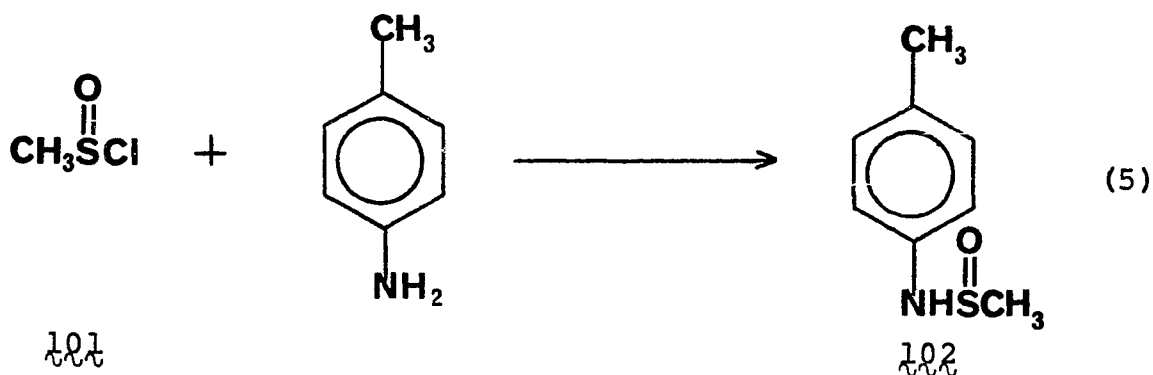
100

A. According to the original procedure developed by Gilman and VanEss⁷¹, treatment of acid ketal 99 with excess methyl lithium gave methyl ketone 100 , scheme 4. The isolated yields ranged from 46% to 83%. This variability is common for reactions which involve methyl lithium and has generally been attributed to the varying degrees of decomposition of the

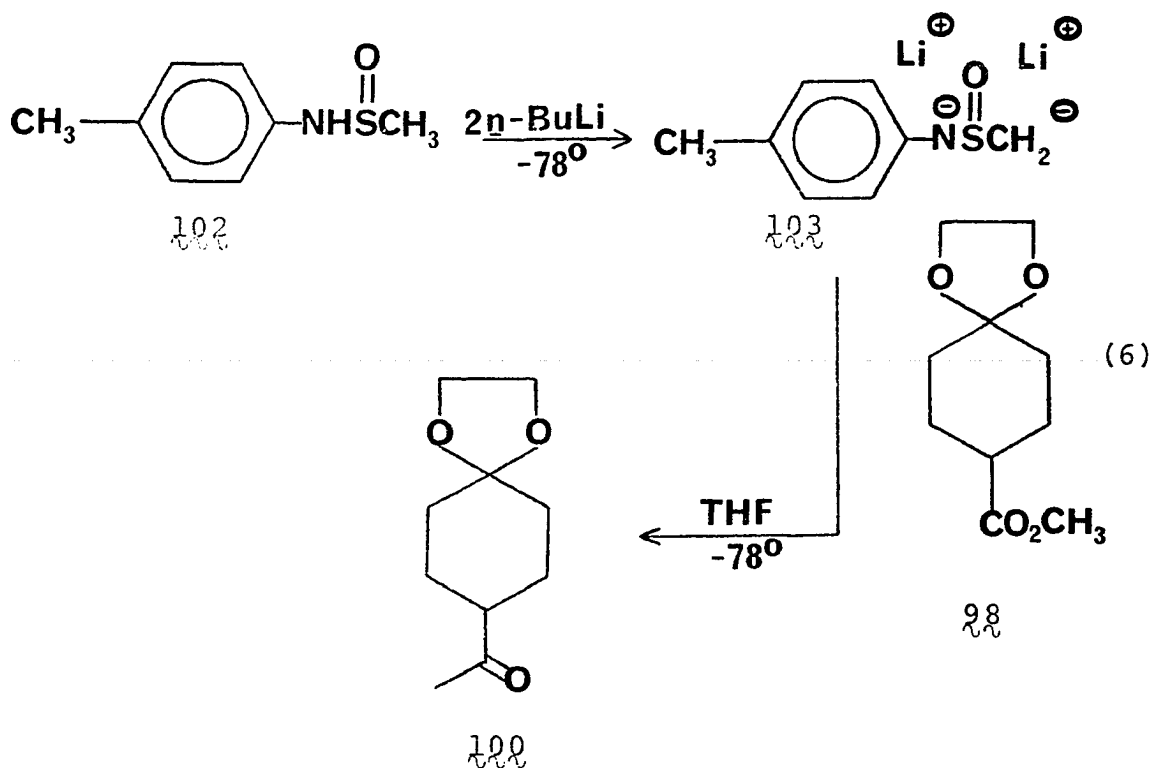


methyl lithium stock solution. In any case, due to the relatively low and unreproducible yield of the methyl ketone, alternative methods were investigated.

B. According to the general procedure published by Douglass et al.,⁷² methane sulfin-p-toluidine (102) was prepared by reaction of methane sulfinyl chloride (101) with p-toluidine, scheme 5. The methane sulfinyl chloride (101) was prepared from dimethyldisulfide and chlorine⁷³.

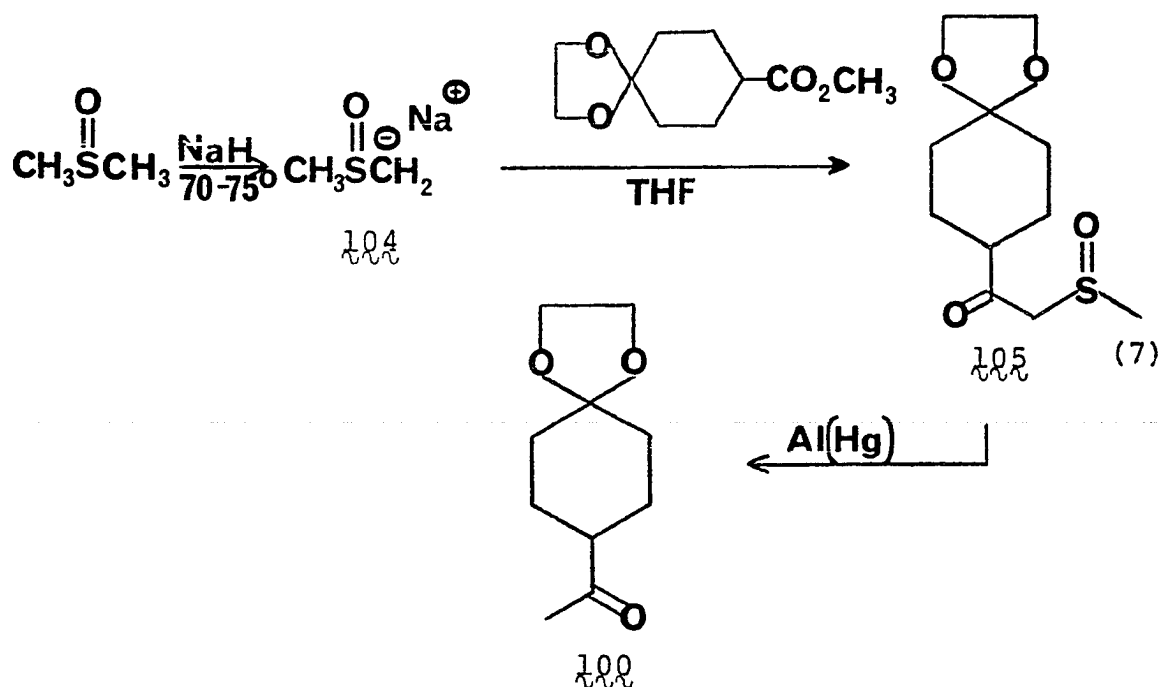


Treatment of ketal ester **98** with the dilithio anion **103** of methane sulfin-*p*-toluidine (prepared by reaction of **102** with two moles of *n*-butyl lithium) at -78° in tetrahydrofuran (THF) according to Corey and Durst⁷⁴ gave, after appropriate workup, methyl ketone **100** in excellent yield and purity, scheme 6.



However, the preparation of the methane sulfin-*p*-toluidine (**102**) reagent was both difficult and time-consuming. In addition, exceedingly erratic results were obtained on various occasions, presumably due to decomposition of the dilithio anion **103** during the reaction. For these reasons then, a third method for the preparation of methyl ketone **100** was explored.

C. With some modifications, the procedure of general utility for the conversion of esters to methyl ketones published by Corey and Chaykovsky⁷⁵ was employed. A suspension of sodium hydride in dimethylsulfoxide (DMSO) was heated to 70-75° and maintained at that temperature until hydrogen

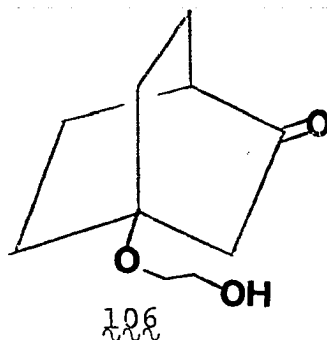


evolution ceased (approximately 25 minutes). Treatment of the methylsulfinyl carbanion (104) thus produced with ketal ester 98, followed by addition of water and appropriate workup, gave methyl sulfinylmethyl 4,4-ethylenedioxy cyclohexyl ketone (105) in 94% crude yield. Cleavage of the adduct was accomplished by brief treatment with aluminum amalgam. This procedure gave the methyl ketone 100 in a 65% yield, scheme 7.

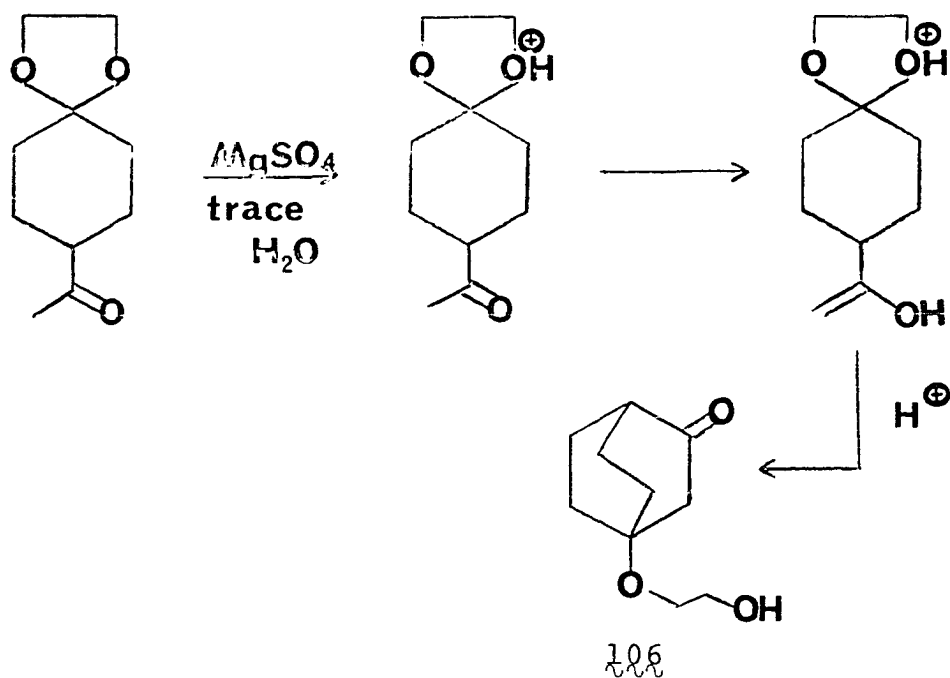
By a combination of these three alternative methods, a sufficient quantity of highly pure methyl ketone 100 became

available. Also, from extensive reconsideration of the three procedures, the author would like to suggest that the method outlined in scheme 7 is the most generally useful and should prove to have numerous applications in synthetic organic chemistry.

As an interesting side-light, it might be noted that during one particular preparation of methyl ketone 100, a waxy solid was isolated to the complete exclusion of the desired product, which is a low-boiling liquid. This unexpected solid was later identified as 4-(2'-hydroxyethoxy)bicyclo[2.2.2]octan-2-one (106). A consideration of the experiment revealed that



the reaction product had been allowed to stand for 14 days over anhydrous magnesium sulfate. It was reasoned therefore, that protonation of the ethylenedioxy ketal protecting group occurred, followed by enolization of the methyl ketone moiety and cyclization to the observed bicyclic structure. These mechanistic suggestions are purely speculative of course, although similar cyclizations have been reported⁷⁶.

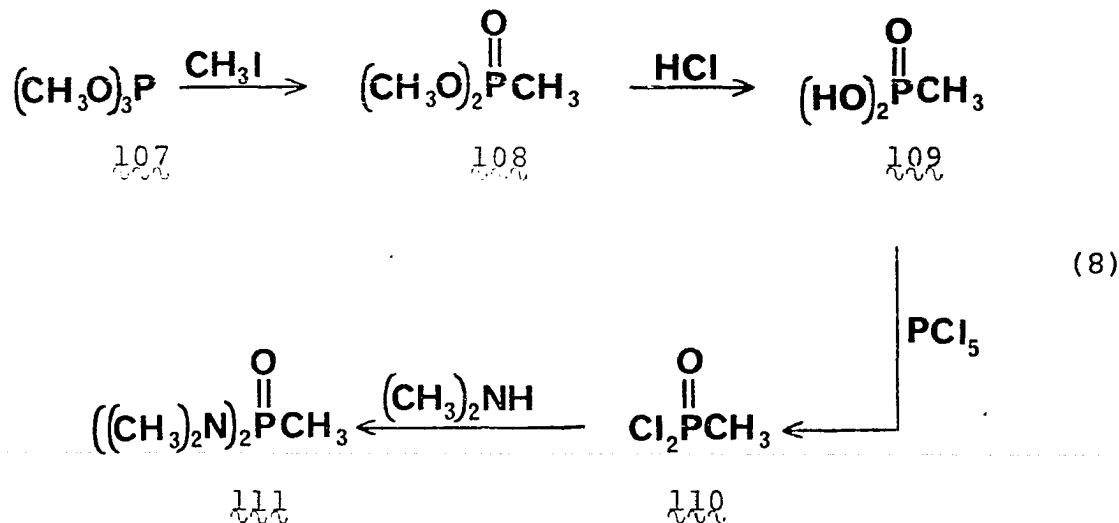


In order to convert the acetyl moiety into an isopropenyl group, preliminary consideration was given to a Wittig reaction⁷⁷ which would involve the use of triphenylmethylphosphonium bromide in dimethylsulfoxide. However, a survey of the pertinent literature revealed several experimental difficulties which had been experienced by earlier workers. These difficulties involved removal of the triphenylphosphine oxide produced in the reaction as well as removal of the last traces of the dimethylsulfoxide solvent. For these reasons, an alternative procedure originally presented in general form by Corey and Kwiatkowski⁷⁸ was investigated.

The necessary reagent for this procedure, methylphosphonic acid bis-(N,N-dimethylamide) (111) was prepared as shown in scheme 8. Contrary to the experimental procedures which lead

to methane sulfin-*p*-toluidine (102), those developed for the preparation of 111 were all amenable to large-scale reactions and most proceeded in amazingly high yield.

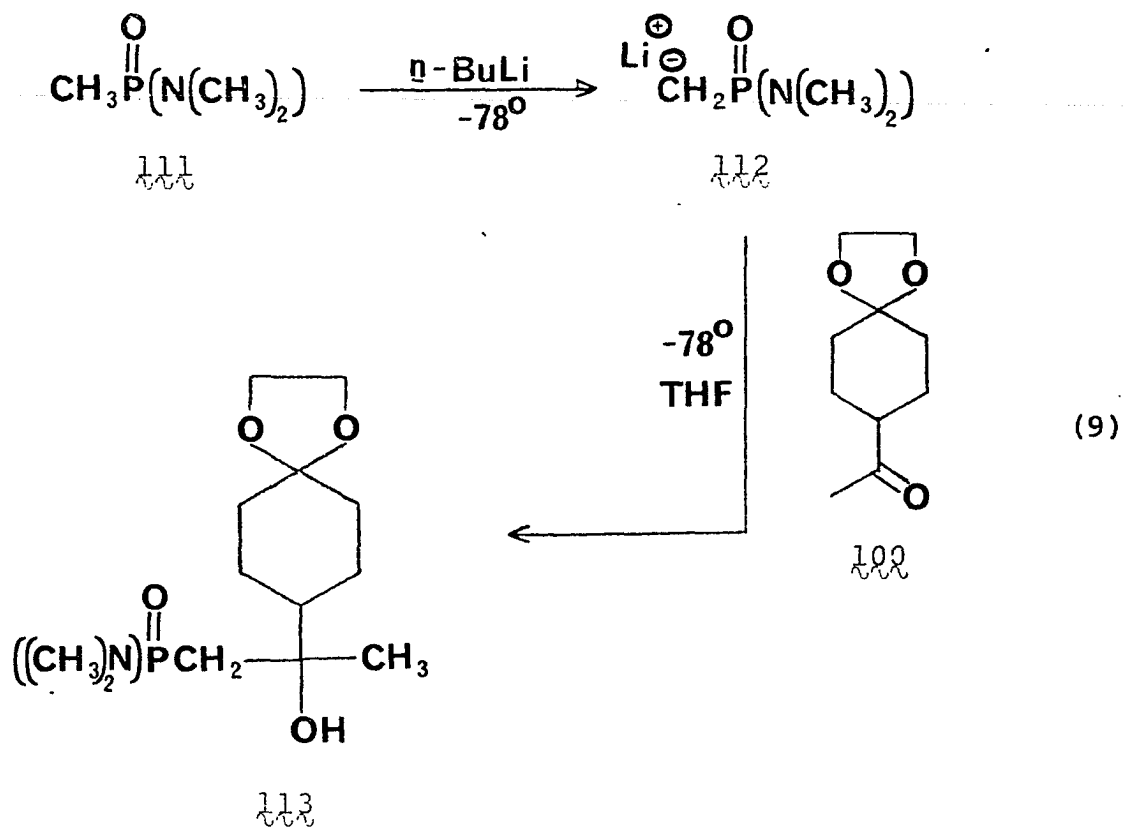
Methyl dimethylphosphonate (108) was prepared by reaction



of trimethylphosphite (107) with methyl iodide^{79,80}. Treatment of the product with concentrated hydrochloric acid gave methylphosphonic acid (109) in nearly quantitative yield⁸¹. Conversion of the acid 109 to methylphosphonyl dichloride (110) was accomplished by treatment of the acid 109 with phosphorous pentachloride in benzene⁸². By this procedure, the dichloride 110 was isolated in 90% yield. Finally, conversion of the dichloride 110 to methyl phosphonic acid bis-(*N,N*-dimethylamide) (111) was effected by treatment of the dichloride with anhydrous dimethylamine in heptane⁸³. This procedure gave the diamide 111 in 87% yield. As mentioned above, these procedures are all

well documented and with minor modifications, gave the desired products in high yield and purity.

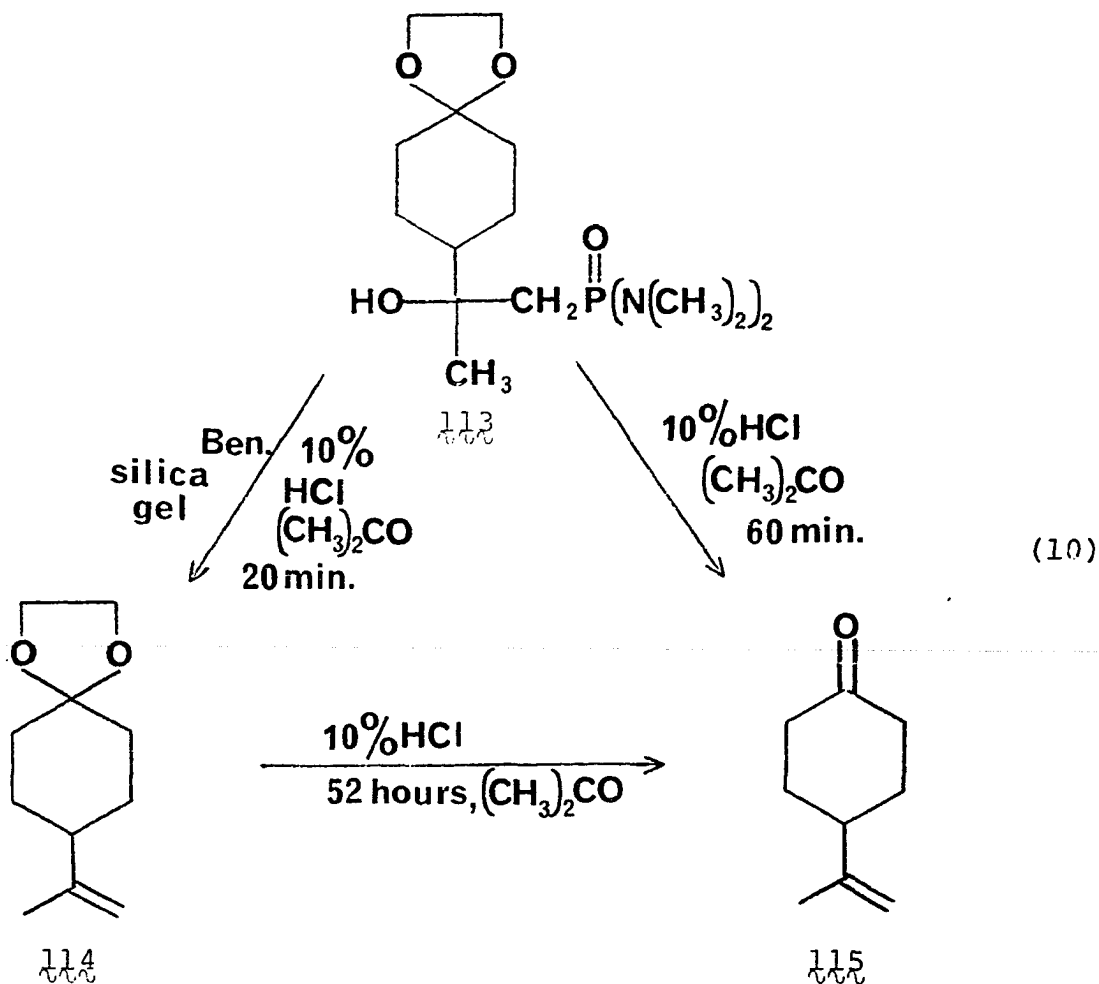
As outlined by Corey and Kwiatkowski⁷⁸, treatment of methyl ketone **100** with the α -lithio anion **112** of methylphosphonic acid bis-(N,N-dimethylamide) (**111**), prepared by reaction of **111** with exactly one equivalent of *n*-butyl lithium⁸⁴ gave 2-(4',4'-ethylenedioxcyclohexyl)-2-hydroxypropylphosphonic acid bis-(N,N-dimethylamide) (**113**) in 71% yield, scheme 9. The β -hydroxyphosphonamide **113** was isolated as a



powdery solid which could be easily purified by simple recrystallization and could be stored for months without noticeable change.

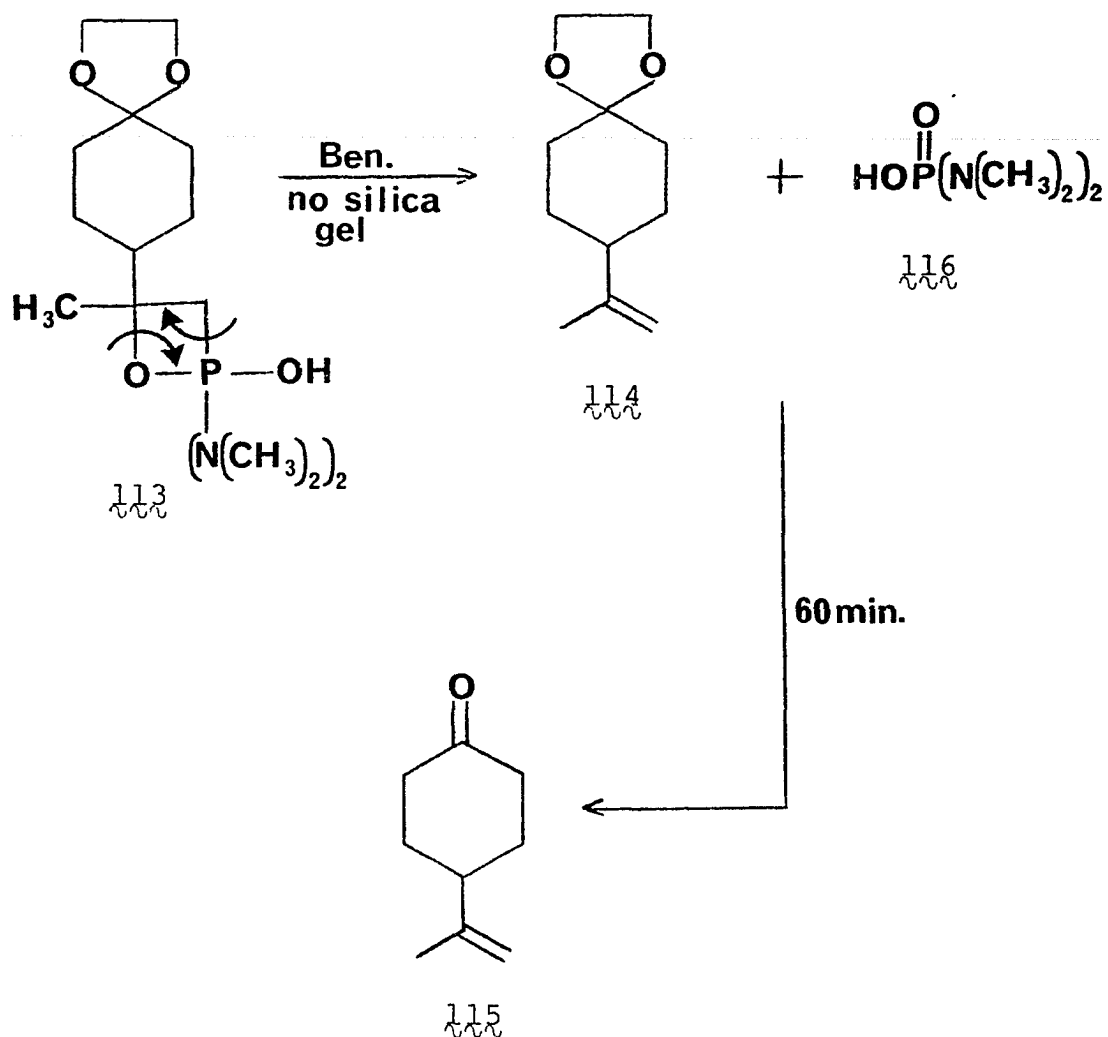
Decomposition of the β -hydroxyphosphonamide 113 was accomplished by a modification of the method suggested by Corey and Kwiatkowski⁷⁸, who recommended heating a reflux temperature in dry benzene or toluene for 24 hours, or in the presence of silica gel, for 12 hours. While this method was found to yield 4,4-ethylenedioxyisopropenylcyclohexane (114) in 48%, treatment of the β -hydroxyphosphonamide with 10% aqueous hydrochloric acid in an acetone solvent at reflux temperature for 20 minutes gave the isopropenyl ketal 114 in 63% yield, scheme 10. In addition, treatment of the β -hydroxyphosphonamide under identical conditions for 60 minutes gave 4-isopropenylcyclohexanone (115) directly in 94% yield.

It may be interesting to note that decomposition of the β -hydroxyphosphonamide 113 with aqueous acid proceeded in such a manner that the phosphonamide moiety was completely decomposed to an isopropenyl group before cleavage of the ethylene ketal was initiated. This was detected by the isolation of an analytically pure sample of the isopropenyl ketal 114 from the reaction mixture after 20 minutes at reflux temperature as well as by the observation that cleavage of the ethylene ketal from the material remaining was complete within 60 minutes.



In contrast, removal of the carbonyl protecting group from 4,4-ethylenedioxyisopropenylcyclohexanone (114) after isolation and purification of the material proved extremely difficult. In fact, treatment of pure isopropenyl ketal 114 with 10% aqueous hydrochloric acid in acetone as described above gave no detectable carbonyl containing product after 60 minutes. Only

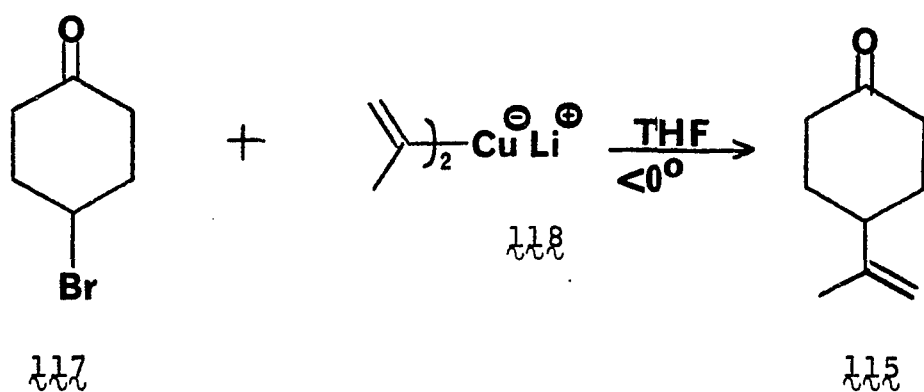
after an extended period at reflux temperature was the cleavage complete to the extent of 91%. Apparently, the phosphonic acid bis-(N,N-dimethylamide) (116) liberated from decomposition of the β -hydroxyphosphonamide 113 catalyzed cleavage of the ethylene ketal and hence allowed isolation of 4-isopropenyl-cyclohexanone (115) from the reaction mixture after only 60 minutes. This suggestion was supported by the fact that during thermal decomposition of the β -hydroxyphosphonamide in the



presence of silica gel, no cleavage of the ketal was observed after several hours. In this case, the phosphonic acid 116 liberated was adsorbed onto the silica gel and was therefore not available for catalysis.

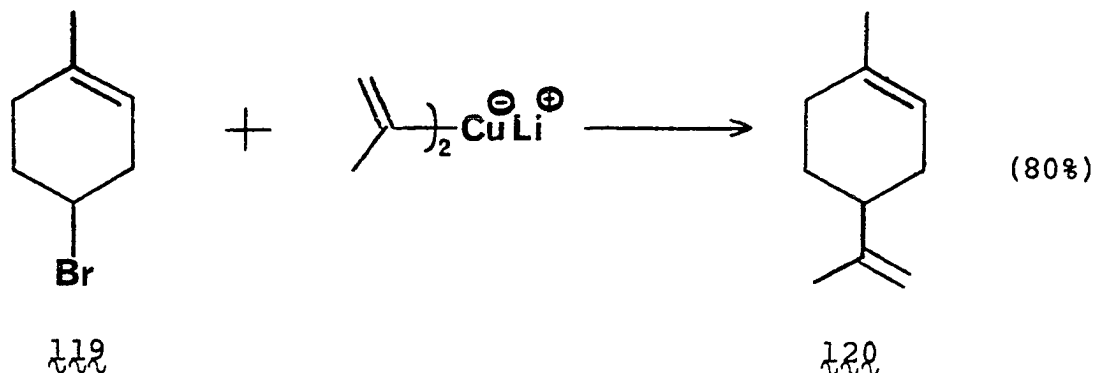
In any event, this method for the conversion of methyl ketone 100 to isopropenyl ketone 115 proved highly convenient and allowed the preparation of 4-isopropenylcyclohexanone (115) in 67% overall yield.

At this point, two publications by O. P. Vig and his collaborators^{85,86} which related the synthesis of 4-isopropenylcyclohexanone (115) in a 65% yield from 4-bromocyclohexanone (117) appeared. The reported synthesis involved reaction of the keto bromide 117 with lithium diisopropenyl cuprate (118) in an anhydrous tetrahydrofuran (THF) solvent at

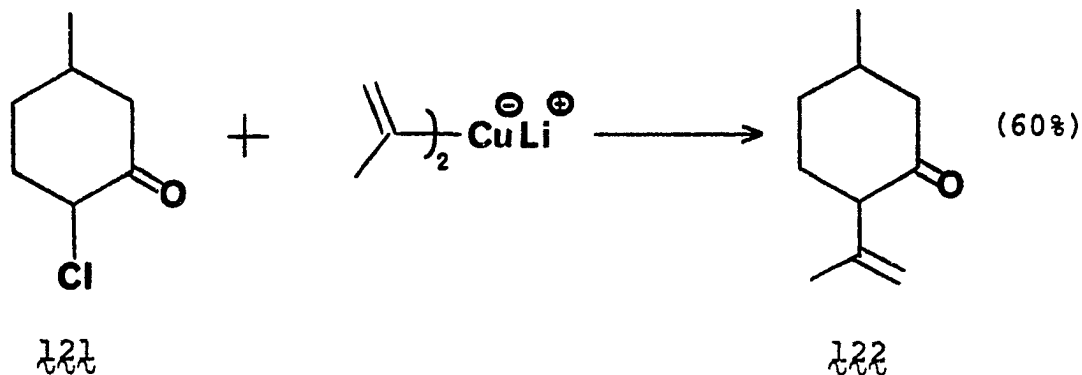


a temperature below 0° . In addition, Vig reported several other transformations which involved replacement of halogen by an isopropenyl group through reaction of the halide with lithium diisopropenyl cuprate. For example, the synthesis of

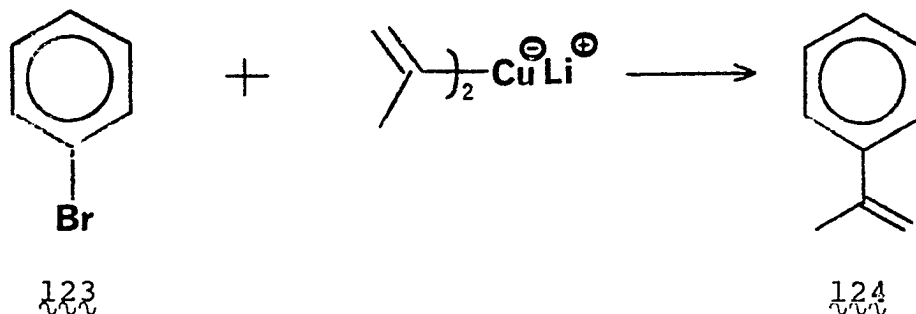
racemic dipentene (120) was accomplished by treatment of 1-methyl-4-bromocyclohex-1-ene (119) with lithium diisopropenyl cuprate. Also, racemic isopulegone (122) was prepared in 60%



from 2-chloro-4-methylcyclohexanone (121). Finally, methyl



styrene (124) was prepared by reaction of bromobenzene (123) with excess lithium diisopropenyl cuprate. These results indicated an extreme diversity for the replacement reaction as outlined by Vig and his coworkers^{85,86}.

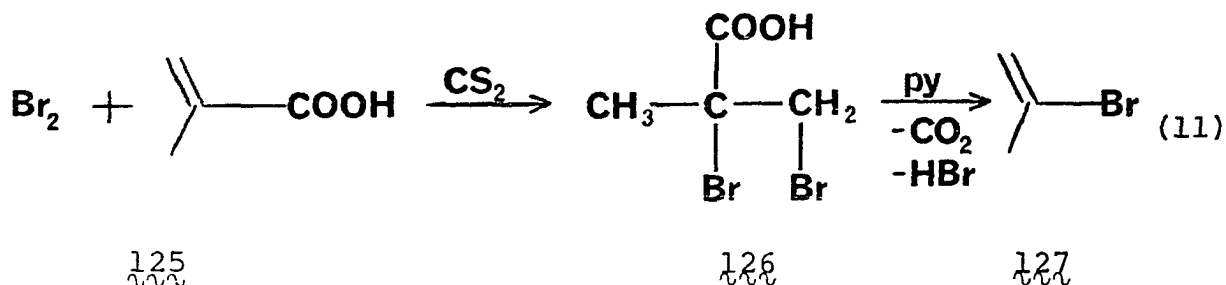


In addition, House^{87,88}, Whitesides⁸⁹ and their respective collaborators, had demonstrated the synthetic utility of organocopper reagents for conjugate addition to α,β -unsaturated carbonyl compounds. Also, Corey and Posner⁹⁰ had devised an elegant synthetic method for attachment of a methyl group to alkyl, aryl, and vinyl systems based on reaction of lithium dimethyl cuprate with various halides.

Based on the results reported by Vig and his coworkers^{85,86} as well as the other work described above, we initiated an investigation of the reactions of lithium diisopropenyl cuprate with various oxygenated halides with the exception of developing an alternative synthesis for 4-isopropenylcyclohexanone.

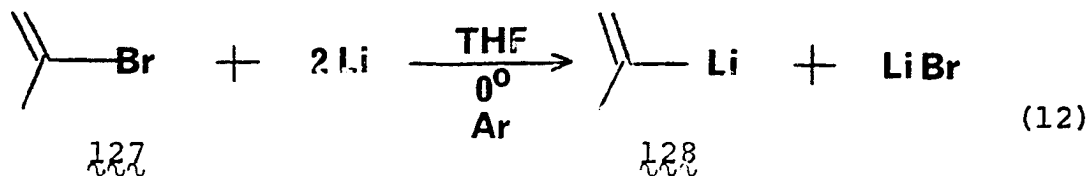
Isopropenyl bromide (2-bromopropene) (127) was prepared⁹¹ in carbon disulfide solution by direct bromination of α -methylacrylic acid (125), followed by decarboxylation and dehydrobromination of the crude dibromide 126 thus formed with

pyridine. Steam distillation afforded isopropenyl bromide (127) in 58% yield, scheme 11.



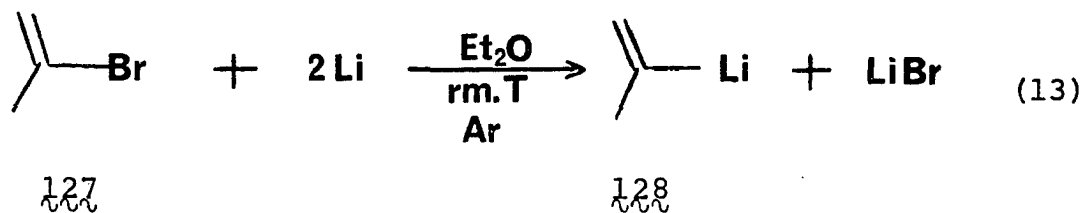
It should be emphasized that extreme care must be taken to insure complete removal of the carbon disulfide solvent used in the bromination reaction, since if the solvent were not completely removed before treatment of the dibromide with pyridine, the isolation technique described above gives a mixture of isopropenyl bromide (127) and carbon disulfide. In addition, it was found that as little as 3% carbon disulfide in the isopropenyl bromide prohibited any reaction with metallic lithium. Purification of the contaminated isopropenyl bromide could be accomplished only by an extended spinning band distillation using a reflux to take-off ratio in excess of 35:1.

Reaction of the purified isopropenyl bromide with metallic lithium (which contained 1% sodium) was first attempted in anhydrous tetrahydrofuran (THF) as reported by Vig et al.,^{85,86} scheme 12. Instantaneous commencement of the reaction was observed followed immediately by a dark discoloration of the solvent. In addition, the reaction media became extremely



viscous or jelly-like, and all efforts to filter the solution in order to remove residual lithium proved futile. Since we felt that complete removal of any residual lithium was essential to the success of future reactions with carbonyl-containing compounds, the use of "super-dry" ether as a solvent for the preparation of isopropenyl lithium was investigated. (Consult p. 156 for the preparation and handling of "super-dry" ether).

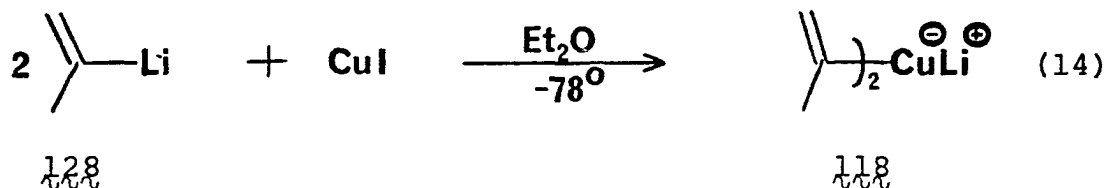
Treatment of a suspension of finely-divided metallic lithium in "super-dry" ether under an argon atmosphere at room temperature with a few drops of rigorously pure isopropenyl



bromide (127) initiated an instantaneous reaction, scheme 13. Dropwise addition of the remaining isopropenyl bromide gave a purple solution which was easily filtered free of any residual lithium metal. The solution of isopropenyl lithium (128) was completely homogeneous and showed no decomposition after 72

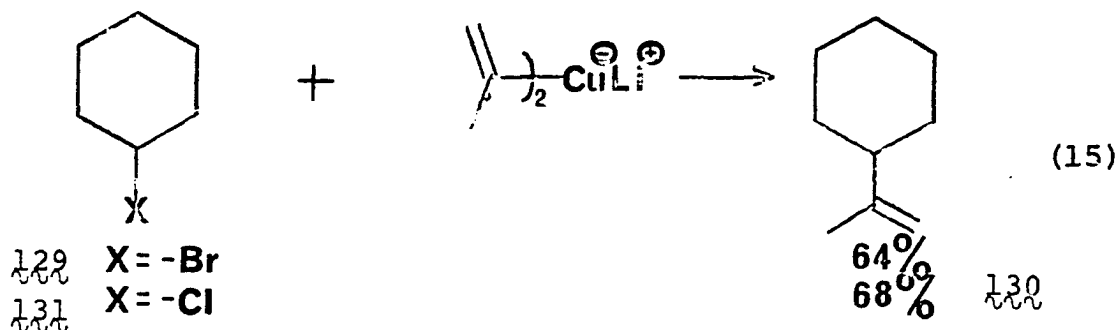
hours at room temperature⁹¹.

The isopropenyl lithium (128) solution thus prepared was filtered through a column of glass wool into a suspension of anhydrous cuprous iodide in "super-dry" ether at -78° , scheme 14. This procedure gave a gray, heterogeneous solution which



after 20 minutes at -78° exhibited a negative reaction to color test 1^{92} thus confirming the absence of isopropenyl lithium.

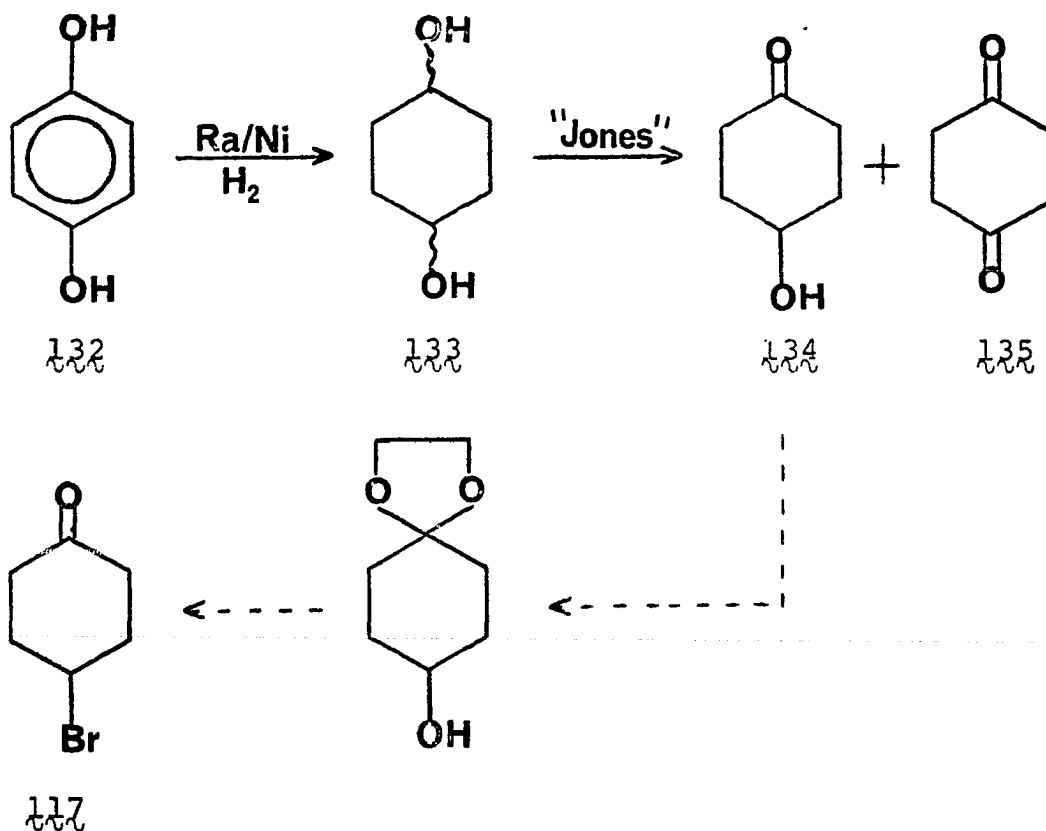
Having perfected a convenient method for the preparation of lithium diisopropenyl cuprate (118), we undertook first to test the reactivity of the cuprate 118 thus produced. Addition of bromocyclohexane (129) to the ethereal lithium diisopropenyl cuprate solution prepared as described above gave, after addition of aqueous ammonium chloride and appropriate workup, isopropenylcyclohexane (130) in 64%, scheme 15. The product 130 was essentially pure when isolated from the reaction mixture.



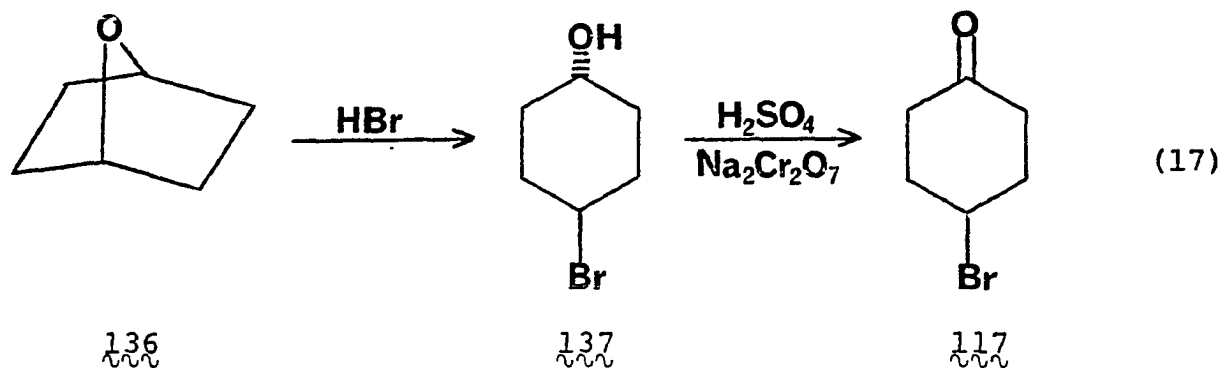
The addition of chlorocyclohexane (131) to the lithium diisopropenyl cuprate solution gave the product 130 in a 68% distilled yield. The fact that a slightly higher yield was obtained with chlorocyclohexane than with bromocyclohexane was surprising in view of the results obtained by Whitesides *et al.*,⁹³ who found that the order of reactivity of organic halides toward replacement by lithium dimethyl cuprate was chloride < bromide < iodide. This reactivity order was interpreted in terms of an $\text{S}_{\text{N}}2$ mechanism for the replacement reaction. In addition, results to be discussed later in the present work confirm this reactivity order.

Satisfied that the lithium diisopropenyl cuprate prepared in an ethereal solvent was indeed of sufficient reactivity, we proceeded to investigate the reactions of the cuprate with 4-bromocyclohexanone (117), with a view toward repetition of the work reported by Vig and his students^{85,86}.

Our initially envisioned sequence for the preparation of 4-bromocyclohexanone (117) was as illustrated in scheme 16.

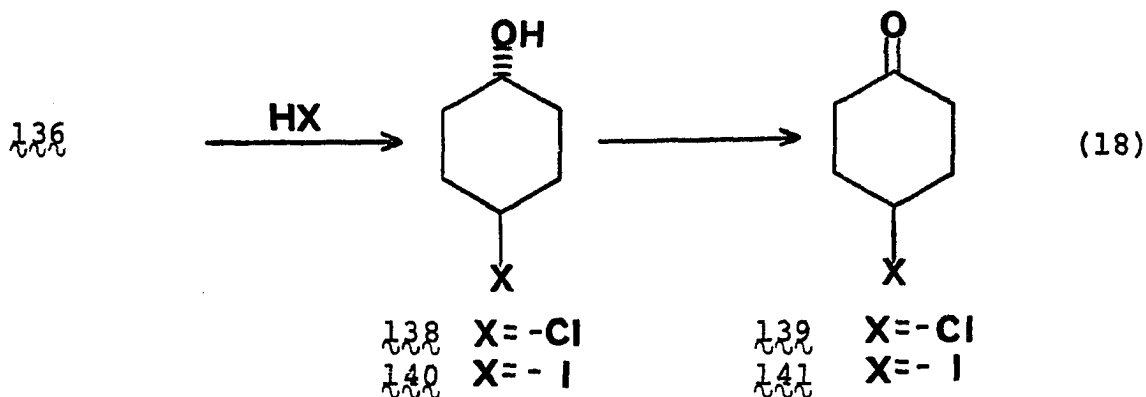


Catalytic hydrogenation of hydroquinone (132) over a Raney nickel catalyst gave 1,4-dihydroxycyclohexane (133) as a mixture of isomers in nearly quantitative yield⁹⁴. However, attempted monooxidation of 133 by the use of limited Jones reagent⁹⁵ according to the published procedure of Stolow and Groom⁹⁶ gave only 40% of the desired product, 134. In addition, approximately 8% of 1,4-cyclohexanedione (135) was isolated. At this point, the synthetic sequence illustrated in scheme 16 was abandoned in favor of that illustrated in



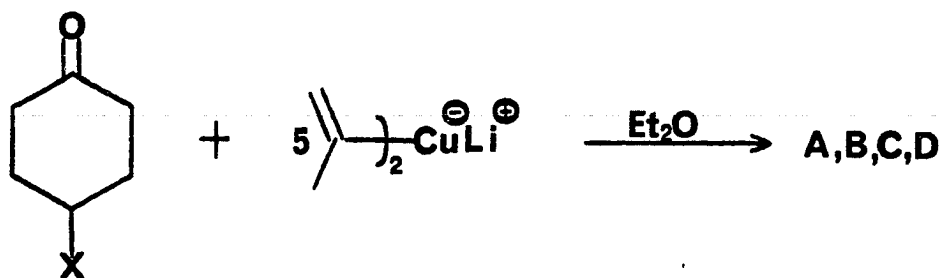
scheme 17. Treatment of 7-oxabicyclo[2.2.1]heptane (136) (available commercially) with a 48% aqueous hydrobromic acid solution gave *trans*-4-bromocyclohexanol (137) in 95% crude yield⁹⁷. Oxidation of 137 by the general procedure developed during this work and described in detail under the preparation of methyl 4-oxocyclohexanecarboxylate (97) gave 4-bromocyclohexanone (117) in 91% yield.

In addition, 4-chlorocyclohexanone (139) and 4-iodocyclohexanone (141) were prepared by similar reactions, scheme 18.



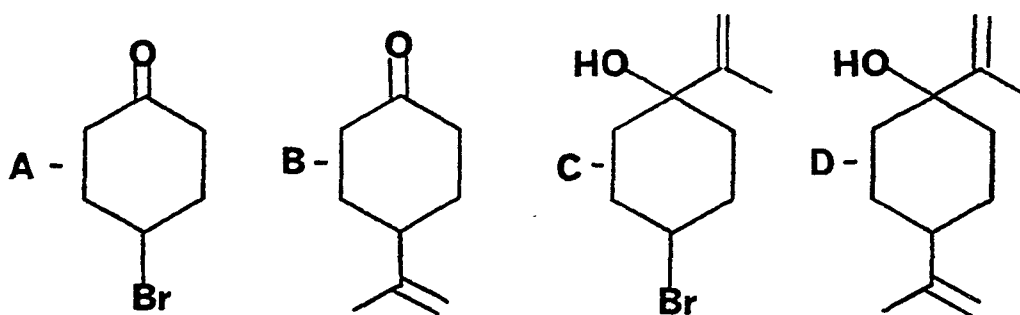
The only difference between the individual preparations was in the conditions necessary to effect opening of oxide $\overset{136}{\text{R}}\text{R}'\text{R}''$ by the particular halide involved. (See experimental section for details).

Reaction of 4-bromocyclohexanone ($\overset{117}{\text{R}}\text{R}'\text{R}''$) with a five-fold excess^{85,86,90} of lithium diisopropenyl cuprate in ether gave a complex mixture which was shown by thin layer chromatography (TLC) to contain four major products, arbitrarily designated A-D, scheme 19. Separation of the products by preparative



$\overset{117}{\text{R}}\text{R}'\text{R}''$	X = - Br
$\overset{139}{\text{R}}\text{R}'\text{R}''$	X = - Cl
$\overset{141}{\text{R}}\text{R}'\text{R}''$	X = - I

thin layer chromatography and examination of nmr, infrared, and mass spectral data revealed olefinic functionality in three of the products (B,C,D) and bromine in two (A,C). In addition, two products (A,B) contained carbonyl groups while two others (C,D) contained a hydroxyl group but no carbonyl group. These products are identified as shown below with the



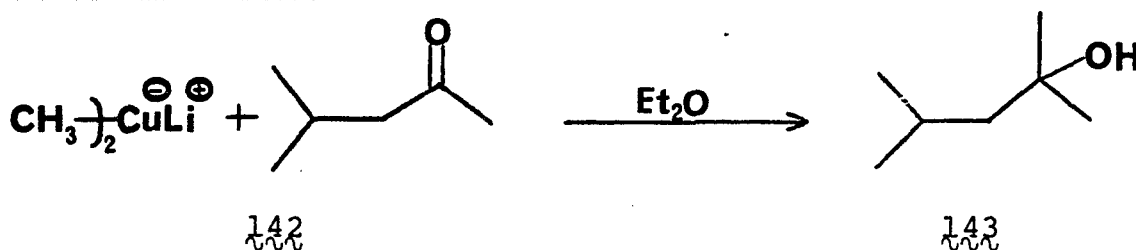
reservation that the structures of only A and B have been positively confirmed; the structures assigned to C and D should be considered tentative. Also, a fifth product, E, was observed during the chromatographic separation of B which, on the basis of results to be discussed later, was identified as a cyclohexene derivative.

Repetition of the above reaction with 4-chlorocyclohexanone (139) and 4-iodocyclohexanone (141) gave comparable results, the only difference being the relative amounts of each of the four products, scheme 19.

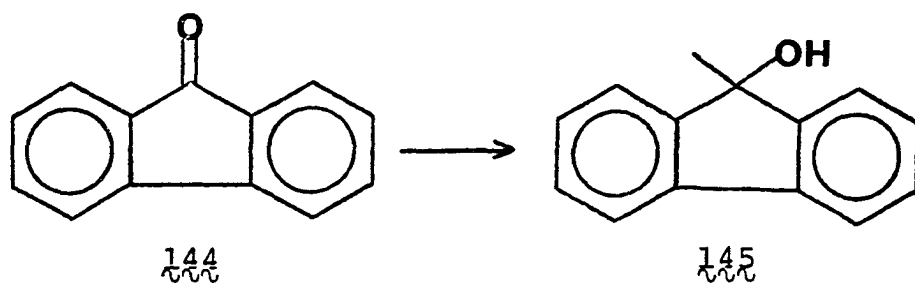
These results are in direct contrast to the work reported by Vig and his students^{85,86}, who made no mention of a possible reaction of lithium diisopropenyl cuprate with the carbonyl group. In fact, Vig implied⁸⁶ that the only isolable product was that which resulted from replacement of halogen by the isopropenyl group. However, closer examination revealed that Vig reported⁸⁵ four different values for the melting point range of the 2,4-dinitrophenylhydrazone derivative of

4-isopropenylcyclohexanone (115). The values quoted ranged from 120° to 131° , whereas the 2,4-dinitrophenylhydrazone derivative prepared from the 4-isopropenylcyclohexanone (115) obtained as described earlier (scheme 10) had mp $141.0 - 141.5^\circ$. It may be however, that since Vig and his coworkers were able to conduct the reaction in tetrahydrofuran, they did in fact isolate 4-isopropenylcyclohexanone (115) slightly contaminated with other materials not detected in their product analysis, (infrared only).

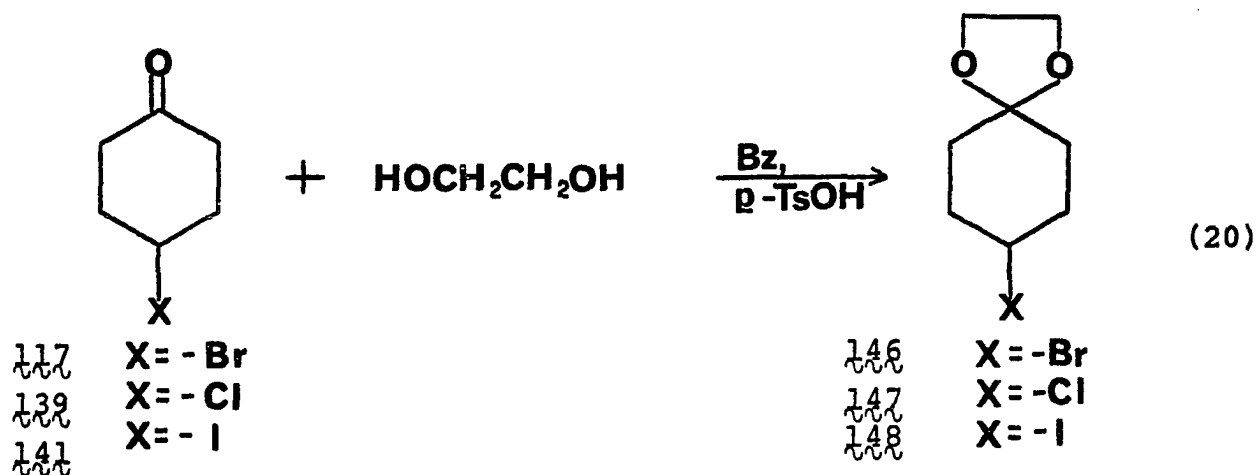
The results reported herein are in complete accord with those of other workers such as House *et al.*,⁸⁸, who reported



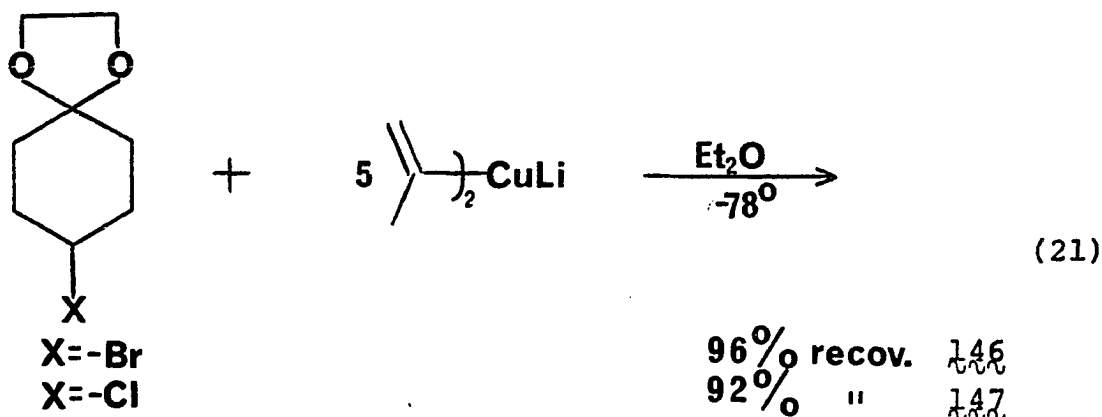
the conversion of 4-methyl-2-pentanone (142) to 2,4-dimethyl-2-pentanol (143) by reaction of the ketone with lithium dimethyl cuprate in an ether solvent to be 31% complete in 2 minutes. Also, the conversion of 144 to 145 was reported⁸⁸ to occur when 144 was treated with lithium dimethyl cuprate in ether.



It appeared then, that, at least in an ethereal solvent, preparative reactions with lithium diisopropenyl cuprate could not be conducted in the presence of an unprotected carbonyl group. In order to prevent addition of the reagent to the carbonyl group, we prepared the ethylenedioxy derivatives of 4-bromo-, 4-chloro-, and 4-iodocyclohexanone according to standard procedures, scheme 20.

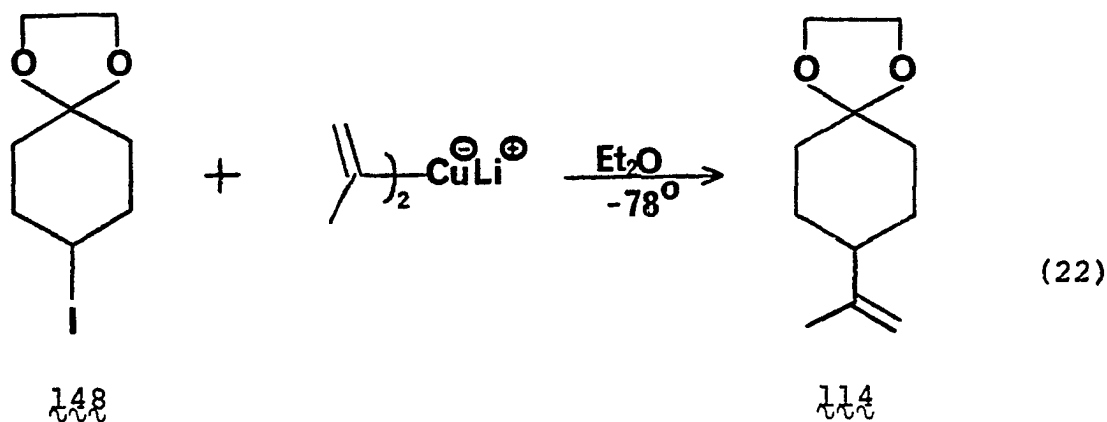


Treatment of 4,4-ethylenedioxychlorocyclohexane (147) as well as 4,4-ethylenedioxybromocyclohexane (146) with the lithium diisopropenyl cuprate solution prepared exactly as described above gave the results shown in scheme 21. Only the

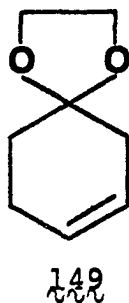


bromo-derivative 146 gave any 4,4-ethylenedioxyisopropenylcyclohexane (114), the expected product, and that amounted to only a few percent.

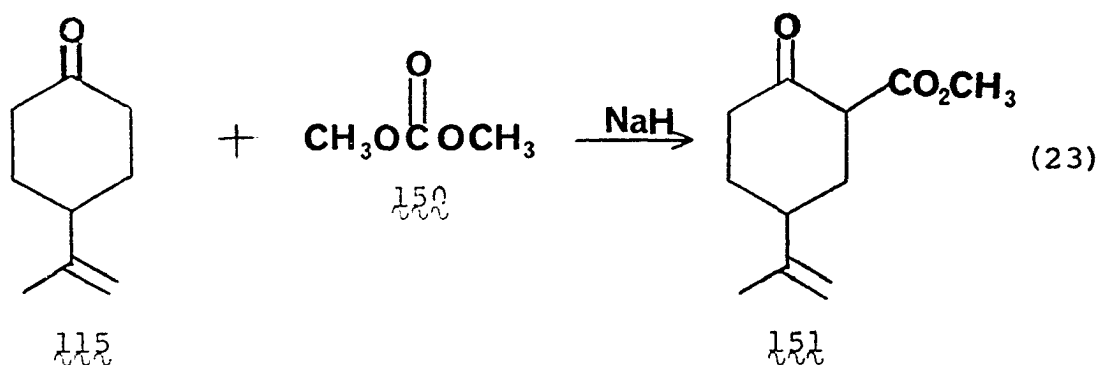
In contrast however, treatment of 4,4-ethylenedioxyiodocyclohexane (148) with lithium diisopropenyl cuprate in an ether solvent gave a 72% distilled yield of 114, scheme 22, identical with the material prepared as described earlier. Cleavage of the carbonyl protecting group was accomplished by treatment of 114 with a 10% aqueous hydrochloric acid solution, scheme 10.



Thus we had available a convenient and high yield procedure for the preparation of 4-isopropenylcyclohexanone (115) in reasonably large amounts and exceptional purity. In fact, the only isolable impurity (3-6%) was shown to be 4,4-ethylene-dioxycyclohex-1-ene (149), and this was easily removed by simple distillation.



Carbomethoxylation of 115 was accomplished by treatment of the ketone with dimethylcarbonate (150) in the presence of sodium hydride^{98,99}, scheme 23. This procedure gave methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) in 87% distilled yield. The nmr spectrum of β -keto ester 151 is shown



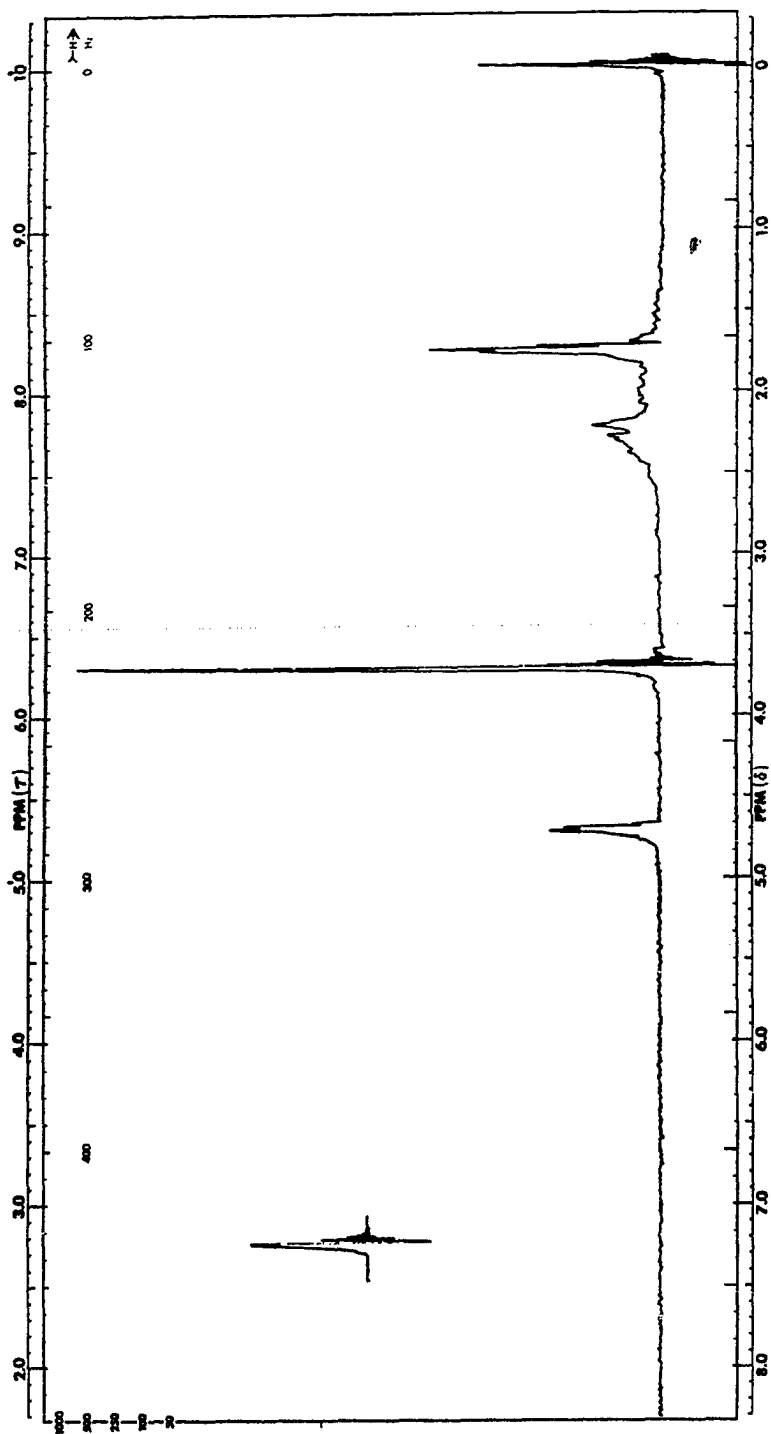
in Figure 5. As can be seen, the material exists partially in the enol form, which is consistent with the β -keto ester moiety, and in addition, exhibits distinguishable coupling from the vinylmethyl group to the terminal vinyl hydrogens.

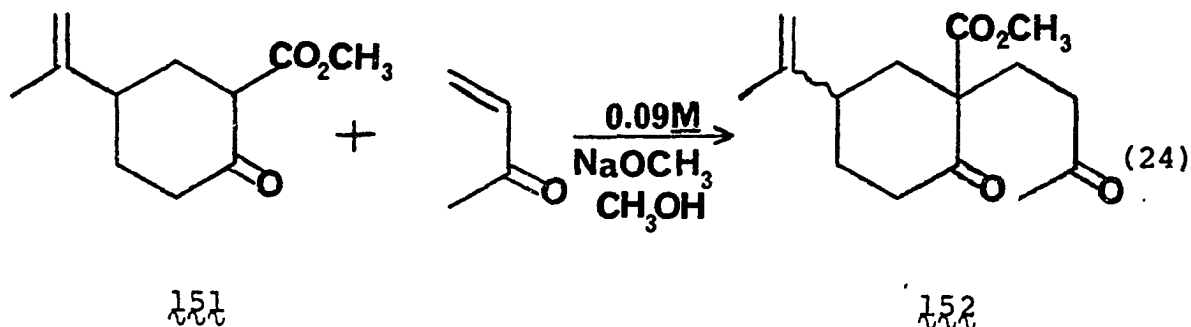
With the synthesis of the β -keto ester thus completed, we proceed to investigate the Robinson annulation of 151 with methyl vinyl ketone and with trans-3-penten-2-one.

Reactions of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate with methyl vinyl ketone and with trans-3-penten-2-one

Treatment of β -keto ester 151 with methyl vinyl ketone under conditions very similar to those described earlier (0.087M sodium methoxide in methanol) gave a negative alcoholic ferric chloride test after a 4.5 hour reaction period, scheme 24. Neutralization of the basic reaction mixture and appropriate workup gave a product which displayed the chemical, physical, and spectral properties expected for methyl 2-oxo-1-(3'-oxobutyl)-5-isopropenylcyclohexane-1-carboxylate (152). Analysis of the crude isolate by vapor phase chromatography showed it to

Figure 5. 60 MHz nmr spectrum of methyl 2-oxo-5-isopropenyl-
cyclohexanecarboxylate (151); enol hydrogen
absorption offset 137 Hz





consist of one major (93%) component and three minor components.

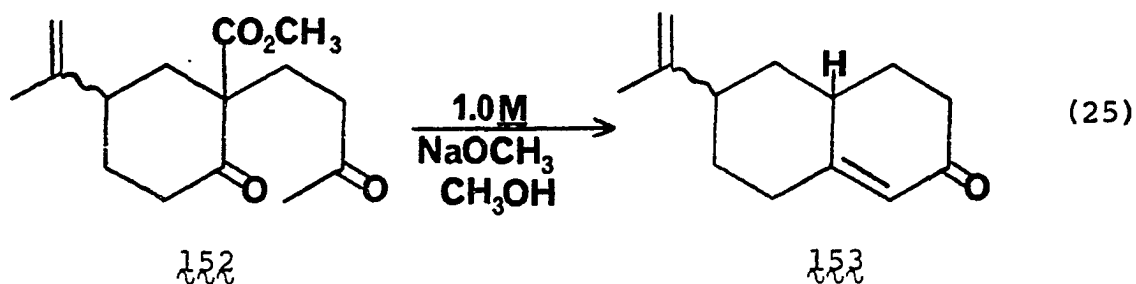
Guided by our earlier experience, we did not attempt to purify dione 152 by conventional means but instead decided to effect direct cyclization of the crude material.

In analogy with the cyclization of 85 to 86, treatment of dione 152 with a trace of pyrrolidine in refluxing benzene with continuous removal of water was expected to yield the desired product in high yield. However, under these experimental conditions, no reaction was observed after a total reaction time of 155 hours.

We reasoned therefore, that the reactivity of the present system might more closely parallel that of dione 80 rather than 85, and for this reason attempted cyclization of 152 as described below:

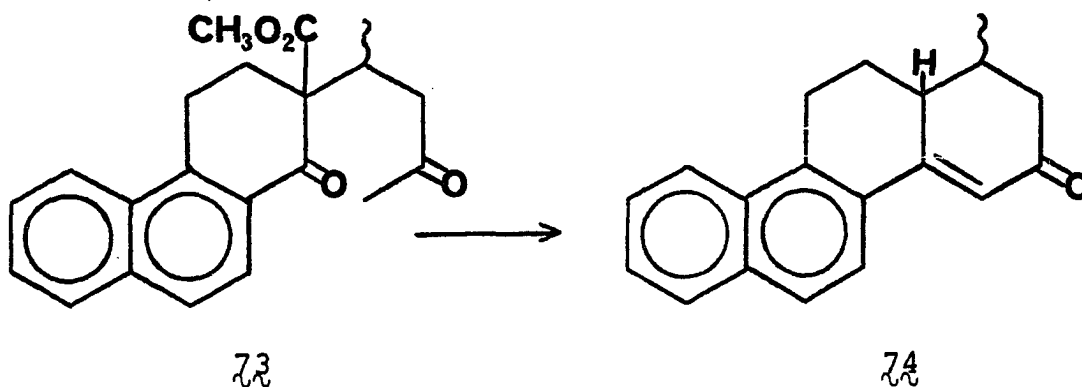
Treatment of dione 152 with a 1.0M sodium methoxide in methanol solution gave, after a six hour reaction period, a crude product which clearly contained (infrared) an

α,β -unsaturated ketone system indicating that cyclization had occurred. Unfortunately, this material lacked an angular carbomethoxy group, scheme 25. The crude product was partially

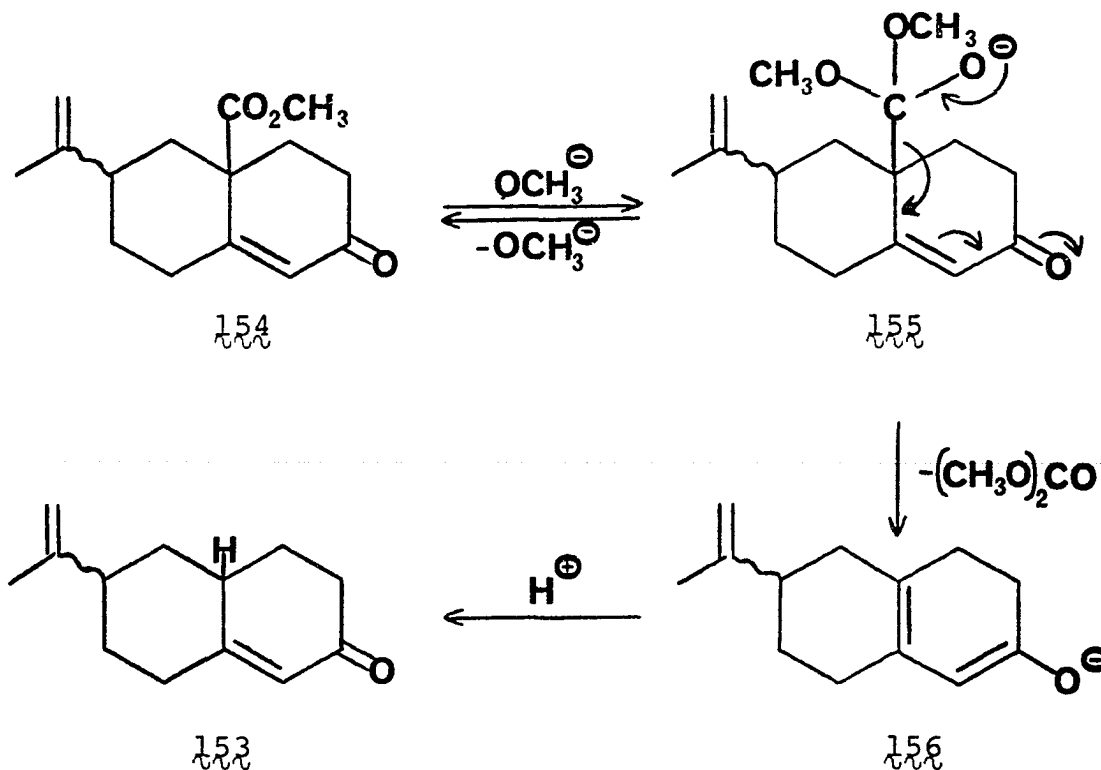


purified and upon further examination of the pertinent spectral data assigned structure 153 , resulting from loss of the angular carbomethoxy group.

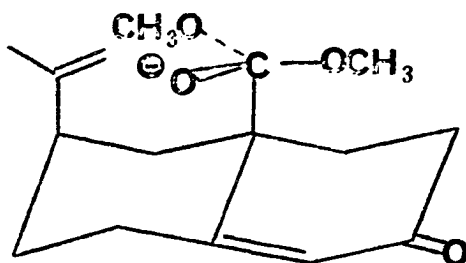
The isolation of a material which had experienced loss of the carbomethoxy group during attempted cyclization of a dione such as 73 was not totally unexpected however, since Wilds and Djerassi⁶³ had observed a similar occurrence during cyclization of dione 73 (p. 41).



The decarbomethoxylation of dione **152** upon treatment with base could be expected to occur from the initially formed vinylogous β -keto ester **154** by a mechanism such as that shown below. The intermediate **155** could either lose methoxide ion



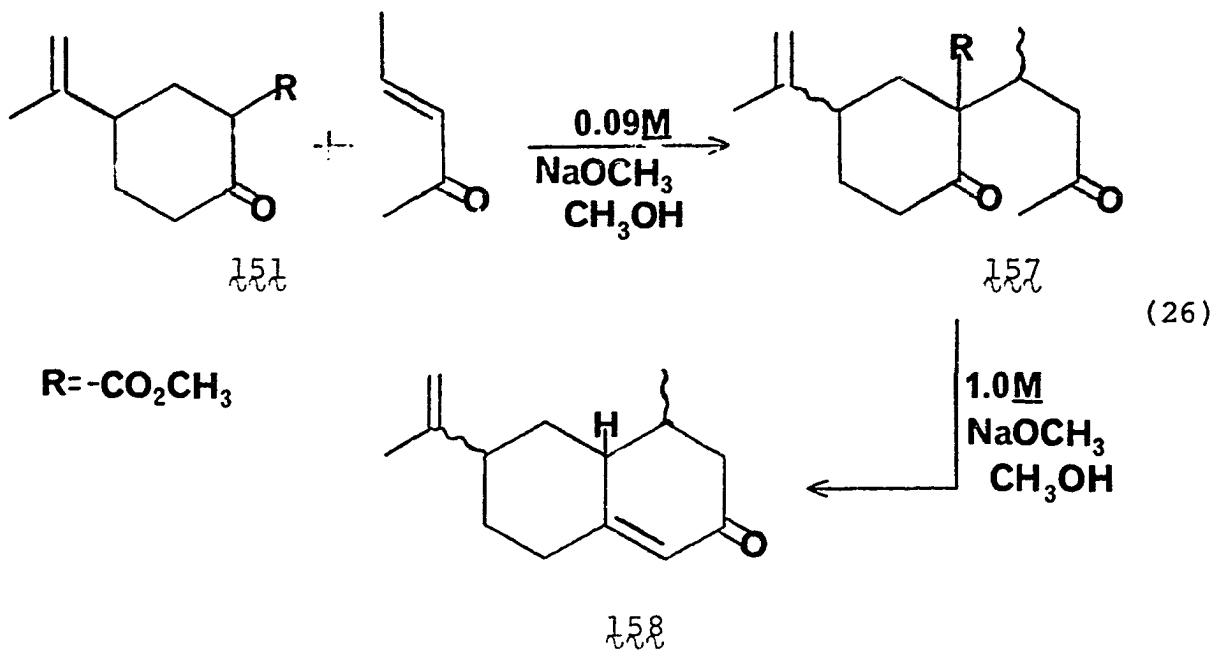
to regenerate β -keto ester **154** or dimethylcarbonate to yield **156**, which upon protonation would form the observed product **153**. The necessary impetus for the decarbomethoxylation may be inferred from an examination of the expected conformation of intermediate **155**, which, if the initial Michael addition had occurred as anticipated (see discussion pp. 43 to 47) would be as illustrated below. Elimination of the angular carbomethoxy group can be seen to provide an excellent pathway



by which the molecule might relieve the 1,3-diaxial interaction between the angular carbomethoxy and the isopropenyl groups. In fact, the isolation of a product which had suffered decarbomethoxylation can be offered in support of the postulate that the initial Michael addition did occur as expected to yield a product (such as 154 or 155) containing an axial isopropenyl group. However, no definite proof regarding this point can be offered.

Examination of the reaction of β -keto ester 151 with trans-3-penten-2-one under similar conditions gave, unfortunately, the same result, scheme 26. Attempted cyclization of the intermediate dione 157, either crude or partially purified, gave only decarbomethoxylated material. Despite many attempts, which included variation of reaction time, temperature, base strength, etc., no cyclized product containing an angular carbomethoxy group could be isolated.

In addition, the Michael addition reaction which gave dione 157 was exceptionally slow and proceeded in very poor yield. While, by analogy with the systems studied earlier

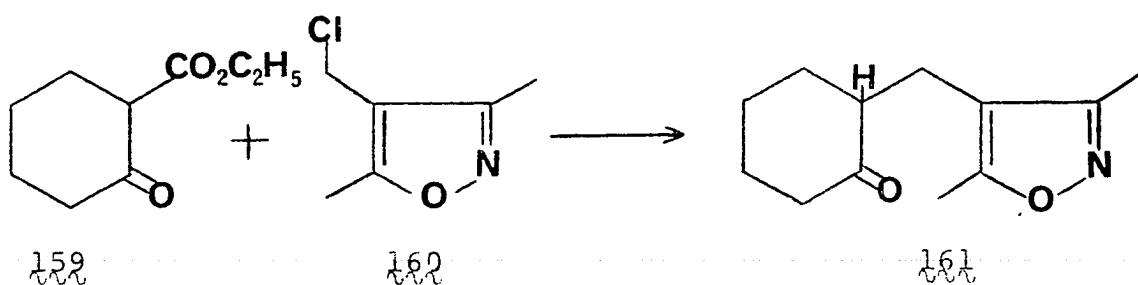


(scheme 1) it was anticipated that the alkylation of β -keto ester 151 would be somewhat slower with trans-3-penten-2-one than with methyl vinyl ketone, the magnitude of the observed retardation was totally unexpected. For example, the Michael addition of β -keto ester 151 with methyl vinyl ketone was complete after 4.5 hours, whereas that with trans-3-penten-2-one was only partially complete after 43 hours. Furthermore, this extended exposure of the reactants to the basic reaction media may well account, at least in part, for the low yields observed.

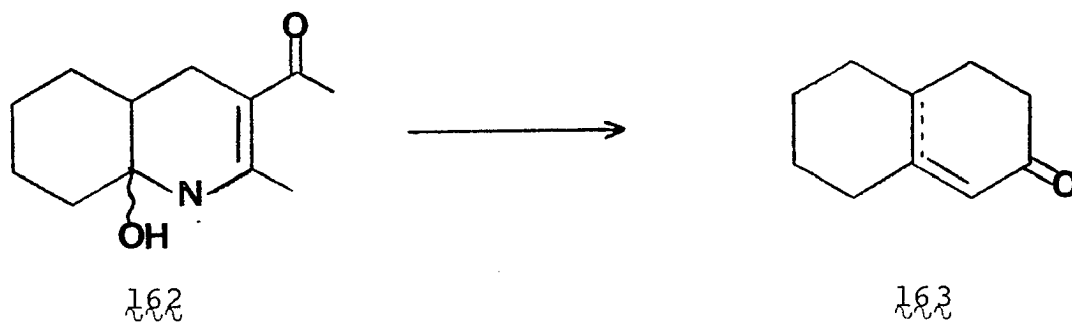
In any event, after extended consideration and investigation, it was decided that this particular annulation procedure was inapplicable to the present system and a search for an

alternative procedure was initiated.

In 1967, Stork and his coworkers^{100,101} reported a novel annulation procedure which involved the use of substituted 4-halomethylisoxazoles as the annulating agents. For example, alkylation of ethyl 2-oxocyclohexanecarboxylate (159) with 4-chloromethyl-3,5-dimethylisoxazole (160), followed by acid hydrolysis, gave the alkylated product 161 in good yield.

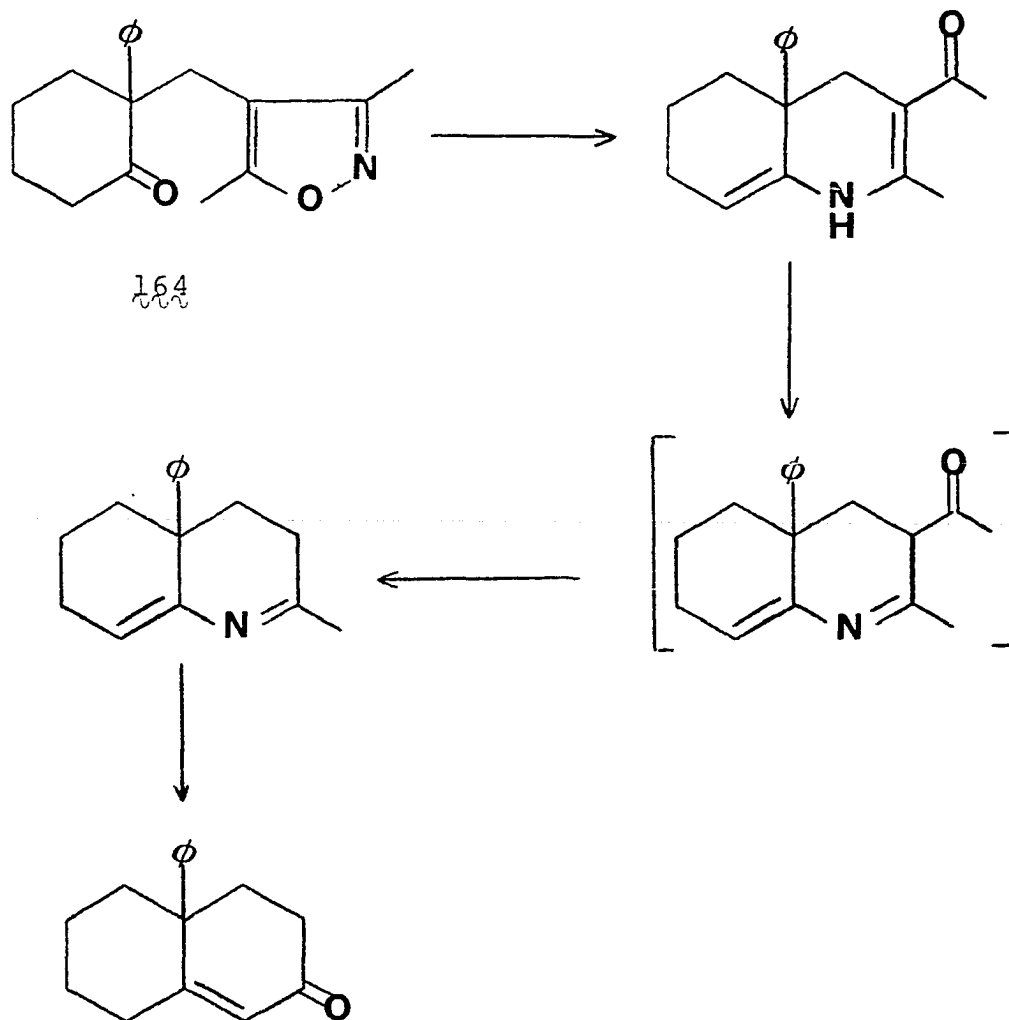


Cleavage of the isoxazole ring was achieved with hydrogen and palladium/charcoal to afford the vinylogous carbinolamide 162, which upon treatment with base gave the naphthalenone 163 in high yield.



The mechanism of the annulation was postulated¹⁰¹ to be as shown below, illustrated with the substituted ketone 164 in

which the angular phenyl group was incorporated to prevent aromatization of the intermediates. It is evident that

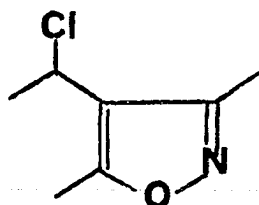


cleavage of the isoxazole ring in the alkylated ketone (**161** or **164**) affords a product identical to that which would have been obtained by alkylation with methyl vinyl ketone followed by

cyclization as in the classical Robinson annulation.

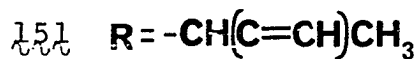
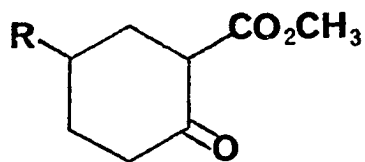
In addition, Ohashi and his students^{102,103} have reported synthetic methods for the preparation of phenolic diterpenoids and eremophiloids which utilize the general isoxazole annulation reaction for the introduction of a methyl vinyl ketone moiety.

It seemed therefore, that the use of 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165) as the annulating agent might

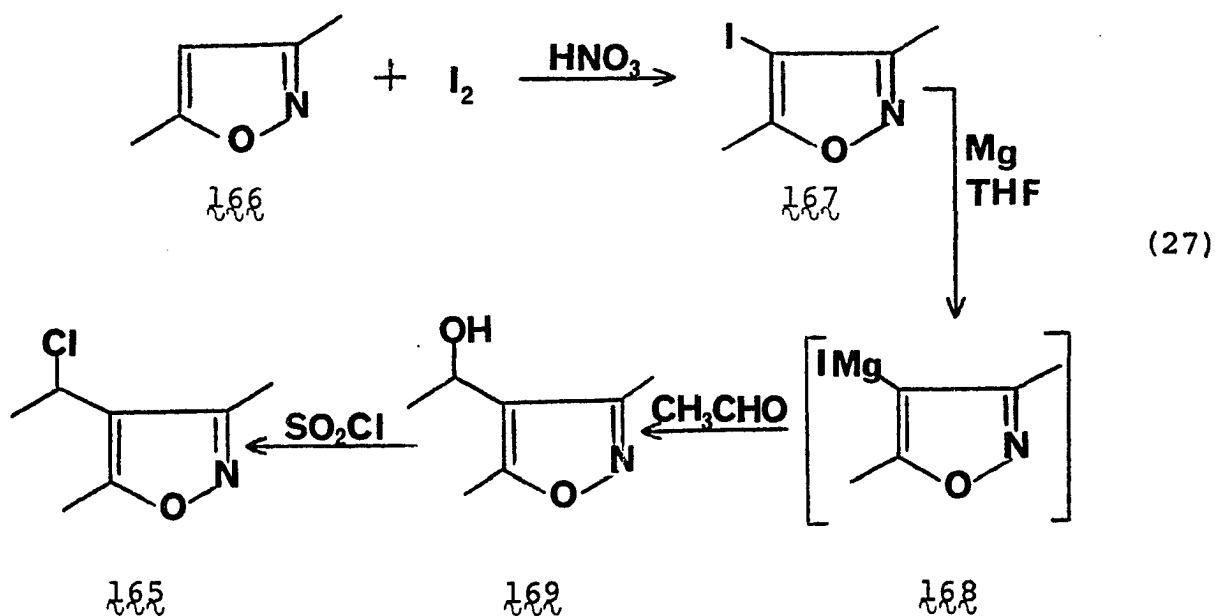


165

allow the formal introduction of a 3-penten-2-one group in the same manner as the 4-chloromethylisoxazole 160 allowed the introduction of a methyl vinyl ketone group. Since it did not appear that such an attempt had been made previously, and since the experimental details for annulations with 4-chloromethyl-3,5-dimethylisoxazole (160) were well worked out, chloroisoxazole 165 was prepared and its utility in the annulation of β -keto esters 84 and 151 was investigated.

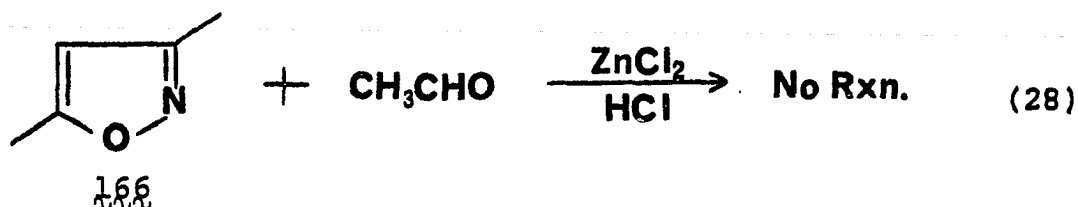


The preparation of 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165) was accomplished by the route outlined in scheme 27. Oxidation of commercially available 3,5-dimethylisoxazole (166) with nitric acid in the presence of iodine gave 4-iodo-3,5-dimethylisoxazole (167) in good yield¹⁰⁴. Preparation of the corresponding Grignard derivative 168 was accomplished by reaction of the 4-iodoisoxazole 167 with magnesium metal in

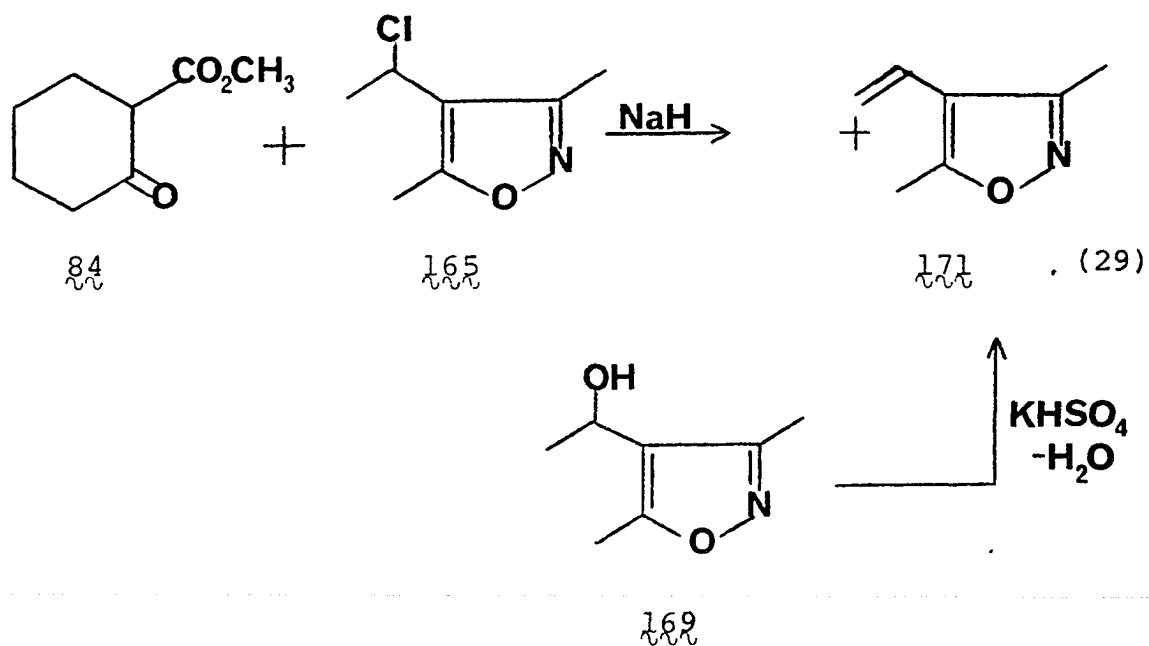


anhydrous tetrahydrofuran¹⁰⁵. Treatment of the Grignard derivative 168 in situ with acetaldehyde¹⁰⁶ gave 4-(1'-hydroxyethyl)-3,5-dimethylisoxazole (169). Conversion of the alcohol 169 to the desired product was completed by reaction with thionyl chloride in ether. This procedure¹⁰⁷ gave 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165) in 32% overall yield from 3,5-dimethylisoxazole.

It should be mentioned that attempted preparation of the chloroethylisoxazole 165 under conditions reported¹⁰⁸ for the chloromethylation of 3,5-dimethylisoxazole failed, scheme 28.

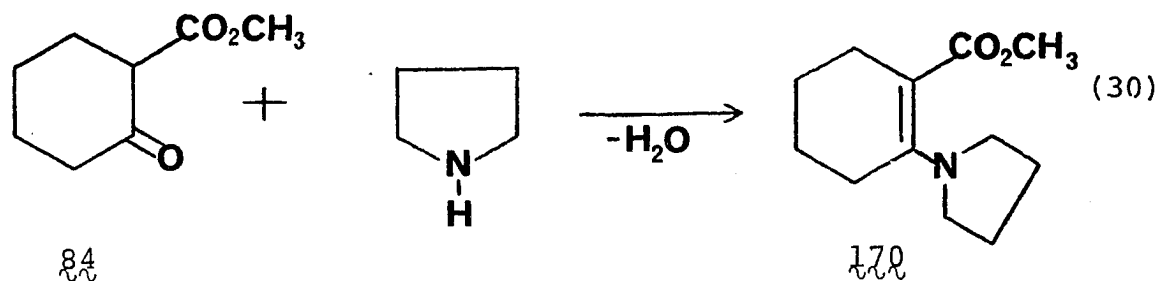


Attempted alkylation of β -keto ester 84 , which was used as a model substrate, according to the general procedure published originally by Stork¹⁰⁰ and which had been successfully employed by Ohashi¹⁰³, gave a mixture of starting β -keto ester and a second product. This material was identified as 4-vinyl-3,5-dimethylisoxazole (170) by comparison with an authentic sample prepared by acid-catalyzed dehydration of 4-(1'-hydroxyethyl)-3,5-dimethylisoxazole (169), scheme 29.



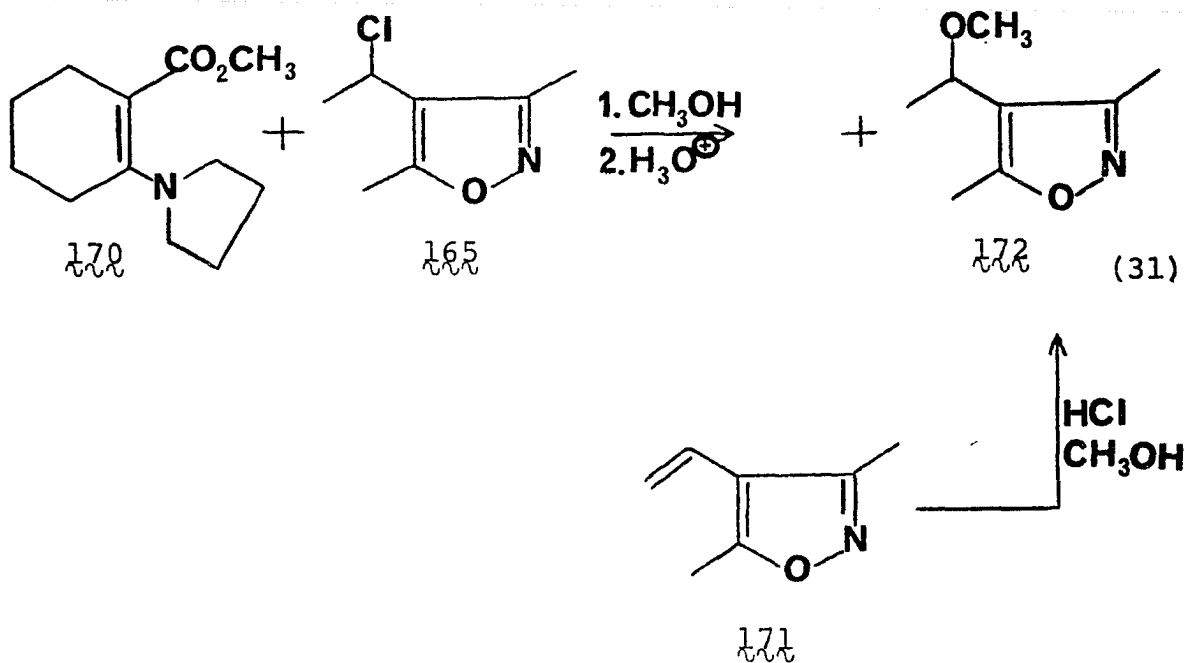
Following this initial failure, the alkylation was attempted via the pyrrolidine enamine 170 of β -keto ester 84, a procedure used by Stork¹⁰⁰ for the annulation of cyclohexanone with 4-chloromethyl-3,5-dimethylisoxazole.

Preparation of the required enamine was accomplished in high yield by reaction of 84 with pyrrolidine in a benzene solvent followed by azeotropic removal of water¹⁰⁹, scheme 30.

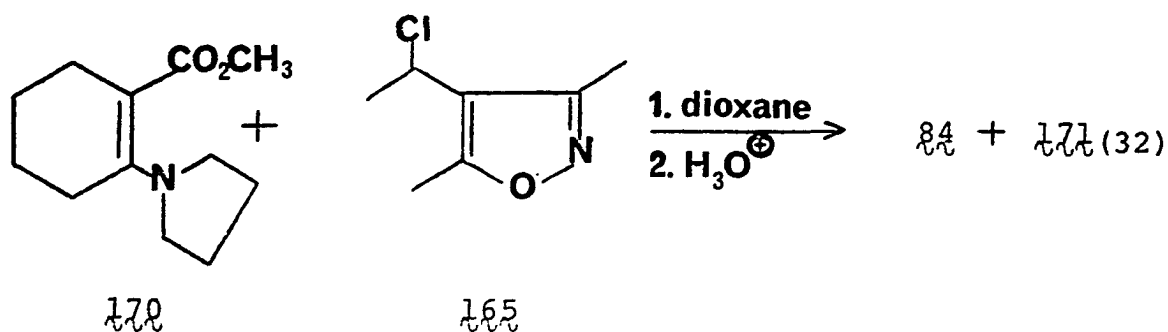


The enamine $\overset{\sim}{170}$ was isolated as a white, fluffy solid and appeared to be stable indefinitely if stored under nitrogen below 0° .

Attempted alkylation of enamine $\overset{\sim}{170}$ with the chloroethylisoxazole $\overset{\sim}{165}$ in absolute methanol¹⁰⁹ followed by hydrolysis with dilute acid gave a quantitative recovery of β -keto ester $\overset{\sim}{84}$ as well as a second product identified as 4-(1'-methoxyethyl)-3,5-dimethylisoxazole ($\overset{\sim}{172}$) by comparison with an authentic sample prepared by treatment of 4-vinyl-3,5-dimethylisoxazole ($\overset{\sim}{171}$) with methanol in dilute acid, scheme 31.



Repetition of the above reaction using anhydrous dioxane as the solvent gave only β -keto ester $\overset{\sim}{84}$ and the 4-vinyl derivative $\overset{\sim}{171}$, scheme 32.



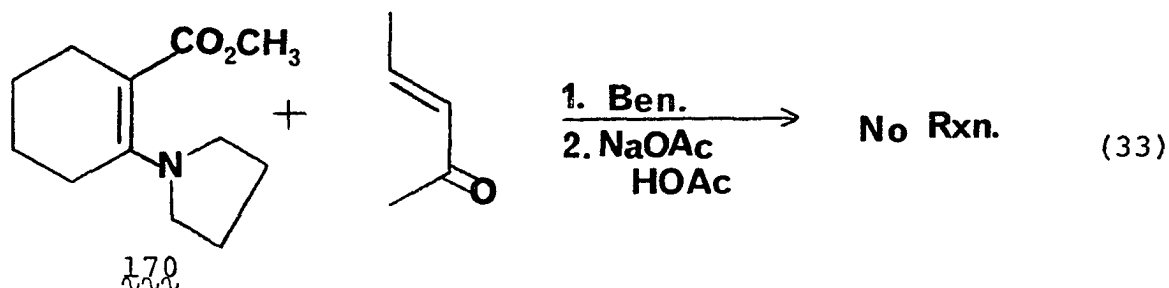
Further investigation, which involved the systematic variation of reaction conditions such as temperature, solvent, etc., showed the 4-vinyl derivative **171** to be the major isolable product in all cases except that noted above, scheme 31. However, it is likely that the 4-vinyl derivative **171** was also the primary product of this reaction, and that the observed product **172** was derived from **171** by addition of methanol to the vinylic double bond during acidic hydrolysis of the enamine. This interpretation was supported by the conversion of **171** to **172** under similar conditions, scheme 31.

Apparently, the conversion of 4-(1'-chloroethyl)-3,5-dimethylisoxazole **165** to 4-vinyl-3,5-dimethylisoxazole **171** is so facile under the reaction conditions investigated that the desired alkylation reaction was not able to compete successfully. This approach was therefore abandoned.

Our second alternative annulation procedure was based on the unexpected stability and ease of preparation of the enamine of β -keto ester **84**, namely **170**. Generally, enamines of simple carbonyl compounds as well as those derived from β -keto

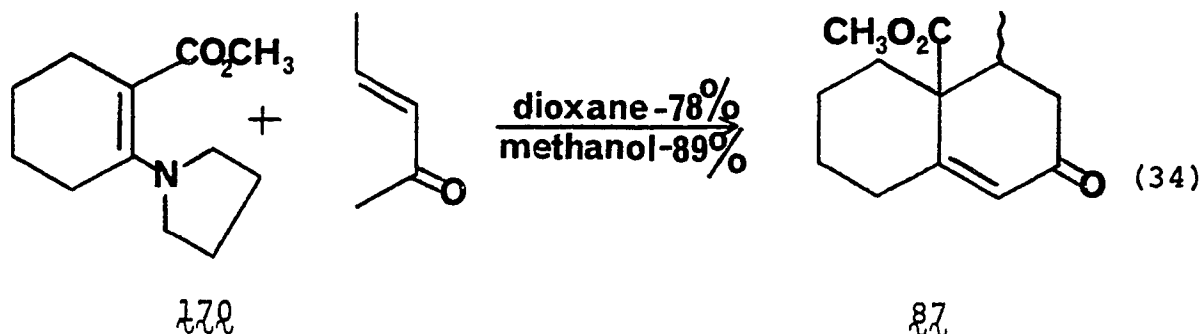
esters^{109,110} are relatively unstable and tend to decompose rather rapidly. In addition, most enamines are isolated as liquids which must be subjected to distillation in order to be obtained in a pure state, whereas enamine 170 of β -keto ester 84 was isolated as a reasonably pure solid. Therefore, we felt that if a successful alkylation procedure could be developed using the readily accessible enamine 170, application of this method to the enamine of the isopropenyl-containing β -keto ester 151 might allow introduction of the desired 3-penten-2-one group into the molecule.

Our initial attempt to effect alkylation of 170 with trans-3-penten-2-one involved treatment of the enamine with a slight excess of trans-3-penten-2-one in an anhydrous benzene solvent at reflux temperature, scheme 33. Following a 24 hour reaction period at reflux temperature and decomposition of the



the enamine by addition of a sodium acetate-acetic acid buffer solution¹¹⁰, appropriate workup gave a 96% recovery of β -keto ester 84. Repetition of the above reaction using formamide as the solvent gave a similar result as did the use of a number of other solvents typically used in alkylation reactions.¹¹⁰

However, treatment of **170** with a 2-fold excess of trans-3-penten-2-one in an anhydrous dioxane solvent at 50° for 210 hours followed by addition of the sodium acetate-acetic acid buffer solution afforded the desired naphthalenone **87** in a 78% yield after chromatographic purification, scheme 34. Furthermore, the use of an anhydrous methanol solvent with a 2-fold



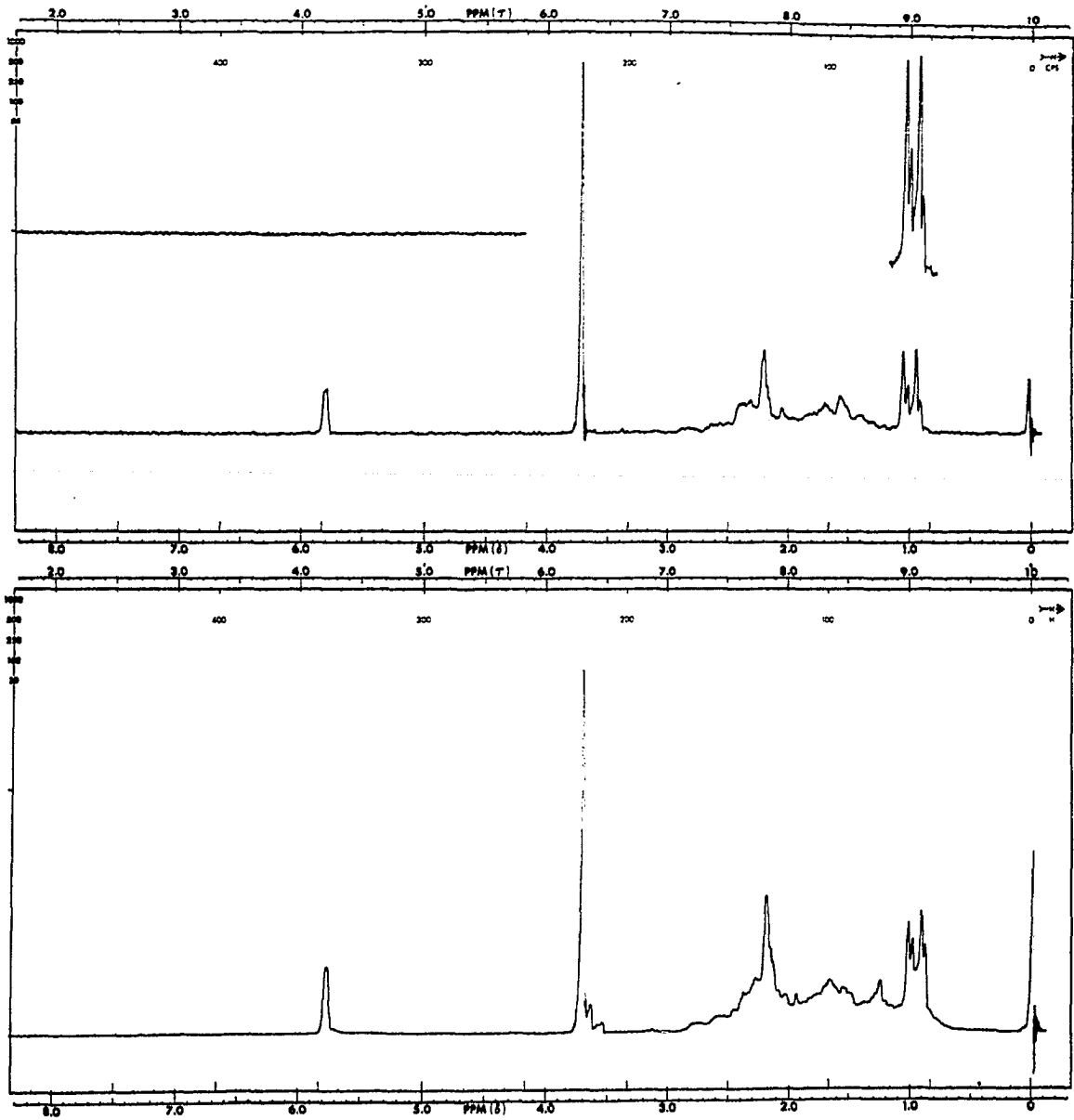
excess of the unsaturated ketone gave the naphthalenone **87** in 89% yield. Also, the use of methanol shortened the reaction time to 72 hours.

The naphthalenone **87** thus isolated appeared to be a mixture of cis and trans isomers similar to that isolated earlier by the sodium methoxide catalyzed reaction of β -keto ester **84** with trans-3-penten-2-one, p. 48. Indeed, a comparison of the 60 MHz nmr spectra of the naphthalenones prepared by both methods showed nearly identical isomer ratios, Figure 6. Apparently, despite the bulk of the pyrrolidino group, it exerted little influence on the stereochemistry of the Michael addition.

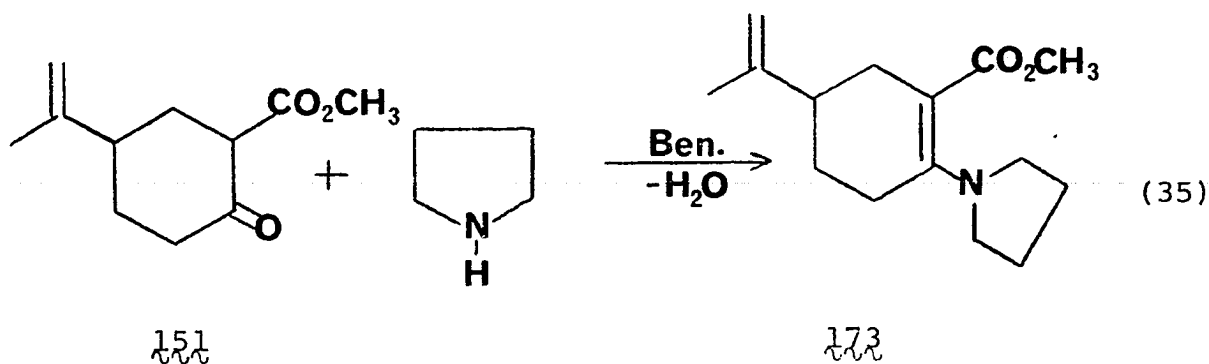
Figure 6. Nmr spectrum of methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenecarboxylate (87)

Top: 60 MHz nmr spectrum of methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenecarboxylate (87) prepared by base catalyzed annulation of methyl 2-oxocyclohexanecarboxylate (84) with trans-3-penten-2-one

Bottom: 60 MHz nmr spectrum of methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenecarboxylate (87) prepared by reaction of trans-3-penten-2-one with methyl 2-pyrrolidino-1-cyclohexene-carboxylate (170)

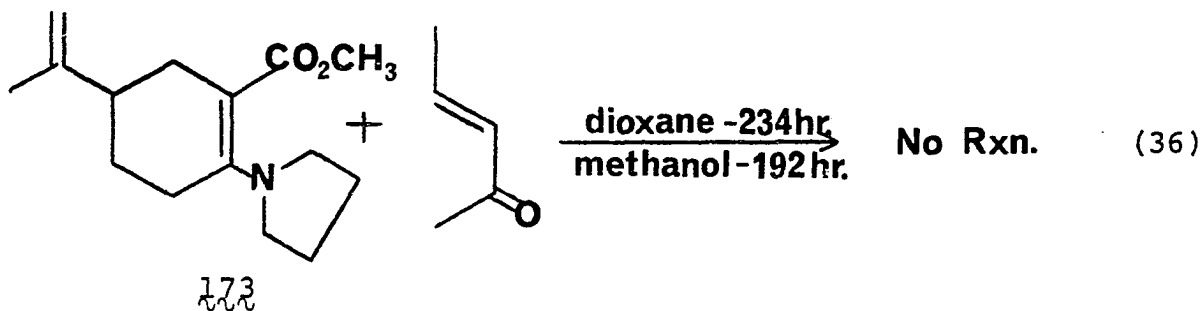


With the hope that this alkylation procedure would be at least partially successful when applied to the isopropenyl-containing β -keto ester 151 , we prepared the pyrrolidine enamine 173 of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) under conditions identical to those employed for the preparation of 170 , scheme 30. Treatment of 151 with pyrrolidine in benzene followed by azeotropic removal of water gave a red, waxy solid presumed to be enamine 173 , scheme 35. The



material resisted all attempts at purification, yielding in each case a waxy solid. Also, enamine 173 displayed an instability characteristic of most enamines¹⁰⁹. Whereas the unsubstituted enamine 170 was stable for a few hours at room temperature and was stored at -20° under a nitrogen atmosphere for 11 months without noticeable change, enamine 173 appeared to decompose within a few minutes at room temperature. For some reason, addition of the isopropenyl substituent to the β -keto ester molecule rendered the resulting enamine extremely susceptible to decomposition.

Whether due to the instability of the isopropenyl-containing enamine 173 or simply to its unreactivity, treatment of 173 with a 2-fold excess of trans-3-penten-2-one in either anhydrous dioxane or methanol gave no naphthalenone product, scheme 36. The reaction in dioxane was continued for 234 hours



and that in methanol for 192 hours. In neither case was any alkylation detected.

We feel that the complete lack of reactivity of enamine 173 was probably due to its decomposition under the reaction conditions rather than to an inherent lack of reactivity. Based on the observation that the successful alkylation of the unsubstituted enamine 170 with trans-3-penten-2-one had involved reasonably lengthy reaction times (a minimum of 72 hours in methanol and 210 hours in dioxane), we had anticipated the same would be true for the isopropenyl-containing enamine 173 . However, since this enamine was obviously susceptible to rapid decomposition during lengthy reaction times, an alternative alkylation procedure applicable to both enamines 170 and 173 was envisioned. It was hoped that this procedure would

allow alkylation of 170 (and possibly 173) using much shorter reaction times.

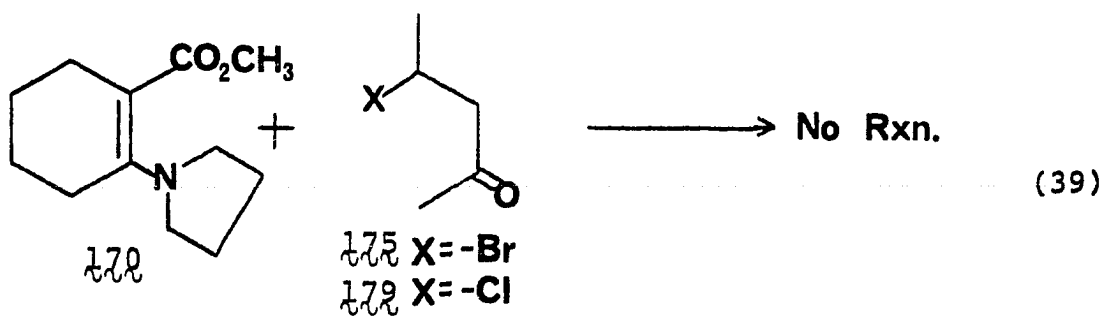
According to Stork et al.,¹⁰⁹, enamines derived from simple carbonyl compounds may be successfully alkylated by reaction with primary or secondary halides in a variety of solvents. The alkylations generally proceed in high yield and under fairly mild reaction conditions (low temperature, short time). The corresponding reactions with enamines derived from β -keto esters, however, have not been reported.

It seemed therefore, that 4-halo-2-pentanones might serve as useful alkylating agents for enamines 170 and 173.

The preparation of 4-bromo-2-pentanone (175) and 4-chloro-2-pentanone (179) was accomplished as shown in scheme 37. Condensation of acetaldehyde with acetone⁶³ gave 4-hydroxy-2-pentanone (174). Treatment of 174 with phosphorous tribromide gave 4-bromo-2-pentanone (175) in a 67% distilled yield¹¹¹. Reduction of hydroxyketone 174 with sodium borohydride gave 2,4-pentanediol (176) in 90%. Also, hydrogenation of 2,4-pentanedione (177) over a rhodium on alumina catalyst gave the diol in nearly quantitative yield. Treatment of diol 176 with concentrated hydrochloric acid¹¹² gave 4-chloro-2-pentanol (178), which upon oxidation with sodium dichromate and sulfuric acid afforded 4-chloro-2-pentanone (179).

with either phosphorous trichloride¹¹¹ or thionyl chloride gave the chloroketone 179 contaminated with varying amounts of the α,β -unsaturated ketone.

Attempted alkylation of enamine 170 with the 4-halo-2-pentanones (175 and 179) in a variety of solvents gave, after hydrolysis and appropriate workup, recovered β -keto ester 84 as the major product (> 94%). The alkylation was attempted in anhydrous formamide, benzene, dioxane, and methanol, scheme 39.



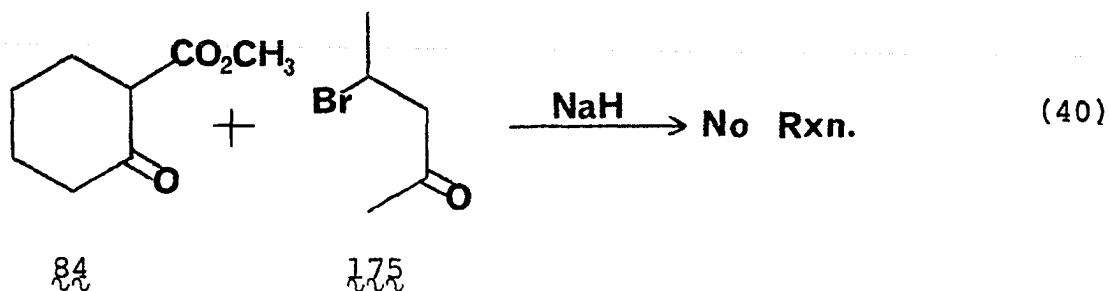
In each case, a number of independent reactions were conducted in which the reaction time as well as the temperature was varied between wide limits. In addition, the haloketones were shown to be stable under the reaction conditions by a nearly quantitative recovery (shown by vapor phase chromatography) of each following hydrolysis of the reaction mixture.

At this point, it became obvious that alkylation of enamine 170 with halopentanones 175 and 179 could not be accomplished under reaction conditions which would not cause decomposition of enamine 173. Further studies with enamines

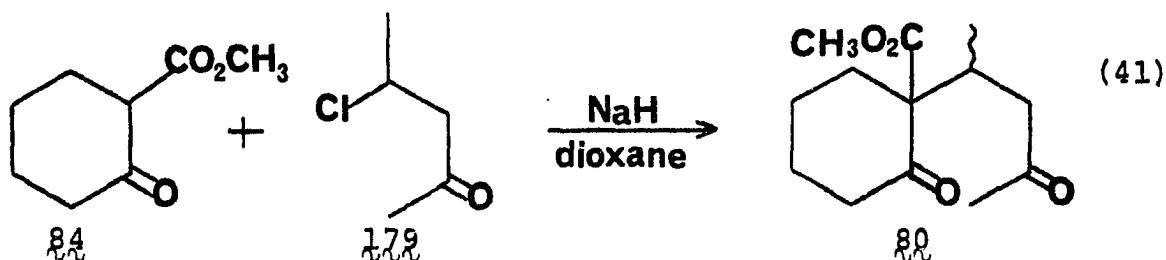
170 and 173 were therefore not pursued.

Finally, we decided to attempt the alkylation of β -keto ester 84 itself with halopentanones 175 and 179 with the hope that an alkylation procedure could be developed, which, when applied to the isopropenyl-containing β -keto ester 151 would prove successful.

Reaction of β -keto ester 84 with 4-bromo-2-pentanone 175 in a variety of common solvents under the influence of sodium hydride gave no alkylated product, scheme 40. Dehydrobromination of the haloketone 175 to give trans-3-penten-2-one was

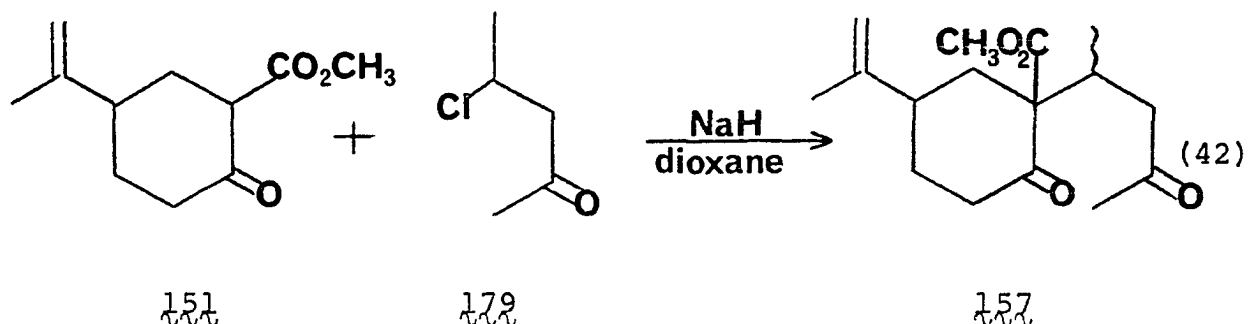


observed during extended reaction periods. In contrast, treatment of the β -keto ester 84 with 4-chloro-2-pentanone (179), in an anhydrous dioxane solvent, with sodium hydride as the base, gave a 64% yield of the ester dione 80, scheme 41.



The material thus isolated was not cyclized.

Treatment of β -keto ester 151 under identical conditions with the 4-chloropentanone 179 gave the alkylated product 157 in 58% yield, unpurified, scheme 42. However, as in the other

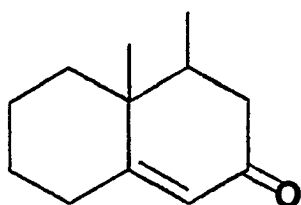


cases, attempted cyclization under a variety of conditions gave only products which had suffered decarbomethoxylation, as illustrated in scheme 25.

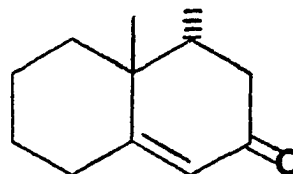
It appeared then, that although we had accomplished our initial objective of preparing methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) and were also able to effect alkylation of the material with a 3-penten-2-one moiety through a variety of methods, the dione 157 could not be cyclized. As discussed earlier in the text, we had anticipated that cyclization from the initial dione 157 to the desired naphthalenone 68 would entail serious steric interactions and that cyclization would probably be slow; we did not however, anticipate that decarbomethoxylation would occur as readily as it did.

In view of these last results, the synthetic scheme originally envisioned for the synthesis of naphthalenone **68** was reluctantly abandoned and the work described in the second part of this manuscript was initiated.

Stereoselective Synthesis of Cis- and Trans-
4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-
naphthalenone (**69c** and **69t**)



69c

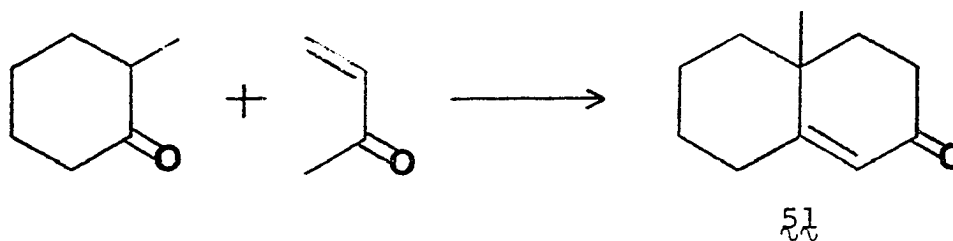


69t

Methods of synthesis

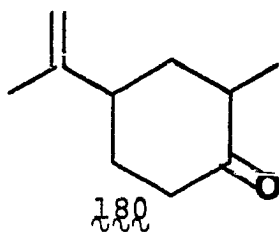
As was evident from the discussion of the Robinson annulation reaction presented in the historical section of this manuscript, the use of unactivated cycloalkanones such as cyclohexanone or 2-methylcyclohexanone affords the desired naphthalenone products in low yield and questionable purity. This is in direct contrast to those Robinson annulation reactions in which the cycloalkanones contain an activating group (carboxyaldehyde or carboxylate). For example, the best experimental procedure for the annulation of 2-methylcyclohexanone with methyl vinyl ketone has been reported by

Ross and Levine⁵⁷, who were able to obtain naphthalenone **51** in

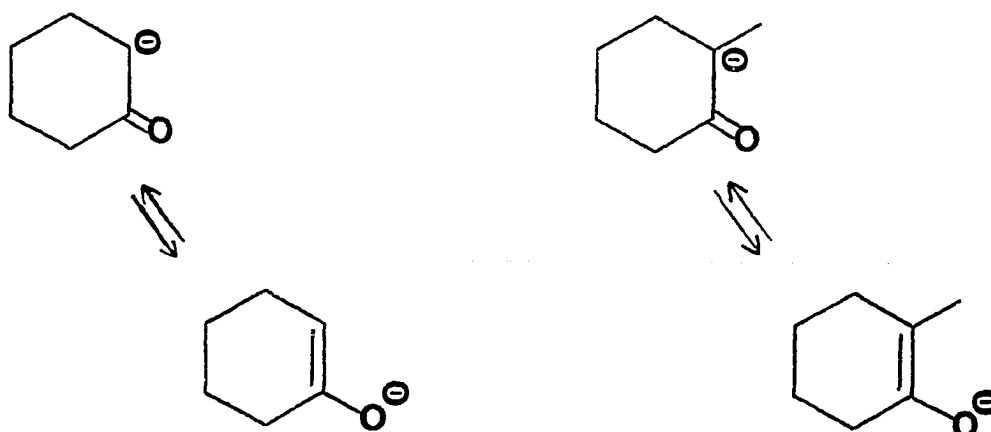


only 50-55% yield. Furthermore, the use of trans-3-penten-2-one in place of methyl vinyl ketone has been shown⁶² to give an even lower yield of naphthalenone product.

In view of these results and the large amount of effort which had already been expended in this area (see historical section), the possibility that a procedure could be developed whereby an unactivated cycloalkanone such as 2-methylcyclohexanone could be condensed with trans-3-penten-2-one in reasonable yield seemed unlikely. However, due to the failure of the annulation reactions studied in part A of this work, the necessity of the development of a successful annulation procedure which could be applied to 2-methylcyclohexanone and also to 2-methyl-4-isopropenylcyclohexanone (**180**) was undeniable.



Most investigators have rationalized the low yield of Robinson annulation reactions with unactivated cycloalkanones as due primarily to the polymerization of the unsaturated ketone (methyl vinyl ketone or trans-3-penten-2-one) during the long reaction times necessary to allow generation of a sufficient concentration of the enolate anion, for example:

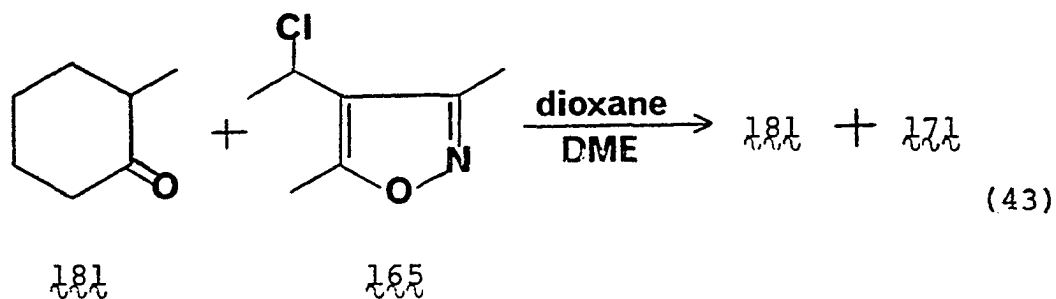


With this interpretation in mind then, two mechanisms by which this polymerization might be prevented come immediately into focus. First, the use of an alternative annulating agent which would allow preparation of a naphthalenone product analogous to that expected from reaction with trans-3-penten-2-one but which would not be subject to polymerization under the influence of base. Second, employment of reaction conditions under which generation of the necessary enolate anion would be rapid and thereby the amount of polymerization reduced. Also,

the use of experimental conditions under which generation of the enolate anion would be essentially complete before introduction of the alkylation agent might allow annulation to compete successfully with polymerization. The experimental variables were seen as solvent, reaction temperature, and base strength, as well as the nature of the base with respect to either reversible or irreversible generation of the enolate anion.

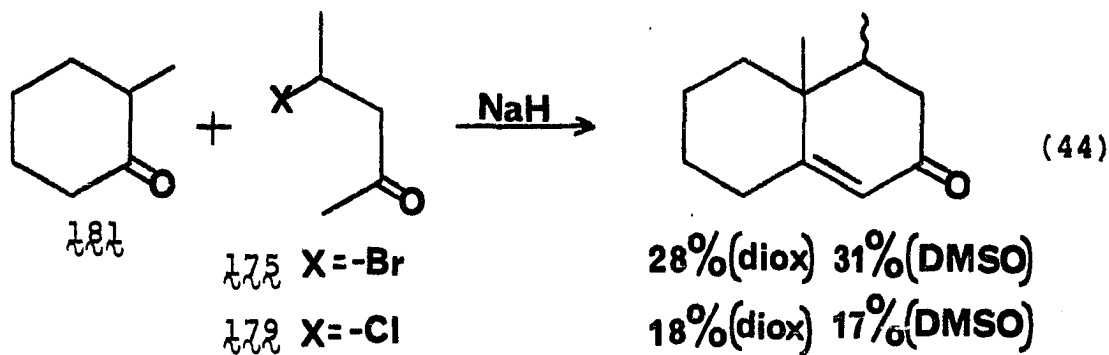
Our initial investigations were directed toward the use of an alternative annulating agent since the systematic variation of a number of experimental conditions was anticipated to be an exceedingly lengthy process.

Attempted alkylation of 2-methylcyclohexanone (181) which was used as a model substrate for 180, with 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165)¹⁰⁰⁻¹⁰³ in either anhydrous dioxane or 1,2-dimethoxyethane (DME) under the influence of sodium hydride gave 2-methylcyclohexanone (181) and 4-vinyl-3,5-dimethylisoxazole (171) as the only isolable products, scheme 43. It was inferred from these results as well as those described earlier in part A that the isoxazole 165 was simply too easily dehydrochlorinated to be useful as an alkylation agent for 2-methylcyclohexanone and work with this material was terminated.



Following this initial failure, we proceeded to investigate the alkylation of 2-methylcyclohexanone with 4-bromo-2-pentanone (175) and 4-chloro-2-pentanone (179), prepared as described in part A above. We were considerably more successful with this system.

Treatment of 2-methylcyclohexanone (181) with either 4-bromo- or 4-chloro-2-pentanone (175 or 179) in either anhydrous dimethylsulfoxide (DMSO) or anhydrous dioxane, with sodium hydride as the base, gave the indicated yields of



naphthalenone 69 , scheme 44. While these yields are obviously considerably less than those obtained by Ross and Levine⁵⁷ for annulation of 2-methylcyclohexanone with methyl vinyl ketone, they are comparable to any previously reported for the annulation of 2-methylcyclohexanone with β -halo ketones. (See for example reference 48). In addition, the successful annulation of an unactivated cycloalkanone under relatively mild experimental conditions provided the basis for future work which eventually culminated in a stereoselective synthesis of the cis- and trans-naphthalenones 69c and 69t .

However, before continuing to a discussion of this synthesis, two aspects of the annulation reaction discussed above merit comment. First, the experimental conditions were such that generation of the enolate anion was essentially complete before the haloketone was added. In addition, the use of exactly one equivalent of sodium hydride allowed the enolate anion to be generated irreversibly, thus eliminating any complicating effects due to the presence of a base other than the enolate itself (i.e., no residual potassium hydroxide, sodium ethoxide, etc.). Second, based on the fact that only 4-chloro-2-pentanone (179) and not 4-bromo-2-pentanone (175) could be used to successfully annulate methyl 2-oxocyclohexanecarboxylate (84) (scheme 41), it was somewhat surprising to find that in the present case the bromopentanone 175 gave the higher yield of annulated product. This may be

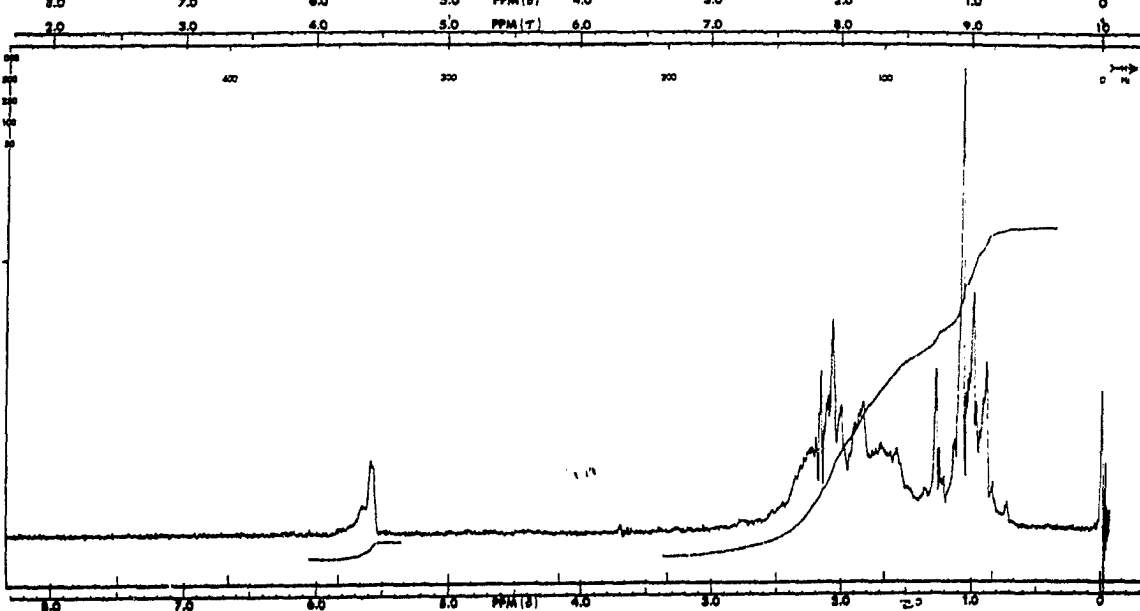
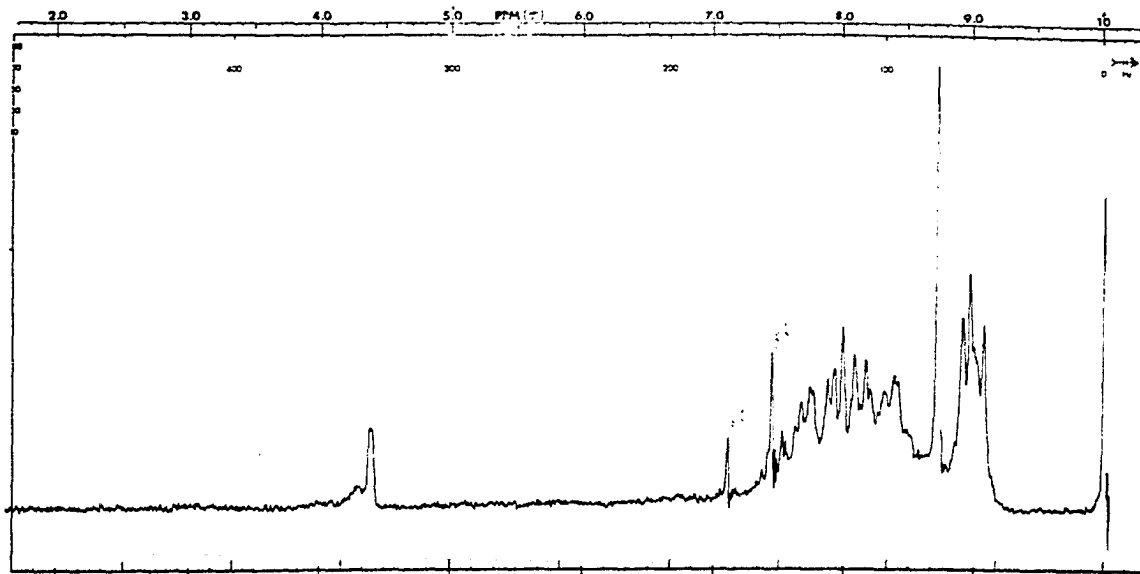
easily rationalized however, since it was shown earlier (p. 114) that dehydrobromination of bromoketone 175 to unreactive trans-3-penten-2-one occurred to the complete exclusion of alkylation under the reaction conditions employed with β -keto ester 84, whereas under similar conditions, dehydrochlorination of chloroketone 179 was slow relative to alkylation. In the present case with 2-methylcyclohexanone, neither haloketone suffered dehydrohalogenation and the relative yields obtained reflect simply the expected greater ease of displacement of bromide ion relative to chloride.

In addition to the experimental aspects discussed above, a careful examination of the naphthalenone product 69 obtained by annulation of 2-methylcyclohexanone with the haloketones 175 and 179 revealed an unexpected solvent dependency. When the reaction was conducted in dimethylsulfoxide, a product was obtained which displays the nmr spectrum shown in Figure 7-top, whereas when anhydrous dioxane was used as the solvent, the isolated product displays the nmr spectrum shown in Figure 7-bottom. As can be seen, the most obvious difference involves the chemical shift position of the angular methyl group. The product isolated from reaction in dimethylsulfoxide displays a singlet due to the angular methyl group at 1.27δ (CCl_4) downfield from internal tetramethylsilane, whereas that from reaction in dioxane displays a singlet at 1.08δ (CCl_4). Further examination revealed that the observed solvent dependency could

Figure 7. Nmr spectrum of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthaleneone (69)

Top: 60 MHz nmr spectrum of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69) from reaction of 2-methylcyclohexanone and 4-bromo-2-pentanone in dimethylsulfoxide

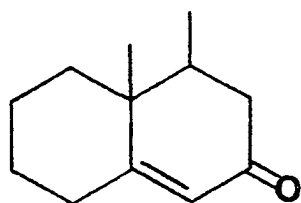
Bottom: 60 MHz nmr spectrum of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69) from reaction of 2-methylcyclohexanone and 4-bromo-2-pentanone in dioxane



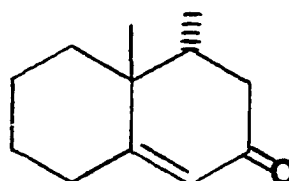
be reproduced under a variety of reaction conditions (temperature, time, etc.) and that the use of either 4-bromo- or 4-chloro-2-pentanone ($\delta_{\text{C}} 175$ or $\delta_{\text{C}} 179$) had no apparent effect on the nature of the primary product. The infrared and mass spectra showed only subtle differences, such as those which might be expected for nearly identical materials.

The only reasonable rationalization for the observed difference in the chemical shift positions of the angular methyl groups in the compounds isolated from the two different solvent systems is that the reactions had produced different isomers. In fact, each of the two products could be shown to contain a fairly large ($\sim 25\%$) amount of the alternative product. This was demonstrated by vapor phase chromatography as well as by the presence of a weak singlet absorption in the nmr spectrum (Figure 7) of each product at a position corresponding to the chemical shift position of the angular methyl group in the alternative product. In other words, the nmr spectrum of the product isolated from reaction in dimethylsulfoxide (Figure 7-top) displays a small singlet at 1.08 δ corresponding to the angular methyl group in the product isolated from reaction in dioxane, while the nmr spectrum of this material in turn (Figure 7-bottom) shows a weak absorption at 1.27 δ attributed to the angular methyl group in the dimethylsulfoxide product.

We postulated therefore, that the annulation of 2-methylcyclohexanone with the haloketones 175 or 179 had produced a product mixture which contained either cis-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69c), or the corresponding trans-isomer 69t, as the major product depending on whether the reaction were conducted in dimethylsulfoxide or dioxane.

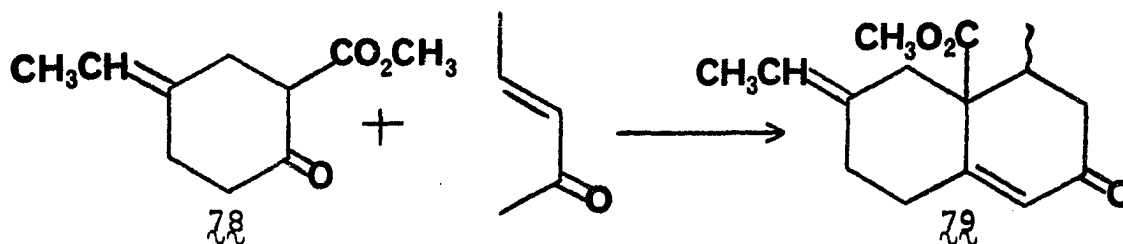


69c

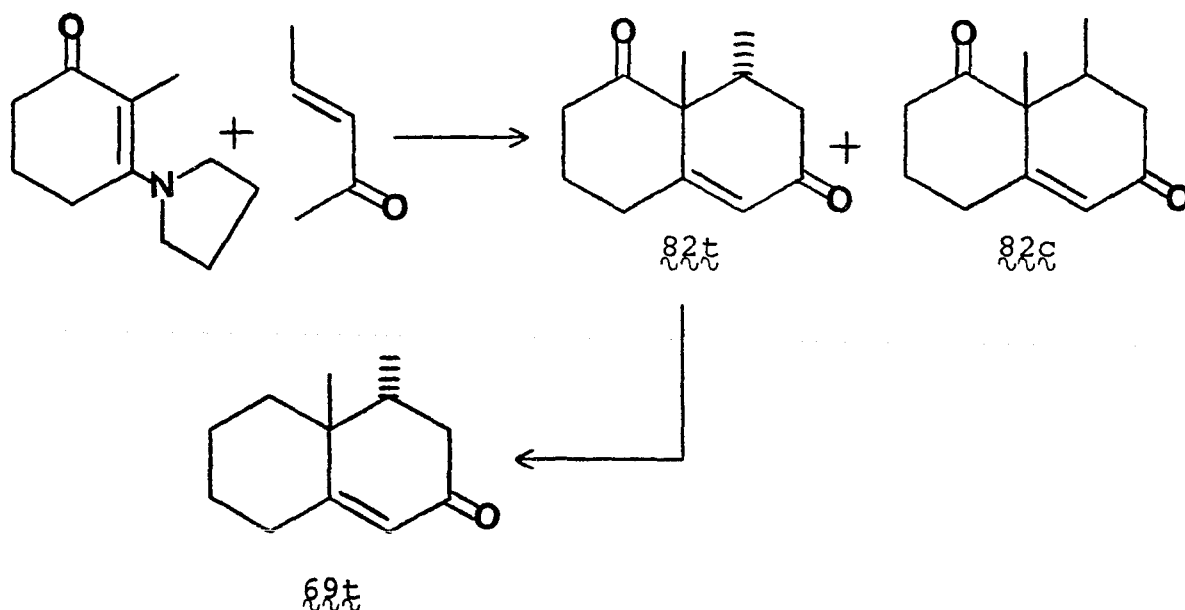


69t

In support of this postulate, the work of Marshall and Ruden⁴⁰ discussed earlier may be recalled. A footnote revealed that studies by T. M. Warne, Jr.,⁶⁴ as yet unpublished, had indicated a solvent dependency for the stereochemical outcome of the Robinson annulation reaction of β -keto ester 78 with trans-3-penten-2-one.

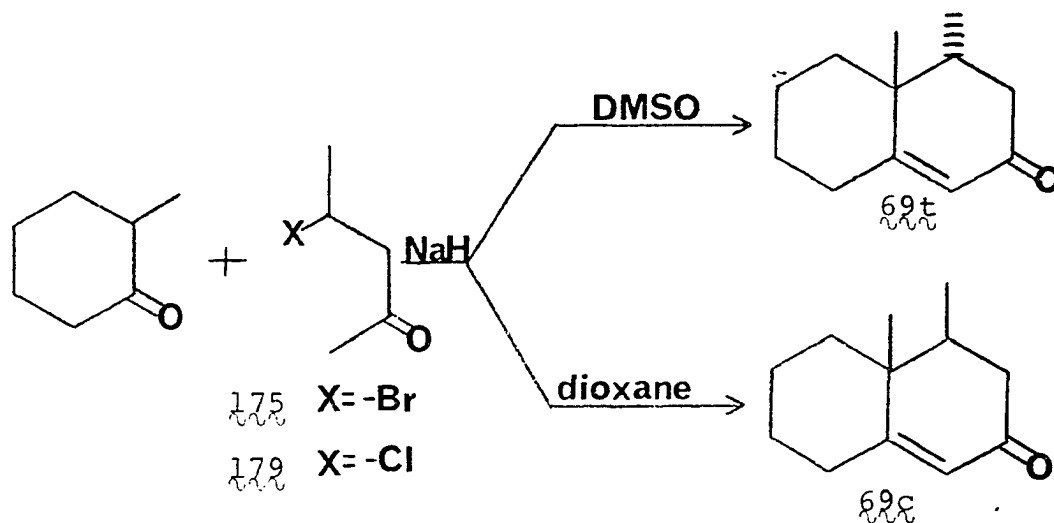


A preliminary assignment of the stereochemistry of the two isomers was made on the basis of recent work by Coates and Shaw^{65,113}. These workers prepared trans-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone ($\delta\delta\delta$) by Wolff-Kishner reduction of the unconjugated carbonyl group in $\delta\delta\delta$ following



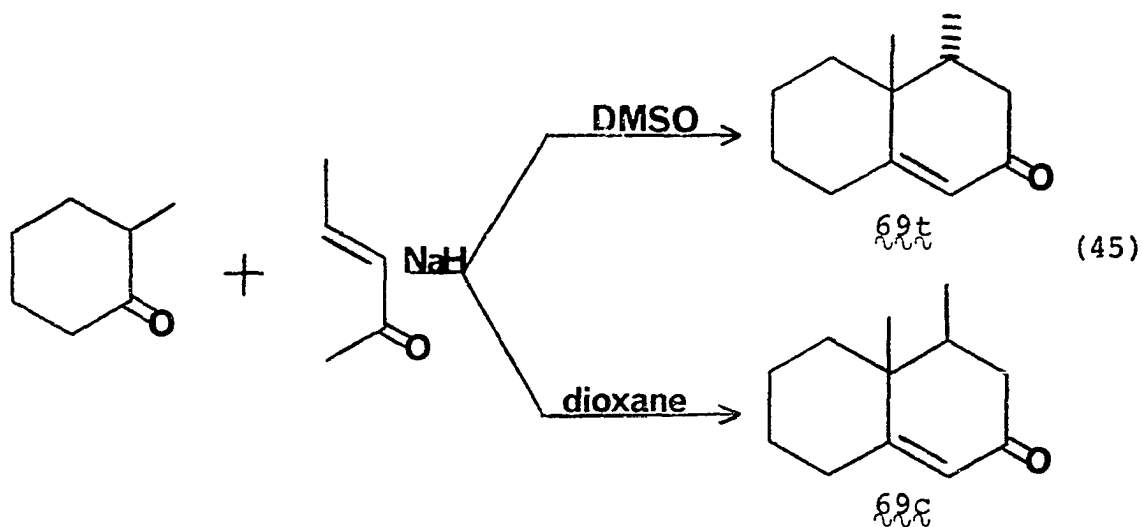
separation of the material from the corresponding cis isomer $\delta\delta\delta$, which they did not characterize further. The nmr data reported for the trans isomer $\delta\delta\delta$ listed a singlet for the angular methyl group at 1.28 δ (CCl_4) downfield relative to internal tetramethylsilane. Thus, the product isolated in the present work by annulation of 2-methylcyclohexanone with the haloketones $\delta\delta\delta$ and $\delta\delta\delta$ in a dimethylsulfoxide solvent must be the trans isomer $\delta\delta\delta$. Also, if it can be assumed that the naphthalenone produced by reaction in dioxane⁶ was isomeric with

that isolated from dimethylsulfoxide, this product can be assigned the cis configuration. These configurational



assignments are illustrated above. The initial postulate advanced to explain the observed solvent dependency as well as the stereochemical assignments of the isomeric products thus produced were subsequently shown to be correct (vida infra).

Since the experimental conditions which were finally developed for annulation of 2-methylcyclohexanone with the haloketones 175 and 179 were exceptionally mild, we felt that if reaction with trans-3-penten-2-one itself could be persuaded to proceed rapidly, the amount of concomitant polymerization might be held to a minimum. This was indeed the case, as reaction of the enolate anion, generated as described briefly above, with a slight excess of trans-3-penten-2-one gave the results shown below, scheme 45. An identical solvent



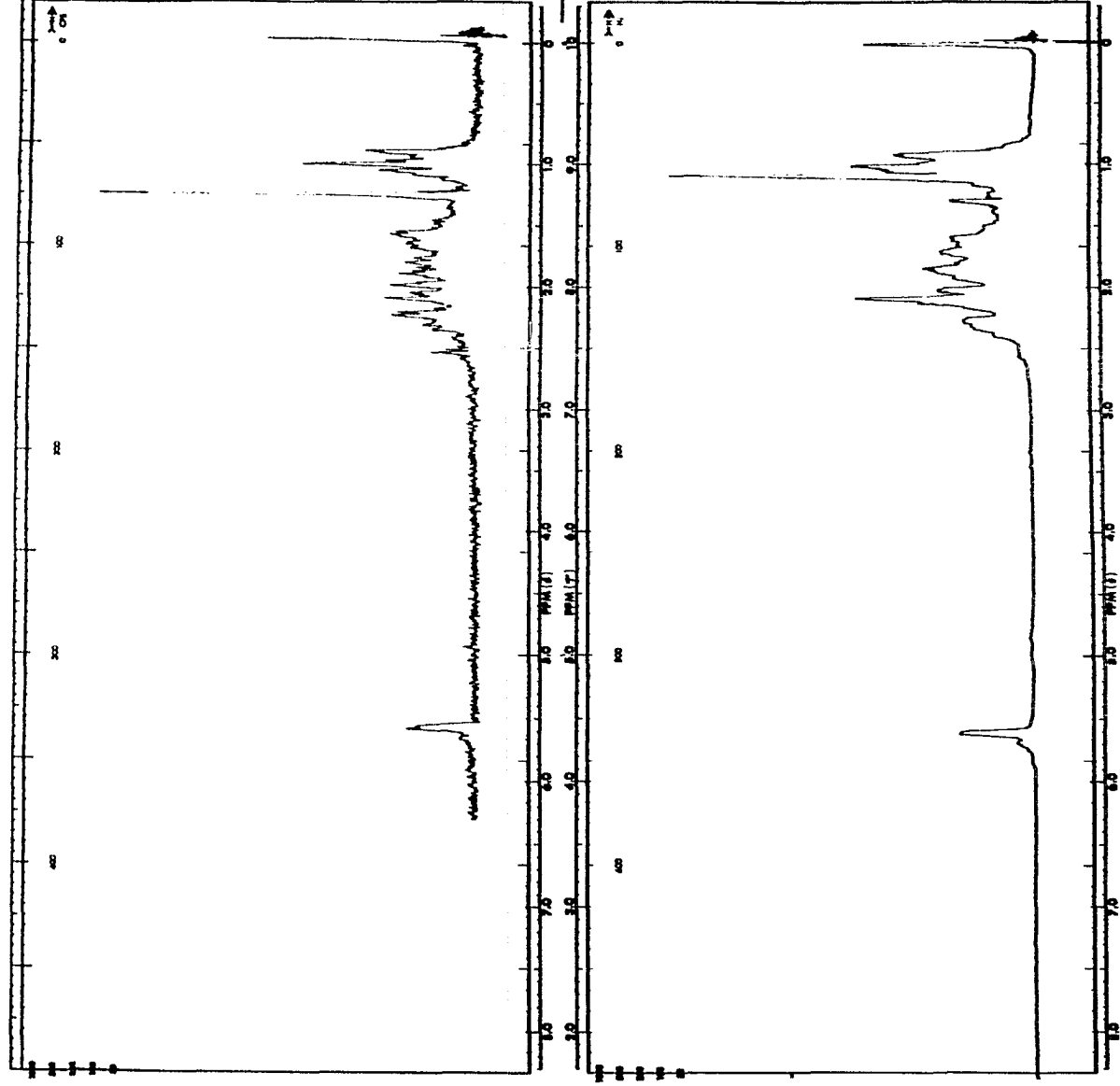
dependency was observed in this case, and, in addition, the stereochemical purity of the isolated products was much higher than that of those isolated from reaction with the haloketones. Whereas the mixtures isolated from annulation with the halo-ketones were contaminated with approximately 25% of the minor isomer, the mixtures isolated from annulation with trans-3-penten-2-one contained greater than 95% of one isomer. The nmr spectra of the isolated materials are displayed in Figure 8.

Thus we had successfully developed a modification of the Robinson annulation reaction which allowed preparation of either cis- or trans-4,4a-dimethylnaphthalenone, 69c or 69t, in reasonably high yield and stereochemical purity. The new annulation procedure was clearly superior to any previously

Figure 8. Nmr spectrum of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69)

Top: 60 MHz nmr spectrum of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69) from reaction of 2-methylcyclohexanone (181) and trans-3-penten-2-one in dimethylsulfoxide

Bottom: 60 MHz nmr spectrum of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69) from reaction of 2-methylcyclohexanone (181) and trans-3-penten-2-one in dioxane

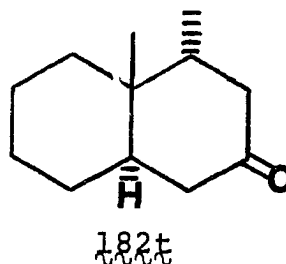
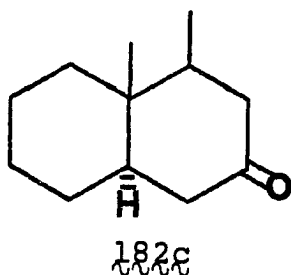


reported for an unactivated cycloalkanone with trans-3-penten-2-one. In fact, no stereoselective synthesis of 4,4a-dimethylnaphthalenones such as ~~182c~~ and ~~182t~~ which could be conducted under such convenient and high yield conditions was known, let alone one which allowed either isomer to predominate to the almost complete exclusion of the other simply by changing solvents! It remained only to unambiguously prove the stereochemistry of the isolated products.

Unambiguous synthesis of trans-4 β ,4a β -dimethyl- and trans-4 α ,4a β -dimethyl-3,4,5,6,7,8,8a-octahydro-2(1H)-naphthalenone

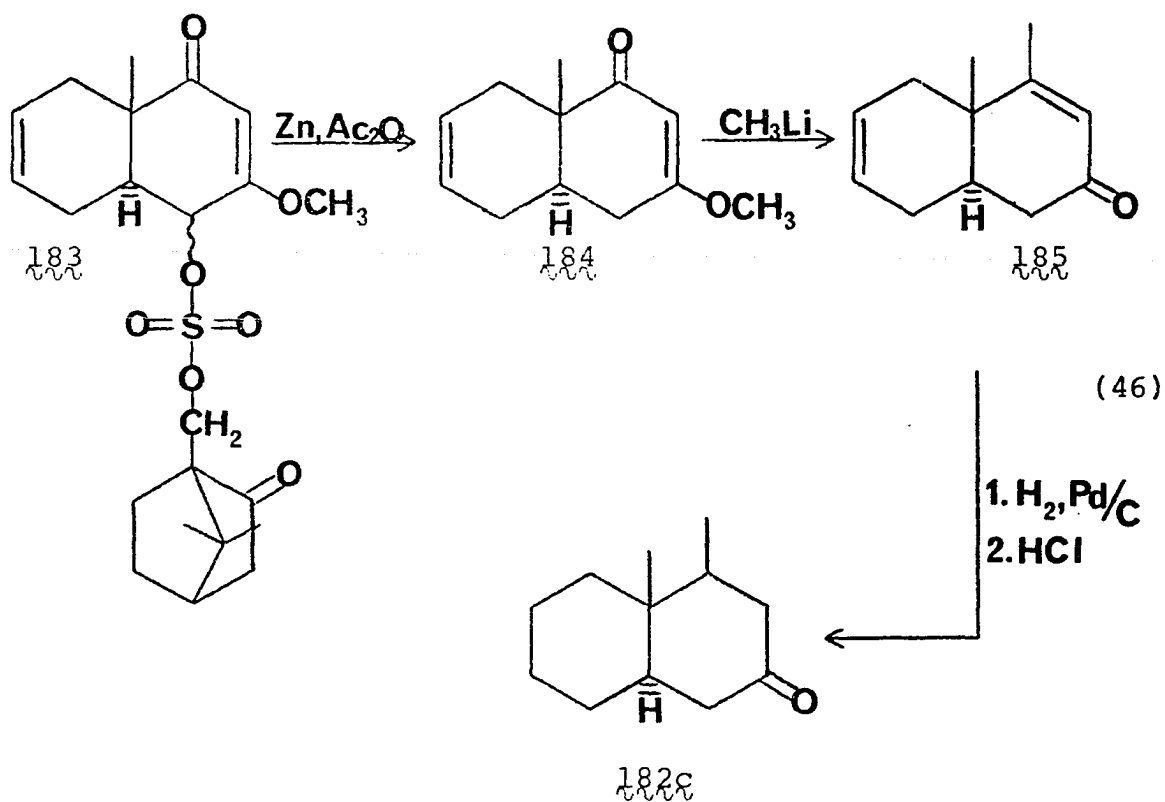
For convenience, we will designate the major product isolated from annulation in a dimethylsulfoxide solvent as the "DMSO product", and that isolated from reaction in dioxane the "dioxane product".

In planning our proof of the stereochemistry of the "DMSO and dioxane products", we decided to use the readily accessible and well characterized trans-4,4a-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenones ~~182c~~ and ~~182t~~. [The trans



prefix refers here to the stereochemistry of the ring junction, ie. positions 4a and 8a. The relative stereochemistry of the methyl groups is designated by an α (down) or β (up) following the substituent number.]

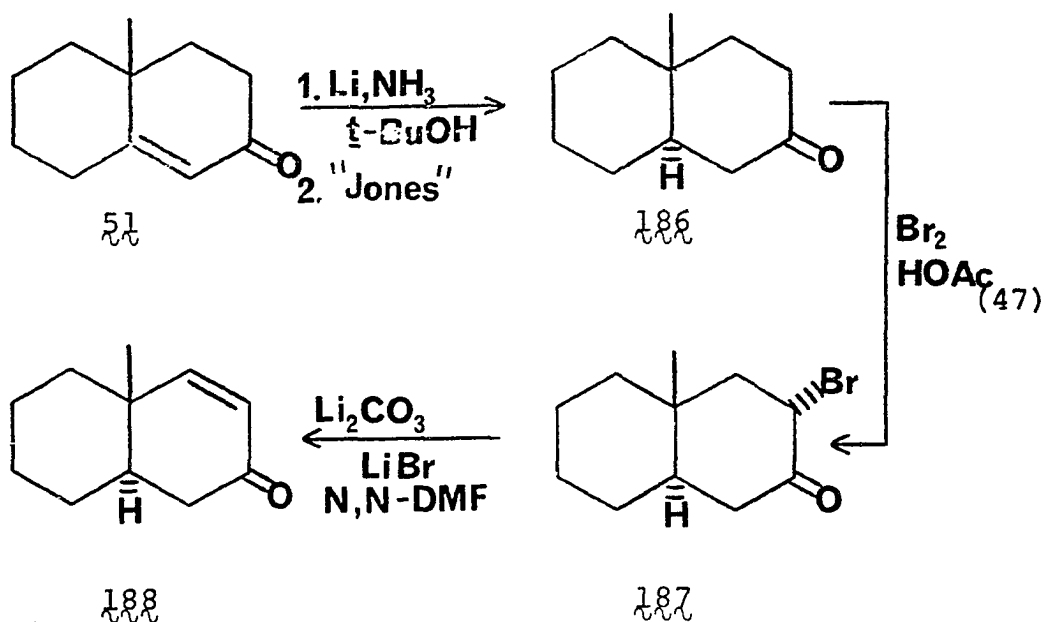
The 4 β ,4a β -dimethylnaphthalenone **182c** was prepared by the method of Djerassi and his coworkers²³, scheme 46. Treatment of camphorsulfonate **183**^{*} with zinc dust in acetic anhydride and



* We wish to thank the Monsanto Co., St. Louis, Missouri, for a generous gift of the camphorsulfonate.

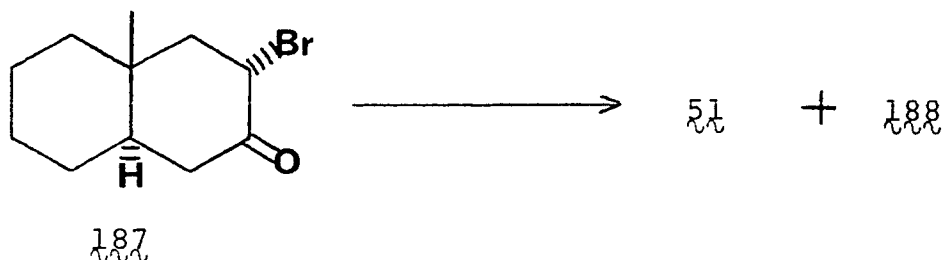
acetic acid gave trans-4 α ,5,8,8 α -tetrahydro-2-methoxy-4 α -methyl-4(1H)-naphthalenone (184) in 81% yield, scheme 46¹¹⁴. Treatment of methoxy ketone 184 with methyl lithium in ether followed by dehydration of the resulting carbinol with sulfuric acid gave trans-4 α ,5,8,8 α -tetrahydro-4,4 α -dimethyl-2(1H)-naphthalenone (185). Hydrogenation of dienone 185 at moderate pressure with a 10% palladium on charcoal catalyst in absolute methanol, followed by brief treatment with hydrochloric acid in dioxane to cleave any dimethyl ketal which might have been produced, afforded trans-4 β ,4 $\alpha\beta$ -dimethyl-3,4,4 α ,5,6,7,8,8 α -octahydro-2(1H)-naphthalenone (182c) in 90% distilled yield. The material thus isolated was identical in all respects to that described by Zalkow, Markley, and Djerassi²³ as the 4 β ,4 $\alpha\beta$ -isomer. These workers demonstrated the cis stereochemistry of the 4,4 α -dimethyl substituents by the familiar ketal dispersion technique.

The immediate precursor which was to be used for the synthesis of the 4 α ,4 $\alpha\beta$ -isomer was prepared as illustrated in scheme 47. Treatment of naphthalenone 51 with lithium in ammonia followed by oxidation of the resulting alcohol with Jones reagent according to the general procedure of House et al.,¹¹⁵ gave the trans-naphthalenone 186 in 72% yield. Bromination was accomplished by the addition of bromine in acetic acid⁵⁷ affording the 3 α -bromonaphthalenone 187. The



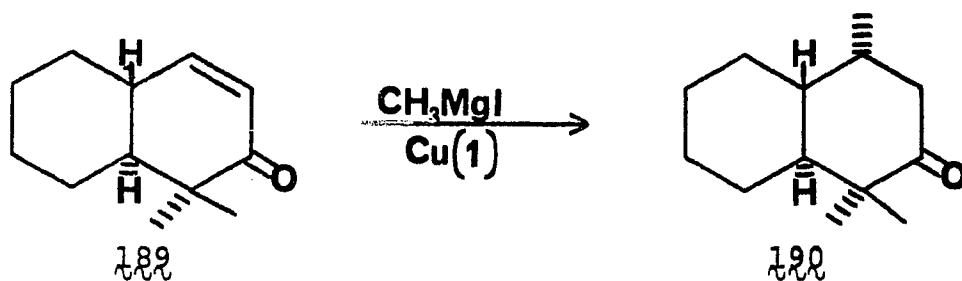
bromonaphthalenone **187** was identical in all respects to that described by Djerassi and Marshall as trans-3 α -bromo-3,4,4a,5,6,7,8,8a-octahydro-4a-methyl-2(1H)-naphthalenone (**187**). Dehydrobromination of **187** was accomplished by a modification of the Joly procedure^{116,117}, which involved brief exposure of the bromoketone **187** to an N,N-dimethylformamide solution of lithium carbonate and lithium bromide at reflux temperatures¹¹⁸. This procedure afforded the α,β -unsaturated ketone, 4a,5,6,7,-8,8a-hexahydro-4a-methyl-2(1H)-naphthalenone (**188**) in high yield. That the dehydrobromination reaction had indeed produced the 3,4 olefin was evident from the nmr spectrum of **188** which displayed a distinct AB coupling pattern in the olefinic

region. The absence of any rearrangement product, namely 51, was demonstrated by vapor phase chromatography on a variety of columns. This product was anticipated as a possible contaminant due to previous results with λ -collidine¹¹⁹.

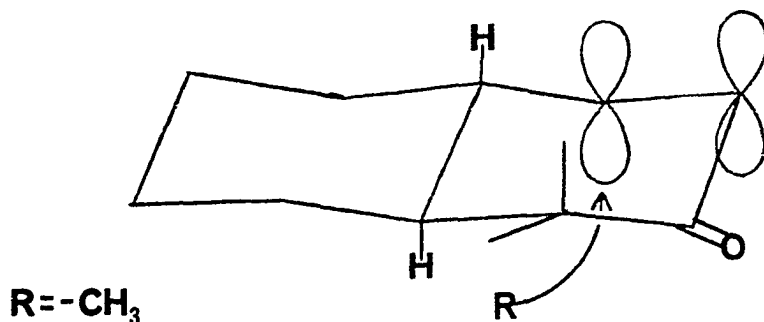


Ample precedent for the conversion of α,β -unsaturated ketone 188 to the desired 4 α ,4 β -dimethylnaphthalenone 182t can be derived from the work of Marshall and Andersen¹²⁰ as well as that of Schudel and coworkers³⁹.

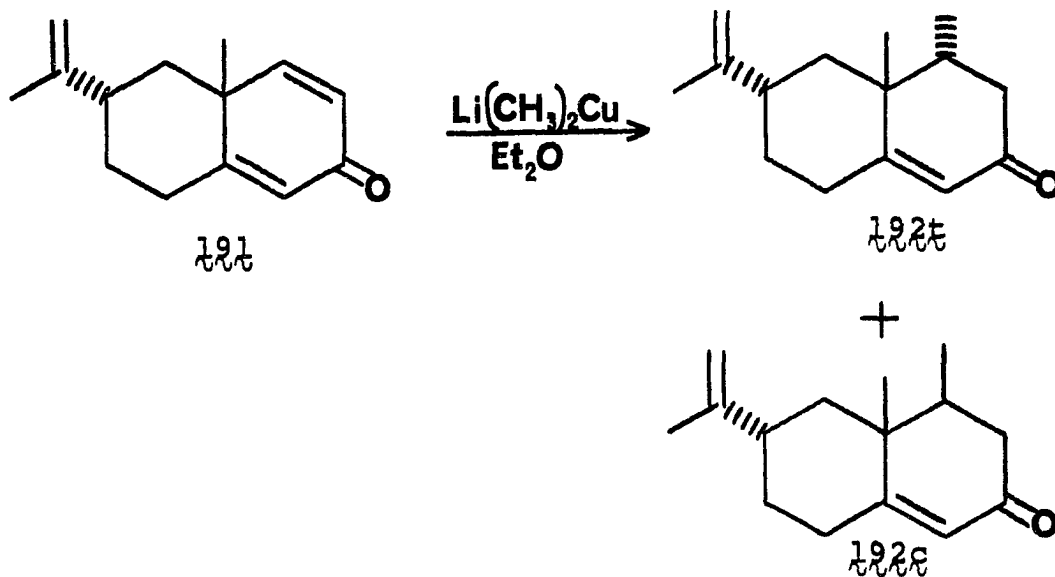
Marshall and Andersen¹²⁰ demonstrated that cuprous ion catalyzed addition of methylmagnesium iodide to the α,β -unsaturated ketone system in 189 gave 190 as the major isolable product. The highly stereoselective formation of 190 by axial introduction of the methyl group may be rationalized by the concept of "stereoelectronic control"⁶⁷, which predicts axial



introduction of the entering moiety thus allowing continuous overlap of the π orbital system throughout the transition state (see p. 58 for a further application of stereoelectronic control.)

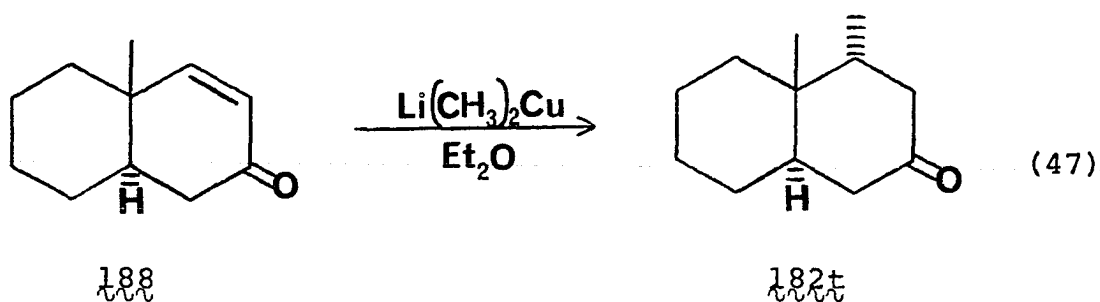


In a system more closely analogous to that of interest in the present work, Schudel and his coworkers³⁹ found that treatment of the isopropenyl-containing dienone **191** with lithium dimethyl cuprate gave the $4\alpha,4\beta$ -dimethyl product **192a**

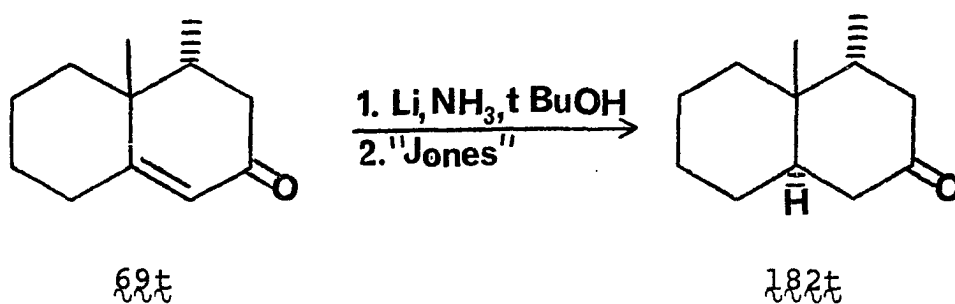


in high yield. The alternative product $192c$ was present in only trace amounts. Again, the axial introduction of the methyl group was governed by stereoelectronic factors.

With this and similar work in mind then, it was not surprising to find that treatment of the α,β -unsaturated ketone 188 , prepared as described above, with lithium dimethyl cuprate⁹¹ gave the $4\alpha,4a\beta$ -dimethyl-naphthalenone $182t$ in high yield, scheme 47. The material thus prepared was identical in

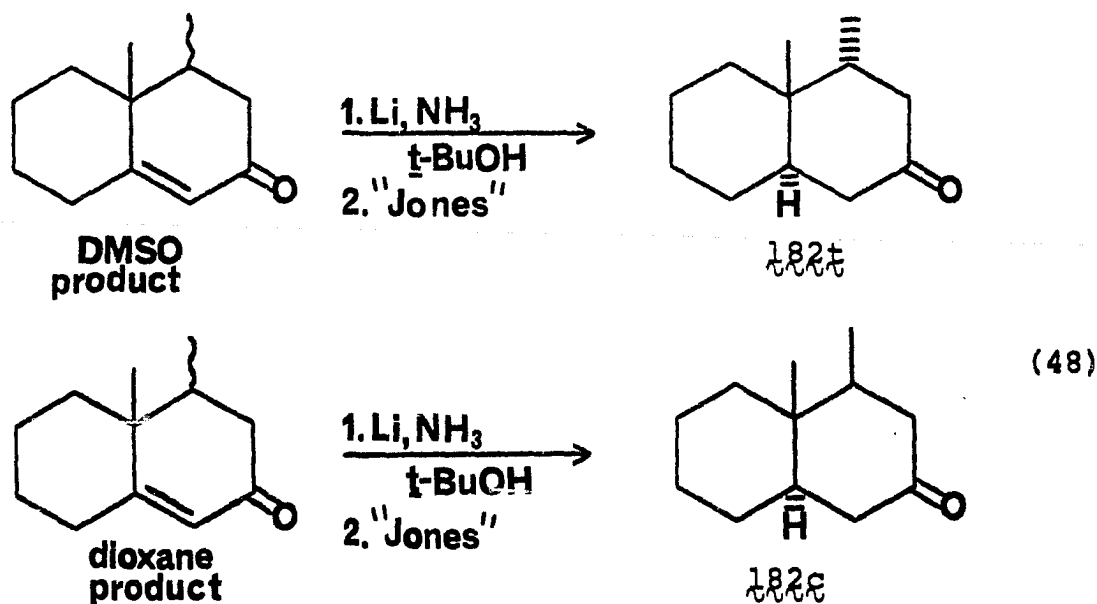


all respects to that described by Coates and Shaw¹¹³, who obtained the compound by reduction of the trans naphthalenone



$189t$ (prepared as described on p. 127) with lithium in ammonia.

With the necessary comparison compounds in hand, we proceeded to subject both the "dioxane product" and the "DMSO product" to reduction with lithium in ammonia, followed by oxidation with Jones reagent, a procedure known to afford exclusively products with a trans ring fusion¹¹⁵. Much to our delight, we found that the "DMSO product" gave the 4 α ,4 β -dimethylnaphthalenone 182t while the "dioxane product" gave the



4 β ,4 α -dimethylnaphthalenone 182c . The nmr and infrared spectra of the isomeric naphthalenones prepared by lithium in ammonia reduction of the "DMSO" and "dioxane products", as well as those of the comparison compounds 182c and 182t are reproduced in Figures 9-12. After examination of the spectral data as well as a comparison of several derivatives of all the

Figure 9. Nmr spectrum of trans-4 α ,4 β -dimethyl-
3,4,4a,5,6,7,8,8a-octahydro-2(1H)-
naphthalenone (182t)

Top: 60 MHz nmr spectrum of trans-
4 α ,4 β -dimethyl-3,4,4a,5,6,7,8,8a-
octahydro-2(1H)-naphthalenone (182t) prepared
by reduction (Li,NH₃) of the "DMSO product"

Bottom: 60 MHz nmr spectrum of authentic
trans-4 α ,4 β -dimethyl-3,4,4a,5,6,7,8,8a-
octahydro-2(1H)-naphthalenone (182t)

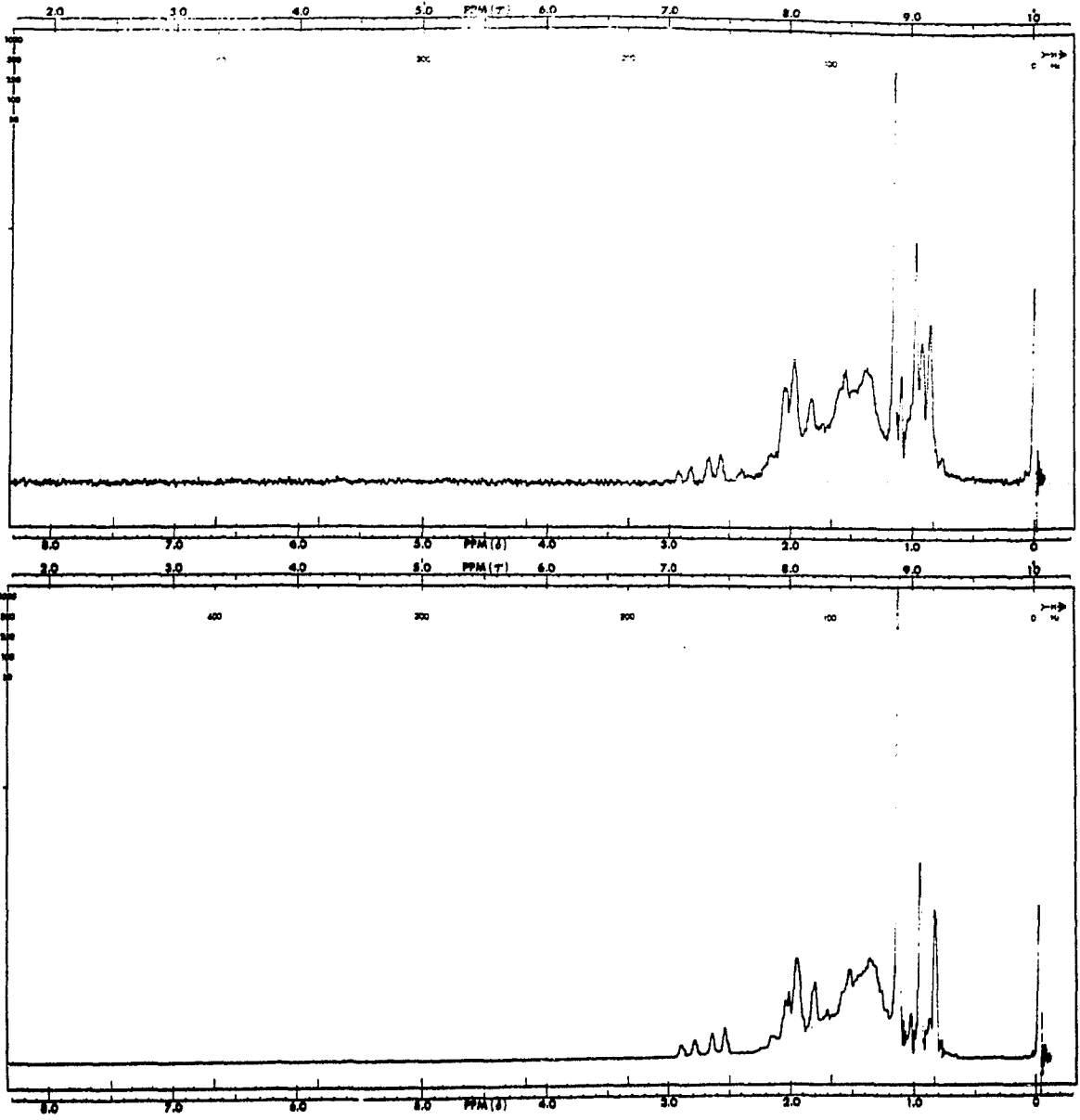


Figure 10. Nmr spectrum of trans-4 β ,4a β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182c)

Top: 60 MHz nmr spectrum of trans-4 β ,4a β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182c) prepared by reduction (Li,NH₃) of the "dioxane product"

Bottom: 60 MHz nmr spectrum of authentic trans-4 β ,4a β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182c)

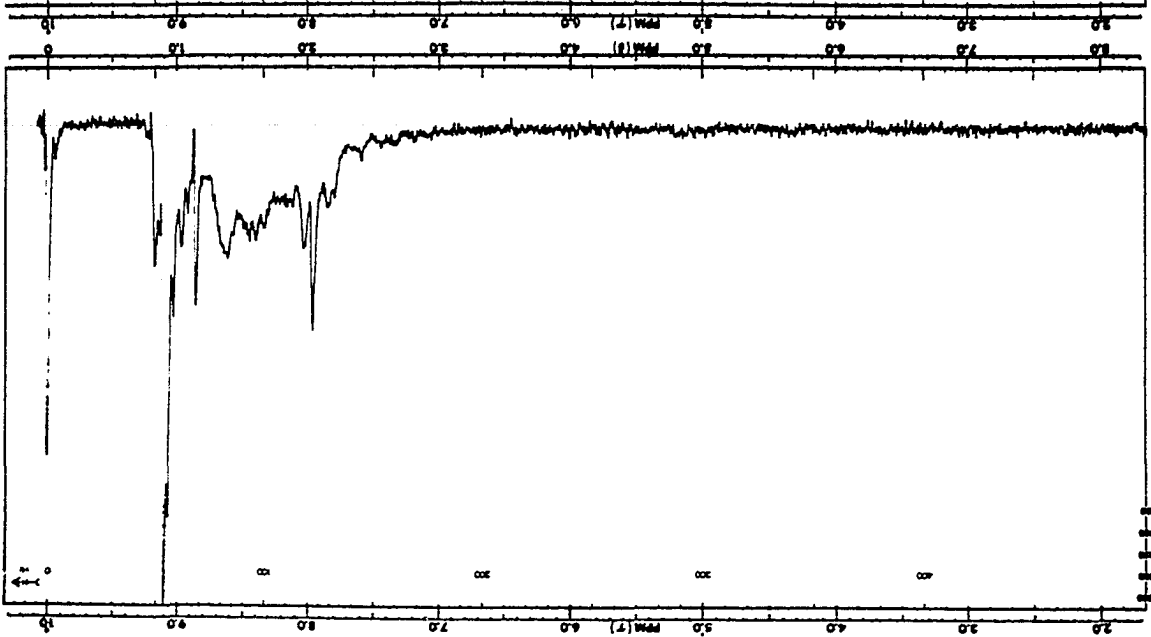
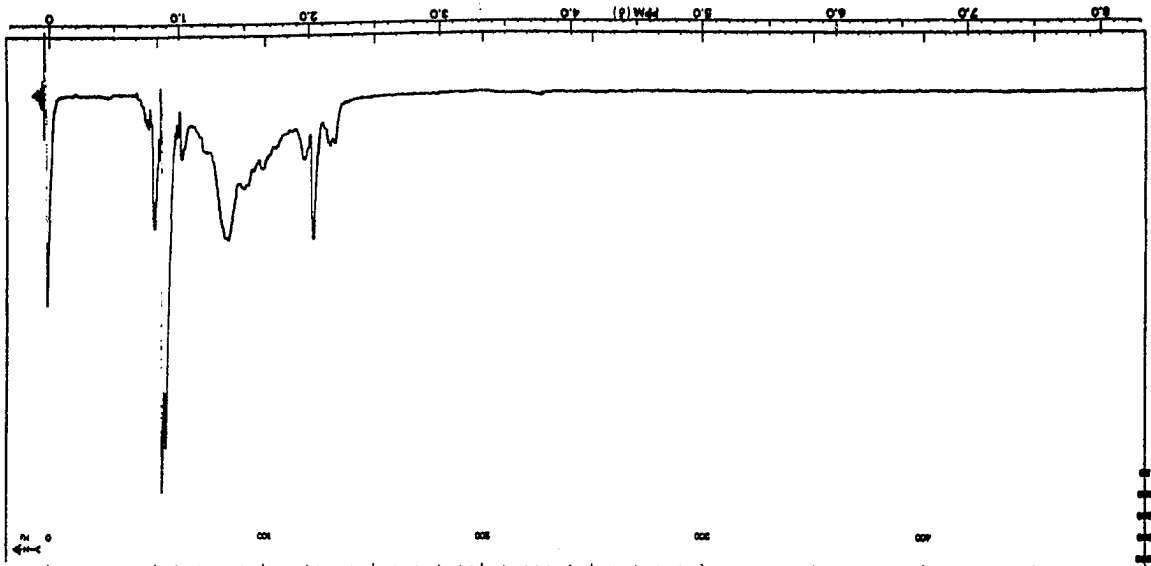


Figure 11. Infrared spectrum of trans-4 α ,4 β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone

Top: Infrared spectrum of trans-4 α ,4 β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182t) prepared by reduction (Li, NH₃) of the "DMSO product"

Bottom: Infrared spectrum of authentic trans-4 α ,4 β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182t)

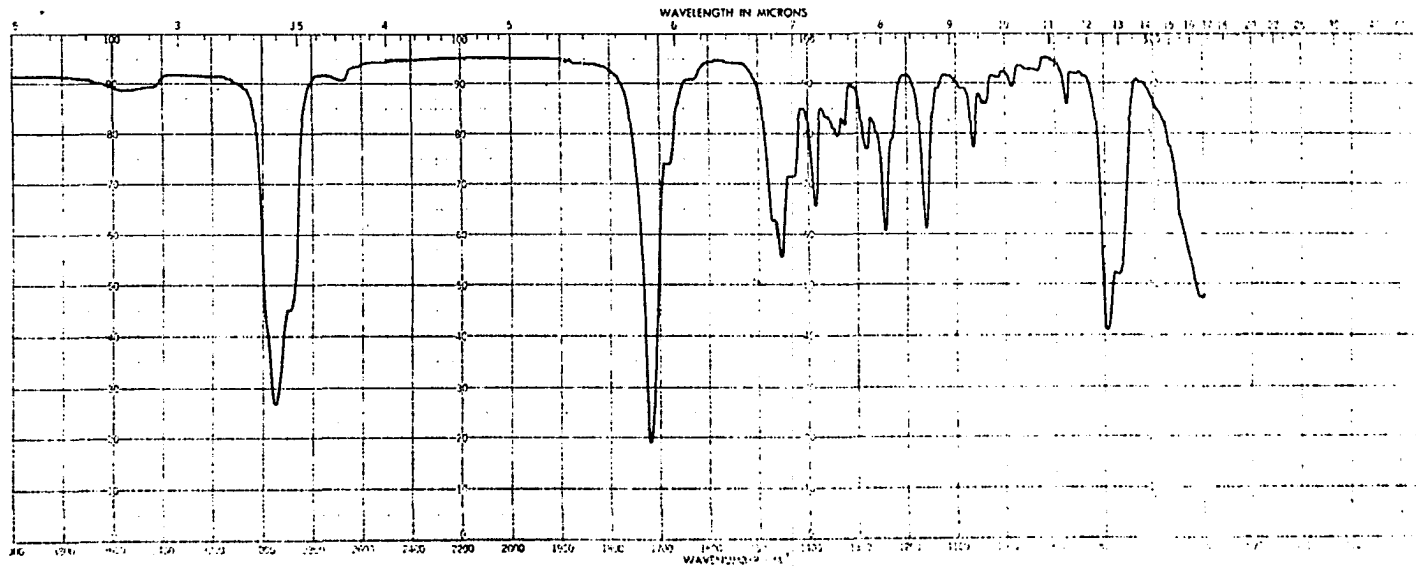
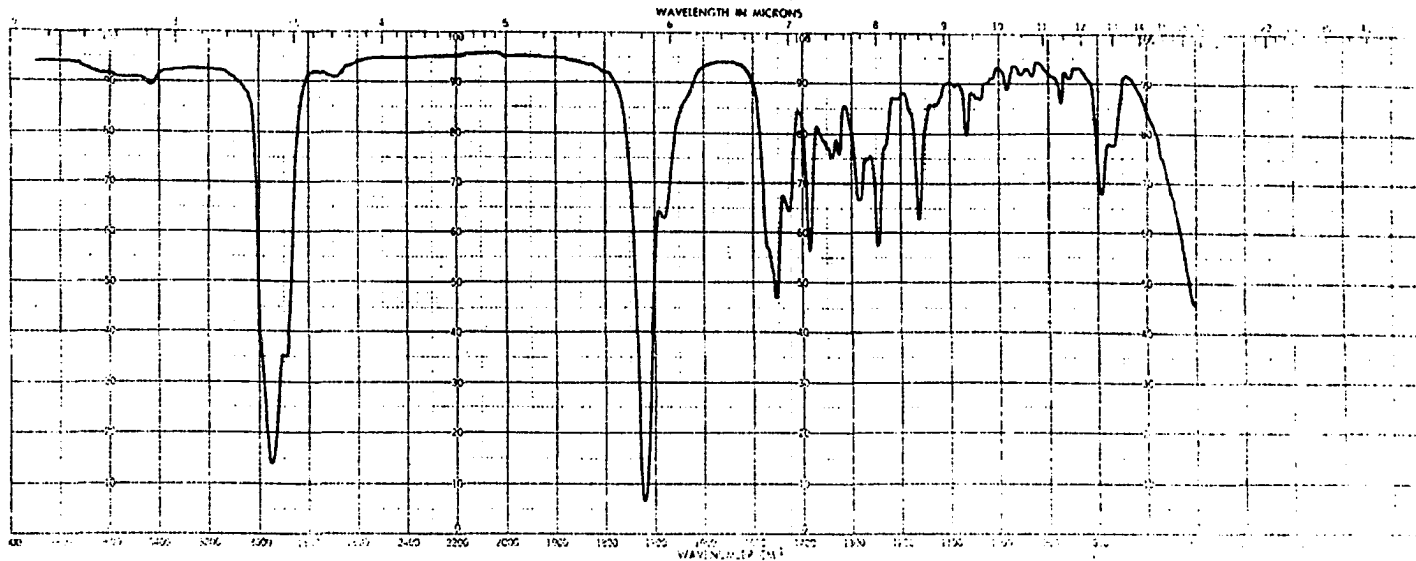
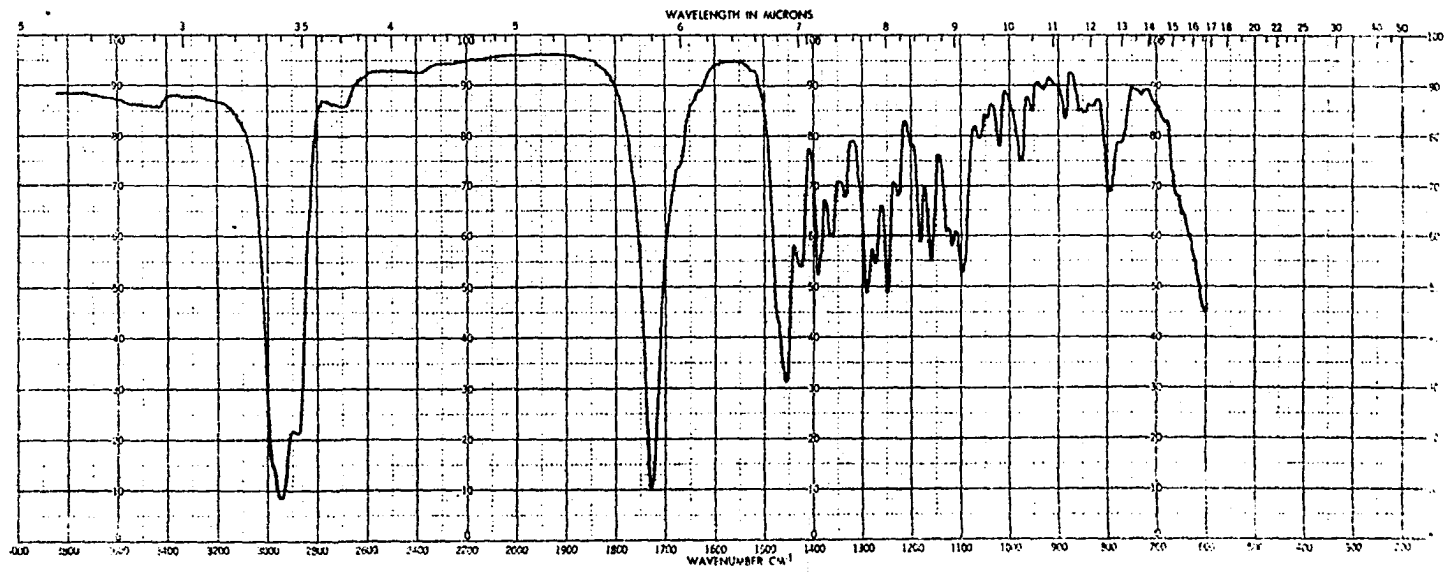
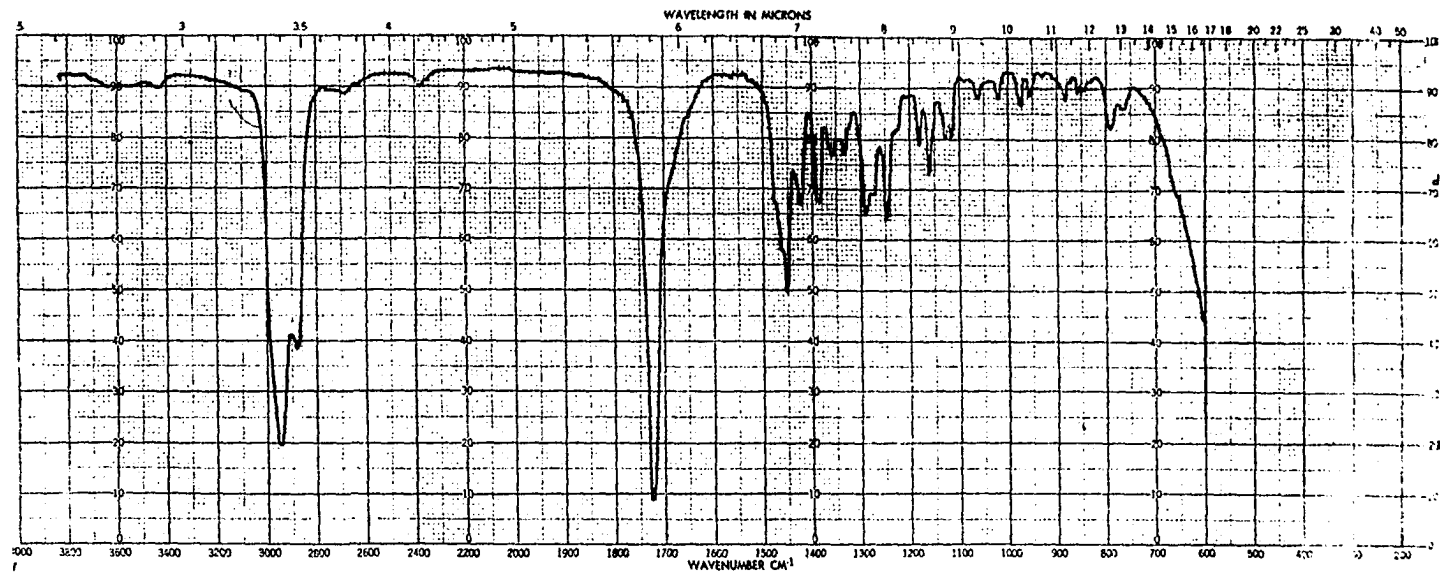


Figure 12. Infrared spectrum of trans-4 β ,4a β -dimethyl-
3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone

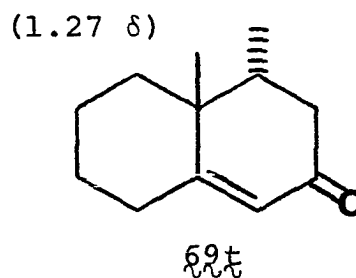
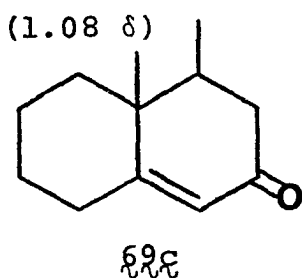
Top: Infrared spectrum of trans-4 β ,4a β -dimethyl-
3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone
(182c) prepared by reduction (Li,NH₃) of the
"dioxane product"

Bottom: Infrared spectrum of authentic trans-
4 β ,4a β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-
2(1H)-naphthalenone (182c)



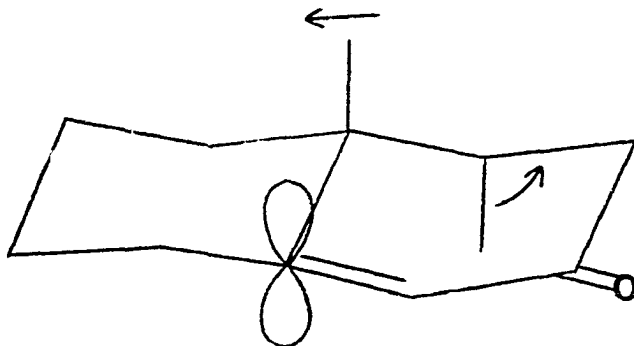
materials prepared, it was concluded that the Robinson annulation of 2-methylcyclohexanone with trans-3-penten-2-one conducted under conditions described briefly above was highly stereoselective for the preparation of cis- and trans-4,4a-dimethylnaphthalenones. In addition, the reasonably high yield obtained for the annulation rendered the procedure extremely useful on a synthetic scale. Finally, as the evidence described above warrants, there can be no doubt as to the stereochemical assignments.

A preliminary rationalization concerning the dramatic chemical shift difference between the angular methyl group protons of the two isomeric naphthalenones δ_{cis} and δ_{trans} might



involve the difference in distance between the two angular methyl groups and the π orbital of the β olefinic carbon due to a deformation of the unsaturated 6-membered ring. This deformation could be caused by the axial or equatorial nature of the secondary methyl group, which, when axial, would tend to distort the unsaturated ring in such a manner so as to force the angular methyl group away from the π orbital on the β olefinic carbon. This would in turn be expected to deshield

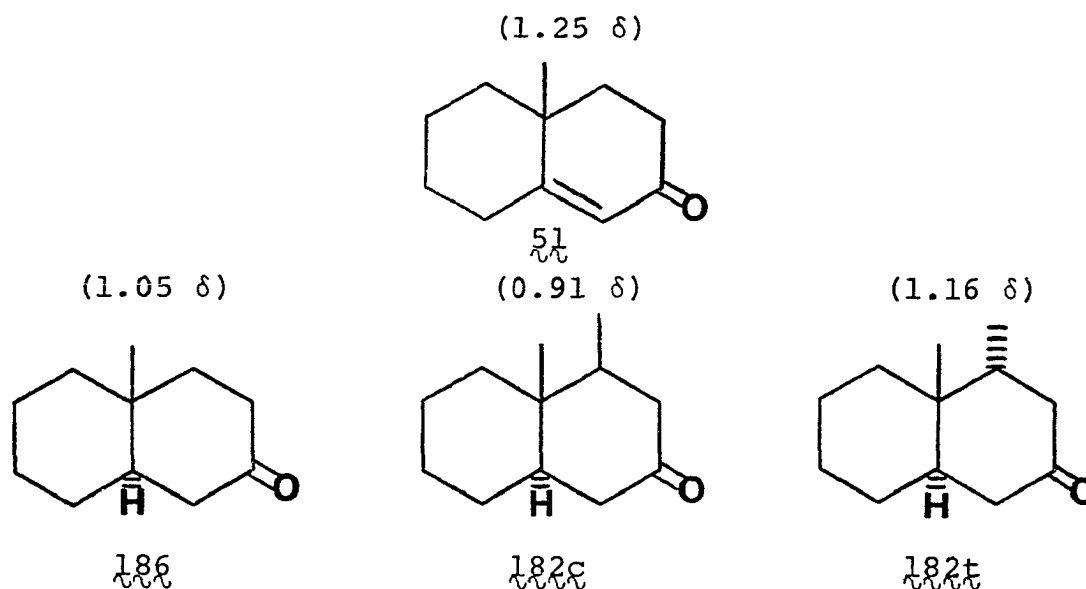
the methyl group protons and cause their resonance to appear



at a lower field.

However, the nmr spectrum of the unsubstituted naphthalenone 51 exhibits a singlet at 1.25δ (CCl_4) for the angular methyl group; a position nearly identical to that observed for $69t$ in which abnormal distortion was predicted. In addition, the saturated naphthalenones $182c$, $182t$, and 186 show similar chemical shift differences, see below. Consequently, proximity to the π orbitals is clearly not the cause of the observed differences. The double bond does, of course, tend to deshield the angular methyl group of both $69c$ and $69t$ relative to the saturated isomers, but it appears to do so to approximately the same extent in both compounds.

A detailed consideration of the data discussed above leads one to attribute the observed chemical shift differences entirely to the proximity of the angular methyl group to the secondary methyl group and to long-range shielding by the C-C and C-H bonds of the secondary methyl group. That this type



of bond can in fact be expected to give rise to significant long-range shielding has been adequately documented by Jackman and Sternhell¹²¹, who quote data which illustrate shift differences of greater than 1.5 ppm attributed entirely to long-range shielding by C-C and C-H bonds.

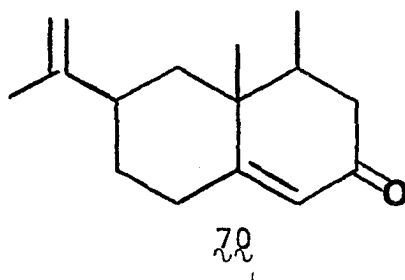
In the present case, (compare 182c, 182t, and 51) introduction of an equatorial secondary methyl group may be seen to cause a 0.17 ppm upfield shift in the absorption position of the angular methyl group relative to the unsubstituted material. In addition, introduction of an axial methyl group may be seen to cause only a 0.02 ppm downfield shift. That an axial group should have a minimal effect relative to an equatorial one might be expected, since any electronic effect exerted by the secondary methyl group would decrease as the distance between the two groups increased.

In the saturated systems mentioned earlier, a similar effect may be noted, compare 182c, 182t, and 186. Introduction of an equatorial substituent causes a shielding of 0.14 ppm relative to the unsubstituted material, and introduction of an axial substituent causes a 0.11 ppm deshielding effect.

In any event, regardless of the cause, the observed chemical shift difference between the angular methyl groups in the trans and cis-4,4a-dimethylnaphthalenones (69t and 69c) has obvious diagnostic application. Since the absorptions are considerably separated, the presence of either isomer may be deduced simply from the presence or absence of the singlet absorption, and furthermore, integration of the peak area may afford a rough estimate of the amounts of each isomer present.

Synthesis of 2-methyl-4-isopropenylcyclohexanone (180)

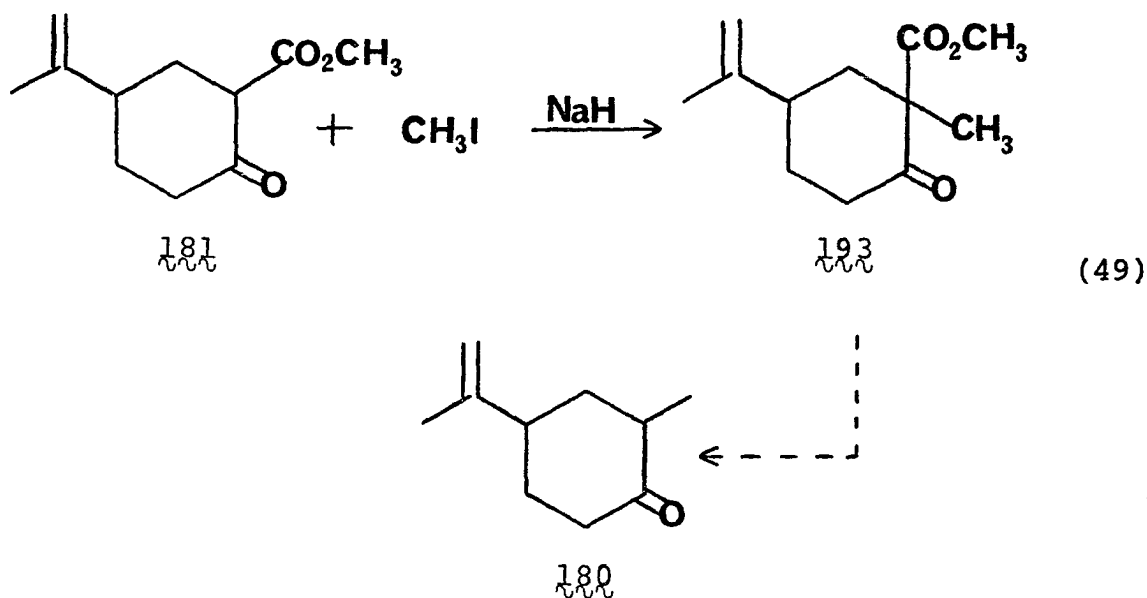
In order that the above described synthetic scheme be applicable to a synthesis of compound 70, as well as



eremophilone and related sesquiterpenes, it was necessary to develop a convenient synthesis of 2-methyl-4-isopropenylcyclohexanone (180). This in fact proved reasonably difficult to do.

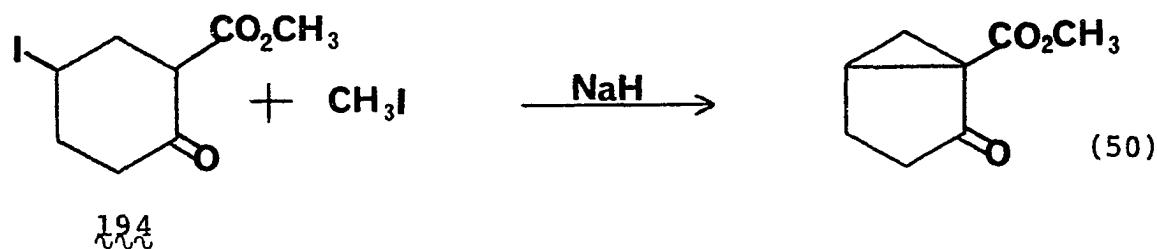
Odom and Pinder¹²² reported the preparation of 2-methyl-4-isopropenylcyclohexanone (180) in twelve steps. Some of the methods described by Pinder, although undoubtedly well worked out, are clearly laborious (i.e., Michael addition of diethyl malonate to acrylonitrile, Dieckmann cyclization, and several decarboxylations). In addition, there is some question as to the correctness of the structure proposed by Odom and Pinder¹²² in view of the fact that the total synthesis of nootkatone, in which the preparation of 180 appeared, has been retracted.⁴⁰ We decided, therefore, that development of a superior synthesis was a worthwhile venture.

Initially, attempts to methylate methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (181) with methyl iodide under the influence of sodium hydride were investigated, scheme 49.

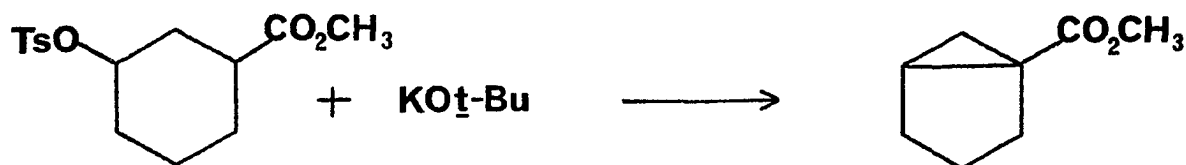


The product initially formed, namely 193, would be expected to undergo ready hydrolysis and decarboxylation to yield 2-methyl-4-isopropenylcyclohexanone (180). However, methylation under a variety of experimental conditions repeatedly gave over-methylated products. It appeared that methylation was occurring on both sides of the carbonyl, despite the fact that only one equivalent of sodium hydride was used.

Interestingly, attempts to methylate methyl 2-oxo-5-iodocyclohexanecarboxylate (194) under similar conditions gave the bicyclic structure shown in scheme 50. This product was not unexpected based on the work of McDonald and Reitz¹²³, who

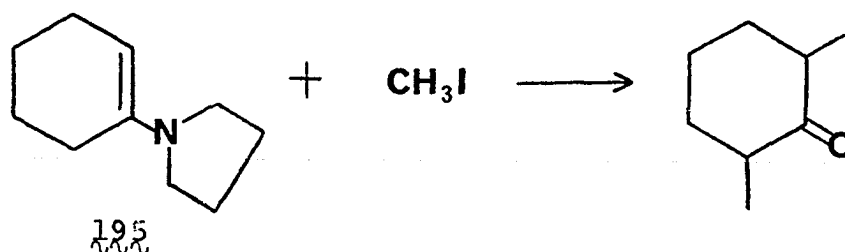


accomplished the transformation shown below.

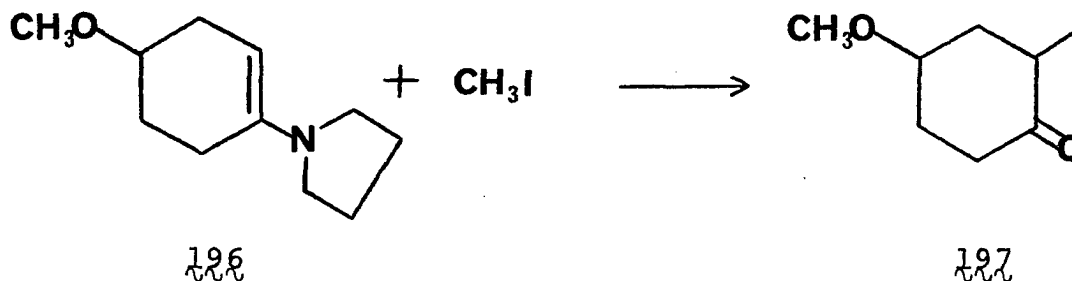


A number of other synthetic schemes were investigated for the preparation of 180, but none showed promise.

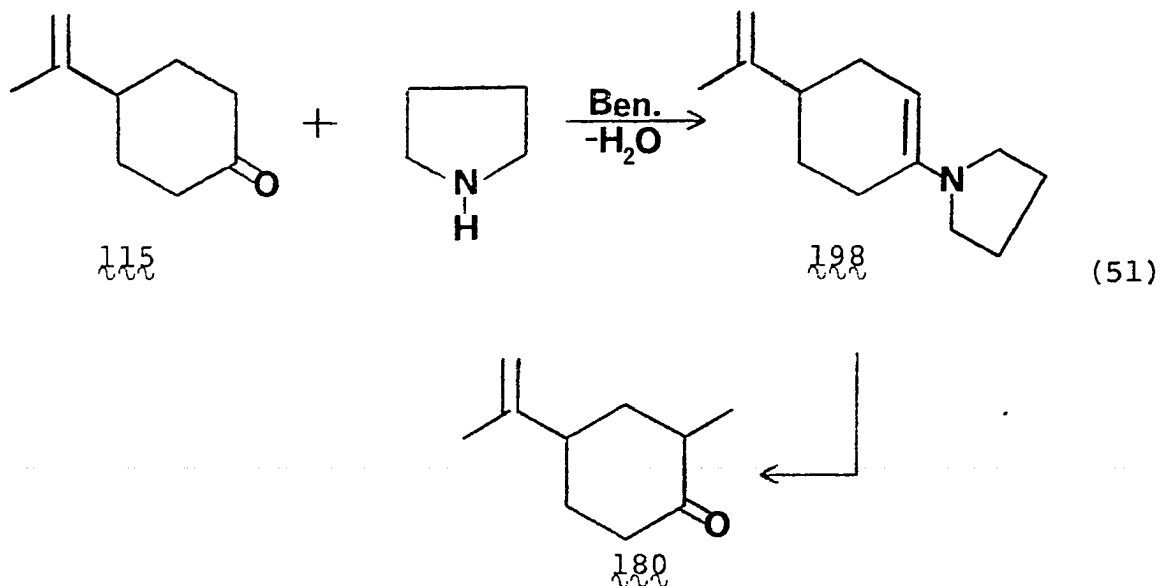
Finally, we considered alkylation of the pyrrolidine enamine of 4-isopropenylcyclohexanone (115), the preparation of which was discussed at length earlier. Although Stork, *et al.*,¹⁰⁹ reported that alkylation of the pyrrolidine enamine of cyclohexanone with a limited amount of methyl iodide gave 5- 10% of 2,6-dimethylcyclohexanone as illustrated below, a



subsequent publication⁶⁸ related the synthesis of 2-methyl-4-methoxycyclohexanone (90) by methylation of 1-pyrrolidino-4-methoxycyclohexene (196) with limited methyl iodide, see below.



Therefore, 4-isopropenylcyclohexanone (115) was treated with pyrrolidine in the usual way to afford 1-pyrrolidino-4-isopropenylcyclohexene (197). The enamine was not purified



but was treated with slightly more than one equivalent of methyl iodide in a toluene solvent at reflux temperature. This procedure gave 2-methyl-4-isopropenylcyclohexanone (181) in 61% overall yield, scheme 51.

Unfortunately, time did not permit an investigation of the annulation of 2-methyl-4-isopropenylcyclohexanone (181) with trans-3-penten-2-one under the reaction conditions discussed above. However such work is forthcoming.

EXPERIMENTAL

Reagents

Common chemicals and solvents were obtained from commercial sources and were generally distilled prior to use. When anhydrous solvents were required by the experimental procedure, reagent grade materials were treated according to the following:

Diethyl ether (anhydrous) - distilled from lithium aluminum hydride or metallic sodium.

Diethyl ether (super dry) - distilled from a mixture of sodium-benzophenone, which displayed a constant purple color, directly into a flame-dried reaction vessel.

Dimethylcarbonate - distilled from calcium hydride.

Methanol - distilled from magnesium methoxide.

Benzene - distilled from either lithium aluminum hydride or sodium-benzophenone which exhibited a constant purple color.

Tetrahydrofuran - same as benzene.

Methylene chloride - washed with 5% sodium carbonate, water, and distilled from anhydrous potassium carbonate.

Pentane - dried over anhydrous calcium chloride and distilled from potassium hydroxide.

Dimethylsulfoxide - distilled under vacuum from calcium hydride.

Heptane - dried over anhydrous calcium sulfate and distilled from potassium hydroxide.

Ethyl bromide - dried over anhydrous calcium chloride and carefully distilled.

p-Dioxane - distilled from calcium hydride.

N,N-dimethylformide - same as dioxane.

Formamide - dried over anhydrous magnesium sulfate and distilled under vacuum.

1,2-Dimethoxyethane - distilled from either lithium aluminum hydride or sodium-benzophenone which displayed a constant purple color.

Characterization of Compounds

All melting points were determined on a Kofler Micro Hot Stage melting point apparatus, are uncorrected, and are reported in degrees centigrade. Infrared spectra were taken on a Perkin-Elmer Model 21 Double Beam spectrometer, or a Beckman IR 12 spectrometer. Nmr spectra were recorded at room temperature on a Varian A-60 spectrometer, a Varian HA-100 spectrometer, or a Hitachi Perkin-Elmer R20-B spectrometer and chemical shifts are reported as parts per million (δ scale) from tetramethylsilane as internal standard. Mass spectra were measured using an Atlas CH₄ mass spectrometer with a direct solid inlet system. High resolution mass spectra were determined using an AEI MS 209 mass spectrometer. Only the molecular ion is reported. Microanalyses were performed by Ilse Beetz Microanalytical Laboratories, Kronach, West Germany.



Whenever necessary, chromatographic procedures were employed for separation and purification of products. Micro-analytical, air-dried, thin layer chromatography plates were prepared by immersion coating of microscope slides in a chloroform slurry of Merck silica gel H obtained from Merck Distributors, Brinkmann Instruments, Incorporated, Westbury, New York. The preparative thin layer chromatography plate was prepared by manual spreading of a 3:1 aqueous-silica gel (Merck silica gel Pf₂₅₄ with calcium sulfate binder) slurry on a 20 x 60 cm glass plate, followed by 7 hours of activation at 110°. Column chromatography was performed on Baker analyzed silica gel (60-200 mesh). Elution solvents were established by microanalytical thin layer chromatography, and column elution was followed by thin layer examination of consecutive effluent aliquots.

Preparation of Compounds

Acetonyltriphenylphosphonium chloride

A solution of 10.3 g (0.039 moles) of triphenylphosphine and 3.33 g (0.036 moles) of chloroacetone in 30.0 ml of chloroform was heated at reflux temperature for 45 minutes. The chloroform solution was cooled and filtered into 300 ml of anhydrous ether. The white solid which resulted was collected on a sintered glass funnel and air-dried to afford 10.5 g (0.030 moles - 76.9%) of acetonyltriphenylphosphonium chloride.

The product, as isolated, had a mp of 233-234°; [lit.¹²⁴ mp 234-237°].

Triphenylphosphineacetylmethylene

A mixture of 10.5 g (0.003 moles) of acetyltriphenylphosphonium chloride and 300 ml of a 10% aqueous sodium carbonate solution was shaken in air for 8 hours. The white solid which resulted was collected on a sintered glass funnel and air-dried to afford 8.41 g (0.0026 moles - 89.6%) of triphenylphosphineacetylmethylene. The product was recrystallized from methanol-water to yield material with mp 199-200° [lit.¹²⁴ mp 199-202°].

Trans-3-penten-2-one

A. (Wittig Reaction) The procedure of House, Respass, and Whitesides⁸⁸ was employed. A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and a reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 95.5 g (0.298 moles) of triphenylphosphineacetylmethylene in 300 ml of methylene chloride. To this solution was added, with stirring, a solution of 26.1 g (0.591 moles) of acetaldehyde in 50.0 ml of methylene chloride. The reaction mixture was then heated to reflux temperature (40.1°), maintained at that temperature for 6 hours, cooled, and allowed to stand at room

temperature for 6 hours. The solvent was distilled through a 65.5 cm Vigreux column and the residue diluted with 200 ml of pentane. The crystalline triphenylphosphine oxide which separated was filtered, the organic filtrate concentrated and fractionally distilled to afford 12.4 g (0.148 moles) of trans-3-penten-2-one, bp 115-120°; [lit.⁸⁸ bp 113-119°; lit.⁶³ bp 121.0-122.5°]. One-percent by weight of hydroquinone was added to stabilize the product. Ir(film) 2950(CH), 1678 (conj C=O), 1638 (conj C=C), 1448, 1365, 1252 cm^{-1} ; nmr(CCl_4) δ 6.97, 6.72 (dq, 1H, J=6, 16Hz, $\text{CH}_3\text{-CH}=\text{CH-}$), 6.15, 5.90 (dq, 1H, J=2, 16Hz, $\text{CH}_3\text{-CH}=\text{CH-}$), 2.17 (s, 3H, $\text{CH}_3\text{-CO-}$), 1.90 (dd, 3H, J=2Hz, $\text{CH}_3\text{-CH}=\text{CH-}$), ppm.

B. The procedure of Wilds and Djerassi⁶³ was followed. A 100-ml, one-necked flask was charged with 50.0 g (0.490 moles) of 4-hydroxy-2-pentanone (174). To this was added 0.040 g of concentrated sulfuric acid. The resulting red liquid was slowly distilled at atmospheric pressure and the fraction boiling in the range 64-95° was collected in an ice-cooled receiver. The distillate (approx. 40 ml) was taken up in 250 ml of ether, washed three times with 100-ml portions of brine, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation at atmospheric pressure and the distillation continued to yield 22.7 g (0.280 moles - 55.1%) of trans-3-penten-2-one as a colorless liquid: bp 112-118°; [lit.⁶³ bp 121-122.5°, lit.⁸⁸ 113-119°]. One-percent by weight

of hydroquinone was added to stabilize the product. Ir and nmr data were identical to those cited in A above. The product is a powerful lachrymator.

Methyl 2-oxocyclohexanecarboxylate (84)

Following the general procedure of S. J. Rhoads and her coworkers⁹⁸, a 3000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-compensating addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 150 g of a 48% sodium hydride-mineral oil dispersion (72.0 g - 3.00 moles active hydride). The hydride was covered with 500 ml of anhydrous benzene, stirred briefly, and the benzene removed through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean hydride was then covered with 1450 ml of dimethylcarbonate (Aldrich Chemical Co.). To this was added, dropwise and with stirring, 147.0 g (1.50 moles) of cyclohexanone over a 90 minute period. Following a short induction period (10-30 minutes), a rapid evolution of hydrogen occurred, accompanied by warming of the reaction mixture sufficient to boil the dimethylcarbonate. Within 10 minutes after hydrogen evolution began, the entire reaction mixture had solidified. The solid enolate thus formed was broken up by the slow, cautious addition of 179 ml of glacial acetic acid in 100 ml of ether. Stirring was continued until all the enolate had

reacted and the reaction mixture was acidic to litmus paper. Distilled water was added to dissolve the suspended sodium acetate and the phases were separated. The aqueous phase was extracted with three 75-ml portions of ether, and the combined organic phases were washed with three 35-ml portions of water, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 187.2 g (1.21 moles - 80.6%) of methyl 2-oxocyclohexanecarboxylate (84) as a clear, colorless liquid: bp 113-114°; [lit.¹²⁵ bp 94-95° (10mm)]; ir(film) 2940(CH), 1753(C=O ester), 1720(C=O ketone), 1657(C=O conj. chel.), 1616 (C=C conj. chel.), 1441,1296,1259,1216 (C-O) cm^{-1} ; nmr(CCl_4) δ 12.0(s,1H,enol), 3,68(s,3H, $\text{CH}_3\text{O}_2\text{C}$ -), ppm; mass spectrum (70ev) M^+ 156.

Methyl 2-oxo-1-(3'-oxobutyl)cyclohexane-1-carboxylate (85)

Conditions described in this preparation were based on those described by Meyer and Levinson¹²⁶ for a similar system. A 100-ml, three-necked, round-bottomed flask which had been fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel was evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with 28.0 mg (0.00122 moles) of sodium metal dissolved in 14.0 ml of anhydrous methanol. The solution was cooled to 5° with an external ice bath and treated with 10.0 g (0.0641 moles) of methyl 2-oxocyclohexanecarboxylate (84) dropwise, with stirring, over a 15 minute period. Following complete addition, the

reaction mixture was allowed to stir for 15 minutes at 5° and treated with 5.80 g (0.0829 moles) of methyl vinyl ketone dropwise, with vigorous stirring, over a 30 minute period. The reaction mixture was stirred for an additional 30 minutes at 5° and then allowed to warm slowly to room temperature (approx. 23°). Stirring was continued at room temperature until the material afforded a negative alcoholic ferric chloride test¹²⁷. The time necessary was generally 10-15 minutes. The crude product mixture was acidified by the dropwise addition of glacial acetic acid (to pH 4-5) and the methanol removed under vacuum. The residue was taken up in 100 ml of ether and washed with two 10-ml portions of water, two 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 8.33 g (0.037 moles - 57.6%) of the colorless diketone 85 : bp 129-131(0.3mm) [lit.¹²⁸ ethyl ester bp 138-140(0.4-0.5mm)]; ir(film) 3450 (trace OH), 2930(CH), 1695-1724(C=O), 1210(C-O) cm^{-1} ; nmr(CCl_4) δ 3.86(s, 3H, $\text{CH}_3\text{O}_2\text{C}$ -), 2.04(s, 3H, CH_3CO -) ppm; mass spectrum (70ev) M^+ 226.

Methyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2H)-naphthalenecarboxylate
(86)

A. Following the procedure of Meyer and Levinson¹²⁶, a 50-ml, one-necked, round-bottomed flask was fitted with a 25-ml capacity Dean-Stark trap, evacuated, flame-dried, and

filled with prepurified nitrogen. The apparatus was charged with 8.33 g (0.037 moles) of methyl 2-oxo-1-(3'-oxobutyl)cyclohexane-1-carboxylate (85) dissolved in 18.7 ml of anhydrous benzene. To this solution was added 4.46 g (5.13 ml - 0.0627 moles) of pyrrolidine via a flame-dried pipet. The reaction mixture was heated slowly to reflux temperature (84°) and maintained at that temperature for 5 hours, during which time 0.71 ml of water were removed from the system. The crude product mixture was poured into 46.0 ml of brine and the phases were separated. The organic phase was washed with three 10-ml portions of a 4% aqueous hydrochloric acid solution, followed by brine. The original brine solution was acidified by the addition of 7.5 ml of concentrated hydrochloric acid and extracted with benzene. The organic extracts were combined and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to yield 2.41 g of a dark brown liquid: bp 164-169° (0.7 mm). Due to the low yield, discrepancies concerning the reported boiling point, and spectral data which could not be correlated with the isolated material, an alternative cyclization procedure was investigated.

B. According to the procedure of Ramachandran and Newman⁶¹ developed for a similar system, 5.00 g (0.022 moles) of methyl 2-oxo-1-(3'-oxobutyl)cyclohexane-1-carboxylate (85) was dissolved in 25.0 ml of anhydrous benzene. To this was added 0.14 ml of pyrrolidine via a flame-dried pipet. The

reaction mixture was heated to reflux temperature under a Dean-Stark water trap prepared as described in part A above. The reaction mixture was maintained at reflux temperature for 27 hours, during which time 0.6 ml of water were removed from the system. The crude product mixture was diluted with 50 ml of ether, washed with two 25-ml portions of water containing 7.5 ml of a 10% aqueous hydrochloric acid solution, and then with 50 ml of distilled water. The aqueous washings were combined and back-extracted with two 25-ml portions of ether. The combined organic extracts were washed with 20 ml of water, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 4.61 g (0.0212 moles - 96.2%) of methyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2H)-naphthalenecarboxylate (86) as a colorless liquid: bp 124-126° (1.0 mm); [lit.^{5,48,128} bp 125-132° (1.0 mm)]; ir (film) 2950(CH), 1722(ester C=O), 1673(conj C=O), 1625(conj C=C), 1209(C-O) cm^{-1} ; nmr(CCl_4) δ 5.57(t,1H,J=1 Hz,-CH=C-), 3.70(s,3H,CH₃O₂C-) ppm; mass spectrum (70ev) M⁺ 208.

Methyl 2-oxo-1-(4'-oxo-2'-pentyl)cyclohexane-1-carboxylate (80)

The procedure briefly described by Marshall, Faubl, and Warne⁴⁴ was investigated. A 250-ml, three-necked, round-bottomed flask which had been fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with 100 ml of a freshly

prepared 0.087M solution of sodium methoxide in anhydrous methanol. The solution was cooled to 0° with an external ice bath and 15.6 g (0.100 moles) of methyl 2-oxocyclohexanecarboxylate (84) were added dropwise with stirring over a 20 minute period. The reaction mixture was allowed to stir for an additional 15 minutes at 0° and treated with 13.2 g (0.157 moles) of trans-3-penten-2-one, dropwise and with vigorous stirring, over a 20 minute period. Stirring was continued at that temperature for 10.5 hours. During the first 2-3 hours, a fluffy white solid appeared, presumably the enolate anion of the β -keto ester 84. After 10.5 hours, the reaction mixture exhibited a negative alcoholic ferric chloride test and the enolate had dissolved. The reaction mixture was neutralized by the dropwise addition of glacial acetic acid, the methanol removed under vacuum, and the residue taken up in 100 ml of ether. The ethereal phase was washed with 10 ml of water, three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum and distillation of the residue afforded 10.4 g (0.0436 moles - 43.6%) of the ester dione 80, as a colorless liquid: bp 140-142° (0.25 mm); ir (film) 2950 (CH), 1730-1694 (C=O ester, ketone), 1234, 1209 cm^{-1} ; nmr (CCl_4) δ 3.68 (s, 3H, $\text{CH}_3\text{O}_2\text{C}$ -), 2.05 (s, 3H, CH_3CO -), 0.83 (d, 3H, $\text{J}=7\text{Hz}$, $-\text{CHCH}_3$) ppm.

In subsequent preparations, it was noted that the isolated ester dione 80 was frequently contaminated with varying (10-40%) amounts of the cyclized product 87 , the exact amount depending on the base strength, reaction time, etc., and for this reason analytical data (C,H anal.) are reported for the cyclized product only. However, the spectral data quoted above were obtained on reasonably pure material (> 98%).

Methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalene-carboxylate (87)

A 250-ml, three-necked, round-bottomed flask which had been fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with 100 ml of a 1.10M solution of sodium methoxide in anhydrous methanol to which was added, dropwise and with stirring, 11.2 g (0.047 moles) of methyl 2-oxo-1-(4'-oxo-2'-pentyl)cyclohexane-1-carboxylate (80). After 1.0 hour of stirring at room temperature, the reaction mixture was acidified (pH 4-5) by the dropwise addition of glacial acetic acid. The methanol was removed under vacuum and the residue taken up in 100 ml of ether, washed with 10 ml of water, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum affording 8.11 g of a slightly yellow oil, which readily solidified upon cooling in ice. The solid was recrystallized from pentane affording

7.61 g (0.0343 moles - 71.3%) of methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenecarboxylate (87) as white, needle-like crystals; mp 60.5-61.5°; ir(KBr) 2951(CH), 2850(OMe), 1730(C=O ester), 1674(C=O conj), 1635(C=C conj), 1441 1292, 1221, 1176 cm^{-1} ; nmr(CCl_4) δ (5.58(t, 1H, $J=1\text{Hz}$, $-\text{CH}=\text{C}-$), 3.70(s, 3H, $\text{CH}_3\text{O}_2\text{C}-$), 0.97(d, 3H, $J=7\text{ Hz}$, $-\text{CHCH}_3$) ppm; mass spectrum (70ev) M^+ 222.

Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$: C, 70.24; H, 8.16

Found: C, 70.31; H, 8.11

A complete discussion of the various nmr spectra, as well as the isomeric mixture obtained from this procedure may be found in the text. A procedure for preparation of the above product without isolation of the intermediate dione follows.

A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 0.230 g (0.010 moles) of sodium metal dissolved in 100 ml of anhydrous methanol. The reaction mixture was cooled to 0° with an external ice bath and treated with 15.6 g (0.100 moles) of methyl 2-oxocyclohexanecarboxylate (84), dropwise and with stirring, over a 15 minute period. The reaction mixture was then allowed to stir for 30 minutes at 0° and treated with 15.1 g (0.180 moles) of trans-3-penten-2-one, dropwise and with rapid stirring, over a 35 minute period.

Following complete addition of the unsaturated ketone, the reaction mixture was allowed to warm to room temperature until a negative alcoholic ferric chloride test was obtained (3-6 hours). The solution was then treated with a freshly prepared solution of 2.30 g of metallic sodium dissolved in 25 ml of anhydrous methanol. The sodium-methanol solution was added portionwise (1-2 ml), and the formation of the desired cyclized product 87 was followed via analytical thin layer chromatography on a silica gel H absorbent with 5% ether-benzene as the developing solvent.

Following complete cyclization, as indicated by thin layer chromatography, the crude product mixture was neutralized by the dropwise addition of glacial acetic acid, and the methanol was removed under vacuum. The residue was diluted with 150 ml of ether, washed twice with brine, and dried over anhydrous magnesium sulfate. The dried solvent was removed under vacuum affording a slightly yellow solid which was recrystallized from pentane affording 19.4 g (0.088 moles - 88.0%) of white, needle-like crystals: mp 59.2-60.1°; ir and nmr identical to those described above.

Methyl 4-hydroxycyclohexanecarboxylate (86)

A 1000 ml packless autoclave was charged with a solution of 148.7 g (0.944 moles) of methyl p-hydroxybenzoate (95) (Aldrich Chemical Co.) dissolved in 600 ml of anhydrous methanol which contained 1.00 g of a 5% rhodium on alumina

catalyst^{129,130}. The reaction mixture was stirred under a constant pressure of 1800 psi of hydrogen for 48 hours. The catalyst was removed by filtration through Celite and the methanol was removed under vacuum. The resulting liquid residue was taken up in 300 ml of ether, washed with three 75-ml portions of a 10% sodium hydroxide solution, three 50-ml portions of a 10% hydrochloric acid solution, saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum affording 138.4 g (0.846 moles - 89.8%) of a colorless liquid. Distillation under vacuum gave 131.3 g (0.803 moles - 85.1%) of methyl 4-hydroxycyclohexanecarboxylate (96) as a sweet smelling liquid: bp 89-91° (0.10 mm); [lit.¹³¹ bp 96-98 (0.35 mm)]; ir (film) 3402(OH), 2945(CH), 1728(C=O), 1153, 1119(C-O), 756 cm⁻¹; nmr(CCl₄) δ 3.70(s, 1H, -CHOH, exchange with D₂O), 3.63(s, 3H, CH₃O₂C-), 3.63(m, 1H, -CHOH) ppm; mass spectrum (70ev) M⁺ 158.

A low boiling fraction amounting to 6.41 g (4.8%) was identified as methyl cyclohexanecarboxylate resulting from hydrogenolysis of the C-O bond⁷⁰, bp 33-35° (0.2 mm). This material was identified by comparison with an authentic sample.

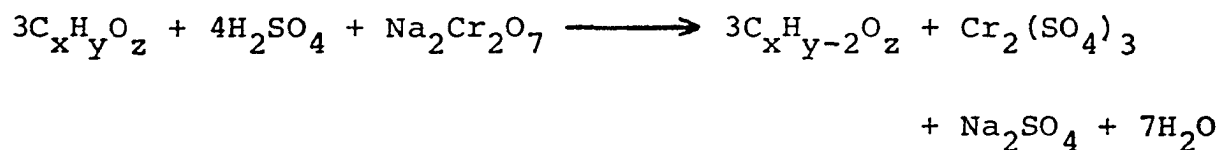
Methyl 4-oxocyclohexanecarboxylate (97)

The procedure of Finnegan and Bachman⁷⁰, developed for ethyl 4-oxocyclohexanecarboxylate, was followed. A 1000-ml, three-necked, round-bottomed flask fitted with a gas-inlet tube, mechanical stirrer, and pressure-equalizing addition

funnel was charged with a solution of 69.0 g (0.437 moles) of methyl 4-hydroxycyclohexanecarboxylate (96) dissolved in 200 ml of ether. The solution was cooled to 3° with an external ice bath and treated with a precooled (0°) oxidizing solution which consisted of 41.0 g (0.137 moles) of sodium dichromate dihydrate and 53.0 g (0.540 moles) of concentrated sulfuric acid dissolved in 200 ml of water. The oxidizing solution was added dropwise, with good stirring, over a 90 minute period. Following complete addition, the dark green solution was stirred for 4 hours at room temperature and the phases were separated. The aqueous phase was saturated with solid sodium chloride and extracted with five 25-ml portions of ether. The combined ethereal phases were washed thoroughly with a saturated sodium bicarbonate solution, followed by brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 53.4 g (0.343 moles - 78.4%) of methyl 4-oxocyclohexanecarboxylate (97) as a clear, colorless liquid: bp 79.5-81.0° (0.3 mm); [lit.⁷⁰ bp 80-81° (0.4 mm)]; ir (film) 2940(CH), 1718(C=O), 1434, 1216(C-O), 1170 cm⁻¹; nmr (CCl₄) δ 3.65(s, 3H, CH₃O₂C-) ppm.

A 2,4-dinitrophenylhydrazone derivative was prepared in the usual manner¹³² and recrystallized twice from anhydrous ethanol; mp 153-154°.

In connection with this particular preparation, a generally useful oxidation procedure was developed based on the following balanced equation.



It was found that the use of an oxidizing solution prepared in accordance with the above molar ratios of reactants would accomplish an easy, complete, and high-yield oxidation of secondary alcohols when used in the above procedure.

The use of this two-phase reaction system, as opposed to the more popular Jones⁹⁵ procedure, has the advantage of maintaining a completely homogeneous aqueous phase. In the Jones procedure, large amounts of chromium salts are precipitated which hamper or completely prevent stirring, and render the procedure completely inapplicable to large (approx. 10 g) scale preparative reactions. However, the oxidizing solution described above will remain appreciably acidic throughout the reaction, whereas the Jones procedure presumably maintains a neutral media. Also, it has been noted¹³³ that certain alcohols are not oxidized by this reagent.

The preparation of 4-iodocyclohexanone (141) may be consulted for experimental details.

Methyl 4,4-ethylenedioxcyclohexanecarboxylate (98)

A 1000-ml, one-necked, round-bottomed flask which has been fitted with a Dean-Stark water trap, reflux condenser, and gas-inlet tube was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with a

solution of 58.9 g (0.378 moles) of methyl 4-oxocyclohexane-carboxylate (97) dissolved in 400 ml of absolute benzene. To this solution was added 47.0 g (0.758 moles) of 1,2-ethanediol and 1.00 g of *p*-toluenesulfonic acid. The resulting suspension was heated slowly to reflux temperature (85°) and held at that temperature for 12 hours, during which time 6.6 ml of water were removed from the system. The Dean-Stark water trap was replaced by a Soxhlet extractor which contained 4A molecular sieves in the thimble, and the reaction mixture was allowed to percolate through the sieves for 12 hours. Following this treatment, the benzene solution was cooled, diluted with 400 ml of ether and washed with three 40-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum affording 77.4 g (0.387 moles - 102%) of a clear, colorless liquid. Attempted distillation of the product at reduced pressure caused visible decomposition, probably by rupture of the ketal. However, a small sample was micro-distilled to yield an analytically pure sample: bp $\sim 103^\circ$ (0.23 mm); ir (film) 2948(CH), 1731(C=O), 1098(C-O), 921 cm^{-1} ; nmr (CCl_4) δ 3.82(s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 3.60(s, 3H, $\text{CH}_3\text{O}_2\text{C}-$) ppm.

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4$: C, 60.00 H, 8.00

Found: C, 60.13 H, 8.03

4,4-Ethylenedioxcyclohexanecarboxylic acid (99)

A 1000-ml, two-necked, round-bottomed flask which had been fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with 61.2 g (0.306 moles) of methyl 4,4-ethylenedioxcyclohexanecarboxylate (98) dissolved in 300 ml of anhydrous methanol. This solution was treated, dropwise and with stirring, with a solution of 40.0 g (0.612 moles) of potassium hydroxide dissolved in 250 ml of anhydrous methanol. The reaction mixture was heated to reflux temperature (65°) and held at that temperature for 24 hours, during which time the solution turned slightly yellow in color. The crude product mixture was cooled, concentrated under vacuum to one-third the original volume, diluted with 200 ml of water, and extracted with three 15-ml portions of ether-benzene (4:1) to remove any unreacted ester. The basic residue was acidified by the dropwise addition of a 5% aqueous sulfuric acid solution, extracted with several 75-ml portions of benzene, and subjected to a 48 hour continuous extraction with benzene¹³⁴. The combined benzene extracts were diluted with an equal volume of ether and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the yellow residue dissolved in 100 ml of an ether-hexane (3:7) solvent. This solution was treated with 2.0 g of activated charcoal, boiled briefly, and rapidly

filtered through Celite. The resulting colorless oil readily crystallized and was recrystallized from ether-hexane affording 54.9 g (0.295 moles - 96.4%) of 4,4-ethylenedioxcyclohexane-carboxylic acid (99) as white needles: mp 52-54°; ir (KBr) 3050(OH), 1690(C=O), 1211, 1098(C-O), 1035, 946 cm^{-1} nmr (CCl_4) δ 11.8(s, 1H, -COOH), 3.87(s, 4H, -OCH₂CH₂O-) ppm; mass spectrum (70ev) M⁺ 186.

Anal. Calcd for C₉H₁₄O₄: C, 58.06 H, 7.53

Found: C, 58.22 H, 7.58

Methyl 4,4-ethylenedioxcyclohexyl ketone (100)

A. A procedure originally developed by Gilman and VanEss⁷¹ and recently elaborated by House and Bare¹³⁵ was followed. A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, and filled with prepurified nitrogen. Following these preliminary operations, the reaction vessel was charged with a solution of 18.0 g (0.097 moles) of 4,4-ethylenedioxcyclohexanecarboxylic acid (99) dissolved in 500 ml of anhydrous ether. The ethereal solution was cooled to 0° with an external ice bath and treated with 8.58 g (0.390 moles) of methyl lithium in ether (Foote Mineral Co.; 1.57M), dropwise, with vigorous stirring, over a 60 minute period. The reaction mixture immediately precipitated a white solid, presumably the

lithium anion of the acid, was allowed to warm to room temperature, and was stirred at that temperature for 4 hours. Following this, the reaction mixture was added, dropwise and with stirring, to 500 ml of ice water. The aqueous solution was saturated with solid sodium chloride and thoroughly extracted with ether. The ethereal extracts were washed with two 25-ml portions of a 10% sodium hydroxide solution, followed by three 25-ml portions of a 10% hydrochloric acid solution, a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled affording 14.7 g (0.080 moles - 83.3%) of the methyl ketone 100 as a colorless liquid:

bp 89-91° (0.23 mm); ir (film) 2945(CH), 1703(C=O), 1362, 1102(C-O), 1032, 918 cm^{-1} ; nmr (CCl_4) δ 3.88(s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 2.10(s, 3H, $\text{CH}_3\text{CO}-$) ppm; mass spectrum (70ev) M^+ 184.

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_3$: C, 65.22 H, 8.69

Found: C, 65.35 H, 8.29

B. A general procedure for the conversion of esters to methyl ketones recently developed by Corey and Durst⁷⁴ was explored. A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 16.9 g (0.100 moles) of N-methane sulfin-p-toluidine (102) dissolved in 500 ml of anhydrous

tetrahydrofuran. The reaction mixture was cooled to an internal temperature of -75° with a Dry Ice-isopropyl alcohol bath and treated, dropwise and with stirring, with 12.7 g (0.200 moles) of n-butyl lithium (Foote Mineral Co.; 1.57M) over a 20 minute period. Following complete addition of the n-butyl lithium, the reaction mixture was stirred for 30 minutes at -75° and treated with 10.0 g (0.050 moles) of methyl 4,4-ethylenedioxcyclohexanecarboxylate (98), dropwise and with stirring, over a 10 minute period. The reaction mixture was then stirred for 2 hours at -75° , allowed to warm slowly to room temperature, and poured onto 250 g of ice. The phases were separated, the aqueous phase saturated with solid sodium chloride, and extracted with five 25-ml portions of ether. The combined organic phases were washed with three 10-ml portions of a 10% hydrochloric acid solution, followed by three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled through a 30.5 cm Vigreux column affording 8.71 g (0.473 moles - 94.5%) of the methyl ketone 100 as a colorless liquid: bp $79-83^{\circ}$ (0.15 mm); ir and nmr essentially identical to those described in part A.

C. A procedure of general utility published by Corey and Chaykovsky⁷⁵ was followed. A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical

stirrer, pressure-equalizing addition funnel, reflux condenser, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 5.03 g (0.020 moles) of methylsulfinylmethyl 4,4-ethylene-dioxycyclohexyl ketone (105) dissolved in 300 ml of 10% aqueous tetrahydrofuran. To this was added 5.40 g (0.20 moles) of aluminum amalgam, freshly prepared as follows: Aluminum squares (1 cm X 1 cm) were immersed, all at once, into a 2% aqueous solution of mercuric chloride for 15 seconds, rinsed with anhydrous ethanol, ether, and introduced directly into the reaction mixture. Following addition of the amalgam, the reaction mixture was heated to 60-70°, with stirring, and maintained at that temperature for 90 minutes. The crude product mixture was then cooled, filtered free of aluminum residue, and concentrated under vacuum. The residue was taken up in 250 ml of ether, washed with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum and distillation of the residue gave 2.41 g (0.013 moles - 65.4%) of ketal ketone 100 as a colorless liquid: bp 89-93 (0.09 mm); ir and nmr identical to those described earlier.

Methane sulfinyl chloride (101)

One of the earlier procedures published by Douglass and Poole⁷³ was followed. A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel and thermometer.

The apparatus was evacuated, flame-dried, filled with pre-purified nitrogen, and charged with a solution of 47.1 g (0.500 moles) of dimethyl disulfide (Aldrich Chemical Co.) dissolved in 200 ml of anhydrous methylene chloride. The reaction mixture was stirred, cooled to an internal temperature of -75° and treated with chlorine gas passed slowed across the surface of the solution. Within 45 minutes, the reaction mixture had become a slurry of white crystals ($\text{CH}_3\text{SO}_2\text{Cl}$). To this was added, dropwise and with stirring, exactly 18.0 ml of distilled water. The cooling bath was removed and the reaction mixture allowed to warm to room temperature, during which time hydrogen chloride and chlorine gases were evolved. Following attainment of room temperature, the methylene chloride was removed by distillation at atmospheric pressure and the residue distilled further to yield 78.1 g (0.791 moles - 79.1%) of the sulfinyl chloride ~~101~~ as a straw-colored liquid: bp $40-43^{\circ}$ (14 mm); [lit.⁷³ bp 57 (32 mm)]; ir (film) 3001 and 2905(CH), 1405, 1367, 1291, 1155-1130(S=O), 946, 928 cm^{-1} ; nmr (CCl_4) δ 3.35 (s, CH_3 -), 3.20 (s, trace $\text{CH}_3\text{SO}_2\text{Cl}$) ppm.

In subsequent preparations varying amounts of $\text{CH}_3\text{SO}_2\text{Cl}$ were present, thereby necessitating a careful fractionation of the product.

A publication noting the instability of methane sulfinyl chloride has recently appeared.¹³⁶

N-methane sulfin-p-toluidine (102)

A 1000-ml three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 84.0 g (0.785 moles) of resublimed p-toluidine dissolved in 400 ml of anhydrous methylene chloride. To this was added, dropwise and with stirring, 30.6 g (0.389 moles) of methane sulfinyl chloride (101) over a 2 hour period. Following complete addition of the methane sulfinyl chloride, the reaction mixture was stirred at room temperature for 2 hours, filtered to remove the p-toluidine hydrochloride which had formed, and concentrated under vacuum. The residue was triturated with ether affording 56.7 g (0.345 moles - 86.2%) of N-methane sulfin-p-toluidine as a white powder: mp 110.5-113.5°; [lit.⁷⁴ mp 115-116°]; ir (KBr) 3120(CH), 1619, 1518, 1230(C-N), 1046(S=O), 825(Ar) cm^{-1} ; nmr (CCl_4) δ 7.95(bs, 1H, -NH-), 6.92(s, 4H, Ar), 2.75(s, 3H, CH_3SO -), 2.22(s, 3H, Ar- CH_3) ppm; mass spectrum (70ev) M^+ 169.

Corey and Durst⁷⁴ reported the preparation of the above compound by using triethylamine to react with the liberated hydrogen chloride, and reported an isolated yield of 86%. This method of preparation is probably superior to that described above, but in fact was published after the above preparation had been completed.

Methylsulfinylmethyl 4,4-ethylenedioxcyclohexyl ketone (105)

The general procedure originally published by Corey and Chaykovsky⁷⁵ was followed with some modifications in the isolation technique. A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, reflux condenser, and thermometer. The apparatus was evacuated, flame-dried, filled with pre-purified nitrogen, and charged with 5.61 g of a 57% sodium hydride-mineral oil dispersion (3.20 g - 0.133 moles active hydride). The mineral oil was removed by washing the hydride with 150 ml of anhydrous pentane under a nitrogen sweep and withdrawing the pentane through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 100 ml of anhydrous dimethylsulfoxide. The reaction mixture was heated, with stirring, to an internal temperature of 70-75°, whereupon hydrogen evolution began and continued for approximately 25 minutes. Following evolution of the hydrogen, the reaction mixture was maintained at 70-75° for 30 minutes, cooled, diluted with 100 ml of anhydrous tetrahydrofuran, and treated with 11.6 g (0.058 moles) of methyl 4,4-ethylenedioxcyclohexanecarboxylate (98). The addition was carried out, with stirring, over a 25 minute period. Following complete addition of ester 98, the reaction mixture was stirred at room temperature for 60 minutes, and poured onto 600 g of ice. The resulting

aqueous solution was extracted with four 15-ml portions of ether to remove any unreacted ester. The aqueous solution was then acidified by the cautious addition of a 10% hydrochloric acid solution and extracted with five 35-ml portions of chloroform. The combined chloroform extracts were washed with two 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The chloroform was removed under vacuum to leave 13.5 g (0.055 moles - 94%) of a reddish, viscous oil which was not further purified. Nmr (CCl_4) δ 3.95 (s, 2H, $-\text{CO}-\text{CH}_2-\text{SO}-$), 3.87 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 2.60 (s, 3H, $\text{CH}_3\text{SO}-$) ppm.

Methyl dimethylphosphonate (108)

The procedure of Ford-Moore and Williams⁷⁹, described for methyl diethylphosphonate, was followed. A 1000-ml, two-necked, round-bottomed flask was fitted with a gas-inlet tube, pressure-equalizing addition funnel, magnetic stirrer, and reflux condenser. The apparatus was briefly flushed with prepurified nitrogen and charged with 240 g (1.93 moles) of trimethylphosphite (107) (Aldrich Chemical Co.) to which was added 10 g of methyl iodide, dropwise and with stirring. Following a brief induction period (20-30 minutes), the reaction became violently exothermic and was cooled in an ice-salt bath. After the initial reaction had subsided, the reaction mixture was warmed to 44° and maintained at that temperature while 264 g (total 1.93 moles) of methyl iodide were added over a 3 hour

period. Following complete addition of the methyl iodide, the reaction mixture was maintained at reflux temperature for 6 hours, cooled, and distilled affording 224.0 g (1.81 moles - 93.5%) of methyl dimethylphosphonate (108) as a colorless liquid: bp 101-103° (55 mm); [lit.¹³⁷ bp 67-68° (12 mm)]; nmr (CCl₄) δ 3.65(d,6H,J=11 Hz, CH₃O-), 1.39(d,3H,J=17.5Hz, CH₃P-) ppm.

Methyl phosphonic acid (109)

A 500-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, reflux condenser, and filled with prepurified nitrogen. The apparatus was charged with a solution of 124 g (1.00 moles) of methyl dimethylphosphonate (108) dissolved in 250 ml of concentrated hydrochloric acid. The reaction mixture was heated slowly to reflux temperature (102°) and maintained at that temperature for 48 hours. The crude product mixture was cooled, diluted with 100 ml of toluene, and concentrated under vacuum. This operation was repeated several times until all traces of water and hydrogen chloride had been removed and the product had solidified to a greenish solid. A final drying of the product was accomplished at 70° under high vacuum affording 94.4 g (0.982 moles - 98.1%) of methyl phosphonic acid (109): mp 105-106°; [lit.⁸⁷ mp 106-107°]; nmr (D₂O) δ 1.57(d,J=17.5 Hz, CH₃P-) ppm.

Methyl phosphonyl dichloride (110)

A 500-ml, two-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and powder addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a suspension of 19.2 g (0.200 moles) of methyl phosphonic acid (109) in 300 ml of anhydrous benzene. The reaction mixture was vigorously stirred and treated with 83.2 g (0.400 moles) of phosphorous pentachloride, portionwise, over a 5 hour period. Following complete addition of the phosphorous pentachloride, the reaction mixture was stirred for 6 hours at room temperature, concentrated under vacuum and distilled giving 23.8 g (0.180 moles - 89.9%) of the dichloride 110 as a colorless liquid which solidified upon cooling to a white, chunky solid: bp 52-53° (9.0 mm), mp 28.5-29.5°; [lit.⁸² bp 163° (756), lit.¹³⁸ bp 159-162° (760), lit.¹³⁹ mp 29-31°]; ir (CCl₄) 1295 (PCH₃) 1271 (P=O), 889 cm⁻¹; nmr (CCl₄) δ 2.52 (d, J=17.5 Hz, -CH₃P-) ppm.

Methyl phosphonic acid bis(N,N-dimethylamide) (111)

A 500-ml, three-necked, round-bottomed flask which had been fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser, was evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with a solution of 54.0 g (1.15 moles) of dimethylamine in 110 ml of anhydrous heptane, and cooled to 0° with an external ice bath. To this solution was added,

dropwise and with stirring, 37.5 g (0.282 moles) of methyl phosphonyl dichloride ($\text{Cl}_2\text{P}(\text{O})\text{CH}_3$) dissolved in 60 ml of warm heptane. Following complete addition of the dichloride solution, the reaction mixture was heated to reflux temperature (99°) and held at that temperature for 24 hours, during which time additional dimethylamine was periodically added to make up volatilization losses. The crude product mixture was cooled, filtered, the solid washed with warm heptane, and the organic filtrate concentrated under vacuum to a volume of approximately 125 ml. The residue was diluted with 35 ml of a 30% aqueous sodium hydroxide solution and stirred under nitrogen at room temperature for 4 hours. The resulting phases were separated and the aqueous phase extracted with three 25-ml portions of ether. The ethereal extracts and heptane were combined and dried over anhydrous sodium sulfate. (Due to the water solubility of the amide the organic phases were not washed with brine prior to drying with sodium sulfate.) The solvent was removed under vacuum to leave a red, viscous residue, which upon distillation gave 34.2 g (0.231 moles - 81.5%) of methyl phosphonic acid bis(N,N-dimethylamide) ($\text{N}(\text{CH}_3)_2\text{P}(\text{O})(\text{N}(\text{CH}_3)_2)\text{CH}_3$) as a colorless liquid; bp $105-107^\circ$ (8 mm); [lit.⁸³ bp 138°]; ir (film) 2965(CH), 1460, 1291, 1199, 990-961, 886, 722 cm^{-1} ; nmr (CCl_4) δ 2.62(d, 12H, $J=10$ Hz, $\text{CH}_3\text{N}-$), 1.43(d, 3H, $J=14.7$ Hz, $\text{CH}_3\text{P}-$) ppm; mass spectrum (70ev) M^+ 150.

2-(4',4'-Ethylenedioxcyclohexyl)-2-hydroxypropylphosphonic acid bis(N,N-dimethylamide) (113)

The general procedure of Corey and Kwiatkowski⁷⁸ was followed with minor modifications. A 500-ml, three-necked, round-bottomed flask which was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 19.0 g (0.127 moles) of methyl phosphonic acid bis(N,N-dimethylamide) (111) dissolved in 250 ml of anhydrous tetrahydrofuran. The reaction mixture was cooled to an internal temperature of -75° by a Dry Ice-isopropyl alcohol bath and treated with 7.68 g (0.121 moles) of n-butyl lithium in hexane (Foote Mineral Co.; 1.57M), dropwise and with stirring, over a 30 minute period. Following complete addition of the n-butyl lithium, the reaction mixture was stirred for 30 minutes at -75° and treated with 21.9 g (0.119 moles) of methyl 4,4-ethylenedioxcyclohexyl ketone (100), diluted with 75 ml of anhydrous tetrahydrofuran, dropwise and with vigorous stirring. The reaction mixture was then allowed to warm slowly to room temperature and stirred at that temperature for 4 hours. The crude product mixture was poured onto 100 g of ice, the phases separated, the aqueous phase saturated with solid sodium chloride, and extracted with three 75-ml portions of ether. The combined ether-tetrahydrofuran phase was washed with brine and dried over anhydrous sodium sulfate. The dried

solvent was removed under vacuum affording 51.2 g of a red, viscous liquid, which readily solidified. Recrystallization of the material from an ether-hexane solvent left 28.1 g (0.841 moles - 70.4%) of the β -hydroxyphosphonamide as white, fluffy crystals: mp 93-95°; ir (KBr) 3350(OH), 2920(CH), 1443, 1300, 1195, 1148, 1092(C-O), 983, 928, 921 cm^{-1} ; nmr (CCl_4) δ 4.73 (bs, 1H, OH, exchange with D_2O), 3.83 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 2.58 (d, 12H, $J=9$ Hz, $-\text{NCH}_3$), 1.80 (d, 2H, $J=14.7$ Hz, $-\text{CH}_2\text{P}-$), 1.13 (s, 3H, $-\text{CH}_3$) ppm.

An analytically pure sample was prepared by two further recrystallizations from hexane, mp 95.5-96.0°.

Anal. Calcd for $\text{C}_{15}\text{H}_{31}\text{N}_2\text{O}_4\text{P}$: C, 53.89 H, 9.28 N, 8.38

Found: C, 53.92 H, 9.33 N, 8.36

Analysis of *n*-butyl lithium solutions prior to use

The double titration method of Gilman was employed⁸⁴. A 3.00 ml sample of the *n*-butyl lithium solution to be analyzed was removed via a dry syringe, introduced into 10 ml of anhydrous ether, and rapidly quenched by the addition of 10 ml of distilled water. The solution was stirred magnetically and titrated with a 0.01N hydrochloric acid solution to a phenolphthalein end point. This procedure gave the total base content.

A second 3.00 ml sample of the *n*-butyl lithium solution was withdrawn and added, under a nitrogen sweep, to a solution

of 10 ml of anhydrous ether and 1.0 ml of allyl bromide. The reaction mixture was stirred for 5 minutes and quenched with 10 ml of distilled water. Titration as described above gave the residual (unreactive) base content, for example

ml 0.10N HCl without allyl bromide	ml 0.10N HCl with allyl bromide
49.91	2.20
50.00	2.22
50.17	2.21
ave 49.93	ave 2.21

Calc'd normality = 1.59

4,4-Ethylenedioxyisopropenylcyclohexane (114)

A. According to the procedure originally devised by Corey and Kwiatkowski⁷⁸ for the cleavage of β -hydroxyphosphonamides, a 150-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, reflux condenser, and thermometer. The apparatus was repeatedly evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 5.00 g (0.015 moles) of 2-(4',4'-ethylenedioxcyclohexyl)-2-hydroxypropylphosphonic acid bis(N,N-dimethylamide) (113) dissolved in 50 ml of anhydrous benzene. To this solution was added, in one portion, 15 g of "Woelm" silica gel. The reaction mixture was slowly stirred, warmed to reflux temperature, and maintained at that temperature for 24 hours. The crude product mixture was cooled, filtered, and concentrated under vacuum affording 2.11 g of a

slightly yellow liquid: bp 56-57° (0.10 mm); ir (film) 2915(CH), 1713(trace C=O), 1640(C=C), 1444, 1363, 1148, 1101(C-O), 1034 cm^{-1} ; nmr (CCl_4) δ 4.65(bq, 2H, $J=1.5$ Hz, $\text{CH}_2=\text{C}-$), 3.85(s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 1.70(t, 3H, $J=1.5$ Hz, CH_3-) ppm; mass spectrum (70ev) M^+ 182.

B. A 100-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube and reflux condenser. The apparatus was evacuated, flame-dried, filled with nitrogen, and charged with a solution of 6.00 g (0.018 moles) of 2-(4',4'-ethylene-dioxycyclohexyl)-2-hydroxypropylphosphonic acid bis(N,N-dimethylamide) (113) dissolved in 50 ml of reagent grade acetone which contained 2.5 ml of a 10% hydrochloric acid solution. The reaction mixture was heated gently on a steam bath for 20 minutes, concentrated to one-half its original volume under vacuum, and the aqueous residue saturated with solid sodium chloride. The aqueous phase was extracted with seven 25-ml portions of ether and the combined ethereal extracts were washed with three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving a yellow residue (1.81 g) which upon distillation gave 1.58 g (0.114 moles - 63.1%) of 4,4-ethylenedioxyisopropenyl-cyclohexane (114) as a colorless liquid: bp 58-60° (0.2 mm); ir (film) and nmr (CCl_4) identical to those described in part A above.

One additional distillation of a micro-sample gave an analytically pure sample, bp 61.5° (0.15 mm).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53 H, 9.89

Found: C, 72.46 H, 9.84

4-Isopropenylcyclohexanone (115)

A. A 50-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 1.00 g (0.0034 moles) of recrystallized β -hydroxyphosphonamide 113 dissolved in 20 ml of reagent grade acetone which contained 2.5 ml of a 10% hydrochloric acid solution. The reaction mixture was heated gently on a steam bath for 60 minutes, concentrated to one-half its original volume under vacuum, and the aqueous residue saturated with solid sodium chloride. The aqueous phase was extracted with seven 35-ml portions of ether, and the combined ethereal extracts were washed with four 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum affording a colorless liquid, which upon distillation gave 0.438 g (0.0032 moles - 94.4%) of 4-isopropenylcyclohexanone (115) as a clear liquid: bp 47-52° (0.25 mm); [lit.⁸⁶ bp 100° (10 mm)]; ir (film) 2930 (CH), 1711 (C=O), 1642 (C=C), 1436, 1160, 889 cm^{-1} ; nmr (CCl_4) δ 4.73 (q, 2H, J=1 Hz, $CH_2=$), 1.74 (q, 3H, J=1 Hz, CH_3) ppm; mass spectrum (70ev) M^+ 138.

A 2,4-dinitrophenylhydrazone derivative was prepared in the usual way¹³² and recrystallized twice from anhydrous ethanol to give yellow plates, mp 138-140°. An analytically pure sample was prepared by two further recrystallizations from ethanol, mp 141-141.5°; [lit.⁸⁶ mp 120-131° see text].

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60 H, 5.70 N, 17.60

Found: C, 56.42 H, 5.92 H, 17.46

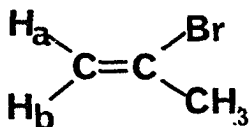
B. A 100-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, filled with prepurified nitrogen, and charged with a solution of 8.00 g (0.044 moles) of 4,4-ethylenedioxyisopropenylcyclohexane (114) dissolved in 44 ml of reagent grade acetone which contained 4.4 ml of a 10% hydrochloric acid solution. The reaction mixture was stirred at room temperature for 48 hours, warmed to reflux temperature for 4 hours, cooled, and diluted with 50 ml of water. The aqueous phase was saturated with solid sodium chloride and extracted with seven 35-ml portions of ether. The combined ethereal extracts were washed with three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled giving 5.36 g (0.040 moles - 91.0%) of 4-isopropenylcyclohexanone (115) as a colorless liquid, identical in all respects with the material described above.

Isopropenyl Bromide (127)

The procedure of Braude and Evans⁹¹ was followed. A 3000-ml, three-necked, round-bottomed Morton flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 400 g (4.65 moles) of α -methyl-acrylic acid (125) (Pflatz and Bauer Chemical Co.) dissolved in 800 ml of carbon disulfide. The reaction mixture was cooled to 0° with an external ice bath and treated with 800 g (5.00 moles) of bromine, dropwise and with rapid stirring, over an 8 hour period. Following complete addition of the bromine, the dark red solution was stirred at 0° for 7 hours, and allowed to warm to room temperature. The carbon disulfide solvent was removed by distillation at atmospheric pressure, with care being taken to remove all of the carbon disulfide (see text). The white solid which resulted on cooling was dissolved in 1500 ml of pyridine, the brown solution thus obtained heated slowly to reflux temperature, and maintained at that temperature for 12 hours. During this period of heating, carbon dioxide gas was evolved as evidenced by the formation of a white precipitate (BaCO_3) upon introduction of the gas into an aqueous barium hydroxide solution. The reaction mixture was cooled, acidified to pH-2 by the dropwise addition of concentrated hydrochloric acid, and cautiously steam

distilled. The resulting water insoluble distillate was washed with two 15-ml portions of 2N hydrochloric acid, followed by brine, and dried over anhydrous calcium chloride. The product was filtered free of the drying agent and distilled from a small piece of sodium giving 326.1 g (2.70 moles - 58.2%) of the vinyl bromide 127 as a sharp-smelling, slightly yellow liquid: bp 47.5-48.0°: [lit.⁹¹ bp 48°]; ir (film) 2960(CH), 1639(C=C), 1434, 1152, 885 cm⁻¹; nmr (CCl₄) δ 5.47(q, 1H, J=1.5 Hz, H_a), 5.28(q, 1H, J=1.0 Hz, H_b), 2.25(d, 3H, J=1.5 Hz, -CH₃) ppm.

The addition of a silver nitrate solution to an aliquot caused the slow formation of a precipitate of silver bromide.



1,4-Cyclohexanediol (133)

According to the general procedure of Sondheimer and Elad⁹⁴, a 1000-ml capacity packless autoclave was briefly flushed with nitrogen and charged with 198 g (1.80 moles) of hydroquinone (132) dissolved in 300 ml of anhydrous methanol which contained 20 g of Raney nickel (W-2). The reaction mixture was heated to 150° and stirred under a constant pressure of 2200 psi of hydrogen. The reaction mixture was stirred under these conditions for 2 days, during which time a rapid uptake of hydrogen was observed. The crude product

mixture was cooled, filtered free of the catalyst, and concentrated under vacuum. The residue was dissolved in 350 ml of ether, washed with three 20-ml portions of a 10% sodium hydroxide solution, two 10-ml portions of a 10% hydrochloric acid solution, two 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the dried solvent left 205.2 g (1.77 moles - 98%) of an extremely viscous oil which showed no evidence of aromatic material remaining (nmr,ir).

4-Bromocyclohexanol (137)

The procedure of Noyce and his coworkers⁹⁷ was followed. A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, reflux condenser, and thermometer. The apparatus was evacuated, briefly flushed with nitrogen, and charged with 25.0 g (0.255 moles) of 7-oxabicyclo-[2.2.1]heptane (Aldrich Chemical Co.) (136). To this was added, dropwise and with stirring, 44.0 g of a 48% aqueous hydrobromic acid solution over a 20 minute period. The resulting homogeneous solution was heated to an internal temperature of 50° and maintained at that temperature for 6 days. Following this period, the crude product was separated, the aqueous phase extracted with seven 20-ml portions of ether, and the combined organic phases washed with three 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum

giving a red oil, which readily crystallized. The product was recrystallized twice from an ether-hexane solvent affording 22.3 g of 4-bromocyclohexanol (137) as a white powder: mp 81-83°; [lit.⁹⁷ 81-83° for pure trans]. Evaporation of the mother liquors and distillation of the residue gave an additional 13.5 g of solid material, mp 78-81°, bp 109-113° (12 mm). Overall yield - 35.8 g (0.201 moles - 96.0%). Nmr (CCl₄) δ 4.10 (m, 1H, -CHBr), 3.68 (m, 1H, -CHOH), 3.30 (s, 1H, -OH).

4-Bromocyclohexanone (117)

A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, briefly flushed with nitrogen, and charged with a solution of 30.9 g (0.172 moles) of unpurified 4-bromocyclohexanol (137) dissolved in 500 ml of ether. The reaction mixture was cooled to an internal temperature of 3° and treated with a precooled (0°) oxidation reagent which consisted of 20.4 g (0.208 moles) of concentrated sulfuric acid and 15.5 g (0.052 moles) of sodium dichromate dihydrate dissolved in 200 ml of distilled water. The cold oxidation reagent was added dropwise, with constant stirring, over a 4 hour period. Following complete addition of the oxidizing solution, the reaction mixture was allowed to warm to room temperature and stirring was continued for 12 hours at that temperature. The resulting phases were separated, the aqueous phase saturated with solid sodium

chloride and extracted with five 25-ml portions of ether. The combined ethereal phases were washed with three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled affording 17.6 g (0.100 moles - 91.0%) of 4-bromocyclohexanone (117) as a colorless liquid: bp 86-88° (0.5 mm); [lit.⁸⁶ bp 100° (5.0 mm)]; ir (film) 3410 (trace OH), 2925 (CH), 1719-1699 (C=O), 1429, 1315, 1227, 1159, 1052 cm^{-1} ; nmr (CCl_4) δ 4.62 (m, 1H, -CHBr) ppm.

The addition of a silver nitrate solution to an aliquot caused the slow formation of a precipitate of silver bromide.

A 2,4-dinitrophenylhydrazone derivative was prepared according to standard procedures and recrystallized twice from anhydrous ethanol; mp 78-84° (dec). High resolution mass spectrum M^+ obs: 356.0114, 358.0130; calcd: 356.0121, 358.0101.

4-Chlorocyclohexanol (138)

Following the procedure of Bennett and Niemann¹³⁹ a 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 25.0 g (0.255 moles) of 7-oxabicyclo[2.2.1]heptane (136). The reaction mixture was cooled to an internal temperature of 5° with an external ice bath and treated with 100 ml of

concentrated (12N) hydrochloric acid, dropwise and with vigorous stirring, over a 45 minute period. Following complete addition of the hydrochloric acid solution, the yellow reaction mixture was stirred for 5 days at room temperature, during which time the solution turned black. Following this period, the reaction mixture was diluted with 100 ml of water, the phases were separated, and the aqueous phase was extracted with six 35-ml portions of ether. The combined organic extracts were washed with five 15-ml portions of water, followed by brine, and dried over anhydrous magnesium sulfate. The solvent was filtered through anhydrous potassium carbonate and concentrated under vacuum giving 28.8 g (0.215 moles - 84.3%) of a brown solid: mp 67-78°; [lit.¹³⁹ mp 60-76° crude]. The alcohol was not purified further. Ir (KBr-crude) 3451(OH), 2950(CH), 1453, 1065(C-O) cm^{-1} .

4-Chlorocyclohexanone (139)

A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, flame-dried, briefly flushed with nitrogen, and charged with a solution of 28.8 g (0.214 moles) of crude 4-chlorocyclohexanol (138) dissolved in 300 ml of ether. The reaction mixture was cooled to an internal temperature of 5° with an external ice bath and treated with a precooled (0°) solution of 21.3 g (0.072 moles) of sodium dichromate dihydrate and 28.0 g

(0.286 moles) of concentrated sulfuric acid dissolved in 150 ml of distilled water. The cold oxidizing solution was added dropwise, with rapid stirring, over a 2 hour period. Following complete addition, the reaction mixture was allowed to warm to room temperature, stirred at room temperature for 24 hours, and the resulting phases were separated. The aqueous phase was saturated with solid sodium chloride and extracted with six 35-ml portions of ether. The combined ethereal phases were washed with three 25-ml portions of a saturated sodium bicarbonate solution, followed by brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving 23.9 g (0.173 moles - 80.5%) of 4-chlorocyclohexanone (139) as a colorless liquid: bp 46-47° (0.075 mm); [lit.¹⁴⁰ bp 95° (17 mm)]; ir (film) 2939 (CH), 1712 (C=O), 1435, 1321, 1251 cm^{-1} ; nmr (CCl_4) δ 4.75 (m, 1H, $-\text{CHCl}$) ppm.

The addition of a silver nitrate solution to an aliquot caused the slow formation of a precipitate of silver chloride.

A 2,4-dinitrophenylhydrazone derivative was prepared according to standard procedures and recrystallized twice from anhydrous ethanol; mp 143-144°. High resolution mass spectrum M^+ obs: 312.0602, 314.0575; calcd: 312.0625, 314.0596.

4-Iodocyclohexanol (140)

A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was

evacuated, flame-dried, filled with prepurified nitrogen, and charged with 25.0 g (0.255 moles) of 7-oxabicyclo[2.2.1]heptane (136). The reaction mixture was vigorously stirred and treated with 45.0 g of a 47% aqueous hydriodic acid solution, dropwise over a 60 minute period. The reaction mixture was heated, with stirring, to an internal temperature of 50° and was maintained at that temperature for 7 days. Following this period, the crude product mixture was cooled, the phases were separated, and the aqueous phase extracted with six 20-ml portions of ether. The combined ethereal extracts as well as the original organic phase were washed with brine and dried over anhydrous potassium carbonate. The solvent was removed under vacuum giving 44.9 g (0.198 moles - 93.6%) of iodoalcohol 140 as a yellow solid: mp 58-62°; [lit.¹⁴¹ mp 59.2-60.3° for trans]; ir (KBr) 3369(OH), 2951(CH), 1453, 1089, 1068(C-O), 790 cm⁻¹; nmr (CCl₄) δ 4.12(m, 1H, -CH₂I), 3.63(m, 1H-CHOH), 3.64(bs, 1H, -OH, exchange with D₂O) ppm. The product failed to sublime as reported and gave off iodine when heated under vacuum.

4-Iodocyclohexanone (141)

A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was briefly flushed with nitrogen and charged with a solution of 44.9 g (0.198 moles) of unpurified 4-iodocyclohexanol (140) dissolved in 600 ml of ether. The reaction mixture was cooled to an

internal temperature of 3° with an external ice bath and treated with a precooled (0°) oxidation reagent which consisted of 30.0 g (0.101 moles) of sodium dichromate dihydrate and 39.8 g (0.406 moles) of concentrated sulfuric acid dissolved in 250 ml of distilled water. The oxidation reagent was added dropwise, with constant stirring, over a 4 hour period. Following complete addition of the oxidation solution, the reaction mixture was allowed to warm to room temperature and stirred at that temperature for 14 hours. The phases were separated, the aqueous phase saturated with solid sodium chloride and extracted with three 35-ml portions of ether. The combined ethereal phases were washed with three 35-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The dried solvent was removed under vacuum giving 41.6 g (0.186 moles - 94.1%) of 4-iodocyclohexanone (141) as yellow plates: mp 43-45°. The product gave off iodine upon attempted distillation under vacuum. Ir (KBr) 2962(CH), 1824(C=O), 1435, 1328, 1220 cm^{-1} ; nmr (CCl_4) 4.20(m, 1H, -CHI) ppm; high resolution mass spectrum M^+ obs: 223.9697; calcd: 223.9699.

4,4-Ethylenedioxybromocyclohexane (146)

A 500-ml, one-necked, round-bottomed flask was fitted with a Dean-Stark water trap, gas-inlet tube, and reflux condenser. The apparatus was repeatedly evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 6.50

g (0.037 moles) of crude 4-bromocyclohexanone (117) and 6.88 g (0.111 moles) of 1,2-ethanediol dissolved in 250 ml of anhydrous benzene. To this solution was added 1.00 g of *p*-toluenesulfonic acid as catalyst. The reaction mixture was heated to reflux temperature and maintained at that temperature for 18 hours, during which time 0.65 ml of water were removed from the system. The crude product mixture was cooled, the Dean-Stark trap replaced by a Soxhlet extractor which contained 4A molecular sieves in the thimble, and the benzene solution was allowed to percolate through the sieves for 12 hours. Following this operation, the product mixture was cooled, diluted with 250 ml of ether, and washed with three 35-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving 8.04 g (0.366 moles - 99%) of the bromoketal 146 as a colorless liquid: ir (film) 2935(CH), 1432, 1362, 1240, 1103(C-O), 1034 cm^{-1} ; nmr (CCl_4) δ 4.25(m, 1H, -CHBr), 3.85(s, 4H, -OCH₂CH₂O-) ppm.

4,4-Ethylenedioxychlorocyclohexane (147)

A 150-ml, one-necked, round-bottomed flask was fitted with a Dean-Stark water trap, gas-inlet tube, and reflux condenser. The apparatus was evacuated, flame-dried, filled with pre-purified nitrogen, and charged with a solution of 7.00 g (0.053 moles) of 4-chlorocyclohexanone (139) and 9.85 g (0.159 moles) of 1,2-ethanediol dissolved in 75 ml of anhydrous

benzene. To this was added 0.25 g of p-toluenesulfonic acid as catalyst. The reaction mixture was heated to reflux temperature and maintained at that temperature for 12 hours, during which time 0.93 ml of water were removed from the system. The solution was then cooled, the Dean-Stark water trap replaced by a Soxhlet extractor which contained 4A molecular sieves in the thimble, and the benzene solution was allowed to percolate through the sieves for 12 hours. The crude product mixture was then cooled, diluted with 100 ml of ether, and washed with three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled giving 8.37 g (0.475 moles - 89.4%) of the chloroketal 147 as a colorless liquid: ir (film) 2930(CH), 1365, 1257 1048(C-O), 1032, 914 cm^{-1} ; nmr (CCl_4) δ 4.12(m, 1H, $-\text{CHCl}$), 3.87(s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$) ppm.

A white precipitate formed upon the addition of a 0.2M alcoholic silver nitrate solution.

4,4-Ethylenedioxyiodocyclohexane (148)

A 1000-ml, one-necked, round-bottomed flask was fitted with a Dean-Stark water trap, gas-inlet tube, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 41.6 g (0.186 moles) of 4-iodocyclohexanone (141) and 34.6 g (0.558 moles) of 1,2-ethanediol dissolved in 500 ml of anhydrous

benzene. To this was added 1.00 g of p-toluenesulfonic acid as catalyst. The reaction mixture was heated to reflux temperature and maintained at that temperature for 13 hours, during which time 3.3 ml of water were removed from the system. The reaction mixture was cooled, the Dean-Stark water trap replaced by a Soxhlet extractor which contained 4A molecular sieves in the thimble, and the benzene solution was allowed to percolate through the sieves for 12 hours. Following this operation, the crude product mixture was cooled, diluted with 400 ml of ether, and washed with four 35-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue rapidly distilled through a short-path still affording 49.8 g (0.186 moles - 97.4%) of iodoketal ¹⁴⁸ as a colorless liquid: bp 70.5-74.5° (0.5 mm); ir (film) 2964(CH), 1375, 1242, 1181, 1111(C-O) cm⁻¹; nmr (CCl₄) δ 4.38(m, 1H, -CHI), 3.83(s, 4H, -OCH₂CH₂O-) ppm.

Anal. Calcd for C₈H₁₃IO₂: C, 35.84 H, 4.89 I, 47.33

Found: C, 36.10 H, 4.95 I, 47.01

General procedure for the preparation of lithium diisopropenyl cuprate (¹¹⁸)

A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, Hershberg wire stirrer¹⁴², pressure-equalizing addition funnel, and reflux condenser. The

apparatus was evacuated, flame-dried, filled with prepurified argon, and charged with 4.50 g (0.643 moles) of finely divided lithium ribbon (Hoote Mineral Co.; 1% sodium content), suspended in 125 ml of "super-dry" ether. The lithium suspension was stirred very rapidly and treated with 42.3 g (0.350 moles) of isopropenyl bromide (127) dropwise, at a rate sufficient to maintain the ether at reflux temperature. Following complete addition of the isopropenyl bromide, the violet-gray reaction mixture was filtered through glass wool into a precooled (-75°) suspension of 30.5 g (0.161 moles) of cuprous iodide (Alfa Inorganic's Inc.) in 675 ml of "super-dry" ether. The resulting gray slurry was stirred at -75° for 45 minutes and treated at that temperature with the materials noted below.

With bromocyclohexane (129) To the preformed slurry of lithium diisopropenyl cuprate prepared as described above was added 5.70 g (0.035 moles) of bromocyclohexane (129) dropwise and with stirring, over a 30 minute period. The reaction mixture was then stirred for 3 days at -75° and allowed to warm slowly to room temperature. The resulting black solution was poured onto 250 g of ice, stirred briefly until all the ice had melted, and the phases were separated. The aqueous phase was saturated with solid sodium chloride and extracted with seven 100-ml portions of ether. The combined ethereal extracts and the original ether phase were filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was

removed under vacuum and the residue distilled giving 2.79 g (0.023 moles - 64.1%) of isopropenylcyclohexane (130) as a colorless liquid: bp 65-67° (15 mm); [lit.¹⁴³ bp 151°]; nmr (CCl₄) δ 4.58 (q, 2H, J=1.5 Hz, CH₂=C-), 1.66 (t, 3H, J=1.5 Hz, CH₃-) ppm.

With 4-chlorocyclohexanone (139) To the preformed slurry of lithium diisopropenyl cuprate prepared as described above was added 4.64 g (0.035 moles) of 4-chlorocyclohexanone (139), dropwise, over a 10 minute period. The reaction mixture was stirred at -75° for 8 hours and poured onto 250 g of ice. The resulting phases were separated, the aqueous phase extracted with seven 45-ml portions of ether, and the combined ethereal phases filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to leave a brown oil, which upon examination by thin layer chromatography using a silica gel H adsorbent and a 10% ethyl acetate-hexane developing solvent showed a complex mixture of 4 major products in approximately equal amounts. Two of the components were subsequently identified as 4-isopropenylcyclohexanone (115) and 4-chlorocyclohexanone (139). The remaining materials were identified as the products of addition of the lithium diisopropenyl cuprate reagent to the carbonyl group (see text for complete discussion).

With 4,4-ethylenedioxychlorocyclohexane (147) To the preformed lithium diisopropenyl cuprate slurry was added 6.17 g (0.035 moles) of 4,4-ethylenedioxychlorocyclohexane (147), dropwise and with stirring, over a 10 minute period. The reaction mixture was stirred at -75° for 6 hours and allowed to warm slowly to room temperature, whereupon the crude product mixture was poured onto 250 g of ice, the phases were separated, and the aqueous phase saturated with solid sodium chloride. Extraction of the aqueous phase was accomplished with seven 35-ml portions of ether, which, combined with the original ether phase, were filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to leave a slightly yellow oil, which upon distillation gave 5.56 g (0.032 moles - 91.6%) of recovered chloroketal 147. No other products were detected by thin layer chromatography.

With 4-bromocyclohexanone (117) To the preformed slurry of lithium diisopropenyl cuprate was added 6.15 g (0.035 moles) of 4-bromocyclohexanone (117), dropwise, over a 10 minute period. The reaction mixture was allowed to stir for 3 hours at -75° , warmed slowly to room temperature over a 2 hour period, and poured onto 250 g of ice. The phases were separated, the aqueous phase saturated with solid sodium chloride and extracted with seven 35-ml portions of ether. The combined ethereal phases were filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving a red oil, which upon examination

by thin layer chromatography using a silica gel H adsorbent and 7% ethyl acetate-hexane developing solvent showed a mixture of 4 major components, in approximately equal amounts. The chromatogram thus obtained closely resembled that obtained from the crude reaction product of lithium diisopropenyl cuprate and 4-chlorocyclohexanone (139). It was subsequently determined that no synthetically useful material could be easily isolated from this mixture and the oil was discarded.

With 4,4-ethylenedioxybromocyclohexane (146) To the preformed slurry of lithium diisopropenyl cuprate was added 7.70 g (0.035 moles) of 4,4-ethylenedioxybromocyclohexane (146), dropwise, over a 15 minute period. The reaction mixture was stirred at -75° for 6 hours, allowed to warm to room temperature, and poured into 250 g of ice water. The resulting phases were separated, the aqueous phase was saturated with solid sodium chloride, and extracted with six 35-ml portions of ether. The combined ethereal phase was filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving a colorless oil, which upon distillation gave one major product, bp 65-85° (0.05 mm). The isolated product was subsequently shown to consist primarily of recovered 4,4-ethylenedioxybromocyclohexane (146), and a small amount of 4,4-ethylenedioxyisopropenylcyclohexane (114). The relative amounts of the two products were determined by vapor phase chromatography to be 96% and 4% respectively.

With 4-iodocyclohexanone (141) The preformed lithium diisopropenyl cuprate slurry was treated with 7.85 g (0.035 moles) of 4-iodocyclohexanone (141), dropwise, over a 20 minute period. The reaction mixture was then stirred for 8 hours at -75° , warmed slowly to room temperature, and poured into 200 ml of cold (10°) water. The resulting phases were separated, the aqueous phase was saturated with solid sodium chloride, and extracted with seven 35-ml portions of ether. The combined ethereal phases were filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving a black liquid, which upon examination by thin layer chromatography using a silica gel adsorbent with a 50% ethyl acetate-hexane developing solvent showed a mixture of four components. The mixture was similar to those isolated from the reactions of 4-chloro- and 4-bromocyclohexanone with the lithium diisopropenyl cuprate reagent. It was determined that no synthetically useful material could be isolated from the mixture and it was discarded.

With 4,4-ethylenedioxyiodocyclohexane (148) The preformed lithium diisopropenyl cuprate slurry was treated with 9.38 g (0.035 moles) of 4,4-ethylenedioxyiodocyclohexane (148), dropwise, over a 35 minute period. The reaction mixture was stirred slowly at -75° for 8 hours, warmed to room temperature over a 6 hour period, and poured onto 250 g of ice. The resulting phases were separated, the aqueous phase was saturated

with solid sodium chloride, and extracted with eight 25-ml portions of ether. The combined ethereal phases were filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to leave a slightly yellow liquid, which upon distillation gave 2.91 g (0.016 moles - 45.7%) of a colorless liquid: bp 57-60° (0.2 mm), identified as 4,4-ethylenedioxyisopropenylcyclohexane (114) by comparison with an authentic sample (ir, nmr, mass spectrum).

It was subsequently discovered that the use of longer reaction times and a larger molar amount of 4,4-ethylenedioxyiodocyclohexane (148) would allow the isolation of the desired product 114 in yields of 53-72%.

The following is a complete experimental procedure which includes the preferred workup procedure and which gave the isopropenyl ketal 114 in a 72% distilled yield.

Preferred procedure for reaction with 4,4-ethylenedioxyiodocyclohexane (148) The preformed slurry of lithium diisopropenyl cuprate was treated with 17.2 g (0.064 moles) of 4,4-ethylenedioxyiodocyclohexane (148), dropwise, over a 45 minute period. The reaction mixture was then stirred at -75° for 3 days, allowed to warm slowly to room temperature, and added dropwise to 250 ml of a rapidly stirred saturated aqueous ammonium chloride solution which contained 2.0 ml of ammonium hydroxide. The resulting phases were separated, the aqueous phase saturated with solid ammonium chloride, and

extracted with seven 35-ml portions of ether. The combined ethereal phases were filtered, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled affording 6.35 g (0.046 moles - 72.1%) of the isopropenyl ketal 114 identical (nmr, ir, mass spectrum) to that described earlier, p 188.

In subsequent preparations, the isolated yield of pure isopropenyl ketal 114 ranged from 53-72%.

Methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151)

A. Following the excellent and general procedure of Rhoads and her coworkers⁹⁸, a 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 6.56 g of 57% sodium hydride-mineral oil dispersion (3.74 g - 0.154 moles active hydride). The mineral oil was removed by washing the solid with 100 ml of anhydrous benzene under a static nitrogen pressure, followed by removal of the benzene through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean hydride was covered with 110 ml of anhydrous dimethylcarbonate. The resulting suspension was cooled to 0° with an external ice bath and treated with 8.60 g (0.062 moles) of 4-isopropenylcyclohexanone (115), dropwise and with stirring, over a 15 minute period. Hydrogen evolution was immediate and

continued until all the ketone had been added, whereupon the reaction mixture was heated slowly to 50°. The resulting light brown slurry was stirred at 50° for 13 hours, warmed briefly to 65°, cooled, and treated with 9.34 g (0.156 moles) of glacial acetic acid in 75 ml of ether. The resulting white solid was broken up by the addition of sufficient water to dissolve all the visible solid, the resulting phases were separated, and the aqueous phase thoroughly extracted with ether. The combined organic phases were washed with three 15-ml portions of a saturated sodium bicarbonate solution, followed by brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving a red oil, which upon distillation gave 9.04 g (0.046 moles - 74.6%) of β -keto ester 151 as a sweet-smelling, colorless liquid: bp 66-73°; ir (film) 3345(OH enol) 29.0(CH), 1739(C=O ester), 1713(C=O ketone), 1652(C=O conj. chel.), 1618 (C=C conj. chel.), 1444, 1353, 1310, 1215(C-O), 1084, 1059 cm^{-1} nmr (CCl_4) δ 12.4(s, approx. 1H, enol), 4.70(m, 2H, $\text{CH}_2=\text{C}-$), 3.70(s, 3H, $\text{CH}_3\text{O}_2\text{C}-$), 1.73(t, 3H, $J=1.2$ Hz, CH_3-) ppm; mass spectrum (70ev) M^+ 196.

Microdistillation of a 100 mg sample gave analytically pure material.

Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3$: C, 67.32 H, 8.22

Found: C, 67.36 H, 8.34

B. Following a general carbomethoxylation procedure submitted to Organic Synthesis by A. Paul Krapcho and his

coworkers⁹⁹, a 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 11.2 g of a 57% sodium hydride-mineral oil dispersion (6.36 g - 0.265 moles active hydride). The mineral oil was removed as described in part A above, and the clean hydride was covered with 300 ml of anhydrous benzene which contained 19.1 g (0.212 moles) of dimethyl carbonate. The suspension was cooled to 0° with an external ice bath and treated with 14.6 g (0.106 moles) of 4-isopropenylcyclohexanone ($\text{C}_9\text{H}_{16}\text{O}$), dropwise and with rapid stirring, over a 20 minute period. Hydrogen evolution was again immediate and continued until all ketone $\text{C}_9\text{H}_{16}\text{O}$ had been added. Following complete addition, the cooling bath was removed and the reaction mixture heated to reflux temperature. After 14 hours at reflux temperature, the crude product mixture was cooled, treated with glacial acetic acid until the solution was acidic to litmus paper, and poured into 200 ml of ice water. The resulting phases were separated, the aqueous phase saturated with solid sodium chloride, and extracted with five 25-ml portions of ether. The combined organic phases were washed with three 15-ml portions of a saturated sodium bicarbonate solution, followed by brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled giving 8.41 g (0.430 moles - 81.1%) of

β -keto ester 151 as a colorless liquid: bp 94-104° (2.0-2.5 mm); ir and nmr identical to those described under part A above.

Methyl 2-oxo-1-(3'-oxobutyl)-5-isopropenylcyclohexane-1-carboxylate (152)

A procedure nearly identical to that described for the preparation of methyl 2-oxo-1-(3'-oxobutyl)cyclohexane-1-carboxylate (85) was followed. A precooled (0°) solution of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) in 15 ml of absolute methanol was treated, under nitrogen and with vigorous stirring, with 76 mg of sodium methoxide. The resulting suspension was rapidly stirred for 15 minutes at 0° and treated with 0.53 g (0.007 moles) of methyl vinyl ketone, dropwise and with constant stirring, over a 3 minute period. The reaction mixture was allowed to warm to room temperature over a 10 minute period and stirred at that temperature for 4.5 hours. At the end of this period, the reaction mixture gave a negative alcoholic ferric chloride test. Acidification was accomplished by the dropwise addition of glacial acetic acid and the methanol was removed under vacuum. The residue was taken up in 50 ml of ether and washed with two 5-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum giving 1.23 g of a light brown liquid; ir (film) 3490 (trace OH), 2910 (CH), 1710 (C=O), 1640 (C=C), 1435, 1245 (C-O) cm^{-1} ; nmr (CCl_4) δ 4.70 (bs, 2H, $\text{CH}_2=\text{C}-$), 3.78 (s,

3H, $\text{CH}_3\text{O}_2\text{C}$ -), 2.10 (s, 3H, CH_3 -), 1.73 (bs, 3H, CH_3C -) ppm.

Analysis of the product mixture as isolated on a 7-1/2 ft. LAC-446 column at 125° showed one major (93%) product, retention time 16.4 minutes.

The crude product was not further purified or characterized.

Attempted cyclization of methyl 2-oxo-1-(3'-oxobutyl)-5-isopropenylcyclohexane-1-carboxylate (152)

A. A procedure analogous to that employed for the cyclization of methyl 2-oxo-1-(3'-oxobutyl)cyclohexane-1-carboxylate (85) was followed. The crude ester dione 152 (1.23 g) was treated with 0.029 g of pyrrolidine in an anhydrous benzene solvent with facility for the azeotropic removal of water. The reaction mixture was heated to reflux temperature and maintained at that temperature for 155 hours, during which time only a trace of water was removed from the system. The reaction mixture was cooled, diluted with 45 ml of ether, washed with two 15-ml portions of water which contained 3.0 ml of a 10% aqueous hydrochloric acid solution, and then with 10 ml of distilled water. The aqueous washings were combined and back-extracted with ether. The combined organic phases were washed with three 10-ml portions of brine and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum left 1.09 g of a red oil, identified as starting ester dione 152.

B. A procedure nearly identical to that employed for the cyclization of methyl 2-oxo-1-(4'-oxo-2'-pentyl)cyclohexane-1-carboxylate (80) to the naphthalenecarboxylic acid ester 87 was followed. To a solution prepared by dissolving 2.70 g (0.050 moles) of sodium methoxide in 50 ml of anhydrous methanol under nitrogen at 0° was added 1.51 g (0.006 moles) of ester dione 152, dropwise and with rapid stirring, over a 3 minute period. Following complete addition of the dione, the reaction mixture was allowed to warm to room temperature and stirred at that temperature for 6 hours. Neutralization of the basic reaction media was accomplished by the dropwise addition of glacial acetic acid, followed by removal of the methanol under vacuum. The red residue was taken up in 50 ml of ether, washed with 10 ml of water, three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum affording 1.33 g of a red liquid. Partial purification was accomplished by evaporative distillation. The material thus purified was identified as having suffered loss of the angular carbomethoxy group, see text.

Methyl 2-oxo-1-(4'-oxo-2'-pentyl)-5-isopropenylcyclohexane-1-carboxylate (157)

A procedure identical to that described for the preparation of methyl 2-oxo-1-(3'-oxobutyl)-5-isopropenylcyclohexane-1-carboxylate (152) was followed. To a precooled (0°) solution

of 0.20 g (0.004 moles) of sodium methoxide in 25 ml of anhydrous methanol was added, with stirring and under nitrogen, 1.00 g (0.005 moles) of methyl 2-oxo-5-isopropenylcyclohexane-carboxylate (151). The reaction mixture was stirred for 15 minutes at 0° and treated with 1.10 g (0.013 moles) of trans-3-penten-2-one, dropwise and with rapid stirring, over a 10 minute period. Following complete addition of the unsaturated ketone, the reaction mixture was stirred at room temperature. Analysis of aliquots (alcoholic ferric chloride test) removed at regular intervals showed the alkylation reaction to be partially complete after 43 hours and totally complete after 161 hours. Neutralization of the reaction mixture was accomplished by the slow addition of glacial acetic acid. Work-up in a manner exactly analogous to that described above gave 0.28 g of light brown liquid: ir (film) 3490 (trace OH), 2913 (CH), 1711 (C=O), 1640 (C=C), 1444, 1436, 1244 (C-O) cm^{-1} ; nmr (CCl_4) δ 4.70 (bs, 2H, $\text{CH}_2=\text{C}-$), 3.78 (s, 3H, $\text{CH}_3\text{O}_2\text{C}-$), 2.10 (s, 3H, $\text{CH}_3\text{CO}-$), 1.74 (bs, 3H, $\text{CH}_3\text{C}-$), 0.97 (d, 3H, $J=6$ Hz, $\text{CH}_3\text{CH}-$) ppm.

The product was not further purified, but analysis by vapor phase chromatography as described above indicated the material to be greater than 90% pure.

Attempted cyclization of methyl 2-oxo-1-(4'-oxo-2'-pentyl)-5-isopropenylcyclohexane-1-carboxylate (157)

In analogy with the attempted cyclization of ester dione 152, treatment of a benzene solution which contained 1.00 g

of crude ester dione 157 with 0.025 g of pyrrolidine, at reflux temperature for 134 hours, gave no evidence of cyclization.

Treatment of the dione 157 recovered from the above treatment with a 1.0M sodium methoxide in methanol solution gave, after an extended reaction period, a product which also showed complete loss of the angular carbomethoxy group, see text.

4-Iodo-3,5-dimethylisoxazole (167)

The procedure of Kochetkov et al.¹⁰⁴ was followed. A 250-ml, three-necked, Morton flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was briefly flushed with nitrogen and charged with a suspension of 37.3 g (0.148 moles) of iodine in 31.3 g (0.323 moles) of 3,5-dimethylisoxazole (166) (Aldrich Chemical Co.). The reaction mixture was heated with a boiling water bath and treated with 13.6 ml of concentrated nitric acid, dropwise and with rapid stirring, over a 45 minute period. Following complete addition of the nitric acid, the reaction mixture was stirred for 30 minutes at 100°, cooled, and filtered through a sintered glass funnel. The resulting red solid was washed on the funnel with three 25-ml portions of a 10% sodium hydroxide solution and dried under vacuum for 12 hours. The crude product was sublimed under high vacuum (0.05 mm) at 43° to yield 46.1 g (0.206 moles - 64.4%) of the iodoisoxazole 167 as a brown powder: mp 52.5-54.5°;

[lit.¹⁰⁴ mp 52.5-54.0]; nmr (CCl₄) δ 2.42(s, 3H, -CH₃), 2.19(s, 3H, CH₃-) ppm.

4-(1'-hydroxyethyl)-3,5-dimethylisoxazole (169)

Preparation of the Grignard derivative of 4-iodo-3,5-dimethylisoxazole (167) The procedure of Cogoli and Grunanger¹⁰⁶ was followed. A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, reflux condenser, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a suspension of 9.75 g (0.406 moles) of dry, activated magnesium in 5.39 g (0.049 moles) of anhydrous ethyl bromide. To this was added 150 ml of a 1:1 tetrahydrofuran-ether solvent. The reaction mixture was then treated with a solution which contained 30.0 g (0.135 moles) of 4-iodo-3,5-dimethylisoxazole (167), 25.1 g (0.229 moles) of anhydrous ethyl bromide, and 50.0 ml of tetrahydrofuran. The addition was carried out dropwise, with constant stirring, over a 45 minute period. Following complete addition of the iodoisoxazole-ethyl bromide mixture, the reaction mixture was warmed to an internal temperature of 40° and maintained at that temperature for 2 hours. After this period, all the magnesium metal had been consumed and the solution presumably contained 0.135 moles of isoxazole Grignard and 0.278 moles of ethyl Grignard.

Reaction of the Grignard of 4-iodo-3,5-dimethylisoxazole with acetaldehyde To the preformed Grignard solution prepared as described above was added 26.8 g (0.610 moles) of acetaldehyde, dropwise, with rapid stirring. The acetaldehyde was added at a rate sufficient to maintain the solvent at reflux temperature. Following complete addition of the acetaldehyde, the crude product mixture was stirred at room temperature for 90 minutes, poured onto 200 g of ice, and acidified by the dropwise addition of a 10% hydrochloric acid solution. The aqueous phase was separated from the organic phase, saturated with solid sodium chloride, and extracted with six 35-ml portions of ether. The combined organic phases were washed with three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 13.8 g (0.098 moles - 72.5%) of 4-(1'-hydroxyethyl)-3,5-dimethylisoxazole (169) as a yellow liquid: nmr (CCl_4) δ 4.73 (q, 1H, $J=7$ Hz, $-\text{CHOH}$), 2.30 (s, 3H, $-\text{CH}_3$), 2.18 (s, 3H, $-\text{CH}_3$), 1.38 (d, 3H, $J=7$ Hz, CH_3CHOH) ppm; mass spectrum (70ev) M^+ 141.

4-(1'-Chloroethyl)-3,5-dimethylisoxazole (165)

A. Attempted preparation according to the procedure used for chloromethylation of 3,5-dimethylisoxazole developed by Kochetkov et al.¹⁰⁸

A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, gas dispersion tube, mechanical stirrer, reflux condenser, and thermometer. The apparatus was briefly flushed with nitrogen and charged with a solution of 20.0 g (0.206 moles) of 3,5-dimethylisoxazole, 11.9 g (0.270 moles) of acetaldehyde, and 10.0 g (0.074 moles) of anhydrous zinc chloride dissolved in 150 ml of anhydrous methylene chloride. The reaction mixture was vigorously stirred and a stream of hydrogen chloride gas was bubbled into the reaction mixture, thereby warming the solution to an internal temperature of 50-55°. The hydrogen chloride gas was passed into the reaction mixture for 2 hours, and the resulting black solution was heated to reflux temperature. Following a 3 hour period at reflux temperature, the crude reaction mixture was cooled and poured onto 150 g of ice. The phases were separated, the aqueous phase was extracted with six 35-ml portions of ether, and the combined ethereal phases were washed with three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to leave a red liquid, identified as starting 3,5-dimethylisoxazole (166) (nmr, ir, mass spectrum).

B. According to a procedure described by Kano and his coworkers¹⁰⁷ for a similar system, a 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried,

filled with prepurified nitrogen, and charged with a solution of 13.8 g (0.098 moles) of 4-(1'-hydroxyethyl)-3,5-dimethylisoxazole (169) dissolved in 500 ml of anhydrous ether. The reaction mixture was cooled to an internal temperature of 3° with an external ice bath and treated with 35.0 g (0.294 moles) of thionyl chloride, dropwise, with rapid stirring, over a 2 hour period. Following complete addition of the thionyl chloride, the reaction mixture was heated slowly to reflux temperature and maintained at that temperature for 60 minutes. The crude product mixture was then cooled, and concentrated under vacuum giving 19.4 g (0.065 moles - 66.8%) of the product 165 as a colorless liquid: bp 65-66° (0.25-0.1 mm); nmr (CCl₄) δ 5.07 (q, 1H, J=7 Hz, CHCl), 2.37 (s, 3H, CH₃-), 2.27 (s, 3H, CH₃-), 1.77 (d, 3H, J=7 Hz, CH₃CH-) ppm; high resolution mass spectrum M⁺ obs: 159.0451, 161.0421; calcd: 159.0451, 161.0421.

Attempted alkylation of methyl 2-oxocyclohexanecarboxylate (84) with 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165)

A. A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 0.756 g of a 57% sodium hydride-mineral oil dispersion. The sodium hydride was covered with 50 ml of anhydrous benzene, allowed to stir for 5 minutes, and the benzene removed through an ultra-fine grade sintered glass gas

dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 5. ml of a 1:1 benzene-N,N-dimethylformamide solvent¹⁰¹ and treated with 2.80 g (0.018 moles) of β -keto ester 84, dropwise, over a 10 minute period. During the addition of the β -keto ester, rapid hydrogen evolution occurred. Following complete addition of the β -keto ester, the hydrogen evolution stopped and the reaction mixture was treated with 2.88 g (0.018 moles) of chloroisoxazole 165, dropwise and with stirring, over a 10 minute period. After 16 hours at room temperature, the reaction mixture gave a positive alcoholic ferric chloride test and was warmed to reflux temperature. Following 12 hours at reflux temperature, a white solid (NaCl) had formed and a positive alcoholic ferric chloride test was still obtained.

The reaction mixture was then cooled, acidified by the addition of a few drops of glacial acetic acid, and taken up in 100 ml of ether. The ethereal solution was washed with 15 ml of water, two 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum gave a colorless liquid, which upon examination by thin layer chromatography was shown to contain β -keto ester 84, chloroisoxazole 165, and a new compound, 4-vinyl-3,5-dimethylisoxazole (171). The vinyl isoxazole 171 was identified by comparison with the material prepared as described below.

B. A 100-ml, three-necked, round-bottomed flask equipped exactly as described above was charged with a solution of 3.00 g (0.014 moles) of methyl 2-pyrrolidino-1-cyclohexenecarboxylate (170) dissolved in 50 ml of anhydrous methanol. To this solution was added 2.28 g (0.015 moles) of 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165), dropwise and with rapid stirring, over a 15 minute period. The reaction mixture was slowly warmed to reflux temperature and maintained at that temperature for 168 hours. At the end of this period, the crude reaction mixture afforded, after acidic hydrolysis, a positive alcoholic ferric chloride test. The reaction mixture was hydrolyzed by the addition of 10 ml of water, followed by heating at reflux temperature for 30 minutes. Following hydrolysis, the reaction mixture was cooled and concentrated under vacuum. The residue was taken up in 100 ml of ether, washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum followed by fractionation of the residue gave two major products, one of which was shown to be the starting β -keto ester 84, resulting from hydrolysis of the enamine 170. The second product was identified as 4-(1'-methoxyethyl)-3,5-dimethylisoxazole (172) by comparison with the material prepared as described below.

C. Repetition of the preparation attempted in part B above using an anhydrous dioxane solvent gave β -keto ester 84 and 4-vinyl-3,5-dimethylisoxazole (171) as the major products.

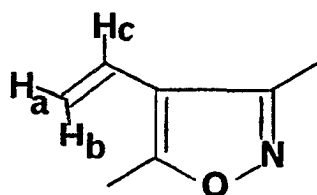
Methyl 2-pyrrolidino-1-cyclohexenecarboxylate (170)

The general procedure for the preparation of enamines as described by Stork and his coworkers¹⁰⁹ was followed. A 500-ml, one-necked, round-bottomed flask was fitted with a Dean-Stark water trap, gas-inlet tube, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 66.7 g (0.427 moles) of methyl 2-oxocyclohexanecarboxylate (84) dissolved in 250 ml of anhydrous benzene. To this solution was added 45.5 g (0.641 moles) of pyrrolidine via a flame-dried pipet. The reaction mixture was heated to reflux temperature and held at that temperature for 24 hours, during which time 7.6 ml of water were removed from the system. The reaction mixture was cooled, the Dean-Stark trap replaced by a Soxhlet extractor containing 4A molecular sieves in the thimble. The benzene solution was allowed to percolate through the sieves for 6 hours, cooled, diluted with 250 ml of ether, and concentrated under vacuum. This gave a slightly yellow liquid which readily solidified upon cooling. The product was recrystallized twice from an ethyl acetate-hexane solvent system to afford 71.9 g (0.340 moles - 80.0%) of the β -keto ester enamine 170 as a yellow powder; mp 68-70° (dec); ir (KBr) 2953(CH), 1685(C=C), 1561, 1438, 1220(C-O) 1171 cm^{-1} ; nmr (CCl_4) δ 3.70(s, 3H, $\text{CH}_3\text{O}_2\text{C}$ -) ppm.

The enamine gave a negative alcoholic ferric chloride test until a trace of water was added.

4-Vinyl-3,5-dimethylisoxazole (171)

According to the procedure reported by Finzi, Caramella, and Gruenanger¹⁴⁴ for a similar system, 5.00 g (0.044 moles) of 4-(1'-hydroxyethyl)-3,5-dimethylisoxazole (169) was distilled slowly, under reduced pressure, from 8.00 g of potassium bisulfite. The fraction boiling from 94-114° (100 mm) was collected and refractionated giving 3.32 g (0.027 moles - 61.5%) of 4-vinyl-3,5-dimethylisoxazole (171) as a colorless liquid: bp 112-114° (100 mm); nmr (CCl₄) δ 6.35 (dd, 1H, $J_{bc}=18$ Hz, $J_{ac}=11$ Hz, H_c), 5.30 (dd, 1H, $J_{bc}=8$ Hz $J_{ab}=2$ Hz, H_b), 5.17 (dd, 1H, $J_{ac}=11$ Hz $J_{ab}=2$ Hz, H_a), 2.30 (s, 3H, $-CH_3$) 2.18 (s, 3H, $-CH_3$) ppm; ir (film) 1654, 1455, 1438, 1409, 1400, 1267, 1205 cm^{-1} ; high resolution mass spectrum M^+ obs: 123.0676, calcd: 123.0684.

4-(1'-methoxyethyl)-3,5-dimethylisoxazole (172)

A 100-ml, one-necked, round-bottomed flask was fitted with a magnetic stirrer and a reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 3.32 g (0.027 moles) of 4-vinyl-3,5-

dimethylisoxazole (171) dissolved in 75 ml of methanol. To this solution was added 1.5 ml of concentrated hydrochloric acid. The reaction mixture warmed noticeably and was stirred at room temperature for 24 hours. Following this reaction period, the methanol was removed under vacuum and the residue distilled giving 3.14 g (0.020 moles - 65-68°) of the methoxyethylisoxazole 172 as colorless liquid: bp 65-68 (0.5 mm); nmr (CCl₄) δ 4.23 (q, 1H, J=7.5 Hz, -CHOCH₃), 3.70 (s, 3H, -OCH₃), 2.30 (s, 3H, -CH₃), 2.17 (s, 3H, -CH₃), 1.35 (d, 3H, J=7.5 Hz, -CHCH₃) ppm; high resolution mass spectrum M⁺ obs: 155.0945; calcd: 155.0946.

Attempted alkylation of methyl 2-pyrrolidino-1-cyclohexene-carboxylate (170) with trans-3-penten-2-one

A. According to the general procedure for the alkylation of enamines with α,β-unsaturated ketones developed by Stork et al.¹⁰⁹, a 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 3.13 g (0.015 moles) of methyl 2-pyrrolidino-1-cyclohexenecarboxylate (170) dissolved in 50 ml of anhydrous benzene. To this solution was added, dropwise and with stirring, 1.51 g (0.018 moles) of trans-3-penten-2-one over a 4 minute period. The reaction mixture was heated to reflux temperature and maintained at that temperature for 24 hours. The mixture was then treated

with 25 ml of a buffer solution (6.25 g of sodium acetate, 12.5 ml of water, 12.5 ml of acetic acid) and held at reflux temperature for an additional 4 hours. The hydrolyzed reaction mixture was cooled and the phases were separated. The aqueous phase was extracted with three 25-ml portions of ether and the combined organic phases were washed with two 10-ml portions of a 10% hydrochloric acid solution, three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum gave 2.30 g of a cloudy liquid, identified as starting β -keto ester 84 resulting from hydrolysis of the unreacted enamine 170 .

B. Repetition of the above experiment in an anhydrous formamide solvent (same quantities) keeping the reaction mixture at 95° for 10 hours, followed by addition of the buffer solution and workup as described in part A above gave 2.09 g of the β -keto ester 84 .

Successful alkylation of methyl 2-pyrrolidino-1-cyclohexene-carboxylate (170) with trans-3-penten-2-one

A. A 100-ml, three-necked, round-bottomed flask equipped as described in part A of the previous section was charged with a solution of 3.00 g (0.014 moles) of methyl 2-pyrrolidino-1-cyclohexenecarboxylate (170) dissolved in 50 ml of anhydrous dioxane. To this solution was added 2.42 g (0.028 moles) of trans-3-penten-2-one, dropwise and with rapid stirring, over

a 10 minute period. The resulting reaction mixture was stirred rapidly at 50° for 210 hours, during which time the solution turned dark brown. Treatment of the crude product mixture with 25 ml of buffer solution (6.25 g of sodium acetate, 12.5 ml of water, 12.5 ml of glacial acetic acid) followed by workup exactly as described above gave 3.63 g of a red oil. Purification of the oil was accomplished by column chromatography on silica gel. Elution with 10% ethyl acetate-hexane gave 2.31 g (0.011 moles - 78.5%) of methyl 1,3,4,5,6,7-hexahydro-5-methyl-7-oxo-4a(2H)-naphthalenone (87) as a white powder: mp 58.5-60.5°; ir and nmr spectra identical to those described earlier.

B. Repetition of the above experiment in an anhydrous methanol solvent (same amounts) gave, after 72 hours at reflux temperature, an 89% yield of naphthalenone 87. The purified product had mp 58-60.5°; ir and nmr identical to those described above.

Methyl 2-pyrrolidino-5-isopropenyl-1-cyclohexanecarboxylate

(173)

According to the general procedure of Stork et al.,¹⁰⁹ a 250-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, Dean-Stark water trap, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 5.61 g (0.029 moles) of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) dissolved in 150 ml of anhydrous

benzene. To this was added 3.03 g (0.043 moles) of pyrrolidine. The reaction mixture was then heated to reflux temperature and maintained at that temperature for 12 hours, during which time 0.35 ml of water were removed from the system. The Dean-Stark trap was replaced by a Soxhlet extractor which contained 4A molecular sieves in the thimble. The benzene solution was allowed to percolate through the sieves for 12 hours, cooled, diluted with 100 ml of ether, and concentrated under vacuum. Complete removal of the solvent under high vacuum left an oil which solidified to a red paste. The nmr and mass spectral data indicated the isolated material to be a mixture of β -keto ester 151 and the desired enamine 173. This mixture was employed in the following experiments. Mass spectrum (70ev) m/e (rel intensity) 196(94), 249(100).

Attempted alkylation of methyl 2-pyrrolidino-5-isopropenyl-1-cyclohexenecarboxylate (173) with trans-3-penten-2-one

A. A procedure identical to that employed for the successful alkylation of methyl 2-pyrrolidino-1-cyclohexenecarboxylate (170) was followed. A 50-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 3.00 g of the mixture which contained β -keto ester 151 and methyl 2-pyrrolidino-5-isopropenyl-1-cyclohexenecarboxylate (173)

dissolved in 25 ml of anhydrous dioxane. To this was added 2.02 g (0.024 moles) of trans-3-penten-2-one, dropwise and with stirring, over a 10 minute period. The resulting reaction mixture was warmed to 55° and maintained at that temperature for 234 hours, during which time the reaction mixture turned completely black. Treatment of the reaction mixture with 25 ml of buffer solution (see above) followed by heating for 1 additional hour and workup gave 3.11 g of a brown liquid, identified as β -keto ester 151 resulting from hydrolysis of the unreacted enamine.

B. Repetition of the above experiment in an anhydrous methanol solvent keeping the reaction mixture at room temperature for 192 hours gave, after addition of the buffer solution and workup recovered β -keto ester 151 as the only product.

4-Hydroxy-2-pentanone (174)

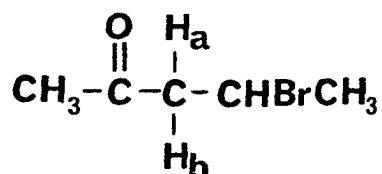
The procedure of Wilds and Djerassi⁶³ was modified as follows. A 5000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, high-speed stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a mixture of 800 g (13.8 moles) of reagent grade acetone, 844 ml of ether, and 400 ml of a 12% (48 g) aqueous sodium hydroxide solution saturated with sodium chloride. The solution was cooled to 0° with an external ice bath, and a pre-cooled (5°) mixture of 600 g (13.6 moles) of acetaldehyde in

1012 ml of reagent grade acetone was added, dropwise and with stirring, over a 5 hour period. During the addition, the internal temperature of the reaction mixture was held at 5-12°. Following complete addition, the reaction mixture was stirred for 60 minutes at 5° and then allowed to warm to room temperature over a 4 hour period. The resulting yellow liquid was transferred to a separatory funnel and the phases separated. The aqueous phase was extracted with seven 50-ml portions of ether and the combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. (The ethereal phase was not washed with water due to the solubility of the product). The solvent was removed at slightly reduced pressure (125 mm) and the residue distilled affording 242.4 g (2.38 moles - 33.1%) of the hydroxyketone 174 as a slightly yellow liquid: bp 50-85° (19 mm); [lit.⁶³ bp 64-75° (16 mm)]; ir (film) 3455(OH), 3000(CH), 1710(C=O) cm^{-1} ; nmr (CCl_4) δ 4.15 (m, 1H, -CHOH), 4.02 (s, 1H, -OH), 2.57 (d, 2H, J=6 Hz, -CH₂-), 2.17 (s, 3H, CH₃CO-), 1.17 (d, 3H, J=7 Hz, CH₃CH-) ppm.

4-Bromo-2-pentanone (175)

According to the procedure of Wohl and Maag¹¹¹, a 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 22.7 g (0.222 moles) of 4-hydroxy-2-pentanone (174) dissolved in

600 ml of anhydrous ether. The reaction mixture was cooled to an internal temperature of 3° with an external ice bath and treated with 19.4 g (0.717 moles) of phosphorous tribromide, dropwise, with good stirring. The reaction mixture rapidly turned black, was allowed to warm to room temperature, and concentrated under vacuum. The resulting crude product was distilled without delay to afford the bromoketone 175 as a cloudy liquid. The yield was 24.5 g (0.147 moles - 66.5%): bp 60-63° (18 mm); [lit.¹¹¹ bp 50-55° (15 mm)]; nmr (CCl₄) δ 4.43(m, 1H, -CHBr), 3.05(d, 1H, J=3.5 Hz, H_a or b), 2.96(d, 1H, J=3.5 Hz, H_a or b), 2.12(s, 3H, CH₃CO-), 1.71(d, 3H, J=7 Hz, CH₃CHBR) ppm.



2,4-Pentandiol (176)

A. A 250-ml capacity pressure bottle was briefly flushed with nitrogen and charged with a solution of 10.0 g (0.100 moles) of 2,4-pentandione (177) dissolved in 125 ml of anhydrous methanol which contained 1.00 g of a 5% rhodium on alumina catalyst (Engelhard Industries). The reaction mixture was shaken under a constant pressure of hydrogen, which measured 60.0 psi at the bottle, for 48 hours. During this period, a rapid uptake of hydrogen was observed. The crude

product mixture was filtered through Celite to remove the catalyst and concentrated under vacuum. The residue which resulted was distilled directly to afford 10.1 g (0.098 moles - 98.1%) of the diol $\overset{\text{176}}{\text{C}_2\text{C}_2}$ as a colorless liquid: bp 72-74° (3.0 mm); [lit.¹⁴⁵ bp 73° (3.0 mm) meso, 74° (3.0 mm) racemic]; nmr (CCl₄) δ 4.79(bs, 2H, -OH, exchange with D₂O), 3.92(m, 2H, -CHOH), 1.47(bt, 2H, J=7 Hz, -CH₂-), 1.12(d, 6H, J=7 Hz, -CH₃) ppm.

The material isolated above was identical to that described by Pritchard and Vollmer¹⁴⁵ as the racemic modification of 2,4-pentanediol (nmr).

B. A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a suspension of 49.0 g (1.29 moles) of sodium borohydride in 500 ml of isopropyl alcohol. The reaction mixture was cooled to 0° with an external ice bath and treated with 65.8 g (0.645 moles) of 4-hydroxy-2-pentanone ($\overset{\text{174}}{\text{C}_2\text{C}_2}$). The addition was carried out dropwise, with constant stirring, over a 45 minute period. Following complete addition of the hydroxyketone $\overset{\text{174}}{\text{C}_2\text{C}_2}$, the cooling bath was removed and the reaction mixture allowed to stir at room temperature for 4 hours. The crude product mixture was then acidified by the dropwise addition, with stirring, of a 10% hydrochloric acid solution. The resulting solution was concentrated under vacuum and the aqueous residue extracted with six 35-ml portions of

ether. The combined ethereal extracts were washed with three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 60.1 g (0.577 moles - 89.5%) of the diol 176 as a colorless liquid: bp 160-180° (16 mm); [lit.¹⁴⁵ 53° (3.0 mm) meso, 54° (3.0 mm) racemic]; nmr (CCl₄) δ 4.50 (bs, 2H, -OH, exchange with D₂O), 4.11 (m, 2H, -CHOH), 1.67 (m, 2H, -CH₂), 1.18 (d, 3H, J=7 Hz, -CH₃), 1.12 (d, 3H, J=7 Hz, -CH₃) ppm.

The material isolated above appeared to be a mixture of the meso and racemic diols as described by Pritchard and Vollmer¹⁴⁵. The mixture was not separated and the difference in the isomer ratio obtained by the two procedures, although of interest, was not investigated.

4-Chloro-2-pentanol (178)

The procedure of Yonemoto¹¹² was modified slightly. A 150-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, evacuated, flame-dried, and filled with prepurified nitrogen. The gas-inlet tube was removed and the flask was fitted with an atmospheric distillation head. The apparatus was briefly flushed with nitrogen again and charged with 39.0 g (0.375 moles) of 2,4-pentanediol (176) and 80.0 ml of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 6 hours and slowly distilled. The distillate with a boiling range of 103-107° was collected,

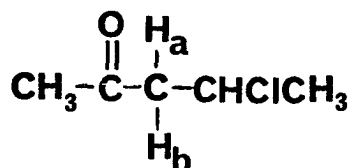
taken up in 100 ml of ether, and washed with three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the yellow residue distilled affording 16.7 g (0.157 moles - 41.9%) of the chloroalcohol 178 as a colorless liquid: bp 67-68° (13 mm); [lit.¹¹² bp 93-95° (60 mm)]; nmr (CCl₄) δ 4.04 (m, 2H, -CH₂OH, -CH₂Cl), 3.65 (bs, 1H, -OH, exchange with D₂O), 1.73 (m, 2H, -CH₂-), 1.51 (d, 3H, J=6.5 Hz, CH₃CHCl), 1.19 (d, 3H, J=.65 Hz, CH₃CHOH) ppm.

4-Chloro-2-pentanol (179)

A. Oxidation of 4-chloro-2-pentanol (178) was accomplished using the procedure described earlier under the preparation of methyl 4-oxocyclohexanecarboxylate (97).

A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was briefly flushed with nitrogen and charged with a solution of 6.45 g (0.053 moles) of 4-chloro-2-pentanol (178) dissolved in 150 ml of ether. The ethereal solution was cooled to an internal temperature of 3° with an external ice bath and treated with a precooled (0°) solution of 10.3 g (0.111 moles) of concentrated sulfuric acid, 7.86 g (0.026 moles) of sodium dichromate dihydrate dissolved in 50 ml of water. The chromic acid solution was added dropwise, with constant stirring, over a 3 hour period. The reaction mixture was then allowed to warm

to room temperature and stirred at that temperature 4 hours. The resulting phases were separated, the aqueous phase saturated with solid sodium chloride and extracted with six 15-ml portions of ether. The combined ethereal phases were washed with three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum gave a colorless liquid, which upon distillation gave 5.90 g (0.049 moles - 93.0%) of the chloroketone 179 as a colorless liquid: bp 66-69° (15 mm); [lit.¹¹¹ bp 159-160]. The product was uncontaminated with trans-3-penten-2-one; ir (film) 2994 (CH), 1730 (C=O), 1374, 1122, 1048 cm^{-1} ; nmr (CCl_4) δ 4.41 (m, 1H, $-\text{CHCl}$), 2.89 (d, 1H, $J=2$ Hz, H_a or b), 2.79 (d, 1H, $J=2$ Hz, H_a or b), 2.12 (s, 3H, $\text{CH}_3\text{CO}-$), 1.50 (d, 3H, $J=7$ Hz, CH_3CHCl) ppm.



B. Analogous to the preparation of 4-bromo-2-pentanone (175), a 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 10.0 g (0.098 moles) of 4-hydroxy-2-pentanone (174) dissolved in

25.0 ml of anhydrous ether. The reaction mixture was cooled to 0° with an external ice bath and treated with 4.36 g (0.317 moles) of phosphorous trichloride, dropwise, with rapid stirring, over a 10 minute period. The resulting blood red slurry was rapidly stirred at 0° for an additional 10 minutes, concentrated under vacuum, and the residue distilled without delay giving 6.99 g (0.057 moles - 58.1%) of the chloroketone 179 as a colorless liquid: bp 45-48 (13 mm); [lit.¹¹¹ bp 159-160]. The product was contaminated with approximately 25% (nmr) of trans-3-penten-2-one, which resulted from dehydration of the starting hydroxy ketone 174 or dehydrohalogenation of the product chloro ketone 179 .

C. A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 15.0 g (0.147 moles) of 4-hydroxy-2-pentanone (174) dissolved in 350 ml of anhydrous ether. The reaction mixture was cooled to an internal temperature of 3° with an external ice bath and treated with 44.4 g (0.441 moles) of thionyl chloride, dropwise, with rapid stirring, over a 45 minute period. Following complete addition of the thionyl chloride, the cooling bath was removed and the reaction mixture warmed slowly to reflux temperature. After 90 minutes at reflux temperature, the black product mixture

was cooled, concentrated under vacuum, and the residue distilled giving 5.80 g (0.048 moles) of the chloroketone 179 as a colorless liquid: bp 66-68° (16 mm); [lit.¹¹¹ bp 159-160]. The product was contaminated with 13-15% (nmr) of trans-3-penten-2-one.

Attempted alkylation of methyl 2-pyrrolidino-1-cyclohexene-carboxylate (170) with 4-chloro- and 4-bromo-2-pentanone (179 and 175)

A. According to the general procedure described by Stork et al.,¹⁰⁹ for the alkylation of enamines with alkyl halides, a 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 3.00 g (0.014 moles) of methyl 2-pyrrolidino-1-cyclohexenecarboxylate (170) dissolved in 35 ml of anhydrous methanol. To this was added, dropwise and with stirring, 3.44 g (0.028 moles) of 4-chloro-2-pentanone (179) dissolved in 15 ml of anhydrous methanol. The reaction mixture was then heated to reflux temperature and maintained at that temperature for 14 days. At the end of this period, the reaction mixture gave a strong positive alcoholic ferric chloride test. Addition of 15 ml of buffer solution (6.25 g of sodium acetate, 12.5 ml of water, 12.5 ml of glacial acetic acid) was followed by removal of the methanol under vacuum. The residue was

taken up in 100 ml of ether, the water phase was separated, and the ethereal phase washed with three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum left 5.11 g of a yellow liquid, which upon distillation gave β -keto ester 84 (bp 47-50 at 0.025 mm) as the sole isolable product. A vapor phase chromatographic analysis of the crude product mixture prior to distillation showed the chloro ketone 179 to be present in > 97% of the theoretical amount.

B. Repetition of the above experiment with 4-bromo-2-pentanone (175) in anhydrous methanol gave, after 10 days at reflux temperatures, β -keto ester 84 as the sole isolable product.

The alkylation was attempted with both 4-chloro- and 4-bromo-2-pentanone using anhydrous benzene, formamide, and dioxane as solvents. In each case, no more than a trace of alkylated product was observed even after extended reaction periods.

Attempted alkylation of methyl 2-oxocyclohexanecarboxylate (84)
with 4-bromo-2-pentanone (175)

A 150-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged

with 0.756 g of a 57% sodium hydride-mineral oil dispersion (0.431 g - 0.018 moles active hydride). The mineral oil was removed by washing the hydride with 50 ml of anhydrous benzene under a static nitrogen pressure and removing the benzene through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 50 ml of anhydrous dioxane and treated with 2.80 g (0.018 moles) of methyl 2-oxocyclohexanecarboxylate (84), dropwise and with vigorous stirring, over a 5 minute period. Hydrogen evolution was noticed immediately and continued until all β -keto ester 84 had been added. The resulting homogeneous solution was stirred at room temperature for 15 minutes and treated with 4.00 g (0.024 moles) of 4-bromo-2-pentanone (175), dropwise and with good stirring, over a 15 minute period. The resulting solution was stirred at room temperature for 41 hours, during which time a white solid precipitated (NaBr). The suspension was filtered and diluted with 150 ml of ether. The ethereal solution was cautiously acidified by slow addition of a few drops of glacial acetic acid, washed with 10 ml of water, three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the dried solvent under vacuum followed by careful fractionation gave 3.04 g of trans-3-penten-2-one resulting from dehydrobromination of the 4-bromo-2-pentanone (175) as well as 1.94 g of β -keto ester 84.

B. Repetition of the above experiment using an anhydrous dioxane solvent held at reflux temperature for 120 hours gave identical results as did the use of a tetrahydrofuran solvent stirred at room temperature for 336 hours.

Successful alkylation of methyl 2-oxocyclohexanecarboxylate (84)
with 4-chloro-2-pentanone (179)

A 100-ml, three-necked, round-bottomed flask was equipped as described in part A of the previous section and charged with 0.756 g of a 57% sodium hydride-mineral oil dispersion (0.431 g - 0.018 moles active hydride). The mineral oil was removed exactly as described in part A above and the clean sodium hydride was covered with 50 ml of anhydrous dioxane. To the resulting suspension was added 2.80 g (0.018 moles) of methyl 2-oxocyclohexanecarboxylate (84), dropwise, with stirring, over a 5 minute period. Hydrogen evolution was noticed immediately and continued until all the β -keto ester had been added. The resulting homogeneous solution was treated with 2.17 g (0.018 moles) of 4-chloro-2-pentanone (179), dropwise and with vigorous stirring. The reaction mixture was stirred at room temperature for 84 hours, at which time an aliquot gave a negative alcoholic ferric chloride test. The remainder of the solution was stirred at room temperature for an additional 80 hours and diluted with 50 ml of water. The reaction mixture was acidified by the dropwise addition of glacial acetic acid and extracted with five 20 ml portions of ether. The combined

ethereal extracts were washed with three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow liquid, which upon distillation gave 2.76 g (0.011 moles - 64.1%) of methyl 2-oxo-1-(4'-oxo-2'-pentyl)cyclohexane-1-carboxylate (80); bp 130-140° (0.5 mm); ir and nmr identical to those described earlier.

Successful alkylation of methyl 2-oxo-5-isopropenylcyclohexane-carboxylate (151) with 4-chloro-2-pentanone (179)

A 50-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 0.378 g of a 57% sodium hydride-mineral oil dispersion (0.215 g - 0.009 moles active hydride). The mineral oil was removed by washing the hydride with 25 ml of anhydrous benzene and removing the benzene through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 25 ml of anhydrous dioxane and to this suspension was added 1.77 g (0.009 moles) of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151), dropwise, with stirring, over a 2 minute period. Hydrogen evolution was noted at once and continued until all the ester 151 had been added. The homogeneous solution which resulted was stirred for 5 minutes at room temperature and treated with 1.13 g (0.009

moles) of 4-chloro-2-pentanone ($\overset{179}{\text{}}_{\text{}}_{\text{}}$), dropwise and with vigorous stirring. The reaction mixture was stirred at room temperature for 141 hours, after which time the reaction mixture gave a negative alcoholic ferric chloride test. The solution was neutralized by the addition of a few drops of glacial acetic acid and diluted with 25 ml of water. The acidic solution was extracted with three 25-ml portions of ether, the combined ethereal extracts washed with two 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The dried solvent was removed under vacuum affording 1.44 g of a slightly yellow liquid, identified as methyl 2-oxo-5-isopropenyl-1-(4'-oxo-2'-pentyl)cyclohexane-1-carboxylate ($\overset{157}{\text{}}_{\text{}}_{\text{}}$), identical with that prepared earlier by the Michael addition of trans-3-penten-2-one to β -keto ester $\overset{151}{\text{}}_{\text{}}_{\text{}}$ (nmr, ir, mass spectrum).

Attempted annulation of 2-methylcyclohexanone with 4-(1'-chloroethyl)-3,5-dimethylisoxazole ($\overset{165}{\text{}}_{\text{}}_{\text{}}$)

A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 1.50 g of a 57% sodium hydride-mineral oil dispersion (0.855 g -0.036 moles active hydride). The sodium hydride was covered with 50 ml of anhydrous pentane, stirred briefly, and the pentane removed through an ultra-fine grade sintered

glass gas dispersion tube attached to a water aspirator. The above operations were all conducted under a static nitrogen pressure. The clean sodium hydride was then covered with 50 ml of anhydrous dioxane, to which was added 4.00 g (0.036 moles) of 2-methylcyclohexanone (181). The resulting suspension was warmed slowly to reflux temperature, whereupon hydrogen evolution began. The reaction mixture was maintained at reflux temperature, with constant stirring, for 4 hours, during which time the hydrogen evolution ceased and the solution became homogeneous. After the reaction mixture was cooled to room temperature, 5.70 g (0.036 moles) of 4-(1'-chloroethyl)-3,5-dimethylisoxazole (165) were added, dropwise and with vigorous stirring. The reaction mixture was then heated to reflux temperature again and held at that temperature for 40 hours, during which time a white solid (NaCl) precipitated. Following this period, the reaction mixture was cooled, filtered, and acidified by the dropwise addition of glacial acetic acid. The resulting solution was diluted with 250 ml of ether and washed with 15 ml of water, two 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum left a yellow oil, which upon fractionation gave 3.49 g of 2-methylcyclohexanone (181) and 4.60 g of 4-vinyl-3,5-dimethylisoxazole (171), identified as described earlier.

Repetition of the above experiment using anhydrous 1,2-dimethoxyethane as the solvent gave identical results. As discussed in the text, dehydrochlorination of the chloroethyl isoxazole 165 was rapid under the reaction conditions employed and hence alkylation was unsuccessful.

Annulation of 2-methylcyclohexanone (181) with 4-bromo- and 4-chloro-2-pentanone (175 and 179) in dioxane and dimethylsulfoxide

General procedure for annulation in dioxane A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 1.50 g of a 57% sodium hydride-mineral oil dispersion (0.855 g - 0.036 moles active hydride). The sodium hydride was covered with 50 ml of anhydrous benzene, stirred briefly, and the solvent removed through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 50 ml of anhydrous dioxane to which was added 4.00 g (0.036 moles) of 2-methylcyclohexanone (181). The reaction mixture was heated slowly to reflux temperature (101.5°) and maintained at that temperature for 5 hours, with continuous stirring. Hydrogen evolution began when the reflux temperature was reached and continued for 2.5 hours. Following the specified time at reflux temperature,

the reaction mixture was cooled and treated with 8.40 g (0.050 moles) of 4-bromo-2-pentanone (175), dropwise and with good stirring, over a 20 minute period. The resulting solution was stirred at room temperature for 41 hours, during which time a white solid formed (NaBr). The crude product mixture was filtered, diluted with 12.5 ml of water, and acidified by the dropwise addition of a 10% acetic acid-ether solution. The ethereal solution was washed with 10 ml of water, three 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum and distillation of the residue gave 1.77 g (0.010 moles - 28.1%) of a mixture of cis and trans-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69c and 69t) as a colorless liquid: bp 75-90° (0.025 mm); [lit.⁶⁹ bp 76-78° (0.5 mm) for trans]; ir (film) 9239 and 2875(CH), 1713(trace C=O), 1671(C=O conj), 1619(C=C conj), 1455, 798 cm⁻¹; nmr (CCl₄) δ 5.58(bs,1H,-CH=C-), 1.27(small singlet, angular -CH₃ trans isomer), 1.08(large singlet, angular -CH₃ cis isomer), 0.92(d,3H,J=6 Hz,-CHCH₃) ppm; mass spectrum (70ev) M⁺ 178.

The ratio of the cis:trans isomers was shown to be approximately 4:1 by integration of the singlet peaks at 1.27 and 1.08 ppm.

Repetition of the annulation reaction under identical conditions with 6.05 g (0.050 moles) of 4-chloro-2-pentanone

(179) gave a naphthalenone product essentially the same as that described above. The isolated yield was 1.15 g (0.0065 moles - 18.1%).

General procedure for annulation in dimethylsulfoxide solvent A 100-ml, three-necked, round-bottomed flask was prepared and equipped as described above. The apparatus was charged with 0.833 g of a 57% sodium hydride-mineral oil dispersion (0.480 g - 0.0198 moles active hydride). The sodium hydride was washed free of the mineral oil by the procedure described above and covered with 50 ml of anhydrous dimethylsulfoxide. To this was added 2.21 g (0.0198 moles) of 2-methylcyclohexanone (181), dropwise and with rapid stirring, over a 15 minute period. The resulting heterogeneous slurry was stirred at room temperature for 3 hours, during which time hydrogen evolution began and continued until a completely homogeneous solution was obtained. The clear solution was then treated with 2.38 g (0.0198 moles) of 4-chloro-2-pentanone (179), dropwise and with rapid stirring, over a 10 minute period. The reaction mixture was stirred at room temperature for 3 days, diluted with 12.5 ml of water, and acidified by the dropwise addition of a 10% acetic acid-ether solution. The phases were separated and the aqueous phase extracted with three 20-ml portions of ether. The combined ethereal phases were washed with 10 ml of water, three 15-ml portions of a saturated sodium chloride solution, brine, and dried over

anhydrous magnesium sulfate.

Removal of the solvent under vacuum and distillation of the residue gave 0.611 g (0.0034 moles - 17.7%) of a mixture of cis and trans- 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69c and 69t): bp 78-90° (0.025 mm); [lit.⁶⁹ bp 76-78° (0.5 mm) for trans]; ir (film) 2938 and 2875(CH), 1713(trace C=O), 1671(C=O conj), 1619(C=C conj), 1454, 1379, 785, 760 cm⁻¹; nmr (CCl₄) δ 5.58(bs, 1H, -CH=C-), 1.27(large singlet, angular -CH₃ trans isomer), 1.08(small singlet, angular -CH₃ cis isomer) 0.97(d, 3H, J=6 Hz, -CHCH₃) ppm; mass spectrum (70ev) M⁺ 178.

The ratio of the cis:trans isomers was shown to be approximately 1:4 by integration of the singlet peaks at 1.27 and 1.08 ppm.

Repetition of the above experiment under identical conditions with 3.29 g (0.0198 moles) of 4-bromo-2-pentanone (175) gave a naphthalenone product essentially the same as that described above. The isolated yield was 1.08 g (0.0061 moles - 31.0%).

Annulation of 2-methylcyclohexanone (181) with trans-3-penten-2-one

General procedure for annulation in dioxane solvent

(cis isomer) A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The

apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 5.64 g of a 57% sodium hydride-mineral oil dispersion (3.22 g - 0.134 moles active hydride). The hydride was covered with 150 ml of anhydrous benzene, stirred briefly, and the benzene removed through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 350 ml of anhydrous dioxane and treated with 15.0 g (0.134 moles) of 2-methylcyclohexanone ($\text{C}_7\text{H}_{12}\text{O}$), dropwise and with stirring, over a 30 minute period. The resulting suspension was heated to reflux temperature (101.5°) and held at that temperature for 4 hours. Hydrogen evolution began when the reflux temperature was reached and continued for about 3 hours. Following the specified reaction period, the solution was cooled to room temperature and treated with 12.9 g (0.154 moles) of trans-3-penten-2-one, dropwise and with vigorous stirring, over a 2 hour period. Following complete addition of the unsaturated ketone, the reaction mixture was stirred at room temperature for 100 hours. The crude product mixture was then diluted with 100 ml of water and acidified by the dropwise addition of 10% glacial acetic acid in ether. The resulting phases were separated and the aqueous phase extracted with seven 35-ml portions of ether. The combined ethereal phases were washed with 10 ml of water, three 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum and distillation of the residue gave 15.1 g (0.087 moles - 65.0%) of cis-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (69c) as a colorless liquid: bp 100-122° (0.25 mm) and 3.47 g (0.031 moles - 23%) of 2-methylcyclohexanone (181). A small amount of tarry residue remained.

Chromatography of the naphthalenone product on silica gel with a 4% ethyl acetate-hexane solvent gave 13.9 g of a colorless liquid. Ir (film) 2939 and 2874(CH), 1671(C=O conj), 1619(C=C conj), 1455, 798 cm^{-1} ; nmr (CCl_4) δ 5.58(bs, 1H, $-\underline{\text{C}}\text{H}=\text{C}-$), 12.7(very small singlet, angular $-\underline{\text{C}}\text{H}_3$ trans isomer), 1.08(s, 3H, $-\underline{\text{C}}\text{H}_3$ cis isomer), 0.97(d, 3H, $J=6$ Hz, $-\text{CH}\underline{\text{C}}\text{H}_3$) ppm.

The ratio of the cis:trans isomers was shown to be approximately 95:5 by integration of the singlet peaks at 1.27 and 1.08 ppm.

General procedure for annulation in dimethylsulfoxide solvent (trans isomer) A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was charged with 5.64 g of a 57% sodium hydride-mineral oil dispersion (3.22 g - 0.134 moles active hydride). The mineral oil was removed as described above and the clean sodium hydride was covered with 350 ml of anhydrous dimethylsulfoxide. To the resulting suspension was added 15.0 g (0.134 moles) of 2-methylcyclohexanone (181),

dropwise and with stirring, over a 30 minute period. The reaction mixture was stirred at room temperature for 3 hours, during which time hydrogen evolution occurred and the solution became homogeneous. The resulting solution was treated with 12.9 g (0.154 moles) of trans-3-penten-2-one, dropwise and with vigorous stirring, over a 2 hour period. Following complete addition of the unsaturated ketone, the reaction mixture was stirred for 3 hours at room temperature, diluted with 100 ml of water, and acidified by the dropwise addition of a 10% acetic acid in ether solution. The resulting phases were separated and the aqueous phase extracted with six 25-ml portions of ether. The combined ethereal phases were washed with 10 ml of water, three 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum and distillation of the residue gave 17.1 g (0.096 moles - 72.1%) of trans-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (ρ_{lit}) as a colorless liquid: bp 111-124° (0.75 mm) and 1.39 g (0.0015 moles - 11%) of 2-methylcyclohexanone.

Chromatography of the naphthalenone product on silica gel with a 4% ethyl acetate-hexane elution solvent gave 15.4 g of a colorless liquid. Ir (film) 2938 and 2874(CH), 1671(C=O conj), 1619(C=C conj), 1454, 1379, 785, 760 cm^{-1} ; nmr (CCl_4) δ 5.58(bs, 1H, $-\text{CH}=\text{C}-$), 1.27(s, 3H, $-\text{CH}_3$ trans isomer), 1.08(very

small singlet, angular $-\text{CH}_3$ cis isomer), 0.97 (d, 3H, J=6 Hz, $-\text{CHCH}_3$) ppm.

The ratio of cis:trans isomers was shown to be approximately 5:95 by the integration of the singlet peaks at 1.27 and 1.08 ppm.

Trans-4a,5,8,8a-tetrahydro-2-methoxy-4a-methyl-4(1H)-naphthalenone (184)

The procedure of Speziale, Stephens, and Thompson¹¹⁴ was modified as follows. A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, powder addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a suspension of 11.2 g of l-1-camphorsulfonyl-4a,5,8,8a-tetrahydro-2-methoxy-4a-methyl-4(1H)-naphthalenone (183), mp 164-166°, (Monsanto Co.) in 26.5 ml of glacial acetic acid and 0.212 ml of acetic anhydride. The reaction mixture was rapidly stirred and treated with 3.45 g of fresh zinc dust, portionwise, over a 30 minute period. Following complete addition of the zinc dust, the reaction mixture was heated to an external temperature of 125° and held at that temperature for 2 hours. After this reaction period, the brown slurry was cooled, filtered through a sintered glass funnel, and the filtrate poured into 300 ml of cold (5°) water. Within 90 minutes, the water solution had deposited fluffy white crystals which were collected on a sintered glass funnel

and air-dried affording 3.94 g (0.021 moles - 80.9%) of the desired product 184: mp 91-93° [lit.¹¹⁴ mp 92-94°]; ir (KBr) 2901(CH), 1641(C=O), 1601(C=C), 1439, 1380, 1318, 1266 cm⁻¹; nmr (CCl₄) δ 5.58(m, 2H, -CH=CH-), 5.12(s, 1H, -CH=C-), 3.65(s, 3H, -OCH₃), 0.94(s, 3H, -CH₃) ppm; mass spectrum (70ev) M⁺ 192.

Trans-4a,5,8,8a-tetrahydro-4,4a-dimethyl-2(1H)-naphthalenone

(185)

The procedure described by Djerassi et al.,²³ was followed. A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 3.16 g (0.016 moles) of 4a-methyl-2-methoxy-4a,5,8,8a-tetrahydro-4(1H)-naphthalenone (184) dissolved in 100 ml of anhydrous ether. The reaction mixture was cooled to an internal temperature of 3° with an external ice bath and treated with 1.09 g (0.049 moles) of methyl lithium in ether (Foote Mineral Co. 1.57M), dropwise and with rapid stirring, over a 35 minute period. Following complete addition of the methyl lithium the reaction mixture was allowed to warm to room temperature and stirred at that temperature for 12 hours. The crude product mixture was then poured onto 200 g of ice, the resulting phases were separated, and the aqueous phase extracted with seven 20-ml portions of ether. The combined ethereal phases were washed with brine and dried over

anhydrous magnesium sulfate.

The ether was removed under vacuum giving 3.44 g of a yellow oil, which was treated, under nitrogen, with a mixture containing 11.9 ml of concentrated sulfuric acid, 84 ml of distilled water, and 100 ml of dioxane. The solution was stirred at room temperature for 3 hours, concentrated under vacuum, and the resulting aqueous phase extracted with five 35-ml portions of ether. The combined ethereal phases were washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum affording 2.41 g (0.014 moles - 87.5%) of a yellow solid: mp 36-39° [lit.²³ mp 39-42°].

A 2,4-dinitrophenylhydrazone derivative was prepared in the usual manner and recrystallized from anhydrous ethanol; mp 171-173° [lit.²³ mp 173-175°].

Trans-4 β ,4a β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182c)

The procedure of Djerassi et al.,²³ was followed. A 250-ml capacity pressure bottle was charged with a solution of 1.41 g (0.080 moles) of 4a,5,8,8a-tetrahydro-4,4a-dimethyl-2(1H)-naphthalenone (185) dissolved in 125 ml of anhydrous methanol which contained 250 mg of a 10% palladized charcoal catalyst. The reaction mixture was shaken for 48 hours under a constant pressure of hydrogen which measured 54 psi at the bottle. Following this period, the crude product mixture was

filtered free of the catalyst on Celite and concentrated under vacuum affording 1.99 g of a slightly yellow liquid. The crude product thus isolated was treated with 150 ml of a 1:1 mixture of 3N hydrochloric acid and dioxane. The solution was stirred for 1 hour, diluted with 50 ml of water, and extracted with three 35-ml portions of ether. The ethereal extracts were washed with three 25-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled to afford 1.29 g (0.716 moles - 89.6%) of the saturated ketone 182c as a colorless liquid: bp 70-75° (0.25 mm); [lit.²³ bp 70-73 (0.5 mm)]; ir (film) 2941(CH), 2860, 1720(C=O), 1451, 1289, 1248, 790 cm^{-1} ; nmr (CCl_4) δ 0.91 (s, 3H, angular - CH_3), 0.87 (d, 3H, $J=6.5$ Hz, - CHCH_3) ppm; mass spectrum (70ev) M^+ 180.

A 2,4-dinitrophenylhydrazone derivative was prepared in the usual manner and recrystallized from anhydrous ethanol; mp 135-136°; [lit.²³ 136-138°].

4a-Methyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (51)

The procedure of Ross and Levine⁵⁷ was followed. A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 70.0 g (0.625 moles) of 2-methylcyclohexanone (181) dissolved in 350

ml of anhydrous ether. The reaction mixture was cooled to 0° with an external ice bath and treated with a solution of 4.22 g of potassium hydroxide in 37.5 ml of anhydrous ethanol, dropwise and with rapid stirring, over a 10 minute period. The basic reaction solution was then treated with 29.5 g (0.422 moles) of methyl vinyl ketone, dropwise, with vigorous stirring, over a 40 minute period. The resulting brown slurry was allowed to warm slowly to room temperature and stirred at that temperature for 8 hours. Following this period, the crude product mixture was diluted with 250 ml of water, acidified by the dropwise addition of a 10% hydrochloric acid solution, and extracted with seven 35-ml portions of ether. The ethereal extracts were washed with three 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure gave a yellow liquid, which upon distillation afforded 34.1 g (0.306 moles - 48.3%) of 2-methylcyclohexanone ($\frac{181}{\text{C}}$), bp 28-31° (0.1 mm) and 50.3 g (0.305 moles - 48%) of a 4a-methyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone ($\frac{51}{\text{C}}$) as a colorless liquid: bp 101-103° (0.1 mm); [lit.^{10,57} bp 111-112° (2.5 mm)]; ir (film) 3040 and 2960 (CH), 1670 (C=O conj), 1618 (C=C conj), 1455, 1439, 1356, 1330, 1265 cm^{-1} ; nmr (CCl_4) δ 5.58 (bt, 1H, $-\underline{\text{CH}}=\text{C}-$), 1.25 (s, 3H- CH_3) ppm; mass spectrum (70ev) M^+ 164.

Trans-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (186)

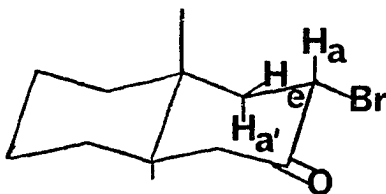
According to the procedure of House et al.,¹¹⁵ a 3000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, Dry Ice condenser, mechanical stirrer, and gas-outlet tube leading to a one-way mercury valve. The apparatus was flame-dried, briefly flushed with nitrogen, and charged with 2000 ml of liquid ammonia, which had been passed through a potassium hydroxide drying tower prior to condensation. Following collection of the liquid ammonia, 8.54 g (1.22 moles) of lithium wire were added portionwise, over a 50 minute period. The resulting blue solution was then treated with 20.0 g (0.122 moles) of 4a-methyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (51) dissolved in 10.6 g (0.144 moles) of t-butyl alcohol and 100 ml of anhydrous ether. The ethereal solution was added dropwise, with constant stirring, over a 45 minute period. The reaction mixture was stirred for 10 minutes and treated with excess ammonium chloride. The ammonia was allowed to evaporate over a 9 hour period, while ether was slowly added to replace the ammonia. The crude product mixture was diluted with 300 ml of water, the phases were separated, and the aqueous phase extracted with six 35-ml portions of ether. The combined ethereal phases were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum left a yellow oil, which was dissolved in 300 ml of reagent grade acetone and cooled to 0° with an external ice

bath. The yellow solution was then treated with "Jones reagent"⁹⁵ until the acetone exhibited a persistent red color (excess oxidizing solution). The crude product mixture was stirred for an additional 15 minutes, isopropyl alcohol was added to decompose the excess oxidizing agent, and approximately 20 g of solid sodium bicarbonate were added. The resulting suspension was filtered, the solid washed with warm acetone, and the combined filtrates concentrated under vacuum. The residue was distilled affording 14.6 (0.088 moles - 71.5%) of trans-4a-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (186) as a colorless liquid: bp 81-83° (3.0 mm); [lit.¹¹⁵ bp 60-61° (0.3 mm)]; ir (film) 2930 and 2850 (CH), 1713 (C=O), 1451 cm^{-1} ; nmr (CCl_4) δ 1.05 (s, 3H, $-\text{CH}_3$) ppm; mass spectrum (70ev) M^+ 166.

Trans-3 α -bromo-4a β -methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (187)

The procedure of Djerassi and Marshall¹⁴⁶ was followed. A 350-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 14.6 g (0.092 moles) of trans-4a-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (186) dissolved in 105 ml of glacial acetic acid. The reaction mixture was cooled to an internal temperature of 3° with an external ice bath and

treated with 14.6 g (0.092 moles) of bromine dissolved in 105 ml of glacial acetic acid. The addition was carried out dropwise, with stirring, over a 60 minute period. The resulting red solution was allowed to stir for an additional 30 minutes at room temperature and poured into 500 ml of ice water. A yellow, puffy solid slowly precipitated over a 4 day period. The material was isolated, recrystallized from aqueous (6%) acetone, and dried under vacuum affording 9.50 g (0.039 moles - 42.3%) of a white powder identified as the bromoketone 187: mp 131-138°, [lit.¹⁴⁶ mp 137-139°]; nmr (CCl₄) δ 4.70 (dd, 1H, J_{Ha-Ha'}=12.5 Hz, J_{Ha'-He}=7 Hz, Ha), 1.11 (s, 3H, -CH₃) ppm.



Trans-4a-methyl-4a,5,6,7,8,8a-hexahydro-2(1H)-naphthalenone

(188)

A modification of the Joly¹¹⁷ method suggested by Corey and his coworkers¹¹⁸ was followed. A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition, and a reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen and charged with a solution of 3.00 g (0.034 moles) of anhydrous lithium bromide and 4.00 g (0.054

moles) of lithium carbonate dissolved in 50.0 ml of anhydrous N,N-dimethylformamide. To this solution was added 5.00 g (0.0204 moles) of trans-3 α -bromo-4 α β -methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (187), dropwise and with stirring, over a 35 minute period. The resulting solution was heated to an internal temperature of 145°, maintained at that temperature for 2 hours, cooled to 100° and held at that temperature for 3 hours. Finally, the reaction mixture was cooled to room temperature and poured into 100 ml of a 10% glacial acetic acid-water solution, which was extracted with seven 40-ml portions of methylene chloride. The methylene chloride extracts were washed with three 35-ml portions of a saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum and distillation of the residue gave 2.96 (0.018 moles - 86.2%) of trans-4a-methyl-4a,5,6,7,8,8a-hexahydro-2(1H)-naphthalenone (188) as a colorless liquid: bp 92-95° (0.5 mm); [lit.¹⁴⁷ bp 69° (0.1 mm)]; ir (film) 2910 and 2850(CH), 1672(C=O conj), 1605(C=C conj), 1449, 1245 cm⁻¹; nmr (CCl₄) δ 6.67(d,1H,J=10 Hz, -CH=CHCO-), 5.67(d,1H,J=10 Hz,-CH=CHCO-), 1.06(s,3H,-CH₃) ppm; mass spectrum (70ev) M⁺ 164.

Trans-4 α ,4 β -dimethyl-3,4,4 α ,5,6,7,8,8 α -octahydro-2(1H)-naphthalenone (182t)

A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a suspension of 8.57 g (0.045 moles) of anhydrous cuprous iodide in 125 ml of anhydrous ether. The ethereal suspension was cooled to 0° with an external ice bath and treated with 1.98 g (0.090 moles) of methyl lithium in ether (Foote Mineral Co.), dropwise and with stirring, over a 15 minute period. The resulting yellow-green slurry was stirred at 0° for 30 minutes and treated with 2.96 g (0.018 moles) of trans-4 α -methyl-4 α ,5,6,7,8,8 α -hexahydro-2(1H)-naphthalenone (188), dropwise and with stirring, over a 15 minute period. The cooling bath was removed and the reaction mixture was stirred at room temperature for 11 hours. The crude product mixture was slowly poured into 250 ml of a saturated ammonium chloride solution which contained 2.0 ml of concentrated ammonium hydroxide. The resulting phases were separated, the aqueous phase extracted with seven 30-ml portions of ether and the combined ethereal phases washed briefly with brine and dried over anhydrous magnesium sulfate.

Removal of the solvent under vacuum and distillation of the residue gave 2.86 g (0.016 moles - 89.1%) of trans-4 α ,4 β -dimethyl-3,4,4 α ,5,6,7,8,8 α -octahydro-2(1H)-naphthalenone (182t)

as a colorless liquid: bp 71-76° (0.5 mm); [lit.⁶⁵ bp 76-78° (0.5 mm), 133-137° (9.0 mm)]; ir (film) 2940 and 2890 (CH), 1721 (C=O), 1445, 1389, 1245, 1163 cm^{-1} ; nmr (CCl_4) δ 1.16 (s, 3H, $-\text{CH}_3$), 0.93 (d, 3H, $-\text{CHCH}_3$) ppm; mass spectrum (70ev) M^+ 180.

A 2,4-dinitrophenylhydrazone derivative was prepared in the usual manner and recrystallized from anhydrous ethanol: mp 163-165°; [lit.⁶⁵ mp 164-166°].

Reduction of the naphthalenone products obtained from annulation of 2-methylcyclohexanone (181) with trans-3-penten-2-one

A 1000-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, Dry Ice condenser, mechanical stirrer, and a gas-outlet tube leading to a one-way mercury valve. The apparatus was flame-dried, briefly flushed with nitrogen, and charged with 500 ml of liquid ammonia which had been passed through a potassium hydroxide drying tower prior to condensation. To the ammonia was added 1.17 g (0.017 moles) of lithium wire, portionwise and with constant stirring, over a 30 minute period. The resulting blue solution was stirred for 15 minutes following complete addition of the lithium and treated with 3.00 g (0.017 moles) of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (59c - "dioxane product") and 1.41 g (0.019 moles) of t-butyl alcohol in 75 ml of anhydrous ether. The ethereal solution was added dropwise, with rapid stirring, over a 25 minute period. Stirring was continued for 10 minutes and excess ammonium chloride was cautiously added. The ammonia

was allowed to evaporate through the mercury valve overnight and was replaced with anhydrous ether. The crude product mixture was diluted with 100 ml of water, the phases were separated, and the aqueous phase extracted with six 35-ml portions of ether. The combined ethereal phases were washed with brine and dried over anhydrous magnesium sulfate.

Removal of the solvent left a yellow oil, which was dissolved in 150 ml of reagent grade acetone and cooled to 0° with an external ice bath. The yellow solution was then treated, with stirring, with "Jones reagent" until the acetone showed a persistent red color, indicating the presence of excess oxidizing solution. The crude product mixture was stirred for an additional 15 minutes, isopropyl alcohol was added to decompose the excess oxidizing solution, and approximately 10-15 g of sodium bicarbonate were added. The resulting suspension was filtered, the solid washed with warm acetone, and the combined filtrates concentrated under vacuum. The residue was distilled to afford 2.41 g (0.0134 moles - 80.1%) of trans-4 β ,4a β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182c) as a colorless liquid: bp 71-75° (0.25 mm). Chromatography of the distilled product on silica gel with a 3% ethyl acetate-hexane elution solvent gave 2.14 g of naphthalenone 182c, identical in all respects to the material described earlier.

Repetition of the above experimental procedure using the "69t-DMSO product" gave trans-4 α ,4 β -dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (182t) as a colorless liquid. Following purification by chromatography, this material proved to be identical in all respects with that prepared as described earlier.

Attempted methylation of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) with methyl iodide

A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 1.32 g of a 57% sodium hydride-mineral oil dispersion (0.75 g - 0.031 moles active hydride). The hydride was covered with 200 ml of anhydrous benzene, stirred briefly, and the benzene removed through an ultra-fine grade sintered glass gas dispersion tube attached to a water aspirator. These operations were conducted under a static nitrogen pressure. The clean sodium hydride was then covered with 200 ml of anhydrous benzene and treated with 4.70 g (0.024 moles) of methyl 2-oxo-5-isopropenylcyclohexanecarboxylate (151) dissolved in 100 ml of anhydrous benzene. The ester solution was added, dropwise, with constant stirring, over a 25 minute period. Hydrogen evolution occurred immediately and continued until all the ester had been added. Following complete addition of the ester, the reaction mixture

was treated with 17.1 g (0.120 moles) of methyl iodide, dropwise and with stirring, over a 15 minute period. The reaction mixture was then stirred at room temperature for 14 hours, diluted with 150 ml of ether, and filtered free of the white solid which had formed (unreacted enolate). The filtrate was diluted with 100 ml of ether and washed with 10 ml of water, brine, and dried over anhydrous magnesium sulfate. Removal of the ether under vacuum left 3.91 g of a yellow oil. The crude product was shown to consist of mostly over methylated products by the presence of large peaks at m/e 224 and 238 in the mass spectrum.

1-Pyrrolidino-4-isopropenyl-1-cyclohexane (198)

A 150-ml, one-necked, round-bottomed flask was fitted with a Dean-Stark water trap, gas-inlet tube, and reflux condenser. The apparatus was evacuated, flame-dried, filled with pre-purified nitrogen, and charged with a solution of 5.23 g (0.038 moles) of unpurified 4-isopropenylcyclohexanone (115) dissolved in 100 ml of anhydrous benzene. To this was added 4.05 g (0.057 moles) of pyrrolidine via a flame-dried pipet. The reaction mixture was heated to reflux temperature and maintained at that temperature for 12 hours, during which time 0.51 ml of water were removed from the system. The Dean-Stark trap was replaced by a Soxhlet extractor containing 4A molecular sieves in the thimble and the benzene solution was

allowed to percolate through the sieves for 12 hours. The crude product mixture was cooled and the benzene removed under vacuum to leave 4.70 g of a brown oil: nmr (CCl_4) δ 4.75 (q, 2H, $J=1$ Hz, $\text{H}_2\text{C}=\text{C}$), 1.74 (t, 3H, $J=1$ Hz, $\text{CH}_3\text{C}=\text{C}$) ppm; mass spectrum (70ev) M^+ 191.

The enamine was not further purified.

2-methyl-4-isopropenylcyclohexanone (180)

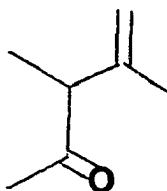
A 50-ml, three-necked, round-bottomed flask was fitted a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 4.70 g of crude 1-pyrrolidino-4-isopropenyl-1-cyclohexene (198) dissolved in 25 ml of anhydrous methanol. To this solution was added 3.98 g (0.0277 moles) of methyl iodide via a flame-dried pipet. The reaction mixture was heated to reflux temperature and held at that temperature for 2 days, during which time the reaction mixture turned black. Following this reaction period, 5.0 ml of water were added to the reaction mixture and heating was continued for 30 minutes. The crude product mixture was then cooled, concentrated under vacuum, and diluted with 100 ml of ether. The ethereal solution was washed with three 10-ml portions of a 10% hydrochloric acid solution, three 10-ml portions of a saturated

sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent left a colorless liquid: bp 68-73 (0.5 mm); ir((film) 2930(CH), 1710(C=O), 1641(C=C), 1436, 1158, 889 cm^{-1} ; nmr (CCl_4) δ 4.72 (q, 2H, $J=1.0$ Hz, $\text{CH}_2=$), 1.74 (q, 3H, $J=1.0$ Hz, $\text{CH}_3-\text{C}=\text{}$), 0.82 (d, 3H, $J=1.0$ Hz, CH_3).

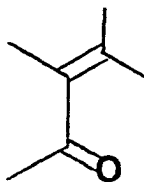
CONCLUSION

The primary value of any purely synthetic effort of the type described in this manuscript which does not culminate in the total synthesis of a valuable natural product must lie in the new synthetic methods which are developed. In the present work, two new and highly successful synthetic procedures are presented.

First, the exact reaction conditions under which lithium diisopropenyl cuprate may be employed to replace an organic halide with an isopropenyl group are discussed in detail. In addition, as if to complement the investigations of Profs. House, Corey, and Whitesides, the nature of the organic halide with respect to the presence of an unprotected carbonyl group is unquestionably defined. It is anticipated that this procedure will find extended use for the preparation of the type of structure illustrated below. This particular group is



present in numerous naturally occurring materials and has proven reasonably difficult to prepare by conventional means due to its ready isomerization to the conjugated isopropylidene form.



Second, the annulation of an unactivated cycloalkanone with trans-3-penten-2-one was completed under reaction conditions which allowed the isolation of the naphthalenone product in unprecedented high yield. In addition, a solvent dependency for the annulation was developed which allowed preparation of both cis- and trans-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone in high stereochemical purity.

It is perhaps the high yield annulation of 2-methylcyclohexanone with trans-3-penten-2-one to product cis-4,4a-dimethyl functionality in the naphthalenone product which is of the most significance in the present work. The completion of such a synthesis has been the goal of a number of synthetic chemists, such as J. A. Marshall, R. M. Coates, and A. R. Pinder. In fact, the latest publication of Prof. Marshall¹⁴⁸ contains, as a foreword, a restatement of the problem, as well as the fact that a solution was not yet available.

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