ANNULATION AND CYCLOAROMATIZATION REACTIONS OF 3-ARYL(ALKYL) THIO-1-TRIMETHYLSILOXY-1-METHOXY-1,3-BUTADIENES

by

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A Thesis Submitted to the Faculty of Graduate Studies and Research in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Montreal, Canada.

September 1986

ISBN 0-315-44366-9

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ABSTRACT

The title compounds were synthesized from methyl 3-aryl(alkyl)thio crotonic acids by deprotonation followed by silylation. The reactions of dienes with a number of carbonyl electrophiles under Lewis-acid catalysed conditions were investigated. The dienes exclusively give γ-alkylated products. The thio substituent enhances the γ-selectivity.

The reactions of dienes with a number of 1,3-dicarbonyl equivalents have been studied and a cycloaromatization reaction has been developed for the regiocontrolled synthesis of aryl sulfides in a 3C+3C combination. The role of dienes in Diels-Alder reactions has also been investigated.

A new 4C+2C annulation reaction has been developed based on the propensity of dienes to undergo Michael reaction with α,β -unsaturated ketones under Lewis-acid catalysed conditions. These Michael adducts in turn were cyclized either with potassium tert-butoxide or with lithium thiophenoxide. Further, the tandem Michael-Claisen annulation reaction can be controlled to give either cis- or trans- fused 9-methyldecalin system with three carbonyl groups which are differently masked. The chemoselective transformations of the carbonyl groups were also described.

The utility of tandem Michael-Claisen annulation sequence in the synthesis of natural products has been demonstrated by the synthesis of aristolone and fukinone. The methods of total synthesis are easily competitive with previous methods.

REACTIONS DE CYCLOAROMATISATION ET D'ANNELATION DES ARYL(ALKYL)THIO-3 TRIMETHYLSILOXY-1 METHOXY-1BUTADIENES-1,3

RESUME

Les composés mentionnés furent synthétisés à partir des acides méthyl aryl(alkyl)thio-3 crotoniques par la déprotonation suivie de la silylation. Les réactions des dienes avec plusieurs carbonyles électrophiliques catalysées par des acides de Lewis furent étudiées. Les dienes donnent exclusivement des composés alkylés en position γ. Le soufre accentue la sélectivité en position γ.

Les réactions des dienes avec plusieurs équivalents de dicarbonyles-1,3 ont été étudiées et une réaction de cycloaromatisation a été développée pour la synthèse régiocontrollée des sulfides d'aryle de façon 3C+3C. Le rôle des dienes dans les réactions de Diels-Alder a aussi été étudié.

Une nouvelle réaction d'annelation de façon 4C+2C a été développée, basée sur la tendance des dienes de subir les réactions de Michael avec les cétones α,β -insaturées catalysée par les acides de Lewis. Ces produits de la réaction de Michael furent ensuite cyclisés soit avec le tert-butoxide de potassium, soit avec le thiophénoxyde de lithium. De plus, l'annelation tandem de Michael-Claisen peut être contrôlée pour donner soit le produit cis- ou le produit trans-méthyl-9 décaline, avec trois groupes carbonyles différemment masqués.

Les transformations chémosélectives des groupes carbonyles furent aussi décrites.

L'utilité de l'annelation tandem de Michael-Claisen dans la synthèse de produits naturels a été démontrée avec la synthèse de l'aristolone et du fukinone. Les méthodes de synthèse totale sont facilement compétitives avec les méthodes précédemment publiées.

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to Prof. T.H. Chan, whose patience, inspiration, kindness, ability to convey an idea and continued good humour have made my stay in his laboratory a most enjoyable experience. Moreover, I would like to thank Prof. Chan for his insight and contagious excitement about organic chemistry which have helped to further kindle my interest in field.

I would also like to thank:

The Chemistry Department, McGill University, for teaching assistanships;

McGill University, for awarding me Bindra Scholarship, Neill-Croll award and the Summer Scholarship;

Dr. J. Finkenbine for recording mass spectra;

Dr. F. Sauriol for 200 MHz ^{1}H nmr and ^{13}C nmr spectra;

Daniel Stössel for translating the Abstract of this thesis into French;

All my co-workers for their friendship and helpful discussions.

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List of Abbreviations

Ac	acetyl
Bn	benzyl
BTAF	benzyltrimethylammonium fluoride
Bu	butyl
C_p	cyclopentadienyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzequinone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
HMDS	hexamethyldisilazane
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
mCPBA	m-chloroperoxybenzoic acid
Me	methyl
Ph	phenyl
TBAH	tetrabutylammonium hydroxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl (tetramethylsilane as an internal standard in nmr)
TMSCl	chlorotrimethylsilane
TMSI	iodotrimethylsilane

With my Love

TO

My Mother

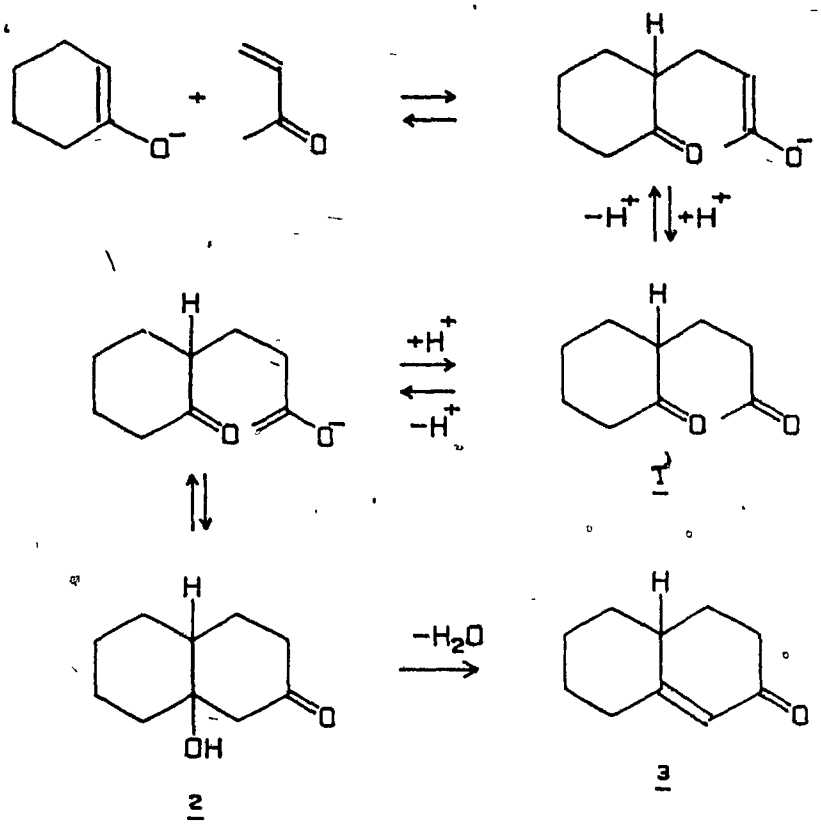
CHAPTER I

INTRODUCTION

Annulation, derived from the Latin word annulatus(ringed) means "the formation of rings". In organic chemistry this term is used to describe the process of building a ring onto a preexisting system, cyclic or non-cyclic. The added ring may be of any size, although 5- and 6-membered rings are most commonly formed. This broad definition includes in a general sense many reactions that are not normally thought of as annulation reactions, such as Diels-Alder reactions,[1] acid-catalysed polyolefinic cyclizations,[2] photochemical,[3] radical,[4] and thermal cyclizations.[5] I will be discussing mainly those processes of annulation which involve construction of a six membered ring onto a preexisting one by the classical Robinson annulation[6] and by the Diels-Alder reaction.

A. Robinson annulation:

The Robinson annulation, since its introduction fifty years ago,[7,8] with its subsequent modifications, has been one of the most widely used synthetic tools in organic chemistry. The original procedure involved nucleophilic attack of a ketone or ketoester enolate, in a Michael reaction, on a vinyl ketone to produce the intermediate "3-ketoalkyl" Michael adduct 1. Subsequent aldol-type ring closure to ketoalcohol 2, followed by dehydration, produces the annulation product such as the octalone 3 (Scheme I).



Scheme I

While the process is of great value, it is nevertheless subject to some restrictions:

(a) Methyl vinyl ketone (the most commonly used Michael acceptor) tends to polymerize;

(b) Alkylation usually occurs at the more highly substituted α-carbon;

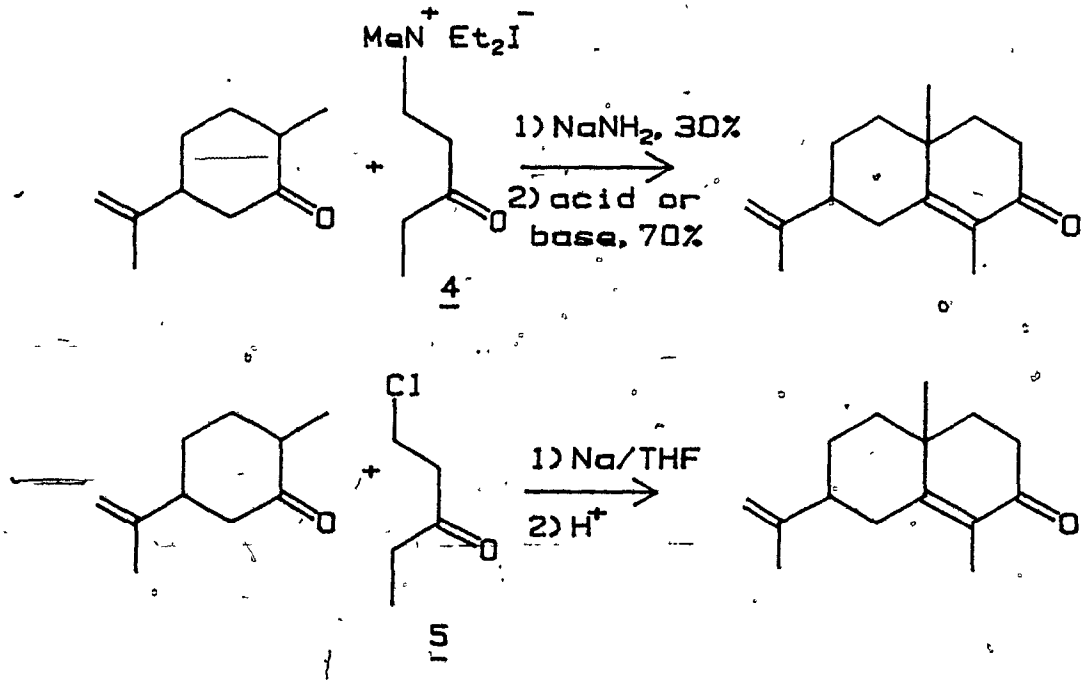
(c) Dialkylation occurs readily.

It is, no doubt, at least partially as a result of these restrictions that the aforementioned "modifications" have been evolved, so that these restrictions might be overcome. Virtually all of the modifications involve the preparation of the initial Michael adduct, 1 or its functionalized equivalent, by some means which maximize yield, minimize side

reactions, or which can be accomplished under mild conditions. These various modifications may be classified in two categories: (a) those involving reaction of Michael acceptor with the nucleophile, and (b) those involving reaction of the nucleophile with an alkyl halide. The electrophilic reagent could either contain a carbonyl group or some latent carbonyl function.[9] In the latter case, the carbonyl moiety would be unmasked after attachment to the ketone substrate.

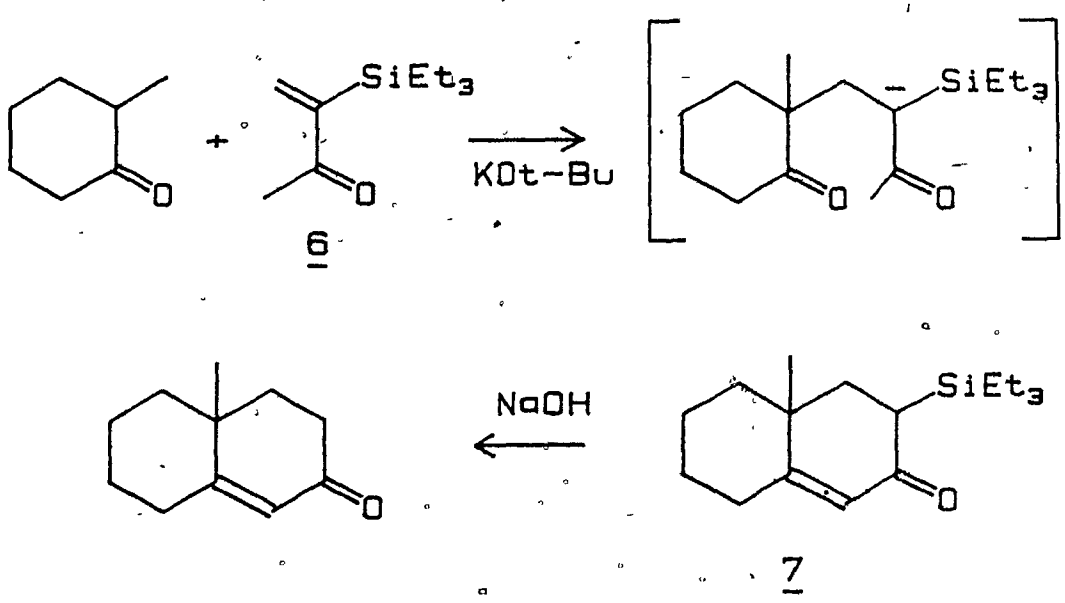
(i) Modifications on Michael acceptor:

Robinson originally used an assortment of substituted vinyl ketones, but had little success in obtaing annulation products when employing the parent compound, methyl vinyl ketone, as the electrophilic reactant.[8] Instead, it was found by both Robinson and others that yields could be improved by the use of quaternized Mannich bases 4 or a β-haloketone 5 to generate the reagent in situ (eq 1).[10,11]



(1)

Stork introduced the α-silyl enone such as 6.[12] The silyl group in 6 stabilizes somewhat the initial negative charge formed by addition of the enolate ion to the enone, and, more importantly, provides strong steric hindrance which slows down anionic polymerization. Once annulation is complete, the silyl group is removed from the α'-silyl enone 7 with base. This method gives improved yields (70-75%) in a number of cases and allows for the first time the general use of the Michael addition with vinyl ketones under aprotic conditions (eq 2).

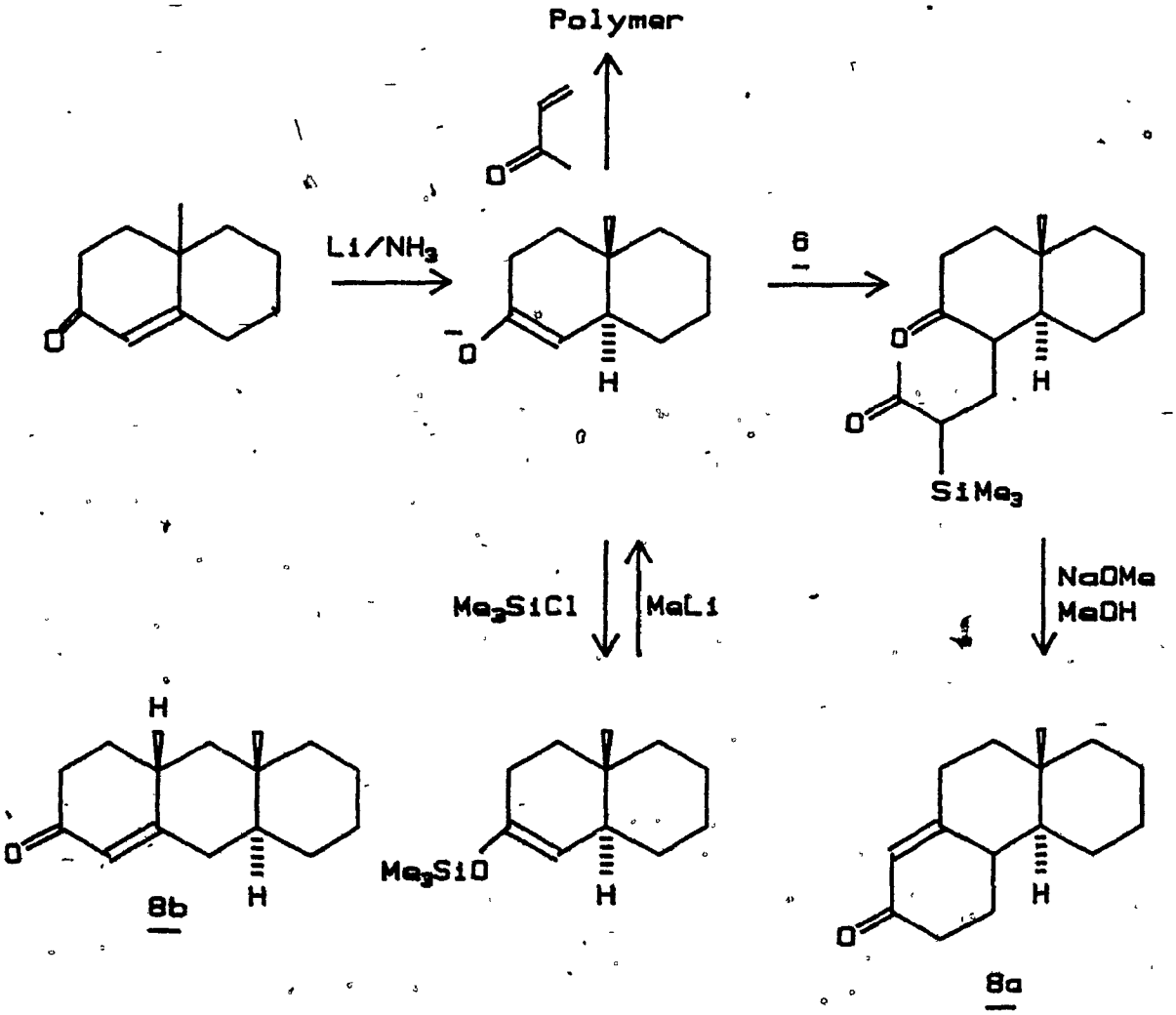


6 7 (2)

The major drawback of the Michael sequence in general is that the reactions are usually not compatible with specifically generated enolate ions under aprotic, non-equilibrating conditions. The reagents are generally not reactive enough to trap the enolates generated by reduction of enones by lithium in liquid ammonia or those generated by attack of methyl lithium on an enol acetate or silyl enol ether.

The use of stronger Michael acceptors, namely, α-silyl ketones such as 6 circumvents these problems since now Michael addition occurs faster than polymerization and, provided that precautions are taken to insure that the medium is truly aprotic, it is also faster than equilibration of the enolates.[13,14]

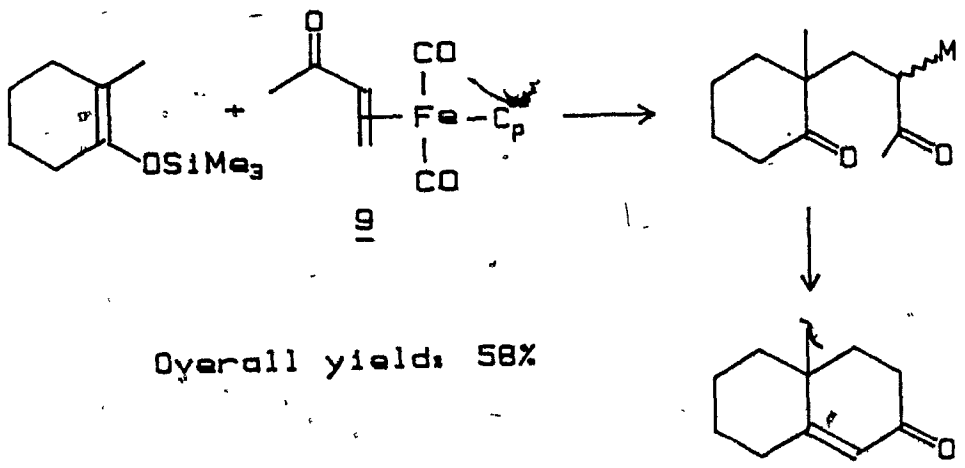
For example, the reductive trapping-cyclization sequence using the silyl derivative 6. furnishes cleanly the tricyclic compound 8a in 60% yield, uncontaminated by isomer 8b (Scheme II).



Scheme II

This is the first instance of the successful trapping of a regiospecifically generated, less stable enolate ion without equilibration by a Michael acceptor. This result increases the potential usefulness of the Michael reaction annulation sequence.

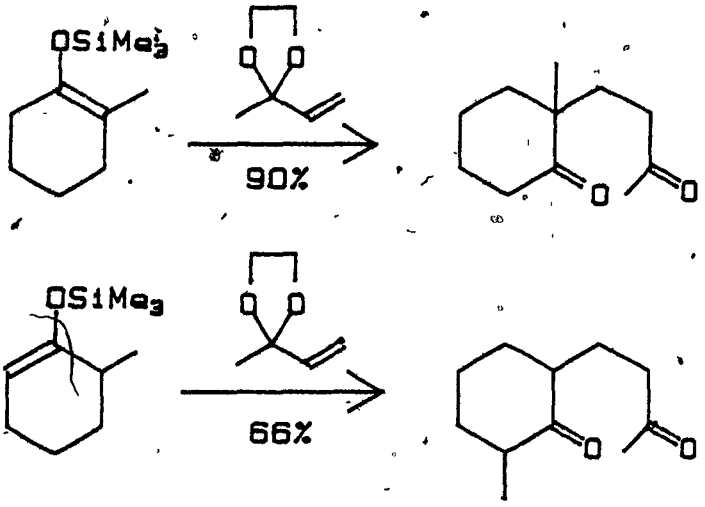
Rosenblum used a methyl vinyl ketone-metal complex[15] 9 in an annulation sequence. The iron-enone complex undergoes Michael addition with regiochemically unstable enolates without equilibration. Perhaps the most potentially useful observation, however, is that the complex will react with a silyl enol ether to give the Michael adduct under completely neutral conditions (eq 3).



9 (3)

Overall yield: 58%

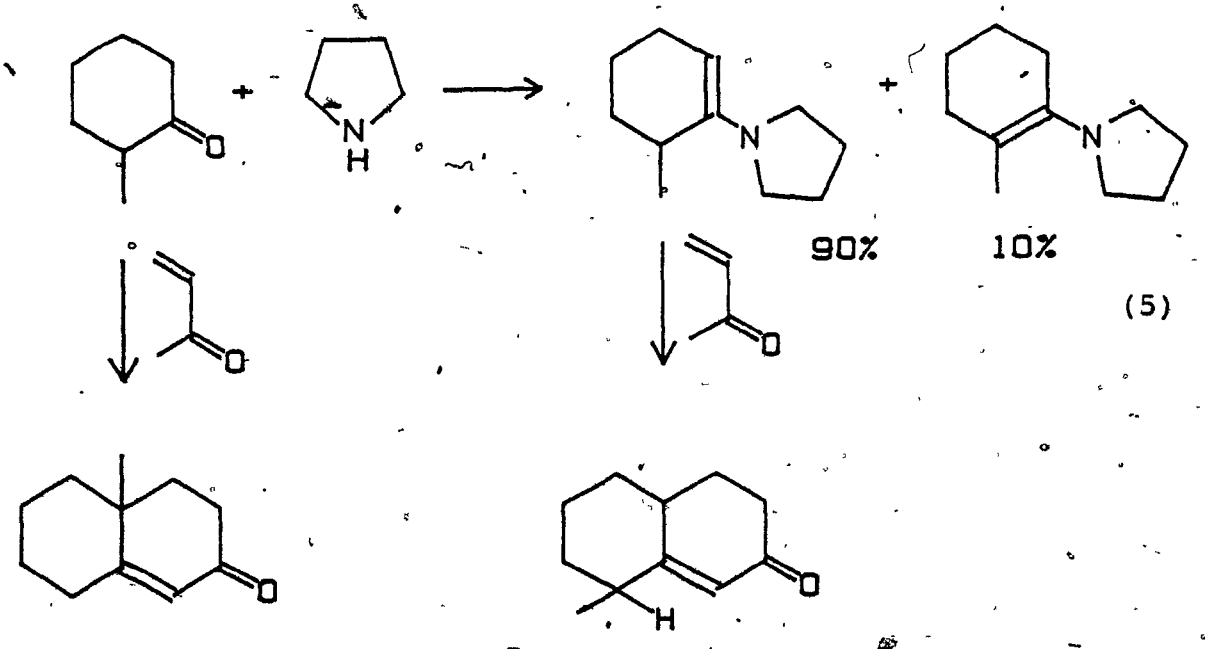
Recently Huffman developed a mild, general alternative to the Robinson annulation which is applicable to both aldehydes and ketones, and which would permit the use of either kinetically or thermodynamically generated enolates. Furthermore, the problem of polymerization of methyl vinyl ketone was also circumvented with the use of ethylene ketal of methyl vinyl ketone as the Michael acceptor which affords a 1,5-diketone under Lewis acid catalysed conditions (eq 4).



(4)

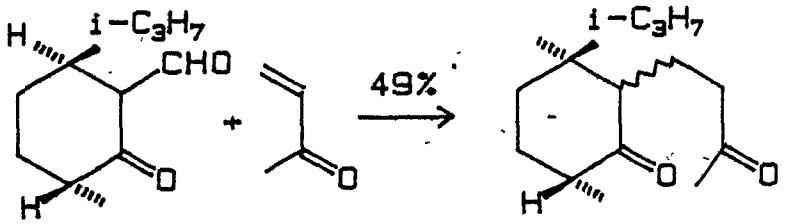
(ii) Modifications on Michael donor:

The use of enamines [17] with their relatively low basicity and high nucleophilicity often produces good yields in annulation reactions with vinyl ketones in those cases where reaction with corresponding enolate fails, due either to self condensation of the carbonyl compound or to the polymerization of the vinyl ketones by the very basic enolates. The advantage in using enamines is that the regiochemistry opposite to that observed under standard Robinson conditions is obtainable (eq 5).[18]



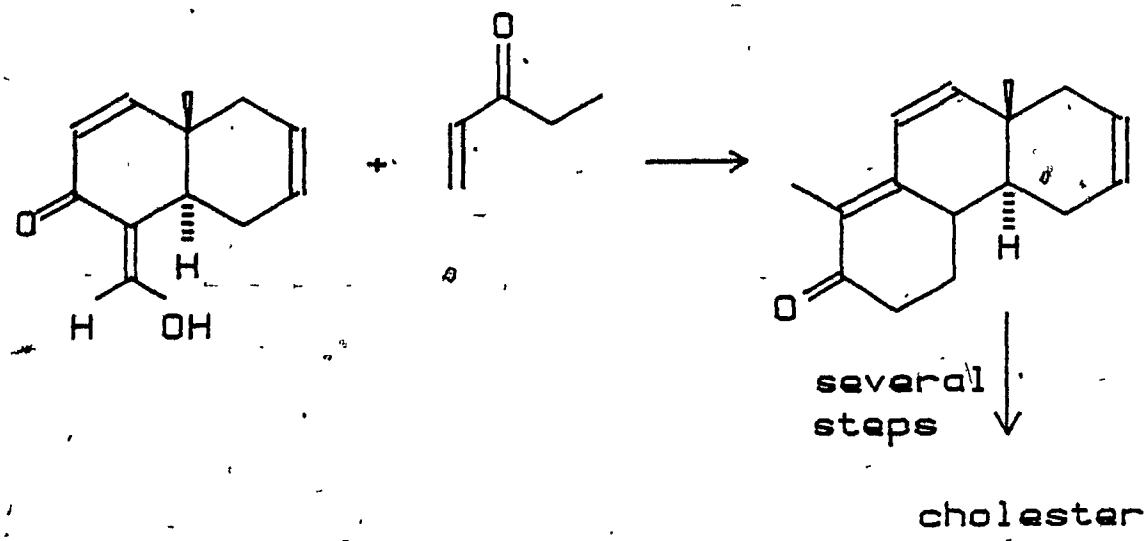
(5)

Alkylation of 1,3-diketones with a Michael acceptor can be accomplished under very mild conditions,[19-22] such that the 3'-oxoalkyl Michael adduct intermediate can be isolated. A similar situation can be realised with mono ketones by first condensing them with an activating group to form a β-dicarbonyl compound, followed by condensation with an appropriate alkylating agent under mild conditions. Most common among these activating groups are the ethoxycarbonyl group[23-25] and the hydroxymethylene group.[26,27] The hydroxymethylene group is also used as a directing group to promote preferential alkylation at the less substituted position (eq 6).[27]



(6)

The hydroxymethylene group was also used as a blocking group to prevent dialkylation and/or to effect regiochemical specificity. As mentioned before, a complication of the Robinson annulation is the possibility of di- or polyalkylation. This is the result of the similar acidities of the starting ketone, the initial Michael adducts, etc. Woodward demonstrated the utility of the hydroxymethylene group as not only an activating group but also as a blocking group to minimize dialkylation in his classic synthesis of cholesterol.[26] The angular formyl group is easily cleaved by base after completion of the Michael reaction (eq 7).



(7)

cholesterol

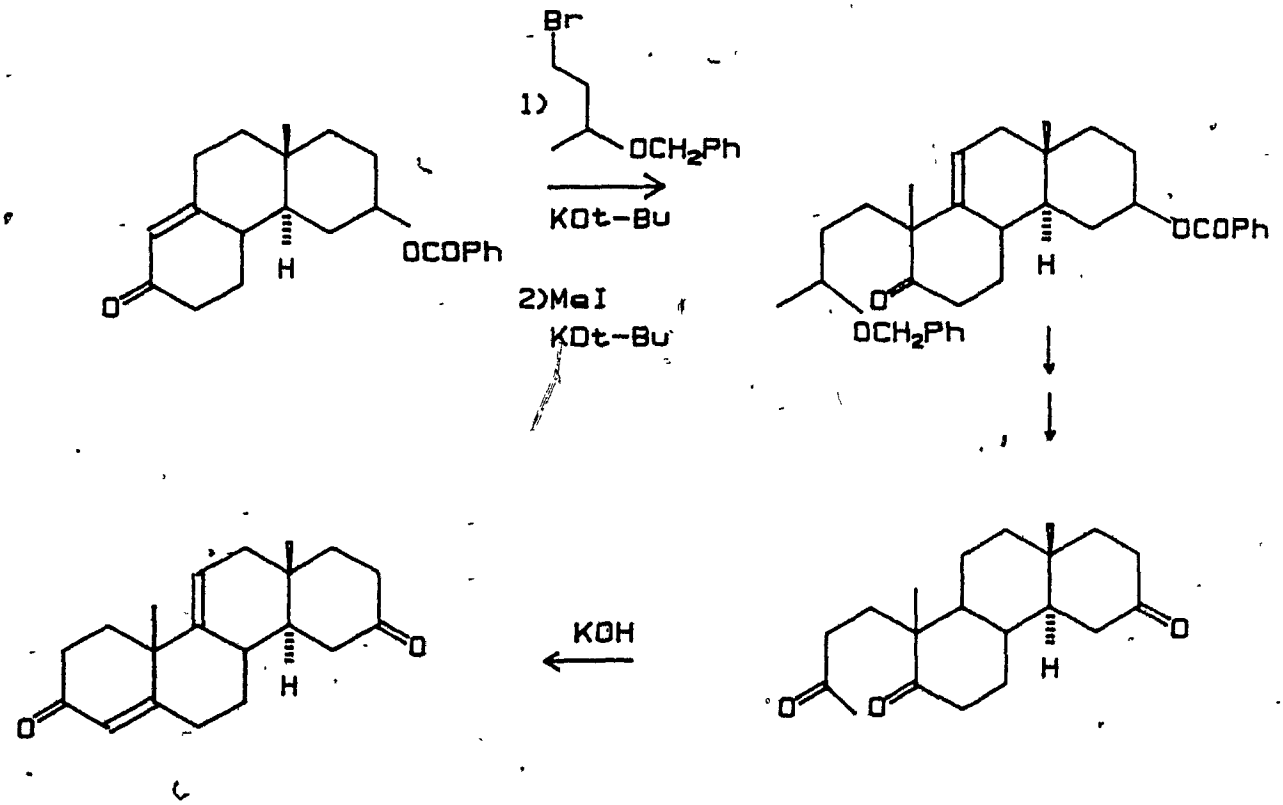
(iii) Annulations using electrophiles with masked carbonyl functions:

Another approach to the attachment of 3'-oxoalkyl side chains on ketones in an annulation sequence has been the use of an alkylating agent which has a protected, or latent, carbonyl group in the molecule. These reagents have the greatest potential since they may be capable of trapping regiospecifically generated enolate ions under aprotic, non-equilibrating conditions. They may be subdivided into alkyl halides (and alkyl sulfonates) and allylic (or benzylic) halides. A minor drawback of any reagent introduced by alkylation rather than by a Michael reaction is that some of the selectivity in the site of attachment may be lost. However, this problem can generally be overcome by the use of highly reactive alkylating agents and the regiospecific enolate ions generated from either enol acetates or enol silyl ethers.[28-31]

(a) alkyl halides: Many alkyl halides have been tried in annulation reactions, with only a moderate degree of success.

Perhaps the most simple of these is a β-haloacetal. Stork has pointed out that halides of this type are relatively unreactive and also have a strong tendency to undergo elimination under the basic conditions of the reaction,[32] factors which have no doubt contributed to its infrequent use.

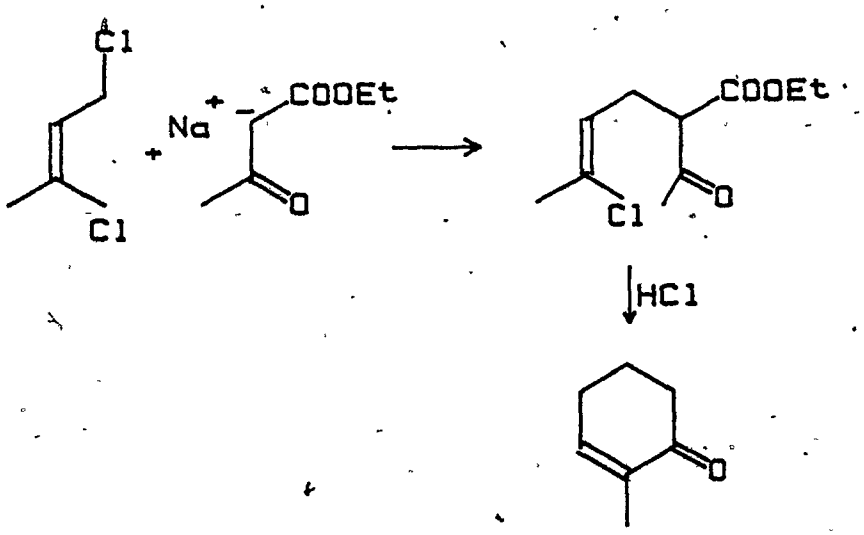
Stork utilized 3-benzyloxybutyl bromide as a 3'-oxoalkyl equivalent.[33] This reagent suffers from the disadvantage that an extra chiral centre is introduced during the alkylation, a fact which often means obtention of diastereomeric products.[32] The second disadvantage is that the means by which the carbonyl function is unmasked is multi-step and somewhat cumbersome (Scheme III).



Scheme III

(b) Allylic halides: One important quality of any truly general annulation reagent is that it be capable of trapping the regiospecifically produced enolate ion formed by reduction of an enone with lithium in liquid ammonia. This reductive alkylation process accomplishes several difficult tasks:[34,35] (1) formation of a trans-decalone system, from starting octalone (2) specific production, if need be, of the thermodynamically less stable enolate ion and (3) monoalkylation of the enolate ion without accompanying dialkylation. In addition to methyl iodide only allylic or benzylic halides have the reactivity required for this type of alkylation to proceed in high yields, and thus they have the greatest possibility of being successful as general annulation reagents.

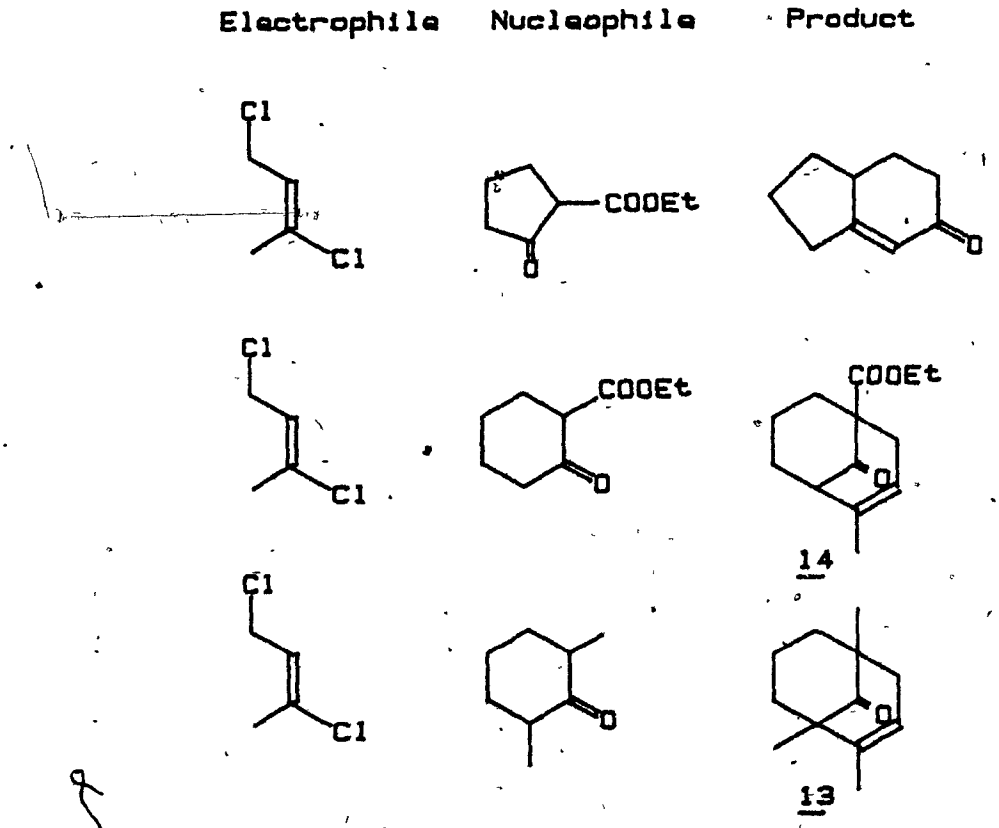
A widely used 3'-oxobutyl equivalent is 1,3-dichloro-2-butene. This reagent was first used by Wichterle in cyclohexenone synthesis illustrated below.[36] Since that time, use of this reagent in an annulation sequence has been commonly referred to as the Wichterle reaction (eq 8).[37]

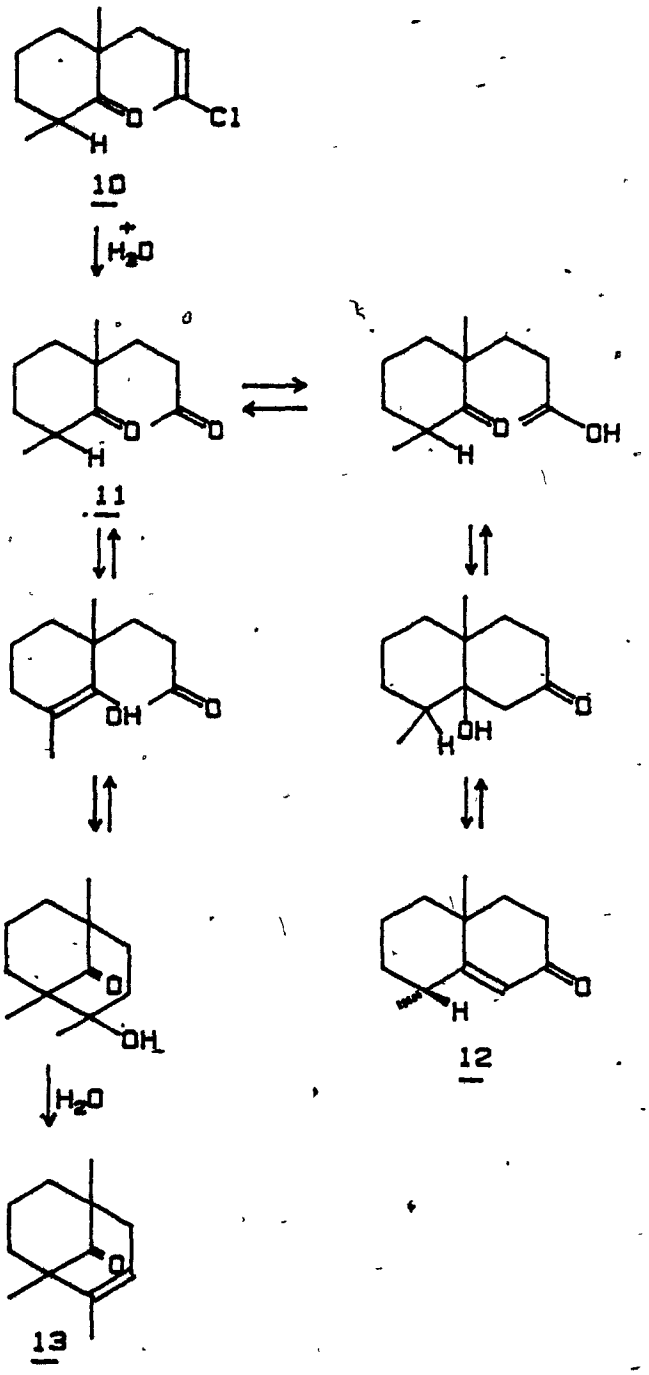


(8)

The chief drawback to the use of this procedure is the fact that extremely harsh acid hydrolysis is required to generate the side chain carbonyl. Quite often these harsh conditions lead to unwanted side products such as 13 and 14 sometimes as the major annulation product.[38,39] These products are formed as a result of enolisation of the endocyclic ketone carbonyl and aldolisation as shown in the series of equations below.

Table I: Annulation using 1,3-dichloro-2-butene.

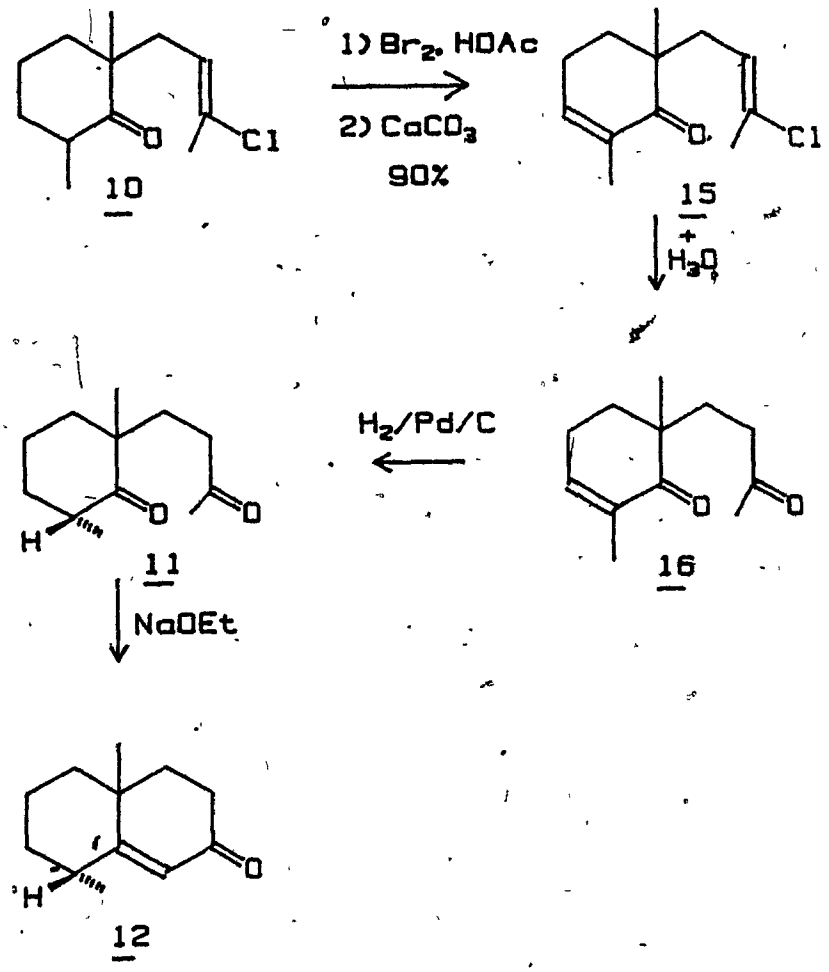




Scheme IV

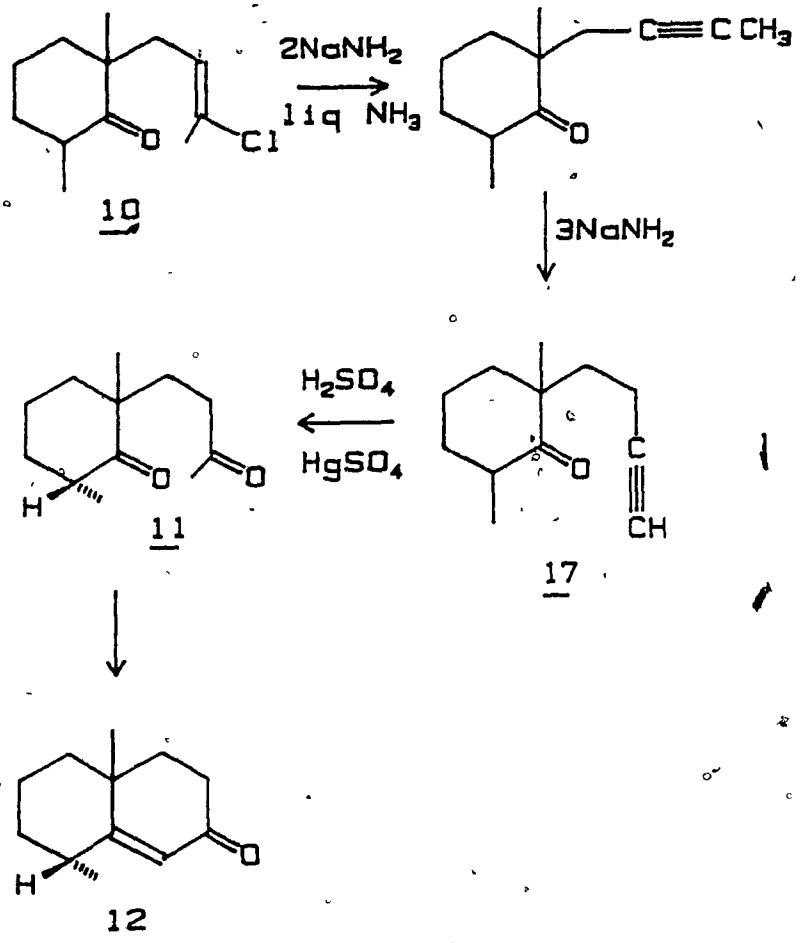
Marshall and Schaeffer[39] have developed the scheme outlined below, which circumvents the above mentioned problems. The scheme involves bromination, dehydrobromination of the ketone 10 to enone 15, followed by strong acid

treatment to hydrolyse the vinyl chloride. Reduction of enedione 16 provided the dione 11, which was cyclized to the desired octalone, 12, in 65% yield (Scheme V).



Scheme V

Caine and Tueller [40] subsequently showed that the vinyl chloride side chain of 10 can be dehydrohalogenated and then isomerized to the terminal acetylene 17 with strong base. Hydration of the alkyne 17 produces the desired diketone 11, which can be cyclized as before to octalone 12 in 62% overall yield from 10 (Scheme VI).



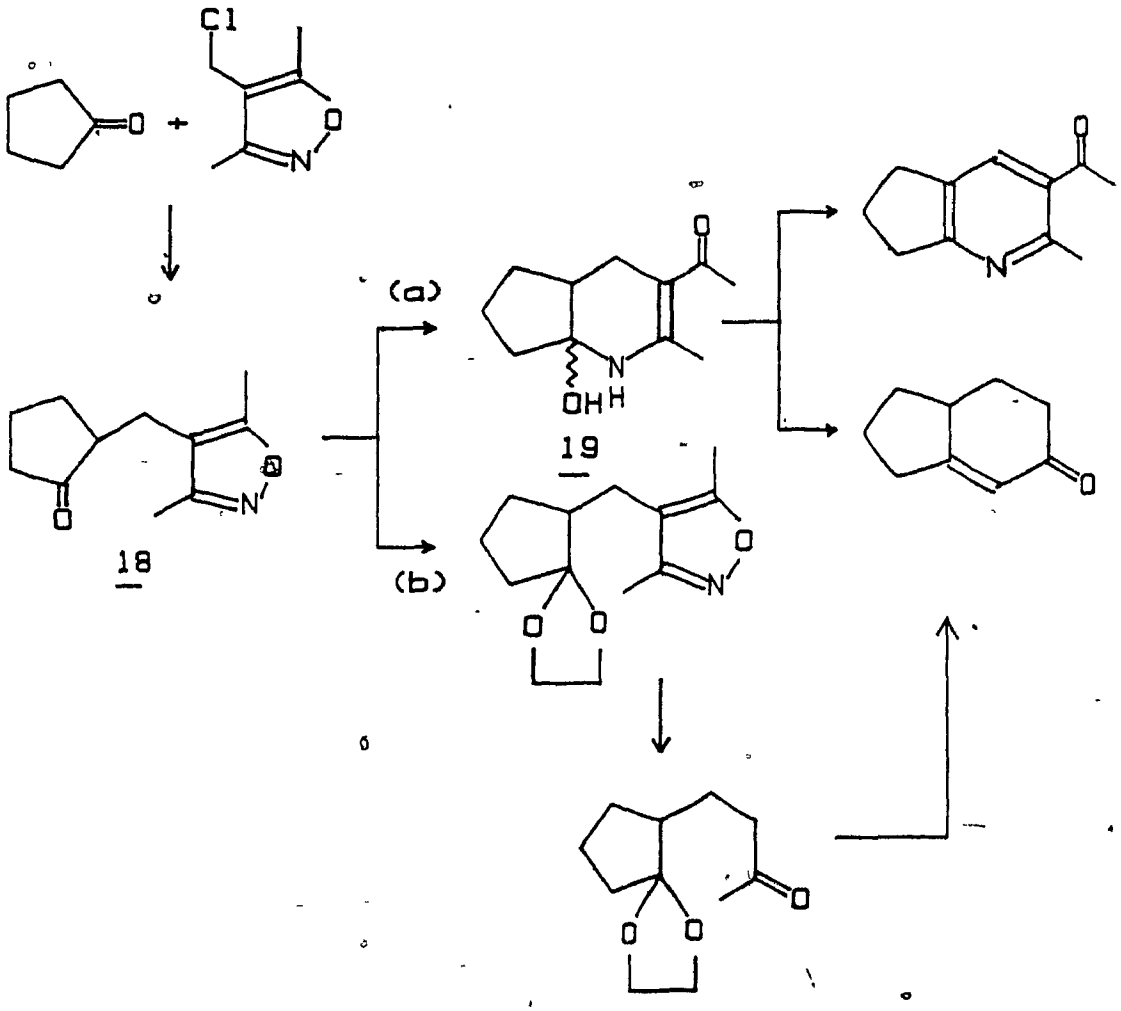
10 11 12 17

Scheme VI

The following three annulation sequences using isoxazole, tiglate, and vinylsilane are probably the most general yet developed. Each possesses to a certain extent most of the properties of an ideal annulation reagent, namely: (1) high reactivity so that normal alkylation occurs in high yield and enolate trapping in the reductive alkylation scheme is successful; (2) moderate stability and an efficient method of preparation; (3) the ability of modifying the preparative scheme so that homologues (including bis-annulation reagents) can be readily produced and (4) an easily unmasked carbonyl function.

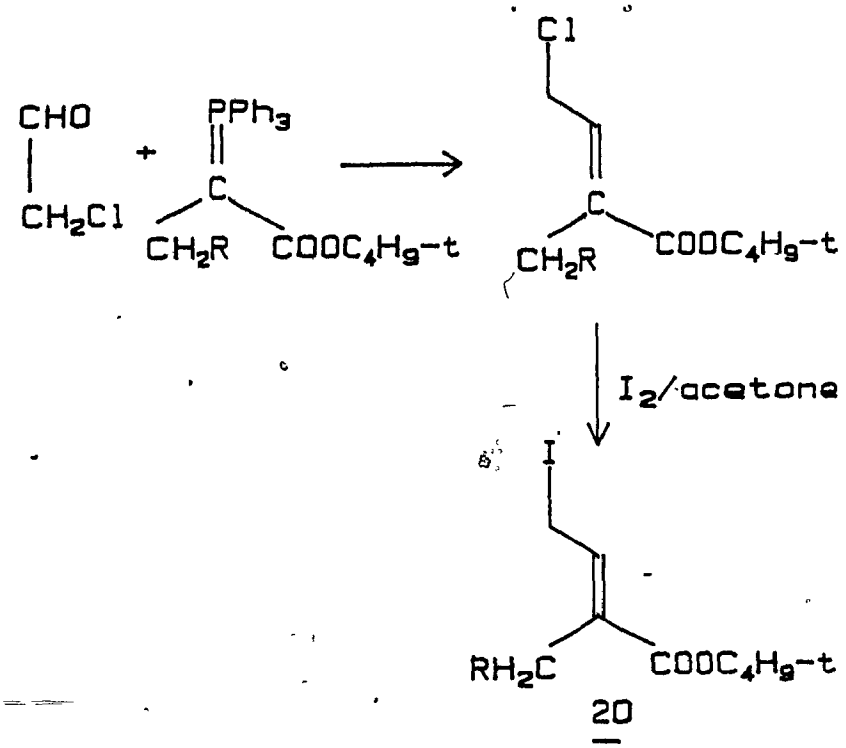
The isoxazole annulation, as first introduced by Stork,[44,42] and later improved by Scott, Banner, and Saucy,[43] has

been shown to be applicable to sequences involving alkylation by either enolates or enamines.[18,41] The only drawback to the original procedure as outlined by Stork is that dihydropyridine intermediate 19, involved in the deprotection/ring closure step can undergo aromatization. This side reaction can be avoided by acetalization of the endocyclic ketone 18 before reducing/hydrolyzing the isoxazole ring (Scheme VII).



Scheme VII

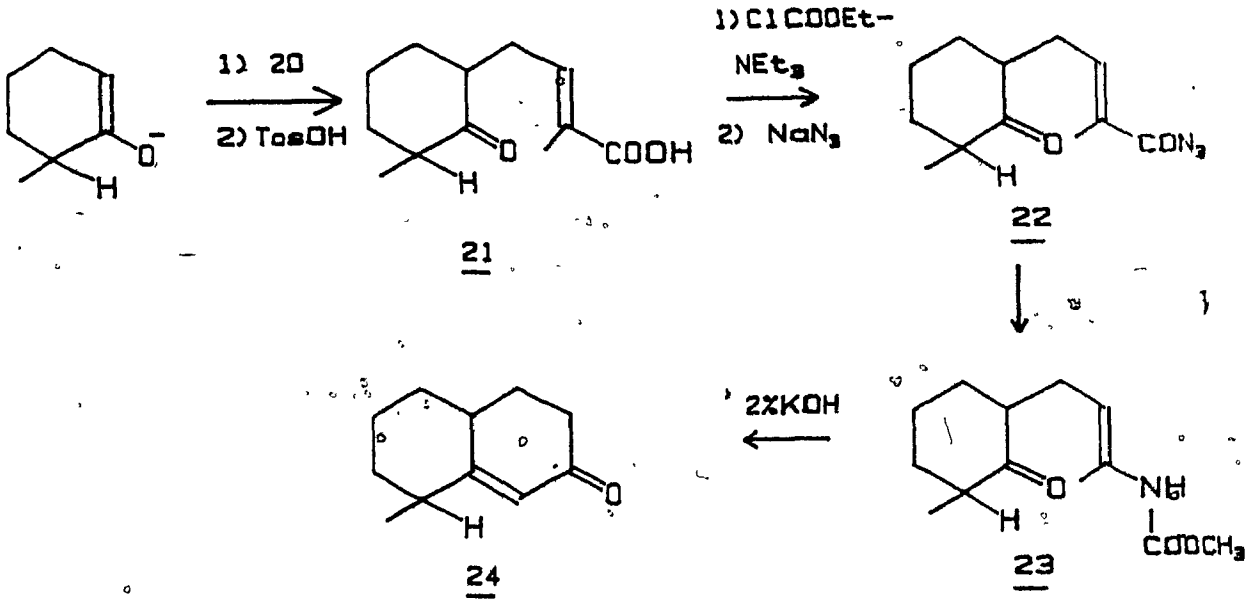
The tiglate sequence, developed by Stotter,[44] employs t-butyl γ-iodotiglate 20 as the annulating reagent. This reagent was also shown to be successful as an alkylating agent for the enamines and enolates. Furthermore, regiochemically unstable enolates, generated in tetrahydrofuran, were shown to undergo alkylation with no prior equilibration of the enolate. The γ-iodotiglate was prepared from the γ-chloro analog, which was prepared via a variant of the Wittig reaction (eq 9).



(9)

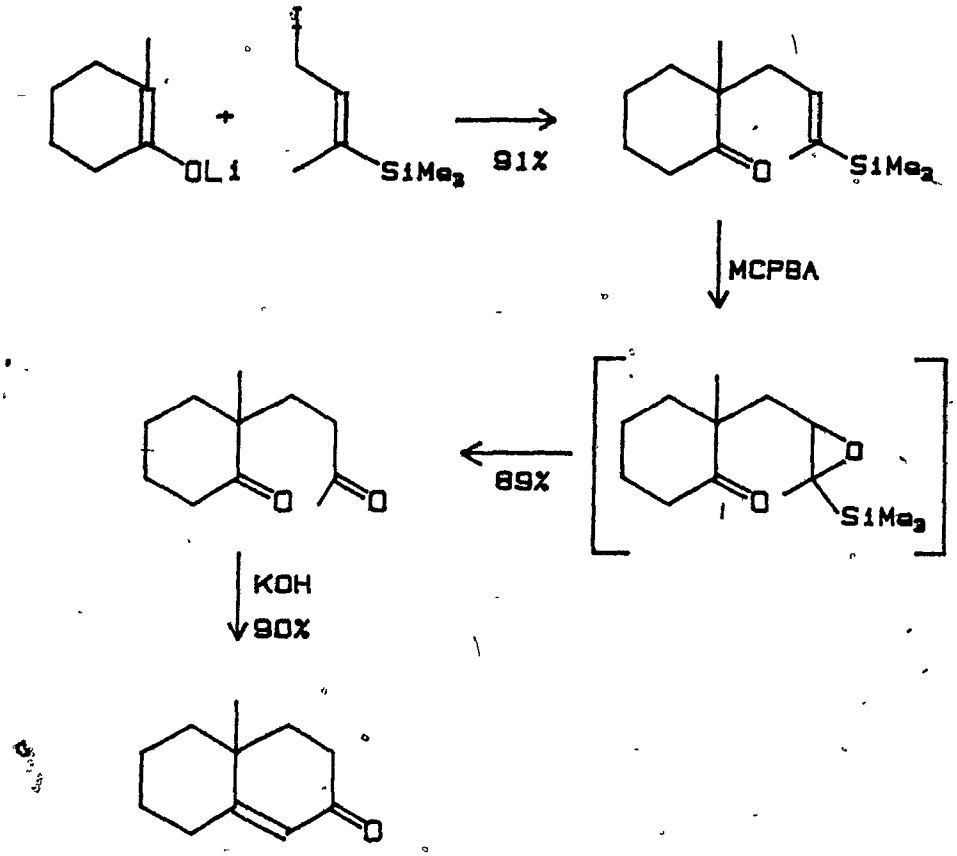
The oxidation of the side chain to the "masked carbonyl" vinyl carbamate 23 was carried out under mildly basic conditions via acyl azide 22 using the Weinstock modification [45] of the Curtis degradation. Hydrolysis of the carbamate and concomitant cyclization/dehydration of the intermediate dione to the enone may be accomplished in one

step. The overall yield for conversion of the α,β - unsaturated acid 21 to 24 is 83% (Scheme VIII).



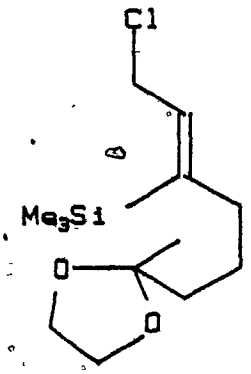
Scheme VIII

Stork and Jung developed a general annulation sequence, the vinylsilane method.[46,47] This procedure employs halomethyl vinylsilanes, and in particular E-3-trimethylsilyl-2-butenyl iodide as reactive alkylating agents. This reagent was shown to be successful in alkylations using both enamines and enolates as nucleophiles. Also, regiochemically unstable enolates were shown to undergo alkylation before equilibration. The general reaction scheme is illustrated for the annulation of 2-methyl cyclohexanone (Scheme IX).



Scheme IX

The vinylsilane reagents are easy to prepare and are quite stable, perhaps due to the inductive effect of the silyl group on the double bond which should decrease the tendency toward 1,4-dehydrohalogenation. Another important advantage of the vinylsilane reagents is the stability of the vinylsilane moiety to dissolving metal reductions. Also a bis-annulation vinylsilane reagent 25 has been prepared and used in annulation sequences.[48]

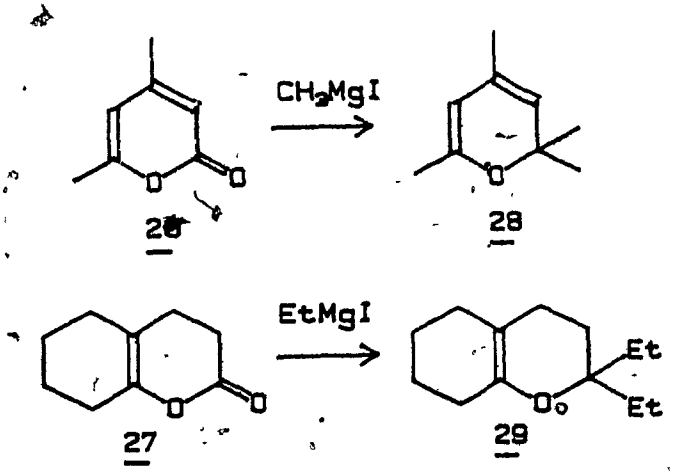


25

B. Fujimoto-Belleau reaction:

The conversion of a δ-enol lactone to a conjugated cyclohexenone by Grignard reaction followed by acid treatment is referred to as the Fujimoto-Belleau reaction.[49]

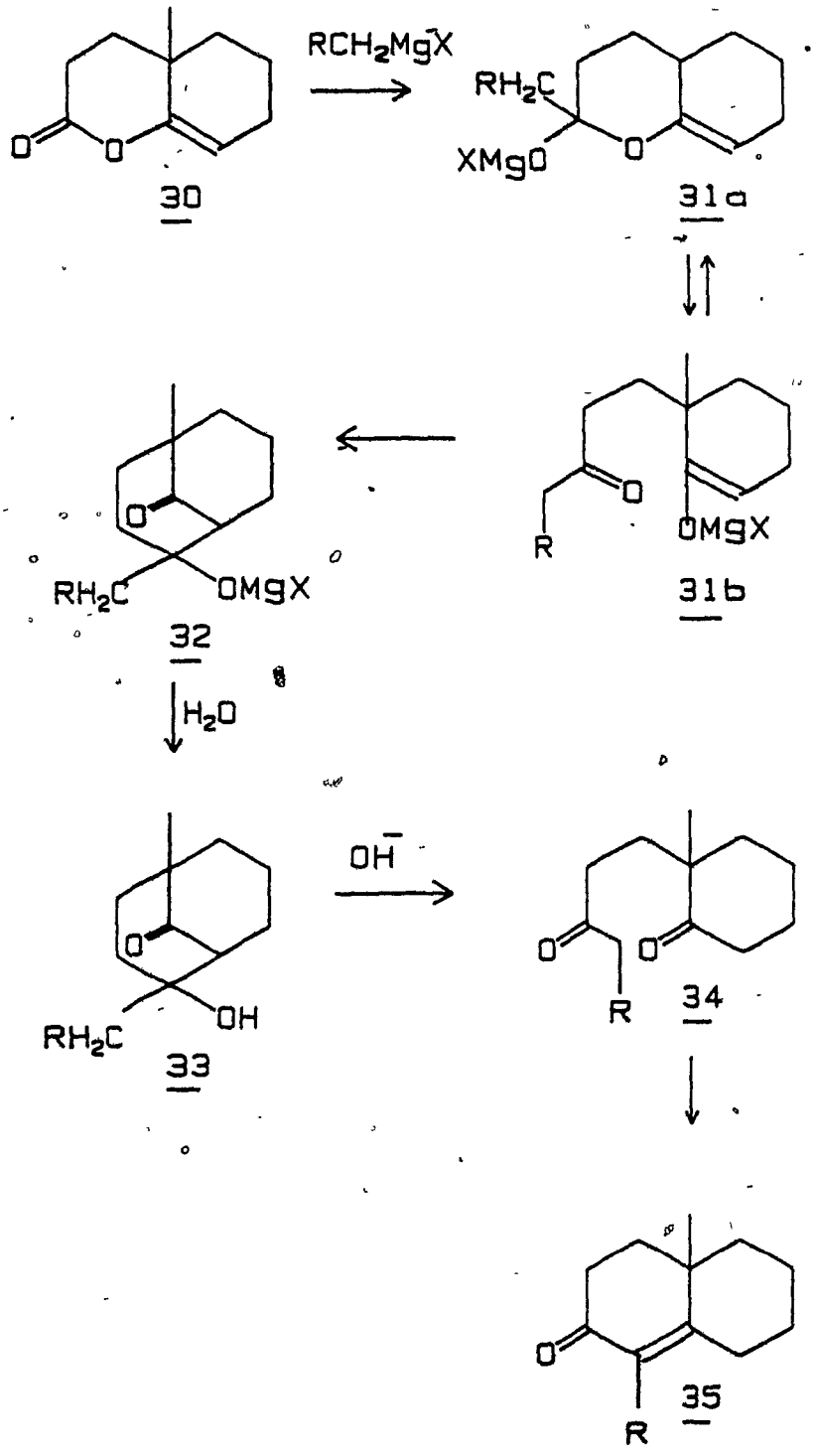
The reaction of Grignard reagents with saturated esters and lactones involves the addition of two equivalents of the reagent to give a tertiary alcohol. Some unsaturated lactones undergo a similar reaction; for instance, α-pyrones 26 or enol lactones containing an endocyclic double bond 27 affords products (28 and 29, respectively)[50,51] in which the carbonyl oxygen atom has been formally replaced by the two organic residues (eq 10).



(10)

If the lactone is annulated to a carbocyclic ring containing a double bond which is exocyclic to the lactone

group and is part of an enol lactone system(i.e., compound 30), usually only one equivalent of the organometallic compound enters into the reaction. After the addition of one equivalent of the Grignard reagent, the reaction gives an give an equillibrium system 31a⇌31b, the enolate form of which easily rearranges to give a bridged keto alcoholate 32. This internal aldolisation (31a ⟶ 32)[52] occurs faster than the reaction of the initial addition product (31a ⇌ 31b) with a second equivalent of Grignard reagent. Furthermore, reaction of Grignard reagent with the keto alcoholate of type 32 is in general prevented by steric hindrance of the keto group, especially when Grignard reagents with bulky organic residues were used.[53] The ketol obtained upon hydrolysis undergoes a base-catalysed reverse aldol condensation to the 1,5-diketone 34, which then cyclizes to the final enone product 35 (Scheme X).


RCH2MgX
RH2C
XMgO
30
31a
31b
OMgX
R
32
RH2C
OMgX
H2O
OH⁻
33
RH2C
OH
34
R
35
R

Scheme X

C. Diels-Alder reaction:

The addition of alkenes to dienes is a very useful method for the formation of six-membered carbocyclic rings. The reaction is known as the Diels-Alder reaction.[54] The concerted nature of the mechanism was generally agreed on and the stereospecificity of the reaction was firmly established even before the importance of orbital symmetry was recognized. In the terminology of orbital-symmetry classification, the Diels-Alder reaction is a $[\pi 4_s + \pi 2_s]$ cycloaddition, an allowed process. The stereochemistry of both the diene and the alkene (the alkene is often called dienophile) is retained in the cyclization process. The transition state for cycloaddition requires the diene to adopt the s-cis conformation. The diene and the dienophile approach each other in parallel planes. The orbital-symmetry properties of the system permit stabilization of the transition state through bonding interactions between C-1 and C-4 of the diene and the carbon atoms of the dienophilic double bond in a six-centre arrangement (Fig. 1).

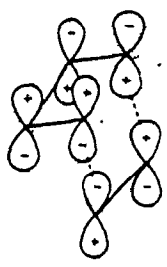
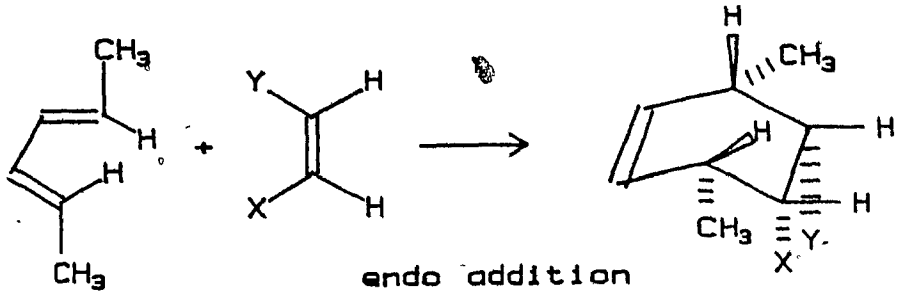


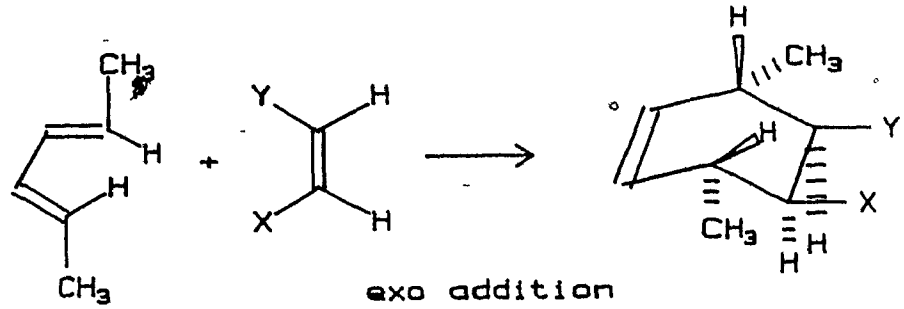
Fig. 1

There is a further stereochemical variable in the transition state, which can lead to mixtures of products in some cases. This involves the relative orientation of the

diene and the dienophile in the transition state. The two possible orientations which are referred to as endo addition and exo addition are illustrated below.



endo addition



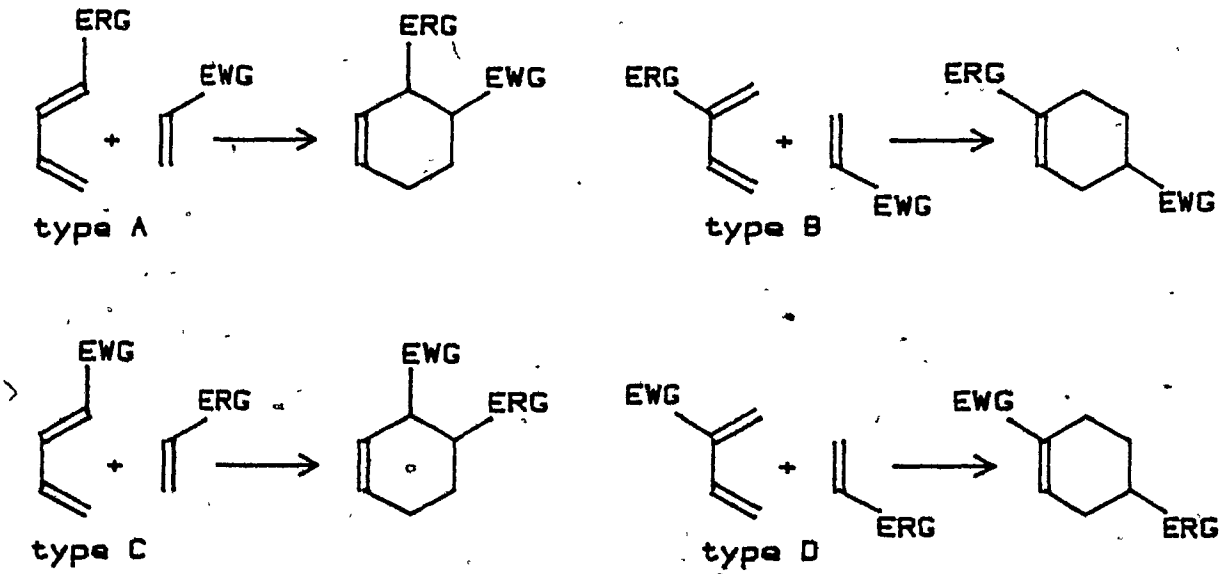
exo addition

Usually, the endo mode of addition is preferred, especially when X or Y is an unsaturated group such as carbonyl. The preference for this mode of addition, which is often sterically more congested, is the result of a combination of dipolar and Van der Wall attractions, as well as orbital interactions involving X or Y and the diene system. The relative importance of each of these factors in determining the exo:endo ratio probably varies from system to system.[55,56]

There is a well established electronic substituent effect in the Diels-Alder addition. The most favorable alkenes for reaction with most dienes are those bearing electron withdrawing groups. Thus, among most reactive dienophiles are

quinones, maleic anhydride, and nitroalkenes. α,β - Unsaturated esters, ketones, and nitriles are also effective dienophiles. It is significant that if a relatively electron-deficient diene is utilized, the polarity of the transition state is apparently reversed, and electron-rich dienophiles are then preferred.[57]

A question of regioselectivity arises when both the diene and the alkene are unsymmetrically substituted. Generally, there is a preference for the "ortho" and "para" orientations. The basis for the regioselectivity of the Diels-Alder reaction can be interpreted very satisfactorily in terms of frontier molecular orbital theory.[58] The pattern of regioselectivity of the Diels-Alder reaction is shown below (Scheme XI).



a. ERG, electron-releasing group
b. EWG, electron-withdrawing group

Scheme XI

The interpretation of these regiochemical effects is based on the orbital approach and the coefficients of the frontier orbitals at the reaction centers. In reactions of type A, it is expected that the frontier orbitals will be the diene HOMO and the diene LUMO. This is because an electron-releasing group will raise the energy of the diene HOMO and an electron-attracting group will lower the energy of the dienophile LUMO. These two orbitals should therefore be quite close in energy and will provide the frontier orbital interaction. In types C and D, the opposite pairing of LUMO and HOMO would be expected, since the diene will posses an orbital lowered in energy by the electron-withdrawing group, while the orbitals of the dienophile will have been raised by the electron-releasing group. These relationships are illustrated in Fig. 2.

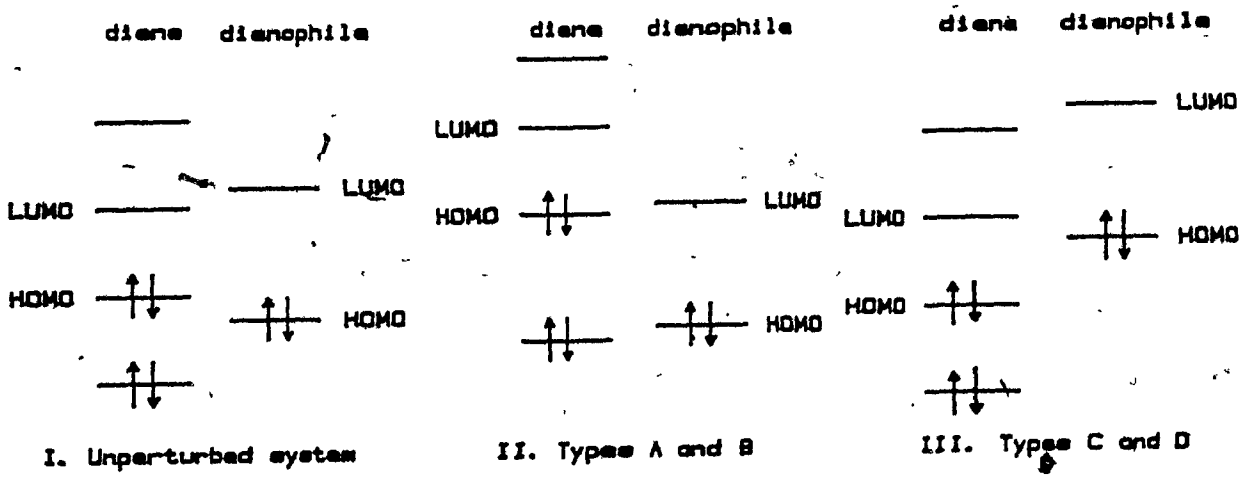
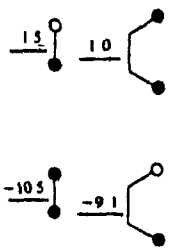


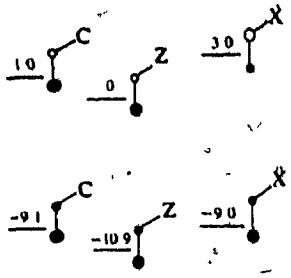
Fig. 2. Frontier orbital interactions in Diels-Alder reactions

Figure 3 gives the approximate values of the orbital coefficients for various substituted dienes and dienophiles. Relative orbital energies are also estimated in the figure.

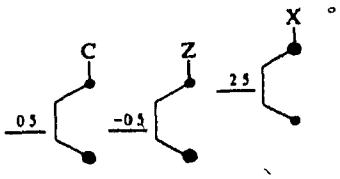
As shown in Figure 3, the LUMO of dienophiles with electron-withdrawing groups has a large coefficient at the carbon which is β to the substituent. For dienes with electron-releasing groups, the HOMO has its largest coefficient at C-4. The stongest frontier orbital interaction therfore occurs between C-4 of the diene and C-2 of the dienophile and leads to the regioselectivity shown in case A of Scheme XI. A similar analysis of each of the other combinations in Scheme XI by using the diagrams in Fig. 3 leads to the regioselectivity indicated.

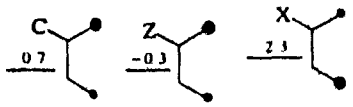


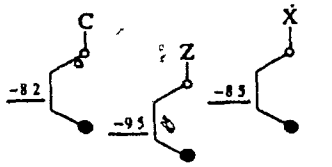
unperturbed system

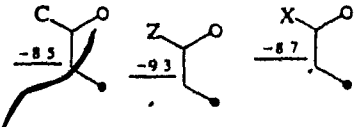


substituted dienophiles









1-substituted dienes

2-substituted dienes

Orbital energies are given in electron volts. The size of the circles give indication of orbital coefficients at each carbon.

Z= conjugated electron-withdrawing substituent, e.g., C=O, NO_2

C= conjugated group with modest electron-releasing capacity.

X= electron donating substituent, e.g., OCH_3, NH_2.

Fig. 3 Coefficients and relative energies of dienophile and diene molecular orbitals

Diels-Alder reactions are sensitive to steric effects of two major types. Bulky substitution on the dienophile or on the temini of the diene can hinder approach of the two components to each other and decrease the rate of the reaction. This can be seen in the reactivity of 1-substituted butadienes toward maleic anhydride.[59]

R	k_{rel}(25° C)
-H	1
$-CH_3$	4.2
$-C(CH_3)_3$	<0.05

Substitution of hydrogen by methyl results in a slight rate increase, probably as a result of an electronic effect, while a 1-tert-butyl substituent produces a significant rate decrease. Apparently, any steric retardation to approach of the dienophile by a methyl substituent is insignificant compared to its electronic effect. With the very large tert-butyl group, the steric effect is dominant.

The other steric effect has to do with intramolecular Van der Wall repulsions between substituents in the diene. Adoption of the s-cis conformation of the diene in the transition state may be accompanied by an unfavorable repulsion between substituents that do not interact strongly in the ground state. Toward tetracyanoethylene, trans-1,3-pentadiene is 10^3 times more reactive than 4-methyl-1,3-pentadiene because of the unfavorable interaction between the additional methyl substituent and the hydrogen at C-1 in the s-cis conformation.[60]

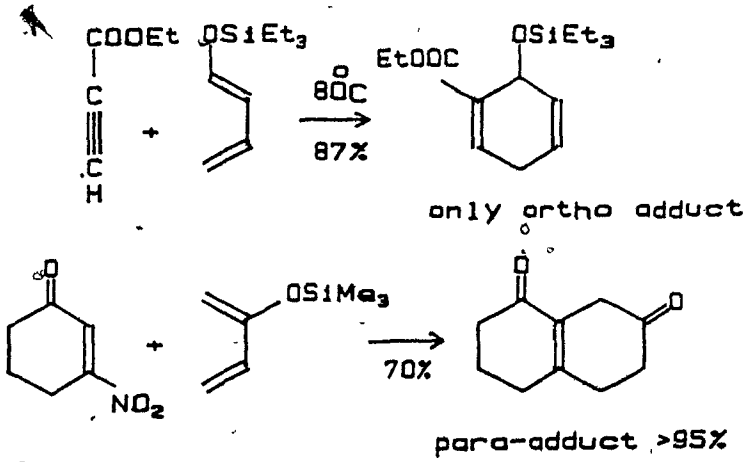
Lewis acids, particularly aluminum chloride, have been noted to catalyse Diels-Alder cycloadditions.[61-63] The catalytic effect is attributed to coordination of the Lewis acid with the dienophile. The complexed dienophile is then more electron deficient toward the normal electron-rich olefins. The mechanism of the addition is still believed to be concerted, and high stereospecificity is observed.

Siloxydienes as enophiles in Diels-Alder reactions:

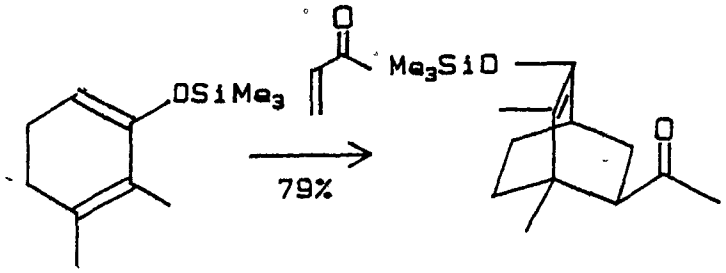
The Diels-Alder reaction of siloxy-substituted 1,3-butadienes has been one of the growth areas of silyl enol ether chemistry in the last ten years. There are now too many examples to be covered completely here. A number of total syntheses, particularly from Danishefsky's group have employed this reaction.[64] The main advantages of siloxybutadienes as Diels-Alder dienes are ease of preparation and high regioselectivity. A siloxy substituent on the diene increases the rate of cycloaddition with electron-poor dienophiles.

Mono-oxygenated butadienes:

1-(Triethylsiloxy)-butadiene[65] and 2-(trimethylsiloxy)-buta-1,3-diene[66] show a good regioselectivity in their reactions with dienophiles as shown below.

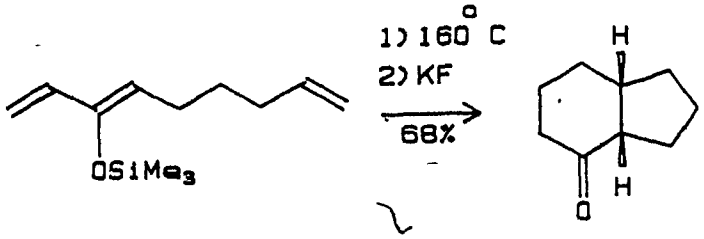


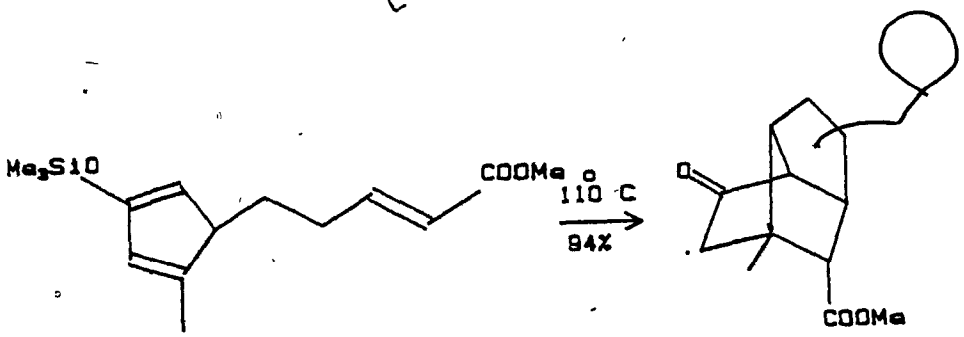
Simple 1- and 2-(trimethylsiloxy)-cyclohexa-1,3-dienes also undergo regioselective Diels-Alder reactions with electron-deficient alkenes, to give high yields of bicyclo[2.2.2]octanones after hydrolysis (eq 11).[67-70]



(11)

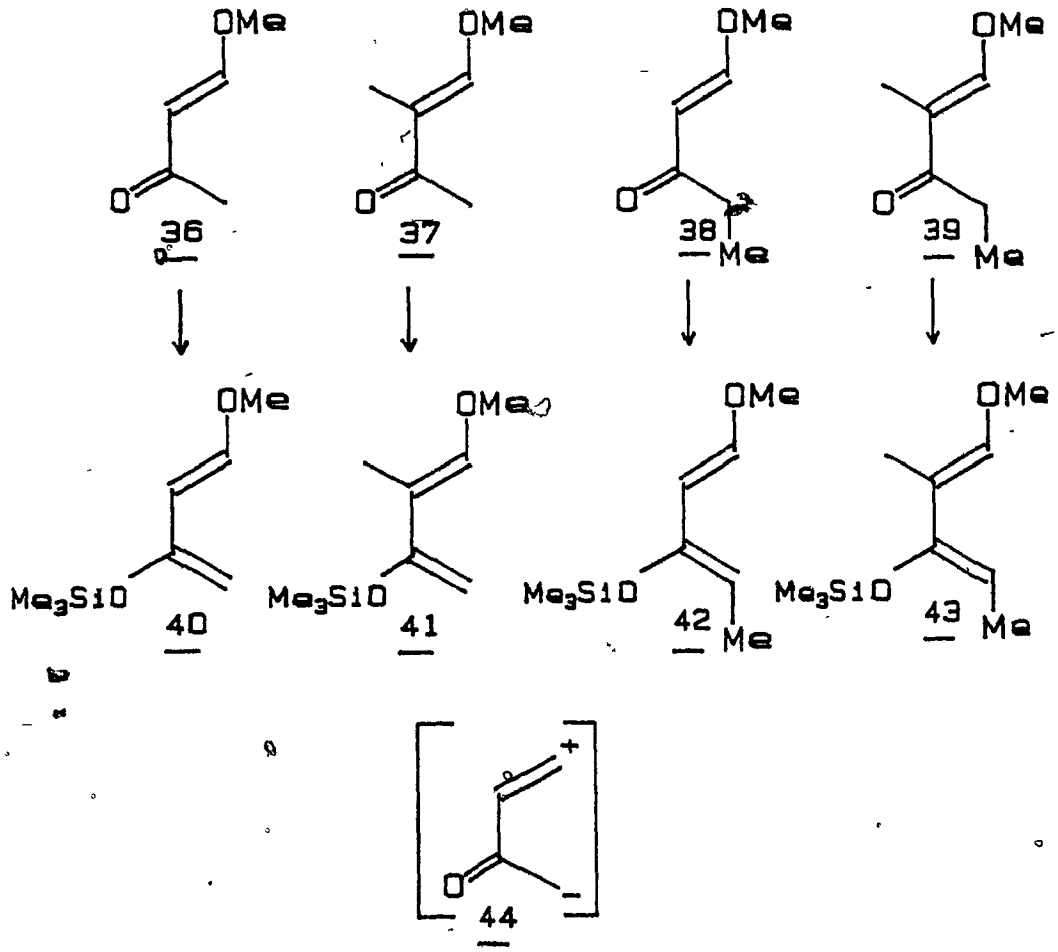
Some intramolecular Diels-Alder reactions of 2-siloxy butadienes are shown below.[71]





Di-oxygenated butadienes:

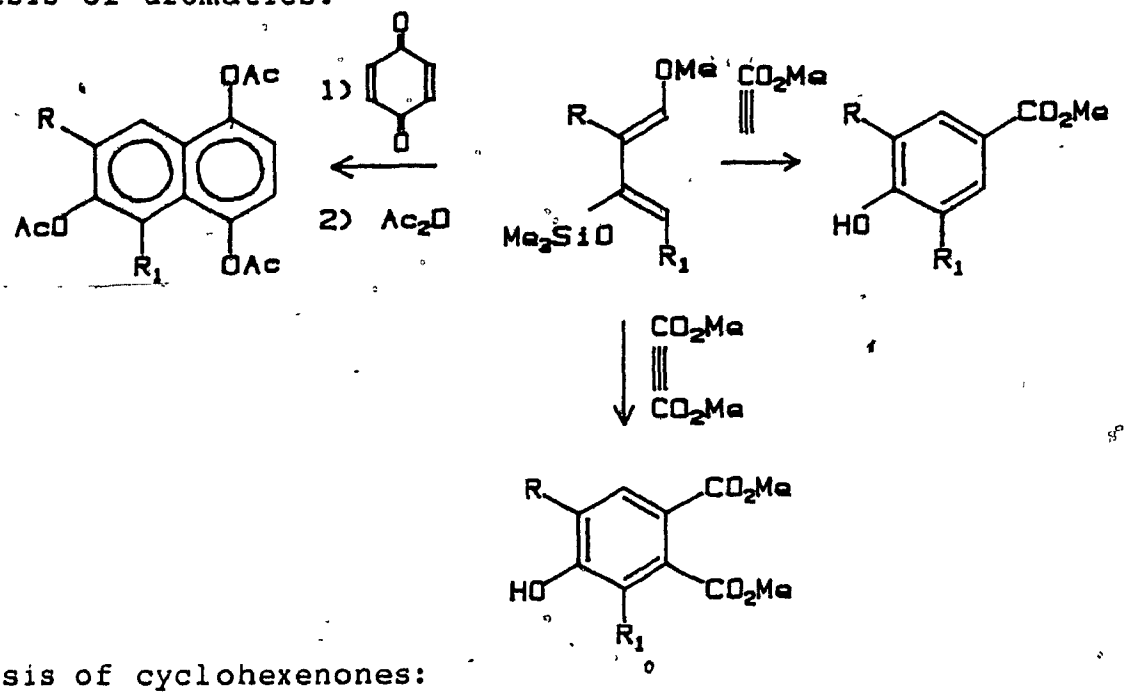
Danishefsky studied the preparation and Diels-Alder reactions of highly functionalized dioxygenated butadienes 40, 41, 42 and 43. These dienes were prepared by enol silylation of 36, 37, 38 and 39, respectively, with trimethylchlorosilane using triethyl amine-zinc chloride.[72-74]



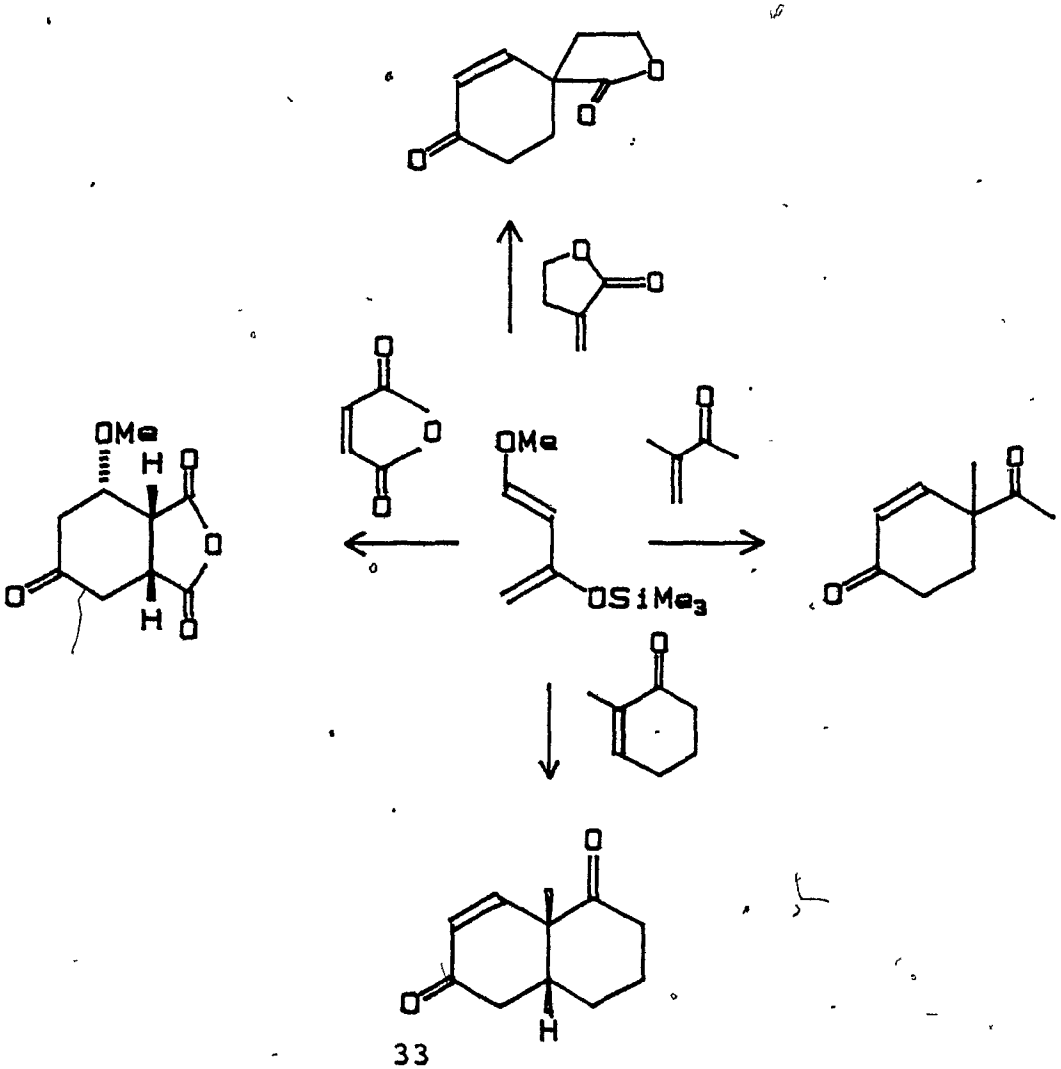
The use of these dienes in Diels-Alder reactions enables rapid access to diversely functionalized aromatics, cyclohexenones, cyclohexadienones, and 3-methoxycyclohexenones. The regioselectivity can be predicted by regarding 40 as a synthetic equivalent of the dipole 44.

Some examples are given below:

Synthesis of aromatics:

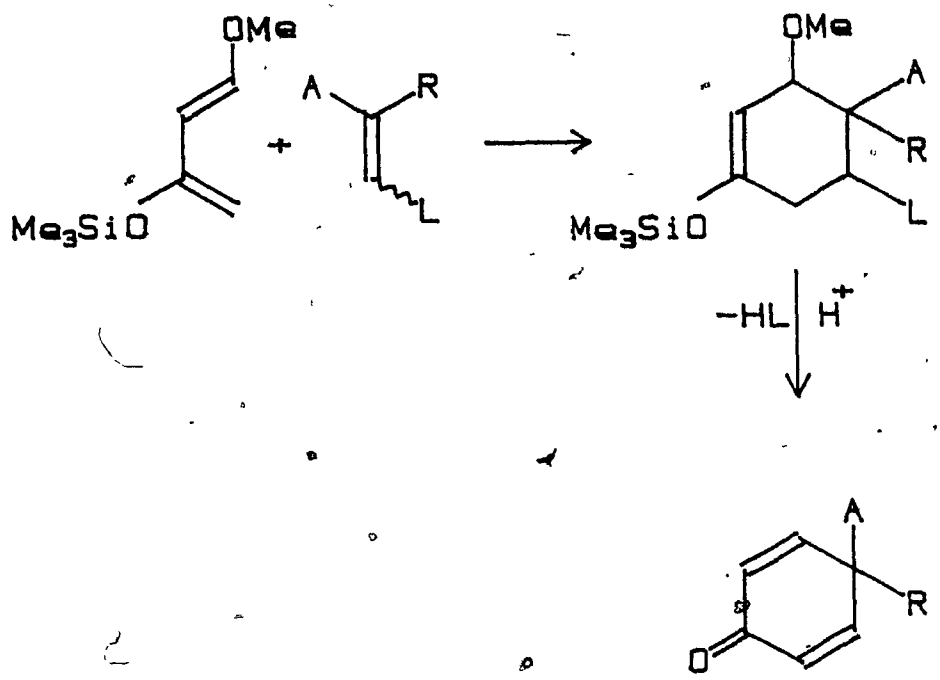


Synthesis of cyclohexenones:



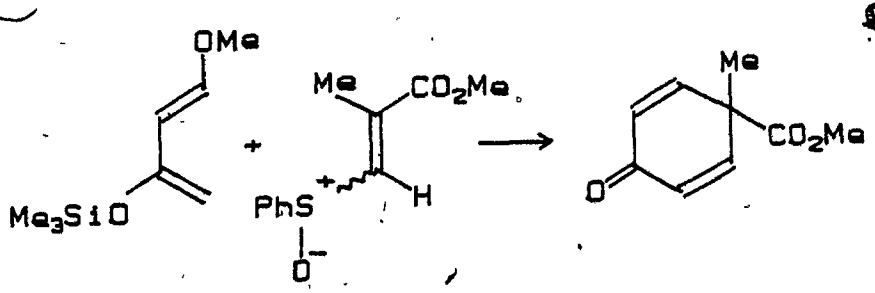
Synthesis of cyclohexadienones:

Cyclohexadienones were prepared according to the following scheme.[75]



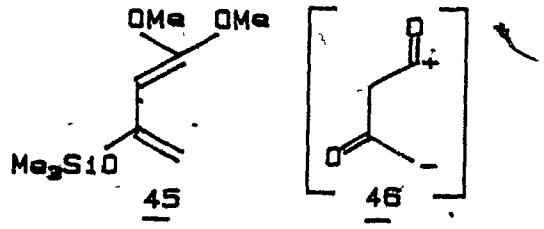
Scheme XII

The key feature of the above scheme is that the leaving group L must not, in itself, compete with the A function for control of the regiochemistry of the cycloaddition step. The arrangement L=PhS(O) nicely optimized the above requirement. Furthermore, the elimination of HL must be facile, and must allow for the survival of the very sensitive target system (eq 12).

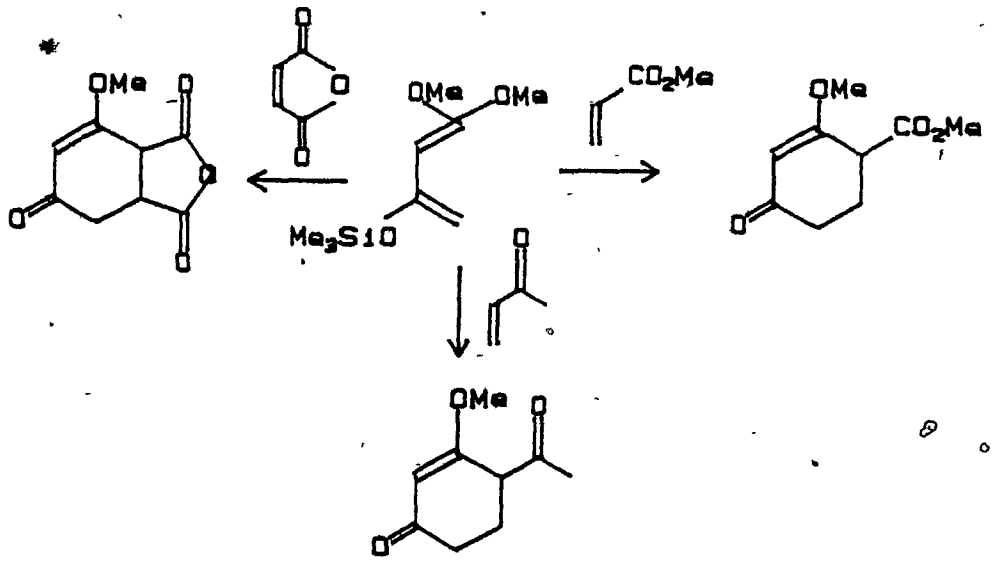


(12)

3-Methoxycyclohexenones: 1,1-Dimethoxy-3-(trimethylsiloxy)-buta-1,3-diene 45, a synthetic equivalent of 46, undergoes Diels-Alder reactions even more readily than Danishefsky's diene 40, and with equally high regioselectivity to give 3-methoxycyclohexenones.[74,76]



45 46

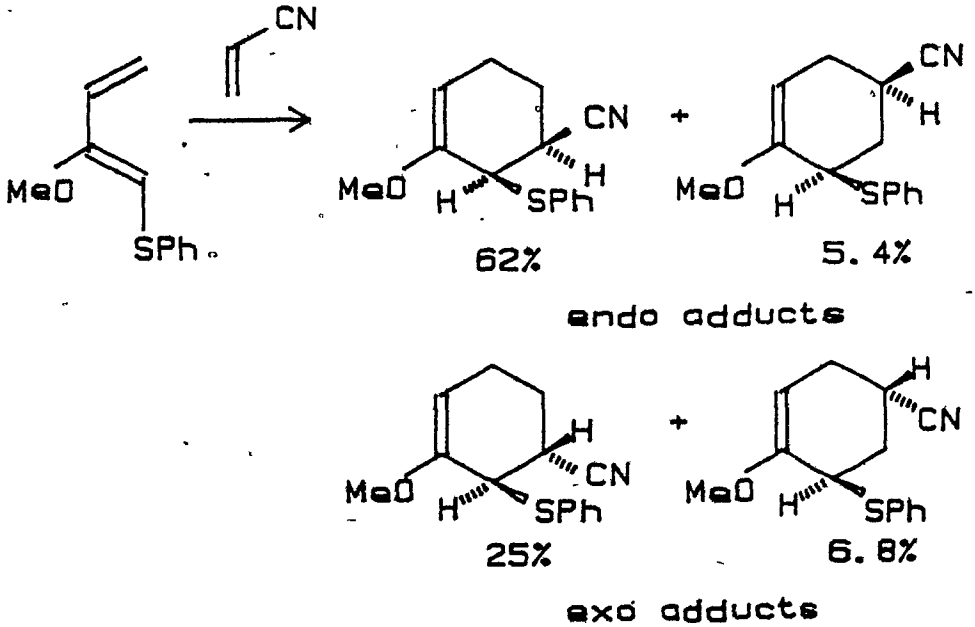


Sulfur as a regiochemical control element in Diels-Alder reactions:

The introduction of hetero-atom substituted dienes as cycloaddition partners has allowed the creation of cyclohexanes with functional groups in masked forms. These dienes have led to several creative applications in the synthesis of complex natural products. Trost, Kozikowski and Cohen have studied the dienes with both sulfur and oxygen substituents in the 1,2- and 1,4- and 2,3- substituted patterns with special emphasis on the role of sulfur as a regiochemical control element in Diels-Alder reactions.[77-81]

1,2-substituted dienes:

Cohen[77] has studied the reactions of 1-(phenylthio)-2-methoxy-1,3-butadiene with a weaker dienophile such as acrylonitrile. Acrylonitrile as a dienophile was chosen in order to probe the weaker secondary orbital intractions in the transition state and also to promote the formation of the other possible isomeric products.



All four possible regio- and stereoisomers were formed and separated. As predicted by frontier molecular orbital theory, the ratio of ortho (phenylthio and cyano groups) to meta regio isomers is greater (three to four times) in the products of endo addition than in the products of exo addition, thus indicating the secondary orbital interactions, which can only ~~occur in~~ the transition state for the endo addition, play a substantial role in controlling regiochemistry.

2,3-substituted dienes:

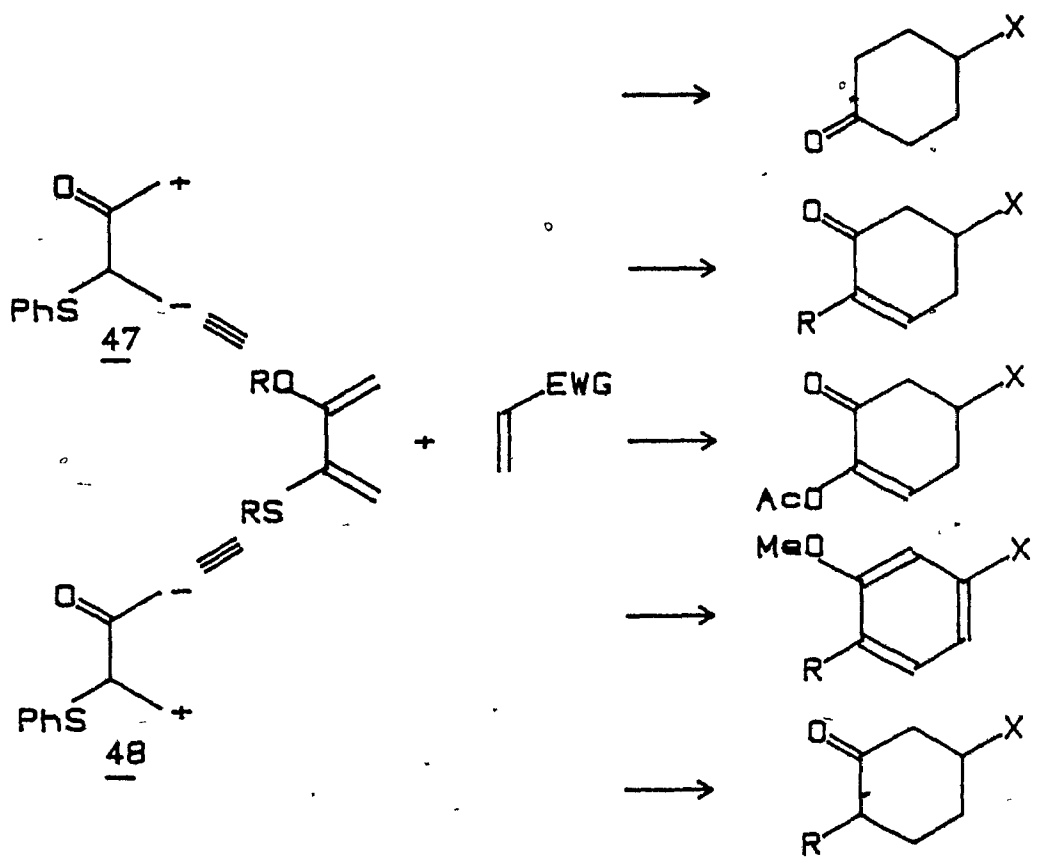
Trost[78,79] studied the preparation and cycloaddition reactions of series of 2,3-dihetero substituted 1,3-butadienes. These cycloadditions offer several advantages.

(i) the versatile β-keto sulfide moiety is introduced in a protected form which allows modification elsewhere;

(ii) dependent on diene substitution and reaction conditions, regiochemical control ranging from >50:1 with sulfur controlling to 1:8 with oxygen controlling could be attained and creates the equivalent of either dipole 47 or 48;

(iii) the regiochemistry obtained by sulfur control complements the normal regiochemistry obtained with 2-oxygenated dienes (combined with ease with which sulfur can be removed from organic molecules may make this a general approach to reversing the normal orientation of Diels-Alder reactions;

(iv) transformations in the following scheme are possible (Scheme XIII).

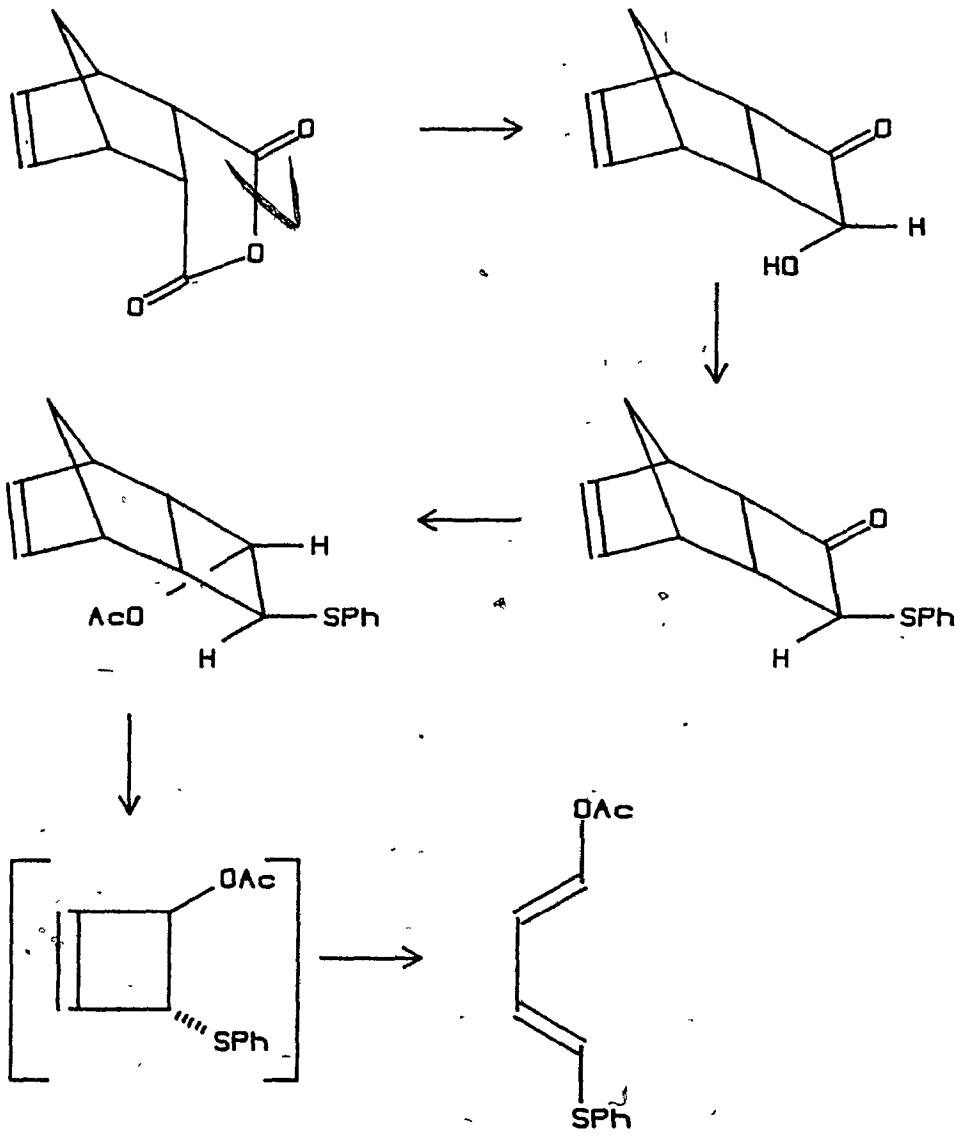


Scheme XIII

1,4-substituted dienes:

Trost prepared 1,4-disubstituted 1,3-butadienes from 4-hydroxy tricyclo[4.2.1.0]non-7-en-3-one which serves as a basic building block for a protected cyclobutene.[80] The rigid tricyclic framework allows stereocontrolled introduction of substituents at the 3,4 positions. Flash vaccum pyrolysis generates cyclopentadiene and a 3,4-disubstituted cyclobutene,

which suffers conrotatory opening <u>in situ</u> to give 1,4-disubstituted 1,3-butadienes. The ability to control the stereochemistry of substituent introduction in the tricyclic system translates into an ability to control diene stereochemistry (Scheme XIV).



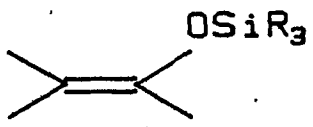
<u>scheme XIV</u>

CHAPTER II

CHEMISTRY OF 1-TRIMETHYLSILOXY-1-METHOXY-3-ALKYL(ARYL)THIO-1,3-BUTADIENES AND THE SYNTHESIS OF ARYL SULFIDES VIA CYCLO-AROMATIZATION REACTION.

A. Preparation of enol silyl ethers and silyl ketene acetals:

Silyl enol ethers 49 have been known for some considerable time,[82] and, from around 1968 on, have been used extensively in organic synthesis. Their utility lies initially in providing regiostable, isolable enol derivatives which can, on demand and after purification and spectral identification, give rise to regio-pure enolate ions.[83]



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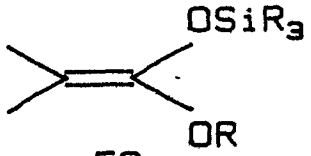


50

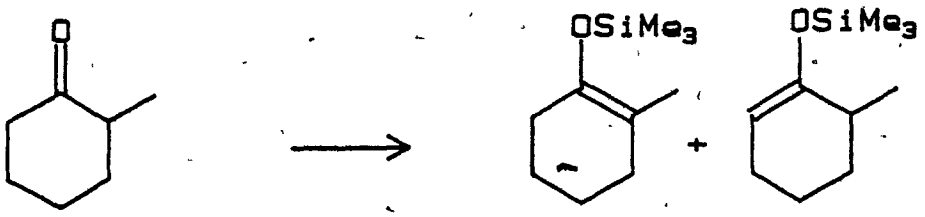
The major synthetic development of silyl enol ethers can be divided into three distinct phases.[84] These separate phases involve

1. The use of silylation as a trap for the kinetically generated or the thermodynamically equilibrated enolate anions, with subsequent isolation, regeneration and reaction with electrophiles under basic conditions.

2. Direct reaction of the silyl enol ether with suitable electrophiles which are reactive in their own right, or can be made so by addition of a Lewis acid catalyst.

3. The use of silyl enol ethers as synthons which give reaction products which are different from those obtainable by either of the first two phases.

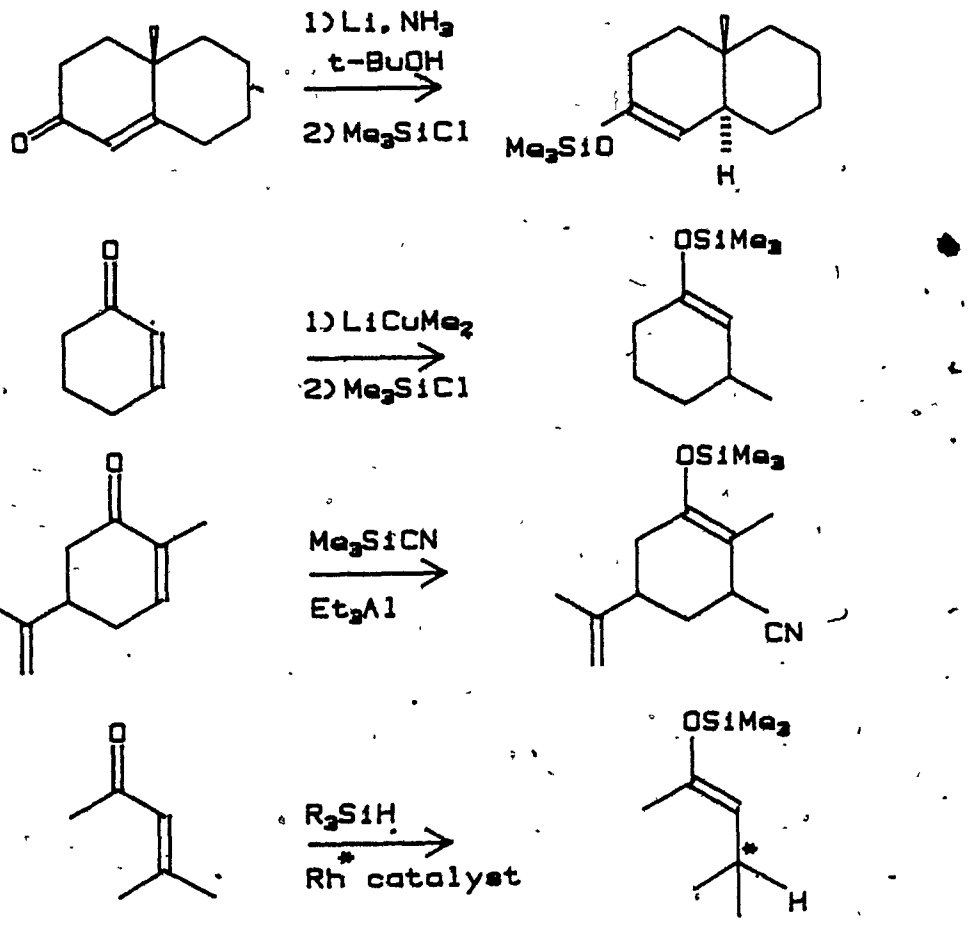
The most frequently used route to the preparation of silyl enol ethers is the trapping of enolate anions[28,84] generated under conditions of either kinetic or equilibrium control. The products of trapping correspond accurately to those of the free enolates in a particular mixture, and considerable regioselectivity can be attained (eq 13).[30,31,37,85,86]



(i) LDA, DME, −78C Me_3SiCl	1	99
(ii) Me_3SiCl, DMF, Et_3N	78	22
(iii) Me_3SiI, $HN(SiMe_3)_2$	90	10

The ability to obtain only one of the two regioisomeric silyl enol ethers derivable from an unsymmetrical ketone is of critical importance to further synthetic utility, and

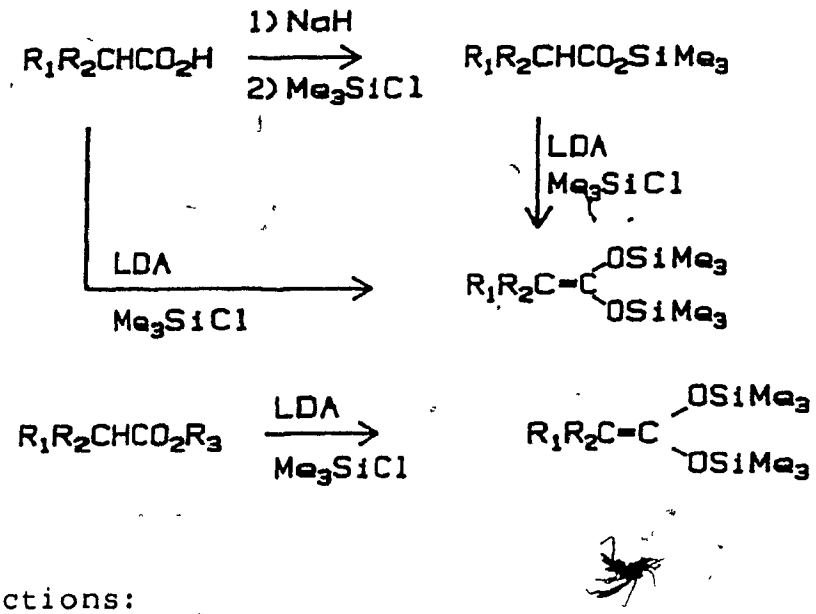
accordingly, much effort has been expended in this direction. Regiospecific generation can be achieved in a number of ways, including the trapping of the enolate ion formed from a α,β-unsaturated ketone by conjugate reduction,[14] conjugative alkylation,[13,87] conjugative hydrocyanation,[88] rhodium-catalyzed hydrosilylation[89,90] etc.



Scheme XV

The most generally applicable route for the preparation of silyl ketene acetals 50 mirrors one of the major routes to silyl enol ethers. Monoanion derived from α-hydrogen abstraction of alkyl and trimethylsilyl ester or carboxylic

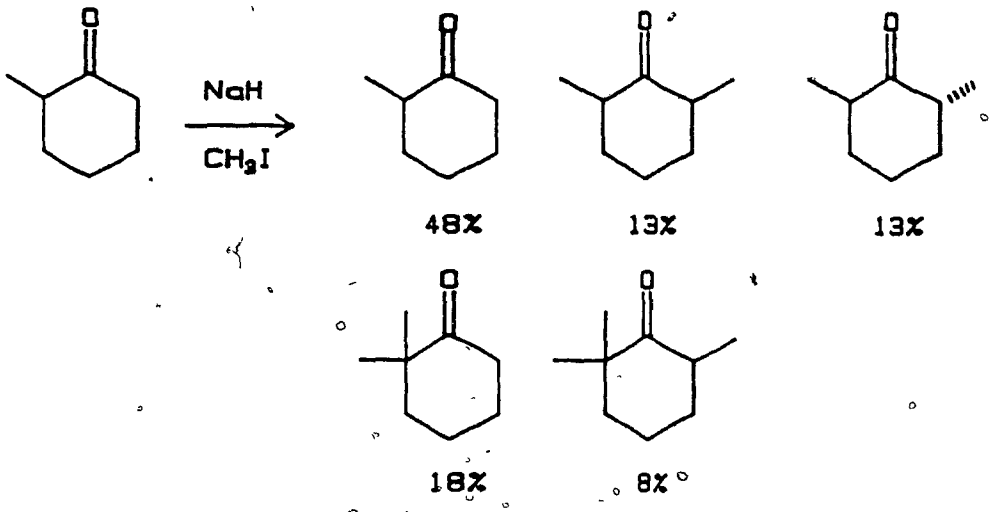
acid dianions, are smoothly silylated with trimethylsilyl chloride to give the corresponding ketene acetals as shown below.[91]



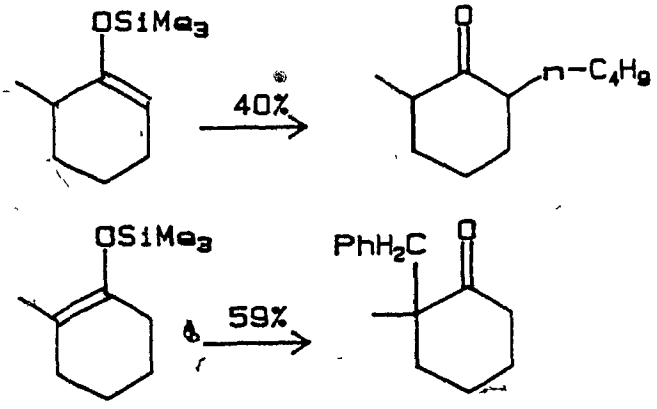
B. Reactions:

It would be impossible to cover here all cases of applications of silyl enol ethers in organic synthesis. The area has been well reviewed and discussed on various occasions.[83,92] Some of the the major uses of silyl enol ethers in organic synthesis will be briefly highlighted here.

(1) Alkylation: The role of enolates in the formation of C-C bond is well recognised, but it is not without problems.[93] These problems include: (a) poly-alkylation, (b) O-alkylation instead of C-alkylation, (c) a specific enolate may not be alkylated regiospecifically and (d) alkylation is limited to primary or secondary halides.[37] For example, alkylation of cyclohexanone with iodomethane under basic conditions gives a mixture of products as shown below.



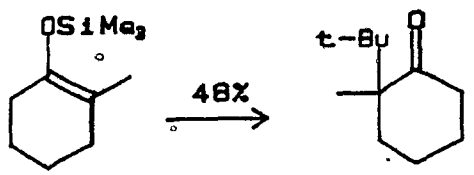
Trimethylsilyl enol ethers, on the other hand are cleaved by flouride ion or with methyllithium to give enolate anions without equilibration.[94,95] In the alkylation reactions of these generated enolates, the crude reaction mixture contained only the regiospecifically monoalkylated ketone, unreacted alkyl halide, and the ketone resulting from simple hydrolysis of the starting silyl enol etner; no product of polyalkylation or of regioisomeric alkylation was detected (eq 14).



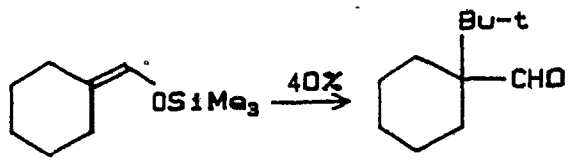
(14)

The attempted introduction of tertiary alkyl groups in the alkylation of enolate anions as nucleophiles resulted in

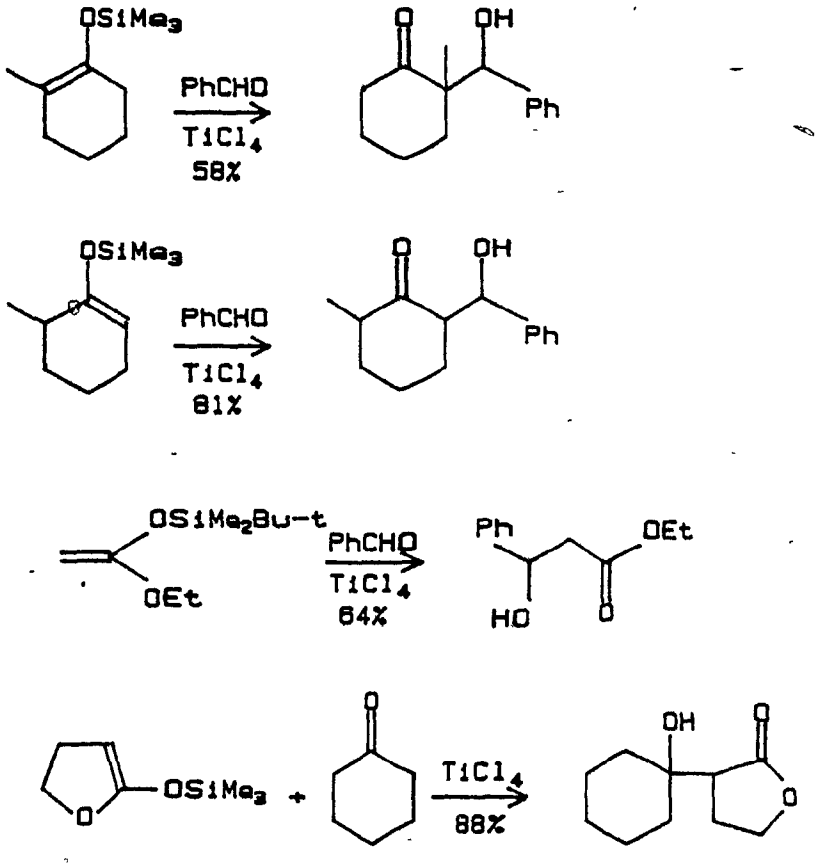
predominant β-elimination processes occuring on the alkylating agent. e.g., a tertiary alkyl halide. On the other hand, using enol silyl ethers, and with the electrophilicity of the alkylating agent enhanced via Lewis acid catalysis, a wide range of tertiary alkyl groups can be smoothly and regiospecifically introduced, even in those cases which result in the establishment of adjacent quaternary carbon atoms (eq 15).[96]



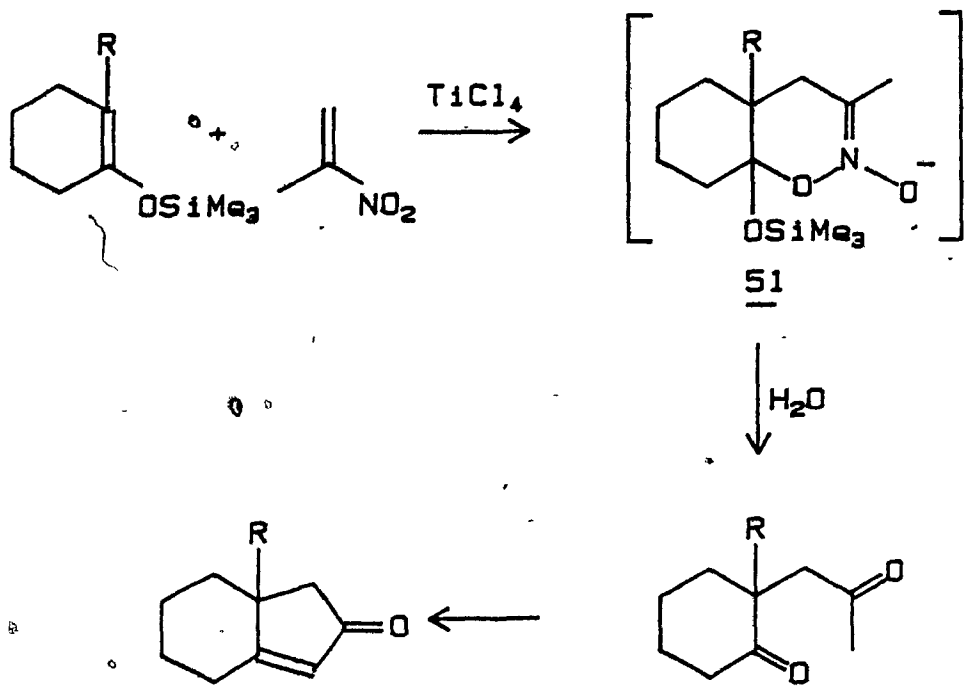
(15)



2. Aldol condensation: The aldol condensation between two carbonyl compounds is normally carried out under basic conditions. Under these conditions, dimers, polymers, and dehydration products are often formed as by-products.[98] More critical is the problem of ensuring specific direction in the condensation, i.e., that one particular carbonyl component will act as nucleophile and the other as the electrophile. The Lewis acid catalyzed condensation of a silyl enol ether with an aldehyde or ketone, unlike the traditional aldol condensation, shows complete regio- and chemoselectivity, and provides high yields of the aldol products.[99] Some examples are shown below. Silyl ketene acetals also follow a similar pattern in their reactions with carbonyl compounds.



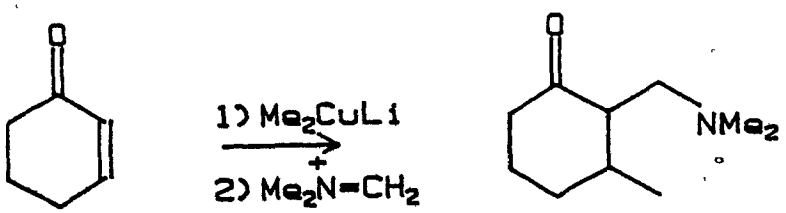
3. Michael reaction: Silyl enol ethers undergo Lewis acid catalyzed Michael addition with α,β-unsaturated carbonyl compounds[100] and their derived acetals, α,β-unsaturated esters and α,β-unsaturated nitro compounds.[101] For example, with α,β-unsaturated nitro compounds, the corresponding 1,4-diketones are obtained directly, possibly by way of a nitronate ester such as 51. The reaction appears to be of wide generality, and is regio-specific, leading, after aldol closure and dehydration, to a variety of substituted cyclopentenones (Scheme XVI).



Overall yield: 50-60%

Scheme XVI

4. Mannich reaction: Ketone-derived silyl enol ethers give products of Mannich condensation regiospecifically and in high yield when treated with dimethyl(methylene)ammonium iodide.[102] Similar regiospecificity is observed with acid-, ester- and lactone-derived silylketene acetals.[103] The enolates generated by conjugative addition to α,β-unsaturated ketones can be trapped similarly (eq 16).



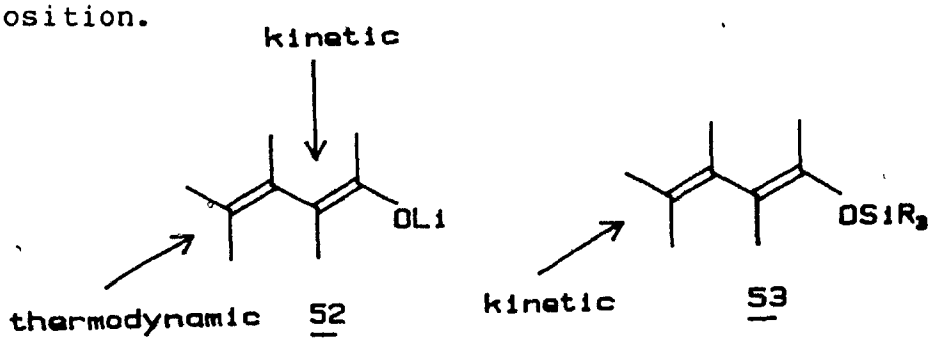
(16)

Silyl enol ethers and silylketene acetals also found wide applicability in reactions such as Claisen

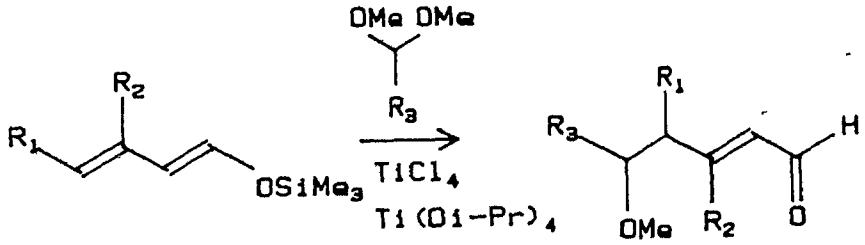
condensation,[104] Stobbe condensation,[105] hydroboration,[106] Simmons-Smith reaction[107] etc.

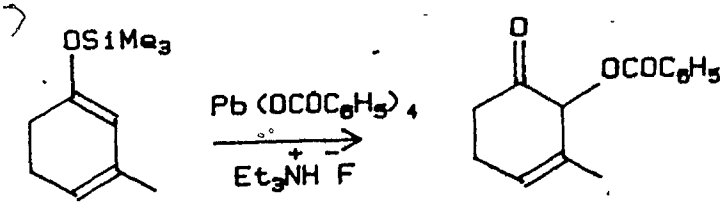
C. Silyl dienol ethers and bis(silylenol) ethers:

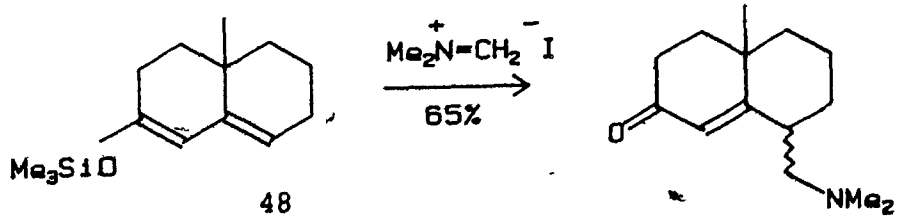
Lithium dienolates 52 undergo electrophilic attack under kinetic conditions to give, generally speaking, products of α-substitution. Under thermodynamic, equilibrating conditions[108] γ-substituted products are usually more favored. Silyl dienol ethers 53, on the other hand, being neutral, have a lower electron density at the α-position, and accordingly show a marked preference for kinetic electrophilic attack at the γ-position.



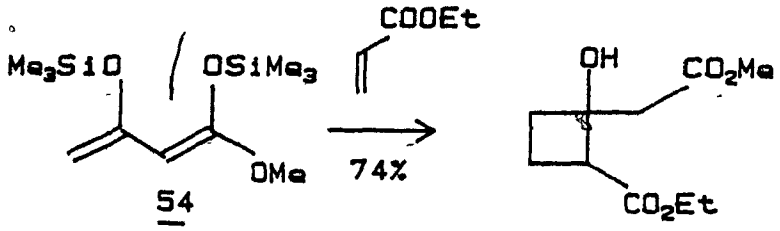
The chemistry of dienolates and dienol silyl ethers complement each other, as evidenced by the following reactions.







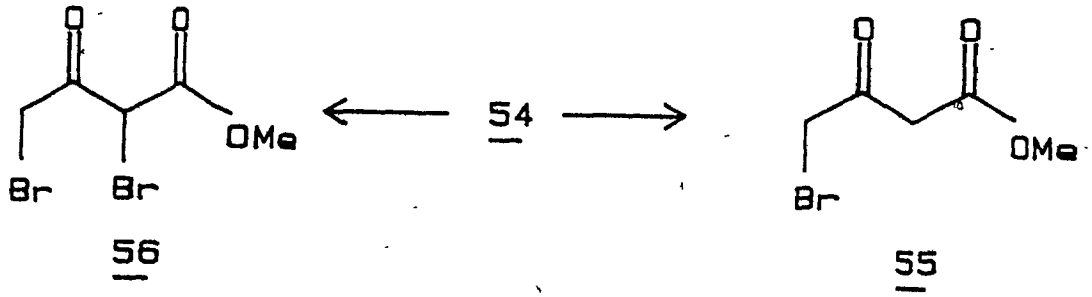
The dianion of methyl acetoacetate functions as a hard nucleophile, attacking α,β-unsaturated carbonyl compounds in a 1,2-fashion.[109] The bis(silylenol) ether 54, on the other hand, behaves as a soft nucleophile, adding conjugatively to α,β-unsaturated substrates.[110] Owing to the functionality of the product, further condensation can then occur. Thus, reaction with ethyl acrylate produces the cyclobutane system (eq .17).



(17)

D. Cycloaromatization reactions of bis(silylenol) ethers:

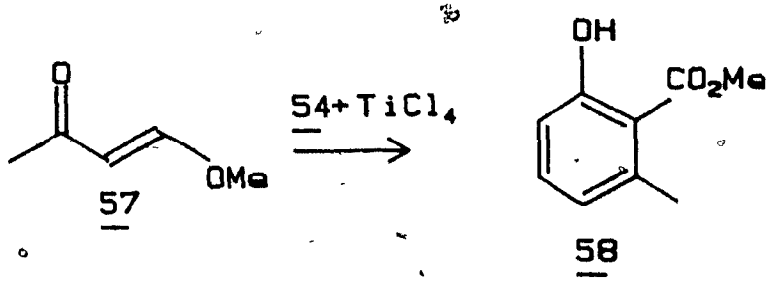
The bis(silylenol) ether 54 behaves as a 1,3-dinucleophile with C-4 being more reactive (δ^{--}) than C-2(δ^{-}). This is illustrated by its reaction with bromine; 54 reacts with 1 mole of bromine to give 55 and with 2 moles of bromine to give 56.[110]



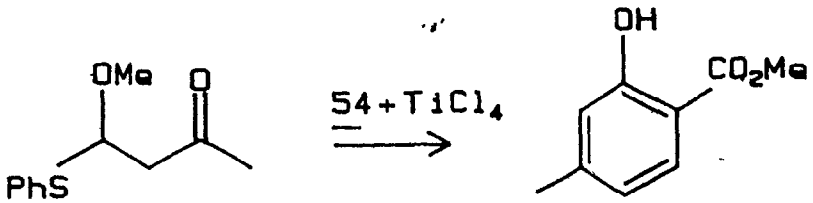
56 55

Because of difference in reactivity between the C-2 and the C-4 positions, the condensation of 54 with unsymmetrical 1,3-diketone derivatives can lead to cycloaromatization products with controlled regiochemistry. Thus the reaction of

with 4-methoxybut-3-en-2-one 57 gave exclusively 58 on the one hand, but with 4-methoxy-4-phenylthiobutan-2-one 59 gave 60.[111]



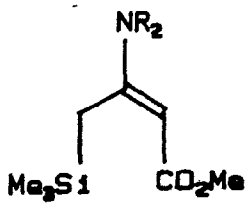
57 58



59 60

A range of other α,β-unsaturated substrates and masked -dicarbonyl compounds can be employed, resulting in a regiospecific (3C+3C) construction of substituted salicylic acid esters. Using this methodology a series of substituted tetralene and phenanthrene derivatives have been synthesized with a high degree of regiocontrol.[111] Such an approach has been used for the synthesis of sclerin[112] and Δ^1-tetrahydrocannabinol.[113]

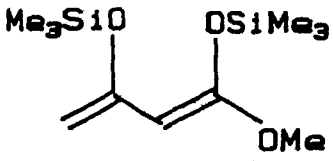
The C-silylated compound 61, a 1,3-dinucleophile, also put into effective use in the synthesis of anilino compounds.[114]



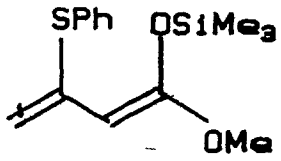
61

E. Proposed research:

In compound 54, two nucleophilic sites are present, each is associated with a silyl enol ether. Compound 63 is a 3-thio analog of 54. Several features of 63 are of interest and a study of its chemistry in detail is warranted.



54



63

(i) One may like to know whether the regioselectivity of 63 in its reactions with electrophiles is influenced by the presence of the thio group.

(ii) The second question relates to the ability of 63 to act as a dinucleophile even though it is only a mono enol silyl ether. The aromatic compounds which are derived from the cycloaromatization of 54 must by necessity be limited to phenolic derivatives. It would be desirable to be able to generalise the cycloaromatization reaction to the synthesis of other functionalized aromatic compounds. Compound 63 offers as an entry to the synthesis of arylsulfides in a regiochemical manner.

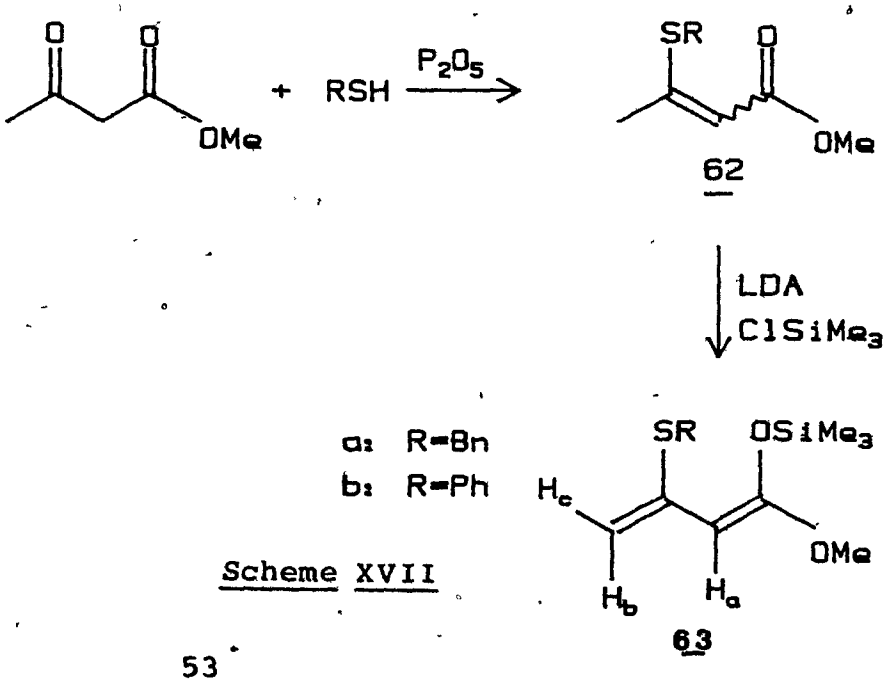
(iii) The role of 63 as a Diels-Alder diene is also of interest. Compound 63, with the oxygen and sulfur substituents in the 1,3 pattern, offers the advantage that the Diels-Alder adduct would be a 1,3-cyclohexadienone with the carbonyl groups differently masked.

(iv) The tendency of 63 to act as a Michael donor is also of interest. It offers certain advantages over the Diels-Alder reaction, however, in that the stereochemistry of the ring junction is amenable to control. The product would have three carbonyl groups which are differently masked and can be manipulated separately. It can serve as the entry point to an array of multifunctional target molecules.

F. Results and Discussions

(i) Preparation of 1-trimethylsiloxy-1-methoxy-3-alkyl(aryl)thio-1,3-butadiene

Methyl 3-thio-E-2-butenoates 62 can be prepared readily by literature procedure from diketene.[115] Alternatively, methyl acetoacetate can react with thiols and P_2O_5[116] to give a mixture of E- and Z- 62. Reaction of 62 and lithium diisopropylamide(LDA) in tetrahydrofuran at -78° followed by quenching of the anion with chlorotrimethylsilane gave the enol silyl ether 63 in good yield (scheme XVII). NOE experiments established the stereochemistry of 63b to be Z. Thus irradiation of methoxy protons resulted in a positive NOE on H_a resonance at 4.11 ppm. Similar NOE measurements established the chemical shifts of H_b and H_c. The stereochemistry of 63a was assigned as Z as well in view of the similar chemical shifts of the vinyl protons in their ^1H nmr spectra. On the other hand, the same stereoisomer was obtained even though the starting 62 contains a mixture of E and Z isomers.

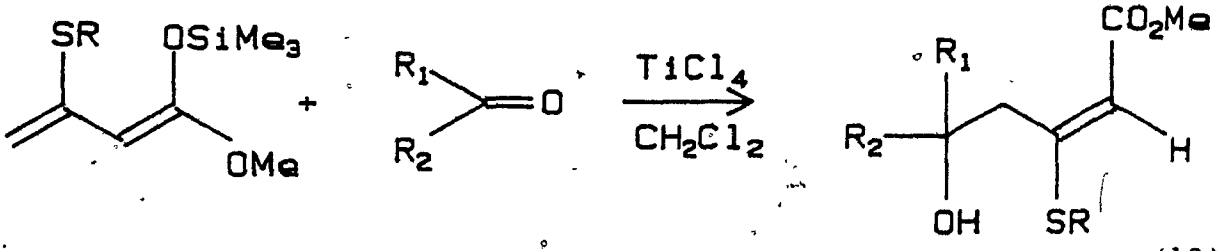


Scheme XVII

Compound 63 appears to be less sensitive to moisture in air than the corresponding bis-enol ether 54. In our hands, 63 can be kept in the freezer (0°C) without deterioration for up to 4 weeks.

Reactions of 63 with carbonyl electrophiles

Compound 63 reacts with a number of carbonyl electrophiles under $TiCl_4$ conditions to give γ-products 64 exclusively in all cases. Regioselectivity in the reaction of dienyl silyl ether with electrophiles has been a subject of much recent studies.[117] Our present results indicate that thio substituent at the 3-position, like the corresponding 3-siloxy substituent, enhances the γ-selectivity. Another interesting observation is the fact the product 64 retains the enethiol ether structure. Furthermore, the stereochemistry of the olefin is predominantly E (eq 18). This raises the possibility that the reaction may have proceeded through a cyclic intermediate 65. A similar intermediate has been proposed for the reaction between 3-siloxy-1-methoxy-1,3-butadiene and carbonyl compounds under Lewis acid conditions (eq 19).[118]



(18)

64

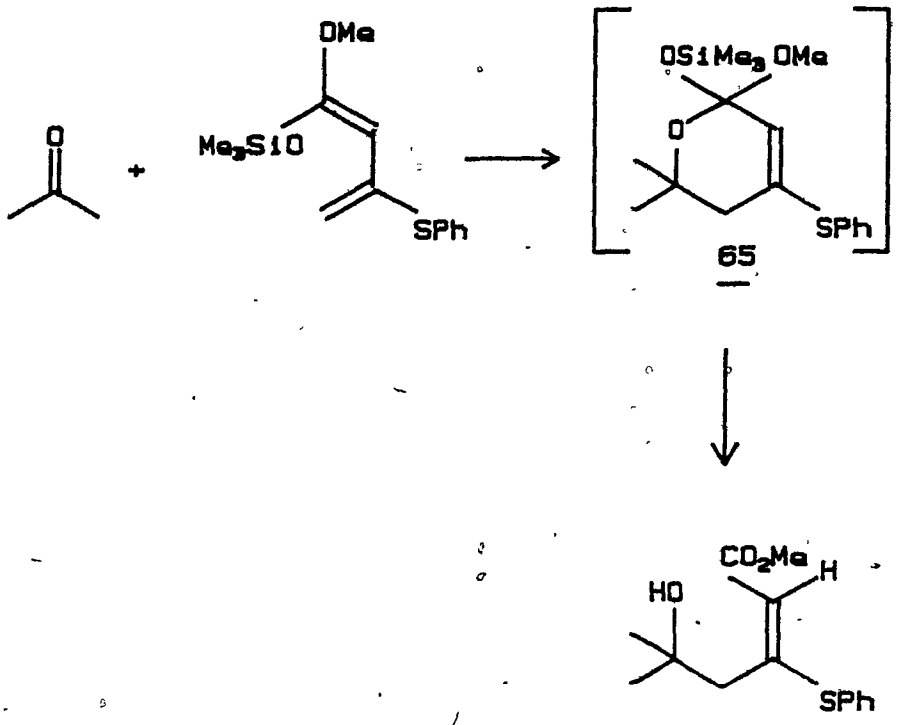
(a) R=Bn R_1=R_2=CH_3

(b) R=Ph R_1, R_2=CH_3

(c) R=Bn R_1, R_2=C_5H_{10}

(d) R=Ph R_1, R_2=C_5H_{10}

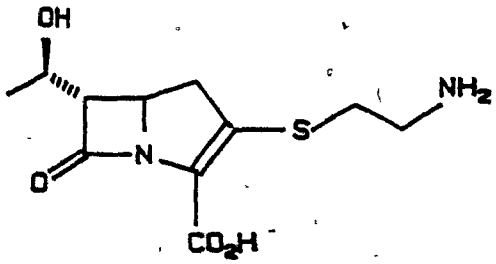
(e) R=Ph R_1=Ph, R_2=H



(19)

We are less inclined to favour such a cyclic intermediate as the sole pathway under our reaction conditions. This is due to the fact that when benzaldehyde was used as the electrophile, the product 64e showed a substantial amount of the Z-isomer. We have shown independently that the Z-isomer could not have been formed by isomerisation of the E-isomer under the reaction conditions.

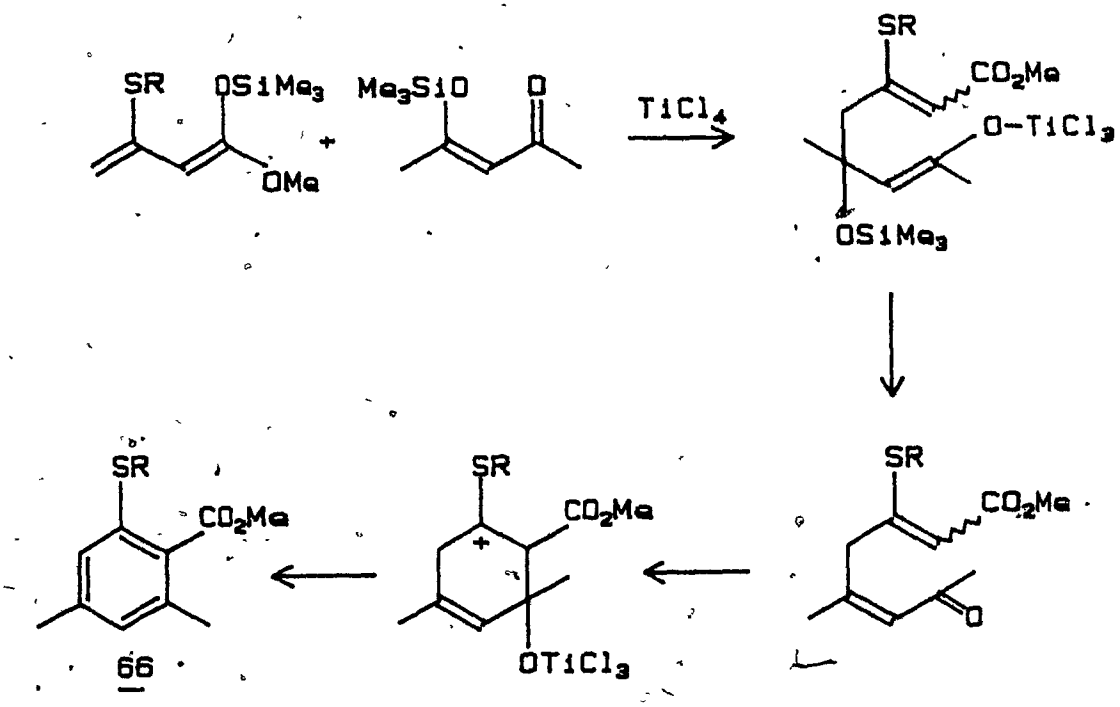
Finally, we note that for thienamycin and similar carbapenems, the structure can in principle be constructed by a combination of a monocyclic β-lactam and 63.[119]



Thienamycin

(11) Cycloaromatization Reaction for the Synthesis of Aryl sulfides

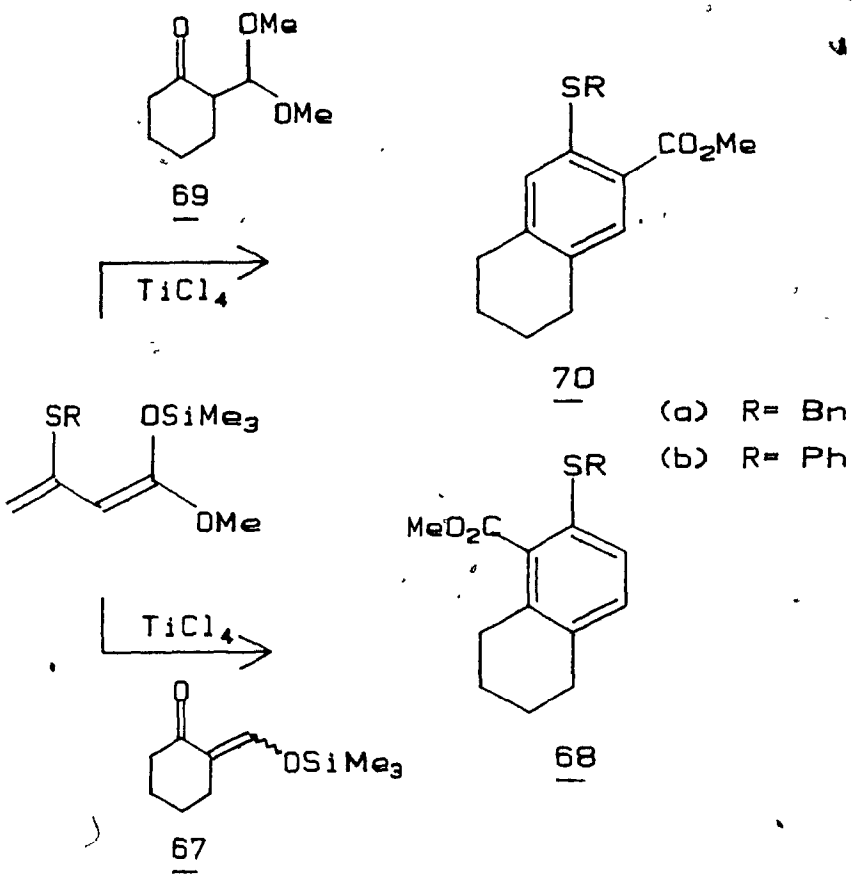
Reaction of 63 with 4-trimethylsiloxy-pent-3-en-2-one, a 1,3-dicarbonyl equivalent, gave the aromatic compound 66 under $TiCl_4$ conditions. The cycloaromatization must have proceeded by reaction of 63 first at the γ-position followed by an intramolecular condensation at the α-position and then



Scheme XVIII

aromatization (scheme XVIII). The reaction is similar to the cycloaromatization reaction we have previously reported for the synthesis of phenolic compounds.[111,120] The direction of the cycloaromatization reaction can be controlled by using 1,3-dicarbonyl equivalents of different reactivities. Thus 63b condensed with compound 69 to give the aromatic compound 70, but with 67 to give the isomeric aromatic compound 68 (scheme XIX). From the structures of 68 and 69, it is clear that, in

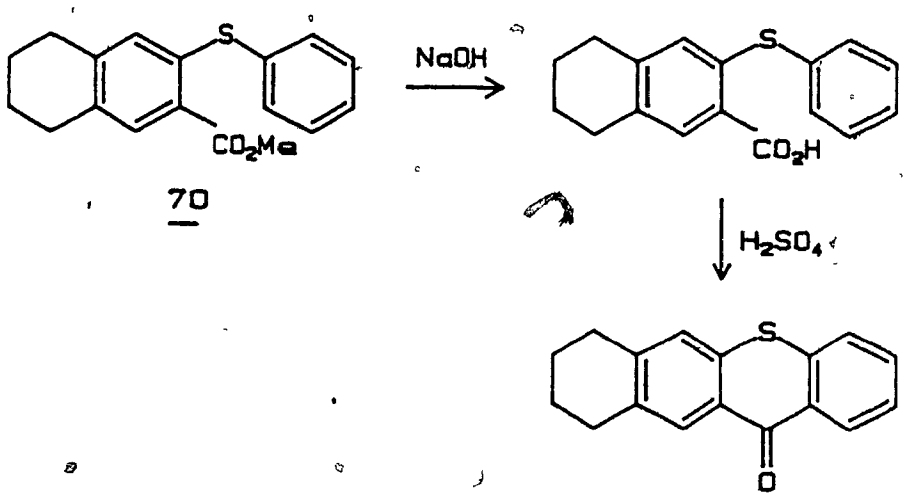
the electrophilic component, the relative reactivities are in the following order: The conjugative position is more reactive than the carbonyl function which is more reactive than the acetal function.[111]



Scheme XIX

Aryl sulfur compounds are usually prepared by substitution reactions, either nucleophilic or electrophilic, of existing aromatic precursor compounds.[121] Such an approach is often plagued with the problem of regio-selection in obtaining the desired substitution pattern. The cycloaromatization process offers the advantage of regio-control in the synthesis of aryl sulfur compounds. This can be illustrated by the synthesis of the tetracyclic thialactone 71. Previous syntheses of this type of compounds often encountered

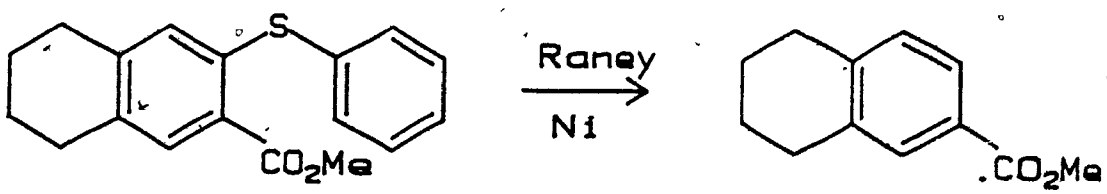
problems of regiochemistry and mixture of isomers were usually obtained.[122] Compound 70, obtained by the cycloaromatization reaction, can only be cyclised in one way. Thus, alkaline hydrolysis of 70 followed by acid cyclisation gave 71 as the only product in good yield.



70

71

These results complement our previous reported cycloaromatization reactions leading to phenolic[111,120] and anilino[114] compounds. Furthermore, the sulfur moiety can be readily removed by hydrogenolysis. For example, when compound 68 was subjected to treatment with Raney Nickel, the desulfurised aromatic compound 72 was obtained in good yield. Thus, the present reaction represents an approach to the synthesis of substituted benzoic acids as well.

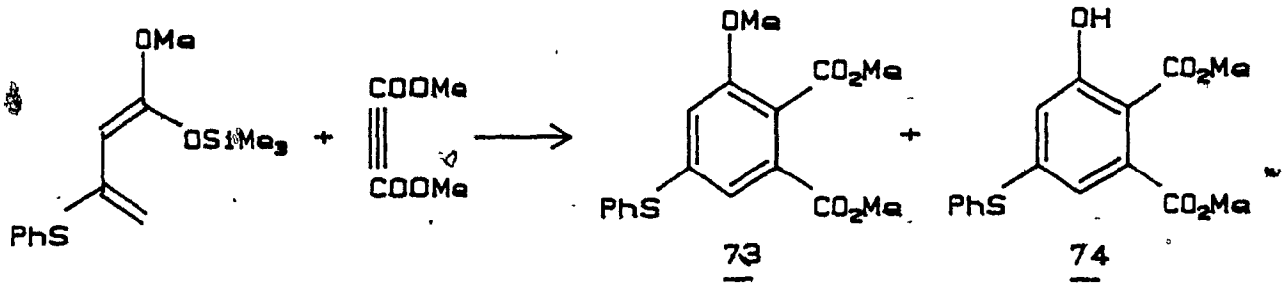


72

(iii) Diels-Alder Reactions

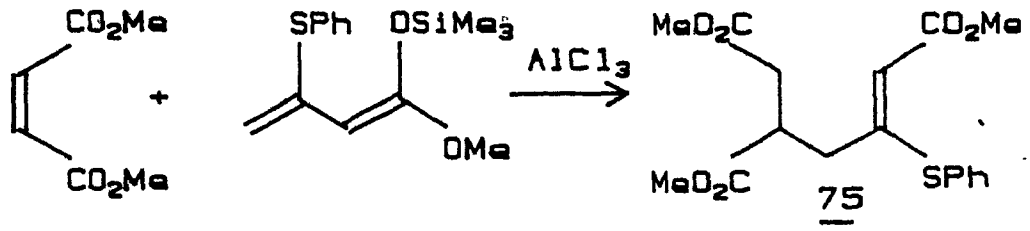
In recent years, the use of heteroatom substituted butadienes in synthesis has received much attention. Dienes with both sulfur and an oxygen substituents in the 1,2- and 1,4- and 2,3- substitution patterns[77-81], have been investigated. Compound 63, with the oxygen and the sulfur substituents in the 1,3- pattern, offers the advantage that the Diels-Alder adduct would be a 1,3-cyclohexanedione with the two carbonyl groups differently masked.

Reaction of 63 with dimethyl acetylenedicarboxylate proceeded readily to give the aromatic compounds 73 and 74 in good yield.



73 74

On the other hand, reaction of 63 with dimethyl maleate did not give any Diels-Alder adduct under thermal conditions. Addition of a Lewis acid, such as aluminum chloride or titanium tetrachloride, gave the Michael adduct 75 (eq 20).



75 (20)

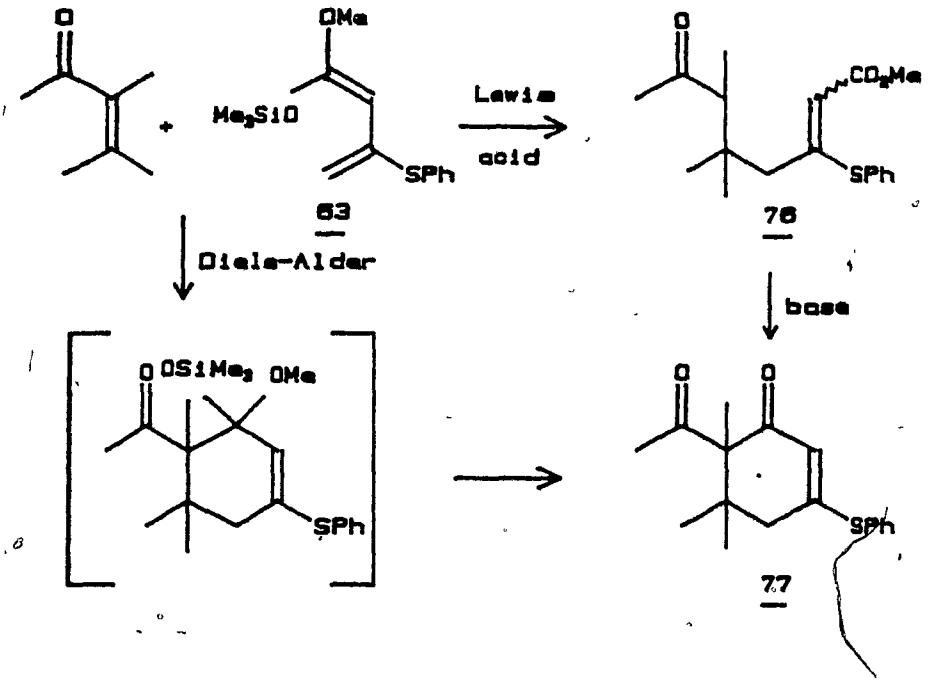
This suggests that compound 63 is not particularly effective as a Diels-Alder diene. On the other hand and its propensity to undergo Michael addition offers some interesting potential in organic synthesis which will be explored in the next chapter.

CHAPTER III

A NEW 4C+2C ANNULATION REACTION BASED ON TANDEM MICHAEL-CLAISEN CONDENSATION

Reactions leading to the formation of six-membered ring are of great importance in organic synthesis.[6] The Diels-Alder reaction and the Robinson annulation have served remarkably well for this purpose, but they are not without limitations. In the Diels-Alder reaction, both the diene and dienophile components must be appropriately activated.[1] For example, cyclohexenone undergoes cycloaddition with most dienes readily, whereas 2- or 3- substituted cyclohexenones react sluggishly or not at all.[123] The Robinson annulation is essentially a 2 carbon plus 4 carbon (2C+4C) tandem Michael-aldol condensation. The reaction is critically dependent on the ability of the 2 carbon fragment to act as Michael donor and the 4 carbon fragment to be Michael acceptor under the basic reaction conditions. Various modifications of the Robinson annulation reaction have been introduced to address these problems.[6] We wish to propose here a new 2C+4C annulation reaction based on tandem Michael-Claisen condensation. It is based on the observation that 3-phenylthio-1-trimethylsiloxy-1-methoxy-1,3-butadiene(63) behaves as a remarkably facile Michael donor in its reactions with α,β -unsaturated carbonyl compounds under Lewis acid catalysed conditions to give the adduct 76. An intramolecular Claisen condensation of 76 under basic conditions should give

the annulated product 77. The reaction differs from the classical Robinson annulation in that the Michael reaction is carried out under acidic conditions. Furthermore, the Michael acceptor α,β -unsaturated ketone serves as the 2 carbon component in this reaction, and the Michael donor serves as the 4 carbon component. In a formal way, it is equivalent to the Diels-Alder reaction of the diene 63 with the α,β -unsaturated carbonyl compound (Scheme XX).



Scheme XX

It offers certain advantages over the Diels-Alder reaction however, in that the stereochemistry of the ring junction is amenable to control by this two step sequence. Finally, the product 77 has three carbonyl groups which are differently masked and can be manipulated separately. It can serve as the entry point to an array of multifunctional targets.

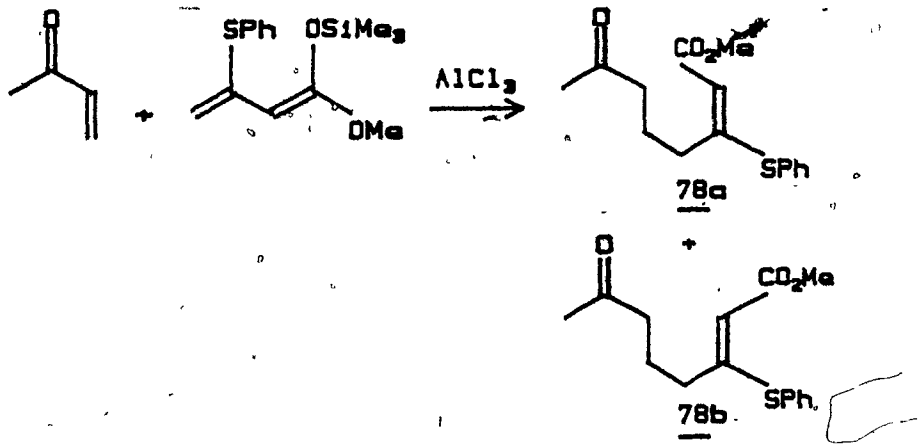
Results and Discussion:

A. Conjugative addition reactions of 3-phenylthio-1-trimethylsiloxy-1-methoxy-1,3-butadiene.

In the previous chapter the preparation and reactions of 3-phenylthio-1-trimethylsiloxy-1-methoxy-1,3-butadiene(63) was described.

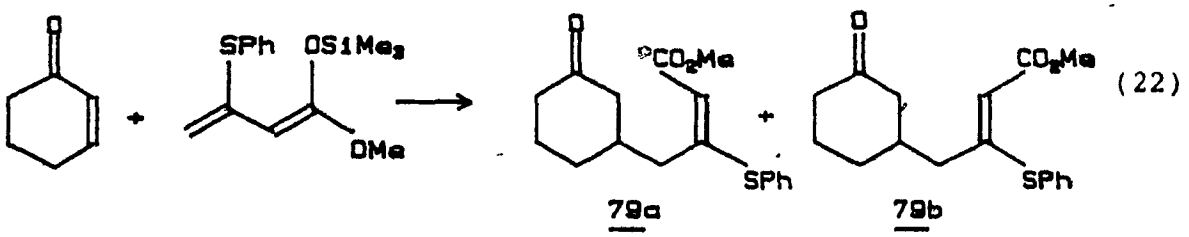
In a general study of its reactivity as a Diels-Alder diene, its reactions with a number of dienophiles were studied. While the reaction of 63 with dimethylacetylenedicarboxylate did give the Diels-Alder adduct, its reaction with dimethyl maleate under thermal conditions gave no adducts at all. Under Lewis acid catalysed conditions, 63 reacted with dimethyl maleate to give the Michael adduct 75 instead (eq 20). This preference of Michael reaction over cycloaddition led us to examine the reaction of 63 with a number of α,β-unsaturated carbonyl compounds.

Indeed, 63 reacted with methyl vinyl ketone under $AlCl_3$ catalysed conditions to give the E- and Z- isomers of 78 (eq 21).



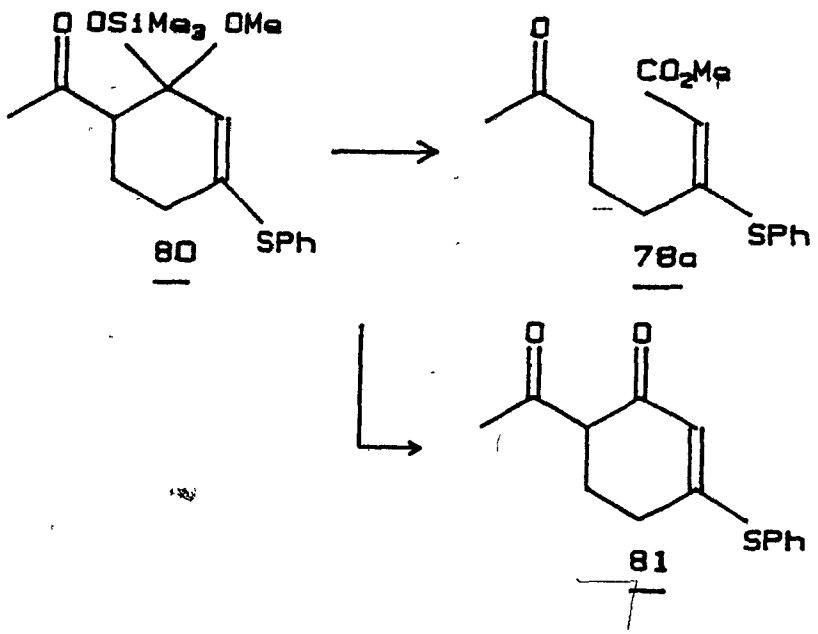
(21)

The diene also reacted with cyclohexenone under $TiCl_4$-$Ti(OiPr)_4$ catalysed conditions to give the E- and Z- isomers of 79 (eq 22).



(22)

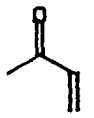
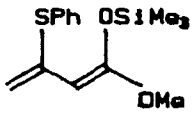
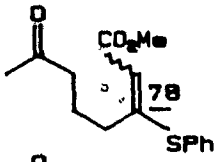
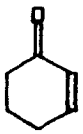
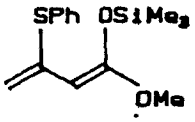
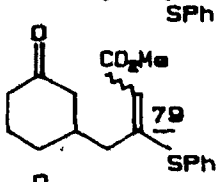
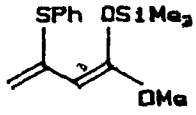
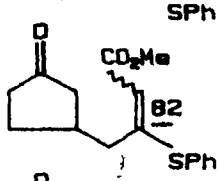
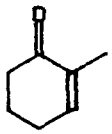
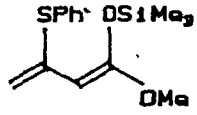
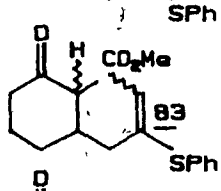
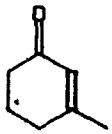
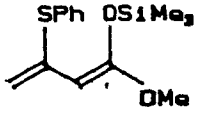
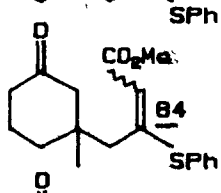
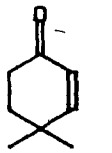
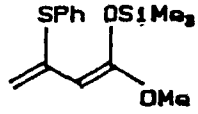
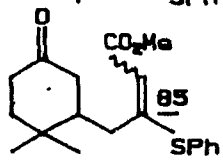
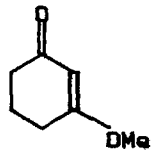
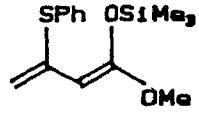
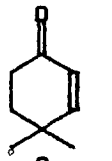
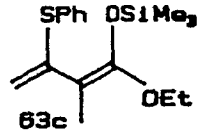
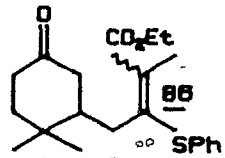
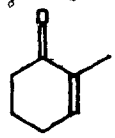
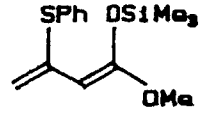
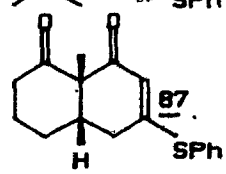
It is clear from these reactions that the diene 63 reacts exclusively at its γ-position and in a 1,4- manner. Another interesting observation is the fact that the products 78 and 79 retain the enethiol structure in both E- and Z- isomers of the Michael adducts with the E- isomer (a) predominating over the Z- isomer (b). This raises the possibility that the reaction may have proceeded through a Diels-Alder cycloaddition pathway followed by ring opening of the adduct 80 during hydrolytic work-up. While this may account for the formation of 78a, it cannot lead to the Z-isomer 78b. We have proved that under the reaction conditions, 78a does not isomerise to 78b. We have also not detected any of the compound 81 which would have been the more likely hydrolytic product (Scheme XXI).



Scheme XXI

The diene also reacted with cyclopentenone, 2-methylcyclohexenone and 3-methylcyclohexenone under Lewis acid catalysed conditions to give the Michael adducts in modest to good yields (Table II). In each case, E- and Z- isomers of the Michael adduct were obtained. The yields in many of these reactions have not been optimised.

Table II: Michael Reactions of 63b and 63c with α,β - unsaturated ketones

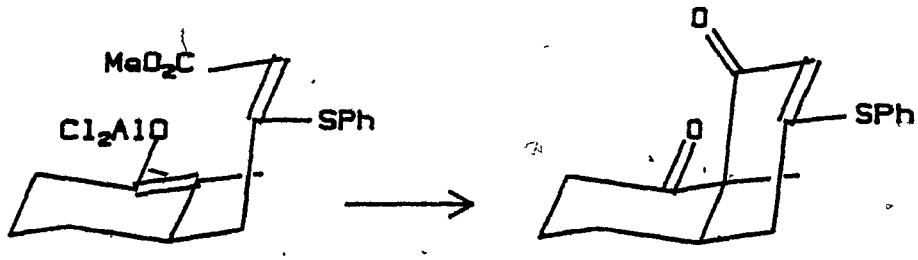
Michael acceptor	Silyl ether	Lewis acid	E/Z	Product	Yield
		$AlCl_3$	1.1		52%
		$TiCl_4$–$Ti(OiPr)_4$	1.4		79%
		$TiCl_4$–$Ti(OiPr)_4$	1.1		55%[a]
		$TiCl_4$–$Ti(OiPr)_4$	1.05		86%
		$TiCl_4$–$Ti(OiPr)_4$	b		23%
		$TiCl_4$	3.0		68%
		$TiCl_4$–$Ti(OiPr)_4$		no reaction	
	 63c	$TiCl_4$	0.36		35%
		$AlCl_3$		 +83a+83b	23%[c]

a. yield calculated on the basis of 20% recovered cyclopentenone

b. yield of the recovered E- isomer; The Z- isomer might have been formed, but we could not purify it.

c. yield of the bicyclic compound. It was separated from the Z-isomer of the Michael adduct by preparative TLC (eluent: 14% t-butanol-carbon tetrachloride)

When the diene 63 reacted with 2-methylcyclohexenone under $TiCl_4$-$Ti(OiPr)_4$ conditions, only the E- and Z-isomers of the Michael adducts 83 were isolated. But when the reaction was catalysed by $AlCl_3$ at room temperature, the bicyclic compound 87 was also isolated in 23% yield (eq 23).



(23)

We have made efforts to increase the yield of 87 by changing the catalyst to $EtAlCl_2$ and /or by changing the solvent, but we could not improve the yield significantly.

We have also used the diene 63c to effect the Michael addition with 4,4-dimethylcyclohexenone. It is noteworthy that the diene 63c is less reactive than 63b and gives a lower ratio of E/Z in the Michael adduct 86.

In addition to $AlCl_3$, $TiCl_4$-$Ti(OiPr)_4$ the following acids: BF_3, $SnCl_4$, $TiCl_4$ also catalyse the Michael addition reactions.

Effect of Solvent: The solvent effect on this reaction was briefly studied by treating the diene 63 with equimolar amounts of 4,4-dimethylcyclohexenone and titanium tetrachloride in various solvents. The results show (Table III) that in methylene chloride a higher ratio E/Z was obtained in addition to better yield. It is the solvent of choice.

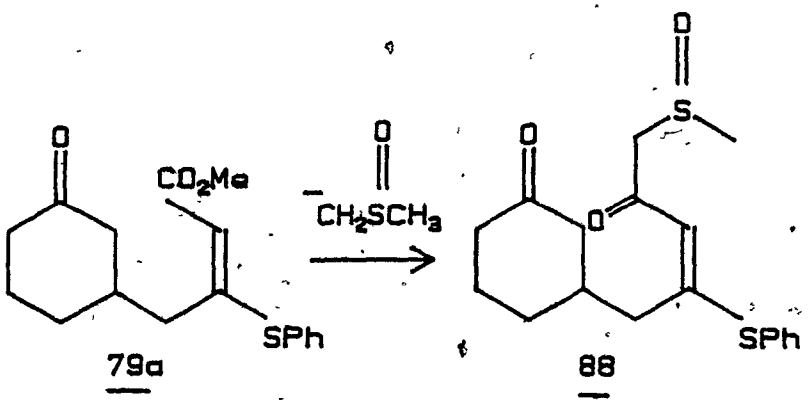
Effect of the amount of Lewis Acid: The amount of Lewis acid was also varied from equimolar to two moles of titanium tetrachloride to α,β -unsaturated compound. In all cases, we did not find any noticeable change in terms of yield and E/Z ratio. In cases where $Ti(OiPr)_4$ was also used in conjunction with $TiCl_4$, the ratio of $TiCl_4$ to $Ti(OiPr)_4$ was varied from 1:0.5 to 1:1. The ratio of one mole of $TiCl_4$ to 0.8 mole of $Ti(OiPr)_4$ appeared to be the best for the reaction in terms of yield.

Table III: Effect of the solvent on the reaction between 4,4-dimethylcyclohexenone and 63:

solvent	temperature	Lewis acid	E/Z	yield
CH_3CN	-23 °C	$TiCl_4$	1.56	34%
CH_2Cl_2	-78 °C	$TiCl_4$	3.0	68%
hexane	-78 °C	$TiCl_4$	1.1	38%

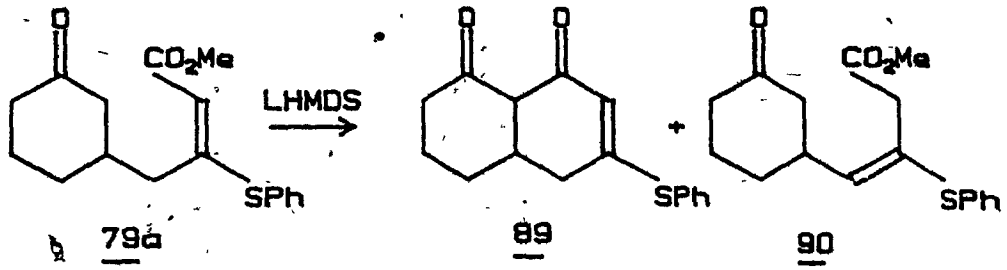
B. Intramolecular Claisen Condensation of the E-isomers:

In order to cyclize the E- isomers of the Michael adducts, one needs to generate the enolate anion from the ketone carbonyl group. We have tried the reaction using NaH in THF but without much success. We then turned our attention to dimsyl anion to effect the Claisen condensation. The adduct 79a on reaction with dimsyl anion, gave product 88 instead of generating the enolate and cyclization (eq 24).



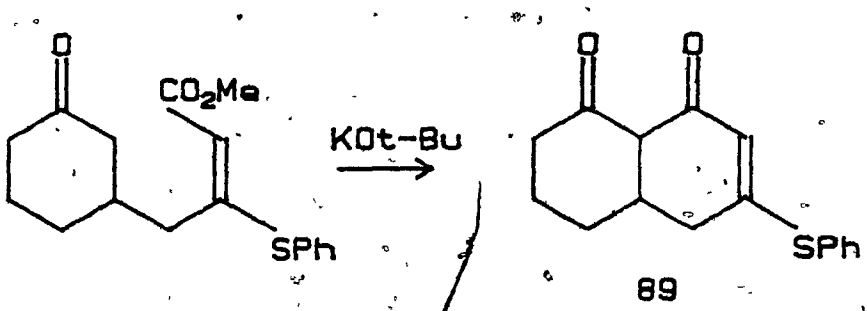
(24)

Nitrogen bases such as lithium hexamethyldisilazide(LHMDS) were tried next. We were gratified to isolate the cyclized product 89, but the low yield of the reaction made us look for improved conditions. The low yield of the reaction is presumably due to a side reaction, where LHMDS is abstracting the γ-hydrogen of the ester functionality, thereby isomerising the double bond to give 90 (eq 25).



79a 89 90 (25)

We therefore examined the weaker oxygen bases like potassium tert-butoxide. When the E-isomer 79a was treated with K^+ O^--t-Bu in THF, the compound smoothly cyclized to give the bicyclic compound 89 in 89% yield (eq 26). The ^1H NMR spectrum of compound 89 in deuterochloroform shows a sharp singlet at 15.06 ppm which indicates that the compound exists predominantly in the enol form. We were able to cyclize the other E-Michael adducts in the presence of K^+ O^--t-Bu. The Michael adducts 82a, 84a, 85a and 86a all cyclized in presence of K^+ O^--t-Bu to give the bicyclic compounds 91, 93, 94 and 95 respectively in 72-89% yield (Table IV).

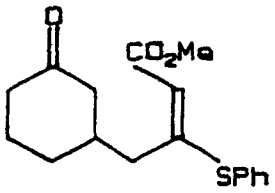
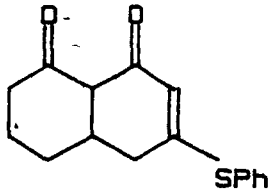
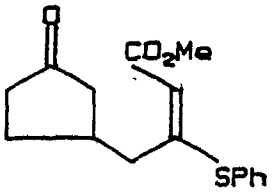
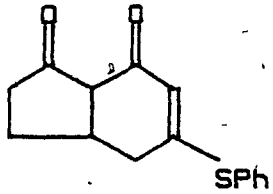
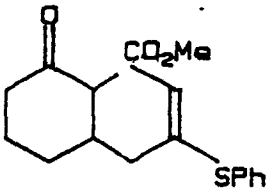
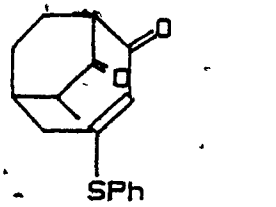
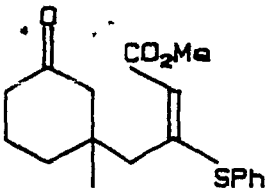
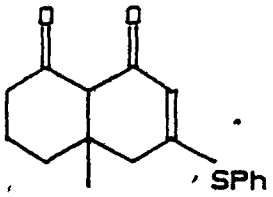
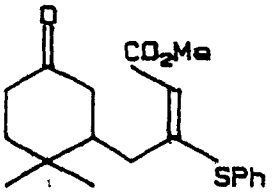
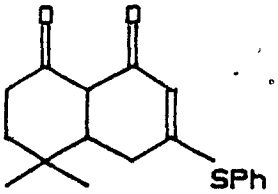
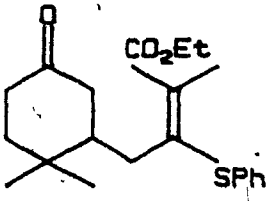
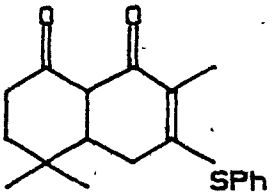


89 (26)

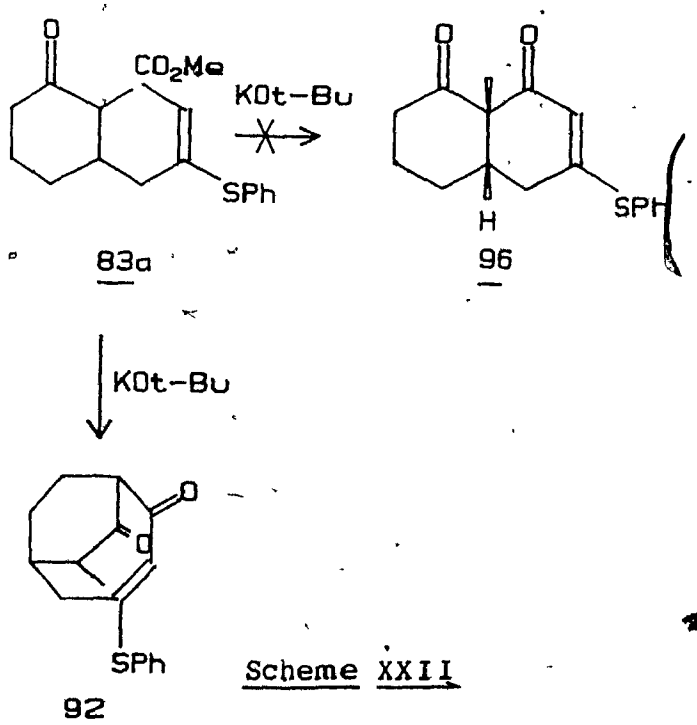
From the ^1H NMR spectra of these bicyclic compounds, it is clear that the three bicyclic compounds 93, 94 and 95 exist in their enol form. Compound 91 however,

exists in both the enol and keto forms in $CDCl_3$ but only in the keto form in CD_3OD.

Table IV Cyclisation of Michael adducts with potassium t-butoxide

Entry	Michael adduct	Product	Yield
1		89 	89%
2		91 	72%
3		92 	63%
4		93 	83%
5		94 	86%
6		95 	79%

Cyclization of Michael adduct 83a gave different results. The diene 63 in its reactions with 2-methyl-2-cyclohexen-1-one in the presence of Lewis acid gave a mixture of the cis and trans isomers of the E- Michael adduct 83a as well as the cis and trans isomers of Z- Michael adduct 83b. Our efforts to separate the cis and trans isomers of each Michael adduct were not successful. Cyclisation of 83a was attempted under K^+ O^--t-Bu conditions at room temperature. No cyclized product was obtained. However, when the reaction was carried out in refluxing THF, compound 83a did undergo cyclization because the isolated product 92 did not show the presence of methoxy group. On the other hand, compound 92 showed a doublet (J=11Hz) for the methyl group which is in contrary to the expected singlet for the methyl group of compound 96. We assigned the [4.2.2]-bicyclo structure to compound 92 from its ^{13}C NMR, ^{1}H NMR and infrared spectra (Scheme XXII).



Scheme XXII

Presumably, our inability to cyclize 83a to compound 96 is due to generation of the kinetically favored enolate instead of the needed thermodynamically favored enolate. Recently, active Fe(0) has been used for effectivly generating the thermodynamically favored enolate from 2-methylcyclohexanone.[124] The cyclization of 83a was attempted with active Fe(0), but in our hands, the cyclization to 96 was still not successful. Only starting material 83a was recovered.

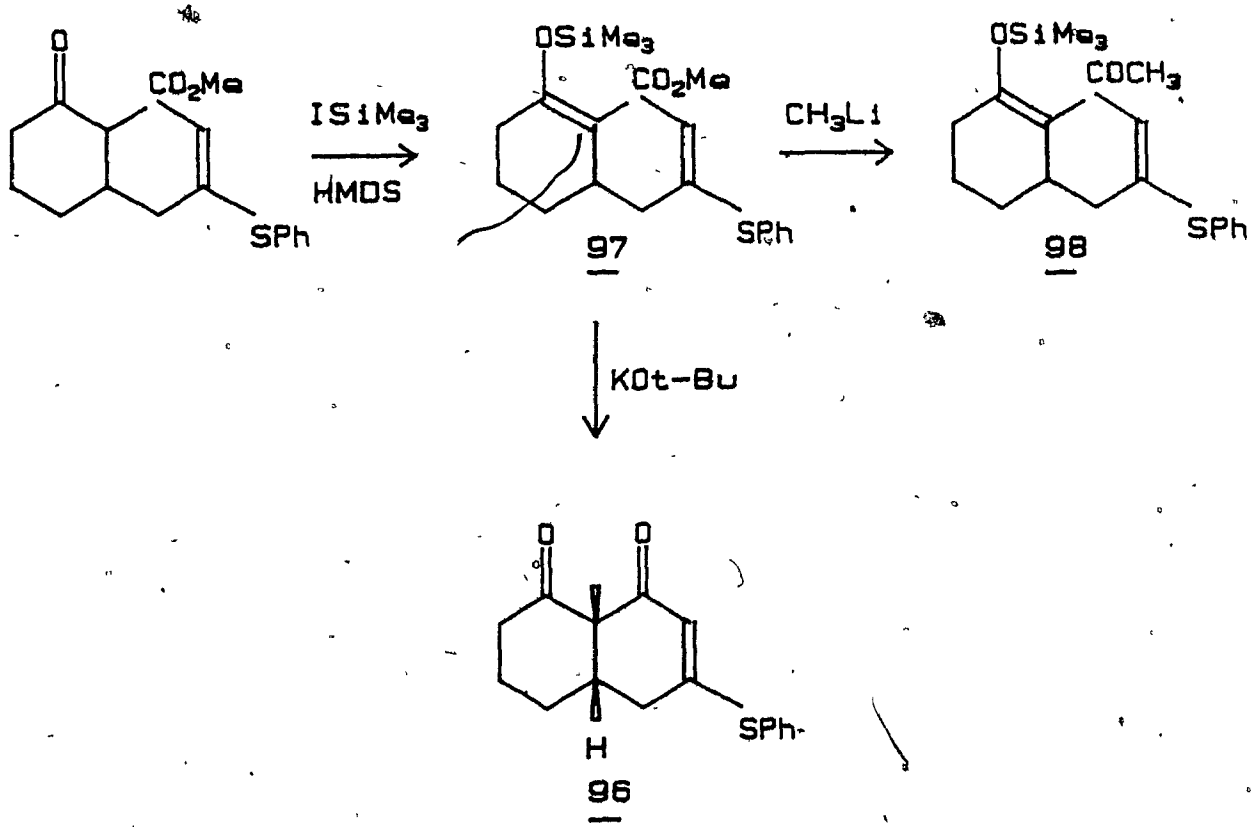
Conversion of 83a to its enol silyl ether was then attempted under NEt_3-DMF/chlorotrimethylsilane as described by House et al.[28] No enol silyl ether was formed under these conditions. The silylation of 83a was finally achieved under iodotrimethylsilane-hexamethyldisilazane conditions[86] to give the thermodynamically favored enol silyl ether 97 (Scheme XXIII).

There are several well established methods for generating the corresponding enolate anion from an enol silyl ether. Among them are treatment of silyl enol ether either with CH_3Li[94] or with flouride ion.[95] When the enol silyl ether 97 in THF was treated with CH_3Li, not unexpectedly, reaction with the ester functionality occurred to give compound 98 (Scheme XXIII).

One of the inherent problems in using tetraalkylammonium flourides to generate enolate anion is that these flouride salts are highly hygroscopic.[125] After taking all possible precautions in drying benzyltrimethylammonium

flouride (BTAF),[95] the silyl enol ether was treated with BTAF in THF. None of the cyclized compound 96 was obtained. We have tried with other flouride ion sources like TASF,[126] KF-18-crown-6 ether[127] also but without any success. In all cases, the Michael adduct 83a was recovered.

We were therefore very pleased to find that the enol silyl ether 88 on reaction with K^+ O^--t-Bu did undergo cyclization in THF-DMF to give the compound 96 in 63% yield (Scheme XXIII).

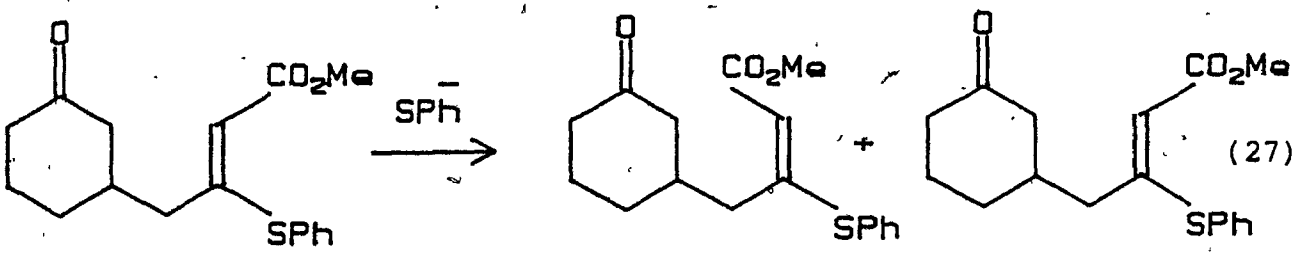


Scheme XXIII

C. Thiophenoxide induced cyclization of the Michael adducts:

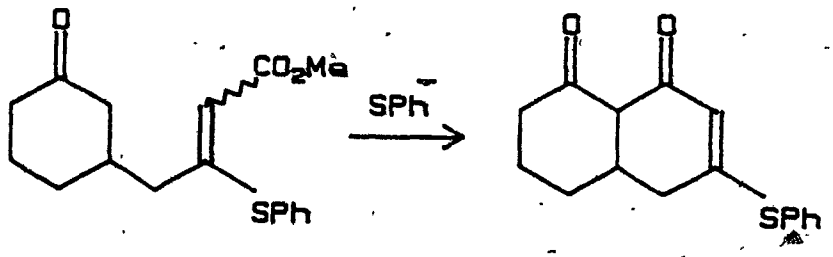
In the reaction of diene 63 with α,β-unsaturated

carbonyl compounds, both the E- and Z- isomers of the Michael adducts were obtained. In some cases the ratio of E- to Z-isomer is as high as 1:1. While the E-isomer of the Michael adducts smoothly cyclized in presence of $K^+ O^-$-t-Bu to the bicyclic compounds in good yield, the tandem Michael-Claisen annulation reaction would be synthetically more useful if it is possible to convert the Z-isomer to the annulated compound as well. Accordingly, the isomerisation of Z-isomer to E-isomer was attempted. In principle, the Z-isomer of Michael adduct should undergo isomerisation of the double bond in the presence of SPh^- (eq 27) to give an equilibrium mixture of E- and Z-isomers of the Michael adduct. To our pleasant



(27)

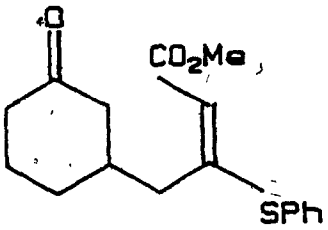
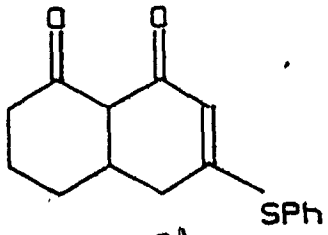
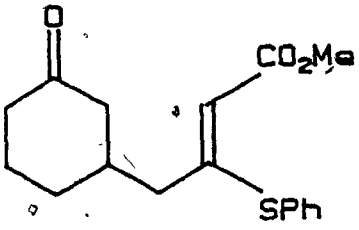
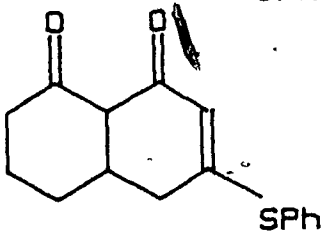
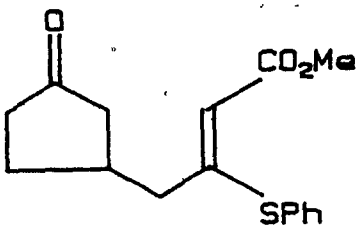
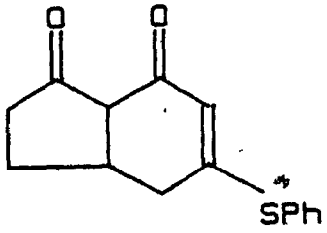
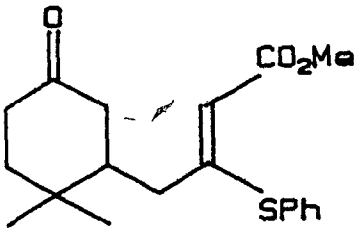
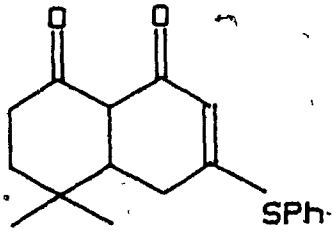
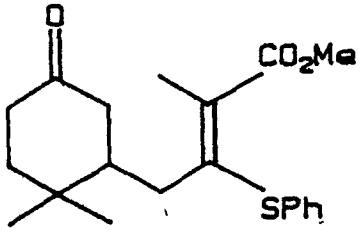
surprise, the thiophenoxide anion not only caused isomerisation of the double bond but also cyclization to generate the annulated compound in one operation (eq 28).



(28)

Thus the Michael adducts 79b, 82b and 85b were converted to the corresponding bicyclic compounds 89, 91 and 94 respectively in excellent yields (Table V).

Table V Thiophenoxide induced cyclization of Michael adducts

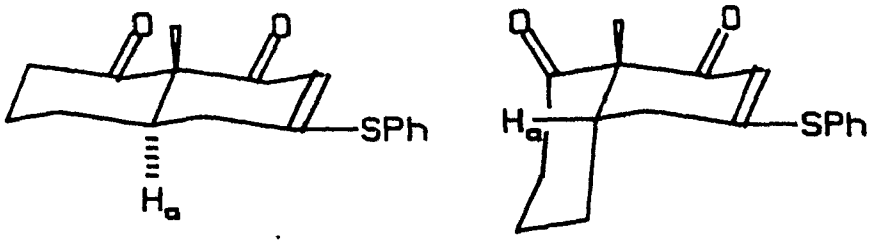
Entry	Michael adduct	Product	Yield
1		89 	93%
2		89 	93%
3		91 	69%
4		94 	91%
5		a	

a) none of the expected bicyclic compound was isolated.

The exception is the cyclization of 86b, which was attempted under thiophenoxide conditions, but we were not able to isolate any bicyclic compound 95 presumably due to the reluctance of the double bond to undergo isomerisation under these conditions. The next question we must face is the stereoselectivity of the annulation reaction. Obviously, it would be most desirable if the annulation reaction can be controlled to yield either the cis- or the trans- fused products. So far, in the case of compound 96, only one stereoisomer was obtained with stereochemistry yet to be established. In cases (compound 89, 91, 93, 94 and 95) where one of the ring junction hydrogen is situated between the two carbonyl groups, either the compound exists in the enol form or enolisation is so facile that separation of the stereoisomers would not be practical. We thus turned our attention to this question.

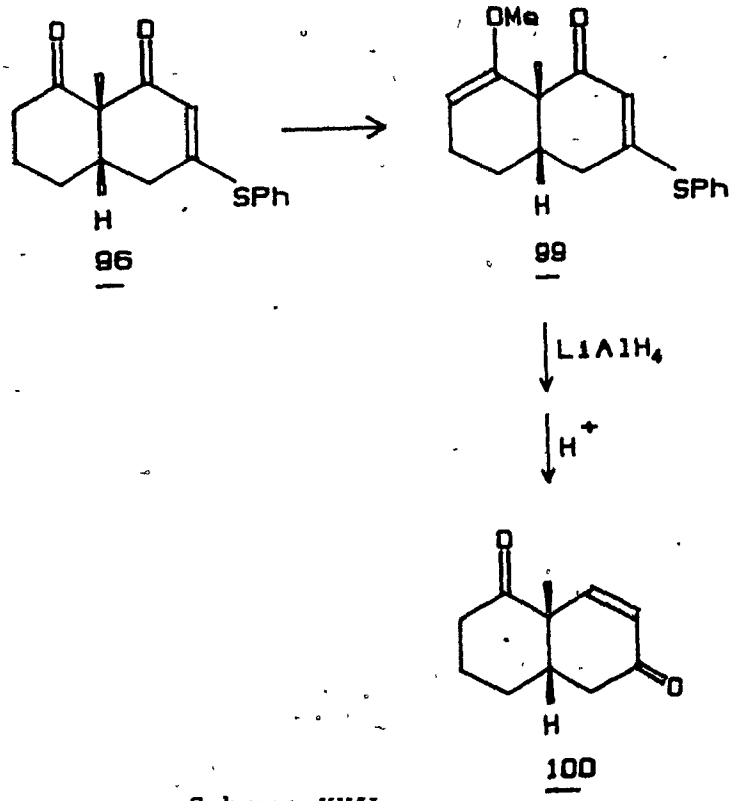
D. Stereoselectivity of the annulation reaction:

We begin by establishing the stereochemistry of compound 96. In principle, NOE can be used to distinguish between the cis- and the trans- isomers. Positive enhancement should be observed for the ring junction proton H_a on irradiation of the methyl protons for the cis- compound (Scheme XXIV). Unfortunately, its chemical shift is such that it is part of a broad multiplet at 2.38-2.13 ppm. The NOE experiment gave equivocal results and no definitive assignment was possible.



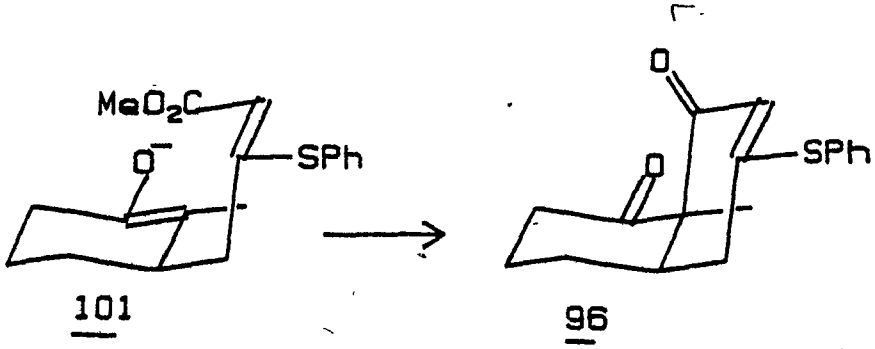
Scheme XXIV

Chemical correlation was next tried according to Scheme XXV. Compound 96 was first converted to the enol methyl ether 99. Lithium aluminum hydride reduction of 99 followed by acid hydrolysis gave the known compound 100 with cis ring junction.[15] It establishes clearly that compound 96 has the cis- stereochemistry.



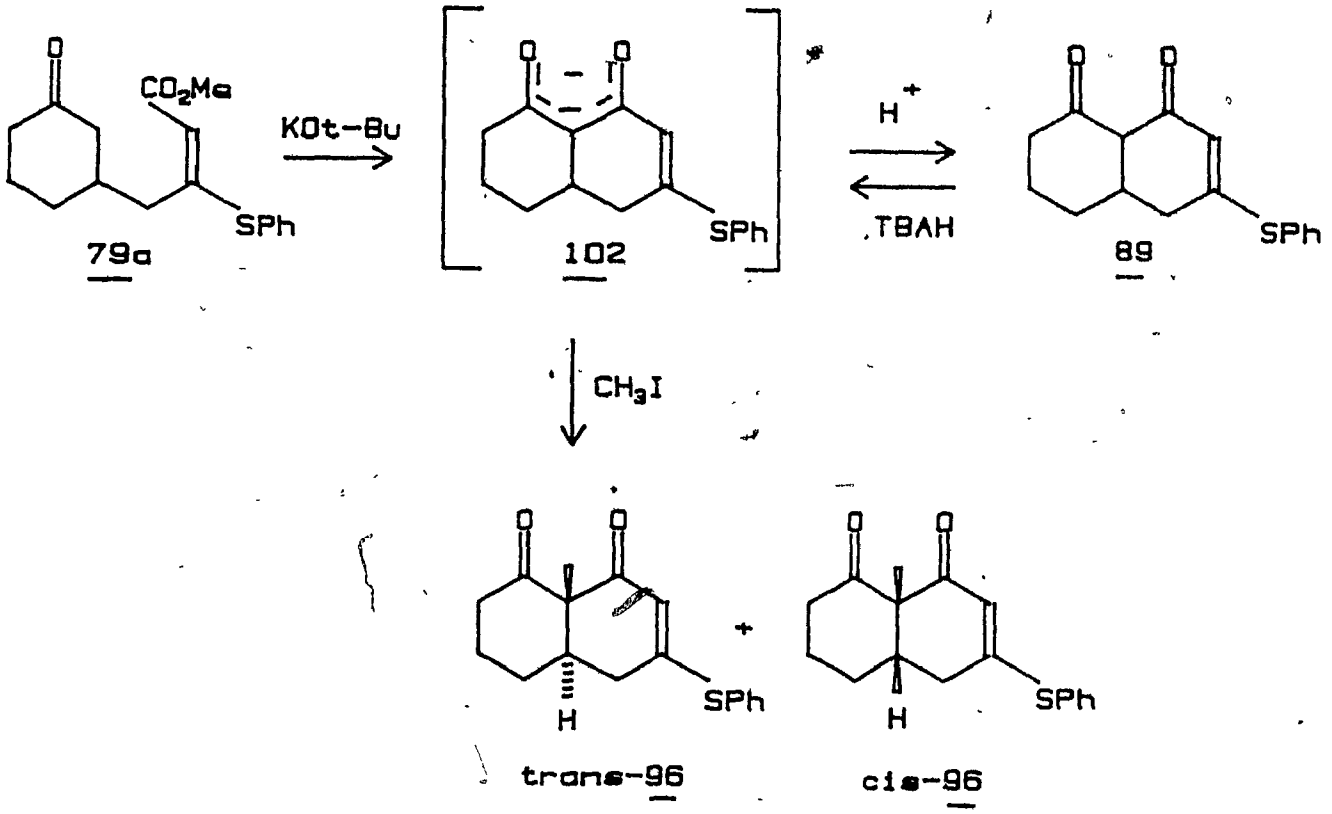
Scheme XXV

The cis- stereochemistry of 96 is not unexpected. In the intramolecular cyclization of the enolate anion 101 derived from the enol silyl ether 97, the electrophile is expected to come from the axial direction thus leading to the cis stereochemistry (eq 29).



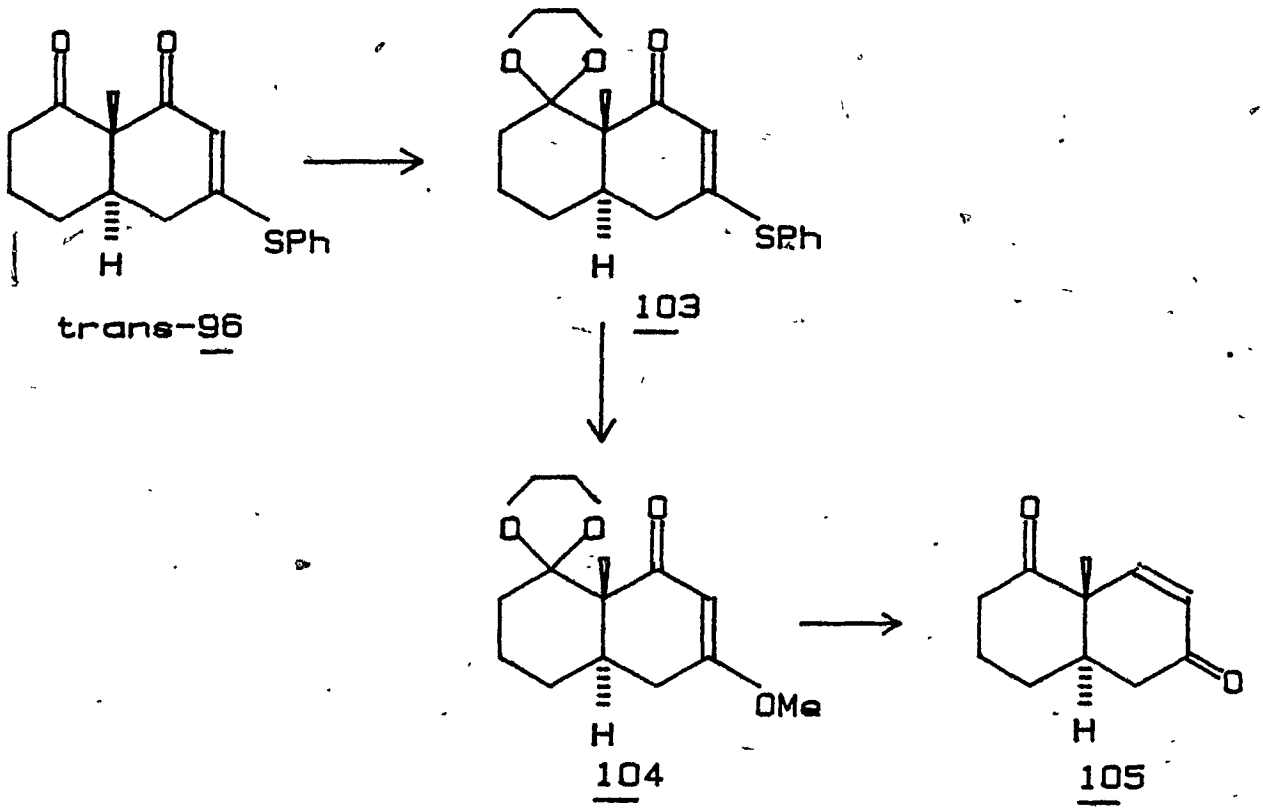
101 96 (29)

The preferred axial approach of the electrophile can be used advantageously to obtain the trans- isomer of compound 96. In the cyclization of 79a to give 89, the intermediate must be the anion 102. If, instead of quenching the reaction mixture with water, methyl iodide is used, compound 96 should be obtained with the trans- isomer as the preferred product. This was found to be the case. On treatment of 79a with K^+ O^--t-Bu in THF followed by CH_3I, a mixture of trans- and cis- 23 was obtained in 72% yield with trans/cis ratio of 9:4 (Scheme XXVI). Furthermore, the trans- 96 could be readily crystallised from the mixture thus facilitating the purification. The stereochemistry of the trans- compound was established also by chemical transformation to the known compound 102 according to Scheme XXVII.[128]



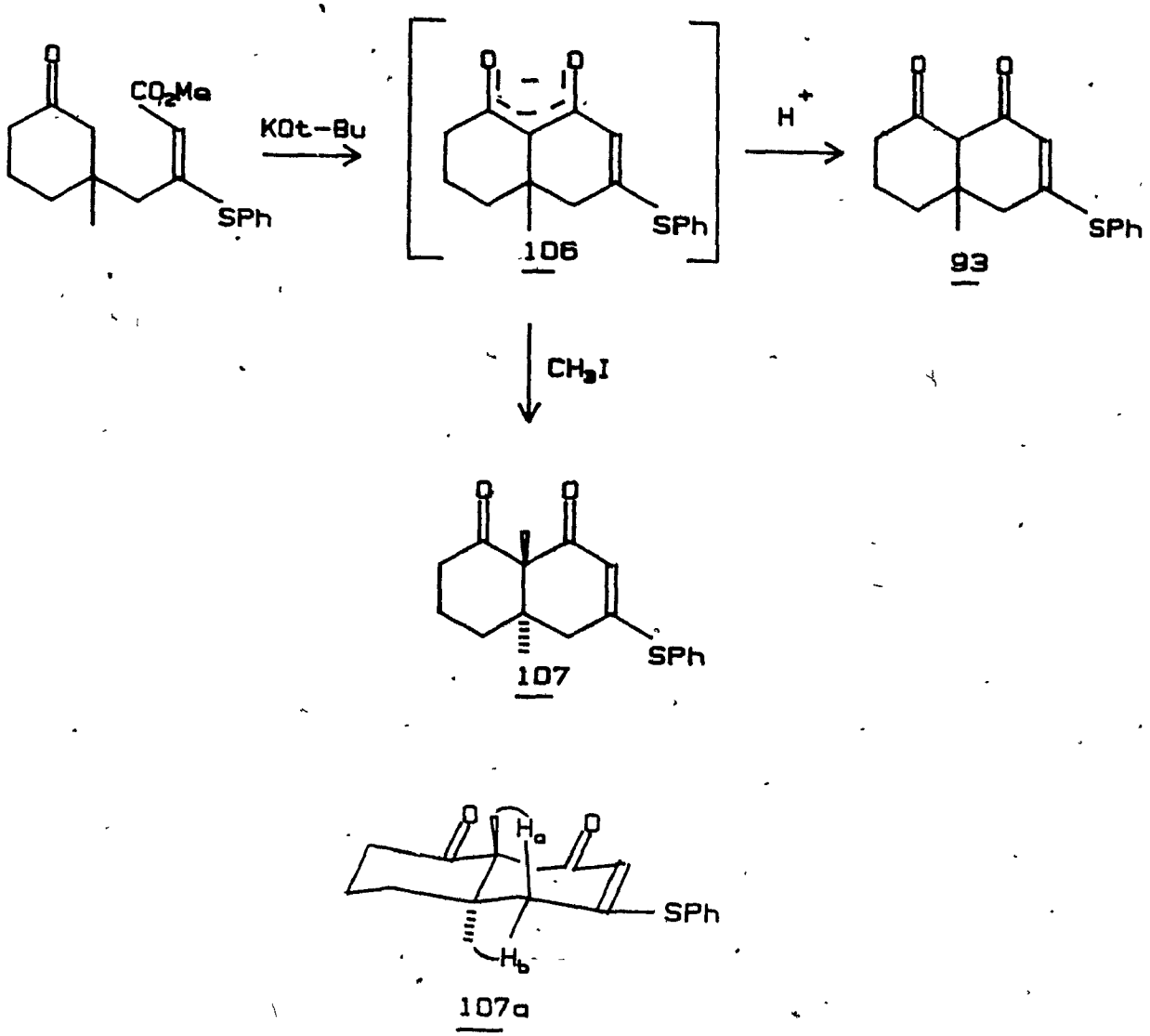
Scheme XXVI

Alternatively, alkylation product 96 can be obtained from 89 under phase transfer conditions using tetrabutylammonium hydroxide (TBAH) and methyl iodide. The yield was improved to 89% with the ratio of trans/cis remaining at 9:4. There is no significant difference between phase transfer conditions and in situ alkylation of the anion during cyclization.



Scheme XXVII

Finally, alkylation of the anion 106 derived from the cyclization of 84 with methyl iodide gave stereoselectively the trans- compound 107, The stereochemistry of 107 was established by NOE experiments. Irradiation of the ring junction methyl groups selectively enhances either H_a or H_b as indicated in 107a. This can only be possible with a ring junction of trans- stereochemistry (Scheme XXVIII).



Scheme XXVIII

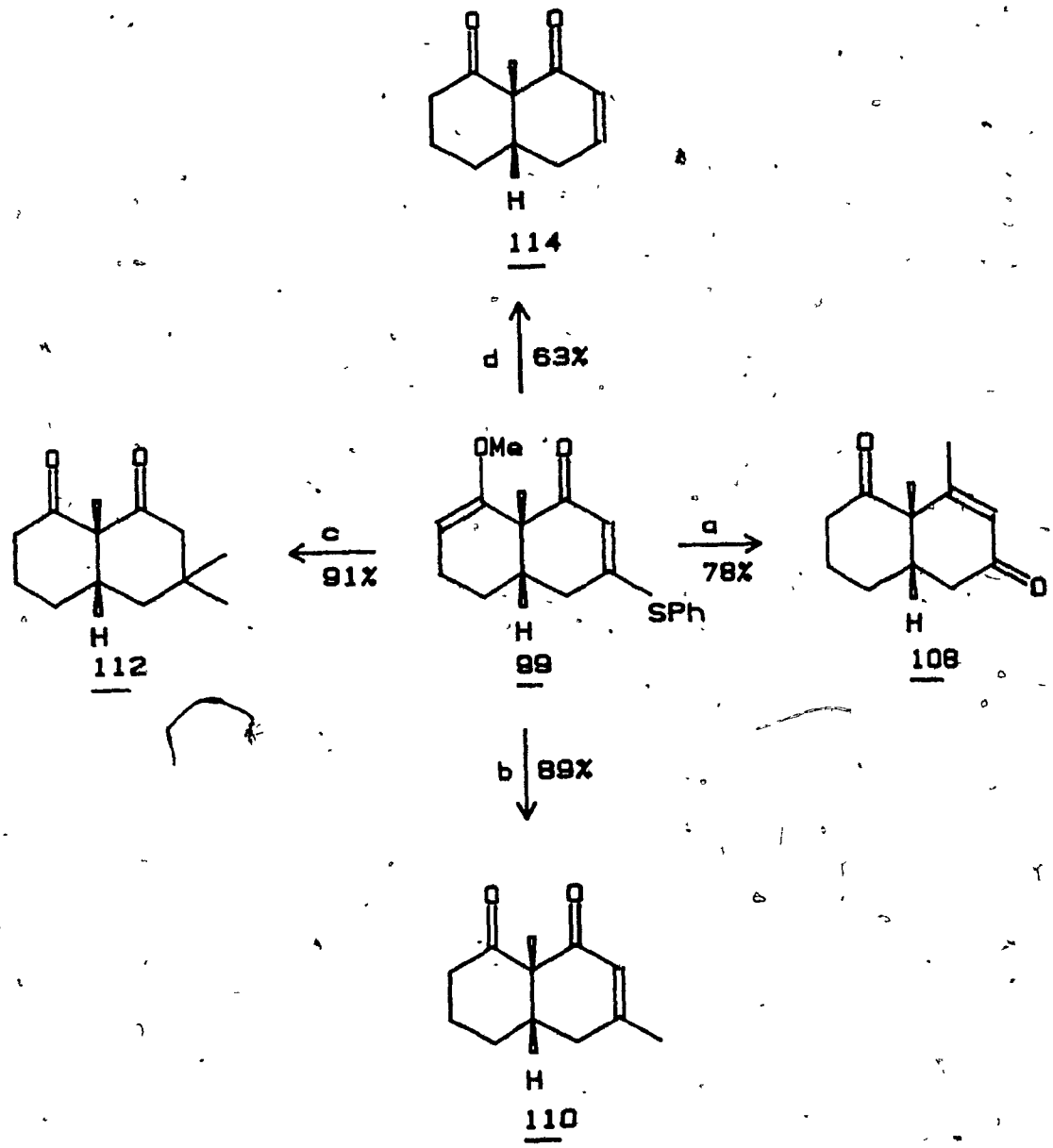
E. Functional group transformation of the decalin system:

The annulation sequence involving the tandem Michael-Claisen condensation allows the conversion of cyclohexenone to a decalin system. Furthermore, in case where there is a methyl group at the 9 position, a reasonable degree of stereocontrol is possible to give either the cis- or trans-

stereoisomers. Since many natural products, including steroids and terpenoids, are based on the decalin structure, the annulation reaction offers the potential as an entry to the synthesis of many of these compounds.

Compound 96 contains three carbonyl groups, with one of them masked in the form of an enol thio ether. In order to use them effectively in organic synthesis, the three carbonyl groups should be differentiated with relative ease. The selective protection of carbonyl at C(8) can be done readily. When cis-96 was treated with trimethyl orthoformate and a catalytic amount of p-toluenesulfonic acid in CH_3OH, the monomethyl enol ether 99 was isolated in 87% yield (Scheme XXV). Similarly trans-96 was protected at C(8) position using ethylene glycol and a catalytic amount of p-toluenesulfonic acid in benzene to give the acetal 103 in 83% yield (Scheme XXVII). It is noteworthy that during either of these conditions, none of the other functional groups in the decalin system were affected. Furthermore, 1,2-ethanedithiol also can be used instead of ethylene glycol with compound 96.

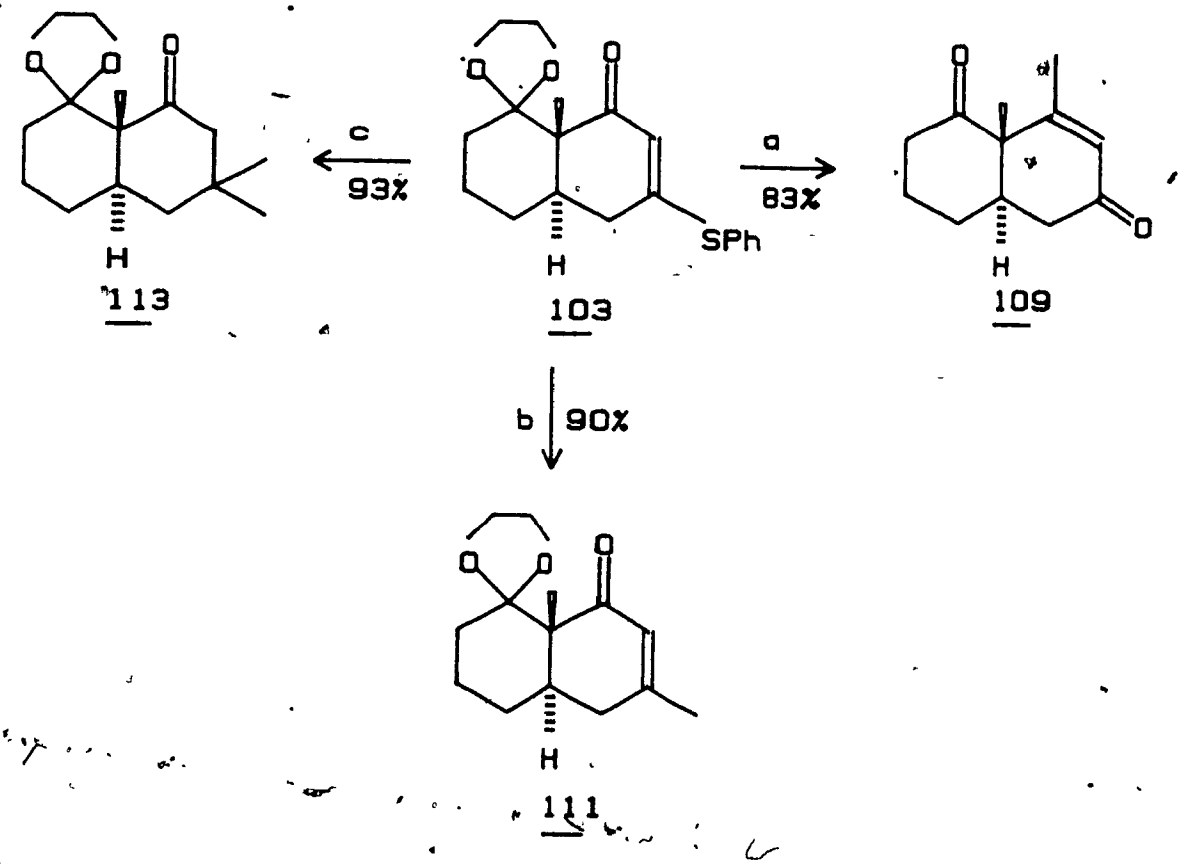
In addition to the conversion of 99 or 104 to the corresponding enedione compounds 100 and 105, other transformations are possible.



(a) CH_3Li, H^+ (b) $(CH_3)_2CuLi$, -78° C, H^+

(c) $(CH_3)_2CuLi$, 0° C, H^+ (d) Raney Ni.

Scheme XXIX



(a) CH_3Li, H^+ (b) $(CH_3)_2CuLi$, -78^o C, H^+

(c) $(CH_3)_2CuLi$, 0^o C, H^+.

Scheme XXX

For example, compounds 99 and 103 reacted smoothly with methyllithium to give the corresponding tertiary alcohols which were hydrolysed in mineral acid to give the methyl substituted enediones 108 and 109 respectively in good yields (Schemes XXIX and XXX). On the other hand, compounds 99 and 103 when treated with lithium dimethylcuprate at -78^o C

followed by quenching with aqueous saturated ammonium chloride at -78° C, gave conjugative addition products. Thus compound 99 gave the β-alkylated enedione 110 whereas compound 103 gave the β-alkylated enone 111 in excellent yields. β,β -Dialkylated compounds were obtained with lithium dimethylcuprate, but at room temperature. Thus, compound 99 gave the β,β -dialkylated dione 112 after acid hydrolysis, whereas compound 103 gave 113 in excellent yields (Schemes XXIX and XXX).

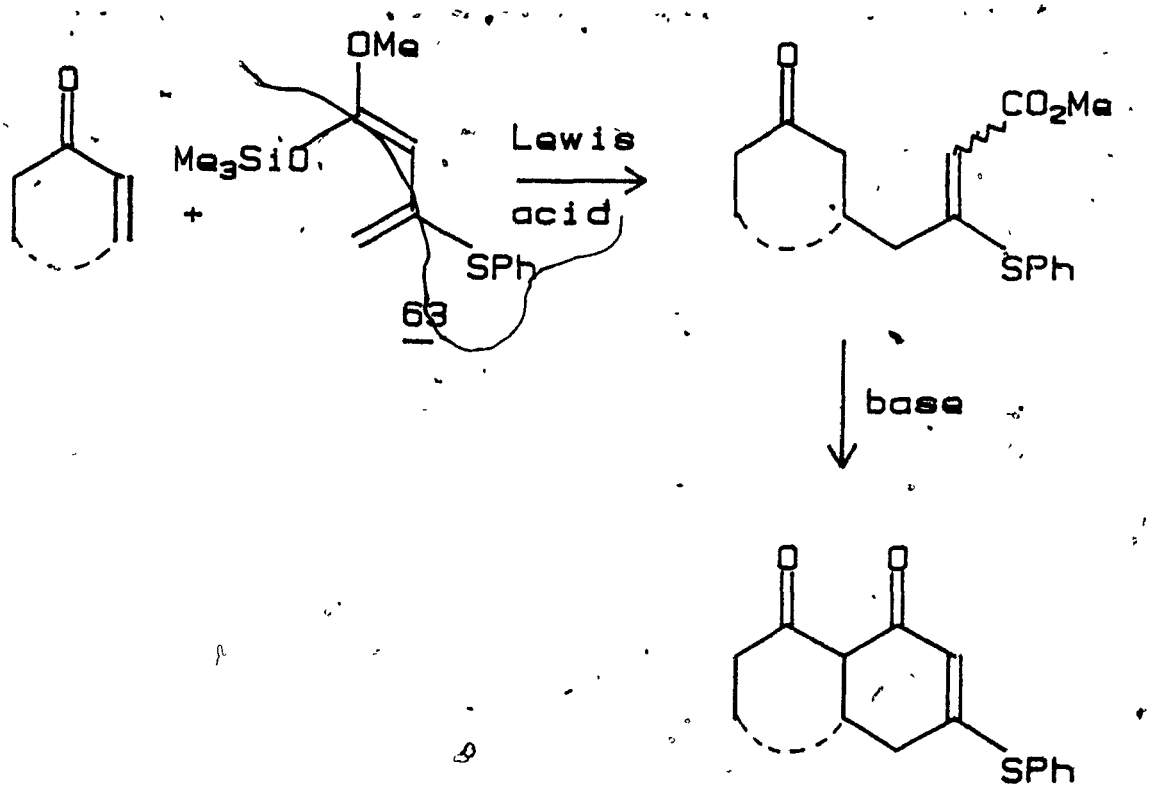
Finally we demonstrated that the sulfur moiety of 99 can be removed by hydrogenolysis with Raney Ni. The reaction went smoothly to give the enedione 114 in 63% yield (Scheme XXIX).

In conclusion, based on the propensity of 3-phenylthio-1-trimethylsiloxy-1-methoxy-1,3-butadiene 63 to undergo Michael reaction with α,β -unsaturated ketones under Lewis acid conditions, we have developed an annulation reaction using the tandem Michael-Claisen condensation. In the 9-methyl substituted decalin system, the annulation reaction can be controlled to give stereoselectively the trans- or cis- fused compounds. Chemoselective transformations of the three carbonyl groups can be effected. It seems reasonable to expect that this annulation reaction can be used for the synthesis of a number of natural products. Efforts in this direction will be described in the following chapter.

CHAPTER IV

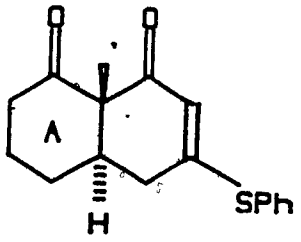
SYNTHESIS OF ARISTOLONE AND FUKINONE

In the preceding chapter, we have described an annulation reaction based on the propensity of 3-phenylthio-1-trimethylsiloxy-1-methoxy-1,3-butadiene(63) to undergo Michael reaction with α,β -unsaturated ketones under Lewis-acid catalysed conditions. The Michael adducts in turn were cyclized either with potassium tert-butoxide or with lithium thiophenoxide to give a six membered ring (Scheme XXXI). Furthermore, for the 9-methyldecalin system, it was possible to stereoselectively

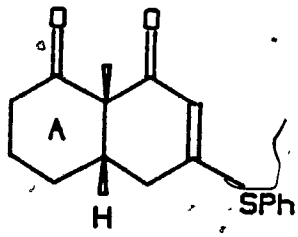


Scheme XXXI

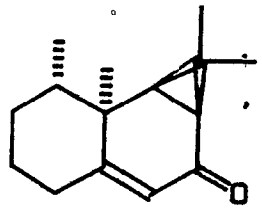
synthesize the trans- or the cis- isomers 96a and 96b using this tandem Michael-Claisen condensation. In this chapter, the utility of this reaction will be described by the synthesis of two sesquiterpens, (±)aristolone(115) and (±)fukinone(116).



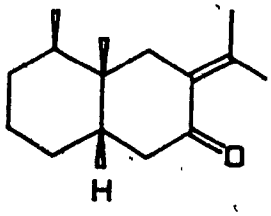
96a



96b



115

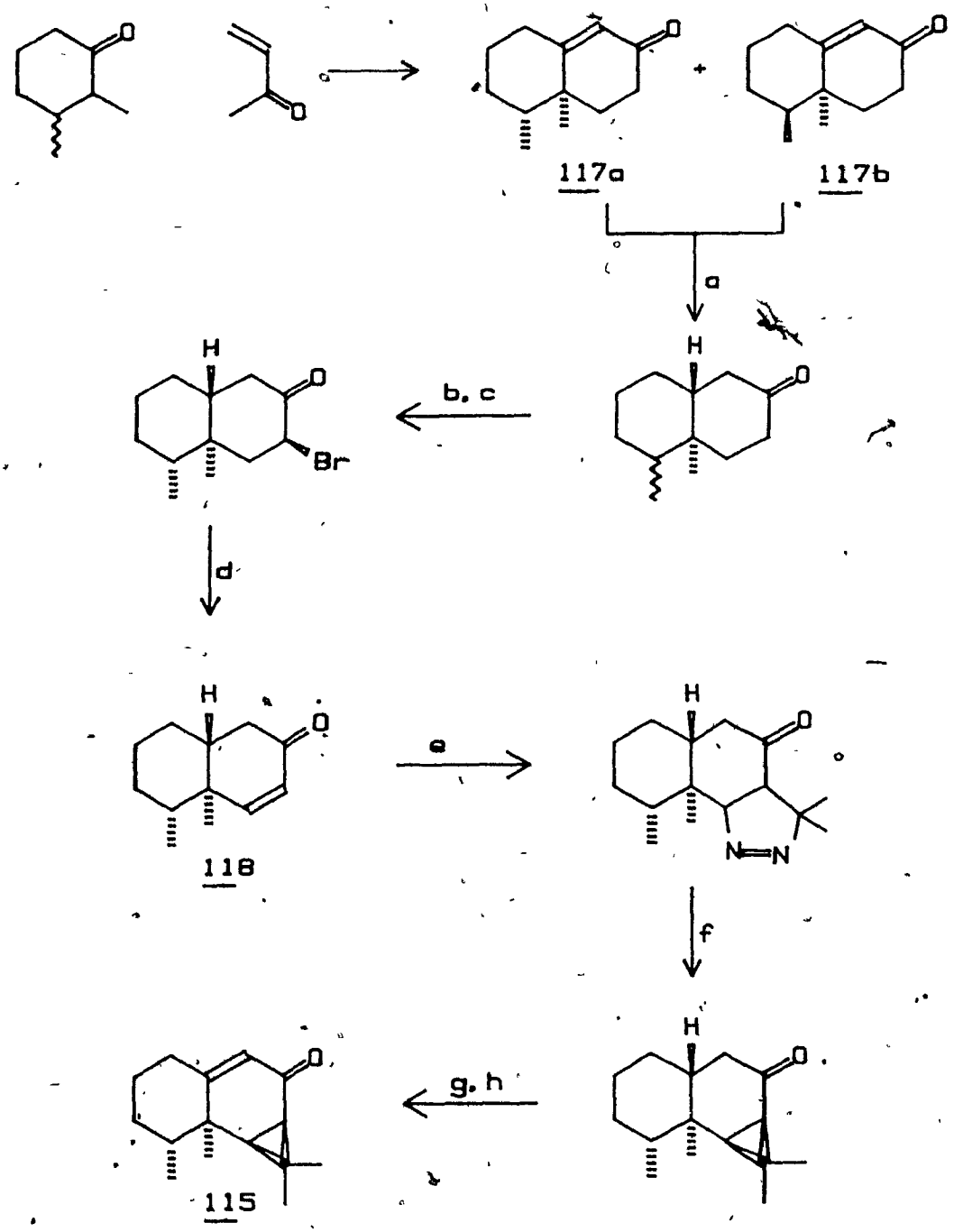


116

Synthesis of Aristolone:

The sesquiterpene (-)aristolone(115) was isolated from Aristolochia debilis Sieb. et Zucc.[129] Its structure[130] and absolute configuaration[131] have been established. Various synthesis of this sesquiterpene have also been reported.[132,133]

Ourisson et al[132] reported the synthesis of 115 in which the isopropylidene moiety was introduced by photolysis of the pyrazoline derivative prepared by 1,3-dipolar addition of diazo-2-propane to the enone 118. The enone 118 in turn was prepared from octalone 117. Ourisson et al prepared this compound from 2,3-dimethylcyclohexanone and methyl vinyl ketone by the Robinson's annulation in very poor yield. Furthermore, the octalone 117 consisted of a mixture of two epimers 117a and 117b in a ratio of approximately 3:2. Quite recently Huffman et al[16] have described a silyl enol ether variation of the Robinson's annulation. Although the ratio of 117a and 117b improved to 3:1 with good yield, the stereocontrol was still not quite satisfactory.



Scheme XXXII: Ourisson's Synthesis of Aristolone

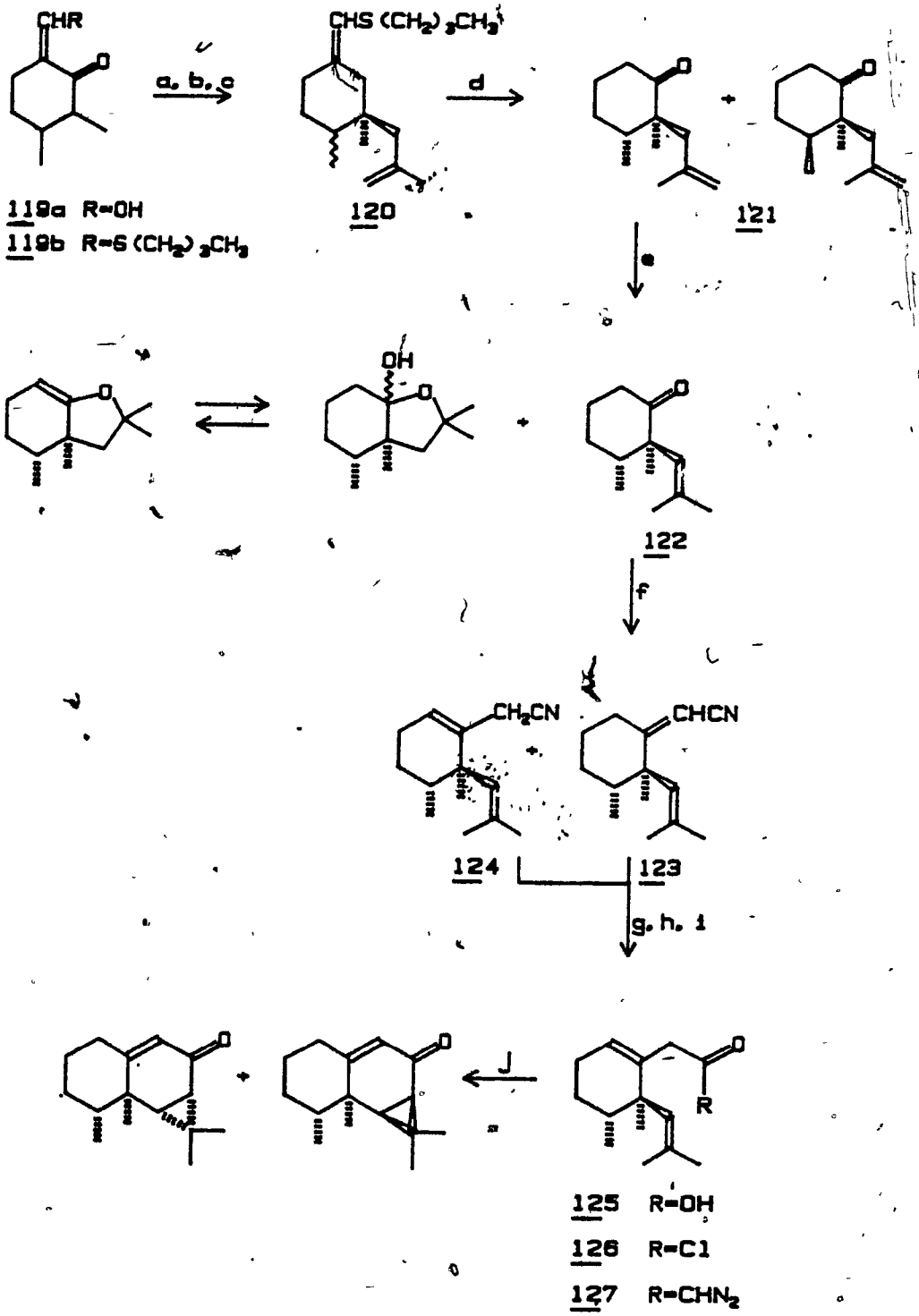
(a) Li-NH_3 (b) HBr-HOAc (c) separate (d) HMPA

(e) 2-diazopropane, (f) $h\nu$

(g) Phenyltrimethyl ammoniumbromide perbromide (h) LiBr-HMPA

Piers and co-workers have reported a very elegant synthesis of aristolone starting from 2,3-

dimethylcyclohexanone.[133] The latter was converted into its 6-n-butylthiomethylene derivative 119b, via the corresponding hydroxymethylene compound 119a. Alkylation of 119b with methallyl chloride in t-butyl alcohol in the presence of potassium t-butoxide gave, in 87% yield, a mixture of the corresponding alkylated products 120. Removal of the blocking group by treatment of 120 with KOH provided, in 90% yield, a mixture of cis- and trans-2,3-dimethyl-2-methallyl cyclohexanone 121 in a ratio of approximately 4:1, respectively. The methallyl group of 121 was transformed into a methylpropenyl moiety by refluxing with p-toluenesulfonic acid to give 122 in 22% yield. Reaction of 122 with diethyl cyanomethyl phosphonate in the presence of methylsulfinyl carbanion in DMSO, produced, in 87% yield, a mixture of the α,β-unsaturated nitrile 123, and the β,γ-unsaturated nitrile 124, in a ratio of approximately 2:1, respectively. Hydrolysis of the mixture of nitriles (123 and 124) with potassium hydroxide in refluxing aqueous ethanol afforded, in 82% yield, the β,γ-unsaturated carboxylic acid 125. The carboxylic acid was converted into its sodium salt, which on reaction with oxalyl chloride, gave the acid chloride 126. The acid chloride was converted to the diazoketone 127, by reaction with dry etheral diazomethane. The olefinic diazoketone 127 underwent a facile intramolecular cyclization to give a mixture of products, the major component of which is (±)-aristolone. This cyclization, however, was not stereoselective since it gave both aristolone and the 6,7-epi compound.



Scheme XXXIII: Pier's Synthesis of Aristolone

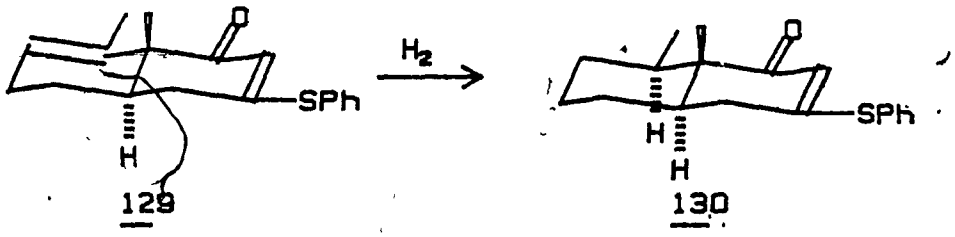
(a) NaOMe, HCOOEt (b) n-BuSH, H^+ (c) KOt-Bu, methallyl chloride (d) aq. KOH (e) H^+ (f) NaH, diethyl cyanomethylphosphonate (g) OH^- (h) oxalyl chloride (i) CH_2N_2 (j) $CuSO_4$,

We decided to seek a solution to the aforementioned problems with compound 96a in our hand. In the conversion of 96 to either aristolone or fukinone, it is necessary to (1) differentiate between the carbonyl groups in 96, (2) transform the ring A carbonyl into a methyl group, preferably with good stereochemical control and (3) introduce the isopropylidene group regioselectively in 116 and stereoselectively in 115. Knowledge gained from the study will be useful in the future to elaborate 96 into natural products of greater structural complexity.

When compound 96a was treated with methyl magnesium bromide, the Grignard reagent added smoothly to give the addition product. The ^1H nmr spectrum of crude reaction mixture indicated the presence of isomeric alcohols 128a and 128b in a ratio of 5:7 which were separated easily. It is noteworthy that the Grignard reagent selectively added to the C(8) carbonyl group instead of the C(1) carbonyl group. When 128a was treated with 80% H_2SO_4 or with polyphosphoric acid, dehydration proceeded smoothly to give compound 129 and other side products. The side products were presumably due to the hydrolysis of the masked 1,3-dione system. We were very pleased to find that with more concentrated H_2SO_4, dehydration proceeded readily to give a single compound 129 in excellent yield without any apparent hydrolysis. On the other hand, when 128b was treated with concentrated H_2SO_4 dehydration proceeded but the rate of dehydration was much slower. We thus tentatively assign the stereochemistry of the hydroxyl group

in 128a and 128b on the basis of the relative ease of dehydration.

In order to create the vicinal methyl groups, hydrogenation of compound 129 was attempted. In principle, upon hydrogenation of 129, the hydrogen delivery should occur selectively from the less hindered side to give compound 130 predominantly.



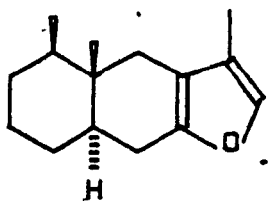
129 130

However, attempted hydrogenation of 129 with Pd or with Pt catalysts at different pressures and/or different concentrations gave only the recovered starting material 129. Presumably our inability to hydrogenate 129 was a result of catalyst poisioning by the sulfur moiety. Accordingly, compound 129 was treated with sodium methoxide in methanol to give 131 in almost quantitative yield. When compound 131 was treated with catalytic amount of 5% Pd-$CaCO_3$ under atmospheric pressure of hydrogen, hydrogenation proceeded smoothly to give a single compound 132 in almost quantitative yield. The ^1H nmr spectrum showed a sharp methyl doublet at 1.20 ppm (J=6.2Hz). It is noteworthy that under this condition, the conjugated double bond was unaffected. The next question that remains to be answered is the stereochemistry of the vicinally substituted methyl groups.

Reduction of compound 132 with lithium aluminum hydride gave compound 133 after acidic hydrolysis. The ^1H nmr

spectrum of compound 133 showed sharp doublets at 0.94(J=6.1Hz), 5.84(J=10.4Hz), 7.08(J=10.3Hz) and a sharp singlet at 0.91 ppm. Although compound 133 is known, but, because of the conflicting reports[134,135] on its ^1H nmr data in the literature, we could not establish the stereochemistry of 133 unequivocally at this point. Reaction of compound 133 with diazo-2-propane proceeded smoothly to give the cycloadduct 134 in quantitative yield. Photolysis of compound 134 gave dihydroaristolone 135 in excellent yield. The ^1H nmr spectrum of 135 is identical in all respects to the data reported[135] for dihydroaristolone. The identity of dihydroaristolone clearly suggests that hydrogenation of 131 is highly stereoselective to give cis-substituted vicinal methyl groups. The synthesis of aristolone from dihydroaristolone has already been accomplished by bromination-dehydrobromination.[132] This clearly shows that aristolone can be prepared with a high degree of stereocontrol using our tandem Michael-Claisen annulation sequence.

We note in passing that the intermediate 133 may be a valuable intermediate in the synthesis of other eremophilane sesquiterpenes such as furanoligularone (136)[136] and tetrahydroligularenolide (137)[137].



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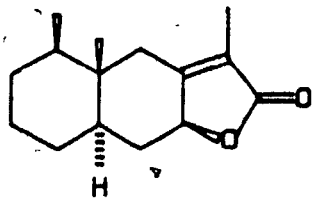
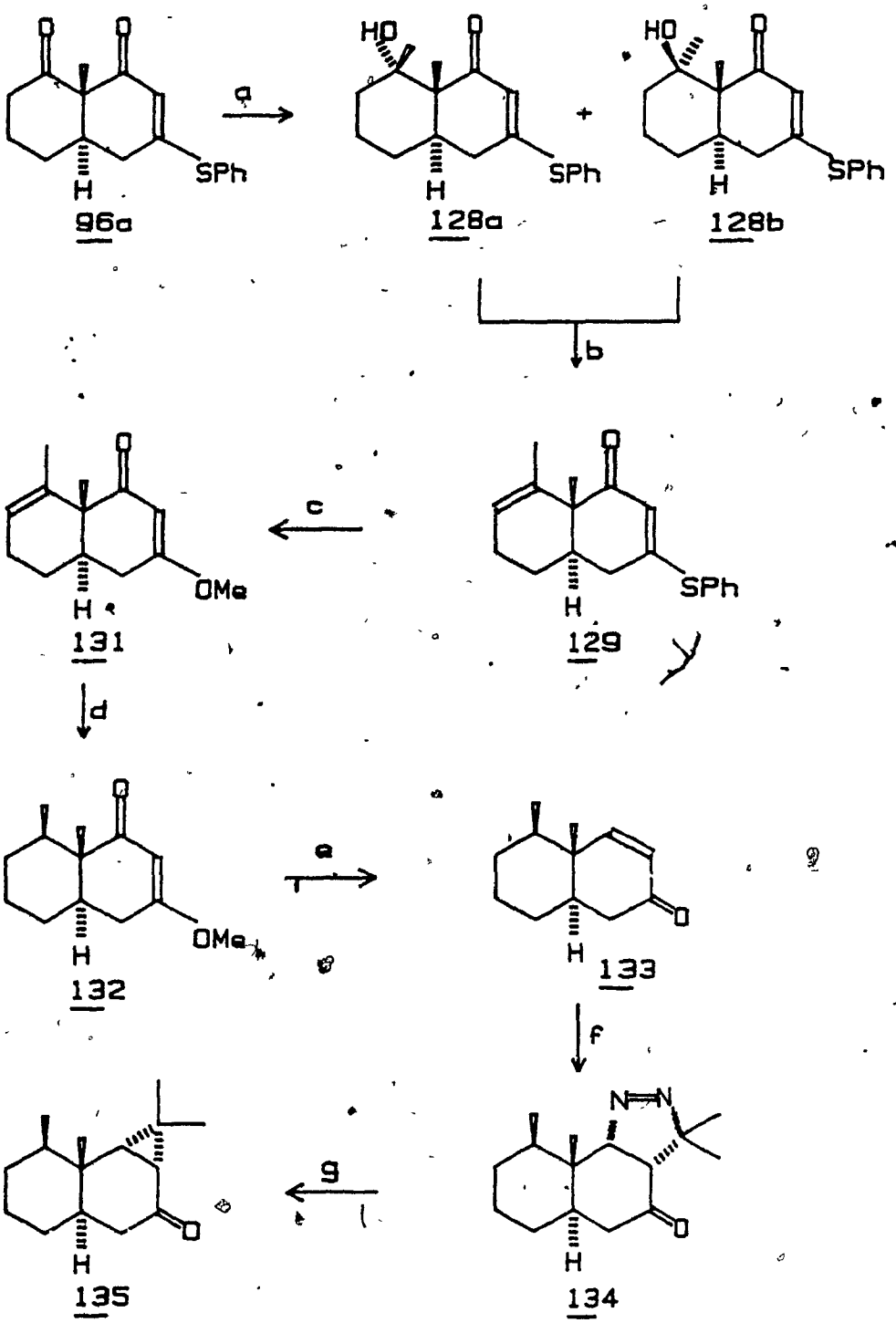


137



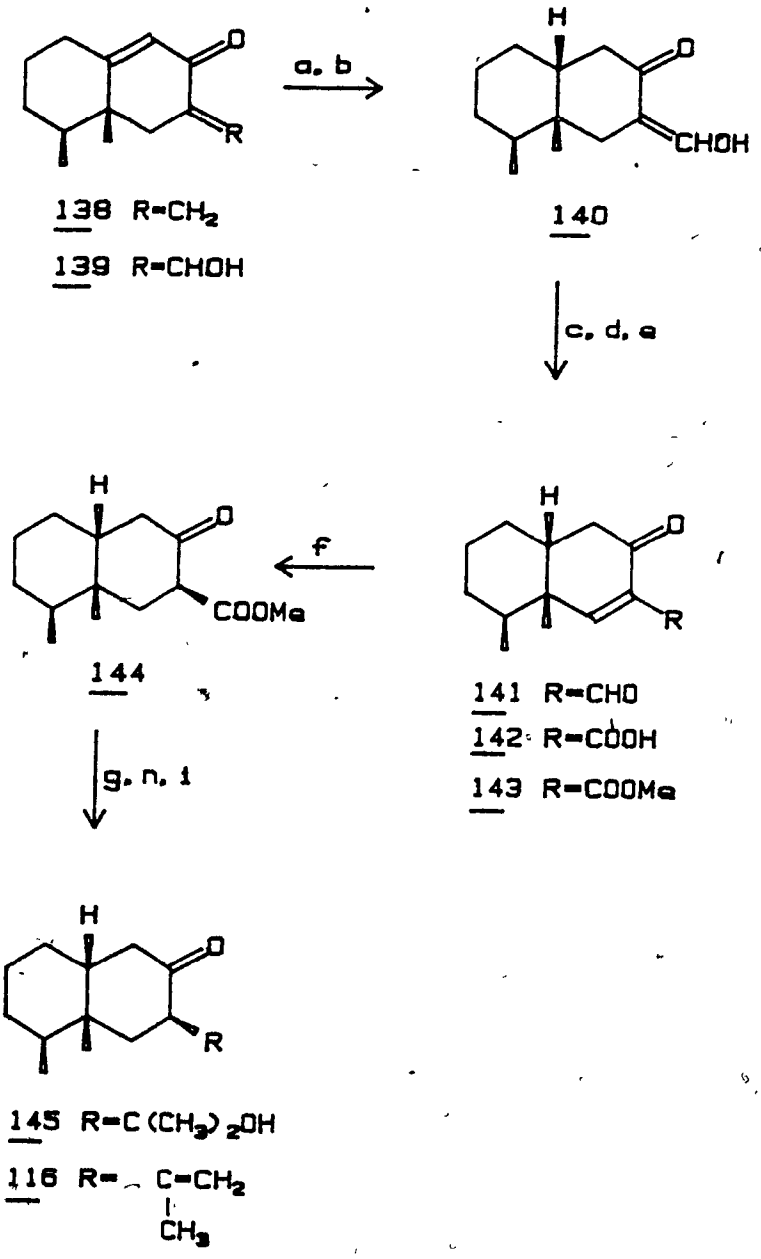
Scheme XXXIV

(a) CH_3MgBr (b) H_2SO_4 (c) $NaOCH_3$-CH_3OH (d) 5% Pd-$CaCO_3$, H_2 (e) $LiAlH_4$, H^+ (f) $(CH_3)_2CN_2$ (g) $h\nu$

Synthesis of Fukinone:

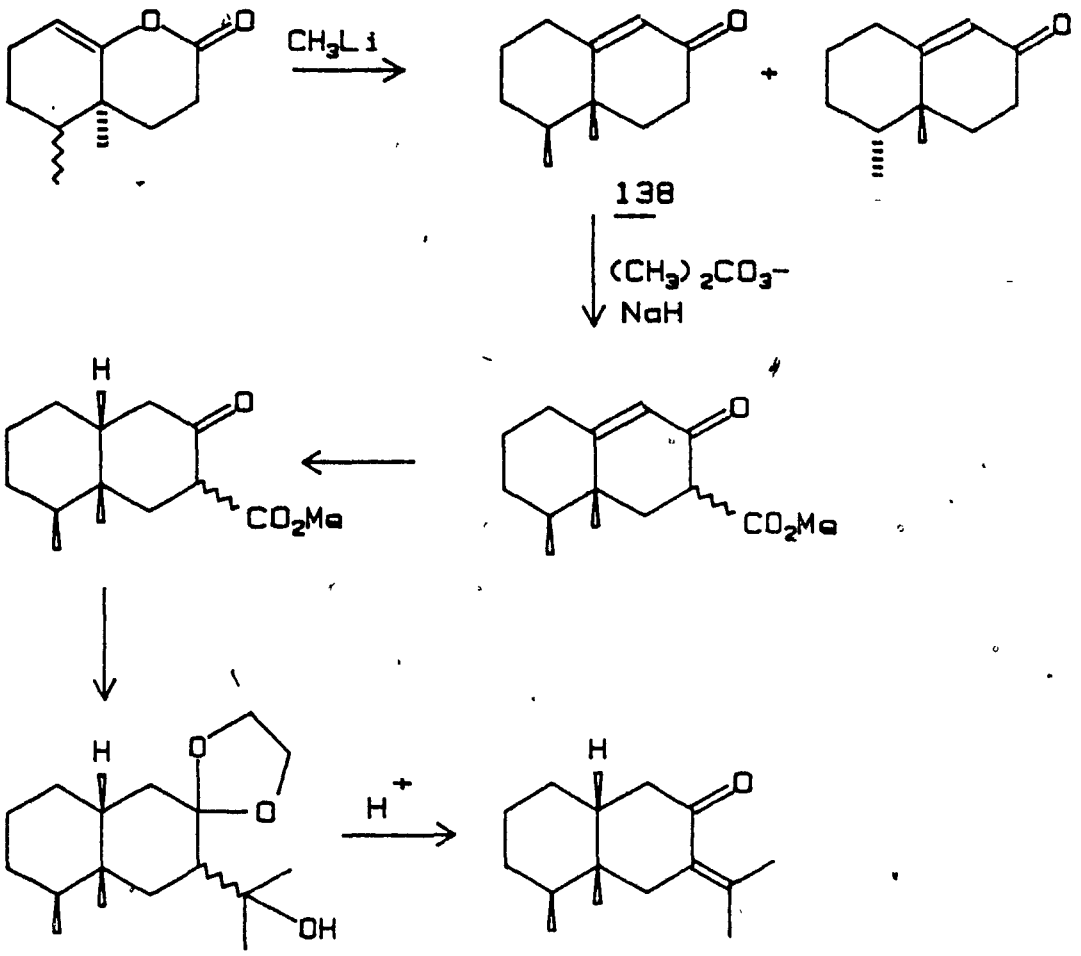
The eremophilane type sesquiterpene, (+)-fukinone, isolated from Petasites japonicus Maxim., has been assigned structure and absolute stereochemistry as depicted in 116.[138]

Three independent syntheses of this sesquiterpene have been reported. In the first of these,[139] Piers and Smillie converted the octalone 138, which they have previously used in connection with their synthesis of aristolone,[135] into 140 by treatment with ethyl formate followed by catalytic reduction. Dehydrogenation of 140 with 2,3-dichloro-5,6-dicyanobenzoquinone and subsequent oxidation and esterification yielded 143. This keto-ester was converted into fukinone 116 by hydrogenation followed by methylation of the enolate ester and dehydration of the resultant keto-alcohol 145. Torrence and Pinder have also completed the synthesis of fukinone using the octalone 138 as the key intermediate.[140]



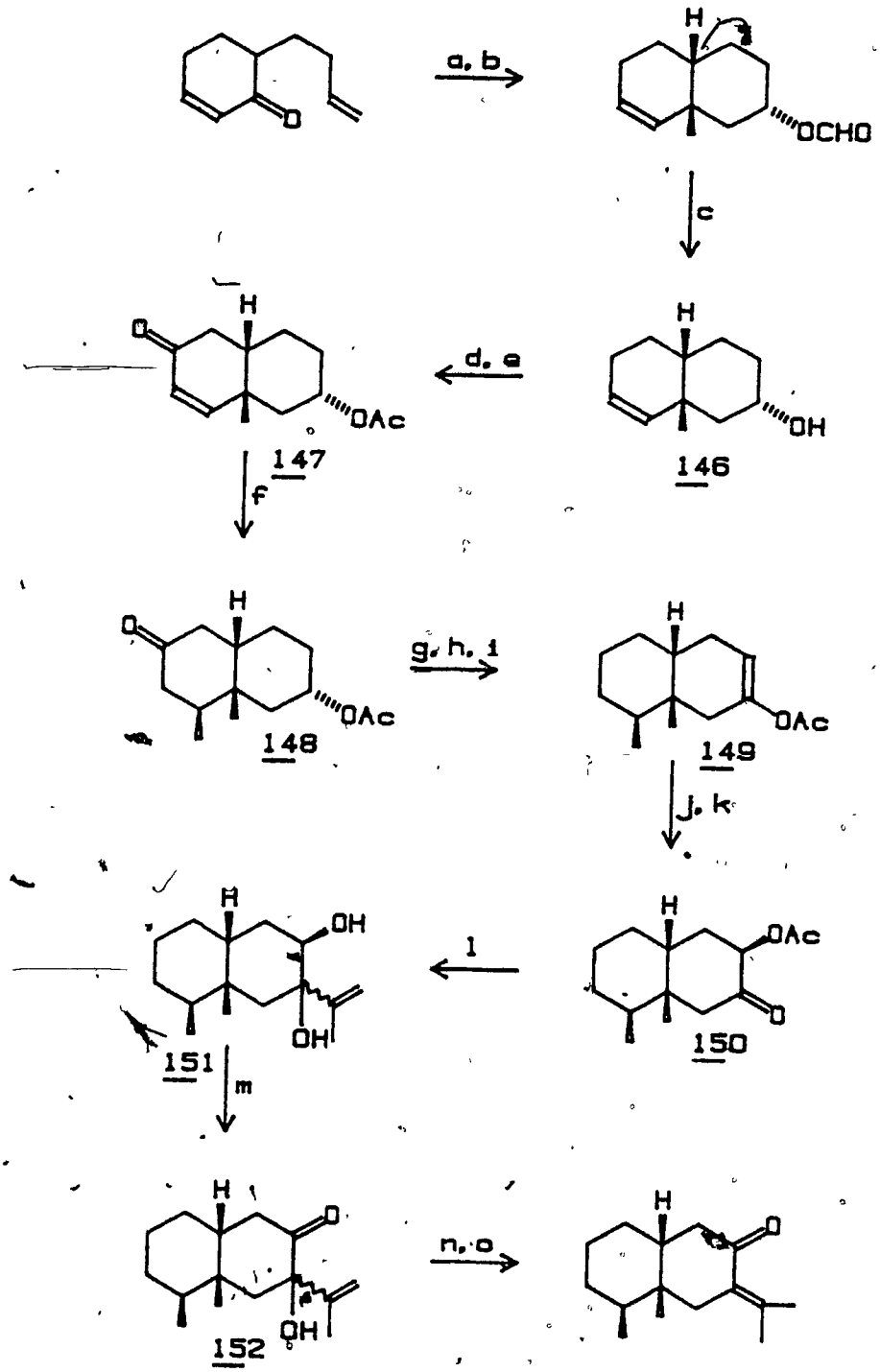
Scheme XXXV: Pier's Synthesis of Fukinone

(a) NaOMe, HCOOEt (b) 10%Pd-alc. NaOH (c) DDQ (d) AgO (e) CH_3I, AgO (f) Adams catalyst (g) NaH, CH_3Li (h) thionyl chloride, pyridine (i) H^+.



Scheme XXXVI: Pinder's Synthesis of Fukinone

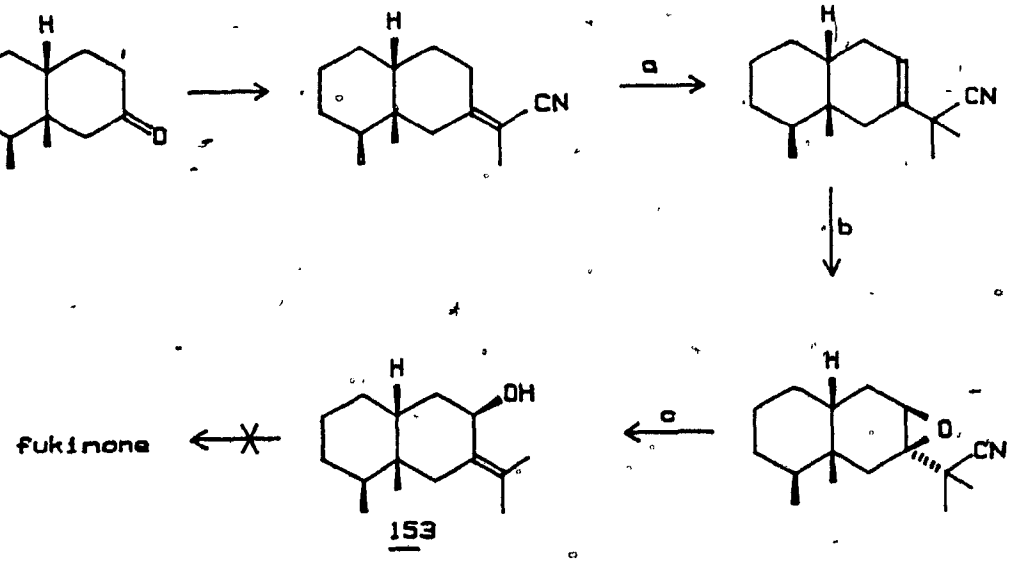
In their synthesis of fukinone, Marshall and Cohen converted the known enol 146 into 147 by acetylation and allylic oxidation.[141] The second methyl group was introduced by cuprate addition to obtain keto ester 148. Stereoselectivity in this addition is a result of the folded nature of the cis-octalin system. In such molecules, reagents invariably attack trigonal carbons adjacent to the bridgeheads from the convex face. A Wolff-Kischner reduction of 148 followed by oxidation of the resultant alcohol and enol-acetylation yielded 149. The epoxide of 149 was thermolysed to give 150 which, on reaction with isopropenyllithium and selective oxidation, gave the ketol 152 which was converted in



Scheme XXXVII: Marshall-Cohen Synthesis of (±)-Fukinone

(a) MeLi (b) HCOOH (c) $LiAlH_4$ (d) Ac_2O (e) Na_2CrO_4, HOAc, Ac_2O (f) Me_2CuLi (g) Wolff-Kishner (h) Jones (i) Ph_3CLi, Ac_2O (j) m-CPBA (k) Δ (l) isopropenyl lithium (m) $DMSO-SO_3$ (n) Ac_2O, H^+ (o) $Ca-NH_3$

two steps into fukinone (Scheme XXXVII). The ensuing transformations serve to transport the carbonyl group to C_3 while introducing the necessary isopropylidene unit ay C_2. This interesting construction was employed because more direct methods were unsuccesful. For example, the following sequence fails in the last step, as unsaturated alcohol 153 cannot be oxidized to (±)-fukinone (XXXVIII).



Scheme XXXVIII

(a) Ph_3CLi, MeI (b) m-CPBA (c) $Na-NH_3$

The main difficulty in designing a synthesis of 116 involves the stereocontrol of the vicinally substituted methyl groups and also in introducing the isopropylidene unit regioselectively. With the compound 96b in our hand, we

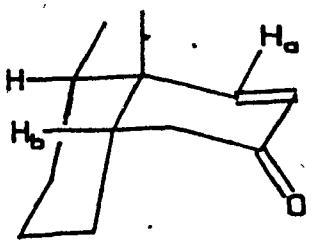
decided to seek an entry into the fukinone skeleton with a strategy similar to the synthesis of aristolone.

When compound 96b was treated with methyl magnesium bromide, the Grignard reagent added smoothly to give the adduct 154 in excellent yield. The ^1H nmr spectrum of the crude reaction mixture indicated the presence of two isomeric alcohols which were not separable in our hands. The alcohol 154 was dehydrated with concentrated H_2SO_4 to give 155 in excellent yield. The sulfur moiety in 155 was then replaced by a methoxy group with sodium methoxide to give 156.

When compound 156 was treated with 5% Pd-$CaCO_3$ in ethyl acetate under atmospheric pressure of hydrogen, hydrogenation took place smoothly. The ^1H nmr spectrum of the crude reaction mixture indicated the presence of two epimers, 157a and 157b, in 1:1 ratio. The two epimers were separated easily by column chromatography. Hydrogenation of compound 156 was also tried with other catalysts such as 10% Pd-charcoal or $Rh(PPh_3)_3Cl$ but it did not improve on the stereoselectivity. Chemical reduction of 156 using diborane gave a complicated mixture with little of reduced products 157.

In spite of the lack of good stereoselectivity in the hydrogenation of 156 we decided to push on with the synthesis. The stereochemistry of 157a and 157b, cannot be established with certainty with the nmr data. On comparision with known compounds[142] of similar structures, it appeared that 157a had cis-substituted vicinal methyl groups and 157b had trans-substituted methyl groups.

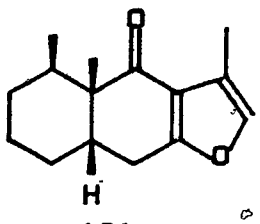
Reduction of compounds 157a and 157b with lithium aluminum hydride gave compounds 158a and 158b respectively after acidic hydrolysis. Compound 158b showed a double doublet for the vinyl hydrogen H_a at 6.8 ppm(J=2Hz and 10Hz). The smaller coupling constant (J=2Hz) which can be explained on the basis of coupling between H_a and H_b protons indicating that they have the W-conformation as depicted. This is in line with the stereochemistry of trans-substituted vicinal methyl groups.[143]



158b

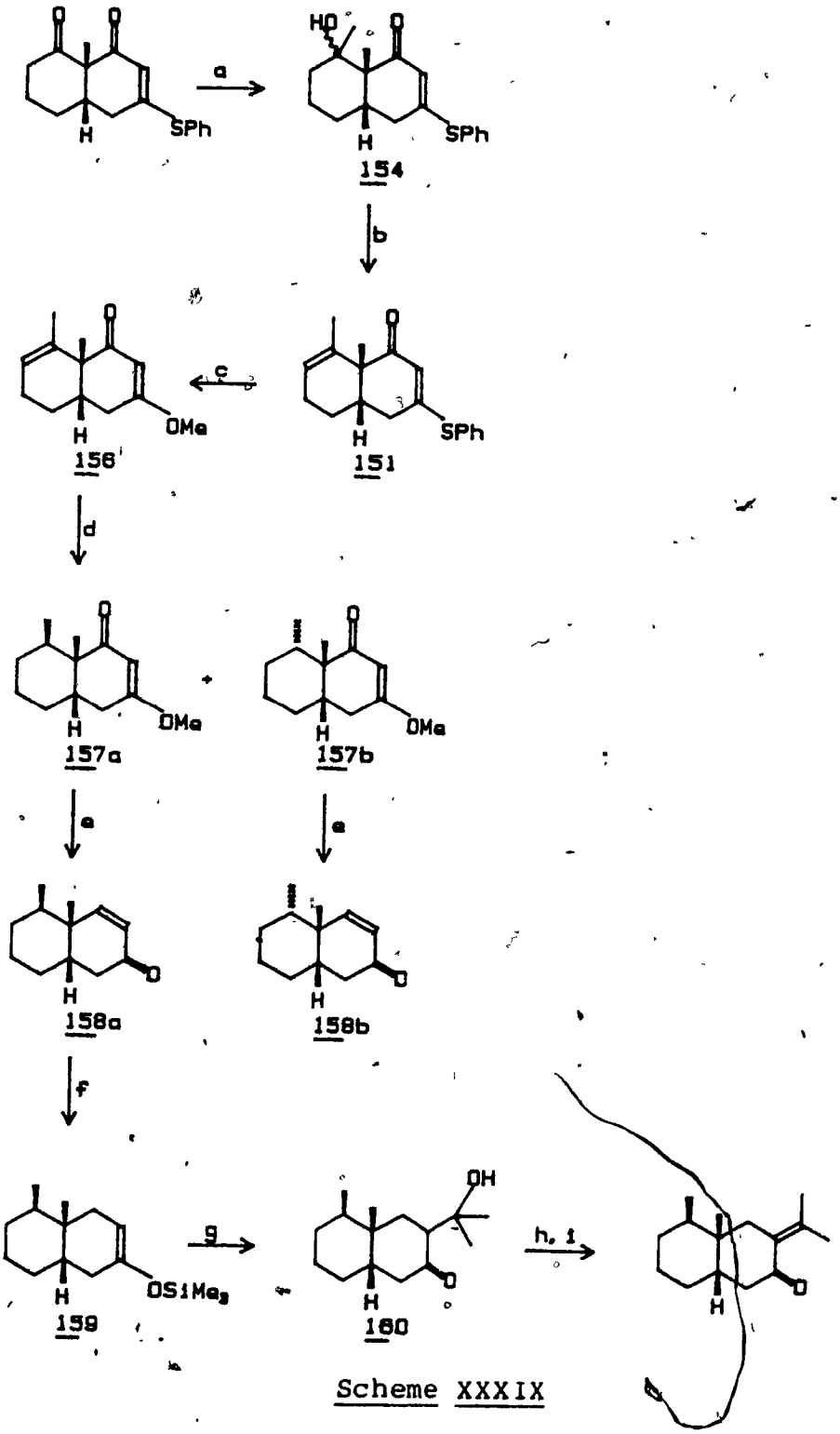
Compound 158a on treatment with Li-NH_3 generated the enolate which upon quenching with chlorotrimethylsilane gave the enol silyl ether 159. The enol silyl ether 159 on reaction with acetone under titanium tetrachloride catalysed conditions gave the aldol 160. Compound 160 was converted to fukinone with the known literature procedure.[139,141] The spectroscopic data of the synthetic material were identical in all respects to those reported for fukinone, thereby establishing the stereochemistry of the methyl groups and the position of the isopropylidene unit. The ease of regiocontrol in the present synthesis is interesting in light of the considerable effort encountered in the previous syntheses on this question.

Finally, we note that compound 157 can be a valuable intermediate in the synthesis of ligularone(161) where the oxo- function can be introduced regioselectively.[144]



161

The successful syntheses of aristolone and fukinone suggest that the annulation reaction can be of considerable utility in the synthesis of natural products. Because of the array of functionalities available in 96, it may serve as a useful entry to the synthesis of the more complicated polyoxygenated diterpenes such as clerodin[145] and forskolin.[146]



Scheme XXXIX

(a) CH_3MgBr (b) H_2SO_4 (c) $NaOCH_3$-CH_3OH (d) 5% Pd-$CaCO_3$, H_2 (e) $LiAlH_4$, H^+ (f) Li-NH_3, Et_3N-$ClSiMe_3$ (g) $(CH_3)_2CO$, $TiCl_4$ (h) $SOCl_2$, pyridine (i) Al_2O_3

CHAPTER V

CONTRIBUTIONS TO KNOWLEDGE

3-Aryl(alkyl)thio-1-trimethylsiloxy-1-methoxy-1,3-butadienes were synthesized and introduced to organic synthesis for the first time. They react with carbonyl electrophiles at its γ-position. The thio substituent enhances the γ-selectivity.

A 3C+3C cycloaromatization reaction has been developed for the synthesis of aryl sulfides using the dienes by reacting them with a number of 1,3-dicarbonyl equivalents.

A new 4C+2C annulation reaction has been developed based on the propensity of the dienes to undergo Michael reaction with α,β -unsaturated ketones under Lewis-acid catalysed conditions. The tandem Michael-Claisen annulation reaction can be controlled to give either cis- or trans- fused 9-methyldecalin system with three carbonyl groups which are differently masked. The chemoselective differentiation of each carbonyl group is demonstrated.

The utility of tandem Michael-Claisen annulation sequence in the synthesis of natural products has been demonstrated by the synthesis of aristolone and fukinone.

CHAPTER VI

EXPERIMENTAL

Melting points (mp) were determined on a Gallen-kamp block and are uncorrected. Likewise, boiling points obtained were uncorrected.

Mass spectra (ms) were obtained on a DuPont 21-492B mass spectrometer, by the direct insertion probe or the batch inlet.

Gas chromatograms were performed on a Hewlett-Packard 5730A Gas Chromatogram: 10' x 1/8" stainless steel column was used; 6% OV-101, chromosorb W 80/100 mesh.

Proton magnetic resonance (^{1}H nmr) spectra were recorded on Varian T-60, T-60A, XL-200, and XL-300 spectrometers, using tetramethylsilane (TMS) or chloroform as an internal standard. Chemical shifts were given in the scale in parts per million (ppm). Doublet (d), triplet (t), quartet (q) and multiplet (m) were recorded at the center of the peaks; other abbreviations used are singlet (s) and broad (b). ^{13}C nmr spectra were recorded on XL-300 or Bruker WH-90 spectrometers.

Infrared spectra (IR) were obtained on a Perkin 297 Spectrophotometer. Spectra were calibrated with the 1601 cm^{-1} or 1028 cm^{-1} band of polystyrene film.

Analytical thin layer chromatography (tlc) was performed

on Merck Silica Gel 60 F_{254} aluminum-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in H_2SO_4/H_2O (10 ml/90 ml) and heating on a hot plate. Merck Silica (Kiesselgel 60, 40-63) was used for flash column chromatography and Kieselgel 60 HF_{254} for TLC-mesh chromatography.

Solvents were reagent grade unless otherwise specified. THF was dried over Na and benzophenone, benzene over Na, CH_3CN, diisopropylamine and triethylamine over CaH_2, CH_2Cl_2, $CHCl_3$ and hexane over P_2O_5, methanol over Mg, DMSO over NaOH, and distilled prior to use. All evaporations were carried out under reduced pressure (water aspirator) with a bath temperature of 25°C ~40°C.

Elemental analyses were performed by Guelph Chemical Lab., Guelph, Ontario, Canada.

(E)-3-Alkylthio-crotonic acids: The carboxylic acids were prepared according to the reported methods.[115]

(E)-3-Benzylthio-crotonic acid: It had mp 111°C (with bubbling); IR($CHCl_3$): 2980 br, 1670, 1591 cm^{-1}; ^1H NMR($CDCl_3$): 2.5(s, 3H), 4.1(s, 2H), 5.72(s, 1H), 7.43(s, 5H), 11.33(br, 1H); MS: 208(M^+, 17), 145(22), 117(22), 91(100); Exact mass calcd for $C_{11}H_{12}O_2S$: 208.056, obs: 208.054.

Methyl (E)-3-phenylthio-crotonate (62b): To a well stirred solution of 10 g (51.6 mmol) of 3-phenylthio-crotonic acid and 20% aqueous KOH (3.76 g, 67 mmol) was added 6.4 ml of

dimethylsulfate (6.34 ml, 67 mmol) slowly. The stirring continued for two hours, then 100 ml of sat $NaHCO_3$ solution was added. The mixture was heated at 70°C for 15 minutes. The ester was extracted with ether and dried over $MgSO_4$. The solvent was evaporated and the ester was distilled under vacuum to give 62b, bp 168°C/7 mm, in 86% yield. It had IR(film): 1710, 1610 cm^{-1}; ^1H NMR($CDCl_3$): 7.38-7.49(m, 5H), 5.21-5.24(q, 1H), 3.58(s, 3H), 2.42(d, J=0.4 Hz, 3H); MS: 208(M^+, 76), 177(76), 149(100), 134(51), 109(57); Exact mass calcd for $C_{11}H_{12}O_2S$: 208.056, obs: 208.054.

1-Trimethylsiloxy-1-methoxy-3-phenylthio-1,3-butadiene (63b): To a solution of 1.7 ml diisopropylamine (12 mmol) in 30 ml of dry THF under N_2, 8.0 ml of 1.5M n-butyllithium in hexane was added after cooling to 0°C. The reaction mixture was cooled to -78°C. A quantity of 2.1 g of 62b in 10 ml of THF was added and the solution stirred for 20 minutes. The yellow colored solution was quenched with 2.0 ml (16 mmol) of chlorotrimethylsilane. The solvent was removed under reduced pressure after a further 20 minutes and the residue was washed and filtered with cold, dry hexane. The hexane was removed from the filtrate under reduced pressure to give 63b in quantitative yield. Compound 63b can be kept in a stoppered container for up to 4 weeks in the freezer without obvious decomposition but is slowly hydrolysed to 62b, when exposed to air. IR(film): 1625, 1580, cm^{-1}; ^1H NMR($CDCl_3$): 7.21-7.44(m, 5H), 5.52(s, H_b), 5.02(s, H_c), 4.11(s, H_a), 3.47(s, 3H), 0.27(s, 9H).

1-Trimethylsiloxy-1-methoxy-3-benzylthio-1,3-butadiene (63a) was prepared as described for 63b using compound 62a. 63a is not as stable as 63b and is used immediately in its reactions. IR(film): 1638, cm^{-1}; ^1H NMR($CDCl_3$): 7.27(s, 5H), 5.28(s, 1H), 4.83(s, 1H), 4.13(s, 1H), 3.92(s, 2H), 3.52(s, 3H), 0.23(s, 9H).

Methyl 5-hydroxy-5-phenyl-3-phenylthio-pent-2-enoate (64e): To a well stirred mixture of 63b (1.12 g, 4 mmol) and benzaldehyde (0.43 g, 4 mmol) in 20 ml CH_2Cl_2 under nitrogen at -78°C, titanium tetrachloride (0.45 ml, 4 mmol) was added. After 3h, the dark red mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give an oil which was column chromatographed (eluent: 20% ethyl acetate-hexane) to give E-(mp 82-84°C) and Z-(viscous oil) isomers of methyl 5-hydroxy-5-phenyl-3-phenylthio-pent-2-enoate in the ratio of 2:1 respectively with 68% yield.

(E)-64e had IR($CHCl_3$): 3430 br, 1702, 1595 cm^{-1}; ^1H NMR($CDCl_3$): 2.91(dd, J=3.4 and 13.7Hz, 1H), 3.5(dd, J=9.8 and 13.7Hz, 1H), 5.39(s, 1H), 3.65(s, 3H), 4.03(d, J=6Hz), 5.01-5.13(m, 1H), 7.21-7.58(m, 10H); MS: 314(M^+, 2), 282(36), 208(89), 176(84), 149(100); Exact mass calcd for $C_{18}H_{18}O_3S$: 314.098, obs: 314.095.

(Z)-64e had IR($CHCl_3$): 3600, 1694, 1578 cm^{-1}; ^1H NMR($CDCl_3$): 2.13(d, J-2.7Hz, 1H), 2.44(dd, J=9.4 and 14Hz, 1H), 2.66(dd, J=3.2 and 14Hz, 1H), 3.75(s, 3H), 4.59-4.68(m, 1H), 5.97(s, 1H), 7.17-7.45(m, 10H); MS: 314(M^+, 4), 208(64), 176(34),

149(69), 28(100); Exact mass calcd for $C_{18}H_{18}O_3S$: 314.098, obs: 314.096.

Methyl 5-hydroxy-5-methyl-3-phenylthio-hex-2-enoate (64b): To a well stirred mixture of 63b (1.12 g, 4 mmol) and acetone (0.29 ml, 4 mmol) in dry CH_2Cl_2 (20 ml) under nitrogen at -78°C was added titanium tetrachloride (0.45 ml, 4 mmol). After 5h, the dark red colored mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 64b (oil) in 71% yield. IR(film): 3455 br, 1682, 1593 cm^{-1}; ^1H NMR($CDCl_3$): 1.39(s, 6H), 3.06(s, 2H), 3.58(s, 3H), 3.6-3.72(br, 1H), 5.3(s, 1H), 7.41-7.53(m, 5H); MS: 266(M^+, 20), 234(27), 176(51), 149(66), 110(85), 59(100); Exact mass calcd for $C_{14}H_{18}O_3S$: 266.098, obs: 266.095.

Methyl 5-hydroxy-5-methyl-3-benzylthio-hex-2-enoate (64a): The reaction was performed as above with 63a and acetone. The product, an oil, was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give methyl 5-hydroxy-5-methyl-3-benzylthio-hex-2-enoate (mp 65-67°C) in 58% yield. IR(film): 3450 br, 1706, 1685, 1585 cm^{-1}; ^1H NMR($CDCl_3$): 1.32(s, 6H), 3.00(s, 2H), 3.57(s, 1H), 3.67(s, 3H), 4.03(s, 2H), 5.75(s, 1H), 7.3(s, 5H); MS: 280(M^+, 1), 262(10), 248(13), 222(14), 131(25), 91(100).

Methyl 4-(1-hydroxycyclohexyl) -3-phenylthio-but-2-enoate (64d): The reaction was performed as above with 63b and

cyclohexanone. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 64d (mp 86-87°C) in 69% yield. IR($CHCl_3$): 3440 br, 1678, 1590 cm^{-1}; ^1H NMR($CDCl_3$): 1.13-2.13(m, 10H), 3.03(s, 2H), 3.5(s, 1H), 3.57(s, 3H), 5.32(s, 1H), 7.45(s, 5H); MS: 306(M^+, 3), 274(28), 208(74), 176(62), 149(87), 110(80), 55(100); When the reaction was allowed to proceed overnight instead of 3h, 4-phenylthio-1-oxaspiro[5.5]undec-3-ene-2-one was also obtained in addition to compound 64d. IR($CHCl_3$): 1681 cm^{-1}; ^1H NMR($CDCl_3$): 0.83-2.17(m, 10H), 2.5(s, 2H), 5.3(s, 1H), 7.4(s, 5H); MS: 274(M^+, 5), 149(22), 109(43), 85(55), 43(100); Exact mass calcd for $C_{16}H_{18}O_2S$: 274.103, obs: 274.107.

Methyl 4-(1-hydroxycyclohexyl) -3-benzylthio-but-2-enoate (64c): The reaction was performed as above with 63a and cyclohexanone. The product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 64c in 67% yield as an oil. IR(film): 3450 br, 1685, 1584 cm^{-1}; ^1H NMR($CDCl_3$): 0.77-2.5(m, 10H), 2.97(s, 2H), 3.47(s, 1H), 3.65(s, 3H), 4.00(s, 2H), 5.73(s, 1H), 7.28(s, 5H); MS: 288(14), 197(24), 190(10), 179(15), 151(15), 125(18), 91(100).

Methyl 4,6-dimethyl-2-phenylthio-benzoate (66): To a well stirred mixture of 63b (1.12 g, 4 mmol), and 4-trimethylsiloxy-pen-3-en-2-one (0.69 g, 4 mmol) in dry CH_2Cl_2 (20 ml) under nitrogen at -78°C was added titanium tetrachloride (0.45 ml, 4 mmol). The mixture became dark red. After 5h, th crude reaction mixture was added to aqueous

$NaHCO_3$ and extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography (eluent: 5% ethyl acetate-hexane) to give 66 as a colorless oil (700 mg, 64%). IR(film): 1728, 1600 cm^{-1}; ^1H NMR($CDCl_3$): 2.17(s, 3H), 2.27(s, 3H), 3.77(s, 3H), 6.83(s, 2H), 7.15(s, 5H); MS: 272(M^+, 91), 241(96), 239(100), 208(76), 177(95); Exact mass calcd for $C_{16}H_{16}O_2S$: 272.087, obs: 272.082.

Methyl 2-phenylthio-5,6,7,8-tetrahydronaphthalene-1-carboxylate (68) was prepared from 63b and 67 as described for 66. The product was purified by column chromatography (eluent: 10% ethyl acetate-hexane) to give 68 as a yellowish colored oil (630 mg, 53%). IR(film): 1730, 1585 cm^{-1}; ^1H NMR($CDCl_3$): 1.5-2.02(m, 4H), 2.37-3.0(m, 4H), 3.83(s, 3H), 7.22(s, 5H), 7.04(d, J=8.1Hz, 1H); MS: 298(M^+, 33), 265(38), 206(49), 174(100), 149(49); Exact mass calcd for $C_{18}H_{18}O_2S$: 298.103, obs: 298.103.

Methyl 3-phenylthio-5,6,7,8-tetrahydronaphthalene-2-carboxylate (70b): To trimethyl orthoformate (0.53 g, 5 mmol) in dry CH_2Cl_2 (5 ml) under nitrogen at -78°C were added $TiCl_4$ (0.56 ml, 5 mmol) and cyclohexanone trimethylsilyl enol ether (0.85 g, 5 mmol). After 2h at -78°C a further 0.56 ml of $TiCl_4$ was added, followed by 63b (1.4 g, 5 mmol) in dry CH_2Cl_2 (5 ml). After a further 3h at -78°C and overnight at room temperature, the crude reaction mixture was worked up as for 66. Column chromatography with 8% ethyl acetate-hexane as eluent gave 70 as light yellowish needles (900 mg, 61%). One

recrystallisation from hexane gave white, large needles, mp 114-115°C). IR($CHCl_3$): 1705 cm^{-1}; ^1H NMR($CDCl_3$): 1.5-2.1(m, 4H), 2.35-3.0(m, 4H), 3.9(s, 3H), 6.57(s, 1H), 7.4(s, 5H), 7.65(s, 1H); MS: 298(M^+, 100), 267(43), 221(25), 239(18); Exact mass calcd for $C_{18}H_{18}O_2S$: 298.103, obs: 298.097.

Methyl 3-benzylthio-5,6,7,8-tetrahydronaphthalene-2-carboxylate 70a was prepared as above using 63a. Recrystallisation from hexane gave 70a as white colorless needles, mp 98-99°C (799 mg, 45%). IR($CHCl_3$): 1705 cm^{-1}; ^1H NMR($CDCl_3$): 1.47-2.03(m, 4H), 2.5-3.0(m, 4H), 3.88(s, 3H), 4.13(s, 2H), 7.0(s, 1H), 7.13-7.57(m, 5H), 7.65(s, 1H); MS: 312(M^+, 56), 280(49), 221(57), 191(31), 91(100); Exact mass calcd for $C_{19}H_{20}O_2S$: 312.118, obs: 312.118.

Methyl 5,6,7,8-tetrahydronaphthalene-2-carboxylate (72): A quantity of 300 mg Raney Ni (ethanol washed) was added to 100 mg of 70b in 5 ml of absolute ethanol. After 6h, the catalyst was filtered and the solvent was evaporated to give 72 as a colorless oil (52mg, 82%). IR(film): 1725, 1613 cm^{-1}; ^1H NMR($CDCl_3$): 1.6-2.13(m, 4H), 2.57-3.03(m, 4H), 3.92(s, 3H), 6.97-7.37(m, 1H), 7.63-7.93(m, 2H); MS: 190(M^+, 49), 159(74), 131(100); Exact mass calcd for $C_{12}H_{14}O_2$: 190.099, obs: 190.096.

3-Phenylthio-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid: A mixture of 596 mg of 70b in 15 ml of methanol and 10 ml of 20% aqueous KOH was refluxed for ten hours. The solvent was removed under reduced pressure and the residue was dissolved

in 5% aqueous KOH and the aqueous phase was washed with ether. The aqueous phase was neutralised with concentrated HCl and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent was removed. The carboxylic acid was recrystallised from methanol as colorless prisms, mp 193-194°C (545 mg, 96%). IR($CHCl_3$): 1685 cm^{-1}; ^1H NMR($CDCl_3$): 1.53-2.03(m, 4H), 2.4-3.17(m, 4H), 6.57(s, 1H), 7.17-7.70(m, 5H), 7.85(s, 1H); MS: 284(M^+, 100), 240(16), 197(24), 191(44), 128(36); Exact mass calcd for $C_{17}H_{16}O_2S$: 284.087, obs: 284.089.

12H-7,8,9,10-Tetrahydro-benzo[b]thioxanthen-12-one (71): A mixture of 250 mg 14 in sulfuric acid (3 ml) was stirred under nitrogen for 1.5h at 100°C. The cooled mixture was poured onto ice and the crude product was extracted with chloroform. Unreacted starting material was removed by extraction with 10% sodium carbonate. The chloroform solution was washed with water, dried ($MgSO_4$) and evaporated to dryness. The resultant yellow solid was recrystallised from chloroform-hexane as yellow crystalline needles, mp 186-187°C (175 mg, 76%). IR($CHCl_3$): 1630, 1595 cm^{-1}; ^1H NMR($CDCl_3$): 1.53-2.13(m, 4H), 2.63-3.2(m, 4H), 7.2(s, 1H), 7.3-7.63(m, 3H), 8.27(s, 1H), 8.35-8.65(m, 1H); MS: 266(M^+, 100), 251(20), 238(39), 221(23), 210(29); Exact mass calcd for $C_{17}H_{14}OS$: 266.077, obs: 266.075.

Dimethyl 3-methoxy-5-phenylthio-o-phthalate (73): A quantity of 0.49 ml of dimethyl acetylenedicarboxylate was added to a well stirred solution of 1.12 g of 63b in 15 ml of benzene at

10°C and stirring continued for 16h. The solvent was removed under reduced pressure and the crude reaction mixture was dissolved in THF. A solution of 5 ml of 5% aqueous HCl was added and stirred for 5 minutes. The solvent was removed and the organic phase was extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent was removed. The mixture was submitted to column chromatography (eluent: 30% ethyl acetate-hexane) to give dimethyl 3-methoxy-5-phenylthio-o-phthalate, mp 85-87°C, and dimethyl 3-hydroxy-5-phenylthio-o-phthalate, mp 75-77°C in 2:1 ratio with 80% yield.

Compound 73 had IR(KBr): 2952, 1740, 1725, 1590 cm^{-1}; ^1H NMR($CDCl_3$): 3.73(s, 3H), 3.82(s, 3H), 3.9(s, 3H), 6.93(d, J=2Hz, 1H), 7.33(s, 5H), 7.45(d, J=2Hz, 1H); MS: 332(M^+, 69), 301(100), 286(13), 269(18), 241(19), 171(17), 134(18); Exact mass calcd for $C_{17}H_{16}O_5S$: 332.072, obs: 332.067.

Compound 74 had IR(KBr): 2960, 1732, 1670 cm^{-1}; ^1H NMR($CDCl_3$): 3.8(s, 3H), 3.83(s, 3H), 6.47(s, 2H), 7.38(m, 5H), 10.63(s, 1H); MS: 318(M^+, 5), 252(29), 208(33), 177(30), 149(49), 134(34), 28(100); Exact mass calcd for $C_{16}H_{14}O_5S$: 318.055, obs: 318.056.

Dimethyl (Z)-3-phenylthio-5-methoxycarbonyl-2-adepate (75): To a well stirred solution of 63b (1.12 g, 4 mmol) and dimethyl maleate (0.5 ml, 4 mmol) in 20 ml of CH_2Cl_2 under nitrogen at -78°C, titanium tetrachloride (0.45 ml, 4 mmol) was added. After 5h, the dark red colored mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give an oil which was column

chromatographed (eluent: 25% ethyl acetate-hexane) to give 75 as an oil in 78% yield. The (E)-isomer of 75 was also formed as a minor product, as evidenced by ^1H NMR.

Compound 75 had IR(film): 2950, 1745, 1730, 1705 cm^{-1}; ^1H NMR($CDCl_3$): 7.13(m, 5H), 5.75(s, 1H), 3.63(s, 3H), 3.50(s, 3H), 3.43(s, 3H), 2.03-2.83(m, 5H); MS: 352(M^+, 27), 320(25), 289(24), 261(38), 183(50), 28(100); Exact mass calcd for $C_{17}H_{20}O_6S$: 352.098, obs: 352.098.

Methyl 3-phenylthio-7-oxo-oct-2-enoate (78). To a well stirred mixture of methyl vinyl ketone(0.33 ml, 4 mmol) and aluminum chloride(536 mg, 4 mmol) in 20ml CH_2Cl_2 under nitrogen at 0° C, 63(1.12 g, 4 mmol) was added. After 6h, the orange colored mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give an oil which was column chromatographed (eluent: 20% ethyl acetate-hexane) to give E-(viscous oil) and Z- (viscous oil) isomers of methyl 3- phenylthio-7-oxo-oct-2-enoate in the ratio of 1.1:1 respectively with 52% yield.

(E)-78a had IR(neat): 2948, 1710, 1596 cm^{-1}; ^1H NMR($CDCl_3$): 7.42(s, 5H), 5.18(s, 1H) 3.58(s, 3H), 2.15(s, 3H), 3.02-1.48(m, 6H); MS: 278(M^+, 38), 246(64), 189(52), 169(69), 137(90), 109(89), 43(100); Exact mass calcd for $C_{15}H_{18}O_3S$: 278.098, obs: 278.099.

(Z)-78b had IR(neat): 2956, 1705, 1580cm^{-1}; ^1H NMR($CDCl_3$): 7.57(m, 5H), 5.8(s, 1H), 3.73(s, 3H), 2.0(s, 3H), 2.43-1.23(m, 6H); MS: 278(M^+, 29), 246(44), 189(58), 169(45), 110(100), 43(93); Exact mass calcd for $C_{15}H_{18}O_3S$: 278.098, obs: 278.096.

Methyl 3-phenylthio-4-(3'-oxo-cyclohexyl)-but-2-enoate (79): To a well stirred mixture of titanium tetrachloride (0.44 ml, 4 mmol) and titanium isopropoxide (0.95 ml, 3.2 mmol) in 20 ml CH_2Cl_2 under nitrogen at -78° C, a mixture of 63 (1.12 g, 4 mmol) and 2-cyclohexene-1-one (0.39 ml, 4 mmol) in 5 ml CH_2Cl_2 was added. After 4h, the dark red mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give an oil which was column chromatographed (eluent: 20% ethyl acetate-hexane) to give E- (mp 89-91° C) and Z- (mp 88-90° C) isomers of methyl 3-phenylthio-4-(3'-oxo-cyclohexyl)-but-2- enoate in the ratio of 1.4:1 respectively with 79% yield.

(E)-79a had IR(KBr): 2980, 2930, 1710, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): 7.38(s, 5H), 5.2(s, 1H), 3.55(s, 3H), 3.05-1.38(m, 11H); MS: 304(M^+, 57), 273(37), 208(43), 195(22), 176(48), 163(39), 134(70), 28(100); Exact mass calcd for $C_{17}H_{20}O_3S$: 304.113, obs: 304.120.

(Z)-79b had IR(KBr): 2942, 1705, 1690, 1680 cm^{-1}; ^1H NMR($CDCl_3$):7.6-7.2(m, 5H), 5.78(s, 1H), 3.7(s, 3H), 2.53-1.03(m, 11H); MS: 304(M^+, 36), 273(32), 208(36), 195(23), 163(46), 134(64), 110(72), 41(100); Exact mass calcd for $C_{17}H_{20}O_3S$: 304.113, obs: 304.115.

Methyl 3-phenylthio-4-(3'-oxo-cyclopentyl)-but-2-enoate(82): The reaction was performed as above with 2-cyclopenten-1-one (0.34 ml, 4 mmol) and the oil was column chromatographed (eluent: 20% ethyl acetate-hexane) to give E- (viscous oil) and Z- (viscous oil) isomers of methyl 3-phenylthio-4-(3'-oxo-

cyclopentyl)-but-2-enoate in the ratio of 1.1:1 respectively with 55% yield. (The yield was calculated on the basis that 20% of unreacted 2-cyclopenten-1-one was also recovered)

(E)-82a had IR(film): 2952, 1742, 1710, 1600 cm^{-1}; ^1H NMR($CDCl_3$): 7.5(s, 5H), 5.27(s, 1H), 3.63(s, 3H), 3.23-1.6(m, 9H); MS: 290(M^+, 75), 259(47), 208(61), 181(36), 149(86), 134(64), 110(96), 28(100); Exact mass calcd for $C_{16}H_{18}O_3S$: 290.098, obs: 290.091.

(Z)-82b had IR(KBr): 2950, 1735, 1695 cm^{-1}; ^1H NMR($CDCl_3$): 7.65-7.27(m, 5H), 5.9(s, 1H), 3.78(s, 3H), 2.5-1.33(m, 9H); MS: 290(M^+, 40), 208(23), 176(10), 147(30), 135(39), 110(60), 86(100); Exact mass calcd for $C_{16}H_{18}O_3S$: 290.098, obs: 290.100.

Methyl 3-phenylthio-4-(3'-oxo-2'-methylcyclohexyl)-but-2-enoate(83): The reaction was performed as above with 2-methyl-2-cyclohexen-1-one (0.44 g, 4 mmol) and the oil was column chromatographed (eluent: 20% ethyl acetate -hexane) to give E- (viscous oil) and Z- (viscous oil) isomers of methyl 3-phenylthio -4-(3'-oxo-2'-methylcyclohexyl)-but-2-enoate in the ratio of 1:1 respectively with 86% yield.

(E)- 83a had IR(film):2940, 1705, 1595 cm^{-1}; MS:318(M^+, 16), 208(43), 176(26), 149(34), 134(55), 111(52), 31(100); Exact mass calc for $C_{18}H_{22}O_3S$: 318.129, obs: 318.126; ^1H NMR($CDCl_3$): 7.4(s, 5H), 5.33(s, 1H), 5.23(s, 1H)3.6(s, 3H), 3.57(s, 3H), 3.2-1.6(m, 10H), 1.13(d, J=7Hz, 3H), 1.09(d, J=7Hz, 3H).

(Z)- 83b had IR(KBr): 2950, 1702, 1685 cm^{-1}; MS: 318(M^+, 8),

208(51), 192(4[illegible], 177(33), 150(65), 135(70), 110(63), 28(100); Exact mass calc for $C_{18}H_{22}O_3S$: 318.129, obs: 318.132; ^1H NMR($CDCl_3$): 7.67-7.23(m, 5H), 5.9(s, 1H), 5.83(s, 1H), 3.83(s, 3H) 3.75(s, 3H), 3.1-0.93(m, 10H), 0.48(d, J=7Hz, 3H), 0.43(d, J=7Hz, 3H).

Methyl 3-phenylthio-4-(3'-oxo-3'-methylcyclohexyl)-but-2-enoate(84). To a well stirred mixture of titanium tetrachloride (0.44 ml, 4 mmol) and titanium isopropoxide (0.95 ml, 3.2 mmol) in 2 ml CH_2Cl_2 under nitrogen at -78° C, a mixture of 63 (1.12g, 4 mmol) and 3-methyl-2-cyclohexen-1-one (0.44 g, 4 mmol) in 3 ml CH_2Cl_2 was added. After 4h, the dark red mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give an oil which was column chromatographed (eluent: 20% ethyl acetate- hexane) to give 84 (viscous oil) in 23% yield. (The formation of (Z)-isomer of 84 cannot be ruled out, but we could isolate only the (E)-isomer in pure form)
(E)-84a had IR(film): 2960, 1715, 1602 cm^{-1}; ^1H NMR($CDCl_3$): 7.4(s, 5H), 5.27(s, 1H), 3.57(s, 3H), 3.17-1.67(m, 10H), 1.1(s, 3H); MS: 318(M^+, 24), 208(34), 177(21), 149(42), 134(31), 111(52), 55(100); Exact mass calcd for $C_{18}H_{22}O_3S$: 318.129, obs: 318.127.

Methyl 3-phenylthio-4-(3'-oxo-6',6'-dimethylcyclohexyl)-but-2-enoate(85). To a well stirred mixture of 63 (1.12 g, 4 mmol) and 4,4-dimethyl-2-cyclohexen-1-one (0.53 ml, 4 mmol) in 20 ml CH_2Cl_2 under nitrogen at -78° C, titanium tetrachloride (0,44

ml, 4 mmol) was added. After 5h, the dark red mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give an oil which was column chromatographed (eluent: 20% ethyl acetate- hexane) to give (E)- (mp 146-148° C) and (Z)- (mp 134-136° C) isomers of methyl 3-phenylthio-4-(3'-oxo-6',6'-dimethylcyclohexyl)but-2-enoate in the ratio of 3:1 respectively with 68% yield. In several runs the (E) and (Z) isomers of 85 were also obtained in pure form from the crude reaction mixture by crystallisation from 10% ethyl acetate-hexane.

(E)-85a had IR(KBr): 2930, 1690, 1590cm^{-1}; ^1H NMR($CDCl_3$): 7.42(s, 5H), 5.28(s, 1H), 3.58(s, 3H), 3.42-1.48(m, 9H), 1.12(s, 3H), 1.08(s, 3H); MS: 332(M^+, 39), 301(16), 219(26), 176(29), 134(29), 55(100); Exact mass calcd for $C_{19}H_{24}O_3S$: 332.145, obs: 332.148.

(Z)- 85b had IR(KBr): 2940, 1690, 1678 cm^{-1}; ^1H NMR($CDCl_3$): 7.67-7.1(m, 5H), 5.82(s, 1H), 3.77(s, 3H), 2.87-1.23(m, 9H), 0.73(s, 3H), 0.4(s, 3H); MS: 332(M^+, 56), 300(16), 258(39), 223(41), 205(60), 149(49), 110(60), 28(100); Exact mass calcd for $C_{19}H_{24}O_3S$: 332.145, obs: 332.141.

Ethyl 3-phenylthio-2-methyl-4(3'-oxo-6',6'-dimethylcyclohexyl) but-2-enoate(86). The reaction was performed as above with 3-phenylthio-2-methyl-1-trimethylsiloxy-1-ethoxy-1,3-butadiene (1.18 g, 4 mmol) and the oil was column chromatographed (eluent: 20% ethyl acetate- hexane) to give (E)- (viscous oil) and (Z)- (viscous oil) isomers of ethyl 3-phenylthio-2-methyl-4-(3'-oxo-6',6'-dimethylcyclohexyl)but-2-enoate in the ratio

of 1:2.9 respectively with 35% yield.

(E)-86a had IR(film): 2950,1708,1582 cm^{-1}; ^1H NMR($CDCl_3$): 7.25(s, 5H), 4.18(q, J=7Hz, 2H), 3.03-0.8(m, 9H), 2.17(s, 3H), 1.32(t, J=7Hz, 3H), 0.88(s, 3H), 0.5(s, 3H); MS: 360(M^+, 6), 277(28), 205(21), 190(38), 149(22), 125(37),28(100).

(Z)-86b had IR(film): 2950, 1710, 1582 cm^{-1}; ^1H NMR($CDCl_3$): 7.47-7.13(m, 5H), 4.24(q, J=7Hz, 2H), 2.57-1.47(m, 9H), 2.00(s, 3H), 1.32(t, J=7Hz, 3H), 0.9(s, 3H), 0.7(s, 3H); MS: 360(M^+, 8), 315(5), 205(32), 149(22), 110(44), 28(100).

3-Phenylthio-2-methyl-1-trimethylsiloxy-1-ethoxy-1,3-butadiene(63c). To a solution of 1.7 ml diisopropylamine(12 mmol) in 30 ml of dry THF under nitrogen, 8.0 ml of 1.5M n-butyllithium in hexane was added after cooling to 0° C. The reaction mixture was cooled to -78° C. A quantity of 2.0 ml of chlorotrimethylsilane (16 mmol) was added and the solution stirred for 5 minutes. Then a quantity of 2.36g (10 mmol) of 3-phenylthio-2-methyl-but-2-enoate (contains mixture of E- and Z- isomers) in 5 ml of THF was added and the solution stirred for 10 minutes. Then, the solvent was removed under reduced pressure and the residue was washed and filtered with cold dry hexane. The hexane was removed from the filtrate in vacuo to yield 63c in quantitative yield.

63c had IR(film): 2986, 1660 cm^{-1}; ^1H NMR($CDCl_3$): 7.5-7.07(m, 5H), 5.17(s, 1H), 5.00(s, 1H), 3.7(q, J=Hz, 2H), 1.7(s, 3H), 1.1(t, J=7Hz, 3H), 0.2(s,9H); ^{29}Si NMR($CDCl_3$): 20.52(s).

3-Pnenylthio-5,6,4a,8a-tetrahydro-napnthalene-1,8(4H,7H)-dione (89). To a well stirred solution of methyl 3- phenylthio-4-

(3'-oxo-cyclohexyl)-but-2-enoate (1.22 g, 4 mmol) in 20 ml THF under nitrogen at room temperature, was added potassium tert-butoxide (470 mg, 4 mmol). After 2h, the solvent was removed under vacuum and the crude viscous mass was treated with 5 ml sat. aqueous NH_4Cl solution followed by extraction with ether. The extract was dried (Na_2SO_4) and the solvent was removed. The yellow colored solid was crystallised from hexane to give 89 as yellow colored prisms (mp 129-131° C) in 89% yield.

89 had IR(KBr): 2940, 1595, 1440 cm^{-1}; ^1H NMR($CDCl_3$): 7.4(s, 5H), 5.45(d, J=1.8Hz, 1H), 3.00-1.17(m, 9H), 15.07(s, 1H); MS: 272(M^+, 88), 244(62), 242(40), 163(65), 149(35), 135(88), 28(100); Exact mass calcd for $C_{16}H_{16}O_2S$: 272.087, obs: 272.080.

Anal. calcd for $C_{16}H_{16}O_2S$: C, 70.59; H, 5.88; S, 11.77. Found: C, 70.36; H, 6.28; S, 12.09.

5-Phenylthio-2,3,3a,7a-tetrahydro-(1H)-indene-1,7(4H)-dione (91).

The reaction was performed as above with methyl 3-phenylthio-4(3'-oxo-cyclopentyl)-but-2-enoate (1.16 g, 4 mmol) except that CH_2Cl_2 was used for extraction instead of ether and the crude product was column chromatographed (eluent: 50% ethylacetate- hexane) to give 91 (mp 135-137° C) in 72% yield.

91 had IR(KBr): 2930, 1722, 1615, 1555 cm^{-1}; ^1H NMR(CD_3OD): 7.02(s, 5H), 4.92(br, 1H), 2.73-1.4(m, 8H); MS: 258(M^+, 100), 230(34), 213(36), 202(43),176(33), 149(50), 109(76); Exact mass calcd for $C_{15}H_{14}O_2S$: 258.071, obs: 258.068.

7-Methyl-4-phenylthio-bicyclo[4.2.2]-dec-3-ene-2,8-dione(92).

To a well stirred solution of 83a (1.27 g, 4 mmol, contains mixture of isomers) in 20 ml of THF under nitrogen, was added potassium tert- butoxide (470 mg, 4 mmol) and refluxed for 3h. The solvent was then removed under vacuum and the crude product was treated with 5 ml of sat aqueous NH_4Cl solution followed by extraction with ether. The ether extract was dried (Na_2SO_4) and the solvent removed. THe crude product was column chromatographed (eluent: 30% ethyl acetate- hexane) to give 92 (viscous oil) in 63% yield.

92 had IR(film): 2975, 1715, 1660, 1442 cm^{-1}; ^1H NMR($CDCl_3$): 7.6(m, 5H), 5.57(s, 1H), 3.53(d, J=5Hz, 1H), 2.78-1.67(m, 8H), 1.11(d, J=6Hz, 3H); ^{13}C NMR($CDCl_3$): 206.7, 196.6, 161.6, 135.4, 130.3, 130.1, 121.9, 55.9, 45.5, 41.9, 40.9, 27.1, 22.6; MS: 286(M^+, 72.3), 258(34), 231(39), 209(32), 203(61), 176(44), 131(49), 28(100); Exact mass calcd for $C_{17}H_{18}O_2S$: 286.103, obs: 286.102.

3-Phenylthio-5,6,4a,8a-tetrahydro-4a-methyl-naphthalene-1,8(4H,7H)-dione(93). To a well stirred solution of 84a (1.27 g, 4 mmol) in 20 ml of THF under nitrogen at room temperature was added potassium tert-butoxide (470 mg, 4 mmol). After 2h, the solvent was removed under vacuum and the crude viscous mass was treated with 5 ml sat aqueous NH_4Cl solution followed by extraction with ether. The extract was dried (Na_2SO_4) and the solvent removed. The yellow colored mass was column chromatographed (eluent: 10% ethyl acetate- hexane) to give 93 (mp 76-78° C) in 83% yield.

93 had IR(KBr): 2940, 1595 cm^{-1}; ^1H NMR($CDCl_3$): 7.4(s, 5H),

5.47(d, J=2Hz, 1H), 2.77-1.53(m, 8H), 1.2(s, 3H), 15.3(s, 1H); MS: 286(M^+, 32), 271(100), 244(10), 218(21), 193(34), 176(37), 162(54), 135(58), 105(60); Exact mass calcd for $C_{17}H_{18}O_2S$: 286.103, obs: 286.098.

3-Phenylthio-5,6,4a,8a-tetrahydro-5,5-dimethyl-naphthalene-1,8(4H,7H)-dione(94). The reaction was performed as above with 85a (1.33 g, 4 mmol) and the yellow colored solid was crystallised from hexane to give 94 (mp 124-126° C) in 86% yield.

94 had IR(KBr): 2934, 1565, 1270 cm^{-1}; ^1H NMR($CDCl_3$): 7.5-7.4(m, 5H), 5.41(s, 1H), 2.73-2.13(m, 5H), 1.65-1.47(m, 2H), 1.04(s, 3H), 0.88(s, 3H), 15.15(s, 1H); MS: 300(M^+, 78), 298(100), 283(38), 255(36), 244(59), 191(50), 135(96), 110(52), 28(97); Exact mass calcd for $C_{18}H_{20}O_2S$: 300.118, obs: 300.121.

3-Phenylthio-5,6,4a,8a-tetrahydro-2,5,5-trimethyl-naphthalene-1,8(4H,7H)-dione (95). The reaction was performed as above with 86a (1.44 g, 4 mmol) and the yellow colored mass was column chromatographed (eluent: 10% ethyl acetate- hexane) to give 95 (mp 115-117° C) in 79% yield.

95 had IR(KBr): 2936,1568 cm^{-1}; ^1H NMR($CDCl_3$): 7.37(s, 5H), 2.97-1.23(m, 7H), 2.03(d, 3H), 0.73(s, 3H), 0.7(s, 3H); MS: 314(M^+, 32), 258(31), 236(22), 218(28), 205(34), 110(56), 135(34), 84(100); Exact mass calcd for $C_{19}H_{22}O_2S$: 314.134, obs: 314.137.

General method for the cyclization of Michael adducts with

lithium thiophenoxide:

To a well stirred solution of thiophenol (1.54 ml, 15 mmol) in 20 ml THF at 0° C under nitrogen, was added 6 ml of 2.5M n-BuLi (15 mmol) followed by 85b (498 mg, 1.5mmol) in 5 ml THF and then refluxed for 20h. The solvent was removed and the crude yellow colored crystalline mass was dissolved in ether and washed twice with 8% aqueous sodium hydroxide. The ether extracts were dried (Na_2SO_4) and the solvent was removed. The yellow colored crude mass was crystallised from hexane to give 94 in 91% yield and was identical in all respects to the one prepared by the potassium tert-butoxide method.

Methyl 3-phenylthio-4-(3'-trimethylsiloxy-2'-methyl-2'-cyclohexenyl)-but-2-enoate(97). To a well stirred solution of 83a (750 mg, 2.36 mmol) in 20 ml CH_2Cl_2 under nitrogen at -23° C, was added hexamethyldisilazane (0.6 ml, 2.83 mmol) and iodotrimethylsilane (0.4 ml, 2.83 ml). The reaction mixture is stirred at -23° C for 30 minutes and then 2h at room temperature. The solvent was removed under vacuum and 200 ml of dry hexane was added. The liberated salts were filtered off and the hexane was removed under vacuum to give 97 in quantitative yield.

97 had IR(film): 2950, 1690, 1600 cm^{-1}; ^1H NMR($CDCl_3$): 7.33(s, 5H), 5.2(s, 1H), 3.57(s, 3H), 3.1-0.8(m, 9H), 1.67(br, 3H), 0.22(s, 9H); MS: 390(M^+, 2), 282(7), 183(100), 109(7), 73(41); Exact mass calcd for $C_{21}H_{30}O_3SSi$: 390.169, obs: 390.167.

cis-3-Phenylthio-5,6,4a,8a-tetrahydro-8a-methyl-naphthalene-

1,8(4H,7H,)-dione (cis-96). To a well stirred solution of 97 (390 mg, 1 mmol) in 3 ml THF under nitrogen at room temperature was added potassium tert-butoxide (118 mg, 1.05 mmol). After 20 minutes, 5 ml dry DMF was added and stirring continued for another 20h. The solvent was removed under vacuum and the crude product was treated with 2 ml sat. NH_4Cl solution and extracted with ether. The ether extract was washed twice with 15 ml of sat. aqueous NaCl solution to remove any traces of DMF. The ether extract was dried (Na_2SO_4) and the solvent was evaporated. The crude product was column chromatographed (eluent: 20% ethyl acetate- hexane) to give 96 (mp 109-111° C) in 63% yield.

96 had IR(KBr): 2960, 1715, 1665, 1394, 1321 cm^{-1}; ^1H NMR($CDCl_3$): 7.5-7.43(m, 5H), 5.36(d, J=2Hz, 1H), 2.92(ddd, J=2.2Hz, 5.2Hz, 18.2Hz, 1H), 2.34(dd, J=2.5Hz, 18.2Hz), 2.38-1.5(m, 7H), 1.24(s, 3H); ^{13}C NMR($CDCl_3$): 208.4, 195.7, 163.8, 135.5, 130.4, 130.0, 127.5, 118.2, 60.3, 45.3, 39.9, 33,3, 28.2, 25.5, 18.3; MS: 286(M^+, 62), 176(100), 148(50), 91(20), 85(20), 67(93); Exact mass calcd for $C_{17}H_{18}O_2S$: 286.103, obs: 286.104.

Anal. calcd for $C_{17}H_{18}O_2S$: C, 71.33; H, 6.29; S, 11.19. Found: C, 70.99; H, 6.52; S, 10.98.

trans-3-Phenylthio-5,6,4a,8a-tetrahydro-8a-methyl-naphthalene-1,8(4H,7H)-dione (trans-96). To a well stirred solution of 89 (2.6 g, 9.56 mmol) in 25 ml benzene, was added 10% aqueous solution of tetrabutylammonium hydroxide (2.73 g in 27.3 ml water, 10.52 mmole) followed by iodomethane (2.98 ml, 47.8

mmol) and stirred for 20h. Then, the solvent benzene was removed and the crude product was extracted with ether. At this stage any crystallised tetrabutylammonium iodide was filtered off and the organic phase was dried (Na_2SO_4) and column chromatographed to give trans-96 (mp 115-119° C) and cis-96 in 9:4 ratio with 89% yield. In several runs trans-96 was also obtained in pure form from the crude reaction mixture by crystallisation from 25% ethyl acetate-hexane.

trans-96 had IR(KBr): 3320, 2950, 1660,1550 cm^{-1}; ^1H NMR($CDCl_3$): 7.50-7.40(m, 5H), 5.40(d, J=0.8Hz, 1H), 2.75-1.60(m, 9H), 1.37(s, 3H); MS: 286(M^+, 36), 176(60), 148(39), 109(21), 85(35), 67(73), 28(100); Exact mass calcd for $C_{17}H_{18}O_2S$: 286.103, obs: 286.099;

trans-3-Phenylthio-5,6,4a,8a-tetrahydro-4a,8a-dimethyl-naphthalene-1,8(4H,7H)-dione(107). To a well stirred solution of methyl 3- phenylthio-4-(3'-oxo-1'-methylcyclohexyl)-but-2-enoate (159 mg, 0.5 mmol) in 10 ml THF under nitrogen at room temperature, was added potassium tert-butoxide (59 mg, 0.53 mmol). After 1h, iodomethane (0.16 ml, 2.5 mmol) was added and stirring continued for another 3h. The solvent was removed under reduced pressure and the crude product was extracted with ether. The ether extract was washed with 10% aqueous NH_4Cl solution. The organic phase was dried (Na_2SO_4) and the solvent was removed. The crude product was column chromatographed (eluent: 50% ethyl acetate- hexane) to give 107 in 65% ~~yield.~~ Compound 107 was crystallised from ethyl acetate- hexane as a white crystalline solid (mp 183-185° C).

107 had IR(KBr): 2960, 1714, 1648, 1582 cm^{-1}; ^1H NMR($CDCl_3$): 7.45-7.42(m, 5H), 5.24(d, J=2.2Hz, 1H), 2.79-2.61(m, 1H), 2.74(ddd, J=17.8Hz, 2.2Hz, 0.8Hz, H_a), 2.12(d, J=17.8Hz, H_b) 2.16-1.85(m, 5H), 1.41(s, 3H), 1.02(d, J=0.8Hz, 3H); MS: 300(M^+, 61), 176(94), 147(43), 110(27), 85(37), 67(100); Exact mass calcd for $C_{18}H_{20}O_2S$: 300.118, obs: 300.115.
Anal. calcd for $C_{18}H_{20}O_2S$: C, 72.00; H, 6.67; S, 10.67. Found: C,71.66; H, 6.71; S, 10.88;

cis-3-Phenylthio-8-methoxy-4a,5,6,8a-tetrahydro-8a-methyl-(4H)-naphthalene-1-one(99). To a well stirred solution of cis-96 (1.14 g, 4 mmol) in 30 ml dry CH_3OH at room temperature was added, catalytic amount of p-toluenesulfonic acid and trimethyl orthoformate (2.19 ml, 20 mmol). After 20h, the solvent was removed under vacuum and the crude product was dissolved in ether. The ether extract was washed with 10 ml of sat. aqueous $NaHCO_3$ and the extracts were dried (Na_2SO_4). The crude viscous mass was column chromatographed (eluent: 15% ethyl acetate- hexane) to give 99 in 87% yield.
99 had IR(film): 2936,1660, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): 7.43(s, 5H), 5.45(br, 1H), 4.63(t, J=4Hz, 1H), 3.5(s, 3H), 2.73-1.53(m, 7H), 1.4(s, 3H); MS: 300(M^+, 14), 273(3), 191(5), 176(3), 153(19), 124(40), 109(35), 43(100); Exact mass calcd for $C_{18}H_{20}O_2S$: 300.118, obs: 300.118.

cis-3,4,4a,8a-Tetrahydro-8a-methyl-naphthalene-1,6(2H,5H)-dione(100). To a well stirred solution of 99 (150 mg, 0.5 mmol) in 15 ml dry ether under nitrogen, was added lithium aluminum hydride (5.7 mg, 0.6 mmol). After 30 minutes, once again lithium aluminum hydride (5.7 mg, 0.6 mmol) was added

and refluxed for 60 minutes. The unreacted lithium aluminum hydride was destroyed by adding 5 ml ethyl acetate. The reaction mixture was washed with 5 ml of 10% aqueous HCl and the ether layer was dried (Na_2SO_4). The solvent was removed under vacuum and the crude product was treated with 20% HCl in THF and stirred for 24h. Then the solvent was removed and the crude product was extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed. The crude product was column chromatographed (eluent: 20% ethyl acetate-hexane) to give 100 in 71% yield.

100 had IR(KBr): 2960, 1708, 1670 cm^{-1}; ^1H NMR($CDCl_3$): 6.05(d, J=10Hz, 1H), 6.65(d, J=10Hz, 1H), 1.47(s, 3H), 1.6-2.2(m, 4H), 2.2-2.6(m, 5H); MS: 178(M^+, 24), 150(86), 135(75), 121(97), 109(100); Exact mass calcd for $C_{11}H_{14}O_2$: 178.099, obs: 178.099.

trans-3',4',4a',8a'-Tetrahydro-8a'-methyl-6'-phenylthio-spiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-8'(5'H)-one(103).

To a well stirred solution of trans-96 (1.14 g, 4 mmol) in 50 ml benzene, was added catalytic amount of p-toluenesulfonic acid and ethyleneglycol (0.37 g, 6 mmol). The reaction mixture was refluxed on a Dean-Stark apparatus. After 4h, once again ethyleneglycol (0.12 g, 2 mmol) was added and reflux continued for 2h more. The solvent was removed and the residue was column chromatographed (eluent: 25% ethyl acetate-hexane) to give 103 (mp 128-130° C) in 83% yield.

103 had IR(KBr): 2948, 1660, 1580 cm^{-1}; ^1H NMR($CDCl_3$): 7.33(s, 5H), 5.27(br, 1H), 4.4-3.7(m, 4H), 2.6-2.0(m, 3H), 2.7-1.9(m,

6H), 1.2(s, 3H); MS: 330(M^+, 50), 262(9), 220(49), 176(20), 139(41), 111(88), 28(100); Exact mass calcd for $C_{19}H_{22}O_3S$: 330.129, obs: 330.132.

trans-3',4',4a',8a'-Tetrahydro-8a'-methyl-6'-methoxy-spiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-8'(5'H)-one (104). To a well stirred solution of 103 (1.32 g, 4 mmol) in 15 ml dry CH_3OH, was added sodium methoxide (0.87 g, 16 mmol) and refluxed for 20h. The solvent was removed under vacuum, treated with 10 ml of sat aqueous $NaHCO_3$ solution and extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed. The crude product was column chromatographed (eluent: 30% ethyl acetate-hexane) to give 104 in 96% yield.

104 had IR(KBr): 2956, 1664, 1618 cm^{-1}; ^1H NMR($CDCl_3$): 5.15(s, 1H), 4.47-3.87(m, 4H), 3.65(s, 3H), 2.47-2.03(m, 3H), 1.83-1.30(m, 6H), 1.22(s, 3H); MS: 252(M^+, 40), 237(16), 209(27), 164(17), 140(24), 113(41), 86(100); Exact mass calcd for $C_{14}H_{20}O_4$: 252.136, obs: 253.138.

trans-3,4,4a,8a-Tetrahydro-8a-methyl-naphthalene-1,6(2H,5H)-dione(105). To a well stirred solution of 104 (165 mg, 0.5 mmol) in 15 ml dry ether under nitrogen, was added lithium aluminum hydride (5.7 mg, 0.6 mmol). After 30 minutes, once again lithium aluminum hydride (5.7 mg, 0.6 mmol) was added and refluxed for 1h. Then, the excess lithium aluminum hydride was destroyed by adding 5 ml ethyl acetate. The reaction mixture was washed with 10% aqueous HCl and the organic layer

was dried (Na_2SO_4). The solvent was removed under vacuum and the crude product was treated to 20% HCl-THF and stirred for 20h. Then, the solvent was removed and the crude product was extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed. The crude product was column chromatographed (eluent: 30% ethyl acetate- hexane) to give 105 (mp 65-67° C) in 74% yield.

105-had IR(KBr): 2950, 1705, 1680 cm^{-1}; ^1H NMR($CDCl_3$): 5.88(d, J=10Hz, 1H), 7.5(d, J=10Hz, 1H), 2.9-1.47(m, 9H), 1.33(s, 3H); MS: 178(M^+, 32), 150(64), 134(92), 121(76), 109(64), 28(100); Exact mass calcd for $C_{11}H_{14}O_2$: 178.099, obs: 178.100.

cis-8-Methyl-3,4,4a,8a-tetrahydro-8a-methyl-naphthalene-1,6(2H,5H)-dione(108). To a well stirred mixture of 99 (150 mg, 0.5 mmol) in 20 ml ether under nitrogen at 0° C, was added 0.43 ml of 1.4M CH_3Li (0.6 mmol). After 2h, the reaction mixture was washed with 5 ml of 10% aqueous NH_4Cl solution. The ether extracts were dried (Na_2SO_4) and the solvent was removed under vacuum. The crude product was stirred in 20 ml of 10% HCl-THF for 16h. The solvent was removed under reduced pressure and the crude product was extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed. The crude product was column chromatographed (eluent: 30% ethyl acetate- hexane) to give 108 (mp 96-98° C) in 78% yield.

108 had IR(KBr): 2960, 1710, 1664, 1620 cm^{-1}; ^1H NMR($CDCl_3$): 5.88(q, J=2Hz, 1H), 2.62-1.55(m, 9H), 1.77(d, J=2Hz, 3H), 1.4(s, 3H); MS: 192(M^+,5), 164(79), 149(43), 135(40),

123(100); Exact mass calcd for $C_{12}H_{16}O_2$: 192.115, obs: 192.113.

trans-3,4,4a,8a-Tetrahydro-8,8a-dimethyl-naphthalene-1,6(2H,5H)- dione(109). To a well stirred solution of 103 (165 mg, 0.5 mmol) in 20 ml of ether under nitrogen at 0° C, was added 0.43 ml of CH_3Li (0.6 mmol). After 2h, the reaction was washed with 5 ml of 10% aqueous NH_4Cl solution. The ether extracts were dried (Na_2SO_4) and the solvent was removed under vacuum. The crude product was stirred in 10% HCl-THF for 16h. The solvent was removed and the crude product was extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed. The crude product was purified by column chromatography (eluent: 30% ethyl acetate- hexane) to give 109 in 83% yield.

109 had IR(film): 2948, 1706, 1660, 1615 cm^{-1}; ^1H NMR($CDCl_3$) δ 5.83(q, J=2Hz, 1H), 3.18-1.8(m, 9H), 2.17(d, J=2Hz, 3H), 1.33(s, 3H); MS: 192(M^+, 34), 164(57), 149(33), 135(36), 123(43), 112(84), 28(100); Exact mass calcd for $C_{12}H_{16}O_2$: 192.115, obs: 192.116.

cis-5,6,4a,8a-Tetrahydro-3,8a-dimethyl-naphthalene-1,8(4H,7H,)-dione(110). To a well stirred mixture of CuI (110 mg, 0.58 mmol) in 30 ml dry ether under nitrogen at -78° C, was added 1.4M CH_3Li (0.79 ml, 1.1 mmol). After 5 min, 99 (o.159 mg, 0.5 mmol) was added and stirring continued for another 1h. The reaction mixture was quenched at -78° C with 5 ml sat aqueous NH_4Cl solution and then brought to room temperature. The aqueous phase was separated, washed with

ether and the washing were added to the organic phase. The organic phase was dried (Na_2SO_4) and the solvent was removed under vacuum. The crude product was stirred in 10% HCl-THF solution for 2h. Then the THF was removed under vacuum and extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed under vacuum. The crude product was column chromatographed (eluent: 30% ethyl acetate-hexane) to give 110 (mp 85-87° C) in 89% yield.

110 had IR(KBr): 2940, 1712, 1645, 1630 cm^{-1}; ^1H NMR($CDCl_3$): 5.83(q, 1H), 3.00-1.53(m, 9H), 1.98(d, 3H); MS: 192(M^+, 37), 164(21), 135(11), 123(27), 107(19), 82(100); Exact mass calcd for $C_{12}H_{16}O_2$: 192.115, Obs: 192.114.

cis-3,4,5,6,4a,8a-Hexahydro-3,3,8a-trimethyl-naphthalene-1,8(2H,7H,)-dione(112). The reaction was carried as above except that the reaction mixture was quenched at room temperature. The crude product was column chromatographed (eluent: 25% ethyl acetate-hexane) to give 112 (mp 56-58° C) in 91% yield.

112 had IR(KBr): 2970, 1705, 1690, 1240 cm^{-1}; ^1H NMR($CDCl_3$): 2.77-1.13(m, 11H), 1.4(s, 3H), 0.83(s, 3H), 1.03(s, 3H); MS: 208(M^+, 53), 193(56), 175(30), 165(38), 152(96), 139(41), 124(81), 28(100); Exact mass calcd for $C_{13}H_{20}O_2$: 208.146, obs: 208.143.

trans-3',4',4a',8a'-Tetrahydro-8a',6'-dimethyl-spiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-8'(5'H)-one(111).

To a well stirred solution of CuI (110 mg, 0.58 mmol) in dry ether under nitrogen at -78° C, was added 1.4M CH_3Li (0.79 ml,

1.1 mmol). After 5 minutes, 103 (165 mg, 0.5 mmol) was added and stirring continued for another 1h. The reaction mixture was quenched at -78° C with 5 ml sat NH_4Cl solution and then brought to room temperature. The aqueous phase was separated, washed with ether and the washings were added to the organic phase. The organic phase was dried (Na_2SO_4) and the solvent was removed under vacuum. The crude product was column chromatographed (eluent: 25% ethyl acetate-hexane) to give 111 (oil) in 90% yield.

111 had IR(film): 2940, 1670, 1640 cm^{-1}; ^1H NMR($CDCl_3$): 5.68-5.55(br, 1H), 4.4-3.85(m, 4H), 2.45-1.28(m, 9H), 1.87(d, J=2Hz, 3H), 1.17(s, 3H); MS: 236(M^+, 21), 221(14), 193(19), 148(27), 113(25), 86(100); Exact mass calcd for $C_{14}H_{20}O_3$: 236.141, obs: 236.139.

trans-3',4',6',6',4a',8a'-Hexahydro-6',6',8a'-trimethyl-spiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-8'(5'H)-one (113). The reaction was carried out as above except that the reaction was quenched at room temperature. The crude product was column chromatographed (eluent: 10% ethyl acetate-hexane) to give 113 (oil) in 93% yield.

113 had IR(neat): 2956, 1712, 1170 cm^{-1}; ^1H NMR($CDCl_3$): 4.33-3.73(m, 4H), 2.6-1.07(m, 11H), 1.23(s, 3H), 0.98(s, 6H); MS: 252(M^+, 19), 209(16), 151(19), 112(98), 99(79), 86(93), 28(100); Exact mass calcd for $C_{15}H_{24}O_3$: 252.173, obs: 252.172.

cis-5,6,4a,8a-Tetrahydro-8a-methyl-naphthalene-1,8(4H,7H)-dione (114). To a well stirred solution of 99 (150 mg, 0.5

mmol) in 20 ml absolute ethanol, was added 1.0 g Raney nickel. After 3h, the catalyst was filtered followed by removal of solvent. The crude product was extracted with ether and washed with 10 ml of water. The ether extracts were dried (Na_2SO_4) and the solvent was removed. THe crude product was treated with 10% HCl-THF and stirred for 2h. Then the solvent was removed and extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was removed under vacuum. The crude product was column chromatographed to give 114 in 63% yield.

114 had IR(KBr): 2910, 1692, 1642 cm^{-1}; ^1H NMR($CDCl_3$): 6.92-6.83(m, 1H), 6.01(ddd, J=1.3Hz, 3.0Hz, 10.2Hz, 1H), 2.85-2.55(m, 1H), 2.48-1.50(m, 8H), 1.34(s, 3H); MS: 178(M^+, 52), 150(25), 134(11), 122(20), 82(19), 68(100); Exact mass calcd for $C_{11}H_{14}O_2$: 178.099, obs: 178.100.

trans-3-Phenylthio-8-methyl-4a,5,6,8a-tetrahydro-(4H)-naphthalene-1-one(129): To a solution of 96a (1.14 g, 4 mmol) in THF (30 ml) was added under nitrogen 1.29 ml (4 mmol) of 3.1M methyl magnesium bromide and stirred for 90 minutes. The solvent was evaporated under reduced pressure and the crude reaction mixture was diluted with 100 ml of ether. The reaction mixture was quenched by washing with 5 ml of water and the organic phase was separated. The organic phase was washed twice with two 10 ml portions of water and the washings were added to the aqueous phase. The aqueous phase was washed thrice each with 20 ml of ether and the washings were added to the organic phase. The combined organic phase was dried

(Na_2SO_4) and evaporated. The crude reaction mixture was dissolved in minimum amount of hexane-ethyl acetate and allowed to stand overnight. The crystallised product 96a was filtered off and once again the above operation was performed. Then the filtrate was concentrated at reduced pressure and purified by column chromatography (eluent: 15% hexane-ethyl acetate) to give 128a and 128b in a ratio of 5:7 with 53% yield. To a stirred solution of 128a (0.302 g, 1 mmol) in dry ether (2 ml) under nitrogen, was added 3.0 g of conc. H_2SO_4 and stirred for 2 h at room tempetature. Then the reaction mixture was diluted with 25 ml of ether and quenched with 20 g of crushed ice. The organic and aqueous layer were quickly separated and the aqueous phase was washed twice each with 25 ml of ether. The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (eluent: 10% ethyl acetate-hexane) to give 129 (viscous oil) in 87% yield. The above procedure was followed with 128b also except that stirring was continued for 24 h to give 129 (mp 96-98°C) in 73% yield. IR(KBr): 2910, 1660, 1580 cm^{-1}; ^1H NMR($CDCl_3$): 7.43(s, 5H), 5.37(d, J=2Hz, 1H), 5.53-5.33(m, 1H), 2.5-1.33(m, 7H), 2.02(d, J=2Hz, 3H), 0.9(s, 3H); MS: 284(M^+, 40), 176(37), 175(47), 147(50), 115(20), 108(100), 67(68), 39(78); Exact mass calcd for $C_{18}H_{20}SO$: 284.124, obs: 284.127.

trans-3-Methoxy-8-methyl-4a,5,6,8a-tetrahydro-(4H)-naphthalene-1-one(131): To a well stirred solution of 129 (1.42 g, 5 mmol) in 20 ml of dry methanol under nitrogen was

added sodium methoxide (1.35 g, 25 mmol) and refluxed for 20 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude reaction mixture was diluted with 60 ml of ether. The ether layer was washed twice with 5 ml of water, dried and evaporated. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 131 in 95% yield. IR(film): 2920, 1675 cm^{-1}; ^1H NMR($CDCl_3$): 5.52-5.25(m, 1H), 5.13(s, 1H), 3.65(s, 3H), 2.42-1.42(m, 7H), 2.05(d, J=2Hz, 3H), 1.22(s, 3H); MS: 206(M^+, 41), 139(12), 108(100), 93(46), 68(22), 28(42); Exact mass calcd for $C_{13}H_{18}O_2$: 206.131, obs: 206.133.

trans-3-Methoxy-4a,5,6,7,8a-hexahydro-8β,8aβ-dimethyl-naphthalene-1-one(132): In a 25 ml three necked flask were added 30 mg of 5% Pd-$CaCO_3$ and 15 ml of freshly distilled ethyl acetate. The catalyst was saturated with an atmospheric pressure of hydrogen for 30 minutes followed by addition of 131 (206 mg, 1 mmol) in 1 ml of ethyl acetate. The reaction was followed by measuring the absorption of hydrogen. After the absorption of 22.4 ml of hydrogen, the reaction flask was separated from the hydrogen atmosphere. The catalyst was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 132 in almost quantitative yield. IR(film): 2915, 1670, 1620, 1210 cm^{-1}; ^1H NMR($CDCl_3$): 5.14(d, J=1.4Hz, 1H), 3.65(s, 3H), 2.31(ddd, J=1.4Hz, 11.6Hz, 17.7Hz, 1H), 2.14(dd, J=5.2Hz, 17.7Hz, 1H), 1.94-1.08(m, 8H), 1.78(d, J=6.2Hz, 3H), 0.97(s, 3H); MS: 208(M^+, 36), 178(63), 136(96),

122(40), 109(90), 98(64), 68(60), 28(100); Exact mass calcd for $C_{13}H_{20}O_2$: 208.146, obs: 208.145.

trans-4a,5,6,7,8,8a-Hexahydro-4aβ,5β-dimethyl-2(1H)-naphthalene-2-one(133): To a stirred solution of 132 (416 mg, 2 mmol) in 20 ml of dry ether was added lithium aluminum hydride (38 mg, 4 mmol). After 1 h, once again lithium aluminum hydride (38 mg, 4 mmol) was added and the reaction mixture was refluxed for 2 h. The reaction mixture was quenched with 2 ml of ethyl acetate followed by addition of 10 ml of 10% aqueous hydrochloric acid. The stirring continued for another 4 h. The organic phase was separated from the aqueous phase and the aqueous phase was washed thrice each with 20 ml of ether. The combined organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 133 (viscous oil) in 72% yield. IR(film): 2920, 1683 cm^{-1}; ^1H NMR($CDCl_3$): 7.08(d, J=10.2Hz, 1H), 5.84(d, J=10.2Hz, 1H), 2.35(dd, J=13.8Hz, 17Hz, 1H), 2.28(dd, J=4.8Hz, 17Hz, 1H), 2.00-1.23(m, 8H), 0.94(d, J=6.1Hz, 3H), 0.91(s, 3H); MS: 178(M^+, 35), 163(17), 149(18), 136(76), 121(51), 108(55), 95(60), 28(100); Exact mass calcd for $C_{12}H_{18}O$: 178.136, Obs: 178.139.

1,1aβ,3,3aα,4,5,6,7,7a,7bβ-Decahydro-1,1,7β,7aβ-tetramethyl-2H-cyclopropa[a]naphthalene-2-one(135): Diazopropane was prepared according to the literature procedure.[147] An ethereal solution of diazopropane was added to a solution of 133 (178

mg, 1 mmol) in 10 ml of dry ether at room temperature, until complete reaction occurred, indicated by the persistent color of the diazo compound. Then the solvent was removed under reduced pressure and the crude product was purified by column chromatography (eluent: 20% ethyl acetate-hexane) to give 134 (mp 71-72°C) in almost quantitative yield. Compound 134 was dissolved in 15 ml of dry benzene and photolysed (lamp: Hanovia model no. 608A 36). The reaction was followed by thin layer chromatography. At the end of 8 h, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (eluent: 10% ethyl acetate-hexane) to give 135 in 95% yield. The spectroscopic properties of 135 are identical in all aspects to those reported earlier.[135]

cis-3-Phenylthio-8-methyl-4a,5,6,8a-tetrahydro-(4H)-naphthalene-1-one(155): To a solution of 96b (1.14 g, 4 mmol) in 100 ml of dry ether under nitrogen was added 1.29 ml of 3.1M methyl magnesium bromide and stirred for 2 h. The reaction mixture was diluted with 50 ml of ether and quenched with 10 ml of water. The organic phase was separated and washed twice with two 15 ml portions of water and the washings were added to the aqueous phase. The aqueous phase was then washed thrice with 20 ml of ether and the ether washings were added to the organic phase. The combined organic phase was dried (Na_2SO_4) and was evaporated under reduced pressure. The crude reaction mixture was subjected to dehydration with conc. H_2SO_4.

To a solution of 154 (302 mg, 1 mmol) in 2 ml of dry ether was added 3.0 g of conc. H_2SO_4 and stirred for 2 h. At the end of the reaction, the mixture was diluted with 100 ml of ether and quenched with 15 g of crushed ice. The aqueous and organic layers were quickly separated. The aqueous phase was washed twice with two 50 ml portions of ether and the washings were added to the organic phase. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: 10% ethyl acetate-hexane) to give 155 (viscous oil) in 89% yield (calculated from 96b). IR(film): 1665, 1595, 1440 cm^{-1}; ^1H NMR($CDCl_3$): 7.5-7.30(m, 5H), 5.47-5.43(m, 1H), 5.4(d, J=1.6Hz, 1H), 2.65(ddd, J=1.6Hz, 8.6Hz, 17.7Hz, 1H), 2.45(dd, J=5.1Hz, 17.7Hz, 1H), 2.21-1.50(m, 5H), 1.63(d, J=1.7Hz, 3H), 1.30(s, 3H); MS: 284(M^+, 30), 176(21), 175(30), 147(33), 109(65), 108(100), 67(67), 39(52). Exact mass calcd for $C_{18}H_{20}SO$: 284.124, obs: 284.127.

cis-3-Methoxy-8-methyl-4a,5,6,8a-tetrahydro-(4H)-naphthalene-1-one(156): To a well stirred solution of 155 (1.42 g, 5 mmol) in 20 ml of dry methanol under nitrogen was added sodium methoxide (1.35 g, 25 mmol) and refluxed for 20 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude reaction mixture was diluted with 60 ml of ether. The etheral layer was washed twice with 5 ml of water, dried and concentrared. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 156 in 92% yield. IR(film): 2925, 1665, 1385 cm^{-1}; ^1H

NMR($CDCl_3$): 5.46-5.35(m, 1H), 5.27(br, 1H), 3.68(s, 3H), 2.58-1.50(m, 7H), 1.68(d, J=1.7Hz, 3H), 1.32(s, 3H); MS: 206(M^+, 22), 173(12), 108(100), 93(86), 77(24), 68(25); Exact mass calcd for $C_{13}H_{18}O_2$: 206.131, obs: 208.132.

cis-3-Methoxy-4a,5,6,8a-hexahydro-8β,8aβ-dimethyl-naphthalene-1-one(157a): In a 25 ml three necked flask were added 30 mg of 5% Pd-$CaCO_3$ and 15 ml of freshly distilled ethyl acetate. The catalyst was saturated with an atmospheric pressure of hydrogen for 30 minutes followed by addition of 156 (206 mg, 1 mmol) in 1 ml of ethyl acetate. The reaction was followed by measuring the absorption of hydrogen. After the absorption of 22.4 ml of hydrogen, the reaction flask was sepatated from the hydrogen atmosphere. The catalyst was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 157a (oil) and 157b (mp 72-74°C) in almost quantitative yield.

157a had IR(film): 2925, 1650, 1620, 1375 cm^{-1}; ^1H NMR($CDCl_3$): 5.21(s, 1H), 3.61(s, 3H), 2.45-1.16(m, 10H), 1.01(s, 3H), 0.77(d, J=6.9Hz, 3H); MS: 208(M^+, 81), 193(38), 165(30), 152(33), 139(72), 98(84), 69(100), 41(87); Exact mass calcd for $C_{13}H_{20}O_2$: 208.146, obs: 208.149.

157b had IR(KBr): 2910, 1655, 1615 cm^{-1}; ^1H NMR($CDCl_3$): 5.11(d, J=1.4Hz, 1H), 3.63(s, 3H), 2.80(ddd, J=1.4Hz, 6.0Hz, 18.1Hz, 1H), 2.00(dd, J=2.4Hz, 18.1Hz, 1H), 1.81-1.28(m, 8H), 1.26(d, J=2.2Hz, 3H), 1.21(s, 3H); MS: 208(M^+, 35), 178(46), 139(70), 136(65), 109(90), 98(65), 79(66), 68(65), 28(100);

Exact mass calcd for $C_{13}H_{20}O_2$: 208.146, obs: 208.150.

cis-4a,5,6,7,8,8a-Hexahydro-4aβ,5β-dimethyl-2(1H)-naphthalene-2-one(158a): To a stirred solution of 157a (416 mg, 2 mmol) in 20 ml of dry ether was added lithium aluminum hydride (38 mg, 4 mmol). After 1 h, once again lithium aluminum hydride (38 mg, 4 mmol) was added and the mixture refluxed for 2 h. The reaction mixture was quenched with 2 ml of ethyl acetate followed by addition of 10 ml of 10% aqueous hydrochloric acid. The stirring was continued for another 4 h. The organic phase was separated from the aqueous phase and the aqueous phase was washed twice each with 20 ml of ether. The combined organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 10% ethyl acetate-hexane) to give 158a in 69% yield. IR(film): 2925, 1680, 1375 cm^{-1}; ^1H NMR($CDCl_3$): 6.8(d, J=10Hz, 1H), 5.88(d, J=10Hz, 1H), 2.77-1.23(m, 10H), 1.12(s, 3H), 0.92(d, J=6.5Hz, 3H); MS: 178(M^+, 41), 163(29), 150(15), 136(78), 122(37), 108(82), 94(36), 80(42), 28(100); Exact mass calcd for $C_{12}H_{18}O$: 178.136, obs: 178.133.

cis-4a,5,6,7,8,8a-Hexahydro-4aβ,5α-dimethyl-(2H)-naphthalene-2-dione(158b) was prepared according to the above procedure using 157b (416 mg, 2 mmol) in 71% yield. IR(film): 2905, 1675, 1370 cm^{-1}; ^1H NMR($CDCl_3$): 6.79(dd, J=2.2Hz, 10.2Hz, 1H), 5.92(d, J=10.2Hz, 1H), 2.88(dd, J=5.0Hz, 17.5Hz, 1H), 2.17-1.24(m, 9H), 1.22(s, 3H), 1.04(d, J=7Hz, 3H); MS: 178(M^+, 36),

163(19), 150(17), 136(100), 121(54), 108(73), 94(58), 80(64), 28(88); Exact mass calcd for $C_{12}H_{18}O$: 178.136, obs: 178.134.

Trimethylsilyl Enol Ether 159: A solution of 158a (140 mg, 0.79 mmol) in THF (4 ml) containing tert-butyl alcohol (47 mg, 0.63 mmol) was added dropwise over 10 min to a solution of lithium (16 mg, 2.2 mmol) in ammonia (20 ml). The solution was stirred for 15 min, and the excess lithium was destroyed by addition of a few drops of isoprene. The ammonia was evaporated under a stream of argon at 0°C and finally at room temperature (1 h). THF (5 ml) was then added and the reaction was cooled to 0°C followed by rapid addition of a quenching solution of chlorotrimethylsilane (2.2 mmol) and triethylamine (2.2 mmol) in 3 ml of THF (previously centrifuged to remove the ammonium salt). The reaction was stirred for 15 min and the solvent was evaporated. Then 100 ml of cold, dry hexane was added and the precipitated salts were removed by filtration. The filtrate was concentrated under reduced pressure to give 159 as a colorless oil in almost quantitative yield. NMR analysis indicated a single compound which was used without further purification: IR(film): 1665 cm^{-1}; ^1H NMR($CDCl_3$): 4.7-4.5(m, 1H), 2.6-1.17(m, 12H), 0.83(s, 3H), 0.85(d, J=6.5Hz, 3H), 0.13(s, 9H).

Keto Alcohol 160: To a solution of 159 (112 mg, 0.5 mmol) and acetone (35 mg, 0.6 mmol) in 10 ml of dry CH_2Cl_2 under nitrogen at -78°C, was added titanium tetrachloride (0.06 ml, 0.5 mmol) and stirring continued for 4 h. At the end of 4 h, the reaction was quenched with aqueous $NaHCO_3$ followed by

extraction with ether. The ether extract was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 160 (viscous oil) in 68% yield. IR(film): 3480, 1705 cm^{-1}; ^1H NMR($CDCl_3$): 4.02(s, 1H), 1.26(s, 6H), 0.96(s, 3H), 0.89(d, J=6.6Hz, 3H); MS: 223(3), 180(42), 124(29), 109(92), 55(63), 43(100).

(±)-Fukinone (116): To a solution of the keto alcohol 160 (80 mg) in 5 ml of dry pyridine at 0°C, 50 µl of thionyl chloride was added and the resulting solution was stirred for 15 min. The solvent was removed under reduced pressure at 0°C. Then the crude product was eluted from 10 g of Merck alumina with 30% ethyl acetate-hexane. Finally, the compound was purified by column chromatography (eluent: 15% ethyl acetate-hexane) to give 116 in 81% yield. IR(film): 1685, 1625 cm^{-1}; ^1H NMR($CDCl_3$): 1.93(s, 3H), 1.77(s, 3H), 0.95(s, 3H), 0.88(d, J=7.0Hz, 3H); MS: 220(M^+, 37), 149(32), 135(19), 123(34), 111(32), 109(66), 95(53), 91(43), 68(81), 41(100); Exact mass calcd for $C_{15}H_{24}O$: 220.183, obs: 220.184. These spectral data are in complete agreement with the spectra data reported for the natural product (+)-fukinone.[138]

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