The Chemistry of Silyl Enol Ethers: Titanium(IV) Catalyzed Reactions of 1,3-Bis(trimethylsiloxy)-4-chloro-1-methoxybuta-1,3-diene and its Application in the Synthesis of Nonactic Acid

by

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ABSTRACT

The title compound, 1,3-bis(trimethylsiloxy)-4-chloro-1-methoxybuta-1,3-diene (34), was synthesized and its stereochemistry assigned. Reactions of 34 with electrophiles containing single reactive sites established the reactivity of the C-2 vs C-4 sites. Titanium(IV) catalyzed cycloaromatization reactions of 34 with various 1,3 dielectrophiles was investigated and the synthesis of the anti-fungal agent Griseofulvin was attempted.

Condensation reactions of 34 with 1,4 dielectrophiles gave highly functionalized 8-membered bicyclic systems as products. With this type of reaction as a first step, the synthesis of Nonactic acid, a precursor to the natural product Nonactin, was attempted.

Initial studies were done in the synthesis of a 3-chloro analog of the title compound 34.

RESUME

Le composé d'intérêt, le 1,3-bis(trimethylsiloxy)-4-chloro-1-methoxybuta-1,3-diène (34), fut préparé et sa stéréochimie a été établie. Les réactions du composé 34 avec des électrophiles ne contenant qu'un site réactif ont établi la réactivité sélective des sites C-2 comparés aux sites C-4. La cycloaromatisation catalysée par du titane(IV) de ce composé avec plusieurs 1,3-diélectrophiles a été etudiée, et la préparation de l'agent anti-fongique Griseofulvin a ensuite été tentée.

Les réactions de condensation du composé 34 avec des 1,4-diélectrophiles ont produit des systèmes bicycliques à 8 éléments qui contenaient plusieurs groupes fonctionnels. Ce genre de réaction a été employé comme première étape pour tenter de préparer de l'acide nonactique qui est un précurseur de la nonactine, un produit naturel.

Des études préliminaires portant sur la synthèse d'un composé 3-chloro analogue au compose d'intérêt 34 ont été faites.

ACKNOWLEDGEMENTS

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M. Laurent Blain for the translation of the abstract.

TABLE OF CONTENTS

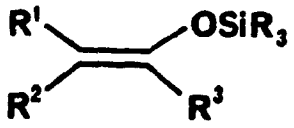
List of Abbreviations

Ac	acetyl
Bu	butyl
Bz	benzyl
C.I.	Chemical Ionization
DBU	1,8-diazabicyclo [5.4.0] undec-7-ene
E	electrophile
Et	ethyl
G.C.	Gas Chromatography
I.R.	Infra-red
INEPT	Insensitive Nuclei Enhanced by Polarization Transfer
LDA	Lithium diisopropylamide
Me	methyl
N.M.R.	Nuclear Magnetic Resonance
N.O.E.	Nuclear Overhauser Effect
Nu	nucleophile
M.S.	Mass Spectrometry
Ph	phenyl
Pr	propyl
THF	tetrahydrofuran
T.L.C.	Thin Layer Chromatography
TMS	trimethylsilyl (or tetramethylsilane as an internal standard in N.M.R.)

To my family.

INTRODUCTION

Silyl enol ethers 1 and silyl ketene acetals 2 have been used extensively in recent years in the alkylation of saturated and unsaturated carbonyl compounds, cycloaromatization reactions, and in a variety of other synthetic transformations. As a result, they have surpassed all other enolate derivatives in usefulness. Their wide applicability in organic synthesis is due in part to their ease of preparation, clean reactions, the mild conditions under which desilylation takes place and the high stereoselectivity in their reactions.



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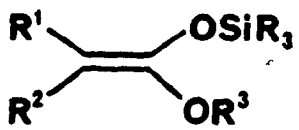


2

Three phases in the development of silyl enol ethers as synthetic reagents have been described:[1]

1) capture of enolate anions by silylation, isolation of the silyl enol ether so formed, and regeneration of the enolates to react with electrophiles under <u>basic</u> conditions;

2) reaction of silyl enol ethers directly with electrophiles under <u>neutral</u> or <u>acidic</u> (Lewis-acid catalyzed) conditions;

3) other uses of silyl enol ethers to give products other than those obtained from the "enolate" and "enol" phases above.

Before proceeding with a description of the chemistry of silyl enol ethers, it is important to review some of the chemistry which led to the development of this new methodology.

The Formation of Carbon-Carbon Bonds

The Aldol Condensation

In organic synthesis, the carbonyl group is intrinsically electrophilic. There are a variety of carbon-carbon bond forming reactions that are related mechanistically, which take advantage of this fact in that they involve the addition of a carbon nucleophile to a carbonyl site according to Figure 1.

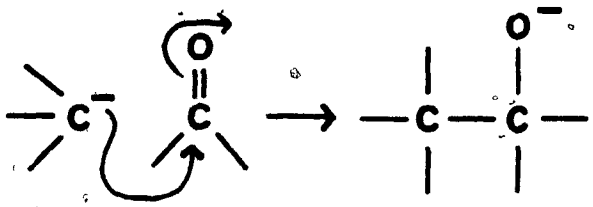
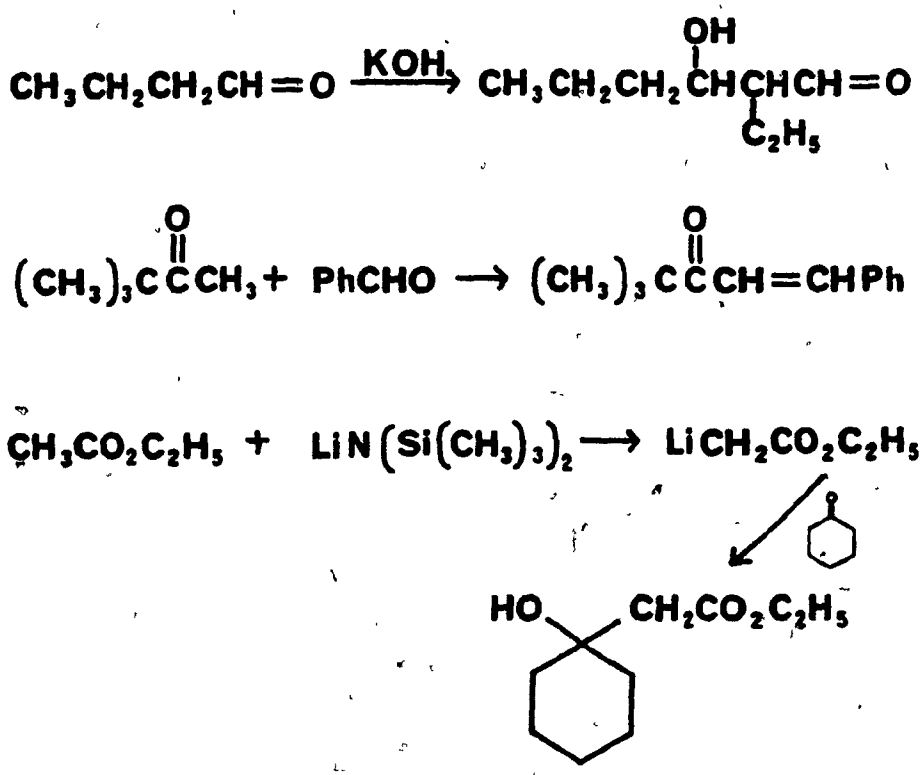


Figure 1

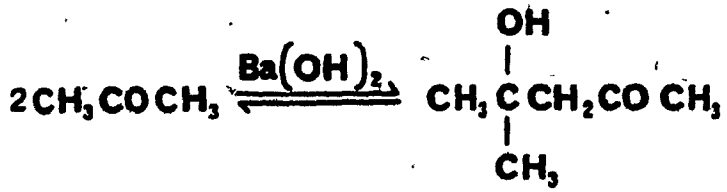
One of the oldest and most important of this class of reaction is the Aldol Condensation, or the acid or base catalyzed condensation of ketones and aldehydes. The term Aldol condensation is a general term which encompasses a variety of reactions including self-condensation of ketones and aldehydes, mixed reactions between different carbonyl compounds as well as reactions in which enolates or enols act as the nucleophilic species in reactions with ketones and aldehydes.

Examples of each reaction are given in Scheme 1.[2]



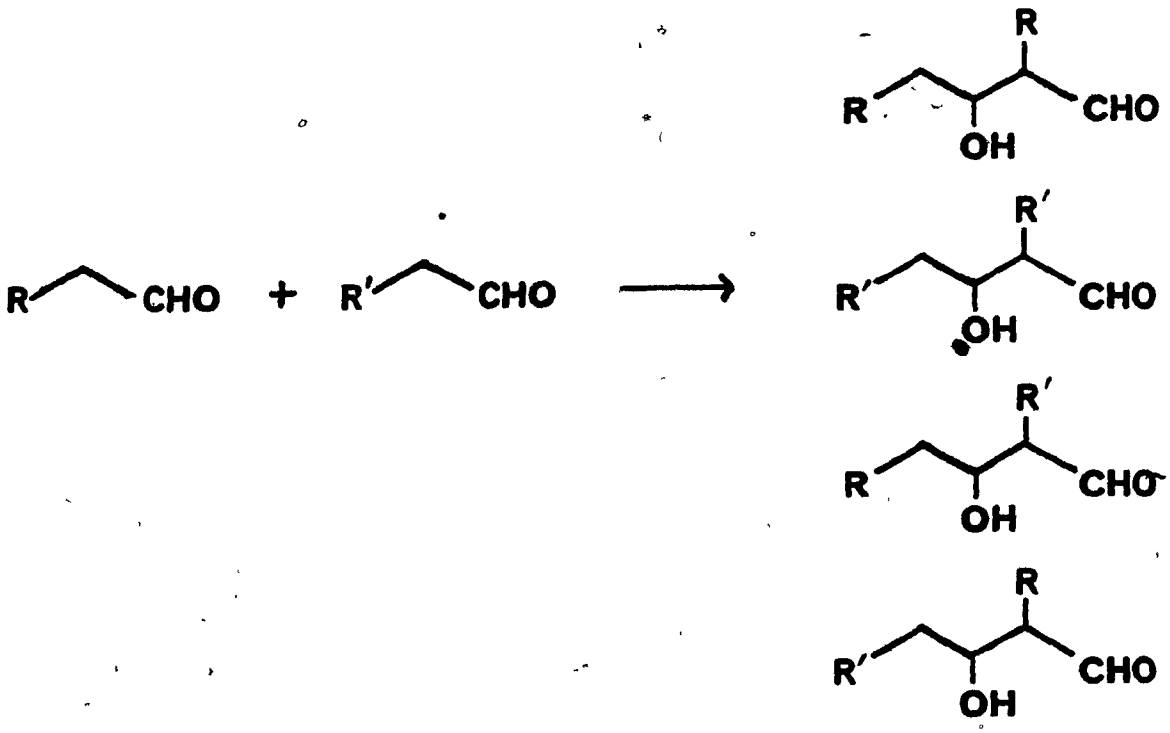
Scheme 1

As useful as they are, aldol reactions have limitations. The equilibrium constant for ketones is not always favorable, although a method has been developed where acetone vapor is passed over barium hydroxide (an insoluble basic catalyst) using a Soxhlet extractor. The condensation product is obtained in reasonable yield.[3] (Scheme 2)



Scheme 2

Condensations of aldehydes often proves to be difficult because both the starting materials and products are prone to side reactions, including polymerization. Also, for mixed aldol condensations to be useful, there must be some appreciable selectivity in the reaction, namely, one component of the reaction must be more likely to act as the nucleophile while the other should behave as the carbonyl acceptor. If the reactivities of the two components are too similar, then a mixture of two self-condensation products as well as both mixed products can result. An example would be the condensation of two different aldehydes. (Scheme 3)



Scheme 3

The Mannich Reaction

Another reaction which can be represented by Figure 1 is

the Mannich Reaction which has been used in the synthesis of nitrogen containing natural products as well as in many other synthetic transformations. By this method, α-alkylation of ketones and aldehydes is carried out in mildly acidic solution with dialkylaminomethyl groups.[4] (Scheme 4)

$$CH_2{=}O + HN(CH_3)_2 \rightleftharpoons HOCH_2N(CH_3)_2 \overset{H^+}{\rightleftharpoons} H_2O + CH_2{=}\overset{+}{N}(CH_3)_2$$

$$CH_2{=}\overset{+}{N}(CH_3)_2 + RCH_2\overset{O}{\overset{\|}{C}}R' \longrightarrow RCH(CH_2N(CH_3)_2)\overset{O}{\overset{\|}{C}}R'$$

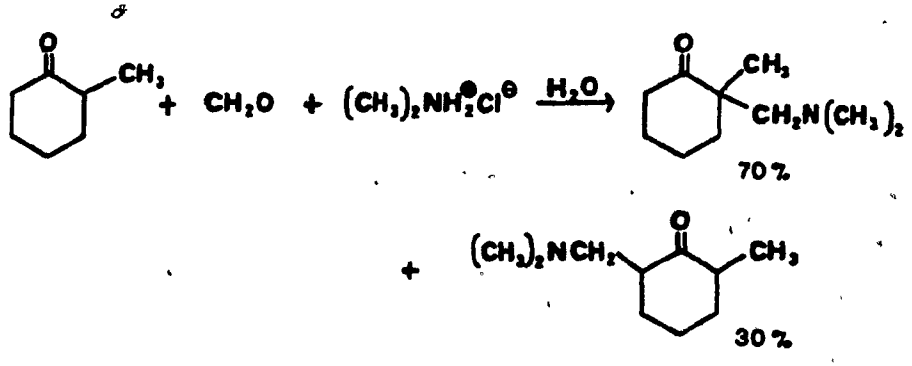
Scheme 4

The synthetic utility of this method comes in part from the further reaction of these "Mannich bases," and often involves the elimination of the amine function from the α-amino ketone to give α,β-unsaturated ketones. (Scheme 5)

$$(CH_3)_2CH\underset{CH_2N(CH_3)_2}{CH}CH{=}O \xrightarrow{\Delta} (CH_3)_2CH\overset{CH_2}{\overset{\|}{C}}CH{=}O$$

Scheme 5

This reaction also has its limitations. Studies have shown that Mannich reaction products from unsymmetrical ketones are generally those which result from attack at the more highly substituted α-position corresponding to the more stable enol.[5] (Scheme 6)



Scheme 6

The Michael Reaction

An α,β -unsaturated carbonyl system can react in an electrophilic manner as depicted in Figure 2.

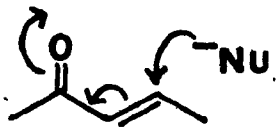
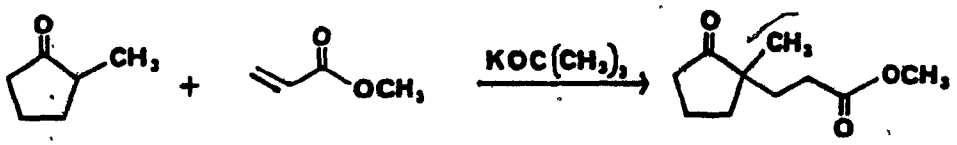


Figure 2

In this respect, the Michael Addition can be viewed as a vinyligous aldol condensation where a nucleophilic carbon species adds to an electrophilic multiple bond, typically an α,β -unsaturated ketone or ester.[6] (Scheme 7)



Scheme 7

The Michael reaction is normally carried out under basic conditions and the product, a 1,5 dicarbonyl compound, tends to undergo further reactions in the presence of base. Side reactions and self-condensation frequently occur as well. Acid catalyzed Michael reactions are known but these products also undergo further transformation.

α-Alkylation of Carbonyl Compounds

In organic synthesis, the carbonyl group is also potentially nucleophilic, thereby making α-alkylation possible according to Figure 3.*

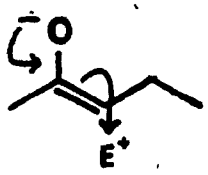
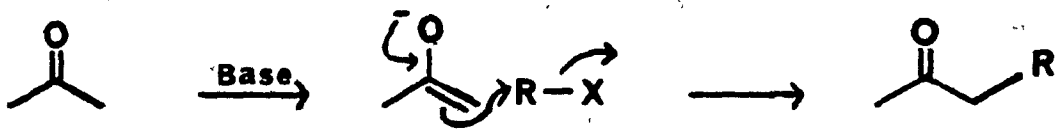


Figure 3

The most obvious method of α-alkylation of a carbonyl compound, whether it be an aldehyde, ketone or ester, would be treatment with base and an alkyl halide. (Scheme 8)

*In cases where the electrophile is a carbonyl compound, this reaction can be considered as a type of Aldol condensation as described earlier.



Scheme 8

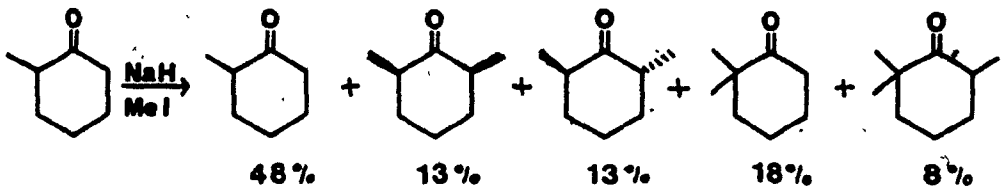
There are several problems with this method, however. Proton transfer between the enolate anion and the unionized carbonyl compound can occur at a comparable rate to the S_N2 reaction with the alkyl halide. (Scheme 9)

Scheme 9

This results in the recovery of unalkylated carbonyl compound 3 and multiple alkylation.[7] (Scheme 10)

Scheme 10

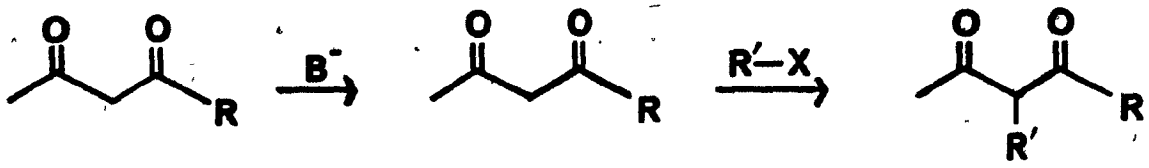
These problems are well illustrated in Scheme 11.[8]



Scheme 11

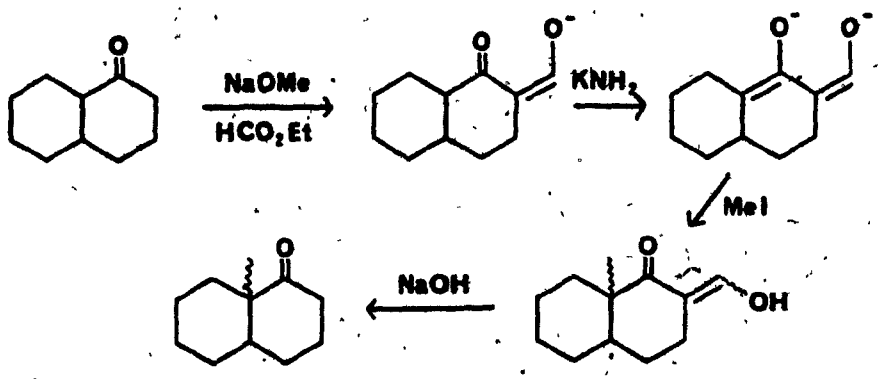
Other problems with this method include; (i) O-alkylation instead of the desired C-alkylation, (ii) competing aldol condensations and (iii) a specific enolate may not be alkylated regiospecifically.

A common solution to some of these problems has been the use of β-dicarbonyl compounds. The addition of a second electron attracting substituent renders the resulting carbanion quite stable and gives the reaction a high specificity. Also, β-dicarbonyl compounds are less prone to polyalkylation.[9] (Scheme 12)



Scheme 12

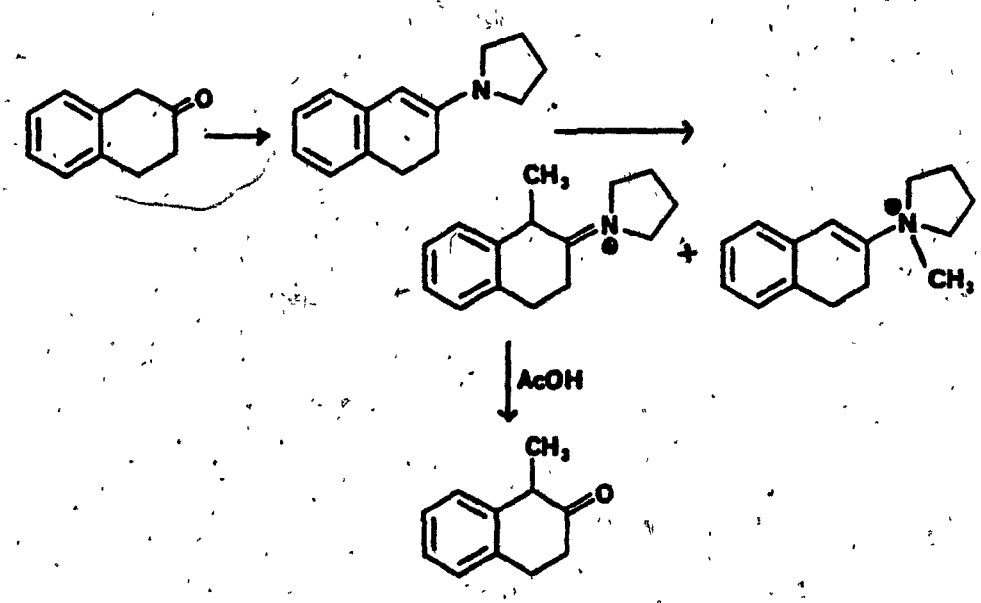
With the use of a very strong base, sequential deprotonation can occur to give dianions. Alkylation takes place at the more basic enolate function, i.e., alkylation occurs at the terminal anion.[10] (Scheme 13)



Scheme 13

The Use of Enol Derivatives

Among the first class of enolate equivalents to be developed were enamines, first introduced by Gilbert Stork in 1954.[11] (Scheme 14)

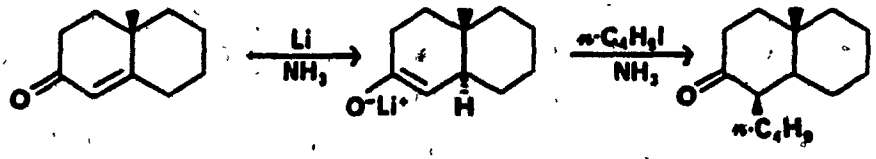


Scheme 14

Enamines were found to be more reactive than enolate anions and their reactions were generally free of dialkylation pro-

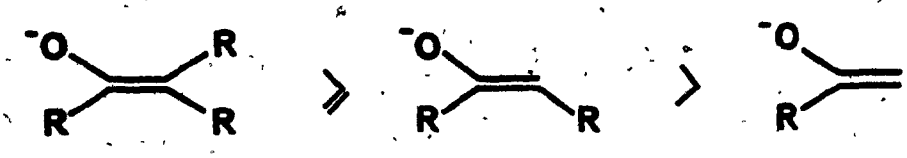
ducts. Their use was restricted, however, to alkylation on the less substituted side of unsymmetrical ketones. Also, these reactions did not work particularly well with aldehydes and N-alkylation is often a serious competing reaction.

Stork then found lithium enolates to be a viable alternative to enamines. They were better behaved than the corresponding sodium or potassium enolates and provided reasonable reactivity while retaining a certain degree of control during the course of the reaction.[12] (Scheme 15)



Scheme 15

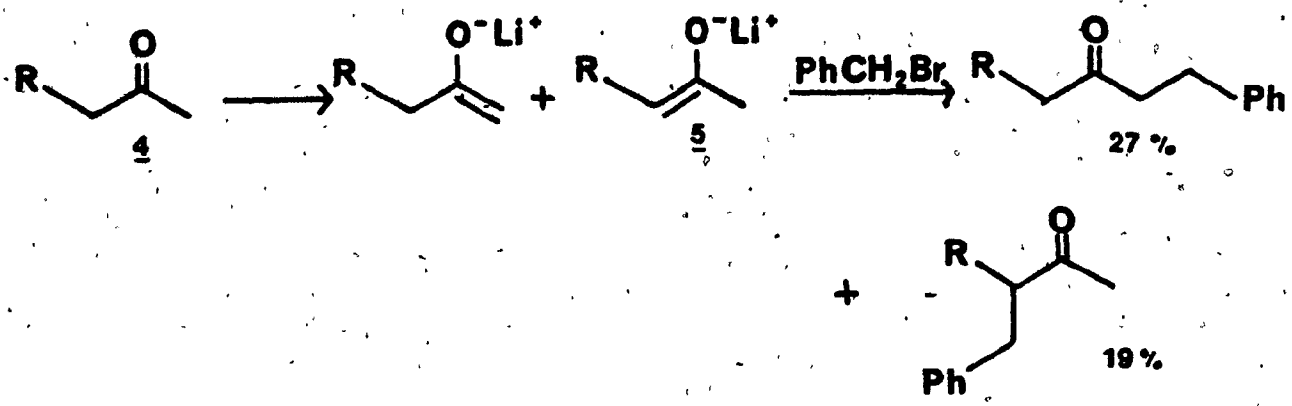
However, enolate equilibration will often make regiospecific alkylation impossible. For a given metal enolate anion the rate of alkylation varies with substitution according to Scheme 16.[13]



Scheme 16

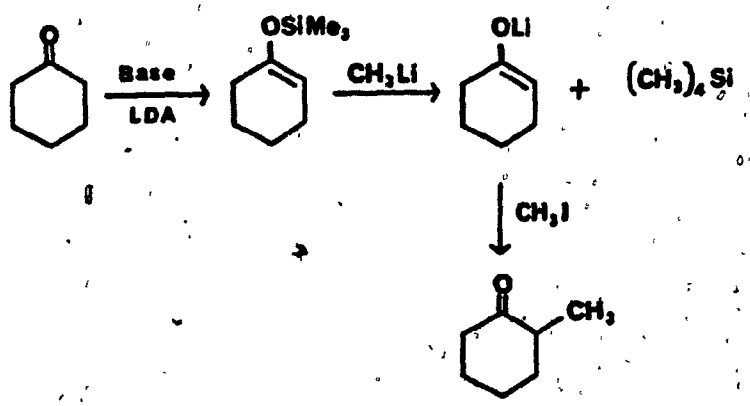
As an example, the regiospecific alkylation on the less substituted side of a methyl alkyl ketone 4 is not possible

because of equilibration to the thermodynamically favored and more reactive isomeric enolate 5.[14] (Scheme 17)



Scheme 17

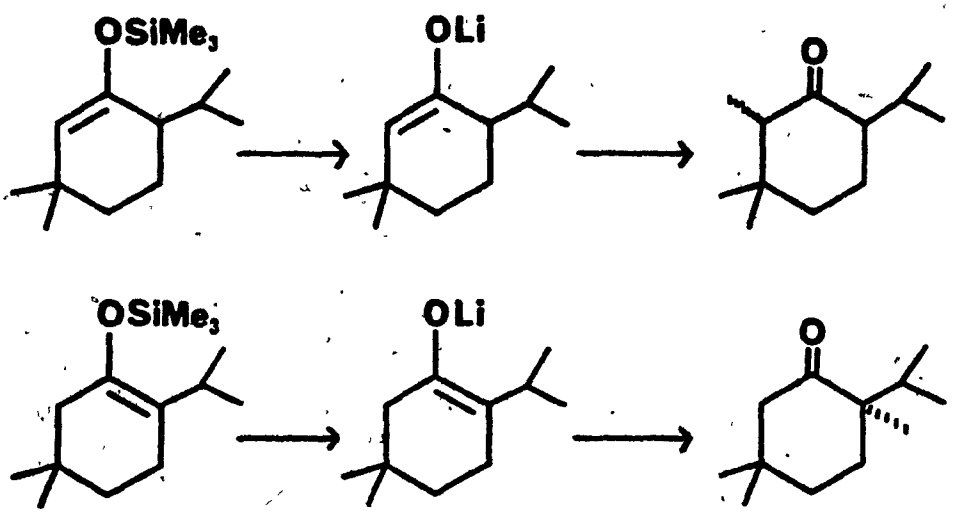
Therefore, the generation of specific lithium enolates under non-equilibrating conditions became of paramount importance. Stork found silyl enol ethers to be the most effective precursor to lithium enolates. By this method the metal enolates were trapped as the isolable silyl derivative from which the enolate could be regenerated and subsequently alkylated.[15] (Scheme 18)



Scheme 18

Silyl enol ethers were used with the expectation that that they could be readily cleaved by organometallic reagents. Also, the products of the reaction would be the lithium enolate and unreactive tetramethylsilane (TMS). Previous syntheses of lithium enolates often produced lithium alkoxides as byproducts which often enhanced the formation of di- and polyalkylated products.

The structural integrity of the enolate is retained during the subsequent alkylation as illustrated in Scheme 19.[16]

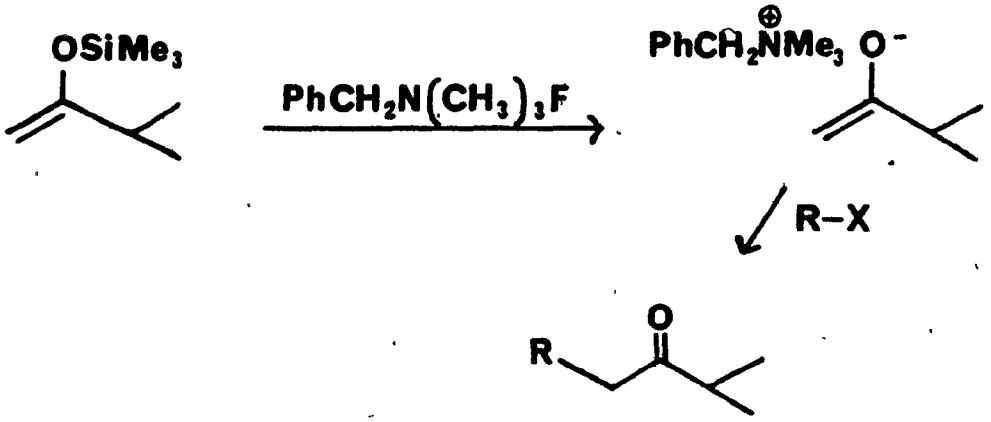


Scheme 19

This method, however, would only be reliable when the alkylating agent was a reactive alkyl halide such as benzyl bromide or methyl iodide , therefore the use of lithium enolates was limited.

Silyl enol ethers have also been used as precursors in the synthesis of quaternary ammonium enolates.[17] Replacement of the countercation from lithium to quaternary ammonium acti-

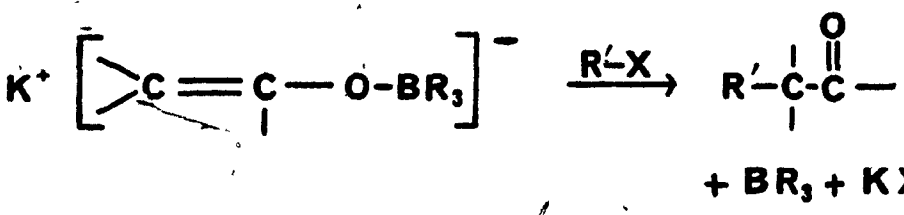
vates the enolate anion and makes regiospecific monoalkylation more feasible. (Scheme 20)



Scheme 20

With this method, less reactive alkylating agents such as butyl iodide and methyl bromoacetate work well , whereas no products are formed with their reaction with the corresponding lithium enolate. This reaction is limited to the alkylation of the less substituted position of an unsymmetrical ketone and thus constitutes a complementary method to the lithium enolate reaction.

Other enol derivatives have been used in the alkylation of carbonyl compounds with varying degrees of success. One such method is the use of potassium enoxytrialkylborates (readily available by treating potassium enolates with trialkyl borates) in a reaction with simple alkyl halides.[18] (Scheme 21)

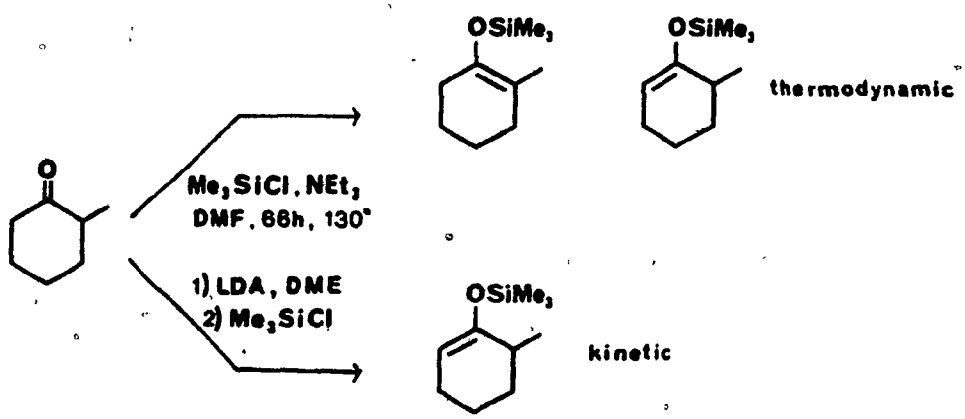


Scheme 21

Other metals such as magnesium, zinc and tin have been used as enolate counterions. Their reactions, however, tend to be difficult for simple alkylations.[19]

The Development of Silyl Enol Ethers

Silyl enol ethers and silyl ketene acetals can be easily synthesized from a wide variety of precursors and their preparation has been widely reviewed.[20,21,22] Of note is the ability to silylate unsymmetrical ketones under "kinetic" (strong base, aprotic solvent)[23] or "thermodynamic"[24] conditions. (Scheme 22)



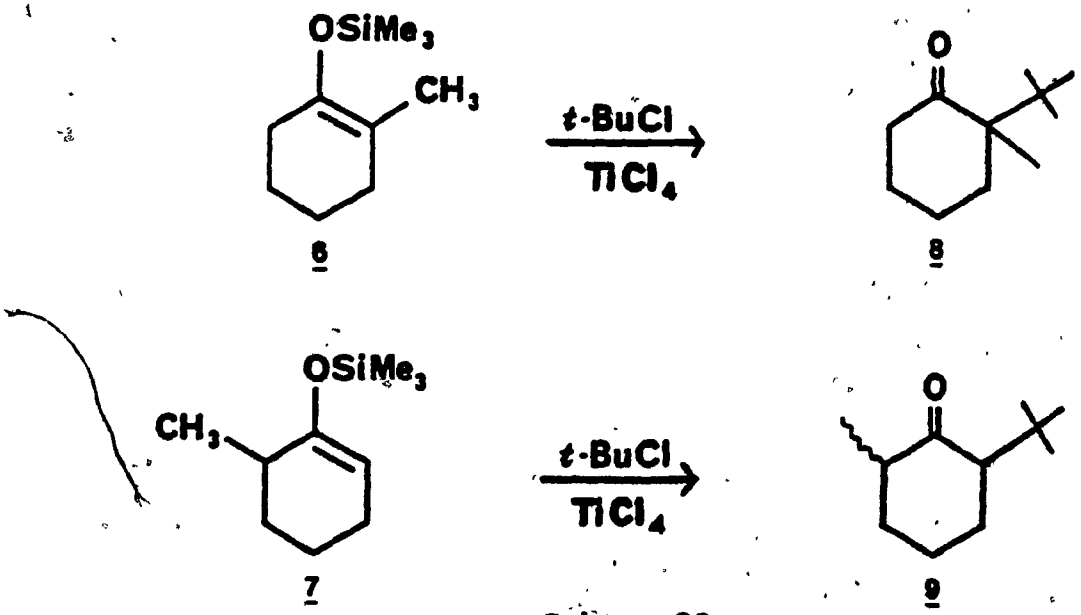
Scheme 22

α-T-butylation of Silyl Enol Ethers

In the α-t-alkylation of carbonyl compounds with the methods so far discussed the alkylating agent must be susceptible to nucleophilic displacement. As a result, primary halides and sulfonates are usually the reagent of choice. Secondary alkyl halides are prone to elimination and their

reactions give low to moderate yields while tertiary alkyl halides (with a α-hydrogen) give only elimination products under these reaction conditions.

α-t-Butylation has been accomplished, however with the Friedel-Crafts alkylation of trimethyl silyl enol ethers.[23] The "kinetic" silyl enol ether 6 and the "thermodynamic" isomer 7 were reacted under identical conditions (-78° C, $TiCl_4$) to give products 8 and 9 respectively. (Scheme 23)



Scheme 23

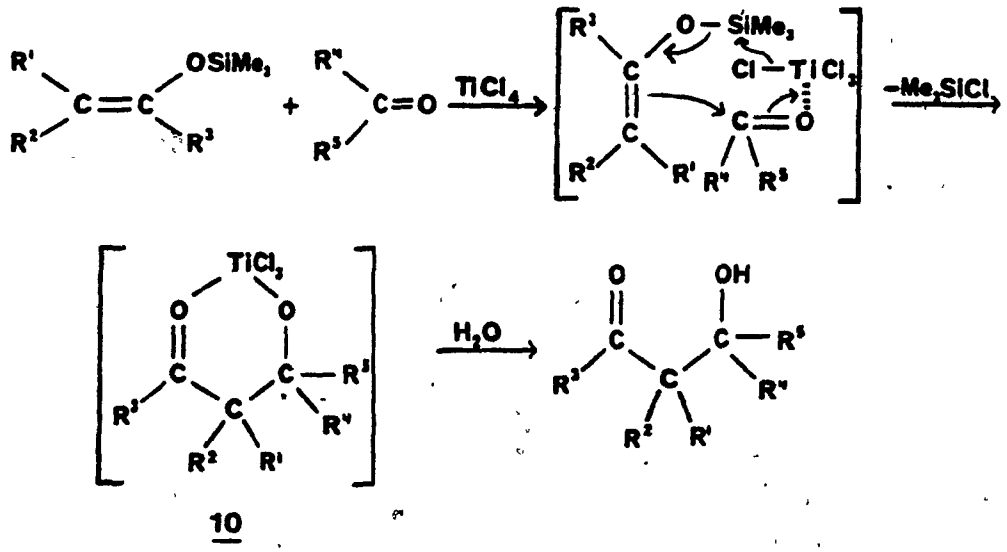
This result not only established the regiospecificity of the reaction but also the absence of any isomerization between 6 and 7. Reetz has studied this area extensively[25] and extended this methodology so that it has become a general method for the introduction of tertiary alkyl groups into a carbonyl system at the α-position.

S_N2 reactions of basic enolates for primary and secondary

alkylating agents and the Lewis acid mediated reaction of silyl enol ethers with tertiary reagents can be seen as complementary methodologies.

Cross Aldol Reactions of Silyl Enol Ethers

Silyl enol ethers had originally been used as precursors for enol derivatives. It was Mukaiyama who first used silyl enol ethers themselves in carbon-carbon bond forming reactions under Lewis acid conditions.[26] Activation of carbonyl groups by titanium tetrachloride followed by condensation with silyl enol ethers has been achieved to give aldol-type products in excellent yields according to Scheme 24.

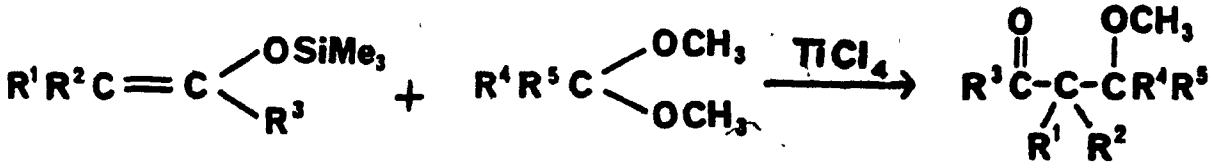


Scheme 24

Many of the problems associated with the regular aldol condensation are avoided using this methodology. No self-

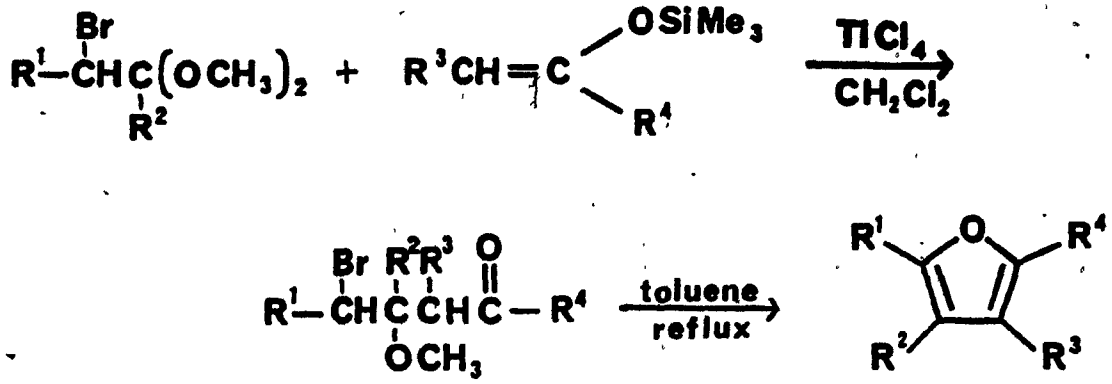
condensation products are observed when the silyl enol ether is treated with stoichiometric amounts of ketone or aldehyde. Dissociation of the aldol product is inhibited by the possible formation of a titanium chelate 10. The regiospecificity of this reaction is readily observed with the reaction of two isomeric silyl enol ethers as previously described (Scheme 23). Chemoselectivity is observed when different carbonyl groups are present, the reaction order being; aldehydes > ketones >>> esters.[27]

Silyl enol ethers were also found to react with acetals and orthoformates under acid conditions.[28] (Scheme 25)



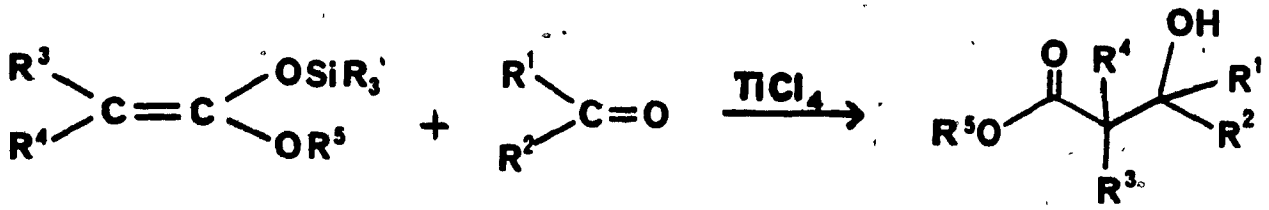
Scheme 25

Reaction with α-halo acetals has led to a simple method for the synthesis of furan derivatives.[29] (Scheme 26)



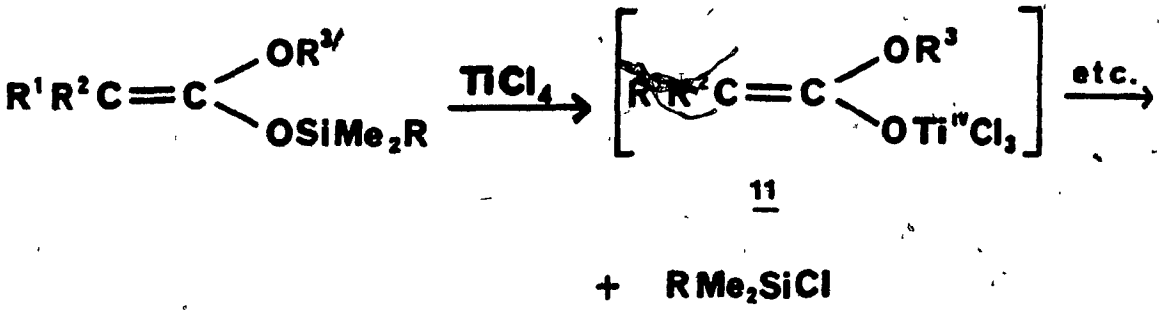
Scheme 26

Similarly, silyl ketene acetals have been used in the synthesis of β-hydroxy esters.[30] (Scheme 27)



Scheme 27

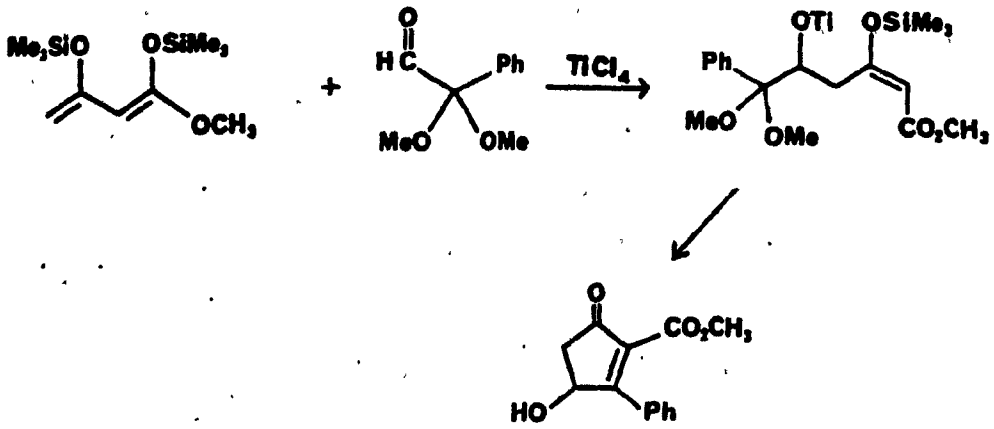
The precise mechanism by which $TiCl_4$ mediates the condensation of a silyl enol ether with a carbonyl electrophile is not known, although several theories have been put forth. Mukaiyama initially proposed the formation of a stable titanium chelate,[28] (Scheme 24), while others[31,32] suggested the formation of a titanium(IV) enolate intermediate 11. (Scheme 28)



Scheme 28

A recent study was carried out in our laboratory which used ^{29}Si-N.M.R. as a means with which to follow the reaction of a silyl enol ether and a carbonyl compound under $TiCl_4$ conditions.[33] At several points during the course of the reaction,

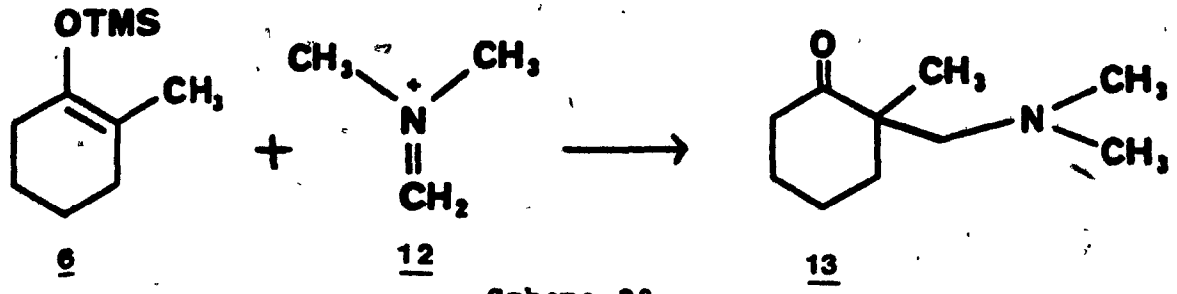
^{29}Si-N.M.R. spectra were taken using the INEPT pulse sequence.[34] It was found that the addition of $TiCl_4$ had little initial effect on the chemical shift of the siloxy group thus ruling out the fast formation of 11 (Scheme 28). It also suggests that there is little coordination between $TiCl_4$ and the siloxy groups. An intermediate was proposed, as illustrated in Scheme 29.



Scheme 29

Mannich Reactions Using Silyl Enol Ethers

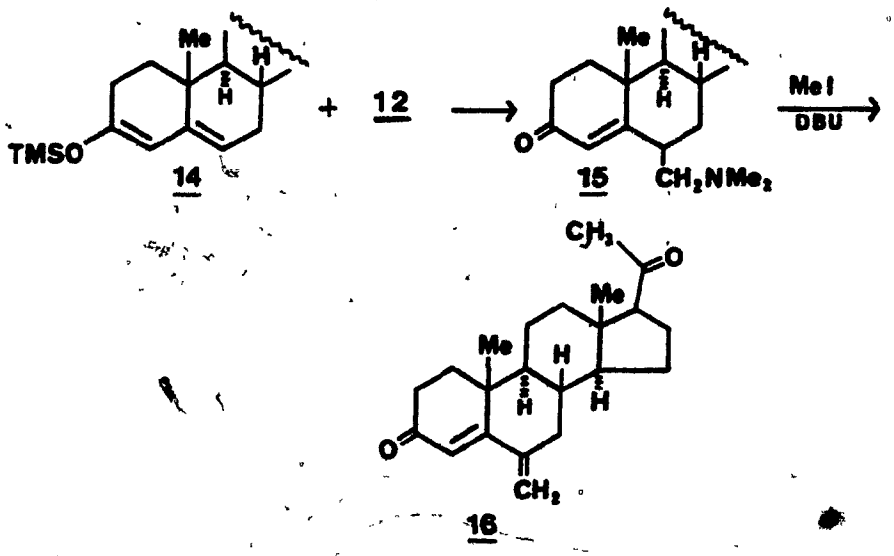
Danishefsky has investigated the use of silyl enol ethers in regioselective Mannich reactions.[35] The Eschenmoser salt 12 was reacted with the silyl enol ether 6 to give the single regioisomer of the Mannich base 13 in 65% yield. (Scheme 30)



6 12 13

Scheme 30

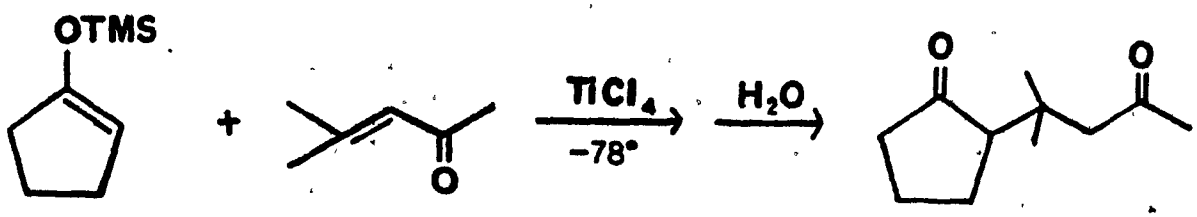
This methodology was extended to natural products synthesis. Reaction of the siloxydiene 14 with 12 also afforded a single isomer 15 which was converted to the steroid 16 in 58% yield.[36] (Scheme 31)



Scheme 31

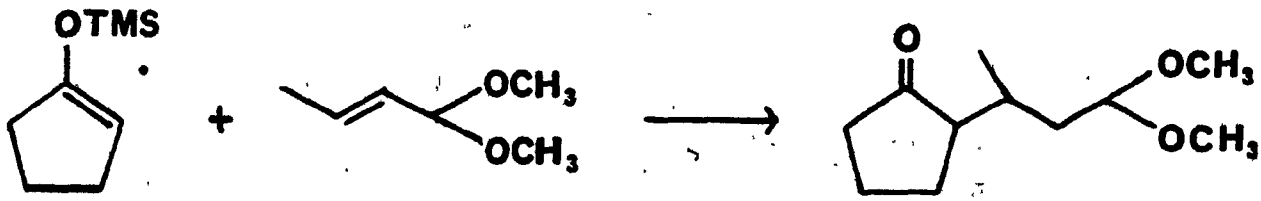
Michael Reactions Using Silyl Enol Ethers

Mukaiyama and co-workers have introduced the use of silyl enol ethers in a Michael fashion under Lewis acid catalyzed conditions to give 1,5 dicarbonyl compounds in good yields.[37] (Scheme 32)



Scheme 32

The reaction conditions are very mild and offer tremendous advantages over the normal base-catalyzed reaction as described earlier. Also, it was found that α,β-unsaturated acetals could be used as Michael acceptors as shown in Scheme 33.[38]



Scheme 33

O-Silylated Dienolates

Dienolates should theoretically give reaction according to Figure 4.

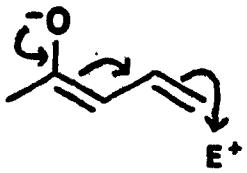
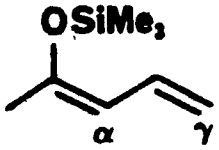


Figure 4

In practice, these reactions are rarely observed under kinetic conditions and α-alkylation predominates. Under thermodynamic, equilibrating conditions γ-substitution is sometimes observed.[39]

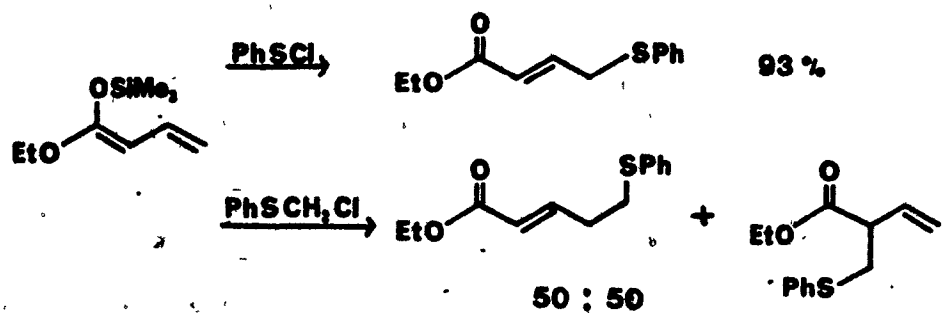
The siloxy group in the silyl dienol ether 17 is less electron-donating than a lithium group which results in a lower electron density at the α-position and accordingly leads to a marked preference for electrophilic attack at the γ-position. (Figure 5)



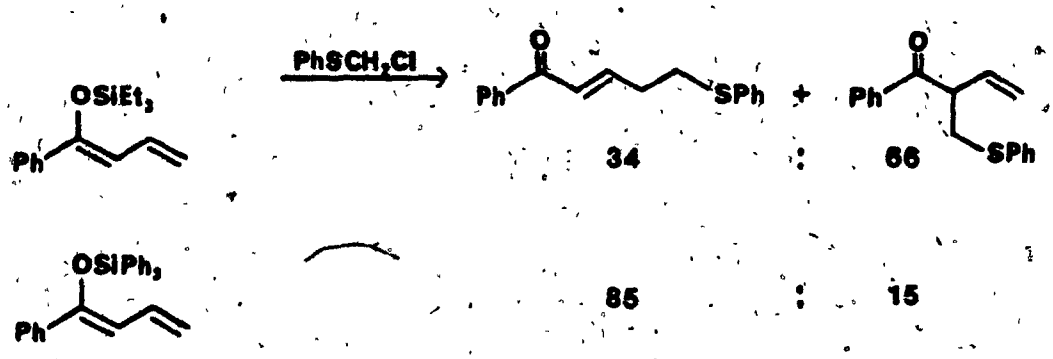
17

Figure 5

Fleming and co-workers undertook a series of studies of the reactions of silyl dienol ethers and found that the extent of γ vs. α attack depended on the type of electrophile (Scheme 34) and on the substituents on the dienolate (Scheme 35).[40]



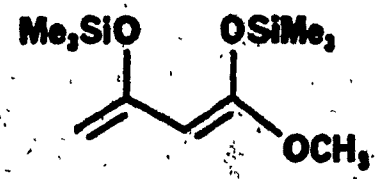
Scheme 34



Scheme 35

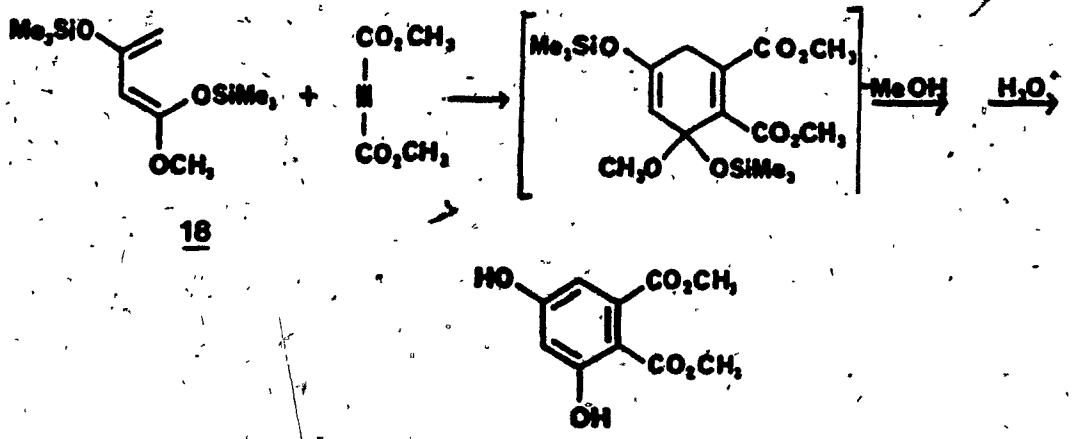
Bis-Silyl Enol Ethers

An extension of this silyl dienol ether chemistry has the addition of a second siloxy substituent to form a bis silyl enol ether. Work has been done in our laboratory on one such compound, 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-butadiene (18).



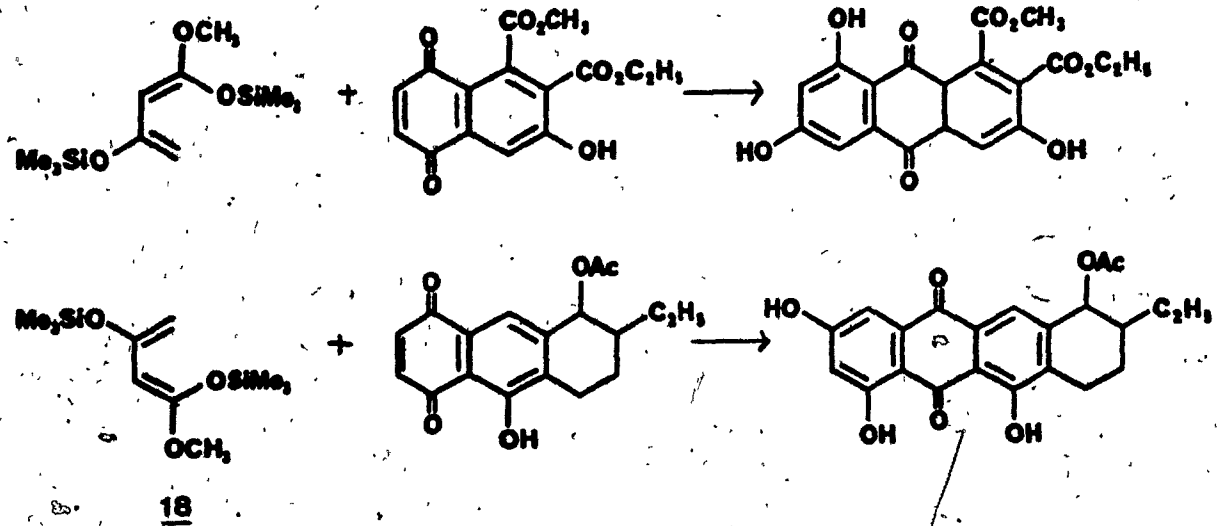
18

Yamamoto and co-workers had originally synthesized 18 and used it in a Diels Alder reaction with dimethyl acetylene-dicarboxylate (19)[41]. (Scheme 36)



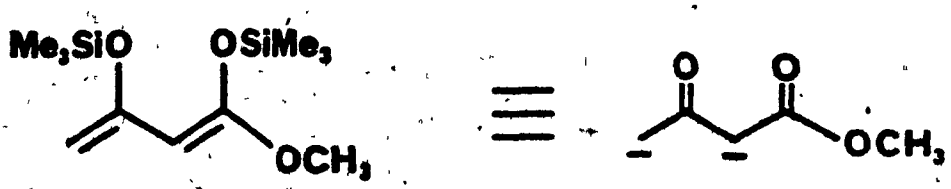
Scheme 36

Compound 18 was being used as a highly functionalized 4-carbon unit in the familiar Diels Alder process. Its application in synthesis is extended to other dienophiles as illustrated in Scheme 37.[42,43]



Scheme 37

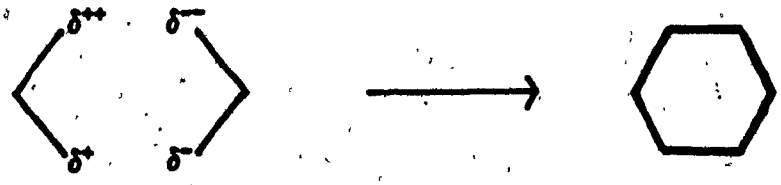
Recently in our laboratory, we introduced the use of 18 as a dianion equivalent of methyl acetoacetate (20).[44] (Figure 6)



18 20

Figure 6

In this respect, 18 can be viewed as a 3-carbon unit containing two nucleophilic sites, at C-4 and C-2. Reaction of 18 with 1,3 dielectrophiles can give six membered rings as represented in Scheme 38.



Scheme 38

On this basis, a novel cycloaromatization reaction has been developed.[44]

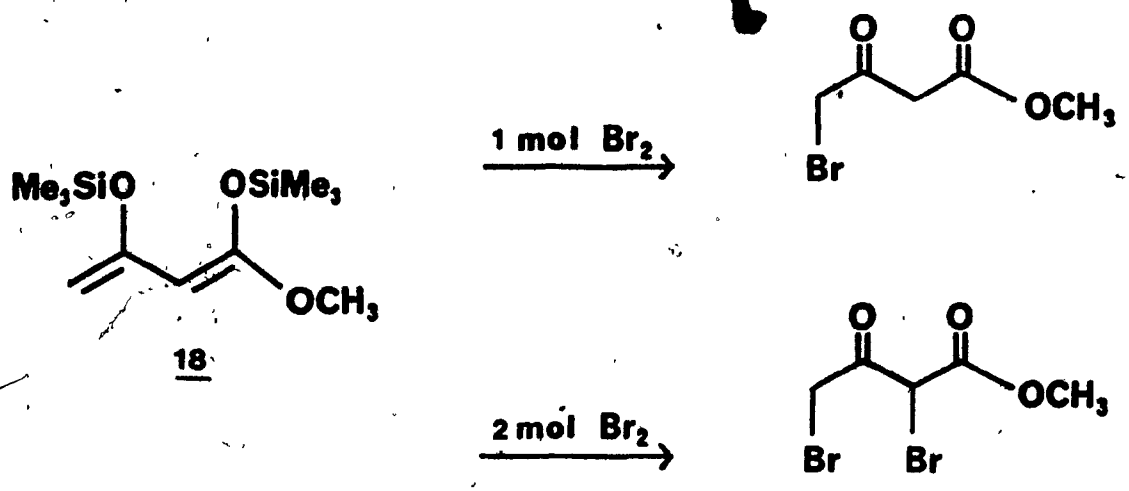
Compound 18 differs from the dianion 20 in two important respects:

- 18 reacts under neutral or acidic conditions as opposed to strongly basic conditions for the dianion and,

- 20 acts as a hard nucleophile, reacting with α,β-unsaturated carbonyl compounds in a 1,2 fashion,[45] while 18 acts as a soft nucleophile, adding in a Michael fashion under mild conditions.

The regiochemistry of the condensation (Scheme 38) is

governed by the varying reactivities of the two nucleophilic sites in 18. It has been shown,[44] that the C-4 site is more reactive than C-2, a fact which is illustrated in Scheme 39.



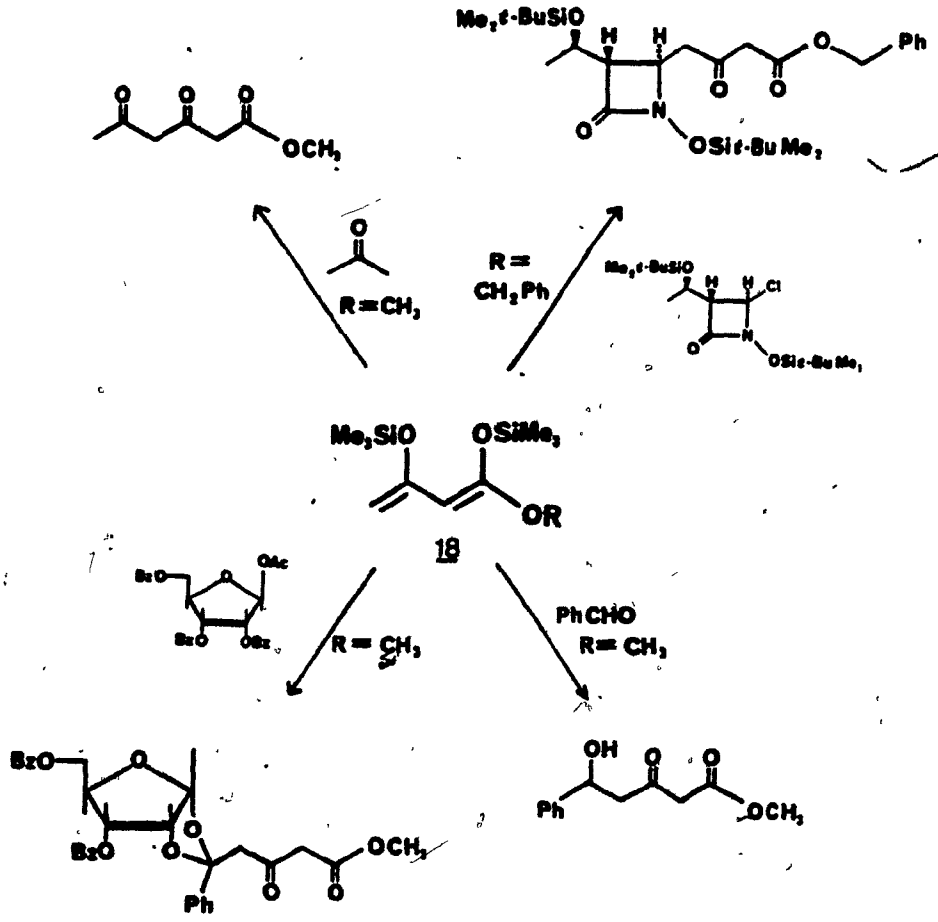
Scheme 39

Reaction of 18 with compounds containing a single electrophilic site consistently give Michael adducts at the C-4 site, examples of which are given in Scheme 40.[44,46,47]

Given that the C-4 site is the more reactive, it is then necessary to examine the relative reactivities of various electrophilic groups under the same reaction conditions for the purposes of choosing an appropriate 1,3 electrophile for the cycloaromatization reaction. It was established,[48] that the reactivities are as follows :

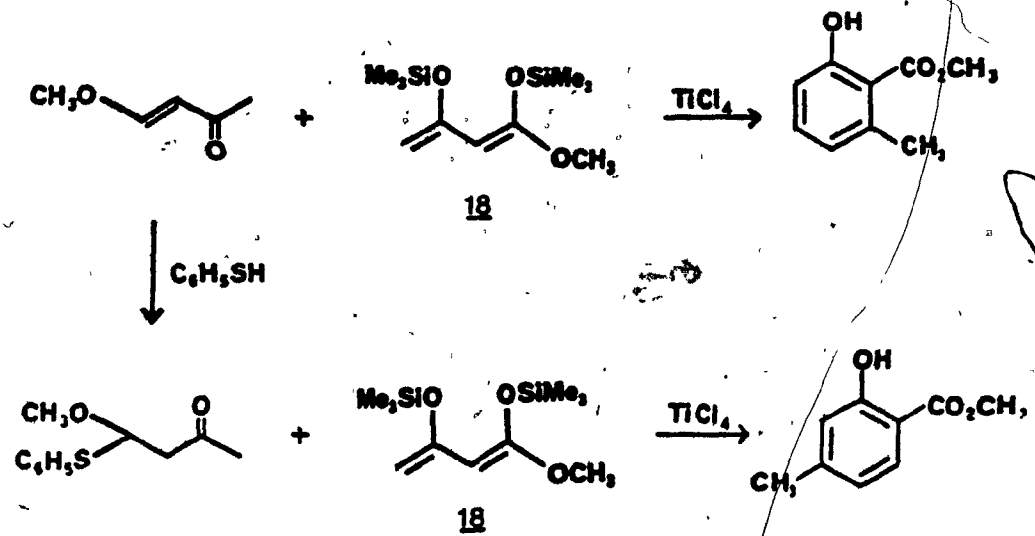
aldehyde > conjugated position of β-oxy- α,β unsaturated ketone ~ isolated ketone > carbonyl position of β-oxy-α,β-unsaturated ketone > acetal or monothioacetal > conjugate position of β-oxy- α,β unsaturated ester or ester carbonyl

With this order in mind it is then possible to have complete



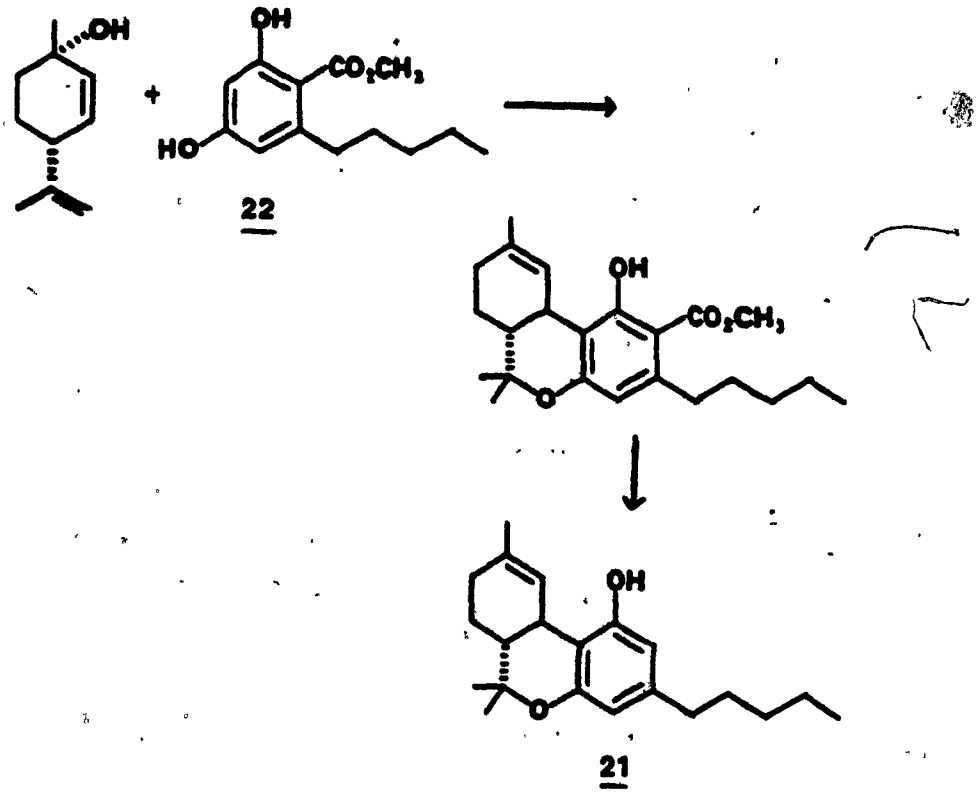
Scheme 40

control over the regiochemistry of the condensation, as demonstrated in Scheme 41.[49]



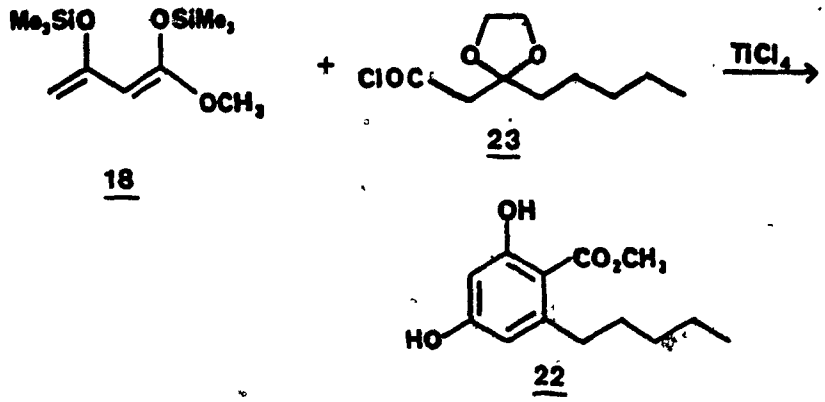
Scheme 41

This methodology has been used in the synthesis of Δ-1-tetrahydrocannabinol (21), the active psychotomimetic component of marijuana.[50] The critical step was the synthesis of methyl olivetolate (22), which was then condensed with an optically active monoterpene to give the desired product. (Scheme 42)



Scheme 42

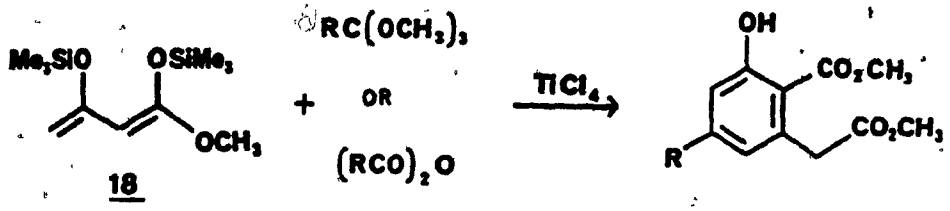
The synthesis of 22 was accomplished with the condensation of the bis silyl enol ether 18 with an appropriate acid chloride 23. (Scheme 43)



Scheme 43

It had been determined that acid chlorides are more reactive than ketals and hence, the regiochemistry of the reaction was controlled.

The reaction of two equivalents of 18 with one equivalent of various orthoesters or anhydrides under Lewis acid conditions resulted in the formation of 5-substituted-3-hydroxy-homophthalates.[51] The first step of the reaction is the formation of a tri-β-carbonyl adduct, followed by condensation with the second equivalent of 18. (Scheme 44)

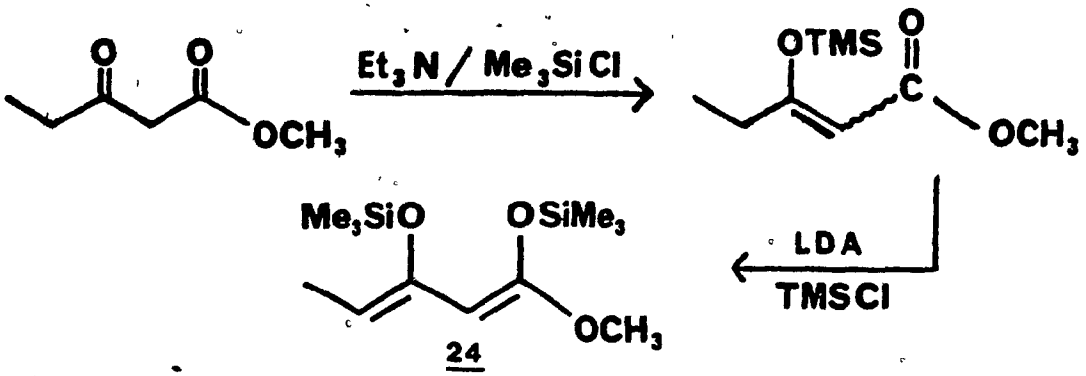


Scheme 44

So far, all of the benzenoid derivatives described are

unsubstituted at the o'-position due to the structure of the nucleophilic component. Substitution at the C-4 site of 18 was investigated,[52] and led to the synthesis of sclerin (23), a plant growth promoter.[53]

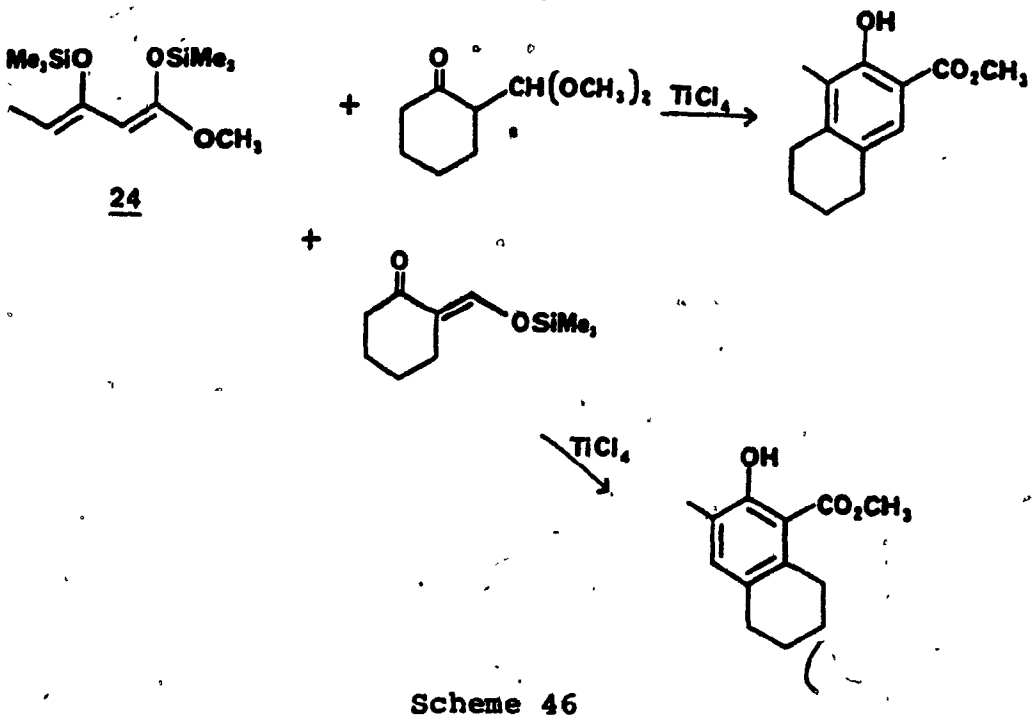
1,3-Bis(trimethylsiloxy)-1-methoxypenta-1,3-diene (24) was prepared according to Scheme 45.



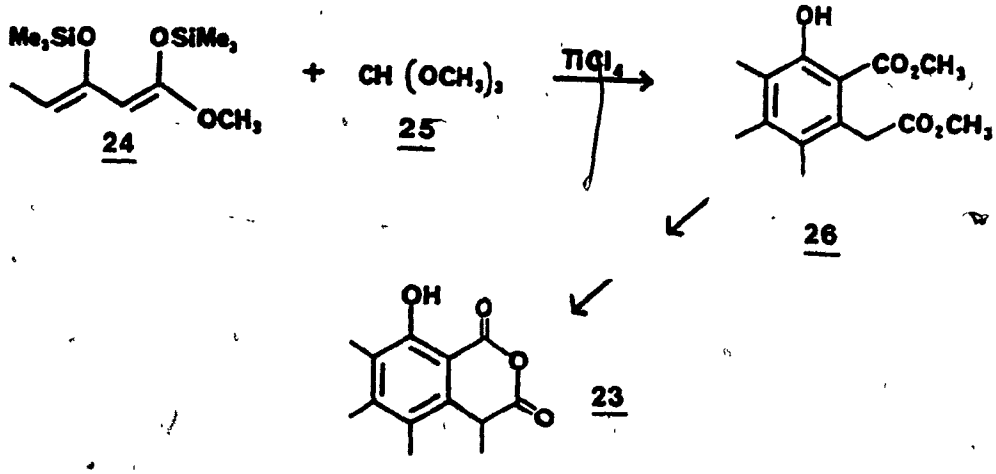
Scheme 45

Reactions of 24 with various electrophiles established that the nucleophilic reactivity had not changed due to the Me group and that C-4 was still the most reactive site. (Scheme 46)

In the synthesis of sclerin (23), two moles of 24 were condensed with methyl orthoacetate (25) in the presence of $TiCl_4$ to yield the aromatic compound 26 which was subsequently converted to the desired product. (Scheme 47)

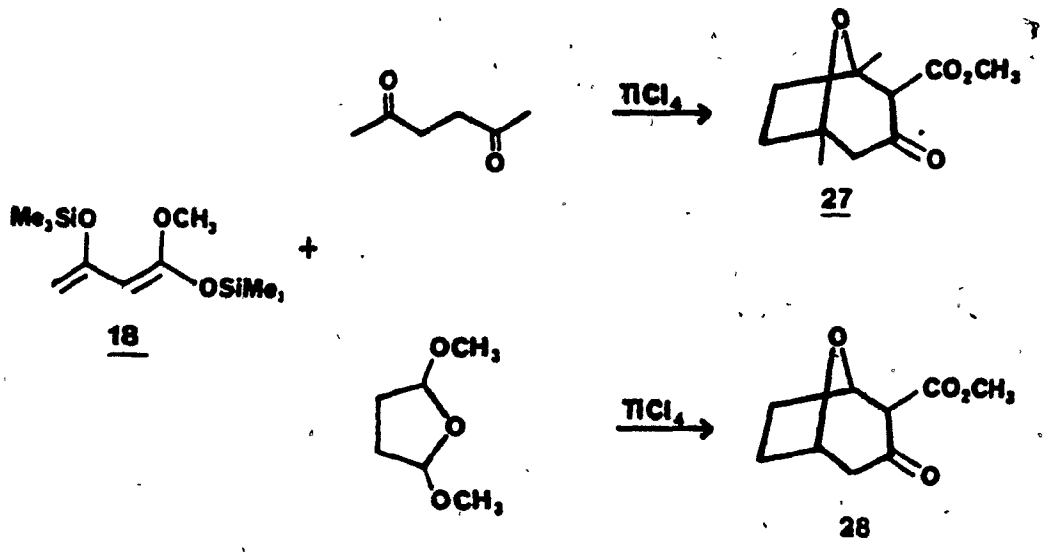


Scheme 46



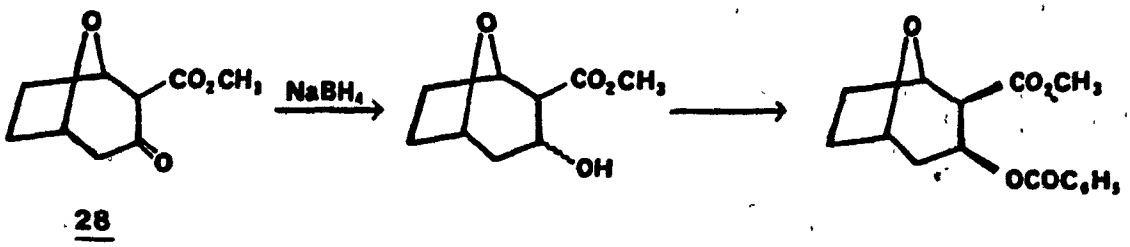
Scheme 47

It was also found that 18 condenses with hexane-2,5-dione or 2,5-dimethoxytetrahydrofuran to give 8-oxabicyclo-[3.2.1]-octyl systems 27 and 28 respectively.[54] (Scheme 48)



Scheme 48

Further reaction of 28 yielded the 8-oxa analog of cocaine. (Scheme 49).



Scheme 49

Recent work in our laboratory has extended the scope of this methodology to include the use of 1,3,5-tris-(trimethylsiloxy)- 1-methoxyhexa-1,3,5-triene (29), the trianion analog, (30), of methyl triacetate. (Figure 7)

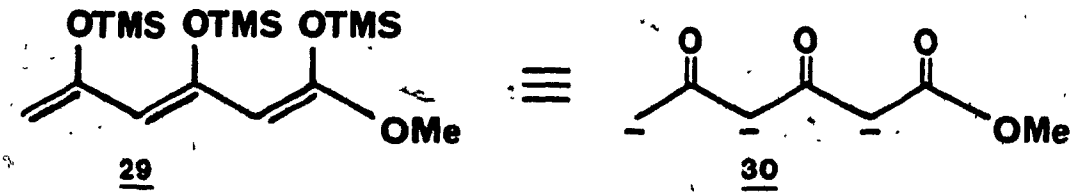
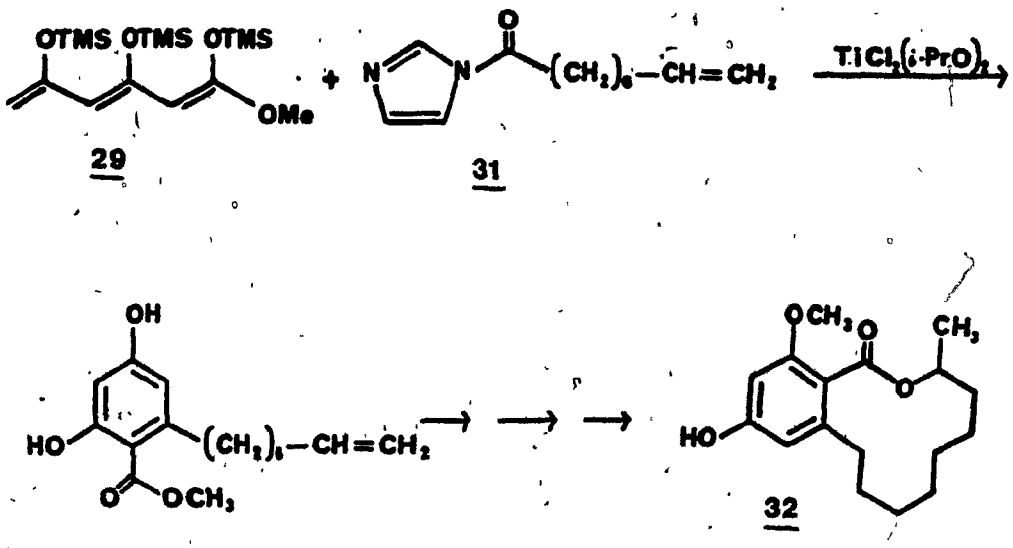


Figure 7

Reaction of 29 with the imidazolide 31 was the key step in the formal synthesis of lasiodiplodin (32).[55] (Scheme 50)



Scheme 50

This bis silyl enol methodology provides a route by which functionalized cyclic systems can be built up from acyclic

starting materials and is especially useful in the synthesis of benzenoid derivatives. This method constitutes a potentially very powerful addition to the methods which already exist, some of which will be discussed here.

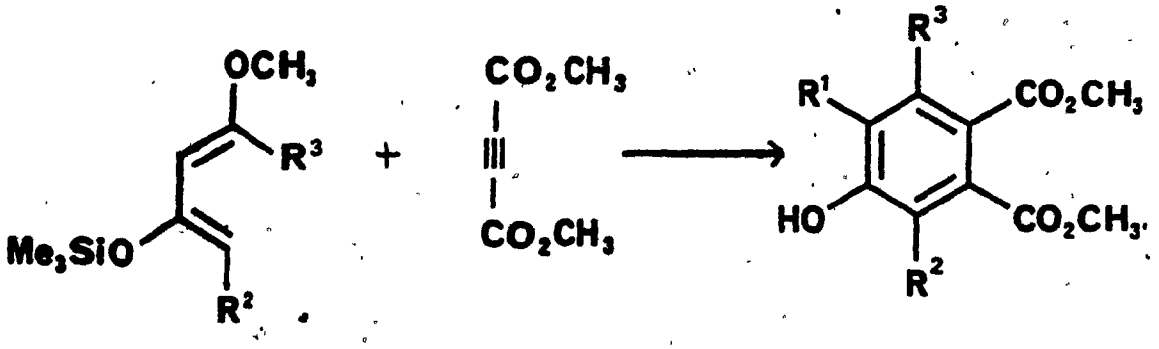
The synthesis of benzenoid compounds from acyclic precursors

The synthesis of aromatic benzenoid compounds has played a very large part in synthetic organic chemistry since the mid-nineteenth century. Various substitution patterns on these compounds have normally been achieved by the stepwise introduction of different functional groups through nitration, halogenation, alkylation and acylation, for example. This simple methodology, however, can result in problems with regioselectivity and the formation of mixtures of products which may be difficult to separate. Nonetheless, nucleophilic and electrophilic substitution is still the most widely used method for the synthesis of substituted benzenoids.

An entirely different method, and one which more closely resembles that which is used in nature, is the construction of these substituted benzene compounds from acyclic precursors which already contain the desired substituents. One such method is the already discussed bis silyl enol ether methodology which provides a route for the regiocontrolled synthesis of highly substituted salicylates. This method is an example of an Aldol type addition to give benzenoid derivatives while other reaction types include cycloadditions

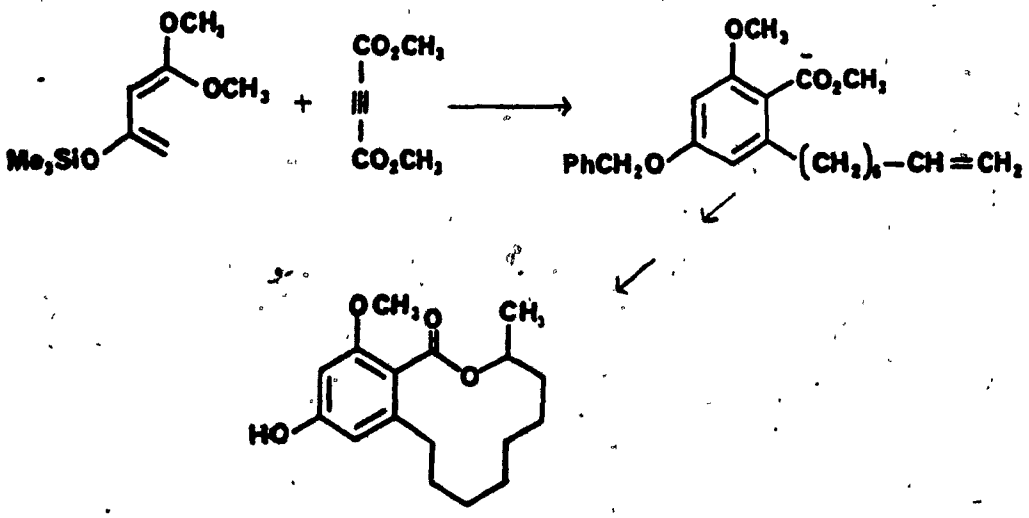
(e.g. Diels-Alder) and condensation reactions (e.g. Michael, Claisen).

The well known Diels-Alder reaction, a [$4\pi + 2\pi$] cycloaddition has been used extensively in the preparation of six-membered rings. The utilization of functionalized dienes and dienophiles has led to the preparation of a variety of polysubstituted benzenoid products. A recent review[56] deals with the use of hetero substituted 1,3 dienes, where the introduction of various substituents onto the diene is shown to have a dominant effect on the regiochemistry the cycloaddition. Of note is the use of siloxy substituted dienes, useful both for their ready availability and their electron-donating capabilities.[57] (Scheme 51)



Scheme 51

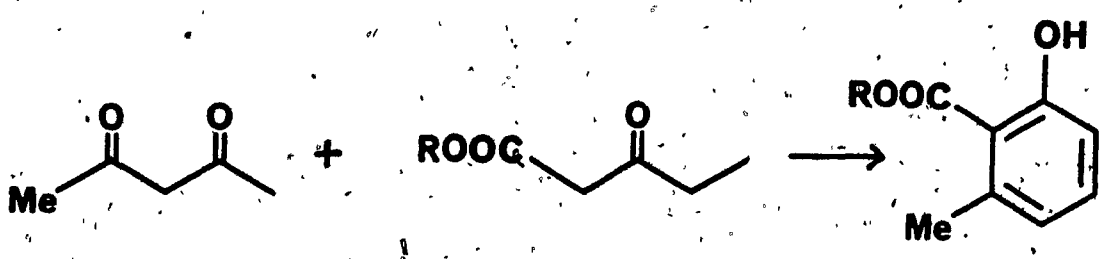
Other examples have already been noted which employ bis silyl enol ethers (Schemes 36 & 37). An application in the synthesis of lasiodiplodin (compare to Scheme 50) is given in Scheme 52.[58]



Scheme 52

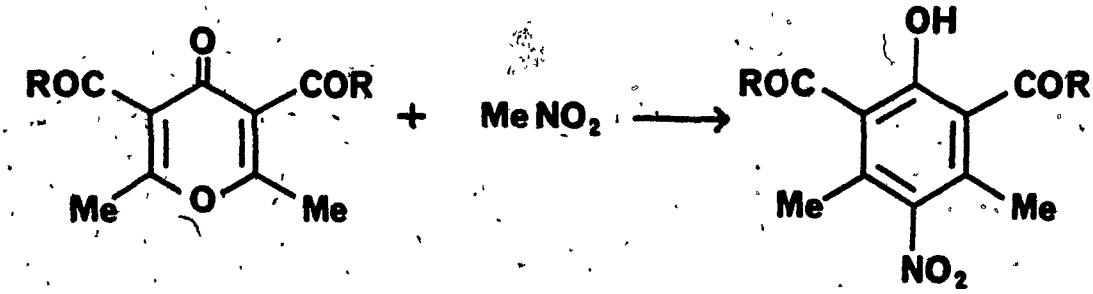
For the purposes of illustration, only the synthesis of substituted phenols will be discussed in the following section, although syntheses of anilines, for example, are well known. A recent review[59] discusses the preparation of a wide variety of benzenoid compounds.

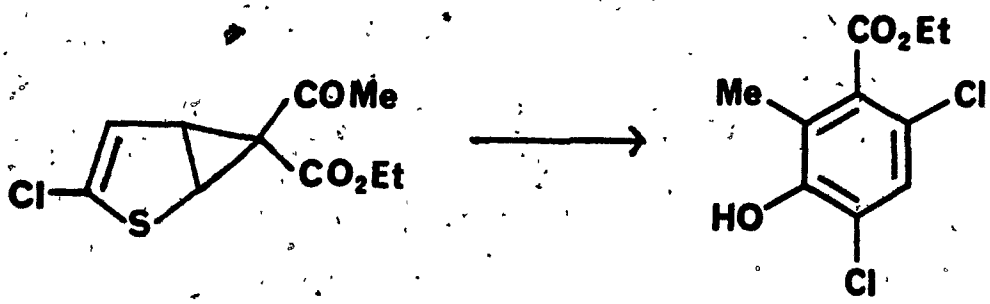
In the synthesis of phenols from acyclic precursors, the hydroxy group usually comes from a ketone or ester group. Ketones usually react via their two active, nucleophilic α-positions, where the co-reactant must have complementary (i.e. electrophilic) reactivity. The most common co-reactant is a β-dicarbonyl or synthetic equivalent. Judicious choice of a ketone which can be enolized preferentially in one direction and a β-dicarbonyl in which one carbonyl is more reactive than the other can result in the regioselective synthesis of highly substituted, unsymmetrical phenols in reasonable yields.[60] (Scheme 53)



Scheme 53

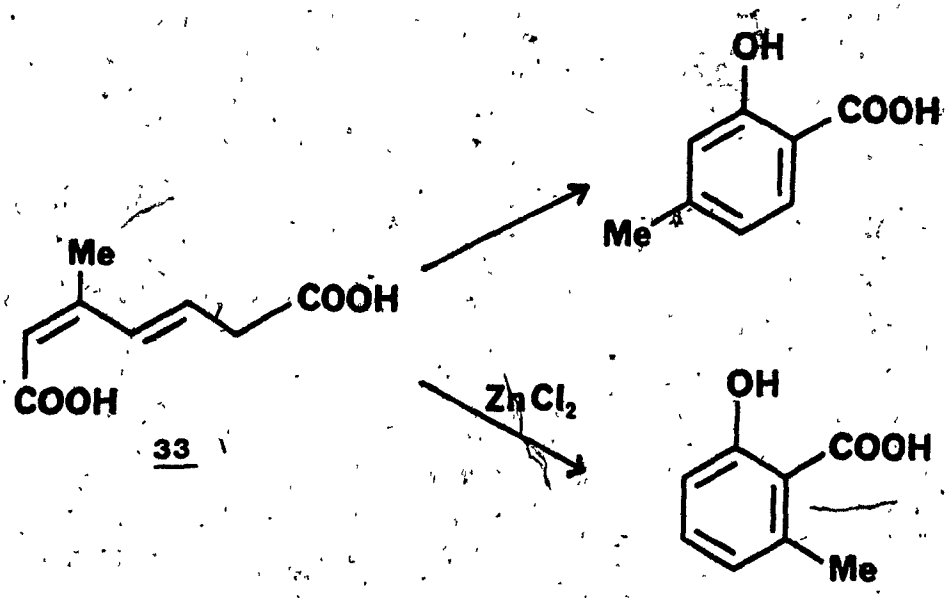
Five and six-membered heterocycles have also been used as a source of phenols through a ring cleavage process, examples of which are given in Scheme 54.[61,62]





Scheme 54

In an example where the phenolic oxygen is supplied by a carboxylic acid group, zinc chloride has been shown to mediate the reaction of a diacid 33.[63] (Scheme 55)

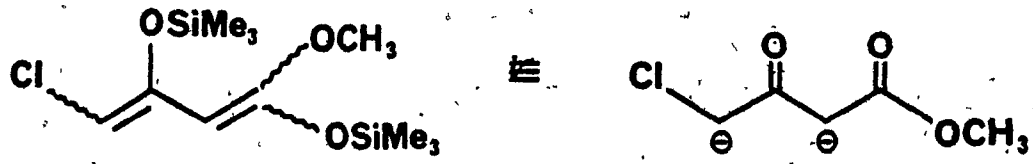


Scheme 55

The literature contains many methods for the synthesis of benzene derivatives with almost any desired substituents in whatever pattern and degree of substitution. However, the yields are not always high and there remain difficulties with regiochemistry. Synthetic organic chemists are constantly coming up with new and improved methods which may overcome some of these problems.

RESULTS AND DISCUSSION

The work in this thesis is based on the silyl enol ether chemistry previously developed in this laboratory and consists of the synthesis of the chlorinated analog, 34, of the bis silyl enol ether 18. Based on the previous work, 34 can be regarded as the dianion equivalent of 4-chloro methyl acetoacetate (35). (Figure 8)



34 35

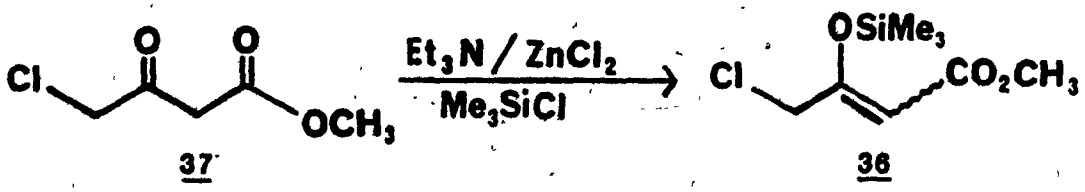
Figure 8

The reaction of 34 with various electrophiles allows for the incorporation of a chlorine atom into a straight chain compound, aromatic benzenoid derivative or bicyclic system. The chlorine may be required in the final product or it can simply act as a functional group which can be manipulated at a later stage in the synthesis.

The chemistry of 34 was examined and its application in the synthesis of several natural products investigated.

Preparation of the Bis Silyl Enol Ether 34

The silyl enol ether 36 was synthesized in the usual manner,[62] starting with the 4-chloro methyl acetoacetate (37). (Scheme 56)



37 36

Scheme 56

The crude product was distilled under high vacuum (0.1 torr, 55 C) to give product 36 in 60% yield. Compound 36 is relatively stable and can be kept under N_2 in the refrigerator for several months without appreciable decomposition.

^{1}H-N.M.R. indicates that there is a 7:2 mixture of two isomers. N.O.E. experiments showed no enhancement in the C-2 proton signal when the C-4 protons were irradiated, so that no structural assignment of the major isomer could be made on this basis. However, a proton coupled ^{13}C-N.M.R. experiment was able to distinguish between the two possible isomers of 36. The coupled spectrum showed C-4 spilt into a triplet by the two adjacent protons and this was further split by the proton at C-2. The coupling constant due to the effect of the proton at C-2 for the major isomer was found to be 6.7 Hz, while for the minor isomer a coupling constant of 4.0 Hz was

found (figure 9). It is known that a trans- isomer will give a larger $^3J_{CH}$ coupling constant,[65] so that on this basis the major isomer of 36 is assigned trans- (or E-) geometry, and the minor isomer cis- (or Z-) geometry.

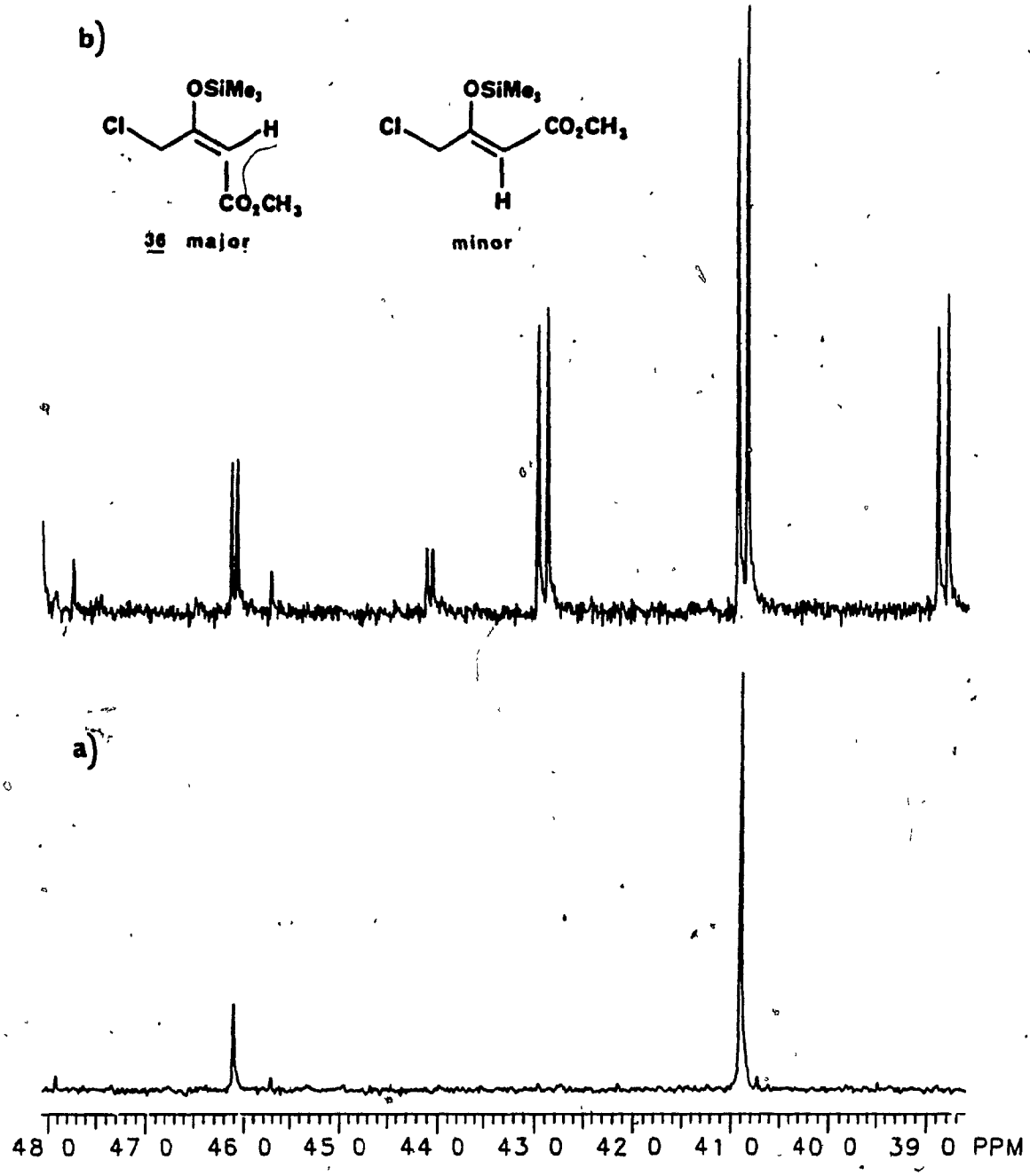


Figure 9: (a) ^{13}C-N.M.R. spectrum for 36 - C-4 carbon.
(b) Proton-coupled ^{13}C-N.M.R..

The silyl enol ether 36 was converted to the chlorinated bis silyl enol ether 34 in the usual manner using LDA/TMSCl. (Scheme 57)

36 34

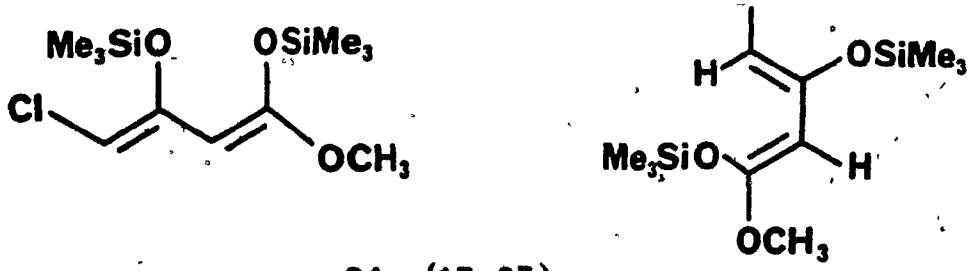
Scheme 57

The product 34 was not purified, as it was quite unstable. It could be kept in the refrigerator for only a few days before extensive decomposition occured. However, ^{1}H-N.M.R. indicated that the crude product was relatively pure. The yield of this reaction is normally >90%.

^{1}H-N.M.R. and ^{29}Si-N.M.R. data indicate that 34 exists mainly as one geometrical isomer. N.O.E. experiments showed no enhancement in the C-2 proton signal when the C-4 proton was irradiated, so that no structural assignment could be made for the C-3 double bond by this experiment. However, on irradiation of $-OCH_3$, the C-2 proton showed a 17% enhancement in signal intensity. This suggests that the C-1 double bond has a cis- (or Z-) geometry. This assignment is in agreement with a recent report[66] which assigned a Z-stereochemistry to a series of 1,1,3-trioxy dienes (including the bis silyl enol ether 18).

A proton coupled ^{13}C-N.M.R. experiment was performed in

order to determine the geometry of the C-3 double bond. The C-2 carbon appears at 75.8 ppm (major isomer) and 72.2 ppm (minor isomer) in the decoupled spectrum. In the coupled spectrum the major isomer carbon peak was split into a doublet by the C-2 proton but was not split by the C-4 proton. The C-2 carbon corresponding to the minor isomer was split into a doublet by the C-2 proton which was further split by the C-4 proton with a coupling constant of approximately 5 Hz. This suggests that the major isomer has a cis- (or Z-) relationship between the C-2 carbon and the C-4 proton while the minor isomer has a trans- (or E-) relationship between the two. These results indicate that 34 has a (1Z,3Z) geometry for the major isomer and (1Z,3E) for the minor. (Figure 10)

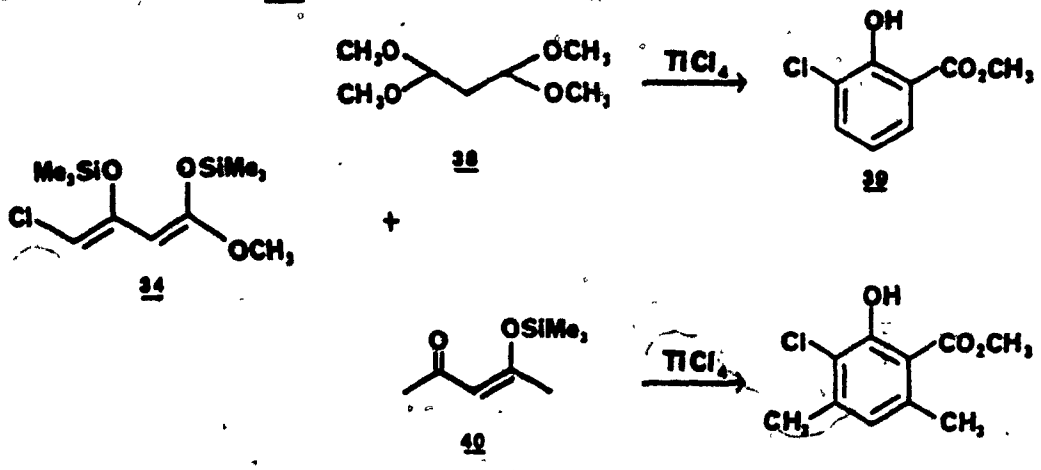


34 (1Z,3Z)

Figure 10

Cycloaromatization reactions of 34

Some of the cycloaromatization reactions described by Chan and Brownbridge[48] were repeated using the chlorinated bis silyl enol ether 34 as shown in Scheme 58.

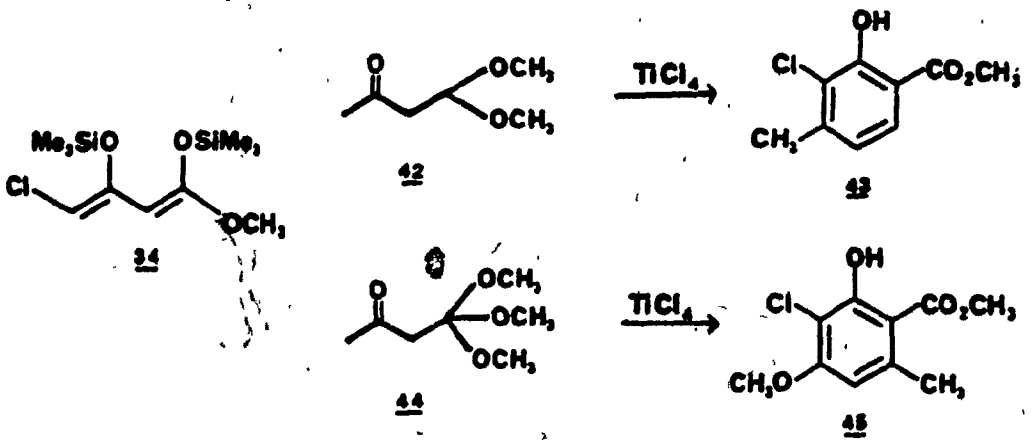


Scheme 58

When malonaldehyde bis(dimethylacetal) (38) was reacted with 34 in the presence of two equivalents of titanium tetrachloride, methyl 3-chlorosalicylate (39) was obtained in 25% yield, while a similar reaction of 34 with 4-trimethylsiloxy-3-penten-2-one (40) gave the chlorinated salicylate derivative 41 in 23% yield. In both cases the desired product was the major isolable component of the crude reaction mixture along with some starting materials.

Since the "bottom" halves of these products are symmetrical, these reactions say nothing about the relative reactivity of the C-4 versus C-2 positions of 34. Two reactions were done in which compounds with two different electrophilic groups were reacted with 34 to give

unsymmetrical products on the basis of the following order of reactivity: ortho ester > ketone > acetal. (Scheme 59)



Scheme 59

When acetal 42 was reacted with 34 in the presence of two equivalents of titanium tetrachloride, the chlorinated adduct 43 was obtained in 29% yield while the titanium tetrachloride catalyzed reaction of 34 with the ortho ester 44 gave the highly substituted salicylate derivative 45 in 24% yield. In neither case was any isomer obtained, so while the yield was low, the reaction was regiospecific.

The structures of these products were determined by ^{1}H-N.M.R. data. It has been shown,[49] that in substituted methyl salicylates the aromatic methyl group at the C-4 position resonates at about 2.30 ppm, whereas the methyl at the C-6 position resonates at about 2.50 ppm due to deshielding by the ortho carboxylate group. On this basis, the structures of 43 and 45 were assigned. (Table 1)

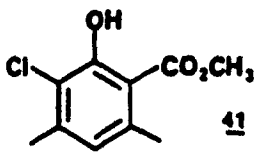
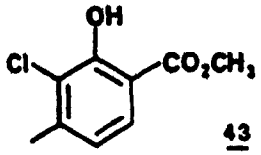
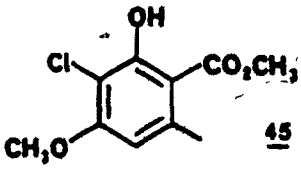
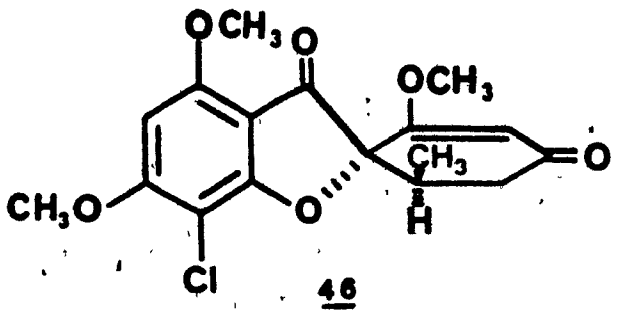
	C-4 ppm	C-6 ppm
 41	2.37	2.48
 43	2.41	
 45		2.55

Table 1

Their structural assignments were supported by other spectral information such as MS and IR.

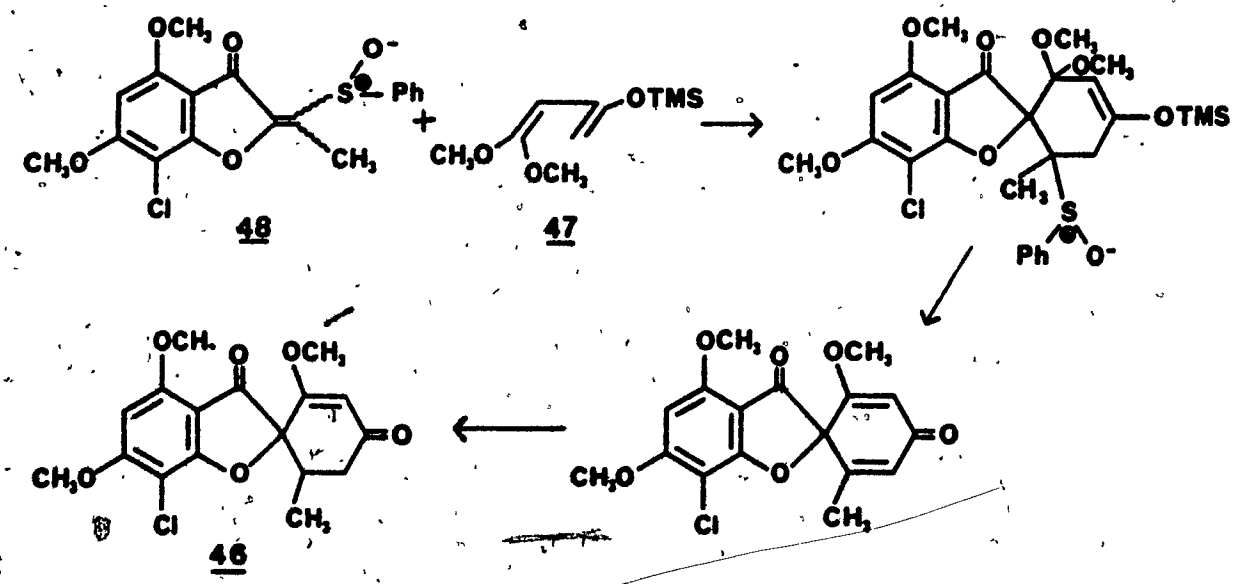
The Attempted Synthesis of Griseofulvin

One possible application of this methodology would be the synthesis of the chlorinated natural product, griseofulvin (46), a commercially important anti-fungal agent. Originally isolated from penicillium griseofulvum,[67] griseofulvin can be administered orally to animals and is easily absorbed into plant roots, thereby making its use quite practical and the development of an efficient scheme for its synthesis desirable. The structure and stereochemistry of griseofulvin was elucidated by McMillan and co-workers in the 1950's.[68,69]



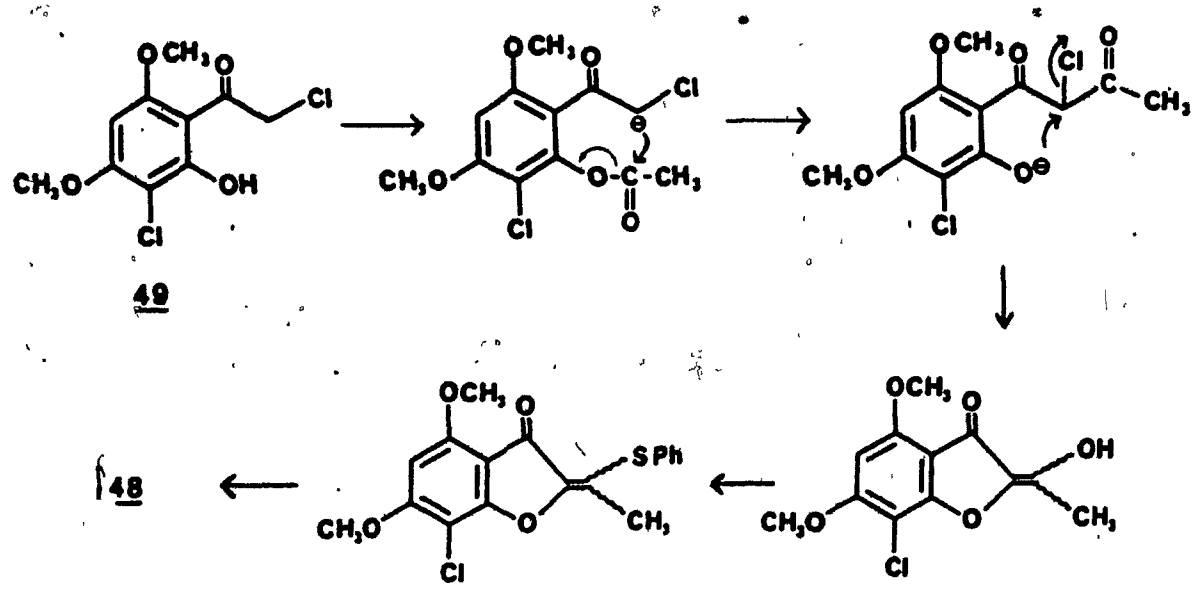
46

Since that time there have been several total syntheses of griseofulvin,[70] a recent one having been accomplished by Danishefsky,[71] which involves ,as a key step, the aforementioned Diels Alder cycloaddition between a highly functionalized diene 47 and compound 48. (Scheme 60)



Scheme 60

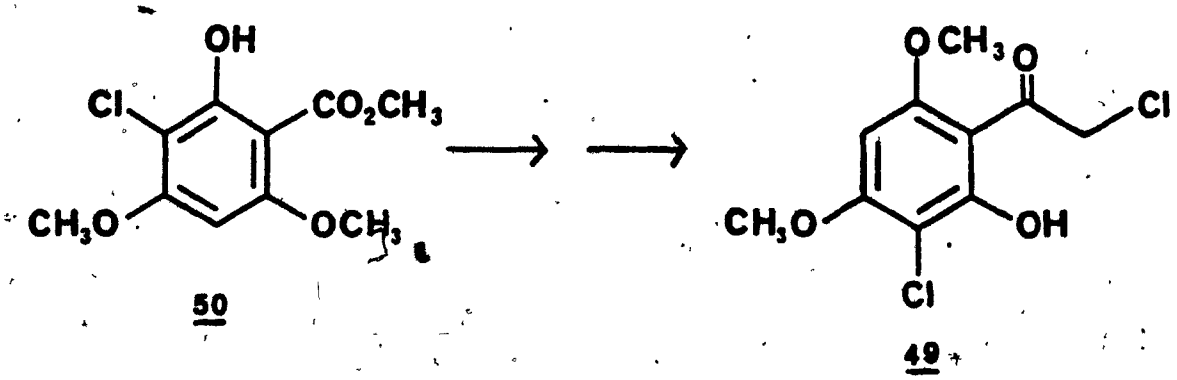
Compound 48 was generated in several steps starting with a highly substituted aromatic compound 49. (Scheme 61)



Scheme 61

In his paper, Danishefsky states, "Any attempts at the commercialization of this process must provide a regio-specific, high yield route to 49."[72]

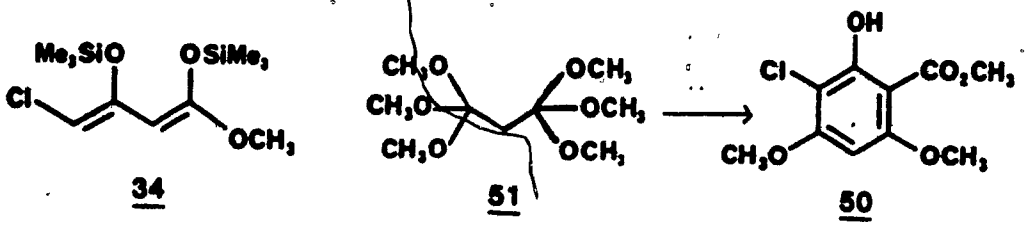
We proposed to synthesize 49 using our cycloaromatization reaction to produce the aromatic compound 50 which could then be converted to 49. (Scheme 62)



Scheme 62

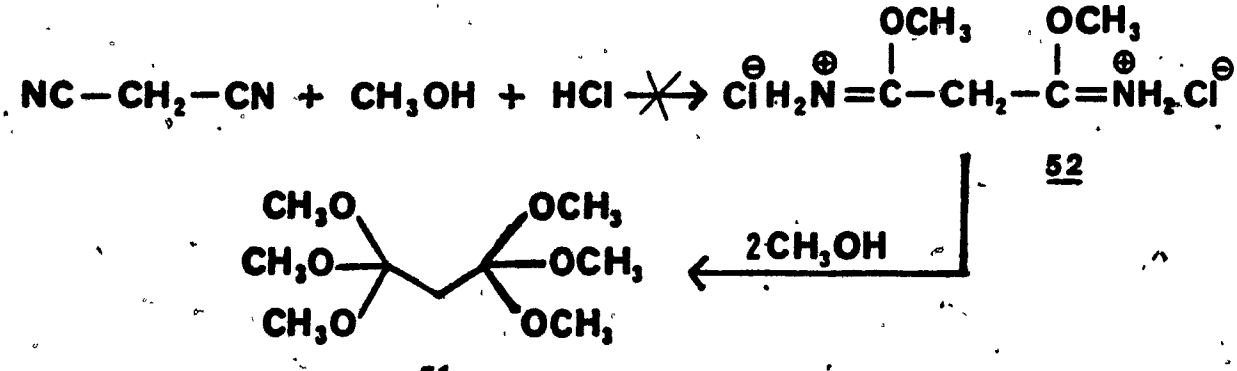
The first step in the synthesis of 50 would be the choice of an appropriate electrophile with which to react the silyl

enol ether 34. The most direct approach, and one which would give the desired product in one step, would be the reaction of 34 with the ortho ester 51. (Scheme 63)



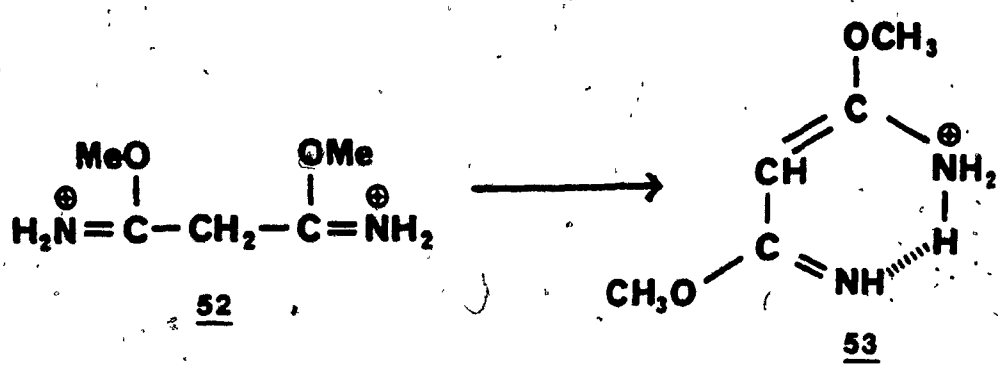
Scheme 63

The synthesis of 51 was attempted in our laboratory,[72] using the Pinner method with malononitrile as the starting material. This synthesis was unsuccessful. (Scheme 64)



Scheme 64

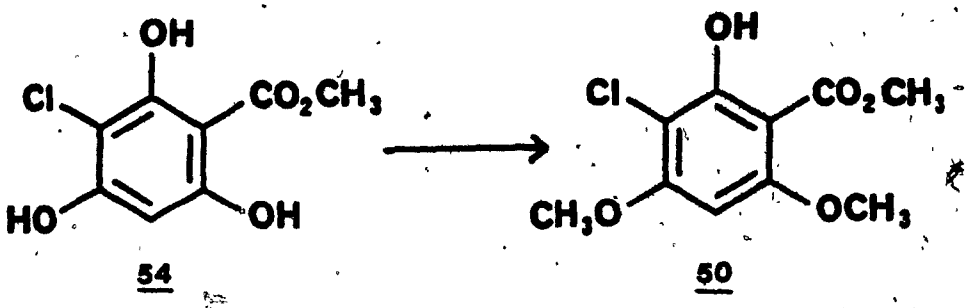
McElvain and Schroeder had previously attempted this synthesis in 1949,[73] and had proposed that the dihydrochloride 52 was insoluble in alcohol and was subsequently converted to the more soluble and resonance stabilized monohydrochloride 53 which would then resist further alcoholysis. (Scheme 65)



52 53

Scheme 65

The synthesis of 50 was then attempted by an indirect route, with the initial formation of the trihydroxy compound 54 which would then be converted to the desired product. (Scheme 66)

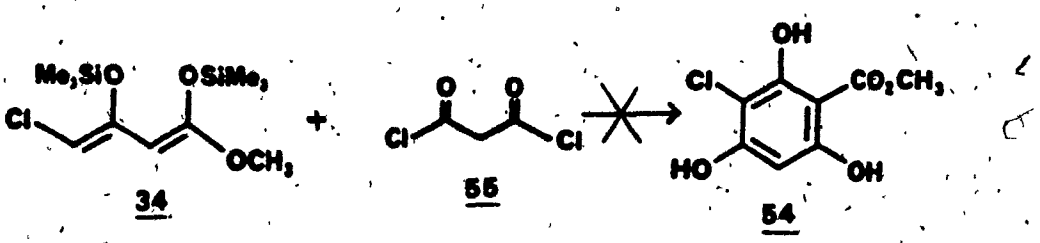


54 50

Scheme 66

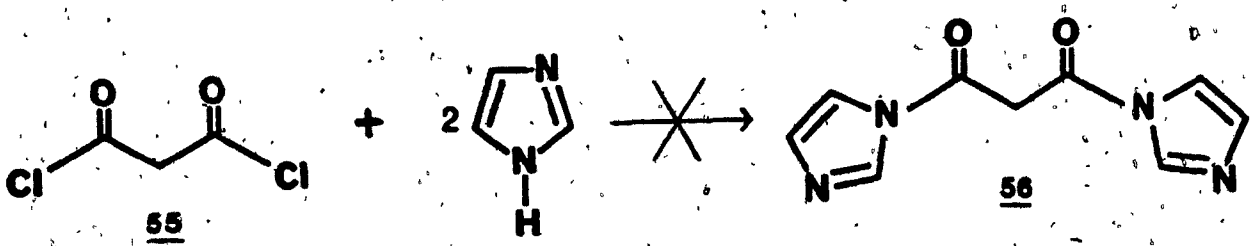
The synthesis of 54 was attempted using malonyl dichloride (55) as the electrophile (Scheme 67). The reaction was performed in the presence of titanium tetrachloride at -78° C. Different orders of addition were attempted [(malonyl dichloride, silyl enol ether, $TiCl_4$) and (malonyl dichloride, $TiCl_4$, silyl enol ether)]. Neither method yielded any product, but gave starting materials instead. Mukaiyama had noted that a mixture of titanium tetrachloride and titanium isopropoxide worked well with reactive electrophiles.[37] The reaction was

attempted using a 1:1 ratio of $TiCl_4$ and $Ti[O\text{-}i\text{-}Pr]_4$ using both orders of addition, but again the reaction was unsuccessful.



Scheme 67

An equivalent reaction would involve the reaction of 34 with the imidazolide of 55. Imidazolides are often crystalline and easily handled when compared to the acid chloride from which they are usually prepared. Normally, the conversion of an acid chloride to its corresponding imidazolide is simple according to the method of Staab[74], and the resulting electrophile is of comparable reactivity to the original acid chloride. But when the conversion of 55 to 56 was attempted the reaction was unsuccessful. (Scheme 68)



Scheme 68

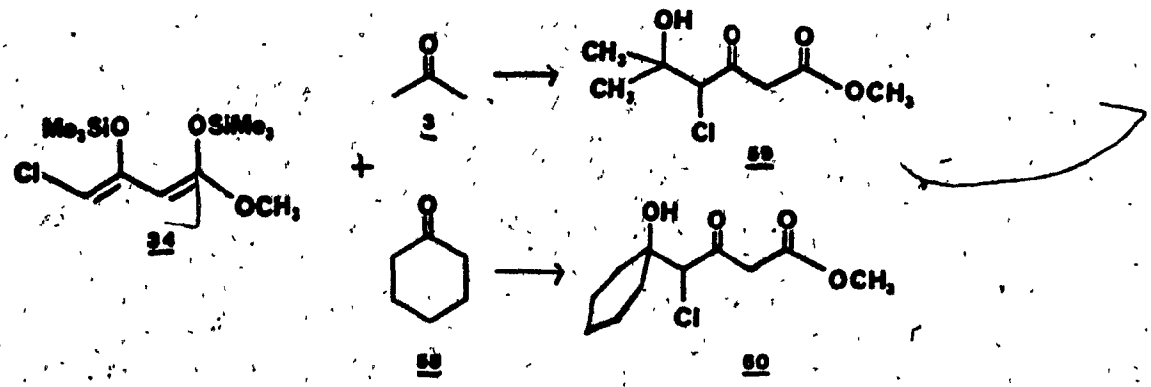
Imidazole (57) and malonyl dichloride (55) were mixed in a 2:1 ratio in dry THF and stirred for 1.5 hours at 0°C, then allowed to come to room temperature and stirred for a further 2.5 hours. The white precipitate which had formed (presumably imidazolinium chloride) was filtered off and the filtrate reduced under vacuum. It was at this point that the product decomposed to give a black residue. An N.M.R. was taken and it showed no trace of the expected product 56, but gave instead starting materials and a product presumably resulting from a polymerization reaction. No further attempt was made to identify the product.

Reaction of 34 with single reactive site carbon electrophiles

In order to further confirm the reactivity of the C-4 site vs C-2 site in 34, reactions were performed with electrophiles containing a single reactive site. The electrophile should attack at the most reactive site of 34 thus establishing the comparitive reactivities. 34 was reacted with acetone (3) and cyclohexanone (58) to give adducts 59 and 60 respectively. (Scheme 69)

^{1}H-N.M.R. data indicate that reaction did in fact occur at the C-4 site with the presence of a signal at 4.25 ppm and 4.20 ppm (for adducts 59 and 60 respectively) corresponding to a single proton at C-4. In neither case was any C-2 adduct observed. The proposed structures of 59 and 60 were further corroborated by MS and IR data. For compound 59, conventional Electron Impact M.S. did not give any heavy ions of structural

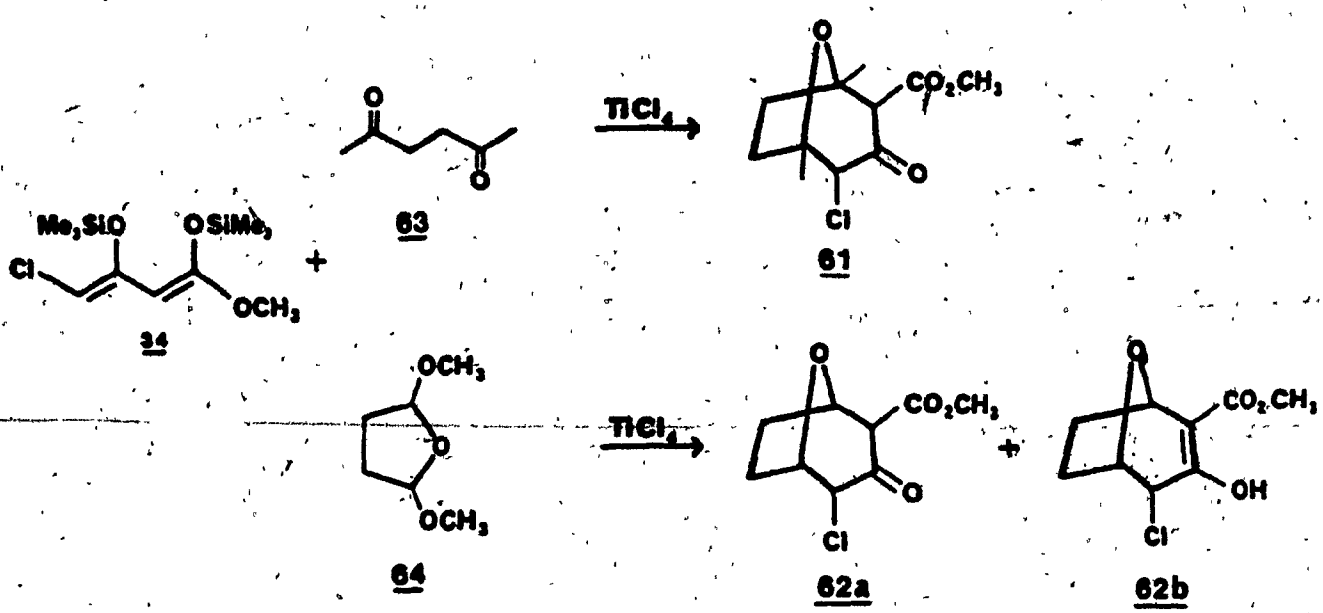
interest, however, Chemical Ionization M.S. gave the expected molecular ion.



Scheme 69

The synthesis of 8-membered bicyclic systems

As described earlier, bis silyl enol ethers have been used to synthesize 8-membered bicyclic systems, or more specifically, 8-oxa-bicyclo-[3.2.1]-octyl systems. These reactions were attempted using 34 and they did give the expected chlorinated analogs 61 and 62 as depicted in Scheme 70.



Scheme 70

Reaction of 34 with acetonylacetone (63) gave bicyclic compound 61 as white crystals in 30% yield. ^{1}H-N.M.R. data showed that the two methyl groups resonated at 1.47 ppm and 1.58 ppm, the methoxy protons at 3.72 ppm and the two single protons at 3.61 ppm and 4.29 ppm (C-2 and C-4 respectively).

Reaction of 34 with 2,5-dimethoxytetrahydrofuran (64) yielded 62 as a mixture of a light yellow oil and clear crystals in 30% yield. The crystals were isolated and found to be the enol tautomer 62b of the product and made up approximately two-thirds of the crystal/oil mixture. ^{1}H-N.M.R. showed a peak at 11.45 ppm which corresponds to the -OH proton, and this was found to occur in a 1:1 ratio with each of the single protons (at C-1, C-4 and C-5). Also, no peak corresponding to the C-2 proton was seen. 62a was not isolated, but crude N.M.R. did show alkyl hydrogen peaks that were proportionally larger as compared to the hydroxy hydrogen peak, indicating the presence of a compound that was structurally similar to 62b but which did not contain a hydroxy group. This compound was assumed to be the keto form of 62b.

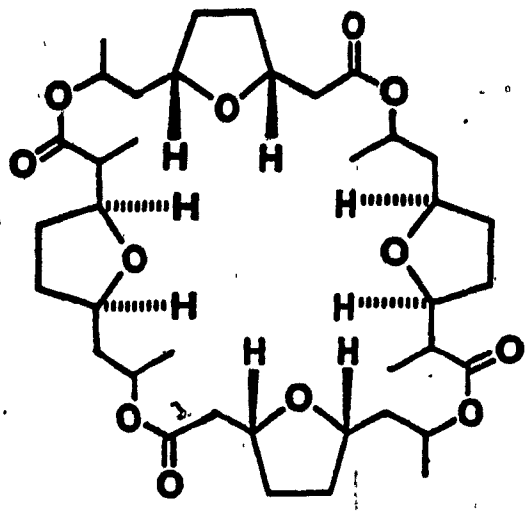
Various attempts were made to improve the yield of 62. Both orders of addition were tried (34, 64, $TiCl_4$) and (64, $TiCl_4$, 34), with the latter being the more successful of the two methods (30% vs 13% yield). Several different Lewis acids were used to catalyze the reaction, including $TiCl_4/Ti[O\text{-}i\text{-}Pr]_4$, $ZnBr_2$, $SnCl_4$ and $BF_3.(OC_2H_5)_2$. None of these acids gave improved results.

The attempted synthesis of Nonactic Acid

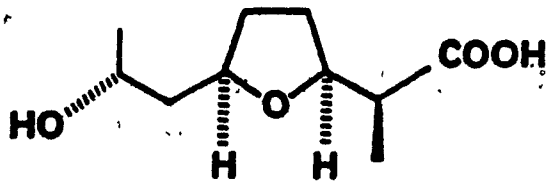
An ionophore can be defined as a molecule which has the ability to complex an ion and to assist in the transport of this ion through a lipophilic interface.[75] This is a general term which describes a variety of structural types. A feature common to these molecules is the presence of heteroatoms capable of acting as ligands for an ion. They also possess a 3-dimensional capability to orient their ligands towards the center of the molecule, thus allowing for inner complexation to the ion of interest while retaining a lipophilic outer shell. Some of these compound types include linear and cyclic peptides, cyclic depsipeptides and the antibiotic polyether monoacids. Many of these compounds display antibiotic properties. In fact, it is this property which in many cases first led to the discovery and characterization of these compounds, and only after some time was their ionophoric character realized.

Nonactin (65), first characterized in 1955[76], is the lowest homologue and most symmetrical member of the actin family of antibiotics which have been isolated from various Streptomyces cultures. It was the first natural product to be identified as a crown ether and one of the first antibiotics to have its activity attributed to its ionophoric properties. Nonactin has been a challange to synthetic chemists for some time time due to its interesting stereochemical qualities. It is made made up of four nonactic acid units with an overall meso configuration. This is due to an alternating (+)-,(-)-

nonactic acid (66) sequence. (Figure 11)



65 - nonactin



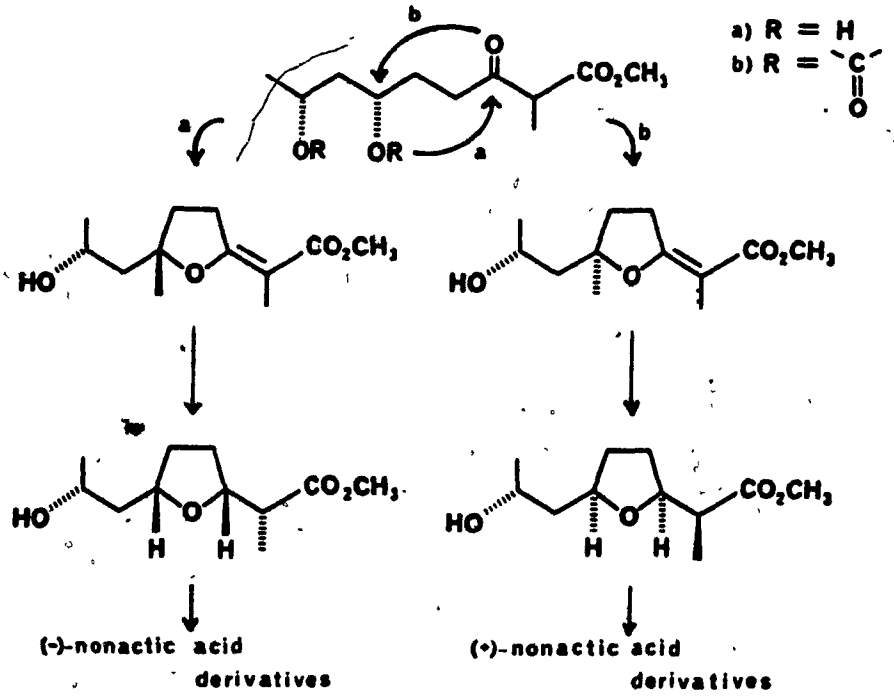
66-nonactic acid

Figure 11

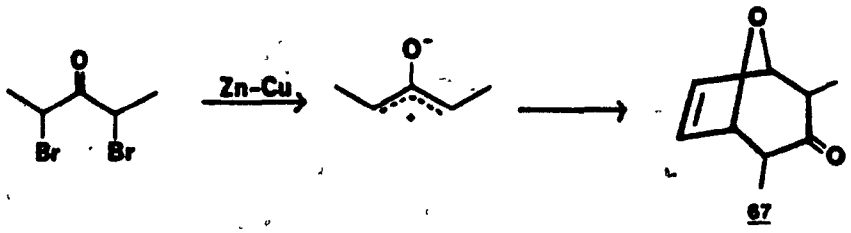
There have been several syntheses of Nonactic acid[77,78], including one by Bartlett[79] which he describes as "stereochemically economical and synthetically convergent". Nonactic acid derivatives of both enantiomeric series ((+) and (-)) were prepared from a single optically active starting material as depicted in Scheme 71.

Another approach for the synthesis of Nonactic acid, put forth by White et. al.[80], has the initial formation of 8-oxabicyclo [3.2.1] octane compound 67 according to the method of Noyori.[81] (Scheme 72)

This particular method is well suited towards the synthesis of nonactic acid since the cis relationship is established in the side chains from the outset.

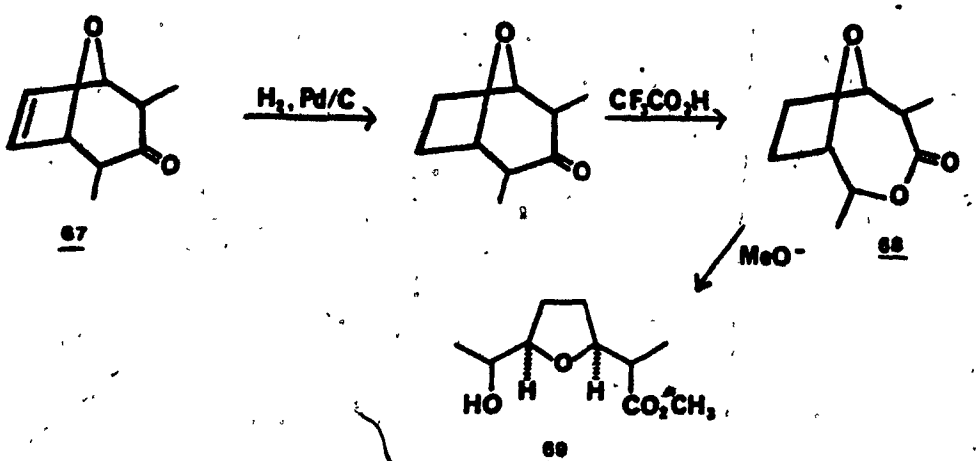


Scheme 71



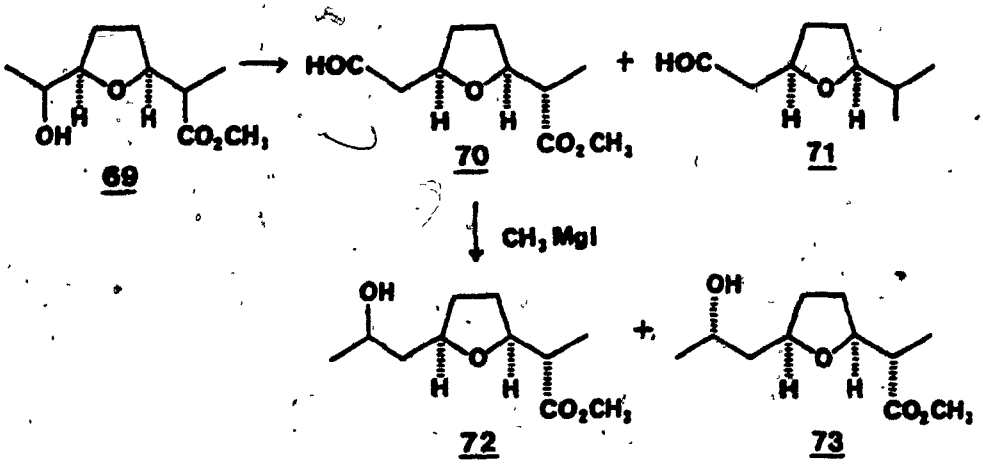
Scheme 72

Hydrogenation of 67 followed by Bayer-Villiger oxidation yielded lactone 68. Methanolysis of 68 gave the hydroxy ester 69. (Scheme 73)



Scheme 73

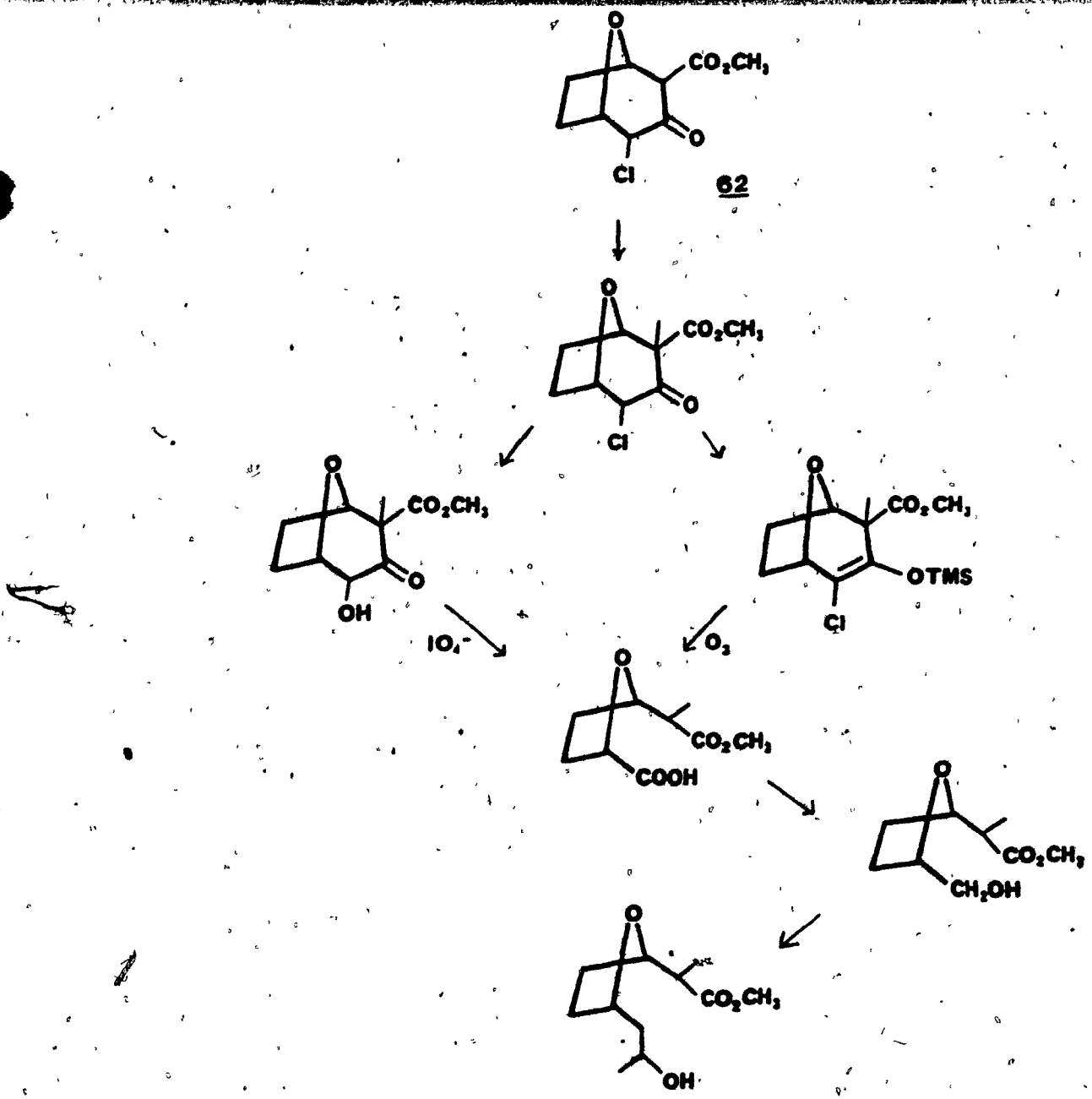
Compound 69 was converted to the epimeric aldehydes 70 and 71 in a few steps. Treatment of 70 with methylmagnesium bromide produced methyl nonactate (72) and methyl 8-epi-nonactate (73) without stereoselectivity. (Scheme 74)



Scheme 74

Saponification of 72 had previously been shown to give nonactic acid.[82]

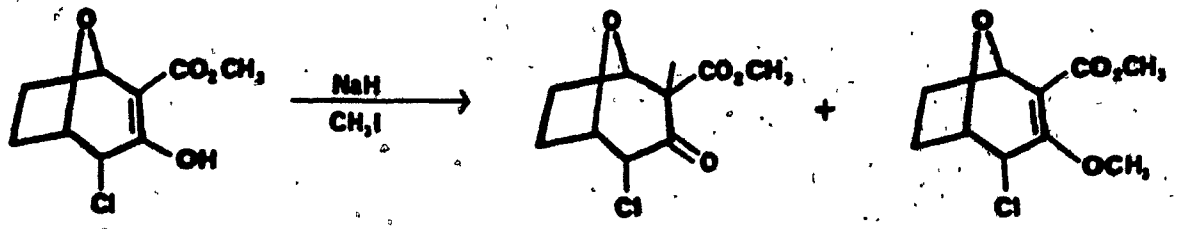
We have proposed an outline for the synthesis of nonactic acid which is similar to that of White in that it involved the initial formation of a bicyclic system 62. This is followed by a methylation and an oxidative cleavage to give a precursor to nonactic acid. (Scheme 75)



Scheme 75

The methylation of 62 was first attempted with sodium hydride and methyl iodide (Scheme 76). The ^{1}H-N.M.R. spectrum indicated that the product was in fact a mixture of O-alkylated and the desired C-alkylated product. ^{1}H-N.M.R. data gave evidence for the presence of both products. Two large peaks

appeared in the 3.80 ppm region corresponding to the methoxy groups in the ester functionality as well as the O-alkylated adduct. TLC showed one large spot (i.e. very similar R_f values for the two compounds) and any separation was extremely difficult regardless of the solvent system used.



62

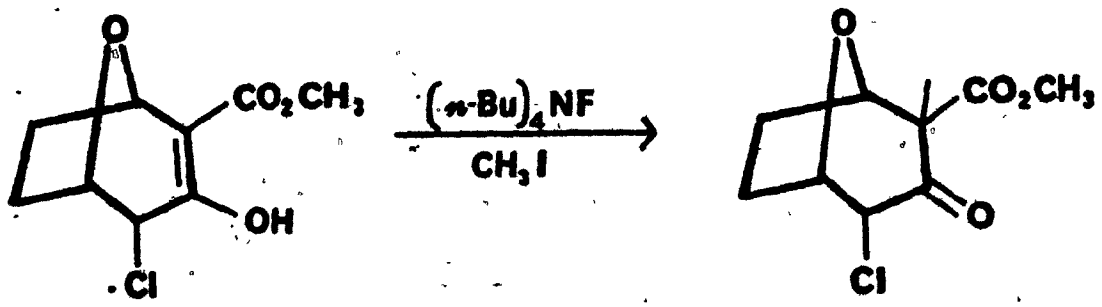
Scheme 76

The formation of O-alkylated products in the alkylation reactions of β-dicarbonyls is especially favored when the equilibrium concentration of the enol tautomer is high, as is the case with β-keto-esters. Considering the fact that the enol form of compound 62 is predominant, the results of this reaction are not surprising.

Various approaches to the problem of C-alkylation of β-dicarbonyls focussed on the idea that O-alkylation could be inhibited by limiting the amount of free enolate ion in the reaction solution. This could be achieved by careful control of reaction conditions or by shielding the oxygen atom by association with a hydrogen bonding solvent or with a metal cation.[83] Clark and Miller[84] found that the reaction of several β-dicarbonyls with alkyl iodides in the presence of

tetra-n-butylammonium fluoride gave exclusively C-alkylated products. The reasoning was that the β-dicarbonyl compound would behave as a hydrogen-bond electron acceptor and thereby form a tightly bonded complex anion with fluoride. The oxygen is shielded both by the large cation and by the enol hydroxy-fluoride hydrogen bond and as a result O-alkylation is inhibited.

This methodology was employed in the C-methylation of 62 and gave the desired product 74 in 70% yield with no apparent formation of the O-alkylated product (Scheme 77).



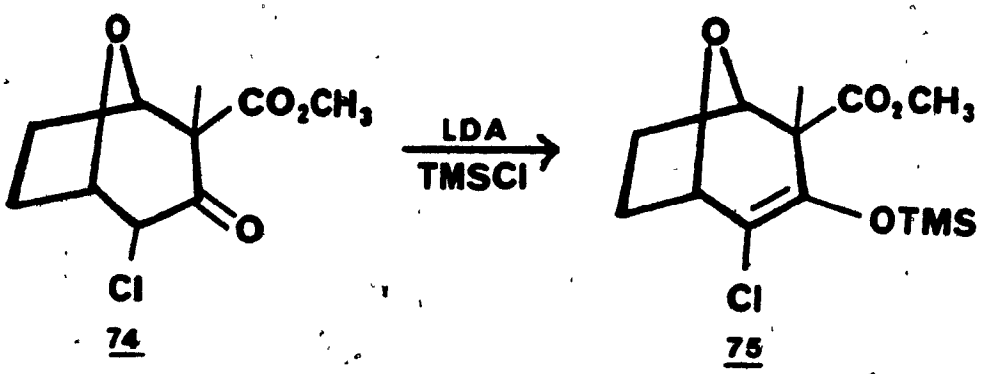
62 74

Scheme 77

^{1}H-N.M.R. data confirmed the structure of the product. A methyl peak appears at 1.68 ppm, while the methoxy protons (corresponding to the ester) appear at 3.78 ppm. There is no evidence of a methoxy peak due to O-methylation. MS and IR data further supported the structural assignnement.

The silylation of 74 was achieved in the usual manner. n-BuLi was added to diisopropylamine and the solution cooled to -78°C. Addition of 74 followed by quenching with TMSCl

yielded the desired product 75 in 96% yield. (Scheme 78)



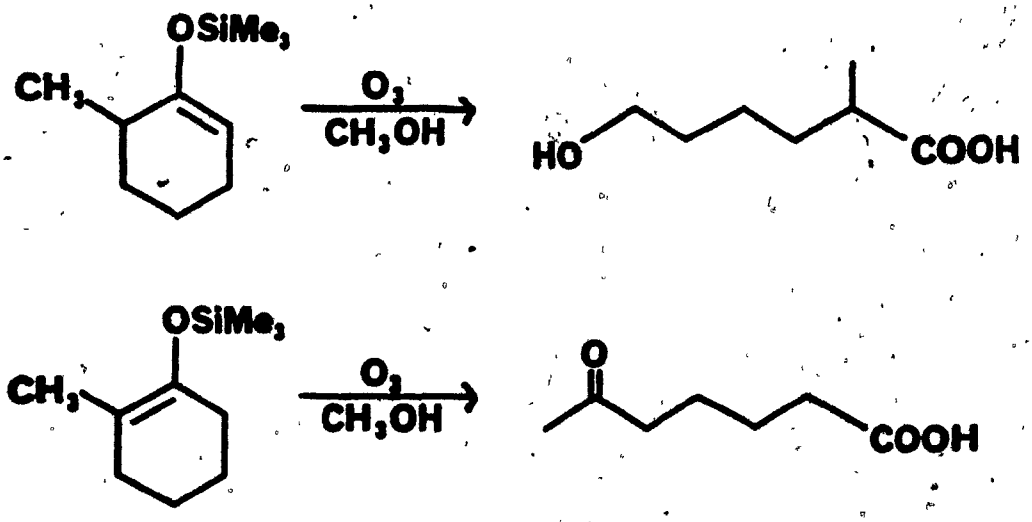
74 75

Scheme 78

^{1}H-N.M.R. data showes the two remaining bridgehead protons at 4.30 and 4.45 ppm (corresponding to C-5 and C-1 respectively) and $-Si(CH_3)_3$ protons (9 total) at 0.25 ppm. IR data shows a much sharper carbonyl peak at 1730 cm^{-1}, which is to be expected since 75 has only one carbonyl group.

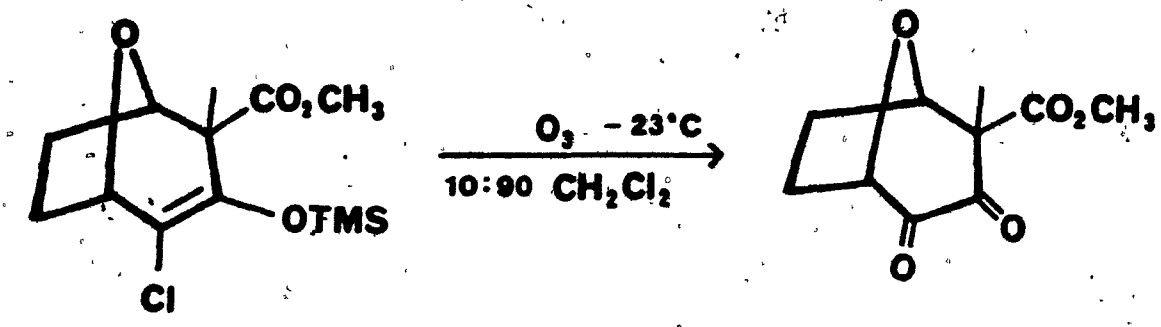
The next step in the synthesis outlined in Scheme 75 has the attempted ozonolysis of compound 75. Heathcock et al.[85] found that when siloxyalkenes were oxidized in the presence of ozone in a methanolic solution, hydroxy acids or ketoacids were isolated according to Scheme 79.

The ozonolysis of 75 was attempted at several different temperatures, (-78°C, -23°C, 0°C), and using different solvent compositions, (10:90, 20:80 CH_2Cl_2/CH_3OH), and the two work-up proceedures suggested by Heathcock (Me_2S, $NaBH_4$). Most of these reaction conditions yielded a mixture of products which



Scheme 79

was impossible to separate. On one occasion, however, some separation was accomplished which yielded 30% of a product. ^{1}H-N.M.R., MS and IR analyses indicated that this product was not the expected product, but was, instead, compound 76. (Scheme 80)



75

Scheme 80

76

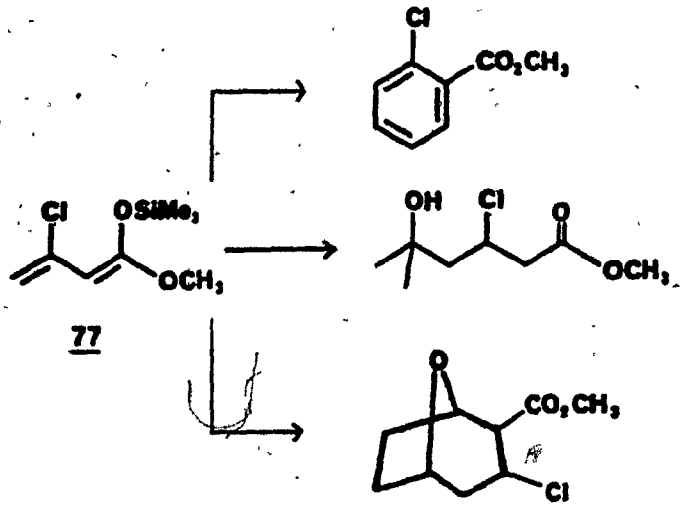
Mass spectral data shows no evidence of a chlorine atom which is usually distinguishable by its characteristic (m/z, m/z + 2) peaks throughout the spectrum. High resolution MS gives a value of m/z= 212.070 which is within 9 ppm of the expected molecular ion value of m/z= 212.068. This result

confirms that the molecular formula is $C_{10}H_{12}O_5$. ^{1}H-N.M.R. and IR data further supported this structural assignment.

The reaction was repeated several times according to Scheme 80. Product 76 was observed by G.C. analysis, but separation of the reaction mixture proved to be difficult.

The attempted synthesis of 3-chloro 1-trimethylsiloxy-1-methoxybuta-1,3-diene

As a variation on the chemistry of the bis silyl enol ether 34, the synthesis of the silyl enol ether, 77, chlorinated at the C-3 position, was investigated. Our aim was to have this compound react in a manner similar to that of 34. (Scheme 81)

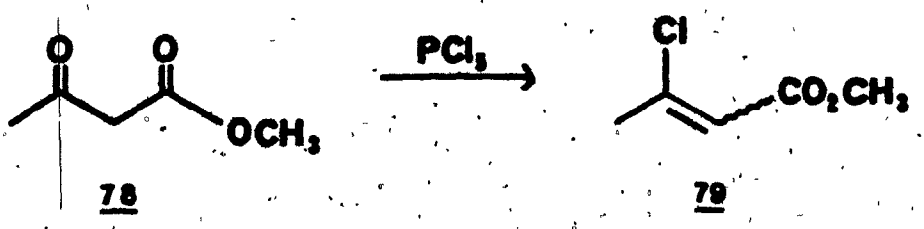


Scheme 81

This diene could prove to be a useful complement to that of the C-4 siloxy substituted diene already described, in that a different substitution pattern could be incorporated

into aromatic, straight chain and bicyclic systems, with a chlorine atom in place of a hydroxy or carbonyl group.

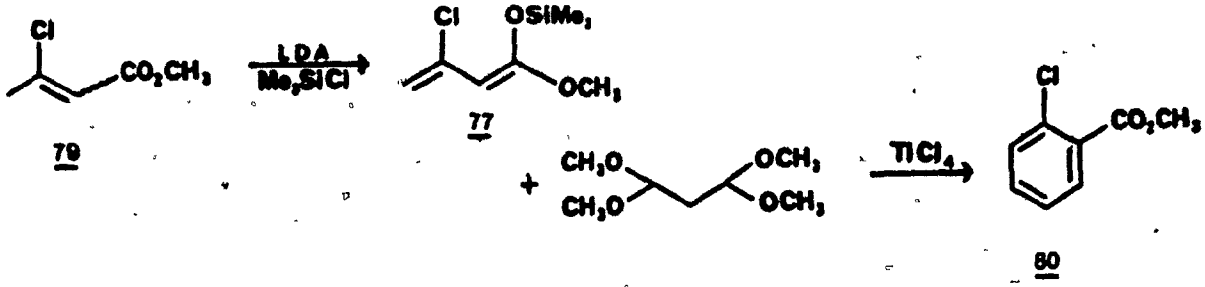
As a first step in the proposed synthesis of 77, methyl acetoacetate (78) was reacted with phosphorous pentachloride according to the method of Marshall[86] to give methyl 3-chloro-2-butenoate (79) in 35% yield. (Scheme 82)



78 79

Scheme 82

The silylation of 79 to give 77 was attempted by several different methods, including LDA/TMSCl and LiHMDS/TMSCl at temperatures of -78°C and -23°C. In most cases the desired product was not observed, however, in one instance a product was obtained which upon reaction with malonaldehyde bis(dimethyl-acetal) gave methyl 2-chlorobenzoate (80) in 10% yield (Scheme 83). In this instance 77 was not purified and spectral information was not obtained.



79 77 80

Scheme 83

Attempts were made to repeat this reaction, but these proved to be unsuccessful. Further work can be done in this area in order to improve on the silylation reaction of 79 so that 77 be fully characterized and its chemistry studied.

Conclusion

Silyl enol ethers have been used extensively in recent years as precursors to a variety of different synthetic transformations. Further functionalization of basic silyl enol ethers allows for the incorporation of these functional groups into the final product, resulting in highly substituted compounds which may be difficult to synthesize by other means. It is with this in mind that we set about to synthesize and study the sterochemistry and reactions of the chlorinated bis silyl enol ether 34.

All of the reactions involving the bis silyl enol ether 34 gave yields which were lower than similar reactions with the unchlorinated compound 18. This may be due in part to the presence of the chlorine atom at the C-4 carbon which renders this position less nucleophilic . Subsequently, the entire molecule is less reactive than its unchlorinated analog. In all cases longer reaction times were necessary to give the desired products, but still, the yields were not significantly increased. However, while yields were low, mixtures of isomers were not observed, and in most cases separation of the desired product from the reaction mixture was straightforward. This

particular feature may be important if a highly functionalized product is required, and other methods for its preparation prove to be difficult to carry out due to the possibility of mixtures of products.

Schemes were investigated by which the synthesis of natural products Griseofulvin and Nonactic acid were attempted. Finally, initial studies were done in the synthesis of a C-3 chlorinated analog of 34.

EXPERIMENTAL

All chemicals used were reagent grade. All solvents were dried prior to use; hexanes and tetrahydrofuran (THF) were dried over sodium metal/benzophenone, and methylene chloride was dried over phosphorous pentoxide.

Proton Magnetic Resonance and Carbon-13 spectra were taken with a Varian T60, T60A, XL-200, XL-300 and a Bruker AM-250 spectrometer with tetramethylsilane (TMS) used as an internal reference. Silicon-29 Magnetic Resonance spectra were taken with the XL-200 using the decoupled INEPT pulse sequence,[87] with TMS as internal reference. All N.M.R. data are reported in parts per million (ppm) and peaks are designated as singlets (s), doublets (d), triplets (t), or multiplets (m).

Infra-red spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer and calibrated with polystyrene film. All I.R. data are reported as wave numbers (cm^{-1}).

Mass Spectra were recorded on a Dupont 21-492B spectrometer using a direct insertion probe with an ionization potential of 60 eV (in all cases unless otherwise indicated), and on a ZAB-HS spectrometer at an ionization potential of 70 eV. The Chemical Ionization mass spectrum was recorded on a Hewlett-Packard 5980A spectrometer.

Gas Chromatographic separations were performed with a Hewlett-Packard 5890 GC using a flame ionization detector.

Column chromatography was performed on Merck silica gel 60 (230-400 microns) using the flash chromatography method.[88]

Melting points were taken on a Gallenkamp apparatus and are uncorrected, as are boiling points.

Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario.

Methyl 4-chloro-3-trimethylsiloxy-but-2-enoate (36):

Zinc chloride (0.5 g) was heated and liquefied over a flame. Triethylamine (26 ml) was added and the solution stirred for 15 minutes. Dichloromethane (50 ml) was added and the solution cooled to 0°C. Methyl 4-chloroacetoacetate (37) (13 g, 86 mmol) was added dropwise and the solution stirred for a further 15 minutes. The reaction was quenched with trimethylchlorosilane (22 ml) and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue dissolved in cold dry hexanes. The solution was filtered under N_2 and the solvent removed to yield a brown oil which was distilled under vacuum (0.1 torr, 55°C) to yield 11.3 g of product 36 (60% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 0.31 (s, 9H, $-Si(CH_3)_3$), 3.69 (s, 3H, $-COOCH_3$), 4.59 (s, 2H, $-CH_2Cl$), 5.20 (s, 1H, =CH);

^{29}Si-N.M.R. ($CDCl_3$): 23.6;

^{13}C-N.M.R. ($CDCl_3$): 40.9 ($-CH_2Cl$, E-isomer), 46.1 (Z-isomer), 50.6 ($-OCH_3$, Z-isomer), 51.0 (E-isomer), 101.1 (-C(OTMS)=CH, E-isomer), 101.5 (Z-isomer), 160.6 ($ClCH_2$-C(OTMS)=CH-, Z-isomer), 164.9 (E-isomer), 166.7 (=CH-CO_2Me);

I.R. (neat): 1710, 1620, 1245, 1135, 840;

M.S. : m/z= 222 (1.5%, M^+), 224 (0.5%, $M^+ + 2$), 207 (100% , M^+-CH_3);

exact mass for $C_7H_{12}O_3SiCl$ (M^+-CH_3) : calc. 207.024
found 207.028

1,3-Bis(trimethylsiloxy)-4-chloro-1-methoxybuta-1,3-diene (34):

Diisopropylamine (0.55 ml) in 15ml THF was cooled to 0°C. N-Butyllithium (2.6 ml, 1.6M in hexanes) was added slowly and the solution cooled to -78°C. Methyl 4-chloro-3-trimethylsiloxy-but-2-enoate (36) (0.73 g, 3.3 mmol) in 5ml THF was added dropwise and the solution stirred for 10 minutes. The reaction was quenched with trimethylchlorosilane (0.66 ml) and stirred for 10 minutes at -78°C then allowed to come to room temperature. The solvent was removed under reduced pressure and the residue dissolved in cold dry hexanes. The solution was filtered under N_2 and the solvent removed under reduced pressure to yield 0.856g of product 34 (89% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 0.227 (s, 9H, $-Si(CH_3)_3$, 0.233 (s, 9H, $-Si(CH_3)_3$), 3.54 (s, 3H, $-COOCH_3$), 3.89 (s, 1H, HC=);

^{29}Si-N.M.R. ($CDCl_3$): 19.6, 22.7;

^{13}C-N.M.R. ($CDCl_3$): 55.0 ($-OCH_3$), 75.8 (-CH=C(OMe)), 97.1 (ClHC=C(OTMS)-), 147.6 (ClHC=C(OTMS)-), 158.4 (-CH=C(OMe)(OTMS);

I.R. (neat): 1645, 1292, 1255, 850;

M.S. : m/z= 294 (15.6%, M^+), 296 (5.8%, $M^+ + 2$), 73 (100%);

exact mass for $C_{11}H_{23}O_3Si_2Cl$: calc. 294.087
found 294.089

Methyl 3-chloro-2-hydroxybenzoate (39):

1,1,3,3-Tetramethoxypropane (38) (0.56 g, 3.4 mmol) was dissolved in 20 ml dichloromethane and the solution cooled to -78°C. Titanium tetrachloride (0.5 ml) was added followed by a dropwise addition of 1,3-bis(trimethylsiloxy)-4-chloro-1-methoxybuta-1,3-diene(34) (1.0 g, 3.4 mmol). The solution was stirred at -78°C for 3 hours and then left stirring overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate solution and extracted with ether. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 215 mg crude product. Purification by flash chromatography (94:6 hexanes-ethyl acetate, v/v) yielded 100 mg product (39) (25% yield). It had:

^1H-N.M.R. ($CDCl_3$): 3.93 (s, 3H, Ar-$COOCH_3$), 6.60-7.90 (m, 3H, Ar-H), 11.53 (s, 1H, Ar-OH);

I.R. (neat): 1678, 1440, 1325, 1255, 1153, 753;

M.S. : m/z= 186 (35.4%, M^+), 188 (20.0%, M^++2), 154 (100%);

exact mass for $C_8H_7O_3Cl$: calc. 186.008
found 186.011

Methyl 2-hydroxy-3-chloro-4,6-dimethylbenzoate (41):

The bis silyl enol ether 34 (1.75 g, 5.9 mmol) was dissolved in 10ml methylene chloride. 4-Trimethylsiloxy-3-penten-2-one (40) (1.0 g, 5.8 mmol) was added and the solution cooled to -78°C. Titanium tetrachloride (2.0 ml, 18 mmol) was added slowly and the resulting dark red solution was stirred at -78°C for 2 hours then left stirring overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate and extracted with ether. The solution was washed with water and the organic layer dried ($MgSO_4$). The solvent was removed under high vacuum to yield 600 mg crude product. Recrystallization from methanol yielded 290 mg product 41 (23% yield). It had:

melting point : 92-94°C.

^{1}H-N.M.R. ($CDCl_3$): 2.37 (s, 3H, Ar-CH_3), 2.48 (s, 3H, Ar-CH_3), 3.96 (s, 3H, Ar-$COOCH_3$), 6.67 (s, 1H, Ar-H) 11.92 (s, 1H, Ar-OH);

I.R. (Nujol): 1665, 1260, 1210, 965, 805;

M.S. : m/z= 214 (32%, M^+), 216 (20%, M^++2), 182 (100%);

exact mass for $C_{10}H_{11}O_3Cl$: calc. 214.040
found 214.038

Anal. Calcd: C, 55.98; H, 5.17. Found: C, 55.86; H, 5.20.

Methyl 2-hydroxy-3-chloro-4-methylbenzoate (43):

3-Ketobutyraldehyde dimethyl acetal (42) (0.33 g, 2.5 mmol) was dissolved in 5ml methylene chloride. The bis silyl enol ether 34 (0.75 g, 2.5 mmol) was added, the solution stirred for 5 minutes then cooled to -78°C. Titanium tetrachloride (0.55 ml, 5 mmol) was added slowly. The dark red solution was stirred for 2 hours at -78°C then overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate solution and extracted with ether. The solution was washed with water, dried ($MgSO_4$) and the solvent removed to yield 400 mg crude product. Purification by flash chromatography (4:1 hexanes-ethyl acetate, v/v) yielded 145 mg of product 43 as white crystals (29% yield). It had:

melting point : 74.5-76°C;

^{1}H-N.M.R. ($CDCl_3$): 2.42 (s, 3H, Ar-CH_3), 3.93 (s, 3H, Ar-$COOCH_3$), 6.6-7.6 (dd, 2H, Ar-H, J=8 Hz), 11.33 (s, 1H, Ar-OH);

I.R. (Nujol): 1660, 1250, 1140, 970, 810;

M.S. : m/z= 200 (27%, M^+), 202 (26%, M^++2), 168 (100%);

exact mass for $C_9H_9O_3Cl$: calc. 200.024
found 200.023

Methyl 2-hydroxy-3-chloro-4-methoxy-6-methylbenzoate (45):

3-Ketobutyraldehyde trimethyl ortho ester (44) (0.40 g, 2.5 mmol) was dissolved in 10ml methylene chloride and the solution cooled to -78°C. The bis silyl enol ether 34 (0.75 g, 2.5 mmol in 5ml methylene chloride) was added slowly and the solution stirred for 15 minutes. Titanium tetrachloride (0.74 ml, 6.8 mmol) was added dropwise. The red-brown solution was srirred at -78°C for 2 hours then left at room temperature overnight. The rection was quenched with aqueous sodium bicarbonate solution and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield 300 mg crude product. Recrystallization from methanol yielded 141 mg of product 45 as white crystals (24% yield). It had:

melting point : 158-160°C;

^{1}H-N.M.R. ($CDCl_3$): 2.55 (s, 3H, Ar-CH_3), 3.91 & 3.93 (s, 3H & 3H, Ar-$COOCH_3$ & Ar-OCH_3), 6.30 (s, 1H, Ar-H), 12.20 (s, 1H, Ar-OH);

I.R. (Nujol): 1650, 1565, 1315, 1300, 1275, 1225, 1105 985, 800;

M.S. : m/z= 230 (39%, M^+), 232 (25.8%, M^++2), 198 (100%);

exact mass for $C_{10}H_{11}O_4Cl$: calc. 230.035
found 230.033

Anal. Calcd: C, 52.10; H, 4.81. Found: C, 51.97; H, 5.09.

Methyl 3-keto-4-chloro-5-hydroxy-5-methylhexanoate (59):

Acetone (3) (0.50 ml, 6.81 mmol) was dissolved in 20ml dry methylene chloride and the solution cooled to -78°C. Titanium tetrachloride (0.40 ml, 3.65 mmol) was added slowly. The silyl enol ether 34 (1.0 g, 3.42 mmol in 5ml methylene chloride) was added dropwise. The brown solution was stirred at -78°C for 3 hours then allowed to come to room temperature. The reaction was quenched with aqueous sodium bicarbonate solution then extracted with ether. The organic layer was washed with water then dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 700 mg crude product. Purification by flash chromatography (7:3 hexanes-ethyl acetate, v/v) yielded 310 mg of product 59 (44% yield) and 170 mg starting material. Compound 59 had:

^{1}H-N.M.R. ($CDCl_3$): 1.38 (s, 3H, R-CH_3), 1.39 (s, 3H, R-CH_3), 2.74 (s, 1H, R-OH), 3.73 (s, 3H, R-$COOCH_3$) 3.80 (s, 2H, -OCCH_2COOMe), 4.25 (s, 1H, -CH);

I.R. (neat) : 3520, 2990, 1730, 1440;

M.S. (CI): m/z = 209 (41%, M+H), 211 (12%, M+H + 2), 151(100%);

Methyl 4-chloro-4-(1'-hydroxycyclohexyl) acetoacetate (60):

Cyclohexanone (58) (0.17 g, 1.76 mmol) was dissolved in 5ml methylene chloride and the solution cooled to -78°C with stirring. Titanium tetrachloride (0.37 ml, 3.4 mmol) was added dropwise and the solution stirred for 15 minutes. Bis silyl enol ether 34 (0.52 g, 1.76 mmol) was added dropwise and the solution stirred at -78°C for two hours then overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate solution, the organic layer washed with water then dried ($MgSO_4$).The solvent was removed under reduced pressure to yield 350 mg crude product. Purification by flash chromatography (3:1 hexanes-ethyl acetate, v/v) yielded 111 mg of product as a yellow oil (25% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 1.2-1.8 (br, 10H, $-(CH_2)_5-$), 3.70 (s, 1H, -OH), 4.10 (s, 3H, $R-COOCH_3$), 4.20 (s, 2H, $-OC\underline{CH_2}COOMe$), 4.67 (s, 1H, -CH);

I.R. (neat) : 3510, 2950, 1750, 1445, 1330, 1245;

M.S. : m/z= 213 (2.4%, M^+-Cl), 28 (100%);

exact mass for $C_{11}H_{16}O_4$ (M^+-Cl) : calc. 213.113
found 213.118

1,5-Dimethyl-2-methoxycarbonyl-3-oxo-4-chloro-8-oxabicyclo-[3.2.1]-octane (61):

The silyl enol ether 33 (0.75 g, 2.54 mmol) was dissolved in 5 ml methylene chloride. Freshly distilled acetonylacetone (59) (0.29g, 2.54 mmol) was added and the solution stirred for 10 minutes then cooled to -78°C. Titanium tetrachloride (0.60 ml, 5.1 mmol) was added slowly. The red-brown solution was stirred at -78°C for 3 hours then left overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate solution and extracted with ether. The solution was washed twice with water, the organic layer dried ($MgSO_4$) and reduced under high vacuum to yield 450 mg crude product. Purification by flash chromatography (4:1 hexanes-ethyl acetate, v/v) yielded 180 mg product 61 as white crystals (30% yield). It had:

melting point : 95-96.5°C;

^{1}-N.M.R. ($CDCl_3$): 1.47 (s, 3H, R-CH_3), 1.58 (s, 3H, R-CH_3), 1.6-2.7 (m, 4H, R-CH_2CH_2-R), 3.61 (s, 1H, -CH), 3.72 (s, 3H, R-$COOCH_3$), 4.29 (s, 1H, -CH);

I.R. (Nujol): 1760, 1735, 1340, 1315, 1220, 1120;

M.S. : m/z= 246 (4.3%, M^+), 248 (1.2%, M^++2), 28 (100%);

exact mass for $C_{11}H_{15}O_4Cl$: calc. 246.066
found 246.065

2-Methoxycarbonyl-3-oxo-4-chloro-8-oxabicyclo-[3.2.1]-octane (62):

2,5-Dimethoxytetrahydrofuran (60) (0.42g, 3.2 mmol) was dissolved in 15ml methylene chloride and the solution cooled to -78°C. Titanium tetrachloride (0.50 ml, 4.6 mmol) was added slowly and the solution stirred for a further 10 minutes. The silyl enol ether 33 (0.65 g, 2.2 mmol in 5 ml methylene chloride) was added dropwise. The resulting dark red solution was stirred at -78°C for 2 hours then left overnight at room temperature. Aqueous sodium bicarbonate was added and the solution extracted with ether , washed with water and dried ($MgSO_4$). The solvent was removed under high vacuum to yield 245 mg crude product. Purification by flash chromatography (4:1 hexanes-ethyl acetate, v/v) yielded 145 mg product, (30% yield), as a mixture of oil and crystals corresponding to the keto (62a) and enol (62b) tautomers of 62. Washing the mixture with cold methanol separated the mixture and gave 98 mg of crystalline product 62b. It had:

melting point: 100.5-102°C;

^{1}-N.M.R. ($CDCl_3$): 1.5-2.3 (m, 4H, $-C-CH_2CH_2-C-$), 3.82 (s, 3H, $R-COOCH_3$), 4.05 (s, 1H, -CH), 4.64 (d, J=4Hz, 1H, -CH), 4.98 (d, J= 2Hz, 1H, C-CHCl-C), 11.45 (s, 1H, -OH);

I.R. (Nujol): 1675, 1625, 1380, 1290, 1250, 1230, 825, 635;

M.S. : m/z= 218 (24%, M^+), 220 (7.7%, M^++2), 69 (100%);

exact mass for $C_9H_{11}O_4Cl$: calc. 218.036
found 218.035

Anal. Calcd: C, 49.44: H, 5.07. Found: C, 49.33; H, 5.24.

2-Methoxycarbonyl-2-methyl-3-oxo-4-chloro-8-oxabicyclo-[3.2.1]-octane (66):

Tetra-n-butylammoniun fluoride trihydrate (0.64 g, 2.0 mmol) was dissolved in 10 ml THF. 2-Carbomethoxy-3-oxo-4-chloro-8-oxabicyclo-[3.2.1]-octane (62) (0.44 g, 2 mmol in 5ml THF) was added and the solution stirred for 30 minutes. Molecular sieves (3A) were added and the solution stirred for 90 minutes. The solution was decanted then quenched with methyl iodide (0.13 ml, 2 mmol) and left stirring at room temperature overnight. The solvent was removed under reduced pressure, the residue dissolved in ether and filtered. The filtrate was washed with water then dried ($MgSO_4$) and the solvent reduced under high vacuum to yield 320 mg of pure product as a yellow oil (70% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 1.67 (s, 3H, R-CH_3), 1.8-2.3 (m, 4H, -C-CH_2CH_2-C), 3.78 (s, 3H, R-$COOCH_3$), 4.50 (d, J=7.9Hz, 1H, -CH), 4.71 (m, 1H, -CH), 4.78 (d, J=1Hz, -C-CHCl-C-);

I.R. (neat): 1728, 1450, 1275, 1050;

M.S. : m/z= 232 (2.3%, M^+), 234 (0.9%, M^++2), 28 (100%);

exact mass for $C_{10}H_{13}O_4Cl$: calc. 232.050
found 232.047

2-Methoxycarbonyl-2-methyl-3-trimethylsiloxy-4-chloro-8-oxa-bicyclo-[3.2.1]-3-octene (67):

Diisopropylamine (0.18 ml) was dissolved in 10ml dry THF and the solution cooled to 0°C. n-Butyllithium (0.56 ml, 2.5M in hexane) was added slowly, the solution cooled to -78°C and stirred for 10 minutes. 2-Methoxycarbonyl-2-methyl-3-oxo-4-chloro-8-oxabicyclo-[3.2.1]-octane (66) (250 mg, 1 mmol in 5 ml THF) was added slowly and the solution stirred for 15 minutes. The reaction was quenched with chlorotrimethylsilane (0.22 ml), stirred for a further 15 minutes at -78°C then allowed to come to room temperature. The solvent was removed under reduced pressure and the residue dissolved in cold dry hexanes. The solution was filtered under N_2 and the solvent removed under high vacuum to yield 160 mg product (67) as a brown oil (55% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 0.25 (s, 9H, $-Si(CH_3)_3$) 1.56 (s, 3H, $R-CH_3$), 1.8-2.3 (m, 4H, $R-CH_2CH_2-R$) 3.70 (s, 3H, $R-COOCH_3$), 4.31 (t, 1H, -CH), 4.45 (d, 1H, $=C(Cl)-CH$);

I.R. (neat): 1730, 1650, 1250, 880, 840;

M.S. : m/z= 304 (1.9%, M^+), 306 (1.0%, M^++2), 28 (100%);

exact mass for $C_{13}H_{21}O_4SiCl$: calc. 304.090
found 304.093

2-Methyl-2-methoxycarbonyl-3,4-dioxo-8-oxabicyclo-[3.2.1]-octane (76):

Silyl enol ether 67 (363 mg, 1.2 mmol) was dissolved in 10:90 CH_2Cl_2/CH_3OH and cooled to -25° C. Ozone was bubbled through the solution for 1 hour at which time the mixture turned a light blue. The bubbling of ozone was discontinued and the solution stirred for an additional 30 minutes. Dimethyl sulfide (2 ml) was added and the solution allowed to come to room temperature and then stirred overnight. The solvent was removed under vacuum and the residue dissolved in methylene chloride. The solution was washed twice with H_2O, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield 110 mg crude product. Purification by flash chromatography (8:2 hexanes-ethyl acetate, v/v) yielded 75 mg of product 76 (30% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 1.81 (s, 3H, R-CH_3), 2.0-2.5 (br, 4H, C-CH_2CH_2-C-), 3.75 (s, 3H, R-$COOCH_3$), 4.58 (d, J=7.1 Hz, 1H, -CH), 4.77 (d, J=7.3Hz, 1H, -CH);

I.R. (neat): 3450, 1735, 1435, 1450, 1270, 1055;

M.S. : m/z= 212 (M^+), 28 (100%);

exact mass for $C_{10}H_{12}O_5$ calc. 212.068
found 212.070

Methyl 3-chloro-2-butenoate (79):

Compound 79 was prepared according to a literature proceedure.[86] Phosphorous pentachloride (25g) was dissolved in 60 ml $CHCl_3$. The solution was stirred for 45 minutes then cooled to 0°C. Methyl acetoacetate (78) (10.8 ml, 0.10 mol) was added dropwise and the stirring continued at 0°C for two hours. The reaction solution was added slowly to 600 ml crushed ice. The organic phase was separated and washed with H_2O (3 x 50 ml), cold 5% NaOH (2 x 50 ml) and saturated brine and the extract dried with $MgSO_4$.

Triethylamine (8.5 ml) was carefully added to the previous solution and the mixture refluxed for 3 hours. After cooling, the solution was washed with H_2O (3 x 50 ml), cold 10% aq. HCl (2 x 50 ml) and saturated brine. The extract was dried over $MgSO_4$, the solvent removed under vacuum and the dark brown residue distilled (5-20 torr, 62°C) to give 5.65 g of product 79 (42% yield). It had:

^{1}H-N.M.R. ($CDCl_3$): 2.60 (s, 3H, R-CH_3), 3.72 (s, 3H, R-$COOCH_3$), 6.06 (s, 1H, -C=CH-CO-);

This is in agreement with literature values.[89]

3-Chloro-1-trimethylsiloxy-1-methoxybuta-1,3-diene (77):

Diisopropylamine (2.1ml, 15mmol) was dissolved in 40 ml THF and the solution cooled to 0°C. n-Butyllithium (10.3 ml, 1.6M in hexane, 16.5mmol) was added dropwise and the solution

cooled to -78°C. TMSCl (2.52 ml, 20mmol) was added dropwise and the solution stirred for 10 minutes. Methyl 3-chloro-2-butenoate (79), (1,3g; 9.4mmol) was added dropwise and the solution stirred for a further 10 minutes. The solvent was removed under reduced pressure and the residue dissolved in cold dry hexanes. This solution was filterred and the solvent removed under vacuum to yield 1.65g of crude product 77 (85% crude yield).

Methyl 2-chlorobenzoate (80)

1,1,3,3-Tetramethoxypropane (38) (1.05 ml, 6.4mmol) was dissolved in 50 ml CH_2Cl_2 and the solution cooled to -78°C. Titanium tetrachloride (1.76 ml) was added dropwise and the solution stirred for 10 minutes. The product of the previous reaction 77 (1.32 g, 6.4mmol)was added and the solution stirred at -78°C for 3 hours followed by stirring overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate and extracted with ether. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under high vacuum to yield 850 mg crude product. Purification by flash chromatography (95:5 hexanes-ethyl acetate, v/v) yielded 105 mg of product 80 (10% yield). ^{1}H-N.M.R. was in agreement with literature values.[90]

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